Electronic Supplementary Material (ESI) for Chemical Communications

Imides: Forgotten Players in the Ugi Reaction. One pot multicomponent synthesis of quinazolinones

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- Synthesis of imide **9** using different experimental conditions
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Experimental section

Commercially available reagents and solvents were used without further purification and were purchased All the liquid aldehydes were distilled before their use. When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2 .

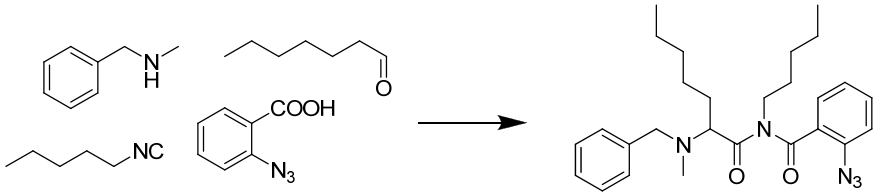
NMR spectra were recorded with a JEOL ECP 300 MHz spectrometer and the δ values are in part per million. Mass spectra were recorded using a Thermo Finningan LCQ Deca XP-*plus* equipped with an ESI source and an ion trap detector. Column chromatography was performed on silica gel Merck Kieselgel (0.063-0.200 mm; 70-230 mesh ASTM). Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$ or Dragendorff reagent. Elemental analysis (C, H, N) of the compounds are within ± 0.4% of the calculated values.

General procedure for the synthesis of the quinazolinones.

Carbonyl compound (1 eq), carboxylic acid (1 eq) and isocyanide (1 eq) were added sequentially to a solution of amine (1 eq) in dry CH_2Cl_2. 4 Å molecular sieves were added and the reaction was stirred at room temperature until the complete formation of the imide. CH_2Cl_2 was evaporated and the reaction crude was dissolved in dry toluene. Triphenylphospine (1 eq) was added and after 10 minutes, the reaction was heated at reflux until the complete disappearance of the iminophosphorane. The solvent was evaporated and the crude reaction mixture was purified by column chromatography.

Compounds **12**[1], **13**[2], **25**[3], **26**[4], **27**[5], **40**[6], and **55**[7] were synthesized as described previously.

- **Synthesis of imide 9 using different experimental conditions**



SOLVENT	CONDITIONS	YIELD
Toluene	2h, reflux	38 %
DCM	overnight, r.t.	64 %
Toluene	2h, r.t.	59 %
DCM	1h, Molecular Sieves 4 Å, r.t.	80 %

References:

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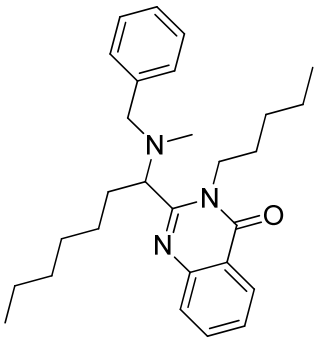
(2) Boeyens, J. C. A.; Cook, L. M.; Ding, Y.; Fernandes, M. A.; Reid, D. H *Org. Biomol. Chem.* **2003**, *1*, 2168-2172.
(3) O'Neil, I.; Murray, C. L.; Hunter, R. C.; Kalindjian, S. B.; Jenkins, T. C. *Synlett* **1997**, 75-78.
(4) Bose, D. S.; Chary, M. V. *Synthesis* **2010**, 643-650.
(5) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241-5245.
(6) Vasilevsky, Sergey F.; Govdi, Anastasiya I.; Shults, El'vira E.; Shakirov, Makhmut M.; Sorokina, Irina V.; Tolstikova, Tatyana G.; Baev, Dmitry S.; Tolstikov, Genrikh A.; Alabugin, Igor V. *Bioorg. Med. Chem.* **2009**, *17*, 5164-5169.
(7) Thanigaimalai, P.; Lee, K.-C.; Bang, S.-C.; Lee, J.-H.; Yun, C.-Y.; Roh, E.; Hwang, B.-Y.; Kim, Y.; Jung, S.-H.

2-(1-(benzyl(methyl)amino)heptyl)-3-pentylquinazolin-4(3H)-one (10)

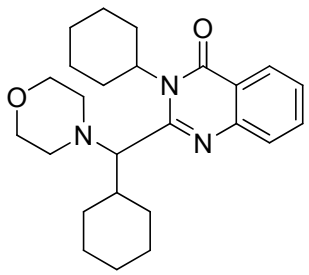


Eluant: PE/EtOAc 95:5

Yield: 80 %; Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K) δ 8.28 (d,J = 8.8 Hz, 1-*H*), 7.69 (br s, 2-H), 7.44 (m, 1-H), 7.30-7.20 (m, 5-H), 4.49 (m, 1-H), 4.04 (m, 1-H), 3.87 (d, J = 13.4 Hz, 1-H), 3.83 (dd, J = 10.4/3.0 Hz, 1-H), 3.55 (d, J = 13.4 Hz, 1-H), 2.46 (m, 1-H), 2.30 (s, 3-H), 1.81 (m, 2-H), 1.55-1.10 (m, 11-H), 0,91 (br s, 6-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K) δ 165.1, 156.7, 149.0, 141.4, 135.9, 130.9, 130.5, 129.8, 129.3, 128.9, 128.8 123.2, 68.9, 59.7, 45.0, 40.5, 33.9, 31.7, 31.5, 29.8 (2C), 24.9 (2c9, 24.7, 16.4, 16.2; MS (ESI) *m/z* 434 (100%) $(M+H)^+$. $C_{28}H_{39}N_3O$: calcd. C 77.55, H 9.07, N 9.69 ; found C 77.64, H 9.12, N 9.84.

3-cyclohexyl-2-(cyclohexyl(morpholino)methyl)quinazolin-4(3H)-one (28)



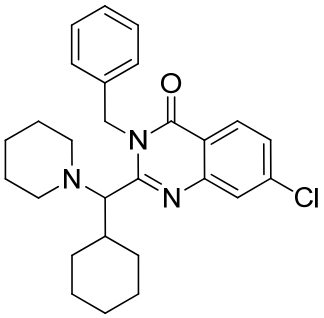
Eluant: PE/EtOAc 9:51

Yield: 81 %; Yellowish amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K, refererred to main rotamer) δ 8.17 (d, J = 8.9 Hz, 1-H), 7.63-7.55 (m, 2-H), 7.35 (t, J = 7.0 Hz, 1-H), 4.08 (m, 1-H9, 3.58 (br s, 5-H), 2,73 (m, 5-H), 1.99-1.10 (m, 20-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K, referred to

main rotamer) δ 162.9, 155.3, 146.1, 133.5, 127.1, 126.2 (2C), 121.8, 69.4, 67.6, 59.5, 49.4, 38.7, 31.1, 30.0, 28.5, 26.7, 25.9, 25.1.; MS (ESI) *m/z* 410 (100%) $(M+H)^+$. $C_{25}H_{35}N_3O$: calcd. C 73,31, H 8.61, N 10.26 ; found C 72.90, H 8.40, N 10.30.

3-benzyl-7-chloro-2-(cyclohexyl(piperidin-1-yl)methyl)quinazolin-4(3H)-one (29)

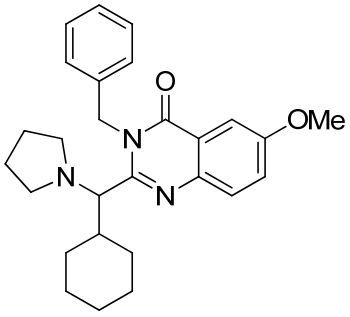


Eluant: PE/EtOAc 97:3 to 95:5.

Yield: 78 %; Yellowishi amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.25 (d, J = 8.5 Hz, 1-H), 7.69 (d, J = 1.9 Hz, 1-H), 7.40-7.14 (m overlapping, 6-H), 5.93 (d, J = 16.2 Hz, 1-H), 5.04 (d, J = 16.2 Hz, 1-H), 3.40 (d, J = 10.4 Hz, 1-Hz), 2.81 (m, 1-H), 2.66 (m, 1-H), 2.36 (m, 1-H), 1.71-1.19 (m overlapping, 16-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.5, 157.0, 148.0, 140.2, 136.8, 128.7, 128.5, 127.5, 127.1, 127.0, 126.6, 119.0, 70.1, 50.5, 45.9, 38.2, 30.9, 30.6, 27.1, 26.5, 26.0, 25.9, 24.9; MS (ESI) *m/z* 450 (100%) $(M+H)^+$. $C_{27}H_{32}ClN_3O$: calcd. C 72.06, H 7.17, N 9.34 ; found C 72.10, H 7.10, N 9.58.

3-benzyl-2-(cyclohexyl(pyrrolidin-1-yl)methyl)-6-methoxyquinazolin-4(3H)-one (30).

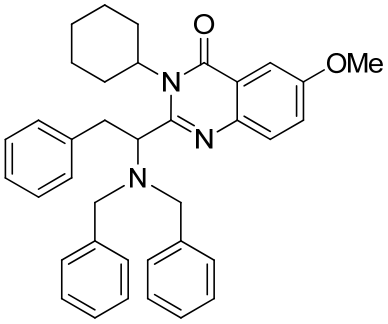


Eluant: PE/EtOAc 8:2.

Yield: 64 %; Brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 7.68 (d, J = 2.7 Hz, 1-H), 7.61 (d, J = 8.5 Hz, 1-H), 7.35-7.10 (m, 6-H), 5.69 (d, J = 15.6 Hz, 1-H), 5.27 (d, J = 15.6 Hz, 1-H), 3.90 (s, 3-H), 3.83 (d, J = 9.1 Hz, 1-H), 2.82 (br s, 1-H), 2.60 (br s,1-H), 2.20 (m, 1-H), 1.97-0.80 (m overlapping, 18-H) ; ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.6, 158.3, 153.6, 141.6, 136.7, 129.2, 128.7, 127.6, 127.2, 124.7, 121.1, 106.1, 65.2, 55.8, 48.5, 46.4, 40.1, 29.9, 26.4, 26.1, 23.4 ; MS (ESI) *m/z* 432 (100%) $(M+H)^+$. $C_{27}H_{33}N_3O$: calcd. C 75.14, H 7.71, N 9.74 ; found C 75.10, H 7.80, N 9.84.

3-cyclohexyl-2-(1-(dibenzylamino)-2-phenylethyl)-6-methoxyquinazolin-4(3H)-one (31).

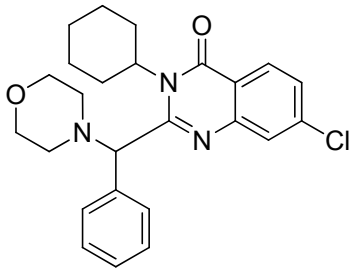


Eluant: PE/EtOAc 98:2 then 95:5.

Yield: 53 %; Orange solid. M.p. 178-179 °C

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 7.63 (d, J = 8.8 Hz, 1-H), 7.53 (d, J = 2.8 Hz, 1-H), 7.34-7.10 (m, 16-H), 4.40 (dd, J = 12.6/3.3 Hz, 1-H), 4.24 (d, J = 13.7 Hz, 1-H), 3.87 (br s overlapping, 5-H), 3.79 (d, J = 13.7, 1-H), 3.40 (dd, J = 12.6/3.3 Hz, 1-H), 2.86 (m, 1-H), 2.25 (m, 1-H), 1.77-1.10 (m, 8-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 163.0, 158.3, 151.9, 140.7, 139.4, 139.1, 129.3, 129.2, 128.6, 128.5, 128.3, 127.2, 126.0, 124.1, 122.8, 105.3, 62.1, 58.0, 55.6, 54.6, 30.7, 28.7, 28.0, 25.6, 25.2, 24.9 ; MS (ESI) *m/z* 558 (100%) $(M+H)^+$. $C_{37}H_{39}N_3O_2$: calcd. C 79.68, H 7.05, N 7.53 ; found C 80.05, H 7.30, N 7.83.

7-chloro-3-cyclohexyl-2-(morpholino(phenyl)methyl)quinazolin-4(3H)-one (32).

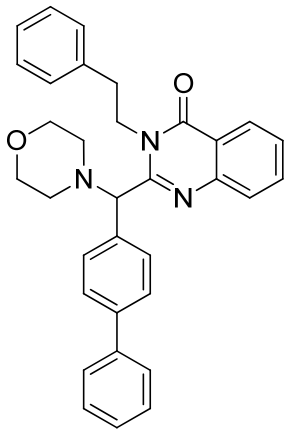


Eluant: PE/EtOAc 9:1

Yield: 80 %; Magenta oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.05 (d, J = 8.5 Hz, 1-H), 7.71 (d, J = 1,9 Hz, 1-H), 7.50-7.20 (m, 6-H), 4.86 (br s, 1-H9, 3.77 (br s, 4-H), 2.84 (br s, 4-H), 2.61-2.37 (br s, 4-H), 1.75-1.00 (m, 10-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.3, 156.7, 147.4, 140.0, 135.2, 128.6 (2C), 128.2, 128.0, 127.4, 126.8, 120.5, 67.0, 58.8, 52.6, 28.4, 28.2, 26.5, 26.0, 25.; MS (ESI) *m/z* 438 (100%) $(M+H)^+$. $C_{25}H_{28}ClN_3O_2$: calcd. C 68.56, H 6.44, N 9.59 ; found C 68.30, H 6.13, N 9.40.

2-([1,1'-biphenyl]-4-yl(morpholino)methyl)-3-phenethylquinazolin-4(3H)-one (33).

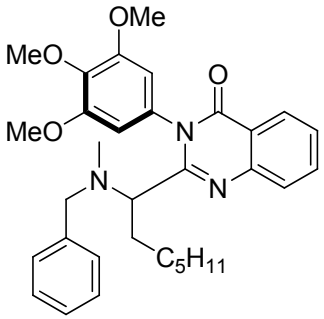


Eluant: PE/EtOAc 9:1

Yield: 74 %; White solid. M.p.=198.5-200.2 °C

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.31 (d, J = 8.4, 1-H), 7.9-7.10 (m, 17-H), 4.64 (s, 1-H), 4.47 (m, 1-H), 4.13 (m, 1-H), 3.75 (br s, 4-H), 2.89 (br s, 2-H), 2.61 (br s, 4-H; ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.4, 154.4, 146.8, 141.6, 140.2, 138.2, 134.2, 130.1, 128.9(5C), 127.9, 127.6, 127.5, 127.0, 126.9, 126.6, 120.8, 67.0, 51.8, 45.2, 34.5; MS (ESI) *m/z* 502 (100%) $(M+H)^+$. $C_{33}H_{31}N_3O_2$: calcd. C 79,01, H 6.23, N 8.38 ; found C 79.40, H 6.40, N 8.10.

2-(1-(benzyl(methyl)amino)heptyl)-3-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (34).

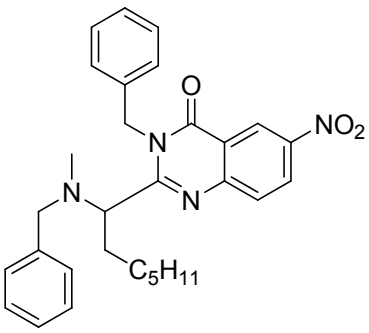


Eluant: PE/EtOAc 8:2

Yield: 70 %; Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.29 (d, J = 7.2 Hz, 1-H), 7.73 (br s, 2-H), 7.45 (m, 1-H), 7.30-7.05 (m, 5-H), 6.74 (s, 1-H), 6.43 (s, 1-H), 4.07 (d, J = 13.7 Hz, 1-H), 3.89 (s, 3-H), 3.81 (s, 3-H), 3.60 (s, 3-H), 3.54 (m, 1-H), 3.33 (d, J = 13.7 Hz, 1-H), 2.88 (m, 1-H), 2.01 (s, 3-H), 1.73 (m, 1-H), 1.22 (br s, 9-H), 0,86 (br s, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 163.0, 155.6, 153.6, 153.5, 147.0, 140.1, 138.2, 134.3, 132.5, 128.6, 128.5, 128.4, 128.1, 127.8, 127.5, 126.9, 126.7, 121.1, 107.4, 105.2, 64.4, 60.9, 56.1, 55.8, 55.5, 38.7, 31.6, 29.2, 26.8, 24.7, 22.6, 14.1; MS (ESI) *m/z* 530 (100%) $(M+H)^+$. $C_{32}H_{39}N_3O_4$: calcd. C 72.56, H 7.42, N 7.93 ; found C 72.70, H 7.88, N 8.20.

3-benzyl-2-(1-(benzyl(methyl)amino)heptyl)-6-nitroquinazolin-4(3H)-one (35).



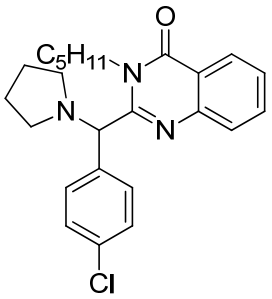
Eluant: PE/EtOAc 8:2

Yield: 73 %; Orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 9.20 (s, 1-H), 8.51 (dd, J = 8.4/2.4 Hz, 1-H), 7.85 (d, J = 8.9 Hz, 1-H), 7.35-7.19 (br s, 8-H), 7.02 (br d, 2-H), 6.05 (d, J = 15.9 Hz, 1-H), 5.33 (d, J = 15.9 Hz, 1-H), 3.84 (m overlapped 2-H), 5.58 (d, J = 13.4 Hz, 1-H), 2.33 (br s, 4-H), 1.68 (br s, 1-H), 1.16 (br s, 9-H), 0,85 (br s, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.0, 158.7, 150.7, 145.7, 138.9, 136.3, 129.3, 128.9, 128.5, 128.1, 127.6, 127.3, 126.0, 123.8, 120.9, 64.5, 57.7, 45.5, 38.2, 31.6, 28.9, 26.4,

22.5, 22.1, 14.1 ; MS (ESI) *m/z* 499 (100%) $(M+H)^+$. $C_{30}H_{34}N_4O_3$: calcd. C 72.26, H 6.87, N 11.24 ; found C 72.47, H 6.88, N 11.52.

2-((4-chlorophenyl)(pyrrolidin-1-yl)methyl)-3-pentylquinazolin-4(3H)-one (36).

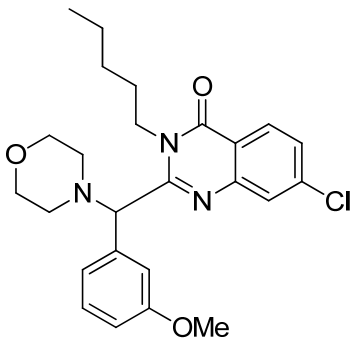


Eluant: PE/EtOAc 9 :1

Yield: 60 %; Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.17 (d, J = 8.5 Hz, 1-H), 7.80 (m, 1-H), 7.67 (m,1-H), 7.50-7.10 (m, 5-H), 4.53 (s, 1-H9, 4.17 (m, 1-H), 3.87 (m, 1-H), 2.64 (br s, 2-H), 2.50 (br s, 2-H), 1.78 (br s, 4-H), 1.50-1.10 (m, 6-H), 0.84 (br s, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.2, 155.0, 146.9, 136.2, 134.3, 134.0, 130.2, 128.9, 127.7, 126.8, 126.6, 120.7, 53.0, 43.3, 29.1, 28.3, 23.3, 22.3, 13.9; MS (ESI) *m/z* 410 (100%) $(M+H)^+$. $C_{24}H_{28}ClN_3O$: calcd. C 70.31, H 6.88, N 10.25 ; found C 70.00, H 6.50, N 10.50.

7-chloro-2-((3-methoxyphenyl)(morpholino)methyl)-3-pentylquinazolin-4(3H)-one (37).

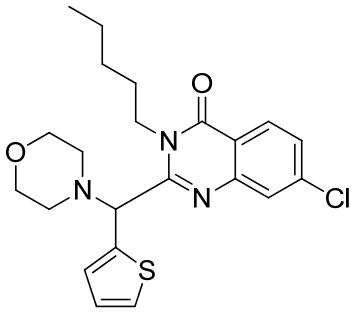


Eluant: PE/EtOAc 8 :2

Yield: 53 %; Orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.13 (d, J = 8.5 Hz, 1-H), 7.79 (d, J = 1.9 Hz, 1-H), 7.38 (dd, J = 8.5/2.2 Hz, 1-H), 7.25 (t, J = 8.3 Hz, 1-H), 7.02 (br s, 1-H), 6.99 (s, 1-H), 6.83 (dd, J =8.4/1.9 Hz, 1-H), 4.64 (br s, 1-H), 4.15 (m, 1-H), 3.81 (m, 1-H), 3.74 (br s, 7-H), 2.72 (m, 1-H), 2.58 (m, 1-H), 1.55 (br s, 1-H), 1.30 (br s, 5-H), 0.88 (br t, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 161.7, 160.0, 156.1, 147.8, 140.2, 136.8, 129.8, 128.1, 127.4, 127.3, 121.8, 119.2, 115.5, 113.5, 67.0, 55.3, 52.0, 43.5, 29.1, 28.4, 22.3, 13.9; MS (ESI) *m/z* 456 (100%) $(M+H)^+$. $C_{25}H_{30}ClN_3O_2$: calcd. C 65.85, H 6.63, N 9.22 ; found C 66.10, H 6.83, N 9.00.

7-chloro-2-(morpholino(thiophen-2-yl)methyl)-3-pentylquinazolin-4(3H)-one (38).

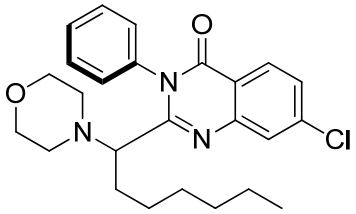


Eluant: PE/EtOAc 9 :1

Yield: 61 %; Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.15 (d, J = 8.5 Hz, 1-H), 7.77 (d, J = 1.8 Hz, 1-H), 7.36 (m, 2-H), 7.03 (d, J = 3.2 Hz, 1-H), 6.97 (t, J = 4.9 Hz, 1-H), 5.09 (s, 1-H), 4.19 (m, 1-H), 4.10 (m, 1-H), 3.69 (br s, 4-H), 2.72 (m, 1-H), 2.56 (m, 1-H), 1.69 (br s, 2-H), 1.38 (br s, 4-H), 0.91 (br t, 1-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 161.6, 154.9, 147.3, 140.2, 136.2, 128.6, 128.2, 127.9, 127.6, 127.1, 125.9, 119.3, 67.0, 50.6, 43.7, 29.2, 28.9, 22.3, 14.0; MS (ESI) *m/z* 432 (100%) $(M+H)^+$. $C_{22}H_{26}ClN_3O_2S$: calcd. C 61.17, H 6.07, N 9.73 ; found C 61.43, H 6.20, N 9.40.

7-chloro-2-(1-morpholinoheptyl)-3-phenylquinazolin-4(3H)-one (39).

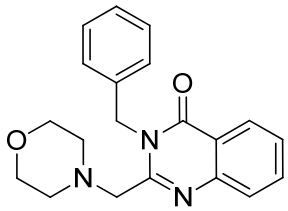


Eluant: PE/EtOAc 8 :2

Yield: 45 %; Orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.20 (d, J = 8.5 Hz, 1-H), 7.75(d, J = 1.9 Hz, 1-H), 7.55-7.35 (m, 5-H), 7.14 (m, 1-H), 3.52 (m, 4-H), 3.23 (dd, J = 10.4/3.8 Hz, 1-H), 2.63 (m, 2-H), 2.10 (m, 3-H), 1.53 (m, 1-H), 1.27 (br s, 8-H), 1.06 (m, 1-H), 0.86 (t, J = 6.3 Hz, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.3, 155.9, 147.9, 140.5, 136.8, 130.2, 129.4, 129.2, 129.1, 128.5, 128.1, 127.5, 127.3, 119.8, 67.4, 64.9, 48.9, 31.6, 29.3, 26.7, 24.2, 22.6, 14.1; MS (ESI) *m/z* 440 (100%) $(M+H)^+$. $C_{25}H_{30}ClN_3O_2$: calcd. C 68.25, H 6.87, N 9.55 ; found C 68.46, H 6.90, N 9.90.

3-benzyl-2-(morpholinomethyl)quinazolin-4(3H)-one (45).

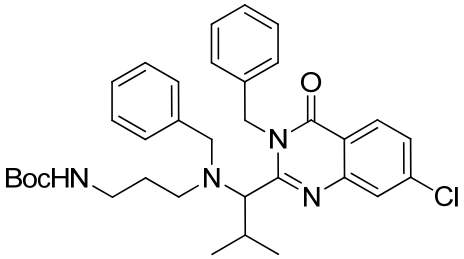


Eluant: PE/EtOAc 8 :2 then 5 :5

Yield: 30 %; colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.32 (d, J = 8.5 Hz, 1-H), 7.8-7.60 (m, 2-H), 7.49 (t, J = 8.3 Hz, 1-H), 7.30-7.10 (m, 5-H), 5.75 (s, 2-H), 3.65 (br s, 4-H), 3.50 (s, 2-H), 2.52 (s, 4-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 162.6, 152.8, 146.9, 136.8, 134.4, 128.9, 127.5, 127.4, 127.2, 127.1, 126.2, 120.9, 66.8, 63.1, 53.6, 45.9; MS (ESI) *m/z* 336 (100%) $(M+H)^+$. $C_{20}H_{21}N_3O_2$: calcd. C 71.62, H 6.31, N 12.53 ; found C 71.80, H 6.40, N 12.70.

***tert*-butyl (3-(benzyl(1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl)amino)propyl)carbamate (56).**

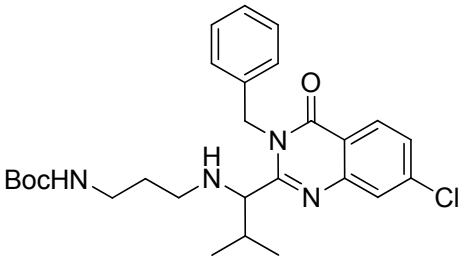


Eluant: PE/EtOAc 9 :1 then 8 :2

Yield: 40 %; Yellow oil.

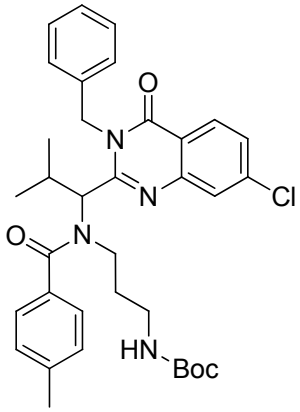
^{1}H-NMR (300 MHz, $CDCl_3$, 323 K, referred to the main rotamer) δ 8.23 (d, J = 8.4 Hz, 1-H), 7.65 (d, J = 1.8 Hz, 1-H), 7.36 (dd, J = 8.5/1.6 Hz, 1-H), 7.30-7.10 (m, 8-H), 6.84 (m, 2-H), 5.96 (d, J = 15.9 Hz, 1-H), 4.48 (d, J = 15.9 Hz, 1-H), 4.01 (d, J = 15.1 Hz, 1-H), 3.75 (d, J = 15.1 Hz, 1-H), 3.52 (d, J = 9.9 Hz, 1-H), 2.98 (m, 4-H), 2.63 (m, 1-H), 1.5 (m, 2-H), 1.40 (br s, 9-H), 1.03 (d, J = 6.3 Hz, 3-H), 0.11 (d, J = 6.3 Hz, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K, referred to the main rotamer) δ 162.3, 158.1, 155.9, 147.8, 140.5, 140.4, 136.5, 128.7, 128.6, 128.5, 128.4, 127.6, 127.2, 127.0, 126.9, 126.6, 119.0, 78.8, 67.3, 55.8, 49.2, 45.7, 38.7, 29.6, 28.4, 20.7, 19.8 (2C); MS (ESI) *m/z* 589 (100%) $(M+H)^+$. $C_{34}H_{41}ClN_4O_3$: calcd. C 69.31, H 7.01, N 9.51 ; found C 69.30, H 7.12, N 9.68.

tert-butyl (3-((1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl)amino)propyl)carbamate (57).



Compound **56** (300 mg) was stirred in dry methanol under a hydrogen atmosphere (1 atm) in the presence of Pearlman's catalyst at room temperature for 8 h. The crude reaction was filtered through a Celite pad and evaporated to give **57** as a yellow oil which was directly used for the following step.

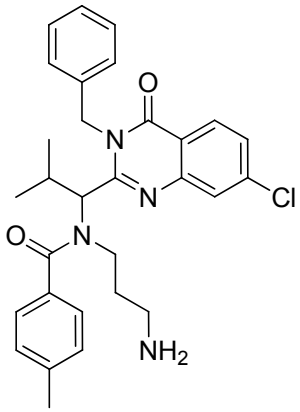
***tert*-butyl(3-(N-(1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl)-4-methylbenzamido)propyl)carbamate**



To a cooled solution (0 °C) of 255 mg of **57** (0,51 mmol, 1 eq) in 3 ml of dry CH_2Cl_2, 2,2, eq of TEA were added. Then, 1 eq of 4-methylbenzoyl chloride (1 eq) was added dropwise. The reaction was stirred at room temperature overnight. The mixture was extracted with CH_2Cl_2 , and the organic layer was washed with water (x1),brine (x1), and dried over sodium sulfate. Evaporation of the solvent gave a crude product which was purified by column cromatography using PE/EtOAc 95 :5 then PE/EtOAc 8 :2 as eluant to give 112 mg of the desired product as yellow oil.

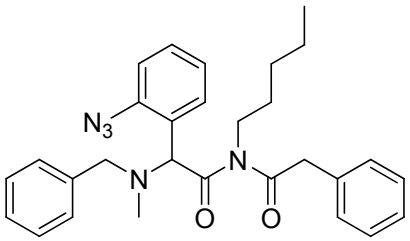
^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.29 (d, J = 8.5 Hz,1-H), 7.74 (d, J = 1.6 Hz, 1-H), 7.50-7.10 (m, 10-H), 6.10 (d, J = 15.6 Hz, 1-H), 5.68 (d, J = 10.7, 1-H), 5.21 (d, J = 15.6 Hz, 1-H), 3.96 (br t, NH), 3.55-3.25 (n, 2-H), 2.80-2.50 (m, 3-H), 2.34 (s, 3-H), 1.33 (br s, 10-H), 0.92 (d, J = 6.9 Hz, 3-H), 0.73 (m, 1-H), 0.33 (d, J = 6.9 Hz, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 173.1, 162.2, 156.0, 155.8, 147.6, 140.9, 139.0, 136.9, 133.7, 129.3, 129.0, 128.8, 128.2, 127.7, 127.3, 126.9, 126.0, 119.4, 79.3, 59.6, 45.6, 42.0, 37.7, 30.8, 28.9, 28.4, 21.5, 19.2, 18.4; MS (ESI) *m/z* 617 (100%) $(M+H)^+$. $C_{35}H_{41}ClN_4O_4$: calcd. C 68.11, H 6.70, N 9.08 ; found C 68.34, H 6.90, N 8.75.

N-(3-aminopropyl)-N-(1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl)-4-methylbenzamide (58).



To a cooled solution (0 °C) of 100 mg of the protected compound (1 eq ; 0.16 mmol) in dry CH_2Cl_2, 20 eq of trifluoroacetic acid (3,24 mmol, 369,6 mg, 248 µL) were added. The reaction was stirred at room temperature for 3 h. NaOH 4 M was added until pH > 12 and the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic phases were then washed with brine and dried over sodium sulphate. Evaporation of the solvent gives ispinesib as a colorless oil. (Yield= 70 % on two steps). ^{1}H-NMR (300 MHz, $CDCl_3$, 323 K,) δ 8.29 (d, J = 8.52 Hz, 1-H), 7.66 (d, J = 1.9 Hz, 1-H), 7.45 (dd, J = 8.5/1.9 Hz, 1-H), 7.40 (br d, 2-H), 7.31-7.16 (m, 7-H), 6.10 (d, J = 15.6 Hz, 1-H), 5.69 (d, J = 10.4 Hz, 1-H), 5.24 (d, J = 15.6 Hz, 1-H), 3.43 (m, 2-H), 2.74 (m, 1-H), 2.34 (s, 3-H), 2.15 (t, J = 6.6 Hz, 2-H), 1.23 (m, 1-H), 0.94 (d, J = 6.9 Hz, 3-H), 0.71 (m, 1-H), 0.63 (br s, -NH_2), 0.37 (d, J = 6.9 Hz, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$, 323 K,) δ 173.0, 162.2, 155.9, 147.7, 140.7, 139.4, 136.9, 133.9, 129.1, 128.8, 128.7, 128.0, 127.6, 127.2, 126.8, 126.0, 119.3, 59.6, 45.5, 42.3, 39.6, 34.1, 28.8, 21.4, 19.2, 18.3; MS (ESI) *m/z* 517 (100%) $(M+H)^+$. $C_{30}H_{33}ClN_4O_2$: calcd. C 69.69, H 6.43, N 10.84 ; found C 69.79, H 6.56, N 8.96.

2-(2-azidophenyl)-2-(benzyl(methyl)amino)-*N*-pentyl-*N*-(2-phenylacetyl)acetamide (49).

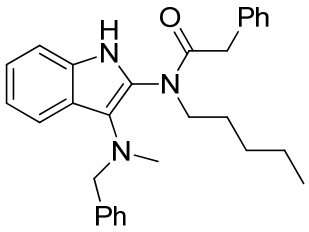


To a solution of 2-azido-benzaldehyde (1.5 eq, 1.02 mmol, 150 mg) in dry CH_2Cl_2 (4mL), N-benzyl-methylamine (1 eq, 0.68 mmol, 82 mg), phenylacetic acid (1 eq, 0.68 mmol, 93 mg) and finally pentyl isocyanide (1 eq, 0.68 mmol, 66 mg) were added. The mixture was heated at 40 °C for 72 h. After evaporation of the solvent, EtOAc and a satured solution of sodium bisulphite in water were added. This mixture was stirred at room temperature for 30 min. The two layers were separated, and the organic layer was washed with 1N HCl solution (x1) and with a satured solution of Na_2CO_3 (x1). The organic layer was then washed

with brine and dried over Na_2SO_4. The crude was purified by column chromatography (PE/EtOAc 95:5) to give 246 mg of **54** as a dark yellow oil (75% yield).

^{1}H NMR (300 MHz, CDCl3): δ 7.42-7.00 (m, 14H), 5.27 (s, 1H), 4.11 (br s, 2H), 3.76 (d, *J*=13.5 Hz, 1H), 3.67 (d, *J*=13.5 Hz, 1H), 3.59 (q, *J*=6.7 Hz, 1H), 3.27 (q, *J*=6.7 Hz, 1H), 2.30 (s, 3H), 1.48-1.05 (m, 6H), 0.87 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (300 MHz, CDCl3) δ 175.1, 174.4, 139.5, 139.0, 134.3, 130.4, 129.6, 129.4, 128.7, 128.5, 128.1 2C, 126.9 2C, 124.7, 118.6, 65.0, 58.3, 45.1, 44.4, 38.6, 29.1, 28.8, 22.2, 13.9. MS (ESI) *m/z* 484(100%) $(M+H)^+$.

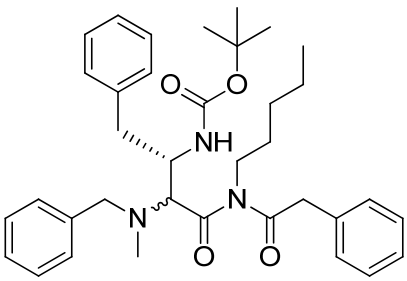
***N*-(3-(benzyl(methyl)amino)-1*H*-indol-2-yl)-*N*-pentyl-2-phenylacetamide (50).**



To a cooled solution (0°C) of **49** (1 eq, 0.48 mmol, 230 mg) in dry toluene (3.5mL), tributhyl phosphine(1.2 eq, 0.58 mmol, 115 mg) was added. This mixture was heated at reflux for 1h. After evaporation of the solvent, EtOAc was added. The organic layer was washed with water, brine and finally dried over Na_2SO_4. The crude was purified by column chromatography (PE/EtOAc 9:1) to give 146 mg of **50** as a white solid (70% yield).

^{1}H NMR (300 MHz, CDCl3): δ 7.85 (d, *J*= 7.7 Hz, 1H), 7.53 (s, 1H), 7.46-7.00 (m, 13H), 4.36 (s, 2H), 4.15 (broad s, 1H), 3.41 (d, *J*= 19.2 Hz, 2H), 3.11 (broad s, 1H)2.89 (s, 3H), 1.70-1.40 (m, 2H), 1.39-1.14 (m, 4H), 0.87 (t, *J*= 6.1 Hz, 3H); ^{13}C NMR (300 MHz, CDCl3) δ 172.2, 139.0, 135.4, 132.0, 128.9, 128.5 2C, 128.4, 128.3, 127.2, 126.8, 124.0, 123.3, 122.8, 120.1, 119.7, 111.6, 61.0, 49.7, 41.5, 41.1, 29.1, 28.2, 22.4, 14.1. MS (ESI) *m/z* 484(100%) $(M+H)^+$. M.p. 126-127 °C. $C_{29}H_{33}N_3O$: calcd. C 79.23, H 7.57, N 9.56 ; found C 79.67, H 7.84, N 9.80.

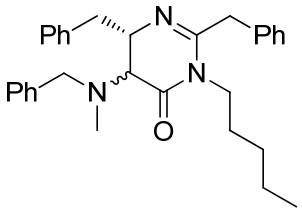
***tert*-butyl ((2*S*)-3-(benzyl(methyl)amino)-4-oxo-4-(*N*-pentyl-2-phenylacetamido)-1-phenylbutan-2-yl)carbamate (52).**



To a cooled solution (0°C) of *(S)-tert*-butyl (1-oxo-3-phenylpropan-yl)carbamate (1eq, 1.6 mmol, 400mg) in dry CH_2Cl_2 (10mL), morpholine (1eq, 1.6 mmol, 194mg), phenylacetic acid (1eq, 1.6 mmol, 220mg) and finally penthyl isocyanide (1eq, 1.6 mmol, 156mg) were added. The mixture was allowed to reach room temperature and then stirred for 30 min. The solvent was evaporated and the crude product was purified by column chromatography (PE/EtOAc 8:2) to give 658 mg of **52** as a dark yellow oil (70% yield).

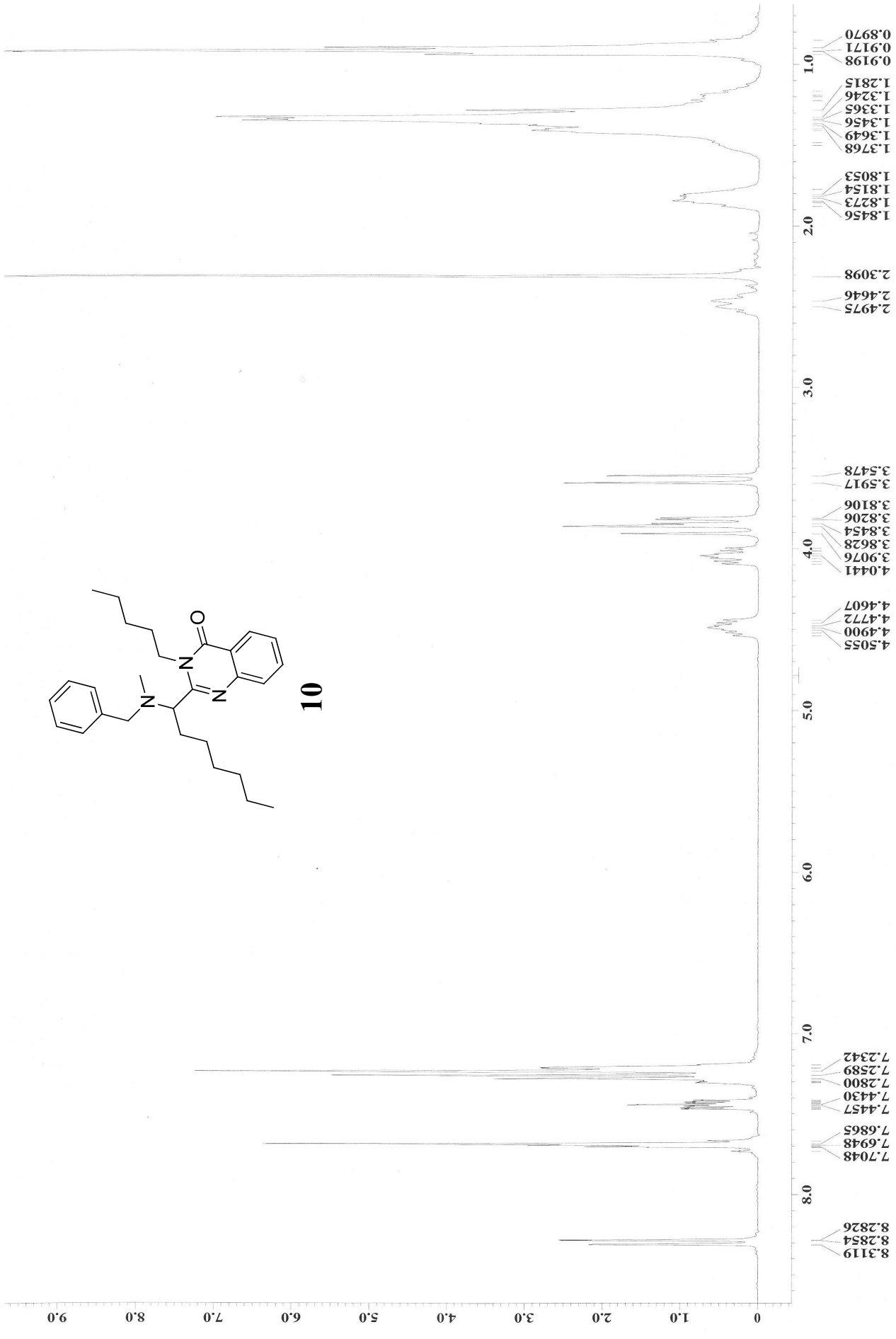
^{1}H NMR (300 MHz, CDCl3, referred to the main rotamer): δ 7.42-7.08 (m, 16H), 5.65 (d, *J*= 9.9 Hz, 1H), 4.57-4.43 (m, 1H), 4.01 (s, 2H), 3.83-3.62 (m, 3H), 3.57 (d, *J*= 14.0 Hz, 1H), 2.95 (d, *J*= 6.6 Hz, 2H), 2.23 (s, 3H), 1.57-1.48 (m, 1H), 1.48-1.34 (s, 9H), 1.34-1.03 (m, 5H), 0.88 (t, *J*= 6.3 Hz, 3H); ^{13}C NMR (300 MHz, CDCl3) δ 177.4 2C, 157.1, 141.1, 140.0, 136.0, 131.6, 131.4, 131.3, 130.7, 130.4 2C, 129.2, 129.1, 128.4, 81.0, 68.4, 60.0, 52.0, 46.7 2C, 41.2, 40.4, 31.3, 31.1, 30.5, 24.3, 16.0.

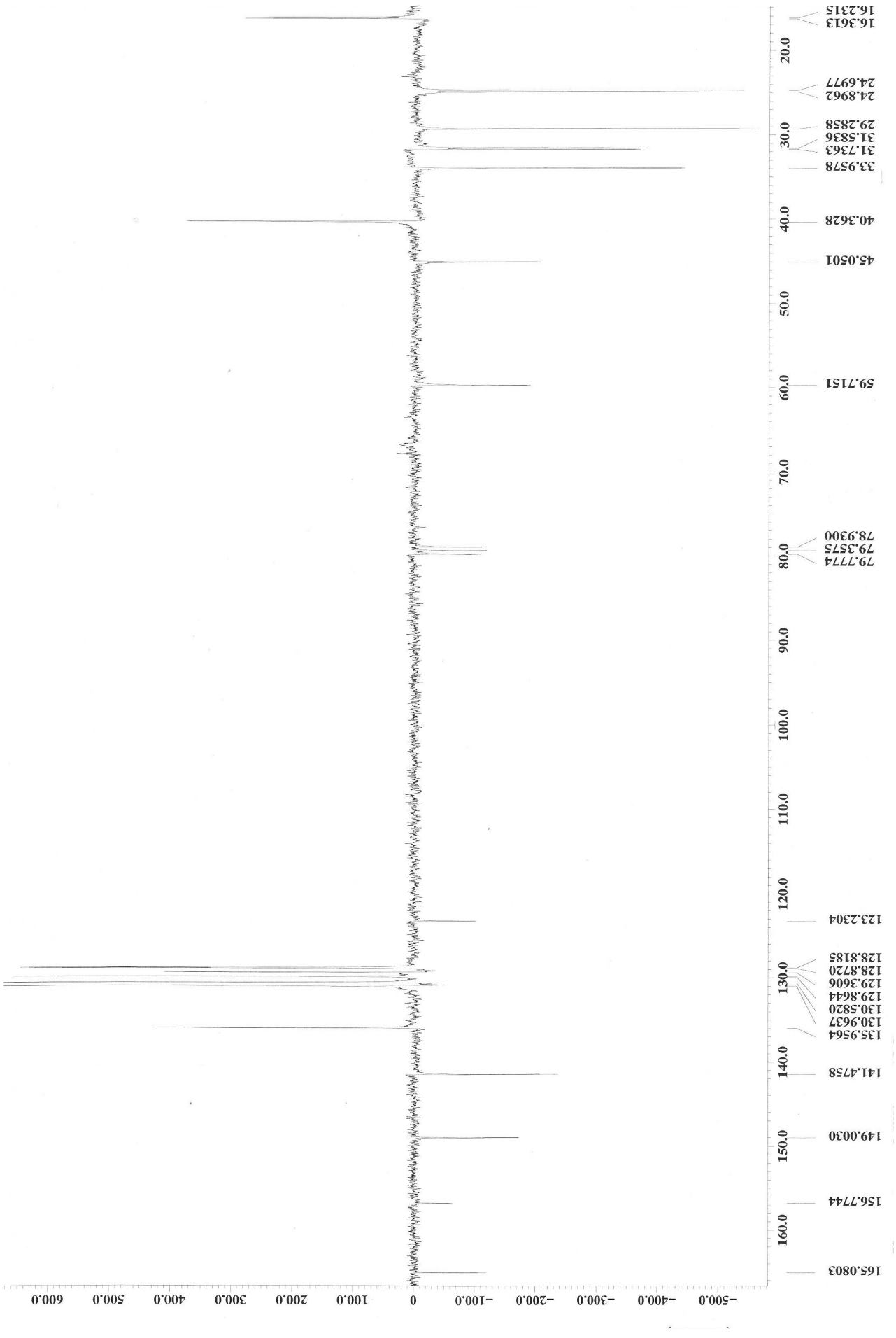
(6*S*)-2,6-dibenzyl-5-(benzyl(methyl)amino)-3-pentyl-5,6-dihydropyrimidin-4(3*H*)-one (53).

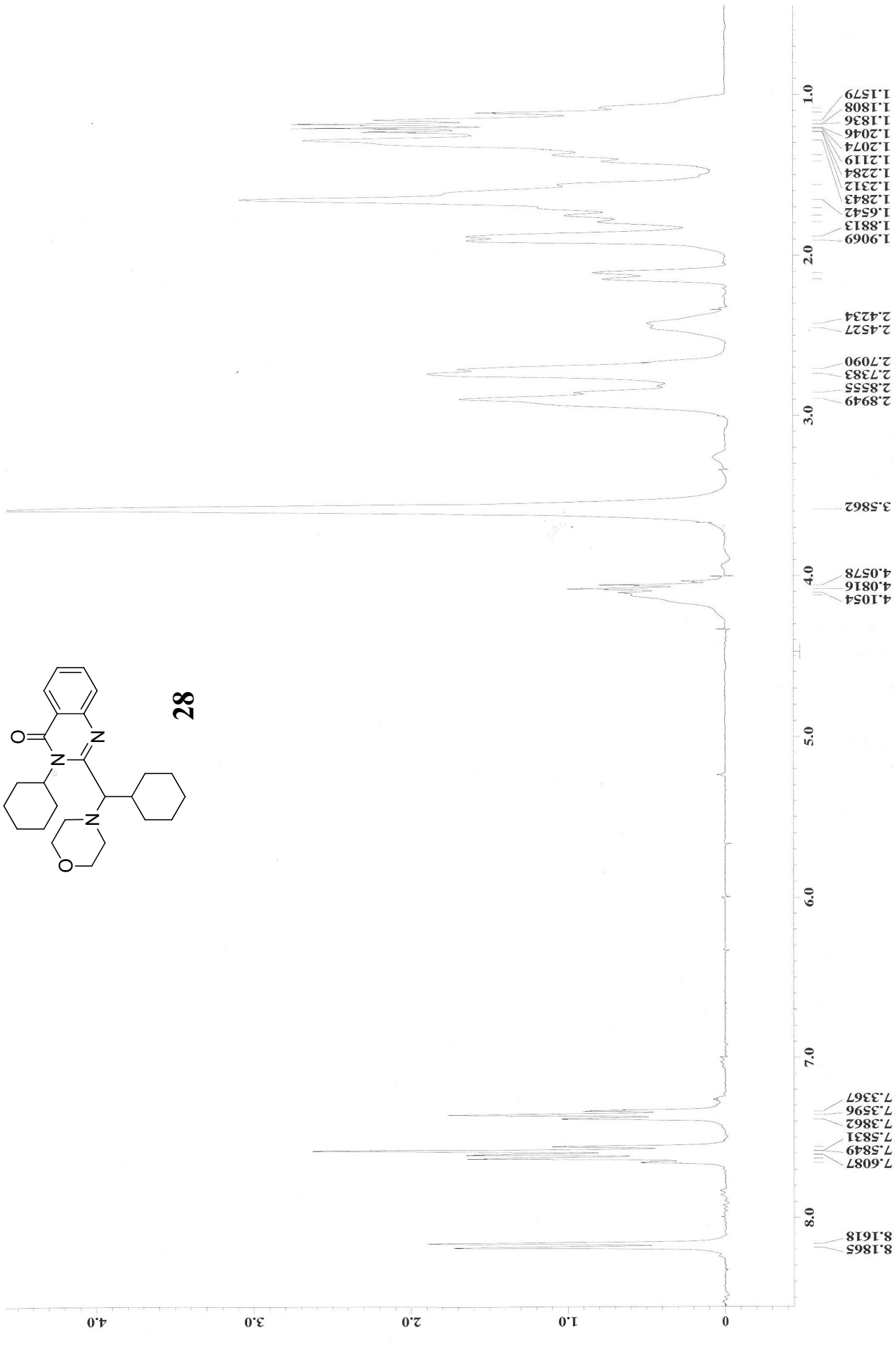


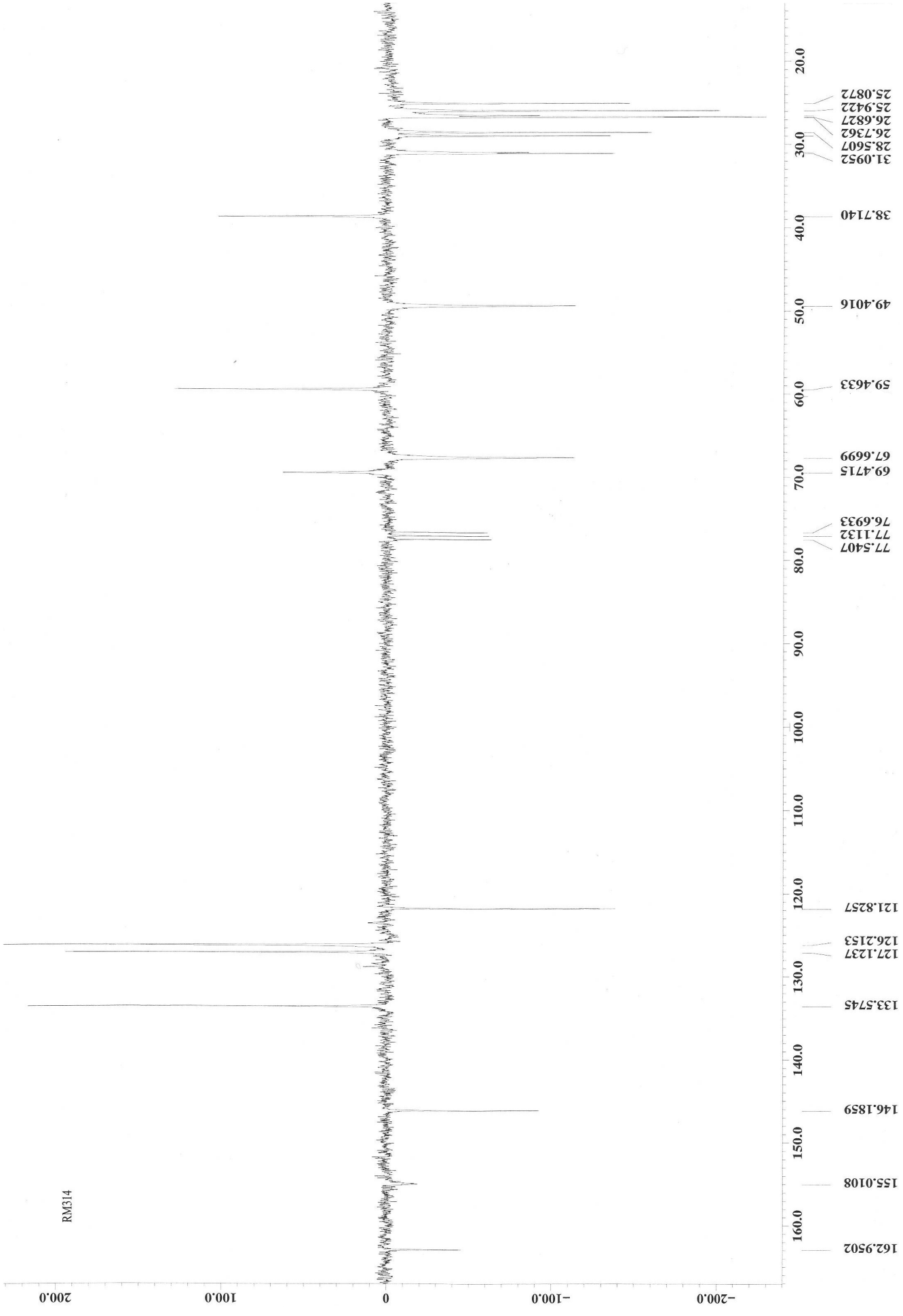
To a solution of **52** (1eq, 0.17 mmol, 100mg**)** in CH_2Cl_2 (1mL) trifluoroacetic acid (23.7eq, 4.04 mmol, 0.3mL) was added. The mixture was allowed to stir for 1h. Then, solvent was evaporated. The crude was dissolved in toluene (10 mL) and TEA was added (438 mg; 4.34 mmol, 26 eq). The reaction was refluxed for 1 h. Toluene was evaporated and the organic layer was diluted with CH_2Cl_2 and washed with Na_2CO_3 (x2), brine (x1) and finally dried over Na_2SO_4. The solvent was evaporated to give 48 mg of **53** as a brown oil (60% yield).

^{1}H NMR (300 MHz, CDCl3): δ 7.42-7.13 (m, 15H), 4.06-3.91 (m, 2H), 3.87)d, *J*= 13.7 Hz, 1H), 3.75 (s, 2H), 3.61 (q, *J*= 7.4 Hz, 1H), 3.33 (q, *J*= 7.4 Hz, 1H), 3.15 (dd, *J*= 14.2 Hz, 5.2 Hz, 1H), 3.07 (d, *J*= 10.7 Hz, 1H), 3.03 (dd, *J*= 14.2 Hz, 5.2 Hz, 1H), 2.37 (s, 3H), 1.40 (q, *J*= 7.4 Hz; 2H), 1.34-1.14 (m, 4H), 0.88 (t, *J*= 6.9 Hz, 3H); ^{13}C NMR (300 MHz, CDCl3) δ 172.5, 155.1, 141.7, 140.5, 137.9, 132.4, 130.8 2C, 130.6, 130.4, 130.1, 129.1, 129.0, 128.3, 65.2, 61.0, 59.8, 44.3, 43.5, 40.7, 39.7, 31.3, 31.1, 24.4, 16.1. MS (ESI) *m/z* 468 (100%) $(M+H)^+$. $C_{31}H_{37}N_3O$: calcd. C 79.62, H 7.97, N 8.99 ; found C 79.80, H 8.14, N 9.30.





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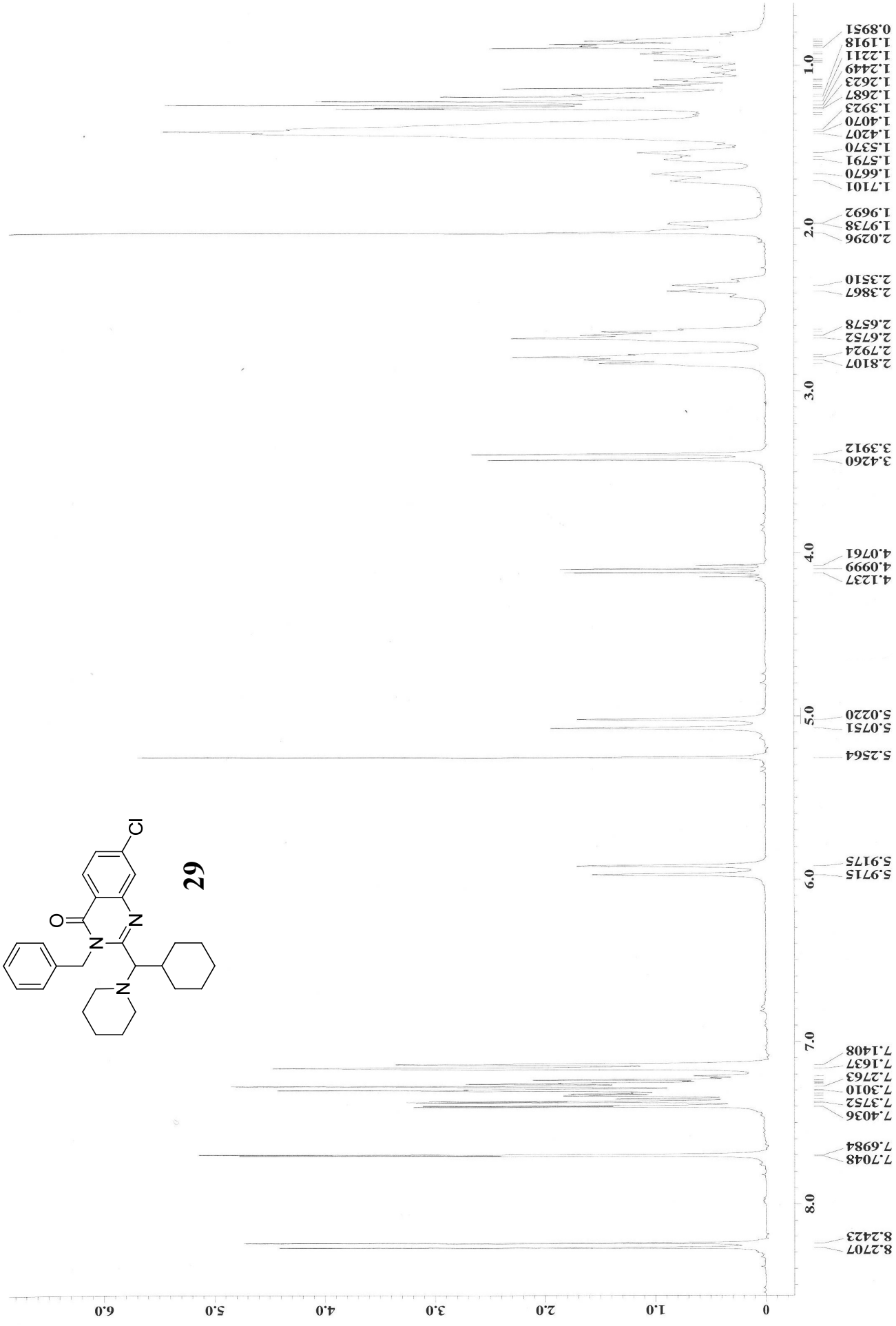

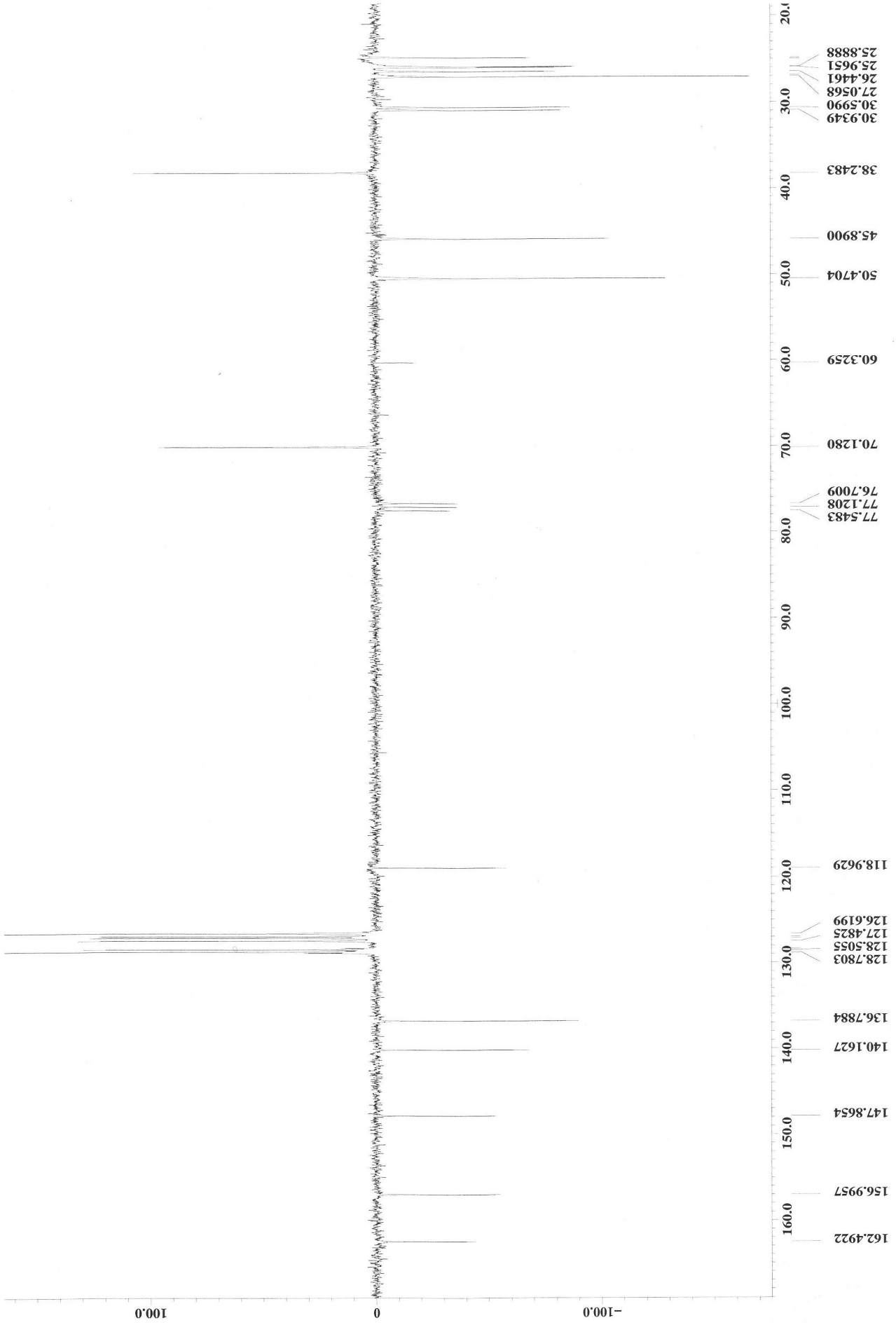
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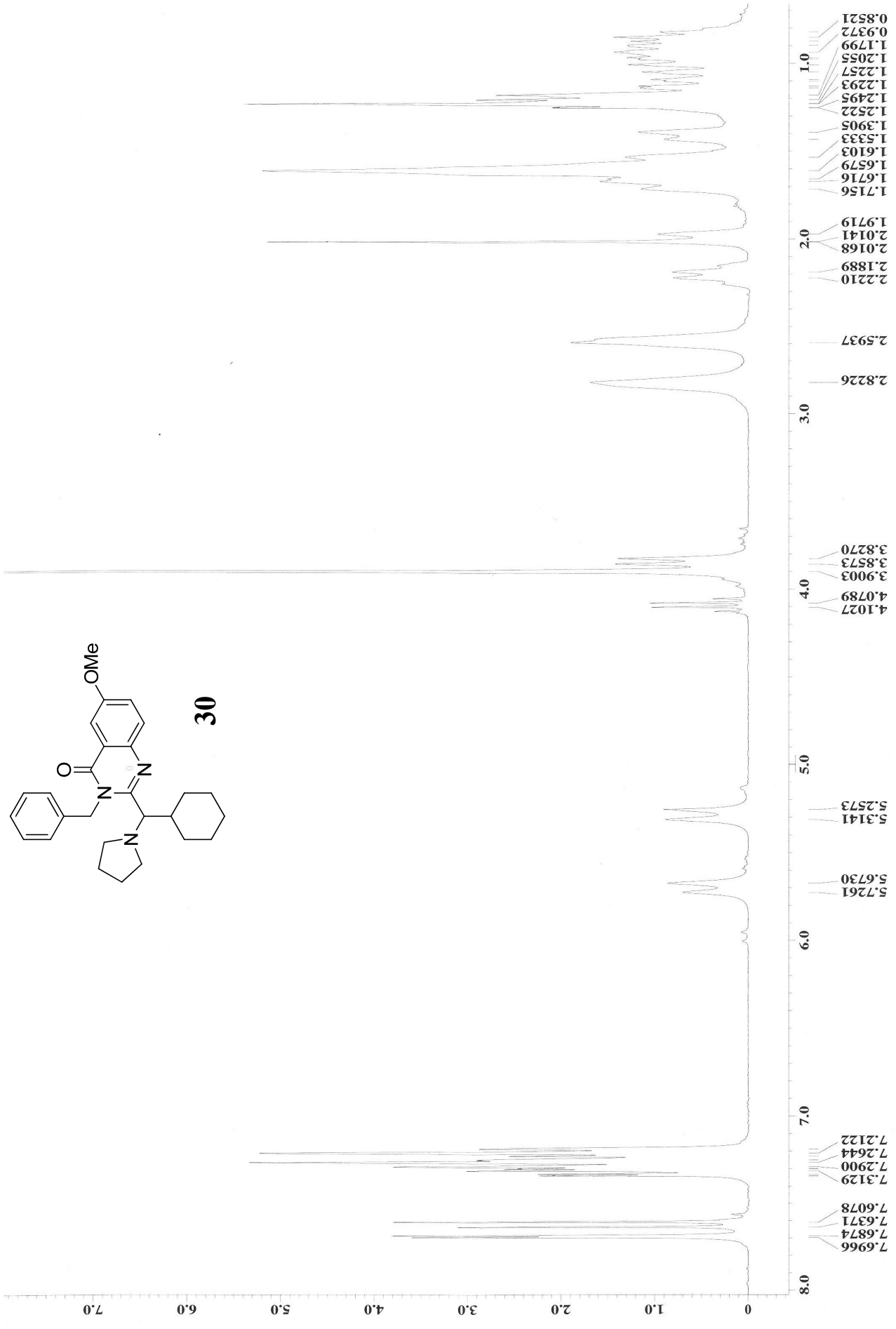

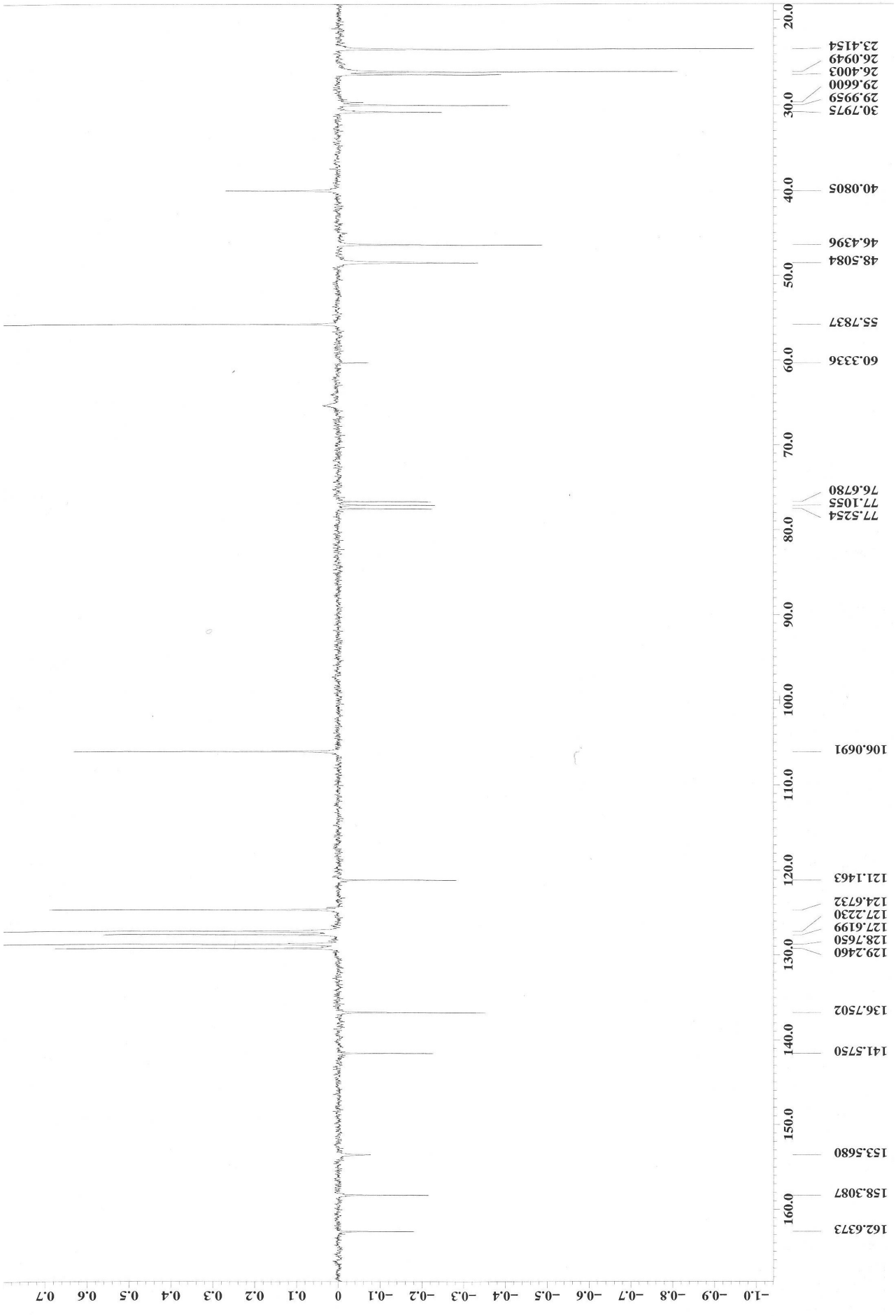

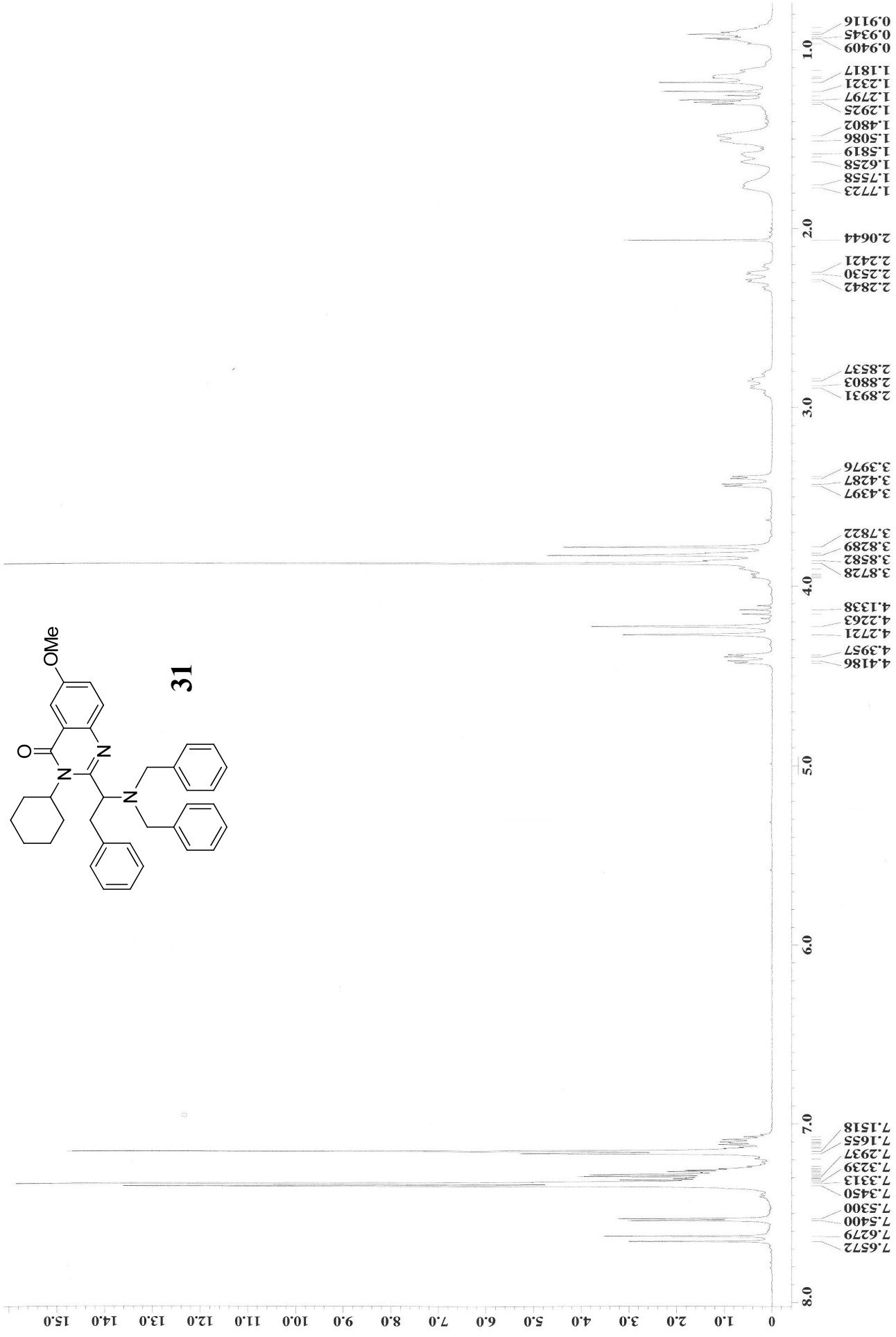

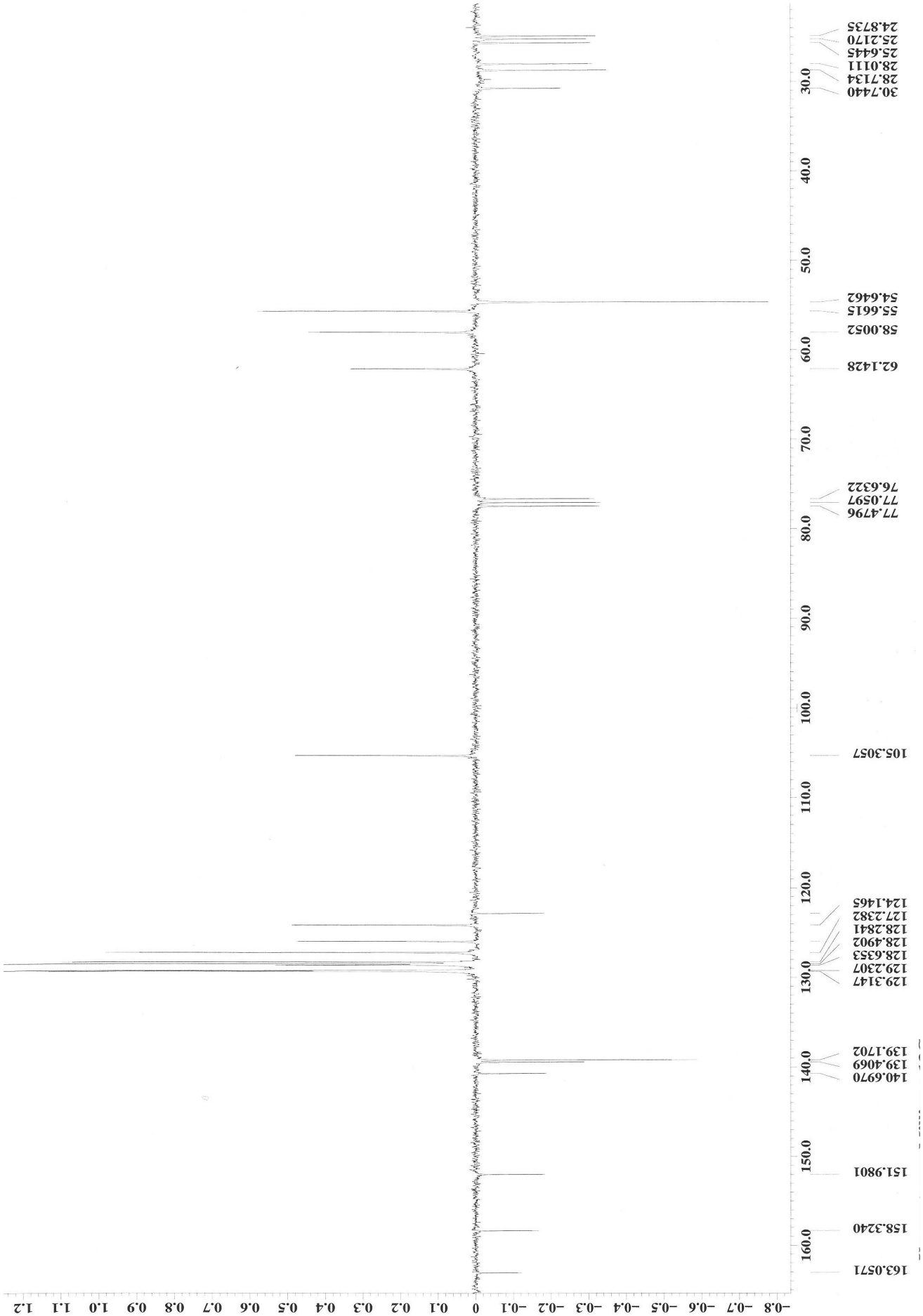

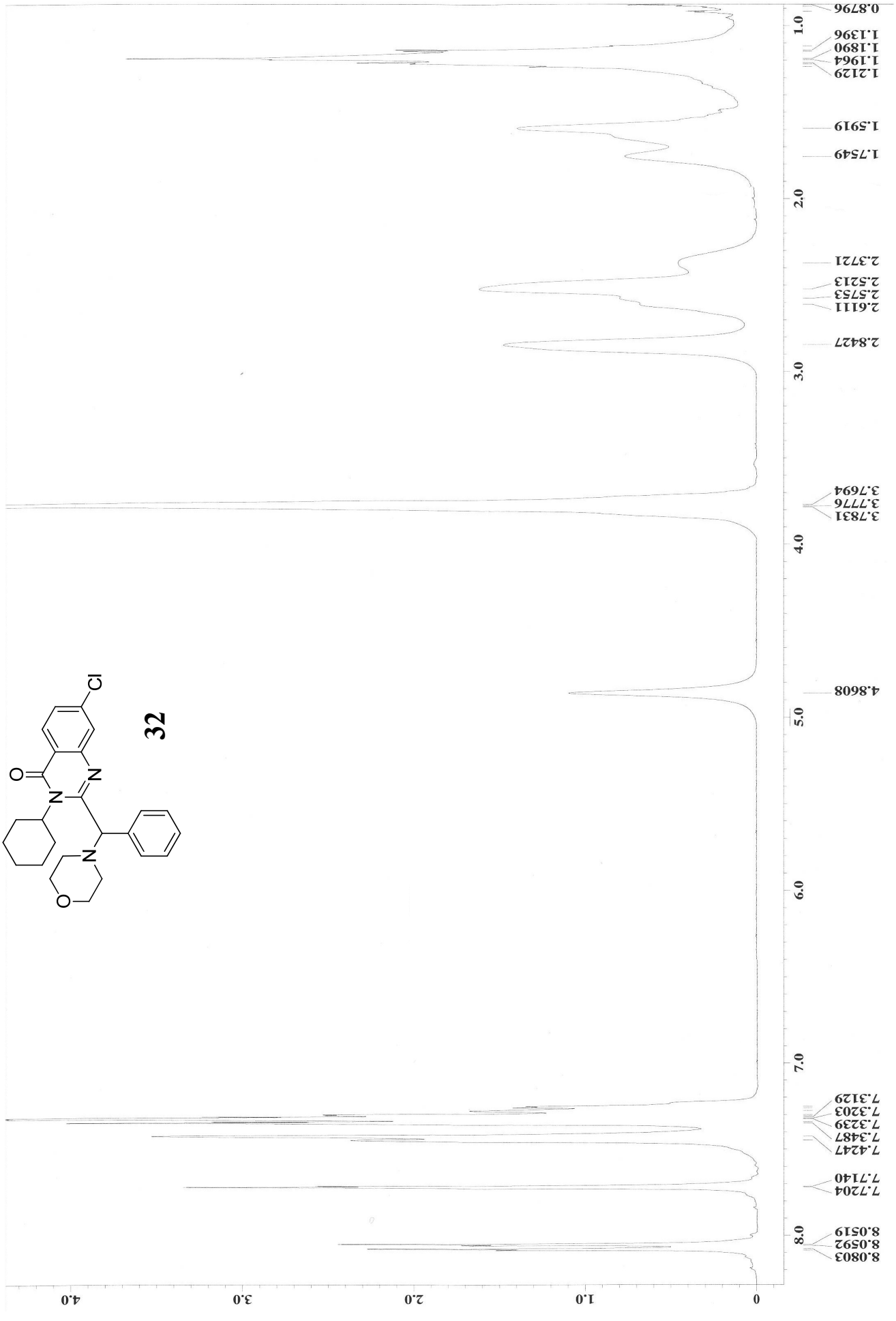

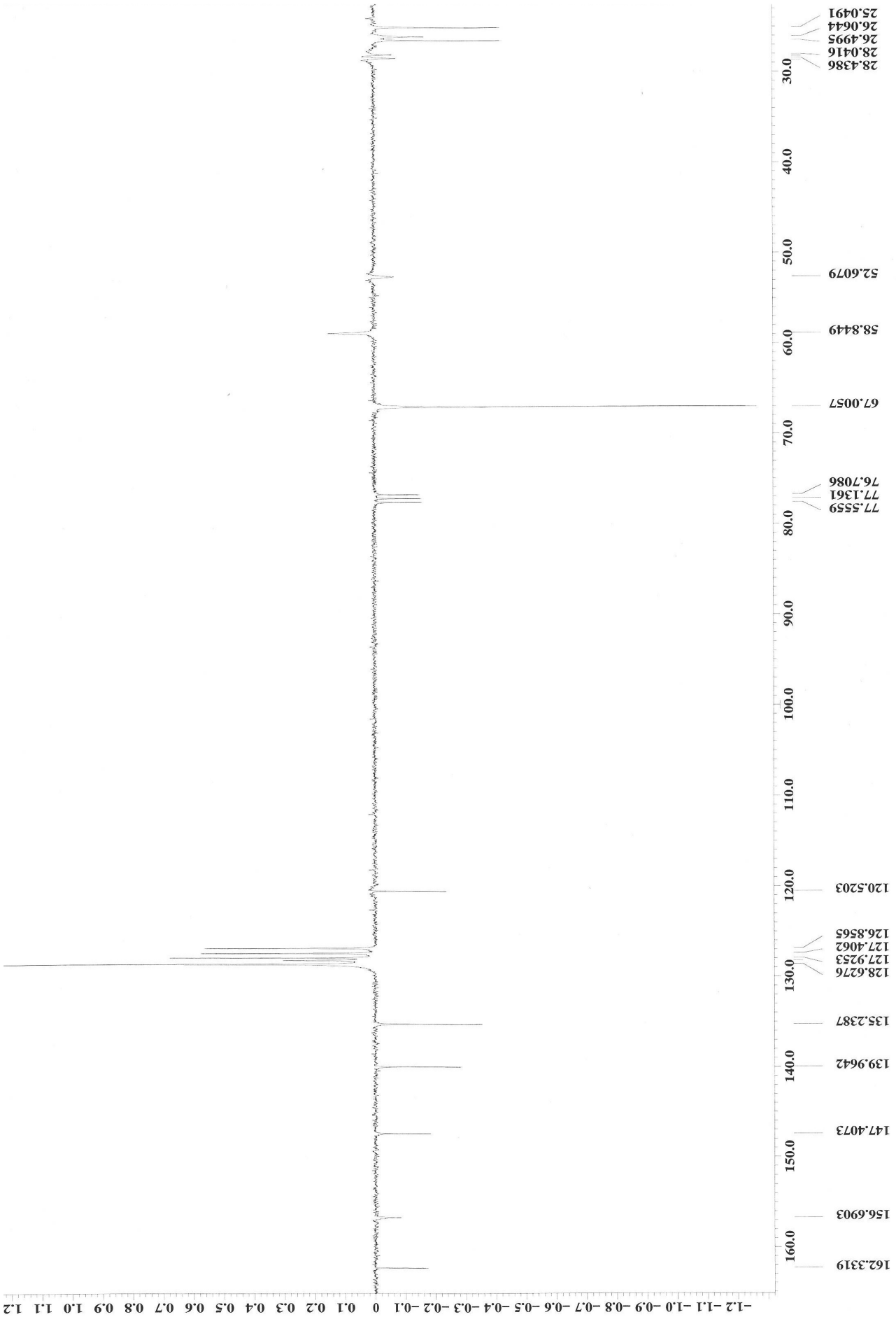

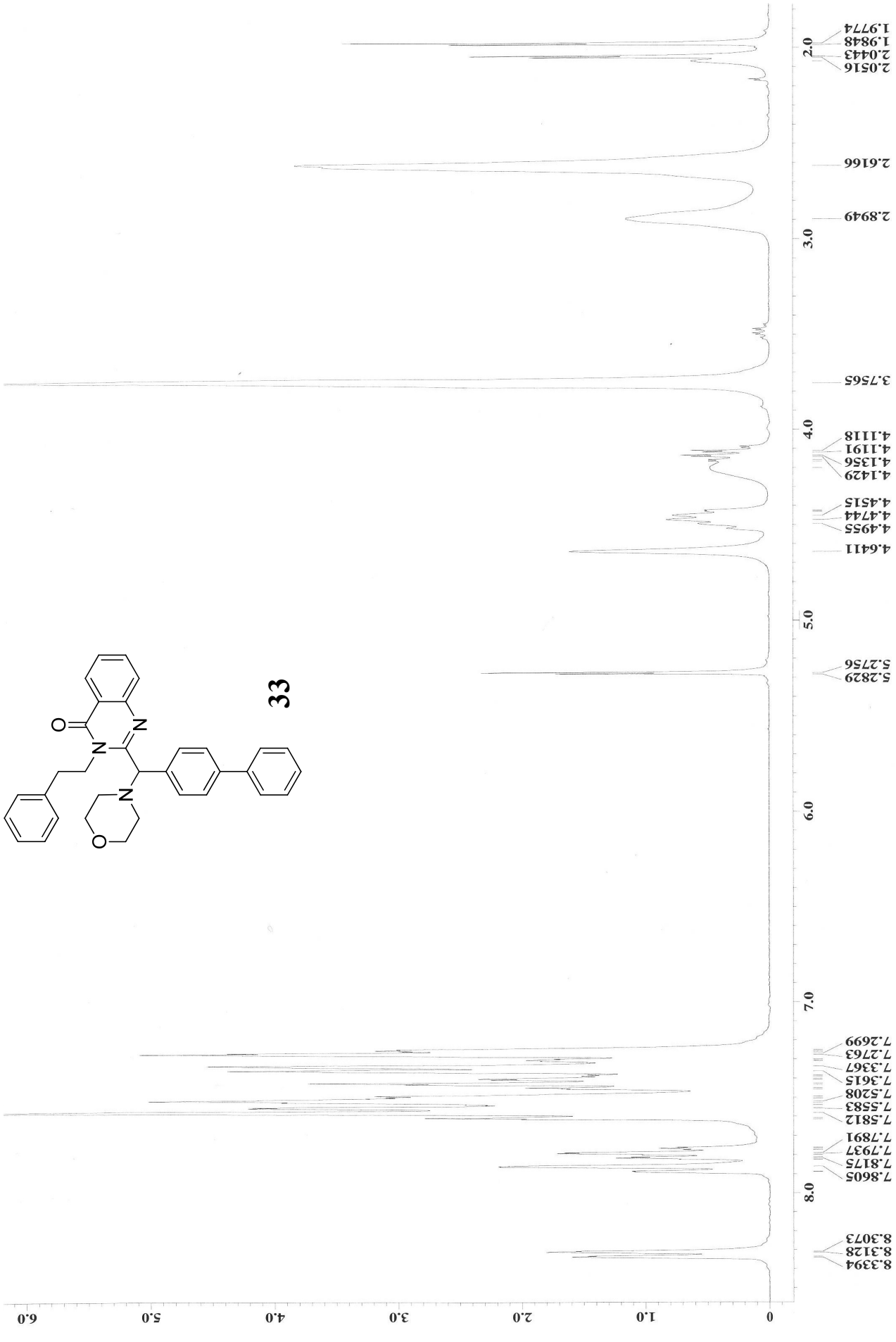

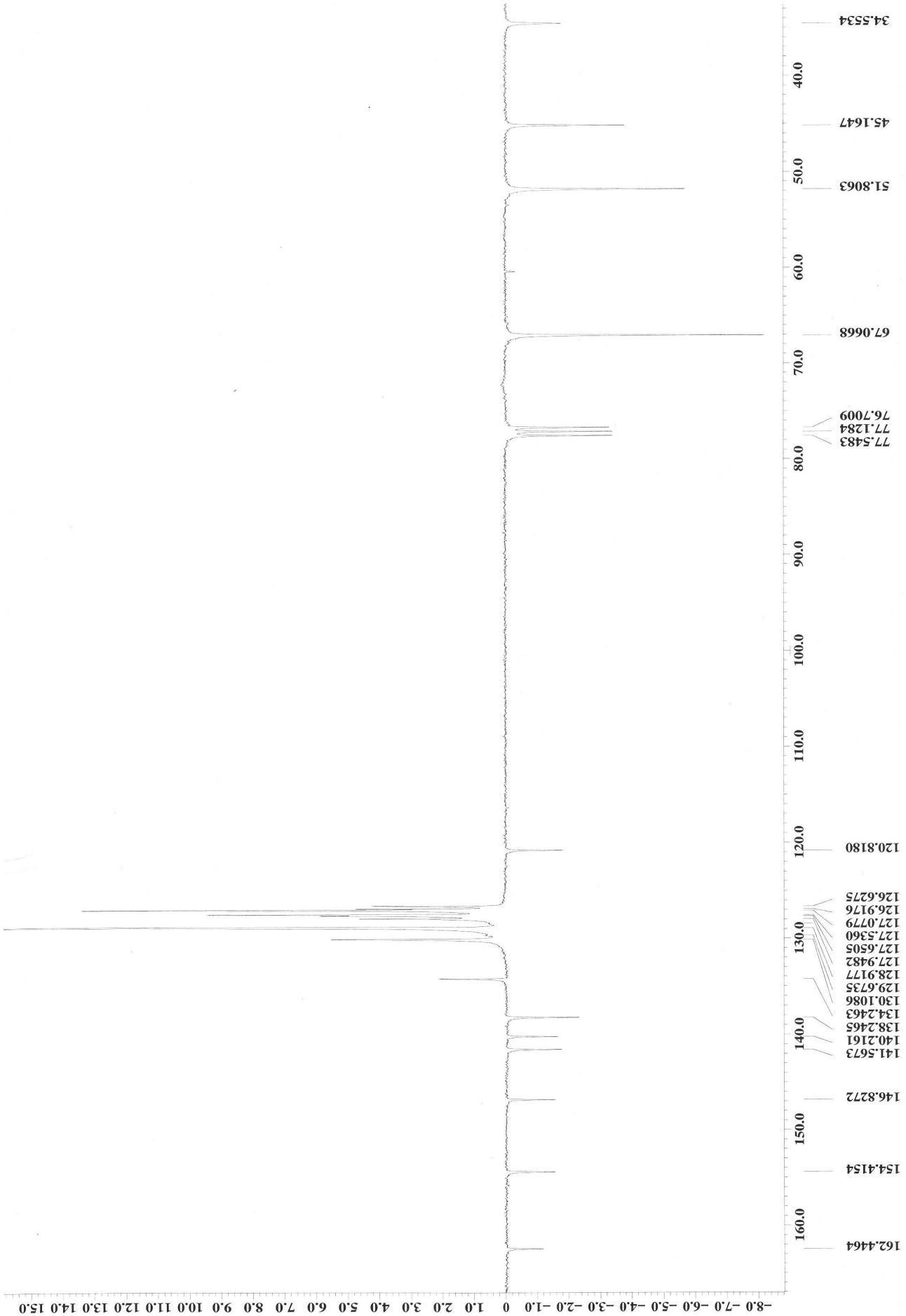

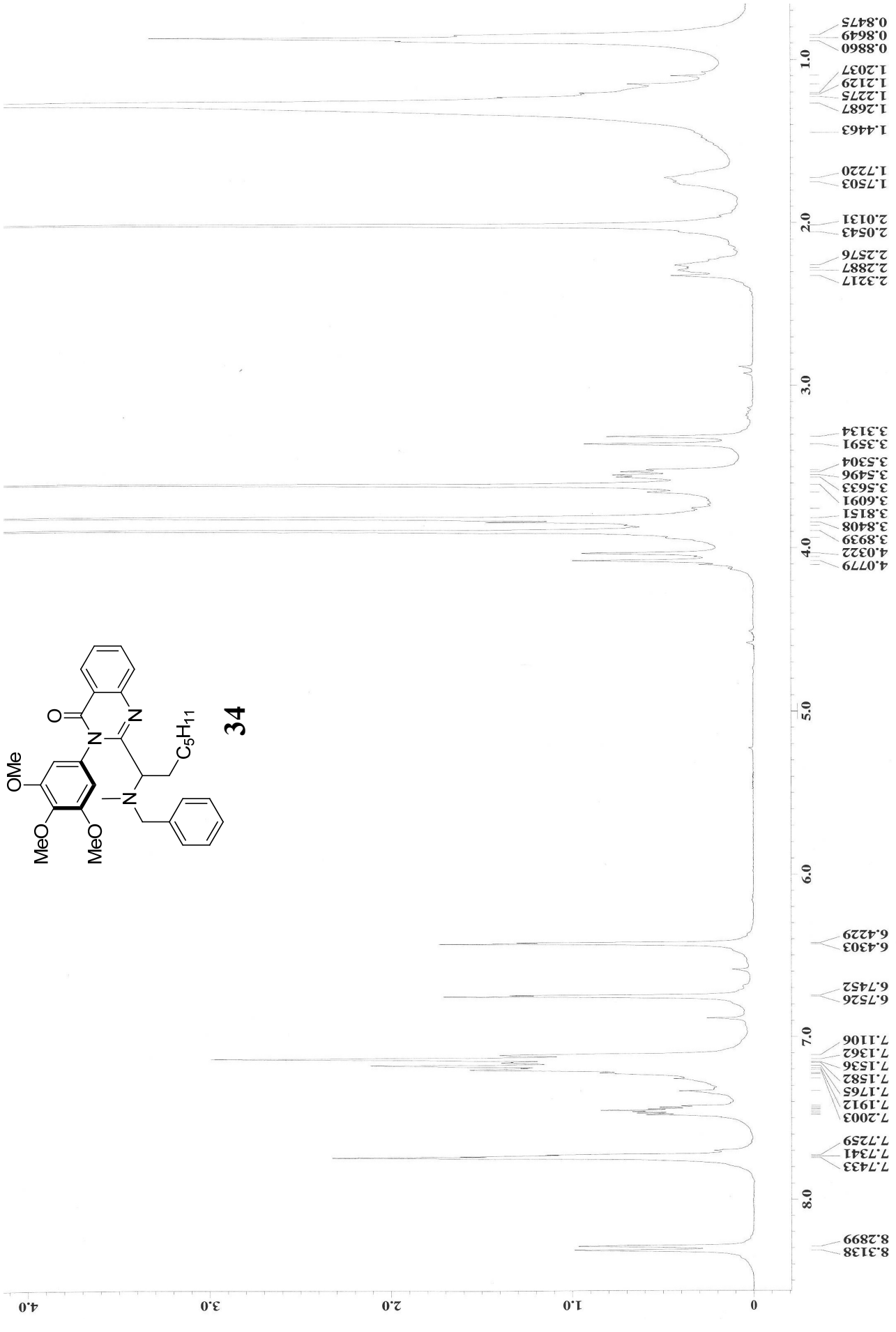

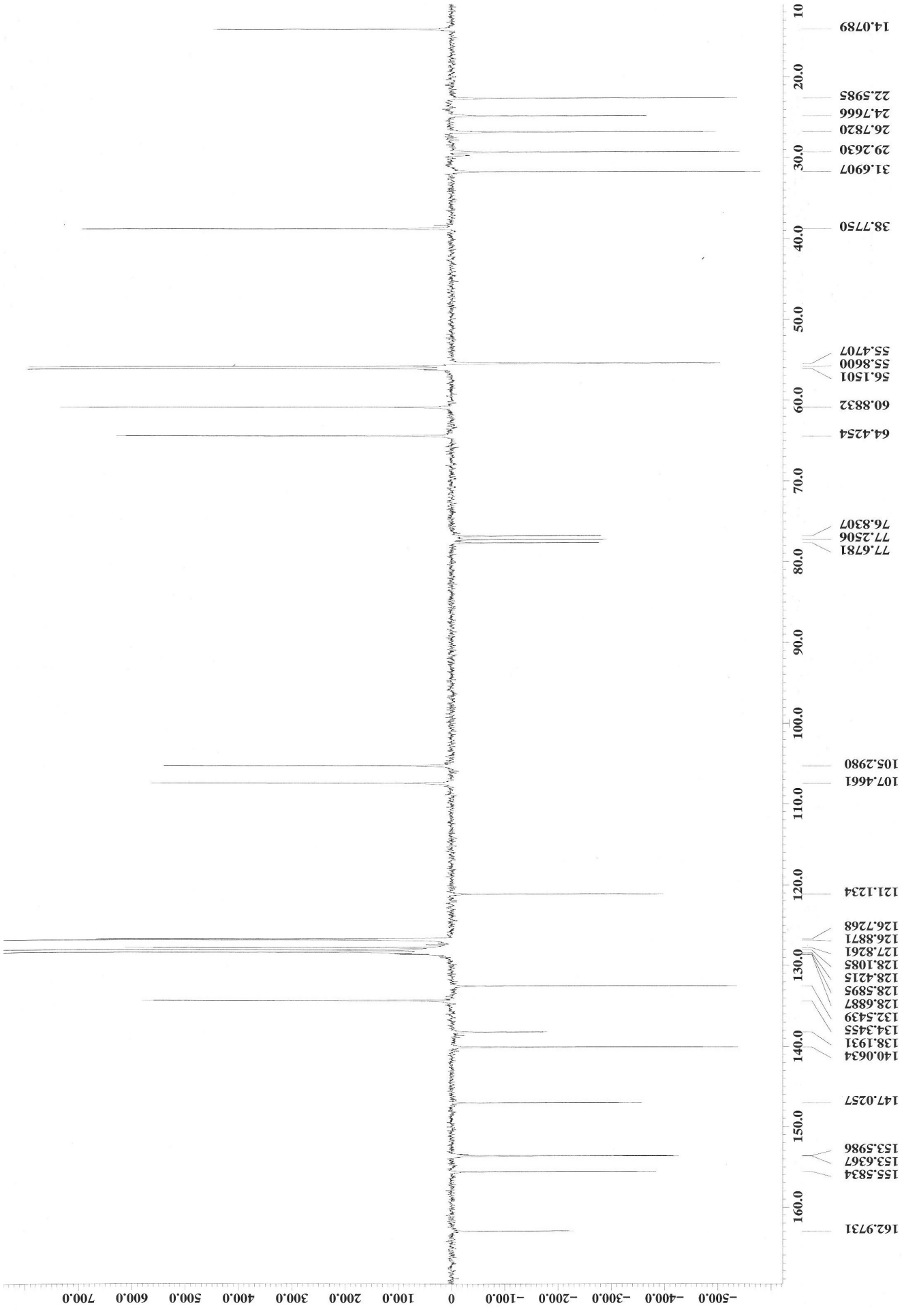

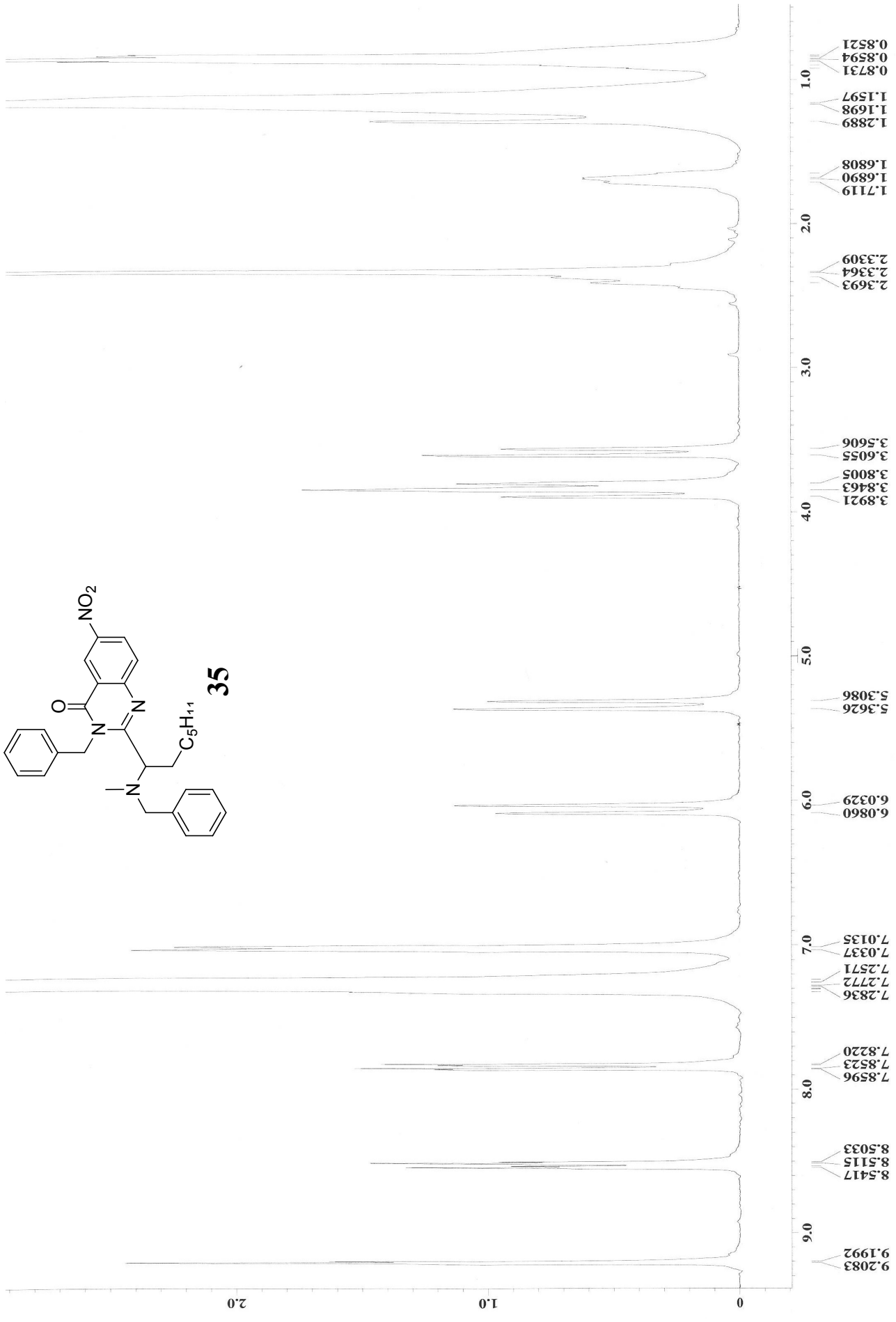

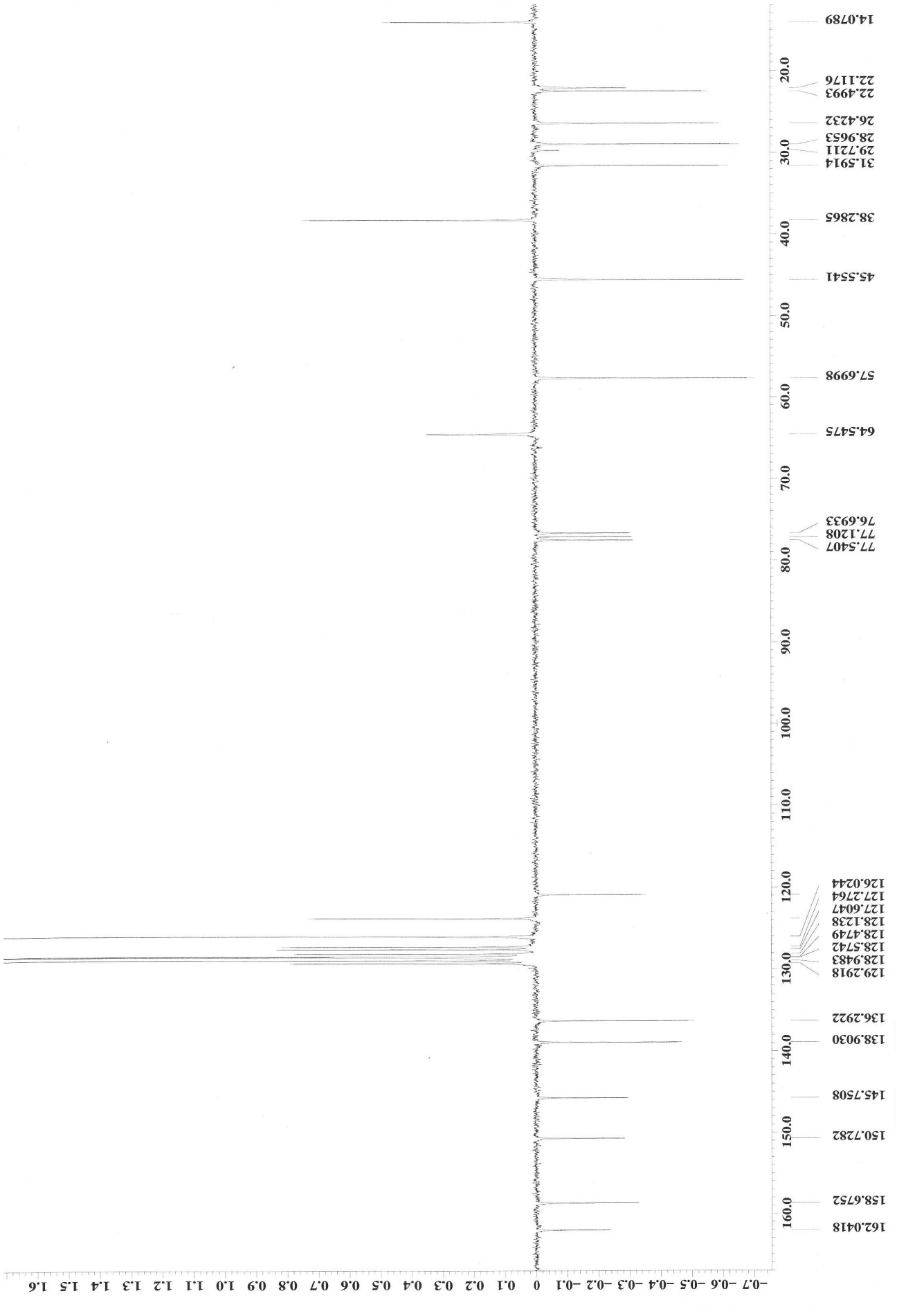

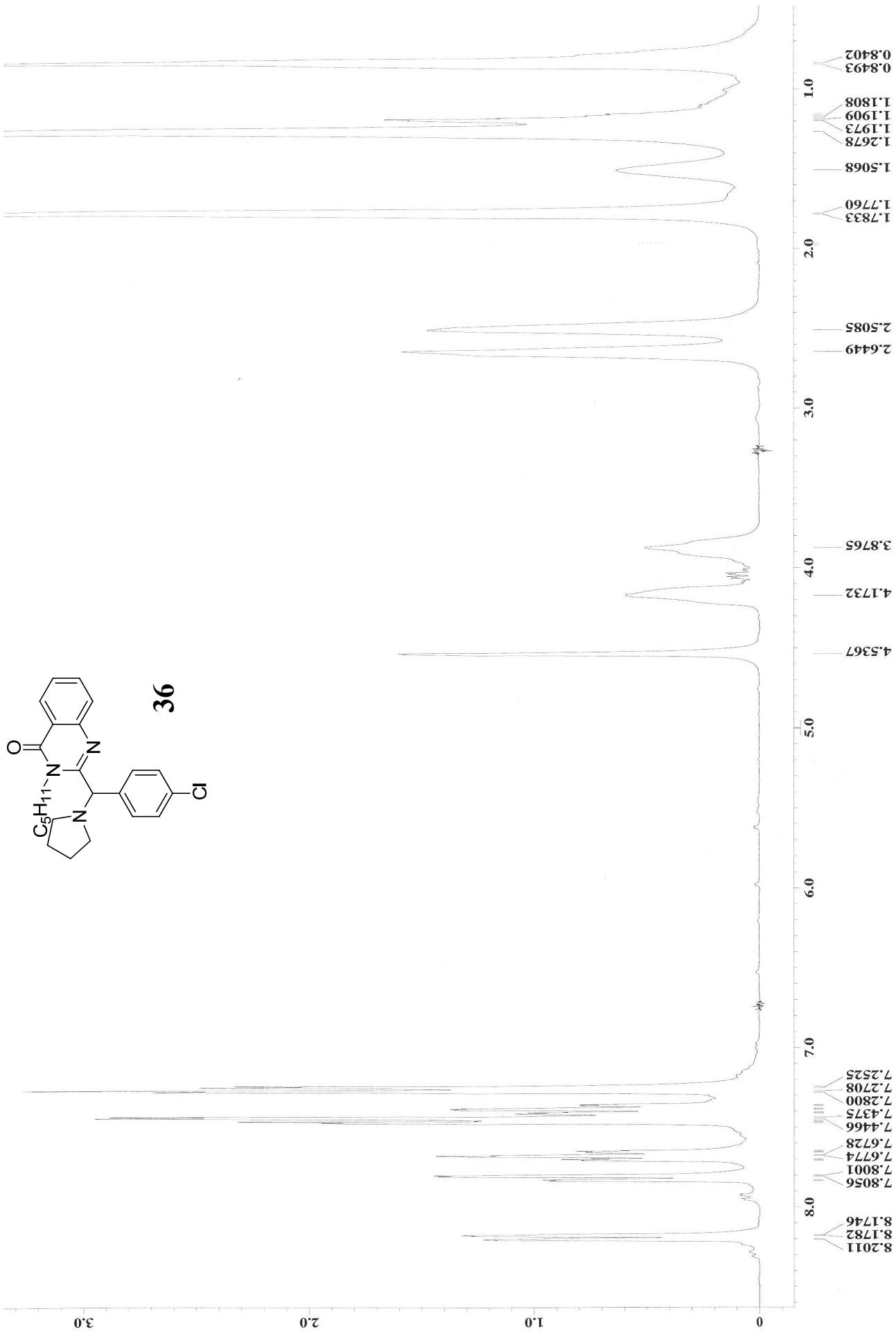

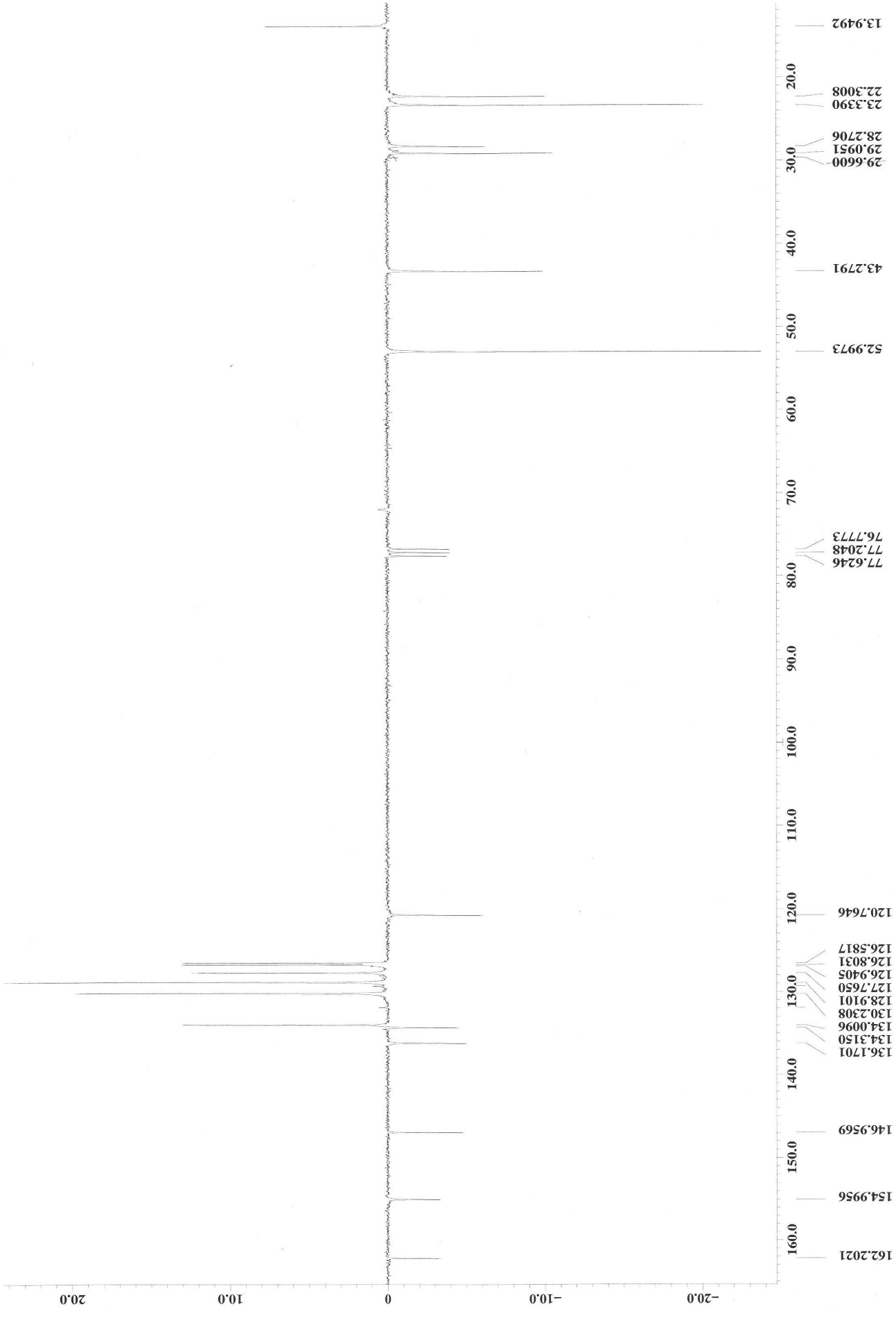

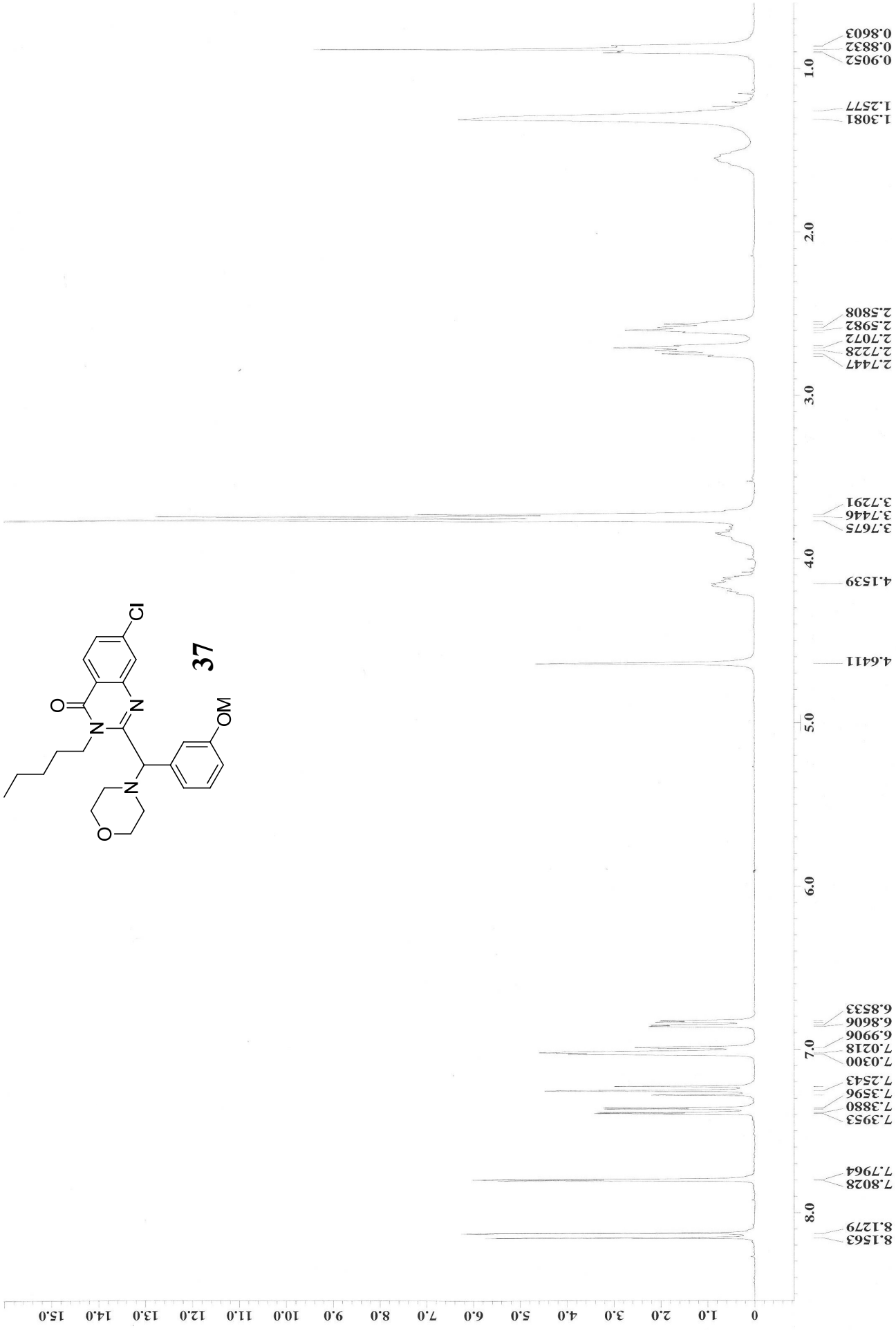

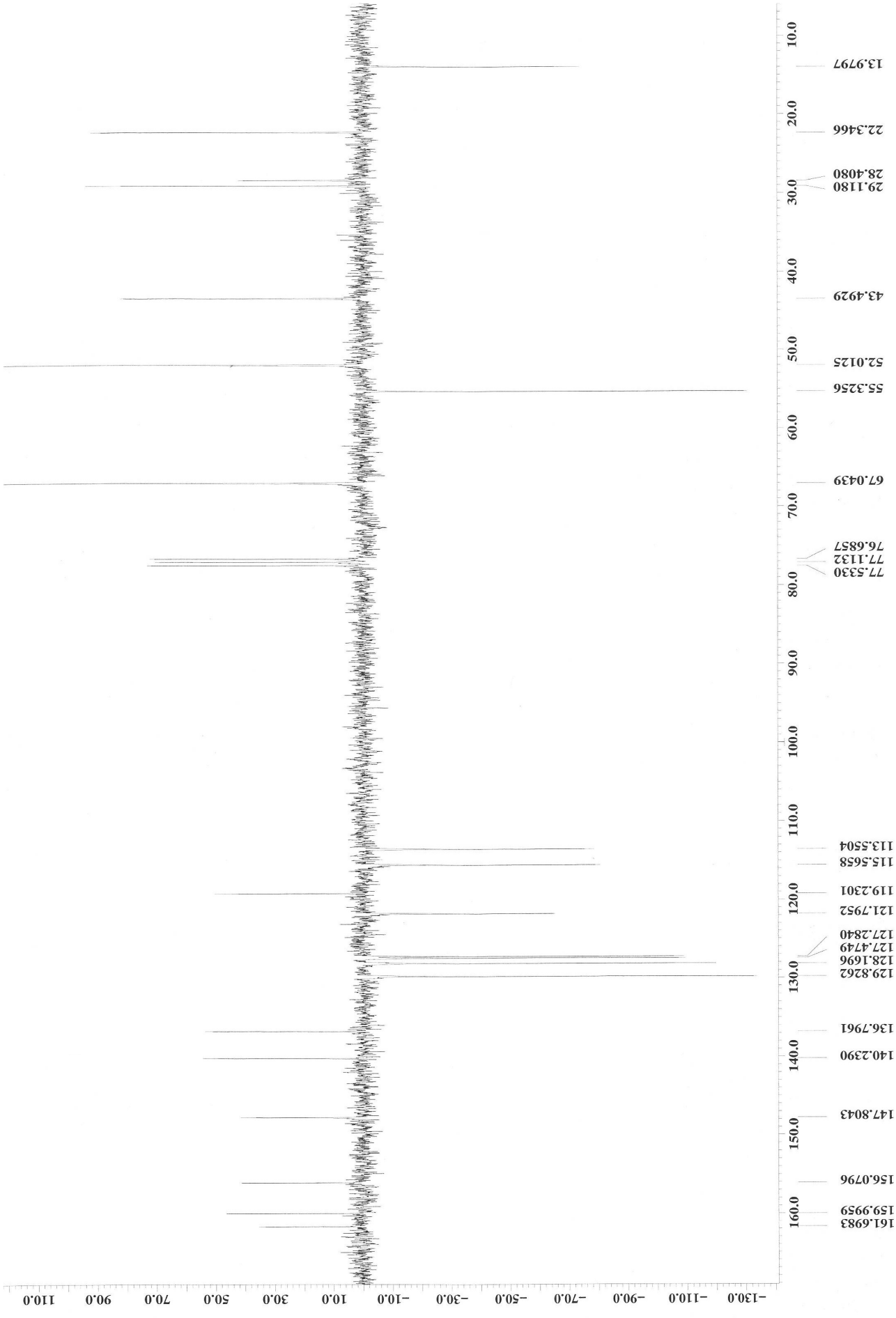

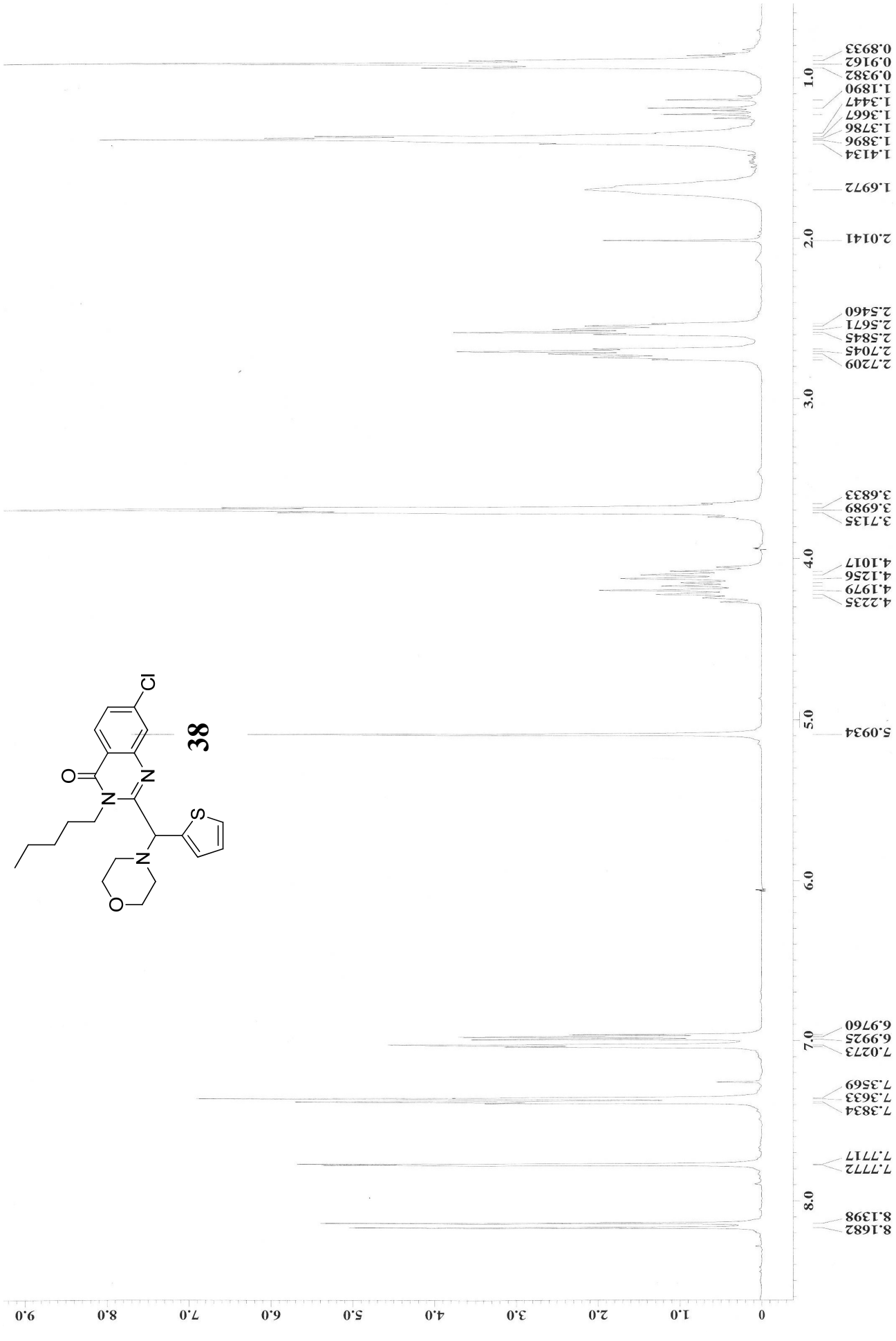

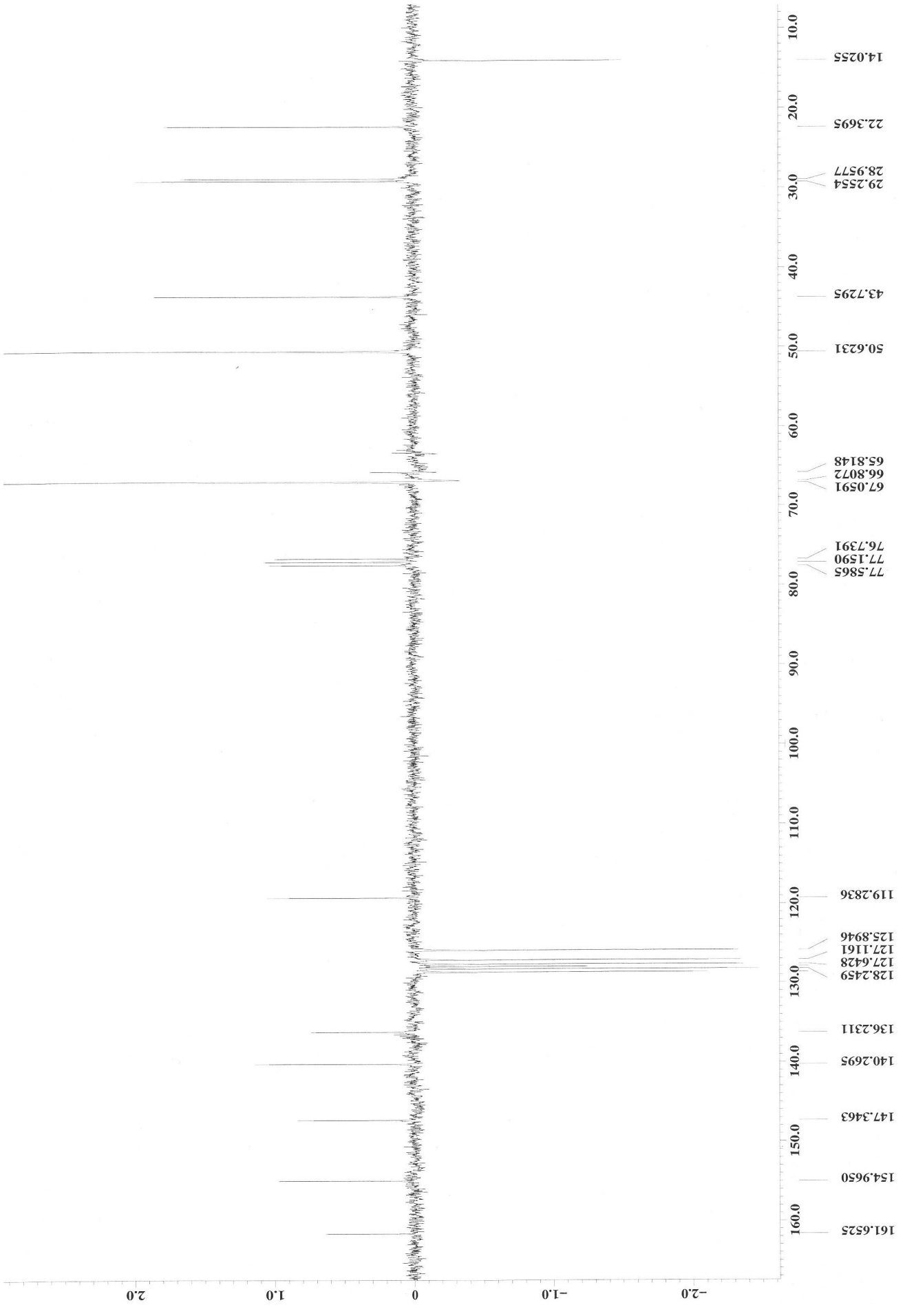

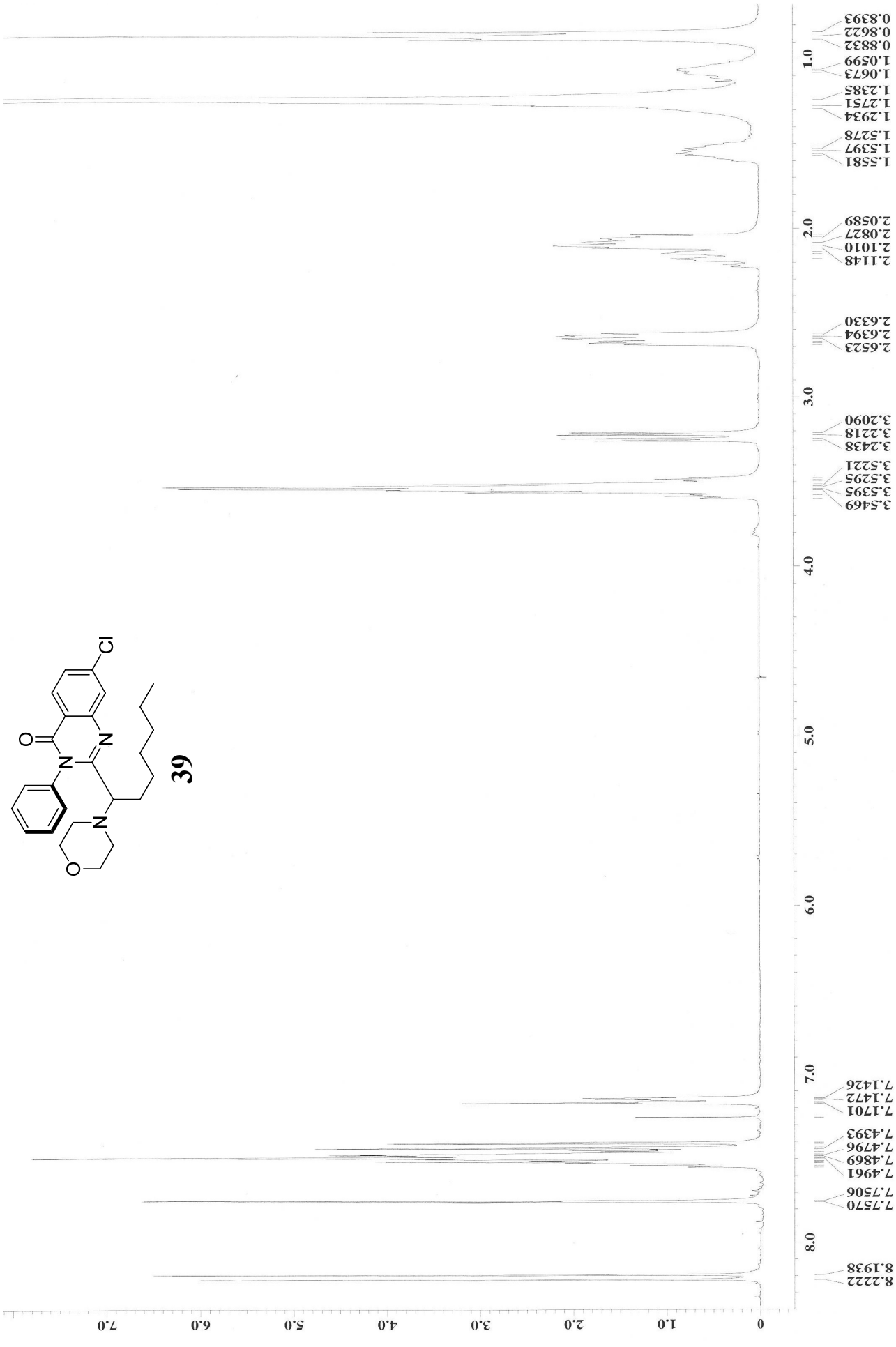

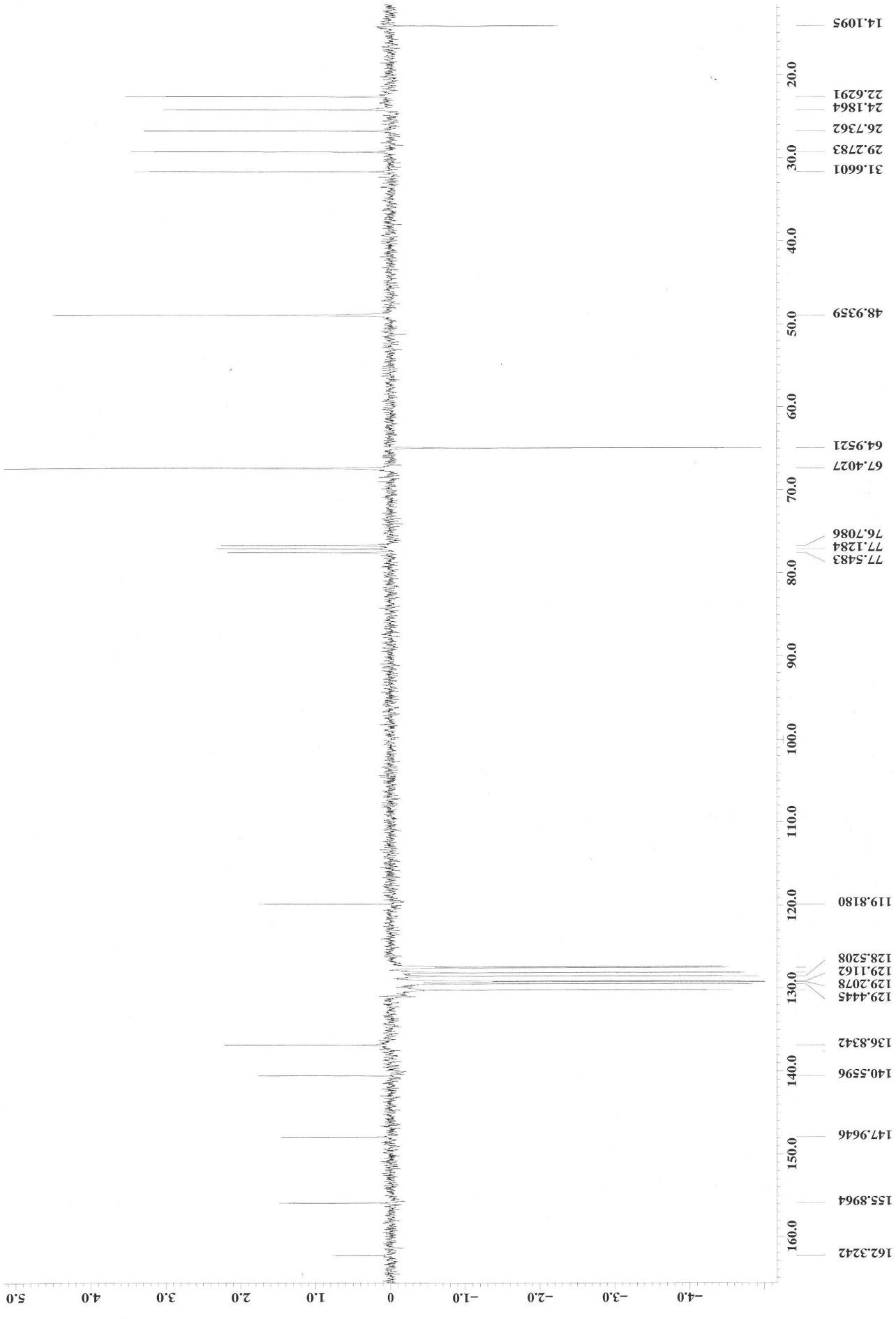

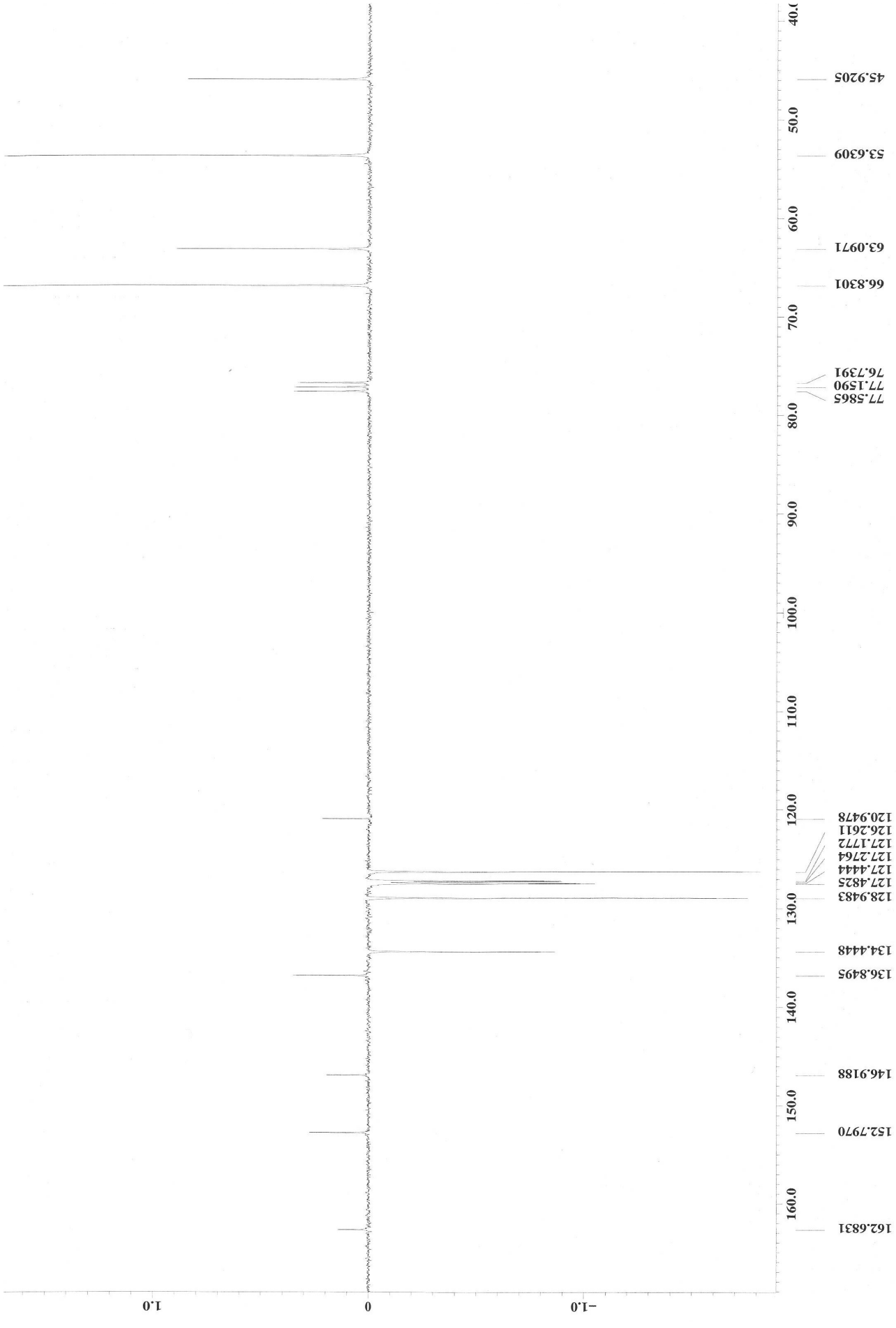

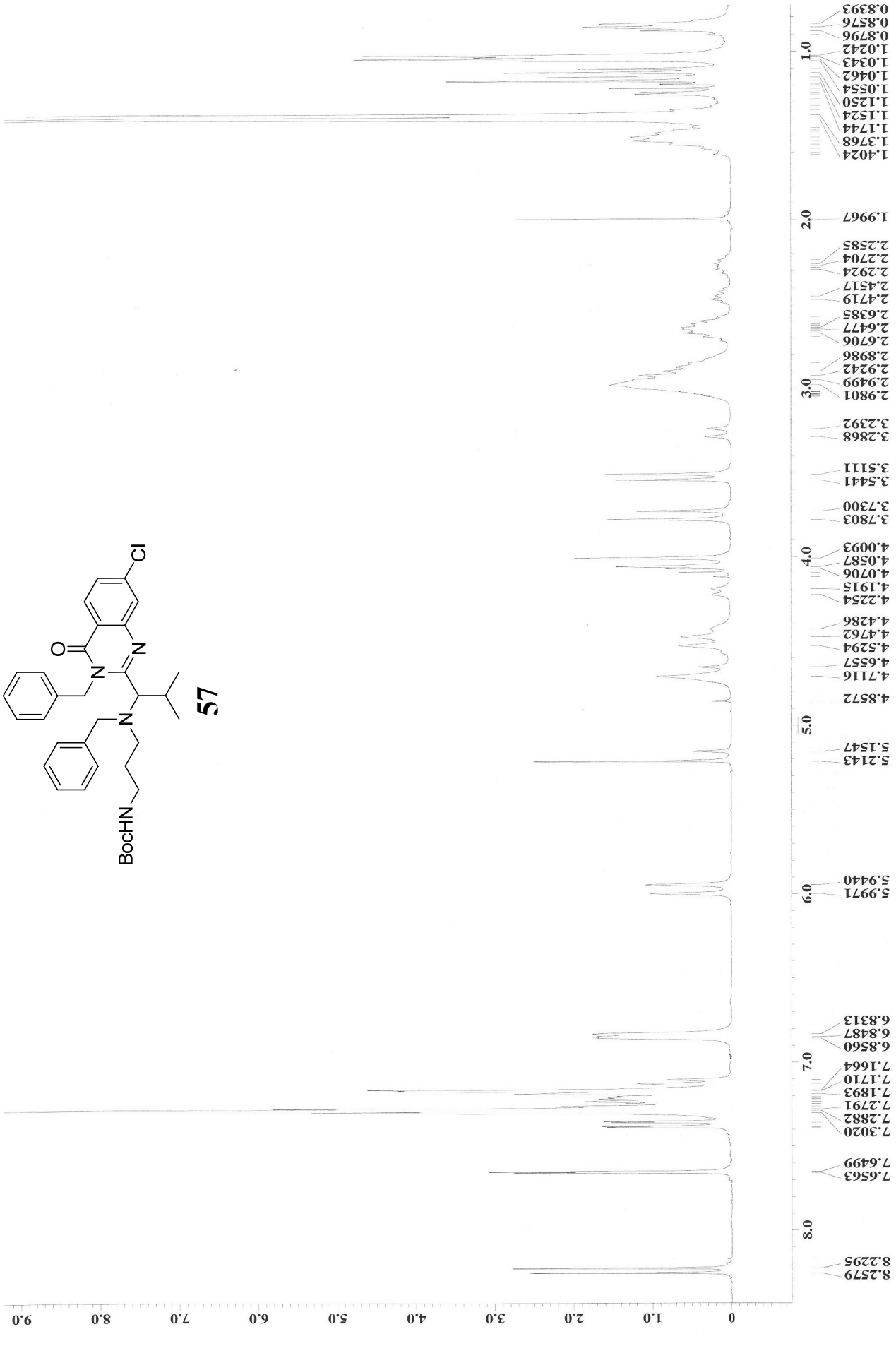

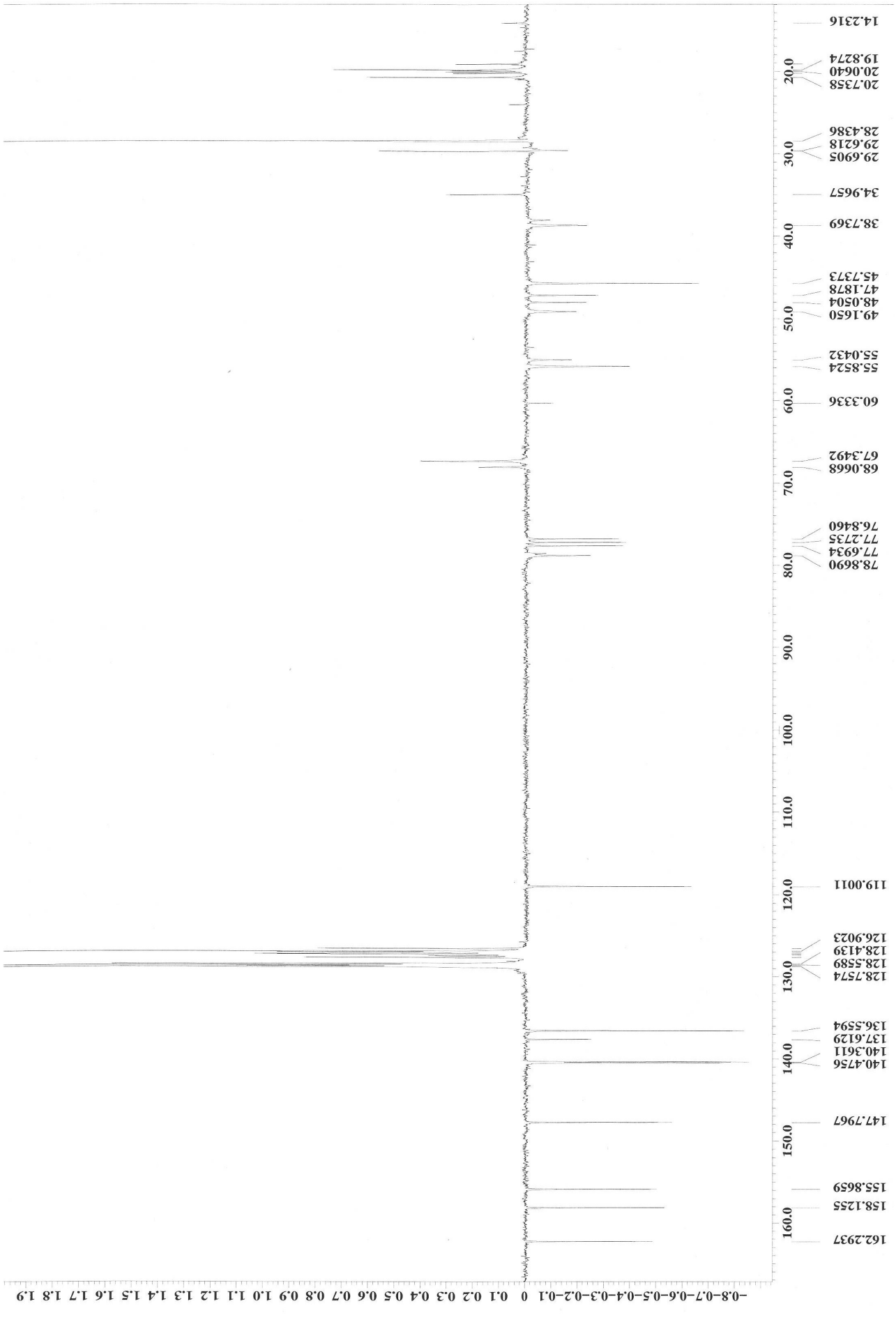

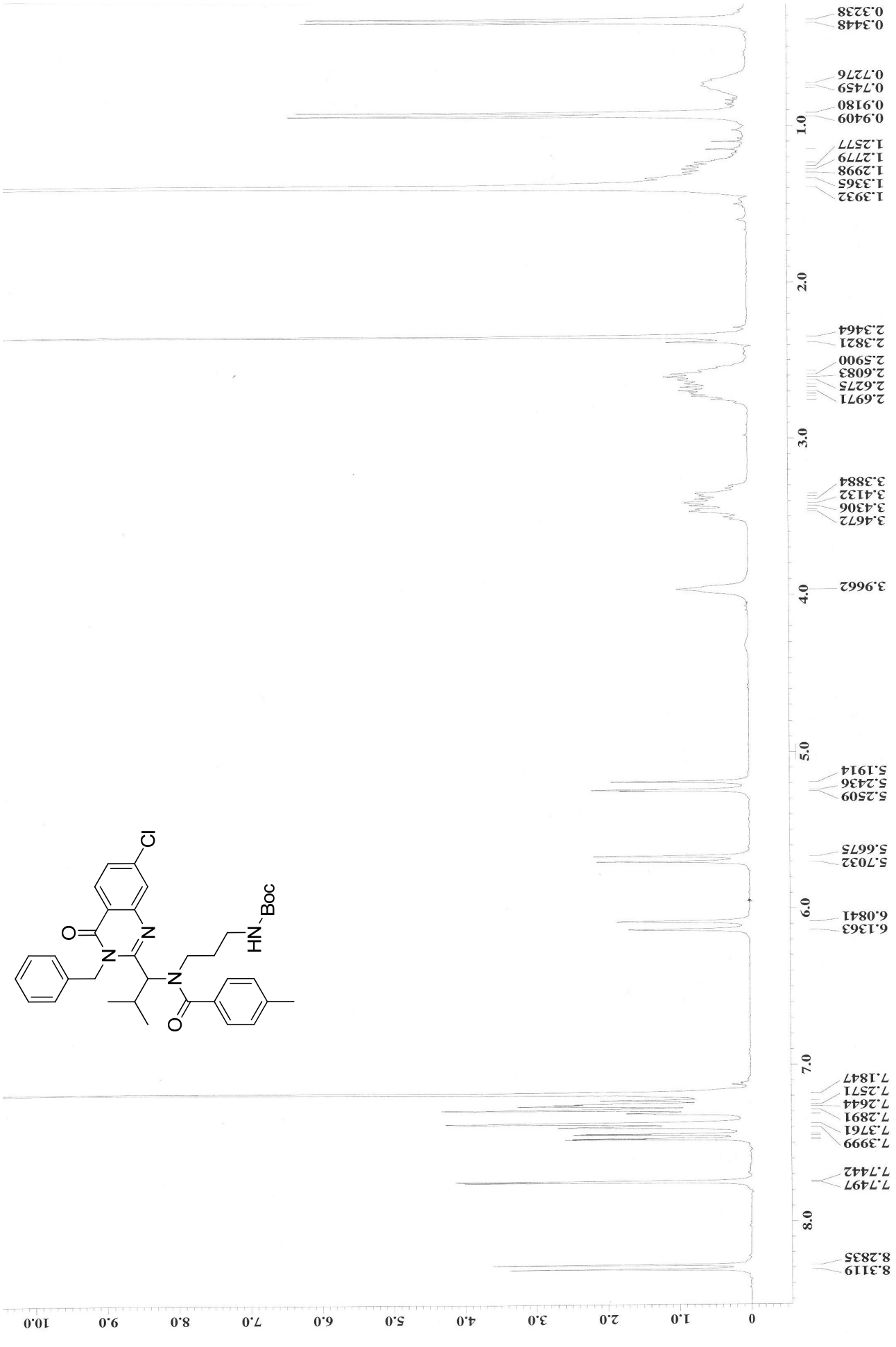
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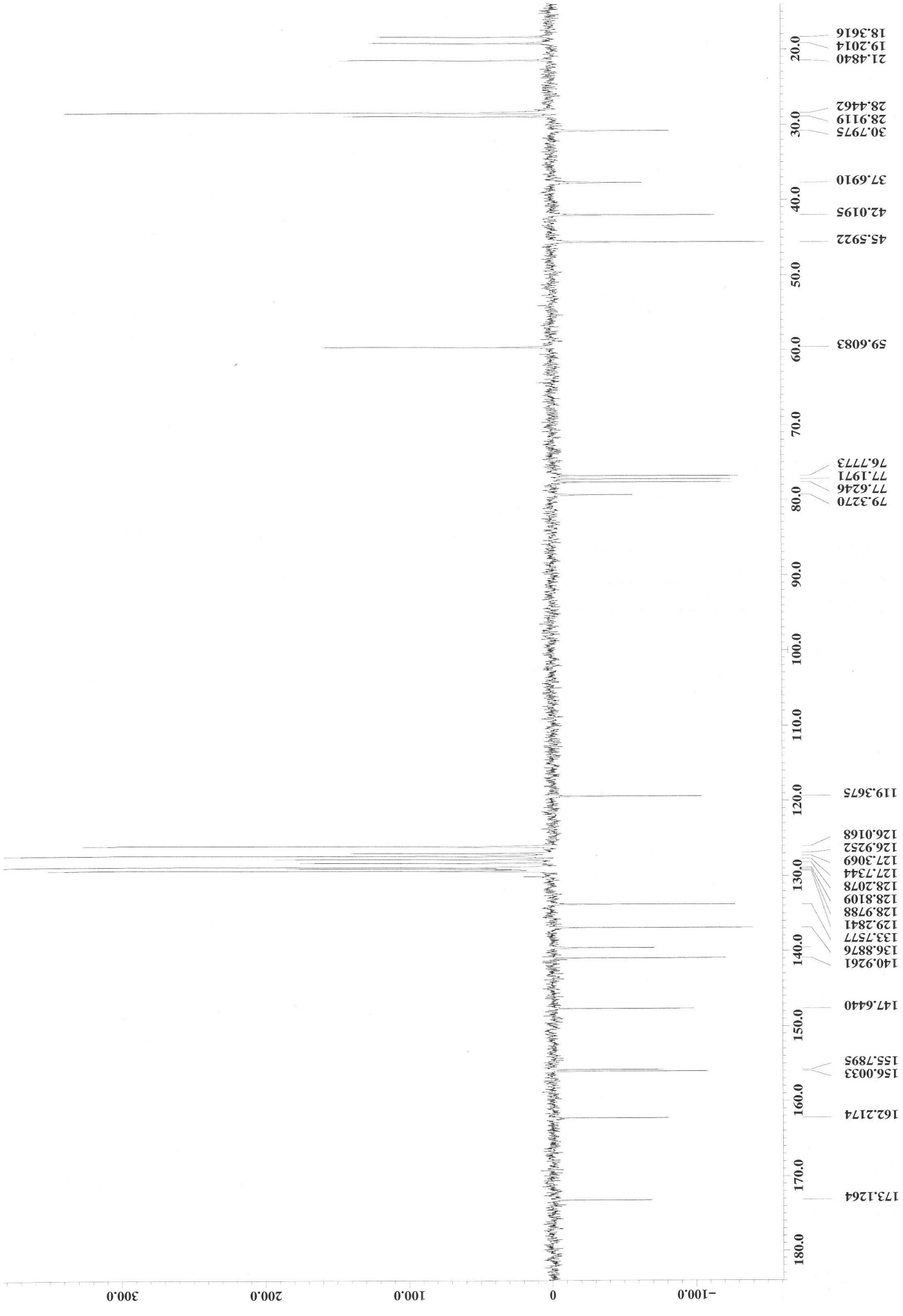


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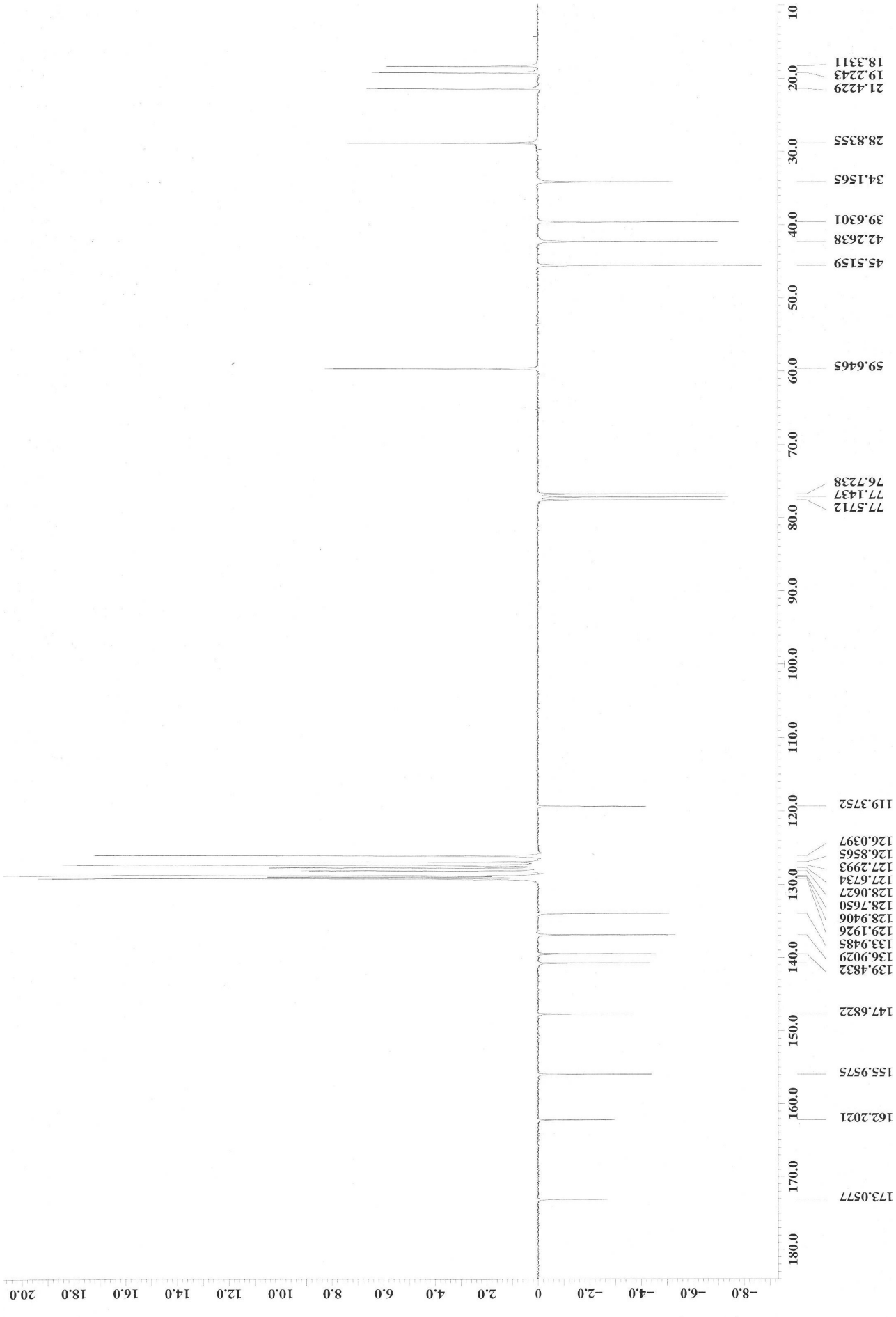

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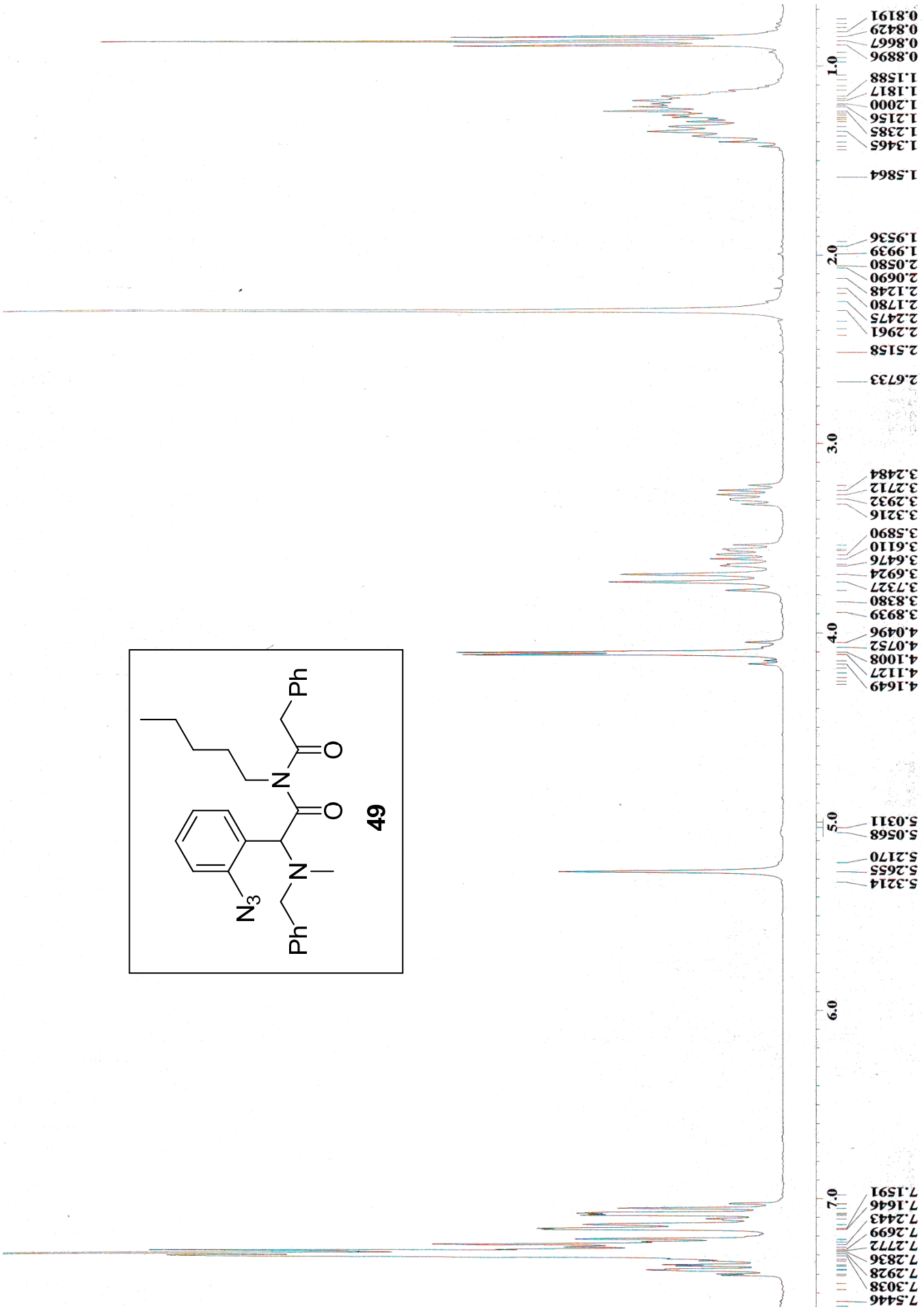

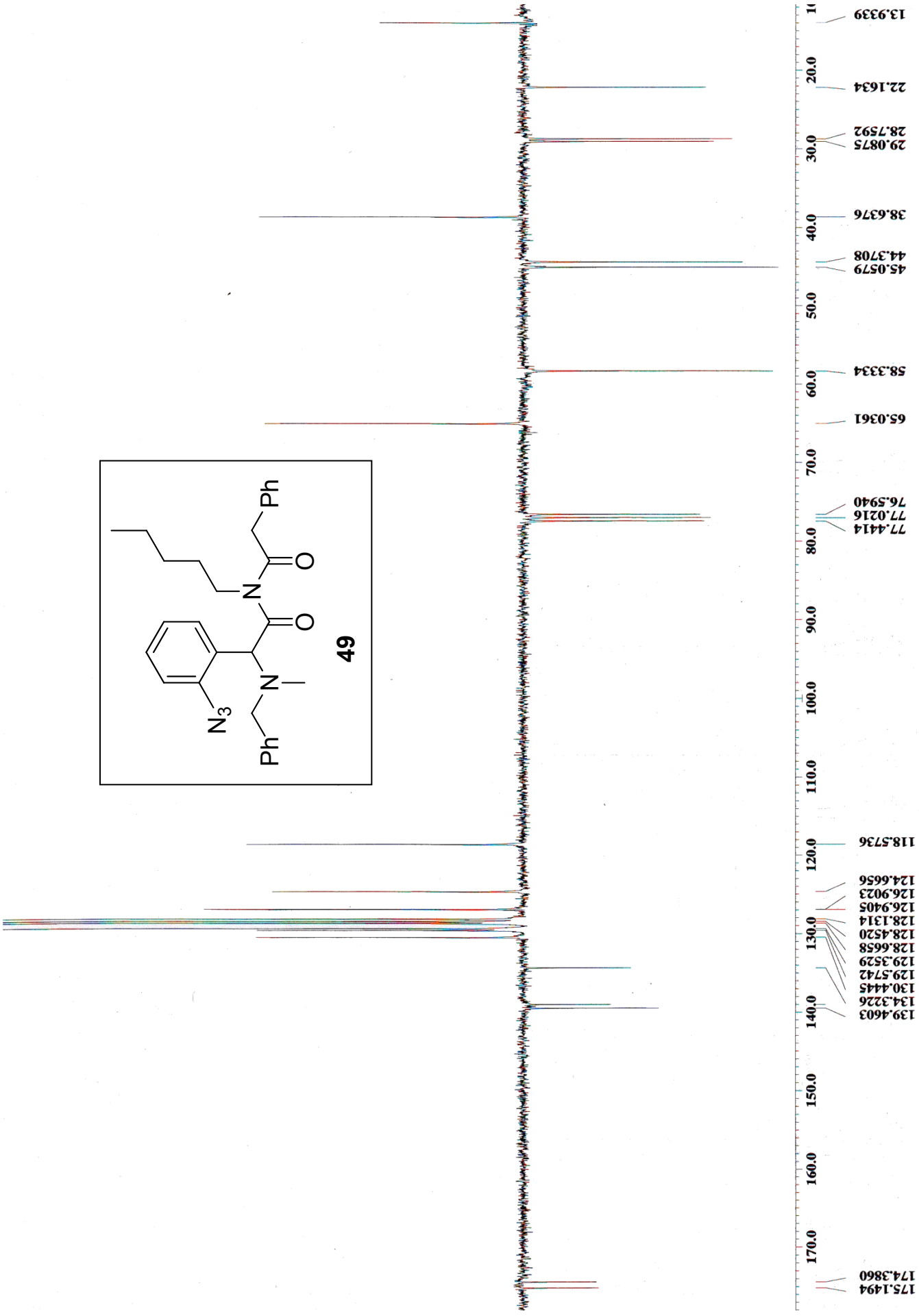

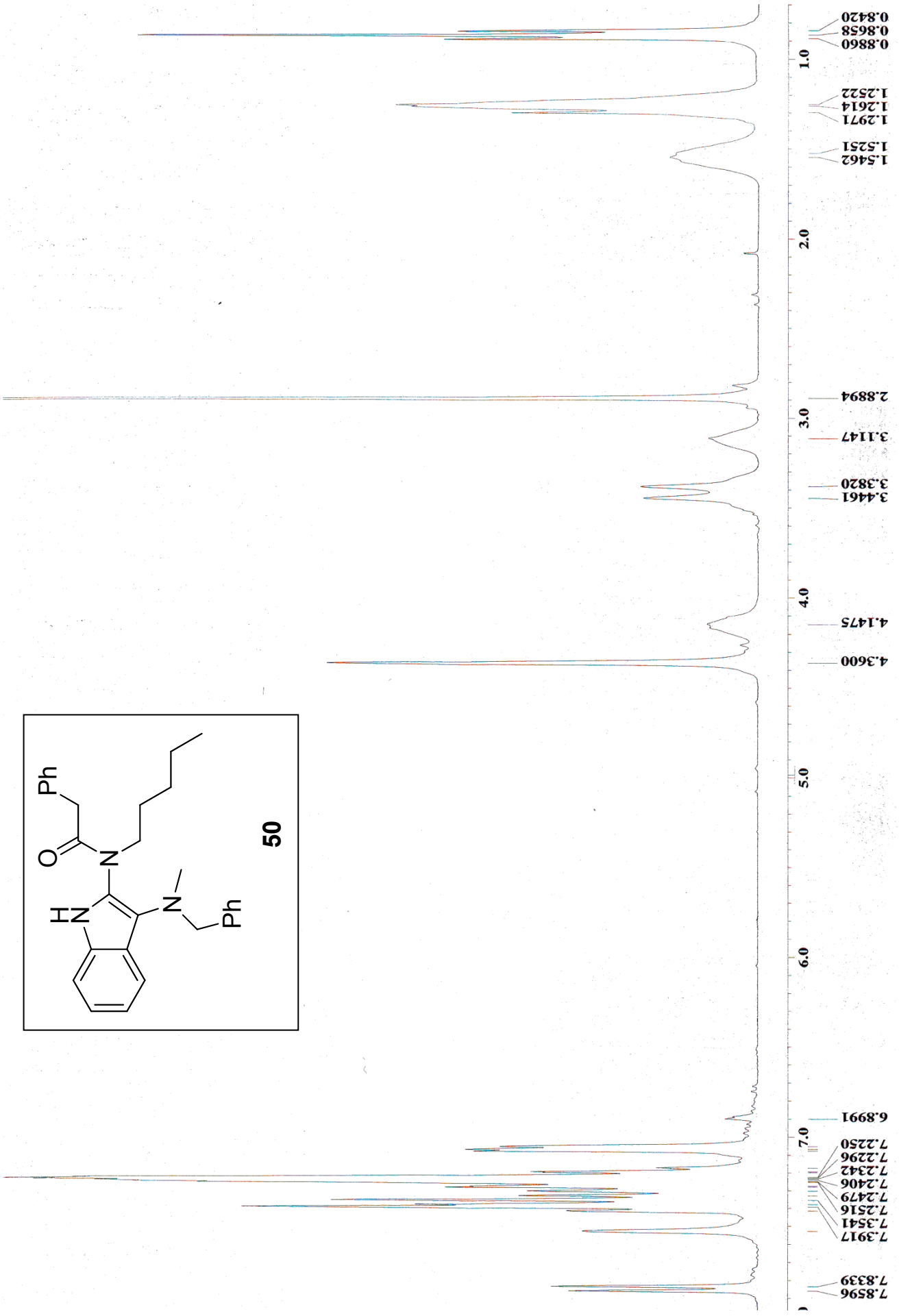

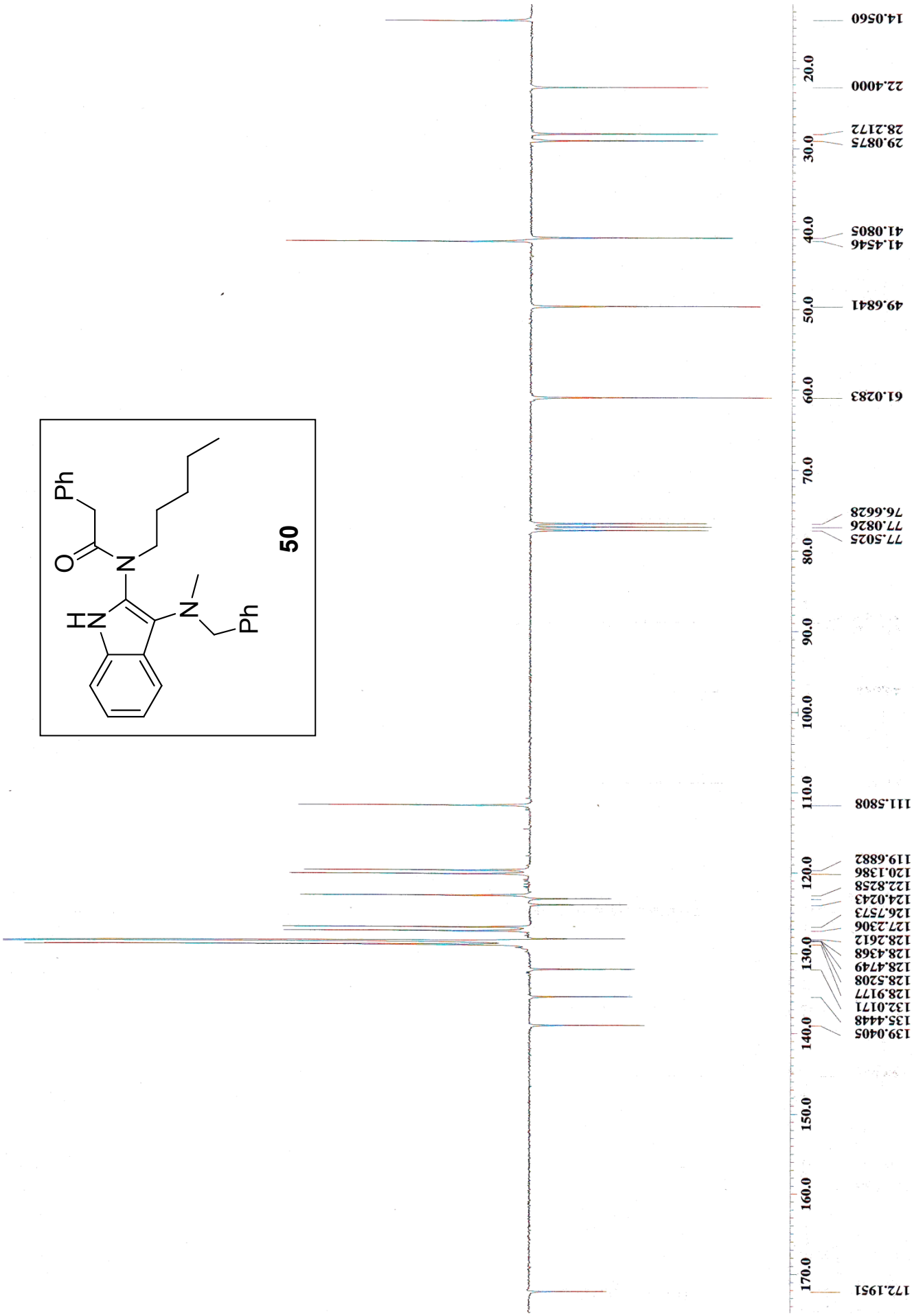

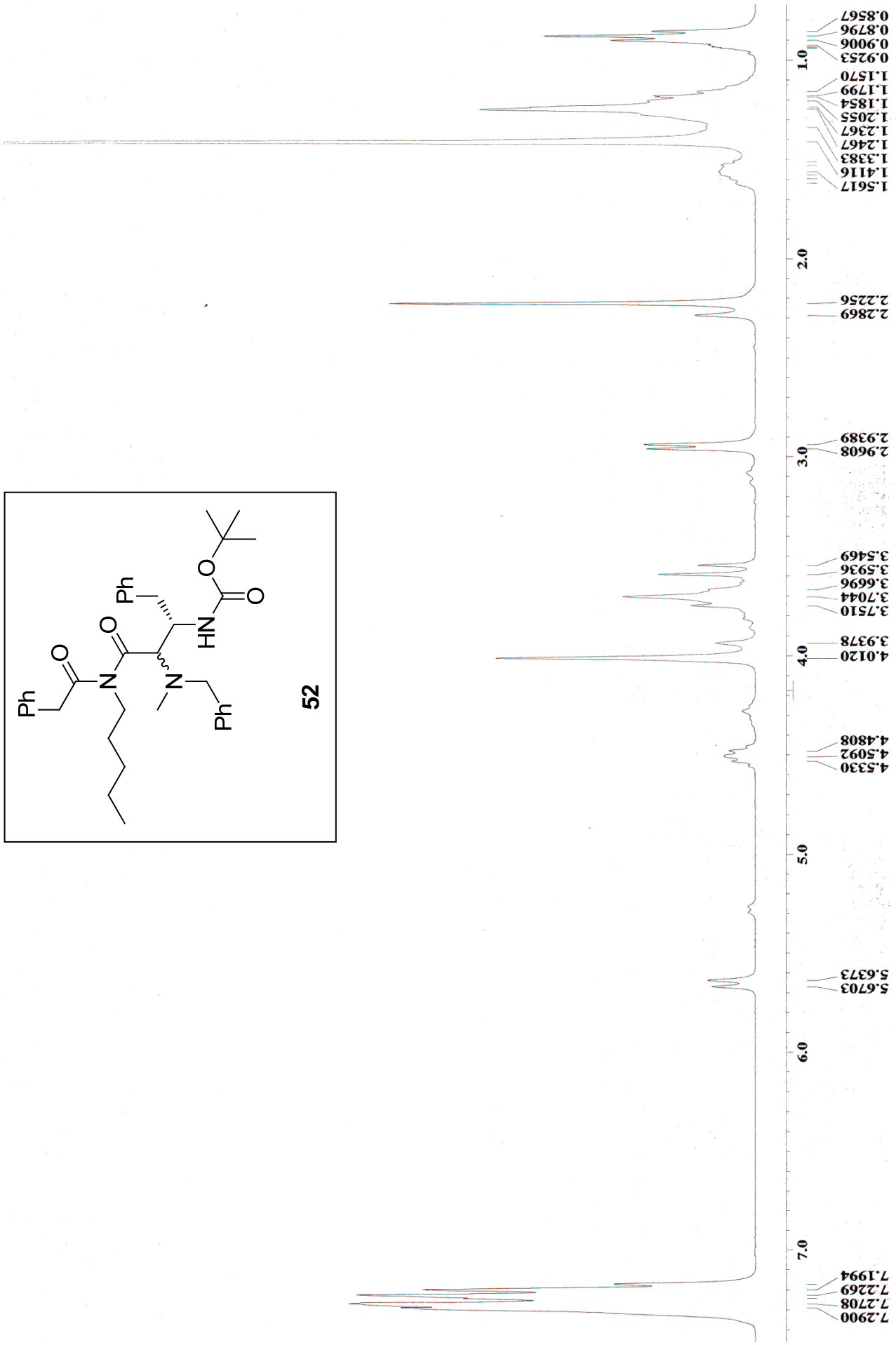

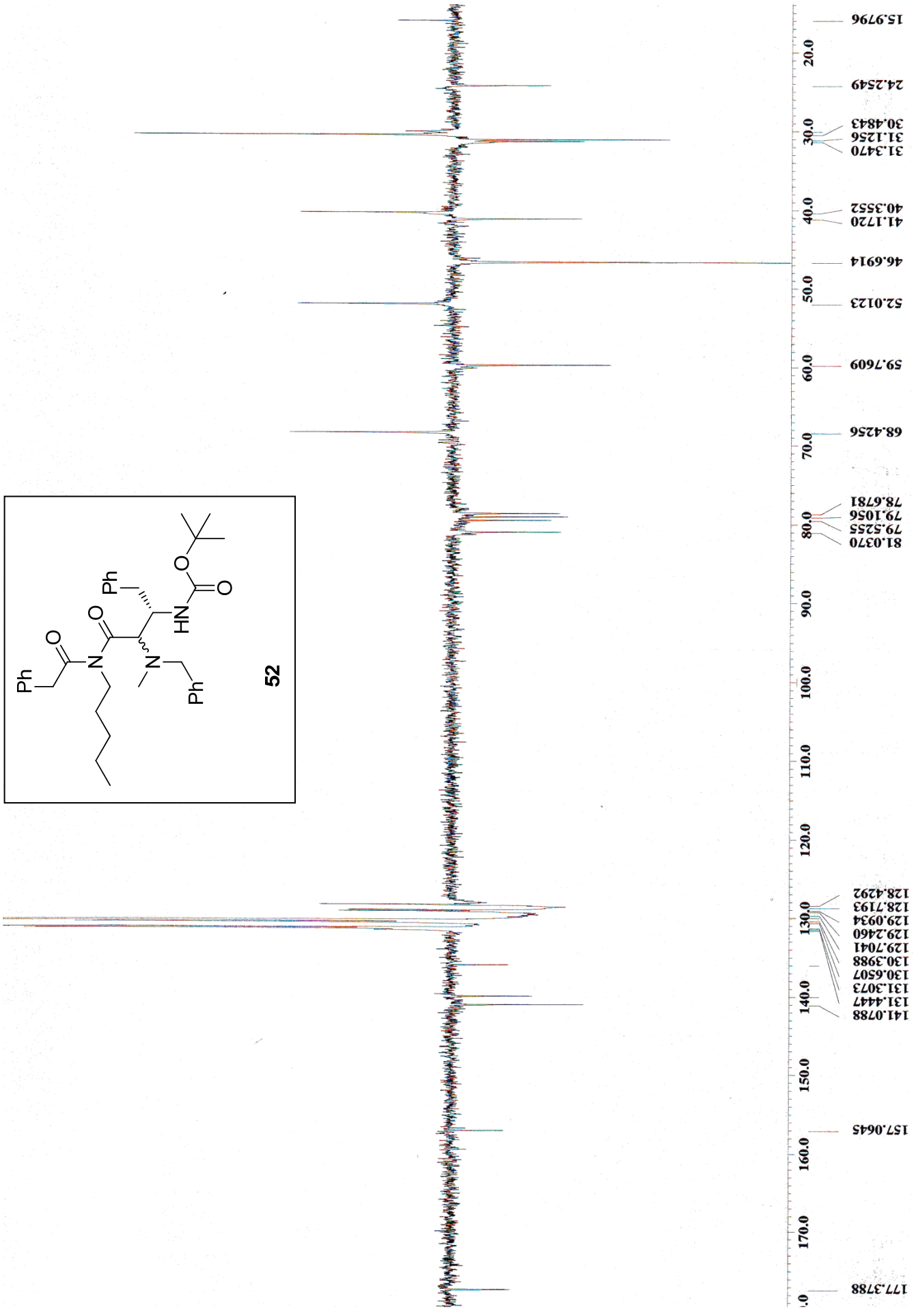

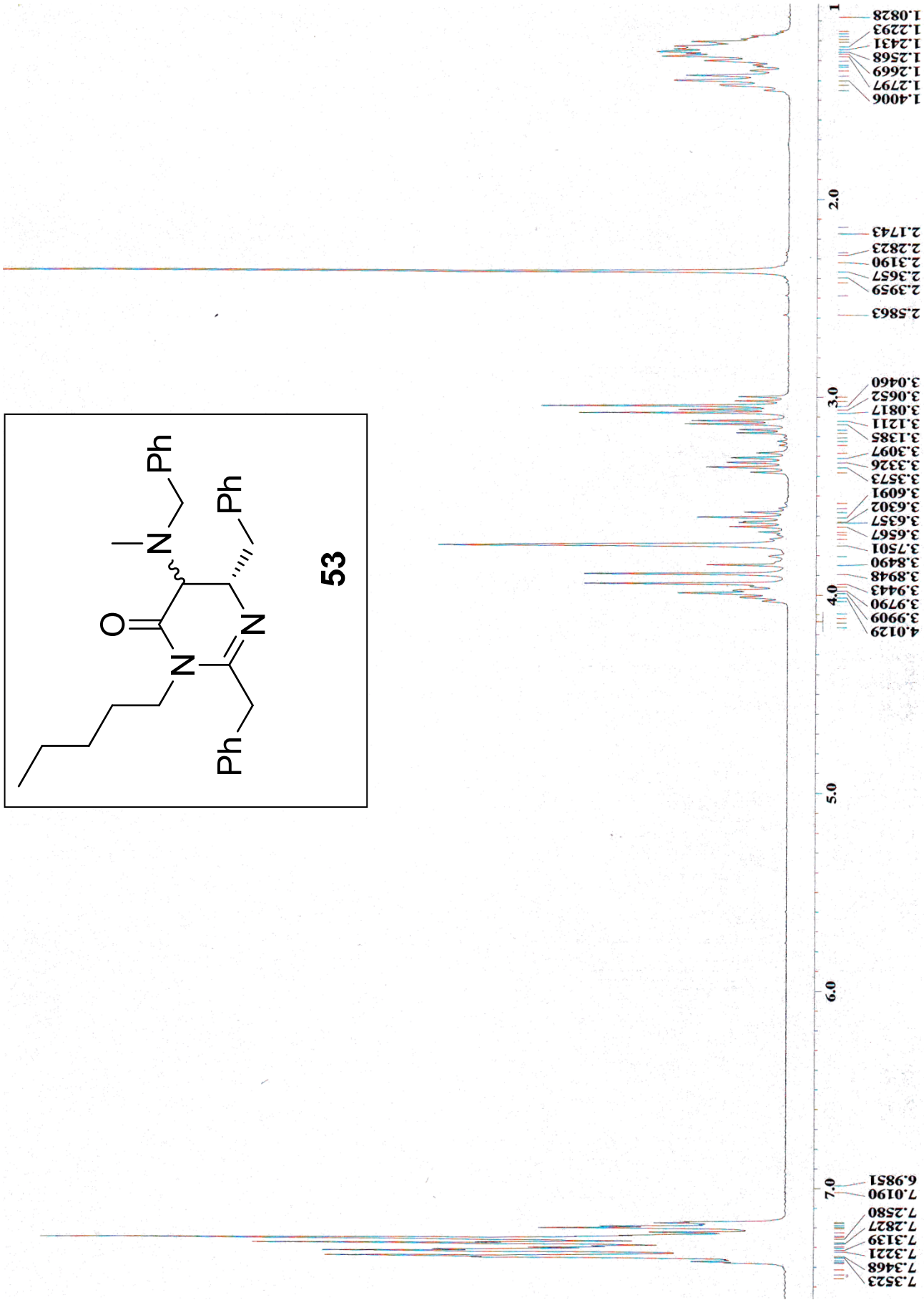

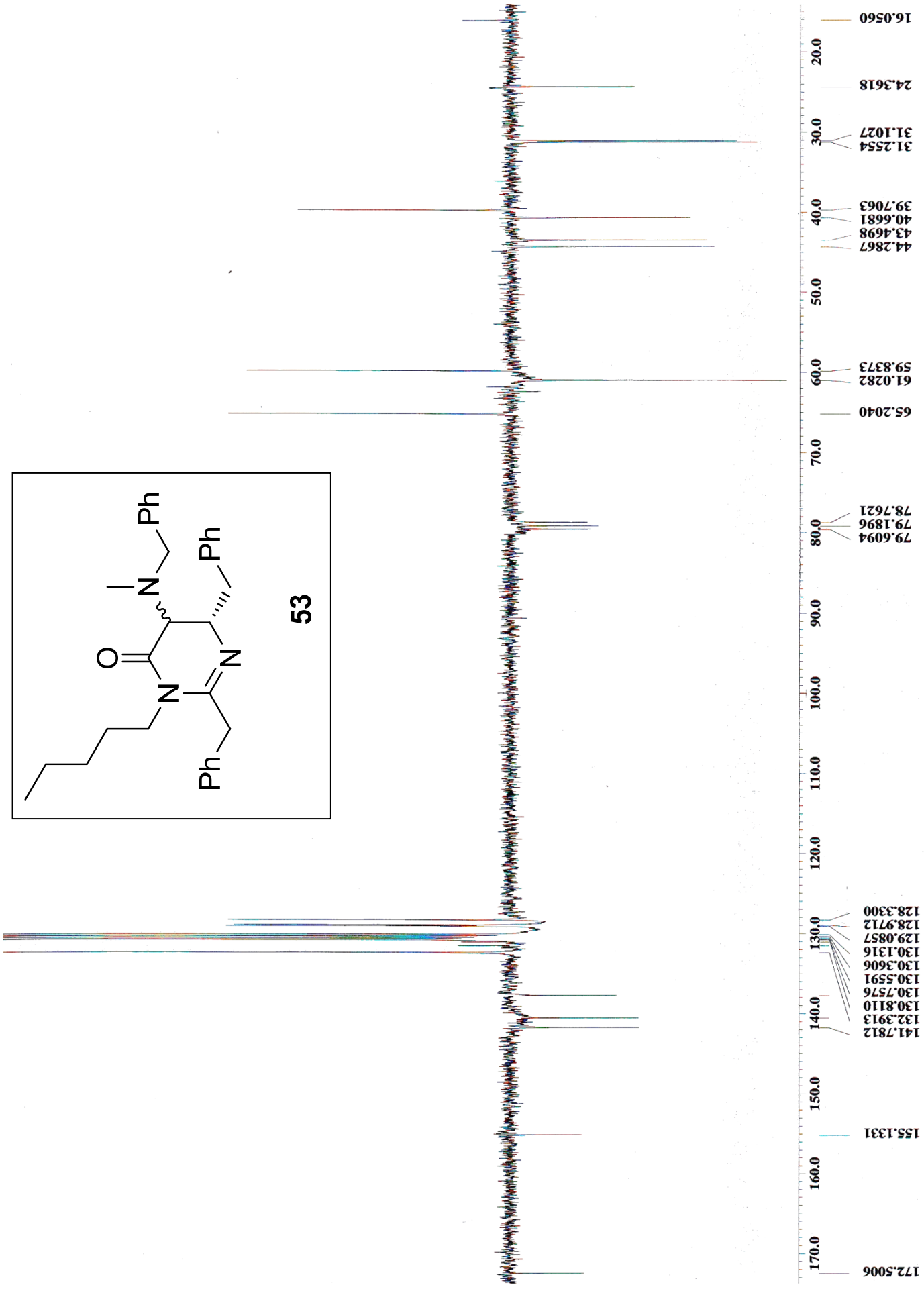

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