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Cyclization cascade of hydrazono Ugi adducts towards pyrazoles.

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Keywords: hydrazone / cycloaddition / aerobic oxidation / copper catalysis /

Acidic hydrolysis of Ugi adducts between α-hydrazonocarboxylic acids and aminoacetaldehyde dimethyl acetal leads to a fragmentation of the aminoacetaldehdye residue with final formation of pyrazoles. An aldol type reaction of the hydrazone is proposed as the key step of the cascade.

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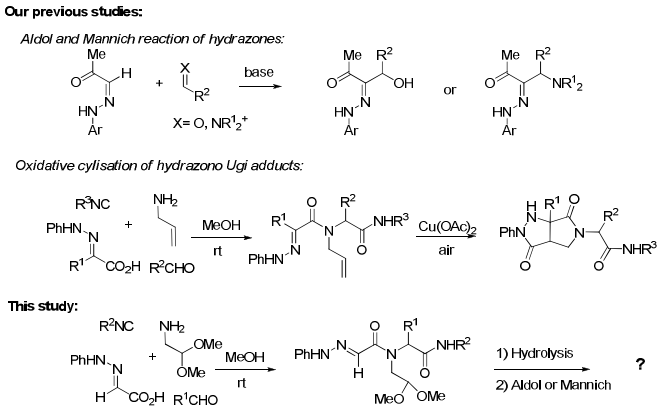
Introduction

Besides its multicomponent nature, the key to the success of Ugi reactions in both drug discovery and green chemistry is certainly the ability to form with high efficiency tertiary amides from primary amines.[1] Indeed, whenever amides are involved in cyclization strategies involving primary amines as starting material, the Ugi reaction avoids a tedious N-alkylative step in order to turn around the preferred, poorly reactive, s-trans conformation of secondary amides. This property has allowed some of the fastest access to nitrogen heterocycles from primary amines. Involved in isocyanide based multicomponent reactions (IMCRs) for the last two decades, our main interest for these reactions is linked to their potential as probes for reactivity study.[2] Stimulated by our previous studies on hydrazone chemistry,[3] we envisioned that the Ugi reaction of α-hydrazonocarboxylic acid could serve as a good synthetic platform to examine the intramolecular aldol type reaction between hydrazones and aldehydes. Herein, we wish to present the results of this study and report a surprising cascade towards pyrazoles.

Results and Discussion

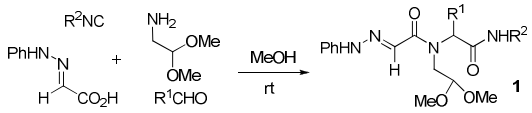
N-Monosusbtituted hydrazones share with isocyanides their ability to act as nucleophiles in aldol and mannich type reactions leading to new carbon-carbon bond formation (Scheme 1).[4] To be efficient, a tethered electron-withdrawing group such as a ketone or an ester is usually required on the carbon moiety of the hydrazone to increase the acidity of the latter. Hydrazones of glyoxylic acids are readily prepared throught condensation with arylhydrazines in water. Related hydrazonoacids may be used as acidic partners in Ugi reactions as shown by our previous report on oxidative cyclisation of *N*-allyl hydrazonoamides (Scheme 1).[5] The Ugi reaction of these acids with aminoacetaldehyde dimethoxy acetal would form, after deprotection of the acetal, ideal substrates for intramolecular aldol and mannich reactions (Scheme 1).



Scheme 1. Ugi strategies with hydrazones.

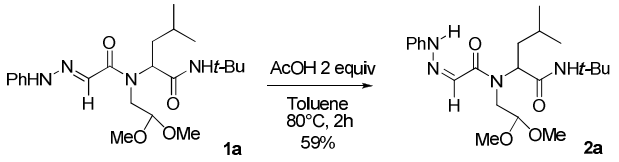
Thus, Ugi reactions of various glyoxilic hydrazones, isocyanides, amines and aldehydes were performed and the results displayed in Table 1.

Table 1. Ugi coupling of glyoxilic acid phenyl hydrazone



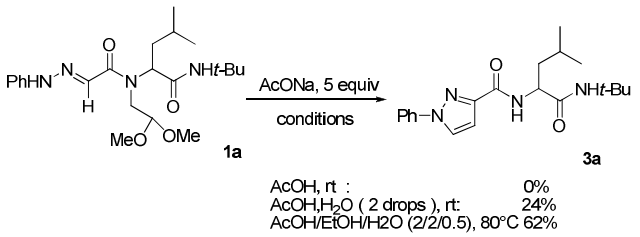
Entry	R^1	R^2	Ugi adduct 1 (yield)
1	*i*-Bu	*t*-Bu	**1a** (65%)
2	4-$MeOC_6H_4$	*t*-Bu	**1b** (56%)
3	Ph	Cy	**1c** (58%)
4	*i*-Bu	Cy	**1d** (48%)
5	4-$MeOC_6H_4$	Cy	**1e** (39%)
6	Et	Cy	**1f** (47%)
7	Et	*t*-Bu	**1g** (39%)
8	*i*-Bu	4-$MeOC_6H_4CH_2$	**1h** (74%)
9	*i*-Bu	4-$ClC_6H_4CH_2$	**1i** (52%)

All Hydrazono adducts were obtained in good to moderate yields as mixture of two rotamers as shown by the NMR data. The study was limited to N-phenyl derivatives as we already observed previously a competition between the more nucleophilic *N*-alkylhydrazones and the primary amines in the Ugi coupling with the aldehydes. The proton NMR chemical shifts observed for all N-H of hydrazones (8.5 to 9.5 ppm) indicate that the trans-conformation of the initial glyoxylic hydrazones is retained during the Ugi process. Under heating with acid, the trans-hydrazone may be converted into the cis-isomer (N-H over 12 ppm) thanks to a stabilizing intramolecular hydrogen bond (Scheme 2).



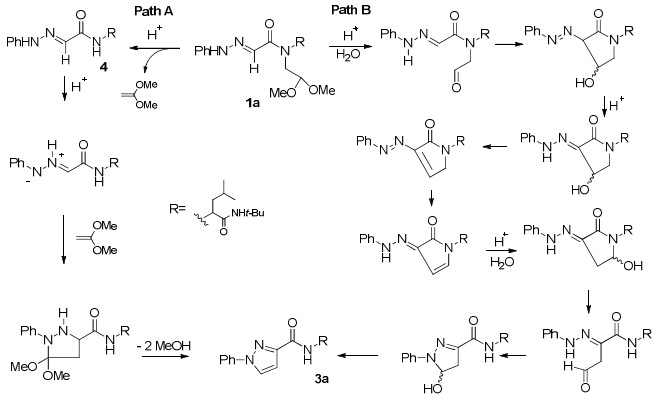
Scheme 2. Isomerisation of Ugi adduct **1a** under acidic condition.

With these Ugi adducts in hands, we next examined the deprotection of the acetal into the aldehyde. Working with **1a**, standard conditions (CF_3CO_2H in various solvents, with and without water) gave either the starting material, its cis-isomer or complex mixtures from which we could not isolate any trace of the aldehyde. This could be associated with a competition between the hydrazone and acetal moieties towards the hydrolysis under strong acidic conditions. Thinking that the aldehyde might be difficult to isolate, we next envisioned a tandem deprotection/aldol process under buffered conditions. Lowering the acidity of the medium would give more stability to the hydrazone and eventually allows it to react with the aldehyde either under its neutral or anionic form. Therefore, **1a** was left at room temperature in acetic acid with several equivalents of sodium acetate. While we could only recover the starting material in moderate yield under these conditions, we were delighted to observe the formation of a new product **3a** when the same reaction was performed with few drops of water at higher temperature (80°C) (Scheme 3). Surprisingly the pyrazole structure of **3a** did not fit with any of our mechanistic expectation. The yield of the latter could be raised to 62% by working under reflux with a mixture of ethanol, acetic acid and water in a 2/2/0.5 ratio.



Scheme 3. Pyrazole **3a** from hydrazone **1a**.

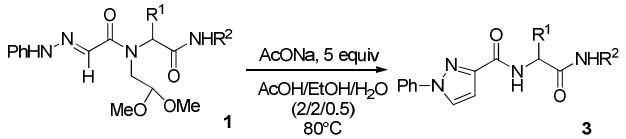
Several mechanisms may be considered for this transformation. [3+2] Cycloadditions of hydrazones towards pyrazoles are well documented[6] and a related mechanistic pathway could involve an intermediate fragmentation of **1a** into 1,1-dimethoxyethylene and **4** followed by a cycloaddition and a double elimination of methanol (Scheme 4, path A),[7] Though this mechanistic scheme is rather straightforward, the intermediacy of an instable and volatile 1,1-dimethoxyethylene is unlikely to occur. An alternative intramolecular process was thus proposed (Scheme 4, path B). It involves a prior hydrolysis of the acetal followed by an aldol addition. The following steps of the cascade towards pyrazole take advantage of the ability of the hydrazone to assist the various additions/eliminations with intermediate formation of azo derivatives.



Scheme 4. Possible mechanisms for the formation of pyrazole **3a**

All other Ugi hydrazones were treated under these optimized conditions forming pyrazoles **3a**-**3i** in moderate to good yields (Table 2). The high yield observed for hydrazone **1e** (Table 2, entry 4) gives a further argument for the preference of an intramolecular mechanism to explain the formation of pyrazoles (Scheme 4, path B).

Table 2. Formation of pyrazoles **3** from Ugi hydrazones **1**



Entry	R^1	R^2	Pyrazole 3 (yield)
1	4-$MeOC_6H_4$	*t*-Bu	**3b** (49%)
2	Ph	Cy	**3c** (54%)
3	*i*-Bu	Cy	**3d** (75%)
4	4-$MeOC_6H_4$	Cy	**3e** (94%)
5	Et	Cy	**3f** (74%)
6	Et	*t*-Bu	**3g** (52%)
7	*i*-Bu	4-$MeOC_6H_4CH_2$	**3h** (54%)
8	*i*-Bu	4-$ClC_6H_4CH_2$	**3i** (47%)

Conclusions

As a conclusion, working on Ugi hydrazone adducts, we have disclosed a new complex cascade leading to pyrazoles. The N-tethered dimethoxy acetaldehyde acetal moiety brings the two-carbon unit for the construction of the pyrazole ring and acts as an equivalent of methoxyacetylene or dimethoxyethylene in a formal [2+3] cycloaddition. The mechanism probably involves an intramolecular aldol reaction leading to a migration of the N-amide alkyl chain across the amide function. In this case, the formation of potential intermediates is shifted towards the more stable aromatic pyrazole. We are exploring further the reactivity of these Ugi adducts and the trappings of various electrophiles at the C-H position of the hydrazone.

Experimental Section

Typical experimental procedure for 1a: To a 1 M solution of isovaleraldehyde (214µl, 2 mmol) in methanol were added successively 1.0 equiv of aminoacetaldehyde dimethylacetal, 1.0 equiv of phenylhydrazono acetic acid and 1.0 equiv of *t*-butylisocyanide. The resulting mixture was stirred at 40 °C overnight. The solvent was removed under reduced pressure to afford after purification by flash chromatography on silica gel **1a** as a mixture of two rotamers A:B in a 6:4 ratio (546 mg, 65% yield). Yellow oil.**^{1}H NMR, 400MHz :** δ (ppm) 9.12 (s, 0.6H_A), 7.64 (s, 0.4H_B), 7.42 (s, 0.6H_A), 7.34 (s, 0.4H_B), 7.32 (m, 2H), 7.17 (d, 2H, *J*= 6.8Hz), 6.94 (t, 1H, *J*= 6.8Hz), 6.70 (s, 0.4H_B), 5.01 (m, 0.6H_A), 4.82 (m, 1H), 4.58 (m, 0.4H_B), 3.73 (m, 2H), 3.42-3.48 (m, 6H), 1.45-1.93 (m, 3H), 1.26 (s, 9H), 0.79-0.89 (m, 6H). **^{13}C NMR, 100MHz :** 170.71 (A), 170.16 (B), 166.05, 143.10 (A), 142.91 (B), 129.30 (A), 129.04 (B), 127.64, 121.88 (A), 121.65 (B), 113.73 (A), 113.59 (B), 103.99 (A), 102.40 (B), 62.03, 56.08 (A), 55.90 (B), 55.76 (A), 54.89 (B), 51.30 (A), 51.11 (B), 47.43, 37.30, 28.68 (B), 28.61 (A), 24.94, 23.37 (A), 22.93 (B), 22.57 (A), 21.72 (B). **IR (ν, cm^{-1}) :** 3329, 3243, 2959, 2870, 1662, 1628, 1535, 1246, 1166. **HRMS :** calculated for $C_{22}H_{36}N_4O_4$ 420.2737, found 420.2736.

Typical experimental procedure for 3a: To a solution of **1a** (84 mg, 0.2 mmol) in ethanol (2 ml) is added sodium acetate (80 mg, 1mmol), acetic acid (2 ml) and water (0.5 ml). The mixture is stirred overnight at 80°C. The ethanol is removed under reduced pressure; dichloromethane is added followed by a saturated aqueous K_2CO_3 solution (20 ml). After extraction with dichloromethane, the combined organic layers were dried over anhydrous MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel affords **3a** (52 mg, 62% yield). Brown oil. **^{1}H NMR, 400MHz :** δ (ppm) 7.86(d, 1H, *J*= 2.4Hz), 7.64 (d, 2H, *J*= 7.6Hz), 7.40 (t, 2H, *J*= 7.6Hz), 7.35 (d, 2H, *J*= 8.4Hz), 7.27 (t, 1H, *J*= 7.6Hz), 6.91 (d, 1H, *J*= 2.4Hz), 6.13 (s, 1H), 4.52 (m, 1H), 1.63 (s, 3H), 1.28 (s, 9H), 0.90 (s, 3H), 0.88 (s,3H). **^{13}C NMR, 100MHz :** 171.78, 161.74, 147.37, 139.58, 129.59, 128.59, 127.47, 119.66, 108.52, 51.95, 51.40, 41.39, 28.73, 24.86, 23.06, 22.24. **IR (ν, cm^{-1}) :** 3401, 3324, 3077, 2960, 1648, 1600, 1539, 1256. **HRMS :** calculated for $C_{20}H_{28}N_4O_2$ 356.2212, found 356.2213.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectral data for all new compounds are detailed.

Acknowledgments

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[1] For some reviews see: a) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210; b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321-3329; c) I. Ugi, B. Werner, A. Dömling, *Molecules* **2003**, *8*, 53-66; d) A. Dömling, *Curr. Opin. Chem. Bio.* **2002**, *6*, 306-313; e) "Multicomponent reactions"; J. Zhu, H. Bienaymé, Eds Wiley-VCH: Weinheim, **2005**; f) A. Dömling, *Chem. Rev.* **2006**, *106*, 17-89; g) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471-1499.

[2] for some examples see: a) R. Gamez-Montano, L. Grimaud, T. Ibarra-Rivera, *Chem. Commun.* **2008**, 1350–1352; b) L. El Kaim, L. Grimaud, S. Wagschal, *Chem. Commun.* **2011**, *47*, 1887-1889; c) A. Dos Santos, L. El Kaïm, L. Grimaud, R. Ramozzi, *Synlett* **2012**, *23*, 438-442.

[3] a) V. Atlan, H. Bienaymé, L. El Kaim, A. Majee, *Chem. Commun.* **2000**, 1585-1586; b) V. Atlan, L. El Kaim, C. Supiot, *Chem. Commun.* **2000**, 1385-1386; c) V. Atlan, L. El Kaim, L. Grimaud, N.K. Jana, A. Majee, *Synlett* **2002**, 352-354; d) L. El Kaim, L. Grimaud, Y. Perroux, C. Tirla, *J. Org. Chem.* **2003**, *68*, 8733-8735; e) L. El Kaïm, L. Gautier, L. Grimaud, V. Michaut, *Synlett* **2003**, 1844-1846; f) L. El Kaïm, L. Gautier, L. Grimaud, L. M. Harwood, V. Michaut, *Green Chem.* **2003**, 5, 477-479.

[4] a) W. Ried, G. Keil, *Liebigs Ann. Chem.*, **1957**, *605*, 167-179; b) K. Bodendorf, W. Wössner, *Liebigs Ann. Chem.* **1959**, *623*, 109; c) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, A. U. Jain, J. N. Kolhe, M. W. D.Perry, I. M. Newington, *J. Chem. Soc., Chem. Commun.* **1984**, 1095; d) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, A. U. Jain, J. N. Kolhe, M. W. D. Perry, I. M. Newington, *Tetrahedron* **1986**, 42, 4247. See also ref 3a,c,d,e,f.

[5] A. Dos Santos, L. El Kaim, L. Grimaud, C. Ronsseray, *Beilstein J Org. Chem.* **2011,** 7, 1310-1314.

[6] a) R. Grigg, J. Kemp, N. Thompson, *Tetrahedron Lett.* **1978**, *19*, 2827-2830; b) R. Grigg, M. Dowling, M. W. Jordan, V. Sridharan, *Tetrahedron* **1987**, *43*, 5873-5886; c) B. B. Snider, R. S. E. Conn, S. Sealfon, *J. Org. Chem.* **1979**, ***44***, 218-221; d) G. L. Fevre, J. Hamelin, *Tetrahedron Lett.* **1979**, *20*, 1757-1760; e) Y. A. Ibrahim,; S. E. Abdou,; S. Selim, *Heterocycles* **1982**, *19*, 819-824; f) M. A. Badawy, S. A. El-Bahaie, A. M. Kadry, Y. A. Ibrahim, *Heterocycles* **1988**, *27*, 7-10; g) V. V. Khau, M. J. Martinelli, *Tetrahedron Lett.* **1996**, *37*, 4323-4326. h) B. Sun, K. Adachi, M. Noguchi, *Tetrahedron* **1996**, *52*, 901-914. i) G. L. Fevre, S. Sinbandhit, J. Hamelin, *Tetrahedron* **1979**, *35*, 1821-1824. j) B. Fouchet, M. Joucla, J. Hamelin, *Tetrahedron Lett.* **1981**, *22*, 1333-1336. k) T. Shimizu, Y. Hayashi, S. Ishikawa, K. Teramura, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2456-2459. l) T. Shimizu, Y. Hayashi,; M. Miki,; K. Teramura *J. Org. Chem.* **1987**, *52*, 2277-2285.

[7] alternative MeOH elimination to give an N-acylenamine followed by an intermolecular cycloaddition would be more difficult to achieve for steric reasons

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Entry for the Table of Contents

Layout 2:

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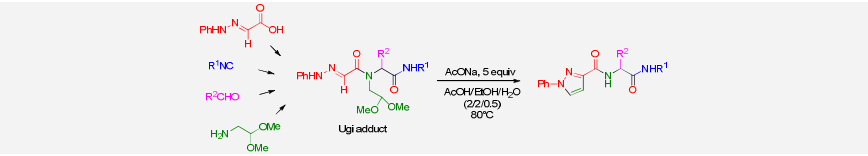


Cyclization cascade of hydrazono Ugi adducts towards pyrazoles.

A. Agrebi, L. El Kaïm, F. Allouche and F. Chabchoub ……..... Page No. – Page No.

Aldol reaction of hydrazones towards pyrazoles

Keywords: hydrazone / pyrazole / Ugi

SUPPORTING INFORMATION

TABLE OF CONTENTS

Experimental procedures and spectral data for compounds 1a-1k

To a solution of the aldehyde (2 mmol) in methanol (2 ml) were added successively 1.0 equiv of amine, 1.0 equiv of phenylhydrazono acetic acid and 1.0 equiv of isocyanide. The resulting mixture was stirred at 40 °C overnight. The solvent was removed under reduced pressure to afford the Ugi product after purification by flash chromatography on silica gel.

(*E*)-*N*-(ter-butyl)-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-4-methylpentanamide 1a.

Obtained as a mixture of two rotamers A:B in a 6:4 ratio

Yield : 65 %

^{1}H NMR, 400MHz : δ (ppm) 9.12 (s, 0.6H_A), 7.64 (s, 0.4H_B), 7.42 (s, 0.6H_A), 7.34 (s, 0.4H_B), 7.32 (m, 2H), 7.17 (d, 2H, *J*= 6.8Hz), 6.94 (t, 1H, *J*= 6.8Hz), 6.70 (s, 0.4H_B), 5.01 (m, 0.6H_A),

4.82 (m, 1H), 4.58 (m, 0.4H_B), 3.73 (m, 2H), 3.42-3.48 (m, 6H), 1.45-1.93 (m, 3H), 1.26 (s, 9H), 0.79-0.89 (m, 6H).
^{13}C NMR, 100MHz : 170.71 (A), 170.16 (B), 166.05, 143.10 (A), 142.91 (B), 129.30 (A), 129.04 (B), 127.64, 121.88 (A), 121.65 (B), 113.73 (A), 113.59 (B), 103.99 (A), 102.40 (B), 62.03, 56.08 (A), 55.90 (B), 55.76 (A), 54.89 (B), 51.30 (A), 51.11 (B), 47.43, 37.30, 28.68 (B), 28.61 (A), 24.94, 23.37 (A), 22.93 (B), 22.57 (A), 21.72 (B).
IR (ν, cm^{-1}) : 3329, 3243, 2959, 2870, 1662, 1628, 1535, 1246, 1166.
HRMS : calculated for $C_{22}H_{36}N_4O_4$ 420.2737, found 420.2736.
Aspect : yellow oil

(*E*)-*N*-cyclohexyl-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-2-(4-methoxyphenyl)acetamide 1b.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 56 %
^{1}H NMR, 400MHz : δ (ppm) 8.80 (s, 0.6H_A), 8.46 (s, 0.4H_B), 8.03 (s, 0.6H_A), 7.71 (s, 0.4H_B), 7.15-7.42 (m, 7H), 6.97 (m, 3H), 5.95 (s, 1H), 5.04(m, 0.6H_A), 3.66-3.84 (m, 5H), 3.32-3.53 (m, 7H+0.4H_B), 1.15-2.05 (m, 10H).
^{13}C NMR, 100MHz : 169.45, 166.79, 159.42, 143.13, 131.08, 130.27, 129.17, 127.38, 121.60, 114.14, 113.78, 104.59 (A), 102.43 (B), 66.68, 55.71, 55.35, 51.64, 48.53, 28.39.
IR (ν, cm^{-1}) : 3292, 3244, 2933, 2854, 1649, 1603, 1535, 1254, 1168.
HRMS : calculated for $C_{25}H_{34}N_4O_5$ 470.2529, found 470.2531.
Aspect : yellow oil

(*E*)-*N*-cyclohexyl-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-2-phenylacetamide 1c.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 58 %
^{1}H NMR, 400MHz : δ (ppm) 9.73 (s, 0.6H_A), 9.22 (s, 0.4H_B), 8.16 (s, 0.6H_A), 7.70 (s, 0.4H_B), 7.13-7.42 (m, 9H+0.6H_A), 6.91 (m, 1H), 6.47 (s, 0.4H_B), 6.06 (s, 1H), 5.02(m, 1H), 2.94-3.93 (m, 9H), 1.15-2.06 (m, 10H).
^{13}C NMR, 100MHz : 168.89, 167.49, 143.23, 135.26, 129.15, 128.84, 128.39, 127.12, 121.55, 113.78, 102.43, 66.92, 55.92, 55.42, 48.85, 33.03, 30.99, 25.54, 25.04.
IR (ν, cm^{-1}) : 3299, 3240, 2932, 2854, 1627, 1602, 1536, 1253, 1163.
HRMS : calculated for $C_{26}H_{34}N_4O_4$ 466.2580, found 466.2595.
Aspect : yellow oil

(*E*)-*N*-cyclohexyl-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-4-methylpentanamide 1d.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 48 %
^{1}H NMR, 400MHz : δ (ppm) 9.51 (s, 0.6H_A), 9.00 (s, 0.4H_B), 7.72 (s, 0.6H_A), 7.62 (s, 0.4H_B), 7.34 (s, 0.6H_A), 7.26 (t, 2H, *J*= 7.6Hz), 7.15 (d, 2H, *J*= 7.6Hz), 6.94 (t, 1H, *J*= 7.6Hz), 6.88 (s, 0.4H_B), 5.05 (m, 0.6H_A), 4.82 (s, 0.6H_A), 4.58 (s, 0.4H_B), 3.77 (m, 2H), 3.40-3.48 (m, 7H), 1.14-1.93 (m, 13H), 0.86-0.96 (m, 6H).

^{13}C NMR, 100MHz : 170.60 (A),170.16 (B), 166.24, 143.22 (A), 143.12 (B), 129.25 (A), 128.87 (B), 127.38, 121.74 (A), 121.54 (B), 113.70 (A), 113.57 (B), 103.85 (A), 102.39 (B), 61.62, 56.18 (A), 55.67 (B), 55.57 (A), 55.28 (B), 48.82, 48.27, 37.24, 33.11 (A), 32.89 (B), 25.55 (A), 25.10 (B), 24.94 (A), 24.80 (B), 23.37, 22.96 (A), 22.73 (B), 21.51.
IR (ν, cm^{-1}) : 3332, 3241, 2931, 2855, 1629, 1603, 1536, 1248, 1168.
HRMS : calculated for $C_{24}H_{38}N_4O_4$ 446.2893, found 446.2900.
Aspect : yellow oil

(*E*)-*N*-cyclohexyl-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-2-(4-methoxyphenyl)acetamide 1e.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 39 %
^{1}H NMR, 400MHz : δ (ppm) 8.80 (s, 0.6H$_A$), 8.46 (s, 0.4H$_B$), 8.03 (s, 0.6H$_A$), 7.71 (s, 0.4H$_B$), 7.15-7.42 (m, 7H), 6.97 (m, 3H), 5.95 (s, 1H), 5.04(m, 0.6H$_A$), 3.66-3.84 (m, 5H), 3.32-3.53 (m, 7H+0.4H$_B$), 1.15-2.05 (m, 10H).
^{13}C NMR, 100MHz : 169.16, 166.88, 159.49, 142.87, 131.09, 130.37, 129.24, 127.31, 121.83, 114.28, 113.75, 102.39, 66.49, 55.82, 55.36, 48.75, 48.45, 33.10, 25.56, 25.06.
IR (ν, cm^{-1}) : 3294, 3241, 2932, 2854, 1651, 1604, 1538, 1250, 1178.
HRMS : calculated for $C_{27}H_{36}N_4O_5$ 496.2686, found .
Aspect : White solid
M.P. = 187-188 °C

(*E*)-*N*-cyclohexyl-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)butanamide 1f.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 47 %
^{1}H NMR, 400MHz : δ (ppm) 9.00 (s, 0.6H$_A$), 8.58 (s, 0.4H$_B$), 7.52 (s, 0.6H$_A$), 7.15-7.20 (m, 3H), 7.05 (d, 2H, *J*= 7.6Hz), 6.85 (t, 1H, *J*= 7.6Hz), 6.71 (s, 0.4H$_B$), 4.92 (s, 0.6H$_A$), 4.59 (s, 0.4H$_B$), 3.78 (m, 2H), 3.51 (m, 7H), 1.02-1.98 (m, 12H), 0.86 (m, 3H).
^{13}C NMR, 100MHz : 170.28 (A), 169.91 (B), 166.19, 143.04, 129.28, 127.38, 121.31, 113.69, 103.91 (A), 102.40 (B), 65.47, 56.01, 55.69, 55.08, 48.71 (A), 48.25 (B), 33.11 (B), 32.89 (A), 25.55 (A), 24.99 (B), 24.98 (A), 24.81 (B), 21.65, 11.28 (A), 10.83 (B).
IR (ν, cm^{-1}) : 3302, 3240, 2932, 2854, 1651, 1602, 1536, 1249, 1166.
HRMS : calculated for $C_{22}H_{34}N_4O_4$ 418.2580, found 418.2584.
Aspect : yellow oil

(*E*)-*N*-(ter-butyl)-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)butanamide 1g.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 39 %
^{1}H NMR, 400MHz : δ (ppm) 9.19 (s, 0.6H$_A$), 8.74 (s, 0.4H$_B$), 7.56 (s, 0.6H$_A$), 7.05-7.29 (m, 5H), 6.84 (t, 1H, *J*= 7.2Hz), 6.62 (s, 0.4H$_B$), 4.88 (m, 1H), 4.49 (m, 1H), 3.64 (m, 1H), 3.31-3.37 (m, 7H), 1.69-2.16 (m, 2H), 1.26 (s, 9H), 0.82-0.84 (m, 3H).

^{13}C NMR, 100MHz : 170.45 (A), 169.94 (B), 166.03, 143.11, 129.24 (A), 129.03 (B), 127.40, 121.71 (A), 121.57 (B), 113.70 (A), 113.56 (B), 103.98 (A), 102.33 (B), 61.77, 55.93, 55.77, 55.71, 51.24, 47.79, 28.59, 21.63, 11.21 (A), 10.77 (B).
IR (ν, cm^{-1}) : 3312, 3242, 2936, 2861, 1655, 1603, 1536, 1251, 1168.
HRMS : calculated for $C_{20}H_{32}N_4O_4$ 392.2424, found 392.2419.
Aspect : yellow oil

(*E*)-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-*N*-(4-methoxybenzyl)-4-methylpentanamide 1h.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 74 %
^{1}H NMR, 400MHz : δ (ppm) 8.90 (s, 0.6H$_A$), 8.57 (s, 0.4H$_B$), 8.09 (s, 0.6H$_A$), 7.48 (s, 0.4H$_B$), 7.07-7.24 (m, 5H), 7.02 (d, 2H, *J*= 7.2Hz), 6.85 (t, 1H, *J*= 7.2Hz), 6.70 (m, 2H), 4.84 (m, 2H), 4.21-4.37 (m, 3H), 3.60-3.70 (m, 4H), 3.10-3.30 (m, 7H), 1.46-1.89 (m, 3H), 0.77-0.84 (m, 6H).
^{13}C NMR, 100MHz : 171.61 (A), 171.02 (B), 166.22, 158.93, 142.84, 129.93 (B), 129.34 (A), 129.13, 128.71 (A), 127.19 (B), 121.92, 113.97 (A), 113.72 (B), 103.83 (A), 102.28 (B), 61.87, 56.01, 55.87 (A), 55.72 (B), 55.23, 47.89, 43.53 (A), 42.90 (B), 37.09, 24.94, 23.35 (A), 22.98 (B), 22.45 (A), 21.52 (B).
IR (ν, cm^{-1}) : 3227, 3243, 2955, 2836, 1626, 1603, 1535, 1253, 1163.
HRMS : calculated for $C_{26}H_{36}N_4O_5$ 484.2686, found 484.2691.
Aspect : yellow oil

(*E*)-*N*-(4-chlorobenzyl)-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-4-methylpentanamide1i.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 52 %
^{1}H NMR, 400MHz : δ (ppm) 8.77 (s, 0.6H$_A$), 8.52 (s, 0.4H$_B$), 8.33 (s, 0.6H$_A$), 7.59 (s, 0.4H$_B$), 7.50 (s, 0.6H$_A$), 7.23-7.31 (m, 6H+0.4H$_B$), 7.12 (m, 2H), 6.99 (t, 1H, *J*= 7.2Hz), 4.87-4.99 (m, 1H+0.4H$_B$), 4.35-4.51 (m, 2H+0.6H$_A$), 3.76 (m, 1H), 3.25-3.41 (m, 7H), 1.58-2.01 (m, 3H), 0.91-0.97 (m, 6H).
^{13}C NMR, 100MHz : 171.90 (A), 171.31 (B), 166.30, 143.16 (A), 143.00 (B), 137.05 (A), 136.52 (B), 129.32, 129.26 (B), 129.11 (A), 129.13, 128.70, 128.52, 121.89 (A), 121.66 (B), 113.72 (A), 113.59 (B), 103.75 (A), 102.42 (B), 58.50, 56.14, 55.54, 48.28, 43.27 (A), 42.78 (B), 37.26, 24.95, 23.34 (A), 22.96 (B), 22.45 (A), 21.45 (B).
IR (ν, cm^{-1}) : 3296, 3239, 2956, 2871, 1625, 1602, 1533, 1243, 1165.
HRMS : calculated for $C_{25}H_{33}ClN_4O_4$ 489.2190, found 489.2203.
Aspect : yellow oil

(*E*)-*N*-(4-chlorobenzyl)-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-4-acetamide 1j.
Obtained as a mixture of two rotamers A:B in a 6:4 ratio
Yield : 52 %
^{1}H NMR, 400MHz : δ (ppm) 9.15 (s, 0.6H$_A$), 8.89 (s, 0.4H$_B$), 7.46 (s, 0.6H$_A$), 7.31 (m, 2H+0.4H$_B$), 7.18 (d, 2H, *J*= 7.2Hz), 6.97 (t, 1H, *J*= 7.2Hz), 6.78 (s, 0.6H$_A$), 6.28 (s, 0.4H$_B$), 4.75 (m, 1H), 4.27 (s, 2H), 3.66 (m, 2H), 3.47 (s, 6H), 1.36 (s, 9H).

^{13}C NMR, 100MHz : 168.55, 165.55, 142.93, 129.31, 127.56, 121.83, 113.78, 102.59, 55.45, 54.95, 51.39, 50.85, 28.69.
HRMS : calculated for $C_{18}H_{28}N_4O_4$ 364.2111, found 364.2105.
Nature: yellow oil

Experimental procedures and spectral data for compounds 2a-2k

To a solution of Ugi product **1** (0.2 mmol) in ethanol (2 ml) is added sodium acetate (80 mg, 1mmol), acetic acid (2 ml) and water (0.5 ml). The mixture is stirred overnight at 80°C. The ethanol is removed under reduced pressure, dichloromethane is added followed by a saturated aqueous K_2CO_3 solution (20 ml). After extraction with dichloromethane, the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product is isolated by flash chromatography on silica gel.

N-(1-(tert-butylamino)-4-methyl-1-oxopentan-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3a.
Yield : 62 %
^{1}H NMR, 400MHz : δ (ppm) 7.86(d, 1H, *J*= 2.4Hz), 7.64 (d, 2H, *J*= 7.6Hz), 7.40 (t, 2H, *J*= 7.6Hz), 7.35 (d, 2H, *J*= 8.4Hz), 7.27 (t, 1H, *J*= 7.6Hz), 6.91 (d, 1H, *J*= 2.4Hz), 6.13 (s, 1H), 4.52 (m, 1H), 1.63 (s, 3H), 1.28 (s, 9H), 0.90 (s, 3H), 0.88 (s,3H).
^{13}C NMR, 100MHz : 171.78, 161.74, 147.37, 139.58, 129.59, 128.59, 127.47, 119.66, 108.52, 51.95, 51.40, 41.39, 28.73, 24.86, 23.06, 22.24.
IR (ν, cm^{-1}) : 3401, 3324, 3077, 2960, 1648, 1600, 1539, 1256.
HRMS : calculated for $C_{20}H_{28}N_4O_2$ 356.2212, found 356.2213.
Aspect : Pale brown oil

N-(2-(tert-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3b.
Yield : 49 %
^{1}H NMR, 400MHz : δ (ppm) 8.28 (d, 1H, *J*= 7.0Hz), 7.95 (d, 1H, *J*= 2.8Hz), 7.78 (d, 2H, *J*= 7.6Hz), 7.51 (t, 2H, *J*= 7.6Hz), 7.46 (d, 2H, , *J*= 8.8Hz), 7.38 (t, 1H, *J*= 7.6Hz), 6.98 (d, 1H, *J*= 2.4Hz), 6.98 (s, 1H), 6.92 (d, 2H, *J*= 8.8Hz), 5.81 (s, 1H), 5.71 (d, 1H, *J*= 7.0Hz), 3.83 (s, 1H), 1.37 (s, 9H).
^{13}C NMR, 100MHz : 169.24, 161.12, 159.44, 147.56, 139.61, 130.87, 129.52, 128.79, 128.32, 127.33, 119.60, 114.43, 108.43, 56.53, 55.31, 51.39, 29.67.
IR (ν, cm^{-1}) : 3401, 3328, 2967, 2934, 1650, 1600, 1532, 1248.
HRMS : calculated for $C_{23}H_{26}N_4O_3$ 406.2005, found 406.2000.
Aspect : Pale brown oil

N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3c.
Yield : 54 %
^{1}H NMR, 400MHz : δ (ppm) 8.26 (d, 1H, *J*= 7.4Hz), 7.83 (d, 1H, *J*= 2.4Hz), 7.64 (d, 2H, *J*= 8.0Hz), 7.37-7.43 (m, 4H), 7.18-7.28 (m, 4H), 6.85 (d, 1H, *J*= 2.4Hz), 6.21 (d, 1H, *J*= 8.0Hz), 5.65 (d, 1H, *J*= 7.4Hz), 3.68 (m, 1H), 0.97-1.84 (m, 10H).
^{13}C NMR, 100MHz : 168.91, 161.29, 147.42, 139.58, 138.42, 129.56, 128.93, 128.40, 128.20, 127.39, 127.35, 119.85, 119.58, 108.47, 56.79, 48.79, 32.86, 32.69, 25.48, 24.83, 24.73.

IR (ν, cm^{-1}) : 3386, 3312, 2931, 2854, 1644, 1599, 1251.
HRMS : calculated for $C_{24}H_{26}N_4O_2$ 402.2056, found 402.2053.
Aspect : Pale brown oil

N-(2-(cyclohexylamino)-4-methyl-1-oxopentan-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3d.
Yield : 75 %
^{1}H NMR, 400MHz : δ (ppm) 7.98(d, 1H, *J*= 2.2Hz), 7.75 (d, 2H, *J*= 7.2Hz), 7.51 (m, 3H), 7.37 (t, 1H, *J*= 7.2Hz), 7.02 (d, 1H, *J*= 2.2Hz), 6.43 (d, 1H, *J*= 8.0Hz), 4.68 (m, 1H), 3.75 (m, 1H), 1.17-1.97 (m, 13H), 1.01 (m, 6H).
^{13}C NMR, 100MHz : 170.94, 161.83, 147.29, 139.58, 129.59, 128.62, 127.50, 119.67, 108.53, 51.64, 48.37, 41.23, 32.98, 32.83, 25.52, 24.87, 24.81, 22.98, 22.25.
IR (ν, cm^{-1}) : 3305, 3285, 2930, 2855, 1642, 1599, 1538, 1251.
HRMS : calculated for $C_{22}H_{30}N_4O_2$ 382.2369, found 382.2366.
Aspect : Pale brown oil

N-(2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3e.
Yield : 94 %
^{1}H NMR, 400MHz : δ (ppm) 8.32 (d, 1H, *J*= 6.8Hz), 7.96 (d, 1H, *J*= 2.4Hz), 7.79 (d, 2H, *J*= 8.4Hz), 7.52 (t, 2H, *J*= 7.6Hz), 7.47 (d, 2H, *J*= 8.4Hz), 7.38 (t, 1H, *J*= 8.0Hz), 6.96 (d, 1H, *J*= 2.4Hz), 6.89 (d, 2H, *J*= 8.8Hz), 6.16 (d, 1H, *J*= 6.0Hz), 5.71 (d, 1H, *J*= 6.8Hz), 3.82 (m, 1H), 3.81 (s, 3H), 1.13-1.97 (m, 10H).
^{13}C NMR, 100MHz : 169.19, 161.26, 159.45, 147.45, 139.58, 130.54, 129.54, 128.72, 128.36, 127.36, 119.56, 114.56, 108.48, 56.37, 56.31, 48.78, 32.87, 32.73, 25.47, 24.83, 24.74.
IR (ν, cm^{-1}) : 3399, 3340, 2932, 2854, 1645, 1600, 1531, 1248.
HRMS : calculated for $C_{25}H_{28}N_4O_3$ 432.2161, found 432.2174.
Aspect : Pale brown oil

N-(1-(cyclohexylamino)-1-oxobutan-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3f.
Yield : 74 %
NMR, 400MHz : δ (ppm) 7.86(d, 1H, *J*= 2.6Hz), 7.65 (d, 2H, *J*= 7.4Hz), 7.28 (d, 1H, *J*= 8.4Hz), 7.41 (t, 2H, *J*= 7.4Hz), 7.28 (t, 1H, *J*= 7.4Hz), 6.91 (d, 1H, *J*= 2.6Hz), 6.19 (d, 1H, *J*= 6.0Hz), 4.45 (m, 1H), 3.71 (m, 1H), 1.07-1.91 (m, 12H), 0.9 (t, 3H, *J*= 7.6Hz).
^{13}C NMR, 100MHz : 170.35, 161.80, 147.40, 139.58, 129.59, 128.57, 127.47, 119.63, 108.45, 54.45, 48.39, 33.09, 32.91, 25.88, 25.52, 24.82, 10.17.
IR (ν, cm^{-1}) : 3343, 3312, 2932, 2855, 1644, 1599, 1251.
HRMS : calculated for $C_{20}H_{26}N_4O_2$ 354.2056, found 354.2056.
Aspect : Pale brown oil

N-(1-(tert-butylamino)-1-oxobutan-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3g.
Yield : 52 %
^{1}H NMR, 400MHz : δ (ppm) 7.86 (d, 1H, *J*= 2.4Hz), 7.65 (d, 2H, *J*= 7.6Hz), 7.50 (d, 2H, *J*= 8.0Hz), 7.41 (t, 2H, *J*= 7.6Hz), 7.27 (t, 1H, *J*= 7.6Hz), 6.90 (d, 1H, *J*= 2.4Hz), 6.04 (s, 1H), 4.40 (m, 1H), 1.29 (s, 9H), 1.8 (m, 2H), 0.9 (t, 3H, , *J*= 7.2Hz).
^{13}C NMR, 100MHz : 170.55, 161.69, 147.40, 139.58, 129.57, 128.51, 127.44, 119.63, 108.44, 54.63, 51.49, 28.78, 26.04, 10.04.

IR (ν, cm^{-1}) : 3390, 3326, 2968, 2935, 1650, 1600, 1537, 1253.
HRMS : calculated for $C_{18}H_{24}N_4O_2$ 328.1899, found 328.1892.
Aspect : Pale brown oil

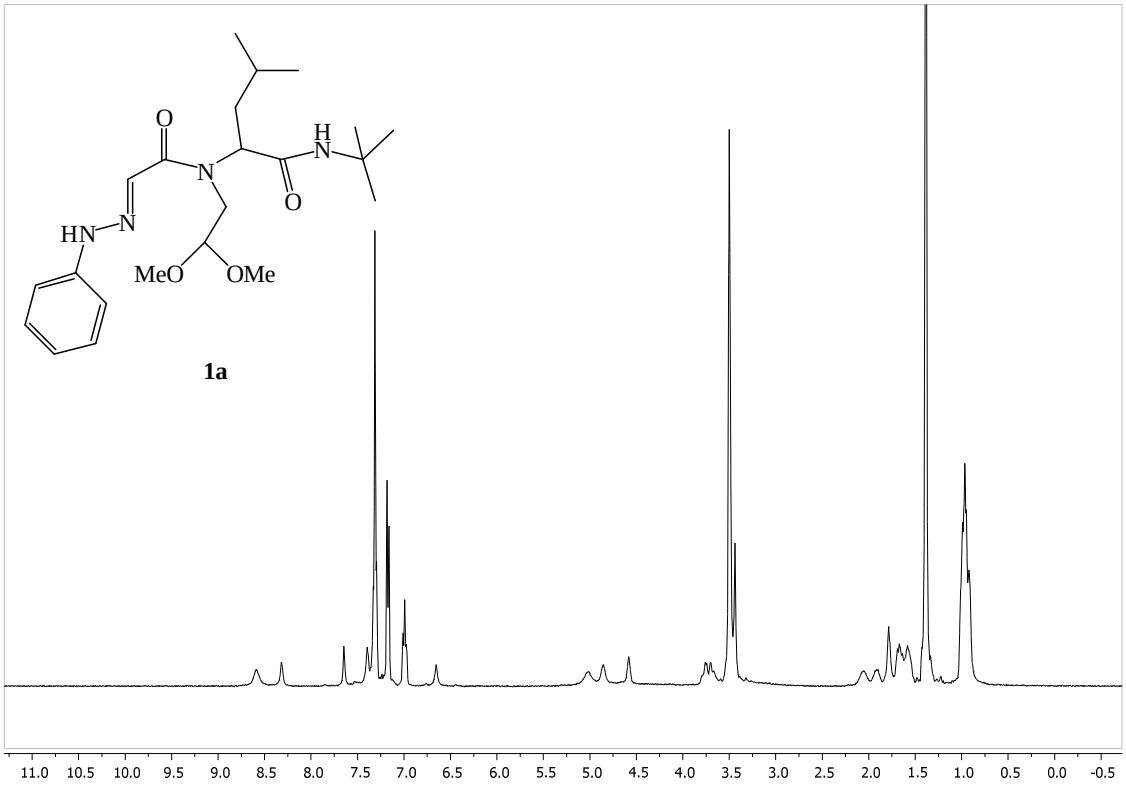
N-(1-(4-methoxybenzylamino)- 4-methyl-1-oxopentan-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3h.
Yield : 54 %
NMR, 400MHz : δ (ppm) 7.84(d, 1H, *J*= 2.4Hz), 7.63 (d, 2H, *J*= 7.6Hz), 7.46 (d, 1H, *J*= 8.4Hz), 7.41 (t, 2H, *J*= 7.6Hz), 7.28 (t, 1H, *J*= 7.6Hz), 7.12 (d, 2H, *J*= 8.4Hz), 6.84 (d, 1H, *J*= 2.4Hz), 6.75 (d, 2H, *J*= 8.4Hz), 6.66 (m, 1H), 4.62 (m, 1H), 4.40 (m, 2H), 3.69 (s, 3H), 1.70 (m, 3H), 0.88 (t, 6H).
^{13}C NMR, 100MHz : 171.78, 161.97, 158.95, 147.19, 139.56, 130.11, 129.62, 129.08, 128.70, 127.55, 119.70, 114.06, 108.57, 55.30, 53.49, 43.08, 41.00, 24.88, 23.04, 22.10.
IR (ν, cm^{-1}) : 3300, 2955, 2869, 1648, 1599, 1540, 1248.
HRMS : calculated for $C_{24}H_{28}N_4O_3$ 420.2161, found 420.2161.
Aspect : Pale brown oil

N-(1-(4-chlorobenzylamino)- 4-methyl-1-oxopentan-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide 3i.
Yield : 47 %
NMR, 400MHz : δ (ppm) 7.97(d, 1H, *J*= 2.0Hz), 7.75 (d, 2H, *J*= 8.4Hz), 7.54 (d, 1H, *J*= 7.2Hz), 7.41 (t, 2H, *J*= 7.6Hz), 7.28 (t, 1H, *J*= 7.4Hz), 7.12 (d, 2H, *J*= 8.4Hz), 6.84 (d, 1H, *J*= 2.4Hz), 6.75 (d, 2H, *J*= 8.4Hz), 4.52 (m, 1H), 4.30 (dd, 2H, *J*= 5.6/6.0Hz), 3.69 (s, 3H), 2.08 (m, 1H), 1.85 (m, 1H), 1.02(t, 3H).
IR (ν, cm^{-1}) : 3326, 3300, 2958, 2869, 1650, 1599, 1538, 1251.
HRMS : calculated for $C_{23}H_{25}ClN_4O_2$ 424.1666, found 424.1656.
Aspect : Pale brown oil

Experimental procedures and spectral data for compound 2a
To a solution of the Ugi product **1a** (1 equiv) in toluene (0.5 M) is added acetic acid (2 equiv) and the mixture stirred at 80°C for 2 hours. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel.

(*Z*)-*N*-(ter-butyl)-2-(*N*-(2,2-dimethoxyethyl)-2-(2-phenylhydrazono)acetamido)-4-methylpentanamide 2a.
Yield : 59 %
^{1}H NMR, 400MHz : δ (ppm) 13.27 (s, 0.4H$_A$), 13.18 (s, 0.6H$_B$), 7.33 (t, 2H, *J*= 7.6Hz), 7.22 (d, 2H, *J*= 7.6Hz), 7.12 (s, 0.6H$_A$), 7.00 (t, 1H, *J*= 7.6Hz), 6.76 (s, 0.4H$_B$), 5.01 (m, 0.6H$_A$), 4.82 (m, 1H), 4.58 (m, 0.4H$_B$), 3.73 (m, 2H), 3.42-3.48 (m, 6H), 1.45-1.93 (m, 3H), 1.26 (s, 9H), 0.79-0.89 (m, 6H).
^{13}C NMR, 100MHz : 170.71 (A), 170.16 (B), 166.05, 143.10 (A), 142.91 (B), 129.30 (A), 129.04 (B), 127.64, 121.88 (A), 121.65 (B), 113.73 (A), 113.59 (B), 103.99 (A), 102.40 (B), 62.03, 56.08 (A), 55.90 (B), 55.76 (A), 54.89 (B), 51.30 (A), 51.11 (B), 47.43, 37.30, 28.68 (B), 28.61 (A), 24.94, 23.37 (A), 22.93 (B), 22.57 (A), 21.72 (B).
IR (ν, cm^{-1}) : 3329, 3243, 2959, 2870, 1662, 1628, 1535, 1246, 1166.

HRMS : calculated for $C_{22}H_{36}N_4O_4$ 420.2737, found 420.2736.
Aspect : yellow oil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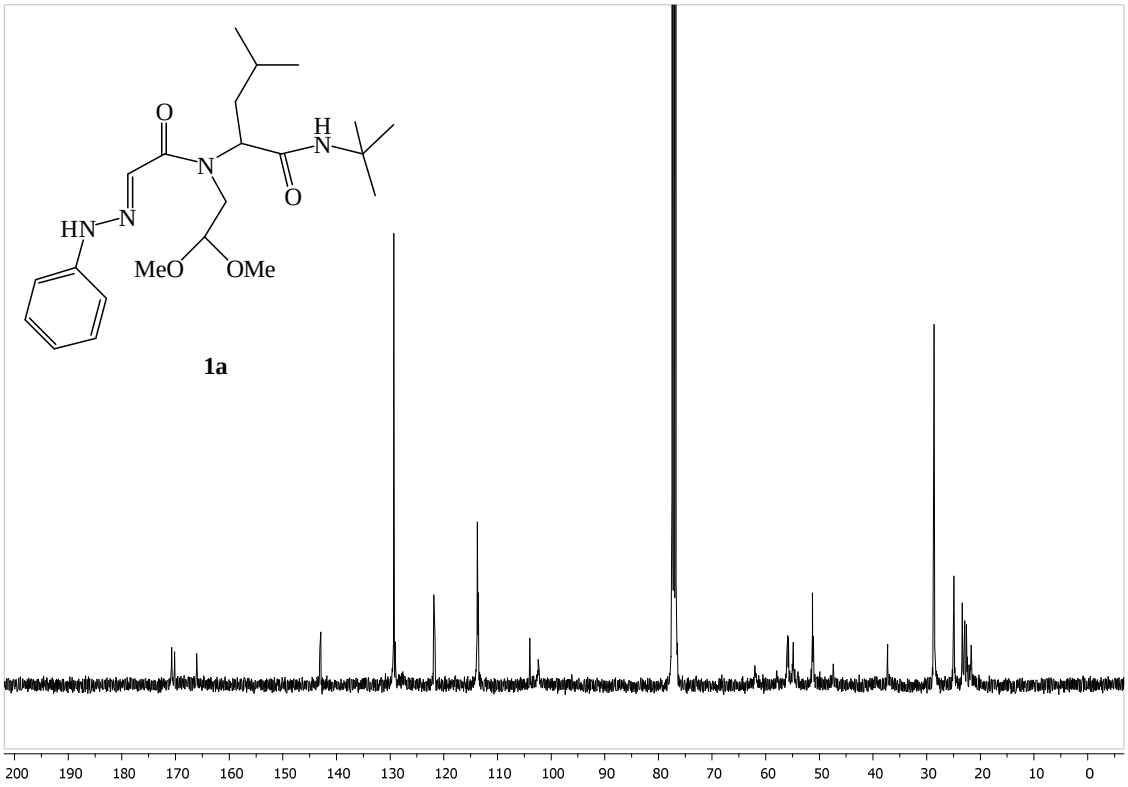
1a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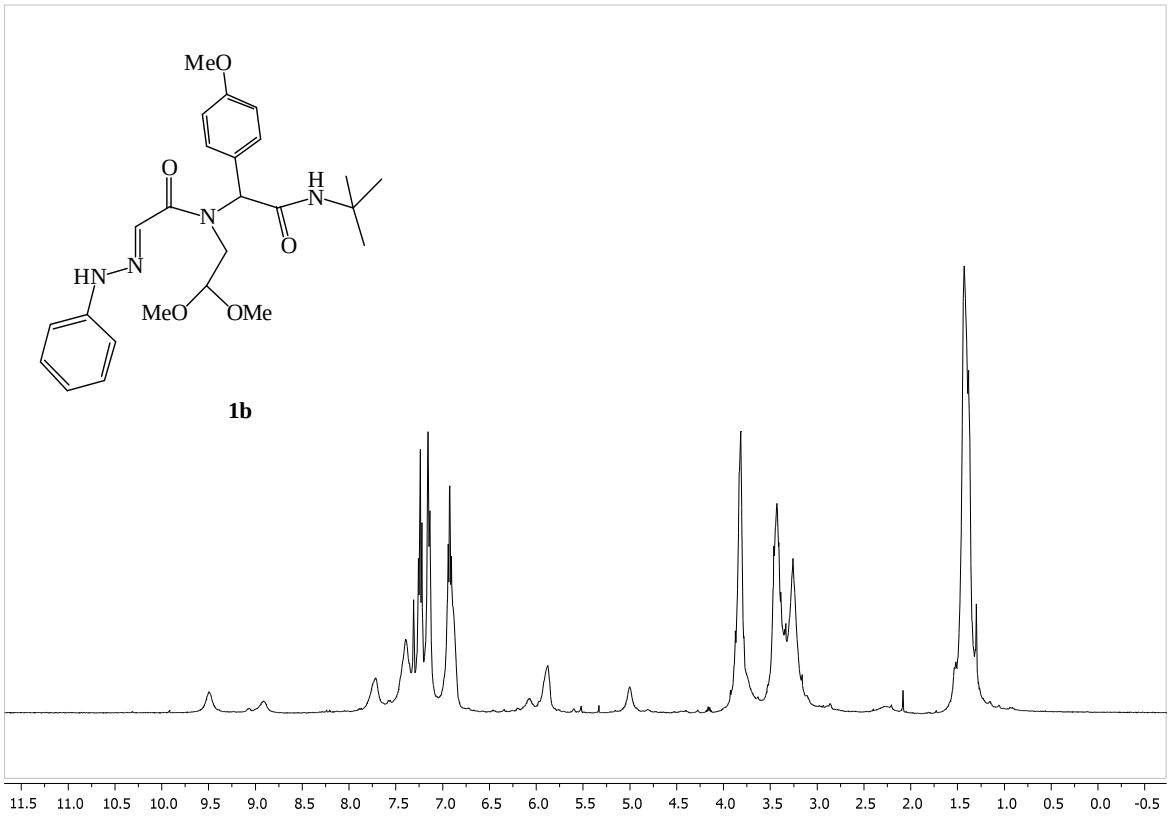
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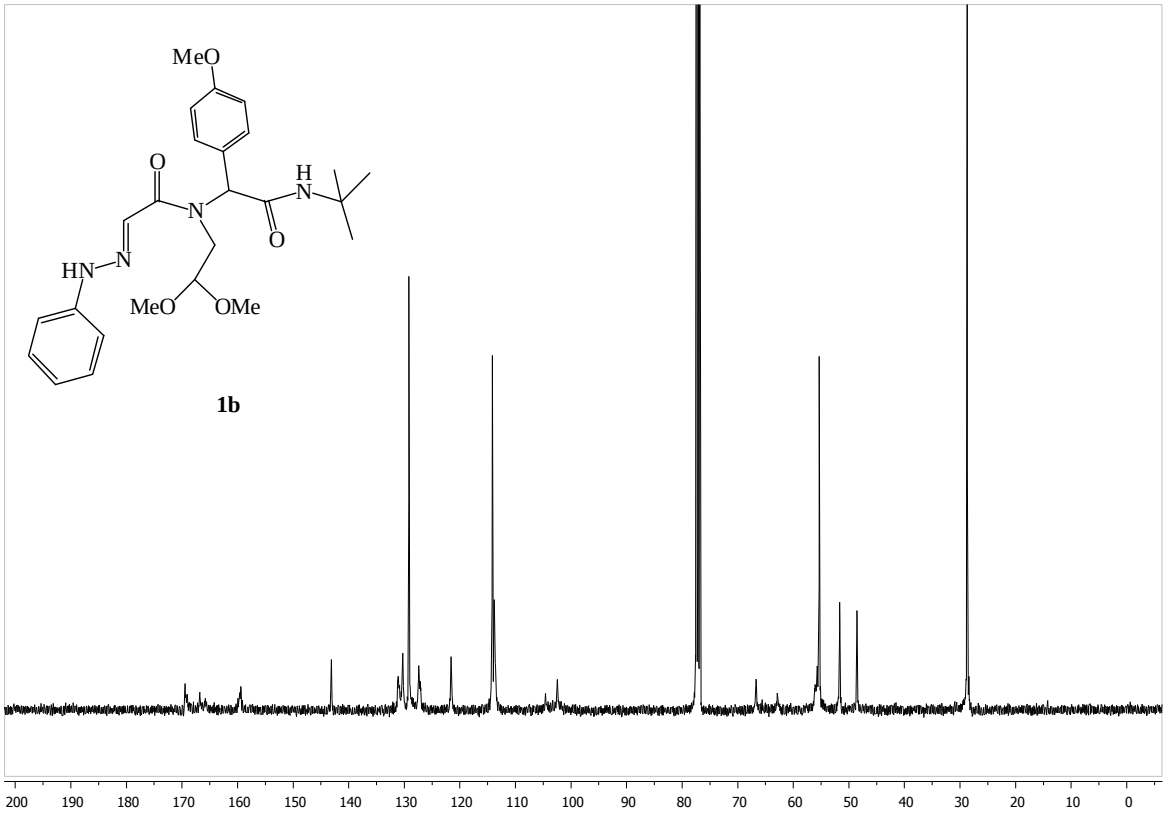
1b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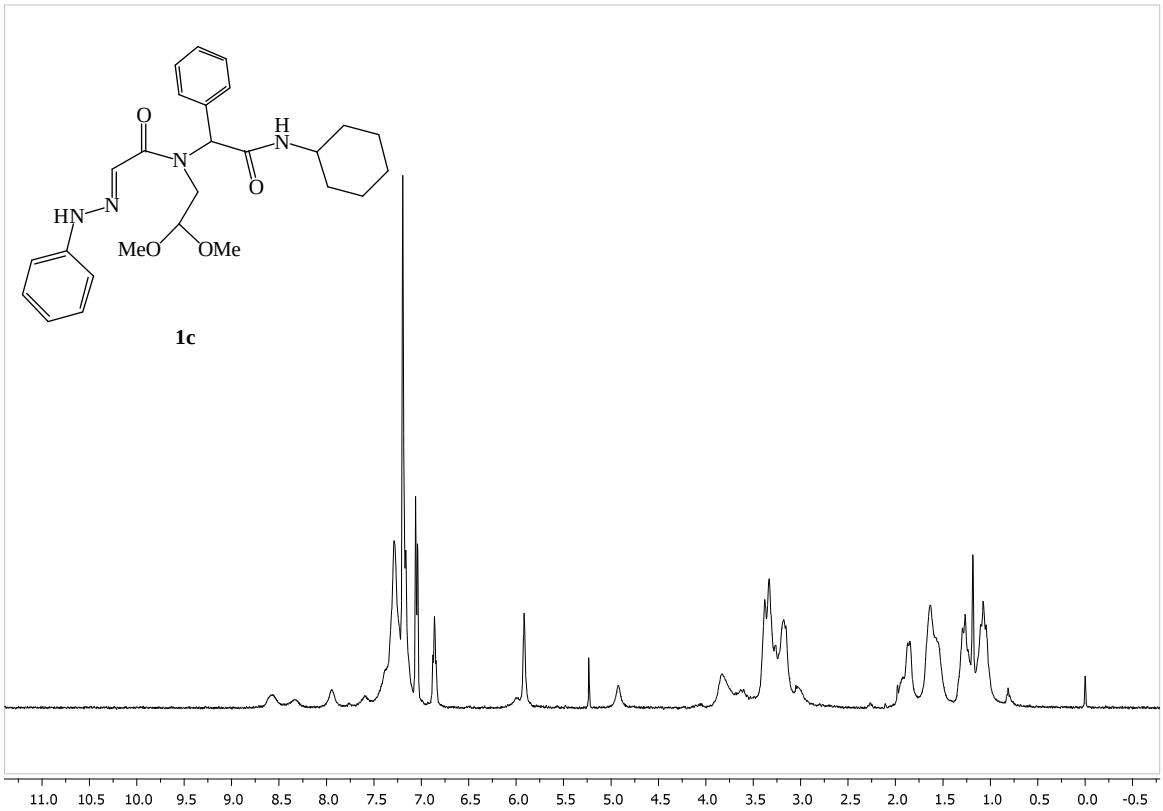
1b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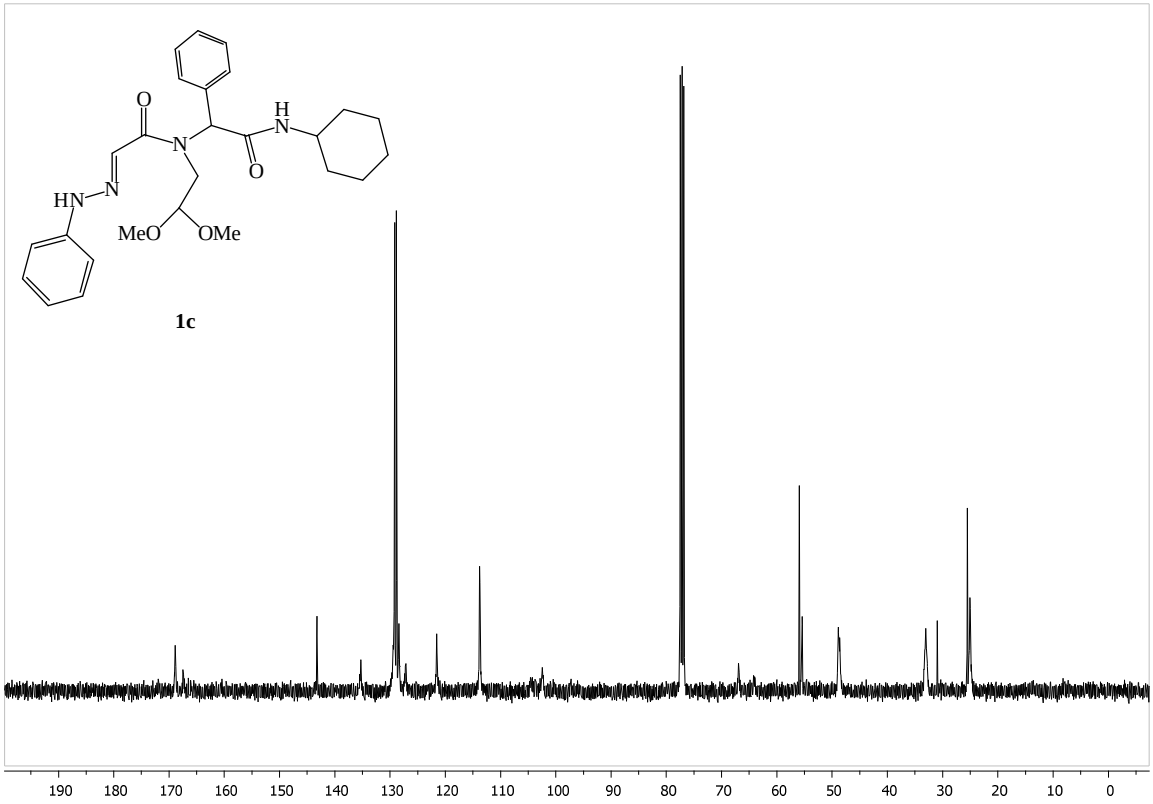
1c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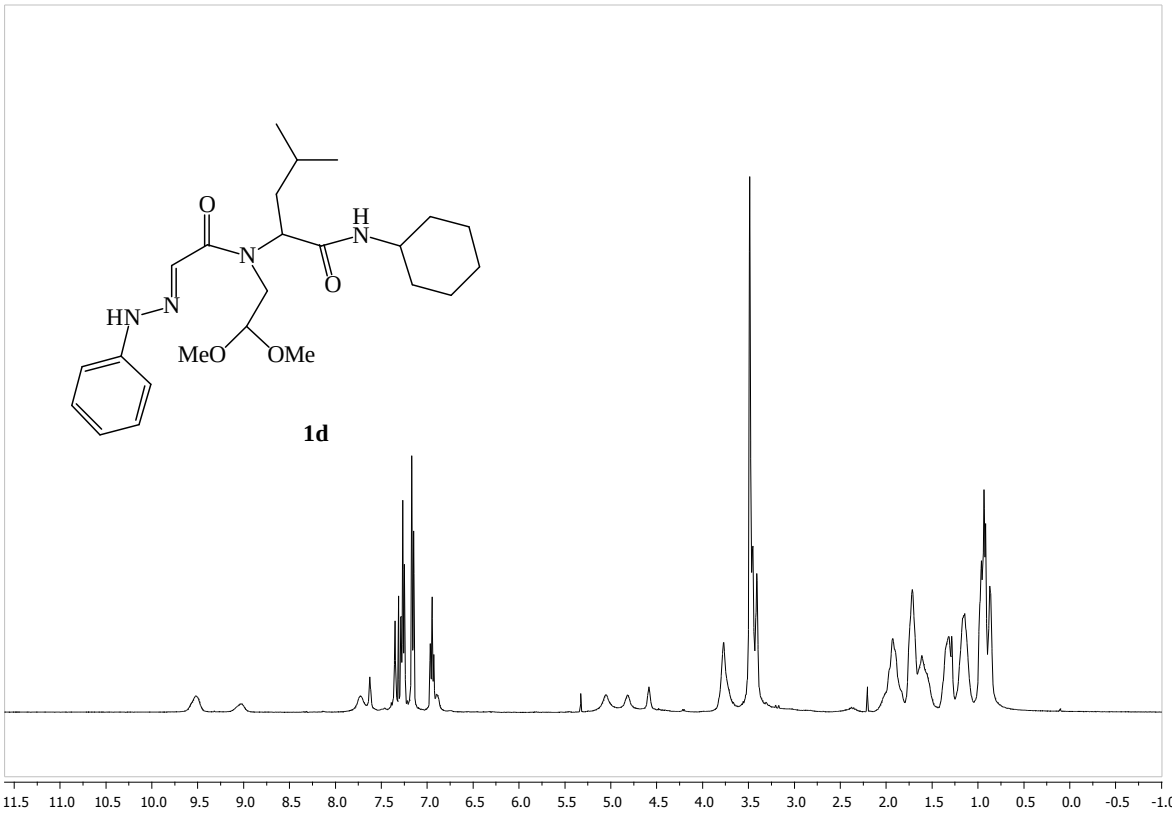
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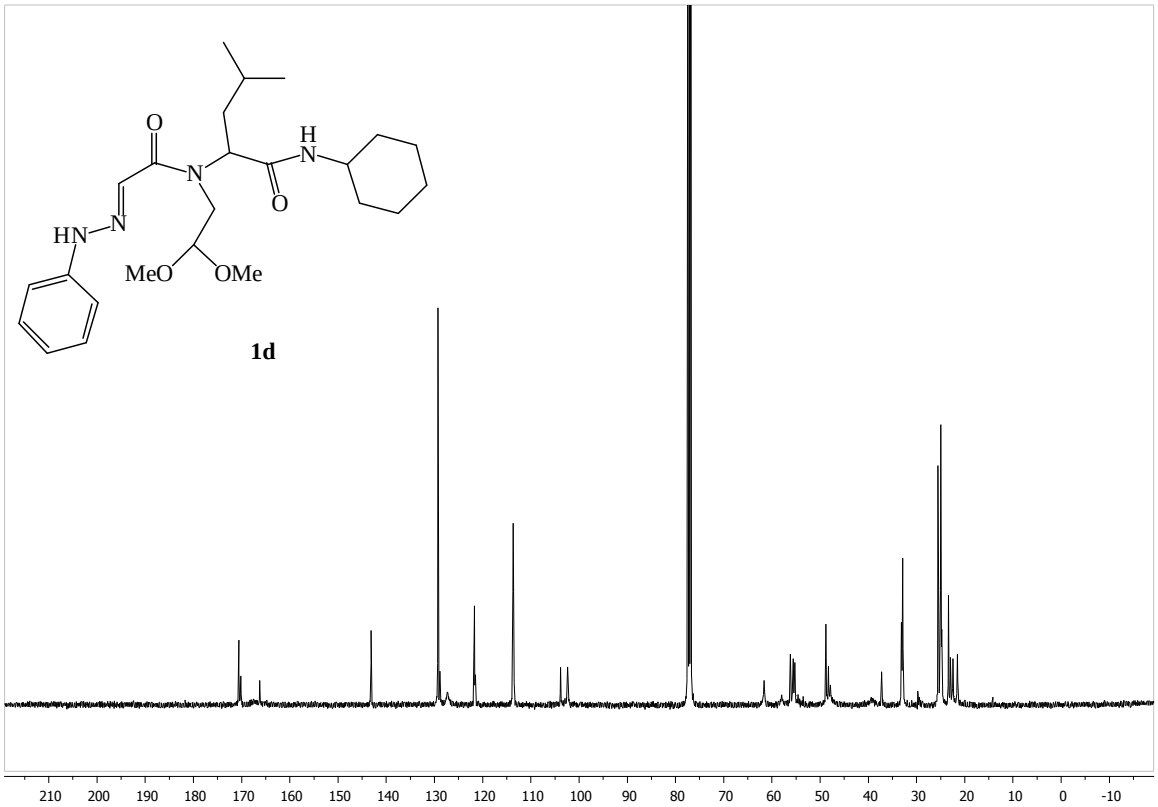
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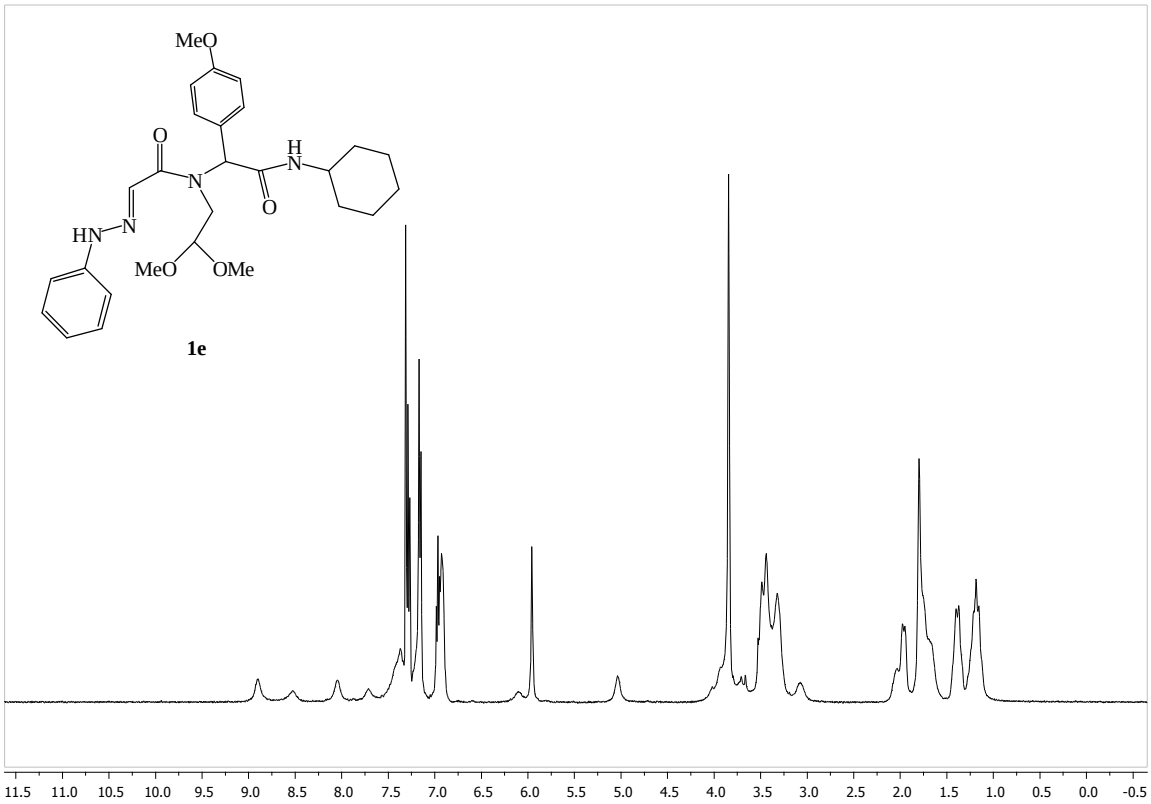
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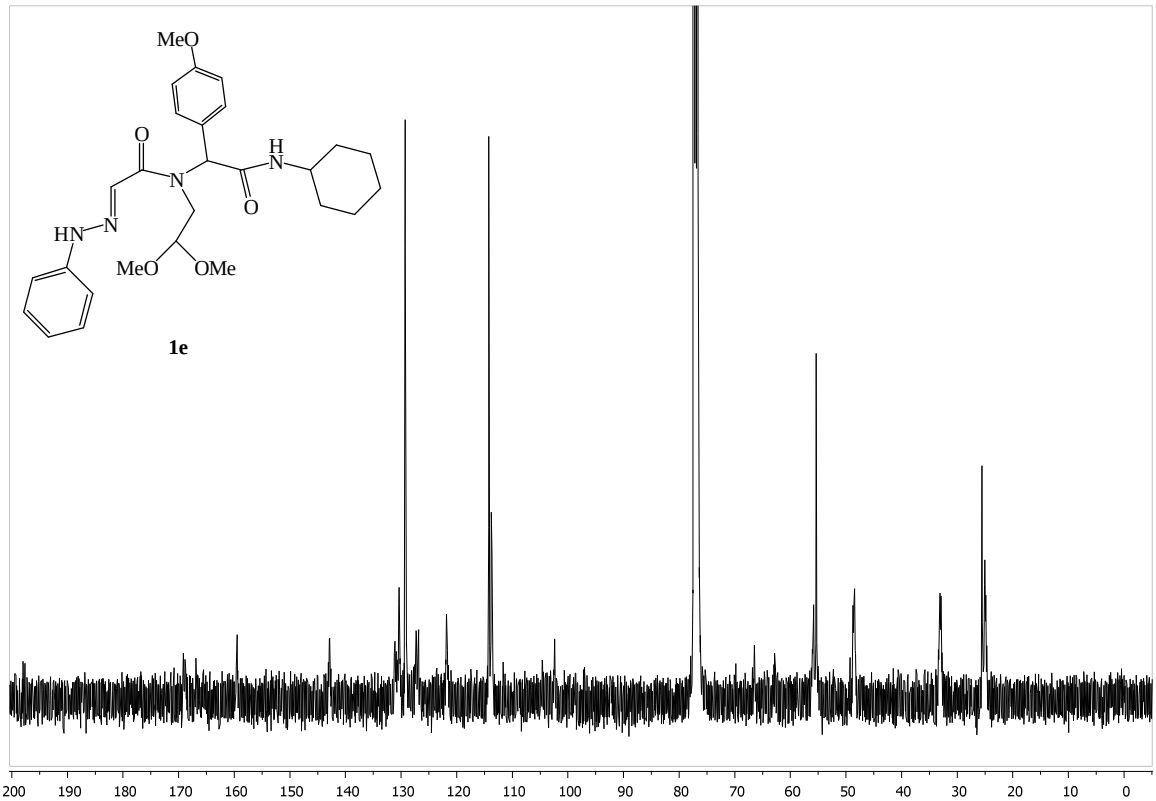
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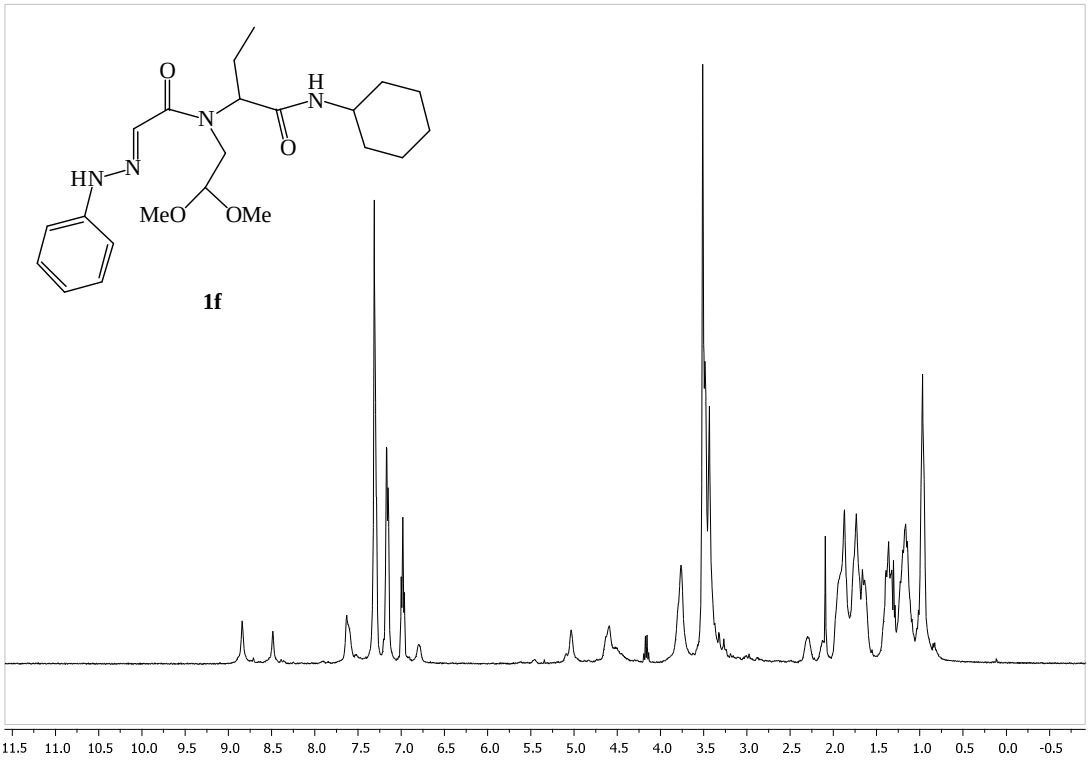
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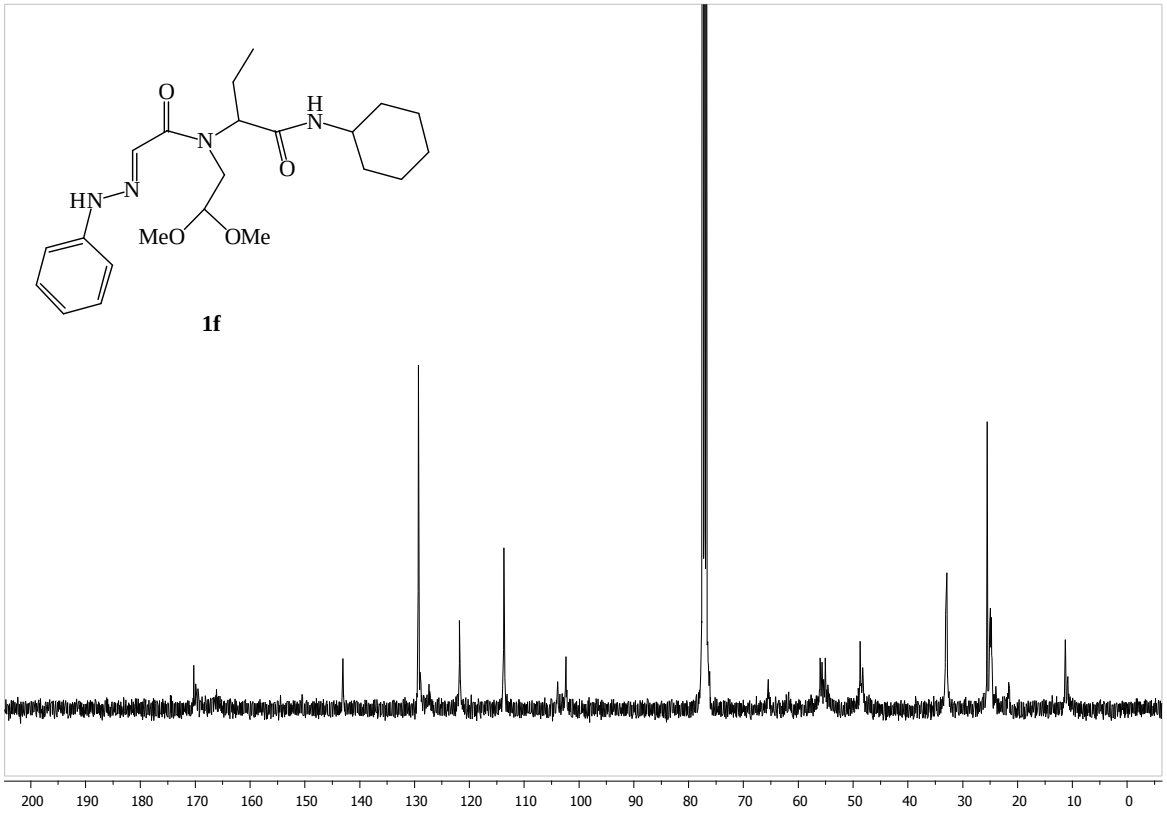
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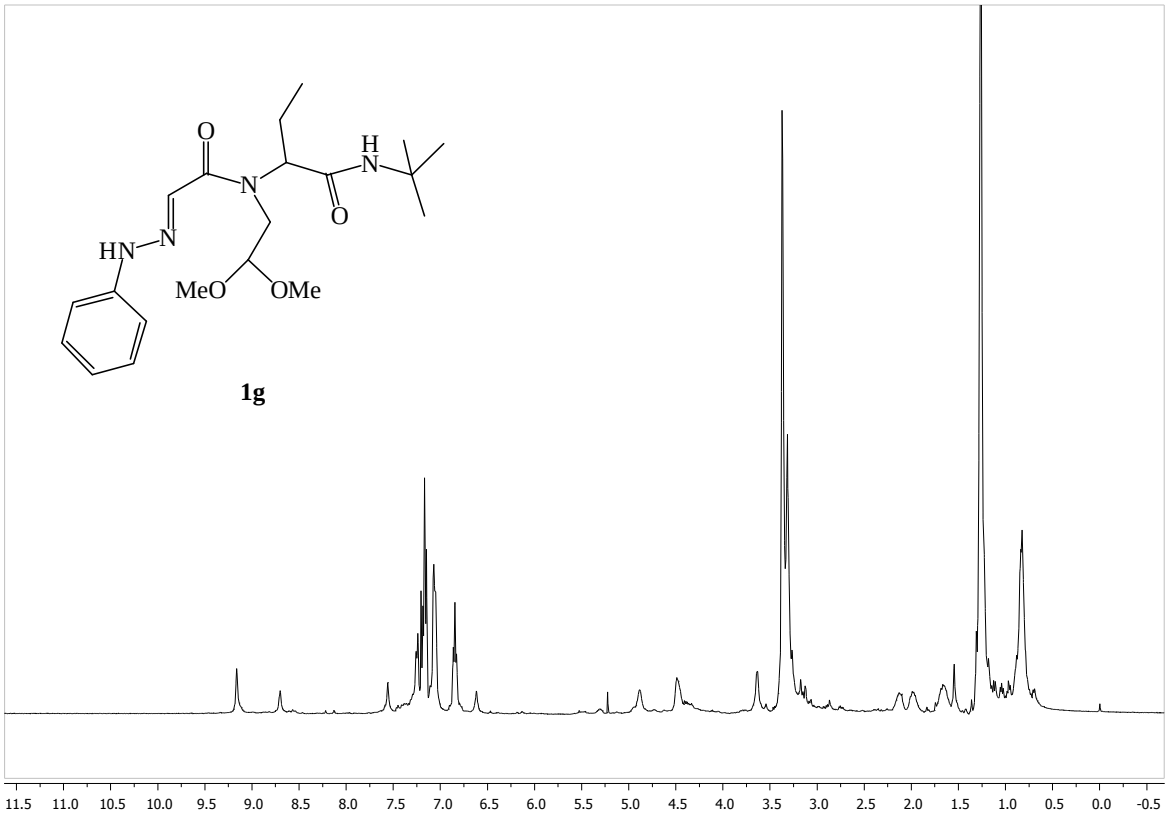
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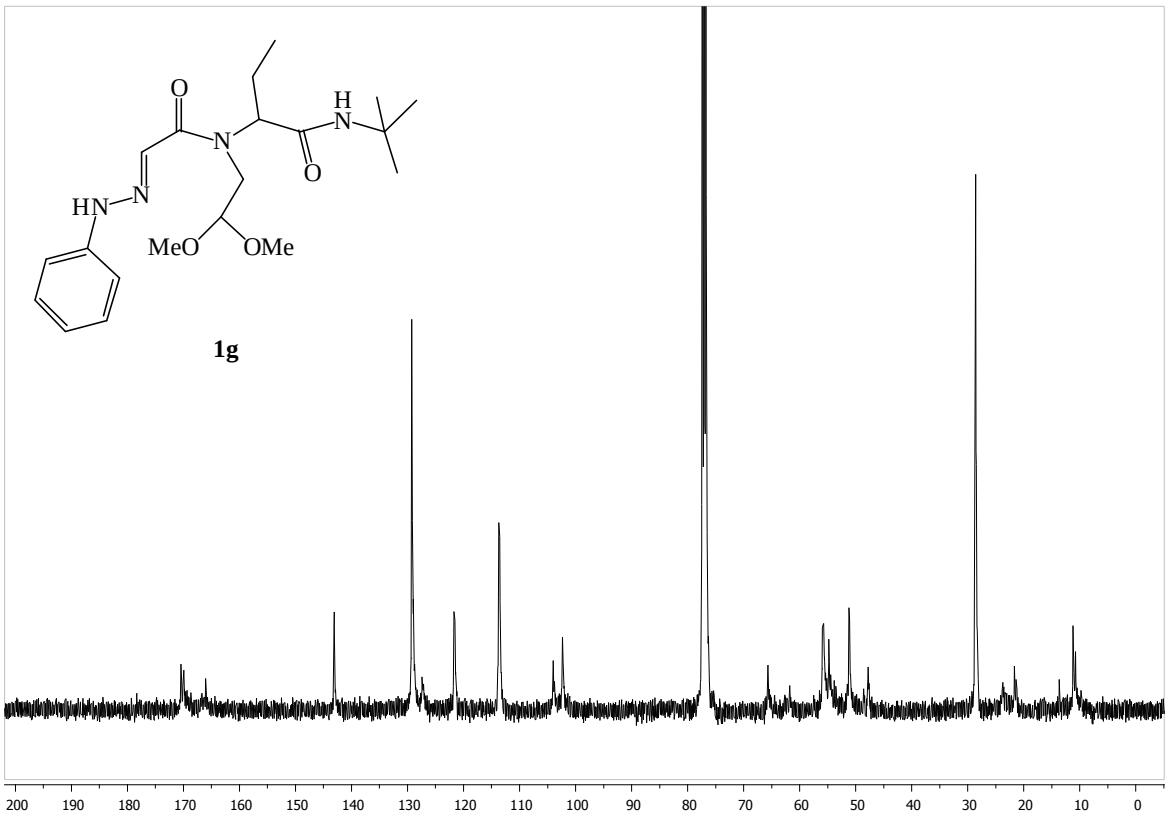
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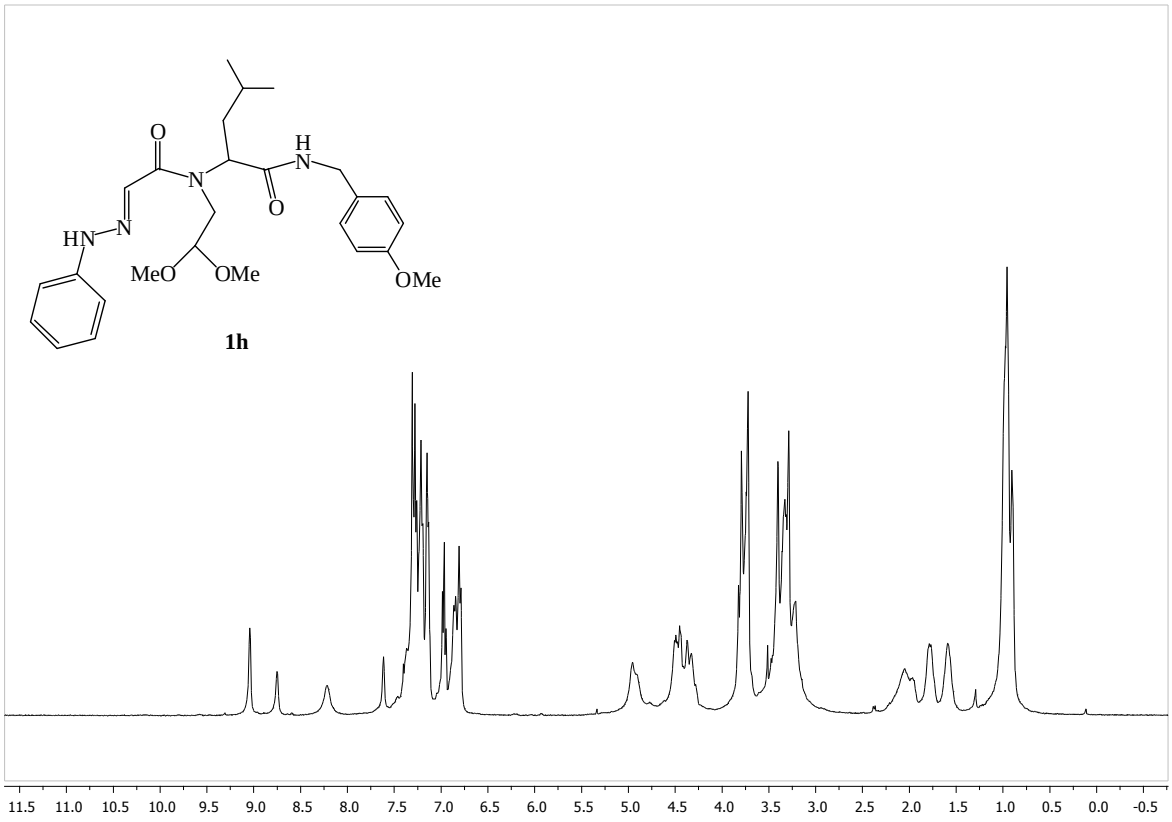
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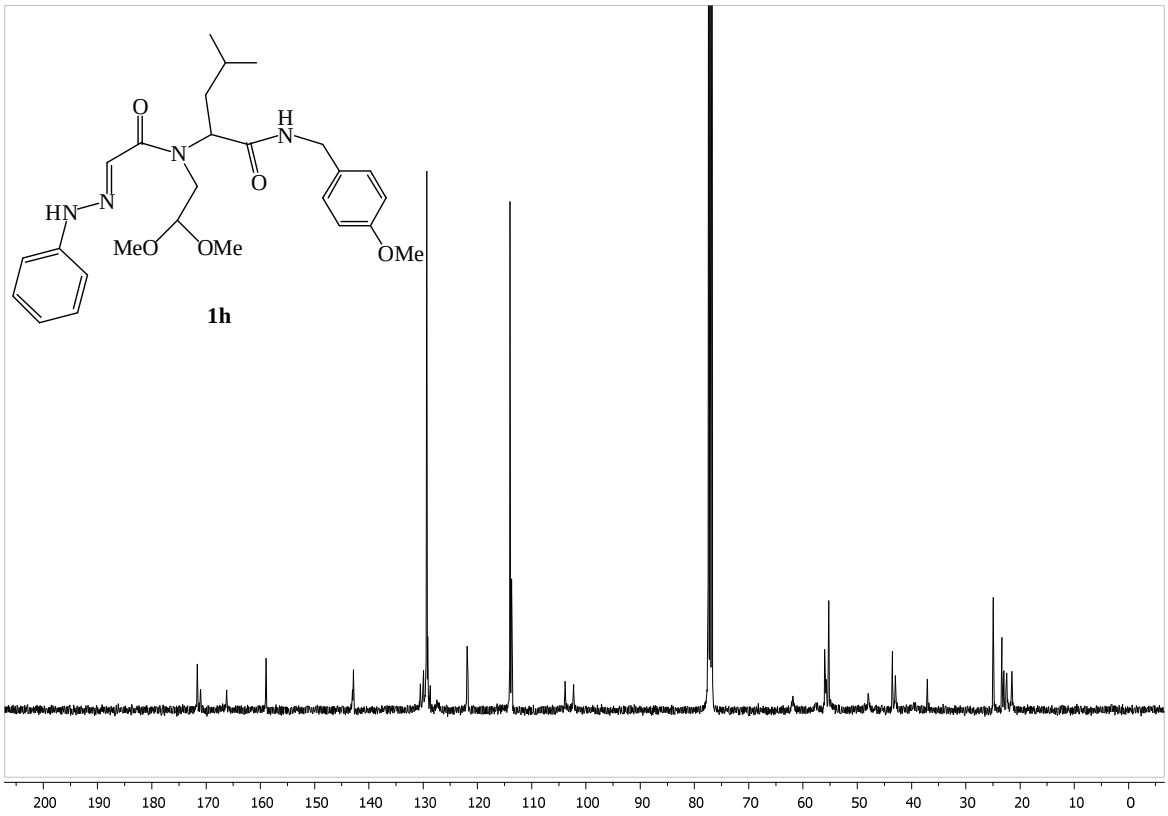
1h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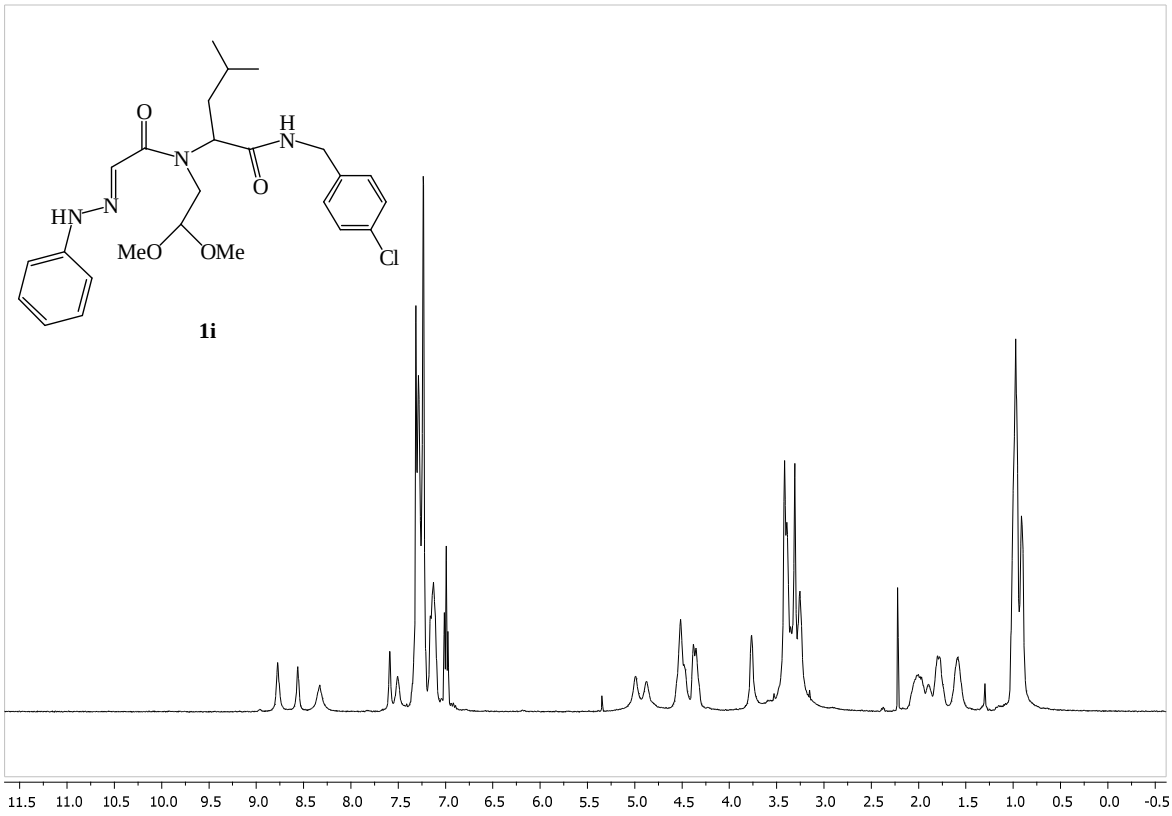
1h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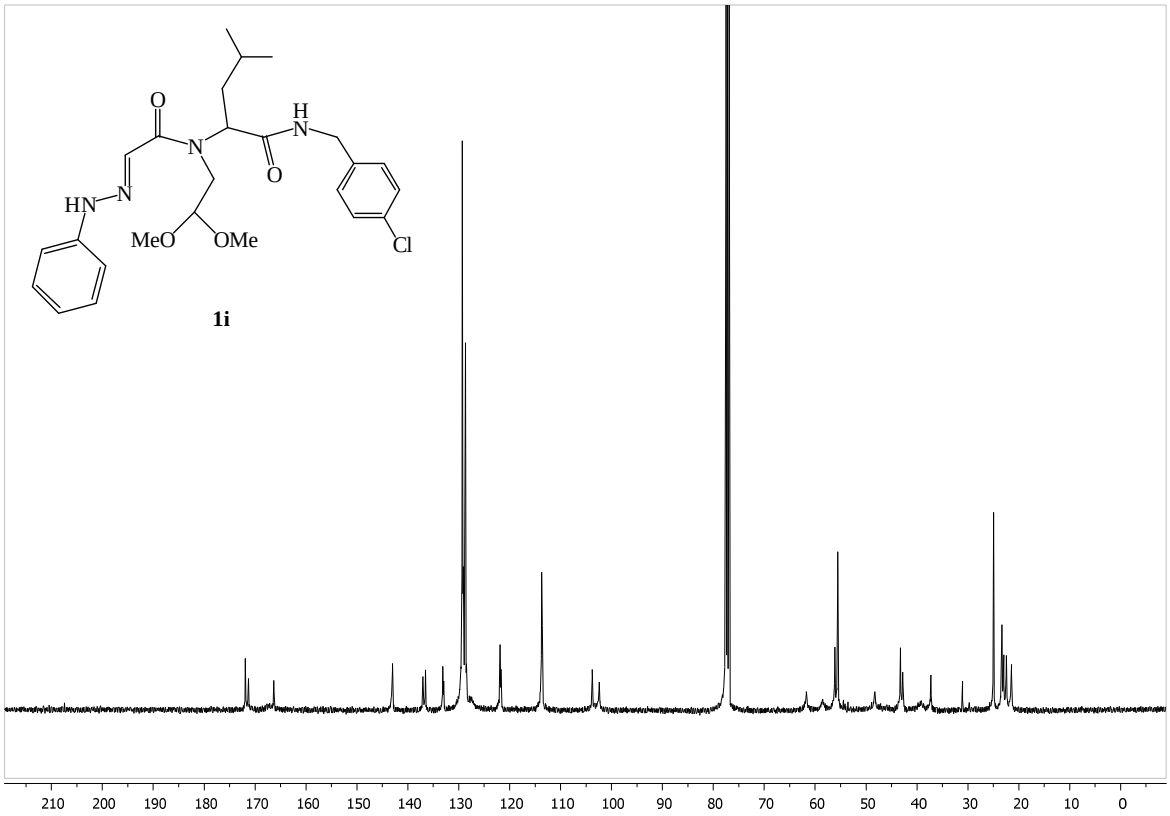
1i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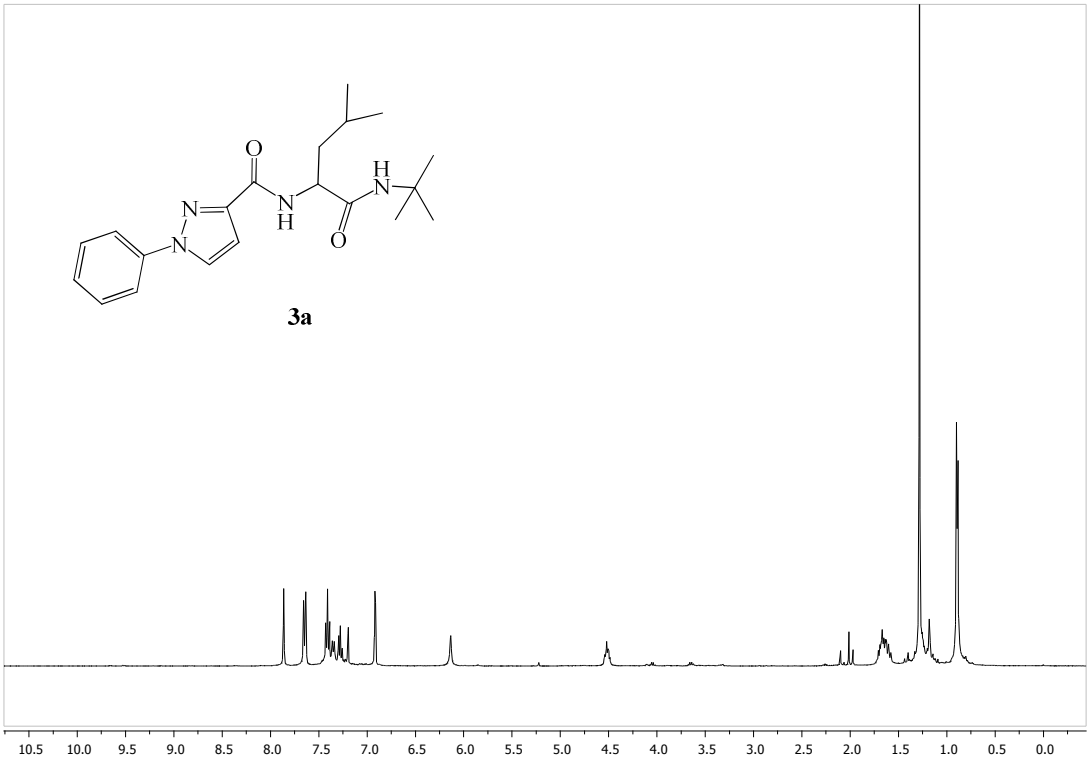
1i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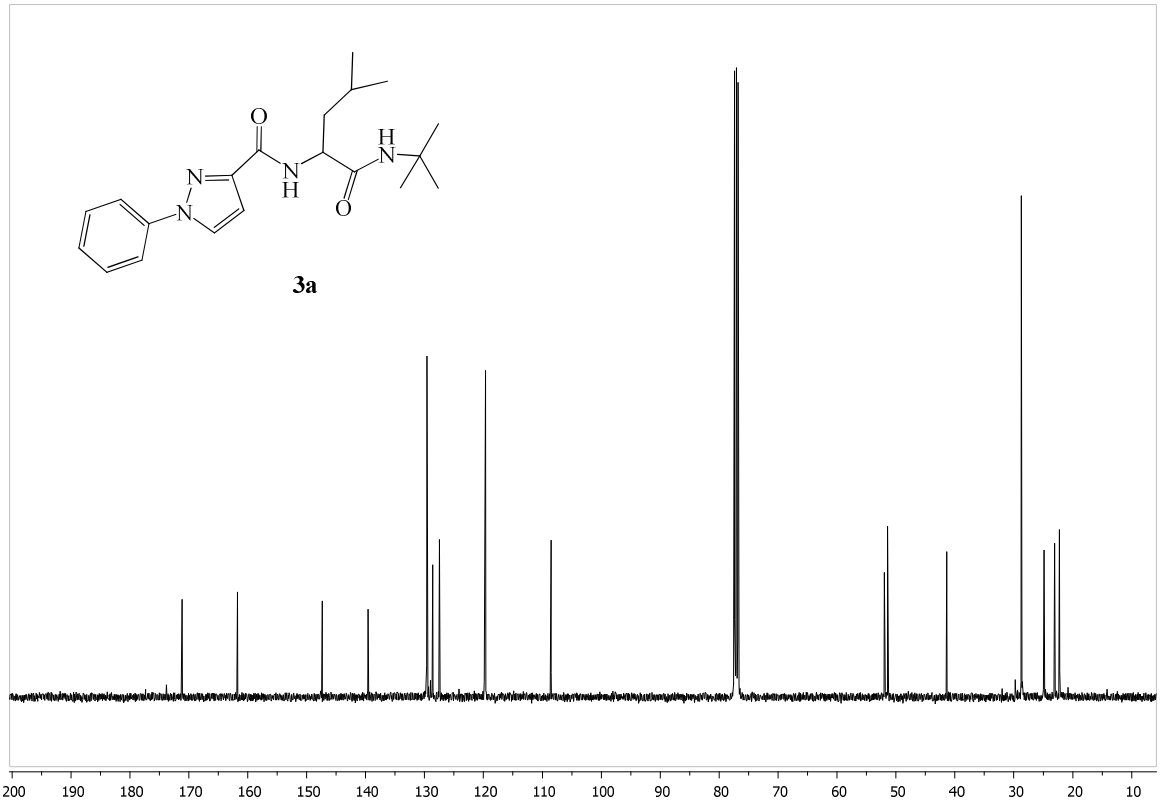
3a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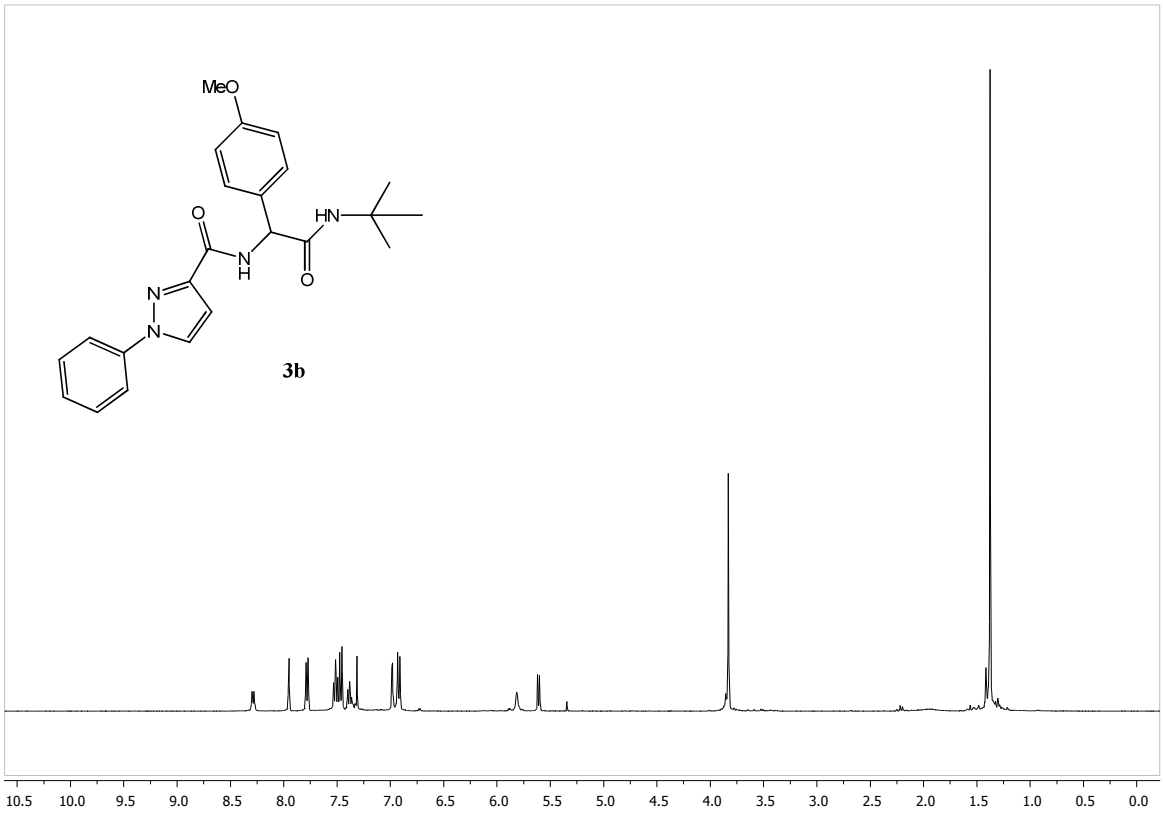
3a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3b
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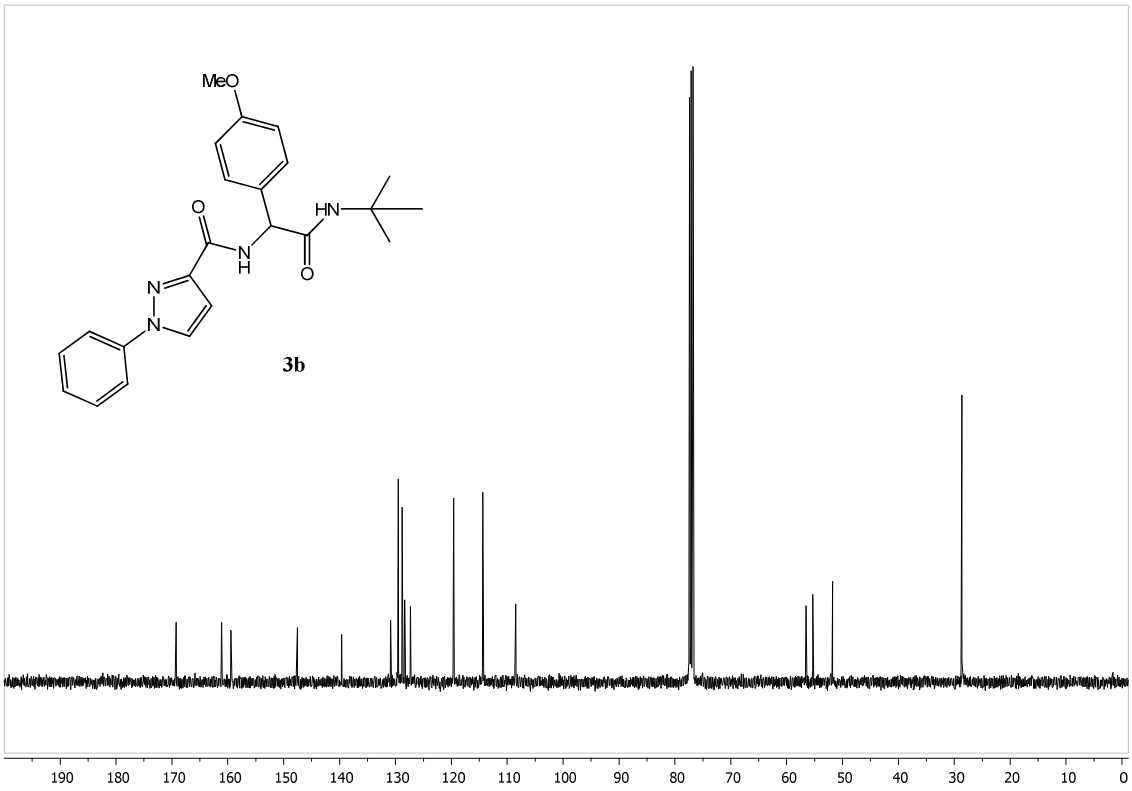
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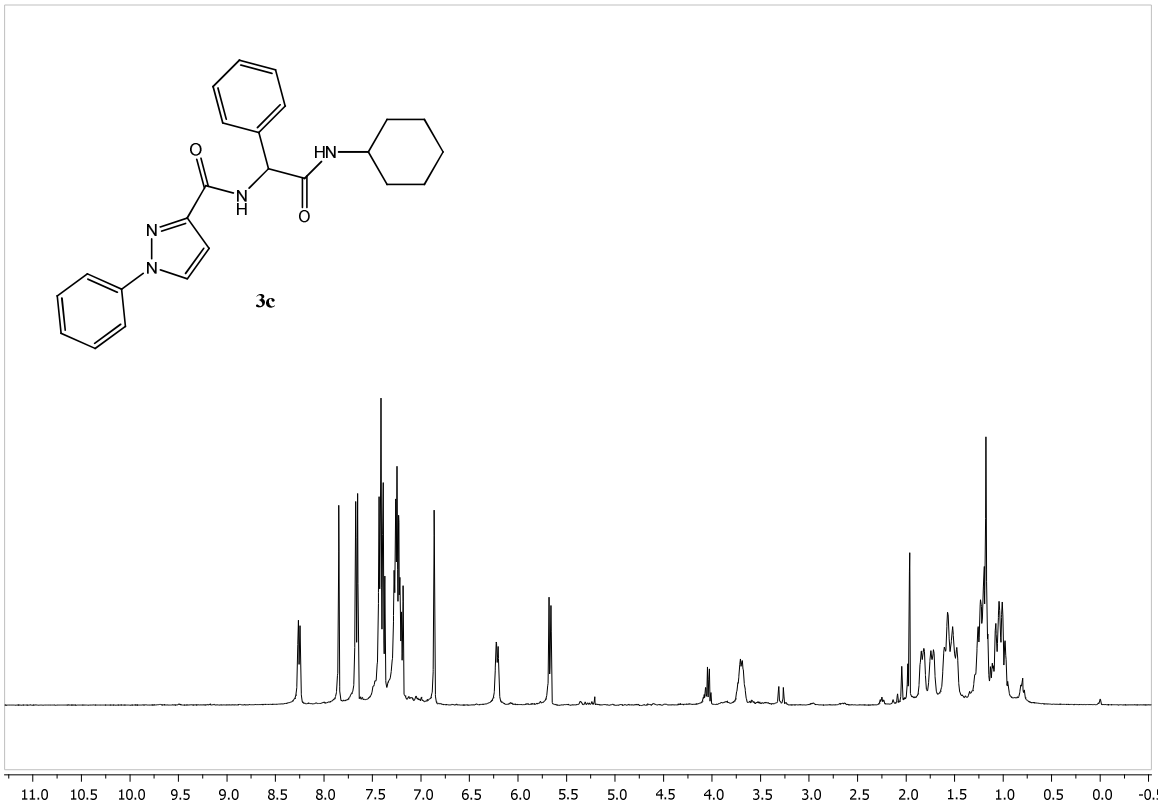
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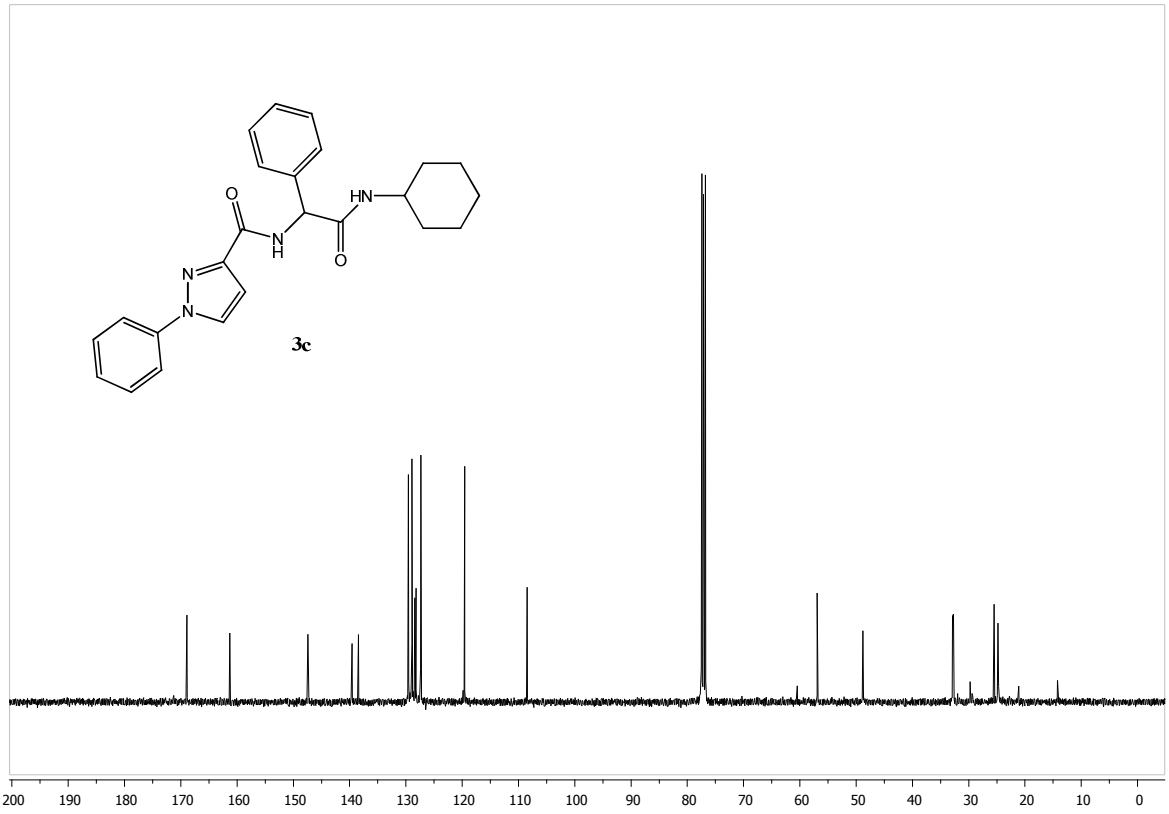
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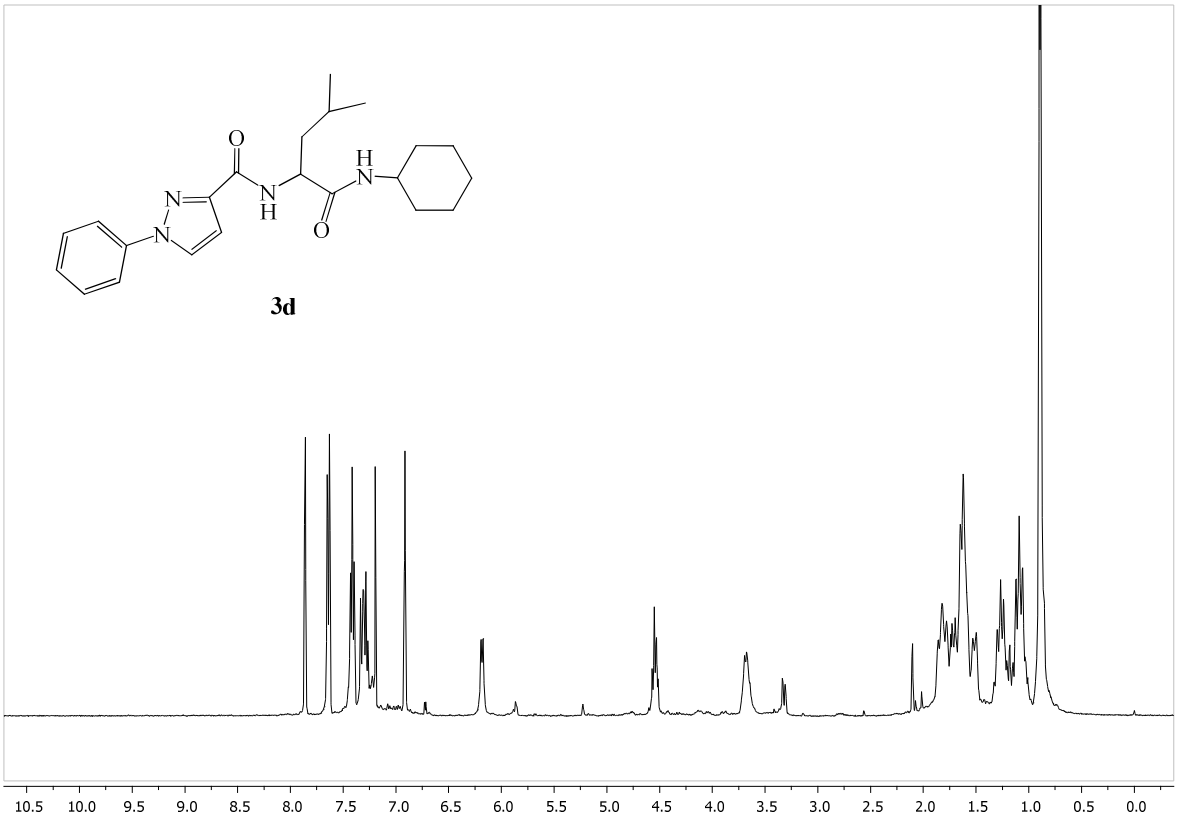
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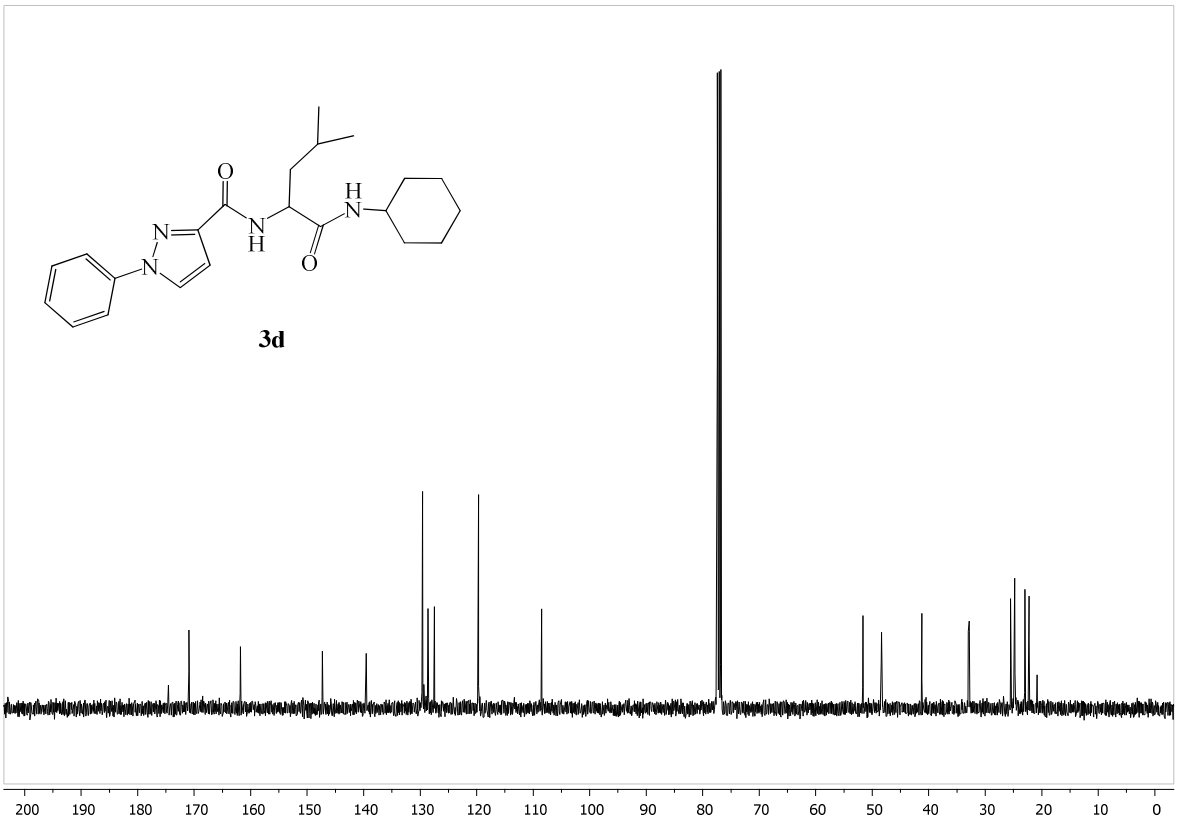
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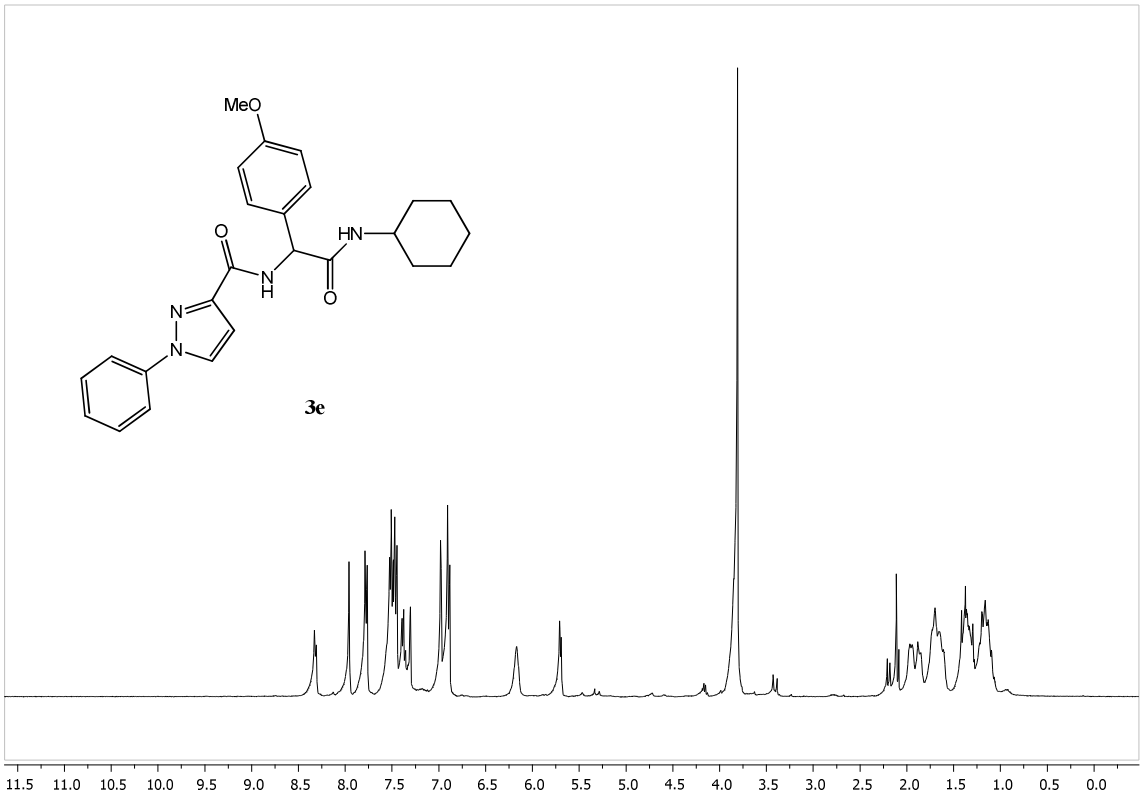
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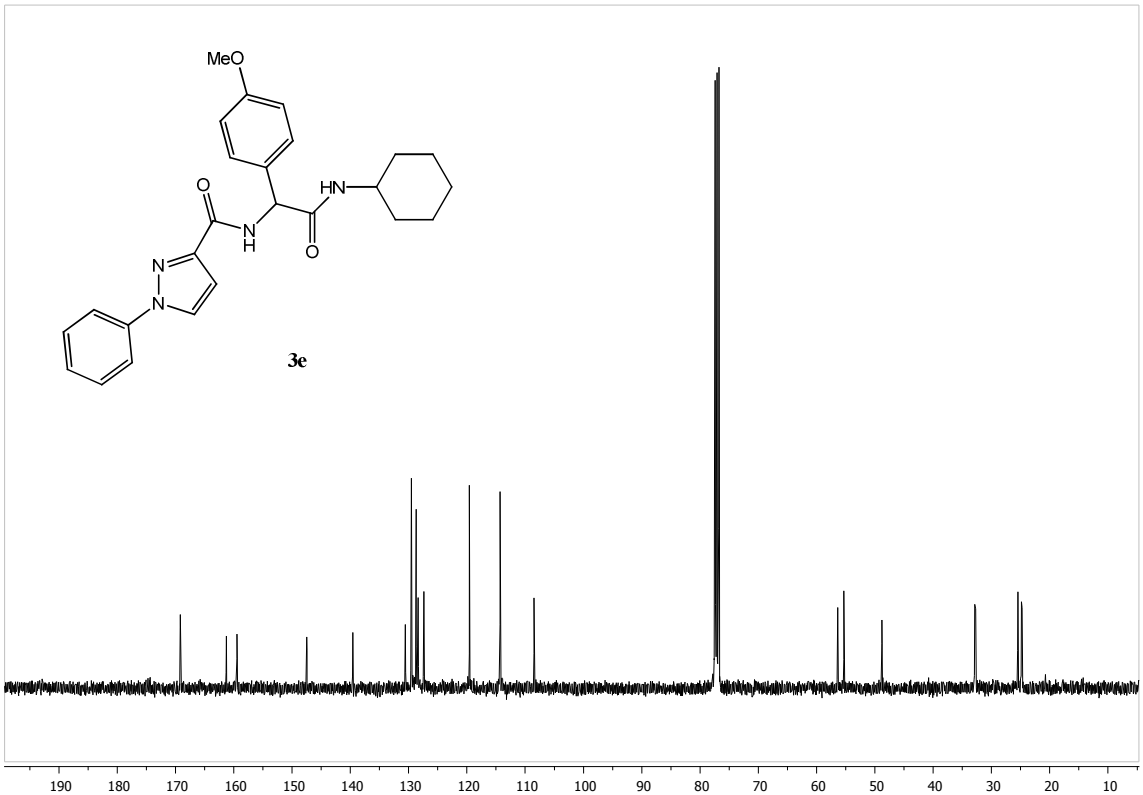
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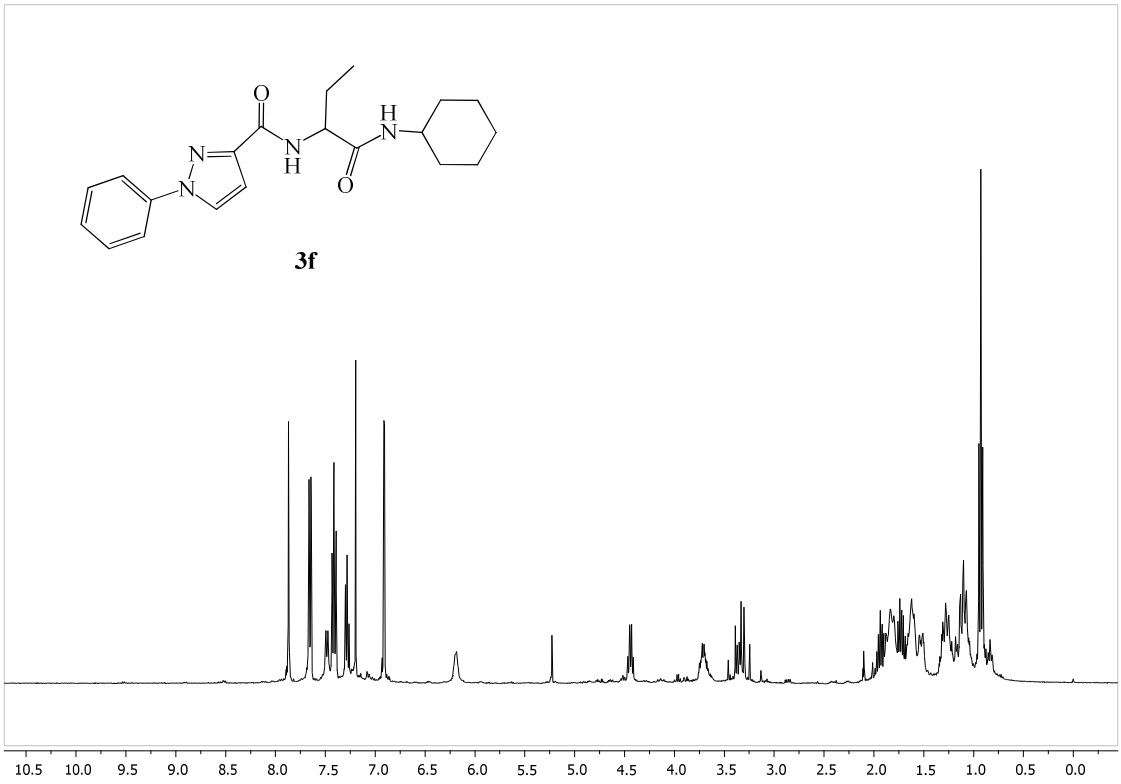
3e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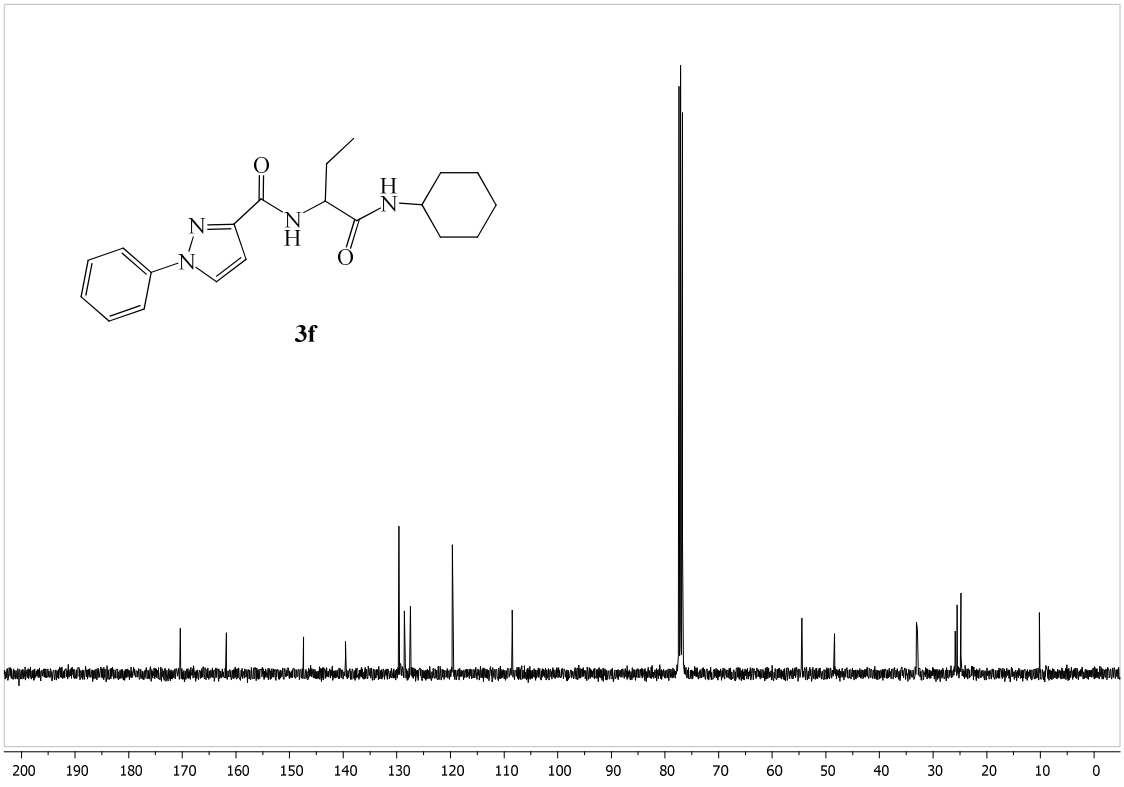
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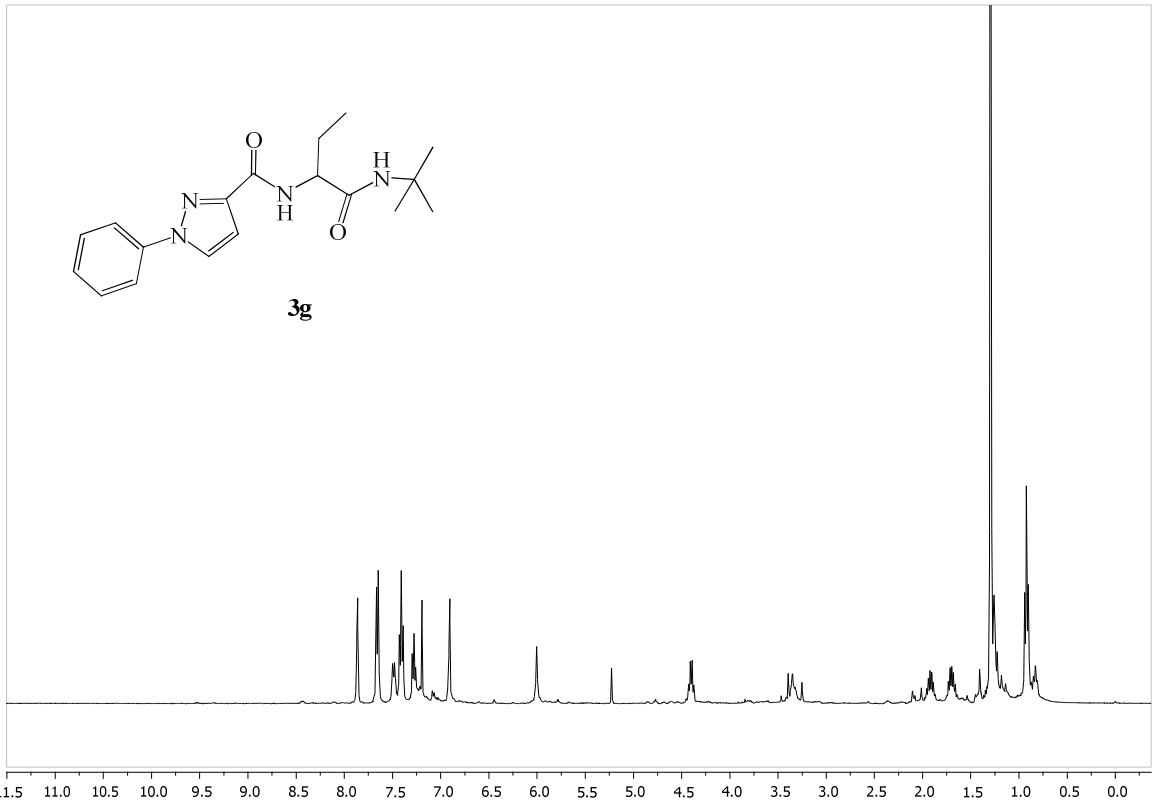
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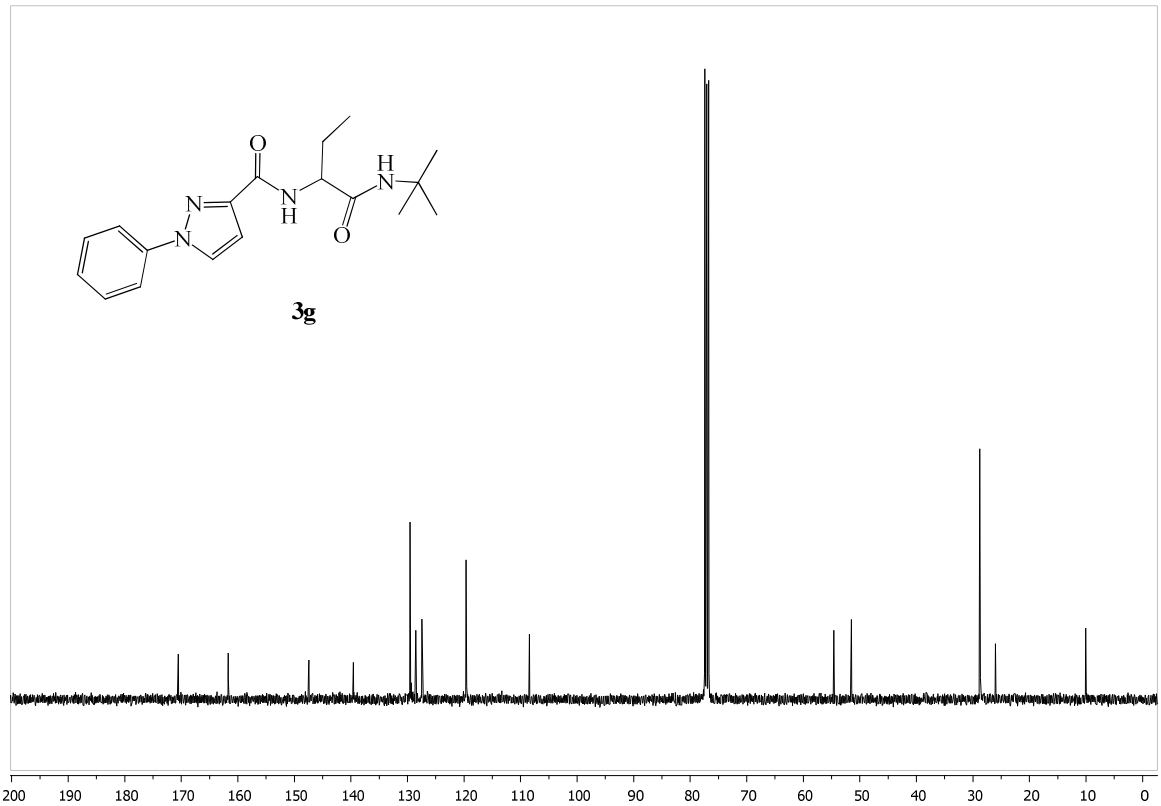
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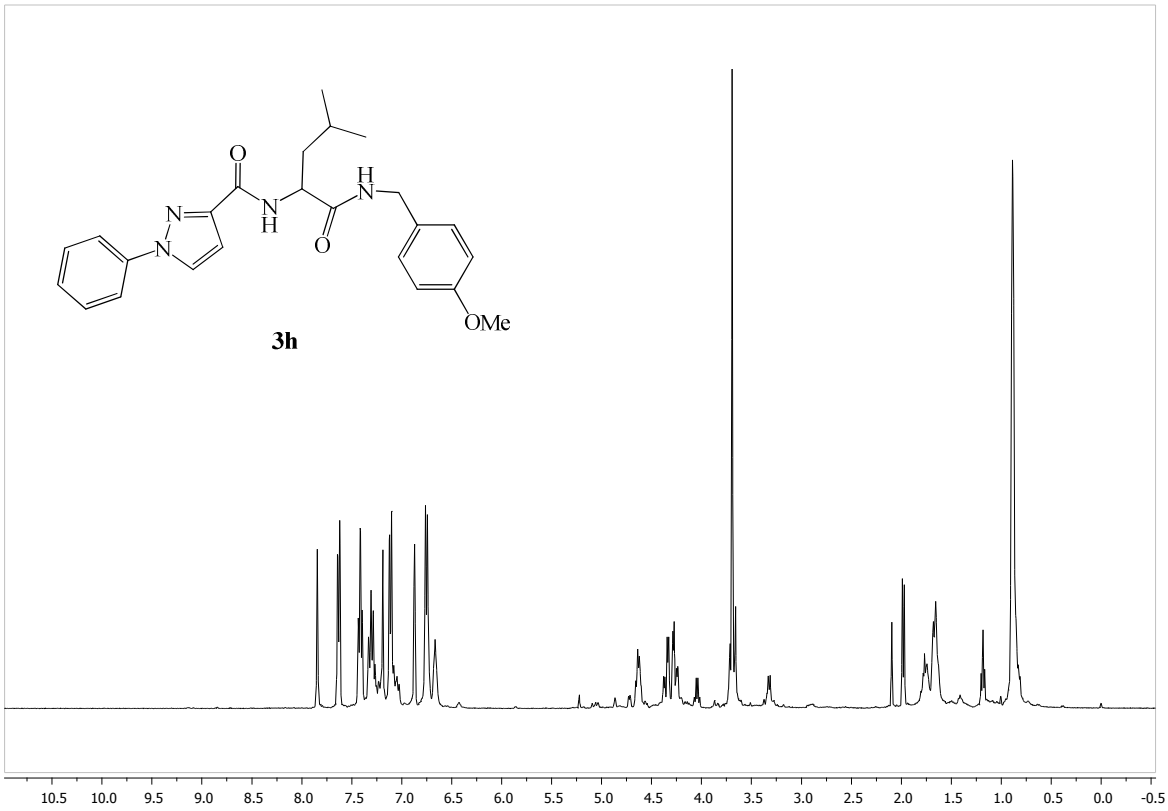
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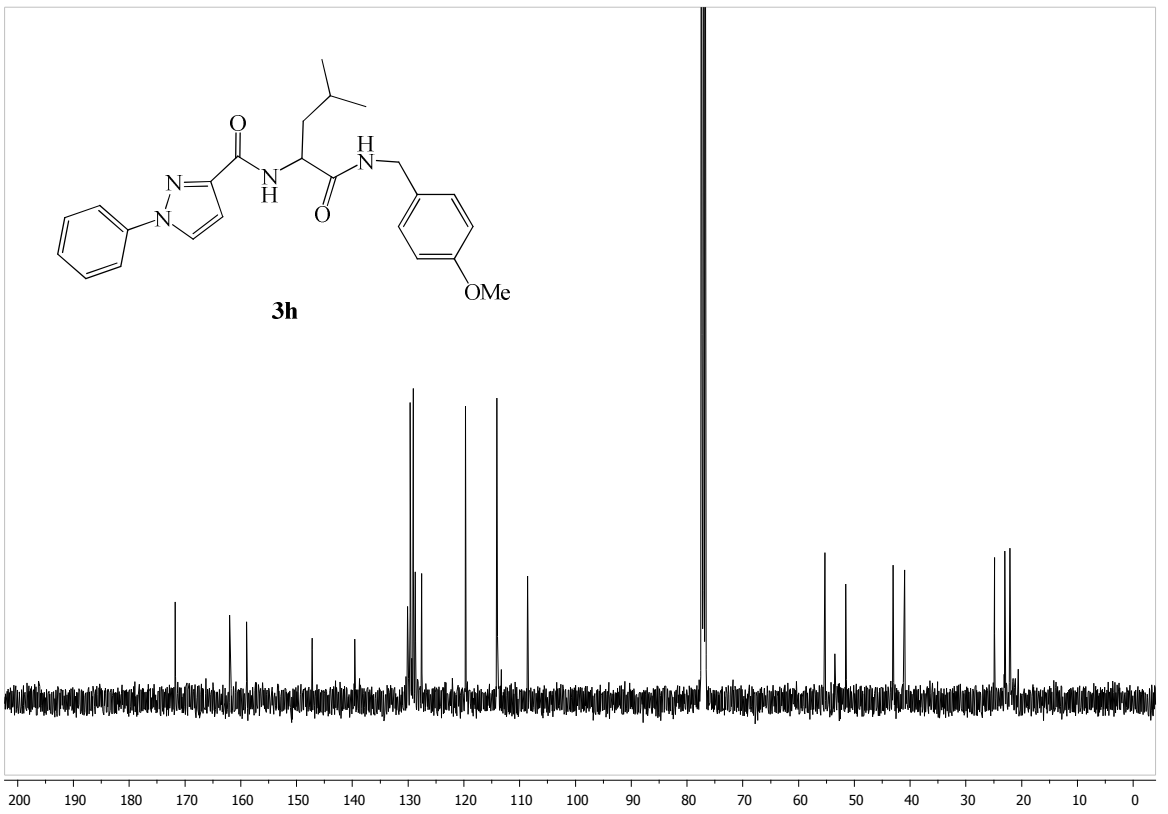
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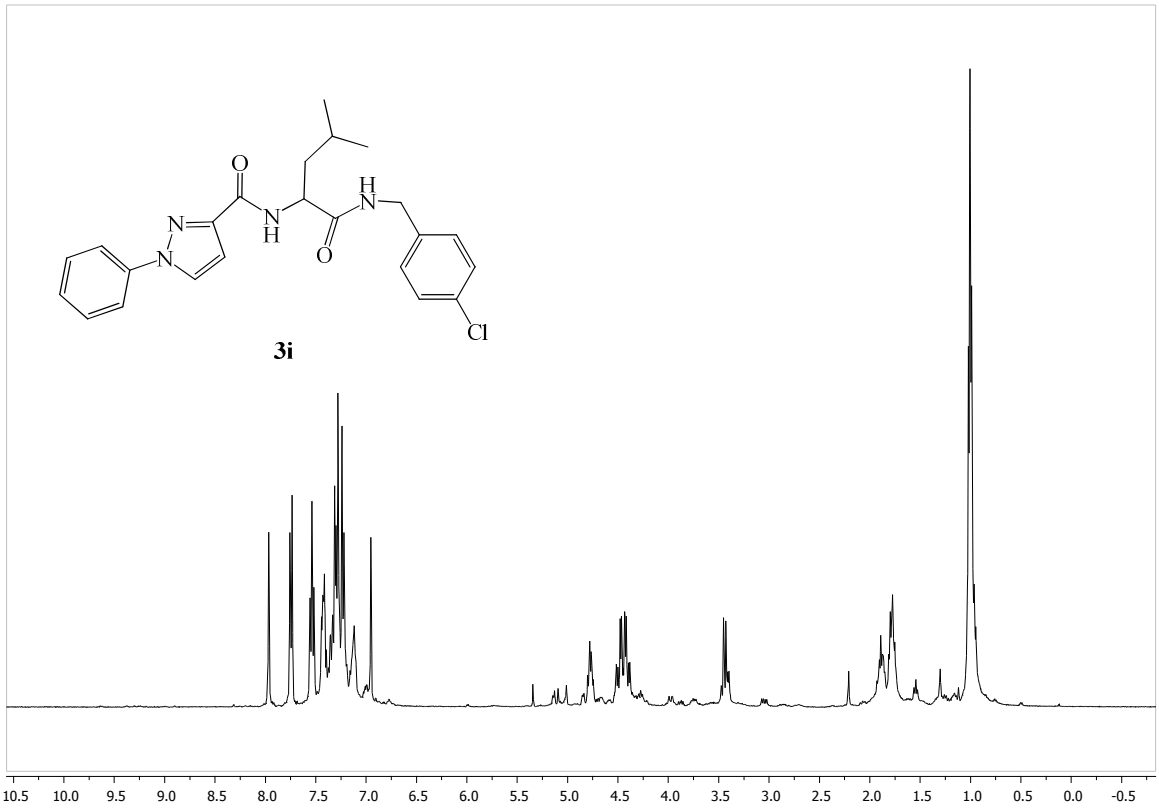
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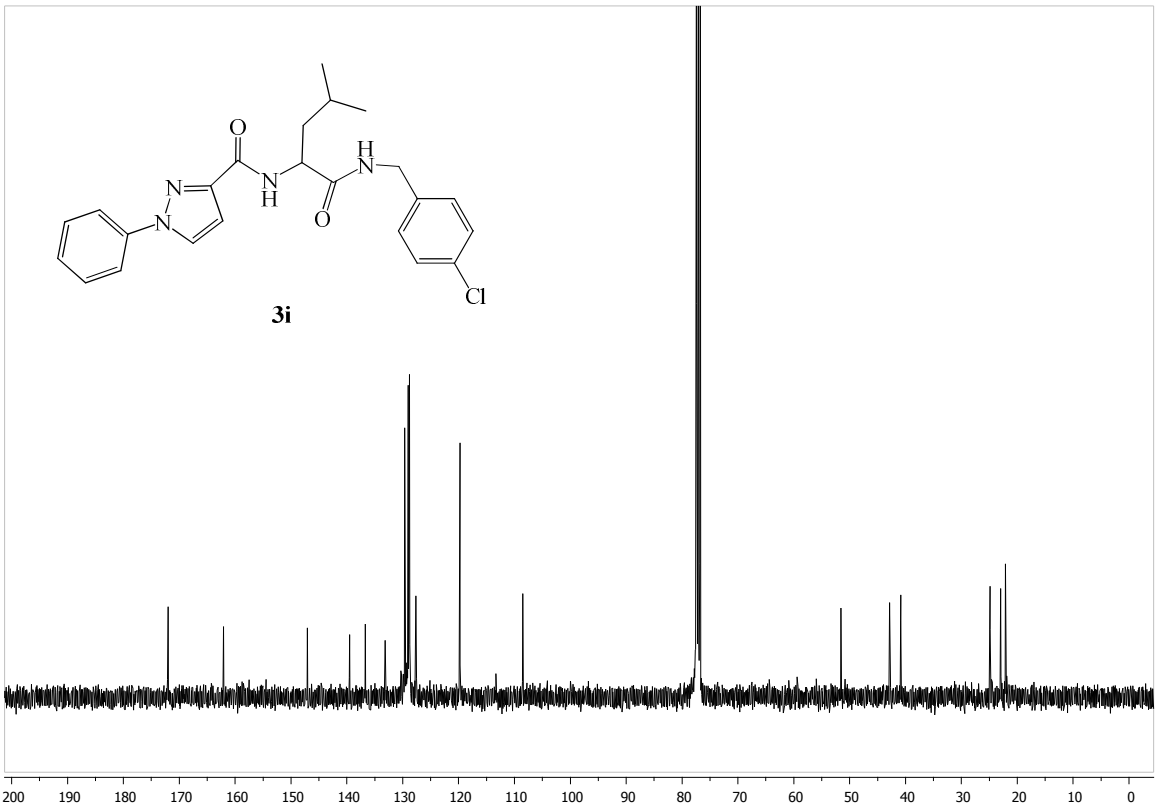
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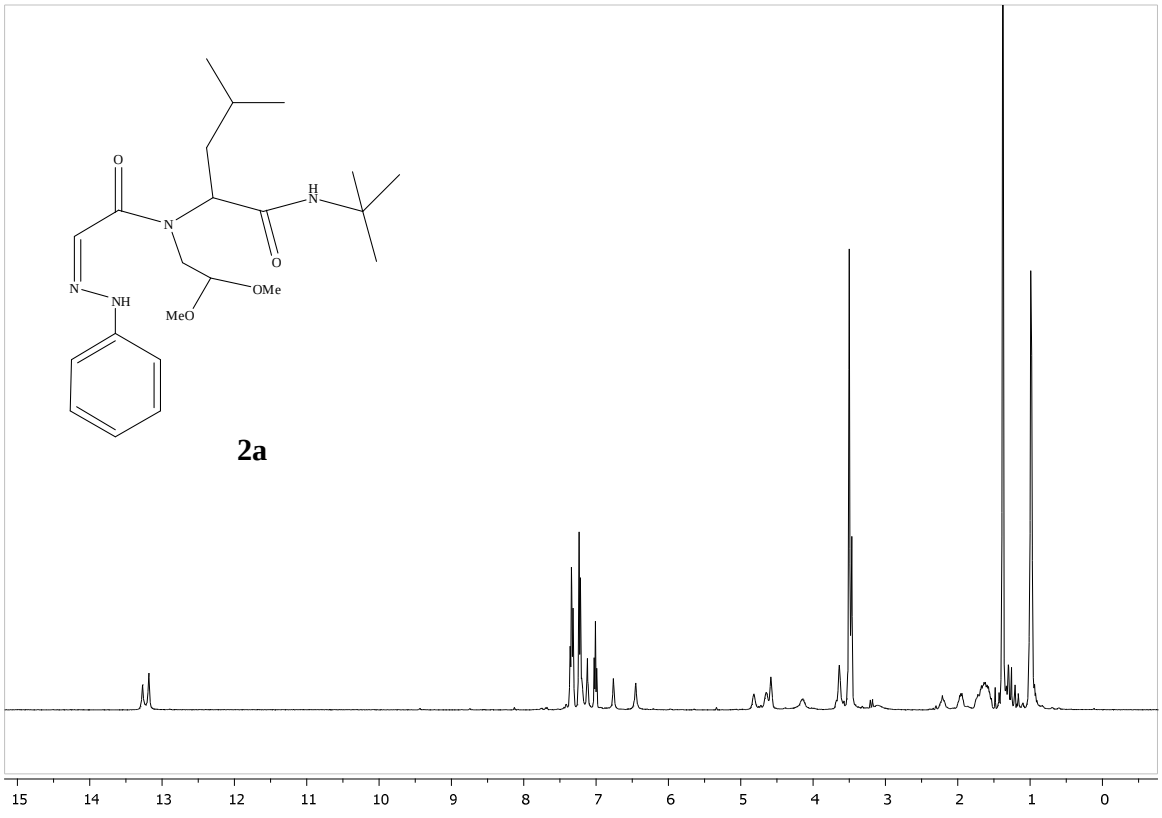
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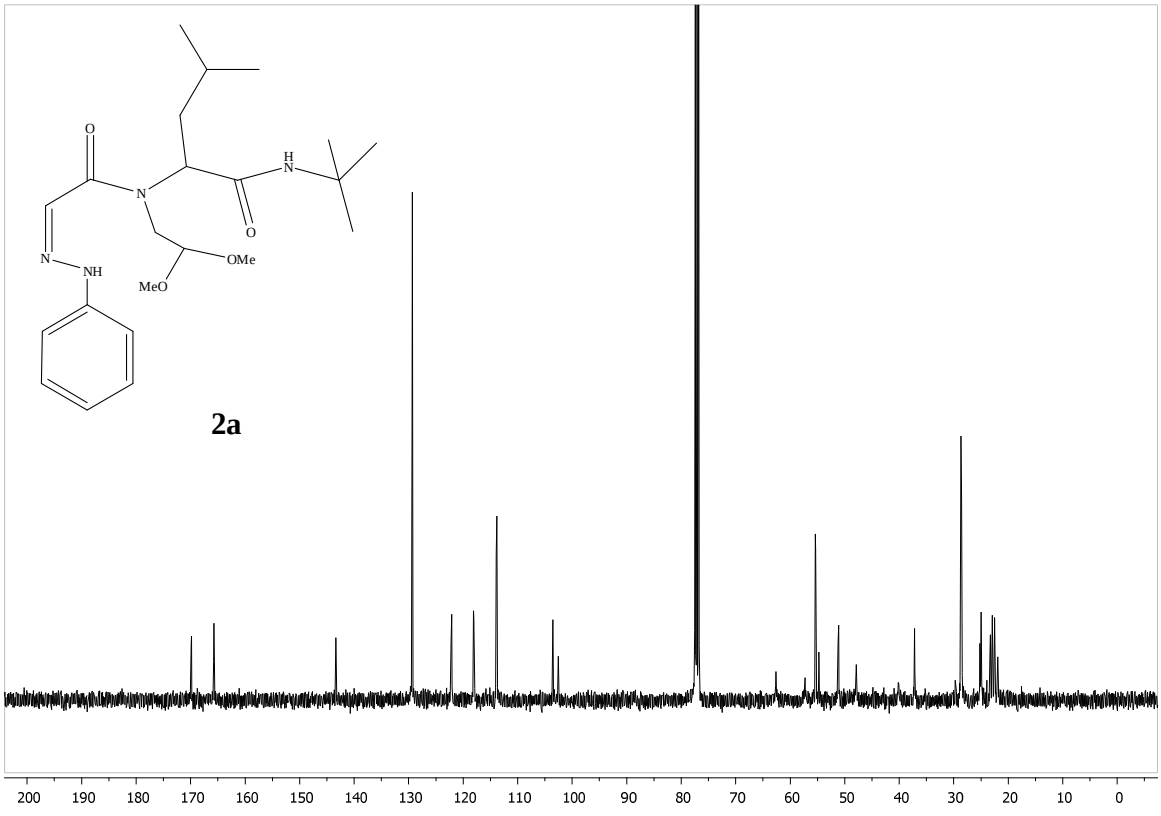
2a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