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Spécialité : Chimie organique

Présentée par

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DOCTEUR DE L'ÉCOLE POLYTECHNIQUE

FROM ISOCYANIDE BASED MULTICOMPONENT REACTIONS TO HETEROCYCLIC SYNTHESIS

Soutenue le 1er Octobre 2012, devant le jury composé de :

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Table of contents

List of abbreviations

List of abbreviations and symbols employed in this thesis, most of them are in common use in the chemical literature.

Units

°C	:	degree Celsius
Hz	:	hertz
MHz	:	megahertz
M	:	mol/L
mg	:	milligram
gm	:	gram
mL	:	milliliter
mmol	:	millimole

Other

δ	:	chemical shift (NMR)
µW	:	microwave irradiation
Ac	:	acetyl
AcCl	:	acetyl chloride
Ar	:	aromatic
Bn	:	benzyl
BMS	:	borane dimethyl sulfide
Boc	:	*tert*-butyloxycarbonyl
t-Bu	:	*tert*-butyl
Bz	:	benzoyl
CAN	:	ceric ammonium nitrate
Cat.	:	catalyst
Cbz	:	benzyloxycarbonyl
CDI	:	1,1'-carbonyldiimidazole
Cy	:	cyclohexyl
m-CPBA:		3-Chloroperoxybenzoic acid
DBU	:	8-diazobicyclo[5.4.0]undec-7-ene
1,2-DCE:		1,2-dichoroethane
DDQ	:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Diglyme: diethylene glycol dimethyl ether
DLP : dilauroyl peroxide
DMA : *N*,*N*-dimethylacetamide
DMAP : 4-dimethylaminopyridine
DMF : *N*,*N*-dimethylformamide
DMS : dimethylsulfide
DMSO : dimethylsulfoxide
equiv : equivalent
Et : ethyl
HBr : hydrobromic acid
HCl : hydrochloric acid
HMDS : hexamethyldisilazide
HRMS : high-resolution mass spectrometry
HOBt : 1-hydroxybenzotriazole
I.R. : infra-red
J : coupling constant (NMR)
LAH : lithium aluminum hydride ($LiAlH_4$)
LDA : lithium diisopropylamide
LHMDS: lithium *bis*(trimethylsilyl)amide
m : meta
MCRs : multi-component reactions
Me : methyl
MeOH : methanol
NBS : *N*-bromosuccinimide
NCS : *N*-chlorosuccinimide
NH*t*Bu : *N*-*tert*-butylamine
NHEt : *N*-ethylamine
NHMe : *N*-methylamine
NMR : nuclear magnetic resonance
NMe_2 : *N*,*N*-dimethylamine
NMP : *N*-methylpyrrolinine
NO_2 : nitro
OEt : ethoxy
o : ortho

p	:	para
PEPPSI:		pyridine-enhanced precatalyst preparation stabilization and initiation
PTC	:	phase transfer catalyst
*i*Pr	:	*iso*-propyl
Py	:	pyridine
rt, RT	:	room temperature
Rf	:	retention factor (chromatography)
SEt	:	ethylthio
SET	:	single-electron transfer
TEA	:	triethylamine
TFA	:	trifluoroacetic acid
Tf	:	triflate (CF_3SO_2)
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
p-Tol	:	*p*-Tolyl
TosMIC	:	*p*-Toluenesulfonylmethylisocyanide
UV	:	ultraviolet spectroscopy
Wt	:	weight

General Introduction

Introduction

Over the last two decades, the world pharmaceutical industry has undergone profound transformations, searching for new drugs. For this purpose most pharmaceutical companies invested heavily in the development of new drugs. But modern drug discovery is faced with the challenge of designing chemical reactions that are highly capable in providing most of the elements of structural complexity and diversity with minimum synthetic steps for the particular target with interesting properties. In this context, combinatorial chemistry has been considered as a fundamental source of novel molecules in the drug discovery process.

The discovery of environmental friendly reactions which are capable to form multiple bonds in a single step is a challenging task for organic chemists.

Multicomponent reactions play an important innovative role to fulfill all these criteria.

Objective

The major objective of this thesis is related to the discovery of new multicomponent reactions involving an isocyanide such as Ugi-Smiles and Nef reactions and further develop it to new methodologies in heterocyclic synthesis.

After a brief introduction on isocyanides and multicomponent reactions, we present the developments of Ugi and Ugi-Smiles couplings and their post-condensation reactions in heterocyclic synthesis.

We have demonstrated the reactivity of 4-hydroxypyridines and pyrimidines in Ugi-Smiles couplings, these reactions have been applied to the synthesis of antimalarial analogues. Several applications of Ugi and Ugi-Smiles adducts have been explored using radical chemistry (xanthates as well as oxidative couplings). It offers spirooxindolines and pyrrolopyrimidine derivative in two steps procedures.

We have also explored the chemistry of *gem*-dibromoisocyanides in various heterocyclic syntheses. The project developed is to use these compounds in cascades that integrate organometallic couplings; this allowed us to get very general synthesis of heterocycles such as oxazole, tetrazole or triazole in one-pot synthesis.

The last chapter of this thesis is the study of a fragmentation reaction of tetrazoles formed through Ugi-azide type couplings. We developed a novel methodology for the preparation of 1,2,3-triazole.

Chapter 1:

Introduction

I. Multicomponent reactions (MCRs) and isocyanide: general considerations

1. Introduction

In the past, most of the drugs have been discovered either by accidental discovery or identifying the active ingredients from traditional remedies. Modern drug discovery is faced with the challenge of designing chemical reactions that are highly capable of providing most of the elements of structural complexity and diversity with minimum synthetic steps for particular target with interesting properties.[1] In the recent past, combinatorial chemistry has been considered as a powerful tool for the fast invention of lead compounds in the drug discovery process.[2] Thus, the major driving force behind the increased interest in this field has been the need to discover and develop new chemical entities with desirable properties in a more efficient and cost-effective manner, and most importantly within a short period of time. Presently, most of the drugs in the market are small organic compounds that contain heterocyclic rings.[1a] However, in combinatorial chemistry; there are some limitations of accessibility and availability of suitably functionalized heterocyclic building blocks for the synthesis of different libraries. As a result, the development of new, efficient and clean synthetic reactions remains a crucial challenge to chemists.[3]

Multicomponent Reactions (MCRs),[4] in which the coupling of at least three or more starting materials in a one-pot reaction to form a new product, where basically all or most of the atoms contribute to the newly formed product. Compared to conventional multistep organic syntheses, MCRs are advantageous due to their greater atom efficiency, and the accessibility to a large number of molecules with broad structural diversity. The experimental simplicity of one-pot procedures is also a major benefit; they are easier to carry out than multistep

[1] a) Domling, A. *Curr. Opin. Chem. Biol*. **2002**, *6*, 303–313. b) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S.; Gordon, *E. M. J. Med. Chem*. **1994**, *37*, 1233–1251. c) Golisade, A.; Wiesner, J.; Herforth, C.; Joma, H.; Link, A. *Bioorg. Med. Chem*. **2002**, *10*, 769–777

[2] a) Teague, S.; Davis, A.; Leeson, P.; Oprea, T. *Angew. Chem., Int. Ed*. **1999**, *38*, 3743–3748. b) Armstrong, R.; Combs, A. P.; Tempest, P.; Brown, S.; Keating, T. *Acc. Chem. Res*. **1996**, *29*, 123–131.

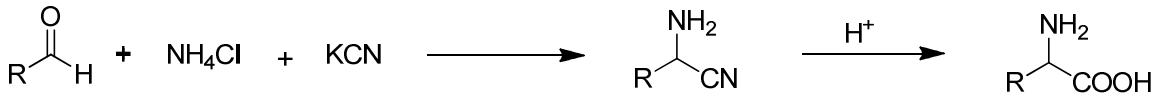
[3] Orru, R.; Greef, M. *Synthesis* **2003**, 1471–1499.

[4] a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed*. **2000**, *39*, 3168–3210. b) Hulme, C.; Gore, V. *Curr. Med. Chem*. **2003**, *10*, 51–80. c) Ugi, I. *Angew. Chem., Int. Ed. Engl*. **1962**, *1*, 8–21.

syntheses. The structure of the reaction product can easily be modified by systematic variation of each input.

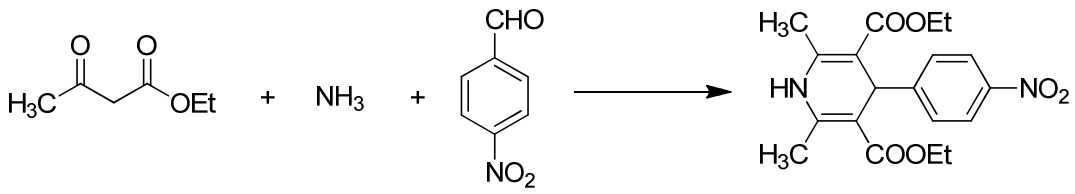
2. History of MCRs:

Multicomponent reactions have been known for more than 150 years. First multicomponent reaction was documented by Strecker.[5] In this reaction an aldehyde is condensed with ammonium chloride in presence of potassium cyanide to form an α-amino nitrile, which could give the α-amino acid after hydrolysis.



Scheme I.1: Strecker Synthesis of α-amino acid.

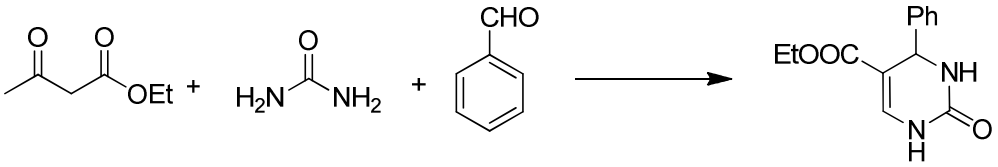
In the literature, there are many important heterocycle synthesises, which are MCRs. For instance, in 1882, Hantzsch[6] develop dihydropyridine synthesis from ammonia, an aldehyde and two equivalents of ethyl acetoacetate.



Scheme I.2: Hantzsch dihydropyridine synthesis.

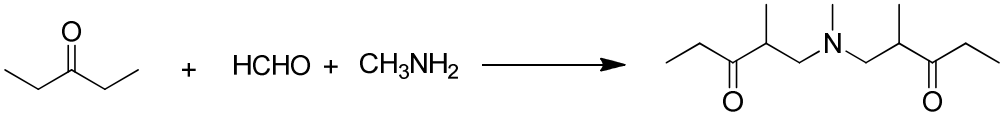
In 1891, Biginelli[7] synthesized 3,4-dihydropyrimidin-2(1*H*)-ones from ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde), and urea.

[5] Strecker, A. *Liebigs Ann.Chem*. **1850**, *75*, 27-51.
[6] Hantzsch, A. *Justus Liebegs Ann. Chem.* **1882**, *215*, 1-82.
[7] a) Biginelli, P. *Ber.* **1891**, *24*, 1317 & 2962. b) Biginelli, P. *Ber.* **1893**, *26*, 447. c) Kappe, O. *Acc. Chem. Res.* **2000**, *33*, 879. d) Kappe, C. *J. Org. Chem.* **1997**, *62*, 7201-7204.



Scheme I.3: Biginelli 3,4-dihydropyrimidin-2(1*H*)-one synthesise.

In 1912, Mannich reaction[8], consists of an amino alkylation of an enol with aldehyde and an amine.



Scheme I.4: Mannich reaction.

Discovered in 1960's, Ugi multicomponent reaction[9] involves a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid to form a *bis*-amide. It will be discussed more in details in the next part of this chapter.

Scheme I.5: Ugi Reaction 4C-MCR.

A vast number of MCRs have been reported in the literature, but the isocyanide based MCRs (IMCRs) are probably the most documented one.

IMCRs allow for the synthesis of the largest number of different scaffolds. Moreover, many of these are assembled from commercially available starting materials, thus potentially large libraries of compounds are accessible through one type of reaction.

[8] a) Mannich, C.; Krosche, W. *Arch. Pharrm*, **1912**, *250*, 647-667; b) Martin, S. *Acc. Chem.Res.* **2002**, *35*, 895-904.
[9] a) Ugi, I; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959,** *71*, 386-388. b) Ugi, I; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267–268. c) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 8-21. d) Gokel, G.; Lüdke, G.; Ugi, I., *"Isonitrile chemistry";* Ugi, I.(Ed), Academic Press, New York, **1971**.

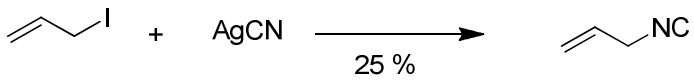
In the next section, we will see in details isocyanides, IMCRs and post condensation studies of various IMCRs.

3. Isocyanides

Isocyanides (isonitriles) represented for a long time the only class of stable organic compounds with a formally divalent carbon. Due to its reactivity, the isocyanide group differs basically from other functional groups. Almost all commercially available isocyanides are volatile and carry this disgusting, sharp, horrible odour. Because of this kind of odour isocyanides have been investigated as potential non-lethal weapons.[10]

a. Synthesis of isocyanides[11]

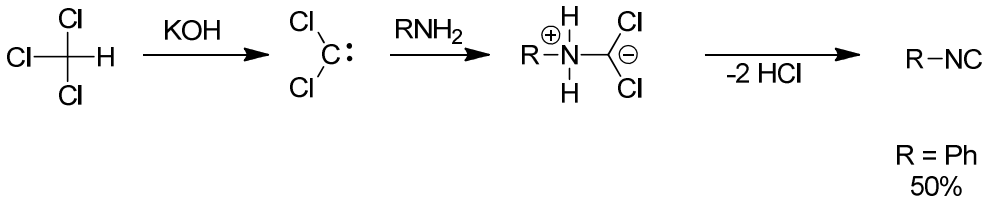
Isocyanides were first synthesized in 1859 by Lieke,[12] who was surprised to obtained product with awful odour, which disappeared by prolonged heating. In 1869, Gautier,[13] proved that such allylation gave the allyl isocyanide and demonstrated isomeric relationship between isocyanides and nitriles. (Hydrolysis of isocyanide gave formamide instead of the corresponding carboxylic acid).



Scheme I.6: Lieke synthesis of isocyanide.

In 1867's, Hofmann[14] found a new approach to isocyanides via the condensation of a primary amine with a dichlorocarbene, generated in situ by heating chloroform with potassium hydroxide (Scheme I.7). However this method suffers from a lack of reproducibility, low yield and difficulties of separation of isocyanides from amines.

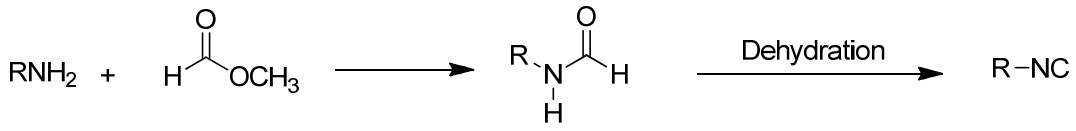
[10] Pirrung, M.; Ghorai, S.; Ibarra-Rivera T. *J. Org. Chem*., **2009**, *74*, *4110–4117*.
[11] Ugi, I.; Meyr, R.; *Angewandte Chemie*, **1958**, *70*, 702–703.
[12] Lieke W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316-321.
[13] Gautier A. *Justus Liebigs Ann. Chem.* **1869**, *146*, 119-124.
[14] Hofmann A. W. *Justus Liebigs Ann. Chem.* **1867,** *144*, 114-120.



Scheme I.7: Hoffmann synthesis of isocyanide (Carbylamine method).

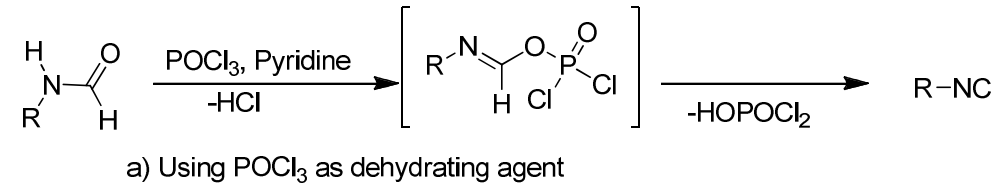
Due to difficult access only few isocyanides have been known for one century and rather few types of reactions have been described.

Ivar Ugi has contributed very significantly in isocyanide chemistry. Ugi optimized the formation of isocyanide using the dehydration of *N*-monosubstituted formamide; these formamides can be prepared from primary amines and methyl or ethyl formate or formic acide.[11]

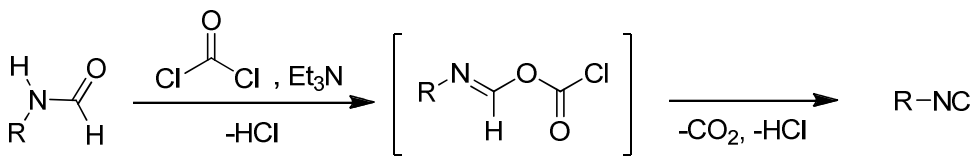


Scheme I.8: Synthesis of isocyanide by dehydration of formamide

Various dehydrating agents can be used (for example phosgene, P_2O_5, $POCl_3$, $(CO)_2Cl_2$, $SOCl_2$, PBr_3) in the presence of a base like pyridine, triethylamine, diisopropyl ethylamine. Ugi reports more than 230 isocyanide syntheses.[6] Few of them are shown in the scheme 9.



a) Using $POCl_3$ as dehydrating agent

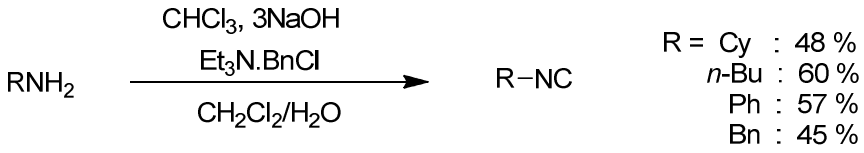


b) Using Phosgene as a dehydrating agent

Scheme I.9: Synthesis of Isocyanide by dehydration of formamide.

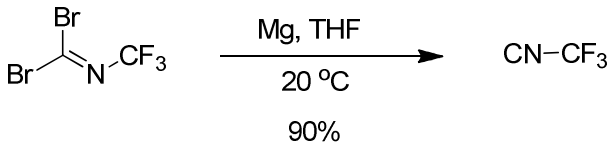
I. Ugi also improved the Hoffman method of carbylamine by carrying it out in a biphasic medium - a mixture dichloromethane and water in the presence of a phase transfer catalyst

(PTC)[15] (Scheme I.10). In this method, the attack of the primary amine on dichlorocarbene is more selective and the method is high yielding (up to 70% after purification) and more reproducible.



Scheme I.10: Hoffman synthesis of isocyanide.

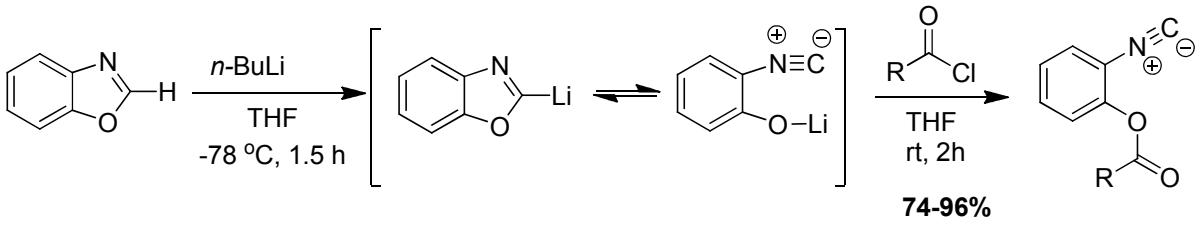
Isocyanides can be prepared from isocyanide *gem*-dihalide. For example, trifluoromethyl isocyanide was obtained from the treatment of magnesium with *gem*-dihalide of trifluromethyl isocyanide.[16]



Scheme I.11: Synthesis of isocyanide from *gem*-dihalo isocyanide with Mg in THF.

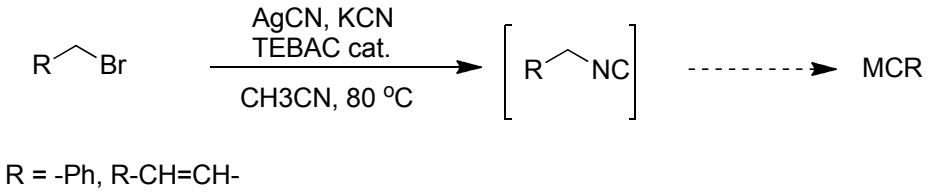
Another route to isocyanides consists in the reaction of organolithium compounds with oxazoles and benzoxazole[17] (Scheme I.12). In this reaction, the H-2 of oxazole is deprotonated by the base, forming 2-isocyanophenolate. This intermediate traps an electrophile, such as an acyl chloride, to give the desired isocyanide.

[15] Weber, W.; Gokel, G.; Ugi, I. *Angew. Chem.*, **1972**, *84*, 587–587.
[16] a) Lentz, D. *J. Fluo. Chem.* **1984**, *24*, 523-530. b) Lentz, D.; *J. Fluo. Chem.* **1985**, *29*, 91. c) Priv.-Doz, Lentz, D.; *Angewandte Chemie*, **1994**, *106*, 1377-1393
[17] Pirrung, M.; Ghorai, S.; *J. Am. Chem. Soc.* **2006**, *128*, 11772-11773.



Scheme I.12: Synthesis of isocyanide from benzoxazole.

Among the various synthetic methods, the purification step is essential, as the laboratory may suffer from horrible smells. To avoid such disadvantages, our lab reported an in situ synthesis of isocyanide,[18] by treating a bromide derivative (like allyl halide or benzyl bromide) with silver and potassium cyanide in acetonitrile at 80°C, in the presence of a catalytic amount of TEBAC. (Scheme I.13).

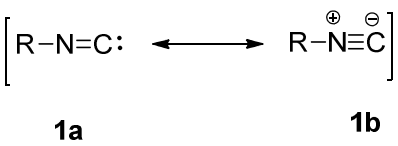


Scheme I.13: In *situ* synthesis of isocyanide from alkyl halides.

b. Reactivity of isocyanides

Structure of isocyanide

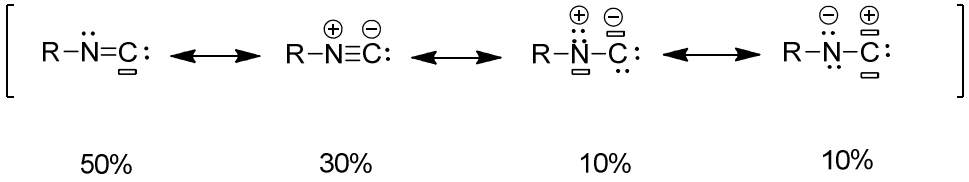
Isocyanides are considered as resonance forms between divalent carbon forms and zwitterions **1a** and **1b**, the carbon atom of the isocyano group exhibits a carbene-like reactivity that is reflected in the resonance structure **1a** (Scheme I.14). Conversely, the linear structure of isocyanides is well represented by the dipolar resonance structure **1b**.



Scheme I.14: Resonance structures of isocyanides.

[18] a) El Kaïm, L.; Grimaud, L.; Schiltz, A. *Synlett* **2009,** *9*,1401-1404. b) El Kaïm, L.; G rimaud, L.; Schiltz A. *Tetrahedron letter*s **2009**, *50*, 5235-5237. c) El Kaïm, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* **2009**, *7*, 3024-3026.

Valence Bond Calculations for methyl isocyanide[19] show that the carbene form is present at about 50% while the zwitterionic form accounts for about 30% of structures and the remaining 20% structures being more complex (Scheme 15). Thus isocyanides are linear because this geometry maximizes the resonance between the carbene and zwitterionic forms.



Scheme I.15: Valence bond study of resonance structures of isocyanides.

Isocyanides are stable under basic treatment (they are often made under basic conditions), but they are quite sensitive to acids. In the presence of aqueous acidic solutions, isocyanides react to give the corresponding formamides, and acidic hydrolysis is a generally convenient method for removing the horrible smell of isocyanides. Most isocyanides polymerize in the presence of acids.[20]

Isocyanide chemistry is characterized by three properties: the α-acidity, the α-addition, the formation of radicals.

Acidity of the proton in the α-position of isocyanide:

The α-acidity of the isocyanides is further increased by electron-withdrawing substituents such as carboxylic ester, nitriles and phosphonic ester or sulfonyl group. In this case, a weak base is sufficient to alkylate the isonitrile. This property has been widely studied for the synthesis of oxazoles[21] pyrroles,[22] triazoles.[23]

For instant, Van Leusen reported an oxazole synthesis to oxazoles from tosylmethyl isocyanides and an aldehyde[22] (Scheme I.16).

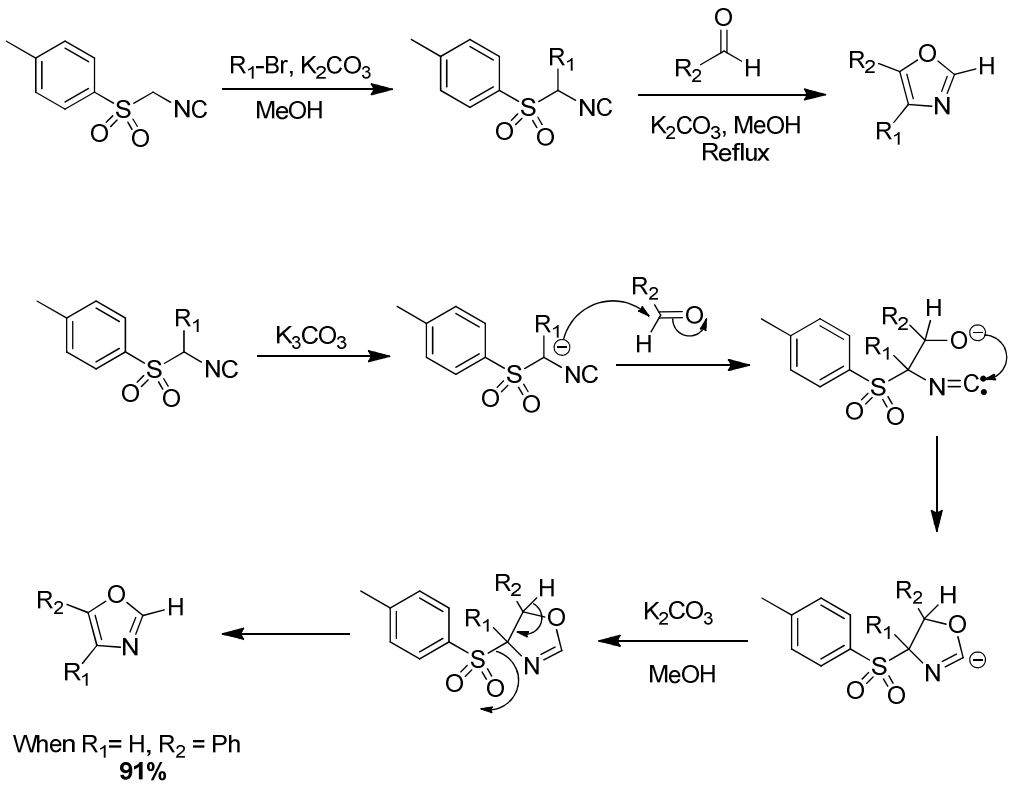
[19] Ramozzi, R.; Chéron, N.; Braïda, B.; Hiberty, P.; Fleurat-Lessard, P. *New J. Chem.*, **2012**, *36*, 1137-1140.

[20] a) van Beijen, A. *Macromolecules* **1983**, *16*, 1679. b) Albert, M.; van Leusen, B.; Hoogenboom, E.; Siderius, H. *Tetrahedron Lett*, **1972**, *13*, 2369–2372.

[21] Siderius H. *Tetrahedron Lett*, **1972**, *13*, 2369–2372. b) Van Leusen, A.; Siderius, H.; Hoogenboom, B.; Van Leusen D.; *Tetrahedron Lett.* **1972**, *13*, 5337-5340.

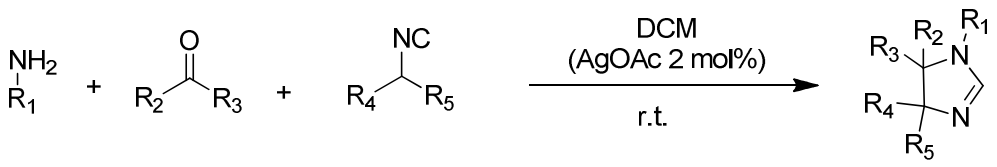
[22] Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533-546.

[23] Van Leusen, A.; Hoogenboom, B.; Houwing, H. *J. Org. Chem.* **1976**, *41*, 711-713.



Scheme I.16: Synthesis of oxazole from tosmic.

Application of this MCR in combinatorial chemistry led to the discovery of pyrroloimidazoles as neurite outgrowth stimulators.[24] Orru *et al*,[25] showed that the multicomponent reaction (MCR) between amines, aldehydes, and isocyanides bearing an acidic *α*-proton gives an easy access to a diverse range of highly substituted 2-imidazolines (Scheme I.17).

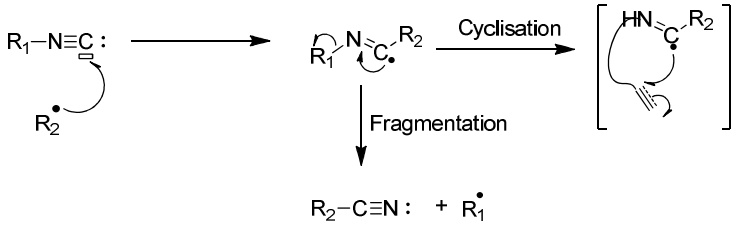


Scheme I.17: Synthesis of substituted 2-imidazolines from isocyanides bearing an acidic *α*-proton.

[24] Beck, B.; Leppert, C.; Mueller, B.; Dömling, A. *QSAR Comb. Sci.* **2006**, *25*, 527–535.
[25] Romano, V.; Orru, R. *J. Org. Chem.* **2005**, *70*, 3542-3553.

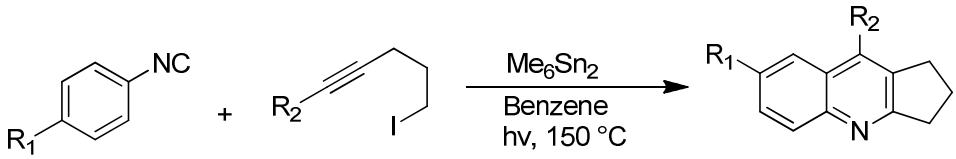
Radical reaction of isocyanides:

Radicals are able to add on isonitriles to form an imidoyl radical species, which can then fragment into a nitrile and an alkyl radical[26] or can react with an unsaturated system to finally reach heterocycles.



Scheme I.18: Addition of a radical on an isonitrile.

Segusa,[27] Bachi,[28] Nanni,[29] and Fukuyama[30] has exploited this reactivity for the formation of various heterocycles. Radical additions have been more recently exploited by Curran in elegant syntheses of polycyclic systems. The addition of the isocyanide on the aliphatic radical led to a vinyl radical, which induced 1,6-cyclization and gave a disubstituted cyclopentaquinoline after oxidation.[31] (Scheme I.19).



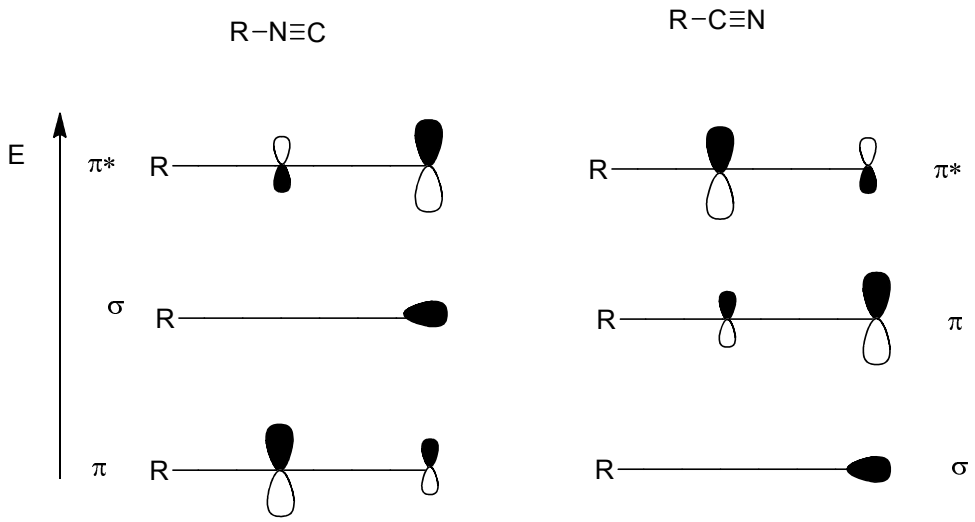
Scheme I.19: Cyclopentaquinoline from aromatic isocyanides and iodopentyne.

[26] Stork, G.; Sher, P. *J. Am. Chem. Soc.* **1986**, *108*, 303-304.
[27] Saegusa, T.*;* Kobayashi, S.; Ito, Y.; Yasuda, N., *J. Am. Chem.* Soc**, 1968**, *90*, 4182-4184.
[28] a) Bachi, M.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, *7752*-7758. b) Bachi M., Bar-Ner N.; Melman. A. *J. Org. Chem.* **1996**, *61*, 7116-7124.
[29] a) Nanni, D.*;*Pareschi, P.; Rizzoli, C. *Tetrahedron*, **1995**, *51*, *9045*–9062. b) Leardini, R.*;* Nanni, D.; Zanardi, G. *J. Org. Chem.* **2000**, *65*, 2763-2772. c) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Strazzari, S.;. Zanardi, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3598-3601.
[30] *Kobayashi, Y.*; Fukuyama, T. *J. Heterocycl. Chem.* **1998,** *35*, *1043*–55.
[31] Curran D., Liu H., Josien H. Ko S. *Tetrahedron*, **1996**, *52*, 11385-11404.

α- addition on isocyanides

Isocyanides react with both nucleophiles and electrophiles at the isocyanide carbon atom- the "*α*-addition", to give "*α*-adducts".

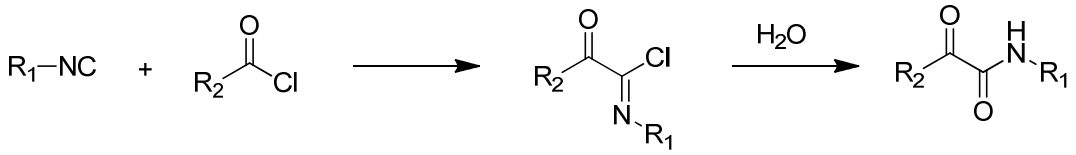
On isocyanide, a nucleophile attacks the carbon atom as it has the largest coefficient in the LUMO (π*) orbital. Moreover, an electrophile interacts with the HOMO (σ) orbital, which is only developed on the same terminal atom. So, both nucleophile and electrophile attacks will occur on the terminal carbon. However, a nitrile behaves differently as a nucleophile interacts on the carbon atom (highest coefficient in LUMO) and an electrophile interacts with the nitrogen atom (highest coefficient in HOMO).



Scheme I.20: Frontier orbitals of isocyanides and cyanides

After the attack of a nucleophile on the isocyanide, the divalent carbon becomes nucleophilic and attacks an electrophile and conversely, it can react first with on an electrophile and nucleophile.

In 1894, Nef described the insertion of an isocyanide in the carbon-chlorine bond of an acyl chloride to obtain an imidoyl chloride.[32] The resulting intermediate could further evolve when treated by a nucleophile. For example, it can be hydrolyzed to yield the α-ketoamide (Scheme I.21).

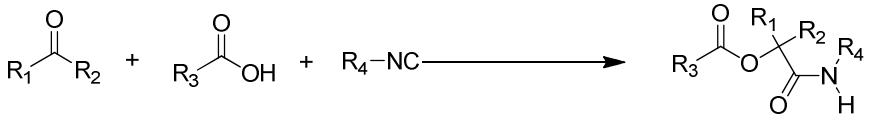


Scheme I.21: Nef reaction formation of ketoamides.

II. Isocyanide based multicomponant reactions (IMCRs)

1. The Passerini reaction

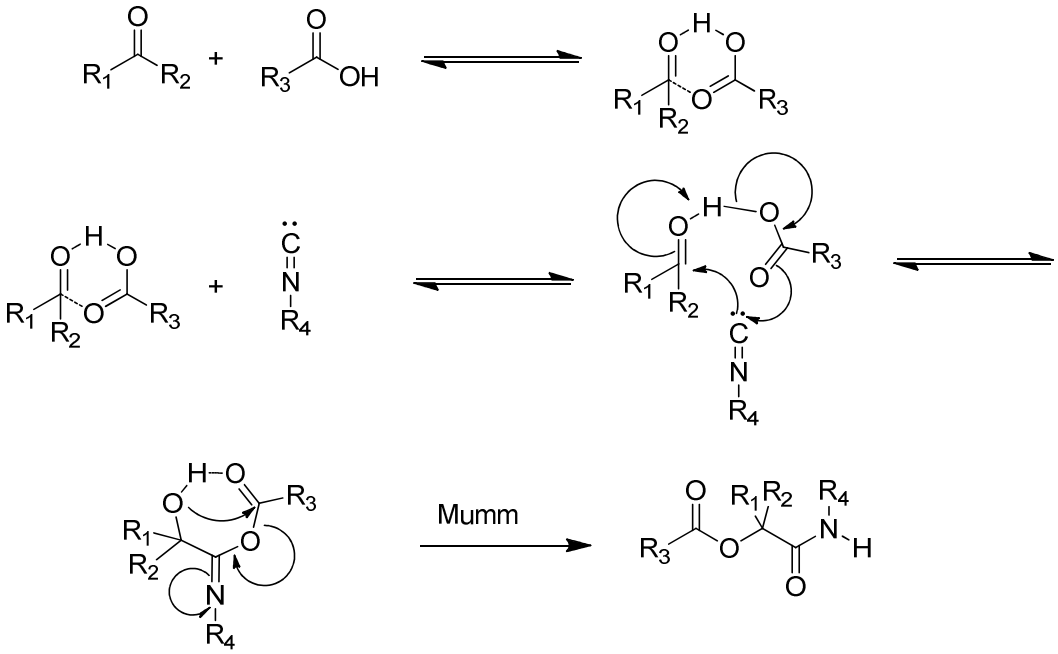
This reaction was discovered by Mario Passerini in 1921. It is the first isocyanide based multi-component reaction. This three-component reaction involves a carboxylic acid, a carbonyl compound (a ketone or aldehyde), and an isocyanide, and it gives direct access to α-hydroxy carboxamides (α-acyloxy carboxamide).[33] The reaction represents a process with an excellent atom economy as every portion of the three components is incorporated in the product.



Scheme I.22: The Passerini Reaction.

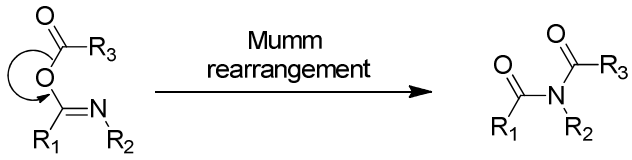
[32] Nef, J.; Justus, U. *Liebig Ann. Chem.* **1892**, *210*, 269.
[33] a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126-129. b) Passerini, M.; Ragni, G. *Gazz. Chim. Ital.* **1931**, *61*, 964-969. c) Banfi, L.; Riva, R. *Org. React.* **2005,** *65*, 1–140.

Mechanism of the Passerini Reaction



Scheme I.23: Mechanism of Passerini Reaction

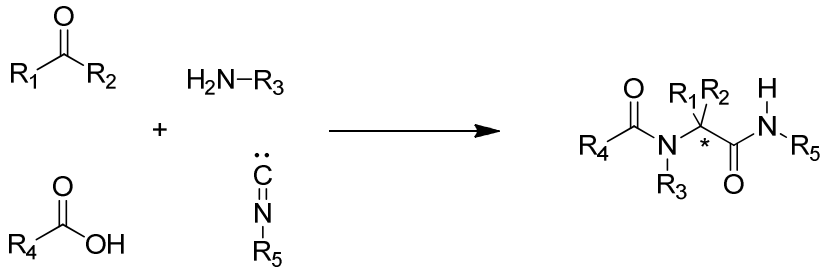
In the early 60's Ugi proposed a mechanism for this coupling, the Passerini reaction proceeds rapidly if the reaction is performed in aprotic non-polar solvents at room temperature. Good yields were obtained with high concentrations of the starting materials. From these findings, it is assumed that the Passerini reaction does not follow an ionic pathway. Hydrogen bonding is believed to play a crucial role in the formation of the presumed cyclic intermediate in which the isocyanide inserts. The whole mechanism will be discussed later. In the Passerini reaction, a Mumm type rearrangement is involved to get the final product. The Mumm rearrangement is a 1,3(O-N) acyl transfer of an acyl imidate or isoimide group to an imide, in the case of Passerini reactions, it involves a 1,4(O-O) acyl transfer.



Scheme I.24: Mumm Rearrangement

2. Ugi reaction

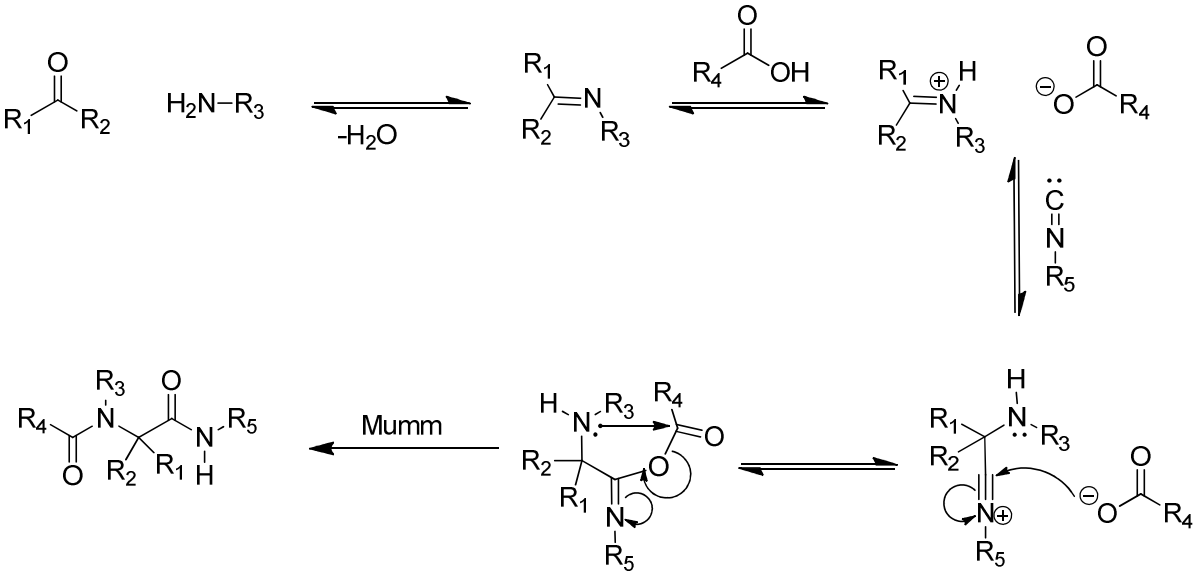
In 1959, Ivar Karl Ugi extended the scope of the Passerini reactions by adding an amine, to form a *bis*-amide[9] (Scheme I.25).



Scheme I.25 : Ugi Reaction.

Mechanism of the Ugi reaction:

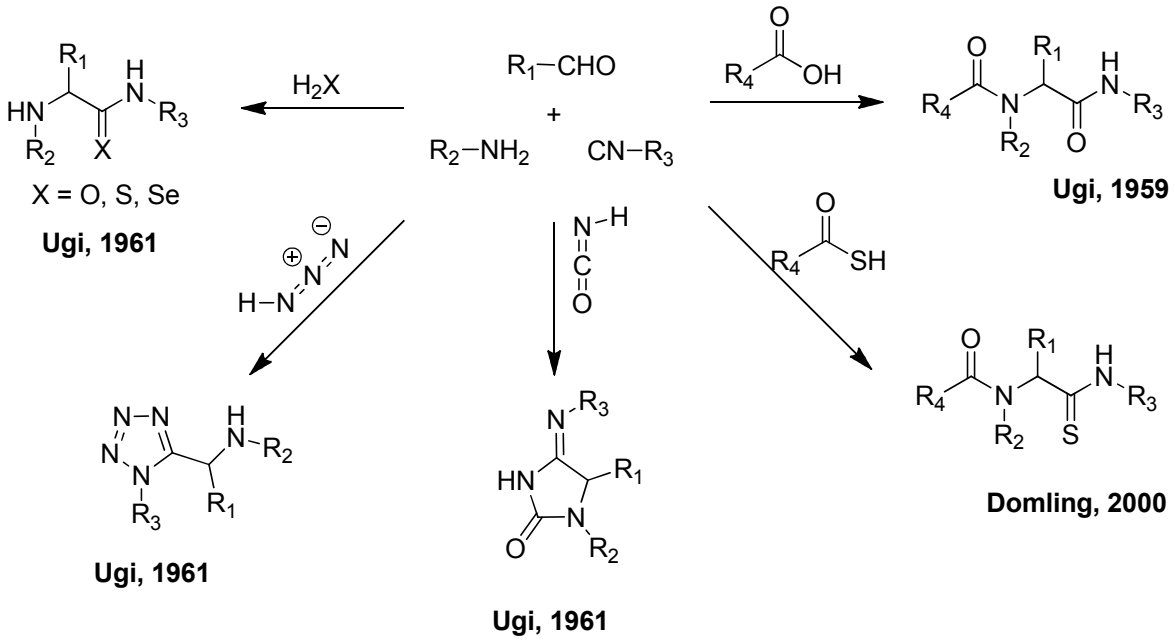
The amine and the ketone form an imine with loss of one equivalent of water. Proton exchange with carboxylic acid activates the imine forming the iminium ion for nucleophilic addition of the isocyanide to give the nitrilium ion. The nucleophilic trapping of this intermediate by the carboxylic acid counteranion affords the acyl imidoyl species. The final step is a Mumm rearrangement with transfer of the acyl group (R_4CO) from the oxygen atom to the nitrogen atom of the former amine (Scheme I.26).



Scheme I.26: Mechanism of Ugi Reaction

Variations in Ugi reactions:

The acidic component in Ugi reaction plays an important role. It protonates the imine and the carboxylate entity is involved in the trapping of the nitrilium intermediate (Scheme I.24). Moreover the structure of the acid allows the final rearrangement via the shift of the acyl moiety. Ugi extended this study (Scheme I.27) using hydrazoic acid,[34] carbonic acid monoesters,[35] hydrogen thiosulfate,[36] isocyanic and isothiocyanic acids,[37] hydrogen selenide and water as carboxylic acid surrogates.[38] More recently, Domling found that thiocarboxylic acids can be use in Ugi reaction to give thioamides.[39] In all these couplings, the final irreversible Mumm-rearrangement step is replaced by an electrocyclisation (hydrazoic acid, isocyanic, and isothiocyanic acid), a final tautomerization (water, hydrogen selenide) or a related Mumm-type process with thiocarboxylic acid (Scheme I.27).



Scheme I.27: Acid surrogates in Ugi-type couplings.

[34] a) Ugi I, *Angew Chem* **1960**, *72*, 639. b) Ugi, I.; Steinbrückner, C. *Chem Ber* **1961**, *94*, 734–742. c) Nixey, T.; Kelly, M. *Tetrahedron Lett* **2002**, *41*, 8729–8733. d) Marcos, C. F. Marcaccini, S; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett*, **2008**, *49*, 149–152.

[35] a) Ugi I, Steinbrückner C, *Chem Ber* **1961**, *94*, 2802–2814. b) Haslinger E, Monatsh Chem **1978**, *109*, 749–750. c) Keating T.; Armstrong R.; *J Org Chem* **1998**, *63*, 867–871. d) Hulme C, Ma L.; Romano J.; Morton G.; Tang, S.; Cherrier, M.; Choi, S.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett*, **2000,** *41*, 1889–1893

[36] Ugi, I.; Steinbruckner, C. *Angew Chem* **1960**, *72*, 267–268

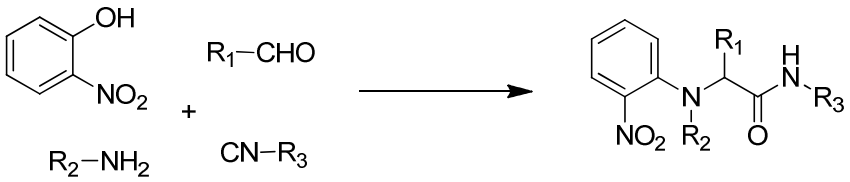
[37] a) Ugi, I.; Rosendhal, F.; Bodesheim, F. *Liebigs Ann Chem* **1963**, *666*, 54–61. b) Ugi, I.; Offerman, K. *Chem Ber* **1964**, *97*, 2276–2281

[38] Ugi I.; *Angew Chem* **1962**, *74*, 9–22.

[39] a) Heck S.; Dömling, A.; *Synlett* **2000,** 424–426. b) Kolb, J.; Beck, B.; Dömling, A.; *Tetrahedron Lett* **2002**, *43*, 6897–6901. b) Kolb, J.; Beck, B.; Almstetter, M.; Heck, S.; Herdtweck, E.; Dömling, A. *Mol Divers* **2003**, 297–313. c) Henkel, B.; Westner, B.; Dömling, A. Synlett **2003**, 2410–2412.

3. Ugi-Smiles reaction

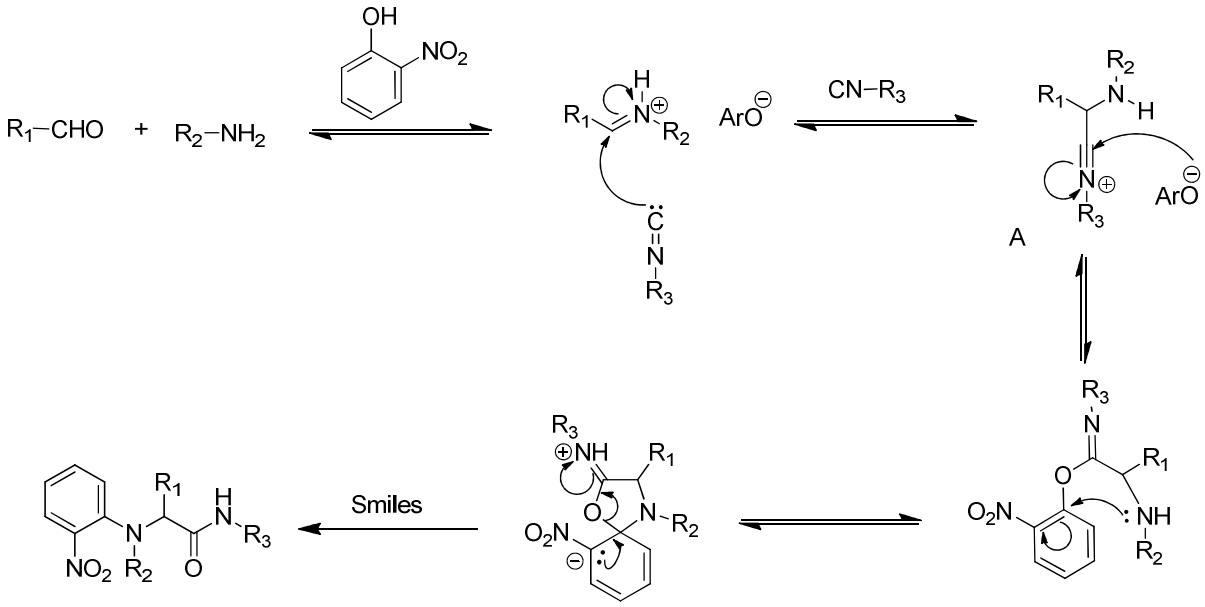
In 2005, Laurent El Kaïm and Laurence Grimaud developed a new Ugi-type coupling using some electron-deficient phenols instead of the carboxylic acid,[40] with a final Smiles rearrangement instead of the classical Mumm acyl transfer (Scheme I.28).



Scheme I.28: Ugi–Smiles coupling

A wide range of carbonyl compounds can successfully undergo this reaction, except *α,β*-unsaturated aldehydes. As traditionally observed in Ugi couplings, ketones require longer reaction times than aldehydes.[41] Various primary amines were shown to be good reactants as well. However, compared with the classical Ugi reaction, the lower efficiency of Ugi–Smiles process is further highlighted by the lack of reactivity of aromatic amines and secondary amines.[42]

Mechanism of Ugi-Smiles reaction**:**



Scheme I.29: Proposed mechanism for Ugi–Smiles coupling

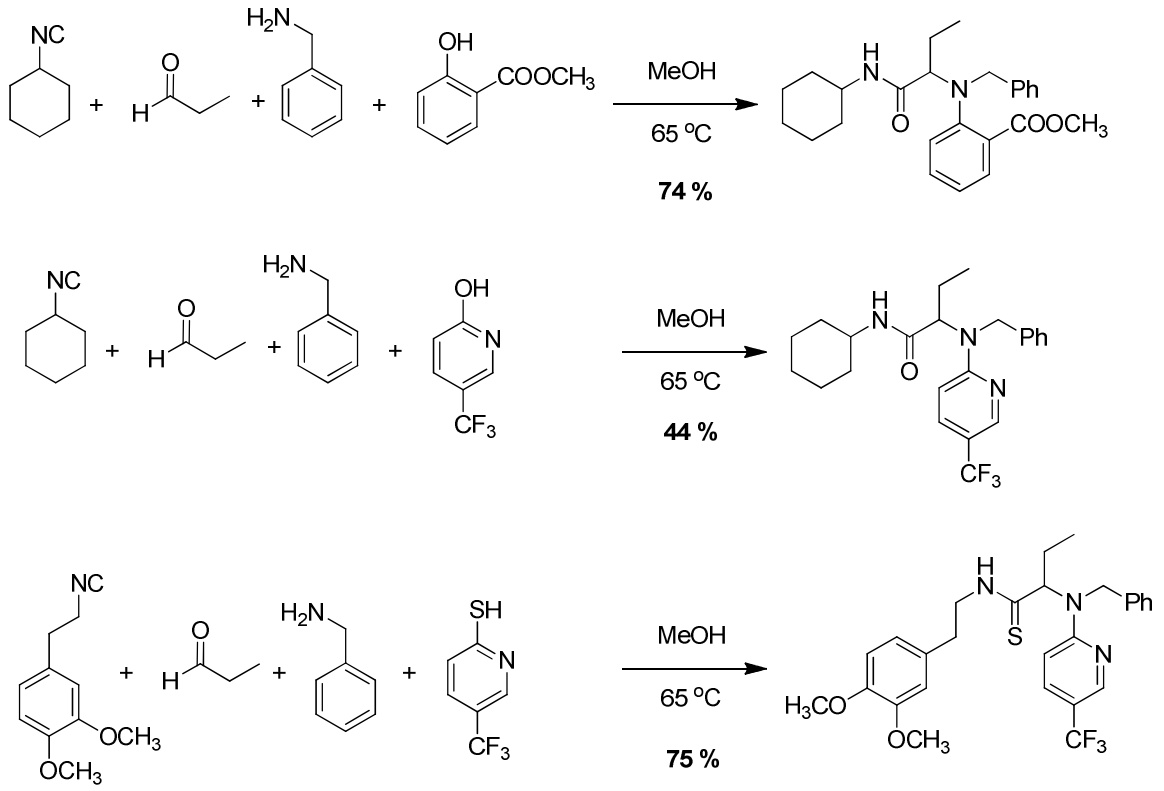
[40] El Kaim, L.; Grimaud, L.; Oble, J., *Angew. Chem. Int. Ed.*, **2005**, *44*, 7961-7964.

[41] Oble, J (**2007**) Nouvelles réactions multicomposant avec des phénols et des isonitriles, PhD dissertation, Ecole Polytechnique

[42] Kazmaier, U.; Hebach, C. *Synlett* **2003**, 1591–1594.

The amine and the aldehyde form an imine with loss of one equivalent of water. Proton exchange with phenol activates the imine forming the iminium ion for nucleophilic addition of the isocyanide to give the nitrilium ion. This intermediate **A** is trapped by the phenolate anion, and the presence of an electron-withdrawing group on the aromatic core allows a final Smiles rearrangement of the resulting intermediate to give the corresponding *N*-aryl carboxamide (Scheme I.29).

In addition, further investigations allowed to extend these results to hydroxy heterocycles[43] such as 2-hydroxypyridines and hydroxypyrimidines, which give the corresponding amino heterocyles with rather good yields (38-96%). The use of 2-mercaptopyrimidines and pyridines directly give substituted thioamides with yields around 70% (Scheme I.30).



Scheme I.30: Some new compounds by Ugi-Smiles coupling.

[43] a) Cristau, P.; Vors, J.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079-4082. (b) Cristau, P.; Vors, J.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859-7870.

III. Applications to heterocyclic synthesis

Multicomponent reactions are extremely powerful synthetic tools for medicinal chemistry and pharmaceutical industry due to the potential of the resulting scaffolds. Indeed, they can be further transformed via post-modifications depending on the functional groups introduced in the different partners of the MCR. In this way, it is really simple and fast to synthesize large libraries of structurally diverse complex molecules for biological screenings.

1. Post-condensation transformations of Ugi adducts

Most of the Ugi post-condensation strategies required the preparation of difunctional components whose additional function may be activated for a secondary reaction as lactonisation,[44] aromatic nucleophilic substitution,[45] Diels-Alder,[46] Heck reaction,[47] Pictet-Spengler cyclization,[48] Knovenagel condensation,[49] amide reduction,[50] metathesis reaction[51] etc.

Metal-catalyzed cycloadditions: The Ugi/Heck tandem reaction (Scheme I.31) can be used to produce isoquinoline derivatives; these scaffolds are present in a number of natural products and therapeutic reagents.[52]

---

[44] Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006,** *8*, 4351-4354.

[45] a) Spatz, J.; Umkehrer, M.; Kalinski, C.; Ross, G.; Burdack, C.; Kolb, J.; Bach, T. *Tetrahedron Lett.* **2007**, *48*, 8060-8064. b) Lu, K.; Luo, T.; Xiang, Z.; You, Z.; Fathi, R.; Chen, J.; Yang, Z. *J. Comb. Chem.* **2005,** *7*, 958-967. c) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004,** *6*, 3155-3158. d) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004,** *6*, 3155-3158

[46] a) Volodymyr K.; Mikhail K.; Kurashvili I.;, Alexandre V. *J. Org. Chem.*; **2006**; 71, 9544-9547; b) Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982,** *21*, 810-819. c) Wright, D.; Robotham, C.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943.

[47] a) El Kaïm, L.; Gamez-Montano, R.; Grimaud, L.; Ibarra-Rivera, T. *Chem. Commun.* **2008**, 1350-1352. b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002,** *124*, 6552-6554. c) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155-3158. d) Gracias, V.; Moore, J.; Djuric, S. *Tetrahedron Lett.* **2004**, *45*, 417-420. e) Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095-3097. f) El Kaïm, L.; Gizzi, M.; Grimaud, L. *Org. Lett.* **2008**, *10*, 3417-3419.

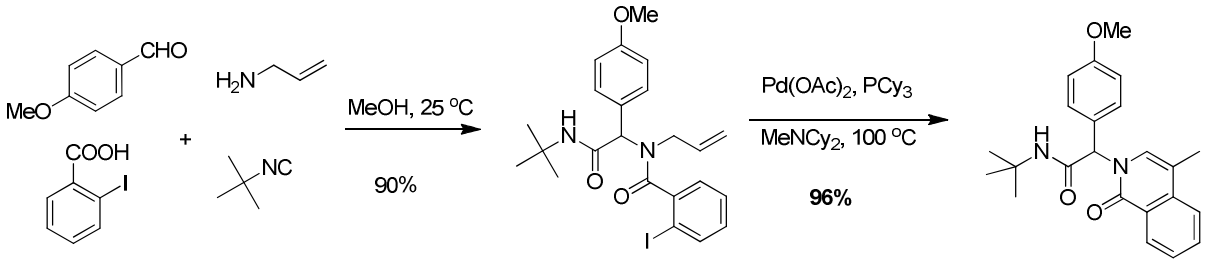
[48] Znabet, A.; Zonneveld, J.; Janssen, E.; De Kanter, F.; Helliwell, M.; Turner, N.; Ruijter, E.; Orru, R. *Chem. Commun.*, **2010,** *46*, 7706-7708.

[49] a) Marcaccini, S.; Pepino, R.; Pozo, M.; Basurto, S.; García-Valverde, M.; Torroba, T. *Tetrahedron Lett*. **2004**, *45*, 3999. b) Marcaccini S. *Tetrahedron Lett.* **2004**, *45* 3999–4001

[50] Giovenzana, G.; Tron, G. *Org. Lett***. 2008,** *10***,** 4199-4202.

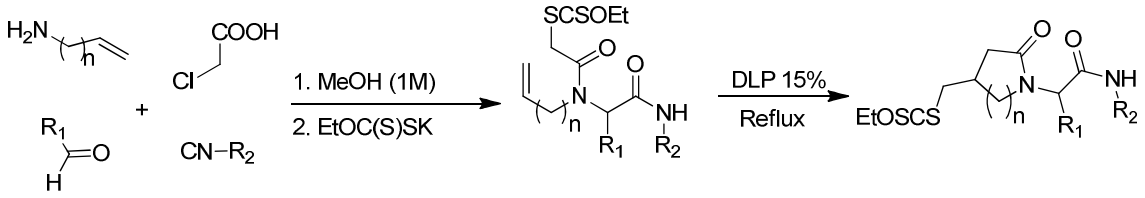
[51]a) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, *45*, 5987-5990. (b) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. T*etrahedron Lett.* **2003**, *44*, 7655-7658. (c) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047-1050. c) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596-579. d) El Kaïm, L.; Grimaud, L.; Gizolme, M.; Oble, J. *J. Org. Chem.* **2007**, *72*, 5835-5838. e) Ribelin, T.; Judd, A.; Akritopoulou-Zanze I.; Henry R.; Cross, J.; Whittern D.; Djuric S. *Org. Lett.* **2007**, *9*, 5119.f) Lee D.; Sello J.; Schreiber,S. *Org. Lett.* **2000**, *2*, 709.

[52] a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002,** *124*, 6552-6554. b) Yang *J. Comb. Chem; **2006**; 8*, 696-704-712.



Scheme I.31: Tandem Ugi/Heck coupling reaction

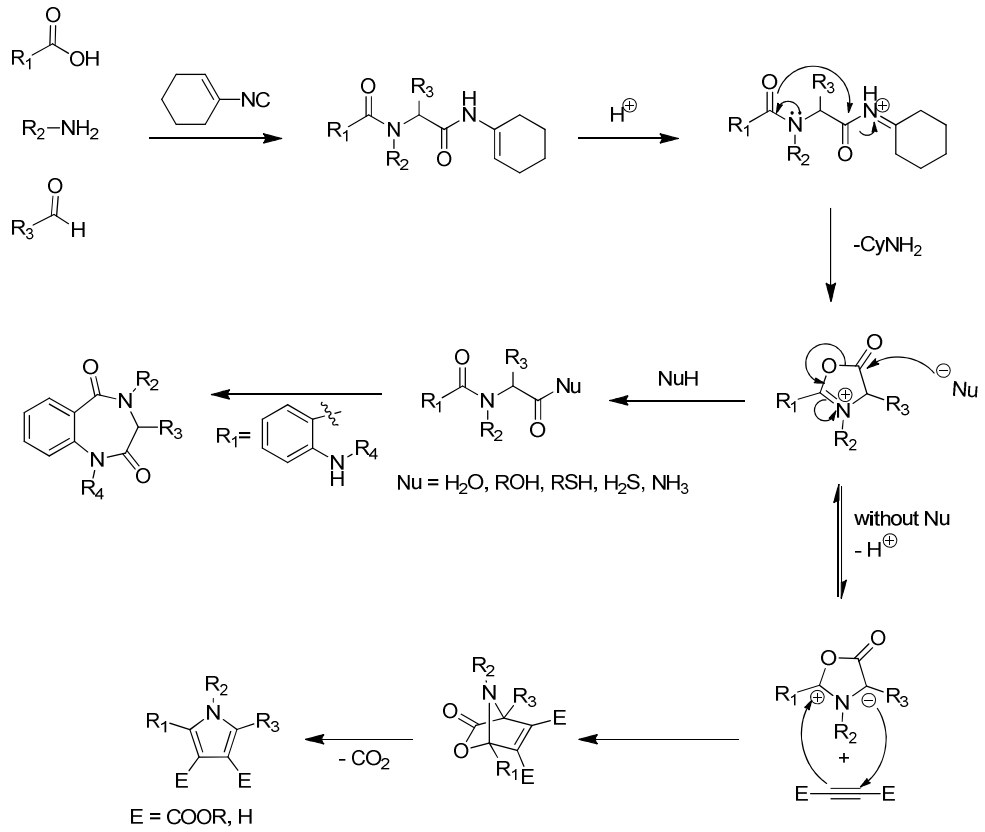
In our research group, various cascades involving radical chemistry as post-condensation in Ugi-coupling were developed. Indeed, the Ugi reaction performed with chloro acetic acid allows to introduce a xanthate which can be further transformed to functionalized pyrrolidinones (Scheme I.32).[53]



Scheme I.32: Ugi reaction followed by Xanthate formation and radical cyclization

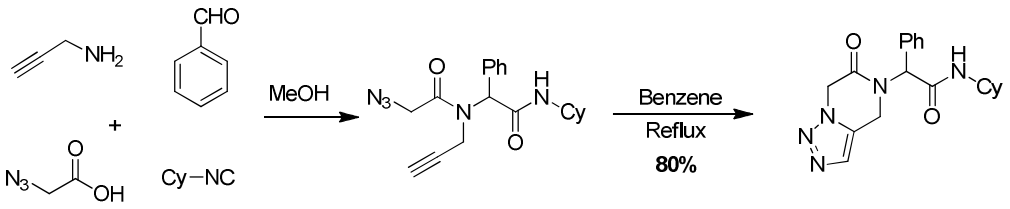
In 1996, Armstrong *et al* described further applications for cyclohexenyl isocyanide which was introduced by Ugi in 1961 as an isocyanide for subsequent cleavage to primary amides. With this reagent, derivatizations to carboxylic acid, esters, thioesters, pyrroles, and benzodiazepines can be carried out after the Ugi four component reactions (U-4CR) (Scheme 33).[54] Because of the versatile transformation possibilities, Armstrong introduces the term "universal isocyanide" or convertible isocyanide for cyclohexenyl isocyanide.

[53] El Kaïm, L.; Grimaud, L.; Miranda, D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259-8261.
[54] a) Rosendahl, F; Ugi, I.; *Liesbigs Ann. Chem*. **1963,** *666*, 65-67. b) Keating, T.; Armstrong, R. *J. Am. Chem. Soc*. **1995**, *117*, 7842-7843.



Scheme I.33: "universal isocyanide" to form α,β-unsaturated amides.

Akritopoulou-Zanze and co-workers worked on [2 +2] and [3 +2] cyclo-additions of Ugi adducts. The carboxylic acid bearing an azide function allows an intramolecular cycloaddition of the Ugi adduct between the dipole and an alkyne to form triazoles.[55] (Scheme I.32)



Scheme I.34: Synthesis of triazole derivatives by tandem Ugi/cyclo-addition [3 +2]

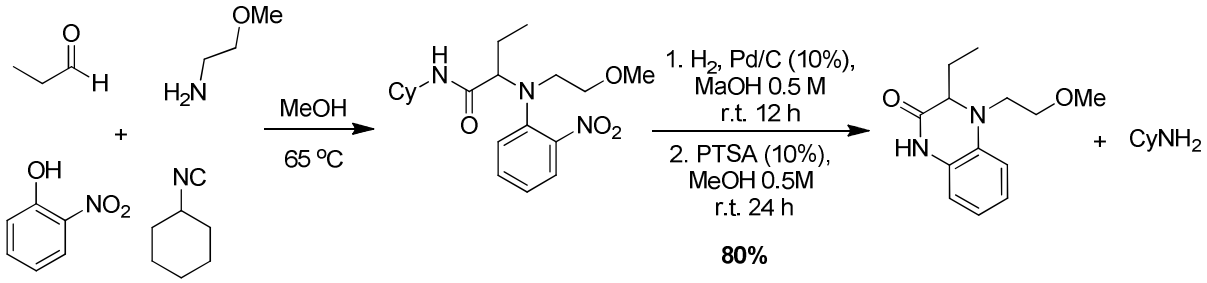
[55] Akritopoulou-Zanze, I.; Gracias, S. *Tetrahedron Lett.* **2004**, *45*, 8439-8441.

2. Post-condensation transformations of Ugi-Smiles adducts

The development of post-condensation transformations of Ugi-Smiles adducts has mainly been done in our laboratory soon after the first report on this new coupling.

Synthesis of 3,4-dihydroquinolinones.[56]

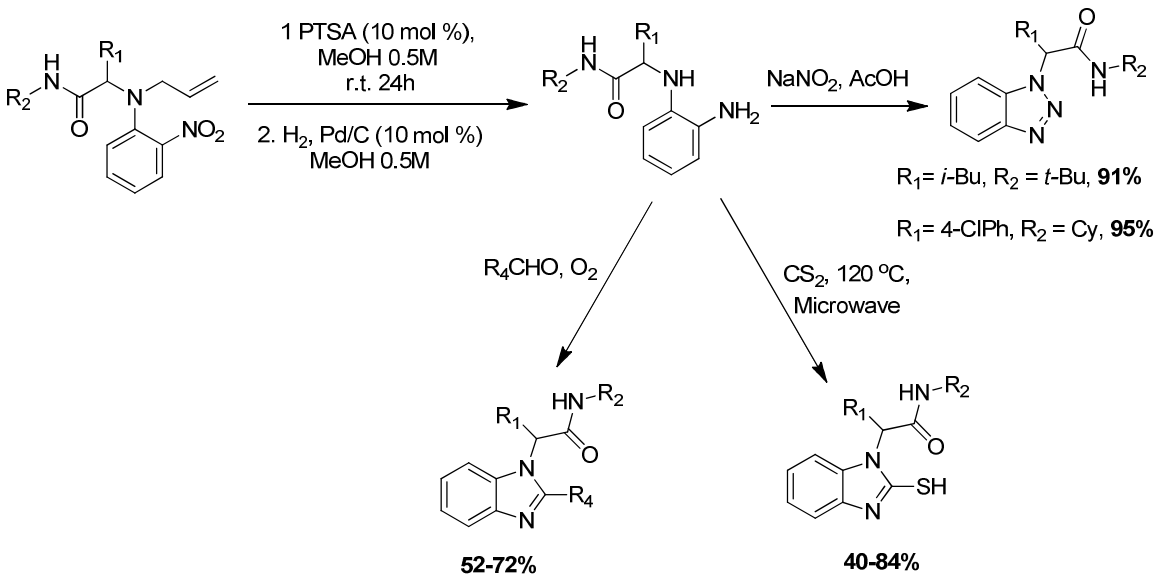
The Ugi-Smiles reaction of propanaldehyde, 2-methoxy ethylamine, cyclohexylisocyanide, and *ortho*-nitrophenol give Ugi-smiles adduct, which can be reduced to the corresponding aniline. Latter, when treated with a catalytic amount of para-toluenesulfonic acid (10 mol %) in methanol at room temperature for 24 hours, the adduct cyclized to give the 3,4-dihydroquinoxalin-2 (1H), after elimination of the cyclohexylamine, with a 80% yield over two steps. (Scheme I.35)



Scheme I.35: Synthesis of 3,4 dihydroquinolinones.

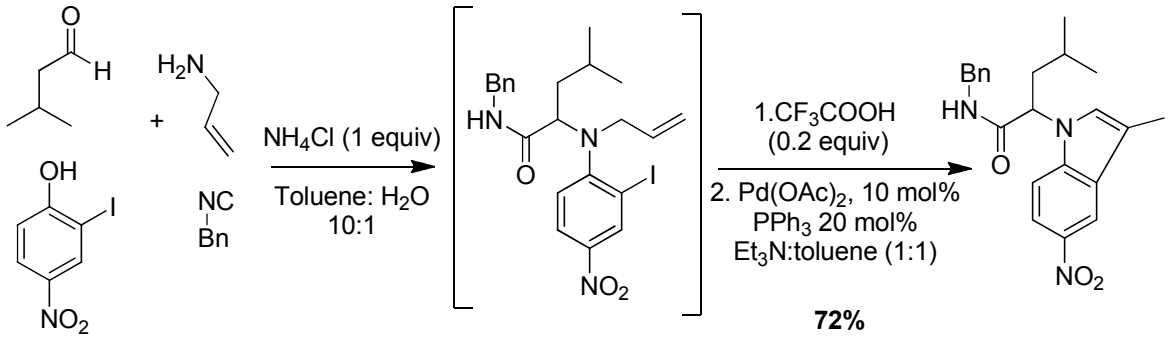
Similarly, Ugi-Smiles adduct of *o*-nitrophenol with allyl amine and various aldehydes and isocyanide undergoes deallylation followed by reduction of nitro group to offer *o*-phenylenediamines, which could then be converted in various products: benzotriazoles under nitrosation conditions, benzimidazoles upon oxidative treatment with an aldehyde or mercapto benzimidazoles after reaction with carbon disulfide (Scheme I.36).[57]

[56] Oble, J.; El Kaïm, L.; Gizzi, M. *;* Grimaud, L.; *Heterocycles*, **2007**, *73*, 503-517.
[57] El Kaim, L.; Grimaud, L.; Coffinier, D. *Org. Lett*. **2009**, *11*, 995-997.



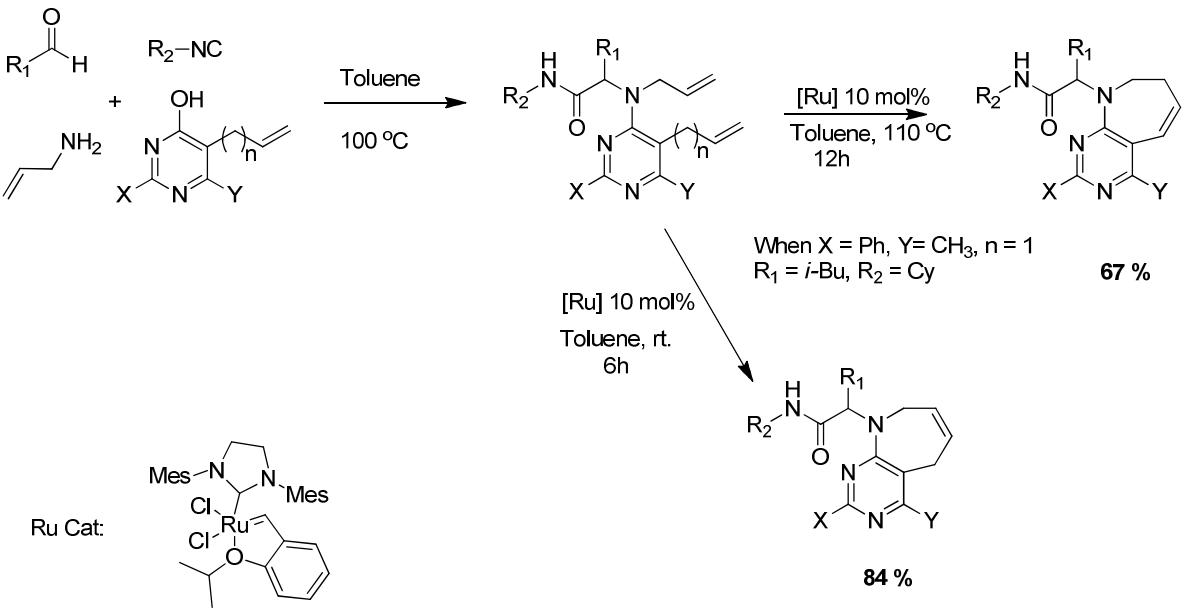
Scheme I.36: Synthesis of benzotriazole in Ugi-Smiles coupling.

A synthesis of indoles was described by a tandem Ugi-Smiles/Heck reaction, by using 2-iodo-4-nitrophenol. This result could be extended to pyridines and pyrimidines and several families of indole derivatives were synthesized in one pot (Scheme I.37).[47f]



Scheme I.37: tandem Ugi-Smiles/Heck reaction for synthesis of indoles.

Cyclization by metathesis of Ugi-Smiles reaction was also carried out using Ugi-smiles adduct obtained from 2-allyl-4-hydroxy pyrimidine, aldehyde, an isocyanide and allylamine, to give pyrimidoazepines (Scheme I.38).[51d]



Scheme I.38: Ugi-Smiles reaction for the synthesis of pyrimidoazepines.

Chapter 2

Ugi-Smiles couplings of substituted pyridine derivatives

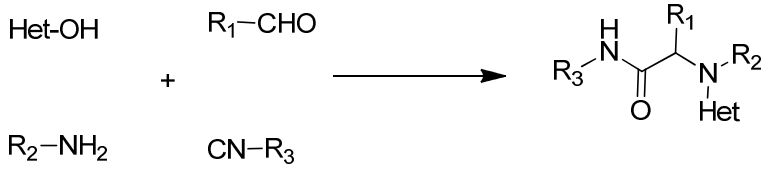
The work described in this chapter has been published in one publication:

El Kaïm , L.; Grimaud, L.; Pravin Patil, *Org. lett.* **2012**, *14*, 476-478.

I. Presentation

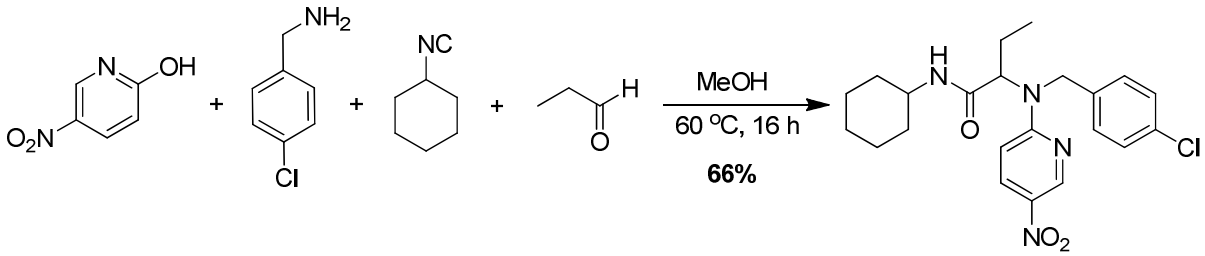
1. Ugi-Smiles couplings of hydroxy heterocycles

In the previous chapter, we introduced the Ugi-smiles reaction for rapid access to aminoaryl and heteroarylcarboxamides, which are important scaffolds in pharmaceutical industry.



Scheme II.1: Ugi–Smiles coupling of heterocyclic phenols.

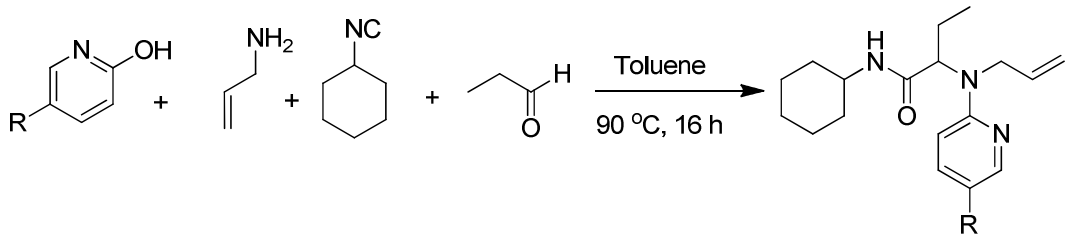
Among the various hydroxy heteroaromatic derivatives tested soon after the first report on Ugi-Smiles coupling, 2-hydroxypyridine failed to give the desired adduct unless substituted with an electron-withdrawing group at 5-position.[40, 58] Indeed, 2-hydroxy-5-nitropyridines react with *p*-chlorobenzylamine, cyclohexylisocyanide and propionaldehyde in methanol at 60 °C (Scheme II.2).



Scheme II.2: Ugi–Smiles coupling of 2-hydroxy-5-nitropyridine.

In the case of 5-chloro-2-hydroxypyridines and 5-trifluoromethyl-2-hydroxy pyridine, toluene was required as solvent and the mixture was heated at 90 °C to obtain the product in moderate yields (Scheme II.3).

[58] a) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019-4021. b) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble J. *J. Org. Chem.* **2007**, *72*, 4169-4180.



R = H, **0%**

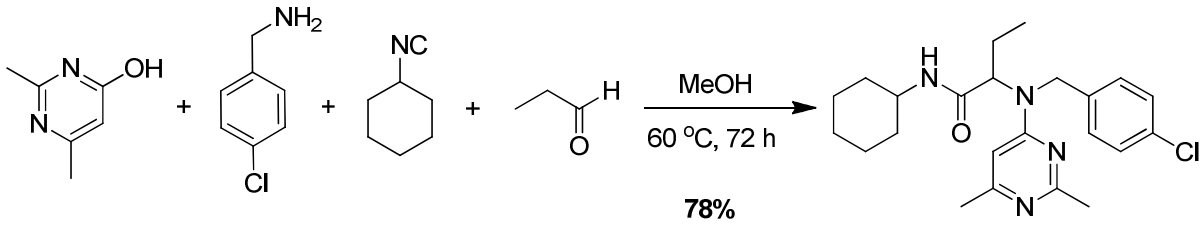
R = Cl 54%

R = CF_3 58%

R = NO_2 96% (in methanol)

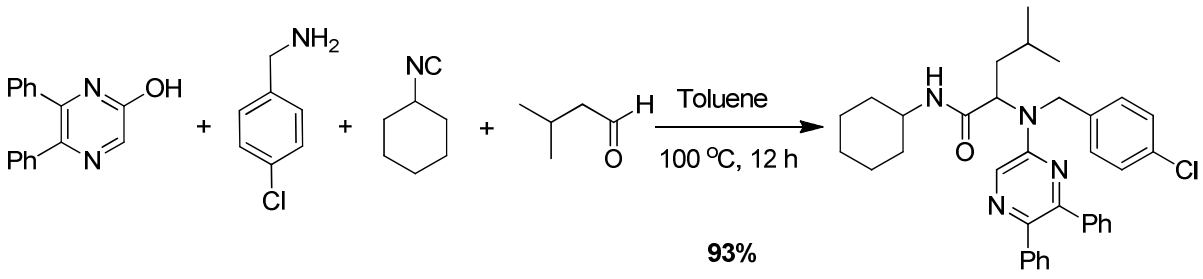
Scheme II.3: Ugi–Smiles coupling of 4-substituted-2-hydroxy pyridines

However, 2-hydroxypyrimidines and 4-hydroxypyrimidines are more efficient, and react as such. In this case, the reaction was performed in methanol at 60 °C, and the desired adduct isolated in good yields (Scheme II.4).[2]



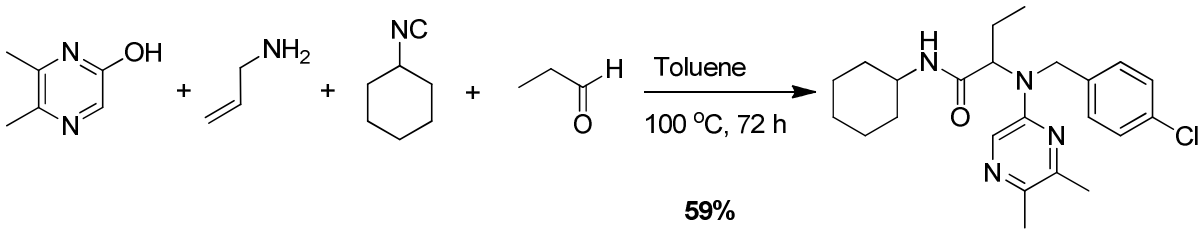
Scheme II.4: Ugi–Smiles coupling of 4-hydroxypyrimidines

5,6-Diphenylpyrazin-2-ol is also efficient, as it gives good yields in toluene at 100 °C for 12 h. However, when 5,6-dimethylpyrazin-2-ol was tested, the yield decreased significantly in the same conditions, probably due to a fast enamine isomerization.[59]



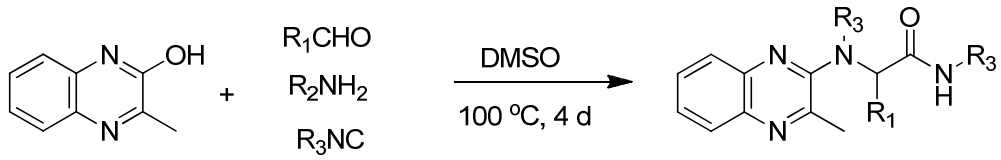
Scheme II.5: Ugi–Smiles coupling of 5,6-diphenylpyrazin-2-ol.

[59] Barthelon, A.; Dos Santos, A.; El kaim, L.; Grimaud, L.; *Tetrahedron Lett*. **2008,** *49*, 3208-3211.



Scheme II.6: Ugi–Smiles coupling of 5,6-dimethylpyrazin-2-ol.

2-Hydroxy quinoxaline were also tested as potential partner in Ugi-Smiles couplings. Due to the poor solubility of quinoxalinone in toluene, DMSO was chosen as solvent, and the reaction was performed at 100 °C. After 98 h, the desired adducts were isolated in very low yield and no further trials were done with pyrazine derivatives.



R_1	R_2	R_3	Yield (%)
i-Bu	CH_2CH_2OMe	Cy	16
i-Bu	All	Cy	8
Et	All	*p*-MeOBn	9

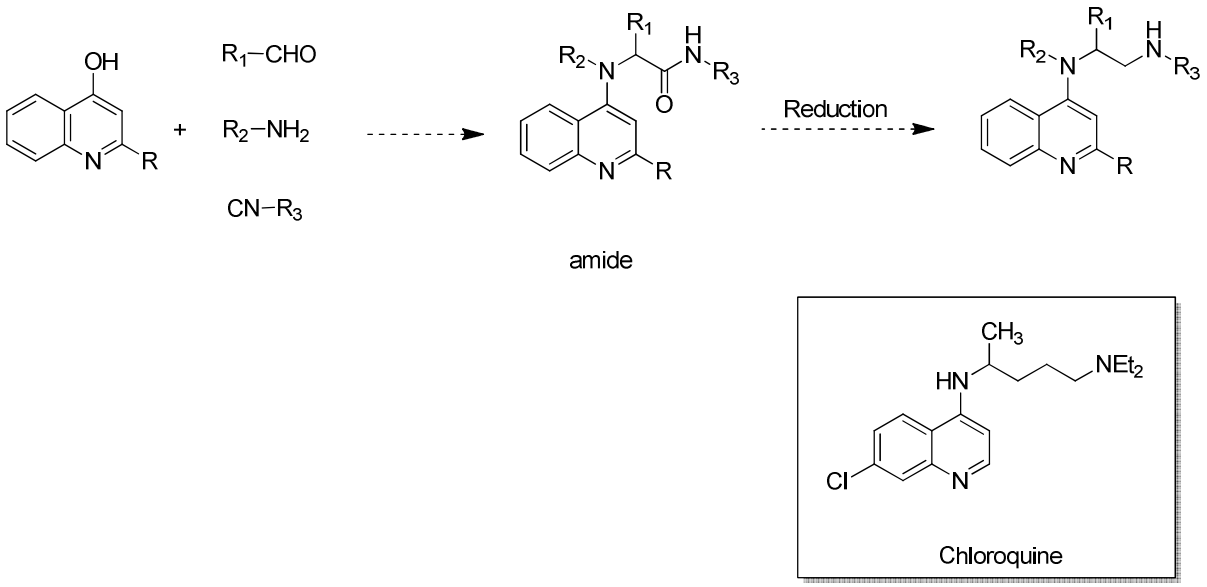
Scheme II.7: Ugi–Smiles coupling of quinoxalinones.

Finally, hydroxytriazines and five-membered hydroxy heterocycle like hydroxytetrazole failed to give any product in Ugi-Smiles coupling.

2. Presentation of the project

Before working on this project, we thought that 4-hydroxy pyridines would probably not be good partners in Ugi-Smiles couplings. Indeed calculations[60] showed that hydrogen bonding with ortho aryl substituents where helpful during the Smiles step of the process.[61]

As the use of 4-hydroxyquinoline could allow very rapid access to some biologically important scaffolds, we decided nevertheless to test these compounds. Indeed, such hydroxy heterocycles could allow the formation of 4-aminoquinolines, which can be easily reduced to give chloroquine analogues (Scheme II.8).

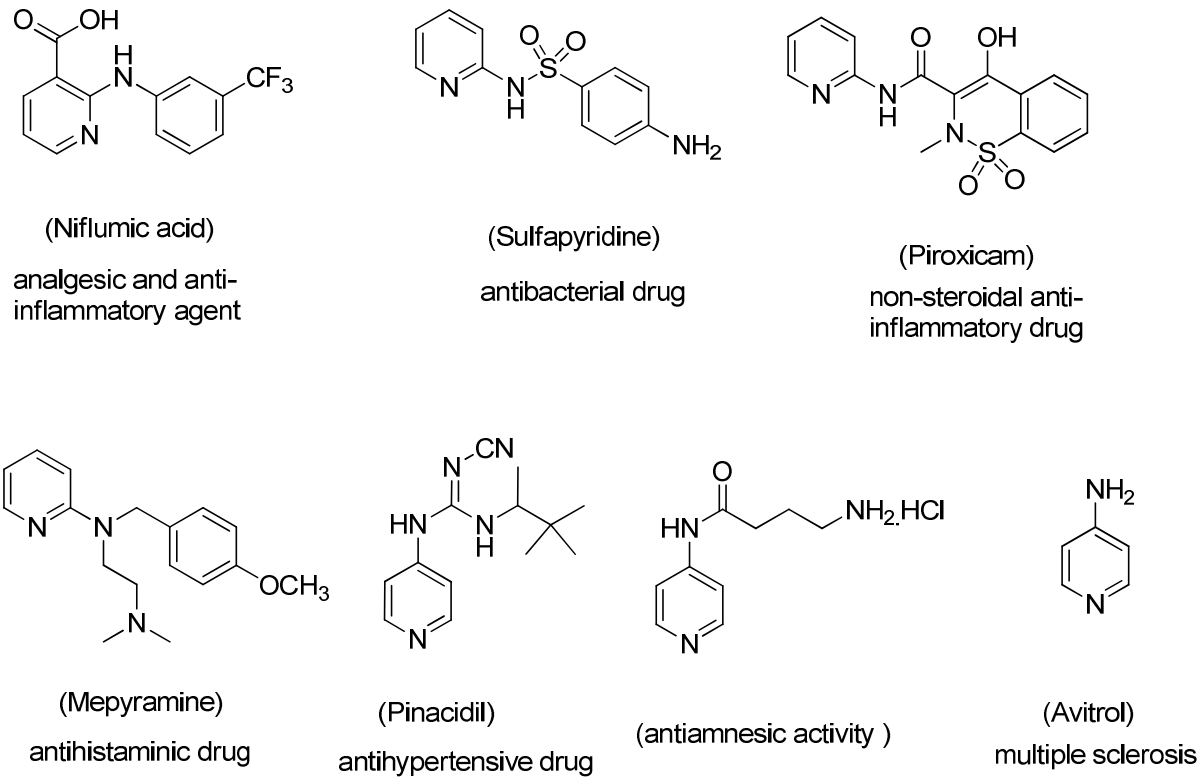


Scheme II.8: Ugi-Smiles coupling reaction of 4-hydroxy quinolone.

In general, 4-aminopyridine (4-AP) is a motif present in a wide number of biologically active compounds such as Pinacidil which is a cyanoguanidine drug, used to treat some of the symptoms of multiple sclerosis.[62] Andreani and Scipione showed that 4-aminopyridine derivatives possess an antiamnesic[63] and anticholinesterase[64] activity. Niflumic acid,[65] an

[60] Nicolas, C.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *Chemistry - A European Journal*, **2011**, *17*, 14929-14934.
[61] Note: "4-nitro phenol is less reactive than 2-nitrophenol due to hydrogen bonding including the spiro intermediate of the Smiles step."
[62] Solari, A.; Uitdehaag, B.; Giuliani, G.; Pucci, E.; Taus, C. *Cochrane Database Syst Rev*. **2001,** (*4*), CD001330
[63] Andreania, A.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Pietra, C.; Villetti, G. *Eur. J. Med. Chem*. **2000**, *35*, 77−82
[64] Scipione, L.; De Vita, D.; Musella, A.; Flammini, L.; Bertoni, S.; Barocelli, E. *Bio.Med. Chem. Lett.* **2008**; *18, 309-312*

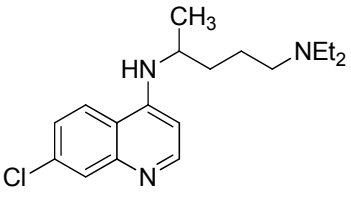
analgesic and anti-inflammatory agent has been developed for the treatment of rheumatoid arthritis. Sulfapyridine is used as antibacterial drug.[66] Picoxicam[67] is a nonsteroidal anti-inflammatory drug. Mepyramine, also known as pyrilamine,[68] is a first generation antihistaminic drug (Scheme II.9).



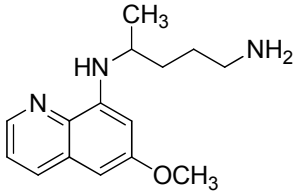
Scheme II.9: 4-amino pyridine derivatives in pharmaceuticals.

Since long time, 4-aminoquinoline derivatives are commercialized as antimalarial drugs such as Chloroquine, Primaqueine, Amodiaquine and some are under clinic tests like Pamaquine, Ablaquine, Trioxaquine, Piperaquine (Scheme II.10).

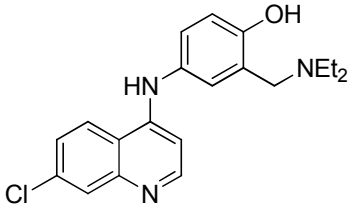
[65] Dreiser, R. E.; Charlot, J.; Lopez, A.; Ditisheim, A. *Current Medical Research and Opinion*, **1990**, *12*, 93-99.
[66] Lesch, J. (**2007**). "Chapter 7". *The First Miracle Drugs* (illustrated ed.). *Oxford University Press.*
[67] Christofis P.; Katsarou, M.; Papakyriakou, A.; Sanakis, Y.; Katsaros, N.; Psomas, G. *J Inorg Biochem*. **2005**, *99*, 2197-2210.
[68] Huttrer, C. P.; Djerassi, W. L.; Beears, R.; Mayer, L.; Scholz, C. R. *J. Am. Chem. Soc*. **1946**, *68*, 1999-2002.



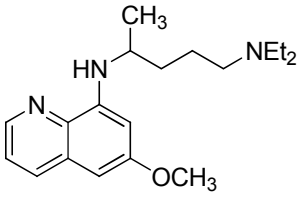
Chloroquine



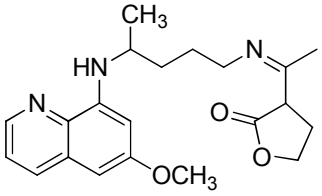
Primaqueine



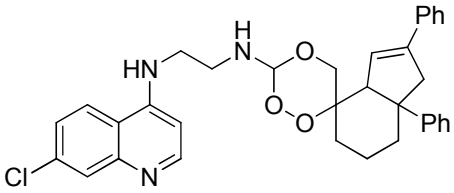
Amodiaquine



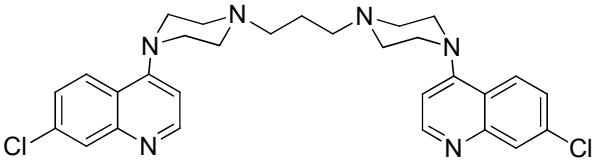
Pamaquine



ablaquine



Trioxaquine



Piperaquine

Scheme II.10: The promising antimalarial drugs and active precursors.[69]

.

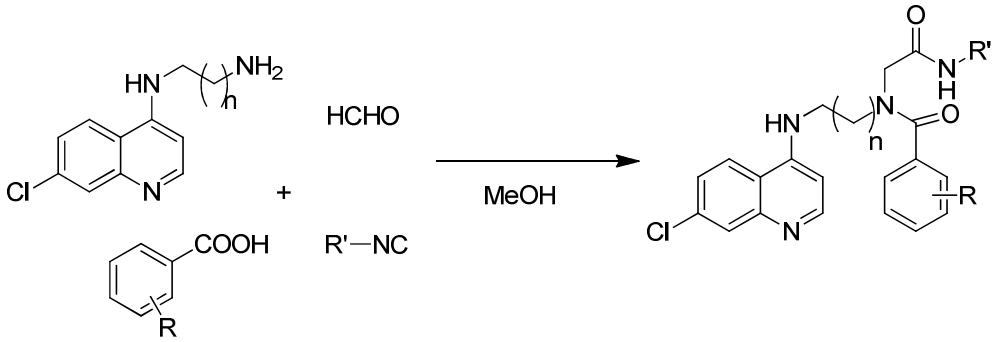
There were an estimated 225 million cases of malaria worldwide in 2009.[70] An estimated 655,000 people died from malaria in 2010,[71] a decrease from the 781,000 who died in 2009 according to the World Health Organization's 2011 World Malaria Report, accounting for 2.23% of deaths worldwide.[14] However, a 2012 meta-study from the University of Washington and University of Queensland estimates that malaria deaths are significantly

[69] Francis; W.; Akira; I.; *Drug Dev Res*. **2010**, *71*, 20–32.
[70] "World Malaria Report summary". *World Health Organization*. Retrieved 5 November **2011.**
[71] "World Malaria Report 2011 summary". *World Health Organization*. Retrieved 15 December **2011**

higher. Published in *The Lancet*, the study estimates that 1,238,000 people died from malaria in 2010.[72] Ninety percent of malaria-related deaths occur in sub-Saharan Africa, with ~60 % of deaths being young children under the age of five.[73]

Drug resistance in malaria is now widespread making treatment increasingly difficult in many parts of the world;[74] therefore it creates continuing demand for new biologically active compounds.

In the field of IMCRs,[4] Chibale and co-workers have recently employed an Ugi coupling of 4-aminoquinolines to synthesize new potential antimalarial compounds (scheme II.11).[75]



Scheme II.11: Synthesis of target compounds by Chibale and co-workers by Ugi reaction.

In this work, the 4-aminoquinoline moiety was introduced on the amine partner of the Ugi coupling leading directly to chloroquine analogues. Considering the adduct obtained via Ugi-Smiles coupling, we decided to investigate the possibility to form the aminoquinoline during the four component coupling (4-CC). The reduction of the amide function would then afford some chloroquine analogues. Due to the molecular diversity offered by the 4-CC, a wide range of libraries could be prepared.

[72] "Global Malaria Mortality Between 1980 and 2010: A Systematic Analysis". *journalistsresource.org*.

[73] Murray; C.; Rosenfeld, L.; Lim, S.; Andrews, K.; Foreman, K.; Haring, D.; Fullman, N.; Naghavi, M.; Lozano, R.; Lopez, A.; *The Lancet*, **2012**, 379, 413 - 431.

[74] Wellems T.; *Science*, **2002,** *298*,124-126.

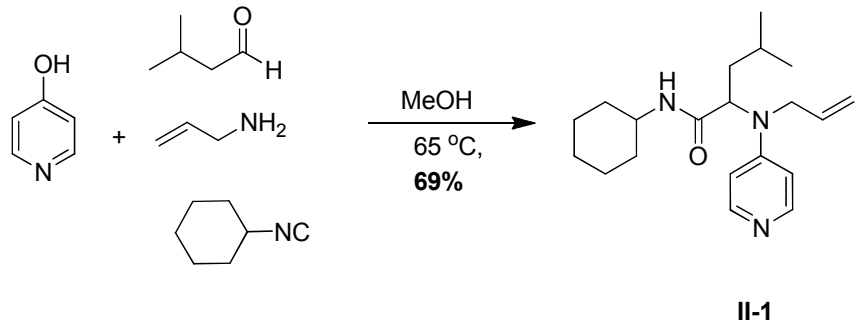
[75] a) Musonda, C.; Taylor, D.; Lehman, J.; Gut, J.; Rosenthal, P.; Chibale, K. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 3901–3905. b) Musonda, C.; Gut, J.; Rosenthal, P.; Yardley, V.; de Souza, R.; Chibale, K. *Bioorg. Med. Chem.* **2006**, *14*, 5605–5615. c) Musonda, C.; Little, S.; Yardley, V.; Chibale, K, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4733–4736.

II. Results and discussion

At the beginning of this work, we have to test the behaviour of the 4-hydroxypyridine in Ugi-Smiles couplings, as the former studies were limited to 2-hydroxypyridine derivatives.

1. Ugi-Smiles reaction of 4-hydroxypyridine

The reaction was performed in methanol at 65 °C as classically draped for 2-hydroxypyridine. A stoichiometric amount of 4-hydroxy pyridine, cyclohexyl isocyanide, allyl amine and isovaleraldehyde were heated for two days at 65 °C. Surprisingly, 4-hydroxy pyridine undergoes smooth coupling under these conditions, affording the corresponding 4-aminopyridine in 69% isolated yield (Scheme II.12).



II-1

Scheme II.12: 4-Hydroxy pyridine in Ugi-Smiles reaction.

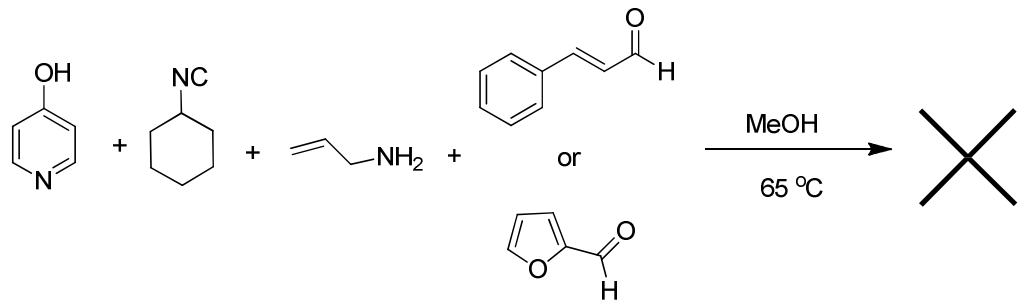
In order to optimize the conditions, the same reaction was performed varying the reaction time summarized below:

Reaction conditions	%Yield
Methanol, 65 °C, 18 hrs	40 %
Methanol 65 °C, 3 days	72 %
Methanol 65 °C, 5 days	73 %

The best yields were obtained after three days and longer reaction time did not improve significantly the efficiency of the process.

The scope of the reaction was next examined by varying the other partners.

Variation of carbonyl group: As observed in Ugi-Smiles reaction of phenols, neither α,β-unsaturated aldehydes nor furfural reacts with 4-hydroxypyridine (Scheme II.13).

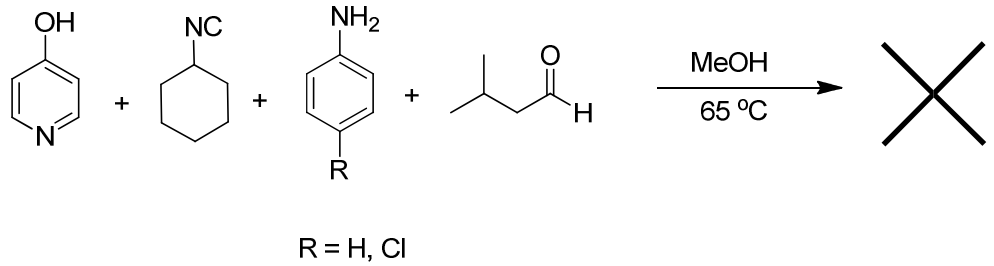


Scheme II.13: α,β-unsaturated aldehydes and 4-Hydroxy pyridine in Ugi-Smiles reaction.

Otherwise, in general, aldehydes give good isolated yields within three days (see table II.1, entries 1-9), while ketones require longer reaction time and are of lower efficiency (see table II.1, entries 10 and 11).

Cyclohexyl isocyanide is a good partner (see table II.1, entries 1-3), but benzyl isocyanide and *t*-butyl isocyanide gave lower yields (see table II.1, entries 4 and 6). *t*-Butyl isocyanide is probably hindered but, for 4-methoxy benzyl isocyanide, the main problem is probably a competitive isomerization which can occur after such a prolonged heating.

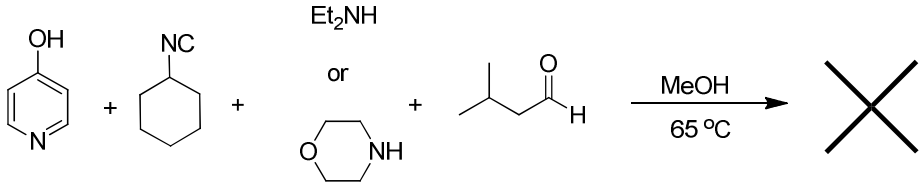
Anilines failed to couple with the 4-hydroxy pyridine as already observed in Ugi-Smiles reactions, this is probably due to the lower nucleophilicity of the aromatic amine which inhibits the Smiles rearrangement (Scheme II.14).



Scheme II.14: Anilines and 4-hydroxypyridine in Ugi-Smiles reactions.

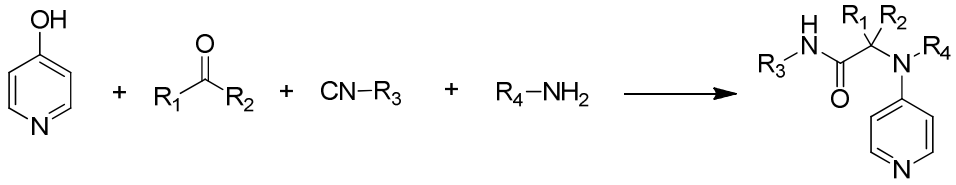
The key role of the Smiles rearrangement was further demonstrated by the lack of any product when secondary amines were tested under the same conditions: diethylamine or

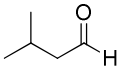
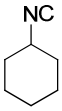
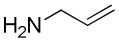
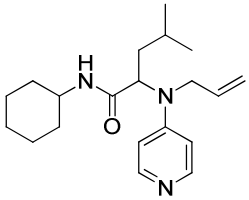
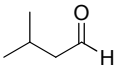
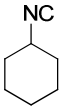
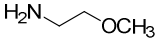
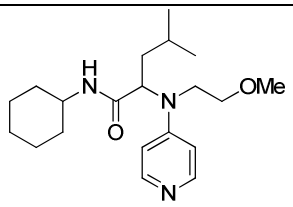
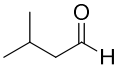
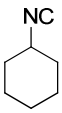
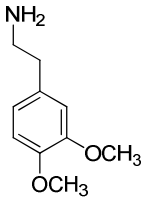
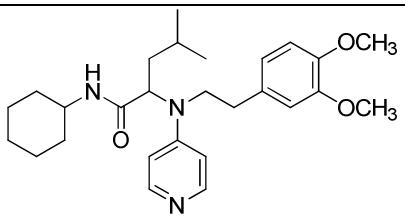
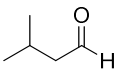
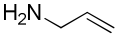
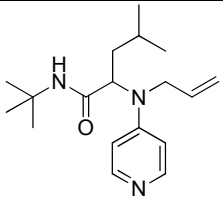
morpholine with 4-hydroxy pyridine, cyclohexyl isocyanide and isovaleraldehyde failed to give the corresponding products (Scheme II.15).

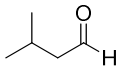
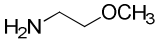
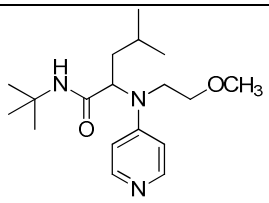
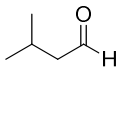
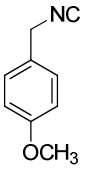
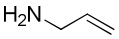
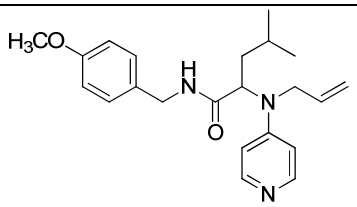
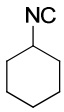
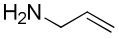
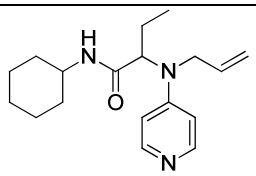
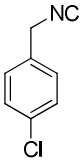
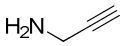
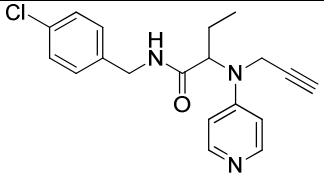
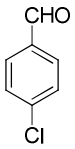
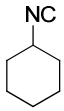
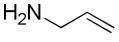
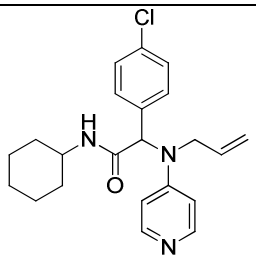
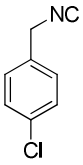
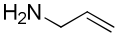
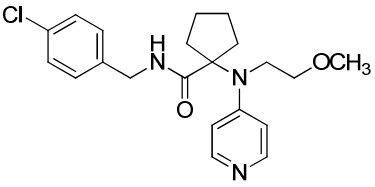
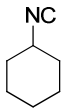
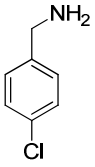
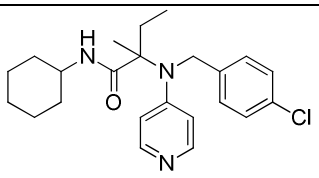
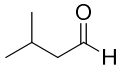
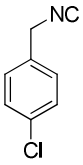
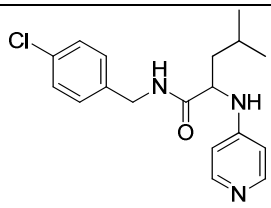


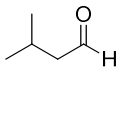
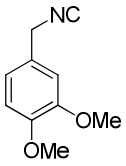
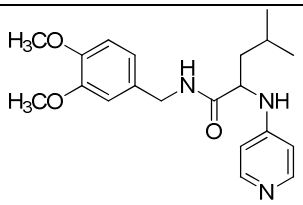
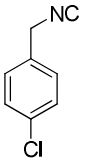
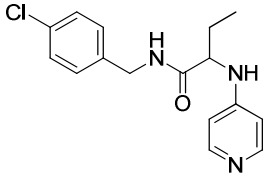
Scheme II.15: Secondary amines and 4-hydroxypyridine in Ugi-Smiles reaction.

TABLE II.1. Ugi-Smiles coupling of 4-hydroxypyridine.



Entry	R_1COR_2	R_3NC	R_4NH_2	Product	Product no.	% yield.[a]
1					**II-1**	69 %
2					**II-2**	65 %
3					**II-3**	72 %
4					**II-4**	43 %

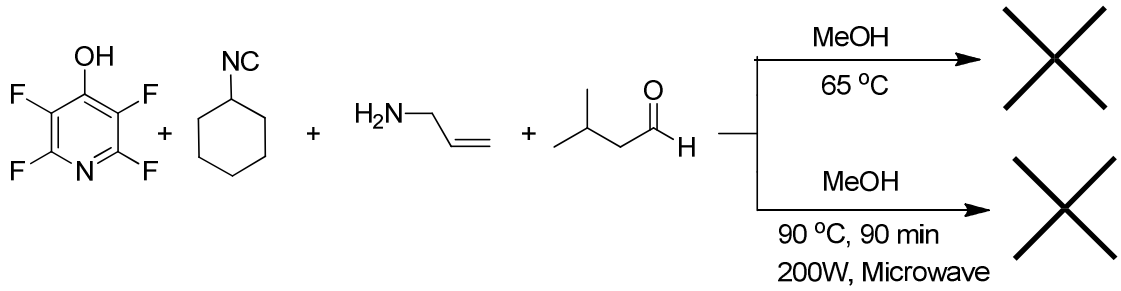
5					**II-5**	42 %
6					**II-6**	39 %
7					**II-7**	39 %
8					**II-8**	50 %
9					**II-9**	46 %
10					**II-10**	26 % 28 %[b]
11					**II-11**	17 % 20 %[b]
12			NH3		**II-12**	40 %[c]

13			NH_3		**II-13**	28 %[c]
14			NH_3		**II-14**	33 %[c]

[a]. isolated yield, [b]. yield after 4 days, [c]. isolated yield under microwave conditions.

When ammonia was used (the source of ammonia is aq. ammonia 30%), the reaction required microwave irradiation. It was performed in methanol with a light excess (1.5 or 2 equivalent) of ammonia at 90 ^{o}C for 90 min. The desired adducts were isolated in moderate yields for benzylic isocyanides, but complex mixture were obtained with cyclohexyl isocyanide and *t*-butyl isocyanide. (see table II.1, entries 12-14).

When 4-hydroxy pyridine was replaced by 2,3,5,6-tetrafluoro-4-hydroxy pyridine, the reaction with isovaleraldehyde, cyclohexyl isocyanide and allyl amine failed to give the corresponding *N*-aminopyridine (Scheme II.16).



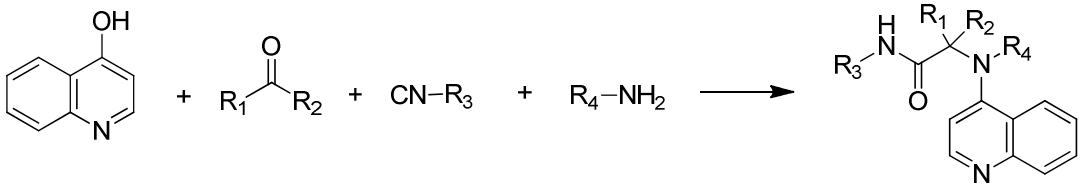
Scheme II.16: 2,3,5,6,-tetrafluoro-4-hydroxy pyridine in Ugi-Smiles reaction.

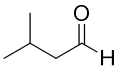
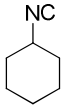
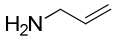
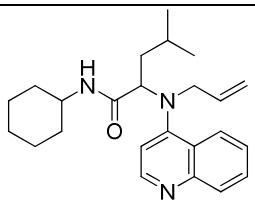
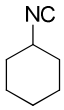
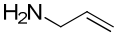
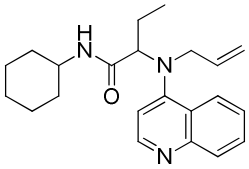
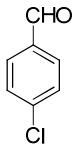
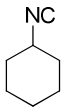
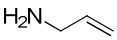
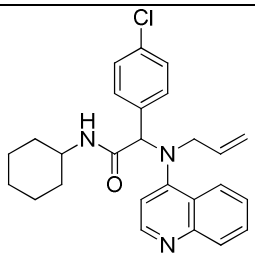
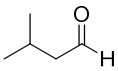
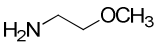
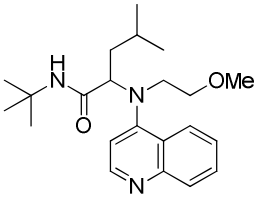
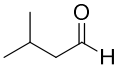
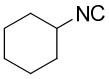
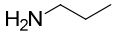
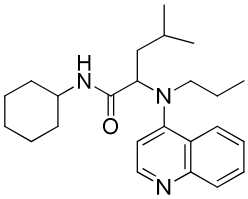
2. Ugi-Smiles reaction of 4-hydroxyquinolines

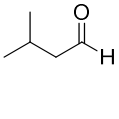
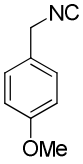
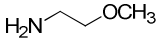
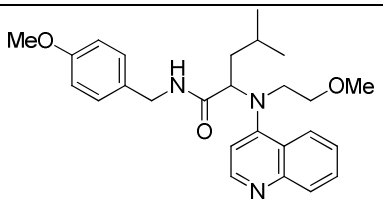
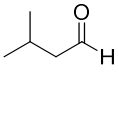
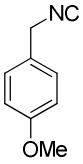
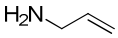
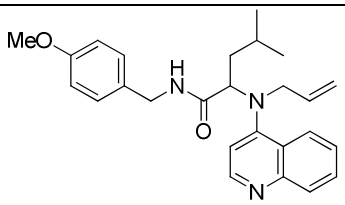
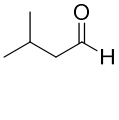
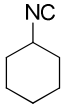
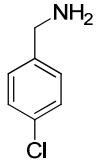
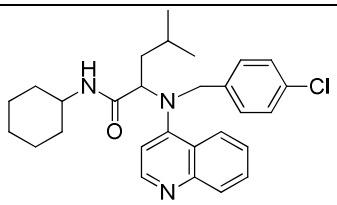
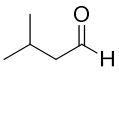
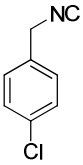
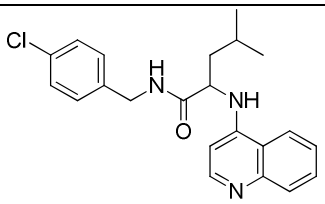
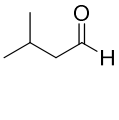
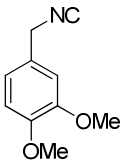
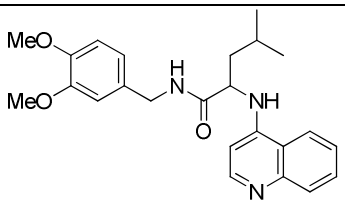
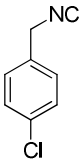
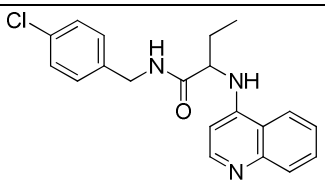
We next examined the behavior of 4-hydroxy quinolines in Ugi-Smiles coupling. The reaction performed in the same conditions settled for 4-hydroxypyridine afforded the desired

products. The results of the Ugi-Smiles couplings of 4-hydroxyquinoline and 2-trifluoromethyl-4-hydroxypyridine are shown in the following tables II.2 and II.3.

TABLE II.2: Ugi-Smiles coupling of 4-hydroxyquinoline.

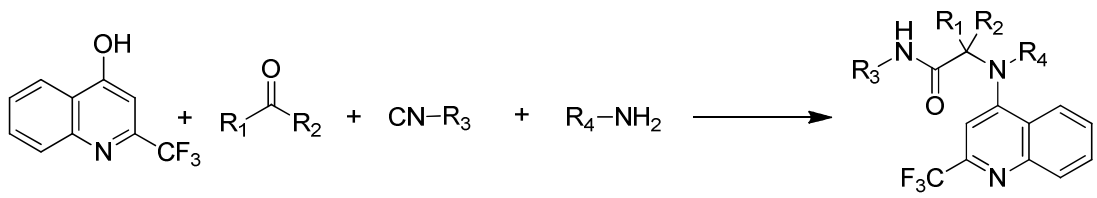


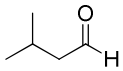
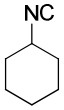
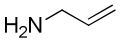
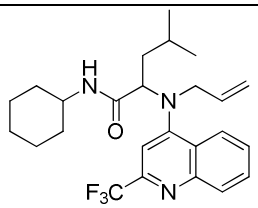
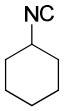
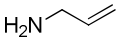
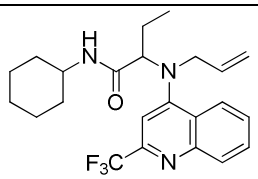
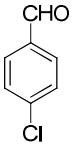
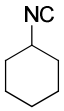
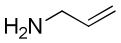
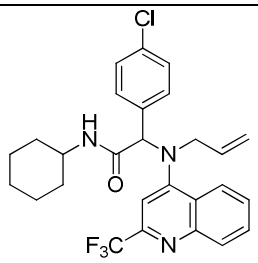
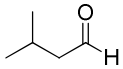
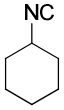
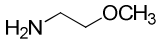
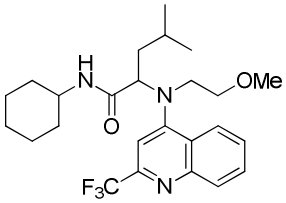
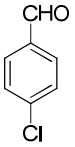
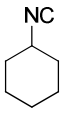
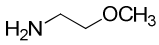
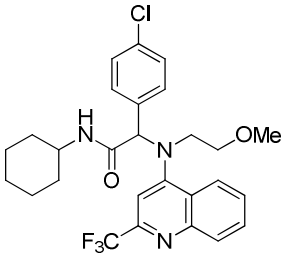
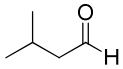
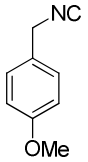
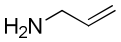
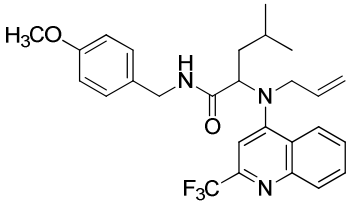
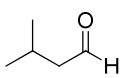
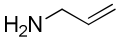
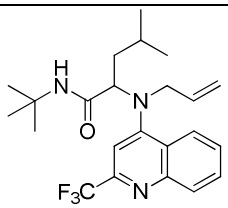
Entry	R_1COR_2	R_3NC	R_4NH_2	Product	Product no.	% yield[a]
1					**II-15**	46 %
2					**II-16**	36 %
3					**II-17**	6 % 21 %[b]
4					**II-18**	7 %
5					**II-19**	47 %

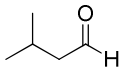
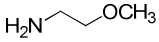
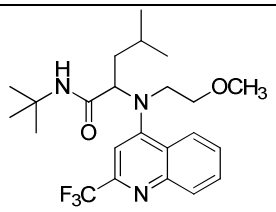
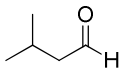
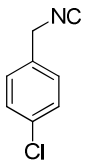
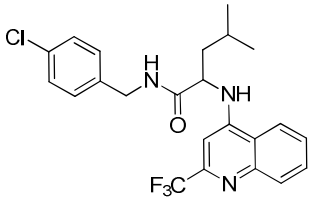
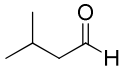
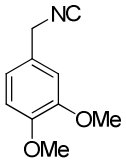
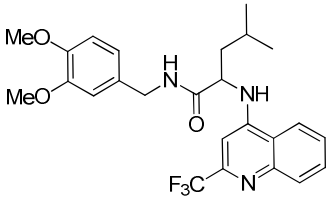
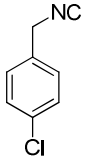
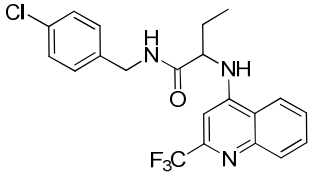
6					**II-20**	60 %
7					**II-21**	47 %
8					**II-22**	49 %
9			NH_3		**II-23**	32 % [c]
10			NH_3		**II-24**	20 % [c]
11			NH_3		**II-25**	15 % [c]

[a] isolated yield, [b] yield after 6 days, [c] isolated yield under microwave conditions.

TABLE II.3: Ugi-Smiles coupling of 2-(trifluoromethyl)quinolin-4-ol.



Entry	R_1COR_2	R_3NC	R_4NH_2	Product	Product no.	% Yield [a]
1					**II-26**	71%
2					**II-27**	38 %
3					**II-28**	72 % 36 %[b]
4					**II-29**	43 %
5					**II-30**	36 %
6					**II-31**	69 %
7					**II-32**	14 %

8					**II-33**	20%
9			NH_3		**II-34**	45 % [c]
10			NH_3		**II-35**	37 % [c]
11			NH_3		**II-36**	48 % [c]

[a] isolated yield, [b] yield after 18 hrs, [c] isolated yield under microwave conditions.

Various aldehydes or ketones, amines, and isocyanides have been coupled successfully as listed in table II.2 and table II.3. As previously observed (for 4-hydroxy pyridine), *ter*t-butyl isocyanide (see table II.2, entries 4 and table II.3, entries 7, 8) is less efficient than cyclohexyl isocyanide and required longer reaction time. 2-(Trifluoromethyl)quinolin-4-ol turned out to be more effective than the 4-hydroxy quinoline (see table II.2, entries 1 and table II.3, entry1), this can be explained by the electron-withdrawing nature of the CF_3 group.

Various primary amines - allyl, benzyl and propargyl amines (see table II.1), were submitted successfully to the Ugi-Smiles coupling, the desired adducts were obtained in moderate to good yield.

Ugi-Smiles reaction of 4-hydroxyquinolines with ammonia gave deceiving results, the yield of products all product are less than 50 %, even when working under microwave conditions. (see table II.2, entries 9-11 and table 3, entries 9-11),

Next, we decided to examine the behaviour of the mercapto heterocycles to form thioamides, which are privileged functional groups for further synthetic transformations.

3. Ugi Smiles reaction of 4-mercapto derivatives

a. General interest of thioamides

Thioamides are useful synthetic intermediates. They are essential building blocks for the preparation of a number of biologically relevant peptides, heterocycles, etc.[76]

The synthesis of thioamides has attracted much attention and many methods have been developed.[77] According to the retrosynthesis, their formation can be classified in four groups.

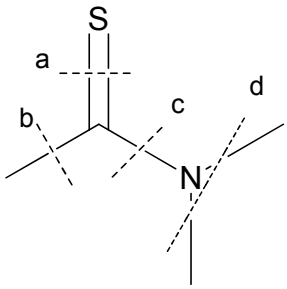


Figure II.1: Possible routes of thioamide.

Formation of bond **a** is based mainly on the transformation of an amide carbonyl to a thiocarbonyl group. This is generally affected by Lawesson's reagent, phosphorous pentasulfide or other sulfurating reagents.[78] Formation of bond **b** generally involves addition of Grignard reagents[79] or other carbanionic entities[80] to isothiocyanates. Formation of bond **c** involves the reaction of an amine with sulphur containing compound to form thioamide,[81] and in path **d,** primary thioamide are *N*-alkylated to get secondary or tertiary thioamides.

[76] a) Jensen, O.; Lawesson, S.; Bardi, R.; Piazzesi, A.; Toniolo, C. *Tetrahedron* **1985**, *4*, 5595-5606. b) Seebach, D.; Ko, S.; Kessler, H.; Kock, M.; Reggelin, M.; Schmieder, P.; Walkinshaw, M.; Bolsterli, J.; Bevec D. *Helv. Cim. Acta* **1191**, *74*, 1953-1990.

[77] Jagodzinski, T. *Chem Rev* **2003**, *103*, 197–227.

[78] a) Zacharie, B; Sauve, G.; Penney, C. *Tetrahedron*, **1993**, *49*, 10489-10500. b) Schwarz G. *Org. Synth. Coll.Vol. III* **1995,** 332. c) Raucher, S; Kelin, P.; *Tetrahedron Lett*.**1980,** *21*, 4061-4064. d) Yokoyama, M.; *Synthesis*, **1984**, 827-829. e) Cava, M.; Levinson, M. *Tetrahedron*, **1985**, *41*, 5061-5087. f) Wolf, P.; Jenny, C.; Heimgartner, H. *Helv. Cim. Acta*, **1987**, *70*, 1001-1011. g) Schimidt, U.; Utz, R., Lieberknecht, A.; Griesser, H., Ptzolli, B.; Bahr, J.; Wanger, K.; Fisher, P. *Synthesis*, **1987**, 233-236.

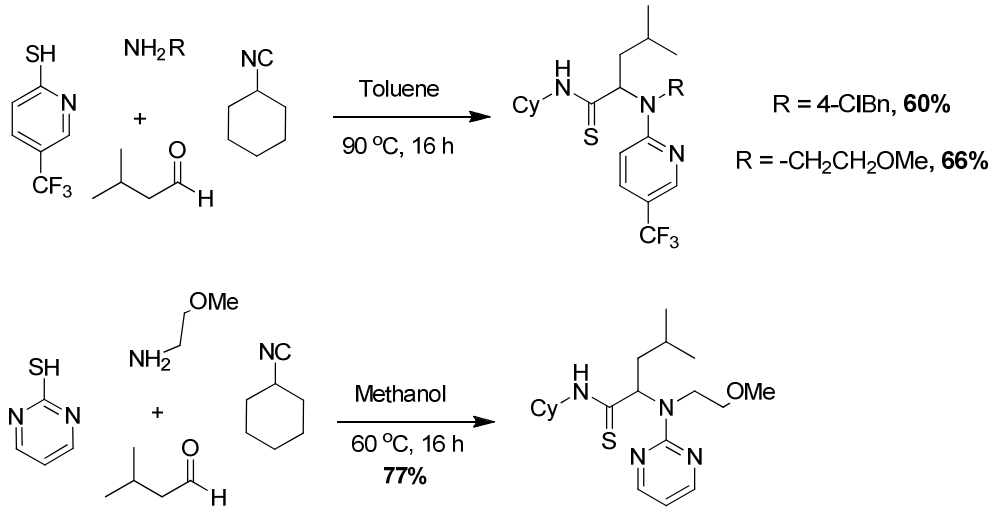
[79] Ares, J. *Synth. Commun.* **1991**, *21*, 625-633.

[80] a) Lang, S.; Cohen, E. *J. Org. Chem*. **1974**, *39*, 1008. b) Mohoareb, R.; Habashi, A.; Ibrahim, N.; Sherif, S. *Synthesis* **1987**, 228-235.

[81] Borths, C.; Chan, J.; Burke, B.; Larsen, R. *Synlett*, **2009**, 3139-3142

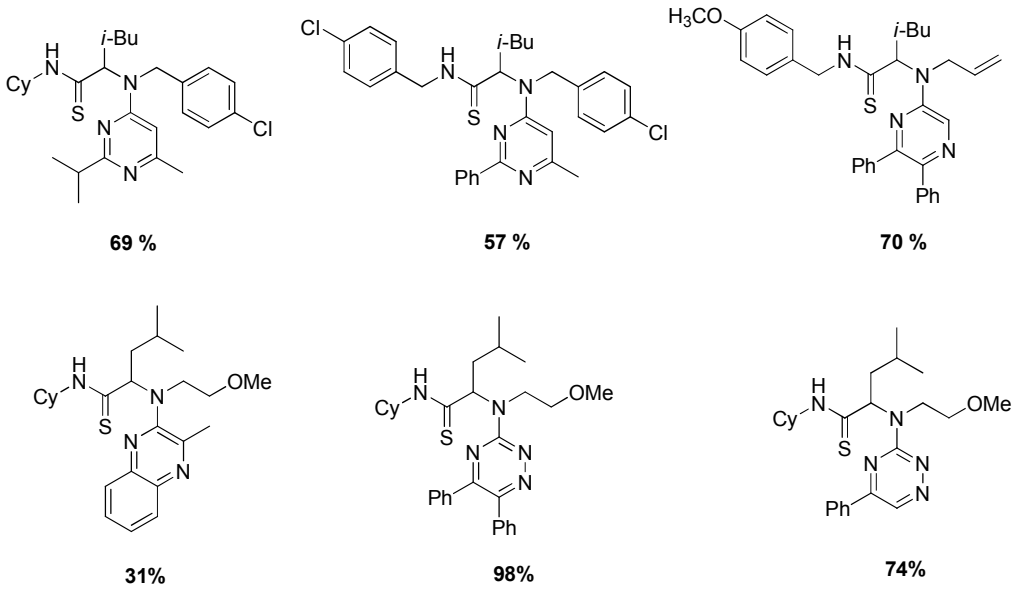
b. Functionalized thioamide formation via Ugi-Smiles couplig

Recently, we have developed a new straightforward synthetic access to functionalized thioamids via 4-CC. In these reactions, thiophenols turned out to be poorly efficient, but more interesting results were obtained with heteroaromatic thiols.[82]



Scheme II.17: Thioamides synthesized from Ugi-Smiles reaction.

2-Mercaptopyridines[83] required a slight activation (with a trifluoromethyl group), but mercapto pyrimidines and pyrazines[59] react efficiently in these reactions as shown in scheme II.17 and scheme II.18.



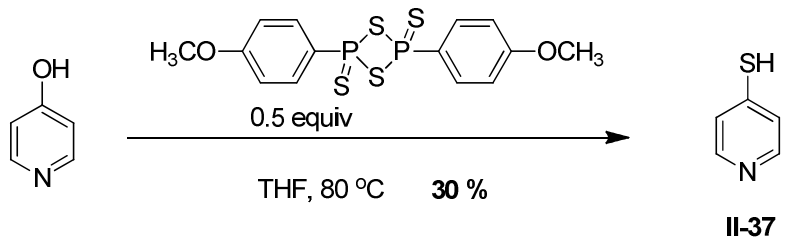
[82] Barthelon, A.; El Kaïm, L.; Gizolme, M.; Grimaud, L. *Eur. J. Org. Chem.* **2008**, *35*, 5974–5987.
[83] El Kaim, L.; Gizolme, M.; Grimaud, L. *Org Lett.* **2006**, *8*, 5021–5023.

Scheme II.18: Thioamides synthesized from Ugi-Smiles coupling reaction.

3-Methylquinoxoline-2-thiol gave low yields of adducts, while 1,2,4-triazin-3-thiol turned out to be one of the best partner in this 4-CC as excellent yields were obtained even with ketones.[37] This method constitutes an efficient access to compounds containing thioamide functionality.

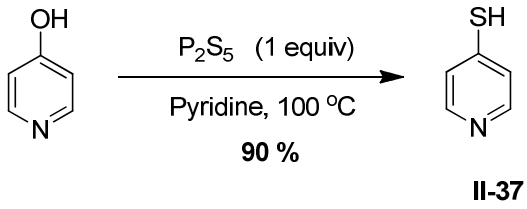
C. Ugi-Smiles reactions of 4-mercaptopyridines

Commercially available 4-hydroxypyridine was treated with Lawesson's reagent[84] to provide the corresponding 4-mercaptopyridine in 30 % yield.



Scheme II.19: Synthesis of 4-mercapto pyridine.

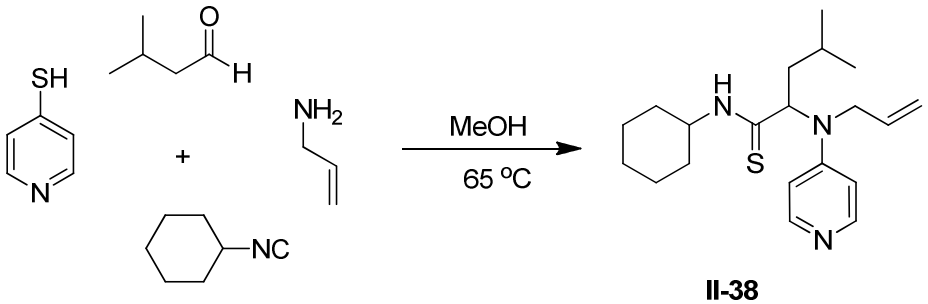
When the same reaction was carried out with phosphorus pentasulfide[85] in pyridine as solvent at 100 °C, the corresponding 4-mercaptopyridine was isolated in 90 % yield.



Scheme II.20: Synthesis of 4-mercapto pyridine

4-Mercaptopyridine was first evaluated in Ugi-Smiles couplings with isovaleraldehyde, cyclohexyl isocyanide and allyl amine using methanol as solvent. The resulting reaction was stirred at 65 °C for 3 days while monitoring by TLC (Scheme II.21).

[84] Neil, S.; Cutshall, Jennifer, L.; Gage, R.; Onrust, D.*Bio.Med. Chem. Lett.* **2011**, *21*, 4155–4159.
[85] Castle, R.; Kaji, K.; Gerhardf, G.; Guither, W.; Weber, C.; Malm, M.; Shoup, R.; Rhoads, W. *J. Het. Chem.* **1996**, *3*, 79-83.



II-38

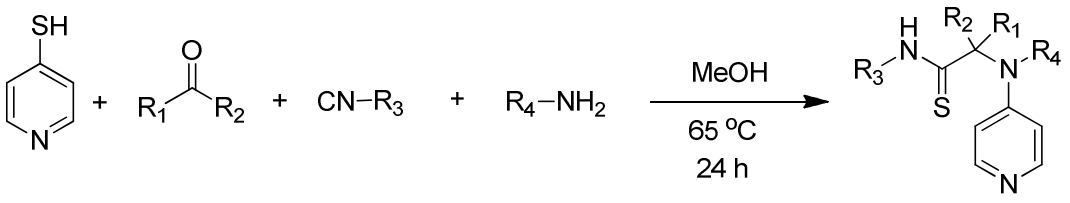
Reaction Time	% yield
18 h	**78%**
24 h	**80%**
72 h	**82%**

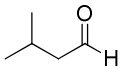
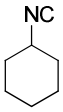
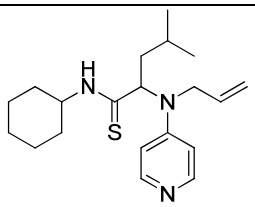
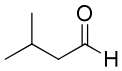
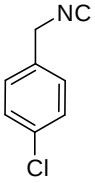
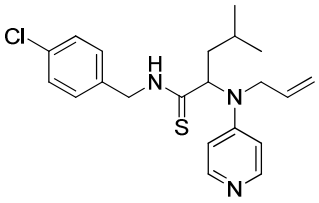
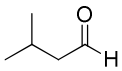
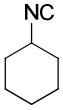
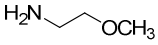
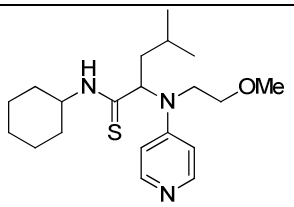
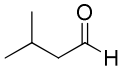
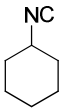
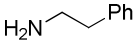
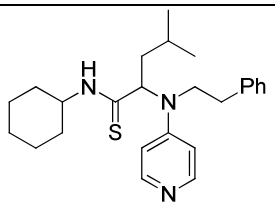
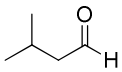
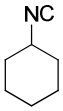
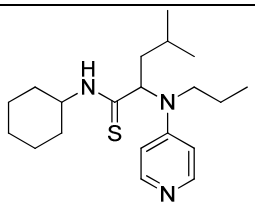
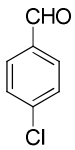
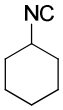
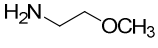
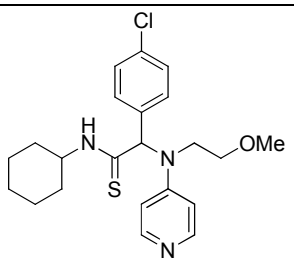
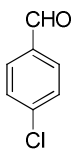
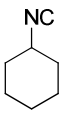
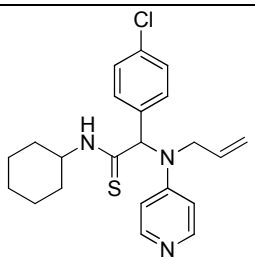
Scheme II.21: Ugi-Smiles coupling of 4-mercapto pyridine.

The yield of thioamide did not vary remarkably when increasing the reaction time. At the same time, by-product formation started and complicated the product isolation. To avoid such a problem, the reaction time was limited at 24 h for the study of the reaction scope. The Ugi-Smiles reactions involving 4-mercaptopyridine appeared to be faster and more efficient than with 4-hydroxypyridine with respect to the same other three partners. Indeed, the isolated yield was about 78 % after 18 h, instead of 40 % in the case of 4-hydroxypyridine after one day (see table II.1).

This reaction was then tested varying the three other partners; the results are tabulated below (Table II.4).

TABLE II.4: Ugi-Smiles coupling of 4-mercaptopyridine.

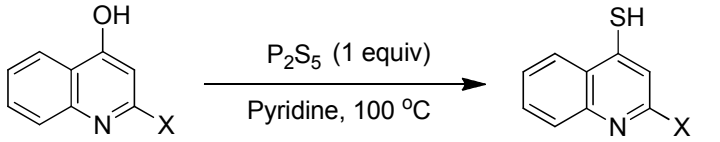


Entry	R_1COR_2	R_3NC	R_4NH_2	Product	Product no.	% yield.[a]
1					**II-38**	80 %
2					**II-39**	57 %
3					**II-40**	55 %
4					**II-41**	60 %
5					**II-42**	55 %
6					**II-43**	34 %
7					**II-44**	40 %

In all the cases, the desired *N*-pyridinothiocarboxamides were isolated in moderate to good yields within 24 hrs. Benzyl isocyanides gave lower yields compared to cyclohexyl isocyanide, and as usual aliphatic aldehydes were more efficient than aromatic ones (see table II.4, entries 1 and 7).

d. Ugi-Smiles reactions of 4-mercaptoquinolines

After the preliminary results with 4-mercaptopyridine, we next examined the behavior of 4-mercaptoquinolines in Ugi-Smiles couplings. 4-Mercaptoquinoline and 2-(trifluoromethyl)-4-mercaptoquinoline were prepared from their respective hydroxy derivatives.[36]



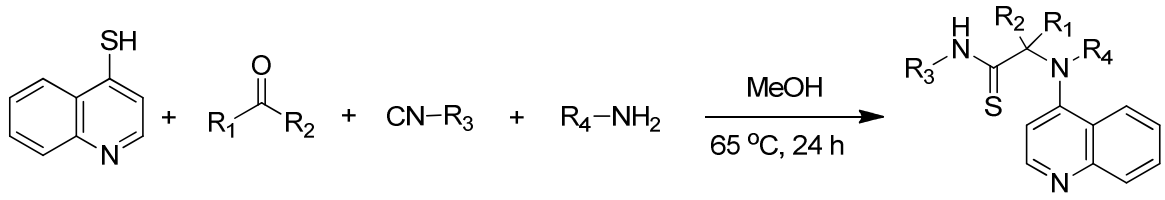
II-45 X = H, **90%**

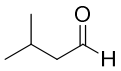
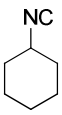
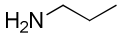
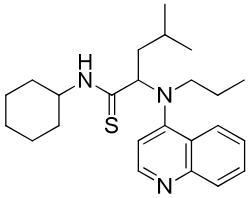
II-46 X = CF_3, **25%**

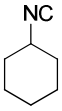
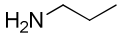
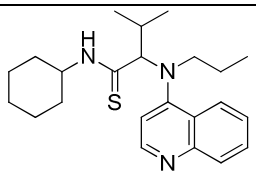
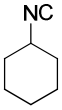
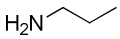
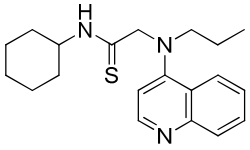
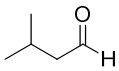
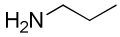
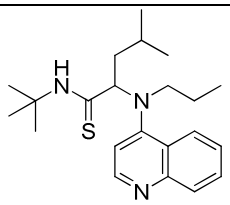
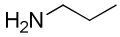
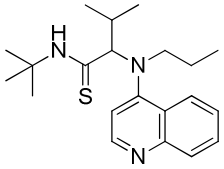
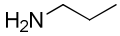
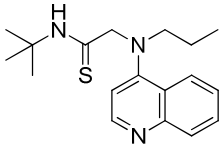
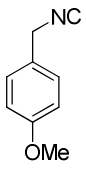
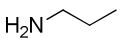
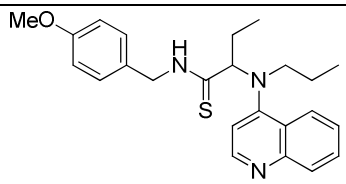
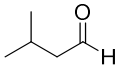
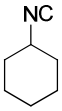
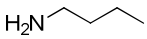
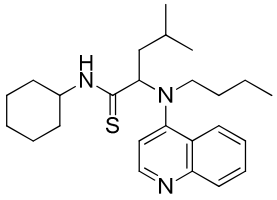
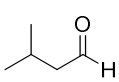
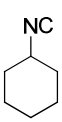
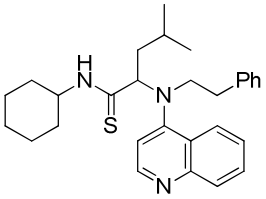
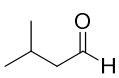
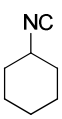
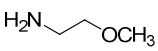
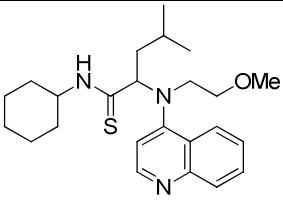
Scheme II.22: Synthesis of 4-mercaptoquinolines.

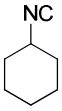
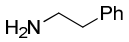
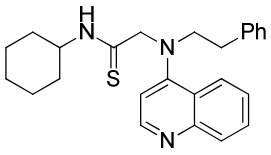
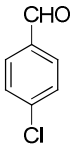
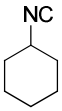
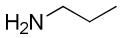
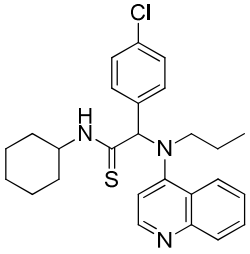
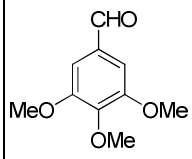
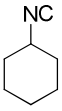
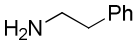
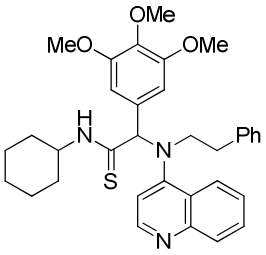
The Ugi-Smiles reactions of 4-mercaptoquinolines were performed under the previously settled conditions. This reaction was tested varying all the partners, the results are listed in the following table (table II.5).

TABLE II.5: Ugi-Smiles coupling of 4-mercaptoyquinoline.



Entry	R_1COR_2	R_3NC	R_4NH_2	Product	Product no.	% yield.[a]
1					**II-47**	87 %

2					**II-48**	81 %
3					**II-49**	56 %
4					**II-50**	81 %
5					**II-51**	78 %
6					**II-52**	51 %
7					**II-53**	51 %
8					**II-54**	99 %
9					**II-55**	98 %
10					**II-56**	82 %

11					**II-57**	44 %
12					**II-58**	71 %
13					**I.59**	64 %

The first reaction was performed with cyclohexyl isocyanide, propyl amine and isovaleraldehyde in methanol and stirred for 24 h at 65 °C to give 87 % of the corresponding thioamide (Table II.5, entry 1).

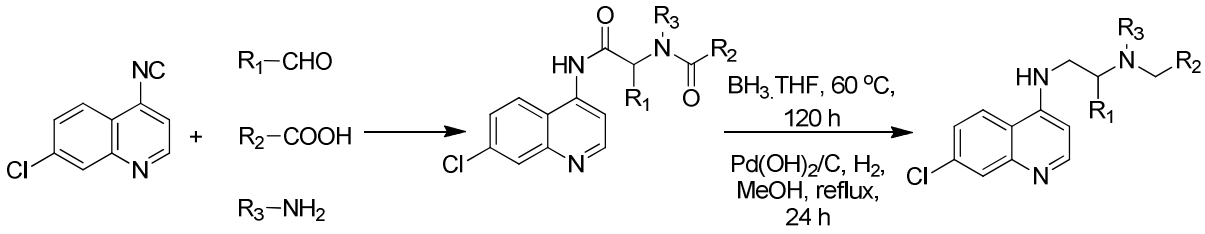
In this reaction, aromatic aldehydes gave lower yields compared to aliphatic ones (Table II.5, entries 12 and 13).

When cyclohexyl isocyanide was replaced by *tert*-butyl isocyanide, the corresponding thioamides were isolated in good yields though slightly lower. (See Table II.5 entry 1-3 and entry 4-6). However, 4-methoxybenzyl isocyanide turned out to be less efficient, as with propionaldehyde and *n*-propylamine, it only gave 51 % of the desired adduct (see table II.5, entry 7).

4. Towards chloroquine analogues

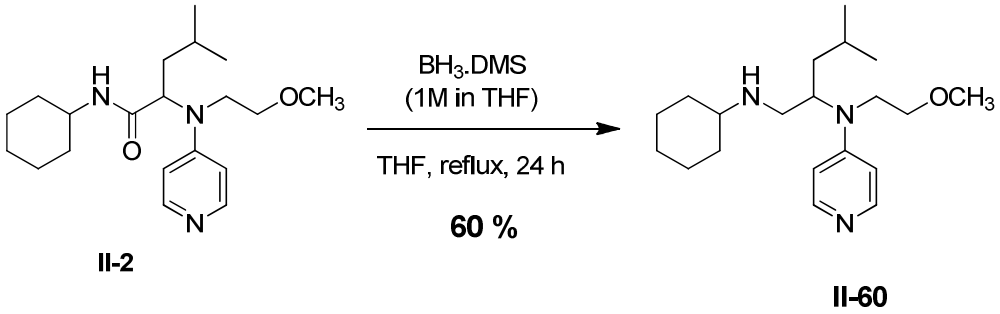
In order to approach closer the structure of active drugs, the amide moiety should be reduced. Borane-induced reduction of Ugi adducts was reported by Tron and Giovenzana[86] (Scheme II.23).

[86] Pirali, T.; Callipari, G.; Ercolano, E.; Genazzani, A.; Giovenzana, G.; Tron, G. *Org. Lett*. **2008**, *10*, 4199–4202



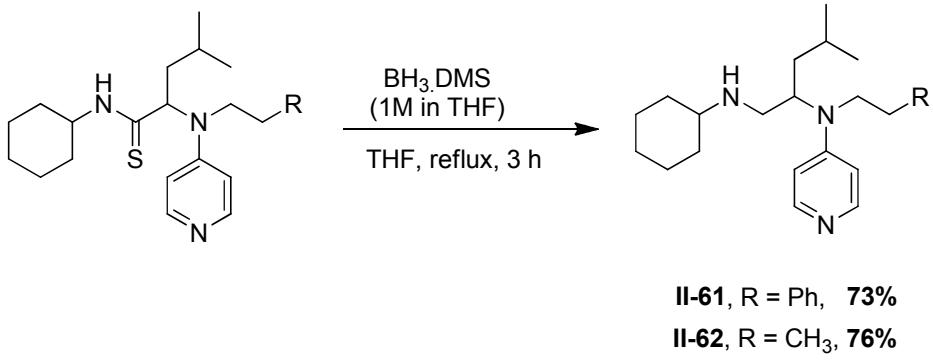
Scheme: II.23: Ugi reaction to access antimalarial drug.

According to the previous work done by Tron and Giovenzana,[93] we first tested compound **II.2** (Table II.1, entry 2) with borane-dimethylsulfide complex in THF. In these conditions, the desired amine was isolated in 60 % yield (Scheme II.24).



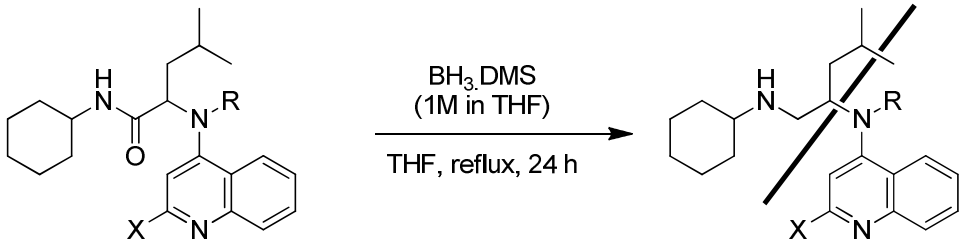
(**Scheme II.24**: Reduction of Ugi-Smiles adduct with Borane.DMS)

This reduction was next tested on thioamides. For this purpose, compounds **II-41** and **II-42** (Table II.4, entries 4 and 5) were treated with borane-dimethylsulfide complex in THF (1M solution) for 3 hrs. The desired diamines were respectively isolated in 73 % and 76 % (Scheme II.25).



Scheme II.25: Reduction of Ugi-Smiles adduct with Borane-DMS complex

Unfortunately, these conditions failed to be general as *N*-quinoline carboxamides could not be reduced. Indeed, the decomposition of starting materials occurred in the reaction mixture. (Scheme II.26).



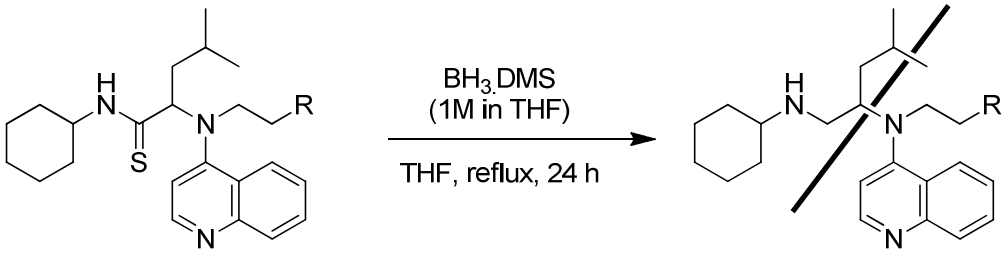
II-14, X = H, R = Allyl

II-16, X = H, R = -CH_2CH_2OMe

II-27, X = -CF_3, R = -CH_2CH_2OMe

Scheme II.26: Reduction of thioamide with Borane.DMS complex.

Similarly, *N*-quinoline thiocarboxamide failed to give the reduced products in these conditions (Scheme II.27).



II-55 R = Ph

II-56, R = OCH_3

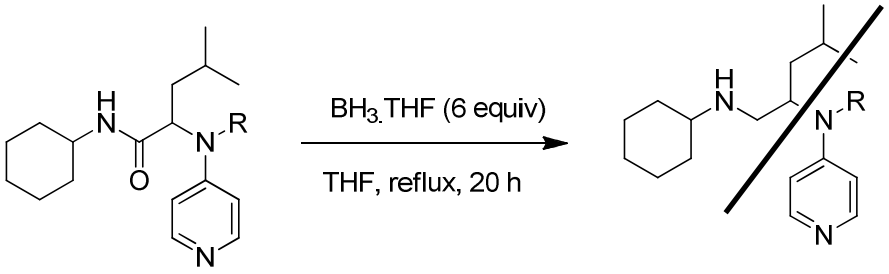
Scheme II.27: Reduction of thioamide with Borane-DMS complex.

Due to the impossible access to aminoquinoline derivatives, we investigated different methods of the literature to perform amide reduction.

The reduction of amides was tested with *N*-pyridino amide as reported by Iwaniuk *et al*[87] Compound **II.1** (Table II.1, entry 1) and compound **II.2** (Table II.1, entry 2) were treated

[87] Iwaniuk, D.; *Bioorg. Med. Chem*. **2009**, *17*, 6560–6566. b) Brown, H.; Helm, P. *J. Org. Chem.* **1973**, *38*, 912-916. c). Dubowchik, G.; Dubowchik, J;. Michne, D. *Bioorg. Med. Chem. Lett.* **2004,** *14*, 3147–3149.

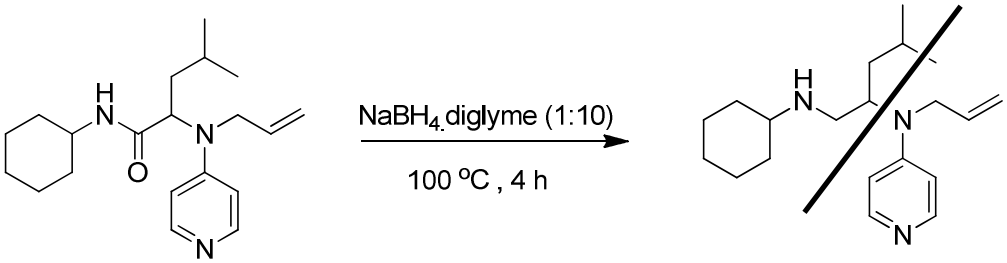
with 6 equivalents of borane tetrahydrofuran complex (1M solution in THF) in THF at reflux for 3hrs. In all cases, the amide remained unchanged, even after long reaction time.



II-1 : R = allyl
II-2 : R = -CH_2CH_2OMe

Scheme II.28: Reduction of Ugi-Smiles adduct with Borane-THF complex.

Sodium borohydride in diglyme is known to reduce amides to the corresponding amines.[88] When the Ugi-Smiles adduct **II.1** (Table II.1, entry 1) was treated with sodium borohydride in diglyme at 100 °C for 4 hrs, a complete mixture was obtained.

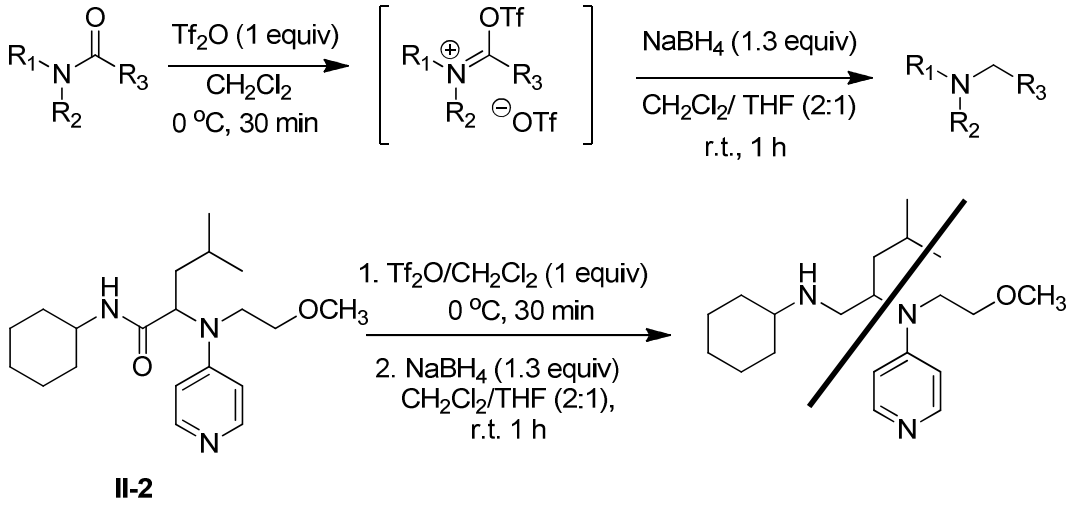


II.1

Scheme II.29: Reduction of Ugi-Smiles adduct with sodium borohydride in diglyme.

Reduction of amides and lactams to amines could be done under activation with Tf_2O followed by treatment with sodium borohydride in THF at room temperature.[89] Unfortunately, when this method was applied to the compound **II.2** (Table II.1, entry 2), decomposition of the starting material was observed.

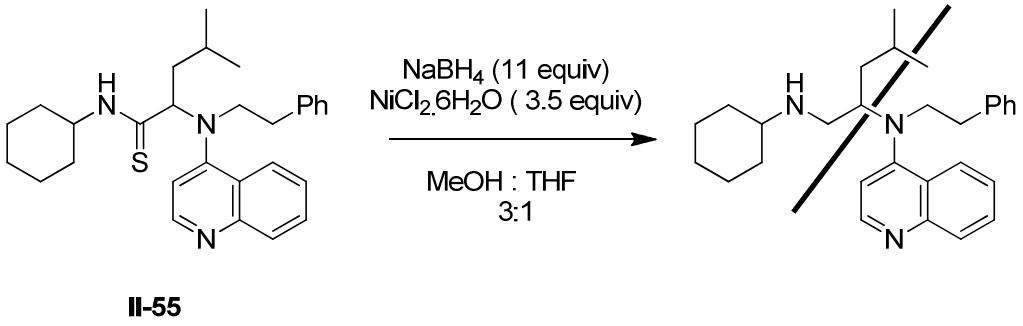
[88] Yang, C.; Pittman, C. *Synthetic Commun*. **1998**, *28*, 2027-2041.
[89] a) Xiang, S. ; Xu, J.; Yuan, H.; Huang, P. *Synlett*, **2010**, 1829-1832. b) Barbe, G; Charrette, A. *J. Am. Chem. Soc.* **2008**, *130*, 18-19.



Scheme II.30: Reduction of Ugi-Smiles adduct with Tf_2O and $NaBH_4$.

Nickel boride has been used for the desulfurization of heterocyclic thiols[90]and thioamides.[91] It allows fast reduction of the thioamide bond in peptides.[92] It is generally prepared by treating nickel chloride hexahydrate in methanol-tetrahydrofuran with sodium borohydride.[93]

Compound **II-55** (Table II.5, entry 9) treated by in situ generated nickel boride in a 1:1 mixture of tetrahydrofurane /methanol failed to give the desired diamine.



Scheme II.31: Reduction of thioamide with Borane-DMS complex.

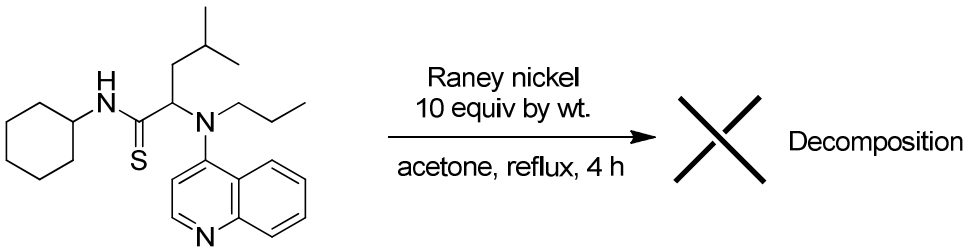
Raney nickel (RaNi) has been widely used in desulfurization reactions, including conversion of a thiocarbonyl moiety into a methylene group.[94] Neutral Raney nickel in alcohol as solvent

[90] Clark, J.; Grantham, R.; Lydiate, J. *J. Chem. Soc. C.* **1968**, 1122-1124.
[91] Claiton, L., Dassonville, A.; Sonnet, P. *Tetrahedron: Asymmetry*, **2008,** *19*, 1689–1697.
[92] Frank, S.; Loide, G.; Wasmund M.. *Tetrahedron Lett.* **1990,** *21*, 23-26.
[93] Thomas, G; *J. Chem. Soc.Chem. Comm.* **1984**, 1417-1418.
[94] a) Komfeld, E. *J. Org. Chem*. **1951**, *16*, 131-138. b) Dale B. *Org. Lett.* **2005**, *7*, 4539-4541.

gives relatively good desulfurization yields.[43] However; a number of drawbacks were noted using this procedure. One major drawback was the removal of the carbobenzoxy groups which occurs concurrently with thioamide reduction. *Trans*-esterification under normal reaction conditions was also noted but it could be avoided using acetone as solvent.[95] Finally, the preparation and the use of neutral Raney nickel is time-consuming and tedious. Different batches of identically prepared reagent often show significantly different reactivities as demonstrated by variation in reaction time and yields. These problems and the potential hazards associated with the pyrophoric nature of Raney nickel led us to test other reductive procedures before starting these studies.

However, considering all the failures with other reducing agents, the reduction with Raney nickel was tested.

Compound **II-47** (Table II.5, entry 1) (1 equiv) was dissolved in acetone and treated with Raney nickel (10 times w/w) at room temperature for 1 hr without any change. After 4 h at reflux, TLC showed the total disappearance of the starting material. After removal of Raney nickel rapidly through Celite® pad and evaporation of the volatiles, the crude mixture turned out to decompose on silica gel (Scheme **II.**32).

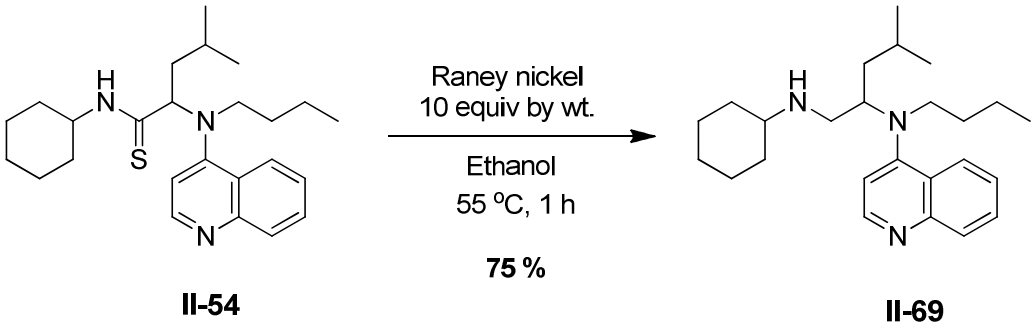


II-47

Scheme II.32: Reduction of thioamide with Raney nickel in acetone.

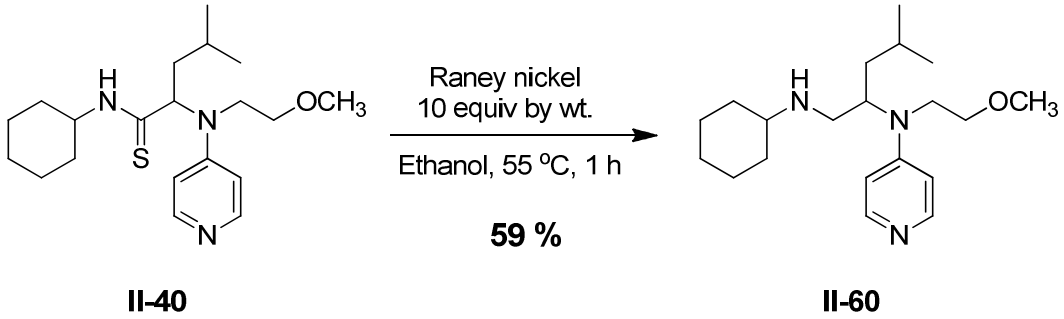
More interestingly, when replacing acetone by ethanol, the reduction proceeded smoothly at 55 °C for 1 h. Indeed, compound II.54 (Table II.5, entry 8) was reduced in 75% isolated yields (Scheme II.33).

[95] Magnus, P.; Turnbull, R. *Tetrahedron Lett.* **2006**, *47*, 6461–6464.



Scheme II.33: Reduction of thioamide with Raney nickel in ethanol.

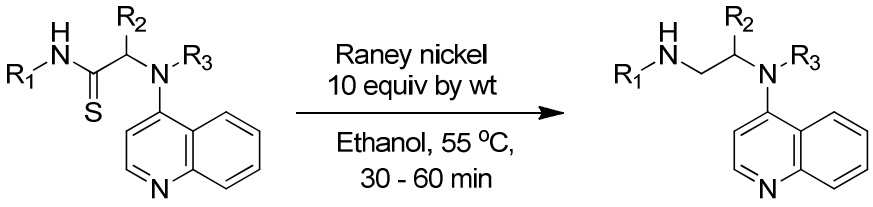
The same conditions were then tested to *N*-pyridino thiocarboxamide, the compound **II.40** (Table II.4, entry 3) gave the corresponding diamine in 59 % isolated yield. It is interesting to notice that these results are similar to those obtained with borane dimethyl sulfide in THF (60 %), (Scheme II.34).

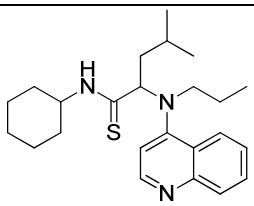
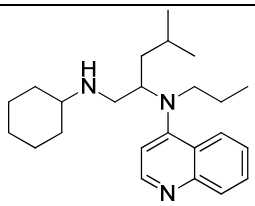
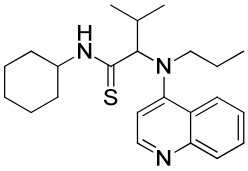
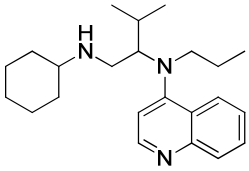
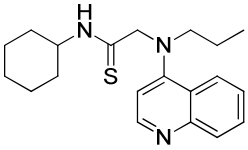
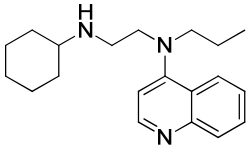
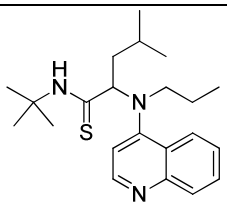
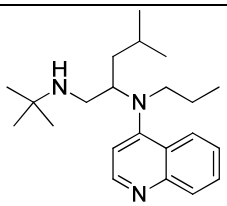
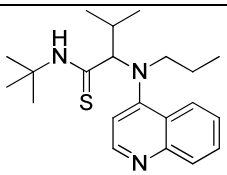
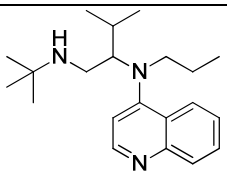
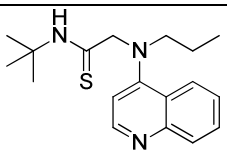
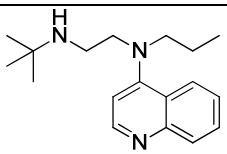
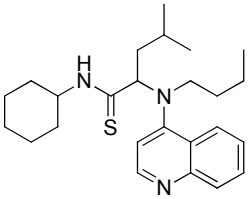
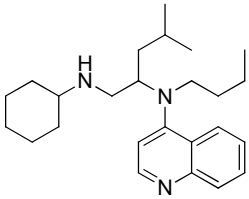
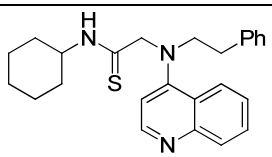
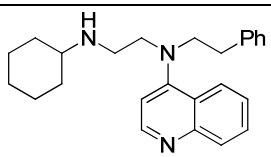


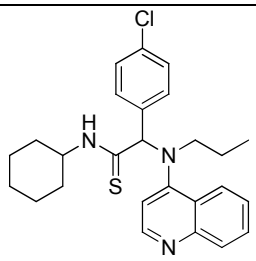
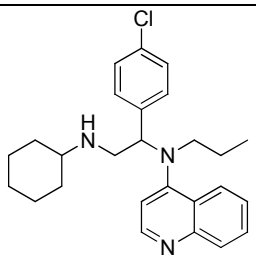
Scheme II.34: Reduction of Ugi-Smiles adduct- thioamide with Raney nikel in ethanol.

This method turned out to be quite efficient for a wide range of thioamides. All the results are tabulated below.

TABLE II.6: Desulfurization of *N*-quinolino thiocarboxamides.

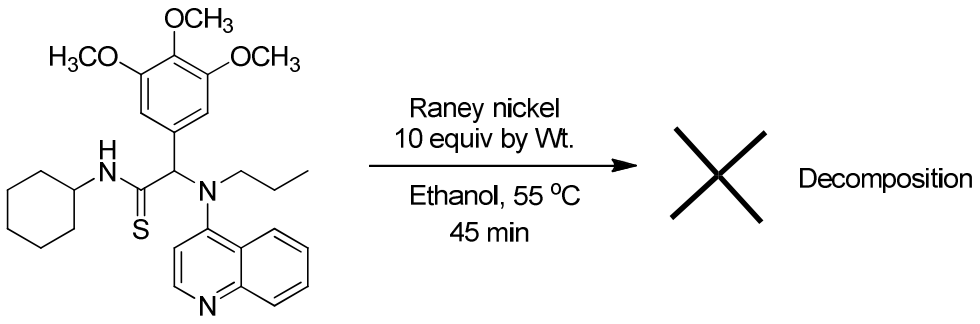


Ugi-smiles product no.	Ugi-Smiles product	After Desulfurization	Product no.	Desulfurization % yield
II-47			**II-63**	55
II-48			**II-64**	42
II-49			**II-65**	67
II-50			**II-66**	39
II-51			**II-67**	41
II-52			**II-68**	67
II-54			**II-69**	75
II-57			**II-70**	21

II-58			**II-71**	37

This method give moderate to good isolated yields irrespective to the isocyanides used for the Ugi-Smiles adduct preparation.

This method is less efficient for Ugi-Smiles adduct prepared from aromatic aldehydes. Compound **II-58** was reduced with Raney nickel in 37 % isolated yield. This result could not be improved as after 3 hrs total decomposition was observed. Similarly, when compound **II-59** was treated with Raney nickel for 45 min, total decomposition was observed as well.

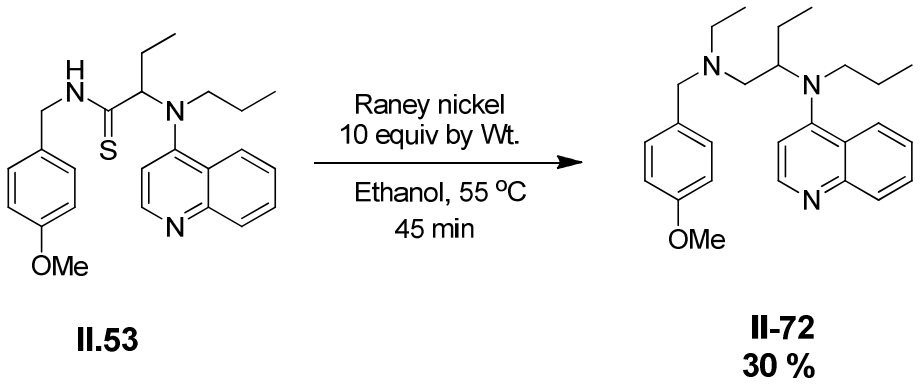


II.59

Scheme II.35: Reduction of Ugi-Smiles thioamide prepared from aromatic aldehyde

When Ugi-Smiles thioamide **II-48** (table II.5, entry 7) was treated with Raney nickel in ethanol at 55 °C, an unexpected *N*-alkylated desulfurized product **II-72**, was isolated in 30 % yield (Scheme II.36). Since the reaction was carried out in ethanol, the latter was probably oxidized in the presence of Raney nickel to form ethanal,[96] which could react with the secondary amine to form iminium, which was finally reduced with Raney nickel to offer the product **II-72.**

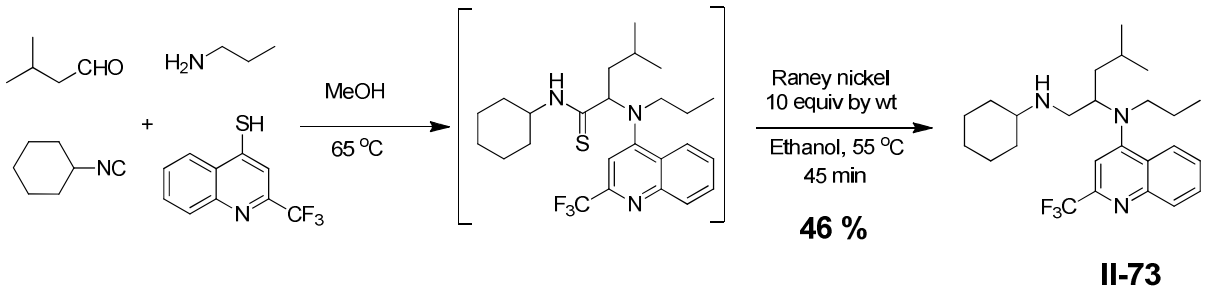
[96] a) Krafft M.; Crooks W.; Zorc B.; Milczanowski S. *J. Org. Chem.*, **1988**, *53*, 3158–3163. b) Krafft M.; Zorc B. *J. Org. Chem.*, **1986,** *51*, 5482–5484, c) Gross B. *Applied Catalysis A: General*, **2001**, *219*, 281–289.



II.53 **II-72** **30 %**

Scheme II.36: Reduction of Ugi-Smiles adduct- thioamide with Raney nikel in ethanol.

More interestingly, the whole sequence could be done according to a one pot procedure. Indeed, a stoichiometric amount of 4-mercapto-2-trifluoromethylquinoline, cyclohexyl isocyanide, *n*-propylamine and isovaleraldehyde was heated in methanol (1M) for one day at 65 °C. The reaction mixture was then cooled and diluted with ethanol before addition of the Raney nickel. It was stirred for 45 min at 55 °C to give the diamine **II-73** in 46% isolated yield over two steps (Scheme II.37).



II-73

Scheme II.37: One-post synthesis of chloroquine analogues.

III. Conclusion

4-hydroxy pyridine derivatives are efficient partners in Ugi-Smiles couplings. They were found more reactive than their 2-substituted analogues, which require further activating groups.

We tested the behavior of quinolines to obtain new multicomponent access to antimalarial drugs: 4-hydroxy quinoline and 2-trifluoromethyl-4-hydoxy quinoline were tested under the same reaction conditions to afford satisfying yields. The scope of these reactions was

examined with various partners. Unfortunately, the reduction of these adducts under borane-DMS conditions failed to give any diamine. To overcome these reduction problems, we examined the behaviour of the mercapto heterocycle analogues. Their Ugi-Smiles couplings form thioamides, privileged functional groups for further synthetic transformations.

4-Mercapto pyridine was first evaluated in Ugi-Smiles couplings. The corresponding *N*-pyridino thiocarboxamides were obtained in moderate to good yields, and they could be further transformed into diamines using BH_3-DMS in THF or Raney nickel in ethanol. The corresponding diamines, which constitute *N,N*-dimethylaminopyridine analogues, were isolated in good yields. Similar behavior was observed with 4-mercapto quinolines.
Finally, we successfully tested one-pot synthesis of chloroquine analogues via Ugi-Smiles coupling followed by reduction.

To conclude, we developed an efficient and straightforward access to 4-aminoquinolines, which makes the method potentially attractive for the synthesis of new antimalarial pharmacophores.

CHAPTER 3

Radical post-condensation transformations

The work described in this chapter has been published in one publication:

El Kaïm, L.; Grimaud, L.; Pravin Patil, *Molecules*. **2011**, *16*, 9261-9273.

I. Introduction

Multi-component reactions (MCRs) offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions. Among multi-component reactions (MCRs), the Ugi reaction has a privileged position due to its broad synthetic importance. Its four points of diversity could be used for the synthesis of molecular libraries. Indeed, even more complex scaffolds have been synthesized using Ugi post-condensation reactions such as cycloaddition,[97] metal-catalyzed processes[98] and cyclocondensations.[99] Among the very impressive literature on this topic, the combination of Ugi or Ugi-Passerini reactions with radical chemistry has been scarcely studied.[53, 100]

In the last few decades, Prof Samir Zard's group has been working on radical chemistry and developed radical chemistry of xanthates. He reported various synthetic approaches towards fused cyclic systems such as indane, indolines or azaindolines.[101]

We will first discuss about the chemistry of xanthates and their applications in cyclization reactions and then about the radical cyclisation as Ugi-post condensation. We will then present our results of xanthate based radical chemistry in Ugi-Smiles coupling.

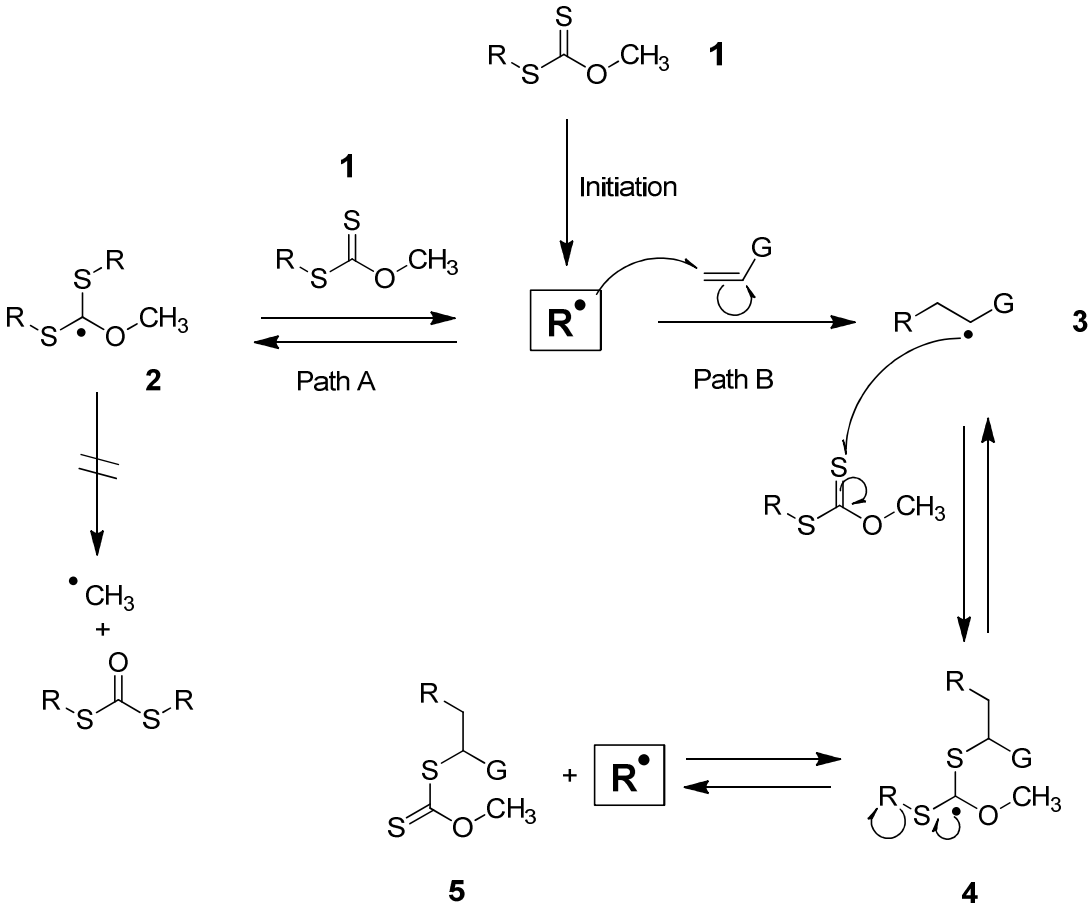
[97] a) Lu, K.; Luo, T.; Xiang, Z.; You, Z.; Fathi, R.; Chen, J.; Yang, Z. *J. Comb. Chem.* **2005**, *7*, 958-967. b) Paulvannan, K. *J. Org. Chem.* **2004**, *69*, 1207-1214.
[98] Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155-3158.
[99] Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 711-713.
[100] a) El Kaim, L.; Grimaud, L.; Miranda, L.D.; Vieu, E. *Org. Lett.* **2007**, *9*, 4171-4173. b) Zamudio-Medina, A.; García-González, M.C.; Padilla, J.; González-Zamora, E. *Tetrahedron Lett.* **2010**, *51*, 4837-4839. c) El Kaim, L.; Grimaud, L.; Miranda, L.D.; Vieu, E.; Cano-Herrera, M.-A.; Perez-Labrada, *Chem. Commun.* **2010**, *46*, 2489-2491. e) Gámez-Montaño, R.; Ibarra-Rivera, T.; El Kaim, L.; Miranda, L.D. *Synthesis* **2010**, *8*, 1285-1290. d) Yu, H.; Gai, T.; Sun, W.L.; Zhang, M.S. *Chin. Chem. Lett.* **2011**, *22*, 379-381.
[101] a) Ly,T. -M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, 40, 2533-2536. b). Bacque, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671-3674. c) El Qacemi, M.; Ricard, L.; Zard, S.Z. *Chem. Commun.* **2006**, 4422-4424. d) Laot, Y.; Petit, L.; Zard, S.Z. *Chem.Commun.* **2010**, *46*, 5784-5786. e) Laot, Y.; Petit, L.; Zard, S. *Org. Lett.* **2010**, *12*, 3426-3429. f) Laot, Y.; Petit, L.; Tran, D. N.; Zard, S. *Aust. J. Chem.* **2011**, *64*, 416-425.

II. Radical cascades involving xanthates

1. State of the art

Prof. Samir Zard[102] studied the chemistry of secondary *O*-alkyl-*S*-methyl xanthates, and found that these xanthates could undergo under radical conditions, cleavage of the weaker carbon-sulfur bond rather than the C-O bond. In these processes, the chain reaction can be sustained without tin or other heavy metals. A variety of synthetically interesting free radicals can thus be produced and captured, the last propagating step being a reversible transfer of the xanthate group.

The general principle of this chemistry is based on the mechanism shown in the diagram below (Scheme III.1).



Scheme III.1: Plausible pathways for the formation and capture of radicals from xanthates

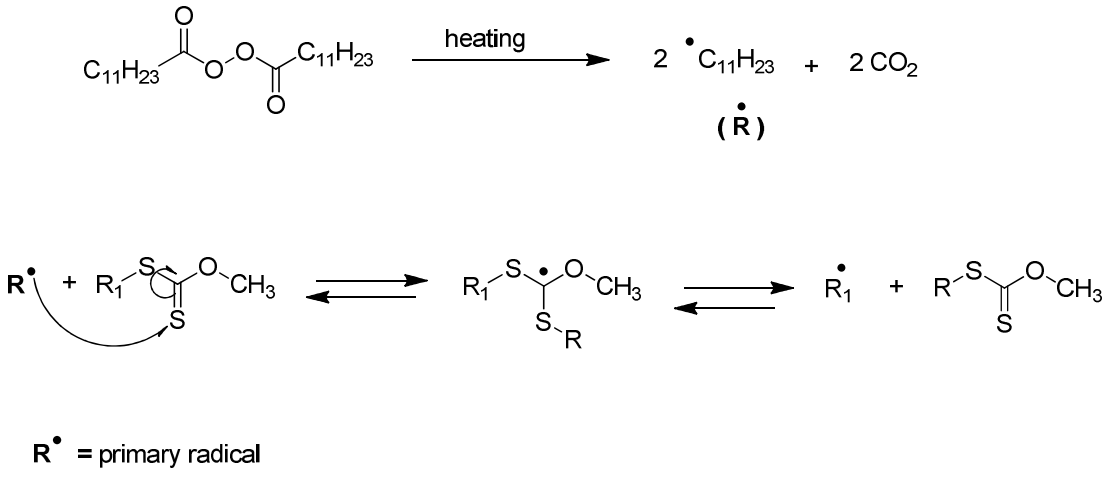
[102] a) Zard, S. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 672-685. b) Liard, A.; Quiclet-Sire, B.; Zard, S. *Tetrahedron Lett*. **1996**, *37*, 5877-5880. c) Quiclet-Sire, B.; Zard, S. *Top. Curr. Chem*. **2006**, *264*, 201-236.

In this reaction, the radical **R**• is easily generated by a chemical initiator or by photoactivation. The addition of a radical **R**• to the olefin leads to the radical intermediate (**3**), which can attack a new xanthate molecule, forming the tertiary radical (**4**). The latter can fragment to generate a new radical **R**• thus forming the product (**5**) and propagating the radical chain by transfer of the xanthate group on the olefin (Path B). This path does not consume radical **R**•. The other possibility (Path A) is the addition of the radical **R**• on the initial xanthate to lead to adduct radical (**2**), for which further *β*-scission of C-O bond is very unfavorable since it would produce a methyl radical, thermodynamically less stable than radical **R**•.

This method is very powerful since xanthates constitute a source of radicals that can add on unactivated olefins. No heavy or toxic metals are involved in this process.

Xanthates (dithiocarbonates) are a general and efficient source of different type of radicals like alkyl, acyl, alkoxycarbonyl, alkoxythiocarbonyl and triphenylstannyl, to name a few.

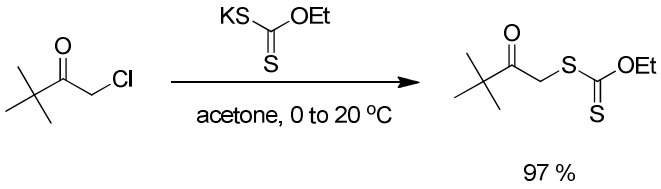
Radical initiation: AIBN is not effective for most xanthates. Crystalline lauroyl peroxide (DLP) was selected for this task (the half lifetime of the DLP in benzene at T = 65 °C is 10 hrs and 2 hrs at 80 °C in 2-propanol), it is inexpensive, safe, and most importantly produces cleanly reactive primary undecyl radicals at a useful rate. The *S*-undecyl xanthate is a stable non polar byproduct, which can be removed by separation techniques.



Scheme III.2: Initiation step for a xanthate radical by a primary radical (with DLP).

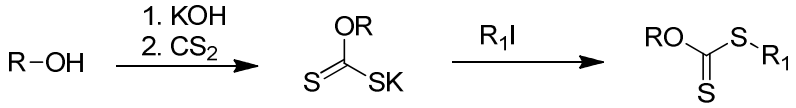
Methods for the preparation of xanthates:

Xanthates can be easily obtained by nucleophilic substitution of the *O*-ethyl potassium xanthate salt as shown in scheme III.3. This nucleophile is cheap and commercially available and able to displace halides, tosylates and other good leaving groups. This method is useful for the synthesis of primary and secondary xanthates.[103]



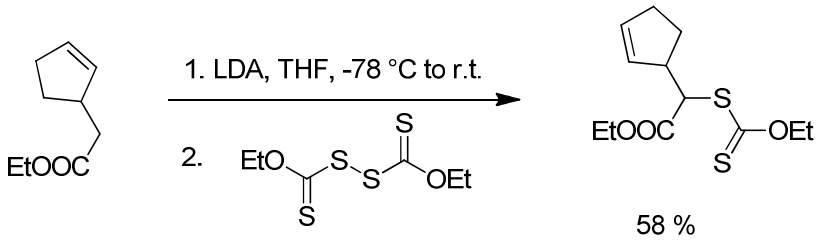
Scheme III.3: Xanthate synthesis: nucleophilic substitution of *O*-ethyl potassium xanthate.

Another method, somewhat less convenient, involves the reaction of an anion (e.g. alkoxide) on carbon disulfide followed by trapping of the intermediate thiolate by an alkyl iodide (scheme III.4).[104]



Scheme III.4: Xanthate synthesis method of Barton-McCombie.

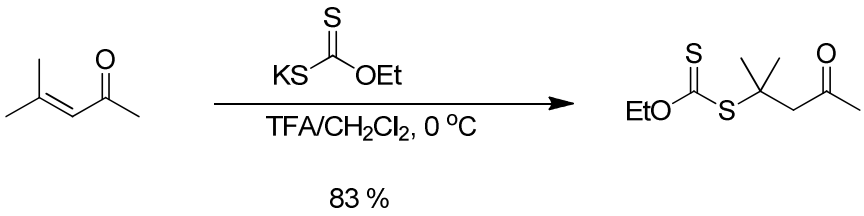
The addition of a carbanion on the *bis*-xanthate $(EtOS(S)S)_2$, obtained by oxidation of potassium xanthate salt by iodine, also forms primary or secondary xanthates (scheme III.5).[105]



Scheme III.5: Xanthate synthesis from *bis*-xanthate.

[103]a) Reyes-Gutierrez, P.; Torres-Ochoa R.; Martinez R.; Miranda L. *Org. Biomol. Chem.***2009**, *7*, 1388-1396 b) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295-7298. c) Jean, B.; Floriane, C.; Rafik, J. *Synthesis* **2006**, *10*, 1664-1672.
[104]Jensen, K. *Acta Chemica Scandinavica* (1947-1973), **1969**, *23*, 1916-1934
[105] Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435-1437.

The addition of potassium xanthate to α,β-unsaturated ketones gives tertiary xanthates, generating quaternary centers (scheme III.6).[106]



Scheme III.6: Synthesis of tertiary xanthate *via* Michael addition reaction.

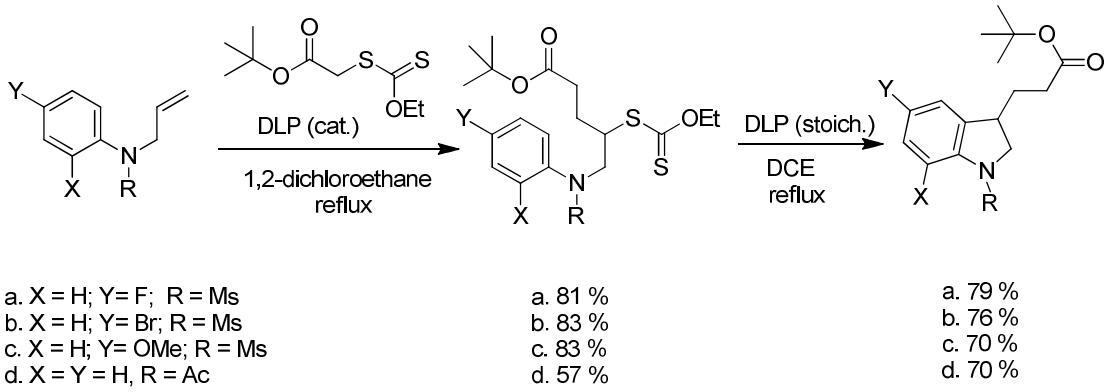
Synthetic applications of xanthates:

Xanthates show huge potential in radical chemistry for organic synthesis.[107] Here we will discuss about few of them reported by Prof. Samir Zard as well as the radical reactions performed on Ugi adduct and disclosed in our research group.

Prof. Samir Zard has reported various synthetic approaches towards fused cyclic systems such as oxindoles,[108] indanes,[101a] indolines[109] or azaindolines.[110] These syntheses feature an inter-molecular addition of a xanthate on an alkene followed by an intramolecular trapping with a suitably positioned aryl group. Cyclization on aromatic rings, which are usually difficult to obtain with classical methods, proceeds smoothly with xanthate.

Radical addition of xanthates to various substituted *N*-allyl anilides gives a new secondary xanthate in good yields, which upon treatment with stoichiometric amounts of lauroyl peroxide in refluxing 1,2-dichloroethane, forms the corresponding indoline in good yields (scheme III.7).[5a]

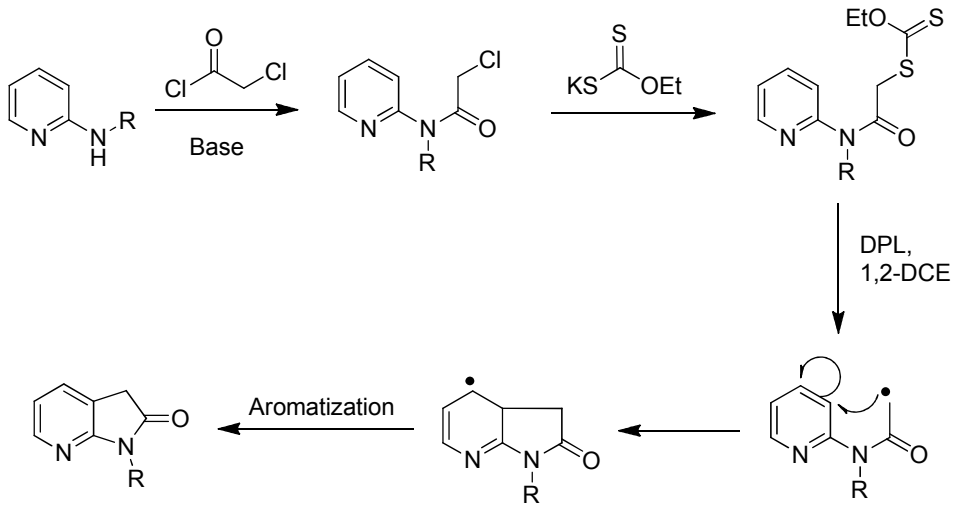
[106] Binot, G.; Quiclet-Sire, B.; Saleh, T.; Zard, S. Z. *Synlett*, **2003**, 382-386.
[107] Quiclet-Sire, B.; Zard, S. *Top. Curr.Chem.* **2006**, *264*, 201-236.
[108] Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard S. *Tetrahedron Lett.* **1994**, *35*,1719-1722.
[109] Gagosz, F.; Zard, S. *Tetrahedron Lett.* **2004**, *45*, 4631-4634.
[110] a) Bacque, E.; El Qacemi, M.; Zard, S. *Org. Lett.* **2004**, *6*, 3671-3674. b) El Qacemi, M.; Ricard, L.; Zard, S. *Chem. Commun.* **2006**, 4422-4424. c) Laot, Y.; Petit, L.; Zard, S. *Chem. Commun.* **2010**, *46*, 5784-5786. d). Laot, Y.; Petit, L.; Zard, S. *Org. Lett.* **2010**, *12*, 3426-3429. e) Laot, Y.; Petit, L.; Diem My Tran, N.; Zard, S. *Aust. J. Chem.* **2011**, *64*, 416-425.



Scheme III.7: Aromatic xanthate radical cyclization: formation of indene and indolines.

Pyridine derivatives are generally resistant to the attack by electrophiles, but not to radicals. Hence, a parallel strategy was applied for the construction of nitrogen containing heterocycles adjoining pyridine rings.

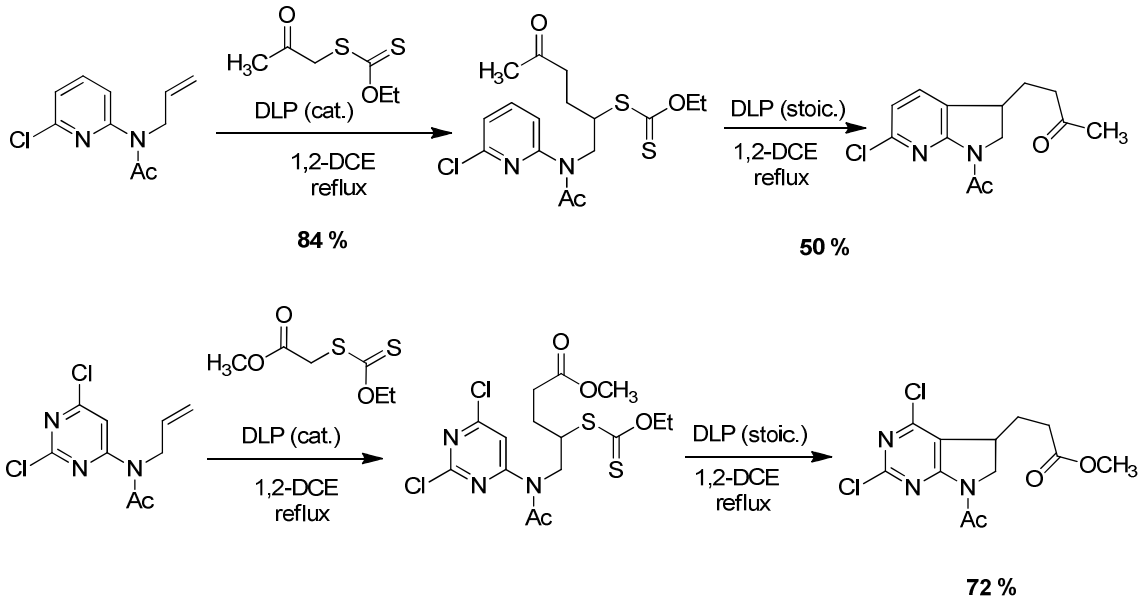
Prof. Zard *et al* reported that xanthate precursors, obtained from 2-aminopyridine derivatives by action of chloroacetyl chloride followed by addition of *O*-ethyldithiocarbonate, afforded azaoxindoles when exposed to lauroyl peroxide (DLP) in 1,2 dichloroethane (1,2-DCE) or chlorobenzene, (scheme III.8).[110b]



Scheme III.8: Synthesis of 7-Azaoxindoles.

Furthermore, Prof. Zard *et al* reported the same methodology using 2-allyl-amino substituted pyridine derivatives. For instance, 2-allylamino-6 chloropyridine was first protected by an acetyl group then treated with a xanthate to afford secondary xanthate intermediate which

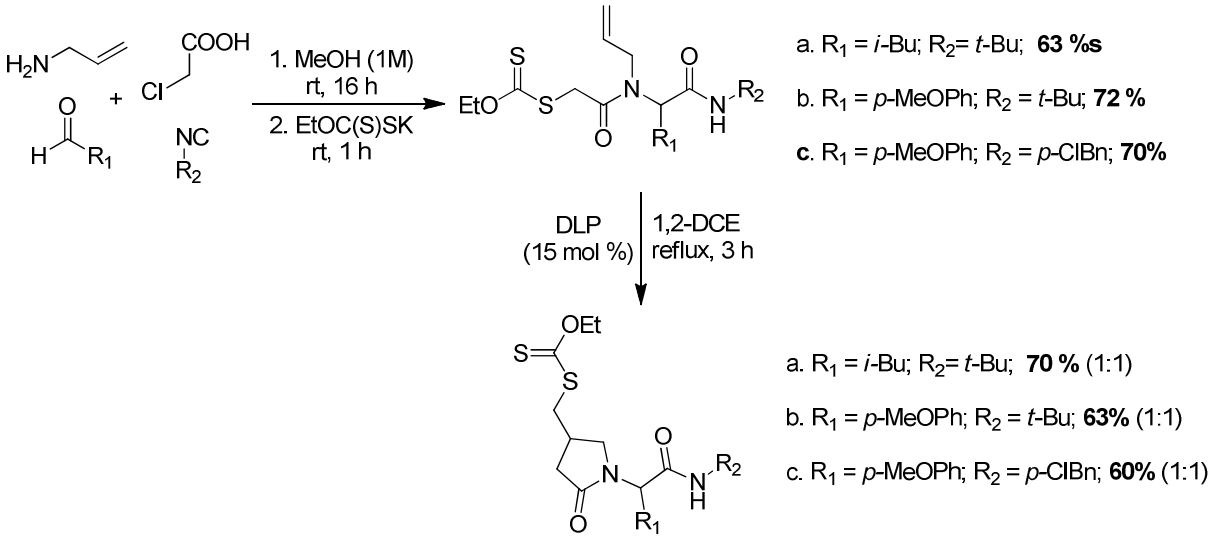
gave azapyridine derivatives (scheme III.9). The same strategy of xanthate radical cyclization was carried out on pyrimidine derivatives.



Scheme III.9: Synthesis of bicyclic aza-indole derivative.

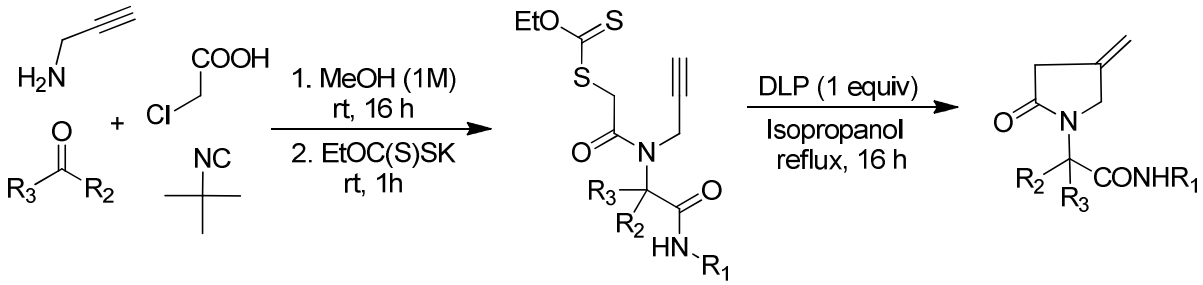
Our research group is interested in both radical and isocyanide chemistry. We have explored the formation of complex structures by combination of xanthate radical cyclizations and Ugi reactions.

When isovaleraldehyde, allylamine, chloroacetic acid and *tert*-butylisocyanide were allowed to react in methanol at room temperature, it gave an Ugi adduct, which upon the addition of potassium *O*-ethyl xanthate furnished the Ugi-xanthate adduct in good yield (scheme III.10). Heating this adduct under radical cyclization conditions (in refluxing 1,2-dichloroethane with 15 mol % DLP) gave a pyrrolidinone as a 1:1 mixture of diastereomers in a 70 % isolated yield. Various aldehydes and isocyanides were tested successfully with allylamine and chloroacetic acid to give the corresponding Ugi-xanthates, which underwent radical cyclization to form pyrrolidinone derivatives.[53]



Scheme III.10: Ugi/Xanthate radical cyclization to afford pyrrolidinone derivatives.

Furthermore, our research group extended this study of Ugi/xanthate cyclizations to propargylamine instead of allyl amine as the amine input in the Ugi reaction (scheme III.11).[110b] The reaction of chloroacetic acid, *tert*-butyl isocyanide, formaldehyde and propargylamine gave the Ugi adduct, which upon treatment with potassium *O*-ethylxanthogenate gave the Ugi-xanthate adduct. The latter was submitted to radical cyclization conditions in the presence of a stoichiometric amount of DLP in isopropanol to afford *exo*-methylene lactams in good yields.

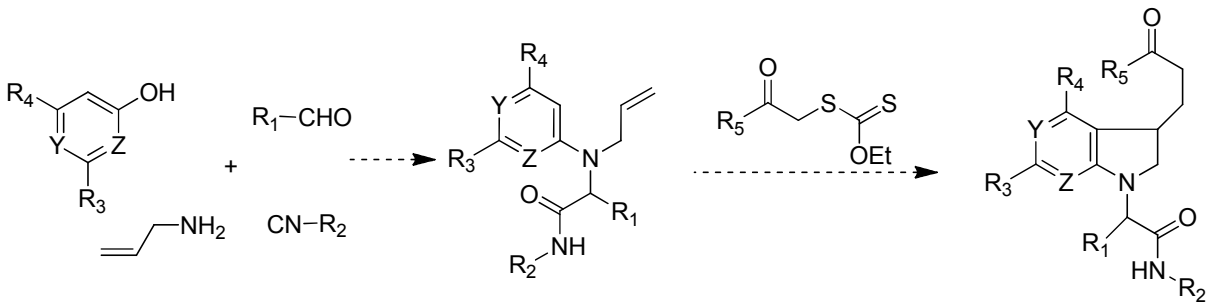


R_2R_3CO	Ugi adduct	lactam.
HCHO	72 %	68 %
EtCHO	70 %	88 %
$(CH_2)_4CO$	99 %	55 %

Scheme III.11: Synthesis of *exo*-methylene lactams.

In all these examples, the xanthate moiety was introduced *via* a nucleophilic substitution involving Ugi adducts. For this purpose, only *α*-chloroacetic acid was exploited as the acidic partner. However, these intramolecular post-condensations did not exploit the full potential of the xanthate radical transfer. In fact, compared to tin hydride chemistry, the reversible nature of the addition of radicals onto the thiocarbonyl group is associated with high yielding intermolecular couplings between radicals and alkenes.[111]

Our goal was to test the radical cyclization of Ugi-Smiles adducts combined with intermolecular xanthate transfer. For this purpose, allylamine will be used as the amine component in an Ugi-Smiles coupling. The xanthate could be then added *via* an intermolecular addition on the allyl moiety (scheme III.12).



Scheme III.12: Proposed synthetic strategy towards pyrrolidine fused system.

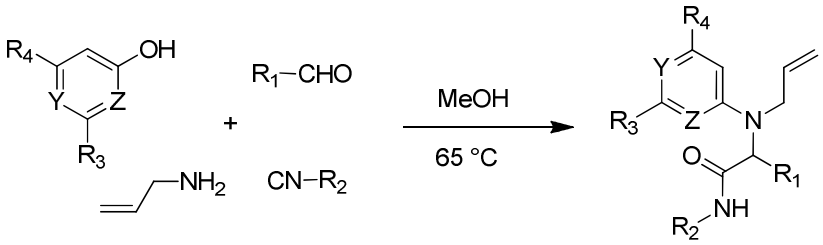
2. Results and Discussion.

a. Synthesis of starting materials

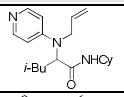
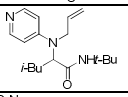
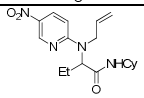
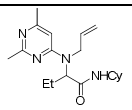
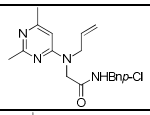
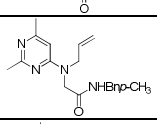
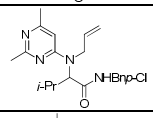
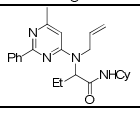
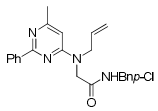
Ugi-Smiles adducts

We decided to investigate this strategy using hydroxy heterocycles such as pyridines and pyrimidines as precursors for further reaction with xanthates (scheme III.13). The Ugi-Smiles coupling was carried out using methanol as solvent to obtain the product in modest to good yields.[58a] The results are tabulated in table III-1.

[111] a) Zard, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 672-685.) Quiclet-Sire, B.; Zard, S. *Top. Curr.Chem.* **2006**, *264*, 201-236.

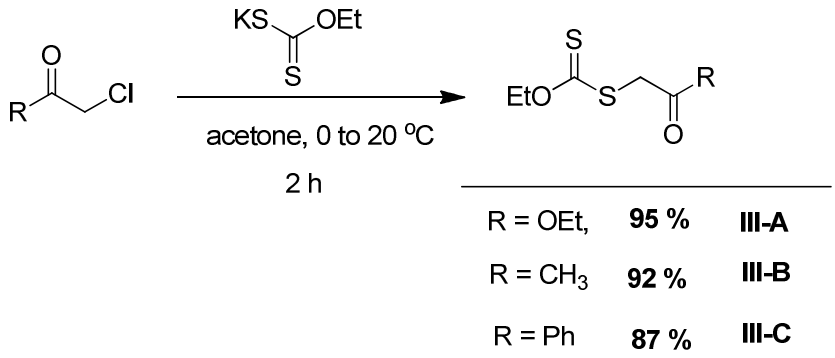


Scheme III.13: General Ugi-Smiles reaction.

Entry	ArOH	RCHO	RNC	Product		Yield (%)
1					**II.1**	69
2					**II.4**	43
3					**III.1**	41
4					**III.2**	38
5					**III.3**	29
6					**III.4**	23
7					**III.5**	68
8					**III.6**	61
9					**III.7**	37
10					**III.8**	60
11					**III.9**	44
12					**III.10**	35

Synthesis of various xanthates:

Xanthates were prepared according to standard methods using a nucleophilic substitution of the *O*-ethyl potassium xanthate.[112] As solution of the alkyl halide in acetone was added to a suspension of *O*-ethyl potassium xanthate in acetone at 0 °C and the reaction mixture was stirred for 2 h at room temperature.



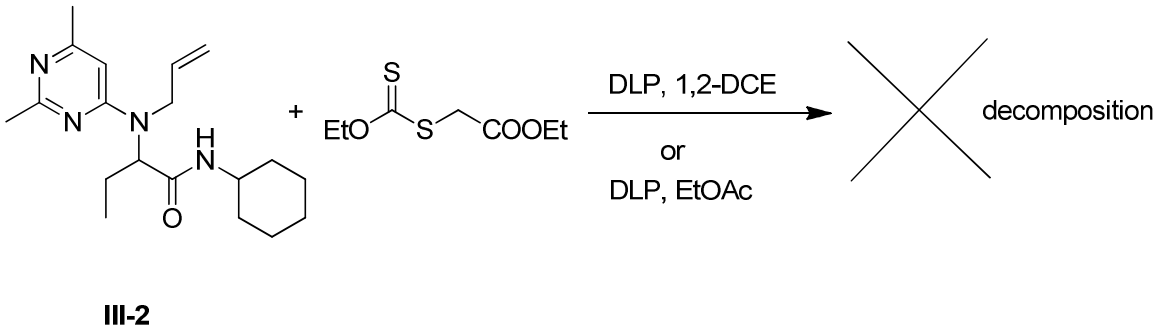
Scheme III.14: Synthesis of xanthates

b. Radical Cascades

In previous studies, Prof. Zard described xanthate additions on *N*-allyl amino -pyridines and -pyrimidines. Initially, these xanthates were added on alkenes using catalytic amount of DPL, to form a 1,2-adduct, which was isolated and characterized. These new derivatives were then cyclized under treatment with a stoichiometric amount of DLP in refluxing 1,2-DCE or ethyl acetate. Even if the yields were expected to be lower, we preferred to perform the whole sequence in a one pot procedure.

Initially, the radical cyclization of Ugi-Smiles adduct with ethyl 2-((ethoxycarbono-thioyl)thio)acetate was tested in 1,2-DCE with 10 mol% of DLP at reflux. The reagents remained unchanged after 2 h and decomposed when adding another 20 mol% of DLP under prolonged heating (8 h).

[112]a) Reyes-Gutierrez, P.; Torres-Ochoa, R.; Martinez, R.; Miranda, L. *Org. Biomol. Chem.* **2009**, *7*, 1388-1396. b) Cholleton, N.; Zard, S. *Tetrahedron Lett.* **1998**, *39*, 7295-7298. c) Boivin, J.; Carpentier, F.; Jrad, R. *Synthesis* **2006**, *10*, 1664-1672.

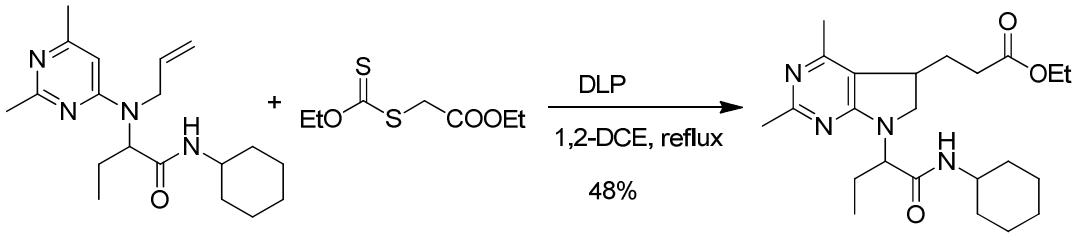


III-2

Scheme III.15: Xanthate addition on Ugi-Smiles adduct**.**

The reaction was then carried out with different amounts of DLP: 10 %, 20 % and 50 mol % were added every 90 minutes. But all these attempts failed and we only observed the decomposition of the starting materials.

A solution of the xanthate and the Ugi-Smiles adduct in 1,2-DCE was then refluxed for 5 min before addition of initiator, and 15 mol% of DLP was loaded to the reaction flask through the top of the condenser under argon flow. A new product was observed according to TLC analysis, an additional 15 mol% of DLP were added every 30 minutes till the starting Ugi-Smiles adduct disappeared. After adding 1.5 equivalent of DPL, the addition was stopped and the reaction mixture was stirred for 8 h at 85 °C. Under these conditions, the required cyclized product was isolated in 48 % yield as a 9:1 mixture of diastereomers (scheme III.16).



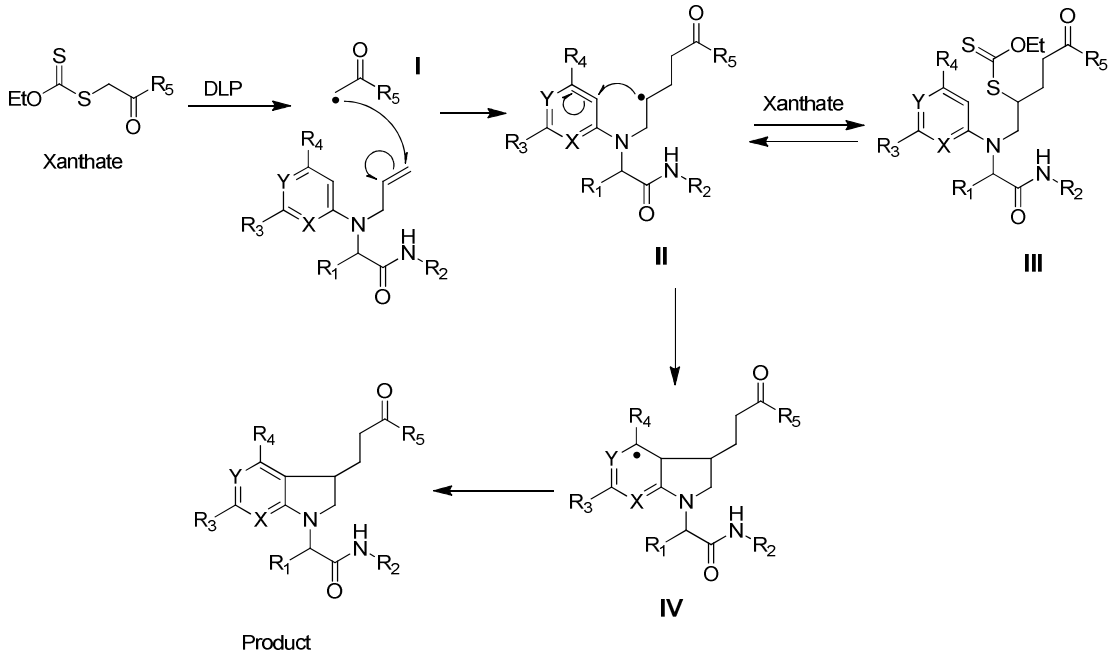
III-2 **III-11,** dr 9:1

Scheme III.16: Synthesis of pyrrolidino-pyrimidine from Ugi-Smiles adduct.

Plausible mechanism of reaction:

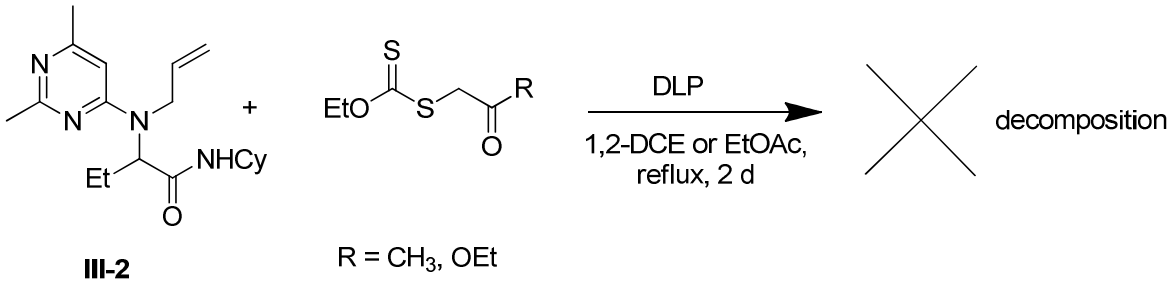
In this reaction, DLP initiates the reaction sequence by decomposition of the xanthate into the electrophilic radical **I**, which is trapped by the olefin (allyl group) present in the Ugi-Smiles adduct to give the intermediate **II**. This electron-rich radical can react with the starting xanthate to form the intermediate **III**.

III is slightly less reactive than the initial xanthate, so it accumulates in the reaction mixture, and when an extra amount of DLP was added to the reaction, it decomposed to give back **II**. This accumulation probably helps the chain process to consume the entire xanthate starting material. The intermediate electron-rich radical finally attacks the aryl ring to give **IV**, which further aromatizes through abstraction of a hydrogen atom by DLP (Scheme III.17).



Scheme III.17: Plausible mechanism of xanthate radical transfer-cyclization on Ugi-Smiles adduct.

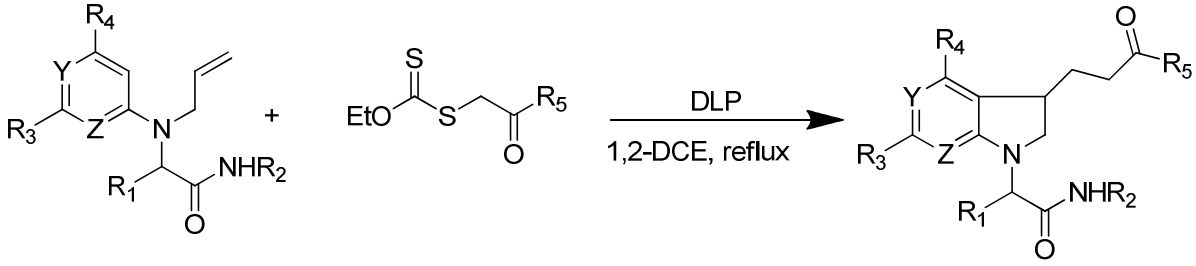
Various attempts to optimize these results were done: lower yields were obtained when using ethyl acetate instead of 1,2-DCE, and prolonged reaction heating had a negative effect, as decomposition occurred.

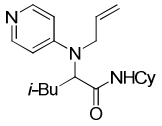
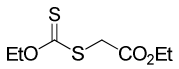
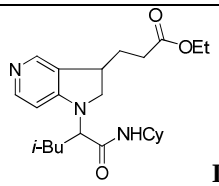
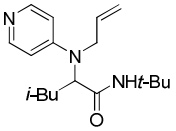
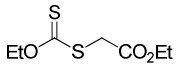
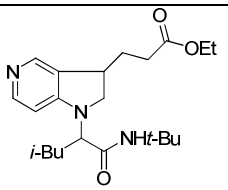
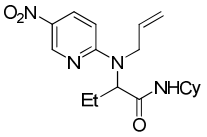
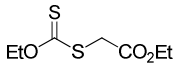
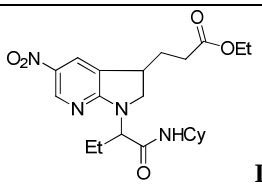
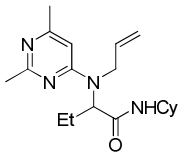
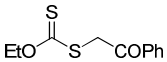
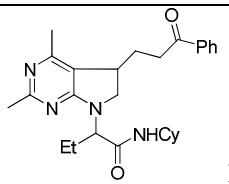
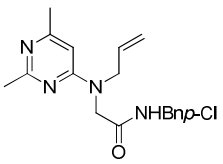
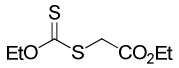
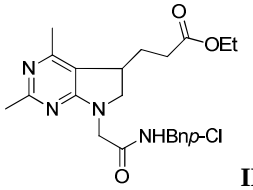
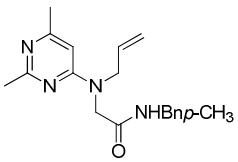
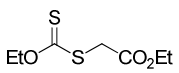
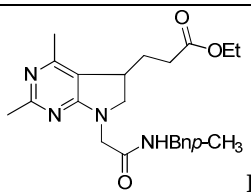


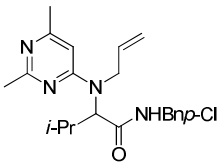
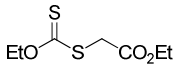
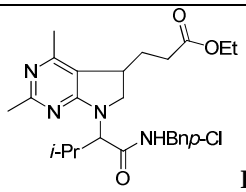
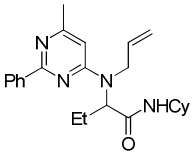
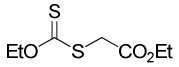
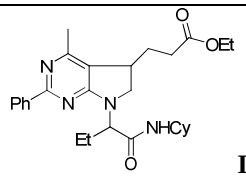
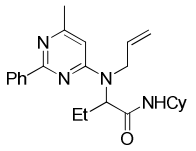
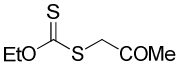
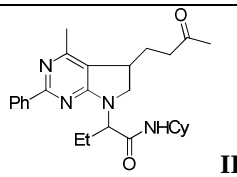
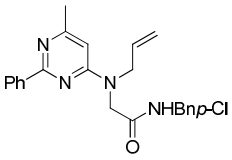
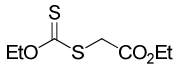
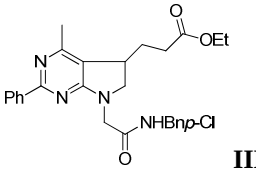
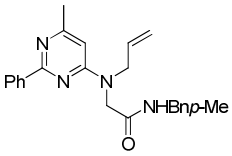
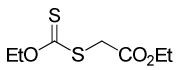
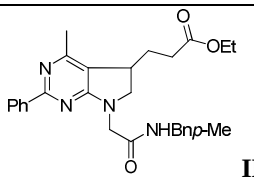
Scheme III.18: Optimization of xanthate radical transfer with Ugi-Smiles adduct.

To evaluate the scope of this cyclization, the reaction was performed on preformed Ugi-Smiles adducts. The results are displayed in the following table III.2.

Table III.2: Radical addition-Cyclization.



Entry	Ugi-Smiles adduct	Xanthate	Cyclized product	% Yield (Diastereomeric ratio)
1			 **III.12**	24 % (*dr* 4:1)
2			 **III.12**	27 % (*dr* 2:1)
3			 **III.14**	48 % (*dr* 3:1)
4			 **III.15**	34 % (*dr* 4:1)
5			 **III.16**	23 %
6			 **III.17**	18 %

7			 **III.18**	43 % (*dr* 2.3:1)
8			 **III.19**	55 % (*dr* 2.3:1)
9			 **III.20**	44 % (*dr* 1.5:1)
10			 **III.21**	19 %
11			 **III.22**	27 %

The Ugi-Smiles precursors were easily prepared and obtained in satisfying yields, while the cyclization gave moderate yields. Earlier studies by Zard group[110a] showed that 2-aminopyridines and 2-amino-5-methylpyridines successfully react to form 1,2-addition products with xanthate, but failed to cyclize to give indolizine. They were only obtained in the case of a chloro or a fluoro substituted heterocyclic core. Such substituents probably lower the electron density on the aromatic ring, favoring thus the addition of the radical.

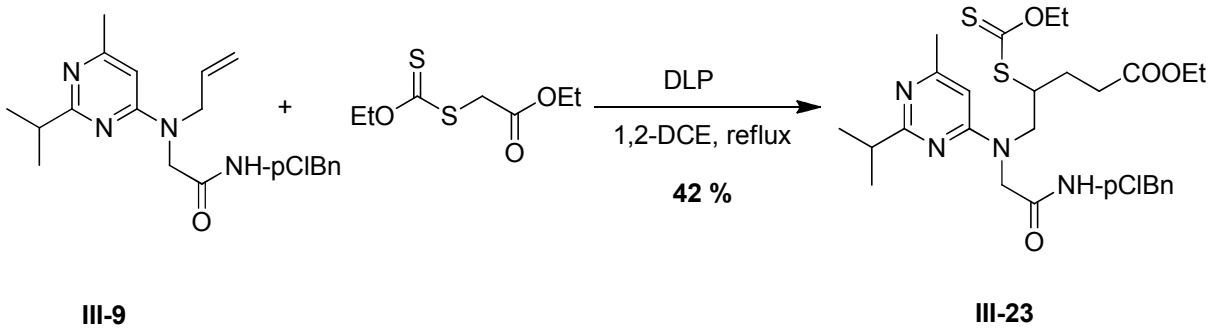
4-Amino pyridines are poorly efficient in this cascade, as yields do not exceed 30% (See table III.2 entry 1-2), except for 5-nitro-2-aminopyridine. In this case, the isolated yield is 48% (see Table III.2, Entry 3), probably due to the presence of the nitro group, which lowers the electron density on the aromatic ring.

Pyrimidines, due to their higher electrophilicity, are better starting materials for this sequence, giving yields over 50% with simple alkyl or aryl substituents on the heterocyclic core (Table III.2, Entry 7-8).

We observed the formation of a mixture of diastereomers during the radical cyclization. The first center was created during the Ugi-smiles coupling and the second formed during the

radical process. The selectivity is difficult to explain since there is no good control of the stereoselectivity by the first centre (see Table III.2, Entries: 1-4, 7-9).

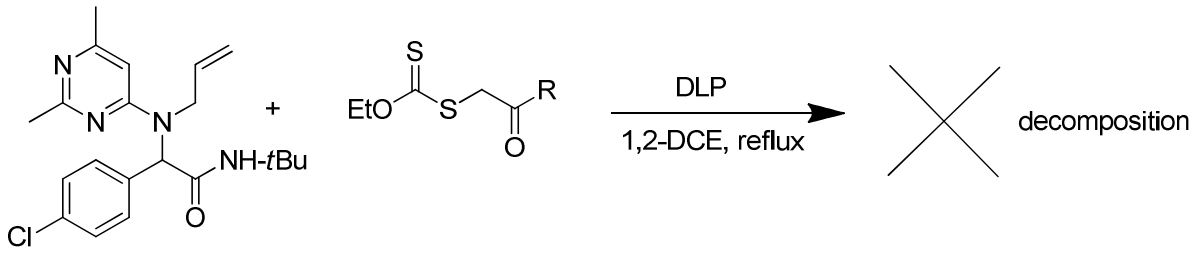
The Ugi-Smiles adduct **III.9** obtained from formaldehyde turned out to be poorly efficient in this cascade. In this peculiar case, the intermediate product **III-23** could be isolated in 42% yield.



III-9 **III-23**

Scheme III.19: Radical transfer reaction in Ugi-Smiles adduct obtained from formaldehyde.

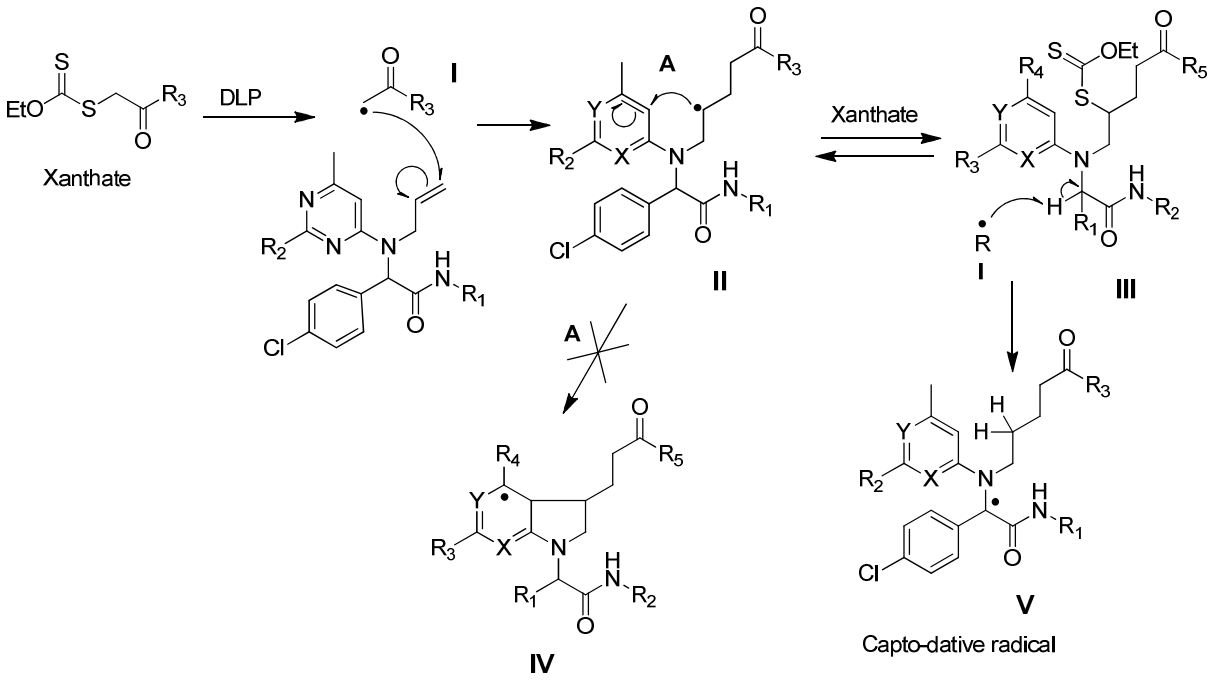
Ugi-Smiles adducts derived from aromatic aldehyde failed to give any pyrrolidino pyridine or pyrimidine. Various starting materials were tested, as shown in scheme III.20, but in all these cases, the reaction mixture rapidly decomposed.



III-10

Scheme III.20: Xanthate radical cyclization of Ugi-Smiles adducts.

One possible explanation could be that an intermolecular S_H2 reaction could occur, after the first radical transfer, to give benzylic radical **V**, which is quite stable due to its *capto-dative* nature and probably too hindered to further evolve.



Scheme III.21: Plausible mechanism for xanthate radical transfer in case of benzylic Ugi-Smiles adduct.

c. Conclusion:

The reported two-step cascade represents the shortest method for synthesis of pyrrolidino-pyridines and pyrimidines. This work is a new example of the potential of radical chemistry in Ugi post-condensations. This method gives a straightforward access to important biological active scaffolds such as adenosine receptor (AR)[113] and corticotropin-releasing factor 1 receptor antagonists.[114]

III. Spirooxindole Synthesis

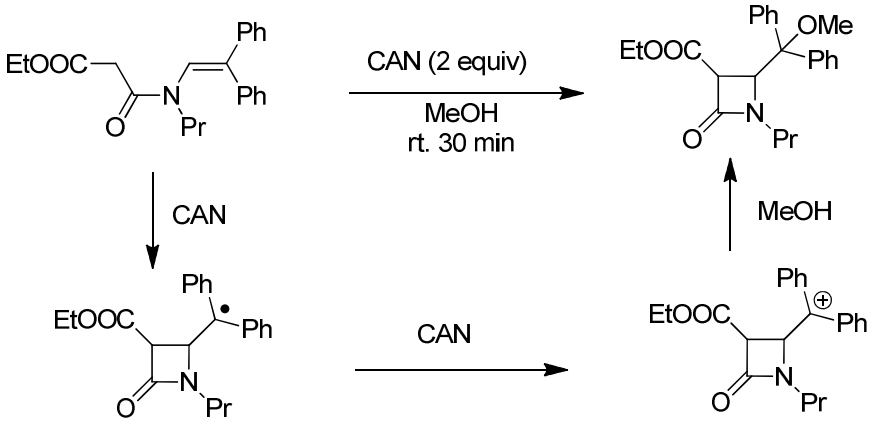
We have studied radical reactions in which radicals were generated by xanthate transfer. Another way to form radicals consists of removing an electron from an anion (oxidation) or adding an electron to a cation (reduction). This type of electron transfer reaction can be done by different transition metals, and their salts such as manganese (III), copper (II), iron (III), cerium (IV) and lead (IV). This field is extremely broad; we could discuss here only a few points.[115]

[113] Muller, C.; Geis, U.; Grahner, B.; Lanzner, W.; Eger K.; *J. Med. Chem*. **1996**, *39*, 2482-2491.
[114] Aso, K.; Kobayashi, K.; Mochizuki, M.; Kanzaki, N.; Sako, Y.; Yano T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2365–2371.
[115] Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.*, **1994**, *94*, 519-564.

1. SET (Single electron transfer) processes

The oxidation reactions using cerium (IV) like CAN (ceric ammonium nitrate)[116] reagent can generate carbon radicals, and its applications involve intermolecular and intramolecular radical addition to olefins.[117]

For example, the reaction of enamides with CAN in methanol affords functionalized β-lactams through a 4-*exo*-ring cyclizalion of *α*-carbamoyl alkyl radicals. Then, a second oxidation occurs on the benzyl radical, forming a cation trapped by methanol (Scheme III.22).[118]

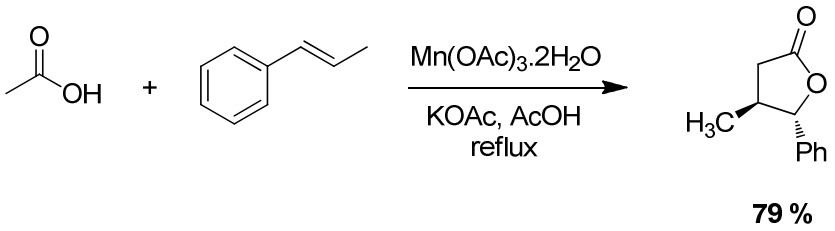


Scheme III.22 : β-lactams formation through radical-oxidation from CAN.

Manganese (III) acetate is a one-electron oxidizing agent, probably the most common one that is particularly effective for the oxidation of enolizable carbonyl compounds.

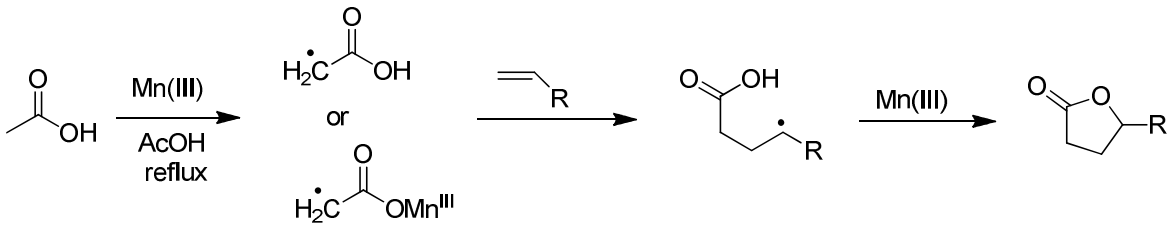
In 1968, Heiba and Dessau[119] described the first manganese (III) oxidative radical addition of acetic acid on alkenes (scheme III.23). At the same time, a similar work was described by Bush and Finkbeiner.[120]

[116] Nair, V.; Deepthi, A. *Chem. Rev.*, **2007**, *107*, 1862-1891.
[117] a) Baciocchi, E.; Ruzziconi, R. *Synth. Comm.* **1988**, *18*, 1841-1846. b) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem* **1991**, *56*, 4772-4778. c) Nair, V.; Mathew, J.; Radhakrishnan, K. *Chem. Soc. Perkin Trans.* **1996**, 1487-1492. d) Roy, S.; Mandal, P. *Tetrahedron* **1996,** *52*, 2193-2198. e) Roy, S.C.; Mandal, P.K. *Tetrahedron* **1996,** *52*, 12495-12498. F). Belli Paolobelli, A.; Ruzziconi, R. *J. Org. Chem.* **1996**, *61*, 6434-3437.
[118] D'Annibale, A.; Pesce, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.*, **1997**, *38*, 1829-1832.
[119] Heiba, E. I., Dessau, R.M.; Koehl, W. *J. Am. Chem. Soc.*, **1968,** *90*, 5905-5906.
[120] Bush, J.; Finkbeiner, H. *J. Am. Chem. Soc*., **1968**, *90*, 5903-5905.



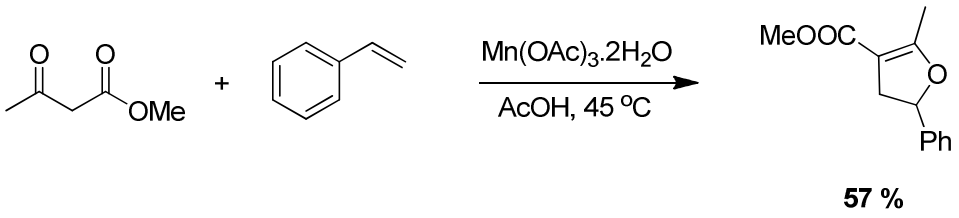
Scheme III.23: Oxidative addition of acetic acid to olefin, via Mn(III).

The reaction mechanism generally proposed involves the gain of an electron by manganese acetate in refluxing acetic acid, generating an acetyl radical which is attacked by the terminal double bond, creating an intermediate secondary radical. The latter can be oxidized by a second equivalent of manganese acetate, thus allowing the formation of the final γ-lactone.



Scheme III.24: Mechanism of oxidative addition of acetic acid to olefin, via Mn(III).

In 1974, Heiba extended this work to β-keto esters and dicarbonyl compounds, these analogues could be oxidized to radicals in acetic acid at lower temperatures (25-70 °C).

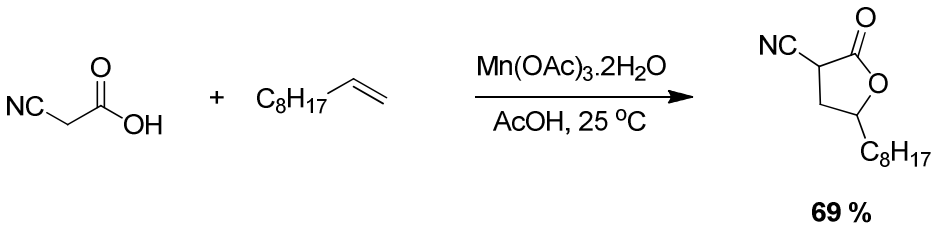


Scheme III.25: Radical generation in β-ketoester, via Mn(III).

This chemistry has been further extended by different groups. In 1984, Corey and Kang have reported the oxidative cyclization of β-unsaturated keto acids.[121] In 1985, Snider *et al* have

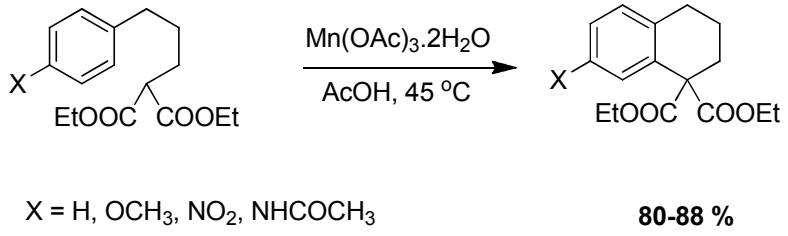
[121] Corey, E. J.; Kang, M. *J. Am. Chem. Soc*., **1984**, *106*, 5384-5385.

described the same reaction with β-keto-unsaturated esters,[122] while Fristad *et al* have studied the cyclizations of cyanoacetic acid and malonic acids with olefins.[123] Due to the difference of acidity of the enolizable protons between acetic acid and the cyanoacetic acid, the cyclization conditions are very different. Since cyano derivative easily enolizes, the cyclization occurs at room temperature.



Scheme III.26: Lactone synthesis from cyanoacetic acid, via oxidative radical addition of Mn(III).

Citterio *et al* have extensively studied the oxidative aromatic cyclization. For example, the cyclization of arylated malonates leads with high yields to the corresponding tetrahydro-naphthalene.[124].



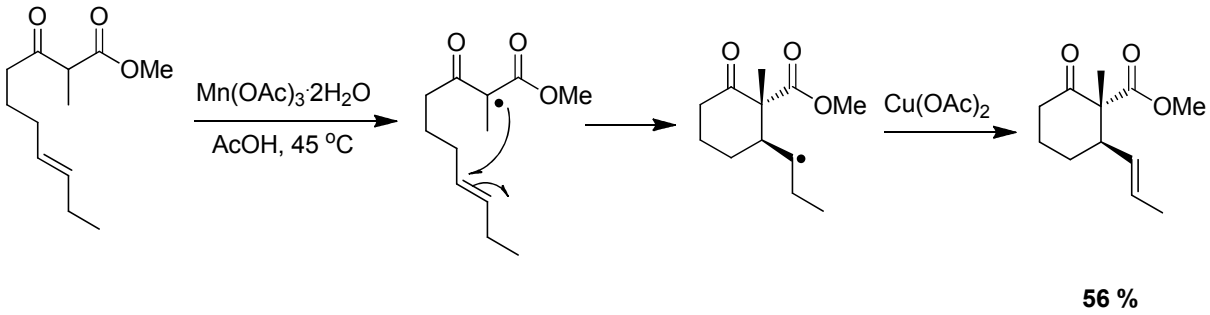
Scheme III.27: Radical oxidative cyclization on aromatic ring**.**

In the early seventies, Heiba and Dessauwere discovered that the primary and secondary radicals are not easily oxidized by manganese acetate (very slow reaction).[125] They showed that, copper acetate (II) oxidizes secondary radicals around 350 times faster than manganese acetate (III). The copper (II) is a less powerful oxidant than manganese (III) (redox oxidation potential for Cu(II) is 0.16V and for Mn(III) it is 1.51V), but Cu(II) acts very rapidly with the radicals.[126]

[122] Snider, B.; Mohan, R.; Kates, S.. *J. Org. Chem*., **1985**, *50*, 3659-3361.
[123] Ernst, A.; Fristad, W. *Tetrahedron Lett.*, **1985**, *26*, 3761-3764.
[124] Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L.; Santi, R. *J. Org. Chem*., **1989**, *54*, 2713-2718.
[125] a) Heiba, E.; Dessau, R. *J. Am. Chem. Soc*., **1971**, *93*, 524-527. (b) Heiba, E.; Dessau, R. *J. Am. Chem. Soc*. **1972**, *94*, 2888-2889.
[126] Kochi, J. "Oxidation and Reduction reactions of free radicals and metal complexes" in Free Radicals, **1973**, vol.1, *Wiley interscience*, New York, pp. 591-683.

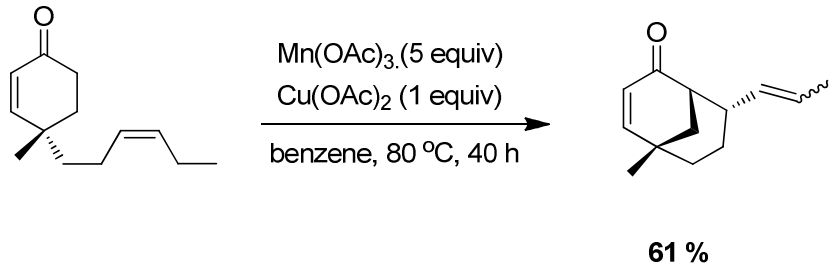
Using both oxidizing agents, the process allows the fast oxidation of the enol by Mn(III) and of the final radical by copper (II), providing a kinetic control on the entire system with less by-product formation (schemes III.28, III.29).

Two equivalents of manganese acetate are used with 0.1-1 equivalent of copper acetate, to form the cyclohexanone in 56 % isolated yield.



Scheme III.28: Radical oxidative cyclization using $Mn(OAc)_3/Cu(OAc)_2$.

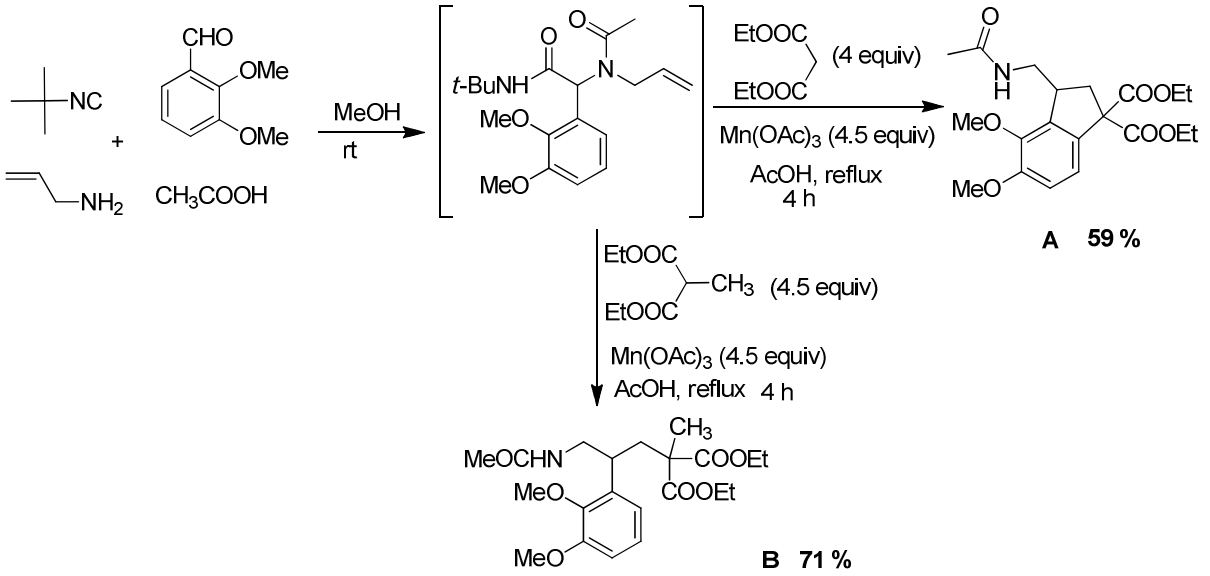
Snider *et al* has shown that appropriately substituted cyclohexenones[127] could form bridged systems, under this oxidizing system $Mn(OAc)_3/Cu(OAc)_2$.



Scheme III.29: Radical oxidative cyclization in cyclohexanone using $Mn(OAc)_3/Cu(OAc)_2$.

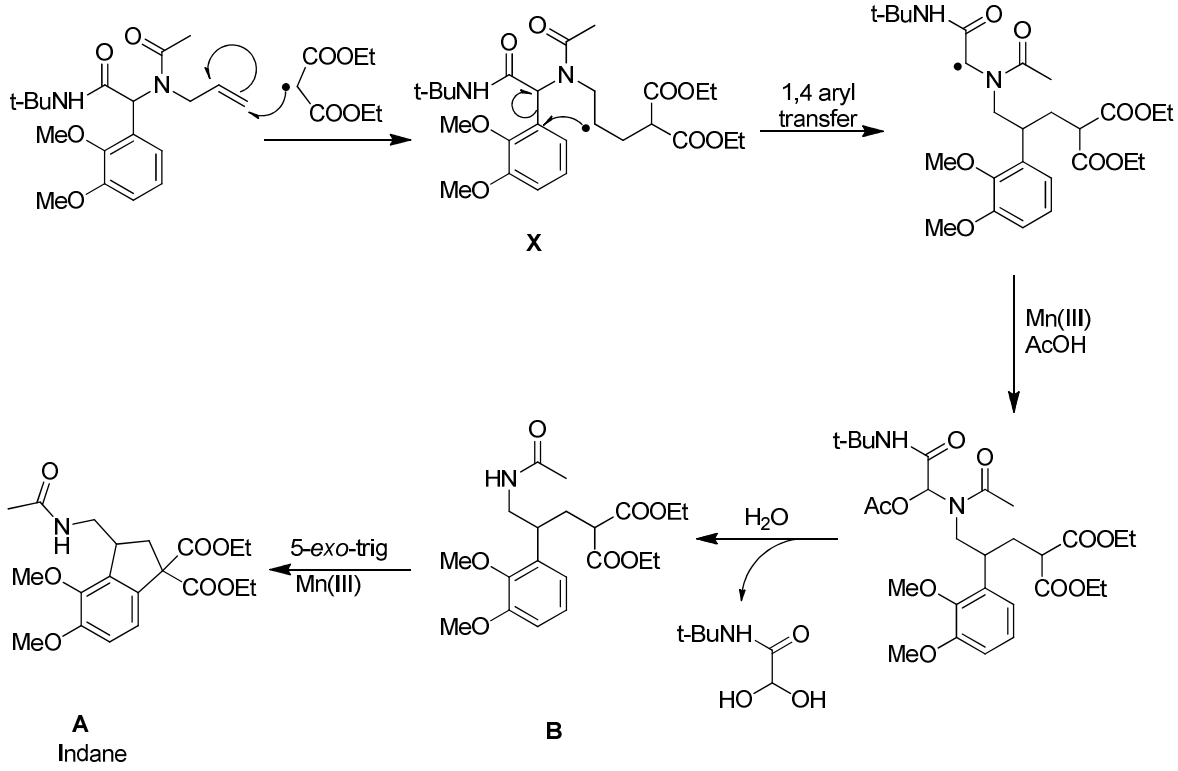
Recently, our research group reported radical chemistry coupled with multicomponent processes,[53,100c,100e] involving a Mn(III) radical oxidative coupling of malonates of various Ugi adducts.[100a] Indanes and δ-aminomalonates were obtained in one-pot using an aromatic aldehyde as starting material in the Ugi reaction.

[127] Snider, B.; Han, L.; Xie, C. *J. Org. Chem*., **1997**, *62*, 6978-6984.



Scheme III.30: Radical oxidation in Ugi reaction to form indane and δ-aminomalonate.

Mn(III) with malonate forms the corresponding radical which attacks the allyl group of the Ugi adduct to form a new radical **X**. The latter undergoes a 1,4 aryl transfer[128] to form a peptidyl radical. It is then oxidized with Mn(III) and cleaved in acetic acid to give δ-aminomalonate **B,** and if there is no substituent on the malonate moiety, it cyclizes to the corresponding indane **A**.



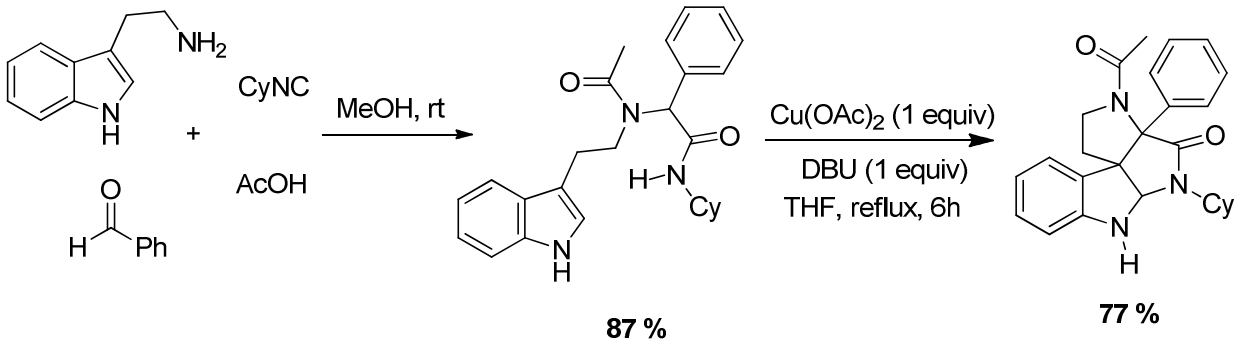
Scheme III.31: Proposed mechanism for indane and δ-aminomalonate.

[128] a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649-9667. b) Palframan, M.; Tchabanenko, K.; Robertson, J. *Tetrahedron Lett*. **2006**, *47*, 8423-8425.

2. Previous results concerning spiroindoline synthesis

More recently, our research group examined different oxidative couplings of indole Ugi adducts in order to further develop radical post-condensations.[129] This strategy gave us spiroindoline or spiroindolenine derivatives under aerobic oxidation.[130]

For this purpose, tryptamine and benzaldehyde were selected as Ugi starting materials. When the resulting Ugi adduct was heated with one equivalent of copper acetate in acetonitrile in the absence of base, the cyclized product was isolated in 5 % yield. When one equivalent of DBU was added to the reaction mixture, the yields were slightly improved (11 % isolated yield). Different solvents were tested for this purpose and THF turned out to be the best choice as the product was isolated in 77 % yield.



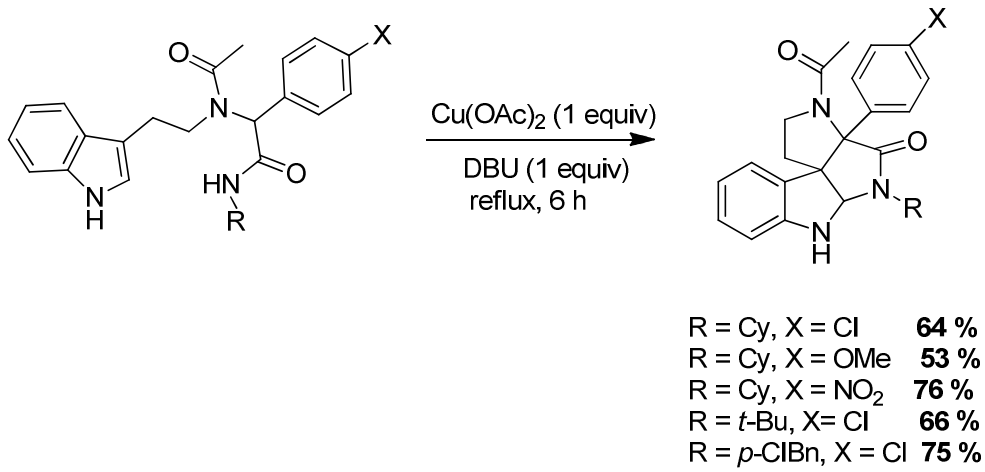
Scheme III.32: Oxidative radical cyclization reaction to form spiroindoline.

In this reaction, the use of one equivalent of copper acetate (Cu(II)) is not required, since it is known that Cu(I) can be oxidized by O_2 to Cu(II). Indeed, the desired polycyclic compound could be obtained using either 0.5 or 0.3 equivalent of copper salt, but the yields were slightly lower in these cases (around 10-15 % lower).

The scope of this oxidative cyclization process was evaluated on different types of Ugi partners keeping tryptamine as the starting amine.

[129] El Kaïm, L.; Grimaud, L.; Menes-Arzate, M.; Miranda, L.*Chem. Commun.*, **2011**,*47*, 8145-8147.

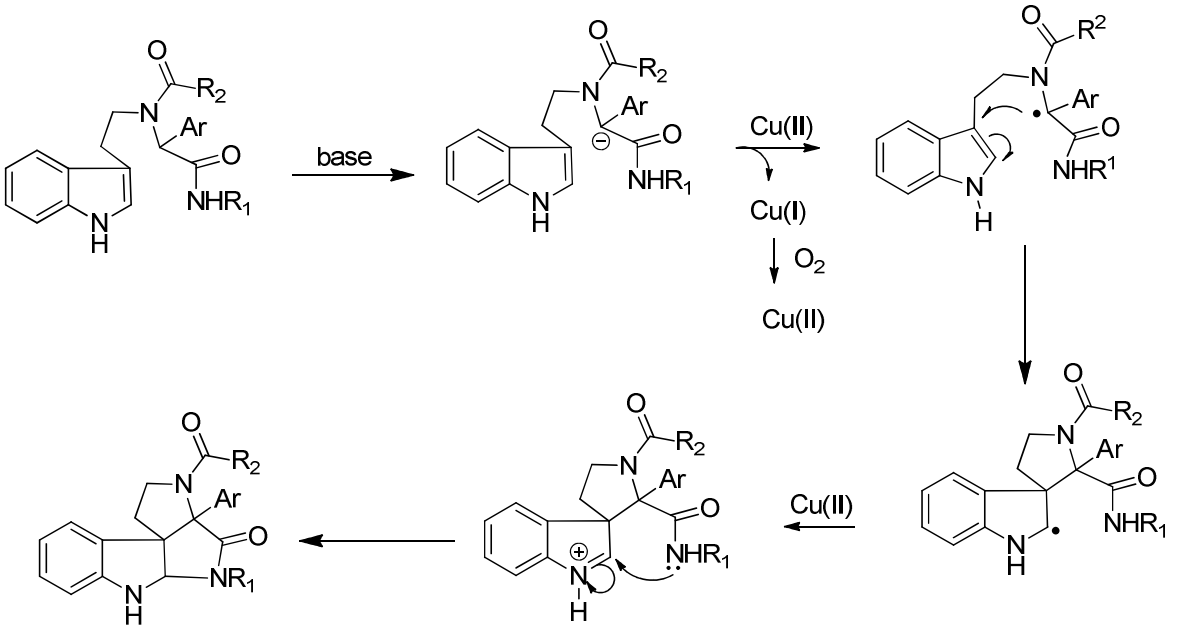
[130] a) Zhan, B.; Thompson A. *Tetrahedron* **2004**, *60*, 2917-2935; b) Schultz, M.; Sigman M. *Tetrahedron* **2006**, *62*, 8227-8241; c) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329-2363. d) Punniyamurthy, T.; Rout, L. *Coord. Chem. Rev.* **2008**, *252*, 134-154; e) Samec, S.; H. Ell, A.; Backvall, -E. *Chem. Eur. J.* **2005**, *11*, 2327-2334. f) Gamez, P.; Aubel, P.; Driessen, W.; Reedijk J. *J. Chem. Soc. Rev*. **2001**, 30, 376-385.



Scheme III.33: Scope of oxidative process for spiroindolines.

The presence of an aliphatic substituent at the peptidic position (by use of an aliphatic aldehyde in the Ugi coupling) inhibited the reaction and no cyclization occurred. However, aromatic substituents bearing either electron-donating or electron-withdrawing groups were introduced successfully at this position.

The reaction mechanism probably involves the oxidative generation of a peptidyl radical triggered by copper (II) salts, which could add onto the sp^2-carbon of the indole ring (5-*exo*-trig cyclization) followed by subsequent oxidation of the α-aminoalkyl radical. This last oxidation step forms an iminium which is trapped by the vicinal amide moiety (Scheme III.34).



Scheme III.34: Proposed reaction mechanism to form spiroindoline.

In this reaction only one diastereomer was predominantly formed, probably because of the rigid polycyclic ring formation. The structures of spiroindoline were confirmed by X-ray analyses (Figure III.1).

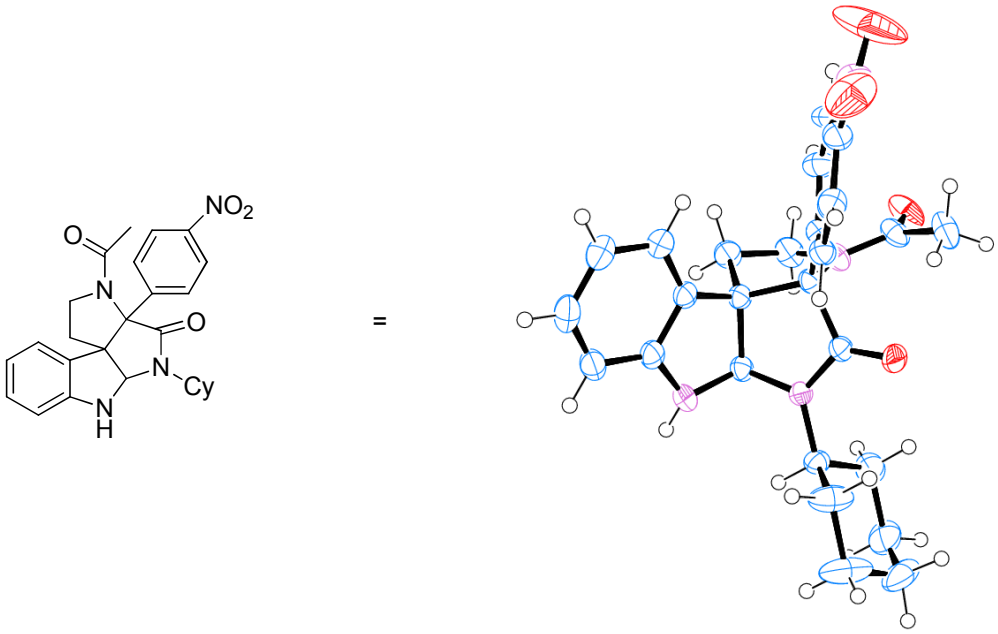
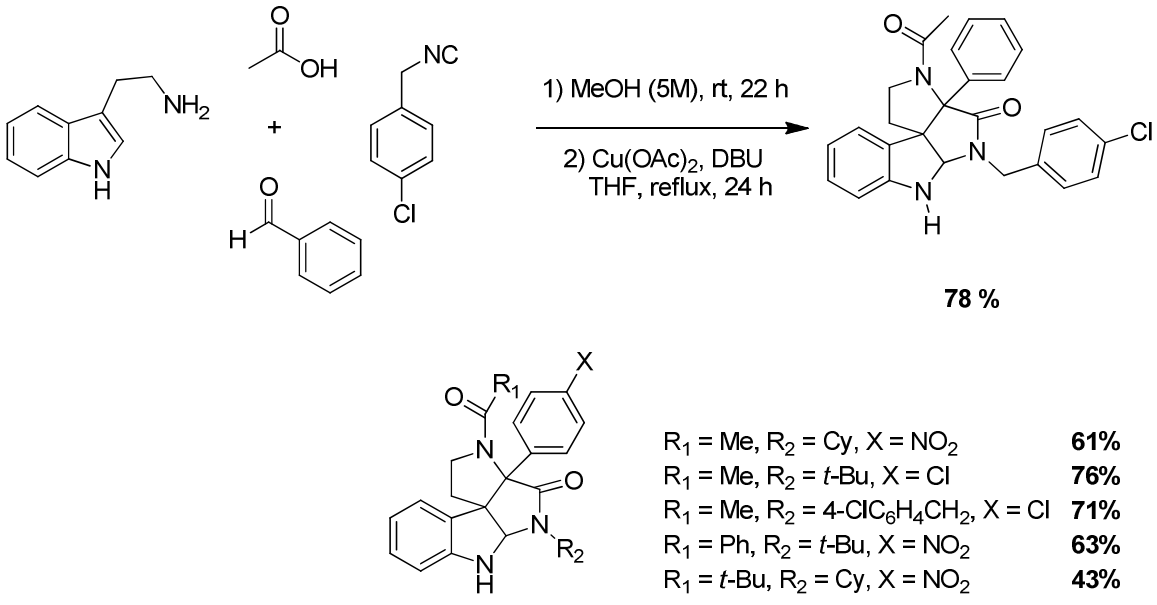


Figure III.1. X-Ray analysis of spiroindoline.

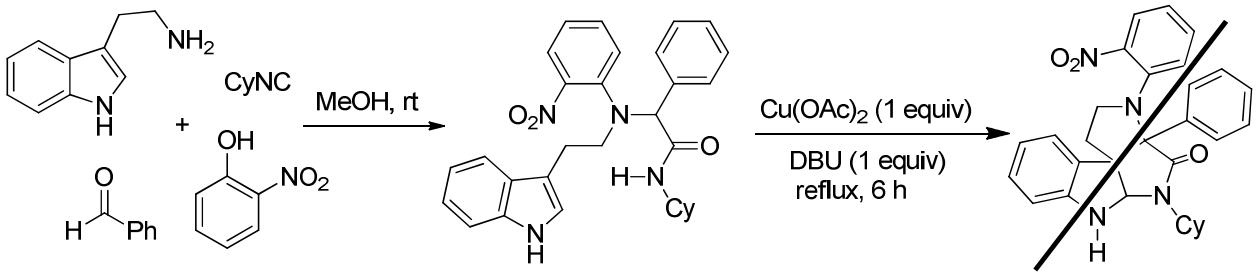
Moreover, the whole reaction sequence could be performed in one-pot. The first step was carried out in a highly concentrated medium (5M in methanol), followed by dilution of the reaction mixture with THF, base, and addition of copper (II).



Scheme III.35: One-pot synthesis of spiroindolines.

This simple procedure gives complex final structures with four points of diversity due to the Ugi coupling. In this reaction, low cost and mild oxidative reagent like copper acetate was used.

Furthermore, this type of oxidative cyclizations was tested on Ugi-Smiles adduct in which tryptamine was used as the amine partner. Unfortunately, the Ugi-Smiles adduct failed to give any cyclized product.

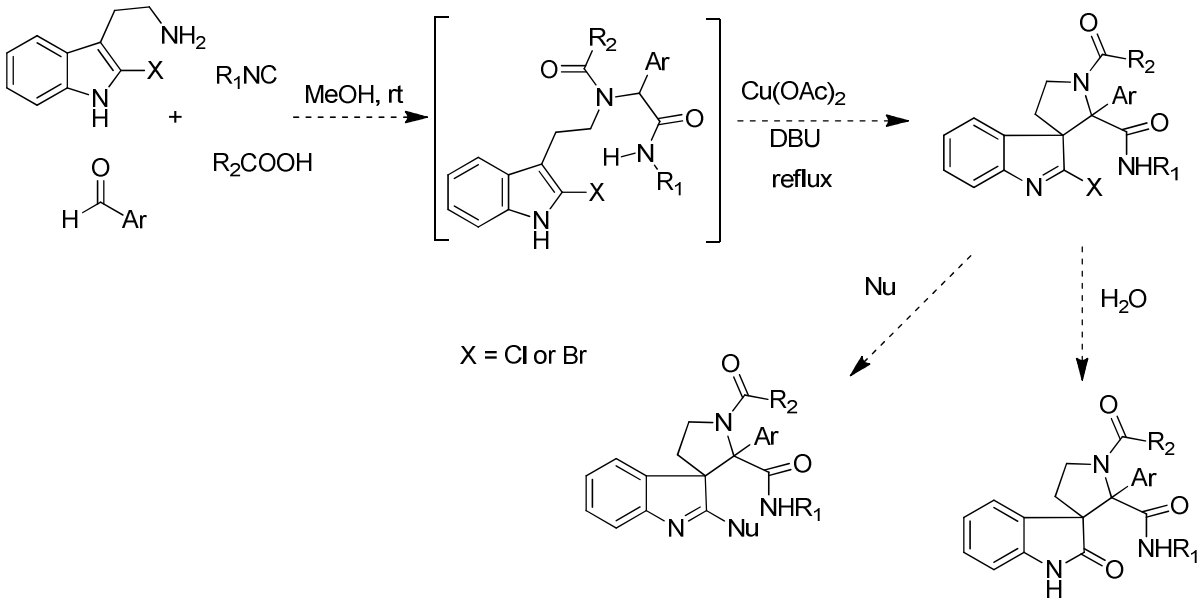


Scheme III.36: synthesis of spiroindolines using Ugi-Smiles coupling.

3. Spirooxindole synthesis

a. Presentation of the project

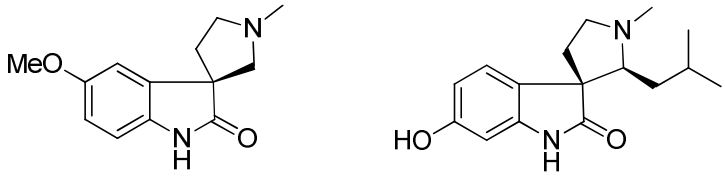
A similar strategy could be imagined for spirooxindole scaffolds using 2-chlorotryptamine as the starting Ugi amine partners (scheme III.37).



Scheme III.37: Proposed pathway to obtain spirooxindoles

b. Biological activities

3,3'-Pyrrolidinyl-spirooxindole scaffolds (some prominent examples are shown in scheme III.38) represent a pharmaceutically valuable class of biologically active compounds, which can be isolated from plants and fungi.[131] These natural products have various biological activities such as anticancer properties, contraceptive action,[132] and antimigraine activity.[133]



Horsfine
(analgesic effects)

Elacomine
(antitumour agents)

Scheme III.38: Bioactive natural products containing the 3,3'-pyrrolidinyl-spirooxindole scaffold.

Deppermann *et al*[134] reported the total synthesis of Horsfiline from Cbz-protected pyrolledine-2-carboxylic acid, which was coupled with aniline derivative with PCl_5 to give the corresponding amide. The α-arylation of this amide with [Pd]-PEPPSI-catalyst system at 110 °C gave the spirooxindole **A**, a known precursor for Horsfiline.[135]

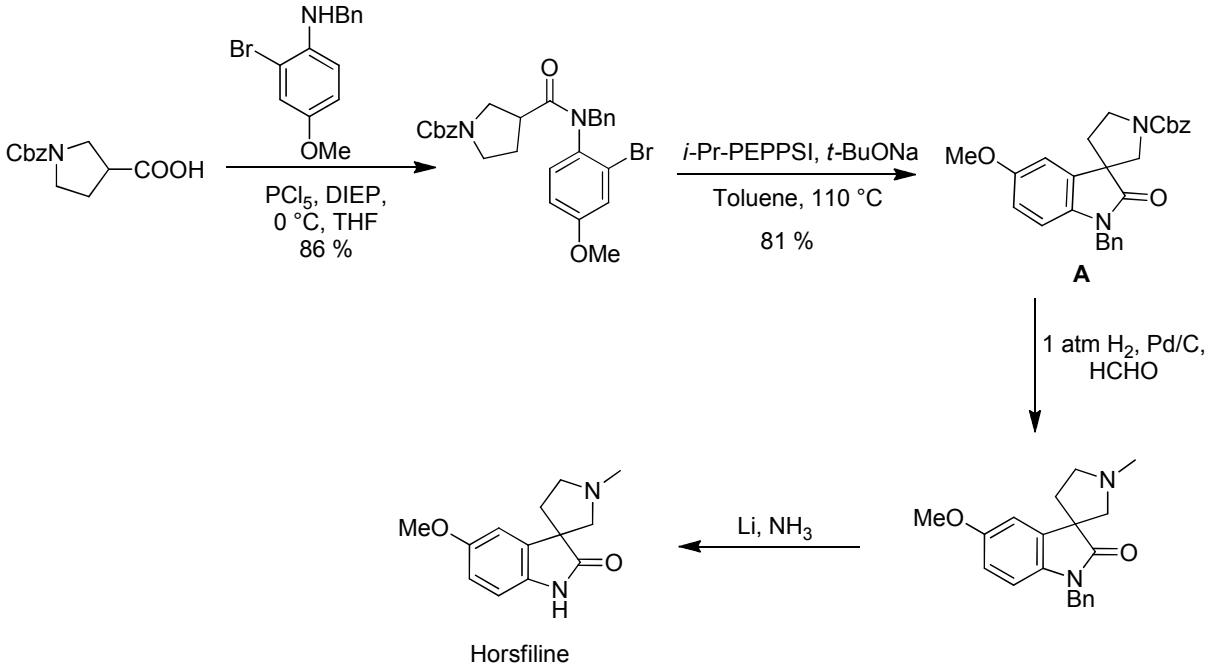
[131] a) Galliford, C.; Scheidt, K. *Angew. Chem., Int. Ed*. **2007**, *46*, 8748-8758. (b) von Nussbaum, F. *Angew. Chem., Int. Ed*. **2003**, *42*, 3068-3071.

[132] Fensome, A.; Adams, W.; Adams, A.; Berrodin, T.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J.; Hudak, V.; Marella, M.; Melenski, E.; McComas, C.; Mugford, C.; Slayden, O.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R.; Wrobel, J. E. *J. Med. Chem*. **2008**, *51*, 1861-1873.

[133] Stump, C.; Bell, I.; Bednar, R.; Bruno, J.; Fay, J.; Gallicchio, S.; Johnston, V.; Moore, E.; Mosser, S.; Quigley, A.; Salvatore, C.; Theberge, C.; Zartman, C.; Zhang, X.; Kane, S.; Graham, S.; Vacca, J.; Williams, T. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 214-217.

[134] Dippermann, N.; Thomanek, H.; Prenzel, A.; Maison, W.; *J. Org. Chem.* **2010**, *75*, 5994-6000.

[135] a) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun*. **1992**, 1767-1769. b) Bascop, S. I.; Sapi, J.; Laronze, J. Y.; Levy, *J. Heterocycles* **1994**, 38, 725-732. c) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979-1992. d) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1-4. e) Lakshmaiah, G.; Kawabata, T.; Shang, M. H.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 16991704. f) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175-1181. g) Cravotto, G.; Giovenzani, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447-8453. h) Kumar, U. K. S.; Illa, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193-4196. i) Lizos, D.; Tripoli, R.; Murphy, *J. A. Chem. Commun*. **2001**, 2732-2733. j) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175-9178. k) Lizos, D.; Murphy, J. *Org. Biomol. Chem.* **2003**, *1*, 117-122. l) Chang, M.; Pai, C.; Kung, Y. *Tetrahedron Lett.* **2005**, *46*, 8463-8465. m) Murphy, J.; Tripoli, R.; Khan, T.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287-3289. n) Trost, B. M.; Brennan, M. K. *Org. Lett.* ***2006***, *8*, 2027-2030. o) Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. P. *Synlett* ***2009***, 2997-2999. p) Reddy, V. J.; Douglas, C. *J. Org. Lett.* **2010**, *12*, 952-955. q) Thomson, J. E.; Kyle, A. F.; Ling, K. B.; Smith, S. R.; Slawin, A. M. Z.; Smith, A. D. *Tetrahedron* **2010**, *66*, 3801-3813.



Scheme III.39: Total synthesis of Horsfiline.

A large number of synthetic methodologies have been reported for the preparation of spirooxindole natural products,[136] a key point in each synthesis is the construction of the spirocyclic scaffold with its quaternary carbon center. Most of the strategies rely on indole precursors for the construction of the key structural element, and only a limited number of procedures construct the indole itself.

Herewith, the 3,3'-pyrrolidinyl-spirooxindoles could result from a cascade involving Ugi coupling of 2-halotryptamines, followed by oxidative radical cyclization with Cu(II).

C. Results and Discussion

Synthesis of the 2-chlorotryptamine:

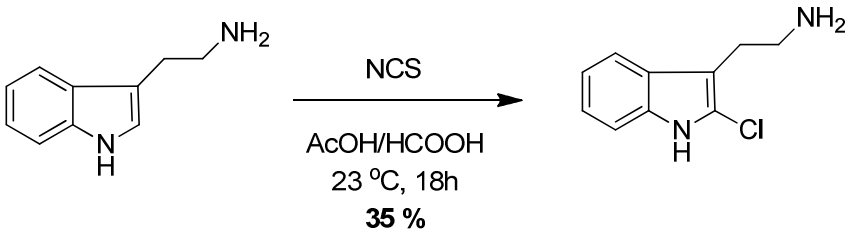
Although 2-halo-tryptamines are potentially useful intermediates in indole alkaloid synthesis, only few reports mention the preparation of 2-chloro- and 2-bromotryptamine.[137] In 2003, David Horne *et al* reported that tryptamine hydrochloride salt undergoes efficient regioselective chlorination at the 2-position using *N*-chlorosuccinimide in a 10:3 acetic acid/formic acid solution (23 °C) to form 2-chlorotryptamine in 70 % isolated yield.[138]

[136] a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem*. **2003**, 2209-2219. (b) Maison, W. *Targets Heterocycl. Syst*. **2005**, *9*, 87-113. (c) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003-3025.

[137] Iodotryptamine has been reported: (a) Kline, T. *J. Heterocycl. Chem.* **1985**, *22*, 505-509. (b) Sintas, J. A.; Vitale, A. A. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 677-684. and Enzymatic chlorination of tryptamine derivatives has been reported: Ho¨lzer, M.; Burd, W.; Riebig, H.-U.; van Pee, K.-H. *Adv. Synth. Catal.* **2001**, *343*, 591-595.

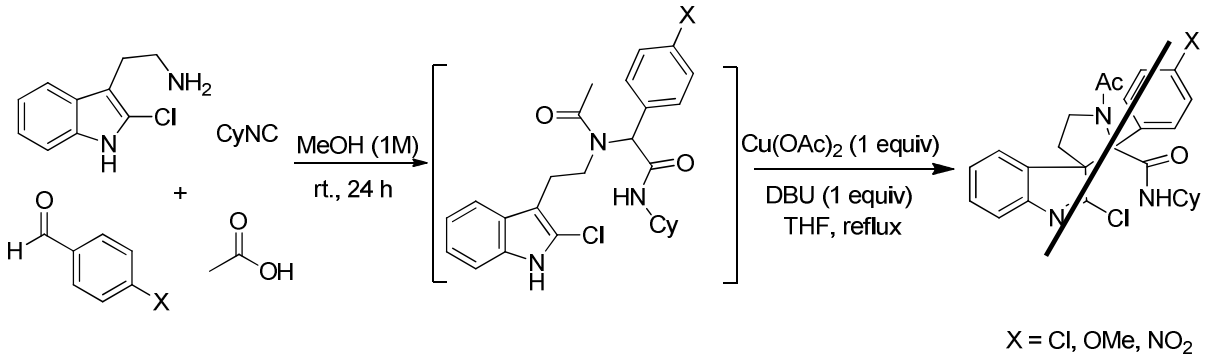
[138] Miyake, F.; Yakushijin K.; Horne, D. *Org. Lett.*, **2004,** *6*, 711-713.

This synthetic route was chosen for the 2-chlorotryptamine synthesis, but we never managed to reproduce these results. In all our trials, the yields did not exceed 35 % and the formation of various by-products was observed.



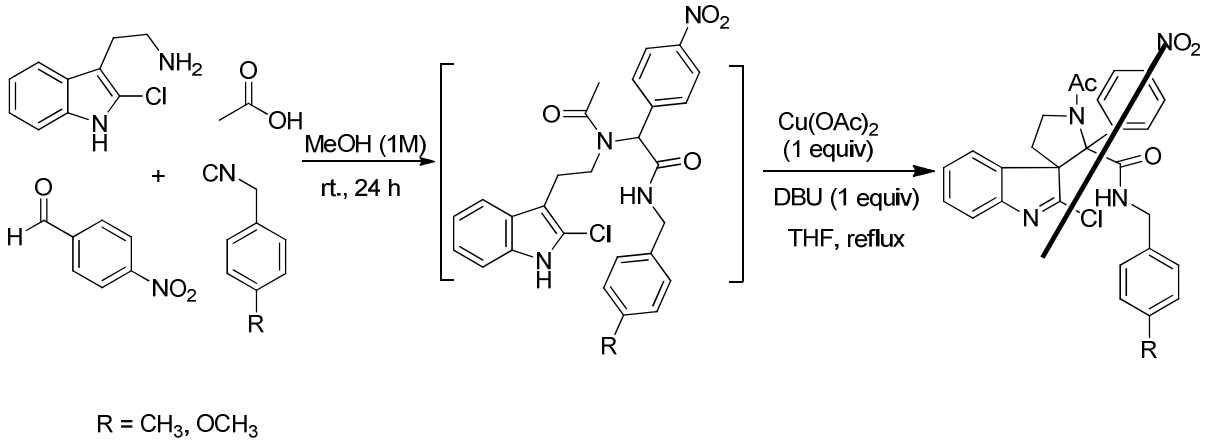
Scheme III.40: Preparation of 2-chlorotryptamine.

The Ugi adducts were then prepared using 2-chlorotryptamine, 4-nitrobenzaldehyde, cyclohexyl isocyanide and acetic acid as staring materials. The resulting mixture was stirred for 24 hrs in methanol and diluted with THF, then copper acetate and DBU were successively added at 0 °C. The reaction mixture was refluxed for 24 hrs, but total decomposition occurred. The same behavior was observed with 4-methoxybenzaldehyde or 4-nitrobenzaldehyde.



Scheme III.41: Oxidative radical cyclization reaction involving 2-chlorotryptamine.

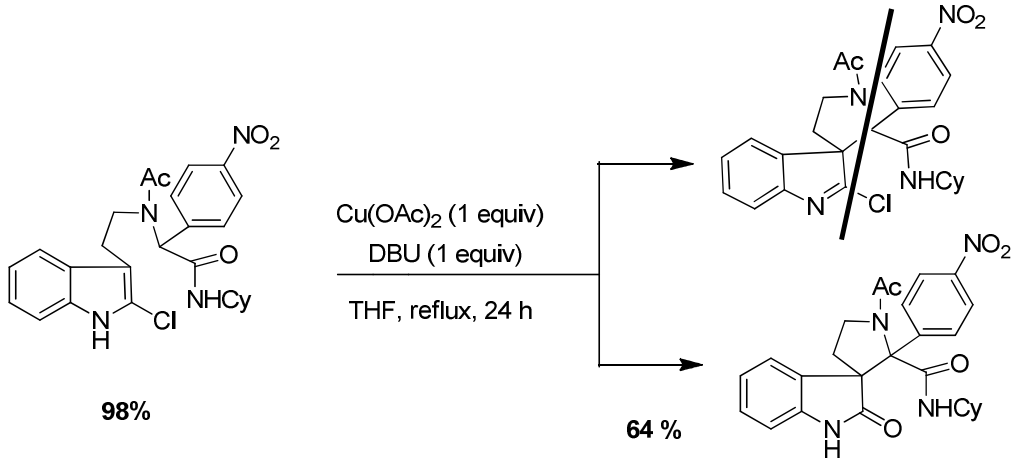
As post condensation transformations strongly depend on the nature of the isocyanide, the same sequence was tested with a benzyl isocyanide. Unfortunately, using either 4-methoxy benzyl isocyanide or 4-methyl benzyl isocyanide, no desired cyclized product could be isolated and total decomposition was observed.



R = CH_3, OCH_3

Scheme III.42: Oxidative radical cyclization reaction involving 2-chlorotryptamine and benzyl isocyanide**.**

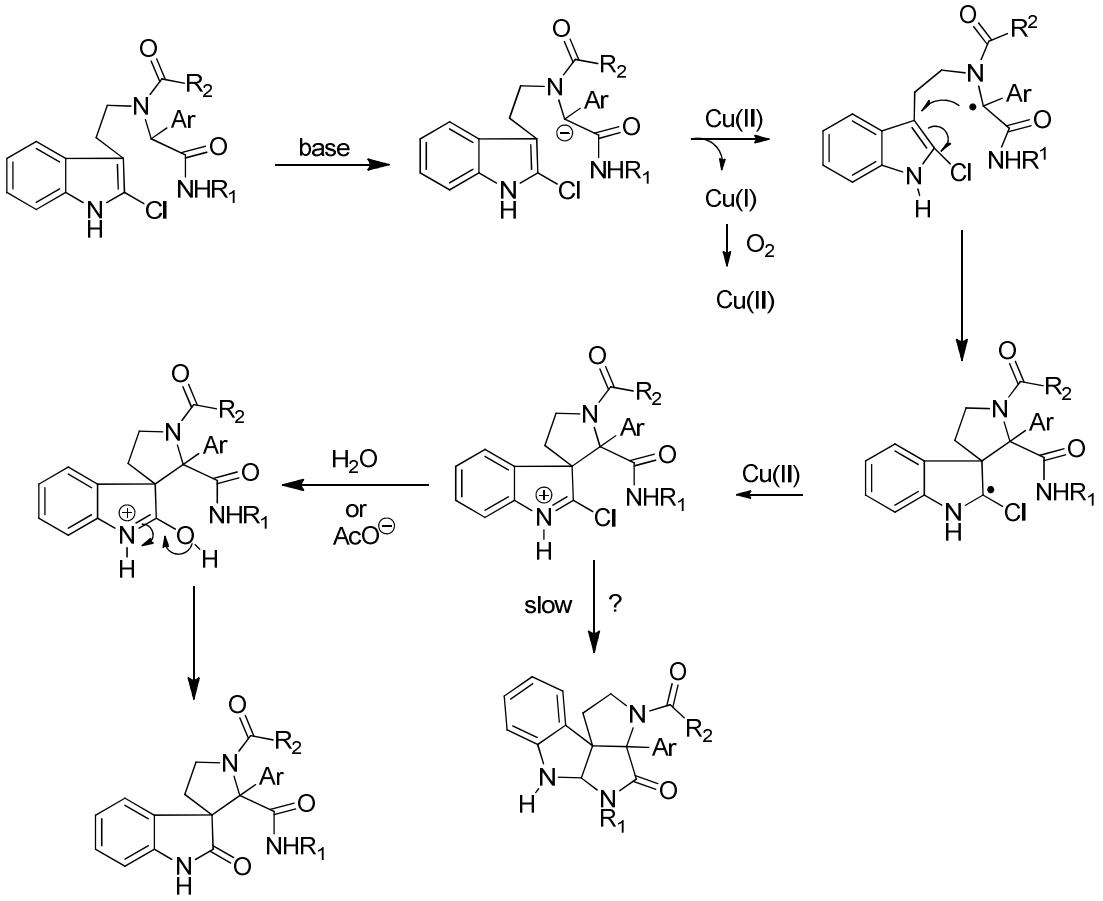
In order to investigate further this sequence, we isolated the Ugi adducts with 2-chlorotryptamine and treated them with one equivalent of copper acetate and DBU in refluxing THF under air. Surprisingly, the reaction proceeded smoothly and the desired 3,3'-spirooxindole derivative was isolated in 64 % (scheme III.43).



Scheme III.43. Synthesis of spiroxindoline from oxidation of Ugi adduct with Cu(II).

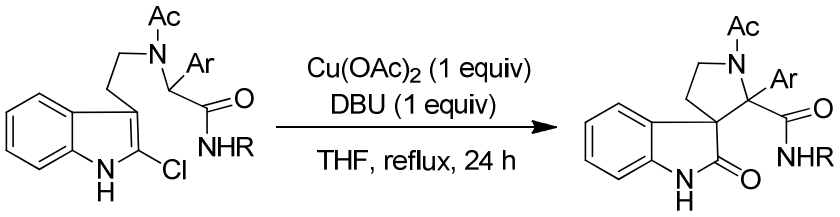
Mechanism of Spirooxyindoline formation:

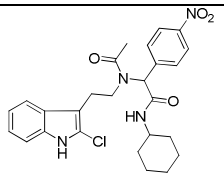
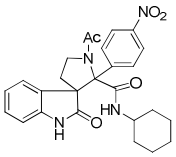
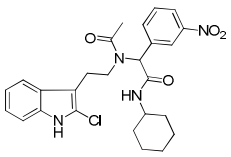
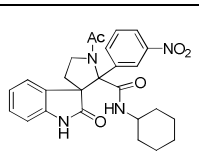
The reaction probably proceeds according to a similar pathway as we previously proposed for the spiroindoline formation but the vicinal amidic NH does not trap the iminium. Due to steric constraint, the amidic attack on the iminium chloride is perhaps not as fast as the addition of water or acetate, which can afford the spirooxindole formation along the process.

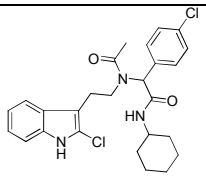
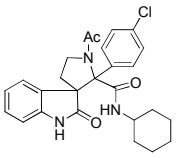
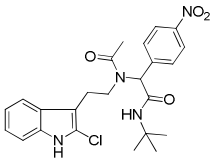
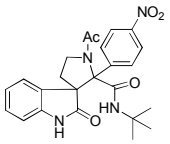
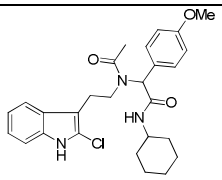
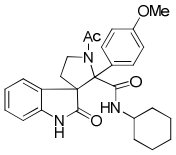
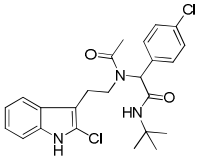
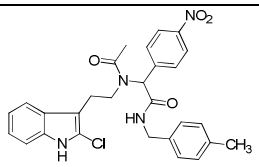


Scheme III.44: Proposed mechanism for synthesis of spirooxindoline from Ugi adduct with Cu(II).

The scope of this reaction was investigated with various partners for Ugi reaction as shown in the following table:



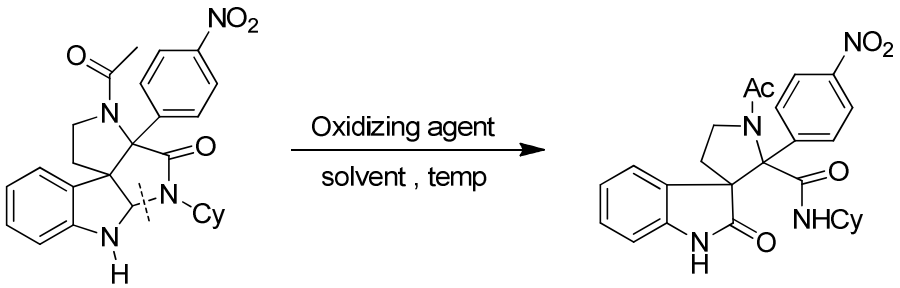
Entry	Ugi adduct (Yields)	Cyclized product (Yields)	Entry	Ugi adduct (Yields)	Cyclized product (Yields)
1	 **III.24 99%**	 **III.31 64%**	5	 **III.28 99%**	 **III.34 50%**

2	 **III.25 47%**	 **III.32 54%**	6	 **III.29 88%**	 **III.35 21%**
3	 **III.26 80%**	 **III.33 45%**	7	 **III.30 49%**	NA -
4	 **III.27 45%**	NA			

The reaction proceeds smoothly either with electron-withdrawing groups or with electron-donating ones. Probably, due to an easier enolization, the starting material bearing a nitro group (64 %), gave better yields than the one with a methoxy group (45 %). Ugi adducts resulting from the use of the *tert*-butyl isocyanide are less efficient as compared to cyclohexyl one, whereas benzyl substituted Ugi adduct failed to give any cyclized product.

In this reaction, one of the diastereomer is formed predominantly in the mixture, probably for steric reasons. We tried different solvents and techniques for isolation of single crystal of the spirooxindole, but in all our attempts we failed to obtain crystalline product for X-ray analysis.

To overcome this problem, we imagined to develop a synthetic path to the spirooxindole from of 3,3'-spiroindolines obtained in our previous study. For this purpose, various oxidizing agents have been tested to cleave the aminal functional group of the polycyclic spiroindoline (scheme **III.45**).



Oxidizing agent	solvent	temp	Result.
$PhI(OAc)_2$	DCE	rt	decomposition
m-CPBA	CH_2Cl_2	rt	No reaction
m-CPBA	CH_2Cl_2	40 ^oC	Multiple products

Scheme III.46: Oxidation of spiroindoline to access spiroxindoline

Unfortunately, no oxidized product could be isolated and the limited trials were not pursued any longer.

Since the synthesis and the isolation of the 2-chlorotryptamine constitute a difficult process, this methodology will meet a limited success. However, even if the availability of the starting material is still an important issue, this sequence constitutes an additional example of the potential of MCR-radical processes for the construction of complex molecules.

Chapter 4

Isocyanide Dibromides

The work described in this chapter has been published in two publications:

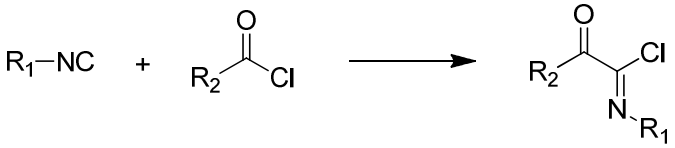
a) El Kaïm, L.; Grimaud, L.; Pravin Patil, *Org. Lett.* **2011**, *13*, 1261-1263.

b) El Kaïm, L.; Grimaud, L.; Pravin Patil, *Synlett*. **2012**, 23, 1361-1363.

In this chapter, we will discuss about the use of dihalogenated isocyanides in heterocyclic chemistry for the synthesis of oxazoles, tetrazoles and triazoles.

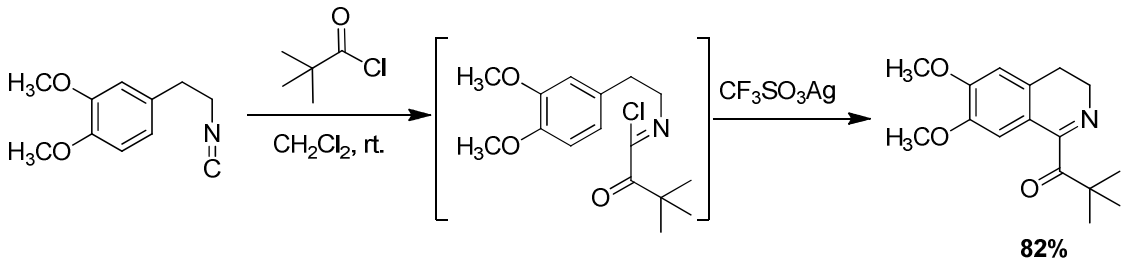
I. Introduction

As discussed in earlier part of this thesis, the Nef reaction[139] of isocyanides involves insertion of an isocyanide into a C-Cl bond of an acyl chloride, affording valuable intermediate imidoyl halides.



Scheme IV.1: Nef Reaction formation of imidoyl halides.

First discovered by Nef in 1892, it gives a direct access to acyl imidoyl chlorides, which are precursors of acyl nitriliums. Intramolecular trappings of acyl imidoyl chlorides have been widely studied by Livinghouse and co-workers to synthesize various heterocycles.[140] (scheme IV.2).

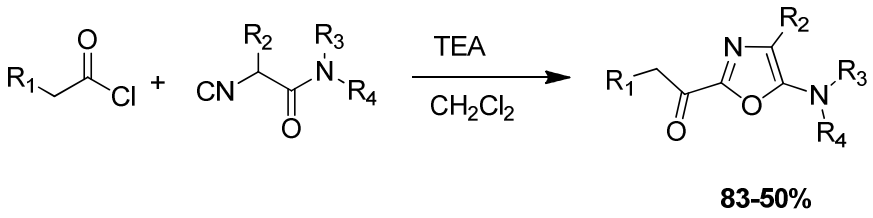


Scheme IV.2: Intramolecular trappings of acyl imidoyl chlorides.

[139] a) Nef, J. *Justus Liebigs Ann. Chem.* **1892**, *270*, 267–335. b) Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*,116–1121. c) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159–1165. d) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089–4095. e) Livinghouse, T. *Tetrahedron* **1999**, *55*, 9947–9978. f) Van Wangenen, B. C.; Cardenilla, J. H. *Tetrahedron Lett.* **1989,** *30*, 3605–3608. g) Adlington, R. M.; Barrett, A. G. M. *Tetrahedron* **1981**, *37*, 3935–3942. h) El Kaim, L.; Pinot, -P. *Tetrahedron* **1998**, *54*, 3799–3806. i) Chen, J.; Deshpande, S. *Tetrahedron Lett.* **2003**, *44*, 8873–8876.

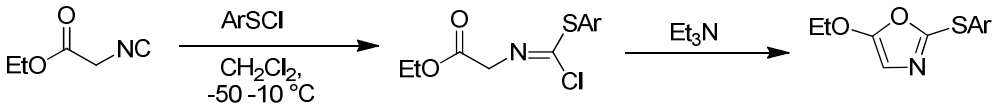
[140] a) Westling, M.; Livinghouse T. *Tetrahedron Lett.*, **1985**, *26*, 5389-5392. b) Livinghouse, T. *Tetrahedron* **1999**, *55*, 9947-9978.

More recently, Zhu, Tron and Pirali[141] have reported an oxazole synthesis with insertion of isocyanoacetamides in an acyl chloride. The resulting nitrilium ion cyclizes and, after proton transfer, gives the 2-acyl-5-aminooxazole. [142]



Scheme IV.3: Oxazole synthesis using isocyanoacetamides in the Nef reaction.

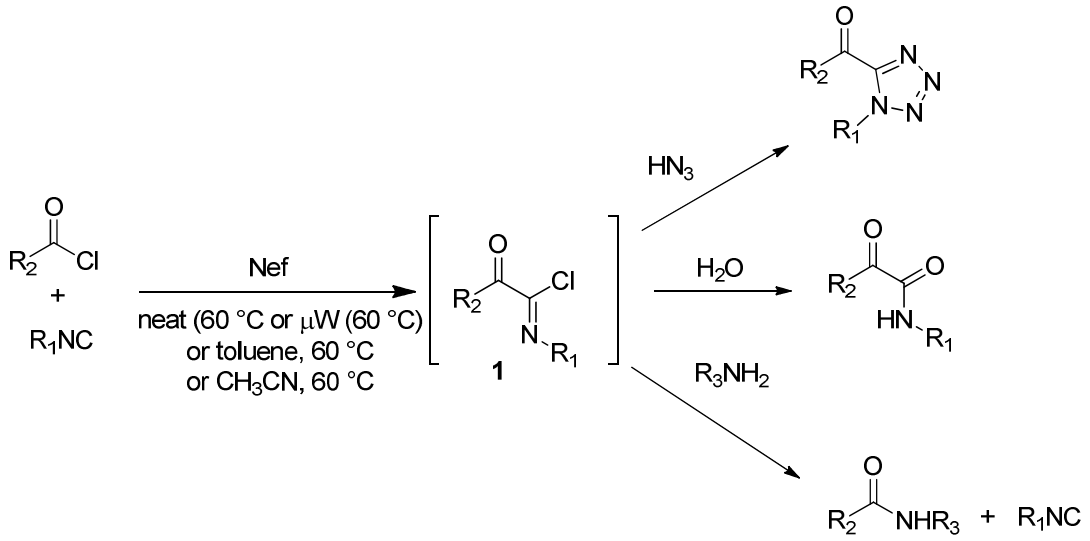
Similarly, aryl sulfenyl chlorides react with isocyanides to give unstable thioimidoyl chlorides, which react with adjacent nucleophilic functional groups, for example the adducts of α-isocyanoester undergo cyclization to form 2-arylthio-5-alkoxy oxazole (scheme IV.4).[143]



Scheme IV.4: Oxazoles synthesis by Marcaccini.

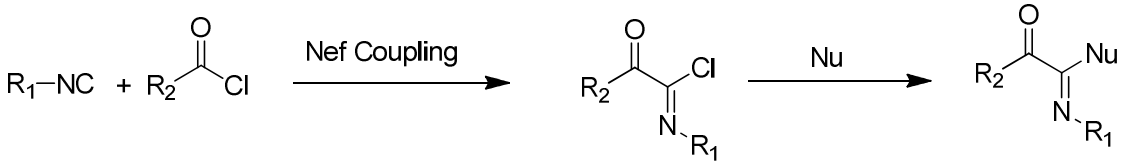
Surprisingly, few intermolecular trappings of acyl imidoyl chlorides have been described as they behave differently depending on the nucleophile.[152a] Indeed, addition of water affords pyruvamides,[144] and hydrazoic acid gives the corresponding tetrazole.[145] However, the addition of an amine provides the amide instead of the desired amidine.[152a]

[141] Mossetti, R.; Pirali, T.; Tron, G.; Zhu, J. *J. Org. Lett.* **2010**, *12*, 820-823.
[142] a) Sun, X., Janvier, P., Zhao, G., Bienayme, H., Zhu, J. *Org. Lett.* **2001**, *3*, 877-880. b) Sun, X.; Janvier, P.; Bienayme, H. Zhu J. *J. Am. Chem. Soc.* **2002**, *124*, 2560-2567. c) Montaño, R.G.; Zhu J. *Chem. Commun.* **2002**, 2448-2449. d) Bonne, D.; Dekhane, M.; Zhu J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2485-2488.
[143] Bossio, R., Marcaccini, S., Pepino, R., *Heterocycles*, **1986**, *24*, 2003-2005.
[144] Chen, J.; Deshpande, S. *Tetrahedron Lett.* **2003**, *44*, 8873-8876.
[145] Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*, 1116-1121.



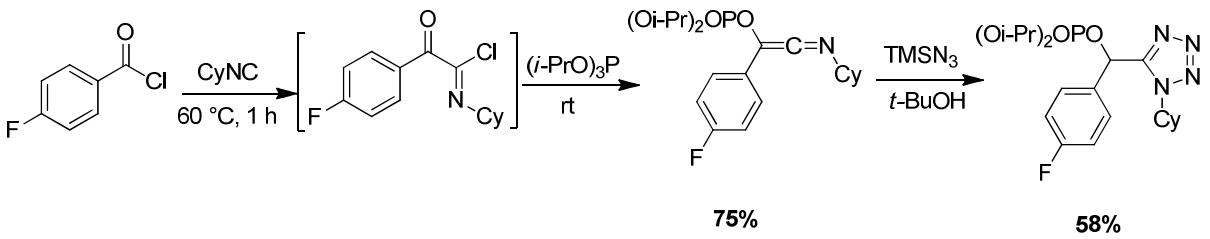
Scheme IV.5: Reactions of acyl imidoyl chlorides with various nucleophiles.

Recently, our research group reported several synthetic applications of the isocyanide-Nef reaction[146] by allowing various nucleophiles to trap the intermediate imidoyl chloride (scheme IV.6).



Scheme IV.6: 3-CR involving imidoyl halide from acyl chloride and isocyanides.

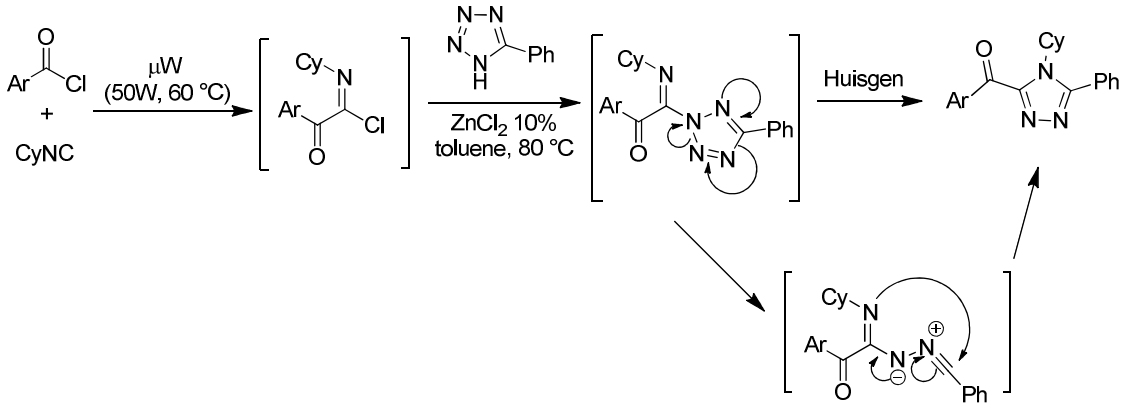
Our group explored the addition of trialkylphosphites on imidoyl chlorides to afford new keteneimines in a Perkow-type reaction. The whole sequence may be performed without any solvent, and the resulting keteneimine may easily be converted to phosphorylated tetrazoles and triazoles.



Scheme IV.7: Acyl imidoyl chlorides in synthesis of tetrazole via Nef reaction.

[146] We give this name to avoid confusion with the more well known Nef reaction of nitro derivatives.

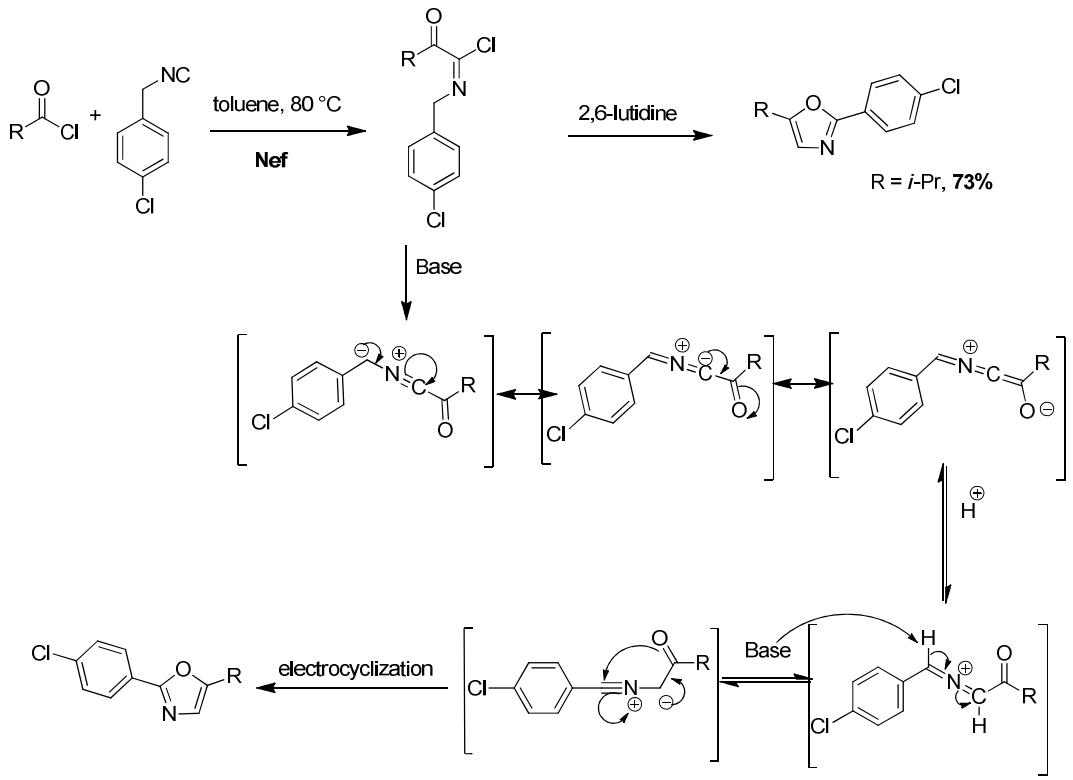
Moreover, we have developed a new three-component triazole synthesis involving a Nef-Huisgen cascade.[147] After the α-addition of acyl chlorides on isocyanides, the resulting imidoyl chloride was treated with tetrazole under suitable Lewis acid activation ($ZnCl_2$). The resulting adduct is rather unstable above 80 °C, and gives the corresponding triazole according to a Huisgen fragmentation.



Scheme IV.8: Synthesis of triazoles via a Nef-Huisgen cascade.

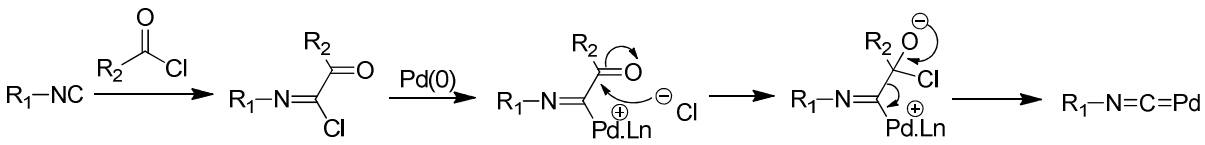
Along this study, we have observed that the use of benzyl isocyanides affords oxazoles under basic conditions. Indeed, in the presence of a relatively weak base such as 2,6-lutidine at 80 °C, acyl chlorides react with an isocyanide and, after different prototropies, the resulting nitrilium cyclized to provide 2,5-disubstituted oxazoles.[148]

[147] El Kaim, L.; Grimaud, L.; Wagschal, S.; *Synlett* **2009**, 1315-1317.
[148] dos Santo,s A.; El Kaïm, L.; Grimaud, L.; Ronsseray, C. *Chem. Commun.* **2009**, 3907-3909.



Scheme IV.9: Synthesis of oxazoles via Nef reaction with weak base.

Different trials have been made to perform organometallic couplings using the Nef-imidoyl halides. However, when settling such strategy, we observed the deactivation of the catalyst and the reaction failed. In fact, under basic conditions, the Nef reaction turns out to be reversible and the isocyanide is regenerated, inhibiting the catalytic activity of the metal (scheme IV.10).

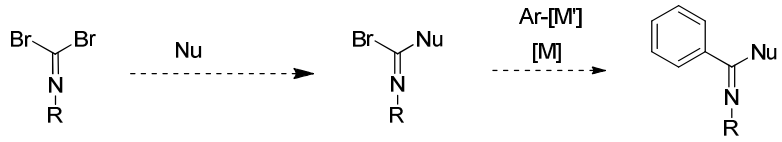


Scheme IV.10: Addition of palladium on imidoyl halide.

Imidoyl chlorides are important synthons for the construction of a large variety of heterocycles. They can be readily prepared as discuss above *i.e. via* isocyanide-Nef reaction, by direct

halogenation of isocyanide or by the insertion of alkyl halide to isocyanide via organometallic couplings.[149]

In order to test the possibility to perform organometallic couplings with imidoyl halide, we select *gem*-dibromo isocyanide as a potent partner. Indeed, *gem*-dihalogenoisocyanides could react with nucleophiles to form imidoyl halides which could further undergo metal catalyzed cyclization to form a heterocycle.



Scheme IV.11: Plausible pathway for the addition of a nucleophile on *gem*-dihalogeno isocyanides.

In the continuation of our previous efforts in developing new methodologies using IMCRs, we were encouraged to explore the potential of dihalogenated isocyanides.

II. Chemistry of *gem*-dihalide isocyanides

The addition of bromine to isocyanide was first described in 1875 by Tscherniak,[150] whereas the addition of chlorine was first reported in 1892 by Nef.[152a]

The isocyanide dihalides which are sometimes also referred as carbylamine dihalides, dihalomethyleneamines, carbonyldihalide imines or iminophosgenes, are carbonic acid derivatives.

[149] a) Saluste, C.; Whitby, R.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156-4158. b) Saluste, C.; Whitby, R.; Furber, M. *Tetrahedron Lett.* **2001**, *42*, 6191-6194. c) Kishore, K.; Tetala, R.; Whitby, R. J.; Light, M. E.; Hurtshouse, M. B. *Tetrahedron Lett.* **2004**, *45*, 6991-6994. d) Saluste, C. G.; Crumpler, S.; Furberb, M.; Whitby, R. J. *Tetrahedron Lett.* **2004**, *45*, 6995-6996. e) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* **2011**, *13*, 1028-1031. f) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496-6499 g) Saluste, C., Crumpler, S.; Furber M.; Whitby, R. *Tetrahedron lett.* **2004**, *45*, 6995-6996.

[150] a) Tscherniak, M. *Bull*. Soc. *Chim. France [2]*, **1878,** *30*, 185. b) H. Guille-mard *Ann. Chimie* [E] **1908**, *14*, 324-328.

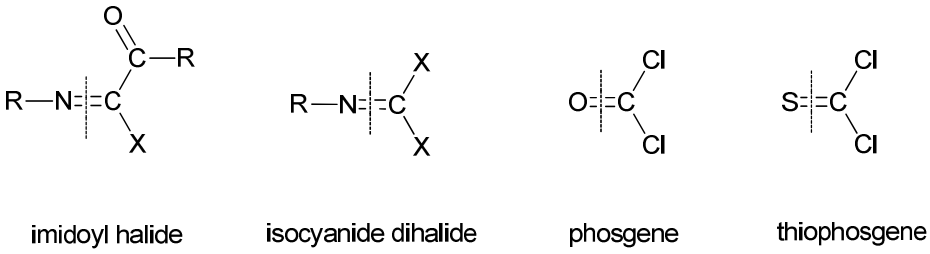
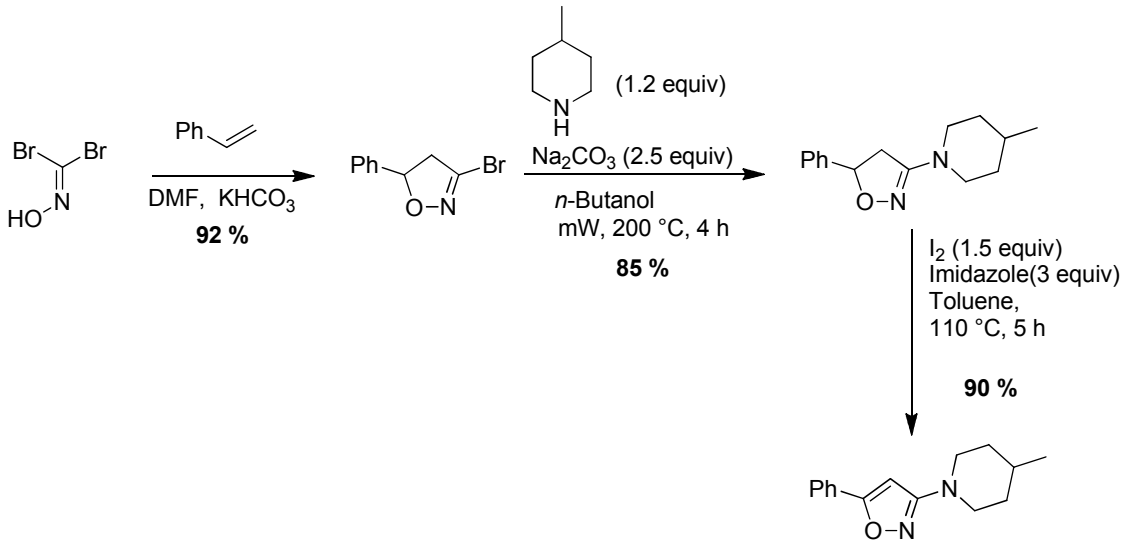


Figure IV.1: Structural similarity between imidoyl halide with *gem*-dihaloisocyanide, phosgene, thiophosgene.

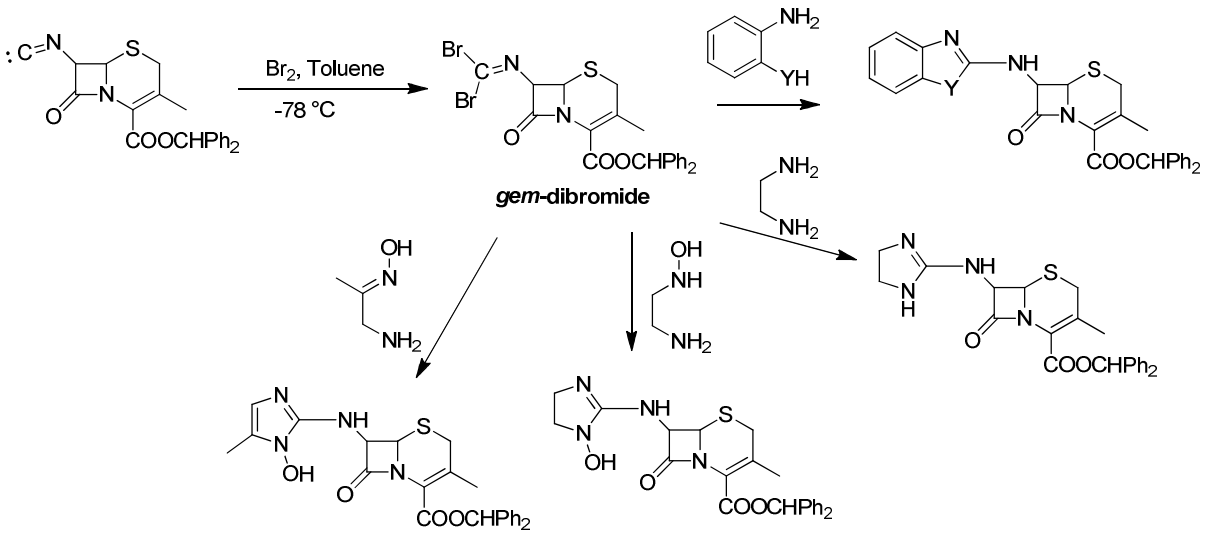
The structure of isocyanide dihalide i.e. isocyanide dichloride or isocyanide dibromide is quite close to phosgene and thiophosgene. They are highly electrophilic species and their use has been explored in heterocyclic synthesis. For instance, they have been widely studied in cycloaddition processes.[151] Indeed, Girardin *et al* developed the synthesis of 3-amino-5-substituted-isoxazoles in high yields from cycloaddition of alkenes with *gem*-dibromoformaldoxime[163a] (scheme IV.12).



Scheme IV.12: cycloaddition of alkenes with *gem*-dibromoformaldoxime.

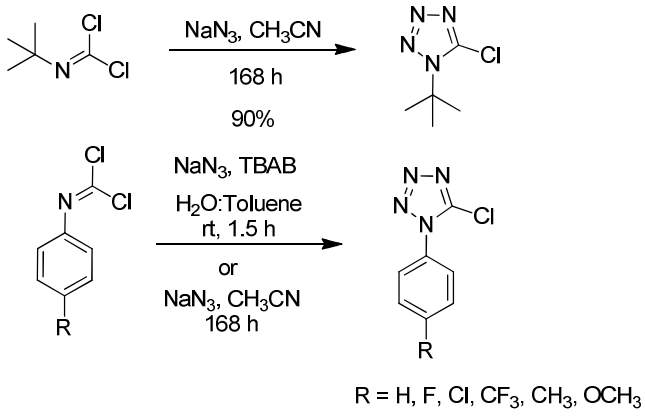
[151]For some recent examples, see: (a) Girardin, M.; Alsabeh, P.; Lauzon, S.; Dolman, S.; Ouellet, S.; Hughes, G. *Org. Lett.* **2009**, *11*, 1159-1162. (b) Moore, J.; Davies, M.; Goodenough, K.; Wybrow, R.; York, M.; Johnson, C.; Harrity, J. *Tetrahedron* **2005**, *61*, 6707-6714. (c) Moore, J.; Goodenough, K.; Spinks, D.; Harrity, J. *Synlett* **2002**, 2071-2073. (d) Caldilora, P.; Ciancaglione, M.; De Amici, M.; De Micheli, C. *Tetrahedron Lett.* **1986**, *27*, 4647-4650. (e) Stevens, R.; Polniaszek, R. *Tetrahedron* **1983**, *39*, 743-748.

Direct addition of a nucleophile on *gem*-dihaloisocyanides has been yet reported. For example, they are the key intermediates in the synthesis of a variety of cephalosporines with novel C-7 heterocyclic substituent.[152]



Scheme IV.13: Synthesis of 7-imidazolylamino cephalosporins from its gem-dibromide.

The reaction of dibromoisocyanide with azide has been reported by various groups to form the corresponding bromotetrazole.[153]

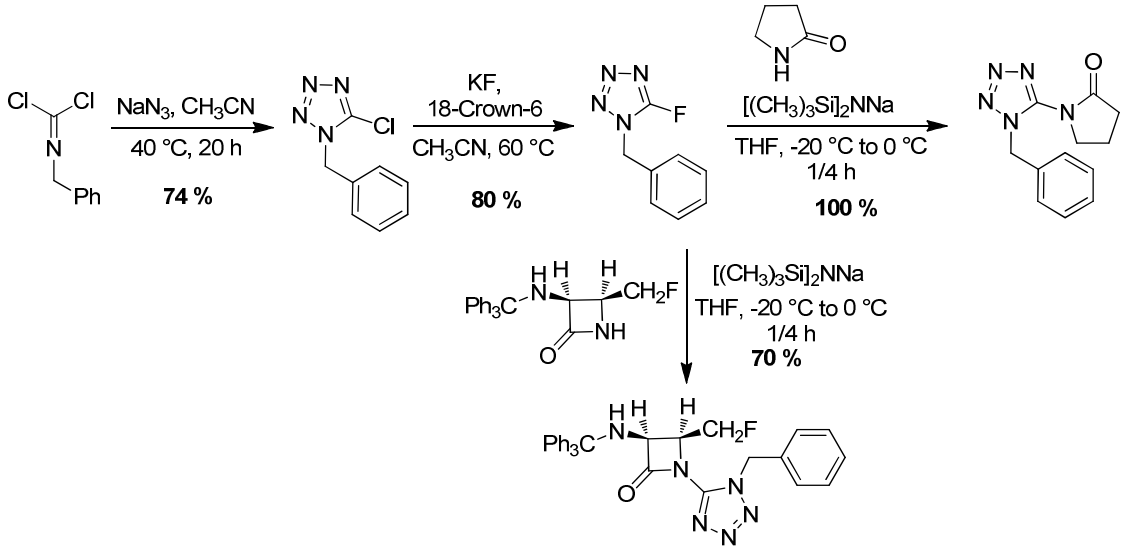


Scheme IV.14: synthesis of 5-chlorotetrazole.

[152] a) Jung, F.; Delvare, C.; Boucherot, D.; Hamon, A. *Tetrahedron letter*, **1989**, *30*, 2375-2378,. b) US patent 4463178/**1984.**

[153] For tetrazole formation from isocyanide dichlorides see: a) Cristiano, M.; Lurdes, S.; Johnstone, R. A. W. *J. Chem. Research Synopses* **1997**, *3*, 164–165. b) Alves, J. A.; Johnstone, R. A. W. *Synth. Commun.* **1997**, *27*, 2645–2650. c) Mloston, G.; Galindo, A.; Bartnik, R.; Marchand, A. P.; Rajagopal, D. *J. Het. Chem.* **1996**, *33*, 93–96. d) Quast, H.; Bieber, L. *Chem. Ber.* **1981**, *114*, 3253–3272. For an alternative three-component palladium catalyzed preparation of tetrazole using a Tsuji-Trost reaction see: e) Kamijo, S.; Jin, T.; Huo, Z.; Young Soo, G.; Shim, J; Yamamoto, Y. *Mol. Div.* **2003**, *6*, 181–192. For tetrazole formation from isocyanide and X−N3, see: f) Fowler, F.; Hassner, A.; Levy, L. *J. Am. Chem. Soc.* **1967**, *89*, 2077–2082. g) Collibee, W.; Nakajima, M.; Anselme, J. *J. Org. Chem.* **1995**, *60*, 468–469.

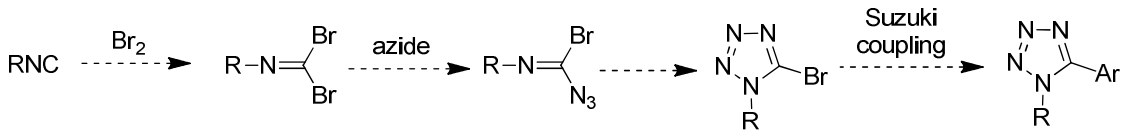
Teutsch *et al*[154] synthesized β-lactam tetrazoles from dibromoisocyanides. 5-Chloro-tetrazole treated with potassium fluoride in presence of crown ether in acetonitrile gave 5-fluorotetrazaole in 74 % isolated yield. The latter underwent nucleophilic substitution with cyclic amides forming the corresponding β-lactam in quantitative yields (Scheme IV.15).



Scheme IV.15: Synthesized β-lactam tetrazoles from dibromoisocyanides.

To the best of our knowledge, 5-halogeno substituted tetrazole were evaluated for nucleophelic substitution reactions, but have never been tested in the organometallic coupling reactions.

We postulated that such bromotetrazole could undergo organo-metallic reaction such as Suzuki coupling to give 5-substituted tetrazole and that it should be possible to perform the whole sequence in one-pot. (Scheme IV.16).

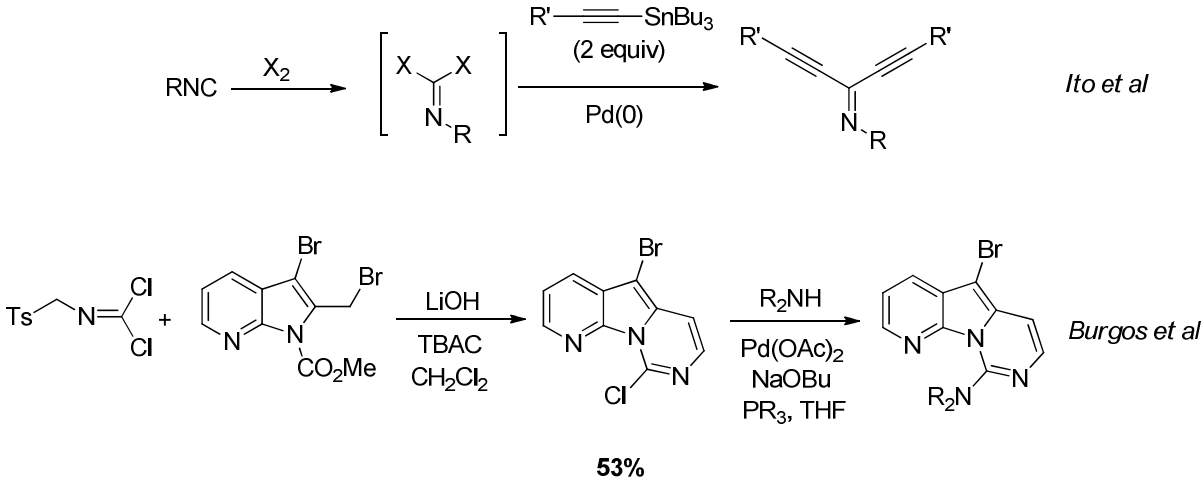


Scheme IV.16: Proposed synthesis tetrazole from gem-dibromides.

The use of metal-induced reactions involving *gem*-dihalide isocyanide were only reported by two groups. Ito and co-workers described a double Stille coupling,[155] and Burgos *et al*

[154] Klich, M.; Teutsch, G.; *Tetrahedron* **1986**, *42*, 2684-2684.
[155] a) Ito, Y.; Inouye, M.; Yokota, H.; Murakami, M. *J. Org. Chem.* **1990**, *55*, 2567-2568. b) Ito, Y.; Inouye, M.; Murakami, M. *Tetrahedron Lett.* **1988**, *29*, 5379-5382.

proposed a cascade involving *gem*-dihalide tosyl methyl isocyanide in a heterocyclization with isolation of the intermediate imidoyl chloride followed by a pallado-catalyzed amination[156] (Scheme IV.17).



Scheme IV.17: Metal-induced reactions involving *gem*-dihalide isocyanide

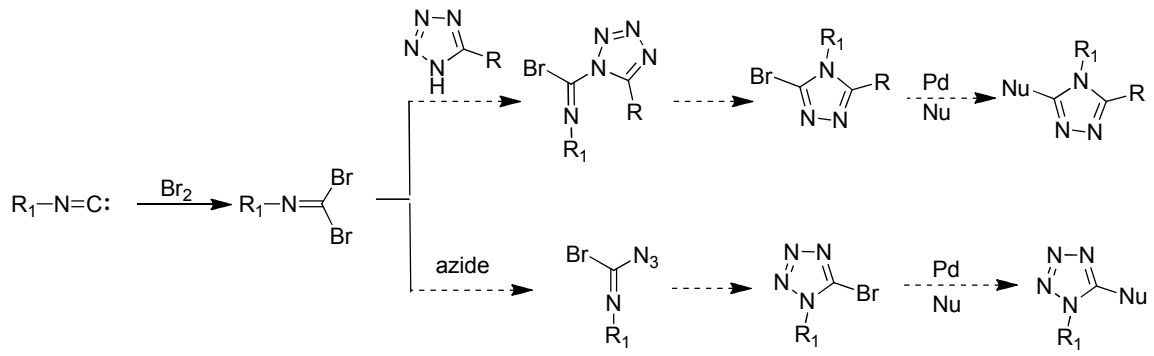
III. Isocyanide dibromides and organometallic couplings

1. Project

Our strategy with isocyanide dihalide was to explore organometallic couplings in one of the steps of the trapping sequence.

Due to our previous tests on acylimidoyl chlorides, we surmised that the metal should be added at a late step to avoid the regeneration of the starting isocyanide. In order to get more stable imidoyl bromide, the addition of a nucleophile such as a tetrazole could give a bromotriazole via a huisgen fragmentation (as we reported previously). This stable form of an imidoyl bromide could easily undergo orgamometallic coupling. Similarly, the addition of azide could give a bromotetrazole, which could be involved in organometallic couplings. As the cyclization with azide is expected to be more efficient and carried out at lower temperature as compared to Huisgen reaction of tetrazole, we started this study considering the azide as a manner to block the reversibility of the bromine addition before the metal catalyzed process.

[156] Baeza, A.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. *J. Tetrahedron Lett.*, **2007**, *48*, 2597-2601.

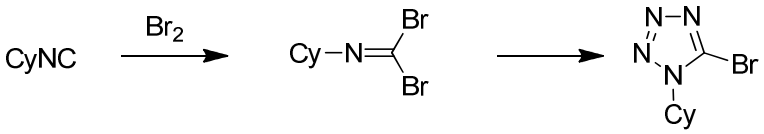


Scheme IV.18: 3-CR involving imidoyl halide from *gem*-dihalide isocyanide.

2. Towards tetrazoles: Results and discussion

In order to validate our strategy, each step of the whole reaction sequence was optimized separately. Cyclohexyl isocyanide was chosen as standard isocyanide for all trials. *Gem*-dibromo isocyanide could be easily prepared in dichloromethane or in acetonitrile, both solvents were tested for the tetrazole formation. The addition of a slight excess of $TMSN_3$ to a solution of *gem*-dibromocyclohexyl isocyanide in dichloromethane failed to give any coupling. The same results were obtained in acetonitrile as solvent (even in the presence of a catalytic amount of methanol).

The addition of a Lewis acid such as silver perchlorate (40 mol %) gave about 50 % of the product, while the use of silver acetate (10 mol %) afforded the bromotetrazole in quantitative yield after 3 days (Scheme IV.19). Considering the long reaction times and the need of a Lewis acid as a catalyst, we investigated the use sodium azide.



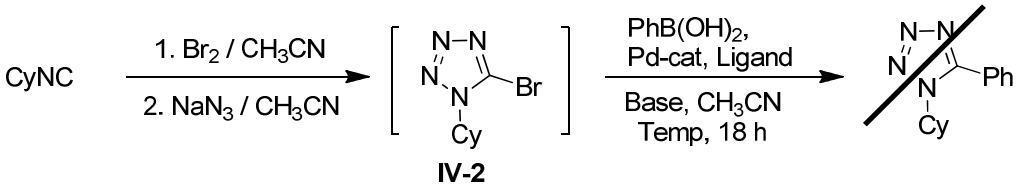
IV-1 **IV-2**

Conditions	yield
$TMSN_3$, CH_2Cl_2, rt.	-
$TMSN_3$, CH_3CN, rt.	-
$TMSN_3$, CH_2Cl_2, MeOH (cat) rt.	-
$TMSN_3$, CH_3CN MeOH (cat) rt.	-
$TMSN_3$, CH_2Cl_2, AgClO (40%), 18 h, rt.	54 %
$TMSN_3$, CH_2Cl_2, $Ag(OAc)_2$ (10 mol%), 3d, rt	100 %
NaN_3, DMF, 5 min, 50 °C	100 %
NaN_3, CH_3CN, 30 min, 50 °C	100 %
NaN_3, CH_3CN, 1 h, rt	100 %

Scheme IV.19: Optimization of the tetrazole formation.

DMF was thus selected as solvent and the temperature *raised* to 50 °C. Under these conditions quantitative yields of the desired tetrazole **IV-2** were obtained within 5 min. Since we used either dichloromethane or acetonitrile in the formation of *gem*-dibromide **IV-1**, sodium azide in acetonitrile was also evaluated. It afforded a quantitative yield of tetrazole **IV-2** within 30 min at 50 °C. When the same reaction carried out at room temperature, quantitative yield was obtained in 1h (Scheme IV.19).

Next, we examined the Suzuki coupling on bromotetrazole **IV-2**. After bromotetrazole formation, the phenyl boronic acid (3 equiv), potassium carbonate (3 equiv) and a catalytic amount of palladium source were added. The reaction mixture was stirred at reflux of acetonitrile. Bases like potassium carbonate, cesium carbonate and Pd-catalysts such as *tetrakis*(triphenyl-phosphine) palladium and palladium acetate were tested, but all attempts failed to give the desired product (Scheme IV.20).

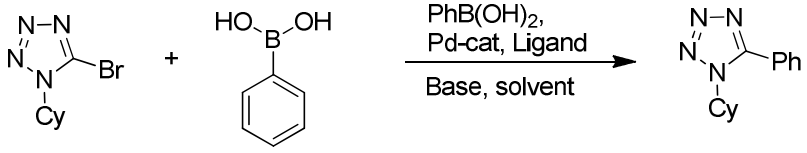


IV-2

Pd-cat.	Ligand	base	Temp.
$Pd(PPh_3)_4$	-	K_2CO_3	80 °C
$Pd(PPh_3)_4$	-	Cs_2CO_3	80 °C
$Pd(OAc)_2$	PPh_3	K_2CO_3	80 °C
$Pd(OAc)_2$	PPh_3	Cs_2CO_3	80 °C

Scheme IV.20: Optimization of one-pot Suzuki coupling to form substituted tetrazole.

Considering these results, a set of various solvents was next evaluated for this step. In DMF, the intermediate bromotetrazole turned out to rapidly decompose. The metal catalyzed coupling was also tested neat as reported by Tang *et al*[157] without any success. The use of *tetrakis*(triphenylphosphine) palladium in a 3:1 toluene/ water mixture gave traces of product (scheme IV.21).



IV-2 **IV-3**

Catalyst/ligand	base	Solvent	% Yield[a]
$Pd(PPh_3)_4$	K_3PO_4	*n*-BuOH	Decomposed
$Pd(PPh_3)_4$	Cs_2CO_3	*n*-BuOH	Decomposed
$Pd(PPh_3)_4$	K_2CO_3	*n*-BuOH	Decomposed
$PdCl_2(dppf)$	K_3PO_4	*n*-BuOH	Decomposed
$Pd(OAc)_2$/XPhos	K_3PO_4	*n*-BuOH/H_2O[b]	Decomposed
$Pd(OAc)_2$/SPhos	K_3PO_4	*n*-BuOH/H_2O[b]	Decomposed
$Pd(PPh_3)_4$	K_2CO_3	toluene/H_2O[b]	trace
$Pd(PPh_3)_4$	K_2CO_3	toluene	90 %[c]

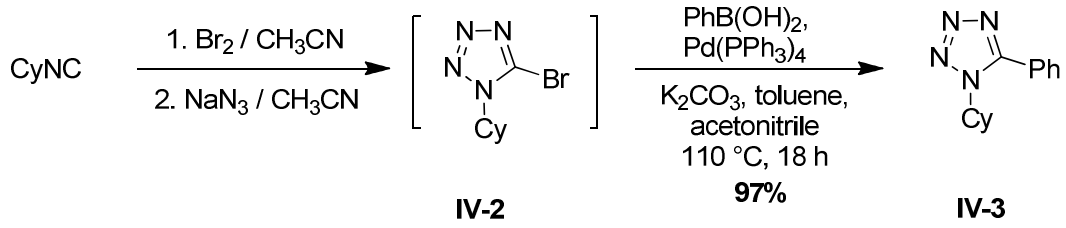
[a] Reaction conditions: ArBr(1 equiv), phenylboronic acid (3 equiv), Pd catalyst (5%), ligand (10%), solvents (2 mL), base (3 equiv), MW 30 min at 150 °C
[b] 3:1 ratio.
[c] Reaction conditions: ArBr(1 equiv), phenylboronic acid (3 equiv), Pd catalyst (5%), solvents (2 mL), base (3 equiv), 18h at 150 °C

Scheme IV.21: Optimization of Suzuki coupling on tetrazole **IV-2** to form aryl tetrazole **IV-3**.

[157] Tang, Q.; Gianatassio, R. *Tetrahedron Lett.* **2010,** *51*, 3473–3476.

Our attempts met success with toluene as solvent, boronic acid (3 equiv), potassium carbonate (3 equiv) and a catalytic amount of *tetrakis*(triphenylphosphine) palladium (5 mol %). The resulting mixture was refluxed for 18 h to afford the desired aryl tetrazole **IV-3** in 90 % yield. The amount of boronic acid could be decreased to 1.5 equiv without compromising the yield. Thus, the desired aryl tetrazole **IV-3** was obtained in three steps in a 90 % overall yield.

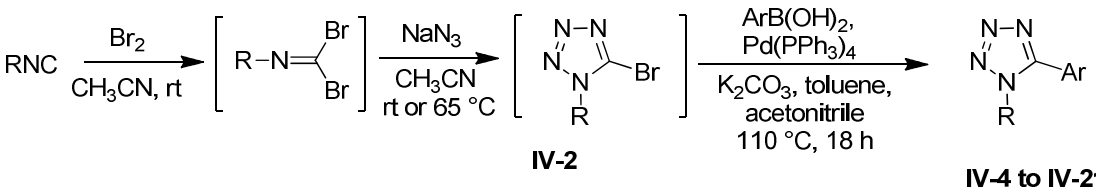
Since both steps (bromotetrazole formation from isocyanide and Suzuki coupling) proceeded with exclusive product formation, the whole reaction sequence could be performed without purification of the intermediate. Under these optimized conditions, the desired aryl tetrazole **IV-3** was isolated in 97 % yield in a one-pot sequence. The same reaction tested with the combination of $Pd(OAc)_2/PPh_3$ gave lower yields of the desired disubstituted tetrazole (76 %) (Scheme IV.22).

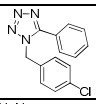
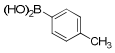
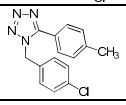
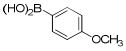
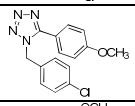
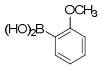
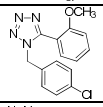
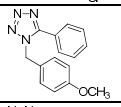
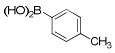
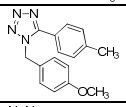
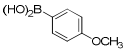
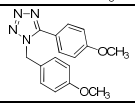
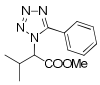
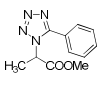
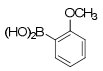
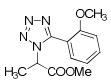
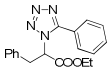
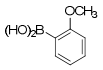
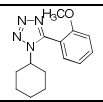


Scheme IV.22: Three component one-pot synthesis of 1,5-disubstituted tetrazole **IV-3** from isocyanide.

The scope of this sequence was next examined with various isocyanides and boronic acids as shown in the following Table IV-A.

Table IV-A: List of 1,5-disubstituted tetrazoles **IV-4 to V-21**.



Entry	RNC	$ArB(OH)_2$	Product		Yield (%)
1				**IV-4**	64
2				**IV-5**	86
3				**IV-6**	70
4				**IV-7**	17
5				**IV-8**	82
6				**IV-9**	82
7				**IV-10**	41
8				**IV-11**	62
9				**IV-12**	67
10				**IV-13**	15
11				**IV-14**	36
12				**IV-15**	70
13				**IV-16**	70
14				**IV-17**	41
15				**IV-18**	23
16				**IV-19**	98
17				**IV-20**	90
18				**IV-21**	12

In all the cases, the corresponding 1,5-disubstituted tetrazoles **IV-4 to IV-21** were obtained following a sequential one-pot procedure affording product in moderate to good yields. With some isocyanides (Table IV-A, entries 8-12), the electrocyclisation required higher temperatures (60 °C for 30 min) to proceed smoothly.

In the case of 3,4-dimethoxy phenyl ethyl isocyanide (Table IV-A, entry 18), yields were quite low, as *gem*-dibromo formation probably competed with the bromination of the electron-rich aromatic core.

In conclusion, we have developed a one-pot robust protocol for the formation of aryl tetrazoles, which are important cores in medicinal chemistry. Indeed, tetrazoles are considered to be bioisosteres of the carboxylic acid functional group without the rapid metabolism of acid in biological systems, increasing thus the retention time of the drug in the body. (Figure IV-2). Both tetrazoles and carboxylic acid possess comparable acidity and size.[158]

Figure IV-2: Structural comparison of the carboxylic acid moiety with the tetrazole ring.

1,5-Disubstituted tetrazoles are useful heterocycles because of their huge biological and pharmacological applications. They act as NADPH oxidase inhibitors,[159] glucokinase activators,[160] α-methylene tetrazole based peptidomimetics as HIV protease inhibitors,[161] calcitonin gene-related peptide receptor antagonists and antimigraine agents.[162] They have been shown to be potential P2X7-antagonists[163] and TNF-α inhibitors.[164]

[158] a) Holland, G.; Pereira, J. *J. Med. Chem.* **1967**, *10*, 149–154. b) Butler, R.; Garvin, V. *J. Chem. Res. (S)* **1982**, 122–123. c) Herr, R. *J. Bioorg. Med. Chem*. **2002**, *10*, 3379–3393.
[159] Seki, M.; Tarao, Y.; Yamada, K.; Nakao, A.; Usui, Y.; Komatsu, Y. *PCT Int. Appl.* WO 2005-JP2974, **2005**.
[160] Nonoshita, K.; Ogino, Y.; Ishikawa, M.; Sakai, F.; Nakashima, H.; Nagae, Y.; Tsukahara, D.; Arakawa, K.; Nishimura, T.; Eiki, J. *PCT Int. Appl*. WO 2004-JP19843, **2005**.
[161] May, B. C. H.; Abell, A. D. *J. Chem. Soc., Perkin. Trans*. **2002**, *1*, 172–178;
[162] Luo, G.; Chen, L.; Degnan, A.; Dubowchik, G.; Macor, J.;T ora, G.; Chaturvedula, P. *PCT Int. Appl.* WO 2004-US40721, **2005**.
[163] Nelson, D.; Gregg, R.; Kort, M.; Perez-Medrano, A.; Voight, E.; Wang,Y.; Grayson, G.; Namovic, M.; Donnelly-Roberts, D.; Niforatos, W.; Honore, P.; Jarvis, M.; Faltynek, C.; Carroll, W. *J. Med. Chem*. **2006**, *49*, 3659-3666.
[164] Srihari, P.; Dutta, P.; Srinivasa Rao, R.; Yadav, J.; Chandrasekhar, S.; Thombare, P.; Mohapatra, J.; Chatterjee, A.; Jain, M. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5569-5572.

Wuest *et al*[165] synthesized 1,5-disubstituted tetrazoles and tested them as cyclo-oxygenase (COX) inhibitors.

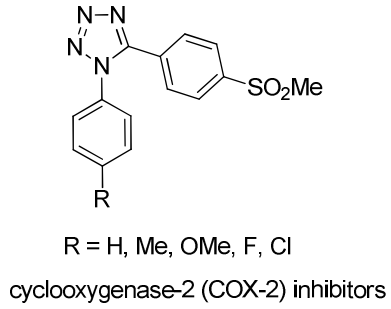


Figure IV-3: 1,5-Disubstituted tetrazoles as a COX-2 inhibitors.

Romagnoli *et al*[166] synthesized 1,5-disubstituted tetrazoles and showed that these compounds are rigid analogues of combretastatin A-4 with potent antiproliferative and antitumor activity**.**

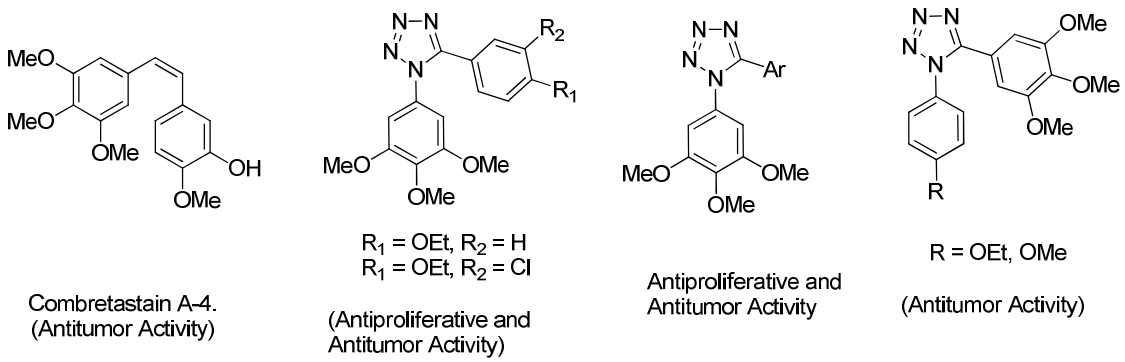


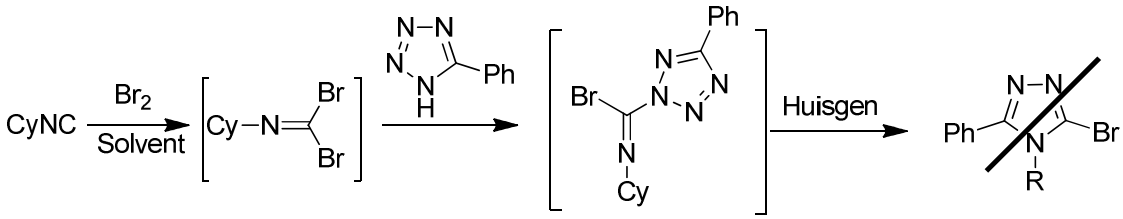
Figure IV-4: 1,5-Disubstituted tetrazoles as potent antiproliferative and antitumor activity.

[165] a) Wuest, F.; Sharma, S.; Al-Hourani, B.; Wuest, M.; Mane ,J.; Tuszynski, J.; Baracos, V.; Suresh, M. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 1823–1826. b) Frank Wuest *Bioorg. Med. Chem. Lett*. **2012**, *22*, 2235-2238

[166] Romagnoli, R.; Baraldi, P.; Salvador, M.; Preti, D.; Tabrizi, M.; Brancale, A.; Fu, X.; Li, J.; Zhang, S.; Hamel, E.; Bortolozzi, R.; Basso, G; Viola, G. *J. Med. Chem.* **2012**, *55*, 475-488.

3. Novel Synthesis of 1,2,4-Triazoles

Phenyl tetrazole was added to a solution of *gem*-dibromo-cyclohexyl isocyanide and the resulting mixture was stirred for 36 h at room temperature in the presence of various bases. Only triethylamine gave traces of tetrazole imidoyl bromide (Scheme IV.23).



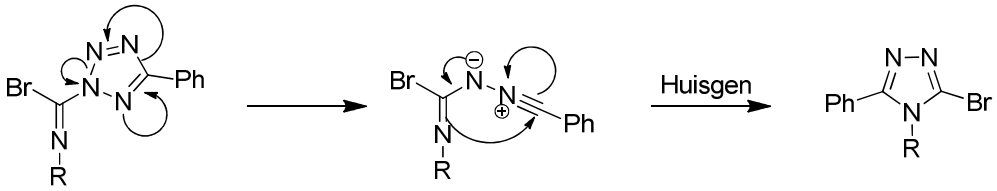
Solvent	Base	Solvent	Base
CH_2Cl_2	DBU	CH_3CN	K_3PO_3
CH_2Cl_2	DIPEA	CH_3CN	Cs_2CO_3
CH_2Cl_2	Et_3N	CH_3CN	DBU
CH_2Cl_2	K_2CO_3	CH_3CN	DIPEA
CH_2Cl_2	$NaHCO_3$	CH_3CN	Et_3N
		CH_3CN	K_2CO_3

Scheme IV.23: Addition of phenyl tetrazole to *gem*-dibromocyclohexyl isocyanide.

To our surprise, the yields were noteworthy improved when triethylamine was added at 0 °C. The solution was allowed to warm gradually at room temperature and stirred for 30 minutes. Under these conditions, quantitative tetrazole formation was observed using either dichloromethane or acetonitrile.

The Huisgen rearrangement requires higher temperatures, but even in refluxing acetonitrile, no rearrangement occurred. To address this issue, the solvent of the two first steps was removed, and toluene was added to the crude iminotetrazole. The resulting solution was then heated at reflux for 2.5 hrs, affording the corresponding bromotriazole in 72 % isolated yield.

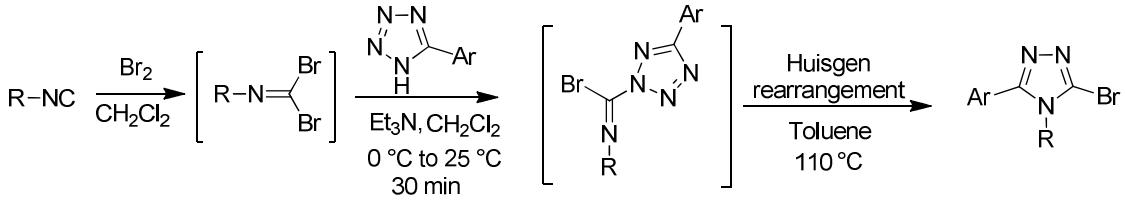
The imidoyl tetrazole, heated at 110 °C, looses a nitrogen molecule and undergoes a Huisgen rearrangement to form the corresponding bromo triazole *via* an electrocyclization (scheme IV.26).

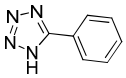
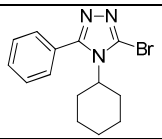
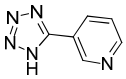
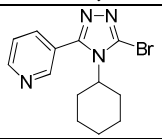
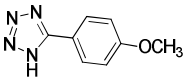
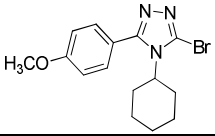
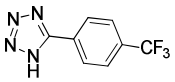
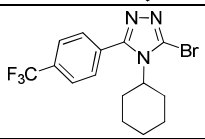
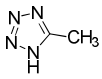
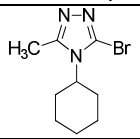


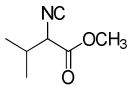
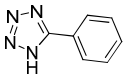
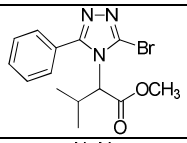
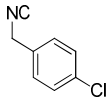
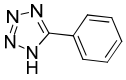
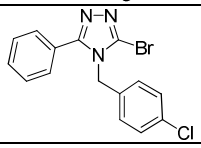
Scheme IV.24: Mechanism of Huisgen rearrangement to form bromotriazole.

The scope of this reaction was tested with various isocyanides and aryl terazoles. The reaction proceeded smoothly except for methyl tetrazole. In this case, enamine formation could compete with the desired pathway compromising the obtention of the desired adduct. The results obtained are tabulated in Table IV-B.

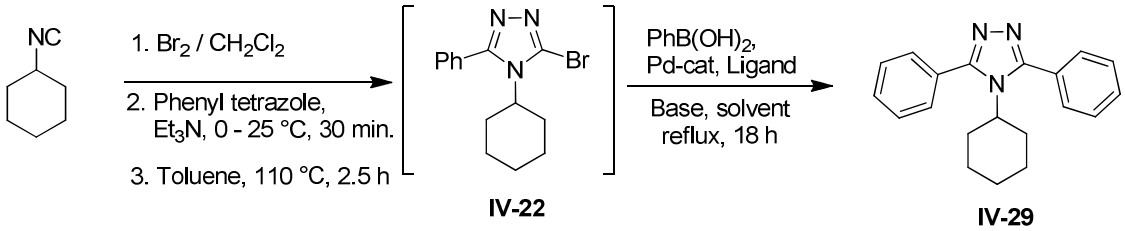
Table IV-B: Synthesis of bromo-triazole from isocyanides**.**



Entry	RNC	Aryl tetrazole	Product		Yield (%)
1				**IV-22**	**72 %**
2				**IV-23**	**65 %**
3				**IV-24**	**66 %**
4				**IV-25**	**27 %**
5				**IV-26**	**10 %**

6				**IV-27**	**53 %**
7				**IV-28**	**60 %**

Concerning the final Suzuki coupling, different sets of experimental conditions were evaluated based on the previous experiments: 3 equiv of phenyl boronic acid, 3 equiv of a base and the Pd-catalyst. The reaction mixture was heated up to 100 °C for 18 hrs. Palladium acetate with triphenyl phosphine, tricyclohexyl phosphine, SPhos gave only few amount of product but with 1,1'-*bis*(diphenyl-phosphino) ferrocene (dppf) as ligand, 40 % of the desired aryltriazole was isolated when using K_2CO_3 as a base. Similar results were obtained for the palladium-tetrakis(triphenyl- phosphine) (scheme IV.25).



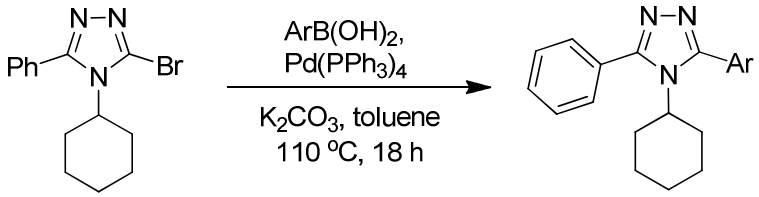
Catalyst/ligand	base	Solvent	% Yield[a]
$Pd(OAc)_2/PPh_3$	K_2CO_3	toluene	**traces**
$Pd(PPh_3)_4$	K_2CO_3	toluene	**37 %**
$Pd(OAc)_2/PPh_3$	Na_2CO_3	DME	**traces**
$Pd(PPh_3)_4$	Cs_2CO_3	toluene	**26 %**
$Pd(OAc)_2/PCy_3$	K_2CO_3	toluene	**12 %**
$Pd(OAc)_2$/SPhos	K_2CO_3	toluene	**21 %**
$Pd(OAc)_2$/dppe	K_2CO_3	toluene:H_2O (9:1)	-
$Pd(OAc)_2$/dppf	K_2CO_3	toluene	**40 %**
$Pd(OAc)_2$/dppf	K_3PO_4	toluene	**35 %**
$Pd_2(dba)_3$	K_2CO_3	toluene	-

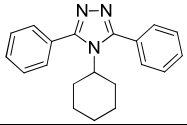
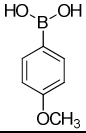
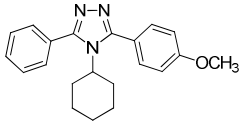
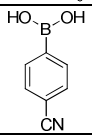
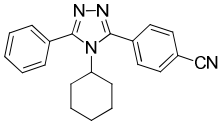
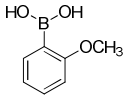
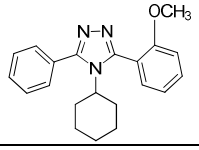
[a] Reaction conditions: phenylboronic acid (3.0 equiv), Pd catalyst (5%), ligand (10%), solvents (0.2M), base (3 equiv),

Scheme IV.25: Optimization of reaction for synthesis of 1,2,4 trisubstituted triazole.

Unfortunately, the whole sequence could not be done efficiently in a single pot. So, we decided to perform final Suzuki coupling separately after isolation of the bromotriazole. In these conditions, the Suzuki coupling of **IV-22** with various aromatic boronic acids gave moderate to good isolated yields, as tabulated below (see Table **IV-C**).

Table IV-C: Synthesis of 1,2,4-triazoles:



Entry	$ArB(OH)_2$	Product		Yield (%)
1			**IV-29**	**90 %**
2			**IV-30**	**96%**
3			**IV-31**	**65 %**
4			**IV-32**	**25 %**

Even if performed according to a two-step procedure, this method affords a straightforward access to trisubstituted 1,2,4-triazoles, which are important scaffolds in the pharmaceutical and agrochemical fields. Several potent drugs possessing triazole ring are available in the market, like, Alprazolam (anxiolytic agent, tranquilizer), Estazolam (hypnotic, sedative and tranquilizer), Triazolam (sedative and hypnotic).[167]

[167] a) Patel, K.; Mistry, B.; Desai, K. *J. Indian Chem. Soc.* **2002,** *79*, 964-965. b) Kane, J.; Baron, B.; Dudley, W.; Sorensen, S.; Staeger, M.; Miller, P. *J. Med. Chem.* **1990,** *33*, 2772-2777

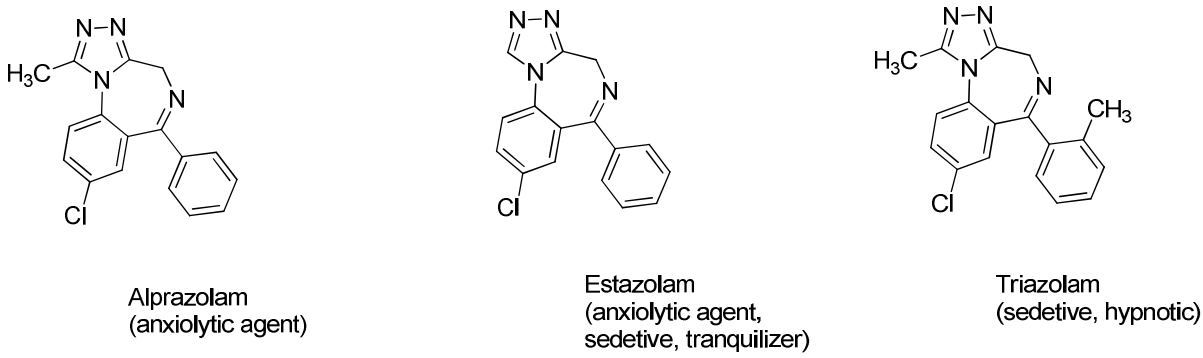


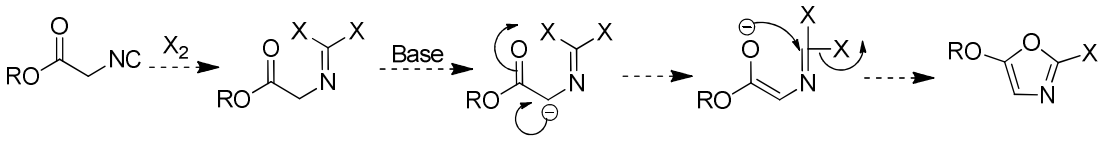
Figure IV-5: Structure of 1,2,4-triazole active drugs.

4. Novel oxazole synthesis

a. Presentation

As discussed earlier, α-isocyanoacetamides or α-isocyanoesters undergo isocyanide-Nef reaction to corresponding imidoyl halides, which under basic conditions give oxazole derivatives. Bromination of isocyanides would afford *gem*-dibromo isocyanides of α-isocyanoesters which could give bromooxazole. We imagined that the latter could then be involved in organometallic couplings to form substituted oxazoles.

In order to validate this strategy, we decided to investigate the behavior of dihalogeno-isocyanoacetates.

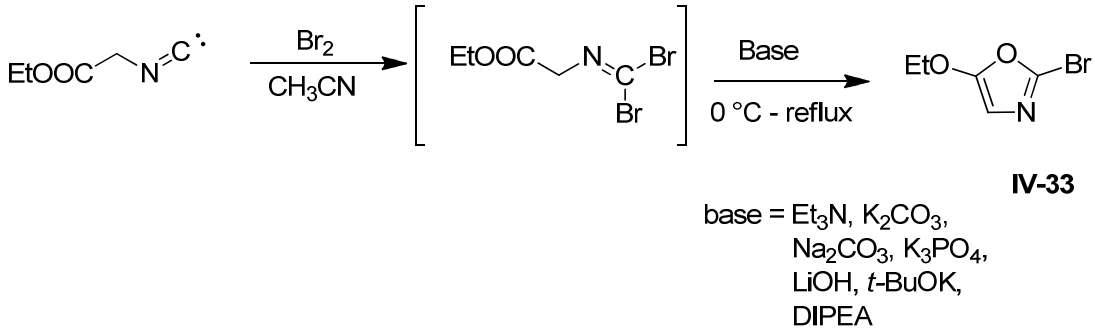


Scheme IV.26: Proposed path for halogeno-oxazole**.**

b. Results and Discussion

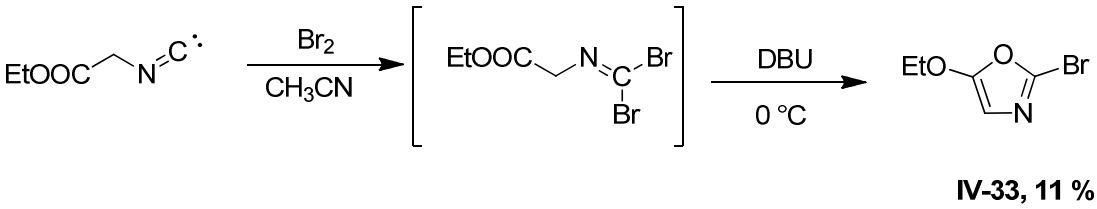
Bromination of the ethyl-α-isocyano acetate proceeded smoothly in dichloromethane at room temperature, as decoloration of the solution occurred within a few minutes giving quantitative formation of the desired *gem*-dibromo isocyanoester intermediate. Unfortunately, when treating the latter with triethylamine, the isocyanide was recovered as the major compound (the same behavior was observed in acetonitrile as solvent).

Different bases were explored in acetonitrile such as potassium phosphate, potassium carbonate, sodium carbonate, sodium bicarbonate, lithium hydroxide and potassium *tert*-butoxide. In all cases, the starting isocyanide was recovered (up to 60 %).



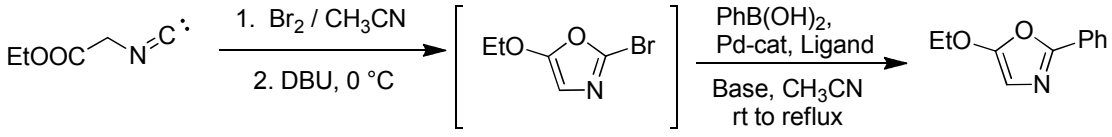
Scheme IV.27: Different trials for bromo-oxazole synthesis.

When *gem*-dibromo isocyanoacetate was treated with one equivalent of DBU at 0 °C, the desired 2-bromo-oxazole was isolated in 11 % yield, but it turned out to be quite unstable.



Scheme IV.28: Synthesis of bromo oxazole from α-isocyano acetate.

Considering the instability of the product, we decided to perform the whole sequence in a single-pot. For this purpose, the intermediate 2-bromo oxazole was tested under the Suzuki conditions, but all attempts failed.

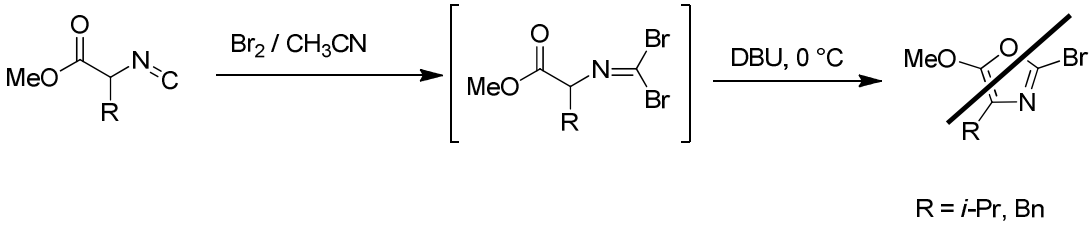


Pd-cat.	Ligand	base
$Pd(OAc)_2$	PPh_3	K_2CO_3
$Pd(OAc)_2$	PPh_3	Cs_2CO_3
$Pd(OAc)_2$	X-phos	K_2CO_3
$Pd(PPh_3)_4$	-	K_2CO_3
$Pd(PPh_3)_4$	-	Cs_2CO_3

.

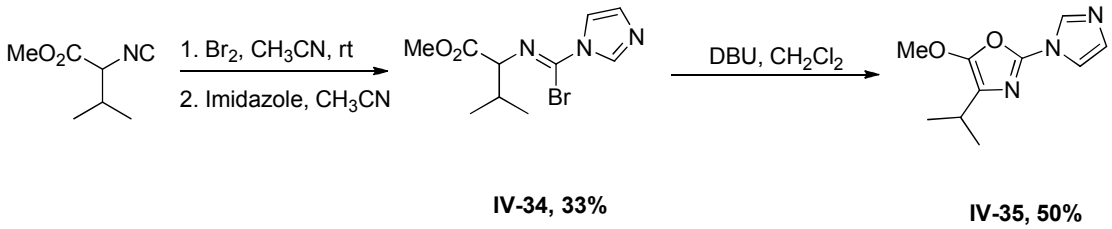
Scheme IV.29: Attempted synthesis of oxazole from α-isocyano acetate.

Due to the instability of the intermediate 2-bromo-oxazole **IV-33**, the sequence was repeated with substituted isocyanide such as valine and phenylalanine derivatives. However, these trials failed to give any cyclized adducts.



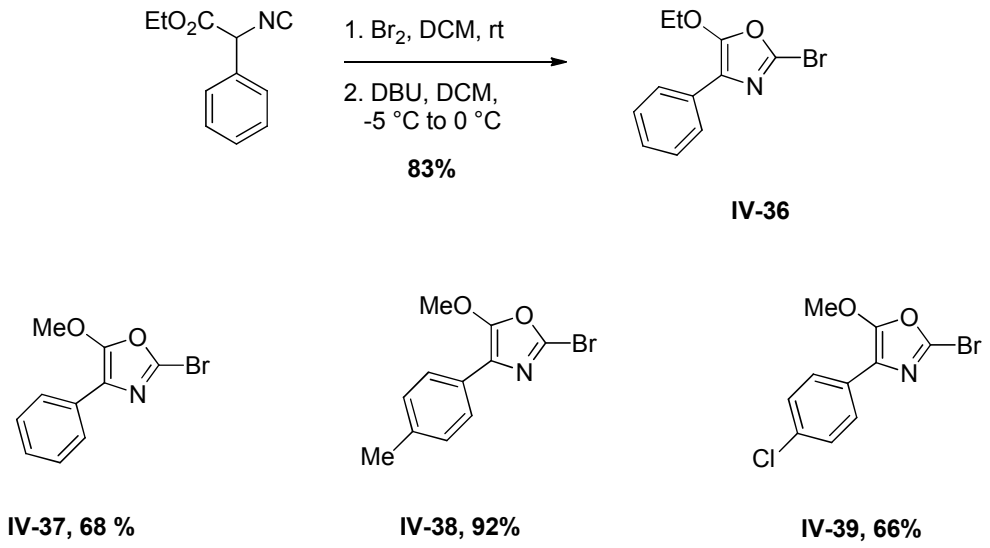
Scheme IV.30: Attempted synthesis of oxazole from valine and phenylalanine derivatives.

Surprisingly, when treated with two equivalents of imidazole, *gem*-dibromo isocyano-valinate gave 33 % of the corresponding bromoamidine **IV-34**, which cyclized upon treatment with DBU to afford the imidazolo oxazole **IV-35** in 50 % yield (Scheme IV.31).



Scheme IV.31: Attempted oxazole formation in the presence of imidazole.

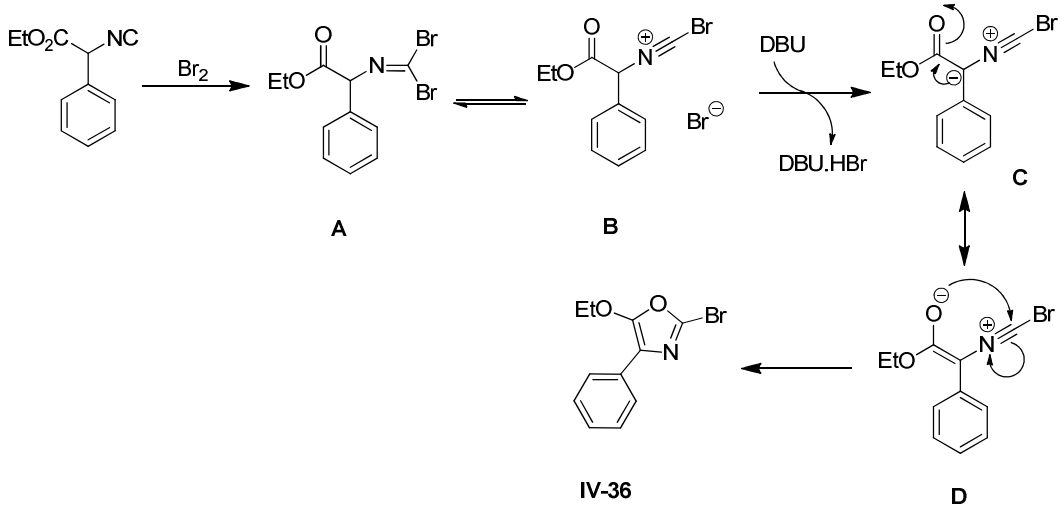
When the alkyl substituent was replaced by an aromatic group (ethyl-2-isocyano-2-phenylacetate), the desired bromooxazole **IV-36** was formed in 83 % yield. The reaction turned out to be efficient when the substituent on the aromatic ring as bromooxazoles were isolated in good yields with a methyl or a chloro substituent.



Scheme IV.32: 2-Bromooxazole synthesis from isocyanides.

Plausible reaction mechanism:

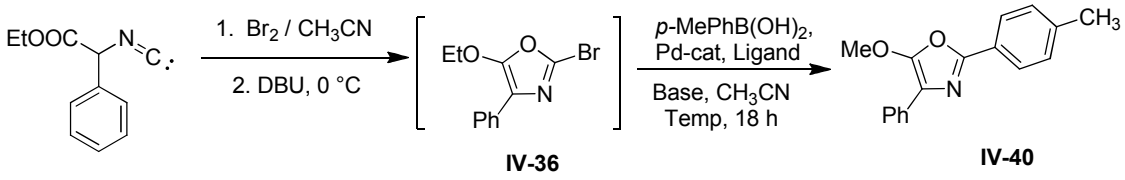
The presence of two halogen atoms on the terminal C-atom activates the C=N bond upon addition of nucleophiles in a sequential manner. The g*em*-dibromoisocyanide **A** may form the nitrilium **B**. Under basic conditions, the enolate **D** is generated and cyclizes to give the 2-bromooxazole **IV-36**. The phenyl substituent probably enhances the acidity of the proton present at the α-position in the imidoyl bromide **B**.



Scheme IV.33: Plausible mechanism of oxazole formation.

These phenyl substituted 2-bromo-oxazoles **IV-36** decomposed within 24 hrs at room temperature. To overcome this problem, we decided to trap this unstable intermediate with an arylboronic acid in a one-pot reaction. We chose acetonitrile as solvent, *p*-tolyl boronic acid,

potassium carbonate and a catalytic amount of Pd(0) were added to the reaction mixture containing both 2-bromo-oxazole **IV-36** and DBU hydrobromide salt (Scheme IV.34).

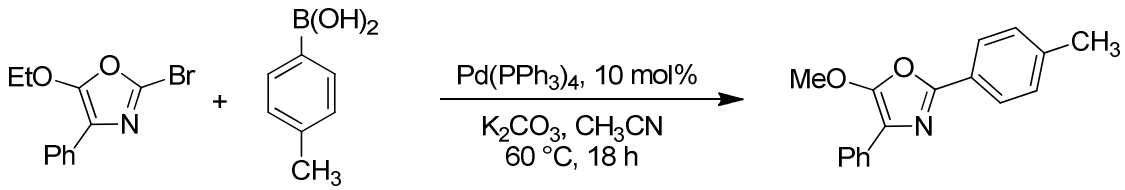


IV-36 **IV-40**

Pd-cat.	Ligand	base	Temp.
$Pd(OAc)_2$	PPh_3	K_2CO_3	80 °C
$Pd(OAc)_2$	PPh_3	K_2CO_3	70 °C
$Pd(OAc)_2$	PPh_3	Cs_2CO_3	80 °C
$Pd(PPh_3)_4$	-	K_2CO_3	80 °C
$Pd(PPh_3)_4$	-	K_2CO_3	50 °C

Scheme IV.34: Attempted synthesis of 2,4,5-trisubstituted oxazole.

No traces of cross-coupling could be detected under these reaction conditions. The salt DBU.HBr might contribute to the decomposition of the oxazole at high temperature. So, it was removed by filtration on a small silica pad. Dichloromethane was chosen in the first step, as it is easier to remove than acetonitrile. The Suzuki coupling was then attempted on the crude bromooxazole **IV-36** using 3 equivalents of *p*-tolyl boronic acid, 10 mol% of *tetrakis*(triphenylphosphine)palladium and a slight excess of potassium carbonate in acetonitrile, under stirring for 16 h at 60 °C. In these conditions, the desired 2,4-diaryl oxazole **IV-40** was isolated in 59 % isolated yield.



IV-36 **59 %** **IV-40**

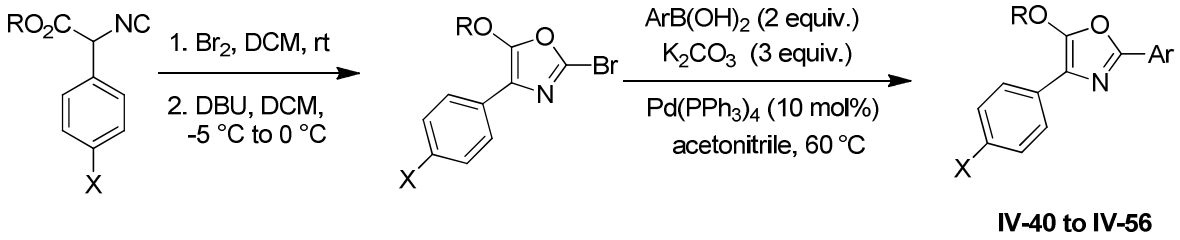
Scheme IV.35: Synthesis of 5-methoxy-4-phenyl-2-(p-tolyl)oxazole.

In order to improve the yield of the Suzuki coupling, acetonitrile was replaced by to toluene, and the reaction was carried out at different temperatures ranging from 60 °C to reflux. Beyond 60 °C, the rate of decomposition of 2-bromo-oxazole **IV-36** surpassed the rate of

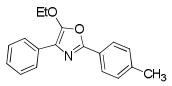
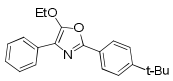
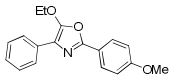
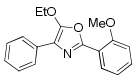
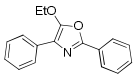
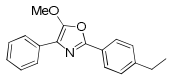
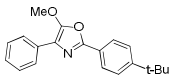
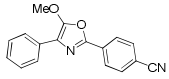
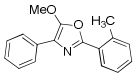
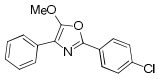
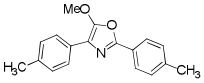
formation of the desired 2,4-diaryloxazole. So, it turned out that our initial conditions i.e. acetonitrile as solvent at 60 °C were optimal.

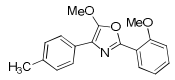
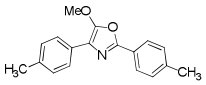
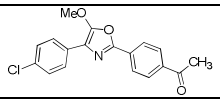
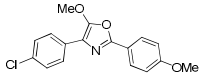
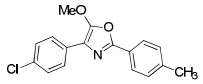
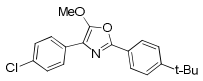
Under these optimized conditions, different arylated oxazoles have been synthesized using various boronic acids (Table IV-D).

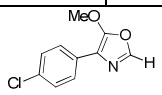
Table IV-D: 2,4-diaryloxazole synthesis.



IV-40 to IV-56

Entry	R	X	Ar	Oxazole		Yield (%)
1	Et	H	4-MeC_6H_4		**IV-40**	**59**
2	Et	H	4-*t*BuC_6H_4		**IV-41**	**33**
3	Et	H	4-MeOC_6H_4		**IV-42**	**49**
4	Et	H	2-MeOC_6H_4		**IV-43**	**30**
5	Et	H	C_6H_5		**IV-44**	**23**
6	Me	H	4-EtC_6H_4		**IV-45**	**33**
7	Me	H	4-*t*BuC_6H_4		**IV-46**	**53**
8	Me	H	4-NCC_6H_4		**IV-47**	**-**
9	Me	H	2-MeC_6H_4		**IV-48**	**19**
10	Me	H	4-ClC_6H_4		**IV-49**	**18**
11	Me	Me	4-MeOC_6H_4		**IV-50**	**18**

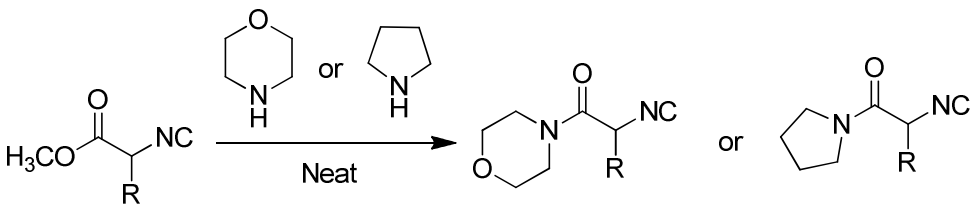
12	Me	Me	2-$MeOC_6H_4$		**IV-51**	**54**
13	Me	Me	4-MeC_6H_4		**IV-52**	**29**
14	Me	Cl	4-$MeCOC_6H_4$		**IV-53**	**-[a]**
15	Me	Cl	4-$MeOC_6H_4$		**IV-54**	**45**
16	Me	Cl	4-MeC_6H_4		**IV-55**	**58**
17	Me	Cl	4-*t*BuC_6H_4		**IV-56**	**49**

[a] The reduced oxazole was isolated in 62 % yields.  **IV-57**

The oxazole formation proceeded smoothly with electron-donating groups and halogens on the boronic acid. However, when bearing an electron-withdrawing group such as an acetyl (Table IV.D, entry 14) or a cyano (Table IV.D, entry 8), the reaction failed even with an excess of boronic acid. For less efficient couplings, the reduced oxazole was isolated as side product: for instance, the 4-(*p*-chlorophenyl)-5-methoxyoxazole (Table IV.D, entry 14) was isolated as the major compound.

Considering the three-component aminooxazole formation as reported by Zhu *et al*,[3] we thought that a similar sequence could be performed starting with the corresponding isocyano amides (pyrrolidino and morpholino derivatives).

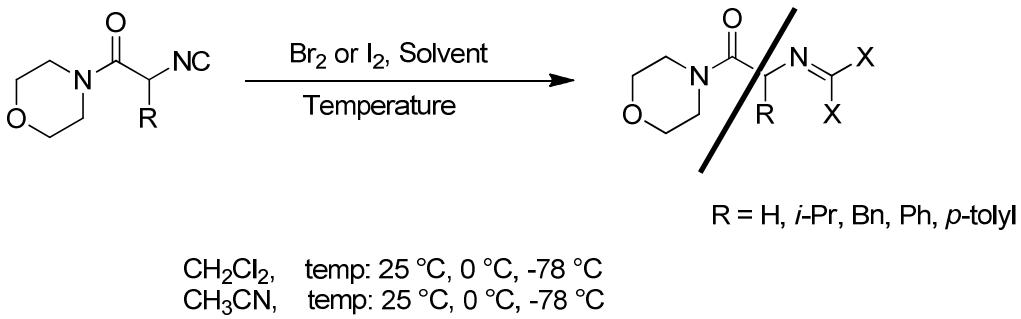
The synthesis of α-isocyanoacetamides was reported by Domling,[168] via neat aminolysis of methyl isocyanoacetate (Scheme IV.36).



Scheme IV.36: Synthesis of α-isocyanoacetamides.

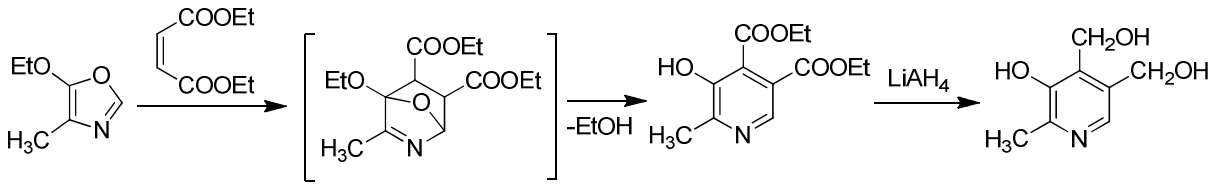
[168] Domling, A.; Beck, B.; Fuchs, T.; Yazback, A. *J. Comb. Chem.* **2006**, *8*, 872–880.

Addition of bromine on α-isocyanomorpholino acetamide was carried out in different conditions. All attempts failed to give the dibromoisocyanide, since its decomposition occurred rapidly (Scheme IV.37). When α-isocyanopyrrolidino acetamide was treated with bromine, similar behavior was observed.



Scheme IV.37: Bromination of α-isocyanoacetamides.

Even if limited to the ester derivatives of isocyanides, this methodology constitutes a new access to oxazole derivatives starting with isocyanide. Oxazole scaffolds have been found in a large number of natural compounds isolated from various marine sources as well as numerous bacteria.[169] Due to their low aromatic stabilization, they play an important role as synthetic intermediates of various heterocycles and aliphatic compounds.[170] For example, Vitamine-B_6 (pyridoxine) is synthesized from [4+2]-cycloaddition reactions between a 5-ethoxy oxazole and electron poor maleate to give the functionalized 3-hydroxypyridine.[171]



Scheme IV.38: Synthesis of Vitamine-B_6 (pyridoxine).

[169] a) Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero, M.; Donald, C.; Taylor, R. J. K. *Tetrahedron* **2008**, *64*, 4778-4791. b) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812-6815. c) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506-9509. For a review on the synthesis of natural occurring oxazoles see: (d) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995-12042.

[170] a) Turchi, I. J.; Dewar, M. J. S.; *Chem. Rev.* **1975**, *75*, 389-432. b) Palmer, D. C.; Taylor, E. C. in *Oxazoles: Synthesis, Reactions and Spectroscopy, Parts A & B, Chemistry of Heterocyclic Compounds*, John Wiley & sons, New York, **2004**, Vol 60.

[171] a) Firestone, R.A.; Harris, E.E.; Reuter, W. *Tetrahedron,* **1967**, *23*, 943–955. b) Graham Sandforda, Ian Wilsona, Christopher Timperley *Journal of Fluorine Chemistry* **2004**, *125*, 1425–1430.

Oxazole derivatives in the pharmaceutical industry have been especially noteworthy. Several non-steroidal anti-inflammatory, anti-diabetics drugs and antimicrobial medications with oxazoles as pharmacophores are in various stages of development (Figure IV-6).

For example, the oxazole derivatives listed below, are in the advanced clinical trials for type 2 diabetics.[172]

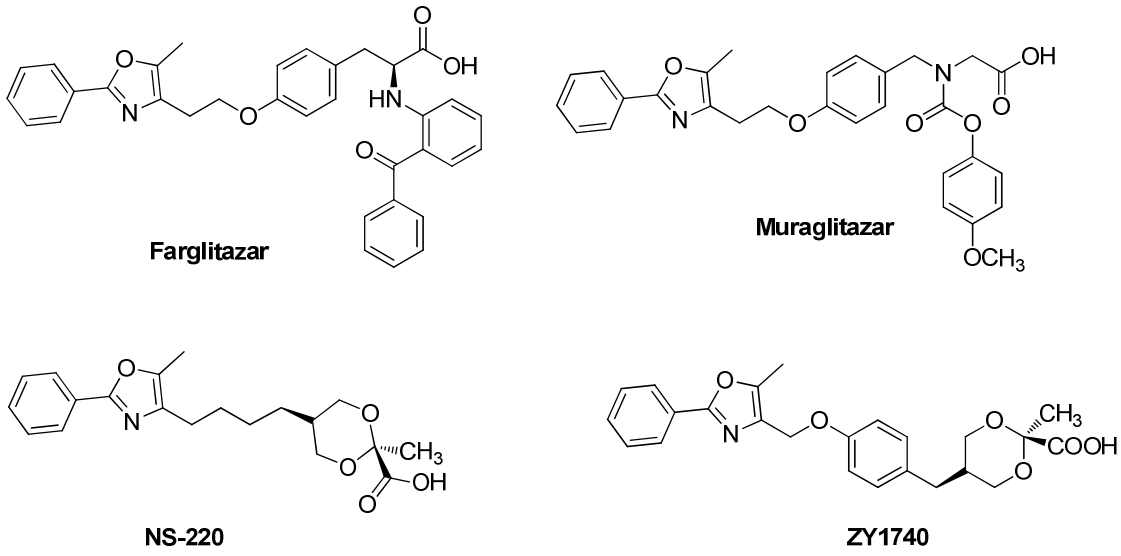
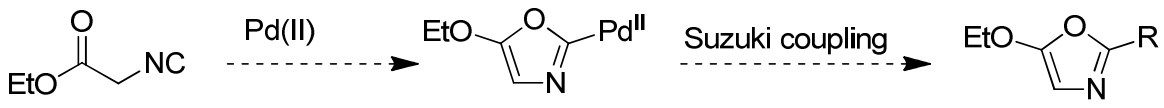


Figure IV-6: Oxazole derivative in drug discovery as PPAR α/γ dual agonists.

To conclude, dibromoisocyanides were found to be suitable precursors for the synthesis of various heterocycles such as oxazoles, tetrazoles and 1,2,4-triazoles. Isocyanide dihalides may be considered as isocyanide surrogates suitable for transition metal catalyzed couplings. However, this chemistry should be even more convenient without prior bromination of isocyanide. For this purpose, we surmised that simple coordination of the isocyanide glycinate with Pd(II), would afford the corresponding heterocycle-Pd complex, which could be further involved in Suzuki coupling (scheme IV.41). This approach will be further developed in our research group.



Scheme IV.39: Propose future path for oxazole from glycinoisocyanide.

[172] Pingali, H.; Jain, M.; Shah, S.; Patil, P.; Makadia, P.; Zaware, P.; Sairam, K.V. M.; Jamili, J.; Goel, A.; Patel, P.; Patel, P. *Bioorg. Med. Chem. Lett*. **2008** *14*, 6471–6475.

Chapter 5

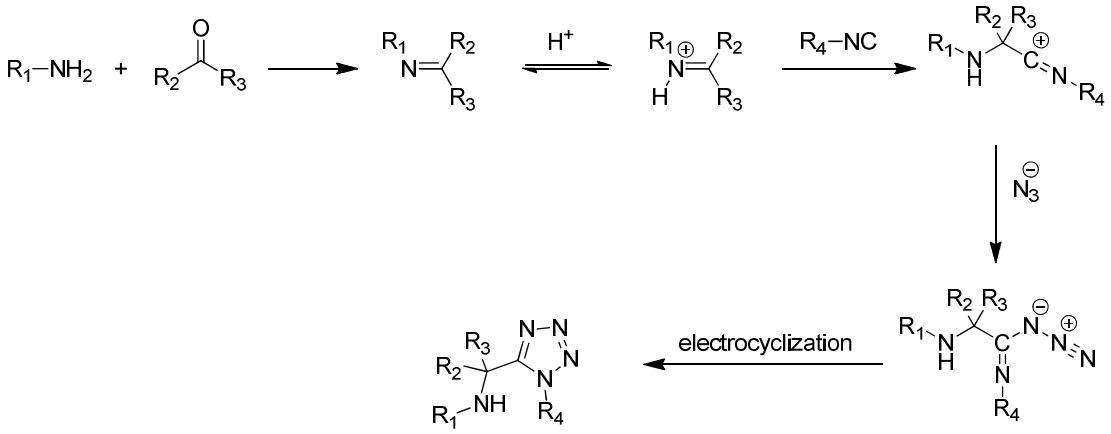
1,2,3-Triazole synthesis

The work described in this chapter has been submitted for publication:

El Kaïm, L.; Grimaud, L.; Pravin Patil.

I. The Ugi-azide reaction

In 1961, Ugi reported the synthesis of tetrazoles using hydrazoic acid instead of carboxylic acid in the classical Ugi reaction.[9c,34a] The condensation of an aldehyde or a ketone with a primary or a secondary amine and subsequent reaction with an isocyanide produces the intermediate nitrilium ion, which reacts with azide. A final electrocyclization affords the desired tetrazole (Scheme V.1).



Scheme V.1: Mechanism of the tetrazole-U-4CR.

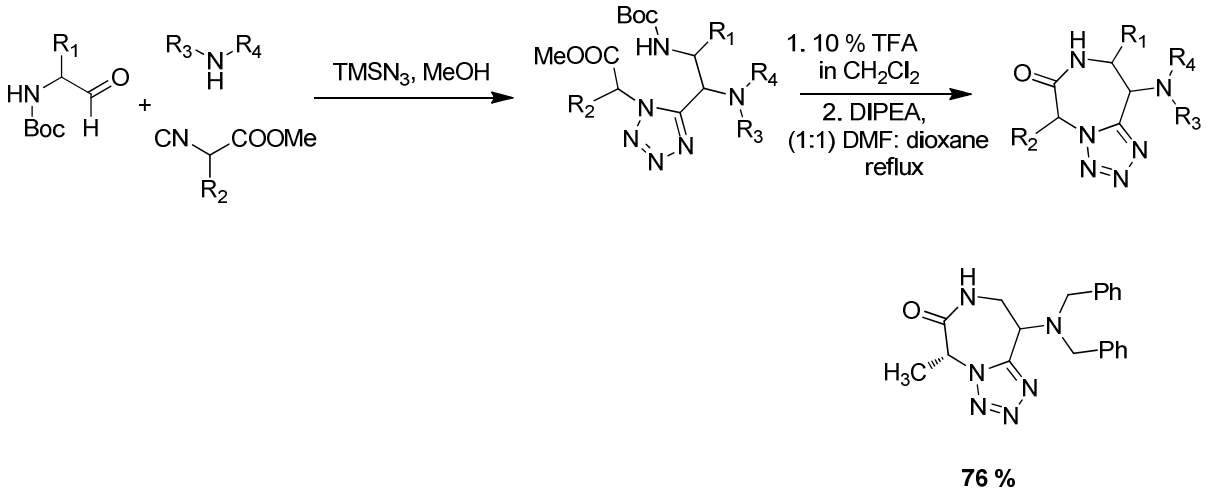
Due to the extreme toxicity and the explosive nature, hydrazoic acid was generated in situ from addition of sodium azide to the amine hydrochloride. $TMSN_3$ in methanol as solvent was later preferred for HN_3 generation.

Several syntheses of fused tetrazole systems were reported as post-condensation transformation.[173] We will discuss here selected examples.

In 2002, Hulme *et al* synthesized fused azepine-tetrazole libraries,[174] *via* the reaction of a *N*-Boc-amino aldehyde, a secondary amine, the methyl isocyanoacetate and trimethyl silylazide in methanol, followed by a deprotection of the *tert*-butyloxycarbamate (BOC) group (scheme V.2).

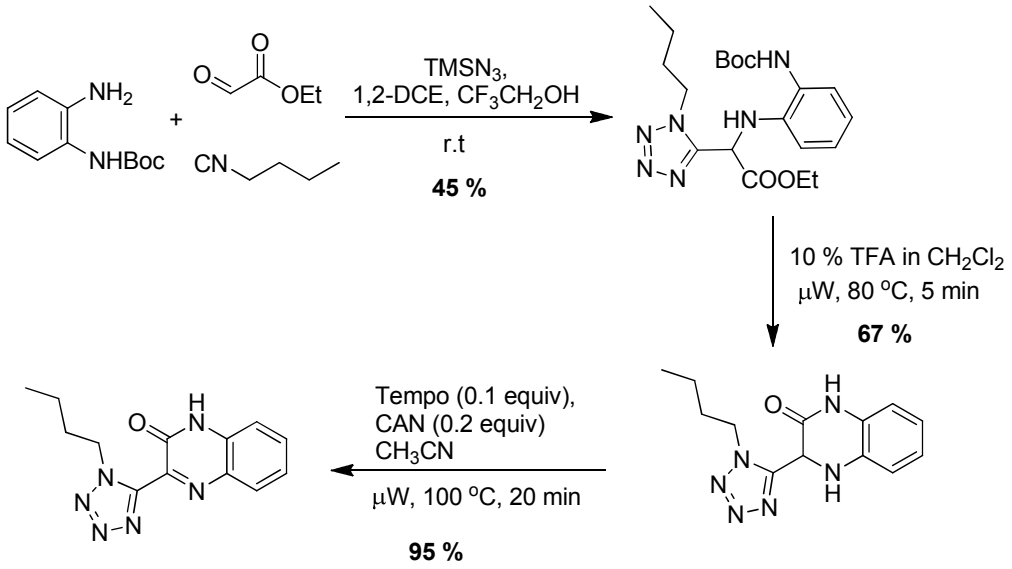
[173] a) Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett*. **2000**, *41*, 8729-7733. b) Bienayme, H.; Bouzid, K. *Tetrahedron Lett*. **1998**, *39*, 2735-2738.

[174] Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002,** *43*, 3681-3684.



Scheme V.2: Synthesis of bicyclic azepine-tetrazoles.

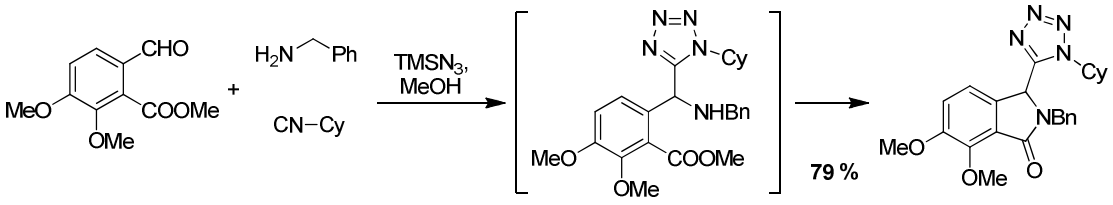
The same group recently reported a novel synthesis of 3-(tetrazol-5-yl)quinoxalin-2(1*H*)-ones.[175] The use of ethyl glyoxalate and mono-*N*-Boc-protected-*o*-phenylene diamine derivatives in the Ugi-Azide reaction gave 1,5-disubstituted tetrazoles. *N*-Boc deprotection and intramolecular cyclization lead to bis-3,4-dihydroquinoxalinone tetrazoles, which formed *bis*-quinoxalinone tetrazoles after oxidation (scheme V.3).



Scheme V.3: Synthesis of 3-(tetrazol-5-yl)quinoxalin-2(1*H*)-ones.

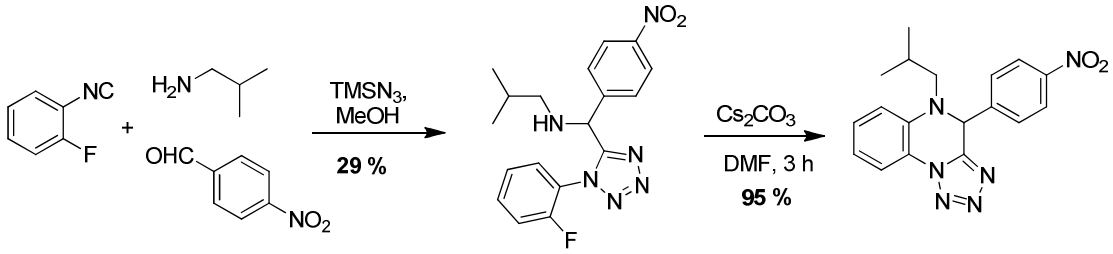
[175] Gunawan, S.; Nichol, G.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1664-1667.

Marcaccini *et al*[176] proposed a novel isoindolinone synthesis. In this case, the intermediate secondary amine cyclized on an additional ester present on the aldehyde used as starting material (scheme V.4).



Scheme V.4: Marcaccini's isoindolino synthesis.

Kalinski *et al*[177] described the synthesis of fused tetrazolo[1,5-a]quinoxalines. The use 2-fluorophenylisocyanide in the Ugi-azide reaction followed by a nucleophilic aromatic substitution (SNAr) afforded the tricylic tetrazolo[1,5-a]quinoxaline moiety in good yields (scheme V.5).



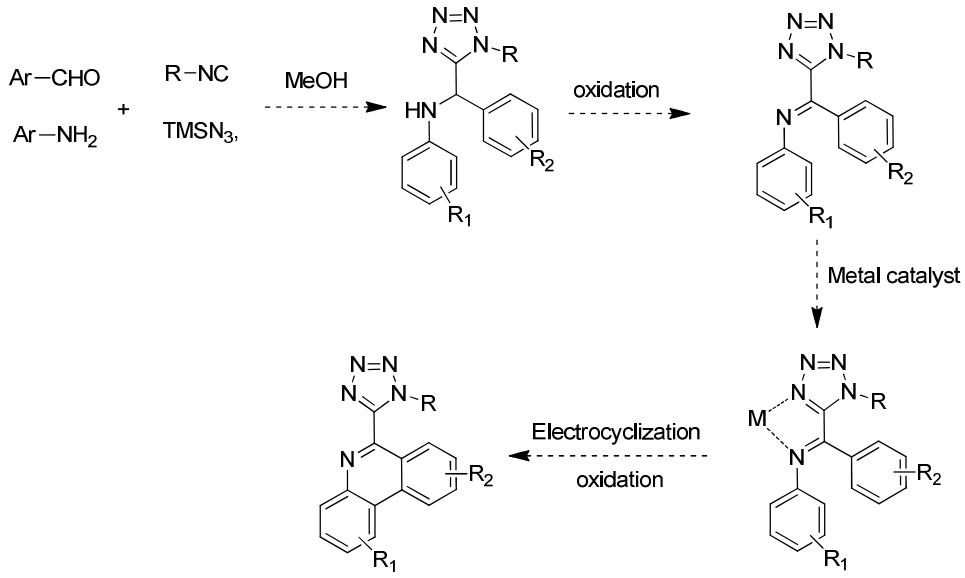
Scheme V.5: Synthesized fused 4,5-dihydrotetrazolo[1,5-a]quinoxaline.

As in tetrazole formation, the amine partner does not participate in the last cyclization step, primary and secondary amines behave efficiently. When a primary amine is used, Ugi-azide reaction gives a secondary amine which may be involved in further post-condensation as shown in the previous example.

[176] Marcos, C.; Marcaccini, S.; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett.* **2008**, *49*, 149-152.
[177] Kalinski, C., Umkehrer, M., Gonnard, S., Jager, N., Ross G., Hiller W. *Tetrahedron Lett.* **2006,** *47,* 2041-2044.

II. Presentation of the project

Our idea was to test these secondary amines in further annulation processes through intermediate oxidation. The resulting imine could evolve via an electro-cyclization to give quinoline-tetrazole derivatives (scheme V.6).



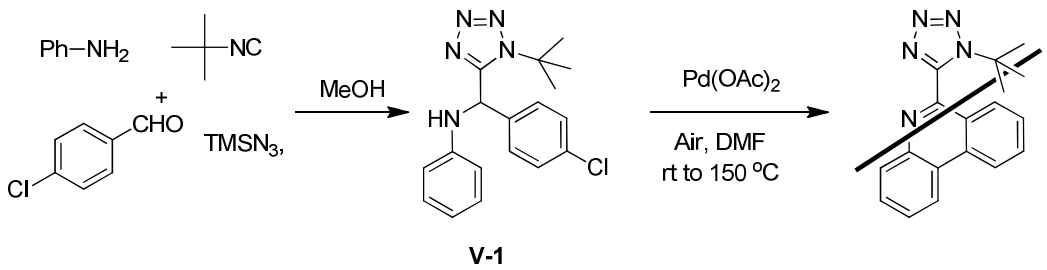
Scheme V.6: Proposed root for quinoline synthesis from Ugi-tetrazole reaction.

III. Results and discussion

1. 1,2,3-Triazole obtention

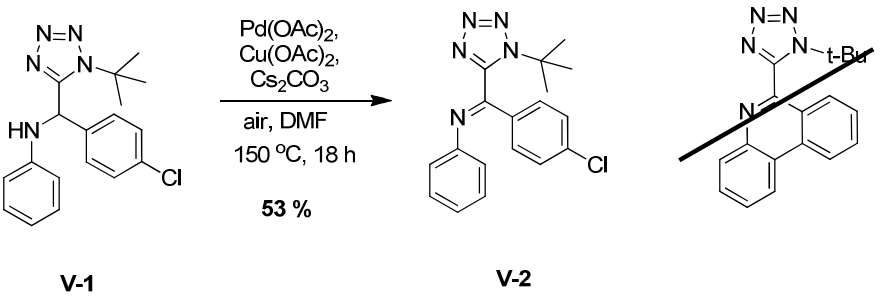
To test such a reaction sequence, the Ugi reaction was performed with aniline as an amine, 4-chlorobenzaldehyde and *tert*-butyl isocyanide with $TMSN_3$ in methanol at room temperature, the corresponding Ugi-azide adduct was obtained quantitatively.

Oxidative cyclization was first tested under air, in the presence of palladium acetate in DMF at 150 °C temperature. The reaction failed to give any product, since degradation occurred (scheme V.7).



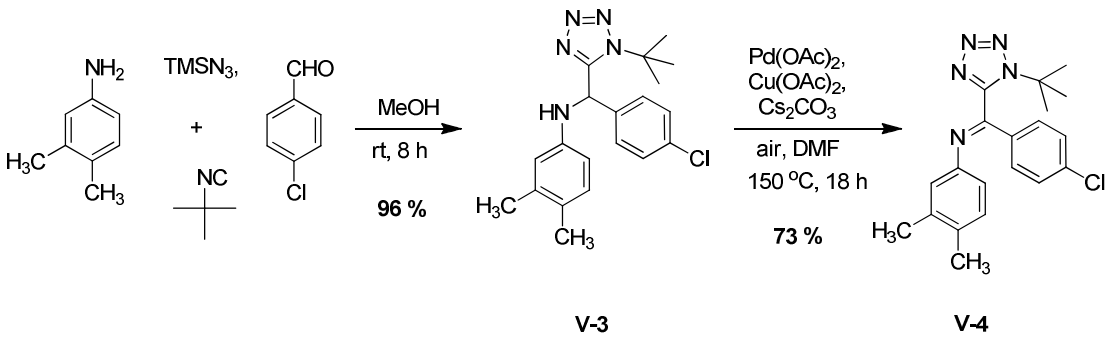
Scheme V.7: First trial of electrocyclization.

When the reaction was carried out with copper (II) acetate (3 equiv), cesium carbonate (1 equiv) and $Pd(OAc)_2$ (10 mol%), the expected imine was formed in moderate yield. However, no cyclization was observed (scheme V.8)



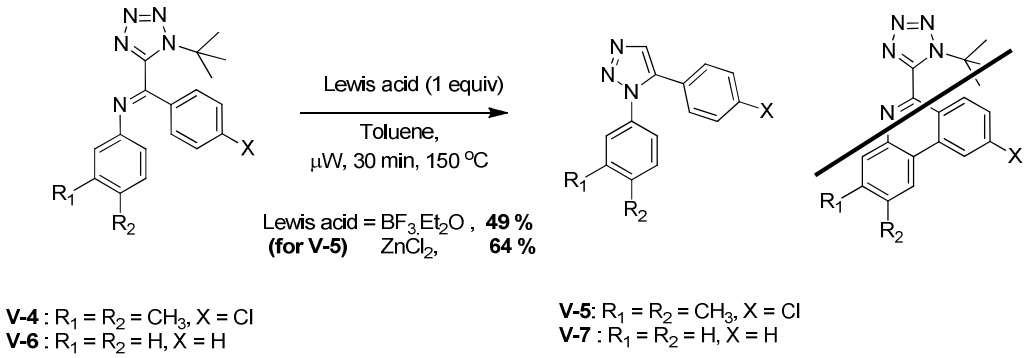
Scheme V.8: Oxidative imine formation.

Ugi-azide reaction of 3,4-dimethyl aniline formed the tetrazole **V-3** quantitatively (96 % isolated yield). Treated under oxidizing conditions, the corresponding imine **V-4** was then obtained in 73 % isolated yield (scheme V.9).



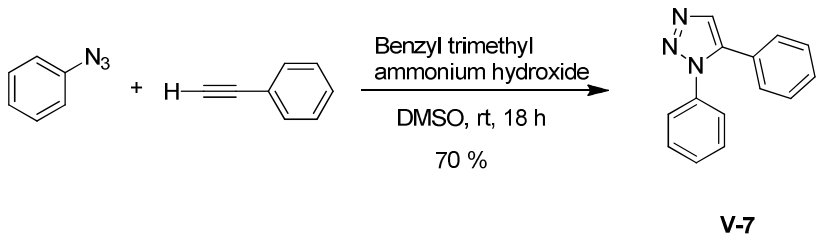
Scheme V.9: Oxidative imine formation in substituted.

Thermal cyclization of this imine under microwave irradiation at high temperature failed to give any product. The electrocyclization was then tested using different Lewis acids. When imine was heated under microwave irradiation with $BF_3.Et_2O$, 1,5-aryl substituted 1,2,3-triazole **V-5** was obtained in 49 % isolated yield, instead of the expected quinoline. $ZnCl_2$ gives the same product with a slightly higher yield (64 %) (Scheme V.10).



Scheme V.10: Synthesis of 1,5-disubstituted-1*H*-1,2,3-triazole

The formation of this triazole was surprising but the structure was confirmed by synthesizing the 1,5-diphenyl-1*H*-1,2,3-triazole from a known literature method (scheme V.11).[178] After a cycloaddition between phenyl acetylene and phenyl azide, we obtained the diphenyl triazole **V-7** with all spectral and physical properties matching with those previously obtained.



Scheme V.11: synthesis of 1,5-diphenyl-1*H*-1,2,3-triazole according to litrature**.**

2. Tetrazole fragmentation: state of the art

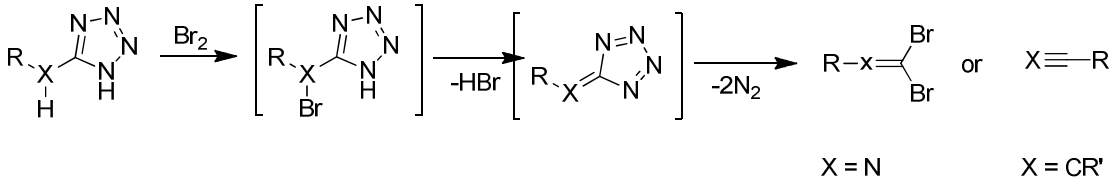
There are a number of methods and approaches that have been described in the literature for the synthesis of 1,2,3-triazoles.[179] Among them, the cycloaddition method mentioned above is the shortest and generally gives good yields.

[178] Kwok, S.; Fotsing, J.; Fraser, R.; Rodionov, V.; Fokin V, *Org. Lett.*, **2010**, *12*, 4217-4219

[179] a) Wamhoff, H. *Comprehensive Heterocyclic Chemistry I, Pergamon, Oxford* **1984**, *4*, 669-732. b) Fan W., Katritzky A. (editors), *Comprehensive Heterocyclic Chemistry II*, Vol. 4, *Elsevier Science, Oxford* **1996**, 1-126. c) Finley, T. K. Montgomery, J. *The Chemistry of Heterocyclic Compounds, Intersci. Publ., John Wiley & Sons Inc., New York* **1980**, *39*, 1. d) Benson, F., Savell, W. *Chem. Rev.*, **1950**, *146*, 1-68. e) Boyer J., *Heterocyclic Compounds* [Russian translation Moscow], **1965**, *7*, 296. f) Albert, A.*Adv. Heterocycl. Chem*., **1986,** *39*, 117-180.

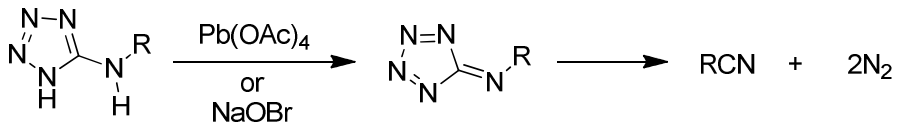
The reaction observed here under Lewis acid conditions; let us examine the fragmentation of tetrazole reported in literature.

A total ring fragmentation, involving loss of two molecules of nitrogen is observed in electrophilic addition of bromine on tetrazoles. In this reaction, *gem*-dibromo-isocyanide was obtained. The reaction mechanism involves exocyclic halogenation and loss of a hydrogen bromide molecule generating a tetraazafulvene intermediate which fragments to give the respective product. (scheme V.12).[180]



Scheme V.12: Electrophilic ring fragmentation.

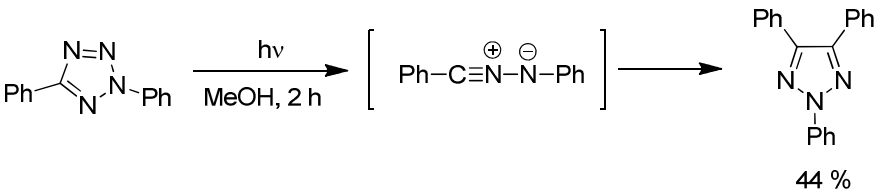
The oxidation of 5-(alkylamino)tetrazole with sodium hypobromite or lead tetraacetate leads the corresponding Schiff base which further evolves to a nitrile with loss of two nitrogen molecules (scheme V.13).[181]



Scheme V.13: Oxidative fragmentation of tetrazole ring.

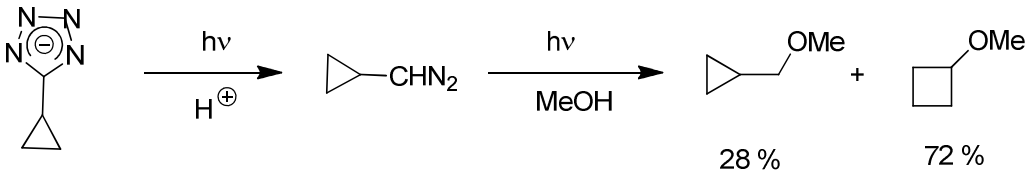
The photolysis of 2,5-diphenyltetrazole promotes the cleavage of the tetrazole ring and gives the corresponding nitrilimine, which after electrocyclization affords the 2,4,5-triphenyl-1,2,3-triazole (scheme V.14).[182]

[180] Butler, R. *Adv. Heterocycl. Chem*. **1977**, *21*, 323-435.
[181] Hofle, G.; Lange, B. *Angew. Chem. (Int. Ed. Engl.),* **1976**, *15*, 113-114.
[182] Bhat, V.; Dixit, V.; Ugarkar, B.; Trozzolo, A.; George, M. *J. Org. Chem*. **1979**, *44*, 2957-2961.



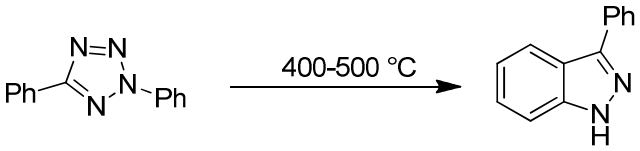
Scheme V.14: Photolysis of 2,5-diphenyltetrazole.

Similarly, photolysis of 5-substituted tetrazolate anions results in the loss of two molecules of nitrogen and generation of a carbene which gives normal insertion reaction.[183] 5-cyclopropyltetrazolate on photolysis gives the cyclobutyl methyl ether as the major product.



Scheme V.15: Photolysis of 5-substituted tetrazolate anions.

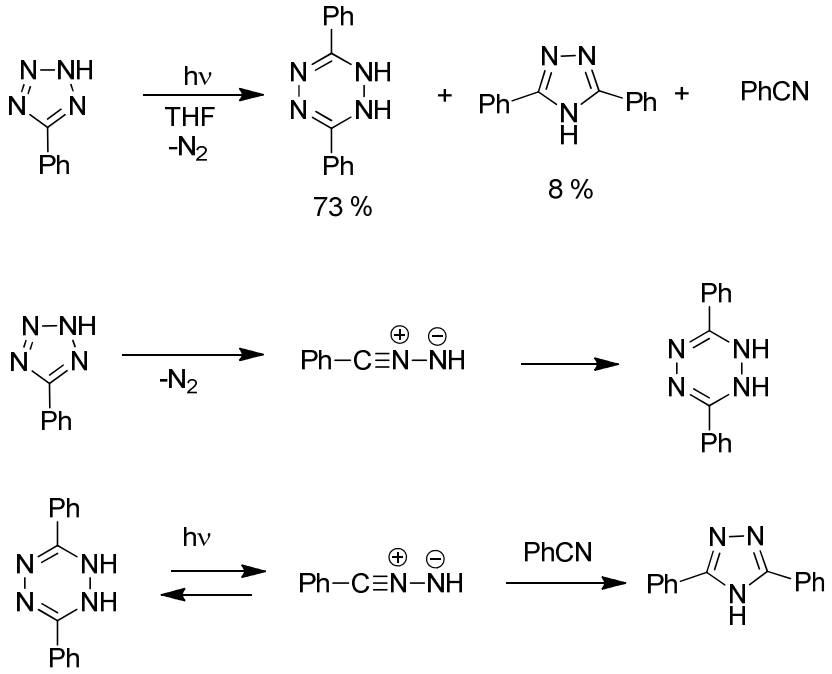
Flash thermolysis of 2,5-diaryltetrazoles at 400-500 °C gives 96-100 % yield of 3-arylindazoles in a reaction involving nitrilimine intermediates (scheme V.16).[184]



Scheme V.16: Flash thermolysis of 2,5-diaryltetrazoles

When using mono-substituted tetrazole, the photolysis affords 3,6-disubstituted 1,2-dihydro-1,2,4,5-tetrazines as the major compound. This reaction proceeds through the dimerization of a *N*-substituted nitrilimine species (scheme V.17).[185]

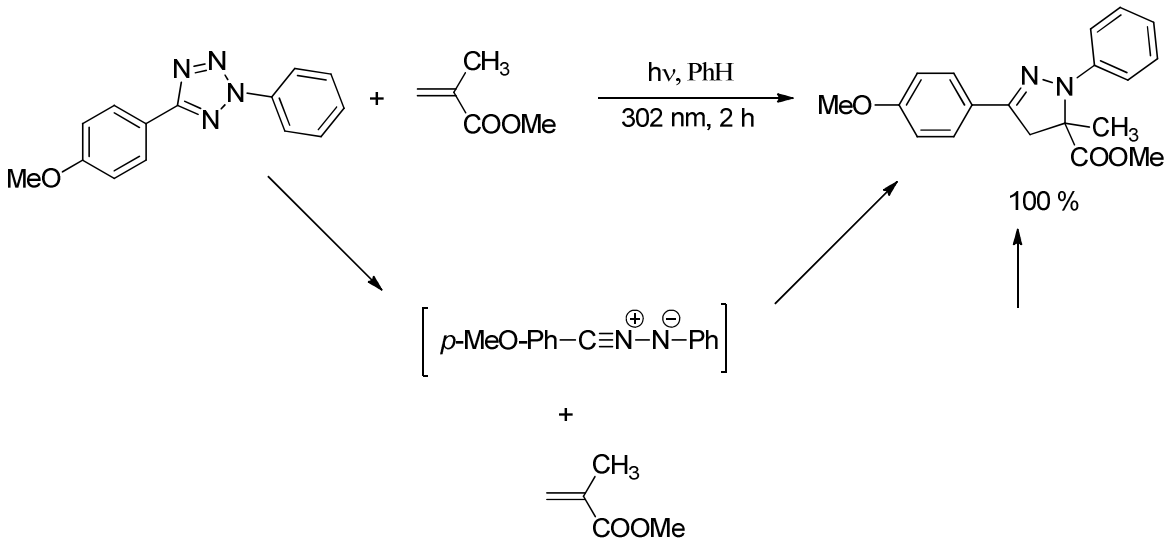
[183] Scheiner, P.; *Tetrahedron Lett*. **1971**, *12*, 4489-4492.
[184] Wentrup, C.; Damerius, A.; Reichen, W. *J. Org. Chem.* **1978**, *43*, 2037-2041.
[185] Sheiner, P.; Dinda, J.; *Tetrahedron*,**1970**, 26, 2619-2627.



Scheme V.17: Photolysis of 5-substituted tetrazole in THF

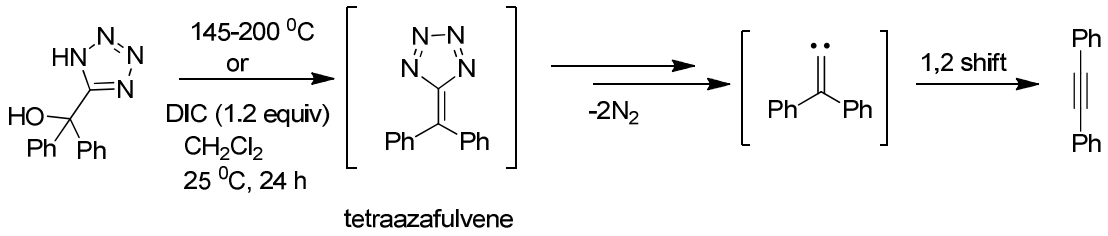
More interestingly, the nitrilimine intermediate could be trapped with an unsaturated substituent. For instance, Huisgen and co-workers reported a photoactivated 1,3-dipolar cycloaddition reaction between 2,5-diphenyltetrazole and methyl crotonate in benzene.[186] In a related work, Lin *et al*[187] reported an extremely mild photoactivation process for the synthesis of highly functionalized pyrazolines from diaryl tetrazoles. This procedure involves the in situ generation of the reactive nitrilimine using a UV lamp at 302 nm, followed by cycloaddition with an olefin (scheme V.18).

[186] Clovis, J.; Eckell, A.; Huisgen, R.; Sustmann, R. *Chem. Ber*. **1967**, *100*, 60-70.
[187] Wang. Y.; Vera. R.; Lin, Q.; *Org. Lett.*, **2007**, *9*, 4155-4158.



Scheme V.18: Synthesis of pyrazolines from diaryl-tetrazoles.

Behringer *et al*[188] described thermolysis and rearrangement of 5-hydroxyalkyl-1*H*-tetrazole and related derivative to form diarylalkynes. This reaction proceeds through dehydration of 5-hydroxyalkyl-1*H*-tetrazole to give unstable tetraazafulvene intermediate, which further rearranges to give the corresponding alkylidenecarbene. Recently, Wardrop *et al*[189] reported the same reaction under milder conditions, using *N*,*N'*-diisopropylcarbodiimide (DIC) at room temperature instead of thermolysis (scheme V.19).

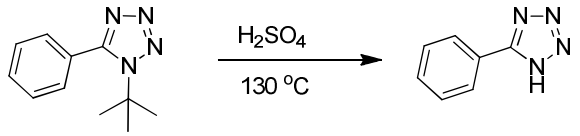


Scheme V.19: Synthesis of alkyenes from 5-hydroxyalkyl-1*H*-tetrazole by thermolysis.

[188] Behringer, H.; Matner, M. *Tetrahedron Lett.*, **1966**, *24*, 1663-1669.
[189] Wardrop, D.; Komenda, J. *Org. lett.*, **2012,** *14*, 1548-1551.

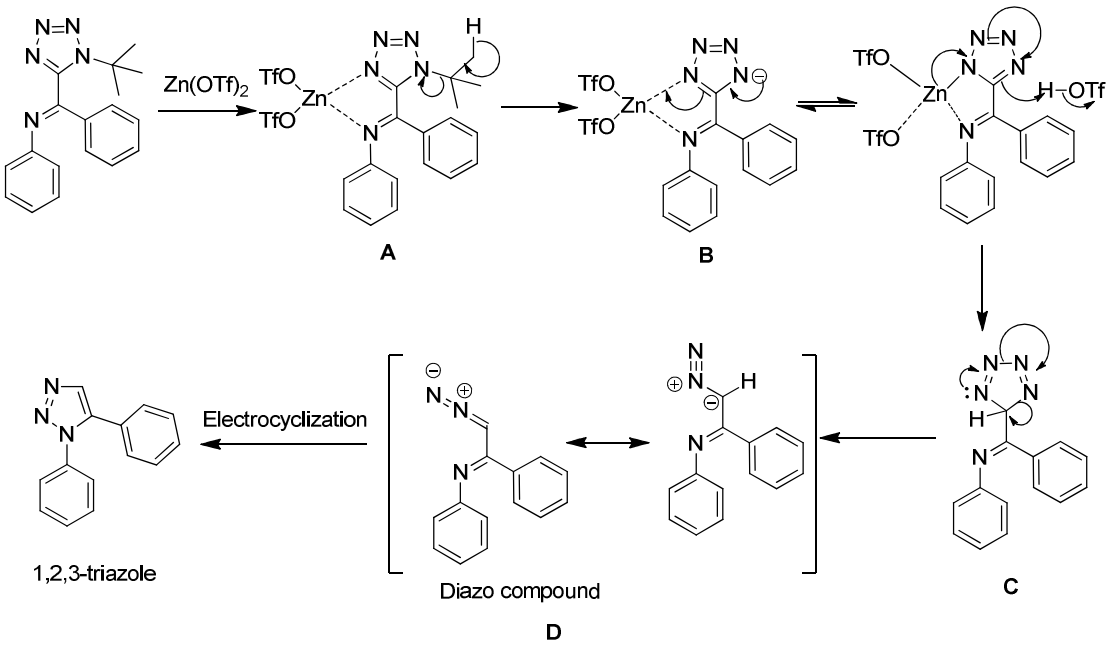
3. Possible mechanism for this new 1,2,3-triazole synthesis

The first step of the process is certainly the cleavage of the *N*-*tert*-butyl bond, which is found to be easily cleaved under acidic conditions. In 1911, Schroeter[190] discovered that *N*-alkyl tetrazole undergoes β-elimination of hydrogen atom to give *1H*-tetrazole (scheme V.20).



Scheme V.20: Cleavage of *N*-*tert*-butyl group in tetrazole in presence of acid.

The formation of a complex between the metal triflate and the tetrazole imine probably triggers the removal of the *tert*-butyl group to form **B.** The complex could then be protonated by triflic acid to give **C** which undergoes a ring opening with elimination of a nitrogen molecule to form the diazo **D**. A final electrocyclization forms the 1,5-disubstituted 1,2,3-triazole (scheme 21).

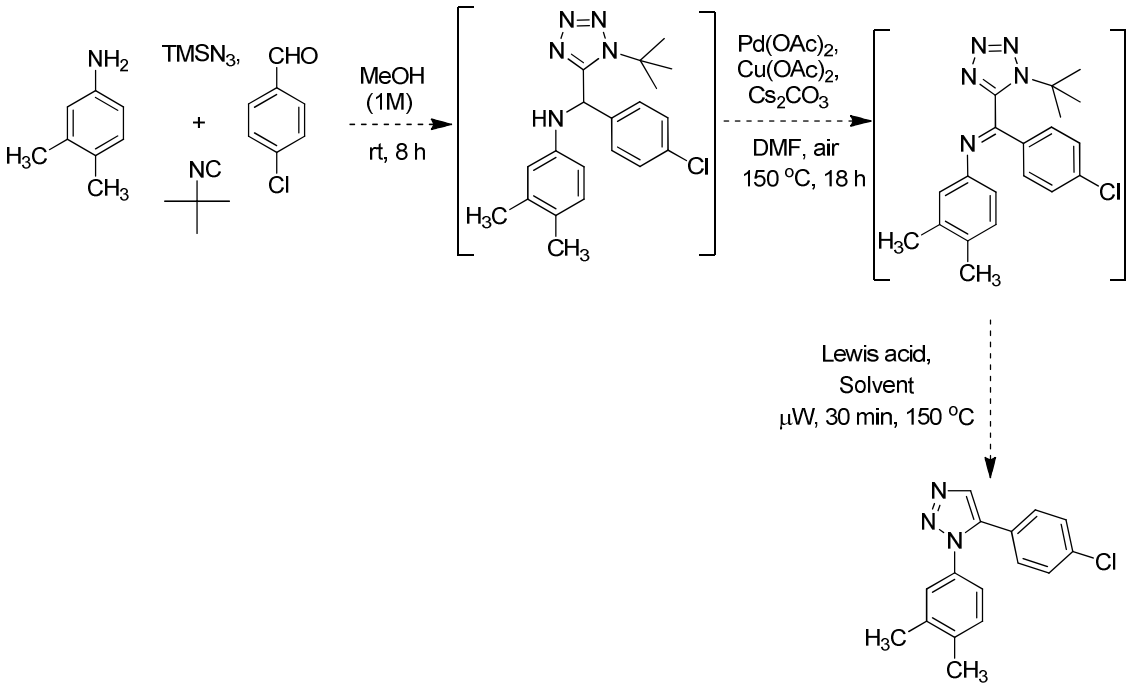


Scheme V.21: Possible reaction mechanism of 1,2,3-triazole formation from imine.

[190] a) Schroeter, *Berichte C.*, **1911**, *44*, 1202-1205.

4. Scope of the reaction

To test the one-pot synthesis of 1,2,3 triazole, the reactions were performed as previously settled for Ugi coupling and the oxidation step (scheme V.9). $ZnCl_2$ was added to the reaction mixture just after the oxidation. The resulting reaction mixture, heated under microwave irradiation at 150 °C for 30 min, totally decomposed.

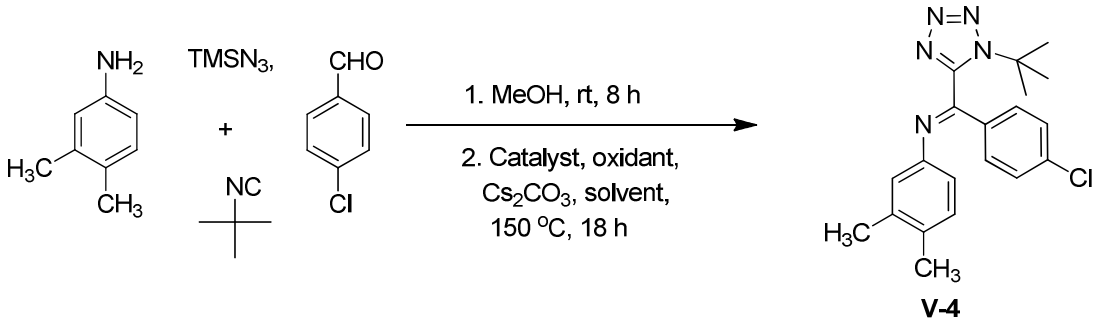


Scheme V.22: Proposed one-pot synthesis of 1,2,3-triazole.

N,*N*-dimethylacetamide and toluene were tested as solvents instead of DMF, but these solvents failed to give any product. Different palladium catalysts such as palladium acetate, *bis*-(2,2,2-trifluoroacetoxy) palladium, *tetrakis*(triphenylphosphine)palladium(0) were used as well, but no desired product could be isolated.

Facing such difficulties to settle a one-pot synthesis of 1,2,3- triazole, we decided to develop a two step procedure. For this purpose, the Ugi-azide coupling and oxidation were performed in one-pot and the last step -fragmentation-electrocyclization - was carried out separately.

The imine was obtained in two separate steps with 73 % isolated yield. Same conditions were used in a one-pot procedure. Methanol (1M) was selected as a solvent for the Ugi-azide reaction. After 18 hrs, DMF was added in the reaction mixture followed by addition of palladium acetate (10 mol%), copper acetate (1 equiv). The resulting mixture was heated under air at 150 °C for 18 hrs to obtain the corresponding imine **V-4** in a 75 % isolated yield.
Reaction was tested with different bases such as potassium carbonate, DBU, triethylamine and without base, the reaction is slow and give lower yields.
When replacing copper acetate by silver acetate, no significant change was observed. Finally, palladium(II) was not required in this process as same results were obtained.
In these conditions, the best solvent was found to be *N*,*N*-dimethylacetamide, which gave better yield than DMF. When two equivalents of copper acetate were used, the imine formation was faster and the reaction completed within 6 hrs to give 93 % isolated yield of the corresponding imine **V-4** (scheme V.23).



V-4

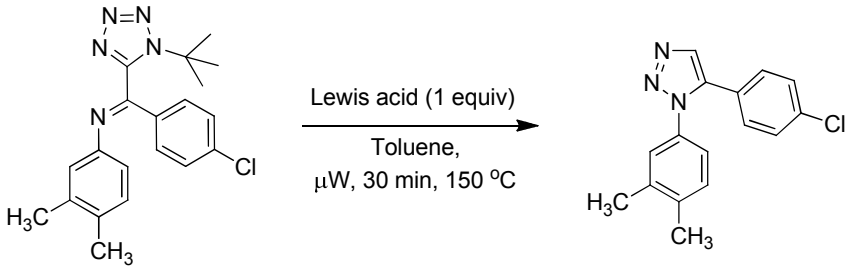
Catalyst	Oxidant	solvent	% yield
$Pd(OAc)_2$ (10 mol%)	$Cu(OAc)_2$, (1 equiv)	DMF	75 %
$Pd(OAc)_2$ (10 mol%)	AgOAc, (1 equiv)	DMF	70 %
$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2$, (1 equiv)	DMF	73%
None	$Cu(OAc)_2$, (1 equiv)	DMF	74 %
None	$Cu(OAc)_2$, (1 equiv)	DMA	82 %
None	$Cu(OAc)_2$, (2 equiv)	DMA	93 %

Scheme V.23: Optimization of one-pot imine formation.

1,2,3-Triazole was first synthesized by treating the iminotetrazole in toluene with a stoichiometric amount of $BF_3.Et_2O$ under microwave irradiation at 150 °C for 30 minutes.

Various Lewis acids were screened for this reaction such as cesium triflate, copper triflate, zinc triflate, aluminium triflate, silver triflate, iron trichloride, ytterbium triflate, indium triflate, samarium triflate.

Iron trichloride and samarium triflate failed to give any product but all the others gave the desired 1,2,3-triazole. However, the best yields were obtained with zinc triflate, forming the triazole in 74 %. (Scheme V.24).



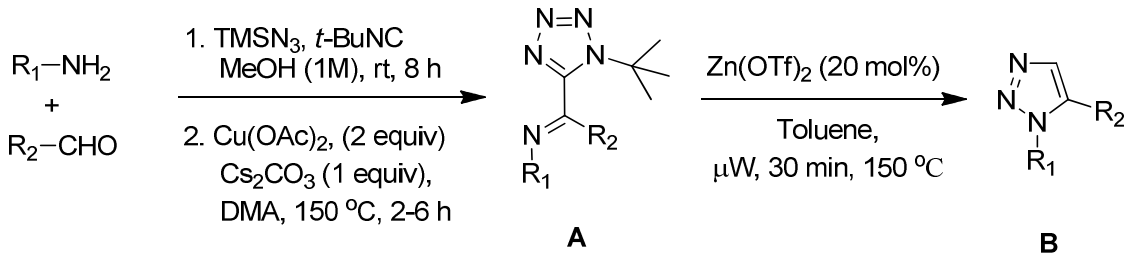
V-4 **V-5**

Lewis Acid	% yield	Lewis Acid	% yield
$ZnCl_2$ (50 mol%)	45 %	Cu(I)OTf (20 mol%)	45 %
$ZnCl_2$ (20 mol%)	37 %	$In(OTf)_3$ (20 mol%)	58 %
$Zn(OTf)_2$ (20 mol%)	74 %	$Yb(OTf)_3$ (20 mol%)	42 %
$Al(OTf)_3$ (20 mol%)	62 %	$FeCl_3$ (50 mol%)	--
AgOTf (20 mol%)	23 %	$Sm(OTf)_3$ (20 mol%)	--
CsOTf (20 mol%)	20 %		

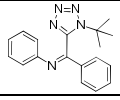
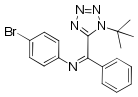
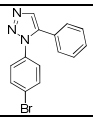
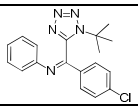
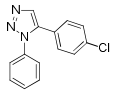
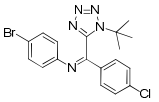
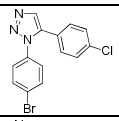
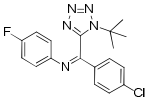
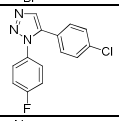
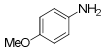
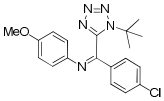
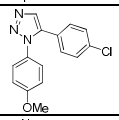
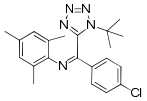
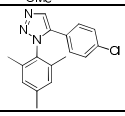
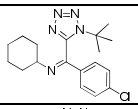
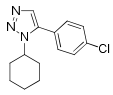
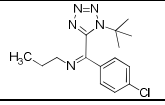
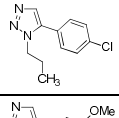
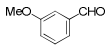
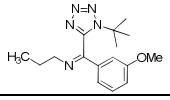
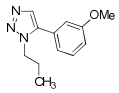
Scheme V.24: Optimization of 1,5-disubstituted 1,2,3-triazole from imine-tetrazole.

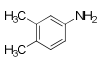
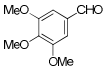
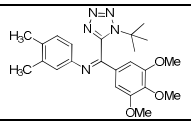
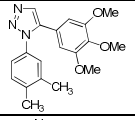
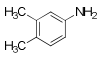
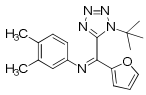
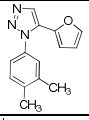
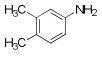
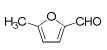
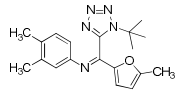
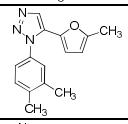
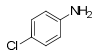
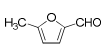
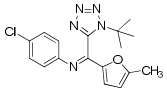
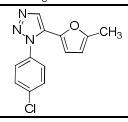
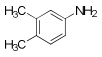
The formation of 1,2,3-triazoles requires high temperature as no product could be detected when performed at 80 °C or 120 °C.

The scope of both reactions was evaluated with various aromatics and aliphatic amines and aromatic aldehydes. Results are listed in table V-1.



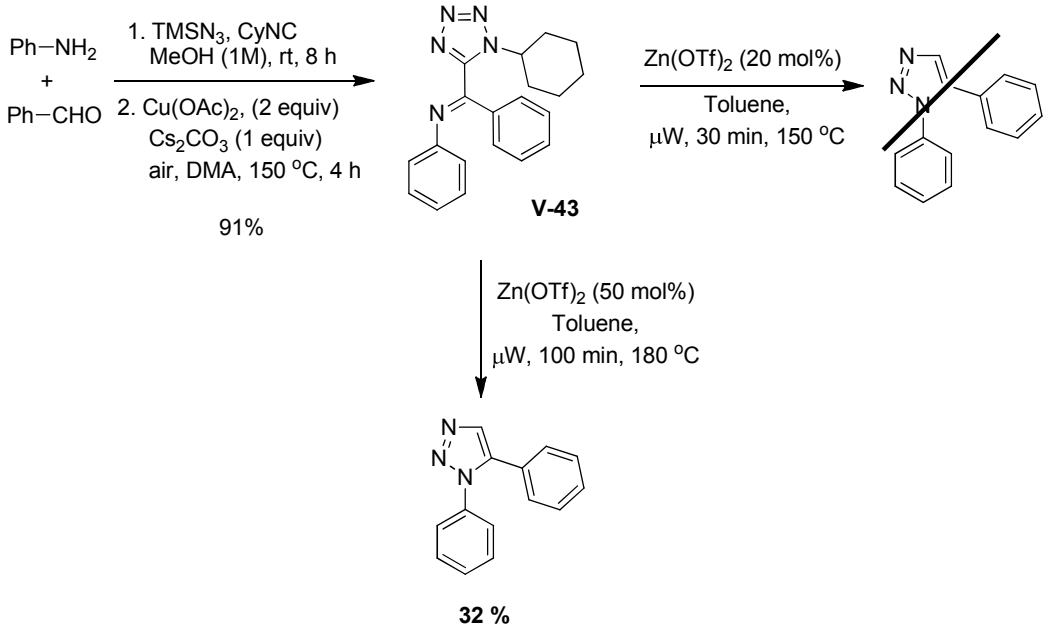
A **B**

Entry	R1-NH2	R1-CHO	Imine adduct A (Yield %)		1,2,3-tetrazole B (Yield%)	
1				V-6 63 %		V-7 69 %
2				V-8 68 %		V-9 71 %
3				V-2 84 %		V-10 66 %
4				V-11 48 %		V-12 83 %
5				V-13 46 %		V-14 61 %
6				V-15 54 %		V-16 72 %
7				V-17 39 %		V-18 59 %
8				V-19 49 %		V-20 44 %
9				V-21 87 %		V-22 55 %
10				V-23 53 %		V-24 56 %
11				V-25 51 %		V-26 78 %
12				V-27 50 %		V-28 57 %
13				V-29 72 %		V-30 54 %
14				V-31 72 %		V-32 72 %
15				V-33 87 %		V-34 64 %

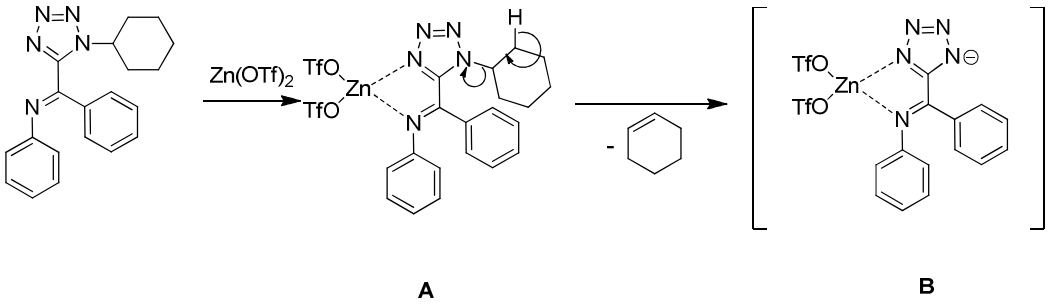
16				V-35 39 %		V-36 71 %
17				V-37 50%		V-38 54 %
18				V-39 39 %		V-40 37 %
19				V-41 31 %		V-42 44 %
20			-	-	-	-
21			-	-	-	-
22			-	-	-	-

Oxidative products of Ugi-azide adducts were obtained in moderate to good isolated yields with various aromatic aldehydes and amines bearing electron-withdrawing as well as electron-donating groups. Aliphatic amines gave the corresponding imino-tetrazole in good yields. However, the rearrangement turned out to be less effective in this case. Aliphatic aldehydes failed to give any oxidized product since imine formed from aliphatic aldehydes were highly unstable and could decompose rapidly.

When the same reaction sequence was carried out replacing *tert*-butyl isocyanide by cyclohexyl isocyanide, the iminotetrazole was isolated in excellent yield (91%). However, this product failed to give the 1,2,3-triazole under microwave irradiation using a catalytic amount of Lewis acid. But when using 50 mol% of zinc triflate at 180 °C for 100 minutes in toluene, the 1,2,3-triazole was isolated in 32% yield (scheme V.25). This is certainly due to the more difficult cyclohexene formation occurring during the first part of the process (scheme V.26).



Scheme V.25: 1,2,3-triazole synthesis from cyclohexyl isocyanide, aniline and benzaldehyde.



Scheme V.26: From cyclohexyl isocyanide.

5. Conclusion

1,2,3-triazoles are associated with a wide range of biological properties[191] such as antiviral, antiepileptic, antiallergic[192], anticancer[193], anti HIV[194] and antimicrobial activity against gram positive bacteria.

Some 1,2,3-triazole-containing molecules are in the market or are at the last stage of clinical studies, few of them are shown in the following Figure V.1.

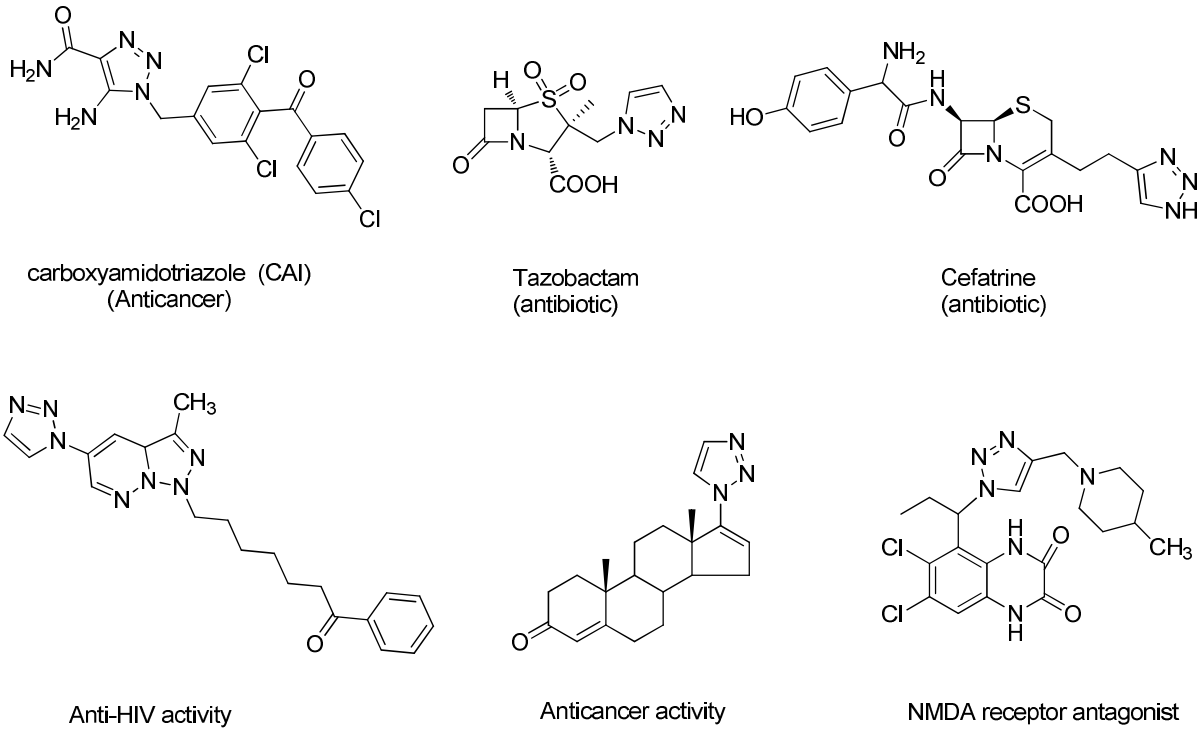


Figure V.1: Potential pharmaceuticals based on 1,2,3-triazoles.

Several 1,5-disubstituted 1,2,3-triazole analogues of combretastatin A-4 were prepared by Odlo *et al*[195] The 2-methoxy-5-[1-(3,4,5-trimethoxyp phenyl)-1 H-1,2,3-triazol-5-yl]aniline shows potent cytotoxic activity against several cancer cell (figure V.1)

[191] Agalave, S.; Maujan, S.; Pore, V.; *Chem. Asian J*. **2011**, *6*, 2696-2718.
[192] Palhagen, S.; Canger, R.; Henriksen, O.; van Parys, J. A.; Riviere, M.-E.; Karolchyk, M. A. *Epilepsy Res.* **2001**, *43*, 115-124.
[193] a) Pagliai, F.; Pirali, T.; Grosso, E.D.; Brisco, R.D.; Tron, G.C.; Sorba, G.; Genazzani, A.A. *J. Med. Chem.* **2006,** *49*, 467-470. (b) Bakunov, S.A.; Bakunova, S.M.; Wenzler, T.; Ghebru, M.; Werbovetz, K.A.; Brun, R.; Tidwell, R.R. *J. Med. Chem.* **2010,** 254-272. (c) Banday, A.H.; Shameem, S.A.; Gupta, B.D.; Sampath Kumar, H.M. *Steroids* **2010,** *75*, 801-1038.
[194] Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C.F.; Karlesson, A.; Balzarini, J.; Camarasa, M.J. *J. Med. Chem.* **1994**, *37*, 4185-4194.
[195] Odlo, K.; Hentzen, J.; Chabert, F.; Ducki, S.; Gani, Oi; Sylte, I.; Skrede M.; A.; Flørenes V.; Hansen T. *Bioorg. Med. Chem*. **2008**, *16*, 4829-4838.

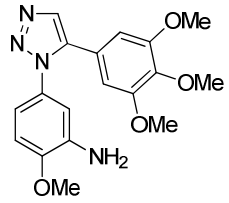


Figure V.1: Structure of 1,2,3-triazole as potent anticancer agent.

To conclude, we settled 1,5-disubstituted-1*H*-1,2,3-triazoles from Ugi post-condensation in moderate to good yields.

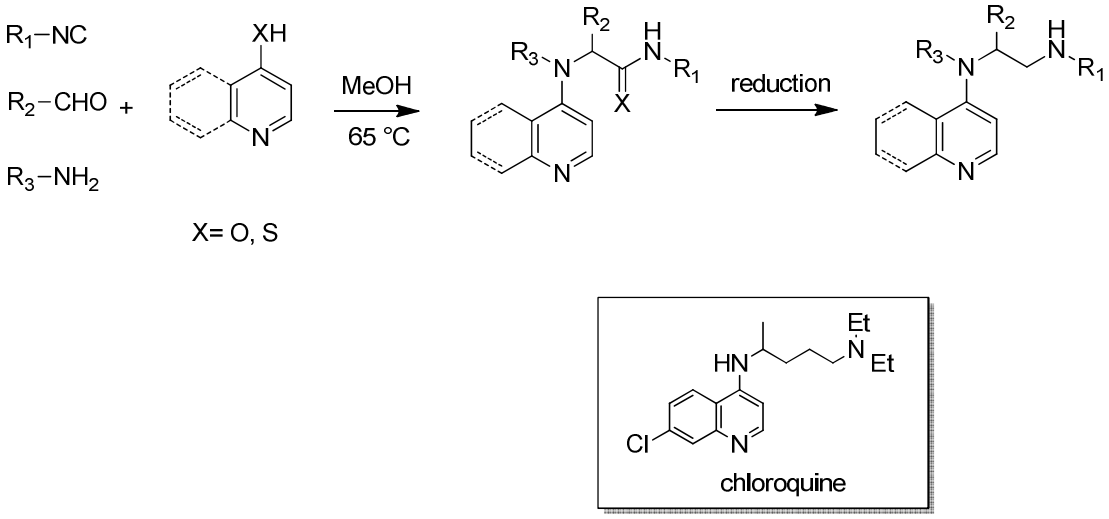
Though this is not a conventional method for the synthesis of 1,2,3 triazole, it has an advantage over the other mentioned methods. Indeed, in most cases, an aromatic azide is required as starting material, which is not convenient and not easy to prepare. However, in this method, the 1,2,3-triazole was synthesized from simple starting materials within two steps.

General conclusion

General conclusion

This thesis explores various multicomponent reactions based on isocyanides. In the first part it covers a study on the applications of the Ugi-Smiles reaction. The scope of the study was then extended to the use of dibromoisocyanides in three-component couplings. In the last part of this thesis, a new fragmentation reaction of tetrazoles (formed through Ugi-azide couplings) is described.

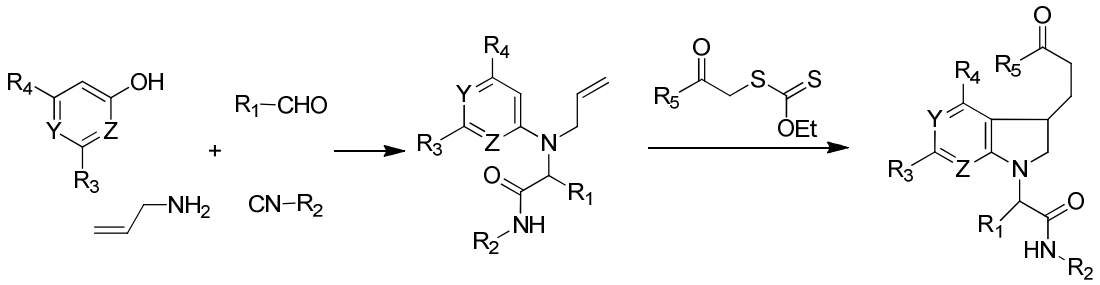
Our lab has discovered the Ugi-Smiles coupling in 2005. In this coupling various hydroxy phenols, hydroxy pyridines and pyrimidines were coupled with isocyanides, aldehydes and amines. Due to theoretical studies showing the importance of intramolecular hydrogen bonds in Smiles rearrangements, 4-hydroxypyridine derivatives had not been tested so far. In the first part of the thesis, we showed that these compounds react relatively well in Ugi-Smiles couplings. We synthesized various 4-aminoquenoline derivatives from 4-hydroxyquinolines. This study has been subsequently extended to 4-mercaptopyridines and quinolines. In the latter case, the reduction by Raney nickel leads to the preparation of analogues of chloroquine (antimalarial drug).



Scheme 1: Ugi-Smiles couplings involving 4-hydroxy/4-mercaptopyridines.

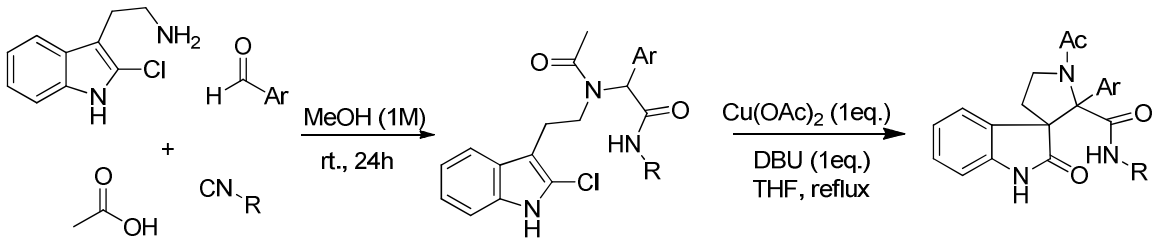
Influence by our interest in radical chemistry, we developed a radical sequence between *N*-allyl Ugi-Smiles adducts and xanthates. The results obtained allow to expand the scope of radical couplings developed by the group of Prof. S. Zard. Our reported two-step cascade is

the shortest method for synthesis of complex pyrrolidinopyridines and pyrimidines heterocycles.



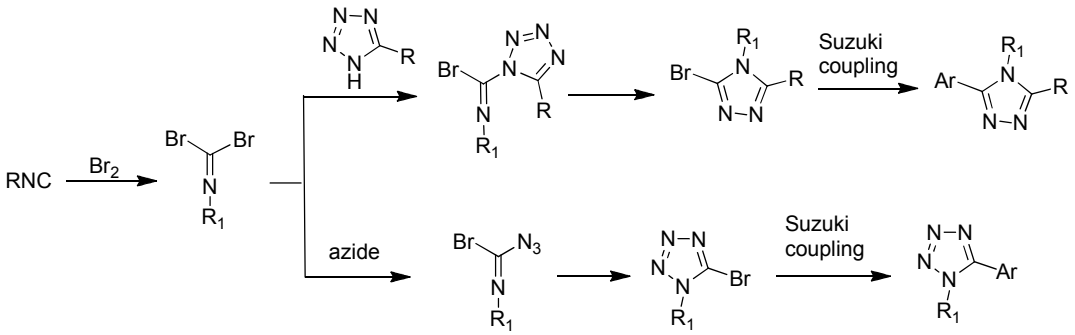
Scheme 2: Ugi-Smiles - xanthate radical cascade for synthesis of pyrrolidinopyridines and pyrimidines heterocycles.

Another study of post-radical condensation was carried out on Ugi adducts of tryptamine. The oxidative sequence catalyzed by copper salts gives a straightforward access to spiroindolines.



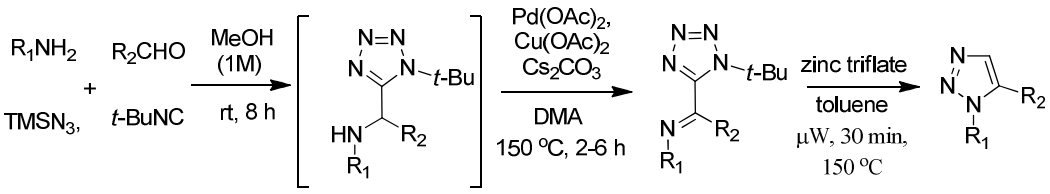
Scheme 3: Synthesis of spirooxindolines.

In the following part of the manuscript we explored the reactivity of *gem*-dihalogenated isocyanides and their use in heterocyclic chemistry. We have developed a synthetic methodology for the synthesis of tetrazoles and triazoles using *gem*-dihalogenated isocyanides. Suzuki reactions are involved in the last step of the sequence (Scheme 2).



Scheme 4: Synthesis of tetrazole and triazole via *gem*-dihalo isocyanide.

The final part of the manuscript deals with the fragmentation of tetrazoles obtained by Ugi-azide couplings. Ugi-azide reactions followed by oxidation with copper acetate and heating with zinc triflate give triazoles. Nitrogen is lost in the process. The fragmentation of tetrazoles under such Lewis acid catalyzed conditions is most noteworthy. Application of such fragmentations will be tested on other substrates to test their generality.



Scheme 5: Synthesis of tri-substituted oxazole

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Exprimental Part

General information

Equipment and analytical techniques

^{1}H NMR spectra were recorded on a Brucker Avance 400 MHz spectrometer, using $CDCl_3$ solvent as reference and/or internal deuterium lock. ^{13}C NMR spectra were recorded on a 100.6 MHz spectrometer. Two-dimensional NMR spectroscopy [^{1}H -^{1}H COSY spectra, ^{1}H -^{13}C COSY spectra (HSQC) and long-range ^{1}H -^{13}C COSY spectra (HMBC)], were carried out to determine the correlation between ^{1}H and ^{13}C. The chemical shifts for all NMR spectra are expressed in parts per million. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz.

The IR spectra were obtained using a Perkin-Elmer FT 1600 or a Brucker IFS 66 spectrophotometer. Wavelengths are reported in cm^{-1}.

High-resolution (HR) mass spectra were performed on a JEOL JMS-Gcmate II spectrophotometer.

Melting points were obtained using Stuart SMP3 melting point apparatus and remain uncorrected.

TLC was carried out using precoated plates of silica gel 60F254.

Experimental Part

Chapter 2

Experimental Part : Chapter 2

I. General Procedures:

a. General Procedure II-A: (Ugi-Smiles coupling involving 4-hydroxy pyridine.

To a 1 M solution of pyridin-4-ol derivatives in methanol were added successively 1.0 equiv of amine, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was stirred at 65 °C for two days. The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles product after purification by flash chromatography on silica gel.

b. General procedure II-B: (Ugi-Smiles coupling involving ammonia.)

To a 1 M solution of pyridin-4-ol in methanol were added successively 1.0 equiv of ammonia, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was heated under microwave irradiation (130 ^{o}C, 90 min, 100W). The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles products after purification by flash chromatography on silica gel.

c. General procedure II-C: (Ugi-Smiles coupling involving 4-hydroxyquinoline.)

To a 1 M solution of quinolin-4-ol derivatives in methanol were added successively 1.0 equiv. of amine, 1.0 equiv of aldehyde and 1.0 equiv. of isocyanide. The resulting mixture was stirred at 65 °C for two days. The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles product after purification by flash chromatography on silica gel.

d. General procedure II-D: (Ugi-Smiles coupling involving 4-thiopyridine.)

To a 1 M solution of pyridin-4-thiol derivatives in methanol were added successively 1.0 equiv of amine, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was stirred at 65 °C for one day. The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles product after purification by flash chromatography on silica gel.

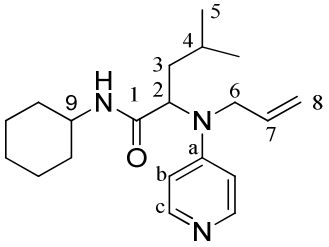
e. General procedure II-E: (Reduction of amide with borane–dimethyl sulfide complex.)

A solution of thioamide (1.0 mmol) in 10 mL of THF was heated to reflux and borane–dimethyl sulfide complex (6.0 mmol) was added. After 2.5 h, 6 M HCl (10.0 mmol) and 2 mL of water were added and the mixture was heated to reflux for 1.5 h. The clear solution was cooled to room temperature, basified with saturated NaOH and extracted with a 1:1 mixture of CH_2Cl_2 and $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography using EtOH/Pet.Ether/Et_3N (1:1:0.1 v/v) gave the corresponding amine.

f. General procedure II-F: (*Desulfurization with Raney nickel.)*

To the suspension of Raney nickel (10 equiv. by mass) in ethanol (25 ml), was added a solution of the thioamide compound (1.0 mmol, 1.0 equiv.). The mixture was heated at 55 °C under an argon atmosphere for 30 to 60 min. and filtered through a plug of celite 545®. The celite was washed with a solution of 20% ethanol in dichloromethane (3 x 15 mL) and the solution concentrated under reduced pressure to yield the crude product was purified by flash chromatography to give the pure product.

2-(allyl(pyridin-4-yl)amino)-*N*-cyclohexyl-4-methylpentanamide (II-1).



This compound was synthesized according to the general procedure II-A, using 2.1 mmol of isocyanide. The desired product was isolated in 69 % yield (475 mg).

Mol. Wt.: 329.48, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{20}H_{31}N_3O$: 329.2467, Found : 329.2467

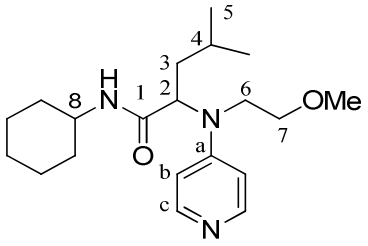
M.P. = 110 - 111 ^oC,

I.R. (thin film): 2930, 2853, 1652, 1596, 1544, 1513, 1450, 1235, 1169 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.23 (dd, 2H, *J* = 1.6, 5.2 Hz, H-c), 6.59 (dd, 2H, *J* = 1.6, 5.2 Hz, H-b), 5.95-5.80 (m, 2H, H-7, NH), 5.29-5.21 (m, 2H, H-8), 4.25 (t, 1H, *J* = 6.9 Hz, H-2), 4.00 (dd, 1H, *J* = 5.2, 17.2 Hz, H-6), 3.90 (dd, 1H, *J* = 5.2, 17.2 Hz, H-6), 3.80-3.69 (m, 1H, H-9), 2.08-2.00 (m, 1H, H-3), 1.86-1.76 (m, 2H, H-cy), 1.70-1.53 (m, 5H, H-cy, H-3, H-4), 1.39-1.25 (m, 2H, H-cy), 1.15-1.00 (m, 3H, H-cy), 0.92 (d, 3H, *J* = 6.7, Hz, H-5), 0.90 (d, 3H, *J* = 6.7, Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.9 (C-1), 153.0 (C-a), 150.2 (C-c), 133.2 (C-7), 118.1 (C-8), 108.3 (C-b), 61.0 (C-2), 49.7 (C-6), 48.4 (C-9), 37.7 (C-3), 32.9 (C-cy), 25.4 (C-cy), 25.2 (C-4), 24.7 (C-cy), 22.9 (C-5), 22.1 (C-5).

***N*-cyclohexyl-2-((2-methoxyethyl)(pyridin-4-yl)amino)-4-methylpentanamide (II-2)**



This compound was synthesized according to the general procedure II-A, using 5.3 mmol of isocyanide. The desired product was isolated in 65 % yield (1.18 gm.).

Mol. Wt.: 347.49, Nature: Pale yellow solid

HRMS: Calcd. for $C_{20}H_{33}N_3O_2$: 347.2573, Found : 347.2576

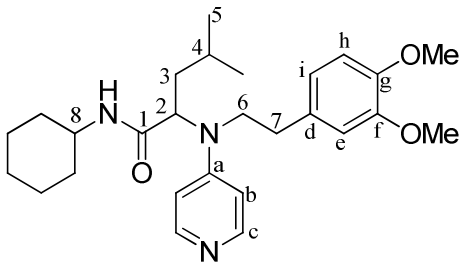
M.P. = 115 - 116 ^oC

I.R. (thin film): 3305, 2930, 2857, 1657, 1596, 1544, 1513, 1454, 1346, 1231, 1117 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.22 (dd, 2H, *J* = 1.6, 5.0 Hz, H-c), 7.38 (d, 1H, *J* = 7.9 Hz, NH), 6.52 (dd, 2H, *J* = 1.6, 5.0 Hz, H-b), 3.96 (dd, 1H, *J* = 4.8, 9.6 Hz, H-2), 3.87-3.80 (m, 1H, H-6), 3.76-3.66 (m, 2H, H-7), 3.64-3.58 (m, 1H, H-6), 3.52-3.43 (m, 1H, H-8), 3.38 (s, 3H, OCH_3), 2.03 (ddd, 1H, *J* = 4.8, 9.6, 14.2 Hz, H-3), 1.87-1.74 (m, 3H, H-3, H-cy), 1.69-1.48 (m, 4H, H-4, H-cy), 1.35-1.26 (m, 2H, H-cy), 1.12-0.91 (m, 3H, H-cy), 0.89 (d, 3H, *J* = 6.6 Hz, H-5), 0.87 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.9 (C-1), 151.5 (C-a), 149.8 (C-c), 108.8 (C-b), 69.2 (C-7), 64.4 (C-2), 58.7 (OCH_3), 49.8 (C-6), 48.2 (C-8), 36.9 (C-3), 33.0 (C-cy), 32.9 (C-cy), 25.5 (C-cy), 25.1 (C-cy), 25.0 (C-cy), 24.8 (C-4), 23.3 (C-5), 21.8 (C-5).

***N*-cyclohexyl-2-((3,4-dimethoxyphenethyl)(pyridin-4-yl)amino)-4-methyl pentanamide. (II-3)**



This compound was synthesized according to the general procedure II-A, using 5.3 mmol of isocyanide. The desired product was isolated in 72 % yield (1.71 gm).

Mol. Wt.: 453.62, Nature : Pale yellow solid.

HRMS: Calcd. for $C_{27}H_{39}N_3O_3$: 453.2991, Found : 453.3008.

M.P. = 85 - 86 ^oC

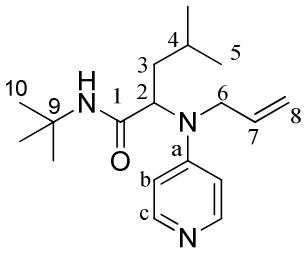
I.R. (thin film): 2933, 2857, 1665, 1589, 1509, 1457, 1349, 1259, 1152, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.27 (dd, 2H, *J* = 1.4, 5.1 Hz, H-c), 6.84 (d, 1H, *J* = 8.2 Hz, H-h), 6.78 (dd, 1H, *J* = 1.8, 8.2 Hz, H-i), 6.71 (d, 1H, *J* = 1.8 Hz, H-e), 6.61 (dd, 2H, *J* = 1.4, 5.1 Hz, H-b), 5.97 (d, 1H, *J* = 8.2 Hz, NH), 4.20 (t, 1H, *J* = 6.9 Hz, H-2), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.78-3.71 (m, 1H, H-8), 3.63-3.54 (m, 1H, H-6), 3.47-3.38 (m, 1H, H-6), 2.84 (t, 2H, *J* = 8.1 Hz, H-7), 2.11-2.04 (m, 1H, H-3), 1.84-1.75 (m, 2H, H-3, H-4), 1.65-1.54 (m, 5H, H-cy), 1.34-1.25 (m, 2H, H-cy), 1.09-0.96 (m, 3H, H-cy), 0.93 (d, 3H, *J* = 6.8 Hz, H-5), 0.91 (d, 3H, *J* = 6.8 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.6 (C-1), 152.6 (C-a), 150.1 (C-c), 149.0 (C-g), 147.9 (C-f), 130.6 (C-d), 120.3 (C-i), 111.7 (C-e), 111.4 (C-h), 108.1 (C-b), 61.2 (C-2), 55.9

(OCH_3), 55.8 (OCH_3), 49.1 (C-6), 48.4 (C-8), 37.5 (C-3), 33.4 (C-7), 32.8 (C-cy), 25.3 (C-cy), 25.1 (C-4), 24.7 (C-cy), 24.6 (C-cy), 22.9 (C-5), 22.3 (C-5).

2-(allyl(pyridin-4-yl)amino)-*N*-(tert-butyl)-4-methylpentanamide (II-4)



This compound was synthesized according to the general procedure II-A, using 2.6 mmol of isocyanide. The desired product was isolated in 43 % yield (360 mg).

Mol. Wt.: 303.44, Nature: Pale yellow solid

HRMS: Calcd. for $C_{18}H_{29}N_3O$: 303.2311, Found : 303.2309.

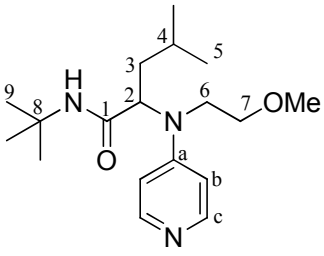
M.P. = 111 - 112 ^oC

I.R. (thin film): 2964, 2930, 2871, 1676, 1596, 1544, 1513, 1454, 1367, 1266, 1231, 1172 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.25 (dd, 2H, *J* = 1.6, 5.0 Hz, H-c), 6.59 (dd, 2H, *J* = 1.6, 5.0 Hz, H-b), 5.90-5.80 (m, 2H, NH, H-7), 5.28-5.19 (m, 2H, H-8), 4.19 (dd, 1H, *J* = 5.9, 8.0 Hz, H-2), 4.00 (ddt, 1H, *J* = 1.5, 5.0, 17.2 Hz, H-6), 3.89 (ddt, 1H, *J* = 1.5, 5.0, 17.2 Hz, H-6), 2.04-1.95 (m, 1H, H-3), 1.65-1.53 (m, 2H, H-3, H-4), 1.27 (s, 9H, H-10), 0.91 (d, 3H, *J* = 6.6 Hz, H-5), 0.89 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.0 (C-1), 153.0 (C-a), 149.8 (C-c), 133.1 (C-7), 117.9 (C-8), 108.3 (C-b), 61.4 (C-2), 51.4 (C-9), 49.6 (C-6), 37.5 (C-3), 28.5 (C-10), 25.0 (C-4), 22.8 (C-5), 22.2 (C-5).

***N*-(tert-butyl)-2-((2-methoxyethyl)(pyridin-4-yl)amino)-4-methylpentanamide (II-5)**



This compound was synthesized according to the general procedure II-A, using 5.3 mmol of isocyanide. The desired product was isolated in 42 % yield (700 mg).

Mol. Wt.: 321.46. Nature: Pale white solid.

HRMS: Calcd. for $C_{18}H_{31}N_3O_2$: 321.2416, Found : 321.2404.

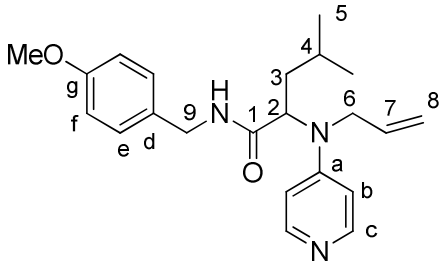
M.P. = 106 - 107 ^oC

I.R. (thin film): 3319, 2961, 2930, 2871, 2360, 1672, 1600, 1540, 1509, 1457, 1360, 1228, 1113 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.14 (dd, 2H, *J* = 1.6, 5.0 Hz, H-c), 7.22 (br s, 1H, NH), 6.48 (dd, 2H, *J* = 1.6, 5.0 Hz, H-b), 3.89-3.76 (m, 2H, H-2, H-7), 3.74-3.66 (m, 1H, H-7), 3.54-3.47 (m, 1H, H-6), 3.44-3.36 (m, 1H, H-6), 3.31 (s, 3H, OCH_3), 1.99-1.89 (m, 1H, H-3), 1.75-1.66 (m, 1H, H-3), 1.48-1.38 (m, 1H, H-4), 1.20 (s, 9H, H-9), 0.83 (d, 3H, *J* = 6.6 Hz, H-5), 0.80 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.0 (C-1), 151.3 (C-a), 149.3 (C-c), 108.7 (C-b), 69.2 (C-7), 64.7 (C-2), 58.7 (OCH_3), 50.6 (C-8), 50.2 (C-6), 36.5 (C-3), 28.3 (C-9), 24.9 (C-4), 23.1 (C-5), 21.8 (C-5).

2-(allyl(pyridin-4-yl)amino)-*N*-(4-methoxybenzyl)-4-methylpentanamide (II-6)



This compound was synthesized according to the general procedure II-A, using 2.1 mmol of isocyanide. The desired product was isolated in 39 % yield (300 mg).

Mol. Wt.: 367.48. Nature: Pale yellow solid.

HRMS: Calcd. for $C_{22}H_{29}N_3O_2$: 367.2260, Found : 367.2268.

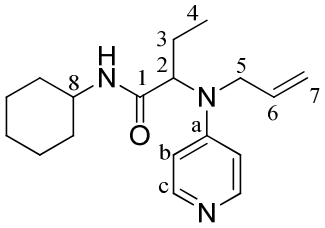
M.P. = 93 - 94 ^oC

I.R. (thin film): 3294, 2956, 2937, 1662, 1596, 1509, 1457, 1245, 1178, 1033 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17 (dd, 2H, *J* = 1.5, 5.1 Hz, H-c), 7.10 (dd, 2H, *J* = 1.9, 6.8 Hz, H-e), 6.80 (dd, 2H, *J* = 1.9, 6.8 Hz, H-f), 6.56 (d, 1H, *J* = 5.1 Hz, NH), 6.54 (dd, 2H, *J* = 1.5, 5.1 Hz, H-b), 5.77 (dtd, 1H, *J* = 5.5, 10.5, 15.0Hz, H-7), 5.18-5.16 (m, 1H, H-8), 5.15 (dd, 1H, *J* = 1.1, 5.5 Hz, H-8), 4.38-4.28 (m, 3H, H-9, H-2), 3.98 (dd, 1H, *J* = 5.5, 17.2 Hz, H-6), 3.89 (dd, 1H, *J* = 5.5, 17.2 Hz, H-6), 3.77 (s, 3H, OCH_3), 1.98 (ddd , 1H, *J* = 6.1, 7.9, 14.1 Hz, H-3), 1.70-1.55 (m, 2H, H-3, H-4), 0.91 (t, 6H, *J* = 6.2 Hz, H-5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 170.8 (C-1), 158.9 (C-a), 153.0 (C-g), 150.0 (C-c), 133.1 (C-7), 129.9 (C-d), 129.1 (C-f), 117.8 (C-8), 113.9 (C-e), 108.1 (C-b), 60.4 (OCH_3), 55.2 (C-2), 49.4 (C-9), 43.1 (C-6), 37.7 (C-3), 25.0 (C-4), 22.3 (C-5), 22.2 (C-5).

2-(allyl(pyridin-4-yl)amino)-*N*-cyclohexylbutanamide (II-7)



This compound was synthesized according to the general procedure II-A, using 2.6 mmol of isocyanide. The desired product was isolated in 39 % yield (310 mg).

Mol. Wt.: 301.43. Nature: Pale brown solid.

HRMS: Calcd. for $C_{18}H_{27}N_3O$: 301.2154, Found : 301.2155.

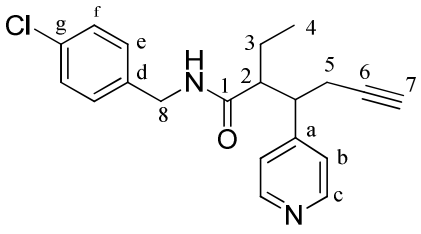
M.P. = 99 - 100 ^oC

I.R. (thin film): 3287, 3200, 3041, 2930, 2853, 1652, 1600, 1544, 1513, 1450, 1346, 1231, 1172 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.18 (dd, 2H, *J* = 1.4, 5.2 Hz, H-c), 6.56 (dd, 2H, *J* = 1.4, 5.2 Hz, H-b), 6.33 (d, 1H, *J* = 7.77 Hz, NH), 5.84 (ddd, 1H, *J* = 5.2, 10.4, 17.0 Hz, H-6), 5.25 -5.18 (m, 2H, H-7), 4.09 (dd, 1H, *J* = 6.4, 8.3 Hz, H-2), 4.05-3.90 (m, 2H, H-5), 3.77 (m, 1H, H-8), 2.23-2.12 (m, 1H, H-3), 1.85-1.74 (m, 3H, H-3, H-cy), 1.65-1.50 (m, 3H, H-cy), 1.35-1.23 (m, 2H, H-cy), 1.10-0.99 (m, 3H, H-cy), 0.90 (t, 3H, *J* = 7.41 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.5 (C-1), 153.1 (C-a), 149.8 (C-c), 133.2 (C-6), 117.9 (C-7), 108.3 (C-b), 64.4 (C-2), 49.8 (C-5), 48.3 (C-8), 32.9 (C-cy), 25.3 (C-cy), 24.7 (C-cy), 24.1 (C-cy), 22.0 (C-3), 11.5 (C-4).

***N*-(4-chlorobenzyl)-2-ethyl-3-(pyridin-4-yl)hex-5-ynamide (II-8)**



This compound was synthesized according to the general procedure II-A, using 2.6 mmol of isocyanide. The desired product was isolated in 50 % yield (450 mg).

Mol. Wt.: 341.83, Nature: Pale brown liquid.

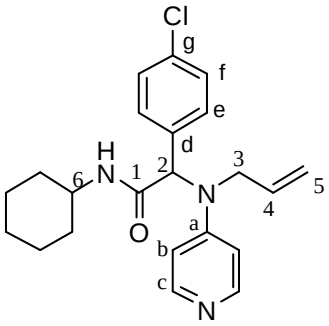
HRMS: Calcd. for $C_{19}H_{20}ClN_3O$: 341.1295, Found : 341.1286.

I.R. (thin film): 3301, 2971, 2933, 1662, 1596, 1509, 1353, 1266, 1231, 1176, 1089, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (dd, 2H, *J* = 1.5, 5.0 Hz, H-c), 7.23 (d, 2H, *J* = 8.4 Hz, H-e), 7.15 (t, 1H, *J* = 5.4 Hz, NH), 7.10 (d, 2H, *J* = 8.4 Hz, H-f), 6.62 (dd, 2H, *J* = 1.5, 5.0 Hz, H-b), 4.37 (d, 2H, *J* = 5.4 Hz, H-8), 4.19 (dd, 1H, *J* = 5.6, 9.2 Hz, H-2), 4.13 (dd, 1H, *J* = 2.4, 18.5 Hz, H-5), 4.06 (dd, 1H, *J* = 2.4, 18.5 Hz, H-5), 2.30-2.22 (m, 1H, H-3), 2.20 (t, 1H, *J* = 2.4 Hz, H-7), 1.93-1.85 (m, 1H, H-3), 0.94 (t, 3H, *J* = 7.3 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.5 (C-1), 152.1 (C-a), 150.0 (C-c), 136.4 (C-d), 133.2 (C-g), 129.1 (C-f), 128.7 (C-e), 108.1 (C-b), 78.8 (C-7), 73.5 (C-6), 64.2 (C-2), 42.9 (C-8), 36.4 (C-5), 22.3 (C-3), 11.4 (C-4).

2-(allyl(pyridin-4-yl)amino)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide (II-9)



This compound was synthesized according to the general procedure II-A, using 2.6 mmol of isocyanide. The desired product was isolated in 46 % yield (460 mg).

Mol. Wt.: 383.91. Nature: Pale yellow solid.

HRMS: Calcd. for $C_{22}H_{26}ClN_3O$: 383.1764, Found : 383.1759.

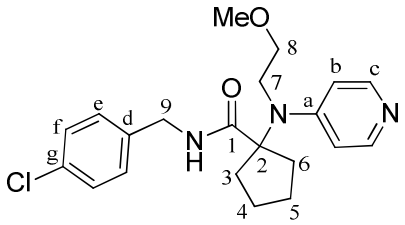
M.P. = 101 - 102 ^oC

I.R. (thin film):: 3284, 3041, 2933, 2851, 1655, 1596, 1544, 1506, 1388, 1266, 1231, 1096, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.27 (dd, 2H, *J* = 1.4, 5.0 Hz, H-c), 7.33 (d, 2H, *J* = 8.5 Hz, H-e), 7.21 (d, 2H, *J* = 8.5 Hz, H-f), 6.61 (dd, 2H, *J* = 1.4, 5.0 Hz, H-b), 6.15-6.03 (br s, 1H, NH), 5.68 (ddt, 1H, *J* = 5.1, 10.3, 17.0 Hz, H-4), 5.36 (s, 1H, H-2), 5.13 (dd, 1H, *J* = 1.0, 10.3 Hz, H-5), 5.07 (dd, 1H, *J* = 1.0, 17.0 Hz, H-5), 3.91-3.81 (m, 3H, H-3, H-6), 1.92-1.82 (m, 2H, H-cy), 1.76-1.55 (m, 3H, H-cy), 1.40-1.31 (m, 2H, H-cy), 1.15-1.05 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 168.0 (C-1), 153.3 (C-a), 150.0 (C-c), 134.5 (C-d), 133.5 (C-g), 133.1 (C-4), 130.6 (C-f), 129.0 (C-e), 117.7 (C-5), 108.4 (C-b), 66.3 (C-2), 49.9 (C-3), 48.6 (C-6), 33.0 (C-cy), 32.7 (C-cy), 25.3 (C-cy), 24.7 (C-cy), 24.6 (C-cy).

N-(4-chlorobenzyl)-1-((2-methoxyethyl)(pyridin-4-yl)amino)cyclopentane carboxamide (II-10)



This compound was synthesized according to the general procedure II-A, using 2.6 mmol of isocyanide. The desired product was isolated in 26 % yield (230 mg).

Mol. Wt.: 387.90¸ Nature : brown liquid.

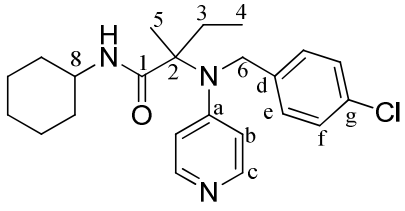
HRMS: Calcd. for $C_{21}H_{26}ClN_3O_2$: 387.1714, Found : 387.1715.

I.R. (thin film): 3298, 2944, 2874, 1662, 1593, 1534, 1499, 1339, 1193, 1092, 1013 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (dd, 2H, *J* = 1.5, 5.1 Hz, H-c), 8.09 (br t, 1H, *J* = 5.5 Hz, NH), 7.17 (d, 2H, *J* = 8.3 Hz, H-e), 6.98 (d, 2H, *J* = 8.3 Hz, H-f), 6.54 (dd, 2H, *J* = 1.5, 5.1 Hz, H-b), 4.30 (d, 2H, *J* = 5.5 Hz, H-9), 3.68 (t, 2H, *J* = 4.6 Hz, H-7), 3.62-3.54 (m, 2H, H-8), 2.92 (s, 3H, OCH_3), 2.49-2.25 (m, 2H, H-cp), 2.23-2.03 (m, 2H, H-cp), 1.86-1.74 (m, 2H, H-cp), 1.62-1.40 (m, 2H, H-cp).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 175.8 (C-1), 150.8 (C-a), 149.6 (C-c), 137.0 (C-d), 132.9 (C-g), 128.8 (C-f), 128.6 (C-e), 109.9 (C-b), 74.1 (C-2), 69.4 (C-8), 58.3 (-OCH_3), 43.8 (C-7), 43.0 (C-9), 36.1 (C-6, C-3), 24.8 (C-4, C-5).

2-((4-chlorobenzyl)(pyridin-4-yl)amino)-*N*-cyclohexyl-2-methylbutanamide (II-11)



This compound was synthesized according to the general procedure II-A, using 2.6 mmol of isocyanide. The desired product was isolated in 17 % yield (193mg).

Mol. Wt.: 399.96. Nature: off white solid

HRMS: Calcd. for $C_{23}H_{30}ClN_3O$: 399.2077, Found : 399.2064.

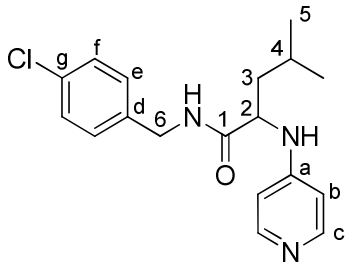
M.P. = 96 - 97 ^oC

I.R. (thin film): 3308, 3051, 2978, 2930, 2846, 2360, 2339, 1652, 1596, 1509, 1492, 1450, 1374, 1343, 1089, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.15 (d, 2H, *J* = 5.2 Hz, H-c), 7.29 (d, 2H, *J* = 8.4 Hz, H-e), 7.13 (d, 2H, *J* = 8.4 Hz, H-f), 6.59 (d, 2H, *J* = 5.2 Hz, H-b), 6.03 (d, 1H, *J* = 8.0 Hz, NH), 4.66 (d, 1H, *J* = 18.3 Hz, H-6), 4.57 (d, 1H, *J* = 18.3Hz, H-6), 3.73-3.64 (m, 1H, H-7), 2.09-2.03 (m, 1H, H-3), 1.78-1.70 (m, 2H, H-3, H-cy), 1.66-1.61 (m, 1H, H-cy), 1.56-1.48 (m, 2H, H-cy), 1.46 (s, 3H, H-5), 1.33-1.18 (m, 3H, H-cy), 1.10-1.03 (m, 1H, H-cy), 0.97-0.83 (m, 2H, H-cy), 0.79 (t, 3H, *J* = 7.4 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.8 (C-1), 153.3 (C-a), 149.5 (C-c), 138.0 (C-d), 132.9 (C-g), 129.1 (C-e), 127.2 (C-f), 110.3 (C-b), 66.8 (C-2), 50.3 (C-6), 48.0 (C-7), 32.6 (C-cy), 32.3 (C-cy), 30.3 (C-3), 25.2 (C-cy), 24.3 (C-cy), 20.3 (C-5), 8.5 (C-4).

***N*-(4-chlorobenzyl)-4-methyl-2-(pyridin-4-ylamino)pentanamide (II-12)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 40 % yield (130 mg).

Mol. Wt.: 331.84, Nature : white solid.

HRMS: Calcd. for $C_{18}H_{22}ClN_3O$: 331.1451, Found : 331.1452.

M.P. = 161-162 ^oC

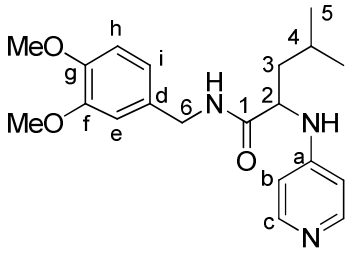
I.R. (thin film):: 3280, 2961, 2930, 1655, 1603, 1520, 1492, 1346, 1211, 1169, 1089, 1013 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.18 (dd, 2H, *J* = 1.4, 4.9 Hz, H-c), 7.22 (d, 2H, *J* = 8.4 Hz, H-e), 7.08 (d, 2H, *J* = 8.4 Hz, H-f), 6.99 (br t, 1H, *J* = 5.9 Hz, NH), 6.46 (dd, 2H, *J* = 1.4, 4.9 Hz, H-b), 4.67 (br d, 1H, *J* = 5.0 Hz NH), 4.41 (dd, 1H, *J* = 5.9, 15.0 Hz, H-6), 4.33 (dd, 1H, *J* = 5.9, 15.0 Hz, H-6), 3.88 (td, 1H, *J* = 5.0, 9.6 Hz, H-2), 1.89-1.72 (m, 2H, H-3, H-

4), 1.63 (ddd, 1H, *J* = 5.0, 9.6, 13.4 Hz, H-3), 0.99 (d, 3H, *J* = 6.4 Hz, H-5), 0.92 (d, 3H, *J* = 6.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.8 (C-1), 152.5 (C-a), 150.0 (C-c), 136.6 (C-d), 133.4 (C-g), 129.0 (C-f), 128.8 (C-e), 106.4 (C-b), 56.7 (C-2), 42.7 (C-6), 42.3 (C-3), 25.1 (C-4), 23.0 (C-5), 21.6 (C-5).

***N*-(3,4-dimethoxybenzyl)-4-methyl-2-(pyridin-4-ylamino)pentanamide (II-13)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 28 % yield (100 mg).

Mol. Wt.: 357.45, Nature: white solid.

HRMS: Calcd. for $C_{20}H_{27}N_3O_3$: 357.2052, Found : 357.2051

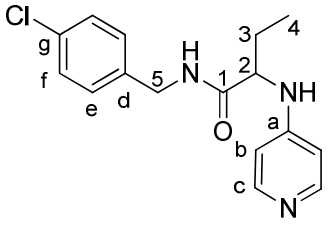
M.P. = 161-162 ^{o}C

IR : 3343, 3273, 2957, 2871, 2360, 1672, 1648, 1603, 1516, 1464, 1263, 1238, 1141, 1030, cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.19 (dd, 2H, *J* =1.5, 4.9 Hz, H-c), 6.85 (d, 1H, *J* = 8.1 Hz, H-h), 6.78 (t, 1H, *J* = 5.7 Hz, NH), 6.69 (dd, 1H, *J* = 1.8, 8.1 Hz, H-i), 6.66 (d, 1H, *J* = 1.8 Hz, H-e), 6.48 (dd, 2H, *J* = 1.5, 4.9 Hz, H-b), 4.62 (d, 1H, *J* = 4.9 Hz, H-2), 4.35 (d, 2H, *J* = 5.7 Hz, H-6), 3.83 (s, 3H, OMe), 3.81 (br s, 1H, NH), 3.73 (s, 3H, OMe), 1.90-1.81 (m, 1H, H-3), 1.80-1.73 (m, 1H, H-4), 1.68-1.59 (m, 1H, H-3), 1.00 (d, 3H, *J* = 6.4 Hz, H-5), 0.92 (d, 3H, *J* = 6.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.7 (C-1), 152.6 (C-a), 149.6 (C-c), 148.9 (C-f), 148.1 (C-g), 130.5 (C-d), 119.6 (C-i), 110.8 (C-h), 110.5 (C-e), 108.1 (C-b), 55.7 (OMe), 55.5 (OMe), 42.9 (C-6), 42.1 (C-3), 24.9 (C-4), 22.9 (C-5), 21.6 (C-5).

_N_-(4-chlorobenzyl)-2-(pyridin-4-ylamino)butanamide (II-14)



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 33 % yield (100 mg).

Mol. Wt.: 303.79, Nature: white solid

HRMS: Calcd. for $C_{16}H_{16}ClN_3O$: 303.1138, Found : 303.1152

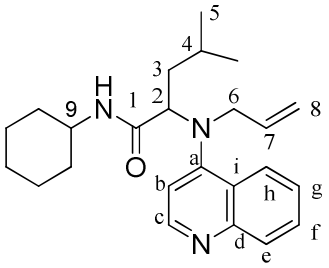
M.P. = 112-113 ^oC

IR : 3287, 3044, 2968, 2933, 1652, 1603, 1523, 1353, 1217, 1158, 1092 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.03 (d, 2H, *J* = 6.3 Hz, H-c), 7.67 (t, 1H, *J* = 5.1 Hz, NH), 7.17 (d, 2H, *J* = 8.4 Hz, H-e), 7.07 (d, 2H, *J* = 8.4 Hz, H-f), 6.45 (d, 2H, *J* = 6.3 Hz, H-b), 5.54 (d, 1H, *J* = 5.7 Hz, NH), 4.34 (d, 2H, *J* = 6.0 Hz, H-5), 3.86 (dd, 1H, *J* = 6.0, 12.8 Hz, H-2), 2.02-1.90 (m, 1H, H-3), 1.86-1.74 (m, 1H, H-3), 0.99 (t, 3H, *J* = 7.5 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.2 (C-1), 152.7 (C-a), 149.5 (C-c), 136.6 (C-d), 133.2 (C-g), 126.9 (C-f), 126.7 (C-e), 108.3 (C-b), 59.0 (C-2), 42.5 (C-5), 26.3 (C-3), 10.3 (C-4).

2-(allyl(quinolin-4-yl)amino)-_N_-cyclohexyl-4-methylpentanamide (II-15)



This compound was synthesized according to the general procedure II-C, using 1.7 mmol of isocyanide. The desired product was isolated in 46 % yield (300 mg).

Wt.: 379.54, Nature: white solid.

HRMS: Calcd. for $C_{24}H_{33}N_3O$: 379.2624, Found : 379.2629.

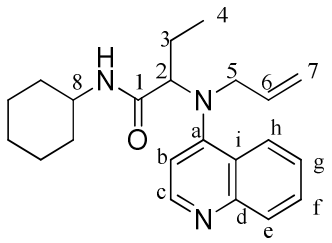
M.P. = 103-104 ^oC

I.R. (thin film): 3315, 2930, 2853 1659, 1575, 1501, 1454, 1304, 1106 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.68 (d, 1H, *J* = 5.1 Hz, H-c), 8.07 (dd, 1H, *J* = 1.2, 8.4 Hz, H-h), 7.98 (dd, 1H, *J* = 1.2, 8.4 Hz, H-e), 7.67 (ddd, 1H, *J* = 1.2, 6.9, 8.4 Hz, H-f), 7.46 (ddd, 1H, *J* = 1.2, 6.9, 8.4 Hz, H-g), 6.91 (d, 1H, *J* = 5.1 Hz, H-b), 6.69 (br d, 1H, *J* = 8.1 Hz, NH), 5.79 (tdd, 1H, *J* = 5.2, 10.4, 17.1 Hz, H-7), 5.18 (dd, 1H, *J* = 1.3, 17.1 Hz, H-8), 5.13 (dd, 1H, *J* = 1.2, 10.4 Hz, H-8), 4.31 (dd, 1H, *J* = 6.5, 7.5 Hz, H-2), 4.22-4.13 (m, 1H, H-6), 3.90-3.78 (m, 1H, H-9), 3.79-3.71 (m, 1H, H-6), 2.01 (tdd, 1H, *J* = 6.5, 8.3, 14.4 Hz, H-3), 1.94-1.82 (m, 2H, H-cy), 1.75-1.60 (m, 3H, H-3, H-cy), 1.59-1.47 (m, 2H, H-cy), 1.42-1.29 (m, 2H, H-cy), 1.16-1.01 (m, 3H, H-4, H-cy), 0.75 (d, 3H, *J* = 6.6 Hz, H-5), 0.48 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.2 (C-1), 153.5 (C-a), 150.1 (C-c), 150.0 (C-d), 133.0 (C-7), 130.5 (C-e), 129.1 (C-f), 125.6 (C-g), 123.7 (C-i), 122.6 (C-h), 117.8 (C-8), 111.6 (C-b), 65.9 (C-2), 48.8 (C-6), 48.0 (C-9), 38.5 (C-3), 33.1 (C-cy), 32.9 (C-cy), 25.3 (C-4), 24.6 (C-cy), 22.7 (C-5), 21.6 (C-5).

2-(allyl(quinolin-4-yl)amino)-*N*-cyclohexylbutanamide (II-16)



This compound was synthesized according to the general procedure II-C, using 1.722 mmol of isocyanide. The desired product was isolated in 36 % yield (220 mg).

Mol. Wt.: 351.4852. Nature: oil.

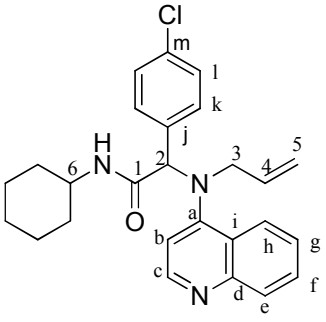
HRMS: Calcd. for $C_{22}H_{29}N_3O$: 351.2311, Found : 351.2330

I.R. (thin film): 3301, 2930, 2850, 1655, 1572, 1506, 1450, 1297, 1263, 922, 766, 731 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.70 (d, 1H, *J* = 5.1 Hz, H-c), 8.08 (dd, 1H, *J* = 1.2, 8.4 Hz, H-h), 8.01 (dd, 1H, *J* = 1.2, 8.4 Hz, H-e), 7.68 (ddd, 1H, *J* = 1.2, 6.9, 8.4 Hz, H-f), 7.49 (ddd, 1H, *J* = 1.2, 6.9, 8.4 Hz, H-g), 6.95 (d, 1H, *J* = 5.1 Hz, H-b), 6.48 (br d, 1H, *J* = 8.3 Hz, NH), 5.77 (tdd, 1H, *J* = 5.4, 10.6, 17.1 Hz, H-6), 5.16 (dd, 1H, *J* = 1.2, 17.1 Hz, H-7), 5.12 (dd, 1H, *J* = 1.2, 10.6 Hz, H-7), 4.20-4.09 (m, 2H, H-5, H-2), 3.84-3.75 (m, 2H, H-5, H-8), 2.23-2.11 (m, 1H, H-3), 1.92-1.82 (m, 2H, H-3, H-cy), 1.79-2.71 (m, 1H, H-cy), 1.66–1.50 (m, 4H, H-cy), 1.37-1.28 (m, 2H, H-cy), 1.12 -1.00 (m, 2H, H-cy), 0.87 (t, 3H, *J* = 7.5 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.0 (C-1), 153.9 (C-a), 150.2 (C-c), 150.1 (C-d), 132.8 (C-6), 130.5 (C-e), 129.2 (C-f), 125.8 (C-g), 124.0 (C-i), 122.7 (C-h), 118.0 (C-7), 112.3 (C-b), 68.9 (C-2), 49.6 (C-5), 47.9 (C-8), 33.1 (C-cy), 32.8 (C-cy), 25.3 (C-cy), 24.6 (C-cy), 24.5 (C-cy), 23.0 (C-3), 11.7 (C-4).

2-(allyl(quinolin-4-yl)amino)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide (II-17)



This compound was synthesized according to the general procedure II-C, using 1.722 mmol of isocyanide. The desired product was isolated in 6 % yield (40 mg).

Mol. Wt.: 433.9730, Nature: Pale brown solid.

HRMS: Calcd. for $C_{26}H_{28}ClN_3O$: 433.1921, Found : 433.1921

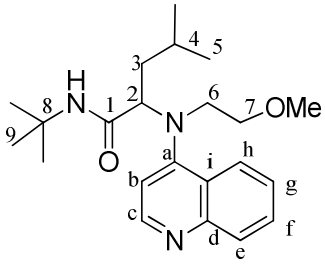
M.P. = 153-154 ^oC

I.R. (thin film): 3291, 3055, 2926, 2853, 1655, 1568, 1508, 1301, 1092, 766, 731 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.70 (d, 1H, *J* = 5.0 Hz, H-c), 8.19 (d, 1H, *J* = 8.4 Hz, H-h), 8.11 (d, 1H, *J* = 8.4 Hz, H-e), 7.71 (ddd, 1H, *J* = 1.1, 7.1, 8.4 Hz, H-f), 7.58 (ddd, 1H, *J* = 1.1, 7.1, 8.4 Hz, H-g), 7.29 (d, 2H, *J* = 8.5 Hz, H-k), 7.21 (d, 2H, *J* = 8.5 Hz, H-l), 6.88 (d, 1H, *J* = 5.0 Hz, H-b), 6.57 (br d, 1H, *J* = 8.2 Hz, NH), 5.69-5.58 (m, 1H, H-4), 5.18 (s, 1H, H-2), 5.06 (dd, 1H, *J* = 1.0, 10.3 Hz, H-5), 4.90 (dd, 1H, *J* = 1.0, 17.2 Hz, H-5), 3.77 (dd, 1H, *J* = 6.0, 15.8 Hz, H-3), 3.73–6.62 (m, 1H, H-6), 3.57 (dd, 1H, *J* = 6.0, 15.8 Hz, H-3), 1.78-1.68 (m, 1H, H-cy), 1.58 – 1.41 (m, 3H, H-cy), 1.39-1.09 (m, 4H, H-cy), 1.06 -0.92 (m, 2H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 168.2 (C-1), 153.0 (C-a), 150.2 (C-c), 149.9 (C-d), 134.2 (C-j), 133.8 (C-m), 131.3 (C-4), 130.5 (C-e), 129.9 (C-l), 129.5 (C-f), 128.7 (C-k), 126.6 (C-g), 124.4 (C-i), 122.3 (C-h), 119.3 (C-5), 113.8 (C-b), 70.2 (C-2), 52.4 (C-3), 47.8 (C-6), 32.6 (C-cy), 32.2 (C-cy), 25.2 (C-cy), 24.3 (C-cy), 24.1 (C-cy).

***N*-(tert-butyl)-2-((2-methoxyethyl)(quinolin-4-yl)amino)-4-methylpentanamide (II-18)**



This compound was synthesized according to the general procedure II-C, using 1.7 mmol of isocyanide. The desired product was isolated in 7 % yield (45 mg).

Mol. Wt.: 371.52, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{22}H_{33}N_3O$: 371.2573, Found : 371.2573.

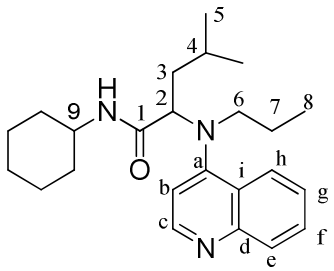
M.P. = 135-136 ^oC

I.R. (thin film): 2919, 2864, 1662, 1568, 1502, 1388, 1304, 1224, 1103 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.67 (d, 1H, *J* = 5.1 Hz, H-c), 8.11 (br s, 1H, NH), 8.05 (d, 1H, *J* = 8.0 Hz, H-h), 7.98 (d, 1H, *J* = 8.5 Hz, H-e), 7.65 (ddd, 1H, *J* = 1.2, 6.9, 8.5 Hz, H-f), 7.43 (ddd, 1H, *J* = 1.2, 6.9, 8.0 Hz, H-g), 6.88 (d, 1H, *J* = 5.1 Hz, H-b), 4.25 (dd, 1H, *J* = 4.6, 10.0 Hz, H-2), 3.76-3.68 (m, 1H, H-6), 3.63 (dt, 1H, *J* = 1.6, 11.5 Hz, H-7), 3.53-3.46 (m, 1H, H-7), 3.37-3.33 (m, 1H, H-6), 3.16 (s, 3H, -OCH_3), 1.91 (ddd, 1H, *J* = 4.6, 10.0, 14.5 Hz, H-3), 1.70 (ddd, 1H, *J* = 4.6, 10.0, 14.5 Hz, H-3), 1.43 (s, 9H, H-9), 0.93-0.91 (m, 1H, H-4), 0.68 (d, 3H, *J* = 6.5 Hz, H-5), 0.27 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.5 (C-1), 154.0 (C-a), 149.7 (C-d), 149.4 (C-c), 129.9 (C-e), 129.4 (C-f), 125.5 (C-g), 124.0 (C-i), 123.2 (C-h), 110.0 (C-b), 67.8 (C-7), 66.8 (C-2), 58.6 (-OCH_3), 51.2 (C-8), 45.8 (C-6), 38.9 (C-3), 28.6 (C-9), 25.2 (C-4), 23.1 (C-5), 20.8 (C-5).

***N*-cyclohexyl-4-methyl-2-(propyl(quinolin-4-yl)amino)pentanamide (II-19)**



This compound was synthesized according to the general procedure II-C, using 1.0 mmol of isocyanide. The desired product was isolated in 47 % yield (177 mg).

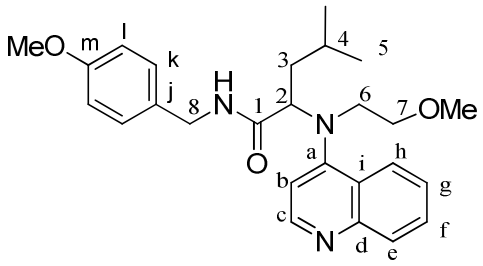
Mol. Wt.: 381.55, Nature: oil.

HRMS: Calcd. for $C_{24}H_{35}N_3O$: 381.2780, Found : 381.2790.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.73 (d, 1H, *J* = 5.0 Hz, H-c), 8.04 (d, 1H, *J* = 8.3 Hz, H-e), 7.98 (d, 1H, *J* = 8.3 Hz, H-h), 7.68 (t, 1H, *J* = 7.6 Hz, H-f), 7.48 (t, 1H, *J* = 7.6 Hz, H-g), 6.95 (d, 1H, *J* = 5.0 Hz, H-b), 6.48 (br d, 1H, *J* = 8.1 Hz, NH), 4.17 (t, 1H, *J* = 6.9 Hz, H-2), 3.90-3.78 (m, 1H, H-9), 3.41 (ddd, 1H, *J* = 5.2, 9.1, 14.0 Hz, H-3), 3.04 (ddd, 1H, *J* = 5.2, 9.1, 14.0 Hz, H-3), 2.08-1.99 (m, 1H, H-4), 1.95-1.85 (m, 2H, H-cy), 1.65-1.32 (m, 7H, H-7, H-cy), 1.18-1.05 (m, 3H, H-cy), 0.98-0.88 (m, 5H, H-cy, H-8), 0.74 (d, 3H, *J* = 6.5 Hz, H-5), 0.55 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.2 (C-1), 153.8 (C-a), 150.2 (C-c, C-d), 130.5 (C-e), 129.2 (C-f), 125.6 (C-g), 124.3 (C-i), 122.8 (C-h), 111.6 (C-b), 66.2 (C-2), 48.1 (C-9), 47.8 (C-6), 38.3 (C-3), 33.4 (C-cy), 33.0 (C-cy), 25.4 (C-4), 25.3 (C-cy), 24.8 (C-cy), 24.7 (C-cy), 22.6 (C-5), 22.0 (C-5), 20.2 (C-7), 11.8 (C-8).

***N*-(4-methoxybenzyl)-2-((2-methoxyethyl)(quinolin-4-yl)amino)-4-methyl-pentanamide (II-20)**



This compound was synthesized according to the general procedure II-C, using 1.7 mmol of isocyanide. The desired product was isolated in 60 % yield (446 mg).

Mol. Wt.: 435.56, Nature: Pale brown liquid..

HRMS: Calcd. for $C_{26}H_{33}N_3O_3$: 435.2522, Found : 435.2517.

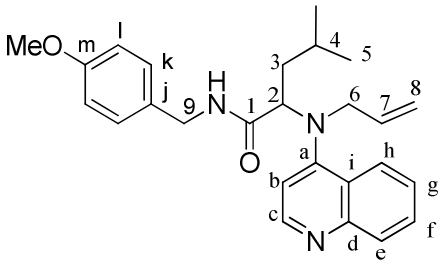
I.R. (thin film): 3315, 2954, 2930, 1659, 1572, 1509, 1308, 1249, 1110, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.94 (br t, 1H, *J* = 4.3 Hz, NH), 8.66 (d, 1H, *J* = 5.0 Hz, H-c), 8.04 (d, 1H, *J* = 8.3 Hz, H-h), 7.88 (d, 1H, *J* = 8.3 Hz, H-e), 7.64 (dt, 1H, *J* = 1.0, 8.3, Hz, H-f), 7.35 (dt, 1H, *J* = 1.0, 8.3, Hz, H-g), 7.31 (d, 2H, *J* = 8.6 Hz, H-l), 6.88 (d, 2H, *J* = 8.6 Hz, H-k), 6.85 (d, 1H, *J* = 5.0 Hz, H-b), 4.73 (dd, 1H, *J* = 6.6, 14.3 Hz, H-8), 4.40 (dd, 1H, *J* = 4.3, 10.3 Hz, H-2), 4.28 (dd, 1H, *J* = 4.3, 14.3 Hz, H-8), 3.79 (s, 3H, -OCH_3), 3.78-3.73 (m, 1H, H-6), 3.57 (dt, 1H, *J* = 1.3, 11.5 Hz, H-7), 3.45-3.40 (m, 1H, H-7), 3.36 (td, 1H,

J = 3.2, 11.4, Hz, H-6), 2.91 (s, 3H, -OCH_3), 1.96 (ddd, 1H, *J* = 4.3, 10.3, 14.5 Hz, H-3), 1.79 (ddd, 1H, *J* = 4.3, 10.3, 14.5 Hz, H-3), 1.55-1.44 (m, 1H, H-4), 0.74 (d, 3H, *J* = 6.6 Hz, H-5), 0.27 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.2 (C-1), 158.8 (C-m), 153.6 (C-a), 150.2 (C-d), 149.7 (C-c), 130.6 (C-e), 130.2 (C-f), 129.3(C-k), 129.2(C-j), 125.5 (C-g), 123.9 (C-i), 123.3 (C-h), 113.9 (C-l), 109.7 (C-b), 68.0 (C-7), 66.5 (C-2), 58.8 (-OCH_3), 55.2 (-OCH_3), 44.6 (C-6), 43.4 (C-8), 39.4 (C-3), 25.2 (C-4), 23.3 (C-5), 20.6 (C-5).

2-(allyl(quinolin-4-yl)amino)-*N*-(4-methoxybenzyl)-4-methylpentanamide (II-21)



This compound was synthesized according to the general procedure II-C, using 1.7 mmol of isocyanide. The desired product was isolated in 47 % yield (350 mg).

Wt.: 417.54, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{26}H_{31}N_3O_2$: 417.2416, Found : 417.2437.

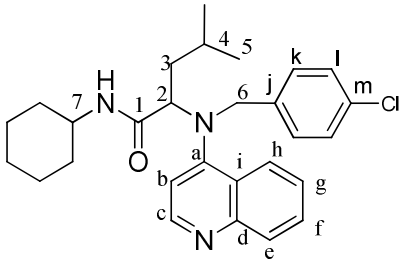
M.P. = 120-121 ^oC

I.R. (thin film): 2954, 2871, 1655, 1565, 1506, 1297, 1245, 1174, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.65 (d, 1H, *J* = 5.1 Hz, H-c), 8.05 (d, 1H, *J* = 8.5 Hz, H-h), 7.91 (d, 1H, *J* = 8.5 Hz, H-e), 7.65 (t, 1H, *J* = 7.5 Hz, H-f), 7.41 (t, 1H, *J* = 7.5 Hz, H-g), 7.10 (d, 2H, *J* = 8.6 Hz, H-l), 6.93-6.84 (m, 2H, NH, H-b), 6.82 (d, 2H, *J* = 8.6 Hz, H-k), 5.75-5.63 (m, 1H, H-7), 5.12-5.00 (m, 2H, H-8), 4.41 (d, 2H, *J* = 5.8 Hz, H-9), 4.33 (t, 1H, *J* = 7.0 Hz, H-2), 4.14 (dd, 1H, *J* = 5.3, 16.4 Hz, H-6), 3.78 (s, 3H, OCH_3), 3.74 (dd, 1H, *J* = 5.3, 16.4 Hz, H-6), 2.06 (td, 1H, *J* = 7.0, 14.2 Hz, H-3), 1.74 (td, 1H, *J* = 7.0, 14.2 Hz, H-3), 1.62-1.50 (m, 1H, H-4), 0.78 (d, 3H, *J* = 6.6 Hz, H-5), 0.54 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.2 (C-1), 159.0 (C-m), 153.5 (C-a), 150.1 (C-c), 150.0 (C-d), 132.9 (C-7), 130.5 (C-e), 130.1 (C-j), 129.1 (C-f), 129.0 (C-k), 125.7 (C-g), 123.8 (C-i), 122.7 (C-h), 117.9 (C-8), 114.0 (C-l), 111.9 (C-b), 65.7 (C-2), 55.3 (OCH_3), 49.3 (C-6), 43.1 (C-9), 38.7 (C-3), 25.4 (C-4), 22.6 (C-5), 21.9 (C-5).

2-((4-chlorobenzyl)(quinolin-4-yl)amino)-*N*-cyclohexyl-4-methylpentanamide (II-2)



This compound was synthesized according to the general procedure II-C, using 1.7 mmol of isocyanide. The desired product was isolated in 49 % yield (390 mg).

Mol. Wt.:464.04, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{28}H_{34}ClN_3O$: 463.2390, Found : 463.2406.

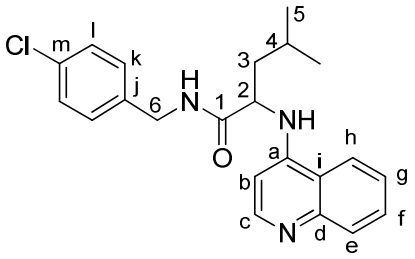
M.P. = 118-119 ^{o}C

I.R. (thin film): 2930, 2860, 1652, 1574, 1544, 1504, 1461, 1259, 1092, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.58 (d, 1H, *J* = 5.0 Hz, H-c), 8.11 (d, 1H, *J* = 8.4 Hz, H-h), 8.06 (d, 1H, *J* = 8.4 Hz, H-e), 7.70 (t, 1H, *J* = 7.7 Hz, H-f), 7.56 (t, 1H, *J* = 7.7 Hz, H-g), 7.19-7.12 (m, 4H, H-k, H-l), 6.81 (d, 1H, *J* = 5.0 Hz, H-b), 5.72 (br s, 1H, NH), 4.65 (d, 1H, *J* = 16.2 Hz, H-6), 4.40 (d, 1H, *J* = 16.2 Hz, H-6), 4.16 (dd, 1H, *J* = 6.0, 8.0 Hz, H-2), 3.84-3.72 (1H, m, H-7), 2.20 (td, 1H, *J* = 6.0, 14.4 Hz, H-3), 1.82-1.72 (m, 3H, H-3, H-cy), 1.67-1.50 (m , 5H, H-cy), 1.39-1.23 (m, 2H, H-cy), 1.12-0.98 (m, 2H, H-cy), 0.85 (d, 3H, *J* = 6.5 Hz, H-5), 0.73 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.1 (C-1), 153.3 (C-a), 150.1 (C-c), 150.0 (C-d), 135.9 (C-j), 132.7 (C-m), 130.5 (C-e), 129.3 (C-f), 128.7 (C-l), 128.4 (C-k), 126.0 (C-g), 124.0 (C-i), 122.8 (C-h), 112.6 (C-b), 66.3 (C-2), 49.0 (C-6), 48.2 (C-7), 39.0 (C-3), 33.3 (C-cy), 32.9 (C-cy), 25.5 (C-4), 25.3 (C-cy), 24.6 (C-cy), 22.6 (C-5), 22.4 (C-5).

***N*-(4-chlorobenzyl)-4-methyl-2-(quinolin-4-ylamino)pentanamide (II-23)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 32 % yield (120 mg).

Chemical Formula: $C_{22}H_{24}ClN_3O$

Mol. Wt.: 381.90, Nature: Pale brown solid

HRMS: Calcd. for $C_{22}H_{24}ClN_3O$: 381.1608, Found : 381.1605

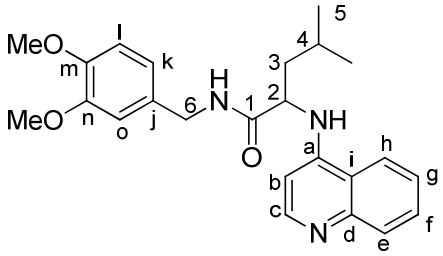
M.P. = 181-182 ^oC

IR : 3299, 3280, 3082, 2957, 2933, 1655, 1579, 1534, 1391, 1346, 1259, 1092, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.55 (d, 1H, *J* = 5.2 Hz, H-c), 8.01 (d, 1H, *J* = 8.2 Hz, H-h), 7.78 (d, 1H, *J* = 8.2 Hz, H-e), 7.67 (dd, 1H, *J* = 7.1, 8.2 Hz, H-f), 7.48 (dd, 1H, *J* = 7.1, 8.2 Hz, H-g), 7.22 (d, 2H, *J* = 8.3 Hz, H-k), 7.08 (d, 2H, *J* = 8.3 Hz, H-l), 6.91 (br d, 1H, *J* = 6.0 Hz, NH), 6.39 (d, 1H, *J* = 5.2 Hz, H-b), 5.26-5.21 (br s, 1H, NH), 4.45 (dd, 1H, *J* = 6.3, 15.0 Hz, H-6), 4.33 (dd, 1H, *J* = 5.9, 15.0 Hz, H-6), 4.10-4.03 (m, 1H, H-2), 2.05-1.96 (m, 1H, H-3), 1.91-1.76 (m , 2H, H-4, H-3), 1.5 (d, 3H, *J* = 6.3 Hz, H-5), 0.96 (d, 3H, *J* = 6.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.4 (C-1), 150.9 (C-c), 148.3 (C-a, C-d), 136.4 (C-j), 133.3 (C-m), 130.2 (C-h), 129.4 (C-f), 128.9 (C-l), 128.8 (C-k), 128.6 (C-m), 128.4 (C-i), 125.4 (C-g), 118.9 (C-e), 118.6 (C-i), 100.3 (C-b), 57.1 (C-2), 42.6 (C-6), 42.3 (C-3), 25.3 (C-4), 23.1 (C-5), 21.7 (C-5).

***N*-(3,4-dimethoxybenzyl)-4-methyl-2-(quinolin-4-ylamino)pentanamide (II-24)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 20 % yield (80 mg).

Mol. Wt.: 407.51, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{24}H_{29}N_3O_3$: 407.2209, Found : 407.2208

M.P. = 110-111 ^oC

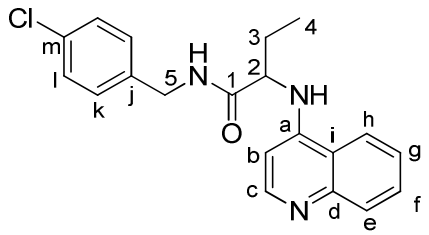
IR : 3364, 3305, 2954, 2933, 1662, 1582, 1513, 1461, 1263, 1238, 1138, 1026 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.57 (d, 1H, *J* = 5.2 Hz, H-c), 8.01 (d, 1H, *J* = 8.2 Hz, H-h), 7.77 (d, 1H, *J* = 8.2 Hz, H-e), 7.67 (ddd, 1H, *J* = 1.1, 7.0, 8.2 Hz, H-f), 7.47 (ddd, 1H, *J* = 1.1, 7.0, 8.2 Hz, H-g), 6.73-6.70 (m, 2H, NH, H-l), 6.68 (dd, 1H, *J* = 1.2, 8.2 Hz, H-k), 6.63

(d, 1H, *J* = 1.7 Hz, H-o), 6.43 (d, 1H, *J* = 5.8, Hz, H-b), 5.23 (br d, 1H, *J* = 4.4 Hz, NH), 4.40 (dd, 2H, *J* = 5.8, 14.7 Hz, H-6), 4.08-4.02 (m, 1H, H-2), 3.81 (s, 3H, OMe), 3.66 (s, 3H, OMe), 1.99 (ddd, 1H, *J* = 4.7, 8.1, 13.2 Hz, H-3), 1.90-1.75 (m, 2H, H-4, H-3), 1.04 (d, 3H, *J* = 6.4 Hz, H-5), 0.95 (d, 3H, *J* = 6.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.2 (C-1), 151.0 (C-c), 149.0(C-a), 148.4 (C-n, C-d), 148.3 (C-m), 130.2 (C-i), 130.1 (C-k), 129.4 (C-f), 125.3 (C-g), 119.8 (C-h), 119.0 (C-e), 118.7 (C-j), 111.0 (C-l), 110.6 (C-o), 100.2 (C-b), 57.1 (C-2), 55.8 (OMe), 55.6 (OMe), 43.2 (C-6), 42.3 (C-3), 25.3 (C-4), 23.1 (C-5), 21.7 (C-5).

***N*-(4-chlorobenzyl)-2-(quinolin-4-ylamino)butanamide (II-25)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 15 % yield (40 mg).

Mol. Wt.: 353.85, Nature: white solid.

HRMS: Calcd. for $C_{20}H_{20}ClN_3O$: 353.1295, Found : 353.1300

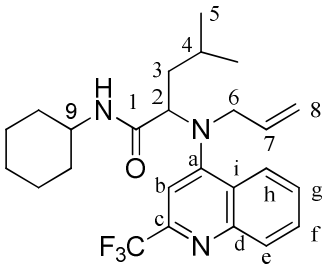
M.P. = 96-97 ^oC

IR : 3277, 3262, 2964, 2933, 1659, 1617, 1579, 1527, 1495, 1395, 1346, 1266, 1141, 1089, 1013 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.45 (d, 1H, *J* = 5.4 Hz, H-c), 7.92 (d, 1H, *J* = 8.4 Hz, H-h), 7.88 (d, 1H, *J* = 8.3 Hz, H-e), 7.61-7.57 (m, 1H, H-g), 7.55 (d, 1H, *J* = 3.6 Hz, NH), 7.44-7.38 (m, 1H, H-f), 7.17 (d, 2H, *J* = 8.4 Hz, H-k), 7.09 (d, 2H, *J* = 8.4 Hz, H-l), 6.35 (d, 1H, *J* = 5.4 Hz, H-b), 5.89 (br d, 1H, *J* = 5.3 Hz, NH), 4.44 (dd, 1H, *J* = 6.0, 15.0 Hz, H-5), 4.37 (dd, 1H, *J* = 6.0, 15.0 Hz, H-5), 4.11-4.05 (m, 1H, H-2), 2.17-2.08 (m, 1H, H-3), 2.03-1.94 (m, 1H, H-3), 1.08 (t, 3H, *J* = 7.4 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.1 (C-1), 150.4 (C-c), 148.9 (C-a), 147.9 (C-d), 136.5 (C-e), 133.1 (C-m), 129.5 (C-i), 129.2 (C-f), 128.9 (C-l), 128.6 (C-k), 125.1 (C-g), 119.7 (C-h), 116.7 (C-j), 99.8 (C-b), 59.0 (C-2), 42.6 (C-5), 26.3 (C-3), 10.3 (C-4).

2-(allyl(2-(trifluoromethyl)quinolin-4-yl)amino)-*N*-cyclohexyl-4-methyl- pentanamide (II-26)



This compound was synthesized according to the general procedure II-C, using 1.5 mmol of isocyanide. The desired product was isolated in 71 % yield (480 mg).

Mol. Wt.: 447.54, Nature: White solid.

HRMS: Calcd. for $C_{25}H_{32}F_3N_3O$: 447.2497, Found : 447.2496.

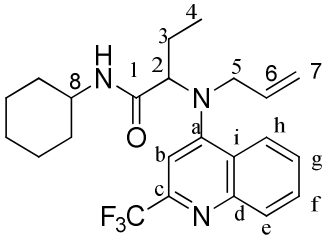
M.P. = 105-106 ^oC

I.R. (thin film): 2933, 2857, 1652, 1582, 1509,1402, 1336, 1277, 1183, 1134, 1096 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (d, 1H, *J* = 8.3 Hz, H-e), 8.02 (d, 1H, *J* = 8.3 Hz, H-h), 7.76 (ddd, 1H, *J* = 1.2, 6.9, 8.3 Hz, H-f), 7.58 (ddd, 1H, *J* = 1.2, 6.9, 8.3 Hz, H-g), 7.19 (s, 1H, H-b), 6.43 (br d, 1H, *J* = 8.2 Hz, NH), 5.78 (tdd, 1H, *J* = 5.2, 10.4, 17.0 Hz, H-7), 5.24-5.16 (m, 2H, H-8), 4.34 (t, 1H, *J* = 7.0 Hz, H-2), 4.21 (dd, 1H, *J* = 5.2, 17.0 Hz, H-6), 3.91-3.80 (m, 2H, H-6, H-9), 2.07 (ddd, 1H, *J* = 7.0, 8.3, 14.5 Hz, H-3), 1.97-1.82 (m, 2H, H-cy), 1.78-1.57 (m, 4H, H-cy, H-3, H-4), 1.53-1.43 (m, 1H, H-cy), 1.43-1.29 (m, 2H, H-cy), 1.19-1.00 (m, 3H, H-cy), 0.78 (d, 3H, *J* = 6.6 Hz, H-5), 0.50 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.6 (C-1), 155.7 (C-a), 149.1 (C-d), 148.0 (q, J_{C-F} = 34.0 Hz, C-c), 132.5 (C-7), 131.3 (C-e), 130.2 (C-f), 127.4 (C-g), 124.1 (C-i), 122.8 (C-h), 121.6 (q, J_{C-F} = 277.6 Hz, CF_3), 118.4 (C-8), 107.1 (d, J_{C-F} = 1.8 Hz, C-b), 66.4 (C-2), 48.9 (C-6), 48.2 (C-9), 38.7 (C-3), 33.1 (C-cy), 32.9 (C-cy), 25.3 (C-4), 24.5 (C-5), 22.7 (C-5), 21.6 (C-5).

2-(allyl(2-(trifluoromethyl)quinolin-4-yl)amino)-*N*-cyclohexylbutanamide (II-27)



This compound was synthesized according to the general procedure II-C, using 1.0 mmol of isocyanide. The desired product was isolated in 38 % yield (160 mg).

Mol. Wt.: 419.4831, Nature: oil.

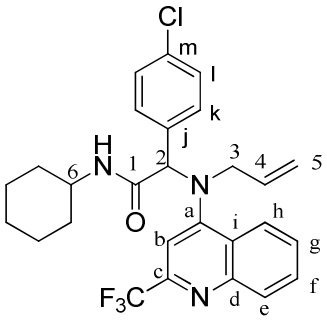
HRMS: Calcd. for $C_{23}H_{28}F_3N_3O$: 419.2184, Found : 419.2193

I.R. (thin film): 3295, 3075, 2933, 2857, 1649, 1586, 1509, 1457, 1401, 1336, 1277, 1186, 1134, 919, 767 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (d, 1H, *J* = 8.4 Hz, H-e), 8.04 (d, 1H, *J* = 8.4 Hz, H-h), 7.77 (ddd, 1H, *J* = 1.3, 6.9, 8.4 Hz, H-f), 7.59 (ddd, 1H, *J* = 1.2, 6.9, 8.4 Hz, H-g), 7.24 (s, 1H, H-b), 6.30 (br d, 1H, *J* = 8.0 Hz, NH), 5.78 (tdd, 1H, *J* = 5.4, 10.6, 17.1 Hz, H-6), 5.23 -5.16 (m, 2H, H-7), 4.23 (dd, 1H, *J* = 5.3, 17.1 Hz, H-5), 4.17 (dd, 1H, *J* = 6.5, 7.7 Hz, H-2), 3.92-3.79 (m, 2H, H-5, H-8), 2.29-2.17 (m, 1H, H-3), 1.96-1.82 (m, 3H, H-3, H-cy), 1.68-1.56 (m, 4H, H-cy), 1.42-1.32 (m, 2H, H-cy), 1.15-1.02 (m, 2H, H-cy), 0.86 (t, 3H, *J* = 7.5 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.4 (C-1), 156.1 (C-a), 149.2 (C-d), 148.0 (q, J_{C-F} = 34 Hz, C-c), 132.5 (C-6), 131.3 (C-e), 130.3 (C-f), 127.5 (C-g), 124.2 (C-i), 122.9 (C-4), 121.5 (d, J_{C-F} = 275.0 Hz, CF_3), 118.5 (C-7), 107.5 (d, J_{C-F} = 1.7 Hz, C-b), 69.8 (C-2), 49.3 (C-5), 48.2 (C-8), 33.2 (C-cy), 32.9 (C-cy), 25.3 (C-cy), 24.6 (C-cy), 25.5 (C-cy), 23.2 (C-3), 11.8 (C-4).

2-(allyl(2-(trifluoromethyl)quinolin-4-yl)amino)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide (II-28)



This compound was synthesized according to the general procedure II-C, using 1.0 mmol of isocyanide. The desired product was isolated in 72 % yield (150 mg).

Mol. Wt.: 501.97, Nature: white solid.

HRMS: Calcd. for $C_{27}H_{27}ClF_3N_3O$: 501.1795, Found : 501.1794.

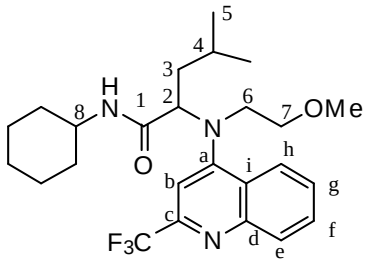
M.P. = 168 - 169 ^oC

I.R. (thin film): 3294, 3072, 2933, 2857, 1652, 1582, 1509, 1492, 1391, 1343, 1252, 1183, 1141, 1092 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.25 (d, 1H, *J* = 8.3 Hz H-e), 8.20 (d, 1H, *J* = 8.3 Hz H-h), 7.83 (ddd, 1H, *J* = 1.3, 6.9, 8.3 Hz, H-f), 7.69 (ddd, 1H, *J* = 1.1, 6.9, 8.3 Hz, H-g), 7.33 (dd, 2H, *J* = 1.8, 8.5 Hz, H-l), 7.21 (dd, 2H, *J* = 1.8, 8.5 Hz, H-k), 7.15 (s, 1H, H-b), 6.37-6.35 (br d, 1H, *J* = 8.5 Hz, NH), 5.65-5.67 (m, 1H, H-4), 5.26 (s, 1H, H-2), 5.14 (dd, 1H, *J* = 1.0, 10.3 Hz, H-5), 5.01 (dd, 1H, *J* = 1.0, 17.2 Hz, H-5), 3.87 (dd, 1H, *J* = 5.5, 16.0 Hz, H-3), 3.81-3.70 (m, 1H, H-6), 3.68 (dd, 1H, *J* = 6.4, 16.0 Hz, H-3), 1.86-1.78 (m, 1H, H-cy), 1.73-1.42 (m, 4H, H-cy), 1.37-1.22 (m, 2H, H-cy), 1.14-1.01 (m, 2H, H-cy), 0.93-0.83 (m, 1H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 167.8 (C-1), 155.4 (C-a), 149.0 (C-d), 148.0 (d, J_{C-F} = 34.3 Hz, C-c), 134.5 (C-j), 133.5 (C-4), 131.3 (C-m), 131.7 (C-e), 130.6 (C-f), 129.9 (C-l), 128.9 (C-k), 128.3 (C-g), 124.8 (C-h), 122.8 (C-i), 121.5 (d, J_{C-F} = 276.0 Hz, CF_3), 119.6 (C-4), 109.2 (d, J_{C-F} = 2.0 Hz, C-b), 70.6 (C-2), 52.3 (C-3), 48.1 (C-6), 32.9 (C-cy), 32.5 (C-cy), 25.5 (C-cy), 24.5 (C-cy), 24.3 (C-cy).

***N*-cyclohexyl-2-((2-methoxyethyl)(2-(trifluoromethyl)quinolin-4-yl)amino)-4-methylpentanamide (II-29)**



This compound was synthesized according to the general procedure II-C, using 1.0 mmol of isocyanide. The desired product was isolated in 43 % yield (210 mg).

Chemical Formula: $C_{25}H_{34}F_3N_3O_2$

Mol. Wt.: 465.5516, Nature: oil.

HRMS: Calcd. for $C_{25}H_{34}F_3N_3O_2$: 465.2603, Found : 465.2603

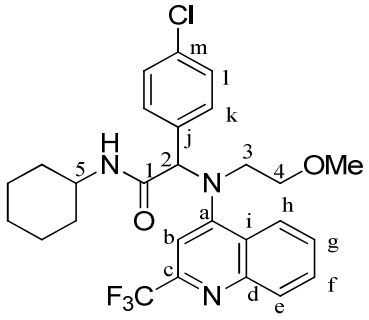
I.R. (thin film): 3319, 3065, 2930, 2857, 1659, 1586, 1509, 1412, 1339, 1280, 1176, 1134, 1108, 936, 766 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.37 (br d, 1H, *J* = 7.9 Hz, NH), 8.19 (d, 1H, *J* = 8.3 Hz, H-e), 8.00 (d, 1H, *J* = 8.3 Hz, H-h), 7.75 (ddd, 1H, *J* = 1.1, 6.9, 8.3 Hz, H-f), 7.4 (ddd, 1H, *J* = 1.1, 6.9, 8.3 Hz, H-f), 7.14 (s, 1H, H-b), 4.37 (dd, 1H, *J* = 4.3, 10.2 Hz, H-2), 3.92

(ttd, 1H, *J* = 3.6, 7.9, 11.6 Hz, H-8), 3.85-3.78 (m, 1H, H-6), 3.71-3.67 (m, 1H, H-6), 3.59-3.53 (m, 1H, H-7), 3.50-3.42 (m, 1H, H-7), 3.24 (3H, s, OCH_3), 2.02-1.92 (m, 2H, H-3, Hcy), 1.82-1.64 (m, 5H, H-cy, H-3), 1.47-1.37 (m, 3H, H-cy, H-4), 1.32-1.17 (m, 3H, H-cy), 0.76 (d, 3H, *J* = 6.6 Hz, H-5), 0.28 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.7 (C-1), 156.0 (C-a), 149.3 (C-d), 147.5 (q, J_{C-F} = 34.0 Hz, C-c), 131.0 (C-e), 130.4 (C-f), 127.2 (C-g), 124.3 (C-i), 123.2 (C-h), 121.6 (q, J_{C-F} = 277.6 Hz, CF_3), 105.0 (d, J_{C-F} = 34.0 Hz, C-b), 67.7 (C-7), 66.9 (C-2), 58.8 (OCH_3), 48.6 (C-8), 45.8 (C-6), 39.4 (C-3), 33.5 (C-cy), 32.8 (C-cy), 25.6 (C-cy), 25.2 (C-4), 25.1 (C-cy), 25.0 (C-cy), 23.2 (C-5), 20.5 (C-5).

2-(4-chlorophenyl)-*N*-cyclohexyl-2-((2-methoxyethyl)(2-(trifluoromethyl) quinolin-4-yl) amino)acetamide (II-30)



This compound was synthesized according to the general procedure II-C, using 1.0 mmol of isocyanide. The desired product was isolated in 36 % yield (200 mg).

Mol. Wt.: 519.99, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{27}H_{29}ClF_3N_3O_2$: 519.1900, Found : 519.1935.

M.P. = 175-176 ^oC

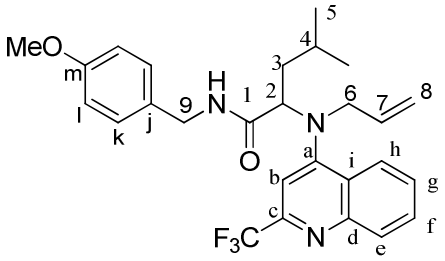
I.R. (thin film): 2933, 2857, 1652, 1537, 1388, 1346, 1277, 1188, 1131, 1095, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.54 (d, 1H, *J* = 8.1 Hz, NH), 8.17 (d, 1H, *J* = 8.3 Hz, H-e), 8.05 (d, 1H, *J* = 8.3 Hz, H-h), 7.77-7.72 (m, 1H, H-f), 7.59-7.54 (m, 1H, H-g), 7.17 (d, 2H, *J* = 8.4 Hz, H-l), 6.90 (s, 1H, H-b), 6.78 (d, 2H, *J* = 8.4 Hz, H-k), 5.28 (s, 1H, H-2), 4.05-3.94 (m, 1H, H-5), 3.37-3.33 (m, 2H, H-4), 3.18 (s, 3H, OCH_3), 3.17-3.11 (m, 1H, H-3), 3.00 (d, 1H, *J* = 15.0 Hz, H-3), 2.08-1.97 (m, 2H, H-cy), 1.78-1.70 (m, 2H, H-cy), 1.67-1.58 (m, 1H, H-cy), 1.45-1.33 (m, 2H, H-cy), 1.30-1.10 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 168.0 (C-1), 155.3 (C-a), 149.4 (C-d), 147.8 (q, J_{C-F} = 34.0 Hz, C-c), 134.1 (C-m), 133.7 (C-j), 131.1 (C-e), 130.8 (C-f), 130.2 (C-l), 128.6 (C-k), 128.1 (C-g), 124.8 (C-i), 123.1 (C-h), 121.5 (q, J_{C-F} = 275.7 Hz, CF_3), 106.6 (d, J_{C-F} = 1.9

Hz, C-b), 72.3 (C-2), 68.0 (C-4), 58.8 (OCH_3), 48.6 (C-5), 47.6 (C-3), 33.2 (C-cy), 32.0 (C-cy), 25.6 (C-cy), 25.0 (C-cy).

2-(allyl(2-(trifluoromethyl)quinolin-4-yl)amino)-*N*-(4-methoxybenzyl)-4-methylpentanamide (II-31)



This compound was synthesized according to the general procedure II-C, using 1.5 mmol of isocyanide. The desired product was isolated in 69 % yield (502 mg).

Mol. Wt.: 485.54, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{27}H_{30}F_3N_3O_2$: 485.2290, Found : 485.2287.

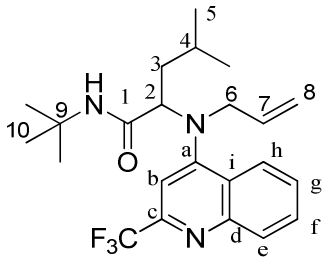
M.P. = 108-109 ^oC

I.R. (thin film): 3065, 2957, 2874, 2839, 1659, 1586, 1513, 1464, 1405, 1339, 1249, 1179, 1134, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.16 (d, 1H, *J* = 8.4 Hz, H-e), 7.94 (d, 1H, *J* = 8.4 Hz, H-h), 7.60 (ddd, 1H, *J* = 1.3, 6.9, 8.4 Hz, H-f), 7.52 (ddd, 1H, *J* = 1.3, 6.9, 8.4 Hz, H-g), 7.16 (s, 1H, H-b), 7.14 (d, 2H, *J* = 8.5 Hz, H-k), 6.83 (d, 2H, *J* = 8.5 Hz, H-l), 6.70 (br t, 1H, *J* = 5.5 Hz, NH), 5.69 (tdd, 1H, *J* = 5.0, 10.5, 16.5 Hz, H-7), 5.14-5.06 (m, 2H, H-8), 4.49-4.34 (m, 3H, H-9, H-2), 4.19 (dd, 1H, *J* = 5.0, 16.5 Hz, H-6), 3.85-3.80 (m, 1H, H-6), 3.79 (s, 3H, OCH_3), 2.12 (td , 1H, *J* = 6.9, 13.9 Hz, H-3), 1.75 (td , 1H, *J* = 6.9, 13.9 Hz, H-3), 1.57-1.44 (m, 1H, H-4), 0.80 (d, 3H, *J* = 6.5 Hz, H-5), 0.55 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.6 (C-1), 159.1 (C-m), 155.6 (C-a), 149.1 (C-d), 147.8 (q, J_{C-F} = 33.8 Hz, C-c), 132.4 (C-7), 131.3 (C-e), 130.3 (C-f), 129.9 (C-j), 129.1 (C-k), 127.0 (C-g), 124.4 (C-i), 122.8 (C-h), 121.5 (q, J_{C-F} = 275.7 Hz, CF_3), 118.6 (C-8), 114.1 (C-l), 107.1 (J_{C-F} = 1.8 Hz, C-b), 66.2 (C-2), 55.3 (OCH_3), 49.2 (C-6), 43.2 (C-9), 38.8 (C-3), 25.3 (C-4), 22.6 (C-5), 21.8 (C-5).

2-(allyl(2-(trifluoromethyl)quinolin-4-yl)amino)-*N*-(tert-butyl)-4-methylpentanamide (II-32)



This compound was synthesized according to the general procedure II-C, using 1.1 mmol of isocyanide. The desired product was isolated in 14 % yield (70 mg).

Mol. Wt.: 421.4990, Nature: oil.

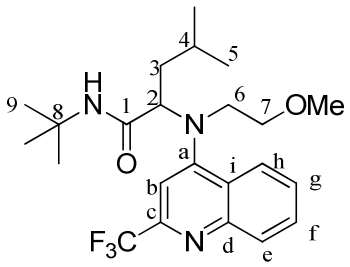
HRMS: Calcd. for $C_{23}H_{30}F_3N_3O$: 421.2341, Found : 421.2339

I.R. (thin film): 3395, 2961, 2930, 2871, 1680, 1583, 1506, 1460, 1394, 1281, 1184, 1139, 1093, 931, 766, 734 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (d, 1H, *J* = 8.3 Hz, H-e), 8.03 (d, 1H, *J* = 8.3 Hz, H-h), 7.77 (ddd, 1H, *J* = 1.1, 6.9, 8.3 Hz, H-f), 7.60 (ddd, 1H, *J* = 1.1, 6.9, 8.3 Hz, H-g), 7.18 (s, 1H, H-b), 6.36 (br s, 1H, NH), 5.78 (ddt, 1H, *J* = 5.2, 10.4, 17.0 Hz, H-7), 5.24-5.15 (m, 2H, Hz, H-8), 4.26 (t, 1H, *J* = 7.0 Hz, H-2), 4.19 (dd, 1H, *J* = 5.1, 17.0 Hz, H-6), 3.83 (dd, 1H, 1H, *J* = 5.1, 17.0 Hz, H-6), 2.10-2.01 (m, 1H, H-3), 1.74-1.66 (m, 1H, H-3), 1.52-1.45 (m, 1H, H-4), 1.34 (s, 9H, H-10), 0.78 (d, 3H, *J* = 6.6 Hz, H-5), 0.53 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.9 (C-1), 155.7 (C-a), 149.1 (C-d), 147.8 (q, J_{C-F} = 34.0 Hz, C-c), 132.5 (C-7), 131.3 (C-e), 130.3 (C-f), 127.4 (C-g), 124.0 (C-i), 122.7 (C-h), 121.0 (q, J_{C-F} = 276.0 Hz, CF_3), 118.4 (C-8), 107.1 (d, J_{C-F} = 1.9 Hz C-b), 66.8 (C-2), 51.5 (C-9), 49.0 (C-6), 38.6 (C-3), 28.7 (C-10), 25.4 (C-4), 22.7 (C-5), 21.8 (C-5).

***N*-(tert-butyl)-2-((2-methoxyethyl)(2-(trifluoromethyl)quinolin-4-yl)amino)-4-methylpentanamide (II-33)**



This compound was synthesized according to the general procedure II-C, using 1.0 mmol of isocyanide. The desired product was isolated in 20 % yield (94 mg).

Mol. Wt.: 439.5143, Nature: oil.

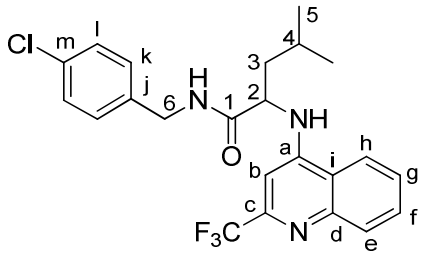
HRMS: Calcd. for $C_{23}H_{32}F_3N_3O_2$: 439.2447, Found : 439.2441

I.R. (thin film): 3332, 2961, 2871, 1665, 1579, 1461, 1360, 1277, 1224, 1183, 1138, 1113, 936, 769 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.17 (d, 1H, *J* = 8.4 Hz, H-e), 8.08 (br s, 1H, NH), 8.03 (d, 1H, *J* = 8.4 Hz, H-h), 7.79-7.73 (m, 1H, H-g), 7.58-7.53 (m, 1H, H-f), 7.14 (s, 1H, H-b), 4.29 (dd, 1H, *J* = 4.5, 9.9 Hz, H-2), 3.83-3.75 (m, 1H, H-6), 3.65-3.61 (m, 1H, H-7), 3.57-3.53 (m, 1H, H-7), 3.47-3.40 (m, 1H, H-6), 3.19 (s, 3H, -OCH_3), 1.96 (ddd, 1H, *J* = 4.5, 10.2, 14.5 Hz, H-3), 1.74 (ddd, 1H, *J* = 4.5, 9.9, 14.44 Hz, H-3), 1.46 (s, 9H, H-9), 1.32-1.28 (m, 1H, H-4), 0.72 (d, 3H, *J* = 6.6 Hz, H-5), 0.28 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.1 (C-1), 155.9 (C-a), 149.2 (C-d), 147.5 (q, J_{C-F} = 33.8 Hz, C-c), 131.0 (C-e), 130.4 (C-f), 127.2 (C-g), 124.4 (C-i), 123.2 (C-h), 121.6 (q, J_{C-F} = 275.4 Hz, CF_3), 105.3 (d, J_{C-F} = 2.0Hz, C-b), 67.5 (C-2), 67.3 (C-7), 58.8 (OCH_3), 51.4 (C-8), 45.9 (C-6), 39.1 (C-3), 28.6 (C-9), 25.3 (C-4), 23.1 (C-5), 20.6 (C-5).

***N*-(4-chlorobenzyl)-4-methyl-2-((2-(trifluoromethyl)quinolin-4-yl)amino) pentanamide (II-34)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 45 % yield (200 mg).

Mol. Wt.: 449.90, Nature: oil.

HRMS: Calcd. for $C_{23}H_{23}ClF_3N_3O$: 449.1482, Found : 449.1482

M.P. = 148 - 149 ^oC

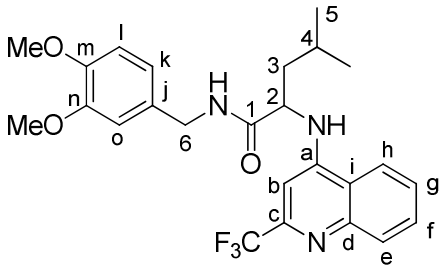
IR : 3280, 3236, 2957, 2360, 2336, 1665, 1593, 1547, 1461, 1290, 1179, 1138 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.08 (d, 1H, *J* = 8.3 Hz, H-h), 7.80 (d, 1H, *J* = 8.3 Hz, H-e), 7.72 (ddd, 1H, *J* = 1.1, 7.0, 8.3 Hz, H-f), 7.55 (ddd, 1H, *J* = 1.1, 7.0, 8.3 Hz, H-g), 7.24 (d, 2H, *J* = 8.4 Hz, H-k), 7.11 (d, 2H, *J* = 8.4 Hz, H-l), 6.68 (s, 1H, H-b), 6.60 (br t, 1H, *J* =

5.8 Hz, NH), 5.59 (d, 1H, *J* = 5.4 Hz, NH), 4.46 (dd, 1H, *J* = 5.8, 14.9 Hz, H-6), 4.40 (dd, 1H, *J* = 5.8, 14.9 Hz, H-6), 4.16-4.09 (m, 1H, H-2), 2.05-1.94 (m, 1H, H-3), 1.89-1.79 (m, 2H, H-4, H-3), 1.05 (d, 3H, *J* = 6.3 Hz, H-5), 0.96 (d, 3H, *J* = 6.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.7 (C-1), 150.0 (C-a), 148.7 (d, *J* = 33.7 Hz, C-c), 147.4 (C-d), 136.0 (C-m), 133.5 (C-i), 130.9 (C-e), 130.5 (C-f), 128.9 (C-l,C-k), 127.0 (C-g), 121.6 (q, *J* = 277.0 Hz, CF_3), 119.0 (C-h), 118.6 (C-j), 95.2 (d, *J* = 2.3 Hz, C-b), 57.6 (C-2), 42.8 (C-6), 42.3 (C-3), 24.3 (C-4), 22.0 (C-5), 21.9 (C-5).

***N*-(3,4-dimethoxybenzyl)-4-methyl-2-((2-(trifluoromethyl)quinolin-4-yl)amino)pentanamide (II-35)**



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 37 % yield (175 mg).

Mol. Wt.: 475.50, Nature: white solid.

HRMS: Calcd. for $C_{25}H_{28}ClF_3N_3O_3$: 475.2083, Found : 475.2085

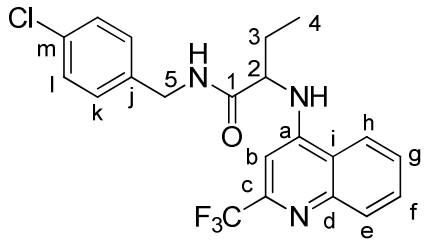
M.P. = 154-155 ^{o}C

IR : 3305, 2957, 1659, 1593, 1579, 1516, 1461, 1419, 1263, 1134, 1026 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.10 (d, 1H, *J* = 8.4 Hz, H-e), 7.81 (d, 1H, *J* = 8.3 Hz, H-h), 7.74 (t, 1H, *J* = 7.4 Hz, H-g), 7.56 (t, 1H, *J* = 7.4 Hz, H-f), 6.77-6.67 (m, 4H, H-l, H-k, H-b, H-o), 6.48-6.42 (br s, 1H, NH), 5.60 (d, 1H, *J* = 5.2 Hz, NH), 4.46-4.35 (m, 2H, H-6), 4.12 (td, 1H, *J* = 5.2, 8.3 Hz, H-2), 3.83 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.02-1.95 (m , 1H, H-3), 1.90-1.77 (m , 2H, H-4, H-3), 1.05 (d, 3H, *J* = 6.3 Hz, H-5), 0.96 (d, 3H, *J* = 6.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.5 (C-1), 150.1 (C-a), 149.0 (C-m), 148.8 (d, *J* = 33.7 Hz, C-c), 148.5 (C-n), 147.4 (C-d), 130.8 (C-f), 130.5 (C-e), 130.0 (C-j), 126.9 (C-g), 124.1 (q, *J* = 285.2 Hz CF_3), 119.9 (C-h), 119.1 (C-l), 118.7 (C-i), 111.1 (C-k), 110.8 (C-o), 95.2 (d, *J* = 2.1 Hz, C-b), 56.6 (C-2), 55.8 (OCH_3), 55.7 (OCH_3), 43.5 (C-6), 42.3 (C-3), 25.2 (C-5), 23.0 (C-5), 21.9 (C-4).

_N_-(4-chlorobenzyl)-2-((2-(trifluoromethyl)quinolin-4-yl)amino)butanamide (II-36)



This compound was synthesized according to the general procedure II-B, using 1.0 mmol of isocyanide. The desired product was isolated in 48 % yield (200 mg).

Mol. Wt.: 421.84, Nature: white solid.

HRMS: Calcd. for $C_{21}H_{19}ClF_3N_3O$: 421.1169, Found : 421.1168

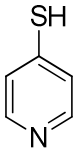
M.P. = 125-126 ^oC

IR : 3291, 3065, 2971, 2933, 1655, 1589, 1575, 1530, 1409, 1290, 1176, 1138, 1089 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.05 (t, 1H, *J* = 7.6 Hz, H-h), 7.85 (d, 1H, *J* = 8.5 Hz, H-e), 7.74-7.67 (m, 1H, H-f), 7.58-7.51 (m, 1H, H-g), 7.25 (dd, 2H, *J* = 1.8, 8.0 Hz, H-k), 7.14 (d, 2H, *J* = 8.0 Hz, H-l), 6.72-6.55 (m, 2H, H-b, NH), 5.90 (d, 1H, *J* = 5.6 Hz, NH), 4.53-4.39 (m, 2H, H-5), 4.12 (dd, 1H, *J* = 5.8, 11.8 Hz, H-2), 1.95 (dq, 2H, *J* = 7.0, 14.2 Hz, H-3), 1.08 (t, 3H, *J* = 7.0 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.0 (C-1), 150.0 (C-a), 148.7 (q, *J* = 34.6 Hz C-c), 147.5 (C-d), 136.0 (C-j), 133.5 (C-m), 130.7 (C-e), 130.4 (C-f), 129.0 (C-l), 128.9 (C-k), 126.9 (C-g), 121.7 (q, *J* = 275.6 Hz, CF_3), 119.2 (C-h), 118.7 (C-i), 95.1 (d, *J* = 2.3 Hz, C-b), 58.4 (C-2), 42.9 (C-5), 26.2 (C-3), 9.9 (C-4).

Pyridine-4-thiol (II-37)



To a solution of 4-hydroxypyridine (500 mg, 5.2 mmol) in pyridine (10ml) was added P_2S_5 (1.15 gm, 5.2 mmol, 1.0 equiv.) in small portions with in 5 min, at 25 ^oC, the resulting mixture was heated at 100 ^oC for 2 hrs. then , the heating was stopped, water was added and the resulting mixture was stirred for 30 min. The aqueous layer was extracted with diethyl ether (4 X 25ml), and the combined organic phases were washed with aqueous saturated

NaCl Solution, dried over $MgSO_4$ and volatiles removed in vacuum. The crude product was purified by flash chromatography on silica gel with CH_2Cl_2 as an eluent.

Yield : 500mg, Yield = 90 %

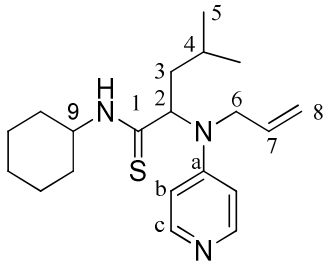
Nature: yellow solid**,**

M.P. = 177-178 ^oC

I.R. (thin film): 3434, 3192, 3099, 2848, 1611, 1477, 1279, 1201, 1110, 1018, 796 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.75 (dd, 2H, *J* = 1.3, 5.3 Hz, H-c), 7.54 (dd, 2H, *J* = 1.3, 5.3 Hz, H-b).

2-(allyl(pyridin-4-yl)amino)-*N*-cyclohexyl-4-methylpentanethioamide (II-38)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 80 % yield (300 mg).

Mol. Wt.: 345.55, Nature: white solid.

HRMS: Calcd. for $C_{20}H_{31}N_3S$: 345.2239, Found : 345.2228.

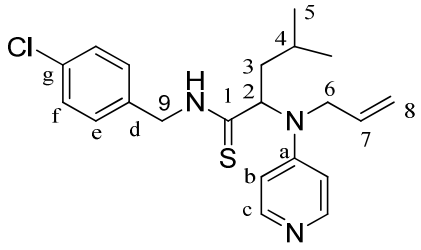
M.P. = 165-166 ^oC

I.R. (thin film): 2933, 2852, 1598, 1545, 1509, 1450, 1387, 1235, 1169, 1109 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.27 (dd, 2H, *J* = 1.3, 5.1 Hz, H-c), 7.86 (d, 1H, *J* = 6.5 Hz, NH), 6.60 (dd, 2H, *J* = 1.3, 5.1 Hz, H-b), 5.91 (tdd, 1H, *J* = 5.4, 10.6, 16.0 Hz, H-7), 5.34-5.22 (m, 2H, H-8), 4.50 (dd, 1H, *J* = 4.4, 9.8 Hz, H-2), 4.40-4.29 (m, 1H, H-9), 4.08-3.94 (m, 2H, H-6), 2.46 (ddd, 1H, *J* = 4.4, 9.8, 14.3 Hz, H-3), 1.99-1.89 (m, 2H, H-4, H-cy), 1.84 (ddd, 1H, *J* = 4.4, 9.8, 14.3 Hz, H-3), 1.66-1.54 (m, 4H, H-cy), 1.41-1.30 (m, 2H, H-cy), 1.16-1.02 (m, 3H, H-cy), 0.92 (d, 3H, *J* = 6.6, Hz, H-5), 0.88 (d, 3H, *J* = 6.6, Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 200.5 (C-1), 153.0 (C-a), 150.2 (C-c), 132.8 (C-7), 119.0 (C-8), 108.8 (C-b), 69.0 (C-2), 53.9 (C-9), 48.7 (C-6), 40.9 (C-3), 31.3 (C-cy), 31.1 (C-cy), 25.4 (C-4), 25.3 (C-cy), 24.4 (C-cy), 23.2 (C-5), 21.5 (C-5).

2-(allyl(pyridin-4-yl)amino)-*N*-(4-chlorobenzyl)-4-methylpentanethioamide (II-39)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 57 % yield (219 mg).

Mol. Wt.: 387.97, Nature: white solid.

HRMS: Calcd. for $C_{21}H_{26}ClN_3S$: 387.1536, Found : 387.1525.

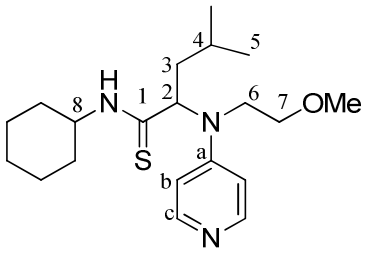
M.P. = 176 - 177 ^{o}C

I.R. (thin film): 2958, 1599, 1540, 1510, 1489, 1404, 1385, 1231, 1169, 1091 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.75 (br s, 1H, NH), 7.98 (d, 2H, *J* = 6.4 Hz, H-c), 7.20 (d, 2H, *J* = 8.3 Hz, H-e), 7.10 (d, 2H, *J* = 8.3 Hz, H-f), 6.55 (d, 2H, *J* = 6.4 Hz, H-b), 5.77 (tdd, 1H, *J* = 5.0, 10.4, 16.0 Hz, H-7), 5.16-5.07 (m, 2H, H-8), 4.83-4.73 (m, 2H, H-9), 4.63 (t, 1H, *J* = 7.0 Hz, H-2), 4.19 (dd, 1H, *J* = 5.0, 16.0 Hz H-6), 4.03 (dd, 1H, *J* = 5.0, 16.0 Hz, H-6), 2.33 (ddd, 1H, *J* = 6.0, 7.0, 14.0 Hz, H-3), 1.79 (ddd, 1H, *J* = 6.0, 7.0, 14.0 Hz, H-3), 1.68-1.57 (m, 1H, H-4), 0.92 (d, 3H, *J* = 6.5 Hz, H-5), 0.89 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 203.1 (C-1), 153.2 (C-a), 149.7 (C-c), 134.5 (C-d), 133.8 (C-g), 133.0 (C-7), 129.5 (C-f), 128.9 (C-e), 118.3 (C-8), 108.6 (C-b), 67.4 (C-2), 49.0 (C-6), 48.5 (C-9), 41.2 (C-3), 25.3 (C-4), 22.9 (C-5), 21.9 (C-5).

N-cyclohexyl-2-((2-methoxyethyl)(pyridin-4-yl)amino)-4-methyl-pentanethioamide (II-40)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 55 % yield (200 mg).

Mol. Wt.: 363.56, Nature: Pale brown solid.

HRMS: Calcd. for $C_{20}H_{33}N_3O$: 363.2344, Found : 363.2340.

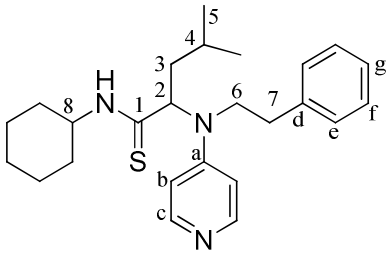
M.P. = 124-125 ^oC

I.R. (thin film): 2933, 2852, 1641, 1591, 1537, 1506, 1448, 1344, 1227, 1164, 1105 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.39 (br d, 1H, *J* = 7.2 Hz, NH), 8.27 (dd, 2H, *J* = 1.4, 5.1 Hz, H-c), 6.58 (dd, 2H, *J* = 1.4, 5.1 Hz, H-b), 4.45-4.35 (m, 1H, H-8), 4.32 (dd, 1H, *J* = 3.4, 10.9 Hz, H-2), 3.86-3.69 (m, 2H, H-7), 3.64-3.56 (m, 2H, H-6), 3.38 (s, 3H, OCH_3), 2.45-2.35 (m, 1H, H-3), 2.01-1.88 (m, 3H, H-3, H-4, H-cy), 1.74-1.61 (m, 3H, H-cy), 1.54-1.44 (m, 1H, H-cy), 1.40-1.28 (m, 2H, H-cy), 1.10-0.93 (m, 3H, H-cy), 0.91 (d, 3H, *J* = 6.6 Hz, H-5), 0.87 (d, 3H, *J* = 6.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 201.6 (C-1), 152.4 (C-a), 150.1 (C-c), 109.6 (C-b), 71.7 (C-2), 69.1 (C-7), 58.8 (OCH_3), 54.4 (C-6), 41.1 (C-8), 31.3 (C-3), 33.2 (C-cy), 25.5 (C-cy, C-4), 24.8 (C-cy), 23.5 (C-5), 21.0 (C-5).

***N*-cyclohexyl-4-methyl-2-(phenethyl(pyridin-4-yl)amino)pentanethioamide (II-41)**



This compound was synthesized according to the general procedure II-D, using 2.0 mmol of isocyanide. The desired product was isolated in 60 % yield (488 mg).

Mol. Wt.: 409.63, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{25}H_{35}N_3S$: 409.2552, Found : 409.2547.

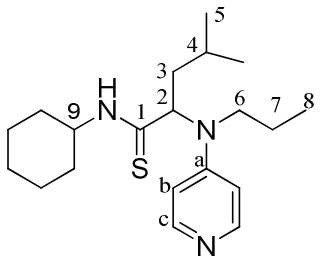
M.P. = 173-174 ^oC

I.R. (thin film): 3200, 2930, 2857, 1600, 1513, 1450, 1363, 1270, 1224, 1150, 1080 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.30 (dd, 2H, *J* = 1.5, 5.0 Hz, H-c), 8.00 (br d, 1H, *J* = 7.6 Hz, NH), 7.37 (t, 2H, *J* = 7.3 Hz, H-f), 7.31-7.23 (m, 3H, H-e, H-g), 6.63 (dd, 2H, *J* = 1.5, 5.0 Hz, H-b), 4.47-4.34 (m, 2H, H-2, H-8), 3.66-3.57 (m, 1H, H-6), 3.55-3.45 (m, 1H, H-6), 2.97-2.83 (m, 2H, H-7), 2.57 (ddd, 1H, *J* = 5.0, 9.0, 14.2 Hz, H-3), 2.00-1.91 (m, 2H, H-cy), 1.81 (ddd, 1H, *J* = 5.0, 9.0, 14.2 Hz, H-3), 1.63-1.52 (m, 4H, H-cy), 1.41-1.30 (m, 2H, H-cy), 1.13-1.04 (m, 3H, H-cy), 0.93 (d, 3H, *J* = 6.3 Hz, H-5), 0.92 (d, 3H, *J* = 6.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 199.9 (C-1), 152.6 (C-a), 150.4 (C-c), 137.8 (C-d), 129.0 (C-f), 128.5 (C-e), 127.0 (C-g), 108.6 (C-b), 68.1 (C-2), 53.9 (C-8), 48.7 (C-6), 40.4 (C-3), 34.1 (C-7), 31.1 (C-cy), 31.0 (C-cy), 25.5 (C-5), 25.2 (C-cy), 24.4 (C-cy), 23.1 (C-4), 21.9 (C-5).

***N*-cyclohexyl-4-methyl-2-(propyl(pyridin-4-yl)amino)pentanethioamide (II-42)**



This compound was synthesized according to the general procedure II-D, using 2.0 mmol of isocyanide. The desired product was isolated in 55 % yield (380 mg).

Mol. Wt.: 347.56, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{20}H_{33}N_3S$: 347.2395, Found : 347.2404

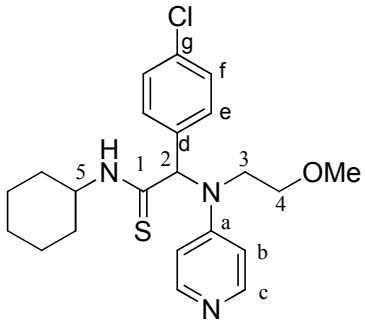
M.P. = 157-158 ^{o}C

I.R. (thin film): 3166, 2930, 2866, 1596, 1509, 1434, 1231, 1099 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.26 (dd, 2H, *J* = 1.4, 5.1 Hz, H-c), 7.81 (br d, 1H, *J* = 7.1 Hz, NH), 6.51 (dd, 2H, *J* = 1.4, 5.1 Hz, H-b), 4.44-4.32 (m, 2H, H-2, H-9), 3.34-3.15 (m, 2H, H-6), 2.56 (ddd, 1H, *J* = 4.0, 9.6, 14.0 Hz, H-3), 1.99-1.90 (m, 2H, H-cy), 1.84 (ddd, 1H, *J* = 4.0, 9.6, 14.0 Hz, H-3), 1.70-1.52 (m, 6H, H-4, H-7, H-cy), 1.43-1.30 (m, 2H, H-cy), 1.12-1.04 (m, 3H, H-cy), 0.98 (t, 3H, *J* = 7.4 Hz, H-8), 0.94-0.88 (m, 6H, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 200.2 (C-1), 152.6 (C-a), 150.3 (C-c), 108.5 (C-b), 68.9 (C-2), 53.7 (C-9), 49.1 (C-6), 40.4 (C-3), 31.2 (C-cy), 31.1 (C-cy), 25.5 (C-4), 25.2 (C-cy), 24.3 (C-cy), 23.3 (C-5), 21.6 (C-5), 21.2 (C-7), 11.3 (C-8).

2-(4-chlorophenyl)-*N*-cyclohexyl-2-((2-methoxyethyl)(pyridin-4-yl)amino)-ethanethioamide (II-43)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 34 % yield (140 mg).

Mol. Wt.: 418.00, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{22}H_{28}ClN_3OS$: 417.1642, Found : 417.1648.

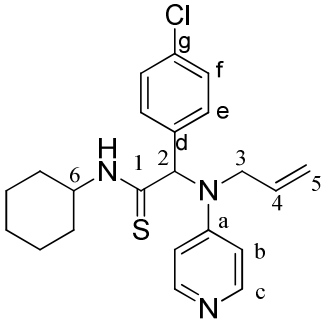
M.P. = 96-97 ^{o}C

I.R. (thin film): 2933, 2852, 1641, 1590, 1537, 1510, 1491, 1448, 1445, 1343, 1234, 1164 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.80 (br d, 1H, *J* = 8.0 Hz, NH), 8.26 (d, 2H, *J* = 6.4 Hz, H-c), 7.30 (d, 2H, *J* = 8.4 Hz, H-e), 7.10 (d, 2H, *J* = 8.4 Hz, H-f), 6.62 (d, 2H, *J* = 6.4 Hz, H-b), 5.65 (s, 1H, H-2), 4.52-4.40 (m, 1H, H-5), 3.87-3.78 (m, 1H, H-4), 3.30 (s, 3H, OCH_3), 3.29-3.25 (m, 1H, H-4), 3.22-3.17 (m, 1H, H-3), 3.07-2.96 (m, 1H, H-3), 2.20-2.10 (m, 1H, H-cy), 1.90-1.60 (m, 4H, H-cy), 1.40-1.23 (m, 2H, H-cy), 1.20-0.99(m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 198.5 (C-1), 153.1 (C-a), 150.2 (C-c), 134.8 (C-d), 134.7 (C-g), 131.4 (C-f), 129.3 (C-e), 109.1 (C-b), 76.9 (C-2), 69.1 (C-4), 59.0 (OCH_3), 54.5 (C-5), 45.2 (C-3), 31.8 (C-cy), 31.3 (C-cy), 25.5 (C-cy), 25.0 (C-cy), 24.9 (C-cy).

2-(allyl(pyridin-4-yl)amino)-2-(4-chlorophenyl)-*N*-cyclohexylethanethioamide (II-44)



This compound was synthesized according to the general procedure using II-D, mmol of isocyanide. The desired product was isolated in 40 % yield (160 mg).

Mol. Wt.: 399.98, Nature: oil..

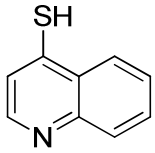
HRMS: Calcd. for $C_{22}H_{26}ClN_3S$: 399.1536, Found : 399.1541

I.R. (thin film): 2961, 1592, 1543, 1507, 1481, 1400, 1391, 1226, 1164, 1088 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.71 (br s, 1H, NH), 8.20 (d, 2H, *J* = 6.4 Hz, H-c), 7.30 (d, 2H, *J* = 8.1 Hz, H-e), 7.20 (d, 2H, *J* = 8.1 Hz, H-f), 6.62 (d, 2H, *J* = 6.4 Hz, H-b), 5.81 (tdd, 1H, *J* = 5.4, 10.6, 16.0 Hz, H-4), 5.65 (s, 1H, H-2), 5.34-5.22 (m, 2H, H-5), 4.47-4.36 (m, 1H, H-6), 3.91-3.83 (m, 2H, H-3), 2.11-2.03 (m, 1H, H-cy), 1.93-1.85 (m, 1H, H-cy), 1.74-1.54 (m, 3H, H-cy), 1.40-1.00 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 198.5 (C-1), 153.1 (C-a), 150.2 (C-c), 134.6 (C-d), 133.5 (C-g), 132.9 (c-4), 131.1 (C-f), 128.9 (C-e), 117.9 (C-5), 108.6 (C-b), 73.7 (C-2), 53.9 (C-6), 49.3 (C-3), 40.3 (C-6), 31.5 (C-cy), 30.8 (C-cy), 25.2 (C-cy), 24.5 (C-cy), 24.3 (C-cy).

Quinoline-4-thiol (II-45)



To a solution of 4-hydroxyquinoline (300 mg, 2.1 mmol) in pyridine (10ml) was added P_2S_5 (466 mg, 2.1 mmol, 1.0 equiv.) in small portions with in 5 min, at 25 ^oC, the resulting mixture was heated at 100 ^oC for 2 hrs. then, the heating was stopped, water was added and the resulting mixture was stirred for 30 min. The aqueous layer was extracted with diethyl ether (4 X 25ml), and the combined organic phases were washed with aqueous saturated NaCl Solution, dried over $MgSO_4$ and volatiles removed in vacuum. The crude product was purified by flash chromatography on silica gel with CH_2Cl_2 as an eluent.

Yield : 290 mg, % Yield = 90 %.

Nature : Yellow solid,

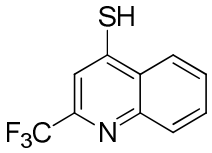
M.P. = 160-162 ^oC

I.R. (thin film): 3433, 3191, 3092, 2847, 1608, 1475, 1279, 1201, 1110, 1018 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.85 (d, 1H, *J* = 8.3 Hz, H-Ar), 7.61 (t, 1H, *J* = 7.6 Hz, H-Ar), 7.50-2.45 (m, 2H, H-Ar), 7.41 (t, 2H, *J* = 7.41 Hz, H-Ar)

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 135.6, 132.7, 132.6, 132.5, 129.2, 125.9, 124.8, 118.9.

2-(trifluoromethyl)quinoline-4-thiol (II-46)



To a solution of 2-(trifluoromethyl)quinoline-4-thiol (250 mg, 1.1 mmol) in pyridine (10ml) was added P_2S_5 (244 mg, 1.1 mmol, 1.0 equiv.) in small portions with in 5 min, at 25 ^oC, the resulting mixture was heated at 100 ^oC for 2 hrs. then, the heating was stopped, water was added and the resulting mixture was stirred for 30 min. The aqueous layer was extracted with diethyl ether (4 X 25ml), and the combined organic phases were washed with aqueous saturated NaCl Solution, dried over $MgSO_4$ and volatiles removed in vacuum. The crude product was purified by flash chromatography on silica gel with CH_2Cl_2 as an eluent.

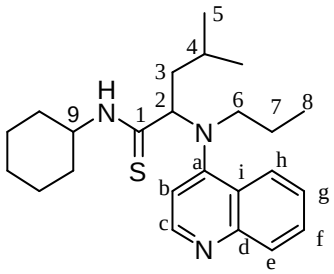
Yield : 63 mg, % Yield = 25 %.

Nature: semisolid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.32 (t, 2H, *J* = 7.8 Hz), 7.93 (t, 1H, *J* = 7.8 Hz), 7.77 (t, 1H, *J* = 7.8 Hz), 7.47 (s, 1H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.5 (d, J_{F-C} = 35.1 Hz), 147.3, 143.8, 131.8, 131.2, 129.8, 127.7, 124.4, 121.1 (q, J_{F-C} = 276 Hz), 118.9 (d, J_{F-C} = 2.0 Hz).

***N*-cyclohexyl-4-methyl-2-(propyl(quinolin-4-yl)amino)pentanethioamide (II-47)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 87 % yield (346 mg).

Mol. Wt.: 397.62, Nature : Pale yellow solid.

HRMS: Calcd. for $C_{24}H_{35}N_3S$: 397.2552, Found : 397.2552

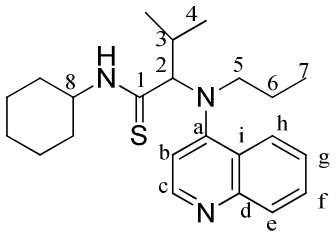
M.P. = 118-119 ^{o}C

I.R. (thin film): 3291, 3173, 2930, 2860, 1575, 1502, 1454, 1428, 1384, 1290, 1079 cm^{-1}

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 8.74 (d, 1H, *J* = 5.0 Hz, H-c), 8.53 (br d, 1H, *J* = 7.1 Hz, NH), 8.09 (d, 1H, *J* = 8.3 Hz, H-e), 7.82 (d, 1H, *J* = 8.3 Hz, H-h), 7.68 (t, 1H, *J* = 8.3 Hz, H-f), 7.48 (t, 1H, *J* = 8.3 Hz, H-g), 7.01 (d, 1H, *J* = 5.0 Hz, H-b), 4.50-4.40 (m, 2H, H-2, H-9), 3.46-3.36 (m, 1H, H-6), 3.00-1.91 (m, 1H, H-6), 2.43-2.33 (m, 1H, H-3), 2.07-1.96 (m, 2H, H-7), 1.81-160 (m, 6H, H-3, H-4, H-cy), 1.45-1.35 (m, 3H, H-cy), 1.21-1.07 (m, 3H, H-cy), 0.91 (t, 3H, *J* = 7.4 Hz, H-8), 0.77 (d, 3H, *J* = 6.5 Hz, H-5), 0.53 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR (CDCl$_3$, 100.6 MHz): δ (ppm) 199.8 (C-1), 153.5 (C-a), 150.1 (C-c), 149.9 (C-d), 130.6 (C-e), 129.2 (C-f), 126.0 (C-g), 124.4 (C-i), 122.2 (C-h), 112.4 (C-b), 72.5 (C-2), 53.6 (C-9), 48.5 (C-6), 41.3 (C-3), 31.6 (C-cy), 31.1 (C-cy), 25.5 (C-cy), 25.3 (C-4), 24.5 (C-cy), 24.4 (C-cy), 22.8 (C-5), 21.8 (C-5), 20.1 (C-7), 11.7 (C-8).

***N*-cyclohexyl-3-methyl-2-(propyl(quinolin-4-yl)amino)butanethioamide (II-48)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 81 % yield (310 mg).

Mol. Wt.: 383.59, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{23}H_{33}N_3S$: 383.2395, Found : 383.2410.

M.P. = 109 - 110 ^{o}C

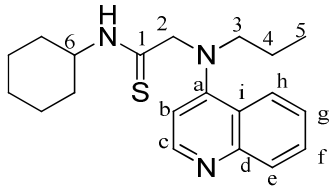
I.R. (thin film): 2930, 2857, 1575, 1502, 1422, 1391, 1304, 1363, 1165, 1075 cm^{-1}

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 8.75 (d, 1H, *J* = 5.0 Hz, H-c), 8.19 (d, 1H, *J* = 8.3 Hz, H-e), 8.09 (d, 1H, *J* = 8.3 Hz, H-h), 7.70 (t, 1H, *J* = 8.3 Hz, H-f), 7.56 (t, 1H, *J* = 8.3 Hz, H-g), 7.18 (d, 1H, *J* = 5.0 Hz, H-b), 6.5 (br s, 1H, NH), 4.19-4.07 (m, 1H, H-8), 3.91 (d, 1H, *J* = 7.7 Hz, H-2), 3.53 (ddd, 1H, *J* = 4.5, 10.0, 14.1 Hz, H-5), 3.26 (ddd, 1H, *J* = 6.7, 10.0, 14.1 Hz, H-5), 2.71-2.60 (m, 1H, H-3), 1.67-1.59 (m, 1H, H-cy), 1.54-1.32 (m, 9H, H-cy, H-4, H-

6), 1.27-1.09 (m, 2H, H-cy), 0.99-0.88 (m, 4H, H-4, H-cy), 0.81 (t, 3H, *J* = 7.4 Hz, H-7), 0.71-0.58 (m, 1H, H-cy), 0.56-0.42 (m, 1H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 196.8 (C-1), 153.9 (C-a), 150.5 (C-c), 149.9 (C-d), 130.4 (C-e), 129.2 (C-f), 126.2 (C-g), 125.4 (C-i), 123.0 (C-h), 115.4 (C-b), 79.1 (C-2), 52.9 (C-8), 49.4 (C-5), 31.5 (C-cy), 31.0 (C-cy), 28.5 (C-3), 25.1 (C-cy), 24.4 (C-cy), 24.3 (C-cy), 20.0 (C-4), 19.9 (C-6), 18.9 (C-4), 11.6 (C-7).

***N*-cyclohexyl-2-(propyl(quinolin-4-yl)amino)ethanethioamide (II-49)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 56 % yield (190 mg).

Mol. Wt.: 341.51, Nature: Pale yellow liquid.

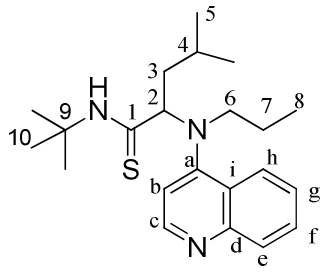
HRMS: Calcd. for $C_{20}H_{27}N_3S$: 341.1926, Found : 341.1924.

I.R. (thin film): 3294, 2930, 2853, 1686, 1572, 1506, 1454, 1398, 1280, 1079 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.76 (d, 1H, *J* = 4.9 Hz, H-c), 8.68 (br d, 1H, *J* = 6.0 Hz, NH), 8.11 (d, 1H, *J* = 8.3 Hz, H-e), 7.93 (d, 1H, *J* = 8.3 Hz, H-h), 7.71 (t, 1H, *J* = 8.3 Hz, H-f), 7.54 (t, 1H, *J* = 8.3 Hz, H-g), 6.99 (d, 1H, *J* = 4.9 Hz, H-b), 4.46-4.36 (m, 1H, H-6), 4.34 (s, 2H, H-2), 3.23 (t, 2H, *J* = 7.6 Hz, H-3), 1.91 (d, 2H, *J* = 10.2 Hz, H-cy), 1.70-1.51 (m, 5H, H-cy, H-4), 1.43-1.30 (m, 2H, H-cy), 1.18-1.05 (m, 3H, H-cy), 0.90 (t, 3H, *J* = 7.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 195.9 (C-1), 153.5 (C-a), 150.6 (C-c), 149.9 (C-d), 130.7 (C-e), 129.4 (C-f), 126.2 (C-g), 123.9 (C-i), 121.9 (C-h), 111.1 (C-b), 65.2 (C-2), 56.6 (C-3), 52.9 (C-6), 31.1 (C-cy), 25.2 (C-4), 24.1 (C-cy), 20.2 (C-cy), 11.5 (C-5).

***N*-(tert-butyl)-4-methyl-2-(propyl(quinolin-4-yl)amino)pentanethioamide (II-50)**



This compound was synthesized according to the general procedure II.D, using 1.0 mmol of isocyanide. The desired product was isolated in 81 % yield (300 mg).

Mol. Wt.: 371.58, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{22}H_{33}N_3S$: 371.2395, Found : 371.2385

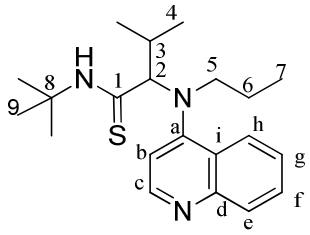
M.P. = 129-130 ^oC

I.R. (thin film): 2957, 2930, 2871, 1572, 1502, 1426, 1363, 1297, 1211, 1079 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.75 (d, 1H, *J* = 5.0 Hz, H-c), 8.35 (br s, 1H, NH), 8.08 (d, 1H, *J* = 8.3 Hz, H-e), 7.91 (d, 1H, *J* = 8.3 Hz, H-h), 7.68 (t, 1H, *J* = 8.3 Hz, H-f), 7.50 (t, 1H, *J* = 8.3 Hz, H-g), 7.06 (d, 1H, *J* = 5.0 Hz, H-b), 4.38 (t, 1H, *J* = 6.4 Hz, H-2), 3.35 (ddd, 1H, *J* = 5.1, 10.3, 15.0 Hz, H-6), 3.01 (ddd, 1H, *J* = 5.1, 10.3, 15.0 Hz, H-6), 2.27-2.15 (m, 1H, H-3), 1.75-1.60 (m, 3H, H-3, H-7), 1.40 (s, 9H, H-10), 1.38-1.26 (m, 1H, H-4), 0.87 (t, 3H, *J* = 7.4 Hz, H-8), 0.81 (d, 3H, *J* = 6.2 Hz, H-5), 0.63 (d, 3H, *J* = 6.2 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 200.1 (C-1), 153.5 (C-a), 150.2 (C-c), 149.9 (C-d), 130.6 (C-e), 129.2 (C-f), 126.0 (C-g), 124.8 (C-i), 122.3 (C-h), 113.4 (C-b), 73.5 (C-2), 55.2 (C-9), 49.6 (C-6), 41.2 (C-3), 27.4 (C-10), 25.5 (C-4), 22.6 (C-5), 22.4 (C-5), 19.8 (C-7), 11.6 (C-8).

***N*-(tert-butyl)-3-methyl-2-(propyl(quinolin-4-yl)amino)butanethioamide (II-51)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 78 % yield (280 mg).

Mol. Wt.: 357.56, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{21}H_{31}N_3S$: 357.2239, Found : 357.2238.

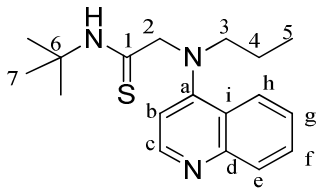
M.P. = 94-95 ^{o}C

I.R. (thin film): 2961, 2923, 2864, 1572, 1502, 1461, 1422, 1391, 1211, 1079, 1040 cm^{-1}

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 8.77 (d, 1H, *J* = 5.0 Hz, H-c), 8.17 (d, 1H, *J* = 8.3 Hz, H-e), 8.10 (d, 1H, *J* = 8.3 Hz, H-h), 7.69 (ddd, 1H, *J* = 1.3, 7.0, 8.3 Hz, H-f), 7.55 (ddd, 1H, *J* = 1.3, 7.0, 8.3 Hz, H-g), 7.21 (d, 1H, *J* = 5.0 Hz, H-b), 6.74 (br s, 1H, NH), 4.04 (d, 1H, *J* = 6.6 Hz, H-2), 3.41 (ddd, 1H, *J* = 4.5, 10.5, 14.6 Hz, H-5), 3.23 (ddd, 1H, *J* = 6.1, 10.5, 14.6 Hz, H-5), 2.62-2.48 (m, 1H, H-3), 1.52-1.41 (m, 1H, H-6), 1.39-1.28 (m, 4H, H-6, H-4), 1.03 (s, 9H, H-9), 0.97 (d, 3H, *J* = 6.6 Hz, H-4), 0.78 (t, 3H, *J* = 7.4 Hz, H-7).

^{13}C NMR (CDCl$_3$, 100.6 MHz): δ (ppm) 196.7 (C-1), 153.7 (C-a), 150.6 (C-c), 149.8 (C-d), 130.4 (C-e), 129.2 (C-f), 126.2 (C-g), 125.3 (C-i), 122.8 (C-h), 115.8 (C-b), 79.5 (C-2), 55.1 (C-8), 50.3 (C-5), 27.9 (C-3), 27.0 (C-9), 20.3 (C-4), 19.1 (C-6), 18.3 (C-4), 11.5 (C-7).

***N*-(tert-butyl)-2-(propyl(quinolin-4-yl)amino)ethanethioamide (II-52)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 51 % yield (160 mg).

Mol. Wt.: 315.48, Nature: Pale brown liquid.

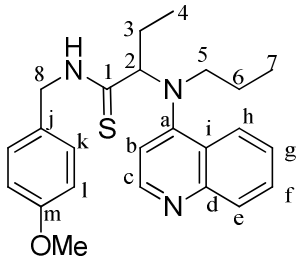
HRMS: Calcd. for $C_{18}H_{25}N_3S$: 315.1769, Found : 315.1784.

I.R. (thin film): 3273, 2964, 2930, 2878, 1575, 1513, 1422, 1395, 1363, 1294, 1211, 1082 cm^{-1}

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 8.76 (d, 1H, *J* = 5.0 Hz, H-c), 8.70 (br s, 1H, NH), 8.11 (d, 1H, *J* = 8.3 Hz, H-e), 7.97 (d, 1H, *J* = 8.3 Hz, H-h), 7.70 (ddd, 1H, *J* = 1.2, 6.9, 8.3 Hz, H-f), 7.54 (ddd, 1H, *J* = 1.2, 6.9, 8.3 Hz, H-g), 6.99 (d, 1H, *J* = 5.0 Hz, H-b), 4.25 (s, 2H, H-2), 3.21 (t, 2H, *J* = 7.9 Hz, H-3), 1.66-1.56 (m, 2H, H-4), 1.41 (s, 9H, H-7), 0.87 (t, 3H, *J* = 7.4 Hz, H-5).

^{13}C NMR (CDCl$_3$, 100.6 MHz): δ (ppm) 195.9 (C-1), 153.5 (C-a), 150.6 (C-c), 149.8 (C-d), 130.6 (C-e), 129.3 (C-f), 126.2 (C-g), 124.0 (C-i), 121.9 (C-h), 111.4 (C-b), 66.2 (C-2), 57.0 (C-3), 55.2 (C-6), 27.5 (C-7), 20.2 (C-4), 11.4 (C-5).

_N_-(4-methoxybenzyl)-2-(propyl(quinolin-4-yl)amino)butanethioamide (II-53)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 51 % yield (210 mg).

Mol. Wt.: 407.57, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{24}H_{29}N_3OS$: 407.2031, Found : 407.2020

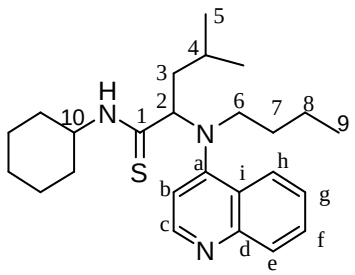
M.P. = 96 - 97 ^{o}C

IR : 3312, 3183, 2961, 2933, 2874, 1613, 1572, 1509, 1491, 1301, 1249, 1172, 1037 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.73 (d, 1H, *J* = 5.0 Hz, H-c), 8.28 (br s, 1H, NH), 8.07 (d, 1H, *J* = 8.3 Hz, H-h), 7.82 (d, 1H, *J* = 8.3 Hz, H-e), 7.65 (t, 1H, *J* = 8.3 Hz, H-f), 7.40 (t, 1H, *J* = 8.3 Hz, H-g), 7.07 (d, 1H, *J* = 5.0 Hz, H-b), 6.76 (d, 2H, *J* = 8.5 Hz, H-k), 6.63 (d, 2H, *J* = 8.5 Hz, H-l), 4.72 (dd, 1H, *J* = 5.7, 14.7 Hz, H-8), 4.56 (t, 1H, *J* = 5.7 Hz, H-2), 4.50 (dd, 1H, *J* = 4.4, 14.7 Hz, H-8), 3.75 (s, 3H, OMe), 3.37-3.27 (m, 1H, H-5), 3.14-3.04 (m, 1H, H-5), 2.40-2.28 (m, 1H, H-3), 2.16-2.04 (m, 1H, H-3), 1.58-1.45 (m, 1H, H-6), 1.25-1.12 (m, 1H, H-6), 0.92 (t, 3H, *J* = 7.4 Hz, H-4), 0.72 (t, 3H, *J* = 7.3 Hz, H-7).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 200.9 (C-1), 159.2 (C-a), 153.7 (C-m), 150.2 (C-c), 149.9 (C-d), 130.4 (C-e), 129.2 (C-k), 129.1(C-f), 127.6 (C-j), 126.2 (C-g), 124.7 (C-i), 122.4 (C-h), 114.0 (C-l), 113.5 (C-b), 73.6 (C-2), 55.2 (OMe), 50.8 (C-5), 49.2 (C-8), 25.4 (C-3), 18.8 (C-6), 11.3 (C-7), 10.7 (C-4).

2-(butyl(quinolin-4-yl)amino)-_N_-cyclohexyl-4-methylpentanethioamide (II-54)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 99 % yield (406 mg).

Mol. Wt.: 411.65, Nature: Pale yellow semisolid.

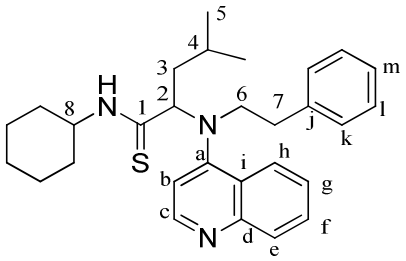
HRMS: Calcd. for $C_{25}H_{37}N_3S$: 411.2708, Found : 411.2710.

I.R. (thin film): 3287, 3183, 2930, 2860, 1572, 1508, 1426, 1301, 1263, 1096 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.74 (d, 1H, *J* = 5.0 Hz, H-c), 8.53 (br d, 1H, *J* = 7.3 Hz, NH), 8.09 (d, 1H, *J* = 8.3 Hz, H-e), 7.80 (d, 1H, *J* = 8.3 Hz, H-h), 7.68 (t, 1H, *J* = 8.3 Hz, H-f), 7.48 (t, 1H, *J* = 8.3 Hz, H-g), 7.01 (d, 1H, *J* = 5.0 Hz, H-b), 4.51-4.36 (m, 2H, H-2, H-10), 3.49-3.38 (m, 1H, H-6), 3.04-2.93 (m, 1H, H-6), 2.38 (ddd, 1H, *J* = 6.2, 7.8, 14.0 Hz, H-3), 2.07-1.95 (m, 2H, H-7), 1.82-1.58 (m, 5H, H-3, H-4, H-cy), 1.49-1.25 (m, 5H, H-8, H-cy), 1.21-1.06 (m, 2H, H-cy), 0.97-0.84 (m, 5H, H-cy, H-9), 0.77 (d, 3H, *J* = 6.5 Hz, H-5), 0.52 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 199.8 (C-1), 153.6 (C-a), 150.1 (C-c), 149.9 (C-d), 130.6 (C-e), 129.3 (C-f), 126.0 (C-g), 124.4 (C-i), 122.2 (C-h), 112.3 (C-b), 72.5 (C-2), 53.6 (C-10), 46.6 (C-6), 41.3 (C-3), 31.7 (C-cy), 31.1 (C-cy), 29.1 (C-7), 25.5 (C-cy), 24.5 (C-cy), 24.4 (C-cy), 22.8 (C-5), 21.8 (C-5), 20.5 (C-8), 13.9 (C-9).

***N*-cyclohexyl-4-methyl-2-(phenethyl(quinolin-4-yl)amino)pentanethioamide (II-55)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 98 % yield (450 mg).

Mol. Wt.: 459.69, Nature : Pale yellow solid.

HRMS: Calcd. for $C_{29}H_{37}N_3S$: 459.2708, Found : 459.2683.

M.P. = 81- 82 ^oC

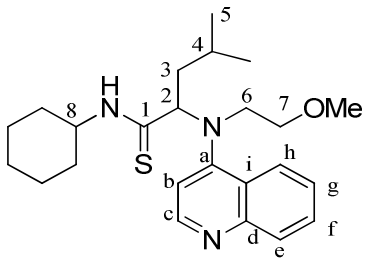
I.R. (thin film): 3284, 3180, 2930, 2857, 1575, 1502, 1454, 1304, 1103 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.83 (d, 1H, *J* = 5.0 Hz, H-c), 8.23 (br d, 1H, *J* = 6.5 Hz, NH), 8.14 (d, 1H, *J* = 8.3 Hz, H-e), 7.80 (d, 1H, *J* = 8.3 Hz, H-h), 7.72 (t, 1H, *J* = 8.3 Hz, H-f), 7.51 (t, 1H, *J* = 8.3 Hz, H-g), 7.31-7.22 (m, 3H, H-l, H-m), 7.17 (d, 1H, *J* = 5.0 Hz, H-

b), 7.04 (d, 2H, *J* = 7.4 Hz, H-k), 4.46-4.34 (m, 2H, H-2, H-8), 3.75-3.65 (m, 1H, H-6), 3.34-3.22 (m, 1H, H-6), 2.87 (ddd, 1H, *J* = 5.2, 9.0, 14.0 Hz, H-3), 2.82-2.72 (m, 1H, H-3), 2.38-2.28 (m, 1H, H-7), 2.00-1.84 (m, 2H, H-cy), 1.73-1.57 (m, 5H, H-7, H-4, H-cy), 1.44-1.30 (m, 2H, H-cy), 1.17-1.05 (m, 1H, H-cy), 0.99- 0.85 (m, 2H, H-cy), 0.72 (d, 3H, *J* = 6.3 Hz, H-5), 0.56 (d, 3H, *J* = 6.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 199.5 (C-1), 153.3 (C-a), 150.2 (C-c), 150.1 (C-d), 138.6 (C-j), 130.6 (C-e), 129.4 (C-f), 128.9 (C-l), 128.7 (C-k), 126.7 (C-g), 126.2 (C-m), 124.5 (C-i), 122.3 (C-h), 112.9 (C-b), 72.3 (C-2), 53.6 (C-8), 48.3 (C-6), 41.1 (C-7), 33.0 (C-3), 31.3 (C-cy), 30.8 (C-cy), 25.6 (C-4), 25.2 (C-cy), 24.6 (C-cy), 24.5 (C-cy), 22.6 (C-5), 22.0 (C-5).

_N_-cyclohexyl-2-((2-methoxyethyl)(quinolin-4-yl)amino)-4-methyl-pentanethioamide (II-56)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 82 % yield (340 mg).

Mol. Wt.: 413.62, Nature : Pale yellow solid.

HRMS: Calcd. for $C_{24}H_{35}N_3OS$: 413.2501, Found : 413.2503.

M.P. = 154 - 155 ^{o}C

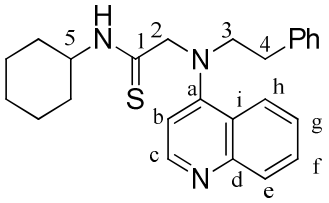
I.R. (thin film): 3246, 2930, 2857, 1572, 1502, 1388, 1346, 1308, 1103, 1054 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.13 (d, 1H, *J* = 7.3 Hz, NH), 8.70 (d, 1H, *J* = 5.1 Hz, H-c), 8.06 (d, 1H, *J* = 8.6 Hz, H-e), 7.66 (m, 2H, H-h, H-f), 7.44 (t, 1H, *J* = 7.4 Hz, H-g), 6.90 (d, 1H, *J* = 5.1 Hz, H-b), 4.69-4.54 (m, 2H, H-2 H-8), 3.82-3.68 (m, 2H, H-7), 3.57-3.50 (m, 1H, H-6), 3.33-3.25 (m, 1H, H-6), 3.24 (s, 3H, OMe), 2.56 (ddt, 1H, *J* = 3.7, 11.0, 14.6 Hz, H-3), 2.25-2.08 (m, 2H, H-4, H-3), 1.91-1.68 (m, 4H, H-cy), 1.60-1.38 (m, 3H, H-cy), 1.36-1.23 (m, 2H, H-cy), 1.22-1.10 (m, 1H, H-cy), 0.78 (d, 3H, *J* = 6.5 Hz, H-5), 0.30 (d, 3H, *J* = 6.5 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 200.2 (C-1), 153.6 (C-a), 150.2 (C-d), 149.7 (C-c), 130.4 (C-e), 129.3 (C-f), 125.8 (C-g), 124.1 (C-i), 122.7 (C-h), 110.1 (C-b), 73.0 (C-2), 67.9

(C-7), 58.8 (OMe), 54.7 (C-8), 45.5 (C-6), 42.7 (C-cy), 31.1 (C-cy), 25.6 (C-cy), 25.5 (C-4), 25.0 (C-cy), 23.4 (C-5), 20.4 (C-5).

_N_-cyclohexyl-2-(phenethyl(quinolin-4-yl)amino)ethanethioamide (II-57)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 44 % yield (180 mg).

Mol. Wt.: 403.58, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{25}H_{29}N_3S$: 403.2082, Found : 403.2089.

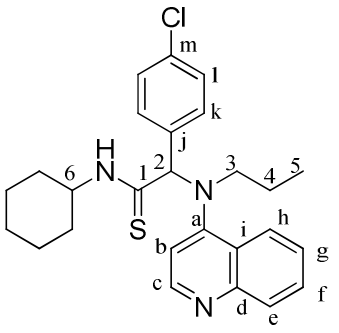
M.P. = 122-124 ^oC

I.R. (thin film): 2929, 2860, 1571, 1498, 1390, 1347, 1304, 1101, 1048 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.77 (d, 1H, *J* = 5.0 Hz, H-c), 8.33(br d, 1H, *J* = 8.0 Hz, NH), 8.10 (d, 1H, *J* = 8.6 Hz, H-e), 7.73-7.65 (m, 2H, H-h, H-f), 7.45 (t, 1H, *J* = 7.8 Hz, H-g),7.28-7.17 (m, 3H, H-Ar), 7.10 (d, 1H, *J* = 5.0 Hz, H-b), 7.00-6.90 (m, 2H, H-Ar), 4.35-4.28 (m, 3H, H-5, H-2), 3.45 (t, 2H, *J* = 7.1 Hz, H-3), 2.86 (t, 2H, *J* = 7.1 Hz, H-4), 1.80-1.70 (m, 2H, H-cy), 1.55-1.45 (m, 2H, H-cy), 1.31-1.20 (m, 3H, H-cy), 1.05-0.98 (m, 1H, H-cy), 0.85-0.75 (m, 2H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 195.3 (C-1), 153.1 (C-a), 150.5 (C-c), 150.9 (C-d), 138.5 (C-j), 130.6 (C-e), 129.5 (C-f), 129.0 (C-l), 128.8 (C-k), 126.9 (C-g), 126.4 (C-m), 124.0 (C-i), 121.8 (C-h), 111.5 (C-b), 65.7 (C-2), 55.3 (C-3), 53.0 (C-5), 33.1 (C-4), 30.7 (C-cy), 25.1 (C-cy), 24.2 (C-cy).

2-(4-chlorophenyl)-_N_-cyclohexyl-2-(propyl(quinolin-4-yl)amino)ethanethioamide (II-58)



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 71 % yield (320 mg).

Mol. Wt.: 452.05, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{26}H_{30}ClN_3S$: 451.1849, Found : 451.1834.

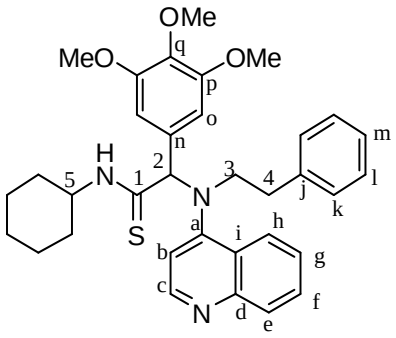
M.P. = 153-154 ^{o}C

I.R. (thin film): 3329, 2930, 2857, 1568, 1502, 1409, 1266, 1092, 1013 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.77 (d, 1H, *J* = 4.9 Hz, H-c), 8.47 (br d, 1H, *J* = 8.3 Hz, NH), 8.23 (d, 1H, *J* = 8.3 Hz, H-e), 8.14 (d, 1H, *J* = 8.3 Hz, H-h), 7.75 (t, 1H, *J* = 8.3 Hz, H-f), 7.64 (t, 1H, *J* = 8.3 Hz, H-g), 7.38 (d, 2H, *J* = 8.5 Hz, H-l), 7.32 (d, 2H, *J* = 8.5 Hz, H-k), 7.10 (d, 1H, *J* = 4.9 Hz, H-b), 5.63 (s, 1H, H-2), 4.19-4.08 (m, 1H, H-6), 3.10-3.00 (m, 1H, H-3), 2.97-2.88 (m, 1H, H-3), 1.88-1.78 (m, 1H, H-cy), 1.60-0.95 (m, 9H, H-4, H-cy), 0.87-0.80 (m, 1H, H-cy), 0.60 (t, 3H, *J* = 7.3 Hz, H-5), 0.55-0.40 (m, 1H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 197.4 (C-1), 152.6 (C-a), 150.4 (C-c), 149.7 (C-d), 134.9 (C-m), 134.4 (C-j), 130.6 (C-e), 129.7 (C-k), 129.5 (C-f), 128.8 (C-l), 126.8 (C-g), 125.1 (C-i), 122.0 (C-h), 114.8 (C-b), 76.5 (C-2), 53.5 (C-3), 52.8 (C-6), 31.1 (C-cy), 30.1 (C-cy), 25.1 (C-4), 24.1 (C-cy), 23.8 (C-cy), 17.8 (C-cy), 11.2 (C-5).

***N*-cyclohexyl-2-(phenethyl(quinolin-4-yl)amino)-2-(3,4,5-trimethoxyphenyl)-ethanethioamide (II-59)**



This compound was synthesized according to the general procedure II-D, using 1.0 mmol of isocyanide. The desired product was isolated in 64 % yield (365.7 mg).

Mol. Wt.: 569.76, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{34}H_{39}N_3O_3S$: 569.2712, Found : 569.2724.

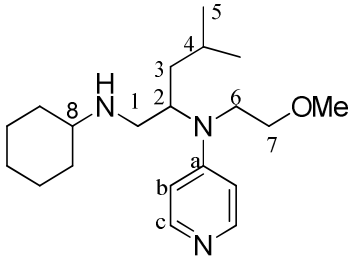
M.P. = 113-114 ^{o}C

I.R. (thin film): 3305, 2930, 2853, 1586, 1502, 1454, 1419, 1325, 1242, 1124, 1006 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.84 (d, 1H, *J* = 5.0 Hz, H-c), 8.31 (br d, 1H, *J* = 8.5 Hz, NH), 8.18 (d, 1H, *J* = 8.3 Hz, H-e), 8.13 (d, 1H, *J* = 8.3 Hz, H-h), 7.78 (t, 1H, *J* = 8.3 Hz, H-f), 7.63 (t, 1H, *J* = 8.3 Hz, H-g), 7.19 (d, 1H, *J* = 5.0 Hz, H-b), 7.16-7.10 (m, 3H, H-k, H-m), 6.79-6.72 (m, 2H, H-l), 6.63 (s, 2H, H-o), 5.68 (s, 1H, H-2), 4.26-4.14 (m, 1H, H-5), 3.86 (s, 3H, OMe), 3.81 (s, 6H, OMe), 3.39-3.21 (m, 2H, H-3), 2.80-2.71 (m, 1H, H-4), 2.62-2.51 (m, 1H, H-4), 1.85-1.76 (m, 1H, H-cy), 1.60-1.42 (m, 2H, H-cy), 1.38-1.20 (m, 3H, H-cy), 1.60-1.08 (m, 1H, H-cy), 1.02-0.88 (m, 2H, H-cy), 0.42-0.29 (m, 1H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 197.3 (C-1), 153.2 (C-a), 152.5 (C-p), 150.4 (C-c), 149.9 (C-d), 138.3 (C-j, C-q), 131.6 (C-n), 130.8 (C-e), 129.6 (C-f), 128.7 (C-l), 128.6 (C-k), 126.9 (C-g), 126.5 (C-m), 125.0 (C-i), 121.9 (C-h), 114.9 (C-b), 105.8 (C-o), 77.0 (C-2), 60.9 (OMe), 56.2 (OMe), 53.3 (C-3), 52.8 (C-5), 31.3 (C-4), 31.0 (C-cy), 30.0 (C-cy), 25.0 (C-cy), 24.2 (C-cy), 23.9 (C-cy).

_N_1-cyclohexyl-_N_2-(2-methoxyethyl)-4-methyl-_N_2-(pyridin-4-yl)pentane-1,2-diamine (II-60)



This compound was synthesized according to the general procedure II-E, using 1 mmol of amide **II-2**. The desired product was isolated in 60 % yield (200 mg).

Mol. Wt.: 333.51, Nature: Pale yellow liquid.

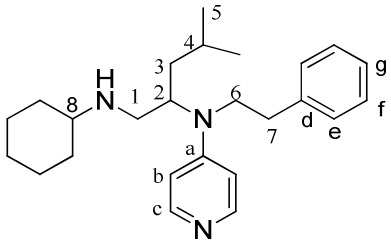
HRMS: Calcd. for $C_{20}H_{35}N_3O$: 333.278, Found : 333.2779.

I.R. (thin film): 2925, 2852, 1592, 1558, 1508, 1488, 1449, 1350, 1231, 1116 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.17 (d, 2H, *J* = 6.5 Hz, H-c), 6.63 (d, 2H, *J* = 6.5 Hz, H-b), 4.12-4.03 (m, 1H, H-8), 3.50-3.32 (m, 4H, H-7, H-1), 3.30 (s, 3H, OMe), 2.75-2.68 (m, 2H, H-6), 2.30 (tt, 1H, *J* = 3.6, 10.5 Hz, H-2), 1.82-1.62 (m, 4H, H-cy, NH), 1.60-1.52 (m, 1H, H-cy), 1.50-1.35 (m, 2H, H-3, H-4), 1.28-1.03 (m, 7H, H-3, H-cy), 0.85 (d, 3H, *J* = 6.4, Hz, H-5), 0.79 (d, 3H, *J* = 6.4, Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.3 (C-a), 150.0 (C-c), 107.8 (C-b), 69.1 (C-7), 58.9 (OMe), 57.0 (C-2), 56.0 (C-8), 49.4 (C-6), 42.0 (C-1), 40.6 (C-3), 33.6 (C-cy), 32.2 (C-cy), 26.0 (C-cy), 25.0 (C-cy), 24.9 (C-cy), 24.7 (C-4), 23.1 (C-5),22.4 (C-5).

_N_1-cyclohexyl-4-methyl-_N_2-phenethyl-_N_2-(pyridin-4-yl)pentane-1,2-diamine (II-61)



This compound was synthesized according to the general procedure II-E, using 1.1 mmol of amide **II-41**. The desired product was isolated in 73 % yield (304 mg).

Mol. Wt.: 379.58, Nature: Pale yellow liquid.

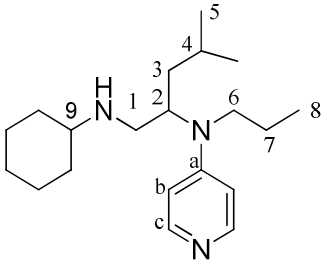
HRMS: Calcd. for $C_{25}H_{37}N_3$: 379.2987, Found : 379.2984.

I.R. (thin film): 2930, 2857, 1593, 1509, 1450, 1356, 1266, 1155 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.22 (d, 2H, *J* = 6.4 Hz, H-c), 7.34 (t, 2H, *J* = 7.3 Hz, H-f), 7.25-7.19 (m, 3H, H-e, H-g), 6.69 (d, 2H, *J* = 6.4 Hz, H-b), 4.15-4.05 (m, 1H, H-8), 3.43-3.28 (m, 2H, H-6), 2.92-2.83 (m, 1H, H-2), 2.75-2.65 (m, 3H, H-1, H-7), 2.32-2.22 (m, 1H, H-1), 1.81-1.62 (m, 4H, H-cy, NH, H-4), 1.60-1.40 (m, 3H, H-cy, H-3), 1.32-1.05 (m, 5H, H-3, H-cy), 1.03-0.90 (m, 2H, H-cy), 0.86 (d, 3H, *J* = 6.4, Hz, H-5), 0.81 (d, 3H, *J* = 6.4, Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.0 (C-a), 150.2 (C-c), 138.8 (C-d), 128.8 (C-f), 128.5 (C-e), 126.7 (C-g), 107.8 (C-b), 57.2 (C-2), 56.1 (C-8), 49.6 (C-6), 44.5 (C-1), 40.7 (C-3), 33.8 (C-cy), 33.7 (C-7), 33.4 (C-cy), 26.0 (C-cy), 24.9 (C-4), 24.8 (C-cy), 23.2 (C-5), 22.5 (C-8).

_N_1-cyclohexyl-4-methyl-_N_2-propyl-_N_2-(pyridin-4-yl)pentane-1,2-diamine (II-62)



This compound was synthesized according to the general procedure II-E, using 0.95 mmol of amide **II-42**. The desired product was isolated in 76 % yield (230 mg).

Mol. Wt.: 317.51, Nature: Pale yellow liquid.

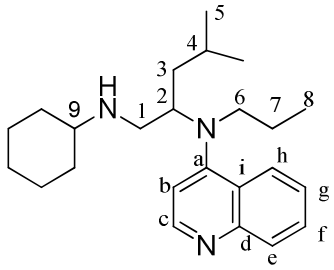
HRMS: Calcd. for $C_{20}H_{35}N_3$: 317.2831, Found : 317.2823

I.R. (thin film): 3277, 2926, 2853, 1596, 1513, 1356, 1235, 1134 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.17 (dd, 2H, *J* = 1.5, 5.2 Hz, H-c), 6.57 (dd, 2H, *J* = 1.5, 5.2 Hz, H-b), 4.15-4.05 (m, 1H, H-9), 3.14-3.00 (m, 2H, H-6), 2.78-2.64 (m, 2H, H-1), 2.37-2.27 (m, 1H, H-2), 1.82-1.38 (m, 10H, H-cy, NH, H-3, H-7, H-4), 1.32-1.07 (m, 4H, H-cy), 1.05-0.96 (m, 2H, H-cy), 0.94 (t, 3H, *J* = 7.4, Hz, H-8), 0.89 (d, 3H, *J* = 6.4, Hz, H-5), 0.84 (d, 3H, *J* = 6.4, Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.1 (C-a), 150.0 (C-c), 107.4 (C-b), 57.1 (C-2), 55.5 (C-9), 49.6 (C-6), 44.5 (C-1), 40.7 (C-3), 33.7 (C-cy), 33.4 (C-cy), 26.0 (C-cy), 25.0 (C-cy), 24.9 (C-cy), 24.8 (C-4), 23.2 (C-5), 22.6 (C-5), 20.7 (C-7), 11.4 (C-8).

***N*1-cyclohexyl-4-methyl-*N*2-propyl-*N*2-(quinolin-4-yl)pentane-1,2-diamine (II-63)**



This compound was synthesized according to the general procedure II-F, using 1.0 mmol of amide **II-47**. The desired product was isolated in 55 % yield (200 mg).

Mol. Wt.: 367.57, Nature: Pale brown liquid.

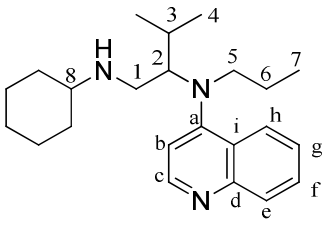
HRMS: Calcd. for $C_{24}H_{37}N_3$: 367.2987, Found : 367.2987.

I.R. (thin film): 2930, 2857, 1572, 1506, 1461, 1388, 1277, 1120, 1051 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.64 (d, 1H, *J* = 5.1 Hz, H-c), 8.42 (d, 1H, *J* = 8.3 Hz, H-e), 8.00 (d, 1H, *J* = 8.3 Hz, H-h), 7.61 (t, 1H, *J* = 8.3 Hz, H-f), 7.43 (t, 1H, *J* = 8.3 Hz, H-g), 6.86 (d, 1H, *J* = 5.1 Hz, H-b), 4.03-3.95 (m, 1H, H-9), 3.30-3.08 (m, 2H, H-6), 2.93 (dd, 1H, *J* = 10.0, 12.1 Hz, H-1), 2.79 (dd, 1H, *J* = 4.0, 12.1 Hz, H-1), 2.36-2.27 (m, 1H, H-2), 1.88-1.66 (m, 4H, H-3, H-4, NH, H-cy), 1.60-1.34 (m, 7H, H-7, H-3, H-cy), 1.24-1.12 (m, 3H, H-cy), 1.10-0.98 (m, 2H, H-cy), 0.89 (t, 3H, *J* = 7.3 Hz, H-8), 0.67 (d, 3H, *J* = 6.0 Hz, H-5), 0.64 (d, 3H, *J* = 6.0 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.3 (C-a), 150.2 (C-d), 149.8 (C-c), 129.8 (C-e), 128.7 (C-f), 124.7 (C-h), 124.6 (C-i), 124.9 (C-g), 110.7 (C-b), 61.4 (C-9), 56.9 (C-2), 49.0 (C-6), 43.8 (C-1), 40.4 (C-3), 33.5 (C-cy), 26.1 (C-cy), 25.2 (C-5), 24.9 (C-cy), 23.1 (C-4), 22.2 (C-5), 20.2 (C-7), 11.9 (C-8).

_N_1-cyclohexyl-3-methyl-_N_2-propyl-_N_2-(quinolin-4-yl)butane-1,2-diamine (II-64)



This compound was synthesized according to the general procedure II-F, using 0.47 mmol of amide **II-48**. The desired product was isolated in 42 % yield (70 mg).

Mol. Wt.: 353.54, Nature: Pale yellow liquid

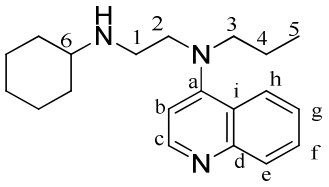
HRMS: Calcd. for $C_{23}H_{35}N_3$: 353.2831, Found : 353.2837.

I.R. (thin film): 2926, 2857, 1506, 1395, 1304, 1110, 1051 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.74 (d, 1H, *J* = 8.3 Hz, H-e), 8.61 (d, 1H, *J* = 5.2 Hz, H-c), 8.00 (d, 1H, *J* = 8.3 Hz, H-h), 7.60 (t, 1H, *J* = 8.3 Hz, H-f), 7.40 (t, 1H, *J* = 8.3 Hz, H-g), 6.84 (d, 1H, *J* = 5.2 Hz, H-b), 3.89-3.81 (m, 1H, H-8), 3.38-3.18 (m, 2H, H-5), 3.00-2.89 (m, 2H, H-1), 2.38-2.30 (m, 1H, H-2), 2.01-1.91 (m, 1H, H-3), 1.83 (br d, 1H, *J* = 12.1 Hz, NH), 1.80-1.65 (m, 4H, H-cy), 1.60-1.46 (m, 3H, H-cy), 1.26-1.16 (m, 3H, H-cy, H-6), 1.11-1.02 (m, 2H, H-cy), 0.93 (t, 3H, *J* = 7.4 Hz, H-7), 0.88 (d, 3H, *J* = 6.7 Hz, H-4), 0.77 (d, 3H, *J* = 6.7 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.8 (C-a), 150.4 (C-d), 149.7 (C-c), 129.8 (C-e), 128.5 (C-f), 125.4 (C-g), 124.1 (C-h), 123.9 (C-i), 109.0 (C-b), 69.5 (C-2), 56.8 (C-8), 47.2 (C-5), 44.7 (C-1), 33.6 (C-cy), 33.5 (C-cy), 30.3 (C-3), 26.2 (C-cy), 26.2 (C-cy), 24.9 (C-cy), 24.8 (C-cy), 21.5 (C-6), 20.6 (C-4), 20.3 (C-4), 11.9 (C-7).

_N_1-cyclohexyl-_N_2-propyl-_N_2-(quinolin-4-yl)ethane-1,2-diamine (II-65)



This compound was synthesized according to the general procedure II-F, using 0.53 mmol of amide **II-49**. The desired product was isolated in 67 % yield (110 mg).

Mol. Wt.: 311.46, Nature: Pale yellow liquid.

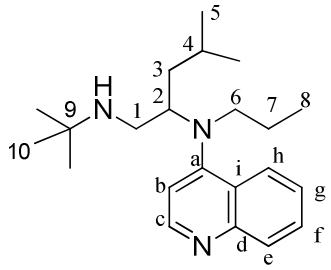
HRMS: Calcd. for $C_{20}H_{29}N_3$: 311.2361, Found : 311.2374.

I.R. (thin film): 2923, 2847, 1569, 1506, 1458, 1448, 1422, 1397, 1382, 1302, 1258, 1098, 1047, 1022 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.68 (d, 1H, *J* = 5.0 Hz, H-c), 8.09 (d, 1H, *J* = 8.3 Hz, H-e), 8.03 (d, 1H, *J* = 8.3 Hz, H-h), 7.64 (t, 1H, *J* = 8.3 Hz, H-f), 7.46 (t, 1H, *J* = 8.3 Hz, H-g), 6.90 (d, 1H, *J* = 5.0 Hz, H-b), 3.47 (t, 2H, *J* = 6.5 Hz, H-2), 3.29 (t, 2H, *J* = 7.6 Hz, H-3), 2.82 (t, 2H, *J* = 6.5 Hz, H-1), 2.32-2.23 (m, 1H, H-6), 1.80-1.70 (m, 2H, H-cy), 1.69-1.52 (m, 5H, H-4, H-cy), 1.25 (br s, 1H, NH), 1.18-1.08 (m, 3H, H-cy), 1.02-0.92 (m, 2H, H-cy), 0.84 (t, 3H, *J* = 7.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.6 (C-a), 150.2 (C-c), 150.0 (C-d), 129.9 (C-e), 128.9 (C-f), 125.0 (C-g), 124.7 (C-i), 123.9 (C-h), 110.7 (C-b), 56.7 (C-6), 55.8 (C-3), 52.0 (C-2), 43.8 (C-1), 33.5 (C-cy), 26.0 (C-cy), 24.9 (C-cy), 20.0 (C-cy), 11.5 (C-5).

***N*1-(tert-butyl)-4-methyl-*N*2-propyl-*N*2-(quinolin-4-yl)pentane-1,2-diamine (II-66)**



This compound was synthesized according to the general procedure II-F, using 0.7 mmol of amide **II-50**. The desired product was isolated in 39 % yield (90 mg).

Mol. Wt.: 341.53, Nature: Pale brown liquid

Exact Mass: 341.2831,

HRMS: Calcd. for $C_{22}H_{35}N_3$: 341.2831, Found : 341.2826.

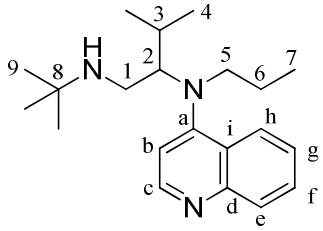
I.R. (thin film): 2961, 2874, 1568, 1506, 1461, 1384, 1231, 1110, 1023 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.65 (d, 1H, *J* = 5.1 Hz, H-c), 8.55 (d, 1H, *J* = 8.3 Hz, H-e), 8.01 (d, 1H, *J* = 8.3 Hz, H-h), 7.61 (t, 1H, *J* = 8.3 Hz, H-f), 7.43 (t, 1H, *J* = 8.3 Hz, H-g), 6.87 (d, 1H, *J* = 5.1 Hz, H-b), 3.96 (tt, 1H, *J* = 5.0, 9.6 Hz, H-2), 3.30-3.20 (m, 1H, H-6), 3.18-3.06 (m, 1H, H-6), 2.92 (dd, 1H, *J* = 9.6, 11.7 Hz, H-1), 2.70 (dd, 1H, *J* = 5.0, 11.7 Hz,

H-1), 1.19-1.17 (m, 1H, NH), 1.62-1.31 (m, 5H, H-3, H-7, H-4), 1.11 (s, 9H, H-9), 0.90 (t, 3H, *J* = 7.4 Hz, H-8), 0.67 (d, 3H, *J* = 6.1 Hz, H-5), 0.64 (d, 3H, *J* = 6.1 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.4 (C-a), 150.1 (C-d), 149.7 (C-c), 129.7 (C-e), 128.8 (C-f), 124.9 (C-g), 124.8 (C-i), 124.6 (C-h), 110.9 (C-b), 62.1 (C-2), 50.1 (C-9), 44.7 (C-6), 43.9 (C-1), 40.6 (C-3), 29.0 (C-10), 25.3 (C-4), 23.1 (C-5), 22.3 (C-5), 20.3 (C-7), 12.0 (C-8).

_N_1-(tert-butyl)-3-methyl-_N_2-propyl-_N_2-(quinolin-4-yl)butane-1,2-diamine (II-67)



This compound was synthesized according to the general procedure II-F, using 0.45 mmol of amide **II-51**. The desired product was isolated in 41 % yield (60 mg).

Mol. Wt.: 327.51, Nature: Pale yellow liquid.

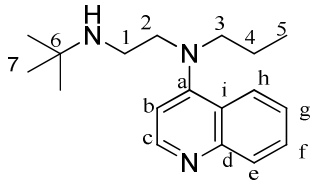
HRMS: Calcd. for $C_{21}H_{33}N_3$: 327.2674, Found : 327.2679.

I.R. (thin film): 2960, 2933, 2869, 1564, 1506, 1461, 1429, 1384, 1357, 1227, 1110, 1056 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.89 (d, 1H, *J* = 8.3 Hz, H-e), 8.60 (d, 1H, *J* = 5.0 Hz, H-c), 8.00 (d, 1H, *J* = 8.3 Hz, H-h), 7.61 (t, 1H, *J* = 8.3 Hz, H-f), 7.40 (t, 1H, *J* = 8.3 Hz, H-g), 6.84 (d, 1H, *J* = 5.0 Hz, H-b), 3.88-3.78 (m, 1H, H-2), 3.40-3.29 (m, 1H, H-1), 3.28-3.12 (m, 1H, H-1), 2.92-2.85 (m, 2H, H-5), 2.03-1.92 (m, 1H, H-3), 1.78-1.62 (m, 1H, H-6), 1.54-1.42 (m, 1H, H-6), 1.25 (br s, 1H, NH), 1.12 (s, 9H, H-9), 0.93 (t, 3H, *J* = 6.6 Hz, H-7), 0.88 (d, 3H, *J* = 6.8 Hz, H-4), 0.73 (d, 3H, *J* = 6.8 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.0 (C-a), 150.2 (C-d), 149.5 (C-c), 129.5 (C-e), 128.7 (C-f), 125.8 (C-g), 124.0 (C-h, C-i), 109.9 (C-b), 70.1 (C-2), 50.1 (C-8), 44.7 (C-5), 42.7 (C-1), 31.9 (C-3), 29.0 (C-9), 21.5 (C-6), 20.6 (C-4), 20.4 (C-4), 11.9 (C-7).

***N*1-(tert-butyl)-*N*2-propyl-*N*2-(quinolin-4-yl)ethane-1,2-diamine (II-68)**



This compound was synthesized according to the general procedure II-F, using 0.42 mmol of amide **II-52**. The desired product was isolated in 67 % yield (92 mg).

Mol. Wt.: 285.43, Nature: Pale brown liquid.

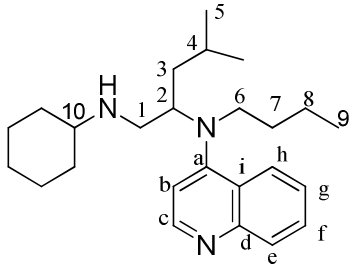
HRMS: Calcd. for $C_{18}H_{27}N_3$: 285.2205, Found : 285.2205.

I.R. (thin film): 2960, 2928, 2869, 1573, 1503, 1460, 1424, 1380, 1298, 1229, 1094, 1051, 1018 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.68 (d, 1H, *J* = 5.0 Hz, H-c), 8.10 (d, 1H, *J* = 8.3 Hz, H-e), 8.03 (d, 1H, *J* = 8.3 Hz, H-h), 7.64 (t, 1H, *J* = 8.3 Hz, H-f), 7.46 (t, 1H, *J* = 8.3 Hz, H-g), 6.91 (d, 1H, *J* = 5.0 Hz, H-b), 3.46 (t, 2H, *J* = 6.5 Hz, H-2), 3.29 (t, 2H, *J* = 7.6 Hz, H-3), 2.75 (t, 2H, *J* = 6.5 Hz, H-1), 1.66-1.55 (m, 2H, H-4), 1.24 (br s, 1H, NH), 0.97 (s, 9H, H-7), 0.84 (t, 3H, *J* = 7.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.5 (C-a), 150.2 (C-c), 150.0 (C-d), 129.9 (C-e), 128.9 (C-f), 125.0 (C-g), 124.7 (C-i), 123.9 (C-h), 110.7 (C-b), 56.0 (C-3), 52.2 (C-2), 50.1 (C-6), 39.6 (C-1), 28.9 (C-7), 20.0 (C-4), 11.5 (C-5).

***N*2-butyl-*N*1-cyclohexyl-4-methyl-*N*2-(quinolin-4-yl)pentane-1,2-diamine (II-69)**



This compound was synthesized according to the general procedure II-F, using 0.81 mmol of amide **II-54**. The desired product was isolated in 75 % yield (295 mg).

Mol. Wt.: 381.60, Nature: Pale yellow liquid.

HRMS: Calcd. for $C_{25}H_{39}N_3$: 381.3144, Found : 381.3172.

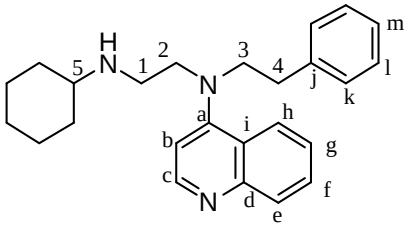
I.R. (thin film): 3308, 2926, 2850, 1572, 1506, 1457, 1304, 1256, 1117 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.64 (d, 1H, *J* = 5.1 Hz, H-c), 8.41 (d, 1H, *J* = 8.3 Hz, H-e), 8.00 (d, 1H, *J* = 8.3 Hz, H-h), 7.61 (t, 1H, *J* = 8.3 Hz, H-f), 7.42 (t, 1H, *J* = 8.3 Hz, H-

g), 6.87 (d, 1H, *J* = 5.1 Hz, H-b), 4.04-3.94 (m, 1H, H-10), 3.30-3.13 (m, 2H, H-6), 2.92 (dd, 1H, *J* = 9.5, 12.3 Hz, H-1), 2.79 (dd, 1H, *J* = 4.7, 12.3 Hz, H-1), 2.36-2.27 (m, 1H, H-2), 1.86-1.66 (m, 4H, H-7, H-4, H-cy), 1.60-1.28 (m, 8H, H-3, H-cy, H-8), 1.22-1.12 (m, 4H, H-cy, NH), 1.09-1.00 (m, 2H, H-cy), 0.86 (t, 3H, *J* = 7.3 Hz, H-9), 0.67 (d, 3H, *J* = 6.1 Hz, H-5), 0.63 (d, 3H, *J* = 6.1 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.4 (C-a), 150.2 (C-d), 149.8 (C-c), 129.8 (C-e), 128.7 (C-f), 124.7 (C-g, C-i), 124.5 (C-h), 110.6 (C-b), 61.5 (C-10), 56.7 (C-2), 49.0 (C-1), 41.9 (C-6), 40.4 (C-3), 33.6 (C-cy), 33.5 (C-cy), 29.3 (C-7), 26.1 (C-cy), 25.2 (C-4), 24.9 (C-cy), 24.8 (C-cy), 23.1 (C-5), 22.2 (C-5), 20.7 (C-8), 14.0 (C-9).

*N*1-cyclohexyl-*N*2-phenethyl-*N*2-(quinolin-4-yl)ethane-1,2-diamine (II-70)



This compound was synthesized according to the general procedure II-F, using 0.4 mmol of amide **II-57**. The desired product was isolated in 21 % yield (80 mg).

Mol. Wt.: 373.53, Nature: Pale yellow liquid.

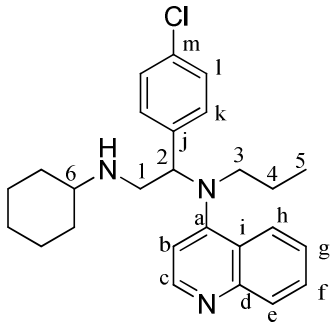
HRMS: Calcd. for $C_{25}H_{31}N_3$: 373.2518, Found : 373.2523

I.R. (thin film): 3310, 2928, 2851, 1568, 1505, 1461, 1307, 1253, 1110 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.72 (d, 1H, *J* = 5.0 Hz, H-c), 8.08-8.00 (m, 2H, H-e, H-h), 7.66 (t, 1H, *J* = 8.0 Hz, H-f), 7.45 (t, 1H, *J* = 8.0 Hz, H-g), 7.26-7.17 (m, 3H, H-k, H-m), 7.08 (d, 2H, *J* = 8.0 Hz, H-l), 6.96 (d, 1H, *J* = 5.0 Hz, H-b), 3.59 (t, 2H, *J* = 7.5 Hz, H-2), 3.52 (t, 2H, *J* = 5.9 Hz, H-3), 2.89-2.79 (m, 4H, H-1, H-4), 2.32-2.21 (m, 1H, H-5), 1.80-1.70 (m, 3H, H-cy, NH), 1.69-1.62 (m, 2H, H-cy), 1.60-1.53 (m, 1H, H-cy), 1.20-1.05 (m, 1H, H-cy), 1.10-0.91 (m, 2H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.1 (C-a), 150.2 (C-c), 150.0 (C-d), 139.1 (C-j), 129.9 (C-e), 129.1 (C-f), 128.7 (C-l), 128.4 (C-k), 126.3 (C-g), 125.2 (C-m), 124.7 (C-i), 123.9 (C-h), 111.1 (C-b), 56.7 (C-5), 55.5 (C-3), 52.2 (C-2), 43.8 (C-4, C-1), 33.4 (C-cy), 33.2 (C-cy), 26.0 (C-cy), 24.9 (C-cy).

1-(4-chlorophenyl)-*N*2-cyclohexyl-*N*1-propyl-*N*1-(quinolin-4-yl)ethane-1,2-diamine (II-71)



This compound was synthesized according to the general procedure II-F, using 0.78 mmol of amide **II-58**. The desired product was isolated in 37 % yield (120 mg).

Mol. Wt.: 422.01, Nature: Pale yellow liquid.

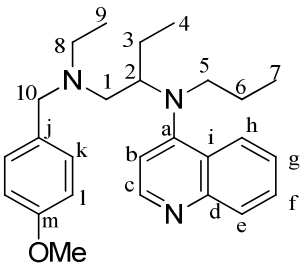
HRMS: Calcd. for $C_{26}H_{32}ClN_3$: 421.2285, Found : 285.2205.

I.R. (thin film): 2928, 2852, 1569, 1502, 1488, 1460, 1449, 1420, 1398, 1303, 1238, 1125, 1092, 1037, 1012 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.66 (d, 1H, *J* = 5.0 Hz, H-c), 8.42 (d, 1H, *J* = 8.3 Hz, H-e), 8.08 (d, 1H, *J* = 8.3 Hz, H-h), 7.68 (t, 1H, *J* = 8.3 Hz, H-f), 7.51 (t, 1H, *J* = 8.3 Hz, H-g), 7.25 (d, 2H, *J* = 8.4 Hz, H-l), 7.04 (d, 2H, *J* = 8.4 Hz, H-k), 6.69 (d, 1H, *J* = 5.0 Hz, H-b), 4.81 (t, 1H, *J* = 7.2 Hz, H-2), 3.40 (dd, 1H, *J* = 7.2, 12.0 Hz, H-1), 3.15 (dd, 1H, *J* = 7.2, 12.0 Hz, H-1), 3.11-3.04 (m, 1H, H-3), 2.94-2.86 (m, 1H, H-3), 2.45-2.36 (m, 1H, H-6), 1.86-1.76 (m, 2H, H-cy), 1.74-1.65 (m, 2H, NH, H-cy), 1.62-1.55 (m, 1H, H-cy), 1.50-1.37 (m, 2H, H-4), 1.27-1.14 (m, 4H, H-cy), 1.08-0.99 (m, 2H, H-cy), 0.82 (t, 3H, *J* = 7.3 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.5 (C-a), 150.2 (C-d), 150.0 (C-c), 136.5 (C-j), 133.3 (C-m), 130.0 (C-e), 129.2(C-l), 129.1 (C-k), 128.4 (C-f), 125.6 (C-g), 125.5 (C-i), 123.9 (C-h), 113.3 (C-b), 66.1 (C-2), 56.7 (C-6), 48.0 (C-3), 47.3 (C-1), 33.6 (C-cy), 33.4 (C-cy), 26.1 (C-cy), 24.9 (C-cy), 24.8 (C-cy), 19.6 (C-4), 11.9 (C-5).

***N*1-ethyl-*N*1-(4-methoxybenzyl)-*N*2-propyl-*N*2-(quinolin-4-yl)butane-1,2-diamine (II-72)**



This compound was synthesized according to the general procedure II-F, using 0.44 mmol of amide **II-53**. The desired product was isolated in 30 % yield (50 mg).

Mol. Wt.: 405.58, Nature: Pale yellow liquid.

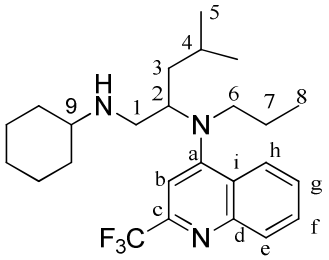
HRMS: Calcd. for $C_{26}H_{35}N_3O$: 405.2780, Found : 405.2771

IR : 2964, 2933, 2871, 1631, 1572, 1509, 1384, 1245, 1172, 1099, 1037 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.64 (d, 1H, *J* = 5.0 Hz, H-c), 8.27 (d, 1H, *J* = 8.3 Hz, H-e), 8.02 (d, 1H, *J* = 8.3 Hz, H-h), 7.60 (t, 1H, *J* = 8.3 Hz, H-f), 7.38 (t, 1H, *J* = 8.3 Hz, H-g), 7.02 (d, 2H, *J* = 8.5 Hz, H-k), 6.83 (d, 1H, *J* = 5.0 Hz, H-b), 6.77 (d, 2H, *J* = 8.5 Hz, H-l), 3.79-3.70 (m, 4H, H-2, OMe), 3.38 (d, 1H, *J* = 13.3 Hz, H-10), 3.29 (d, 1H, *J* = 13.3 Hz, H-10), 3.13-2.99 (m, 2H, H-5), 2.74 (dd, 1H, *J* = 6.8, 13.3 Hz, H-1), 2.39 (dd, 1H, *J* = 6.3, 13.3 Hz, H-1), 2.35-2.24 (m, 2H, H-8), 1.77-1.63 (m, 2H, H-3), 1.53-1.35 (m, 2H, H-6), 0.94-0.79 (m, 9H, H-4, H-7, H-9).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 158.4 (C-a), 155.7 (C-m), 150.2 (C-d), 149.8 (C-c), 131.1 (C-e), 130.0 (C-k), 129.8 (C-j), 128.5 (C-f), 124.7 (C-i), 124.5 (C-g), 124.1 (C-h), 113.3 (C-*l*), 110.7 (C-b), 63.9 (C-2), 57.8 (C-10), 55.5 (C-1), 55.1 (OMe), 47.5 (C-5), 44.3 (C-8), 25.0 (C-3), 20.0 (C-6), 12.0 (C-9), 11.8 (C-7), 11.4 (C-4).

_N_1-cyclohexyl-4-methyl-_N_2-propyl-_N_2-(2-(trifluoromethyl)quinolin-4-yl)pentane-1,2-diamine (II-73)



This compound was synthesized as 1 M solution of 2-(trifluoromethyl)quinolin-4-ol in methanol were added successively 1.0 equiv of amine, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was stirred at 65 °C for one day. The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles adduct (thioamide).

To the suspension of Raney nickel (10 equiv. by mass) in ethanol (25 ml), was added a solution of the thioamide compound (1.0 mmol, 1.0 equiv.). The mixture was heated at 55 ^oC under an argon atmosphere for 30 to 60 min. and filtered through a plug of celite 545®. The

celite was washed with a solution of 20 % ethanol in dichloromethane (3 x 15 mL) and the solution concentrated under reduced pressure to yield the crude product was purified by flash chromatography to give the desired product 46 % yield (200 mg).

Mol. Wt.: 435.57, Nature: Pale yellow liquid.

HRMS: Calcd. for $C_{25}H_{36}F_3N_3$: 435.2861, Found : 435.2856.

I.R. (thin film): 2930, 2857, 1579, 1509, 1471, 1339, 1277, 1183, 1134, 1086 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.49 (d, 1H, *J* = 8.3 Hz, H-e), 8.12 (d, 1H, *J* = 8.3 Hz, H-h), 7.70 (t, 1H, *J* = 8.3 Hz, H-f), 7.52 (t, 1H, *J* = 8.3 Hz, H-g), 7.15 (s, 1H, H-b), 4.12-4.03 (m, 1H, H-9), 3.34-3.20 (m, 2H, H-6), 2.95 (dd, 1H, *J* = 10.0, 12.5 Hz, H-1), 2.81 (dd, 1H, *J* = 4.0, 12.5 Hz, H-1), 2.31 (tt, 1H, *J* = 4.0, 10.0 Hz, H-2), 1.86-1.65 (m, 4H, H-4, NH, H-cy), 1.63-1.49 (m, 4H, H-3, H-7, H-cy), 1.47.1.40 (m, 2H, H-cy, H-3), 1.28-1.12 (m, 4H, H-cy), 1.08-0.95 (m, 2H, H-cy), 0.92 (t, 3H, *J* = 7.4 Hz, H-8), 0.73 (d, 3H, *J* = 6.0 Hz, H-5), 0.66 (d, 3H, *J* = 6.0 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 157.6 (C-a), 149 3 (C-d), 147.6 (d, J_{C-F} = 34.6 Hz, C-c), 130.6 (C-e), 129.9 (C-f), 126.1 (C-g), 124.8 (C-h, C-i), 124.6 (q, J_{C-F} = 266.5 Hz, CF_3), 105.6 (d, J_{C-F} = 1.9 Hz, C-b), 62.3 (C-9), 56.6 (C-2), 49.0 (C-1), 44.0 (C-6), 40.8 (C-3), 33.5 (C-cy), 26.1 (C-cy), 25.3 (C-4), 24.8 (C-cy), 24.7 (C-cy), 23.1 (C-5), 22.3 (C-5), 20.1 (C-7), 12.0 (C-8).

Experimental Part

Chapter 3

General Procedures:

General Procedure III-A: (Ugi-Smiles coupling procedure).

To a 1 M solution of hydroxy heteroaromatic compounds in methanol were added successively 1.0 equiv of amine, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was stirred at 65°C for 18-36 hrs. The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles product after purification by flash chromatography on silica gel.

General Procedure III-B: (Xanthate synthesis).

To the solution of 1.0 equiv ethylchloroacetate in acetone (0.1 M) was added 1. 2 equiv of potassium ethyl xanthogenate. The resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine (2x20 mL), dried over anhydrous MgSO4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes) to afford xantate.

General Procedure III-C: (DLP- cyclization reaction procedure).

DLP- cyclization reaction procedure: A solution of Ugi-Smiles adduct (1.0 mmol) and xanthate (1.2 mmol) in1,2-dichloroethane (1 M) was refluxed for 5min under argon before DLP was added (60mg, 0.15 mmol) from the top of the condenser. Portions of DLP (60mg, 0.15 mmol) were added every 20 min until complete disappearance of Ugi-Smile adduct and the starting xanthate, then the remaining DLP was added every 20 min until complete disappearance of the intermediate (TLC monitoring). And on concentration under reduced pressure afforded an oily pale brown residue, which was purified by flash chromatography eluting with petroleum ether/diethyl ether to give pure product.

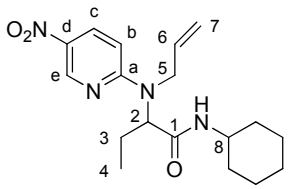
General Procedure III-D: (Ugi coupling procedure).

To a 1 M solution of 2-chlorotryptamine in methanol were added successively 1.0 equiv of aldehyde, 1.0 equiv of acid and 1.0 equiv of isocyanide. The resulting mixture was stirred at room tempatature for 18 hrs. The solvent was removed afterwards under reduced pressure to afford the Ugi product after purification by flash chromatography on silica gel.

General Procedure III-E: (Synthesis of spirooxiindoline).

To a solution of Ugi adduct (1.0 equiv) in anhydrous THF (0.2 M) was added copper acetate (1.0 equiv) at 0 °C and then DBU (1.0 equiv). The mixture was heated to reflux, until completion of the reaction checked with TLC analysis (24 h). Then, the reaction mixture was cooled at room temperature and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using a gradient of EtOAc in petroleum ether (60:40 - 80:20) as eluant to give spirooxuindoline.

2-(allyl(5-nitropyridin-2-yl)amino)-*N*-cyclohexylbutanamide (III.1)



This compound was synthesized according to the general procedure III-A, using 3.57 mmol of isocyanide. The desired product was isolated in 41 % yield (550 mg).

Chemical Formula: $C_{18}H_{26}N_4O_3$, Nature: yellow solid.

Exact Mass: 346.2005, Mol. Wt.: 346.42

HRMS: Calcd. for $C_{18}H_{26}N_4O_3$, : 346.2005, Found : 346.2016

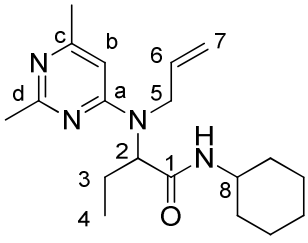
M.P. = 112-113 ^oC,

I.R. (thin film): 2924, 2850, 1657, 1588, 1570, 1496, 1413, 1325, 1286, 1251, 1111 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.04 (d, 1H, *J* = 2.2 Hz, H-e), 8.21 (dd, 1H, *J* = 2.2, 9.4 Hz, H-c), 6.52 (d, 1H, *J* = 9.4 Hz, H-b), 6.18 (br s, 1H, NH), 5.87-5.72 (m, 1H, H-6), 5.38-5.11 (m, 3H, H-7, H-2), 4.23 (dd, 1H, *J* = 4.8, 17.0 Hz, H-5), 4.03 (d, 1H, *J* = 17.0 Hz, H-5), 3.78-3.66 (m, 1H, H-8), 2.19-2.03 (m, 1H, H-3), 1.96-1.83 (m, 1H, H-cy), 180-1.49 (m, 6H, H-cy, H-3), 1.43-1.22 (m, 2H, H-cy), 1.21-1.06 (m, 2H, H-cy), 1.05-0.88 (m, 4H, H-cy, H4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.2 (C-1), 160.7 (C-a), 145.6 (C-e), 132.9 (C-6), 132.7 (C-c), 126.7 (C-d), 117.6 (C-7), 106.7 (C-b), 60.0 (C-2), 48.0 (C-8), 47.9 (C-5), 32.9 (C-cy), 32.8 (C-cy), 25.4 (C-cy), 24.5 (C-cy), 21.9 (C-2), 10.8 (C-4).

2-(allyl(2,6-dimethylpyrimidin-4-yl)amino)-*N*-cyclohexylbutanamide (III-2)



This compound was synthesized according to the general procedure III-A, using 8.06 mmol of isocyanide. The desired product was isolated in 38 % yield (1.0 gm).

Chemical Formula: $C_{19}H_{30}N_4O$, Nature: yellow solid.

Exact Mass: 330.2420, Mol. Wt.: 330.47

HRMS: Calcd. for $C_{19}H_{30}N_4O$: 330.2420, Found : 330.2425

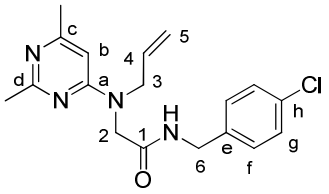
M.P. = 125 ^oC,

I.R. (thin film): 2929, 2855, 2356, 1657, 1583, 1539, 1479, 1448, 1403, 1343, 1273, 1177, 1089 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.69 (br s, 1H, NH), 6.11 (s, 1H, H-b), 5.86-5.69 (m, 1H, H-6), 5.27-5.01 (m, 3H, H-7, H-2), 4.08 (dd, 1H, *J* = 4.8, 17.0 Hz, H-5), 3.84 (d, 1H, *J* = 17.0 Hz, H-5), 3.75-3.63 (m, 1H, H-8), 2.51 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 2.13-2.00 (m, 1H, H-3), 1.92-1.81 (m, 1H, H-cy), 1.78-1.59 (m, 3H, H-3, H-cy), 1.58-1.46 (m, 2H, H-cy), 1.40-1.22 (m, 2H, H-cy), 1.20-1.06 (m, 2H, H-cy), 1.02-0.93 (m, 1H, H-cy), 0.90 (t, 3H, *J* = 7.3 Hz, H4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.1 (C-1), 166.1 (C-a), 165.3 (C-c), 162.6 (C-d), 133.5 (C-6), 116.9 (C-7), 100.3 (C-b), 58.8 (C-2), 47.6 (C-8), 47.3 (C-5), 32.9 (C-cy), 32.7 (C-cy), 26.1 (-CH_3), 25.5 (C-cy), 24.5 (C-cy), 24.4 (C-cy), 24.3 (-CH_3), 21.9 (C-3), 10.9(C-4).

2-(allyl(2,6-dimethylpyrimidin-4-yl)amino)-*N*-(4-chlorobenzyl)acetamide (III-3)



This compound was synthesized according to the general procedure III-A, using 1 mmol of isocyanide. The desired product was isolated in 29 % yield (100 mg).

Mol. Wt.: 344.84 Nature: white semisolid.

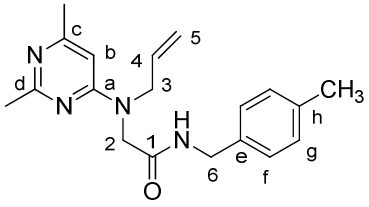
HRMS: Calcd. for $C_{18}H_{21}ClN_4O$: 344.1404, Found : 344.1408

I.R. (thin film): 2928, 1661, 1590, 1575, 1529, 1481, 1419, 1408, 1370, 1280, 1242, 1170, 1065, 1008 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.04 (d, 2H, *J* = 8.2 Hz, H-f), 7.08 (d, 2H, *J* = 8.2 Hz, H-g), 6.95 (br s, 1H, NH), 6.13(s, 1H, H-b), 5.85-5.73 (m, 1H, H-4), 5.26-5.03 (m, 2H, H-5), 4.39 (s, 2H, H-6), 4.17 (s, 2H, H-2), 4.16 (m, 2H, H-3), 2.40 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.8 (C-1), 166.8 (C-a), 164.9 (C-c), 162.0 (C-d), 136.5 (C-Ar), 131.2 (C-4), 128.7 (C-g, C-f), 128.7 (C-Ar), 126.7 (C-Ar), 117.8 (C-5), 99.0 (C-b), 52.2 (C-2), 51.4 (C-3), 42.4 (C-6), 26.0 (CH_3), 24.3 (-CH_3).

2-(allyl(2,6-dimethylpyrimidin-4-yl)amino)-*N*-(4-methylbenzyl)acetamide (III-4)



This compound was synthesized according to the general procedure III-A, using 1 mmol of isocyanide. The desired product was isolated in 18 % yield (58 mg).

Mol. Wt.: 324.42 Nature: white solid.

HRMS: Calcd. for $C_{19}H_{24}N_4O$: 324.1950, Found : 324.1970

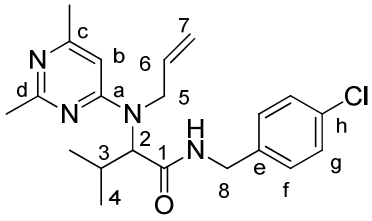
M.P. = 130 ^oC,

I.R. (thin film): 2930, 1658, 1585, 1576, 1531, 14431, 1420, 1407, 1345 1272, 1242, 1171, 1080, 1010 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.20-7.00 (m, 7H, H-Ar), 6.86 (br s, 1H, NH), 6.13(s, 1H, H-b), 5.85-5.70 (m, 1H, H-4), 5.25-5.10 (m, 2H, H-5), 4.40 (d, 2H, *J* = 4.8 Hz, H-6), 4.18 (s, 2H, H-2), 4.09 (m, 2H, H-3), 2.40 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.6 (C-1), 166.8 (C-a), 165.8 (C-c), 162.0 (C-d), 137.2 (C-Ar), 134.8 (C-Ar), 131.3 (C-4), 129.4 (C-Ar), 127.4 (C-Ar), 117.7 (C-5), 99.9 (C-b), 52.1 (C-2), 51.3 (C-3), 43.1 (C-6), 25.9 (CH_3), 24.2 (-CH_3), 21.0 (-CH_3).

2-(allyl(2,6-dimethylpyrimidin-4-yl)amino)-*N*-(4-chlorobenzyl)-3-methylbutanamide (III-5)



This compound was synthesized according to the general procedure III-A, using 8.0 mmol of isocyanide. The desired product was isolated in 68 % yield (2.1 gm).

Chemical Formula: $C_{21}H_{27}ClN_4O$, Nature: white solid.

Exact Mass: 386.1873, Mol. Wt.: 386.92

HRMS: Calcd. for $C_{21}H_{27}ClN_4O$: 386.1873, Found : 386.1868

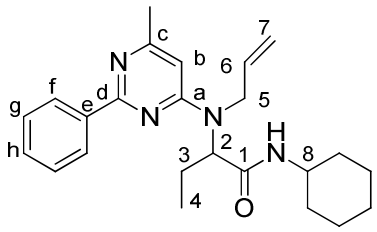
M.P. = 98 ^oC,

I.R. (thin film): 2968, 1671, 1583, 1535, 1474, 1403, 1339, 1268, 1203, 1085 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.23 (d, 2H, *J* = 8.2 Hz, H-g), 7.07 (d, 2H, *J* = 8.2 Hz, H-f), 6.13 (s, 1H, H-b), 5.70-5.55 (m, 1H, H-6), 5.13 (d, 2H, *J* = 13.3 Hz, H-7), 4.91 (br s, 1H, NH), 4.40-4.25 (m, 2H, H-8), 4.10-3.90 (m, 2H, H-5), 2.56-2.42 (m, 1H, H-3), 2.38 (s, 3H, -CH_3), 2.33 (s, 3H, -CH_3), 1.02 (d, 3H, *J* = 6.4, Hz, H-4), 0.81 (d, 3H, *J* = 6.4, Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.9 (C-1), 166.1 (C-a), 165.4 (C-c), 162.6 (C-d), 136.7 (C-e), 133.1 (C-h), 133.0 (C-6), 128.9 (C-g), 128.7 (C-f), 117.4 (C-7), 100.6 (C-b), 42.6 (C-5 & C-8), 26.5 (-CH_3), 26.1 (-CH_3), 24.1 (C-3), 19.9 (C-4), 19.1 (C-4).

2-(allyl(6-methyl-2-phenylpyrimidin-4-yl)amino)-*N*-cyclohexylbutanamide (III-6)



This compound was synthesized according to the general procedure III-A, using 2.5 mmol of isocyanide. The desired product was isolated in 61 % yield (600 mg).

Chemical Formula: $C_{24}H_{32}N_4O$, Nature: white solid.

Exact Mass: 392.2576, Mol. Wt.: 392.54

HRMS: Calcd. for $C_{24}H_{32}N_4O$: 392.2576, Found : 392.2575

M.P. = 115 ^oC,

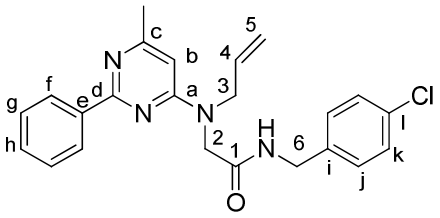
I.R. (thin film): 2929, 2850, 11658, 1591, 1570, 1526, 1474, 1443, 1377, 1260, 1208, 1181, 1024 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.50-8.27 (m, 2H, H-f), 7.60-7.38 (m, 3H, H-h, H-g), 6.60 (br s, 1H, NH), 6.24 (s, 1H, H-b), 5.94-5.76 (m, 1H, H-6), 5.42-5.03 (m, 3H, H-7, H-2), 4.11 (d, 1H, *J* = 17.0 Hz, H-5), 3.96 (d, 1H, *J* = 17.0 Hz, H-5), 3.77-3.61 (m, 1H, H-8), 2.45 (s, 3H, CH_3), 2.24-2.08 (m, 1H, H-3), 1.89-1.74 (m, 2H, H-cy, H-3), 1.68-1.36 (m, 4H, H-cy), 1.33-1.13 (m, 2H, H-cy), 1.04-0.80 (m, 6H, H-cy, H4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.2 (C-1), 166.0 (C-a), 162.8 (C-c), 162.6 (C-d), 138.2 (C-e), 133.5 (C-6), 130.2 (C-h), 128.4 (C-g), 127.9 (C-f), 117.1 (C-7), 101.3 (C-b),

59.7 (C-2), 47.7 (C-8 & C-5), 32.8 (C-cy), 32.6 (C-cy), 25.3 (-CH_3), 24.6 (C-cy), 24.4 (C-cy), 24.3 (C-cy), 21.6 (C-3), 11.1 (C-4).

2-(allyl(6-methyl-2-phenylpyrimidin-4-yl)amino)-*N*-(4-chlorobenzyl)butanamide (III-7)



This compound was synthesized according to the general procedure III-A, using 2.5 mmol of isocyanide. The desired product was isolated in 37 % yield (401 mg).

Mol. Wt.: 434.96, Nature: white solid.

HRMS: Calcd. for $C_{25}H_{27}ClN_4O$: 434.1873, Found : 434.1881

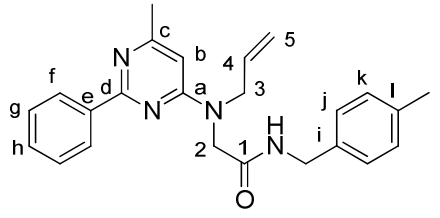
M.P. = 123 ^oC,

I.R. (thin film): 2926, 1655, 1592, 1574, 1528, 1471, 1420, 1379, 1243, 1208, 1135, 1011 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.35-8.27 (m, 2H, H-f), 7.50-7.38 (m, 3H, H-h, H-g), 7.08-7.02 (m, 4H, H-Ar), 6.90 (br s, 1H, NH), 6.27 (s, 1H, H-b), 5.92-5.79 (m, 1H, H-4), 5.30-5.15 (m, 2H, H-5), 4.38 (s, 2H, H-6), 4.32 (s, 2H, H-2), 4.16 (m, 2H, H-3), 2.45 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.8 (C-1), 166.6 (C-a), 163.4 (C-c), 137.8 (C-Ar), 136.3 (C-Ar), 133.1 (C-4), 131.2 (C-Ar), 130.4 (C-Ar), 128.8 (C-Ar), 128.8 (C-Ar), 128.4 (C-Ar), 128.0 (C-Ar), 118.0 (C-5), 99.9 (C-b), 52.4 (C-2), 51.6 (C-3), 42.5 (C-6), 24.6 (CH_3).

2-(allyl(6-methyl-2-phenylpyrimidin-4-yl)amino)-*N*-(4-methylbenzyl)acetamide (III-8)



This compound was synthesized according to the general procedure III-**A**, using 2.15 mmol of isocyanide. The desired product was isolated in 60 % yield (498 mg).

Nature: white solid. Mol. Wt.: 386.49

HRMS: Calcd. for $C_{24}H_{26}N_4O$: 386.2107, Found : 386.2111

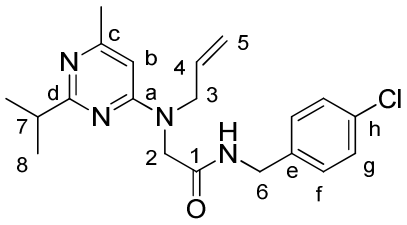
M.P. = 125 ^oC

I.R. (thin film): 2920, 2356, 1653, 1591, 1570, 1531, 1496, 1439, 1408, 1374, 1260, 1230, 1194, 1068, 1020 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.43-8.24 (m, 2H, H-f), 7.52-7.35 (m, 3H, H-g, H-h), 7.02 (d, 2H, *J* = 8.0 Hz, H-j), 6.94 (d, 2H, *J* = 8.0 Hz, H-k), 6.79 (br s, 1H, NH), 6.25 (s, 1H, H-b), 5.91-5.80 (m, 1H, H-4), 5.31-5.14 (m, 2H, H-5), 4.39 (s, 2H, H-6), 4.29 (s, 2H, H-2), 4.16 (s, 2H, H-3), 2.44 (s, 3H, CH_3), 2.25 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.5 (C-1), 166.4 (C-a), 163.3 (C-c), 162.1 (C-d), 137.9 (C-i), 136.9 (C-l), 134.7 (C-4), 131.3 (C-e), 130.2 (C-h), 129.2 (C-k), 128.2 (C-g), 128.0 (C-f), 127.3 (C-j), 117.8 (C-5), 99.9 (C-b), 52.2 (C-2), 51.4 (C-3), 42.9 (C-6), 24.5 (CH_3), 21.0 (CH_3).

2-(allyl(2-isopropyl-6-methylpyrimidin-4-yl)amino)-*N*-(4-chlorobenzyl)acetamide (III-9)



This compound was synthesized according to the general procedure III-A, using 2.5 mmol of isocyanide. The desired product was isolated in 44 % yield (410 mg).

Nature: oil. Mol. Wt.: 344.84

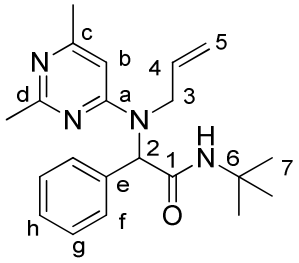
HRMS: Calcd. for $C_{20}H_{25}ClN_4O$: 372.1717, Found : 372.1709

I.R. (thin film): 2925, 1662, 1585, 1534, 1465, 1435, 1411, 1373, 1289, 1260, 1151, 1080, 1011 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.25 (d, 2H, *J* = 8.2 Hz, H-f), 7.14 (d, 2H, *J* = 8.2 Hz, H-g), 7.07 (br s, 1H, NH), 6.15(s, 1H, H-b), 5.86-5.74 (m, 1H, H-4), 5.25-5.12 (m, 2H, H-5), 4.38 (s, 2H, H-6), 4.21 (m, 2H, H-2), 4.07 (m, 2H, H-3), 2.97-2.87 (m, 1H, H-7), 2.35 (s, 3H, CH_3), 1.61 (d, 6H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 174.3 (C-1), 166.0 (C-a), 162.1 (C-c), 136.6 (C-Ar), 136.5 (C-Ar), 131.3 (C-4), 131.2 (C-g), 128.9 (C-Ar), 128.7 (C-Ar), 126.8 (C-Ar), 117.8 (C-5), 99.2 (C-b), 52.2 (C-2), 51.5 (C-3), 42.6 (C-6), 37.4 (C-7), 24.4 (CH_3), 21.7 (CH_3).

2-(allyl(2,6-dimethylpyrimidin-4-yl)amino)-*N*-(tert-butyl)-2-phenylacetamide (III-10)



This compound was synthesized according to the general procedure A, using 2.5 mmol of isocyanide. The desired product was isolated in 35 % yield (308 mg).
Nature: oil. Mol. Wt.: 352.47

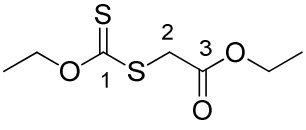
HRMS: Calcd. for $C_{21}H_{28}N_4O$: 352.2263, Found : 352.2270

I.R. (thin film): 2930, 1658, 1570, 1510, 1469, 1420, 1428, 1345, 1270, 1231, 1112, 1052 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38-7.28 (m, 4H, H-Ar), 6.34 (s, 1H, H-b), 6.18(s, 1H, H-2), 6.00 (br s, 1H, NH), 5.60-5.47 (m, 1H, H-4), 5.05-4.97 (m, 2H, H-5), 3.96 (m, 2H, H-3), 2.50 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.34 (s, 9H, H-7).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 169.2 (C-1), 166.2 (C-a), 165.4 (C-c), 162.2 (C-d), 134.4 (C-Ar), 134.0 (C-Ar), 133.3 (C-4), 130.9 (C-Ar), 128.7 (C-Ar), 116.9 (C-5), 100.4 (C-b), 61.7 (C-2), 51.6 (C-3), 48.6 (C-6), 28.7 (C-7), 26.1 (CH_3), 24.3 (CH_3).

Ethyl ethoxythiocarbonylsulfanylacetate (III-A)



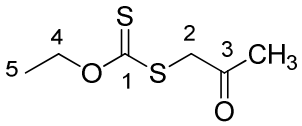
This compound was synthesized according to the general procedure III-**B**, using 10 mmol of potassium ethyl xanthogenate. The desired product was isolated in 95 % yield (1.9 gm).
Mol. Wt.: 208.30 Nature: pale yellow liquid.

I.R. (thin film): 2970, 1740, 1446, 1370, 1295, 1231, 1151, 1120, 1052 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.62 (q, 2H, *J* = 7.1 Hz, CH_2), 4.19 (q, 2H, *J* = 7.1 Hz, CH_2), 3.89 (s, 2H, H-2), 1.41 (t, 3H, *J* = 7.1 Hz, CH_3), 1.28 (t, 3H, *J* = 7.1 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 212.6 (C-1), 167.8 (C-2), 70.5, 61.85, 37.9 (C-2), 14.1, 13.6

O-ethyl S-(2-oxopropyl) carbonodithioate (III-B)



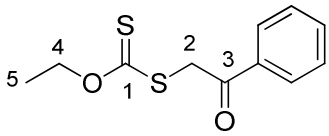
This compound was synthesized according to the general procedure III-**B**, using 10 mmol of potassium ethyl xanthogenate. The desired product was isolated in 92 % yield (1.6 gm).

Mol. Wt.: 178.27 Nature: pale yellow liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.60 (q, 2H, *J* = 7.1 Hz, H-4), 3.96 (s, 2H, H-2), 2.29 (s, 3H, CH_3), 1.38 (t, 3H, *J* = 7.1 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 213.5 (C-1), 200.1 (C-3), 70.5(C-4), 45.9 (C-2), 29.11 (CH_3), 13.5 (C-5).

***O*-ethyl *S*-2-oxo-2-phenylethyl carbonodithioate (III-C)**



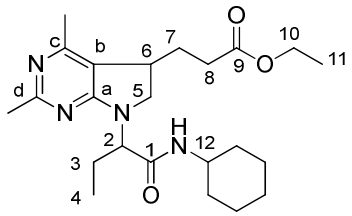
This compound was synthesized according to the general procedure III-**B**, using 10 mmol of potassium ethyl xanthogenate. The desired product was isolated in 87 % yield (2.8 gm).

Mol. Wt.: 240.34 Nature: pale yellow liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.08-7.93 (m, 2H, H-Ar), 7.68-7.55 (m, 1H, H-Ar), 7.54-7.39 (m, 2H, H-Ar), 4.66 (s, 2H, H-2), 4.62 (q, 2H, *J* = 7.6 Hz, H-4), 1.40 (t, 3H, *J* = 7.1 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 213.3 (C-1), 192.4 (C-3), 135.8 (C-Ar), 133.8 (C-Ar), 128.9 (C-Ar), 128.5 (C-Ar), 70.8(C-4), 43.6 (C-2), 13.8 (C-5).

Ethyl 3-(7-(1-(cyclohexylamino)-1-oxobutan-2-yl)-2,4-dimethyl-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-11)



This compound was synthesized according to the general procedure III-C, using 1.0 mmol of Ugi-Smiles adduct III-2. The desired product was isolated in 48 % yield (200 mg).

Nature: yellow liquid. Mol. Wt.: 416.56

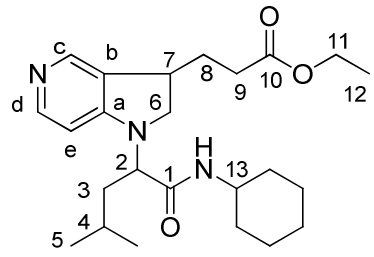
HRMS: Calcd. for $C_{23}H_{36}N_4O_3$: 416.2787, Found : 416.2767

I.R. (thin film): 2929, 2855, 2356, 1731, 1657, 1609, 1570, 1517, 1448, 1400, 1312, 1277, 1260, 1168, 1168, 1089, 1028 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.43 (d, 1H, *J* = 7.5 Hz, NH), 4.40 (t, 1H, *J* = 7.7 Hz H-2), 4.06 (q, 2H, *J* = 6.8 Hz, H-10), 3.80-3.63 (m, 2H, H-12, H-5), 3.40-3.25 (m, 2H, H-5, H-6), 2.45 (s, 3H, -CH_3), 2.34-2.20 (m, 5H, H-8, -CH_3), 2.10-1.95 (m, 2H, H-7, H-3), 1.90-1.70 (m, 4H, H-7, H-3, H-cy), 1.69-1.46 (m, 3H, H-cy), 1.40-1.05 (m, 8H, H-cy, H-11), 0.88 (t, 3H, *J* = 7.3 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.8 (C-9), 169.1 (C-1), 166.3 (C-a), 166.2 (C-d), 157.2 (C-c), 116.4 (C-b), 60.6 (C-10), 57.9 (C-2), 50.5 (C-5), 47.8 (C-12), 35.0 (C-6), 32.9 (C-cy), 32.8 (C-cy), 30.4 (C-8), 28.9 (C-7), 25.8 (-CH_3), 25.4 (C-cy), 24.5 (C-cy), 24.4 (C-cy), 20.8 (C-3), 20.5 (-CH_3), 14.2 (C-11), 10.7 (C-4).

Ethyl 3-(1-(1-(cyclohexylamino)-4-methyl-1-oxopentan-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,2-c]pyridin-3-yl)propanoate (III-12)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **II-2**. The desired product was isolated in 24 % yield (100 mg).

Nature: Pale yellow liquid. Mol. Wt.: 415.57

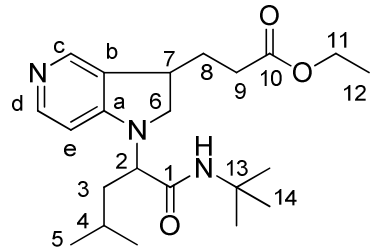
HRMS: Calcd. for $C_{24}H_{37}N_3O_3$: 415.2835, Found : 415.2837

I.R. (thin film): 29224, 2840, 2361, 1727, 1644, 1660, 1517, 1448, 1374, 1277, 1260, 1163, 1098, 1064, 1028 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.21 (s, 1H, H-c), 8.12 (d, 1H, *J* = 5.8 Hz H-d), 6.55 (d, 1H, *J* = 5.8 Hz, H-e), 6.04 (br s, 1H, NH), 4.10 (q, 2H, *J* = 7.1 Hz, H-11), 3.93 (t, 1H, *J* = 6.5 Hz, H-2), 3.80-3.60 (m, 3H, H-6, H-7, H-13), 3.00-2.88 (m, 1H, H-6), 2.29 (t, 2H, *J* = 7.0 Hz, H-9), 2.02 (dd, 1H, *J* = 7.0, 13.4 Hz, H-3), 1.95-1.78 (m, 4H, H-3, H-4, H-8), 1.74-1.50 (m, 6H, H-cy), 1.35-1.15 (m, 11H, H-cy, H-5, H-12), 0.95-0.82 (m, 2H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 173.0 (C-10), 171.1 (C-1), 148.1 (C-c), 147.6 (C-d), 146.1 (C-a), 127.0 (C-b), 107.0 (C-e), 60.4 (C-11), 60.2 (C-2), 49.3 (C-6), 48.2 (C-13), 39.6 (C-7), 33.7 (C-3), 33.0 (C-cy), 32.8 (C-cy), 30.3 (C-9), 30.0 (C-8), 29.0 (C-4), 25.3 (C-5), 24.8 (C-cy), 24.7 (C-cy), 24.5 (C-cy), 22.2 (C-5), 14.1 (C-12).

Ethyl 3-(1-(1-(tert-butylamino)-4-methyl-1-oxopentan-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,2-c]pyridin-3-yl)propanoate (III-13)



This compound was synthesized according to the general procedure III-C, using 0.825 mmol Ugi-Smiles adduct **II-4**. The desired product was isolated in 27 % yield (85 mg).

Chemical Formula: $C_{22}H_{35}N_3O_3$, Nature: Pale brown liquid.

Exact Mass: 389.2678, Mol. Wt.: 389.53

HRMS: Calcd. for $C_{22}H_{35}N_3O_3$: 389.2678, Found : 389.2679

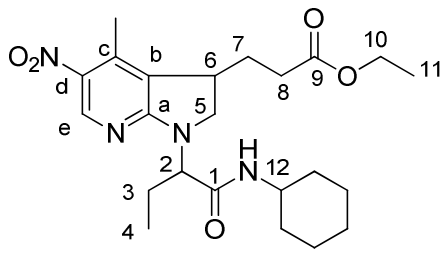
I.R. (thin film): 2960, 2933, 22361, 1727, 1666, 1596, 1543, 1505, 1448, 1365, 1277, 1255, 1220, 1163 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.23 (s, 1H, H-c), 8.14 (d, 1H, *J* = 5.8 Hz H-d), 6.55 (d, 1H, *J* = 5.8 Hz, H-e), 5.85 (br s, 1H, NH), 4.10 (q, 2H, *J* = 7.1 Hz, H-11), 3.82 (t, 1H, *J* = 6.5 Hz, H-2), 3.74-3.62 (m, 2H, H-6, H-7), 3.00-2.87 (m, 1H, H-6), 2.30 (t, 2H, *J* = 7.0 Hz,

H-9), 2.26-2.17 (m, 1H, H-4), 2.06-196 (m, 1H, H-3), 1.94-1.83 (m, 1H, H-3), 1.65-1.55 (m, 2H, H-8), 1.32 (s, 9H, tBu), 1.31-1.18 (m, 9H, H-5, H-12).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 173.0 (C-10), 171.1 (C-1), 156.2 (C-a), 148.0 (C-c), 146.7 (C-d), 127.4 (C-b), 107.0 (C-e), 60.9 (C-11), 60.4 (C-2), 51.2 (C-6), 49.4 (C-13), 39.6 (C-7), 33.8 (C-3), 33.3 (C-9), 30.3 (C-8), 28.5 (C-14), 24.6 (C-5), 22.2 (C-4), 14.2 (C-12).

Ethyl 3-(1-(1-(cyclohexylamino)-1-oxobutan-2-yl)-5-nitro-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoate (III-14)



This compound was synthesized according to the general procedure **III-C**, using 1.34 mmol Ugi-Smiles adduct **III-1**. The desired product was isolated in 48 % yield (300 mg).

Chemical Formula: $C_{22}H_{32}N_4O_5$, Nature: Pale brown liquid

Exact Mass: 432.2373, Mol. Wt.: 432.51

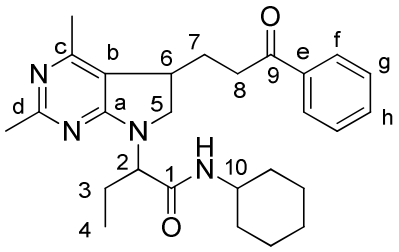
HRMS: Calcd. for $C_{22}H_{32}N_4O_5$: 432.2373, Found : 432.2386

I.R. (thin film): 2933, 2850, 2356, 1731, 1657, 1609, 1574, 1517, 1496, 1443, 1377, 1291, 1186, 1090, 1024 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.86 (s, 1H, H-e), 7.92 (s, 1H, H-c), 6.04 (br s, 1H, NH), 4.05 (t, 1H, *J* = 7.5 Hz, H-2), 4.15 (q, 2H, *J* = 7.2 Hz, H-10), 4.00-3.83 (m, 1H, H-12), 3.79-3.62 (m, 1H, H-5), 3.55-3.30 (m, 2H, H-5, H-6), 2.44-2.30 (m, 2H, H-8), 2.20-1.98 (m, 2H, H-7, H-3), 1.94-1.76 (m, 3H, H-7, H-3, H-cy), 1.74-1.64 (m, 3H, H-cy), 1.34-1.25 (m, 6H, H-cy, H-11), 1.20-1.10 (m, 1H, H-cy), 0.95 (t, 3H, *J* = 7.2 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.5 (C-9), 168.1 (C-1), 164.6 (C-a), 146.7 (C-e), 136.6 (C-c), 126.7 (C-d), 125.7 (C-b), 60.8 (C-10), 58.5 (C-2), 51.9 (C-5), 48.2 (C-12), 36.2 (C-6), 33.0 (C-cy), 31.0 (C-cy), 30.9 (C-8), 29.5 (C-7), 25.4 (C-cy), 24.6 (C-cy), 24.5 (C-cy), 21.4 (C-3), 14.3 (C-11), 10.7 (C-4).

_N_-cyclohexyl-2-(2,4-dimethyl-5-(3-oxo-3-phenylpropyl)-5_H_-pyrrolo[2,3-d]pyrimidin-7(6_H_)-yl)butanamide (III-15)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-2**. The desired product was isolated in 34 % yield (150 mg).

Nature: Pale brown liquid, Mol. Wt.: 448.60

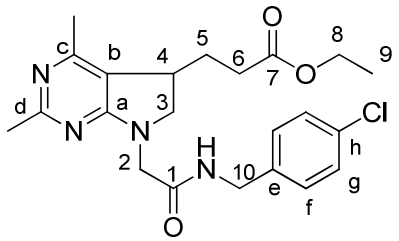
HRMS: Calcd. for $C_{27}H_{36}N_4O_2$: 448.2838, Found : 448.2843

I.R. (thin film): 2929, 2853, 1671, 1611, 1568, 1515, 1446, 1404, 1358, 1317, 1270, 1259, 1202, 1083 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.90 (d, 2H, *J* = 7.8 Hz, Hf), 7.58-7.54 (m, 1H, H-h), 7.48-7.41 (m, 2H, H-g), 6.48 (d, 1H, *J* = 7.8 Hz, NH), 4.41 (t, 1H, *J* = 7.7 Hz, H-2), 3.80-3.65 (m, 2H, H-10, H-5), 3.46-3.30 (m, 2H, H-5, H-6), 3.08-2.83 (m, 2H, H-8), 2.45 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3), 2.26-2.14 (m, 1H, H-7), 2.08-1.96 (m, 1H, H-7, 1.94-1.40 (m, 7H, H-3, H-cy), 1.30-0.98 (m, 5H, H-cy), 0.90 (t, 3H, *J* = 7.3 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 199.3 (C-9), 169.2 (C-1), 166.3 (C-a), 166.1 (C-c), 157.2 (C-d), 136.6 (C-e), 133.2 (C-h), 128.6 (C-f), 127.9 (C-g), 116.8 (C-b), 58.0 (C-2), 50.7 (C-5), 47.9 (C-10), 35.2 (C-6), 34.1 (C-8), 33.0 (C-cy), 32.8 (C-cy), 28.2 (C-7), 25.8 (-CH_3), 25.4 (C-cy), 24.4 (C-cy), 21.1 (C-3), 20.6 (-CH_3), 10.8 (C-4).

Ethyl 3-(7-(2-((4-chlorobenzyl)amino)-2-oxoethyl)-2,4-dimethyl-6,7-dihydro-5_H_-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-16)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-3**. The desired product was isolated in 23 % yield (99 mg).

Nature: Pale brown liquid, Mol. Wt.: 430.93

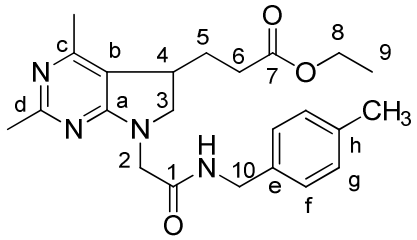
HRMS: Calcd. for $C_{22}H_{27}ClN_4O_3$: 430.1772, Found : 430.1784

I.R. (thin film): 2927, 1673, 1613, 1571, 1520, 1451, 1410, 1361, 1310, 1262, 1249, 1186, 1060 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.25 (d, 2H, *J* = 8.2 Hz, Hg), 7.16 (d, 2H, *J* = 8.2 Hz, Hf), 7.09 (br s, 1H, NH), 4.47-4.32 (m, 2H, H-8), 4.22-3.80 (m, 4H, H-10, H-2), 3.70-3.60 (m, 1H, H-4), 3.42-3.28 (m, 2H, H-3), 2.39 (s, 3H, CH_3), 2.31 (CH_3), 2.28 (m, 5H, CH_3, H6), 1.2 (t, 3H, *J* = 7.0 Hz, H-9).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.9 (C-7), 168.6 (C-1), 166.6 (C-a), 166.5 (C-c), 157.6 (C-d), 1337.1 (C-e), 134.9 (C-h), 129.3 (C-g), 127.6 (C-f), 116.3 (C-b), 60.7 (C-2), 55.5 (C-8), 49.1 (C-3), 43.1 (C-10), 35.5 (C-4), 30.6 (C-6), 28.6 (C-5), 25.6 (CH_3), 21.0 (CH_3), 20.5 (CH_3), 14.1 (CH_3).

Ethyl 3-(2,4-dimethyl-7-(2-((4-methylbenzyl)amino)-2-oxoethyl)-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-17)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-4**. The desired product was isolated in 18 % yield (73mg).

Nature: liquid, Mol. Wt.: 410.51

HRMS: Calcd. for $C_{23}H_{30}N_4O_3$: 410.2318, Found : 410.2314.

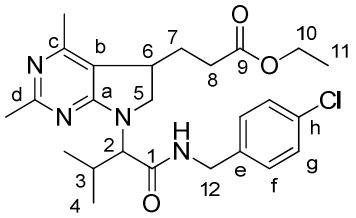
I.R. (thin film): 2929, 1668, 1615, 1574, 1515, 1454, 1376, 1321, 1280, 1215, 1180, 1020 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.17-702 (m, 4H, H-Ar), 6.88 (br s, 1H, NH), 4.48-4.28 (m, 2H, H-8), 4.22-3.96 (m, 4H, H-10, H-2), 3.92-3.82 (m, 1H, H-4), 3.70-3.60 (m, 2H, H-3), 2.40 (s, 3H, CH_3), 2.30-2.22 (m, 5H, CH_3, H6), 2.04-1.80 (m, 2H, H-5), 1.2 (t, 3H, *J* = 7.0 Hz, H-9).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.9 (C-7), 168.7 (C-1), 166.6 (C-a), 166.5 (C-c), 157.3 (C-d), 136.6 (C-e), 133.2 (C-h), 128.9 (C-f), 128.7 (C-g), 116.3 (C-b), 60.7 (C-2), 55.5

(C-8), 49.0 (C-3), 42.6 (C-10), 35.4 (C-4), 30.6 (C-6), 28.5 (C-5), 25.5 (CH_3), 20.3 (CH_3), 14.1 (CH_3).

Ethyl 3-(7-(1-((4-chlorobenzyl)amino)-3-methyl-1-oxobutan-2-yl)-2,4-dimethyl-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-18)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-5**. The desired product was isolated in 43 % yield (203 mg).

Nature: Pale yellow liquid. Mol. Wt.: 472.2241

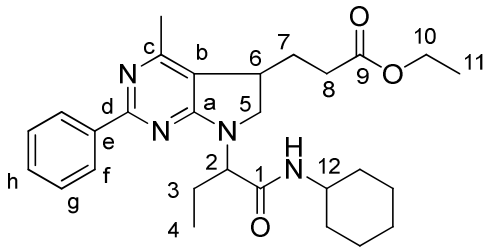
HRMS: Calcd. for $C_{25}H_{33}ClN_4O_3$: 472.2241, Found : 472.2244

I.R. (thin film): 2964, 2924, 1731, 1671, 11609, 1570, 1531, 1469, 1403, 1273, 1177, 1094, 1011 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.22 (d, 2H, *J* = 8.0 Hz, H-g), 7.07 (d, 2H, *J* = 8.0 Hz, H-f), 6.97 (d, 1H, *J* = 6.0 Hz, NH), 4.39 (dd, 2H, *J* = 6.0, 14.7 Hz, H-12), 4.12 (q, 2H, *J* = 7.0 Hz, H-10), 4.04-3.97 (m, 1H, H-5), 3.73 (t, 1H, *J* = 7.0 Hz, H-2), 3.40-3.20 (m, 2H, H-5, H-6), 2.51-2.38 (m, 1H, H-3), 2.35 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.23 (t, 2H, *J* = 7.5 Hz, H-8), 2.10-1.90 (m, 1H, H-7), 1.80-1.65 (m, 1H, H-7), 1.25 (t, 3H, *J* = 7.0 Hz, H-11), 1.00 (d, 3H, *J* = 7.0 Hz, H-4), 0.87 (d, 3H, *J* = 7.0 Hz, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.8 (C-9), 169.6 (C-1), 166.1 (C-a), 165.9 (C-c), 157.3 (C-d), 136.7 (C-e), 133.2 (C-h), 128.9 (C-g), 128.7 (C-f), 116.6 (C-b), 64.0 (C-2), 60.6 (C-10), 51.5 (C-5), 42.6 (C-12), 35.2 (C-6), 30.6 (C-3), 28.9 (C-8), 26.4 (C-7), 25.7 (-CH_3), 20.6 (-CH_3), 19.5 (C-4), 19.1 (C-4), 14.2 (C-11).

Ethyl 3-(7-(1-(cyclohexylamino)-1-oxobutan-2-yl)-4-methyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-19)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-6**. The desired product was isolated in 55 % yield (265 mg).

Nature: Pale yellow liquid. Mol. Wt.: 478.63

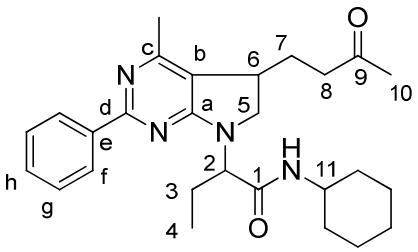
HRMS: Calcd. for $C_{28}H_{38}N_4O_3$: 478.2944, Found : 478.2950.

I.R. (thin film): 2972, 2929, 2850, 1731, 1662, 1605, 1562, 1531, 1452, 1377, 1312, 1246, 1163 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.40-8.30 (m, 2H, H-f), 7.54-7.38 (m, 3H, H-h, H-g), 6.52 (br s, 1H, NH), 4.63-4.45 (m, 1H, H-2), 4.09 (q, 2H, *J* = 7.0 Hz, H-10), 3.80-3.60 (m, 2H, H-12, H-5), 3.50-3.25 (m, 2H, H-5, H-6), 2.40 (s, 3H, CH_3), 2.37-2.24 (m, 2H, H-8), 2.18-1.96 (m, 2H, H-7, H-3), 1.94-1.70 (m, 4H, H-7, H-3, H-cy), 1.63-1.38 (m, 3H, H-cy), 1.34-1.14 (m, 6H, H-cy, H-11), 1.05-0.80 (m, 5H, H-cy, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.8 (C-9), 169.3 (C-1), 166.6 (C-a), 163.0 (C-d), 157.9 (C-c), 138.2 (C-e), 130.0 (C-h), 128.2 (C-g), 127.7 (C-f), 117.5 (C-b), 60.6 (C-10), 58.2 (C-2), 50.7 (C-5), 47.9 (C-12), 35.2 (C-6), 32.8 (C-cy), 32.7 (C-cy), 30.4 (C-8), 28.8 (C-7), 25.3 (C-cy), 24.4 (C-cy), 24.2 (C-cy), 21.0 (C-3), 20.9 (CH_3), 14.2 (C-11), 10.8 (C-4).

***N*-cyclohexyl-2-(4-methyl-5-(3-oxobutyl)-2-phenyl-5*H*-pyrrolo[2,3-d]pyrimidin-7(6*H*)-yl)butanamide (III-20)**



This compound was synthesized according to the general procedure **III-C**, using 0.38 mmol of Ugi-Smiles adduct **III-6**. The desired product was isolated in 44 % yield (75 mg).

Nature: yellow liquid. Mol. Wt.: 448.60

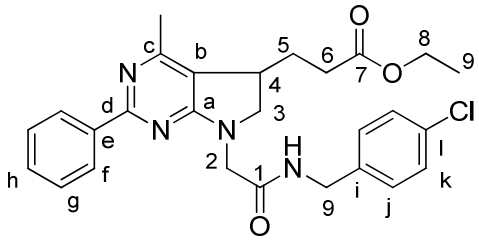
HRMS: Calcd. for $C_{27}H_{36}N_4O_2$: 448.2838, Found : 448.2836

I.R. (thin film): 3322, 2929, 2853, 1710, 1656, 1603, 1564, 1508, 1454, 1377, 1317, 1247, 1159, 1064 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.40-8.25 (m, 2H, H-f), 7.55-7.35 (m, 3H, H-h, H-g), 6.50 (d, 1H, *J* = 8.0Hz, NH), 4.50 (t, 1H, *J* = 6.6 Hz, H-2), 3.78-3.58 (m, 2H, H-11, H-5), 3.45-3.25 (m, 2H, H-5, H-6), 2.47 (t, 2H, *J* = 7.5 Hz, H-8), 2.40 (s, 3H, -CH_3), 2.16-2.00 (m, 5H, H-3, H-7, H-10), 1.90-1.66 (m, 4H, H-7, H-3, H-cy), 1.60-1.34 (m, 4H, H-cy), 1.30-1.14 (m, 2H, H-cy), 1.10-0.85 (m, 5H, H-cy, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 207.9 (C-9), 169.3 (C-1), 166.5 (C-a), 162.9 (C-d), 157.8 (C-c), 138.1 (C-e), 130.0 (C-h), 128.2 (C-g), 127.7 (C-f), 117.7 (C-b), 58.2 (C-2), 51.2 (C-5), 47.8 (C-11), 39.4 (C-8), 35.1 (C-6), 32.7 (C-cy), 30.0 (C-10), 27.4 (C-7), 25.3 (C-cy), 24.4 (C-cy), 24.3 (C-cy), 21.1 (C-3), 21.0 (-CH_3), 10.8 (C-4).

Ethyl 3-(7-(2-((4-chlorobenzyl)amino)-2-oxoethyl)-4-methyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-21)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-7**. The desired product was isolated in 27 % yield (135 mg).

Mol. Wt.: 493.00, Nature: liquid.

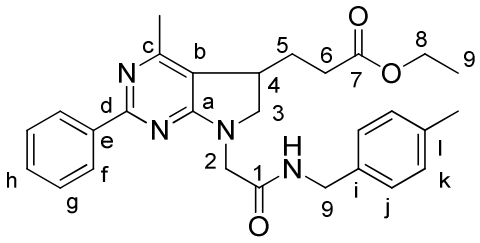
HRMS: Calcd. for $C_{27}H_{29}ClN_4O_3$: 492.1928 Found : 492.1930

I.R. (thin film): 2929, 1729, 1659, 1624, 1576, 1533, 1467, 1382, 1331, 1226, 1180, 1010 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.35-8.23 (m, 2H, H-f), 7.50-7.35 (m, 4H, H-Ar, NH), 7.24-7.08 (m, 4H, H-Ar), 4.47-4.25 (m, 3H, H-2, H-10), 4.20-3.90 (m, 3H, H-2, H-8), 3.75-3.65 (m, 1H, H-3), 3.55-3.37 (m, 2H, H-3, H-4), 2.41 (s, 3H, CH_3), 2.35-2.25 (m, 2H, H-6), 2.10-1.90 (m, 2H, H-5), 1.20 (t, 3H, *J* = 7.0 Hz, H-9).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.9 (C-7), 169.1 (C-1), 166.9 (C-a), 163.5 (C-c), 158.5 (C-d), 137.8 (C-e), 136.5 (C-l), 133.1 (C-i), 130.2 (C-h), 128.9 (C-j), 128.7 (C-g), 128.3 (C-k), 127.9 (C-f), 117.3 (C-b), 60.8 (C-8), 55.8 (C-2), 49.5 (C-3), 42.6 (C-10), 35.7 (C-4), 30.7 (C-6), 28.5 (C-5), 20.9 (CH_3), 14.1 (C-9).

Ethyl 3-(4-methyl-7-(2-((4-methylbenzyl)amino)-2-oxoethyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (III-22)



This compound was synthesized according to the general procedure **III-C**, using 1.0 mmol of Ugi-Smiles adduct **III-8**. The desired product was isolated in 27 % yield (125 mg).

Nature: Pale yellow liquid. Mol. Wt.: 472.58

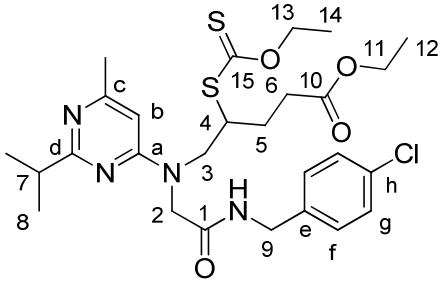
HRMS: Calcd. for $C_{28}H_{32}N_4O_3$: 472.2474, Found : 472.2473

I.R. (thin film): 2924, 2356, 1731, 1662, 1605, 1583, 1570, 1518, 1448, 1377, 1325, 1260, 1172, 1024 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.28 (d, 2H, *J* = 7.6 Hz, H-f), 7.45-7.34 (m, 3H, H-h, H-g), 7.10 (d, 2H, *J* = 7.6 Hz, H-j), 7.00 (d, 2H, *J* = 7.6 Hz, H-k), 6.95 (br s, 1H, NH), 4.50-4.25 (m, 3H, H-2, H-10), 4.08-3.95 (m, 3H, H-2, H-8), 3.75-3.65 (m, 1H, H-3), 3.45-3.35 (m, 2H, H-3, H-4), 2.40 (s, 3H, -CH_3), 2.33-2.20 (m, 5H, H-6, -CH_3), 2.10-2.00 (m, 1H, H-5), 1.96-1.85 (m, 1H, H-5), 1.20 (t, 3H, *J*= 7.0 Hz, H-9).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 173.0 (C-7), 169.0 (C-1), 167.0 (C-a), 163.6 (C-c), 158.5 (C-d), 138.0 (C-e), 137.1 (C-i), 135.0 (C-l), 130.1 (C-h), 129.4 (C-j), 128.3 (C-g), 128.0 (C-k), 127.6 (C-f), 117.4 (C-b), 60.8 (C-8), 55.8 (C-2), 49.5 (C-3), 43.2 (C-10), 35.8 (C-4), 30.8 (C-6), 28.7 (C-5), 21.1 (-CH_3), 21.0 (-CH_3), 14.2 (C-9).

Ethyl 5-((2-((4-chlorobenzyl)amino)-2-oxoethyl)(2-isopropyl-6-methylpyrimidin-4-yl)amino)-4-((ethoxycarbonothioyl)thio)pentanoate (III-23)



This compound was synthesized according to the general procedure **III-C**, using 2.0 mmol of Ugi-Smiles adduct **III-9**. The desired product was isolated in 44 % yield (510 mg).

Nature: liduid. Mol. Wt.: 581.19

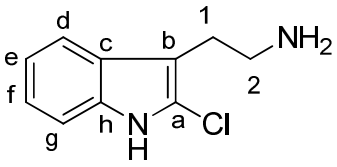
HRMS: Calcd. for $C_{27}H_{37}ClN_4O_4S_4$: 580.1945, Found : 580.1952.

I.R. (thin film): 2928, 1669, 1570, 1540, 1470, 1480, 1401, 1360, 1280, 1236, 1080, 1050, 1008 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.22 (d, 2H, *J* = 8.2 Hz, H-f), 7.10 (d, 2H, *J* = 8.2 Hz, H-g), 6.95 (br s, 1H, NH), 6.22(s, 1H, H-b), 4.57 (q, 2H, *J*= 7.1 Hz H-11), 4.38 (d, 2H, *J* = 5.9 Hz, H-2), 4.24 (s, 2H, H-9), 4.15-400 (m, 4H, H-3, H-13), 3.76-3.58 (m, 1H, H-4), 3.00-2.88 (m, 1H, H-7), 2.55-2.44 (m, 2H, H-6), 2.34 (s, 3H, CH_3), 2.33-2.15 (m, 2H, H-5), 1.36 (t, 3H, *J* = 7.1 Hz, H-12), 1.30-109 (m, 9H, H-14, H-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 213.1 (C-15), 174.2 (C-10), 172.7 (C-1), 169.3 (C-a), 166.1 (C-d), 162.4 (C-c), 136.6 (C-e), 133.1 (C-f), 128.8 (C-g), 128.6 (C-h), 99.4 (C-b), 70.5 (C-13), 60.7 (C-11), 53.8 (C-3), 53.3 (C-2), 49.5 (C-9), 42.6 (C-4), 37.4 (C-6), 31.2 (C-7), 26.2 (C-5), 24.3 (CH_3), 21.6 (C-8), 14.1 (CH_3), 13.6 (CH_3).

2-Chlorotrriptamine (III-D)



To the stirred suspension of hydrochloride salt of tryptamine (1.0 gm, 5.0 mmol) in a 10:3 acetic acid/formic acid solution was added *N*- chlorosuccinimide (679 mg, 5 mmol) at room temperature and allowed to stirred it for 18 h. After completion of reaction (checked by TLC), solvents were removed under vaccum, the residue obtained was purified with fash

chromatography using 10% aqueous ammonia in 9:1 CH_2Cl_2:MeOH soution as an eluent to afford the 2-Chlorotrriptamine products.

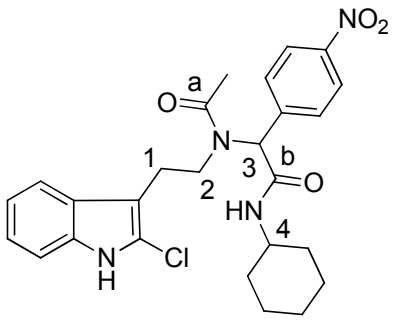
isolated yield : 340 mg, % yield = 35 %

Nature : Oil.

^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.58-7.52 (m, 1H, H-d), 7.36-7.31 (m, 1H, H-g), 7.22-7.08 (m, 2H, H-e, H-f), 3.25-3.10 (m, 4H, H-1, H-2), 2.00 (brs, 2H, NH_2).

^{13}C NMR (CD_3OD, 100.6 MHz): δ (ppm) 136.3 (C-h), 127.9 (C-c), 123.0 (C-f), 122.9 (C-a), 120.8 (C-e), 118.2 (C-d), 106.1 (C-b), 40.3 (C-2), 22.8 (C-1).

2-(*N*-(2-(2-chloro-1*H*-indol-3-yl)ethyl)acetamido)-*N*-cyclohexyl-2-(4-nitrophenyl)acetamide (III-24)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 99 % yield (490 mg).

Mol. Wt.: 496.99, Nature: white solide.

HRMS: Calcd. for $C_{26}H_{29}ClN_4O_4$: 496.1877, Found : 498.1869.

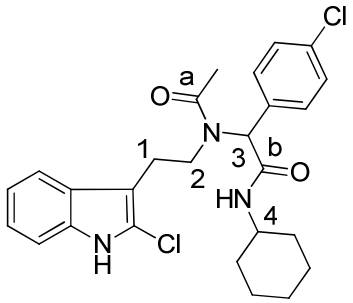
M.P. = 145-146 ^oC

I.R. (thin film): 3295, 2932, 2856, 1653, 1632, 1527, 1454, 1419, 1342, 1182, 1014 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.27 (br s, 1H, NH), 8.15 (d, 2H, *J* = 8.6 Hz, H-ar), 7.57 (d, 2H, *J* = 8.6 Hz, H-ar), 7.22 (t, 2H, *J* = 7.8 Hz, H-ar), 7.14 (t, 1H, *J* = 7.8 Hz, H-ar), 7.06 (t, 1H, *J* = 7.8 Hz, H-ar), 6.09 (br d, 1H, *J* = 7.6 Hz, NH), 6.05 (s, 1H, H-3), 3.90-3.75 (m, 1H, H-4), 3.58 (t, 2H, *J* = 8.0 Hz, H-2), 3.00-2.85 (m, 1H, H-1), 2.68-2.57 (m, 1H, H-1), 2.38 (s, 3H, -CH_3), 1.97-1.85 (m, 2H, H-cy), 1.73-1.50 (m, 3H, H-cy), 1.40-1.10 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.2 (C-a), 167.9 (C-b), 147.5 (C-ar), 142.8 (C-ar), 134.2 (C-ar), 129.9 (C-ar), 126.9 (C-ar), 123.7 (C-ar), 122.6 (C-ar), 121.0 (C-ar), 120.4 (C-ar), 117.7 (C-ar), 110.6 (C-ar), 107.9 (C-ar), 61.4 (C-3), 48.7 (C-4), 47.2 (C-2), 32.8 (C-cy), 32.7 (C-cy), 25.4 (C-cy), 24.7 (C-cy), 24.4 (C-1), 21.9 (C-CH_3).

2-(*N*-(2-(2-chloro-1*H*-indol-3-yl)ethyl)acetamido)-2-(4-chlorophenyl)-*N*-cyclohexylacetamide (III-25)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 47 % yield (227 mg).

Mol. Wt.: 4856.43, Nature: white solide.

HRMS: Calcd. for $C_{26}H_{29}Cl_2N_3O_2$: 485.1637, Found : 485.1645.

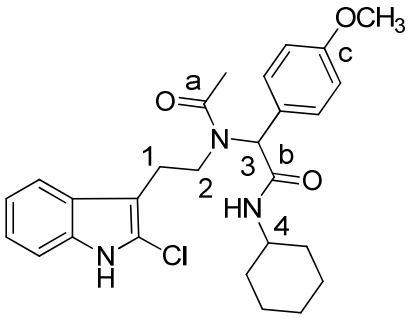
M.P. = 161-162 ^{o}C

I.R. (thin film): 3256, 3056, 2932, 2856, 1719, 1656, 1621, 1544, 1496, 1450, 1419, 1346, 1265, 1231, 1091, 1014 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.48 (br s, 1H, NH), 7.43 (d, 2H, *J* = 8.6 Hz, H-ar), 7.38 (d, 2H, *J* = 8.6 Hz, H-ar), 7.23 (t, 1H, *J* = 7.6 Hz, H-ar), 7.16-7.10 (m, 1H, H-ar), 7.08-7.02 (m, 2H, H-ar), 5.98 (s, 1H, H-3), 5.80 (br d, 1H, *J* = 7.8 Hz, NH), 3.85-3.72 (m, 1H, H-4), 3.46 (t, 2H, *J* = 8.4 Hz, H-2), 3.88-2.78 (m, 1H, H-1), 2.47-2.37 (m, 1H, H-1), 2.33 (s, 3H, -CH_3), 1.98-1.84 (m, 2H, H-cy), 1.74-1.55 (m, 3H, H-cy), 1.40-1.25 (m, 2H, H-cy), 1.18-1.04 (m, 2H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.9 (C-a), 168.6 (C-b), 134.6 (C-ar), 134.3 (C-ar), 133.9 (C-ar), 131.1 (C-ar), 129.1 (C-ar), 127.0 (C-ar), 122.3 (C-ar), 121.0 (C-ar), 120.2 (C-ar), 117.7 (C-ar), 110.7 (C-ar), 108.1 (C-ar), 61.2 (C-3), 48.6 (C-4), 46.6 (C-2), 32.8 (C-cy), 32.7 (C-cy), 25.4 (C-cy), 24.7 (C-cy), 24.5 (C-1), 21.9 (C-CH_3).

2-(N-(2-(2-chloro-1H-indol-3-yl)ethyl)acetamido)-N-cyclohexyl-2-(4-methoxyphenyl)acetamide (III-26)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 80 % yield (385 mg).
Mol. Wt.: 482.01, Nature: oil.

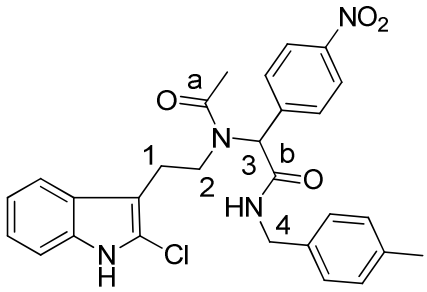
HRMS: Calcd. for $C_{27}H_{32}ClN_3O_3$: 481.2132, Found : 481.2133.

I.R. (thin film): 3229, 3067, 1665, 1620, 1527, 1512, 1438, 1345, 1251, 1230, 1171, 1023 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.36 (br s, 1H, NH), 7.37 (d, 2H, *J* = 8.6 Hz, H-ar), 7.14 (d, 1H, *J* = 8.1 Hz, H-ar), 7.08-7.02 (m 1H, H-ar), 6.99-6.93 (m, 2H, H-ar), 6.89 (d, 2H, *J* = 8.6 Hz, H-ar), 5.92 (s, 1H, H-3), 5.57 (br d, 1H, *J* = 7.8 Hz, NH), 3.90-3.65 (m, 4H, H-4, -CH_3), 3.45-3.27 (m, 2H, H-2), 2.77-2.65 (m, 1H, H-1), 2.35-2.20 (m, 4H, H-1, CH_3), 1.89-1.79 (m, 2H, H-cy), 1.64-1.45 (m, 3H, H-cy), 1.33-1.15 (m, 2H, H-cy), 1.10-0.95 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.8 (C-a), 169.3 (C-b), 159.8 (C-c), 134.2 (C-ar), 131.3 (C-ar), 127.2 (C-ar), 127.1 (C-ar), 122.2 (C-ar), 120.9 (C-ar), 119.9 (C-ar), 117.9 (C-ar), 114.4 (C-ar), 110.5 (C-ar), 108.4 (C-ar), 61.3 (C-3), 55.3 (C-4), 48.5 (CH_3), 46.3 (C-2), 32.7 (C-cy), 25.4 (C-cy), 24.8 (C-cy), 24.7 (C-cy), 24.5 (C-1), 21.9 (C-CH_3).

2-(N-(2-(2-chloro-1H-indol-3-yl)ethyl)acetamido)-N-(4-methylbenzyl)-2-(4-nitrophenyl)acetamide (III-27)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 45 % yield (233 mg).
Mol. Wt.: 518.99, Nature: white solide.

HRMS: Calcd. for $C_{28}H_{27}ClN_4O_4$: 518.9914, Found : 518.9901.

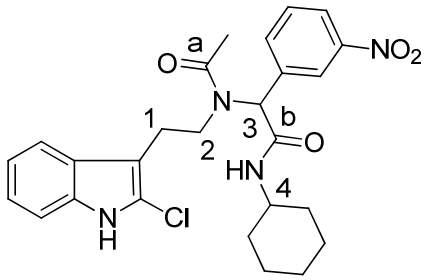
M.P. = 215-216 ^oC

I.R. (thin film): 3285, 2929, 1656, 1628, 1520, 1422, 1349, 1238, 1189, 1108, 1014 cm^{-1}

^{1}H NMR ($CDCl_3$+ DMSO-d_6 one drop, 400 MHz): δ (ppm) 8.13 (d, 2H, *J* = 8.7 Hz, H-ar), 7.56 (d, 2H, *J* = 8.7 Hz, H-ar), 7.22-7.06 (m, 8H,H-ar), 6.50 (t, 1H, *J* = 5.4 Hz, NH), 6.04 (s, 1H, H-3), 4.50-4.35 (m, 2H, H-4), 3.59 (t, 2H, *J* = 8.0 Hz, H-2), 2.94-2.83 (m, 1H, H-1), 2.65-2.54 (m, 1H, H-1), 2.35 (s, 3H, -CH_3), 2.31 (s, 3H, -CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.2 (C-a), 168.7 (C-b), 147.5 (C-ar), 142.4 (C-ar), 134.4 (C-ar), 134.2 (C-ar), 130.0 (C-ar), 129.4 (C-ar), 127.7 (C-ar), 126.9 (C-ar), 123.7 (C-ar), 122.6 (C-ar), 121.0 (C-ar), 120.4 (C-ar), 117.6 (C-ar), 110.6 (C-ar), 107.9 (C-ar), 61.6 (C-3), 47.3 (C-2), 43.6 (C-4), 24.3 (C-1), 21.9 (C-CH_3), 21.1 (C-CH_3).

2-(*N*-(2-(2-chloro-1*H*-indol-3-yl)ethyl)acetamido)-*N*-cyclohexyl-2-(3-nitrophenyl)acetamide (III-28)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 50 % yield (248 mg).

Mol. Wt.: 496.99, Nature: yellow oil.

HRMS: Calcd. for $C_{26}H_{29}ClN_4O_4$: 496.1877, Found : 498.1867.

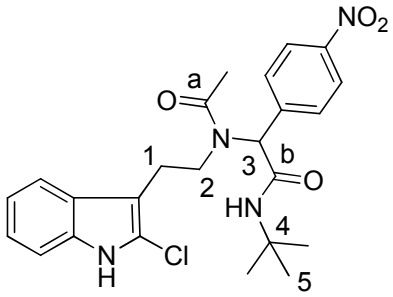
I.R. (thin film): 3285, 2936, 2856, 1653, 1625, 1530, 1450, 1415, 1349, 1227, 1171, 1098, 1021 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.35 (br s, 1H, NH), 8.29 (s, 1H, H-ar), 8.13 (d, 1H, *J* = 8.1 Hz, H-ar), 7.78 (d, 1H, *J* = 7.6 Hz, H-ar), 7.50 (t, 1H, *J* = 8.1 Hz, H-ar), 7.26-7.17 (m, 2H, H-ar), 7.13 (t, 1H, *J* = 7.6 Hz, H-ar), 7.06 (t, 1H, *J* = 7.6 Hz, H-ar), 6.17 (br d, 1H, *J* = 7.6 Hz, NH), 6.11 (s, 1H, H-3), 3.90-3.78 (m, 1H, H-4), 3.58 (t, 2H, *J* = 8.6 Hz, H-2), 2.98-2.88 (m, 1H, H-1), 2.64-2.54 (m, 1H, H-1), 2.38 (s, 3H, -CH_3), 1.97-1.85 (m, 2H, H-cy), 1.72-1.55 (m, 3H, H-cy), 1.40-1.26 (m, 2H, H-cy), 1.20-1.05 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.2 (C-a), 167.9 (C-b), 148.2 (C-ar), 137.6 (C-ar), 135.2 (C-ar), 134.2 (C-ar), 129.6 (C-ar), 126.9 (C-ar), 124.0 (C-ar), 123.2 (C-ar), 122.5

(C-ar), 121.1 (C-ar), 120.4 (C-ar), 117.9 (C-ar), 110.6 (C-ar), 107 (C-ar), 60.9 (C-3), 48.7 (C-4), 46.9 (C-2), 32.8 (C-cy), 32.9 (C-cy), 25.4 (C-cy), 24.7 (C-cy), 24.3 (C-1), 21.9 (C-CH_3).

_N_-(tert-butyl)-2-(_N_-(2-(2-chloro-1_H_-indol-3-yl)ethyl)acetamido)-2-(4-nitrophenyl)acetamide (III-29)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 99 % yield (465 mg).
Mol. Wt.: 470.95, Nature: white solide.

HRMS: Calcd. for $C_{24}H_{27}ClN_4O_4$: 470.1721, Found : 470.1734.

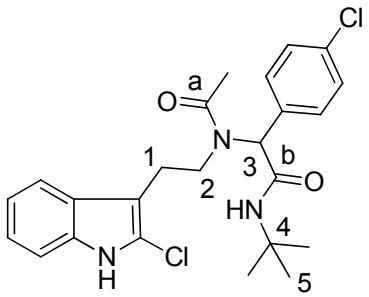
M.P. = 181-182 ^oC

I.R. (thin film): 1659, 1618, 1558, 1527, 1454, 1412, 1346, 1269, 1224, 1171, 1014 cm^{-1}

^{1}H NMR ($CDCl_3$ + DMSO-d_6 one drop, 400 MHz): δ (ppm) 8.11 (dd, 2H, *J* = 2.0, 8.6 Hz, H-ar), 7.49 (dd, 2H, *J* = 2.0, 8.6 Hz, H-ar), 7.18-7.03 (m, 3H, H-ar), 7.01-6.94 (m, 1H, H-ar), 5.96 (s, 1H, H-3), 5.27 (br s, 1H, NH), 3.64-3.45 (m, 2H, H-2), 2.90-2.78 (m, 1H, H-1), 2.57-2.48 (m, 1H, H-1), 2.34 (s, 3H, -CH_3), 1.31 (s, 9H, H-*5*).

^{13}C NMR ($CDCl_3$ + DMSO-d_6 one drop, 100.6 MHz): δ (ppm) 172.2 (C-a), 168.2 (C-b), 147.3 (C-ar), 142.9 (C-ar), 134.2 (C-ar), 129.9 (C-ar), 126.7 (C-ar), 123.6 (C-ar), 122.1 (C-ar), 121.5 (C-ar), 119.9 (C-ar), 117.4 (C-ar), 110.6 (C-ar), 107.2 (C-ar), 61.3 (C-3), 51.7 (C-4), 46.8 (C-2), 28.4 (-CH_3), 24.4 (C-1), 21.8 (CH_3).

_N_-(tert-butyl)-2-(_N_-(2-(2-chloro-1_H_-indol-3-yl)ethyl)acetamido)-2-(4-chlorophenyl)acetamide. (III-30)



This compound was synthesized according to the general procedure **III-D**, using 1.0 mmol of 2-chlorotryptamine. The desired product was isolated in 49 % yield (226 mg).
Mol. Wt.: 460.40, Nature: white solide.

HRMS: Calcd. for $C_{24}H_{27}Cl_2N_3O_2$: 459.1480, Found : 459.1470.

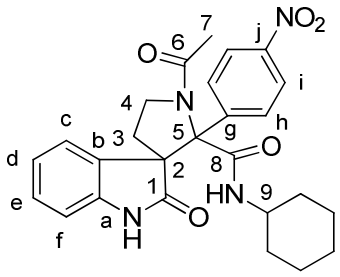
M.P. = 210-211 ^{o}C

I.R. (thin film): 3278, 2984, 1656, 1621, 1555, 1492, 1447, 1360, 1276, 1213, 1095, 1011 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.19 (br s, 1H, NH), 7.45-7.35 (m, 4H, H-ar), 7.22-6.99 (m, 4H, H-ar), 5.95 (s, 1H, H-3), 5.66 (br s, 1H, NH), 3.54 (m, 2H, H-2), 2.87-2.76 (m, 1H, H-1), 2.43-2.35 (m, 1H, H-1), 2.34 (s, 3H, CH_3), 1.34 (s, 9H, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.9 (C-a), 168.8 (C-b), 134.6 (C-ar), 134.2 (C-ar), 134.1 (C-ar), 131.2 (C-ar), 129.2 (C-ar), 127.0 (C-ar), 122.4 (C-ar), 120.9 (C-ar), 120.2 (C-ar), 117.8 (C-ar), 110.5 (C-ar), 108.2 (C-ar), 61.2 (C-3), 51.7 (C-4), 46.4 (C-2), 28.6 (C-5), 24.5 (C-1), 21.9 (C-CH_3).

1'-acetyl-_N_-cyclohexyl-2'-(4-nitrophenyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2'-carboxamide (III-31)



This compound was synthesized according to the general procedure **III-E**, using 0.5 mmol of Ugi adduct **III**-24. The desired product was isolated in 64 % yield (140 mg).
Mol. Wt.: 476.52, Nature: white solide.

HRMS: Calcd. for $C_{26}H_{28}N_4O_5$: 476.2060, Found : 476.2072.

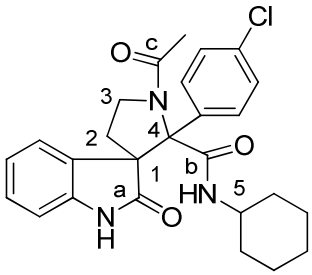
M.P. = 247-246 ^oC

I.R. (thin film): 2948, 2852, 1729, 1639, 1520, 1394, 1349, 1269, 1185, 1112 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.09 (br d, 1H, *J* = 7.4 Hz, NH), 8.40-8.05 (m, 2H, H-h), 7.93 (br s, 1H, NH), 7.34-7.26 (m, 2H, H-i), 7.08 (t, 1H, *J* = 7.7 Hz, H-e), 6.68 (d, 1H, *J* = 7.7 Hz, H-f), 6.52 (t, 1H, *J* = 7.7 Hz, H-d), 4.99 (d, 1H, *J* = 7.7 Hz, H-c), 4.69-4.58 (m, 1H, H-9), 4.03 (t, 1H, *J* = 9.2 Hz, H-4), 3.73-3.62 (m, 1H, H-4), 2.38 (s, 3H, H-7), 2.30-2.17 (m, 1H, H-3), 2.12-2.03 (m, 1H, H-3), 1.88-1.73 (m, 2H, H-cy), 1.62-1.45 (m, 3H, H-cy), 1.30-1.01 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 180.4 (C-1), 172.1 (C-8), 169.3 (C-6), 147.6 (C-j), 144.1 (C-g), 141.2 (C-a), 128.4 (C-e, C-h), 127.8 (C-b), 124.1 (C-c), 121.3 (C-i, C-d), 109.9 (C-f), 82.0 (C-5), 61.2 (C-2), 48.8 (C-9), 48.7 (C-4), 32.4 (C-3), 32.3 (C-cy), 31.7 (C-cy), 25.6 (C-7), 25.4 (C-cy), 24.5 (C-cy), 24.3 (C-cy).

1'-acetyl-2'-(4-chlorophenyl)-*N*-cyclohexyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2'-carboxamide (III-32)



This compound was synthesized according to the general procedure **III-E**, using 0.5 mmol of Ugi adduct **III-25.** The desired product was isolated in 54 % yield (110 mg).

Mol. Wt.: 465.97, Nature: white solide.

HRMS: Calcd. for $C_{26}H_{28}ClN_3O_3$: 465.1819, Found : 465.1821.

M.P. = 160-161^oC

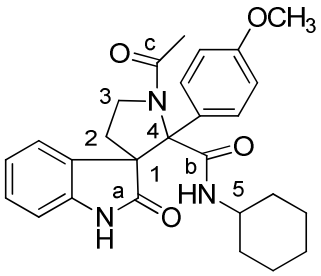
I.R. (thin film): 3054, 2930, 2849, 1708, 1653, 1621, 1531, 1468, 1398, 1335, 1284, 1189, 1091, 1014 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.09 (d, 1H, *J* = 7.5 Hz, NH), 8.35 (d, 1H, *J* = 7.6 Hz, H-ar), 7.52-7.35 (m, 1H, H-ar), 7.14-6.95 (m, 4H, H-ar), 6.76 (d, 1H, *J* = 7.6 Hz, H-ar), 6.54 (t, 1H, *J* = 7.6 Hz, H-ar), 5.07 (d, 1H, *J* = 7.6 Hz, H-ar), 4.63-4.53 (m, 1H, H-5), 3.97 (t, 1H, *J* = 9.3 Hz, H-3), 3.70-3.60 (m, 1H, H-3), 2.34 (s, 3H, CH_3), 2.22 (dd, 1H, *J* = 3.9, 12.7 Hz,

H-2), 2.01 (dd, 1H, *J* = 6.8, 13.9 Hz H-2), 1.85-1.71 (m, 2H, H-cy), 1.62-1.40 (m, 3H, H-cy), 1.25-1.08 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 180.4 (C-a), 172.1 (C-b), 169.3 (C-c), 141.4 (C-ar), 135.5 (C-ar), 134.2 (C-ar), 128.4 (C-ar), 128.0 (C-ar), 124.5 (C-ar), 121.0 (C-ar), 109.7 (C-ar), 80.1 (C-4), 61.3 (C-1), 48.6 (C-5), 48.5 (C-3), 32.3 (C-2), 32.2 (C-cy), 31.7 (C-cy), 25.6 (CH_3), 25.5 (C-cy), 24.5 (C-cy), 24.3 (C-cy).

1'-acetyl-2'-(4-methoxyphenyl)-*N*-cyclohexyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2'-carboxamide (III-33)



This compound was synthesized according to the general procedure **III-E**, using 0.7 mmol of Ugi adduct **III-26.** The desired product was isolated in 45 % yield (151 mg).

Mol. Wt.: 461.55, Nature: white semisolide.

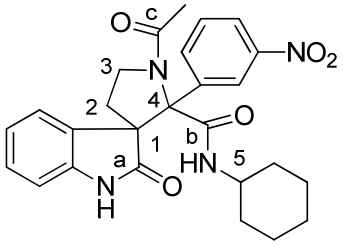
HRMS: Calcd. for $C_{27}H_{31}N_3O_4$: 461.2315, Found : 461.2328.

I.R. (thin film): 2932, 2859, 1714, 1653, 1621, 1548, 1513, 1471, 1398, 1285, 1085, 1028 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.39 (br d, 1H, *J* = 7.4 Hz, NH), 8.24 (s, 1H, H-ar), 7.10-6.90 (m, 4H, H-ar), 6.77 (d, 1H, *J* = 7.6 Hz, H-ar), 6.52 (d, 1H, *J* = 7.6 Hz, H-ar), 5.07 (d, 1H, *J* = 7.6 Hz, H-ar), 4.61-4.52 (m, 1H, H-5), 3.95 (t, 1H, *J* = 9.3 Hz, H-3), 3.83 (s, 3H, CH_3), 3.70-3.60 (m, 1H, H-3), 2.32 (s, 3H, CH_3), 2.29-2.24 (m, 1H, H-2), 1.98 (dd, 1H, *J* = 6.2, 13.3 Hz H-2), 1.82-1.10 (m, 6H, H-cy), 1.25-1.02 (m, 4H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 181.5 (C-a), 171.8 (C-b), 170.1 (C-c), 159.4 (C-ar), 141.2 (C-ar), 128.9 (C-ar), 127.8 (C-ar), 124.8 (C-ar), 121.0 (C-ar), 113.5 (C-ar), 109.5 (C-ar), 82.4 (C-4), 61.5 (C-1), 48.6 (C-5), 48.5 (C-3), 33.0 (C-2), 32.3 (C-cy), 32.1 (C-cy), 31.8 (C-cy), 25.8 (CH_3), 25.5 (C-cy).

1'-acetyl-*N*-cyclohexyl-2'-(3-nitrophenyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2'-carboxamide (III-34)



This compound was synthesized according to the general procedure **III-E**, using 1 mmol of Ugi adduct **III-28**. The desired product was isolated in 50 % yield (238 mg).
Mol. Wt.: 476.52, Nature: white solide.

HRMS: Calcd. for $C_{26}H_{28}N_4O_5$: 476.2060, Found : 476.2075.

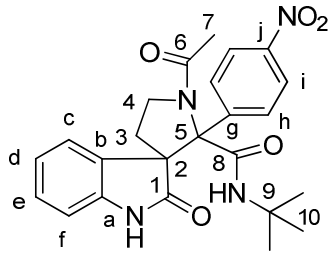
M.P. = 170-172 ^{o}C

I.R. (thin film): 3058, 2929, 2856, 1715, 1656, 1618, 1548, 1510, 1401, 1255, 1182, 1035 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.13 (br s, 1H, NH), 8.25 (dd, 1H, *J* = 1.6, 8.6 Hz H-ar), 8.0 (s, 1H, H-ar), 7.45 (br s, 1H, NH), 7.07 (t, 1H, *J* = 7.6 Hz, H-ar), 6.81 (d, 1H, *J* = 7.6 Hz, H-ar), 6.49 (t, 1H, *J* = 7.6 Hz, H-ar), 4.93 (d, 1H, *J* = 7.6 Hz, H-ar), 4.70-4.57 (m, 1H, H-5), 4.12-4.00 (m, 1H, H-3), 3.73-3.64 (m, 1H, H-3), 2.39 (s, 3H, CH_3), 2.28-2.18 (m, 1H, H-2), 2.08 (dd, 1H, *J* = 6.0, 13.4 Hz H-2), 1.85-1.68 (m, 2H, H-cy), 1.64-1.42 (m, 3H, H-cy), 1.25-1.02 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 180.5 (C-a), 172.2 (C-b), 169.2 (C-c), 148.1 (C-ar), 141.3 (C-ar), 139.4 (C-ar), 129.7 (C-ar), 128.4 (C-ar), 127.9 (C-ar), 124.2 (C-ar), 123.4 (C-ar), 122.8 (C-ar), 121.1 (C-ar), 110.0 (C-ar), 81.1 (C-4), 61.3 (C-1), 48.8 (C-5), 48.5 (C-3), 32.3 (C-2), 32.2 (C-cy), 31.7 (C-cy), 25.6 (CH_3), 25.4 (C-cy), 24.4 (C-cy), 24.3 (C-cy) .

1'-acetyl-*N*-(*ter*-buyl)-2'-(4-nitrophenyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2'-carboxamide. (III-35)



This compound was synthesized according to the general procedure **III-E**, using 0.9 mmol of Ugi adduct **III-29**. The desired product was isolated in 21 % yield (79 mg).
Mol. Wt.: 450.49, Nature: oil.

HRMS: Calcd. for $C_{24}H_{26}N_4O_5$: 450.1903, Found : 450.1915.
I.R. (thin film): 3232, 3068, 2978, 1712, 1666, 1612, 1520, 1471, 1394, 1349 cm^{-1}
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.03 (br s, 1H, NH), 8.35-8.10 (m, 3H, H-h, NH), 7.33 (d, 2H, *J* = 8.6 Hz, H-i), 7.05 (t, 1H, *J* = 7.7 Hz, H-e), 6.78 (d, 1H, *J* = 7.7 Hz, H-f), 6.51 (t, 1H, *J* = 7.7 Hz, H-d), 4.99 (d, 1H, *J* = 7.7 Hz, H-c), 4.66-4.56 (m, 1H, H-4), 4.02 (t, 1H, *J* = 9.3 Hz, H-4), 2.38 (s, 3H, H-7), 2.25-2.15 (m, 1H, H-3), 2.65 (dd, 1H, *J* = 6.0, 13.4 Hz, H-3), 1.25 (s, 9H, H-10).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 180.6 (C-1), 172.1 (C-8), 169.0 (C-6), 147.6 (C-g), 144.2 (C-j), 141.1 (C-a), 128.3 (C-e, C-h), 128.1 (C-b), 124.0 (C-c), 123.6 (C-d), 121.3 (C-i), 110.1 (C-f), 82.3 (C-5), 61.4 (C-2), 51.3 (C-9), 48.4 (C-4), 32.6 (C-3), 28.1 (C-10), 25.6 (C-7).

Experimental Part

Chapter 4

General Procedures:

General Procedure IV-A: (Synthesis of Tetrazole derivatives).

To a well-stirred solution of isocyanide (1.0 equiv.) in acetonitrile, was added bromine (1.0 equiv.), and after 5 minutes at room temperature, sodium azide (1.5 equiv.) was added. The resulting mixture was stirred at 65 °C for 2h. after completion of reaction (checked by TLC analysis), the acetonitrile was removed and toluene was added under argon atmosphere, potassium carbonate (3.0 equiv.) was added and after for 5 minutes at room temperature, boronic acid (1.5 equiv.), and *tetrakis*(triphenylphosphine) palladium (5 mole%) were added. The resulting mixture was stirred under argon atmosphere at 110 °C for 18 h. It was then cooled to room temperature, filtered off and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (diethyl ether: petroleum ether) to afford the corresponding product.

General Procedure IV-B: (Synthesis of bromotriazole derivatives).

To a well-stirred solution of isocyanide (1.0 equiv) in dichloromethane, was added bromine (1.0 equiv), and after 5 minutes at room temperature, a solution of aryl tetrazole (1.0 equiv.) and triethyl amine (2.0 equiv.) in dichloromethane was added. The resulting mixture was stirred at room temperature for 45 minutes, after completion of reaction (checked by TLC analysis), the dichloromethane was removed and toluene was added under argon atmosphere. The resulting solution refluxed for 2.5 h, the flask was cooled to room temperature. Toluene concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (diethyl ether: petroleum ether), to afford the corresponding product.

General Procedure IV-C: (Synthesis of 1,2,4-triazole derivatives)

To a well-stirred solution of 3-bromo-1,2,4-triazole (1.0 equiv) in toluene (0.2 M) were successively added potassium carbonate (3.0 equiv.), aryl boronic acid (2.0 equiv.) and *tetrakis*(triphenylphos-phine) palladium (5 mol %). The resulting mixture was stirred under argon atmosphere at 110 °C for 18 h. It was cooled to room temperature, filtered off and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (diethyl ether : petroleum ether), to afford the corresponding product.

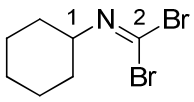
General Procedure IV-D: (2-Bromo-5-alkoxy-4-substituted oxazole.)

To a solution of 2-substituted-2-isocyano-glycinate (1.0 equiv.) in dichloromethane (0.2 M), was added bromine (1.0 equiv.), it was stirred for 2 minutes at room temperature. The resulting mixture was then cooled at 0 °C before dropwise addition of DBU (2.5 equiv.) and stirred at -5 °C to 0 °C for an additional 10 minutes. After completion of the reaction (checked by TLC analysis), dichloromethane was evaporated. The crude residue was purified by flash chromatography on silica gel using a 1:9 mixture of diethyl ether/petroleum ether as eluant and the volatiles were evaporated under reduced pressure at 25-30 °C to give corresponding bromo oxazole.

General procedure IV-E: (Suzuki coupling involving 2-bromo-5-alkoxy oxazole.)

5-alkoxy-2,4-disubstituted oxazole: To a well-stirred solution of 2-bromo-5-alkoxy-4-aryl oxazole (1.0 equiv.) in acetonitrile (0.2 M) under argon atmosphere, were successively added potassium carbonate (3.0 equiv.), aryl boronic acid (2.0 equiv.) and *tetrakis*(triphenylphosphine) palladium (5 mol %). The resulting mixture was stirred under argon atmosphere at 55-60 °C for 16 h. It was then cooled at room temperature, filtered off and the volatiles were evaporated. The crude residue was purified by flash chromatography on silica gel (diethyl ether: petroleum ether) to afford corresponding 5-alkoxy-2,4-disubstituted oxazole.

Dibromocyclohexyl isocyanide (IV-1)



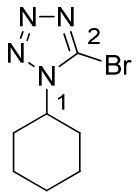
To a well-stirred solution of cyclohexyl isocyanide (109 mg, 1.0 mmol) in acetonitrile (1M), was added bromine (160 mg, 1.0 mmol.), and after 5 minutes at room temperature, concentrated under reduced pressure to afford dibromocyclohexyl isocyanide (269 mg, 100 %).

Mol. Wt.: 268.98, Nature: colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.44-3.33 (m, 1H, H-1), 1.84-1.70 (m, 4H, H-cy), 1.67-1.57 (m, 1H, H-cy), 1.56-1.44 (m, 2H, H-cy), 1.41-1.20 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 86.4 (C-2), 68.4 (C-1), 31.9 (C-cy), 25.2 (C-cy), 24.1 (C-cy).

5-Bromo-1-cyclohexyl-1*H*-tetrazole (IV-2)



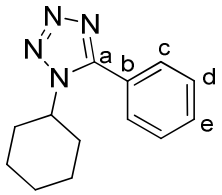
To a well-stirred solution of cyclohexyl isocyanide (109 mg, 1.0 mmol.) in acetonitrile (0.5M), was added bromine (160 mg, 1.0 mmol), and after 5 minutes at room temperature, sodium azide (98 mg, 1.5 mmol) was added. The resulting mixture was stirred at room temperature for 1h. after completion of reaction (checked by TLC analysis), the acetonitrile was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (diethyl ether: petroleum ether) to afford the corresponding product IV-27 (231 mg, 100 %).

Mol. Wt.: 231.09, Nature: colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.34-3.23 (m, 1H, H-1), 2.06-1.84 (m, 6H, H-cy), 1.76-1.67 (m, 1H, H-cy), 1.45-1.20 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 132.0 (C-2), 59.2 (C-1), 32.2 (C-cy), 25.1 (C-cy), 24.7 (C-cy).

1-Cyclohexyl-5-phenyl-1*H*-tetrazole (IV-3)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 97 % yield (220 mg).

Mol. Wt.: 228.23, Nature: White Solid.

HRMS: Calcd. for $C_{13}H_{16}N_4$: 228.1375, Found : 228.1364.

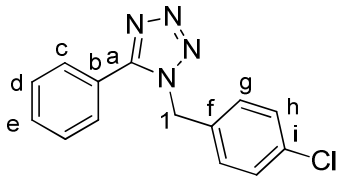
M.P. = 129-130 °C.

I.R. (thin film): 3065, 2937, 2857, 1454, 1391, 1162, 1117, 1006 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.53 (m, 5H, Ar-H), 4.34 (tt, 1H, *J* = 4.2, 11.3 Hz, H-cy), 2.16-1.90 (m, 6H, H-cy), 1.77-1.70 (m, 1H, H-cy), 1.39-1.29 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 153.6 (C-a), 131.1 (C-e), 129.3, 128.8 (C-d and C-c), 124.4 (C-b), 58.2 (C-cy), 33.2 (C-cy), 25.3 (C-cy), 24.7 (C-cy).

1-(4-Chlorobenzyl)-5-phenyl-1*H*-tetrazole (IV-4)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 64 % yield (172 mg).

Mol. Wt.: 270.72, Nature: Pale yellow oil.

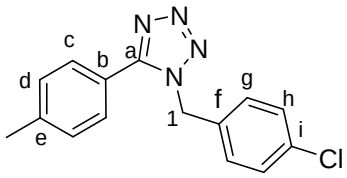
HRMS: Calcd. for $C_{14}H_{11}ClN_4$: 270.0672, Found : 270.0672.

I.R. (thin film): 3065, 3035, 2919, 2850, 1544, 1495, 1470, 1455, 1410, 1277, 1096, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.48 (m, 5H, Ar-H), 7.30 (d, 2H, *J* = 8.5 Hz, H-h), 7.08 (d, 2H, *J* = 8.5 Hz, H-g), 5.58 (s, 2H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 154.6 (C-a), 134.7 (C-f), 132.2 (C-i), 131.4 (C-e), 129.3 (C-h), 129.2, 128.7 (C-d and C-c), 128.6 (C-g), 123.4 (C-b), 50.3 (C-1).

1-(4-Chlorobenzyl)-5-phenyl-1*H*-tetrazole (IV-5)



This compound was synthesized according to the general procedure IV-A, using 0.43 mmol of isocyanide. The desired product was isolated in 86 % yield (105 mg).

Mol. Wt.: 284.74, Nature: White solid.

HRMS: Calcd. for $C_{15}H_{13}ClN_4$: 284,0829, Found : 284.0823.

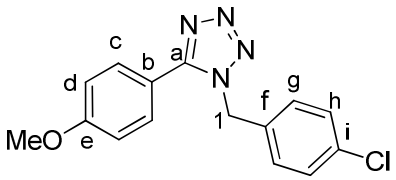
M.P. = 100-101 °C

I.R. (thin film): 3044, 2957, 2919, 2864, 1492, 1492, 1475, 1450, 1412, 1266, 1090, 1013 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, 2H, *J* = 8.1 Hz, H-c), 7.35-7.29 (m, 4H, H-d, H-h/H-g), 7.10 (d, 2H, *J* = 8.4 Hz, H-g/H-h), 5.57 (s, 2H, H-1), 2.43 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 154.7 (C-a), 142.0 (C-e), 134.8 (C-f), 132.4 (C-i), 130.0, 129.4, 128.6 (C-g, C-h, C-d and C-c), 120.5 (C-b), 50.6 (C-1), 21.5 (CH_3).

1-(4-Chlorobenzyl)-5-(4-methoxyphenyl)-1*H*-tetrazole (IV-6)



This compound was synthesized according to the general procedure IV-A, using 0.43 mmol of isocyanide. The desired product was isolated in 70 % yield (90 mg).

Mol. Wt.: 300.74, Nature: Pale Yellow solid.

HRMS: Calcd. for $C_{15}H_{13}ClN_4O$: 300.0778, Found : 300.0783.

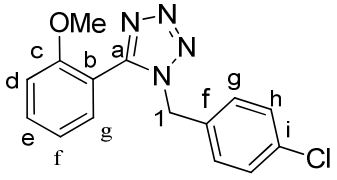
M.P. = 94-95 °C.

I.R. (thin film): 3009, 2961, 2933, 2830, 1610, 1478, 1450, 1301, 1260, 1180, 1096, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 2H, *J* = 8.8 Hz, H-c), 7.32 (d, 2H, *J* = 8.4 Hz, H-h/H-g), 7.10 (d, 2H, *J* = 8.4 Hz, H-g/H-h), 7.00 (d, 2H, *J* = 8.8 Hz, H-d), 5.57 (s, 2H, H-1), 3.86 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.9 (C-e), 154.4 (C-a), 134.7 (C-f), 132.4 (C-i), 130.3, 129.4, 128.5 (C-h, C-g, C-c), 115.4 (C-b), 114.7 (C-d), 55.5 (OCH_3), 50.7 (C-1).

1-(4-Chlorobenzyl)-5-(2-methoxyphenyl)-1*H*-tetrazole (IV-7)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 17 % yield (51 mg).

Mol. Wt.: 300.74, Nature: Oil.

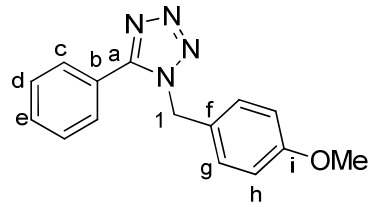
HRMS: Calcd. for $C_{15}H_{13}ClN_4O$: 300.0778, Found : 300.0778.

I.R. (thin film): 3070, 3006, 2957, 2926, 2853, 1610, 1540, 1481, 1440, 1409, 1256, 1092, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (dt, 1H, *J* = 1.6, 7.5 Hz, H-e), 7.33 (dd, 1H, *J* = 1.6, 7.6 Hz, H-c), 7.22 (d, 2H, *J* = 8.4 Hz, H-k), 7.06 (d, 1H, *J* = 7.5 Hz, H-d), 7.01 (d, 1H, *J* = 8.4 Hz, H-b), 6.98 (d, 2H, *J* = 8.4 Hz, H-j), 5.04 (s, 2H, H-1), 3.70 (s, 3H, $-OCH_3$).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 156.7 (C-a), 152.8 (C-g), 134.4 (C-i), 133.1 (C-c), 132.3 (C-l), 131.7 (C-e), 129.2 (C-j), 128.9 (C-k), 121.2 (C-d), 112.8 (C-f), 111.2 (C-b), 55.5 ($-OCH_3$), 50.8 (C-1).

1-(4-Methoxybenzyl)-5-phenyl-1*H*-tetrazole (IV-8)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 82 % yield (51 mg).

Mol. Wt.: 266.30, Nature: Oil.

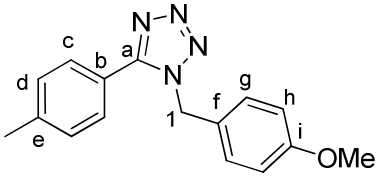
HRMS: Calcd. for $C_{15}H_{14}N_4O$: 266.1168, Found : 266.1168.

I.R. (thin film): 3065, 3006, 2961, 2933, 2839, 1610, 1517, 1457, 1402, 1250, 1183, 1110, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.49 (m, 5H, H-c, H-d, H-e), 7.09 (d, 2H, *J* = 8.7 Hz, H-g), 6.85 (d, 2H, *J* = 8.7 Hz, H-h), 5.54 (s, 2H, H-1), 3.78 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 159.7 (C-i), 154.4 (C-a), 131.2 (C-e), 129.3 (C-f), 129.1, 128.8, 128.7 (C-c, C-d, C-g), 123.8 (C-b), 114.4 (C-h), 55.3 (CH_3), 50.9 (C-1).

1-(4-Methoxybenzyl)-5-(p-tolyl)-1*H*-tetrazole (IV-9)



This compound was synthesized according to the general procedure IV-C, using 0.5 mmol of isocyanide. The desired product was isolated in 82 % yield (115 mg).

Mol. Wt.: 280.32, Nature: White solid.

HRMS: Calcd. for $C_{16}H_{16}N_4O$: 280.1324, Found : 280.1335.

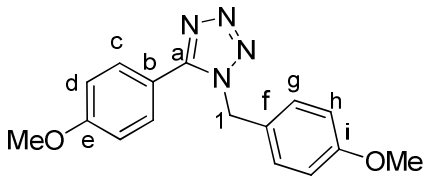
I.R. (thin film): 3037, 3006, 2981, 2937, 2839, 1613, 1516, 1478, 1457, 1426, 1301, 1252, 1180, 1110, 1033 cm^{-1}

M.P. = 75-76 °C**.**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 2H, *J* = 8.1 Hz, H-c), 7.31 (d, 2H, *J* = 8.1 Hz, H-d), 7.11 (d, 2H, *J* = 8.6 Hz, H-g), 6.86 (d, 2H, *J* = 8.6 Hz, H-h), 5.53 (s, 2H, H-1), 3.79 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 159.7 (C-i), 154.5 (C-a), 141.7 (C-e), 129.8 (C-g), 128.7 (C-d and C-c), 126.0 (C-f), 120.8 (C-b), 114.4 (C-h), 55.3 (OCH_3), 50.9 (C-1), 21.5 (CH_3).

1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-1*H*-tetrazole (IV-10)



This compound was synthesized according to the general procedure IV-A, using 0.5 mmol of isocyanide. The desired product was isolated in 41 % yield (60 mg).

Mol. Wt.: 296.32, Nature: White solid.

HRMS: Calcd. for $C_{16}H_{16}N_4O_2$: 296.1273, Found : 296.1273.

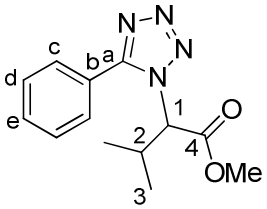
M.P. = 122-123 °C.

I.R. (thin film): 3075, 3009, 2964, 2937, 2839, 1613, 1516, 1478, 1461, 1447, 1301, 1252, 1179, 1110 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, 2H, *J* = 8.8 Hz, H-c), 7.11 (d, 2H, *J* = 8.7 Hz, H-g), 7.00 (d, 2H, *J* = 8.8 Hz, H-d), 6.86 (d, 2H, *J* = 8.7 Hz, H-h), 5.53 (s, 2H, H-1), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.8 (C-e), 159.7 (C-i), 154.3 (C-a), 130.4 (C-g), 128.6 (C-c), 126.0 (C-f), 115.8 (C-b), 114.6, 114.4 (C-h, C-d), 55.4 (OCH_3), 55.3 (OCH_3), 50.8 (C-1).

Methyl 3-methyl-2-(5-phenyl-1*H*-tetrazol-1-yl)butanoate (IV-11)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 62 % yield (160 mg).

Mol. Wt.: 260.29, Nature: Pale yellow oil.

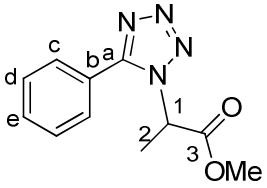
HRMS: Calcd. for $C_{13}H_{16}N_4O_2$: 260.1273, Found : 260.1279.

I.R. (thin film): 2968, 2937, 2881, 1749, 1457, 1426, 1395, 1280, 1208, 1009 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.51 (m, 5H, Ar-H), 4.76 (d, 1H, *J* = 8.7 Hz, H-1), 3.77 (s, 3H, OCH_3), 2.92-2.79 (m, 1H, H-2), 0.97 (d, 3H, *J* = 6.8 Hz, H-3), 0.80 (d, 3H, *J* = 6.8 Hz, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.4 (C-4), 155.6 (C-a), 131.4 (C-e), 129.3, 129.0 (C-d and C-c), 123.4 (C-b), 66.2 (C-1), 53.1 (-OCH_3), 30.9 (C-2), 19.2 (C-3), 18.7(C-3).

Methyl 2-(5-phenyl-1*H*-tetrazol-1-yl)propanoate (IV-12)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 67 % yield (156 mg).

Mol. Wt.: 232.24, Nature: oil.

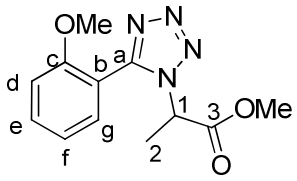
HRMS: Calcd. for $C_{11}H_{12}N_4O_2$: 232.096, Found : 232.0970.

I.R. (thin film): 3062, 3009, 2957, 1749, 2853, 1610, 1540, 1481, 1440, 1409, 1256, 1092, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.53 (m, 5H, Ar-H), 5.25 (q, 1H, *J* = 7.3 Hz, H-1), 3.76 (s, 3H, OCH_3), 1.95 (d, 3H, *J* = 7.3 Hz, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.5 (C-3), 154.8 (C-a), 131.5 (C-e), 129.4, 128.9 (C-c and C-d), 123.6 (C-b), 56.0 (C-1), 53.5 (-OCH_3), 17.4 (C-2).

Methyl 2-(5-(2-methoxyphenyl)-1*H*-tetrazol-1-yl)propanoate (IV-13)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 15 % yield (40 mg).

Mol. Wt.: 262.26, Nature: oil.

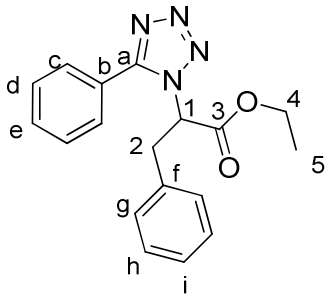
HRMS: Calcd. for $C_{12}H_{14}N_4O_3$, : 262.1066, Found : 262.1061.

I.R. (thin film): 3006, 2954, 2850, 1752, 1610, 1478, 1457, 1290, 1260, 1228, 1158, 1075, 1020 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (dt, 1H, *J* = 1.6, 8.4 Hz, H-e), 7.51 (dd, 1H, *J* = 1.6, 7.5 Hz, H-g), 7.12 (t, 1H, *J* = 7.6 Hz, H-f), 7.03 (d, 1H, *J* = 8.4 Hz, H-d), 5.04 (q, 1H, *J* = 7.3 Hz, H-1), 3.78 (s, 3H, Ar-OCH_3), 3.68 (s, 3H, -OCH_3), 1.92 (d, 3H, *J* = 7.3 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.8 (C-3), 156.5 (C-c), 153.0 (C-a), 133.2, 132.1 (C-g and C-e), 121.5 (C-f), 112.5 (C-b), 111.3 (C-d), 56.1 (C-1), 55.6 (-OCH_3), 53.0 (-OCH_3), 17.3 (C-2).

Ethyl 3-phenyl-2-(5-phenyl-1*H*-tetrazol-1-yl)propanoate (IV-14)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 36 % yield (120 mg).

Mol. Wt.: 322.36, Nature: Pale yellow oil.

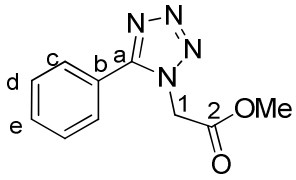
HRMS: Calcd. for $C_{18}H_{18}N_4O_2$: 322.1430, Found : 322.1426.

I.R. (thin film): 3065, 3030, 2990, 2944, 1749, 1771, 1454, 1402, 1370, 1273, 1231, 1183, 1096, 1013 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.38 (t, 2H, *J* = 7.7 Hz, Ar-H), 7.20-7.13 (m, 3H, Ar-H), 6.99 (d, 2H, *J* = 7.7 Hz, Ar-H), 6.86 (dd, 2H, *J* = 1.5, 7.7 Hz, Ar-H), 5.13 (dd, 1H, *J* = 7.2, 8.5 Hz, H-1), 4.26 (q, 2H, *J* = 7.1 Hz, H-4), 3.66 (d, 2H, *J* = 8.0 Hz, H-2), 1.25 (t, 3H, *J* = 7.1 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.8 (C-3), 155.9 (C-a), 135.0 (C-f), 131.1 (C-e), 129.0, 128.9, 128.8, 128.7 (C-c, C-d, C-g and C-h), 127.5 (C-i), 123.2 (C-b), 62.9 (C-4), 62.0 (C-1), 37.3 (C-2), 14.0 (C-5).

Methyl 2-(5-phenyl-1*H*-tetrazol-1-yl)acetate (IV-15)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 70 % yield (153 mg).

Mol. Wt.: 218.21, Nature: oil.

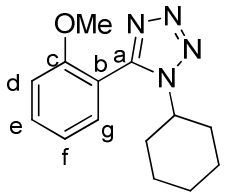
HRMS: Calcd. for $C_{10}H_{10}N_4O_2$: 218.0804, Found : 218.0801.

I.R. (thin film): 2958, 1753, 1458, 1444, 1367, 1225, 1183, 1110 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.62 (m, 2H, Ar-H), 7.61-7.52 (m, 3H, Ar-H), 5.21 (s, 2H, H-1), 3.81 (s, 3H, -OCH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 186.0 (C-2), 155.3 (C-a), 131.7 (C-e), 129.5, 128.7 (C-c and C-d), 123.3 (C-b), 53.5 (-OCH_3), 48.8 (C-1).

1-cyclohexyl-5-(2-methoxyphenyl)-1*H*-tetrazole (IV-16)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 70 % yield (181 mg).

Mol. Wt.: 258.32, Nature: White solid.

HRMS: Calcd. for $C_{14}H_{18}N_4O$: 258.1481, Found : 258.1485.

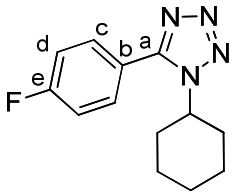
M.P. = 98-99 °C.

I.R. (thin film): 3009, 2864, 1610, 1474, 1450, 1405, 1287, 1256, 1162, 1110, 1023 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (dt, 1H, *J* = 1.6, 8.5 Hz, H-e), 7.40 (dd, 1H, *J* = 1.6, 7.5 Hz, H-g), 7.08 (t, 1H, *J* = 7.5 Hz, H-f), 7.03 (d, 1H, *J* = 8.5 Hz, H-d), 4.06-3.97 (m, 1H, H-cy), 3.78 (s, 3H, -OCH_3), 2.04-1.90 (m, 4H, H-cy), 1.88-1.81 (m, 2H, H-cy), 1.69-1.63 (m, 1H, H-cy), 1.30-1.19 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 156.7 (C-c), 151.5 (C-a), 132.7 (C-e), 131.7 (C-g), 121.1 (C-f), 113.3 (C-b), 111.2 (C-d), 58.3 (C-cy), 55.4 (-OCH_3), 32.8 (C-cy), 25.2 (C-cy), 24.7 (C-cy).

1-Cyclohexyl-5-(4-fluorophenyl)-1*H*-tetrazole (IV-17)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 41 % yield (102 mg).

Mol. Wt.: 246.28, Nature: White solid.

HRMS: Calcd. for $C_{13}H_{15}FN_4$: 246.1281, Found : 246.1279.

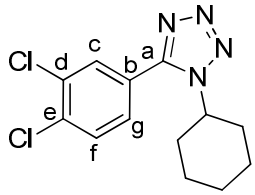
M.P. = 108-109 °C.

I.R. (thin film): 3065, 2930, 2864, 1610, 1582, 1474, 1454, 1429, 1266, 1231, 1158, 1096, 1002 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.59 (m, 2H, H-c), 7.27 (t, 2H, *J* = 8.6 Hz, H-d), 4.27 (tt, 1H, *J* = 4.3, 11.6 Hz, H-cy), 2.16-1.90 (m, 6H, H-cy), 1.78-1.72 (m, 1H, H-cy), 1.38-1.29 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 164.3 (d, *J* = 252.6 Hz, C-e), 152.8 (C-a), 131.0 (d, *J* = 8.8 Hz, C-c), 120.5 (d, *J* = 3.4 Hz, C-b), 116.7 (d, *J* = 22.1 Hz, C-d), 58.3 (C-cy), 33.2 (C-cy), 25.2 (C-cy), 24.7 (C-cy).

1-Cyclohexyl-5-(3,4-dichlorophenyl)-1*H*-tetrazole (IV-18)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 23 % yield (68 mg).

Mol. Wt.: 297.18, Nature: Light pink oil**.**

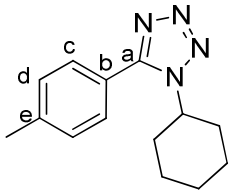
HRMS: Calcd. for $C_{13}H_{14}Cl_2N_4$: 296.0596, Found : 296.0602.

I.R. (thin film): 2938, 2860, 1540, 1450, 1419, 1374, 1270, 1186, 1096 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, 1H, *J* = 2.0 Hz, H-c), 7.67 (d, 1H, *J* = 8.3 Hz, H-f), 7.44 (dd, 1H, *J* = 2.0, 8.3 Hz, H-g), 4.32-4.22 (m, 1H, H-cy), 2.14-1.93 (m, 6H, H-cy), 1.79-1.73 (m, 1H, H-cy), 1.45-1.30 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 151.8 (C-a), 135.9, 133.9 (C-d and C-e), 131.4, 130.8 (C-f, C-c), 127.7 (C-g), 124.2 (C-b), 58.6 (C-cy), 33.2 (C-cy), 25.2 (C-cy), 24.7 (C-cy).

1-Cyclohexyl-5-(p-tolyl)-1*H*-tetrazole (IV-19)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 98 % yield (238 mg).

Mol. Wt.: 242.32, Nature: White solid.

HRMS: Calcd. for $C_{14}H_{18}N_4$: 242.1531. Found: 242.1518.

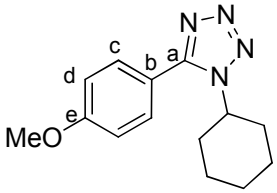
M.P. = 130-131 °C.

I.R. (thin film): 2944, 2923, 2857, 1478, 1457, 1409, 1395, 1332, 1277, 1096, 1006 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 2H, *J* = 8.0 Hz, H-c), 7.37 (d, 2H, *J* = 8.0 Hz, H-d), 4.32 (tt, 1H, *J* = 4.2, 11.5 Hz, H-cy), 2.46 (s, 3H, CH_3), 2.12-1.90 (m, 6H, H-cy), 1.79-1.70 (m, 1H, H-cy), 1.39-1.29 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 153.7 (C-a), 141.5 (C-e), 130.0 (C-d), 128.7 (C-c), 121.4 (C-b), 58.1 (C-cy), 33.2 (C-cy), 25.3 (C-cy), 24.8 (C-cy), 21.5 (CH_3).

1-Cyclohexyl-5-(4-methoxyphenyl)-1*H*-tetrazole (IV-20)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 90 % yield (232 mg).

Mol. Wt.: 258.32, Nature: White solid.

HRMS: Calcd. for $C_{14}H_{18}N_4O$: 258.1481, Found : 258.1477.

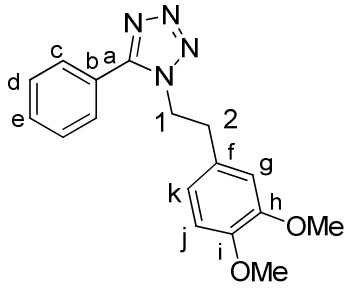
M.P. = 118-119 °C.

I.R. (thin film): 3058, 2940, 2864, 1613, 1481, 1481, 1461, 1391, 1297, 1260, 1178, 1096, 1023, 1002 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, 2H, *J* = 8.1 Hz, H-c), 7.07 (d, 2H, *J* = 8.1 Hz, H-d), 4.31 (tt, 1H, *J* = 4.1, 11.5 Hz, H-cy), 3.90 (s, 3H, CH_3), 2.15-1.90 (m, 6H, H-cy), 1.79-1.69 (m, 1H, H-cy), 1.42-1.29 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.6 (C-e), 153.5 (C-a), 130.3 (C-c), 116.4 (C-b), 114.7 (C-d), 58.1 (C-cy), 55.5 (OCH_3), 33.2 (C-cy), 25.3 (C-cy), 24.8 (C-cy).

1-(3,4-Dimethoxyphenethyl)-5-phenyl-1*H*-tetrazole (IV-21)



This compound was synthesized according to the general procedure IV-A, using 1.0 mmol of isocyanide. The desired product was isolated in 12 % yield (37 mg).

Mol. Wt.: 310.35, Nature: Oil.

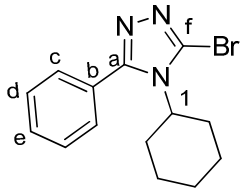
HRMS: Calcd. for $C_{17}H_{18}N_4O_2$: 310.1430, Found : 310.1430.

I.R. (thin film): 3062, 3003, 2954, 2926, 2836, 1516, 1461, 1419, 1263, 1235, 1155, 1141, 1028 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (t, 1H, *J* = 7.5 Hz, H-Ph), 7.41 (t, 2H, *J* = 7.5 Hz, H-Ph), 7.22 (d, 2H, *J* = 7.5 Hz, H-Ph), 6.64 (d, 1H, *J* = 8.1 Hz, H-j), 6.41 (dd, 1H, *J* = 1.8, 8.1 Hz, H-k), 6.27 (d, 1H, *J* = 1.8 Hz, H-g), 4.60 (t, 2H, *J* = 6.8 Hz, H-1), 3.81 (s, 3H, -OCH_3), 3.66 (s, 3H, -OCH_3), 3.14 (t, 2H, *J* = 6.8 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 154.9 (C-a), 148.9, 148.1(C-h and C-i), 130.8 (C-e), 128.8, 128.6 (C-c and C-d), 128.3 (C-f), 123.6 (C-b), 120.6 (C-k), 111.2 (C-g and C-j), 55.8 (-OCH_3), 55.6 (-OCH_3), 49.2 (C-1), 35.7 (C-2).

3-Bromo-4-cyclohexyl-5-phenyl-4*H*-1,2,4-triazole (IV-22)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 72 % yield (220 mg).

Mol. Wt.: 306.20, Nature: White Solid.

HRMS: Calcd. for $C_{14}H_{16}BrN_3$: 305.0528, Found : 305.0528.

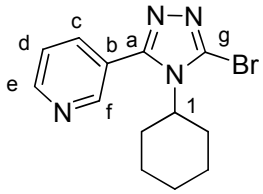
M.P. = 129-130 °C.

I.R. (thin film): 3059, 2938, 2863, 1465, 1382, 1170, 1135, 1012 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27-8.22 (m, 2H, Ar-H), 7.54-7.49 (m, 3H, Ar-H), 3.78-3.68 (m, 1H, H-1), 1.94-1.82 (m, 4H, H-cy), 1.76-1.64 (m, 3H, H-cy), 1.50-1.28 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 164.8 (C-a), 131.1 (C-e), 129.3 (C-d), 127.5 (C-c), 126.2 (C-b), 114.7 (C-f), 65.9 (C-1), 32.0 (C-cy), 25.3 (C-cy), 24.2 (C-cy).

3-(5-Bromo-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl)pyridine (IV-23)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 65 % yield (200 mg).

Mol. Wt.: 307.19, Nature: oil.

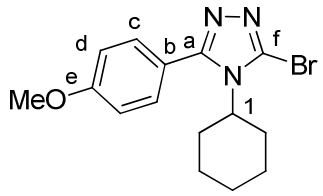
HRMS: Calcd. for $C_{13}H_{15}BrN_4$: 306.0480, Found: 306.0485.

I.R. (thin film): 3135, 3059, 1615, 1525, 1482, 1309, 1268, 1068, cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.47 (s, 1H, H-f), 8.76 (d, 1H, *J* = 4.6 Hz, H-e), 8.52 (d, 1H, *J* = 7.8 Hz, H-c), 7.50-7.44 (m, 1H, H-d), 3.80-3.69 (m, 1H, H-1), 1.97-1.83 (m, 4H, H-cy), 1.77-1.65 (m, 3H, H-cy), 1.50-1.25 (m, 4H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 153.9 (C-a), 151.4 (C-f), 149.5 (C-e), 137.0 (C-c), 128.4 (C-g), 123.8 (C-b), 123.6 (C-d), 58.5 (C-1), 31.3 (C-cy), 25.6 (C-cy), 24.5 (C-cy).

3-Bromo-4-cyclohexyl-5-(4-methoxyphenyl)-4*H*-1,2,4-triazole (IV-24)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 66 % yield (221 mg).

Mol. Wt.: 336.23, Nature: oil.

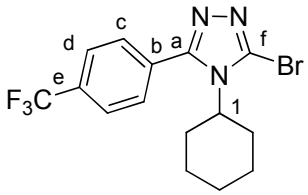
HRMS: Calcd. for $C_{15}H_{18}BrN_4O$: 335.0633, Found: 335.0637.

I.R. (thin film): 2938, 1620, 1535, 1477, 1339, 1272, 1070 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, 2H, *J* = 8.6 Hz, H-c), 7.01 (d, 2H, *J* = 8.6 Hz, H-d), 3.88 (s, 3H, CH_3), 3.77-3.65 (m, 1H, H-1), 1.95-1.80 (m, 4H, H-cy), 1.75-1.62 (m, 3H, H-cy), 1.50-1.25 (m, 4H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.1 (C-e), 156.8 (C-a), 130.8 (C-c), 119.4 (C-f), 114.2 (C-d), 58.0 (C-1), 55.4 (CH_3), 31.2 (C-cy), 25.8 (C-cy), 24.7 (C-cy).

3-Bromo-4-cyclohexyl-5-(4-(trifluoromethyl)phenyl)-4*H*-1,2,4-triazole (IV-25)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 27 % yield (105 mg).

Mol. Wt.: 374.20, Nature: oil.

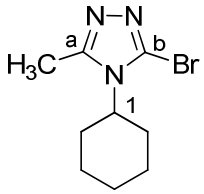
HRMS: Calcd. for $C_{15}H_{15}BrF_3N_3$: 373.0401, Found: 373.0402.

I.R. (thin film): 2920, 1615, 1534, 1468, 1342, 1260, 1071 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, 2H, *J* = 7.2 Hz, H-c), 7.62 (d, 2H, *J* = 7.2 Hz, H-d), 4.16-4.00 (m, 1H, CH_3), 2.24-2.06 (m, 2H, H-cy), 1.90-1.77 (m, 4H, H-cy), 1.70-1.61 (m, 1H, H-cy), 1.30-1.10 (m, 4H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 155.4 (C-a), 132.3 (q, *J* = 33.1 Hz, C-e), 130.9 (C-b), 129.8 (C-c), 128.0 (C-f), 125.8 (d, *J* = 3.5 Hz C-d), 123.5 (q, *J* = 273.0 Hz, CF_3), 58.4 (C-1), 31.2 (C-cy), 25.6 (C-cy), 24.6 (C-cy).

3-Bromo-4-cyclohexyl-5-methyl-4*H*-1,2,4-triazole (IV-26)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 10 % yield (25 mg).

Mol. Wt.: 244.13, Nature: oil.

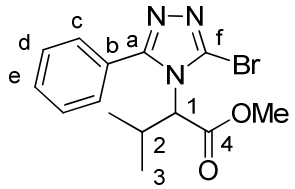
HRMS: Calcd. for $C_{15}H_{18}BrN_4O$: 243.0371, Found: 243.0379.

I.R. (thin film): 1618, 1538, 1470, 1336, 1275, 1060 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76-3.63 (m, 1H, H-1), 2.73 (s, 3H, CH_3), 1.90-1.74 (m, 4H, H-cy), 1.72-1.60 (m, 1H, H-cy), 1.62-1.30 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 152.0 (C-a), 113.8 (C-b), 65.0 (C-1), 32.3 (C-cy), 32.1 (C-cy), 23.8 (C-cy), 12.0 (C-cy).

Methyl 2-(3-bromo-5-phenyl-4*H*-1,2,4-triazol-4-yl)-3-methylbutanoate (IV-27)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 53 % yield (179 mg).

Mol. Wt.: 338.20, Nature: oil.

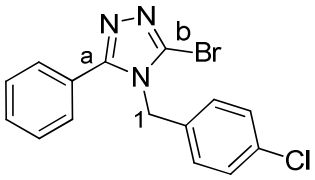
HRMS: Calcd. for $C_{14}H_{16}BrN_3O_2$: 337.0426, Found: 337.0429.

I.R. (thin film): 3030, 2990, 2944, 1742, 1632, 1540, 1454, 1370, 1273, 1231, 1180, 1080 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.50 (m, 5H, Ar-H), 4.47 (d, 1H, *J* = 10.9 Hz, H-1), 3.79 (s, 3H, CH_3), 2.85-2.72 (m, 1H, H-2), 1.06 (d, 3H, *J* = 6.6 Hz, H-3), 0.59 (d, 3H, *J* = 6.6 Hz, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.7 (C-4), 157.8 (C-a), 130.9 (C-Ar), 129.6 (C-Ar), 129.12 (C-Ar), 128.8 (C-b), 126.4 (C-c), 64.3 (C-1), 53.1 (CH_3), 28.8 (C-2), 21.3 (C-3), 18.9 (C-3).

3-Bromo-4-(4-chlorobenzyl)-5-phenyl-4*H*-1,2,4-triazole (IV-28)



This compound was synthesized according to the general procedure IV-B, using 1.0 mmol of isocyanide. The desired product was isolated in 60 % yield (208.8 mg).

Mol. Wt.: 348.63, Nature: oil.

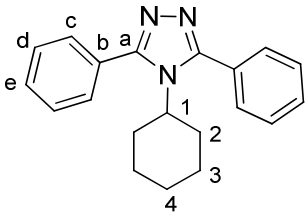
HRMS: Calcd. for $C_{15}H_{11}BrClN_3$: 346.9825, Found : 346.9818.

I.R. (thin film): 3065, 3035, 2920, 2850, 1621, 1535, 1471, 1277, 1096, 1016 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55-7.41 (m, 5H, Ar-H), 7.33 (d, 2H, *J* = 8.5 Hz, Ar-H), 6.93 (d, 2H, *J* = 8.5 Hz, Ar-H), 5.2 (s, 2H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 155.6 (C-a), 134.4 (C-Ar), 133.7 (C-Ar), 131.3 (C-Ar), 129.4 (C-Ar), 129.0 (C-Ar), 128.0 (C-Ar), 127.5 (C-Ar), 126.1 (C-Ar), 113.8 (C-b), 50.4 (C-1).

4-Cyclohexyl-3,5-diphenyl-4*H*-1,2,4-triazole (IV-29)



To a well-stirred solution of cyclohexyl isocyanide (0.124 mL, 1.0 mmol) in dichloromethane (0.5 M), was added bromine (160 mg, 1.0 mmol), and after 5 minutes at room temperature, a solution of phenyl tetrazole (146 mg, 1.0 mmol) and triethyl amine (0.278 mL, 2.0 mmol) in dichloromethane (0.5 M) was added. The resulting mixture was stirred at room temperature for 45 minutes, after completion of reaction (checked by TLC analysis), the dichloromethane was removed and toluene (0.2 M) was added under argon atmosphere. The resulting solution refluxed for 2.5 h, the flask was cooled to room temperature and potassium carbonate (414 mg, 3.0 mmol) was added. After 5 min phenyl boronic acid (366 mg, 3.0 mmol) and palladium (II) acetate (5 mole %), 1,1'-*bis*(diphenylphosphino) ferrocene (5 mole%) were added, and the resulting mixture was stirred under argon atmosphere at 110 °C for 18 h. It was cooled to room temperature, filtered off and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (diethyl ether:petroleum ether), to afford the corresponding product IV-53, (40 %, 121 mg).

Mol. Wt.: 303.4008, Nature: White Solid.

HRMS: Calcd. for $C_{20}H_{21}N_3$: 303.1735, Found : 303.1720.

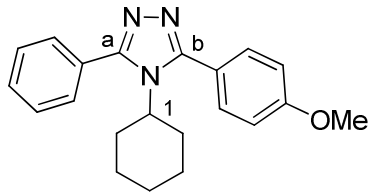
M.P. = 156-157 °C.

I.R. (thin film): 3058, 2937, 2857, 1471, 1450, 1381, 1343, 1270, 1075, 1026 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.48 (m, 10H, Ar-H), 4.03-3.92 (m, 1H, H-1), 1.89-1.82 (m, 2H, H-cy), 1.72-1.64 (m, 2H, H-cy), 1.62-1.46 (m, 3H, H-cy), 1.16-104 (m, 2H, H-cy), 0.86-0.74 (m, 1H, H-cy),

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 153.3 (C-a), 130.0 (C-Ar), 128.8, (C-b), 128.5 (C-Ar), 57.7 (C-cy), 33.3 (C-cy), 25.9 (C-cy), 24.8 (C-cy).

4-Cyclohexyl-3-(4-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazole (IV-30)



This compound was synthesized according to the general procedure IV-C, using 0.5 mmol of compound **IV-22**. The desired product was isolated in 96 % yield (161 mg).

Mol. Wt.: 333.43, Nature: oil.

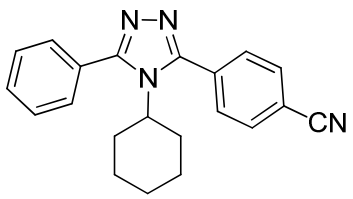
HRMS: Calcd. for $C_{21}H_{23}N_3O$: 333.1841, Found: 333.1842.

I.R. (thin film): 2937, 2857, 1469, 1455, 1383, 1350, 1272, 1080, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.42 (m, 7H, Ar-H), 7.00 (2H, d, *J* = 8.4 Hz, Ar-H), 4.03-3.92 (m, 1H, H-1), 3.86 (s, 3H, CH_3), 1.87-1.77 (m, 2H, H-cy), 1.72-1.61 (m, 2H, H-cy), 1.60-1.43 (m, 3H, H-cy), 1.15-103 (m, 2H, H-cy), 0.88-0.73 (m, 1H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 160.7 (C-Ar), 155.1 (C-a), 131.2 (C-Ar), 129.9 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 120.7 (C-Ar), 113.9 (C-Ar), 57.6 (C-cy), 55.3 (C-cy), 33.2 (C-cy), 25.9 (C-cy), 24.7 (C-cy).

4-(4-Cyclohexyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)benzonitrile (IV-31)



This compound was synthesized according to the general procedure IV-C, using 0.5 mmol of compound **IV-22**. The desired product was isolated in 65 % yield (107 mg).

Mol. Wt.: 328.41, Nature: oil.

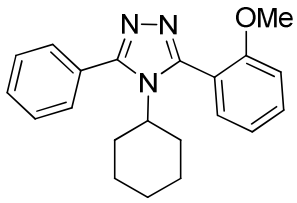
HRMS: Calcd. for $C_{21}H_{20}N_4$: 328.1688, Found: 328.1690.

I.R. (thin film): 2928, 2225, 1670, 1472, 1451, 1370, 1345, 1261, 1069, 1025 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60-7.45 (m, 7H, Ar-H), 7.19 (t, 2H, *J* = 8.3 Hz, Ar-H), 4.02-3.90 (m, 1H, H-1), 1.88-1.77 (m, 2H, H-cy), 1.73-1.62 (m, 2H, H-cy), 1.59-1.43 (m, 3H, H-cy), 1.17-101 (m, 2H, H-cy), 0.87-0.72 (m, 1H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 155.2 (C-Ar), 154.1 (C-Ar), 131.8 (C-Ar), 131.7 (C-Ar), 129.8 (C-Ar), 129.6 (C-Ar), 128.3 (C-Ar), 124.7 (C-Ar), 124.6 (C-Ar), 115.6 (CN), 115.4 (Ar-C), 57.5 (C-cy), 33.0 (C-cy), 25.6 (C-cy), 24.5 (C-cy).

4-Cyclohexyl-3-(2-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazole (IV-32)



This compound was synthesized according to the general procedure IV-C, using 0.5 mmol of compound **IV-22**. The desired product was isolated in 25 % yield (42 mg).

Mol. Wt.: 333.43, Nature: oil.

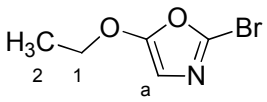
HRMS: Calcd. for $C_{21}H_{23}N_3O$: 333.1841, Found: 333.1855.

I.R. (thin film): 2929, 2835, 1470, 1465, 1388, 1354, 1265, 1078, 1035 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.63 (m, 1H, Ar-H), 7.60-7.42 (m, 8H, Ar-H), 7.22 (t, 1H, *J* = 7.3 Hz, Ar-H), 7.05-6.96 (m, 2H, Ar-H), 4.06-3.93 (m, 1H, H-cy), 3.83 (s, 3H, CH_3), 2.36-2.20 (m, 2H, H-cy), 1.97-1.80 (m, 4H, H-cy), 1.70-1.60 (m, 1H, H-cy), 1.35-1.15 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 158.9 (C-Ar), 152.1 (C-Ar), 150.6 (C-Ar), 142.6 (C-Ar), 132.0 (C-Ar), 129.8 (C-Ar), 129.2 (C-Ar), 128.7 (C-Ar), 126.5 (C-Ar), 121.7 (C-Ar), 120.9 (C-Ar), 112.8 (C-Ar), 56.1 (C-cy), 55.9 (C-cy), 30.7 (C-cy), 25.7 (C-cy), 24.8 (C-cy).

2-Bromo-5-ethoxyoxazole (IV-33)



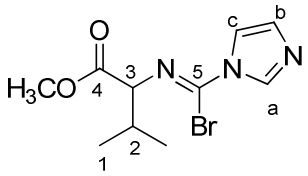
This compound was synthesized according to the general procedure IV-D, using 1mmol of isocyanide. The desired product was isolated in 11 % yield (22 mg).

Mol. Formula: $C_5H_6BrNO_2$, Mol. Wt.: 192.01,

Nature: Pale yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.11 (s, 1H, H-a), 4.13 (q, 2H, *J* = 7.07 Hz, H-1), 1.41 (t, 3H, *J* = 7.07, Hz, H-2).

Methyl 2-((bromo(1*H*-imidazol-1-yl)methylene)amino)-3-methylbutanoate (IV-34)



To a solution of methyl isocyanovalinate (282 mg, 2.0 mmol) in acetonitrile (10 mL), was added bromine (0.104 ml, 2.0 mmol), it was stirred for 2 minutes at room temperature. The resulting mixture was then cooled at 0 ^oC before addition of imidazole (272 mg, 4.0 mmol) and stirred at -5 °C to 0 °C for an additional 10 minutes. After completion of the reaction (checked by TLC analysis), dichloromethane was evaporated. The crude residue was purified by flash chromatography on silica gel using a 1:2 mixture of diethyl ether/petroleum ether as eluant and the volatiles were evaporated under reduced pressure at 25-30 ^oC to give **IV-2** (190 mg, 33 %) as pale yellow oil.

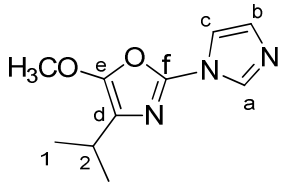
Mol. Formula: $C_{10}H_{14}BrN_3O_2$, Mol. Wt.: 288.14,

Nature: Pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.27 (s, 1H, H-a), 7.69 (s, 1H, H-c), 7.09 (s, 1H, H-b), 4.13 (d, 1H, *J* = 4.8 Hz, H-3), 3.74 (s, 3H, CH_3), 2.47-2.34 (m, 1H, H-2), 0.99 (d, 3H, *J* = 6.8, Hz, H-1), 0.96 (d, 3H, *J* = 6.8, Hz, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 170.0 (C-4), 137.6 (C-a), 129.9 (C-b), 120.1 (C-5), 119.2 (C-c), 73.4 (C-3), 52.3 (CH_3), 31.8 (C-2), 19.4 (C-1), 18.1 (C-1).

5-Ethoxy-2-(1*H*-imidazol-1-yl)-4-isopropyloxazole (IV-35)



To a solution of **IV-2** (144mg, 0.5 mmol) in acetonitrile (2.5 mL), was added dropwise of DBU (1.0 mL, 6.62 mmol) at 0 °C and stirred at -5 °C to 0 °C for an additional 10 minutes. After completion of the reaction (checked by TLC analysis), acetonitrile was evaporated. The crude residue was purified by flash chromatography on silica gel using a 1:3 mixture of diethyl ether/petroleum ether as eluant and the volatiles were evaporated under reduced pressure at 25-30 °C to give **IV-3** (55 mg, 50 %) as colourless oil.

Mol. Wt.: 221.26, Nature: colourless oil.

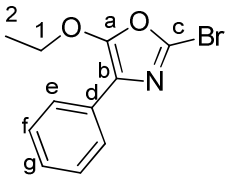
HRMS: Calcd. for $C_{11}H_{15}N_3O_2$: 221.1164, Found : 221.1160.

I.R. (thin film): 2930, 1738, 1670, 1620, 1601, 1447, 1258, 1215, 1211, 1178, 1086 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.10 (s, 1H, H-a), 7.47 (s, 1H, H-c), 7.13 (s, 1H, H-b), 3.94 (s, 3H, CH_3), 2.89-2.75 (m, 1H, H-2), 1.23 (d, 6H, *J* = 6.8, Hz, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 151.4 (C-f), 141.9 (C-e), 134.7 (C-a), 130.3 (C-b), 123.0 (C-d), 116.1 (C-c), 62.7 (CH_3), 25.2 (C-2), 21.4(C-1).

2-Bromo-5-ethoxy-4-phenyloxazole (IV-36)



This compound was synthesized according to the general procedure IV-D, using 2.6 mmol of isocyanide. The desired product was isolated in 83 % yield (590 mg).

Mol. Wt.: 268.11, Nature: Pale yellow liquid.

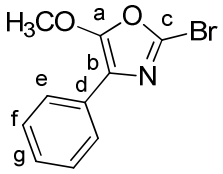
HRMS: Calcd. for $C_{11}H_{10}BrNO_2$: 266.9895, Found : 266.9885.

I.R. (thin film): 1739, 1683, 1595, 1456, 1270, 1207, 1176 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 (dd, 2H, *J* = 1.2, 7.4 Hz, H-e), 7.39 (t, 2H, *J* = 7.4 Hz, H-f), 7.28-7.22 (m, 1H, H-g), 4.36 (q, 2H, *J* = 7.1 Hz, H-1), 1.47 (t, 3H, *J* = 7.1 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.7 (C-a), 130.2 (C-d), 128.5 (C-f), 127.0 (C-g), 124.9 (C-e), 122.8 (C-b), 119.1 (C-c), 70.7 (C-1), 15.1 (C-2).

2-Bromo-5-methoxy-4-phenyloxazole (IV-37)



This compound was synthesized according to the general procedure IV-D, using 5.7 mmol of isocyanide. The desired product was isolated in 68 % yield (984 mg).

Mol. Wt.: 254.08, Nature: Pale yellow semi solid.

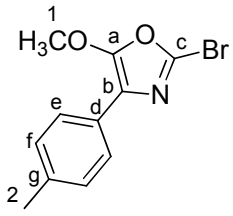
HRMS: Calcd. for $C_{10}H_8BrNO_2$: 252.9738, Found : 252.9739.

I.R. (thin film): 1740, 1688, 1597, 1454, 1324, 1280, 1208, 1178, 1001 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.75 (d, 2H, *J* = 7.8 Hz, H-e), 7.38 (t, 2H, *J* = 7.8 Hz, H-f), 7.25 (m, 1H, H-g), 4.10 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.4 (C-a), 1330.0 (C-d), 128.5 (C-f), 127.0 (C-g), 124.9 (C-e), 122.5 (C-b), 118.3 (C-c), 60.8 (C-1).

2-Bromo-5-methoxy-4-(p-tolyl)oxazole (IV-38)



This compound was synthesized according to the general procedure IV-D, using 1.0 mmol of isocyanide. The desired product was isolated in 92 % yield (247 mg).

Mol. Wt.: 268.11, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{11}H_{10}BrNO_2$: 266.9895, Found : 266.9900.

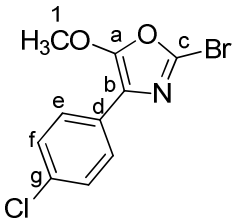
M.P. = 90-91 °C.

I.R. (thin film): 1740, 1681, 1608, 1444, 1412, 1210, 1175, 1007 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.57 (dd, 2H, *J* = 1.9, 8.3 Hz, H-e), 7.12 (dd, 2H, *J* = 1.9, 8.3 Hz, H-f), 4.00 (s, 3H, H-1), 2.29 (s, 3H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.1 (C-c), 136.8 (C-a, C-g), 129.3 (C-f), 127.2 (C-d), 124.9 (C-e), 116.6 (C-b), 60.9 (C-1), 21.3 (C-2).

2-Bromo-4-(4-chlorophenyl)-5-methoxyoxazole (IV-39)



This compound was synthesized according to the general procedure IV-D, using 2.9 mmol of bromo oxazole. The desired product was isolated in 66 % yield (550 mg).

Mol. Wt.: 288.53, Nature: Pale brown solid.

HRMS: Calcd. for $C_{10}H_7BrClNO_2$: 286.9349, Found : 286.9338.

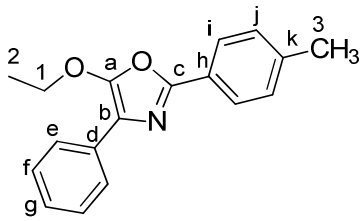
M.P. = 56-57 °C.

I.R. (thin film): 1740, 1684, 1615, 1590, 1489, 1402, 1256, 1206, 1175, 1091, 1007 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.68 (d, 2H, *J* = 8.5 Hz, H-e), 7.35 (d, 2H, *J* = 8.5 Hz, H-f), 4.10 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.4 (C-c), 153.3 (C-a), 132.6 (C-g), 128.7 (C-f), 126.1 (C-e), 122.5 (C-d), 117.2 (C-b), 60.7 (C-1).

5-Ethoxy-4-phenyl-2-(p-tolyl)oxazole (IV-40)



This compound was synthesized according to the general procedure IV-E, using 0.8 mmol of bromo oxazole **IV-36**. The desired product was isolated in 59 % yield (135mg).

Mol. Wt.: 279.33, Nature: Pale yellow semisolid.

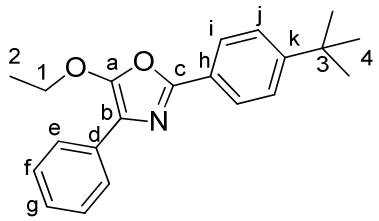
HRMS: Calcd. for $C_{18}H_{17}NO_2$: 279.1259, Found : 279.1252.

I.R. (thin film): 1738, 1686, 1499, 174, 1384, 1277, 1200, 1179, 1016 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85-7.77 (m, 4H, H-e, H-i), 7.30 (t, 2H, *J* = 7.8 Hz, H-j), 7.17-7.12 (m, 3H, H-g, H-f), 4.32 (q, 2H, *J* = 7.1 Hz, H-1), 2.30 (s, 3H, H-3), 1.40 (t, 3H, *J* = 7.1 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.6 (C-c), 152.2 (C-a), 139.8 (C-k), 131.5 (C-d), 129.4 (C-j), 128.4 (C-f), 126.3 (C-g), 125.5 (C-e), 125.0 (C-i), 124.9 (C-h), 116.7 (C-b), 69.8 (C-1), 21.5 (C-3), 15.2 (C-2).

2-(4-(*Tert*-butyl)phenyl)-5-ethoxy-4-phenyloxazole (IV-41)



This compound was synthesized according to the general procedure IV-E, using 1.0 mmol of bromo oxazole **IV-36**. The desired product was isolated in 33 % yield (80 mg).

Mol. Wt.: 321.41, Nature: Pale yellow liquid.

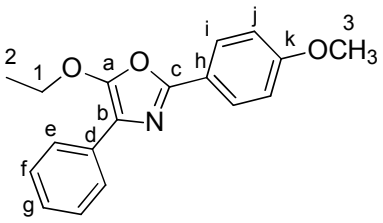
HRMS: Calcd. for $C_{21}H_{23}NO_2$: 321.1729, Found : 321.1772.

I.R. (thin film): 1734, 1691, 1639, 1597, 1451, 1276, 1203, 1178, 1018 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.97-7.90 (m, 4H, H-e, H-i), 7.77 (dd, 2H, *J* = 1.7, 8.5 Hz, H-j), 7.41 (t, 2H, *J* = 7.7 Hz, H-f), 7.27-7.21 (m, 1H, H-g), 4.43 (q, 2H, *J* = 7.1 Hz, H-1), 1.51 (t, 3H, *J* = 7.1 Hz, H-2), 1.36 (s, 9H, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.7 (C-c), 153.0 (C-k), 152.2 (C-a), 131.6 (C-d), 128.4 (C-f), 126.3 (C-g), 125.6 (C-e), 125.3 (C-i), 125.1 (C-j), 124.9 (C-h), 116.8 (C-b), 69.8 (C-1), 34.9 (C-3), 31.2 (C-4), 15.2 (C-2).

5-Ethoxy-2-(4-methoxyphenyl)-4-phenyloxazole (IV-42)



This compound was synthesized according to the general procedure IV-E, using 0.8 mmol of bromo oxazole **IV-36**. The desired product was isolated in 49 % yield (108 mg).

Mol. Wt.: 295.33, Nature: white solid.

HRMS: Calcd. for $C_{18}H_{17}NO_3$: 295.1208, Found : 295.1223.

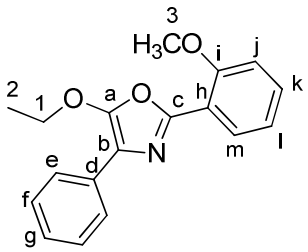
M.P. = 74-75 °C.

I.R. (thin film): 1739, 1670, 1601, 1445, 1259, 1210, 1176, 1020 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (d, 2H, *J* = 8.9 Hz, H-i), 7.92 (dd, 2H, *J* = 1.2, 7.4 Hz, H-e), 7.40 (t, 2H, *J* = 7.4 Hz, H-f), 7.24 (t, 1H, *J* = 7.3 Hz, H-g), 6.97 (d, 2H, *J* = 8.9 Hz, H-j), 4.42 (q, 2H, *J* = 7.1 Hz, H-1), 3.87 (s, 3H, H-3), 1.51 (t, 3H, *J* = 7.1 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 160.8 (C-k), 153.5 (C-c), 152.2 (C-a), 131.6 (C-d), 128.4 (C-i), 127.2 (C-e), 126.3 (C-g), 125.0 (C-f), 120.5 (C-h), 116.7 (C-b), 114.1 (C-j), 69.8 (C-1), 55.4 (C-3), 15.2 (C-2).

5-Ethoxy-2-(2-methoxyphenyl)-4-phenyloxazole (IV-43)



This compound was synthesized according to the general procedure IV-E, using 1.0 mmol of bromo oxazole **IV-36**. The desired product was isolated in 30 % yield (88 mg).

Mol. Wt.: 295.33, Nature: Pale yellow semi solid.

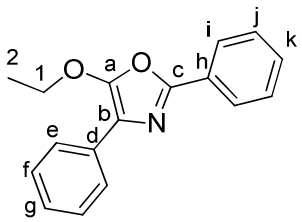
HRMS: Calcd. for $C_{18}H_{17}NO_3$: 295.1208, Found : 295.1199.

I.R. (thin film): 1735, 1665, 1593, 1466, 1377, 1259, 1204, 1020 $cm^{-1.}$

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.01-7.96 (m, 3H, H-e, H-m), 7.49-7.41 (m, 3H, H-f, H-k), 7.29 (d, 1H, *J* = 8.3 Hz, H-j), 7.12-7.03 (m, 2H, H-g, H-l), 4.48 (q, 2H, *J* = 7.1 Hz, H-1), 4.00 (s, 3H, H-3), 1.55 (t, 3H, *J* = 7.1 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 157.3 (C-i), 153.8 (C-c), 150.6 (C-a), 131.6 (C-d), 131.1 (C-k), 129.7 (C-m), 128.3 (C-e), 126.2 (C-g), 125.0 (C-f), 120.6 (C-l), 116.8 (C-b), 116.2 (C-h), 111.9 (C-j), 69.5 (C-3), 56.0 (C-1), 15.2 (C-2).

5-Ethoxy-2,4-diphenyloxazole (IV-44)



This compound was synthesized according to the general procedure IV-E, using 0.8 mmol of bromo oxazole **IV-36**. The desired product was isolated in 23 % yield (60 mg).

Mol. Wt.: 265.31, Nature: Pale yellow semi solid.

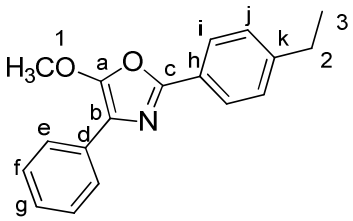
HRMS: Calcd. for $C_{17}H_{15}NO_2$: 265.1103, Found : 265.1103.

I.R. (thin film): 1738, 1676, 1634, 1450, 1245, 1204, 1047, 1016 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.01 (dd, 2H, *J* = 1.5, 8.1 Hz, H-i), 7.93 (dd, 2H, *J* = 1.2, 8.3 Hz, H-e), 7.48-7.38 (m, 5H, H-f, H-j, H-k), 7.28-7.22 (m, 1H, H-g), 4.45 (q, 2H, *J* = 7.1 Hz, H-1), 1.52 (t, 3H, *J* = 7.1 Hz, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.8 (C-c), 152.0 (C-a), 131.5 (C-d), 129.6 (C-k), 128.7 (C-i), 128.5 (C-e), 127.6 (C-h), 126.4 (C-g), 125.5 (C-j), 125.1 (C-f), 116.9 (C-b), 69.8 (C-1), 15.2 (C-2).

2-(4-Ethylphenyl)-5-methoxy-4-phenyloxazole (IV-45)



This compound was synthesized according to the general procedure IV-E, using 0.5 mmol of bromo oxazole **IV-37**. The desired product was isolated in 33 % yield (45 mg).

Mol. Wt.: 279.33, Nature: Pale yellow semi solid.

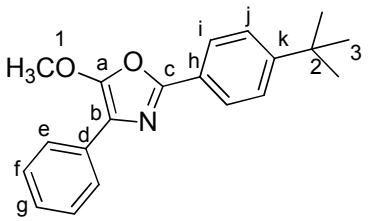
HRMS: Calcd. for $C_{18}H_{17}NO_2$: 279.1259, Found : 279.1295.

I.R. (thin film): 1744, 1677, 1608, 1454, 1280, 1252, 1210, 1175, 1056, 1004 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.00-7.91 (m, 4H, H-e, H-i), 7.45 (t, 2H, *J* = 7.6 Hz, H-f), 7.35-7.27 (m, 3H, H-g, H-j), 4.18 (s, 3H, H-1), 2.74 (q, 2H, *J* = 7.1 Hz, H-2), 1.31 (t, 3H, *J* = 7.1 Hz, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.4 (C-c), 152.0 (C-a), 146.2 (C-k), 130.3 (C-d), 128.4 (C-f), 128.2 (C-j), 127.7 (C-h), 126.4 (C-g), 125.6 (C-e), 125.0 (C-i), 115.8 (C-b), 60.1 (C-1), 28.8 (C-2), 15.4 (C-3).

2-(4-(*Tert*-butyl)phenyl)-5-methoxy-4-phenyloxazole (IV-46)



This compound was synthesized according to the general procedure IV-E, using 0.5 mmol of bromo oxazole **IV-37**. The desired product was isolated in 53 % yield (80 mg).

Mol. Wt.: 307.38, Nature: white solid.

HRMS: Calcd. for $C_{20}H_{21}NO_2$: 307.1572, Found : 307.1576.

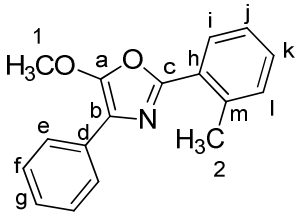
M.P. = 66-67 °C.

I.R. (thin film): 1740, 1670, 1640, 1595, 1490, 1250, 1210, 1172, 1091, 1057, 1015 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.97 (d, 2H, *J* = 8.4 Hz, H-i), 7.94 (d, 2H, *J* = 8.1 Hz, H-e), 7.51 (d, 2H, *J* = 8.4 Hz, H-j), 7.45 (t, 2H, *J* = 7.6 Hz, H-f), 7.32-7.28 (m, 1H, H-g), 4.18 (s, 3H, H-1), 1.39 (s, 9H, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.4 (C-c), 153.0 (C-k), 152.0 (C-a), 131.4 (C-d), 128.5 (C-f), 126.4 (C-g), 125.6 (C-e), 125.3 (C-i), 125.1 (C-j), 124.8 (C-h), 115.9 (C-b), 60.1 (C-1), 34.8 (C-2), 31.2 (C-3).

5-Methoxy-4-phenyl-2-(o-tolyl)oxazole (IV-48)



This compound was synthesized according to the general procedure IV-E, using 0.5 mmol of bromo oxazole **IV-37**. The desired product was isolated in 19 % yield (25 mg).

Mol. Wt.: 265.31, Nature: Pale yellow semi solid.

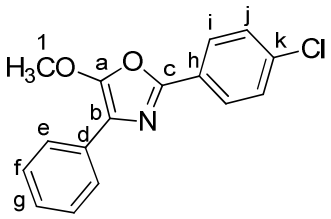
HRMS: Calcd. for $C_{17}H_{15}NO_2$: 265.1103, Found : 265.1109.

I.R. (thin film): 1740, 1691, 1639, 1597, 1499, 1451, 1374, 1206, 1175, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.04-7.91 (m, 3H, H-e, H-i), 7.45 (t, 2H, *J* = 7.4 Hz, H-f), 7.38-7.26 (m, 4H, H-g, H-j, H-k, H-l), 4.18 (s, 3H, H-1), 2.79 (s, 3H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.3 (C-c), 151.9 (C-a), 137.0 (C-m), 131.6 (C-l), 131.5 (C-d), 129.3 (C-k), 128.4 (C-e), 127.9 (C-g), 126.3 (C-h), 126.2 (C-k), 125.9 (C-i), 125.0 (C-f), 115.4 (C-b), 59.9 (C-1), 22.1 (C-2).

2-(4-Chlorophenyl)-5-methoxy-4-phenyloxazole (IV-49)



This compound was synthesized according to the general procedure IV-B, using 0.6 mmol of bromo oxazole **IV-37**. The desired product was isolated in 18 % yield (25 mg).

Mol. Wt.: 285.73, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{16}H_{12}ClNO_2$: 285.0557, Found : 285.0547.

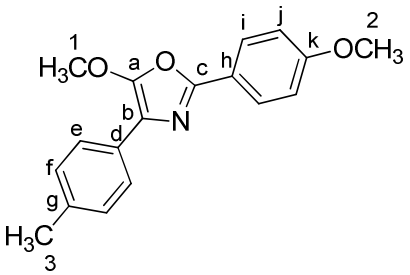
M.P. = 94-95 °C.

I.R. (thin film): 1740, 1670, 1594, 1482, 1255, 1206, 1171, 1088, 1014 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.97 (d, 2H, *J* = 8.5 Hz, H-i), 7.90 (d, 2H, *J* = 8.0 Hz, H-e), 7.47-7.41 (m, 4H, H-j, H-f), 7.28 (t, 1H, *J* = 7.4 Hz, H-g), 4.18 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.6 (C-c), 150.8 (C-a), 135.6 (C-k), 131.1 (C-d), 129.0 (C-j), 128.5 (C-f), 126.8 (C-i), 126.6 (C-g), 126.0 (C-h), 125.0 (C-e), 116.2 (C-b), 60.2 (C-1).

5-Methoxy-2-(4-methoxyphenyl)-4-(p-tolyl)oxazole (IV-50)



This compound was synthesized according to the general procedure IV-E, using 0.4 mmol of bromo oxazole **IV-38**. The desired product was isolated in 18 % yield (20 mg).

Mol. Wt.: 295.33, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{18}H_{17}NO_3$: 295.1208, Found : 295.1230.

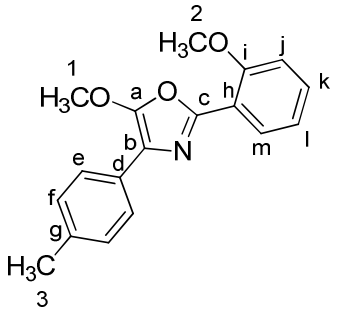
M.P. = 167-168 °C.

I.R. (thin film): 1709, 1615, 1493, 1454, 1381, 1332, 1234 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (d, 2H, *J* = 8.9 Hz, H-i), 7.78 (d, 2H, *J* = 8.1 Hz, H-e), 7.22 (d, 2H, *J* = 8.1 Hz, H-f), 6.97 (d, 2H, *J* = 8.9 Hz, H-j), 4.12 (s, 3H, H-1), 3.86 (s, 3H, H-3), 2.37 (s, 3H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 160.8 (C-k), 153.9 (C-c), 152.0 (C-a), 136.0 (C-g), 129.1 (C-f), 128.6 (C-d), 127.2 (C-e), 125.0 (C-i), 120.5 (C-h), 116.1 (C-b), 114.1 (C-j), 60.2 (C-1), 55.3 (C-3), 21.3 (C-2).

5-Methoxy-2-(2-methoxyphenyl)-4-(p-tolyl)oxazole (IV-51)



This compound was synthesized according to the general procedure IV-E, using 0.4 mmol of bromo oxazole **IV-38**. The desired product was isolated in 54 % yield (60 mg).

Mol. Wt.: 295.33, Nature: Pale yellow semi solid.

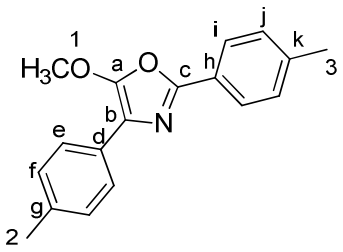
HRMS: Calcd. for $C_{18}H_{17}NO_3$: 295.1208, Found : 295.1208.

I.R. (thin film): 1740, 1681, 1608, 1444, 1412, 1210, 1175, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.93 (dd, 1H, *J* = 1.7, 7.7 Hz, H-m), 7.79 (d, 2H, *J* = 8.0 Hz, H-e), 7.43-7.37 (m, 1H, H-k), 7.21 (d, 2H, *J* = 8.0 Hz, H-f), 7.07-7.00 (m, 2H, H-j, H-l), 4.13 (s, 3H, H-1), 3.96 (s, 3H, H-2), 2.39 (s, 3H, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 157.3 (C-i), 154.2 (C-c), 150.4 (C-a), 135.9 (C-g), 131.0 (C-k), 129.8 (C-m), 129.0 (C-f), 128.6 (C-d), 125.0 (C-e), 120.6 (C-l), 116.9 (C-b), 115.7 (C-h), 111.9 (C-j), 60.0 (C-1), 56.0 (C-2), 21.3 (C-3).

5-Methoxy-2,4-di-p-tolyloxazole (IV-52)



This compound was synthesized according to the general procedure IV-E, using 0.6 mmol of bromo oxazole **IV-38**. The desired product was isolated in 29 % yield (45 mg).

Mol. Wt.: 279.33, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{18}H_{17}NO_2$: 279.1259, Found : 279.1266.

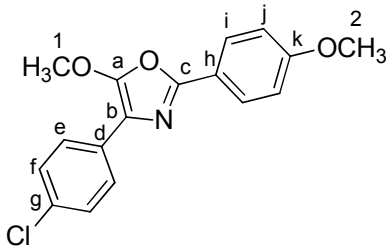
M.P. = 99-100 °C.

I.R. (thin film): 1740, 1681, 1648, 1615, 1520, 1451, 1377, 1206, 1175, 1105, 1011 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.90 (d, 2H, *J* = 8.2 Hz, H-i), 7.79 (dd, 2H, *J* = 1.9, 8.2 Hz, H-e), 7.28-7.19 (m, 4H, H-f, H-j), 4.13 (s, 3H, H-1), 2.41 (s, 3H, H-2), 2.38 (s, 3H, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.0 (C-c), 152.0 (C-a), 139.8 (C-k), 136.1 (C-g), 129.4 (C-f), 129.2 (C-i), 128.5 (C-d), 125.5 (C-j), 125.0 (C-e), 124.9 (C-h), 116.1 (C-b), 60.2 (C-1), 21.5 (C-2 or C-3), 21.3 (C-3 or C-2).

4-(4-Chlorophenyl)-5-methoxy-2-(4-methoxyphenyl)oxazole (IV-54)



This compound was synthesized according to the general procedure IV-E, using 0.4 mmol of bromo oxazole **IV-39**. The desired product was isolated in 45 % yield (50 mg).

Mol. Wt.: 315.75, Nature: white solid.

HRMS: Calcd. for $C_{17}H_{14}ClNO_3$: 315.0662, Found : 315.0665.

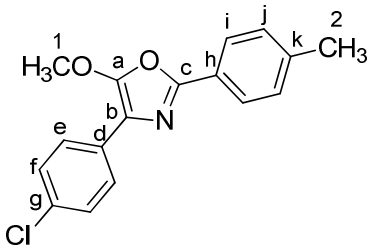
M.P. = 111-112 °C.

I.R. (thin film): 1740, 1674, 1635, 1601, 1503, 1252, 1231, 1164, 1088 1011 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.93 (d, 2H, *J* = 8.6 Hz, H-i), 7.81 (d, 2H, *J* = 8.4 Hz, H-f), 7.36 (d, 2H, *J* = 8.4 Hz, H-e), 6.97 (d, 2H, *J* = 8.6 Hz, H-j), 4.14 (s, 3H, H-1), 3.86 (s, 3H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 160.9 (C-k), 154.3 (C-c), 152.0 (C-a), 131.7 (C-g), 130.0 (C-d), 128.6 (C-f), 127.2 (C-e), 126.2 (C-i), 120.2 (C-h), 114.9 (C-b), 114.1 (C-j), 60.0 (C-1), 55.4 (C-2).

4-(4-Chlorophenyl)-5-methoxy-2-(p-tolyl)oxazole (IV-55)



This compound was synthesized according to the general procedure IV-E, using 0.4 mmol of bromo oxazole **IV-39**. The desired product was isolated in 58 % yield (60 mg).

Mol. Wt.: 299.75, Nature: Pale yellow solid.

HRMS: Calcd. for $C_{17}H_{14}ClNO_2$: 299.0713, Found : 299.0712.

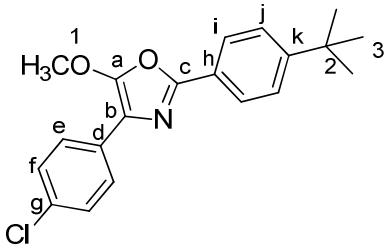
M.P. = 84-85 °C.

I.R. (thin film): 1744, 1677, 1635, 1611, 1594, 1496, 1248, 1210, 1171, 1091, 1056, 1011 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.87 (d, 2H, *J* = 7.9 Hz, H-i), 7.82 (d, 2H, *J* = 8.2 Hz, H-e), 7.35 (d, 2H, *J* = 8.2 Hz, H-f), 7.25 (d, 2H, *J* = 7.9 Hz, H-j), 4.14 (s, 3H, H-1), 2.40 (s, 3H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.4 (C-c), 152.0 (C-a), 140.0 (C-k), 131.7 (C-g), 130.0 (C-d), 129.4 (C-j), 128.6 (C-f), 126.2 (C-i), 125.5 (C-e), 124.6 (C-h), 114.7 (C-b), 59.9 (C-1), 21.5 (C-2).

2-(4-(*Tert*-butyl)phenyl)-4-(4-chlorophenyl)-5-methoxyoxazole (IV-56)



This compound was synthesized according to the general procedure IV-E, using 0.4 mmol of bromo oxazole **IV-39**. The desired product was isolated in 49 % yield (58 mg).

Mol. Wt.: 341.83, Nature: off white solid.

HRMS: Calcd. for $C_{20}H_{20}ClNO_2$: 341.1183, Found : 341.1184.

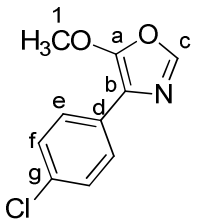
M.P. = 91-92 °C.

I.R. (thin film): 1740, 1674, 1635, 1590, 1496, 1405, 1314, 1255, 1210, 1178, 1091, 1058 1011 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.92 (d, 2H, *J* = 8.4 Hz, H-e), 7.83 (d, 2H, *J* = 8.5 Hz, H-i), 7.48 (d, 2H, *J* = 8.4 Hz, H-f), 7.37 (d, 2H, *J* = 8.5 Hz, H-j), 4.15 (s, 3H, H-1), 1.36 (s, 9H, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.4 (C-c), 153.1 (C-k), 152.0 (C-a), 131.7 (C-g), 130.0 (C-d), 128.6 (C-f), 126.2 (C-e), 125.7 (C-i), 125.3 (C-j), 124.6 (C-h), 114.7 (C-b), 59.9 (C-1), 34.8 (C-2), 31.2 (C-3).

4-(4-Chlorophenyl)-5-methoxyoxazole (IV-57)



This compound was synthesized according to the general procedure IV-E, using 0.4 mmol of bromo oxazole **IV-39**. The desired product was isolated in 62 % yield (45 mg).

Mol. Wt.: 209.63, Nature: oil.

HRMS: Calcd. for $C_{17}H_{14}ClNO_3$: 209.0244, Found : 209.0251.

I.R. (thin film): 1742, 1677, 1638, 1590, 1480, 1223, 1167, 1078 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.74 (d, 2H, *J* = 8.5 Hz, H-f), 7.48 (s, 1H, H-c), 7.35 (d, 2H, *J* = 8.5 Hz, H-e), 4.09 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.7 (C-a), 141.6 (C-c), 131.9 (C-g), 129.6 (C-d), 128.7 (C-f), 126.1 (C-e), 112.8 (C-b), 59.8 (C-1).

Experimental Part

Chapter 5

Experimental Part for Chapter 5

I. General Procedures:

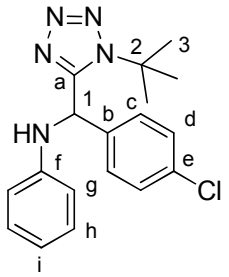
a. General Procedure V-A: (synthesis of iminotetrazole).

To a 1 M solution amine in methanol were added successively 1.0 equiv of aldehyde, 1.0 equiv of isocyanide and 1.0 euiv of trimethylsilyl azide. The resulting mixture was stirred at room temperature for 8 h. After completion of reaction (checked by TLC), N,N-dimethylacetamide (1M), 2 equiv of copper acetate and 1 equiv of cesium carbonate were added in the reaction mixture at room temperature and stirred it at 150 ^{o}C for 2-6 h. After completion of reaction (checked by TLC), solvent was evaporated. The crude was purified by flash chromatography on silica gel (diethyl ether: petrolium ether) to afford corresponding imine.

b. General procedure V-B: (synthesis of 1,2,3-triazole.)

To a 1 M solution of iminotetrazole derivative in toluene was added 20 mol% of zinc triflate. The resulting mixture was heated under microwave irradiation at 150 °C for 30 minutes. The reaction mixture was neutralized with aqueous $NaHCO_3$ solution and and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4. The solvent was removed afterwards under reduced pressure to afford the corresponding products after purification by flash chromatography on silica gel.

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(4-chlorophenyl)methyl)aniline (V-1)



To a 1 M solution of aniline (0.9 mL, 1 mmol) in methanol (1 mL) were added successively *p*-chlorobenzaldehyde (141.5 mg, 1 mmol), *tert*-butyl isocyanide (0.11 mL, 1 mmol) and trimethylsilyl azide (0.13 mL, 1 mmol). The resulting mixture was stirred at room temperature for 18 h. The solvent was removed afterwards under reduced pressure to afford the Ugi-azide product after purification by flash chromatography on silica gel. The desired product was isolated in 99 % yield (336 mg).

Mol. Wt.: 341.84, Nature: semisolid.

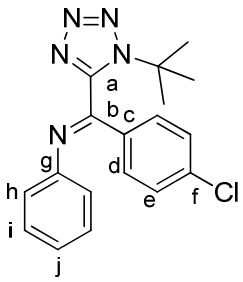
HRMS Calcd. for $C_{18}H_{20}ClN_5$: 341.1407, Found : 341.1408.

I.R. (thin film): 3041, 2932, 1506, 1478, 1454, 1262, 1234, 1095 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.35-7.28 (m, 4H, Ar-H), 7.16 (t, 2H, *J* = 7.5 Hz, Ar-H), 6.78 (t, 1H, *J* = 7.5 Hz, Ar-H), 6.65 (d, 2H, *J* = 8.0 Hz, Ar-H), 6.12 (d, 1H, *J* = 9.4 Hz, H-1), 4.78 (d, 1H, *J* = 9.4 Hz, NH), 1.17 (s, 9H, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.8 (C-a), 145.3 (C-f), 136.6 (C-b), 134.5 (C-e), 129.5 (C-h), 129.3 (C-d), 129.0 (C-c), 119.5 (C-i), 114.2 (C-g), 61.8 (C-2), 53.7 (C-1), 30.1 (C-3).

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(4-chlorophenyl)methylene)aniline (V-2)



This compound was synthesized according to the general procedure **V-A**, using 0.5 mmol of *tert*-butyl isocyanide. The desired product was isolated in 84 % yield (142 mg).

Mol. Wt.: 339.82, Nature: yellow solid.

HRMS Calcd. for $C_{18}H_{18}ClN_5$: 339.1251, Found : 339.1259

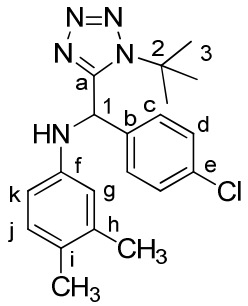
M.P. = 172-173 ^oC

I.R. (thin film): 2990, 1625, 1578, 1469, 1375, 1267, 1238, 1180, 1135, 1080, 1008 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.63 (d, 2H, *J* = 8.6 Hz, H-d), 7.43 (d, 2H, *J* = 8.6 Hz, H-e), 7.24 (t, 2H, *J* = 7.8 Hz, H-i), 7.09 (t, 1H, *J* = 7.8 Hz, H-j), 6.88 (d, 2H, *J* = 7.8 Hz, H-h), 1.30 (s, 9H, H-2)

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.2 (C-b), 148.0 (C-g), 146.8 (C-a), 138.4 (C-f), 135.4 (C-c), 129.3 (C-d), 129.2 (C-e), 129.1 (C-i), 126.2 (C-j), 121.2 (C-h), 62.5 (C-1), 29.3 (C-2).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl)-3,4-dimethylaniline (V-3)**



To a 1 M solution of 3,4-dimethylaniline (121 mg, 1.0 mmol) in methanol were added successively, *p*-chlorobenzaldehyde (141.5 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 mL, 1.0 mmol) and trimethylsilyl azide (0.13 mL, 1.0 mmol). The resulting mixture was stirred at room temperature for 18 h. The solvent was removed afterwards under reduced pressure to afford the Ugi-azide product after purification by flash chromatography on silica gel.

The desired product was isolated in 96 % yield (355 mg).

Mol. Wt.: 369.89, Nature: yellow solid.

HRMS: Calcd. for $C_{20}H_{24}ClN_5$: 369.1720, Found : 369.1722.

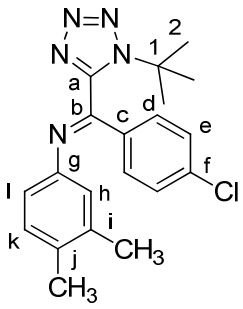
M.P. = 154 - 155 ^oC

I.R. (thin film): 3040, 2925, 1614, 1496, 1454, 1387, 1241, 1178, 1129, 1021 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.35-7.27 (m, 4H, Ar-H), 6.91 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.48 (s, 1H, H-g), 6.41 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.08 (d, 1H, *J* = 9.7 Hz, H-1), 4.59 (d, 1H, *J* = 9.7 Hz, NH), 2.15 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.72 (s, 9H, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.0 (C-Ar), 143.4 (C-Ar), 137.6 (C-Ar), 136.8 (C-Ar), 134.4 (C-Ar), 130.3 (C-Ar), 129.2 (C-Ar), 129.0 (C-Ar), 127.6 (C-Ar), 116.3 (C-Ar), 111.4 (C-Ar), 61.9 (C-2), 54.0 (C-1), 30.1(C-3), 20.0 (CH_3), 18.7 (CH_3).

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(4-chlorophenyl)methylene)-3,4-dimethylaniline (V-4)



This compound was synthesized according to the general procedure V-A, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 93 % yield (355 mg).

Mol. Wt.: 367.88, Nature: yellow solid.

HRMS: Calcd. for $C_{20}H_{22}ClN_5$: 367.1564, Found : 387.1568

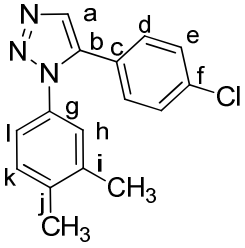
M.P. = 154 - 155 ^oC

I.R. (thin film): 2925, 1622, 1592, 1505, 1473, 1374, 1308, 1085, 1024 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.61 (d, 2H, *J* = 8.6 Hz, H-d), 7.41 (d, 2H, *J* = 8.6 Hz, H-e), 6.96 (d, 1H, *J* = 8.0 Hz, H-k), 6.68 (s, 1H, H-h), 6.57 (d, 1H, *J* = 8.0 Hz, H-l), 2.16 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 1.30 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.0 (C-b), 147.2 (C-a), 145.8 (C-Ar), 128.1 (C-Ar), 137.4 (C-Ar), 135.6 (C-Ar), 134.9 (C-Ar), 130.1 (C-Ar), 129.2 (C-Ar), 129.1 (C-Ar), 122.7 (C-Ar), 118.5 (C-Ar), 62.4 (C-1), 29.3 (C-2), 19.7 (CH_3), 19.3 (CH_3).

_N_-5-(4-chlorophenyl)-1-(3,4-dimethylphenyl)-1_H_-1,2,3-triazole (V-5)



This compound was synthesized according to the general procedure **V-B**, using 1.0 mmol of imine **V-4.** The desired product was isolated in 74 % yield (210 mg).

Mol. Wt.: 283.76, Nature: white solid.

HRMS Calcd. for $C_{16}H_{14}FN_3$: 283.0876, Found : 283.0878.

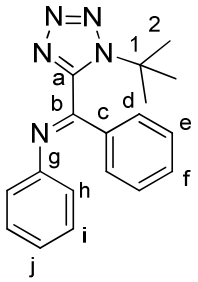
M.P. = 117-118 °C

I.R. (thin film): 2920, 1615, 1556, 1490, 1449, 1228, 1070 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85 (s, 1H, H-a), 7.32 (d, 2H, *J* = 8.5 Hz, H-d), 7.22 (s, 1H, H-h), 7.19-7.14 (m, 3H, H-e, H-l), 6.96 (d, 1H, *J* = 8.0 Hz, C-k), 2.31 (s, 3H, CH_3), 2.28 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 138.3 (C-Ar), 138.2 (C-Ar), 135.2 (C-Ar), 134.0 (C-Ar), 133.2 (C-a), 130.5 (C-Ar), 130.3 (C-Ar), 129.7 (C-Ar), 129.0 (C-Ar), 126.1 (C-Ar), 125.3 (C-Ar), 122.4 (C-Ar), 19.8 (CH_3), 19.6 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(phenyl)methylene)aniline (V-6)**



This compound was synthesized according to the general procedure **V-A**, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 63 % yield (192 mg).

Mol. Wt.: 305.38, Nature: yellow solid.

HRMS Calcd. for $C_{18}H_{19}N_5$: 305.1640, Found : 305.1637.

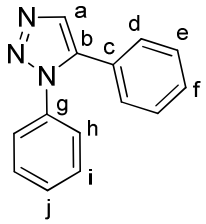
M.P. = 122-123 °C.

I.R. (thin film): 2992, 1697, 1499, 1478, 1454, 1269, 1231, 1133, 1056 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.68 (d, 2H, *J* = 8.1 Hz, H-d), 7.53 (t, 1H, *J* = 7.3 Hz, H-f), 7.45 (t, 2H, *J* = 7.3 Hz, H-e), 7.24 (t, 2H, *J* = 7.3 Hz, H-i), 7.08 (t, 1H, *J* = 7.3 Hz, H-j), 6.91 (d, 2H, *J* = 8.1 Hz, H-h), 1.32 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.4 (C-b), 148.3 (C-g), 147.1 (C-a), 136.9 (C-c), 132.1 (C-f), 129.0 (C-i), 128.9 (C-d), 128.1 (C-e), 125.9 (C-j), 121.1 (C-h), 62.4 (C-1), 29.3 (C-2).

1,5-diphenyl-1*H*-1,2,3-triazole (V-7)



This compound was synthesized according to the general procedure **V-B**, using 0.4 mmol of iminotetrazole **V-6**. The desired product was isolated in 69 % yield (60 mg).

Mol. Wt.: 221.26, Nature: white solid.

HRMS Calcd. for $C_{14}H_{11}N_3$: 221.0953, Found : 221.0954

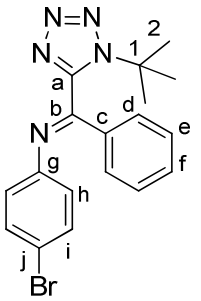
M.P. = 113-114 °C.

I.R. (thin film): 2920, 1593, 1499, 1450, 1231, 1138, 1049 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.87 (s, 1H, H-a), 7.46-7.42 (m, 3H, H-Ar), 7.40-7.32 (m, 5H, H-Ar), 7.25-7.21 (m, 2H, H-Ar).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 137.7 (C-g), 136.5 (C-c), 133.4 (C-a), 129.3 (C-h), 129.2 (C-e),128.8 (C-h, C-f), 128.6 (C-i), 126.7 (C-b), 125.2 (C-d).

4-bromo-*N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(phenyl)methylene)aniline (V-8)



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 68 % yield (522 mg).

Mol. Wt.: 384.27, Nature: white solid.

HRMS Calcd. for $C_{18}H_{18}BrN_5$: 384.0746, Found : 384.0747

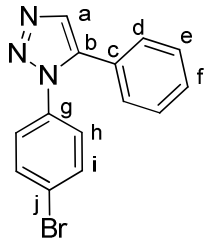
M.P. = 120-121 °C.

I.R. (thin film): 2988, 1621, 1579, 1482, 1370, 1265, 1234, 1192, 1140, 1077, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.65 (d, 2H, *J* = 7.8 Hz, H-d), 7.54 (t, 1H, *J* = 7.3 Hz, H-f), 7.45 (t, 2H, *J* = 7.3 Hz, H-e), 7.36 (dd, 2H, *J* = 1.9, 8.7 Hz, H-i), 6.81 (dd, 2H, *J* = 1.9, 8.7 Hz, H-h), 1.36 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.1 (C-b), 147.3 (C-a), 146.8 (C-g), 136.7 (C-c), 132.4 (C-f), 132.1 (C-i), 129.0 (C-e), 128.1 (C-d), 122.8 (C-h), 119.2 (C-j), 62.5 (C-1), 29.5 (C-2).

1-(4-bromophenyl)-5-phenyl-1*H*-1,2,3-triazole (V-9)



This compound was synthesized according to the general procedure **V-B**, using 1.3 mmol of iminotetrazole **V-8.** The desired product was isolated in 70 % yield (275 mg).

Mol. Wt.: 300.15, Nature: yellow oil.

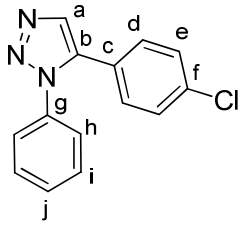
HRMS Calcd. for $C_{14}H_{10}BrN_3$: 299.0058, Found : 299.0059

I.R. (thin film): 3050, 1597, 1492, 1475, 1273, 1237, 1134, 1076, 1060, 1012 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 1H, H-a), 7.59 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.45-7.36 (m, 3H, Ar-H), 7.30-7.22 (m, 4H, Ar-H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 137.7 (C-Ar), 135.5 (C-Ar), 133.6 (C-a), 132.6 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 128.6 (C-Ar), 126.5 (C-Ar), 123.2 (C-Ar), 116.6 (C-Ar).

5-(4-chlorophenyl)-1-phenyl-1*H*-1,2,3-triazole (V-10)



This compound was synthesized according to the general procedure **V-B**, using 0.4 mmol of iminotetrazole V-2. The desired product was isolated in 66 % yield (67 mg).

Mol. Wt.: 255.70, Nature: yellow solid.

HRMS Calcd. for $C_{14}H_{10}ClN_3$: 255.0563, Found : 255.0561.

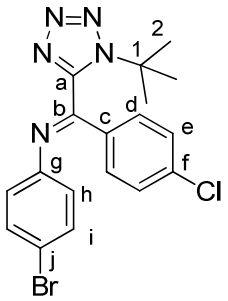
M.P. = 123-124 °C.

I.R. (thin film): 3061, 1597, 1499, 1485, 1279, 1234, 1129, 1095, 1053, 1014 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.86 (s, 1H, H-a), 7.48-7.43 (m, 3H, H-i, H-j), 7.37-7.30 (m, 4H, H-d, H-h), 7.16 (d, 2H, *J* = 8.6 Hz, H-e).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 136.6 (C-Ar), 136.3 (C-Ar), 135.4 (C-Ar), 133.4 (C-a), 129.8 (C-Ar), 129.5 (C-Ar), 129.4 (C-Ar), 129.2 (C-Ar).

(4-bromo-*N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl) methylene)aniline (V-11)



This compound was synthesized according to the general procedure **V-A**, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 48 % yield (200 mg).

Mol. Wt.: 418.72, Nature: yellow solid.

HRMS Calcd. for $C_{18}H_{17}BrClN_5$: 417.0356, Found : 417.0356

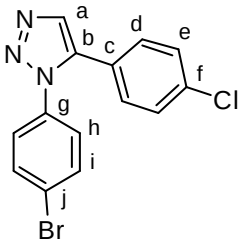
M.P. = 141-142 °C.

I.R. (thin film): 2056, 1625, 1572, 1476, 1356, 1260, 1253, 1185, 1135, 1080, 1060, 1008 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.60 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.43 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.36 (d, 2H, *J* = 8.6 Hz, Ar-H), 6.79 (d, 2H, *J* = 8.6 Hz, Ar-H), 1.34 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 152.2 (C-b), 146.9 (C-Ar), 146.5 (C-Ar), 138.8 (C-Ar), 135.1 (C-Ar), 132.1 (CAr), 129.4 (C-Ar), 129.3 (C-Ar), 122.9 (C-Ar), 119.6 (C-Ar), 62.6 (C-1), 29.5 (C-2).

1-(4-bromophenyl)-5-(4-chlorophenyl)-1*H*-1,2,3-triazole (V-12)



This compound was synthesized according to the general procedure **V-B**, using 0.4 mmol of iminotetrazole **V-11**. The desired product was isolated in 83 % yield (110 mg).

Mol. Wt.: 334.60, Nature: yellow solid.

HRMS Calcd. for $C_{14}H_9BrClN_3$: 332.9668, Found : 334.9669

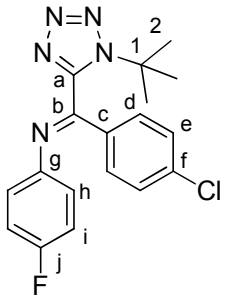
M.P. = 110-111 °C.

I.R. (thin film): 2928, 1598, 1510, 1480, 1234, 1160, 1060 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.86 (s, 1H, H-a), 7.60 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.36 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.24 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.17 (d, 2H, *J* = 8.6 Hz, Ar-H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 136.6 (C-Ar), 135.8 (C-Ar), 135.2 (C-Ar), 133.7 (C-a), 132.7 (C-Ar), 129.8 (C-Ar), 129.4 (C-Ar), 126.5 (C-Ar), 124.8 (C-Ar), 123.5 (C-Ar).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methylene)-4-fluoroaniline (V-13)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 46 % yield (327 mg).

Mol. Wt.: 357.81, Nature: yellow solid.

HRMS Calcd. for $C_{18}H_{17}ClFN_5$: 357.1157, Found : 357.1159

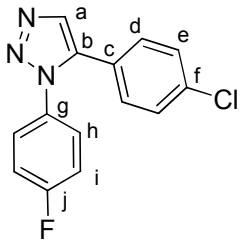
M.P. = 158-159 °C.

I.R. (thin film): 2980, 1615, 1576, 1483, 1368, 1231, 1186, 1074, cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.61 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.43 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.98-6.84 (m, 4H, Ar-H), 1.32 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 160.8 (d, $J_{C\text{-}F}$ = 247.1 Hz, C-j), 154.3 (C-b), 146.8 (C-Ar), 144.1 (d, $J_{C\text{-}F}$ = 2.9 Hz, C-g), 138.6 (C-Ar), 135.3 (C-Ar), 129.3 (C-Ar), 129.2 (C-Ar), 123.1 (d, $J_{C\text{-}F}$ = 8.2 Hz, C-h), 116.0 (d, $J_{C\text{-}F}$ = 22.5 Hz, C-i), 62.6 (C-1), 29.4 (C-2).

5-(4-chlorophenyl)-1-(4-fluorophenyl)-1*H*-1,2,3-triazole (V-14)



This compound was synthesized according to the general procedure **V-B**, using 0.84 mmol of iminotetrazole **V-13**. The desired product was isolated in 61 % yield (140 mg).

Mol. Wt.: 273.69, Nature: yellow solid.

HRMS Calcd. for $C_{14}H_9ClFN_3$: 273.0469, Found : 273.0468

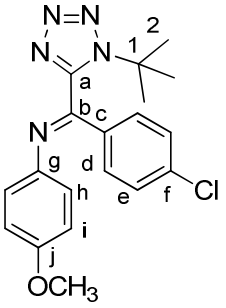
M.P. = 130-131 °C.

I.R. (thin film): 1607, 1517, 1485, 1231, 1157, 1095, 1049 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85 (s, 1H, H-a), 7.37-7.31 (m, 4H, Ar-H), 7.17-7.12 (m, 4H, Ar-H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 162.8 (d, J_{C-F} = 251.0 Hz, C-j), 136.7 (C-Ar), 135.6 (C-Ar), 133.4 (C-a), 132.3 (d, J_{C-F} = 3.0 Hz, C-g), 129.8 (C-Ar), 129.3 (C-Ar), 127.0 (d, J_{C-F} = 8.8 Hz, C-h), 124.9 (C-Ar), 116.6 (d, J_{C-F} = 23.4 Hz, C-i).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methylene)-4-methoxyaniline (V-15)**



This compound was synthesized according to the general procedure **V-A**, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 54 % yield (200 mg).

Mol. Wt.: 369.85, Nature: yellow solid.

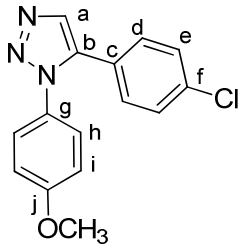
HRMS Calcd. for $C_{19}H_{20}ClN_5O$: 369.1356, Found : 369.1356.

I.R. (thin film): 2939, 28335, 1593, 1513, 1461, 1405, 1332, 1262, 1231, 1147, 1028 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.61 (d, 2H, *J* = 8.8 Hz, H-d), 7.41 (d, 2H, *J* = 9.0 Hz, H-h), 6.82 (d, 2H, *J* = 8.8 Hz, H-e), 6.76 (d, 2H, *J* = 9.0 Hz, H-i), 3.74 (s, 3H, OCH_3), 1.31 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 158.2 (C-b), 152.2 (C-j), 147.4 (C-g), 141.1 (C-a), 138.0 (C-f), 135.7 (C-c), 129.1 (C-d, C-h), 123.3 (C-e), 114.3 (C-i), 62.5 (C-1), 55.4 (OCH_3), 29.3 (C-2).

5-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (V-16)



This compound was synthesized according to the general procedure **V-B**, using 0.5 mmol of iminotetrazole **V-15**. The desired product was isolated in 72 % yield (102 mg).

Mol. Wt.: 285.73, Nature: dark brown oil.

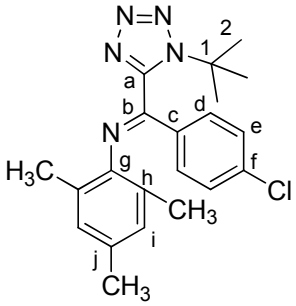
HRMS Calcd. for $C_{15}H_{12}ClN_3O$: 285.0669, Found : 285.0674.

I.R. (thin film): 1607, 1513, 1482, 1394, 1300, 1248, 1171, 1095 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.89 (s, 1H, H-a), 7.33 (d, 2H, *J* = 8.6 Hz, H-h), 7.27 (d, 2H, *J* = 8.8 Hz, H-d), 7.16 (d, 2H, *J* = 8.8 Hz, H-e), 6.95 (d, 2H, *J* = 8.6 Hz, H-i), 3.85(s, 3H, -OCH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 160.1 (C-j), 136.6 (C-Ar), 135.3 (C- Ar), 133.2 (C-a), 129.7 (C-Ar), 129.2 (C-Ar), 126.6 (C-Ar), 125.2 (C-Ar), 116.4 (C-Ar), 114.6 (C-Ar), 55.6 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methylene)-2,4,6-trimethylaniline (V-17)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 39 % yield (300 mg).

Mol. Wt.: 381.90, Nature: yellow solid.

HRMS Calcd. for $C_{21}H_{24}ClN_5$: 381.1720, Found : 381.1728

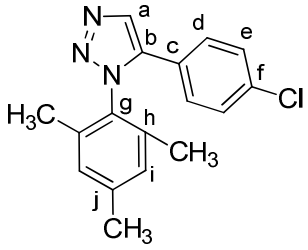
M.P. = 135-136 °C.

I.R. (thin film): 2922, 1628, 1593, 1482, 1373, 1248, 1224, 1154, 1095, 1018 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.22 (dd, 2H, *J* = 2.0, 8.6 Hz, H-d), 7.04 (dd, 2H, *J* = 2.0, 8.6 Hz, H-e), 6.82 (s, 2H, H-i), 2.26 (s, 3H, -CH_3), 2.03 (s, 6H, -CH_3), 1.76 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.0 (C-b), 152.0 (C-g), 143.9 (C-a), 137.1 (C-j), 134.0 (C-f), 132.8 (C-h), 129.8 (C-e), 129.3 (C-d), 128.9 (C-i), 126.6 (C-c), 62.7 (C-1), 29.9 (C-2), 20.7 (CH_3), 18.6 (CH_3).

5-(4-chlorophenyl)-1-mesityl-1*H*-1,2,3-triazole (V-18)



This compound was synthesized according to the general procedure **V-B**, using 0.68 mmol of iminotetrazole **V-17**. The desired product was isolated in 59 % yield (120 mg).

Mol. Wt.: 297.78, Nature: yellow oil.

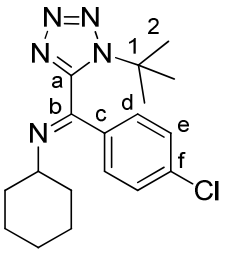
HRMS Calcd. for $C_{17}H_{16}ClN_3$: 297.1033, Found : 297.1031

I.R. (thin film): 1612, 1524, 1472, 1393, 1321, 1250, 11072, 1082, 1008 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.00 (s, 1H, H-a), 7.27 (d, 2H, *J* = 8.5 Hz, H-d), 7.10 (d, 2H, *J* = 8.5 Hz, H-e), 6.98 (s, 2H, H-i), 2.36 (s, 3H, CH_3), 1.87 (s, 6H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 140.3 (C-Ar), 137.2 (C-Ar), 135.3 (C-Ar), 135.2 (C-Ar), 132.4 (C-Ar), 132.2 (C-a), 129.4 (C-Ar), 129.3 (C-Ar), 128.1 (C-i), 125.0 (C-Ar), 21.2 (CH_3), 17.5 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methylene) cyclohexanamine (V-19)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 49 % yield (342 mg).

Mol. Wt.: 345.87, Nature: yellow oil.

HRMS Calcd. for $C_{18}H_{24}ClN_5$: 345.1720, Found : 345.1718

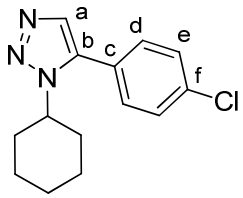
M.P. = 158-159 °C.

I.R. (thin film): 2929, 2856, 1621, 1593, 1482, 1401, 1370, 1255, 1213, 1091, 1044 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.43-7.30 (m, 4H, H-Ar), 2.76-2.64 (m, 1H, H-cy), 1.86-1.65 (m, 4H, H-cy), 1.64-1.48 (m, 12H, H-cy, H-2), 1.35-1.07 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 152.0 (C-b), 147.4 (C-a), 137.3 (C-c), 135.8 (C-f), 129.0 (C-d), 128.7 (C-e), 64.5 (C-cy), 62.3 (C-1), 33.2 (C-cy), 31.0 (C-cy), 29.8 (C-cy), 25.3 (C-2), 24.0 (C-cy), 23.9 (C-cy).

5-(4-chlorophenyl)-1-cyclohexyl-1*H*-1,2,3-triazole (V-20)



This compound was synthesized according to the general procedure **V-B**, using 0.80 mmol of iminotetrazole **V-19**. The desired product was isolated in 44 % yield (92 mg).

Mol. Wt.: 261.75, Nature: yellow oil.

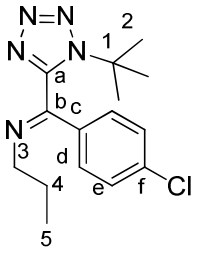
HRMS Calcd. for $C_{14}H_{16}ClN_3$: 261.1033, Found : 261.1032

I.R. (thin film): 2938, 2854, 1478, 1453, 1415, 1238, 1091 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.26 (s, 1H, H-a), 7.46 (d, 2H, *J* = 8.0 Hz, H-d), 7.25 (d, 2H, *J* = 8.0 Hz, H-e), 4.18-4.05 (m, 1H, H-cy), 2.15-2.02 (m, 2H, H-cy), 2.00-1.82 (m, 4H, H-cy), 1.75-1.94 (m, 1H, H-cy), 1.35-1.20 (m, 3H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 135.9 (C-b), 135.6 (C-f), 132.8 (C-a), 130.2 (C-e),129.4 (C-d),125.9 (C-c), 58.0 (C-cy), 33.5 (C-cy), 25.5 (C-cy), 24.9 (C-cy).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methylene)propan-1-amine (V-21)**



This compound was synthesized according to the general procedure **V-A**, using 0.9 mmol of *tert*-butyl isocyanide. The desired product was isolated in 87 % yield (242 mg).

Mol. Wt.: 305.81, Nature: white solid.

HRMS Calcd. for $C_{15}H_{20}ClN_5$: 305.1407, Found : 305.1405.

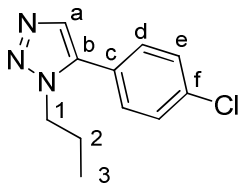
M.P. = 89-99 °C.

I.R. (thin film): 2967, 2938, 1628, 1590, 1461, 1405, 1370, 1255, 1213, 1147, 1091 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45-7.34 (m, 4H, H-Ar), 3.28 (dt, 1H, *J* = 6.9, 13.0 Hz, H-3), 3.07 (dt, 1H, *J* = 6.9, 13.0 Hz, H-3), 1.84-1.72 (m, 2H, H-4), 1.56 (s, 9H, H-2), 0.97 (t, 3H, *J* = 7.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.4 (C-b), 147.4 (C-a), 137.5 (C-f), 129.1 (C-d), 128.6 (C-e), 62.3 (C-3), 57.7 (C-1), 29.8 (C-4), 23.7 (C-2), 12.0 (C-5).

5-(4-chlorophenyl)-1-propyl-1*H*-1,2,3-triazole (V-22)



This compound was synthesized according to the general procedure **V-B**, using 1.0 mmol of iminotetrazole **V-21**. The desired product was isolated in 55 % yield (120 mg).

Mol. Wt.: 221.69, Nature: pale brown oil.

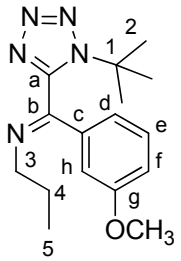
HRMS Calcd. for $C_{11}H_{12}ClN_3$: 221.0720, Found : 221.0719.

I.R. (thin film): 2940, 2860, 1475, 1455, 1415, 1238, 1080, 1006 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.66 (s, 1H, H-a), 7.46 (d, 2H, *J* = 8.4 Hz, H-d), 7.31 (d, 2H, *J* = 8.4 Hz, H-e), 4.27 (t, 2H, *J* = 7.4 Hz, H-1), 1.87 (m, 2H, H-2), 0.84 (t, 3H, *J* = 7.4 Hz, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 136.5 (C-b), 135.6 (C-f), 133.1 (C-a), 129.9 (C-e), 129.3 (C-d), 125.6 (C-c), 49.8 (C-1), 23.4 (C-2), 11.0 (C-3).

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(3-methoxyphenyl)methylene)propan-1-amine (V-23)



This compound was synthesized according to the general procedure **V-A**, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 53 % yield (160 mg).

Mol. Wt.: 301.39, Nature: yellow solid.

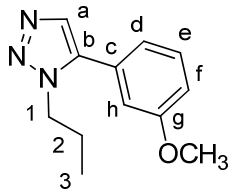
HRMS Calcd. for $C_{16}H_{23}N_5O$: 301.1903, Found : 301.1900

I.R. (thin film): 267, 2932, 1632, 1600, 1579, 1415, 1374, 1335, 1234, 1129, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.26 (t, 1H, *J* = 8.3 Hz, Ar-H), 7.21 (s, 1H, H-h), 7.00 (d, 1H, *J* = 8.3 Hz, Ar-H), 6.82 (d, 1H, *J* = 8.3 Hz, Ar-H), 3.81 (s, 3H, CH_3), 3.32-3.23 (m, 1H, H-3), 3.13-3.04 (m, 1H, H-3), 1.83-1.71 (m, 2H, H-4), 1.56 (s, 9H, H-2), 0.96 (t, 3H, *J* = 7.6 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 159.9 (C-b), 155.3 (C-Ar), 147.7 (C-Ar), 138.5 (C-Ar), 129.7 (C-Ar), 120.4 (C-Ar), 117.4 (C-Ar), 111.6 (C-Ar), 62.2 (C-1), 57.6 (C-3), 55.4 (-OCH_3), 29.7 (C-2), 23.8 (C-4), 12.0 (C-5).

5-(3-methoxyphenyl)-1-propyl-1_H_-1,2,3-triazole (V-24)



This compound was synthesized according to the general procedure **V-B**, using 0.5 mmol of iminotetrazole **V-23**. The desired product was isolated in 56 % yield (60 mg).

Mol. Wt.: 217.27, Nature: oil.

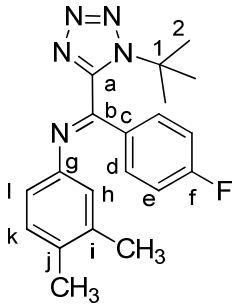
HRMS Calcd. for $C_{12}H_{15}N_3O$: 217.1215, Found : 217.1214

I.R. (thin film): 2840, 1615, 1514, 1483, 1395, 1330, 1247, 1165, 1085 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.68 (s, 1H, H-a), 7.40 (t, 1H, *J* = 7.8 Hz, H-e), 7.00 (d, 1H, *J* = 8.1 Hz, H-d), 6.95 (d, 1H, *J* = 7.8 Hz, H-f), 6.89 (s, 1H, H-h), 4.31 (t, 2H, *J* = 7.3 Hz, H-l), 3.85 (s, 3H, CH_3), 1.86 (m, 2H, H-2), 0.87 ((t, 3H, *J* = 7.3 Hz, H-3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 159.8 (C-g), 137.5 (C-b), 133.0 (C-a), 130.2 (C-e), 128.5 (C-c), 120.9 (C-d), 114.6 (C-f), 114.5 (C-h), 55.4 (CH_3), 49.9 (C-1), 23.5 (C-2), 11.0 (C-3).

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(4-fluorophenyl)methylene)-3,4-dimethylaniline (V-25)



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 51 % yield (360 mg).

Mol. Wt.: 351.42, Nature: yellow solid.

HRMS Calcd. for $C_{20}H_{22}FN_5$: 351.1859, Found : 351.1861.

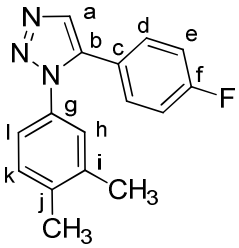
M.P. = 160-161 °C.

I.R. (thin film): 2978, 2925, 1621, 1593, 1510, 1471, 1374, 1304, 1265, 1234, 1157, 1105, 1001 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.68 (t, 2H, *J* = 8.3 Hz, H-d), 7.13 (t, 2H, *J* = 8.3 Hz, H-e), 6.96 (d, 1H, *J* = 8.0 Hz, H-k), 6.69 (s, 1H, H-h), 6.57 (d, 1H, *J* = 8.0 Hz, H-l), 2.16 (s, 3H, H-CH_3), 2.15 (s, 3H, H-CH_3), 1.31 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 164.9 (d, J_{C-F} = 254.0 Hz, C-f), 153.0 (C-b), 147.3 (C-a), 145.9 (C-g), 137.4 (C-j), 134.7 (C-i), 133.5 (d, J_{C-F} = 3.1 Hz, C-c), 130.2 (d, J_{C-F} = 18.0 Hz, C-d), 130.1 (C-k), 122.7 (C-h), 118.5 (C-l), 116.0 (d, J_{C-F} = 18.0 Hz, C-e), 62.4 (C-l), 29.3 (C-2), 19.7 (C-CH_3), 19.3 (C-CH_3).

1-(3,4-dimethylphenyl)-5-(4-fluorophenyl)-1_H_-1,2,3-triazole (V-26)



This compound was synthesized according to the general procedure **V-B**, using 0.8 mmol of iminotetrazole **V-25**. The desired product was isolated in 78 % yield (170 mg).

Mol. Wt.: 267.30, Nature: white solid.

HRMS Calcd. for $C_{16}H_{14}FN_3$: 267.1172, Found : 267.1160.

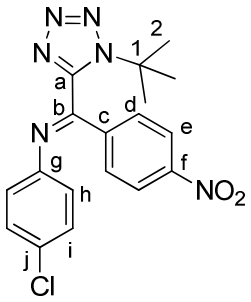
M.P. = 173-174 °C.

I.R. (thin film): 2915, 1611, 1555, 1492, 1454, 1227, 1164, 1060 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.83 (s, 1H, H-a), 7.25-7.18 (m, 3H, H-d, H-h), 7.15 (d, 1H, *J* = 8.0 Hz, H-l), 7.04 (t, 2H, *J* = 8.6 Hz, H-e), 6.96 (d, 1H, *J* = 8.0 Hz, C-k), 2.30 (s, 3H, CH_3), 2.27 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 163.0 (d, J_{C-F} = 250.0 Hz, C-f), 138.2 (C-Ar), 136.7 (C-Ar), 134.0 (C-Ar), 133.1 (C-a), 130.5 (C-Ar), 130.4 (d, J_{C-F} = 20.0 Hz, C-Ar), 126.1 (C-Ar), 123.0 (d, J_{C-F} = 3.3 Hz, C-c), 122.4 (C-Ar), 116.0 (d, J_{C-F} = 20.0 Hz, C-Ar), 19.9 (CH_3), 19.6 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(4-nitrophenyl)methylene)-4-chloroaniline (V-27)**



This compound was synthesized according to the general procedure **V-A**, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 50 % yield (190 mg).

Mol. Wt.: 384.82, Nature: yellow oil.

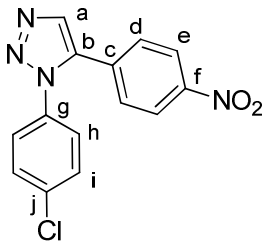
HRMS Calcd. for $C_{18}H_{17}ClN_6O_2$: 384.1102, Found : 384.1096

I.R. (thin film): 2995, 1628, 1604, 1523, 1485, 1405, 1374, 1349, 1248, 1192, 1095, 1011 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.31 (d, 2H, *J* = 8.6 Hz, H-e), 7.87 (d, 2H, *J* = 8.6 Hz, H-d), 7.25 (d, 2H, *J* = 8.6 Hz, H-i), 6.87 (d, 2H, *J* = 8.6 Hz, H-h), 1.33 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.8 (C-b), 149.8 (C-f), 146.2 (C-a), 146.0 (C-g), 141.8 (C-c),132.7 (C-j), 129.4 (C-i), 129.1 (C-e), 124.1 (C-d), 122.7 (C-h), 62.8 (C-1), 29.4 (C-2).

1-(4-chlorophenyl)-5-(4-nitrophenyl)-1*H*-1,2,3-triazole (V-28)



This compound was synthesized according to the general procedure **V-B**, using 0.5 mmol of iminotetrazole **V-27**. The desired product was isolated in 57 % yield (84 mg).

Mol. Wt.: 300.70, Nature: yellow solid.

HRMS Calcd. for $C_{14}H_9ClN_4O_2$: 300.0414, Found : 300.0414

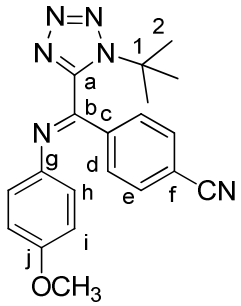
M.P. = 161-162 °C.

I.R. (thin film): 3107, 1604, 1520, 1492, 1412, 1342, 1234, 1234, 1133, 1098, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.23 (d, 2H, *J* = 8.6 Hz, H-e), 7.98 (s, 1H, H-a), 7.46 (d, 2H, *J* = 8.6 Hz, H-d), 7.43 (d, 2H, *J* = 8.6 Hz, H-h), 7.30 (d, 2H, *J* = 8.6 Hz, H-i).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 148.0 (C-f), 135.9 (C-g), 135.6 (C-j), 134.3 (C-a, C-c), 132.6 (C-b), 130.0 (C-h), 129.3 (C-i), 126.3 (C-d), 124.3 (C-e).

4-((1-(tert-butyl)-1*H*-tetrazol-5-yl)((4-methoxyphenyl)imino)methyl) benzonitrile (V-29)



This compound was synthesized according to the general procedure **V-A**, using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 72 % yield (260 gm).

Mol. Wt.: 360.41, Nature: yellow solid.

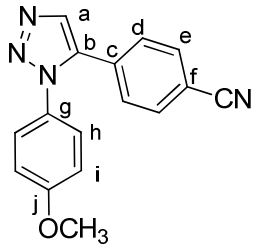
HRMS Calcd. for $C_{20}H_{20}N_6O$: 360.1699, Found : 360.1706

I.R. (thin film): 2933, 2245, 1630, 1601, 1513, 1304, 1180, 1107, 1021 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2H, *J* = 8.4 Hz, H-d), 7.74 (d, 2H, *J* = 8.4 Hz, H-e), 6.83 (d, 2H, *J* = 9.0 Hz, H-h), 6.79 (d, 2H, *J* = 9.0 Hz, H-i), 3.76 (s, 3H, OCH_3), 1.30 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 158.8 (C-j), 151.0 (C-b), 147.1 (C-g), 140.9 (C-a), 140.6 (C-c), 132.6 (C-e), 128.3 (C-d), 123.7 (C-h), 118.1 (-CN), 114.8 (C-f), 114.4 (C-i), 63.6 (C-1), 55.4 (OCH_3), 29.3 (C-2).

4-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-5-yl)benzonitrile (V-30)



This compound was synthesized according to the general procedure **V-B**, using 0.6 mmol of iminotetrazoel **V-29**. The desired product was isolated in 54 % yield (89 mg).

Mol. Wt.: 276.29, Nature: brown solid.

HRMS Calcd. for $C_{16}H_{12}N_4O$: 276.1011, Found : 279.1010.

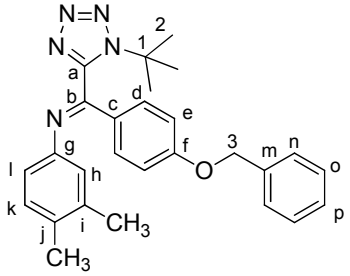
M.P. = 125-126 °C.

I.R. (thin film): 2930, 2243, 1680, 1607, 1513, 1304, 1251, 1175, 1108, 1028 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94 (s, 1H, H-a), 7.64 (d, 2H, *J* = 8.6 Hz, H-d), 7.35 (d, 2H, *J* = 8.6 Hz, H-e), 7.25 (d, 2H, *J* = 9.0 Hz, H-h), 6.97 (d, 2H, *J* = 9.0 Hz, H-i), 3.86 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 160.4 (C-j), 135.9 (C-c), 133.7 (C-a), 132.6 (C-e), 131.3 (C-b), 128.9 (C-d), 128.8 (C-g), 126.6 (C-h), 118.0 (-CN), 114.8 (C-i), 112.8 (C-f), 55.6 (-OCH_3).

***N*-((4-(benzyloxy)phenyl)(1-(tert-butyl)-1*H*-tetrazol-5-yl)methylene)-3,4-dimethylaniline (V-31)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 72 % yield (630 mg).

Mol. Wt.: 439.55, Nature: yellow solid.

HRMS Calcd. for $C_{27}H_{29}N_5O$: 439.2372, Found : 439.2375

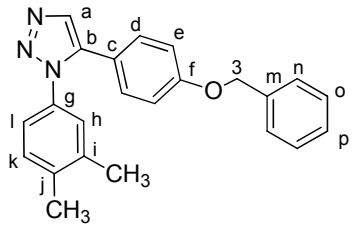
M.P. = 152-153 °C.

I.R. (thin film): 2981, 3932, 1593, 1513, 1445, 1374, 1307, 1248, 1175, 1112, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.59 (d, 2H, *J* = 8.6 Hz, H-d), 7.46-7.32 (m, 5H, H-Ar), 7.01 (d, 2H, *J* = 8.6 Hz, H-e), 6.94 (d, 1H, *J* = 8.0 Hz, H-k), 6.68 (s, 1H, H-h), 6.57 (d, 1H, *J* = 8.0 Hz, H-l), 5.11 (s, 2H, H-3), 2.15 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 1.32 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 161.6 (C-b), 153.6 (C-Ar), 147.6 (C-Ar), 146.3 (C-Ar), 137.2 (C-Ar), 136.2 (C-Ar), 134.0 (C-Ar), 130.2 (C-Ar), 130.0 (C-Ar), 129.8 (C-Ar), 128.7 (C-Ar), 128.2 (C-Ar), 127.5 (C-Ar), 122.7 (C-Ar), 118.5 (C-Ar), 115.0 (C-Ar), 70.1 (C-3), 62.3 (C-1), 29.3 (C-2), 19.7 (CH_3), 19.2 (CH_3).

5-(4-(benzyloxy)phenyl)-1-(3,4-dimethylphenyl)-1*H*-1,2,3-triazole (V-32)



This compound was synthesized according to the general procedure **V-B**, using 1.0 mmol of iminotetrazole **V-31**. The desired product was isolated in 72 % yield (255 mg).

Mol. Wt.: 355.43, Nature: pale brown oil.

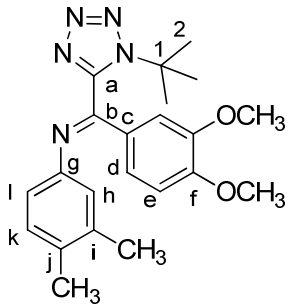
HRMS Calcd. for $C_{23}H_{21}N_3O$: 355.1685, Found : 355.1681

I.R. (thin film): 2925, 1614, 1496, 1454, 1387, 1241, 1178, 1129, 1021 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.83 (s, 1H, H-a), 7.47-7.33 (m, 5H, Ar-H), 7.29 (s, 1H, H-h), 7.22-7.15 (m, 3H, Ar-H), 7.02 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.96 (d, 2H, *J* = 8.6 Hz, Ar-H), 5.09 (s, 2H, H-3), 2.34 (s, 3H, CH_3), 2.30 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 159.3 (C-Ar), 138.0 (C-Ar), 137.9 (C-Ar), 137.3 (C-Ar), 136.3 (C-Ar), 134.4 (C-Ar), 132.8 (C-a), 130.2 (C-Ar), 129.8 (C-Ar), 128.6 (C-Ar), 128.2 (C-Ar), 127.5 (C-Ar), 126.2 (C-Ar), 122.4 (C-Ar), 119.3 (C-Ar), 115.1 (C-Ar), 70.0 (C-1), 19.8 (CH_3), 19.6 ($CH_{3)}$.

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(3,4-dimethoxyphenyl)methylene)-3,4-dimethylaniline (V-33)



This compound was synthesized according to the general procedure **V-A,** using 1.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 87 % yield (341 mg).

Mol. Wt.: 339.48, Nature: yellow solid.

HRMS Calcd. for $C_{22}H_{27}N_5O_2$: 393.2165, Found : 393.2173

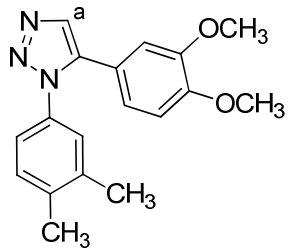
M.P. = 130-130 °C.

I.R. (thin film): 2967, 2938, 1583, 1513, 1461, 1422, 1374, 1269, 1171, 1133, 1028 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.70 (s, 1H, Ar-H), 6.95 (d, 1H, *J* = 7.5 Hz, Ar-H), 6.81 (d, 1H, *J* = 8.2 Hz, Ar-H), 6.73-6.64 (m, 2H, Ar-H), 6.58 (d, 1H, *J* = 7.2 Hz, Ar-H), 3.96 (s, 3H, H-CH_3), 3.93 (s, 3H, H-CH_3), 2.15 (s, 3H, H-CH_3), 1.33 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.7 (C-b), 152.3 (C-Ar), 149.4 (C-Ar), 147.6 (C-Ar), 146.3 (C-Ar), 137.2 (C-Ar), 134.0 (C-Ar), 130.4 (C-Ar), 130.0 (C-Ar), 123.0 (C-Ar), 122.6 (C-Ar), 118.4 (C-Ar), 110.1 (C-Ar), 108.9 (C-Ar),62.3 (C-l), 56.0 (CH_3), 29.3 (CH_3), 19.3 (CH_3), 19.2 (CH_3).

5-(3,4-dimethoxyphenyl)-1-(3,4-dimethylphenyl)-1_H_-1,2,3-triazole (V-34)



This compound was synthesized according to the general procedure **V-B**, using 0.5 mmol of iminotetrazole **V-33**. The desired product was isolated in 64 % yield (99 mg).

Mol. Wt.: 309.15, Nature: oil.

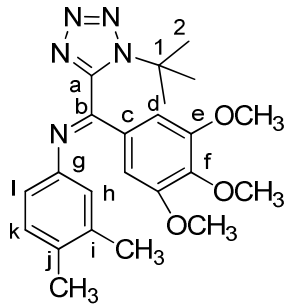
HRMS Calcd. for $C_{18}H_{19}N_3O_2$: 309.3624, Found : 309.3625

I.R. (thin film): 2938, 1588, 1506, 1544, 1325, 1255, 1231, 1131, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81 (s, 1H, H-a), 7.23 (s, 1H, Ar-H), 7.16 (d, 1H, *J* = 8.1 Hz, Ar-H),7.01 (d, 1H, *J* = 8.1 Hz, Ar-H), 6.84-6.80 (m, 2H, Ar-H), 6.67 (s, 1H, Ar-H), 3.88 (s, 3H, H-CH_3), 3.67 (s, 3H, H-CH_3), 2.29 (s, 3H, H-CH_3), 2.26 (s, 3H, H-CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 149.5 (C-Ar), 148.7 (C-Ar), 138.0 (C-Ar), 137.9 (C-Ar), 137.5 (C-Ar), 134.4 (C-Ar), 132.6 (C-Ar), 130.1 (C-Ar), 126.3 (C-Ar), 122.6 (C-Ar), 121.4 (C-Ar), 119.2 (C-Ar), 111.3 (C-Ar), 111.1 (C-Ar), 55.8 (CH_3), 55.7 (CH_3), 19.8 (CH_3), 19.5 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methylene)-3,4-dimethylaniline (V- 35)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 39 % yield (330 mg).

Mol. Wt.: 423.51, Nature: yellow solid.

HRMS Calcd. for $C_{23}H_{29}N_5O_3$: 423.2270, Found :423.2271

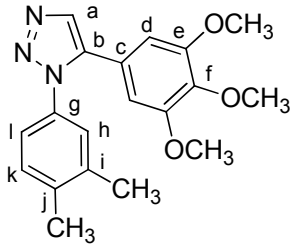
M.P. = 165-166 °C.

I.R. (thin film): 2978, 2943, 1579, 1506, 1457, 1415, 1374, 1335, 1234, 1129, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.95 (d, 1H, *J* = 8.0 Hz, H-k), 6.87 (s, 2H, H-d), 6.69 (d, 1H, *J* = 2.0 Hz, H-h), 6.57 (dd, 1H, *J* = 2.0, 8.0 Hz, H-l), 3.91 (s, 3H, CH_3), 3.82 (s, 6H, CH_3), 2.16 (s, 3H, H-CH_3), 2.14 (s, 3H, CH_3), 1.34 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.8 (C-b), 152.4 (C-e), 147.5 (C-g), 146.2 (C-a), 141.4 (C-f), 137.4 (C-i), 134.5 (C-j), 132.6 (C-c), 130.1 (C-k), 122.6 (C-h), 116.5 (C-l), 105.3 (C-d), 62.5 (C-l), 61.1 (CH_3), 56.3 (CH_3), 29.4 (C-2), 19.8 (CH_3), 19.3 (CH_3).

1-(3,4-dimethylphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (V-36)



This compound was synthesized according to the general procedure **V-B**, using 0.7 mmol of iminotetrazole **V-35**. The desired product was isolated in 71 % yield (170 mg).

Mol. Wt.: 339.39, Nature: brown solid.

HRMS Calcd. for $C_{19}H_{21}N_3O_3$: 339.1583, Found : 339.1584

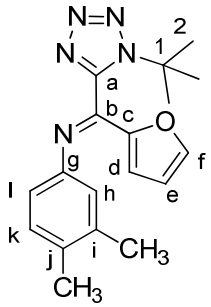
M.P. = 112-113 °C.

I.R. (thin film): 2938, 1691, 1590, 1498, 1457, 1234, 1122, 1007 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.83 (s, 1H, H-a), 7.22 (s, 1H, H-h), 7.17 (d, 1H, *J* = 8.1 Hz, H-k), 7.02 (d, 1H, *J* = 8.1 Hz, H-l), 6.41 (s, 2H, H-d), 3.84 (s, 3H, CH_3), 3.66 (s, 6H, CH_3), 2.30 (s, 3H, CH_3), 2.27 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.2 (C-e), 138.5 (C-f), 138.1 (C-i), 138.0 (C-j), 137.5 (C-b), 134.3 (C-g), 132.7 (C-a), 130.2 (C-k), 126.3 (C-h), 122.7 (C-l), 122.0 (C-c), 105.7 (C-d), 60.9 (CH_3), 56.0 (CH_3), 19.7 (CH_3), 19.5 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(furan-2-yl)methylene)-3,4-dimethylaniline (V-37)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 50 % yield (320 mg).

Mol. Wt.: 323.39, Nature: yellow solid.

HRMS Calcd. for $C_{18}H_{21}N_5O$: 323.1746, Found : 323.1748

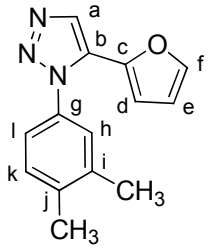
M.P. = 97-98 °C.

I.R. (thin film): 2980, 1670, 1580, 1515, 1478, 1439, 1377, 1225, 1080, 1015 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.58 (s, 1H, H-a), 6.88 (d, 1H, *J* = 8.1 Hz, Ar-H), 6.64 (s, 1H, Ar-H), 6.54-6.47 (m, 3H, Ar-H), 2.09 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.28 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 151.8 (C-b), 146.4 (C-f), 145.5 (C-a), 144.1 (C-g), 137.4 (C-c), 135.0 (C-j), 134.9 (C-i), 130.1 (C-k), 123.2 (C-h), 119.0 (C-l), 116.8 (C-d), 112.6 (C-e), 62.6 (C-1), 29.2 (C-2), 19.7 (CH_3), 13.3 (CH_3).

1-(3,4-dimethylphenyl)-5-(furan-2-yl)-1*H*-1,2,3-triazole (V-38)



This compound was synthesized according to the general procedure **V-B**, using 0.6 mmol of iminotetrazole **V-37**. The desired product was isolated in 54 % yield (80 mg).

Mol. Wt.: 239.27, Nature: Oil

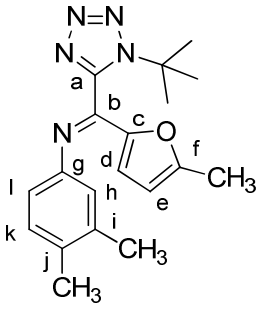
HRMS Calcd. for $C_{14}H_{13}N_3O$: 239.1059, Found : 23.1058.

I.R. (thin film): 2838, 1607, 1513, 1482, 1394, 1300, 1248, 1171, 1095 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.98 (s, 1H, H-a), 7.45 (s, 1H, H-h), 7.29-7.23 (m, 2H, H-d, H-l), 7.15 (d, 1H, *J* = 7.8 Hz, H-k), 6.36 (m, 1H, H-e), 6.06 (t, 1H, *J* = 2.5 Hz, H-f), 2.36 (s, 3H, CH_3), 2.32 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 143.3 (C-f), 141.7 (C-c), 138.9 (C-j), 138.2 (C-i), 134.2 (C-b), 131.6 (C-a), 130.3 (C-l), 126.7 (C-g), 123.0 (C-h), 111.5 (C-e), 109.9 (C-d), 19.8 (-CH_3), 19.7 (CH_3).

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(5-methylfuran-2-yl)methylene)-3,4-dimethylaniline (V-39)**



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 39 % yield (260 mg).

Mol. Wt.: 337.42, Nature: yellow solid.

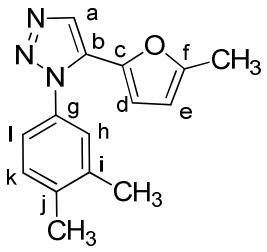
HRMS Calcd. for $C_{19}H_{23}N_5O$: 337.1903, Found : 337.1905

I.R. (thin film): 2981, 1677, 1593, 1530, 1499, 1454, 1377, 1227, 1088, 1021 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.92 (d, 1H, *J* = 8.0 Hz, H-k), 6.68 (d, 1H, *J* = 1.9 Hz, H-h), 6.57 (dd, 1H, *J* = 1.9, 8.0 Hz, H-l), 6.36 (d, 1H, *J* = 3.3 Hz, H-d), 6.15 (d, 1H, *J* = 3.3 Hz, H-e), 2.43 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.33 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 157.8 (C-b), 150.3 (C-Ar), 146.8 (C-Ar), 145.8 (C-Ar), 143.9 (C-Ar), 137.2 (C-Ar), 134.4 (C-Ar), 130.0 (C-Ar), 123.2 (C-Ar), 119.2 (C-Ar), 119.0 (C-Ar), 109.3 (C-Ar), 62.5 (C-1), 29.3 (C-2), 19.6 (CH_3), 19.2 (CH_3), 14.2 (CH_3).

1-(3,4-dimethylphenyl)-5-(5-methylfuran-2-yl)-1*H*-1,2,3-triazole (V-40)



This compound was synthesized according to the general procedure **V-B**, using 0.6 mmol of iminotetrazole **V-39**. The desired product was isolated in 37 % yield (55 mg).

Mol. Wt.: 253.30, Nature: yellow oil.

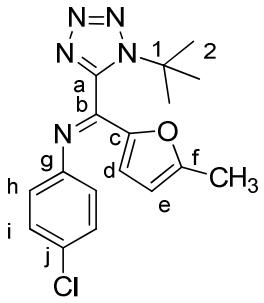
HRMS Calcd. for $C_{15}H_{15}N_3O$: 253.1215, Found : 253.1220

I.R. (thin film): 2922, 1656, 1579, 1510, 1450, 1297, 1234, 1115, 1021 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (s, 1H, H-a), 7.30-7.24 (m, 2H, H-h, H-k), 7.17 (d, 1H, *J* = 7.5 Hz, H-l), 5.93 (d, 1H, *J* = 3.2 Hz, H-d), 5.87 (d, 1H, *J* = 3.2 Hz, H-e), 2.36 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.5 (C-c), 140.0 (C-f), 138.8 (C-i), 138.1 (C-j), 134.3 (C-g), 130.9 (C-a), 130.3 (C-k), 130.2 (C-b), 126.9 (C-l), 123.1 (C-h), 110.8 (C-d), 107.6 (C-e), 19.8 (CH_3), 19.7 (CH_3), 13.5 (CH_3).

_N_-((1-(tert-butyl)-1_H_-tetrazol-5-yl)(5-methylfuran-2-yl)methylene)-4-chloroaniline (V-40)



This compound was synthesized according to the general procedure **V-A**, using 2.0 mmol of *tert*-butyl isocyanide. The desired product was isolated in 31 % yield (210 mg).

Mol. Wt.: 343.81, Nature: yellow semisolid.

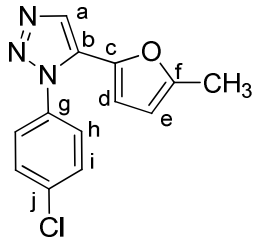
HRMS Calcd. for $C_{17}H_{18}ClN_5O$: 343.1200, Found : 343.1210

I.R. (thin film): 1670, 1592, 135, 1482, 1450, 1372, 1211, 1070, 1015 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.17 (d, 2H, *J* = 8.6 Hz, H-i), 6.85 (d, 2H, *J* = 8.6 Hz, H-h), 6.42 (d, 1H, *J* = 3.2 Hz, H-d), 6.19 (d, 1H, *J* = 3.2 Hz, H-e), 2.44 (s, 3H, -CH_3), 1.39 (s, 9H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 158.5 (C-b), 153.3 (C-f), 150.0 (C-g), 146.5 (C-a), 131.3 (C-c), 129.6 (C-j), 129.1 (C-i), 123.1 (C-h), 120.3 (C-d), 109.3 (C-e), 62.7 (C-1), 29.4 (C-2), 14.2 (CH_3).

1-(4-chlorophenyl)-5-(5-methylfuran-2-yl)-1_H_-1,2,3-triazole (V-42)



This compound was synthesized according to the general procedure **V-B**, using 0.5 mmol of iminotetrazole **V-41**. The desired product was isolated in 44 % yield (60 mg).

Mol. Wt.: 259.69, Nature: yellow oil.

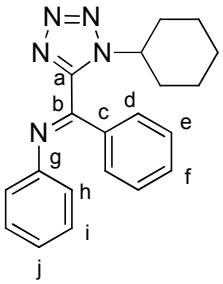
HRMS Calcd. for $C_{13}H_{10}ClN_3O$: 259.0512, Found : 259.0515

I.R. (thin film): 1596, 1492, 1409, 1283, 1231, 1206, 1098, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94 (s, 1H, H-a), 7.94 (dd, 2H, *J* = 2.0, 8.7 Hz, H-i), 7.43 (dd, 2H, *J* = 2.0, 8.7 Hz, H-h), 6.02-5.95 (m, 2H, H-d, H-e), 2.30 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.0 (C-Ar), 139.3 (C-Ar), 135.2 (C-Ar), 135.2 (C-Ar), 131.4 (C-a), 129.6 (C-Ar), 129.1 (C-Ar), 127.1 (C-Ar), 111.4 (C-Ar), 107.7 (C-Ar), 13.5 (CH_3).

***N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(phenyl)methylene)aniline (V-43)**



This compound was synthesized according to the general procedure V-**A**, using 3.0 mmol of cyclohexyl isocyanide. The desired product was isolated in 90.63 % yield (900 mg).

Mol. Wt.: 331.41, Nature: yellow solid.

HRMS Calcd. for $C_{20}H_{21}N_5$: 331.1797, Found :331.1795

M.P. = 123-124 °C

I.R. (thin film): 3060, 1627, 1586, 1472, 1458, 1228, 1121, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (d, 2H, *J* = 8.2 Hz, H-Ar), 7.55 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.46 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.23 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.09 (t, 1H, *J* = 7.3 Hz, H-Ar), 6.82 (d, 2H, *J* = 8.2 Hz, H-Ar), 3.74-3.61 (m, 1H, H-cy), 1.80-1.57 (m, 5H, H-cy), 1.25-0.95 (m, 5H, H-cy).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 153.8 (C-b), 148.6 (C-Ar), 148.5 (C-Ar), 136.3 (C-Ar), 132.4 (C-Ar), 129.2 (C-Ar), 128.9 (C-Ar), 128.3 (C-Ar), 126.0 (C-Ar), 120.6 (C-Ar), 58.7 (C-cy), 32.6 (C-cy), 32.5 (C-cy), 25.1 (C-cy), 24.5 (C-cy).

***