Supplementary Information

Synthesis and Biological Evaluation of New Naphthalimide-thiourea Derivatives as Potent Antimicrobial Agents Active against multidrug-resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis*

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1. Experimental section

1.1 General methods

All the reagents and solvents were obtained from commercial suppliers and were used without further purification. Analytical thin layer chromatography (TLC) was performed on MERCK precoated silica gel 60-F254 (0.5 mm) aluminium plates. Visualisation of the spots on T.L.C. plates were achieved by U.V. light. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz by making a solution of samples in the DMSO-d_6 as solvent using tetramethyl silane (T.M.S.) as the internal standard. Chemical shifts for ^{1}H and ^{13}C NMR are reported in parts per million (ppm) downfield from tetramethyl silane. Spin multiplicities are described as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constant (J) values are reported in hertz (Hz). HRMS were determined with Agilent QTOF mass spectrometer 6540 series instrument. Wherever required, column chromatography was performed using silica gel (60-120). The reactions are carried under positive nitrogen pressure using freshly distilled solvents wherever anhydrous conditions are required. All evaporation of solvents was carried out under reduced pressure using a rotary evaporator below 45 °C. Melting point of compounds were determined with an electrothermal digital melting point apparatus IA9100 and is uncorrected. The names of all the compounds given in the experimental section were taken from ChemDraw Professional, Version 20.0.

1.2 General experimental procedure for synthesis of intermediate 3

To the solution of 1,8 naphthalic anhydride (1 mmol) in ethanol, aminoethyl piperazine (1.2 mmol) was added and allowed to reflux for 8 h. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate. The combined organic layer was washed with water, dried over sodium sulphate and evaporated to give crude product. This crude product was further purified by column chromatography to obtain pure product **3.**

2-(2-(Piperazin-1-yl)ethyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dq, J = 7.2, 1.5 Hz, 2H), 8.21 (dt, J = 8.3, 1.6 Hz, 2H), 7.76 (ddt, J = 8.3, 7.2, 1.9 Hz, 2H), 4.36 (ddt, J = 7.2, 5.7, 1.7 Hz, 2H), 2.90 – 2.85 (m, 4H), 2.70 (ddd, J = 8.7,

6.5, 1.5 Hz, 2H), 2.58 (s, 4H).^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 133.9, 131.6, 131.2, 128.2, 126.9, 122.7, 56.3, 54.8, 46.2, 37.4. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{18}H_{20}N_3O_2$ 310.1550; found 310.1564.

1.3 General experimental procedure for the synthesis of 5a-b, 7a-b, 11a-b, and 15

To the mixture of acid (1 mmol) and HATU (1 mmol), *N*, *N*-dimethyl formamide (DMF) was added and allowed to stir at room temperature for 10 min. Then, amine (1.2 mmol) was added under nitrogen atmosphere followed by addition of DIPEA (2.5 mmol) and allowed to stir at room temperature until completion of reaction. Upon completion of the reaction as monitored by TLC, crushed ice was added to the reaction mixture. The resulting precipitate was subjected to vaccum filtration; excess water was used to wash off the insoluble solids to obtain crude solids which was purified by using column chromatography.

2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetic acid (5a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 – 8.55 (m, 2H), 8.27 – 8.20 (m, 2H), 7.77 (dt, *J* = 8.2, 6.9 Hz, 2H), 4.93 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 163.7, 134.3, 131.6, 131.4, 131.1, 128.2, 126.9, 122.2, 77.5, 77.3, 77.0, 41.3, 40.2, 40.1, 39.9, 39.7, 39.6, 29.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{10}NO_4$ 256.0604; found 256.0610.

3-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoic acid (5b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 7.3 Hz, 2H), 8.23 (d, *J* = 8.2 Hz, 2H), 7.76 (t, *J* = 7.7 Hz, 2H), 4.50 (t, *J* = 7.7 Hz, 2H), 2.77 (t, *J* = 7.7 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 163.9, 134.1, 131.6, 131.2, 128.1, 126.9, 122.4, 40.3, 40.1, 39.9, 39.8, 39.6, 36.2, 32.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{15}H_{12}NO_4$ 270.0761; found 270.0764.

Tert-butyl 4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperazine-1-carboxylate (7a)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 2H), 8.50 (q, *J* = 1.2 Hz, 2H), 7.90 (dd, *J* = 8.2, 7.3 Hz, 2H), 4.96 (s, 2H), 3.65 (dd, *J* = 6.6, 3.8 Hz, 2H), 3.47 (q, *J* = 5.4 Hz, 4H), 3.35 (t, *J* = 5.6 Hz, 2H), 1.44 (s, 9H).^{13}C NMR (125 MHz, DMSO- d_6) δ 165.4, 163.7, 154.3, 135.2, 131.9, 131.4, 127.9, 127.8,

122.2, 79.7, 44.5, 41.9, 41.7, 28.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{23}H_{26}N_3O_5$ 424.1867; found 424.1853.

Tert-butyl 4-(3-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)piperazine-1-carboxylate (7b)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.47 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.88 (dd, *J* = 8.2, 7.3 Hz, 2H), 4.29 – 4.23 (m, 2H), 3.45 (td, *J* = 6.5, 3.8 Hz, 4H), 3.37 (dd, *J* = 6.7, 3.7 Hz, 2H), 3.33 (s, 2H), 2.73 (dd, *J* = 8.8, 7.0 Hz, 2H), 1.42 (s, 9H).^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 163.8, 154.3, 134.9, 131.8, 131.2, 127.8, 127.7, 122.5, 79.6, 45.1, 41.2, 36.8, 31.5, 28.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{28}N_3O_5$ 438.2023; found 438.2008.

Tert-butyl 4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetamido)piperidine-1-carboxylate (11a)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 – 8.48 (m, 4H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.93 – 7.86 (m, 2H), 4.64 (s, 2H), 3.85 (d, *J* = 13.3 Hz, 2H), 3.76 (m, 1H), 2.84 (s, 2H), 1.72 (dt, *J* = 12.0, 3.7 Hz, 2H), 1.40 (s, 9H), 1.32 – 1.21 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.3, 163.8, 154.4, 135.0, 131.8, 131.3, 128.0, 127.8, 122.5, 79.1, 46.4, 42.9, 31.8, 28.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{28}N_3O_5$ 438.2023; found 438.2009.

Tert-butyl 4-(3-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanamido)piperidine-1-carboxylate (11b)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (dd, *J* = 7.3, 1.6 Hz, 2H), 8.48 – 8.45 (m, 2H), 7.92 – 7.85 (m, 3H), 4.30 – 4.23 (m, 2H), 3.84 – 3.73 (m, 2H), 3.70 (dt, *J* = 11.1, 6.1 Hz, 1H), 2.84 (d, *J* = 1.8 Hz, 2H), 2.44 (td, *J* = 7.4, 1.8 Hz, 2H), 1.67 (dd, *J* = 13.3, 4.0 Hz, 2H), 1.38 (d, *J* = 1.8 Hz, 9H), 1.17 (tt, *J* = 12.0, 4.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.6, 163.8, 154.4, 134.7, 131.8, 131.1, 127.8, 127.7, 122.6, 79.1, 45.9, 37.1, 34.4, 31.6, 28.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{30}N_3O_5$ 452.2180; found 452.2166.

Tert-butyl (1-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperidin-4-yl)carbamate (15)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.3, 1.1 Hz, 2H), 8.22 (dd, J = 8.3, 1.1 Hz, 2H), 7.75 (dd, J = 8.2, 7.3 Hz, 2H), 5.03 (s, 2H), 4.53 (d, J = 7.6 Hz, 1H), 4.47 (d, J = 14.0 Hz, 1H), 3.95 (dq, J = 14.2, 3.2 Hz, 1H), 3.74 (s, 1H), 3.29 (m, 1H), 2.88 – 2.78 (m, 1H), 2.14 (d, J = 12.8 Hz, 1H), 1.97 (dt, J = 14.5, 3.8 Hz, 1H), 1.55 – 1.49 (m, 1H), 1.46 (s, 9H), 1.37 (dd, J = 12.6, 4.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 164.2, 155.1, 134.2, 131.7, 131.5, 128.4, 126.9, 122.4, 47.8, 43.8, 41.4, 41.2, 32.9, 32.0, 28.4. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{28}N_3O_5$ 438.2023; found 438.2007.

1.4 General experimental procedure for the synthesis of intermediate 8a-b, 12a-b and 16

To the stirred solution of boc protected compound in DCM, add a solution of HCl in dioxan (4N) slowly under ice conditions and allowed to stir at room temperature for 12 h. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated under vaccum to obtain solid product.

2-(2-Oxo-2-(piperazin-1-yl)ethyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione hydrochloride (8a)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (s, 2H), 8.53 (s, 2H), 8.51 (s, 2H), 7.91 (t, J = 7.7 Hz, 2H), 5.01 (s, 2H), 3.94 (t, J = 5.2 Hz, 2H), 3.72 (t, J = 5.1 Hz, 2H), 3.22 (s, 2H), 3.08 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.8, 163.7, 135.2, 131.9, 131.5, 127.9, 127.8, 122.2, 66.8, 43.2, 42.9, 41.7, 41.5, 40.5, 38.8. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{18}H_{18}N_3O_3$ 324.1343; found 324.1352.

2-(3-Oxo-3-(piperazin-1-yl)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione hydrochloride (8b)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 2H), 8.52 – 8.42 (m, 4H), 7.88 (q, J = 6.2 Hz, 2H), 4.26 (q, J = 6.5 Hz, 2H), 3.74 (d, J = 5.0 Hz, 2H), 3.70 (t, J = 4.6 Hz, 2H), 3.13 (s, 2H), 3.05 (d, J = 6.6 Hz, 2H), 2.76 (t, J = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4, 163.8, 134.9, 131.8, 131.2, 127.8, 127.7, 122.5, 66.8, 42.9, 42.7, 42.2, 38.1, 36.6, 31.3. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{19}H_{20}N_3O_3$ 338.1499; found 338.1513.

2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-N-(piperidin-4-yl)acetamide hydrochloride (12a)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (s, 2H), 8.27 (d, J = 6.8 Hz, 4H), 8.22 (d, J = 6.7 Hz, 1H), 7.67 (d, J = 7.2 Hz, 2H), 4.44 (s, 2H), 3.62 (s, 1H), 3.02 (d, J = 11.5 Hz, 2H), 2.72 (d, J = 12.2 Hz, 2H), 1.67 (d, J = 12.9 Hz, 2H), 1.44 (q, J = 11.6 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.7, 163.8, 135.1, 131.9, 131.3, 128.0, 127.8, 122.4, 66.8, 44.3, 42.8, 42.1, 28.4. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{19}H_{20}N_3O_3$ 338.1499; found 338.1486.

3-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-N-(piperidin-4-yl)propanamide hydrochloride (12b)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (s, 2H), 8.49 – 8.42 (m, 4H), 8.25 (d, J = 7.5 Hz, 1H), 7.87 (dd, J = 8.2, 7.2 Hz, 2H), 4.26 (t, J = 7.2 Hz, 2H), 3.84 – 3.70 (m, 1H), 3.17 (dt, J = 12.3, 3.7 Hz, 2H), 2.88 (dd, J = 14.7, 7.3 Hz, 2H), 2.47 (t, J = 7.3 Hz, 2H), 1.84 (dt, J = 12.8, 4.0 Hz, 2H), 1.61 (qd, J = 10.2, 5.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.0, 163.8, 134.8, 131.8, 131.1, 127.8, 127.7, 122.6, 66.8, 43.6, 42.0, 37.1, 34.3, 28.2. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{20}H_{22}N_3O_3$ 352.1656; found 352.1666.

2-(2-(4-Aminopiperidin-1-yl)-2-oxoethyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (16)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (t, J = 6.2 Hz, 4H), 8.27 (d, J = 21.7 Hz, 2H), 7.91 (t, J = 7.7 Hz, 2H), 5.00 (d, J = 16.3 Hz, 1H), 4.91 (d, J = 16.8 Hz, 1H), 4.30 (d, J = 13.1 Hz, 1H), 4.14 (d, J = 13.5 Hz, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.27 (dd, J = 31.7, 18.8 Hz, 2H), 2.81 – 2.67 (m, 1H), 2.08 (d, J = 12.4 Hz, 1H), 1.61 (d, J = 12.8 Hz, 1H), 1.18 (t, J = 7.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.0, 163.7, 135.2, 131.9, 131.4, 127.8, 122.2, 60.2, 47.8, 42.8, 41.7, 30.6, 29.8, 28.8, 21.3, 14.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{19}H_{20}N_3O_3$ 338.1499; found 338.1511.

1.5 General experimental procedure for the synthesis of 4a-r, 9a-l, 13a-g, and 17a-e

To the stirred solution of compound (1 mmol), triethyl amine (2 mmol) in 10 mL of ACN, was added the corresponding aryl/alkyl/hetero aryl isothiocyanates/ arylisocyanates and allowed to reflux for 1 h. After the completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure and water was added. The resulting solid was subjected to vaccum filtration, and excess water was used to wash off the insoluble solids to obtain crude solids which was purified by using column chromatography.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-phenylpiperazine-1-carbothioamide (4a)

Off white solid (130 mg); yield 90%; m.p. 189-192°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.53 (dt, *J* = 7.6, 2.1 Hz, 2H), 8.50 – 8.47 (m, 2H), 7.90 (td, *J* = 7.8, 2.8 Hz, 2H), 7.28 (q, *J* = 5.0 Hz, 4H), 7.10 (tt, *J* = 5.8, 2.5 Hz, 1H), 4.24 (t, *J* = 7.0 Hz, 2H), 3.85 (t, *J* = 5.2 Hz, 4H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 5.0 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.8, 163.9, 141.5, 134.9, 131.8, 131.3, 128.5, 127.8, 127.7, 125.7, 124.7, 122.5, 55.3, 53.0, 48.5, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{25}N_4O_2S$ 445.1693; found 445.1687.

N-(4-chlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4b)

White solid (123 mg); yield 79%; m.p. 246-248°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.52 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.48 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.89 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.35 – 7.29 (m, 4H), 4.24 (t, *J* = 6.9 Hz, 2H), 3.86 (t, *J* = 5.1 Hz, 4H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.57 (t, *J* = 5.0 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.7, 163.9, 140.5, 134.8, 131.8, 131.3, 128.6, 128.3, 127.8, 127.7, 127.2, 122.5, 55.3, 53.0, 48.5, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{24}ClN_4O_2S$ 479.1303; found 479.1291.

N-(3-chlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4c)

White solid (140 mg); yield 90%; m.p. 229-232°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.52 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.47 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.89 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.42 (t, *J* = 2.0 Hz, 1H), 7.35 – 7.24 (m, 2H), 7.17 – 7.11 (m, 1H), 4.23 (t, *J* = 6.9 Hz, 2H), 3.86 (t, *J* = 4.7 Hz, 4H), 2.68 – 2.63 (m, 2H), 2.58 (t, *J* = 4.9 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.5, 163.9, 143.1, 134.8, 132.5, 131.8, 131.2, 130.0, 127.8, 127.7, 124.9, 124.2, 123.7, 122.5, 55.3, 53.0, 48.6, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{24}ClN_4O_2S$+ 479.1303; found 479.1294.

N-(2-chlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4d)

White solid (135 mg); yield 87%; m.p. 213-215°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.50 (d, *J* = 7.3 Hz, 2H), 8.46 (d, *J* = 8.0 Hz, 2H), 7.88 (q, *J* = 6.4 Hz, 2H), 7.48 (dd, *J* = 7.9, 1.5 Hz,

1H), 7.34 – 7.21 (m, 3H), 4.24 (q, *J* = 5.4 Hz, 2H), 3.88 (t, *J* = 4.9 Hz, 4H), 2.65 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 4.9 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.2, 163.9, 138.8, 134.8, 132.4, 131.8, 131.6, 131.2, 129.7, 128.2, 127.8, 127.7, 127.6, 122.5, 55.3, 53.0, 48.5, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{24}ClN_4O_2S$ 479.1303; found 479.1295.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-(4-methoxyphenyl)piperazine-1-carbothioamide (4e)

White solid (114 mg); yield 74%; m.p. 196-199°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.51 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.46 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.88 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.18 – 7.11 (m, 2H), 6.88 – 6.83 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 3.85 (t, *J* = 4.9 Hz, 4H), 3.74 (s, 3H), 2.65 (t, *J* = 6.9 Hz, 2H), 2.56 (t, *J* = 5.0 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.1, 163.9, 156.9, 134.8, 134.3, 131.8, 131.3, 127.9, 127.8, 127.7, 122.5, 113.7, 55.6, 55.3, 53.0, 48.3, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{27}N_4O_3S$ 475.1798; found 475.1783.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-(p-tolyl)piperazine-1-carbothioamide (4f)

Yellow solid (116 mg); yield 78%; m.p. 213-216°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.22 (s, 1H), 8.52 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.48 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.89 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.14 (dt, *J* = 6.7, 2.2 Hz, 2H), 7.11 – 7.07 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 3.84 (t, *J* = 5.0 Hz, 4H), 2.67 – 2.63 (m, 2H), 2.56 (t, *J* = 5.0 Hz, 4H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.9, 163.9, 138.9, 134.9, 133.9, 131.8, 131.3, 128.9, 127.8, 127.7, 125.9, 122.5, 55.3, 53.0, 48.4, 37.5, 21.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{27}N_4O_2S$ 459.1849; found 459.1836.

N-(3,4-dichlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4g)

White solid (140 mg); yield 84%; m.p. 248-250°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.52 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.48 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.89 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.24 (t, *J* = 6.9 Hz, 2H), 3.86 (t, *J* = 5.0 Hz, 4H), 2.66 (dt, *J* = 13.3, 6.2 Hz, 2H), 2.58 (t, *J* = 5.0 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.3, 163.9, 141.8, 134.9, 131.8, 131.3, 130.4, 130.1, 127.9, 127.7, 125.6, 125.2, 125.3,

122.5, 55.2, 52.9, 48.6, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{23}Cl_2N_4O_2S$ 513.0913; found 513.0898.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-ethylpiperazine-1-carbothioamide (4h)

Off white solid (90 mg); yield 70 %; m.p. 198-201°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (d, *J* = 7.2 Hz, 2H), 8.46 (d, *J* = 8.2 Hz, 2H), 7.88 (t, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 5.4 Hz, 1H), 4.21 (t, *J* = 7.0 Hz, 2H), 3.71 (t, *J* = 4.9 Hz, 4H), 3.54 – 3.46 (m, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 5.0 Hz, 4H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.6, 163.9, 134.8, 131.8, 131.2, 127.8, 127.7, 122.5, 55.3, 53.0, 47.5, 40.5, 37.5, 15.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{21}H_{25}N_4O_2S$ 397.1693; found 397.1674.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-isopropylpiperazine-1-carbothioamide (4i)

White solid (96 mg); yield 72%; m.p. 182-184°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (d, *J* = 7.3 Hz, 2H), 8.46 (d, *J* = 8.2 Hz, 2H), 7.88 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 4.52 (q, *J* = 6.8 Hz, 1H), 4.21 (t, *J* = 7.0 Hz, 2H), 3.75 – 3.66 (m, 4H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.50 – 2.44 (m, 4H), 1.13 (d, *J* = 6.6 Hz, 7H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.8, 163.9, 134.8, 131.8, 131.2, 127.8, 127.7, 122.5, 55.3, 53.0, 47.6, 47.5, 37.5, 22.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{22}H_{27}N_4O_2S$ 411.1849; found 411.1855.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-heptylpiperazine-1-carbothioamide (4j)

White solid (95 mg); yield 62%; m.p. 140-142°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.46 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.88 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.62 (t, *J* = 5.3 Hz, 1H), 4.21 (t, *J* = 7.0 Hz, 2H), 3.71 (t, *J* = 5.1 Hz, 4H), 3.45 (td, *J* = 7.5, 5.3 Hz, 2H), 2.63 – 2.57 (m, 2H), 2.48 (t, *J* = 5.0 Hz, 4H), 1.54 – 1.47 (m, 2H), 1.26 (dq, *J* = 10.6, 6.4 Hz, 9H), 0.88 – 0.80 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.7, 163.9, 134.8, 131.8, 131.2, 127.8, 127.7, 122.5,

55.4, 53.0, 47.6, 45.8, 37.5, 31.7, 29.1, 29.0, 26.8, 22.5, 14.4. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{35}N_4O_2S$ 467.2475; found 467.2473.

N-cyclopropyl-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4k)

Light brown solid (93 mg); yield 70%; m.p. 143-146°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, *J* = 7.3 Hz, 2H), 8.47 (d, *J* = 8.2 Hz, 2H), 7.89 (t, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 3.4 Hz, 1H), 4.21 (p, *J* = 7.2 Hz, 3H), 3.69 (t, *J* = 5.0 Hz, 3H), 3.00 (ddt, *J* = 14.7, 7.3, 4.3 Hz, 1H), 2.69 – 2.62 (m, 2H), 2.61 (t, *J* = 7.0 Hz, 1H), 2.48 (t, *J* = 5.0 Hz, 3H), 0.65 (h, *J* = 4.6 Hz, 2H), 0.54 (p, *J* = 4.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 183.5, 163.9, 134.9, 134.9, 131.8, 131.3, 127.9, 127.7, 122.5, 55.3, 53.0, 44q.7, 37.5, 28.8, 7.2. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{22}H_{25}N_4O_2S$ 409.1693; found 409.1678.

N-cyclopentyl-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4l)

Off white solid (96 mg); yield 68%; m.p. 168-170°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.48 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.89 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 4.61 (h, *J* = 7.5 Hz, 1H), 4.22 (t, *J* = 6.9 Hz, 2H), 3.71 (t, *J* = 4.9 Hz, 4H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 5.0 Hz, 4H), 1.96 – 1.82 (m, 2H), 1.69 – 1.57 (m, 2H), 1.53 – 1.41 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.6, 163.9, 134.8, 131.8, 131.2, 127.8, 127.7, 122.5, 57.5, 55.3, 53.0, 47.7, 37.5, 32.2, 24.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{29}N_4O_2S$ 437.2006; found 437.1986.

N-cyclohexyl-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4m)

White solid (110 mg); yield 75%; m.p. 113-115°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 7.3 Hz, 2H), 8.23 (d, *J* = 8.2 Hz, 2H), 7.77 (t, *J* = 7.8 Hz, 2H), 5.31 – 5.25 (m, 1H), 4.35 (q, *J* = 7.6 Hz, 3H), 3.74 (t, *J* = 5.1 Hz, 4H), 2.75 (t, *J* = 6.7 Hz, 2H), 2.64 (t, *J* = 5.1 Hz, 4H), 2.10 (m, 2H), 1.70 (m, 2H), 1.65 (d, *J* = 3.9 Hz, 1H), 1.41 (m, 2H), 1.16 (m, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9, 164.3, 134.0, 131.6, 131.3, 128.2, 127.0, 122.6, 55.4, 54.2, 52.6, 47.2, 37.4, 33.2, 25.6, 24.9. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{31}N_4O_2S$ 451.2162; found 451.2149.

N-cycloheptyl-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4n)

Off white solid (100 mg); yield 66%; .p. 192-194°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, J = 7.3 Hz, 2H), 8.48 (d, J = 8.3 Hz, 2H), 7.89 (t, J = 7.7 Hz, 2H), 7.28 (d, J = 7.9 Hz, 1H), 4.36 (s, 1H), 4.21 (t, J = 7.0 Hz, 2H), 3.70 (t, J = 4.8 Hz, 4H), 2.61 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 5.1 Hz, 4H), 1.89 – 1.79 (m, 2H), 1.62 (d, J = 11.1 Hz, 2H), 1.57 – 1.43 (m, 6H), 1.42 – 1.30 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.7, 163.9, 134.8, 131.8, 131.2, 127.7, 122.5, 57.0, 55.4, 53.0, 47.7, 37.5, 34.5, 28.1, 24.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{33}N_4O_2S$ 465.2319; found 465.2302.

N-(adamantan-1-yl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carbothioamide (4o)

Off white solid (126 mg); yield 77%; m.p. 197-200°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 7.3 Hz, 2H), 8.22 (dd, J = 8.4, 4.9 Hz, 2H), 7.76 (td, J = 7.7, 3.3 Hz, 2H), 5.23 (s, 1H), 4.35 (t, J = 6.6 Hz, 2H), 3.72 (t, J = 5.1 Hz, 3H), 2.96 (s, 1H), 2.74 (t, J = 6.7 Hz, 3H), 2.63 (t, J = 5.1 Hz, 4H), 2.27 (d, J = 3.0 Hz, 5H), 2.11 (s, 3H), 1.98 (d, J = 2.9 Hz, 1H), 1.74 – 1.61 (m, 5H).^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 164.3, 164.2, 134.0, 134.0, 131.6, 131.6, 131.3, 128.2, 127.0, 127.0, 122.7, 122.6, 77.2, 56.1, 55.4, 54.8, 53.7, 52.7, 47.1, 45.7, 43.8, 41.9, 37.4, 37.3, 36.4, 35.5, 29.7, 29.2.HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{29}H_{35}N_4O_2S$ 503.2475; found 503.2463.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-(pyridin-3-yl)piperazine-1-carbothioamide (4p)

Light pink solid (98 mg); yield 68%; m.p. 214-217°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.52 (d, J = 7.2 Hz, 2H), 8.48 (d, J = 8.2 Hz, 3H), 8.29 (dd, J = 4.7, 1.5 Hz, 1H), 7.89 (t, J = 7.7 Hz, 2H), 7.72 (dt, J = 8.3, 2.0 Hz, 1H), 7.33 (dd, J = 8.2, 4.7 Hz, 1H), 4.24 (t, J = 6.9 Hz, 2H), 3.89 (t, J = 5.0 Hz, 4H), 2.67 (t, J = 7.0 Hz, 2H), 2.59 (t, J = 5.0 Hz, 4H).^{13}C NMR (125 MHz, DMSO-d_6) δ 181.8, 163.9, 147.1, 145.5, 138.2, 134.8, 133.2, 131.8, 131.3, 127.8, 127.7, 123.3, 122.5, 55.3, 52.9, 48.5, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{24}N_5O_2S$ 446.1645; found 446.1638.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)-N-phenylpiperazine-1-carboxamide (4q)

White solid (112 mg); yield 80%; m.p. 187-189°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (dd, J = 7.3, 1.2 Hz, 2H), 8.48 – 8.44 (m, 3H), 7.88 (dd, J = 8.2, 7.2 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.24 – 7.19 (m, 2H), 6.93 (td, J = 7.3, 1.2 Hz, 1H), 4.23 (t, J = 6.9 Hz, 2H), 3.44 – 3.37 (m, 4H), 2.66 – 2.60 (m, 2H), 2.54 – 2.51 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 155.4, 141.0, 134.8, 131.8, 131.2, 128.7, 127.8, 127.7, 122.5, 122.1, 120.1, 55.6, 53.2, 44.3, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{25}N_4O_3$ 429.1921; found 429.1916.

N-(4-chlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)ethyl)piperazine-1-carboxamide (4r)

Off white solid (125 mg); yield 83%; m.p. 218-220°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ^{1}H NMR (500 MHz, DMSO) δ 8.61 (s, 1H), 8.51 (dd, J = 7.7, 4.1 Hz, 2H), 8.47 (dd, J = 8.1, 4.7 Hz, 2H), 7.92 – 7.84 (m, 2H), 7.52 – 7.46 (m, 2H), 7.27 (d, J = 8.7 Hz, 2H), 4.26 – 4.18 (m, 2H), 3.41 (t, J = 4.8 Hz, 4H), 2.63 (t, J = 7.1 Hz, 2H), 2.55 – 2.51 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 155.2, 140.1, 134.8, 131.8, 131.2, 128.6, 127.7, 125.7, 122.5, 121.4, 120.3, 55.5, 53.2, 44.2, 37.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{24}ClN_4O_3$ 463.1531; found 463.1519.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)-N-phenylpiperazine-1-carbothioamide (9a)

White solid (110 mg); yield 77%; .p. 248-250°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.55 – 8.48 (m, 4H), 7.92 (dd, J = 8.2, 7.2 Hz, 2H), 7.36 – 7.30 (m, 4H), 7.17 – 7.10 (m, 1H), 5.01 (s, 2H), 4.10 (dd, J = 6.6, 3.8 Hz, 2H), 3.96 (dd, J = 6.7, 3.9 Hz, 2H), 3.83 (dd, J = 6.7, 3.9 Hz, 2H), 3.61 (dd, J = 6.3, 4.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.2, 165.6, 163.7, 141.4, 135.2, 131.9, 131.5, 128.5, 127.9, 127.8, 125.8, 124.9, 122.2, 48.2, 47.9, 44.0, 41.8, 41.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{23}N_4O_3S$ 459.1485; found 459.1465.

N-(4-chlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperazine-1-carbothioamide (9b)

Off white solid (120 mg); yield 78%; m.p. 246-248°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.53 (dd, *J* = 7.9, 3.3 Hz, 4H), 7.93 (t, *J* = 7.8 Hz, 2H), 7.56 – 7.46 (m, 2H), 7.38 (s, 4H), 5.01 (s, 2H), 4.10 (t, *J* = 5.1 Hz, 2H), 3.96 (t, *J* = 5.3 Hz, 2H), 3.83 (t, *J* = 5.3 Hz, 2H), 3.61 (t, *J* = 5.3 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.0, 165.7, 163.7, 140.4, 135.2, 131.8, 131.5, 130.4, 128.9, 128.8, 128.4, 128.2, 127.9, 127.8, 127.4, 122.2, 48.2, 47.9, 43.9, 41.8, 41.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{22}ClN_4O_3S$ 493.1096; found 493.1081.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)-N-(p-tolyl)piperazine-1-carbothioamide (9c)

Light brown solid (118 mg); yield 80%; m.p. 256-258°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.35 (s, 1H), 8.56 – 8.50 (m, 4H), 7.92 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.24 – 7.19 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 5.00 (s, 2H), 4.08 (dd, *J* = 6.6, 3.8 Hz, 2H), 3.95 (dd, *J* = 6.7, 4.0 Hz, 2H), 3.82 (dd, *J* = 6.6, 3.9 Hz, 2H), 3.63 – 3.56 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 182.5, 165.7, 163.7, 138.8, 135.1, 134.1, 131.9, 131.4, 129.0, 127.9, 127.8, 125.9, 122.3, 48.1, 47.8, 44.0, 41.7, 41.6, 21.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{25}N_4O_3S$ 473.1642; found 473.1636.

4-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)-N-(4-methoxyphenyl)piperazine-1-carbothioamide (9d)

Light yellow solid (123 mg); yield 81%; m.p. 242-244°C; 1H NMR (500 MHz, DMSO- d_6) δ 9.06 (s, 1H), 8.29 (ddd, *J* = 8.3, 4.5, 1.2 Hz, 4H), 7.68 (dd, *J* = 8.2, 7.2 Hz, 2H), 6.99 – 6.94 (m, 2H), 6.67 – 6.64 (m, 2H), 4.76 (s, 2H), 3.85 (t, *J* = 5.1 Hz, 2H), 3.71 (t, *J* = 5.3 Hz, 2H), 3.58 (dd, *J* = 6.5, 3.9 Hz, 2H), 3.52 (s, 3H), 3.36 (d d, *J* = 6.8, 4.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 182.6, 165.7, 163.7, 157.1, 135.1, 134.3, 131.9, 131.4, 127.9, 127.8, 127.8, 122.3, 113.8, 55.7, 48.0, 47.7, 44.0, 41.7, 41.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{25}N_4O_4S$ 489.1591; found 489.1595.

N-(3-chlorophenyl)-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperazine-1-carbothioamide (9e)

Off white solid (126 mg); yield 82%; m.p. 249-252°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.52 (s, 1H), 8.56 – 8.51 (m, 4H), 7.92 (t, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.18

(dt, *J* = 7.2, 2.1 Hz, 1H), 5.01 (s, 2H), 4.10 (t, *J* = 4.9 Hz, 2H), 3.99 – 3.94 (m, 2H), 3.83 (t, *J* = 5.1 Hz, 2H), 3.61 (t, *J* = 5.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 182.1, 165.7, 163.7, 143.1, 135.1, 132.6, 131.9, 131.4, 130.0, 127.9, 127.8, 125.1, 124.4, 123.9, 122.3, 48.0, 44.0, 41.7, 41.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{22}ClN_4O_3S$ 493.1096; found 493.1080.

N-cyclohexyl-4-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperazine-1-carbothioamide (9f)

White solid (113 mg); yield 78%; m.p. 240-242°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 8.52 (d, *J* = 7.3 Hz, 4H), 7.92 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 4.98 (s, 2H), 4.21 (d, *J* = 11.2 Hz, 1H), 3.97 (t, *J* = 5.2 Hz, 2H), 3.80 (t, *J* = 5.3 Hz, 2H), 3.73 (t, *J* = 5.3 Hz, 2H), 3.51 (t, *J* = 5.3 Hz, 2H), 1.91 (d, *J* = 10.0 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.61 (d, *J* = 12.8 Hz, 1H), 1.34 – 1.20 (m, 4H), 1.15 – 1.05 (m, 1H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 180.9, 165.6, 163.7, 135.2, 131.9, 131.5, 127.9, 127.8, 122.2, 55.1, 47.4, 47.0, 44.0, 41.7, 41.5, 32.5, 25.8, 25.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{29}N_4O_3S$ 465.1955; found 465.1938.

4-(3-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)-N-phenylpiperazine-1-carbothioamide (9g)

Off white solid (120 mg); yield 84%; m.p. 216-218°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.38 (s, 1H), 8.53 (d, *J* = 7.2 Hz, 2H), 8.49 (d, *J* = 8.2 Hz, 2H), 7.90 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 4.4 Hz, 4H), 7.12 (td, *J* = 5.5, 2.6 Hz, 1H), 4.30 (t, *J* = 7.8 Hz, 2H), 4.03 – 3.96 (m, 2H), 3.94 (t, *J* = 5.4 Hz, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 3.58 (t, *J* = 5.4 Hz, 2H), 2.78 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 182.0, 169.5, 163.9, 141.4, 134.9, 131.8, 131.2, 128.5, 127.8, 127.7, 125.8, 124.9, 122.5, 48.2, 47.9, 44.6, 41.0, 36.7, 31.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{25}N_4O_3S$ 473.1642; found 473.1628.

N-(4-chlorophenyl)-4-(3-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)piperazine-1-carbothioamide (9h)

White solid (105 mg); yield 69%; m.p. 237-239°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.43 (s, 1H), 8.55 – 8.51 (m, 2H), 8.49 (d, *J* = 8.5 Hz, 2H), 7.90 (t, *J* = 7.8 Hz, 2H), 7.35 (s, 4H), 4.33 – 4.26 (m, 2H), 4.00 (t, *J* = 5.2 Hz, 2H), 3.94 (t, *J* = 5.4 Hz, 2H), 3.62 (dd, *J* = 6.2, 3.7 Hz, 2H), 3.58 (dd, *J* = 6.8, 4.1 Hz, 2H), 2.77 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 181.8, 169.5, 163.9, 140.4, 134.9, 131.8,

131.2, 128.8, 128.3, 127.8, 127.7, 127.4, 122.5, 48.2, 47.9, 44.6, 41.0, 36.7, 31.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{24}ClN_4O_3S$ 507.1252 ; found 507.1249.

4-(3-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)-N-(p-tolyl)piperazine-1-carbothioamide (9i)

Brown solid (110 mg); yield 76%; m.p. 243-245°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.30 (s, 1H), 8.52 (d, *J* = 7.2 Hz, 2H), 8.48 (d, *J* = 8.2 Hz, 2H), 7.89 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 4.29 (t, *J* = 7.9 Hz, 2H), 3.98 (dd, *J* = 6.9, 3.8 Hz, 2H), 3.92 (dd, *J* = 6.9, 4.0 Hz, 2H), 3.63 – 3.58 (m, 2H), 3.57 (t, *J* = 3.6 Hz, 2H), 2.77 (t, *J* = 7.9 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 182.3, 169.5, 163.9, 138.8, 134.8, 134.1, 131.8, 131.2, 128.9, 127.9, 127.7, 125.9, 122.6, 48.2, 47.8, 44.7, 41.1, 36.7, 31.6, 21.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{27}H_{27}N_4O_3S$ 487.1798; found 487.1796.

4-(3-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)-N-(4-methoxyphenyl)piperazine-1-carbothioamide (9j)

White solid (112 mg); yield 72%; m.p. 220-223°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.25 (s, 1H), 8.51 (ddd, *J* = 20.7, 7.8, 1.2 Hz, 4H), 7.90 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.21 – 7.16 (m, 2H), 6.92 – 6.82 (m, 2H), 4.32 – 4.26 (m, 2H), 3.96 (ddd, *J* = 28.9, 6.8, 3.9 Hz, 4H), 3.75 (s, 3H), 3.63 – 3.55 (m, 4H), 2.80 – 2.74 (m, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 182.2, 169.5, 163.9, 157.0, 134.9, 134.2, 131.8, 131.2, 127.9, 127.9, 127.7, 122.6, 113.7, 55.7, 48.0, 47.7, 44.6, 41.0, 36.7, 31.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{27}H_{27}N_4O_4S$ 503.1748; found 503.1745.

N-(2-chlorophenyl)-4-(3-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)piperazine-1-carbothioamide (9k)

Off white solid (115 mg); yield 76%; m.p. 233-235°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.32 (s, 1H), 8.52 (d, *J* = 7.3 Hz, 2H), 8.48 (d, *J* = 8.2 Hz, 2H), 7.89 (t, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.24 (m, 3H), 4.30 (t, *J* = 7.8 Hz, 2H), 3.99 (dt, *J* = 27.5, 5.0 Hz, 4H), 3.61 (dt, *J* = 18.7, 5.1 Hz, 4H), 2.78 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 182.4, 169.5, 163.9, 138.7, 134.9, 132.4, 131.8, 131.6, 131.2, 129.8, 128.3, 127.8, 127.7, 127.7, 122.5, 48.2, 47.9, 44.6, 41.0, 36.7, 31.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{24}ClN_4O_3S$ 507.1252; found 507.1263.

N-cyclohexyl-4-(3-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoyl)piperazine-1-carbothioamide (9l)

Off white solid (55 mg); yield 72%; m.p. 203-205°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 8.51 (d, J = 7.3 Hz, 2H), 8.48 (d, J = 8.2 Hz, 2H), 7.89 (t, J = 7.7 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 4.27 (t, J = 7.8 Hz, 2H), 4.23 – 4.13 (m, 1H), 3.85 (q, J = 5.5 Hz, 2H), 3.79 (t, J = 5.4 Hz, 2H), 3.53 (t, J = 5.3 Hz, 2H), 3.49 (t, J = 5.2 Hz, 2H), 2.74 (t, J = 7.9 Hz, 2H), 1.88 (d, J = 9.4 Hz, 2H), 1.71 (d, J = 10.7 Hz, 2H), 1.60 (d, J = 12.7 Hz, 1H), 1.32 – 1.19 (m, 4H), 1.10 (t, J = 12.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 180.8, 169.4, 163.9, 134.9, 131.8, 131.2, 127.8, 127.7, 122.5, 55.0, 47.4, 47.0, 44.6, 41.0, 36.7, 32.5, 31.5, 25.8, 25.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{31}N_4O_3S$ 479.2111; found 479.2100.

2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-N-(1-(phenylcarbamothioyl)piperidin-4-yl)acetamide (13a)

White solid (116 mg); yield 82%; m.p. 239-241°C; ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.29 (s, 1H), 8.54 – 8.48 (m, 4H), 8.19 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 8.2, 7.2 Hz, 2H), 7.31 – 7.24 (m, 4H), 7.10 (tq, J = 6.7, 2.1 Hz, 1H), 4.66 (s, 2H), 4.59 (d, J = 13.5 Hz, 2H), 3.94 (q, J = 7.7 Hz, 1H), 3.28 – 3.22 (m, 2H), 1.82 (dd, J = 13.4, 4.2 Hz, 2H), 1.48 – 1.37 (m, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 181.5, 166.4, 163.8, 141.6, 135.0, 131.9, 131.3, 128.4, 128.0, 127.8, 125.6, 124.6, 122.5, 47.4, 46.3, 43.0, 31.8. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{25}N_4O_3S$ 473.1642; found 473.1637.

N-(1-((4-chlorophenyl)carbamothioyl)piperidin-4-yl)-2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetamide (13b)

Off white solid (112 mg); yield 79%; m.p. 256-259°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.51 (t, J = 7.0 Hz, 4H), 8.19 (d, J = 7.8 Hz, 1H), 7.91 (t, J = 7.7 Hz, 2H), 7.32 (q, J = 8.5 Hz, 4H), 4.66 (s, 2H), 4.58 (d, J = 13.2 Hz, 2H), 3.95 (s, 1H), 3.27 (d, J = 12.7 Hz, 2H), 1.88 – 1.76 (m, 2H), 1.44 (q, J = 12.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.2, 166.4, 163.8, 140.6, 135.0, 131.8, 131.3, 128.5, 128.3, 128.0, 127.8, 127.2, 122.5, 47.5, 46.2, 43.0, 40.5, 40.4, 40.3, 40.2, 40.2, 40.1, 40.0, 39.9, 39.8, 39.7, 39.5, 31.8. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{24}ClN_4O_3S$ 507.1252; found 507.1241.

N-(1-(cyclopentylcarbamothioyl)piperidin-4-yl)-2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetamide (13c)

Light brown solid (105 mg); yield 76%; m.p. 247-250°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (ddd, *J* = 8.4, 4.7, 1.2 Hz, 4H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.90 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 4.64 (s, 2H), 4.61 – 4.56 (m, 1H), 4.52 (d, *J* = 13.5 Hz, 2H), 3.87 (td, *J* = 9.7, 5.3 Hz, 1H), 3.08 (ddd, *J* = 14.0, 11.8, 2.6 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.72 (dd, *J* = 13.0, 3.8 Hz, 2H), 1.64 (pd, *J* = 7.4, 4.6 Hz, 2H), 1.52 – 1.42 (m, 4H), 1.31 (qd, *J* = 11.5, 3.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 181.0, 166.3, 163.8, 135.0, 131.8, 131.3, 128.0, 127.7, 122.5, 57.6, 46.7, 46.4, 43.0, 32.3, 31.7, 24.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{29}N_4O_3S$ 465.1955; found 465.1944.

N-(1-(cyclohexylcarbamothioyl)piperidin-4-yl)-2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetamide (13d)

Light yellow solid (112 mg); yield 78%; m.p. 252-255°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (dd, *J* = 8.0, 4.7 Hz, 4H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 4.63 (s, 2H), 4.51 (d, *J* = 13.5 Hz, 2H), 4.16 (s, 1H), 3.87 (s, 1H), 3.07 (t, *J* = 12.5 Hz, 2H), 1.83 (d, *J* = 9.3 Hz, 2H), 1.76 – 1.65 (m, 4H), 1.59 (d, *J* = 12.7 Hz, 1H), 1.32 (t, *J* = 12.4 Hz, 2H), 1.27 – 1.15 (m, 4H), 1.06 (d, *J* = 11.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.2, 166.3, 163.8, 135.0, 131.9, 131.3, 128.0, 127.8, 122.5, 55.0, 46.6, 46.4, 43.0, 32.6, 31.7, 25.8, 25.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{31}N_4O_3S$ 479.2111; found 479.2102.

N-(1-(cycloheptylcarbamothioyl)piperidin-4-yl)-2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetamide (13e)

Off white solid (95 mg); yield 65%; m.p. 233-235°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (dd, *J* = 7.7, 4.2 Hz, 4H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 4.63 (s, 2H), 4.51 (d, *J* = 13.6 Hz, 2H), 4.34 (td, *J* = 9.4, 5.0 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.07 (t, *J* = 12.5 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.76 – 1.68 (m, 2H), 1.66 – 1.58 (m, 2H), 1.57 – 1.43 (m, 6H), 1.38 (ddd, *J* = 15.9, 11.2, 8.0 Hz, 2H), 1.28 (dd, *J* = 18.0, 7.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 180.1, 166.3, 163.8, 135.0, 131.8, 131.3, 128.0, 127.8, 122.5, 57.2, 46.7, 46.5, 43.0, 34.6, 31.7, 28.1, 24.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{27}H_{33}N_4O_3S$ 493.2268; found 493.2252.

3-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-N-(1-(phenylcarbamothioyl)piperidin-4-yl)propanamide (13f)

White solid (110 mg); yield 79%; m.p. 240-243°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.51 (dd, *J* = 7.3, 1.1 Hz, 2H), 8.48 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.89 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.31 – 7.22 (m, 4H), 7.09 (tt, *J* = 7.1, 1.5 Hz, 1H), 4.50 (d, *J* = 13.3 Hz, 2H), 4.29 (dd, *J* = 8.0, 6.7 Hz, 2H), 3.92 – 3.83 (m, 1H), 3.29 – 3.23 (m, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 1.82 – 1.72 (m, 2H), 1.40 – 1.29 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.6, 169.7, 163.8, 141.6, 134.7, 131.8, 131.1, 128.4, 127.9, 127.7, 125.6, 124.6, 122.7, 47.4, 45.8, 37.1, 34.5, 31.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{27}H_{27}N_4O_3S$ 487.1798; found 487.1803.

N-(1-((4-chlorophenyl)carbamothioyl)piperidin-4-yl)-3-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanamide (13g)

White solid (115 mg); yield 77%; m.p. 248-251°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.49 (ddd, *J* = 16.7, 7.8, 1.2 Hz, 4H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.36 – 7.31 (m, 2H), 7.31 – 7.25 (m, 2H), 4.50 (d, *J* = 13.3 Hz, 2H), 4.29 (t, *J* = 7.3 Hz, 2H), 3.91 – 3.85 (m, 1H), 3.30 – 3.25 (m, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 1.78 (dd, *J* = 13.1, 4.4 Hz, 2H), 1.38 – 1.28 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.2, 169.7, 163.8, 140.6, 134.8, 131.8, 131.1, 128.5, 128.3, 127.9, 127.7, 127.2, 122.6, 47.4, 45.7, 37.1, 34.4, 31.6. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{27}H_{26}ClN_4O_3S$521.1409 ; found 521.1390.

1-(1-(2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperidin-4-yl)-3-phenylthiourea (17a)

Light brown solid (112 mg); yield 79%; m.p. 289-292°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.54 – 8.49 (m, 4H), 7.91 (t, *J* = 7.8 Hz, 2H), 7.85 (s, 1H), 7.47 – 7.42 (m, 2H), 7.35 – 7.30 (m, 2H), 7.11 (tt, *J* = 7.3, 1.2 Hz, 1H), 5.01 – 4.86 (m, 2H), 4.43 (s, 1H), 4.22 (d, *J* = 13.5 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 2.84 (t, *J* = 12.5 Hz, 1H), 2.12 – 2.04 (m, 1H), 1.96 (d, *J* = 12.1 Hz, 1H), 1.63 – 1.52 (m, 1H), 1.42 – 1.32 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.0, 164.9, 163.7, 135.2, 131.9, 131.4, 129.0, 127.8, 122.2, 51.1, 43.7, 41.7, 41.2, 32.0, 31.2. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{25}N_4O_3S$ 473.1642; found 473.1626.

1-Cyclopentyl-3-(1-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperidin-4-yl)thiourea (17b)

Off white solid (92 mg); yield 66%; m.p. 225-228°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, J = 7.7 Hz, 4H), 7.91 (t, J = 7.8 Hz, 2H), 7.33 (s, 1H), 7.24 (s, 1H), 5.01 – 4.87 (m, 2H), 4.31 (s, 2H), 4.16 (s, 1H), 4.02 (d, J = 13.7 Hz, 1H), 2.81 (d, J = 14.5 Hz, 1H), 2.03 (d, J = 12.5 Hz, 1H), 1.89 (dd, J = 12.5, 6.7 Hz, 3H), 1.63 (s, 2H), 1.58 – 1.44 (m, 3H), 1.39 (d, J = 10.5 Hz, 2H), 1.25 (d, J = 22.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.5, 164.9, 163.7, 135.2, 131.9, 131.4, 127.8, 122.2, 43.6, 41.7, 41.2, 32.7, 32.5, 31.7, 23.8. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{25}H_{29}N_4O_3S$ 465.1955; found 465.1941.

1-Cyclohexyl-3-(1-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperidin-4-yl)thiourea (17c)

White solid (110 mg); yield 77%; m.p. 257-260°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (d, J = 7.4 Hz, 4H), 7.92 (t, J = 7.6 Hz, 2H), 7.30 (s, 1H), 7.20 (s, 1H), 5.02–4.84 (m, 2H), 4.30 (s, 1H), 4.16 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 14.0 Hz, 2H), 2.83 (s, 1H), 2.04 (d, J = 12.6 Hz, 1H), 1.87 (d, J = 13.7 Hz, 3H), 1.67 (d, J = 12.8 Hz, 2H), 1.55 (s, 1H), 1.50 – 1.38 (m, 2H), 1.29 (q, J = 12.7 Hz, 3H), 1.17 (d, J = 11.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.4, 163.7, 135.2, 131.4, 127.8, 122.2, 41.7, 41.2, 40.5, 40.3, 32.8, 32.5, 25.7, 25.0. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{31}N_4O_3S$ 479.2111; found 479.2100.

1-Cycloheptyl-3-(1-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperidin-4-yl)thiourea (17d)

Off white solid (112 mg); yield 76%; m.p. 270-273°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, J = 7.7 Hz, 4H), 7.91 (t, J = 7.8 Hz, 2H), 7.26 (dd, J = 15.4, 7.9 Hz, 2H), 5.00 – 4.87 (m, 2H), 4.29 (s, 1H), 4.16 (d, J = 14.0 Hz, 2H), 4.01 (d, J = 13.8 Hz, 1H), 2.84 (t, J = 12.5 Hz, 1H), 2.05 (d, J = 12.7 Hz, 1H), 1.95 – 1.82 (m, 3H), 1.55 (dq, J = 18.9, 9.5 Hz, 6H), 1.45 (p, J = 9.4 Hz, 6H), 1.25 (d, J = 12.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 184.5, 164.9, 163.7, 135.2, 131.9, 131.4, 127.9, 127.8, 122.2, 43.6, 41.7, 41.2, 34.7, 32.5, 31.7, 28.2, 24.1. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{27}H_{33}N_4O_3S$ 493.2268; found 493.2256.

1-(Adamantan-1-yl)-3-(1-(2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetyl)piperidin-4-yl)thiourea(17e)

White solid (95 mg); yield 70%; m.p. 223-225°C; ^{1}H NMR (500 MHz, DMSO) δ 8.52 (d, J = 7.7 Hz, 4H), 7.92 (t, J = 7.7 Hz, 2H), 7.30 (d, J = 7.6 Hz, 1H), 6.90 (s, 1H), 5.00 – 4.89 (m, 2H), 4.37 – 4.23 (m, 1H), 4.11 (d, J = 13.3 Hz, 1H), 3.99 (d, J = 13.8 Hz, 1H), 2.87 (t, J = 12.1 Hz, 1H), 2.18 (s, 6H), 2.04 (s, 4H), 1.91 (d, J = 12.4 Hz, 1H), 1.63 (s, 6H), 1.40 (t, J = 12.4 Hz, 1H), 1.21 (q, J = 11.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.2, 164.9, 163.7, 135.2, 131.4, 127.8, 122.2, 53.2, 49.5, 43.6, 41.7, 41.1, 36.5, 32.5, 31.7, 29.5. HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{30}H_{35}N_4O_3S$ 531.2424; found 531.2410

1.6. Bacterial strains and media

The ESKAP panel of bacteria consists of *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Klebsiella pneumoniae* BAA-1705, *Acinetobacter baumannii* BAA 1605 and *Pseudomonas aeruginosa* ATCC 27853. NRS10100, NRS10119, NRS10129, NRS10186, NRS10191, NRS10192, NRS193, NRS194, NRS198 are MRSA strains while VRS1, VRS4, VRS12 are VRSA strains. These strains were procured from BEI/NARSA/ATCC (Biodefense and Emerging Infections Research Resources Repository/ Network on Antimicrobial Resistance in *Staphylococcus aureus*/American Type Culture Collection, U.S.A.). These strains are usually cultivated on Mueller-Hinton Agar (MHA). A single colony was picked from MHA plate, inoculated in Mueller-Hinton cation supplemented broth II (CA-MHB), and incubated overnight at 37 ^{o}C while shaking for 18-24 h to get the starter culture. *M. tuberculosis* H37Rv ATCC 27294 and other NTM's were cultured in Middlebrook 7H9 (Difco, Becton, NJ, U.S.A.) media supplemented with 10% (v/v) A.D.C. (Bovine Serum Albumin, Dextrose, NaCl), 0.2% (v/v) glycerol and 0.05% (v/v) Tween-80 (ADC-Tween-80).

1.6.1 Antibiotic susceptibility testing against bacterial pathogen panel

Antibiotic susceptibility testing was performed on the newly synthesised compounds using conventional CLSI criteria to determine the MIC [1,2]. MIC of a compound is defined as the concentration at which there is no visible bacterial growth. Mueller-Hinton cation-enriched broth was used to cultivate bacterial cultures (CAMHB). After measuring the optical density

(OD_{600}) of the cultures, they were diluted to ~ 10^6cfu/mL. This inoculum was placed in a microtitre plate with a series of test wells containing varying concentrations of the substance under test ranging from 64-0.5 μg/mL. The cells with medium (without compound and cells) and Levofloxacin as a reference standard serve as controls. Plates were incubated at 37°C for 16-18 hours before MIC values were determined by the lack or presence of visible growth. MIC determinations were made three times separately for each chemical, each time using duplicate samples.

1.6.2 Antibiotic susceptibility testing against pathogenic mycobacteria

The broth microdilution technique was used to investigate antimycobacterial susceptibility on newly synthesised compounds (**Table 1**) [3,4]. Stock solutions of test and control substances at 10 mg/mL in DMSO were produced and kept at -20 ^oC. Mycobacterial cultures were injected in Middlebrook 7H9 enriched (Difco, Becton, NJ, U.S.A.) media supplemented with 10% ADC-Tween-80 (Bovine Serum Albumin, Dextrose, 0.2 percent glycerol, and 0.05 percent Tween-80) at OD600, then diluted to ~10^6cfu/mL [5]. The newly synthesised compounds were evaluated in a 96-well round bottom microtitre plate with 2.5 mL of each concentration added per well in a two-fold serial diluted way. After that, 97.5 mL of bacterial suspension and appropriate controls were added to each well containing the test chemical. The resazurin-based dye Presto blue (Thermo Fisher, U.S.A.) was employed to visually identify active compounds. The lowest concentration of the active substance that prevented observable development after an incubation period was established to be the MIC of the active compound. MIC determinations were repeated three times with duplicate samples for each compound. For Mtb, the MIC plates were incubated at 37 °C for 7 days for Mtb and 72 h for NTM's.

1.6.3 Cell cytotoxicity assay

Using the MTT assay the newly synthesised active compounds were tested for cell toxicity against Vero cells[6]. ~10^3 cells per well were sown in a 96-well plate and incubated at 37 °C with 5% CO2. After 24 hours, compounds ranging from 5 to 100 mg/L were introduced and incubated for 72 hours at 37 °C in a 5% CO_2 environment. After the incubation period, each well received 5 mg/L MTT and was incubated for another 4 hours at 37 ^oC. The rest of the medium

was thrown away. The formazan crystals were solubilised with 0.1 mL DMSO, and the O.D. was measured at 540 nm to compute the CC_{50}. The CC_{50} value is the lowest concentration of a chemical that reduces cell viability by 50%. Doxorubicin was used as positive control and each experiment was repeated in triplicate.

1.6.4. Time kill study

The bactericidal activity was assessed by the time-kill method[7]. *S. aureus* ATCC 29213 cells were diluted up to ~10^6cfu/mL and treated with compound for concentrations corresponding to 1X and 10X of MIC of 4l, 4m, 4n, 17b and Vancomycin in MHB in triplicate and incubated at 37 ^oC. 100 mL samples were collected after time intervals of 0 h, 1 h, 6 h, and 24 h and serially diluted in PBS and plated on T.S.A. followed by incubation at 37 ^oC for 18-20 h. Kill curves were constructed by counting the colonies from plates and plotting the cfu/mL of surviving bacteria at each time point in the presence and absence of the compound[8].

1.7 Molecular modelling studies

1.7.1 Molecular Docking study- The molecular docking studies were performed by using Maestro (Schrodinger release 2022-1, L.L.C., New York, NY, U.S.A.)[9]. The crystal structure of *S. aureus* DNA gyrase complexed with GSK299423 (PDB ID 2XCS) was obtained from RCSB PDB and prepared by using Protein preparation wizard in maestro. In protein preparation wizard, hydrogen atoms were added, crystal waters beyond 5Å and cocrystal ligands were removed. Other default parameters like pH ionization, optimization and energy minimization was accomplished using OPLS4 force field method. After protein preparation, receptor grid was generated using receptor grid generation module by removing cocrystal. Then, Ligands were prepared by using chemdraw and converted into SDF file, transferred to maestro and prepared by Ligprep module[10]. Finally docking studies on potent compounds were performed using extra precision (XP) docking mode on generated receptor grid.

1.7.2 *In silico* ADME studies Physicochemical and pharmacokinetic properties such as molecular weight, octanol/water coefficient, percentage of oral absrption, hydrogen bond donors (<5), hydrogen bond acceptor (<10) were calculated by QikProp module of Schrodinger software.

This helps in studying the pharmacokinetic parameters such as absorption, distribution, metabolism and excretion (ADME)[11,12]

Table ST1. MIC (μg/mL) values of synthesized derivatives against bacterial pathogen panel.

S. no	Code	MIC *(μg/mL)*				
		E. coli **ATCC 25922**	***S. aureus*** **ATCC 29213**	***K. pneumoniae*** **BAA 1705**	***A. baumannii*** **BAA 1605**	***P. aeruginosa*** **ATCC 27853**
1	**4a**	>64	**2**	>64	>64	>64
2	**4b**	>64	>64	>64	>64	>64
3	**4c**	>64	>64	>64	>64	>64
4	**4d**	>64	>64	>64	>64	>64
5	**4e**	>64	>64	>64	>64	>64
6	**4f**	>64	>64	>64	>64	>64
7	**4g**	>64	>64	>64	>64	>64
8	**4h**	>64	>64	>64	>64	>64
9	**4i**	>64	>64	>64	>64	>64
10	**4j**	>64	>64	>64	>64	>64
11	**4k**	>64	>64	>64	>64	>64
12	**4l**	>64	**0.125**	>64	>64	>64
13	**4m**	>64	**0.125**	>64	>64	>64
14	**4n**	>64	**0.25**	>64	>64	>64
15	**4o**	>64	>64	>64	>64	>64
16	**4p**	>64	>64	>64	>64	>64
17	**4q**	>64	**8**	>64	>64	>64
18	**4r**	>64	>64	>64	>64	>64
19	**9a**	>64	>64	>64	>64	>64
20	**9b**	>64	>64	>64	>64	>64
21	**9c**	>64	>64	>64	>64	>64

22	**9d**	>64	>64	>64	>64	>64
23	**9e**	>64	>64	>64	>64	>64
24	**9f**	>64	**0.5**	>64	>64	>64
25	**9g**	>64	>64	>64	>64	>64
26	**9h**	>64	>64	>64	>64	>64
27	**9i**	>64	>64	>64	>64	>64
28	**9j**	>64	>64	>64	>64	>64
29	**9k**	>64	>64	>64	>64	>64
30	**9l**	>64	**1**	>64	>64	>64
31	**13a**	>64	**4**	>64	>64	>64
32	**13b**	>64	>64	>64	>64	>64
33	**13c**	>64	>64	>64	>64	>64
34	**13d**	>64	**0.25**	>64	>64	>64
35	**13e**	>64	**0.5**	>64	>64	>64
36	**13f**	>64	>64	>64	>64	>64
37	**13g**	>64	>64	>64	>64	>64
38	**17a**	>64	**0.5**	>64	>64	>64
39	**17b**	>64	**0.03125**	>64	>64	>64
40	**17c**	>64	**0.125**	>64	>64	>64
41	**17d**	>64	**0.25**	>64	>64	>64
42	**17e**	>64	**4**	>64	>64	>64
	Levofloxacin	0.0078	0.0625	64	4	0.5

Table ST2. MIC (μg/mL) of synthesized derivatives against mycobacterial pathogen panel.

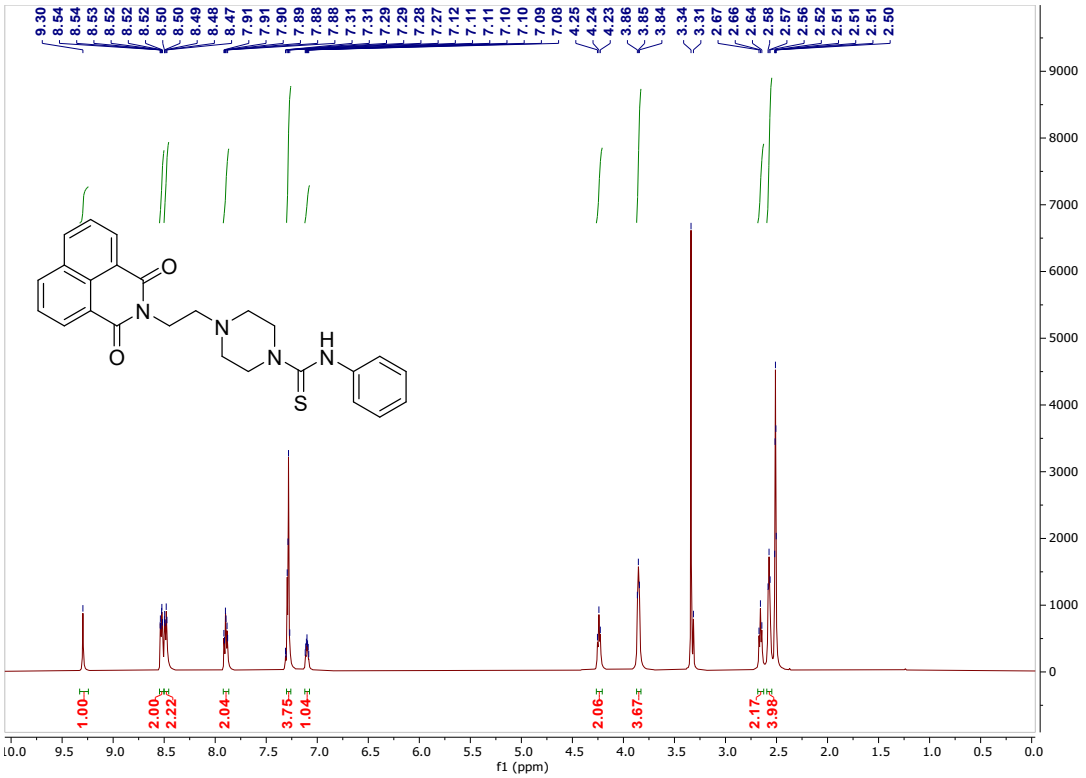
S. no	Code	MIC (μg/mL)			
		Mtb H37Rv ATCC 27294	*M. abscessus* ATCC 19977	*M. fortuitum* ATCC 6841	*M. chelonae* ATCC 35752
1	**4a**	>64	>64	>64	>64
2	**4b**	>64	>64	>64	>64
3	**4c**	>64	>64	>64	>64
4	**4d**	>64	>64	>64	>64
5	**4e**	>64	>64	>64	>64
6	**4f**	>64	>64	>64	>64
7	**4g**	>64	>64	>64	>64
8	**4h**	**64**	>64	>64	>64
9	**4i**	>64	>64	>64	>64
10	**4j**	**64**	>64	>64	>64
11	**4k**	>64	>64	>64	>64
12	**4l**	**2**	>64	>64	>64
13	**4m**	**4**	>64	>64	>64
14	**4n**	>64	>64	>64	>64
15	**4o**	>64	>64	>64	>64
16	**4p**	>64	>64	>64	>64
17	**4q**	**32**	>64	>64	>64
18	**4r**	**8**	>64	>64	>64
19	**9a**	**16**	>64	>64	>64
20	**9b**	**8**	>64	>64	>64
21	**9c**	**64**	>64	>64	>64
22	**9d**	**64**	>64	>64	>64
23	**9e**	**32**	>64	>64	>64
24	**9f**	>64	>64	>64	>64

25	**9g**	**32**	>64	>64	>64
26	**9h**	**64**	>64	>64	>64
27	**9i**	>64	>64	>64	>64
28	**9j**	**8**	>64	>64	>64
29	**9k**	>64	>64	>64	>64
30	**9l**	>64	>64	>64	>64
31	**13a**	>64	>64	>64	>64
32	**13b**	>64	>64	>64	>64
33	**13c**	>64	>64	>64	>64
34	**13d**	>64	>64	>64	>64
35	**13e**	>64	>64	>64	>64
36	**13f**	**64**	>64	>64	>64
37	**13g**	>64	>64	>64	>64
38	**17a**	>64	>64	>64	>64
39	**17b**	>64	>64	>64	>64
40	**17c**	>64	>64	>64	>64
41	**17d**	>64	>64	>64	>64
42	**17e**	**32**	>64	>64	>64
Standard drugs	Isoniazid	0.03	NT	NT	NT
	Rifampicin	0.03	NT	NT	NT
	Streptomycin	1	NT	NT	NT
	Ethambutol	2	NT	NT	NT
	Levofloxacin	0.6	2	0.06	0.06
	Amikacin	0.5	8	0.5	0.5

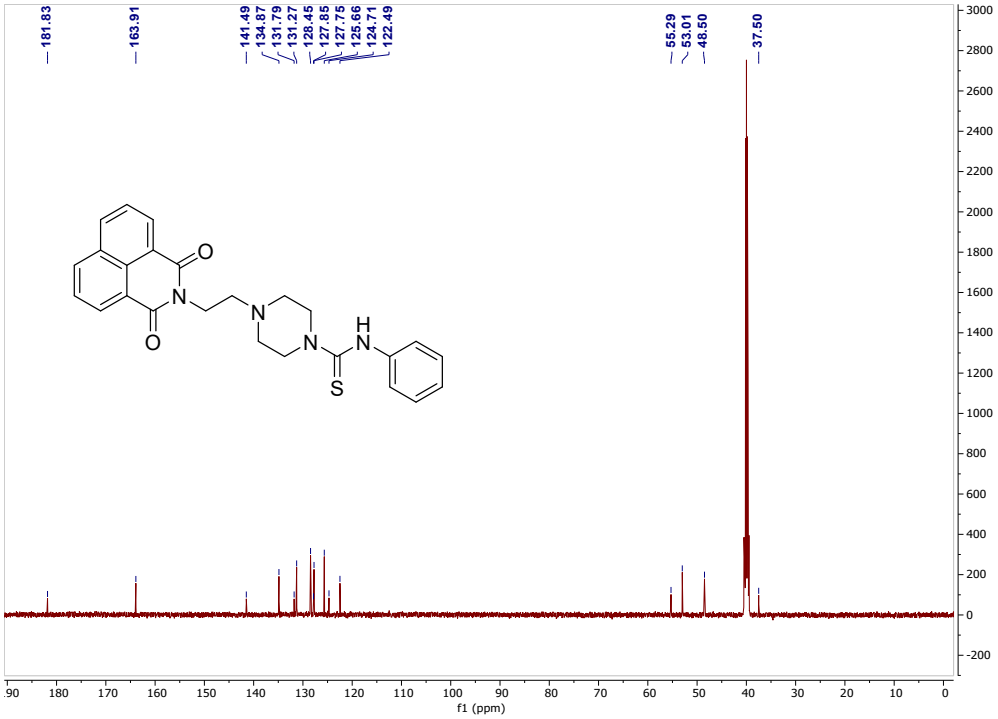
Table ST3. ADME profile predicted by QikProp

S.no	ADME parameters	Range or recommended values	Compound **17b**
1	Rule of five (Number of violations of Lipinski's rule of five)	Maximum is 4	0
2	PSA (Van der Waals surface area of polar nitrogen and oxygen atoms)	7.0-200.0	109.86
3	SASA (Total solvent accessible surface area in square angstroms)	300-1000	798.178
4	Molecular Weight	0-500	464.581
5	Dipole moment	1.0-12.5	9.189
6	Donor H.B.	0-6	2
7	Acceptor H.B.	2-20	8.5
8	QPlogKhsa (Prediction of binding to human serum albumin)	-1.5-1.5	0.314
9	QPlogPo/w (Predicted octanol/water partition coefficient	-2.0-6.5	3.665
10	QPpolrz (Predicted polarizability in cubic angstroms)	13.0-70.0	51.227
11	QPlogBB (Predicted brain/ blood partition coefficient)	-3.0-1.2	-0.853
12	QPlogKp (Predicted skin permeability)	-8.0--1.0	-2.411
13	QPlogHERG (Predicted IC50 value for blockage of HERG K+ channels)	Concern below -5	-5.018
14	QPPCaco (Predicted apparent Caco-2 cell permeability in nm/sec)	<25 is poor, >500 is great	543.258
15	P.O.A. (Predicted human oral absorption on 0–100% scale)	<25% is poor, >80% is high	100

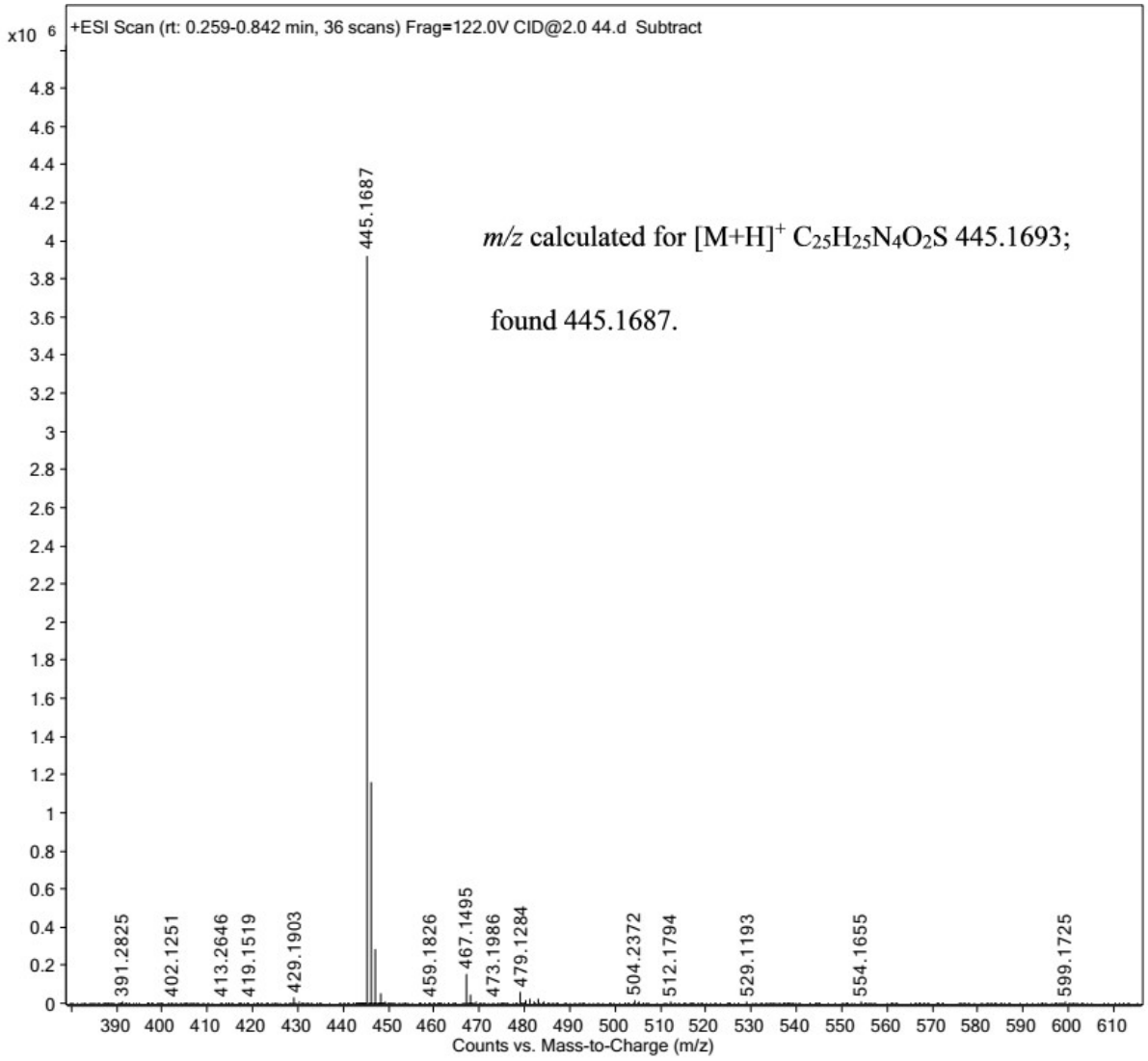
2. ^{1}H NMR, ^{13}C NMR and HRMS spectra



^{1}H spectrum for compound **4a** (500 MHz: DMSO-d_6)

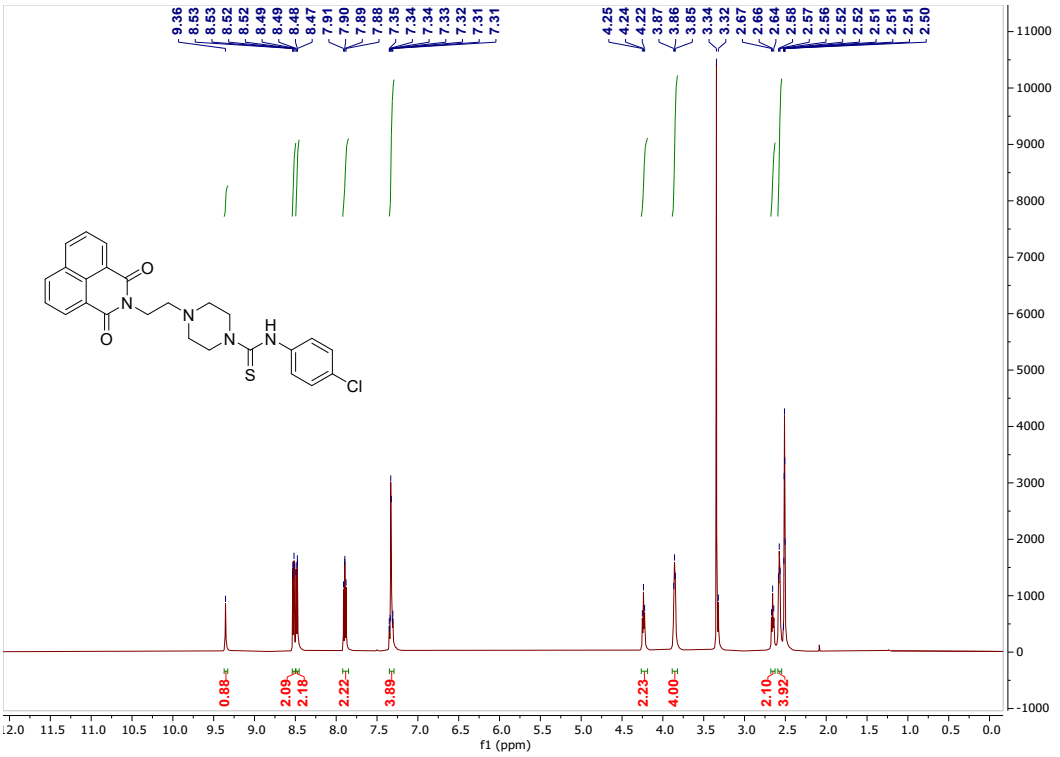


^{13}C spectrum for compound **4a** (125 MHz: DMSO-d_6)

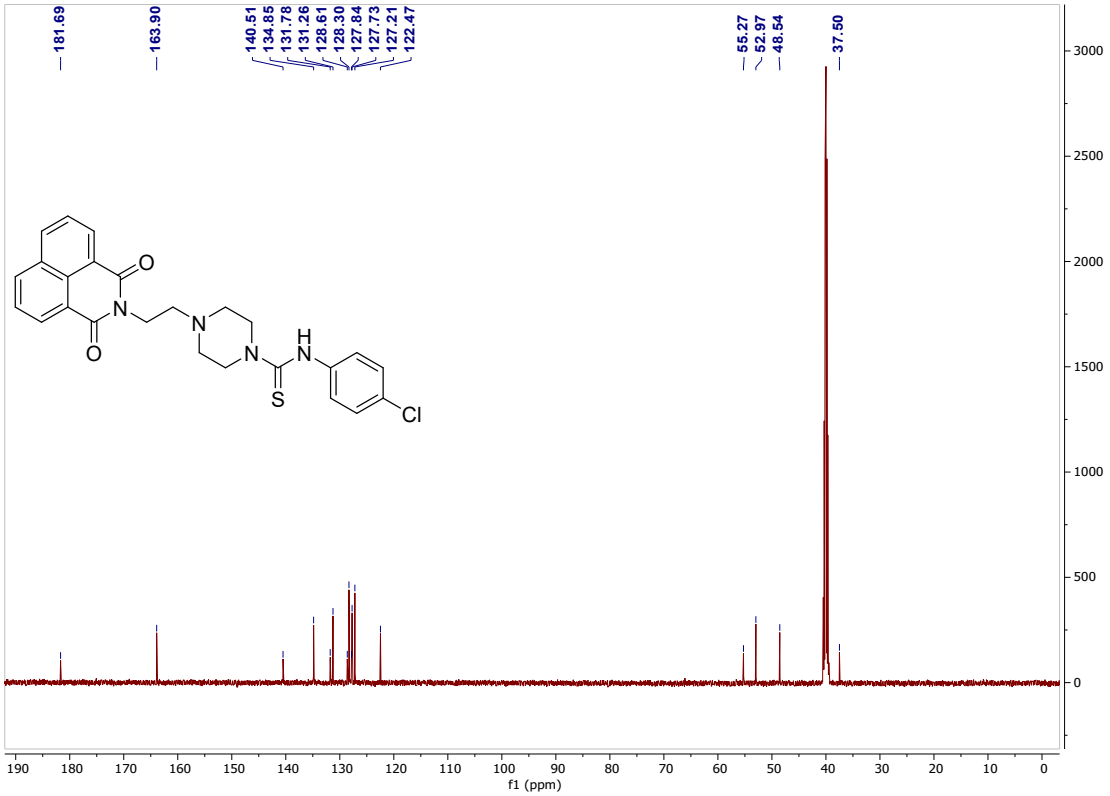


m/z calculated for $[M+H]^+$ $C_{25}H_{25}N_4O_2S$ 445.1693;

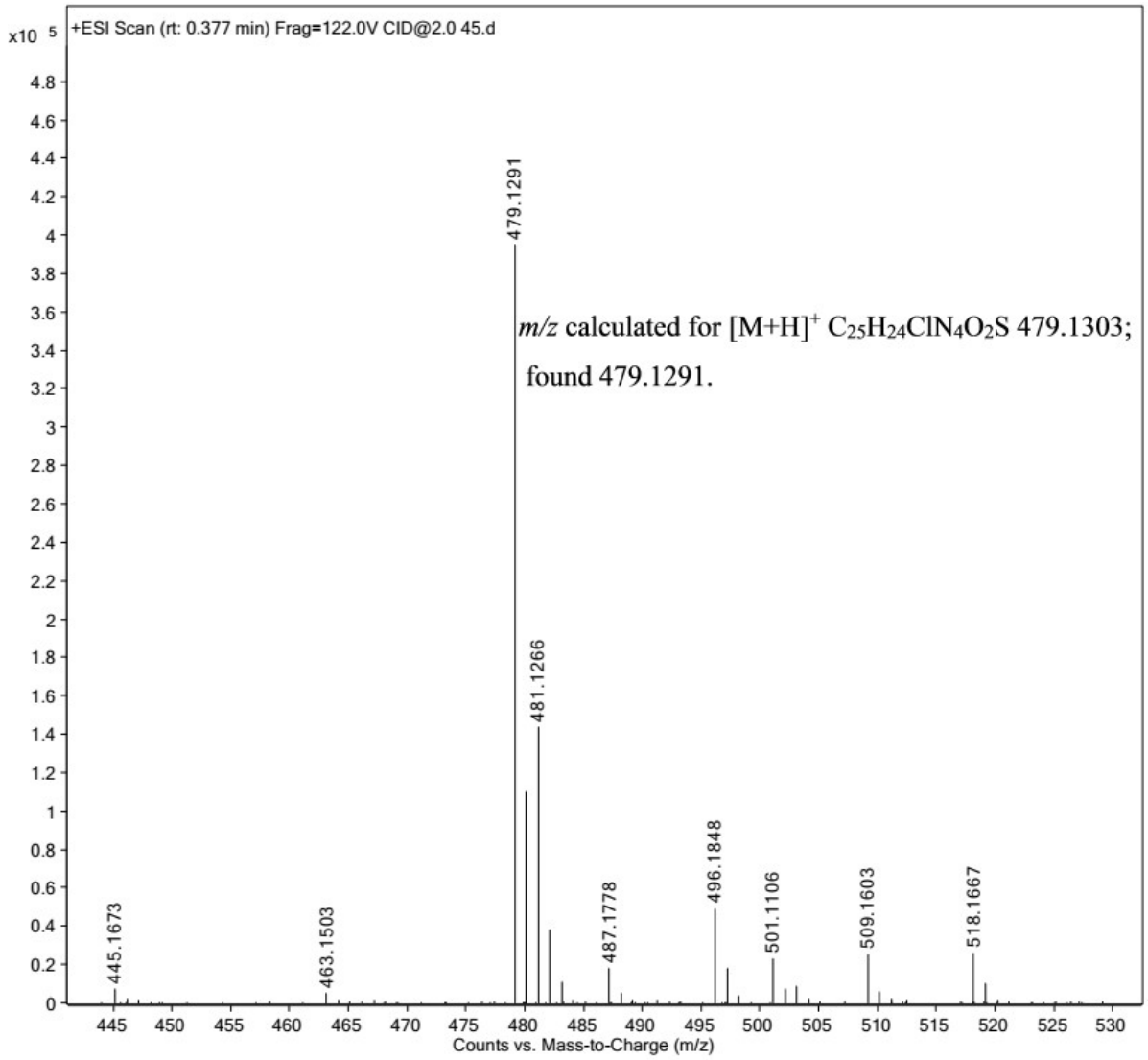
found 445.1687.

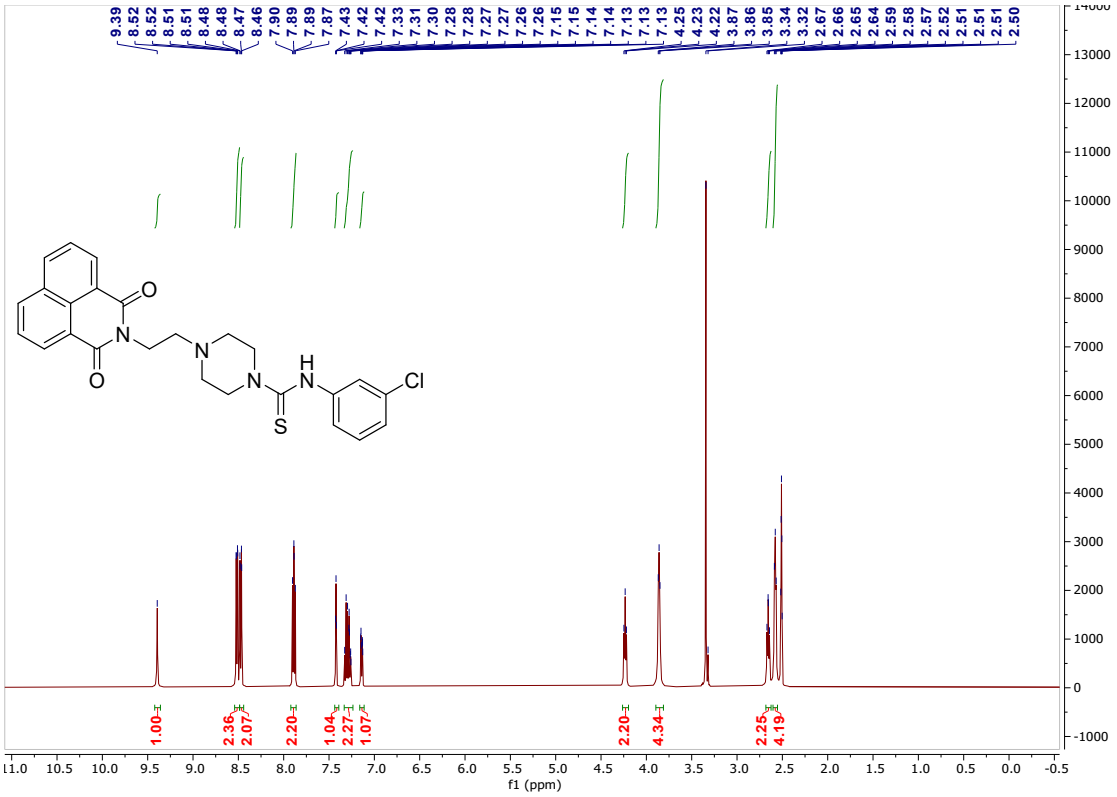


^{1}H spectrum for compound **4b** (500 MHz: DMSO-d_6)

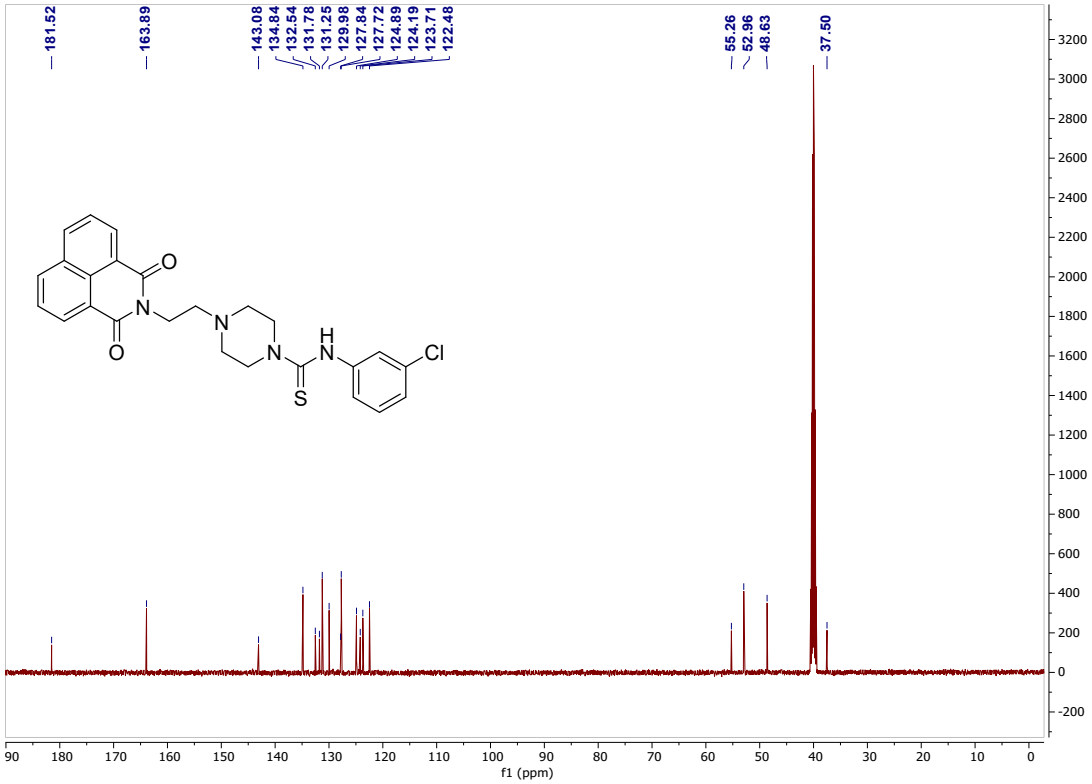


^{13}C spectrum for compound **4b** (125 MHz: DMSO-d_6)

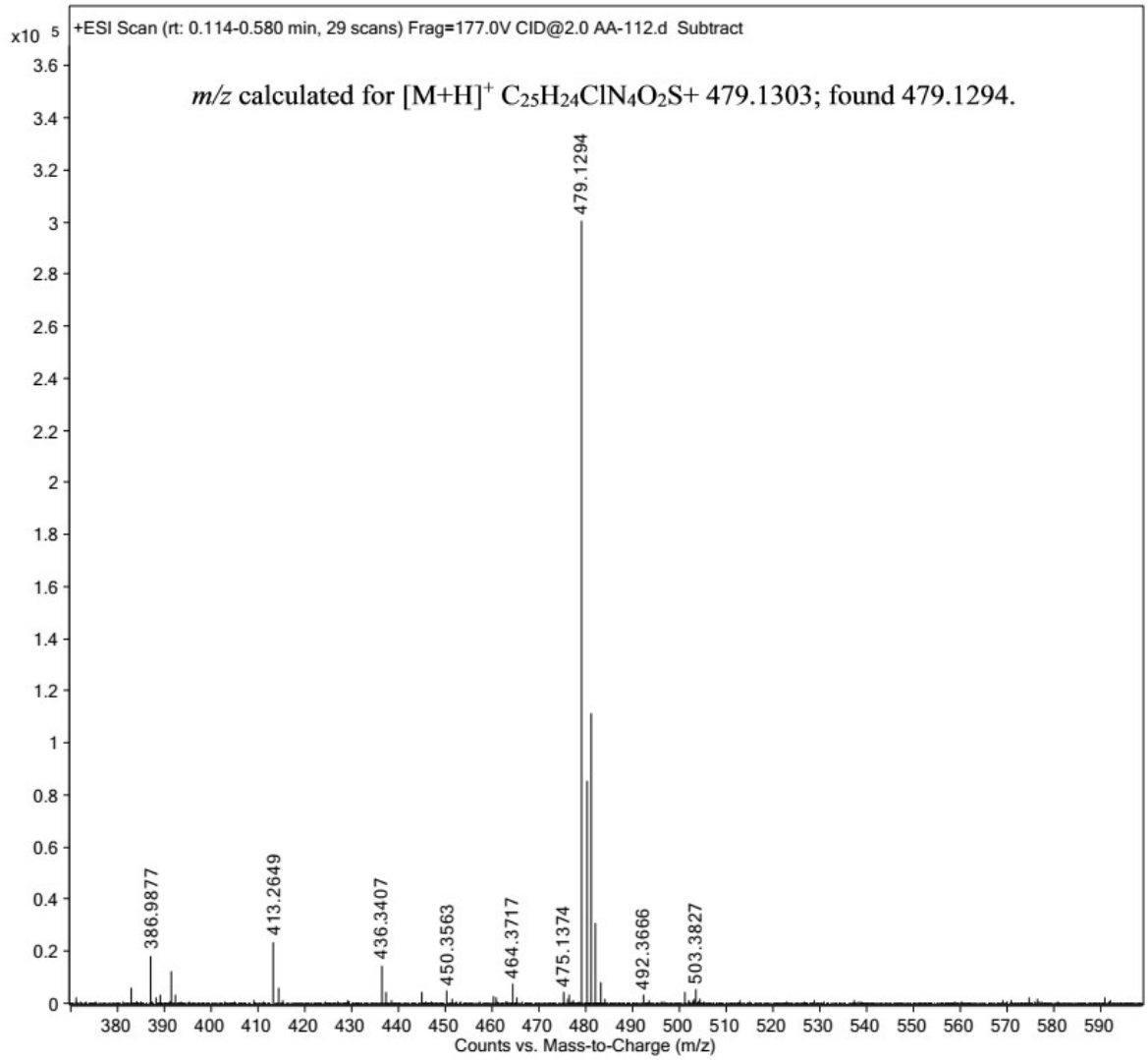

+ESI Scan (rt: 0.377 min) Frag=122.0V CID@2.0 45.d
x10 5
479.1291
481.1266
445.1673
463.1503
487.1778
496.1848
501.1106
509.1603
518.1667
m/z calculated for [M+H]+ C25H24ClN4O2S 479.1303;
found 479.1291.
Counts vs. Mass-to-Charge (m/z)

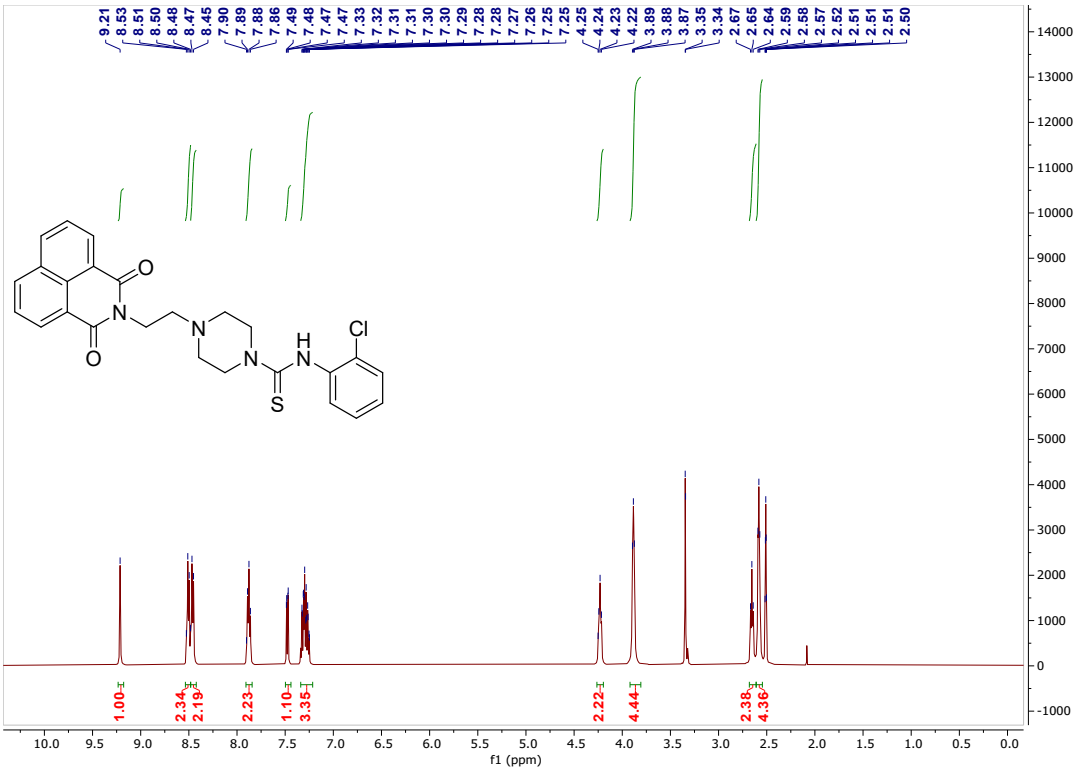


^{1}H spectrum for compound **4c** (500 MHz: DMSO-d_6)

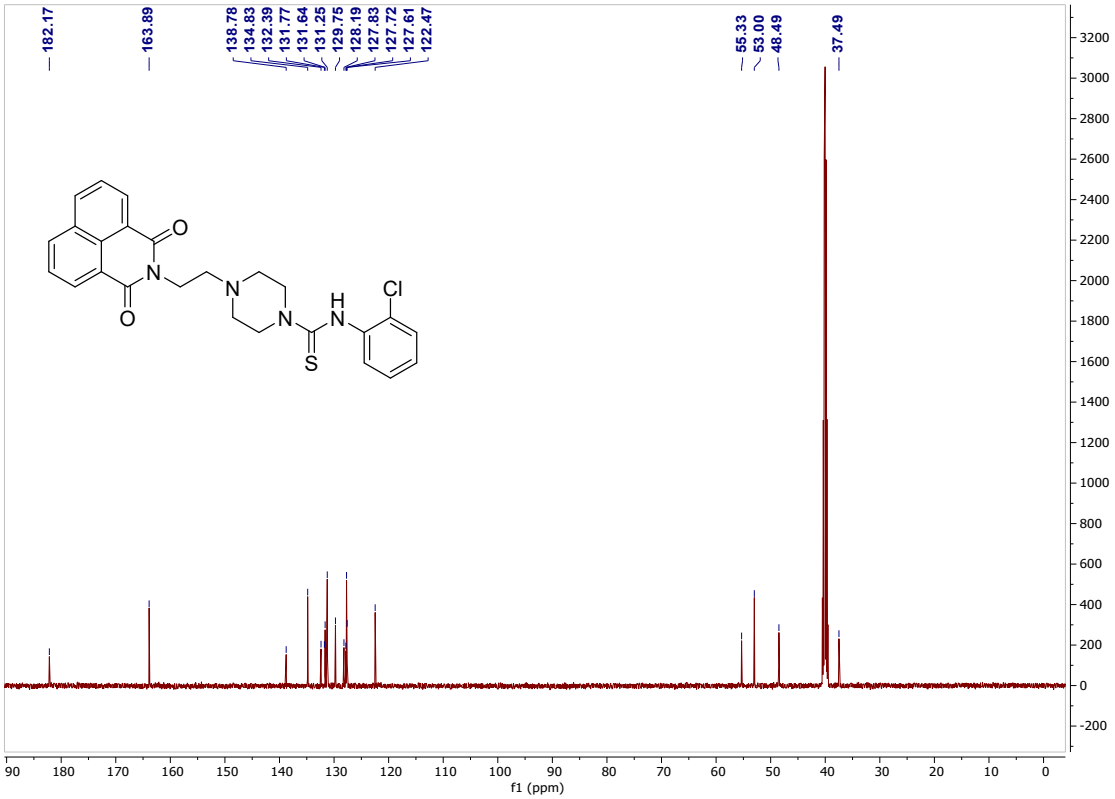


^{13}C spectrum for compound **4c** (125 MHz: DMSO-d_6)

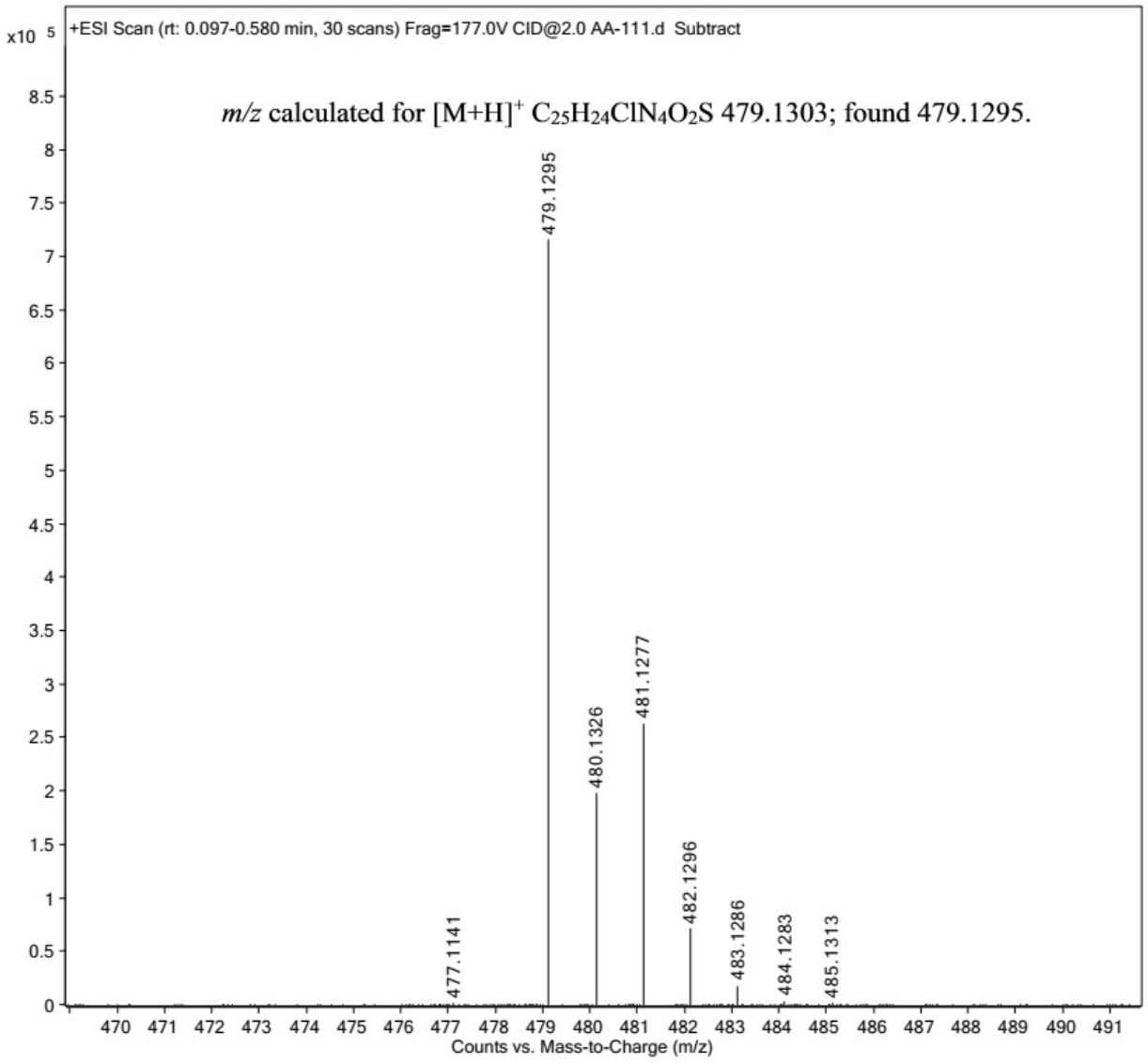

+ESI Scan (rt: 0.114-0.580 min, 29 scans) Frag=177.0V CID@2.0 AA-112.d Subtract
x10 5
m/z calculated for [M+H]+ C25H24ClN4O2S+ 479.1303; found 479.1294.
479.1294
386.9877
413.2649
436.3407
450.3563
464.3717
475.1374
492.3666
503.3827
Counts vs. Mass-to-Charge (m/z)

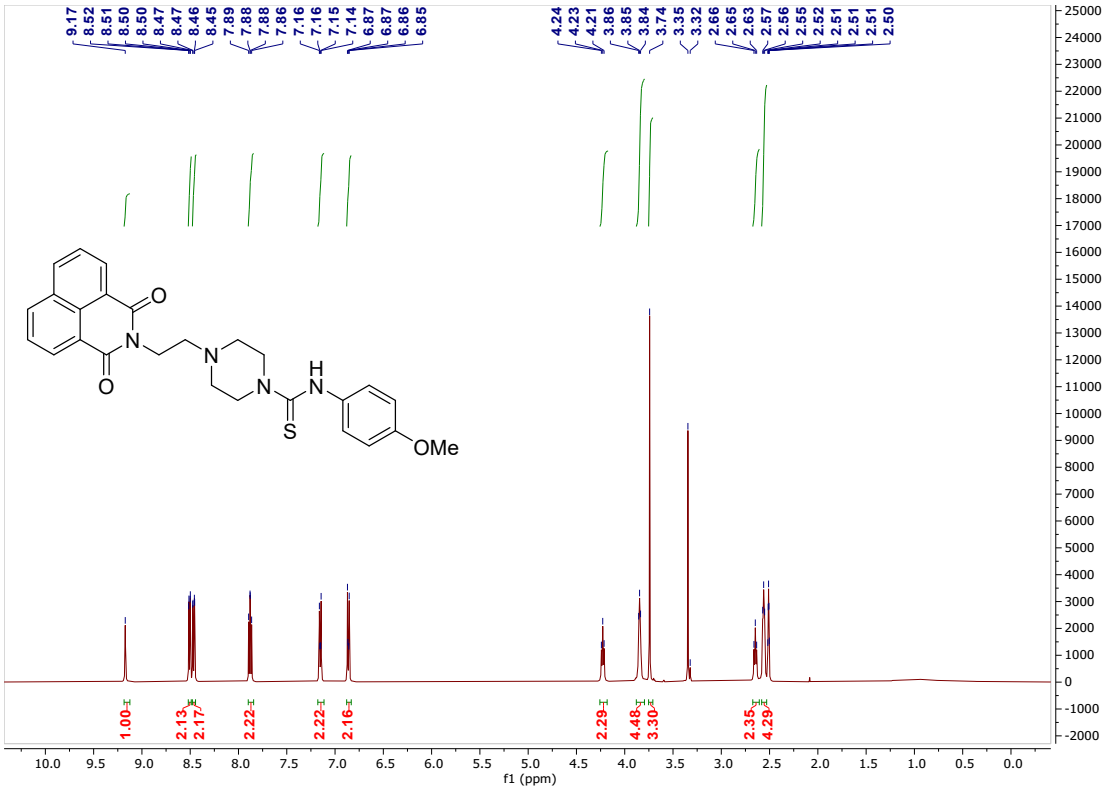


^{1}H spectrum for compound **4d** (500 MHz: DMSO-d_6)

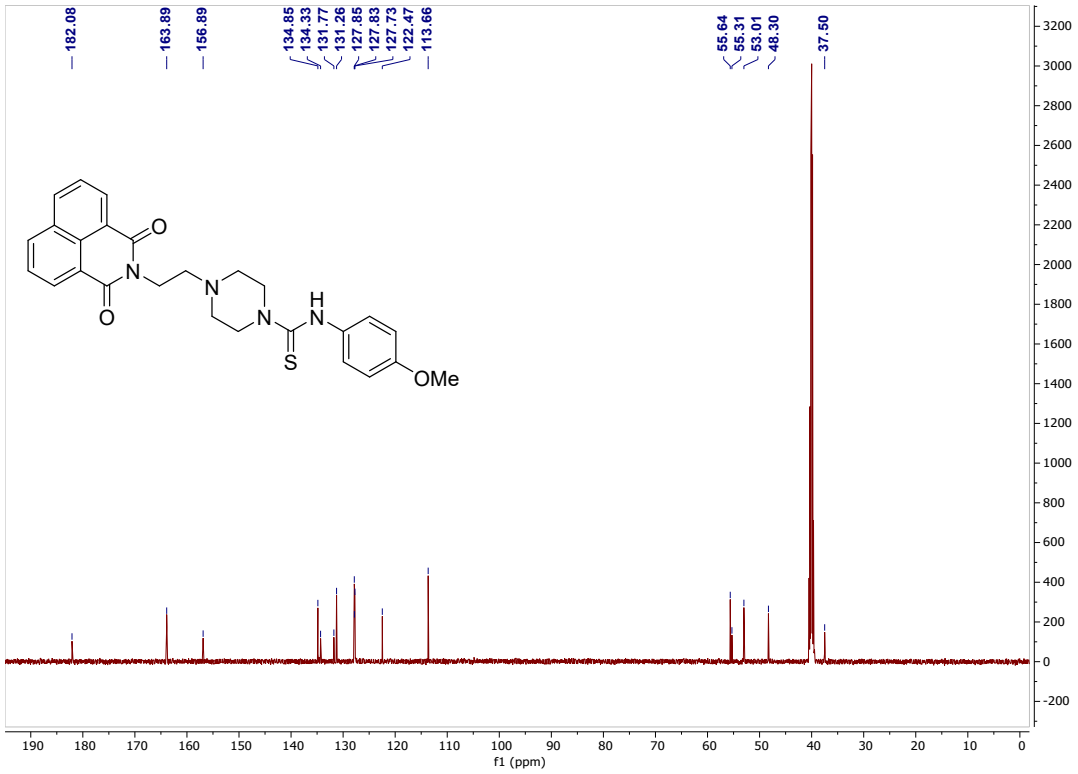


^{13}C spectrum for compound **4d** (125 MHz: DMSO-d_6)

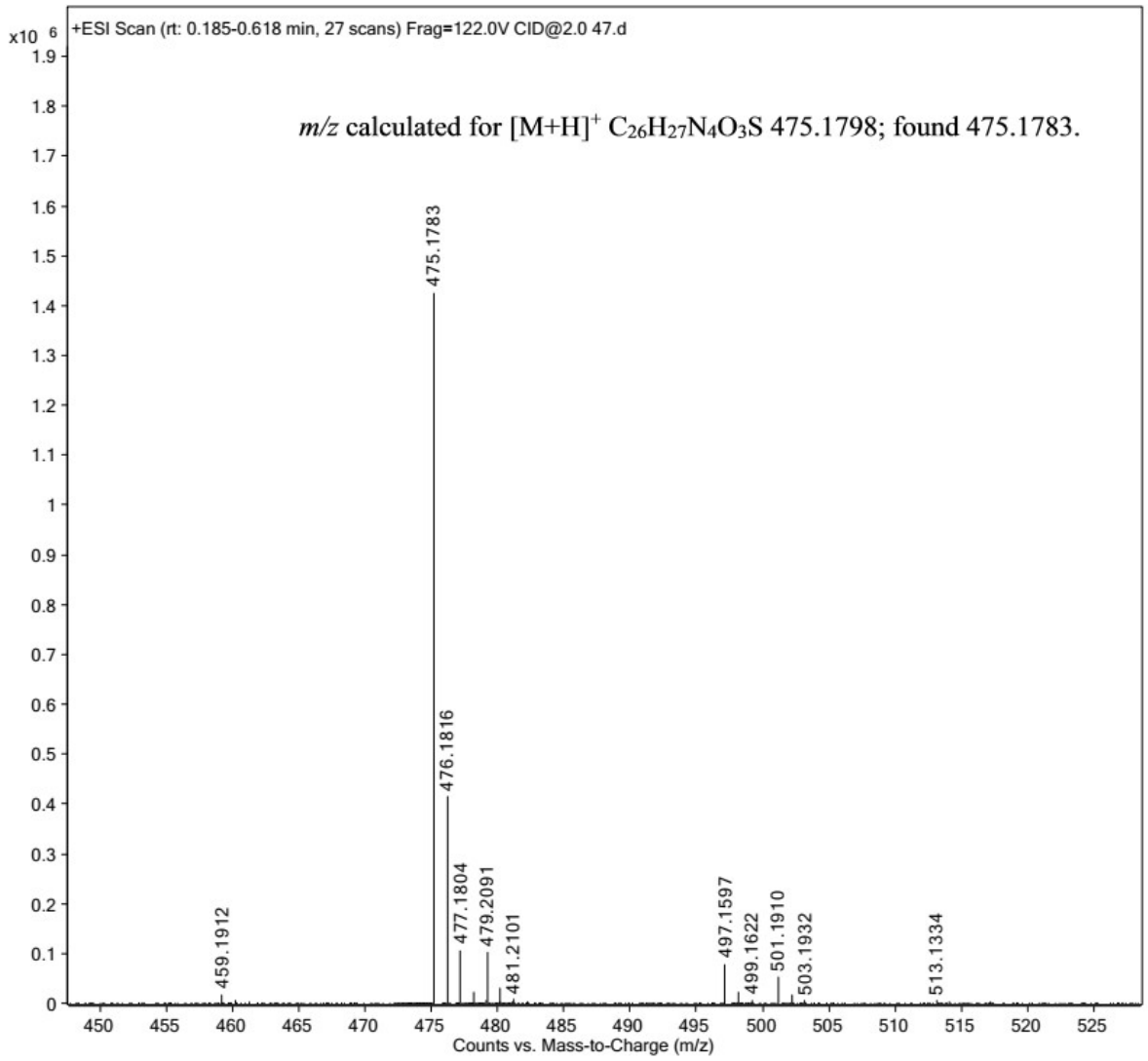

+ESI Scan (rt: 0.097-0.580 min, 30 scans) Frag=177.0V CID@2.0 AA-111.d Subtract
x10 5
m/z calculated for [M+H]+ C25H24ClN4O2S 479.1303; found 479.1295.
479.1295
480.1326
481.1277
482.1296
483.1286
484.1283
485.1313
477.1141
Counts vs. Mass-to-Charge (m/z)

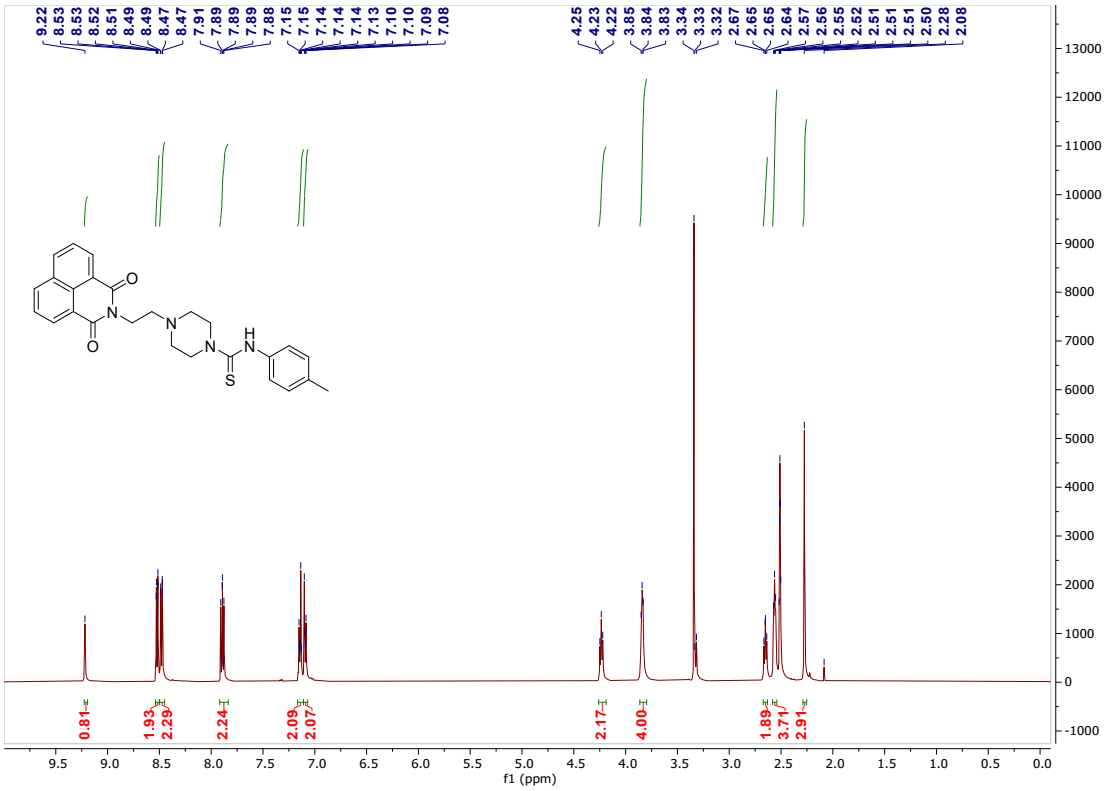


^{1}H spectrum for compound **4e** (500 MHz: DMSO-d_6)

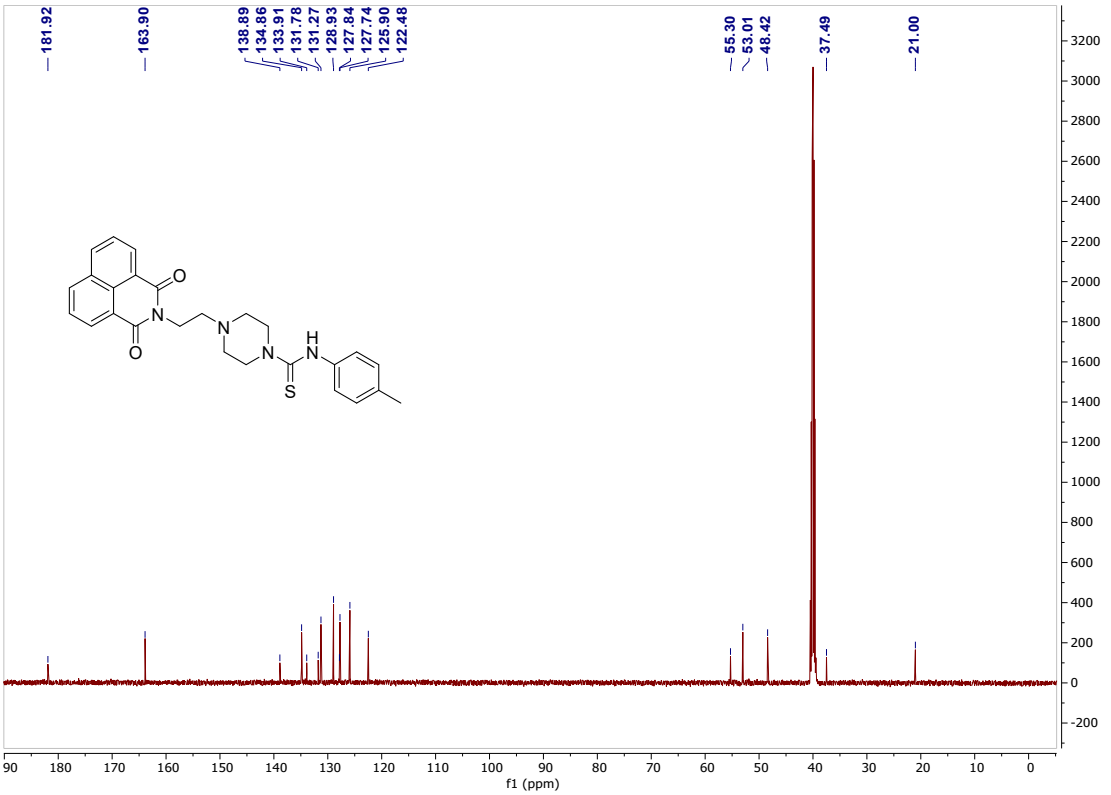


^{13}C spectrum for compound **4e** (125 MHz: DMSO-d_6)

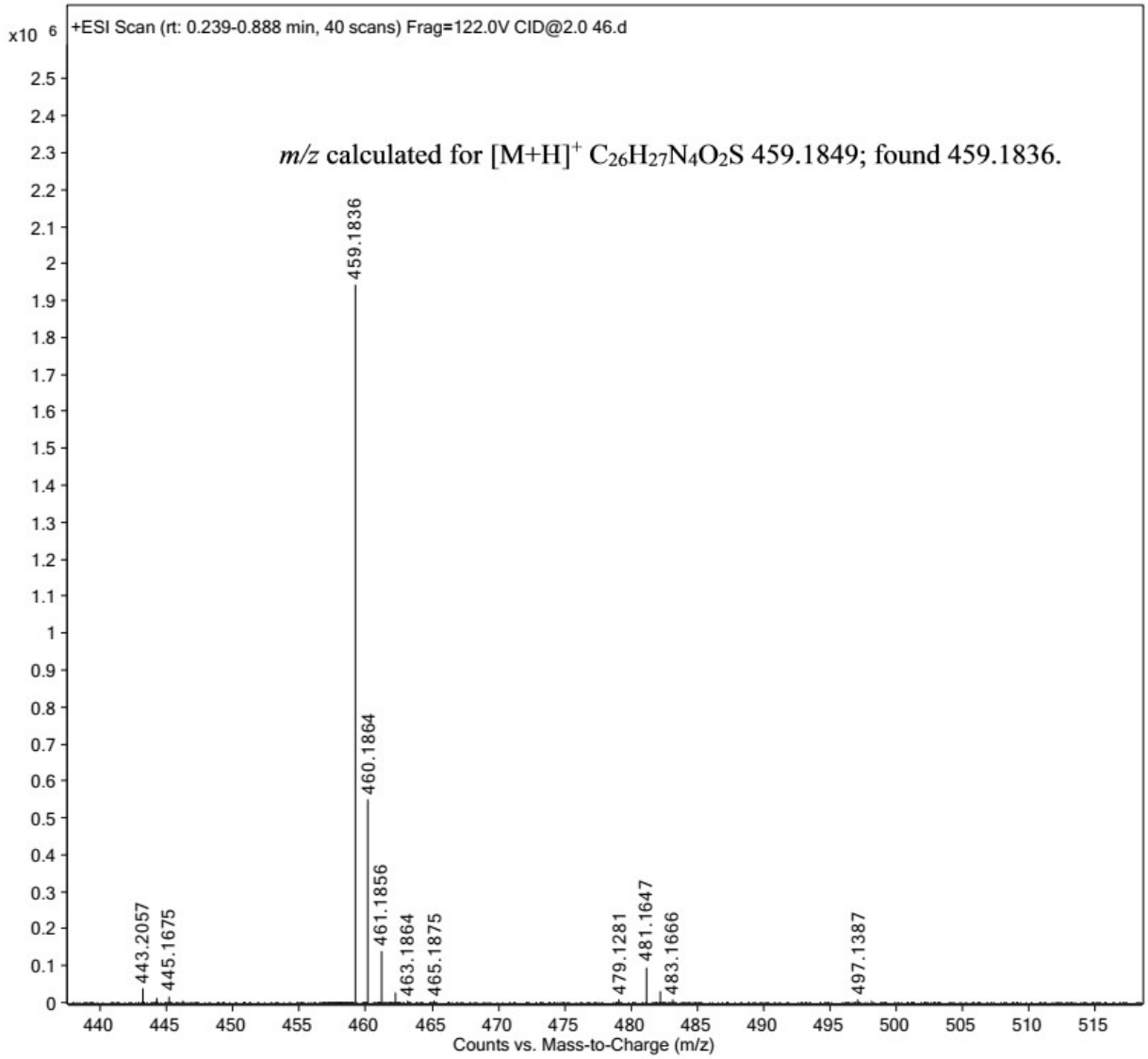

+ESI Scan (rt: 0.185-0.618 min, 27 scans) Frag=122.0V CID@2.0 47.d
x10 6
m/z calculated for [M+H]+ C26H27N4O3S 475.1798; found 475.1783.
475.1783
476.1816
477.1804
479.2091
481.2101
459.1912
497.1597
499.1622
501.1910
503.1932
513.1334
Counts vs. Mass-to-Charge (m/z)

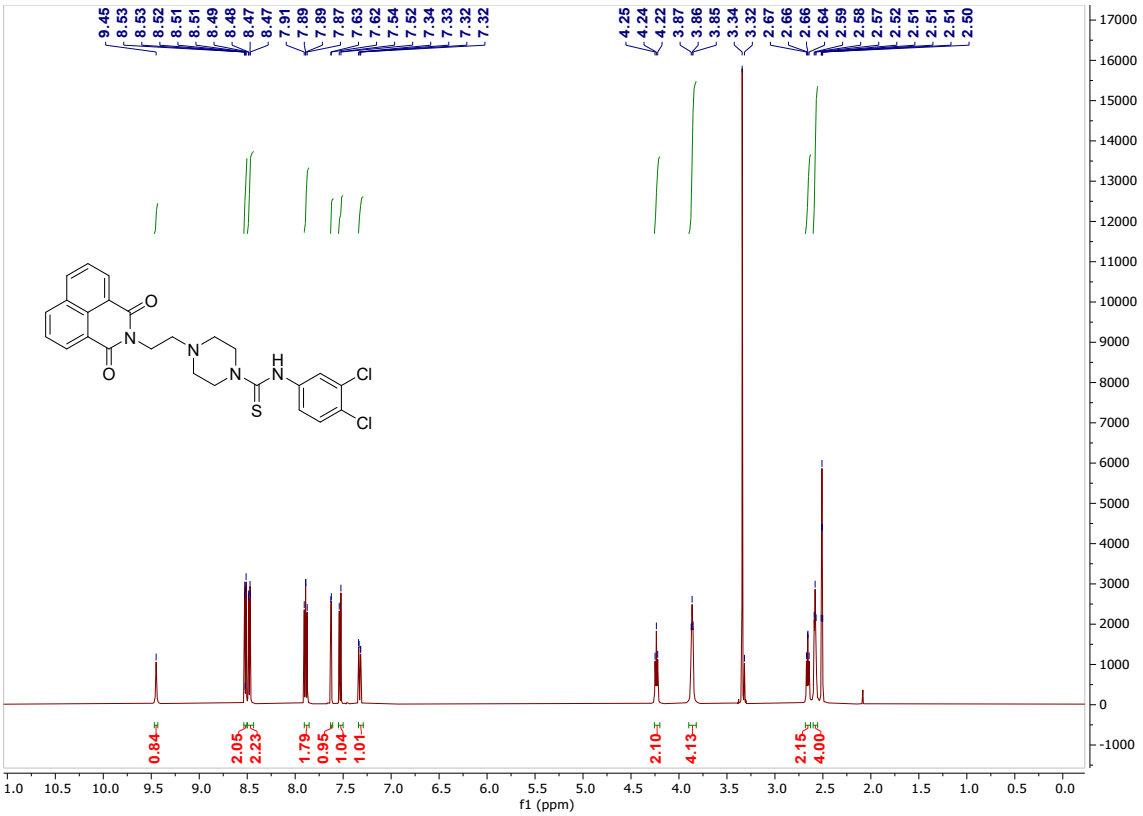


^{1}H spectrum for compound **4f** (500 MHz: DMSO-d_6)

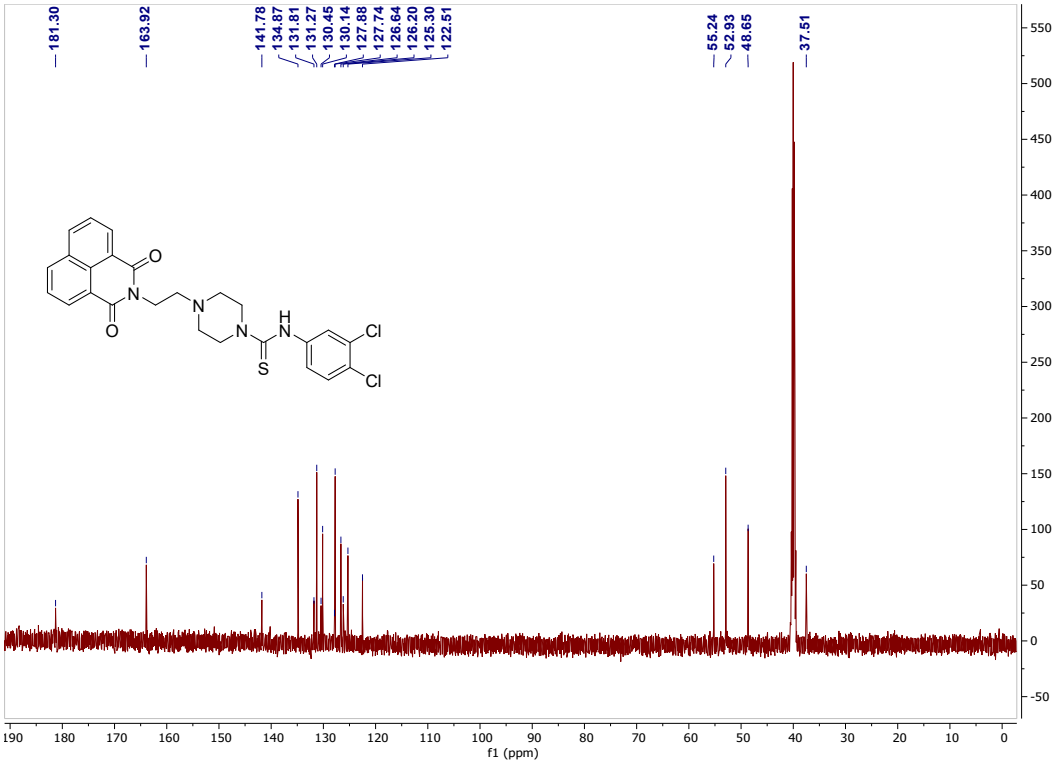


^{13}C spectrum for compound **4f** (125 MHz: DMSO-d_6)

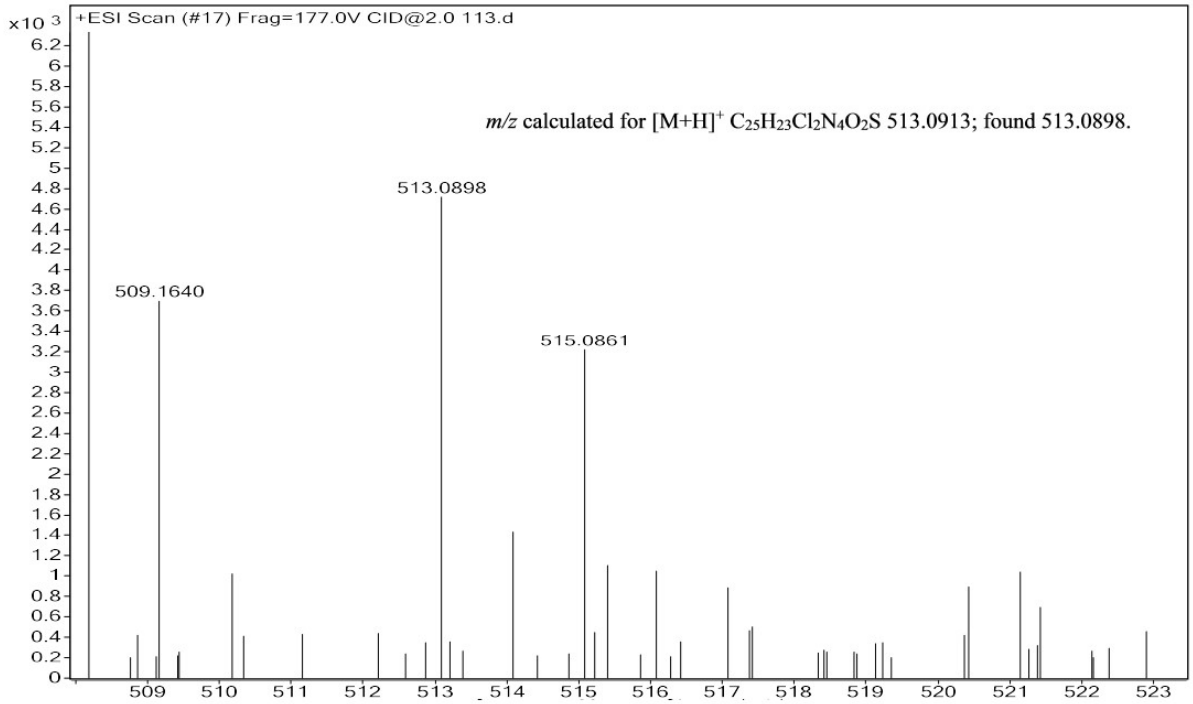

+ESI Scan (rt: 0.239-0.888 min, 40 scans) Frag=122.0V CID@2.0 46.d
x10 6
m/z calculated for [M+H]+ C26H27N4O2S 459.1849; found 459.1836.
459.1836
460.1864
461.1856
443.2057
445.1675
463.1864
465.1875
479.1281
481.1647
483.1666
497.1387
Counts vs. Mass-to-Charge (m/z)

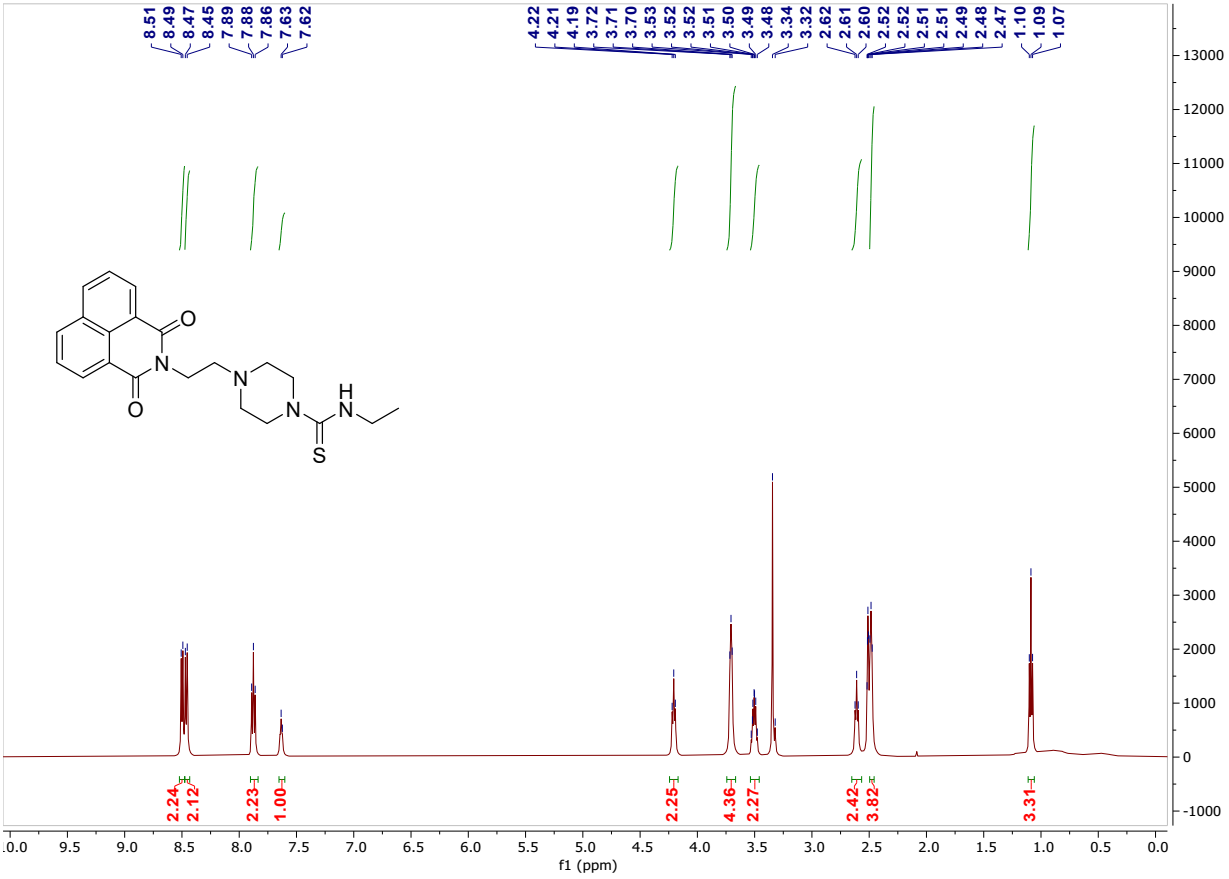


^{1}H spectrum for compound **4g** (500 MHz: DMSO-d_6)

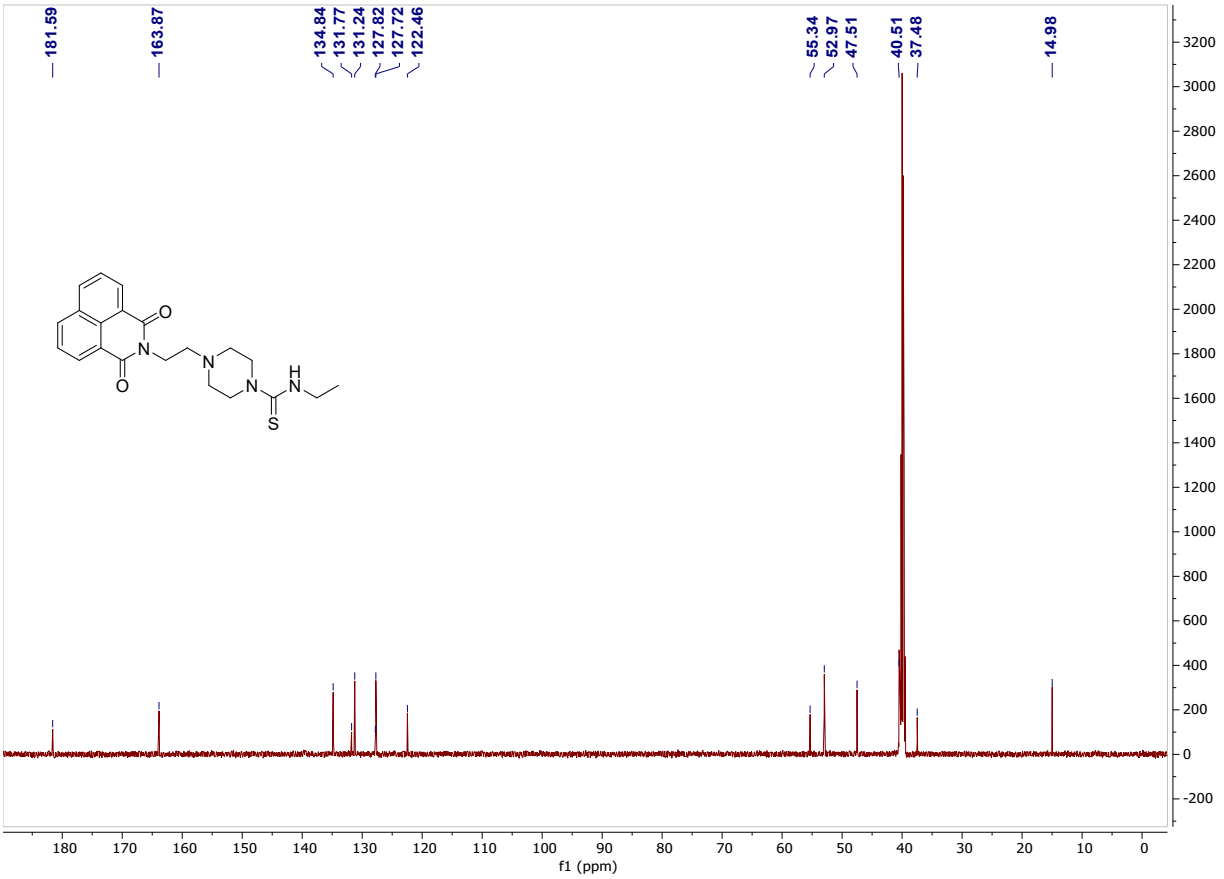


^{13}C spectrum for compound **4g** (125 MHz: DMSO-d_6)

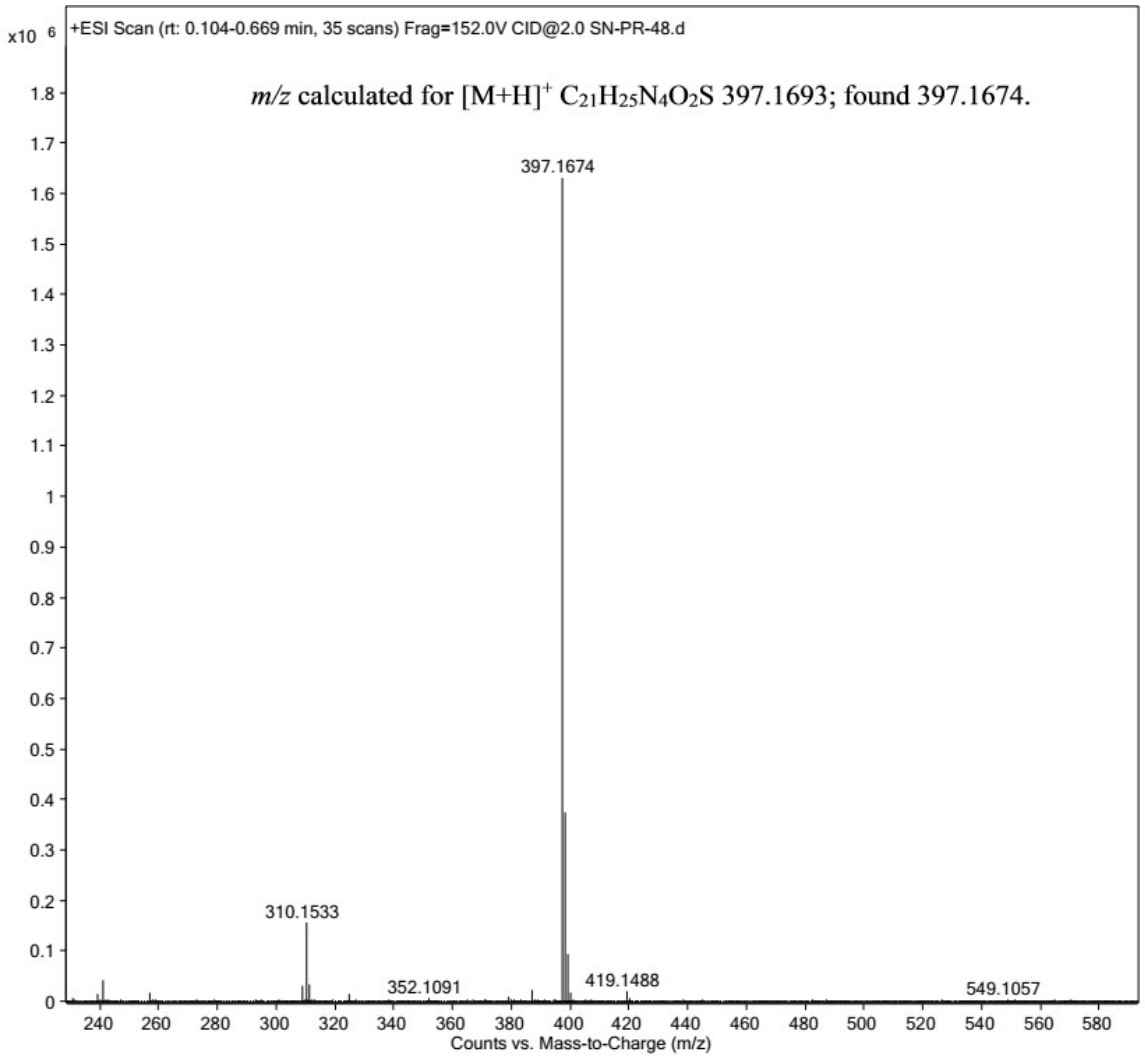


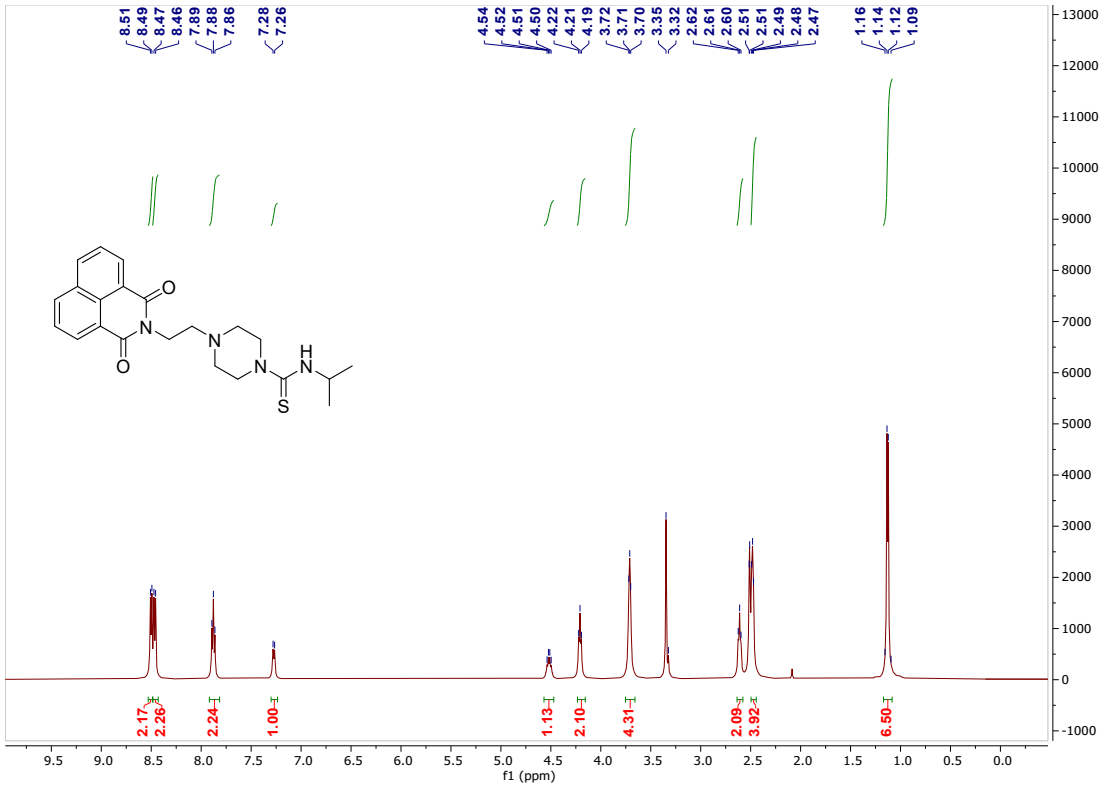


^{1}H spectrum for compound **4h** (500 MHz: DMSO-d_6)

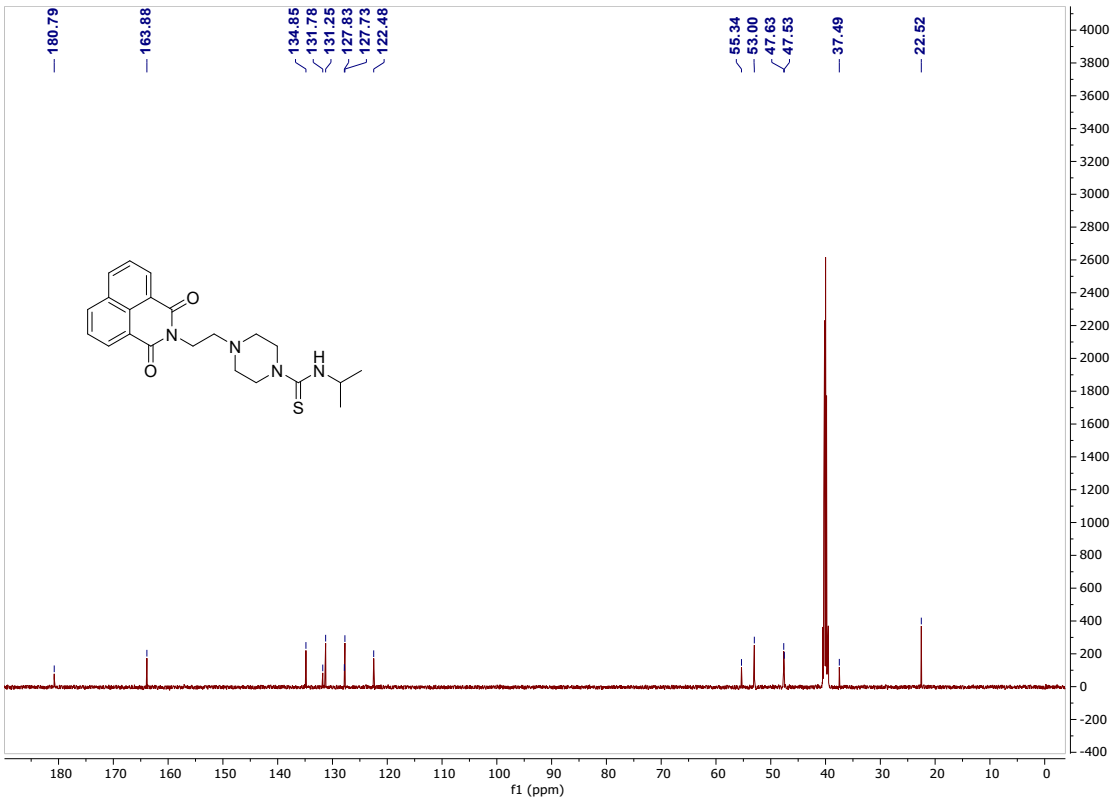


^{13}C spectrum for compound **4h** (125 MHz: DMSO-d_6)

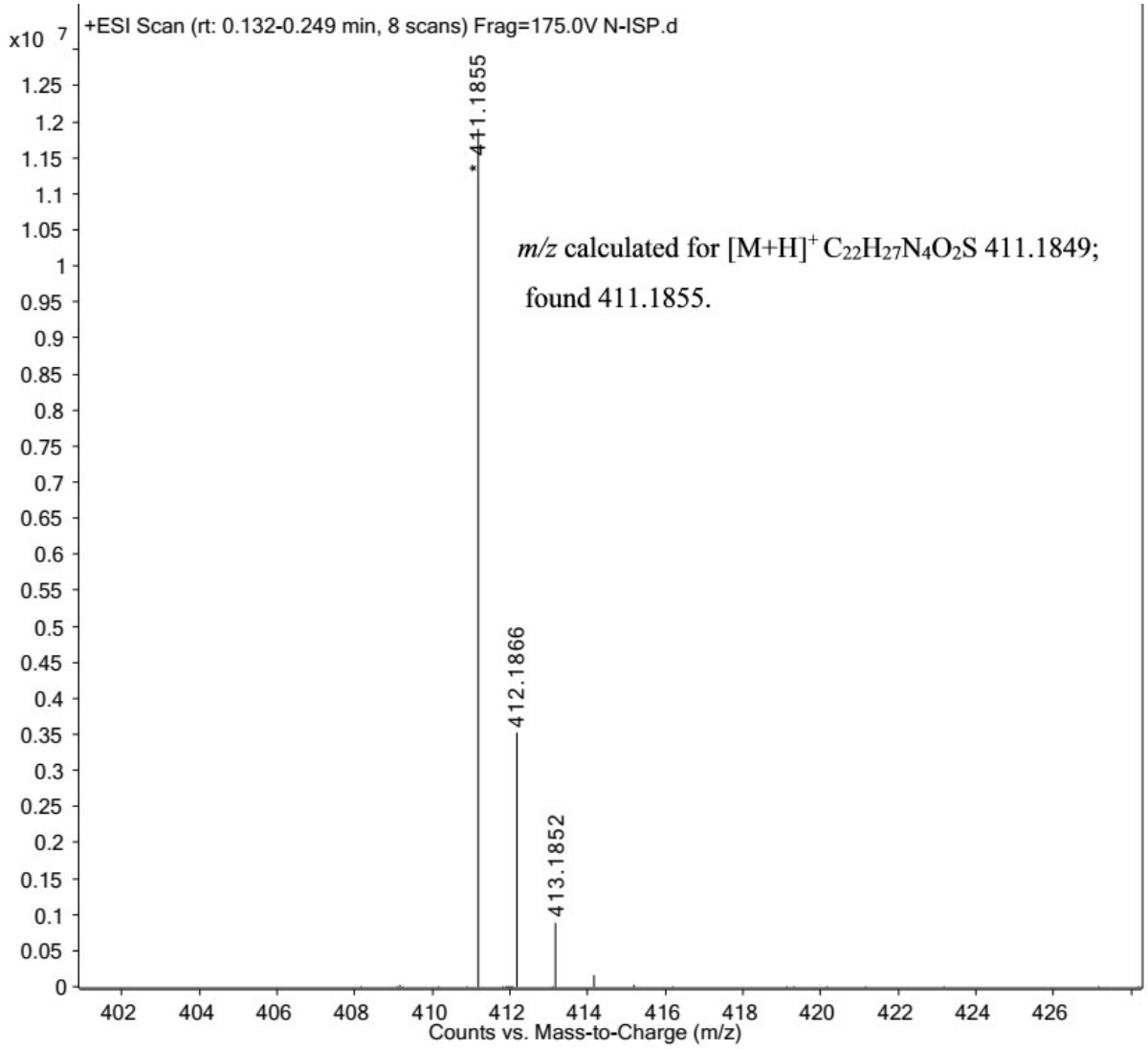

+ESI Scan (rt: 0.104-0.669 min, 35 scans) Frag=152.0V CID@2.0 SN-PR-48.d
x10 6
m/z calculated for [M+H]+ C21H25N4O2S 397.1693; found 397.1674.
397.1674
310.1533
352.1091
419.1488
549.1057
Counts vs. Mass-to-Charge (m/z)



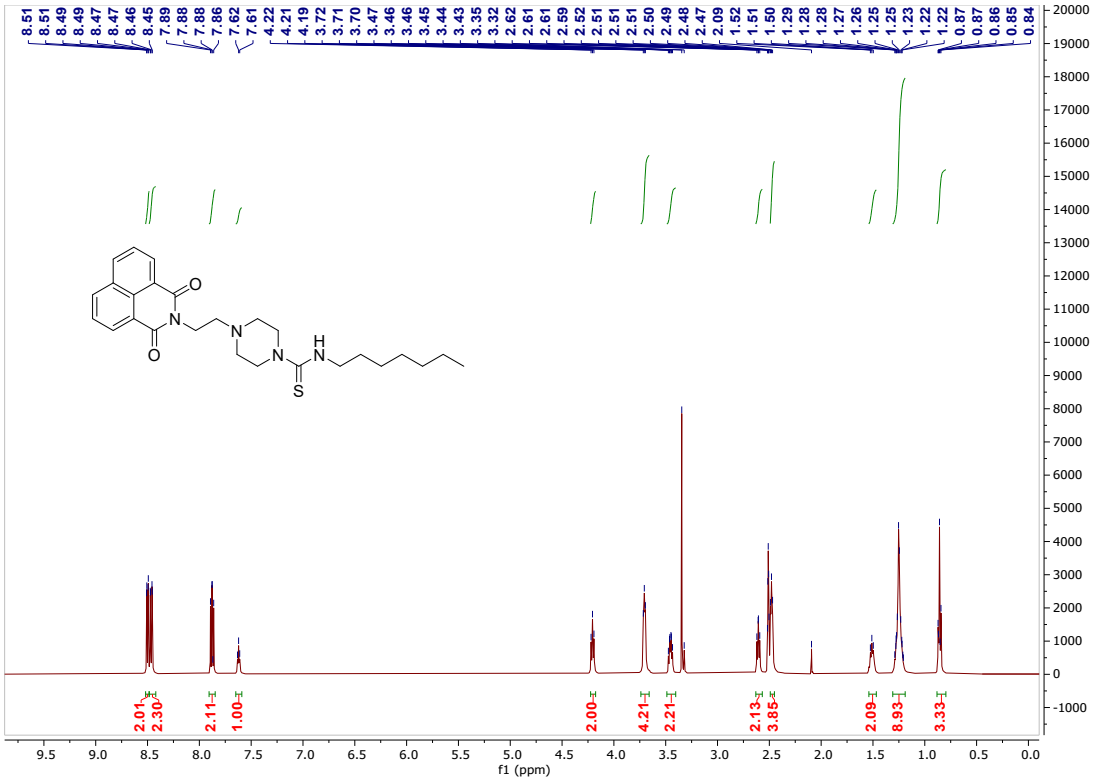
^{1}H spectrum for compound **4i** (500 MHz: DMSO-d_6)



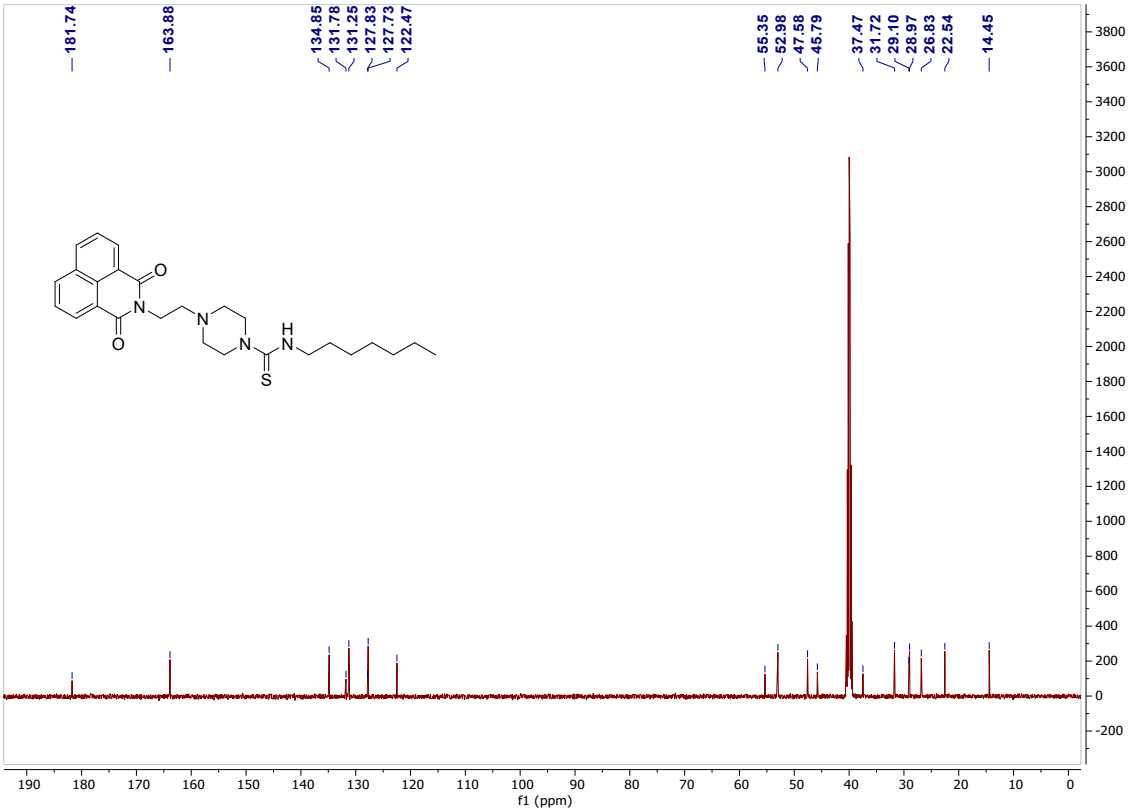
^{13}C spectrum for compound **4i** (125 MHz: DMSO-d_6)



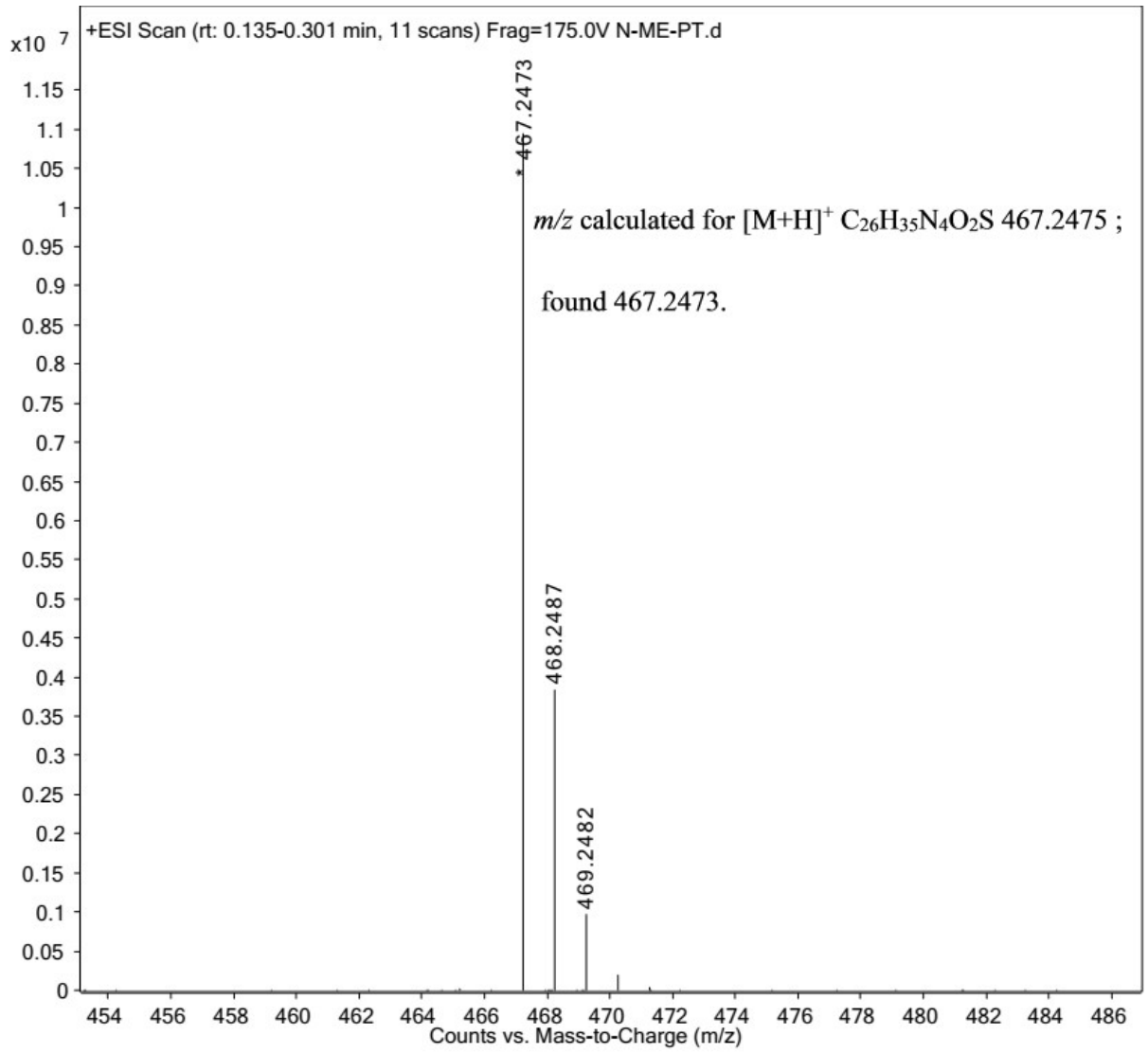
m/z calculated for $[M+H]^+$ $C_{22}H_{27}N_4O_2S$ 411.1849; found 411.1855.

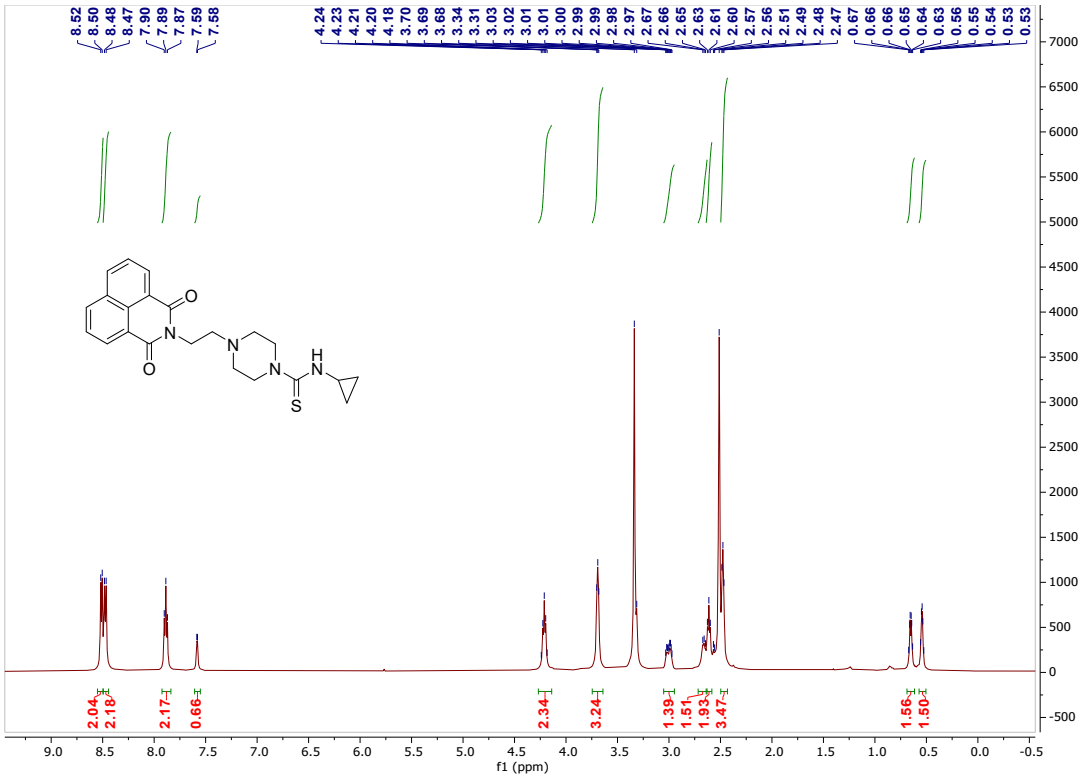


^{1}H spectrum for compound **4j** (500 MHz: DMSO-d_6)

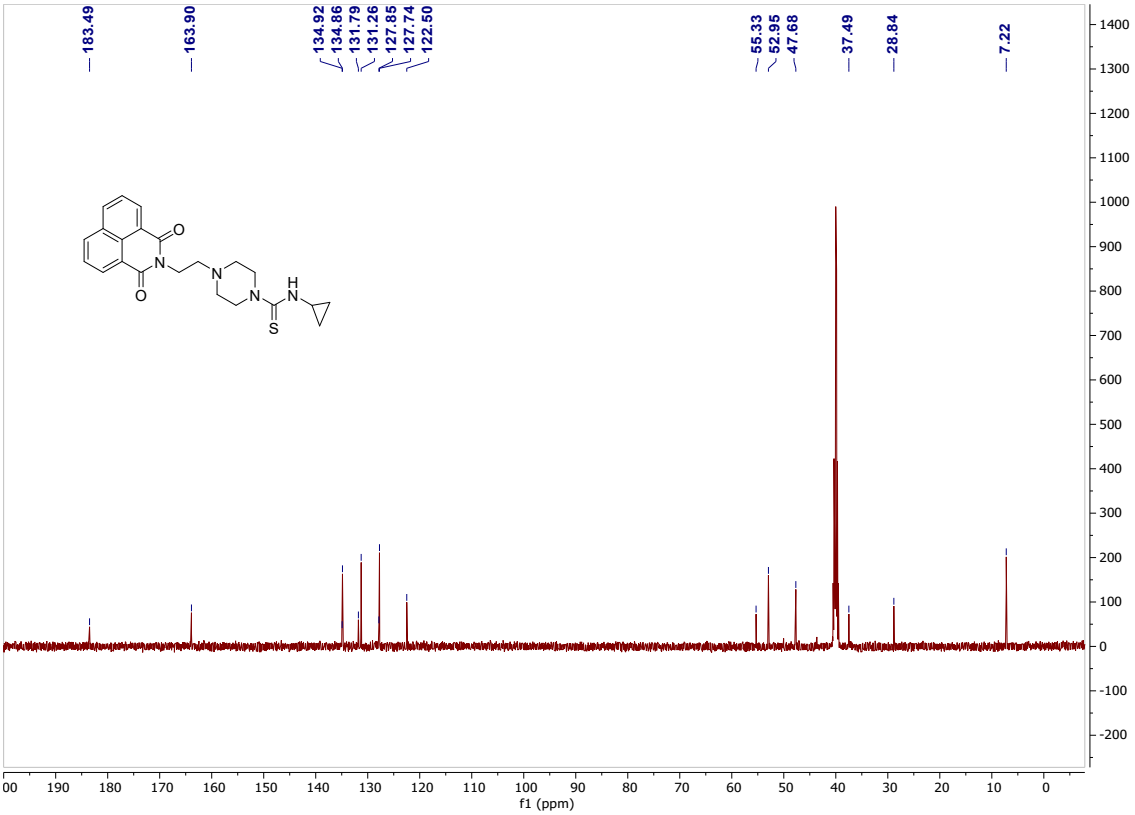


^{13}C spectrum for compound **4j** (125 MHz: DMSO-d_6)

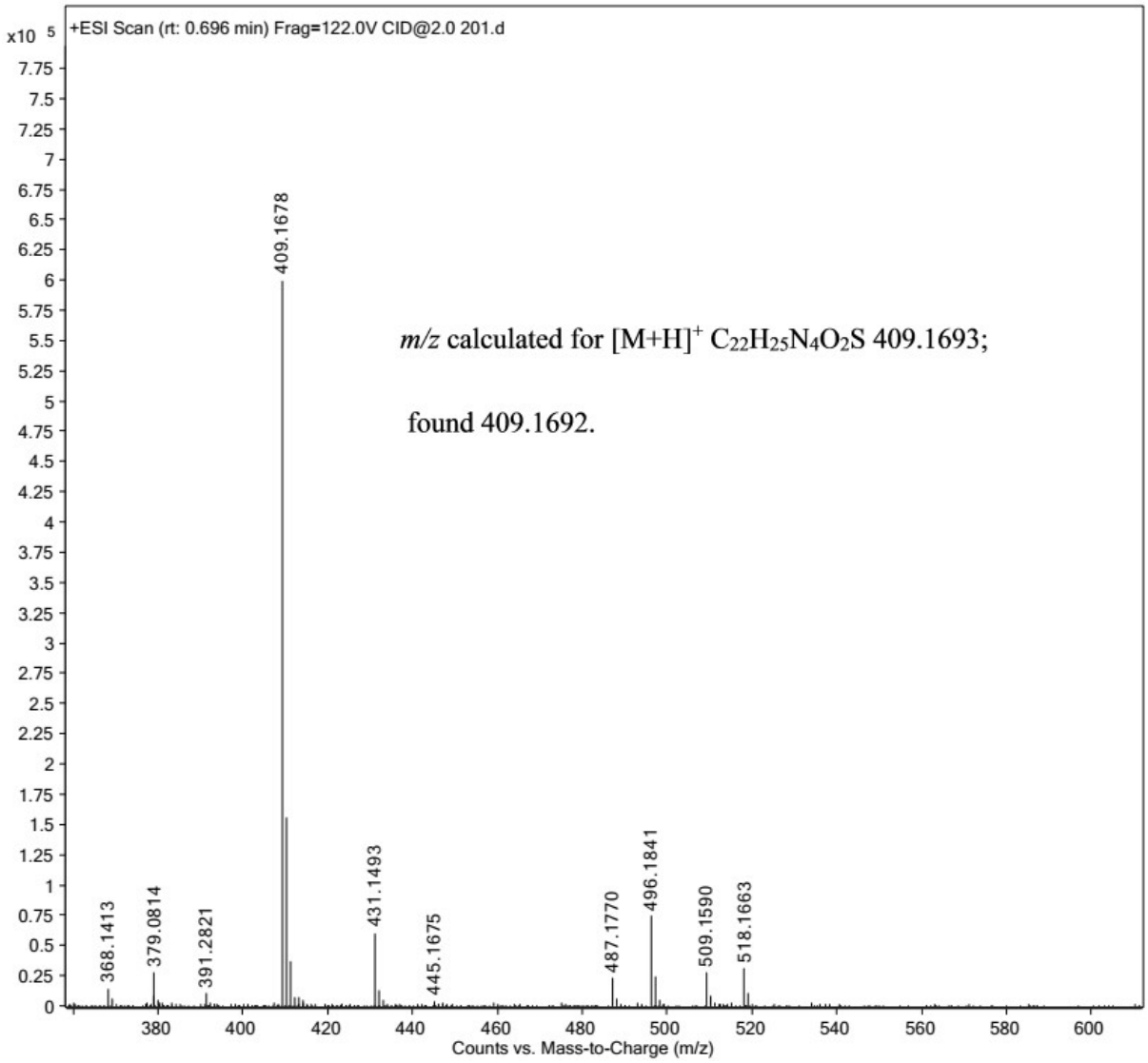

+ESI Scan (rt: 0.135-0.301 min, 11 scans) Frag=175.0V N-ME-PT.d
x10 7
467.2473
468.2487
469.2482
m/z calculated for [M+H]+ C26H35N4O2S 467.2475 ;
found 467.2473.
Counts vs. Mass-to-Charge (m/z)



^{1}H spectrum for compound **4k** (500 MHz: DMSO-d_6)

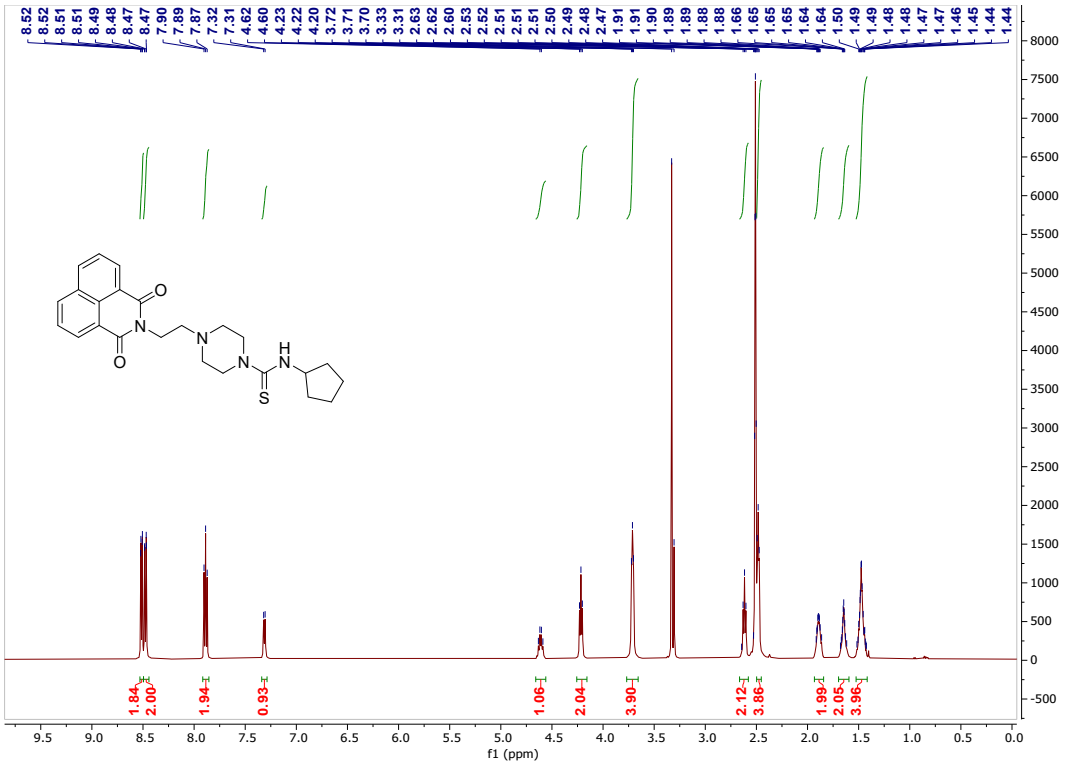


^{13}C spectrum for compound **4k** (125 MHz: DMSO-d_6)

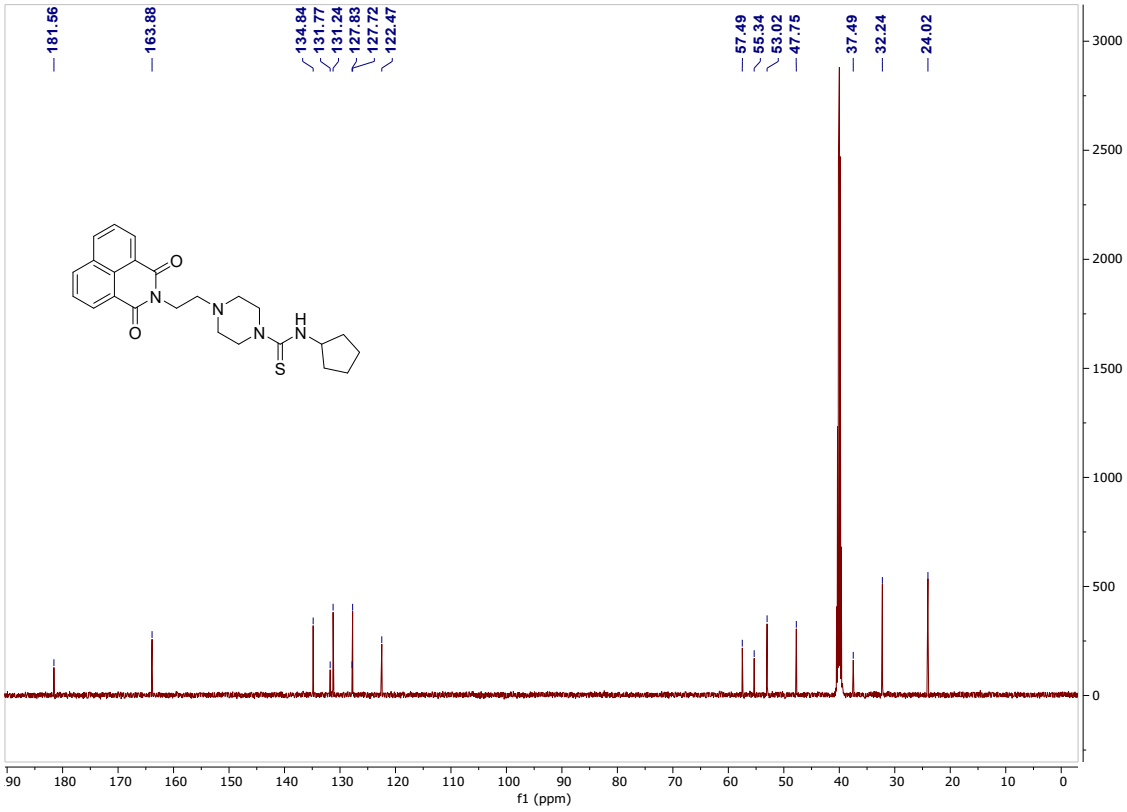


m/z calculated for $[M+H]^+$ $C_{22}H_{25}N_4O_2S$ 409.1693;

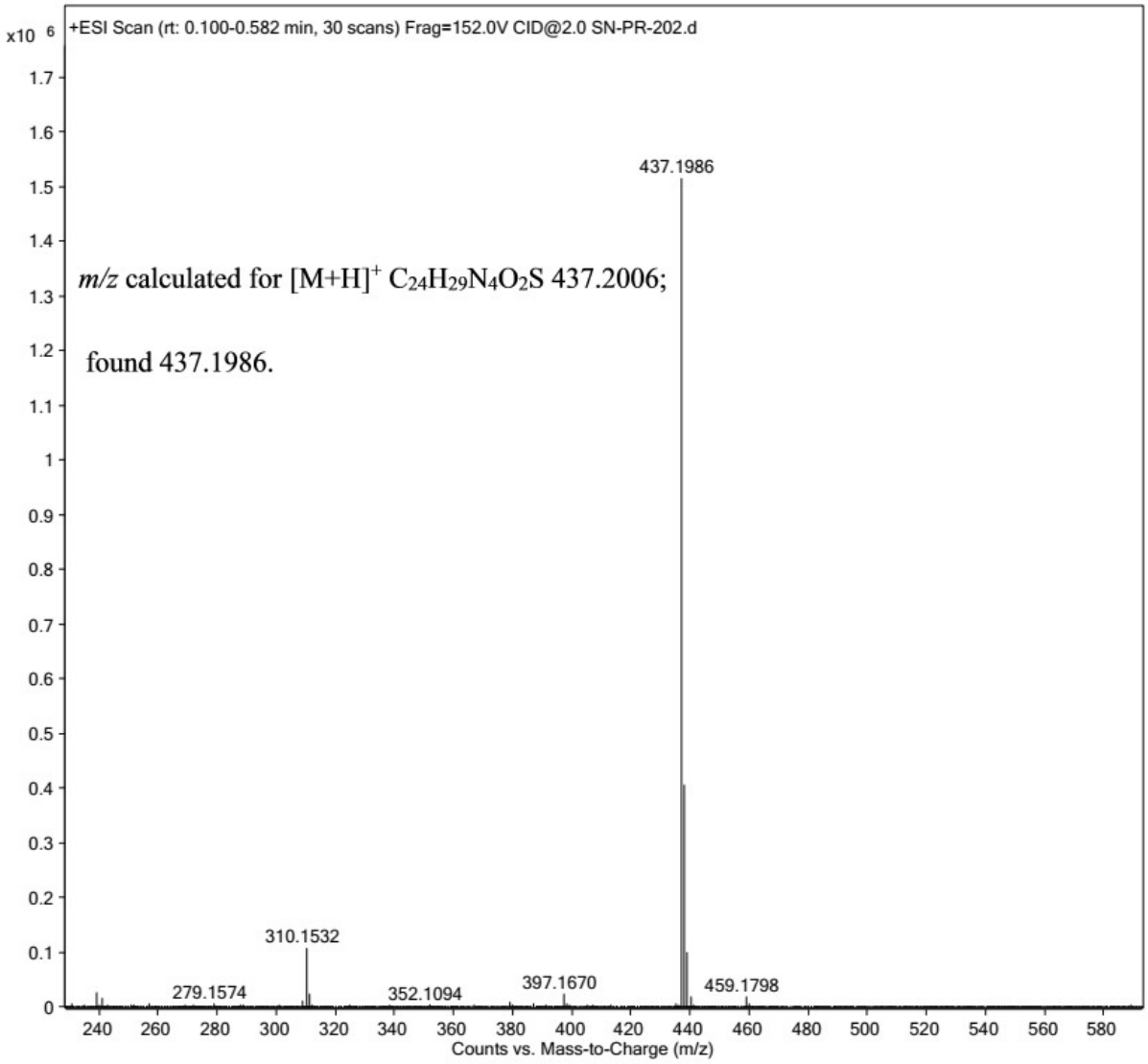
found 409.1692.



^{1}H spectrum for compound **4l** (500 MHz: DMSO-d_6)

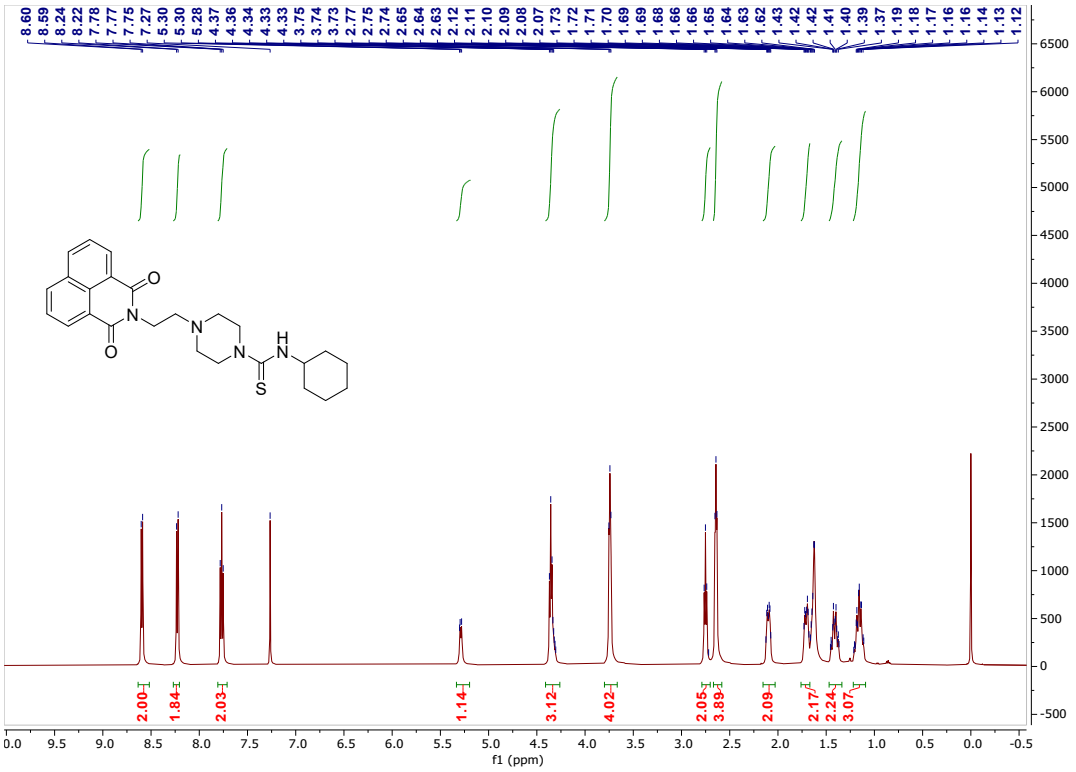


^{13}C spectrum for compound **4l** (125 MHz: DMSO-d_6)

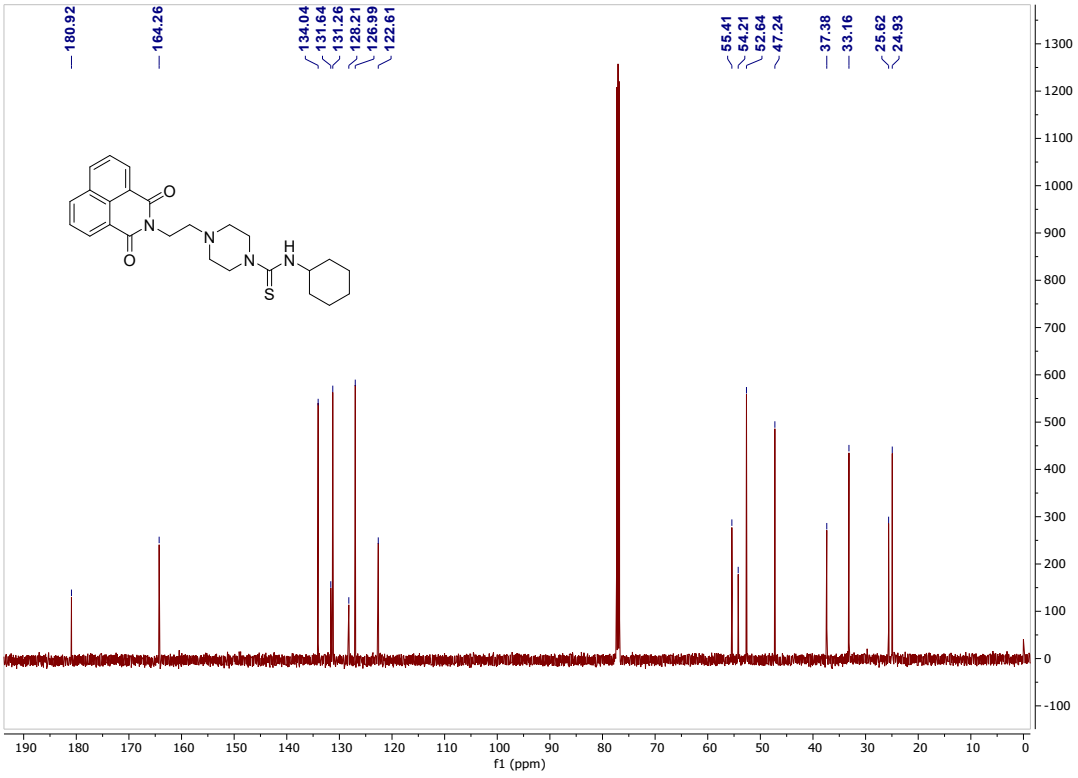


m/z calculated for $[M+H]^+$ $C_{24}H_{29}N_4O_2S$ 437.2006;

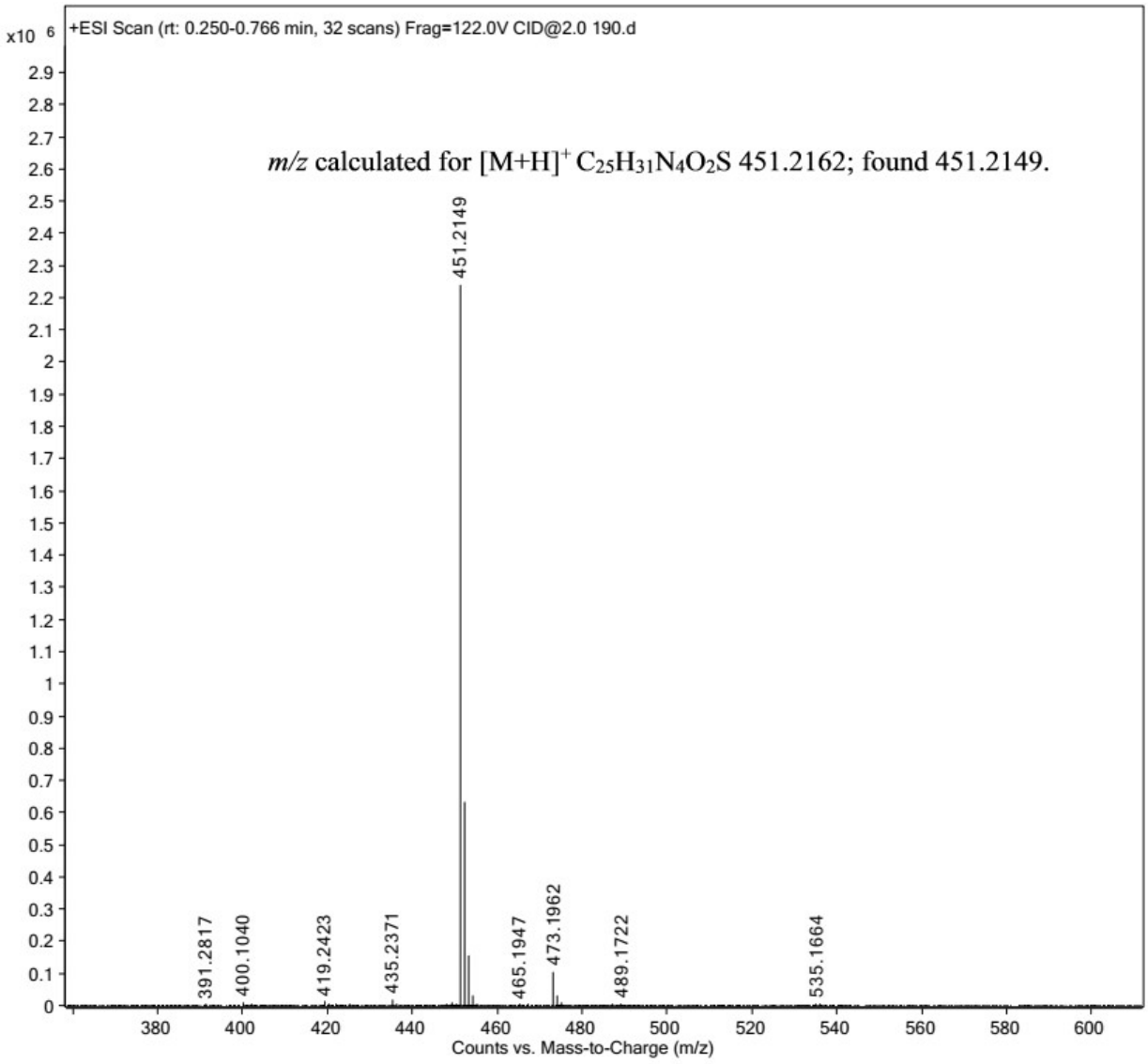
found 437.1986.

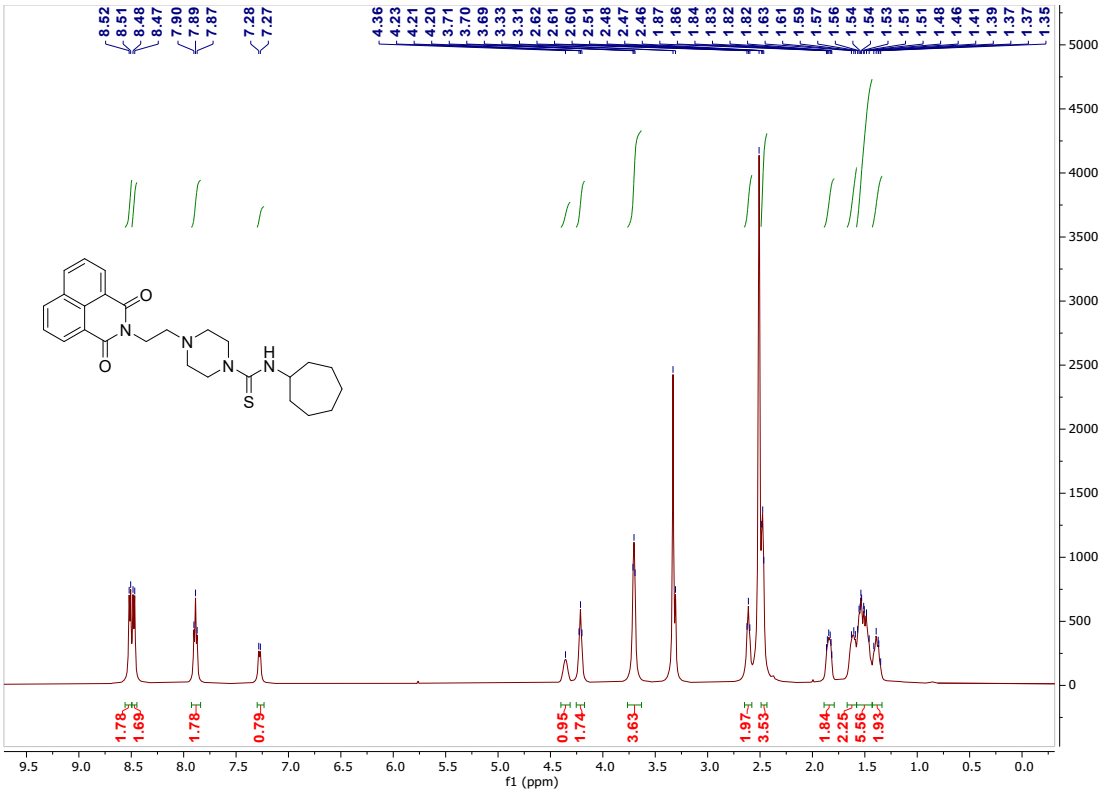


^{1}H spectrum for compound **4m** (500 MHz: $CDCl_3$)

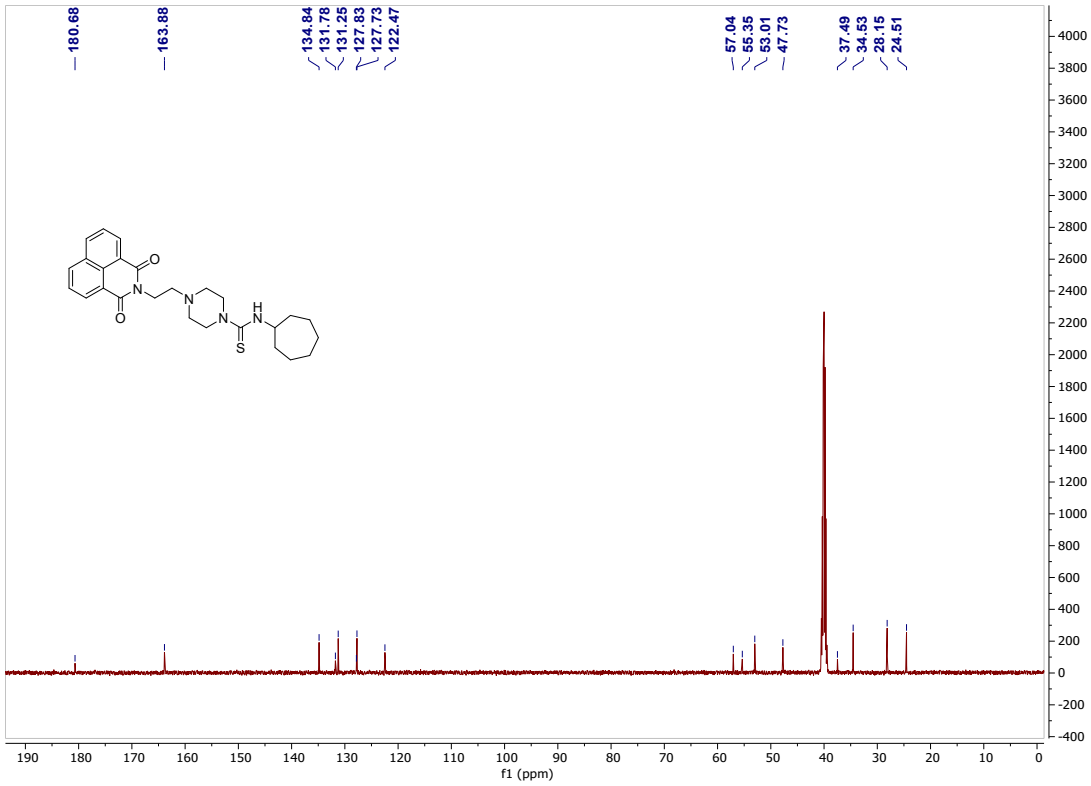


^{13}C spectrum for compound **4m** (125 MHz: $CDCl_3$)

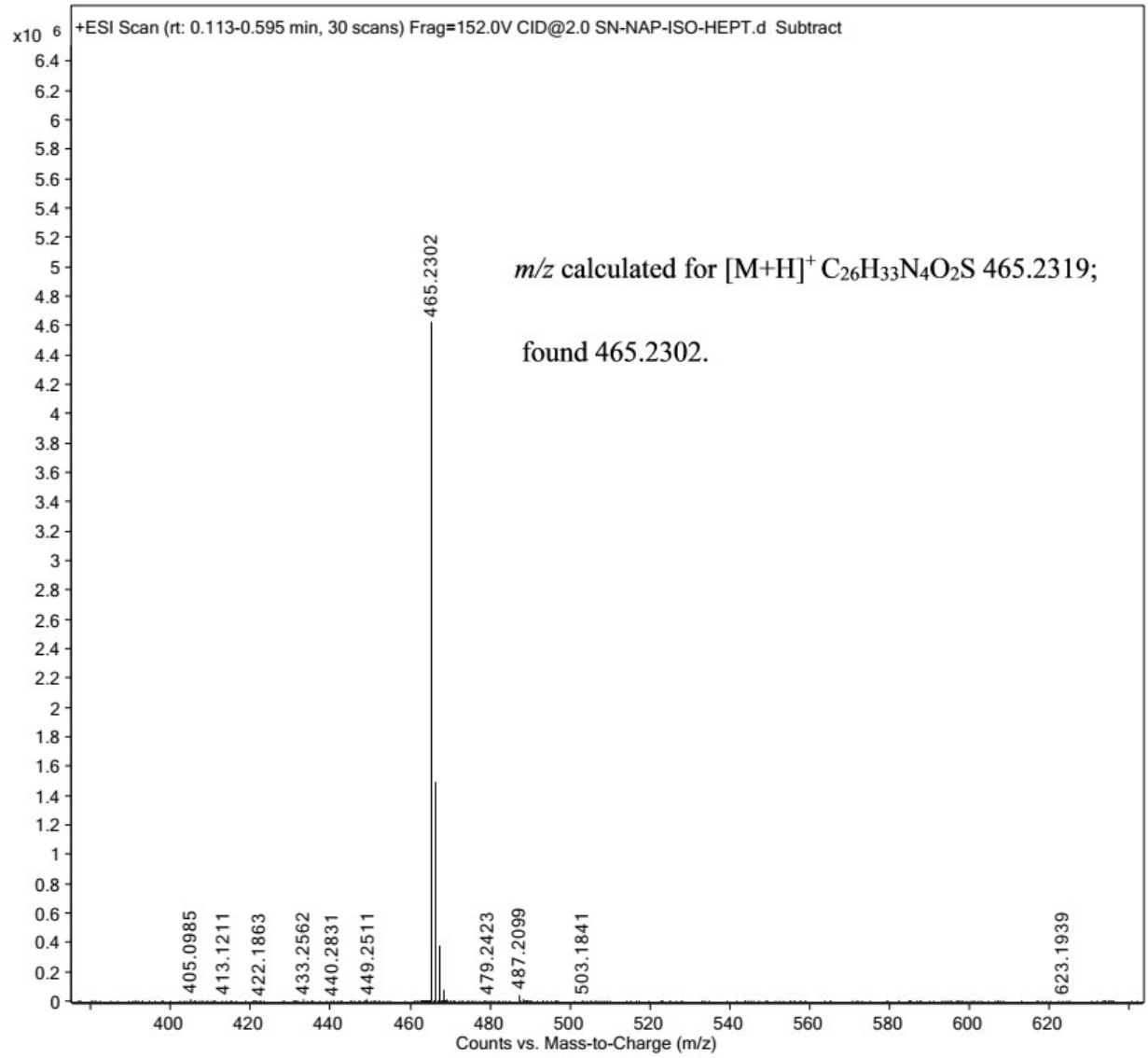

+ESI Scan (rt: 0.250-0.766 min, 32 scans) Frag=122.0V CID@2.0 190.d
x10 6
m/z calculated for [M+H]+ C25H31N4O2S 451.2162; found 451.2149.
451.2149
391.2817
400.1040
419.2423
435.2371
465.1947
473.1962
489.1722
535.1664
Counts vs. Mass-to-Charge (m/z)



^{1}H spectrum for compound **4n** (500 MHz: DMSO-d_6)

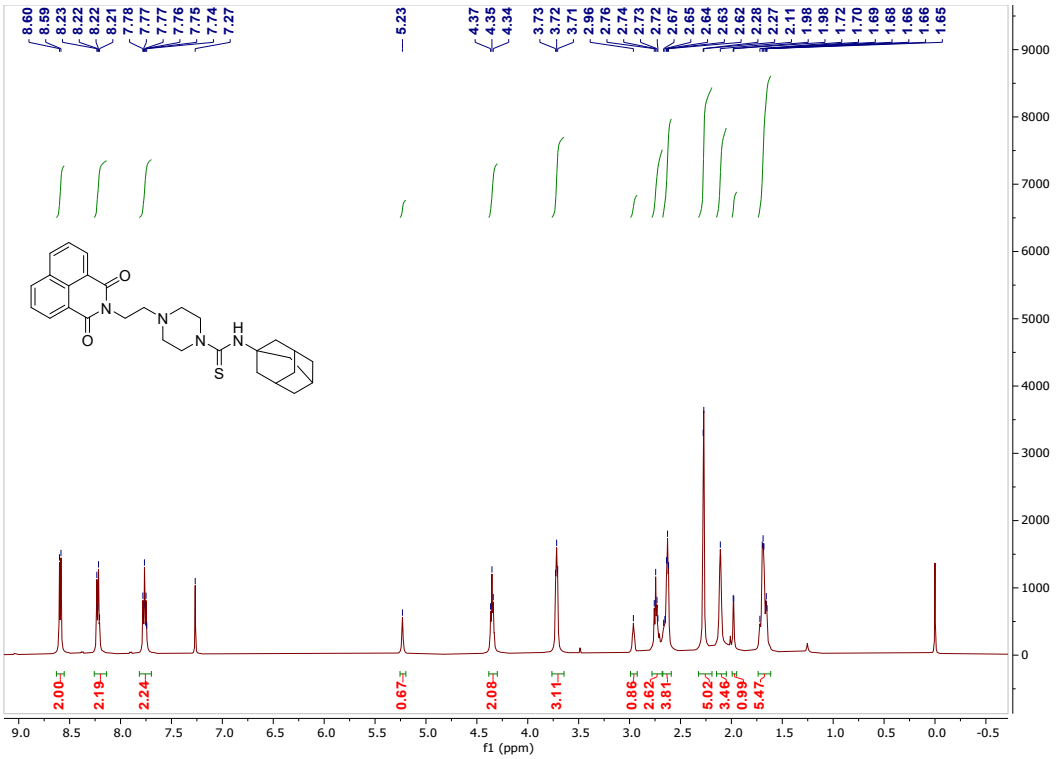


^{13}C spectrum for compound **4n** (125 MHz: DMSO-d_6)

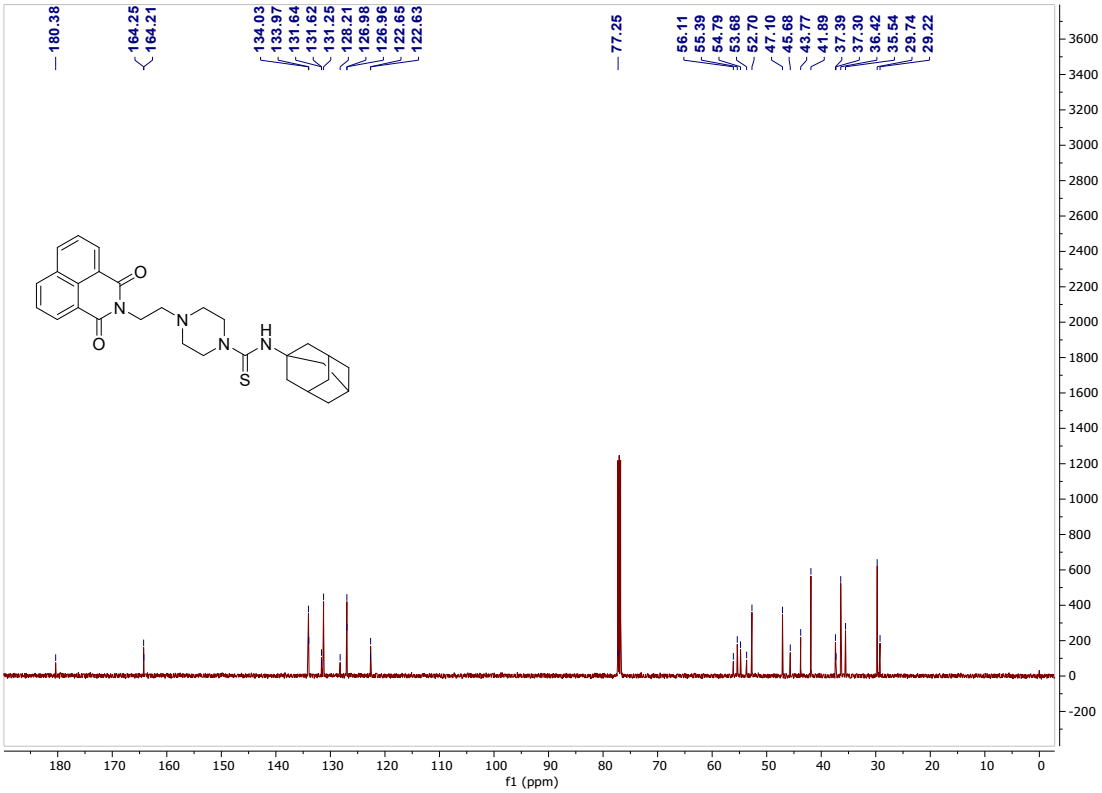


m/z calculated for $[M+H]^+$ $C_{26}H_{33}N_4O_2S$ 465.2319;

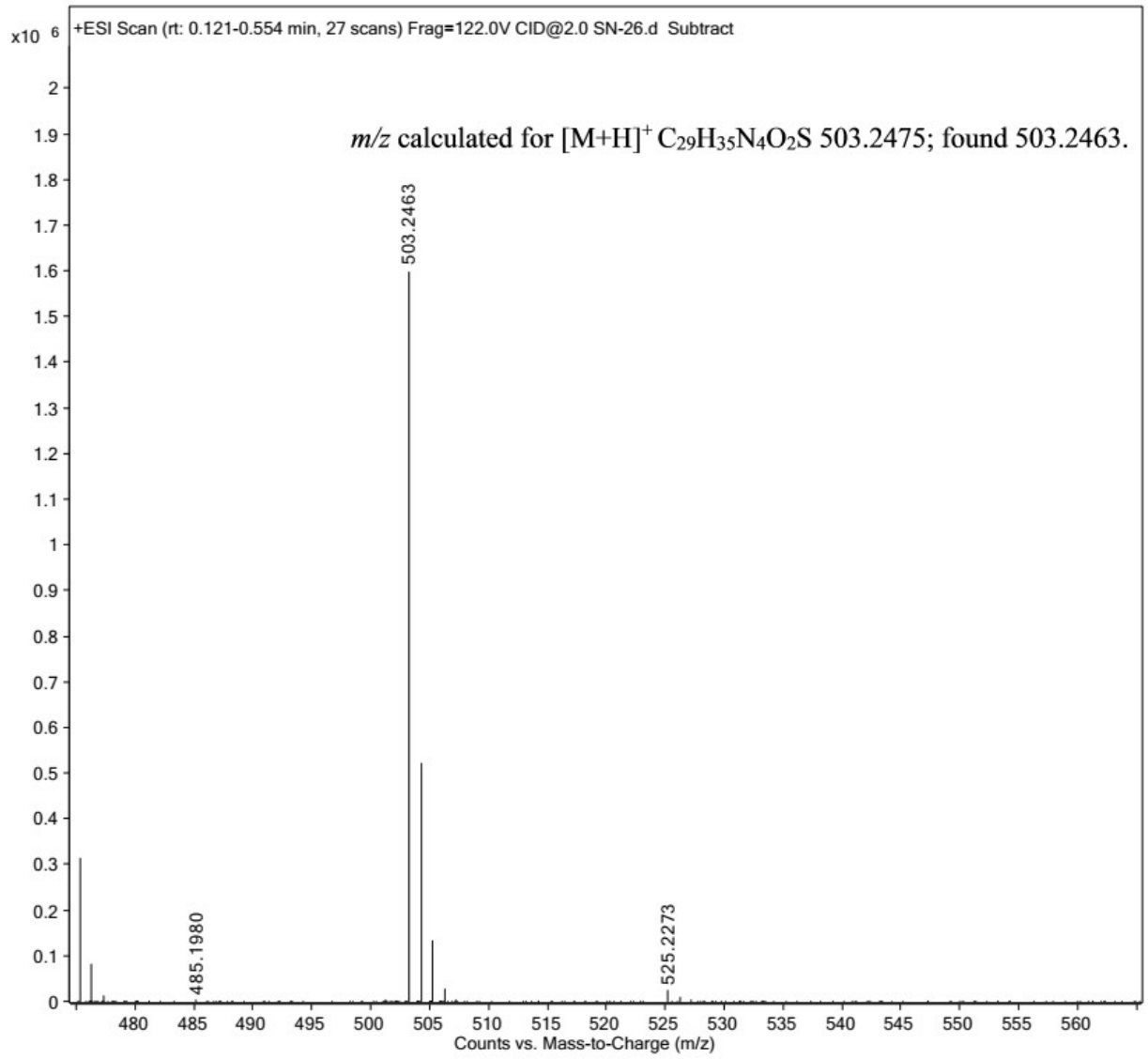
found 465.2302.

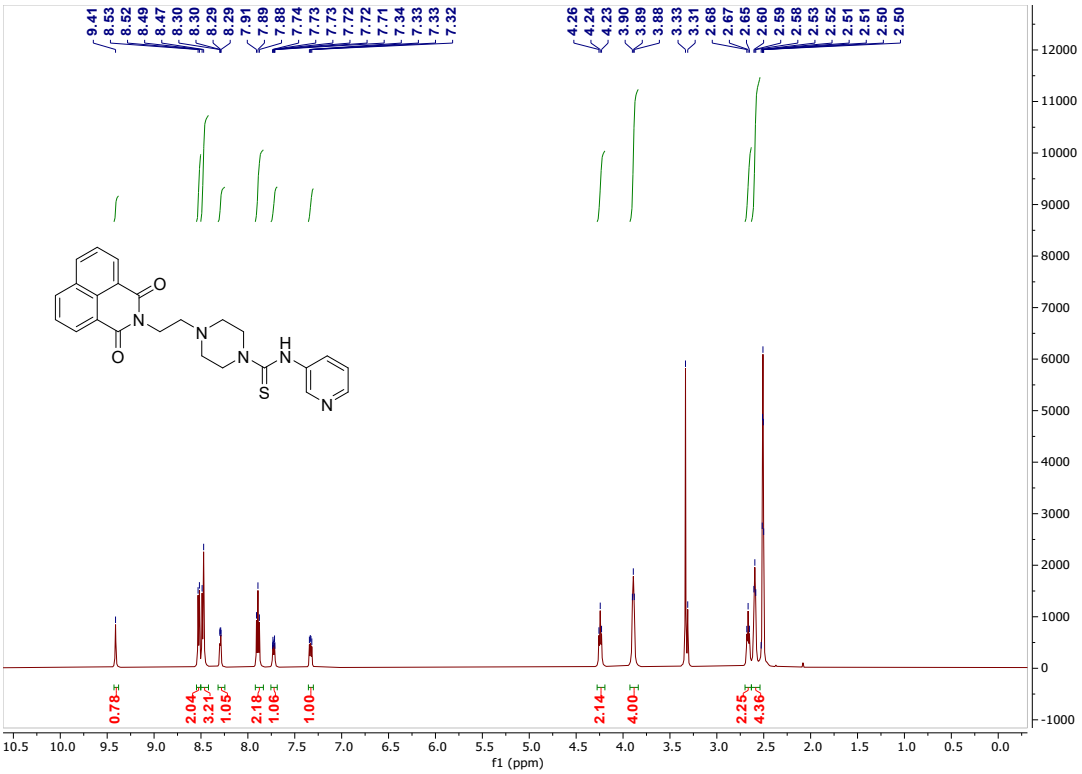


^{1}H spectrum for compound **4o** (500 MHz: $CDCl_3$)

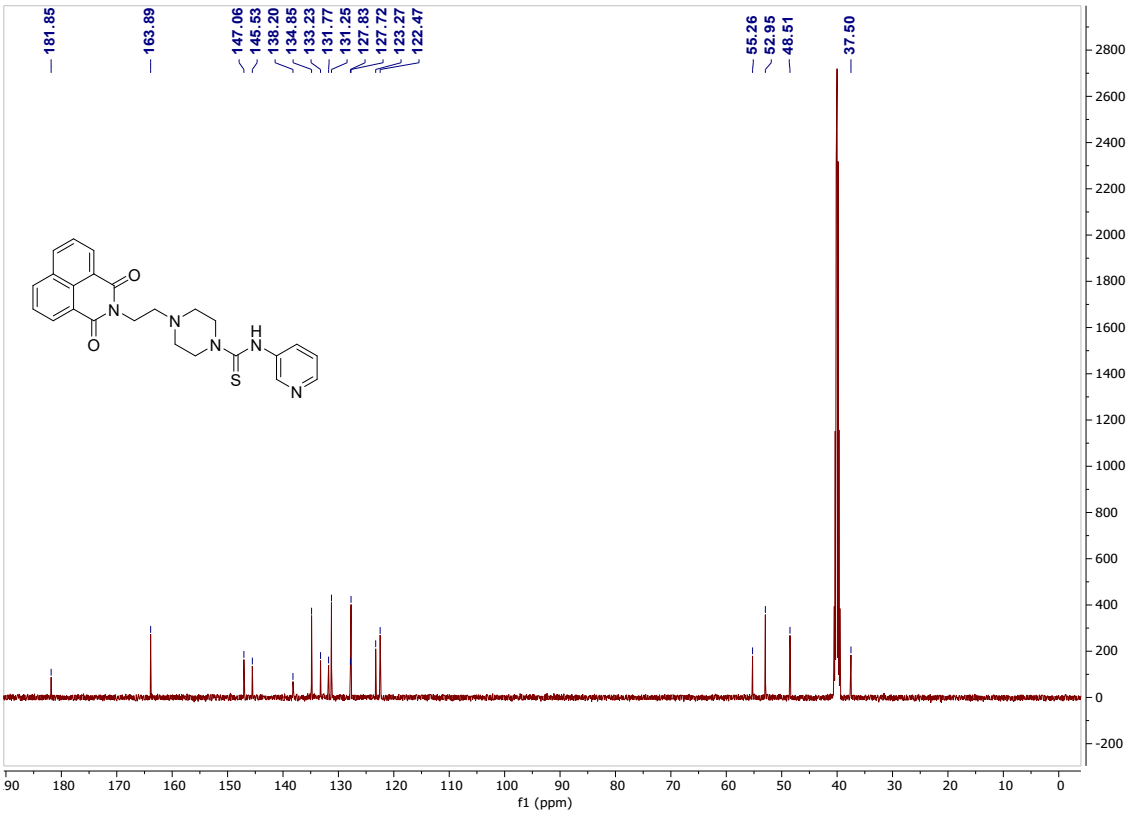


^{13}C spectrum for compound **4o** (125 MHz: $CDCl_3$)

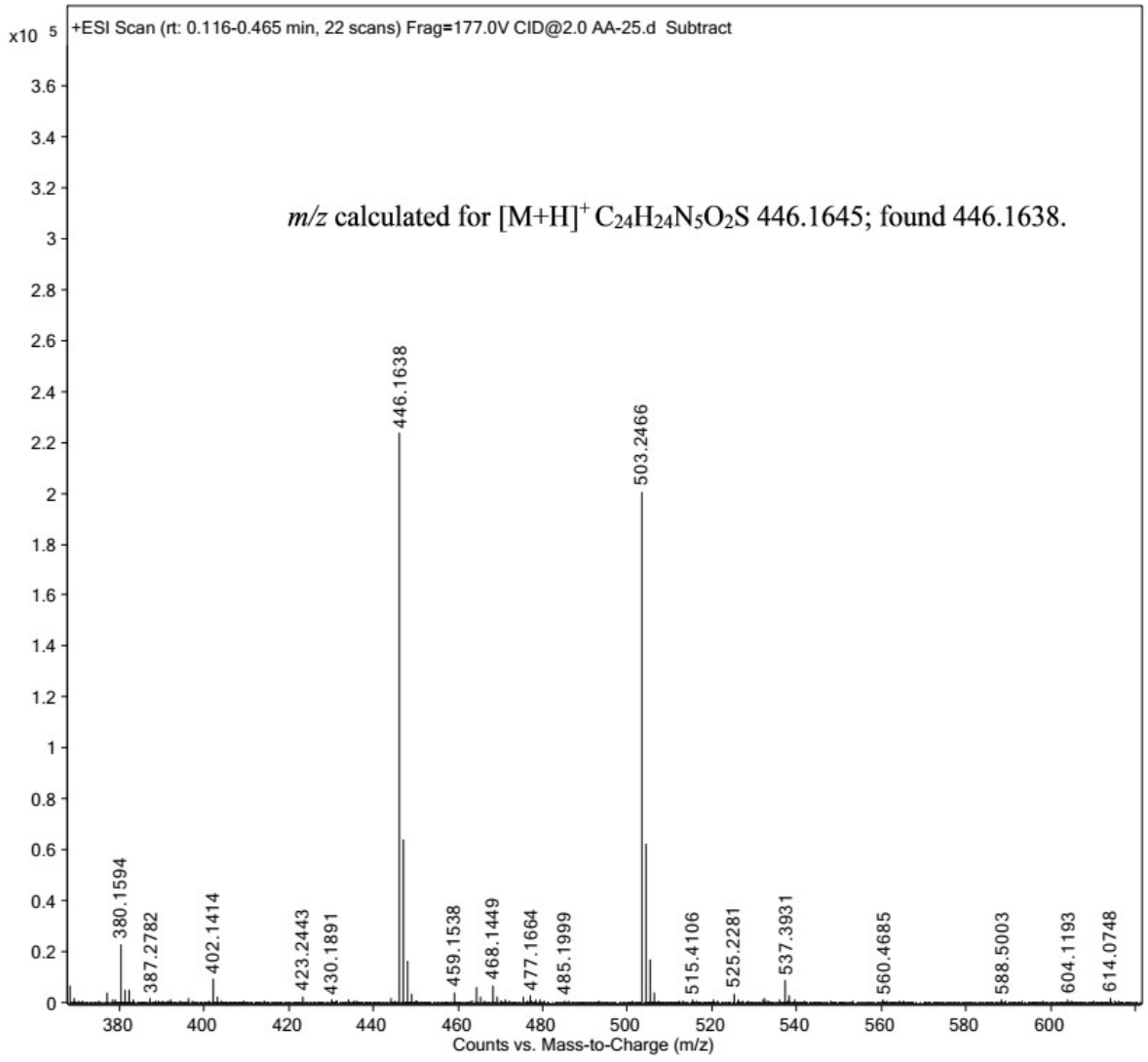

+ESI Scan (rt: 0.121-0.554 min, 27 scans) Frag=122.0V CID@2.0 SN-26.d Subtract
x10 6
m/z calculated for [M+H]+ C29H35N4O2S 503.2475; found 503.2463.
503.2463
485.1980
525.2273
Counts vs. Mass-to-Charge (m/z)

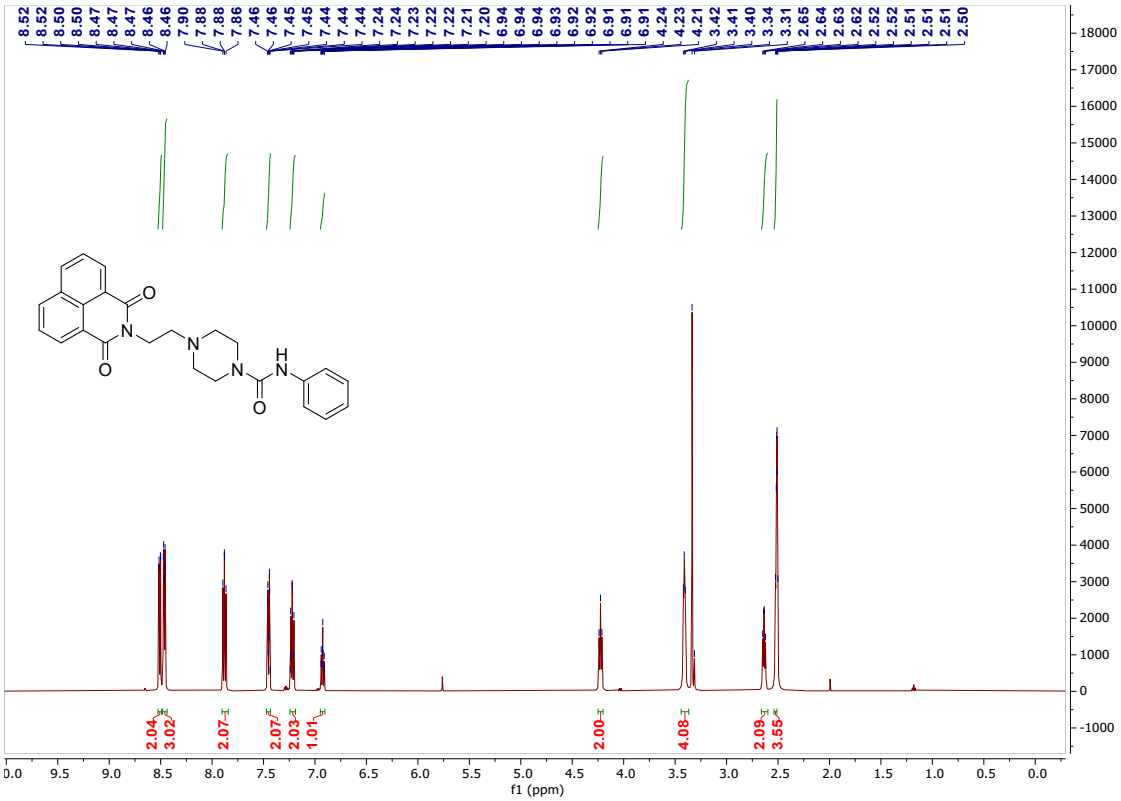


^{1}H spectrum for compound **4p** (500 MHz: DMSO-d_6)

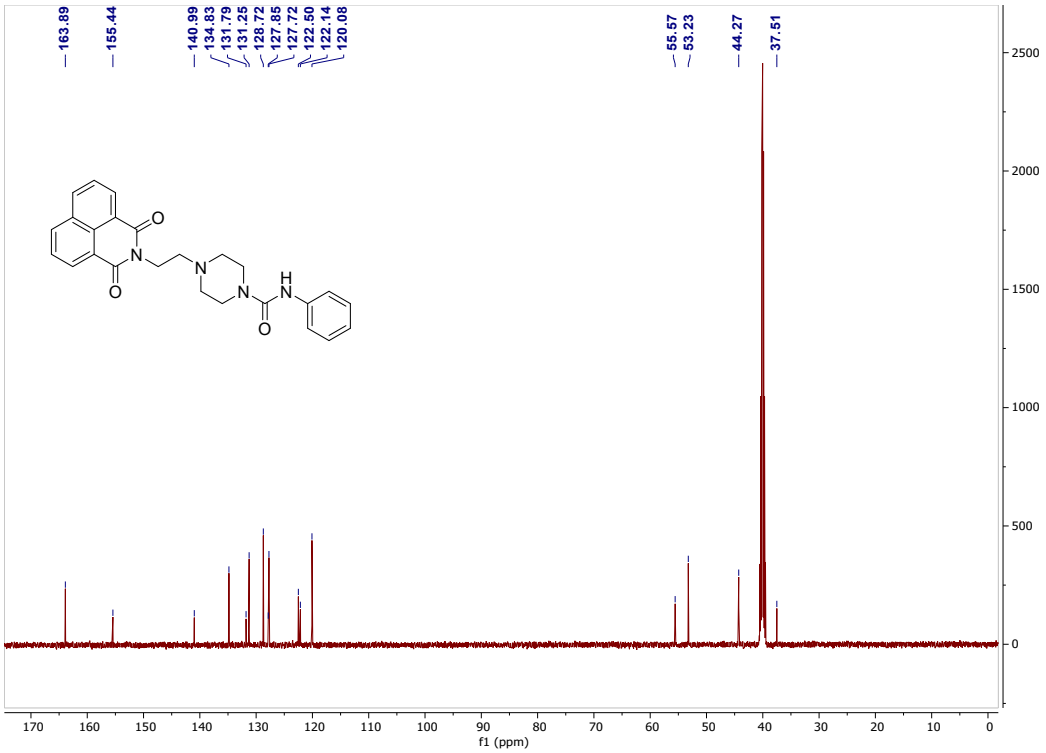


^{13}C spectrum for compound **4p** (125 MHz: DMSO-d_6)

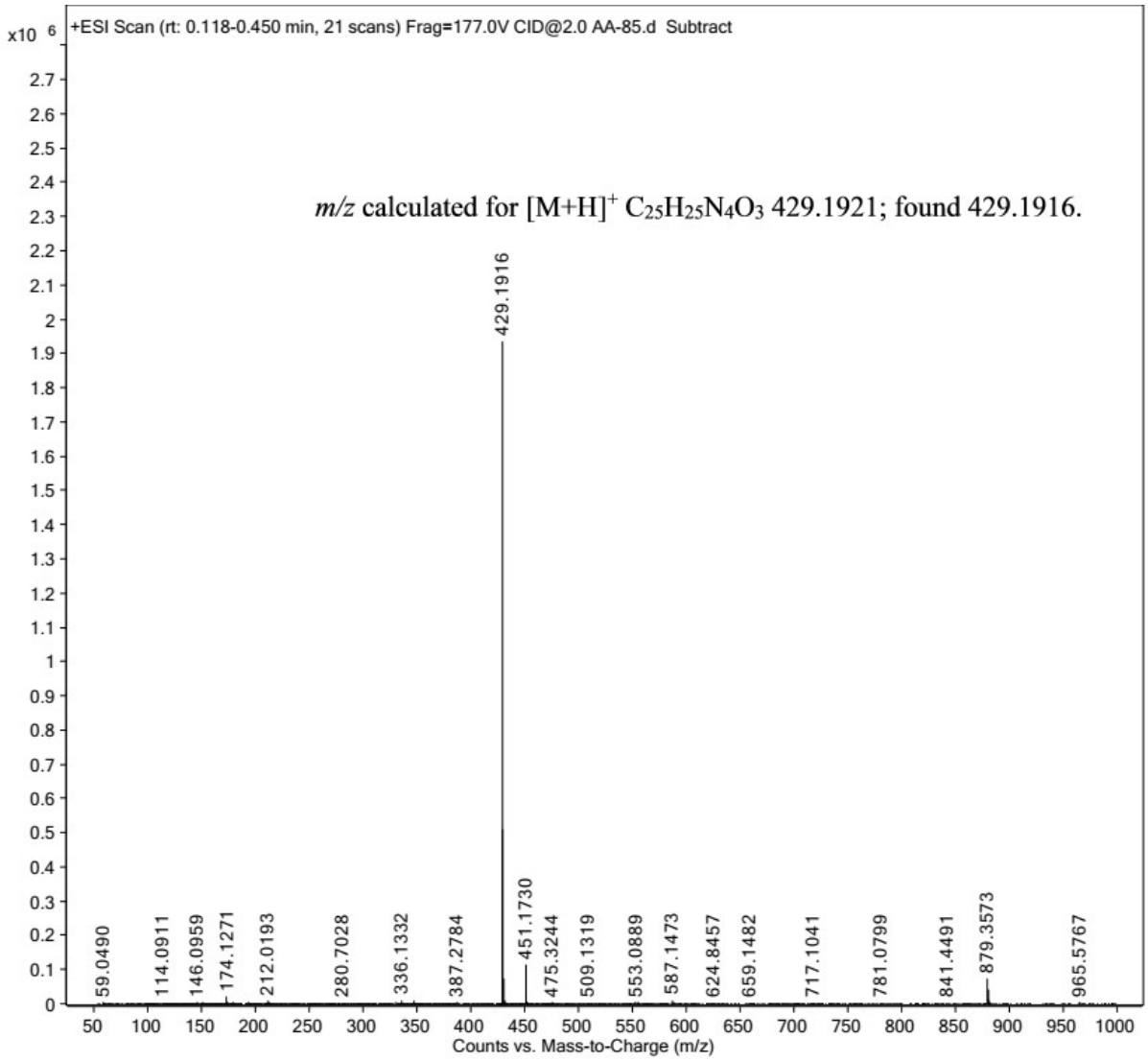

+ESI Scan (rt: 0.116-0.465 min, 22 scans) Frag=177.0V CID@2.0 AA-25.d Subtract
x10 5
m/z calculated for [M+H]+ C24H24N5O2S 446.1645; found 446.1638.
446.1638
503.2466
380.1594
387.2782
402.1414
423.2443
430.1891
459.1538
468.1449
477.1664
485.1999
515.4106
525.2281
537.3931
560.4685
588.5003
604.1193
614.0748
Counts vs. Mass-to-Charge (m/z)

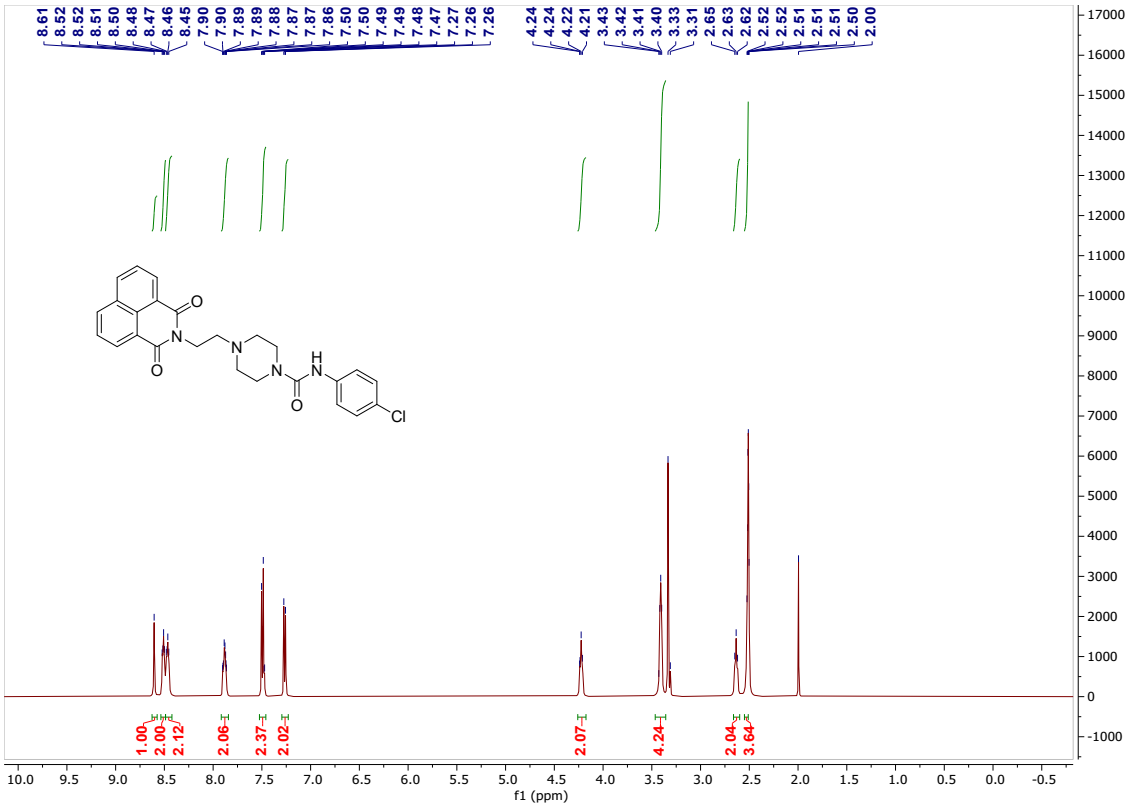


^{1}H spectrum for compound **4q** (500 MHz: DMSO-d_6)

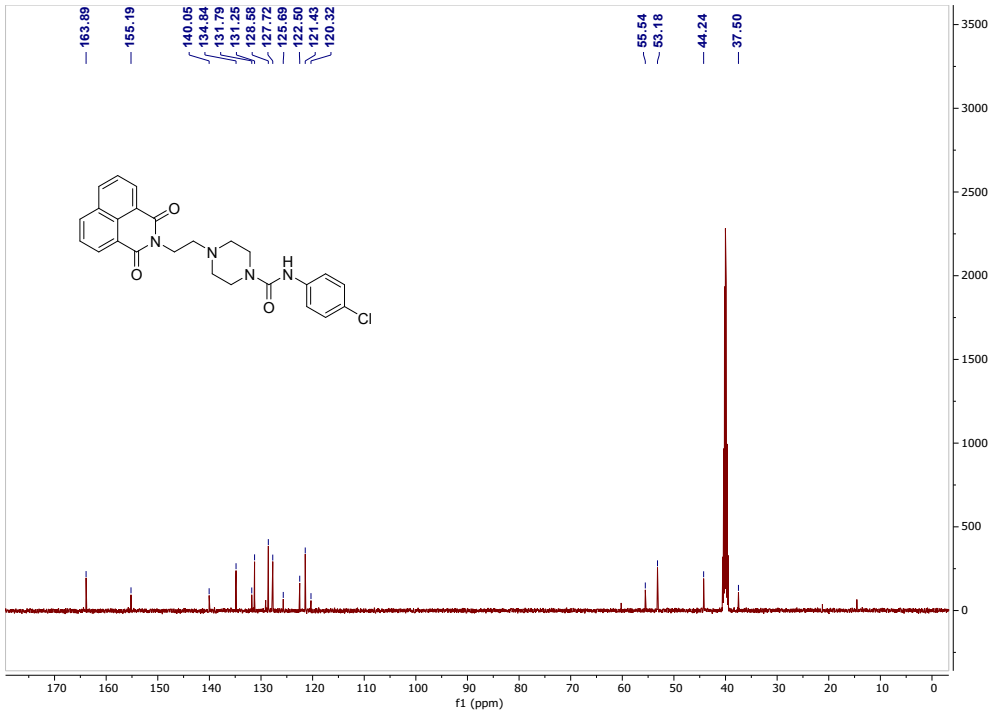


^{13}C spectrum for compound **4q** (125 MHz: DMSO-d_6)

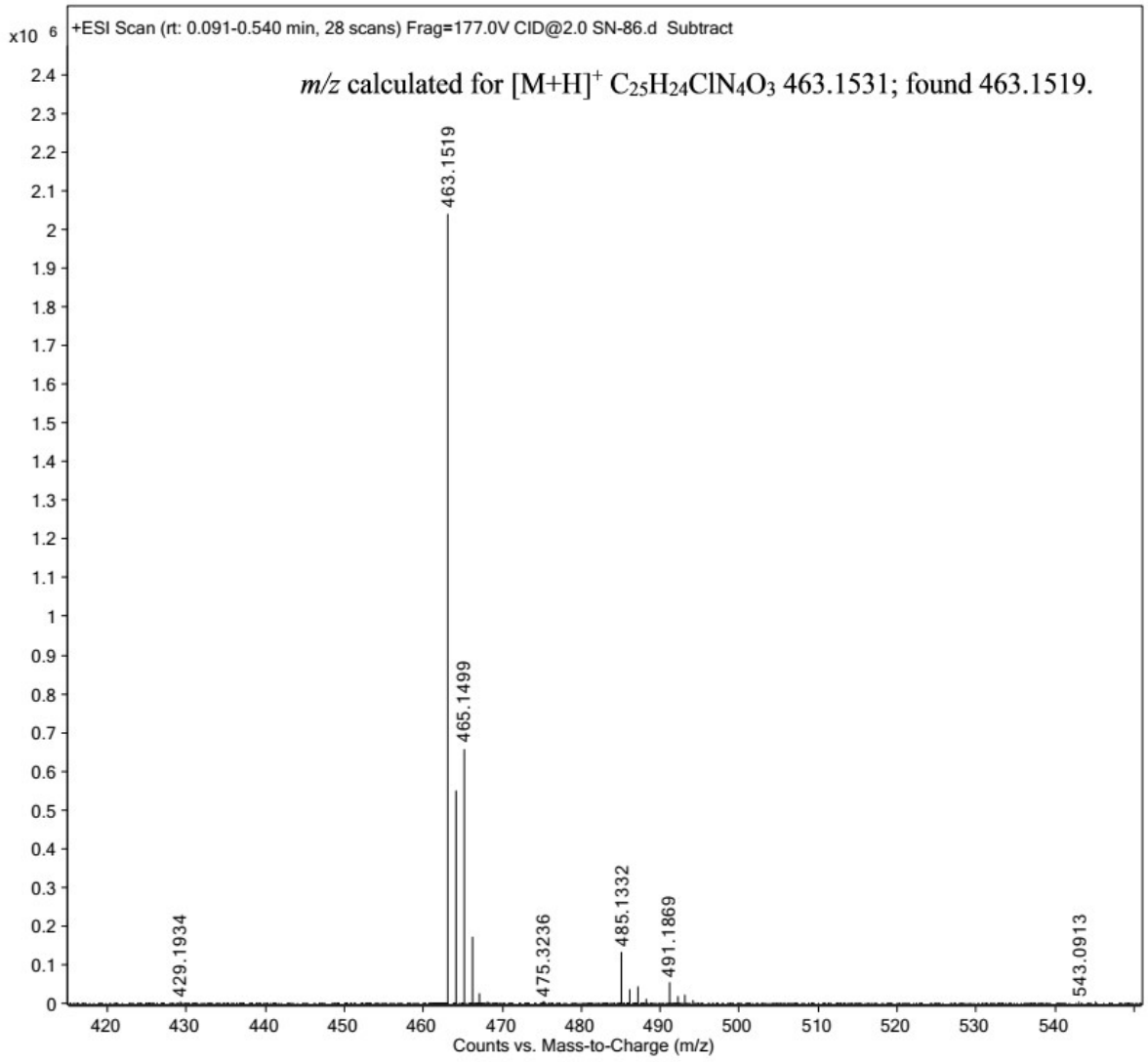

+ESI Scan (rt: 0.118-0.450 min, 21 scans) Frag=177.0V CID@2.0 AA-85.d Subtract
x10 6
m/z calculated for [M+H]+ C25H25N4O3 429.1921; found 429.1916.
429.1916
451.1730
59.0490
114.0911
146.0959
174.1271
212.0193
280.7028
336.1332
387.2784
475.3244
509.1319
553.0889
587.1473
624.8457
659.1482
717.1041
781.0799
841.4491
879.3573
965.5767
Counts vs. Mass-to-Charge (m/z)

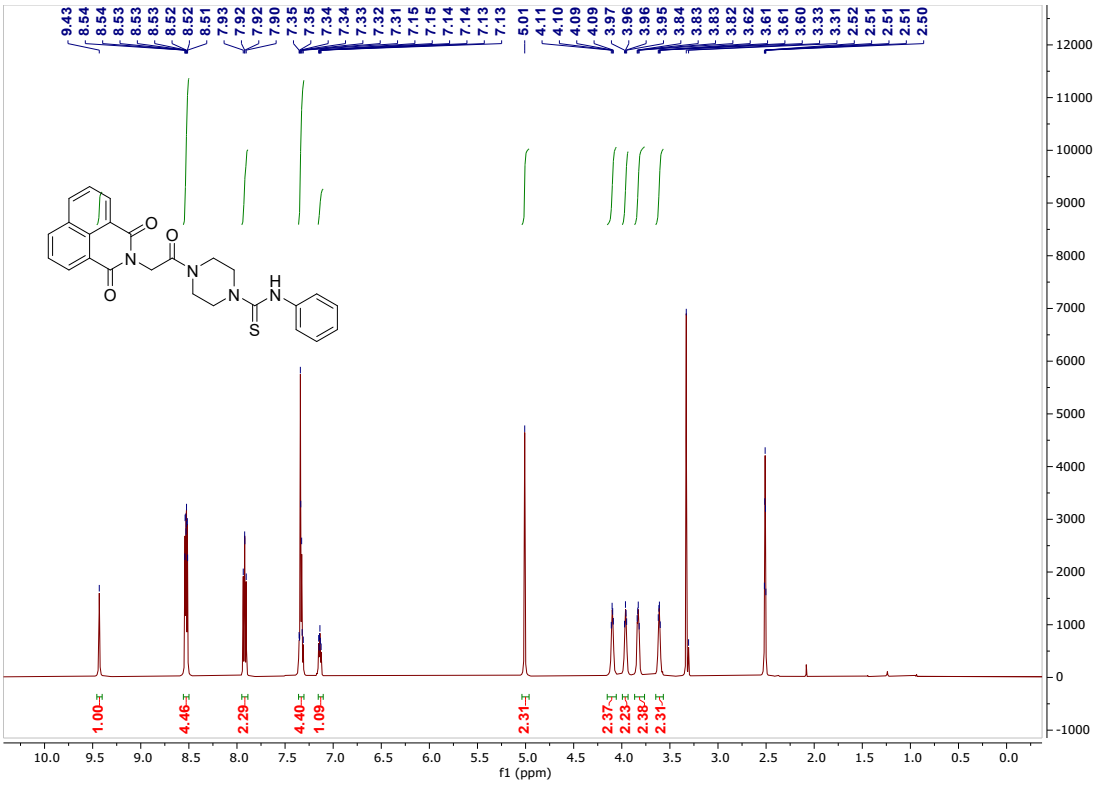


^{1}H spectrum for compound **4r** (500 MHz: DMSO-d_6)

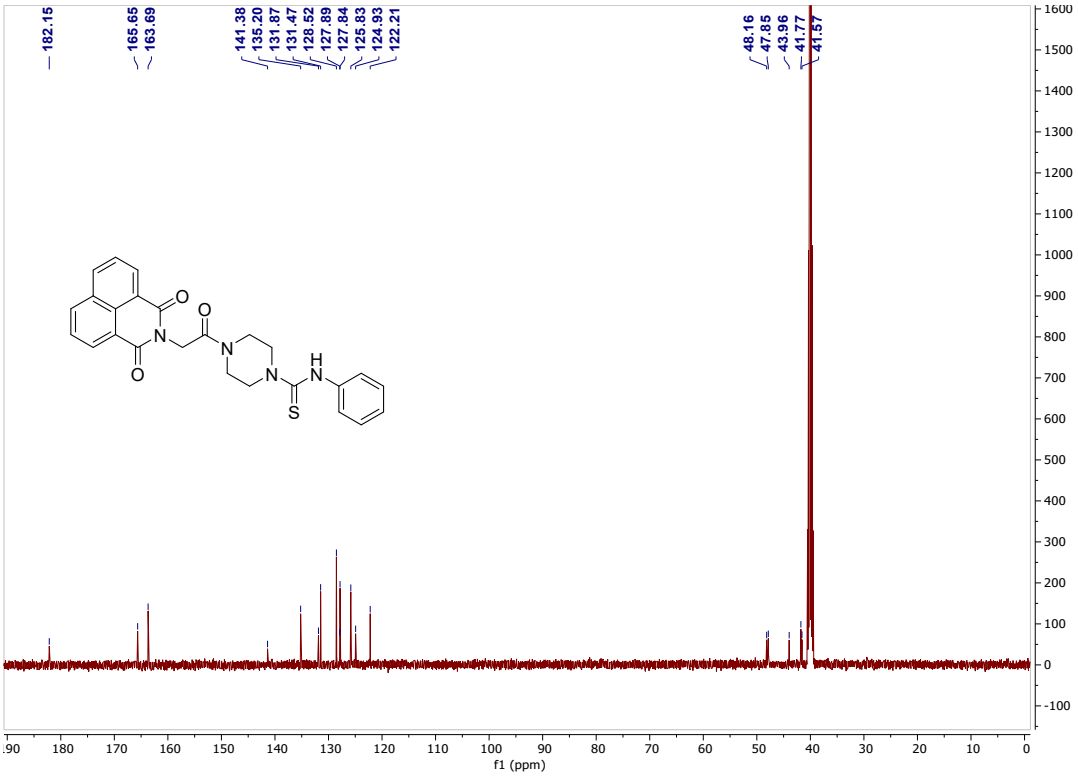


^{13}C spectrum for compound **4r** (125 MHz: DMSO-d_6)

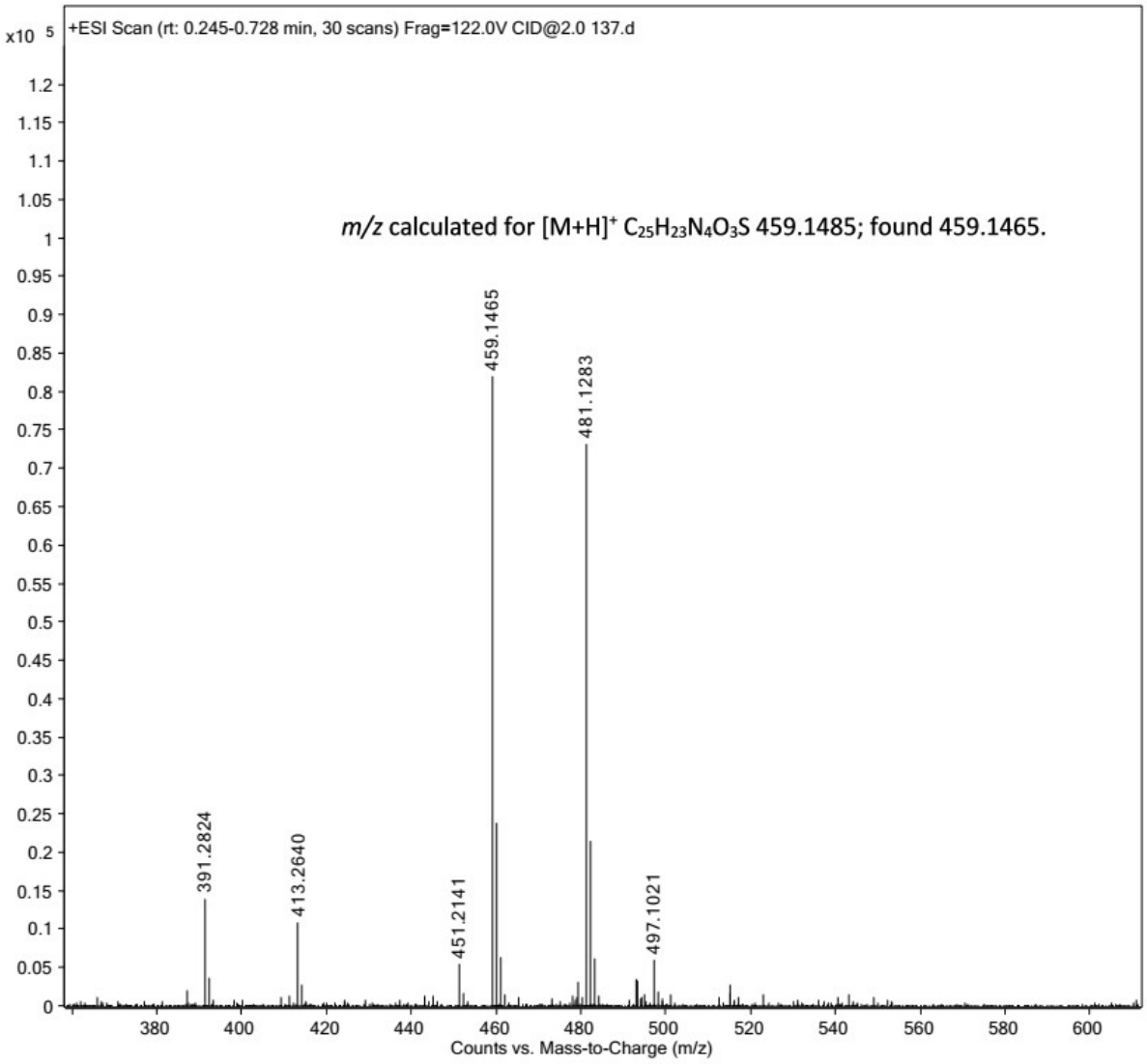

+ESI Scan (rt: 0.091-0.540 min, 28 scans) Frag=177.0V CID@2.0 SN-86.d Subtract
x10 6
m/z calculated for [M+H]+ C25H24ClN4O3 463.1531; found 463.1519.
463.1519
465.1499
429.1934
475.3236
485.1332
491.1869
543.0913
Counts vs. Mass-to-Charge (m/z)

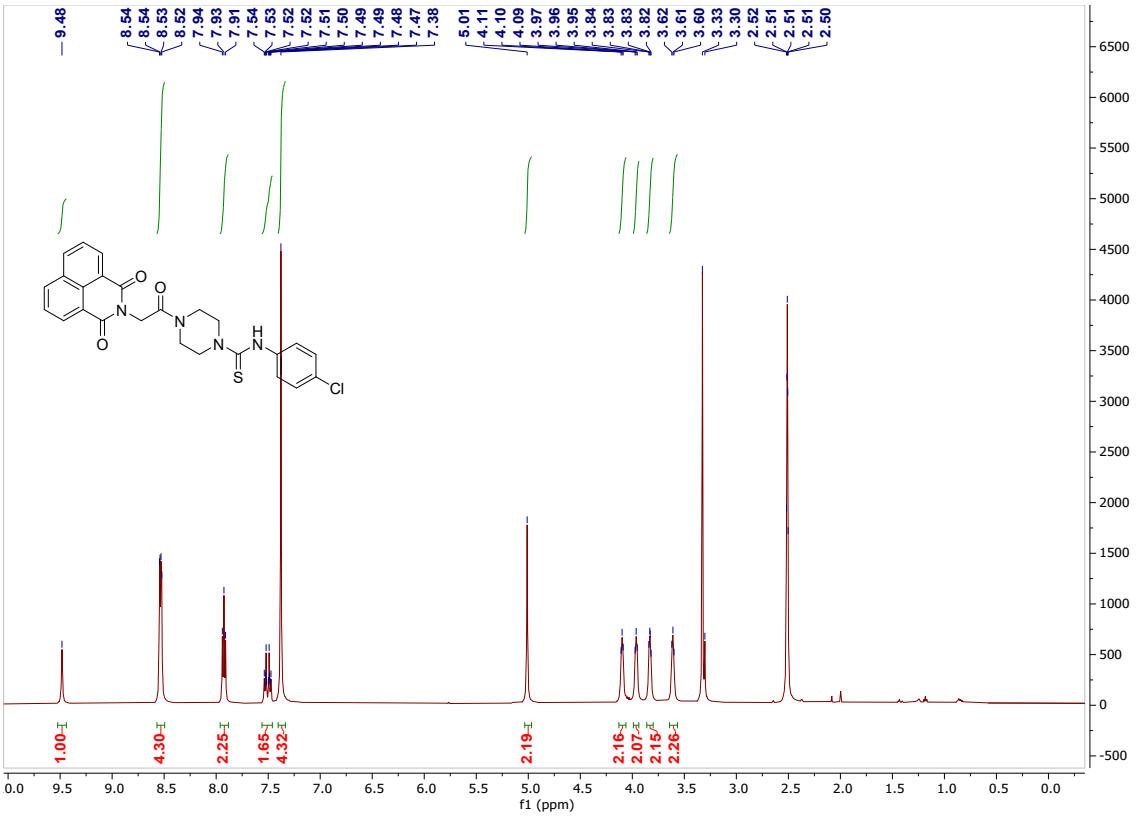


^{1}H spectrum for compound **9a** (500 MHz: DMSO-d_6)

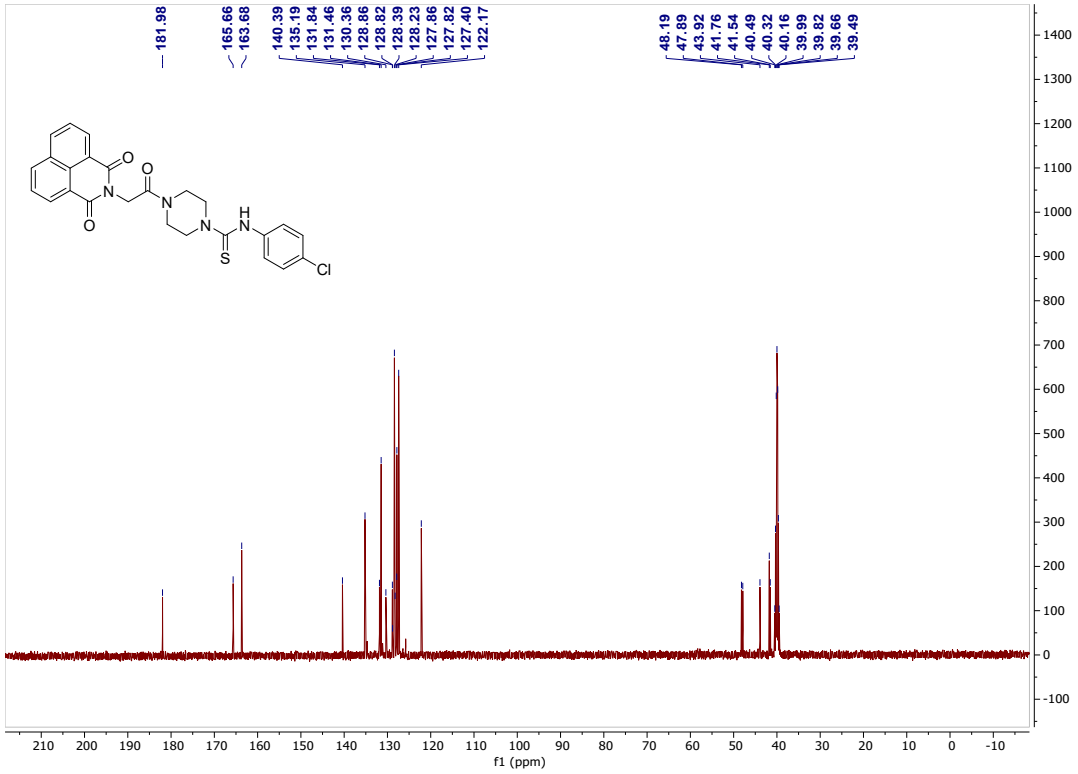


^{13}C spectrum for compound **9a** (125 MHz: DMSO-d_6)

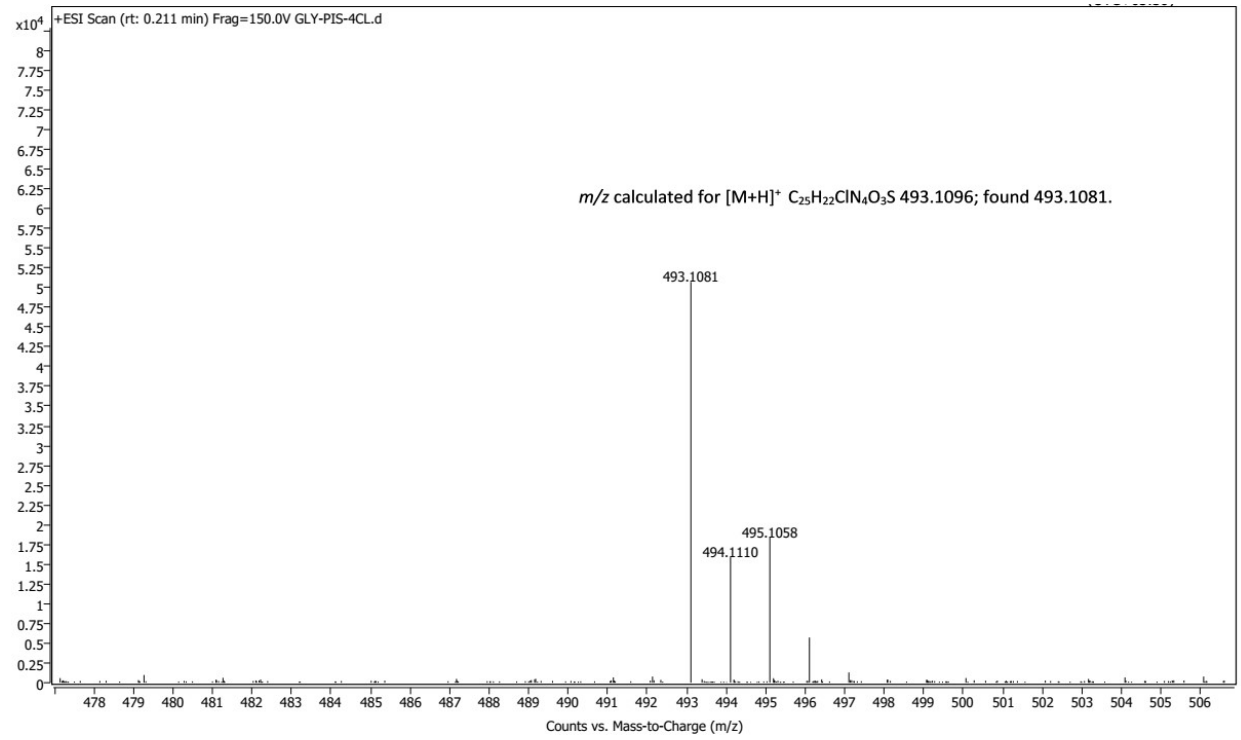

+ESI Scan (rt: 0.245-0.728 min, 30 scans) Frag=122.0V CID@2.0 137.d
x10 5
m/z calculated for [M+H]+ C25H23N4O3S 459.1485; found 459.1465.
459.1465
481.1283
391.2824
413.2640
451.2141
497.1021
Counts vs. Mass-to-Charge (m/z)

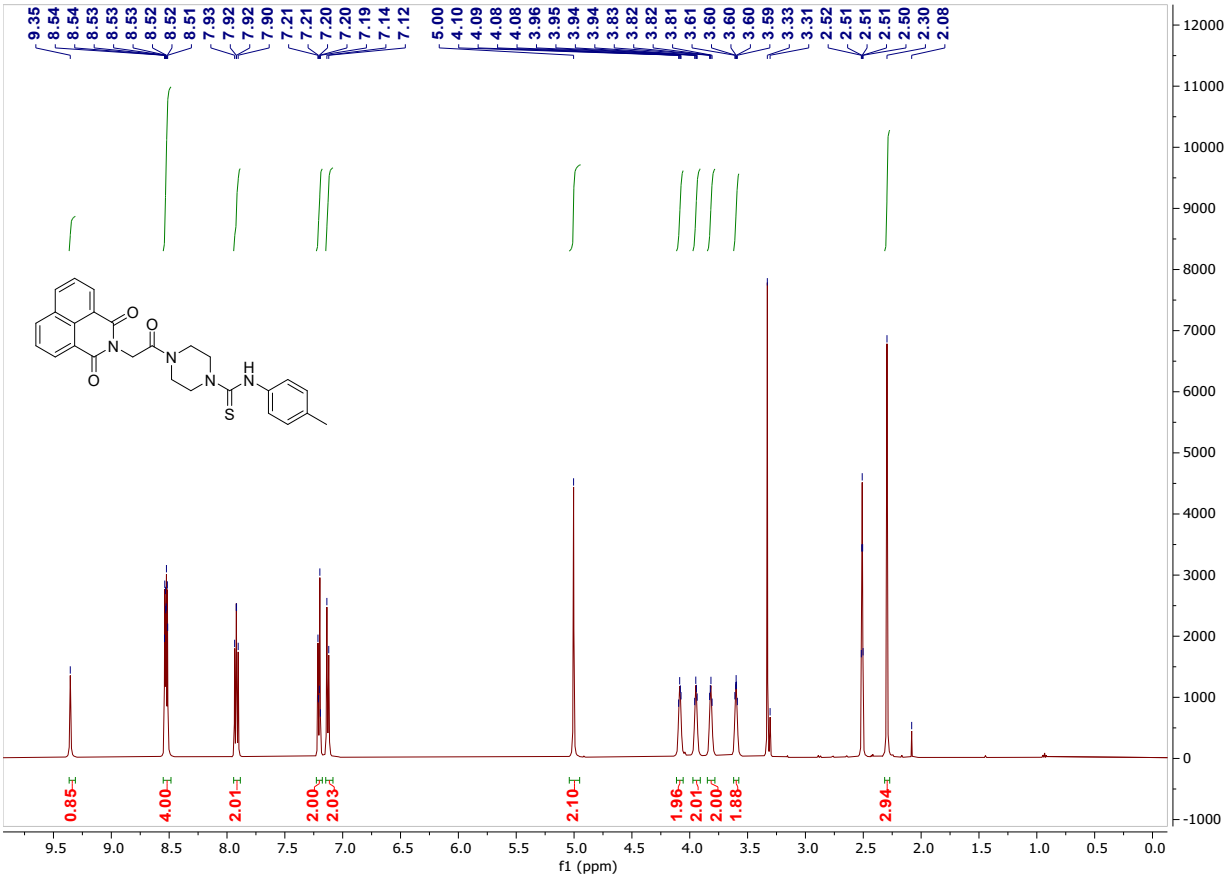


^{1}H spectrum for compound **9b** (500 MHz: DMSO-d_6)

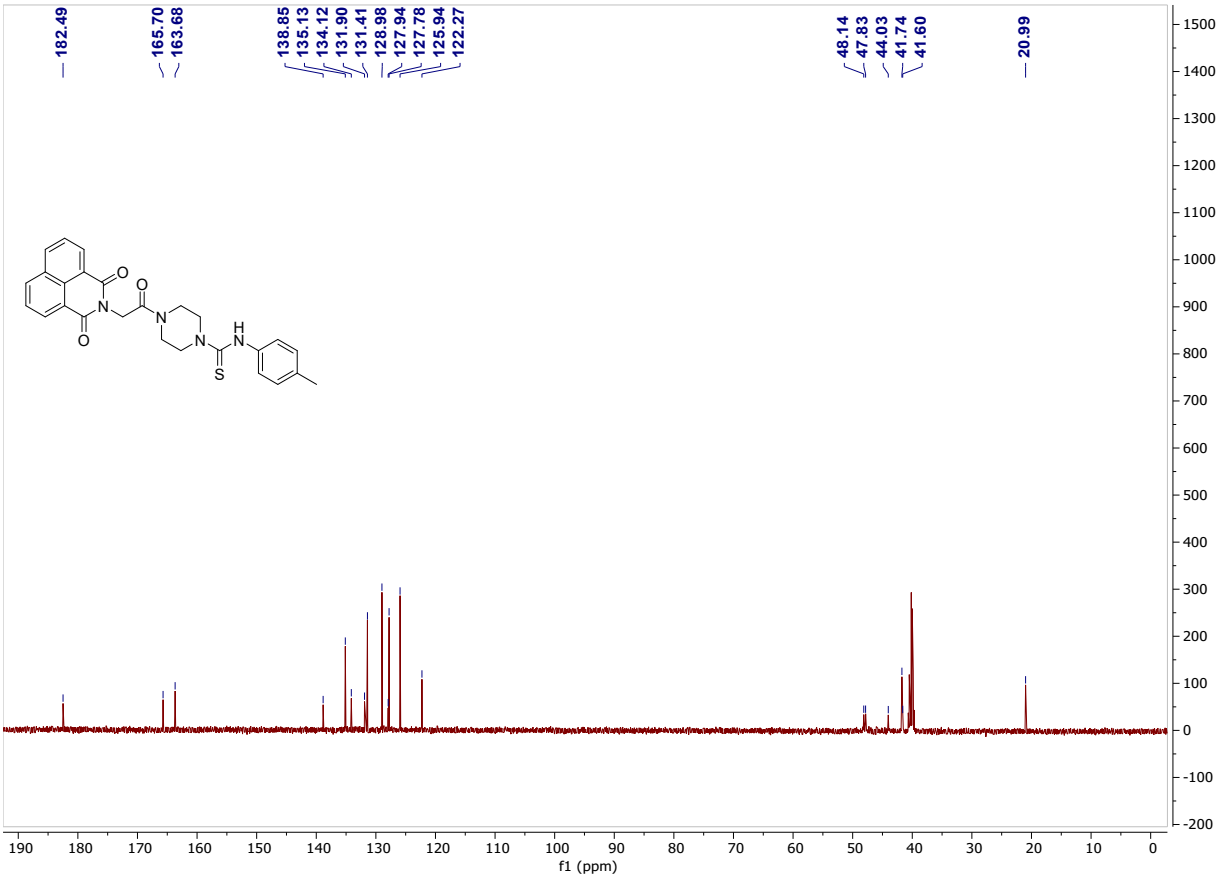


^{13}C spectrum for compound **9b** (125 MHz: DMSO-d_6)

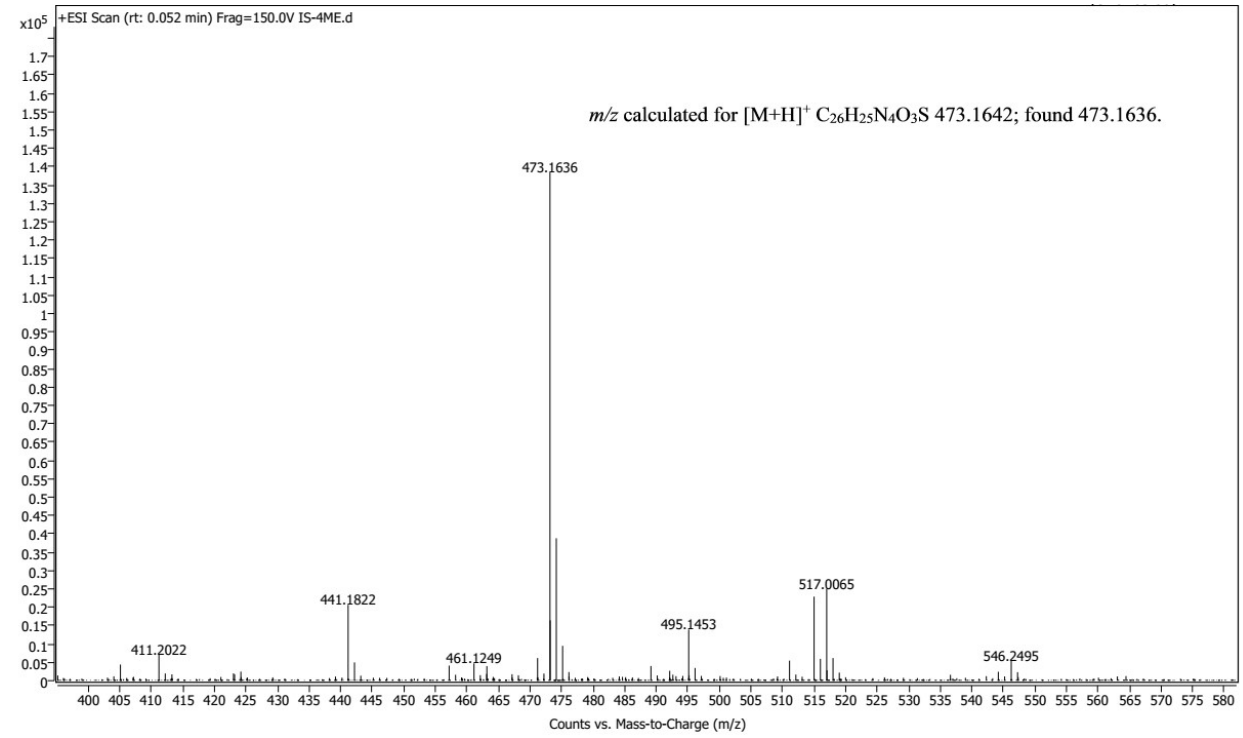


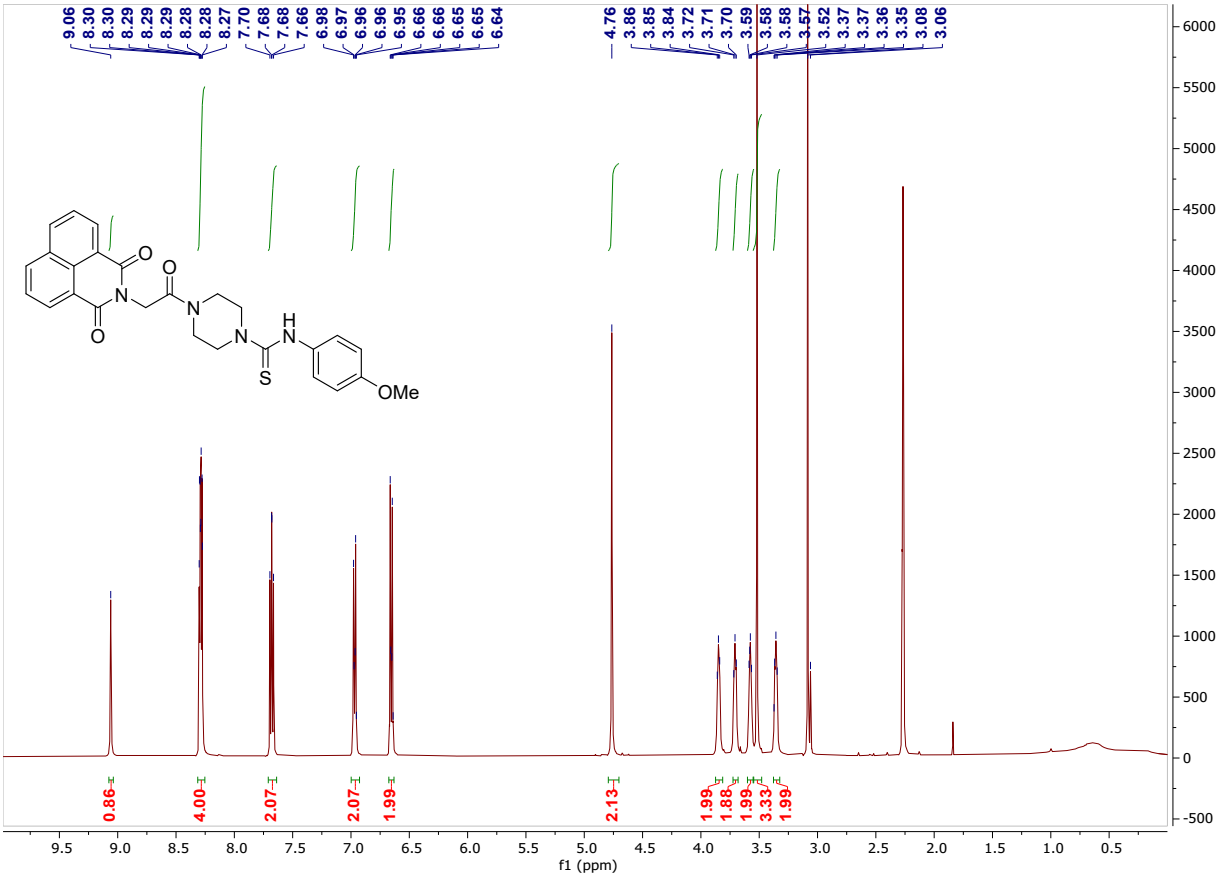


^{1}H spectrum for compound **9c** (500 MHz: DMSO-d_6)

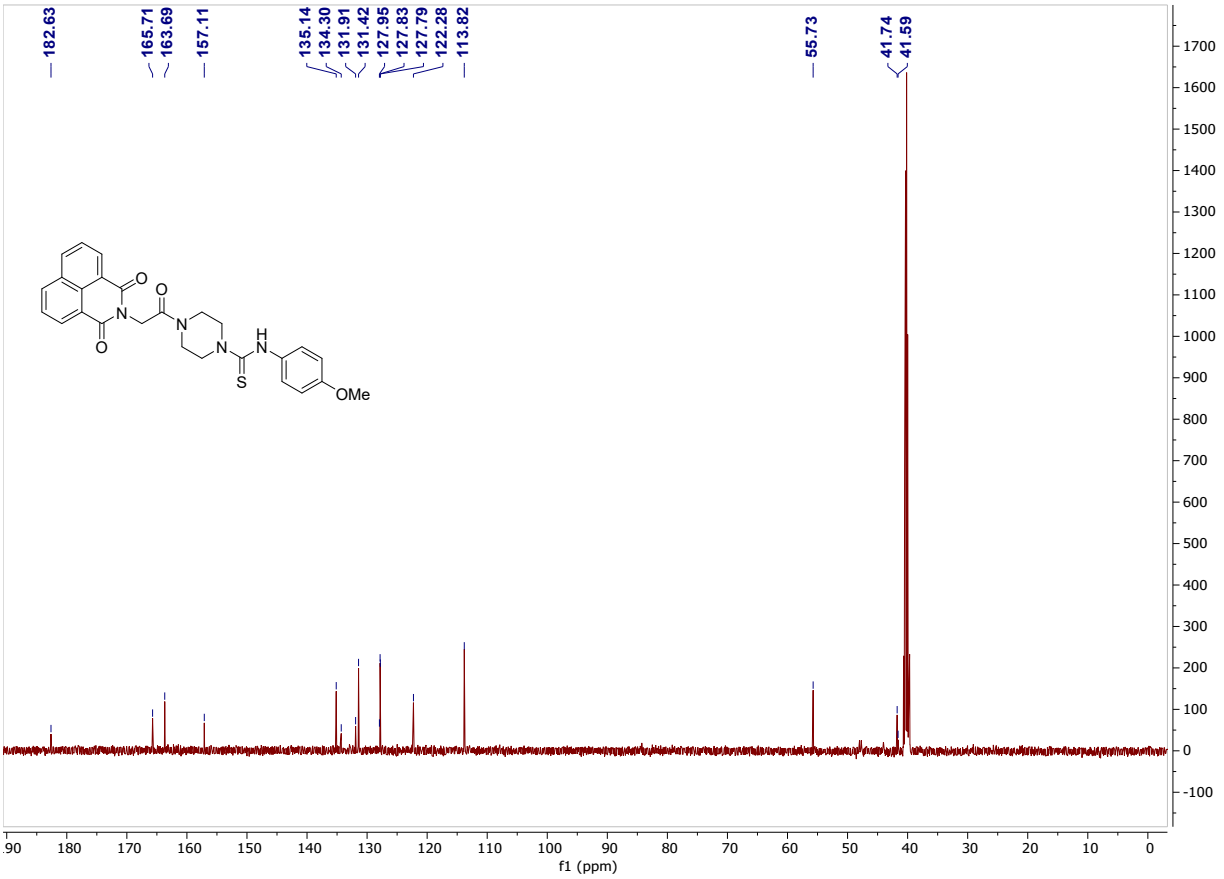


^{13}C spectrum for compound **9c** (125 MHz: DMSO-d_6)

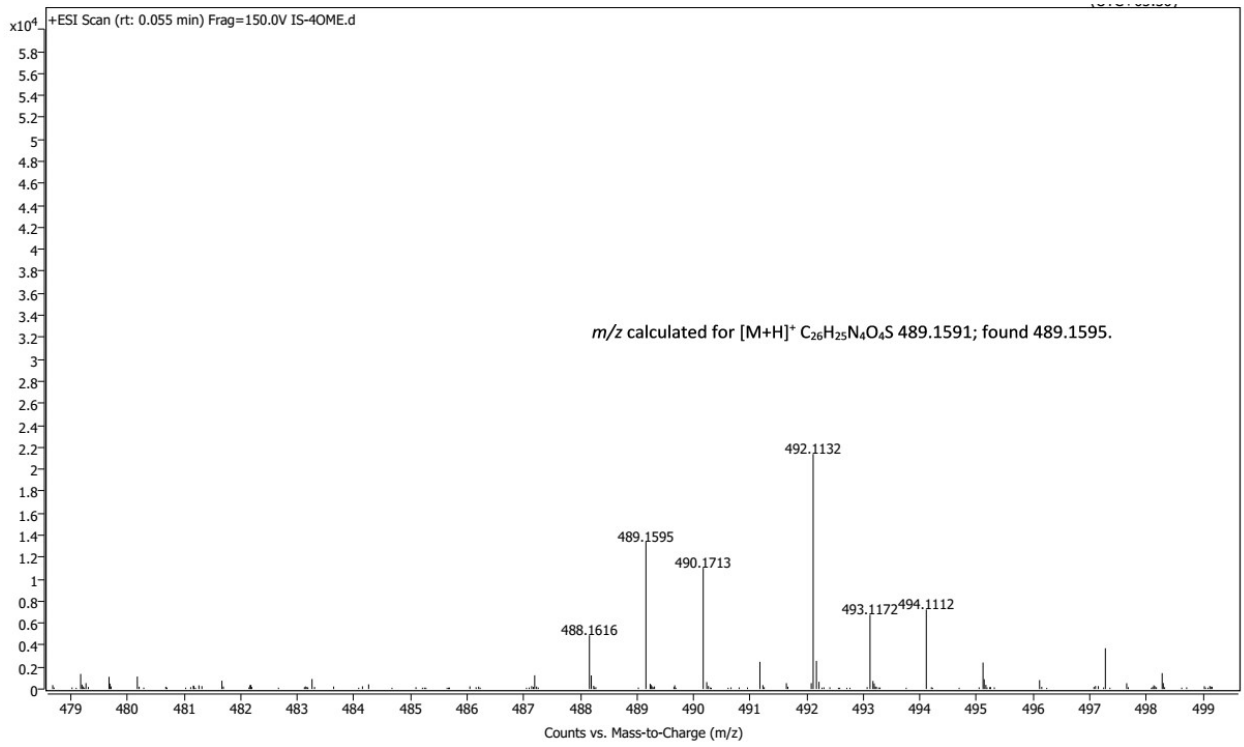


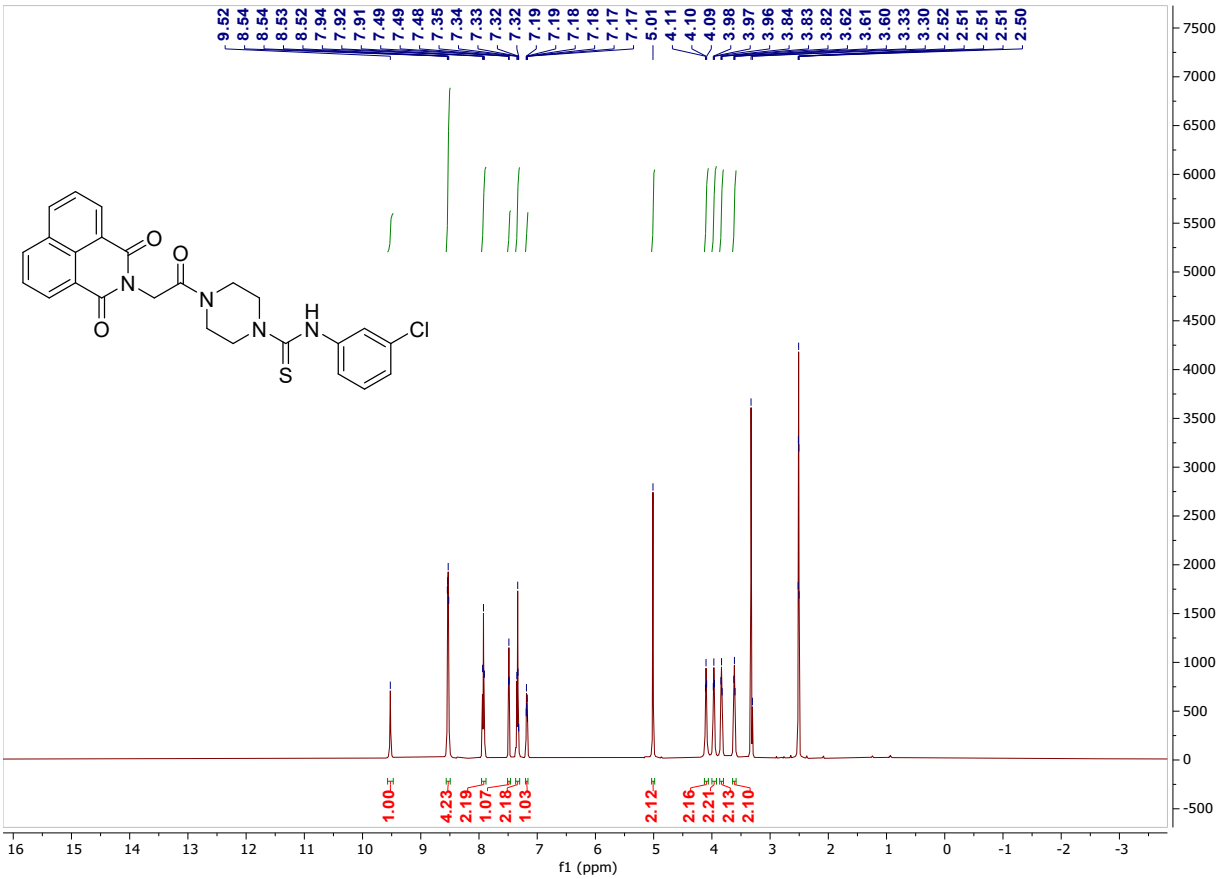


^{1}H spectrum for compound **9d** (500 MHz: DMSO-d_6)

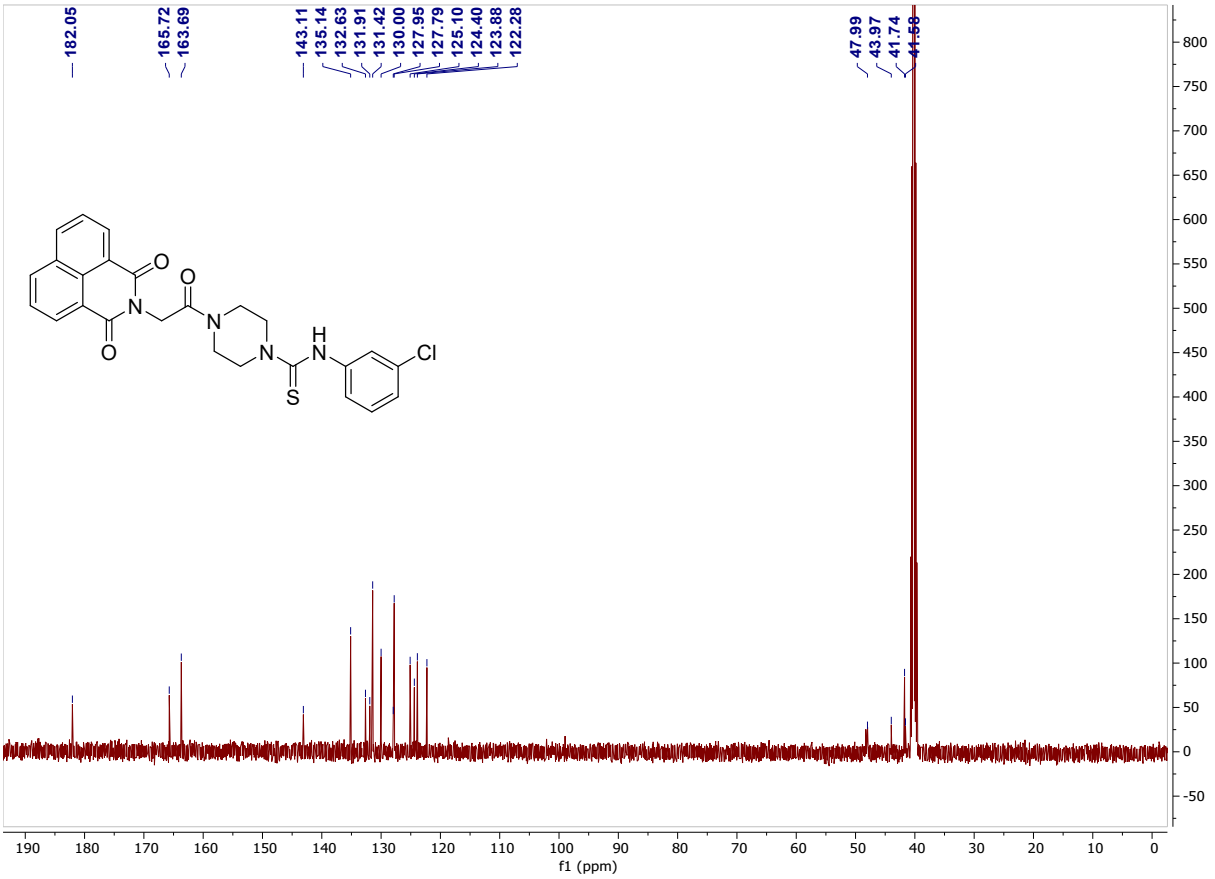


^{13}C spectrum for compound **9d** (125 MHz: DMSO-d_6)

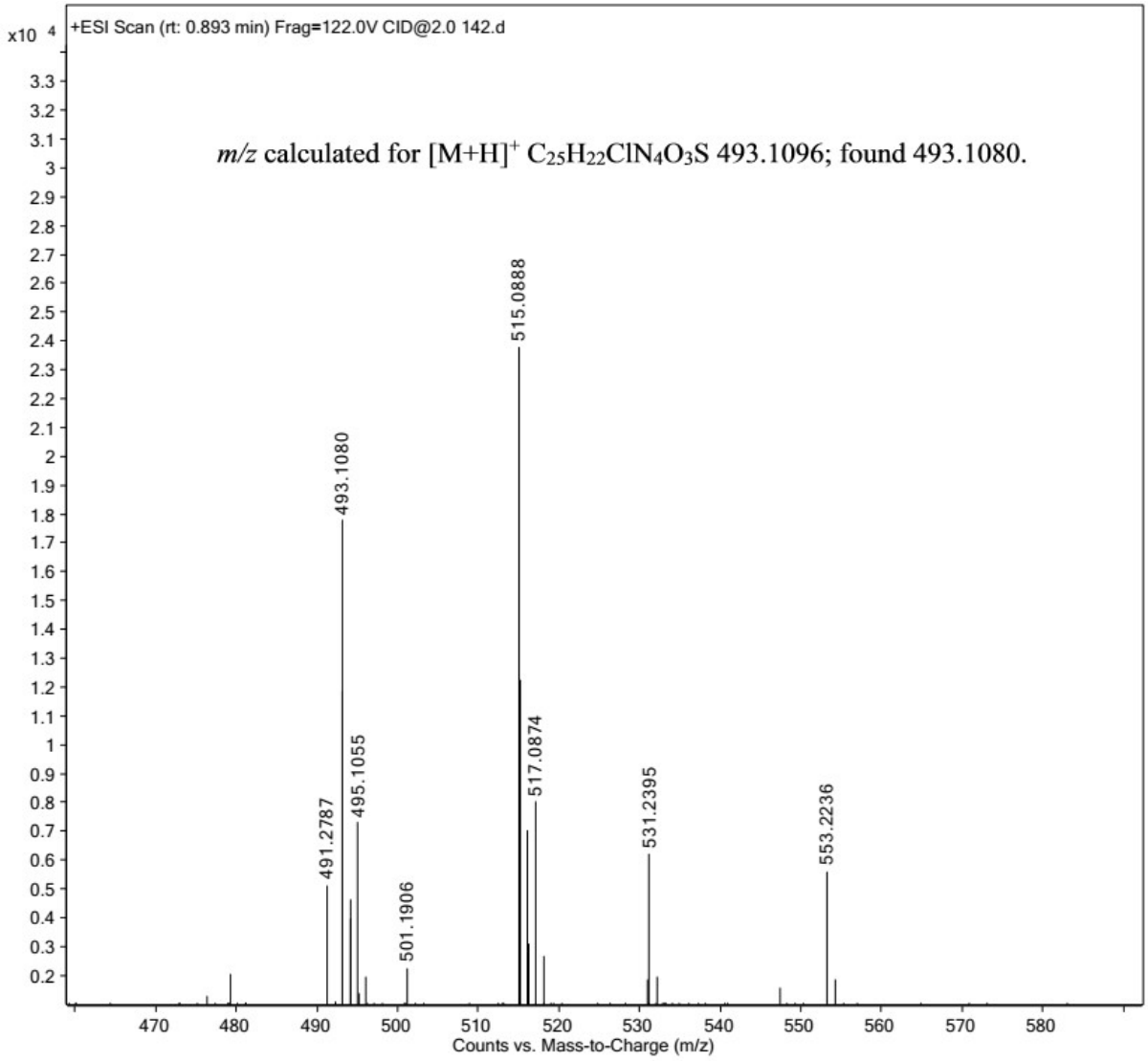


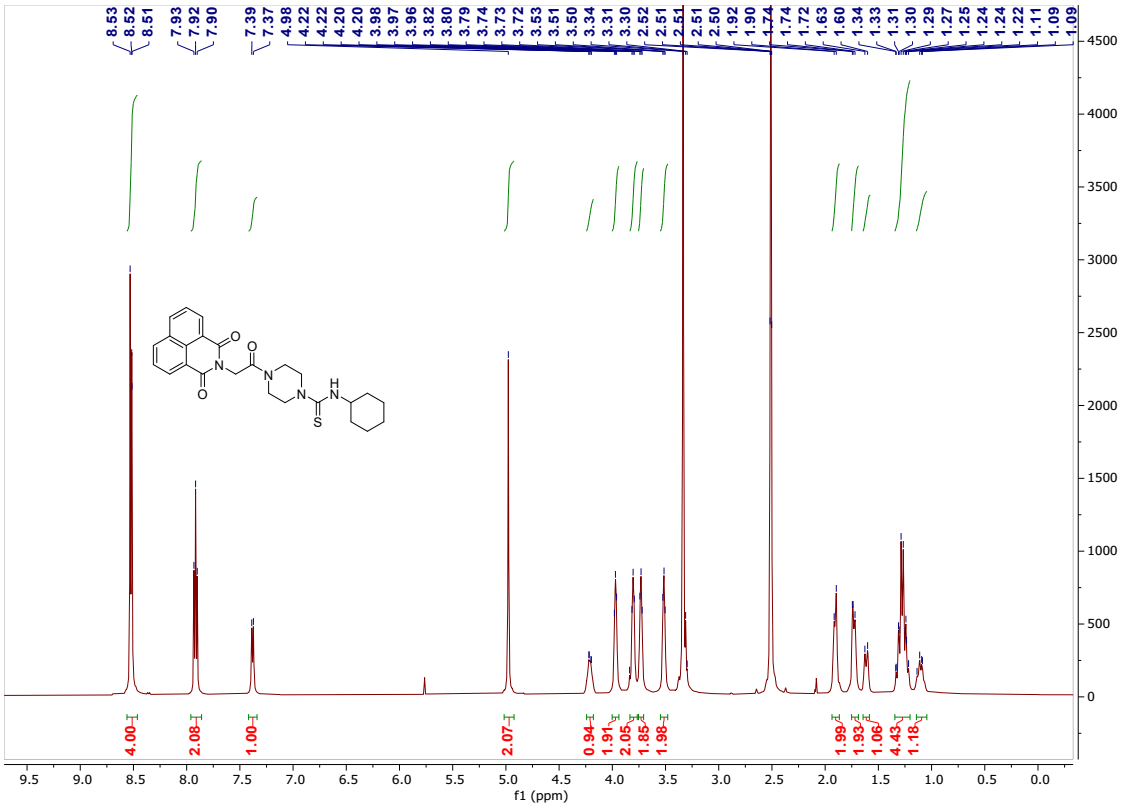


^{1}H spectrum for compound **9e** (500 MHz: DMSO-d_6)

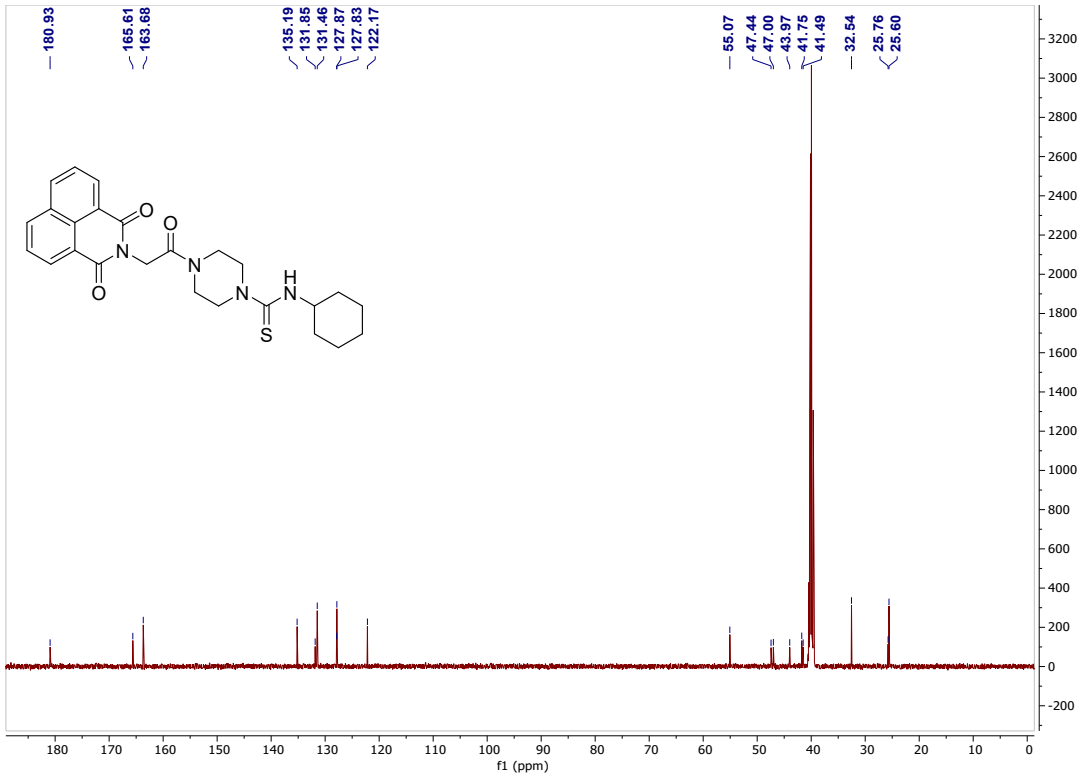


^{13}C spectrum for compound **9e** (125 MHz: DMSO-d_6)

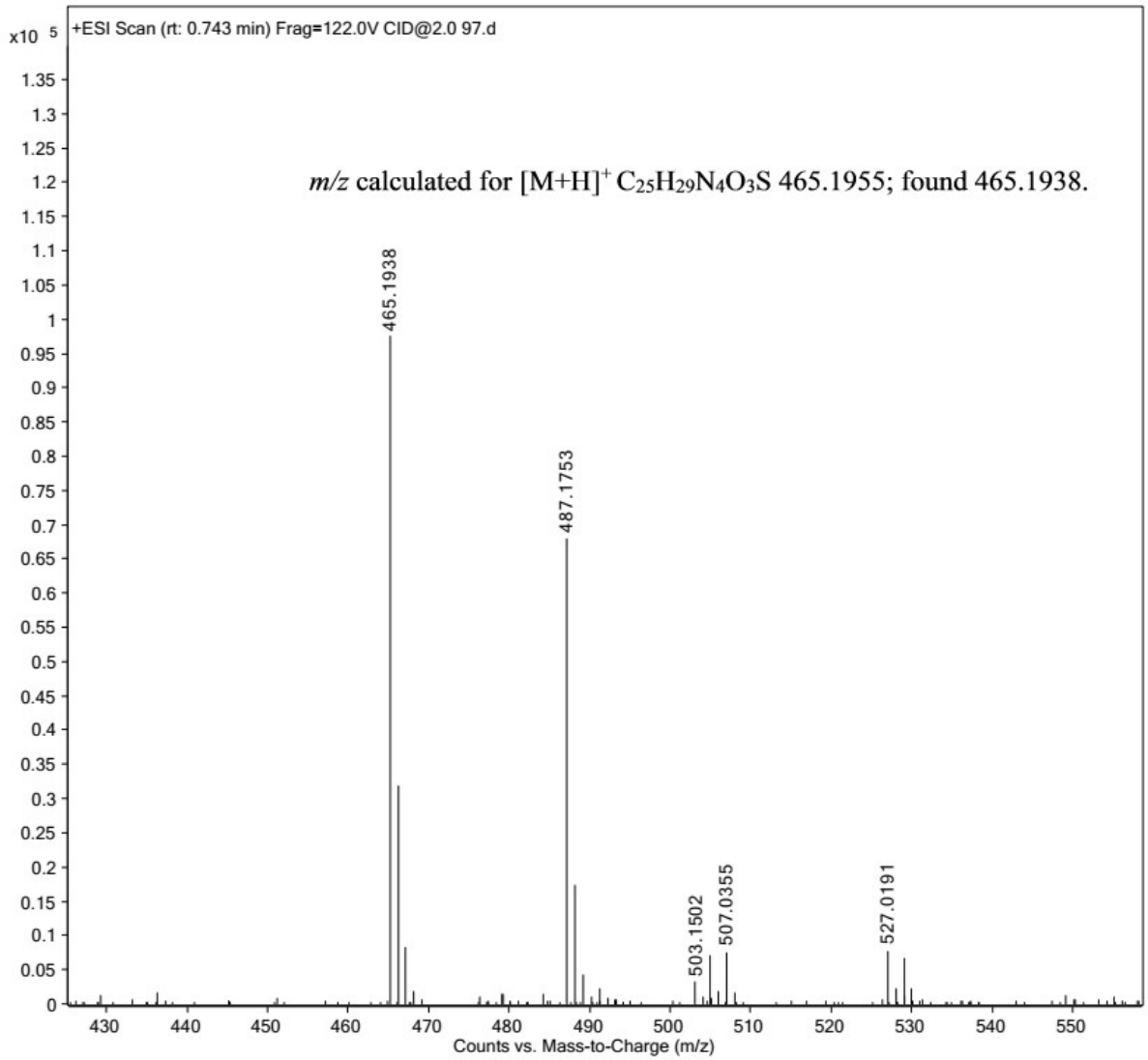

+ESI Scan (rt: 0.893 min) Frag=122.0V CID@2.0 142.d
x10 4
m/z calculated for [M+H]+ C25H22ClN4O3S 493.1096; found 493.1080.
515.0888
493.1080
517.0874
495.1055
491.2787
531.2395
553.2236
501.1906
Counts vs. Mass-to-Charge (m/z)

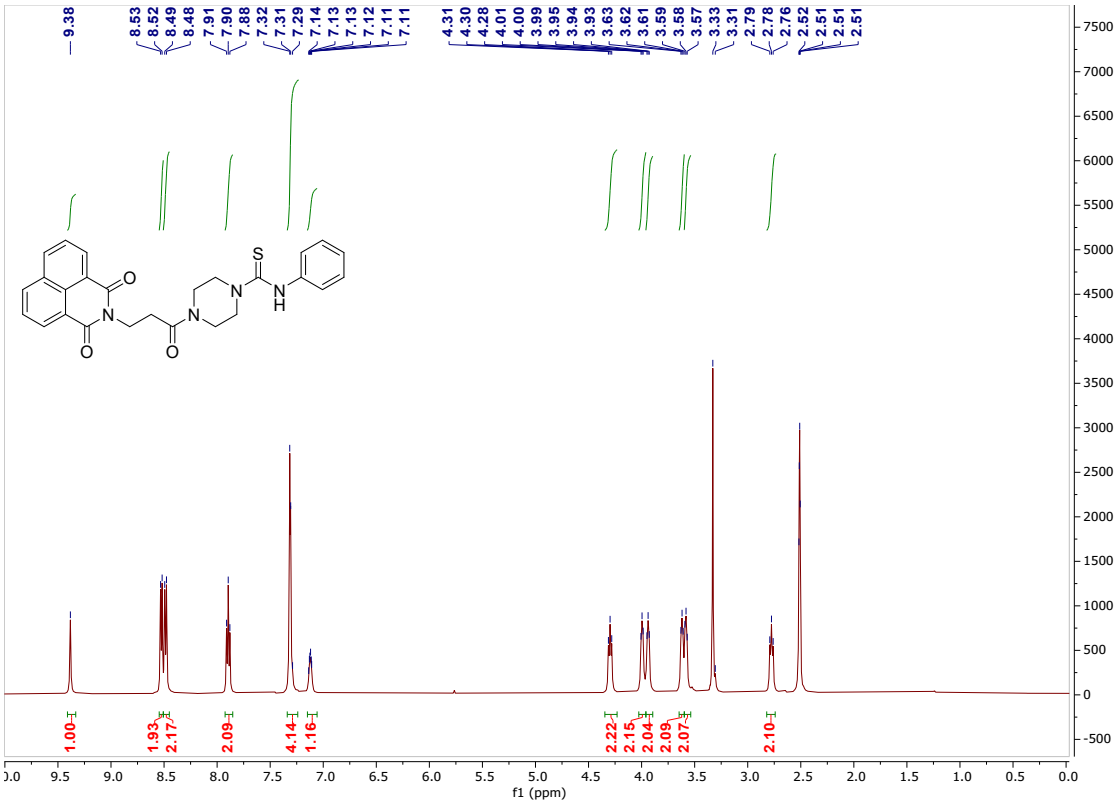


^{1}H spectrum for compound **9f** (500 MHz: DMSO-d_6)

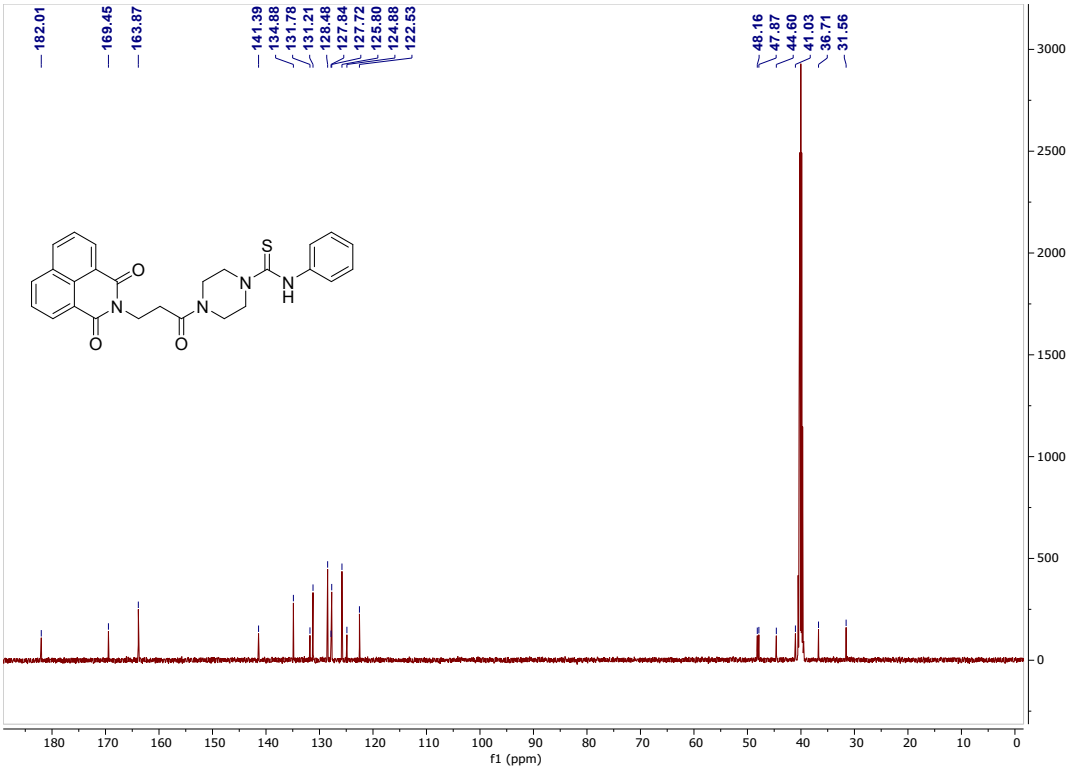


^{13}C spectrum for compound **9f** (125 MHz: DMSO-d_6)

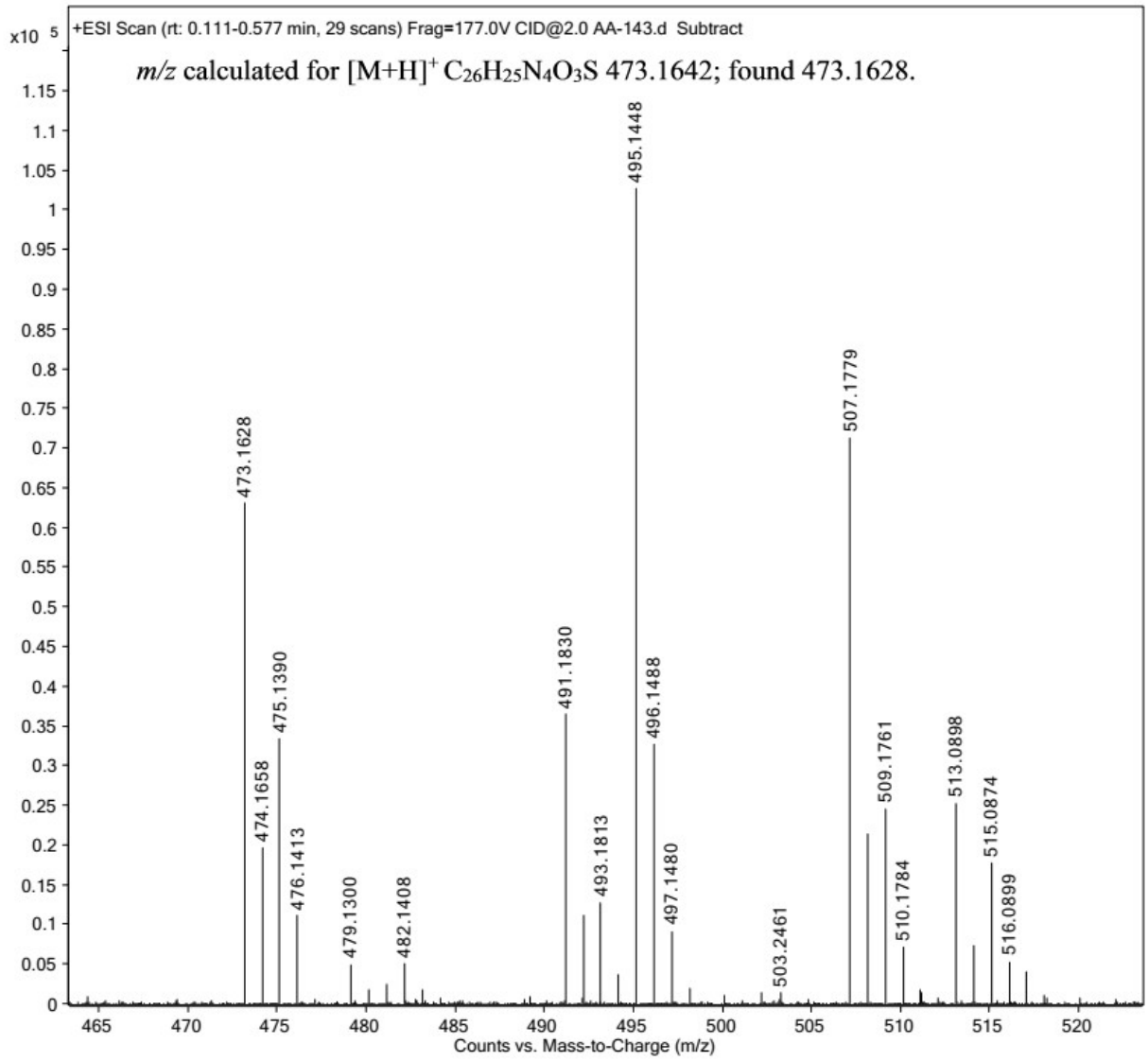

+ESI Scan (rt: 0.743 min) Frag=122.0V CID@2.0 97.d
x10 5
m/z calculated for [M+H]+ C25H29N4O3S 465.1955; found 465.1938.
465.1938
487.1753
503.1502
507.0355
527.0191
Counts vs. Mass-to-Charge (m/z)

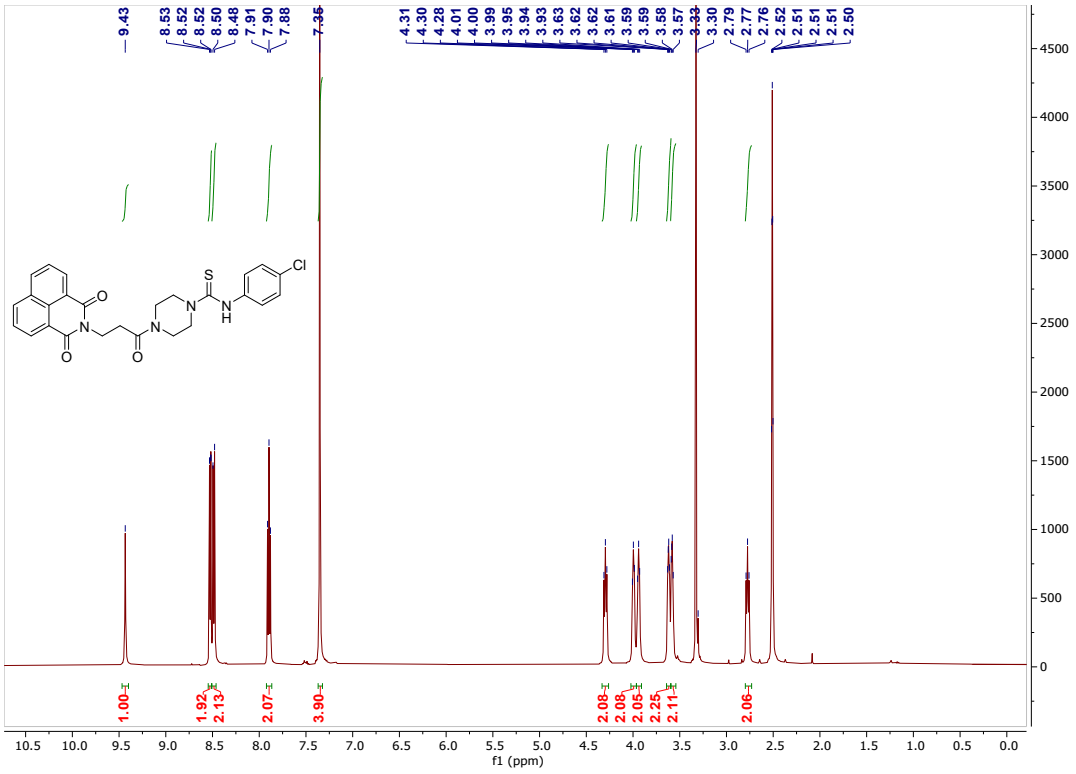


^{1}H spectrum for compound **9g** (500 MHz: DMSO-d_6)

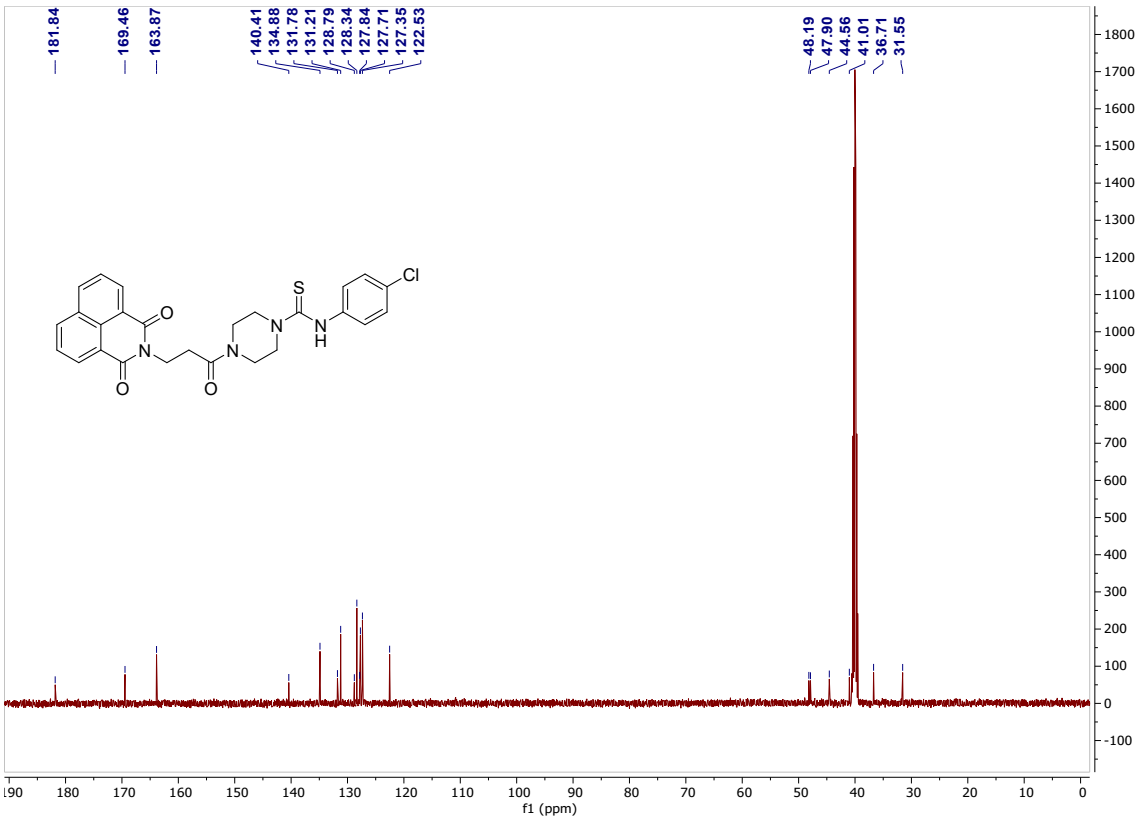


^{13}C spectrum for compound **9g** (125 MHz: DMSO-d_6)

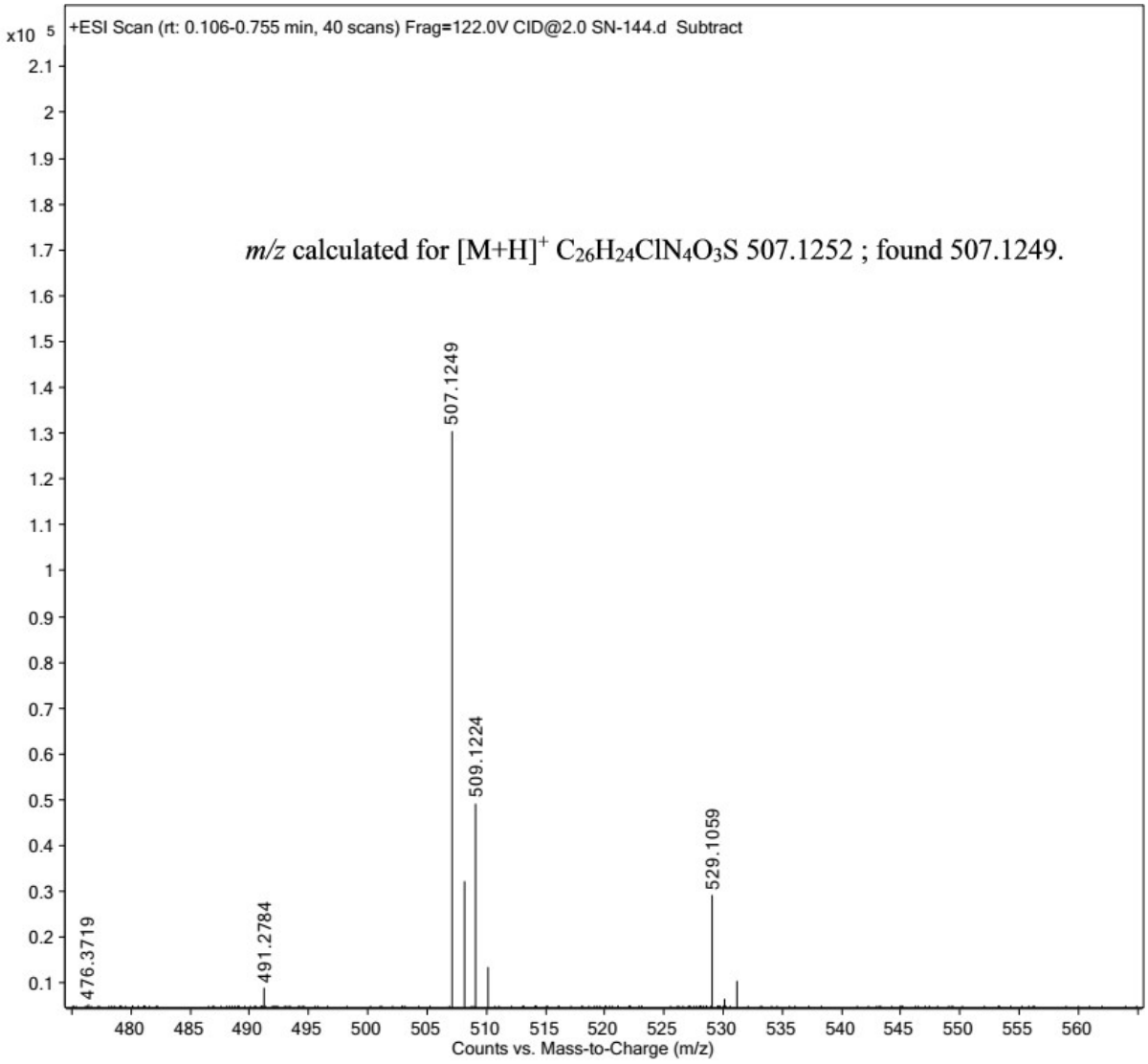

+ESI Scan (rt: 0.111-0.577 min, 29 scans) Frag=177.0V CID@2.0 AA-143.d Subtract
x10 5
m/z calculated for [M+H]+ C26H25N4O3S 473.1642; found 473.1628.
473.1628
474.1658
475.1390
476.1413
479.1300
482.1408
491.1830
493.1813
495.1448
496.1488
497.1480
503.2461
507.1779
509.1761
510.1784
513.0898
515.0874
516.0899
Counts vs. Mass-to-Charge (m/z)

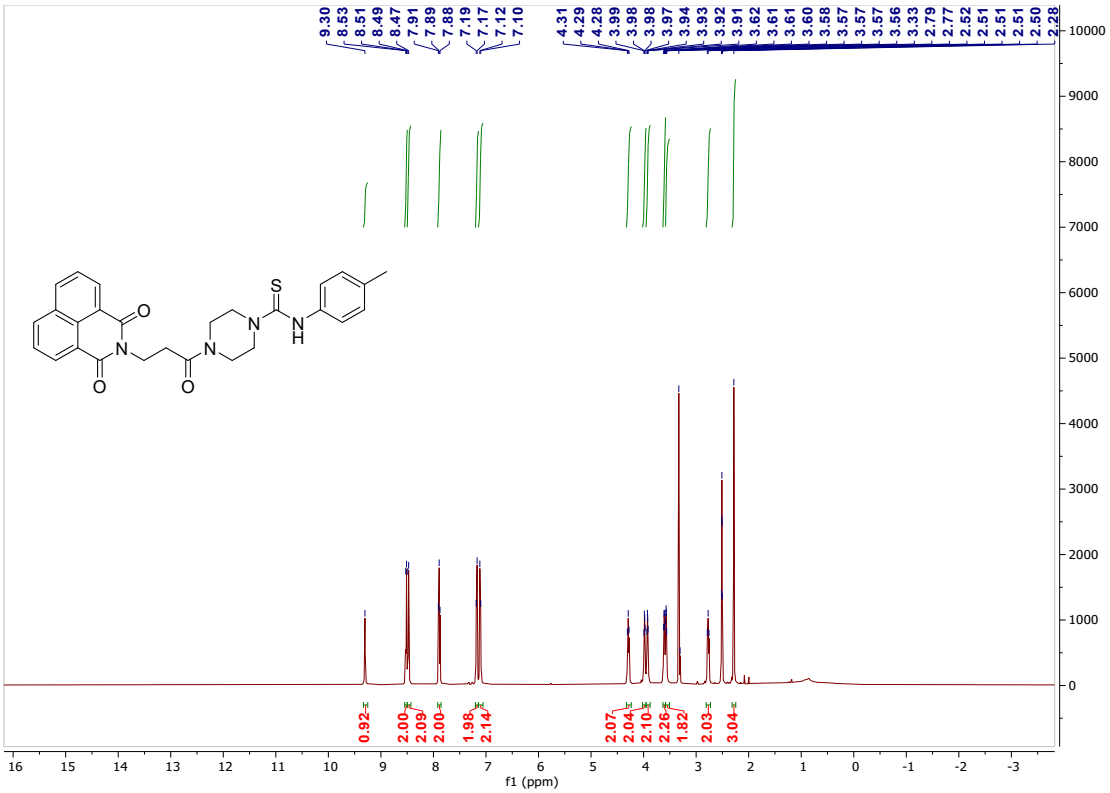


^{1}H spectrum for compound **9h** (500 MHz: DMSO-d_6)

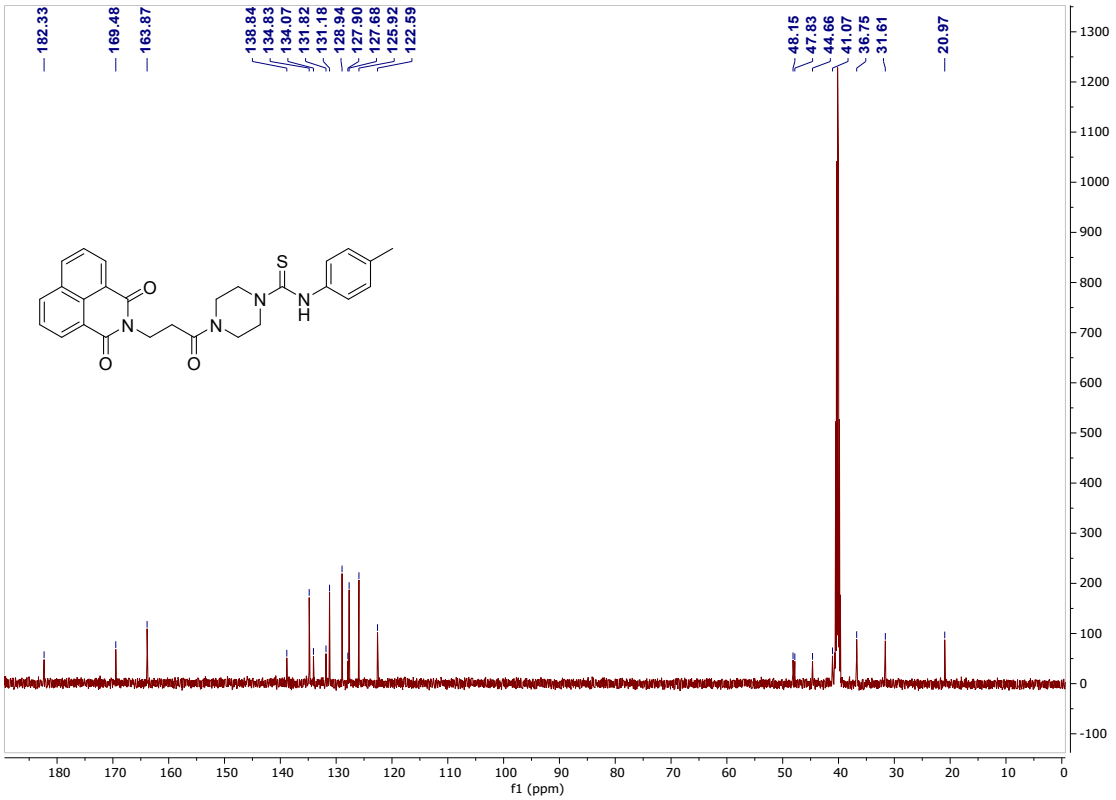


^{13}C spectrum for compound **9h** (125 MHz: DMSO-d_6)

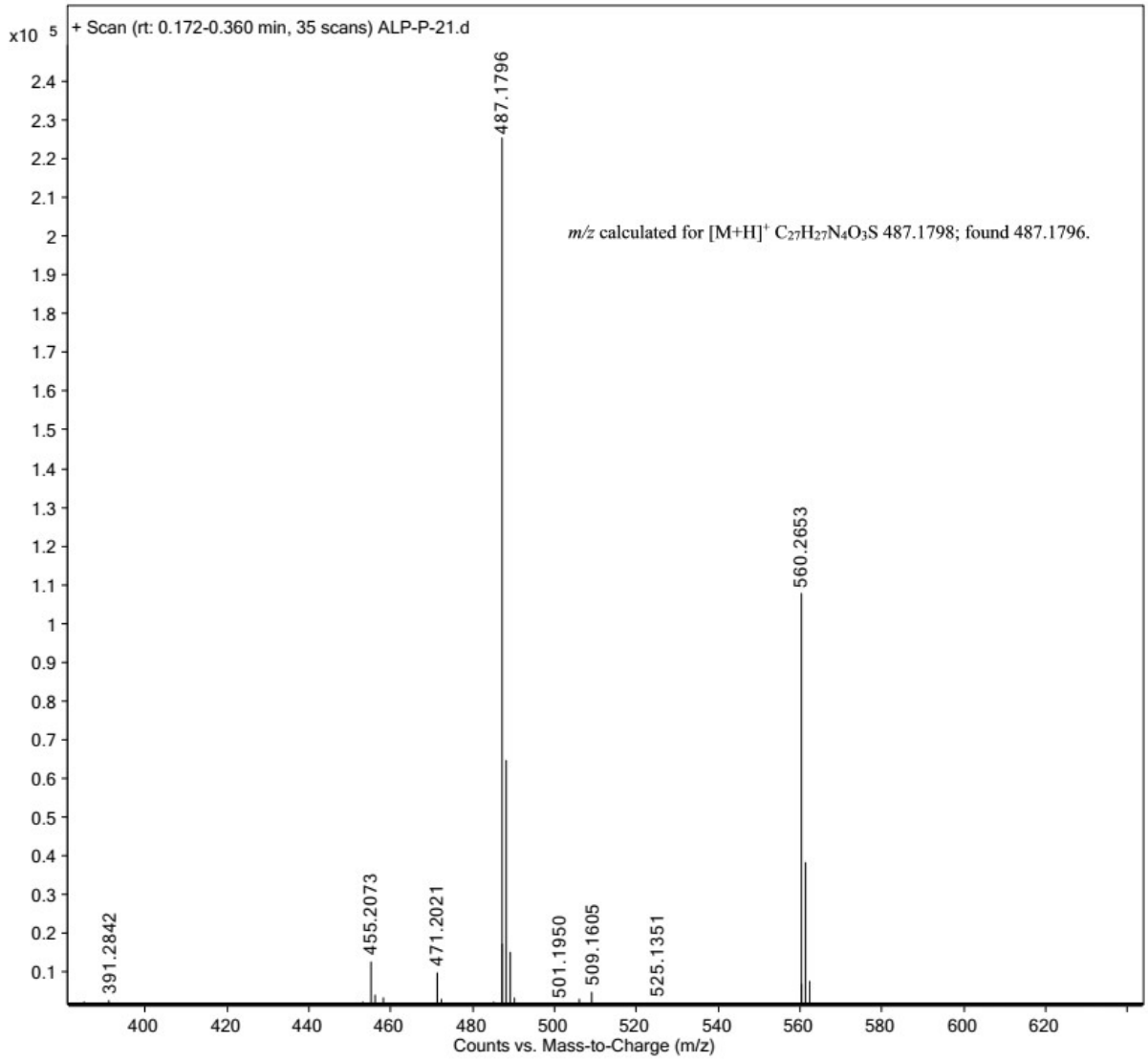

+ESI Scan (rt: 0.106-0.755 min, 40 scans) Frag=122.0V CID@2.0 SN-144.d Subtract
x10 5
m/z calculated for [M+H]+ C26H24ClN4O3S 507.1252 ; found 507.1249.
507.1249
509.1224
529.1059
491.2784
476.3719
Counts vs. Mass-to-Charge (m/z)

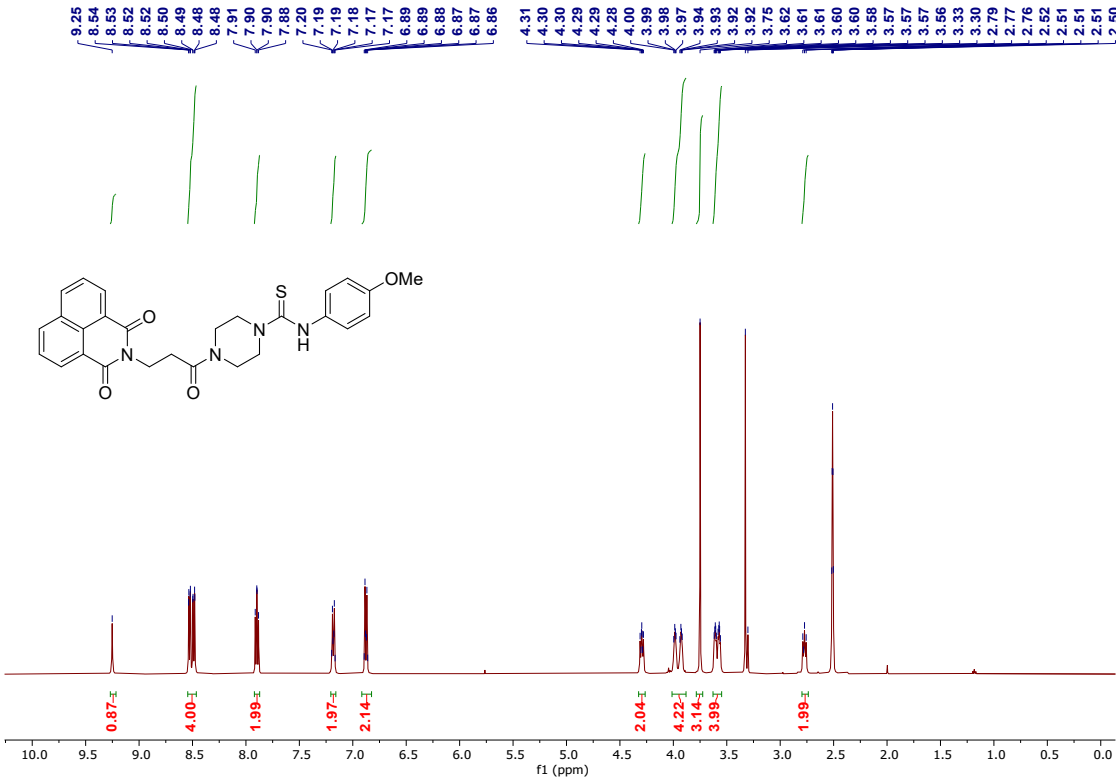


^{1}H spectrum for compound **9i** (500 MHz: DMSO-d_6)

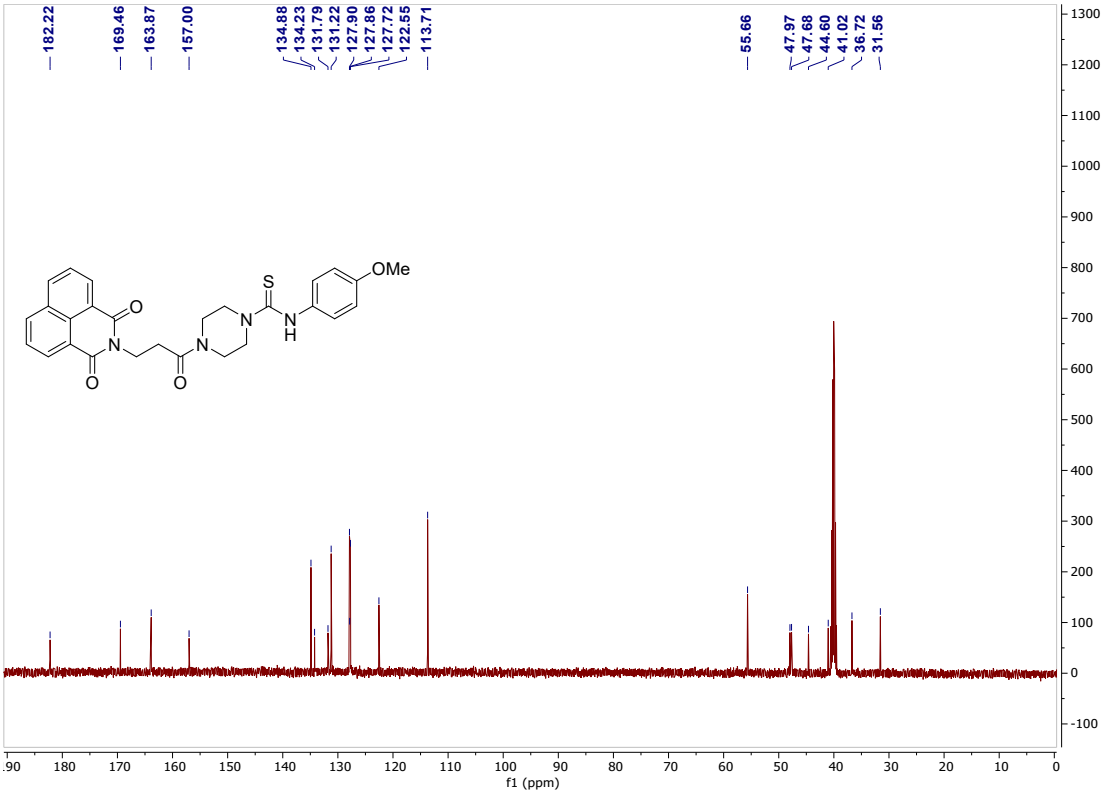


^{13}C spectrum for compound **9i** (125 MHz: DMSO-d_6)

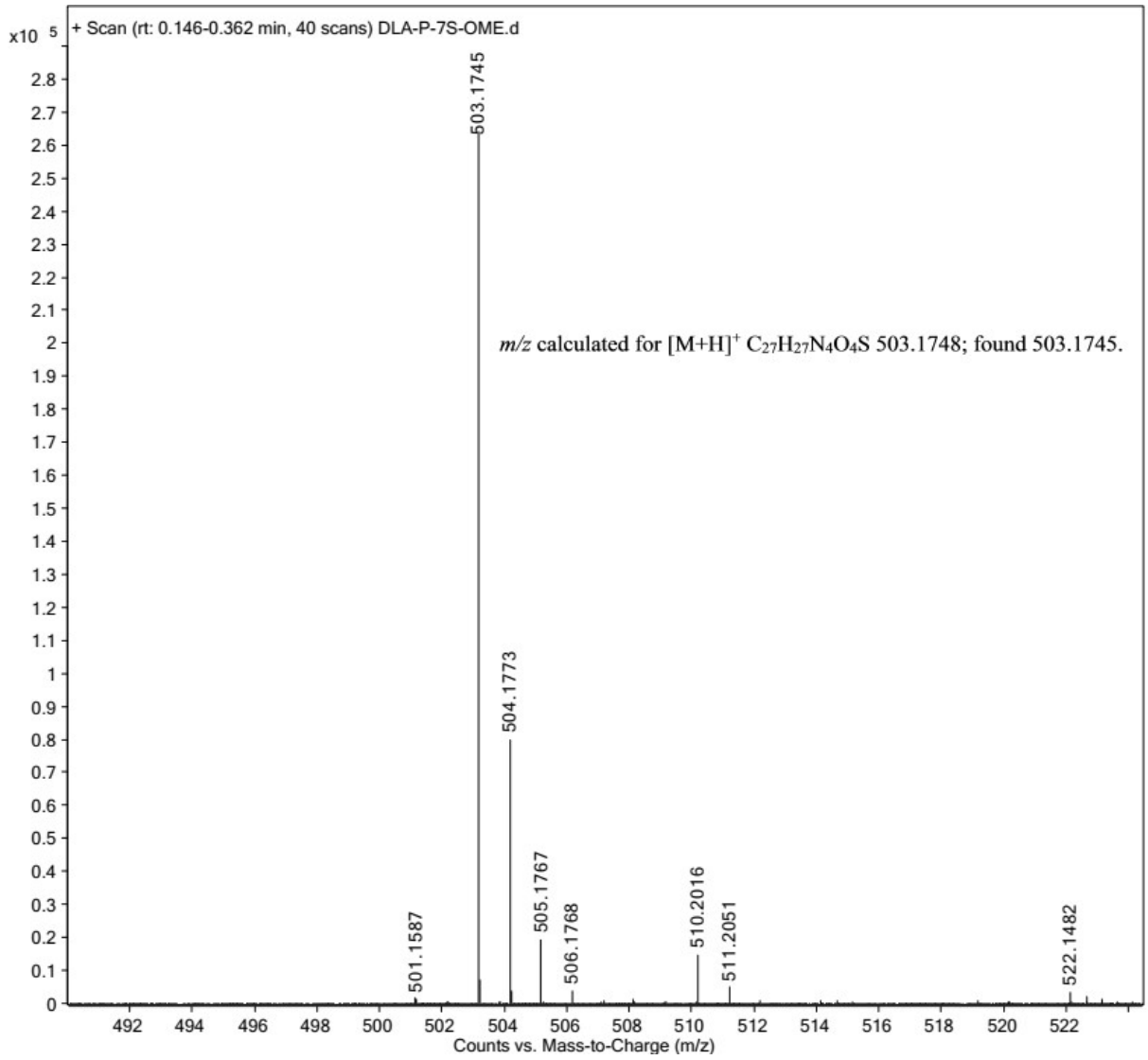

x10 5
+ Scan (rt: 0.172-0.360 min, 35 scans) ALP-P-21.d
487.1796
m/z calculated for [M+H]+ C27H27N4O3S 487.1798; found 487.1796.
560.2653
455.2073
471.2021
391.2842
501.1950
509.1605
525.1351
Counts vs. Mass-to-Charge (m/z)

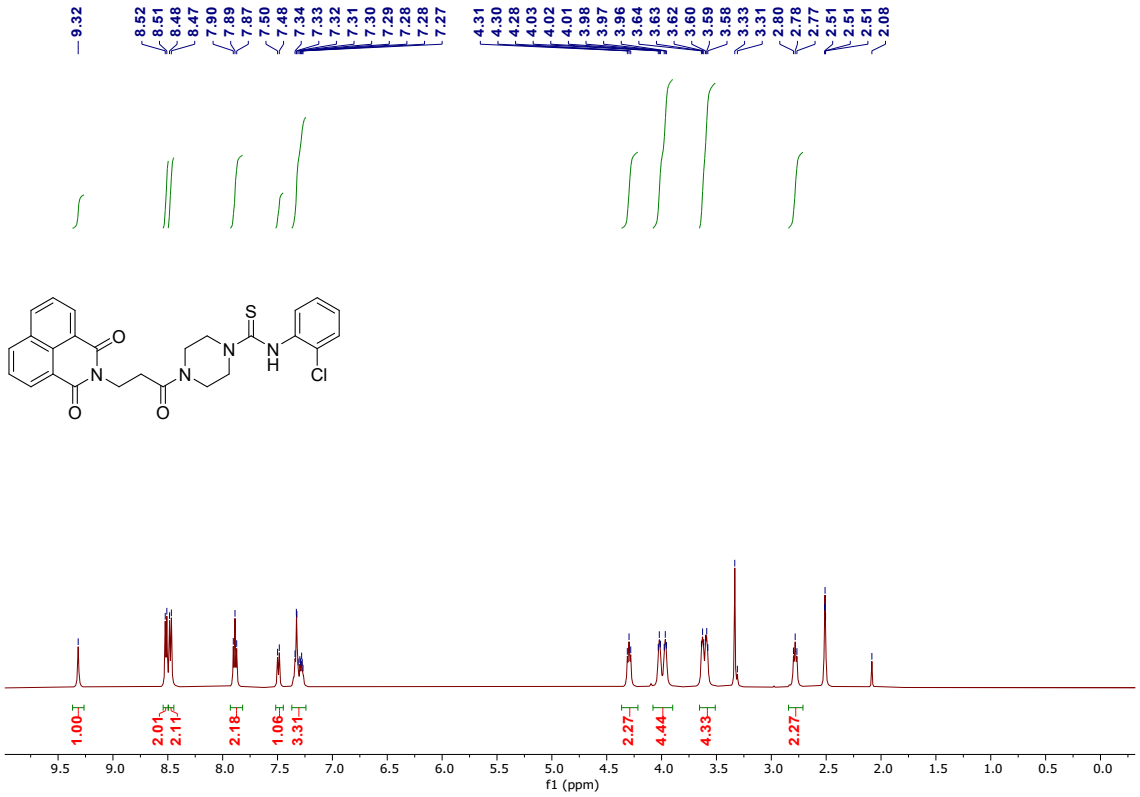


^{1}H spectrum for compound **9j** (500 MHz: DMSO-d_6)

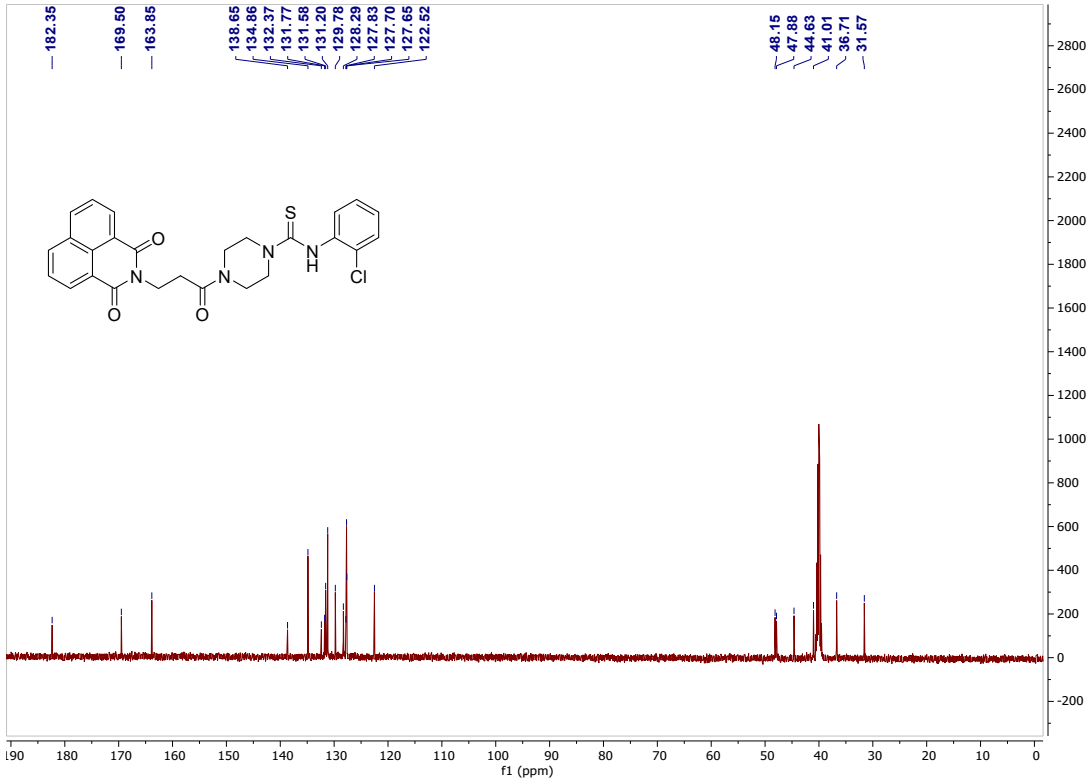


^{13}C spectrum for compound **9j** (125 MHz: DMSO-d_6)

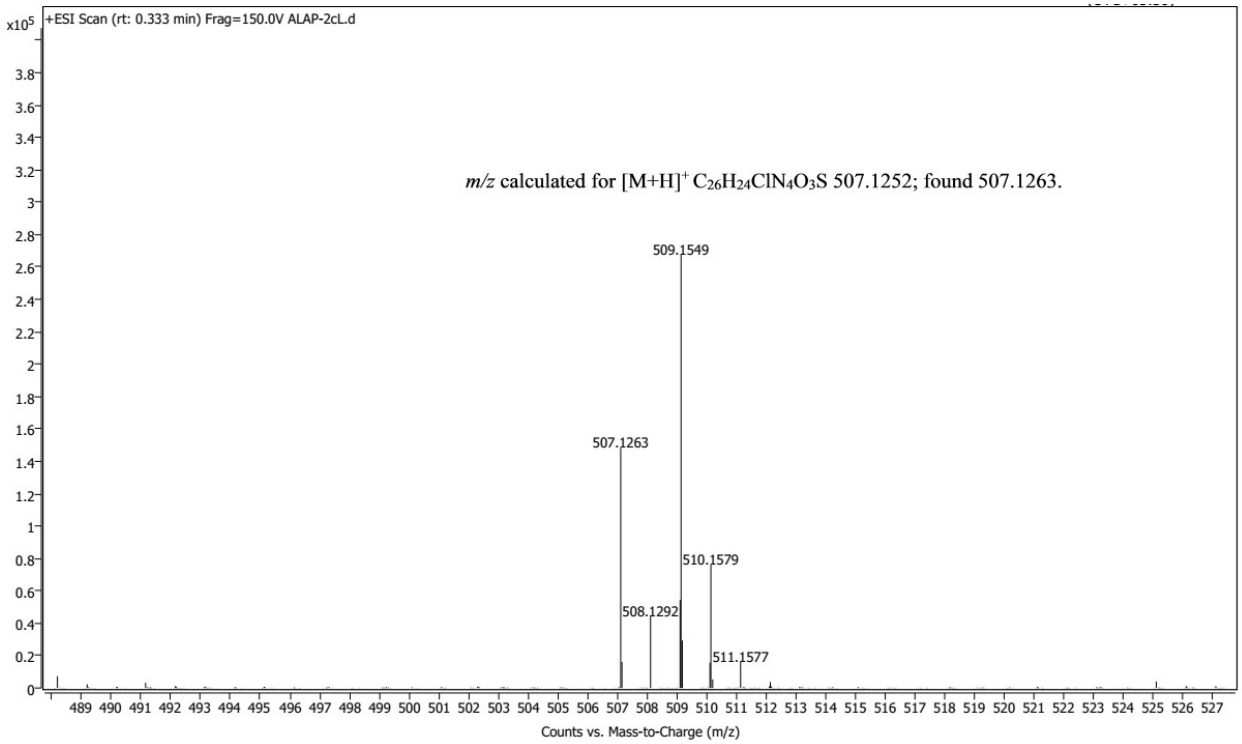

+ Scan (rt: 0.146-0.362 min, 40 scans) DLA-P-7S-OME.d
x10 5
503.1745
504.1773
505.1767
506.1768
501.1587
510.2016
511.2051
522.1482
m/z calculated for [M+H]+ C27H27N4O4S 503.1748; found 503.1745.
Counts vs. Mass-to-Charge (m/z)

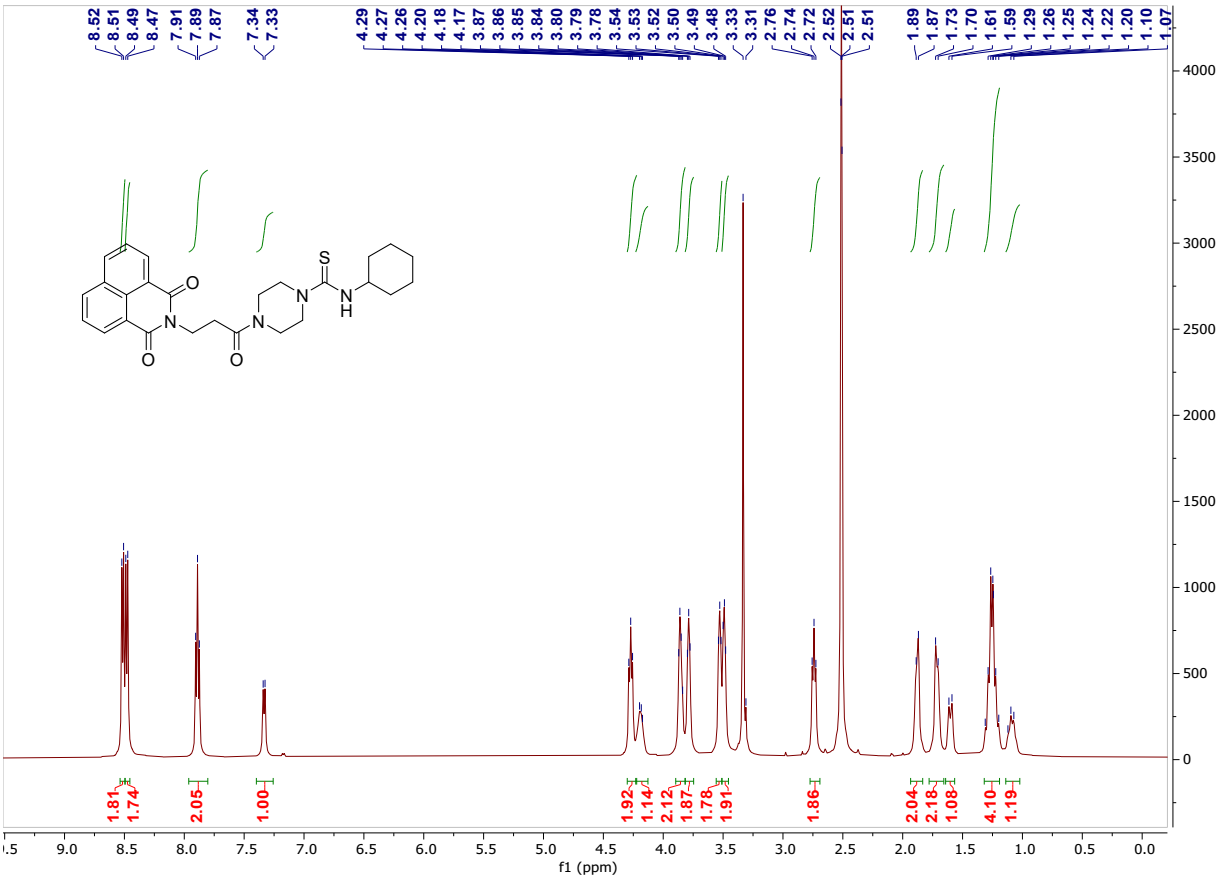


^{1}H spectrum for compound **9k** (500 MHz: DMSO-d_6)

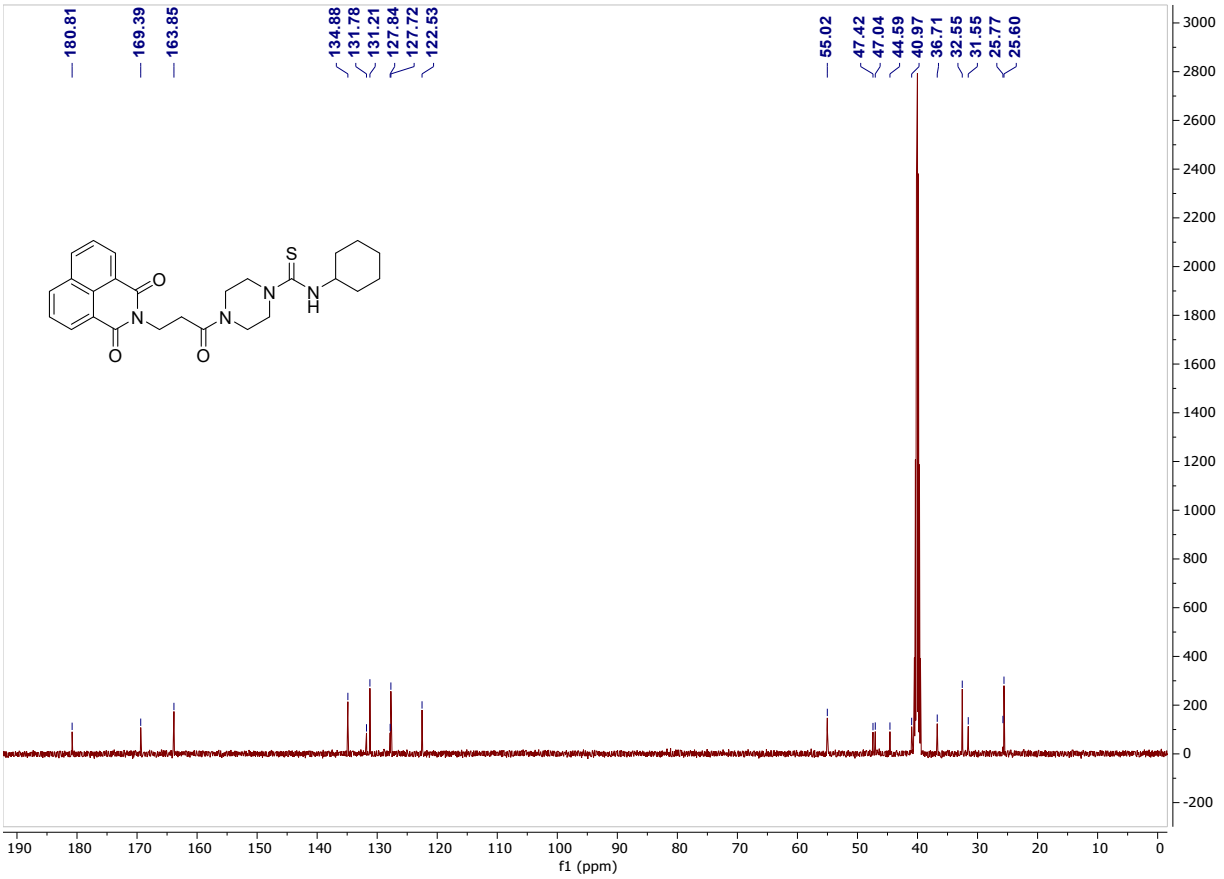


^{13}C spectrum for compound **9k** (125 MHz: DMSO-d_6)

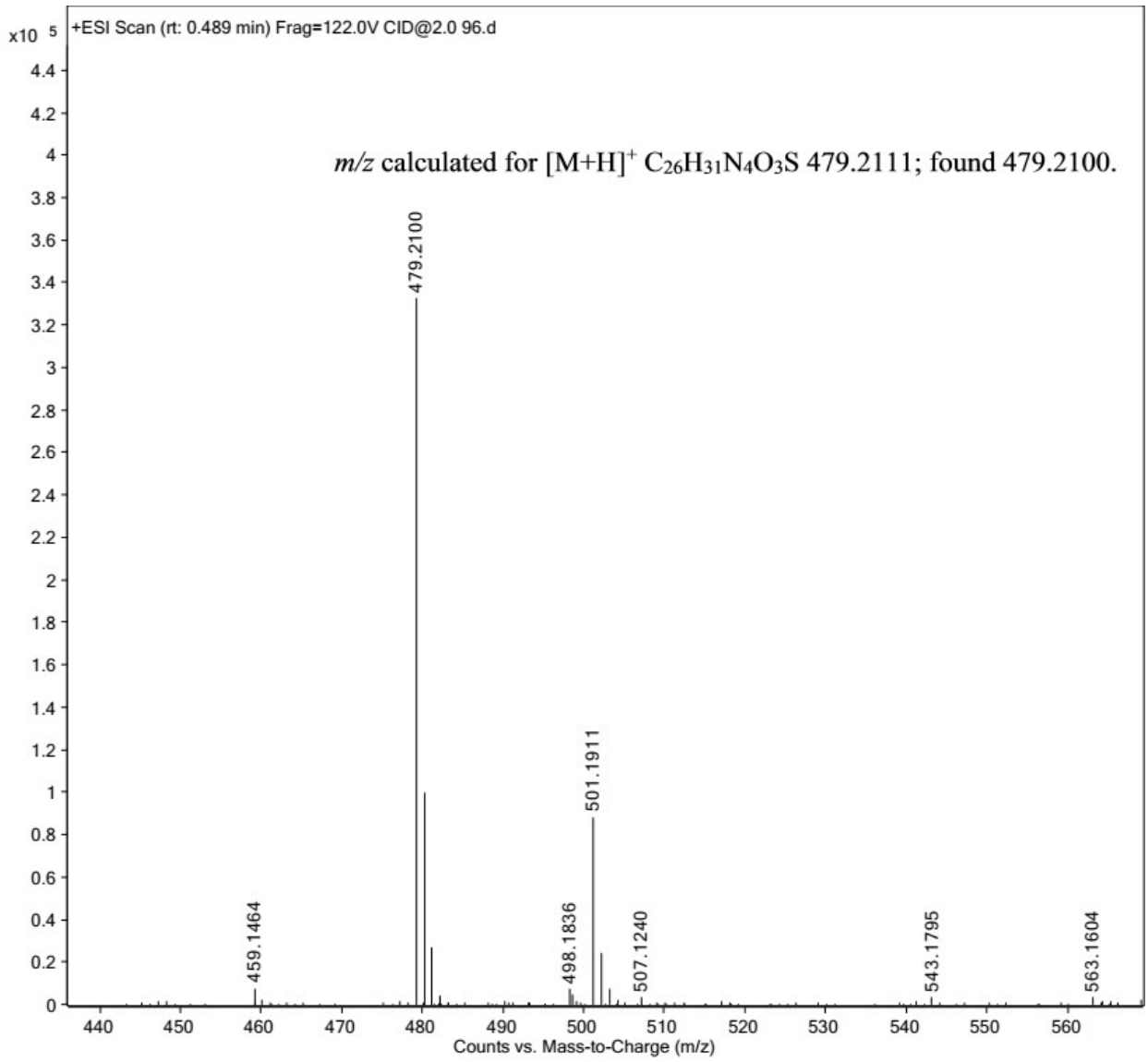


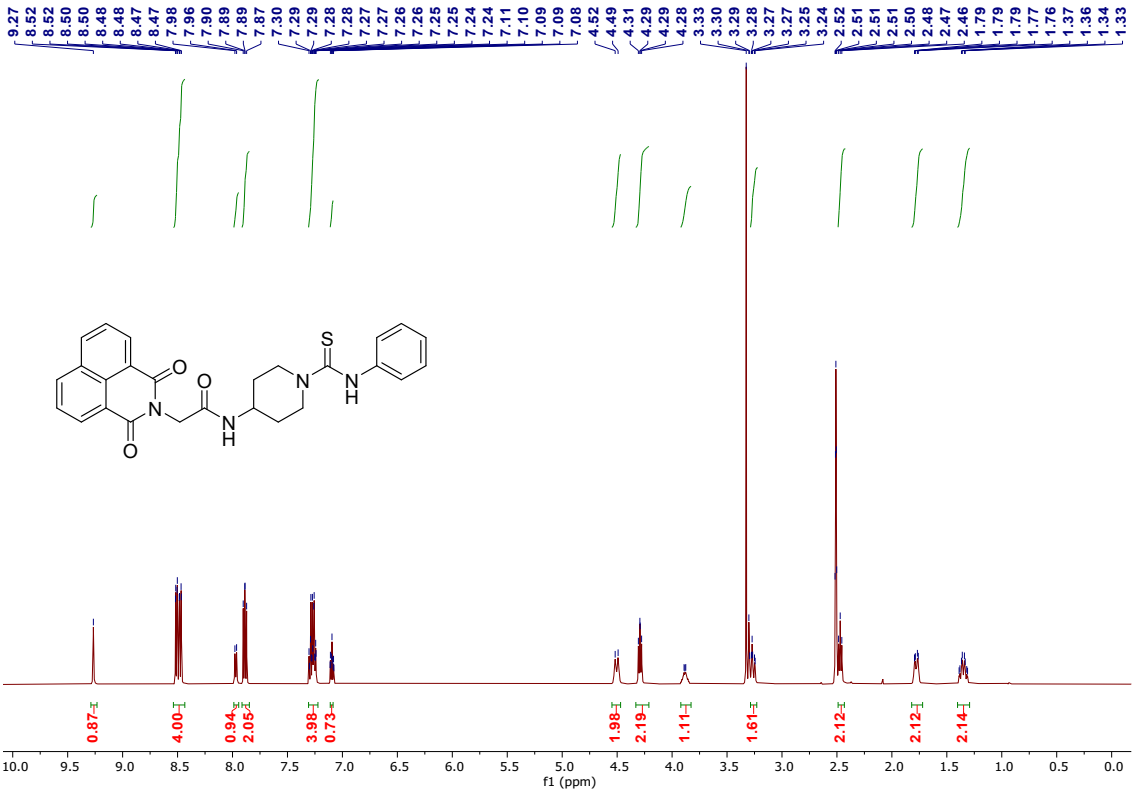


^{1}H spectrum for compound **9l** (500 MHz: DMSO-d_6)

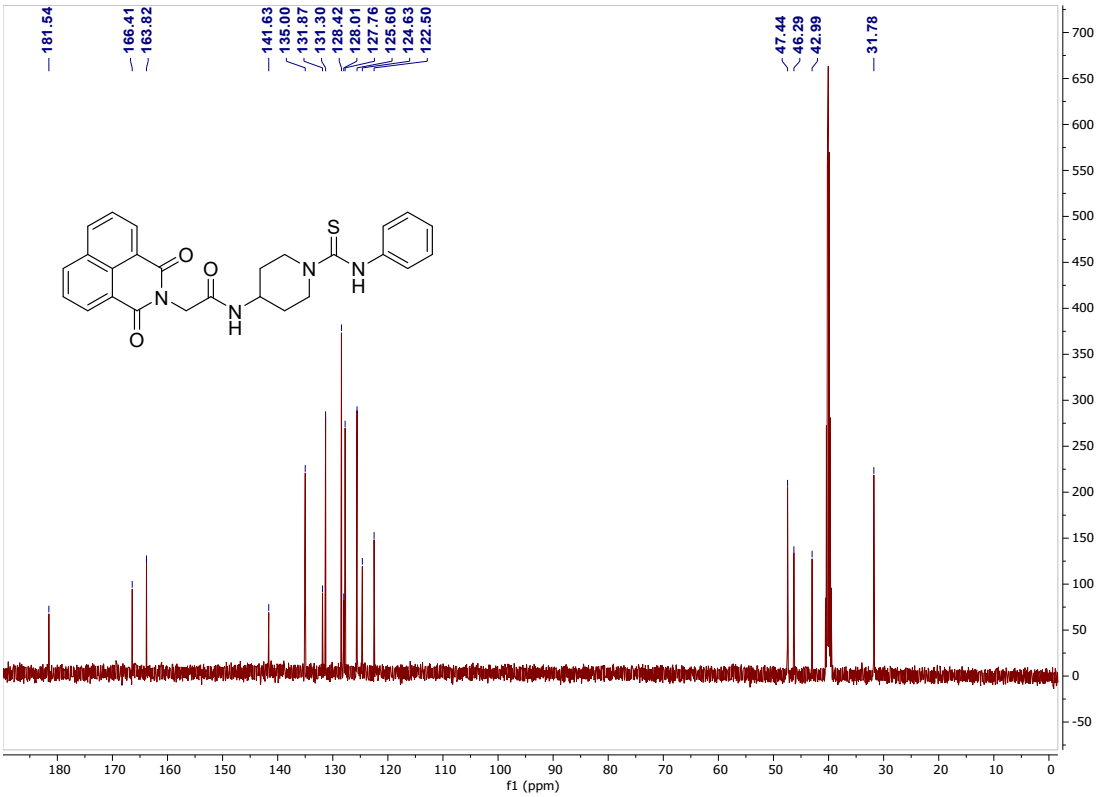


^{13}C spectrum for compound **9l** (500 MHz: DMSO-d_6)

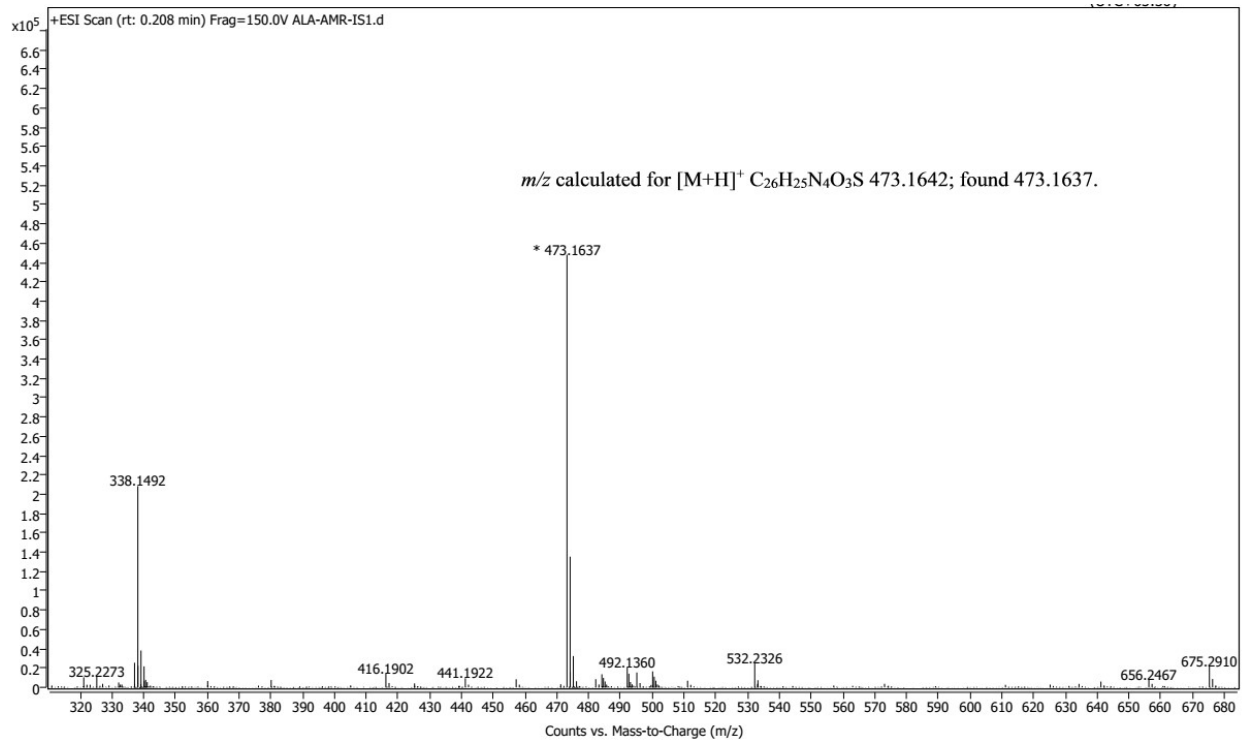

+ESI Scan (rt: 0.489 min) Frag=122.0V CID@2.0 96.d
x10 5
m/z calculated for [M+H]+ C26H31N4O3S 479.2111; found 479.2100.
479.2100
501.1911
459.1464
498.1836
507.1240
543.1795
563.1604
Counts vs. Mass-to-Charge (m/z)

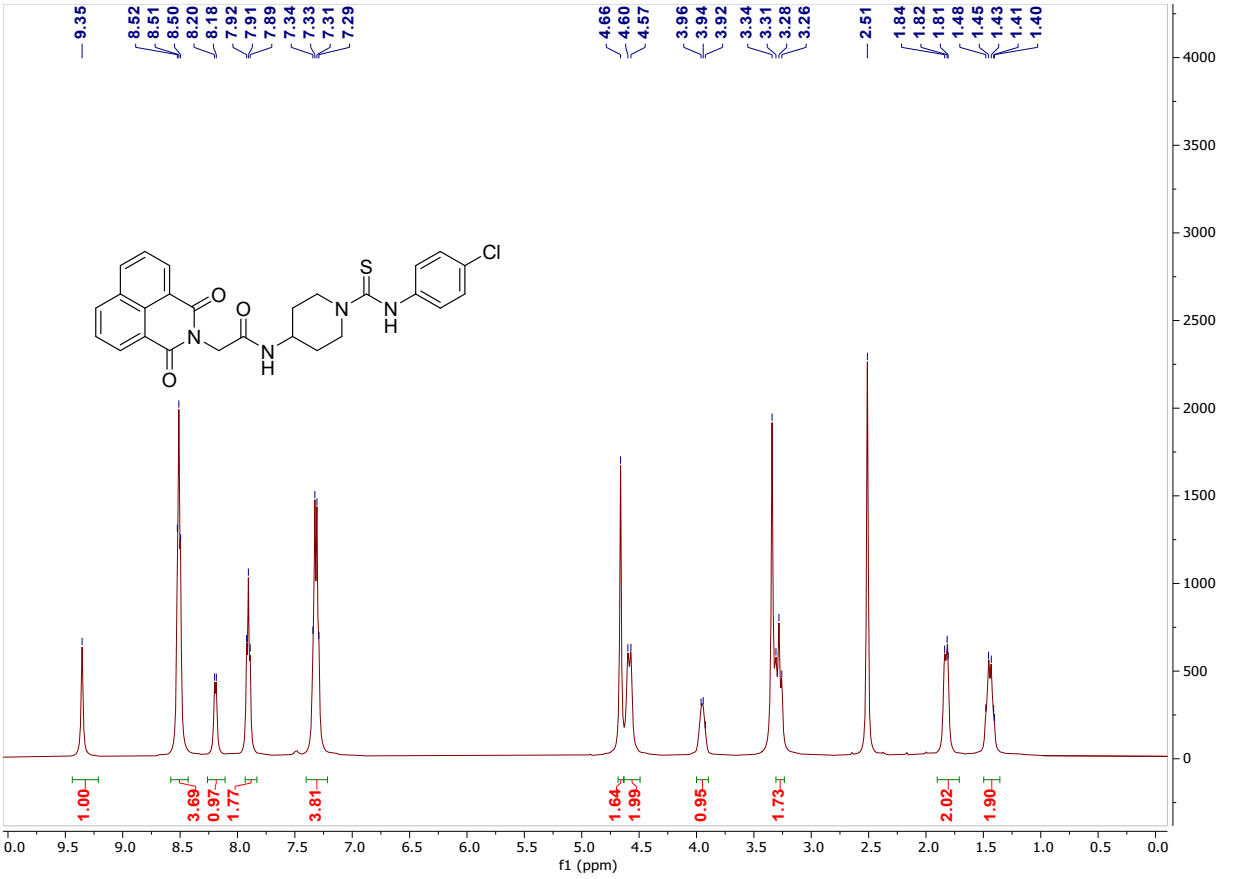


^{1}H spectrum for compound **13a** (500 MHz: DMSO-d_6)

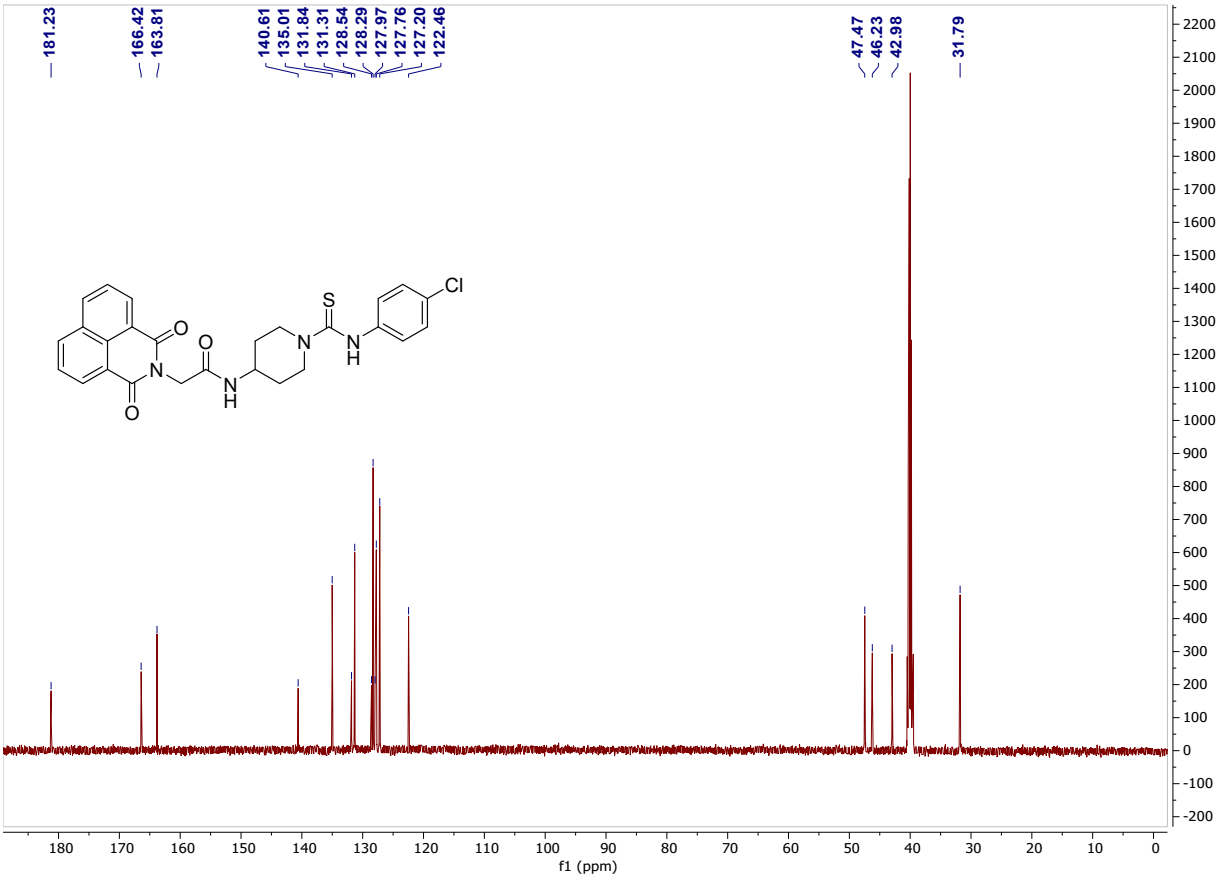


^{13}C spectrum for compound **13a** (125 MHz: DMSO-d_6)

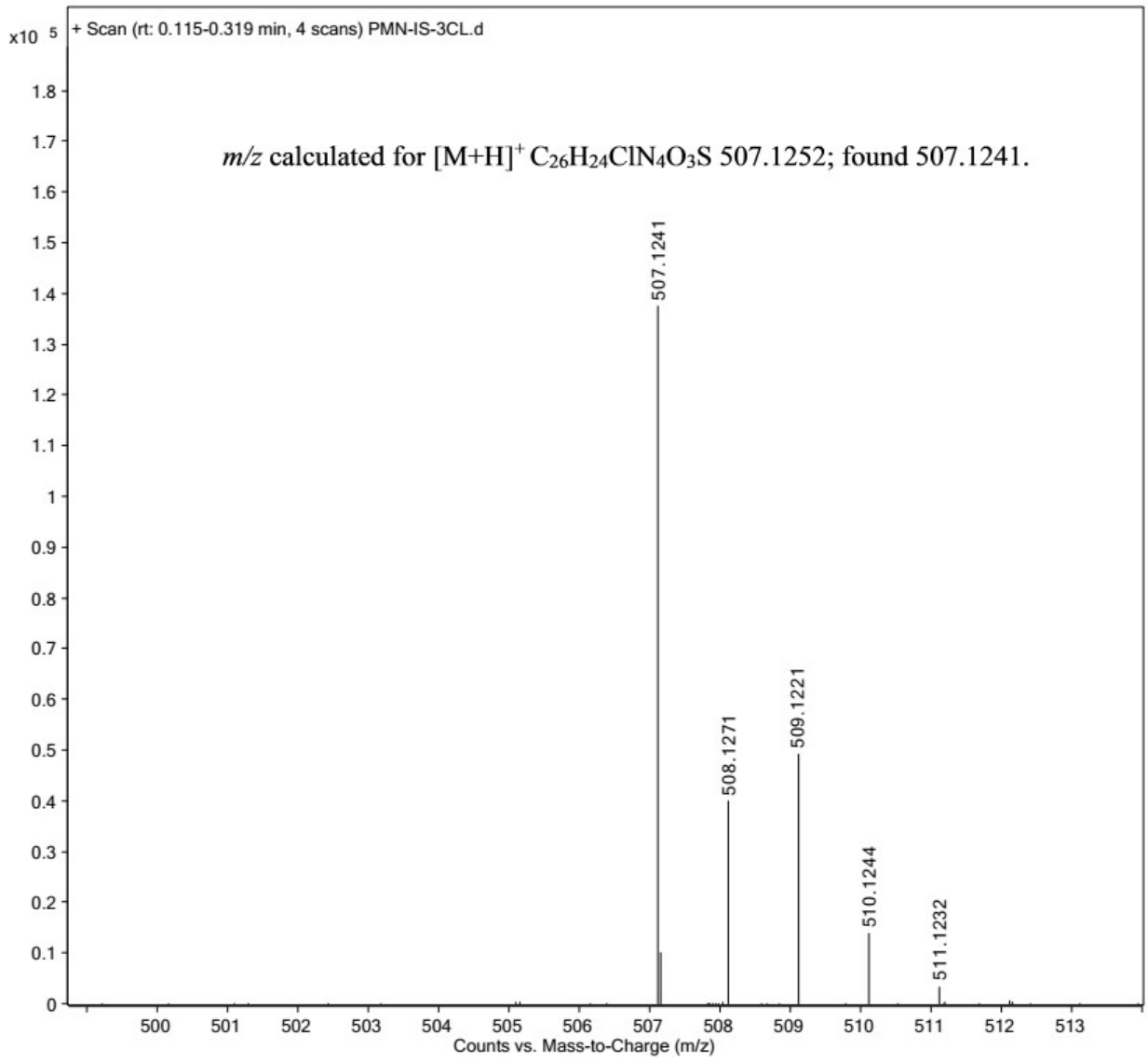


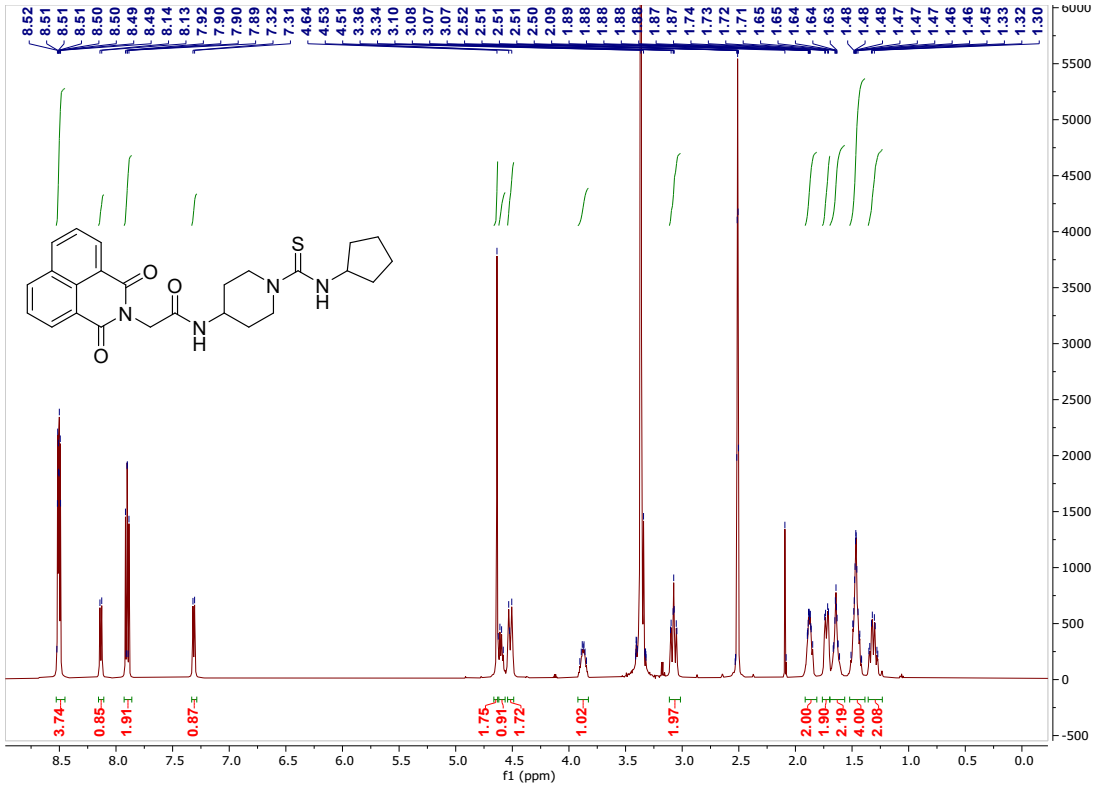


^{1}H spectrum for compound **13b** (500 MHz: DMSO-d_6)

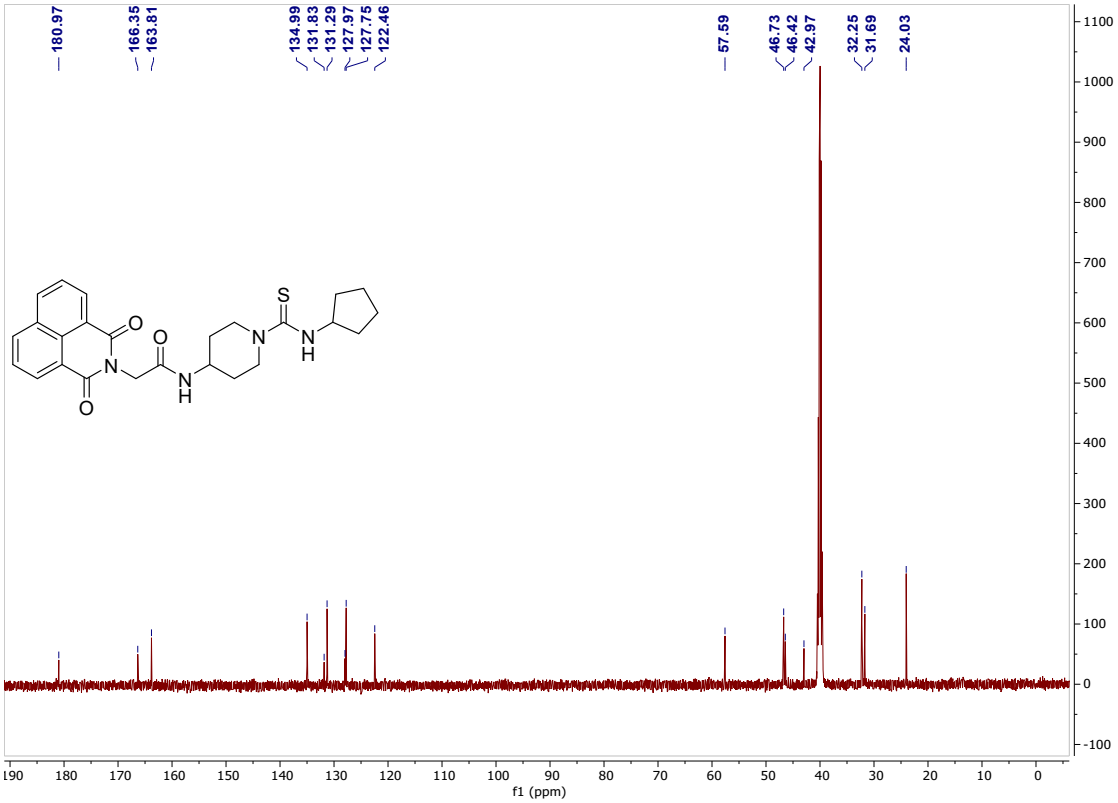


^{13}C spectrum for compound **13b** (125 MHz: DMSO-d_6)

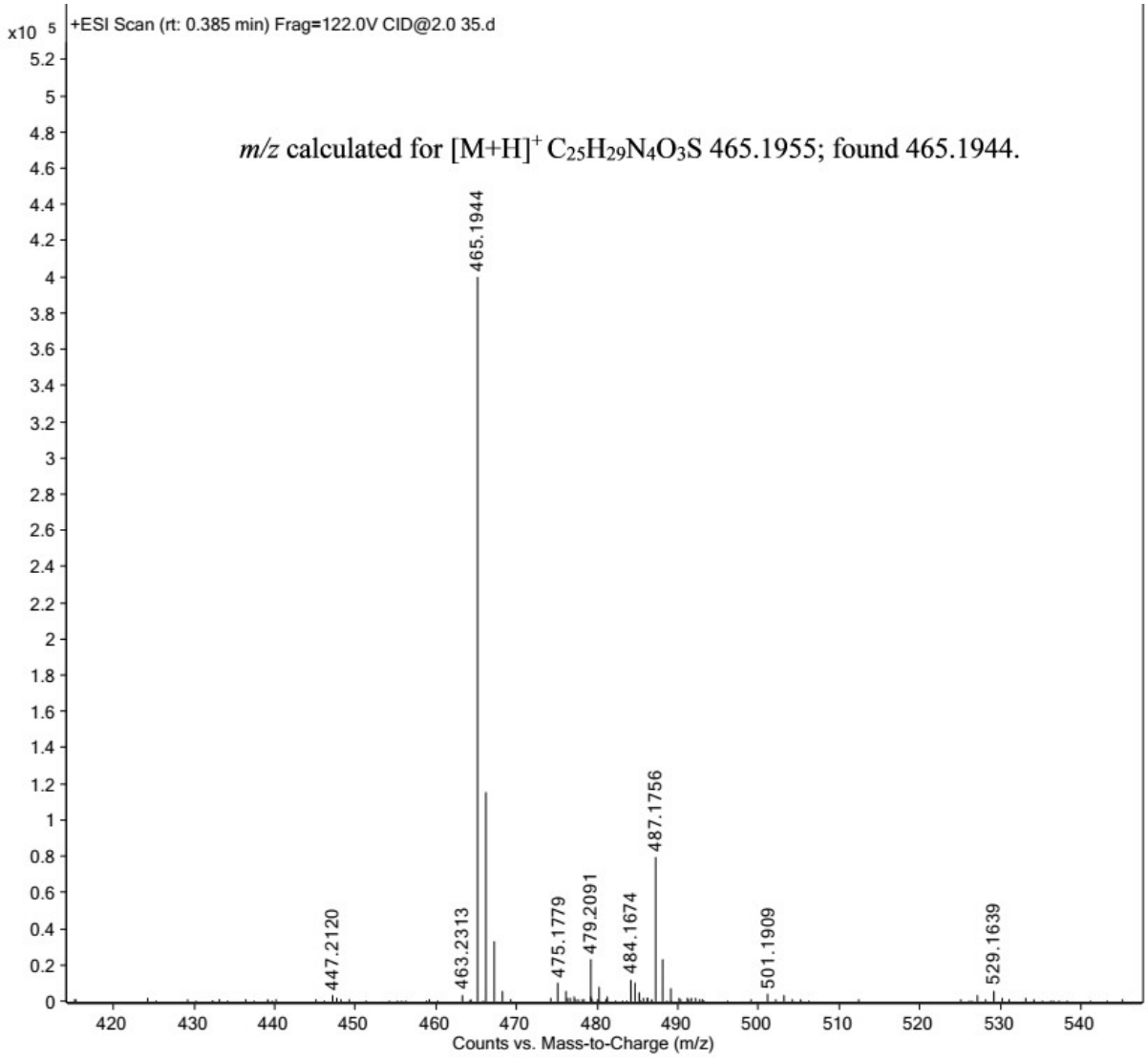

+ Scan (rt: 0.115-0.319 min, 4 scans) PMN-IS-3CL.d
x10 5
m/z calculated for [M+H]+ C26H24ClN4O3S 507.1252; found 507.1241.
507.1241
508.1271
509.1221
510.1244
511.1232
Counts vs. Mass-to-Charge (m/z)

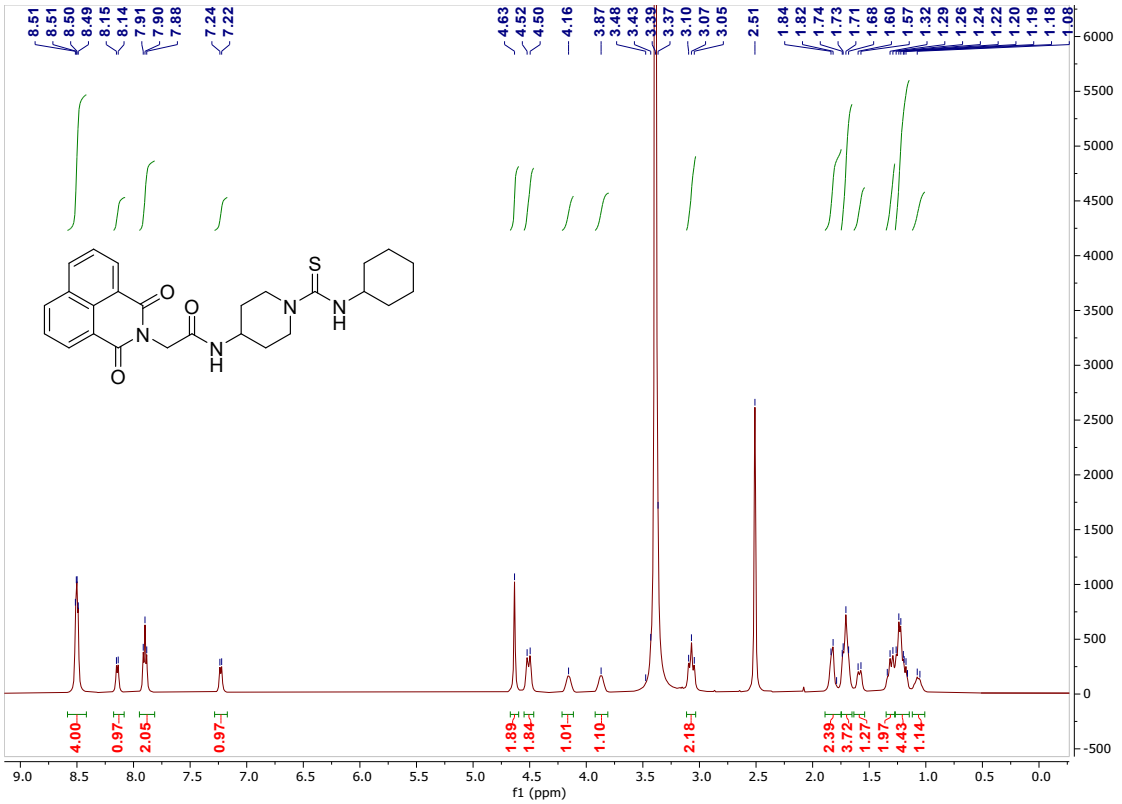


^{1}H spectrum for compound **13c** (500 MHz: DMSO-d_6)

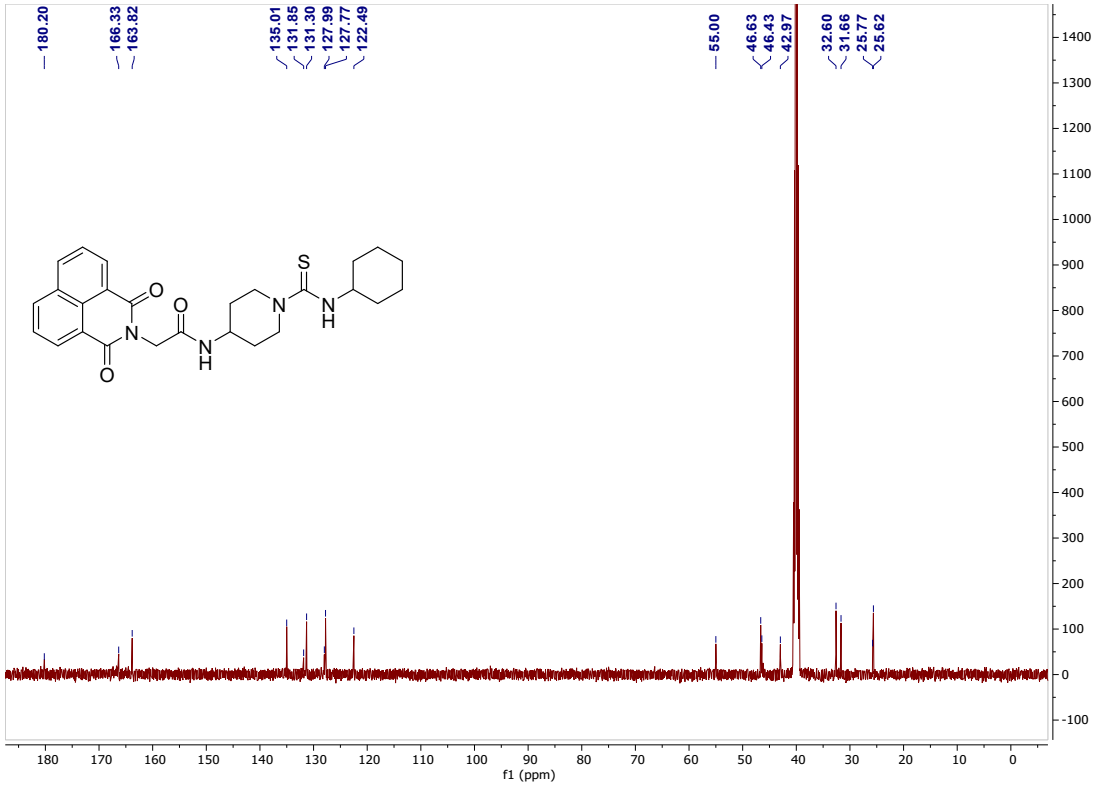


^{13}C spectrum for compound **13c** (125 MHz: DMSO-d_6)

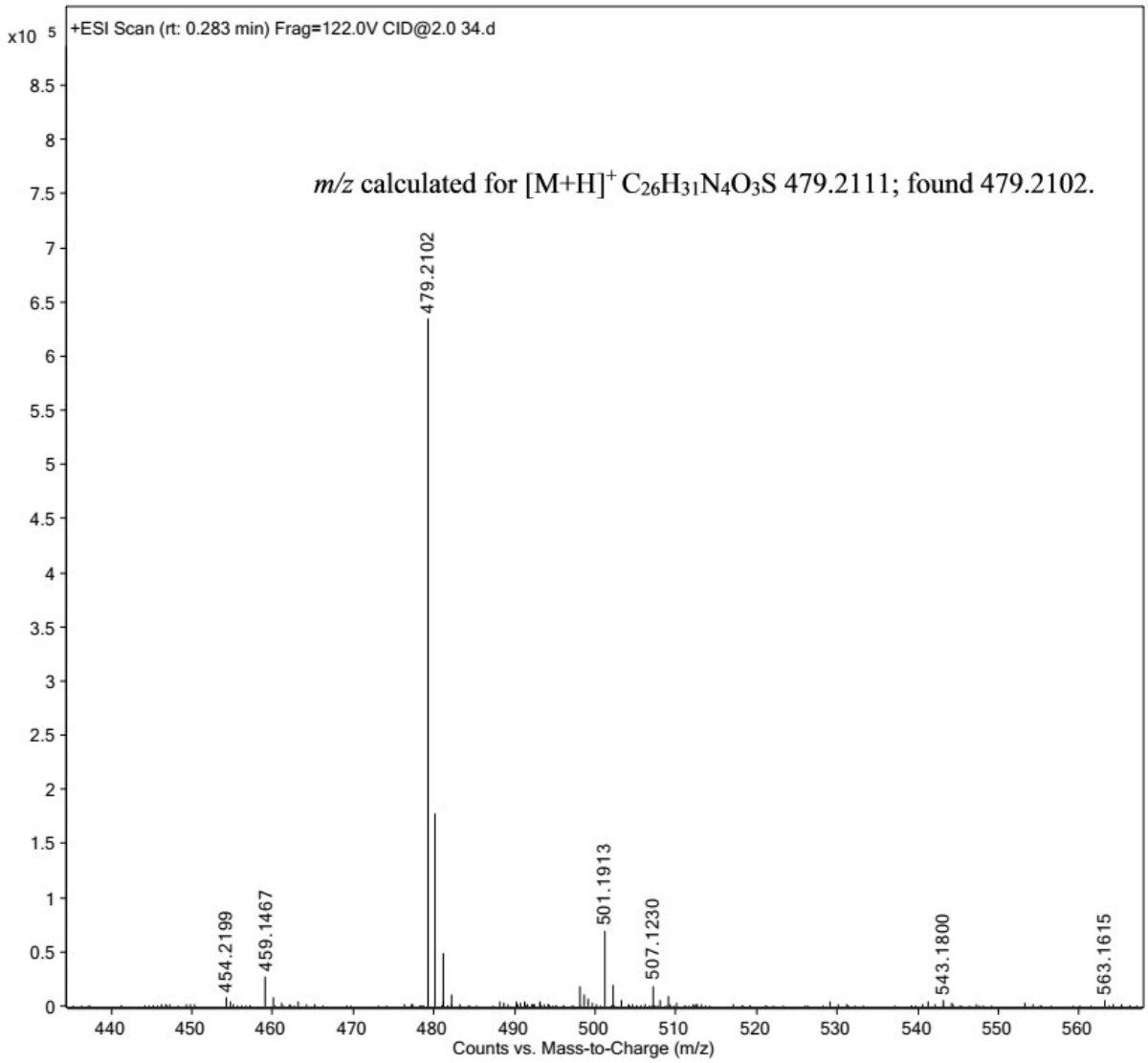

x10 5
+ESI Scan (rt: 0.385 min) Frag=122.0V CID@2.0 35.d
m/z calculated for [M+H]+ C25H29N4O3S 465.1955; found 465.1944.
465.1944
447.2120
463.2313
475.1779
479.2091
484.1674
487.1756
501.1909
529.1639
Counts vs. Mass-to-Charge (m/z)

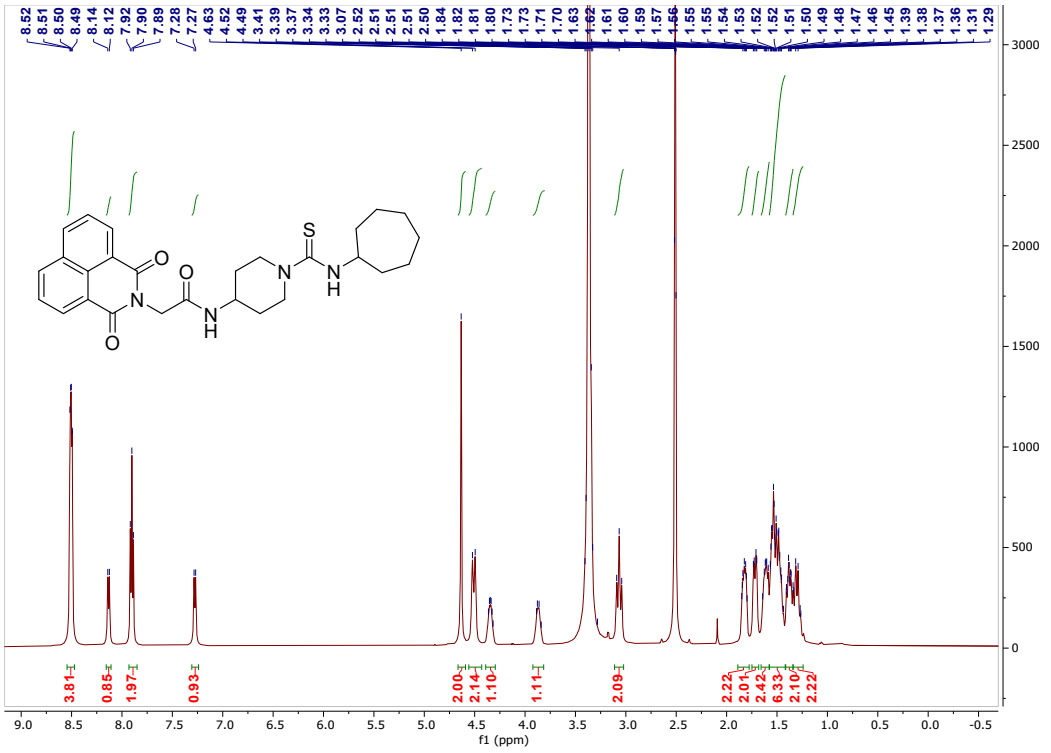


^{1}H spectrum for compound **13d** (500 MHz: DMSO-d_6)

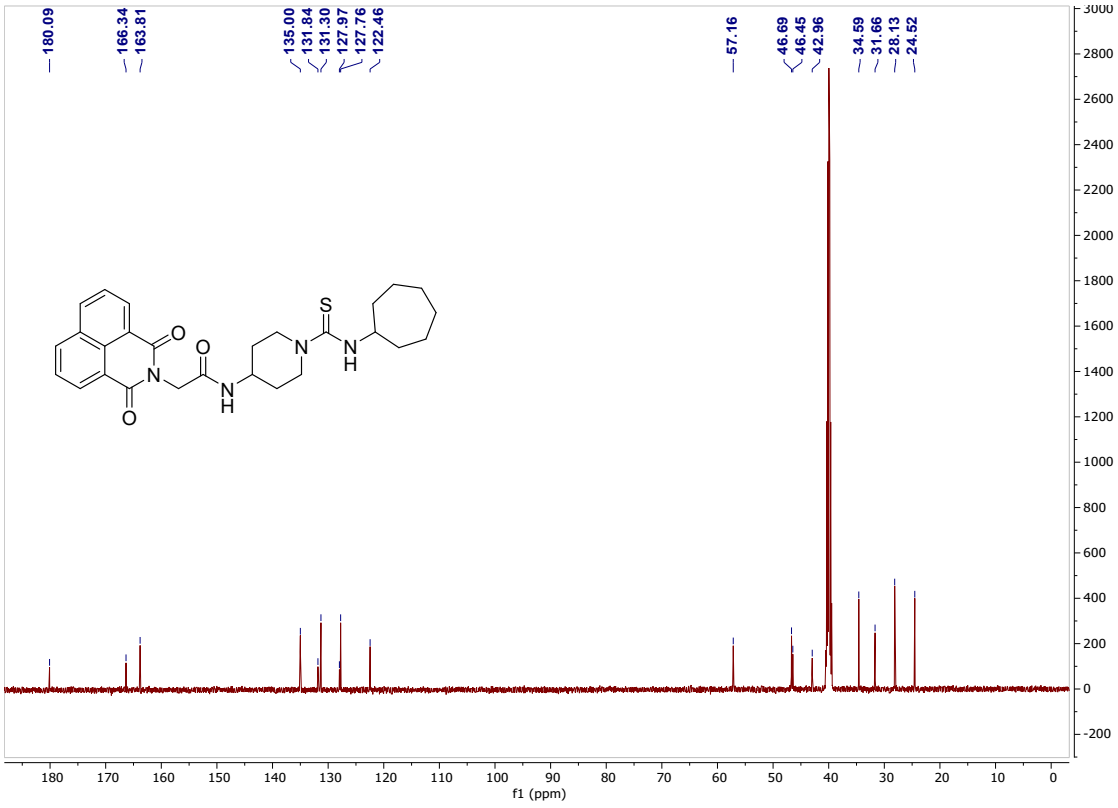


^{13}C spectrum for compound **13d** (125 MHz: DMSO-d_6)

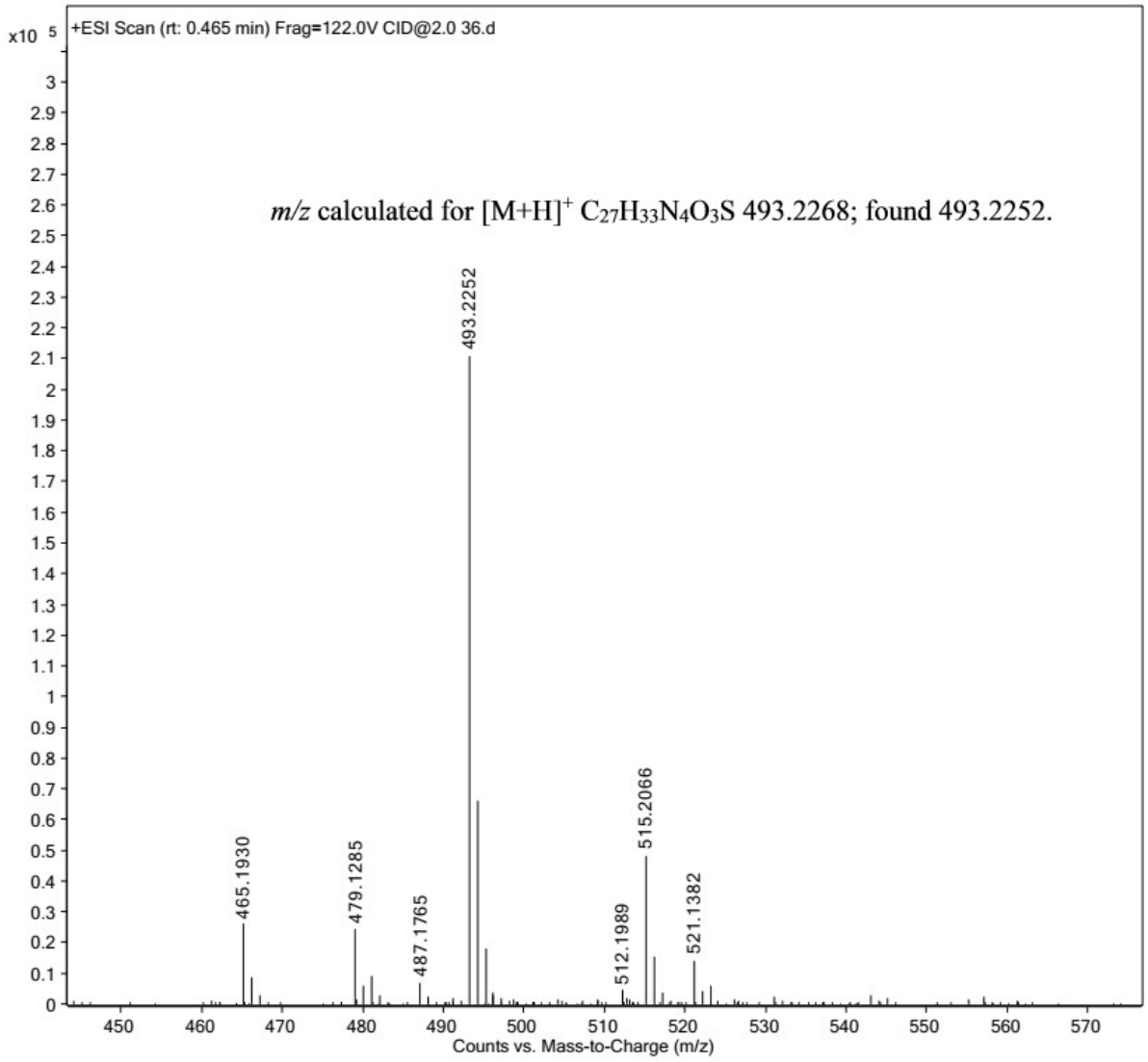

+ESI Scan (rt: 0.283 min) Frag=122.0V CID@2.0 34.d
x10 5
m/z calculated for [M+H]+ C26H31N4O3S 479.2111; found 479.2102.
479.2102
454.2199
459.1467
501.1913
507.1230
543.1800
563.1615
Counts vs. Mass-to-Charge (m/z)

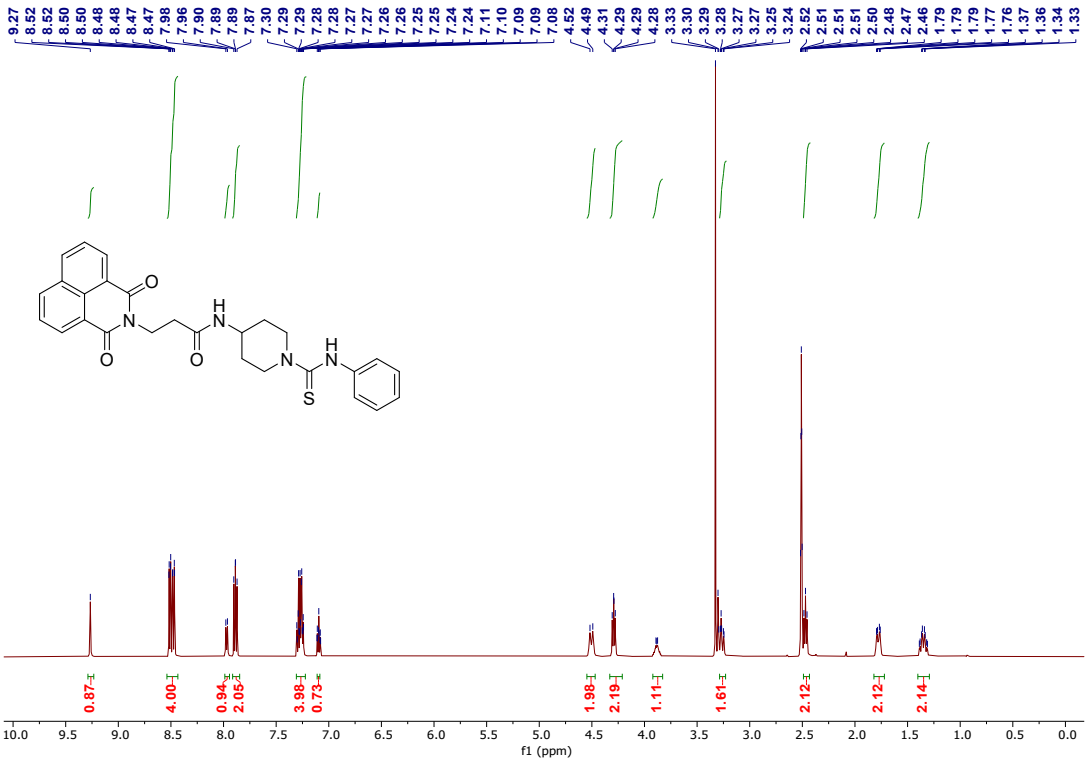


^{1}H spectrum for compound **13e** (500 MHz: DMSO-d_6)

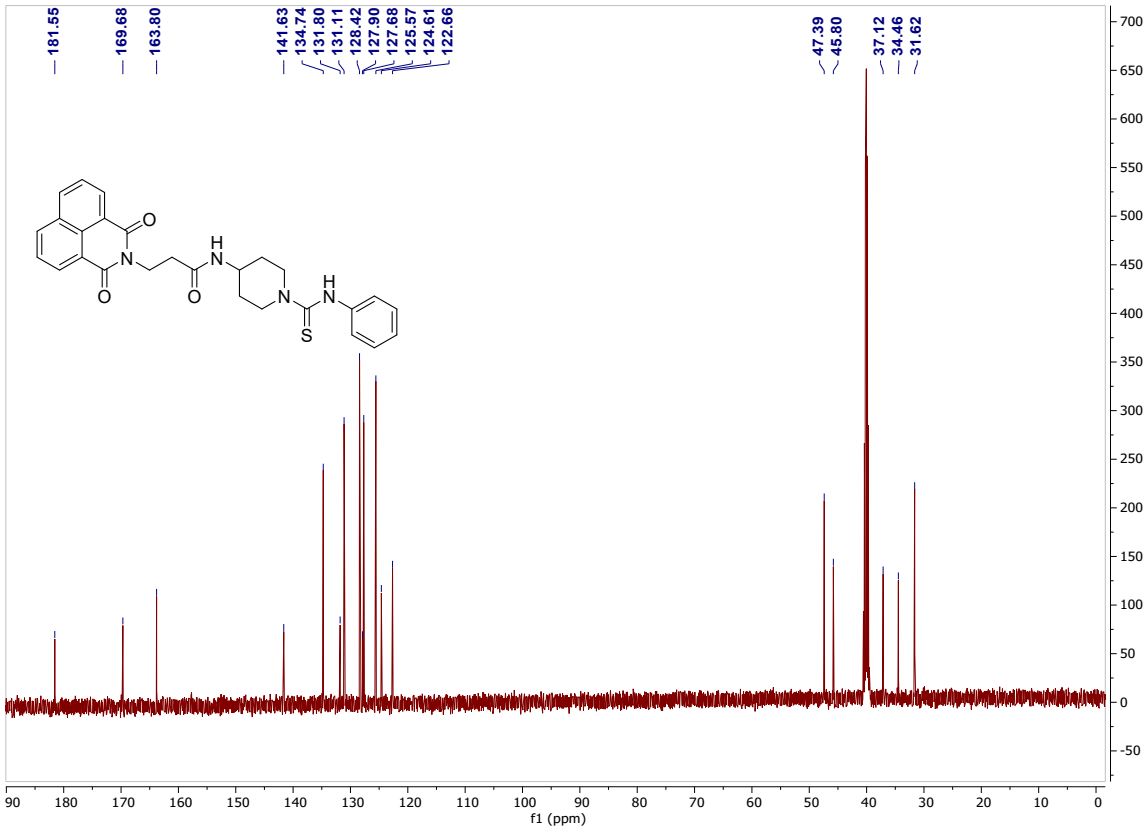


^{13}C spectrum for compound **13e** (125 MHz: DMSO-d_6)

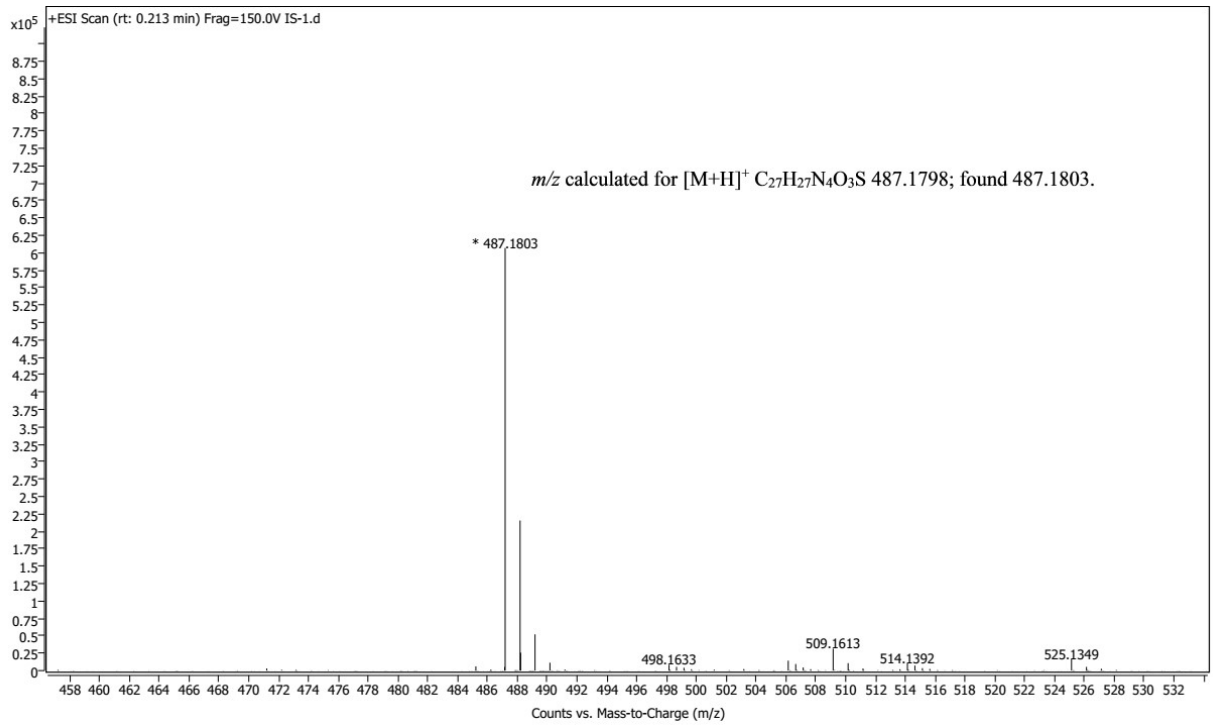

+ESI Scan (rt: 0.465 min) Frag=122.0V CID@2.0 36.d
x10 5
m/z calculated for [M+H]+ C27H33N4O3S 493.2268; found 493.2252.
493.2252
465.1930
479.1285
487.1765
512.1989
515.2066
521.1382
Counts vs. Mass-to-Charge (m/z)

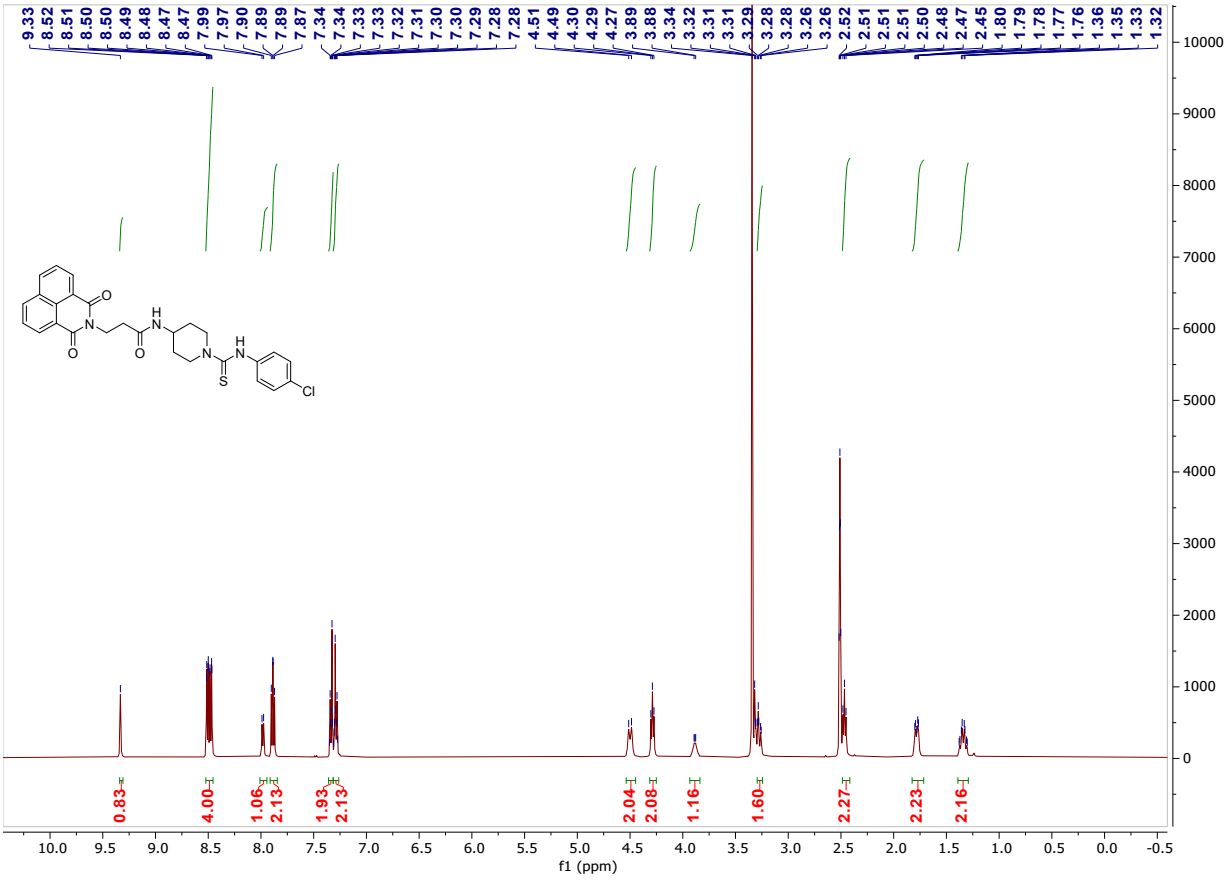


^{1}H spectrum for compound **13f** (500 MHz: DMSO-d_6)

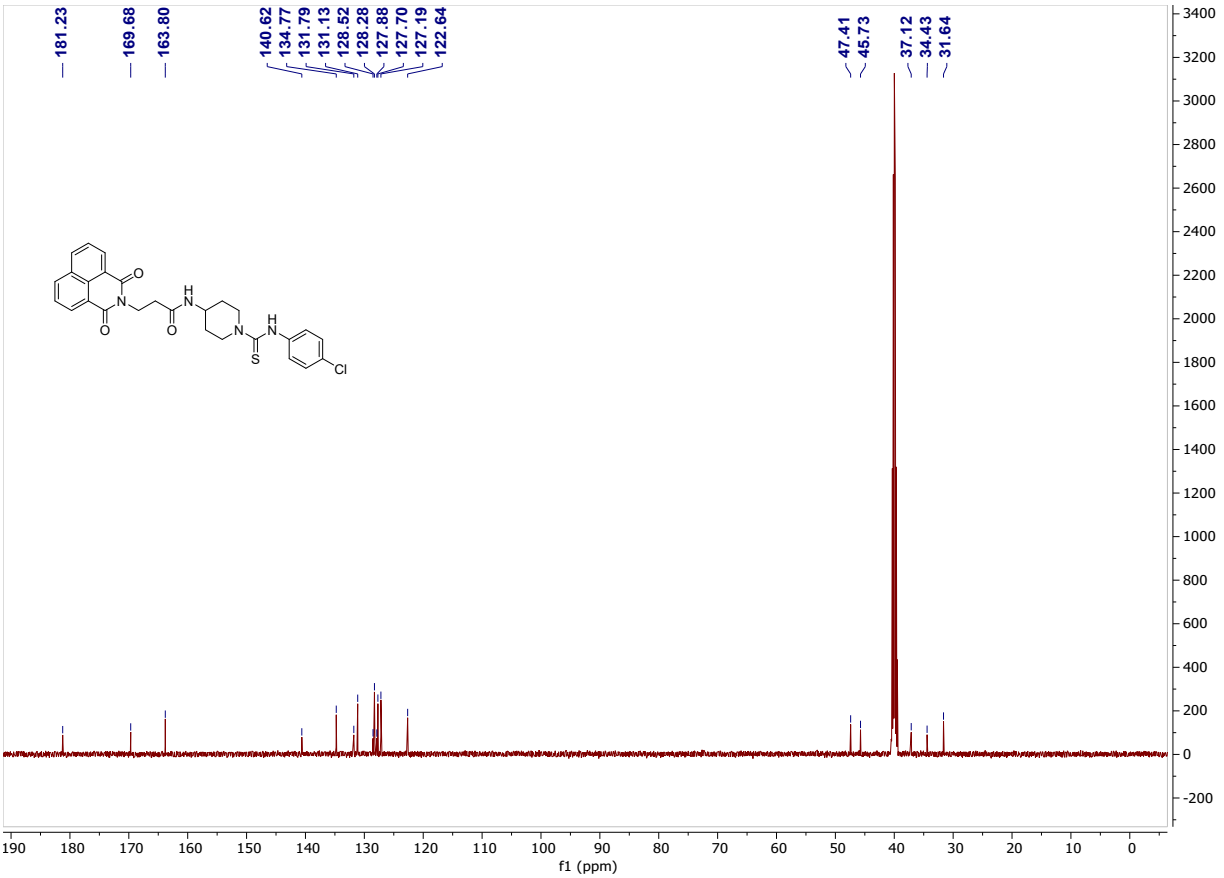


^{13}C spectrum for compound **13f** (125 MHz: DMSO-d_6)

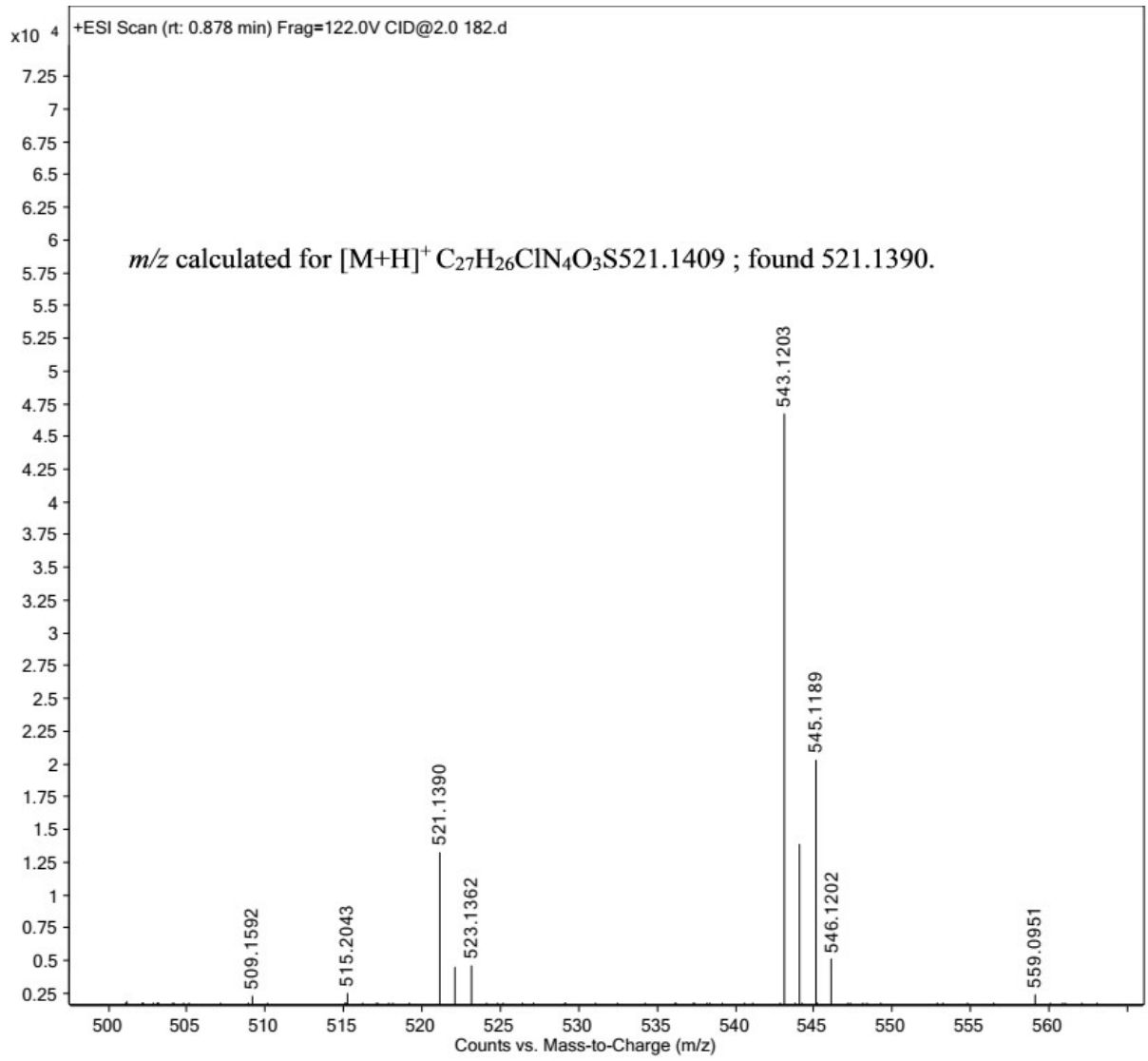


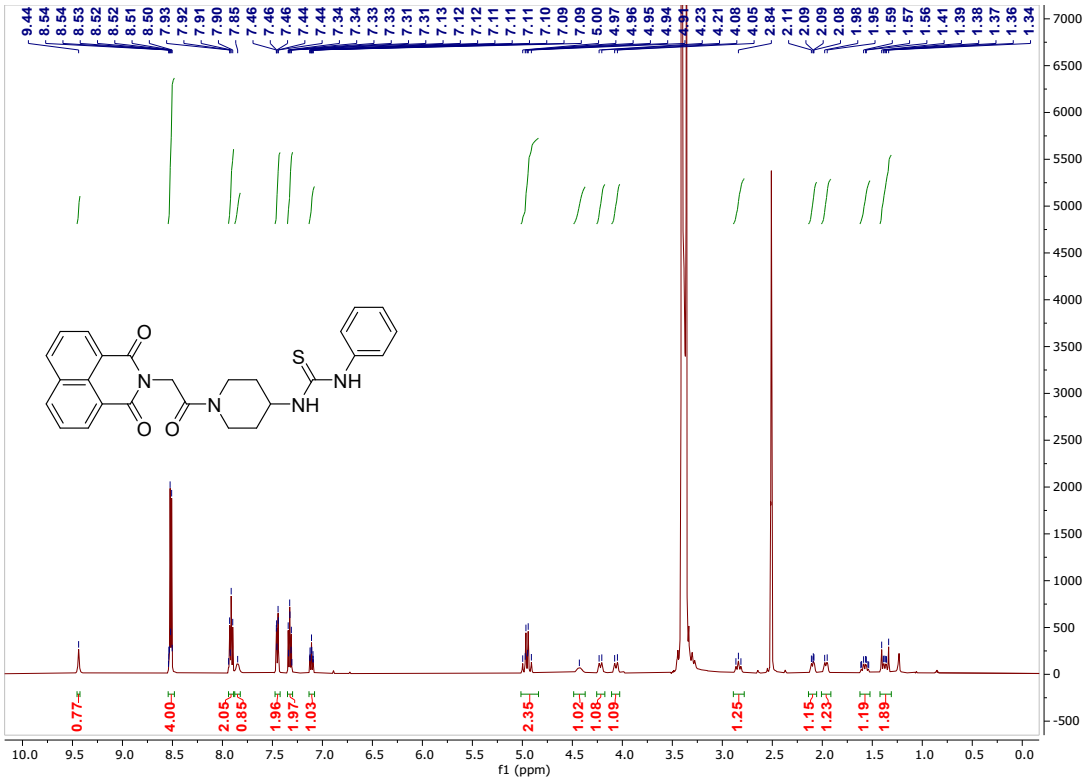


^{1}H spectrum for compound **13g** (500 MHz: DMSO-d_6)

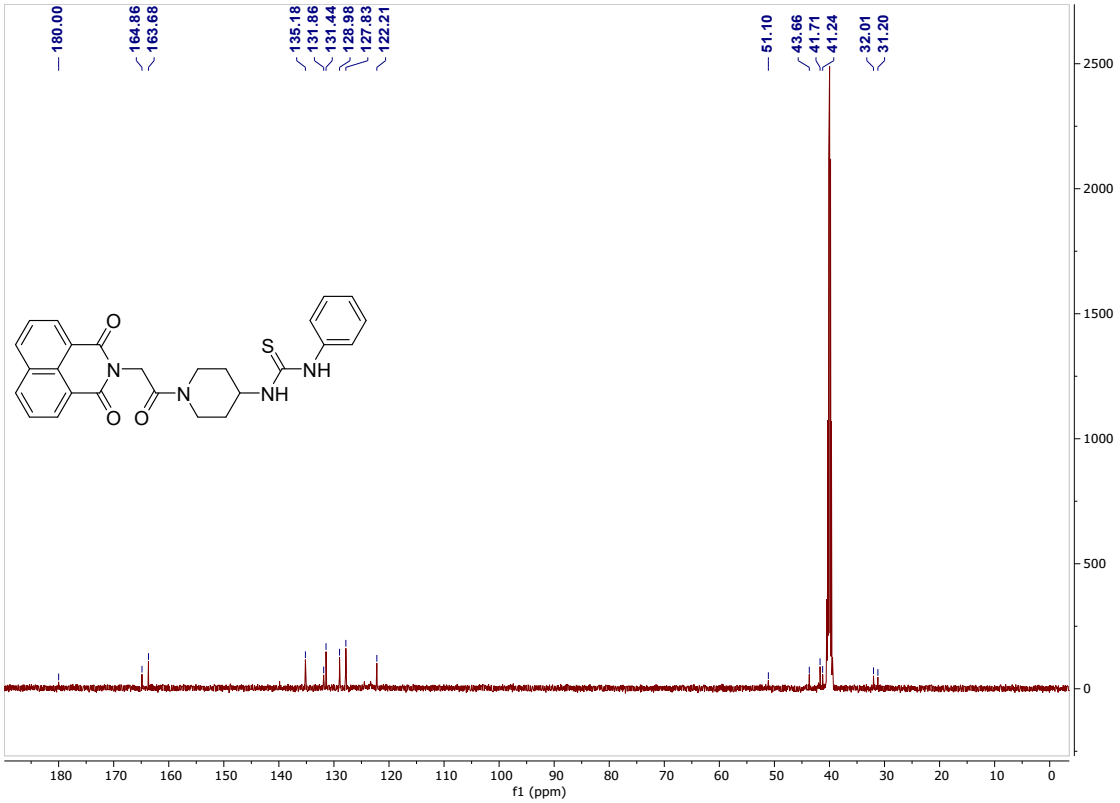


^{13}C spectrum for compound **13g** (125 MHz: DMSO-d_6)

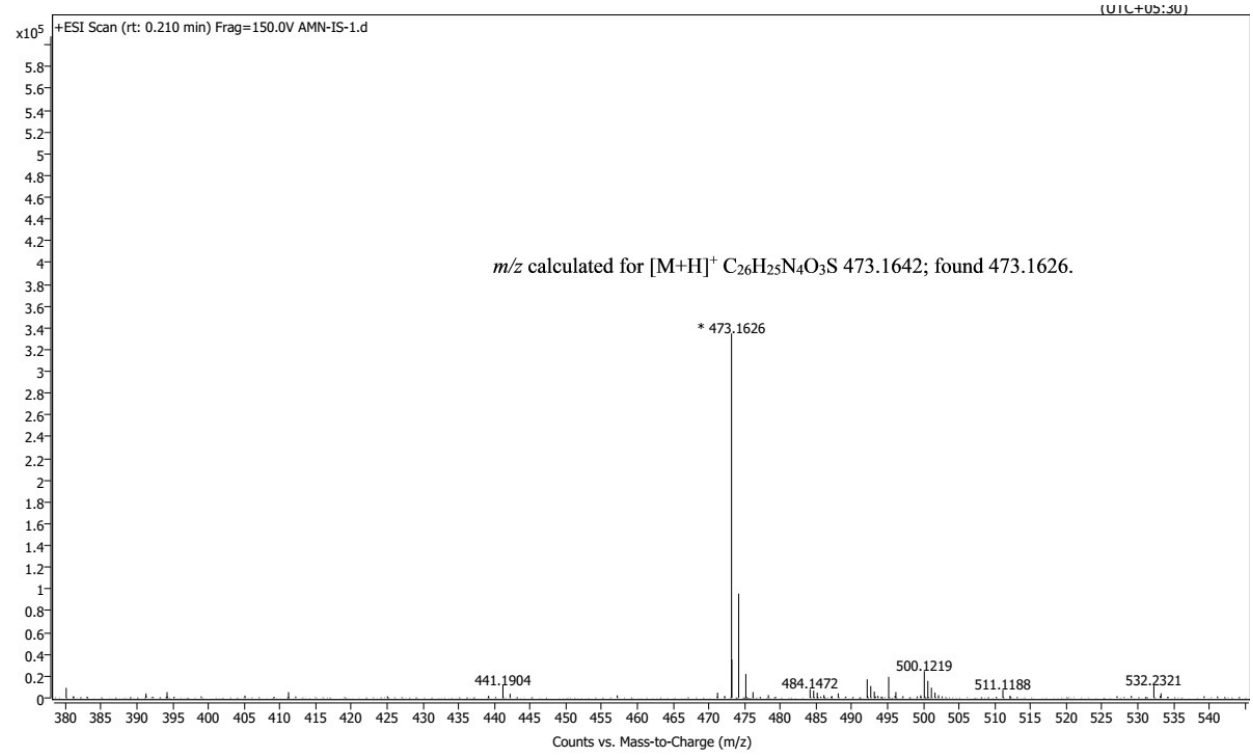

+ESI Scan (rt: 0.878 min) Frag=122.0V CID@2.0 182.d
x10 4
m/z calculated for [M+H]+ C27H26ClN4O3S521.1409 ; found 521.1390.
543.1203
545.1189
521.1390
523.1362
546.1202
509.1592
515.2043
559.0951
Counts vs. Mass-to-Charge (m/z)

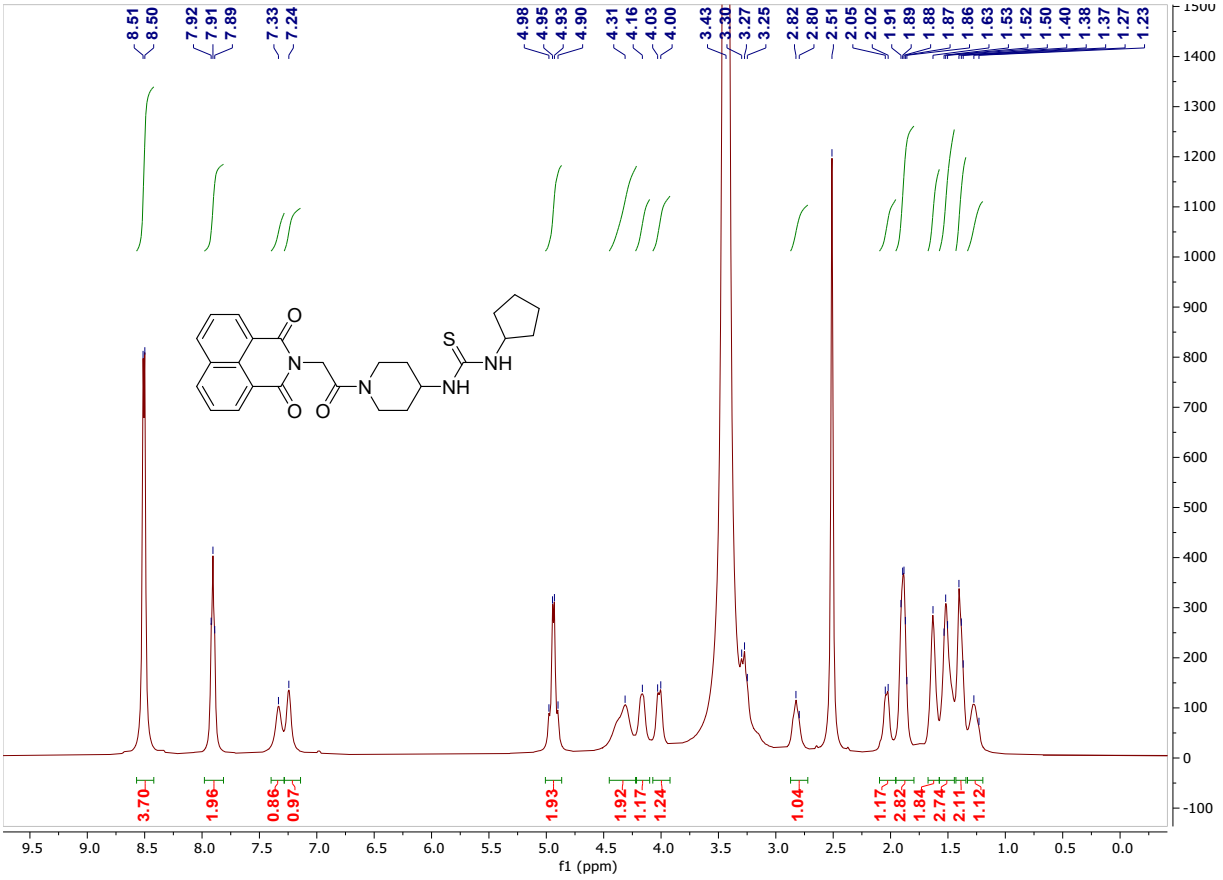


^{1}H spectrum for compound **17a** (500 MHz: DMSO-d_6)

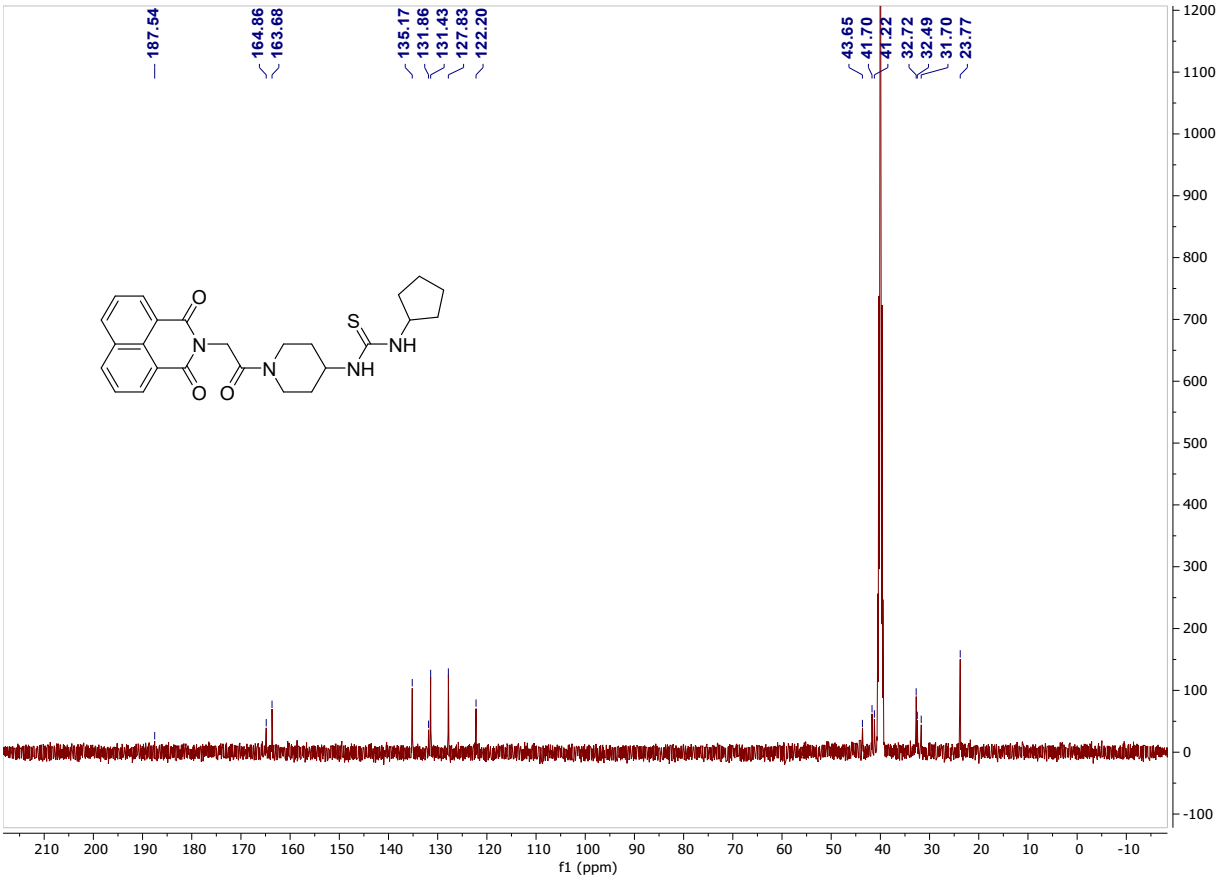


^{13}C spectrum for compound **17a** (125 MHz: DMSO-d_6)

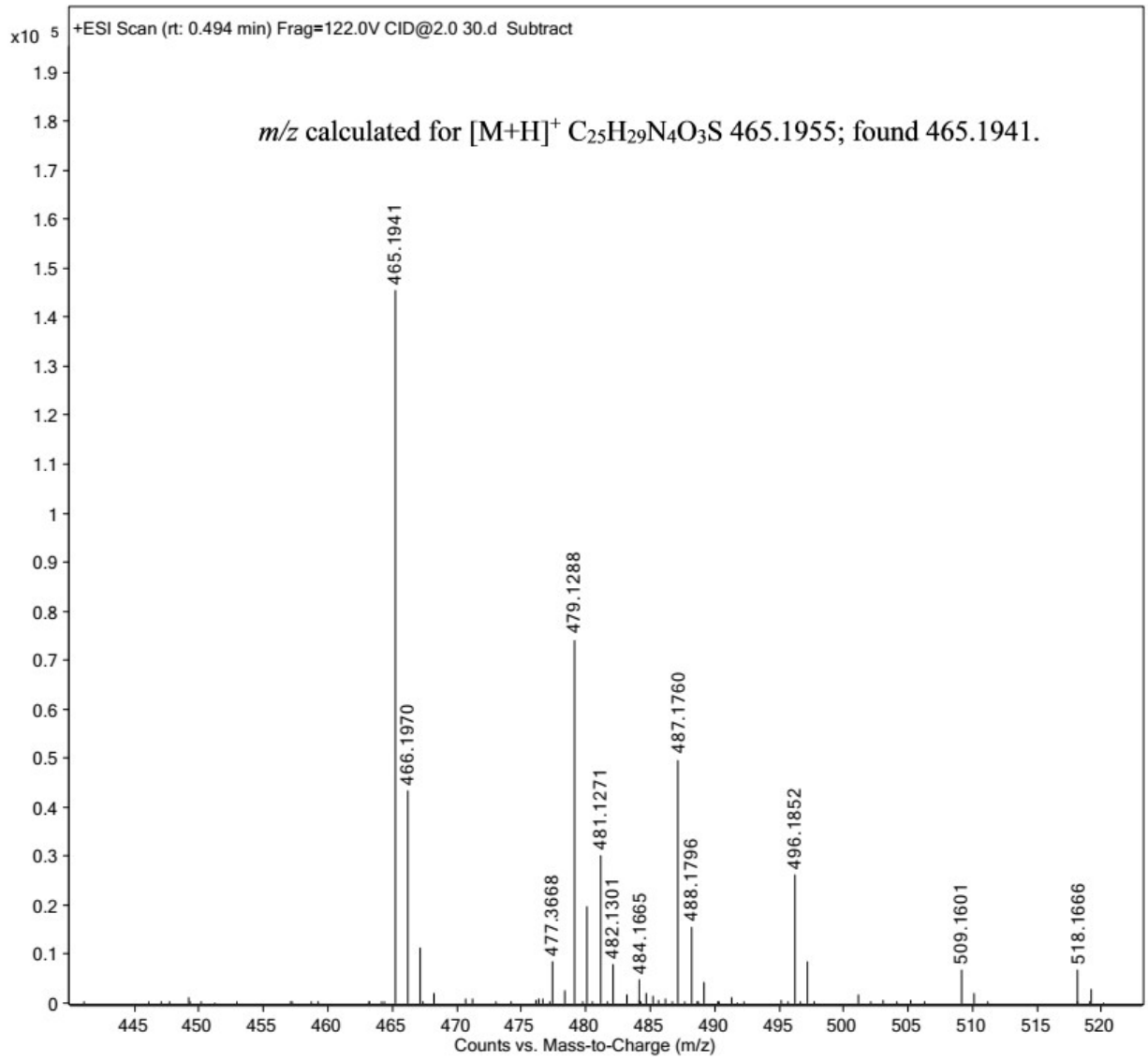

+ESI Scan (rt: 0.210 min) Frag=150.0V AMN-IS-1.d
x10^5
m/z calculated for [M+H]+ C26H25N4O3S 473.1642; found 473.1626.
* 473.1626
441.1904
484.1472
500.1219
511.1188
532.2321
Counts vs. Mass-to-Charge (m/z)

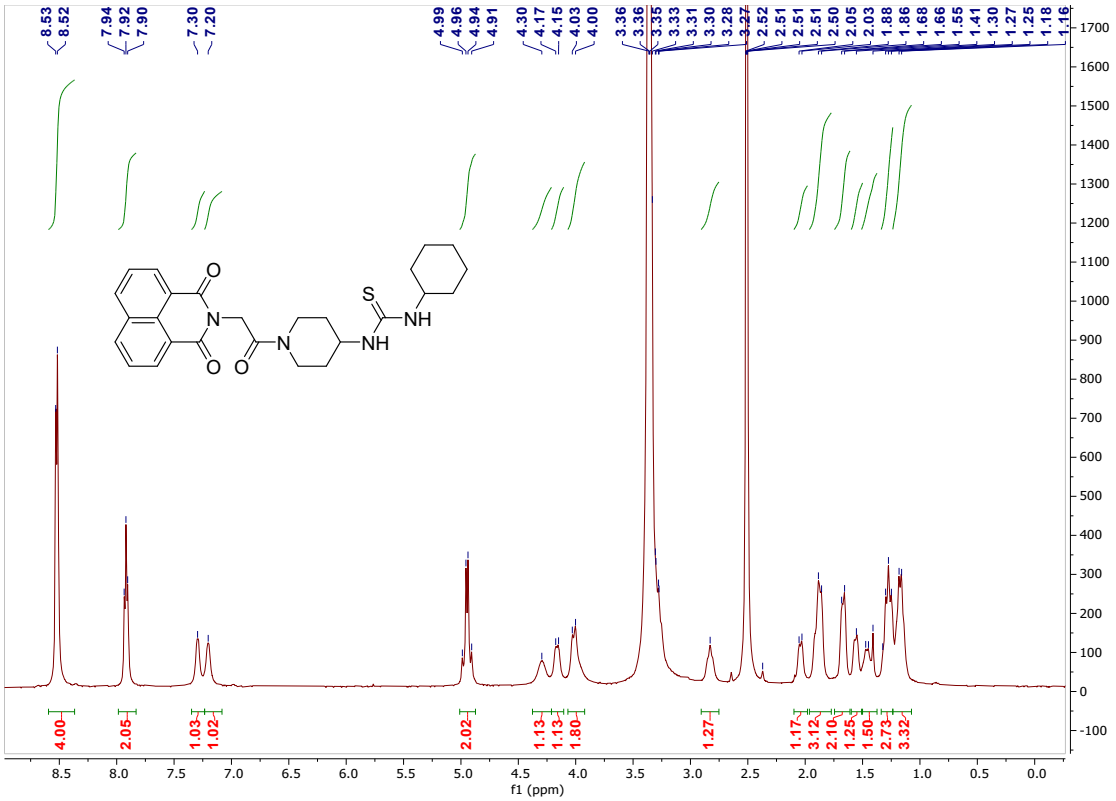

8.51
8.50
7.92
7.91
7.89
7.33
7.24
4.98
4.95
4.93
4.90
4.31
4.16
4.03
4.00
3.43
3.30
3.27
3.25
2.82
2.80
2.51
2.05
2.02
1.91
1.89
1.88
1.87
1.86
1.63
1.53
1.52
1.50
1.40
1.38
1.37
1.27
1.23
3.70
1.96
0.86
0.97
1.93
1.92
1.17
1.24
1.04
1.17
2.82
1.84
2.74
2.11
1.12
f1 (ppm)

^{1}H spectrum for compound **17b** (500 MHz: DMSO-d_6)

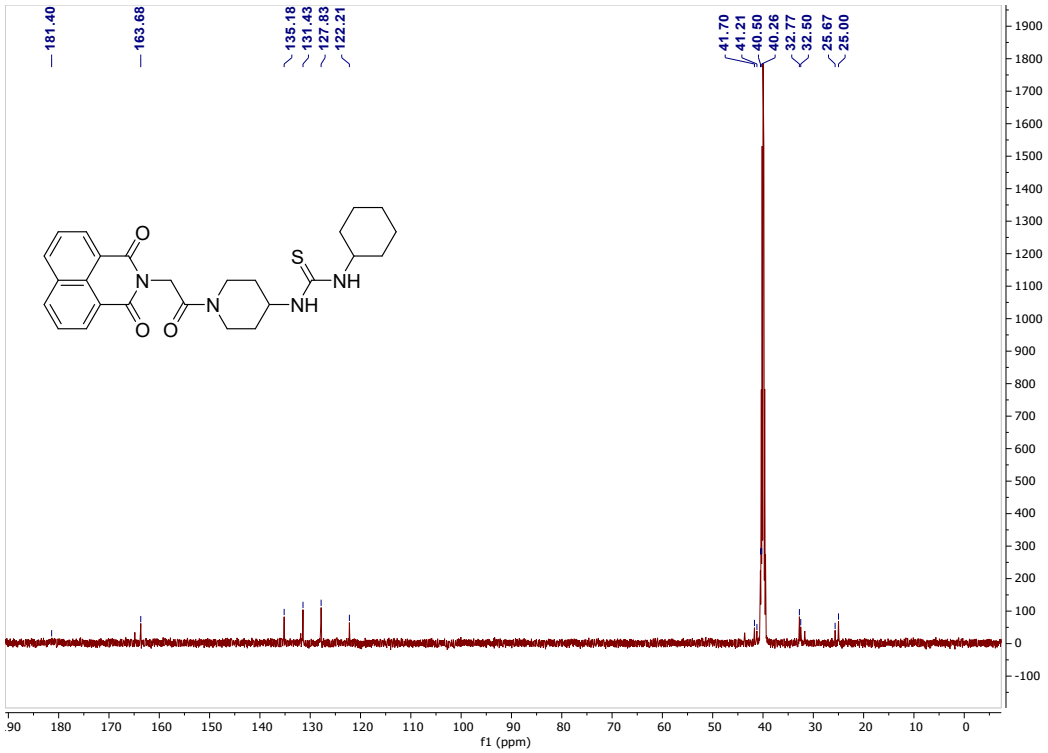


^{13}C spectrum for compound **17b** (125 MHz: DMSO-d_6)

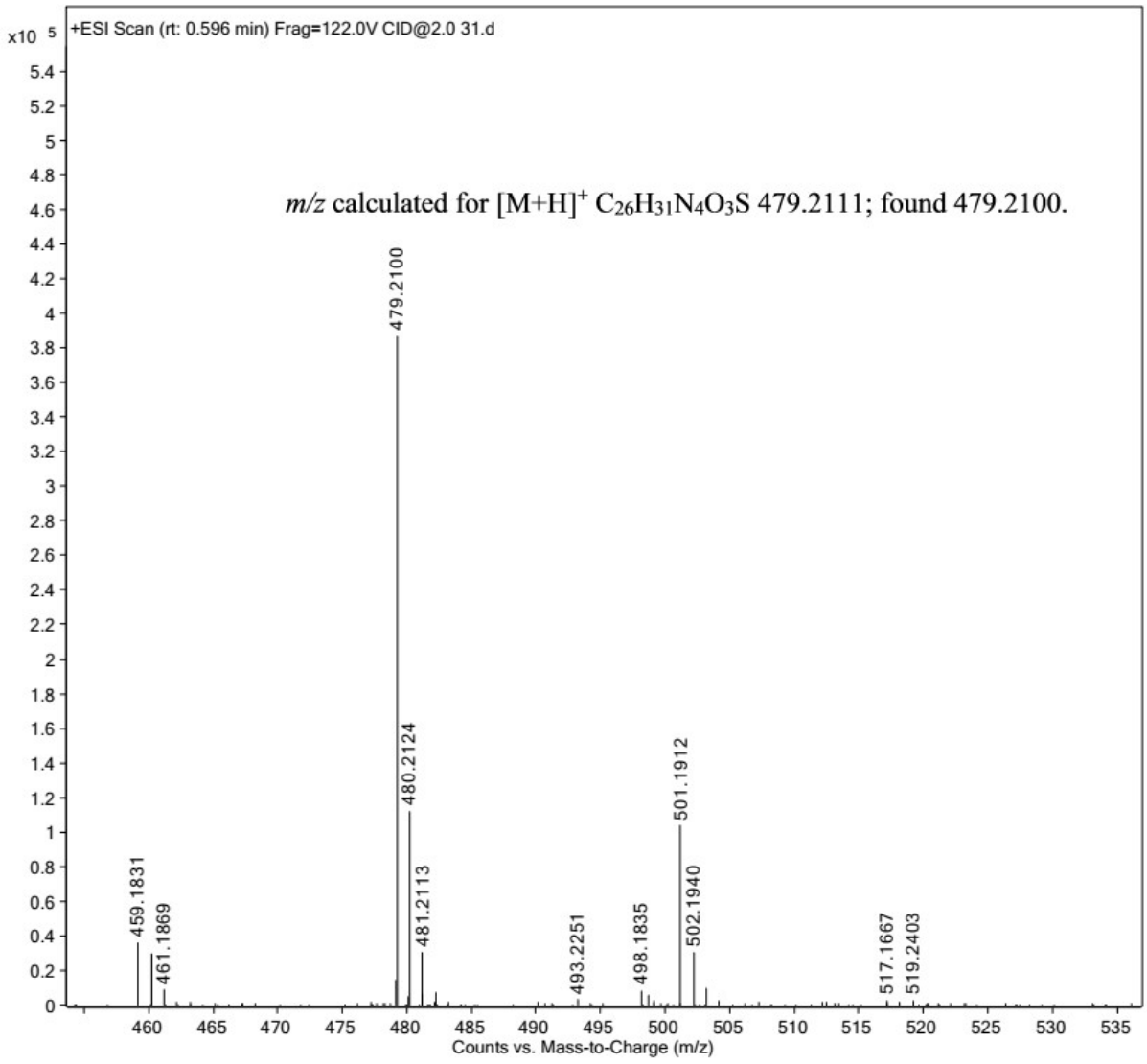

+ESI Scan (rt: 0.494 min) Frag=122.0V CID@2.0 30.d Subtract
x10 5
m/z calculated for [M+H]+ C25H29N4O3S 465.1955; found 465.1941.
465.1941
466.1970
479.1288
487.1760
481.1271
496.1852
488.1796
477.3668
482.1301
484.1665
509.1601
518.1666
Counts vs. Mass-to-Charge (m/z)

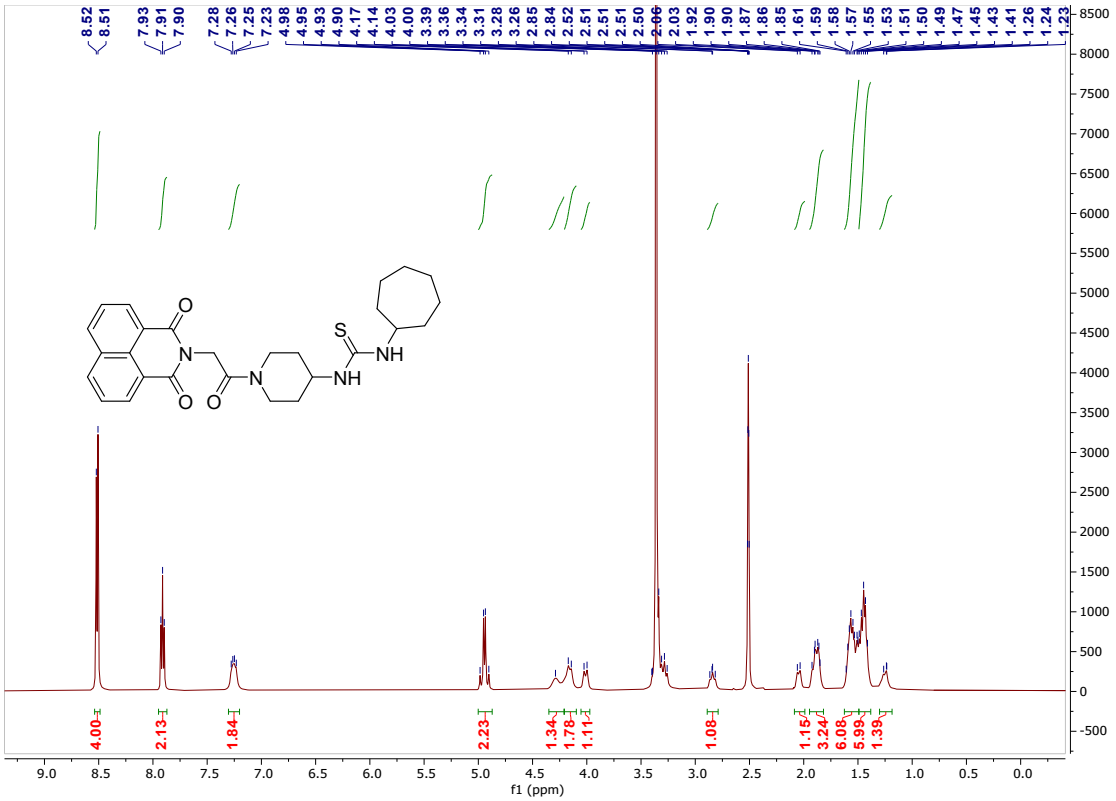


^{1}H spectrum for compound **17c** (500 MHz: DMSO-d_6)

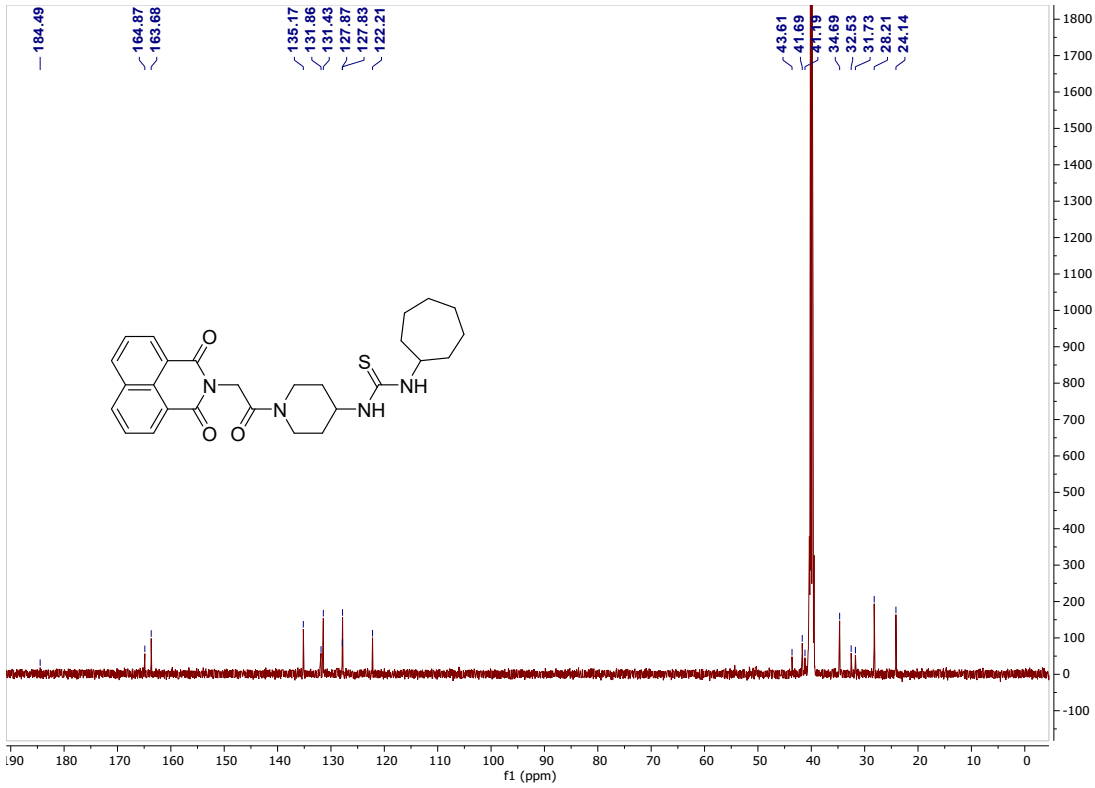


^{13}C spectrum for compound **17c** (125 MHz: DMSO-d_6)

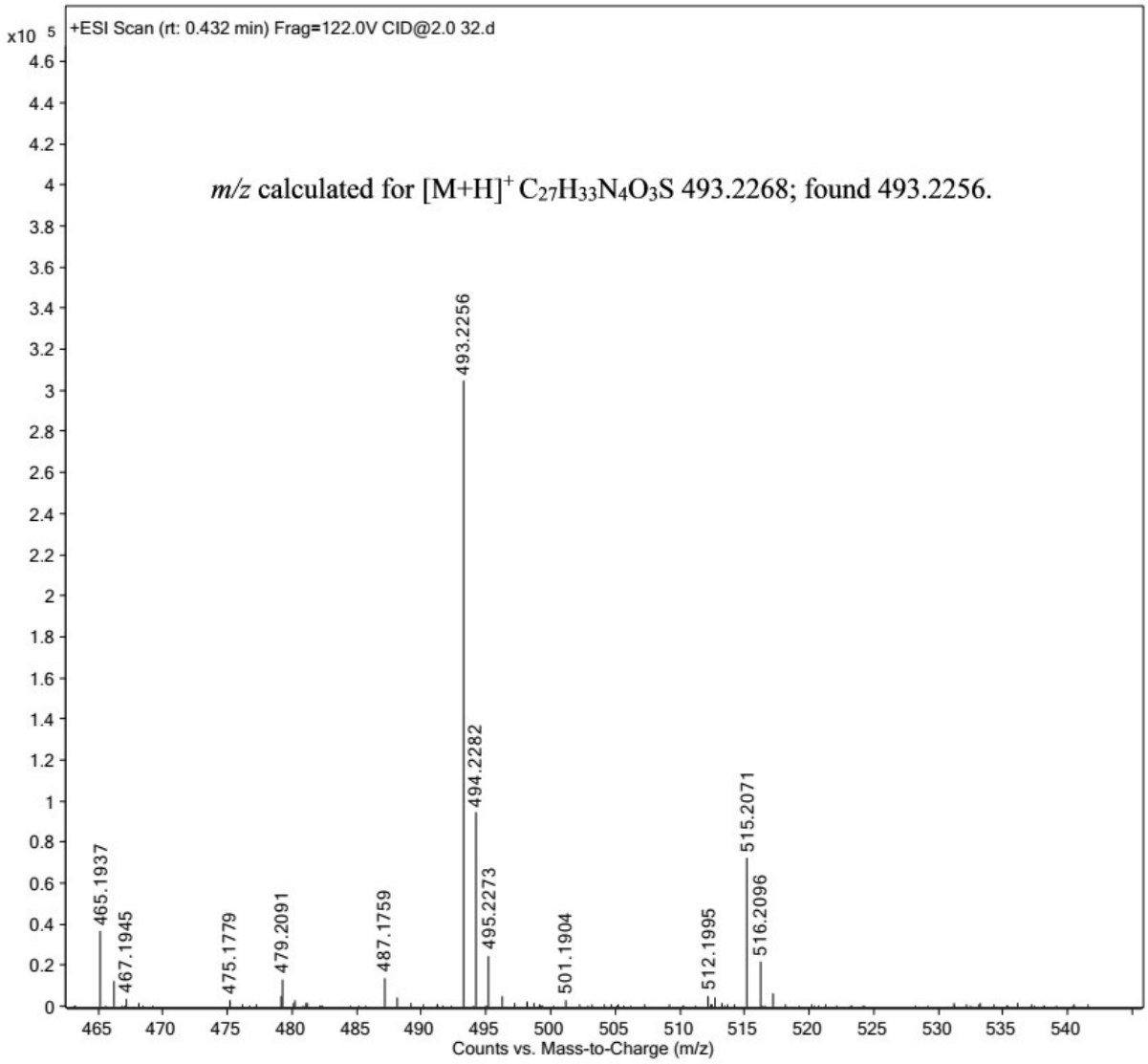

+ESI Scan (rt: 0.596 min) Frag=122.0V CID@2.0 31.d
x10 5
m/z calculated for [M+H]+ C26H31N4O3S 479.2111; found 479.2100.
479.2100
480.2124
481.2113
459.1831
461.1869
493.2251
498.1835
501.1912
502.1940
517.1667
519.2403
Counts vs. Mass-to-Charge (m/z)

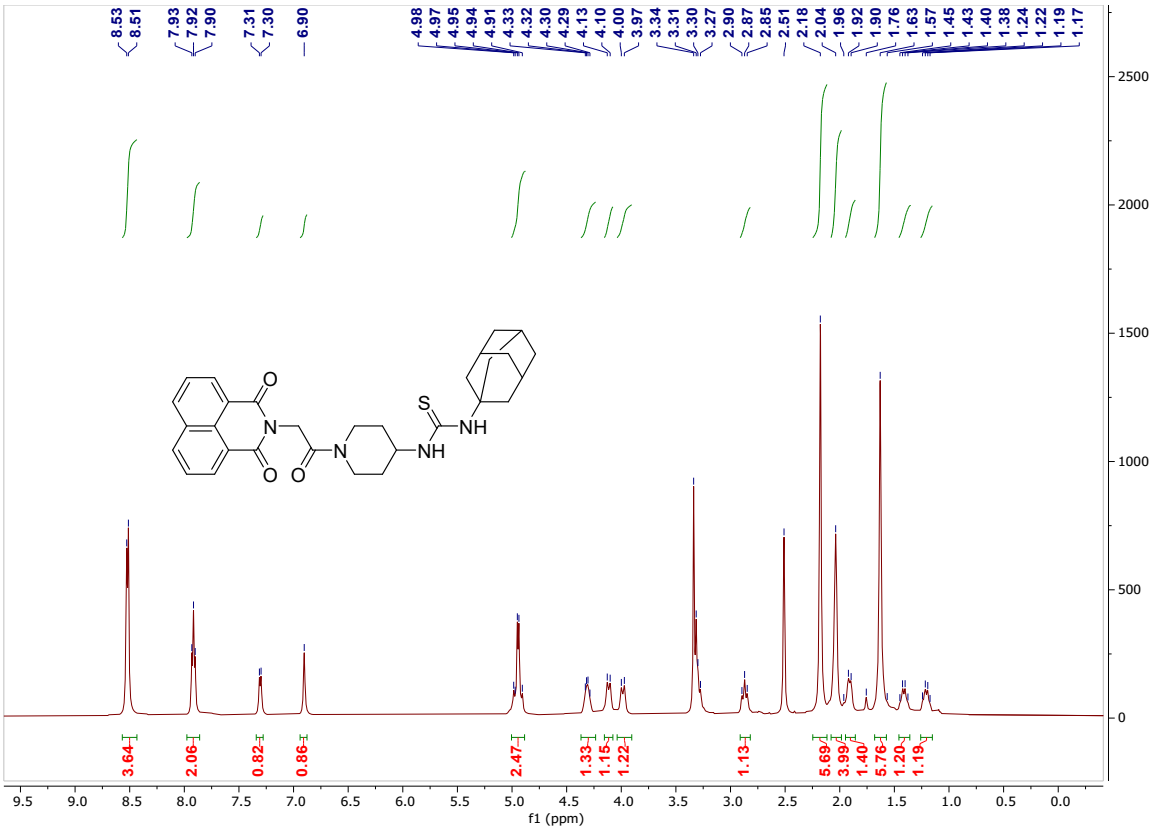


^{1}H spectrum for compound **17d** (500 MHz: DMSO-d_6)

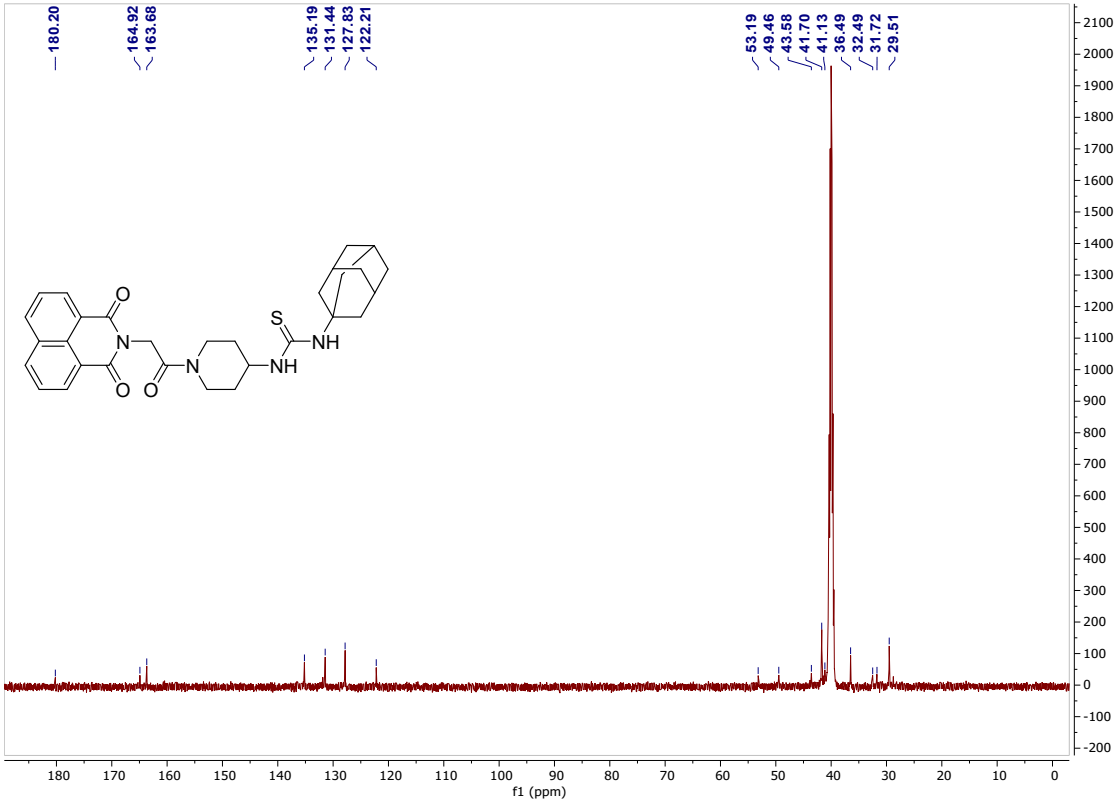


^{13}C spectrum for compound **17d** (125 MHz: DMSO-d_6)

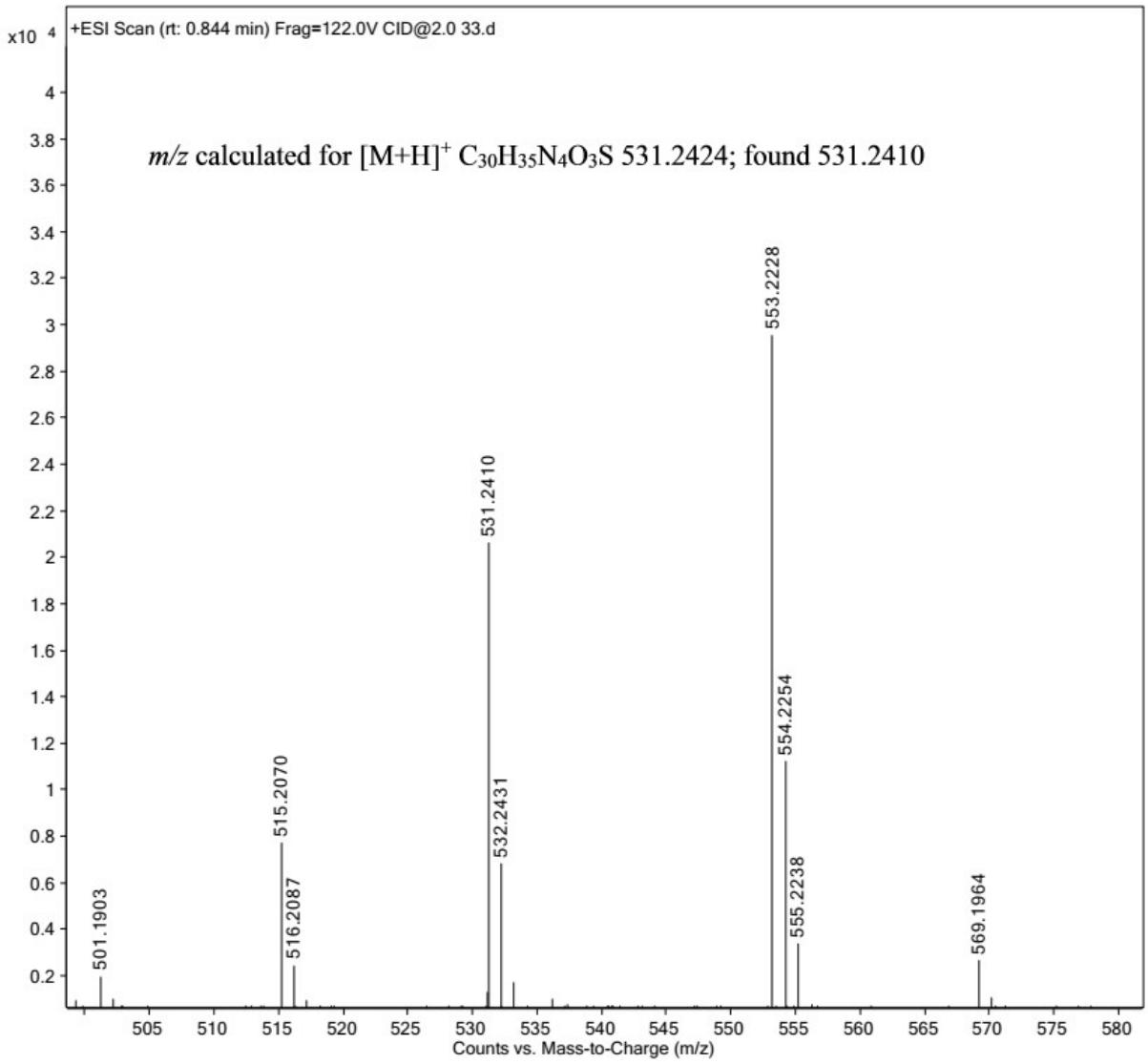

+ESI Scan (rt: 0.432 min) Frag=122.0V CID@2.0 32.d
x10 5
m/z calculated for [M+H]+ C27H33N4O3S 493.2268; found 493.2256.
493.2256
494.2282
515.2071
465.1937
467.1945
475.1779
479.2091
487.1759
495.2273
501.1904
512.1995
516.2096
Counts vs. Mass-to-Charge (m/z)



^{1}H spectrum for compound **17e** (500 MHz: DMSO-d_6)



^{13}C spectrum for compound **17e** (125 MHz: DMSO-d_6)



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