ESI

Benzenesulfonamide Decorated Dihydropyrimidin(thi)ones: Carbonic Anhydrase Profiling and Antiproliferative Activity

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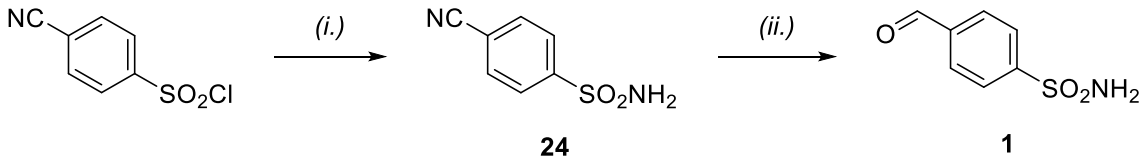
Content List

Chemistry

Synthesis of 4-formyl benzenesulfonamide 1

4-Formyl benzenesulfonamide **1** was obtained through a two-step synthetic pathway (**Scheme S1**) starting from the commercially available 4-cyanobenzenesulfonyl chloride that was converted into sulfonamide **24** by reaction with aqueous ammonia.(1) Then, the cyano group was converted into aldehyde through selective reduction by Raney Nichel.(2)



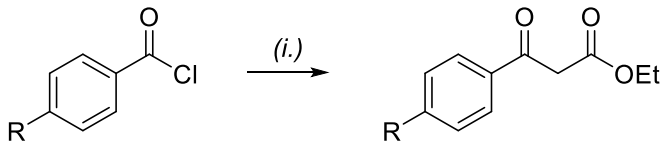
24 **1**

Scheme S1. Synthesis of 4-formyl benzenesulfonamide **1**.

Reagents and conditions: i) NH_4OH, dry THF, 0 °C-r.t., 5 h; ii) Ni Raney, HCOOH, ref., 3 h.

Synthesis of formyl ketoesters 7-8 and amido derivative 9

Ketoesters **7** and **8** were synthesized by reacting the suitable benzoyl chloride and EtOAc in presence of LDA as previously reported (**Scheme S2**).(3)



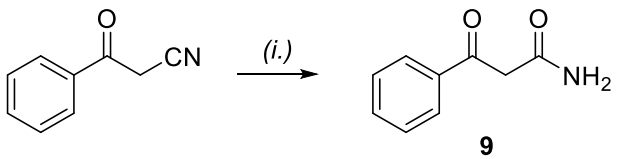
R= F, Cl

7: R = F
8: R = Cl

Scheme S2. Synthesis of ketoesters **7** and **8**.

Reagents and conditions: i) LDA, EtOAc, THF, -78 °C, 2.5 h.

Derivative **9** was obtained by adding H_2SO_4 to the commercial 3-phenyl-3-oxopropanenitrile (**Scheme S3**). (4)



9

Scheme S3. Synthesis of amido derivative **9**.

Reagents and conditions: i) H_2SO_4, r.t., 16 h.

Heat Map for Selectivity Indexes

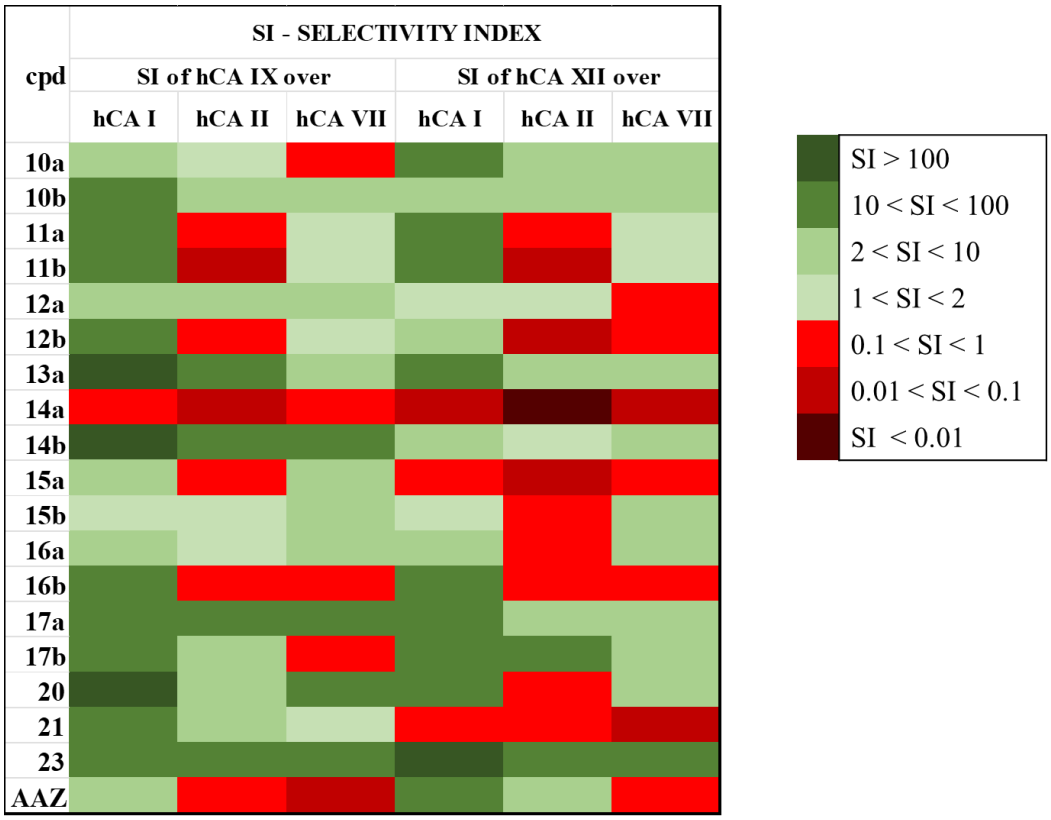


Figure S1. Heat Map for Selectivity Indexes of enzymatic inhibition. Selectivity index (SI) is calculated as the ratio between the K_I value of the test compound on the off-target isoform and that on the referred isoform (*e.g.,* SI of hCA IX over hCA I is calculated as follow: K_I on hCA I / K_I on hCA IX).

Electron density maps of inhibitor 12a

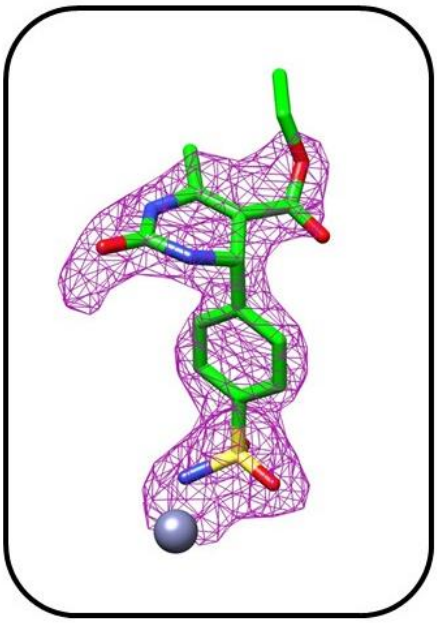


Figure S2. Electron density of inhibitor **12a** bound to zinc (grey) in hCA I active site. 2Fo-Fc maps and contoured to the 1.0 σ level.

Table S1. Summary of data collection and atomic model refinement statistics for hCAI.

	hCA I + 12a
PDB ID	8QGV
Wavelength (Å)	0.9718
Space Group	P212121
Unit cell (a, b, c, α, β, γ) (Å)	62.94, 71.14, 120.92, 90.00, 90.00, 90.00
Limiting resolution (Å)	50.0-1.84 (1.84-1.88)
Unique reflections	48159 (3513)
Rmerge (%)	12.2 (176.2)
Rmeas (%)	12.7 (183.5)
Redundancy	12.76 (12.8)
Completeness overall (%)	100.0 (100.0)
<I/σ(I)>	22.21 (2.28)
CC (1/2)	99.9 (78.1)
Refinement statistics	
Resolution range (Å)	50.0-1.84
Rfactor (%)	19.78
Rfree (%)	24.03
r.m.s.d. bonds (Å)	0.0097
r.m.s.d. angles (°)	1.6577
Ramachandran statistics (%)	
Most favored	97.4
additionally allowed	2.6
outlier regions	0.0
Average B factor (Å^2)	
All atoms	34.334
inhibitors	38.500
solvent	35.482

Chemistry - Experimental

Procedure for the synthesis of 4-formyl benzenesulfonamide 1.

4-Cyanobenzenesulfonamide (24). 4-Cyanobenzenesulfonyl chloride (10 mmol) was dissolved in dry THF (40 mL). Then, an aqueous solution of ammonium hydroxide (30%) (4 mL) was added at 0 °C and the mixture was stirred at room temperature for 5 h. Then, the mixture was extracted with EtOAc three times. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and evaporated under *vacuum*. The obtained solid was triturated with Et_2O. No further purification was required. Yield: 94%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ:7.69 (2H, s, -NH_2), 8.02 (2H, d, *J*= 8.4 Hz), 8.12 (2H, d, *J*= 8.4 Hz) ppm.

4-Formylbenzenesulfonamide (1). To a solution of **24** (1.7 g, 9.3 mmol) in formic acid (75%, 65 mL), Raney Nickel (2.45 g) was added and the mixture was refluxed for 3 h. Then, it was filtered through a Celite cake. The filtrate was concentrated under vacuum, extracted with EtOAc three times, and washed with H_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under *vacuum*. No further purification was required. Yield: 80 %, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.64 (2H, s, -NH_2), 8.06 (2H, d, *J*= 8.4 Hz), 8.14 (2H, d, *J*= 8.4 Hz), 10.13 (1H, s) ppm.

Procedure for the synthesis of ketoesters 7 and 8.

To a flame-dried flask containing LDA solution (5 mL, 2.0 M in heptane, THF, ethylbenzene) at -78 °C, EtOAc (0.49 mL, 5 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 minutes. Then, the suitable benzoyl chloride (5 mmol) in THF (4 mL) was added and the mixture was stirred at the same temperature for 2 hours. Upon completion, aqueous NH_4Cl was added and the crude was extracted with EtOAc three times. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under *vacuum*. The crude mixture was then purified through flash column chromatography on silica gel by using hexane/EtOAc 1:4 as eluent to give the desired keto-ester as a yellow oil.

Ethyl 3-(4-fluorophenyl)-3-oxopropanoate (7). Yield 69 % (keto/enol: 1/0.06); yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: Keto: 1.21 (3H, t, *J*= 7.2 Hz), 4.15 (2H, q, *J*= 6.8 Hz), 4.23 (2H, s), 7.42 (2H, t, *J*= 8.8 Hz), 8.08 (2H, t, *J*= 7.2 Hz); Enol: 1.31 (3H, t, *J*= 6.8 Hz), 4.07 (2H, q, *J*= 7.2 Hz), 5.99 (1H, bs), 7.39 (2H, t, *J*= 8.8 Hz), 7.98 (2H, t, *J*= 6.8 Hz), 12.70 (1H, bs) ppm.

Ethyl 3-(4-chlorophenyl)-3-oxopropanoate (8). Yield 65 % (keto/enol: 1/0.1); yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: Keto: 1.21 (3H, t, *J*= 7.2 Hz), 4.15 (2H, q, *J*= 6.8 Hz), 4.24 (2H, s), 7.67 (2H, d,

J= 8.8 Hz), 8.01 (2H, d, *J*= 8.8 Hz); Enol: 1.31 (3H, t, *J*= 7.2 Hz), 4.07 (2H, q, *J*= 7.2 Hz), 6.03 (1H, bs), 7.59 (2H, d, *J*= 8.8 Hz), 7.93 (2H, d, *J*= 8.8 Hz), 12.64 (1H, bs) ppm.

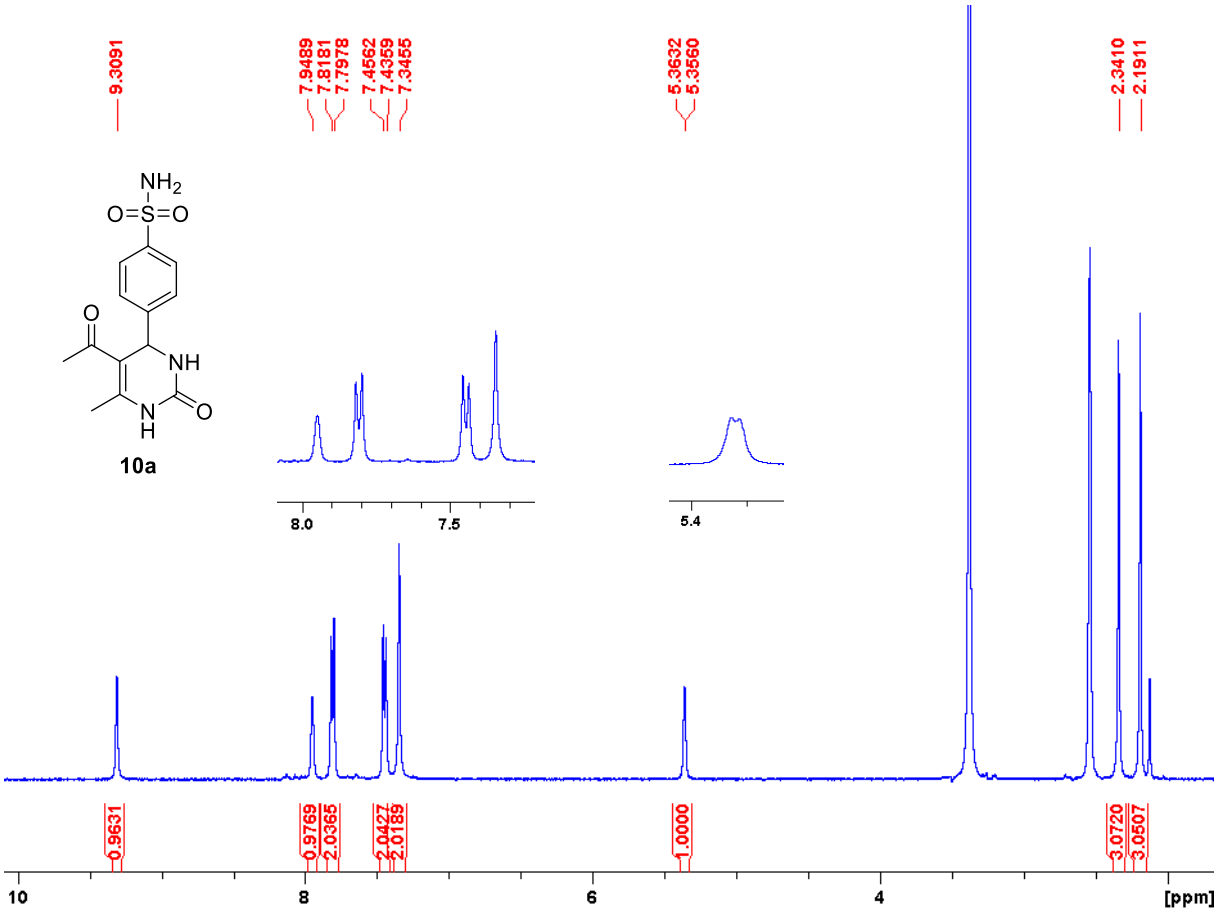
3-Oxo-3-phenylpropanamide (9). 3-Phenyl-3-oxopropanenitrile (725.0 mg, 5.0 mmol) was dissolved in conc. H_2SO_4 (25.0 mL) and the mixture was stirred at r.t. for 16 h. Then, the mixture was poured into ice water, basified with NH_4OH, and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under *vacuum* to provide the desired amide. Yield 71 %; mp: 109-110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.90 (2H, s), 7.15 (1H, bs), 7.64 (1H, bs), 7.58 (2H, t, *J*= 7.6 Hz), 7.69 (1H, t, *J*= 7.6 Hz), 8.01 (2H, d, *J*= 7.2 Hz) ppm.

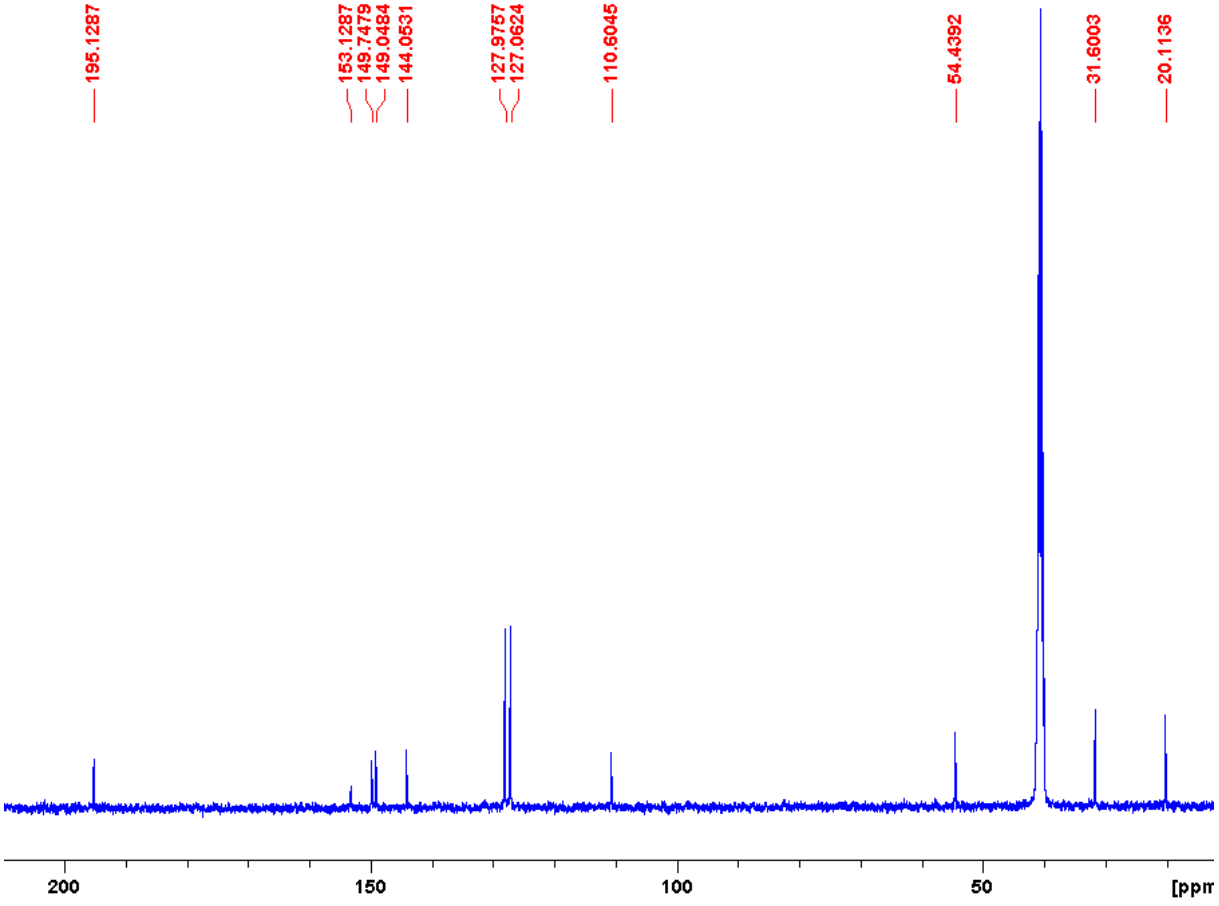
Procedure for the synthesis of 2-aminopyrimidine 23

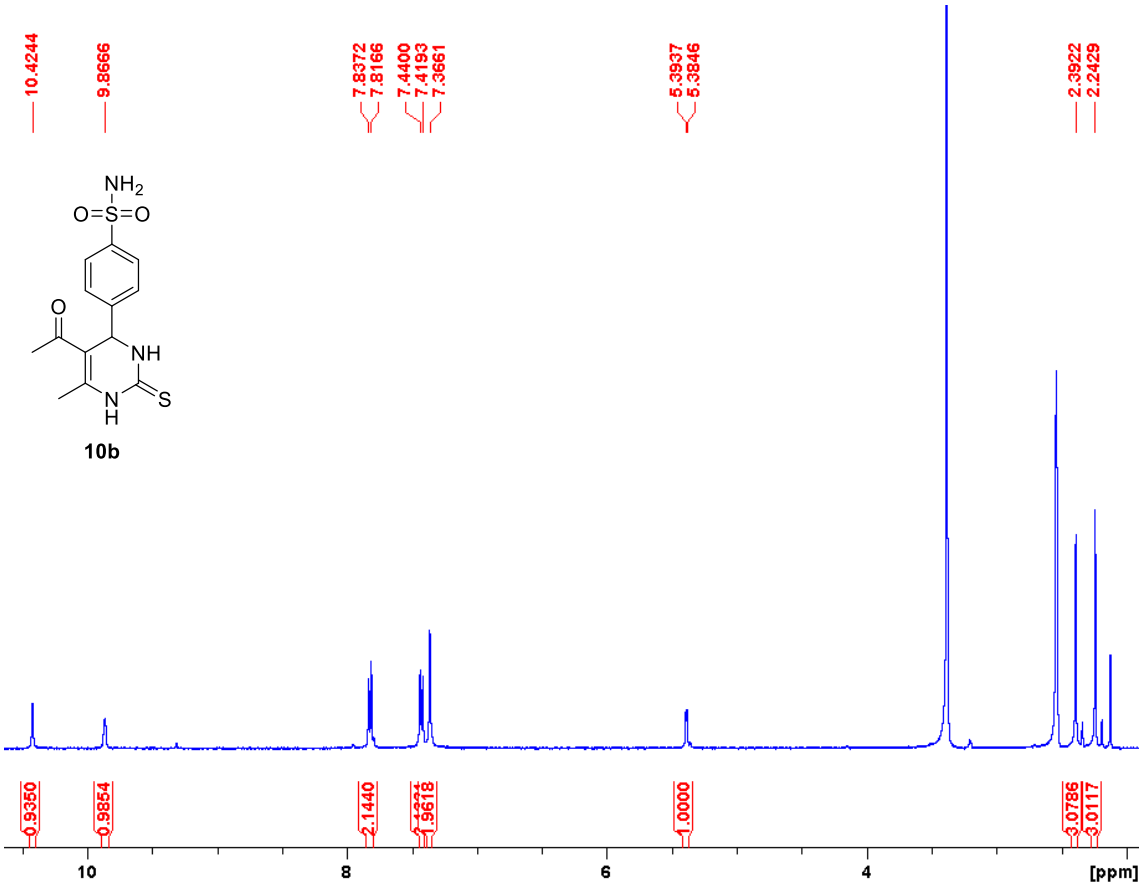
(E)-4-(3-phenyl-3-oxoprop-1-en-1-yl)benzenesulfonamide (22). To an aqueous solution of NaOH (650.0 mg, 6.4 mmol, 3.0 mL), a solution of acetophenone (600.0 mg, 5.0 mmol) in EtOH (5.0 mL) was added slowly at 0 °C. Then, 4-formylbenzenesulfonamide (925.0 mg, 5.0 mmol) in EtOH (5.0 mL) was added dropwise and the mixture was stirred for 16 h at r.t.. After completion, the formed precipitate was filtered under *vacuum* and washed with EtOH and H_2O. Yield 55 %; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.46- 7.52 (3H, m), 7.58 (2H, s, -NH_2), 7.80 (1H, d, *J*= 15.6 Hz), 7.90-7.94 (2H, m), 7.96 (1H, d, *J*= 15.6 Hz), 8.0 (2H, d, *J*= 8.0 Hz), 8.32 (2H, d, *J*= 8.0 Hz) ppm; LC-MS (ESI) (*m/z*): 286.1 $[M-H]^-$

4-(2-amino-6-phenylpyrimidin-4-yl)benzenesulfonamide (23). To a solution of chalcone **22** (287.0 mg, 1.0 mmol) and guanidine hydrochloride (143.2 mg, 1.5 mmol) in EtOH (4.0 mL), 50% aqueous KOH (3.9 mmol) was added and the mixture was stirred till chalcone starting material consumption. Then, 30% aqueous H_2O_2 (0.34 mL, 3.34 mmol) was added portionwise over a period of 1 h and the reaction mixture was left to stir. After that, the reaction mixture was concentrated under *vacuum* and H_2O was added to induce precipitation. The solid obtained was filtered under vacuum and washed with additional H_2O. Then, it was recrystallized from EtOH. Yield 45 %; White solid; mp: 259-261°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.91 (2H, s, -NH_2), 7.52 (2H, s, -NH_2), 7.58 (3H, t, *J*= 3.2 Hz), 7.84 (1H, s, H-C5), 8.01 (2H, d, *J*= 8.4 Hz), 8.27 (2H, d, *J*= 3.6 Hz), 8.44 (2H, d, *J*= 8.4 Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 103.5 (CH), 127.0 (CHx2), 128.1 (CHx2), 128.6 (CHx2), 129.7 (CHx2), 131.7 (CH), 138.2 (C), 141.5 (C), 146.6 (C), 164.5 (C), 165.1 (C), 166.4 (C) ppm; LC-MS (ESI) (*m/z*): 327.1 $[M+H]^+$

NMR spectra of final compounds



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H
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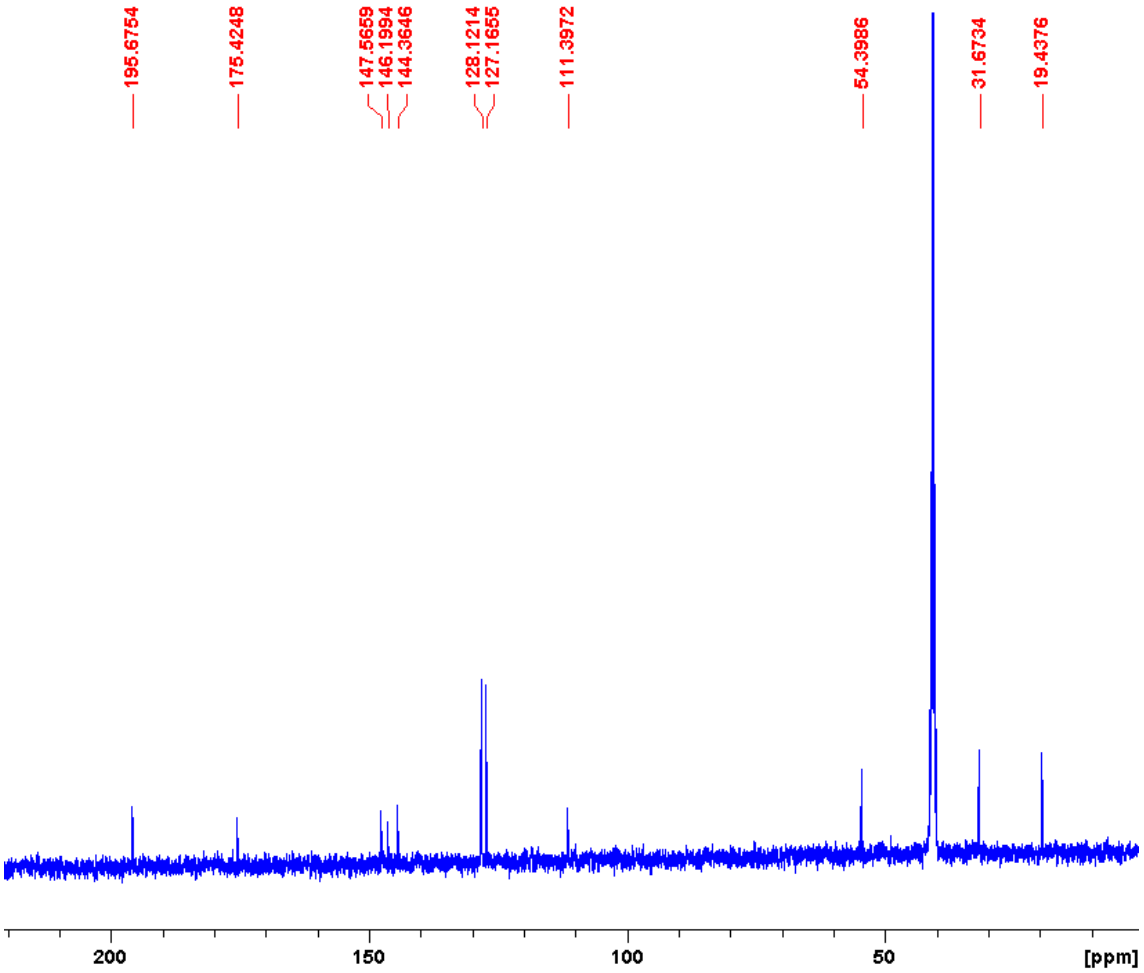
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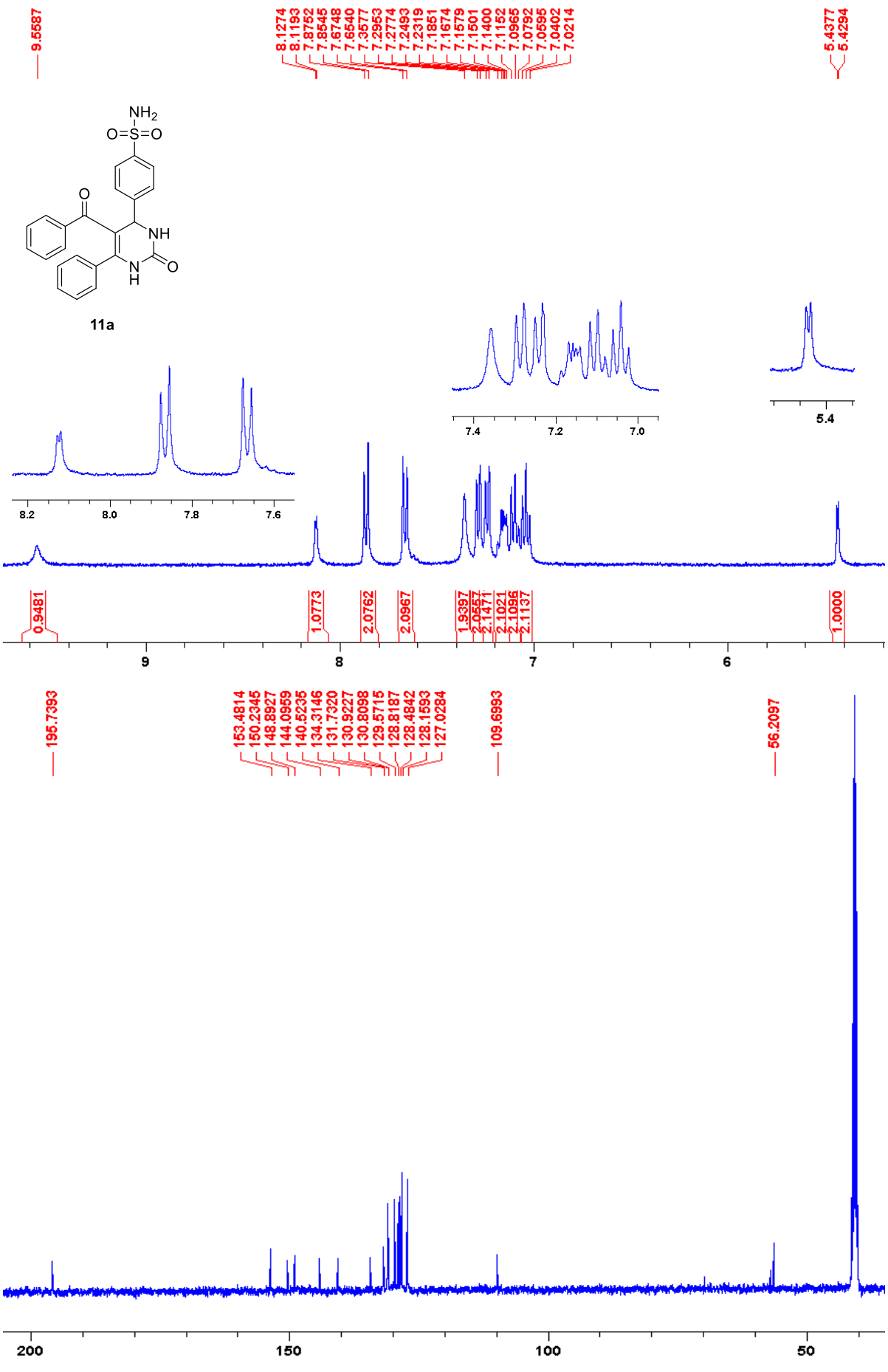
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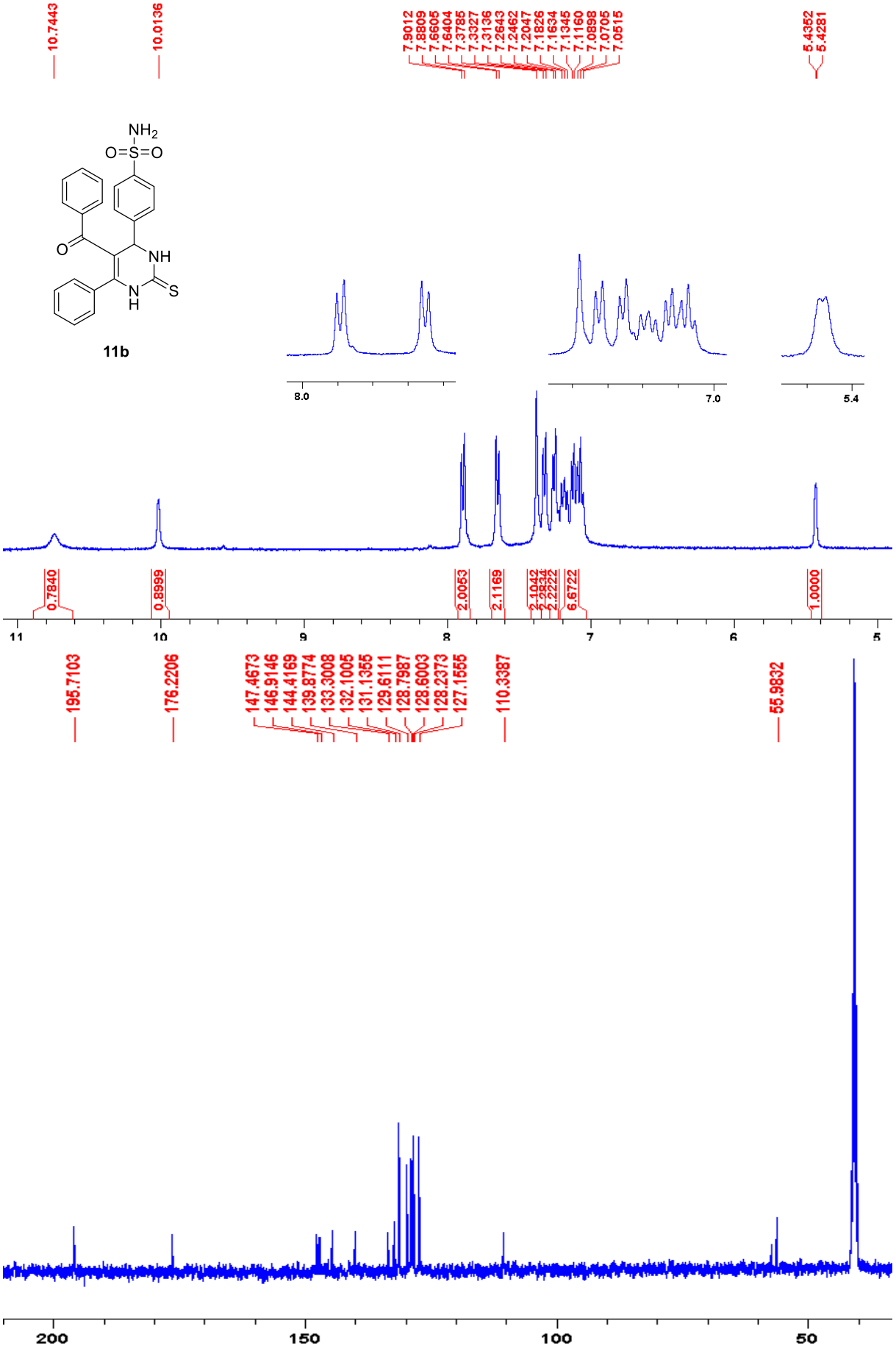
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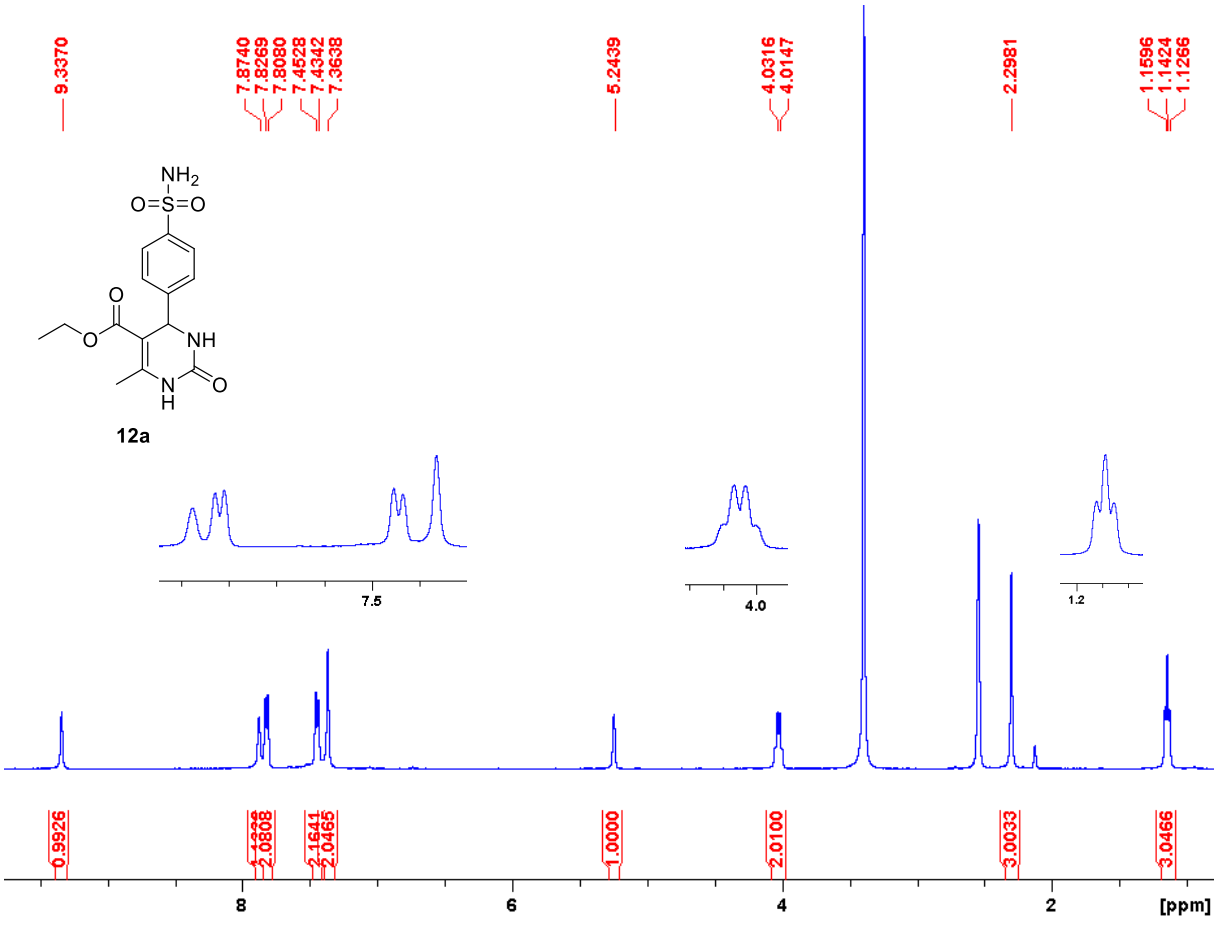
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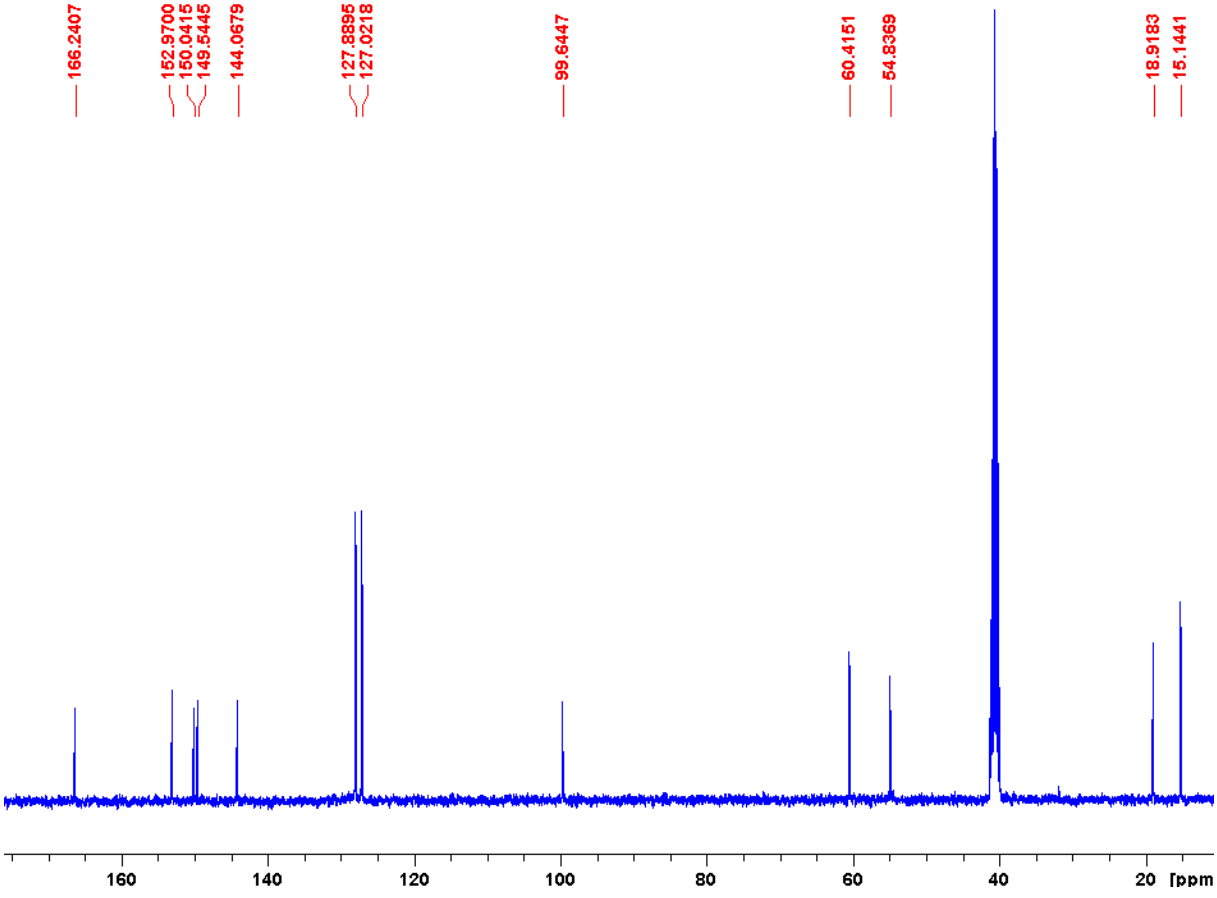
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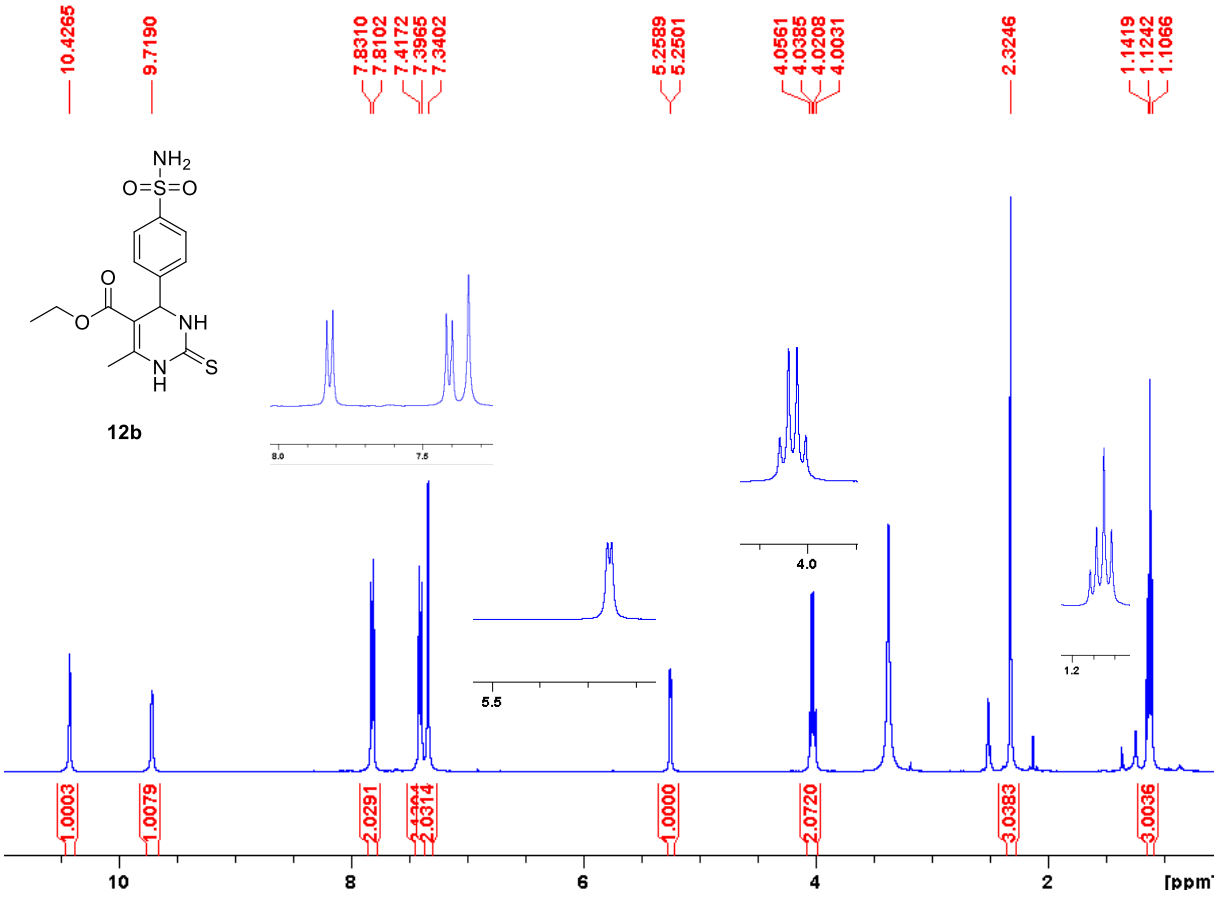
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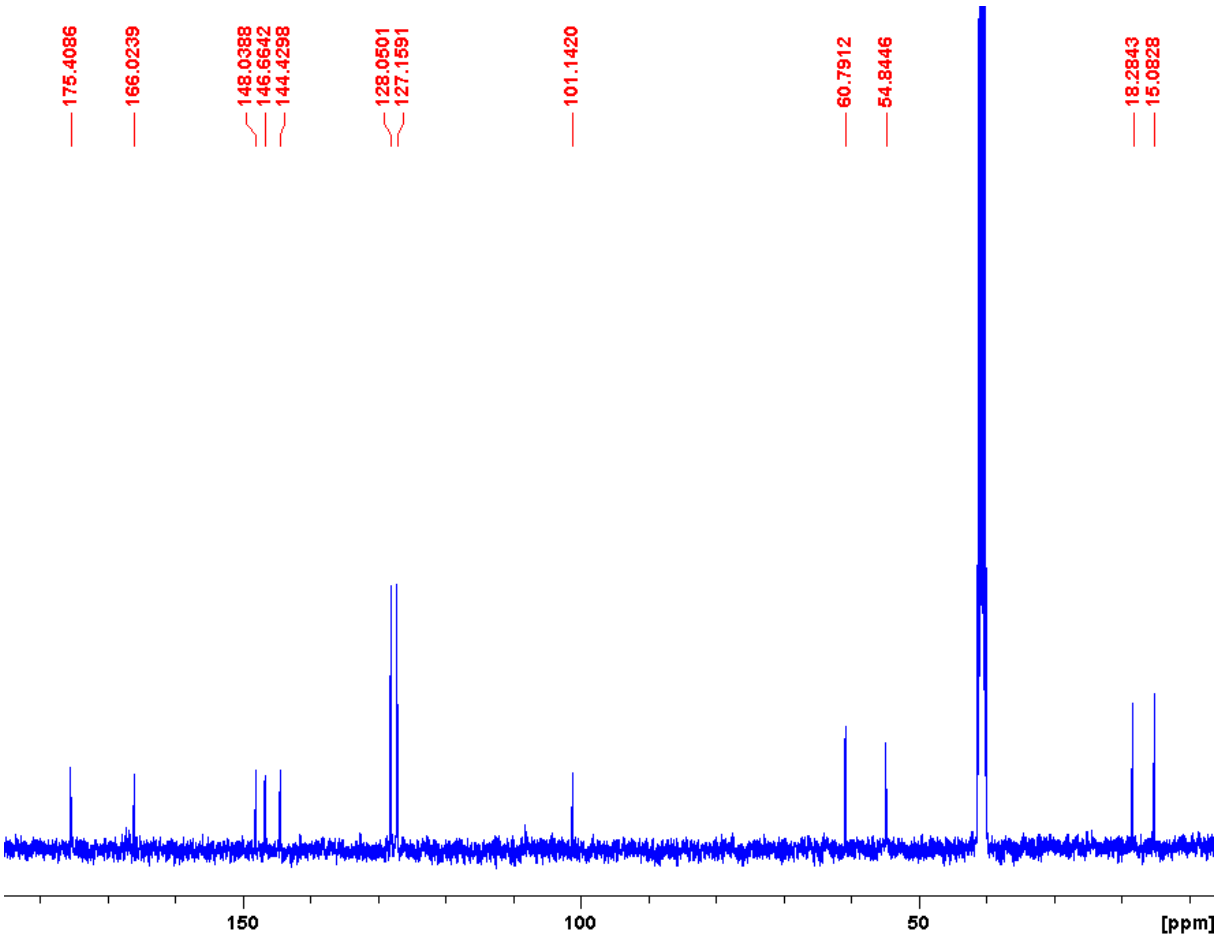
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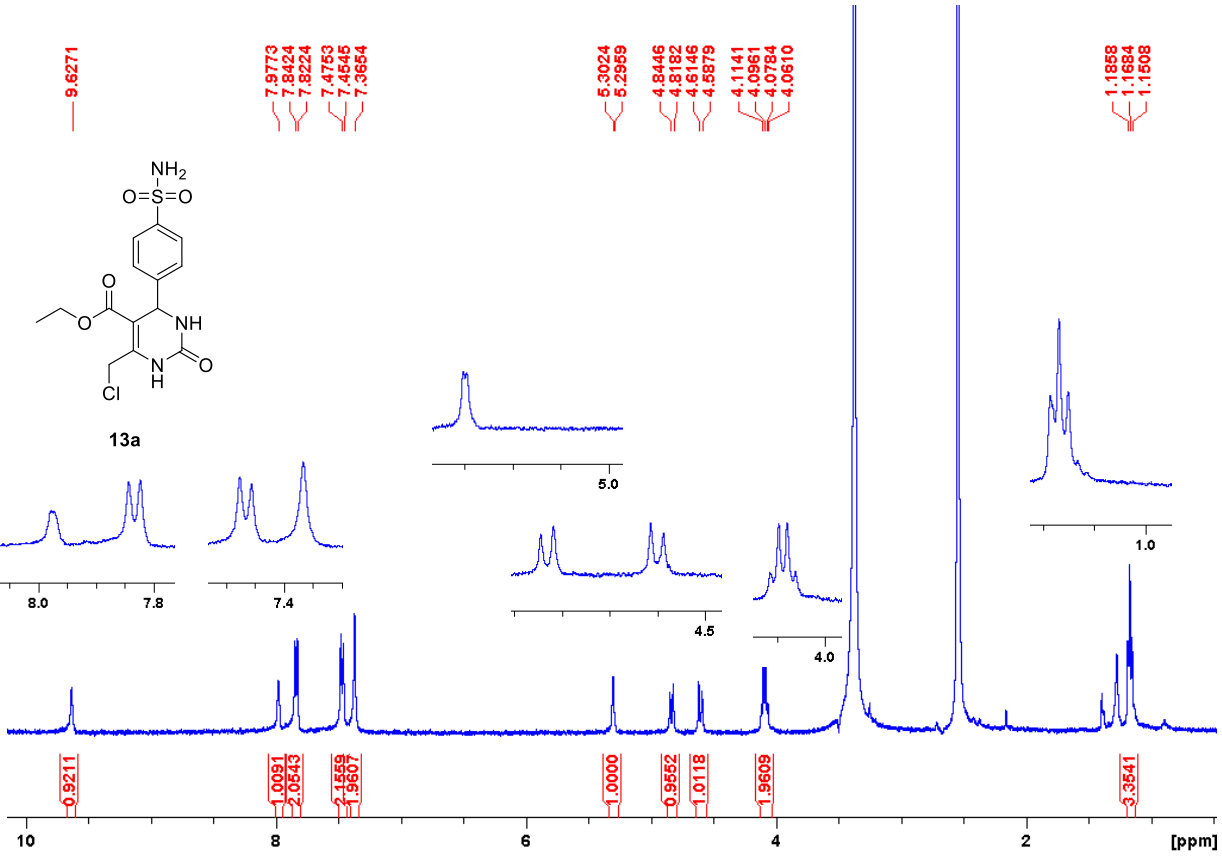
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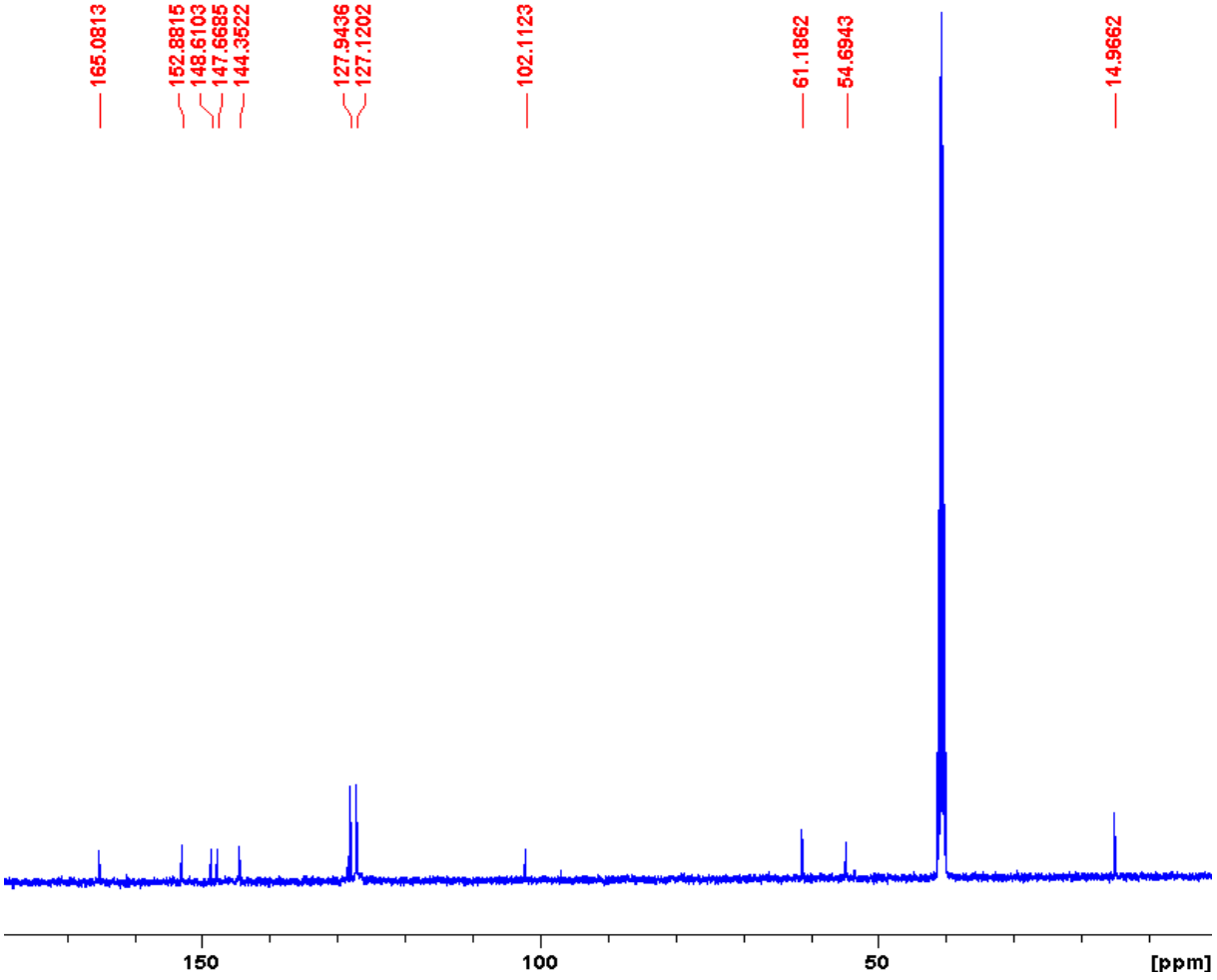
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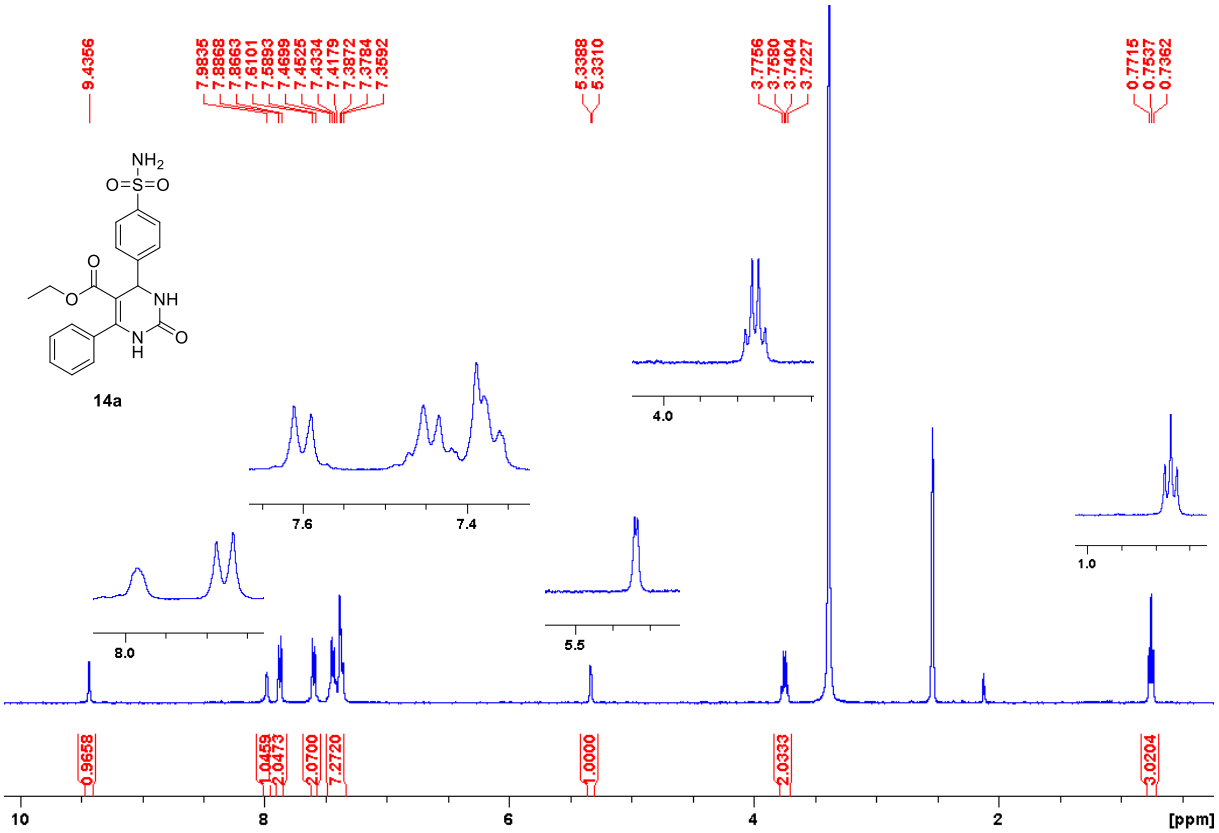
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NH
N
H
O
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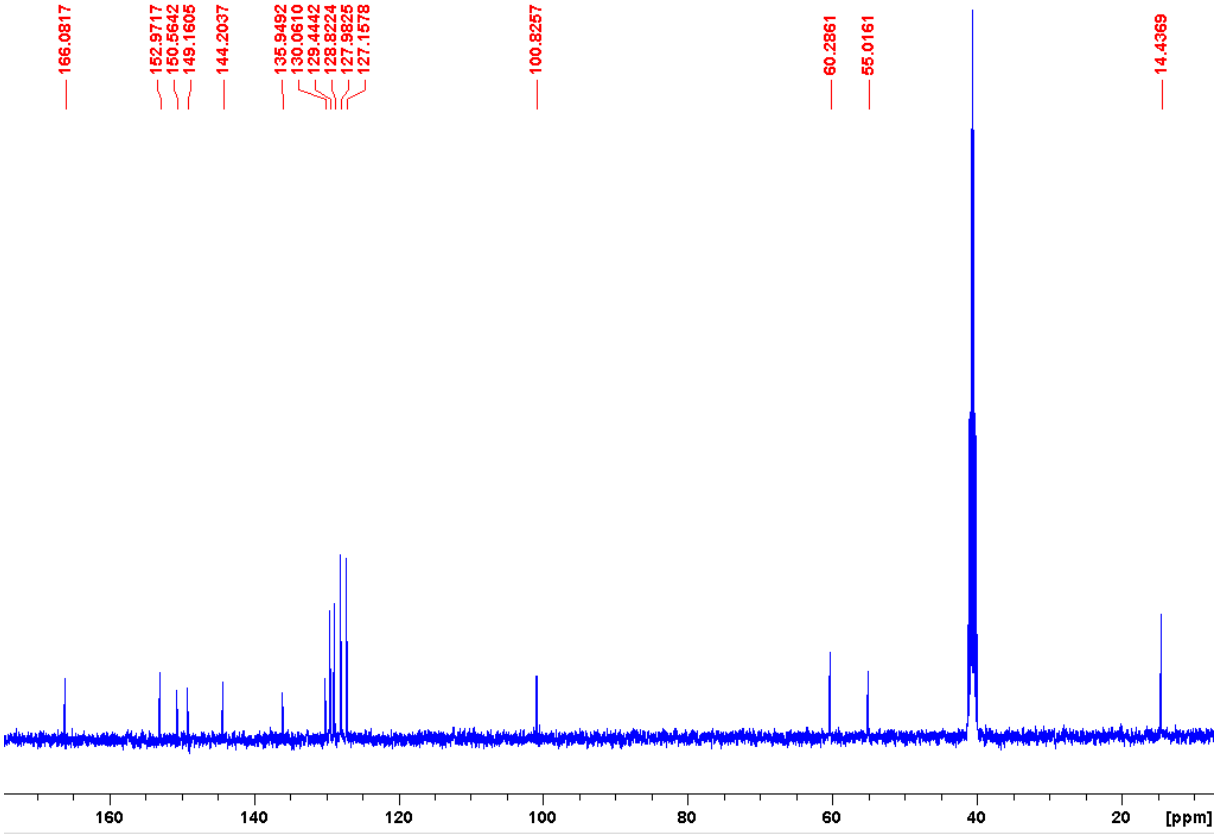
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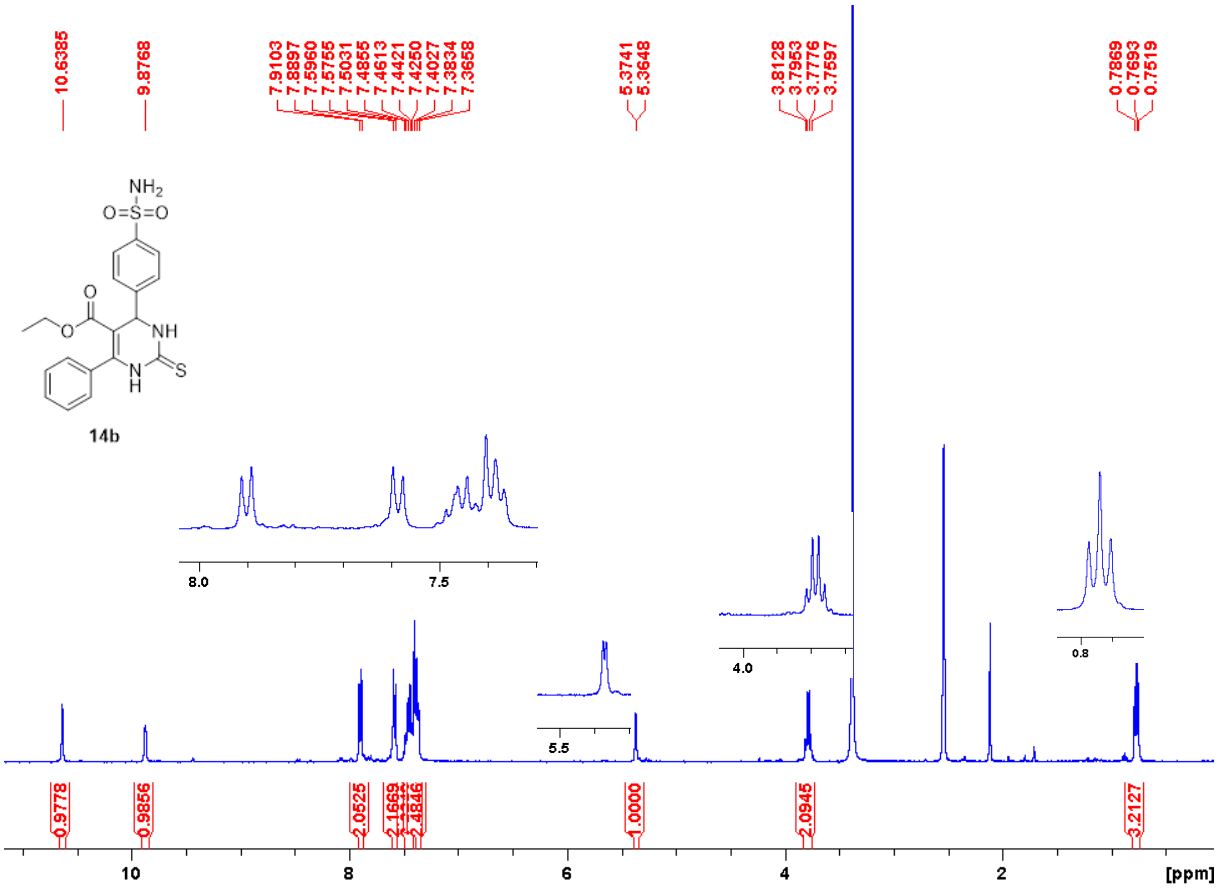
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0.7519
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O
NH
N
H
S
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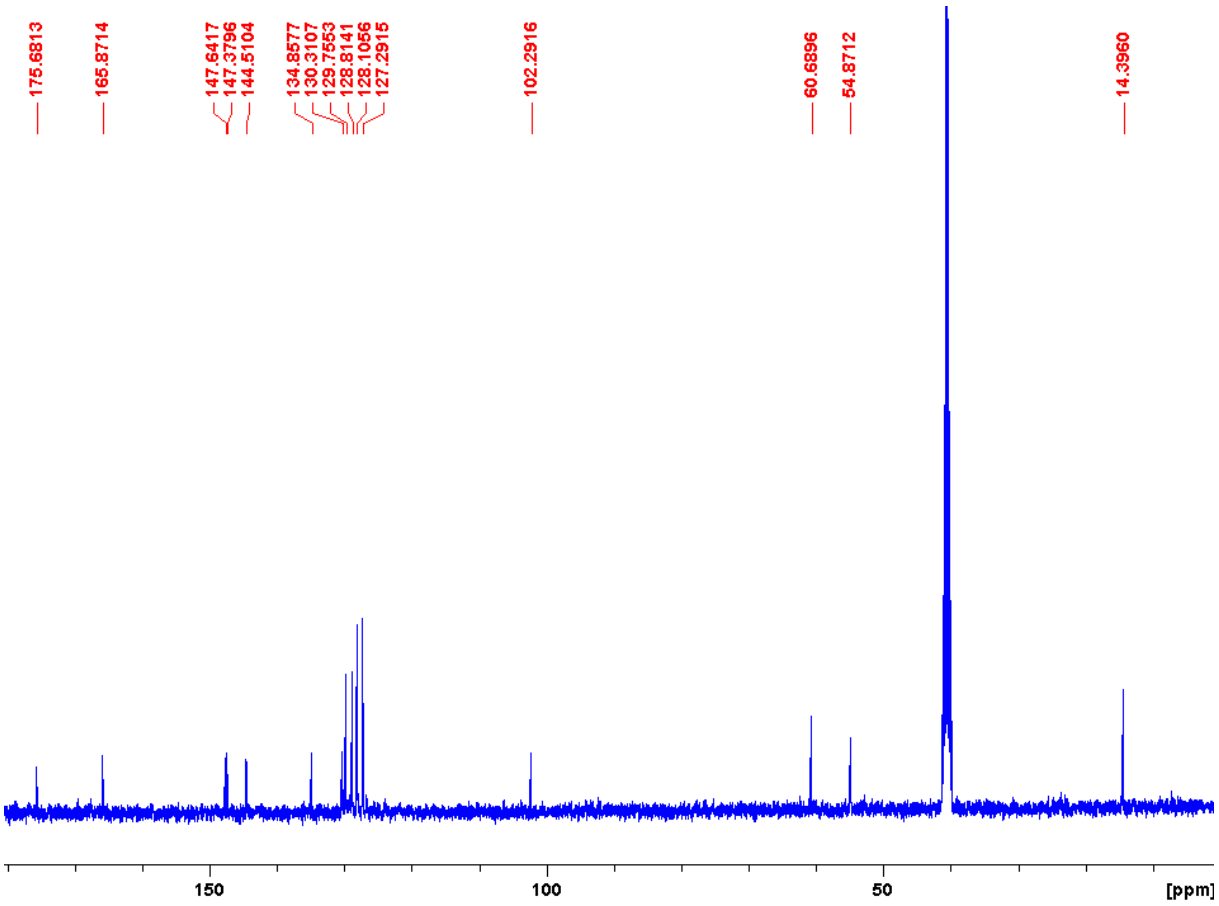
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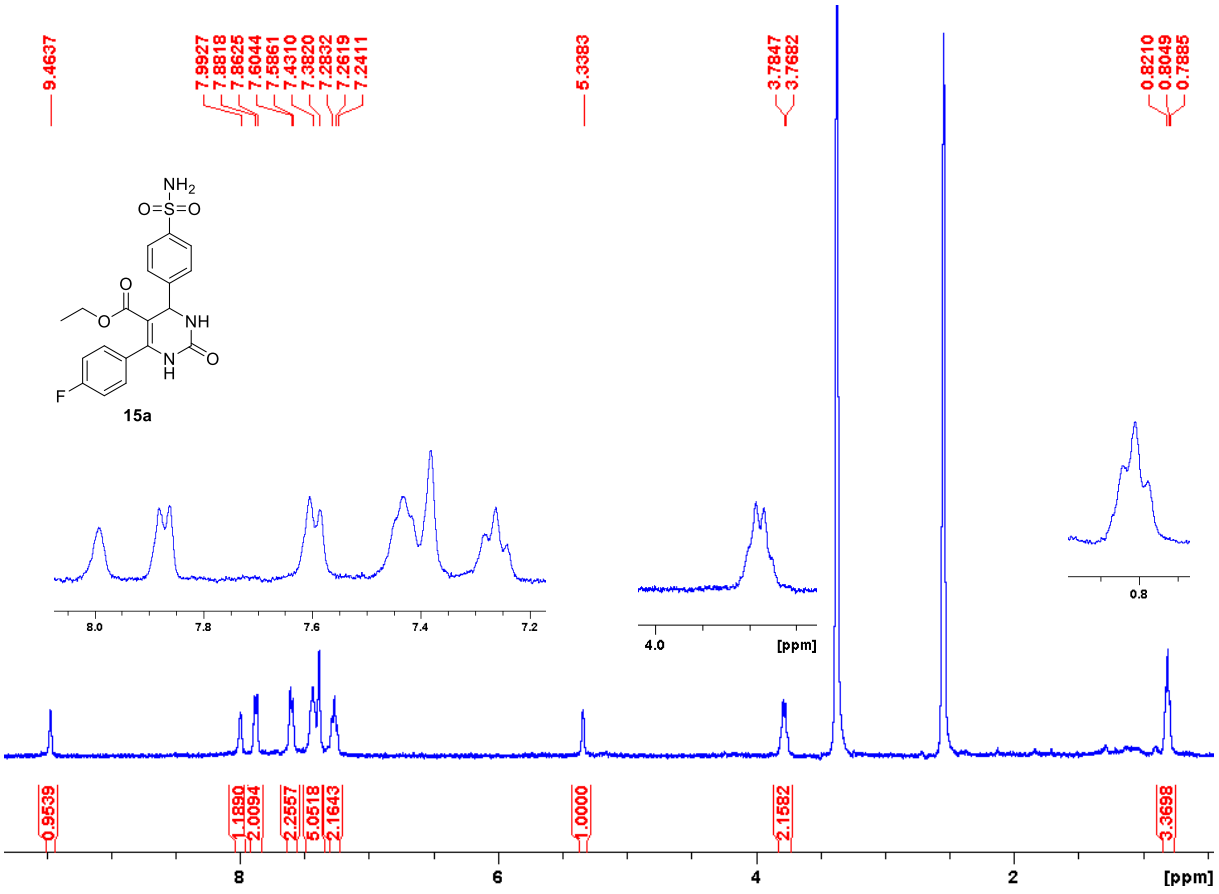
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0.7885
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NH
N
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O
F
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7.6
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7.2
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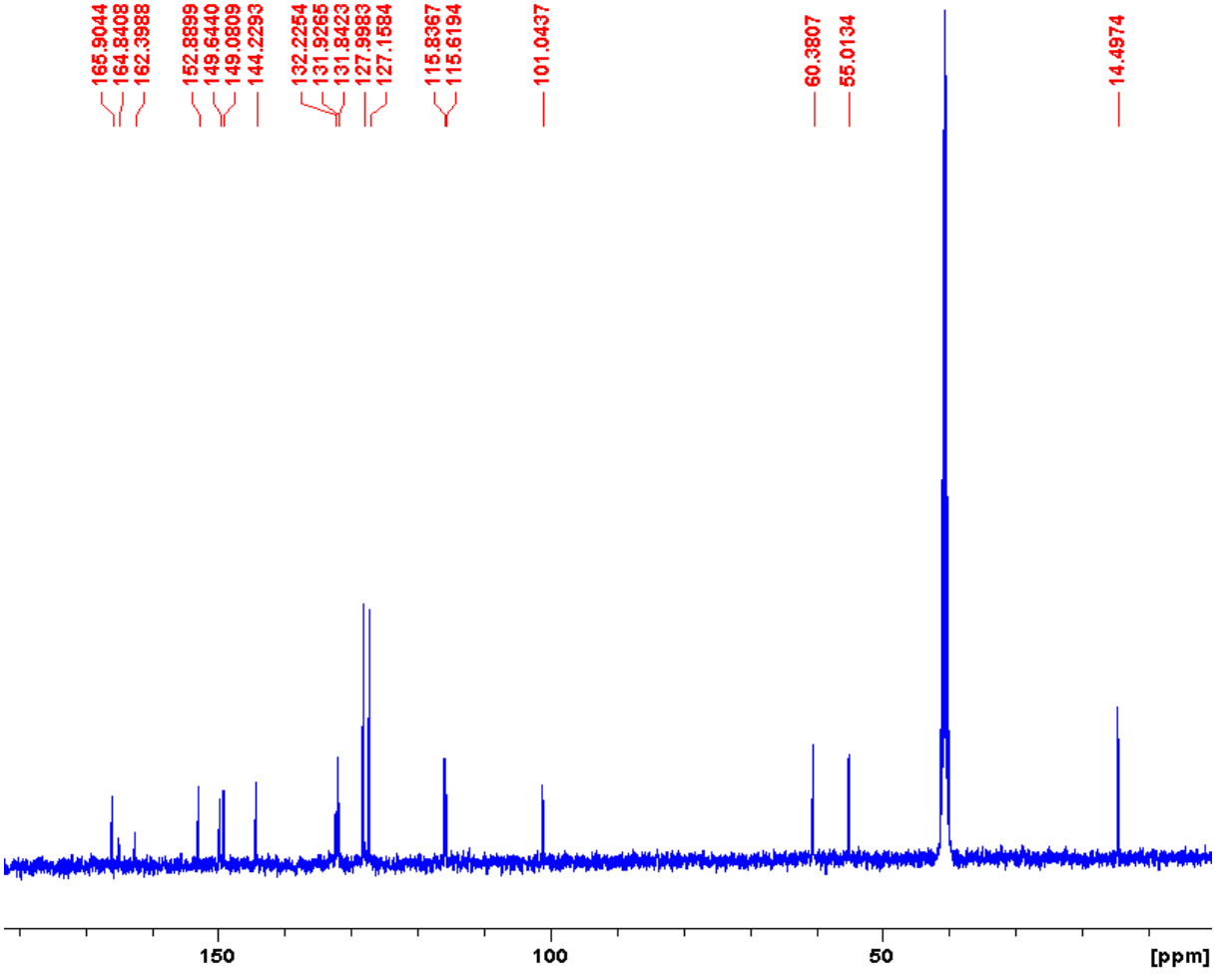
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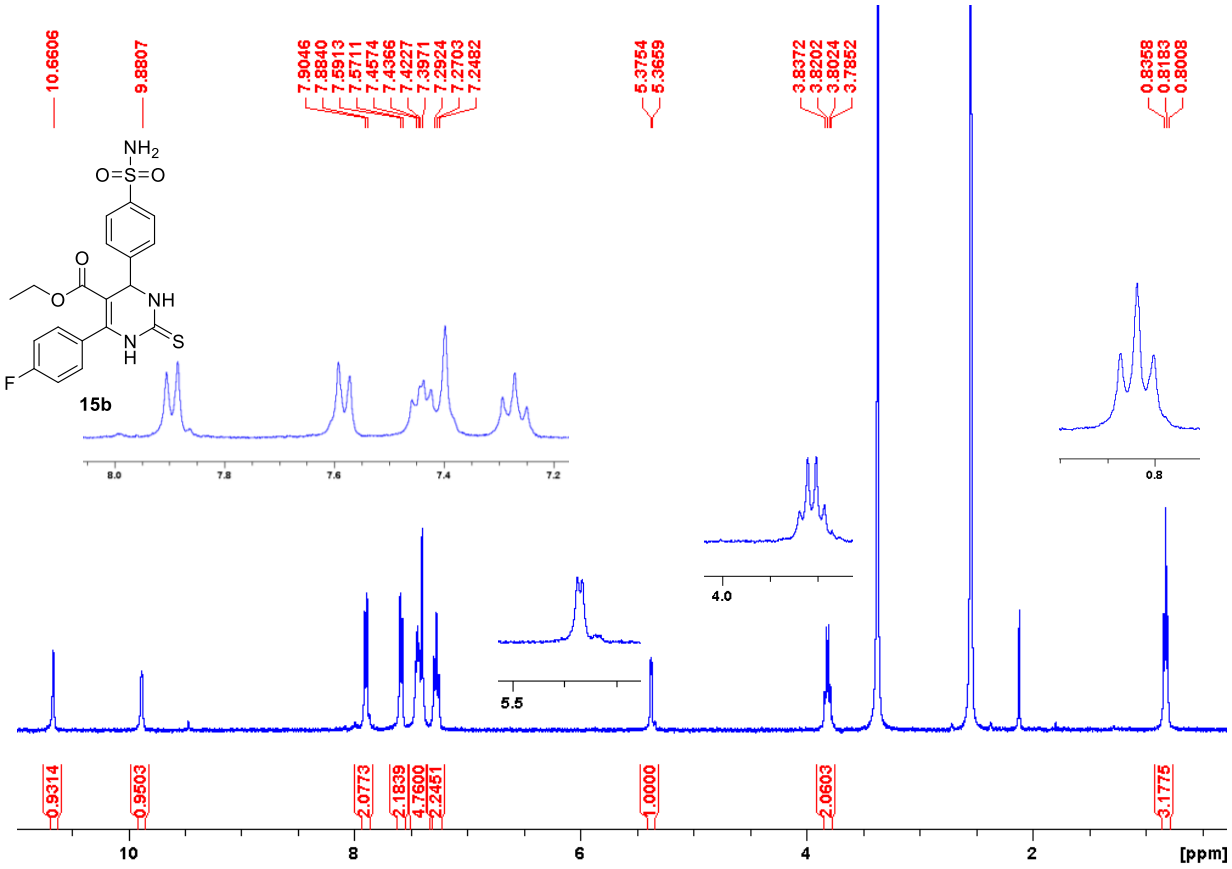
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5.3659
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O
NH
N
H
S
F
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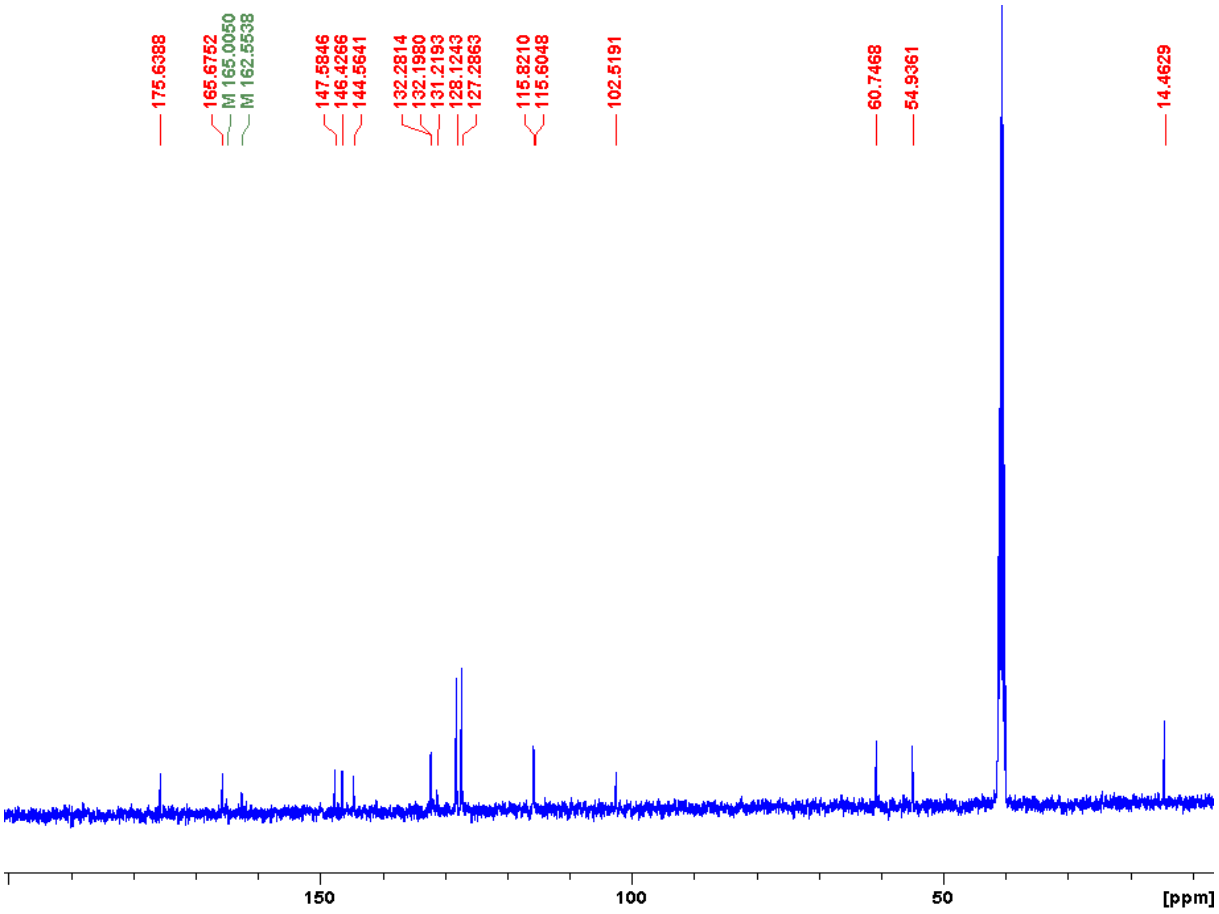
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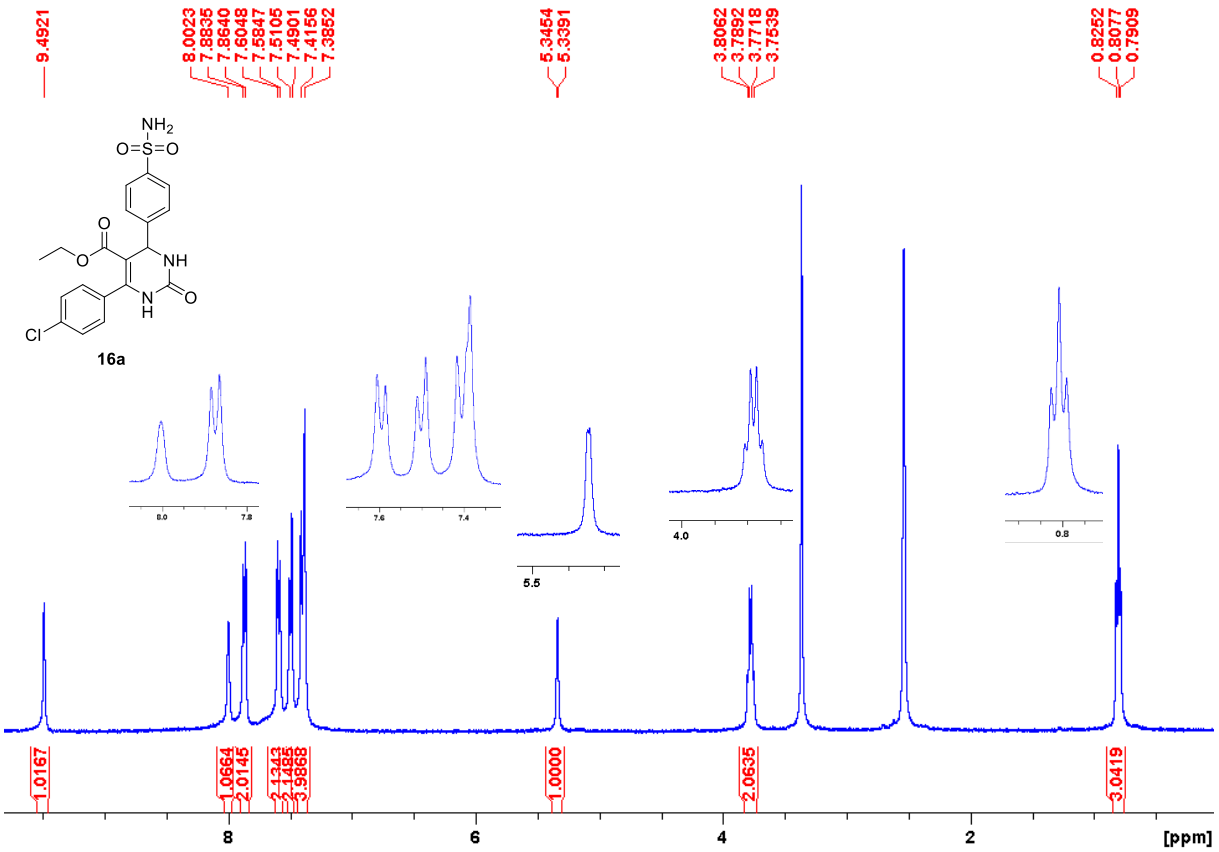
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5.3454
5.3391
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0.8077
0.7909
NH2
O=S=O
O
O
NH
N
H
O
Cl
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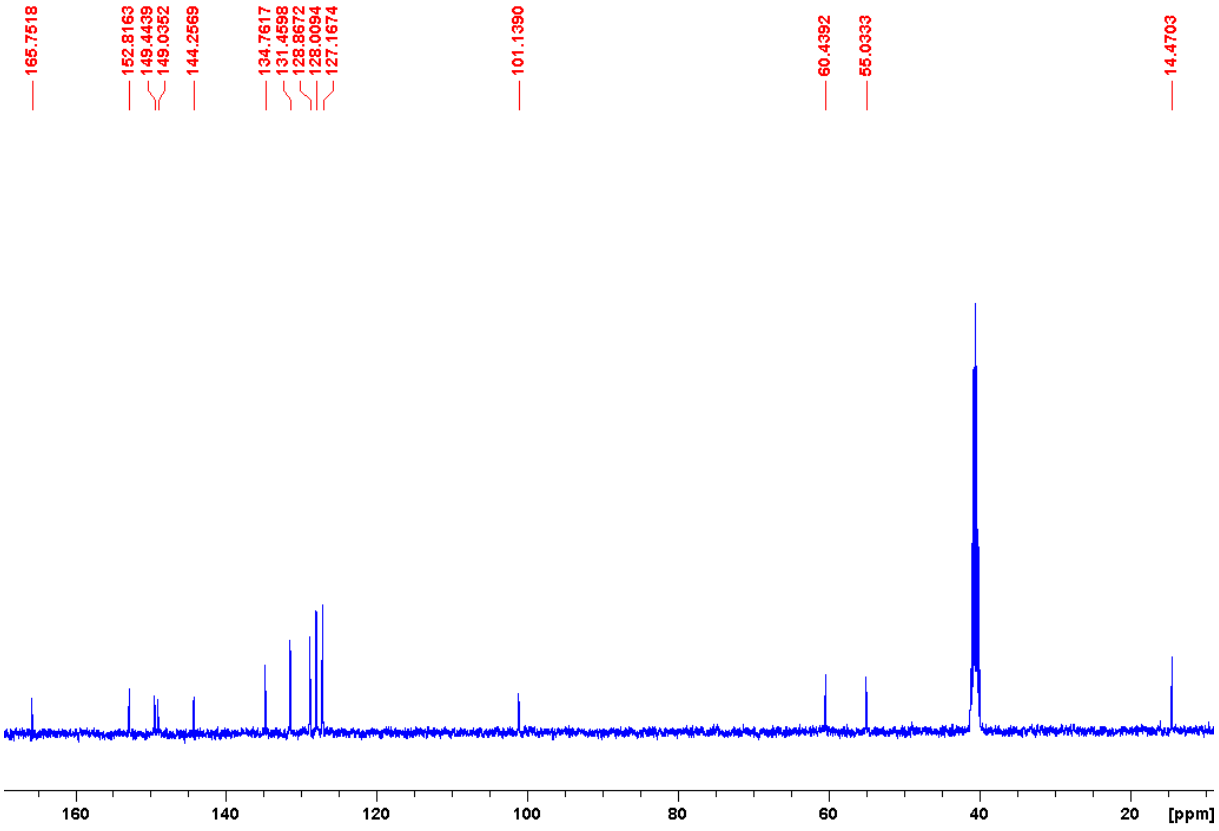
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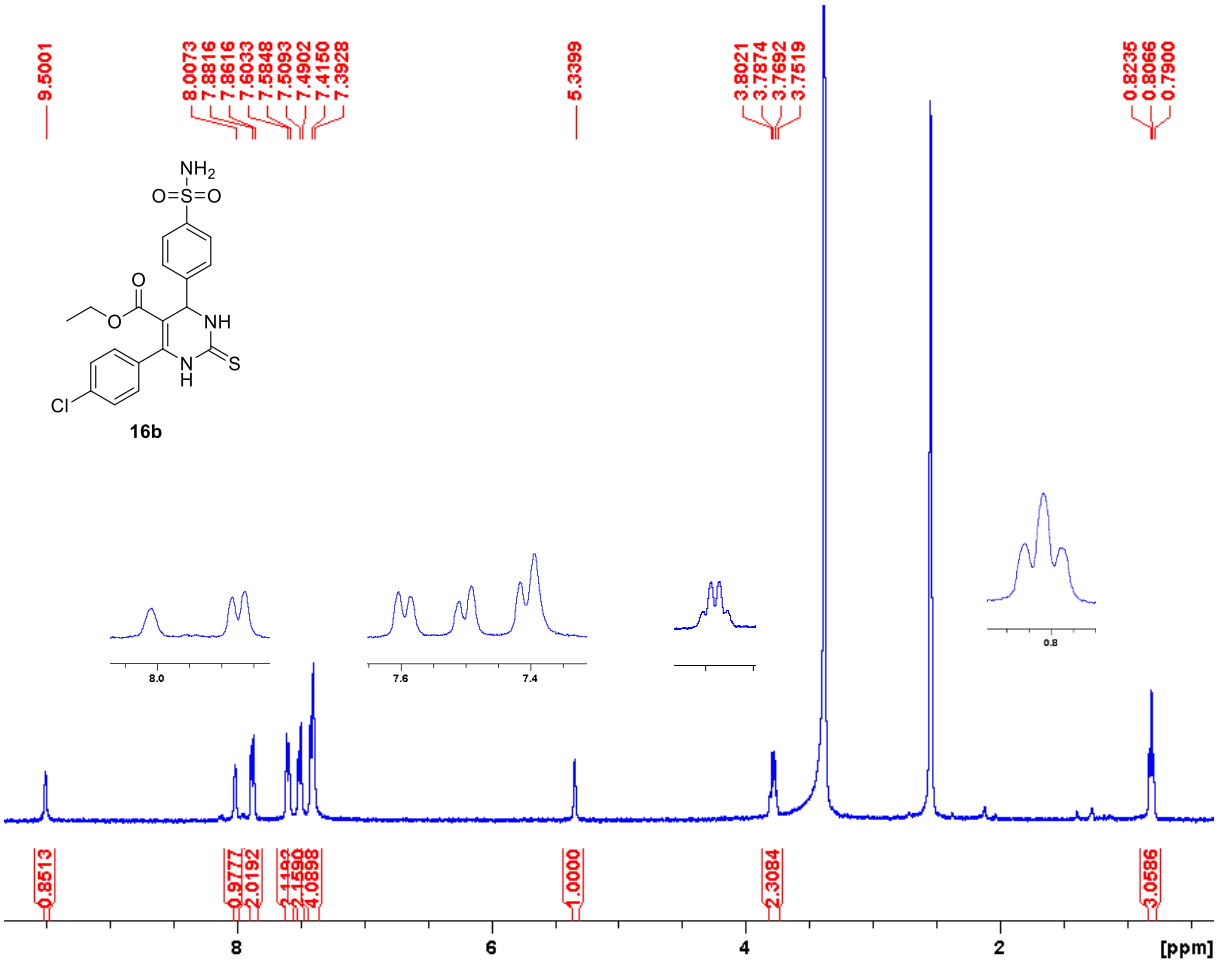
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5.3399
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3.7874
3.7692
3.7519
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0.8066
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NH2
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NH
N
H
S
Cl
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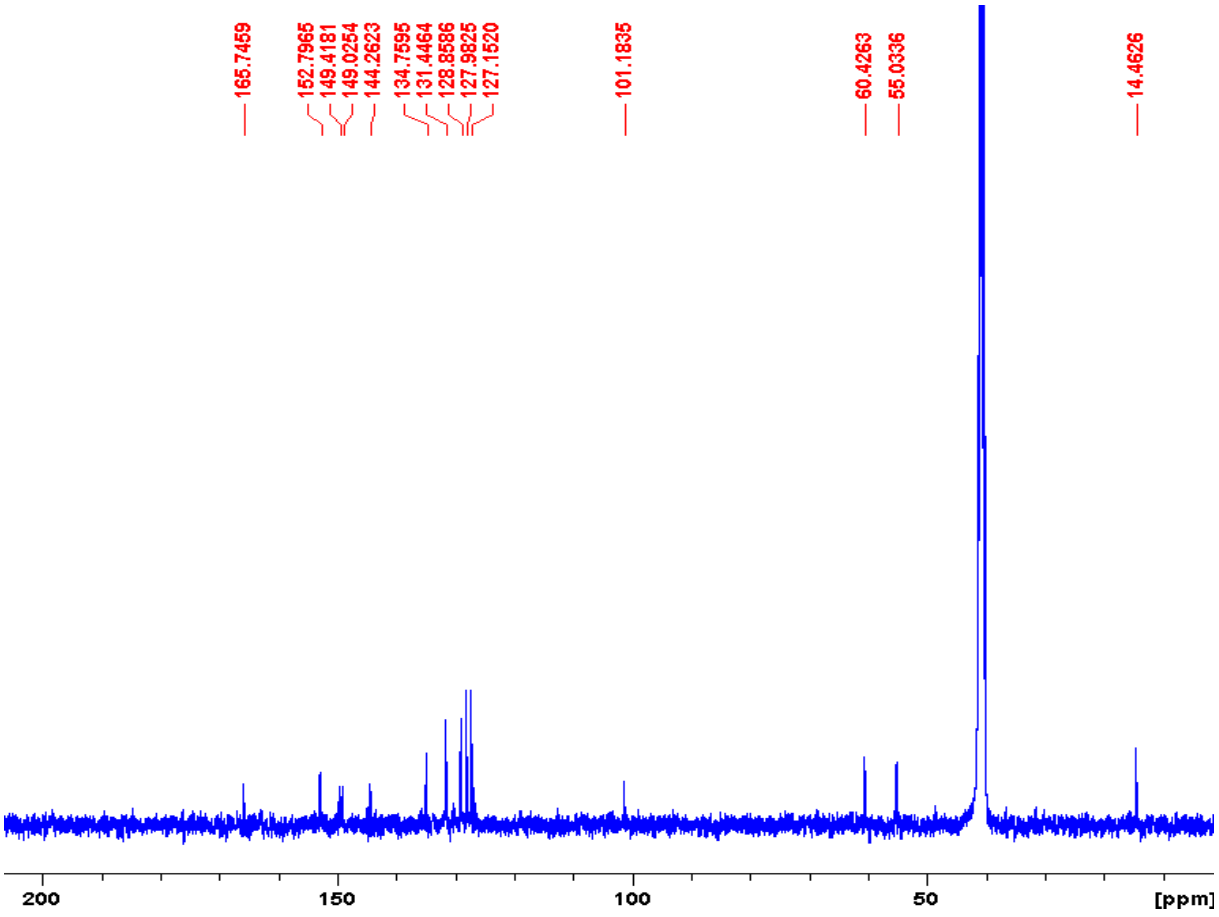
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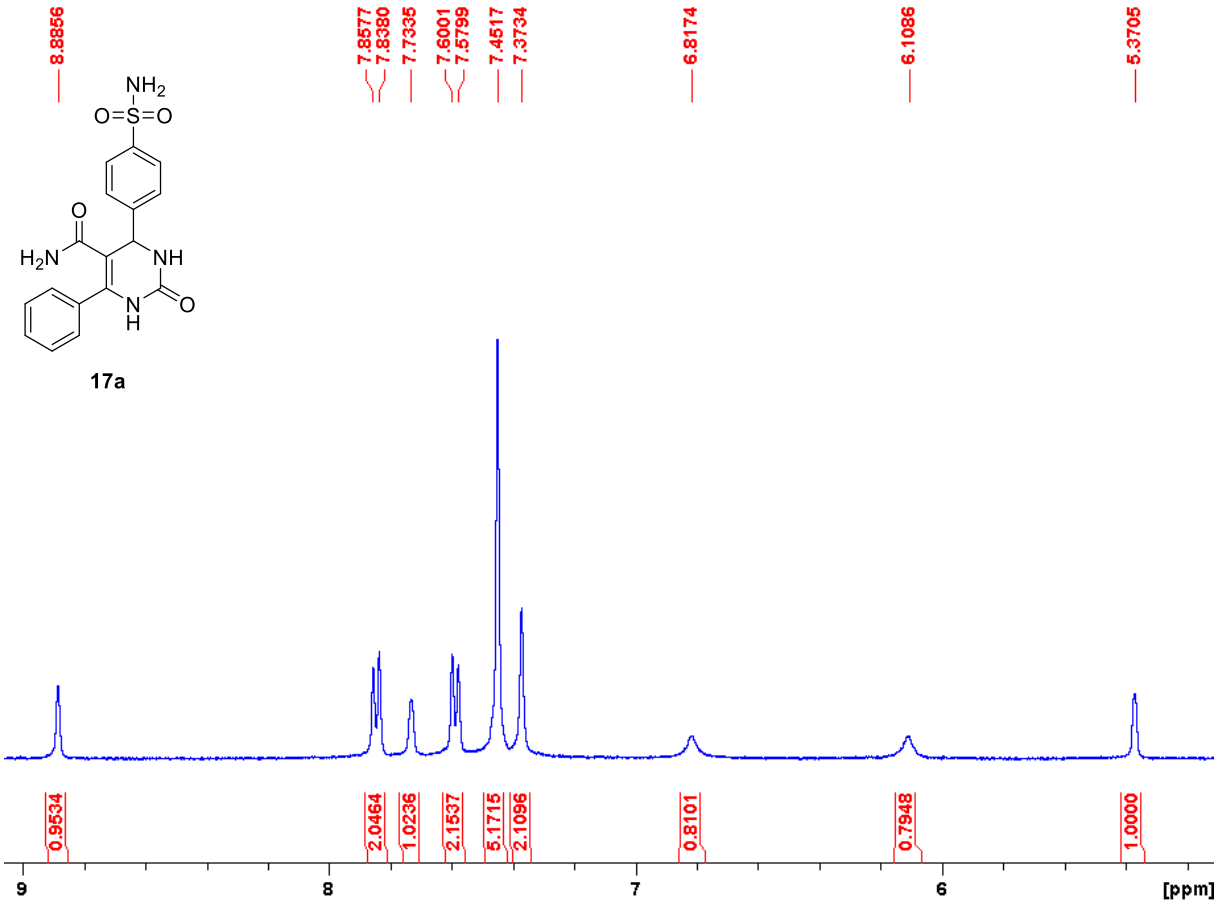
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O=S=O
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NH
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O
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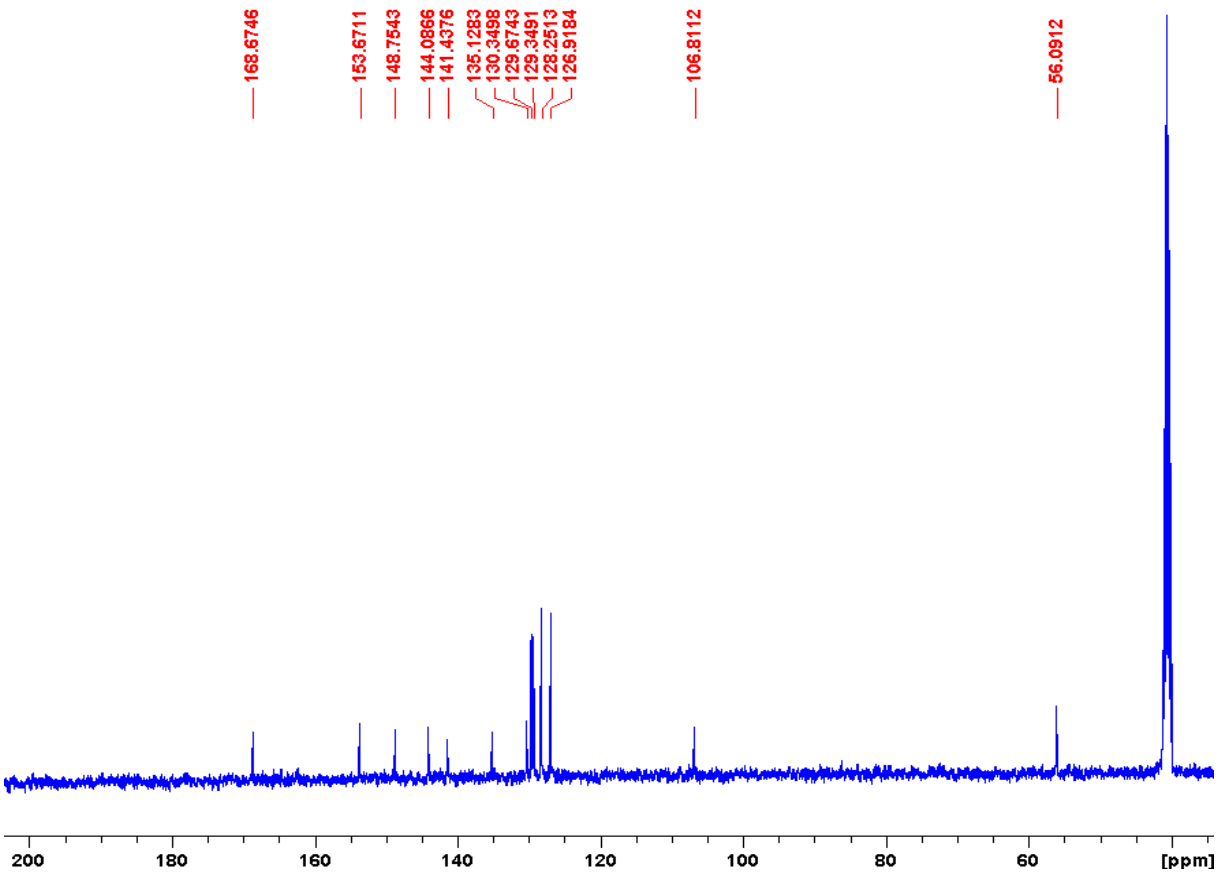
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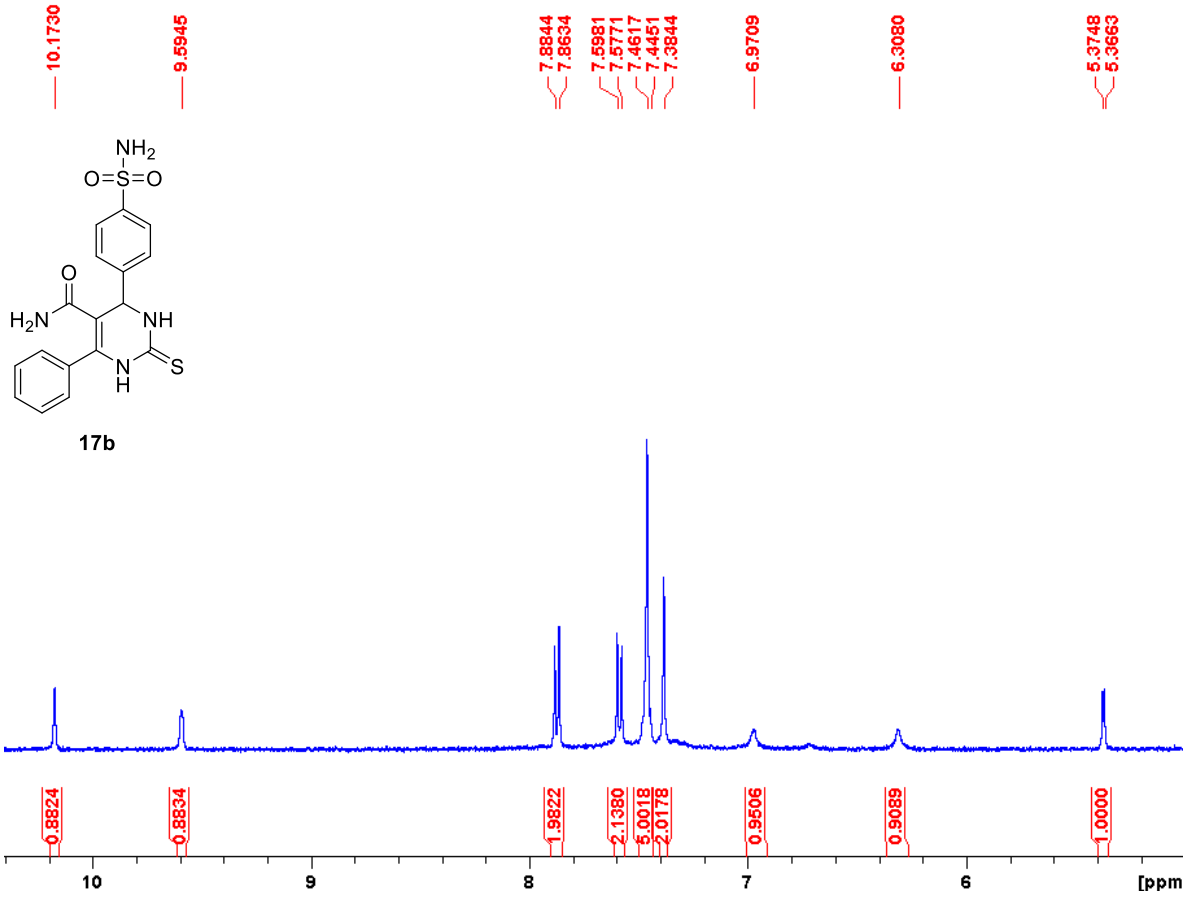
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NH
N
H
S
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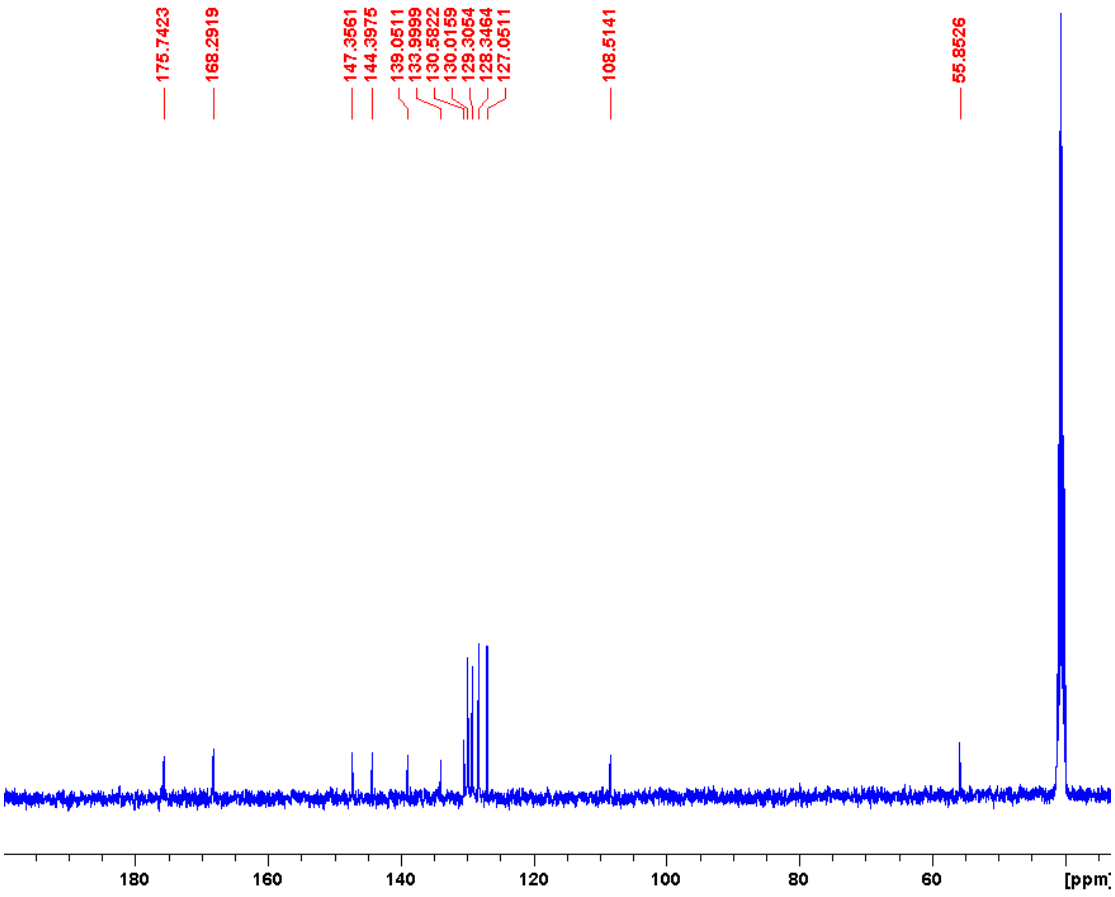
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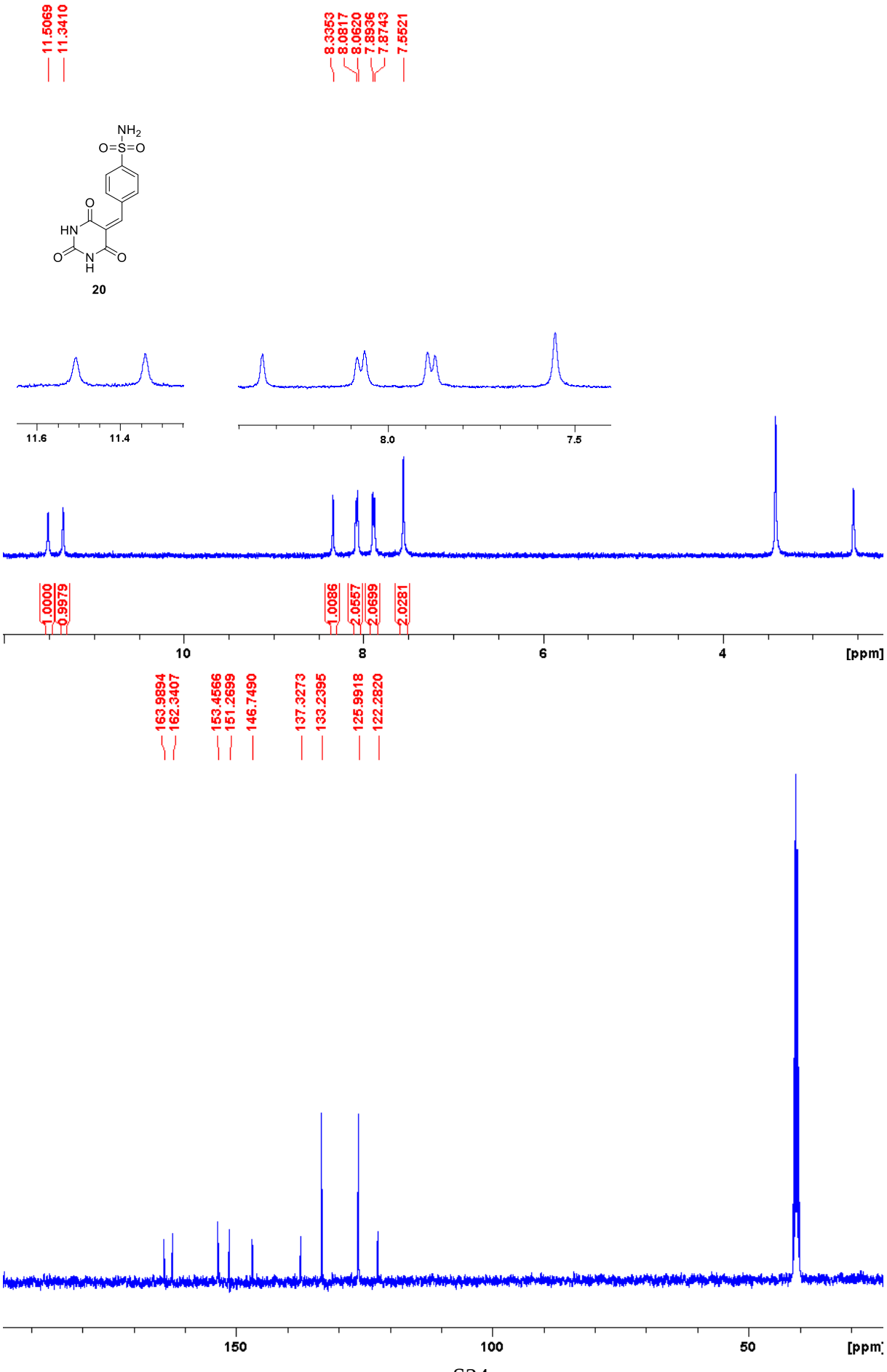
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HN
O
N
H
O
O
20
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11.4
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2.0699
2.0281
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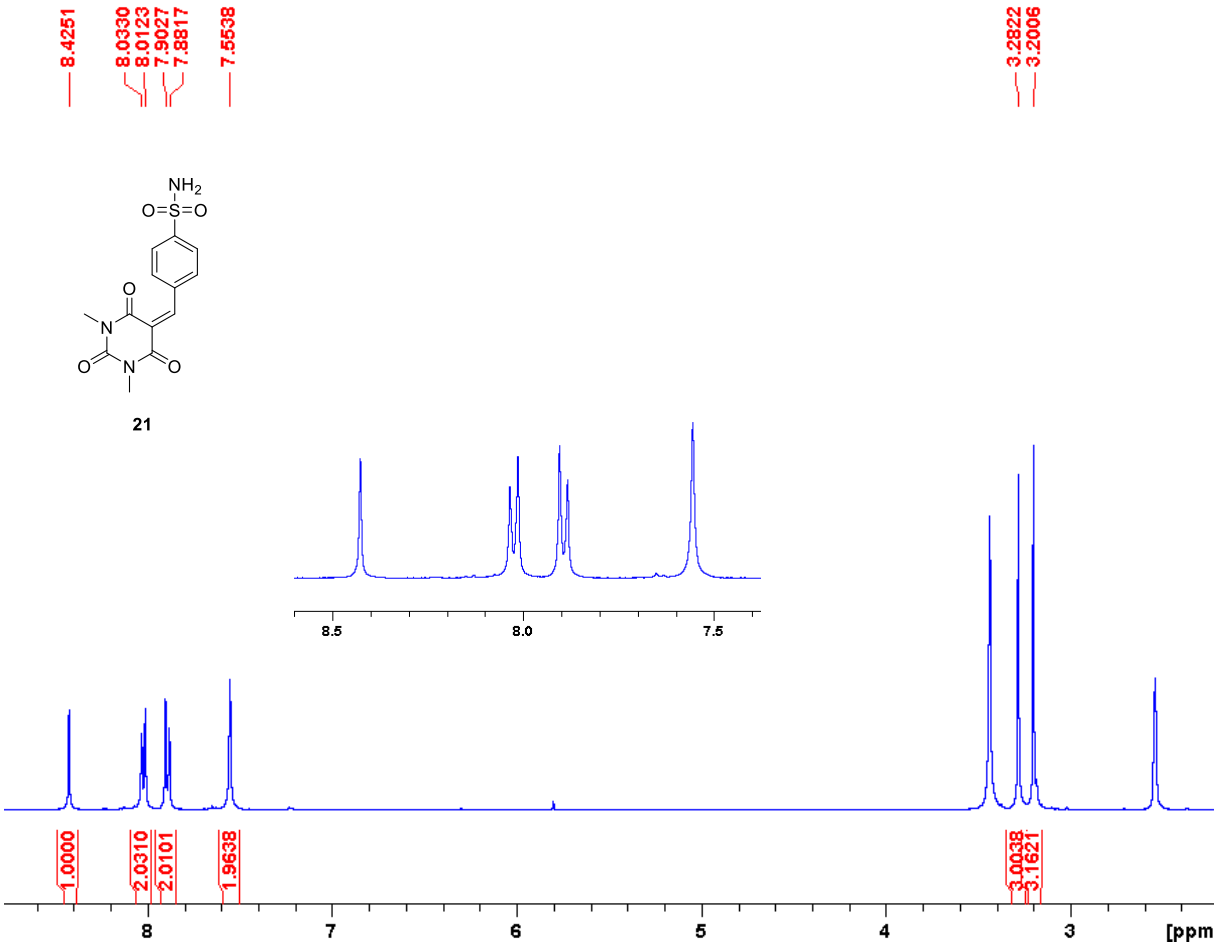
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O
N
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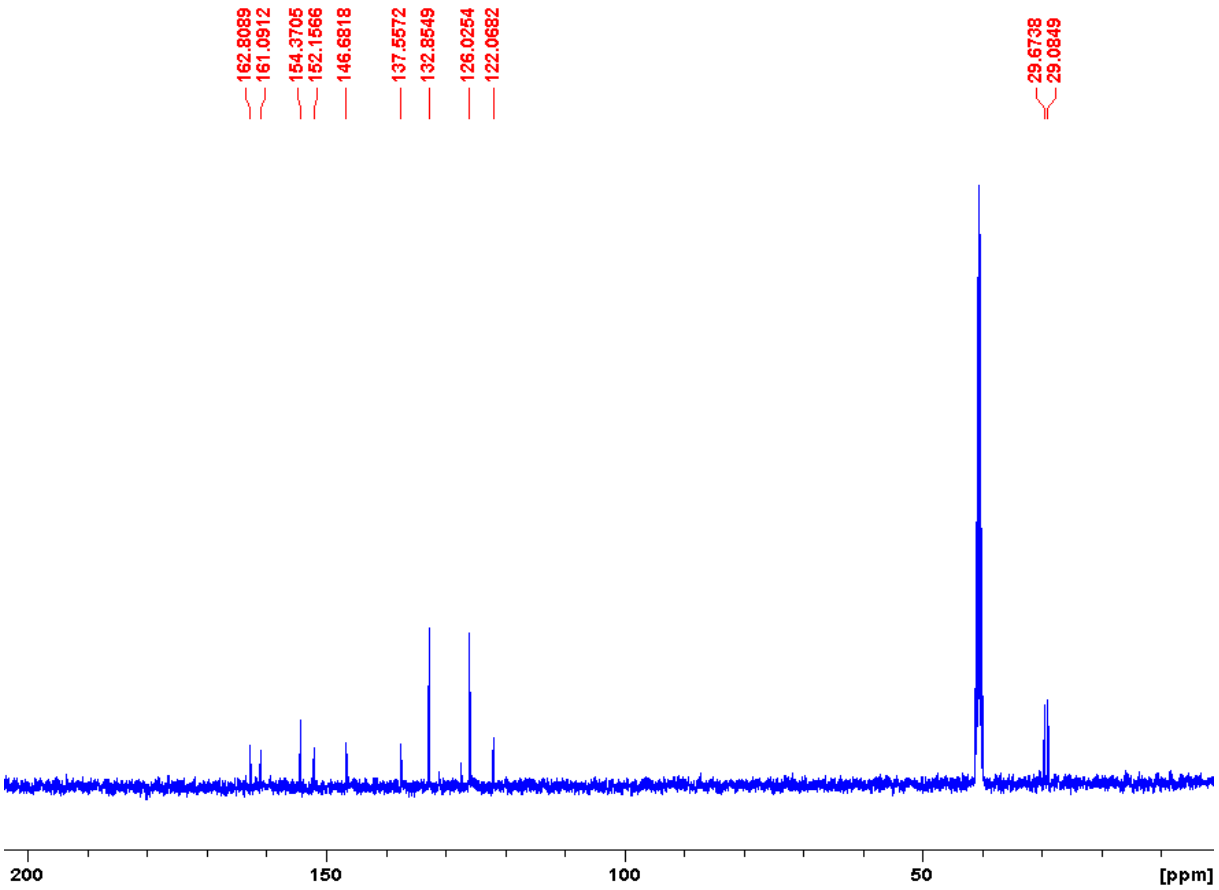
[ppm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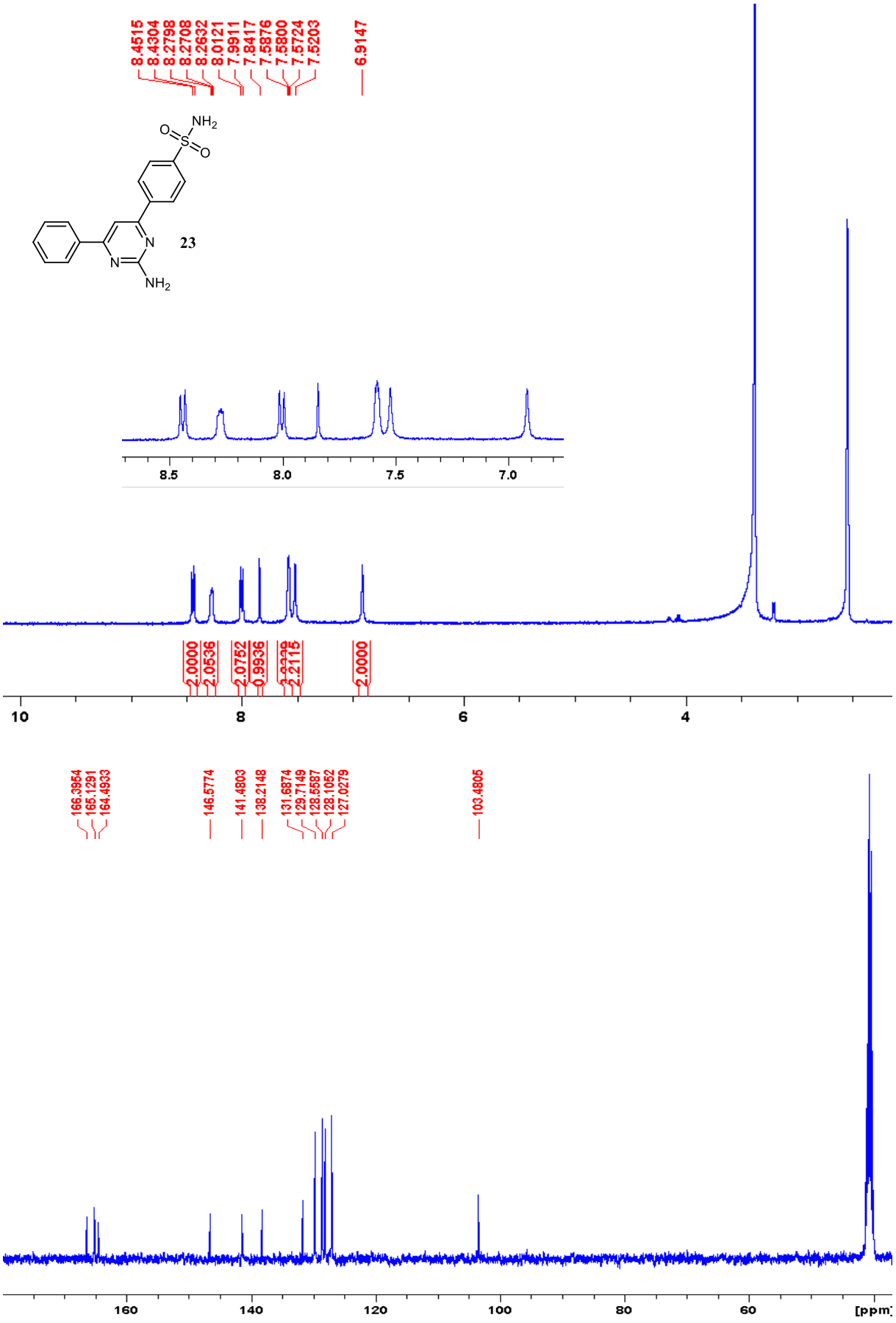
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S
O
N
N
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2.2115
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128.1062
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103.4805
160
140
120
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80
60
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1. Angeli A, Trallori E, Ferraroni M, Di Cesare Mannelli L, Ghelardini C, Supuran CT. Discovery of new 2, 5-disubstituted 1,3-selenazoles as selective human carbonic anhydrase IX inhibitors with potent anti-tumor activity. Eur J Med Chem. 2018 Sep 5;157:1214–22.

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