Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Design, synthesis *via* one-pot approach and molecular docking studies of novel pyrrolo[2,1-*a*]isoquinoline derivatives

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EXPERIMENTAL SECTION

1. Materials and Methods

All the Pyrrolo[2,1-a]isoquinoline derivatives were prepared using isatins, 1,2,3,4-tetrahydroisoquinoline and chalcones under reflux conditions for 10 h. All the starting materials, chemical reagents and solvents except the chalcones were obtained from commercial sellers and used as such without any further purification. The progress of the reaction was monitored by thin-layer chromatography (TLC) performed on silica gel 60 F254 precoated aluminium sheets. TLC was visualised by a 254 nm UV lamp and iodine staining. The reaction products were purified through silica gel (230−400 mesh) column chromatography using ethyl acetate/hexane as eluent in increasing polarity. Melting points were recorded using melting point equipment and are uncorrected. NMR spectra were recorded using 500 MHz for ^{1}H and 126 MHz for ^{13}C using $CDCl_3$ as a solvent. Tetramethylsilane (TMS) was used as internal standard (signal at 0 ppm) for ^{1}H chemical shifts measurements, and coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer using positive electrospray ionisation (ESI^{+}) for ion detection. The structural assignments of products were made by analysing their $^{1}H/^{13}C$ NMR, HRMS spectra of a typical compound.

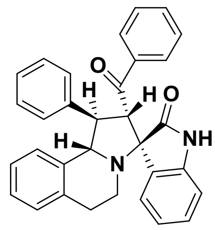
Representative Procedure for the Synthesis of Chalcones:

In a 50 mL round bottom flask, suitably substituted acetophenone (7.35 mmol) was dissolved in ethanol (10 mL). Then 6 mL of 10% NaOH solution was added to it and stirring the reaction mixture for 30 min at 0 ^{o}C. After that, substituted benzaldehydes were added to the reaction mixture and stirring was continued for 3-4 hrs. Next, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate/water. The organic layer was dried over anhydrous sodium sulphate and concentrated in a vacuum to yield the crude product.

Representative Procedure for the Synthesis of Pyrrolo[2,1-a]isoquinoline derivatives: In a 50 mL round bottom flask, substituted isatin (0.5 mmol) was dissolved in toluene (5 mL) followed by the addition of 1,2,3,4-tetrahydroisoquinoline (0.5 mmol) and the mixture was stirred at room temperature for half an hour. After that, substituted chalcones (0.5 mmol) was added to the reaction mixture and stirring was continued at reflux condition for 10 hrs. Next, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate/water. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum to yield the crude product which was purified by column chromatography using ethyl acetate/n-hexane (3:17) as eluent.

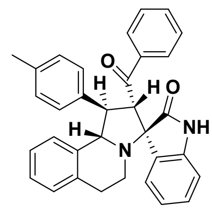
2. Spectral Data:

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4a):



Prepared following the general procedure; pale yellow solid (0.204 g, 87%); R_f = 0.37 (EtOAc/Hexane = 2/5); mp 205-206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.71 – 7.66 (m, 2H), 7.46 – 7.32 (m, 4H), 7.32 – 7.20 (m, 2H), 7.14 – 7.10 (m, 2H), 7.10 – 7.04 (m, 3H), 6.98 – 6.90 (m, 2H), 6.86 (m, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.46 (m, 1H), 5.21 (d, J = 10.1 Hz, 1H), 4.58 (d, J = 9.5 Hz, 1H), 4.34 (t, J = 9.8 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.72 – 2.66 (m, 1H), 2.63 – 2.56 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.69, 180.19, 141.86, 140.53, 137.91, 137.22, 134.49, 132.46, 129.02, 128.97, 128.94, 128.68, 127.91, 127.46, 127.31, 126.86, 126.67, 126.20, 125.39, 124.95, 122.95, 108.81, 70.86, 63.40, 63.26, 50.55, 42.22, 30.20; HRMS (ESI, Orbitrap) calcd for $C_{32}H_{27}N_2O_2$ $[M+H]^+$ = 471.2073, found = 471.2075 .

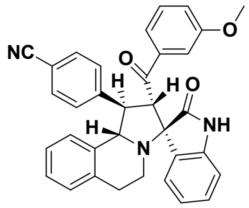
(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4b):



Prepared following the general procedure; pale yellow solid (0.211 g, 87%); R_f = 0.37 (EtOAc/Hexane = 2/5); mp 229-230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.13

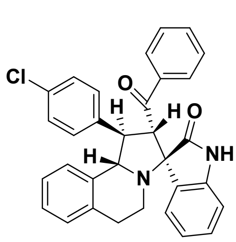
– 7.09 (m, 3H), 7.08 – 7.04 (m, 2H), 6.97 – 6.97 (m, 2H), 6.84 – 6.82 (m, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 10.1 Hz, 1H), 4.56 (d, *J* = 9.5 Hz, 1H), 4.30 (t, *J* = 9.8 Hz, 1H), 3.01 – 2.88 (m, 2H), 2.73 – 2.54 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.90, 180.48, 140.67, 138.86, 138.15, 137.37, 136.50, 134.61, 132.56, 129.76, 129.12, 128.91, 128.78, 128.02, 127.59, 127.50, 126.78, 126.29, 125.51, 125.10, 123.06, 108.97, 70.99, 63.44, 63.39, 50.31, 42.36, 30.33, 21.18; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{29}N_2O_2$ $[M+H]^+$ = 485.2229, found = 485.2241 .

4-((1'R,2'S,3R,10b'S)-2'-(3-methoxybenzoyl)-2-oxo-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-1'-yl)benzonitrile (4c):



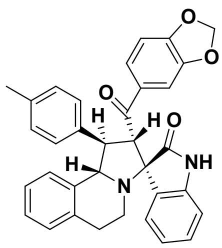
Prepared following the general procedure; white solid (0.223 g, 85%); R_f = 0.31 (EtOAc/Hexane = 2/5); mp 217-218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 2H), 7.73 – 7.68 (m, 2H), 7.58 (s, 1H), 7.15 – 7.07 (m, 2H), 7.07 – 7.01 (m, 2H), 6.98 – 6.93 (m, 3H), 6.90 – 6.81 (m, 3H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 5.22 (d, *J* = 9.9 Hz, 1H), 4.46 (d, *J* = 9.5 Hz, 1H), 4.38 (t, *J* = 9.7 Hz, 1H), 3.67 (s, 3H), 3.00 – 2.89 (m, 2H), 2.73 – 2.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.27, 180.01, 159.42, 147.95, 140.78, 138.48, 137.35, 134.75, 133.02, 130.02, 129.51, 129.16, 127.08, 126.76, 126.72, 125.71, 124.76, 123.26, 120.10, 119.96, 118.98, 111.53, 111.07, 109.20, 71.03, 63.58, 63.51, 55.36, 50.76, 42.34, 30.27. (One peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for $C_{34}H_{28}N_3O_3$ $[M+H]^+$ = 526.2131, found = 526.2133.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(4-chlorophenyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4d):



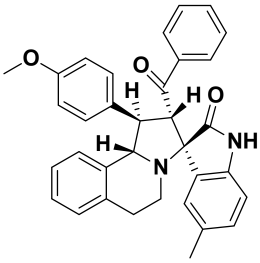
Prepared following the general procedure; yellow solid (0.217 g, 86%); R_f = 0.39 (EtOAc/Hexane = 2/5); mp 235-236 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.65 – 7.60 (m, 2H), 7.42 – 7.34 (m, 4H), 7.30 – 7.24 (m, 1H), 7.14 – 7.10 (m, 3H), 7.09 – 7.03 (m, 2H), 6.99 – 6.92 (m, 2H), 6.87 – 6.84 (m, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.46 (d, J = 7.6 Hz, 1H), 5.17 (d, J = 10.1 Hz, 1H), 4.50 (d, J = 9.4 Hz, 1H), 4.31 (t, J = 9.8 Hz, 1H), 3.00 – 2.87 (m, 2H), 2.73 – 2.54 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.53, 180.23, 140.55, 140.49, 137.59, 137.06, 134.49, 132.68, 132.63, 130.30, 129.15, 128.80, 127.99, 127.43, 127.09, 126.58, 126.36, 125.46, 124.78, 123.02, 108.94, 70.83, 63.29, 63.19, 49.93, 42.18, 30.15 (One peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for $C_{32}H_{26}N_2O_2Cl[M+H]^+$ = 505.1683, found = 505.1684.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4e):



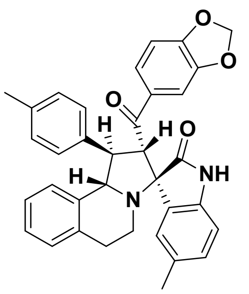
Prepared following the general procedure; white solid (0.229 g, 87%); R_f = 0.51 (EtOAc/Hexane = 2/5); mp 181-182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.0 Hz, 2H), 7.40 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.12 – 7.05 (m, 3H), 7.04 – 6.99 (m, 1H), 6.94 – 6.85 (m, 3H), 6.72 (d, J = 7.8 Hz, 1H), 6.53 (dd, J = 8.0, 1.7 Hz, 2H), 5.87 (q, J = 1.4 Hz, 2H), 5.14 (d, J = 10.1 Hz, 2H), 4.44 (d, J = 9.4 Hz, 1H), 4.27 (t, J = 9.8 Hz, 1H), 2.93 (d, J = 8.0 Hz, 1H), 2.67 (d, J = 11.5 Hz, 1H), 2.64 – 2.54 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.58, 179.96, 151.17, 147.55, 140.42, 138.75, 138.03, 136.32, 134.46, 132.43, 129.60, 128.95, 128.75, 128.60, 127.45, 126.80, 126.11, 125.33, 124.96, 123.66, 122.96, 108.67, 107.34, 107.09, 101.48, 70.91, 63.26, 63.08, 50.41, 42.25, 30.21, 21.01; HRMS (ESI, Orbitrap) calcd for $C_{34}H_{29}N_2O_4$ $[M+H]^+$ = 529.2127, found = 529.2128.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(4-methoxyphenyl)-5-methyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4f):



Prepared following the general procedure; off white solid (0.213 g, 83%); R_f = 0.44 (EtOAc/Hexane = 2/5); mp 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 2H), 7.42 – 7.34 (m, 3H), 7.29 – 7.21 (m, 2H), 7.13 – 7.08 (m, 2H), 7.08 – 7.03 (m, 1H), 6.94 – 6.90 (m, 3H), 6.86 (s, 1H), 6.75 – 6.70 (m, 2H), 6.30 (d, *J* = 7.8 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 4.50 (d, *J* = 9.5 Hz, 1H), 4.25 (t, *J* = 9.8 Hz, 1H), 3.80 (s, 3H), 3.02 – 2.86 (m, 2H), 2.72 – 2.53 (m, 2H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.97, 180.13, 158.41, 138.07, 138.03, 137.46, 134.48, 133.87, 132.42, 132.32, 129.88, 129.22, 128.64, 127.86, 127.42, 127.36, 127.25, 126.13, 125.34, 124.93, 114.31, 108.45, 70.79, 63.29, 55.13, 49.77, 42.24, 30.20, 20.80.(One peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for $C_{34}H_{31}N_2O_3$ $[M+H]^+$ = 515.2335, found = 515.2333.

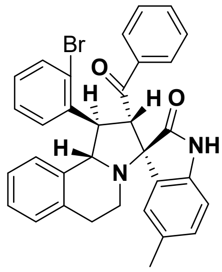
(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-5-methyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4g):



Prepared following the general procedure; pale yellow solid (0.231 g, 85%); R_f = 0.44 (EtOAc/Hexane = 2/5); mp 207-208 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.10 – 6.98 (m, 3H), 6.89 (td, *J* = 7.6, 7.0, 1.8 Hz, 3H), 6.79 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 5.91 – 5.79 (m, 2H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.42 (d, *J* = 9.4 Hz, 1H), 4.25 (t, *J* = 9.7 Hz, 1H), 3.01 – 2.86 (m, 2H), 2.74 – 2.53 (m, 2H), 2.33 (s, 3H), 2.18 (s, 3H). ^{13}C

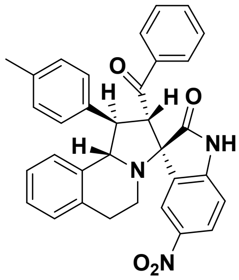
NMR (126 MHz, $CDCl_3$) δ 194.81, 180.31, 151.21, 147.65, 138.97, 138.22, 138.18, 136.41, 134.59, 132.68, 132.57, 129.71, 129.36, 128.88, 128.72, 127.58, 127.49, 126.22, 125.44, 125.08, 123.77, 108.58, 107.42, 107.21, 101.58, 71.13, 63.39, 63.21, 50.49, 42.41, 30.31, 21.14, 20.96; HRMS (ESI, Orbitrap) calcd for $C_{35}H_{31}N_2O_4$ $[M+H]^+$ = 543.2284, found = 543.2289.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(2-bromophenyl)-5-methyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4h):



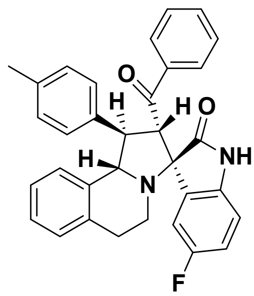
Prepared following the general procedure; pale yellow solid (0.225 g, 80%); R_f = 0.31 (EtOAc/Hexane = 2/5); mp 211-212 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.29 – 7.24 (m, 1H), 7.13 (td, *J* = 7.9, 4.1 Hz, 4H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 5.16 (d, *J* = 9.8 Hz, 1H), 5.01 (d, *J* = 11.2 Hz, 1H), 4.59 (s, 1H), 3.04 – 2.94 (m, 1H), 2.90 (td, *J* = 10.9, 3.7 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.32, 180.21, 160.16, 142.97, 138.06, 137.32, 137.29, 134.28, 133.42, 132.59, 132.40, 130.14, 129.37, 128.67, 128.33, 128.22, 127.92, 127.55, 127.51, 126.82, 126.28, 125.59, 124.62, 108.53, 70.99, 65.39, 63.07, 48.13, 42.31, 30.13, 20.79; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}BrN_2O_2$ $[M+H]^+$ = 563.1334, found= 563.1335.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-nitro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4i):



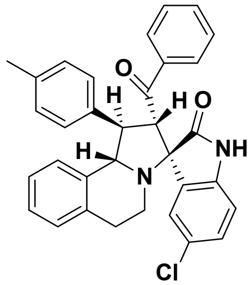
Prepared following the general procedure; pale yellow solid (0.212 g, 80%); R_f = 0.37 (EtOAc/Hexane = 2/5); mp 220-221 °C; ^1H NMR (500 MHz, $CDCl_3$ & DMSO-d_6) δ 10.18 (br s, 1H), 7.89 (t, *J* = 5.9 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 10.7 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.17 – 7.09 (m, 3H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.94 (t, *J*= 7.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.32 (t, *J* = 9.7 Hz, 1H), 2.96 (q, *J* = 12.1, 9.0 Hz, 2H), 2.69 (d, *J* = 11.8 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$ & DMSO-d_6) δ 196.20, 180.57, 147.83X2, 143.20, 138.32, 137.57, 137.04, 136.51, 134.10, 132.77, 129.66, 128.70, 128.62, 128.15, 127.35, 126.30, 125.84, 125.43, 124.83, 122.18, 108.97, 70.54, 63.32, 63.22, 50.11, 42.44, 30.05, 21.01; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}N_3O_4$[M+H]$^+$ = 530.2080, found = 530.2064.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-fluoro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4j):



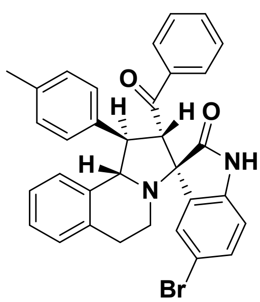
Prepared following the general procedure; pale yellow solid (0.211 g, 84%); R_f = 0.34 (EtOAc/Hexane = 2/5); mp 255-256 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.59 – 7.51 (m, 2H), 7.45 – 7.38 (m, 2H), 7.30 – 7.25 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 2H), 7.10 – 7.04 (m, 2H), 6.93 (td, *J* = 7.4, 1.9 Hz, 1H), 6.82 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.66 (td, *J* = 8.7, 2.7 Hz, 1H), 6.39 (dd, *J* = 8.5, 4.1 Hz, 1H), 5.15 (d, *J* = 10.1 Hz, 1H), 4.55 (d, *J* = 9.5 Hz, 1H), 4.27 (t, *J* = 9.8 Hz, 1H), 3.02 – 2.84 (m, 2H), 2.69 (dd, *J* = 13.0, 7.6 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.62, 180.52, 160.25, 158.33, 138.61, 137.91, 137.30, 136.61, 136.59, 134.42, 132.75, 129.80, 129.47, 129.41, 128.86, 128.78, 128.16, 127.63, 126.38, 125.56, 125.05, 115.78, 115.59, 114.61, 114.41, 109.65, 109.59, 71.29, 71.27, 63.45, 63.39, 50.28, 42.45, 30.28, 21.15; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}FN_2O_2$ [M+H]$^+$ = 503.2135, found = 503.2136.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-chloro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4k):



Prepared following the general procedure; white solid (0.215 g, 83%); R_f = 0.44 (EtOAc/Hexane = 2/5); mp 138-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.65 (d, J = 2.2 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.37 – 7.32 (m, 2H), 7.24 (s, 1H), 7.20 (dd, J = 8.2, 2.2 Hz, 1H), 7.07 (t, J = 7.9 Hz, 3H), 7.04 – 6.96 (m, 3H), 6.82 (t, J = 7.5 Hz, 1H), 6.67 (dd, J = 7.7, 1.4 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 5.80 (d, J = 8.4 Hz, 1H), 5.19 (dd, J = 8.4, 6.7 Hz, 1H), 4.08 (d, J = 6.8 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.78 (dd, J = 9.4, 3.2 Hz, 2H), 2.72 – 2.62 (m, 1H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.28, 177.21, 139.78, 138.80, 137.20, 135.90, 134.62, 132.72, 132.38, 130.46, 129.22, 129.12, 128.98, 128.47, 128.42, 128.36, 128.11, 125.74, 125.65, 125.16, 125.07, 110.24, 63.83, 60.44, 51.31, 43.03, 30.02, 29.59, 20.95; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}ClN_2O_2$ $[M+H]^+$ = 519.1839, found = 519.1845.

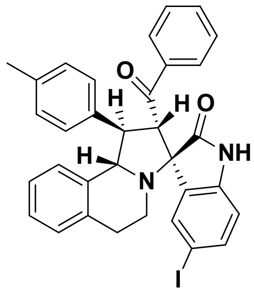
(1'R,2'S,3R,10b'S)-2'-benzoyl-5-bromo-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4l):



Prepared following the general procedure; pale yellow solid (0.228 g, 81%); R_f = 0.63 (EtOAc/Hexane = 2/5); mp 155-156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.7 Hz, 2H), 7.27 (d, J = 12.3 Hz, 1H), 7.22 – 7.18 (m, 3H), 7.15 (t, J = 7.6 Hz, 2H), 7.11 – 7.07 (m, 3H), 6.93 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.31 (d, J = 8.2 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.54 (d, J = 9.4 Hz, 1H), 4.27 (t, J = 9.8

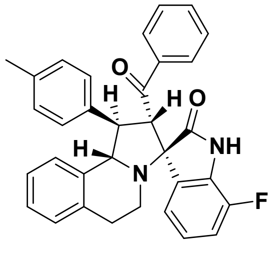
Hz, 1H), 3.04 – 2.88 (m, 2H), 2.72 – 2.65 (m, 1H), 2.63 – 2.54 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.52, 179.59, 139.46, 138.44, 137.73, 137.35, 136.49, 134.24, 132.54, 131.85, 129.68, 128.73, 128.64, 128.04, 127.47, 126.26, 125.42, 124.90, 115.64, 110.20, 70.78, 63.41, 63.34, 50.05, 42.36, 30.13, 21.02. (Two peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}BrN_2O_2$ $[M+H]^+$ = 563.1334, found = 563.1336.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-iodo-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4m):



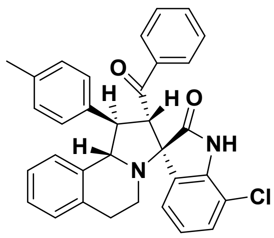
Prepared following the general procedure; pale yellow solid (0.253 g 83%); R_f = 0.43 (EtOAc/Hexane = 2/5); mp 175-176 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.77 – 7.72 (m, 2H), 7.54 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.14 (s, 1H), 7.05 (q, *J* = 6.9, 5.8 Hz, 3H), 6.98 (t, *J* = 9.5 Hz, 3H), 6.86 – 6.77 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 5.78 (d, *J* = 8.3 Hz, 1H), 5.18 (dd, *J* = 8.4, 6.7 Hz, 1H), 4.05 (d, *J* = 6.7 Hz, 1H), 3.19 (m, 1H), 2.76 (dd, *J* = 9.1, 2.7 Hz, 2H), 2.66 (d, *J* = 15.7 Hz, 1H), 2.23 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 202.55, 176.96, 141.15, 139.03, 138.25, 137.41, 136.14, 134.81, 133.66, 132.95, 132.56, 131.23, 129.36, 129.19, 128.69, 128.57, 128.30, 125.94, 125.84, 125.27, 111.43, 85.70, 64.05, 60.68, 51.37, 43.25, 30.21, 21.15; (one peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}IN_2O_2$ $[M+H]^+$ = 611.1195, found = 611.1198.

(1'R,2'S,3R,10b'S)-2'-benzoyl-7-fluoro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4n):



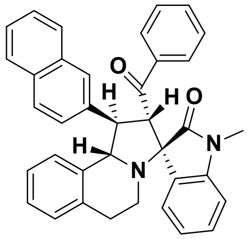
Prepared following the general procedure; pale yellow solid (0.176 g, 70%); R_f = 0.69 (EtOAc/Hexane = 2/5); mp 197-198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.57 – 7.54 (m, 2H), 7.41 – 7.37 (m, 2H), 7.32 – 7.28 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.17 – 7.11 (m, 2H), 7.11 – 7.05 (m, 2H), 6.95 – 6.92 (m, 1H), 6.86 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.81 – 6.79 (m, 1H), 6.76 – 6.70 (m, 2H), 5.17 (d, *J* = 10.1 Hz, 1H), 4.56 (d, *J* = 9.5 Hz, 1H), 4.28 (t, *J* = 9.8 Hz, 1H), 3.01 – 2.88 (m, 2H), 2.74 – 2.64 (m, 1H), 2.63 – 2.55 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.45, 179.32, 146.95, 145.01, 138.48, 137.85, 137.12, 136.47, 134.33, 132.67, 130.16, 130.14, 129.67, 128.75, 128.63, 127.97, 127.74, 127.65, 127.38, 126.21, 125.42, 124.95, 123.47, 123.43, 122.29, 122.27, 115.95, 115.82, 71.12, 71.10, 63.50, 63.25, 50.15, 42.32, 30.15, 21.01; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}FN_2O_2$ $[M+H]^+$ = 503.2135, found = 503.2130.

(1'R,2'S,3R,10b'S)-2'-benzoyl-7-chloro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4o):



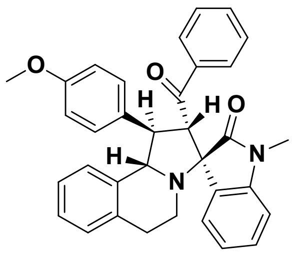
Prepared following the general procedure; pale yellow solid (0.181 g, 70%); Rf = 0.51 (EtOAc/Hexane = 2/6); mp 233-234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.51 (s, 1H), 7.40 – 7.34 (m, 2H), 7.34 – 7.27 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.19 – 7.12 (m, 2H), 7.14 – 7.04 (m, 2H), 6.82 – 6.79 (m,3H), 6.81 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 4.54 (d, *J* = 9.5 Hz, 1H), 4.27 (t, *J* = 9.8 Hz, 1H), 3.02 – 2.89 (m, 2H), 2.69 (d, *J* = 11.5 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.69, 179.37, 138.62, 138.29, 138.02, 137.24, 136.70, 134.52, 132.92, 129.88, 129.28, 128.95, 128.85, 128.14, 127.53, 126.44, 125.63, 125.14, 125.01, 123.92, 114.25, 99.98, 71.60, 66.74, 64.61, 55.13, 44.71, 32.13, 21.87; HRMS (ESI, Orbitrap) calcd for $C_{33}H_{28}ClN_2O_2$ $[M+H]^+$ = 519.1839, found = 519.1843.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1-methyl-1'-(naphthalen-2-yl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4p):



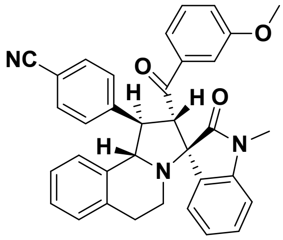
Prepared following the general procedure; pale yellow solid (0.213 g, 82%); Rf = 0.56 (EtOAc/Hexane = 2/6); mp 221-222 °C; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.11 (s, 1H), 7.91 (d, J = 1.2 Hz, 2H), 7.89 – 7.86 (m, 1H), 7.85 – 7.82 (m, 1H), 7.50 – 7.42 (m, 2H), 7.27 – 7.21 (m, 3H), 7.11 (dd, J = 7.4, 1.3 Hz, 1H), 7.09 – 7.03 (m, 4H), 7.03 – 7.00 (m, 1H), 6.92 – 6.89 (m, 1H), 6.86 – 6.83 (m, 1H), 6.73 – 6.69 (m, 1H), 6.34 (d, J = 7.7 Hz, 1H), 5.36 (d, J = 10.0 Hz, 1H), 4.66 (d, J = 9.8 Hz, 1H), 4.48 (t, J = 9.9 Hz, 1H), 3.10 (s, 3H), 3.02 – 2.90 (m, 2H), 2.73 – 2.63 (m, 1H), 2.59 – 2.50 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.84, 178.61, 143.61, 139.40, 138.10, 137.33, 134.70, 133.75, 132.65, 132.46, 129.16, 128.93, 128.82, 128.15, 128.01, 127.79, 127.67, 127.45, 127.04, 126.86, 126.33, 126.21, 126.06, 125.70, 125.54, 125.14, 123.10, 107.23, 71.03, 64.02, 63.54, 50.72, 42.47, 30.30, 25.95; HRMS (ESI, Orbitrap) calcd for $C_{37}H_{231}N_2O_2$ $[M+H]^+$ = 535.2386, found = 535.2388.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(4-methoxyphenyl)-1-methyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4q):



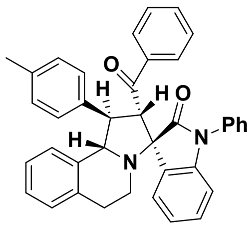
Prepared following the general procedure; pale yellow solid (0.211 g, 82%); Rf = 0.58 (EtOAc/Hexane = 2/6); mp 229-230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.7 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.14 – 7.03 (m, 5H), 7.02 – 6.98 (m, 1H), 6.96 – 6.90 (m, 3H), 6.92 – 6.85 (m, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.32 (d, J = 7.7 Hz, 1H), 5.15 (d, J = 10.1 Hz, 1H), 4.52 (d, J = 9.7 Hz, 1H), 4.24 (t, J = 9.9 Hz, 1H), 3.81 (s, 3H), 3.07 (s, 3H), 2.92 (d, J = 7.7 Hz, 2H), 2.65 (d, J = 12.3 Hz, 1H), 2.52 – 2.47 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.01, 178.63, 158.55, 143.58, 138.24, 137.45, 134.71, 133.83, 132.39, 130.02, 129.07, 128.78, 127.77, 127.46, 127.12, 126.26, 126.15, 125.46, 125.04, 123.04, 114.43, 107.16, 70.87, 64.13, 63.59, 55.26, 49.83, 42.39, 30.32, 25.89; HRMS (ESI, Orbitrap) calcd for $C_{34}H_{31}N_2O_3$ $[M+H]^+$ = 515.1335, found = 515.2333.

4-((1'R,2'S,3R,10b'S)-2'-(3-methoxybenzoyl)-1-methyl-2-oxo-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-1'-yl)benzonitrile (4r):



Prepared following the general procedure; pale yellow solid (0.218 g 81%); Rf = 0.59 (EtOAc/Hexane = 2/6); mp 225-226 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.73 – 7.68 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.08 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.06 – 7.02 (m, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.85 – 6.80 (m, 2H), 6.73 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.42 – 6.36 (m, 1H), 5.23 (d, *J* = 10.0 Hz, 1H), 4.44 (d, *J* = 9.7 Hz, 1H), 4.34 (t, *J* = 9.8 Hz, 1H), 3.65 (s, 3H), 3.11 (s, 3H), 2.98 – 2.86 (m, 2H), 2.71 – 2.69 (m, 1H), 2.55 – 2.49 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.28, 178.32, 159.31, 147.82, 143.70, 138.44, 137.37, 134.76, 132.90, 129.98, 129.40, 129.10, 128.71 X 2, 126.66, 125.99, 125.59, 124.66, 123.15, 119.79, 119.68, 118.91, 111.41, 110.96, 107.44, 70.92, 64.28, 63.61, 55.26, 50.57, 42.32, 30.17, 25.98; HRMS (ESI, Orbitrap) calcd for $C_{35}H_{30}N_3O_3$ $[M+H]^+$ =540.2287, found = 540.2289.

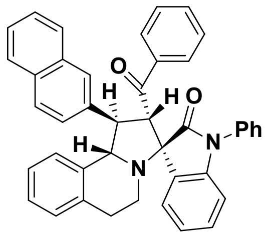
(1'R,2'S,3R,10b'S)-2'-benzoyl-1-phenyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4s):



Prepared following the general procedure; pale yellow solid (0.210 g, 75%); Rf = 0.53 (EtOAc/Hexane = 2/6); mp 233-234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 2H), 7.52 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.44 – 7.38 (m, 3H), 7.33 – 7.22 (m, 3H), 7.19 – 7.15 (m, 3H), 7.15 – 7.11 (m, 2H), 7.11 – 7.05 (m, 2H), 6.97 – 6.90 (m, 3H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.45

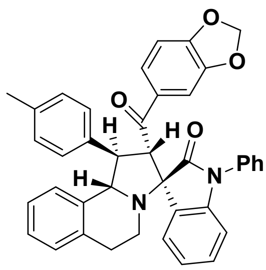
– 6.37 (m, 1H), 5.22 (d, *J* = 10.1 Hz, 1H), 4.65 (d, *J* = 9.6 Hz, 1H), 4.33 (t, *J* = 9.9 Hz, 1H), 3.10 – 2.90 (m, 2H), 2.77 – 2.62 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.73, 177.91, 143.44, 138.74, 138.11, 137.53, 136.37, 134.47, 134.00, 132.43, 129.64, 129.47, 128.84, 128.81, 128.67, 128.01, 127.50, 126.72, 126.55, 126.18, 125.93, 125.38, 124.98, 123.43, 108.48, 70.64, 63.97, 63.54, 50.03, 42.18, 30.27, 21.02(One peak is missing due to overlap); HRMS (ESI, Orbitrap) calcd for $C_{39}H_{33}N_2O_2$ $[M+H]^+$ = 561.2542, found = 561.2540.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(naphthalen-2-yl)-1-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4t):



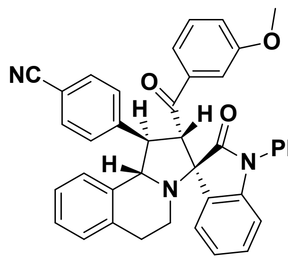
Prepared following the general procedure; yellow solid (0.224 g, 75%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 211-212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.94 – 7.88 (m, 2H), 7.87 – 7.82(m, 2H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.50 – 7.42 (m, 3H), 7.40 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.32 – 7.26 (m, 3H), 7.22 – 7.17 (m, 1H), 7.15 – 7.08 (m, 4H), 6.98 – 6.93 (m, 2H), 6.88 – 6.84 (m, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.47 – 6.41 (m, 1H), 5.41 (d, *J* = 10.1 Hz, 1H), 4.77 (dd, *J* = 9.6, 1.3 Hz, 1H), 4.56 (t, *J* = 9.6 Hz, 1H), 3.10 (td, *J* = 10.7, 3.8 Hz, 1H), 3.01 (td, *J* = 13.8, 11.6, 6.7 Hz, 1H), 2.77 – 2.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.80, 178.04, 143.60, 139.47, 138.08, 137.55, 134.60, 134.10, 133.77, 132.66, 132.64, 129.64, 129.05, 129.00, 128.84 X 2, 128.20, 128.16, 128.12, 128.01, 127.67, 127.60, 126.81, 126.74, 126.70, 126.38, 126.07, 125.71, 125.58, 125.16, 123.62, 108.67, 70.88, 63.97, 63.56, 50.67, 42.37, 30.38; HRMS (ESI, Orbitrap) calcd for $C_{42}H_{33}N_2O_2$ [M+H]+ = 597.2542, found =597.2548.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1-phenyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4u):



Prepared following the general procedure; yellow solid (0.227 g, 75%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 257-258 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (t, *J* = 8.0 Hz, 4H), 7.47 – 7.40 (m, 1H), 7.37 – 7.31 (m, 2H), 7.19 – 7.13 (m, 3H), 7.12 – 7.04 (m, 3H), 7.00 (td, *J* = 7.7, 1.4 Hz, 1H), 6.96 – 6.90 (m, 3H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.56 – 6.49 (m, 2H), 5.89 (dd, *J* = 9.5, 1.3 Hz, 2H), 5.21 (d, *J* = 10.1 Hz, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 4.32 (t, *J* = 9.8 Hz, 1H), 3.08 – 2.93 (m, 2H), 2.74 – 2.65 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.48, 177.98, 151.21, 147.63, 143.48, 138.81, 138.13, 136.33, 134.46, 134.03, 132.53, 129.62, 129.53, 128.87, 128.79, 128.64, 128.08, 126.74, 126.59, 126.14, 126.05, 125.35, 124.97, 123.59, 123.47, 108.53, 107.45, 107.15, 101.55, 70.79, 63.73, 63.48, 50.17, 42.22, 30.26, 21.02; HRMS (ESI, Orbitrap) calcd for $C_{40}H_{33}N_2O_4$ $[M+H]^+$ = 605.2440, found = 605.2435.

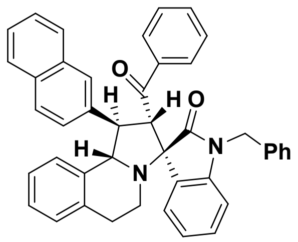
4-((1'R,2'S,3R,10b'S)-2'-(3-methoxybenzoyl)-2-oxo-1-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-1'-yl)benzonitrile (4v):



Prepared following the general procedure; yellow solid (0.220 g, 73%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 207-208 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.71 – 7.66 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.32 – 7.28 (m, 2H), 7.16 – 7.10 (m, 3H), 7.07 (dd, *J* = 9.0, 7.6 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.96 – 6.91 (m, 2H), 6.89 – 6.87 (m, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.49 – 6.44 (m, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 4.55 (d, *J* = 9.5 Hz, 1H), 4.41 (t, *J* = 9.8 Hz, 1H), 3.64 (s, 3H), 3.08 – 2.93 (m, 2H), 2.76 – 2.67

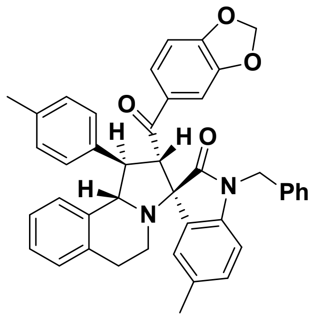
(m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.08, 177.66, 159.33, 147.75, 143.58, 138.54, 137.23, 134.54, 133.78, 132.82, 129.83, 129.51, 129.17, 129.04, 128.99, 128.20, 126.57, 126.35, 126.23, 125.98, 125.51, 124.56, 123.52, 119.80, 119.52, 118.76, 111.65, 110.89, 108.76, 70.69, 64.04, 63.55, 55.15, 50.37, 42.10, 30.12; HRMS (ESI, Orbitrap) calcd for $C_{40}H_{32}N_3O_3$ $[M+H]^+$ = 602.2444 found = 602.2440.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1-benzyl-1'-(naphthalen-2-yl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4w):



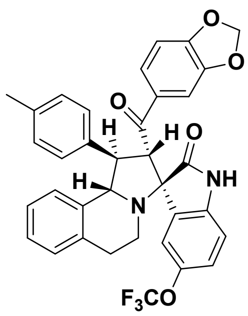
Prepared following the general procedure; yellow solid (0.214 g, 70%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 226-227 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.10 (m, 1H), 7.96 – 7.90 (m, 2H), 7.88 (dd, J = 7.4, 1.9 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.52 – 7.41 (m, 2H), 7.36 – 7.32 (m, 1H), 7.32 – 7.30 (m, 3H), 7.30 (dd, J = 3.9, 1.6 Hz, 1H), 7.28 (d, J = 1.2 Hz, 1H), 7.26 (d, J = 1.4 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.12 (dd, J = 7.4, 1.4 Hz, 1H), 7.10 – 7.06 (m, 2H), 6.98 – 6.90 (m, 3H), 6.88 – 6.80 (m, 2H), 6.72 (dd, J = 7.8, 1.1 Hz, 1H), 6.38 – 6.33 (m, 1H), 5.42 (d, J = 10.1 Hz, 1H), 5.00 (d, J = 15.4 Hz, 1H), 4.74 – 4.61 (m, 2H), 4.54 (t, J = 9.8 Hz, 1H), 3.04 – 2.91 (m, 2H), 2.73 – 2.65 (m, 1H), 2.62 – 2.52 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.81, 178.45, 142.87, 139.41, 137.97, 137.18, 135.69, 134.47, 133.63, 132.53, 132.37, 128.96, 128.87, 128.79, 128.67, 128.00, 127.90, 127.80, 127.69, 127.56, 127.52, 127.40, 126.70, 126.38, 126.21, 125.95, 125.58, 125.44, 125.05, 122.99, 108.20, 70.68, 63.38, 63.28, 50.74, 43.76, 42.30, 30.23. HRMS (ESI, Orbitrap) calcd for $C_{43}H_{35}N_2O_2$ $[M+H]^+$ = 611.2699, found = 611.2695.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1-benzyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4x):



Prepared following the general procedure; yellow solid (0.218 g, 69%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 238-239 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.29 (m, 3H), 7.27 (d, *J* = 17.1 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.12 – 7.03 (m, 2H), 6.95 – 6.88 (m, 2H), 6.88 – 6.82 (m, 2H), 6.76 – 6.73 (m, 2H), 6.32 (d, *J* = 7.9 Hz, 1H), 6.26 (d, *J* = 8.2 Hz, 1H), 5.86 (dd, *J* = 8.9, 1.3 Hz, 2H), 5.20 (d, *J* = 10.1 Hz, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.69 (d, *J* = 15.3 Hz, 1H), 4.46 (d, *J* = 9.4 Hz, 1H), 4.29 (t, *J* = 9.7 Hz, 1H), 2.96 – 2.90 (m, 2H), 2.68 (dd, *J* = 13.4, 7.5 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.35 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.75, 178.38, 151.01, 147.58, 140.47, 138.95, 138.18, 136.30, 135.89, 134.46, 132.57, 132.51, 129.62, 129.12, 128.80, 128.74, 128.61, 127.63, 127.53, 127.11, 126.85, 126.11, 125.32, 124.98, 123.58, 107.90, 107.27, 106.85, 101.44, 70.75, 63.36, 63.28, 50.37, 43.75, 42.32, 30.22, 21.05, 20.81; HRMS (ESI, Orbitrap) calcd for $C_{42}H_{37}N_2O_4$ $[M+H]^+$ = 633.2753, found = 633.2752.

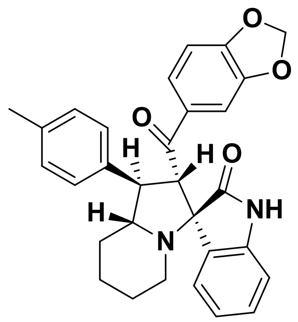
(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1'-(p-tolyl)-5-(trifluoromethoxy)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4y):



Prepared following the general procedure; yellow solid (0.233 g, 76%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 234-235 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.53

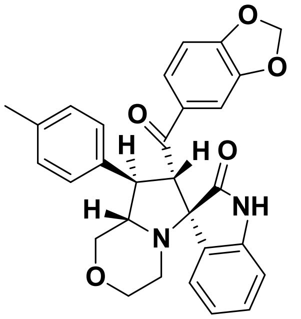
(d, J = 7.7 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 7.12 – 7.01 (m, 3H), 6.95 – 6.88 (m, 3H), 6.84 (dd, J = 8.4, 2.4 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.60 – 6.51 (m, 2H), 5.90 – 5.86 (m, 2H), 5.14 (d, J = 10.1 Hz, 1H), 4.42 (d, J = 9.3 Hz, 1H), 4.24 (t, J = 9.7 Hz, 1H), 2.94 – 2.94 (m, 2H), 2.68 (d, J = 11.7 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.35, 180.35, 151.28, 147.57, 144.07, 140.73, 138.67, 137.83, 136.25, 134.24, 131.97, 129.51, 128.96, 128.61, 128.54, 126.08, 125.21, 124.73, 123.63, 122.23, 121.24, 119.88, 119.20, 109.70, 107.10, 107.07, 101.49, 70.87, 63.18, 62.84, 50.15, 42.25, 30.05, 20.91; HRMS (ESI, Orbitrap) calcd for $C35H_{28}F_3N_2O_5$ $[M+H]^+$ = 613.1950, found = 613.1956.

(1'R,2'S,3R,8a'R)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1'-(p-tolyl)-2',5',6',7',8',8a'-hexahydro-1'H-spiro[indoline-3,3'-indolizin]-2-one (5b):



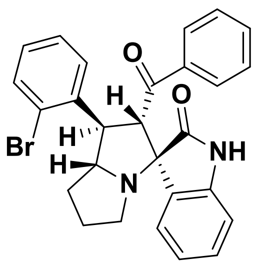
Prepared following the general procedure; yellow solid (0.192 g, 80%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 195-196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.41 – 7.36 (m, 2H), 7.11 (d, J = 7.9 Hz, 2H), 7.11 – 7.06 (m, 1H), 7.05 (dd, J = 8.2, 1.8 Hz, 1H), 6.99 (td, J = 7.6, 1.4 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.53 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 7.7 Hz, 1H), 5.87 (q, J = 1.4 Hz, 2H), 4.31 (d, J = 9.8 Hz, 1H), 3.82 (t, J = 9.9 Hz, 1H), 3.46 (td, J = 10.1, 2.5 Hz, 1H), 2.42 (td, J = 11.5, 11.0, 2.9 Hz, 1H), 2.37 – 2.31 (m, 1H), 2.29 (s, 3H), 1.74 – 1.69 (m, 2H), 1.38 – 1.25 (m, 2H), 1.25 – 1.12 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.40, 180.25, 151.13, 147.52, 140.31, 137.09, 136.20, 132.49, 129.11, 128.65, 128.37, 127.99, 126.76, 123.65, 122.82, 108.49, 107.30, 107.07, 101.47, 72.33, 65.30, 60.82, 51.49, 45.56, 30.36, 25.54, 23.55, 20.94; HRMS (ESI, Orbitrap) calcd for $C_{30}H_{29}N_2O_4$ $[M+H]^+$ = 481.2127 found = 481.2131

(3R,7'S,8'R,8a'S)-7'-(benzo[d][1,3]dioxole-5-carbonyl)-8'-(p-tolyl)-1',3',4',7',8',8a'-hexahydrospiro[indoline-3,6'-pyrrolo[2,1-c][1,4]oxazin]-2-one (5c):



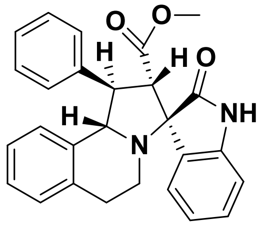
Prepared following the general procedure; yellow solid (0.188 g, 78%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 220-221 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.41 – 7.35 (m, 2H), 7.13 – 7.08 (m, 3H), 7.07 – 6.99 (m, 2H), 6.95 – 6.87 (m, 2H), 6.58 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.85 (dt, *J* = 4.6, 1.4 Hz, 2H), 4.32 (d, *J* = 9.2 Hz, 1H), 3.97 – 3.88 (m, 2H), 3.84 (td, *J* = 10.0, 2.9 Hz, 1H), 3.76 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.43 – 3.34 (m, 2H), 2.75 (td, *J* = 10.9, 3.4 Hz, 1H), 2.29 (s, 3H), 2.24 (dd, *J* = 10.9, 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.94, 179.99, 151.34, 147.62, 140.61, 136.63, 136.10, 132.26, 129.32, 129.08, 128.10, 126.91, 126.69, 123.72, 122.94, 108.99, 107.28, 107.17, 101.55, 72.18, 71.71, 66.42, 62.79, 60.98, 47.68, 45.67, 20.94; HRMS (ESI, Orbitrap) calcd for $C_{29}H_{27}N_2O_5$ $[M+H]^+$ = 483.1920, found = 483.1914.

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(2-bromophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5d):



Prepared following the general procedure; yellow solid (0.200 g, 82%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 235-236 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (brs, 1H), 7.62 (dd, J = 21.0, 7.9 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H), 7.31 (m, 3H), 7.15 (m, 3H), 7.09 – 7.00 (m, 2H), 6.58 (m, 1H), 5.05 (d, J = 11.5 Hz, 1H), 4.65 (t, J = 10.7 Hz, 1H), 4.12 (m, 1H), 2.66 (m, 2H), 2.07 – 1.81 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.70, 180.74, 140.47, 138.86, 136.86, 133.21, 132.76, 129.39, 128.09, 128.03, 127.97, 127.75, 127.31, 125.67, 124.84, 122.49, 109.99, 73.55, 72.92, 64.19, 50.25, 48.24, 29.94, 27(one peak is missing due to overlap); HRMS (ESI, Orbitrap) calcd for $C_{27}H_{24}BrN_2O_2$ $[M+H]^+$ =487.1021, found = 487.1023.

(1'R,2'S,3R,10b'S)-methyl 2-oxo-1'-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinoline]-2'-carboxylate (5e):



Prepared following the general procedure; white solid (0.174 g, 82%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 208-209 °C; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.64 (dd, J = 7.4, 1.3 Hz, 1H), 7.30 (s, 1H), 7.26 – 7.19 (m, 2H), 7.17–7.11 (m, 6H), 7.10–7.06 (m, 3H), 6.64 (d, J = 7.6 Hz, 1H), 5.68 (d, J = 8.4 Hz, 1H), 4.22 (d, J = 6.3 Hz, 1H), 4.15 (dd, J = 8.4, 6.3 Hz, 1H), 3.46 (s, 3H), 3.11–3.03 (m, 1H), 2.71 (dd, J = 9.2, 3.1 Hz, 2H), 2.62 (dd, J = 15.8, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 177.72, 174.78, 141.56, 136.15, 135.86, 135.20, 129.45, 129.22, 128.62, 128.27, 127.51, 126.26, 125.41, 125.05, 123.20, 109.45, 76.06, 62.74, 58.96, 51.65, 50.82, 42.81, 30.25.(two peaks are missing due to overlap). HRMS (ESI, Orbitrap) calcd for $C_{27}H_{25}N_2O_3$ $[M+H]^+$ =425.1865, found = 425.1869.

3. Crystallographic data of product 4q

Sample preparation and crystal structure determination of 5f

The pure compound **4q** as obtained from column chromatography was crystallised from ethanol solvent.

X-ray data for the compounds **4q** was collected at room temperature on a Bruker D8 QUEST instrument with an IμS Mo microsource (λ = 0.7107 A) and a PHOTON-100 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using the intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H =

0.93-0.97 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}(C)$ for other H atoms]. The methyl groups were allowed to rotate but not to tip. The ethanol solvate of **4q** could not be resolved due to extensive disorder, and their assumed presence was removed from the overall scattering by the PLATON SQUEEZE procedure. The N bound H atoms of **4q** were located in a difference density map and refined isotropically.

Crystal Data for **4q**: $C_{34}H_{30}N_2O_3$ (M =514.60 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 9.56320(10) Å, b = 17.8067(3) Å, c = 16.1958(3) Å, β = 103.4627(6)°, V = 2682.18(7) Å^3, Z = 4, T = 294.15 K, μ(MoKα) = 0.081 mm^{-1}, $Dcalc$ = 1.274 g/cm^3, 24289 reflections measured (4.574° ≤ 2Θ ≤ 52.496°), 5392 unique (R_{int} = 0.0552, R_{sigma} = 0.0474) which were used in all calculations. The final R_1 was 0.0549 (I > 2σ(I)) and wR_2 was 0.1500 (all data).

CCDC 1983982 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

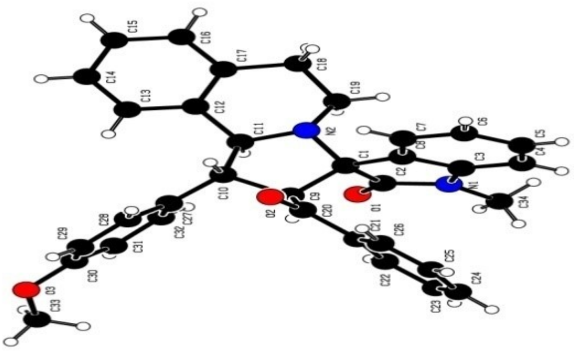


Figure S1: X-ray crystal structure of **5q** Thermal ellipsoids are drown at 30% probability

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) KA904_0m

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: KA904_0m

Bond precision: C-C = 0.0031 A Wavelength=0.71073

Cell:	a=9.5632(1)	b=17.8067(3)	c=16.1958(3)
	alpha=90	beta=103.4627(6)	gamma=90
Temperature:	294 K		

	Calculated	Reported
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Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C34 H30 N2 O3	C34 H30 N2 O3
Sum formula	C34 H30 N2 O3	C34 H30 N2 O3
Mr	514.60	514.60
Dx,g cm-3	1.274	1.274
Z	4	4
Mu (mm-1)	0.081	0.081
F000	1088.0	1088.0
F000'	1088.46	
h,k,lmax	11,22,20	11,22,20
Nref	5399	5392
Tmin,Tmax	0.979,0.990	0.565,0.746
Tmin'	0.979	

Correction method= # Reported T Limits: Tmin=0.565 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 0.999 Theta(max)= 26.248

R(reflections)= 0.0549(4055) wR2(reflections)= 0.1500(5392)

S = 1.057 Npar= 378

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

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PLAT220_ALERT_2_C NonSolvent Resd 1  C   Ueq(max) / Ueq(min) Range       3.1 Ratio
PLAT241_ALERT_2_C High   MainMol Ueq as Compared to Neighbors of       C18 Check
PLAT241_ALERT_2_C High   MainMol Ueq as Compared to Neighbors of       C29 Check
PLAT241_ALERT_2_C High   MainMol Ueq as Compared to Neighbors of       C31 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.600         3 Report
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Alert level G

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PLAT171_ALERT_4_G The CIF-Embedded .res File Contains EADP Records         1 Report
PLAT230_ALERT_2_G Hirshfeld Test Diff for    C29       --C30       .     10.7 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for    C29       --C30D      .     10.0 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for    C30       --C31       .     19.7 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for    C31       --C30D      .      7.0 s.u.
PLAT301_ALERT_3_G Main Residue  Disorder .............(Resd  1  )        8% Note
PLAT413_ALERT_2_G Short Inter XH3 .. XHn     H24       ..H33D      .     2.09 Ang.
                                           1-x,1-y,1-z  =      3_666 Check
PLAT432_ALERT_2_G Short Inter X...Y Contact  C6        ..C33D            3.18 Ang.
                                       1-x,-1/2+y,3/2-z  =     2_646 Check
PLAT793_ALERT_4_G Model has Chirality at C1            (Centro SPGR)       R Verify
PLAT793_ALERT_4_G Model has Chirality at C9            (Centro SPGR)       S Verify
PLAT793_ALERT_4_G Model has Chirality at C10           (Centro SPGR)       R Verify
PLAT793_ALERT_4_G Model has Chirality at C11           (Centro SPGR)       S Verify
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary .    Please Do !
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).         2 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600         2 Note
PLAT913_ALERT_3_G Missing # of Very Strong Reflections in FCF ....         1 Note
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.         4 Info
PLAT992_ALERT_5_G Repd & Actual _reflns_number_gt Values Differ by         1 Check
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   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   5 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  18 ALERT level G = General information/check it is not something unexpected

   1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
  11 ALERT type 2 Indicator that the structure model may be wrong or deficient
   4 ALERT type 3 Indicator that the structure quality may be low
   6 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
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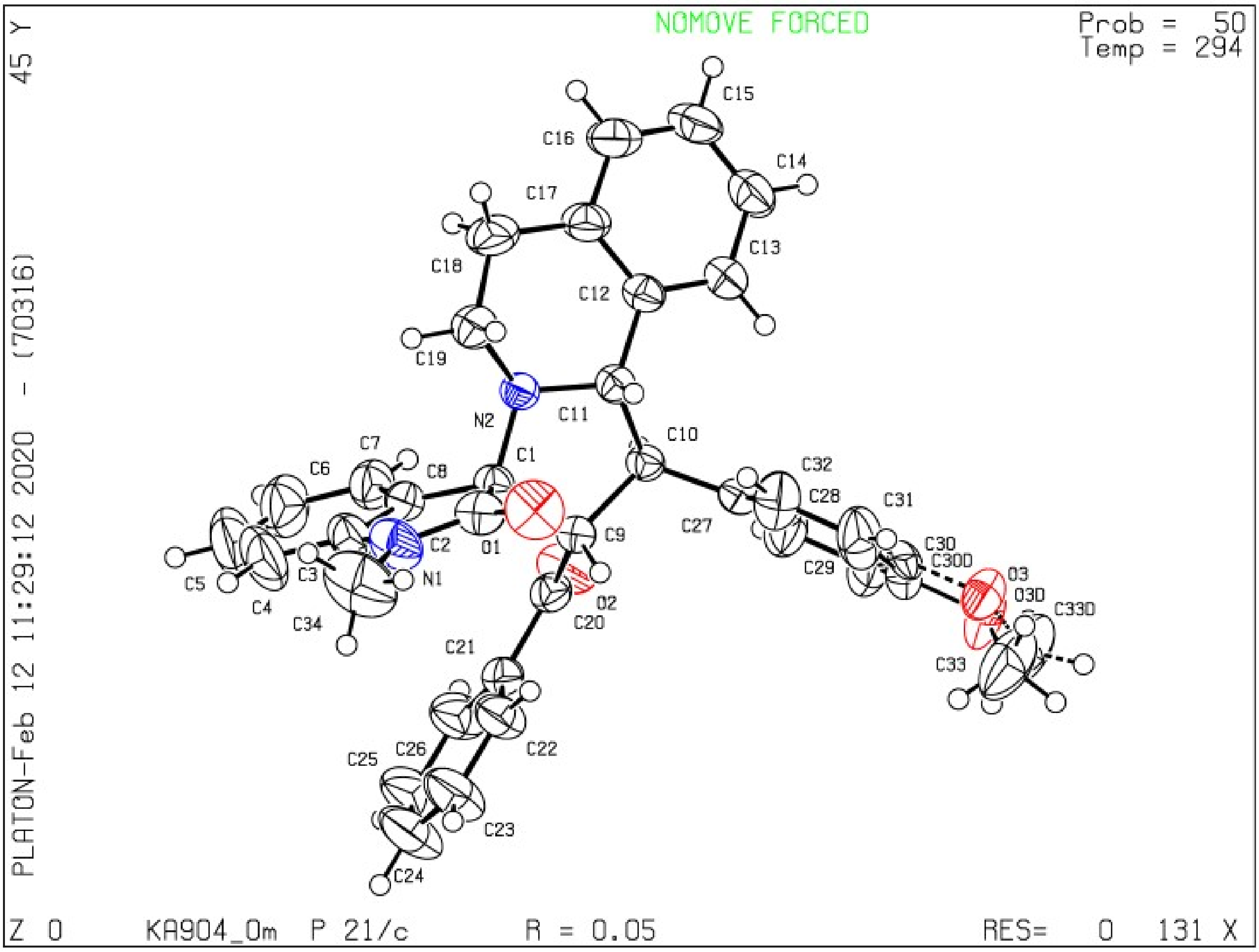
PLATON version of 22/12/2019; check.def file version of 13/12/2019

Data blockshelxl_sq - ellipsoid plot



4. Copies of NMR Spectra

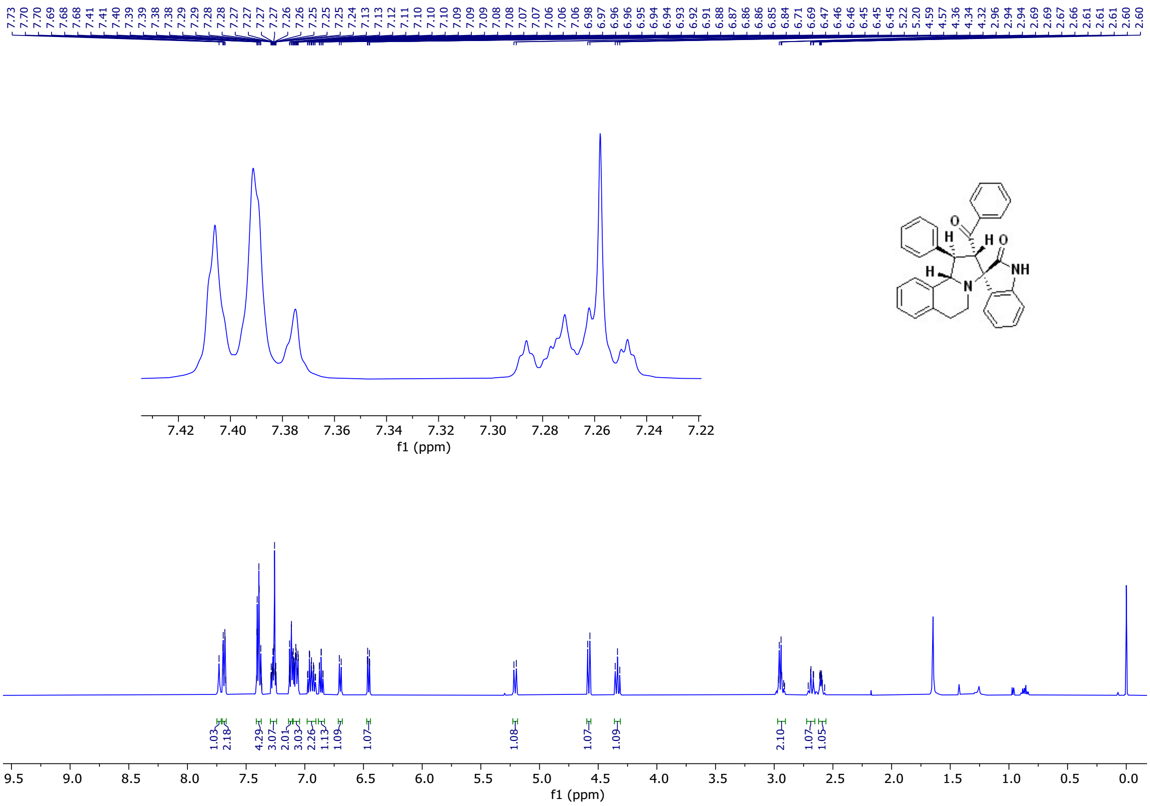


Figure S2: ^{1}H NMR of compound **4a** (500 MHz, $CDCl_3$)

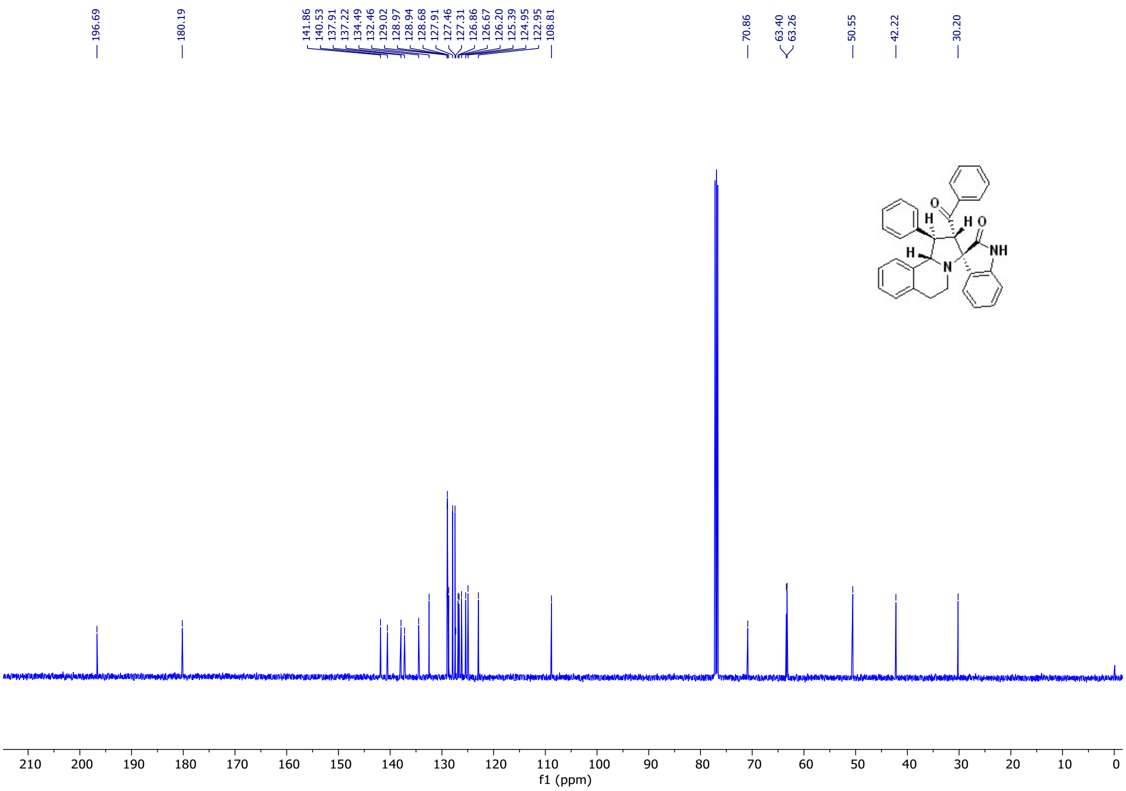


Figure S3: ^{13}C NMR of compound **4a** (126 MHz, $CDCl_3$)

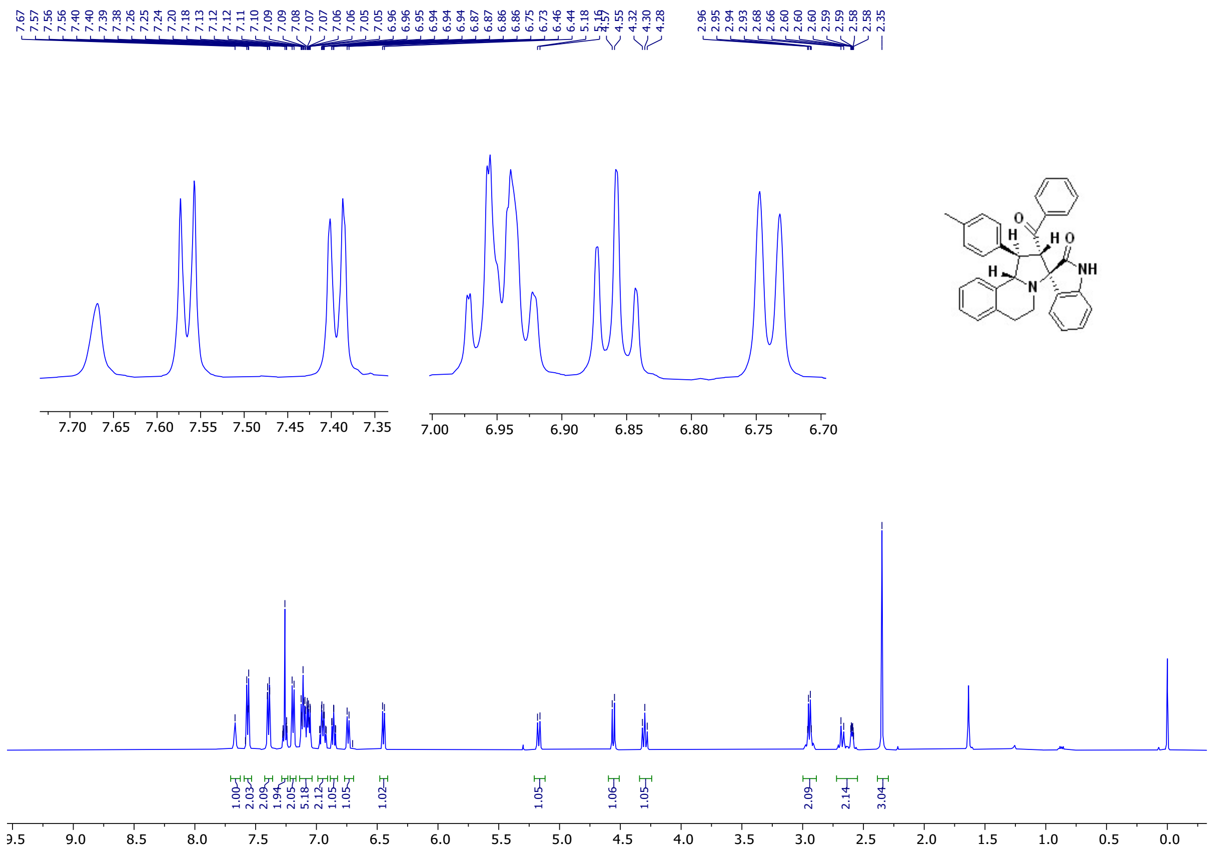


Figure S4: ^{1}H NMR of compound **4b** (500 MHz, $CDCl_3$)

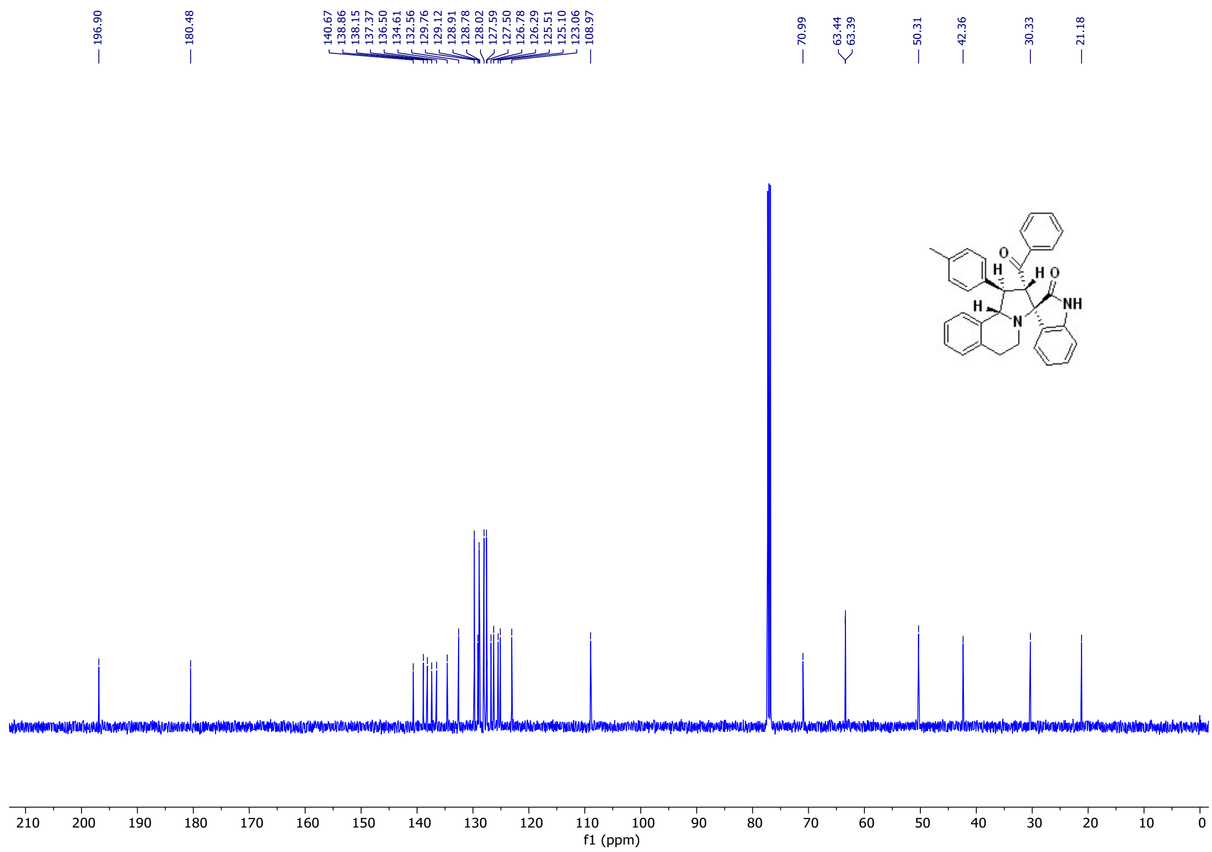


Figure S5: ^{13}C NMR of compound **4b** (126 MHz, $CDCl_3$)

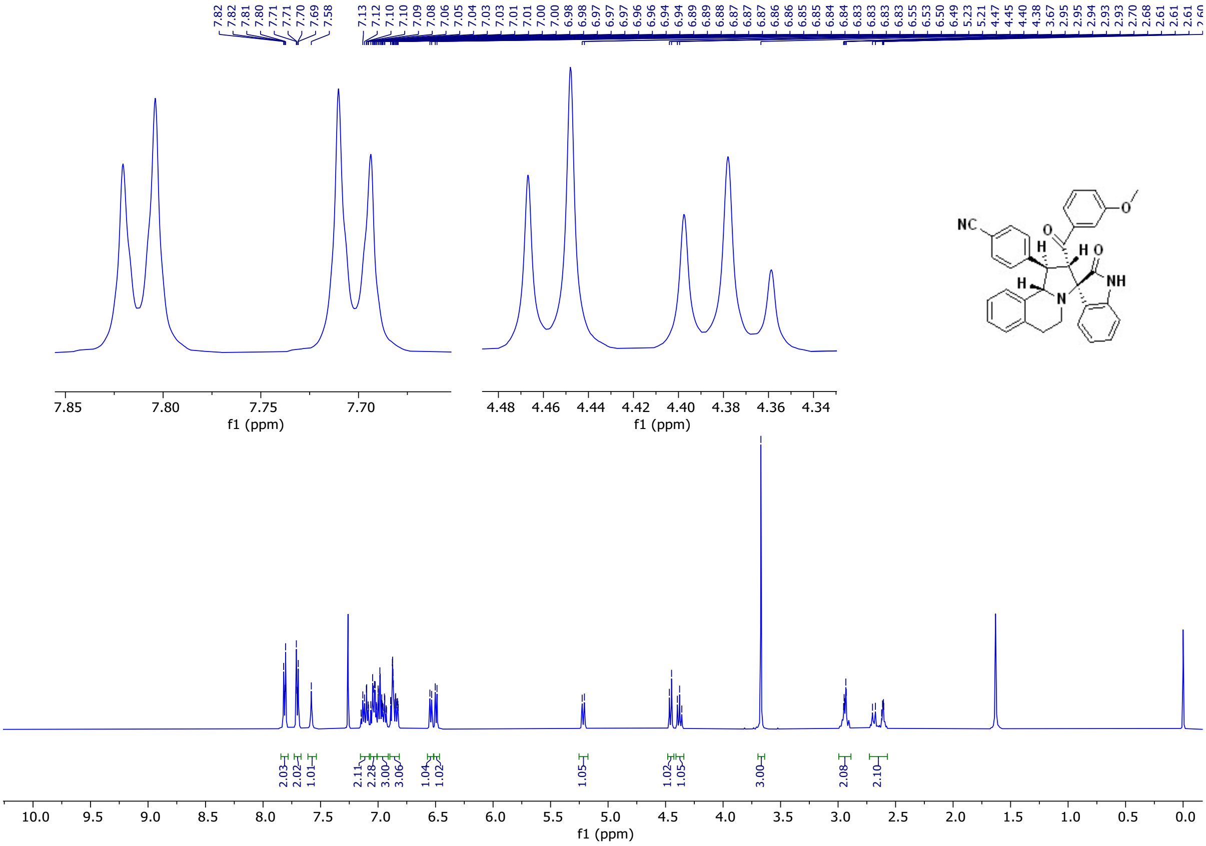


Figure S6: ^{1}H NMR of compound **4c** (500 MHz, $CDCl_3$)

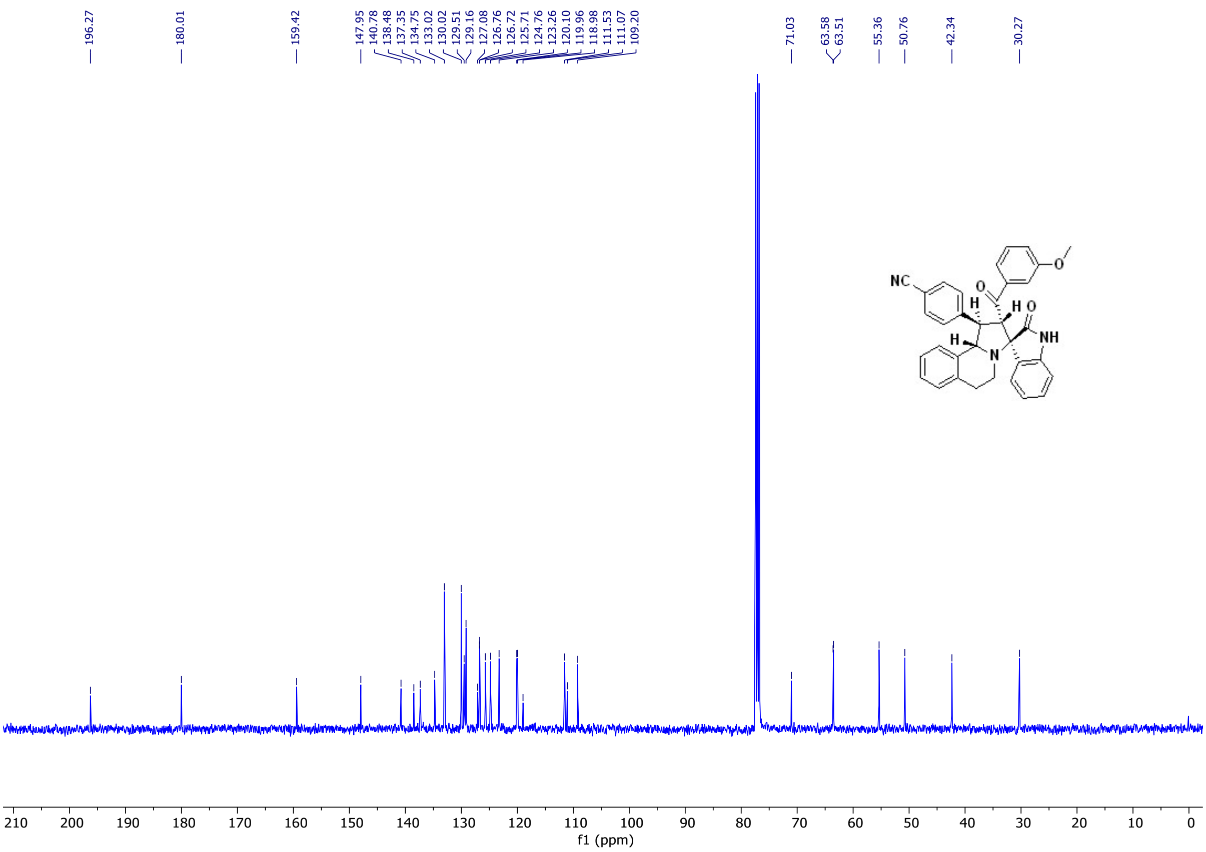


Figure S7: ^{13}C NMR of compound **4c** (126 MHz, $CDCl_3$)

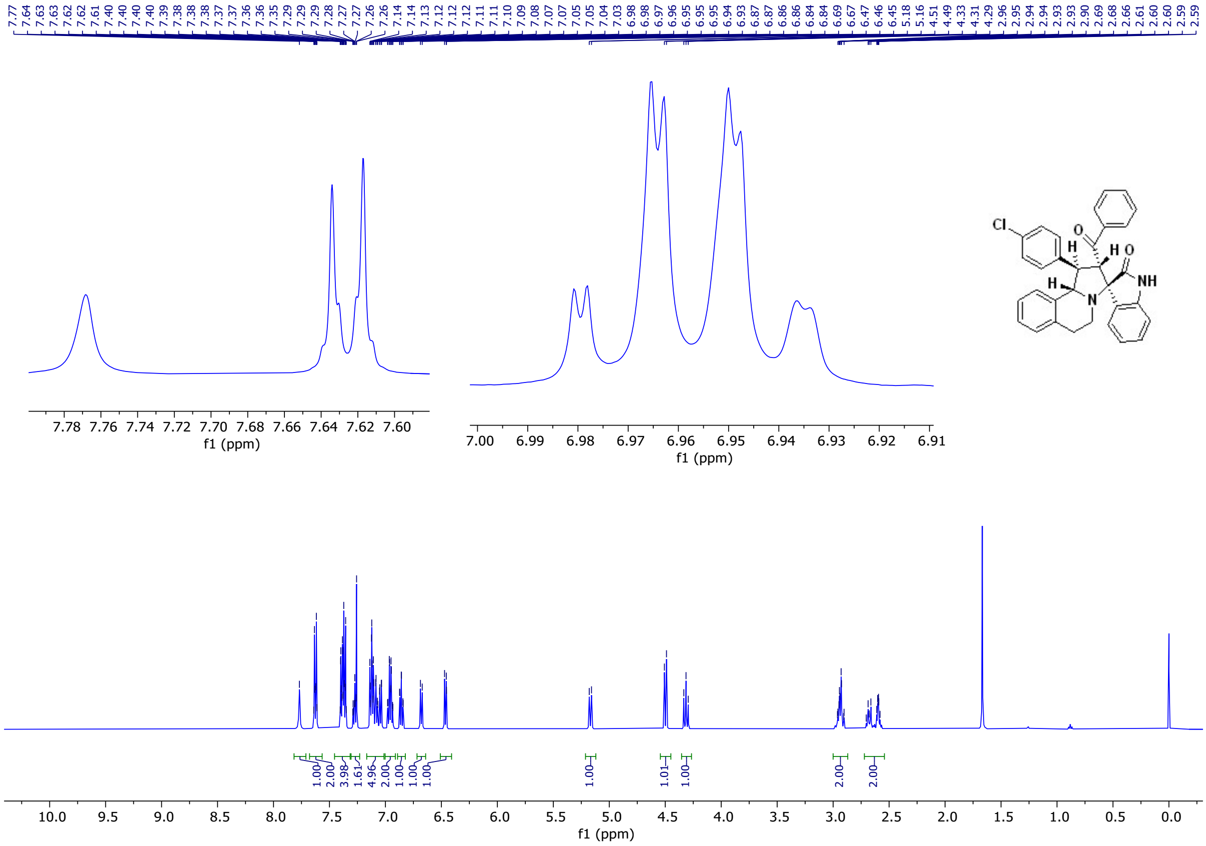


Figure S8: ^{1}H NMR of compound **4d** (500 MHz, $CDCl_3$)

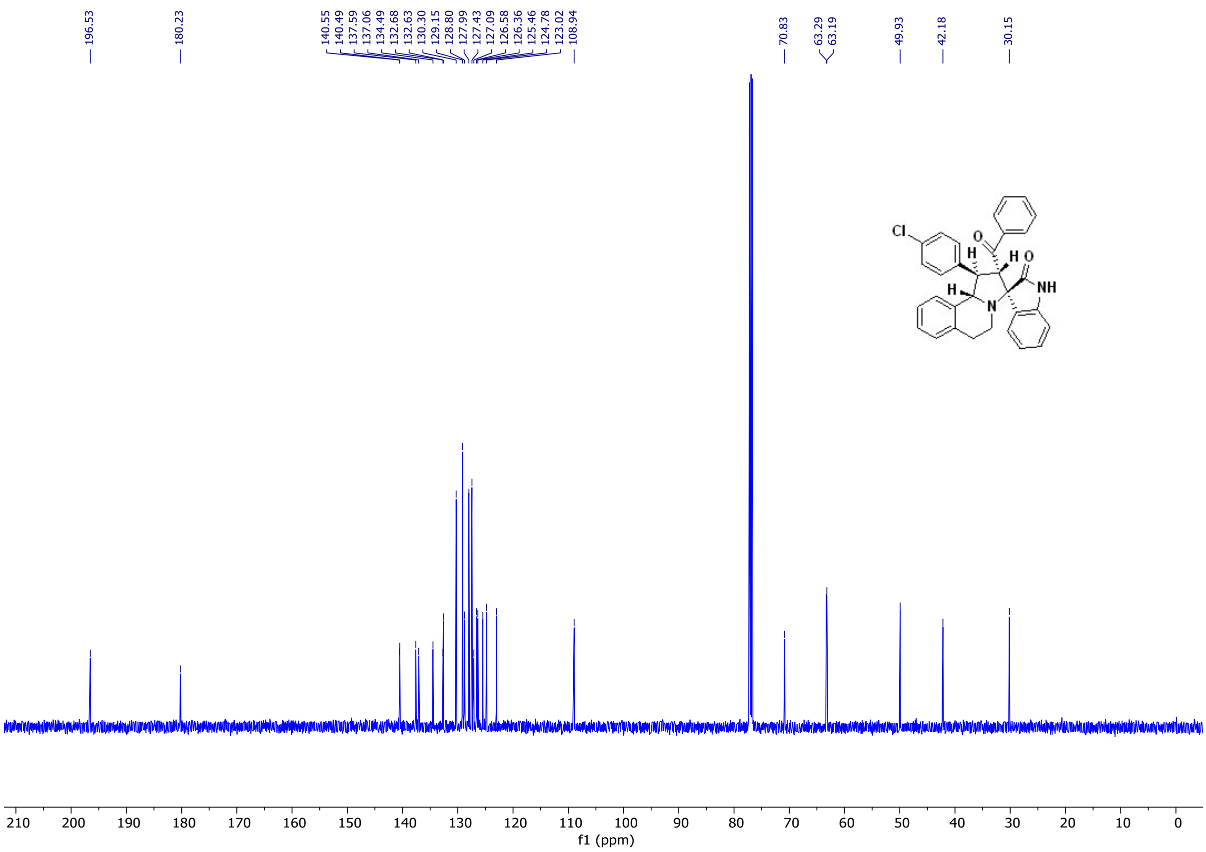


Figure S9: ^{13}C NMR of compound **4d** (126 MHz, $CDCl_3$)

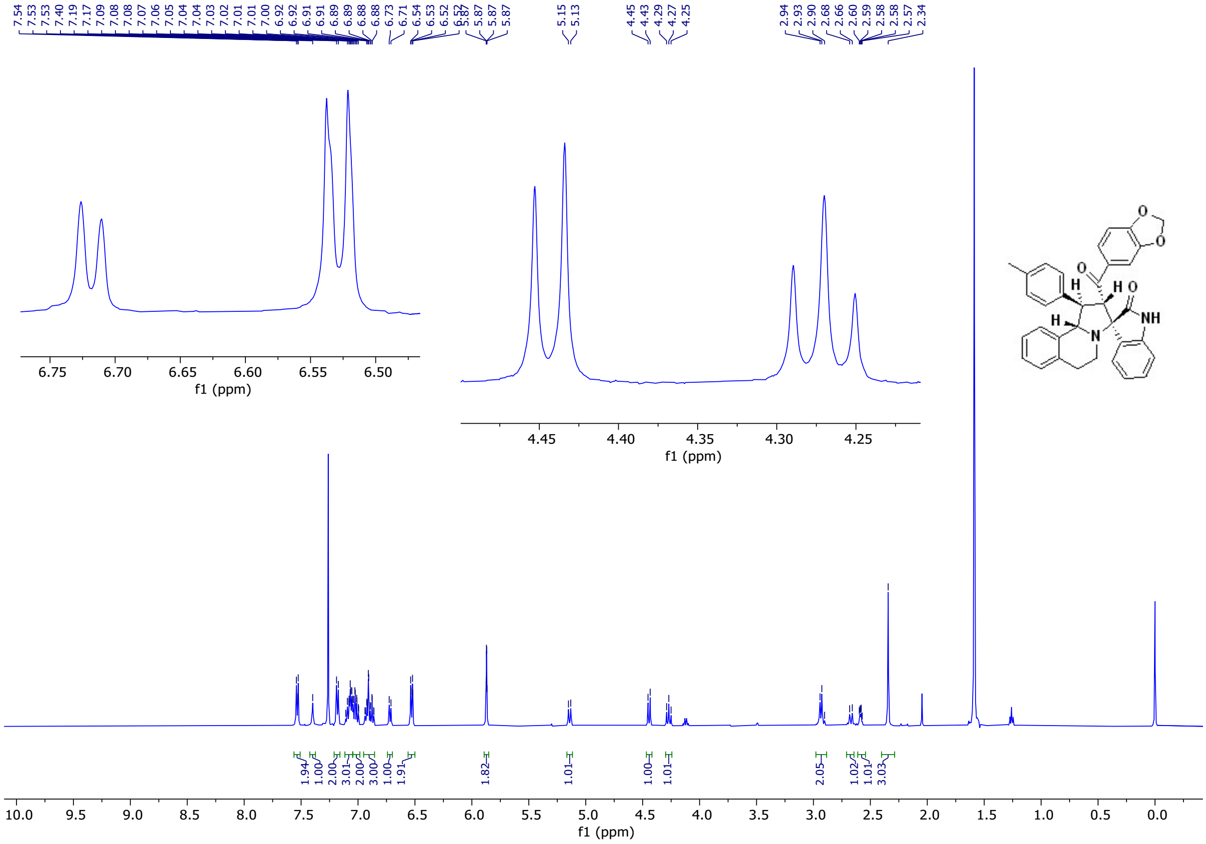


Figure S10: ^{1}H NMR of compound **4e** (500 MHz, $CDCl_3$)

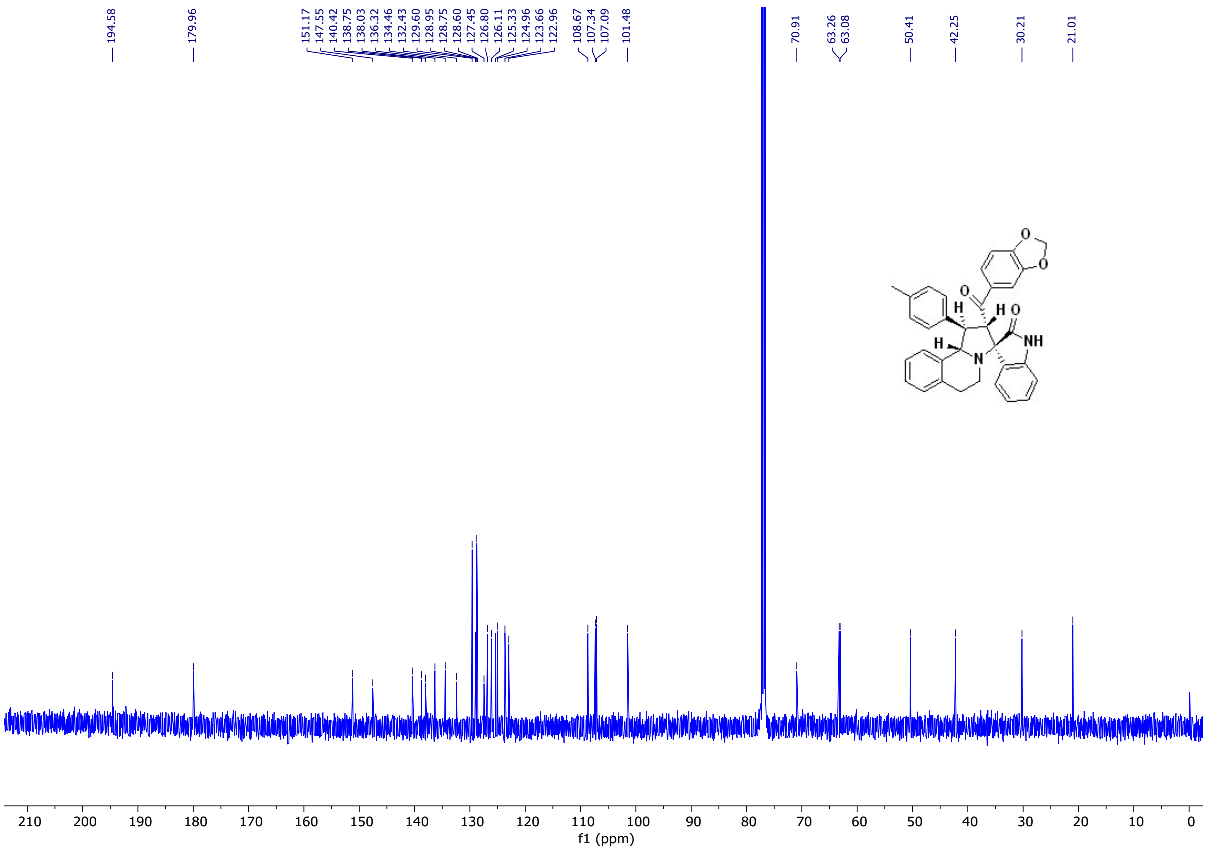


Figure S11: ^{13}C NMR of compound **4e** (126 MHz, $CDCl_3$)

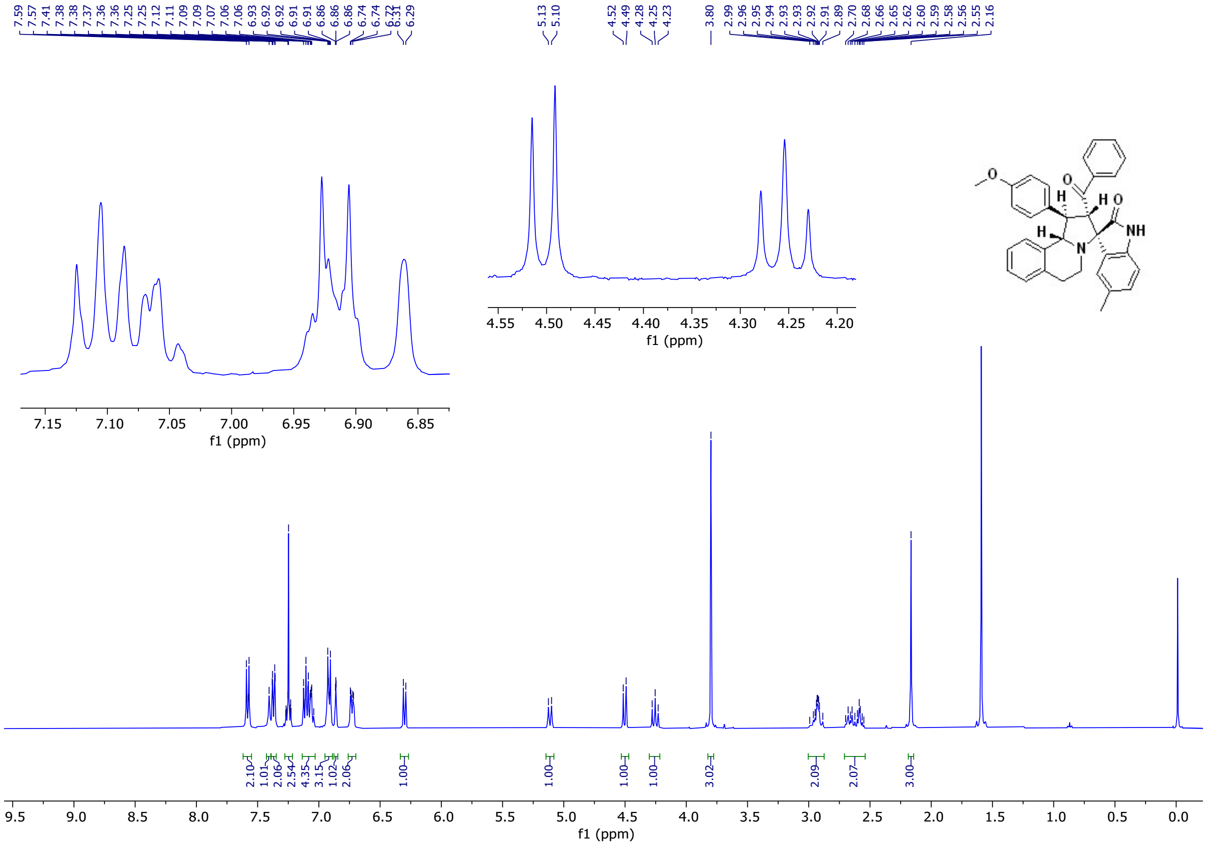


Figure S12: ^{1}H NMR of compound **4f** (500 MHz, $CDCl_3$)

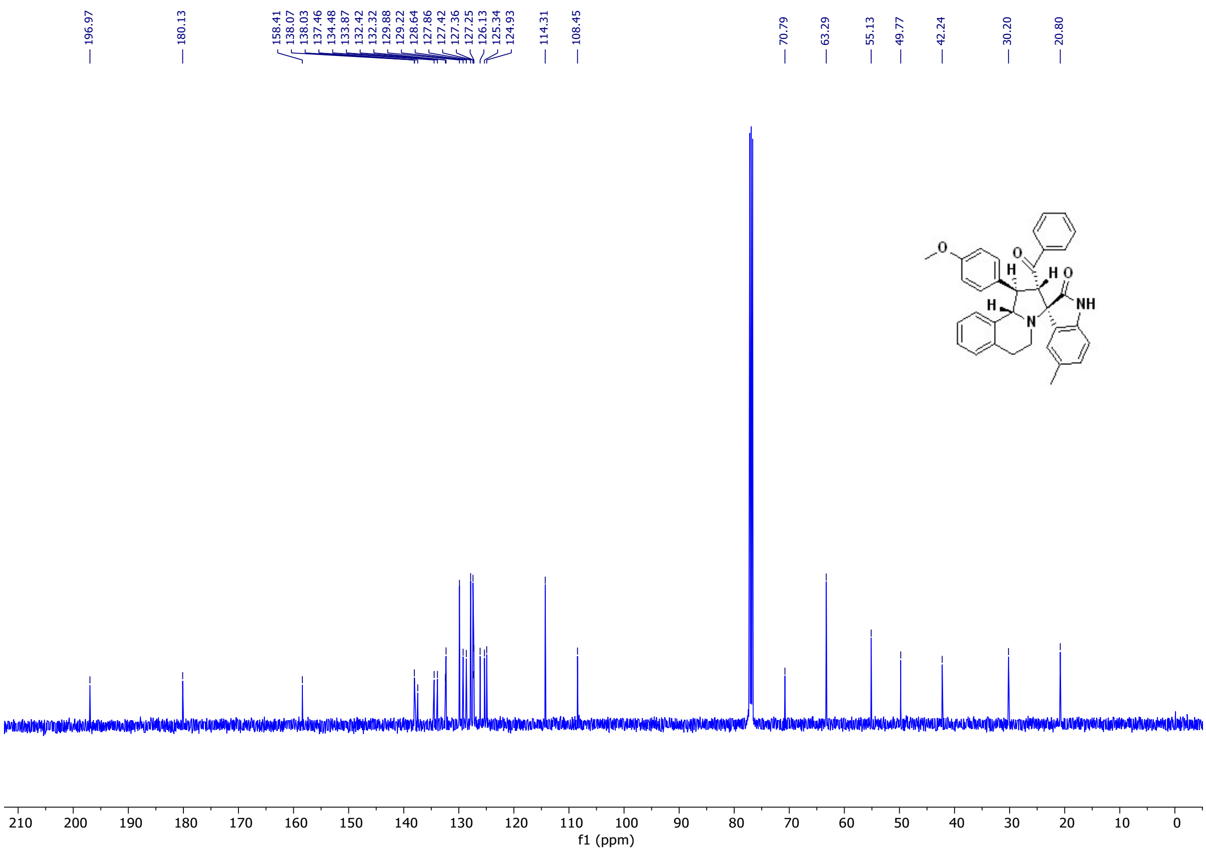


Figure S13: ^{13}C NMR of compound **4f** (126 MHz, $CDCl_3$)

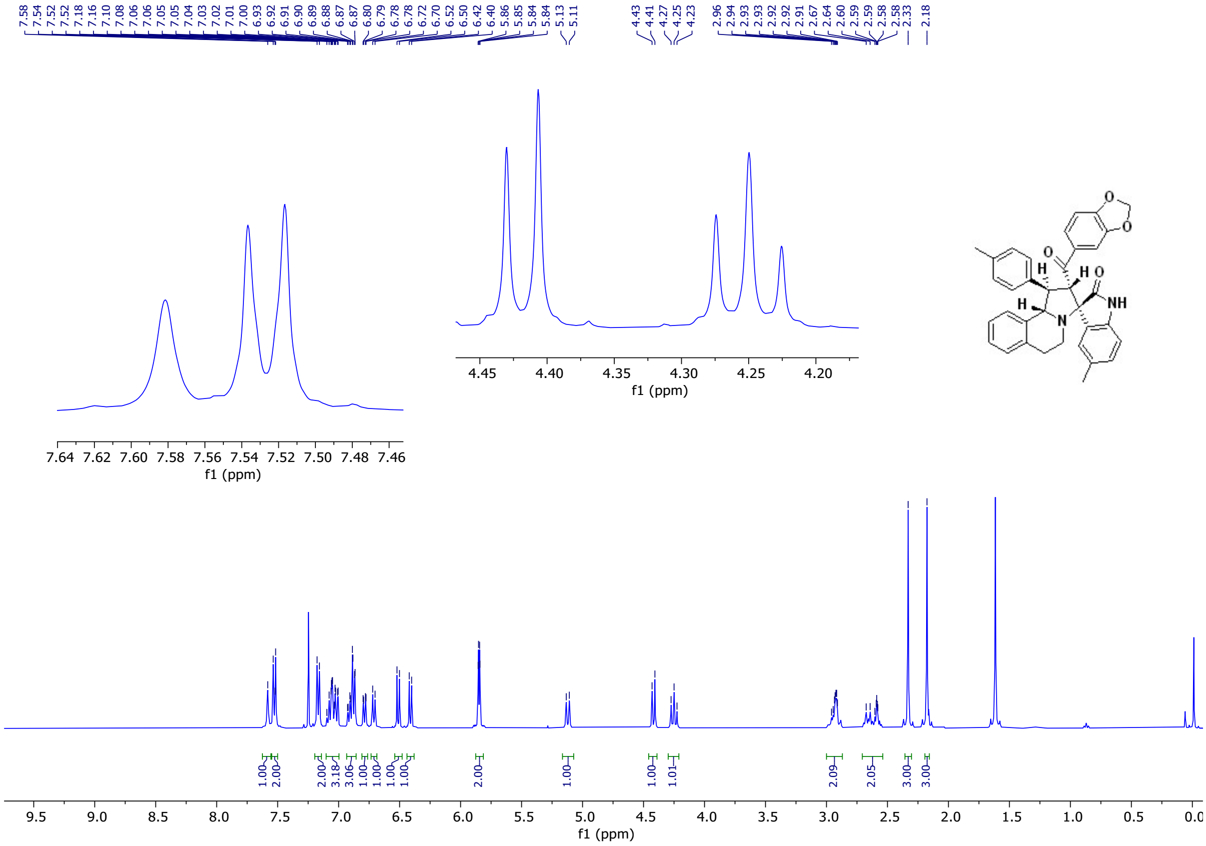


Figure S14: ^{1}H NMR of compound **4g** (500 MHz, $CDCl_3$)

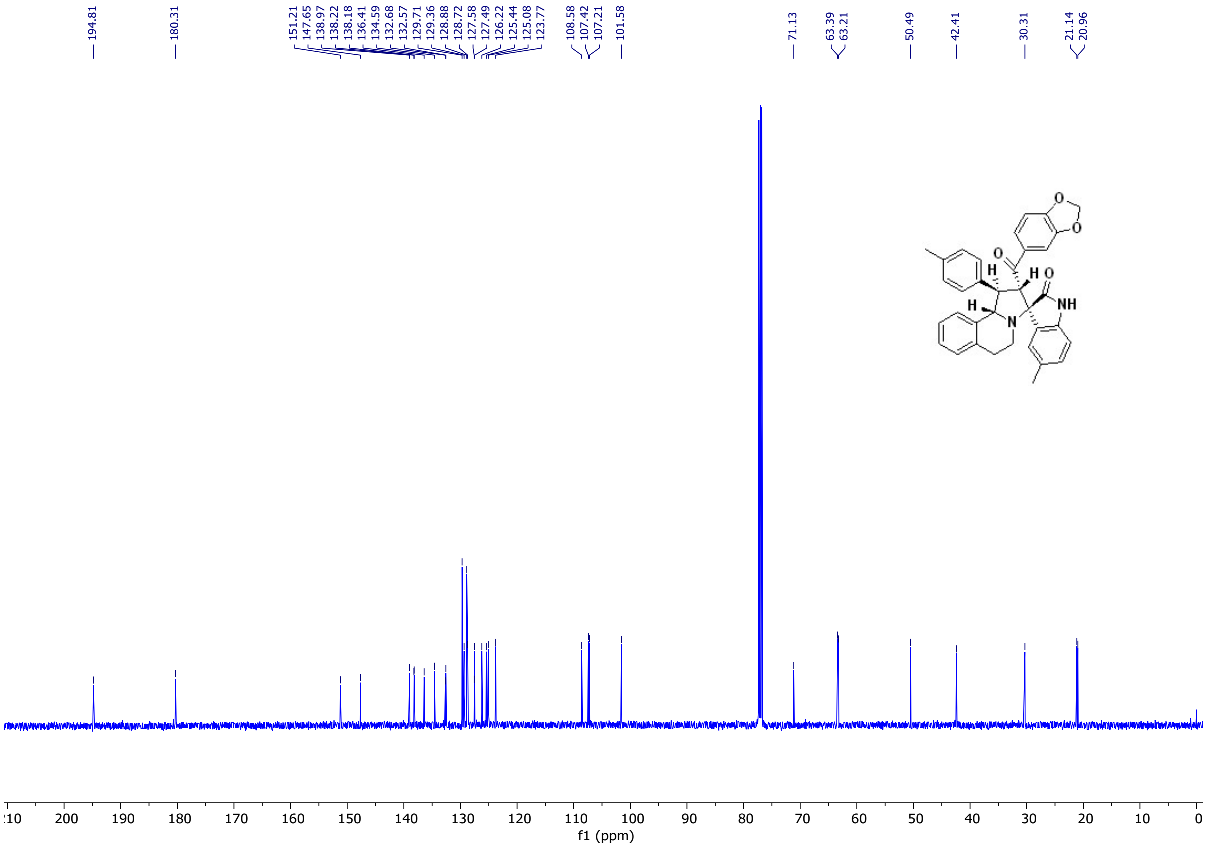


Figure S15: ^{13}C NMR of compound **4g** (126 MHz, $CDCl_3$)

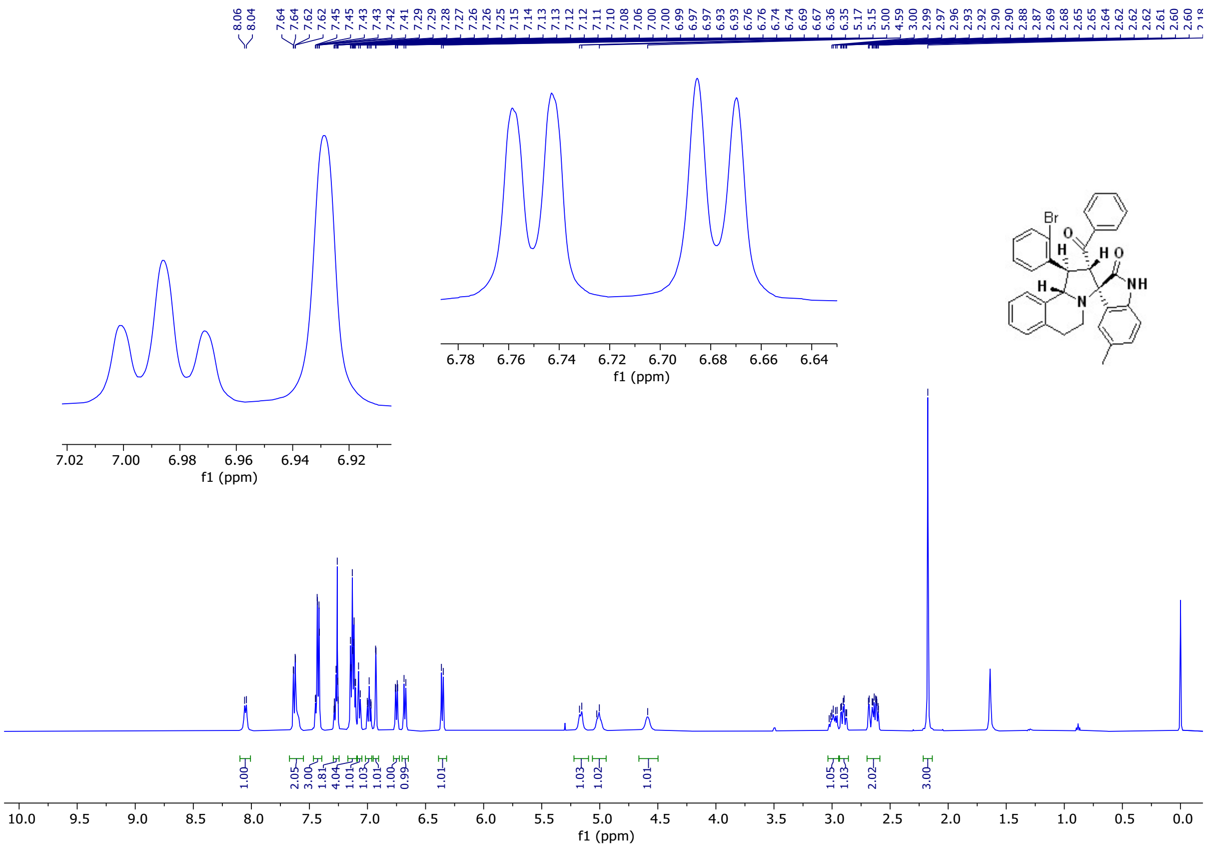


Figure S16: ^{1}H NMR of compound **4h** (500 MHz, $CDCl_3$)

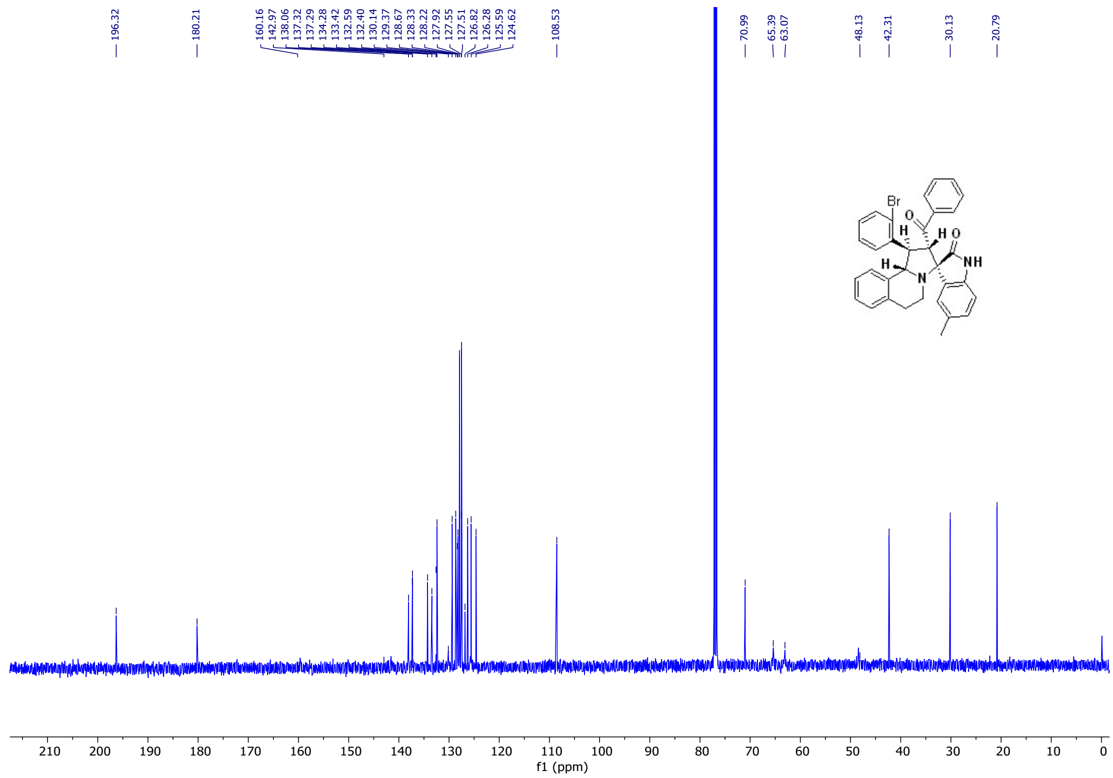


Figure S17: ^{13}C NMR of compound **4h** (126 MHz, $CDCl_3$)

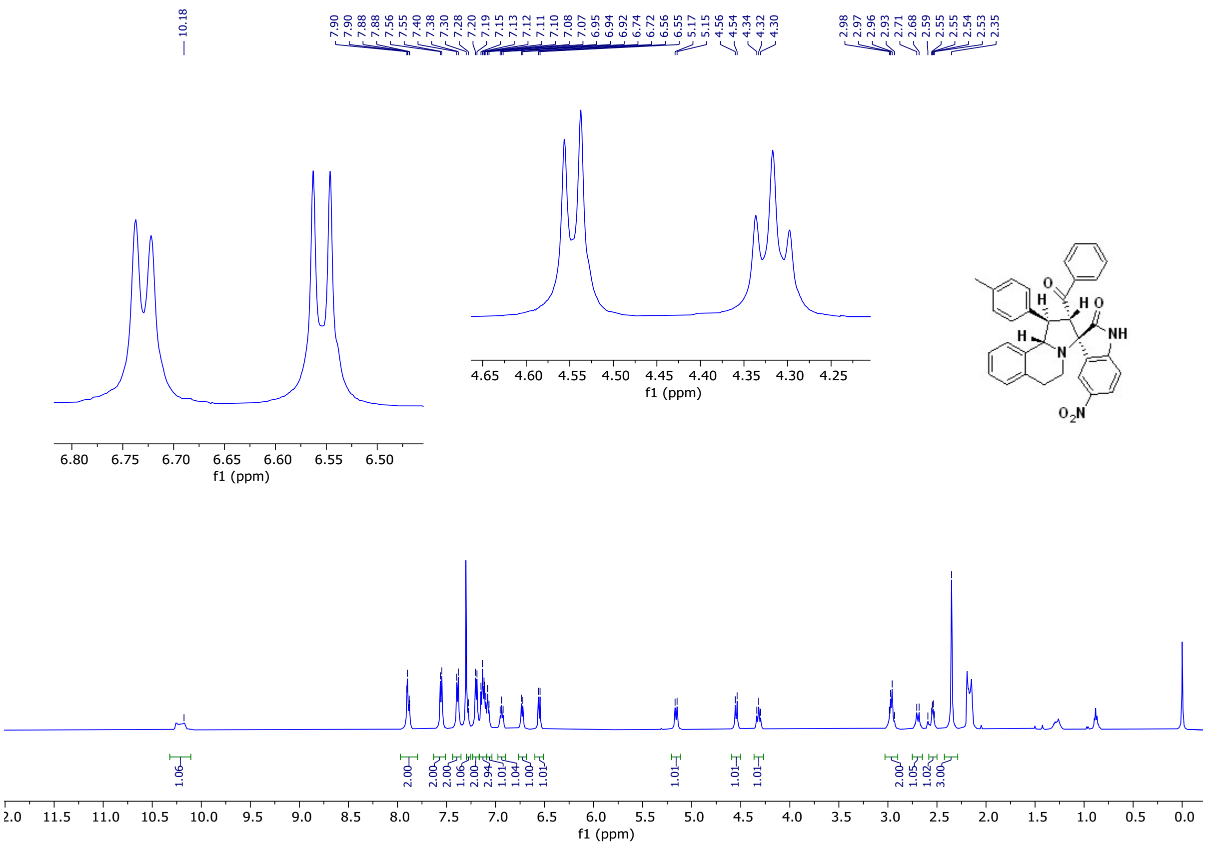


Figure S18: ^{1}H NMR of compound **4i** (500 MHz, $CDCl_3$ + DMSO-d_6)

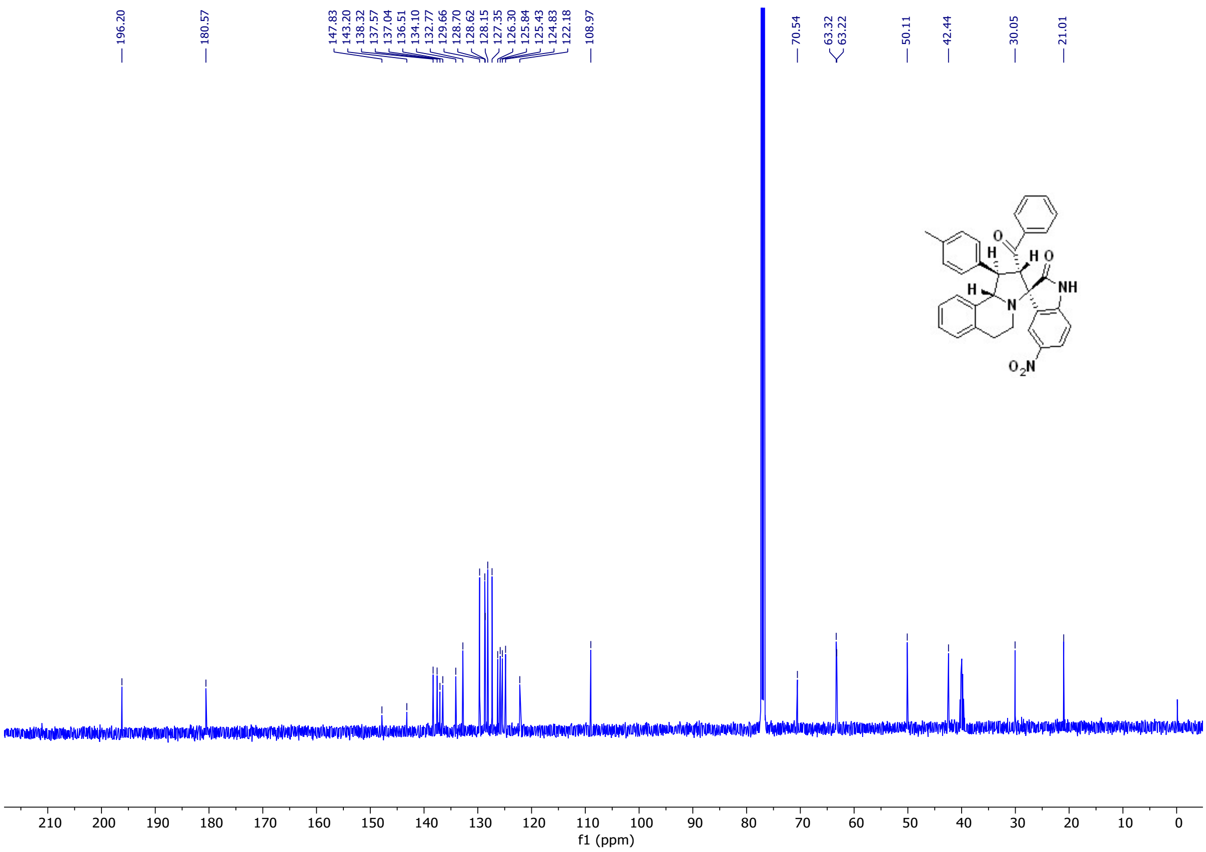


Figure 19: ^{13}C NMR of compound **4i** (126 MHz, $CDCl_3$ + DMSO-d_6)

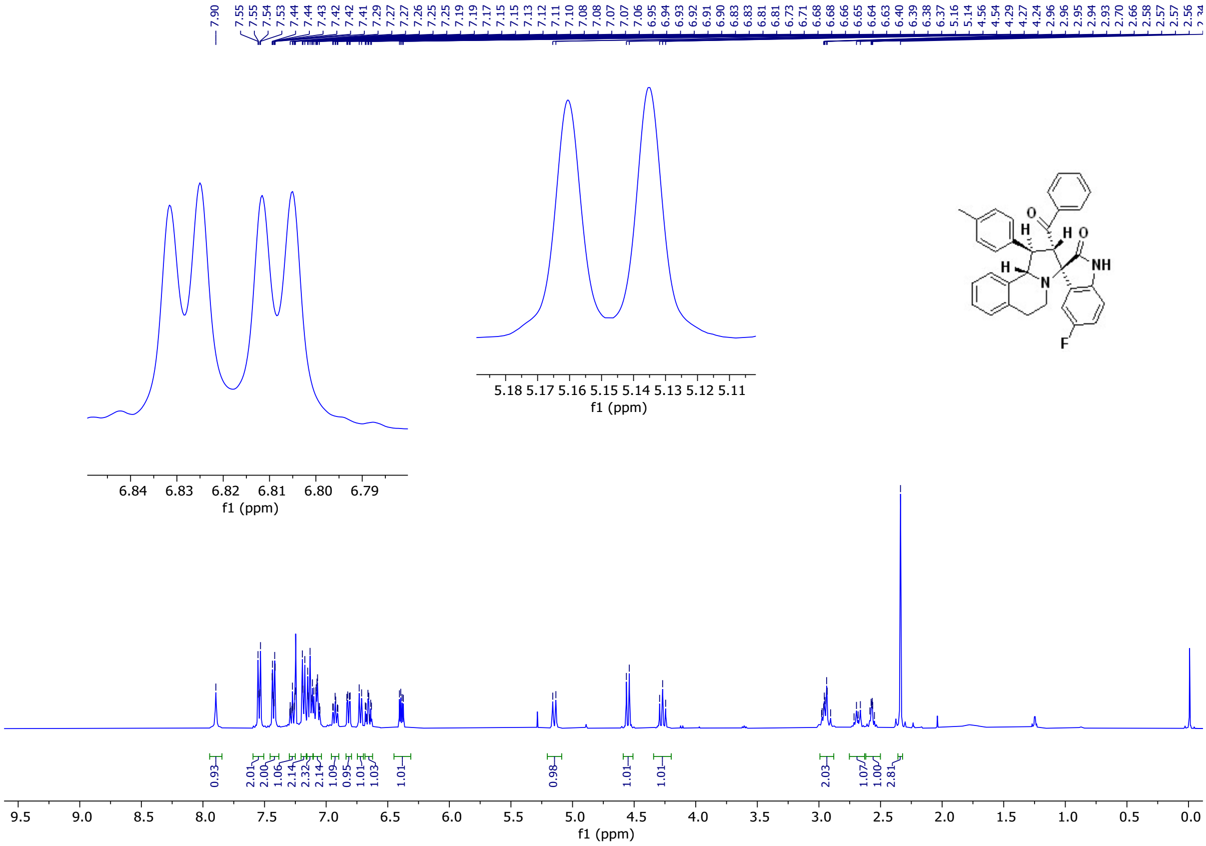


Figure S20: ^{1}H NMR of compound **4j** (500 MHz, $CDCl_3$)

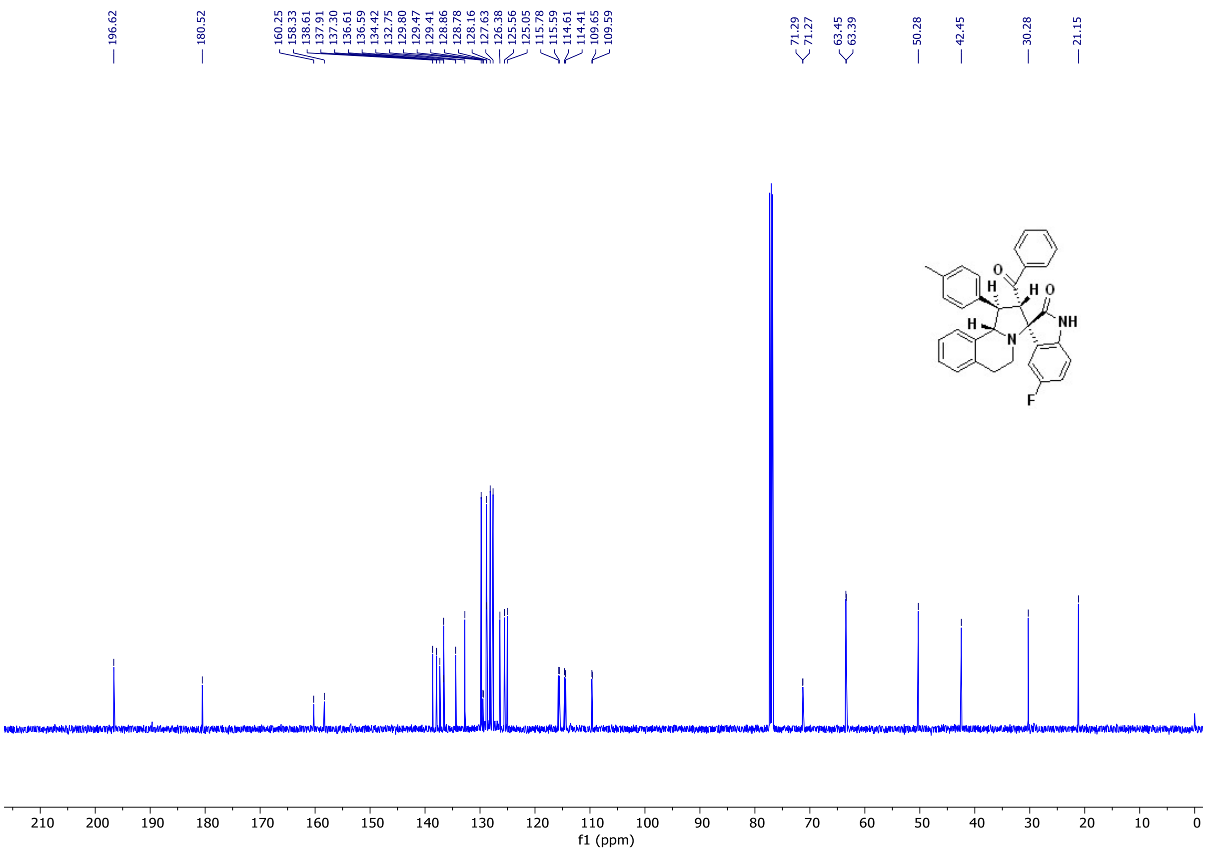


Figure S21: ^{13}C NMR of compound **4j** (126 MHz, $CDCl_3$)

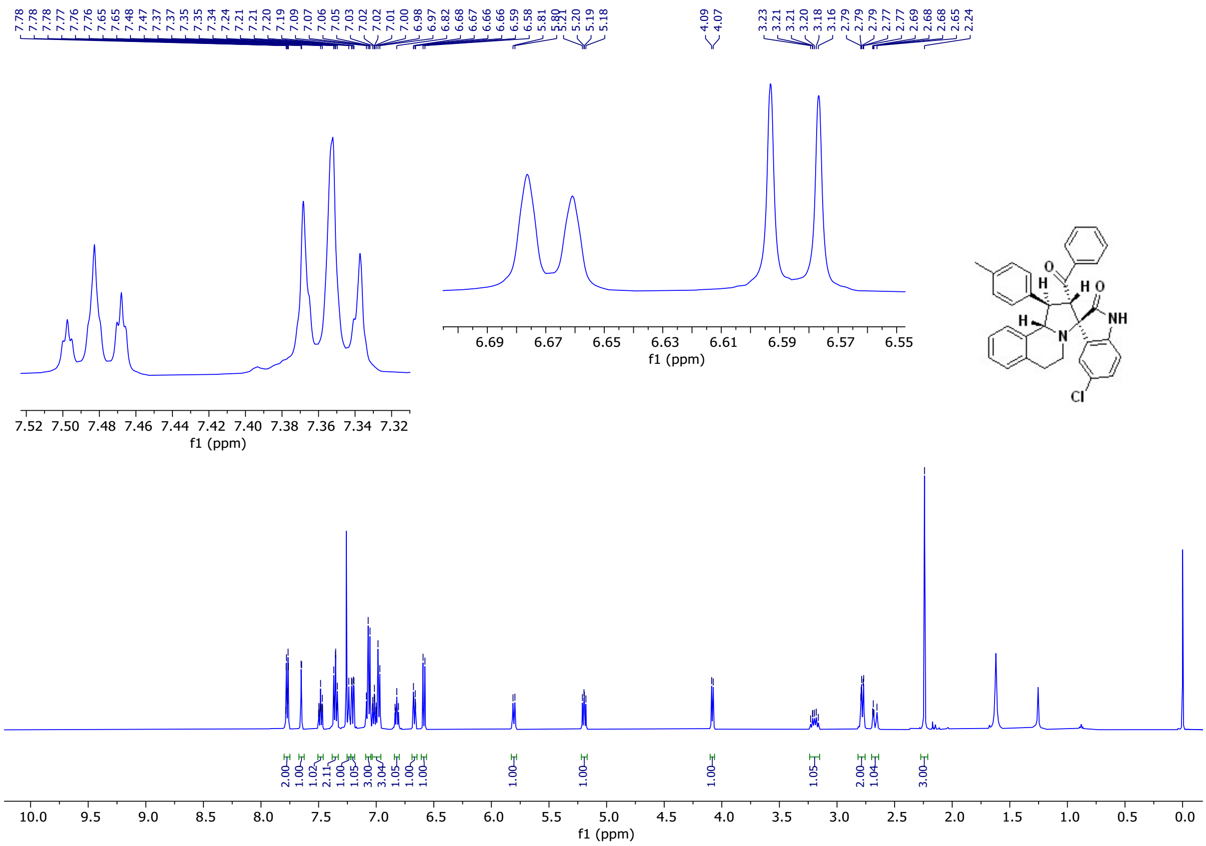


Figure S22: ^{1}H NMR of compound **4k** (500 MHz, $CDCl_3$)

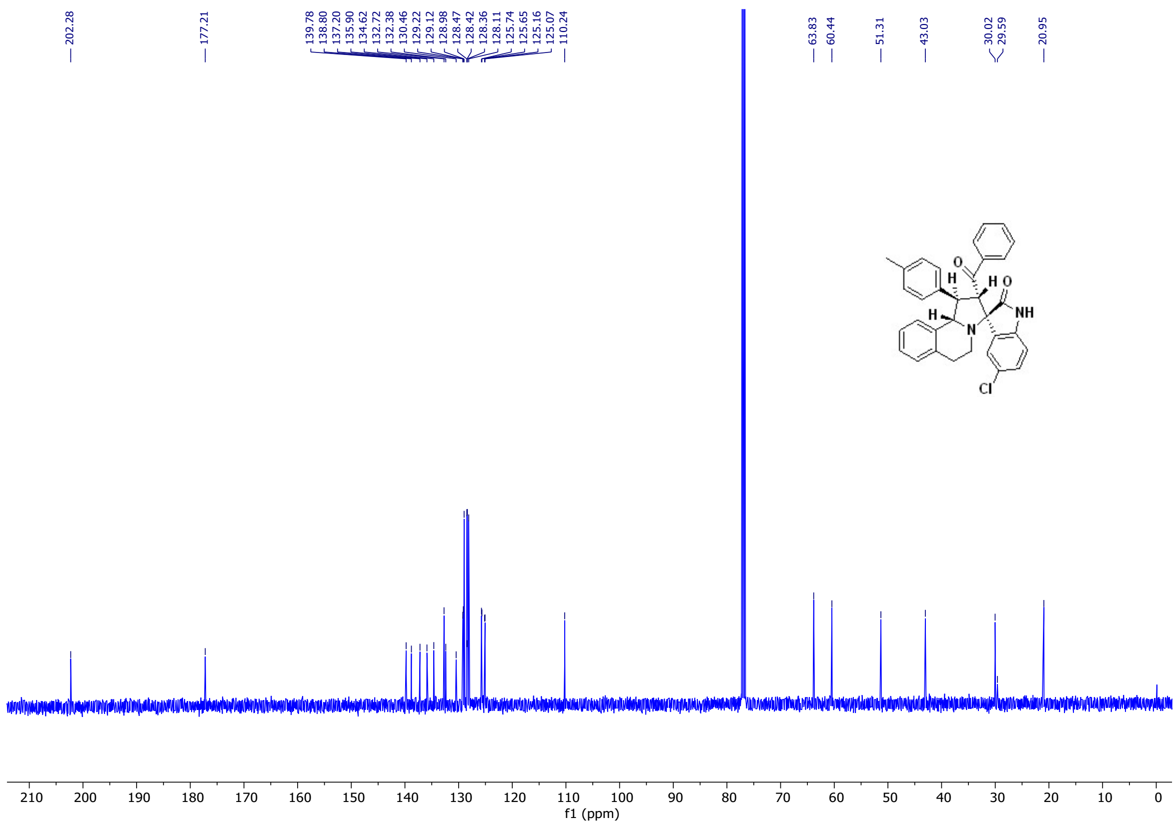


Figure S23: ^{13}C NMR of compound **4k** (126 MHz, $CDCl_3$)

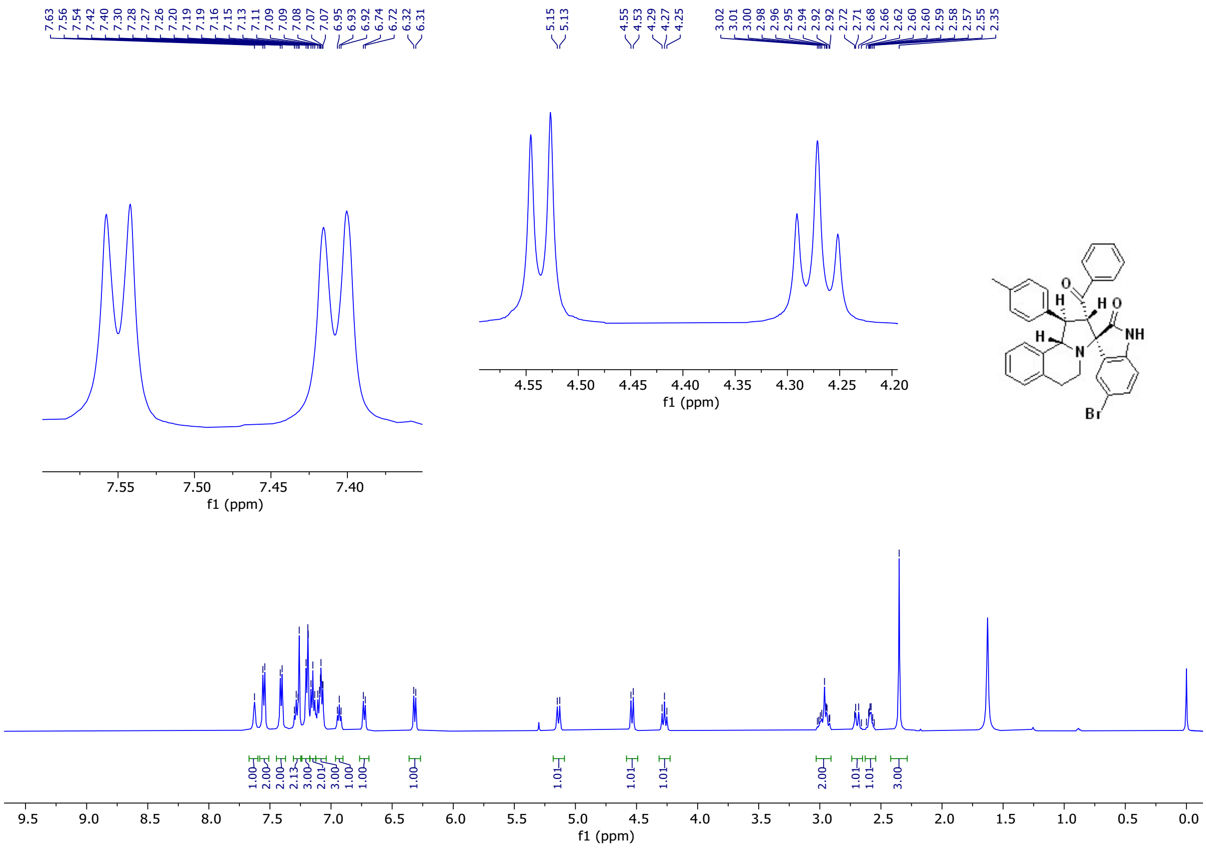


Figure S24: ^{1}H NMR of compound **4l** (500 MHz, $CDCl_3$)

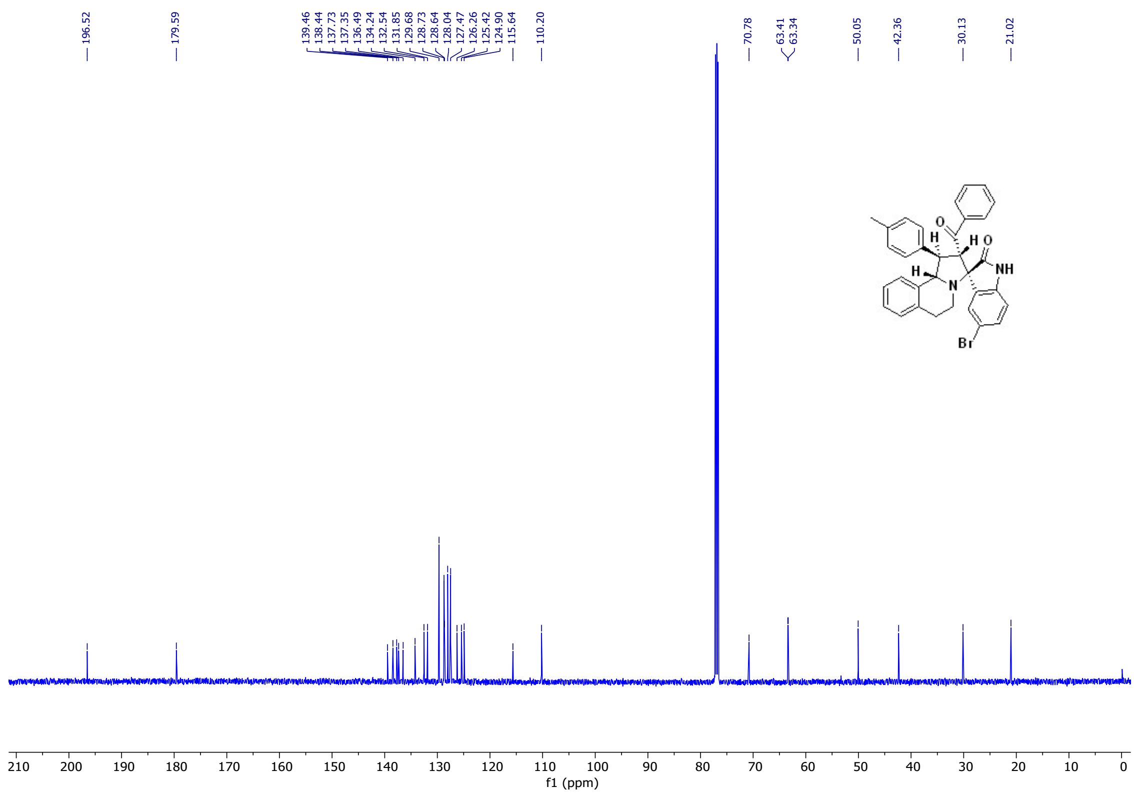


Figure S25: ^{13}C NMR of compound **4l** (126 MHz, $CDCl_3$)

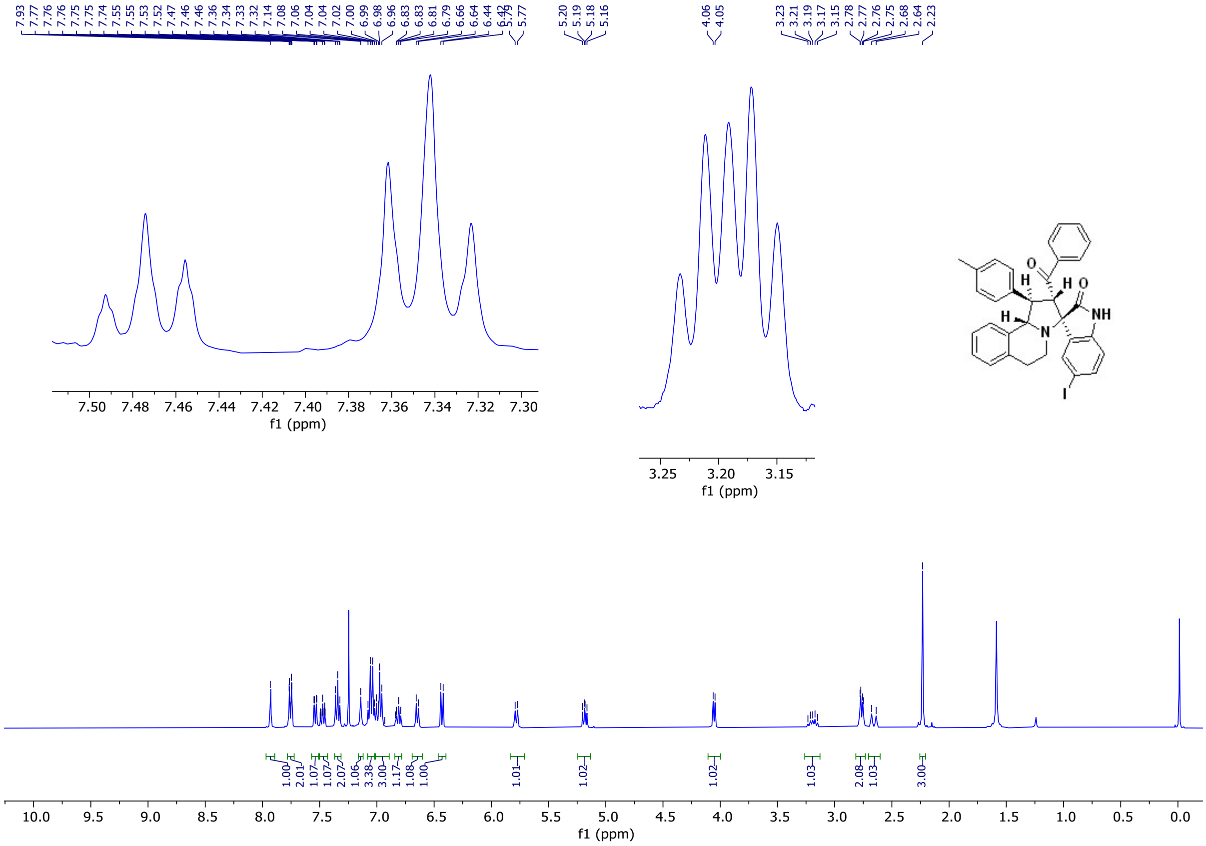


Figure S26: ^{1}H NMR of compound **4m** (500 MHz, $CDCl_3$)

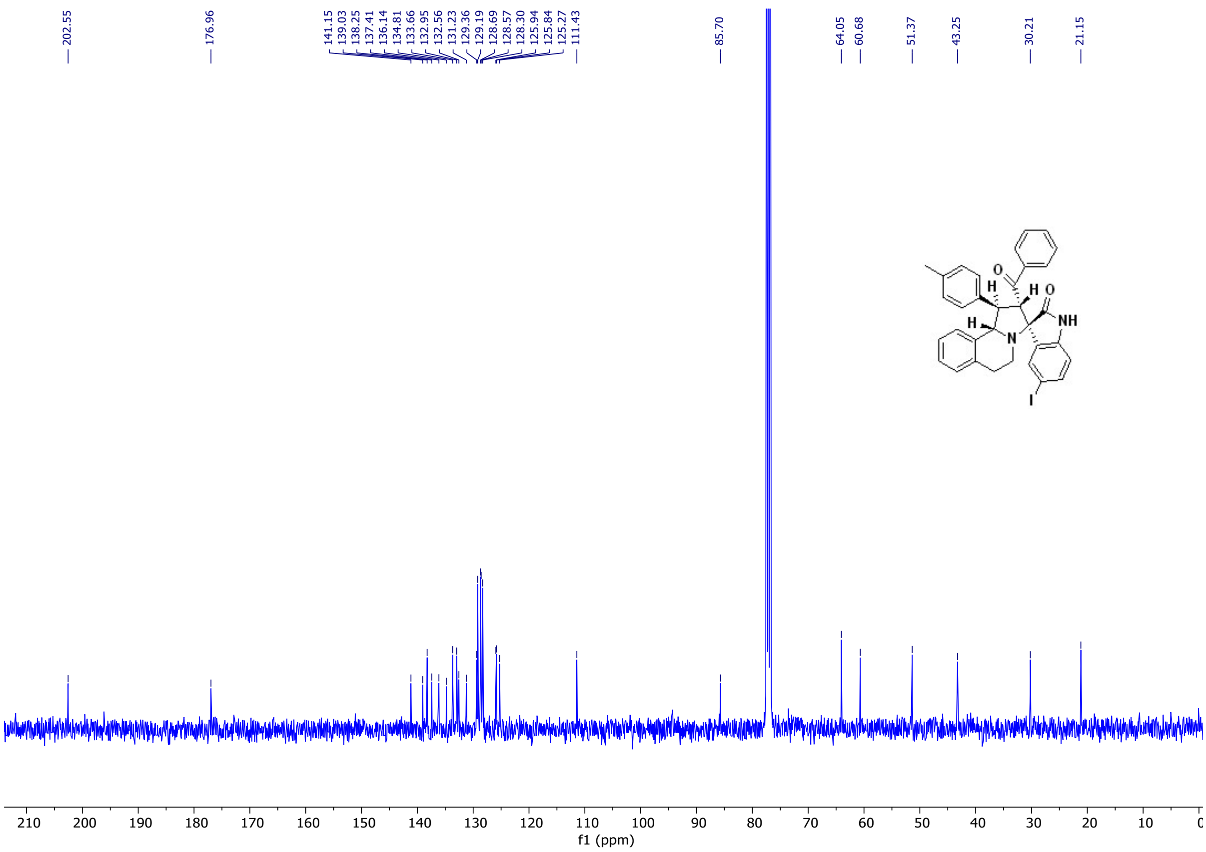


Figure S27: ^{13}C NMR of compound **4m** (126 MHz, $CDCl_3$)

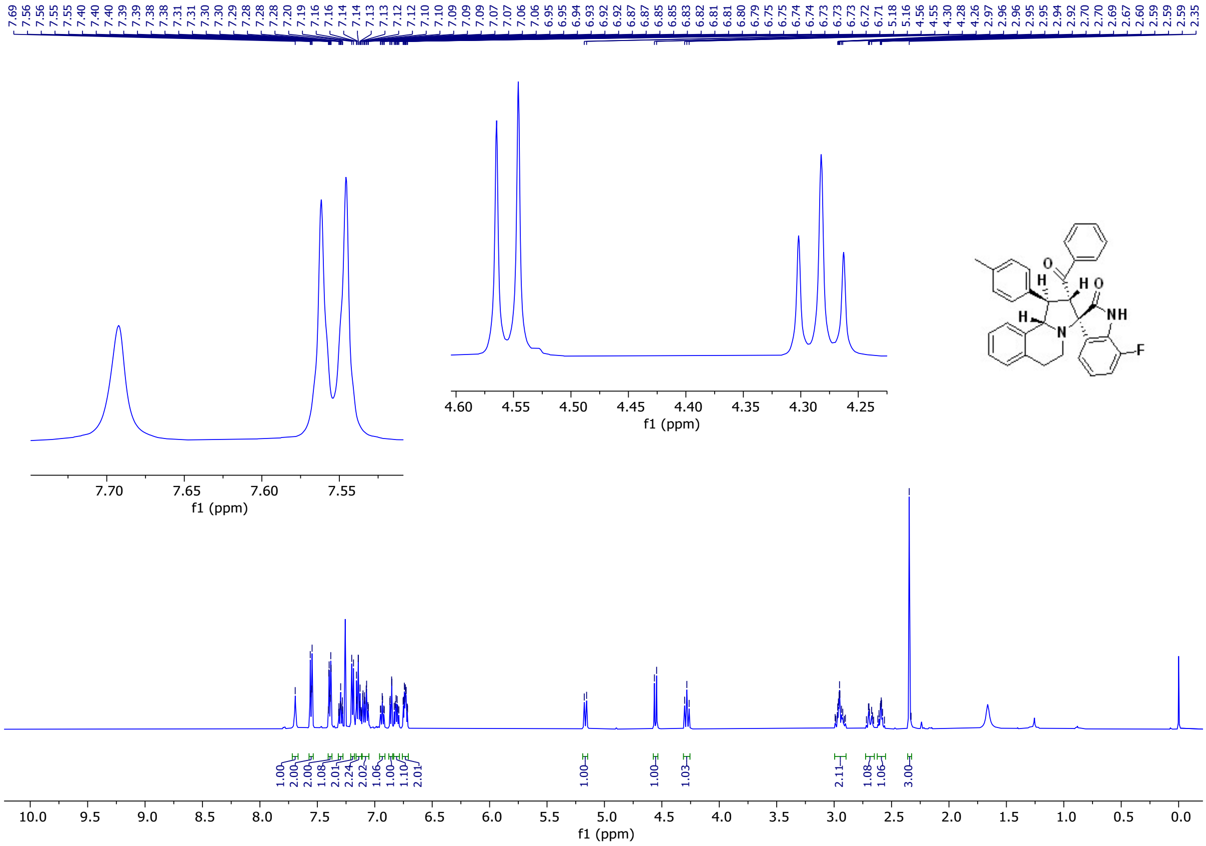


Figure S28: ^{1}H NMR of compound **4n** (500 MHz, $CDCl_3$)

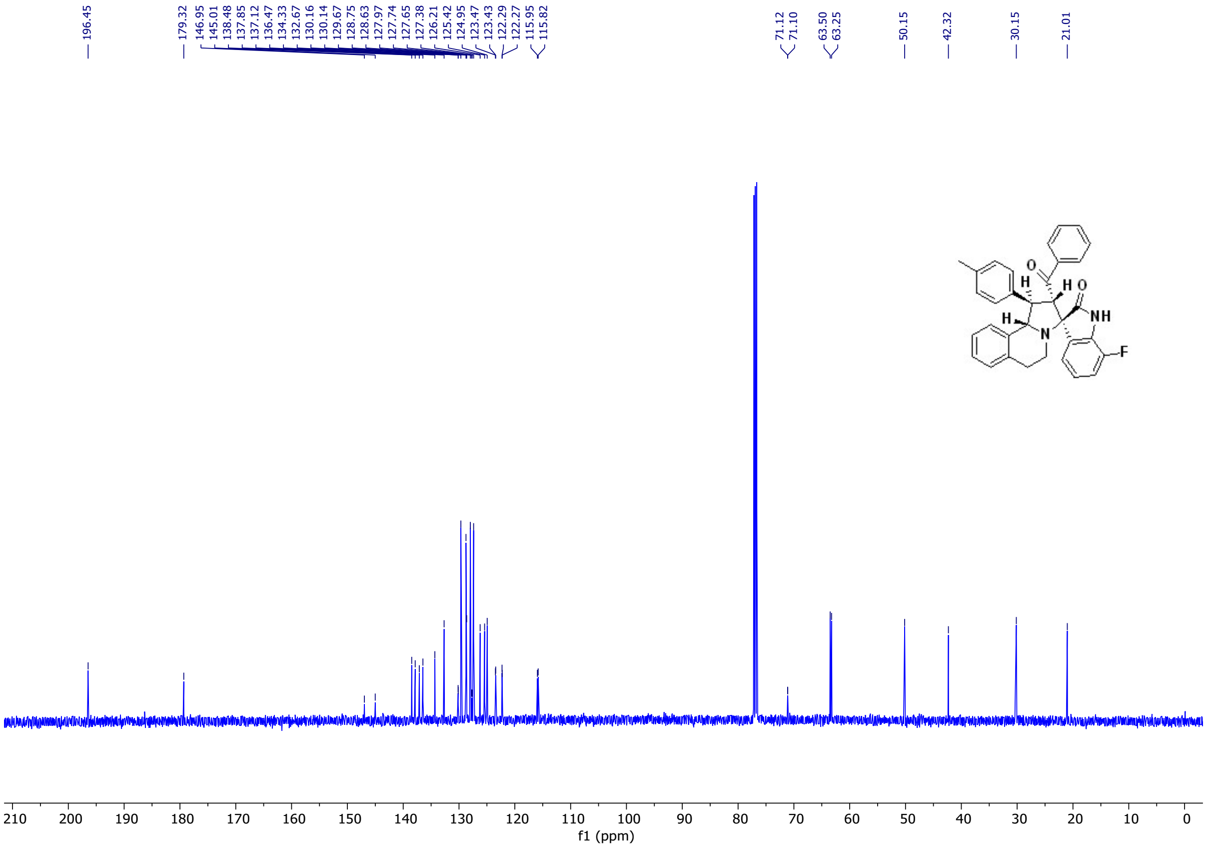


Figure S29: ^{13}C NMR of compound **4n** (126 MHz, $CDCl_3$)

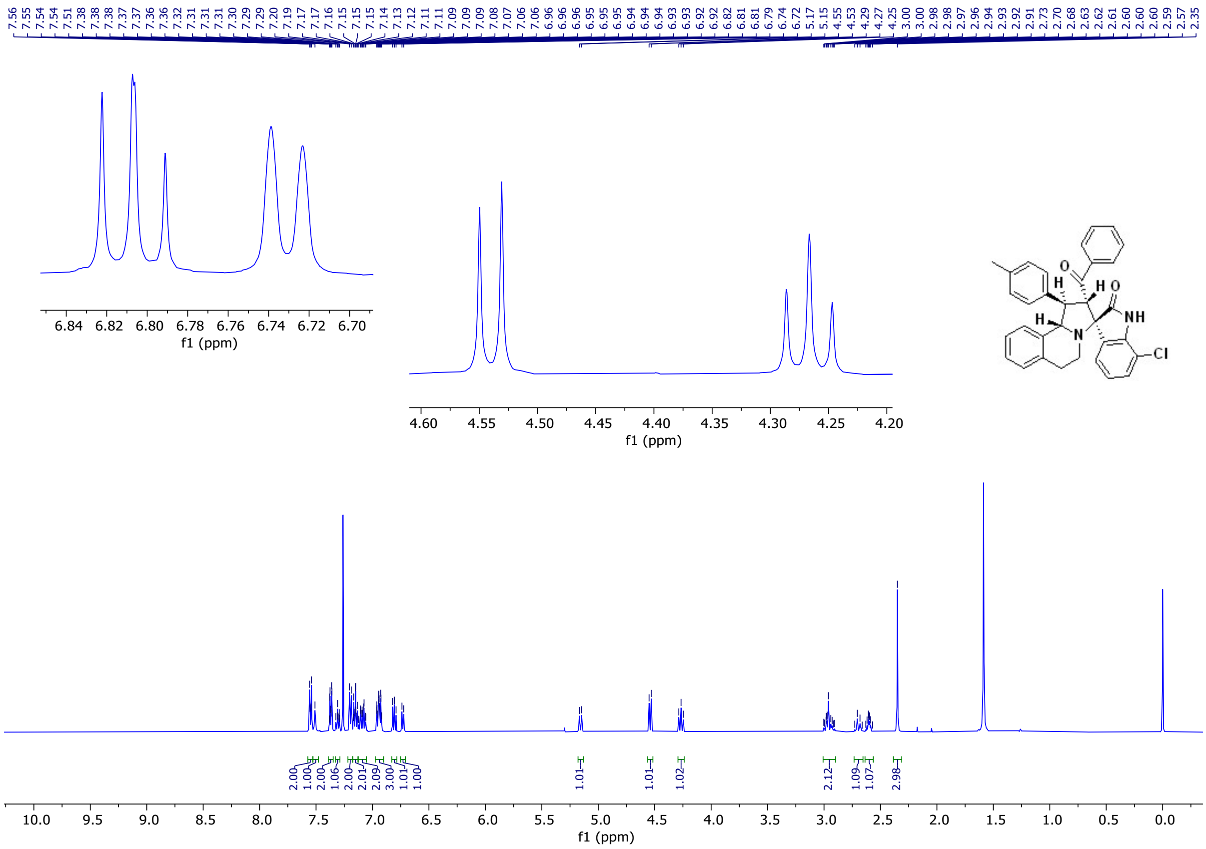


Figure S30: ^{1}H NMR of compound **4o** (500 MHz, $CDCl_3$)

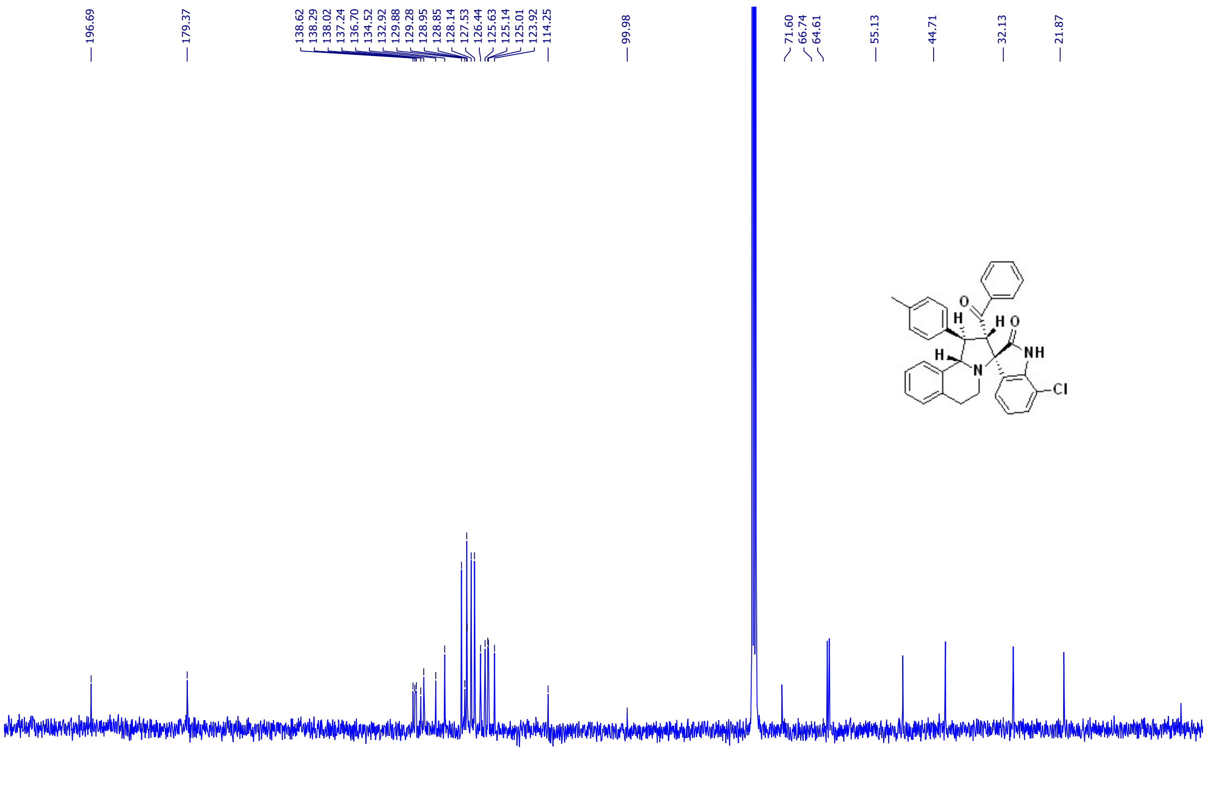


Figure S31: ^{13}C NMR of compound **4o** (126 MHz, $CDCl_3$)

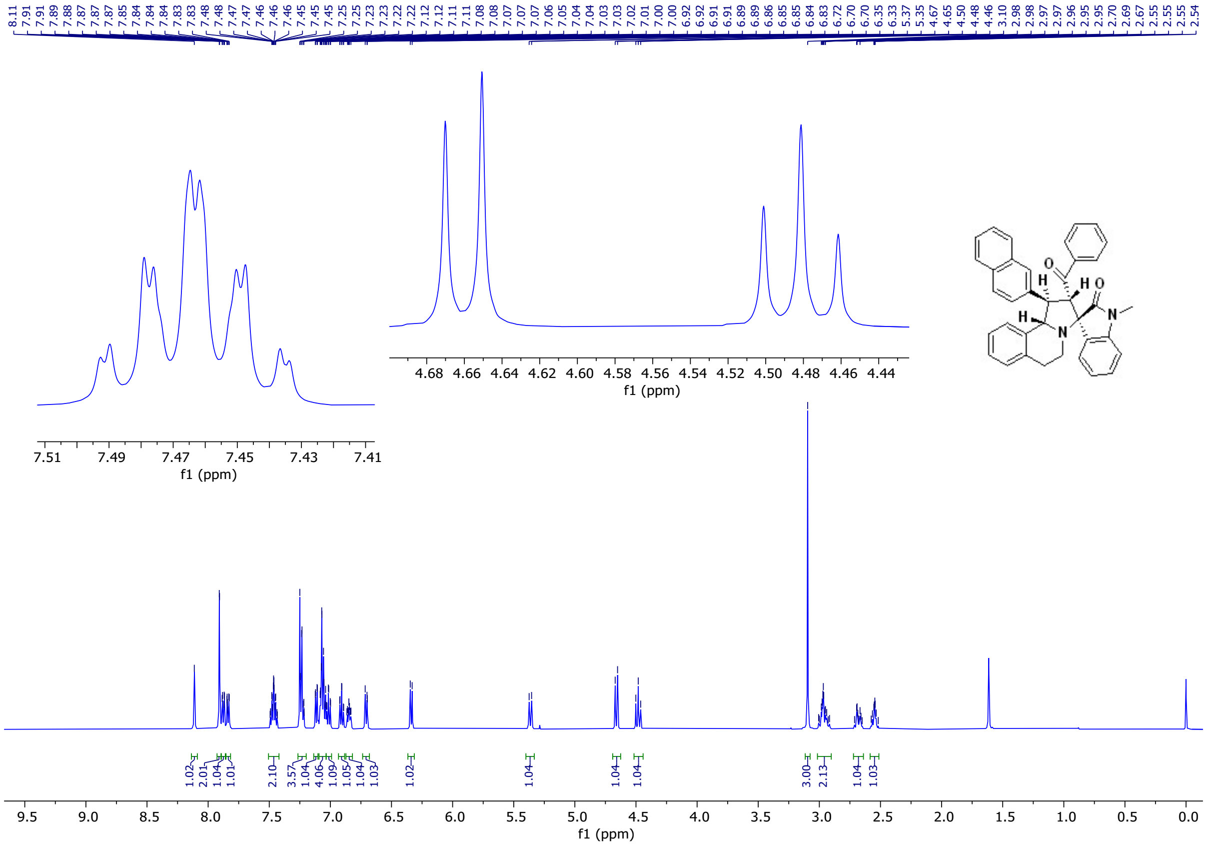


Figure S32: ^{1}H NMR of compound **4p** (500 MHz, $CDCl_3$)

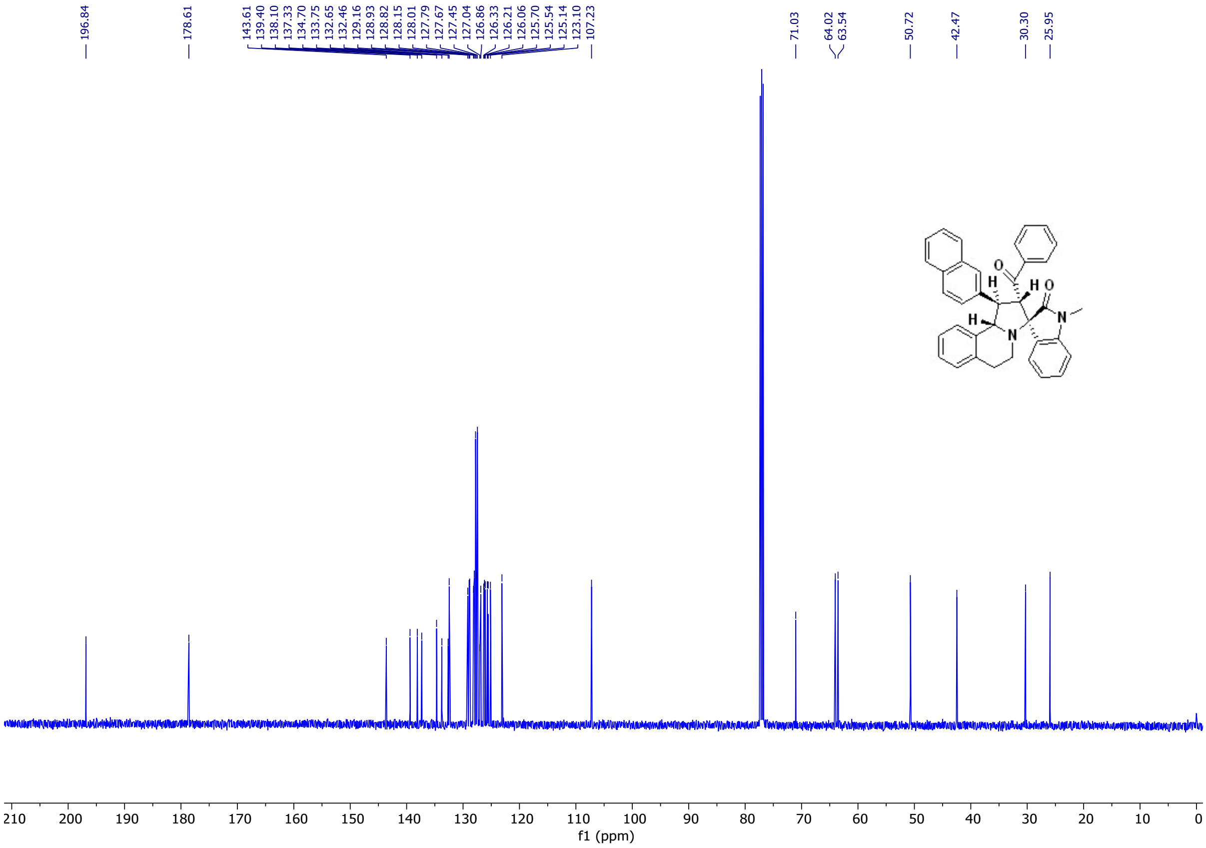


Figure S33: ^{13}C NMR of compound **4p** (126 MHz, $CDCl_3$)

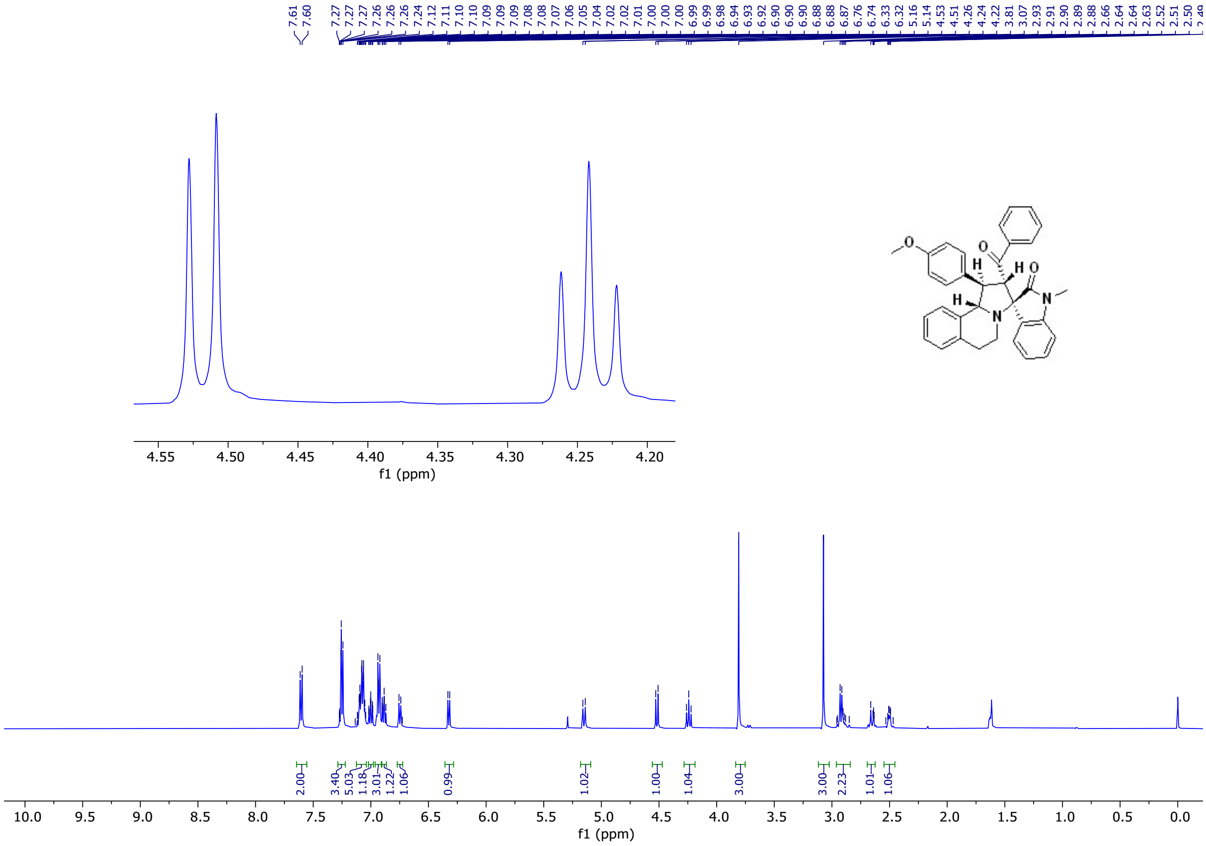


Figure S34: ^{1}H NMR of compound **4q** (500 MHz, $CDCl_3$)

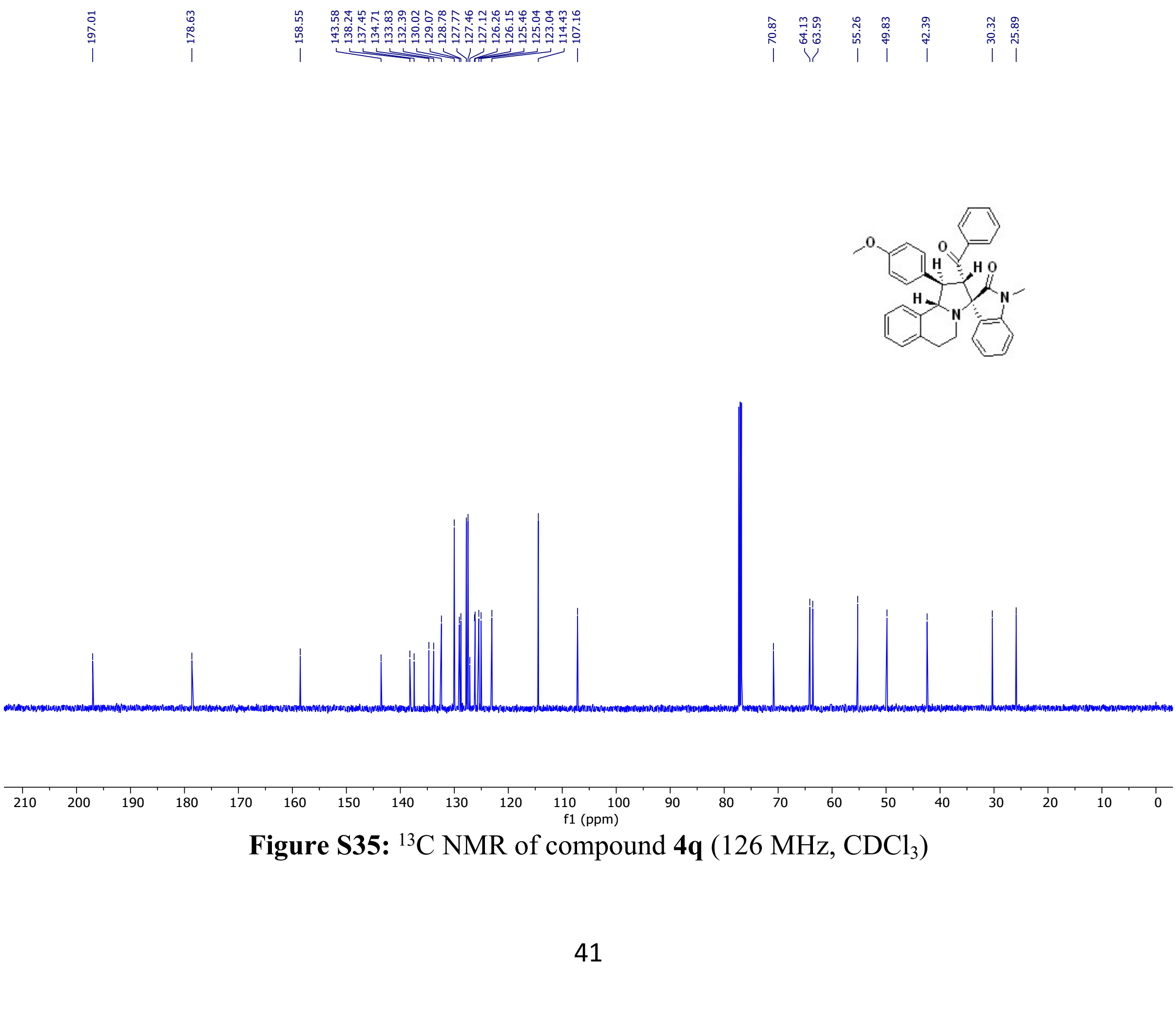


Figure S35: ^{13}C NMR of compound **4q** (126 MHz, $CDCl_3$)

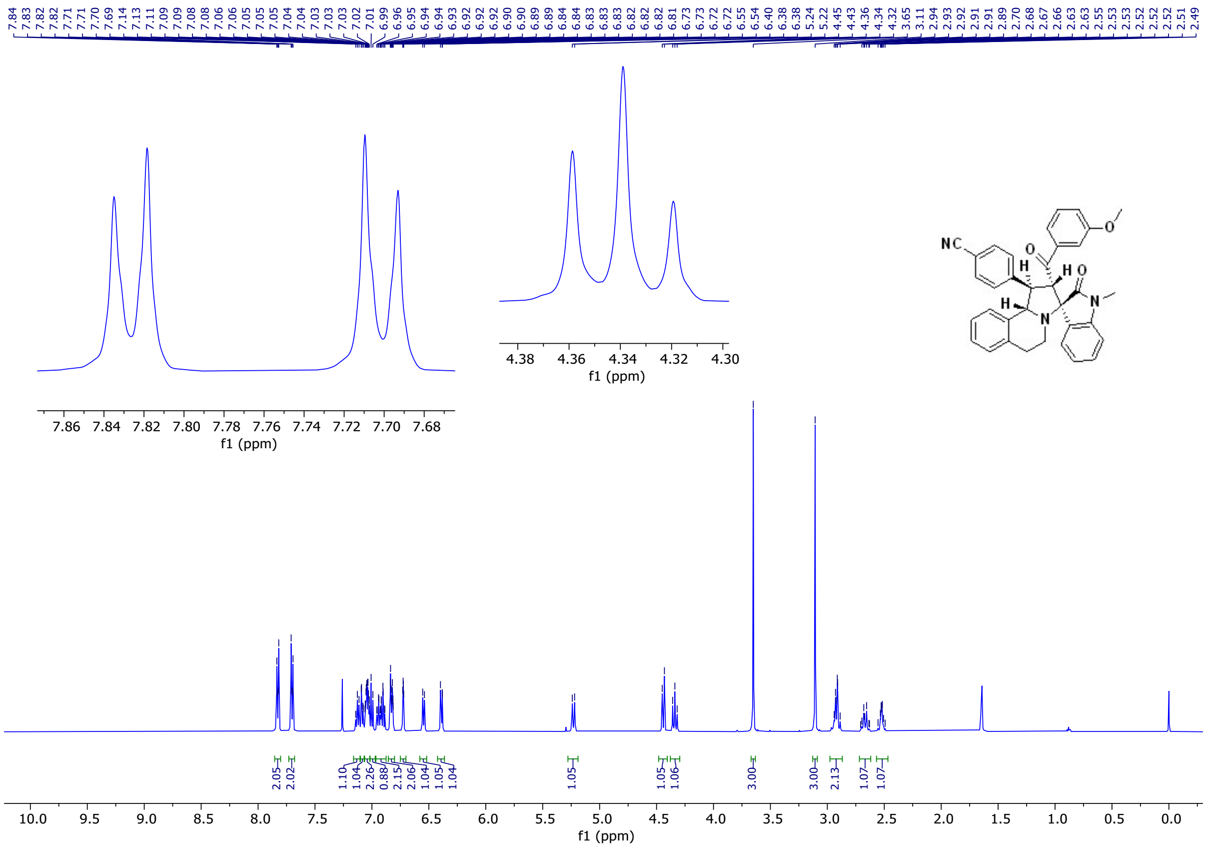


Figure S36: ^{1}H NMR of compound **4r** (500 MHz, $CDCl_3$)

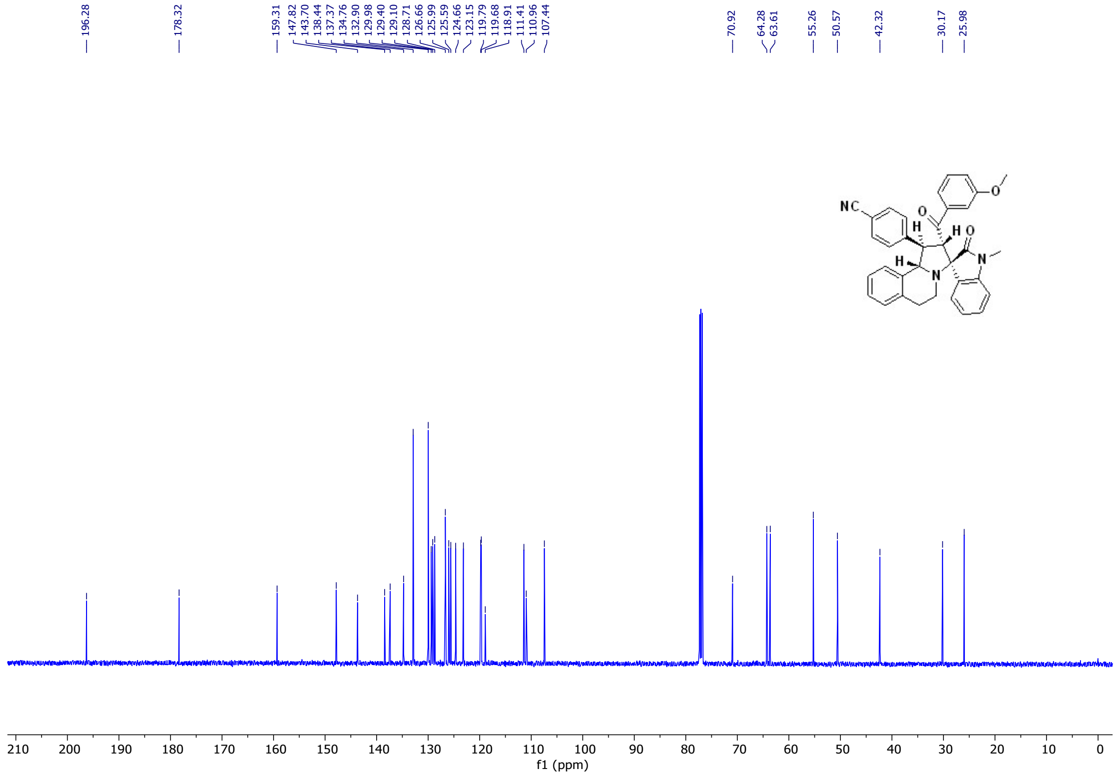


Figure S37: ^{13}C NMR of compound **4r** (126 MHz, $CDCl_3$)

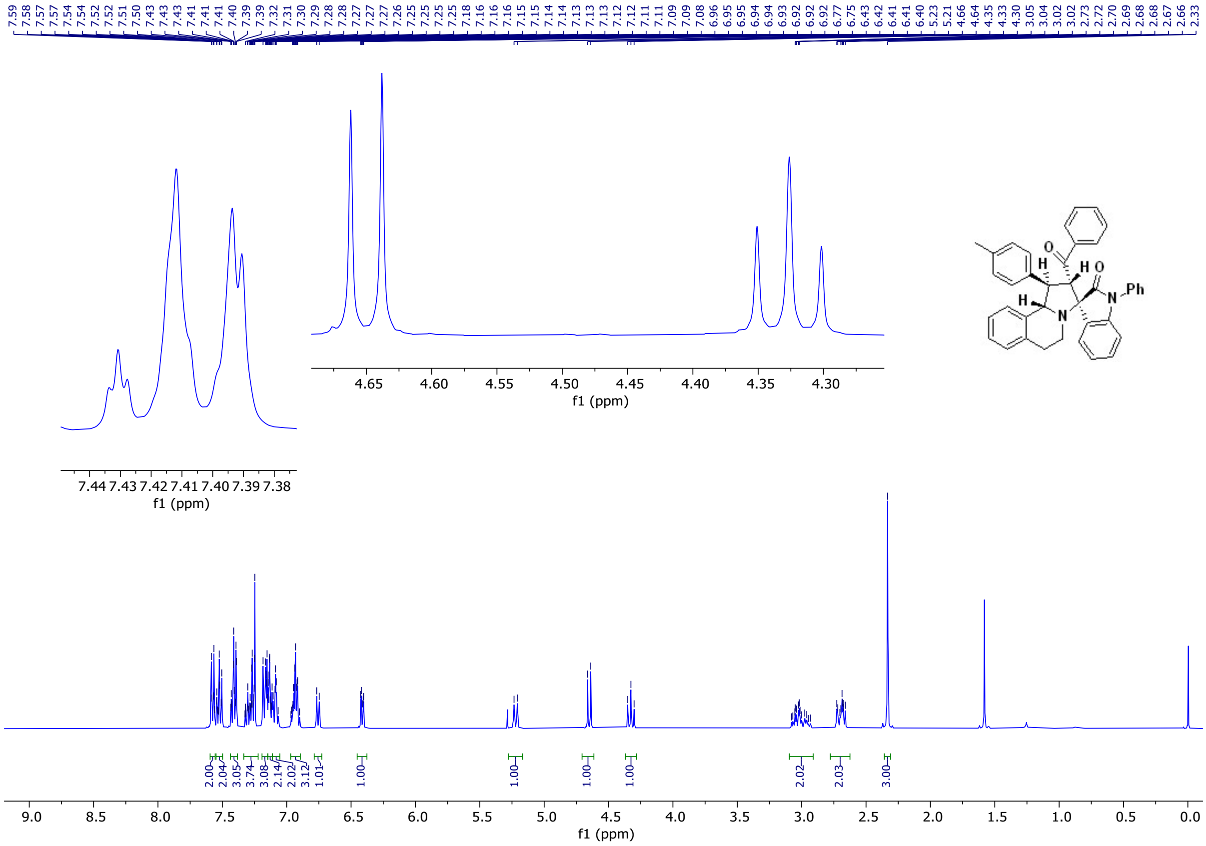


Figure S38: ^{1}H NMR of compound **4s** (500 MHz, $CDCl_3$)

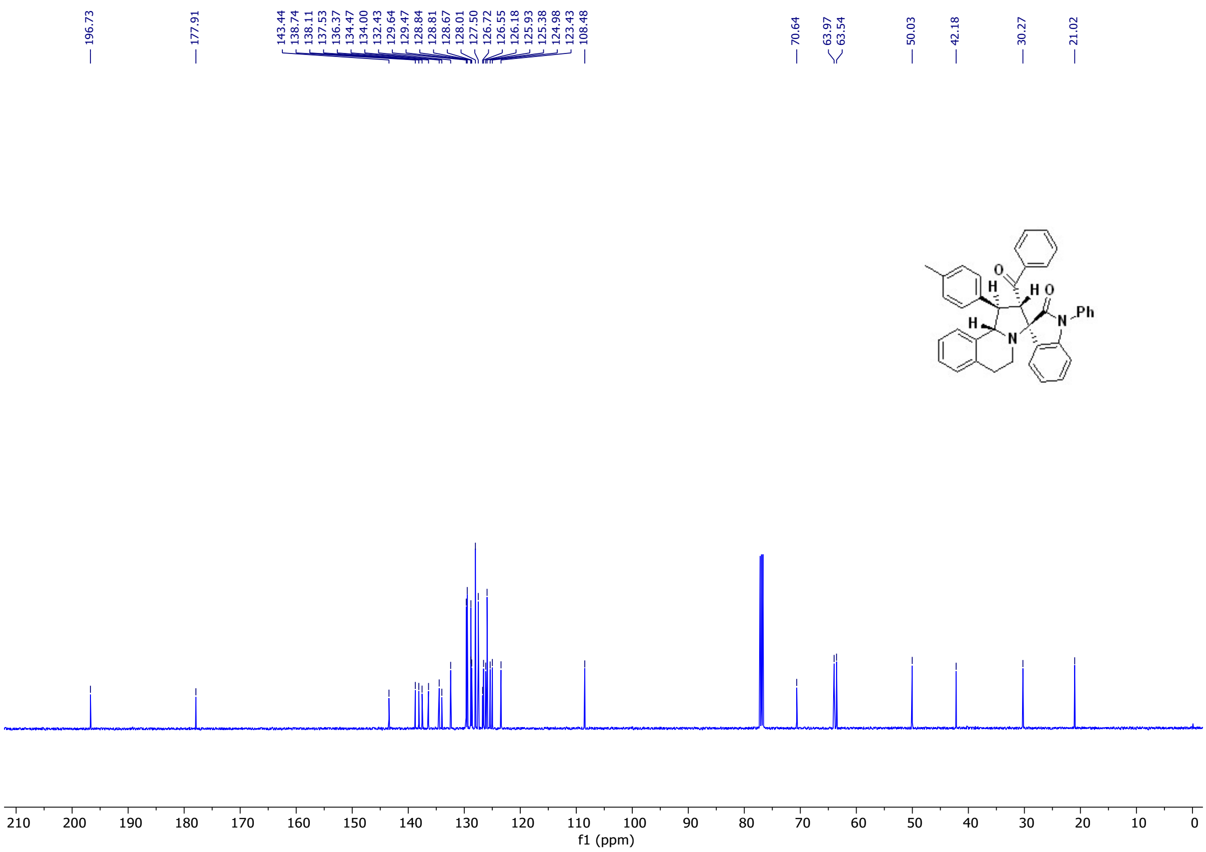


Figure S39: ^{13}C NMR of compound **4s** (126 MHz, $CDCl_3$)

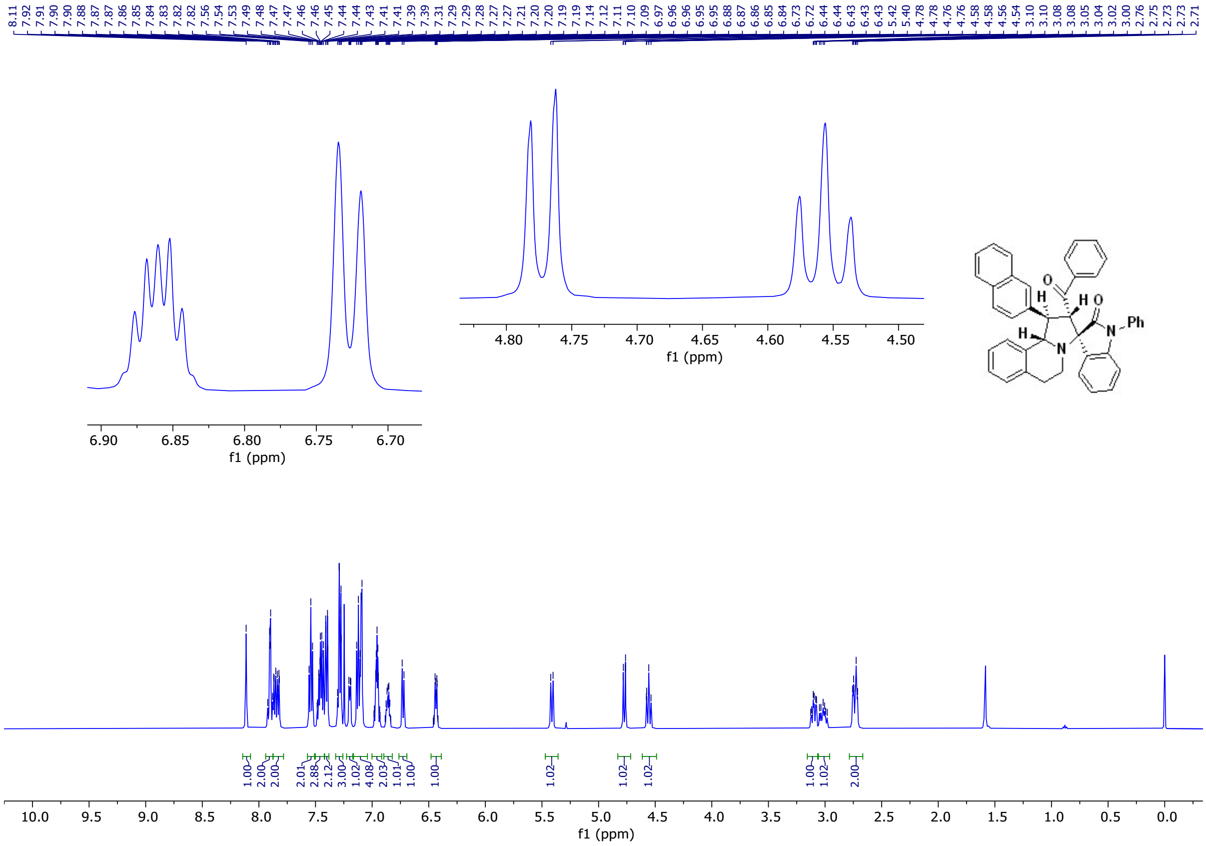


Figure S40: ^{1}H NMR of compound **4t** (500 MHz, $CDCl_3$)

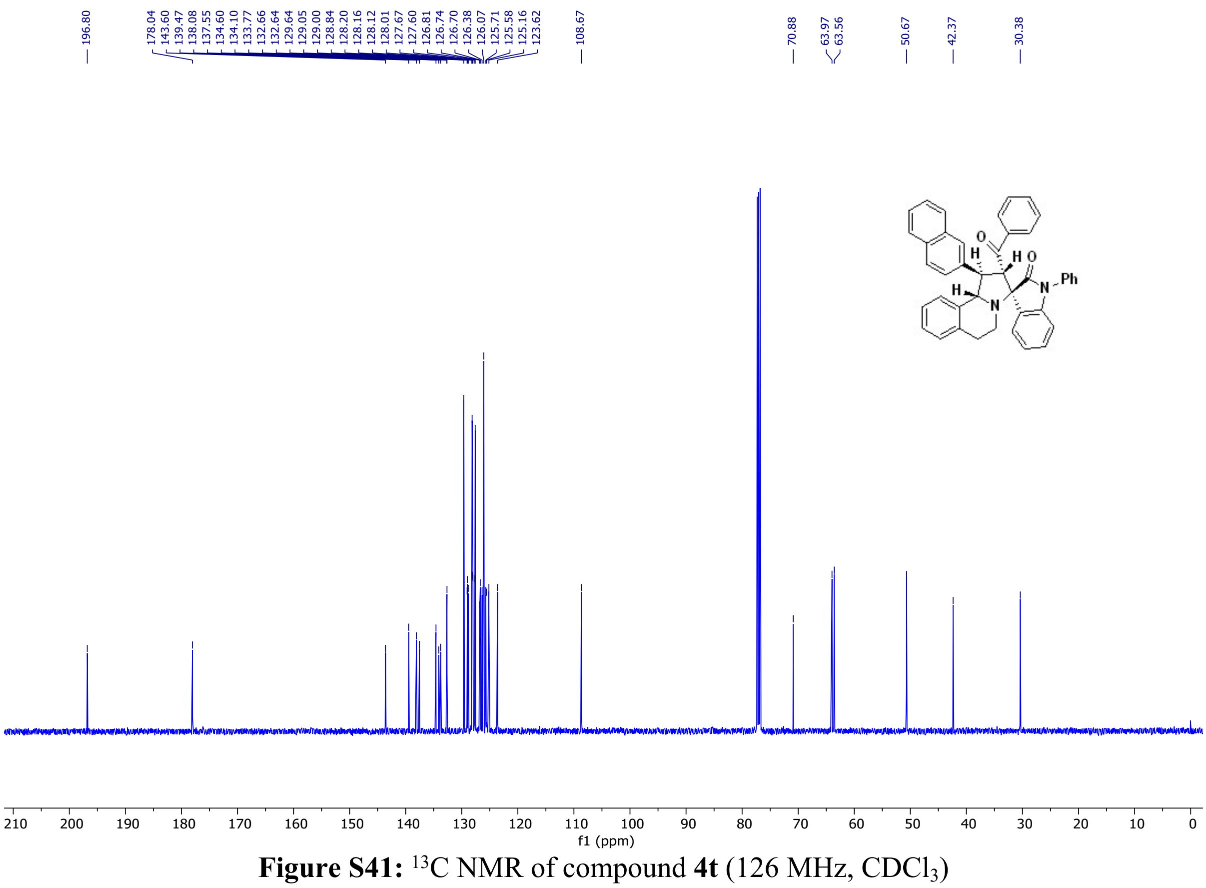


Figure S41: ^{13}C NMR of compound **4t** (126 MHz, $CDCl_3$)

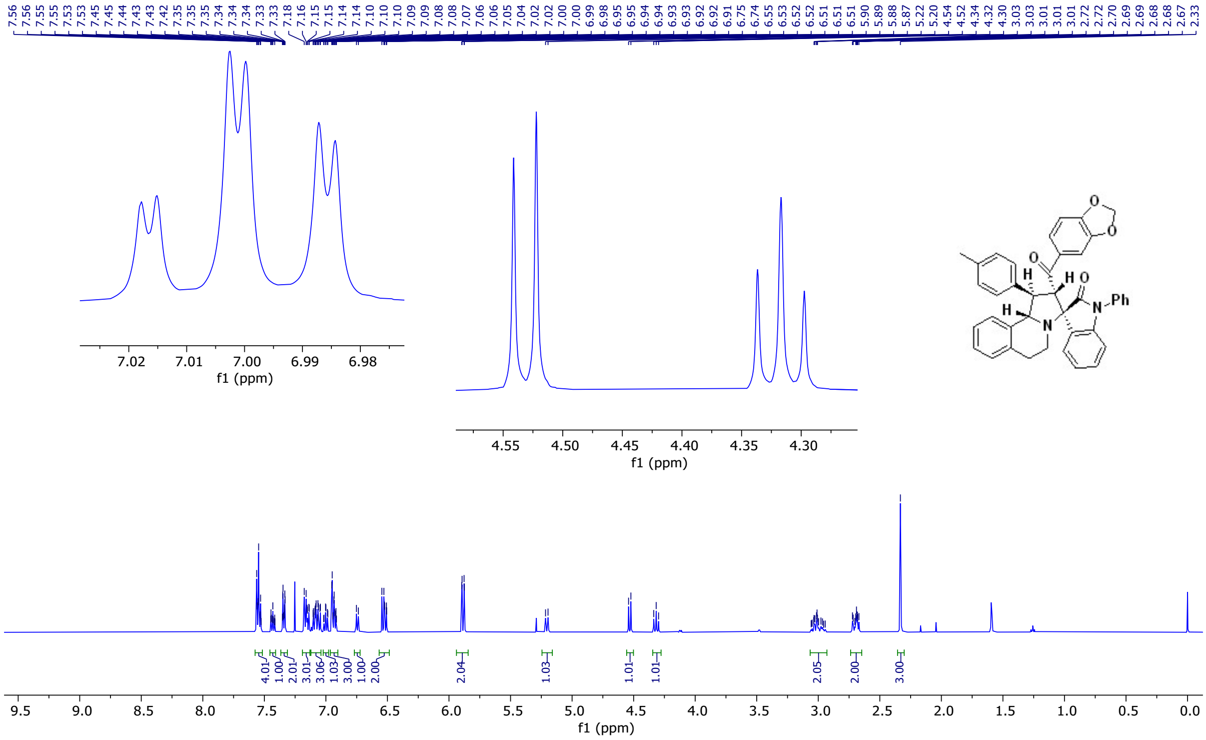


Figure S42: ^{1}H NMR of compound **4u** (500 MHz, $CDCl_3$)

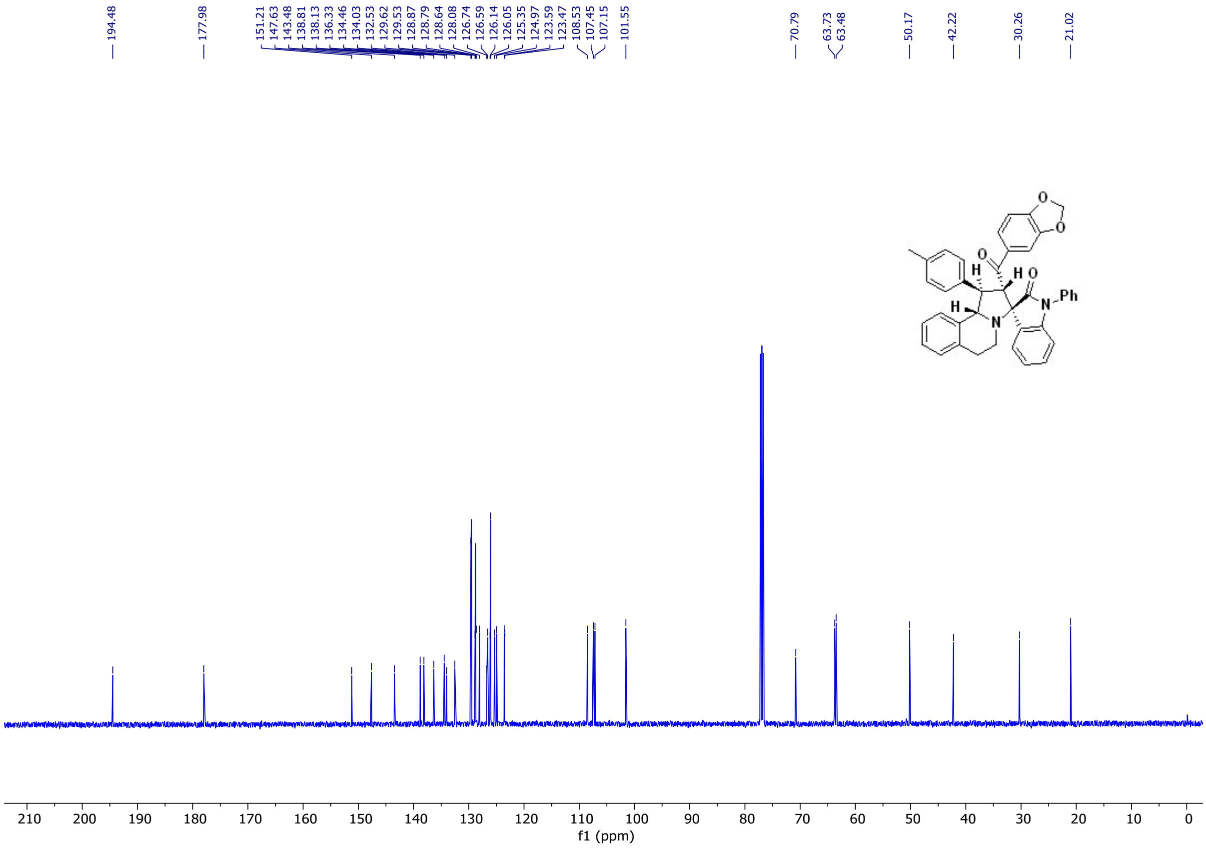


Figure S43: ^{13}C NMR of compound **4u** (126 MHz, $CDCl_3$)

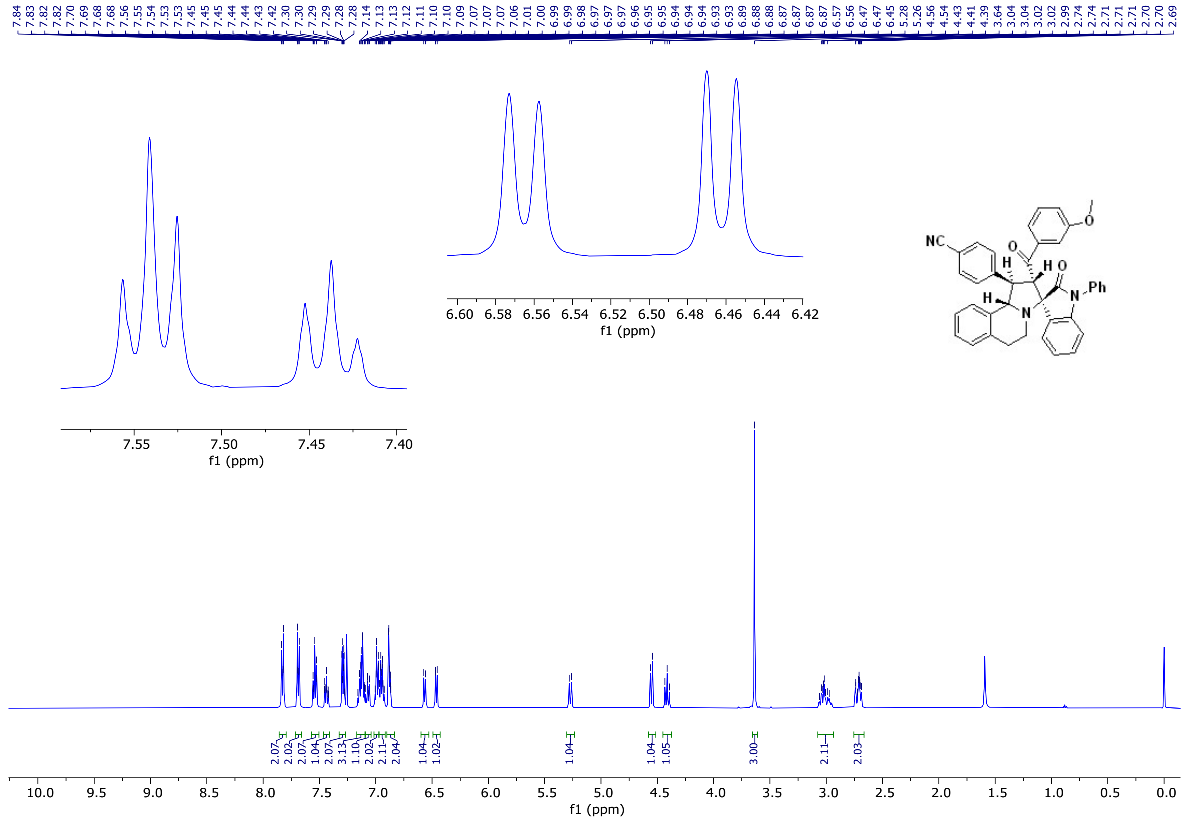


Figure S44: ^{1}H NMR of compound **4v** (500 MHz, $CDCl_3$)

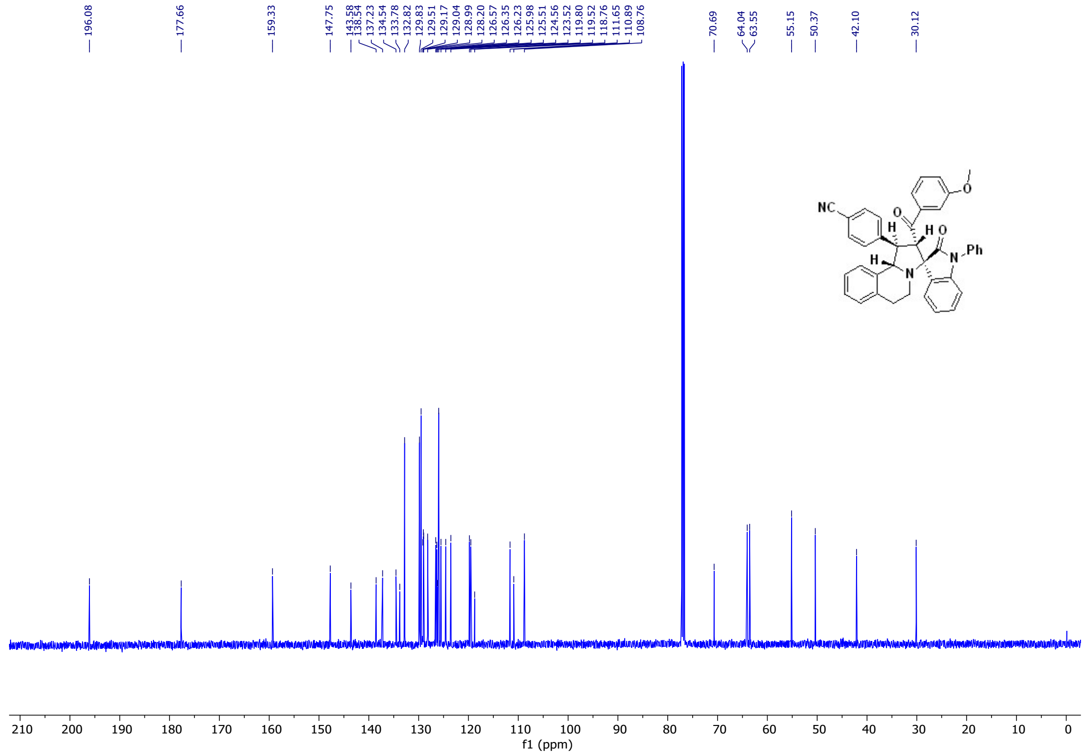


Figure S45: ^{13}C NMR of compound **4v** (126 MHz, $CDCl_3$)

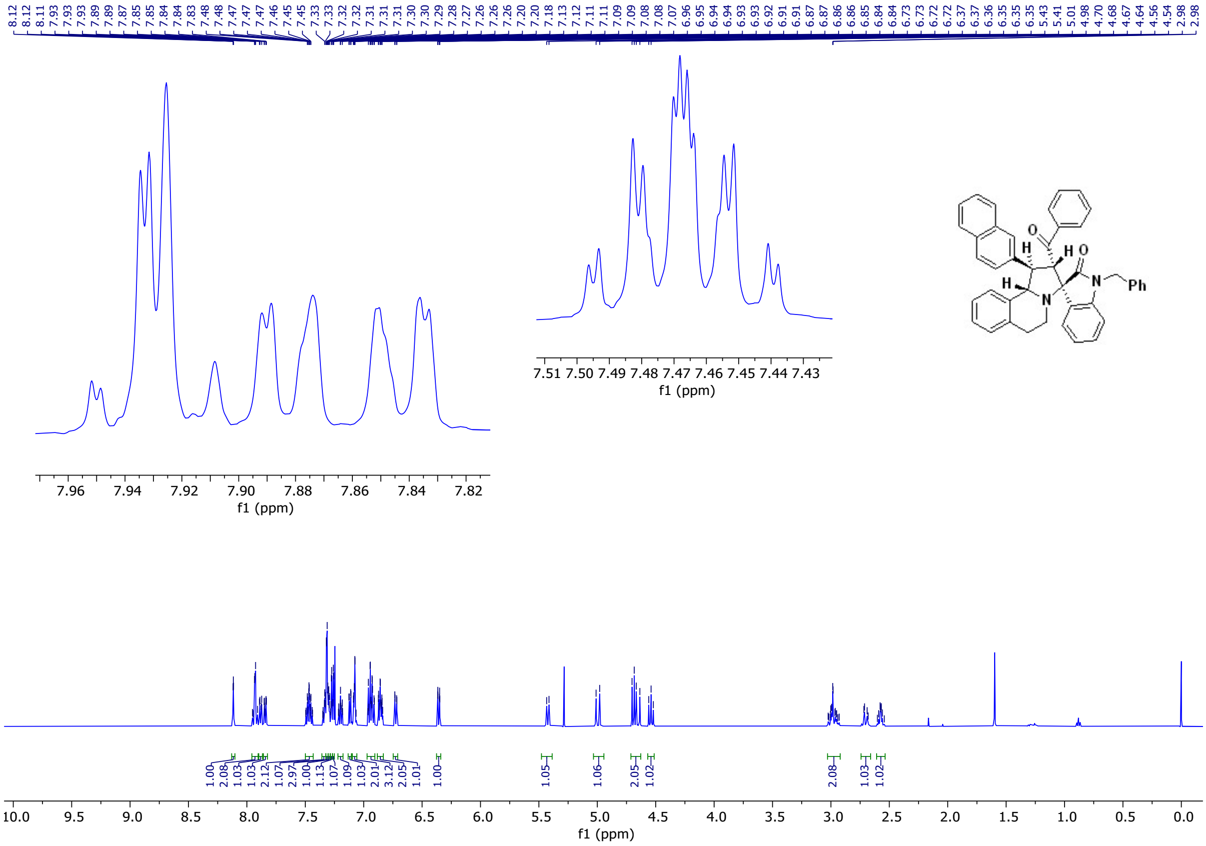


Figure S46: ^{1}H NMR of compound **4w** (500 MHz, $CDCl_3$)

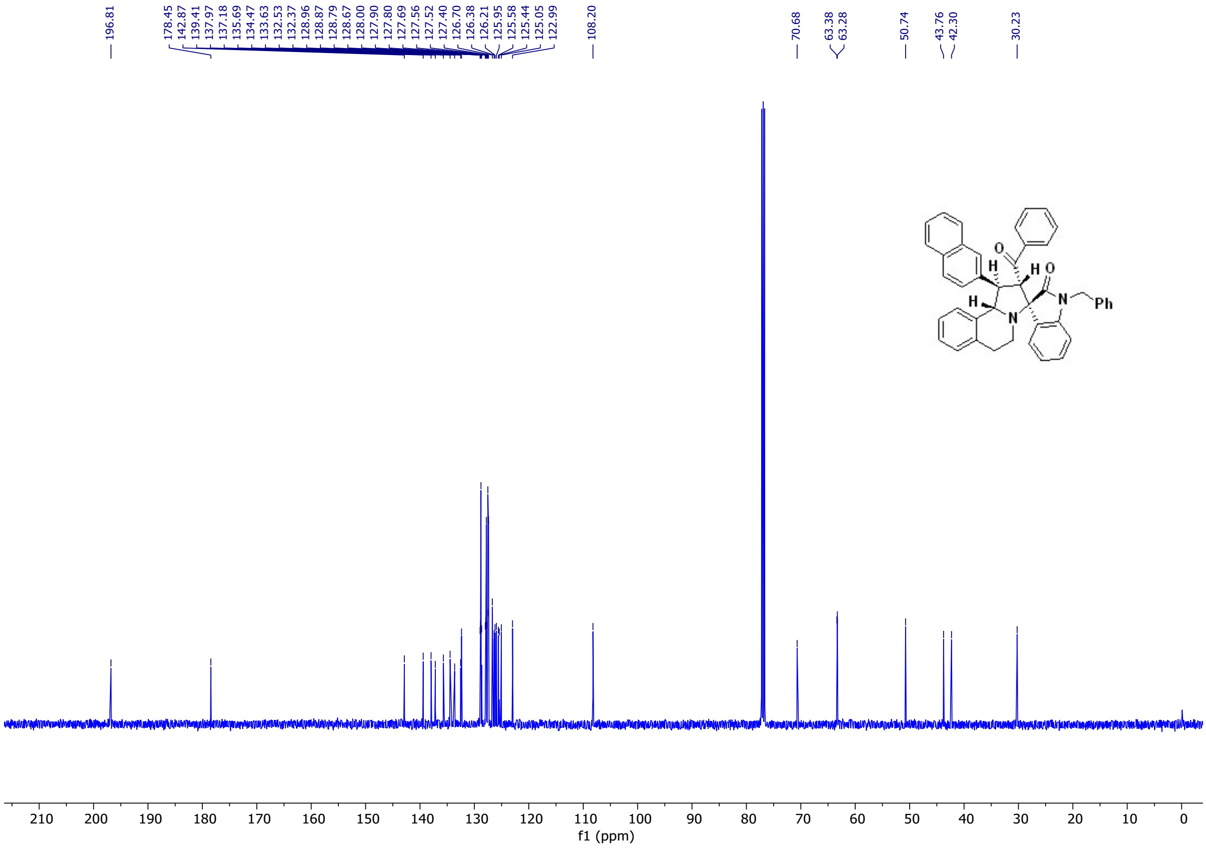


Figure S47: ^{13}C NMR of compound **4w** (126 MHz, $CDCl_3$)

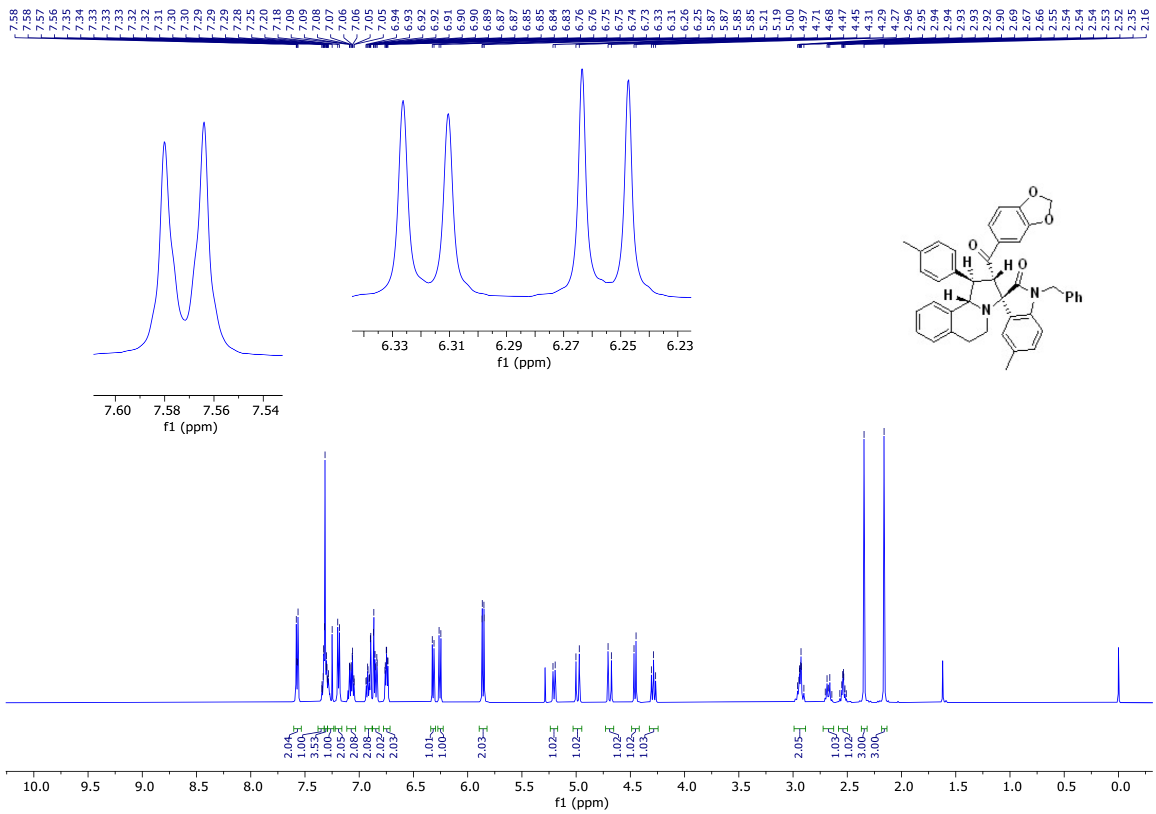


Figure S48: ^{1}H NMR of compound **4x** (500 MHz, $CDCl_3$)

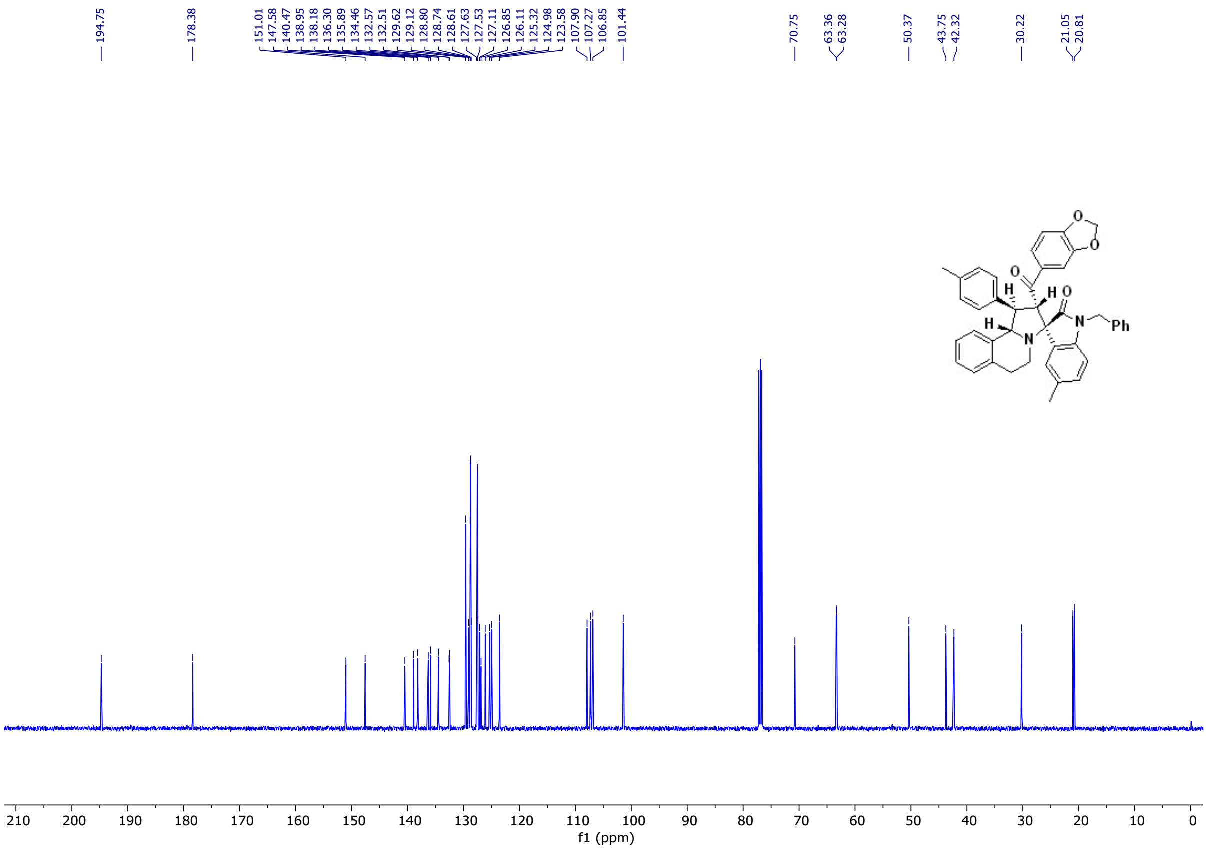


Figure S49: ^{13}C NMR of compound **4x** (126 MHz, $CDCl_3$)

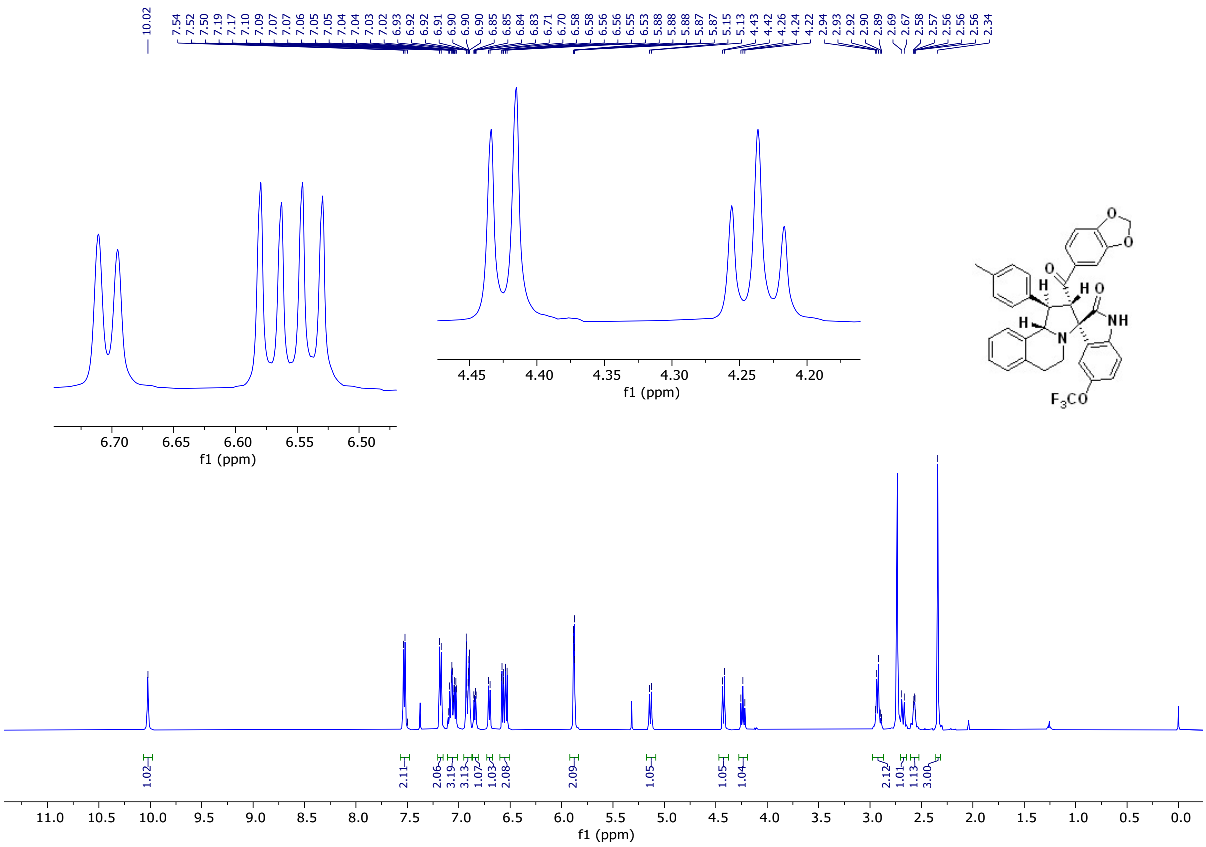


Figure S50: ^{1}H NMR of compound **4y** (500 MHz, $CDCl_3$)

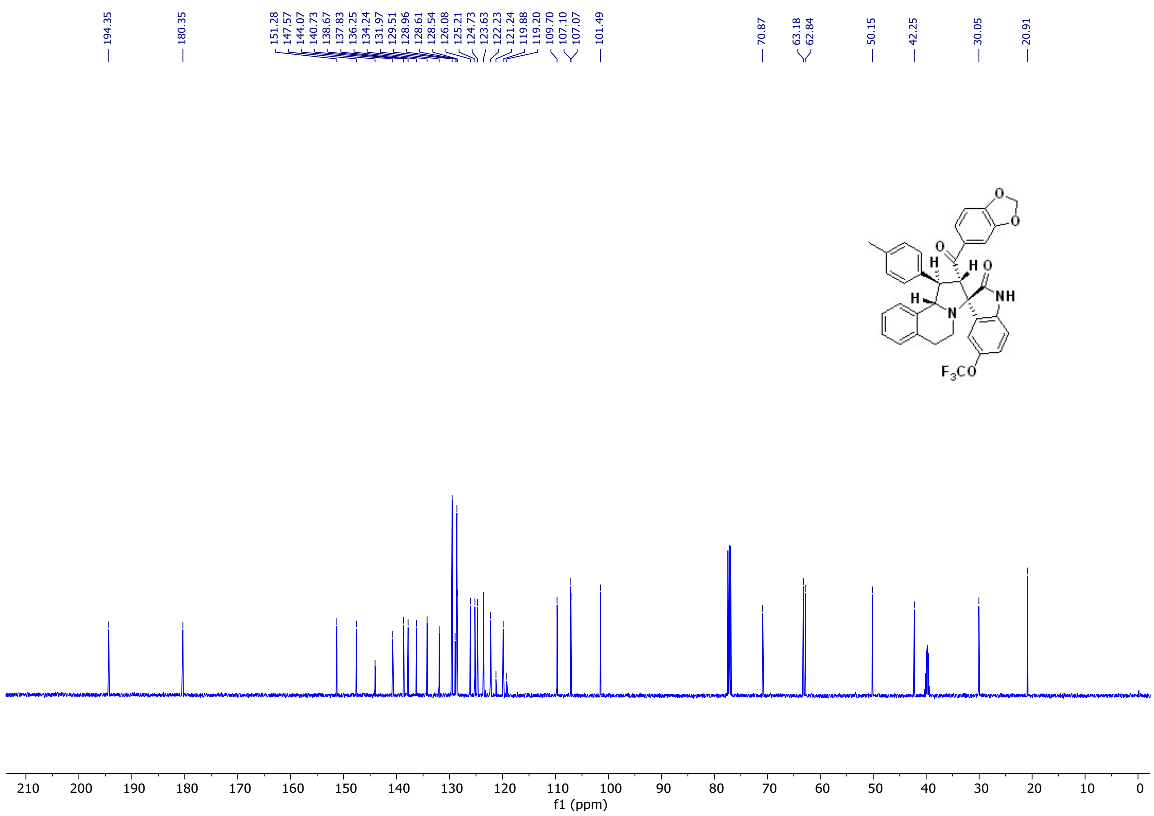


Figure S51: ^{13}C NMR of compound **4y** (126 MHz, $CDCl_3$)

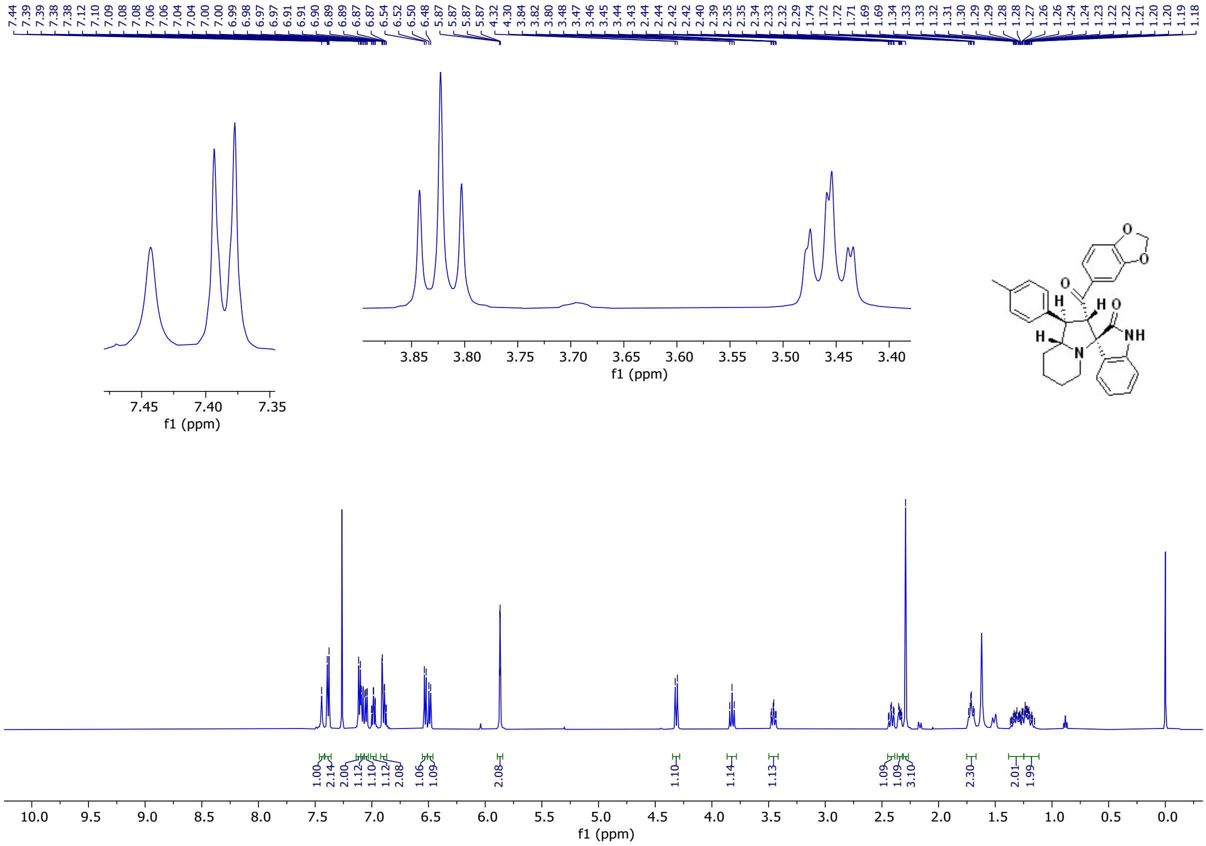


Figure S52: ^{1}H NMR of compound **5b** (500 MHz, $CDCl_3$)

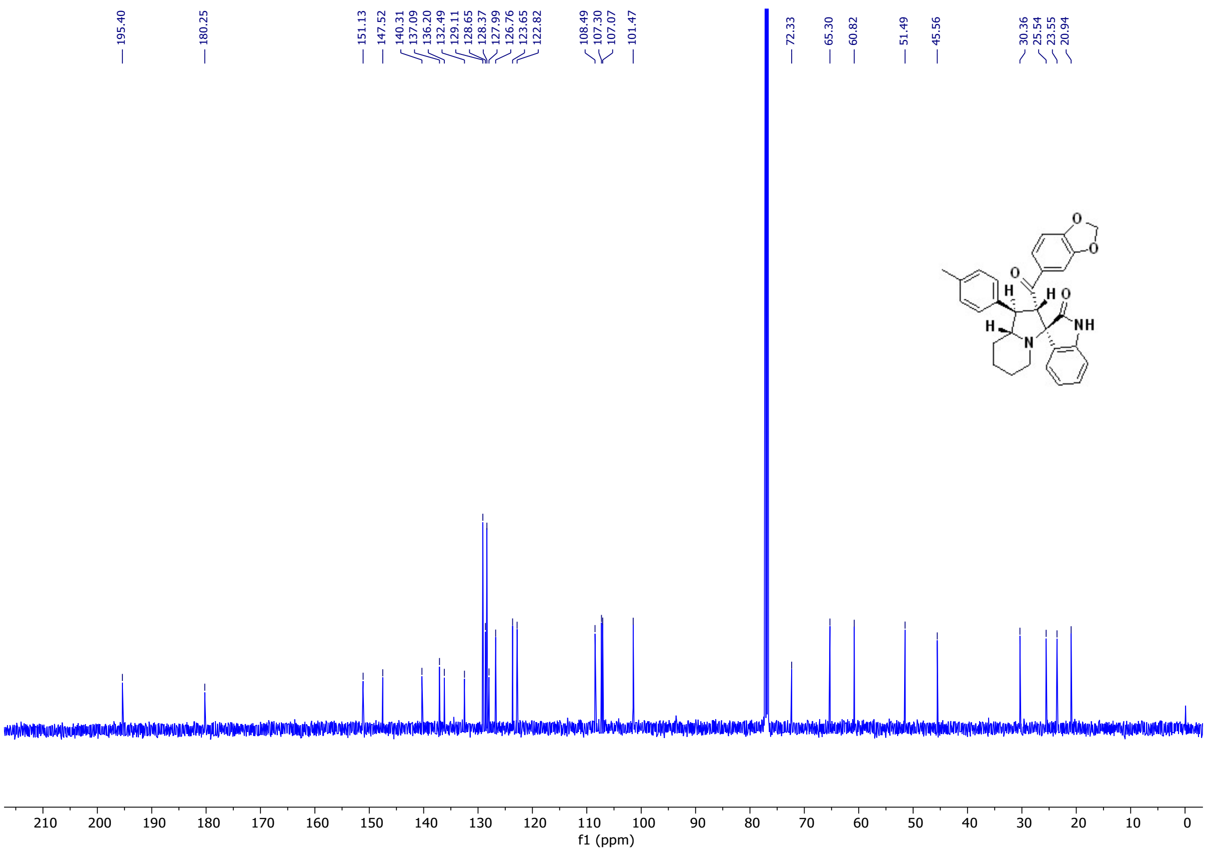


Figure S53: ^{13}C NMR of compound **5b** (126 MHz, $CDCl_3$)

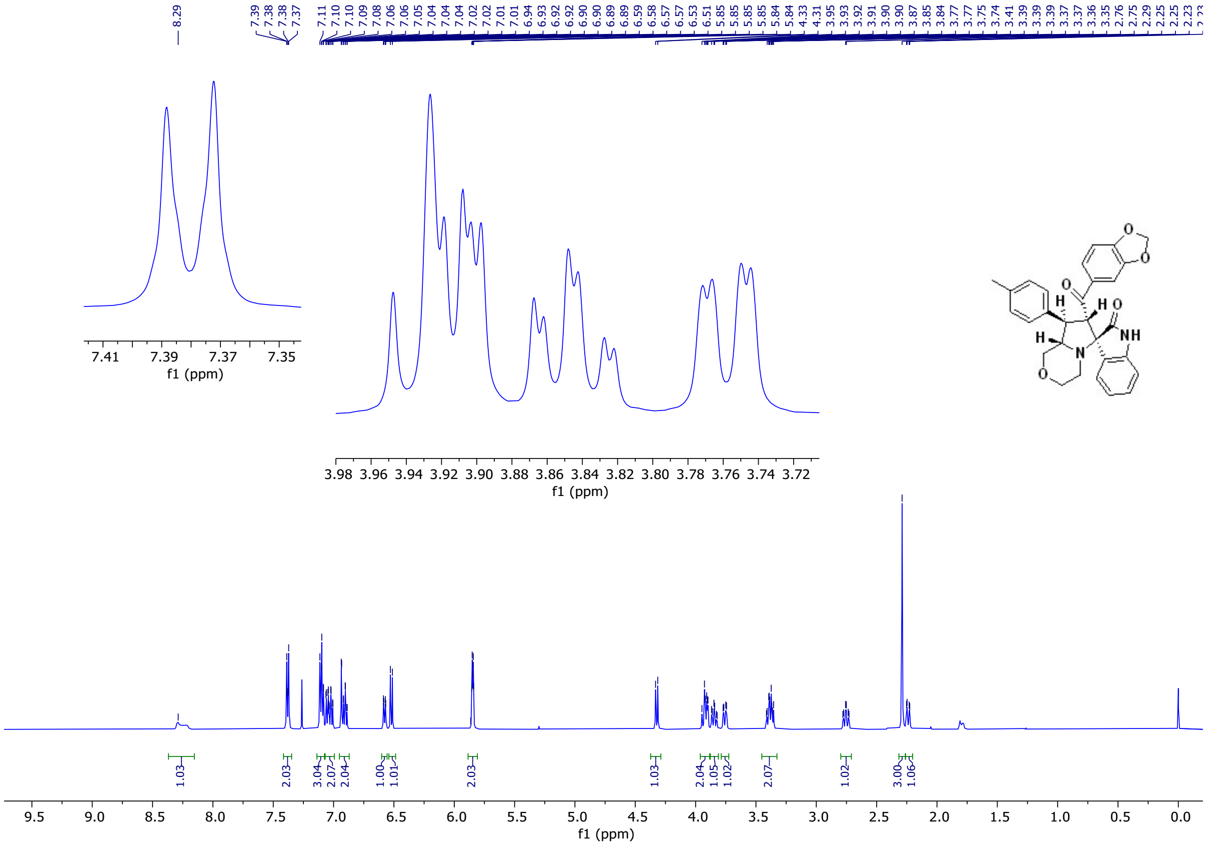


Figure S54: ^{1}H NMR of compound **5c** (500 MHz, $CDCl_3$

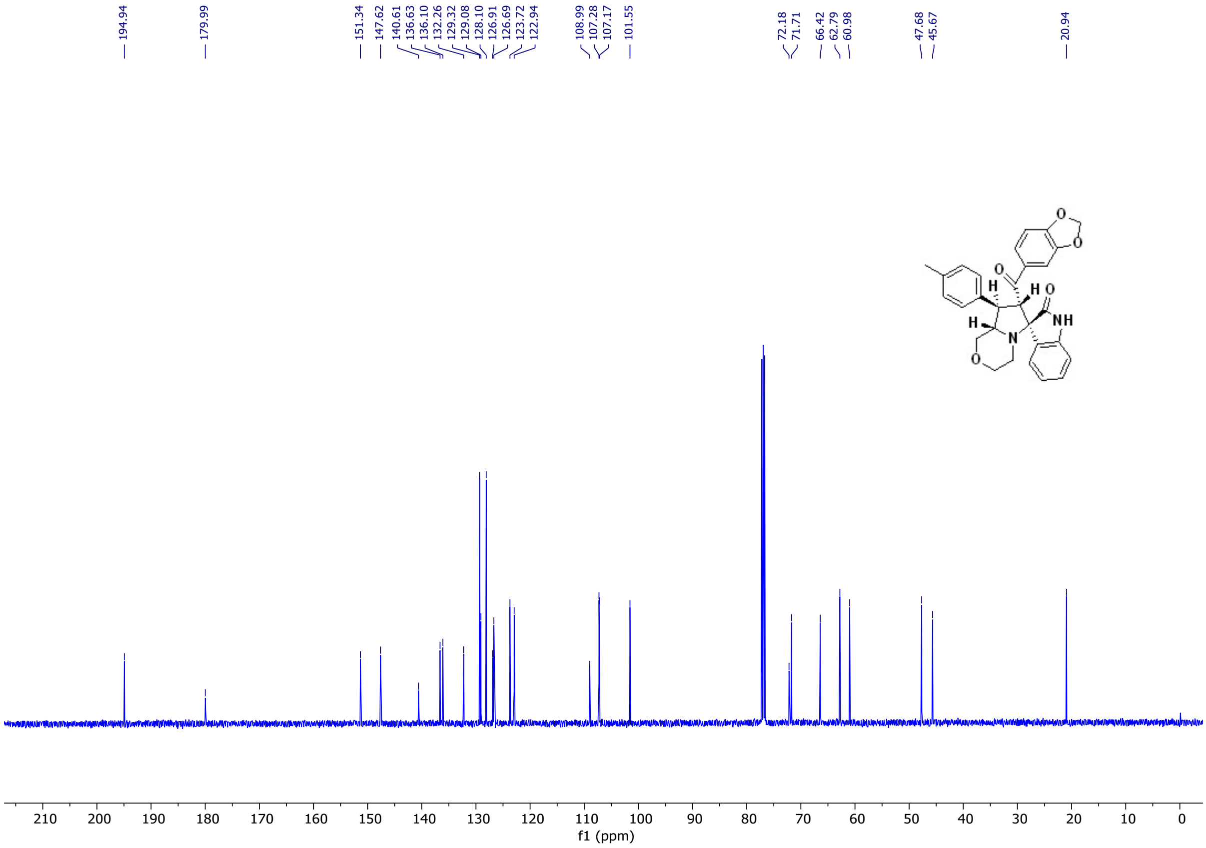


Figure S55: ^{13}C NMR of compound **5c** (126 MHz, $CDCl_3$)

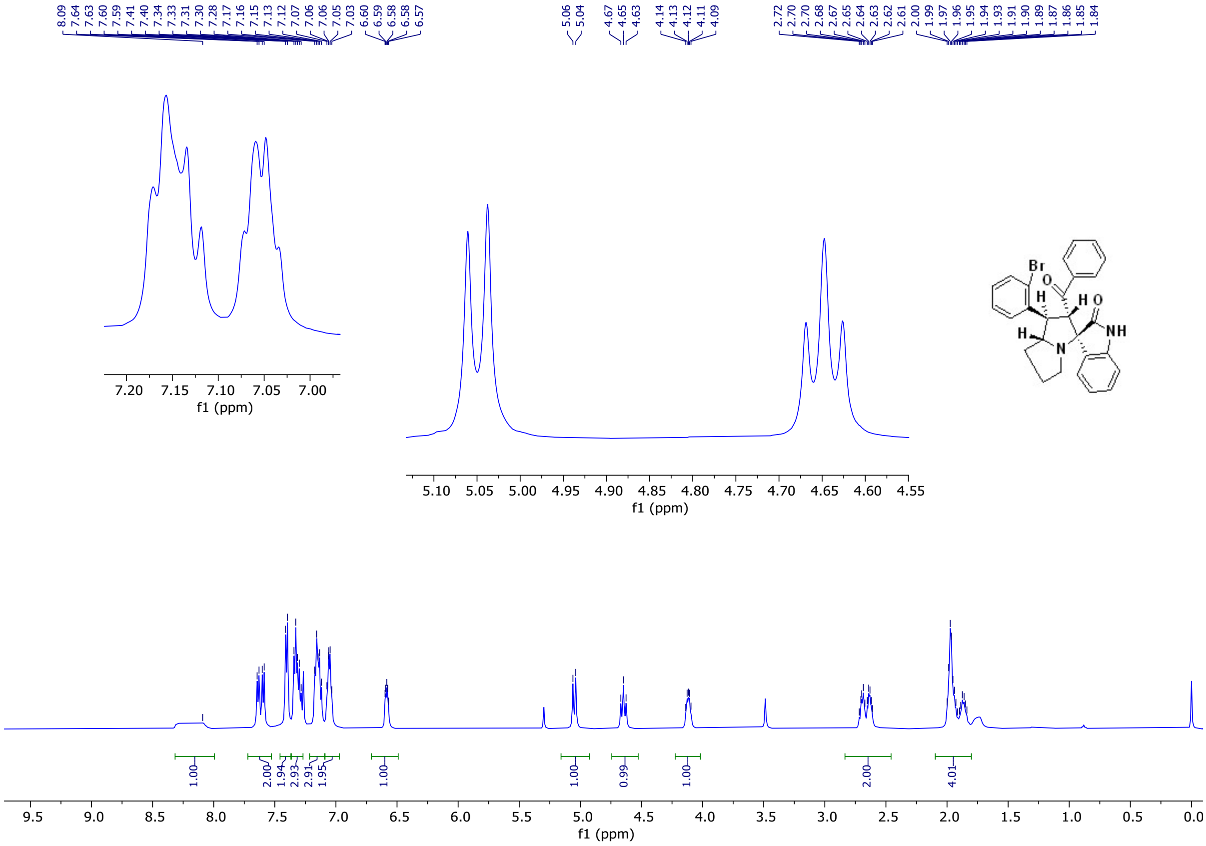


Figure S56: ^{1}H NMR of compound **5d** (500 MHz, $CDCl_3$)

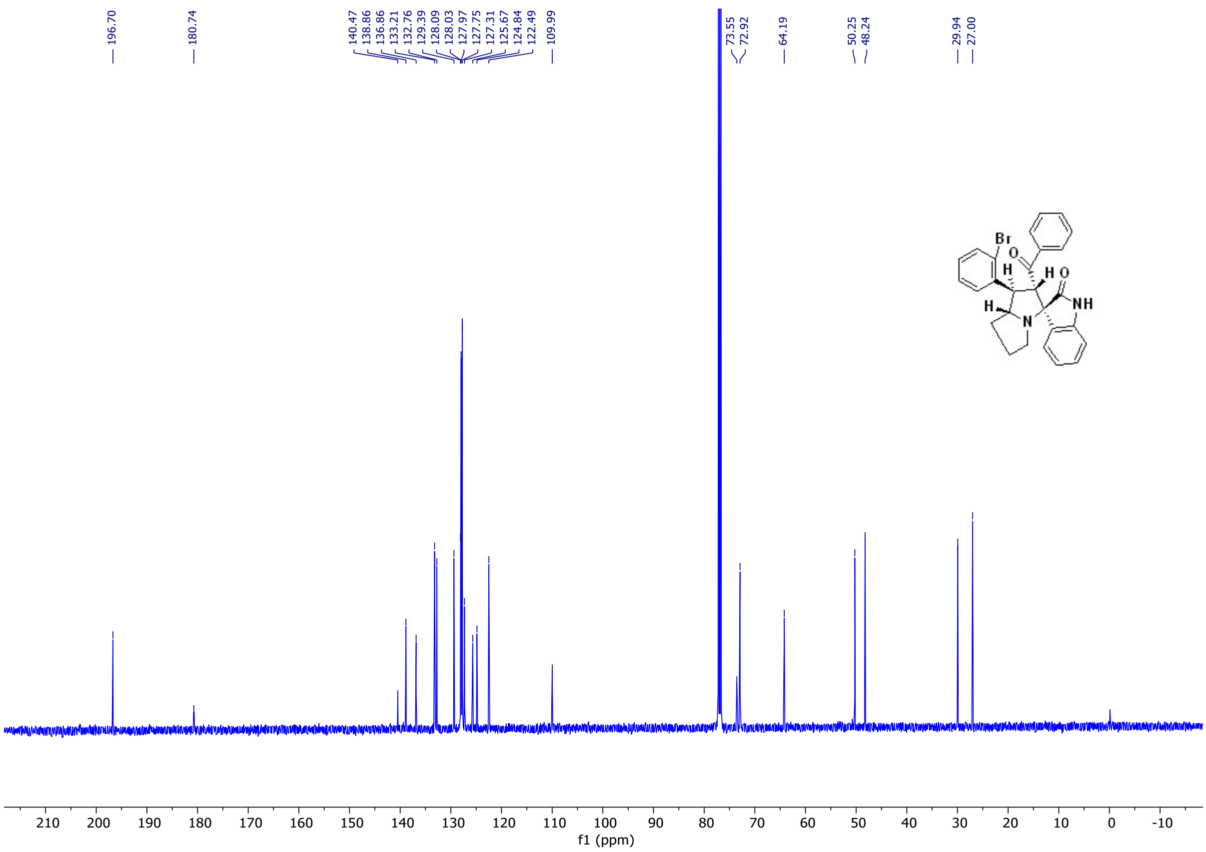


Figure S57: ^{13}C NMR of compound **5d** (126 MHz, $CDCl_3$)

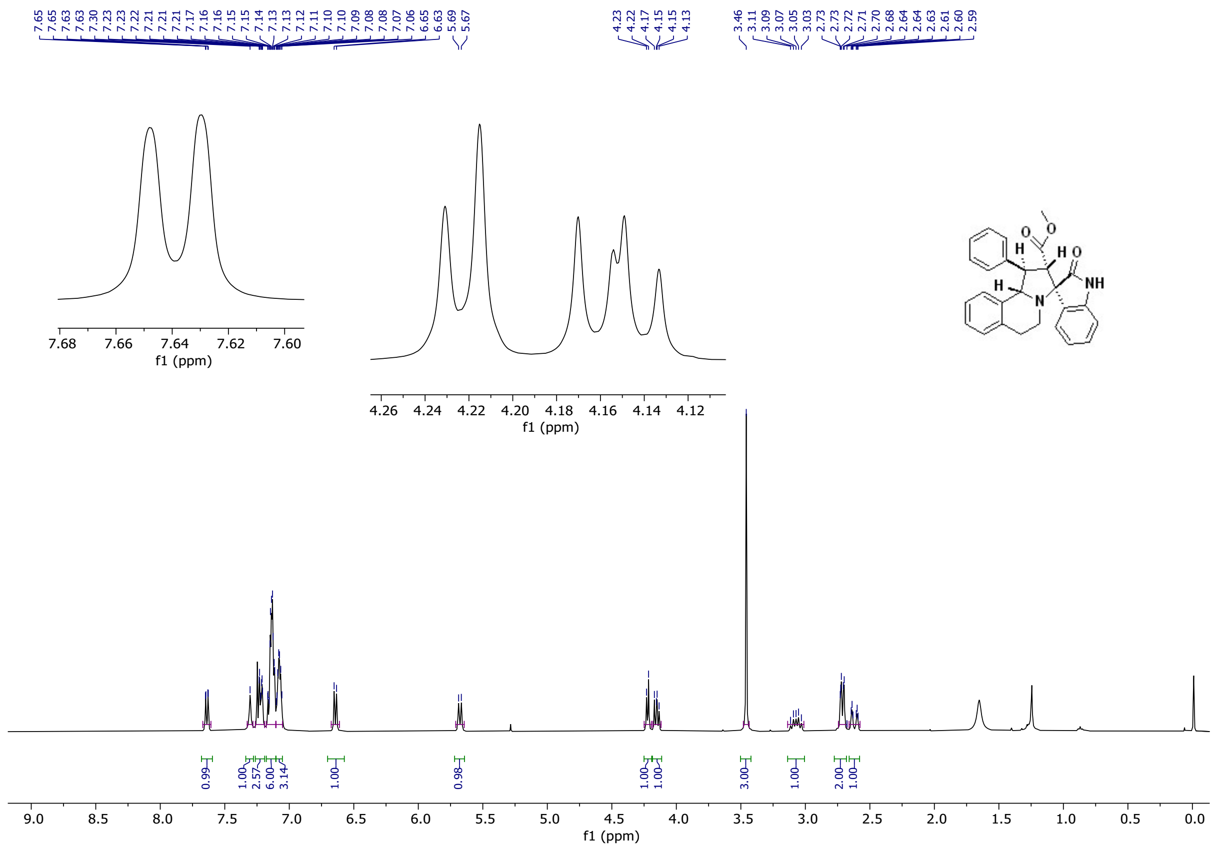


Figure S58: ^{1}H NMR of compound **5d** (500 MHz, $CDCl_3$)

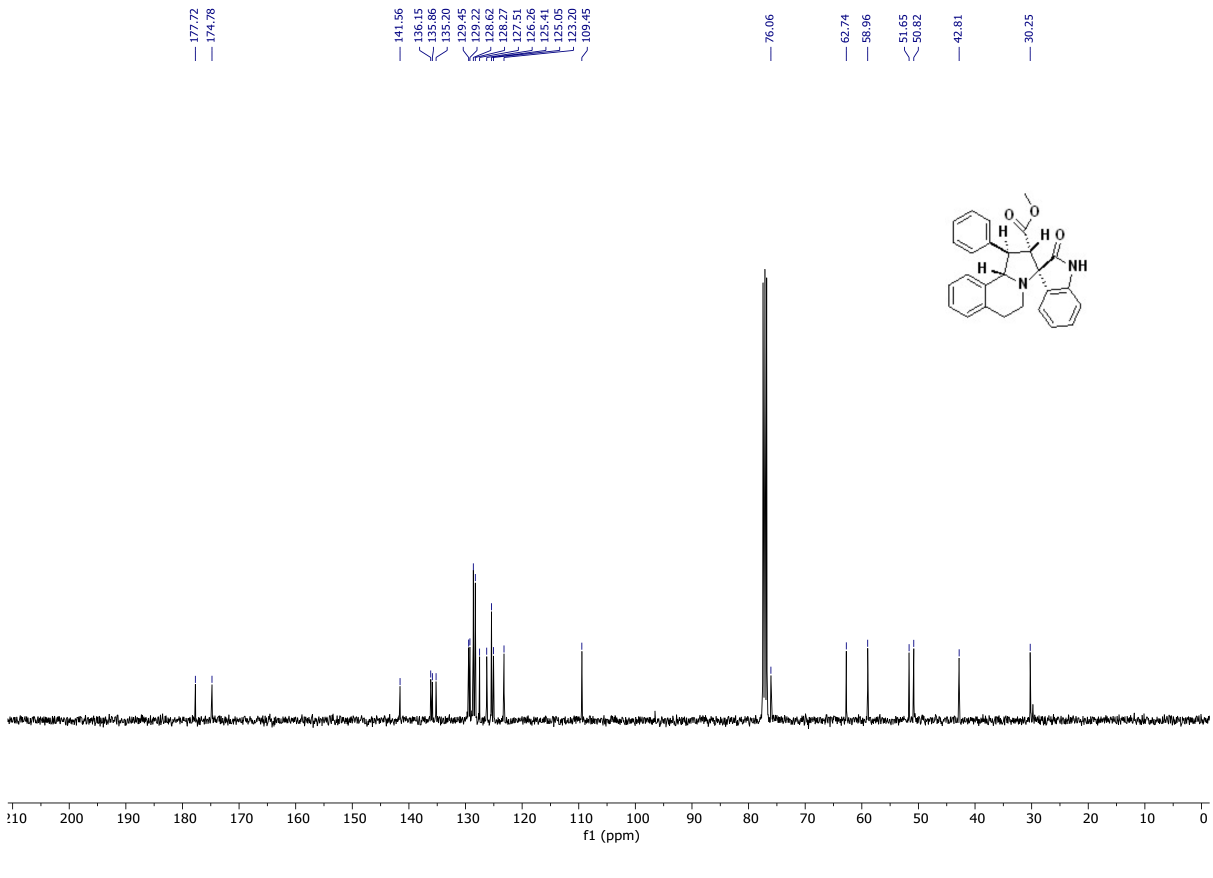


Figure S59: ^{13}C NMR of compound **5d** (126 MHz, $CDCl_3$)

5. Copies of HRMS Spectra

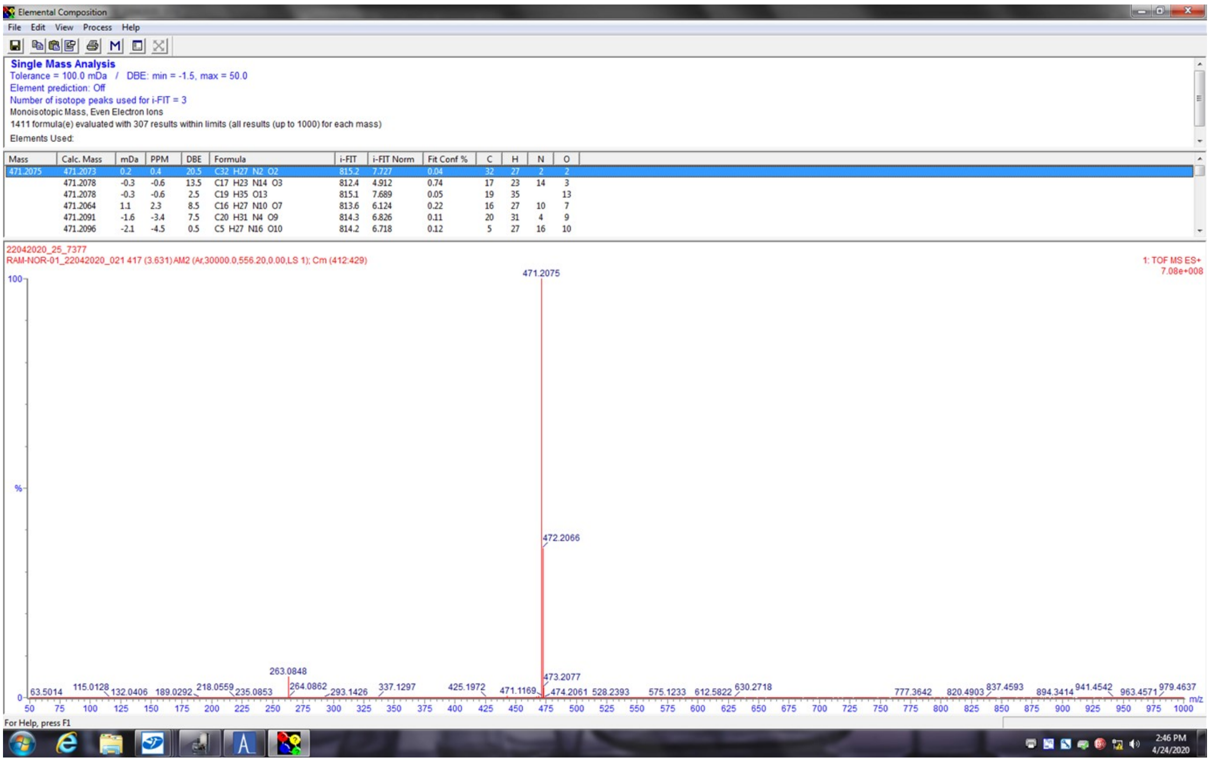


Figure S60: HRMS of Compound **4a**

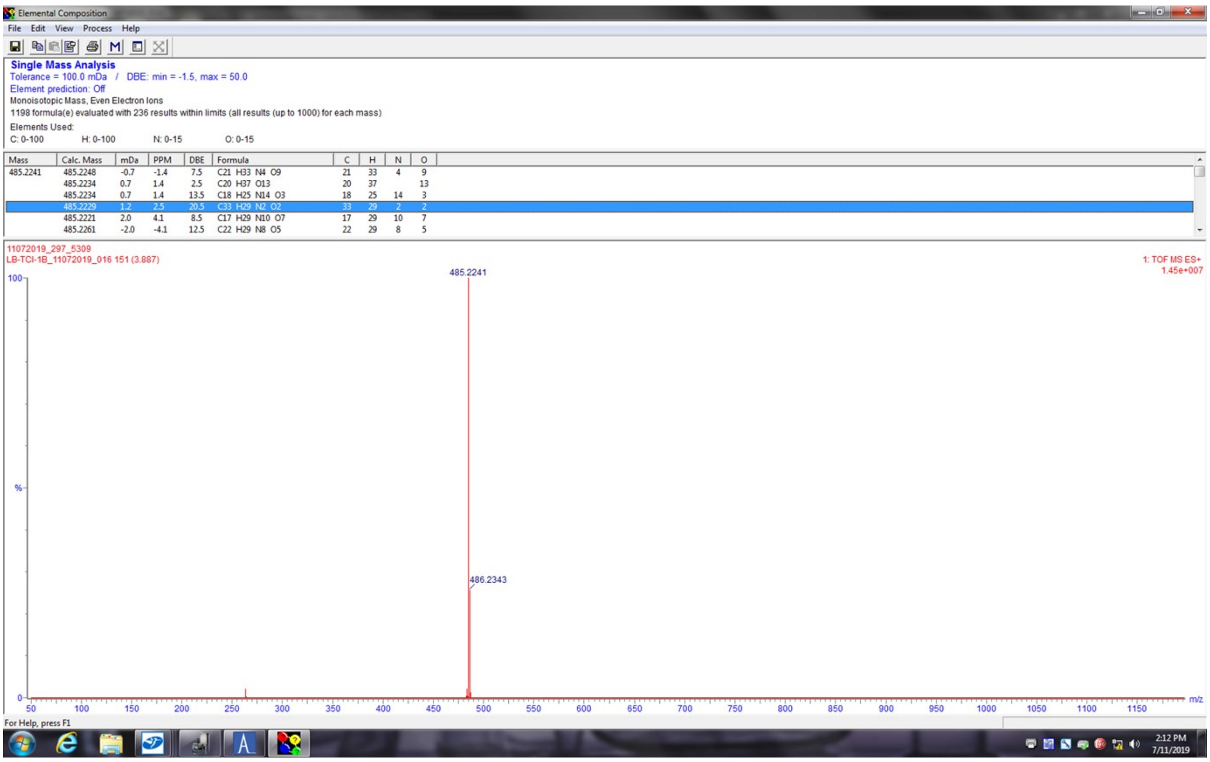


Figure S61: HRMS of Compound **4b**

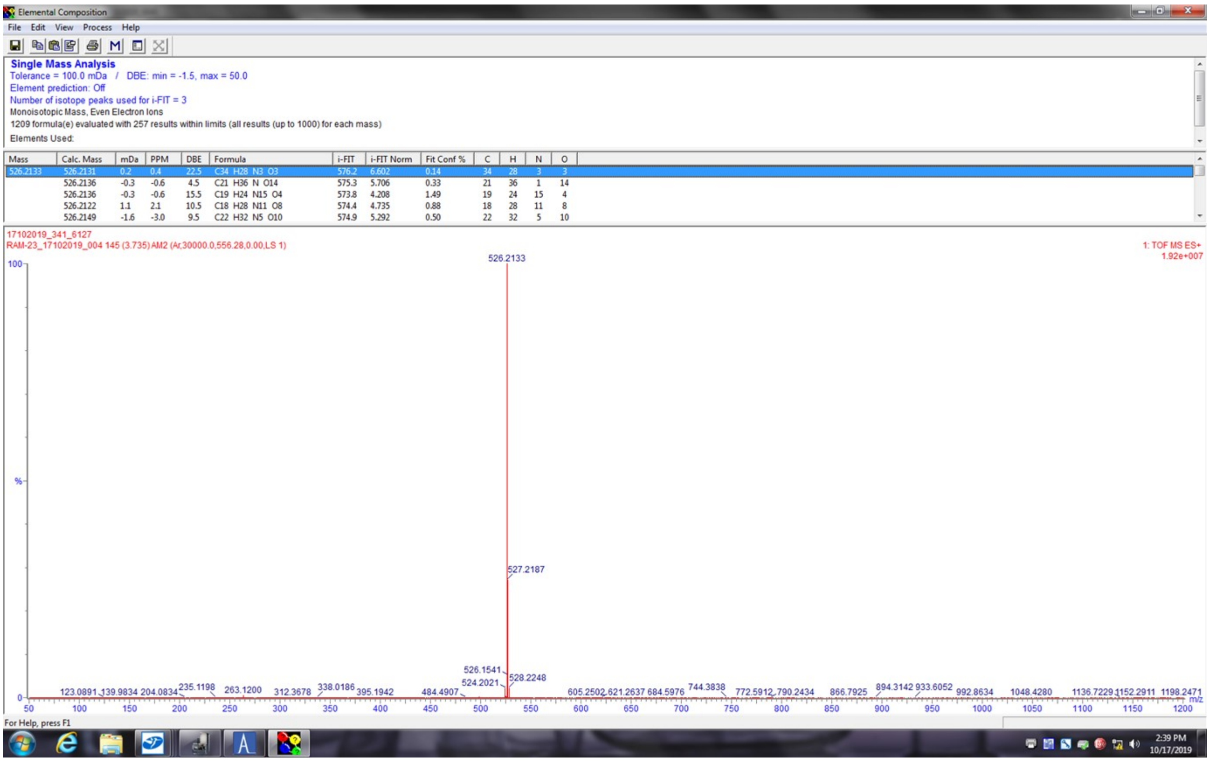


Figure S62: HRMS of Compound **4c**

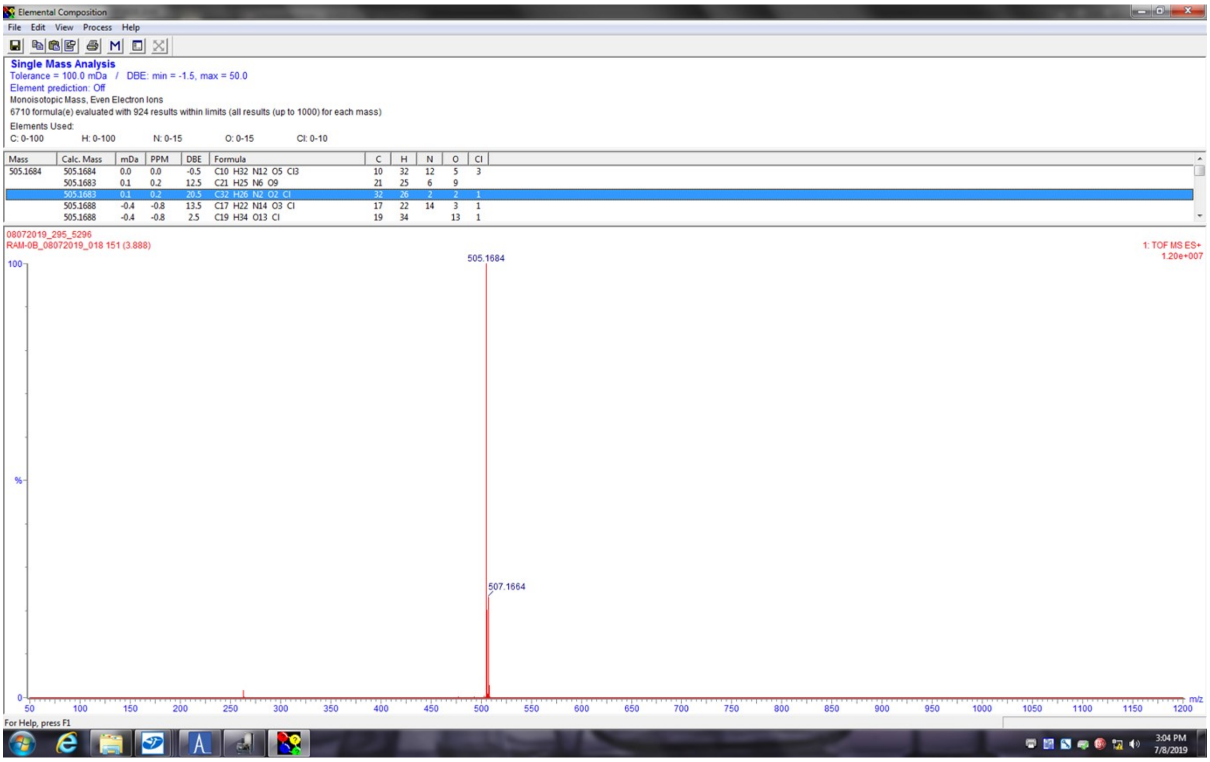


Figure S63: HRMS of Compound **4d**

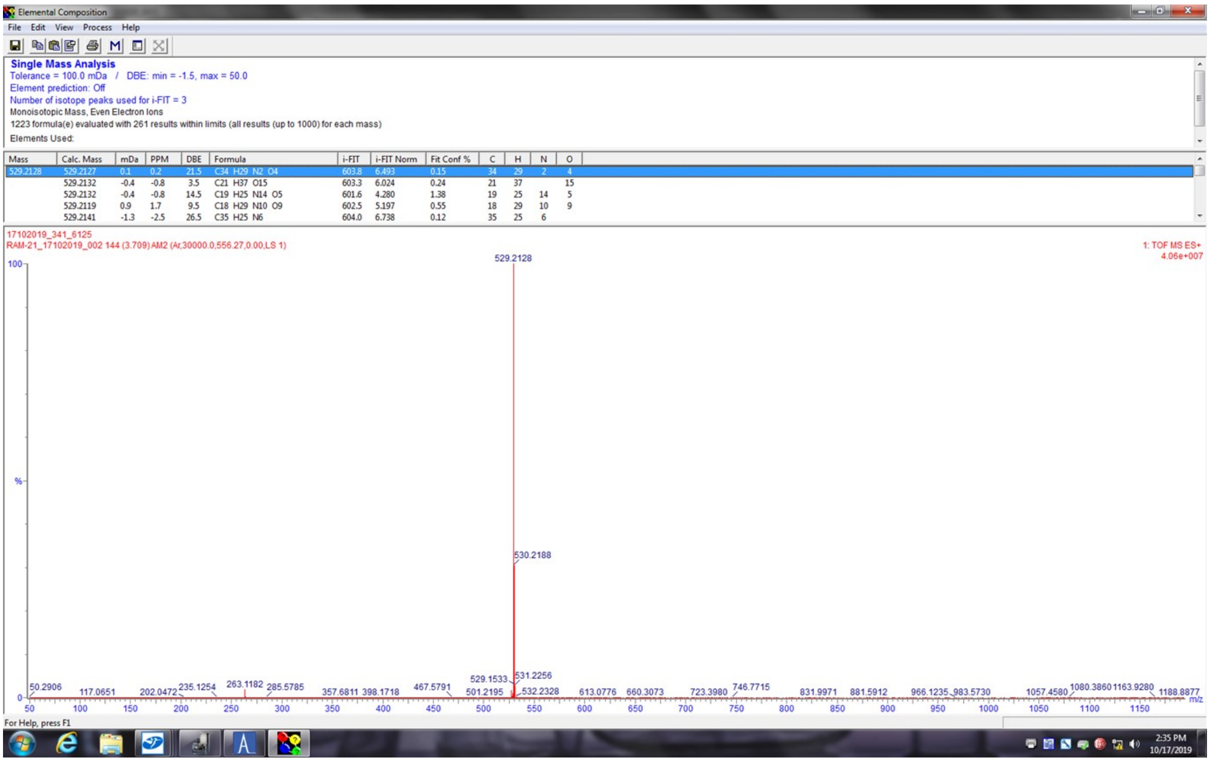


Figure S64: HRMS of Compound **4e**

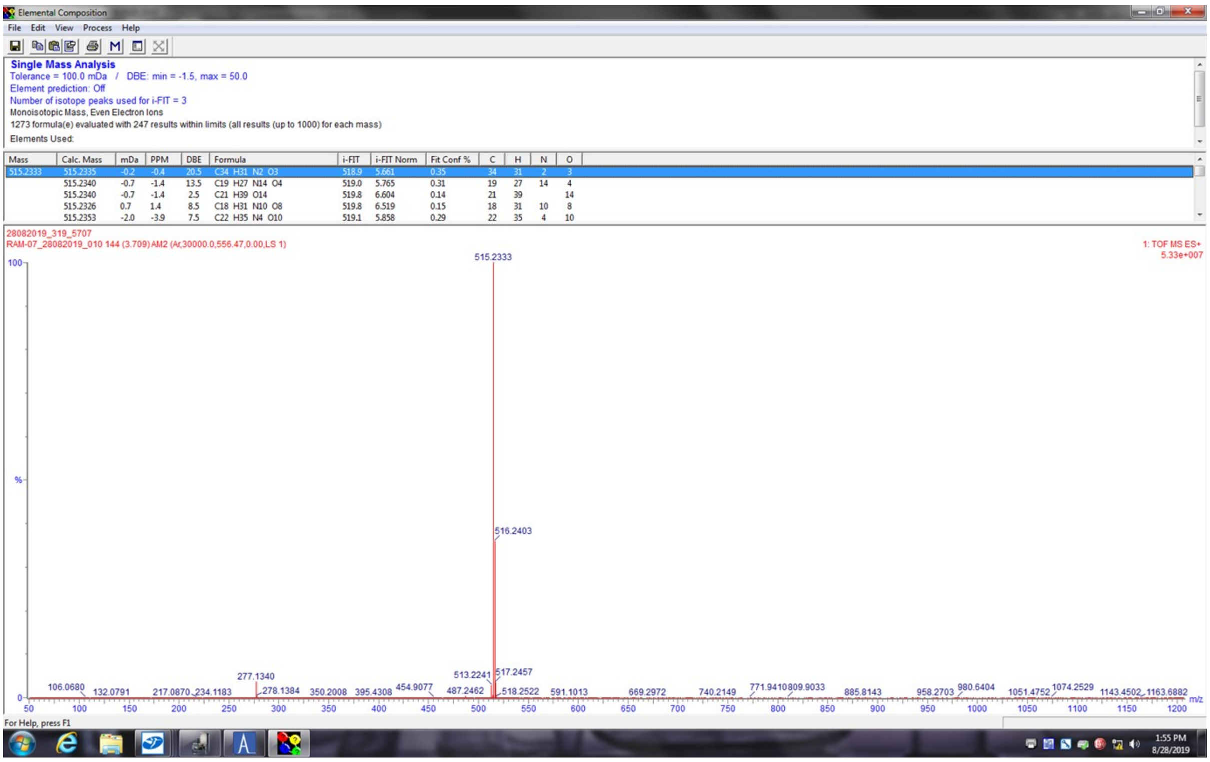


Figure S65: HRMS of Compound **4f**

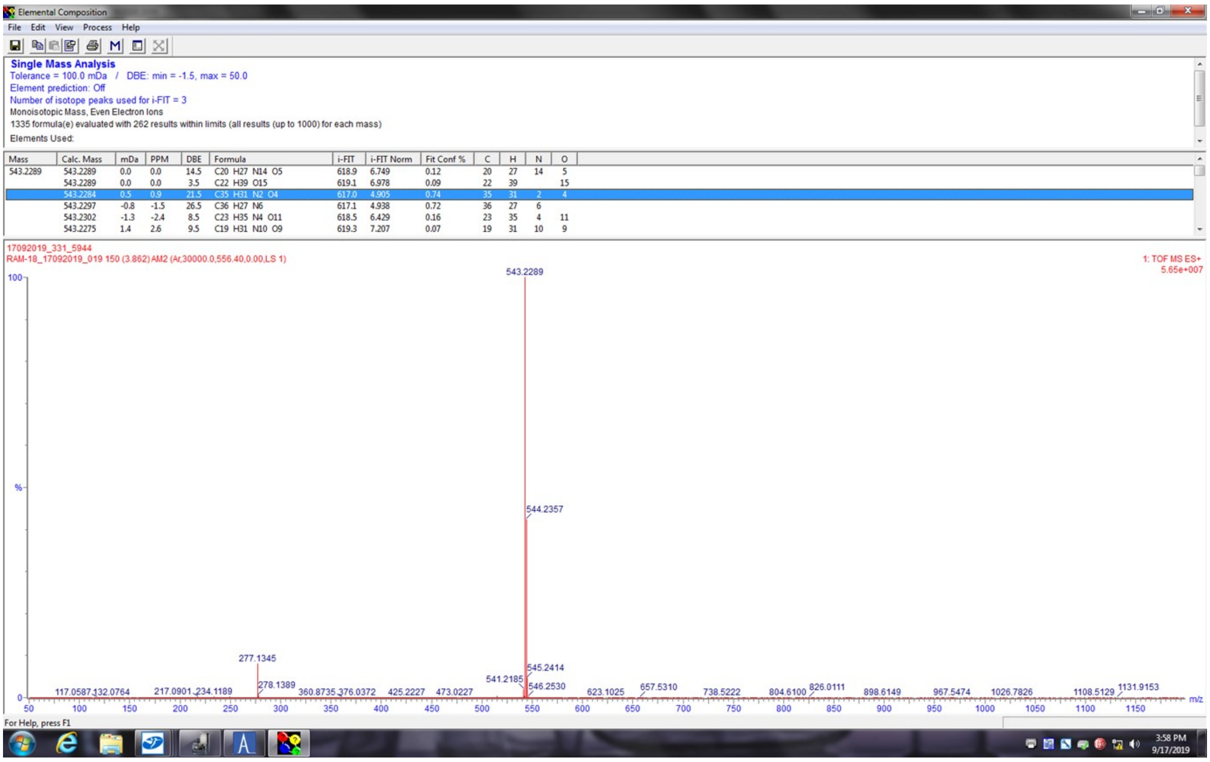


Figure S66: HRMS of Compound **4g**

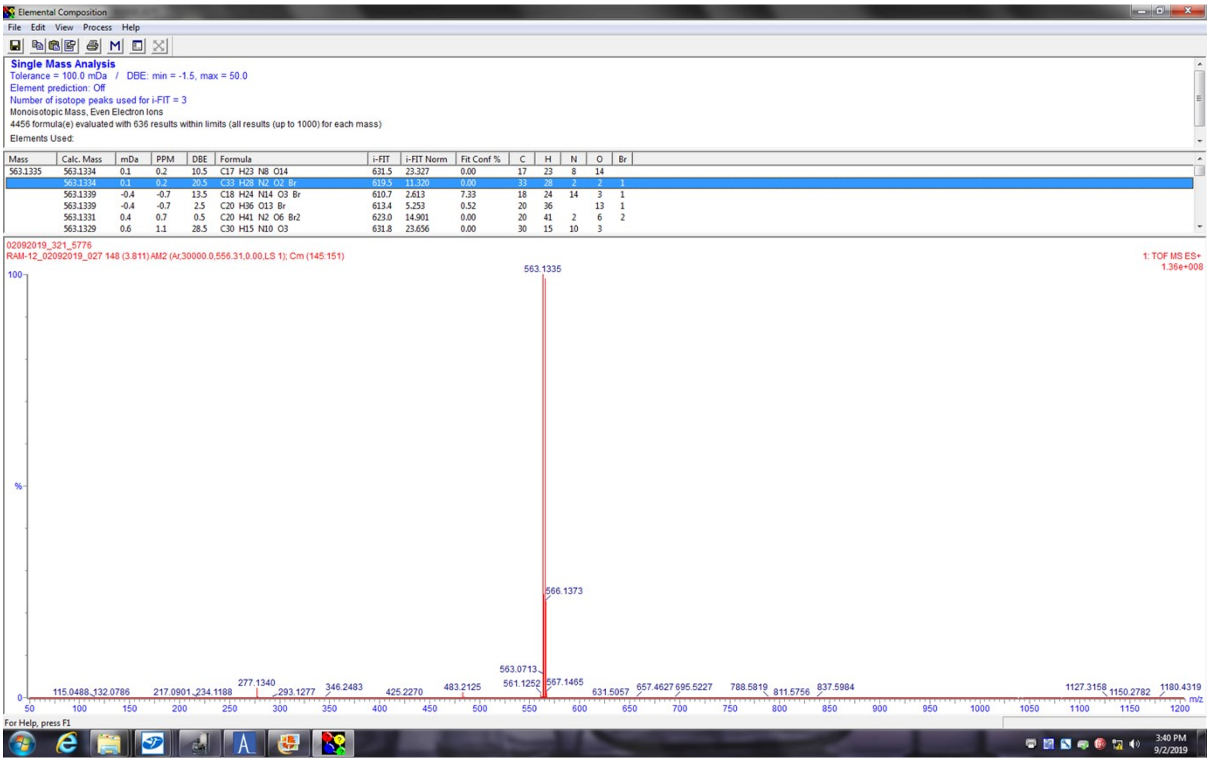


Figure S67: HRMS of Compound **4h**

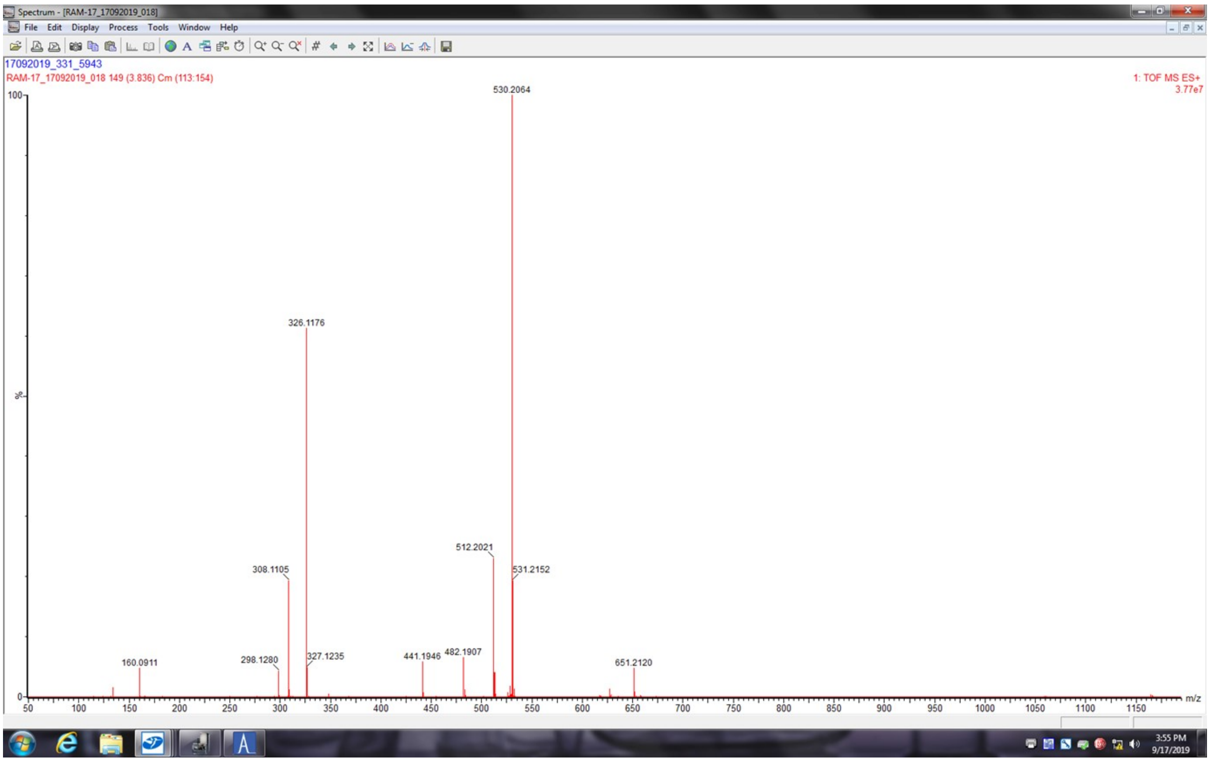


Figure S68: HRMS of Compound **4i**

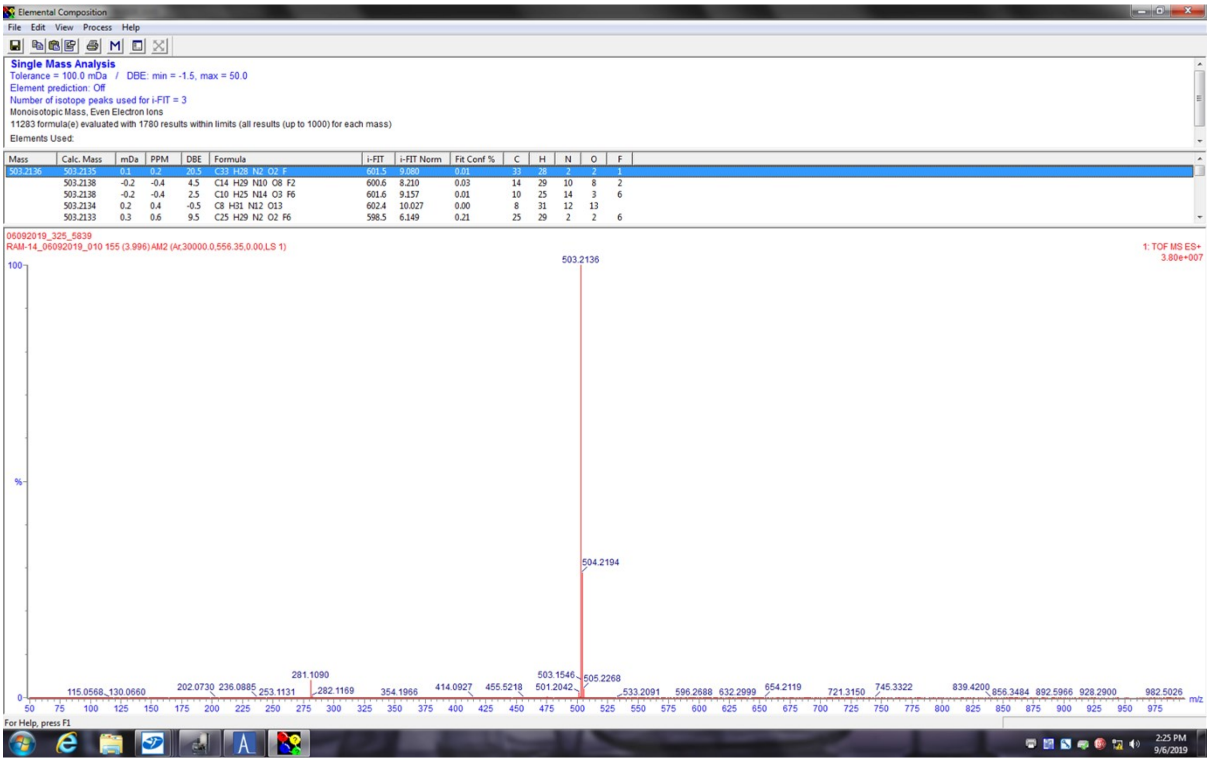


Figure S69: HRMS of Compound **4j**

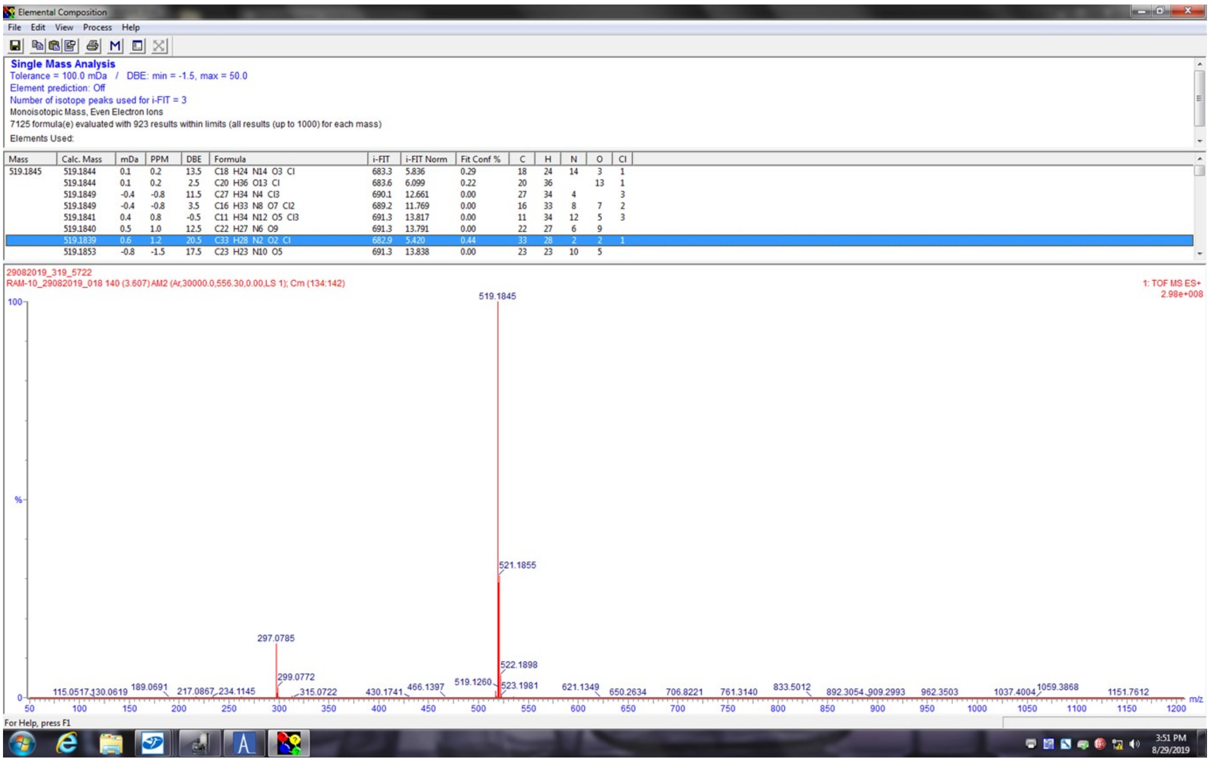


Figure S70: HRMS of Compound **4k**

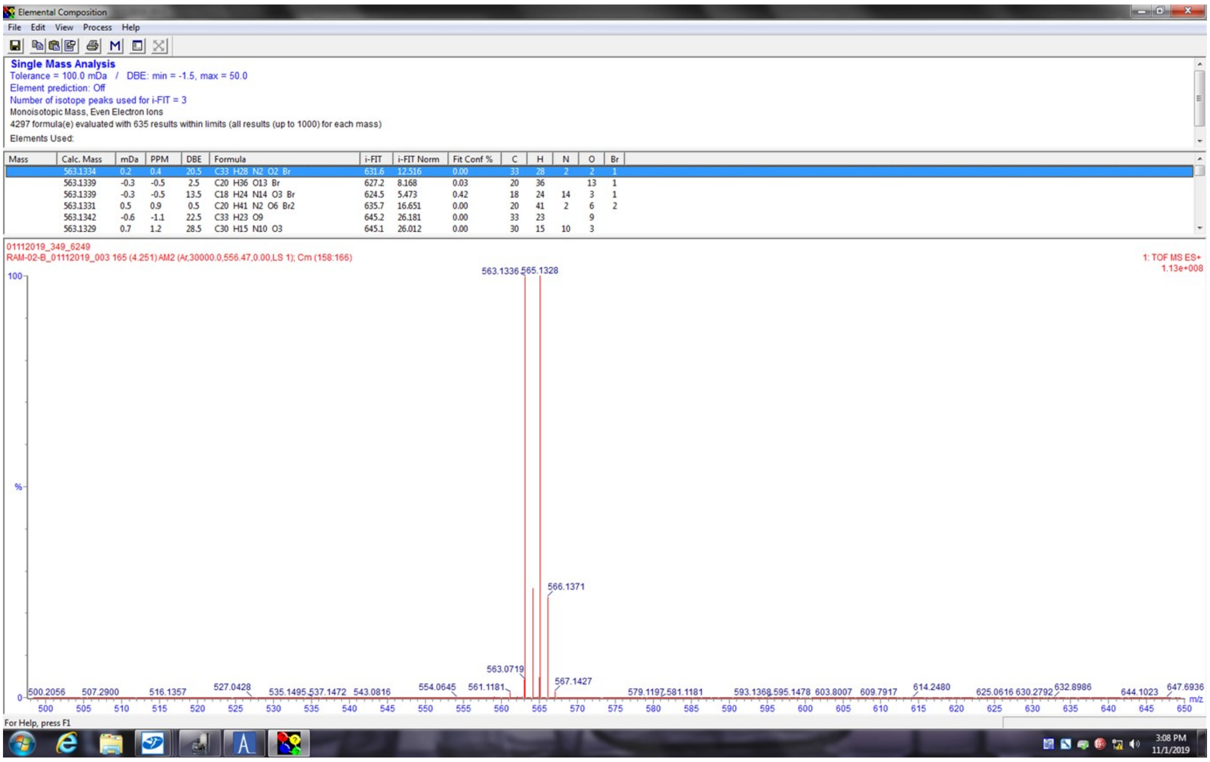


Figure S71: HRMS of Compound **4l**

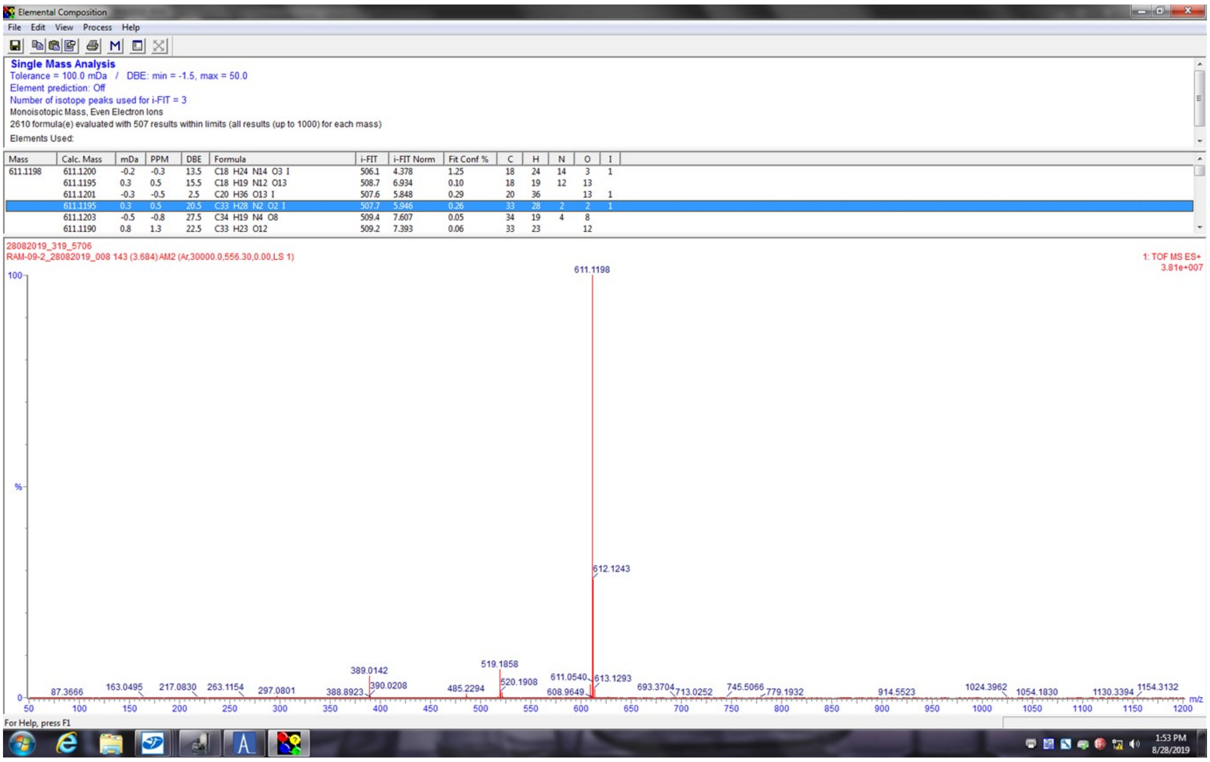


Figure S72: HRMS of Compound **4m**

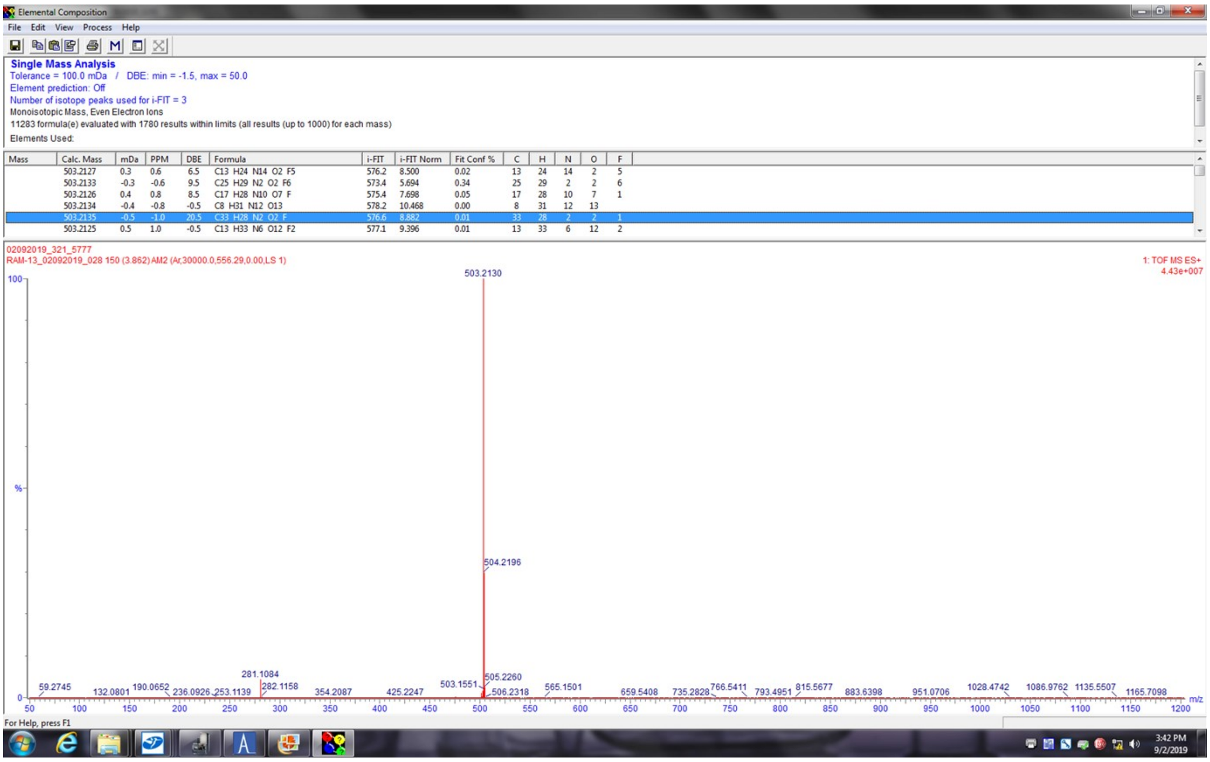


Figure S73: HRMS of Compound **4n**

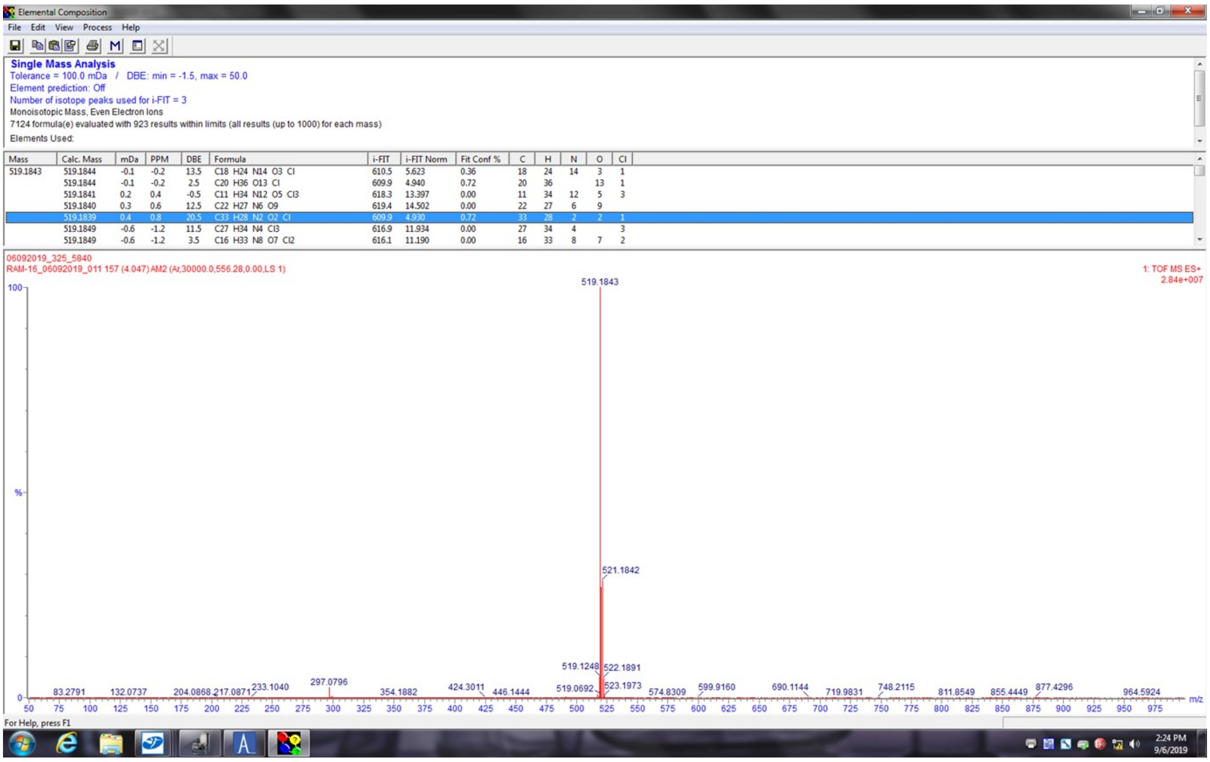


Figure S74: HRMS of Compound **4o**

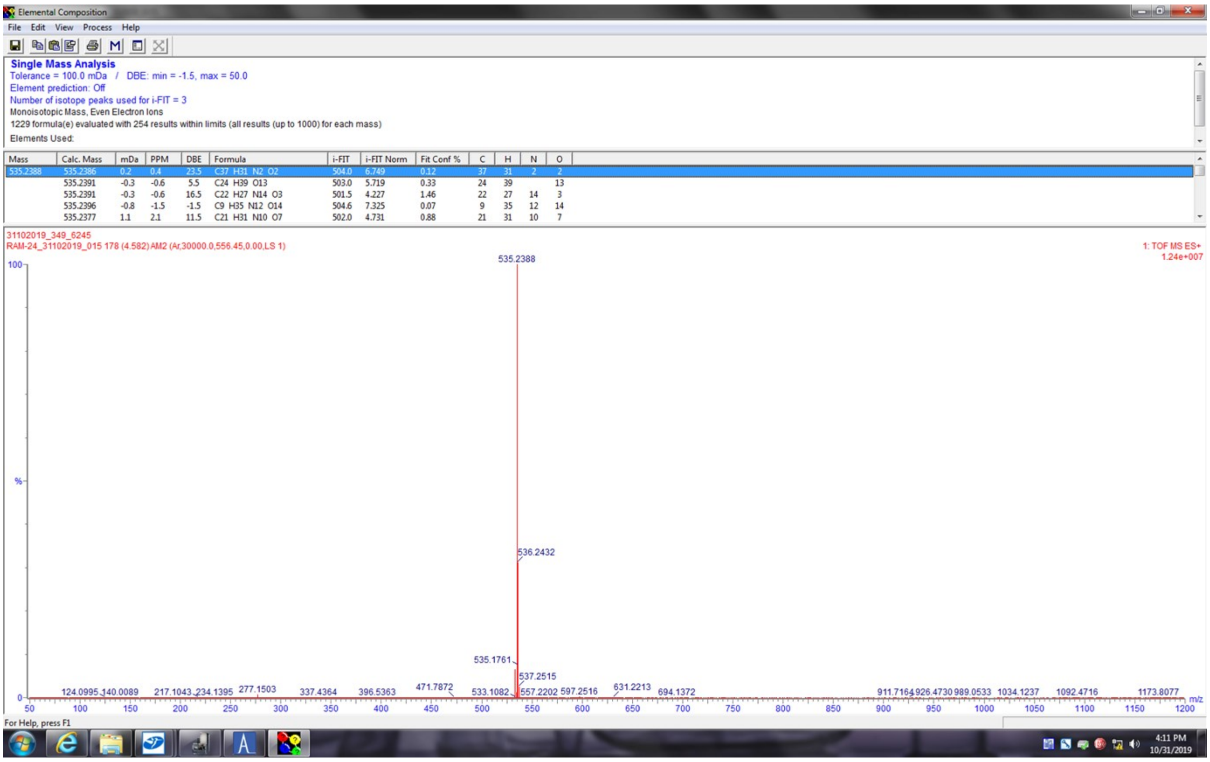


Figure S75: HRMS of Compound **4p**

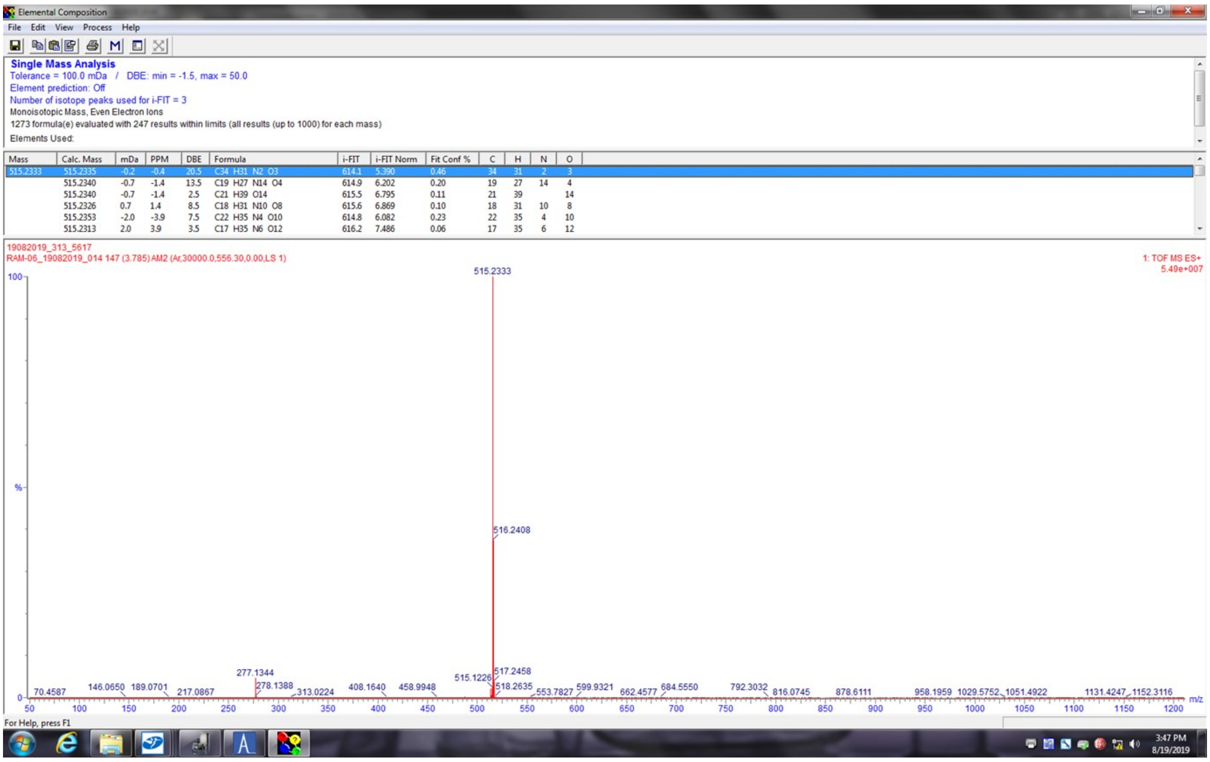


Figure S76: HRMS of Compound **4q**

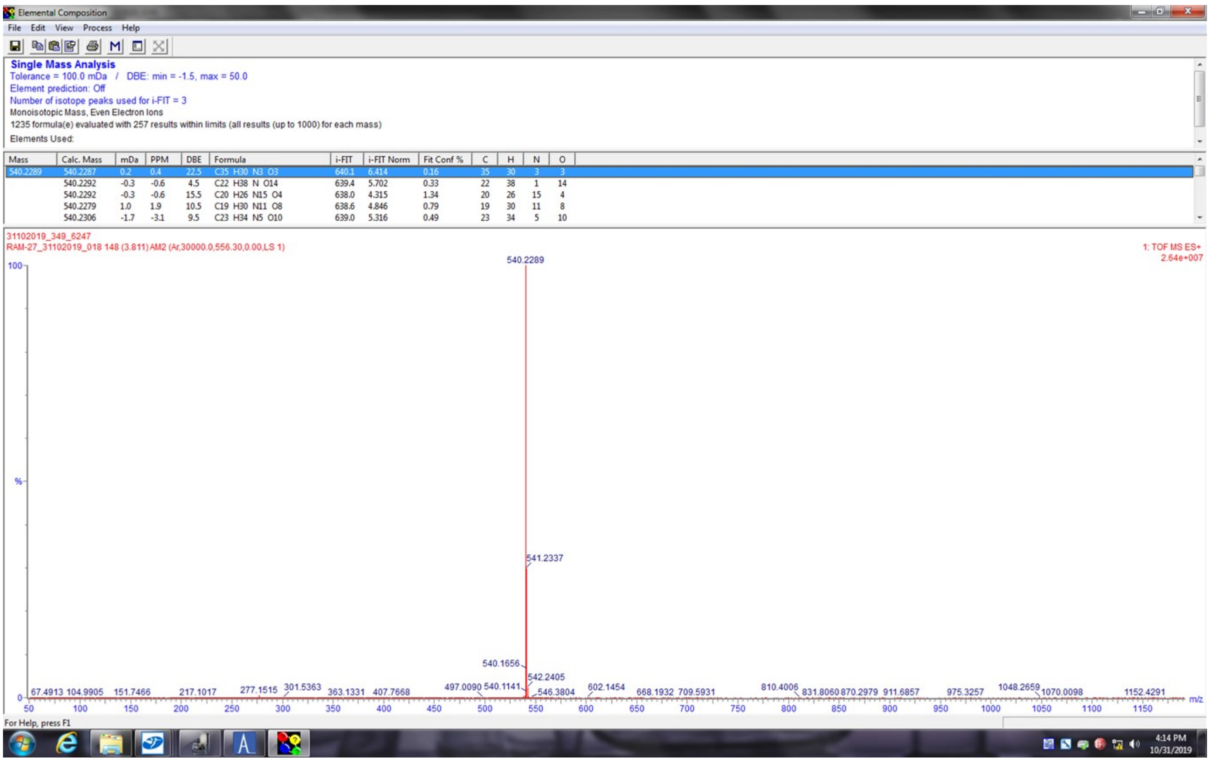


Figure S77: HRMS of Compound **4r**

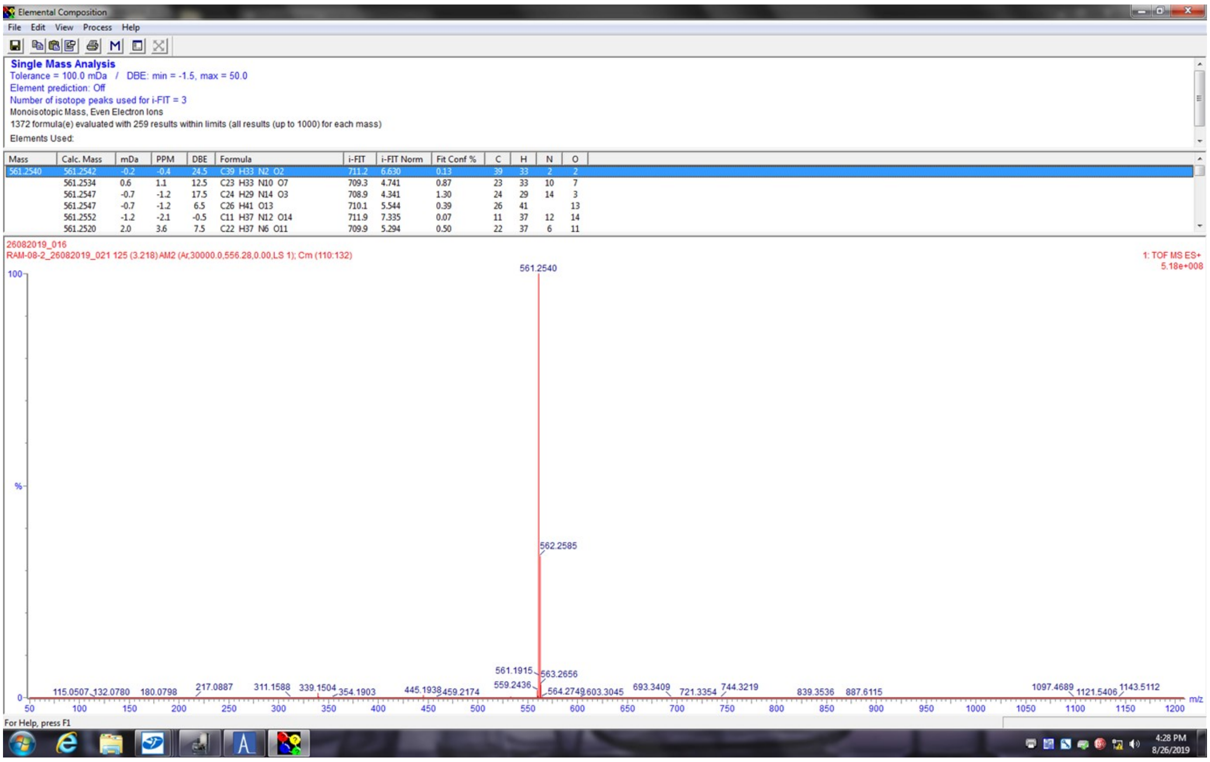


Figure S78: HRMS of Compound **4s**

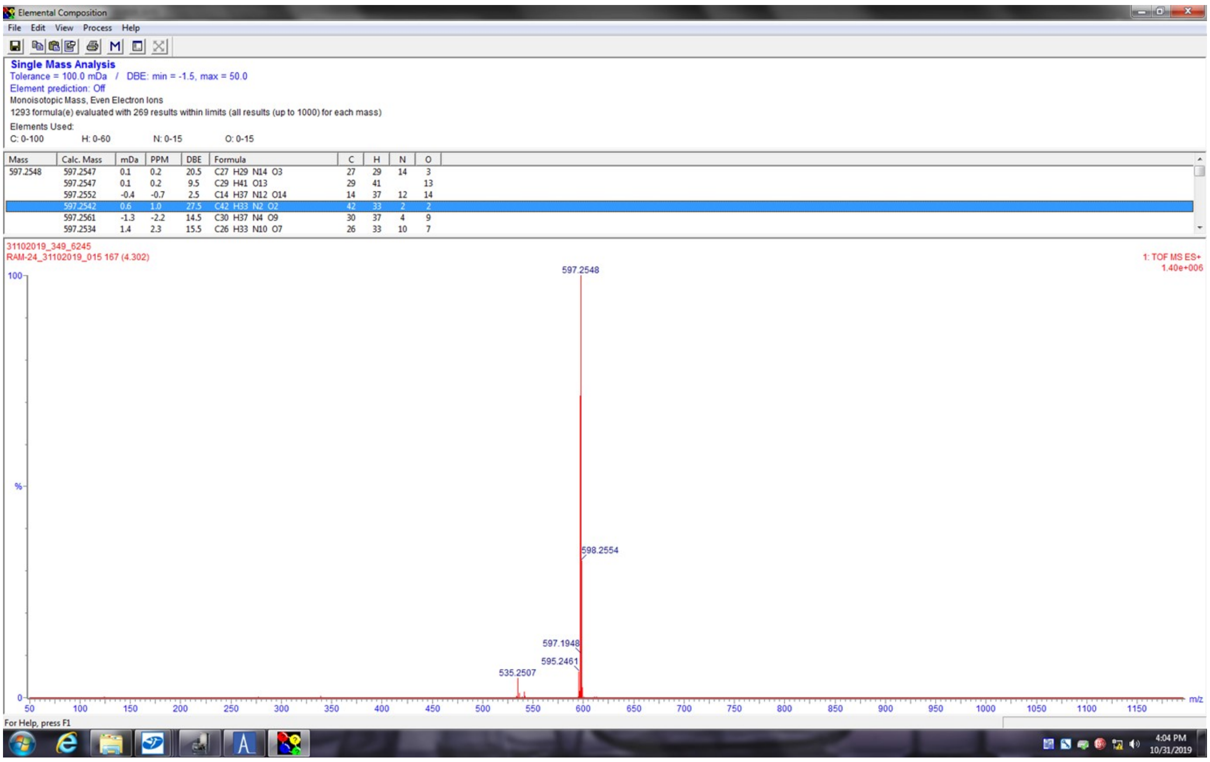


Figure S79: HRMS of Compound **4t**

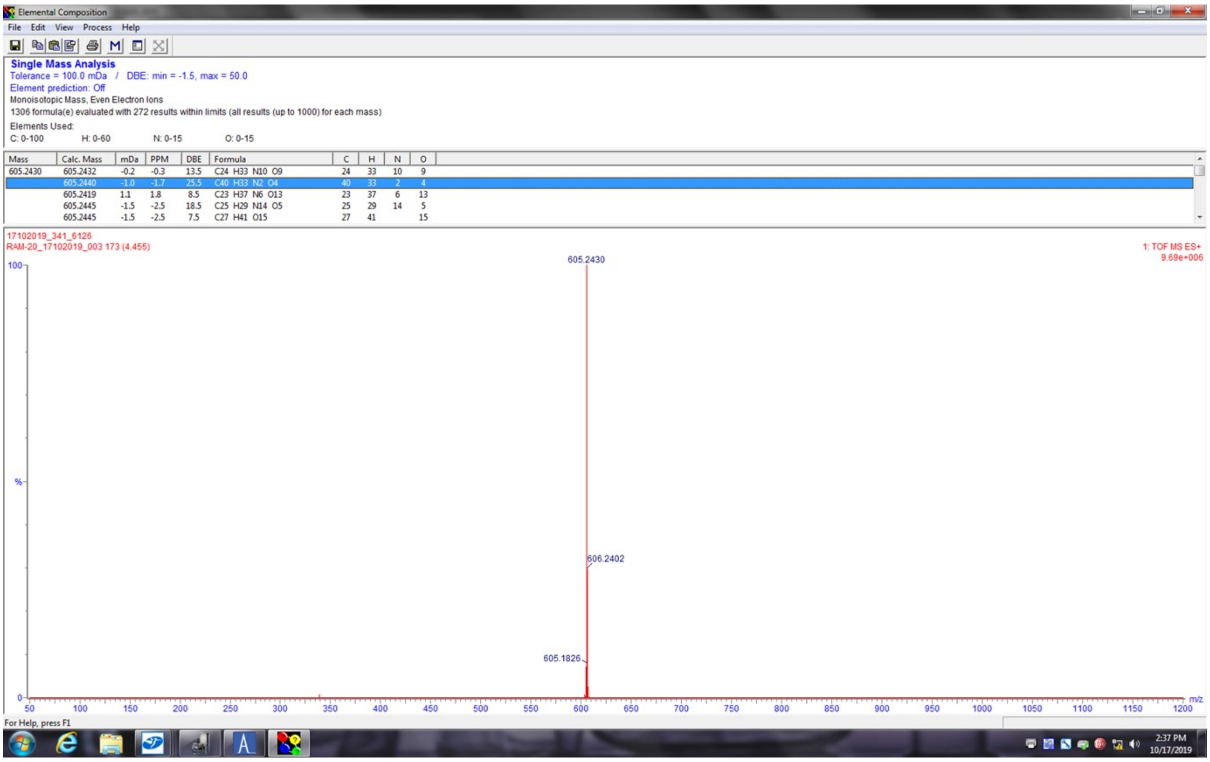


Figure S80: HRMS of Compound **4u**

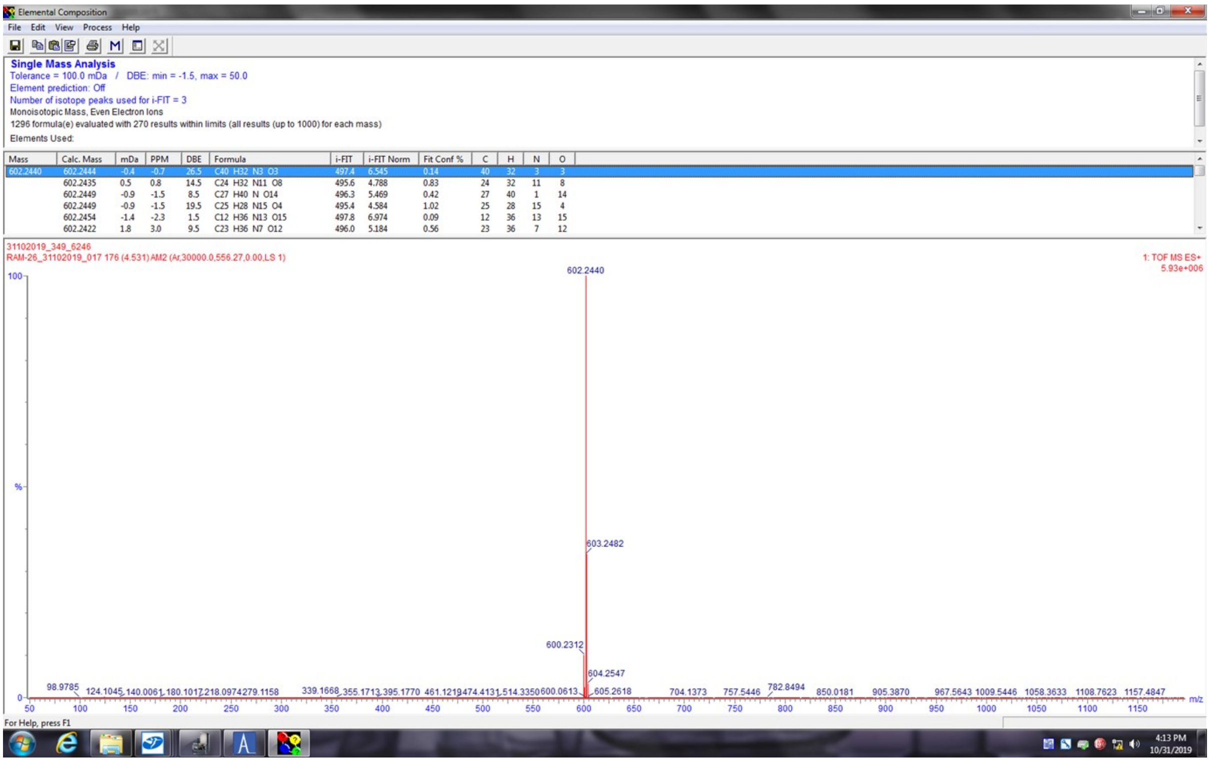


Figure S81: HRMS of Compound **4v**

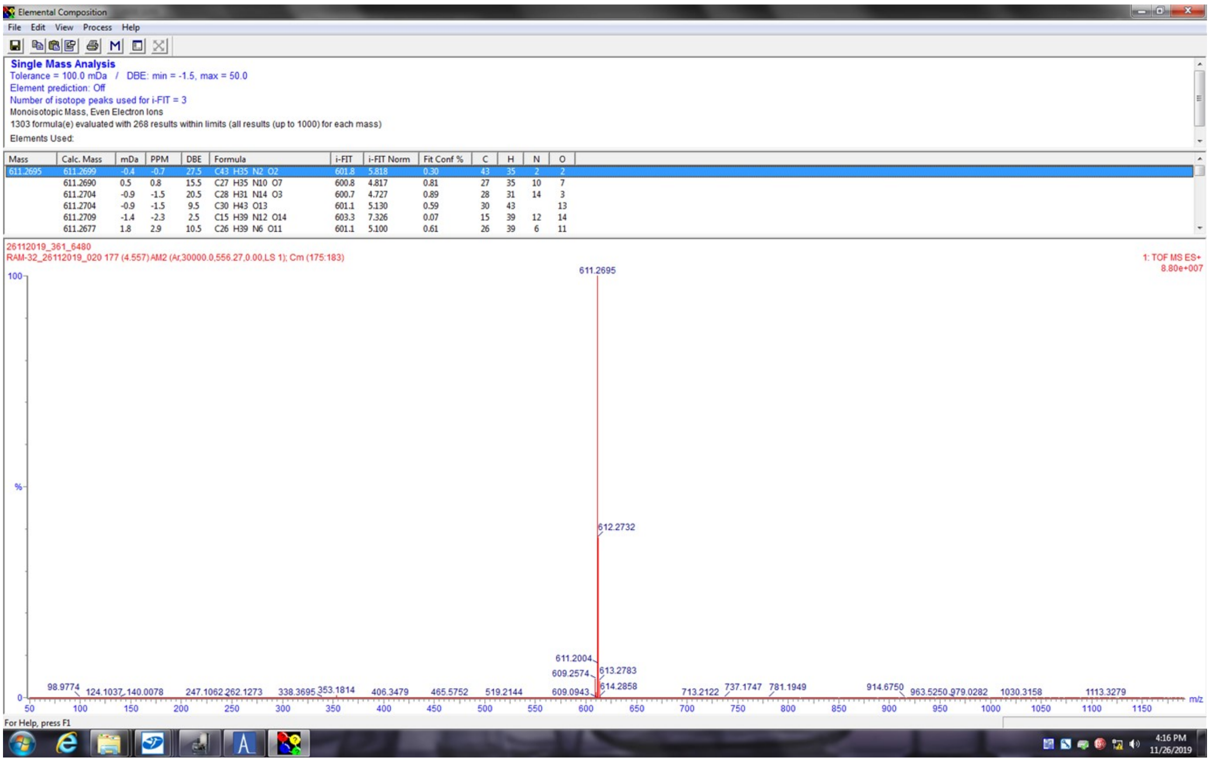


Figure S82: HRMS of Compound **4w**

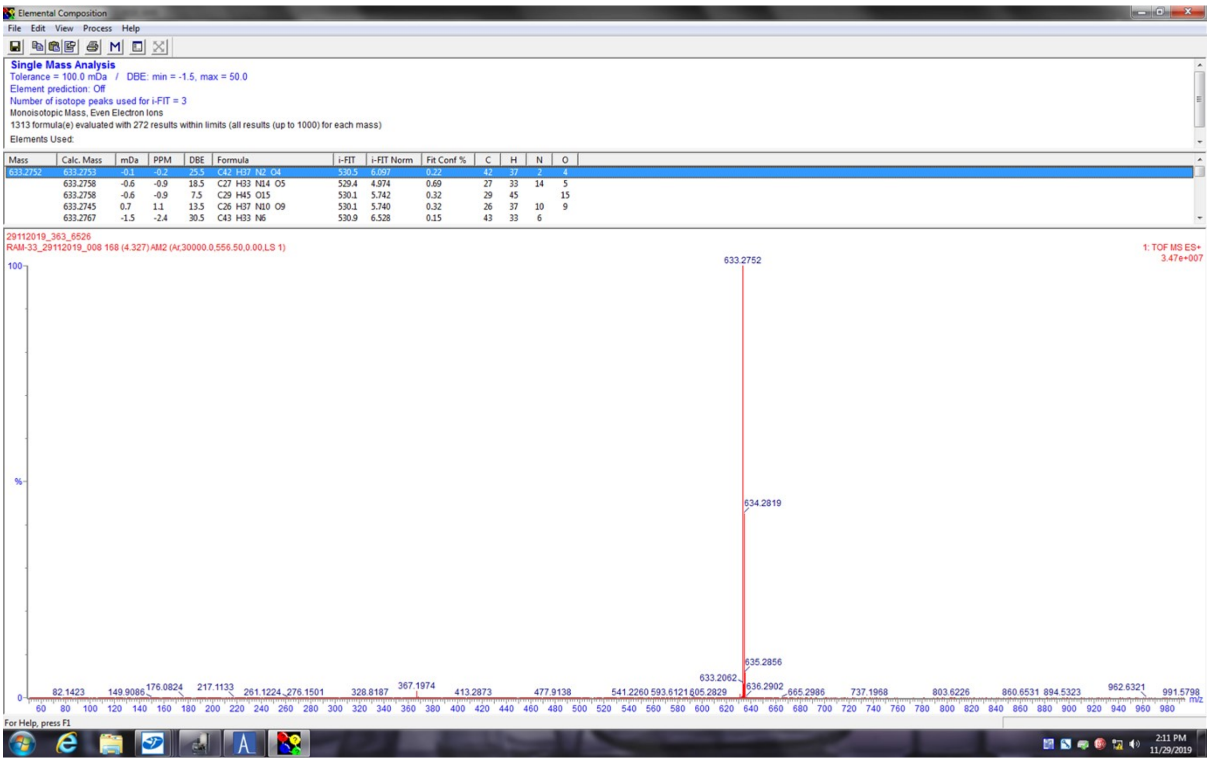


Figure S83: HRMS of Compound **4x**

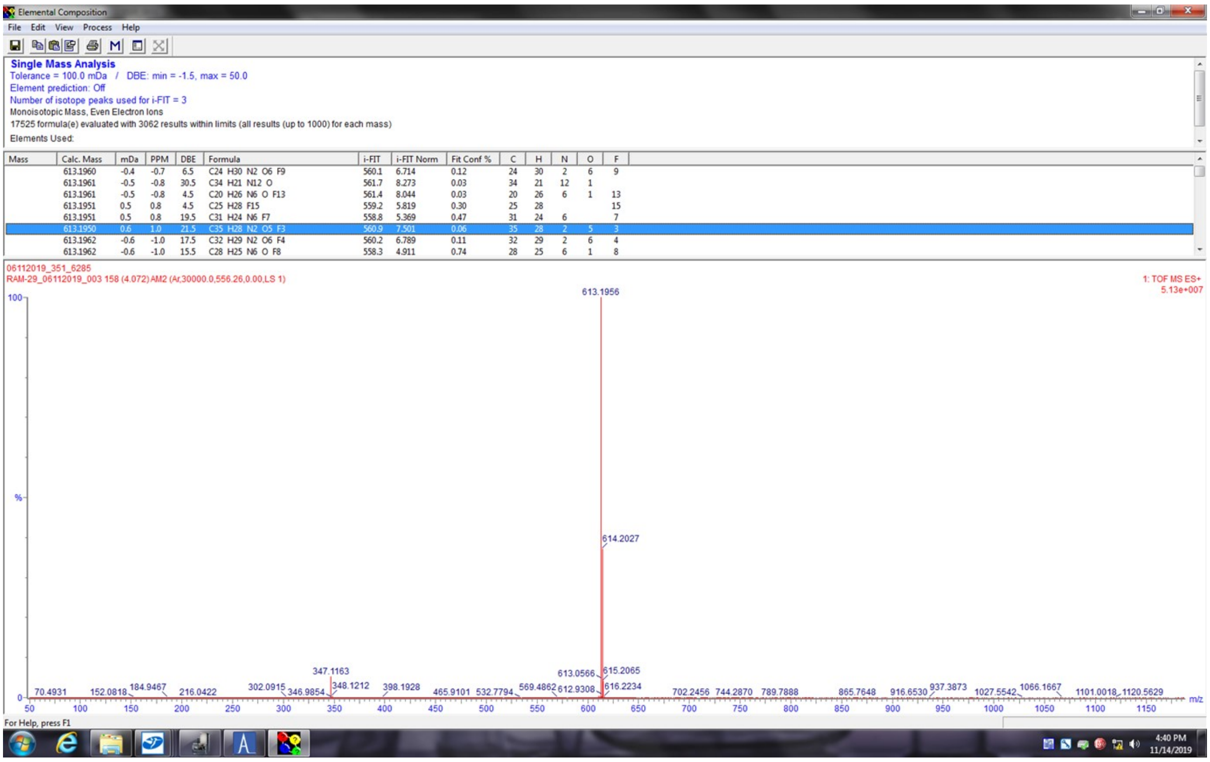


Figure S84: HRMS of Compound **4y**

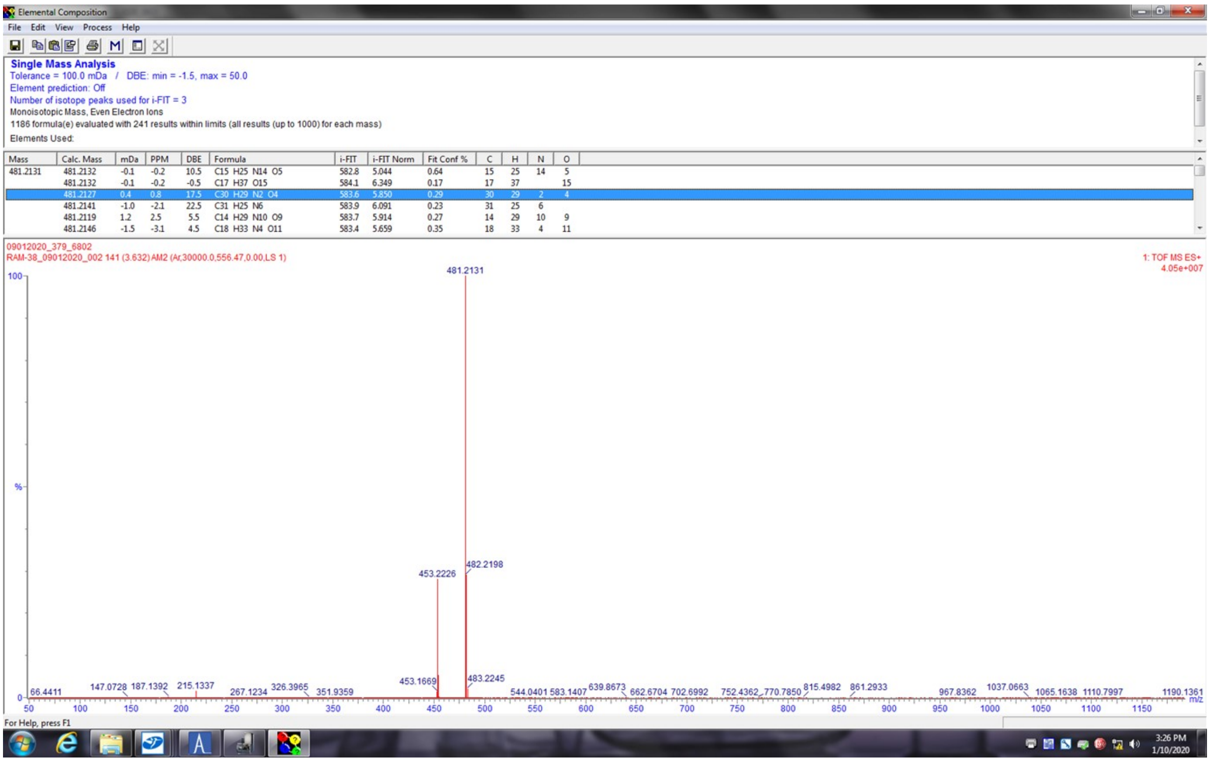


Figure S85: HRMS of Compound **5b**

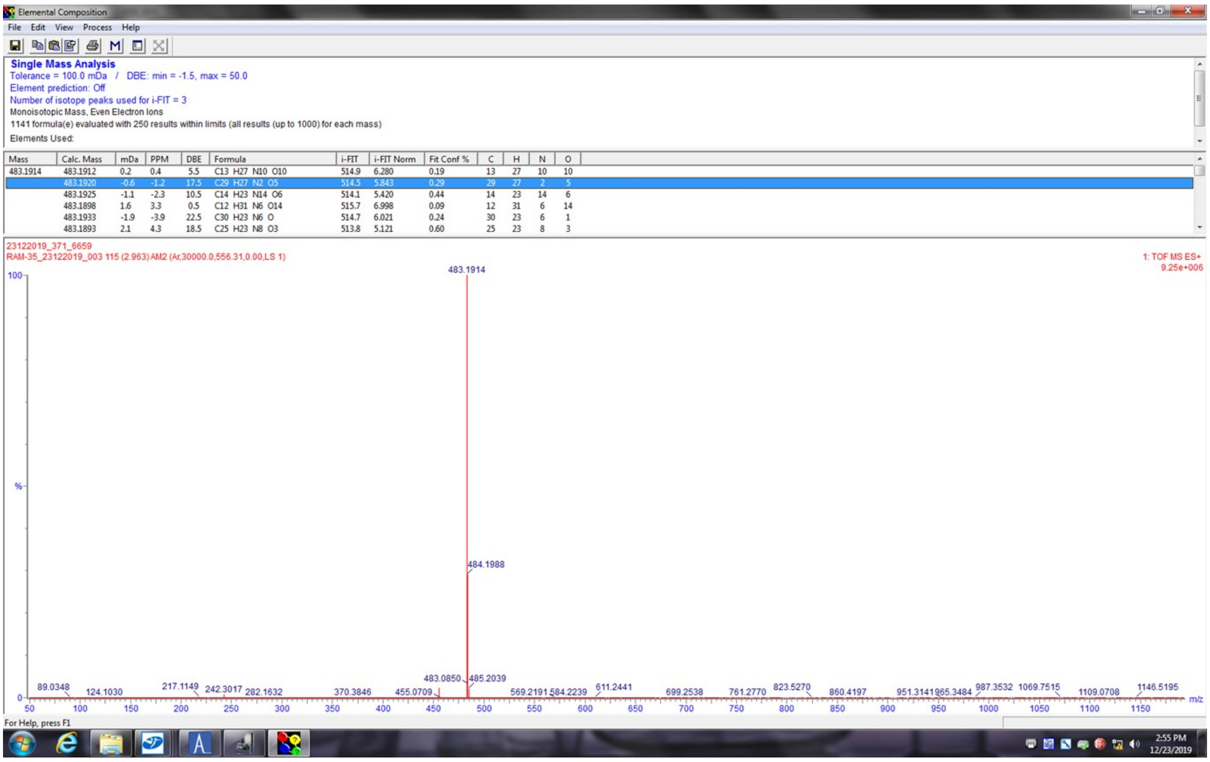


Figure S86: HRMS of Compound **5c**

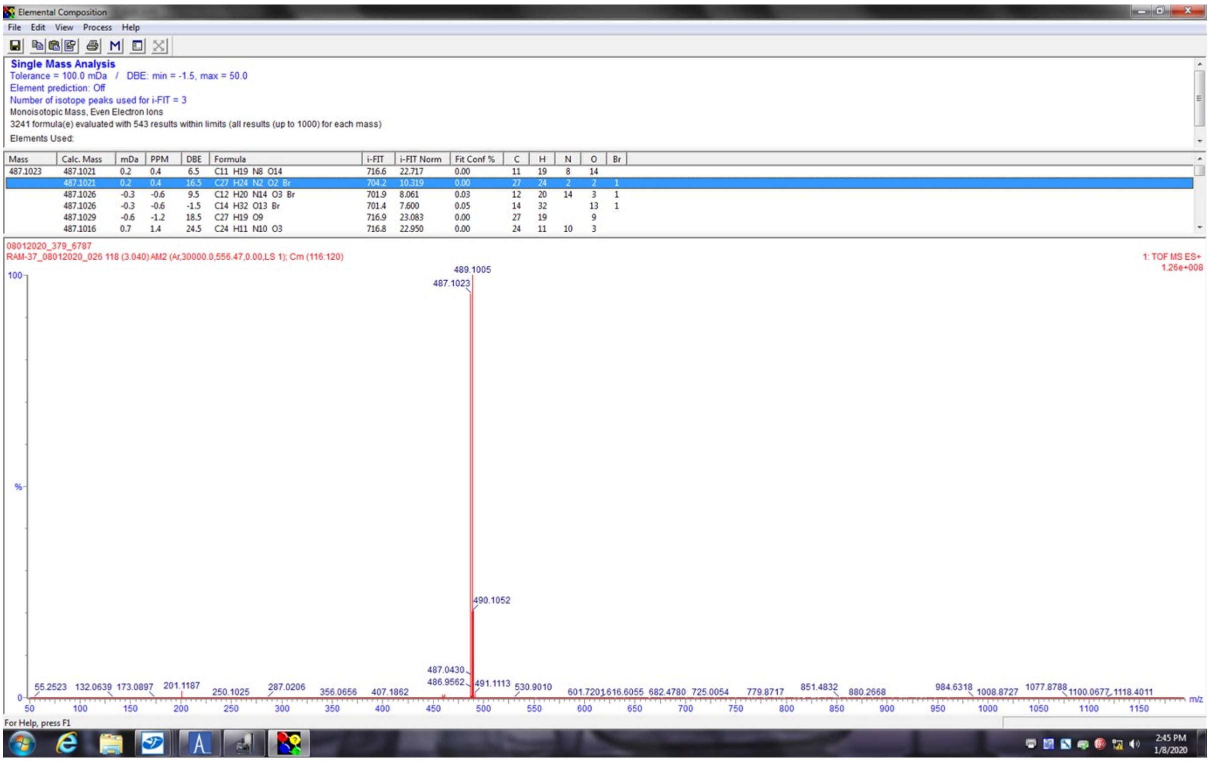


Figure S87: HRMS of Compound **5d**

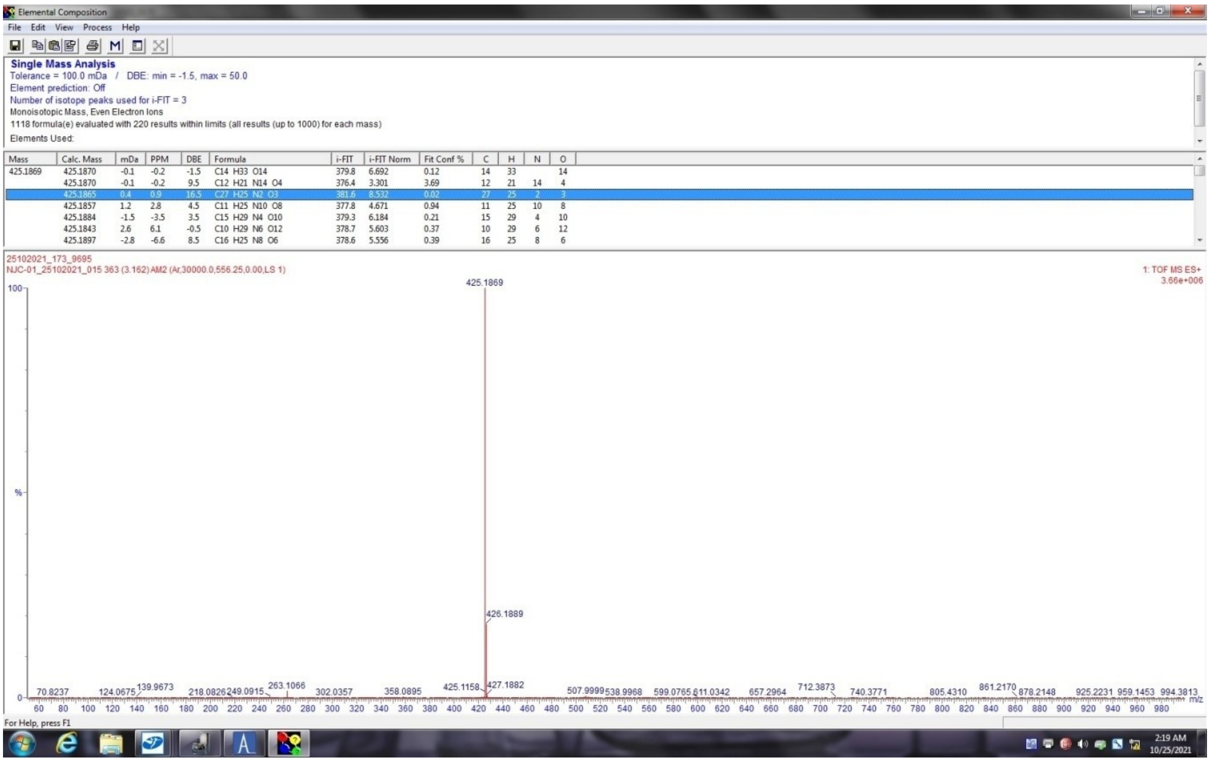


Figure S88: HRMS of Compound **5e**

6. Docking Studies

The docking analysis was developed by Auto Dock Tools (ADT) (Sanner, 1999) version 1.5.6 and Auto dock version 4.2.5.1 programs; (Auto dock, Auto grid, Copyright-1989-2012) from the Scripps Research Institute http://www.scripps.edu/mb/olson/doc/autodock. All the ssynthesised Compounds were docked to target protein complex 4OHU with the protein molecule considered as a rigid body and the ligand as flexible. The search was carried out with the Lamarckian Genetic Algorithm; (Morris et al., 1998) populations of 150 individuals with a mutation rate of 0.02 evolved for 10 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed, and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The output was exported to ADT and Biovia-Discovery Studio for visual inspection of the binding modes and interactions of the compounds with amino acid residues in the active sites.

The docking simulations in the active sites of ACP reductase InhA, is one of the essential enzymes involved in the type II fatty acid biosynthesis pathway of M. tuberculosis (PDB: 4OHU), was performed by the Auto Dock Tools (ADT) version 1.5.6 and Auto dock version 4.2.5.1 programmes.

Compound 4a

(S**89a**) **(S89b)**

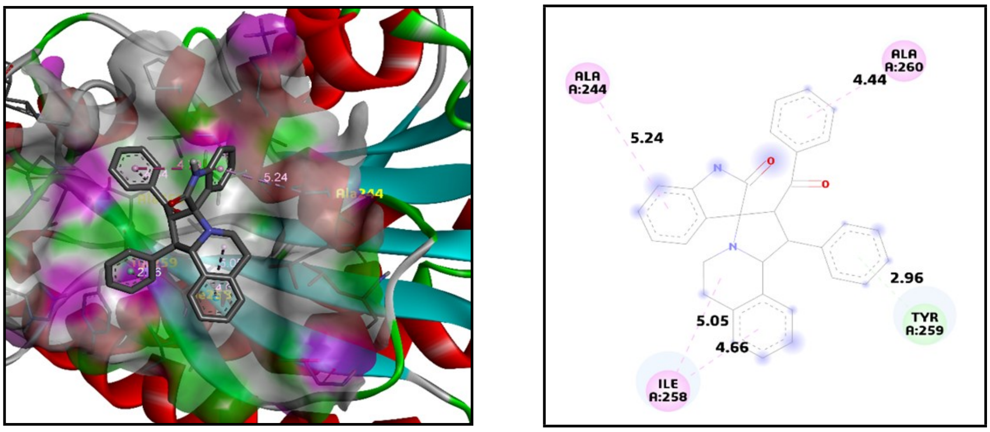


Figure S89(a-b): Molecular docking results of **4a** with ACP reductase (4OHU): (S**89a**) 3D Docking pose of **4a** with the receptor (S**89b**) 2D Docking pose of **4a** with the receptor

Compound 4b

(S90a) (S90b)

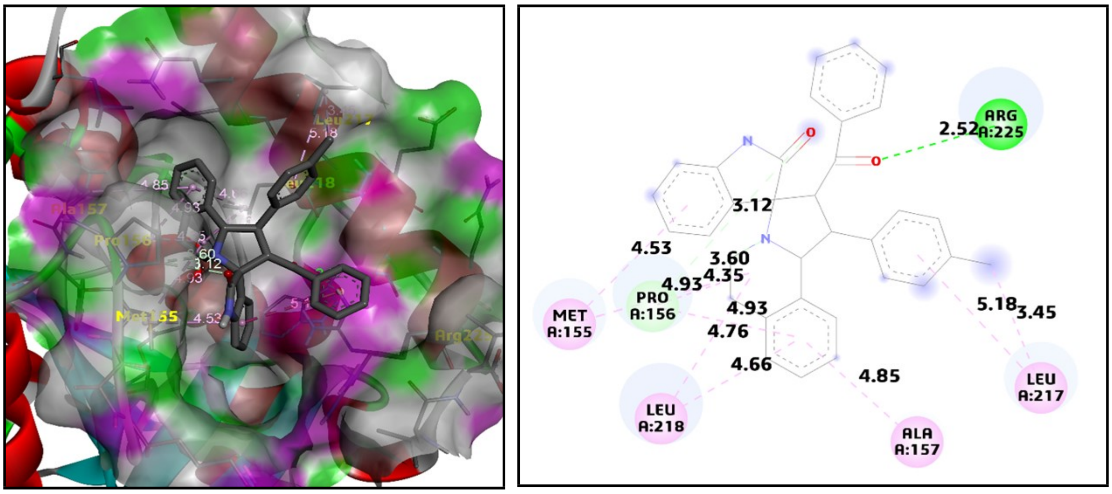


Figure S90(a-b): Molecular docking results of **4b** with ACP reductase (4OHU): **(S90a)** 3D Docking pose of **4b** with the receptor **(S90b)** 2D Docking pose of **4b** with the receptor

Compound 4c

(S91a) (S91b)

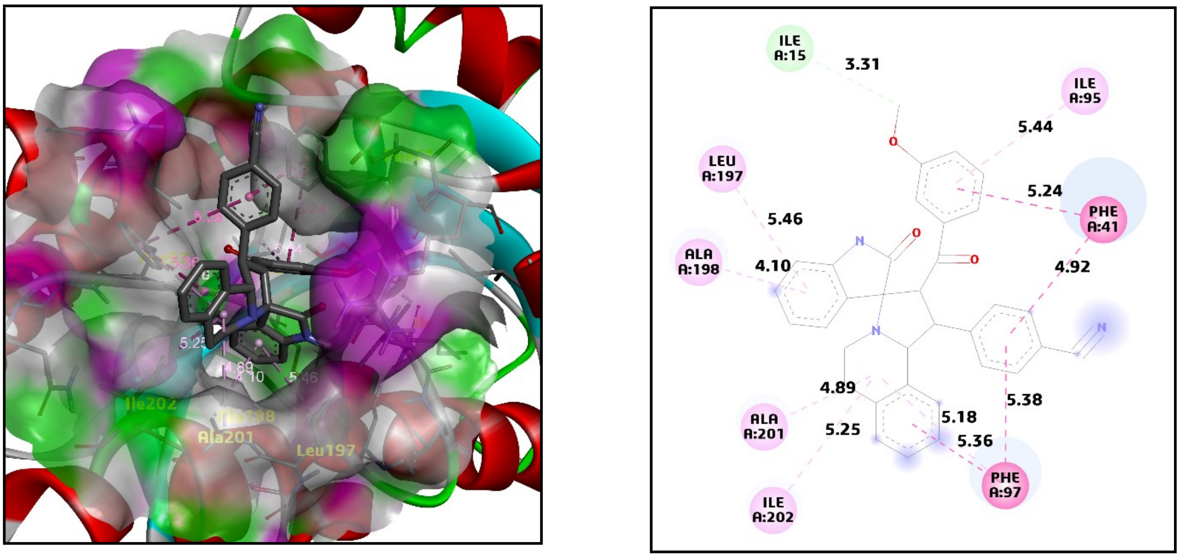
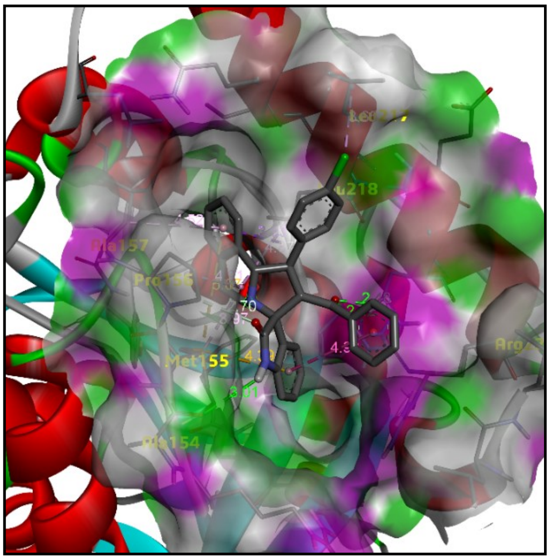


Figure S91(a-b): Molecular docking results of **4c** with ACP reductase (4OHU): **(S91a)** 3D Docking pose of **4c** with the receptor **(S91b)** 2D Docking pose of **4c** with the receptor

Compound 4d

(S92a) **(S92b)**



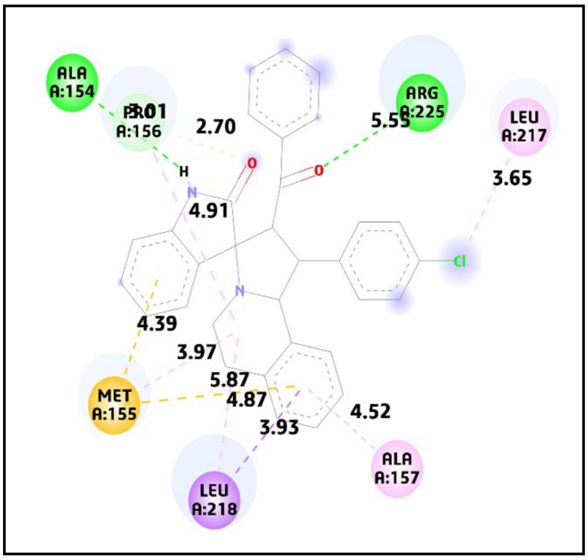
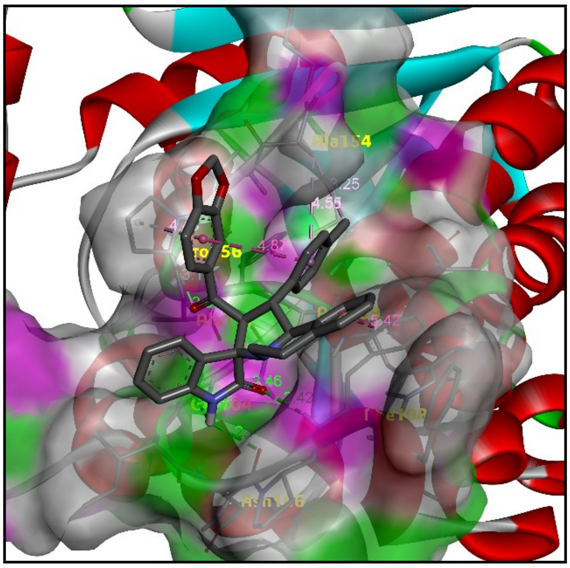


Figure S92(a-b): Molecular docking results of **4d** with ACP reductase (4OHU): **(S92a)** 3D Docking pose of **4d** with the receptor **(S92b)**2D Docking pose of **4d** with the receptor

Compound 4e

(S93a) **(S93b)**



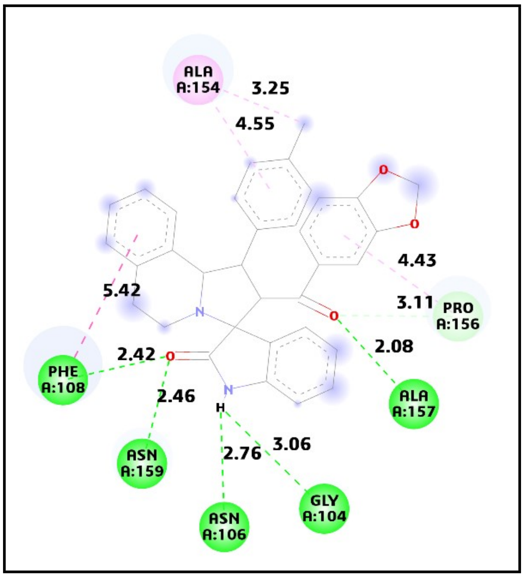
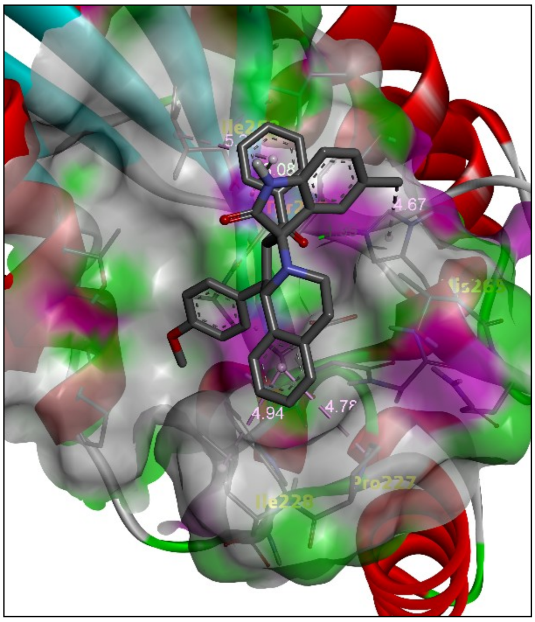


Figure S93(a-b): Molecular docking results of **4e** with ACP reductase (4OHU): **(S93a)** 3D Docking pose of **4e** with the receptor **(S93b)** 2D Docking pose of **4e** with the receptor

Compound 4f

(S94a) **(S94b)**



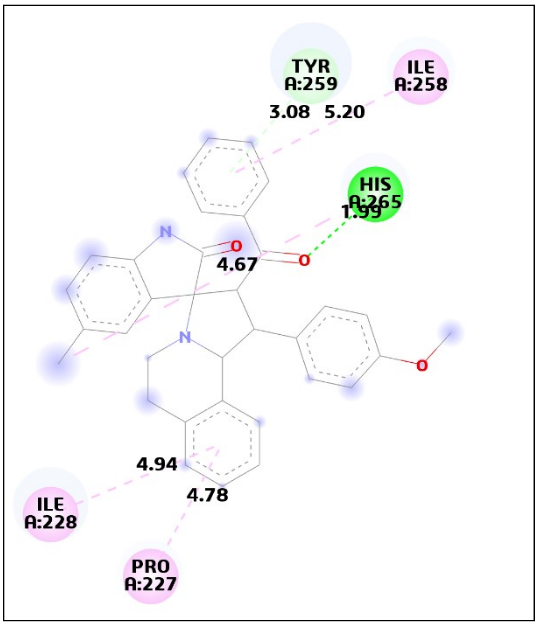
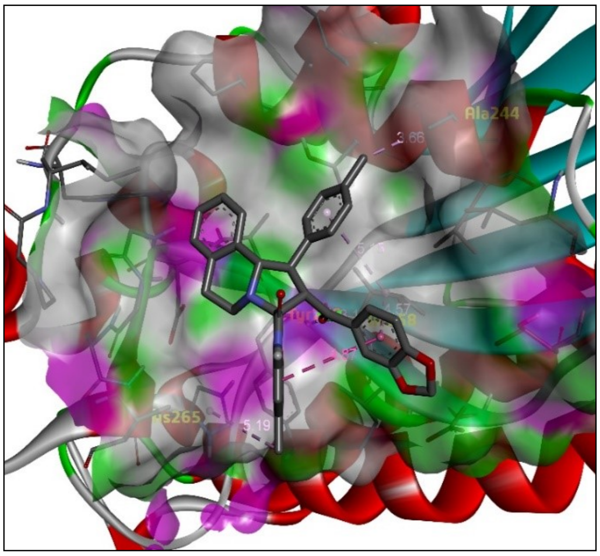


Figure S94(a-b): Molecular docking results of **4f** with ACP reductase (4OHU): **(S94a)** 3D Docking pose of **4f** with the receptor **(S94b)** 2D Docking pose of **4f** with the receptor

Compound 4g

(S95a) **(S95b)**



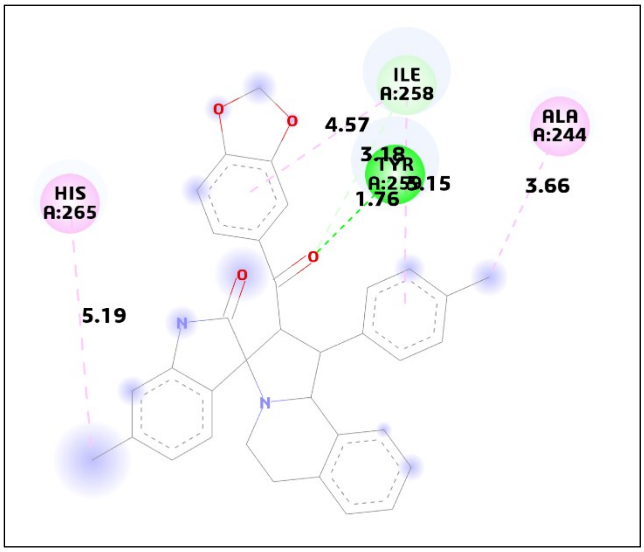
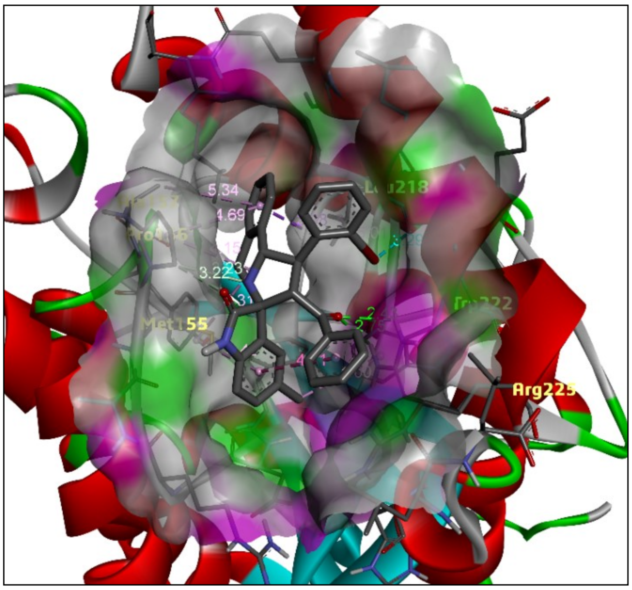


Figure S95(a-b): Molecular docking results of **4g** with ACP reductase (4OHU): **(S95a)** 3D Docking pose of **4g** with the receptor **(S95b)** 2D Docking pose of **4g** with the receptor

Compound 4h

(S96a) **(S96b)**



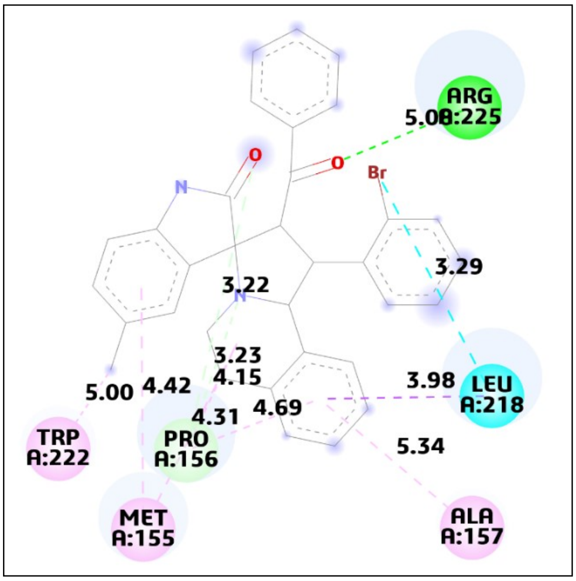
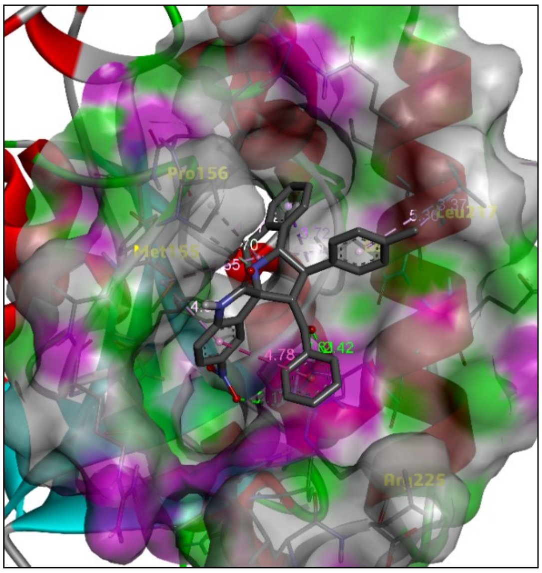


Figure S96(a-b): Molecular docking results of **4h** with ACP reductase (4OHU): (**S96a**) 3D Docking pose of **4h** with the receptor (**S96b**) 2D Docking pose of **4h** with the receptor

Compound 4i

(S97a) **(S97b)**



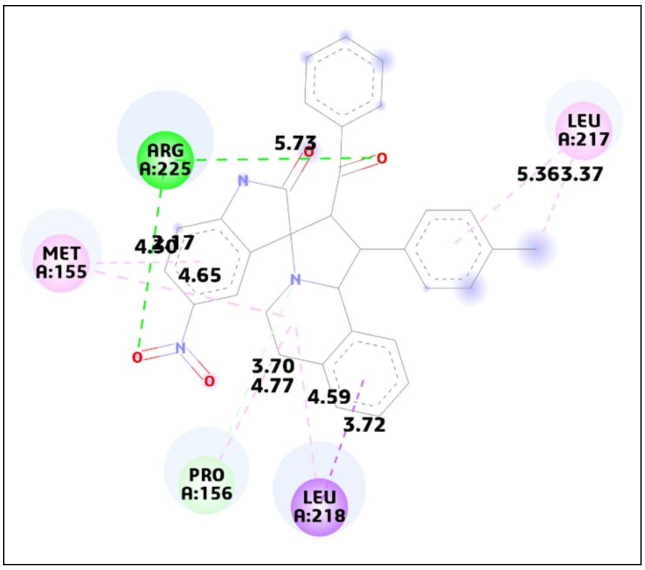
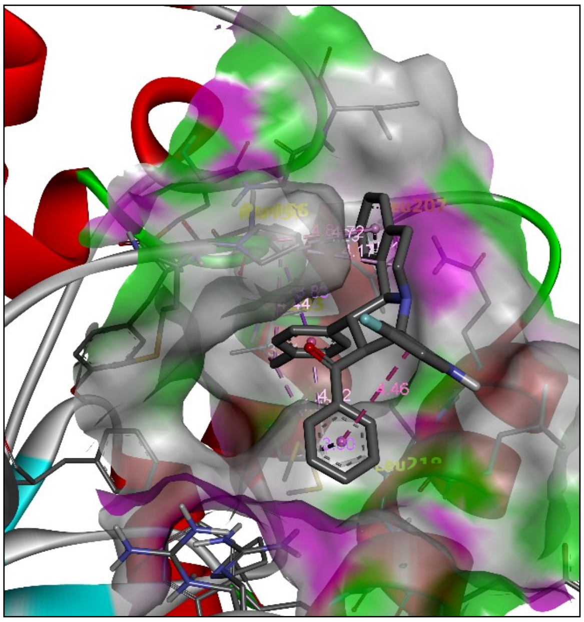


Figure S97(a-b): Molecular docking results of **4i** with ACP reductase (4OHU): **(S97a)** 3D Docking pose of **4i** with the receptor **(S97b)** 2D Docking pose of **4i** with the receptor

Compound 4j

(S98a)



(S98b)

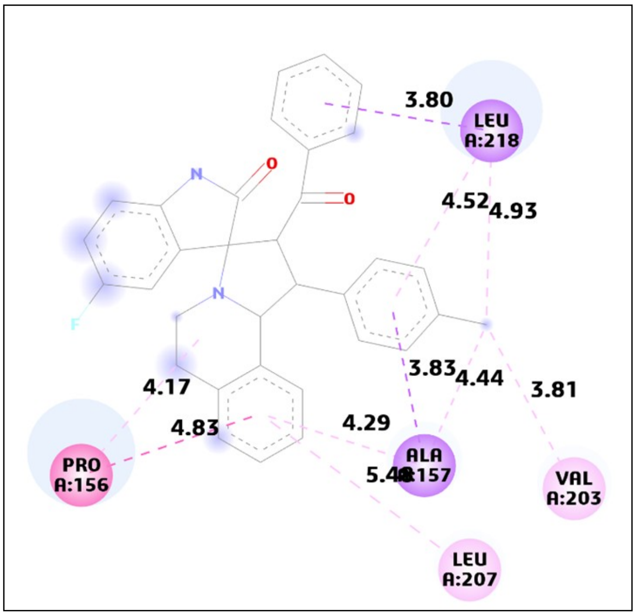
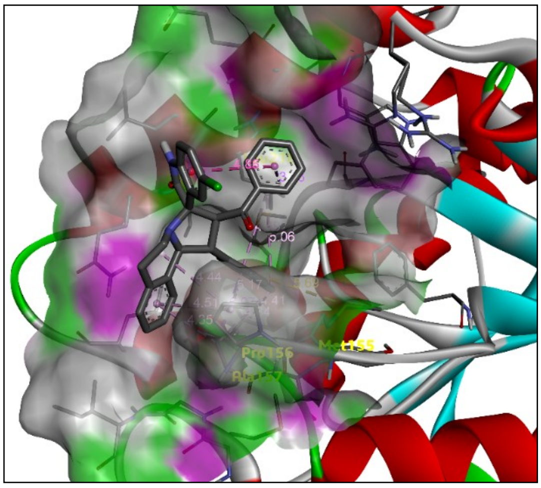


Figure S98(a-b): Molecular docking results of **4j** with ACP reductase (4OHU): **(S98a)** 3D Docking pose of **4j** with the receptor **(S98b)** 2D Docking pose of **4j** with the receptor

Compound 4k

(S99a)



(S99b)

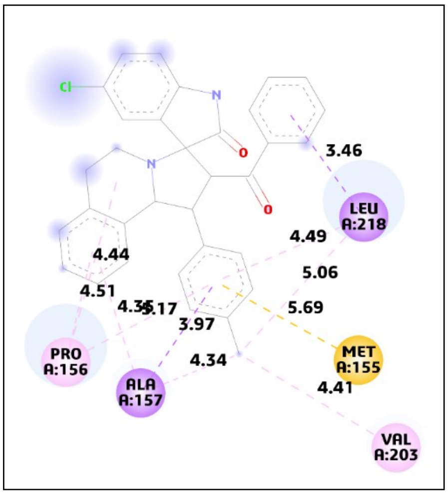
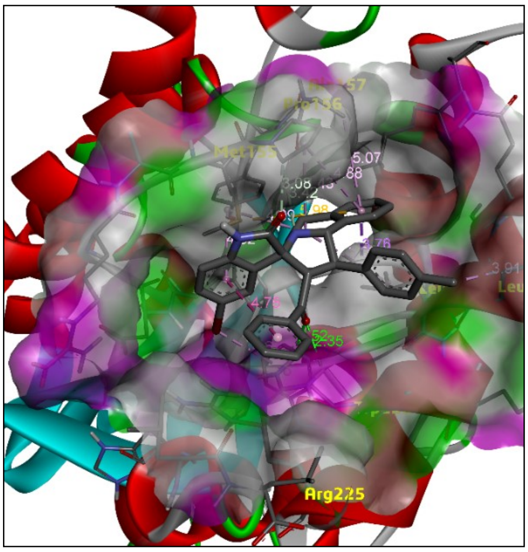


Figure S99(a-b): Molecular docking results of **4k** with ACP reductase (4OHU): **(S99a)** 3D Docking pose of **4k** with the receptor **(S99b)** 2D Docking pose of **4k** with the receptor

Compound 4l

(S100a) **(S100b)**



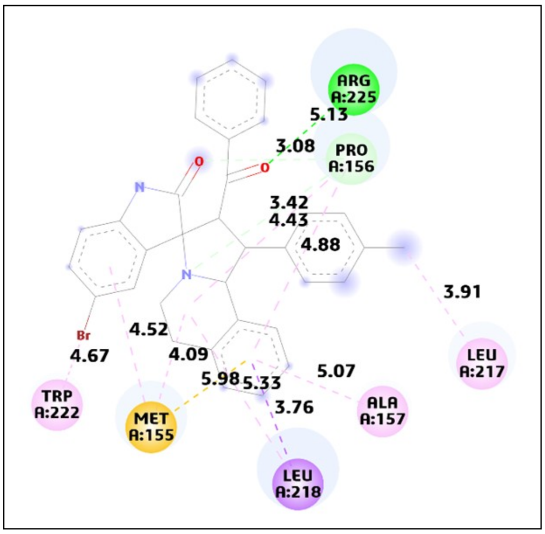
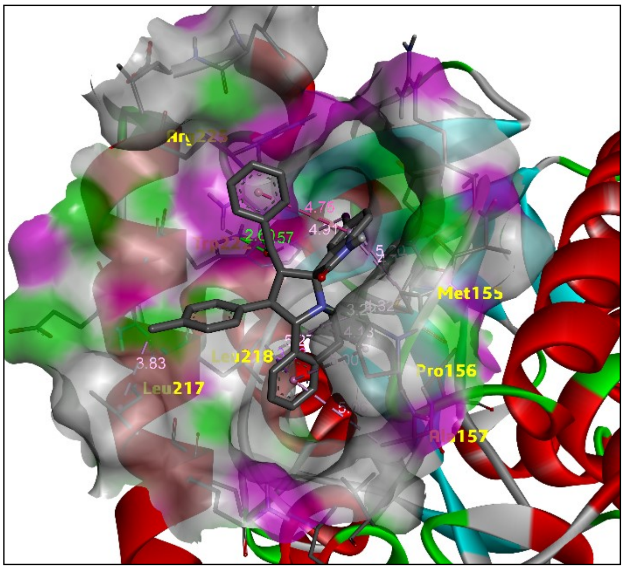


Figure S100(a-b): Molecular docking results of **4l** with ACP reductase (4OHU): **(S100a)** 3D Docking pose of **4l** with the receptor **(S100b)** 2D Docking pose of **4l** with the receptor

Compound 4m

(S101a) **(S101b)**



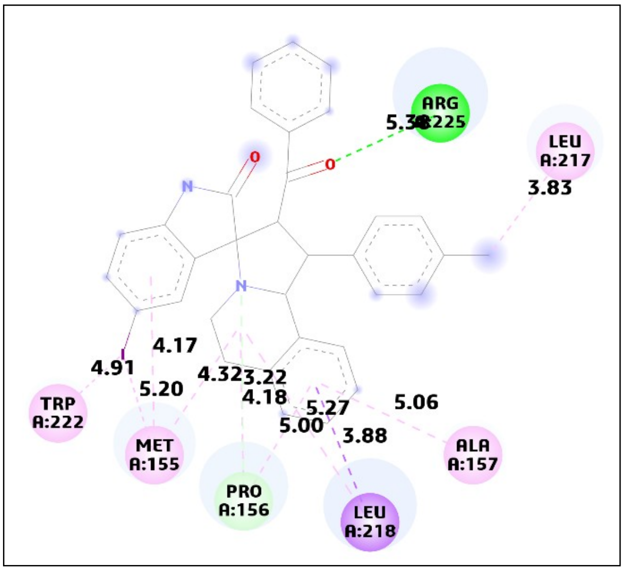


Figure S101(a-b): Molecular docking results of **4m** with ACP reductase (4OHU): **(S101a)** 3D Docking pose of **4m** with the receptor **(S101b)** 2D Docking pose of **4m** with the receptor

Compound 4n

(S102a) (S102b)

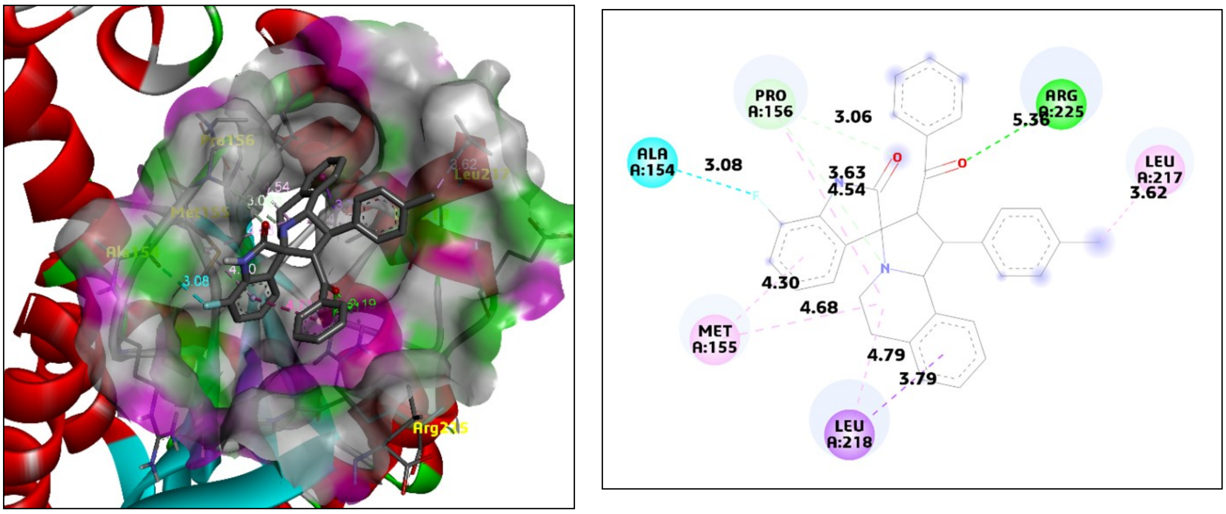


Figure S102(a-b): Molecular docking results of **4n** with ACP reductase (4OHU): (**S102a**) 3D Docking pose of **4n** with the receptor (**S102b**) 2D Docking pose of **4n** with the receptor

Compound 4o

(S103a) (S103b)

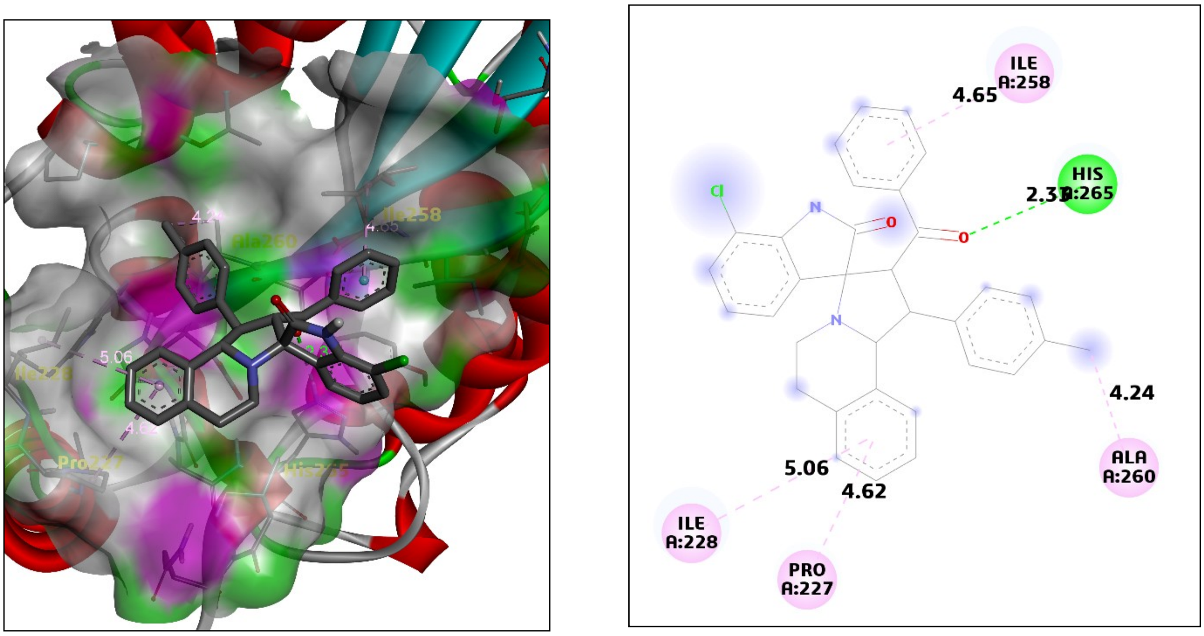
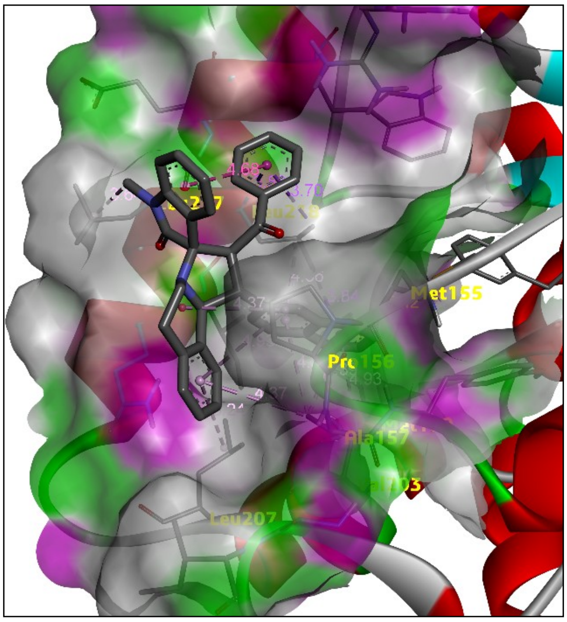


Figure S103(a-b): Molecular docking results of **4o** with ACP reductase (4OHU): (**S103a**) 3D Docking pose of **4o** with the receptor (**S103b**) 2D Docking pose of **4o** with the receptor

Compound 4p

(S104a) **(S104b)**



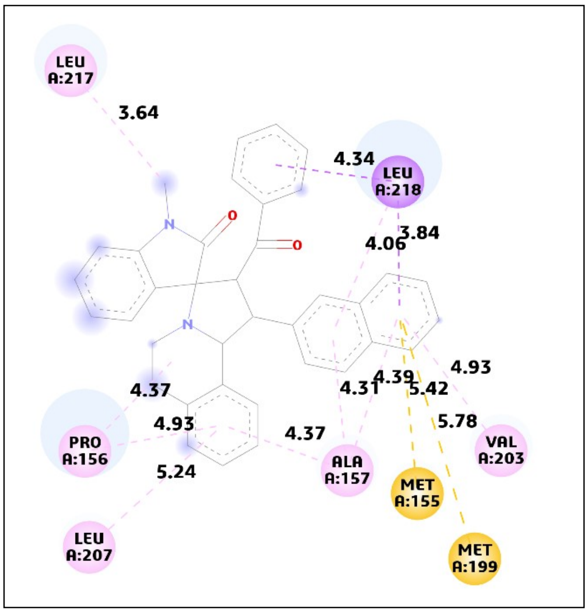
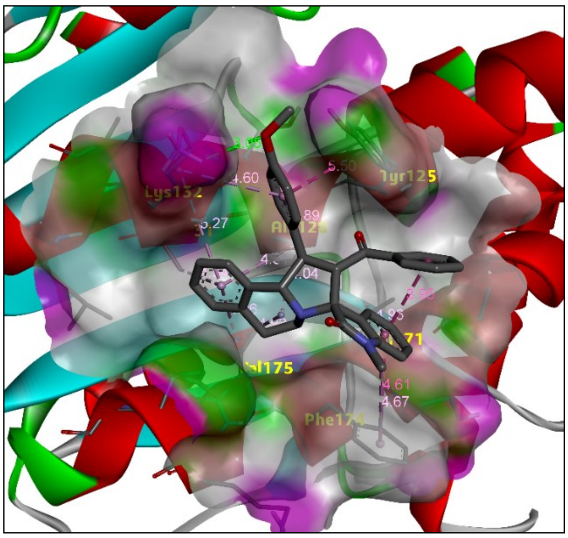


Figure S104(a-b): Molecular docking results of **4p**with ACP reductase (4OHU): (**S104a**) 3D Docking pose of **4p** with the receptor (**S104b**) 2D Docking pose of **4p** with the receptor

Compound 4q

(S105a) **(S105b)**



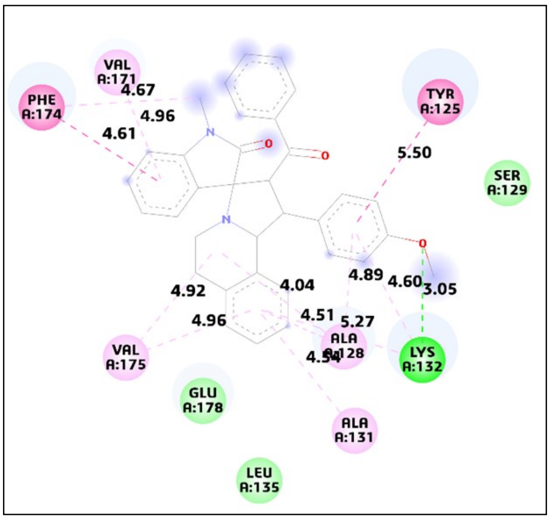
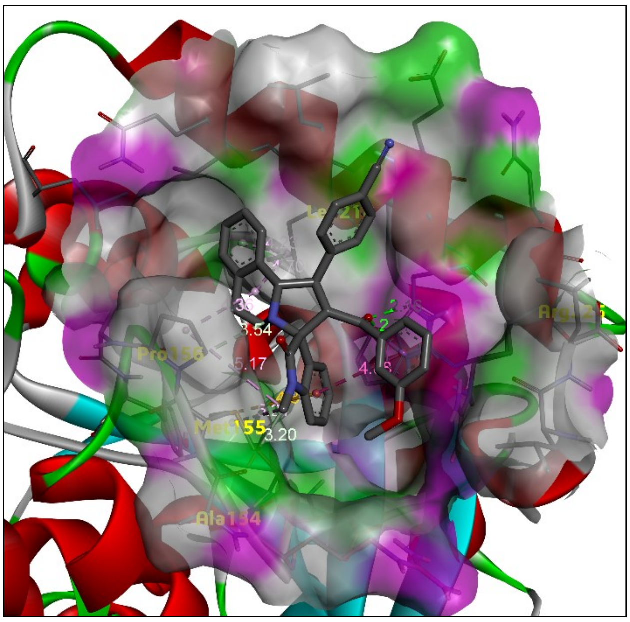


Figure S105(a-b): Molecular docking results of **4q** with ACP reductase (4OHU): (**S105a**) 3D Docking pose of **4q** with the receptor (**S105b**) 2D Docking pose of **4q** with the receptor

Compound 4r

(S106a) **(S106b)**



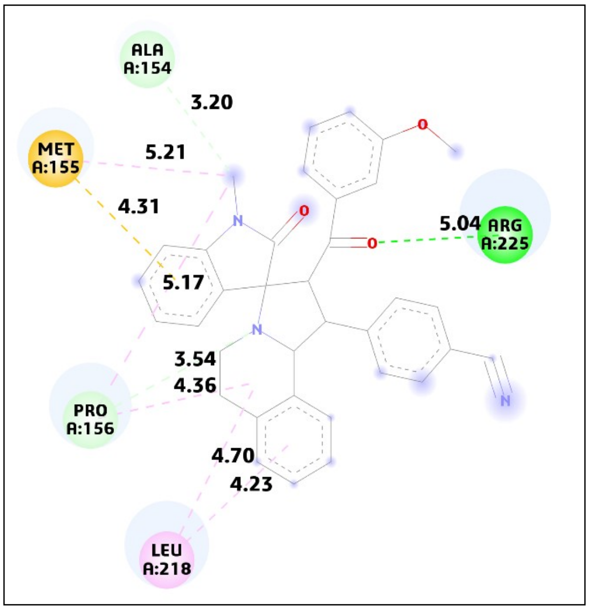
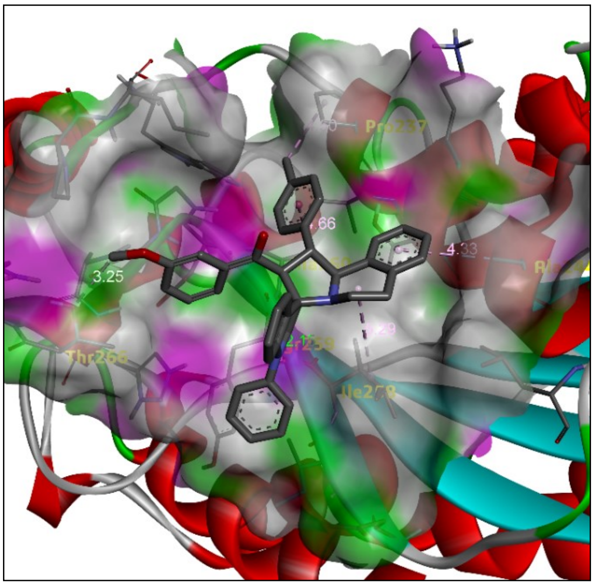


Figure S106(a-b): Molecular docking results of **4r** with ACP reductase (4OHU): (**S106a**) 3D Docking pose of **4r** with the receptor (**S106b**) 2D Docking pose of **4r** with the receptor

Compound 4s

(S107a) **(S107b)**



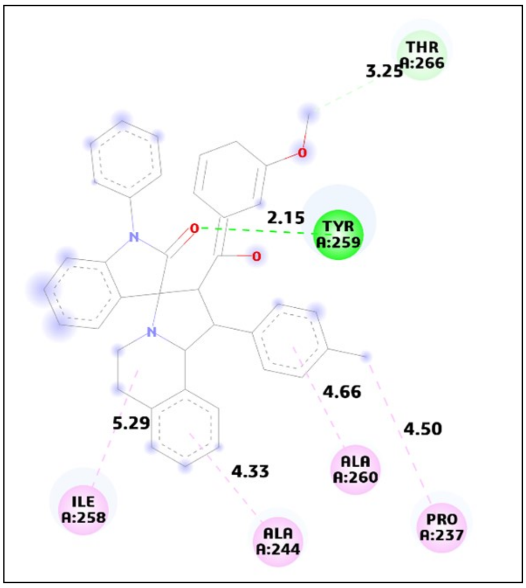
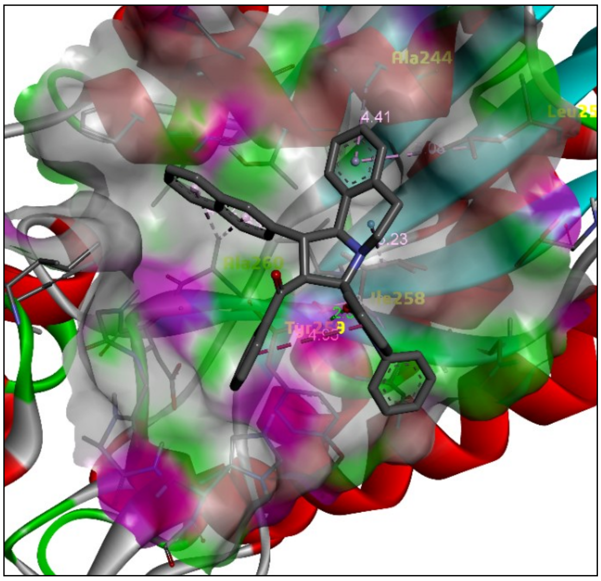


Figure S107(a-b): Molecular docking results of **4s** with ACP reductase (4OHU): (**S107a**) 3D Docking pose of **4s** with the receptor (**S107b**) 2D Docking pose of **4s** with the receptor

Compound 4t

(S108a) **(S108b)**



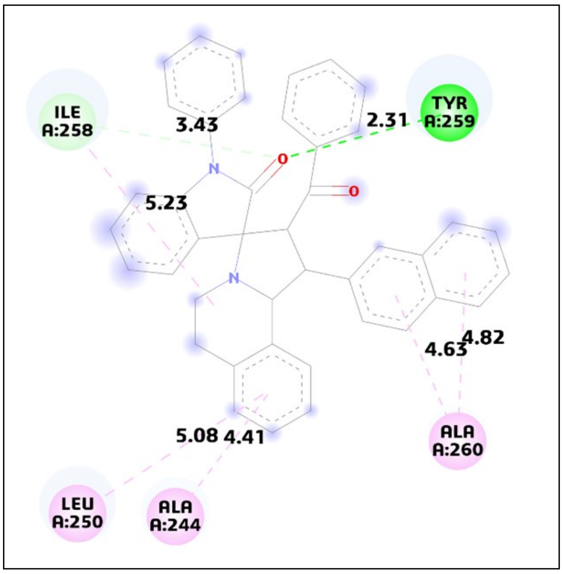
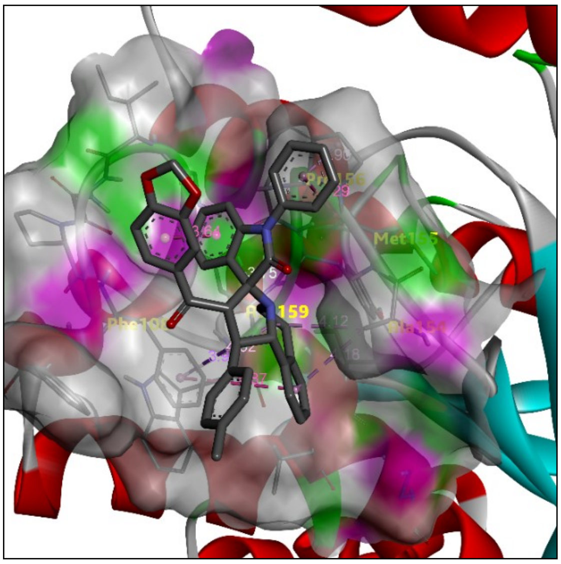


Figure S108(a-b): Molecular docking results of **4t** with ACP reductase (4OHU): (**S108a**) 3D Docking pose of **4t** with the receptor (**S108b**) 2D Docking pose of **4t** with the receptor

Compound 4u

(S109a) **(S109b)**



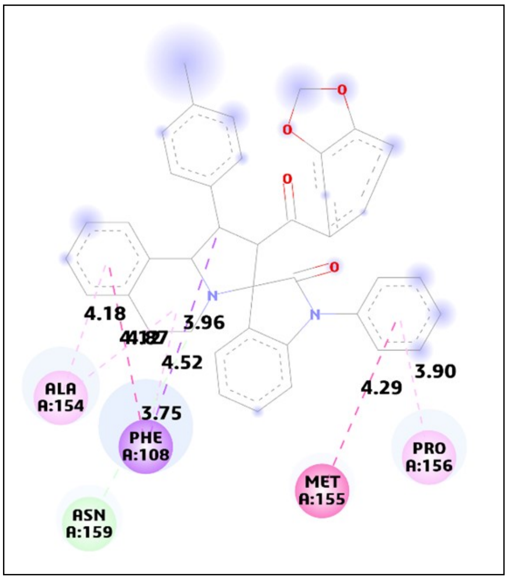
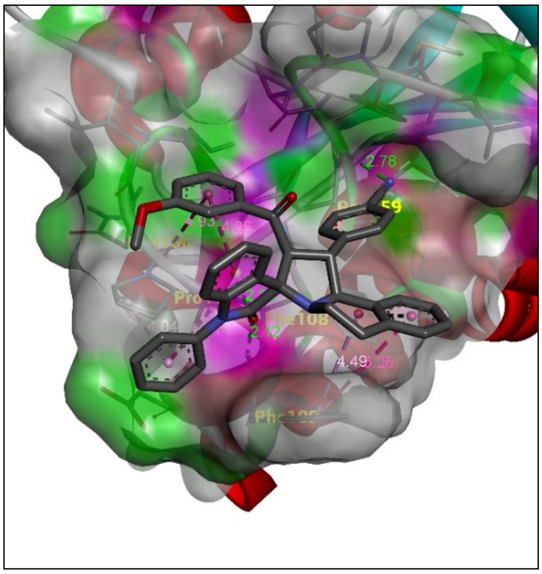


Figure S109(a-b): Molecular docking results of **4u** with ACP reductase (4OHU): (**S109a**) 3D Docking pose of **4u** with the receptor (**S109b**) 2D Docking pose of **4u** with the receptor

Compound 4v

(S110a)



(S110b)

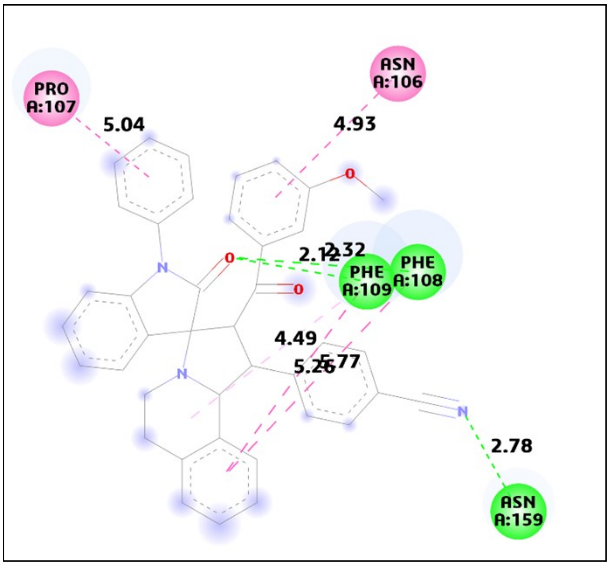
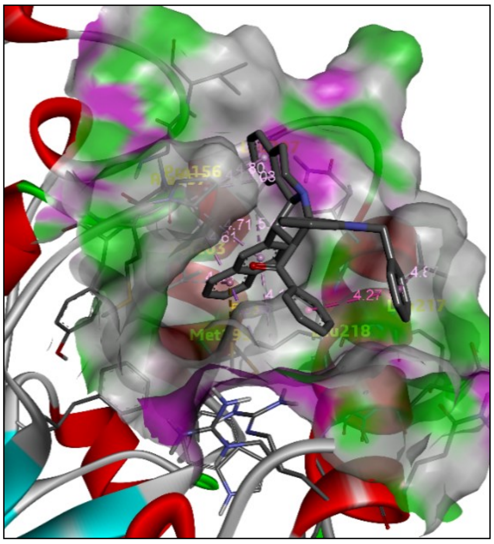


Figure S110(a-b): Molecular docking results of **4v** with ACP reductase (4OHU): (**S110a**) 3D Docking pose of **4v** with the receptor (**S110b**) 2D Docking pose of **4v** with the receptor

Compound 4w

(S111a)



(S111b)

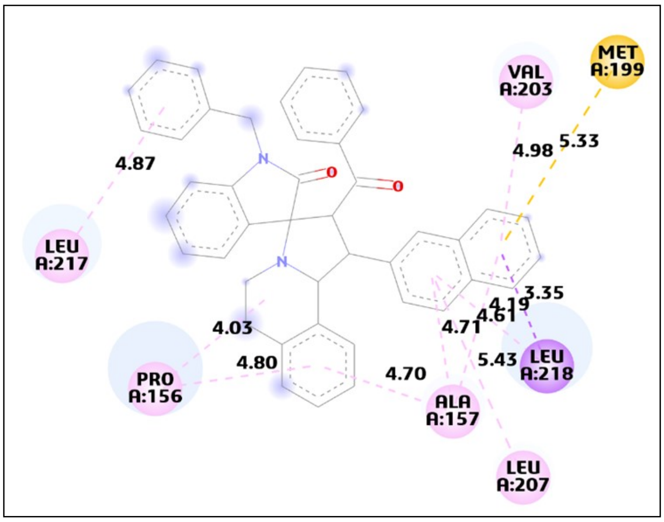
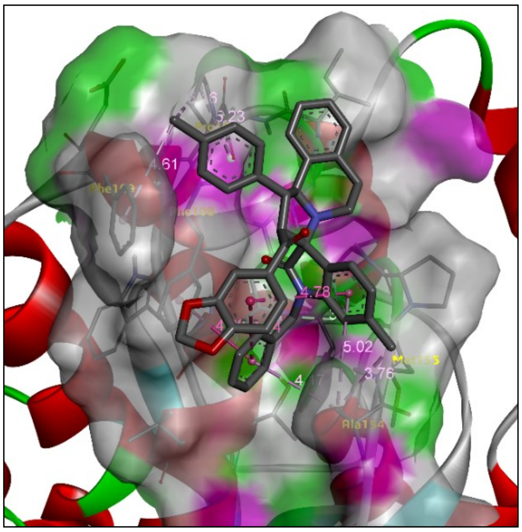


Figure S111(a-b): Molecular docking results of **4w** with ACP reductase (4OHU): (**S111a**) 3D Docking pose of **4w** with the receptor (**S111b**) 2D Docking pose of **4w** with the receptor

Compound 4x

(S112a)



(S112b)

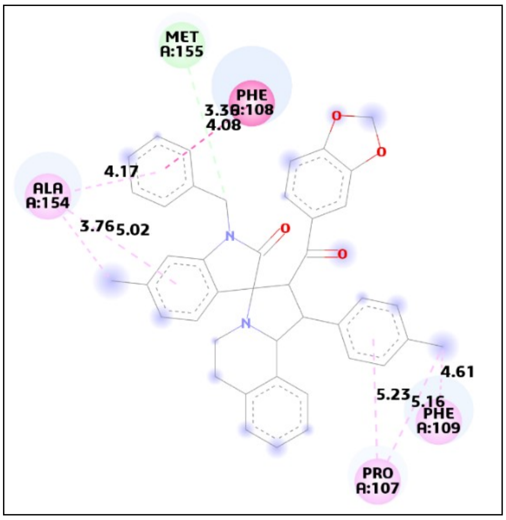
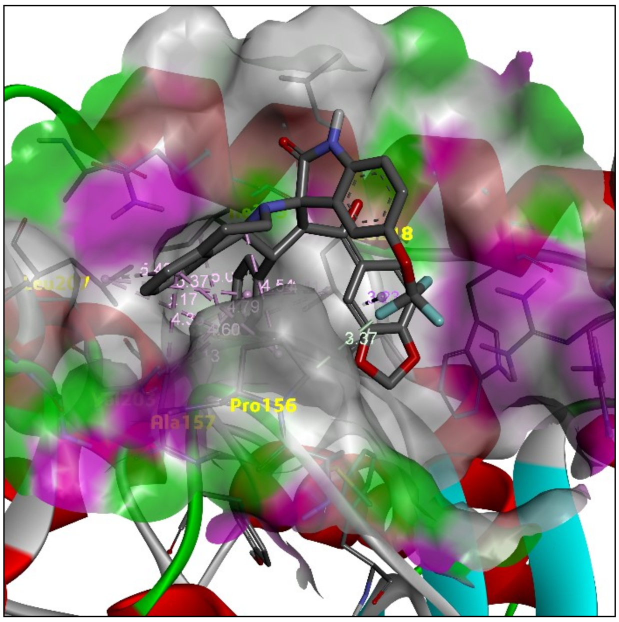


Figure S112(a-b): Molecular docking results of **4x** with ACP reductase (4OHU): (**S112a**) 3D Docking pose of **4x** with the receptor (**S112b**) 2D Docking pose of **4x** with the receptor

Compound 4y

(S113a)



(S113b)

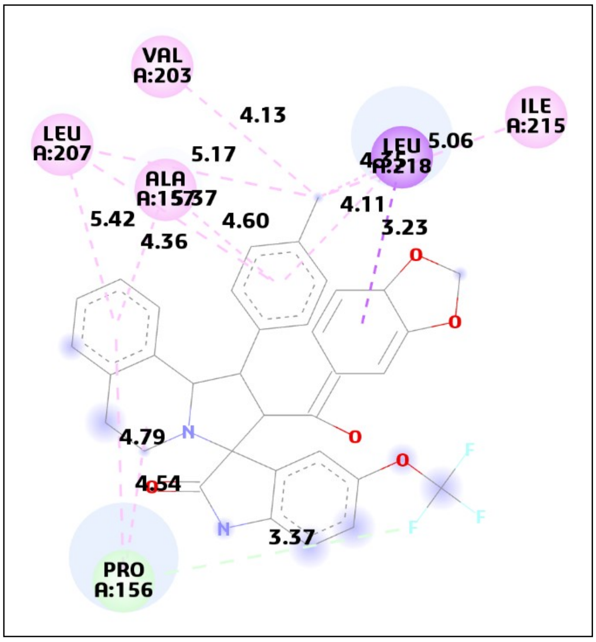
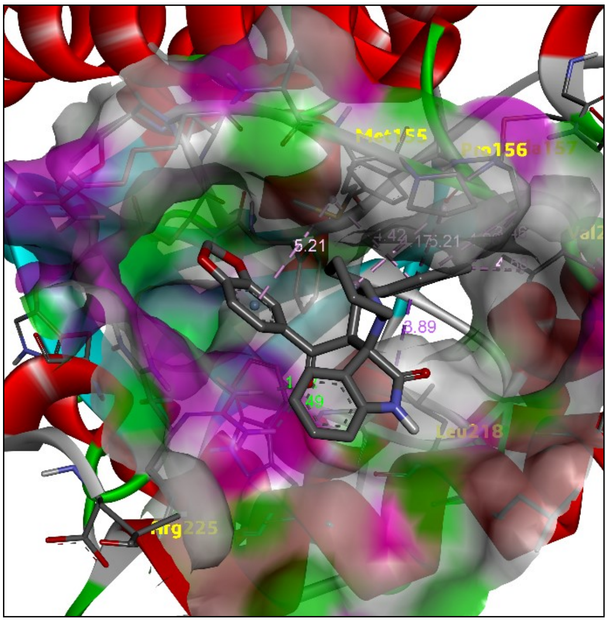


Figure S113(a-b): Molecular docking results of **4y** with ACP reductase (4OHU): (**S113a**) 3D Docking pose of **4y** with the receptor (**S113b**) 2D Docking pose of **4y** with the receptor

Compound 5b

(S114a)



(S114b)

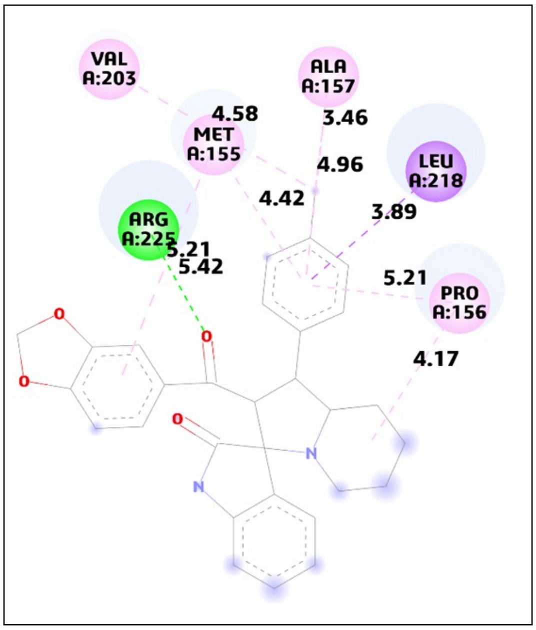
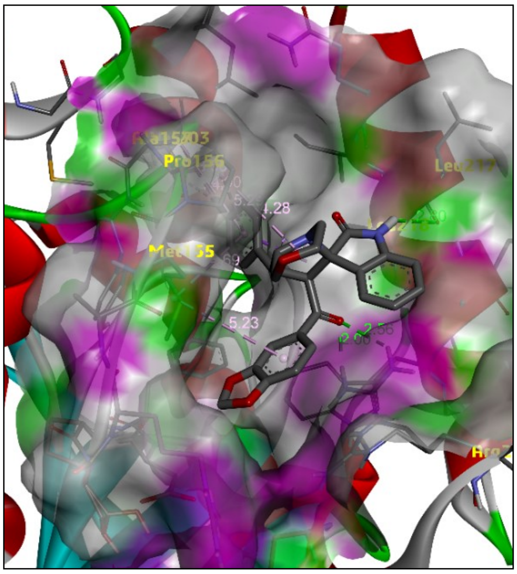


Figure S114(a-b): Molecular docking results of **5b** with ACP reductase (4OHU): (**S114a**) 3D Docking pose of **5b** with the receptor (**S114b**) 2D Docking pose of **5b** with the receptor

Compound 5c

(S115a)



(S115b)

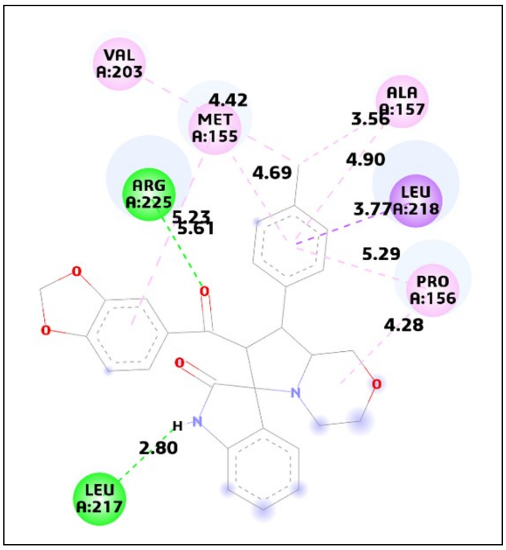
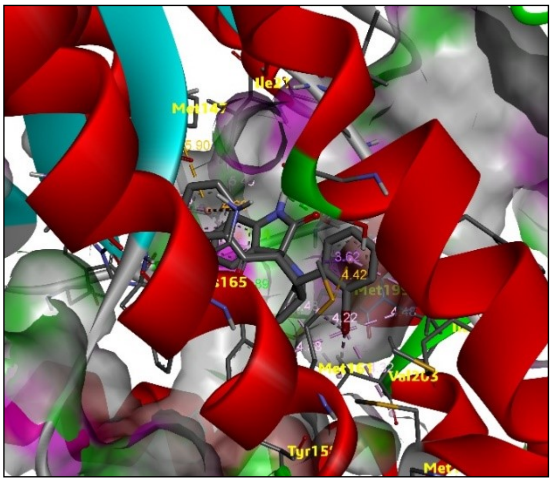


Figure S115(a-b): Molecular docking results of **5c** with ACP reductase (4OHU): (**S115a**) 3D Docking pose of **5c** with the receptor (**S115b**) 2D Docking pose of **5c** with the receptor

Compound 5d

(S116a) **(S116b)**



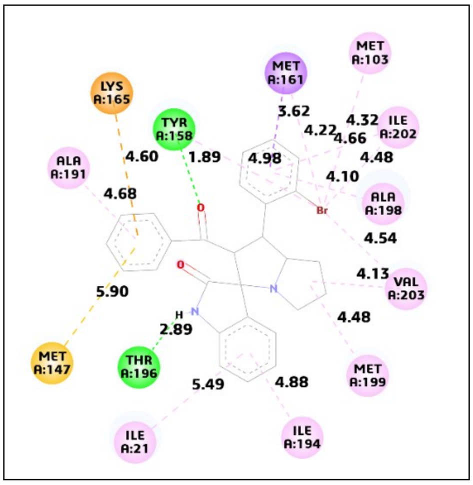
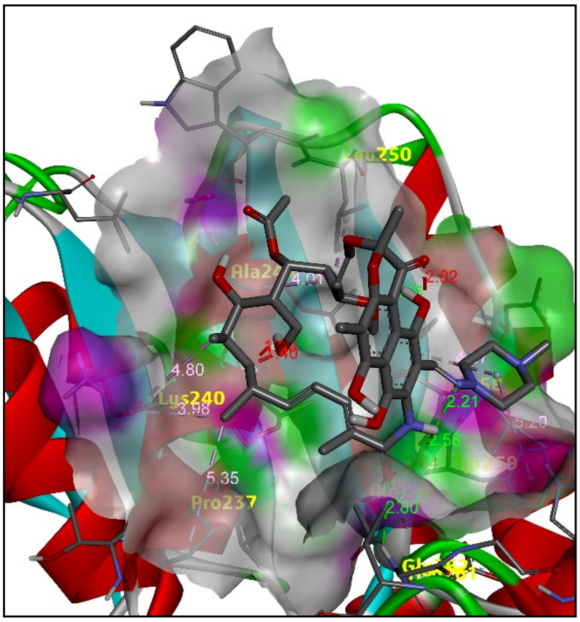


Figure S116(a-b): Molecular docking results of **5d** with ACP reductase (4OHU): (**S116a**) 3D Docking pose of **5d** with the receptor (**S116b**) 2D Docking pose of **5d** with the receptor

Validation (Rifampicin)

(S117a) **(S117b)**



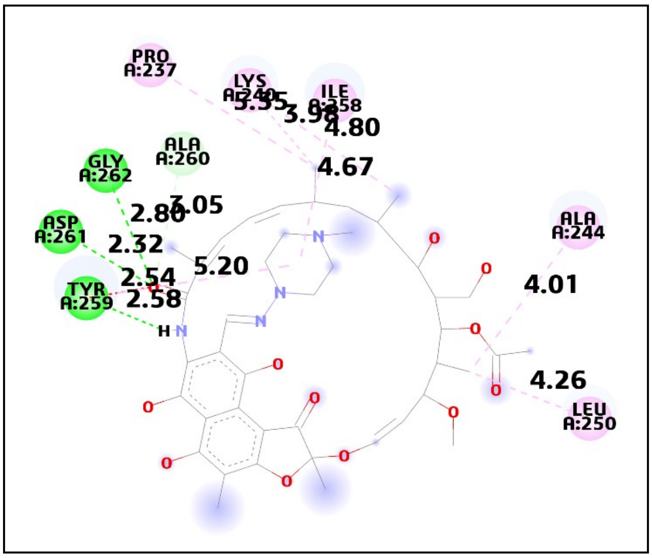


Figure S117(a-b): Molecular docking results of **Rifampicin** with ACP reductase (4OHU): (**S117a**) 3D Docking pose of the **drug** with the receptor (**S117b**) 2D Docking pose of **drug** with the receptor