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Supporting Information

Tandem Mannich/Diels-Alder reactions for the synthesis of indole compound libraries

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List of Contents

General Methods

Unless otherwise noticed, all reactions were run under an argon atmosphere. All solvents were of HPLC quality, and were typically dried over molecular sieves.

All reactions were monitored by thin layer chromatography (TLC), reversed-phase high performance liquid chromatography (RP-HPLC), or reversed-phase ultra-performance liquid chromatography mass spectrometry (RP-HPLC/MS). All yields are unoptimized and generally represent the result of a single experiment.

TLC was conducted using Merck aluminum sheets covered with silica gel C-60 F_{254}. The plates were either visualized under UV-light (254 nm) or stained by dipping in a developing agent followed by heating. $KMnO_4$ dipping solution were used as the developing agents: $KMnO_4$ (1.5 g), K_2CO_3 (10 g), 5% NaOH aqueous solution (2.5 mL), H_2O (150 mL).

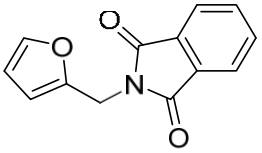
Column chromatography was performed using a glass column packed with Geduran® Si 60 silica gel (40-63 µm particles). A mixture of heptane and ethyl acetate was used as the liquid phase.

LC/MS analysis was performed on a Waters AQUITY UPLC system equipped with a C-18 column (*d* 1.7 µm, 2.1 × 50 mm, column temp: 65 °C), a PDA and SQD MS detector. A linear reversed phase gradient (5% to 100% organic in 2.4 min, hold for 0.1 min, total run-time 2.6 min) combining water and acetonitrile (buffered with 0.1% formic acid) was used.

^{1}H NMR and ^{13}C NMR were recorded using a Bruker Ascend-400 MHz instrument in DMSO-d_6 or $CDCl_3$ using the residual solvent peak as the internal standard. All ^{13}C NMR spectra were proton decoupled. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. Multiplicities of peaks in ^{1}H NMR are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (double doublet), and m (multiplet).

Experimental Procedures and Characterization Data

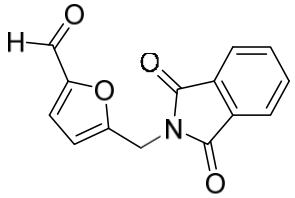
2-(Furan-2-ylmethyl)isoindoline-1,3-dione (7)



Furan-2-ylmethanamine (7.95 ml, 90 mmol), and isobenzofuran-1,3-dione (14.81 g, 100 mmol) was dissolved in AcOH (15 ml) and refluxed for 30 min. The reaction mixture was poured into cold water (150 mL) and neutralized with solid $NaHCO_3$. The precipitate was filtered off and recrystallized from EtOAc(100 mL) and heptane (10 mL). Allowed to crystallize overnight afforded **7** (11 g, 54%) as white crystals.[Lit.]

[Lit.] Nevolina, T.A.; Shcherbinin, V.A.; Uchuskin, M.G.; Serdyuk, O.V.; Trushkov, I.V. *Synthesis*, **2010**, *17*, 2969-2978.

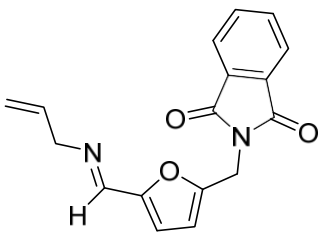
5-((1,3-Dioxoisoindolin-2-yl)methyl)furan-2-carbaldehyde (8)



2-(Furan-2-ylmethyl)isoindoline-1,3-dione **7** (11.10 g, 48.9 mmol) was taken up in DMF (15 ml), cooled to 0 °C, and added dropwise phosphorus oxychloride (45.5 ml, 489 mmol). After addition the reaction mixture was heated at 50 °C for 30 min. The cooled reaction was poured onto ice and neutralized to pH 8, by adding solid NaOH (reacts violently, external cooling required). The precipitate was filtered, washed with water, and dried. Recrystallization from EtOH afforded **8** (10.32 g, 83%) as yellow crystals.[Lit.]

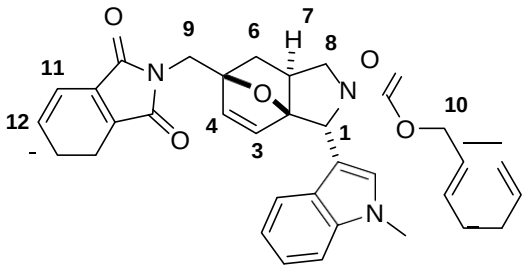
[Lit] Nevolina, T.A., Stroganova, T.A.; Shvlyakov, M.V; Butin, A.V. *Chem. Het. Comp.***2007**,*43*,408-415.

2-((5-((Allylimino)methyl)furan-2-yl)methyl)isoindoline-1,3-dione (4)



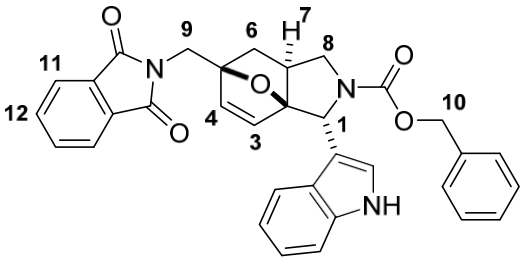
5-((1,3-Dioxoisoindolin-2-yl)methyl)furan-2-carbaldehyde **8** (12.5 g, 49.0 mmol) and allylamine (3.66 mL, 49.0 mmol) was dissolved in CH_2Cl_2 (100 mL) under and argon atmosphere. The reaction mixture was added $MgSO_4$ (4.0 g, 33.2 mmol) and stirred overnight at 21 °C. Filtration, followed by concentration *in vacuo* afforded an orange oil that solidified upon standing, to give **4** (14.6 g, quant.), with trace of starting material, as a yellow powder,. ^{1}H NMR (400 MHz, DMSO) δ 8.09 (s, 1H), 7.89 (m, 4H), 6.85 (d, *J* = 3.4 Hz, 1H), 6.53 (d, *J* = 3.4 Hz, 1H), 5.97 (m, 1H), 5.10 (ddd, *J* = 13.7, 11.7, 1.6 Hz, 2H), 4.82 (s, 2H), 4.11 (dd, *J* = 5.7, 1.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 167.2, 151.9, 151.0, 150.4, 136.4, 134.7, 131.5, 123.3, 115.9, 115.4, 110.2, 62.6, 34.4.

Benzyl (3R,3aS,6S,7aS)-6-((1,3-dioxoisoindolin-2-yl)methyl)-3-(1-methyl-1H-indol-3-yl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3H)-carboxylate (1a)



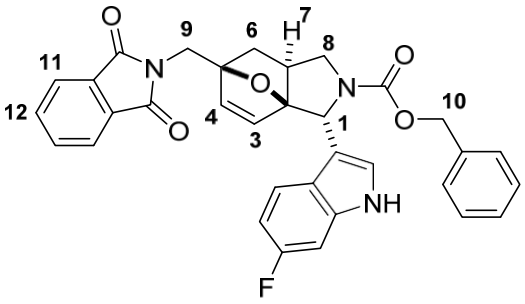
Furane **4** (1.512 g, 5.12 mmol), DIPEA (0.9 mL, 5.15 mmol) and 1-methyl-indole (2.70 g, 20.6 mmol) was dissolved in dry THF (12 mL) at 21 °C, under an argon atmosphere. The temperature was raised to 70 °C and the mixture was added CBzCl (0.73 mL, 5.14 mmol) dropwise over a period of 3 min. The reaction mixture was stirred for 2 days, before 1M HCl (aq.) (50 mL) was added, followed by extraction with EtOAc (3 × 50 mL). The combined organic phases were washed with water (2 × 50 mL), then brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (Silica, EtOAc/heptane, 60/40, v/v, R_f = 0.42) gave the desired compound **1a (**1.70 g, 59%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H; Ar), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H; Ar), 7.57 (d, *J* = 8.0 Hz, 1H; Ar), 7.40 – 7.29 (m, 3H; Ar), 7.24 – 7.17 (m, 1H; Ar), 7.15 – 7.00 (m, 3H; Ar), 6.86 – 6.79 (m, 2H; Ar), 6.24 (d, *J* = 5.7 Hz, 1H; H-4), 5.81 (d, *J* = 5.7 Hz, 1H; H-3), 5.52 (s, 1H; H-1), 5.11 – 4.85 (m, 2H; H-10), 4.26 (s, 2H; H-9), 4.21 – 4.12 (m, 1H; H-8a), 3.72 (s, 1.1H; CH_3), 3.69 (s, 1.9H; CH_3), 3.39 (m, 1H; H-8b), 2.46 (m, 1H; H-7), 1.78 (m, 1H; H-6a), 1.65 (m, 1H; H-6b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 154.9, 136.9, 136.0, 134.2, 132.1, 128.1, 127.4, 127.1, 123.7, 122.0, 119.5, 109.4, 99.3, 90.8, 66.4, 56.1, 52.4, 42.0, 39.8, 36.5, 33.0. UPLC-MS (ESI) calc. for $C_{34}H_{30}N_3O_5^+$ (MH^+) m/z = 560.21, found m/z = 560.27.

Benzyl (3R,3aS,6S,7aS)-6-((1,3-dioxoisoindolin-2-yl)methyl)-3-(1H-indol-3-yl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3H)-carboxylate (1b)



Furane **4** (1.506 g, 5.12 mmol), DIPEA (0.9 mL, 5.15 mmol) and indole (2.400 g, 20.49 mmol) was dissolved in dry THF (12 mL) at 21 °C, under an argon atmosphere. The mixture was added CBzCl (0.73 mL, 5.11 mmol) dropwise, before the temperature was raised to 70 °C and the reaction mixture was stirred for 2 days. Addition of 1M HCl (aq.) (25 mL) followed by extraction with EtOAc (3 × 50 mL). The organic phases were washed with water (2 × 25 mL), then brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (Silica, EtOAc/heptane, 3/2, v/v, R_f = 0.35) gave the desired compound **1a** (1.552 g, 56%) as a yellow foam. ^{1}H NMR (400 MHz, DMSO) δ 11.12 (s, ½H; NH), 11.09 (s, ½H; NH), 7.91 – 7.85 (m, 4H; Ar), 7.45 (d, *J* = 7.9 Hz, 1H; Ar), 7.40 - 7.26 (m, 5H; Ar), 7.15-7.04 (m, 3H; Ar), 6.98 (m, 1H; Ar), 6.82 (d, *J* = 7.3 Hz, 1H; Ar), 6.26 (d, *J* = 5.8 Hz, 1H; H4), 5.61 (d, *J* = 5.8 Hz, 1H; H3), 5.36 (s, ½H; H1), 5.28 (s, ½H; H1), 5.03 – 4.87 (m, 2H; H10), 4.18–4.01 (m, 3H; H9, H8a), 3.23 (m, 1H; H8b), 2.46 (m, 1H; H7), 1.79 (d, *J* = 11.5 Hz, 1H; H6b), 1.62 (m, 1H; H6a). ^{13}C NMR (101 MHz, DMSO) δ 167.8, 153.8, 153.6, 137.7, 137.0, 137.0, 136.4, 134.6, 131.5, 128.4, 128.0, 127.8, 127.5, 127.2, 126.3, 125.4, 125.4, 123.3, 123.2, 123.0, 123.0, 121.2, 118.9, 118.9, 118.3, 118.3, 118.1, 113.6, 113.2, 111.7, 98.6, 97.7, 90.4, 89.8, 65.8, 65.3, 55.9, 55.5, 52.0, 51.7, 42.4, 41.4, 36.1, 36.0. UPLC-MS (ESI) calc. for $C_{33}H_{28}N_3O_5^+$ (MH^+) m/z = 546.23, found m/z = 546.24.

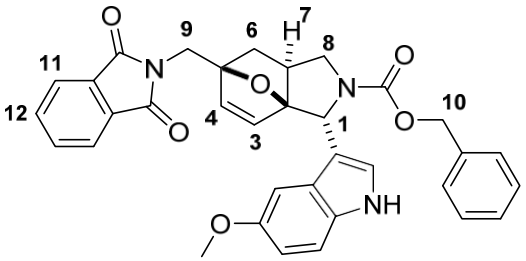
Benzyl (3R,3aS,6S,7aS)-6-((1,3-dioxoisoindolin-2-yl)methyl)-3-(6-fluoro-1H-indol-3-yl)-1,6,7, 7a-tetrahydro-3a,6-epoxyisoindole-2(3H)-carboxylate (1c)



Furane **4** (1.476 g, 5.02 mmol), DIPEA (0.9 mL, 5.15 mmol) and 6-fluoro-1H-indole (2.71 g, 20.1 mmol) was dissolved in dry THF (12 mL) at 21 °C, under an argon atmosphere. The temperature was raised to 70 °C and the mixture was added CBzCl (0.72 mL, 5.02 mmol). The reaction mixture was stirred for 2 days, before 1M HCl (aq.) (50 mL) was added, followed by extraction with EtOAc (3 × 50 mL). The combined organic phases were washed with water (2 × 25 mL), then brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (Silica, EtOAc/heptane, 55/45, v/v, R_f = 0.35) gave the desired compound **1c** (1.76 g, 62%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 0.4H; NH), 8.33 (s, 0.6H; NH), 7.88 (dd, *J* = 5.5,

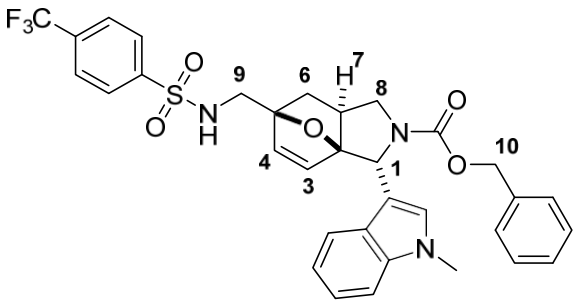
3.0 Hz, 2H; Ar), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H; Ar), 7.47 – 7.29 (m, 4H; Ar), 7.13 – 7.01 (m, 2H; Ar), 6.87 - 6.71 (m, 3H; Ar), 6.25 (d, *J* = 5.8 Hz, 1H; H-4), 5.73 (m, 1H; H-3), 5.47 (s, 0.6H, H-1), 5.44(s, 0.4H, H-1) 5.12 – 4.85 (m, 2H; H-10), 4.26 (s, 2H; H-9), 4.19 – 4.10 (m, 1H; H-8a), 3.45 – 3.33 (m, 1H; H-8b), 2.48 – 2.35 (m, 1H; H-7), 1.81 – 1.72 (m, 1H; H-6a), 1.68 – 1.58 (m, 1H; H-6b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 161.4, 161.1, 155.0, 154.8, 137.1, 136.9, 136.7, 135.7, 135.7, 134.3, 132.1, 128.6, 128.1, 128.0, 127.5, 127.0, 123.7, 123.5, 122.5, 122.0, 120.1, 120.0, 119.7, 118.3, 116.0, 114.4, 108.9, 108.7, 108.6, 108.3, 99.2, 98.6, 97.9, 97.8, 97.6, 90.9, 90.9, 67.0, 66.5, 56.8, 56.0,52.4, 44.7, 43.1, 42.0, 39.9, 39.8, 36.3, 22.8. UPLC-MS (ESI) calc. for $C_{33}H_{27}FN_3O_5^+$ (MH^+) m/z = 564.19, found m/z = 564.25.

Benzyl (3R,3aS,6S,7aS)-6-((1,3-dioxoisoindolin-2-yl)methyl)-3-(5-methoxy-1H-indol-3-yl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3H)-carboxylate (1d)



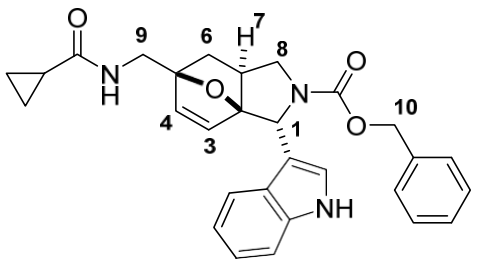
Furane **4** (1.46 g, 5.0 mmol), DIPEA (0.9 mL, 5.15 mmol) and 5-methoxy-1H-indole (2.92 g, 19.8 mmol) was dissolved in dry THF (12 mL) at 21 °C, under an argon atmosphere. The temperature was raised to 70 °C and the mixture was added CBzCl (0.71 mL, 5.0 mmol) dropwise over a period of 3 min. The reaction mixture was stirred for 2 days, before 1M HCl (aq.) (50 mL) was added, followed by extraction with EtOAc (3 × 50 mL). The combined organic phases were washed with water (2 × 50 mL), then brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (Silica, EtOAc/heptane,) gave the desired compound **1d (**2.07 g, 72%) as a white foam. ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 0.5H; NH), 10.94 (s, 0.5H; NH), 7.92 – 7.82 (m, 4H; Ar), 7.37 – 7.20 (m, 4H; Ar), 7.18 – 7.00 (m, 2H; Ar), 6.92 (s, 1H; Ar), 6.85 (d, *J* = 7.3 Hz, 1H; Ar), 6.75 (dd, *J* = 8.8, 1.9 Hz, 1H; Ar), 6.29 (d, *J* = 5.8 Hz, 1H; H-4), 5.67 (d, *J* = 5.7 Hz, 1H; H-3), 5.35 (s, 0.5H; H-1), 5.26 (s, 0.5H; H-1), 5.07 – 4.88 (m, 2H; H-10), 4.14 (s, 2H; H-9), 4.07 (m, 1H; H-8a) 3.69 (s, 0.5H; CH_3), 3.65 (s, 0.5H; CH_3), 3.23 (m, 1H; H-8b), 2.49 – 2.42 (m, 1H; H-7), 1.82 – 1.75 (m, 1H; H-6a), 1.68 – 1.56 (m, 1H; H-6b). ^{13}C NMR (101 MHz, DMSO) δ 167.8, 153.3, 137.7, 137.0, 134.6, 131.5, 128.4, 127.9, 127.4, 127.1, 126.3, 125.8, 123.6, 123.3, 113.4, 112.4, 111.4, 100.1, 100.0, 98.6, 97.7, 90.3, 65.8, 65.3, 55.7, 55.3, 42.4, 41.4, 36.2. UPLC-MS (ESI) calc. for $C_{34}H_{30}N_3O_6^+$ (MH^+) m/z = 576.21, found m/z = 576.31.

Benzyl (3R,3aS,6S,7aS)-3-(1-methyl-1H-indol-3-yl)-6-(((4-(trifluoromethyl)phenyl)sulfonamido)methyl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3H)-carboxylate (2a)



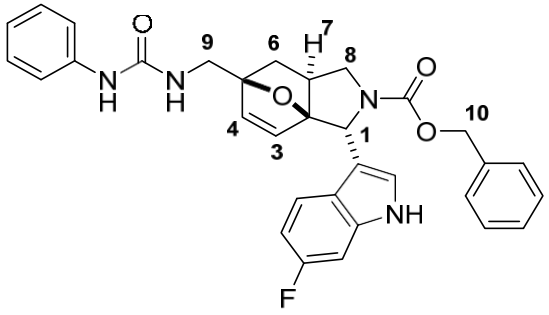
Indole **1a** (507 mg, 0.91 mmol) was taken up in MeOH (4 mL) (not in solution) and added hydrazine (50% in water, 0.170 mL, 2.72 mmol) – The solution becomes clear. The reaction mixture was stirred at 21 °C for 1 h. before 2 M HCl (aq) (5 mL) was added – the solution becomes warm and the color changes from yellow to redish. The resulting mixture was stirred overnight, then extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude amine. 4-(Trifluoromethyl)benzene-sulfonyl chloride (169 mg, 0.69 mmol) and Et_3N (0.10 ml, 0.69 mmol) was dissolved in CH_2Cl_2 (2 mL) under an argon atmosphere and cooled to 0 °C. The above-obtained crude amine (296 mg, 0.69 mmol) dissolved in CH_2Cl_2 (2 mL) was added and the reaction mixture was allowed to warm to 21 °C and stirred. After 30 min, additional 0.1 equivalent reactants were added and the reaction mixture was stirred for additional 1h, before being concentrated *in vacuo*. Purification by flash column chromatography (Silica, eluent: EtOAc/heptane, 1/1, v/v, Rf= 0.45) afforded the desired sulfonamide **2a** (497 mg, quant.) with traces of solvent. ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s, 1H; NH), 8.04 (d, *J* = 8.3 Hz, 2H; Ar), 8.01 – 7.85 (m, 3H; Ar), 7.49 – 7.42 (m, 2H; Ar), 7.38 – 7.27 (m, 4H; Ar), 7.21 – 7.01 (m, 4H; Ar), 6.87 (d, *J* = 7.2 Hz, 1H; Ar), 6.24 (d, *J* = 5.8 Hz, 1H; H-4), 5.61 (d, *J* = 5.8 Hz, 1H; H-4), 5.30 (s, 0.5H; H-1), 5.26 (s, 0.5H; H-1), 5.07 – 4.87 (m, 2H; H-10), 4.07 (m, 1H; H-8a), 3.76 (s, 3H; CH_3), 3.38 (m, 2H; H-9), 3.18 (m, 1H; H-8b), 2.42 (m, 1H; H-7), 1.74 – 1.68 (m, 1H; H-6a), 1.50 – 1.39 (m, 1H; H-6b). ^{13}C NMR (101 MHz, DMSO) δ 153.8, 153.7, 144.8, 144.7, 137.8, 137.0, 136.7, 133.8, 132.0, 128.4, 128.0, 127.8, 127.6, 127.5, 127.3, 127.2, 127.2, 126.6, 126.4, 125.8, 124.9, 122.2, 121.4, 119.0, 118.4, 110.0, 98.5, 97.6, 90.4, 65.9, 65.4, 64.9, 55.7, 55.3, 44.1, 42.4, 41.1, 35.1, 35.0, 32.5, 32.3, 15.3. UPLC-MS (ESI) calc. for $C_{33}H_{31}F_3N_3O_5S^+$ (MH^+) m/z = 638.19, found m/z = 638.27.

Benzyl (3R,3aS,6S,7aS)-6-(cyclopropanecarboxamidomethyl)-3-(1H-indol-3-yl)-1,6,7,7a-tetra-hydro-3a,6-epoxyisoindole-2(3H)-carboxylate (2b)



Indole **1b** (454 mg, 0.83 mmol) was taken up in MeOH (4 mL) and added hydrazine (156 µl, 2.5 mmol) and stirred at 21 °C. After 1 h, 2M HCl (aq) (6 mL) was added and the resulting mixture was stirred overnight. After diluting with water (10 mL), the reaction mixture was washed with diethyl ether (25 mL), which was discarded. The aqueous phase was basified and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give crude amine, which (165 mg, 0.40 mmol) was dissolved in dry DMF (1 mL) and added preactivated acid in DMF (1.5 mL) (cyclopropanecarboxylic acid (0.038 mL, 0.476 mmol), DIPEA (0.083 mL, 0.476 mmol), tetrafluoro-l4-borane, 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium salt (153 mg, 0.47 mmol) - 10 min) and stirred for 1h at 21 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL), added 1 M HCl (25 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with water (20 mL), then brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by Purification by flash column chromatography (silica, eluent 5% MeOH in CH_2Cl_2, R_f = 0.42) gave the amide **2b (**154 mg, 80%) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO) δ 11.15 (s, ½H; NH), 11.10 (s, ½H; NH), 8.33 (br s, 1H; NH), 7.49 (d, *J* = 7.2 Hz, 1H; Ar), 7.44 – 7.26 (m, 5H; Ar), 7.17 – 7.07 (m, 3H; Ar), 7.02 (m, 1H; Ar), 6.87 (d, *J* = 7.3 Hz, 1H; Ar), 6.21 (d, *J* = 5.7 Hz, 1H; H-4), 5.62 (d, *J* = 5.7 Hz, 1H; H-3), 5.41 (s, ½H; H-1), 5.34 (s, ½H; H-1), 5.04- 4.90 (m, 2H; H-10), 4.13 (m, 1H; H-8a), 3.73 (dd, *J* = 14.4, 5.9 Hz, 1H; H-9a), 3.57 (dd, *J* = 14.4, 5.9 Hz, 1H; H-9b), 3.23 (m, 1H; H-8b), 2.45 (m, 1H; H-7), 1.65 (m, 2H; H-11 + H-6a), 1.47 (m, 1H; H-6b), 0.66 (m, 4H; 2 × CH_2). ^{13}C NMR (101 MHz, DMSO) δ 173.5, 138.8, 137.5, 136.9, 135.2 134.5, 128.9, 128.5, 128.1, 127.0, 123.4, 121.7, 119.4, 118.7, 112.2, 100.0, 98.9, 98.0, 91.7, 66.3, 65.8, 56.4, 56.0, 13.8, 6.8. UPLC-MS (ESI) calc. for $C_{29}H_{30}N_3O_4^+$ (MH^+) m/z = 484.22, found m/z = 484.22.

Benzyl (3R,3aS,6S,7aS)-3-(6-fluoro-1H-indol-3-yl)-6-((3-phenylureido)methyl)-1,6,7,7a-tetra-hydro-3a,6-epoxyisoindole-2(3H)-carboxylate (2c)

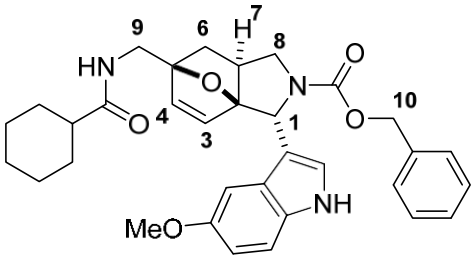


Indole **1c** (1.13 g, 2.0 mmol) was taken up in EtOH (10 mL) and added methylamine (40% in water, 0.9 ml, 10 mmol). The temperature was raised to 70 °C, and the reaction mixture was stirred for 2h, before concentrated *in vacuo*. Purification by flash column chromatography (silica, eluent: CH_2Cl_2, then 2.5% MeOH in CH_2Cl_2, followed by 5% MeOH in CH_2Cl_2). Redissolved in CH_2Cl_2, filtered, and concentrated *in vacuo* to afforded crude amine, which (212 mg, 0.49 mmol) was dissolved in dry DMF (2 mL) and cooled to 0 °C under an argon atmosphere. Phenyl isocyanate (53 µL, 0.49 mmol) was added, followed by Et_3N (68 µL, 0.49 mmol), and the reaction mixture was allowed to warm to 21 °C. The reaction mixture was stirred for 30 min at this temperature, before 1 M HCl (aq.) (25 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo.* Purification by flash column chromatography (silica, eluent: CH_2Cl_2, then 2.5% MeOH in

CH_2Cl_2, followed by 5% MeOH in CH_2Cl_2) afforded the desired urea **2c** (220 mg, 81 %) as a white amorphous solid with minor impurities. An analytical sample was purified by Prep HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.24 (s, 0.5H; NH), 11.20 (s, 0.5H; NH), 8.57 (s, 1H; NH), 7.47 (m, 1H; Ar), 7.41 – 7.28 (m, 6H; Ar), 7.25 – 7.13 (m, 3H; Ar), 7.10 (t, *J* = 7.2 Hz, 1H; Ar), 6.92 – 6.83 (m, 3H; Ar), 6.33 (m, 1H; NH), 6.29 (d, *J* = 5.6 Hz, 1H; H-4), 5.64 (d, *J* = 5.6 Hz, 1H; H-3), 5.39 (s, 0.5H; H-1), 5.32 (s, 0.5H; H-1), 5.07 – 4.88 (m, 2H; H-10), 4.12 (m, 1H; H-8a), 3.74 (m, 1H; H-9a), 3.66 – 3.57 (m, 1H; H-9b), 3.29 – 3.18 (m, 1H; H-8b), 2.46 (m, 1H; H-7), 1.75 – 1.68 (m, 1H; H-6a), 1.55 – 1.45 (m, 1H;H-6b). ^{13}C NMR (101 MHz, DMSO) δ 160.1, 157.7, 155.2, 153.8, 153.7, 140.4, 138.3, 137.0, 136.3, 136.2, 134.2, 128.7, 128.4, 128.0, 127.8, 127.5, 127.3, 126.5, 123.6, 122.4, 121.1, 119.2, 117.5, 114.0, 113.6, 107.6, 107.4, 98.4, 97.8, 97.6, 91.4, 65.9, 65.4, 55.9, 55.5, 51.9, 51.6, 42.5, 41.4, 40.6, 34.8. UPLC-MS (ESI) calc. for $C_{32}H_{30}FN_4O_4^+$ (MH^+) m/z = 553.22, found m/z = 553.34.

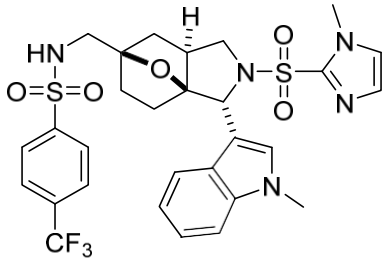
Note: When isocyanate was used in excess acylation of indole at the nitrogen position was observed.

Benzyl (3R,3aS,6S,7aS)-6-(cyclohexanecarboxamidomethyl)-3-(5-methoxy-1H-indol-3-yl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3H)-carboxylate (2d)



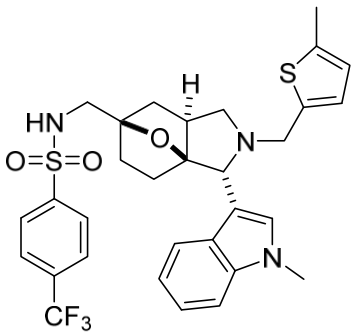
Indole **1d** (557 mg, 0.969 mmol) was taken up in MeOH (4 mL) (not in solution) and added hydrazine (50% in water, 0.170 mL, 2.72 mmol) – The solution becomes clear. The reaction mixture was stirred at 21 °C for 1 h. before 2 M HCl (aq) (5 mL) was added. The resulting mixture was stirred overnight, then extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude amine, which (225 mg, 0.51 mmol) was taken up in CH_2Cl_2 (3 mL) and cooled to 0 °C. Cyclohexanecarbonyl chloride (68 µl, 0.51 mmol) was added follwed by triethylamine (69 µl, 0.51 mmol). The solution became clear and after 10 min the reaction mixture was concentrated in vacou. Purification by flash column chromatography (Eluent: EtOAc/heptanes, 3:1, v/v) afforded the desired amide **2d** (204 mg, 73%). ^{1}H NMR (400 MHz, DMSO) δ 10.99 (s, 0.5H; NH), 10.95 (s, 0.5H; NH), 7.99 (m, 1H; NH), 7.38 – 7.08 (m, 6H; Ar), 6.90 (m, 2H; Ar), 6.78 (d, *J* = 8.8 Hz, 1H; Ar), 6.23 (d, *J* = 5.8 Hz, 1H; H-4), 5.66 (d, *J* = 5.8 Hz, 1H; H-3), 5.36 (s, 0.5H; H-1), 5.29 (s, 0.5H; H-1), 5.10 – 4.90 (m, 2H; CH_2), 4.09 (m, 1H; H-8a), 3.73 (s, 1.5H; OCH_3), 3.70 (s, 1.5H; OCH_3), 3.60 (m, CH_2), 3.19 (m, 1H; H-8b), 2.43 (m, 1H; H-7), 2.18 (m, 1H; CH), 1.72 – 1.54 (m, 6H; Alkyl), 1.54 – 1.09 (m, 6H; Alkyl). ^{13}C NMR (101 MHz, DMSO) δ 175.6, 153.8, 153.6, 153.2, 153.2, 138.3, 137.1, 133.9, 131.5, 128.4, 128.0, 127.8, 127.4, 127.3, 126.5, 125.8, 123.4, 113.5, 113.0, 112.4, 111.4, 100.0, 99.9, 98.3, 97.4, 91.2, 65.8, 65.3, 59.8, 55.9, 55.5, 55.3, 52.0, 51.7, 43.7, 42.3, 41.2, 35.1, 29.4, 29.2, 25.5, 25.2, 20.8, 18.3, 14.1. UPLC-MS (ESI) calc. for $C_{33}H_{38}N_3O_5^+$ (MH^+) m/z = 556.28, found m/z = 556.35.

***N*-(((3*R*,3a*S*,6*R*,7a*S*)-2-((1-Methyl-1H-imidazol-2-yl)sulfonyl)-3-(1-methyl-1H-indol-3-yl)-hexahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)-4-(trifluoromethyl)benzenesulfonamide (3a)**



Sulfonamide **2a** (194 mg, 0.304 mmol) was dissolved in MeOH (2 mL) and DMF (0.5 mL). The flask was charged with argon before 10% Pd/C (32 mg, 10 mol%). The reaction mixture was then charged with H_2 and stirred overnight at 21 °C. Filtration followed by concentration *in vacuo* afforded the free amine as a crude semisolid which was used without further purification. The obtained crude amine (20 mg, 0.040 mmol) was dissolved in DMF (0.5 mL) and added 1-methyl-1H-imidazole-2-sulfonyl chloride (7 mg, 0.040 mmol) followed by Et_3N (6 µl, 0.040 mmol). The reaction mixture was stirred at 21 °C for 1h. Purification by prep HPLC of the reaction mixture afforded the desired sulfonamide **3a** (5 mg, 20%). ^{1}H NMR (400 MHz, DMSO) δ 8.09 (s, 1H; NH), 8.06 -7.85(m, 4H; Ar), 7.58 (d, *J* = 7.9 Hz, 0.2H; Ar), 7.50 (d, *J* = 7.9 Hz, 0.8H; Ar), 7.40 – 7.32 (m, 1H; Ar), 7.18 – 7.08 (m, 2H; Ar), 7.05 – 6.95 (m, 2H; Ar, =CH), 6.90 (s, 1H; =CH), 5.36 (s, 0.2H; H-1), 5.23 (s, 0.8H; H-1), 4.08 (m, 0.8H; H-8a), 3.92 (m, 0.2H; H-8a), 3.70 (s, 0.6H; CH_3), 3.66 (s, 2.4H; CH_3), 3.56 (s, 0.6H; CH_3), 3.38 (m, 0.2H; H-8b),3.29 (s, 2.4H; CH_3), 3.19 – 3.01 (m, 2.8H; H-8b, CH_2), 2.84 (m, 0.8H; H-7), 2.55 (m, 0.2H; H-7) 1.87 – 1.69 (m, 1H; H-6a), 1.62 – 1.21 (m, 4H; H-6b, Alkyl), 1.19 – 1.03 (m, 1H; Alkyl). ^{13}C NMR (101 MHz, DMSO) δ 144.7, 141.3, 136.2, 127.9, 127.8, 127.5, 127.5, 126.4, 126.4, 125.8, 125.4, 124.9, 121.2, 119.1, 118.4, 111.1, 109.8, 109.4, 100.3, 99.5, 98.2, 96.0, 94.9, 86.8, 86.6, 58.9, 54.6, 45.6, 45.1, 34.4, 32.4, 31.0, 29.6. UPLC-MS (ESI) calc. for $C_{29}H_{31}F_3N_5O_5S_2^+$ (MH^+) m/z = 650.17 found m/z = 650.27.

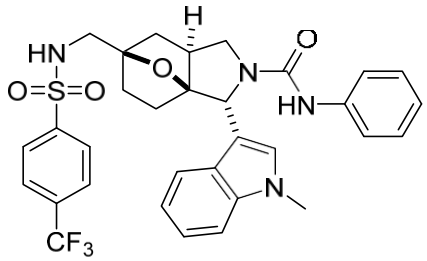
N-(((3R,3aS,6R,7aS)-3-(1-Methyl-1H-indol-3-yl)-2-((5-methylthiophen-2-yl)methyl)hexa-hydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)-4-(trifluoromethyl)benzenesulfonamide (3b)



Sulfonamide **2a** (194 mg, 0.304 mmol) was dissolved in MeOH (2 mL) and DMF (0.5 mL). The flask was charged with argon before 10% Pd/C (32 mg, 10 mol%). The reaction mixture was then charged with H_2 and stirred overnight at 21 °C. Filtration followed by concentration *in vacuo* afforded the free amine as a crude semisolid which was used without further purification. The obtained crude amine (20 mg, 0.040 mmol) was dissolved in DMF (0,5000 ml) and added 5-methylthiophene-2-carbaldehyde (10 mg, 0.080 mmol), $NaBH(OAc)_3$ (9 mg, 0.040 mmol), and

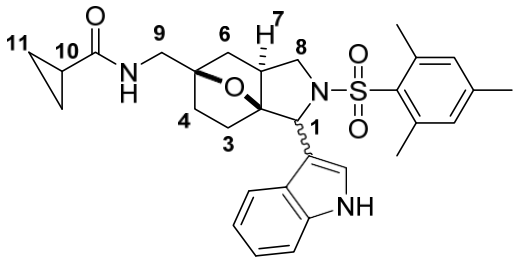
AcOH (3 µl, 0.040 mmol). The reaction mixture was stirred at 21 °C overnight. Purification by prep HPLC of the reaction mixture afforded the desired amine **3b** (6 mg, 25%). ^{1}H NMR (400 MHz, DMSO) δ 8.19 (s, 1H; NH), 8.14 (t, *J* = 6.2 Hz, 1H; Ar), 8.03 (d, *J* = 8.5 Hz, 2H; Ar), 7.98 (d, *J* = 8.5 Hz, 2H; Ar), 7.68 (d, *J* = 7.9 Hz, 1H; Ar), 7.38 (d, *J* = 8.2 Hz, 1H; Ar), 7.26 (s, 1H; Ar), 7.13 (t, *J* = 7.5 Hz, 1H; Ar), 7.02 (t, *J* = 7.4 Hz, 1H; Ar), 6.62 (d,J = 2.8 Hz, 1H; =CH), 6.58 (d,J = 2.8 Hz, 1H; =CH), 3.97 (s, 1H; H-1), 3.76 (s, 3H; CH_3)3.75 (d, *J* = 13.5 Hz, 1H; CH_2), 3.46 (d, *J* = 13.5 Hz, 1H; CH_2), 3.11 (m, 2H; CH_2), 3.05 (t, *J* = 7.5 Hz, 1H; H-8a), 2.48 – 2.41 (m, 1H; H-7), 2.36 (s,3H; CH_3), 2.01 – 1.95 (m, 1H; H-8b), 1.65 (m, 1H; H-6a), 1.45 – 1.37 (m, 3H; H-6b, Alkyl), 1.36 – 1.25 (m, 1H; Alkyl), 1.06 – 0.96 (m, 1H; Alkyl). ^{13}C NMR (101 MHz, DMSO) δ 163.6, 144.9, 139.5, 138.3, 137.3, 128.4, 127.6, 126.8, 126.3, 125.3, 124.6, 121.1, 120.0, 118.4, 112.7, 109.7, 97.1, 86.1, 62.4, 56.7, 50.9, 46.6, 45.7, 37.3, 32.4, 31.4, 31.4, 15.0. UPLC-MS (ESI) calc. for $C_{31}H_{33}F_3N_3O_3S_2^+$ (MH^+) m/z = 616.19 found m/z = 616.26.

(3R,3aS,6R,7aS)-3-(1-Methyl-1H-indol-3-yl)-N-phenyl-6-(((4-(trifluoromethyl)phenyl)sulfonamido) methyl)hexahydro-3a,6-epoxyisoindole-2(3H)-carboxamide (3c)



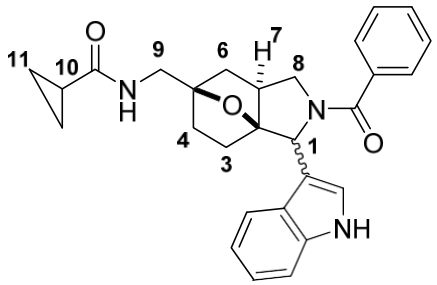
Sulfonamide **2a** (194 mg, 0.304 mmol) was dissolved in MeOH (2 mL) and DMF (0.5 mL). The flask was charged with argon before 10% Pd/C (32 mg, 10 mol%). The reaction mixture was then charged with H_2 and stirred overnight at 21 °C. Filtration followed by concentration *in vacuo* afforded the free amine as a crude semisolid which was used without further purification. The obtained crude amine (20 mg, 0.040 mmol) was dissolved in DMF (0.5 mL) and added Et_3N (6 µl, 0.043 mmol) and phenyl isocyanate (5 µl, 0.046 mmol). The reaction mixture was stirred at 21 °C for 1 h. Purification by prep HPLC of the reaction mixture afforded the desired urea **3c** (11 mg, 45%). ^{1}H NMR (400 MHz, DMSO) δ 8.25 (s, 1H; NH), 8.08 – 7.95 (m, 4H; Ar), 7.90 – 7.86 (m, 1H; Ar), 7.69 – 7.56 (m, 1H; Ar), 7.41 – 7.33 (m, 2H; Ar), 7.28 (s, 1H; Ar), 7.17 – 6.97 (m, 5H; Ar), 6.89 – 6.78 (m, 1H; Ar), 5.48 (s, 0.8H; H-1), 5.34 (s, 0.2H; H-1), 4.20 (t, *J* = 9.6 Hz, 0.8H; H-8a), 3.99 (t, *J* = 9.6 Hz, 0.2H;H-8a), 3.74 (s, 3H; CH_3), 3.24 – 2.99 (m, 1H; H-8b), 2.82 (m, 0.8H; H-7), 2.62 (m, 0.2H; H-7), 1.89 – 1.77 (m, 1.2H; H-6a, Alkyl), 1.75 – 1.56 (m, 1.2H; H-6b; Alkyl), 1.56 – 1.02 (m, 3.6H; Alkyl). ^{13}C NMR (101 MHz, DMSO) δ 153.6, 153.3, 144.8, 144.5, 140.3, 136.6, 136.6, 132.6, 132.3, 132.0, 131.5, 131.3, 128.3, 128.2, 127.5, 127.5, 127.3, 127.2, 126.4, 126.4, 126.0, 124.9, 124.9, 122.2, 121.6, 121.3, 121.1, 120.8, 119.9, 119.2, 118.8, 118.8, 118.5, 113.5, 110.5, 109.9, 109.5, 95.6, 94.6, 86.7, 86.6, 56.5, 55.9, 53.3, 46.0, 45.6, 45.5, 44.8, 38.5, 32.4, 32.3, 31.5, 29.7, 29.6. UPLC-MS (ESI) calc. for $C_{32}H_{32}F_3N_4O_4S^+$ (MH^+) m/z = 625.21 found m/z = 625.30.

N-(((3aS,6R,7aS)-3-(1H-indol-3-yl)-2-(mesitylsulfonyl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)cyclopropanecarboxamide (3d)



Amide **2b** (173 mg, 0.36 mmol) dissolved in DMF (0.5 mL) and MeOH (2 mL) and added 10% Pd/C (4 mg, 10 mol%). The reaction mixture was stirred overnight under H_2 atmosphere at 21 °C. Filtration, followed by concentration *in vacuo* afforded the crude free amine that was used without further purification. The obtained crude secondary amine (24 mg, 0.068 mmol), 2,4,6-trimethylbenzenesulfonyl chloride (18 mg, 0.082 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and added Et_3N (10 µl, 0.7 mmol). The reaction mixture was stirred for 1 h at 21 °C, before concentrated *in vacuo*. Purification by prep. HPLC (HCOOH, 5-70-100) afforded the desired sulfonamide **3d** (17 mg, 47%) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO), major isomer: δ 10.75 (s, 1H; NH), 8.23 (t, *J* = 5.9 Hz, 1H; NH), 7.39 (d, *J* = 7.9 Hz, 1H; Ar), 7.17 (d, *J* = 8.1 Hz, 1H; Ar), 7.05 (d, *J* = 2.3 Hz, 1H; Ar), 6.98 (t, *J* = 7.5 Hz, 1H; Ar), 6.93 - 6.82 (m, 1H), 6.57 (s, 2H; Ar), 5.16 (s, 1H; H-1), 3.81(m, 1H; H8a), 3.52 (dd, *J* = 14.3, 6.0 Hz, 1H; H-9a), 3.40 (dd, *J* = 14.3, 6.0 Hz, 1H; H-9b), 3.04 (m, 1H; H-8b), 2.92 – 2.78 (m, 1H; H-7), 2.34 (s, 6H; CH_3), 2.03 (s, 3H; CH_3), 1.86 – 1.76 (m, 1H; H-6a), 1.72 – 1.61 (m, 1H; H-10), 1.59 – 1.44 (m,1H; H-6b), 1.44 – 1.30 (m, 2H; H-3a, H-4a), 1.30 – 1.10 (m, 2H; H-3b, H-4b), 0.77 – 0.51 (m, 4H; CH_2). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 173.2, 141.6, 141.4, 139.2, 138.9, 136.8, 136.2, 134.3, 133.5, 131.4, 131.3, 127.2, 126.0, 125.7, 124.6, 121.1, 120.7, 120.0, 119.0, 118.8, 118.5, 112.5, 111.6, 111.1, 108.6, 96.9, 95.5, 88.1, 87.9, 59.2, 58.5, 54.1, 53.9, 46.3, 45.9, 42.5, 42.0, 32.7, 31.6, 30.7, 30.0, 22.9, 22.6, 20.7, 13.8, 6.7. UPLC-MS (ESI) calc. for $C_{30}H_{36}N_3O_4S^+$ (MH^+) m/z = 534.24, found m/z = 534.28.

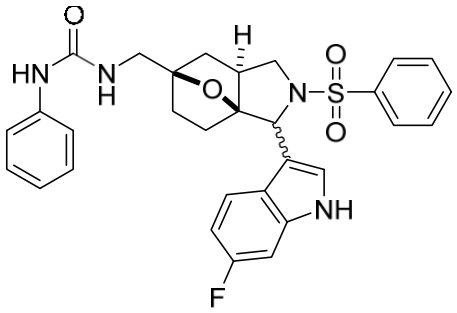
N-(((3aS,6R,7aS)-2-benzoyl-3-(1H-indol-3-yl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)cyclopropanecarboxamide (3e)



Amide **2b** (173 mg, 0.36 mmol) dissolved in DMF (0.5 mL) and MeOH (2 mL) and added 10% Pd/C (4 mg, 10 mol%). The reaction mixture was stirred overnight under H_2 atmosphere at 21 °C. Filtration, followed by concentration *in vacuo* afforded the crude free amine that was used without further purification. The obtained crude secondary amine (18 mg, 0.05 mmol) was taken up in dry DMF (0.5 mL) and added benzoic acid (6.3 mg, 0.05 mmol) followed by TBTU (16.4 mg, 0.05 mmol) and DIPEA (9 µl, 0.05 mmol). The reaction mixture was stirred at 21 °C. After 30 min, 10%

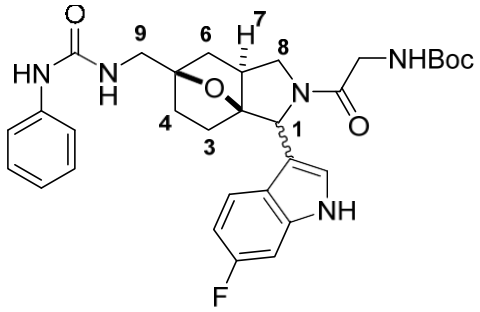
more TBTU and Dipea were added (incomplete reaction- LCMS) and the reaction mixture was stirred for additional 30 min. The crude reaction mixture was purified by prep HPLC to give the desired amide **3e** (10 mg, 43 %) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO), major isomer, δ 11.06 (s, 1H; NH), 8.26 (m, 1H; NH), 7.70 -7.29 (m, 5H; Ar), 7.26 – 7.16 (m, 1H; Ar), 7.12 – 6.89 (m, 4H; Ar), 5.74 (s, 1H; H-1), 4.31 – 4.20 (m, 1H; H-8a), 3.67 – 3.37 (m, 3H; H-9, H-8b), 2.87 – 2.71 (m, 1H; H-7), 1.97 – 1.88 (m, 1H; H-6a), 1.71 – 1.57 (m, 3H; Alkyl), 1.52 – 1.37 (m, 3H; Alkyl), 0.68 – 0.60 (m, 4H; Alkyl). UPLC-MS (ESI) calc. for $C_{28}H_{30}N_3O_3^+$ (MH^+) m/z = 456.22, found m/z = 456.28

1-(((3R,3aS,6R,7aS)-3-(6-Fluoro-1H-indol-3-yl)-2-(phenylsulfonyl)hexahydro-3a,6-epoxyiso-indol-6(1H)-yl)methyl)-3-phenylurea (3f)



Urea **2c** (220 mg, 0.4 mmol) was taken up in MeOH (2 mL) and DMF (0.5 mL). The flask was charged with argon before 10% Pd/C (42 mg, 10 mol%). The reaction mixture was then charged with H_2 and stirred overnight at 21 °C. Filtration followed by concentration in vacuo afforded the free amine as a crude semisolid which was used without further purification. The obtained crude amine (19 mg, 0.044 mmol) was taken up in CH_2Cl_2 (0.5 mL). Benzenesulfonyl chloride (7 µl, 0.055 mmol) was added followed by Et_3N (8 µl, 0.057 mmol) – The solution becomes clear.The reaction mixtue was stirred at 21 °C for 10 min before concentrated in vacuo. Purification by prep HPLC afforded desired sulfonamide **3f** (15 mg, 61%). ^{1}H NMR (400 MHz, DMSO), major isomer, δ 11.10 (d, *J* = 1.8 Hz, 1H; NH), 8.54 (s, 1H; NH), 7.68 – 7.49 (m, 2H; Ar), 7.49 – 7.33 (m, 5H; Ar), 7.25 – 7.18 (m, 3H; Ar), 7.10 (dd, *J* = 10.0, 2 Hz, 1H; Ar), 6.92 – 6.85 (m, 2H; Ar), 6.81 (td, *J* = 9.7, 2.4 Hz, 1H; Ar), 6.13 (t, *J* = 5.8 Hz, 1H; NH), 5.09 (s, 1H; H-1), 3.91 (m, 1H; H-8a), 3.43 (dd, *J* = 14.2, 6.8 Hz, 1H; H-9a), 3.20 (dd, *J* = 14.2, 4.9 Hz, 1H; H-9b), 2.95 (m, 1H; H-8b), 2.88 – 2.79 (m, 1H; H-7), 1.84 (m, 1H; H-6a), 1.58 – 1.36 (m, 3H; Alkyl), 1.34 – 1.24 (m, 1H; Alkyl), 1.17 – 1.08 (m, 1H; Alkyl). ^{13}C NMR (101 MHz, DMSO) δ 159.8, 157.5, 155.1, 140.4, 137.8, 137.5, 136.1, 136.0, 132.4, 129.1, 128.7, 127.0, 127.0, 124.8, 123.5, 122.4, 121.1, 119.7, 119.6, 117.6, 117.5, 113.1, 111.0, 107.4, 107.1, 97.6, 97.3, 95.9, 94.9, 87.9, 87.53, 59.4, 54.5, 45.6, 41.8, 30.7, 29.9. UPLC-MS (ESI) calc. for $C_{30}H_{30}FN_4O_4S^+$ (MH^+) m/z = 561.20 found m/z = 561.23.

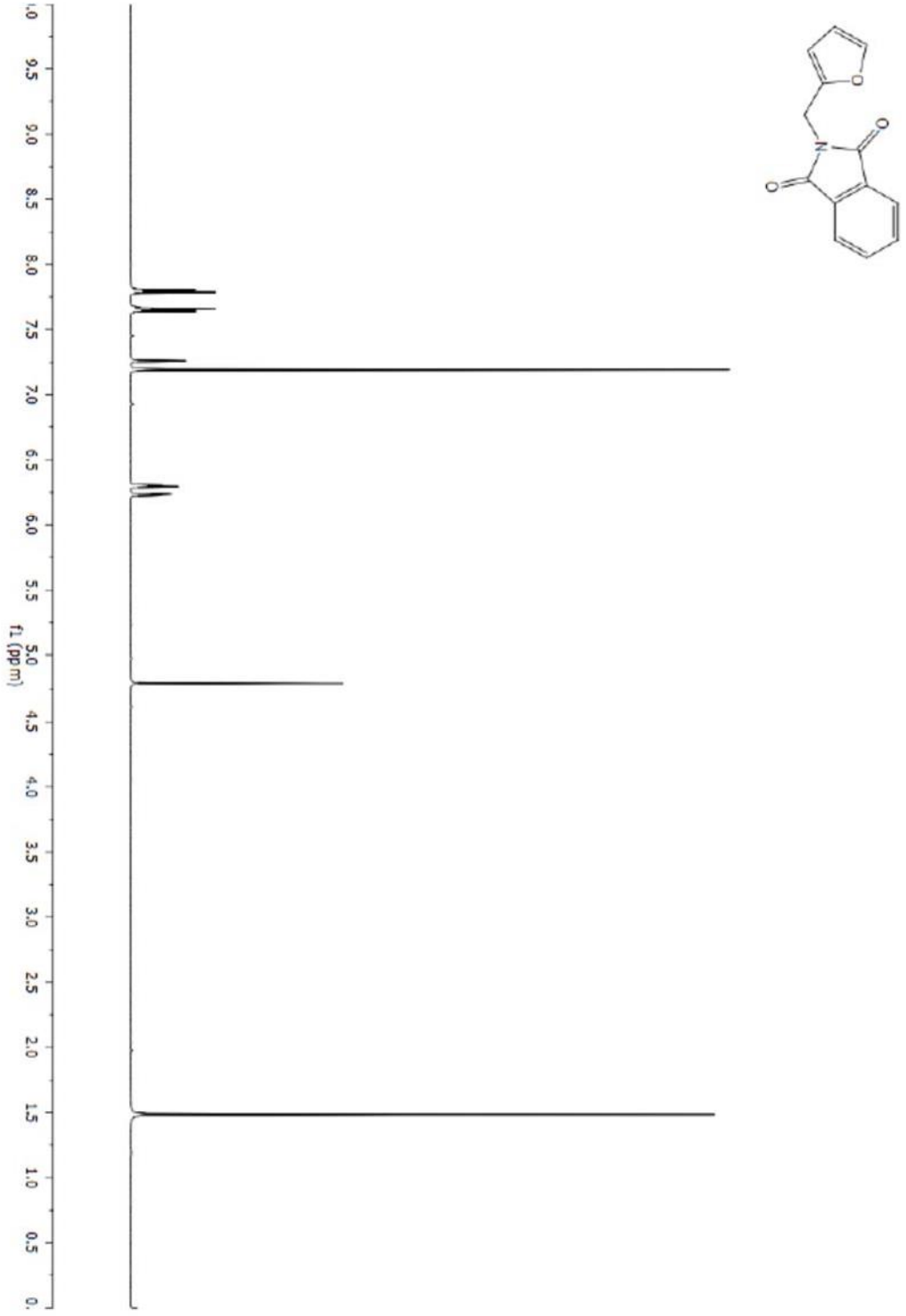
tert-Butyl(2-((3aS,6R,7aS)-3-(6-fluoro-1H-indol-3-yl)-6-((3-phenylureido)methyl)hexahydro-3a,6-epoxyisoindol-2(3H)-yl)-2-oxoethyl)carbamate (3g)



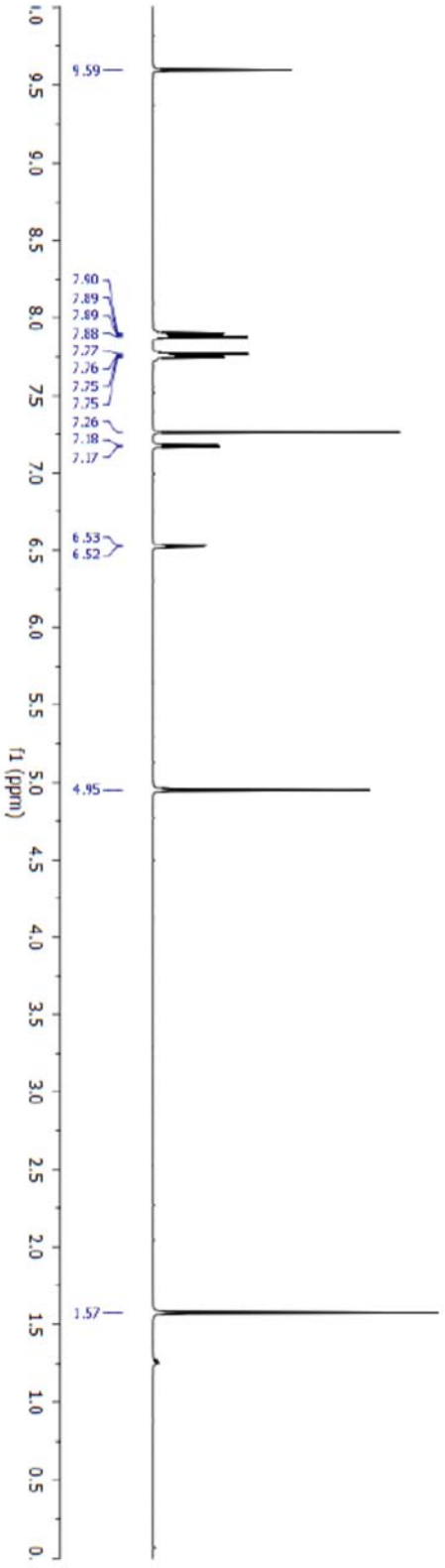
Urea **2c** (220 mg, 0.4 mmol) was taken up in MeOH (2 mL) and DMF (0.5 mL). The flask was charged with argon before 10% Pd/C (42 mg, 10 mol%). The reaction mixture was then charged with H_2 and stirred overnight at 21 °C. Filtration followed by concentration in vacuo afforded the free amine as a crude semisolid which was used without further purification. The obtained crude amine (19 mg, 0.044 mmol) was dissolved in DMF (0.5 ml) and added 2,5-dioxopyrrolidin-1-yl (tert-butoxycarbonyl)glycinate (12 mg, 0.044 mmol) followed by DIPEA (8 µl, 0.044 mmol). The reaction mixture was stirred at 21 °C. After 30 min 10% reactant was added and the mixture was stirred for additional 30 min. Purification by prep HPLC afforded the desired amide **3g** (8 mg, 31%). ^{1}H NMR (400 MHz, DMSO), major isomer, δ 11.26 (s, 1H; NH), 8.61 (s, 1H; NH), 7.41 – 7.34 (m, 3H; Ar), 7.28 – 7.18 (m, 3H; Ar), 7.18 – 7.09 (m, 2H; Ar), 6.91 – 6.81 (m, 1H; Ar), 6.62 (t, *J* = 6.0 Hz, 1H; NH), 6.40 – 6.32 (m, 1H; NH), 5.44 (s,1H; H-1), 4.23 – 4.08 (m, 1H; H-8a), 3.83 (dd, *J* = 17.3, 5.9 Hz, 1H; CH_2) 3.63 – 3.53 (m, 1H ;CH_2), 3.43-3.31 (m, 2H; CH_2) 3.23 – 3.07 (m, 1H; H-8b), 2.78 – 2.67 (m, 1H; H-7), 1.91 – 1.82 (m,1H; H-6a), 1.67 – 1.57 (m, 1H; H-6b), 1.57 – 1.43 (m, 3H; Alkyl), 1.34 (m, 3H; CH_3), 1.31 (s, 6H; CH_3), 1.12 – 1.00 (m, 1H; Alkyl). ^{13}C NMR (101 MHz, DMSO) δ 167.6, 166.9, 160.0, 159.9, 157.7, 157.5, 155.8, 155.7, 155.3, 140.5, 136.2, 136.1, 136.0, 135.9, 128.7, 124.1, 123.3, 122.6, 122.0, 121.0, 119.4, 119.4, 119.3, 117.5, 114.1, 113.3, 107.8, 107.5, 107.2, 107.7, 97.9, 97.7, 96.5, 94.6, 88.0, 87.9, 77.9, 77.8, 56.7, 56.4, 54.9, 53.7, 52.5, 45.2, 42.9, 424, 42.2, 41.7, 31.5, 31.4, 29.7, 29.6, 28.2, 27.6. UPLC-MS (ESI) calc. for $C_{31}H_{37}FN_5O_5^+$ (MH^+) m/z = 578.8 found m/z = 578.33.

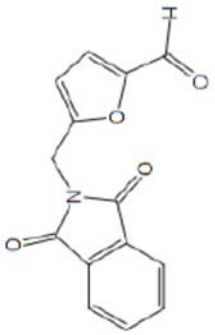
Characterization Spectra

7, ^{1}H NMR (400 MHz, $CDCl_3$):

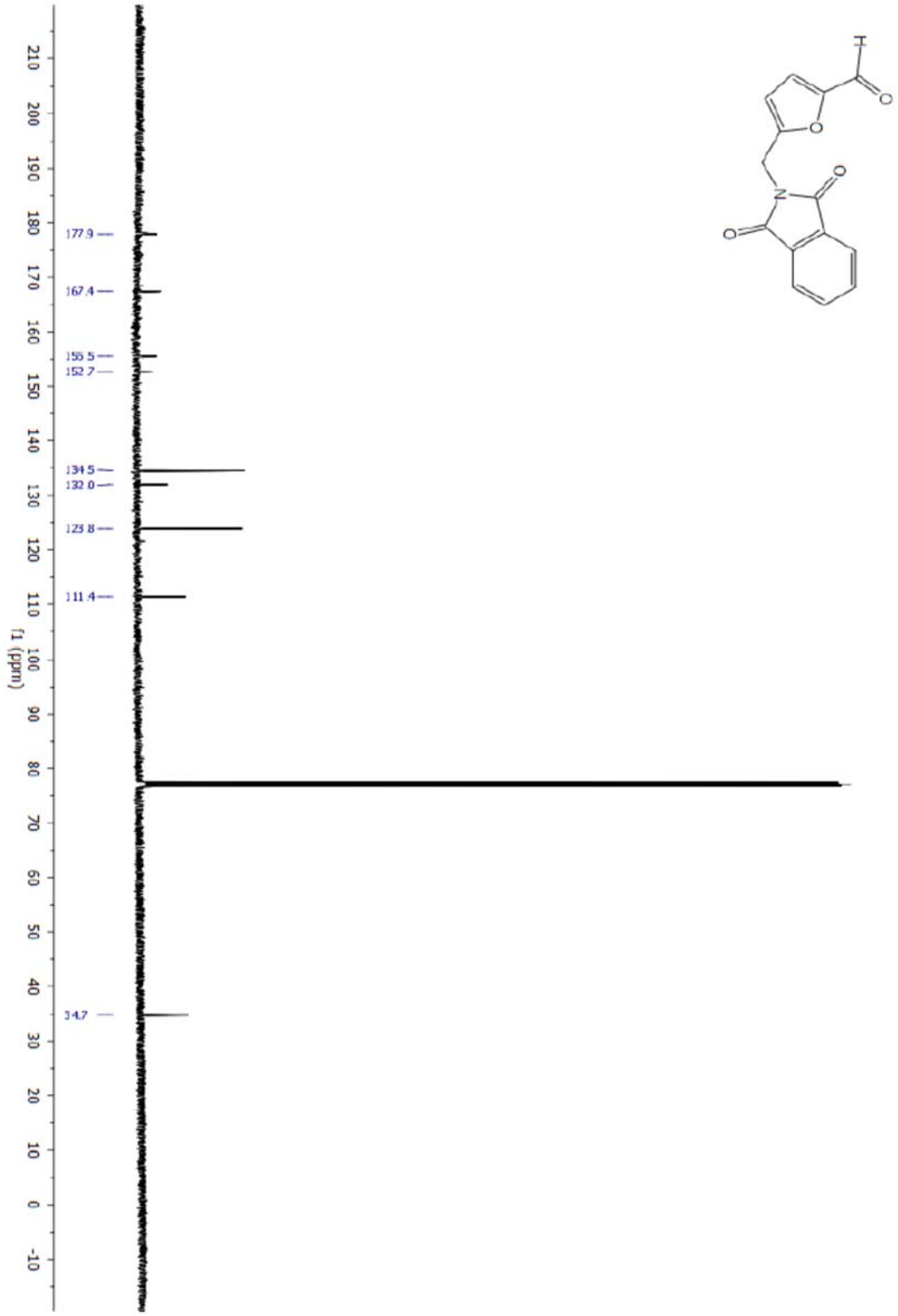


8, ^{1}H NMR (400 MHz, $CDCl_3$):

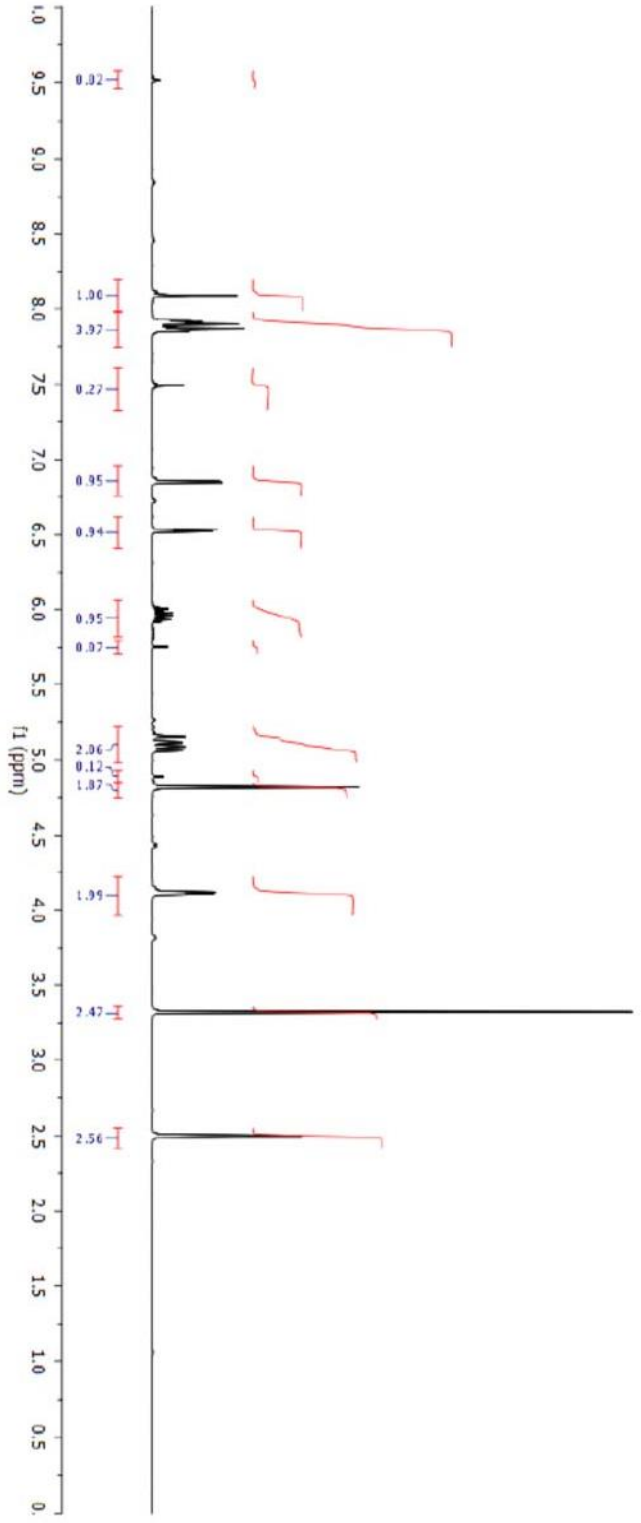


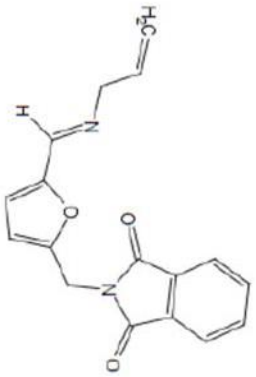


8, ^{13}C NMR (100 MHz, $CDCl_3$)

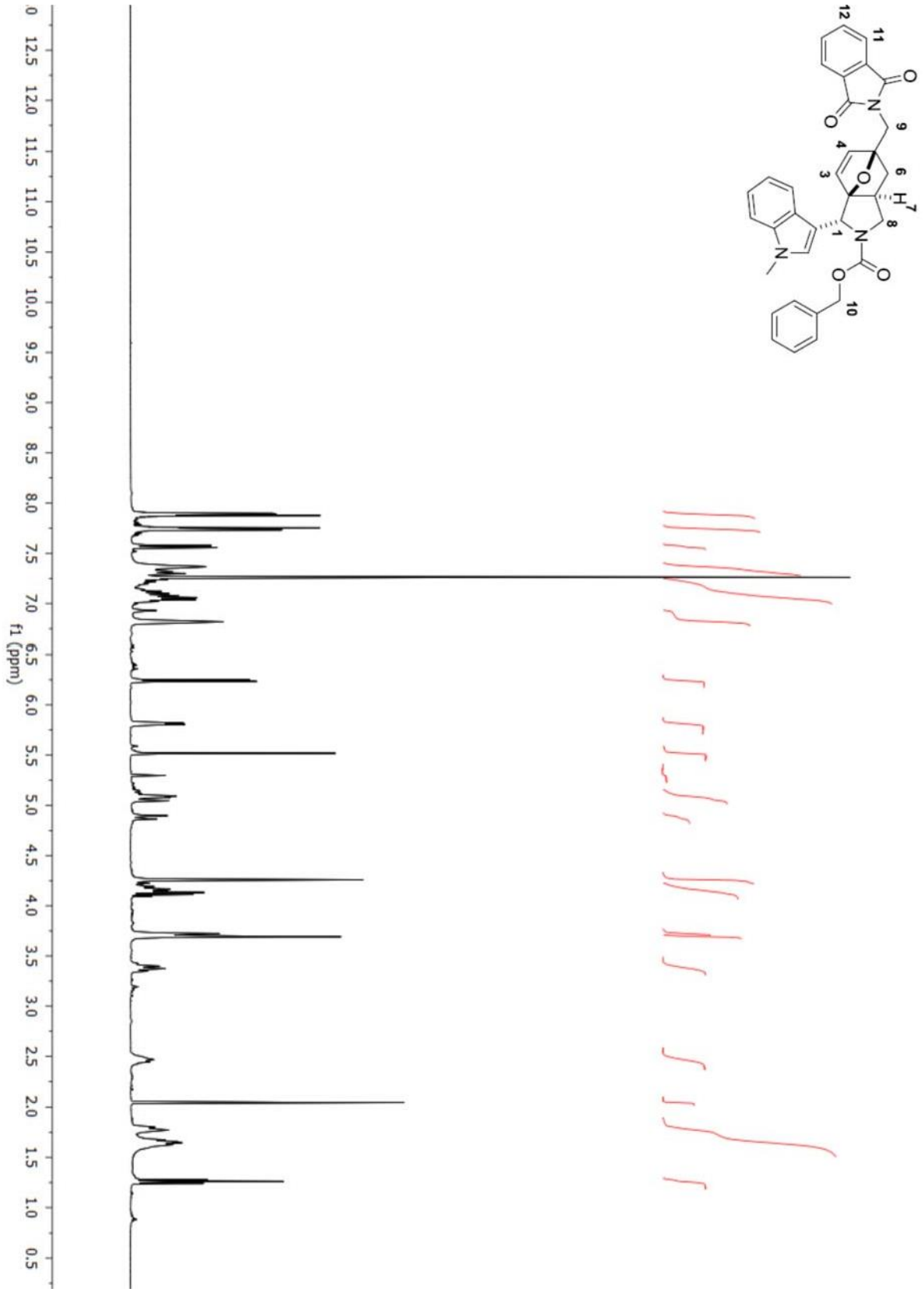


4, ^{1}H NMR (400 MHz, DMSO-d_6):

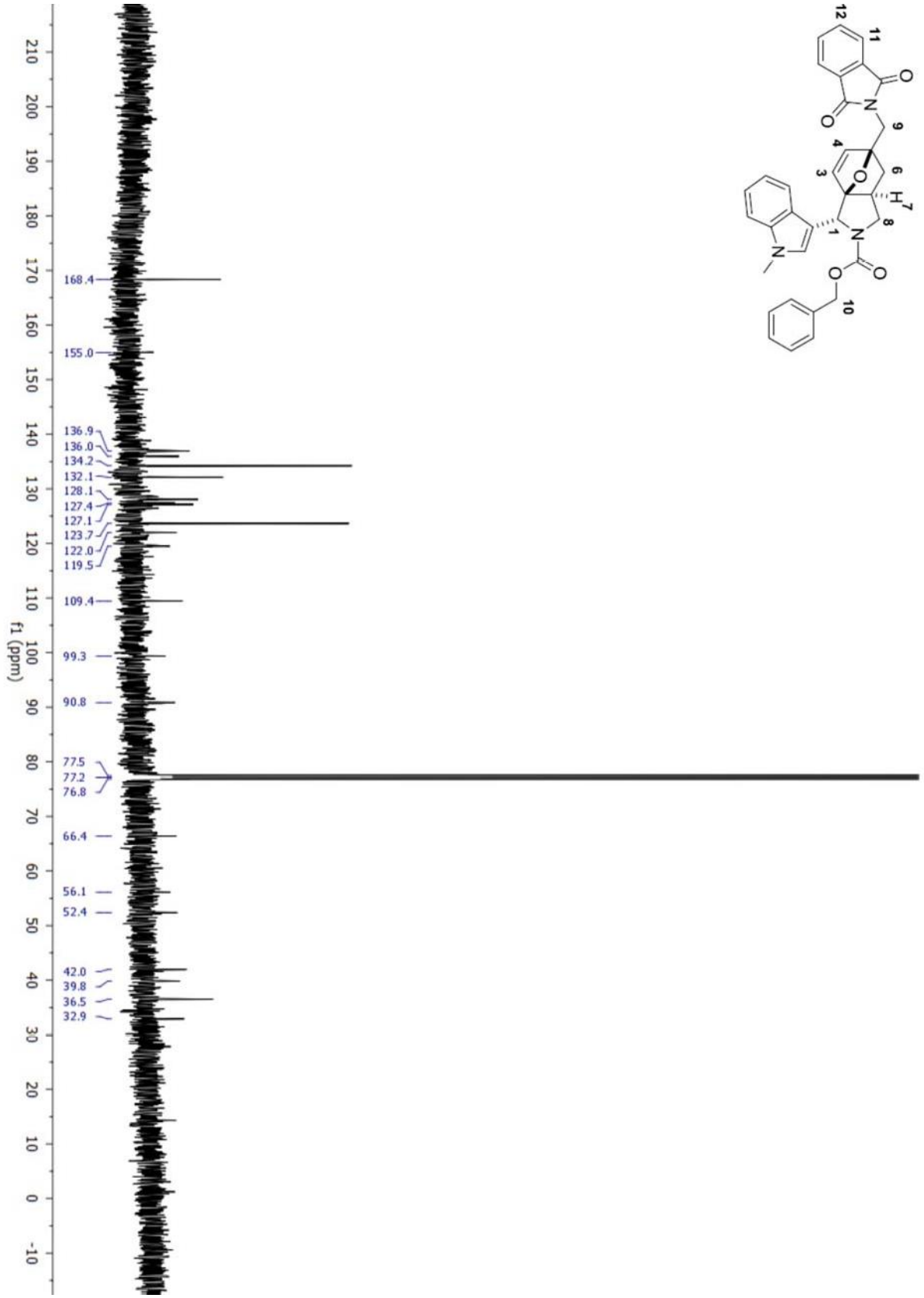




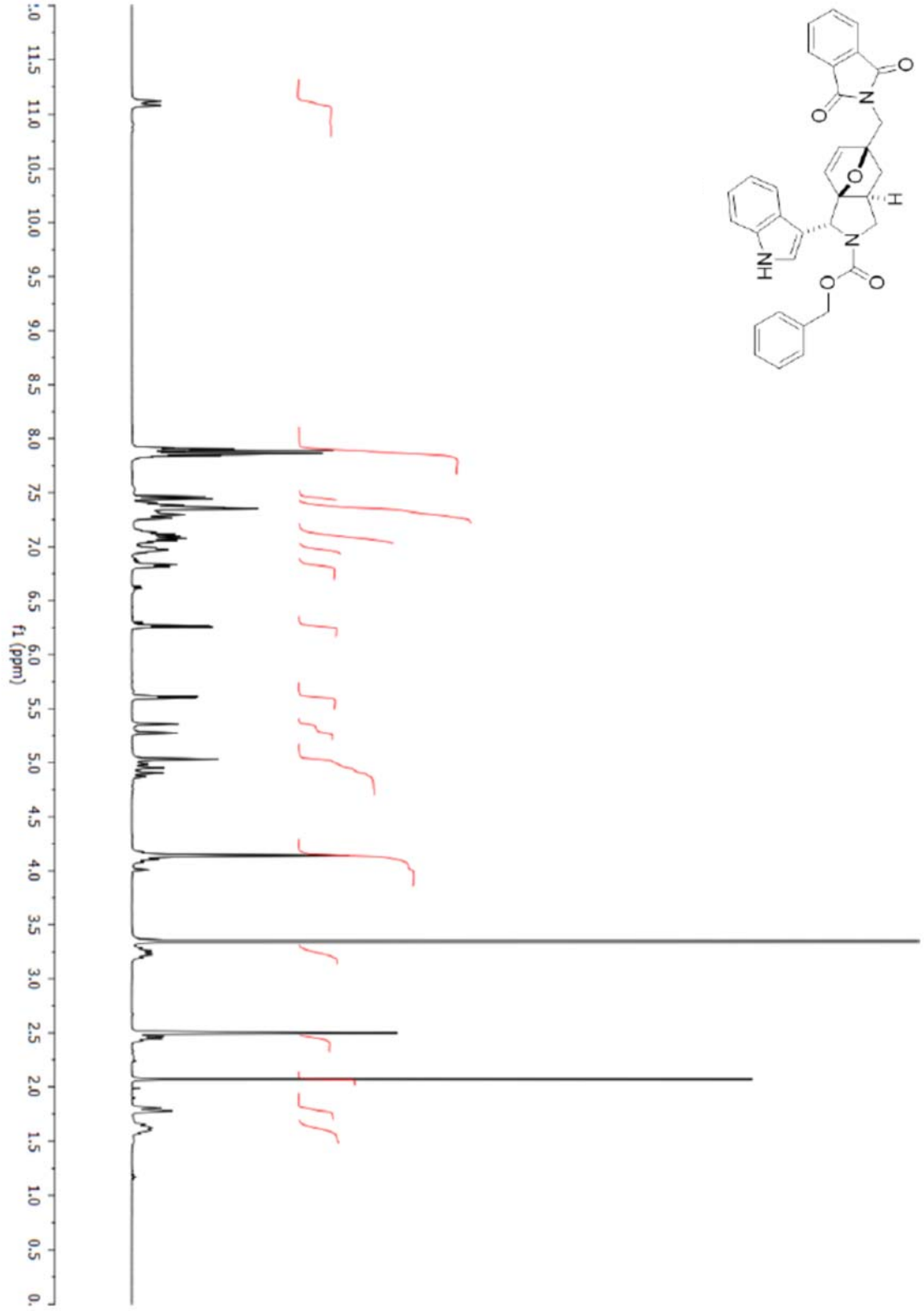
1a, ^{1}H NMR (400 MHz, $CDCl_3$):



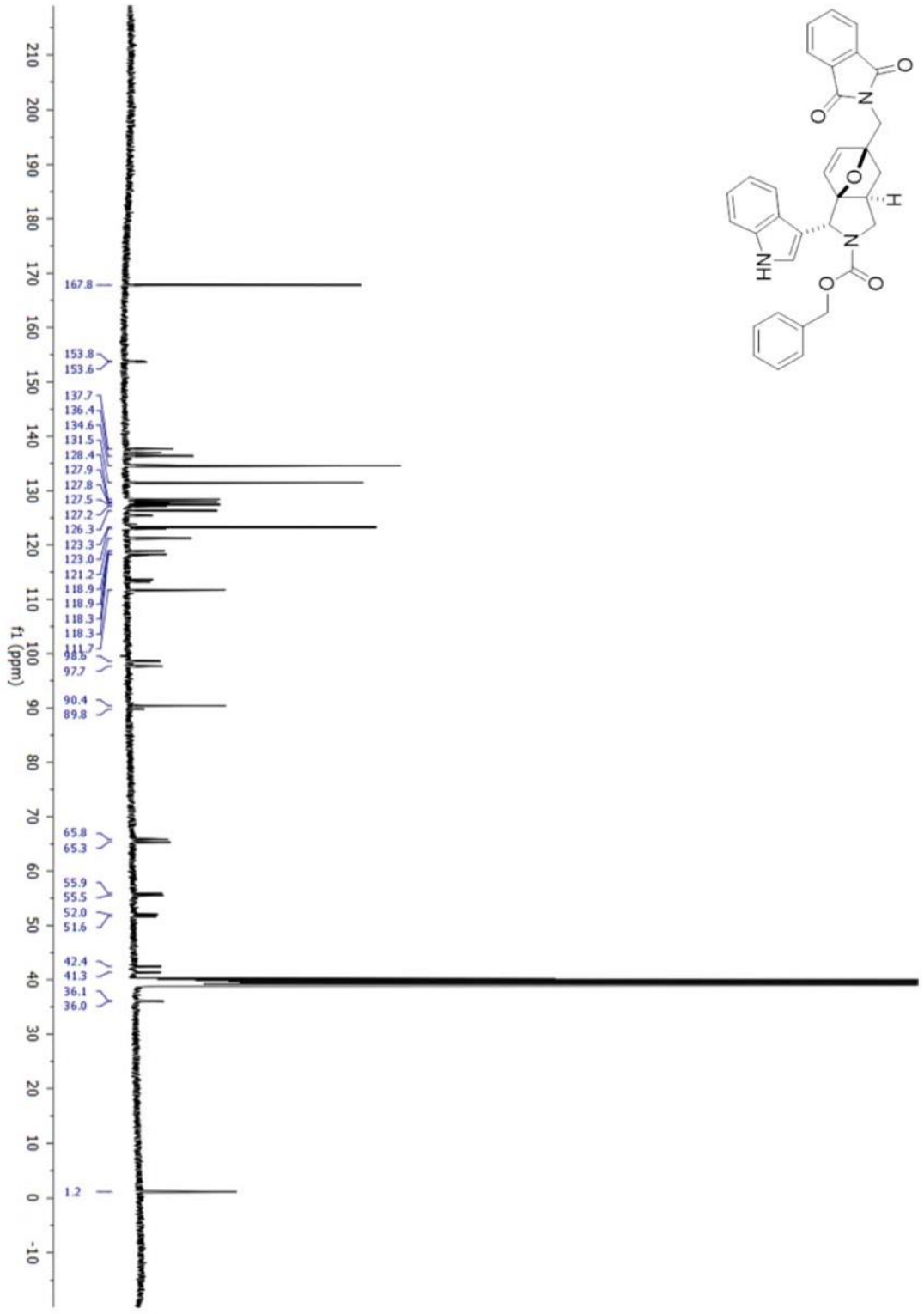
1a, ^{13}C NMR (100 MHz, $CDCl_3$):



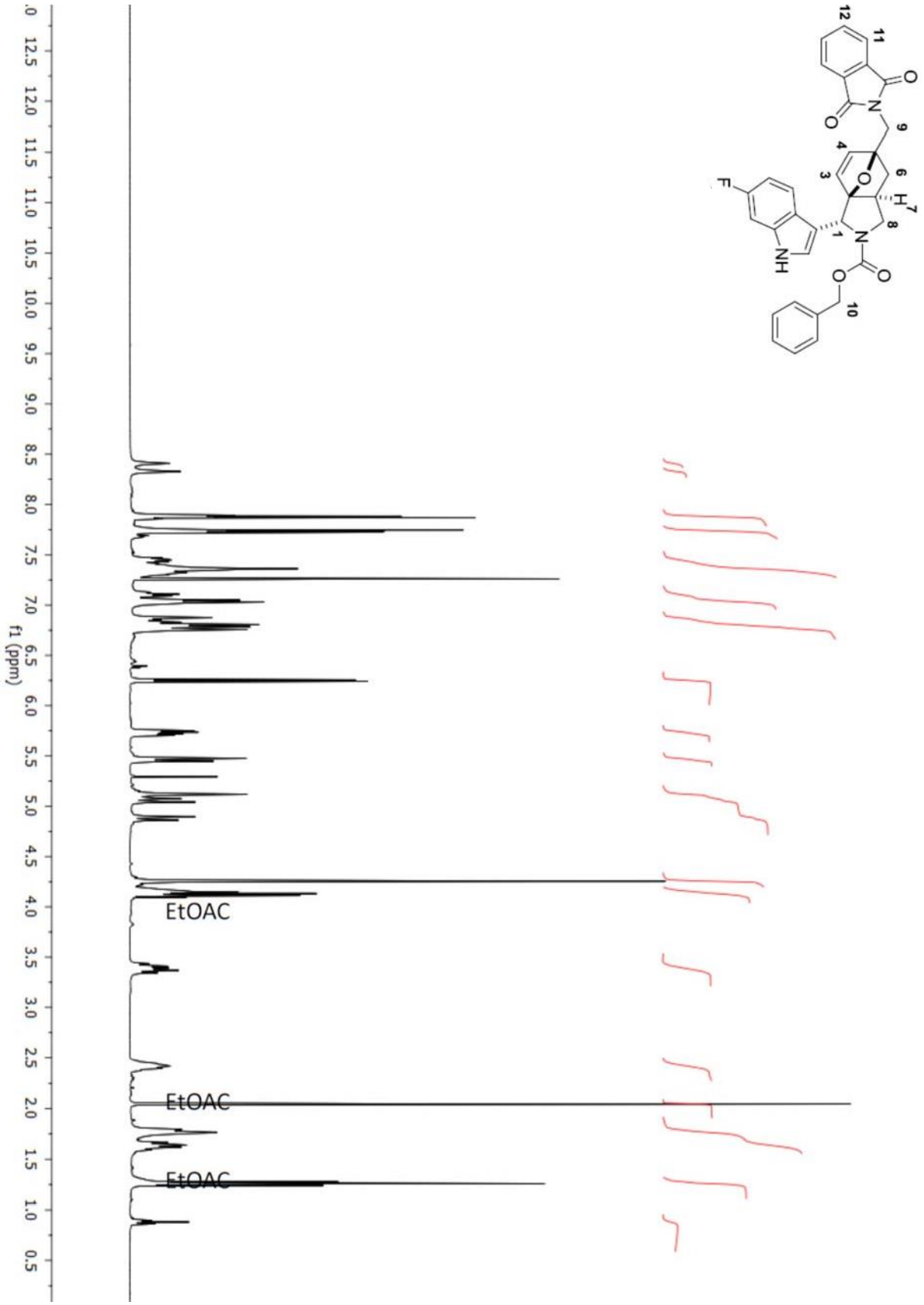
1b, ^{1}H NMR (400 MHz, DMSO-d_6):



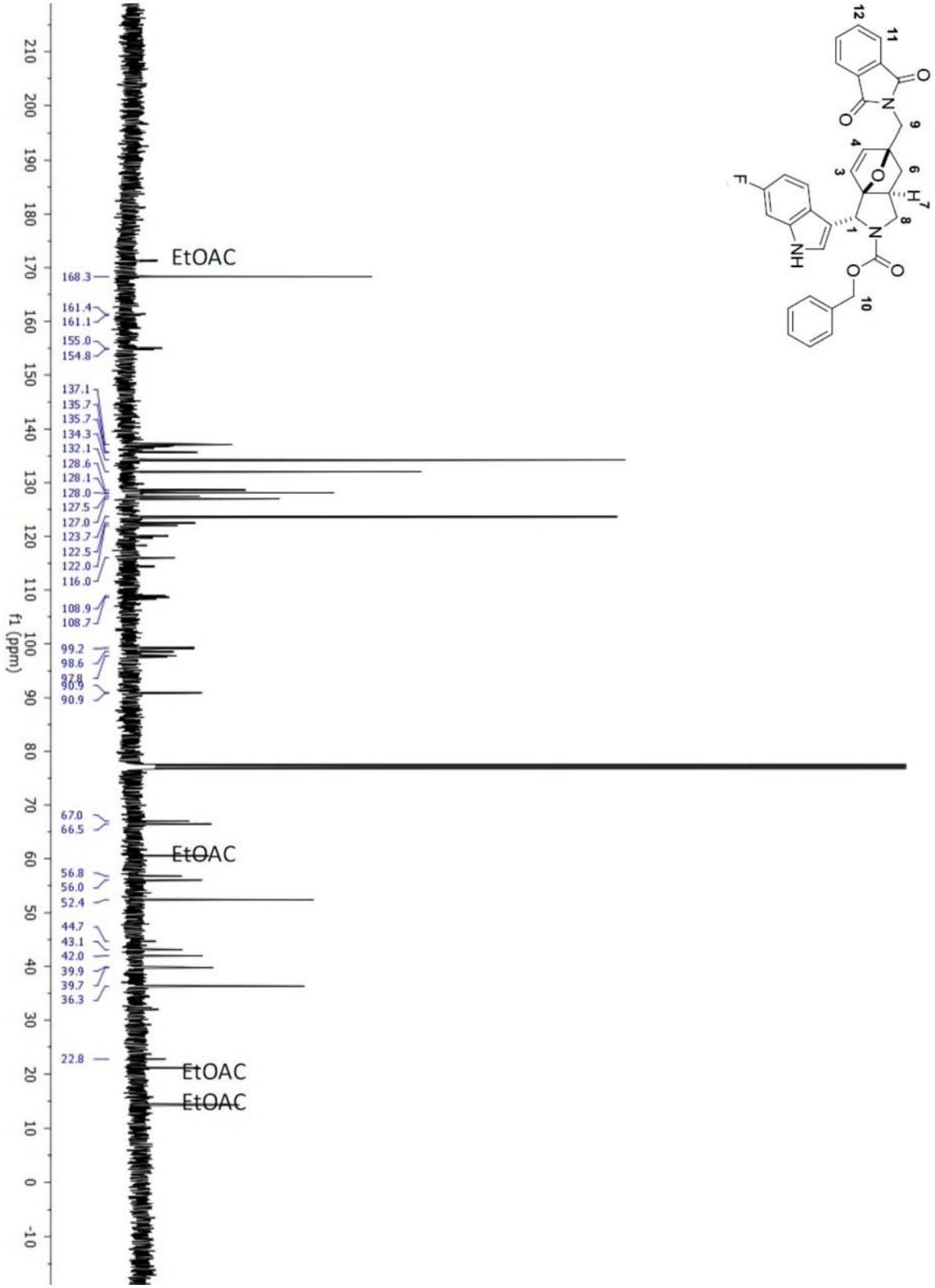
1b, ^{13}C NMR (100 MHz, DMSO-d_6):



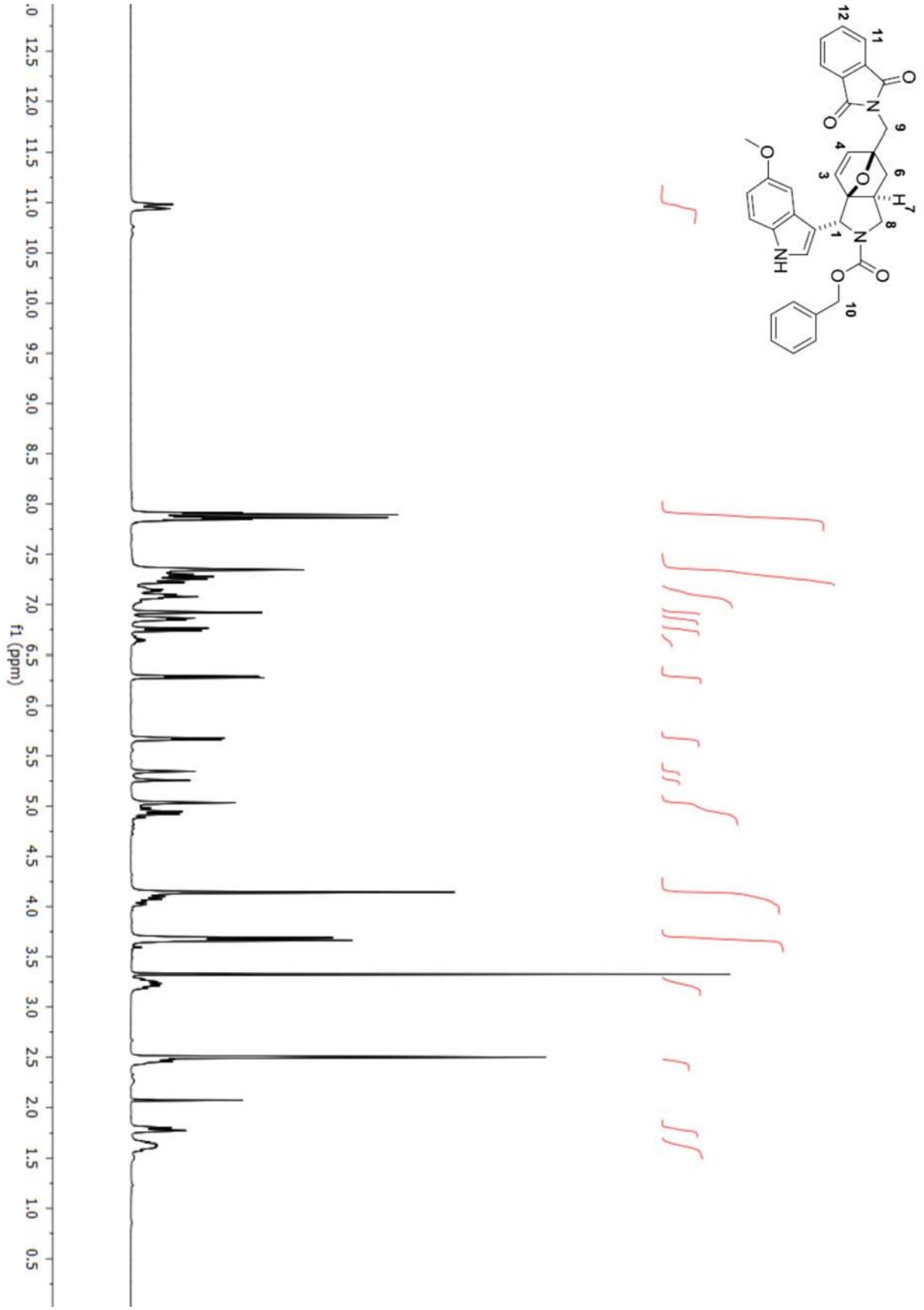
1c, ^{1}H NMR (400 MHz, $CDCl_3$)



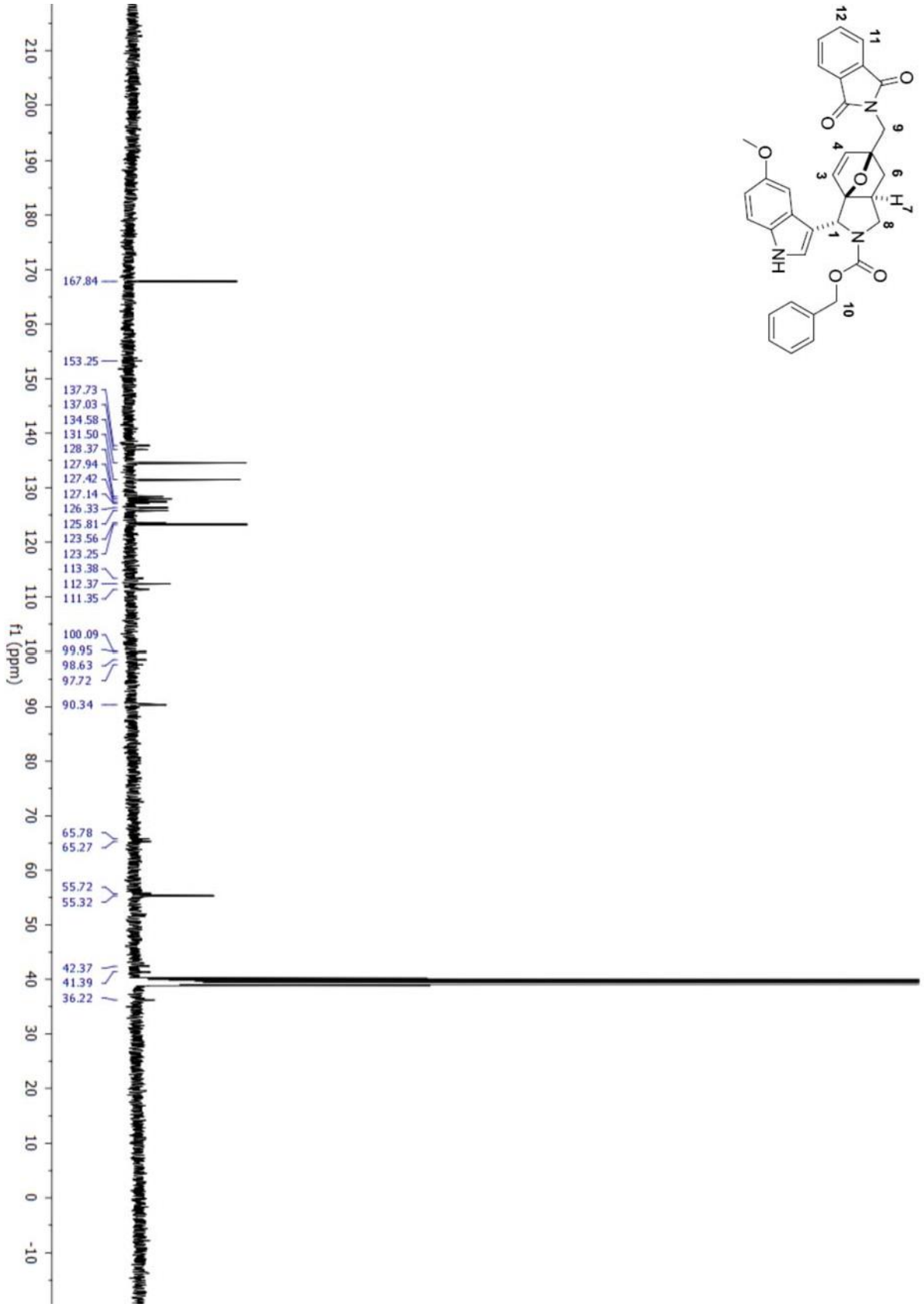
1c, ^{13}C NMR (100 MHz, $CDCl_3$)



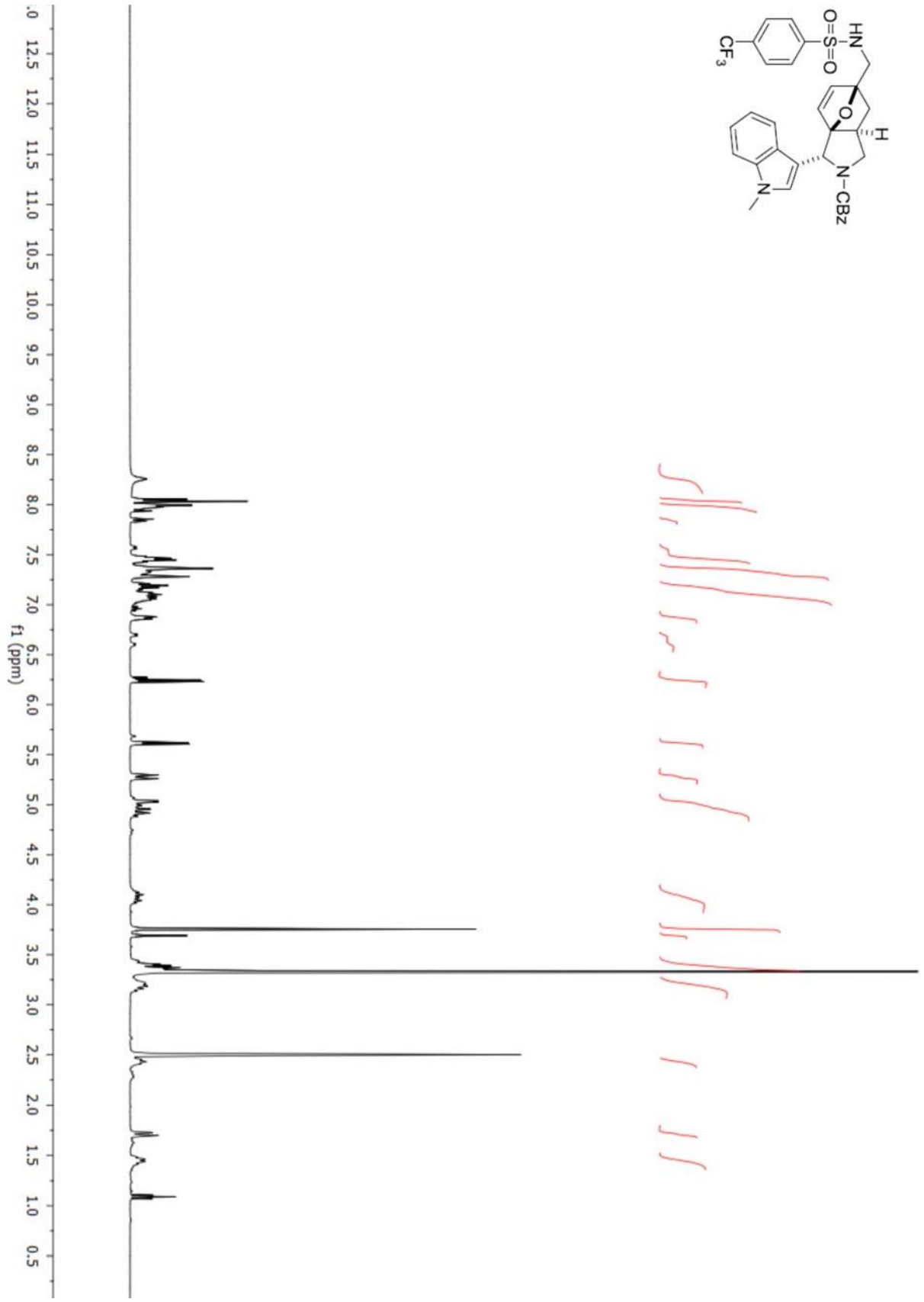
1d, ^{1}H NMR (400 MHz, DMSO-d_6):



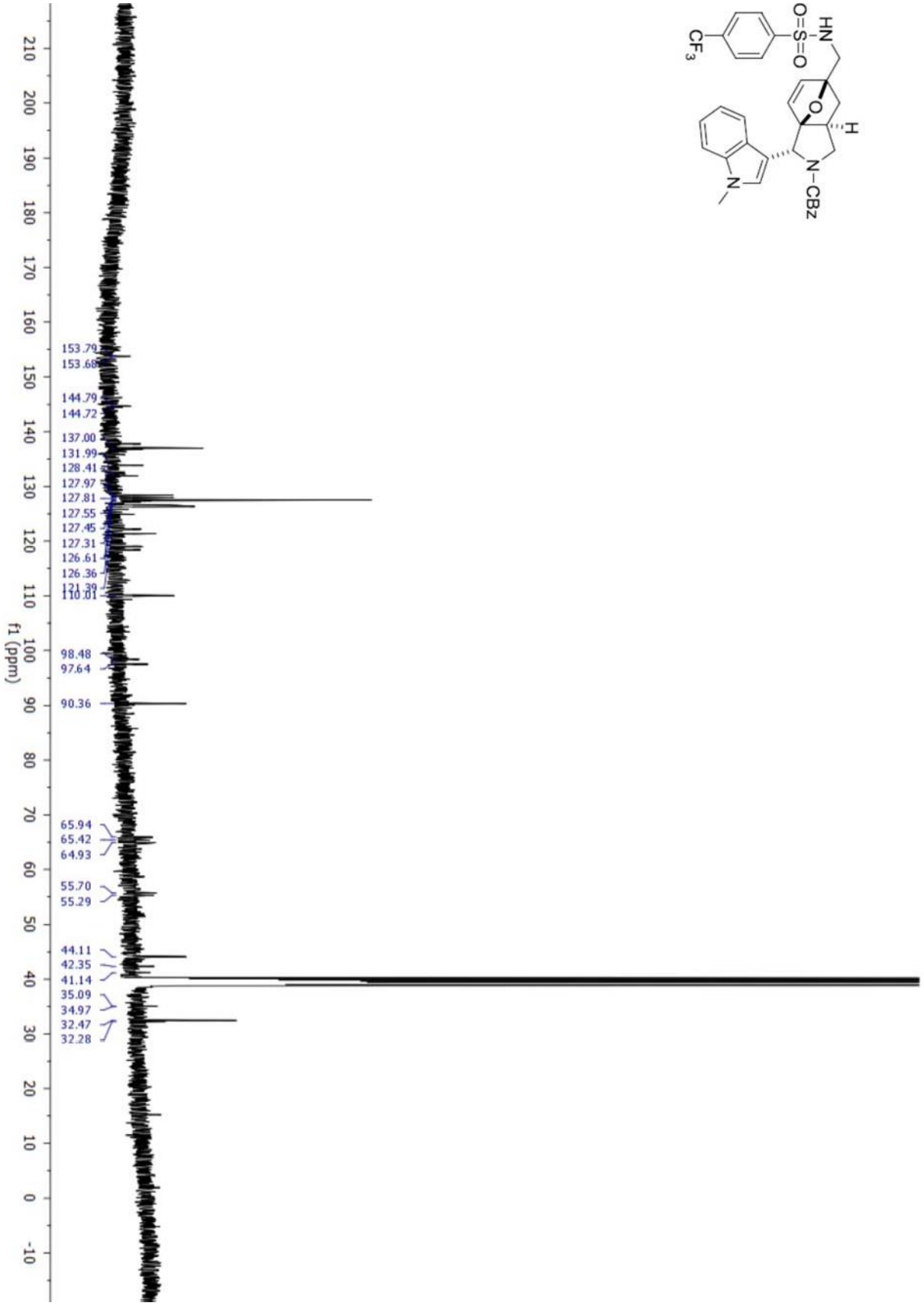
1d, ^{13}C NMR (100 MHz, DMSO-d_6):



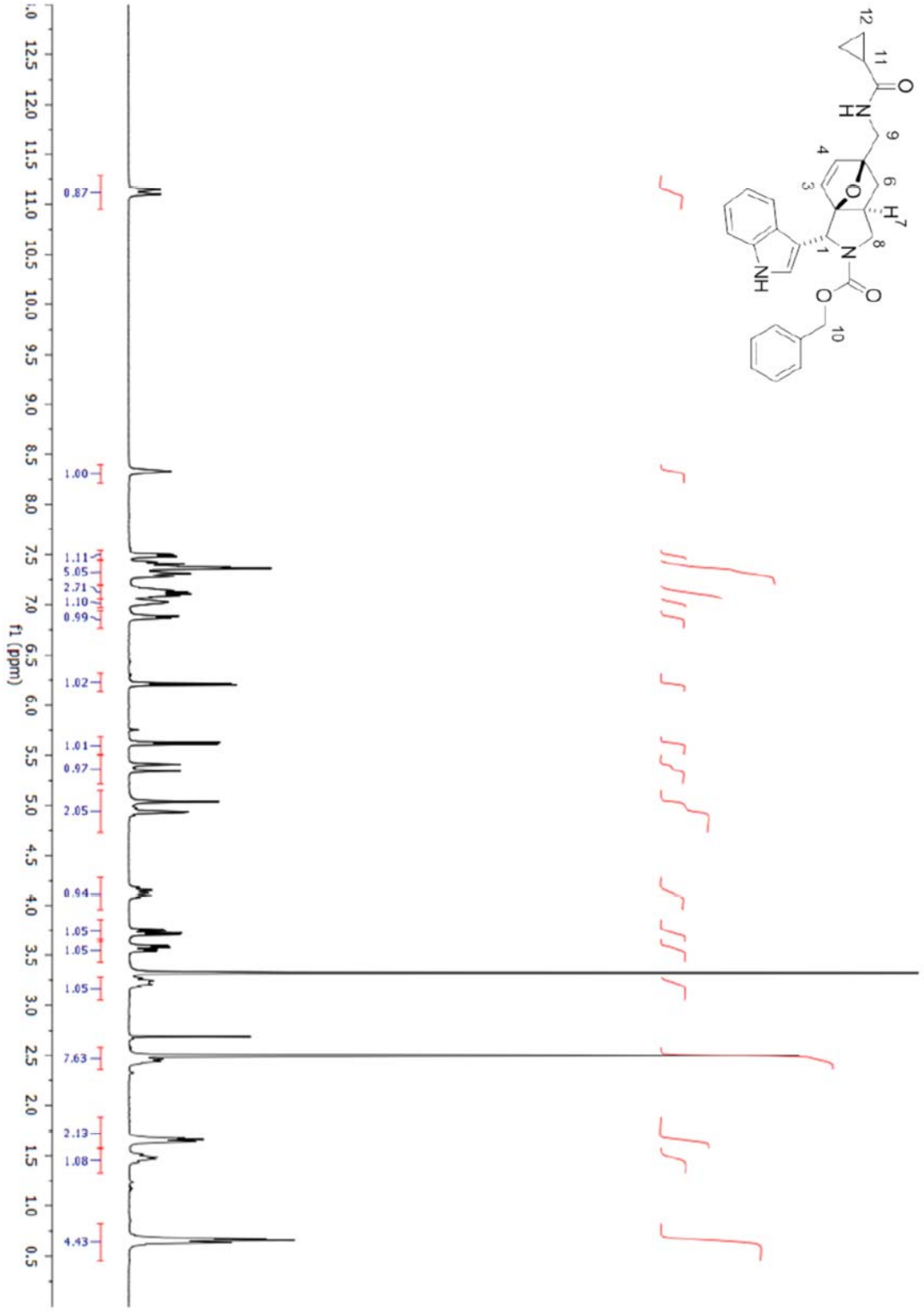
2a, ^{1}H NMR (400 MHz, DMSO-d_6):



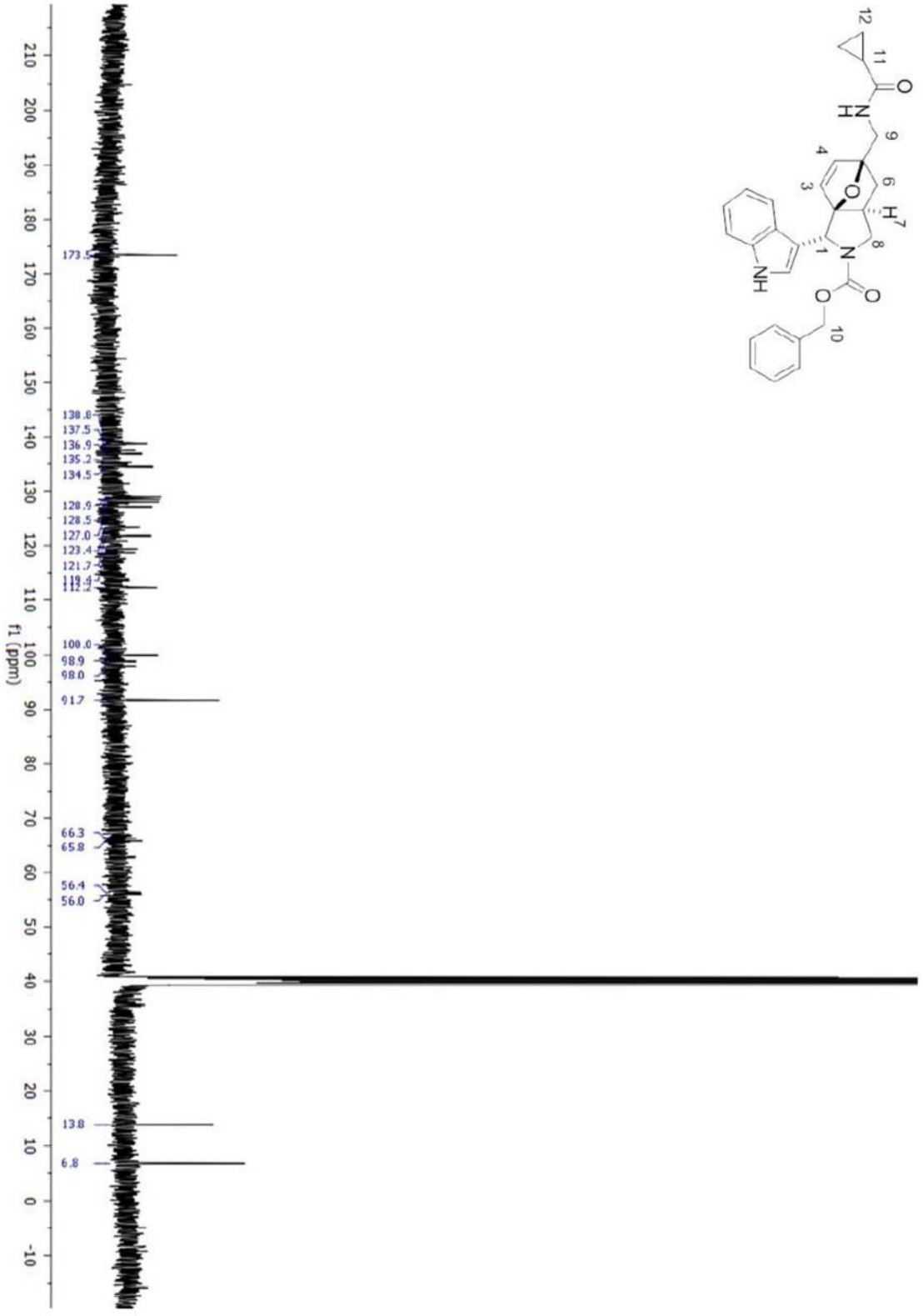
2a, ^{13}C NMR (100 MHz, DMSO-d_6):



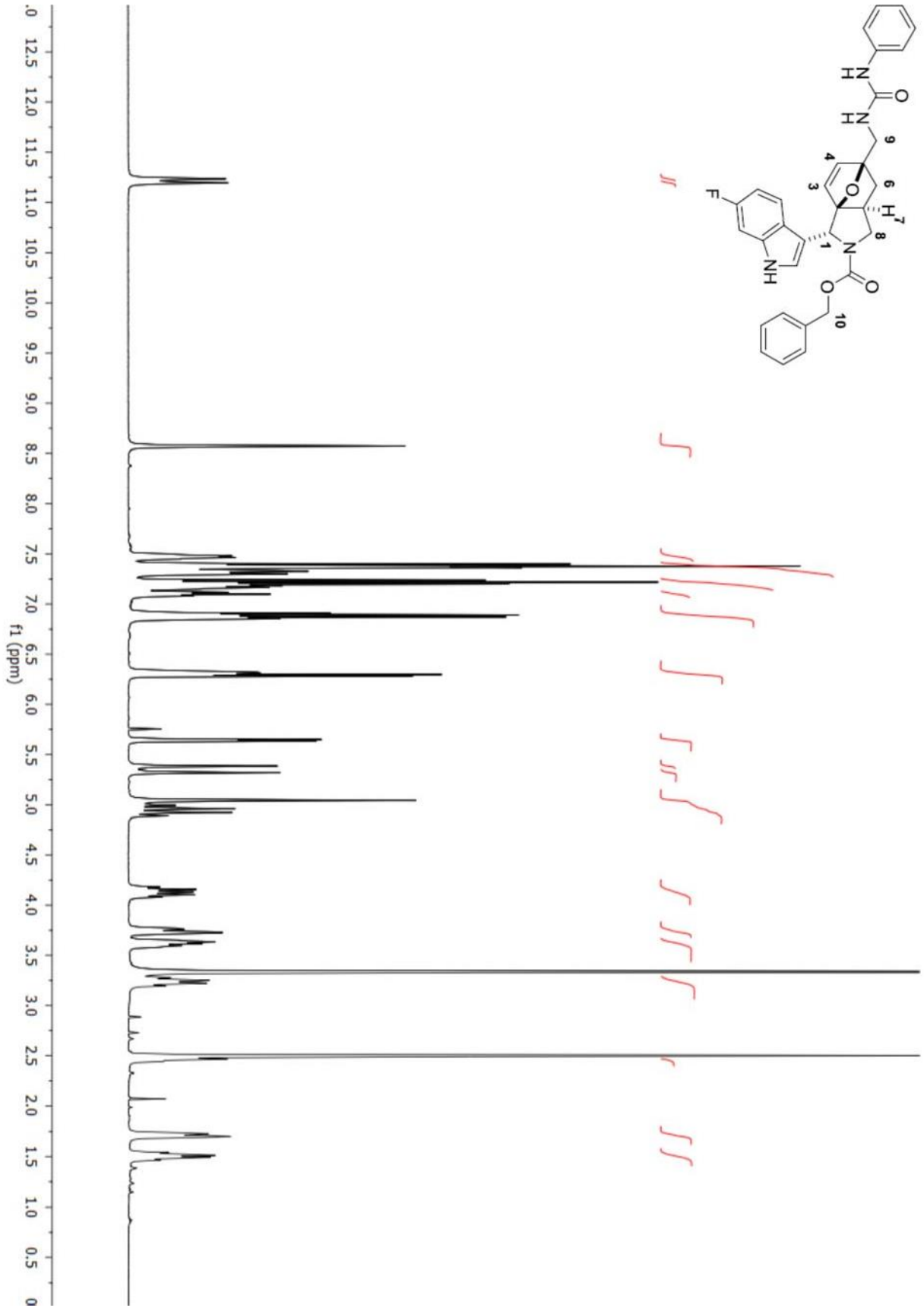
2b, ^{1}H NMR (400 MHz, DMSO-d_6):



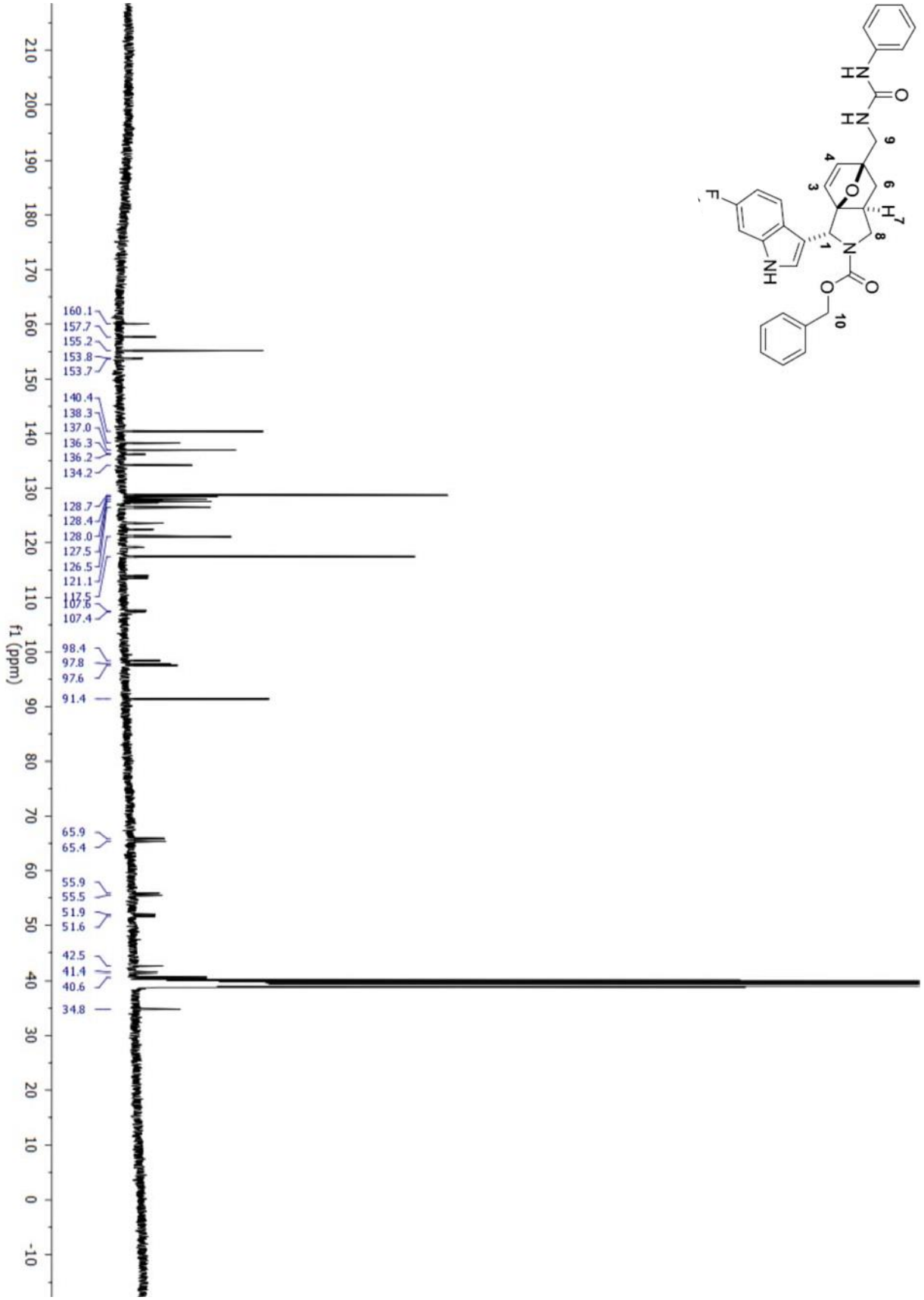
2b, ^{13}C NMR (100 MHz, DMSO-d_6):



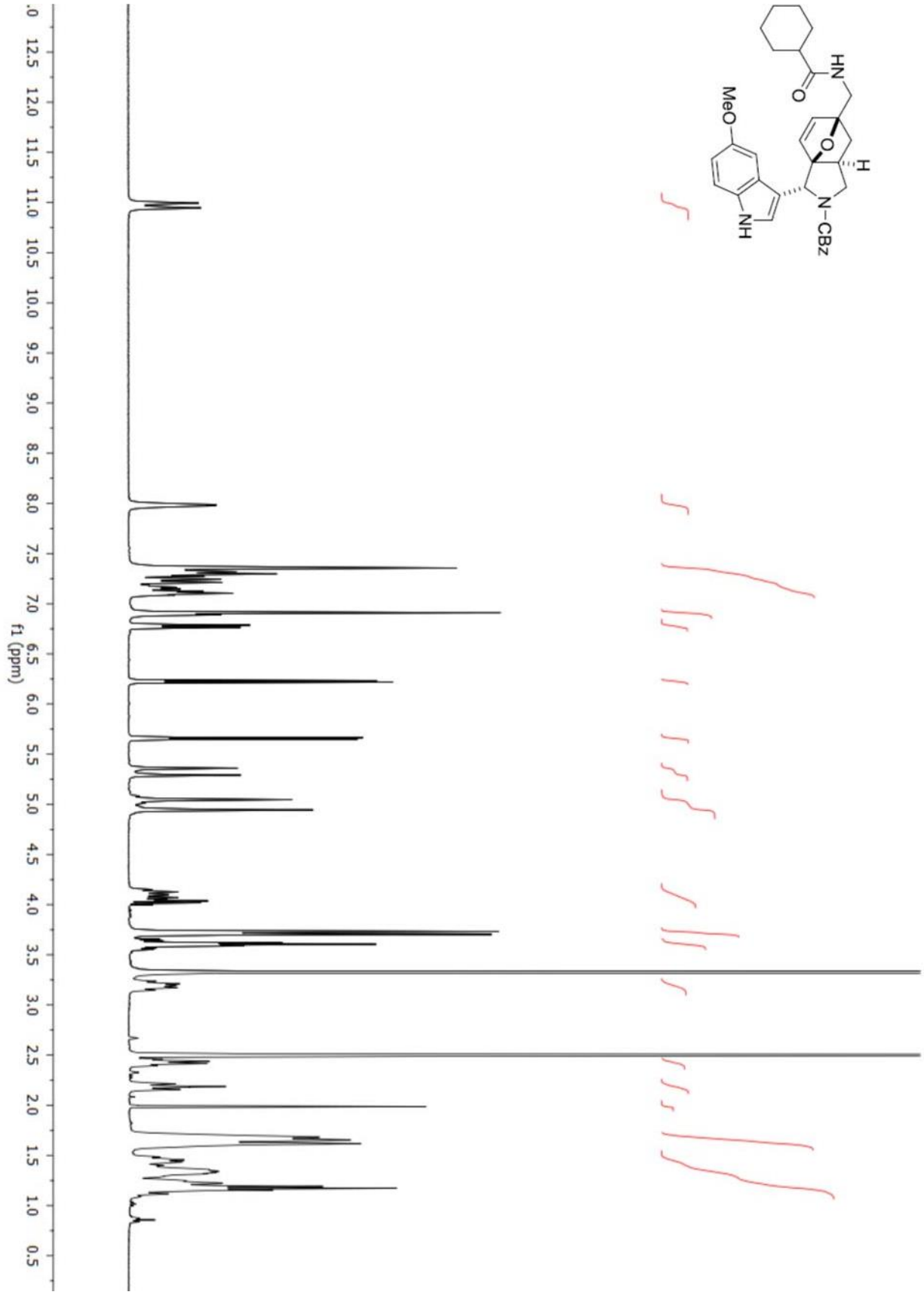
2c, ^{1}H NMR (400 MHz, DMSO-d_6):



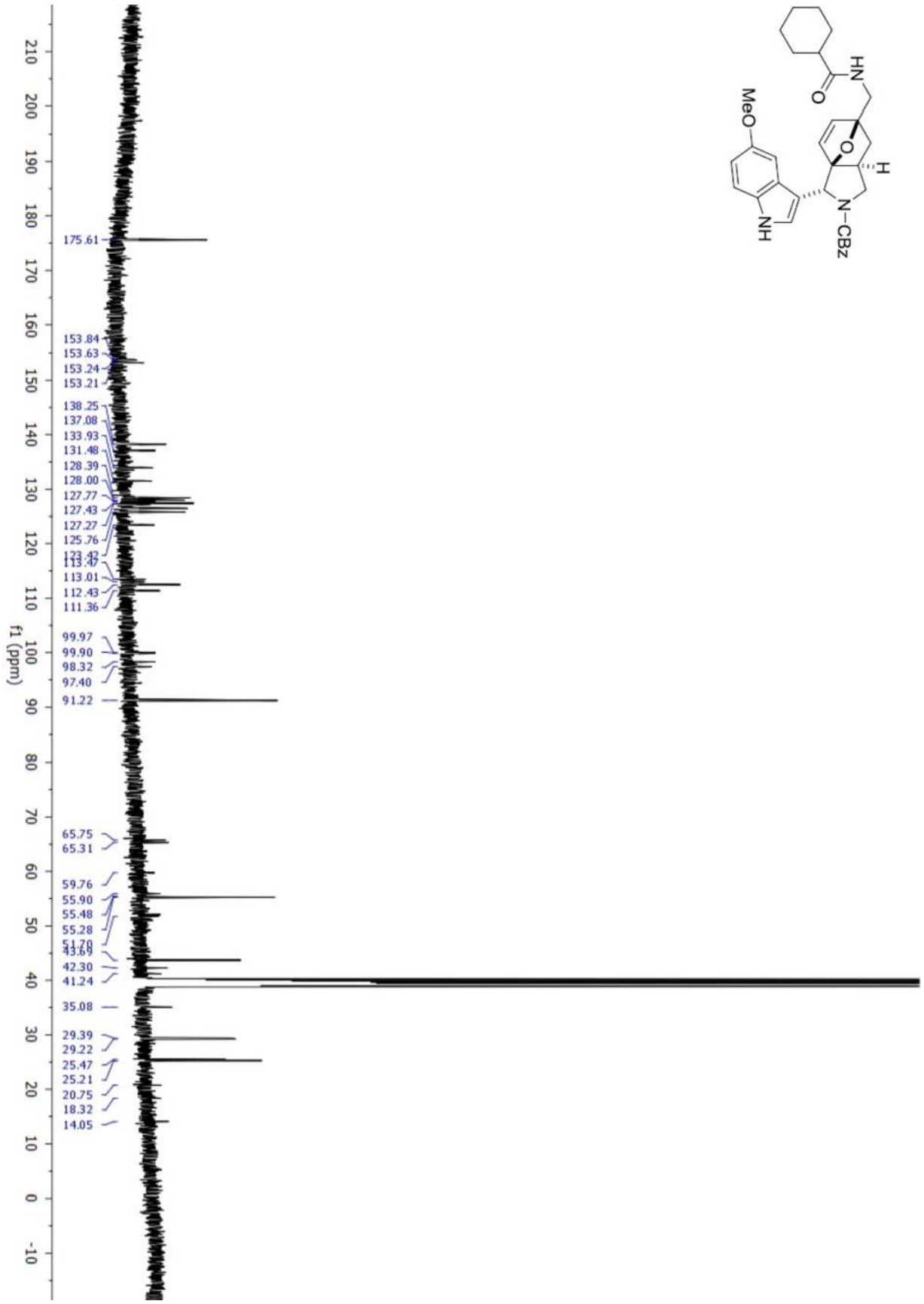
2c, ^{13}C NMR (100 MHz, DMSO-d_6):



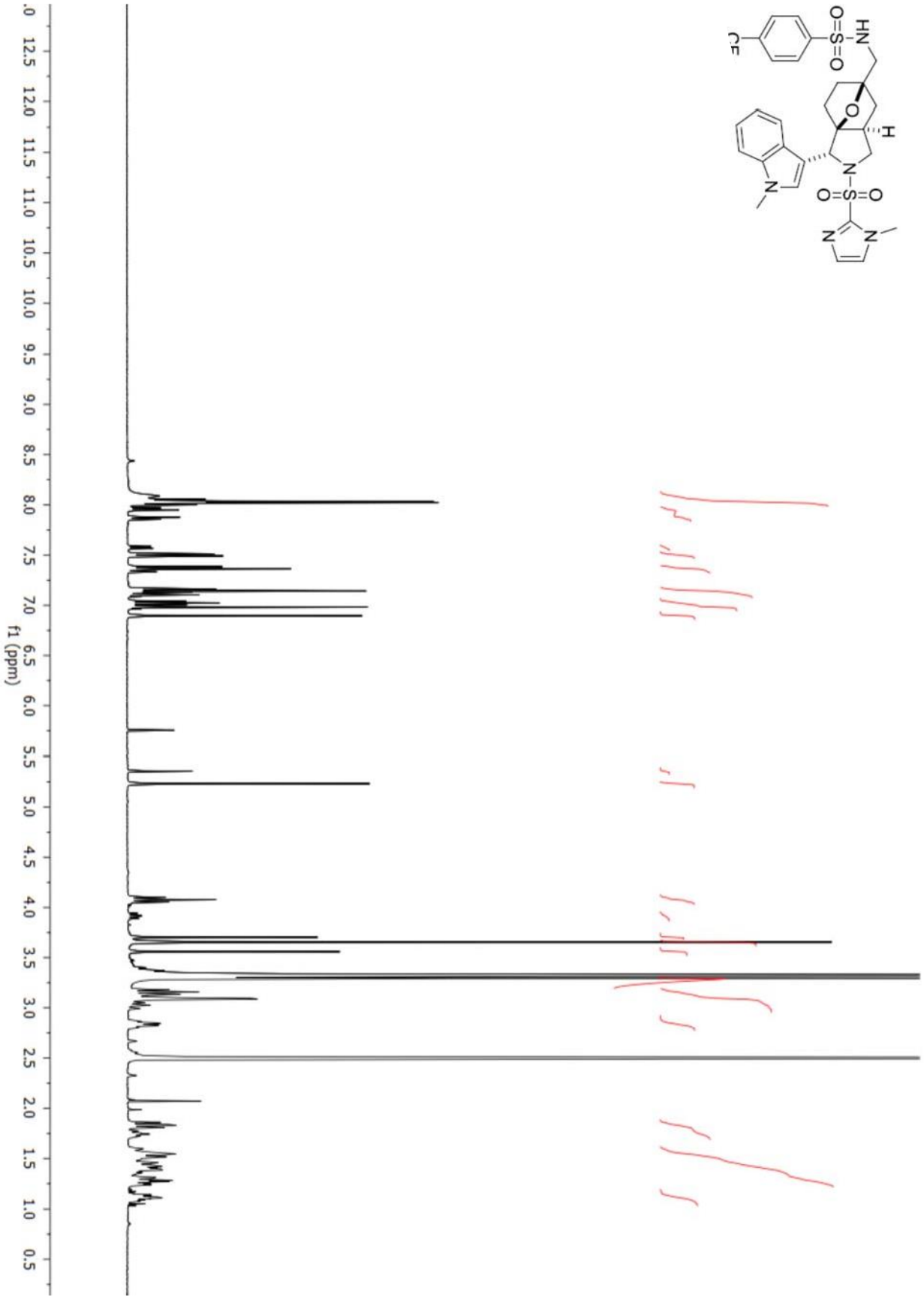
2d, ^{1}H NMR (400 MHz, DMSO-d_6):



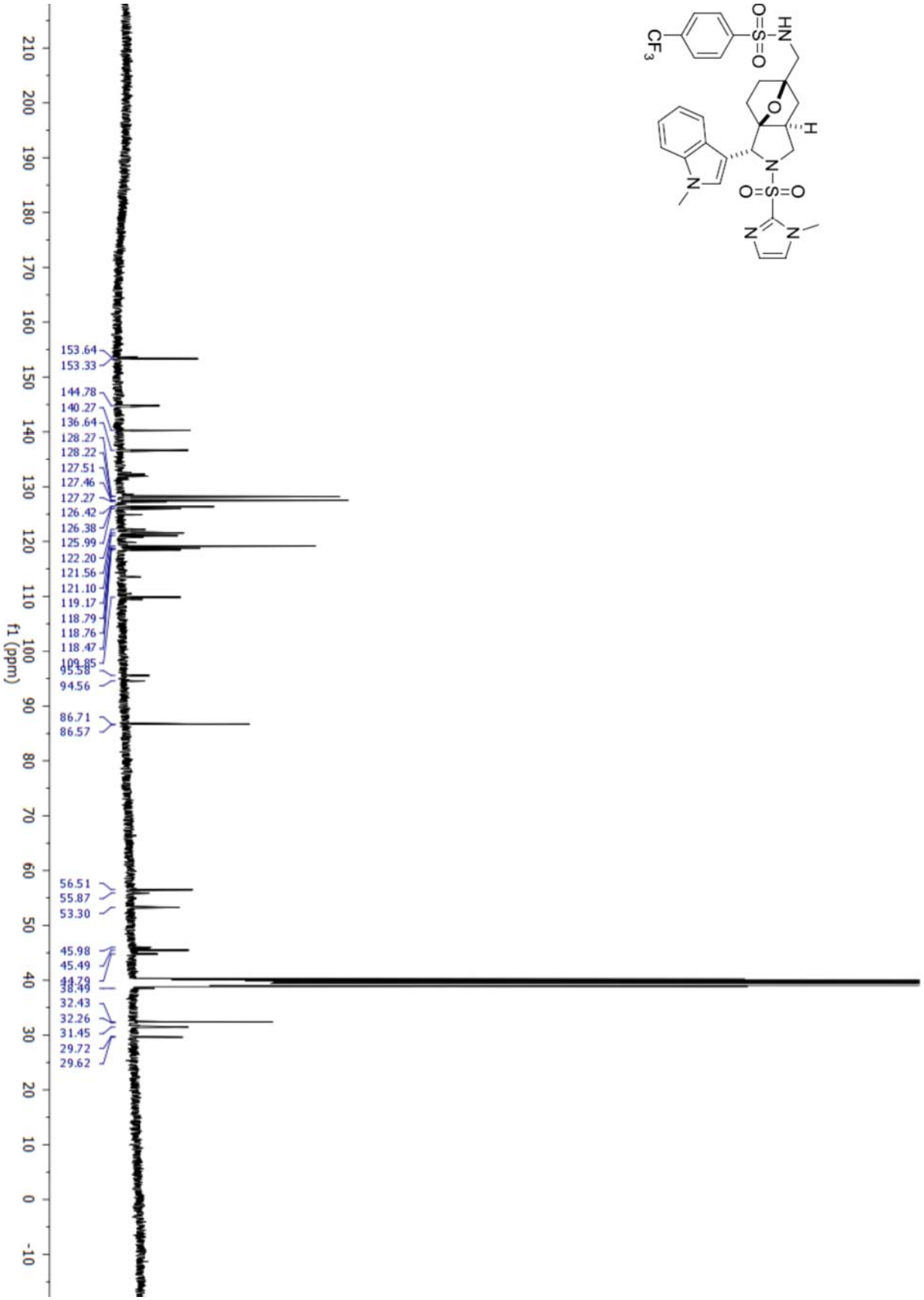
2d, ^{13}C NMR (100 MHz, DMSO-d_6):



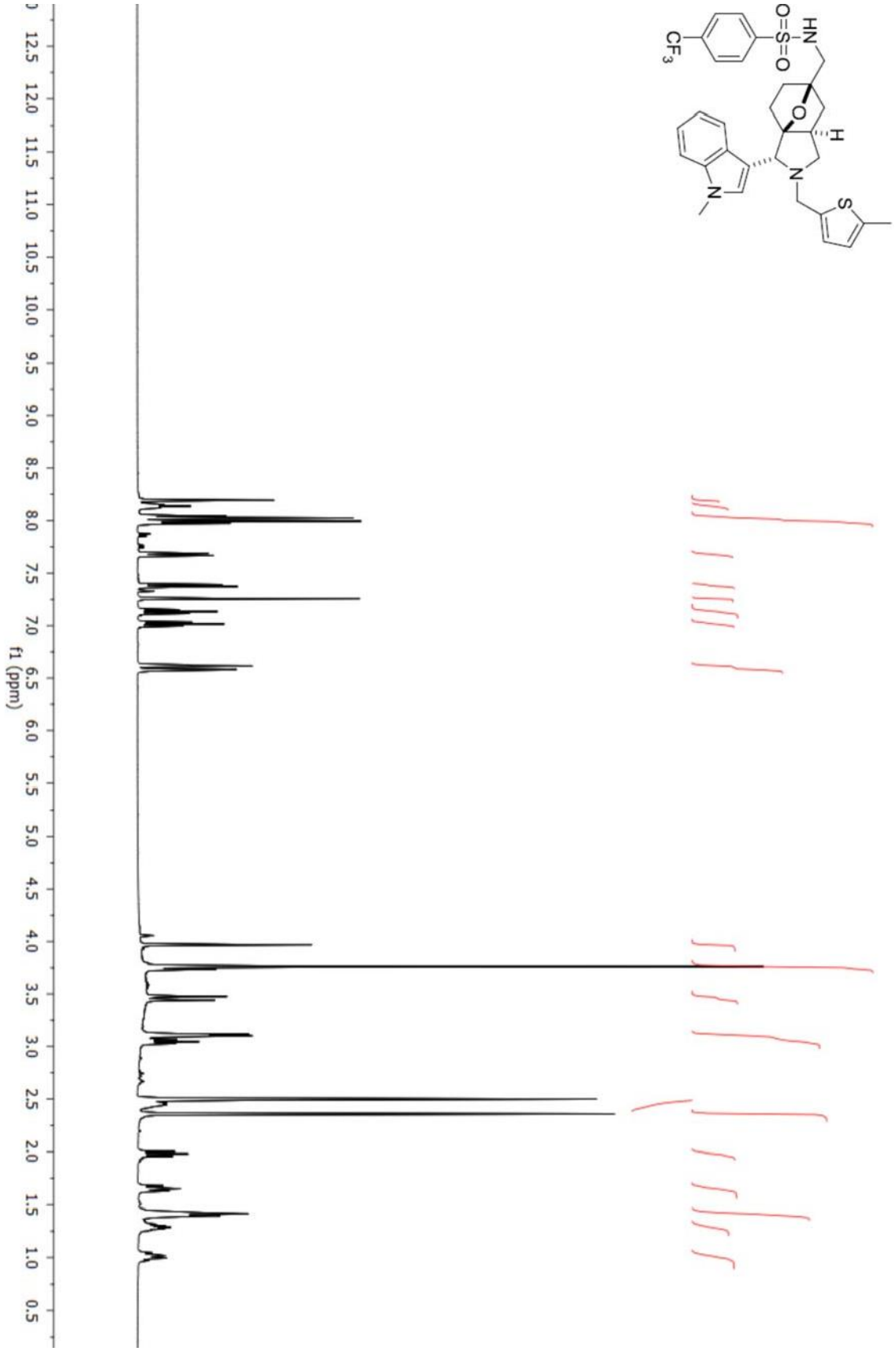
3a, ^{1}H NMR (400 MHz, DMSO-d_6):



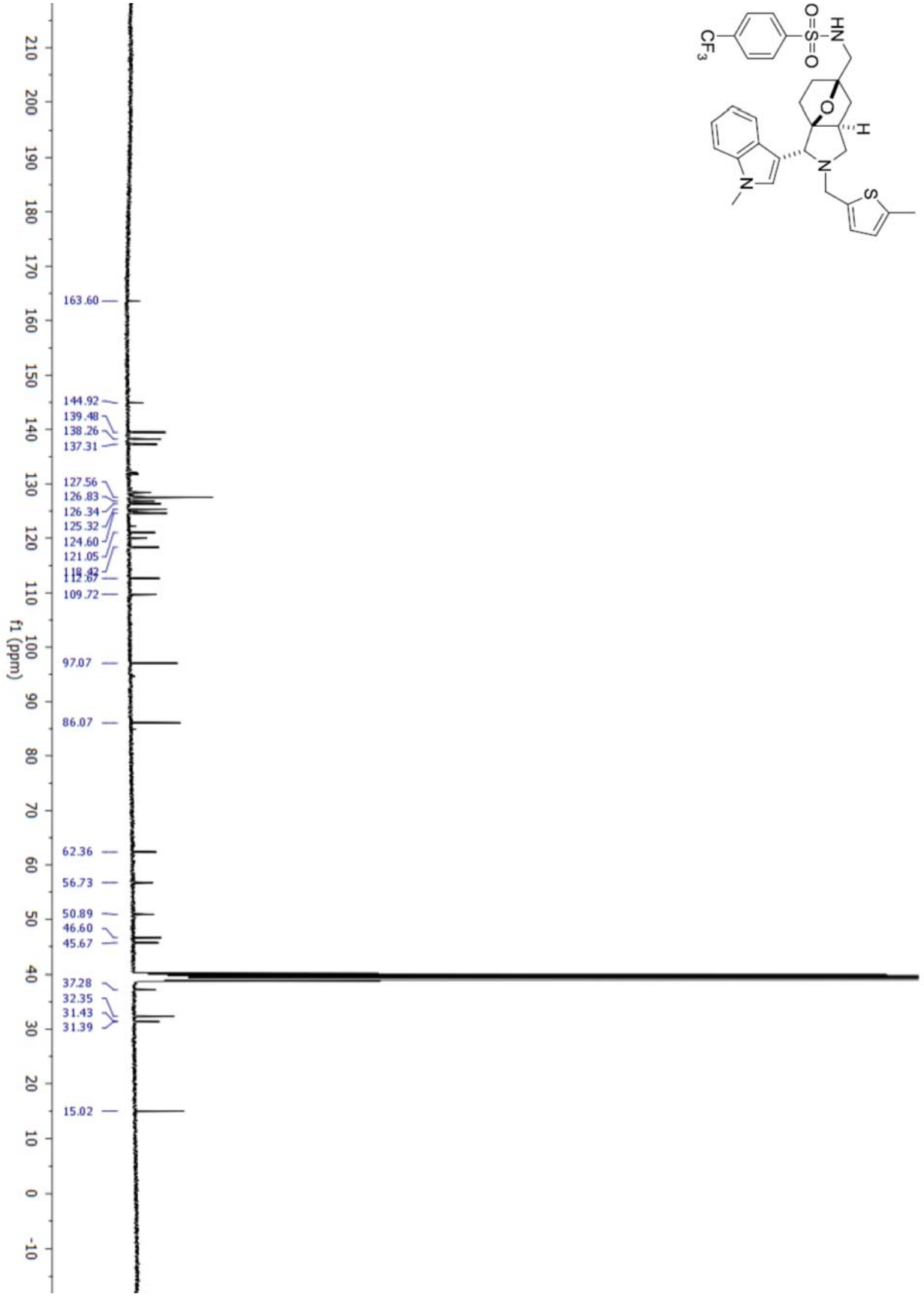
3a, ^{13}C NMR (100 MHz, DMSO-d_6):



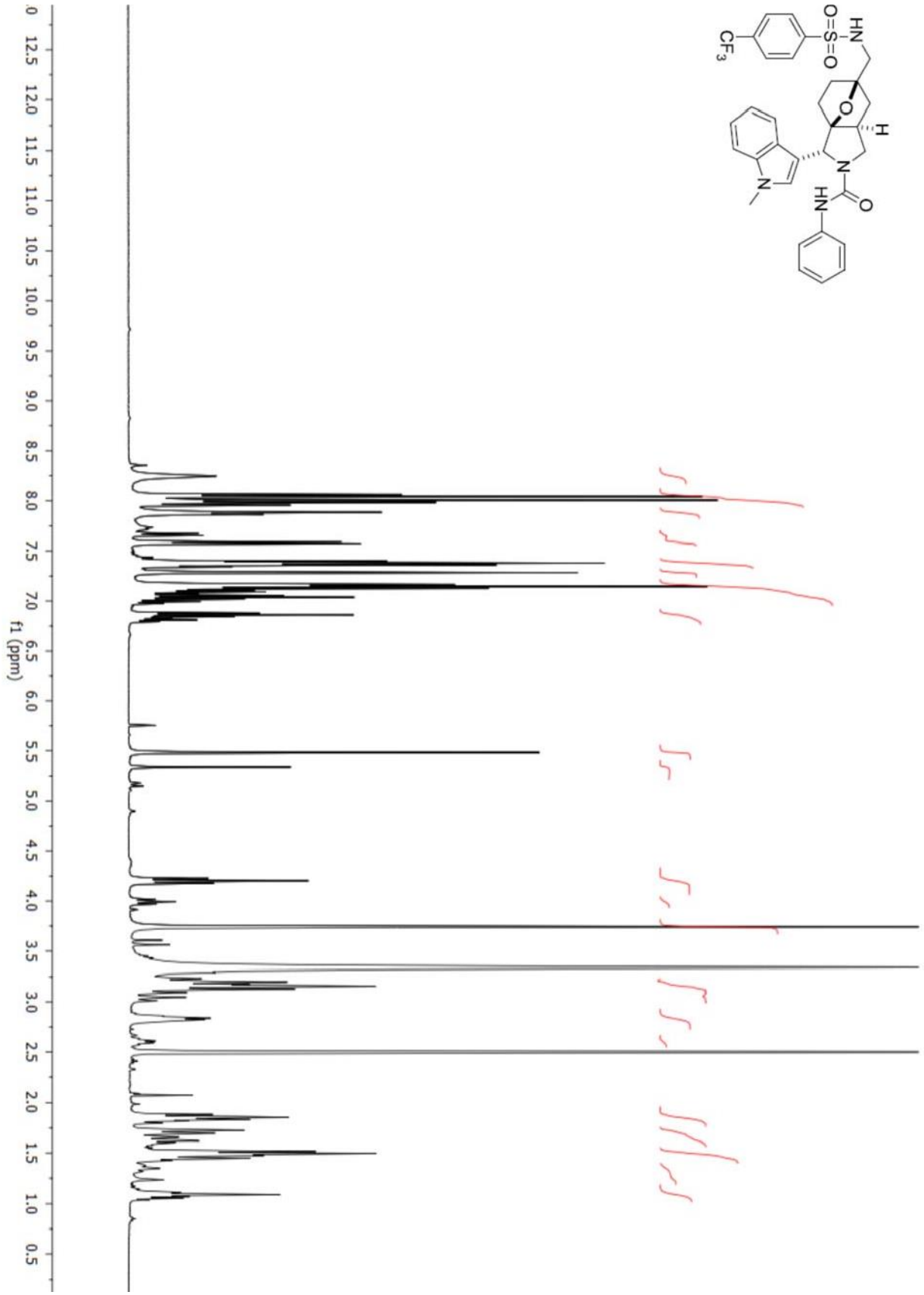
3b, ^{1}H NMR (400 MHz, DMSO-d_6):



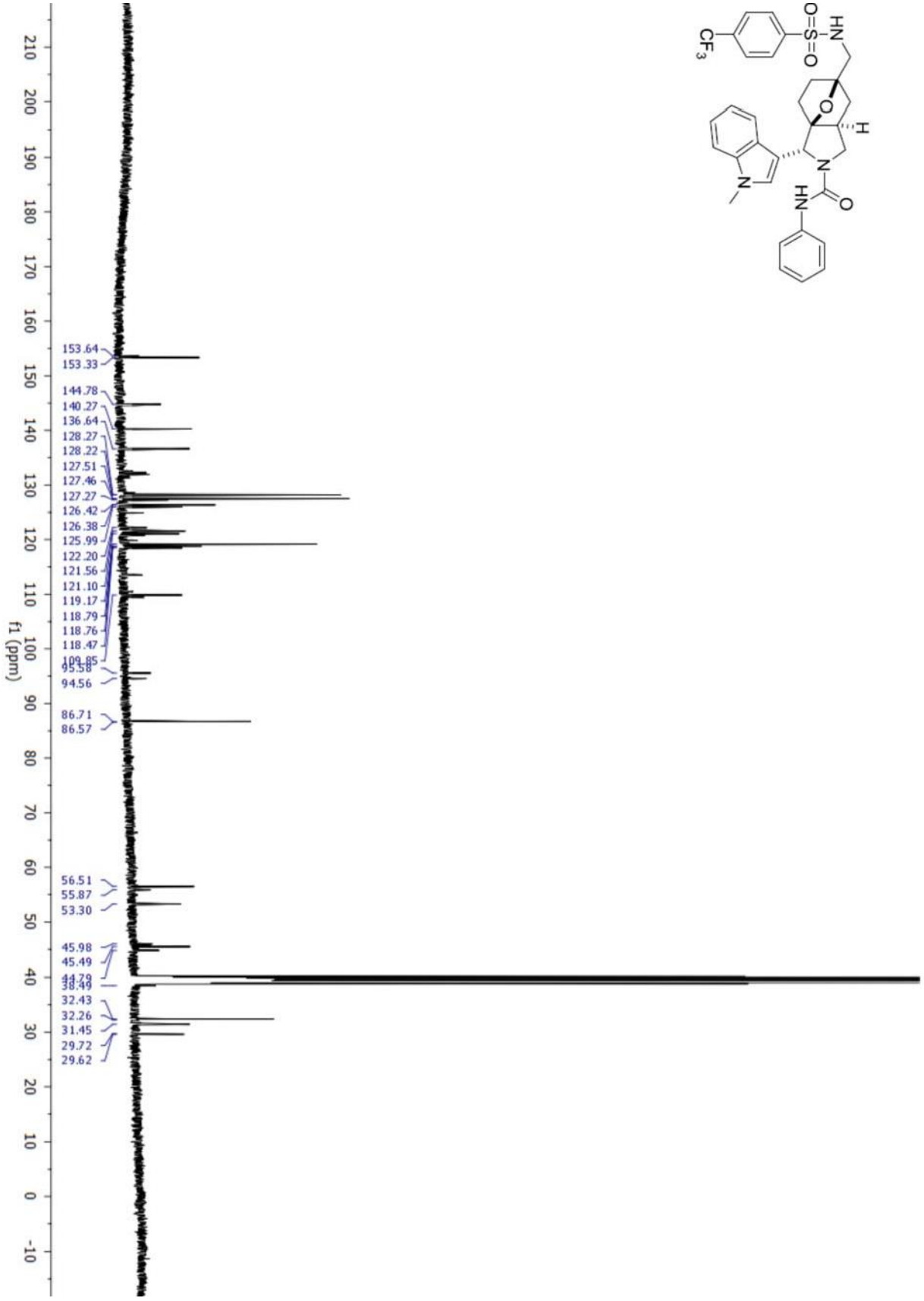
3b, ^{13}C NMR (100 MHz, DMSO-d_6):



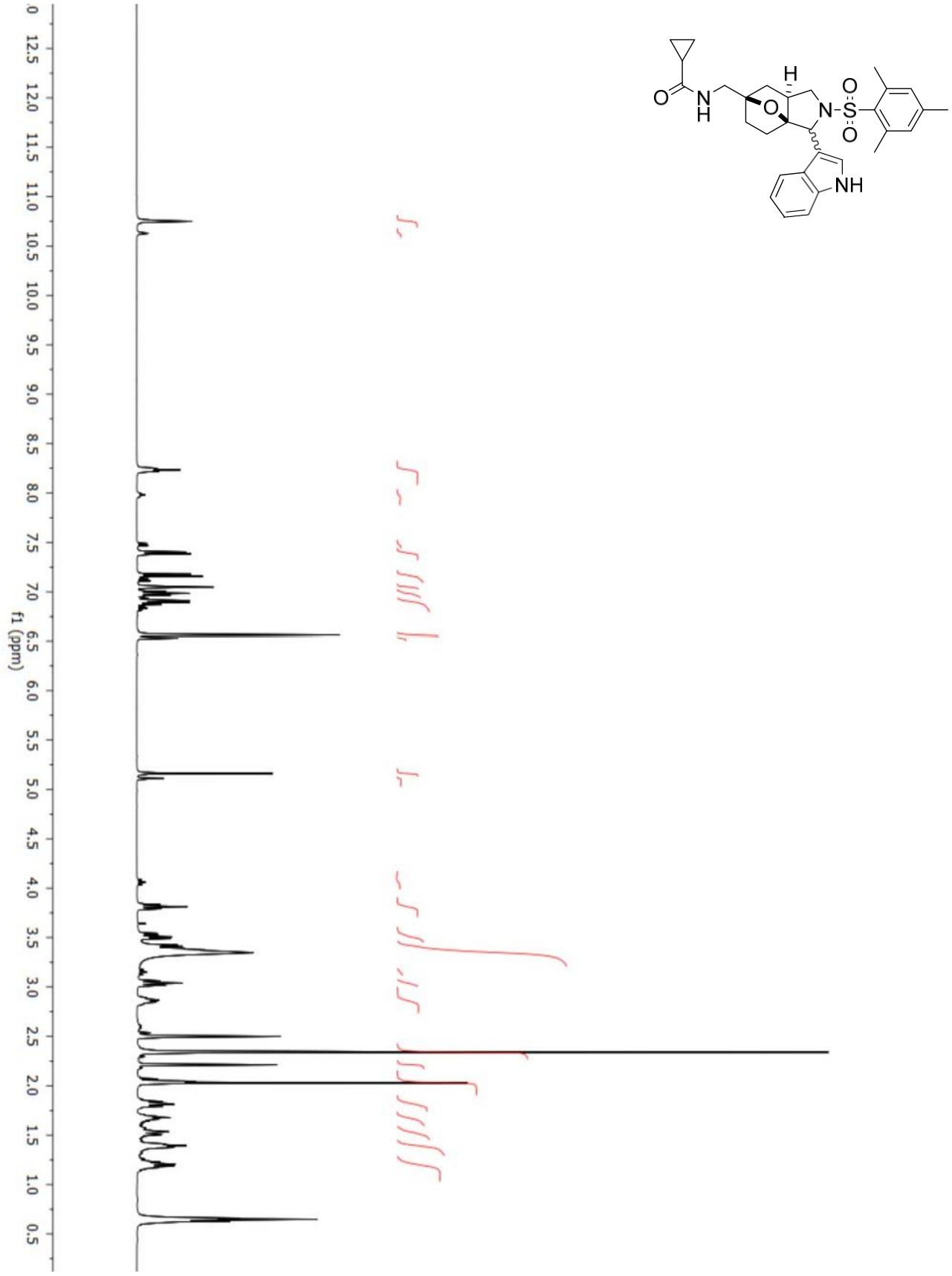
3c, ^{1}H NMR (400 MHz, DMSO-d_6):



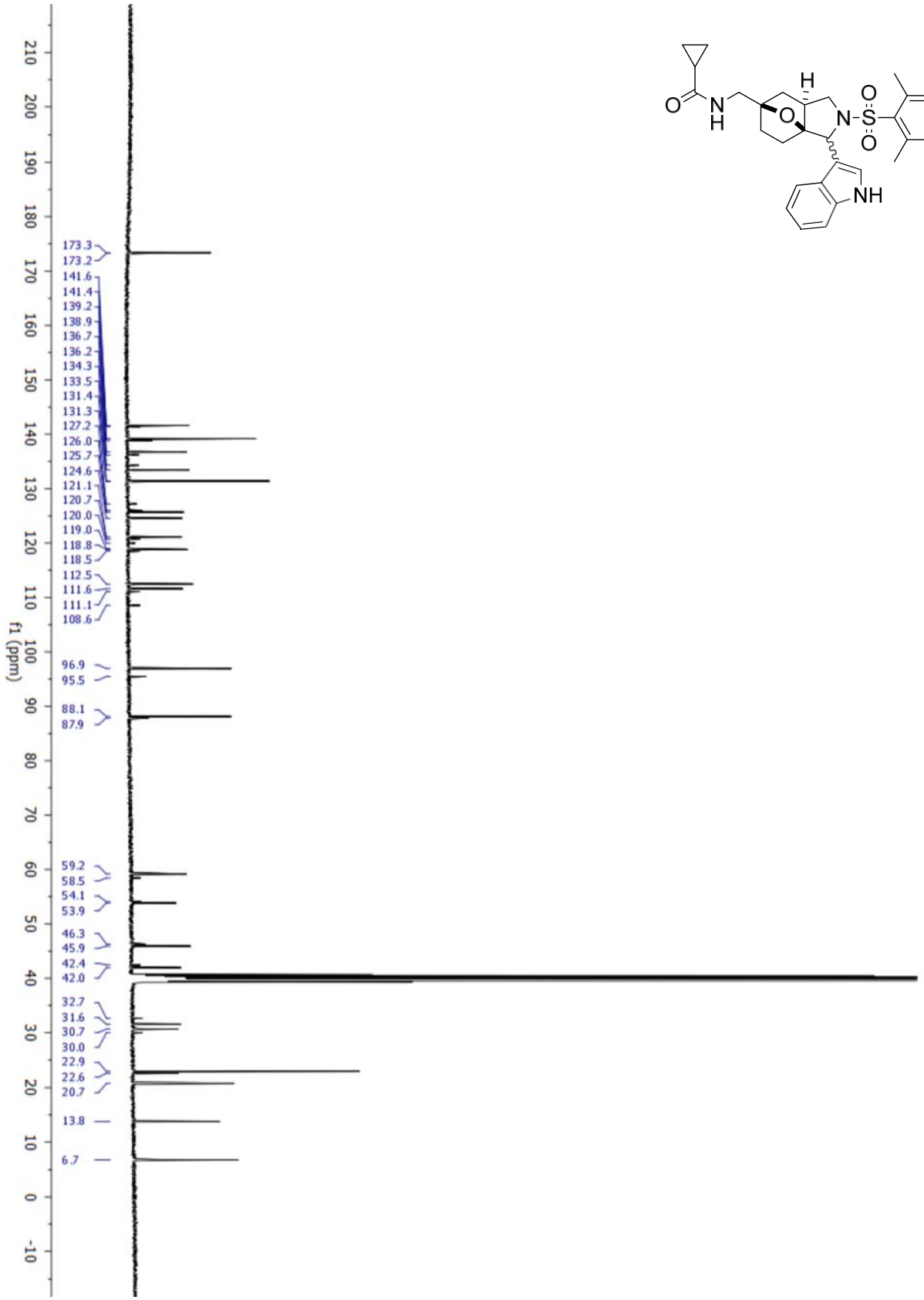
3c, ^{13}C NMR (100 MHz, DMSO-d_6):



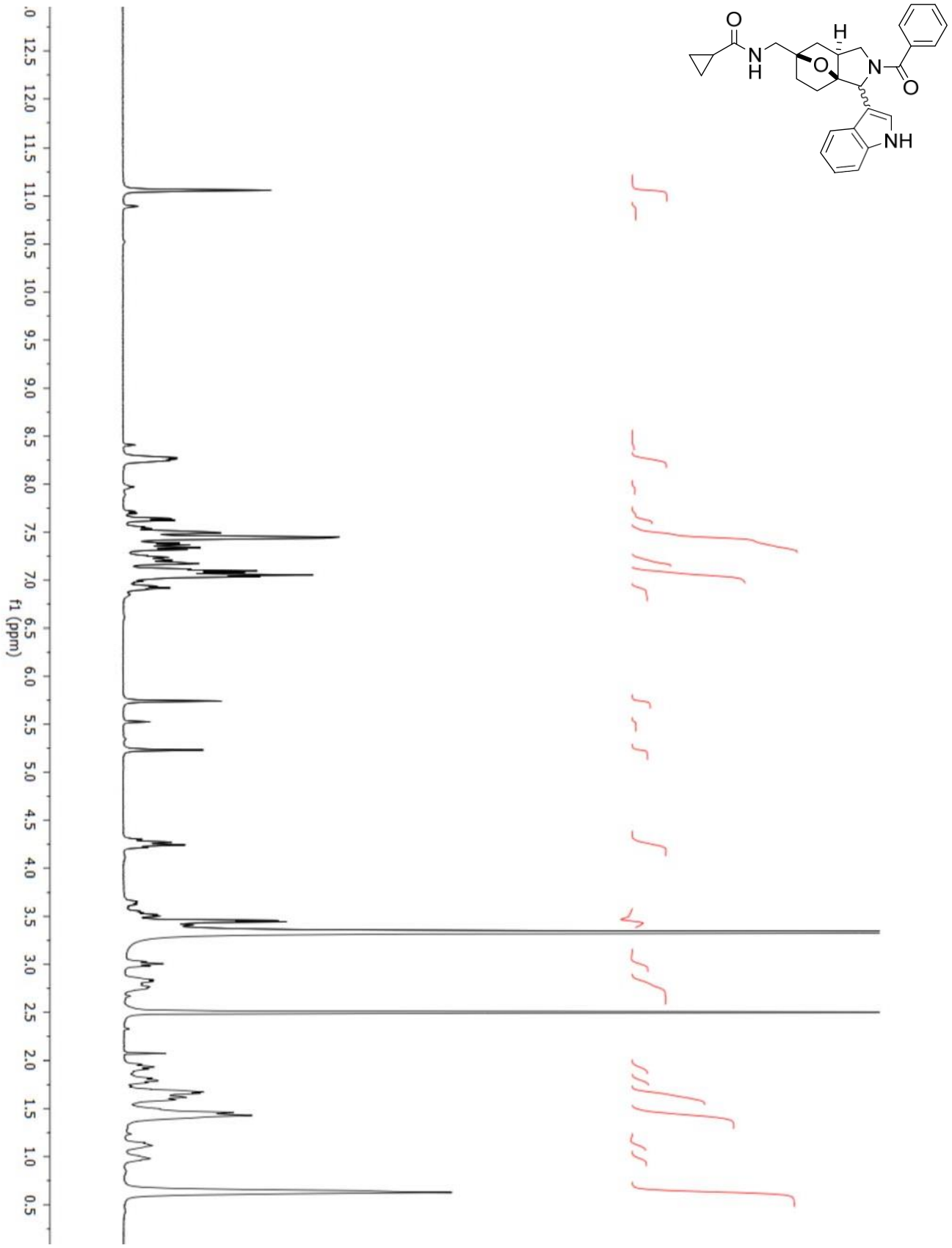
3d, ^{1}H NMR (400 MHz, DMSO-d_6):



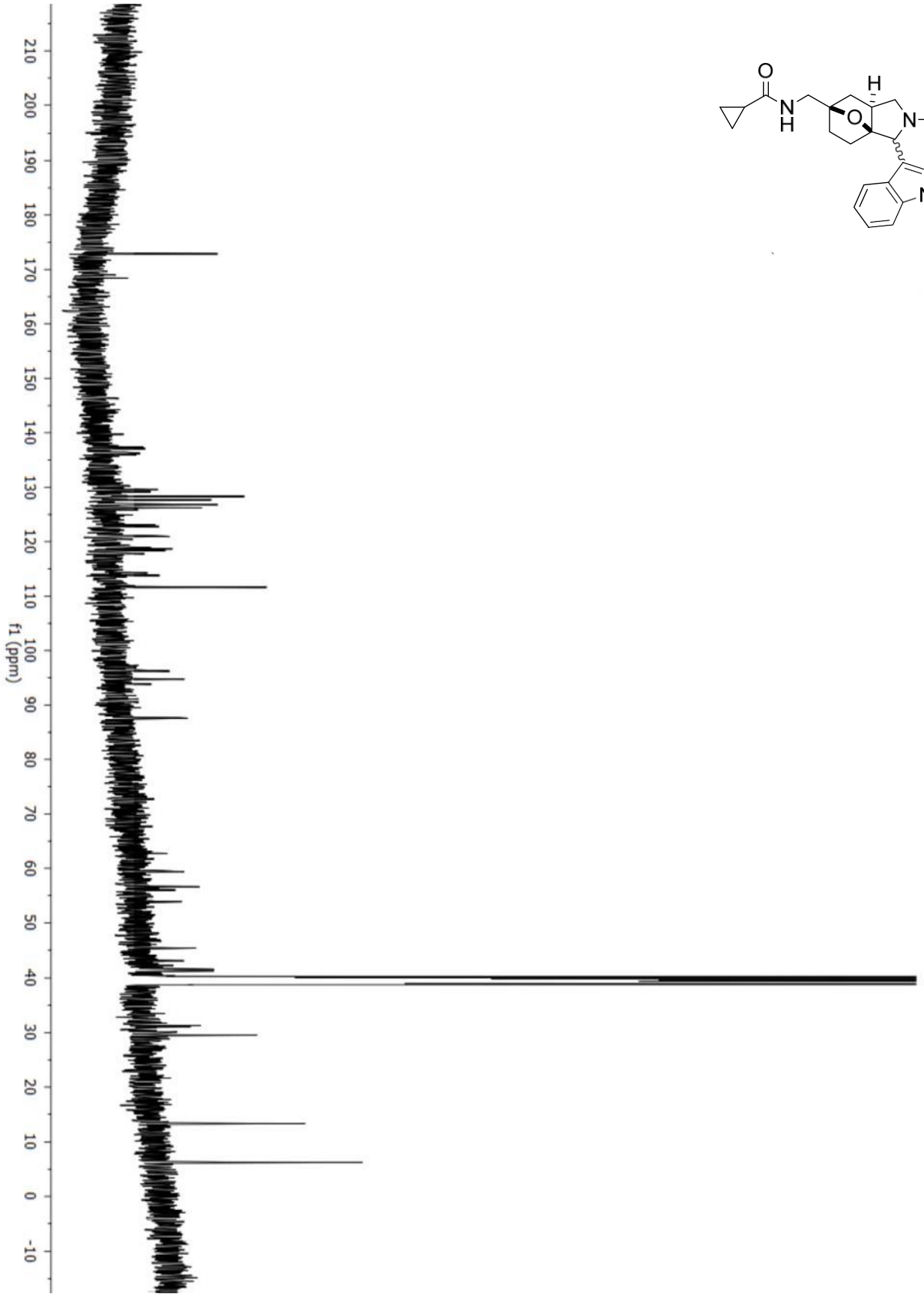
3d, ^{13}C NMR (100 MHz, DMSO-d_6):



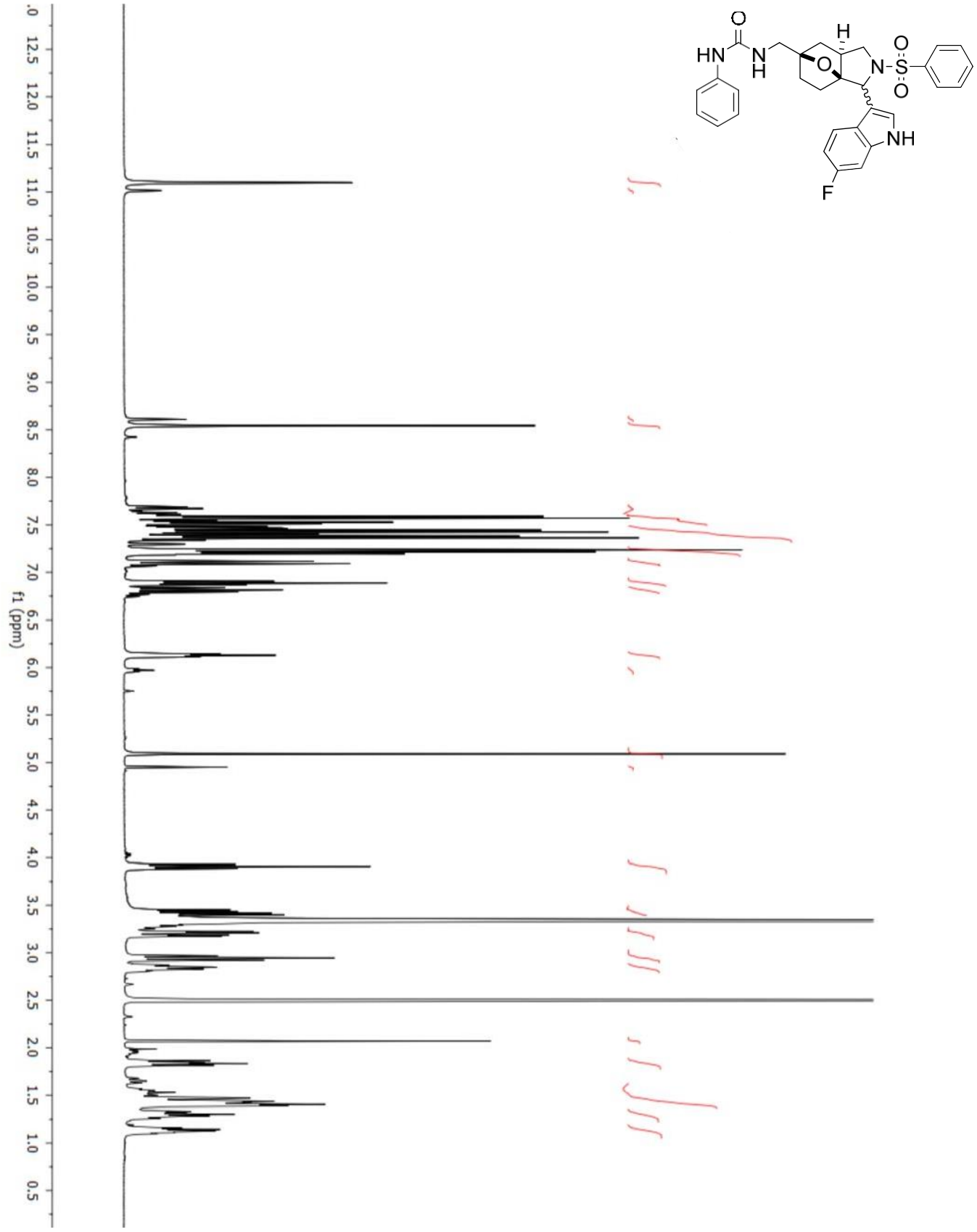
3e, ^{1}H NMR (400 MHz, DMSO-d_6):



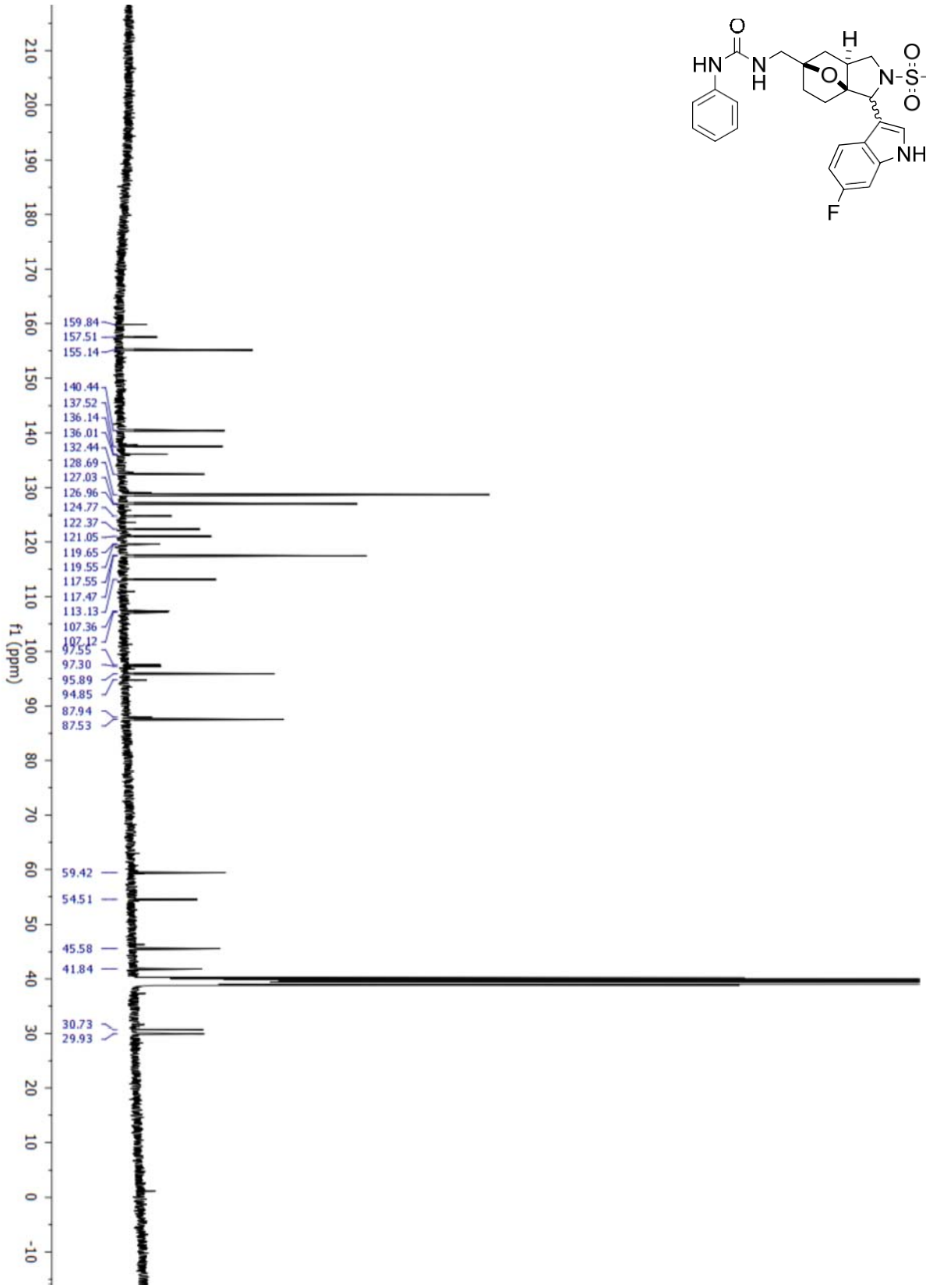
3e, ^{13}C NMR (100 MHz, DMSO-d_6):



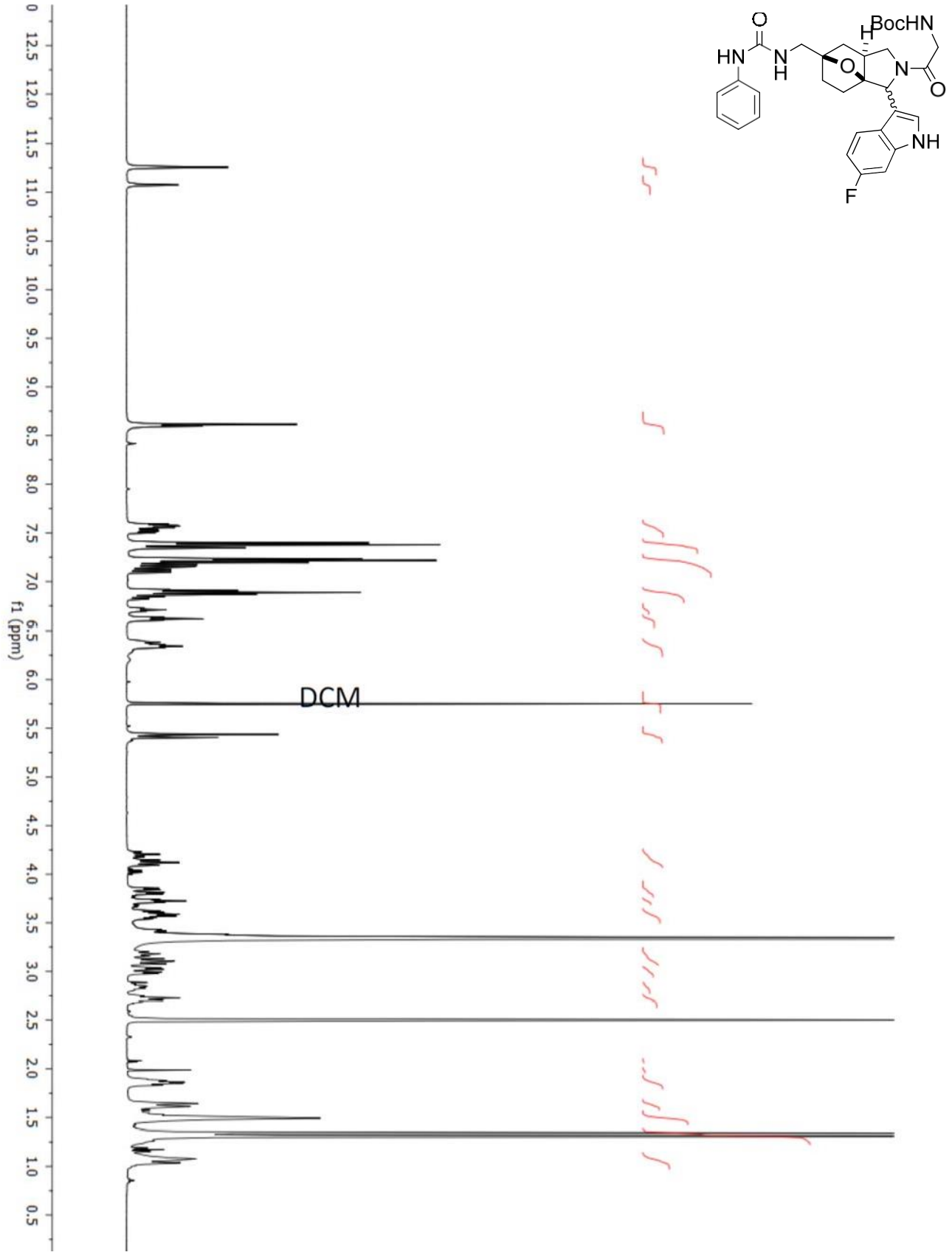
3f, ^{1}H NMR (400 MHz, DMSO-d_6):



3f, ^{13}C NMR (100 MHz, DMSO-d_6):



3g, ^{1}H NMR (400 MHz, DMSO-d_6):



3g, ^{13}C NMR (100 MHz, DMSO-d_6):