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β-Carbolines as intermediates in indirect heteroarylation of tryptamines exemplified by the synthesis of 2-pyrazolyltryptamines

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General Information

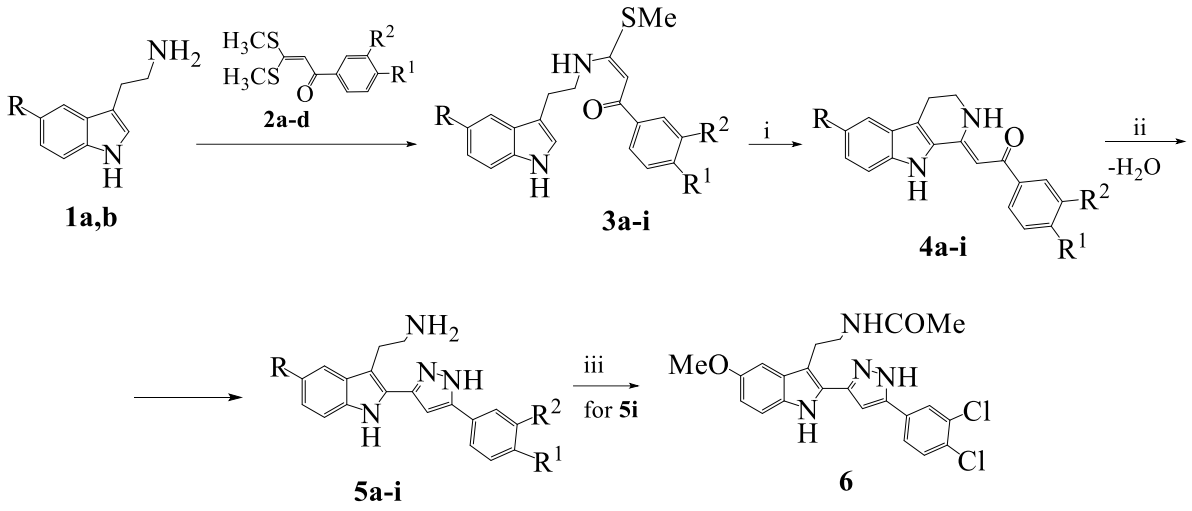
NMR spectra of new compounds were recorded on a spectrometer Bruker Avance 600 (600 MHz) in DMSO-d_6. Chemical shifts of nuclei ^{1}H and ^{13}C were measured relatively the residual signals of deuterated solvent (see δ values in ref. [S1]). Coupling constants (*J*) are reported in Hz. Melting points were determined by using Fisher-Johns Melting Point Apparatus (Fisher Scientific) and are uncorrected. Elemental analysis was performed using a EuroEA 3000 analyzer by burning a portion of the sample in an oxygen flow followed by chromatography of the combustion gases. High Resolution Mass Spectra were registered on a Bruker UHR-TOF MaxisTM Impact instrument. The reaction and purity of the obtained compounds were monitored by TLC (plates with Al_2O_3 III activity grade, eluent $CHCl_3$, development of TLC plates by exposition to iodine vapors in iodine chamber).

Quantum-chemical calculations were performed using quantum chemical program package Firefly 8.0 [S2], which is partially based on the GAMESS (US) [S3] source code at the DFT level of theory (B3LYP/6-311G**).

Tryptamines **1a**,**b** were provided by InterBioScreen Ltd, dithoacetals **2** [S3], carbolines **4a-c** [S4], **4d** [S5], **4g,i** [S6] were synthesized as described previously.

2. Synthesis and characterization of compounds 4-6.

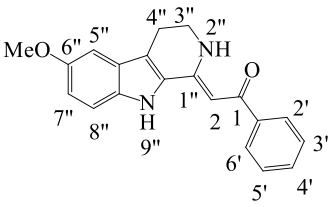
The general heteroarylation scheme:



1 R = H (**a**), OMe (**b**); **2** R^2 = H: R^1 = H (**a**), Cl (**b**), Br (**c**); R^1 = R^2 = Cl (**d**);
3, 4, 5 R = R^2 = H: R^1 = H (**a**), Cl (**b**), Br (**c**); R = H, R^1 = R^2 = Cl (**d**);
R = OMe, R^2 = H: R^1 = H (**e**), Me (**f**), Cl (**g**), Br (**h**); R^1 = R^2 = Cl (**i**)

General procedure for synthesis of 1-aroylmethylidene-1,2,3,4-tetrahydro-β-carbolines **4e,f,h.** A mixture of the corresponding N,S-acetal **3** [S7] (0.002 mol) and CF_3COOH (3 ml) was stirred for 3 h at 40-45 °C, kept for 24h at 20-25°C, and then excess CF_3COOH was distilled off in a vacuum at 30-35 °C. Then H_2O (15 ml) was added to the residue, neutralized with NH_4OH to pH 8-9, the product was extracted with $CHCl_3$ (2 × 5 ml), washed with water (2 × 4 ml), dried with Na_2SO_4, $CHCl_3$ was distilled off in a vacuum, and the residue was passed through a column with Al_2O_3, eluent - $CHCl_3$.

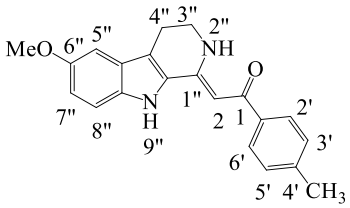
β-Carboline 4e.



Beige crystals, the yield 0.37 g (58%), m. p. 193-195°C (PrOH). ^{1}H NMR (600 MHz), δ, ppm: 2.96 (t, 2H, 2H$^{4"}$, *J* 7.2), 3.62 (td, 2H, 2H$^{3"}$, *J* 7.2, 2.8), 3.78 (s, 3H, OMe), 6.48 (s, 1H, H^2), 6.91 (dd, 1H, H$^{7"}$, *J* 8.8, 2.4), 7.08 (d, 1H, H$^{5"}$, *J* 2.4), 7.35 (d, 1H, H$^{8"}$, *J* 8.8), 7.46-7.51 (m, 3H, H$^{3'}$- H$^{5'}$), 7.85-8.09 (m, 2H, H$^{2', 6'}$), 10.55 (t, 1H, NH$^{2'}$, *J* 2.7), 11.57 (s,1H, NH$^{9'}$). ^{13}C NMR (150 MHz), δ, ppm: 19.84, 39.84, 55.29, 85.46, 100.33, 112.72, 115.24, 125.62, 126.63, 128.03,

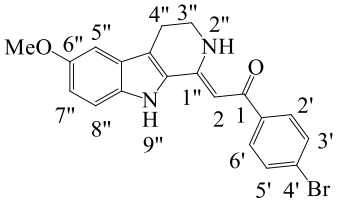
128.14, 130.59, 132.83, 140.19, 152.17, 153.68, 186.47. Found, %: C 75.29; H 5.43; N 8.54. $C_{20}H_{18}N_2O_2$. Calculated, %: C 75.45; H 5.70; N 8.80.

β-Carboline 4f.



Colorless crystals, the yield of **4h** 0.33 g (50%), m. p. 208-210°C (PrOH). ^{1}H NMR (600 MHz), δ, ppm: 2.36 (s, 3H, CMe), 2.95 (t, 2H, 2H$^{4"}$, *J* 7.2), 3.60 (td, 2H, 2H$^{3"}$, *J* 7.2, 2.8), 3.78 (s, 3H, OMe), 6.47 (s, 1H, H^2), 6.90 (dd, 1H, H$^{7"}$, *J* 8.8, 2.4), 7.07 (d, 1H, H$^{5"}$, *J* 2.4), 7.24-7.31 (m, 2H, H$^{3', 5'}$), 7.35 (d, 1H, H$^{8"}$, *J* 8.8), 7.86-7.91 (m, 2H, H$^{2', 6'}$), 10.50 (t, 1H, NH$^{2'}$, *J* 2.8), 11.55 (s,1H, NH$^{9'}$). ^{13}C NMR (150 MHz), δ, ppm: 19.87, 20.89, 39.83, 55.29, 85.33, 100.33, 112.68, 115.10, 115.28, 125.64, 126.72, 128.12, 128.70, 132.79, 137.51, 140.47, 151.94, 153.66, 1864.37. Found, %: C 75.62; H 6.00; N 8.19. $C_{21}H_{20}N_2O_2$. Calculated,%: C75.88; H 6.06; N 8.43.

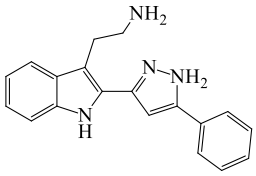
β-Carboline 4h.



Beige crystals, the yield of **4h** 0.47 g (59%), m. p. 123-125°C (PrOH). ^{1}H NMR (600 MHz), δ, ppm: 2.96 (t, 2H, 2H$^{4"}$, *J* 7.2), 3.62 (td, 2H, 2H$^{3"}$, *J* 7.2, 2.8), 3.78 (s, 3H, OMe), 6.46 (s, 1H, H^2), 6.91 (dd, 1H, H$^{7"}$, *J* 8.8, 2.4), 7.08 (d, 1H, H$^{5"}$, *J* 2.5), 7.35 (d, 1H, H$^{8"}$, *J* 8.9), 7.64-7.73 (m, 2H, H$^{3', 5'}$), 7.87-7.94 (m, 2H, H$^{2', 6'}$), 10.54 (t, 1H, NH$^{2'}$, *J* 2.8), 11.57 (s,1H, NH$^{9'}$). ^{13}C NMR (150 MHz), δ, ppm: 19.78, 39.87, 55.30, 85.19, 100.36, 112.75, 115.44, 115.53, 124.32, 125.57, 127.90, 128.68, 131.16, 132.89, 139.22, 152.50, 153.70, 184.85. Found, %: C 60.32; H 4.16; Br 20.36; N 7.02. $C_{20}H_{17}BrN_2O_2$. Calculated,%: C 60.47; H 4.31; Br 20.11; N 7.05.

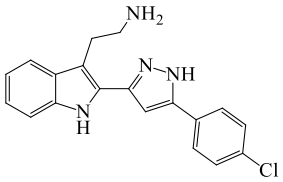
General procedure for synthesis of pyrazolyltryptamines **5**. A mixture of β-carboline **4** (0.002 mol), hydrazine hydrate (1 ml) in PrOH (6 ml) was refluxed for 6 h. Then water (15 ml) was added, and this was incubated for 12 h at 6-8°C, the precipitate of **5** was filtered off and washed with water (3×3 ml).

Pyrazolyltryptamine 5a



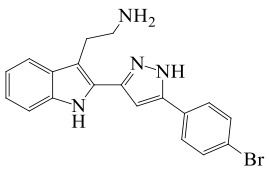
The starting compound was β-carboline **4a**. The yield of **5a** was 0.49 g (81%), m. p. 221-223°C (EtOAc). ^{1}H NMR (600 MHz), δ, ppm: 2.89 (t, *J* 6.9, 2H, CH_2), 3.05 (t, *J* 6.9, 2H, CH_2), 4.62-6.00 (m, 2H, NH_2), 7.00 (t, *J* 7.4, 1H, H-6'), 7.07 (s, 1H, H-5'), 7.10 (t, *J* 7.5, 1H, H-4''), 7.34-7.39 (m, 2H, H-7', H-4'''), 7.46-7.48 (m, 2H, H-3''', H-5'''), 7.56 (d, *J* 7.9, 1H, H-4'), 7.85 (d, 2H, H-2''', H-6'''), 11.16 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.51, 42.36, 100.26, 110.39, 111.07, 118.36, 118.53, 121.47, 125.10, 127.21, 127.76, 128.62, 128.79, 131.06, 135.88, 141.95, 146.22. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{19}N_4$ 303.1583; found: 303.1604.

Pyrazolyltryptamine 5b



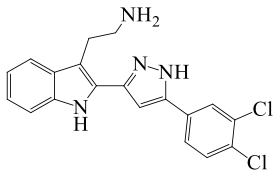
The starting compound was β-carboline **4b**. The yield of **5b** was 0.45 g (67%), m. p. 195-197°C (EtOH). ^{1}H NMR (600 MHz), δ, ppm: 2.89 (t, *J* 6.8, 2H, CH_2), 3.02 (t, *J* 6.8, 2H, CH_2), 3.84-4.64 (m, 2H, NH_2), 7.00 (t, *J* 7.4, 1H, H-5'), 7.07 (s, 1H, H-6'), 7.08-7.13 (m, 1H, H-4''), 7.38 (d, *J* 8.0, 1H, H-7'), 7.52 (d, *J* 8.5, 2H, H-3''', H-5'''), 7.56 (d, *J* 7.9, 1H, H-4'), 7.88 (d, *J* 8.5, 2H, H-2''', H-6'''), 11.20 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.26, 42.17, 100.48, 110.55, 111.10, 118.39, 118.60, 121.61, 126.73, 126.77, 128.50, 128.79, 130.43, 132.16, 135.92, 141.06, 145.96. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{18}ClN_4$ 337.1197; found: 337.1215.

Pyrazolyltryptamine 5c



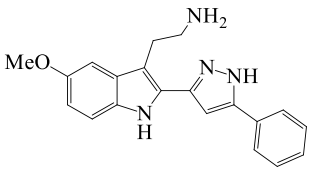
The starting compound was β-carboline **4c.** The yield 0.53 g (70%), m. p. 198-200°C (EtOAc). ^{1}H NMR (600 MHz), δ, ppm: 2.89 (t, *J* 6.8, 2H, CH_2), 3.02 (t, *J* 6.8, 2H, CH_2), 5.35-6.32 (m, 2H, NH_2), 7.00 (t, *J* 7.4, 1H, H-4''), 7.07 (s, 1H, H-5'), 7.10 (t, *J* 7.5, 1H, H-6'), 7.38 (d, *J* 8.0, 1H, H-7'), 7.56 (d, *J* 7.9, 1H, H-4'), 7.66 (d, *J* 8.3, 2H, H-3''' H-5'''), 7.81 (d, *J* 8.3, 2H, H-2''', H-6'''), 11.18 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.30, 42.18, 100.48, 110.59, 111.10, 118.40, 118.60, 120.68, 121.61, 126.71, 127.07, 128.51, 130.82, 131.69, 135.93, 141.09, 146.04. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{18}BrN_4$ 381.0707; found: 381.0709.

Pyrazolyltryptamine 5d



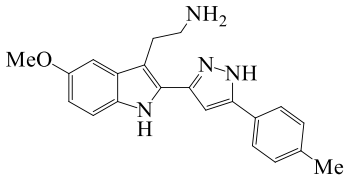
The starting compound was β-carboline **4d**. The yield 0.64 g (86%), m. p. 200-202°C (EtOAc). ^{1}H NMR (600 MHz), δ, ppm: 2.89 (t, *J* 6.6, 2H, CH_2), 3.00 (t, *J* 6.7, 2H, CH_2), 5.61-6.34 (m, 2H, NH_2), 7.00 (t, *J* 7.4, 1H, H-5'), 7.08-7.13 (m, 1H, H-6'), 7.14 (s, 1H, H-4''), 7.38 (d, *J* 8.1, 1H, H-7'), 7.56 (d, *J* 7.9, 1H, H-4'), 7.71 (d, 1H, *J* 8.3, H-5'''), 7.85 (dd, *J* 8.4, 2.0, 1H, H-6'''), 8.11 (d, *J* 2.0, 1H, H-2'''), 11.19 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.13, 42.06, 100.95, 110.77, 111.14, 118.43, 118.66, 121.72, 125,15, 126.33, 126.63, 128.41, 129.87, 130.97, 131.60, 132.60, 135.97, 140.51, 145.47. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{17}Cl_2N_4$ 371.0826; found: 371.0825..

Pyrazolyltryptamine 5e



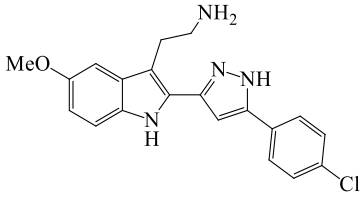
The starting compound was β-carboline **4e**. The yield 0.46 g (69%), m. p. 226-227°C (EtOAc). ^{1}H NMR (600 MHz), δ, ppm: 2.88 (t, *J* 6.9, 2H, CH_2), 3.02 (t, *J* 6.9, 2H, CH_2), 3.78 (s, 3H, OMe), 4.91-6.14 (m, 2H, NH_2), 6.75 (dd, *J* 8,7, 2.4, 1H, H-6'), 7.01-7.07 (m, 2H, H-4'', H-4'), 7.27 (d, *J* 8.6, H-7'), 7.35 (t, *J* 7.4, H-4'''), 7.45-7.48 (m, 2H, H-3''', H-5'''), 7.82-7.88 (m, 2H, H-2''', H-6'''), 11.00 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.51, 42.22, 55.36, 100.11, 100.30, 110.24, 111.63, 111.74, 125.08, 127.73, 127.83, 128.77, 128.96, 131.04, 131.14, 141.85, 146.27, 153.23. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{21}N_4O$ 333.1701; found: 333.1710.

Pyrazolyltryptamine 5f



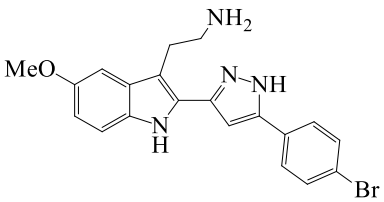
The starting compound was β-carboline **4f**. The yield 0.36 g (52%), m. p. 199-201°C (EtOAc). ^{1}H NMR (600 MHz), δ, ppm: 2.34 (s, 3H, Me), 2.87 (t, *J* 7.0, 2H, CH_2), 3.01 (t, *J* 6.9, 2H, CH_2), 3.78 (s, 3H, OMe), 4.70-6.19 (m, 2H, NH_2), 6.74 (dd, *J* 8,7, 2.4, 1H, H-6'), 6.98 (s, 1H, H-4''), 7.04 (d, *J* 2.4, 1H, H-4'), 7.25-7.28 (m, 3H, H-7', H-3''', H-5'''), 7.73 (d, *J* 7,8, 2H, H-2''', H-6'''), 10.96 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 20.72, 28.59, 42.28, 55.36, 99.79, 100.30, 110.15, 111.55, 111.71, 125.01, 128.03, 128.20, 128.99, 129.33, 131.01, 137.11, 142.13, 145.94, 153.20.-HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{23}N_4O$ 347.1852; found: 347.1866 .

Pyrazolyltryptamine 5g



The starting compound was β-carboline **4g**. The yield 0.62 g (84%), m. p. 219-220°C (EtOAc). ^{1}H NMR (600 MHz), δ, ppm: 2.88 (t, *J* 6.8, 2H, CH_2), 2.99 (t, *J* 6.8, 2H, CH_2), 3.78 (s, 3H, OMe), 5.22-6.15 (m, 2H, NH_2), 6.76 (dd, *J* 8.7, 2.4, 1H, H-6'), 7.02-7.06 (m, 2H, H-4'', H-4'), 7.27 (d, *J* 8.7, 1H, H-7'), 7.52 (d, *J* 8.3, 2H, H-3''', H-5'''), 7.87 (d, *J* 8.2, 2H, H-2''', H-6'''), 11.02 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.31, 42.05, 55.36, 100.30, 100.33, 110.42, 111.79, 126.76, 127.33, 128.77, 128.85, 130.53, 131.09, 132.12, 141.02, 146.03, 153.26. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{20}ClN_4O$ 367.1321; found: 367.1320.

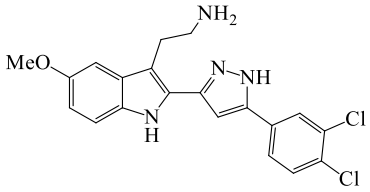
Pyrazolyltryptamine 5h



The starting compound was β-carboline **4h**. The yield 0.62 g (75%), m. p. 220-222°C (MeOH). ^{1}H NMR (600 MHz), δ, ppm: 2.88 (t, *J* 6.8, 2H, CH_2), 2.98 (t, *J* 6.8, 2H, CH_2), 3.78 (s,

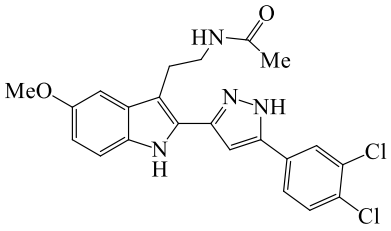
3H, OMe), 5.23-6.21 (m, 2H, NH_2), 6.75 (dd, *J* 8.7, 2.4, 1H, H-6'), 7.03-7.05 (m, 2H, H-4'', H-4'), 7.26 (d, *J* 8.7, 1H, H-7'), 7.62-7.68 (m, 2H, H-3''', H-5'''), 7.78-7.84 (m, 2H, H-2''', H-6'''), 11.00 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.31, 42.04, 55.37, 100.30, 100.32, 110.44, 111.78, 111.80, 120.64, 127.05, 127.30, 128.85, 130.90, 131.09, 131.68, 141.02, 146.11, 153.26. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{20}BrN_4O$ 411.0814; found: 411.0815.

Pyrazolyltryptamine 5i



The starting compound was β-carboline **4i**. The yield 0.59 g (73%), m. p. 206-208°C (EtOH). ^{1}H NMR (600 MHz), δ, ppm: 2.88 (t, *J* 6.6, 2H, CH_2), 2.97 (t, *J* 6.7, 2H, CH_2), 3.78 (s, 3H, OMe), 4.91-6.20 (m, 2H, NH_2), 6.76 (dd, *J* 8.7, 2.4, 1H, H-6'), 7.04 (d, *J* 2.4, 1H, H-4'), 7.11 (s, 1H, H-4''), 7.27 (d, *J* 8.7, 1H, H-7'), 7.71 (d, *J* 8.4, 1H, H-5'''), 7.82-7.87 (m, 1H, H-6'''), 8.10 (d, *J* 2.0, 1H, H-2'''), 11.01 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 28.16, 41.93, 55.36, 100.30, 100.78, 110.62, 111.84, 111.93, 125,14, 126.61, 126.92, 128.76, 128.84, 129.83, 130.96, 131.14, 131.58, 132.69, 140.48, 145.56, 153.29. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{19}Cl_2N_4O$ 401.0928; found: 401.0930.

Pyrazolylmelatonin 6

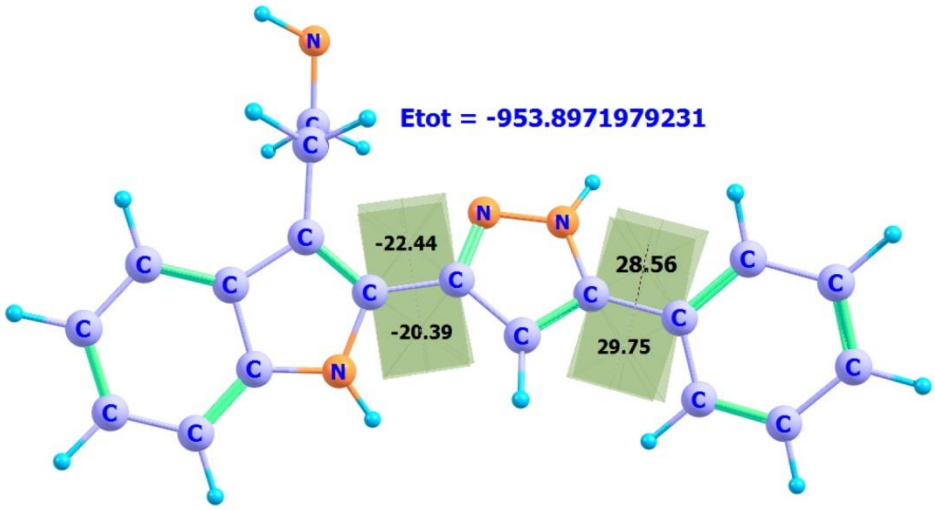


A mixture of pyrazolyltryptamine **5i** (0.80 g, 0.002 mol), acetic anhydride (3 ml) was kept for 10 min at 50-60°C, cooled, water (15 ml) was added, and after decomposition of excess acetic anhydride, NH_4OH solution was added to pH 9. After 24 h (at room temperature), the precipitate formed was filtered off and washed with water (4×4 mL). The yield 0.71 g (78%), m. p. 192-194°C (MeOH). ^{1}H NMR (600 MHz), δ, ppm: 1.82 (s, 3H, Me), 3.09 (s, 2H, CH_2), 3.29 (s, 2H, CH_2), 3.78 (s, 3H, OMe), 6.76 (s, 1H, H-4''), 7.00-7.12 (m, 1H, H-6'), 7.28 (d, *J* 8.8, 1H, H-4'), 7.33-7.46 (m, 1H, H-7'), 7.66-7.82 (m,1H, 1H, H-5'''), 7.86 (s, 1H, H-6'''), 8.15 (s, 1H, H-2'''), 11.01 (s, 1H, NH-1'). ^{13}C NMR (150 MHz), δ, ppm: 22.63, 24.62, 39.55, 55.30, 100.08, 101.51, 109.23. 111.90, 125.10, 126.67, 128.93, 129.72, 130.37, 130.96, 131.79, 134.18, 136.82,

140.72, 145.75, 148.80, 153.31, 169.34. Found (%): C 59.51; H 4.46; Cl 16.04; N 12.56. Calc. for $C_{22}H_{20}Cl_2N_4O$ (%): C 59.60; H 4.55; Cl 15.99; N 12.64.

3. Quantum chemical data (B3LYP/6-311G**) for pyrazolyltryptamine 5a

3-Indolyl-5-phenyl tautomer, conformer 1:



Cartesian coordinates (Å):

41
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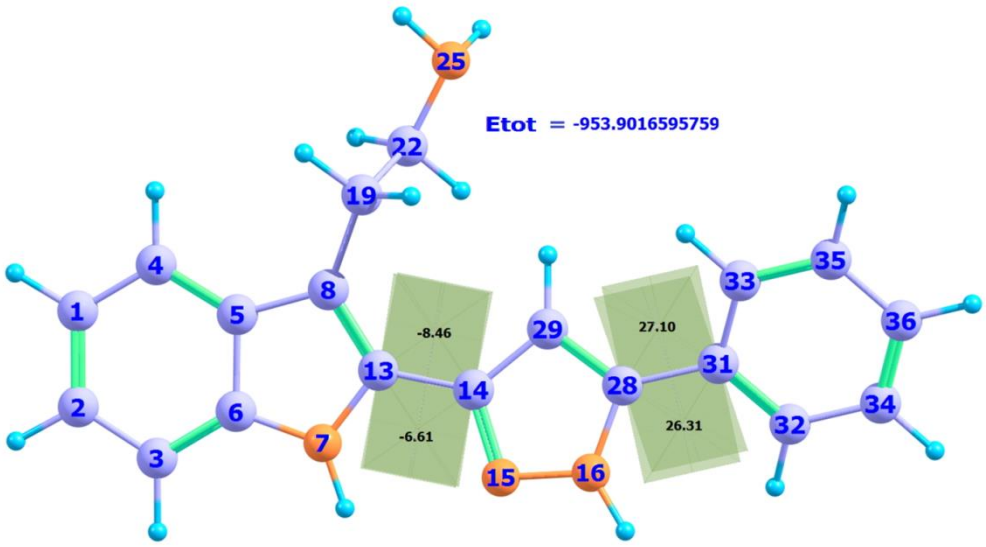
C	-3.687992532	-0.662820587	-0.187571044
C	-2.325411695	-0.429646549	-0.447490809
C	-1.624468464	-1.341126822	-1.284380218
N	-0.320155639	-0.906158456	-1.352314298
C	-1.394034741	0.586709274	-0.029947056
H	-5.360661597	-1.950274140	-0.571366437
H	-4.106734558	-3.497017588	-2.039825568
H	-1.693514762	-3.132405253	-2.510099210
H	-4.249107474	0.011837747	0.453017873
C	-0.181606744	0.269578513	-0.617098577
C	1.118374570	0.917677069	-0.536488216
N	1.234409082	2.210381478	-0.195823923
N	2.562213914	2.438425608	-0.191003233
H	2.890527337	3.378860204	-0.035938926
H	0.376905981	-1.261468567	-1.985906293
C	-1.699499738	1.747060102	0.873002527
H	-0.818215476	2.022301249	1.458943080
H	-2.481029635	1.447747902	1.585608740
C	-2.170472896	3.001337917	0.117475802
H	-1.345917171	3.348298630	-0.513300441
H	-3.000512770	2.725445397	-0.556792885
N	-2.500536413	4.071803640	1.067027890
H	-3.340393000	3.819023717	1.585185617
H	-2.734462853	4.921077137	0.557800298
C	3.312237170	1.353894116	-0.544765657
C	2.394539141	0.339498076	-0.774843549
H	2.624213219	-0.691341526	-0.999416747
C	4.776726147	1.382804466	-0.605892816
C	5.522431394	2.248709277	0.212405936
C	5.464510729	0.535758952	-1.490832252
C	6.913639663	2.274073935	0.137756040
C	6.855414353	0.555141783	-1.554724749
C	7.586012608	1.427103176	-0.744539109
H	5.014328936	2.883629929	0.932992031
H	4.899716422	-0.124647216	-2.141373438
H	7.473323414	2.947801725	0.779716528
H	7.370244761	-0.105351754	-2.246119330
H	8.670205260	1.444296898	-0.798743735

3-Indolyl-5-phenyl tautomer, conformer 2:

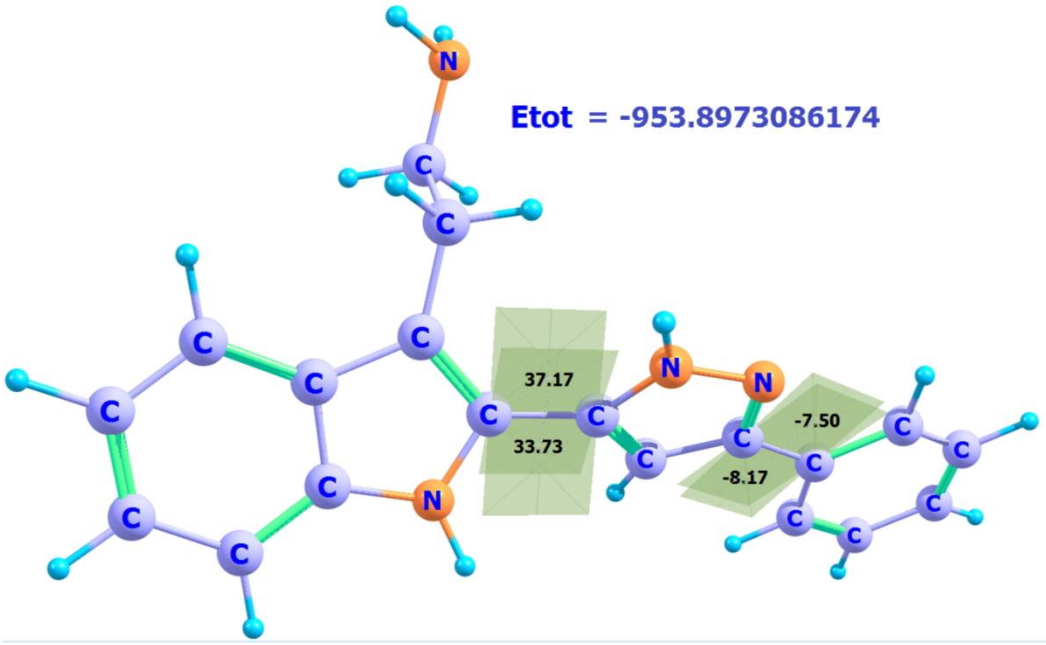


Cartesian coordinates (Å):

41
symmetry c1

C	-4.378259778	-1.684192478	-0.913273738
C	-4.709368834	-0.558025638	-0.131263027
C	-3.739844030	0.358289772	0.259202400
C	-3.070348494	-1.915955565	-1.318201802
C	-2.064361650	-1.008558235	-0.939510962
C	-2.423417655	0.121809535	-0.150779225
N	-1.273664219	0.837133325	0.075896288
C	-0.647740046	-0.934057909	-1.182571638
H	-5.161553622	-2.379399672	-1.200760014
H	-5.741003426	-0.403210972	0.170749456
H	-3.995294022	1.226126558	0.860462709
H	-2.828348764	-2.788072486	-1.919671135
C	-0.201114435	0.209401323	-0.539562332
C	1.115652836	0.818764550	-0.430605234
N	1.220554028	2.029333318	0.143399398
N	2.539903187	2.300402943	0.123458364
H	2.854959695	3.207607513	0.428782670
H	-1.177224923	1.703163897	0.582387238
C	0.173846899	-1.913765444	-1.969370995
H	0.960596610	-1.397856991	-2.530413555
H	-0.463225107	-2.397298581	-2.722042276
C	0.836552436	-3.001328406	-1.105930679
H	1.399035477	-2.521430325	-0.296939925
H	0.046861562	-3.601152262	-0.621629947
N	1.785951757	-3.780094891	-1.910668363
H	1.282349155	-4.287691758	-2.636247327
H	2.228270985	-4.490022080	-1.331211134
C	3.291950060	1.321486908	-0.460495871
C	2.389345781	0.333771972	-0.827782682
H	2.630914482	-0.618926165	-1.271235033
C	4.749105697	1.407713193	-0.596027681
C	5.521685228	2.174323775	0.293225938
C	5.402467116	0.714590962	-1.629024464
C	6.904862042	2.255121665	0.145175760
C	6.786099404	0.787979544	-1.766886345
C	7.542980280	1.561821315	-0.884371088
H	5.043624252	2.685677379	1.124301895
H	4.816668758	0.131215202	-2.332268907
H	7.485726121	2.850422170	0.843420594
H	7.274052169	0.246343543	-2.571743454
H	8.621269622	1.621481353	-0.996420532

5-Indolyl-3-phenyl tautomer, conformer 1:

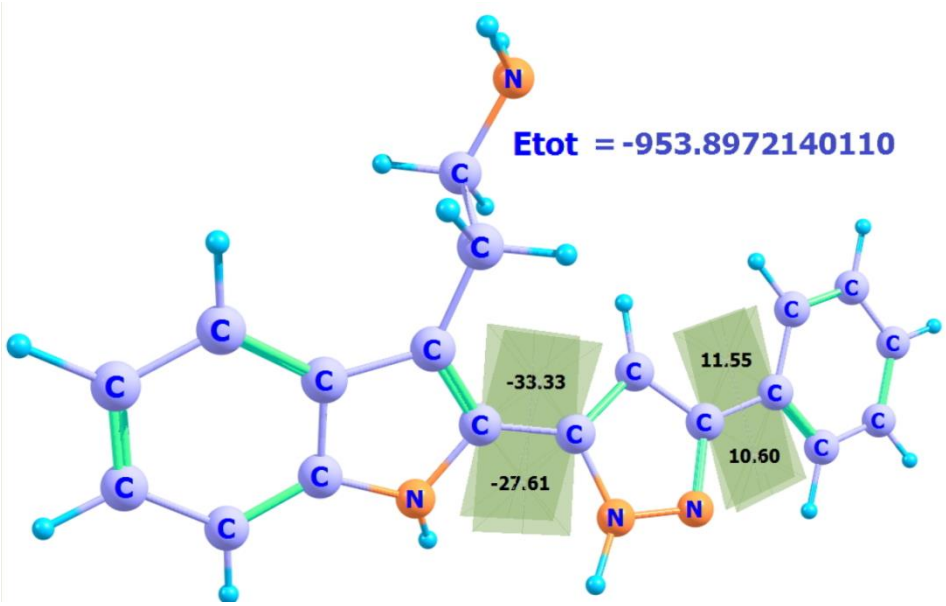


Cartesian coordinates (Å):

41
symmetry c1

C	-4.270556640	-1.811206945	-0.708053472
C	-4.562572290	-0.753248762	0.177660855
C	-3.592275570	0.174864882	0.536056487
C	-3.002800253	-1.959559664	-1.254257414
C	-1.999169400	-1.033201968	-0.916259256
C	-2.316563527	0.019975044	-0.016086624
N	-1.172520965	0.766039725	0.154653460
C	-0.617870337	-0.879098424	-1.299463166
H	-5.052990497	-2.518923894	-0.964958630
H	-5.563848245	-0.662110399	0.587722473
H	-3.816917100	0.988648818	1.219446928
H	-2.791296657	-2.776570702	-1.938245075
C	-0.152621659	0.243939058	-0.635562745
C	1.146301197	0.897251429	-0.615336967
N	1.958713187	1.009905199	-1.707144763
N	3.098898715	1.681043956	-1.464011923
H	-1.119369154	1.663728883	0.608922141
C	0.157279592	-1.836208721	-2.161438717
H	1.095372481	-1.398616442	-2.513333823
H	-0.427619867	-2.072142687	-3.062119775
C	0.512414074	-3.152385534	-1.444778395
H	1.150110598	-2.918780255	-0.584925393
H	-0.408801032	-3.602881979	-1.038131082
N	1.268054244	-4.026258564	-2.347348390
H	0.652036381	-4.386288830	-3.073853040
H	1.607037448	-4.839258531	-1.839007025
C	3.031478260	2.015035950	-0.167930392
C	1.820754408	1.548751092	0.408373049
H	1.502259877	1.616570373	1.437387198
C	4.130460852	2.756655076	0.473678322
C	5.331010649	2.987796318	-0.218604794
C	4.005587689	3.247716603	1.782131168
C	6.372070286	3.689122293	0.383181706
C	5.050341126	3.947679612	2.383702183
C	6.238533569	4.171743625	1.687456083
H	5.431957804	2.608485647	-1.229524914
H	3.083689755	3.089784658	2.333709964
H	7.293495976	3.857759600	-0.166953988
H	4.933715831	4.320304193	3.397364569
H	7.052640258	4.716887953	2.155970070
H	1.755820722	0.709876826	-2.647449272

5-Indolyl-3-phenyl tautomer, conformer 2:



Cartesian coordinates (Å):

41
symmetry c1

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C	-3.654013856	0.179502284	0.539570409
C	-3.055147428	-1.895316060	-1.315636851
C	-2.044363256	-1.006204031	-0.909039542
C	-2.371419475	0.029863961	0.005671229
N	-1.229475138	0.784123013	0.201006707
C	-0.645027596	-0.877833838	-1.231457550
H	-5.120645406	-2.431507896	-1.096225316
H	-5.635507185	-0.637494165	0.526802702
H	-3.884235944	0.973673591	1.243968742
H	-2.838424858	-2.689142522	-2.024801192
C	-0.176085498	0.207933049	-0.516756112
C	1.138450835	0.819989212	-0.484339111
N	1.305680804	2.164052700	-0.274604315
N	2.595817203	2.553347965	-0.282084622
H	-1.084805289	1.382190447	1.000374039
C	0.138649641	-1.746252542	-2.170918729
H	1.025467523	-1.215709873	-2.531335521
H	-0.472713983	-1.971805669	-3.056256318
C	0.596279523	-3.072597353	-1.538063369
H	1.192281230	-2.852457892	-0.644271735
H	-0.291157314	-3.627935434	-1.187477677
N	1.444956518	-3.814141939	-2.475905312
H	0.894690253	-4.097973635	-3.284527262
H	1.768991654	-4.675628027	-2.042502423
C	3.291357943	1.424504028	-0.473722972
C	2.421916735	0.309151718	-0.606738665
H	2.686557027	-0.729352904	-0.726208417
C	4.763753456	1.446031787	-0.509615415
C	5.468028544	2.599434722	-0.125928302
C	5.491762810	0.322196471	-0.929338017
C	6.859484872	2.624016408	-0.161115335
C	6.885209204	0.348373512	-0.960522138
C	7.575545287	1.498567084	-0.576436818
H	4.907991302	3.469370140	0.199395996
H	4.967731536	-0.574484996	-1.245812177
H	7.388221838	3.524185640	0.139410417
H	7.431297606	-0.531036123	-1.289671316
H	8.661134741	1.518762152	-0.601244576
H	0.585166222	2.869415671	-0.286505767

4. References

[S1] http://chem.ch.huji.ac.il/nmr/software/solvent.html.

[S2] A. A. Granovsky, *Firefly version 8*, http://classic.chem.msu.su/gran/firefly/index.html

[S3] R. K. Kuppalli, R. S. Toreshettahally, P. S. Kodipura, B. S. Jeegundipattana, M. A. Seegehally, S. R. Kanchugarakoppal, P. S. Maralinganadoddi, *Synth*., 2019, 51, 4205-4214; doi: 10.1055/s-0039-1690616

[S4] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem*., 1993, **14**, 1347; doi:10.1002/jcc.540141112

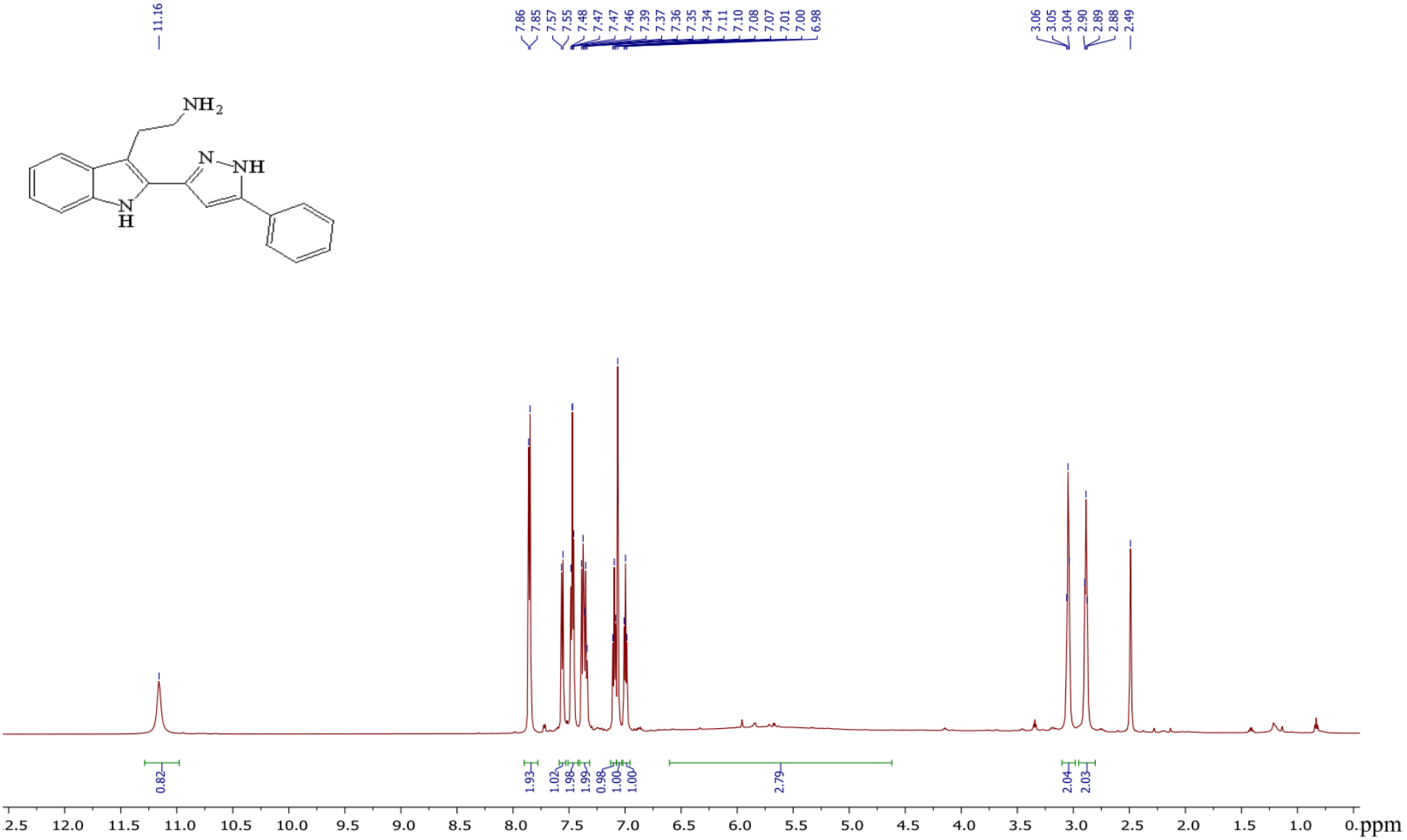
[S5] T. P. Singh, O. M. Singh, *J. Chem. Sci*., 2016, **128**, 565; doi:10.1007/s12039-016-1056-6.

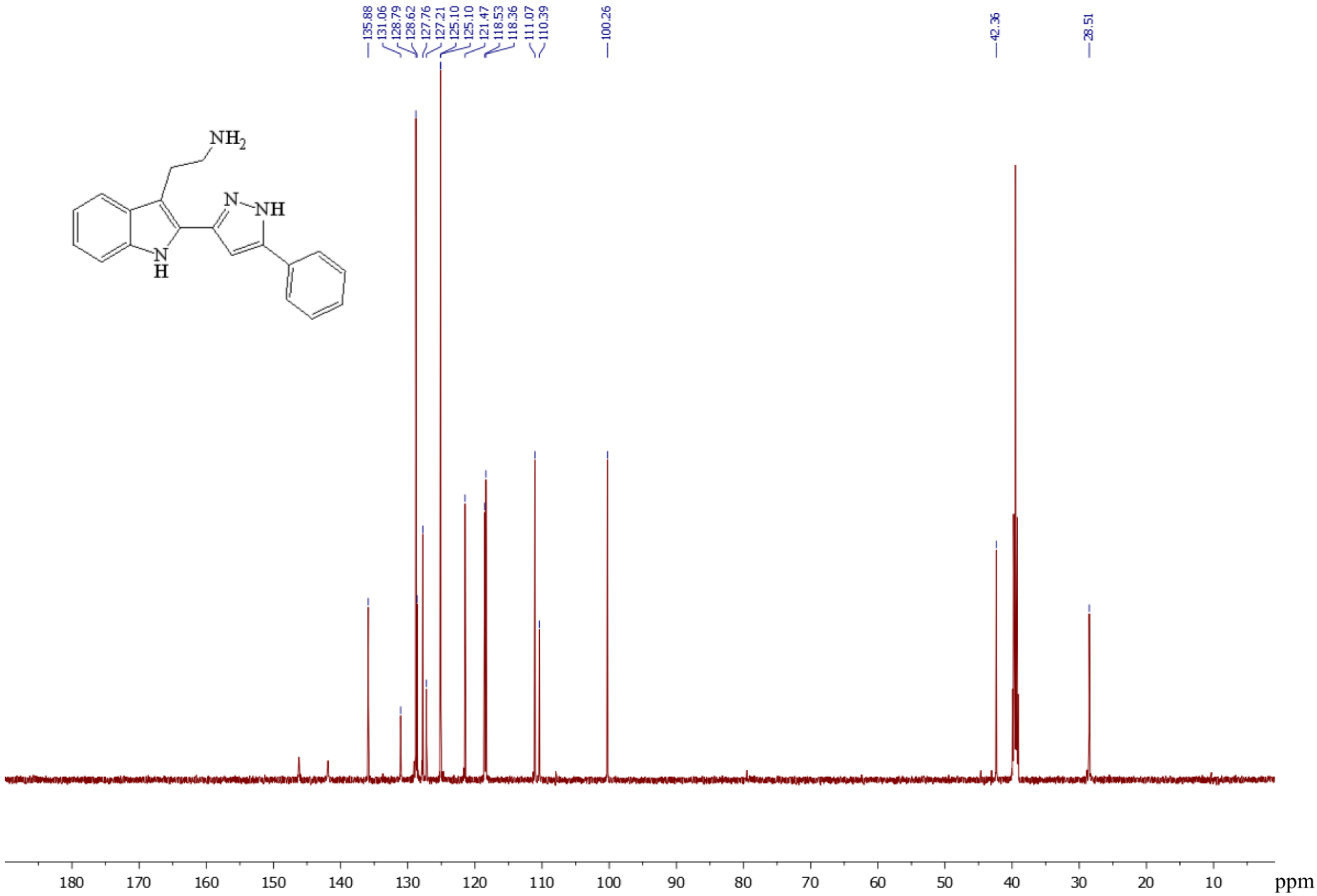
[S6] A. Avadhani, P. Iniyavan, A. Acharya, V. Gautam, S. Chakrabarti, Hiriyakkanavar Ila, *ACS Omega*, 2019, **4**, 17910; doi: 10.1021/acsomega.9b02957.

[S7] J. B. Fourtillan, M. Fourtillan, *Fr. Pat* 2904973, 22.02.08; https://patents.google.com/patent/FR2904973A1/en

5. NMR Spectra of compounds 5, 6.

2-[2-(5-Phenyl-1*H*-pyrazol-3-yl)-1*H*-indol-3-yl]ethanamine **(5a).**

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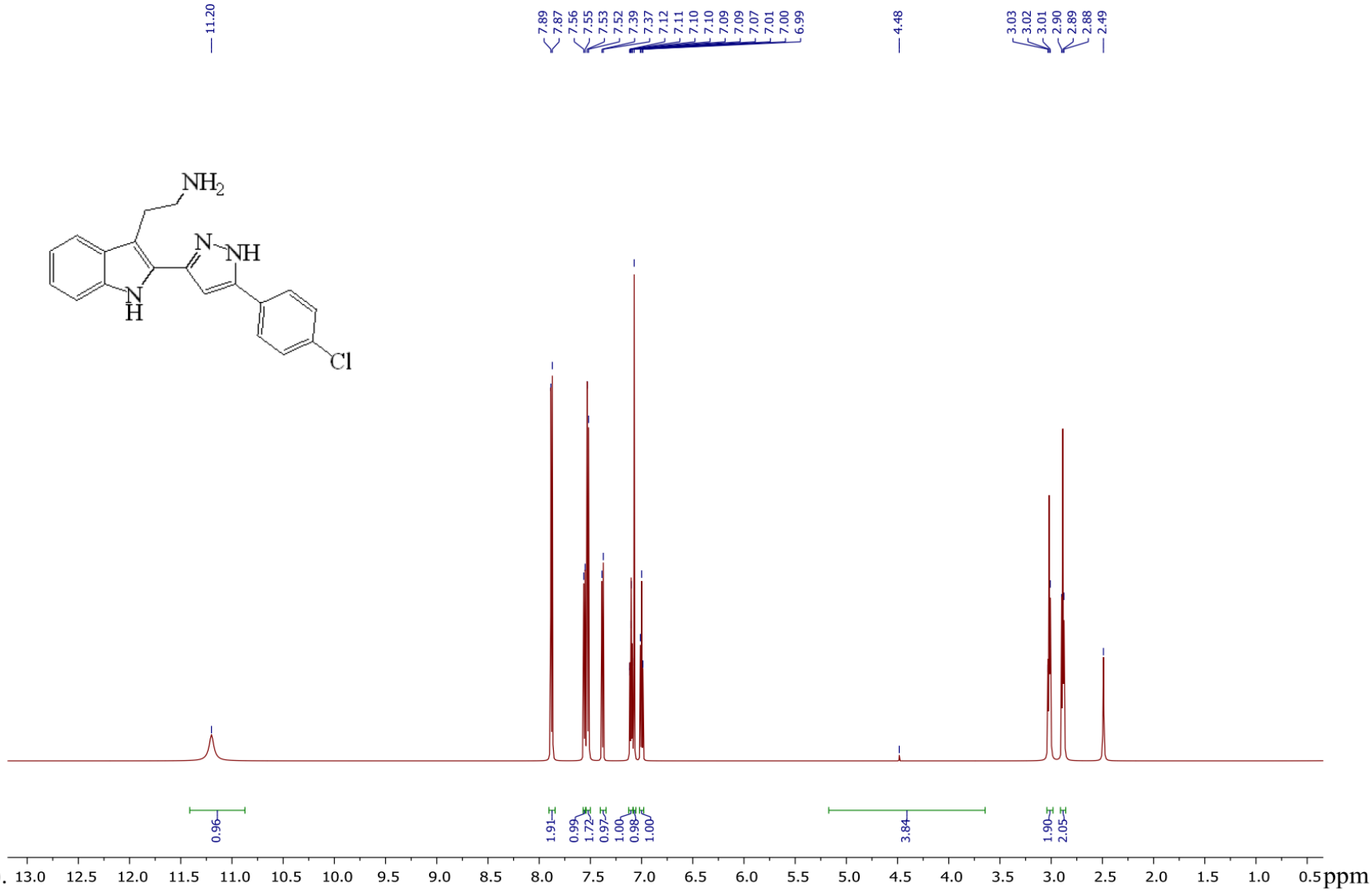
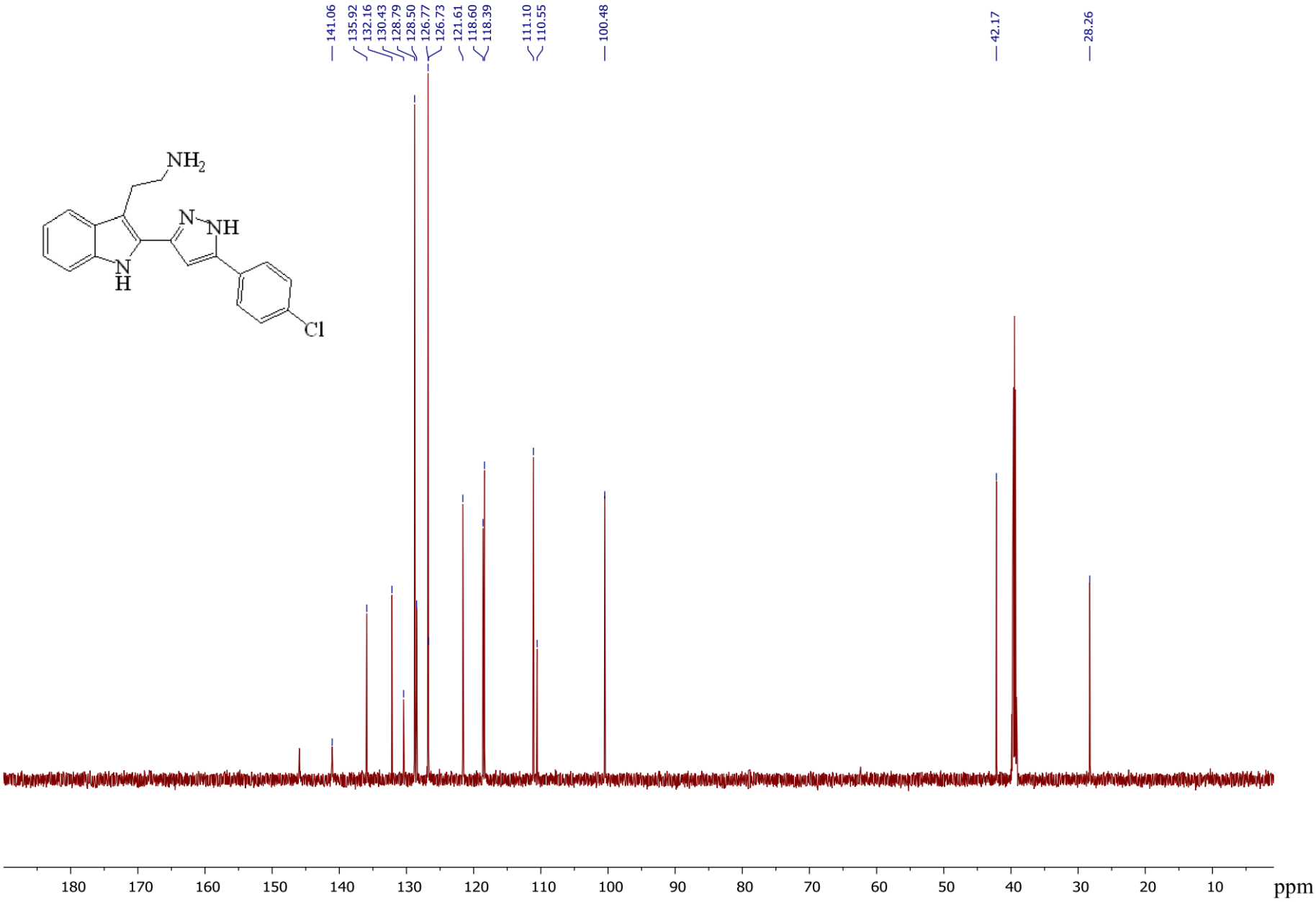
131.06
128.79
128.62
127.76
127.21
125.10
125.10
121.47
118.53
118.36
111.07
110.39
100.26
42.36
28.51
NH2
N
NH
N
H
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

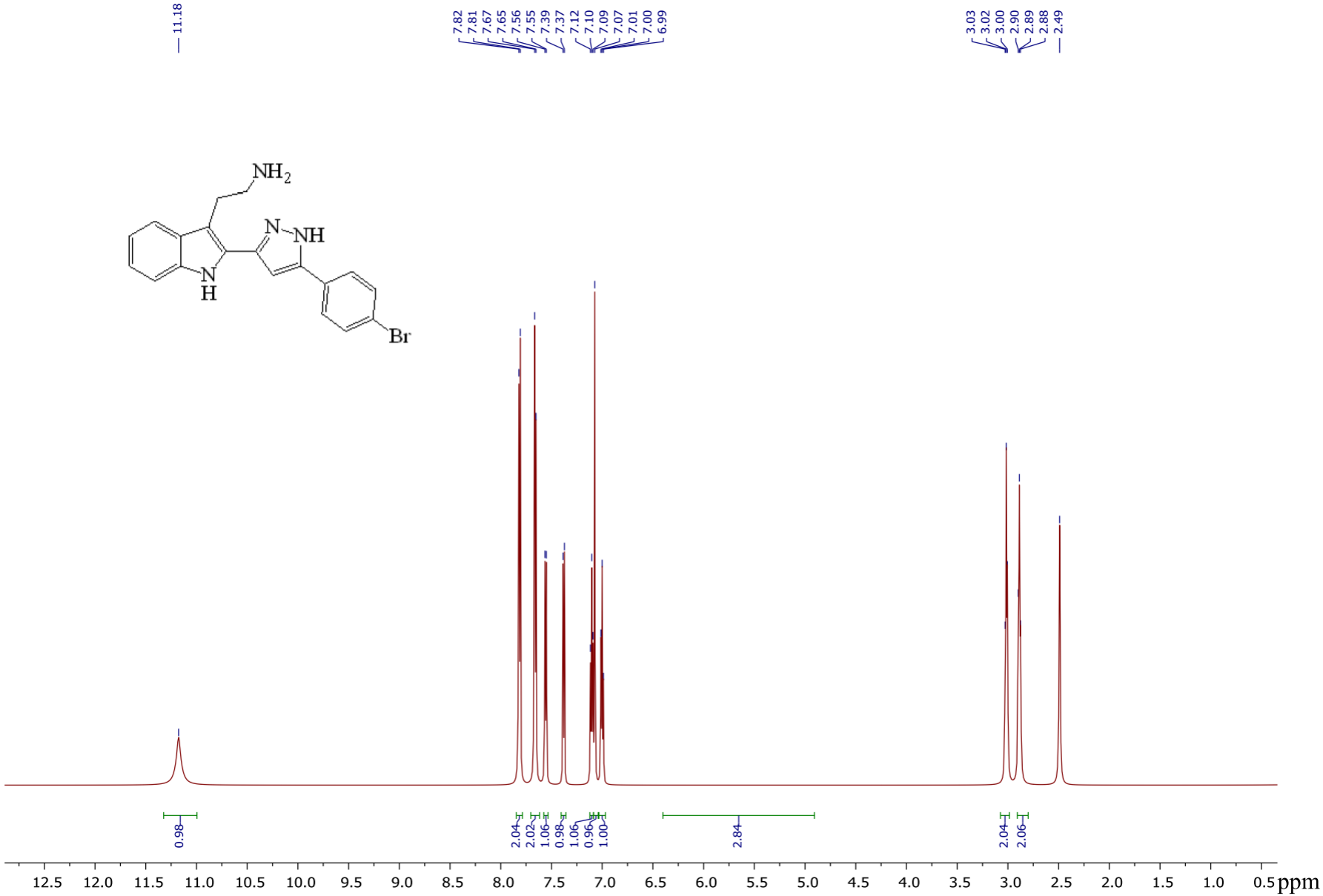
2-{2-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-1*H*-indol-3-yl}ethan-1-amine (**5b**)

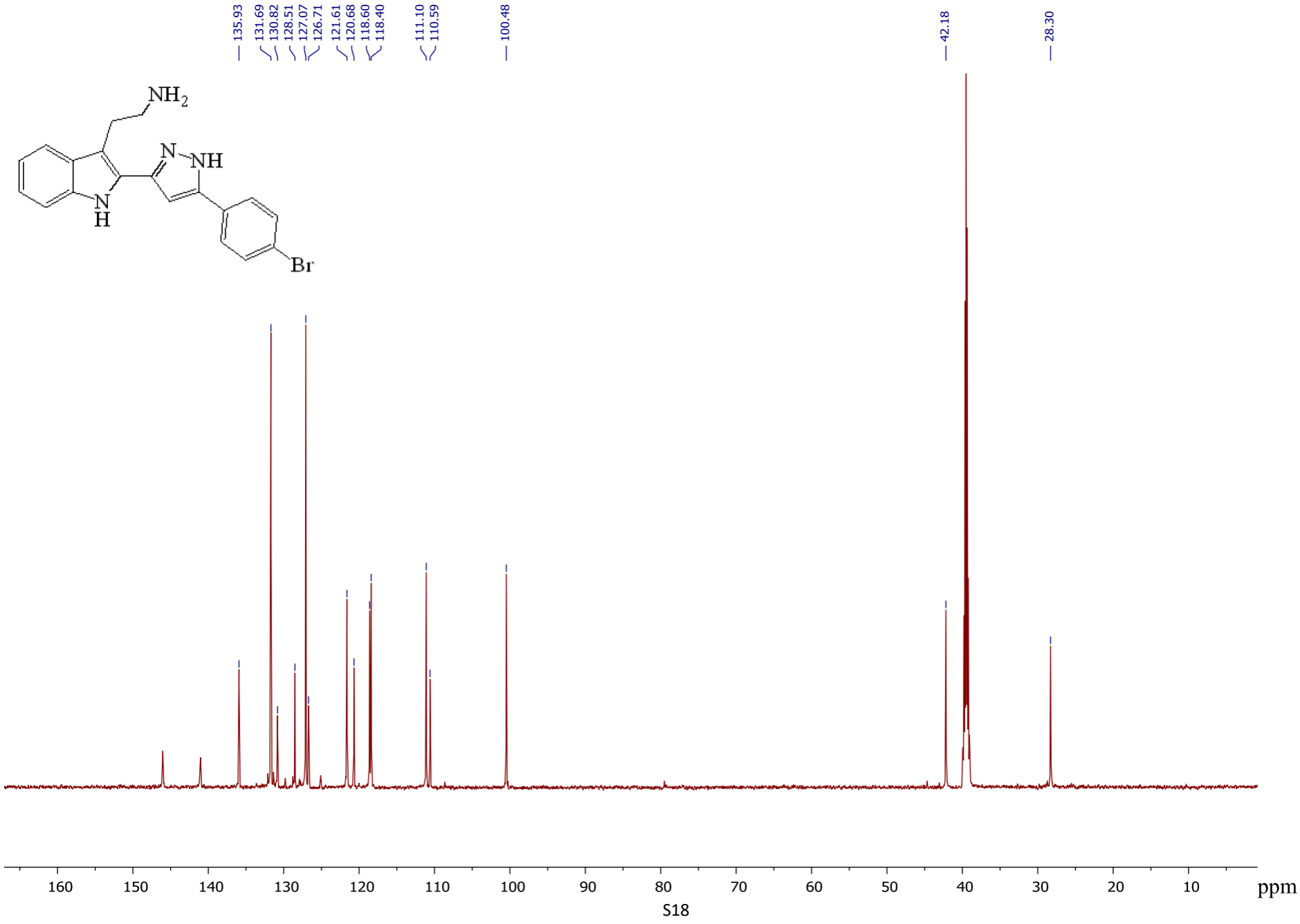


(**5b**).


141.06
135.92
132.16
130.43
128.79
128.50
126.77
126.73
121.61
118.60
118.39
111.10
110.55
100.48
42.17
28.26
NH2
N
NH
N
H
Cl
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2-(2-(5-(4-Bromophenyl)-1*H*-pyrazol-3-yl)-1*H*-indol-3-yl)ethan-1-amine **(5c).**

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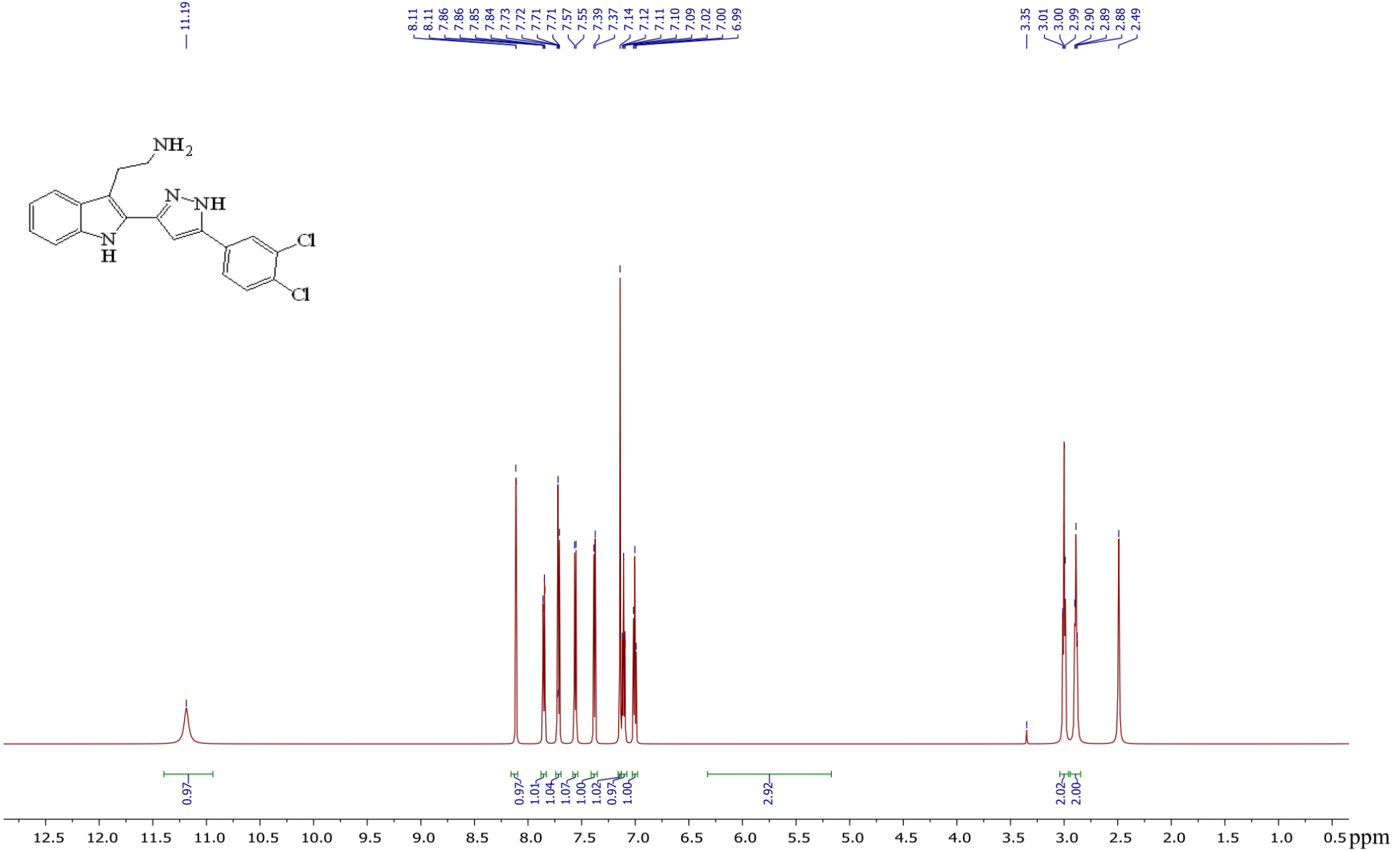
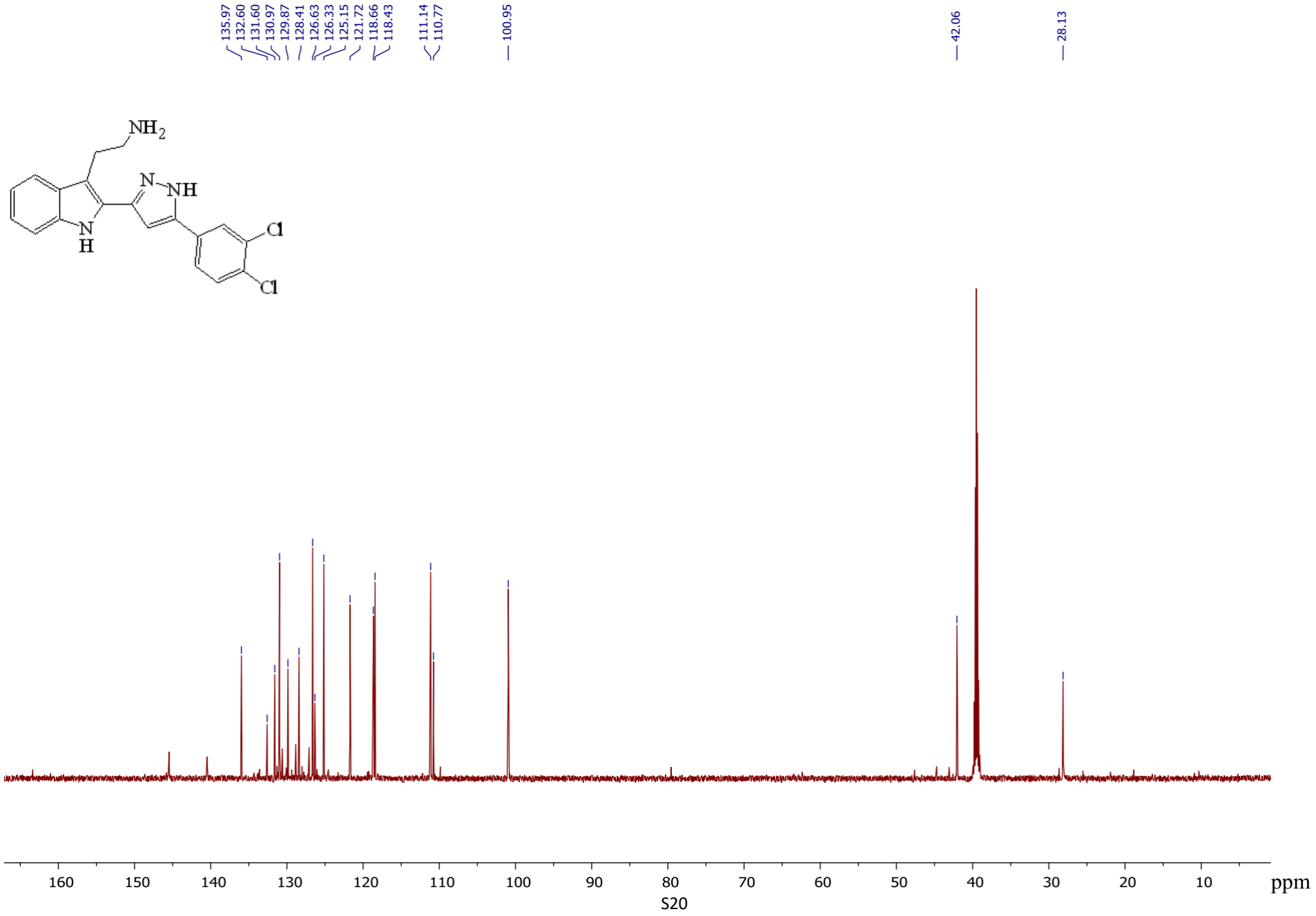
131.69
130.82
128.51
127.07
126.71
121.61
120.68
118.60
118.40
111.10
110.59
100.48
42.18
28.30
NH2
N
NH
N
H
Br
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2-(2-(5-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)-1*H*-indol-3-yl)ethan-1-amine **(5d).**




135.97
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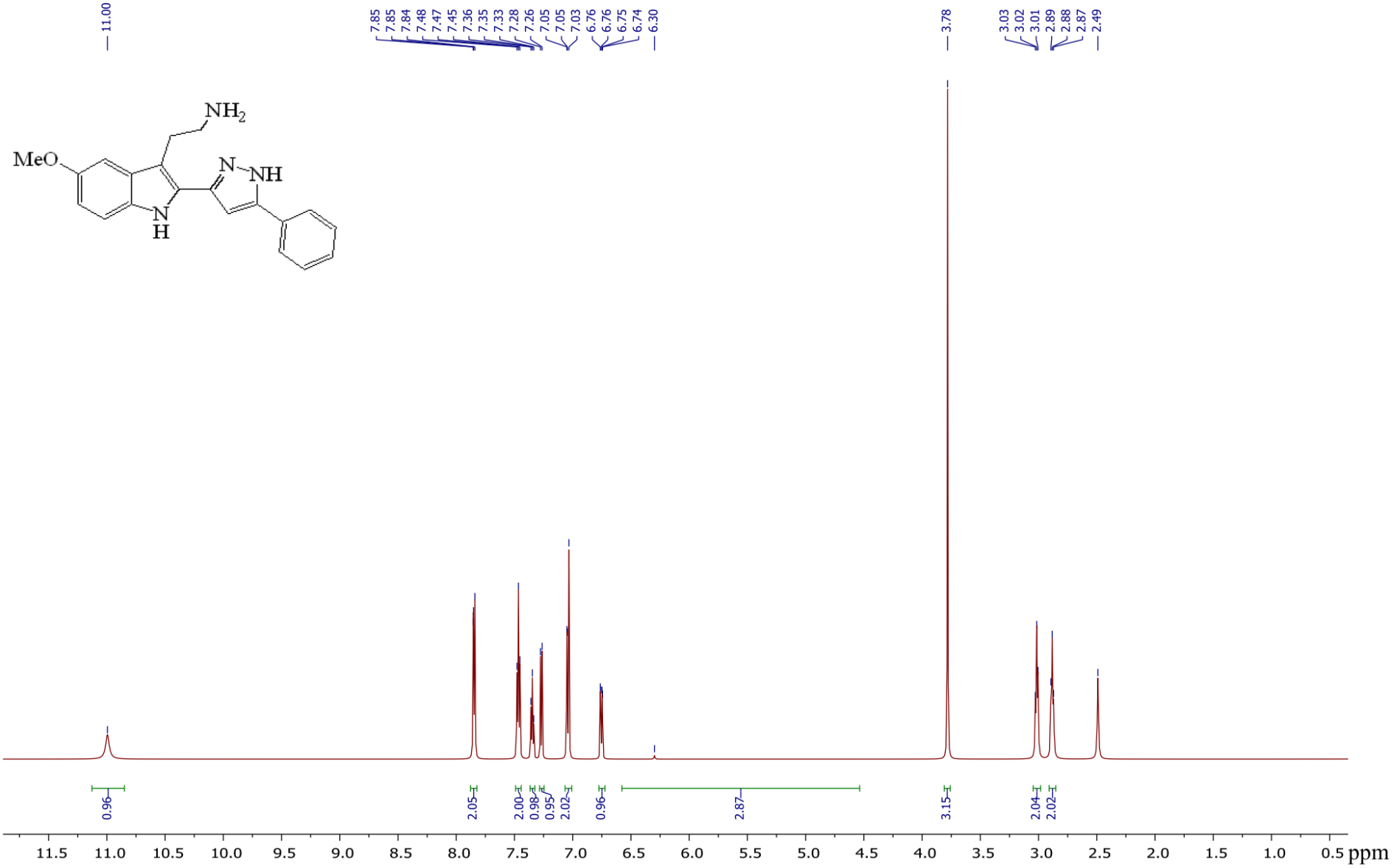
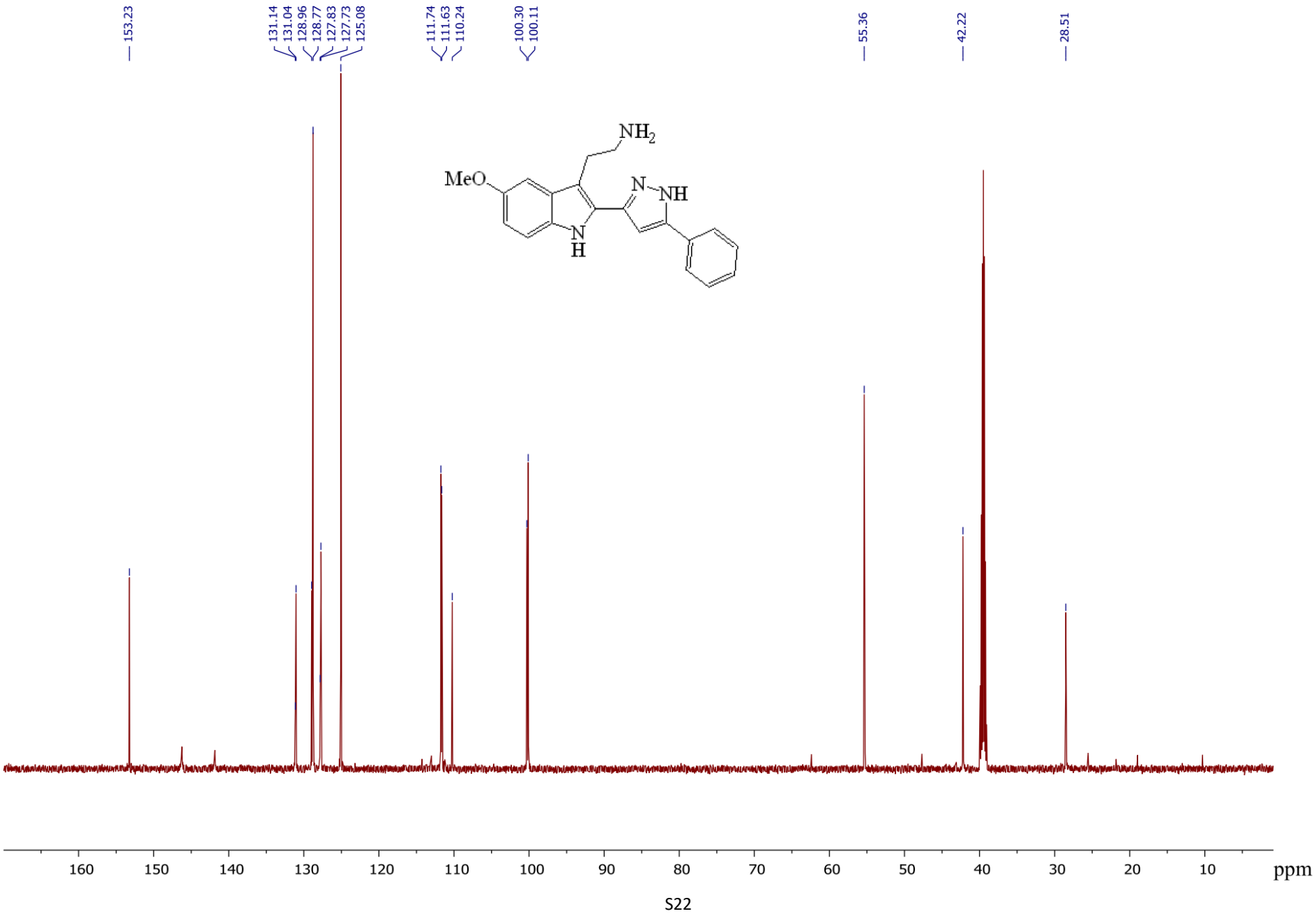
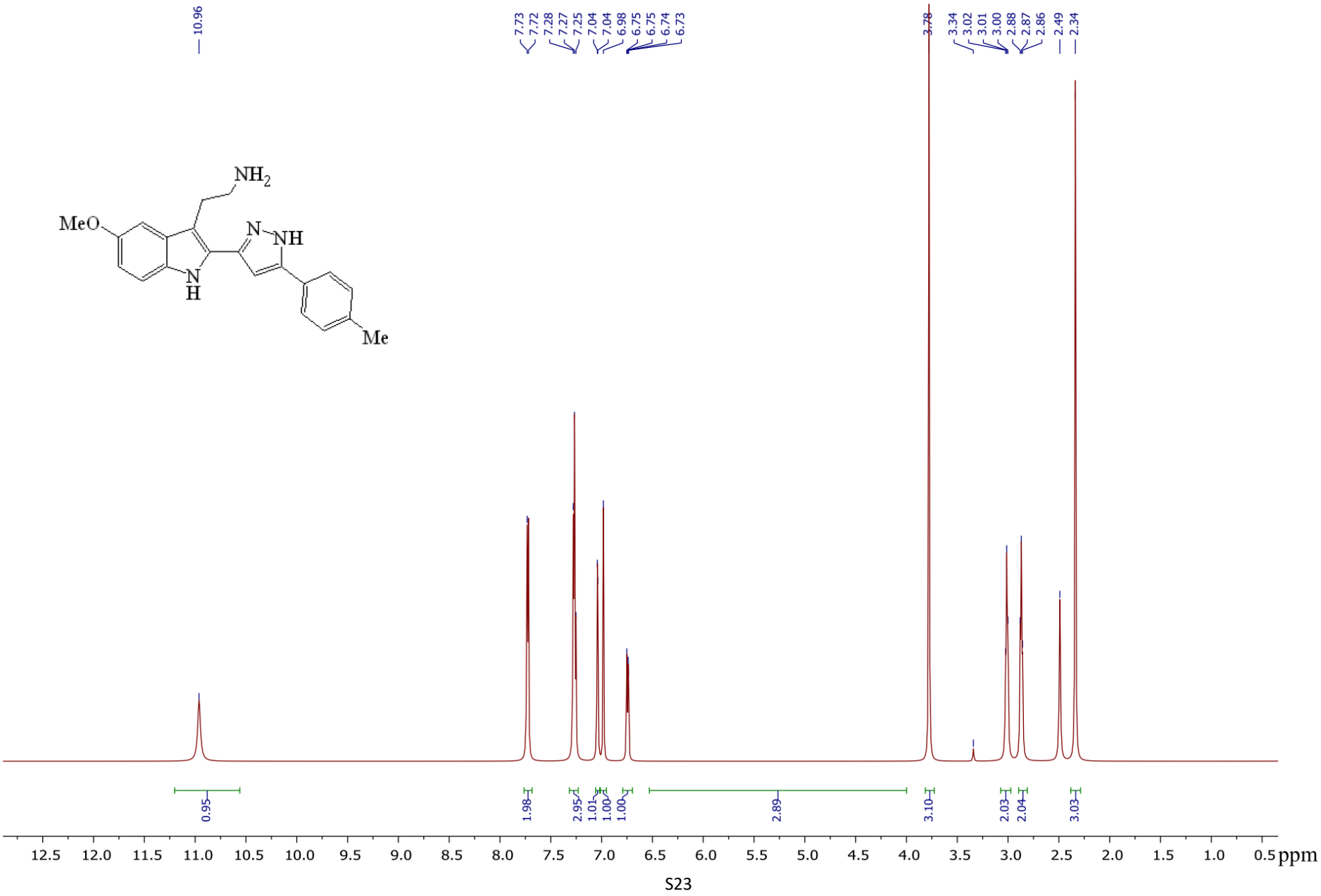
131.60
130.97
129.87
128.41
126.63
126.33
125.15
121.72
118.66
118.43
111.14
110.77
100.95
42.06
28.13
NH2
N
NH
N
H
Cl
Cl
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

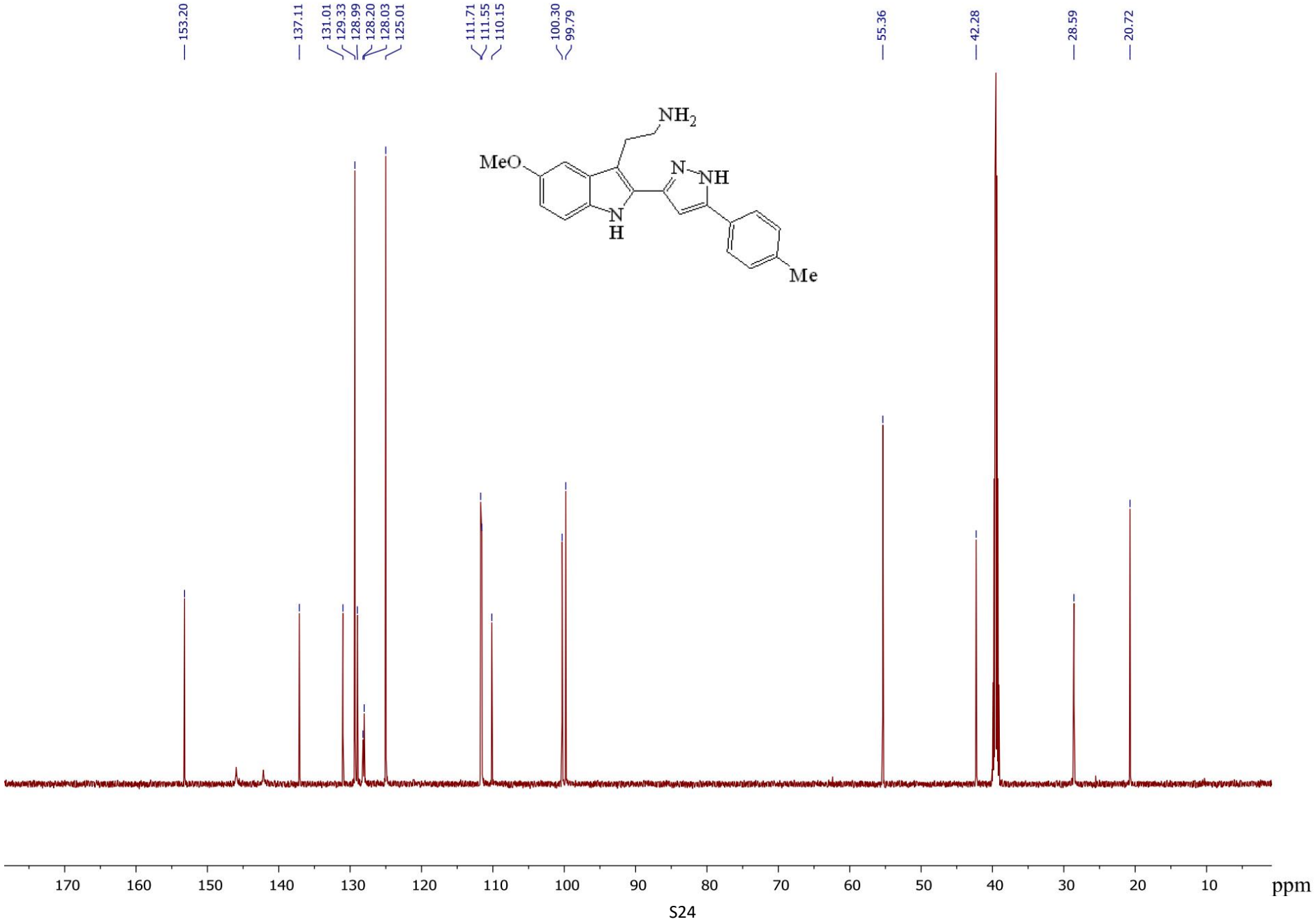
2-(5-methoxy-2-(5-phenyl-1H-pyrazol-3-yl)-1*H*-indol-3-yl)ethan-1-amine **(5e).**



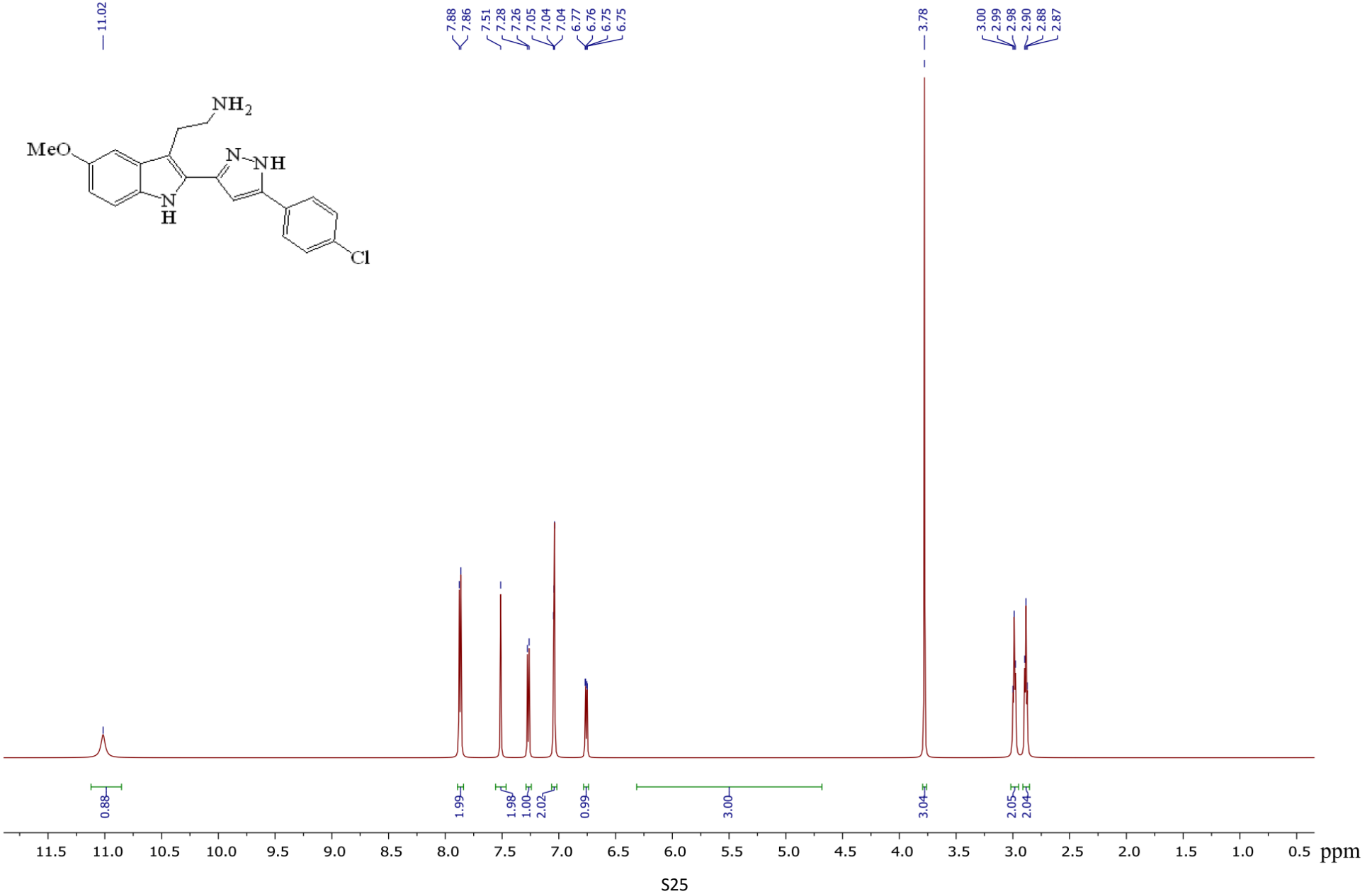

153.23
131.14
131.04
128.96
128.77
127.83
127.73
125.08
111.74
111.63
110.24
100.30
100.11
55.36
42.22
28.51
NH2
MeO
N
NH
N
H
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

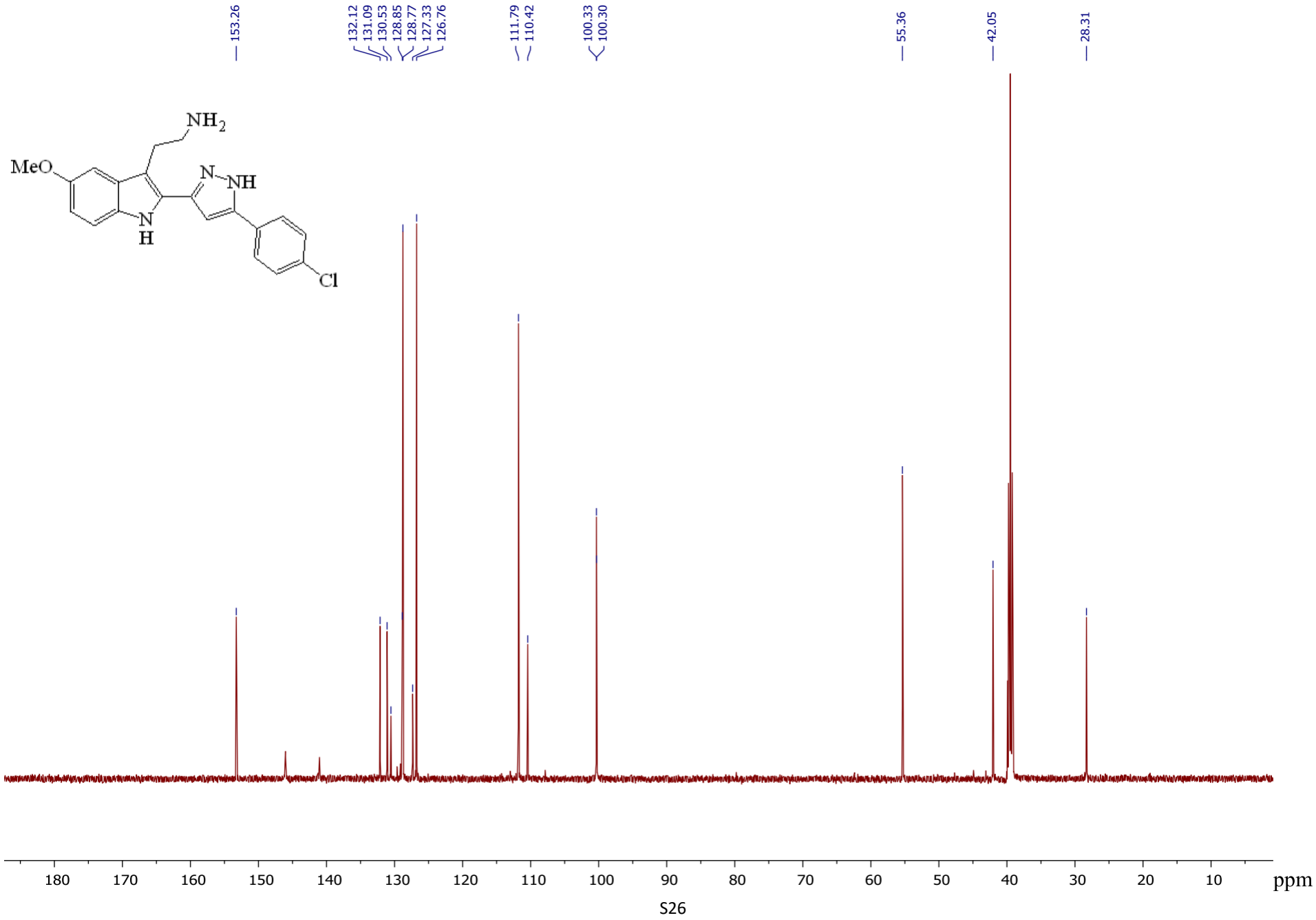
2-{[5-Methoxy-2-[5-(p-tolyl)-1*H*-pyrazol-3-yl]-1*H*-indol-3-yl}ethan-1-amine **(5f).**



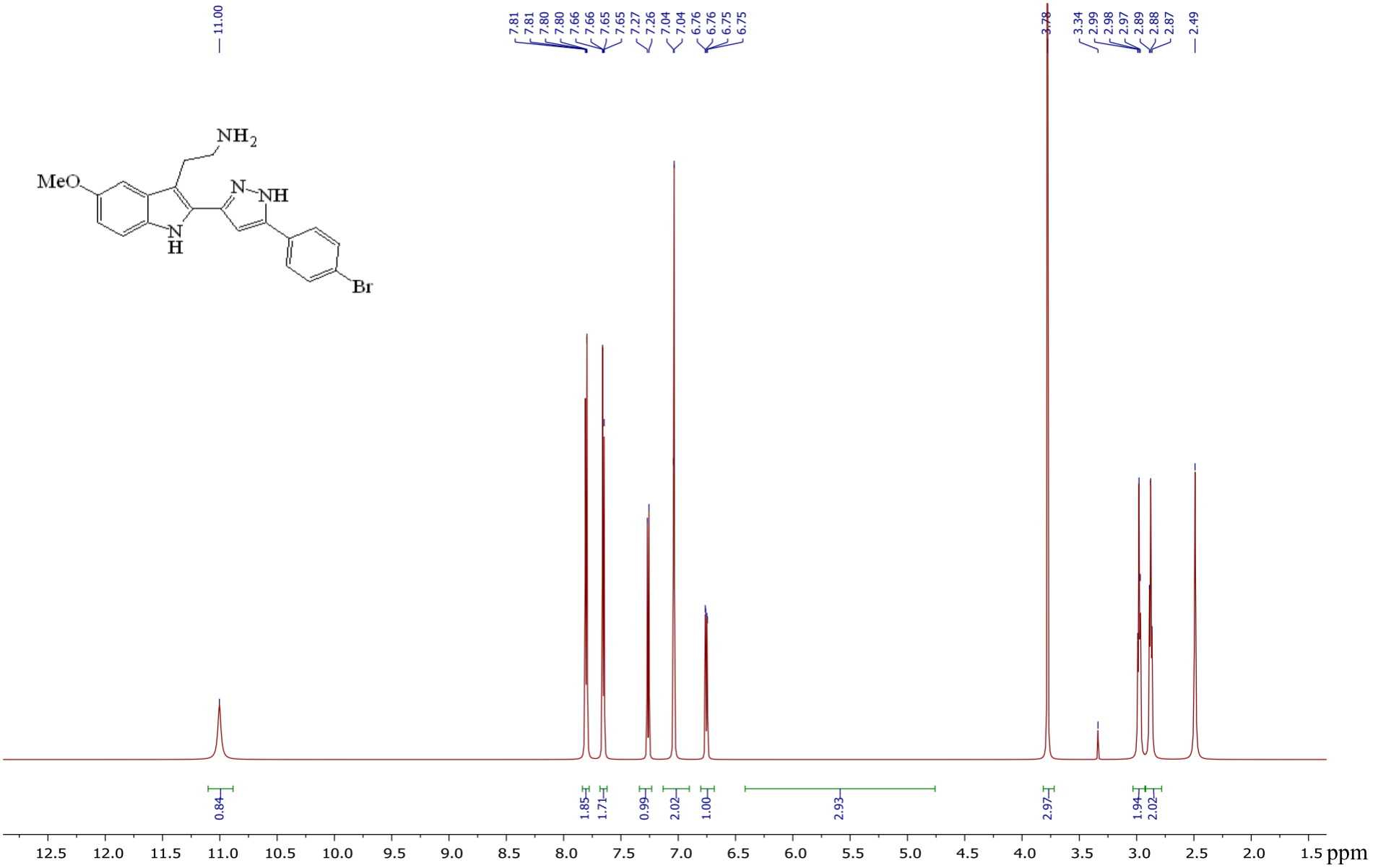

153.20
137.11
131.01
129.33
128.99
128.20
128.03
125.01
111.71
111.55
110.15
100.30
99.79
55.36
42.28
28.59
20.72
NH2
MeO
N
NH
N
H
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

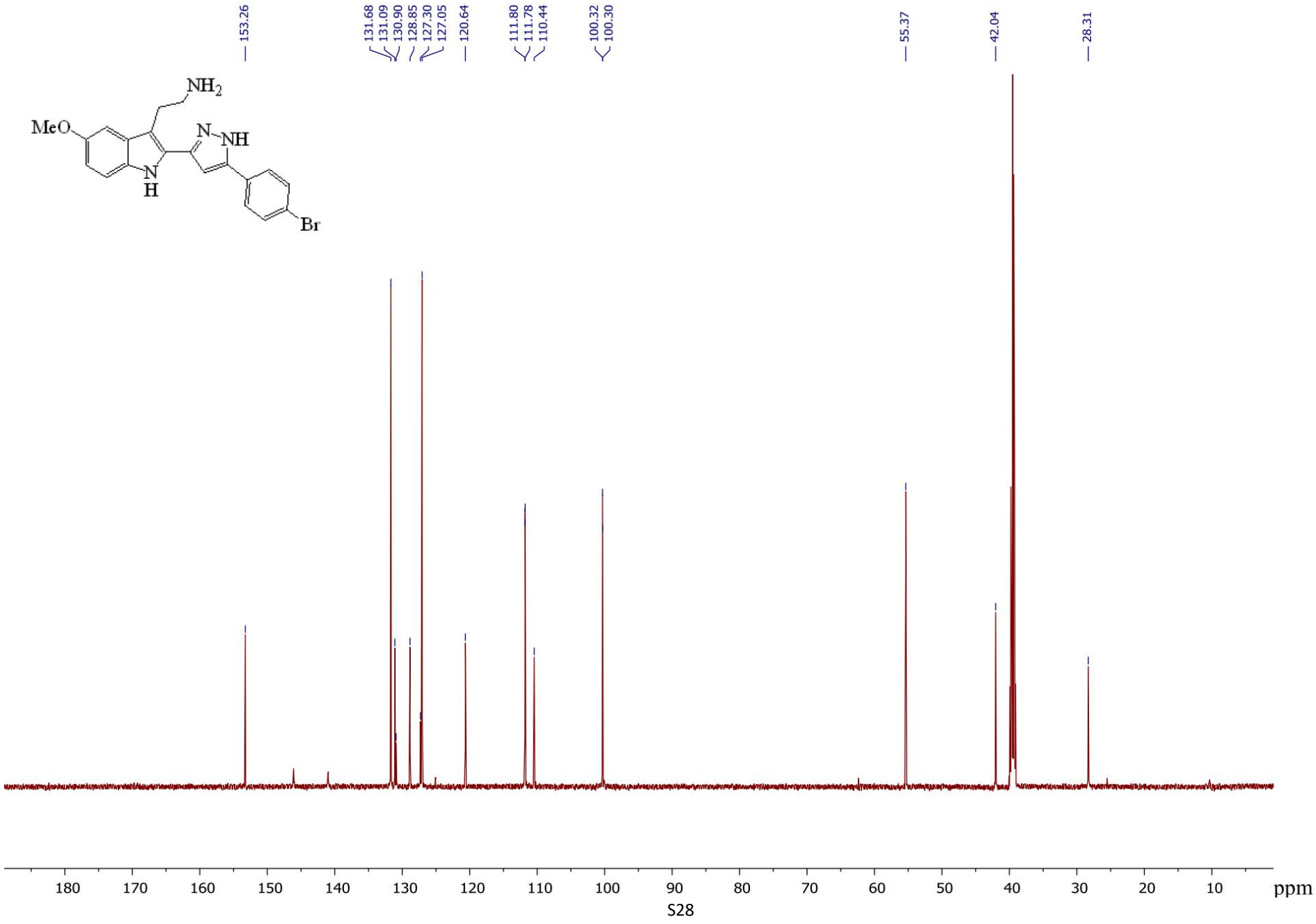
2-{2-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethan-1-amine (**5g**).



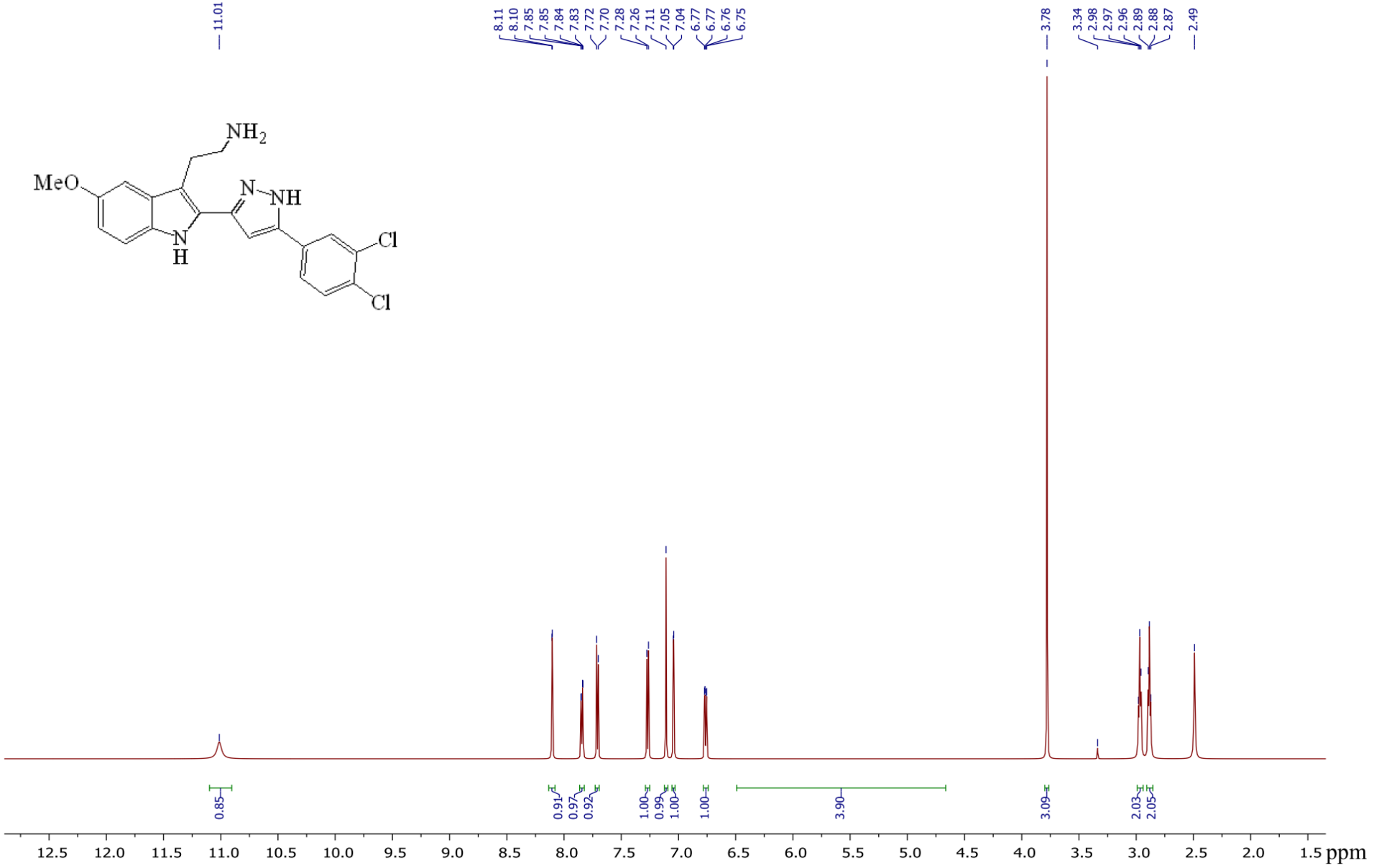

153.26
132.12
131.09
130.53
128.85
128.77
127.33
126.76
111.79
110.42
100.33
100.30
55.36
42.05
28.31
NH2
MeO
N
NH
N
H
Cl
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

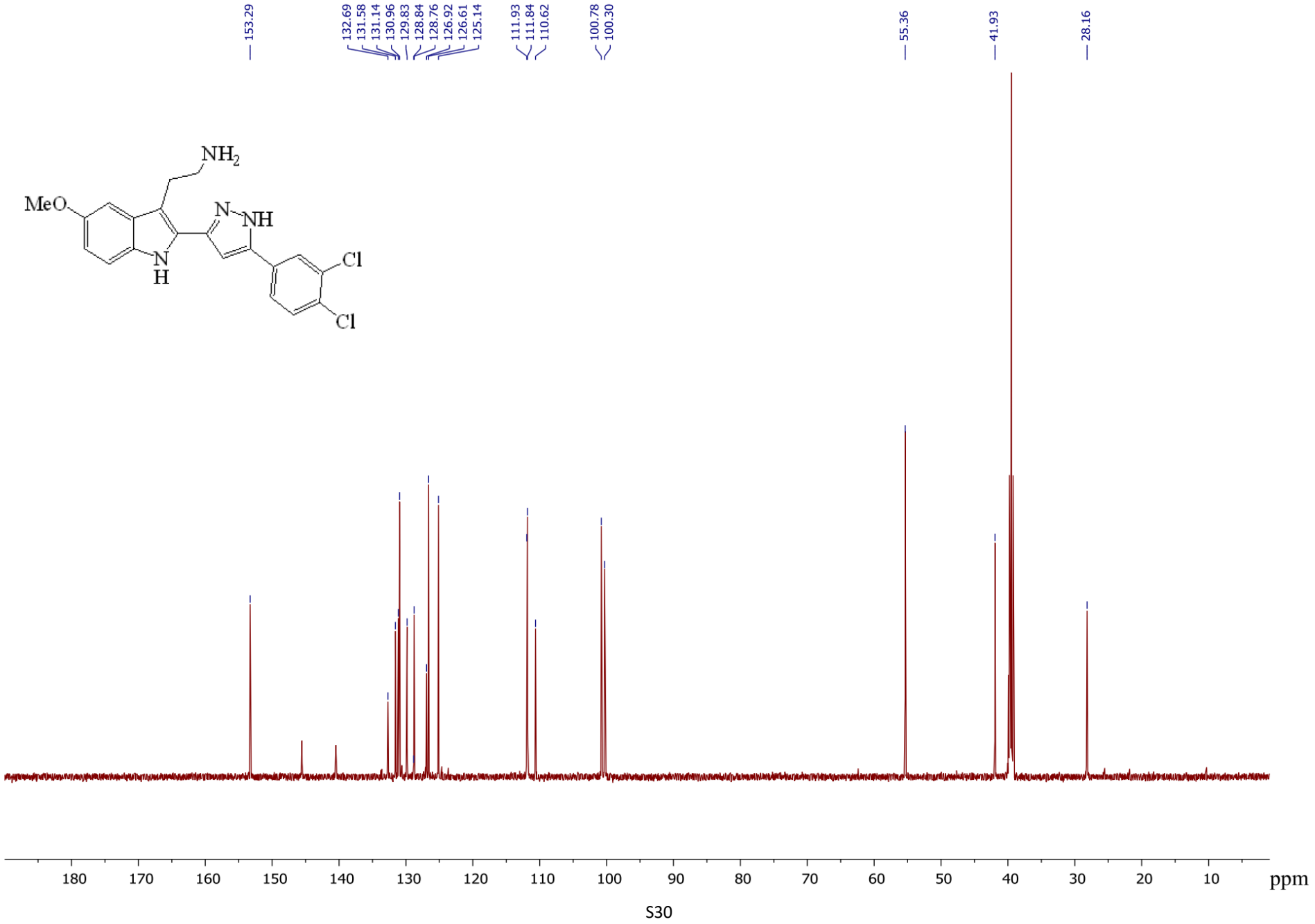
2-{2-[5-(4-Bromophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethan-1-amine (**5h**).



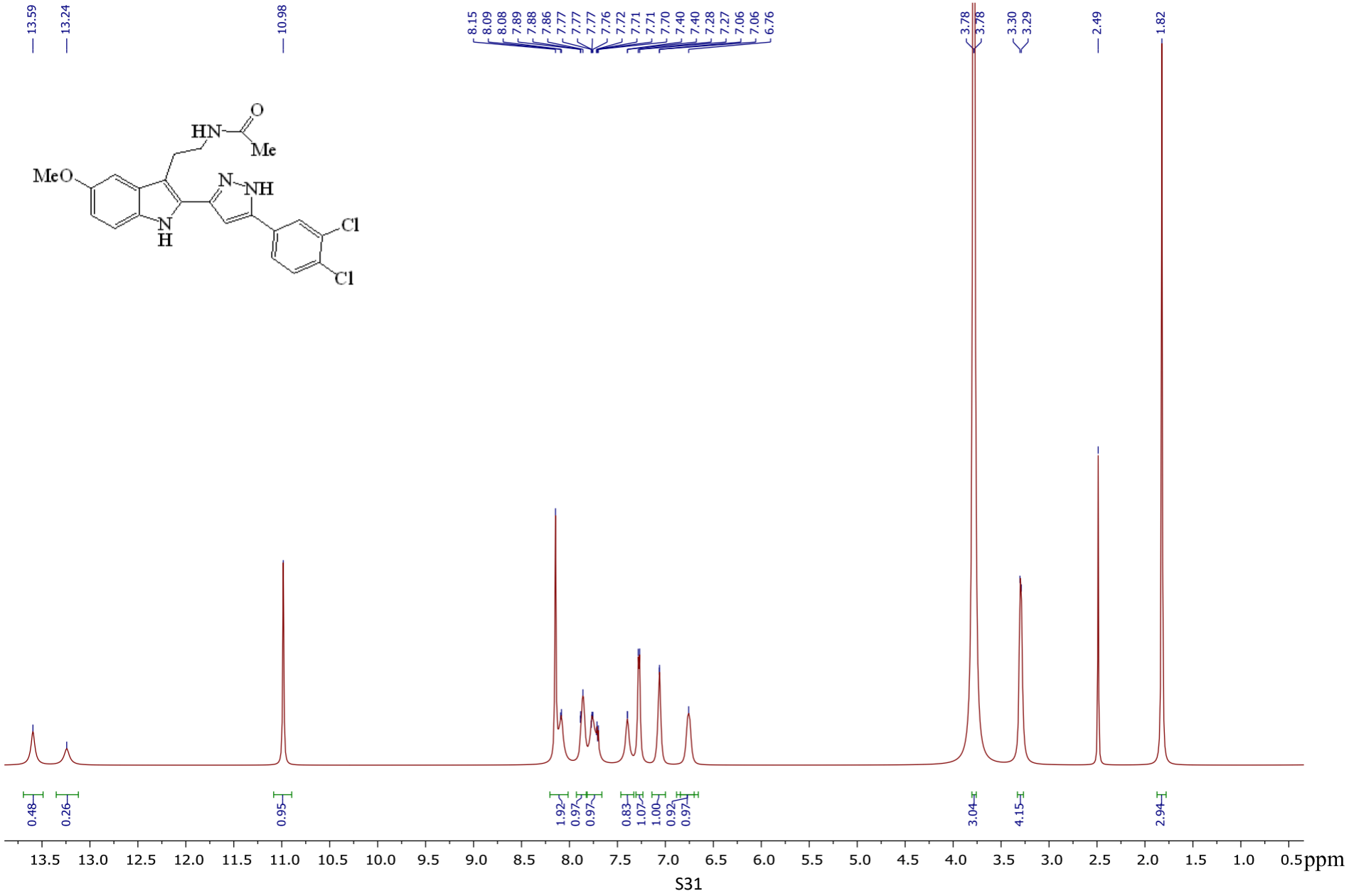

153.26
131.68
131.09
130.90
128.85
127.30
127.05
120.64
111.80
111.78
110.44
100.32
100.30
55.37
42.04
28.31
NH2
MeO
N
NH
N
H
Br
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

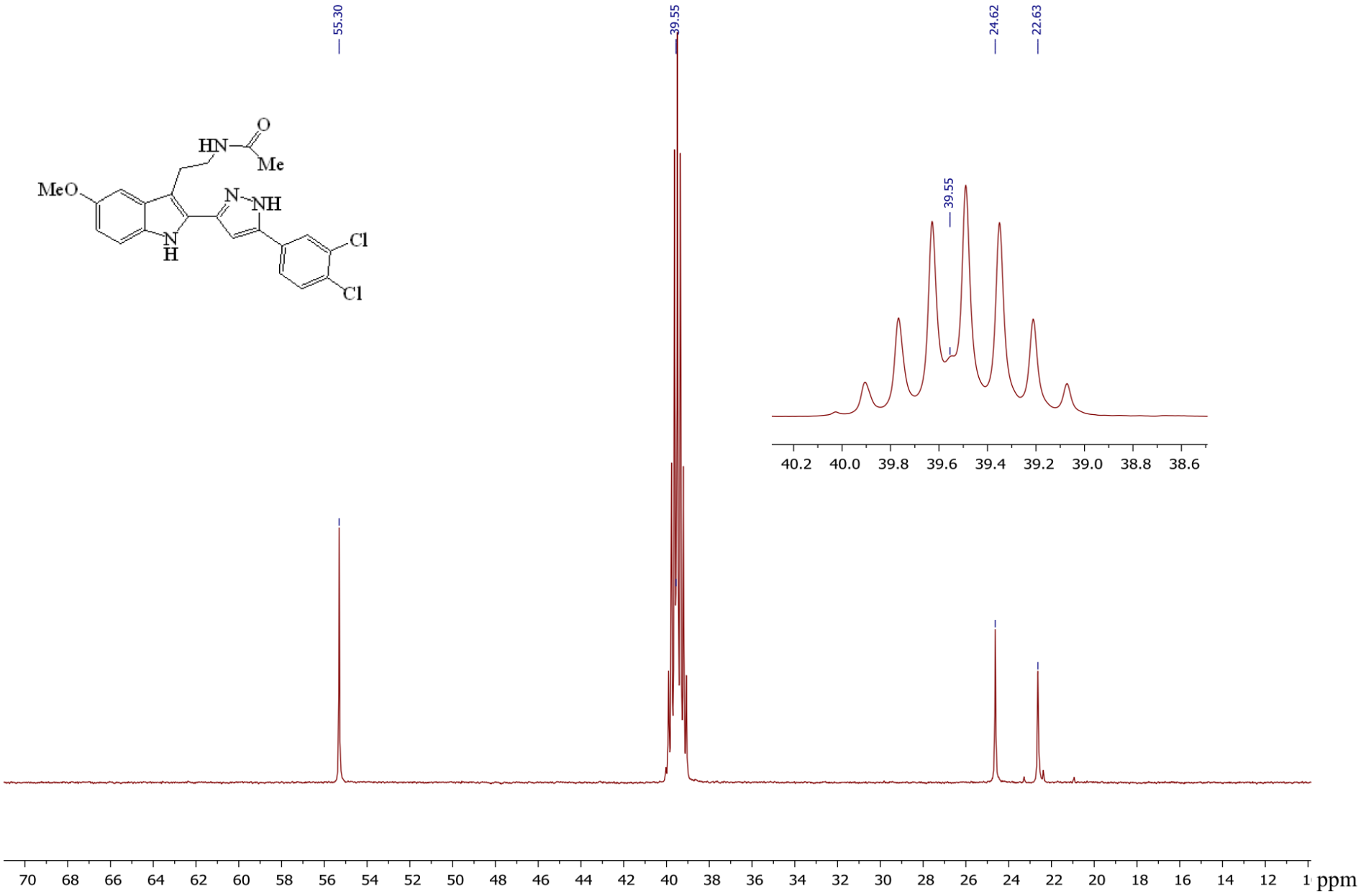
2-{2-[5-(3,4-Dichlorophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethan-1-amine **(5i).**

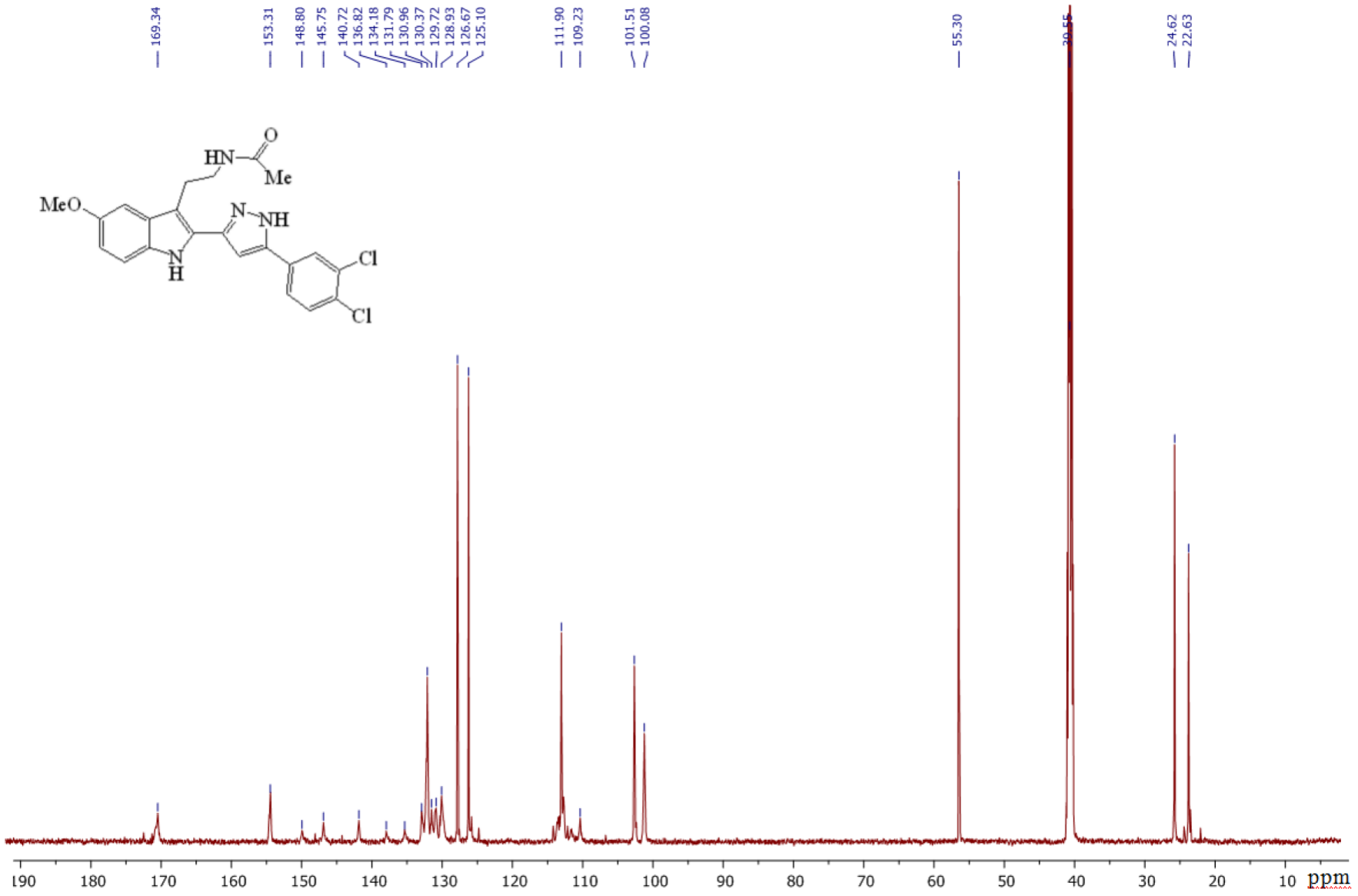



153.29
132.69
131.58
131.14
130.96
129.83
128.84
128.76
126.92
126.61
125.14
111.93
111.84
110.62
100.78
100.30
55.36
41.93
28.16
NH2
MeO
N
NH
N
H
Cl
Cl
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

N-{2-[2-(5-(3,4-Dichlorophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethyl)acetamide **(6)**

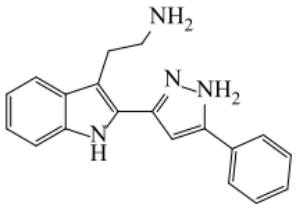



55.30
39.55
24.62
22.63
HN
O
Me
MeO
N
NH
N
H
Cl
Cl
39.55
40.2
40.0
39.8
39.6
39.4
39.2
39.0
38.8
38.6
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
1
ppm


169.34
153.31
148.80
145.75
140.72
136.82
134.18
131.79
130.96
130.37
129.72
128.93
126.67
125.10
111.90
109.23
101.51
100.08
55.30
30.55
24.62
22.63
HN
O
Me
MeO
N
NH
N
H
Cl
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

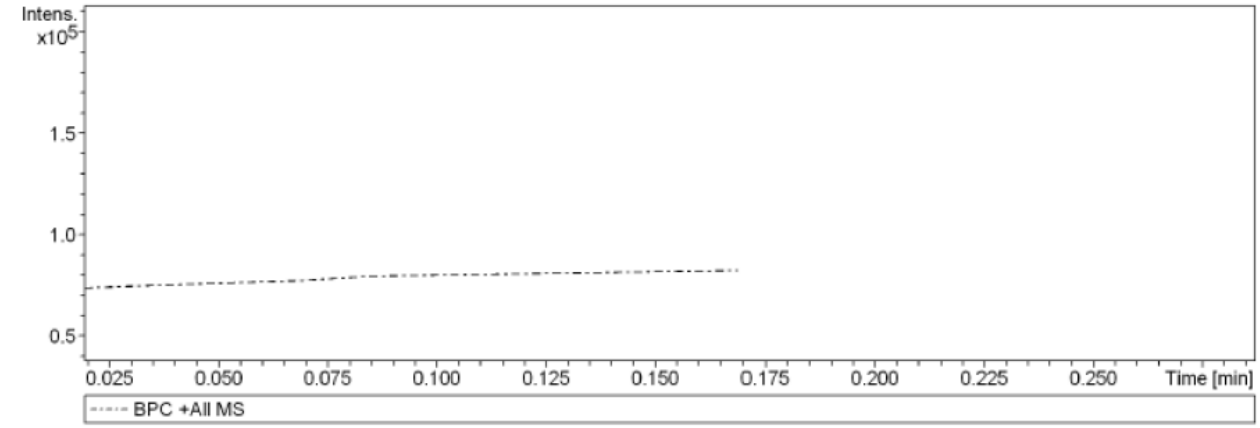
6. High resolution mass spectra for 5a-i

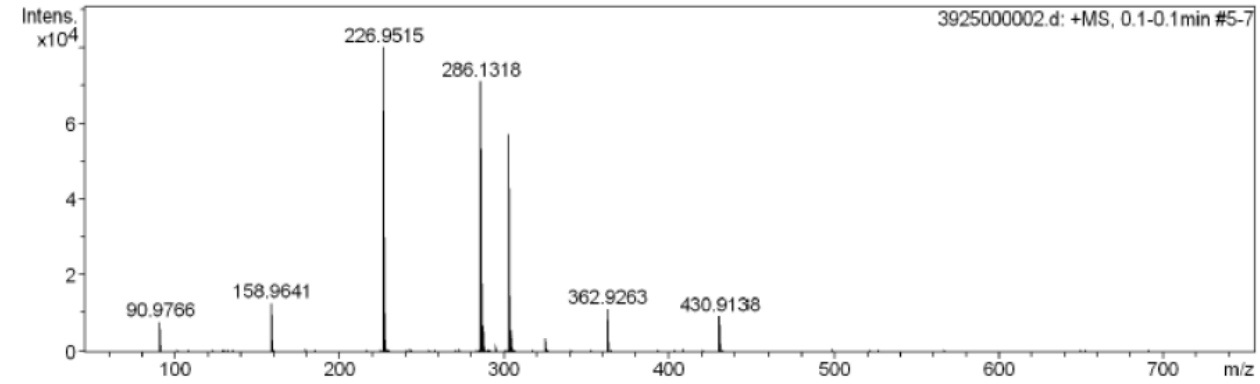
2-[2-(5-Phenyl-1*H*-pyrazol-3-yl)-1*H*-indol-3-yl]ethanamine (**5a**).

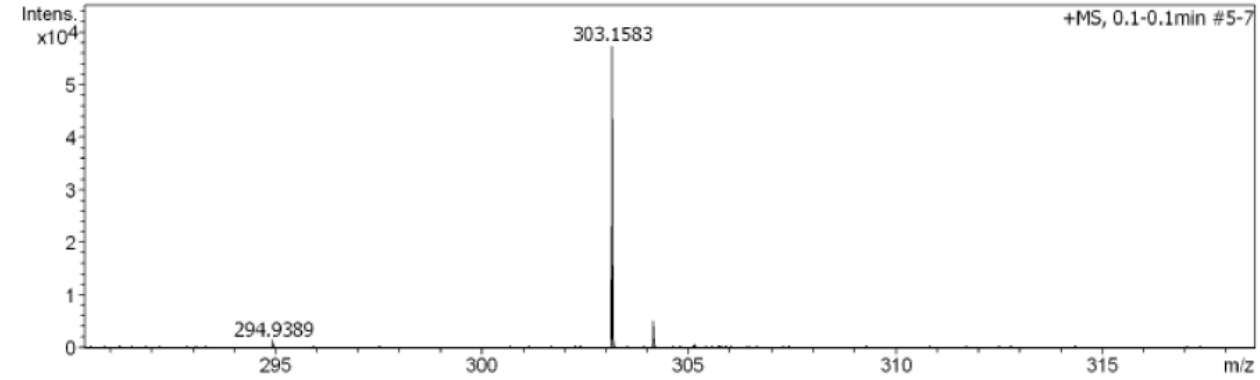


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



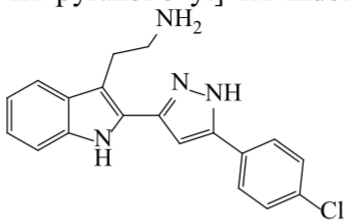




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e⁻ Conf	N-Rule
303.1583	1	C19H19N4	303.1604	7.2	76.5	1	100.00	12.5	even	ok

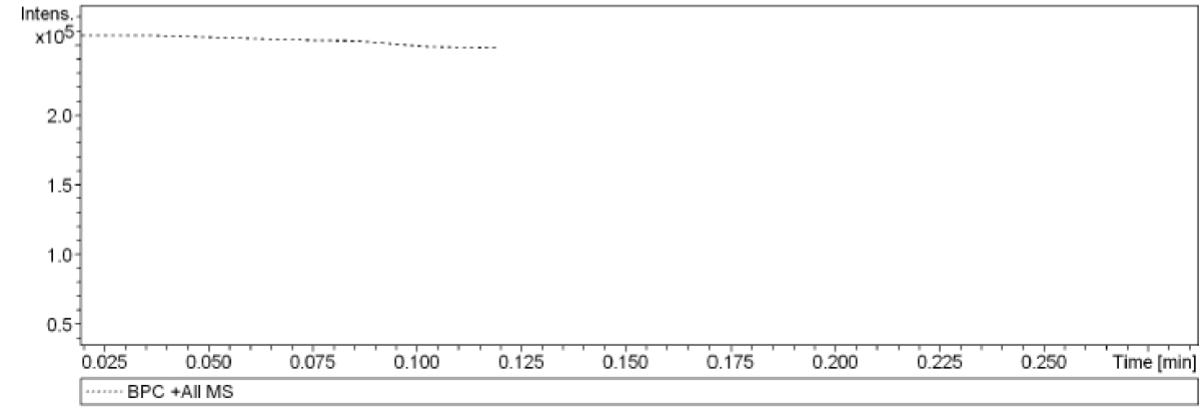
+MS, 0.1-0.1min #5-7

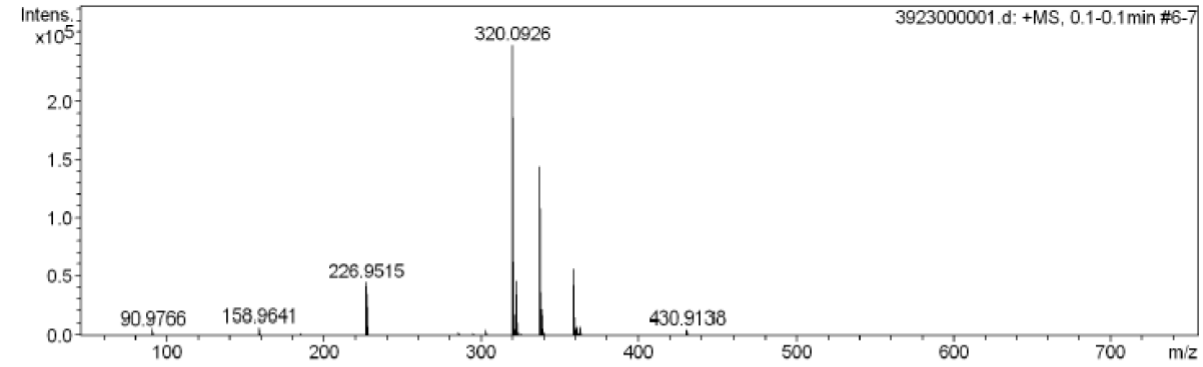
2-{2-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-1*H*-indol-3-yl}ethan-1-amine (**5b**).

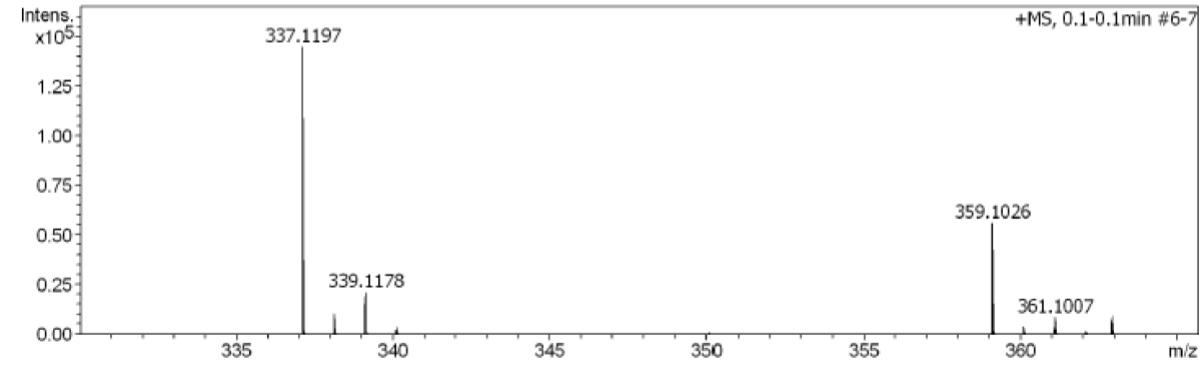


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



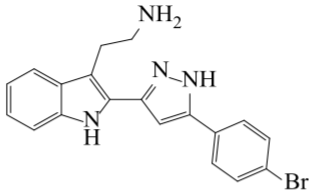




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e¯ Conf	N-Rule
337.1197	1	C19H18ClN4	337.1215	5.1	113.5	1	100.00	12.5	even	ok
359.1026	1	C19H17ClN4Na	359.1034	2.1	110.5	1	100.00	12.5	even	ok

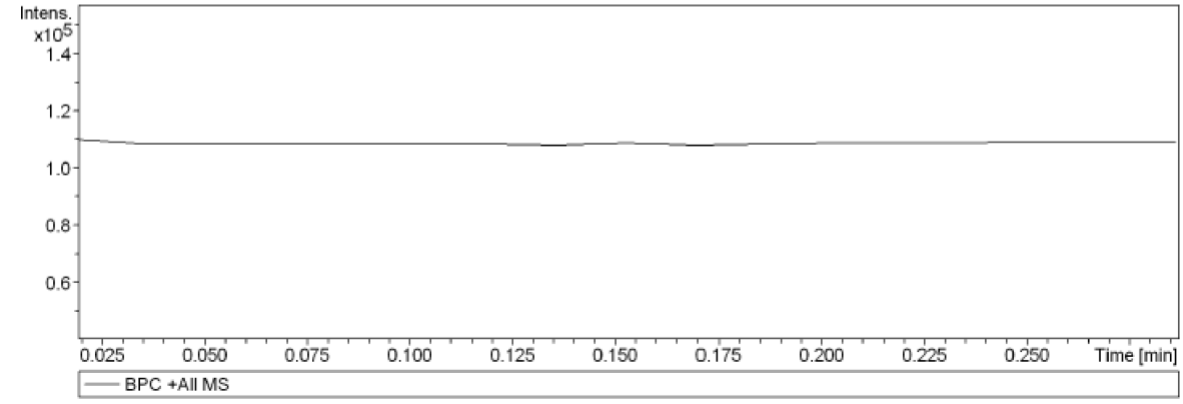
+MS, 0.1-0.1min #6-7

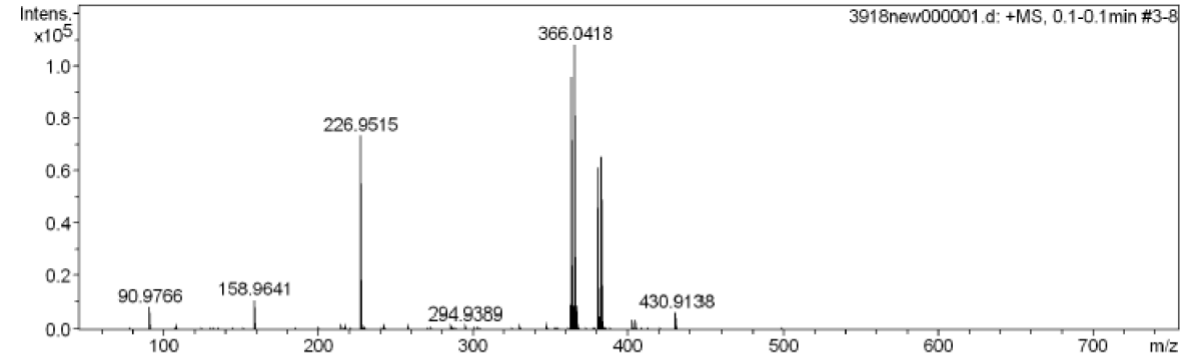
2-(2-(5-(4-Bromophenyl)-1*H*-pyrazol-3-yl)-1*H*-indol-3-yl)ethan-1-amine (**5c**).

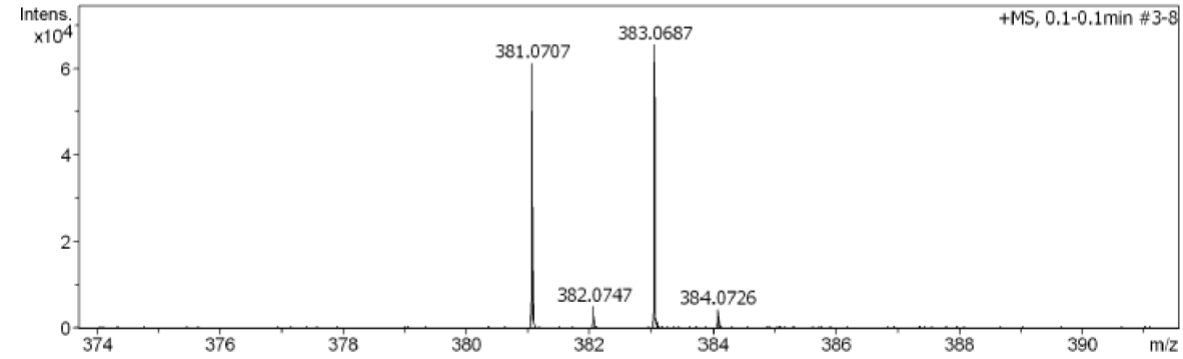


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



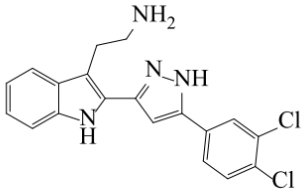




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e¯ Conf	N-Rule
381.0707	1	C19H18BrN4	381.0709	0.6	97.6	1	100.00	12.5	even	ok

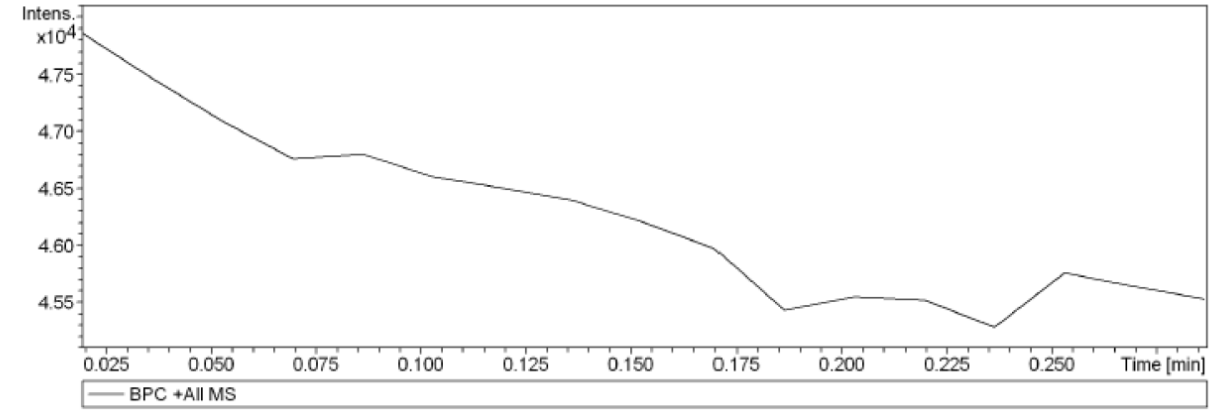
+MS, 0.1-0.1min #3-8

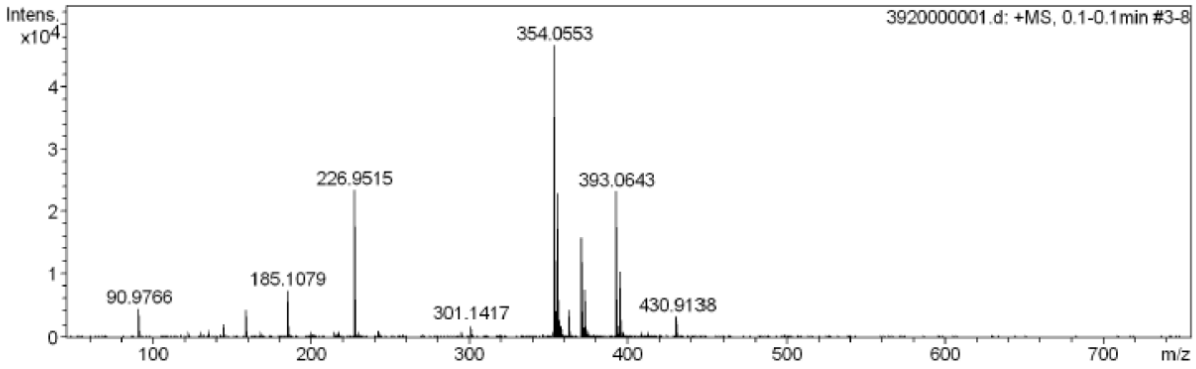
2-{2-[5-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl]-1*H*-indol-3-yl}ethan-1-amine (**5d**).

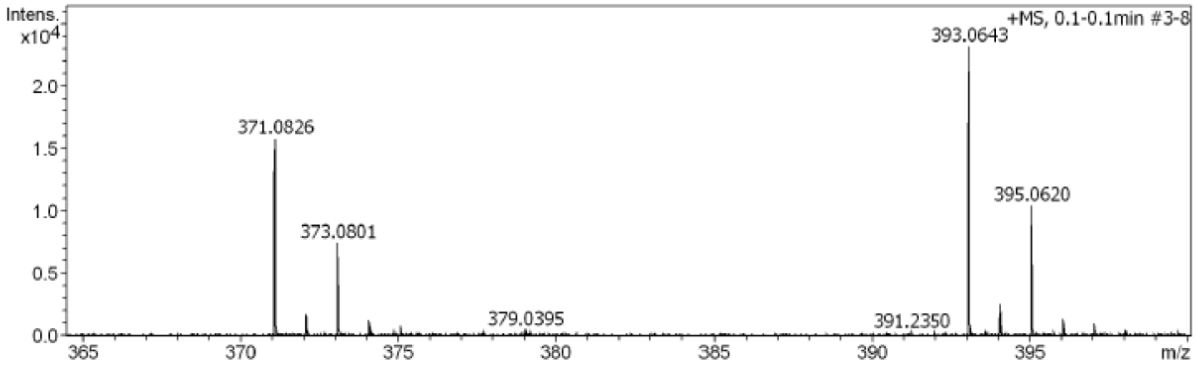


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



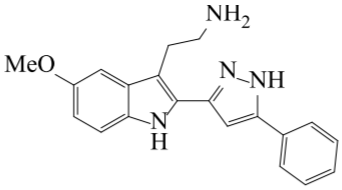




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e¯ Conf	N-Rule
371.0826	1	C19H17Cl2N4	371.0825	-0.4	100.7	1	100.00	12.5	even	ok
	1	C19H17Cl2N4	371.0825	-0.4	100.7	1	100.00	12.5	even	ok
393.0643	1	C20H19Cl2O4	393.0655	3.1	112.0	1	100.00	10.5	even	ok
	1	C19H16Cl2N4Na	393.0644	0.4	109.1	1	100.00	12.5	even	ok

+MS, 0.1-0.1min #3-8

2-[5-Methoxy-2-(5-phenyl-1H-pyrazol-3-yl)-1*H*-indol-3-yl]ethan-1-amine (**5e**).

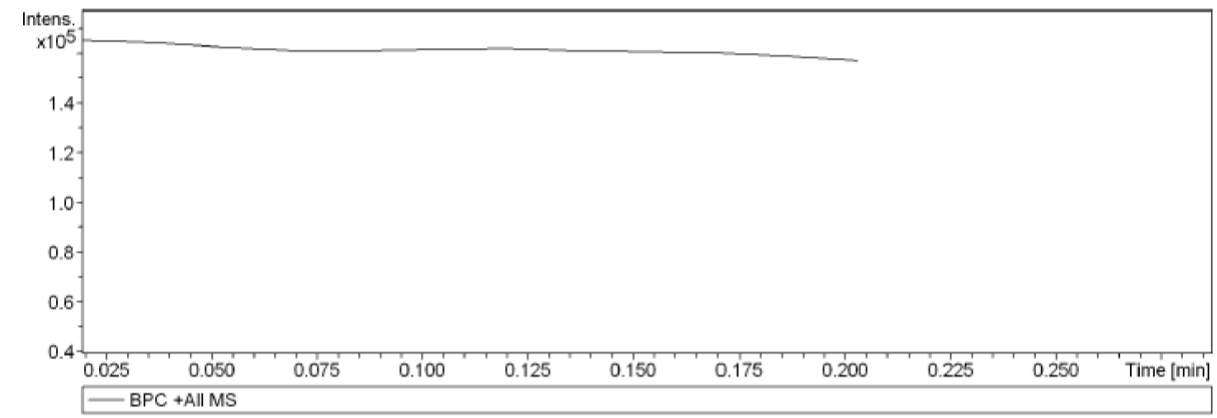


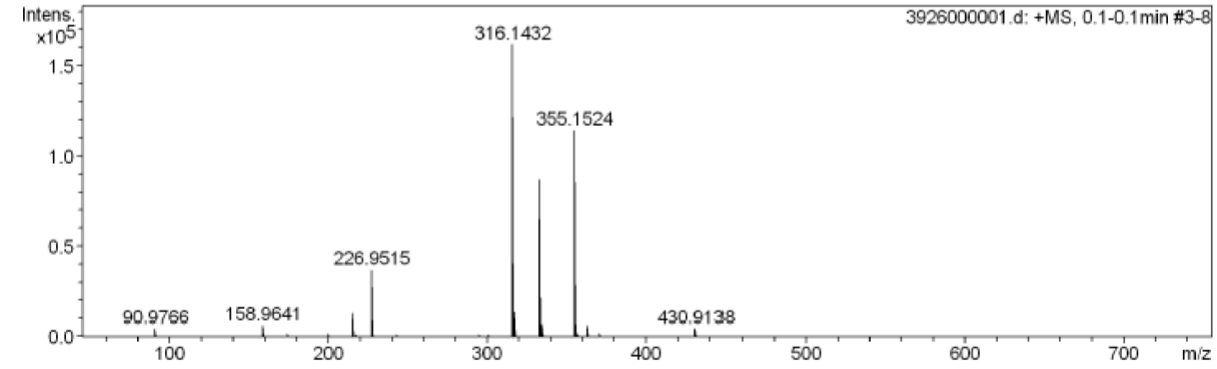
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e⁻ Conf	N-Rule
333.1701	1	C20H21N4O	333.1710	2.8	87.7	1	100.00	12.5	even	ok
355.1524	1	C20H20N4NaO	355.1529	1.6	86.2	1	100.00	12.5	even	ok

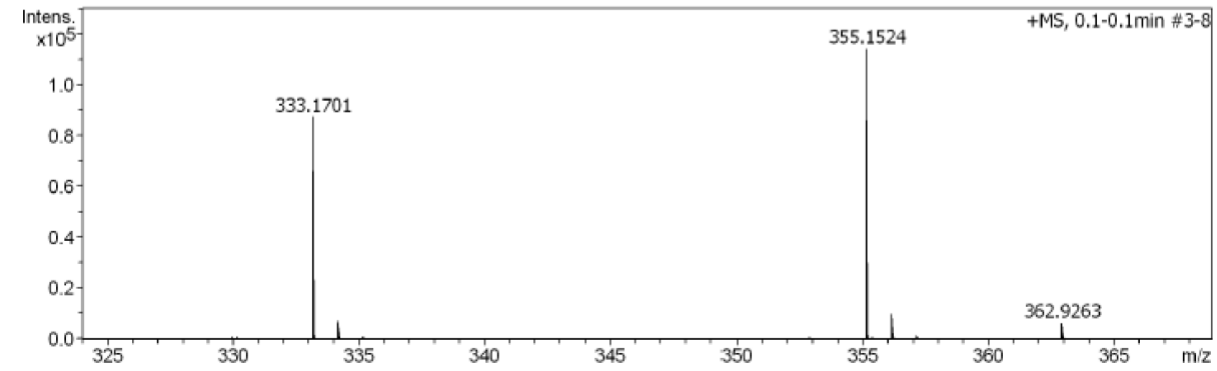
+MS, 0.1-0.1min #3-8

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



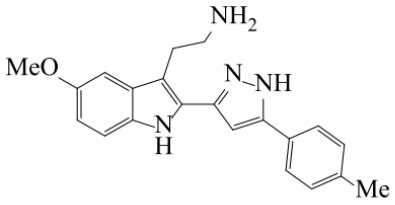




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e⁻ Conf	N-Rule
333.1701	1	C20H21N4O	333.1710	2.8	87.7	1	100.00	12.5	even	ok
355.1524	1	C20H20N4NaO	355.1529	1.6	86.2	1	100.00	12.5	even	ok

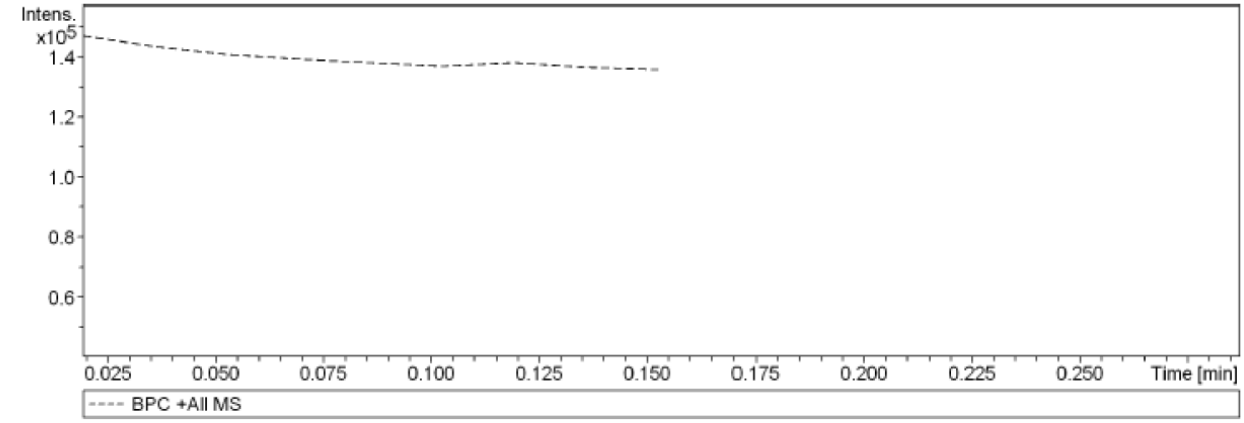
+MS, 0.1-0.1min #3-8

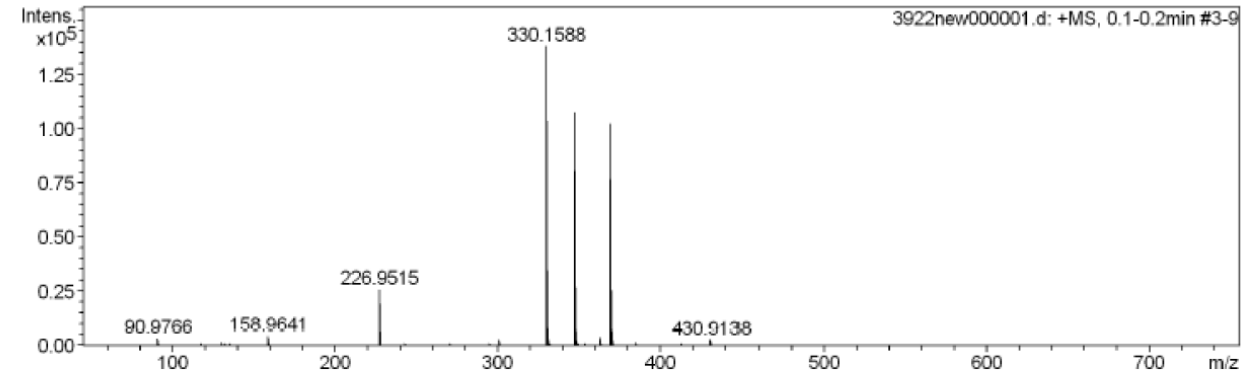
2-{[5-Methoxy-2-[5-(p-tolyl)-1*H*-pyrazol-3-yl]-1*H*-indol-3-yl}ethan-1-amine (**5f**).

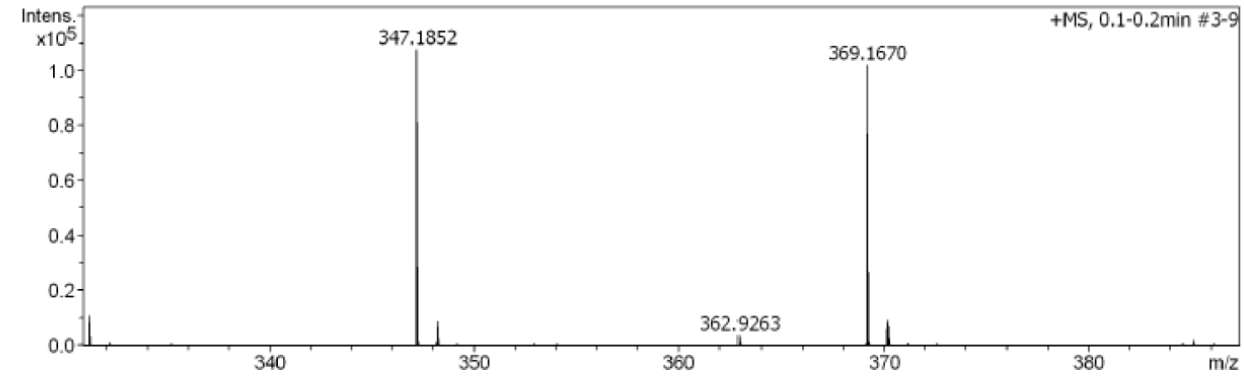


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



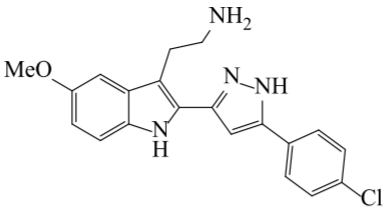




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e¯ Conf	N-Rule
347.1852	1	C21H23N4O	347.1866	4.1	93.5	1	100.00	12.5	even	ok
369.1670	1	C21H22N4NaO	369.1686	4.2	89.6	1	100.00	12.5	even	ok

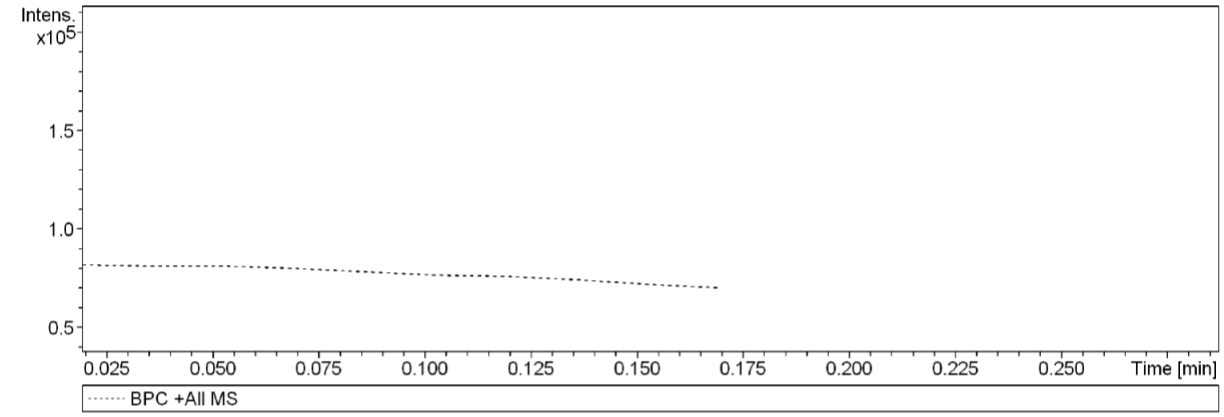
+MS, 0.1-0.2min #3-9

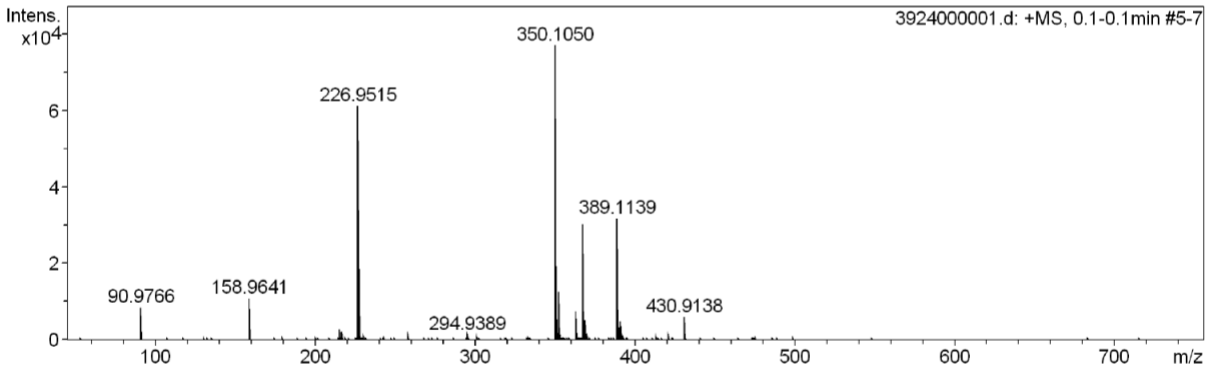
2-{2-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethan-1-amine (**5g**).

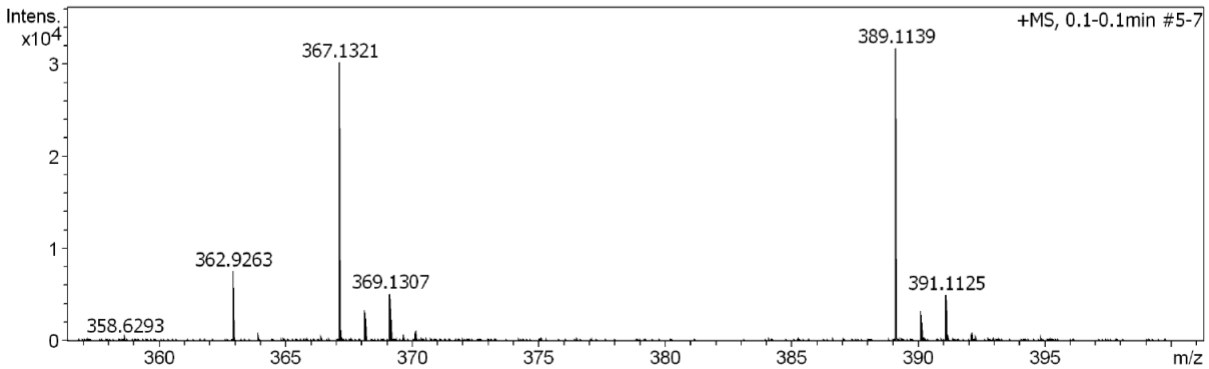


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



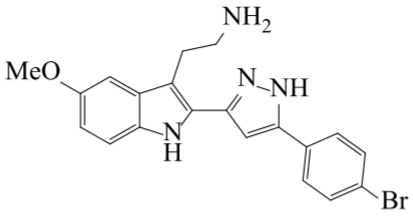




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e⁻ Conf	N-Rule
367.1321	1	C20H20ClN4O	367.1320	-0.2	98.2	1	100.00	12.5	even	ok
389.1139	1	C20H19ClN4NaO	389.1140	0.2	105.7	1	100.00	12.5	even	ok

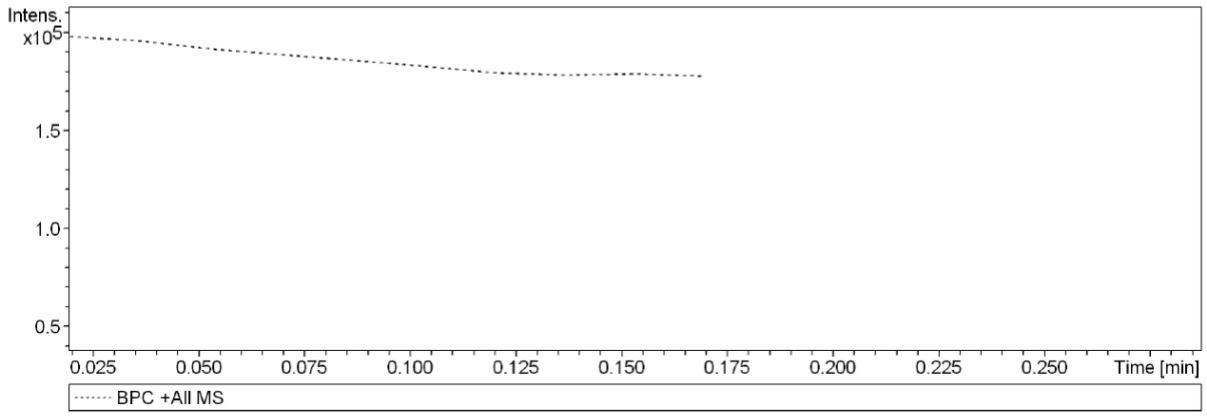
+MS, 0.1-0.1min #5-7

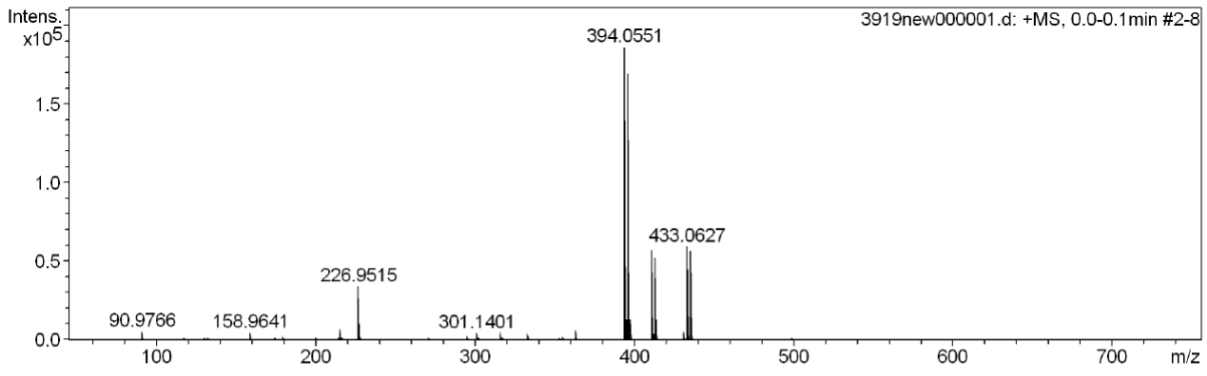
2-{2-[5-(4-Bromophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethan-1-amine (**5h**).

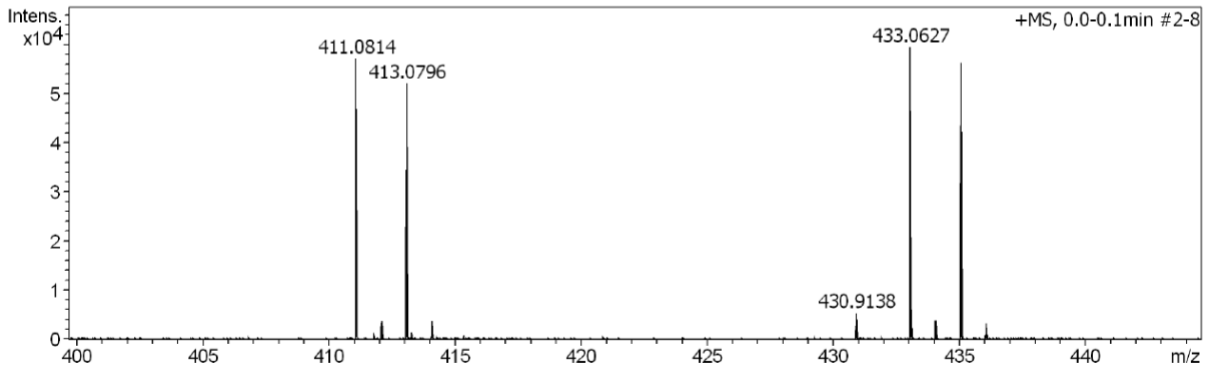


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



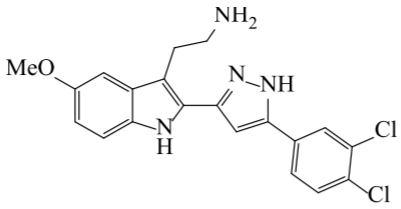




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e⁻ Conf	N-Rule
411.0814	1	C20H20BrN4O	411.0815	0.2	112.2	1	100.00	12.5	even	ok
433.0627	1	C20H19BrN4NaO	433.0634	1.6	111.5	1	100.00	12.5	even	ok

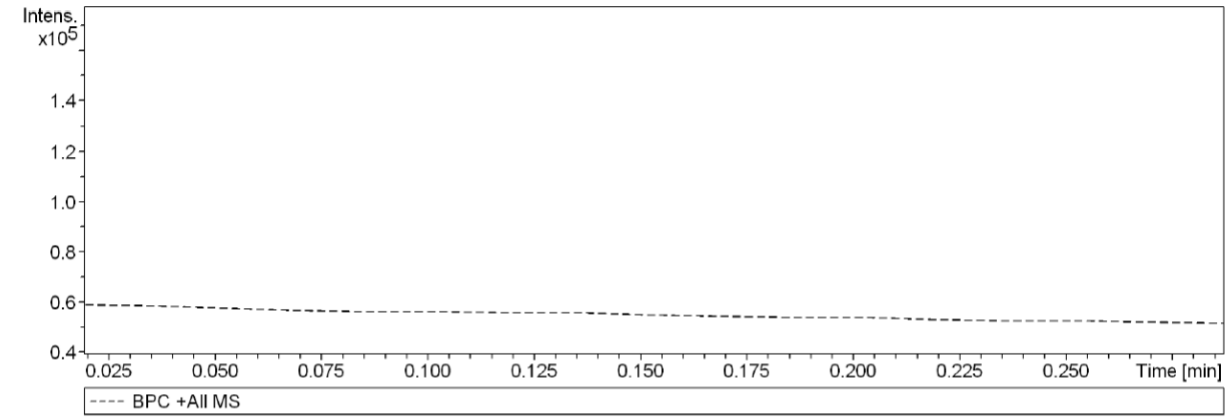
+MS, 0.0-0.1min #2-8

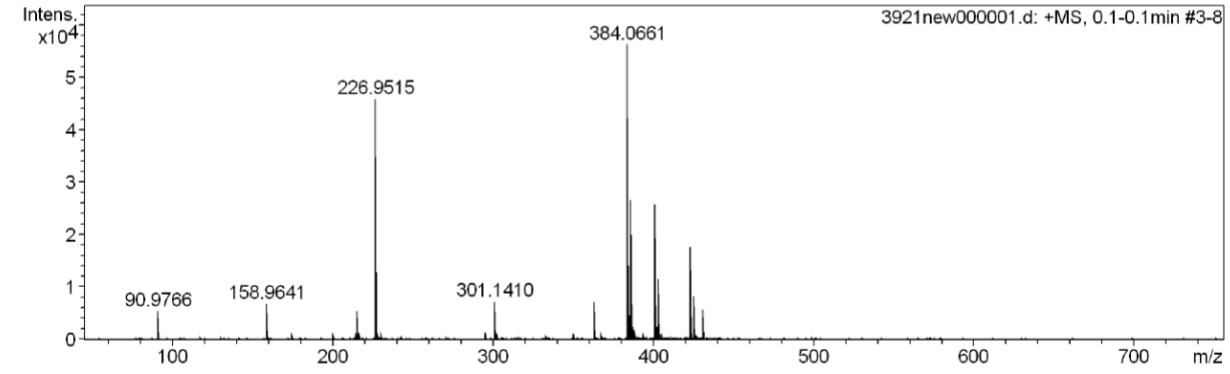
2-{2-[5-(3,4-Dichlorophenyl)-1*H*-pyrazol-3-yl]-5-methoxy-1*H*-indol-3-yl}ethan-1-amine (**5i**).

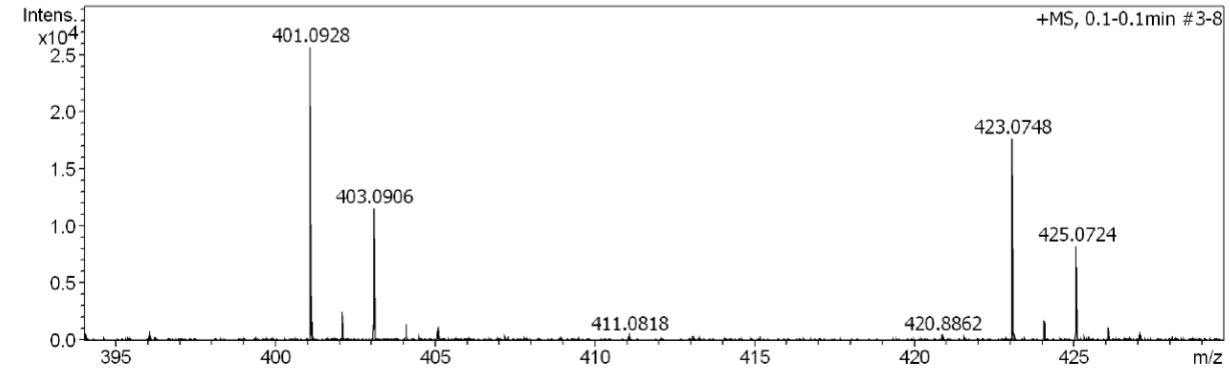


Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	750 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source







Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma		Score	rdb	e¯ Conf	N-Rule
401.0928	1	C20H19Cl2N4O	401.0930	0.7	116.3	1	100.00	12.5	even	ok
423.0748	1	C20H18Cl2N4NaO	423.0750	0.5	112.2	1	100.00	12.5	even	ok