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Design, Synthesis of Spirooxindole-pyrrolidines Embedded with Indole and Pyridine Heterocycles by Multicomponent Reaction: Anticancer and In Silico Studies

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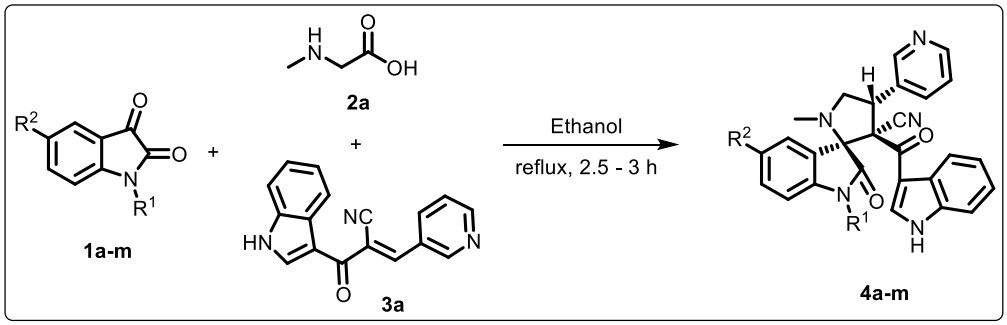
Supporting Information

Contents

1. Materials and Methods

All the chemicals were purchased from commercial sources, especially from Sigma Aldrich and used without any further purification. The synthesis of spirooxindole-pyrrolidine derivatives was carried out using 1,3 dipolar cycloaddition reaction of various isatin derivatives with dipolarophile and sarcosine, L-Proline or thioproline in ethanol under reflux for about 2.5 to 3 h to afford the desired product. The synthetic strategy to obtain these derivatives has been provided in the schemes. The compound characterised for ^{1}H NMR and ^{13}C NMR spectra were performed 400 MHz and 100 MHz Bruker spectrometer. The Chemical shifts values in parts per million (ppm) with TMS (0 ppm) and $CDCl_3$ or DMSO-d_6 as standards for ^{1}H NMR and ^{13}C NMR spectra. Infrared spectroscopy of all the compounds was measured using Bruker-Alpha-p instrument. All the TLC analyses were carried out using Merck silica gel 60 F254 plates. Column chromatography was performed on Merck silica gel (100–200 mesh). IR spectra were measured using a Bruker FT IR spectrometer.

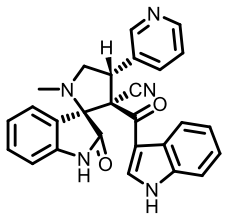
2. General experimental procedure for the synthesis of spirooxindole-pyrrolidine derivatives (4a-m)



In an oven-dried 50 ml round bottom flask fixed with a reflux condenser were added a mixture of substituted isatin **1a-m** (1.0 mmol), sarcosine **2a** (1.0 mmol) and (E)-2-(1H-indole-3-carbonyl)-3-(pyridin-3-yl)acrylonitrile **3a** (1.0 mmol) in ethanol (5.0 mL) for reflux 2.5 to 3 hours. After completion of the reaction, as evidenced by TLC analysis, the reaction mixture was poured into ice water, the resulting solid was filtered off, and the solid was washed with cold ethanol to afford pure spirooxindole-pyrrolidine derivatives in nature of colourless solid (**4a-m**).

3. Spectral data for synthesised compound (4a-m)

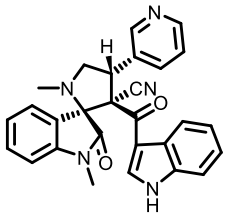
3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2' pyrrolidine]-3'-carbonitrile (4a)



4a

The compound is prepared according to the general reaction procedure. Colourless solid; Yield 96 %; mp 232 ^{o}C; FT-IR (cm^{-1}) Neat; 548, 623, 748, 798, 935, 1025, 1158, 1238, 1327, 1429, 1511, 1625, 1712, 2864, 3216; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.91 (s, 1H), 10.45 (s, 1H), 8.68 (d, *J* = 2.3 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.17 (dt, *J* = 5.2, 3.2 Hz, 1H), 7.98 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.27 (td, *J* = 7.6, 1.2 Hz, 1H), 7.23 – 7.19 (m, 2H), 6.79 (s, 1H), 6.61 (d, *J* = 7.6 Hz, 1H), 5.50 (t, *J* = 8.6 Hz, 1H), 3.70 (d, *J* = 9.4 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 179.81, 174.31, 151.12, 149.43, 143.03, 137.27, 135.99, 134.25, 133.88, 131.43, 126.85, 126.59, 126.57, 125.69, 124.26, 123.91, 123.35, 122.13, 119.33, 112.87, 112.81, 112.16, 76.78, 66.26, 56.01, 43.04, 40.61, 40.40, 40.20, 39.99, 39.78, 39.57, 39.36, 35.58 ppm; ESI MS m/z = 448 [M+H]$^{+}$; Anal. Calculated for $C_{27}H_{21}N_5$: C, 62.08; H, 3.82; N, 12.07. Found: C, 69.12; H, 3.81; N, 12.01.

3'-(1H-indole-3-carbonyl)-1,1'-dimethyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine] -3'-carbonitrile (4b)

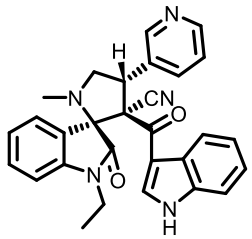


4b

The compound is prepared according to the general procedure. Colourless solid; Yield 90 %; mp 226 ^{o}C; FT-IR (cm^{-1}) Neat; 545, 589, 641, 744, 794, 937, 1008, 1049, 1097, 1158, 1244, 1352, 1438, 1497, 1617, 1700, 2853, 3056, 3033, 3480; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.88 (s, 1H), 8.67 (d, *J* = 1.9 Hz, 1H), 8.52 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.11 (dd, *J* = 6.1, 3.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.39 – 7.29 (m, 2H), 7.21 (dq, *J* = 7.0, 3.9 Hz, 2H), 6.83 – 6.74 (m, 2H), 5.47 (t, *J* = 8.6 Hz, 1H), 3.80 – 3.67 (m, 2H), 2.69 (s,

3H), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.59, 172.42, 150.62, 148.85, 144.85, 136.75, 135.35, 133.64, 133.57, 131.12, 125.91, 124.91, 123.61, 123.57, 123.38, 122.67, 122.63, 121.33, 118.79, 112.34, 112.24, 108.92, 76.53, 65.99, 56.02, 42.38, 35.11, 25.55 ppm; ESI MS m/z = 462 $[M+H]^+$; Anal. Calculated for $C_{28}H_{23}N_5O_2$: C, 72.87; H, 5.02; N, 15.17. Found: C, 72.91; H, 5.07; N, 15.13.

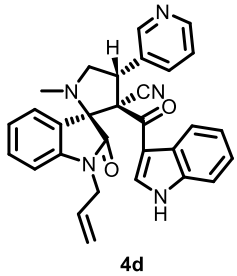
1-ethyl-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4c)



4c

The compound is prepared according to the general procedure. Colourless solid; Yield 89 %; mp 240 ºC; FT-IR (cm^{-1}) Neat; 535, 642, 717, 1160, 1358, 1448, 1603, 1703, 2861, 2973, 3094; ^{1}H NMR (400 MHz, DMSO) δ 11.73 (s, 1H), 8.70 (s, 1H), 8.55 – 8.47 (m, 1H), 8.17 – 8.10 (m, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.24 – 7.14 (m, 2H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.76 (s, 1H), 5.51 (t, *J* = 8.5 Hz, 1H), 3.73 (d, *J* = 8.6 Hz, 2H), 3.48 (dd, *J* = 14.1, 7.2 Hz, 1H), 3.18 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.13 (s, 3H), 0.42 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.03, 171.80, 150.53, 148.71, 143.83, 136.67, 135.29, 133.74, 133.66, 131.11, 126.04, 125.08, 123.69, 123.48, 123.28, 122.60, 122.44, 121.47, 118.74, 112.26, 112.09, 108.93, 76.20, 65.68, 55.51, 42.13, 35.03, 33.55, 11.43 ppm; ESI MS m/z = 476 $[M+H]^+$; Anal. Calculated for $C_{29}H_{25}N_5O_2$: C, 73.25; H, 5.30; N, 14.73. Found: C, 73.21; H, 5.59; N, 14.75.

1-allyl-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4d)

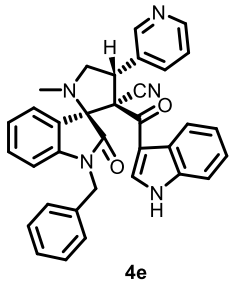


4d

The compound is prepared according to the general procedure. Colourless solid; Yield 86 %; mp 236 ºC; FT-IR (cm^{-1}) Neat; 641, 740, 788, 33, 1052, 1100, 1158, 1234, 1353, 1443, 1604, 1638, 1705, 2684, 2862, 3049; ^{1}H NMR (400 MHz, DMSO-d_6)

δ 11.91 (s, 1H), 8.68 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.13 (dd, *J* = 6.3, 2.9 Hz, 1H), 8.00 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.93 – 7.86 (m, 1H), 7.49 – 7.41 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.18 (m, 2H), 6.79 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.51 (dd, *J* = 9.9, 7.2 Hz, 1H), 5.19 – 5.03 (m, 1H), 4.66 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.52 – 4.42 (m, 1H), 3.88 – 3.68 (m, 4H), 2.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.25, 172.05, 150.65, 148.87, 144.03, 136.82, 135.47, 133.91, 133.64, 131.13, 130.93, 126.19, 125.10, 123.66, 123.43, 122.77, 121.61, 118.88, 116.68, 112.41, 112.22, 109.73, 76.36, 65.85, 55.53, 42.41, 41.24, 35.14 ppm; ESI MS m/z = 488 $[M+H]^+$; Anal. Calculated for $C_{30}H_{25}N_5O_2$: C, 73.90; H, 5.17; N, 14.36. Found: C, 73.87; H, 5.19; N, 14.39.

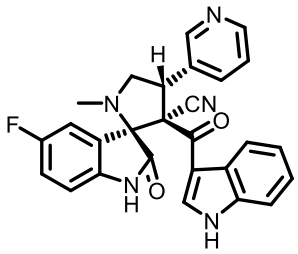
1-benzyl-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4e)



4e

The compound is prepared according to the general procedure. Colourless solid; Yield 87 %; mp 218 ºC; FT-IR (cm^{-1}) Neat; 552,630, 701, 739, 787, 858, 921, 1001, 1101, 1171, 1233, 1346, 1444, 1624, 1705, 2235, 2661, 2739, 2799, 2491, 3049; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.73 (s, 1H), 8.51 (d, *J* = 3.8 Hz, 1H), 8.09 (s, 1H), 7.97 (dd, *J* = 23.5, 7.9 Hz, 2H), 7.43 (dd, *J* = 12.4, 7.8 Hz, 3H), 7.25 – 7.03 (m, 8H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.45 (t, *J* = 8.7 Hz, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 3.85 (t, *J* = 8.7 Hz, 1H), 3.53 (t, *J* = 9.6 Hz, 1H), 2.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.41, 172.75, 150.71, 148.76, 141.93, 137.02, 135.70, 135.60, 133.96, 133.16, 129.93, 128.55, 127.44, 126.98, 126.04, 123.54, 123.24, 122.58, 122.27, 121.34, 118.24, 112.74, 112.38, 109.57, 76.65, 64.58, 55.38, 44.08, 43.10, 34.95 ppm; ESI MS m/z = 538 $[M+H]^+$; Anal. Calculated for $C_{34}H_{27}N_5O_2$: C, 75.96; H, 5.06; N, 13.03. Found: C, 75.92; H, 5.10; N, 14.13.06.

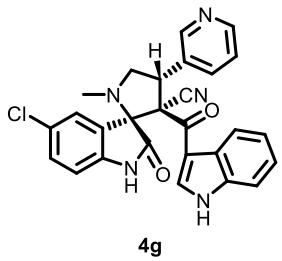
5-fluoro-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4f)



4f

The compound is prepared according to the general procedure. Colourless solid; Yield 84 %; mp 248 ^{o}C; FT-IR (cm^{-1}) Neat; 584, 636, 724, 795, 837, 953, 1020, 1155, 1245, 1038, 1361, 1438, 1485, 1621, 1701, 2797, 2869, 2937, 3262, 3742, 3841; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.94 (s, 1H), 10.52 (s, 1H), 8.67 (d, *J* = 2.1 Hz, 1H), 8.52 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.20 – 8.15 (m, 1H), 7.99 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.59 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.24 (ddd, *J* = 9.2, 7.6, 2.8 Hz, 3H), 6.94 (s, 1H), 6.64 (dd, *J* = 8.6, 4.4 Hz, 1H), 5.48 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.76 – 3.66 (m, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 179.27, 174.10, 159.15, 156.78, 150.63, 148.90, 139.87, 139.85, 136.78, 135.49, 133.88, 133.46, 126.12, 126.05, 125.97, 123.75, 123.41, 122.84, 121.67, 118.84, 117.72, 117.49, 113.02, 112.77, 112.37, 112.35, 111.24, 111.16, 76.59, 76.57, 65.68, 56.04, 42.46, 35.13 ppm; ESI MS m/z = 466 $[M+H]^{+}$; Anal. Calculated for $C_{27}H_{20}FN_5O_2$: C, 69.67; H, 4.33; N, 15.05. Found: C, 69.69; H, 4.35; N, 14.15.01.

5-chloro-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4g)

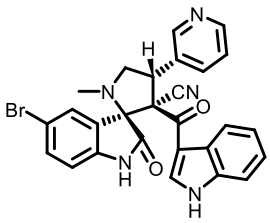


4g

The compound is prepared according to the general procedure. Colourless solid; Yield 90 %; mp 240 ^{o}C; FT-IR (cm^{-1}) Neat; 554, 637, 717, 799, 878, 945, 1011, 1054, 1138, 1187, 1204, 1287, 1345, 1413, 1465, 1516, 1625, 1705, 2676, 2799, 2955, 3742; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.03 (s, 1H), 10.64 (s, 1H), 8.65 (d, *J* = 2.1 Hz, 1H), 8.52 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.16 (dt, *J* = 7.2, 3.6 Hz, 1H), 7.99 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.77 (d, *J* = 2.2 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.39 (dd, *J* = 6.1, 2.9 Hz, 1H), 7.22 (dq, *J* = 7.0, 3.9 Hz, 2H), 6.90 (s, 1H), 6.66 (d, *J* = 8.3

Hz, 1H), 5.43 (dd, *J* = 10.1, 7.0 Hz, 1H), 3.70 (p, *J* = 9.4 Hz, 2H), 2.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.35, 173.84, 150.66, 148.97, 142.57, 136.80, 135.53, 133.79, 133.41, 130.96, 126.39, 126.12, 126.10, 125.23, 123.80, 123.45, 122.89, 121.67, 118.86, 112.40, 112.34, 111.69, 76.31, 65.80, 55.55, 42.58, 35.12. ppm; ESI MS m/z = 482 $[M+H]^+$; Anal. Calculated for $C_{27}H_{20}ClN_5O_2$: C, 67.29; H, 4.18; N, 14.53. Found: C, 67.31; H, 4.16; N, 14.14.50.

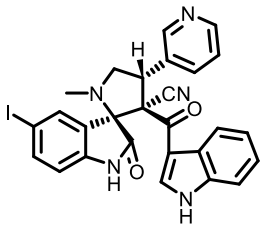
5-bromo-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4h)



4h

The compound is prepared according to the general procedure. Colourless solid; Yield 88 %; mp 260 ^{o}C; FT-IR (cm^{-1}) Neat; 633, 732, 796, 934, 1052, 1150, 1237, 1312, 1360, 1428, 1513, 1618, 1723, 2671, 2800, 3294; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 10.94 (s, 1H), 8.60 (d, *J* = 73.6 Hz, 2H), 8.21 – 7.87 (m, 3H), 7.54 – 7.08 (m, 6H), 6.51 (d, *J* = 7.9 Hz, 1H), 5.32 (s, 1H), 3.79 (t, *J* = 8.1 Hz, 1H), 3.52 (d, *J* = 8.8 Hz, 1H), 2.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.71, 173.88, 150.56, 148.71, 140.82, 136.93, 135.68, 133.60, 133.00, 132.64, 129.34, 125.98, 125.80, 123.55, 123.22, 122.62, 121.24, 118.12, 113.67, 112.90, 112.26, 111.65, 76.86, 64.48, 55.25, 44.11, 34.88 ppm; ESI MS m/z = 526 [M+H]+; Anal. Calculated for $C_{27}H_{20}BrN_5O_2$: C, 61.61; H, 3.83; N, 13.30. Found: C, 61.64; H, 3.80; N, 13.32.

3'-(1H-indole-3-carbonyl)-5-iodo-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4i)

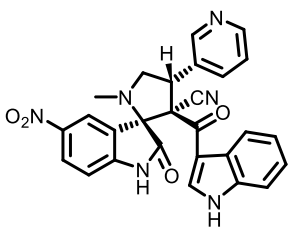


4i

The compound is prepared according to the general procedure. Colourless solid; Yield 80 %; mp 228 ^{o}C; FT-IR (cm^{-1}) Neat; 549, 633, 705, 745, 803, 875, 944, 1031, 1135, 1233, 1312, 1423, 1469, 1515, 1643, 1723, 2318, 2857, 3131, 3360, 3742, 3840; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 10.95 (s, 1H), 8.73 – 8.67 (m, 1H), 8.54 – 8.47 (m, 1H), 8.10 (d, *J* = 3.4 Hz, 1H),

8.04 – 7.99 (m, 1H), 7.94 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.33 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.25 – 7.15 (m, 3H), 6.41 (d, *J* = 8.2 Hz, 1H), 5.30 (t, *J* = 8.7 Hz, 1H), 3.80 (t, *J* = 9.1 Hz, 1H), 3.50 (t, *J* = 9.2 Hz, 1H), 2.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.82, 173.80, 150.55, 148.74, 141.29, 138.45, 136.99, 135.70, 134.78, 133.53, 133.05, 126.13, 126.01, 123.58, 123.29, 122.67, 121.36, 118.29, 113.00, 112.28, 112.08, 84.86, 76.75, 64.43, 55.34, 44.18, 34.92 ppm; ESI MS m/z = 574 [M+H]+; Anal. Calculated for $C_{27}H_{20}IN_5O_2$: C, 56.56; H, 3.52; N, 12.21. Found: C, 56.59; H, 3.49; N, 12.25.

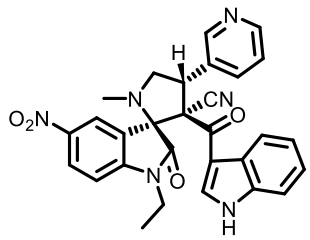
3'-(1H-indole-3-carbonyl)-1'-methyl-5-nitro-2-oxo-4'-(pyridin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4j)



4j

The compound is prepared according to the general procedure. Colourless solid; Yield 78 %; mp 240 ºC; FT-IR (cm^{-1}) Neat; 639, 743, 798, 1093, 1158, 1241, 1338, 1433, 1519, 1635, 1735, 2857, 2929, 3257, 3613, 3742, 3840; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.53 (s, 1H), 8.68 (s, 1H), 8.52 (d, *J* = 3.6 Hz, 1H), 8.11 (d, *J* = 2.9 Hz, 1H), 7.96 – 7.84 (m, 4H), 7.47 – 7.36 (m, 2H), 7.20 – 7.14 (m, 1H), 7.12 – 7.06 (m, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 5.31 (t, *J* = 8.7 Hz, 1H), 3.86 (t, *J* = 9.4 Hz, 1H), 3.59 (t, *J* = 8.9 Hz, 1H), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.87, 174.98, 150.44, 148.93, 147.96, 142.08, 136.99, 135.69, 133.27, 132.70, 126.92, 125.89, 125.13, 123.77, 123.45, 122.75, 121.97, 120.96, 118.14, 113.22, 112.40, 110.16, 76.50, 64.71, 55.39, 44.47, 34.94 ppm; ESI MS m/z = 493 [M+H]+; Anal. Calculated for $C_{27}H_{20}N_6O_4$: C, 65.85; H, 4.09; N, 17.06. Found: C, 65.81; H, 4.11; N, 17.10.

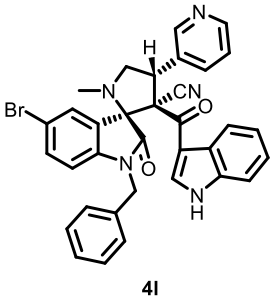
1-ethyl-3'-(1H-indole-3-carbonyl)-1'-methyl-5-nitro-2-oxo-4'-(pyridin-3-yl)spiro [indoline-3,2'-pyrrolidine]-3'-carbonitrile (4k)



4k

The compound is prepared according to the general procedure. Colourless solid; Yield 80 %; mp 248 ^{o}C; FT-IR (cm^{-1}) Neat; 631, 708, 745, 804, 952, 1020, 1074, 1150, 1231, 1328, 1424, 1505, 1603, 1725, 2869, 3203; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.71 – 8.67 (m, 1H), 8.55 – 8.51 (m, 1H), 8.03 (s, 1H), 8.00 – 7.92 (m, 3H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 5.33 (t, *J* = 8.7 Hz, 1H), 3.88 (t, *J* = 9.4 Hz, 1H), 3.75 (dp, *J* = 14.2, 7.2 Hz, 3H), 3.62 (d, *J* = 8.9 Hz, 1H), 2.09 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.65, 172.92, 150.42, 148.91, 147.90, 142.39, 136.93, 135.66, 133.12, 132.58, 126.86, 125.78, 124.66, 123.72, 123.40, 122.66, 121.61, 120.79, 117.87, 113.21, 112.39, 109.12, 75.90, 64.78, 55.42, 44.41, 35.12, 34.82, 12.18 ppm; ESI MS m/z = 521 [M+H]+; Anal. Calculated for $C_{29}H_{24}N_6O_4$: C, 66.91; H, 4.65; N, 16.14. Found: C, 65.88; H, 4.67; N, 16.11.

1-benzyl-5-bromo-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)spiro [indoline-3,2'-pyrrolidine]-3'-carbonitrile (4l)

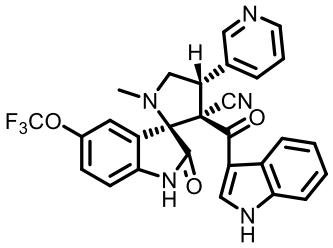


4l

The compound is prepared according to the general procedure. Colourless solid; Yield 85 %; mp 210 ^{o}C; FT-IR (cm^{-1}) Neat; 641, 709, 748, 803, 1074, 1157, 1233, 1331, 1431, 1505, 1638, 1730, 3198; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.62 (d, *J* = 80.5 Hz, 2H), 8.04 (d, *J* = 47.9 Hz, 3H), 7.50 (d, *J* = 38.2 Hz, 3H), 7.17 (t, *J* = 23.7 Hz, 8H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.39 (d, *J* = 9.3 Hz, 1H), 4.84 (dd, *J* = 115.9, 15.9 Hz, 2H), 4.04 – 3.48 (m, 2H), 2.04 (s, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 180.34, 172.35, 150.62, 148.78, 141.21, 136.98, 135.74, 135.23, 133.80, 132.90, 132.72, 129.36, 128.60, 127.54, 126.96, 125.97, 124.92, 123.66, 123.26, 122.73, 121.30, 118.03, 114.79,

112.91, 112.43, 111.40, 76.64, 64.59, 55.28, 44.17, 43.16, 34.96 ppm; ESI MS m/z = 616 [M+H]+; Anal. Calculated for $C_{34}H_{26}BrN_5O_2$: C, 66.24; H, 4.29; N, 11.36. Found: C, 66.26; H, 4.67; N, 11.33.

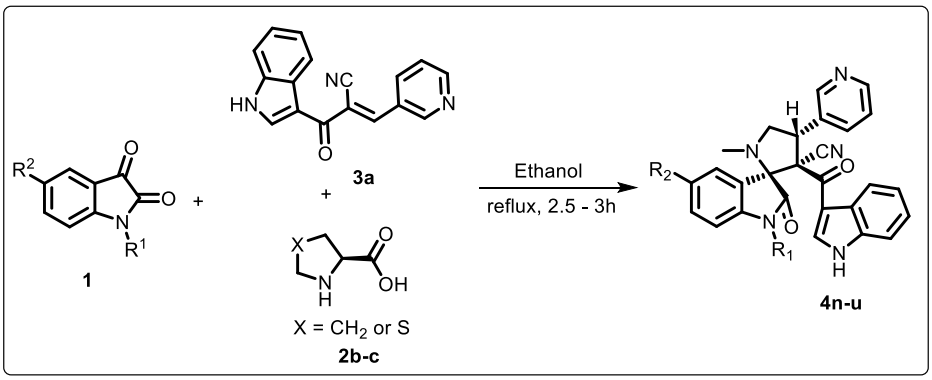
3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(pyridin-3-yl)-5-(trifluoromethoxy)spiro [indoline-3,2'-pyrrolidine]-3'-carbonitrile (4m)



4m

The compound is prepared according to the general procedure. Colourless solid; Yield 78 %; mp 218 ^oC; FT-IR (cm^{-1}) Neat; 556, 630, 718, 791, 1184, 1233, 1427, 1484, 1635, 1713, 3287; ^1H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 10.70 (s, 1H), 8.65 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.17 (dp, *J* = 7.2, 4.1, 3.7 Hz, 1H), 8.00 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.74 (dd, *J* = 2.6, 1.2 Hz, 1H), 7.45 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.23 (dd, *J* = 6.1, 3.1 Hz, 2H), 6.91 (d, *J* = 3.4 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 5.45 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.78 – 3.66 (m, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.31, 174.11, 150.65, 148.96, 142.73, 136.77, 135.56, 133.55, 133.25, 126.06, 125.89, 124.35, 123.79, 123.41, 122.89, 121.67, 118.77, 118.65, 112.44, 112.39, 111.18, 76.29, 65.79, 55.44, 42.55, 35.05 ppm; ESI MS m/z = 532 [M+H]+; Anal. Calculated for $C_{28}H_{20}F_3N_5O_3$: C, 63.28; H, 3.79; N, 13.18. Found: C, 63.25; H, 3.83; N, 13.15.

4. General procedure for the synthesis of spirooxindole-pyrrolidine derivatives (4n-u)

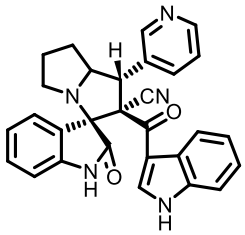


1 **3a** **2b-c** **4n-u**

In an oven-dried 50 ml round bottom flask fixed with a reflux condenser were added mixture of substituted a mixture of substituted isatin **1** (1.0 mmol), L-proline **2b** or thioproline **2c** (1.0 mmol) and (E)-2-(1H-indole-3-carbonyl)-3-(quinolin-3-yl)acrylonitrile **3a** (1.0 mmol) in ethanol (5.0 mL) were refluxed for 2.5 to 3 hours. After completion of the reaction, as evidenced by TLC analysis, the reaction mixture was poured into ice water, the resulting solid was filtered off, and the solid was washed with cold ethanol to afford pure spirooxindole-pyrrolidine compounds in nature of colourless solid (**4n-u**).

5. Spectral data for synthesised compound (4n-u)

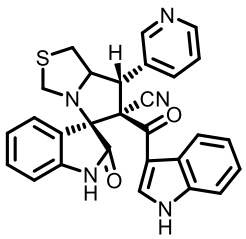
2'-(1H-indole-3-carbonyl)-2-oxo-1'-(pyridin-3-yl)-1',2',5',6',7',7a'-hexahydrospiro [indoline-3,3'-pyrrolizine]-2'-carbonitrile (4n)



4n

The compound is prepared according to the general procedure. Colourless solid; Yield 85 %; mp 202 ºC; FT-IR (cm^{-1}) Neat; 588, 620, 770, 815, 861, 888, 971, 1072, 1122, 1200, 1270, 1315, 1381, 14732, 1543, 1618, 1671, 1738, 1943, 2048, 2098, 2161, 2267, 2528, 2853, 2922; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 10.47 (s, 1H), 8.78 (d, *J* = 2.0 Hz, 1H), 8.49 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.13 (dq, *J* = 7.1, 3.5 Hz, 1H), 8.07 – 8.02 (m, 1H), 7.92 (d, *J* = 6.9 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.20 (dt, *J* = 6.0, 3.5 Hz, 2H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.53 (d, *J* = 7.3 Hz, 1H), 5.11 (d, *J* = 9.7 Hz, 1H), 4.33 (td, *J* = 9.4, 9.0, 5.6 Hz, 1H), 2.76 – 2.62 (m, 1H), 2.58 – 2.52 (m, 1H), 2.22 – 2.12 (m, 1H), 2.03 – 1.82 (m, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.06, 175.05, 151.00, 148.80, 142.57, 136.72, 135.44, 133.79, 131.61, 130.74, 126.75, 126.01, 125.33, 123.61, 123.27, 122.71, 122.07, 121.64, 118.83, 112.37, 112.20, 109.98, 76.46, 69.01, 66.96, 48.30, 47.62, 31.12, 29.03 ppm; ESI MS m/z = 474 [M+H]+; Anal. Calculated for $C_{29}H_{23}N_5O_2$: C, 73.56; H, 4.90; N, 14.79. Found: C, 73.58; H, 4.87; N, 14.84.

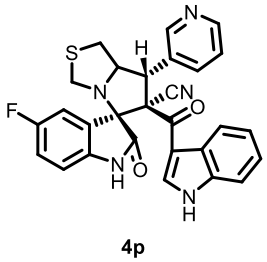
6'-(1H-indole-3-carbonyl)-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4o)



4o

The compound is prepared according to the general procedure. Colourless solid; Yield 96 %; mp 198 ^{o}C; FT-IR (cm^{-1}) Neat; 587, 342, 735, 913, 1121, 1185, 1242, 1324, 1423, 1520, 1648, 1724, 2938, 3186, 3304; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 10.79 (s, 1H), 8.94 (s, 1H), 8.53 (d, *J* = 4.1 Hz, 1H), 8.15 (dd, *J* = 13.9, 5.8 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.18 – 7.11 (m, 1H), 7.08 – 7.01 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 4.69 (dt, *J* = 16.4, 6.6 Hz, 2H), 3.85 (d, *J* = 10.6 Hz, 1H), 3.32 (s, 1H), 3.20 – 3.13 (m, 1H), 3.06 (dd, *J* = 11.5, 2.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.92, 174.92, 151.86, 149.12, 141.82, 137.51, 135.69, 133.73, 130.49, 130.37, 129.52, 125.81, 123.55, 123.11, 122.48, 121.11, 120.93, 120.55, 117.27, 112.46, 112.25, 109.64, 76.00, 69.44, 65.96, 53.44, 50.89, 35.63 ppm; ESI MS m/z = 492 $[M+H]^{+}$; Anal. Calculated for $C_{28}H_{21}N_5O_2S$: C, 68.42; H, 4.31; N, 14.25; S, 6.52. Found: C, 68.39; H, 4.32; N, 14.23; S, 6.54.

5-fluoro-6'-(1H-indole-3-carbonyl)-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4p)

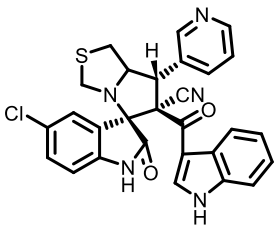


4p

The compound is prepared according to the general procedure. Colourless solid; Yield 88 %; mp 188 ^{o}C; FT-IR (cm^{-1}) Neat; 636, 707, 749, 879, 926, 1141, 1194, 1245, 1312, 1364, 1419, 1483, 1578, 1632, 1731, 3069, 3124, 3228; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (d, *J* = 2.7 Hz, 1H), 10.81 (s, 1H), 8.97 – 8.93 (m, 1H), 8.55 – 8.50 (m, 1H), 8.16 (dd, *J* = 10.9, 5.8 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.58 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.19 – 7.13 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.90 (td, *J* = 9.1, 2.5 Hz, 1H), 6.43 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.75 – 4.64 (m, 2H), 3.87 (d, *J* = 10.9 Hz, 1H), 3.38 (d, *J* = 10.8 Hz, 1H), 3.19 – 3.10 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6)

δ 179.78, 174.81, 158.05, 151.88, 149.13, 138.15, 137.55, 135.71, 133.86, 130.23, 125.78, 123.64, 123.07, 122.61, 122.25, 122.17, 120.99, 117.38, 117.28, 117.12, 117.05, 112.45, 112.32, 110.38, 110.30, 76.36, 69.35, 65.95, 53.56, 50.72, 35.61 ppm; ESI MS m/z = 510 [M+H]+; Anal. Calculated for $C_{28}H_{20}FN_5O_2S$: C, 66.00; H, 3.96; N, 13.74; S, 6.29 Found: C, 66.02; H, 3.99; N, 13.70; S, 6.32.

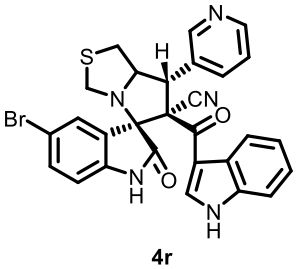
5-chloro-6'-(1H-indole-3-carbonyl)-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4q)



4q

The compound is prepared according to the general procedure. Colourless solid; Yield 93 %; mp 240 °C; FT-IR (cm^{-1}) Neat; 552, 628, 747, 814, 882, 922, 1136, 1244, 1315, 1428, 1473, 1518, 1622, 1728, 3042, 3200; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 10.93 (s, 1H), 8.95 (d, *J* = 1.7 Hz, 1H), 8.56 – 8.50 (m, 1H), 8.15 (dd, *J* = 14.6, 5.7 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.09 (td, *J* = 6.2, 5.4, 2.7 Hz, 2H), 6.44 (d, *J* = 8.3 Hz, 1H), 3.88 – 3.83 (m, 2H), 3.19 – 3.13 (m, 2H), 3.08 (dd, *J* = 10.1, 7.1 Hz, 1H), 2.83 (dd, *J* = 10.1, 6.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.87, 174.61, 172.43, 151.78, 149.15, 140.83, 137.62, 135.72, 133.73, 130.46, 130.16, 129.38, 125.76, 125.03, 123.66, 123.09, 122.61, 122.46, 120.98, 116.98, 112.53, 112.33, 110.99, 76.22, 69.25, 65.91, 65.00, 53.99, 36.11 ppm; ESI MS m/z = 526 [M+H]+; Anal. Calculated for $C_{28}H_{20}ClN_5O_2S$: C, 63.94; H, 3.83; N, 13.31; S, 6.09. Found: C, 63.97; H, 3.80; N, 13.28; S, 6.05.

5-bromo-6'-(1H-indole-3-carbonyl)-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4r)

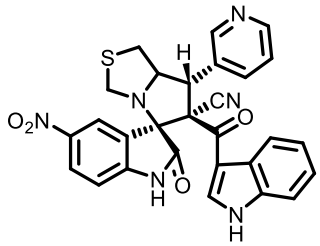


4r

The compound is prepared according to the general procedure. Colourless solid; Yield 90 %; mp 226 °C; FT-IR (cm^{-1}) Neat; 628, 745, 816, 1135, 1172, 1241, 1315, 1425, 1471, 1516, 1627, 1725, 3197; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H),

10.96 (s, 1H), 8.98 (d, J = 2.3 Hz, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 8.24 – 8.14 (m, 2H), 7.82 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.23 – 7.16 (m, 1H), 7.12 (dq, J = 7.1, 2.9, 2.2 Hz, 2H), 6.48 (d, J = 8.3 Hz, 1H), 3.94 – 3.82 (m, 2H), 3.42 (d, J = 11.0 Hz, 1H), 3.19 (t, J = 4.5 Hz, 1H), 3.12 (dd, J = 10.1, 7.1 Hz, 1H), 2.86 (dd, J = 10.1, 6.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.30, 174.04, 171.86, 151.21, 148.57, 140.25, 137.05, 135.15, 133.15, 129.88, 129.59, 128.80, 125.19, 124.46, 123.08, 122.52, 122.03, 121.88, 120.40, 116.41, 111.96, 111.76, 110.41, 75.65, 68.68, 65.34, 64.43, 53.41, 50.26, 35.53 ppm; ESI MS m/z = 570 [M+H]+; Anal. Calculated for $C_{28}H_{20}BrN_5O_2S$: C, 58.95; H, 3.53; N, 12.28; S, 5.62. Found: C, 58.91; H, 3.50; N, 12.30; S, 5.63.

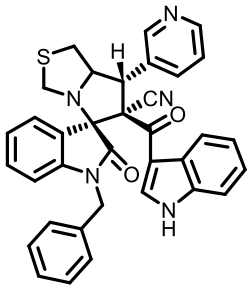
6'-(1H-indole-3-carbonyl)-5-nitro-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4s)



4s

The compound is prepared according to the general procedure. Colourless solid; Yield 78 %; mp 260 ºC; FT-IR (cm^{-1}) Neat; 559, 628, 734, 816, 1138, 1241, 1327, 1418, 1461, 1522, 1634, 1728, 1984, 2188, 2186, 2854, 2918, 3669, 3742, 3845; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 11.51 (s, 1H), 8.93 (d, J = 2.3 Hz, 1H), 8.59 – 8.49 (m, 2H), 8.21 – 8.12 (m, 2H), 7.98 (dd, J = 8.7, 2.3 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.16 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.05 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 3.88 – 3.83 (m, 2H), 3.49 (d, J = 11.3 Hz, 1H), 3.22 – 3.16 (m, 2H), 3.09 (dd, J = 10.1, 7.1 Hz, 1H), 2.83 (dd, J = 10.2, 6.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.91, 175.43, 172.44, 151.60, 149.32, 148.41, 141.18, 137.69, 135.74, 133.64, 129.88, 127.44, 125.66, 124.96, 123.81, 123.24, 122.76, 121.35, 120.73, 116.71, 112.65, 112.44, 110.18, 76.09, 69.07, 65.93, 65.02, 53.97, 36.11 ppm; ESI MS m/z = 537 [M+H]+; Anal. Calculated for $C_{28}H_{20}N_6O_4S$: C, 62.68; H, 3.76; N, 15.66; O, 11.93; S, 5.98. Found: C, 62.65; H, 3.72; N, 15.69; S, 5.95.

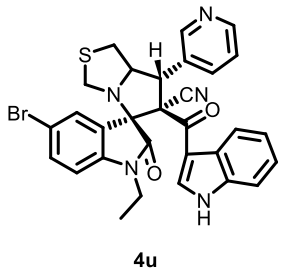
1-benzyl-6'-(1H-indole-3-carbonyl)-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4t)



4t

The compound is prepared according to the general procedure. Colourless solid; Yield 91 %; mp 190 ^{o}C; FT-IR (cm^{-1}) Neat; 549, 631, 684, 742, 820, 874, 961, 1011, 1080, 1131, 1247, 1322, 1367, 1420, 1474, 1520, 1610, 1661, 1715, 3335; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.98 (d, *J* = 3.2 Hz, 1H), 8.48 (d, *J* = 4.0 Hz, 1H), 8.39 (s, 1H), 8.08 (dd, *J* = 22.8, 8.0 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.13 (m, 8H), 6.67 (t, *J* = 6.9 Hz, 3H), 5.20 (dd, *J* = 9.9, 6.3 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 4.66 (s, 1H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.16 (d, *J* = 9.8 Hz, 1H), 3.52 (d, *J* = 9.7 Hz, 1H), 2.89 (dd, *J* = 10.2, 6.3 Hz, 1H), 2.64 (t, *J* = 10.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.82, 174.94, 151.28, 149.29, 143.17, 136.89, 136.34, 135.99, 135.43, 130.56, 130.53, 128.90, 128.43, 127.14, 126.46, 126.04, 125.68, 124.16, 123.25, 122.87, 122.76, 121.34, 120.72, 112.61, 111.47, 109.28, 74.13, 73.50, 54.85, 53.53, 52.21, 42.68, 33.28 ppm; ESI MS m/z = 582 [M+H]+; Anal. Calculated for $C_{35}H_{27}N_5O_2S$: C, 72.27; H, 4.68; N, 12.04; O, 5.50; S, 5.51. Found: C, 72.30; H, 4.62; N, 12.01; S, 5.53.

5-bromo-1-ethyl-6'-(1H-indole-3-carbonyl)-2-oxo-7'-(pyridin-3-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazole]-6'-carbonitrile (4u)

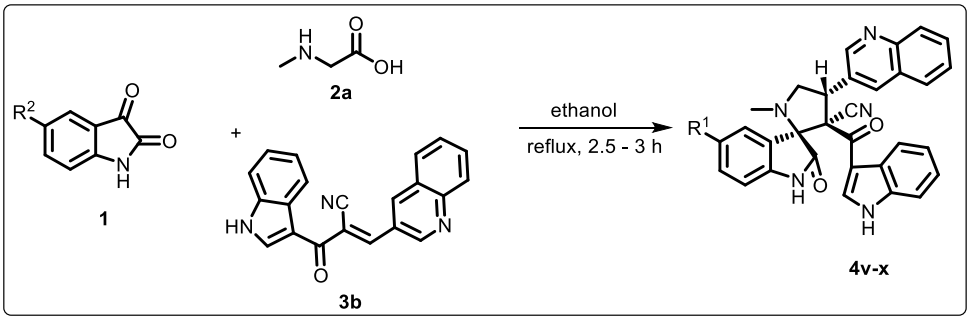


4u

The compound is prepared according to the general procedure. Colourless solid; Yield 78 %; mp 204 ^{o}C; FT-IR (cm^{-1}) Neat; 553, 638, 743, 806, 874, 924, 1048, 1110, 1177, 1239, 1347, 1435, 1629, 1721, 1983, 2148, 2681, 2847, 3041; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.95 (s, 1H), 8.54 (s, 1H), 8.19 – 7.74 (m, 3H), 7.48 – 7.27 (m, 3H), 7.11 (dt, J = 30.7, 7.5 Hz, 2H), 6.65 (d, J = 8.4 Hz, 1H), 4.82 – 4.58 (m, 2H), 4.12 (dd, J = 74.7, 8.8 Hz, 1H), 3.82 (d, J = 11.3 Hz, 2H), 3.45 – 3.30 (m, 5H), 1.06 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.80, 172.40, 151.75, 149.18, 141.68, 137.64, 135.68, 133.54,

133.34, 131.90, 130.10, 125.66, 123.69, 123.11, 122.55, 122.35, 120.85, 116.85, 113.41, 112.63, 112.32, 110.46, 75.73, 69.15, 53.80, 50.84, 35.67, 34.89, 18.52, 11.78 ppm; ESI MS m/z = 598 [M+H]+; Anal. Calculated for $C_{30}H_{24}BrN_5O_2S$: C, 60.20; H, 4.04; N, 11.70; S, 5.36. Found: C, 60.22; H, 4.00; N, 11.66; S, 5.33.

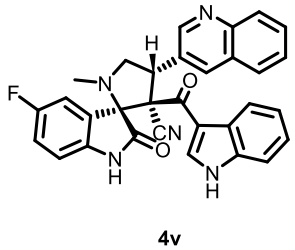
6. General procedure for synthesis of spirooxindole-pyrrolidine derivatives (4v-x)



In an oven-dried 50 ml, round bottom flask fixed with a reflux condenser were added a mixture of substituted isatin **1a** (1.00 mmol), sarcosine **2a** (1.00 mmol) and (E)-2-(1H-indole-3-carbonyl)-3-(quinolin-3-yl) acrylonitrile **3b** (1.00 mmol) in ethanol (5.00 mL) for refluxed 2.5 to 3 hours. After completion of the reaction, as evidenced by TLC analysis, the reaction mixture was poured into ice water, and the resulting solid was filtered off. The solid was washed with ethanol to afford pure quinoline appended spirooxindole-pyrrolidine derivative with moderate to good yields (**4v-x**) in nature of colourless solid.

7. Spectral data for synthesized compound (4v-x)

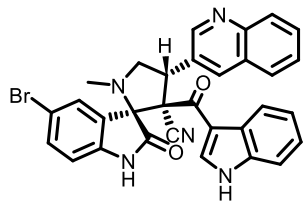
5-fluoro-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(quinolin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4v)



The compound is prepared according to the general procedure. Colourless solid; Yield 90 %; mp 210 ^{o}C; FT-IR (cm^{-1}) Neat; 591, 645, 712, 785, 805, 870, 955, 1131, 1188, 1244, 1359, 1420, 1479, 1624, 1725, 3399; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 10.54 (s, 1H), 8.98 (d, *J* = 2.2 Hz, 1H), 8.60 (d, *J* = 2.3 Hz, 1H), 8.24 – 8.17 (m, 1H), 8.09 – 7.98 (m, 2H), 7.77 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.62 (td, *J* = 8.4, 2.0 Hz, 2H), 7.37 (dt, *J*

= 6.7, 2.8 Hz, 1H), 7.28 – 7.19 (m, 3H), 6.93 (s, 1H), 6.64 (dd, *J* = 8.6, 4.3 Hz, 1H), 5.69 (dd, *J* = 10.4, 6.6 Hz, 1H), 3.89 (dd, *J* = 9.4, 6.6 Hz, 1H), 3.79 (t, *J* = 9.9 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.26, 174.03, 159.14, 156.77, 151.81, 146.99, 139.84, 136.13, 135.45, 133.84, 130.96, 129.70, 128.55, 128.23, 127.20, 126.85, 126.10, 125.94, 123.71, 122.80, 121.64, 118.86, 117.73, 117.50, 112.98, 112.73, 112.34, 112.31, 111.24, 111.16, 76.68, 65.98, 55.60, 42.56, 35.16 ppm; ESI MS m/z = 516 [M+H]+; Anal. Calculated for $C_{31}H_{22}FN_5O_2$: C, 72.22; H, 4.30; N, 13.58. Found: C, 72.19; H, 4.27; N, 13.54.

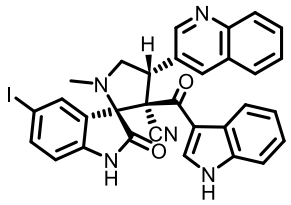
5-bromo-3'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-4'-(quinolin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4w)



4w

The compound is prepared according to the general procedure. Colourless solid; Yield 88 %; mp 236 ^{o}C; FT-IR (cm^{-1}) Neat; 540, 647, 700, 747, 777, 807, 883, 976, 1145, 1240, 1327, 1425, 1459, 1508, 1616, 1653, 1717, 2852, 3039, 3313; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 10.98 (s, 1H), 9.03 (s, 1H), 8.54 (s, 1H), 8.26 – 7.92 (m, 4H), 7.80 – 7.39 (m, 4H), 7.18 (dt, *J* = 13.9, 7.4 Hz, 3H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.56 (t, *J* = 8.5 Hz, 1H), 3.97 (t, *J* = 8.8 Hz, 1H), 3.60 (t, *J* = 9.4 Hz, 1H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.75, 173.83, 151.83, 146.93, 140.84, 136.27, 135.68, 133.66, 132.68, 130.54, 129.60, 129.40, 128.53, 128.17, 127.20, 126.77, 125.99, 125.71, 123.56, 122.64, 121.24, 118.18, 113.72, 112.89, 112.28, 111.69, 76.96, 64.79, 55.38, 44.27, 34.93 ppm; ESI MS m/z = 576 [M+H]+; Anal. Calculated for $C_{31}H_{22}BrN_5O_2$: C, 64.59; H, 3.85; N, 12.15. Found: C, 64.55; H, 3.87; N, 12.17.

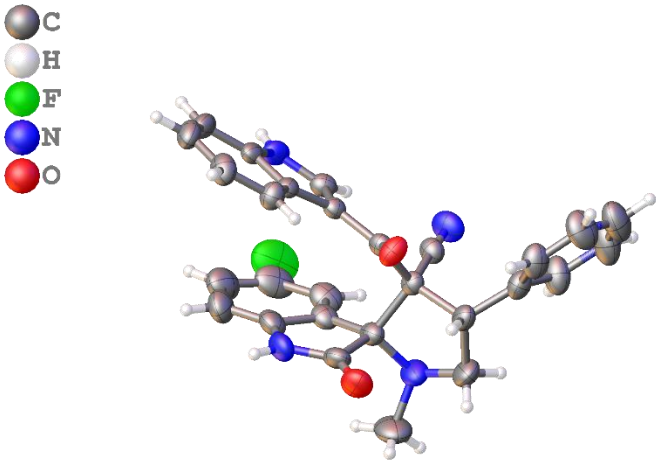
3'-(1H-indole-3-carbonyl)-5-iodo-1'-methyl-2-oxo-4'-(quinolin-3-yl)spiro[indoline-3,2'-pyrrolidine]-3'-carbonitrile (4x)

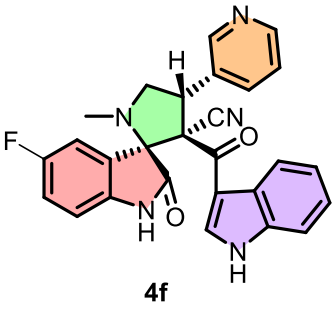


4x

The compound is prepared according to the general procedure. Colourless solid; Yield 75 %; mp 200 ^{o}C; FT-IR (cm^{-1}) Neat; 643, 751, 804, 1141, 1237, 1323, 1421, 1465, 1509, 1637, 1717, 3244; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 10.96 (s, 1H), 9.01 (d, *J* = 2.2 Hz, 1H), 8.52 (d, *J* = 2.3 Hz, 1H), 8.11 – 7.99 (m, 4H), 7.76 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.62 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.34 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.19 (tt, *J* = 7.3, 5.4 Hz, 2H), 6.40 (d, *J* = 8.2 Hz, 1H), 5.51 (t, *J* = 8.6 Hz, 1H), 3.96 (t, *J* = 9.0 Hz, 1H), 3.58 (t, *J* = 9.2 Hz, 1H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 180.86, 173.71, 151.80, 146.92, 141.28, 138.45, 136.26, 135.68, 134.79, 133.53, 130.55, 129.60, 128.54, 128.17, 127.21, 126.78, 126.00, 123.55, 122.63, 121.32, 118.30, 112.97, 112.26, 112.07, 99.47, 84.85, 76.81, 64.70, 55.43, 44.31, 34.92 ppm; ESI MS m/z = 624 $[M+H]^{+}$; Anal. Calculated for $C_{31}H_{22}IN_5O_2$: C, 59.72; H, 3.56; N, 11.23. Found: C, 59.69; H, 3.59; N, 1120.

8. X-ray crystallographic data of compound 4f





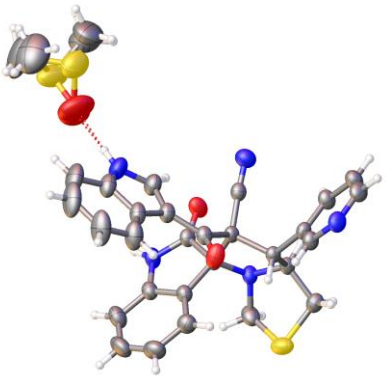
4f

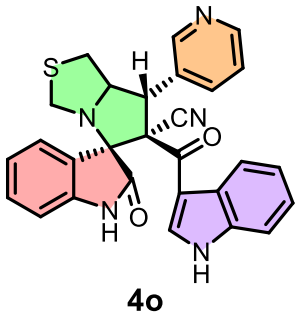
CCDC: **2126489**

Table 1 Crystal data and structure refinement for compound 4f

Parameters	**Compound 4f**
Empirical formula	$C_{27}N_5O_2F_1H_{16}$
Formula weight	465.16
Temperature/K	296.15
Crystal system	orthorhombic
Space group	Pna21
a/Å	16.4758(10)
b/Å	11.0289(8)
c/Å	24.904(2)
α/°	90
β/°	90
γ/°	90
Volume/Å3	4525.3(6)
Z	4
ρcalcg/cm3	1.366
μ/mm-1	0.095
F(000)	1936.0
Crystal size/mm3	0.3 × 0.25 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.27 to 51.066
Index ranges	-19 ≤ h ≤ 19, -13 ≤ k ≤ 13, -30 ≤ l ≤ 30
Reflections collected	51473
Independent reflections	8424 [Rint = 0.0459, Rsigma = 0.0392]
Data/restraints/parameters	8424/1/633
Goodness-of-fit on F2	1.124
Final R indexes [I>=2σ (I)]	R1 = 0.0508, wR2 =0.1236
Final R indexes [all data]	R1 = 0.0841, wR2 = 0.1492
Largest diff. peak/hole / e Å-3	0.27/-0.28
Flack parameter	0.1(4)

9. X-ray crystallographic data of compound 4f





4o

CCDC: **2126948**

Table 2 Crystal data and structure refinement for compound 4f

Parameters	**4o**
Empirical formula	$C_{28}H_{21}N_5O_2S$
Formula weight	491.58
Temperature/K	150
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.6743(8)
b/Å	10.9532(6)
c/Å	17.2489(8)
α/°	90
β/°	104.833(2)
γ/°	90
Volume/Å^3	2862.7(3)
Z	4
ρ_{calc}g/cm^3	1.1405
μ/mm^{-1}	0.144
F(000)	1024.9
Crystal size/mm^3	0.25 × 0.2 × 0.2
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	2.68 to 58.88
Index ranges	$-18 \le h \le 18$, $-13 \le k \le 13$, $-20 \le l \le 20$
Reflections collected	54763
Independent reflections	7870 [R_{int} = 0.0508, R_{sigma} = 0.0450]
Data/restraints/parameters	7870/0/325
Goodness-of-fit on F^2	1.095
Final R indexes [I>=2σ (I)]	R_1 = 0.0649, wR_2 = 0.2050
Final R indexes [all data]	R_1 = 0.1088, wR_2 = 0.2487
Largest diff. peak/hole / e Å^{-3}	0.48/-0.67

10. ^{1}H and ^{13}C NMR spectra of synthesised compounds (4a-x)

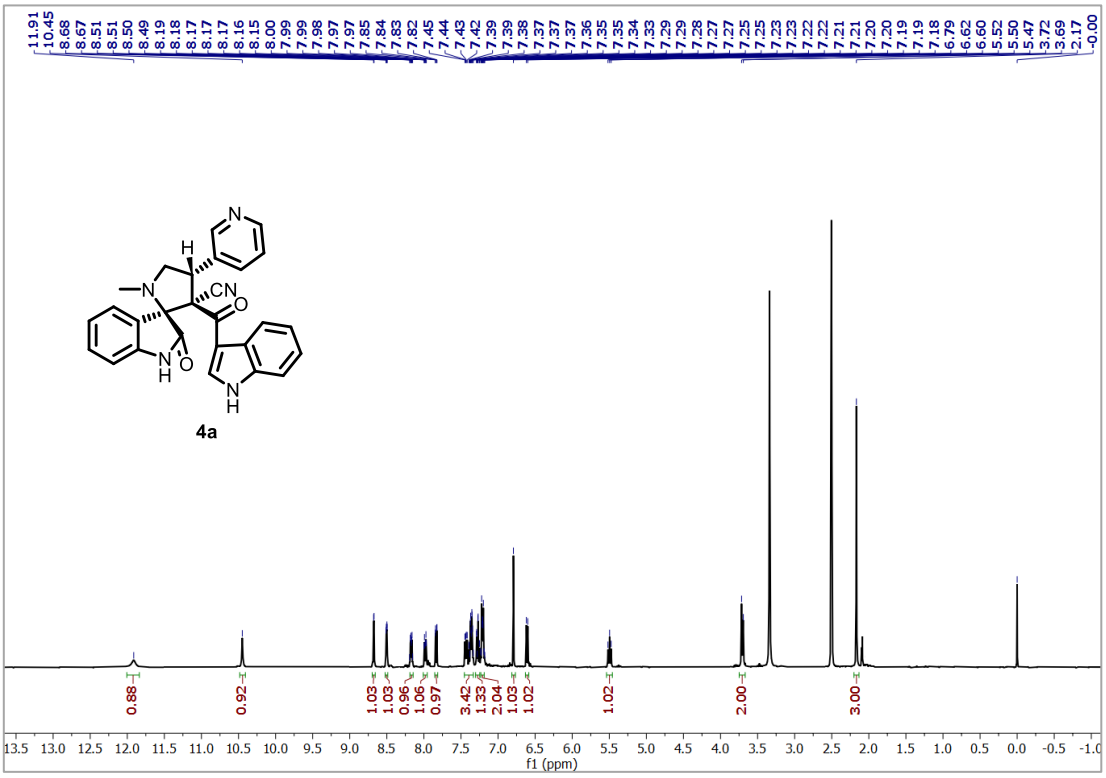


Figure SI-1: ^{1}H NMR spectrum of compound **4a** in DMSO-d_6

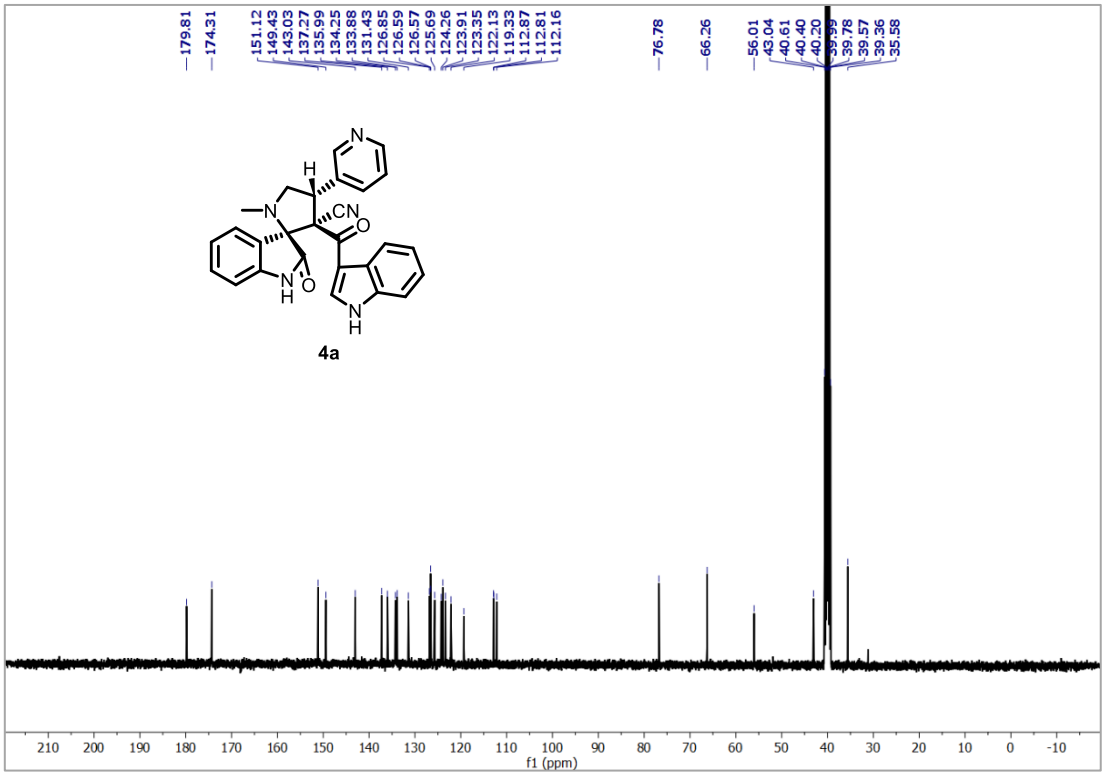


Figure SI-2: ^{13}C NMR spectrum of compound **4a** in DMSO-d_6

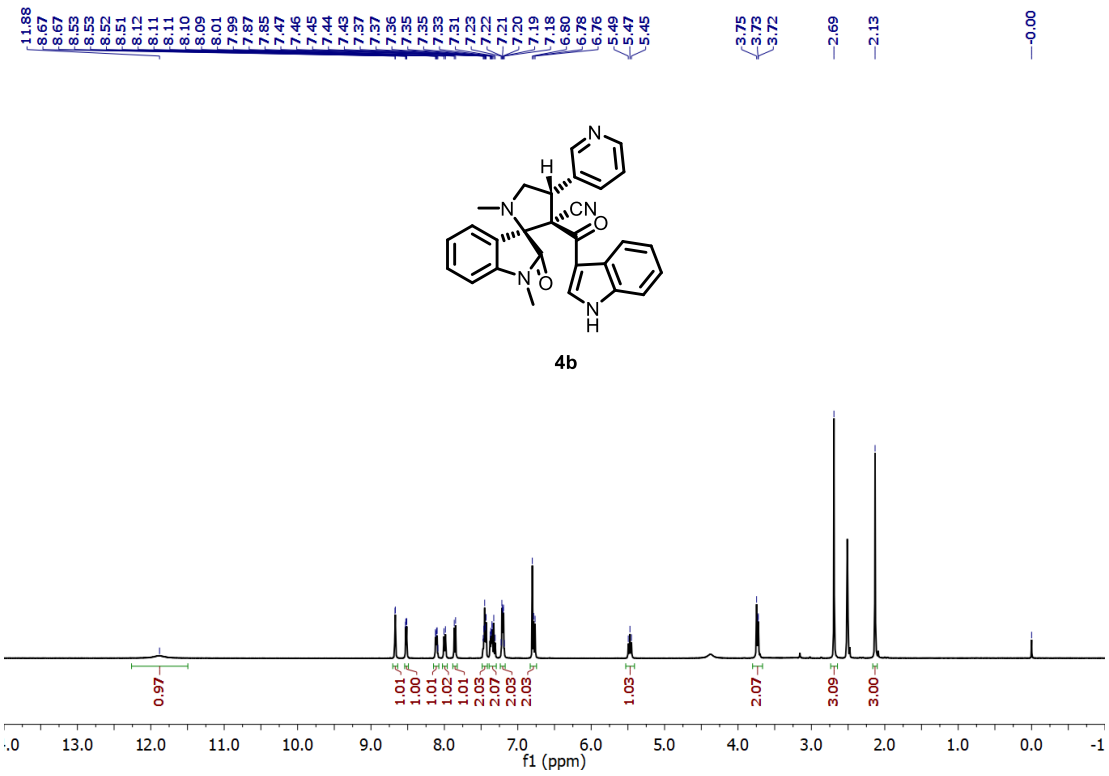


Figure SI-3: ^{1}H NMR spectrum of compound **4b** in DMSO-d$_6$

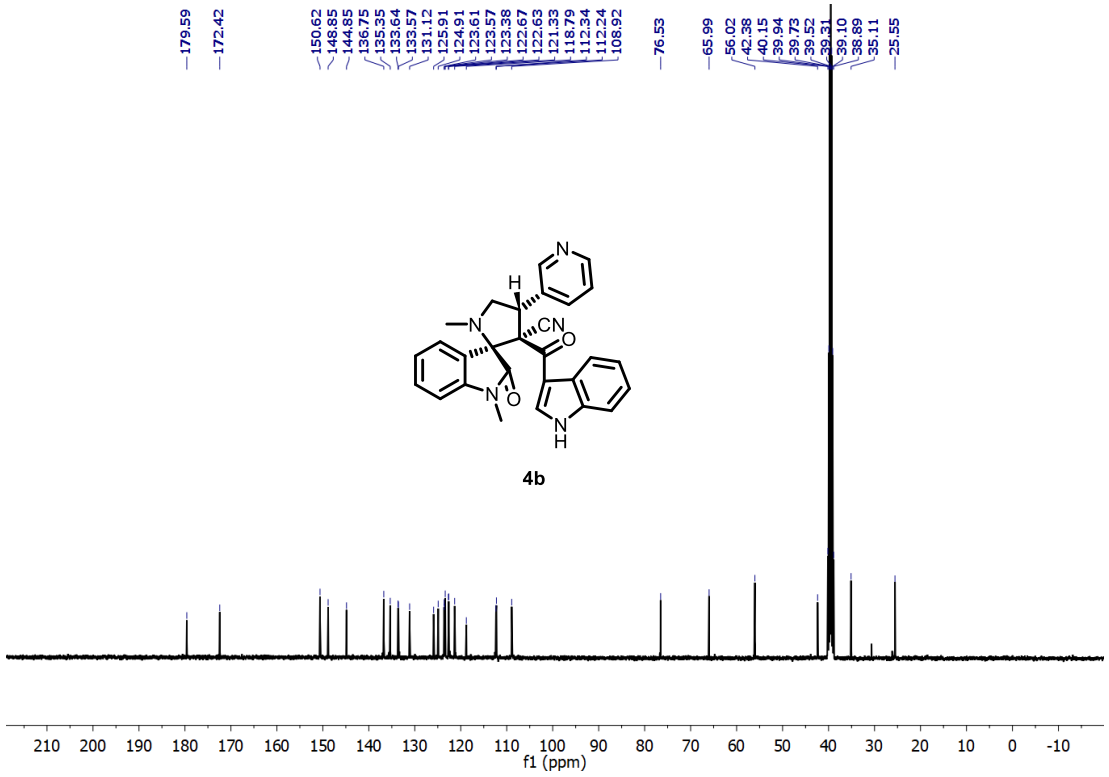


Figure SI-4: ^{13}C NMR spectrum of compound **4b** in DMSO-d$_6$

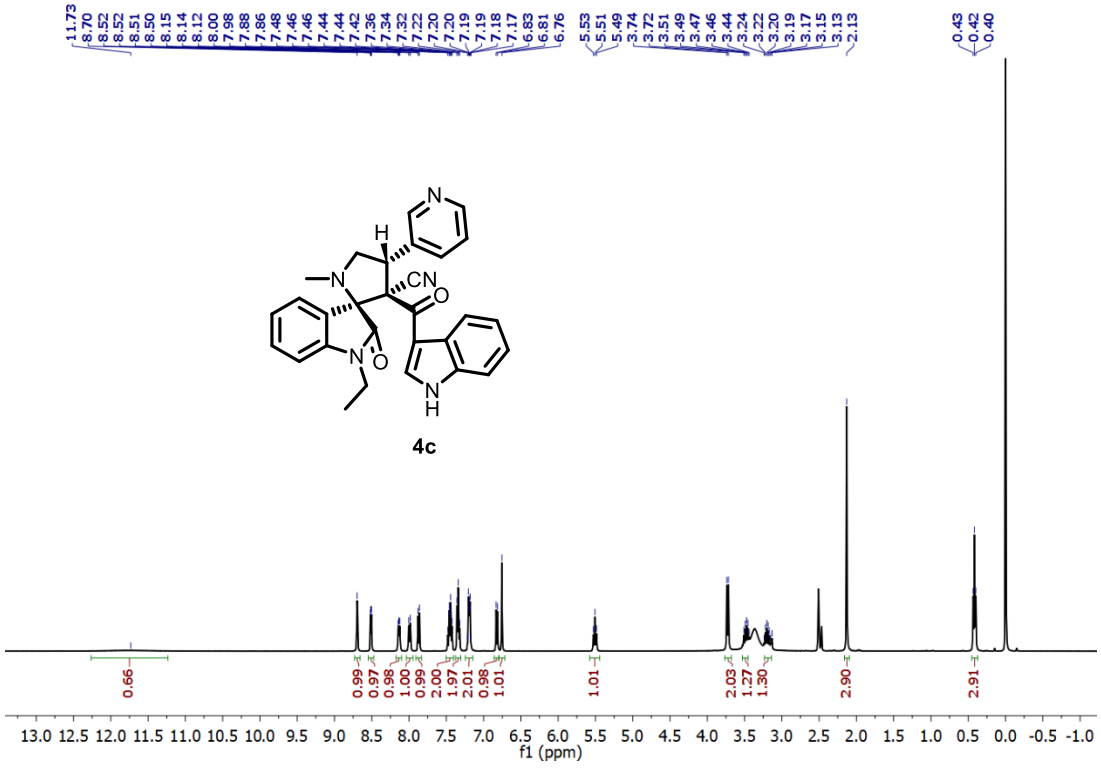


Figure SI-5: ^{1}H NMR spectrum of compound **4c** in DMSO-d$_6$

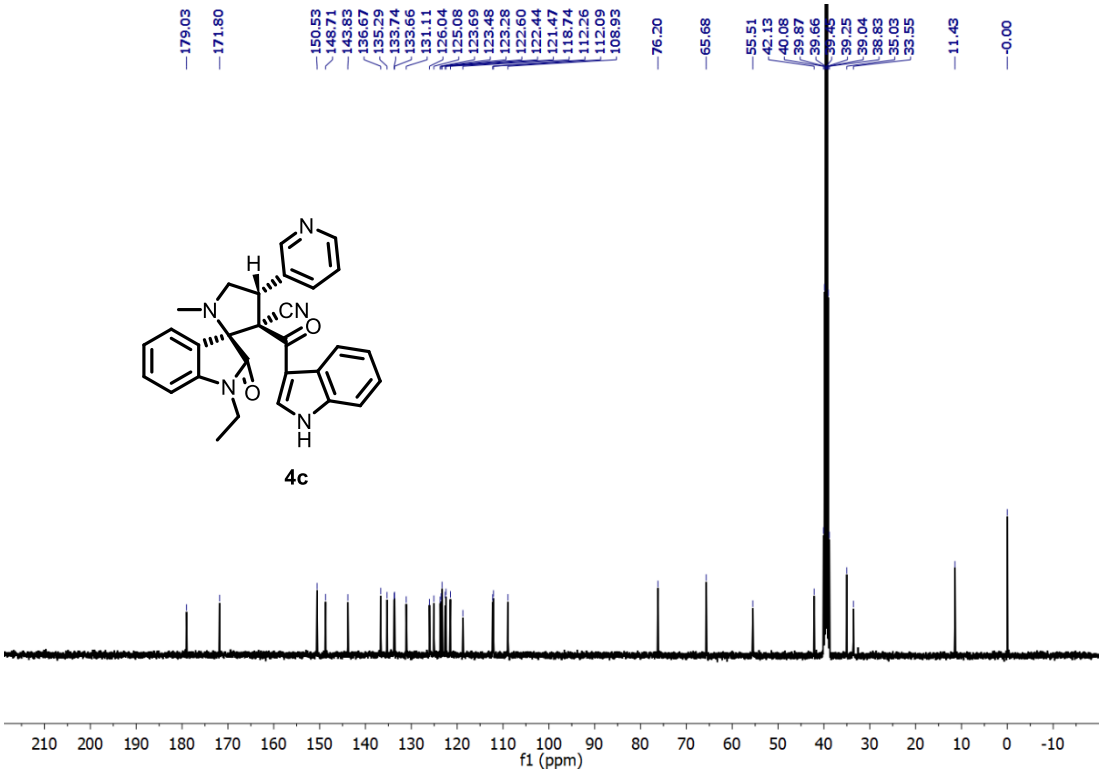


Figure SI-6: ^{13}C NMR spectrum of compound **4c** in DMSO-d$_6$

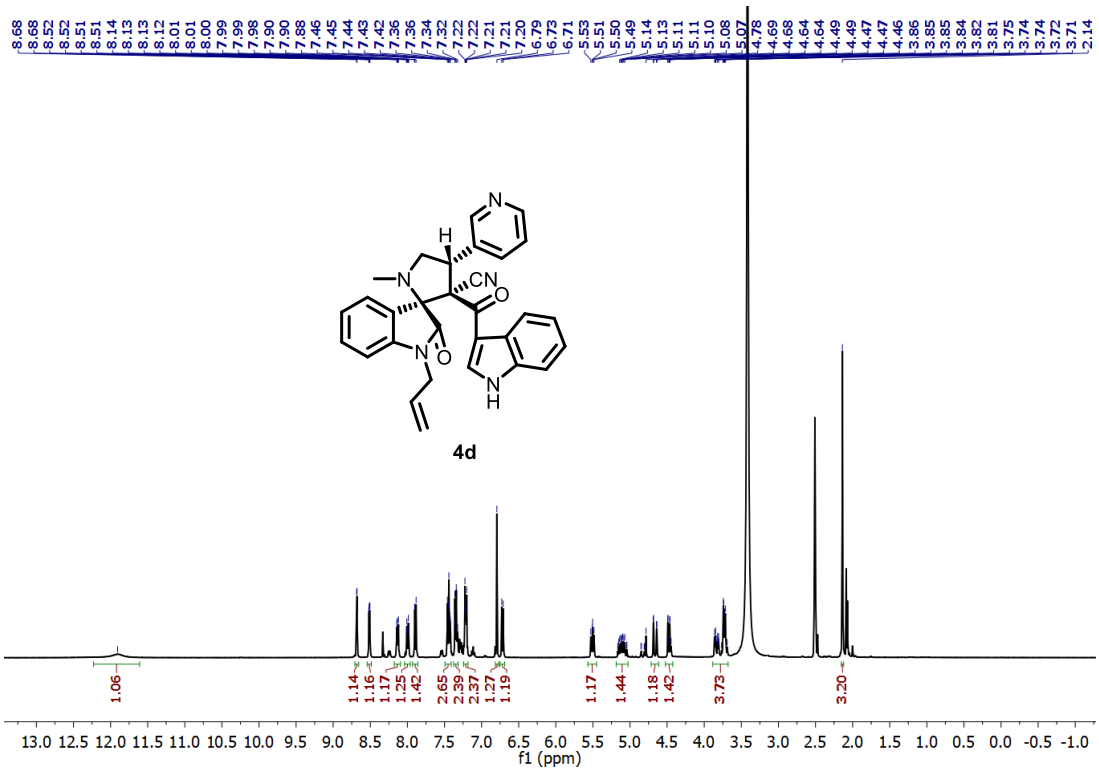


Figure SI-7: ^{1}H NMR spectrum of compound **4d** in DMSO-d$_6$

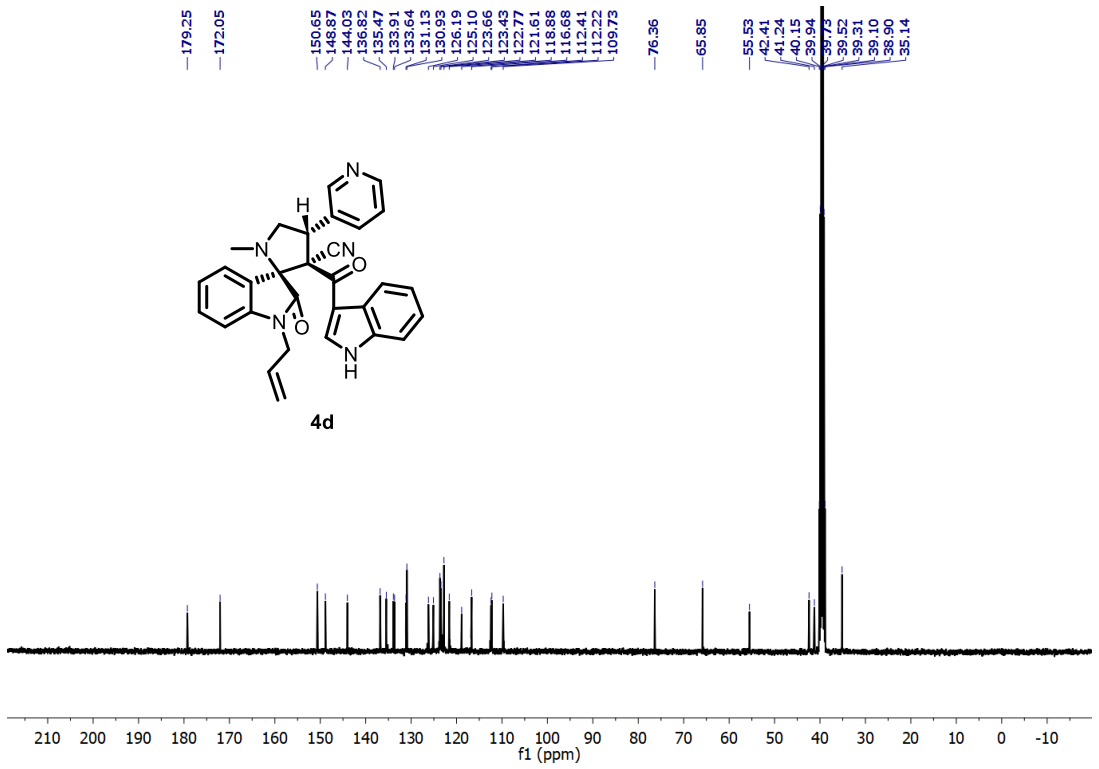


Figure SI-8: ^{13}C NMR spectrum of compound **4d** in DMSO-d$_6$

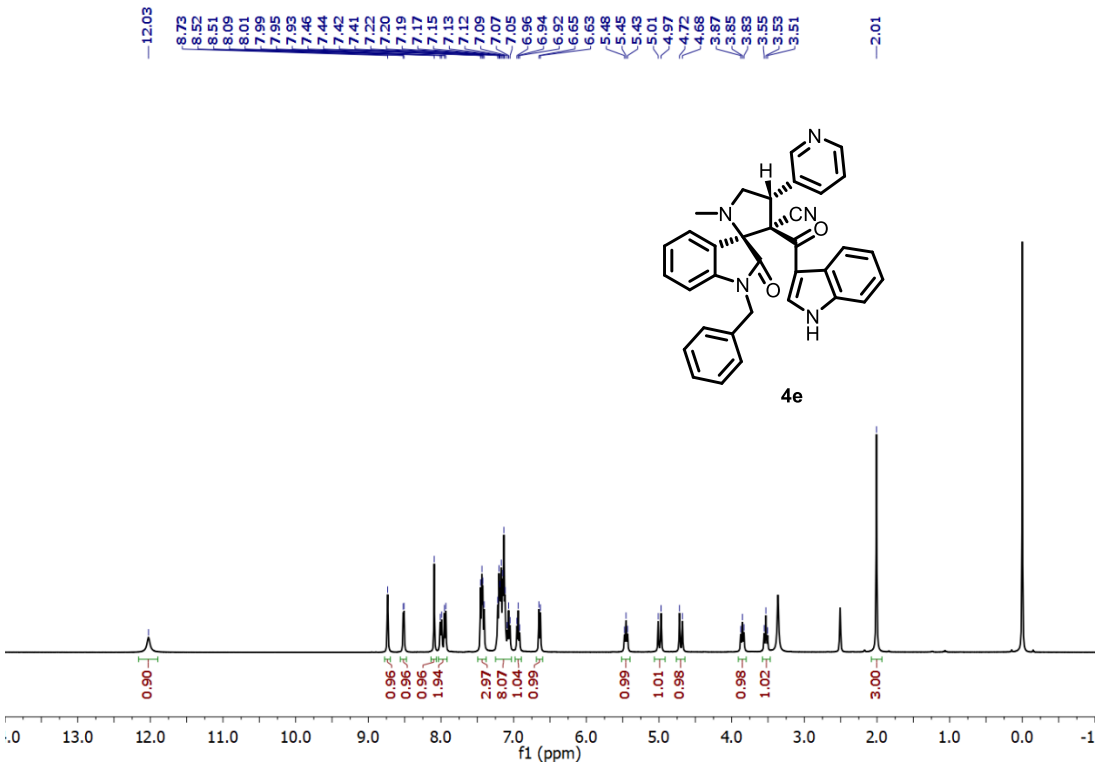


Figure SI-9: ^{1}H NMR spectrum of compound **4e** in DMSO-d_6

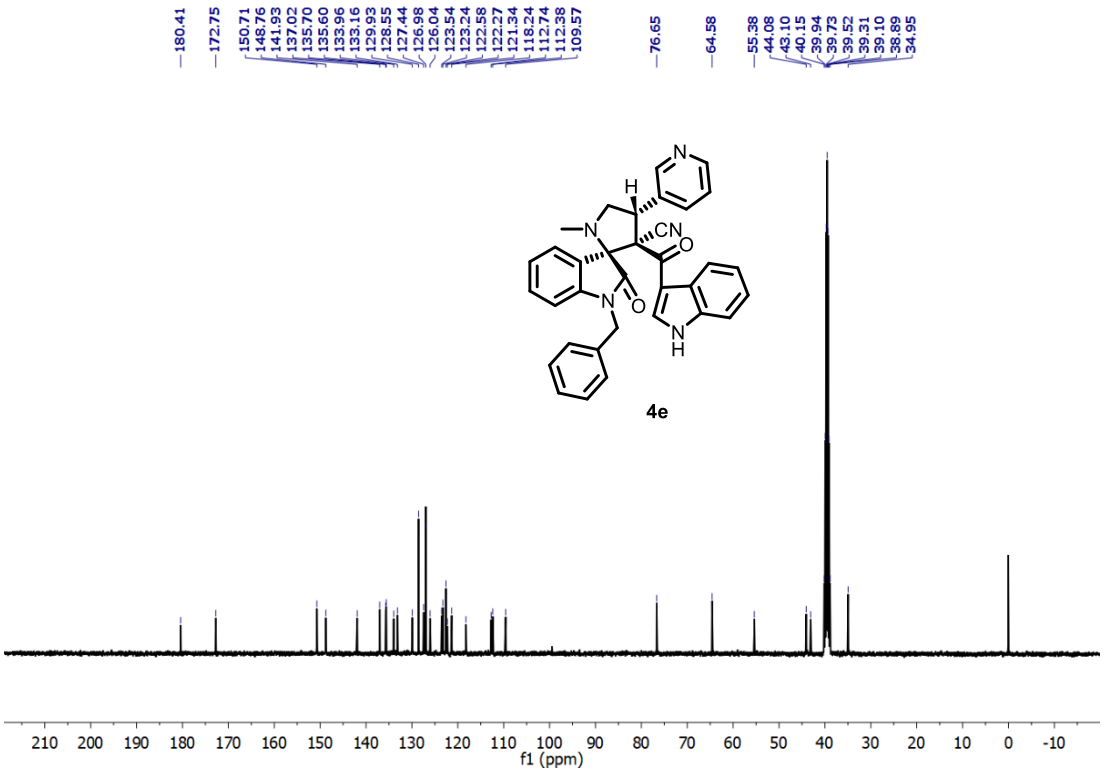


Figure SI-10: ^{13}C NMR spectrum of compound **4e** in DMSO-d_6

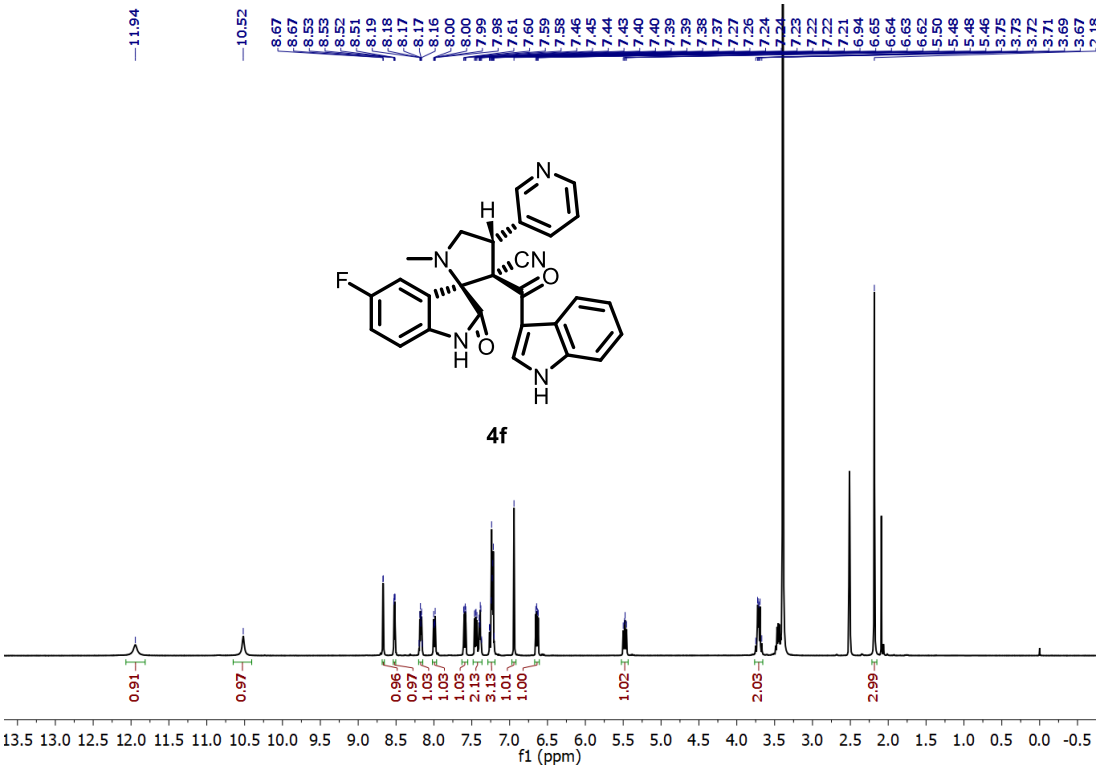


Figure SI-11: ^{1}H NMR spectrum of compound **4f** in DMSO-d_6

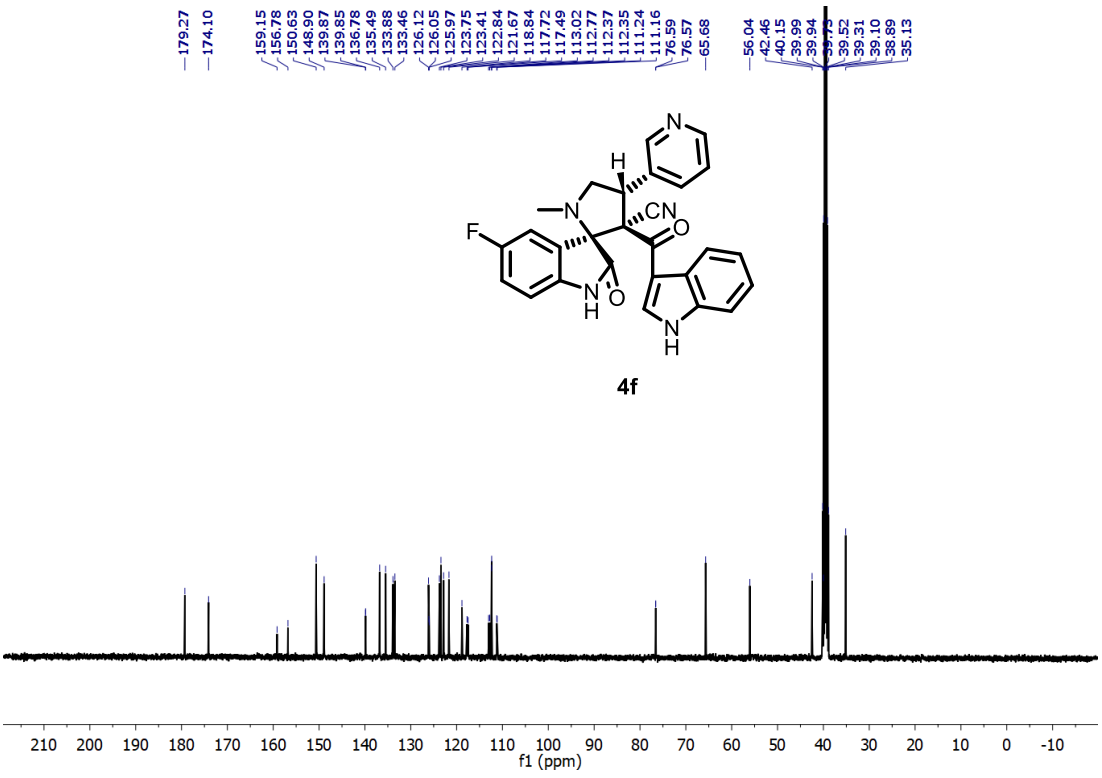


Figure SI-12: ^{13}C NMR spectrum of compound **4f** in DMSO-d$_6$

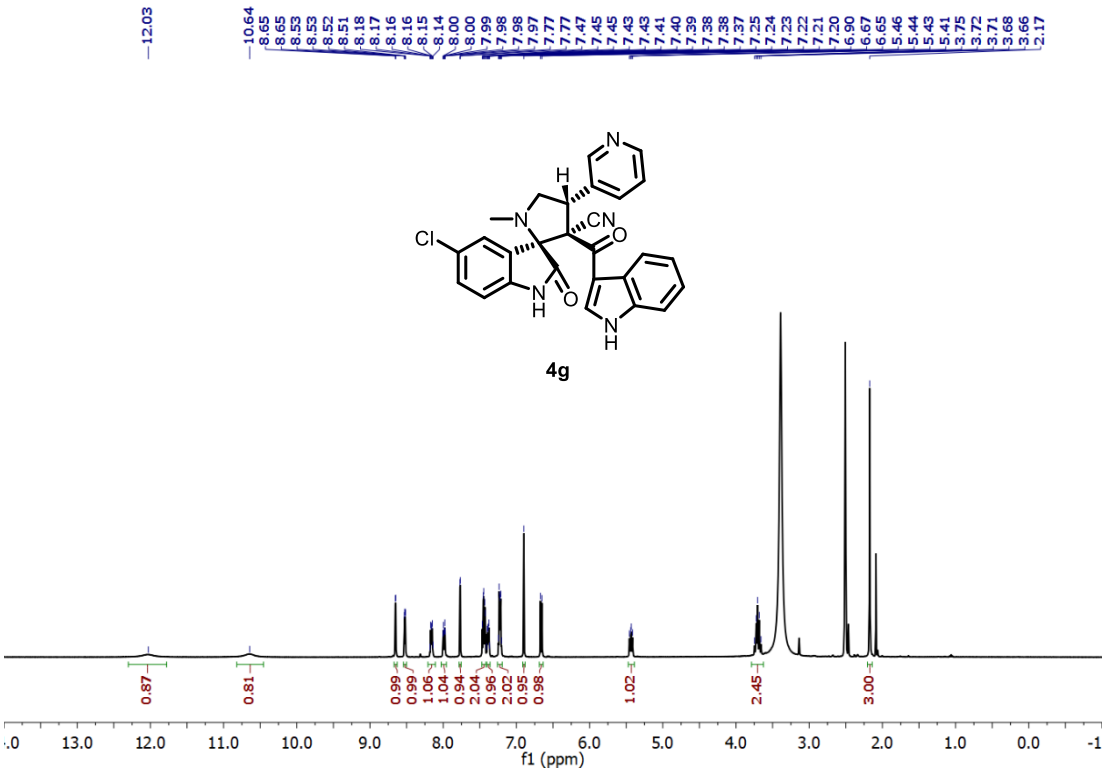


Figure SI-13: ^{1}H NMR spectrum of compound **4g** in DMSO-d$_6$

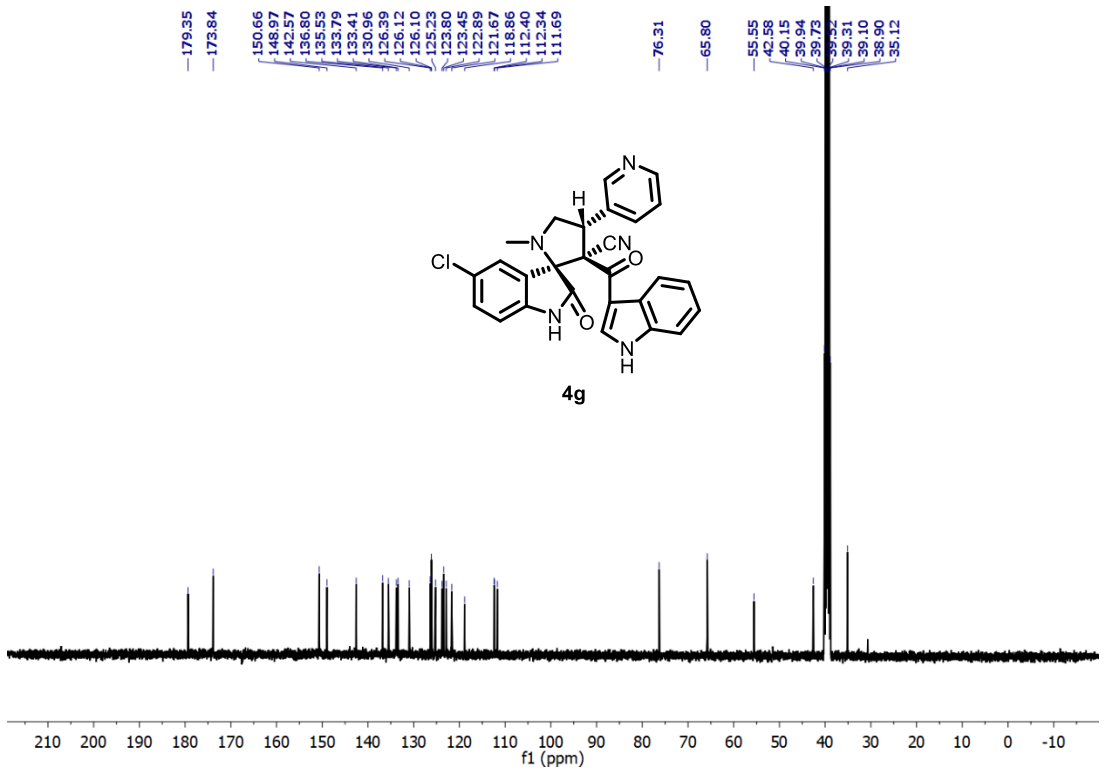


Figure SI-14: ^{13}C NMR spectrum of compound **4g** in DMSO-d$_6$

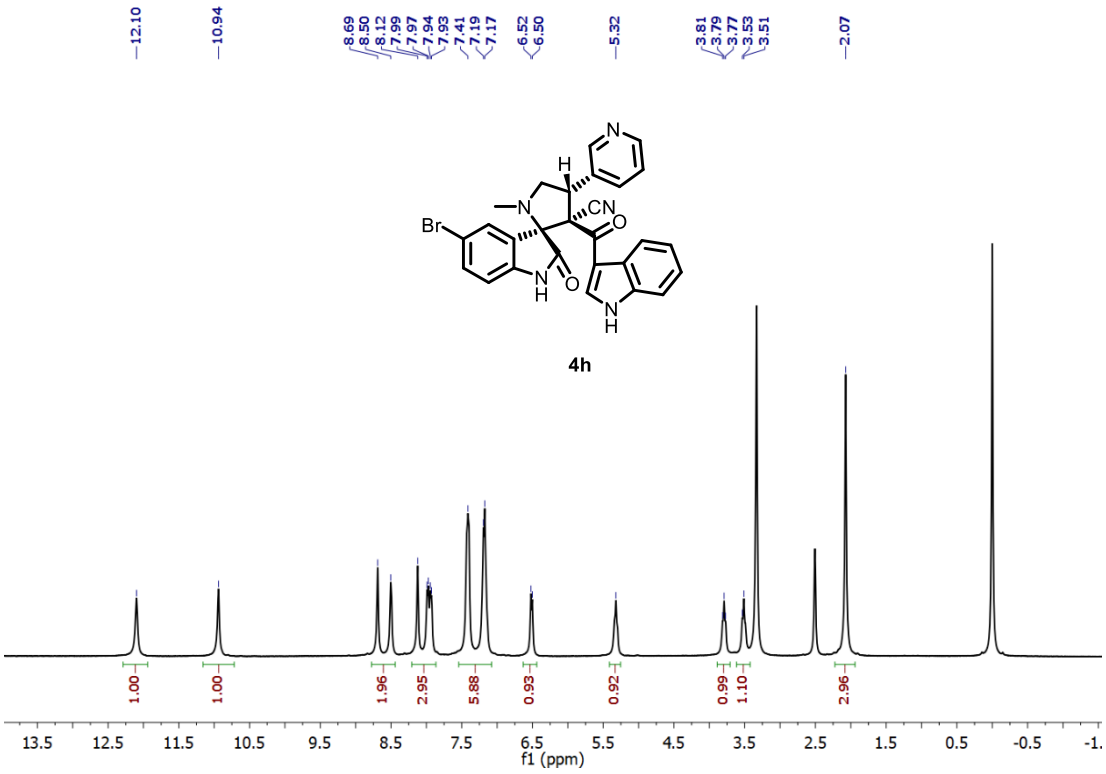


Figure SI-15: ^{1}H NMR spectrum of compound **4h** in DMSO-d$_6$

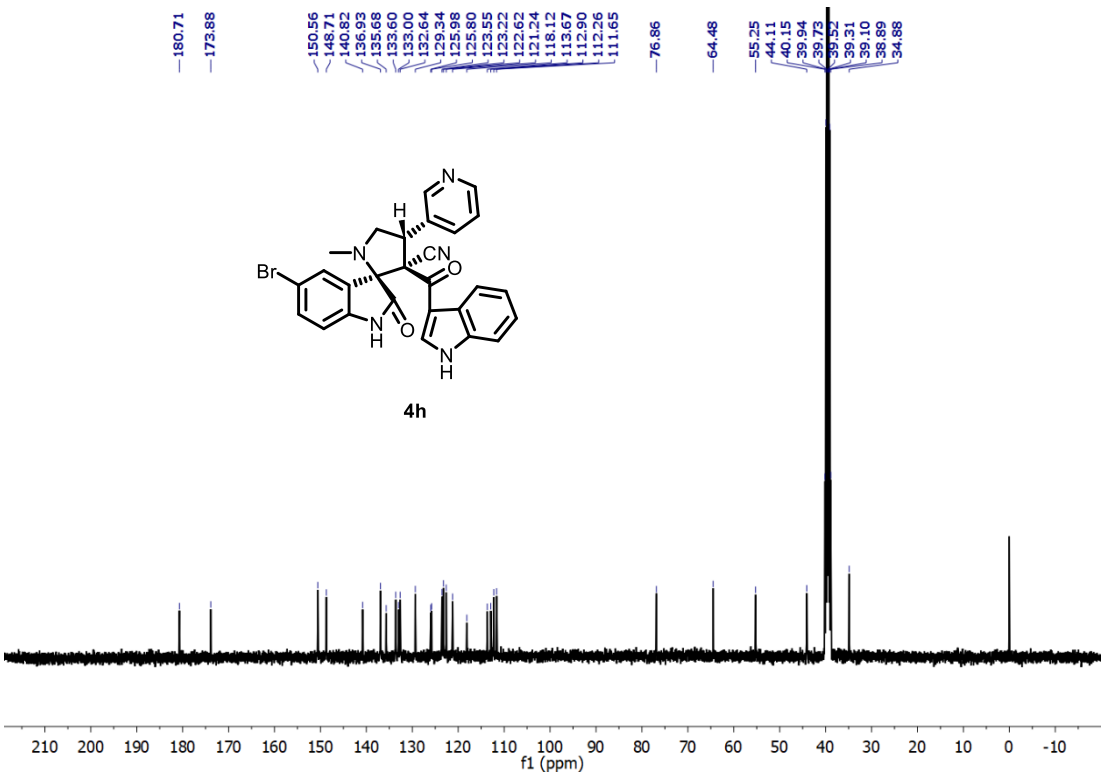


Figure SI-16: ^{13}C NMR spectrum of compound **4h** in DMSO-d$_6$

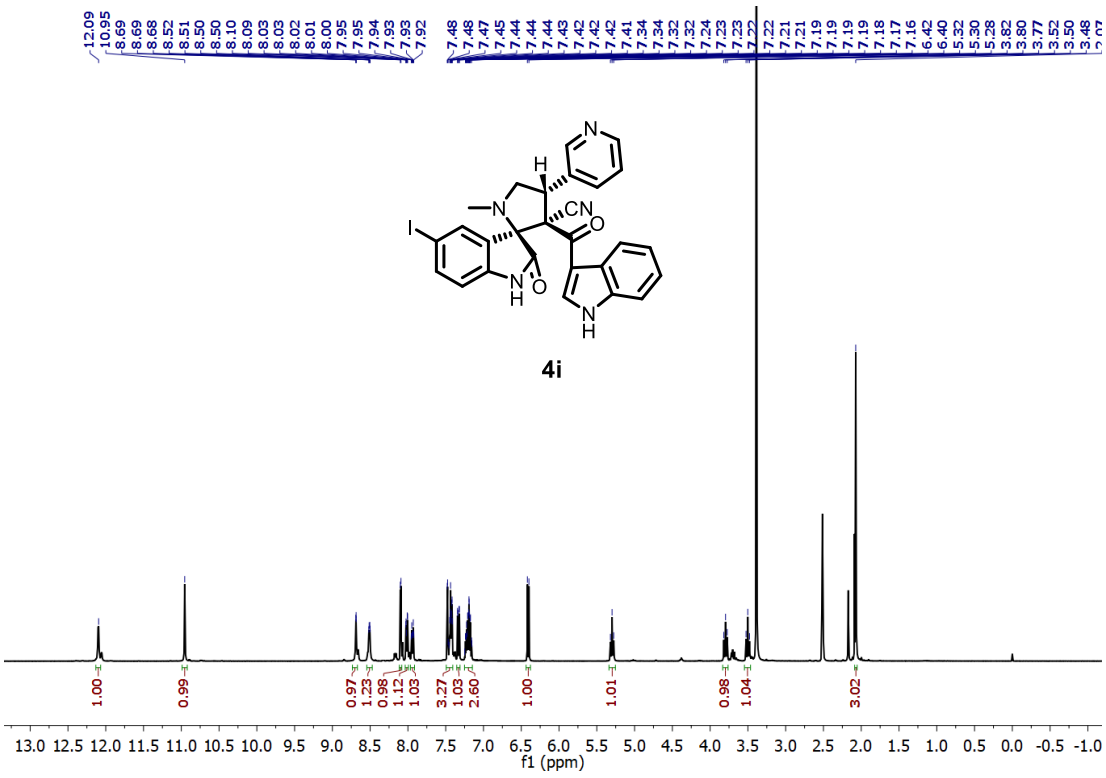


Figure SI-17: ^{1}H NMR spectrum of compound **4i** in DMSO-d$_6$

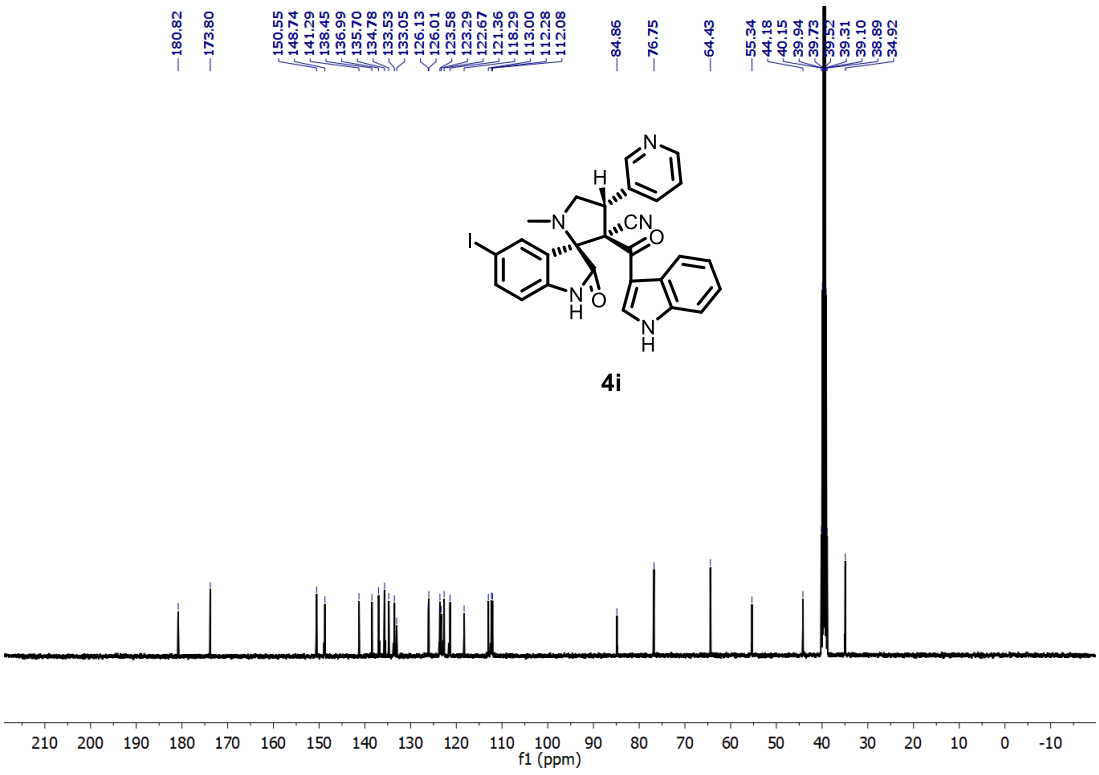
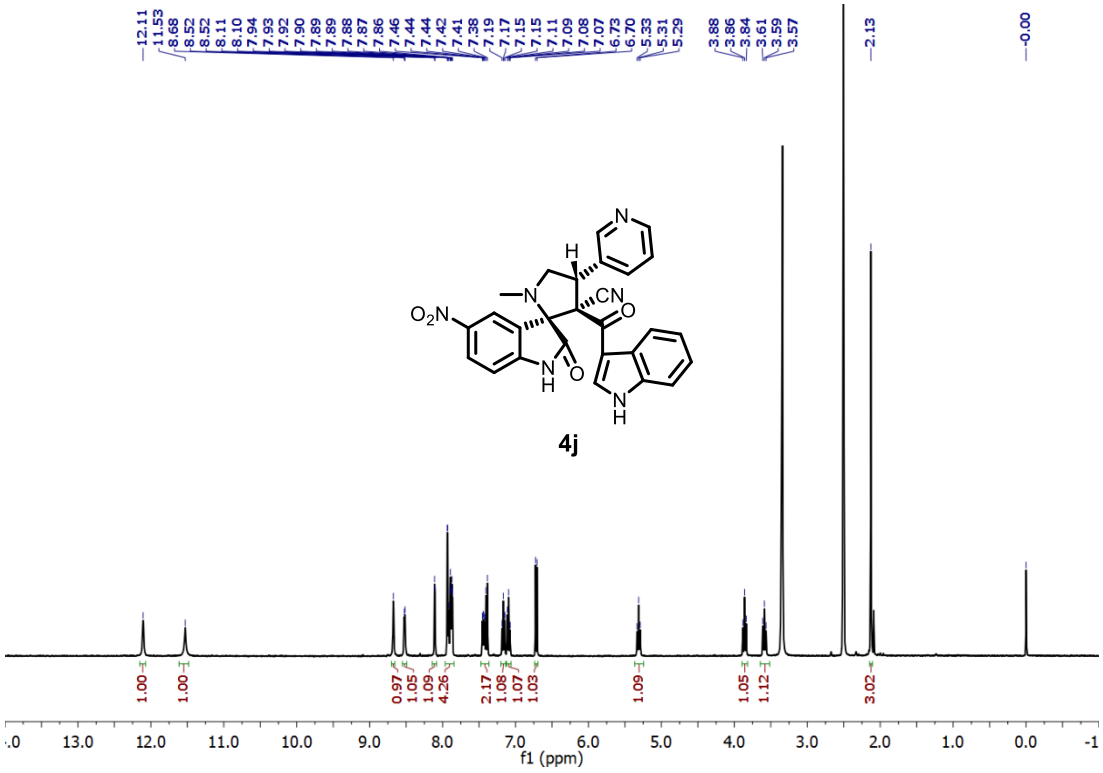
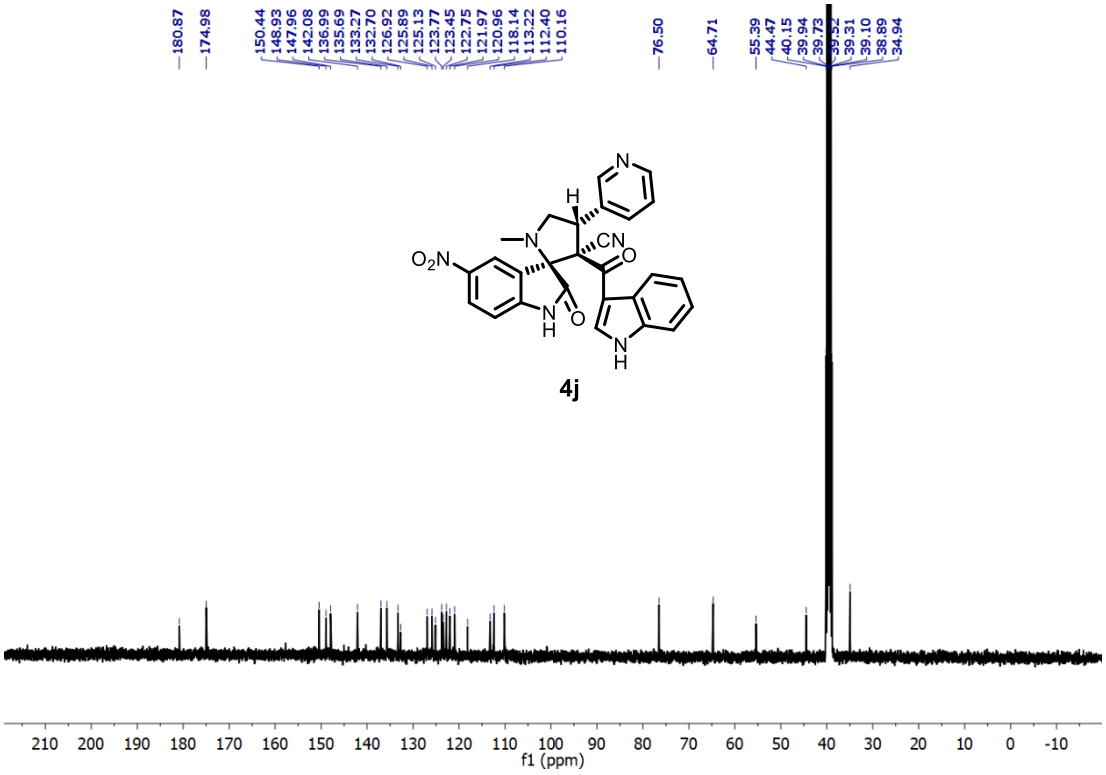


Figure SI-18: ^{13}C NMR spectrum of compound **4i** in DMSO-d$_6$



4j

Figure SI-19: ^{1}H NMR spectrum of compound **4j** in DMSO-d$_6$



4j

Figure SI-20: ^{13}C NMR spectrum of compound **4j** in DMSO-d$_6$

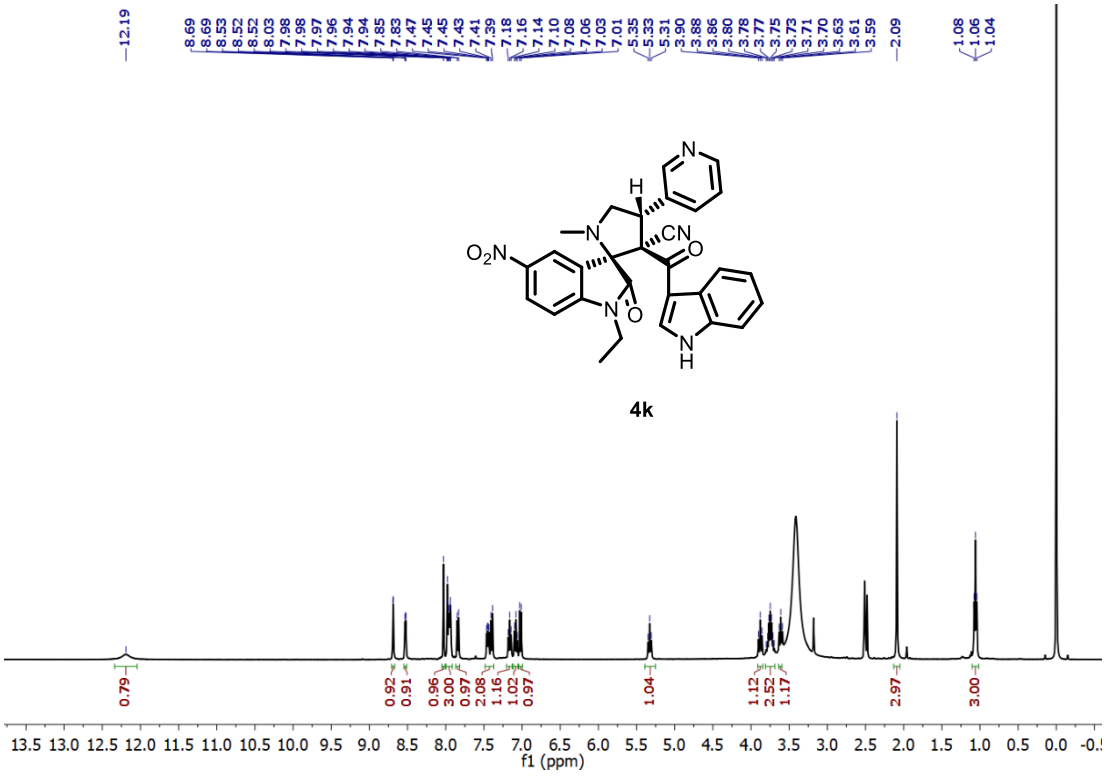


Figure SI-21: ^{1}H NMR spectrum of compound **4k** in DMSO-d$_6$

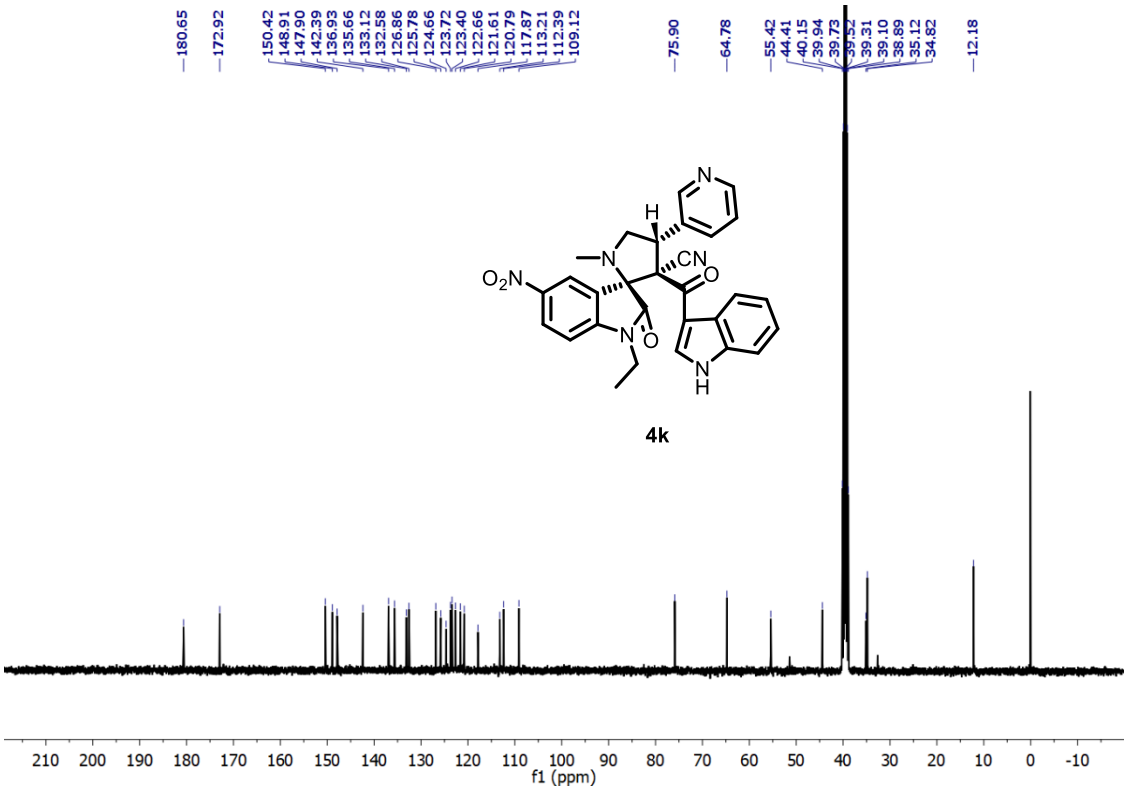


Figure SI-22: ^{13}C NMR spectrum of compound **4k** in DMSO-d$_6$

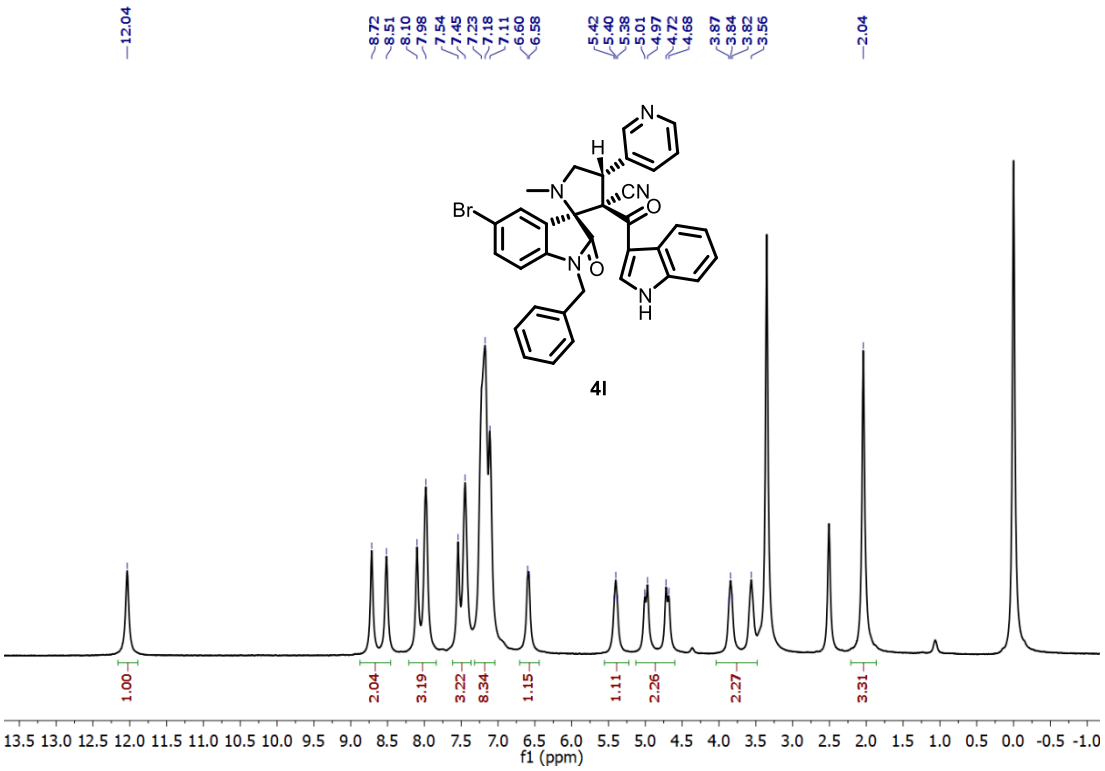


Figure SI-23: ^{1}H NMR spectrum of compound **4l** in DMSO-d$_6$

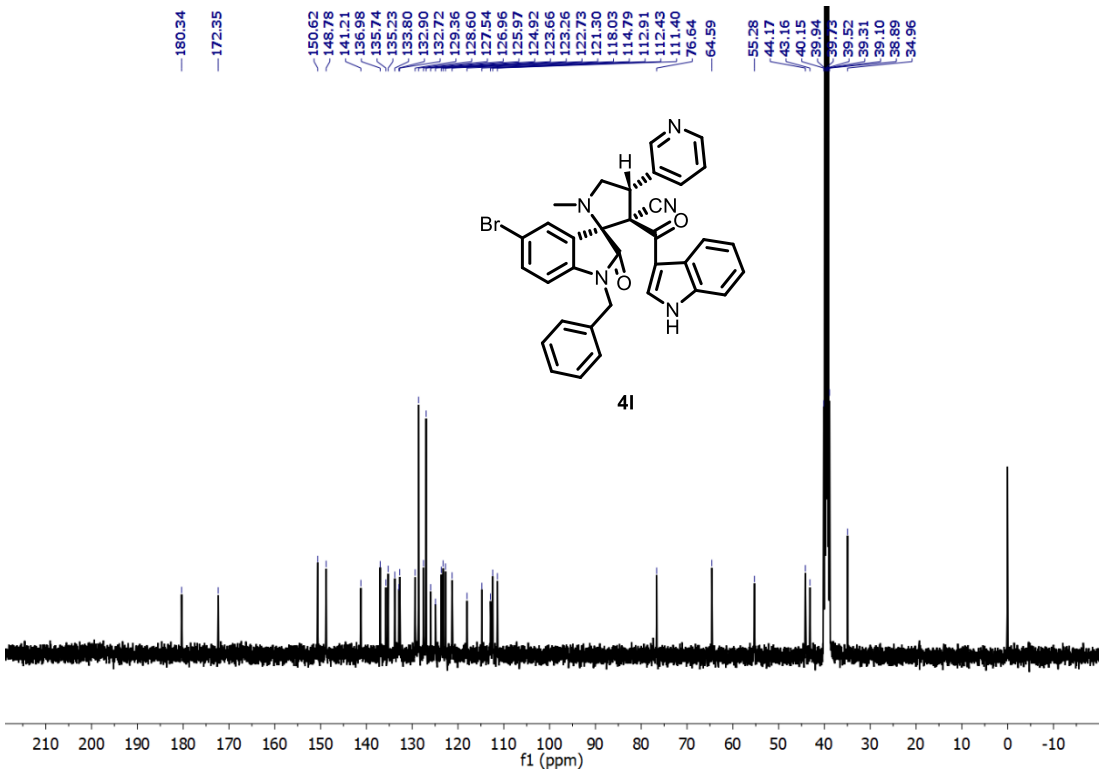


Figure SI-24: ^{13}C NMR spectrum of compound **4l** in DMSO-d$_6$

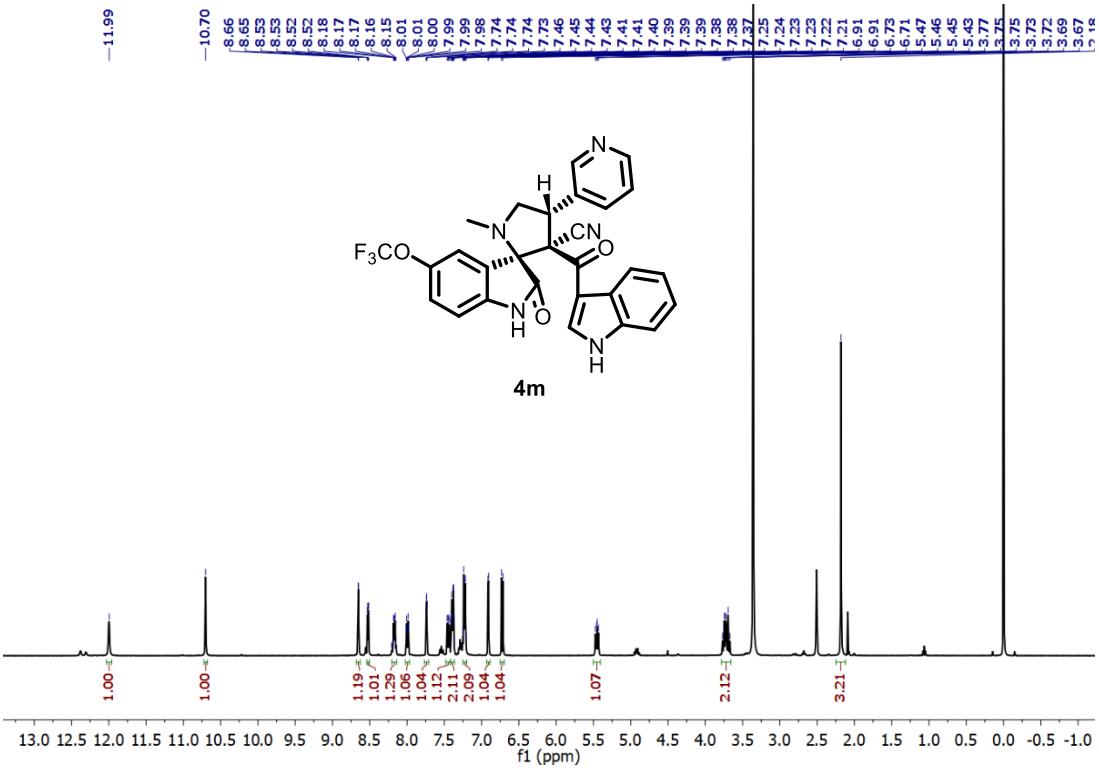


Figure SI-25: ^{1}H NMR spectrum of compound **4m** in DMSO-d$_6$

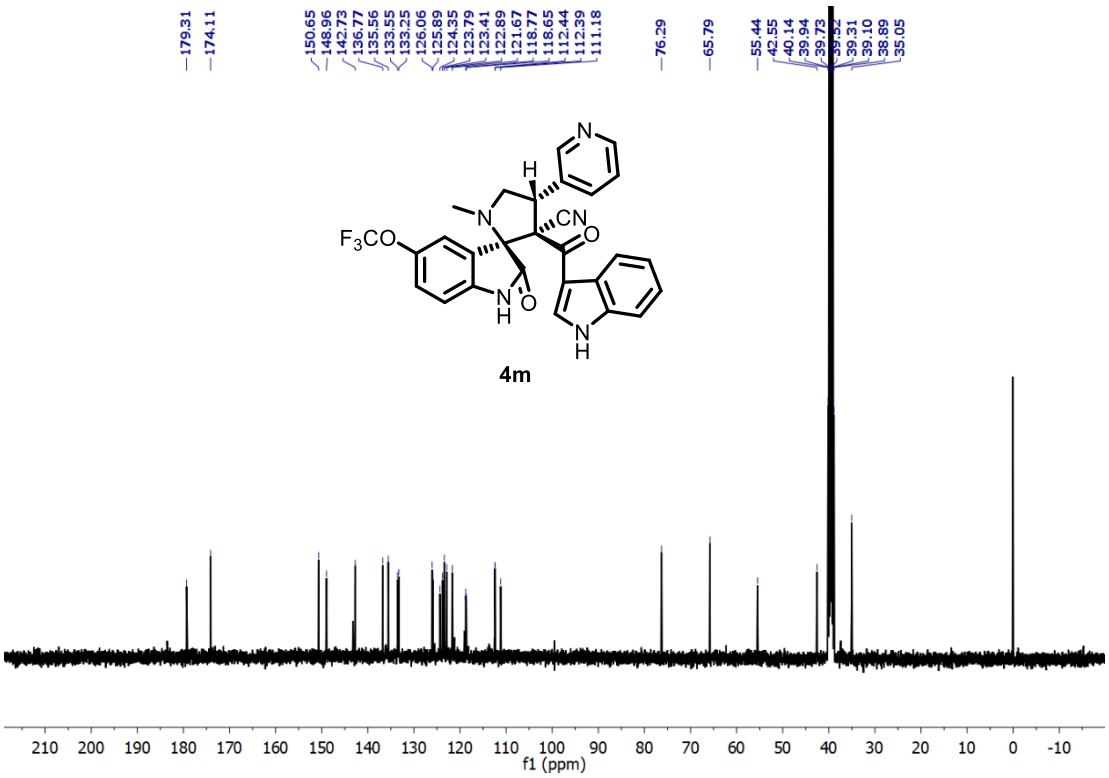


Figure SI-26: ^{13}C NMR spectrum of compound **4m** in DMSO-d$_6$

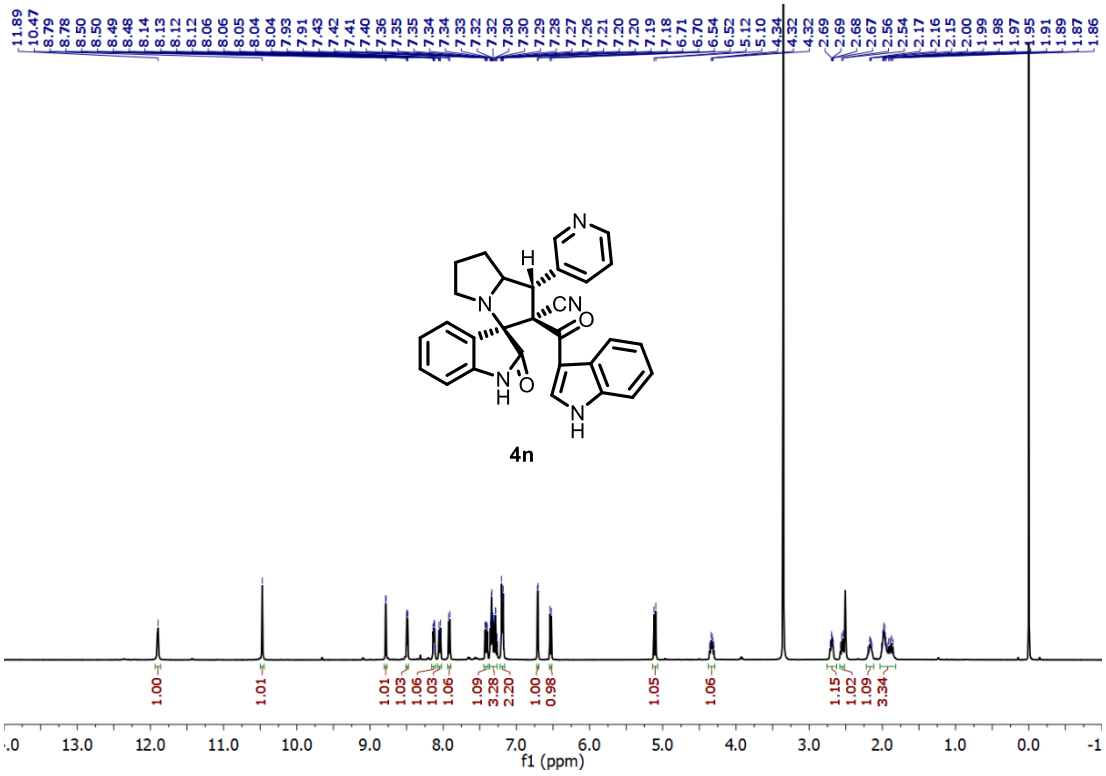


Figure SI-27: ^{1}H NMR spectrum of compound **4n** in DMSO-d$_6$

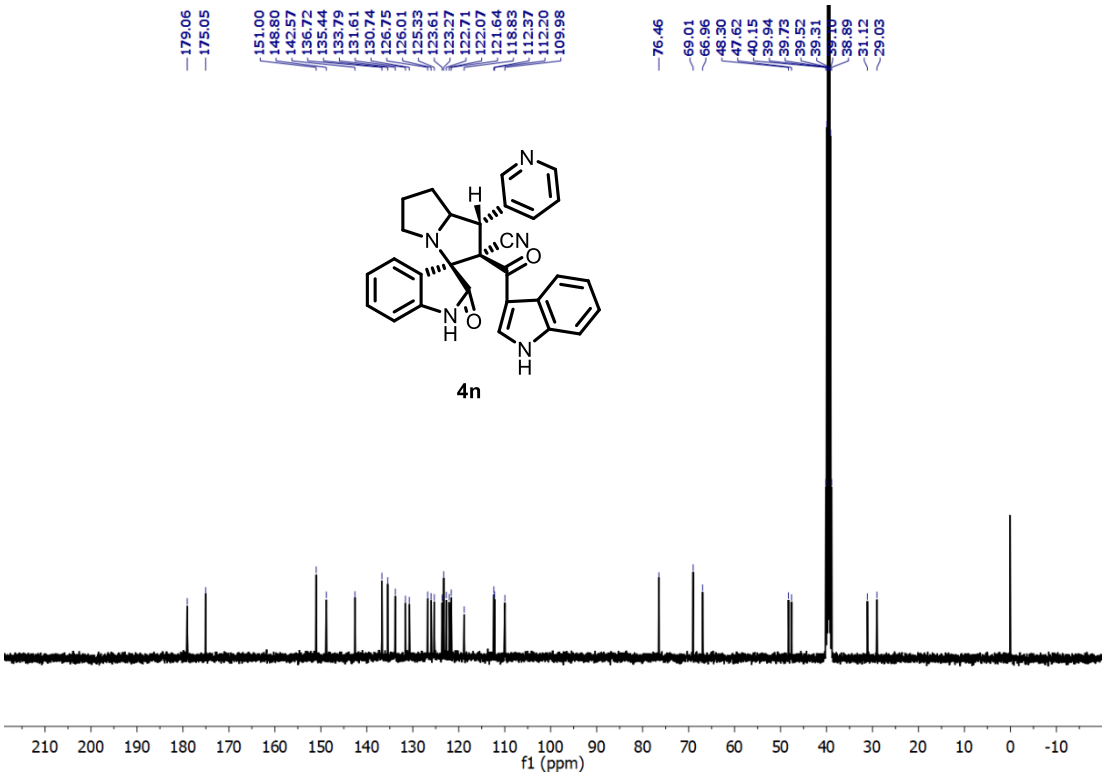


Figure SI-28: ^{13}C NMR spectrum of compound **4n** in DMSO-d$_6$

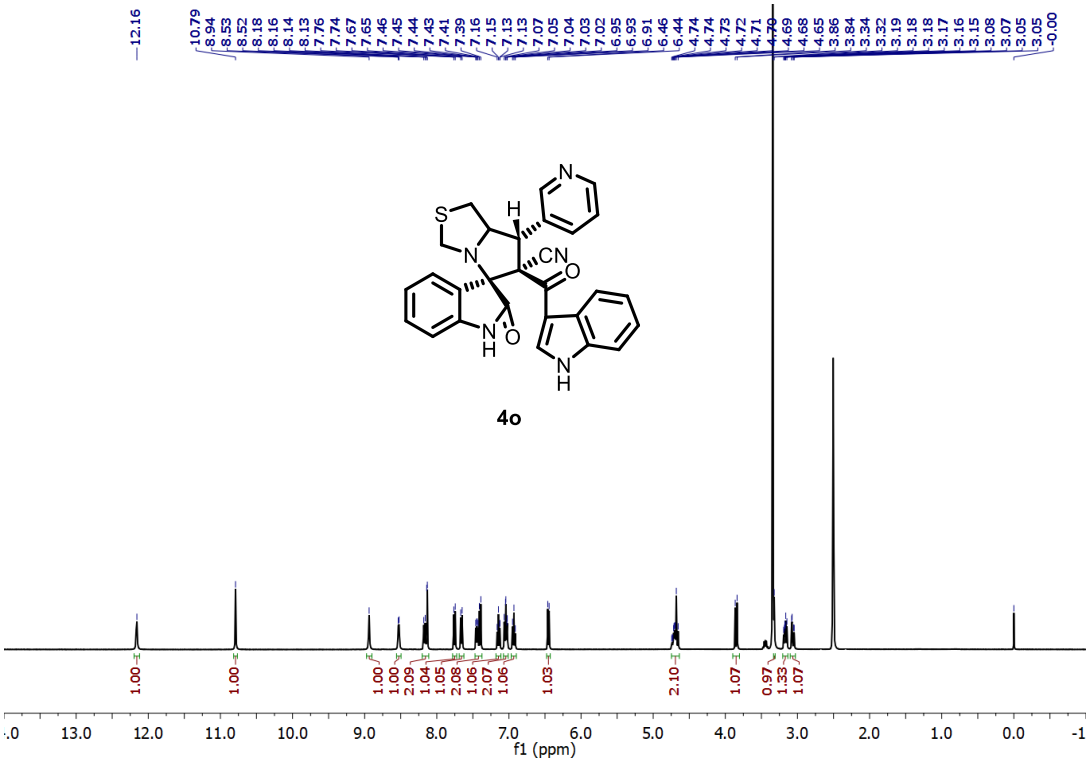


Figure SI-29: ^{1}H NMR spectrum of compound **4o** in DMSO-d$_6$

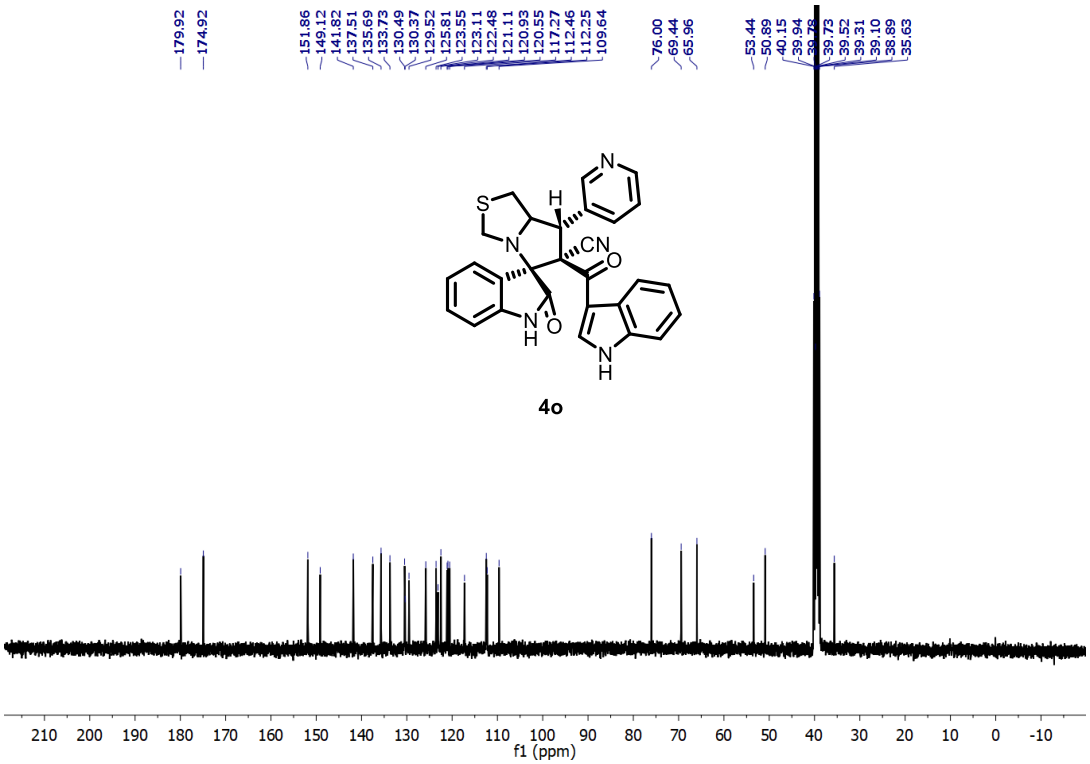


Figure SI-30: ^{13}C NMR spectrum of compound **4o** in DMSO-d$_6$

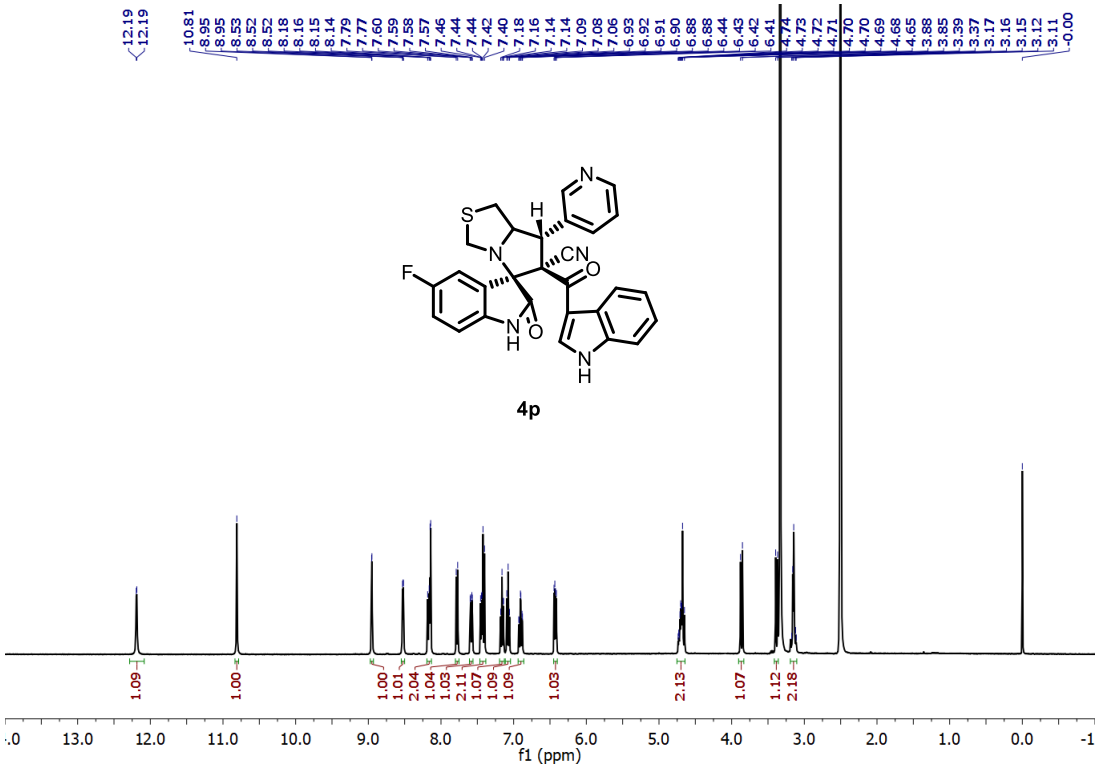


Figure SI-31: ^{1}H NMR spectrum of compound **4p** in DMSO-d$_6$

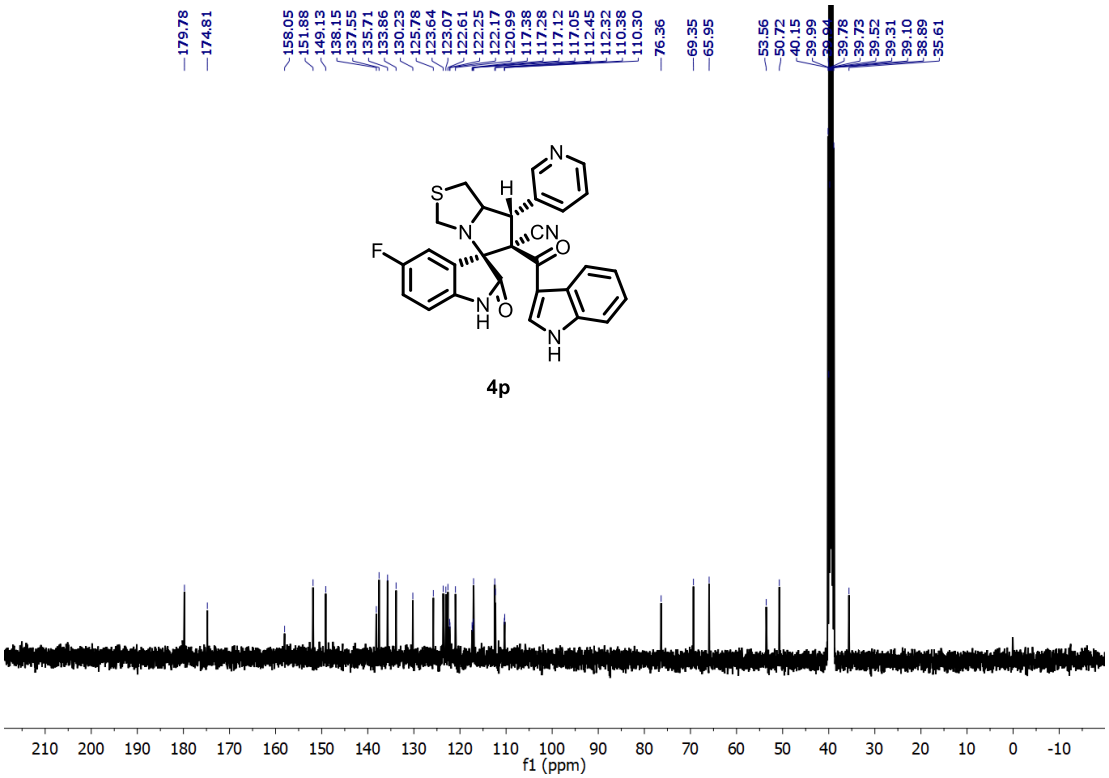


Figure SI-32: ^{13}C NMR spectrum of compound **4p** in DMSO-d$_6$

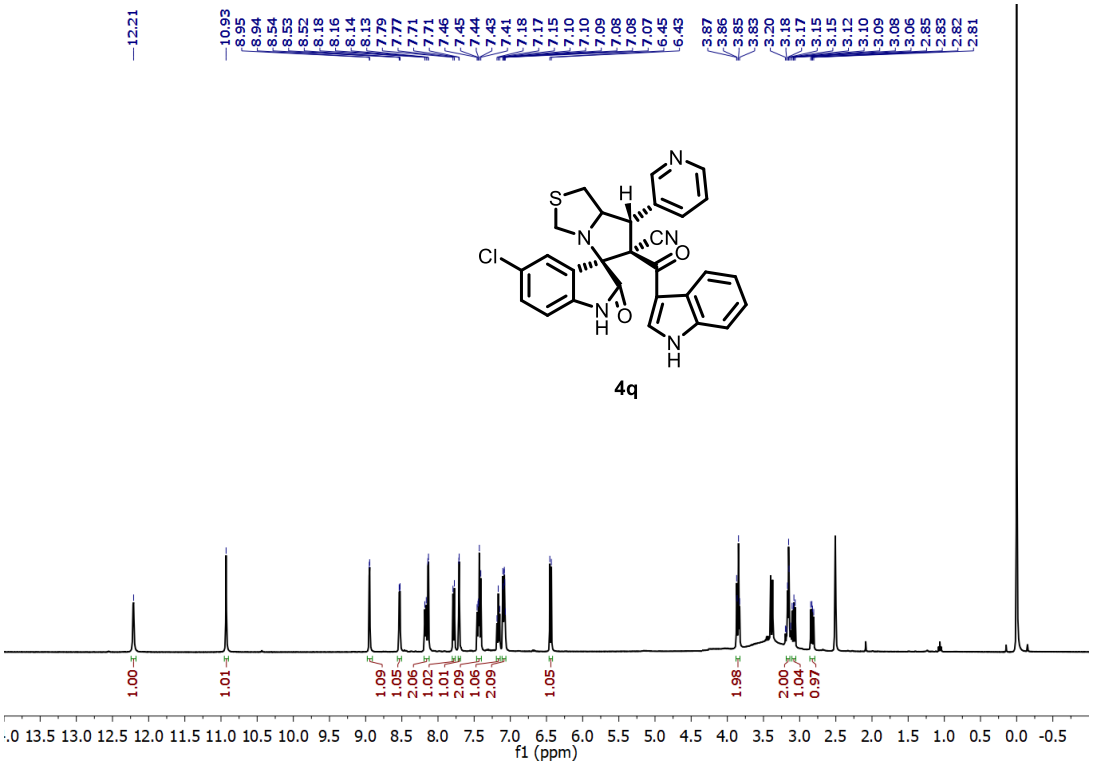


Figure SI-33: ^{1}H NMR spectrum of compound **4q** in DMSO-d$_6$

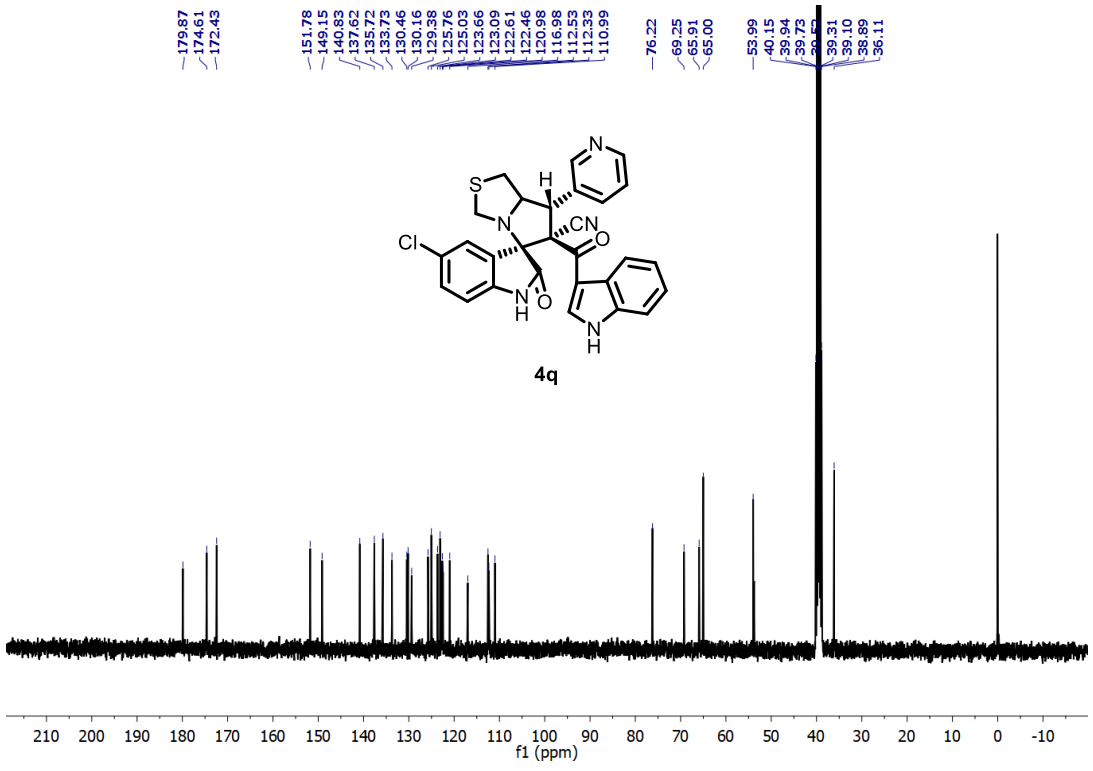


Figure SI-34: ^{13}C NMR spectrum of compound **4q** in DMSO-d$_6$

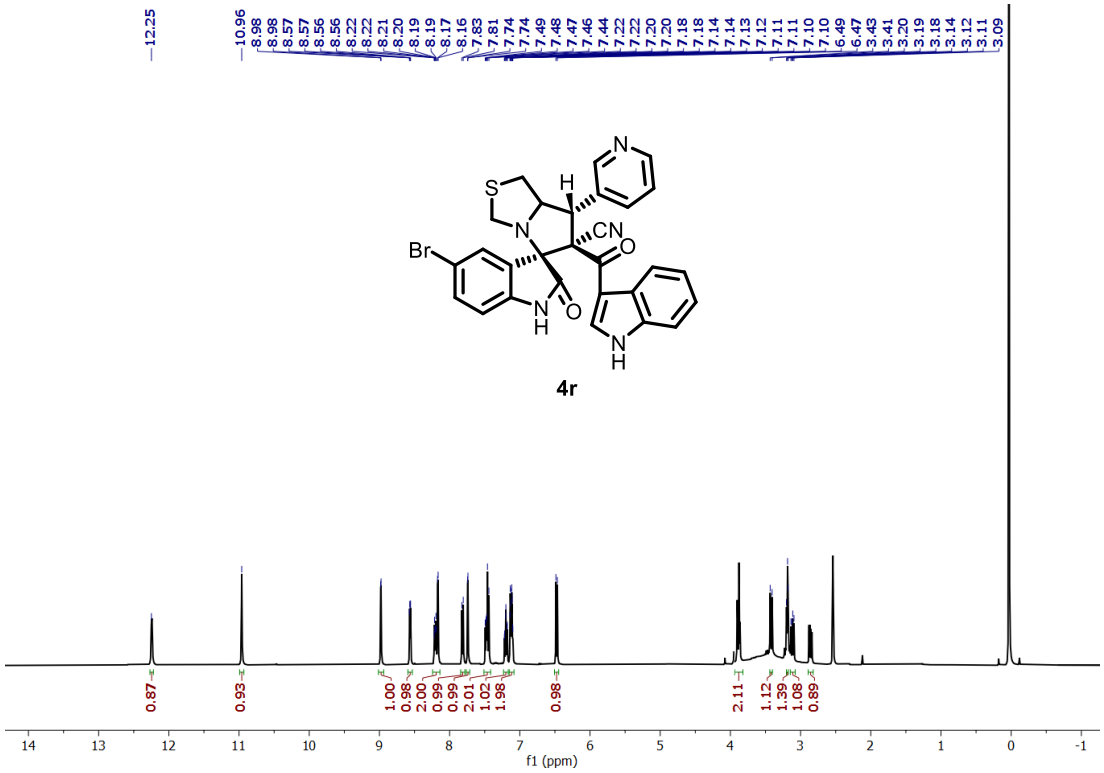


Figure SI-35: ^{1}H NMR spectrum of compound **4r** in DMSO-d$_6$

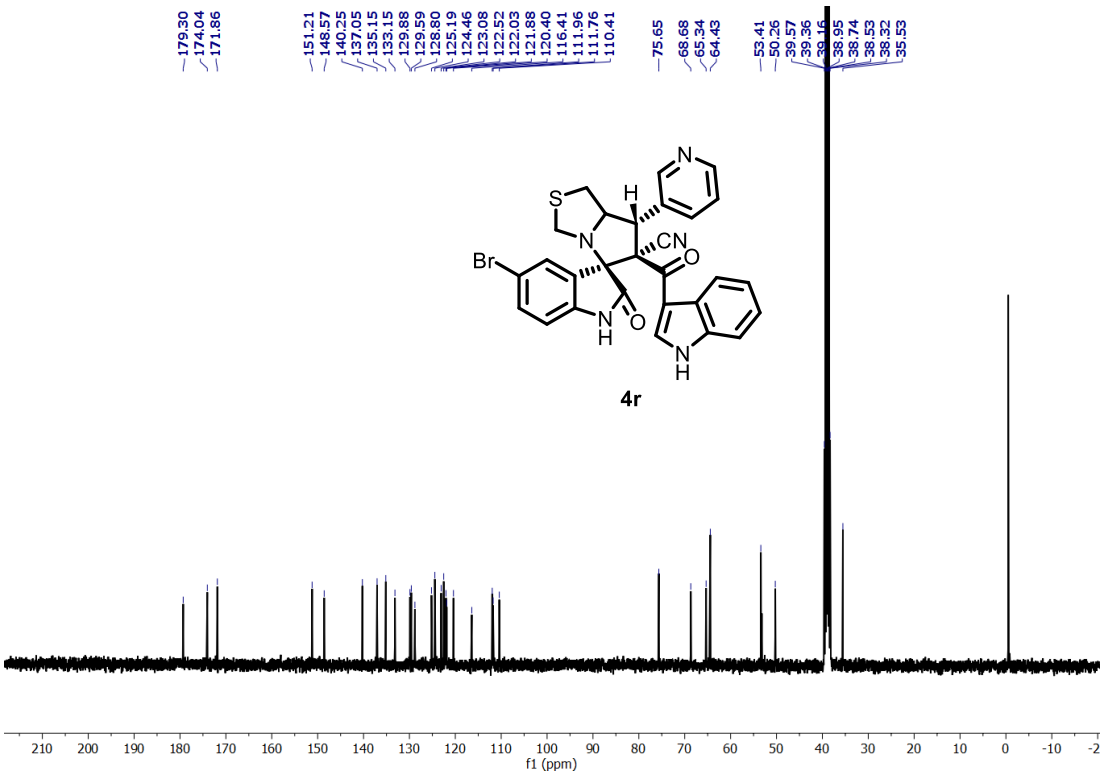


Figure SI-36: ^{13}C NMR spectrum of compound **4r**in DMSO-d$_6$

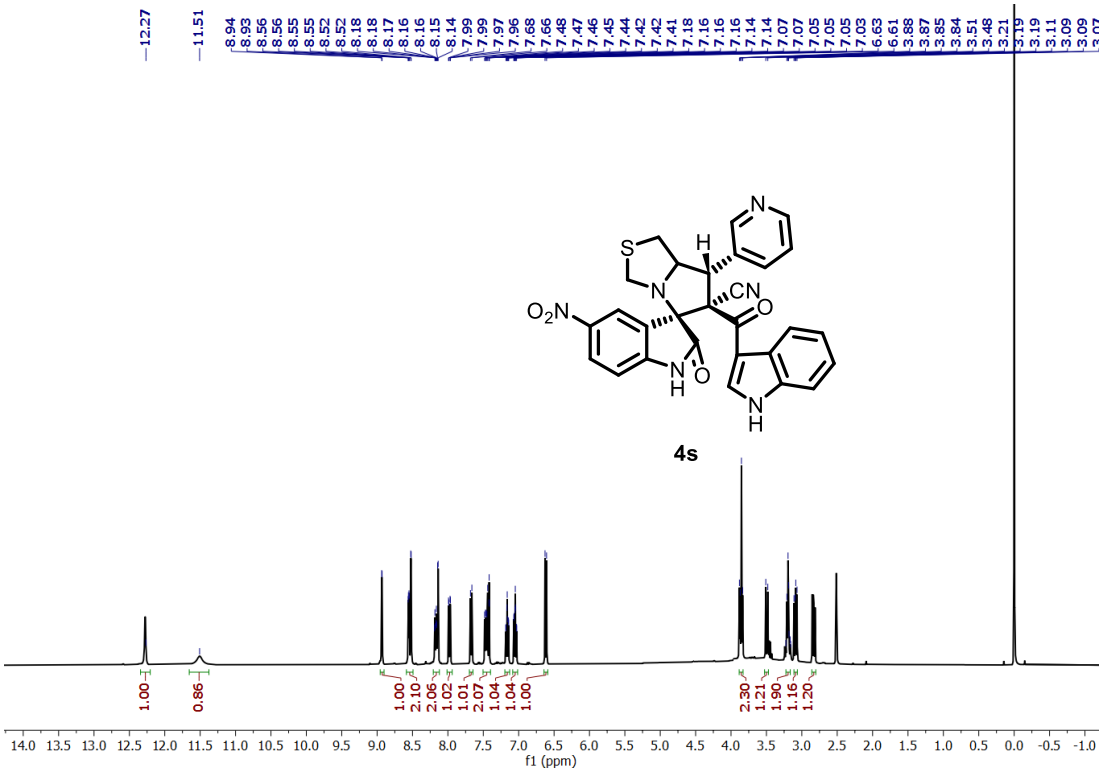


Figure SI-37: ^{1}H NMR spectrum of compound **4s** in DMSO-d$_6$

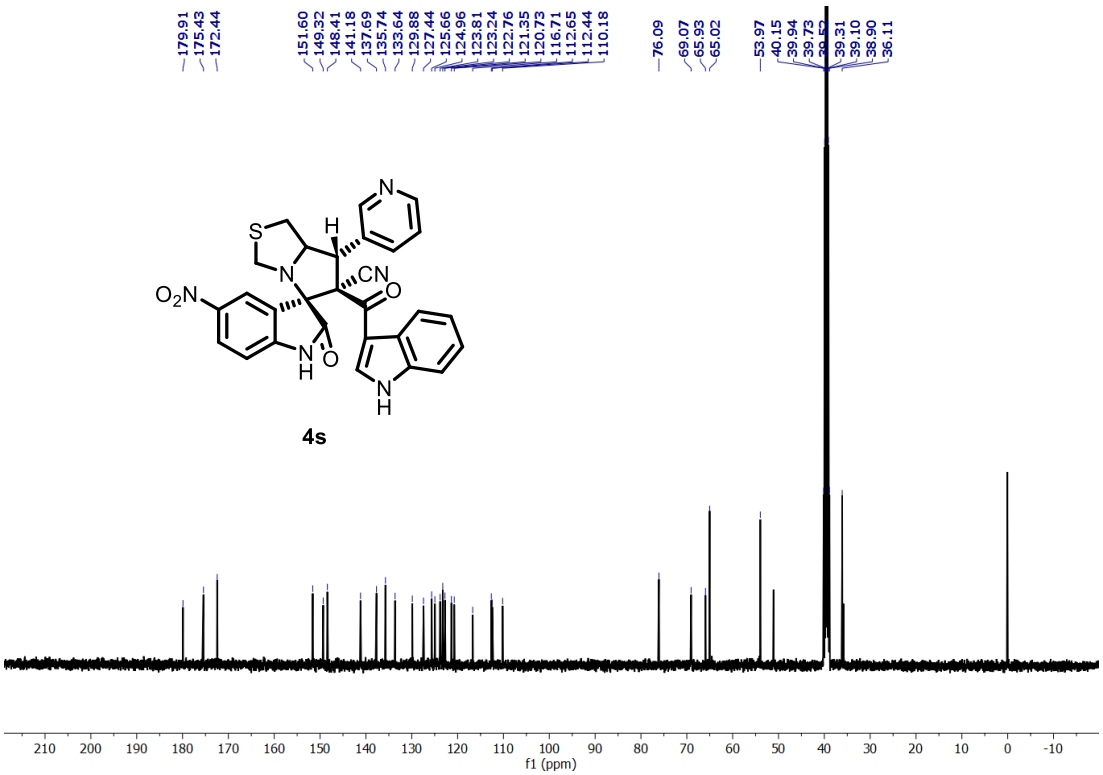


Figure SI-38: ^{13}C NMR spectrum of compound **4s** in DMSO-d$_6$

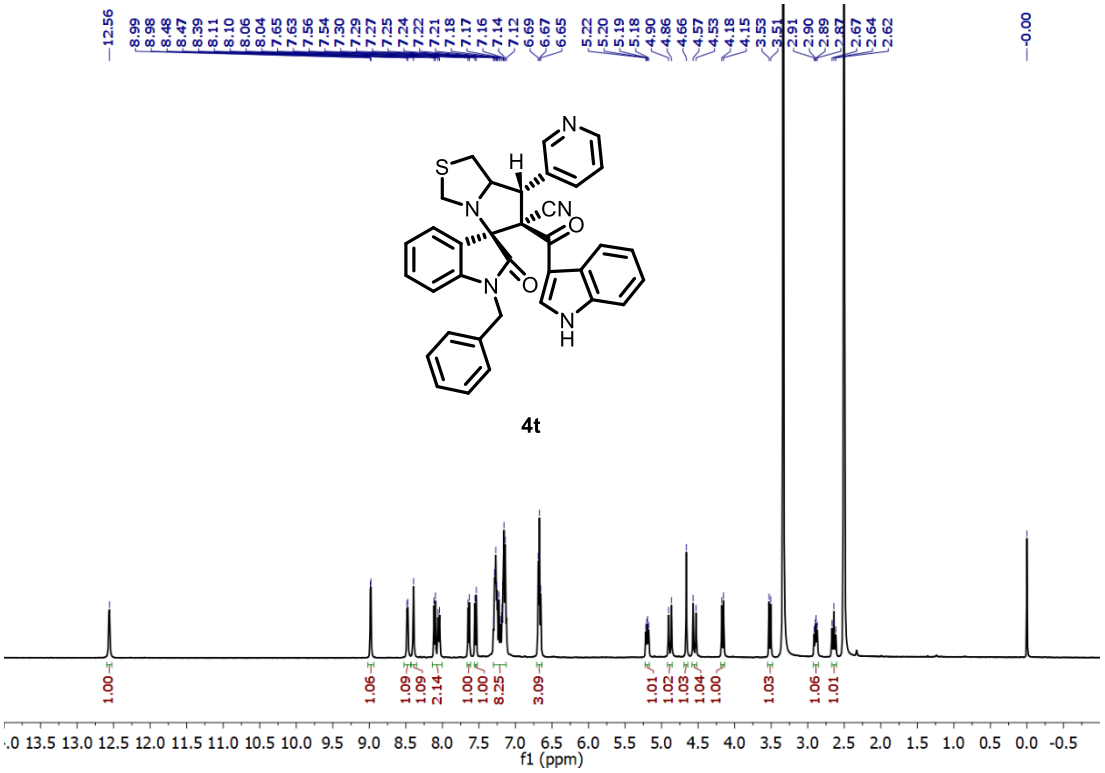


Figure SI-39: ^{1}H NMR spectrum of compound **4t** in DMSO-d$_6$

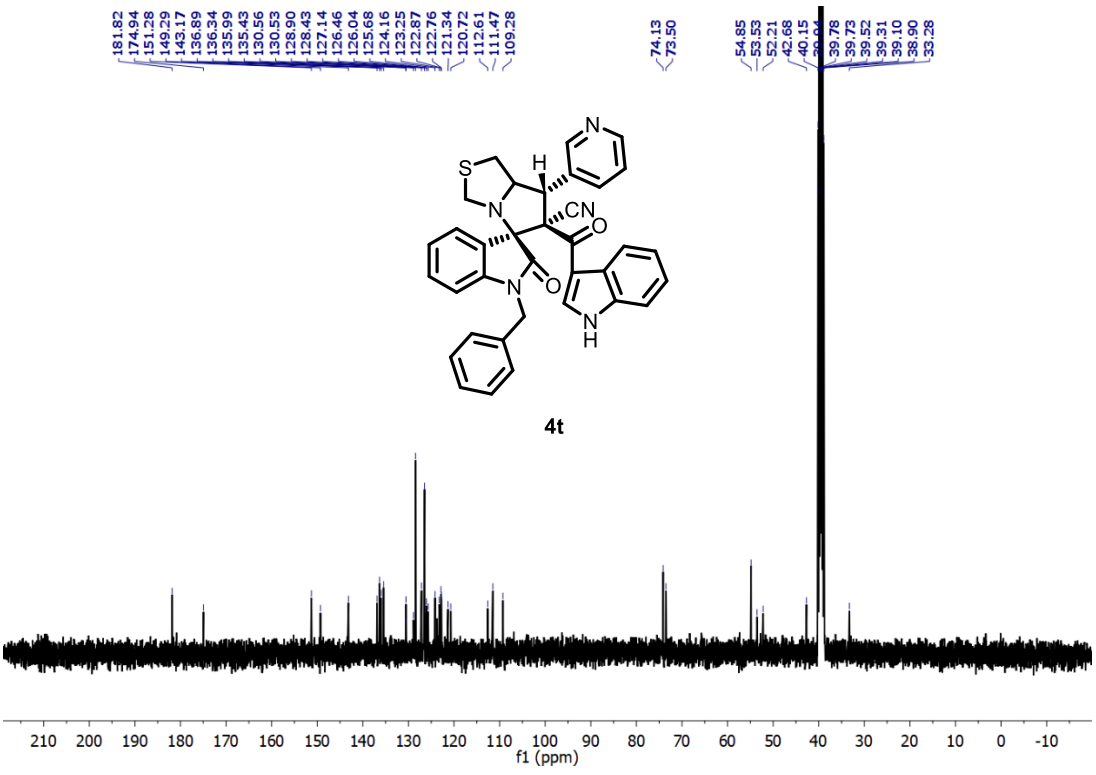


Figure SI-40: ^{13}C NMR spectrum of compound **4t** in DMSO-d$_6$

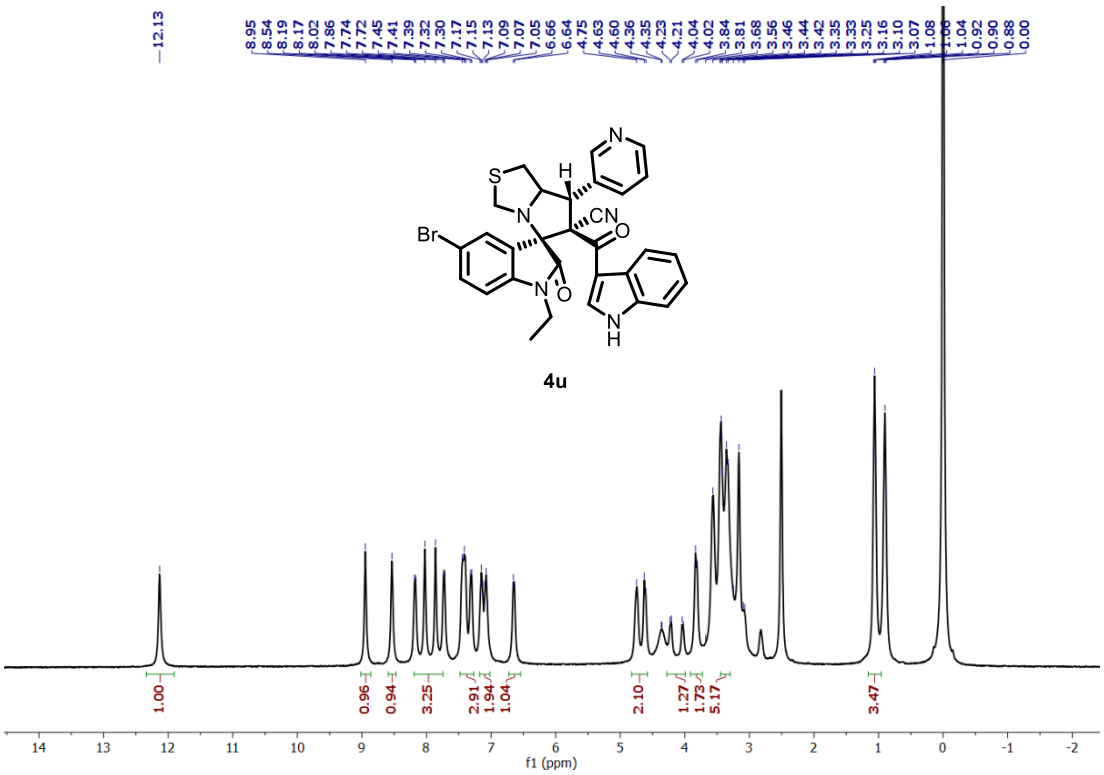


Figure SI-41: ^{1}H NMR spectrum of compound **4u** in DMSO-d$_6$

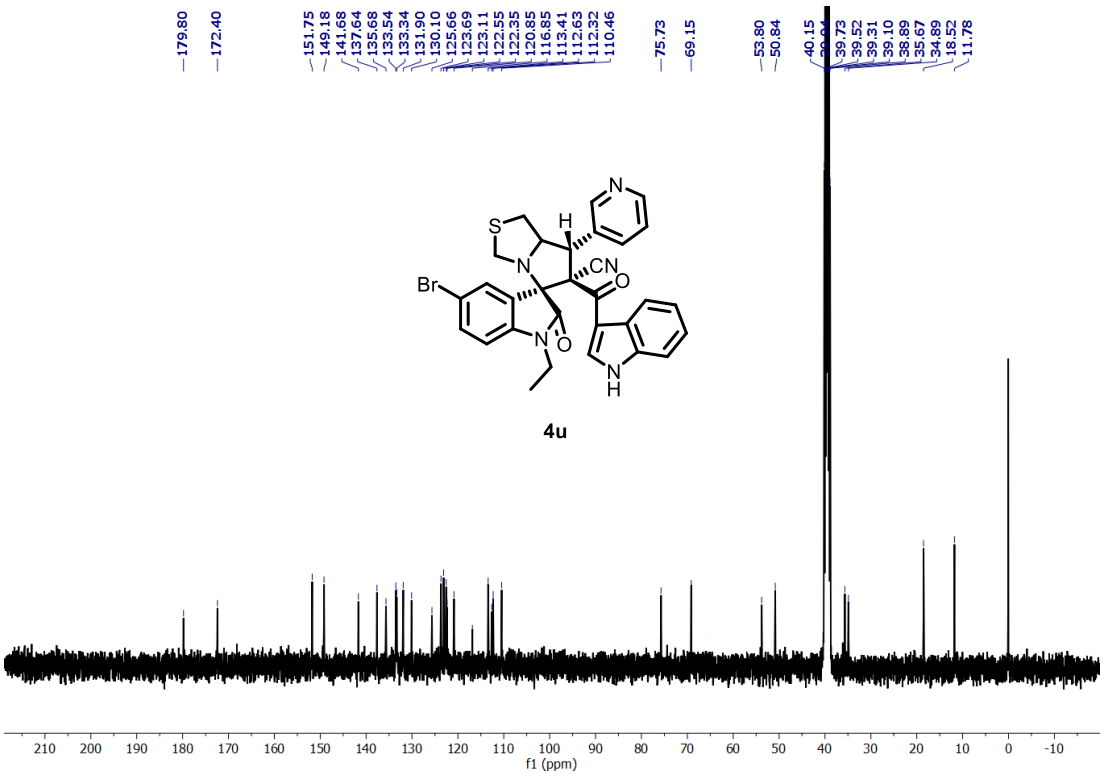


Figure SI-42: ^{13}C NMR spectrum of compound **4u** in DMSO-d$_6$

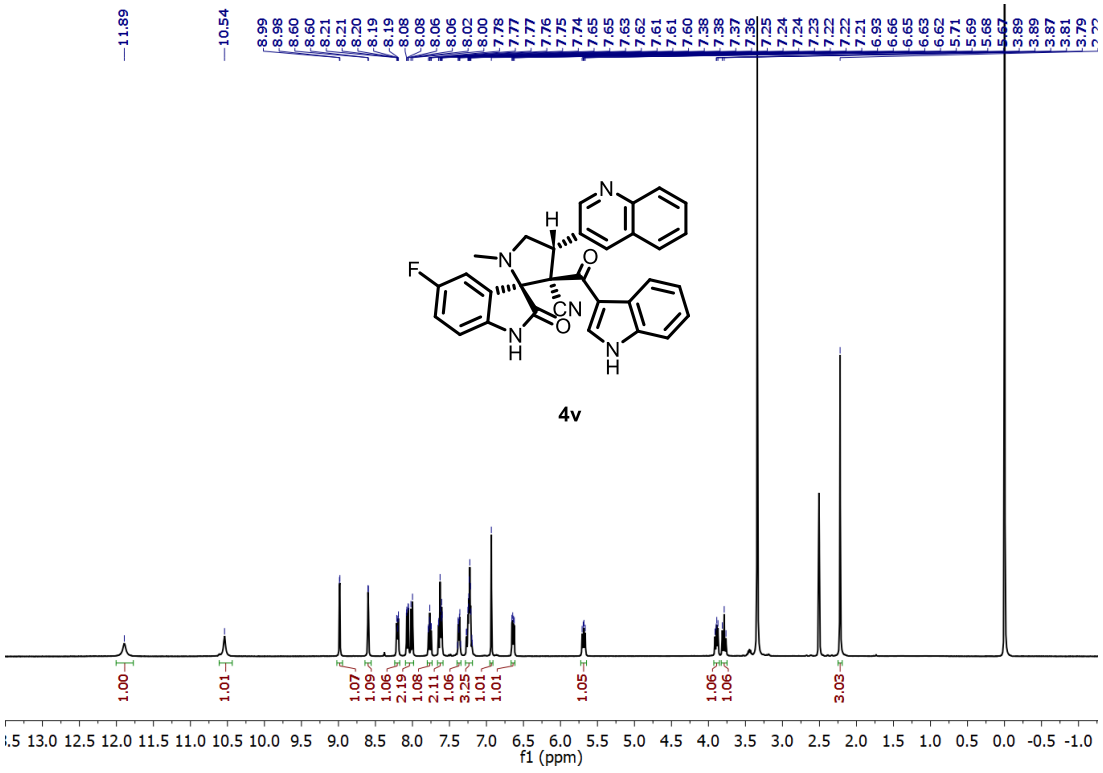


Figure SI-43: ^{1}H NMR spectrum of compound **4v** in DMSO-d$_6$

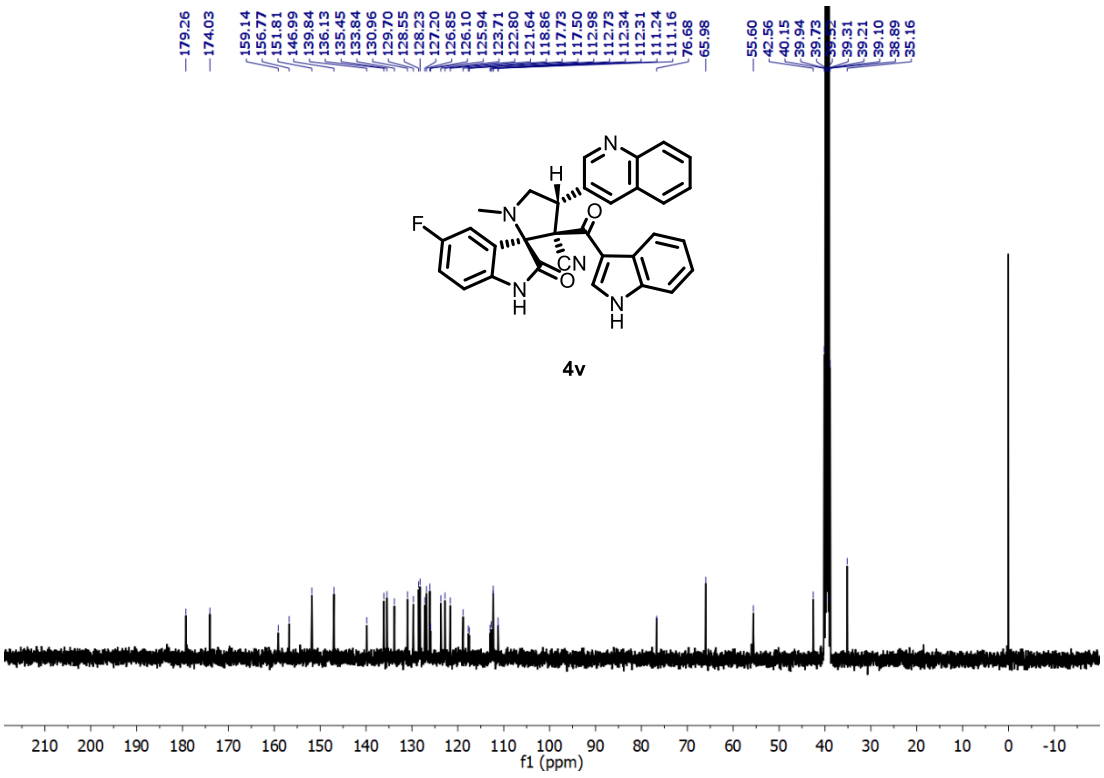


Figure SI-44: ^{13}C NMR spectrum of compound **4v** in DMSO-d$_6$

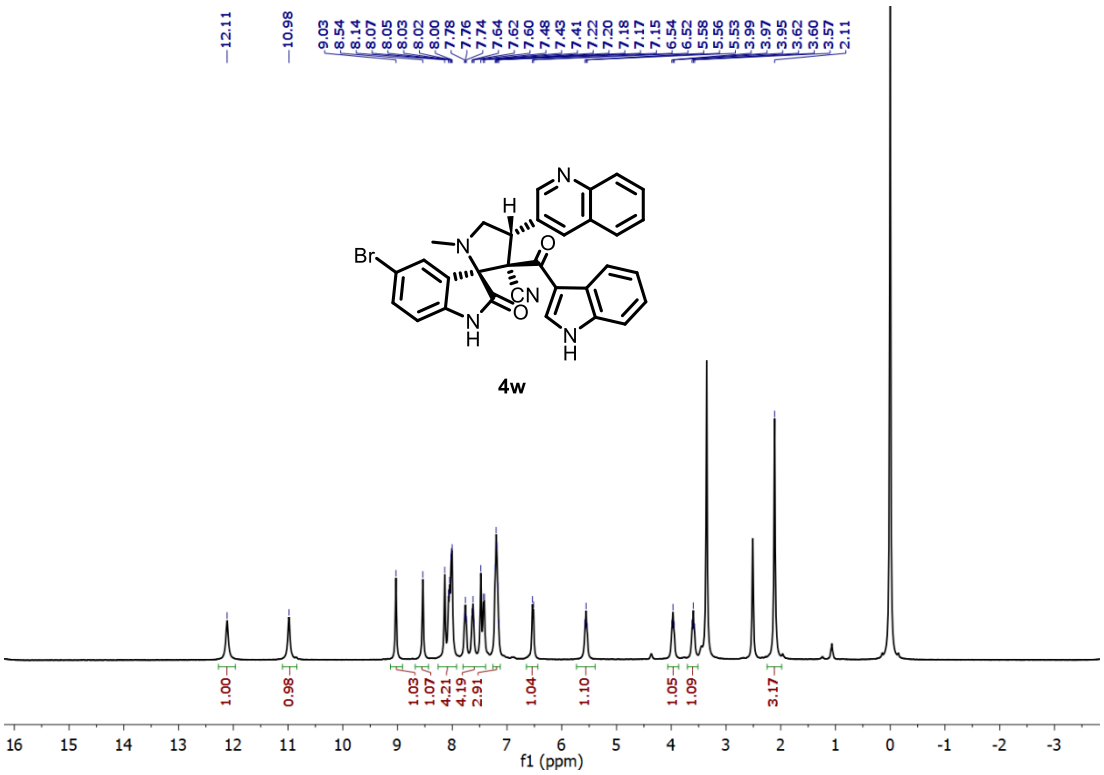


Figure SI-45: ^{1}H NMR spectrum of compound **4w** in DMSO-d$_6$

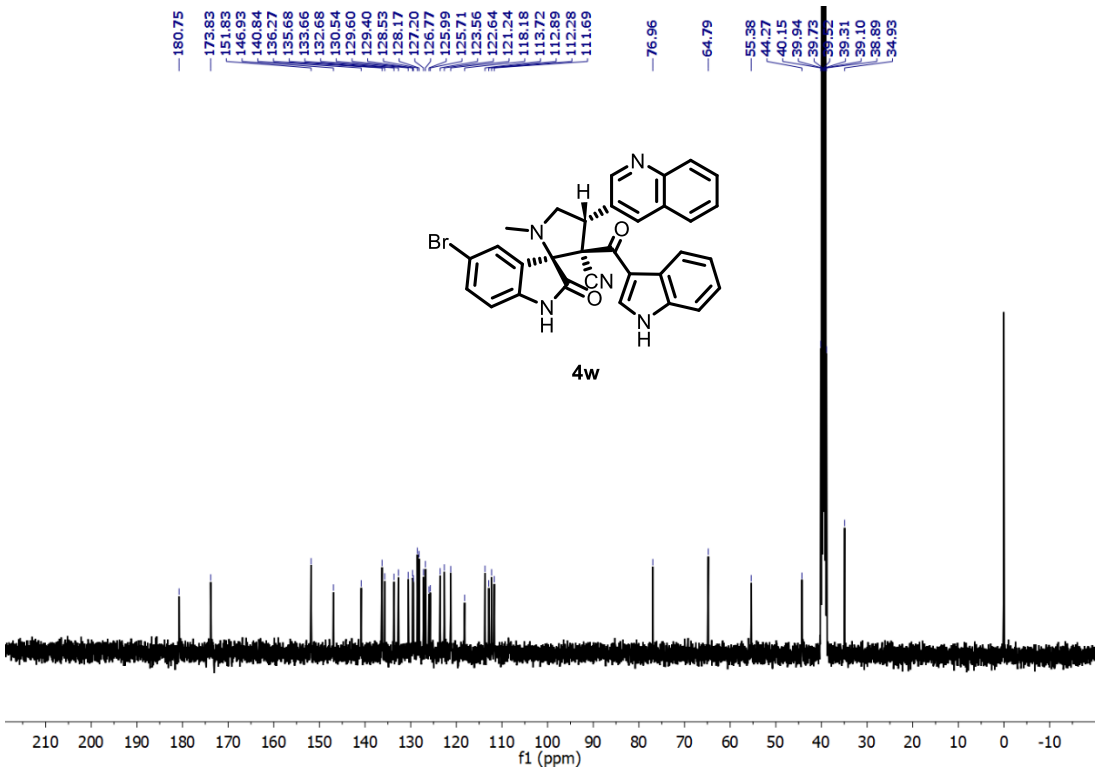


Figure SI-46: ^{13}C NMR spectrum of compound **4w** in DMSO-d$_6$

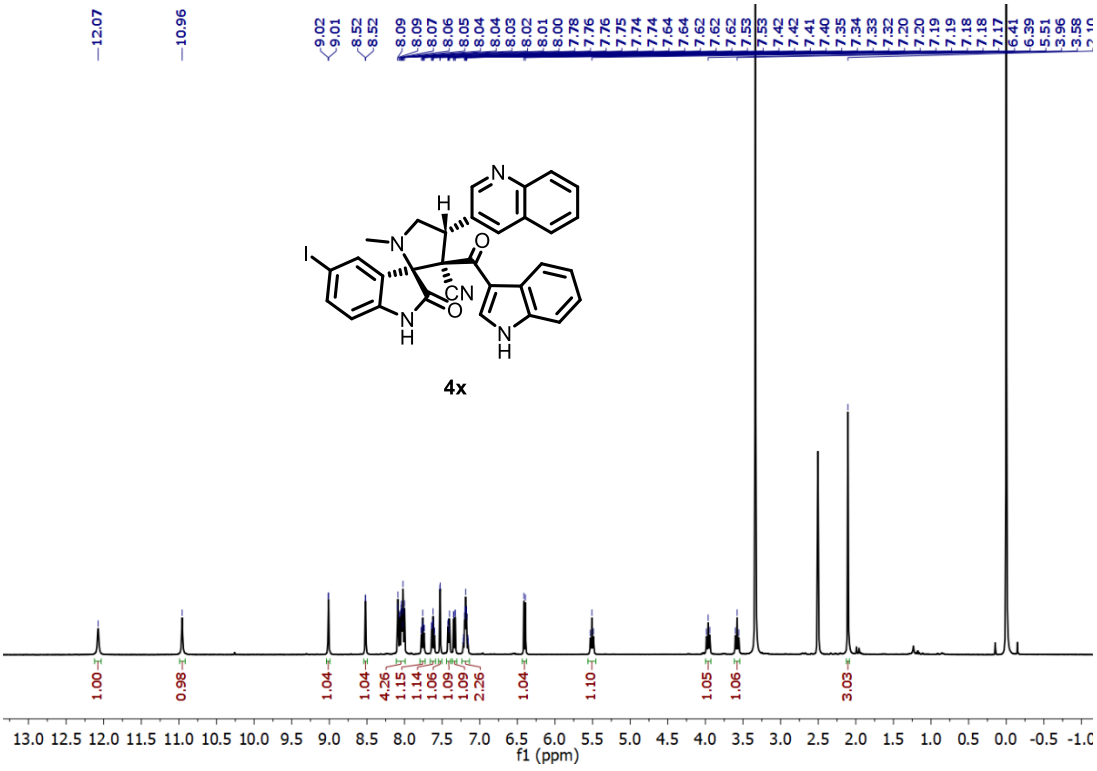


Figure SI-47: ^{1}H NMR spectrum of compound **4x** in DMSO-d$_6$

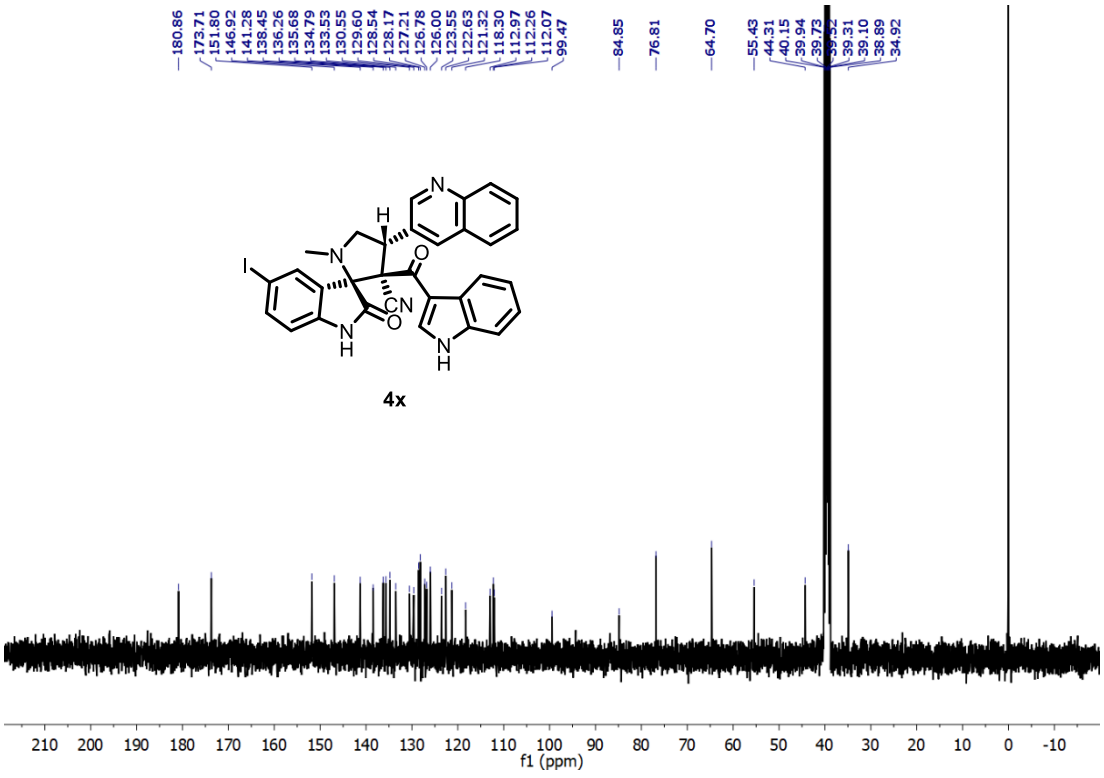


Figure SI-48: ^{13}C NMR spectrum of compound **4x** in DMSO-d$_6$

11. Molecular docking studies of compound (4a-x) with Bcl2-receptor(4IEH)

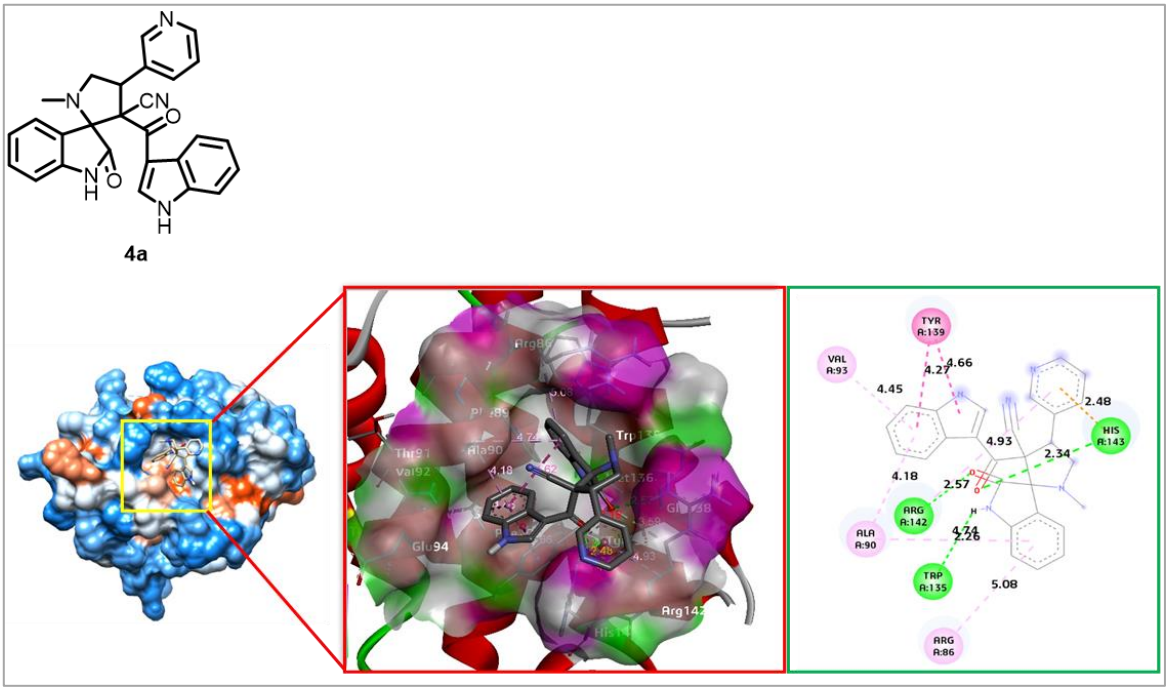


Figure SI-49: Binding mode of compound **4a** in Bcl2-receptor

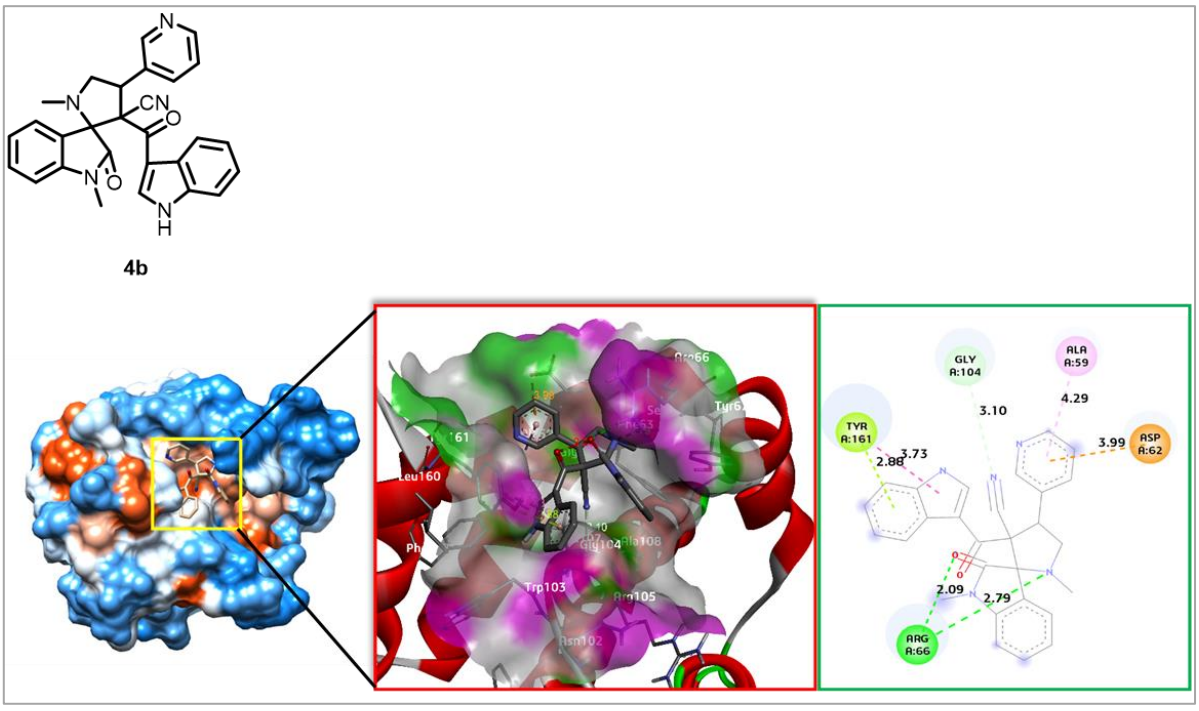


Figure SI-50: Binding mode of compound **4b** in Bcl2-receptor

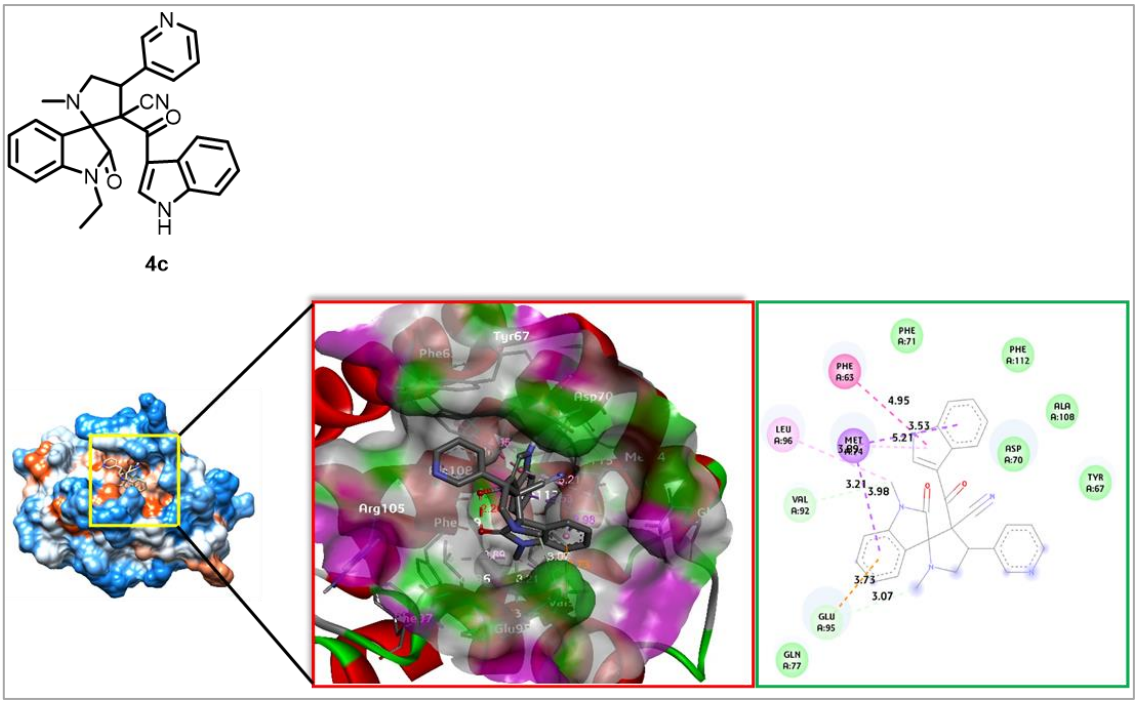


Figure SI-51: Binding mode of compound **4c** in Bcl2-receptor

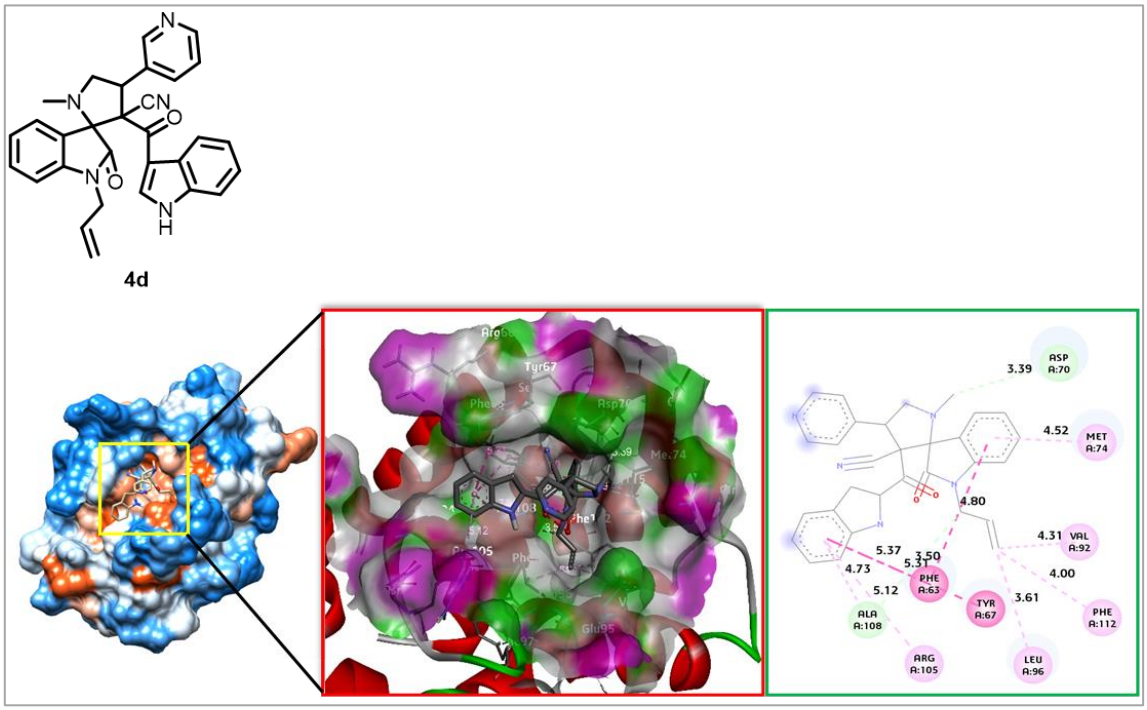


Figure SI-52: Binding mode of compound **4d** in Bcl2-receptor

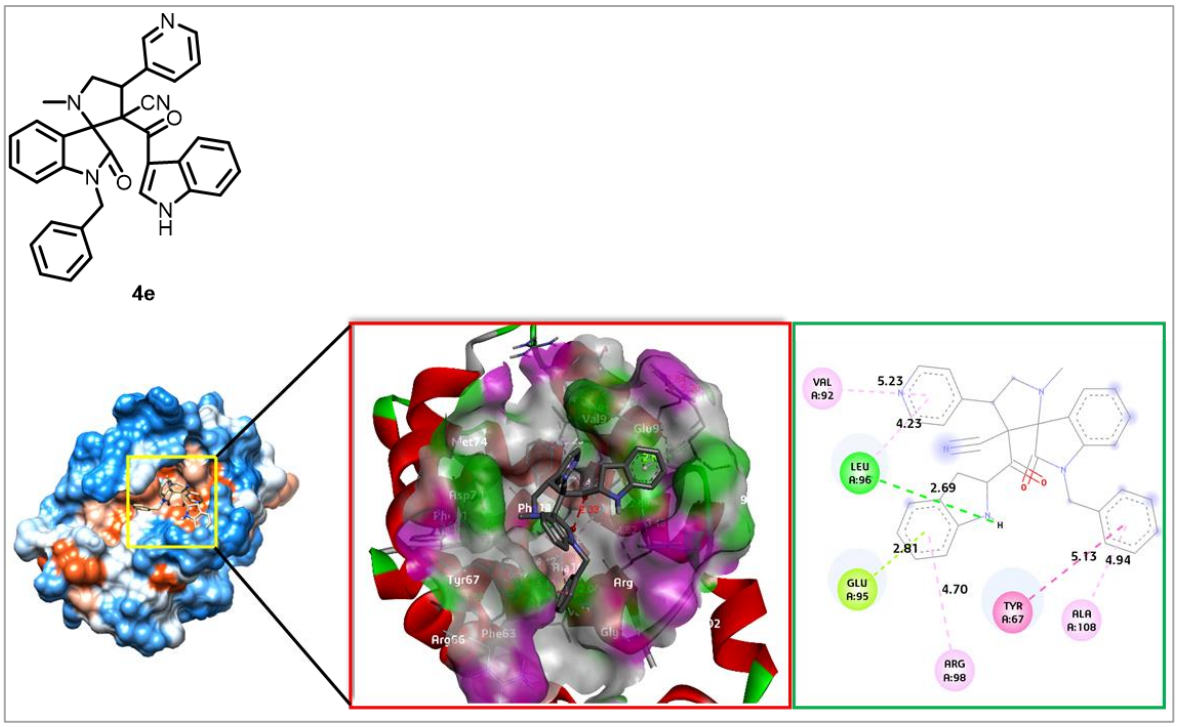


Figure SI-53: Binding mode of compound **4e** in Bcl2-receptor

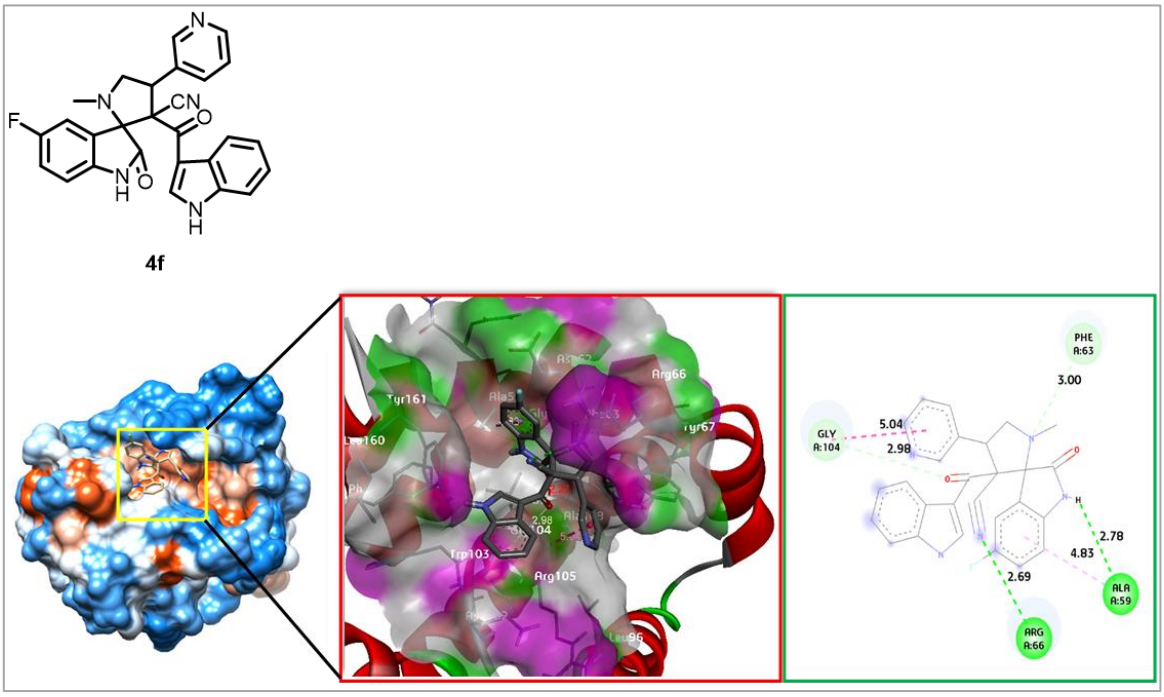


Figure SI-54: Binding mode of compound **4f** in Bcl2-receptor

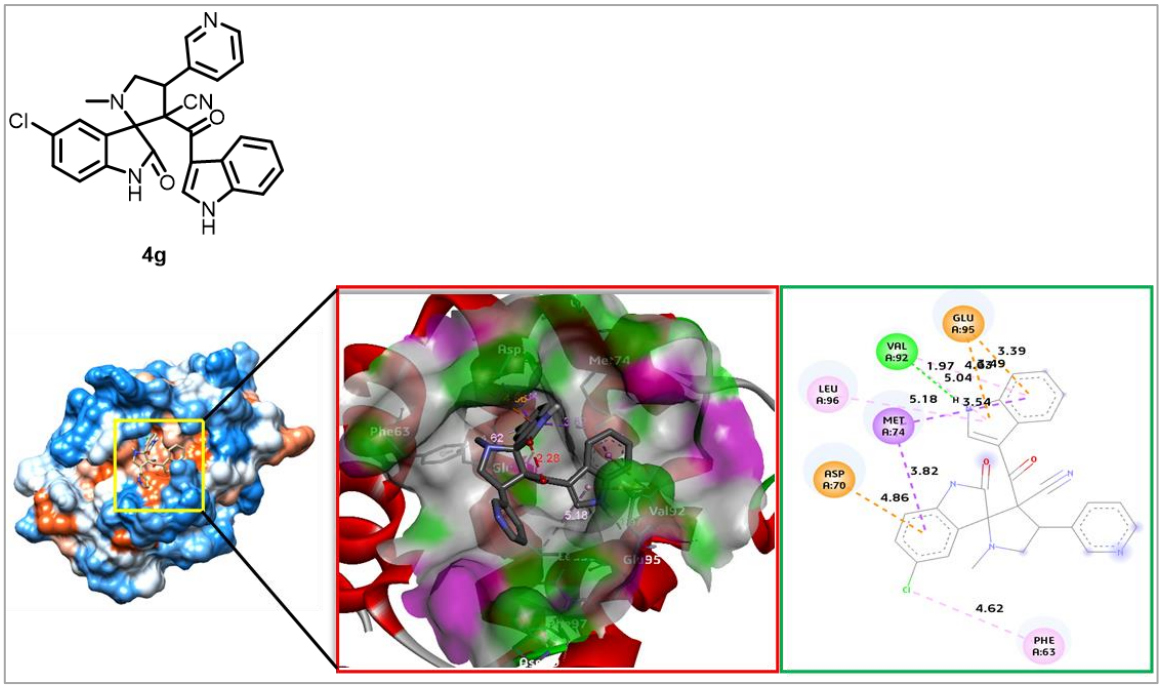


Figure SI-55: Binding mode of compound **4g** in Bcl2-receptor

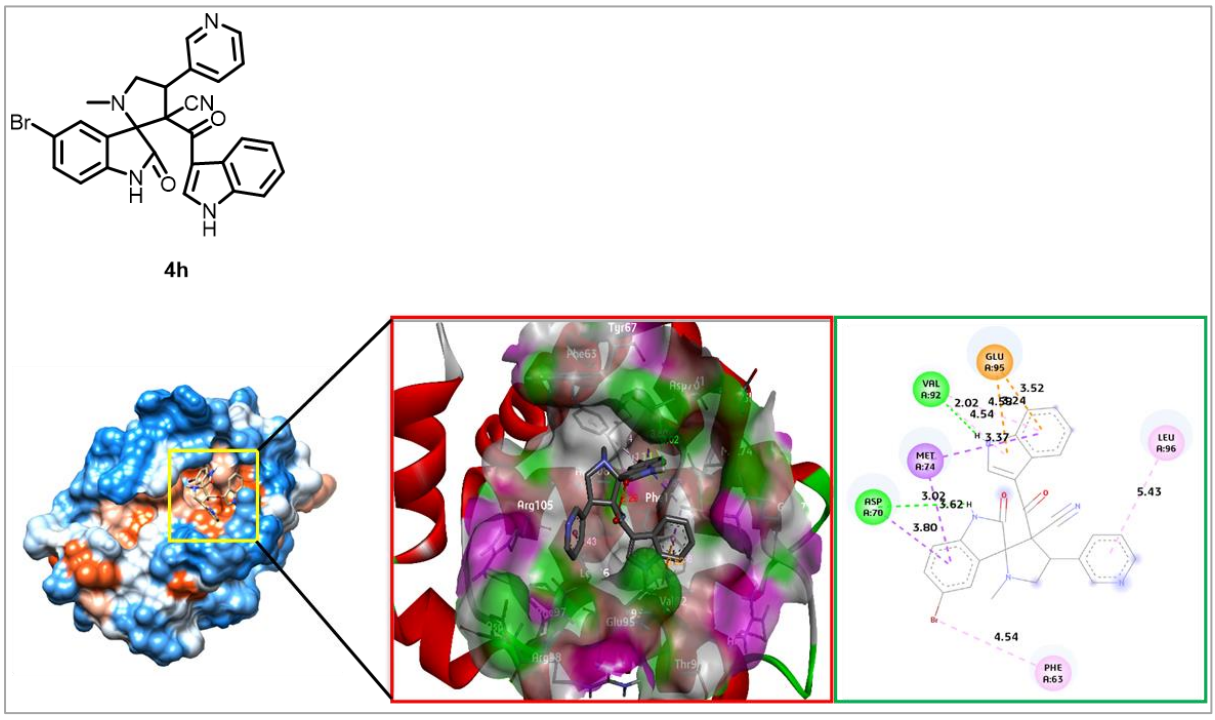


Figure SI-56: Binding mode of compound **4h** in Bcl2-receptor

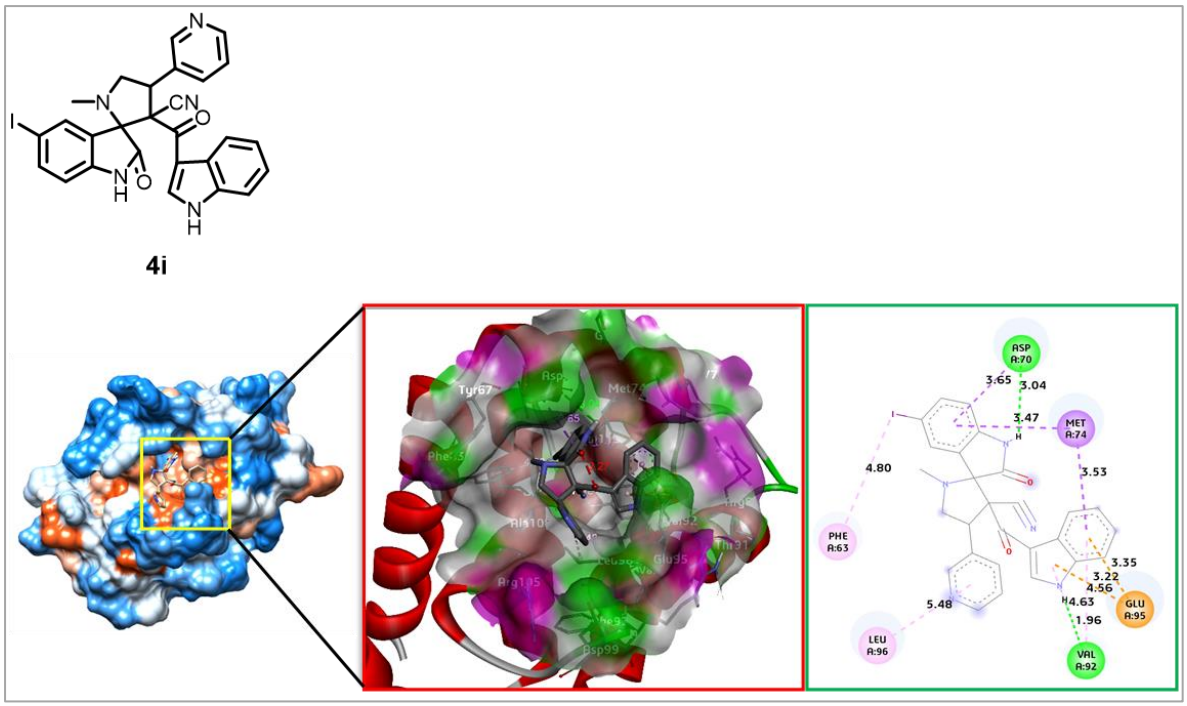


Figure SI-57: Binding mode of compound **4i** in Bcl2-receptor

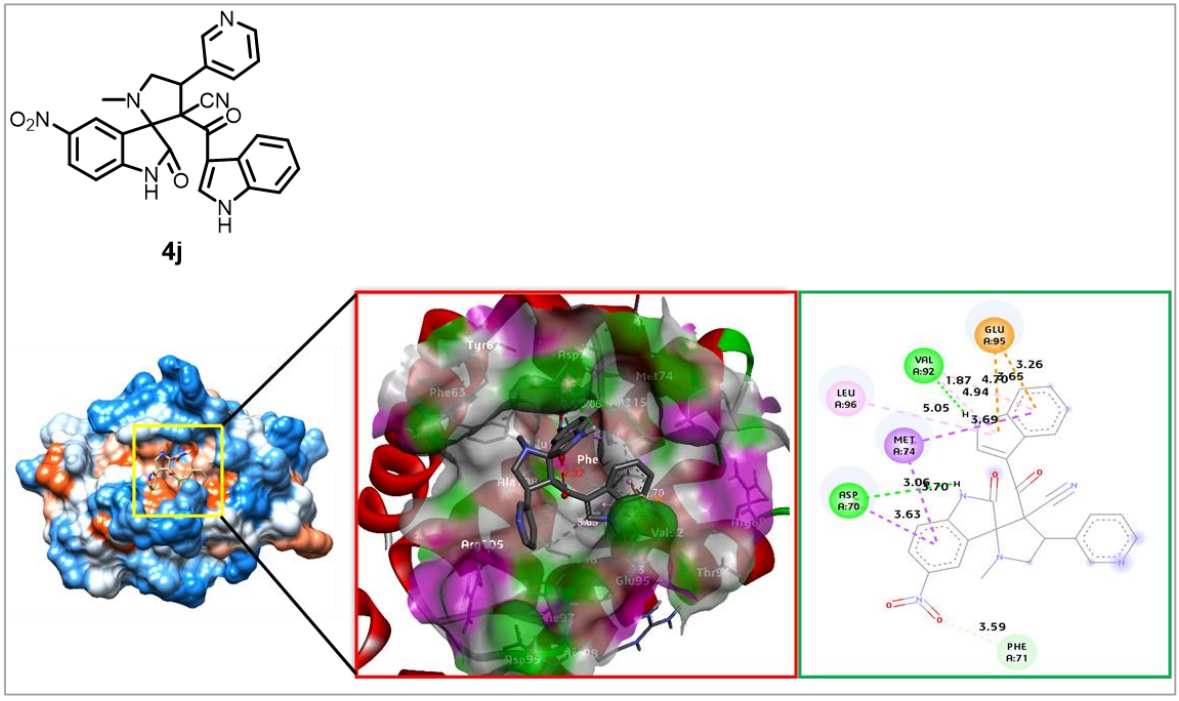


Figure SI-58: Binding mode of compound **4j** in Bcl2-receptor

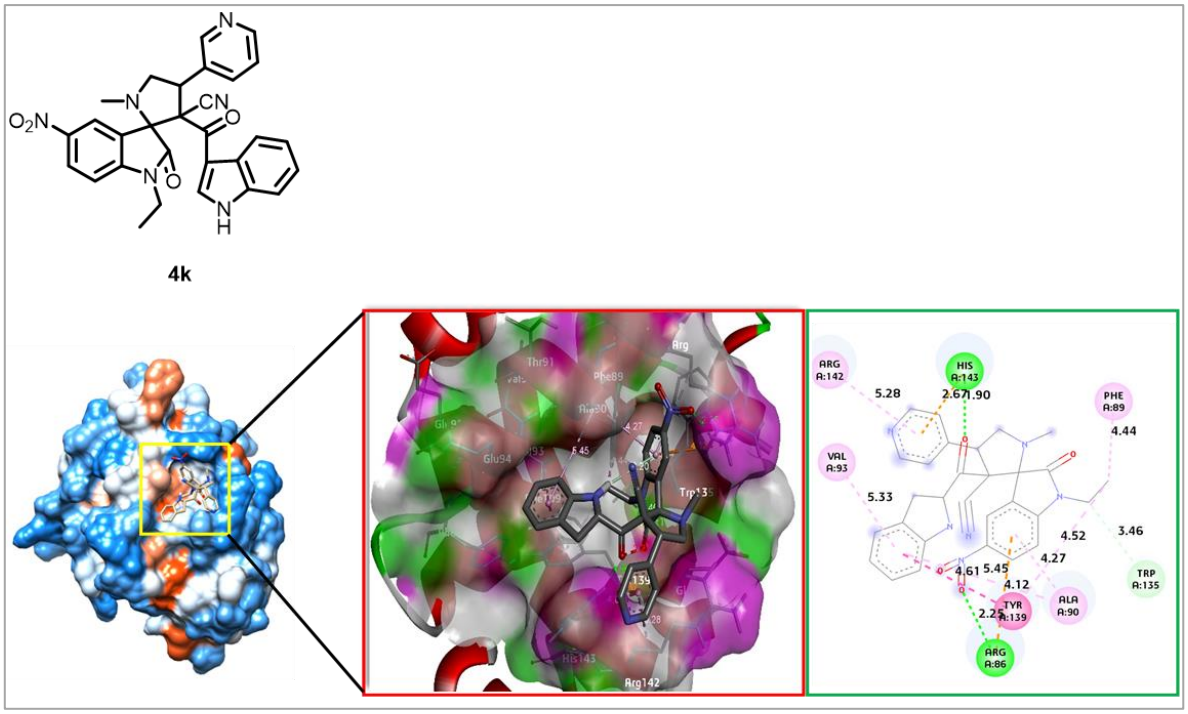


Figure SI-59: Binding mode of compound **4k** in Bcl2-receptor

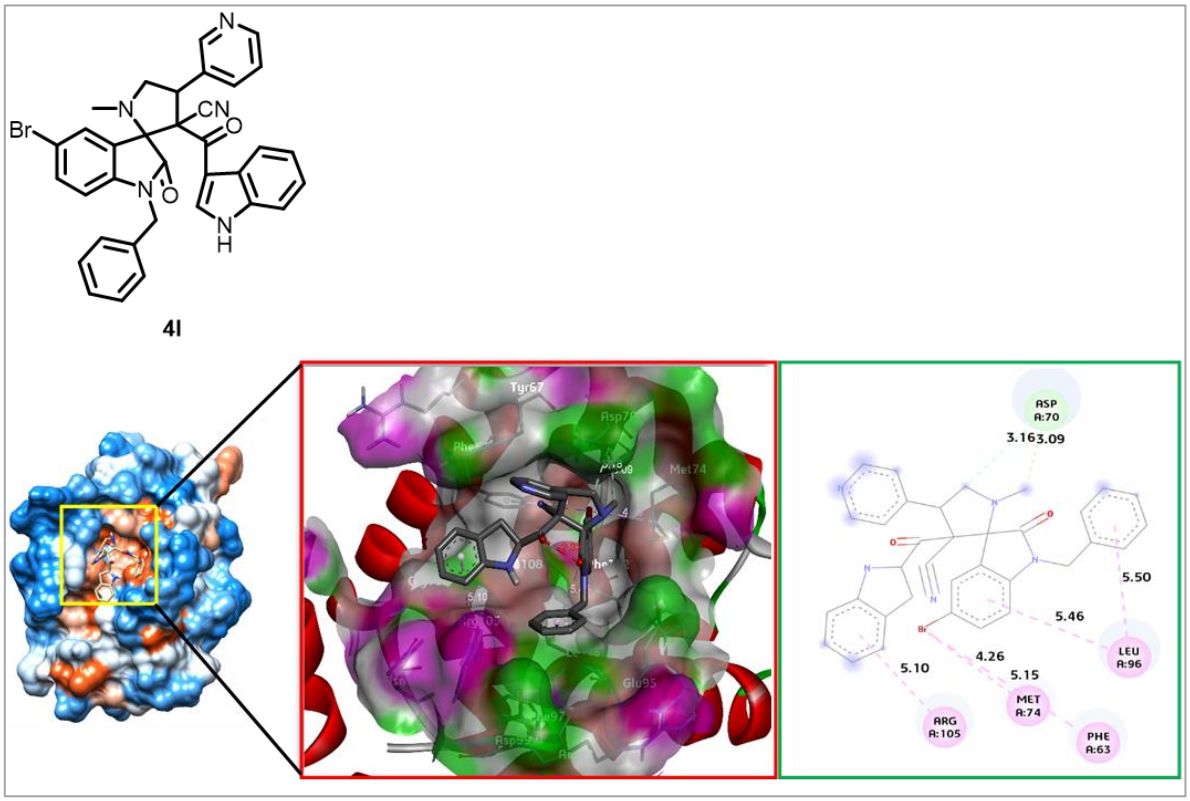


Figure SI-60: Binding mode of compound **4l** in Bcl2-receptor

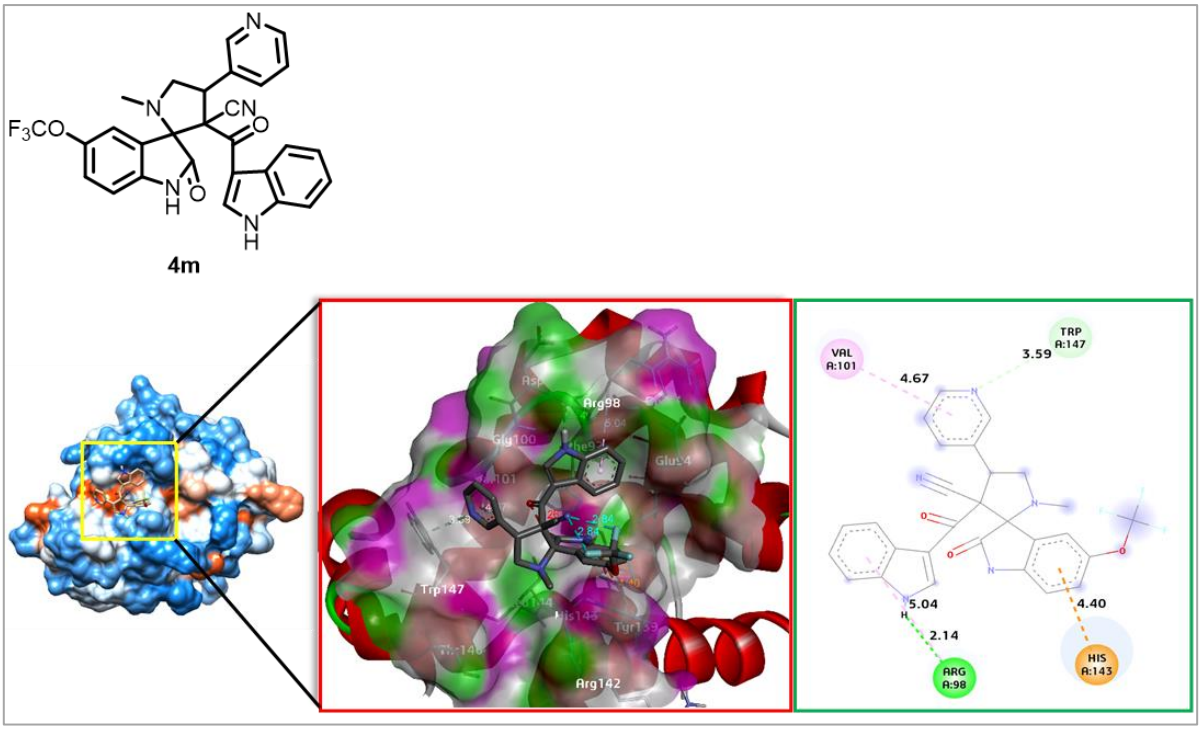


Figure SI-61: Binding mode of compound **4m** in Bcl2-receptor

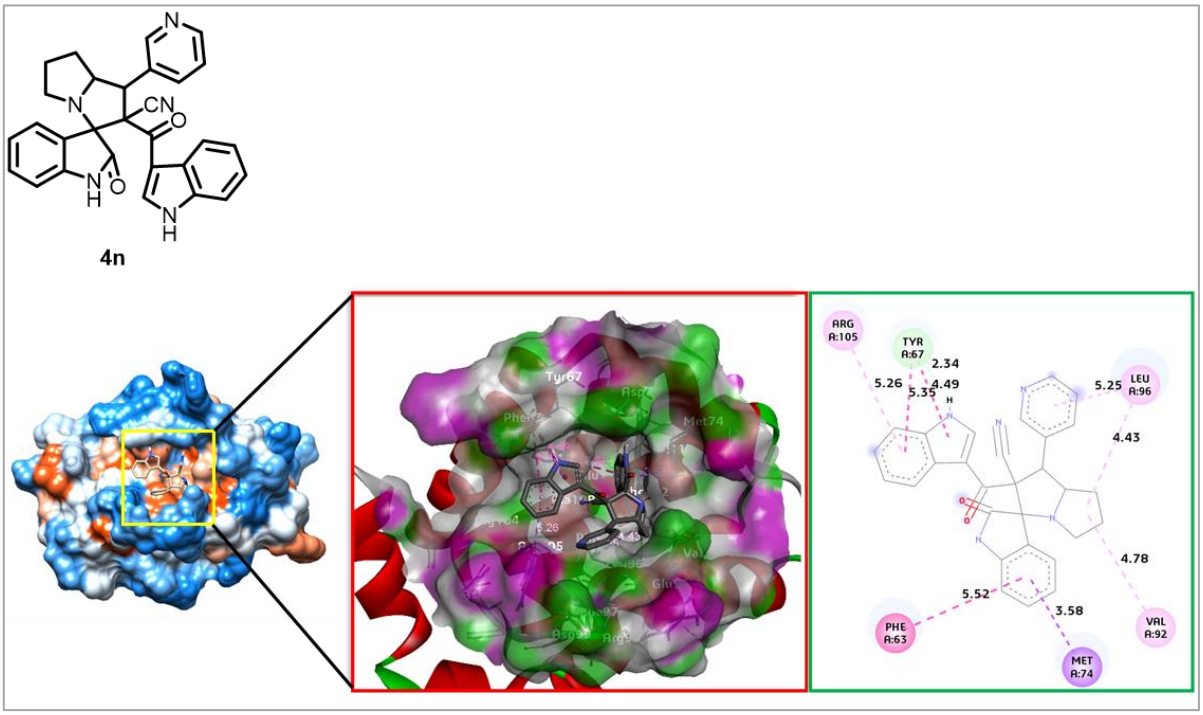


Figure SI-62: Binding mode of compound **4n** in Bcl2-receptor

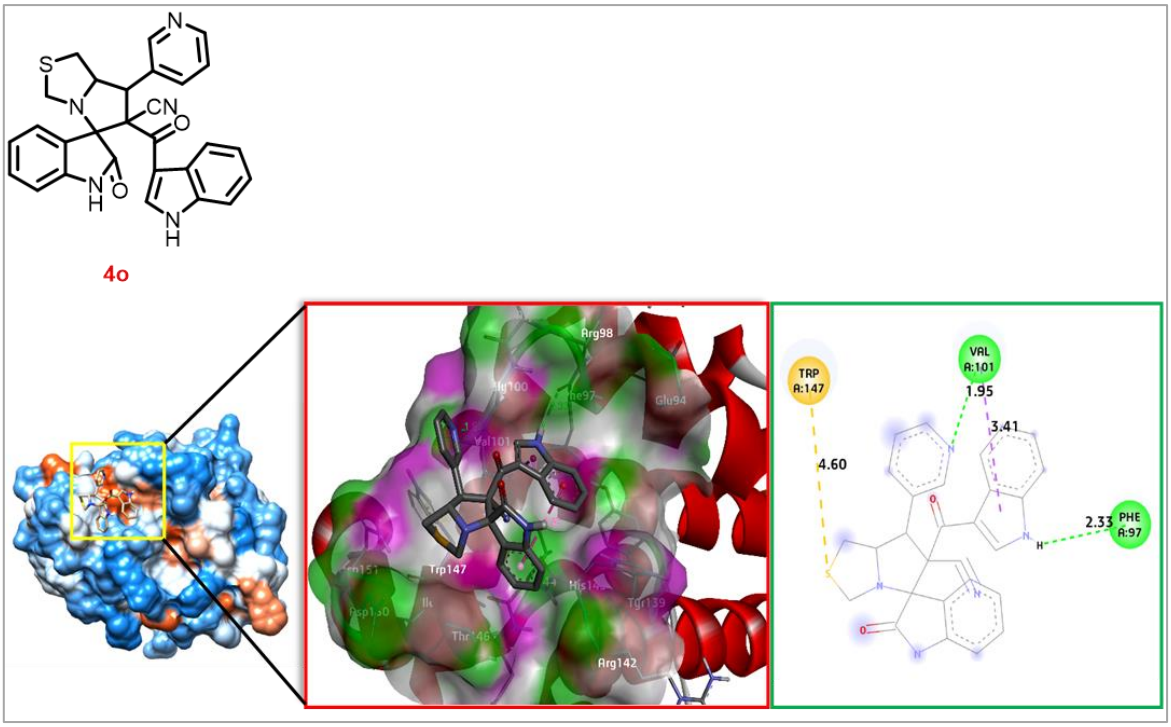


Figure SI-63: Binding mode of compound **4o** in Bcl2-receptor

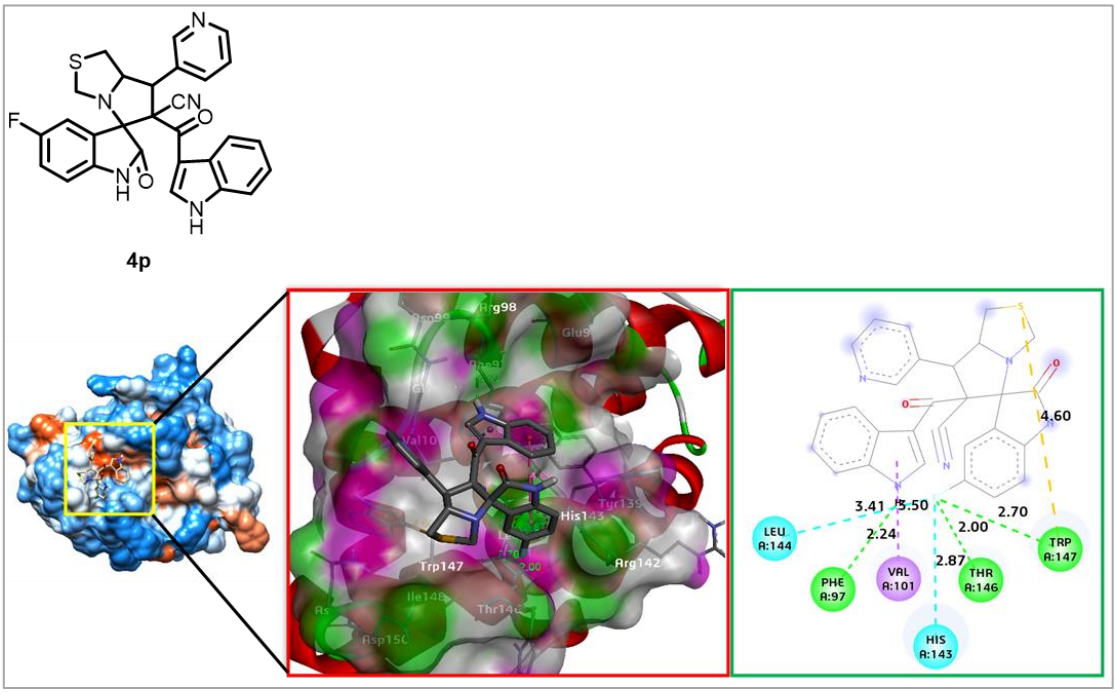


Figure SI-64: Binding mode of compound **4p** in Bcl2-receptor

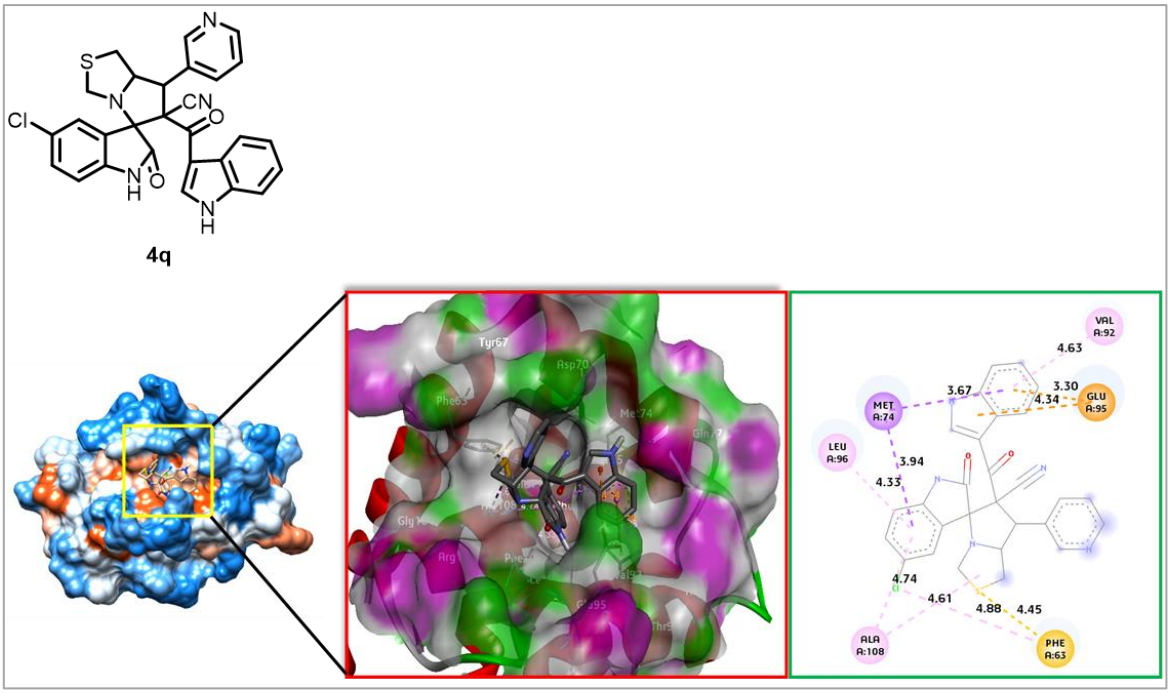


Figure SI-65: Binding mode of compound **4q** in Bcl2-receptor

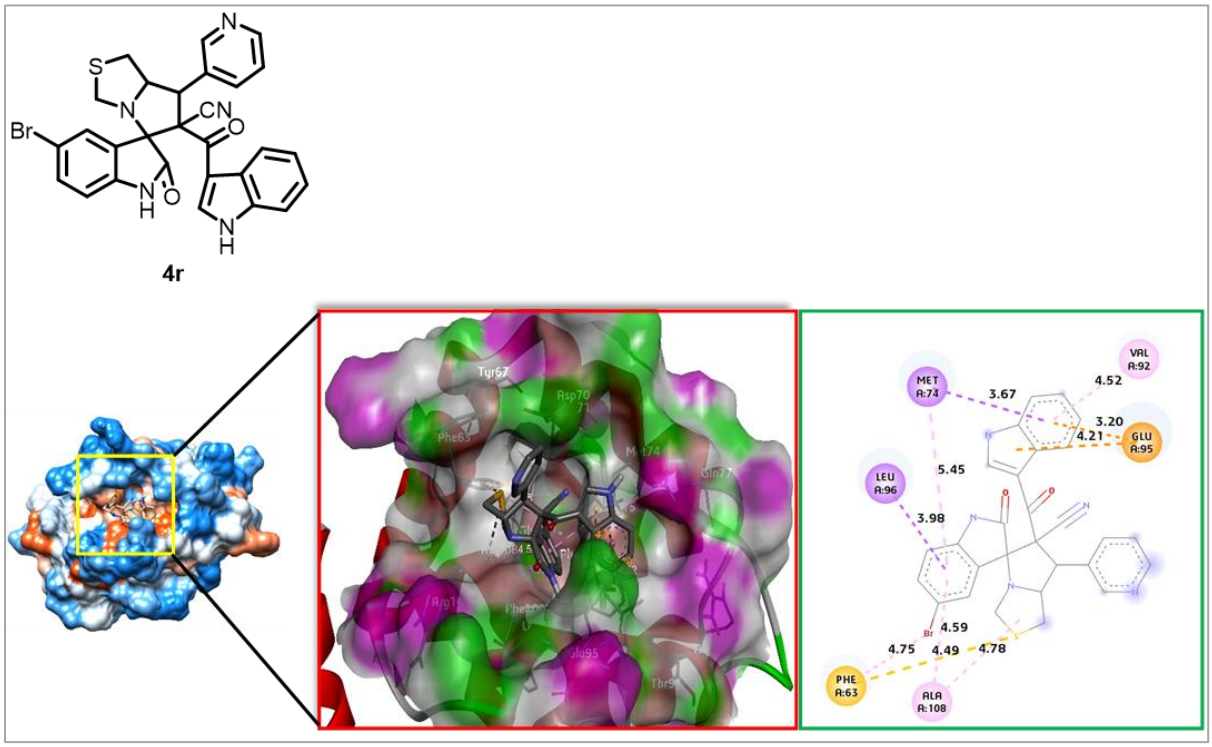


Figure SI-66: Binding mode of compound **4r** in Bcl2-receptor

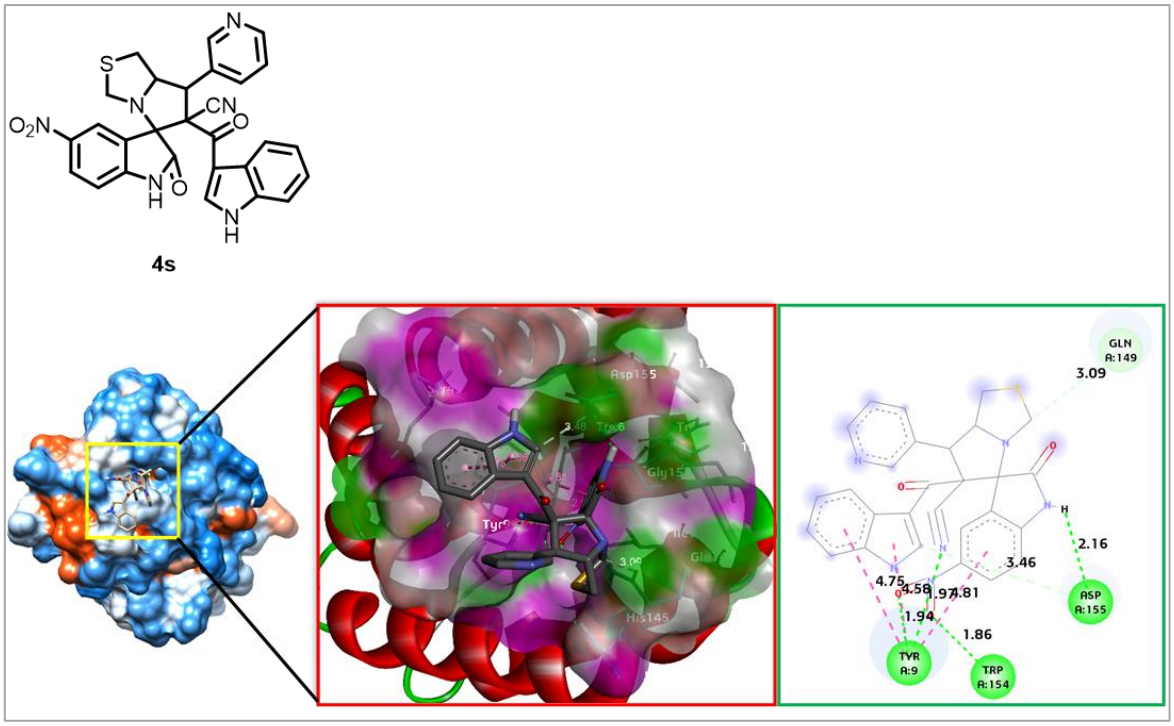


Figure SI-67: Binding mode of compound **4s** in Bcl2-receptor

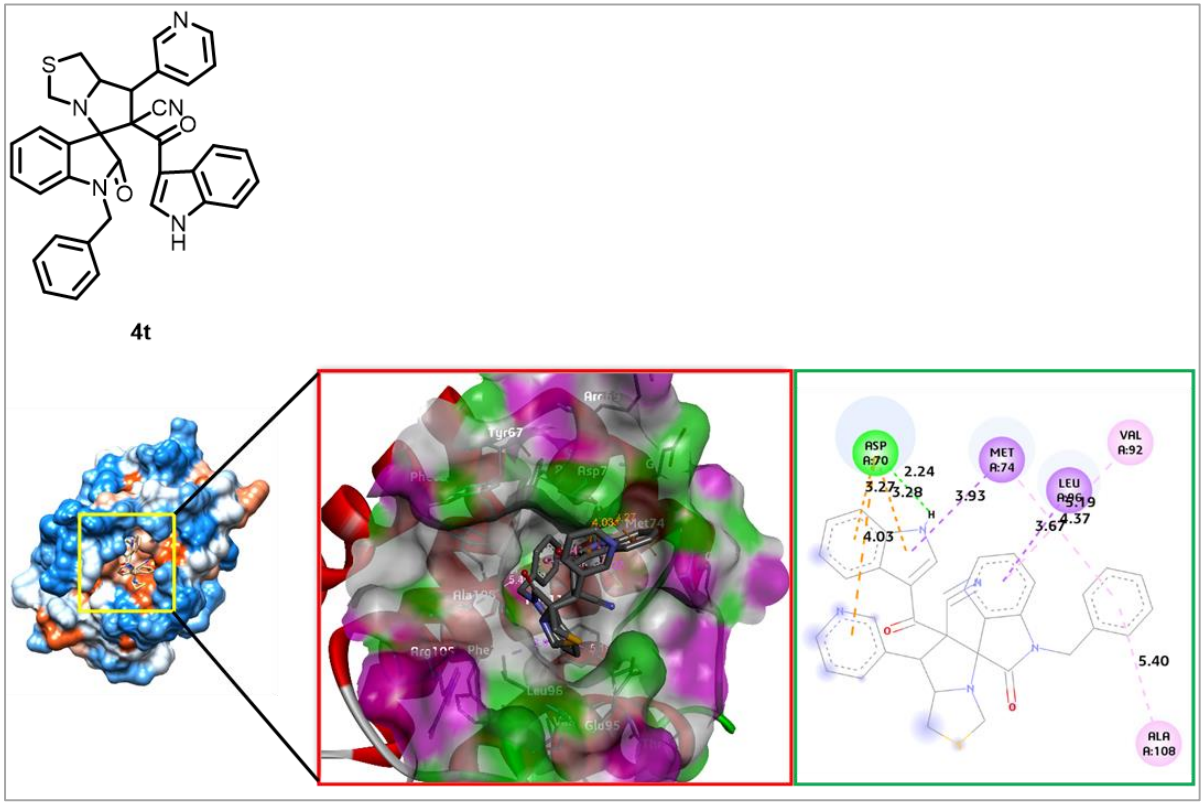


Figure SI-68: Binding mode of compound **4t** in Bcl2-receptor

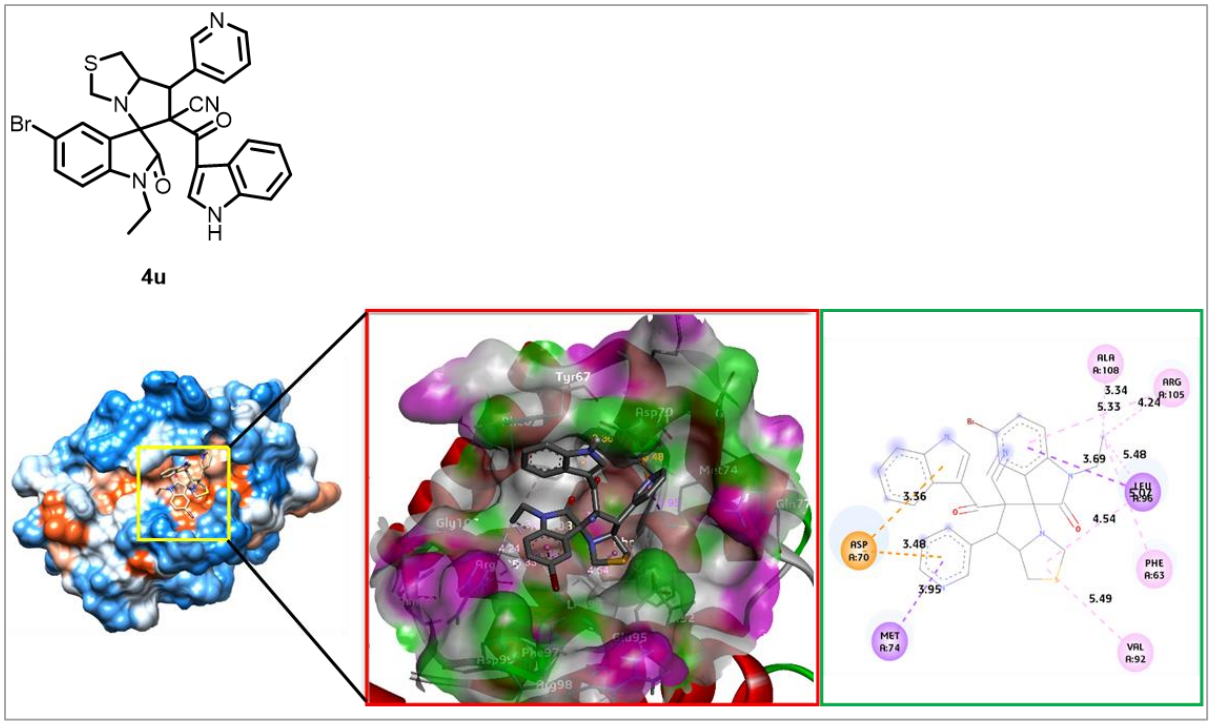


Figure SI-69: Binding mode of compound **4u** in Bcl2-receptor

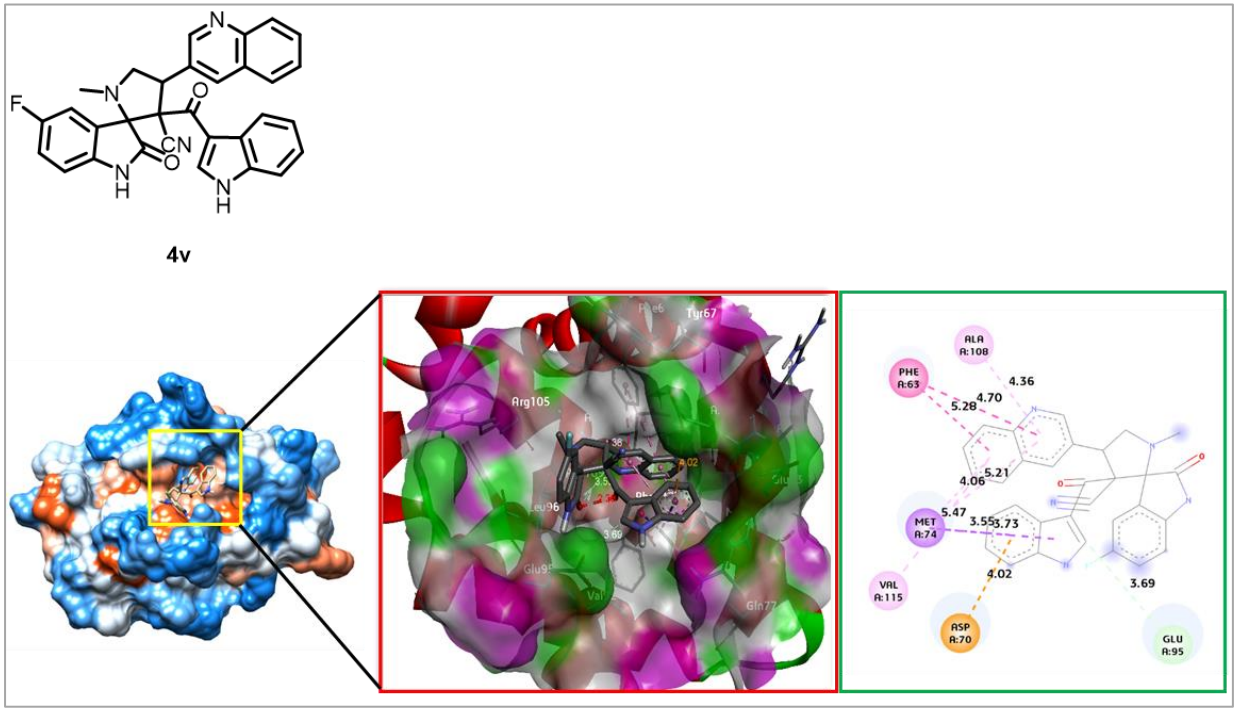


Figure SI-70: Binding mode of compound **4v** in Bcl2-receptor

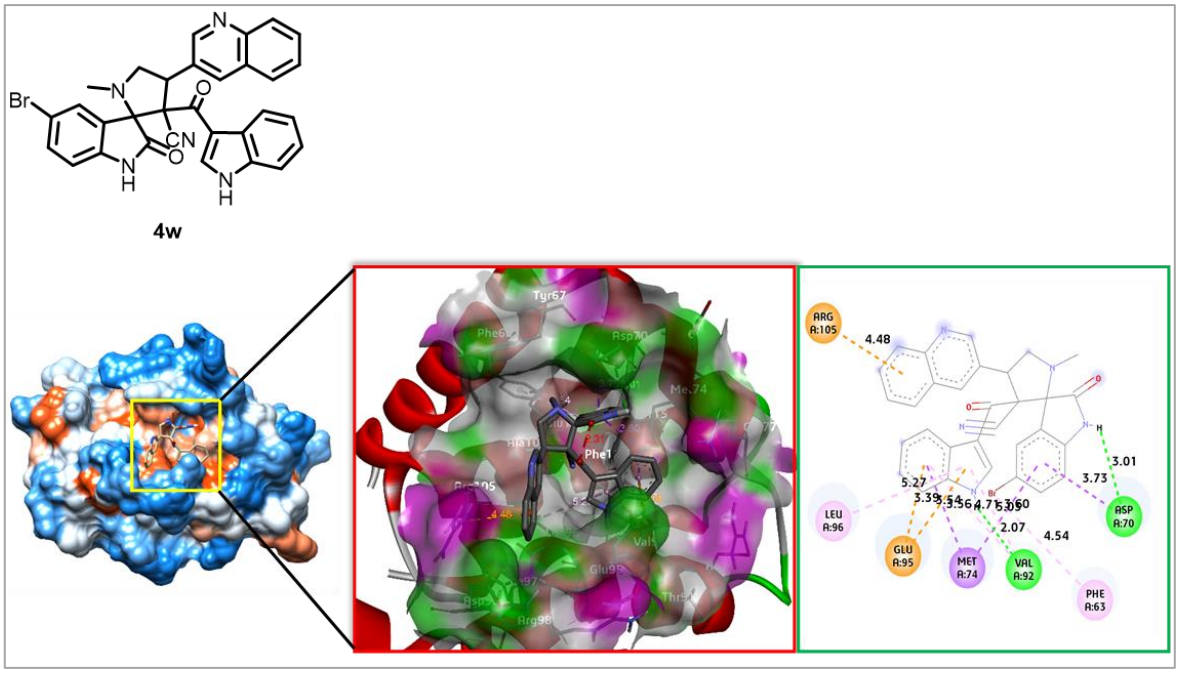


Figure SI-71: Binding mode of compound **4w** in Bcl2-receptor

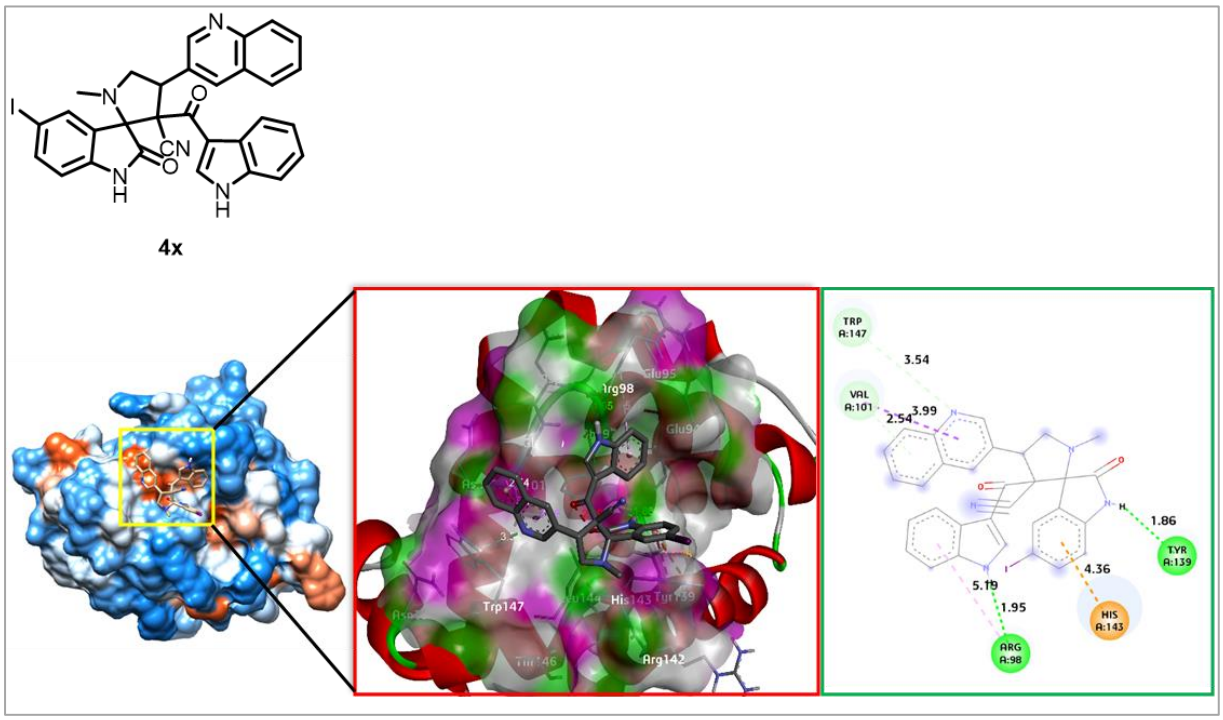


Figure SI-72: Binding mode of compound **4x** in Bcl2-receptor

Crystallised Ligand Bcl2 receptor

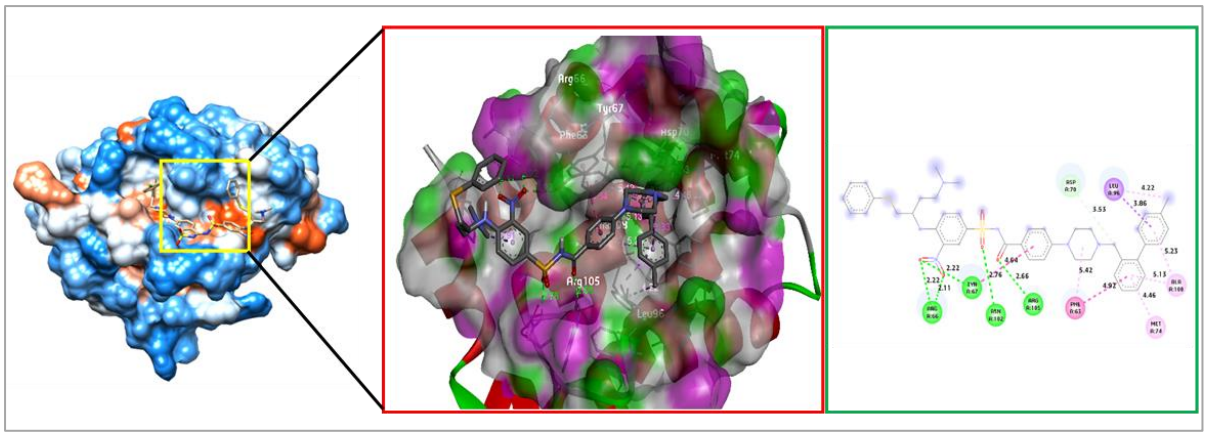


Figure SI-73: Binding mode of compound **crystallised ligand** in Bcl2-receptor

12. Molecular docking studies of compound (4a-x) with ALK-receptor(2XP2)

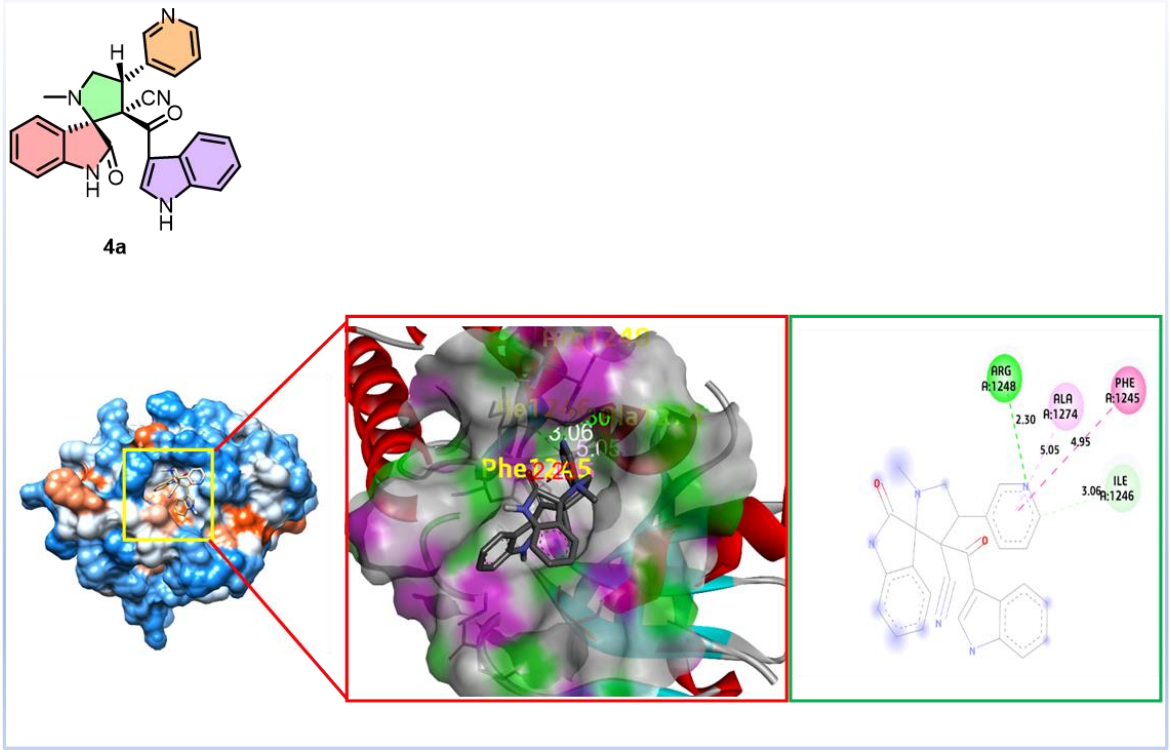


Figure SI-74: Binding mode of compound **4a** in Alk-receptor

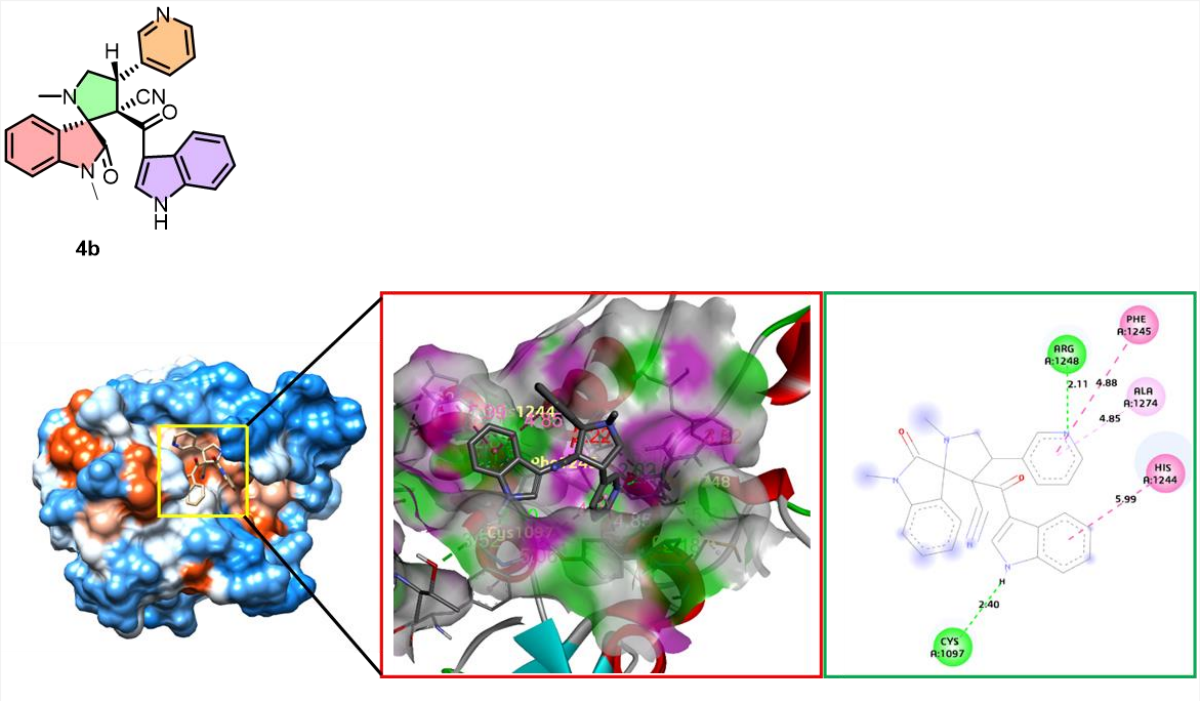


Figure SI-75: Binding mode of compound **4b** in Alk-receptor

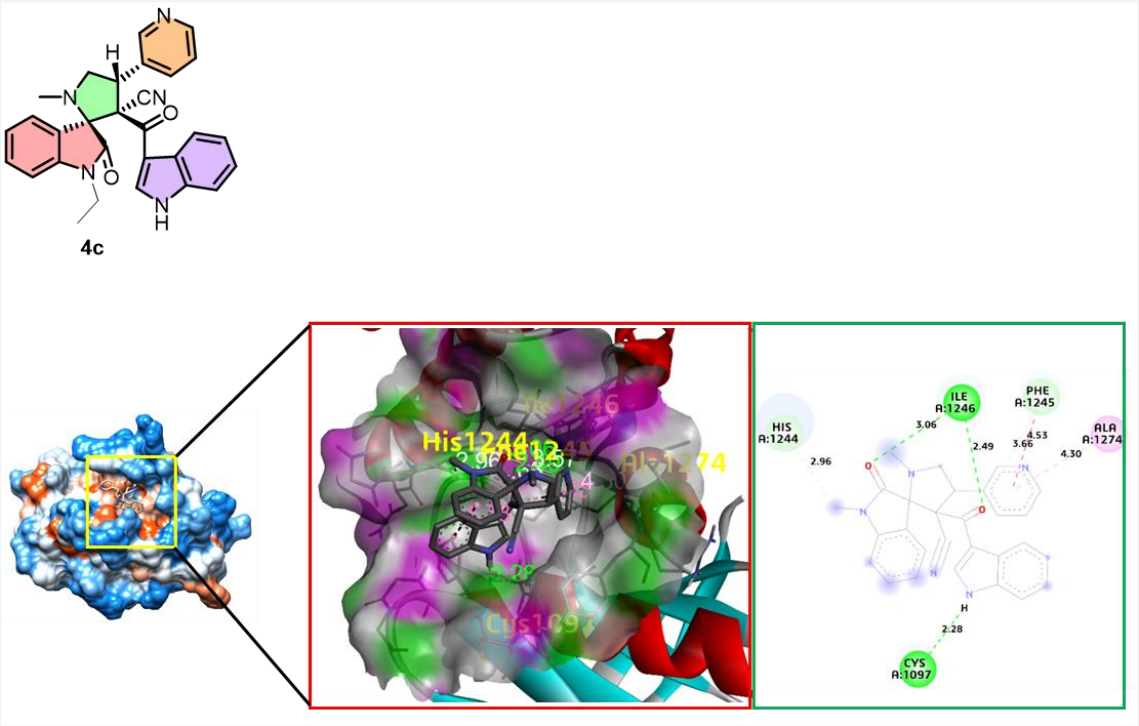


Figure SI-76: Binding mode of compound **4c** in Alk-receptor

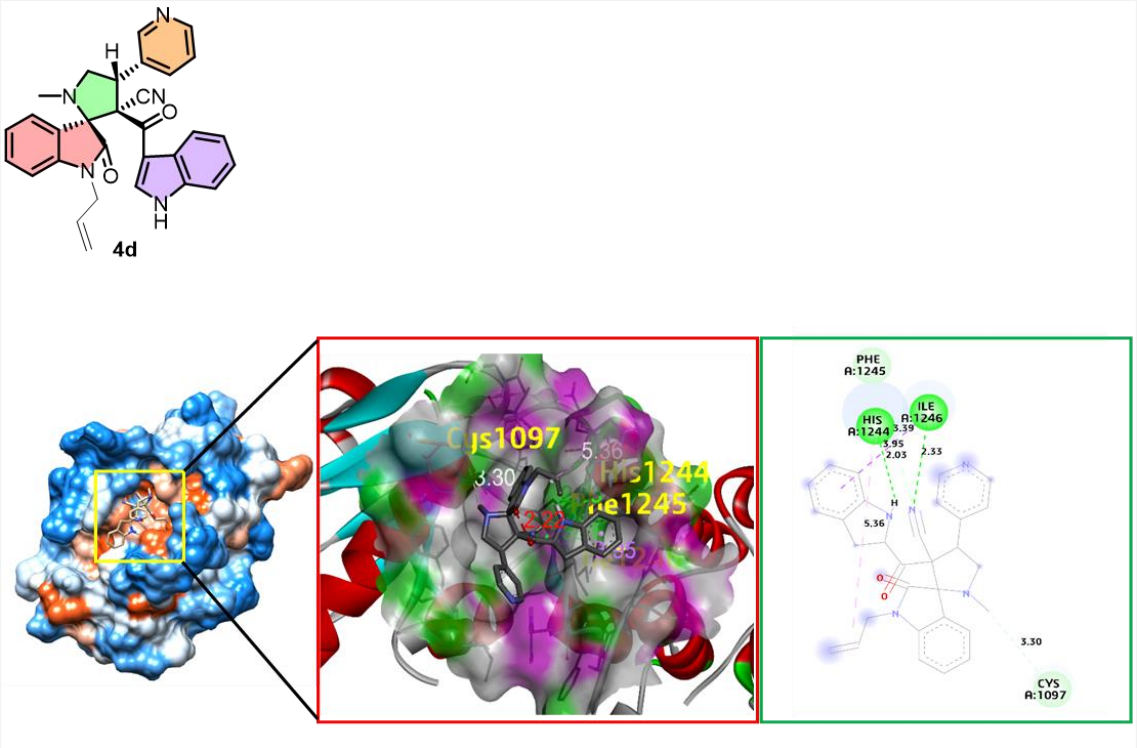


Figure SI-77: Binding mode of compound **4d** in Alk-receptor

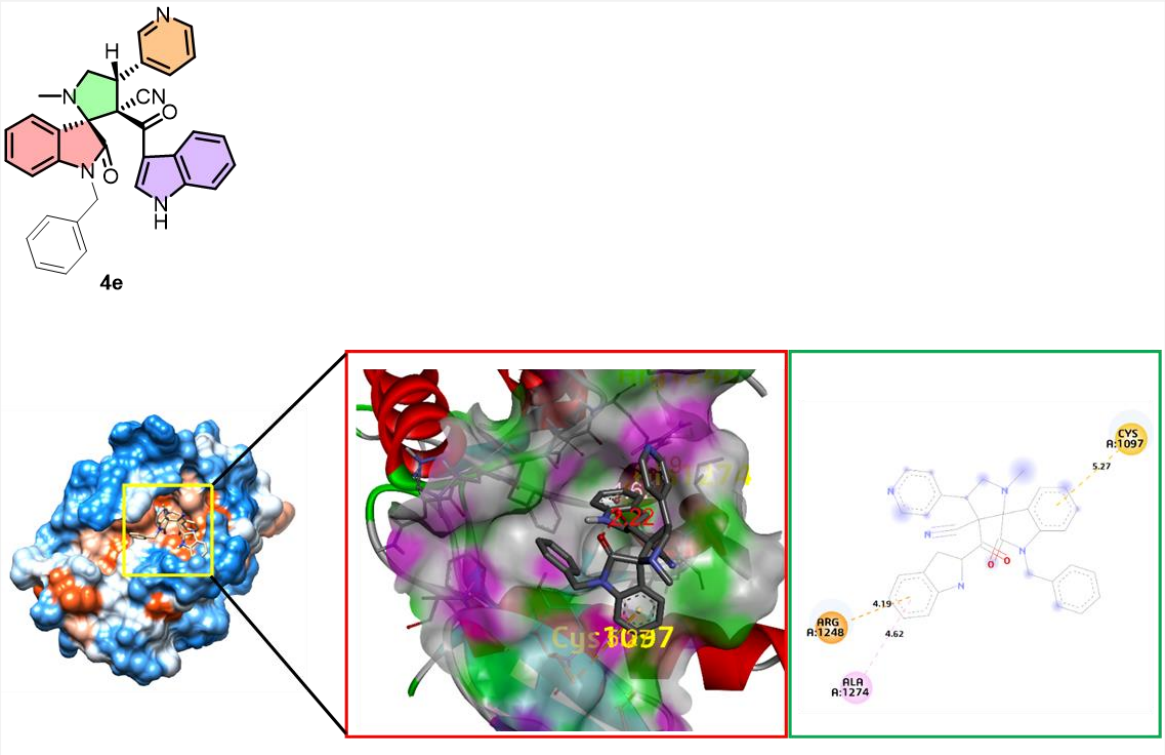


Figure SI-78: Binding mode of compound **4e** in Alk-receptor

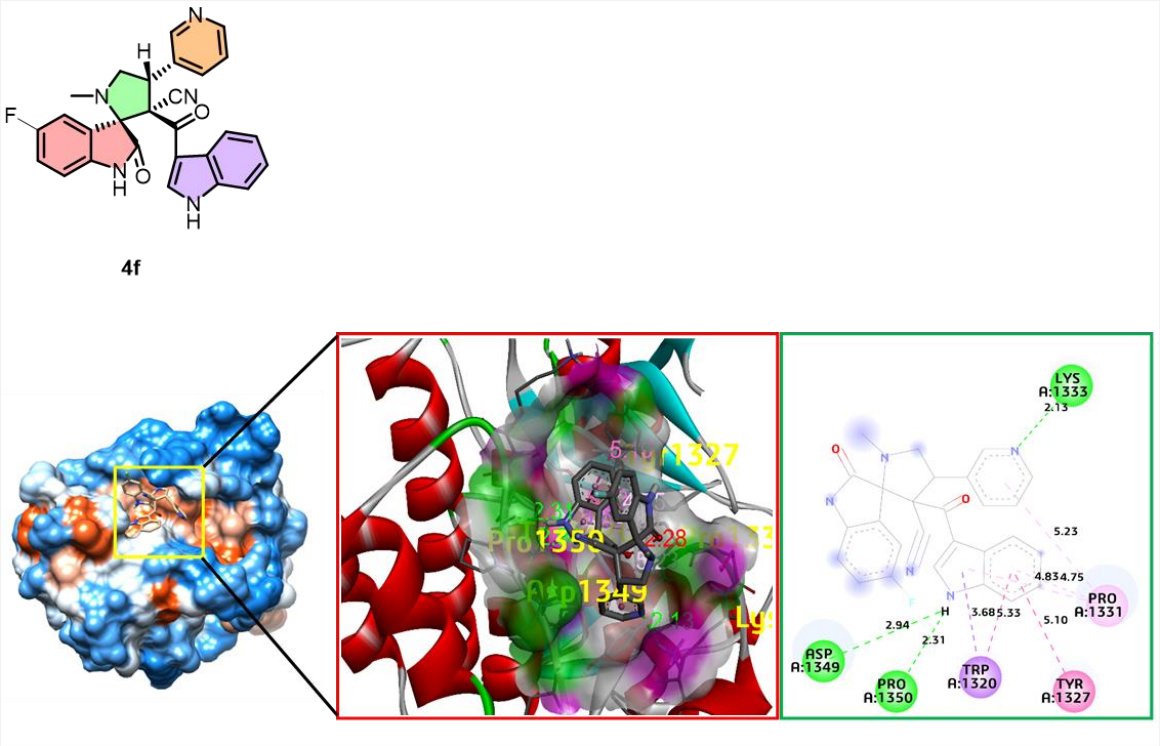


Figure SI-79: Binding mode of compound **4f** in Alk-receptor

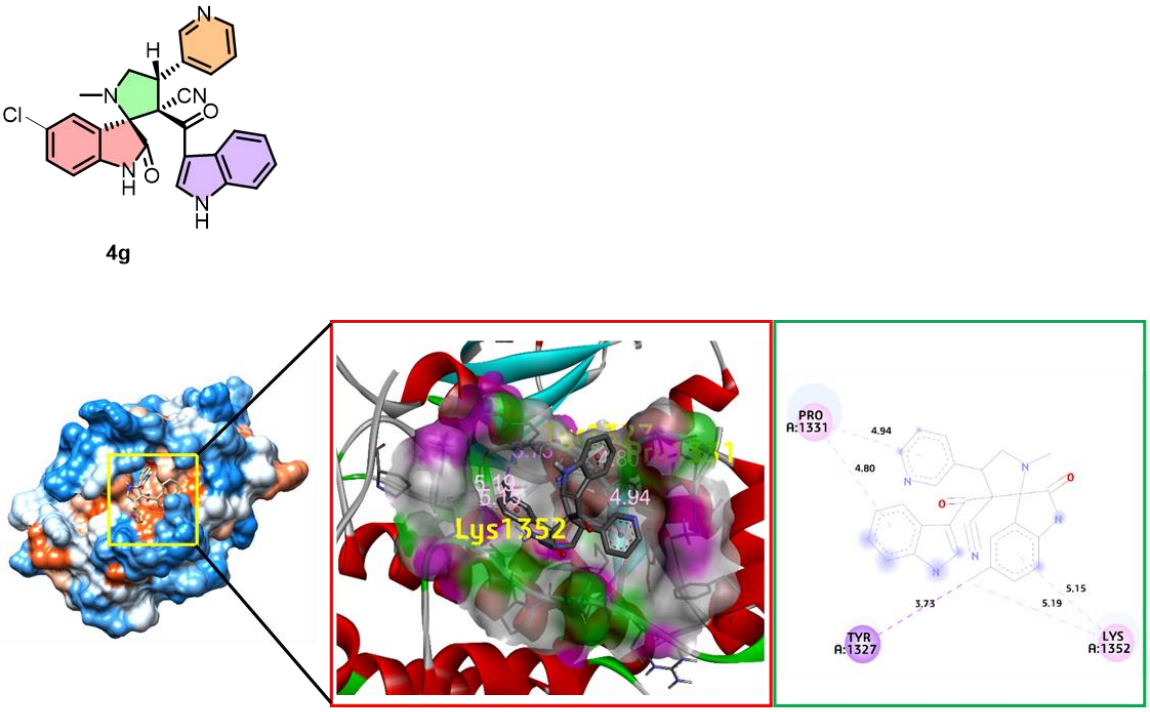


Figure SI-80: Binding mode of compound **4g** in Alk-receptor

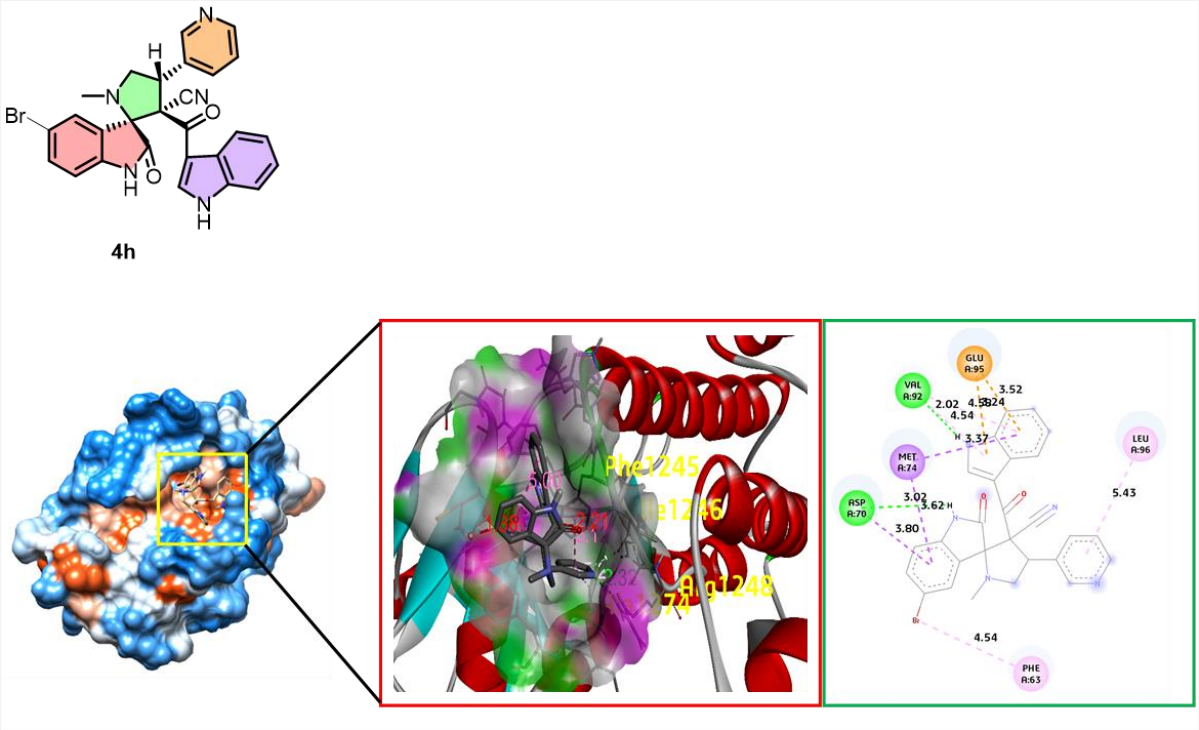


Figure SI-81: Binding mode of compound **4h** in Alk-receptor

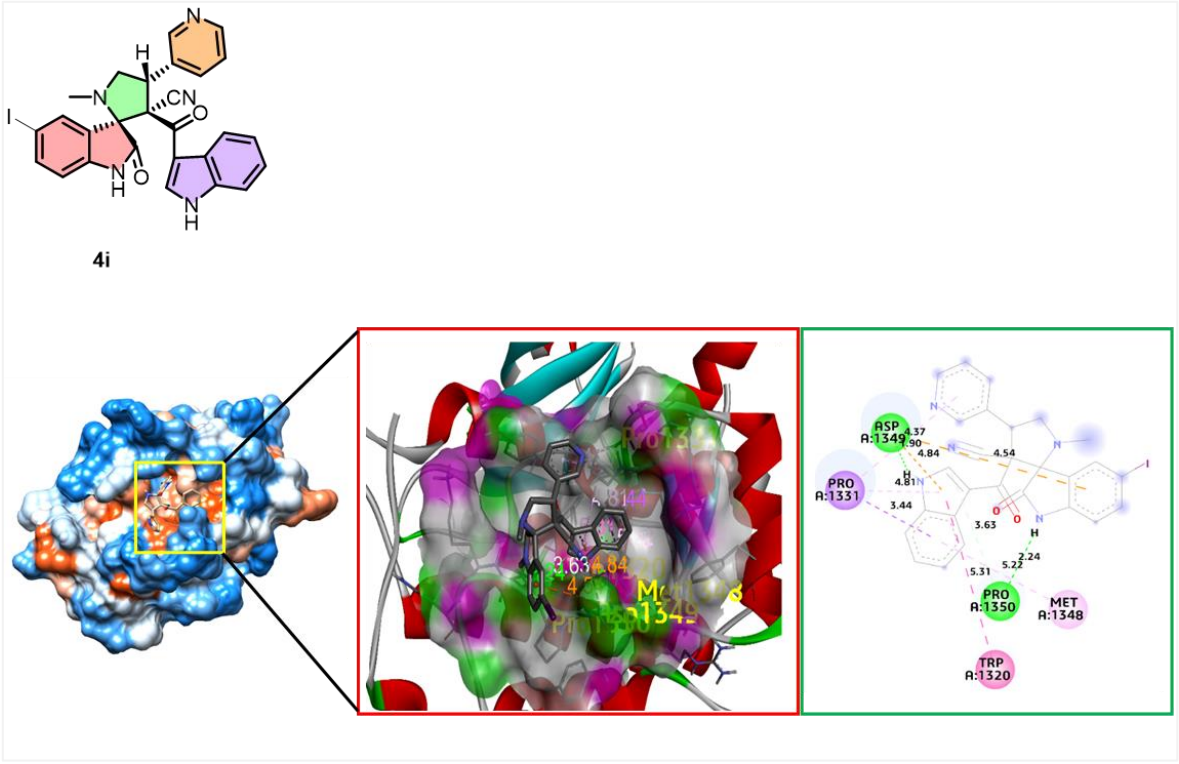


Figure SI-82: Binding mode of compound **4i** in Alk-receptor

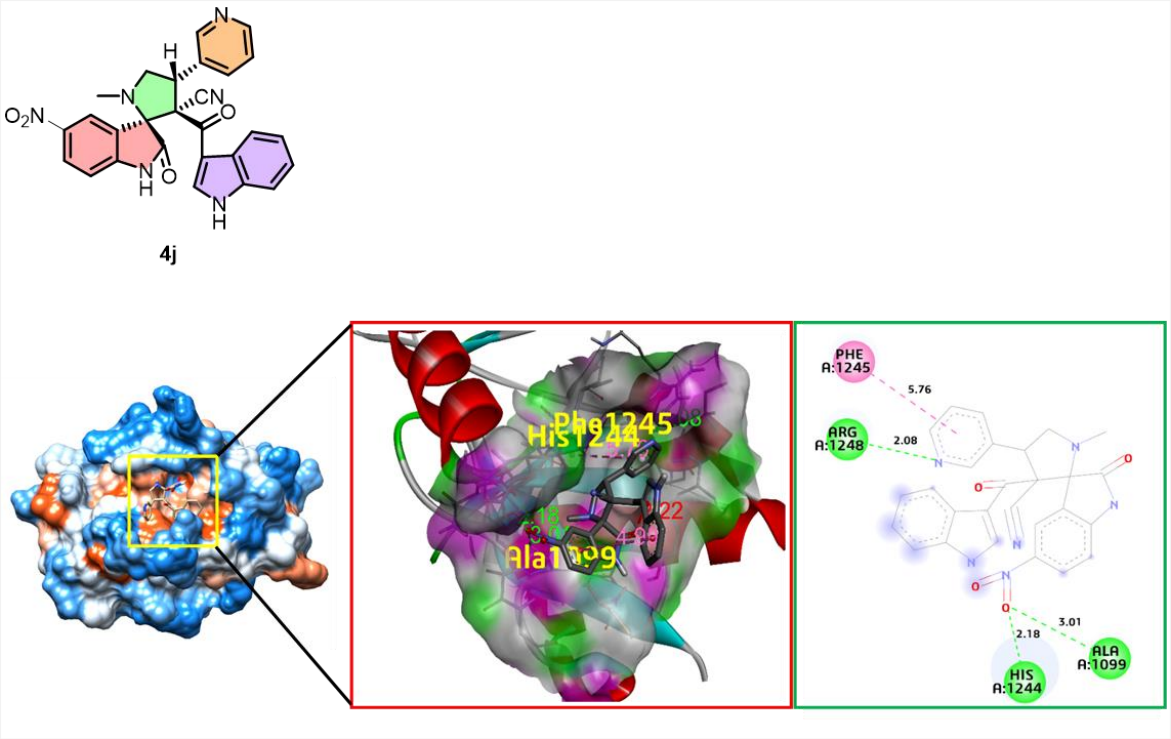


Figure SI-83: Binding mode of compound **4j** in Alk-receptor

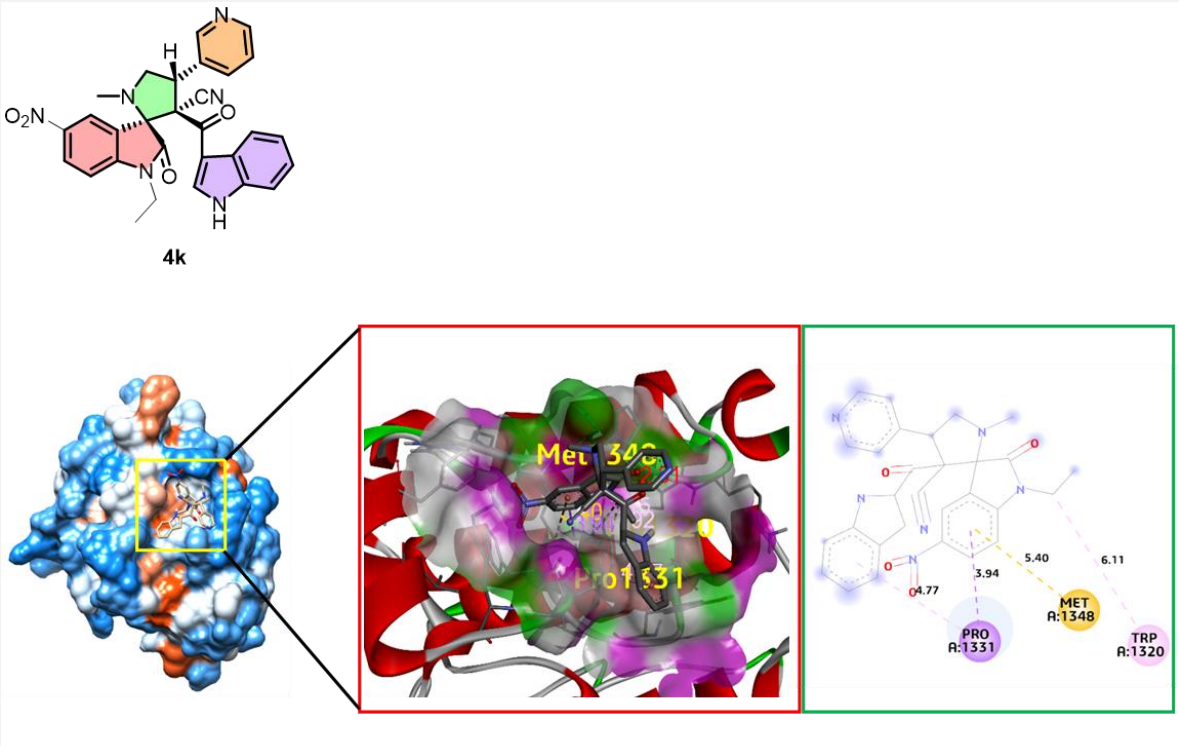


Figure SI-84: Binding mode of compound **4k** in Alk-receptor

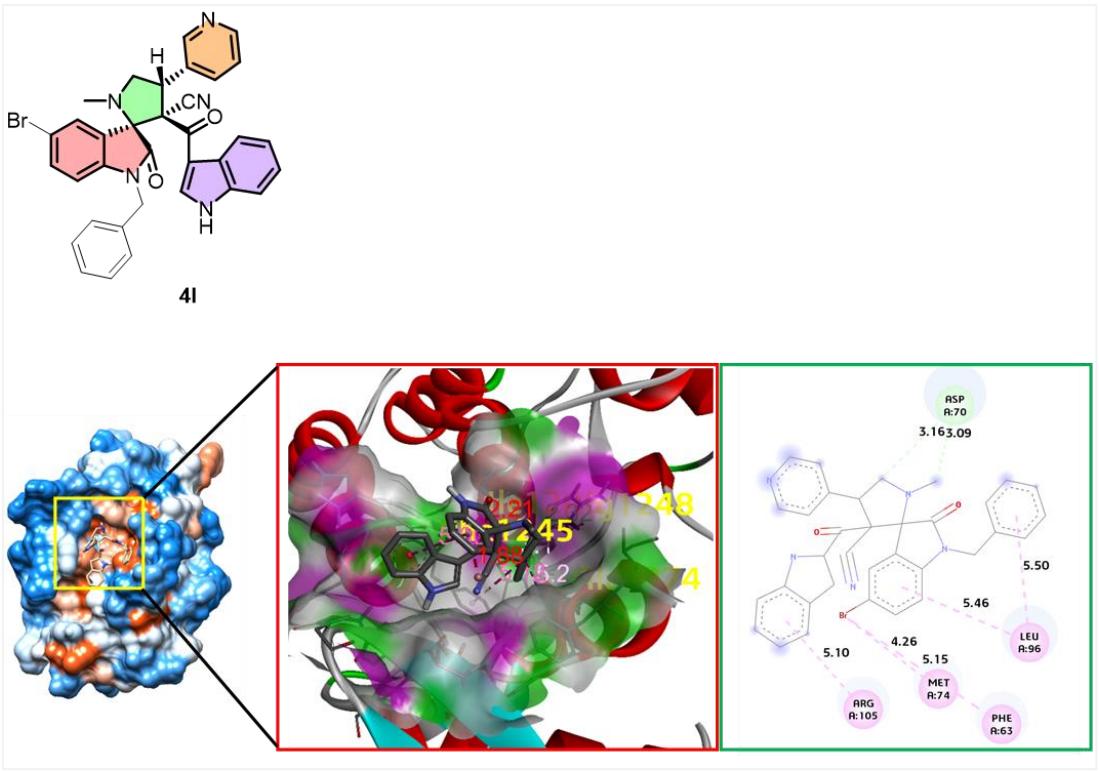


Figure SI-85: Binding mode of compound **4l** in Alk-receptor

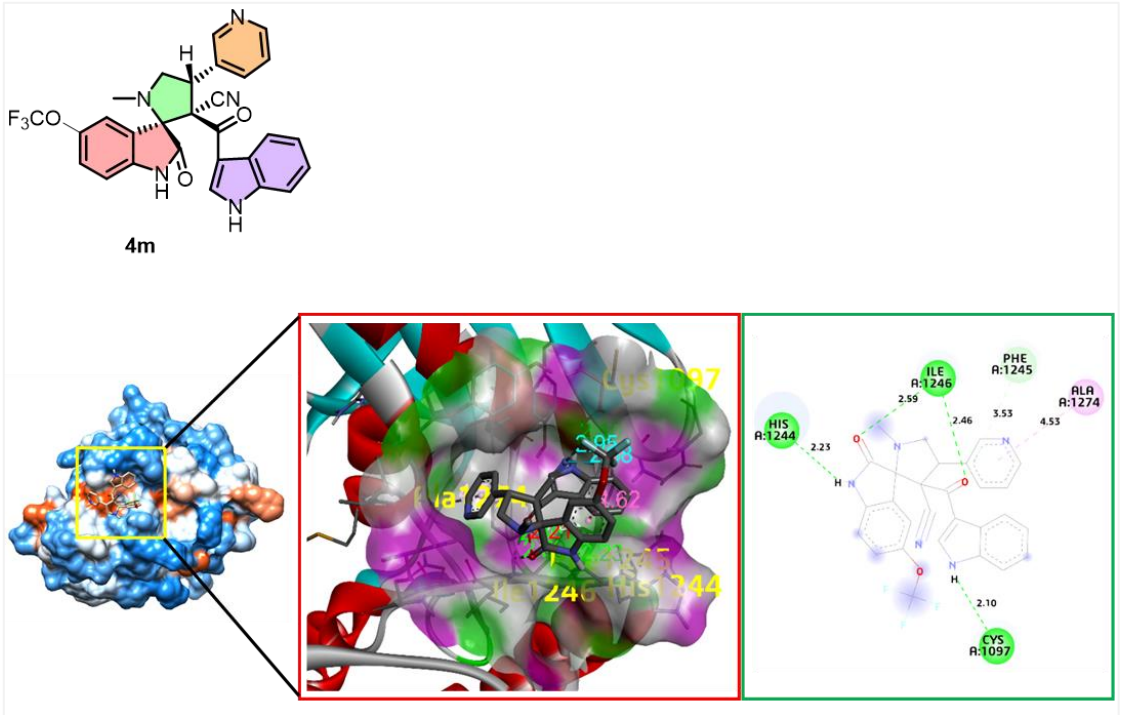


Figure SI-86: Binding mode of compound **4m** in Alk-receptor

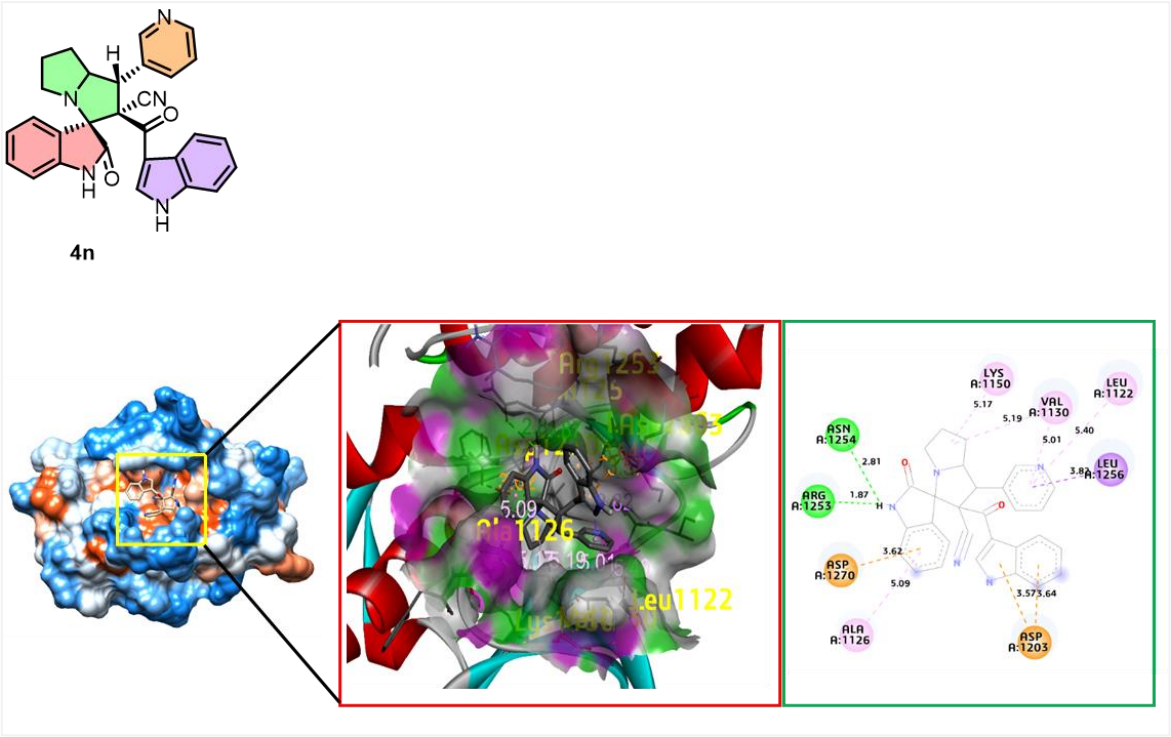


Figure SI-87: Binding mode of compound **4n** in Alk-receptor

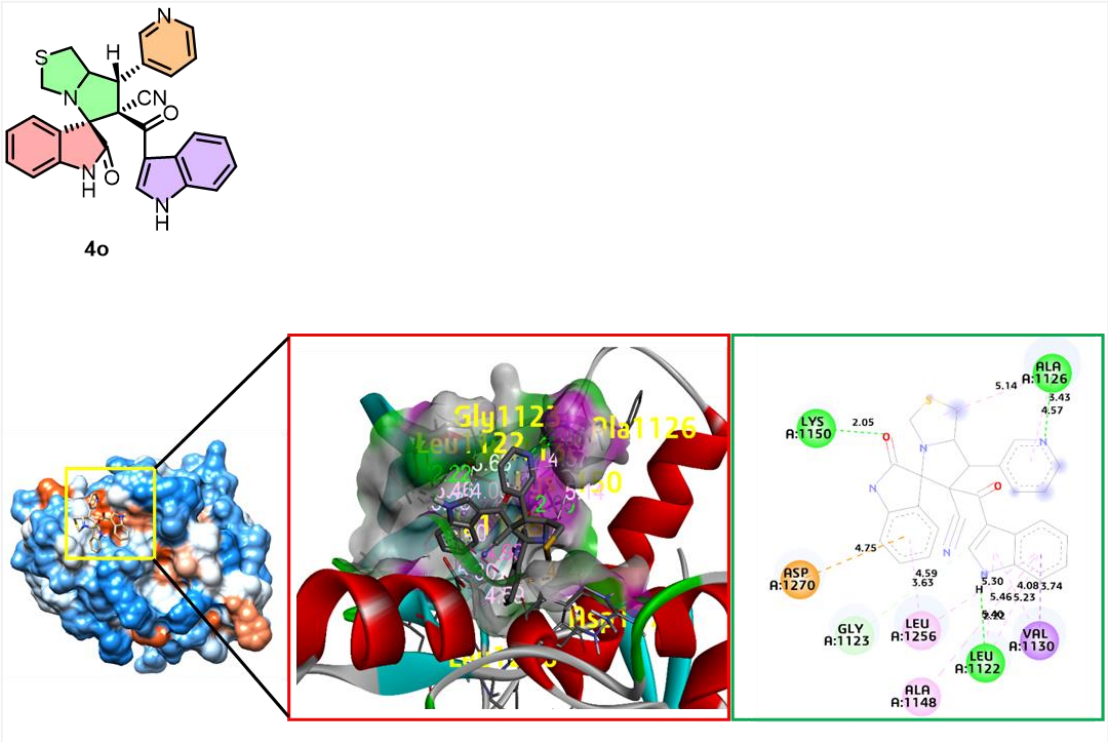


Figure SI-88: Binding mode of compound **4o** in Alk-receptor

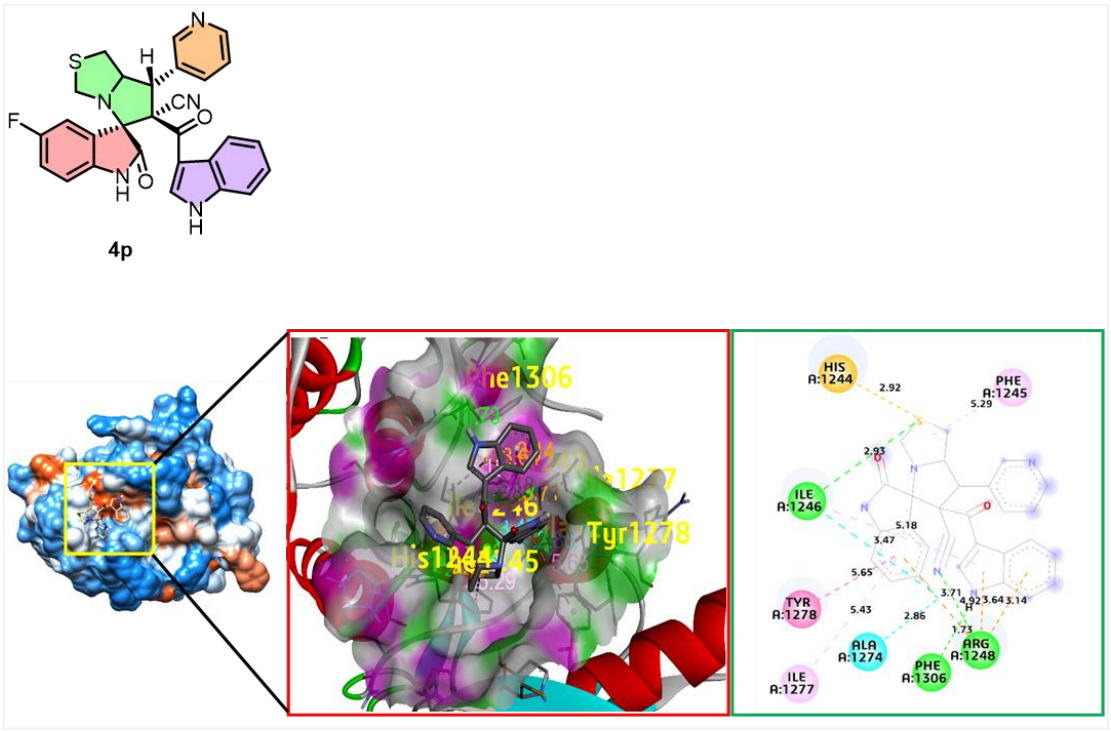


Figure SI-89: Binding mode of compound **4p** in Alk-receptor

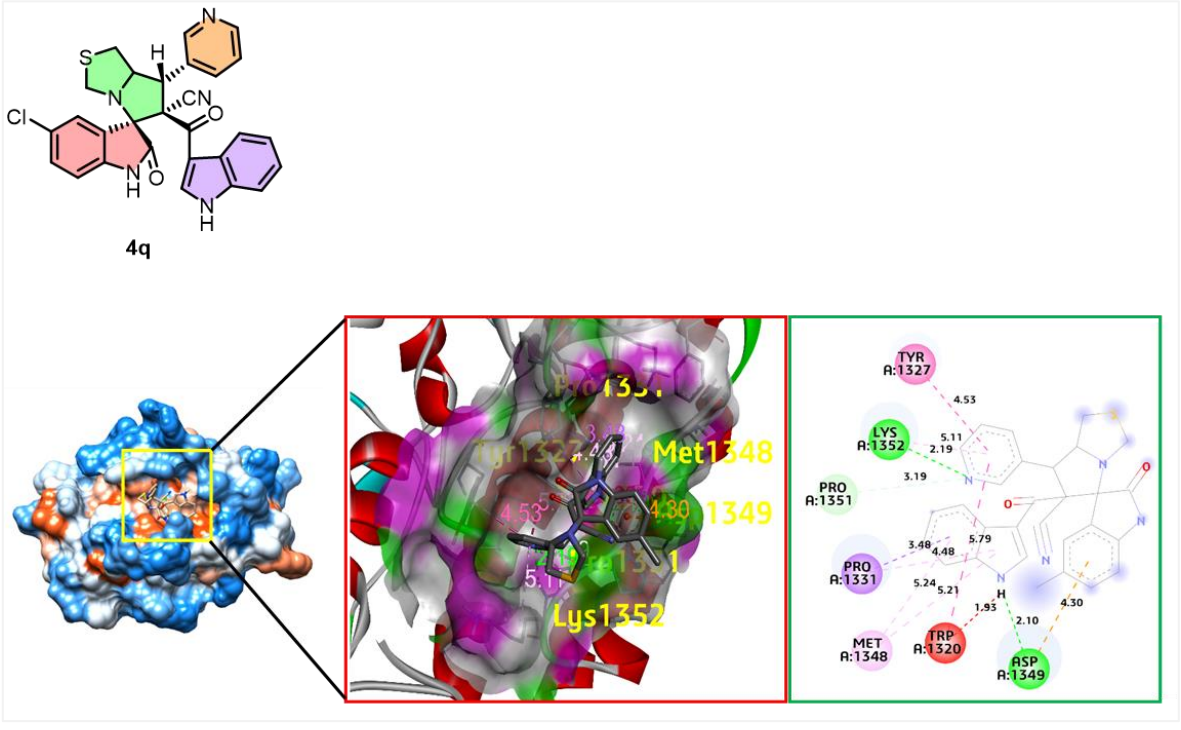


Figure SI-90: Binding mode of compound **4q** in Alk-receptor

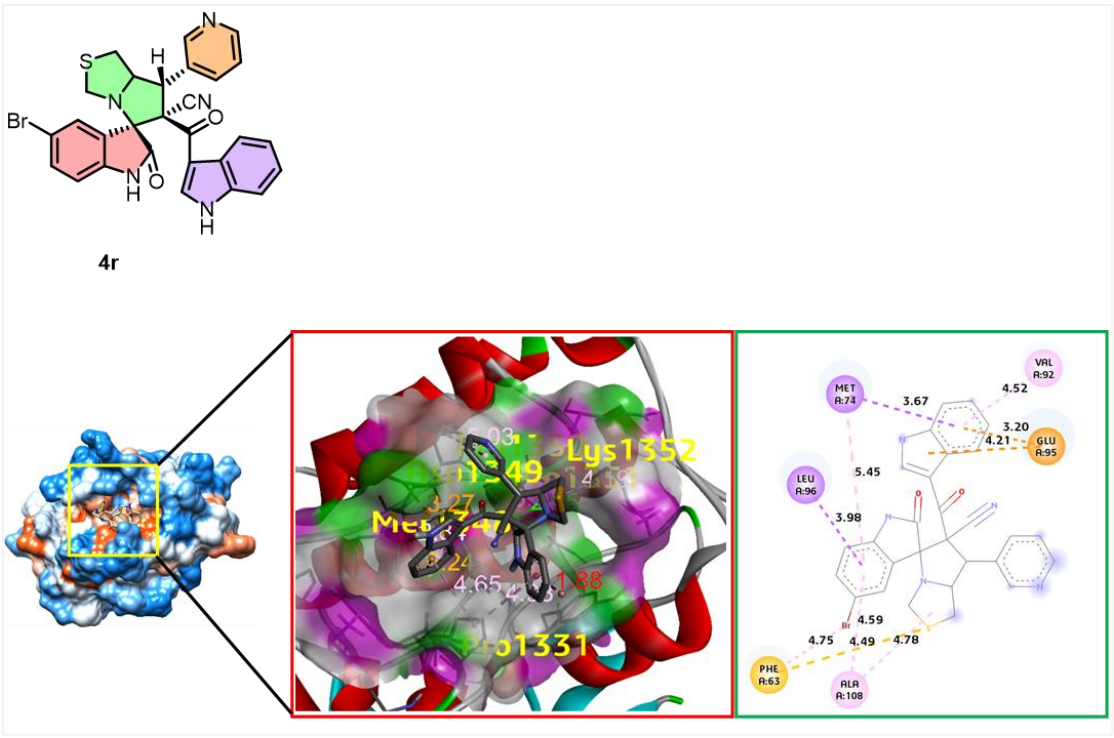


Figure SI-91: Binding mode of compound **4r** in Alk-receptor

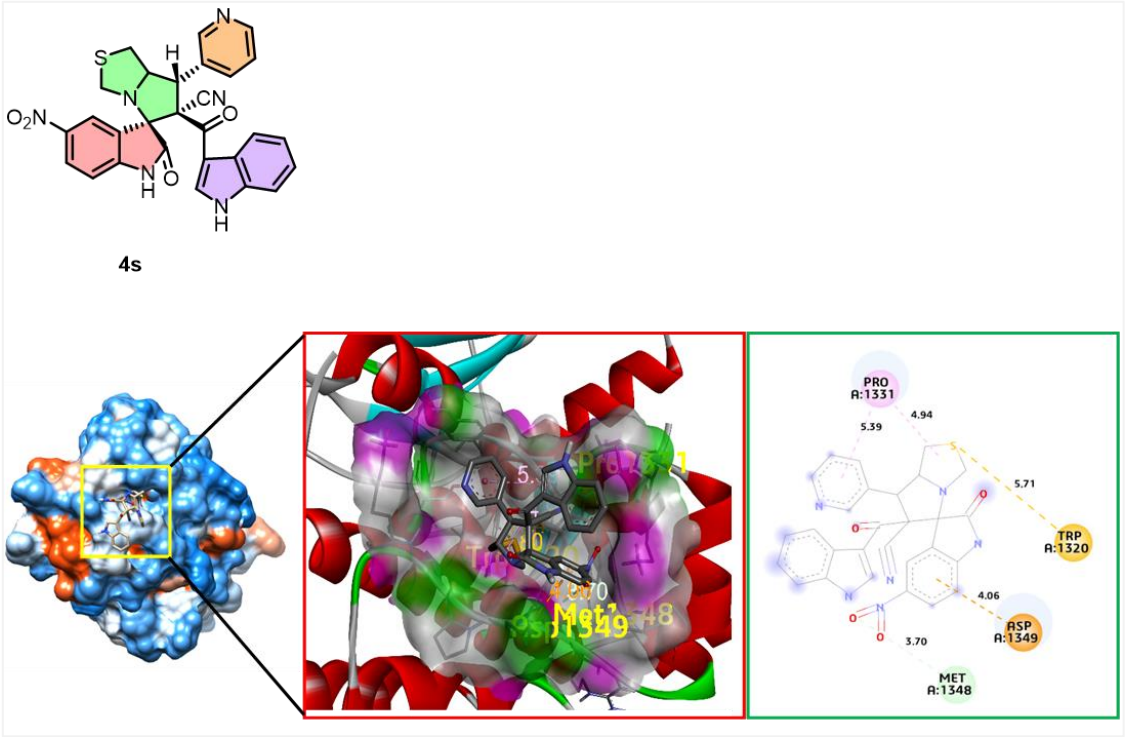


Figure SI-92: Binding mode of compound **4s** in Alk-receptor

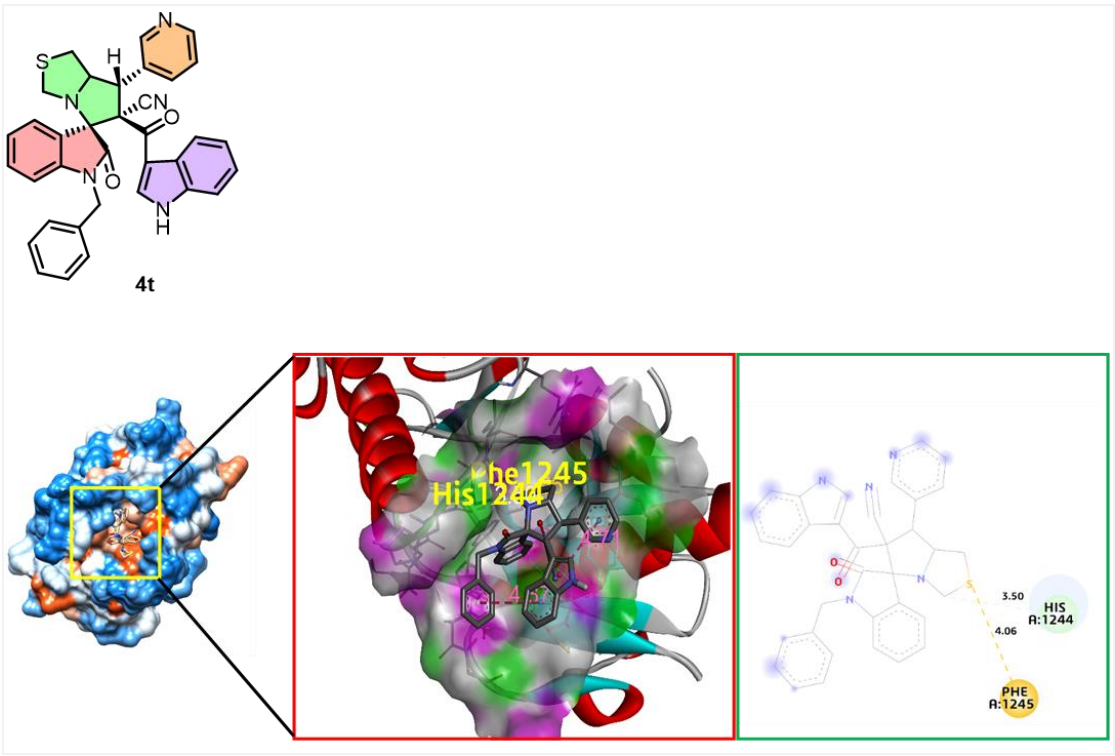


Figure SI-93: Binding mode of compound **4t** in Alk-receptor

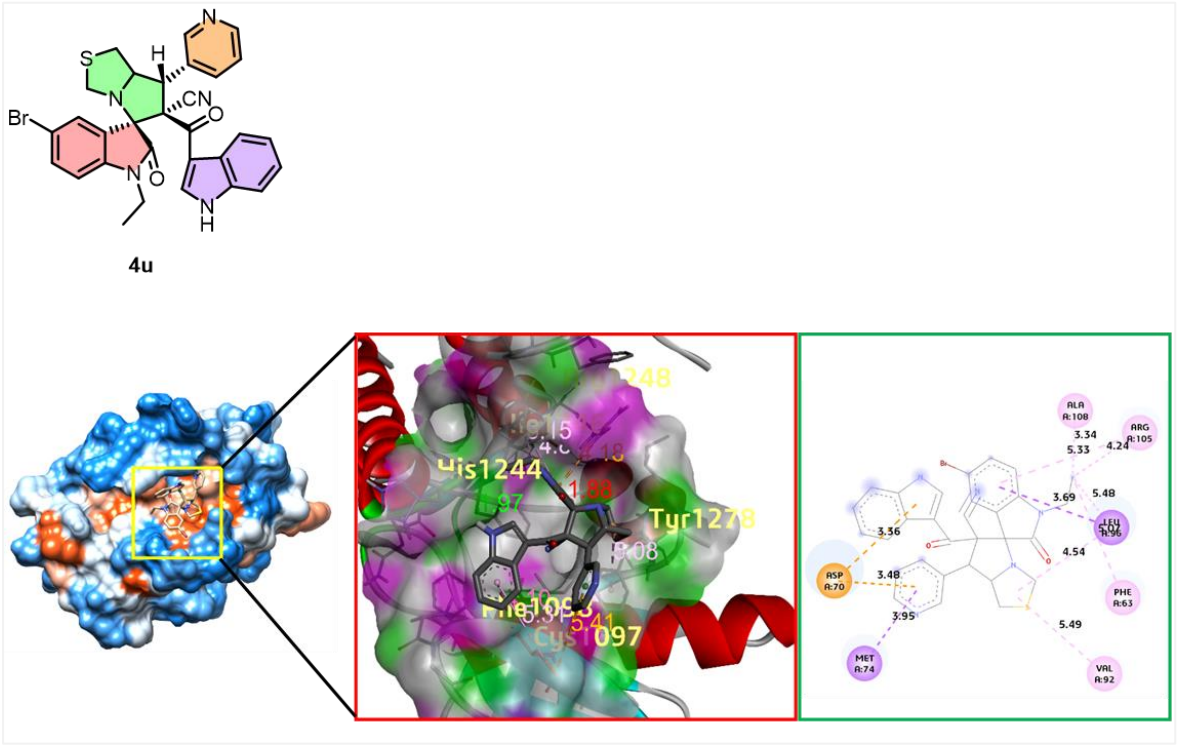


Figure SI-94: Binding mode of compound **4u** in Alk-receptor

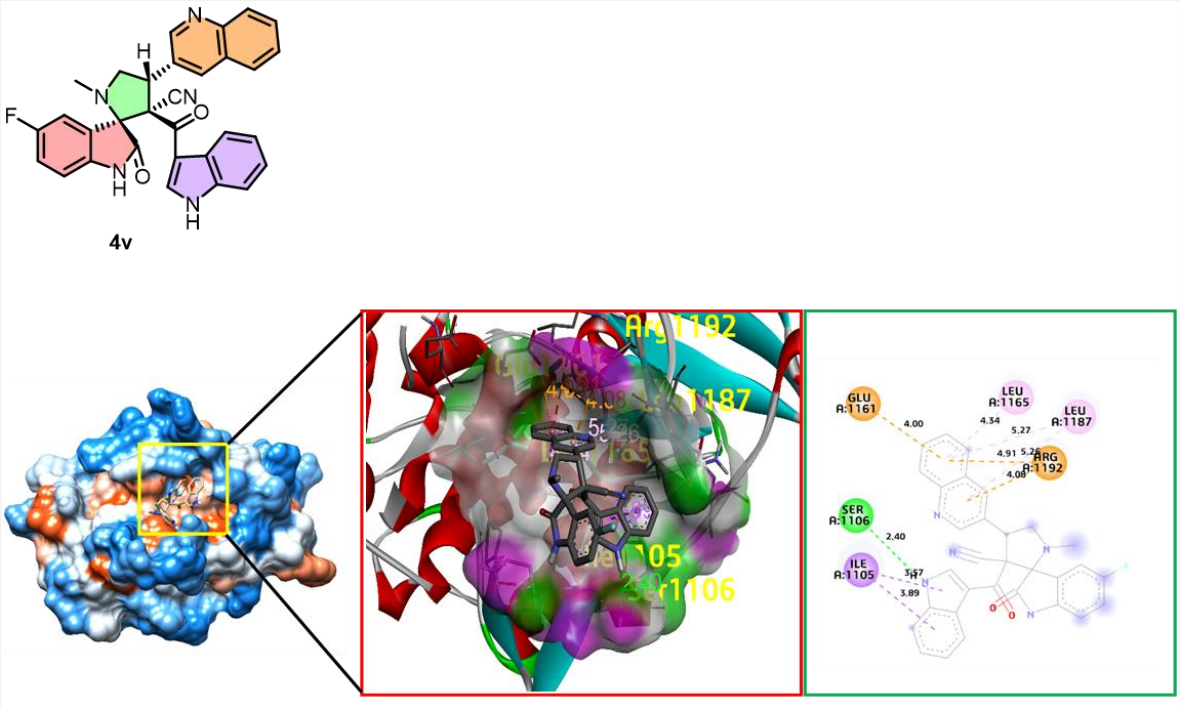


Figure SI-95: Binding mode of compound **4v** in Alk-receptor

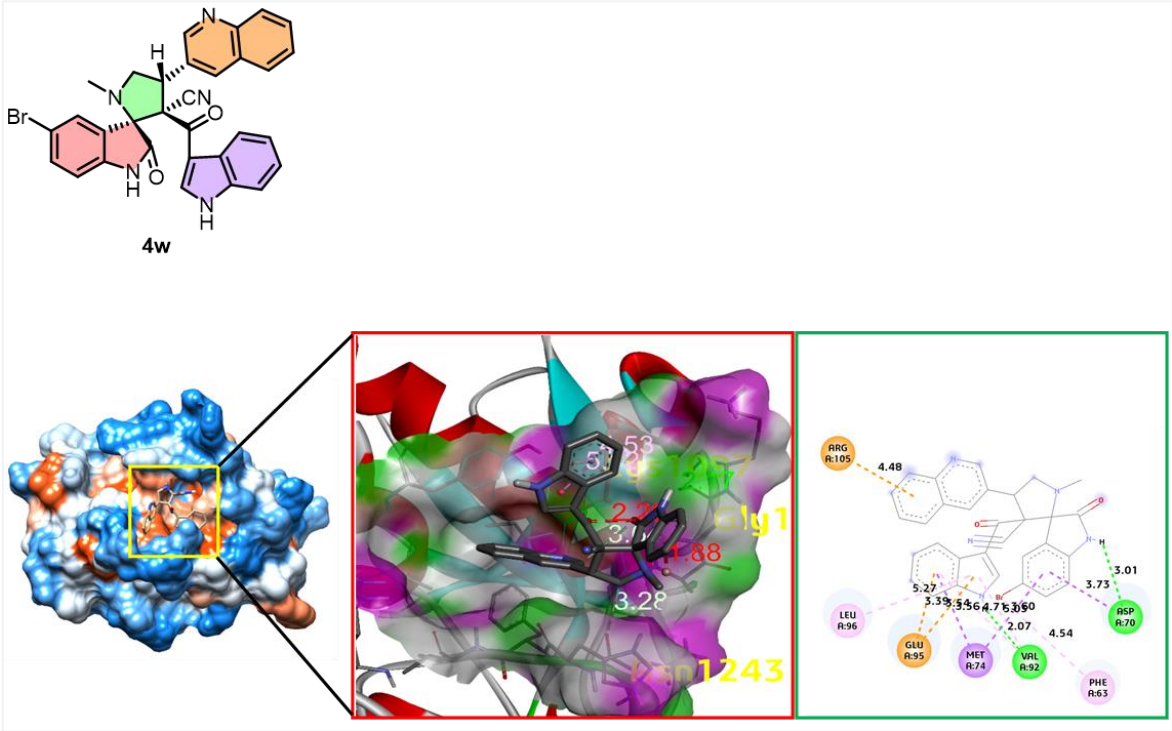


Figure SI-96: Binding mode of compound **4w** in Alk-receptor

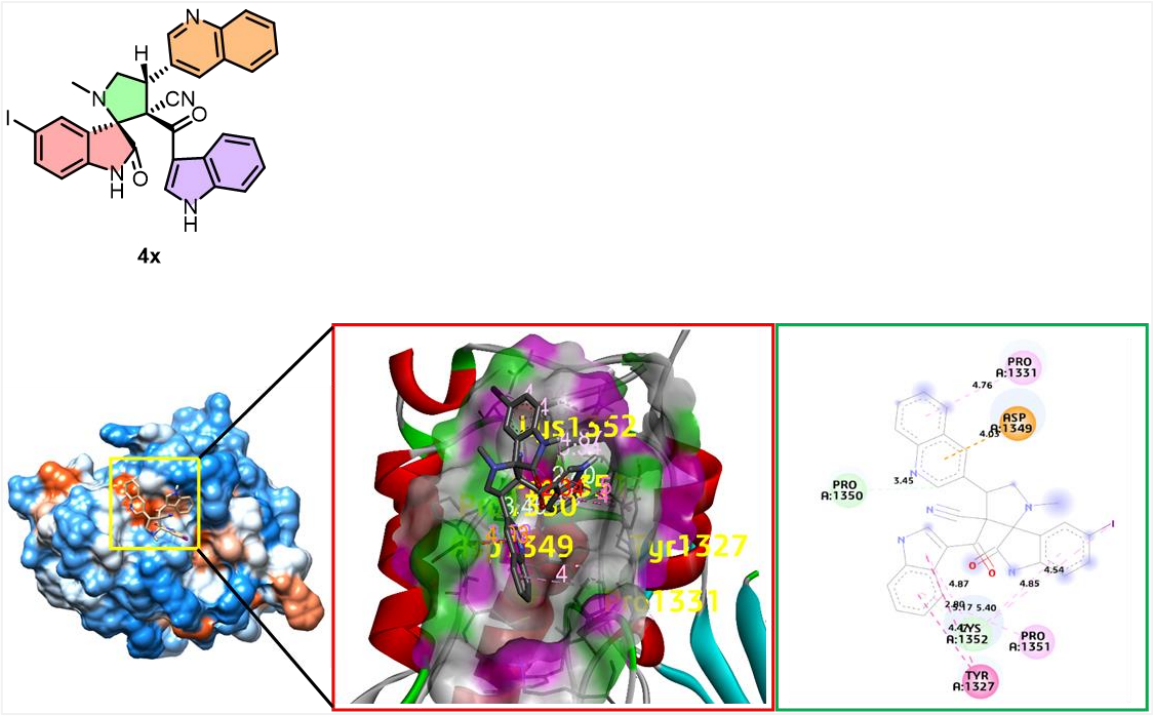


Figure SI-97: Binding mode of compound **4x** in Alk-receptor

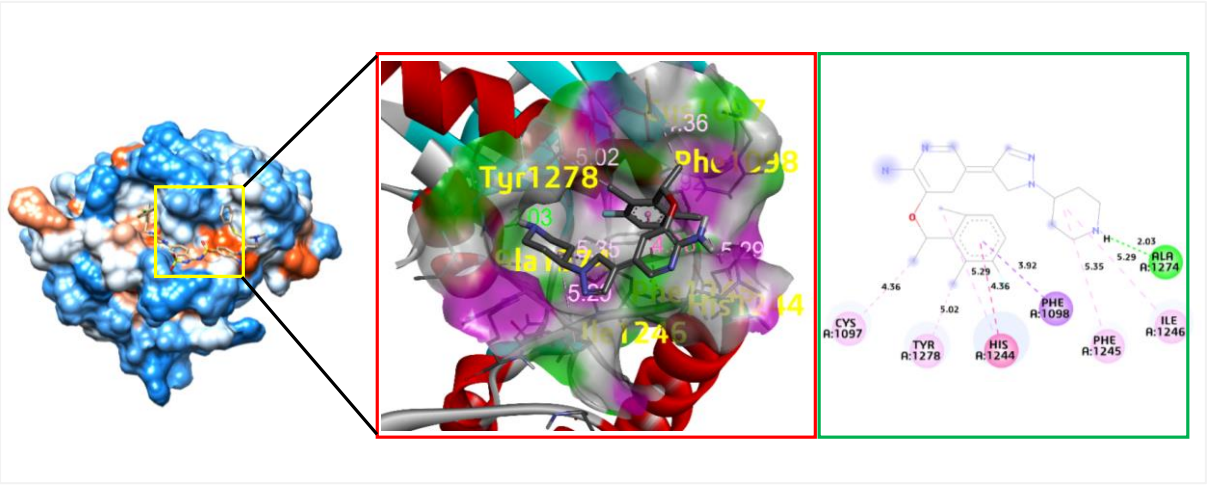


Figure SI-98: Molecular docking interaction of the crystallised ligand (Crizotinib) with the active site amino acids of ALK receptor (**2xp2**).

13. Binding Energy Data from Docking Analysis

Compound (Ligand)	Binding Energy in Bcl2	Binding Energy in ALK
4a	-8.33	-6.1
4b	-7.57	-6.23
4c	-6.24	-6.93
4d	-7.72	-5.21
4e	-8.09	-5.42
4f	-7.05	-5.88
4g	-7.09	-6.3
4h	-7.68	-5.6
4i	-8.06	-5.8
4j	-7.8	-6.13
4k	-6.69	-6.12
4l	-7.16	-5.88
4m	-6.05	-6.59
4n	-7.84	-6.14
4o	-6.89	-7.14
4p	-6.9	-6.53
4q	-7.14	-6.32
4r	-7.45	-6.09
4s	-7.45	-5.65
4t	-8.91	-6.11
4u	-6.56	-6.16
4v	-8.29	-6.09
4w	-8.14	-6.46
4x	-7.9	-6.34
Crystallized Ligand	-5.92	-6.74

14. ^{19}F NMR of compound 4f, 4m and 4p

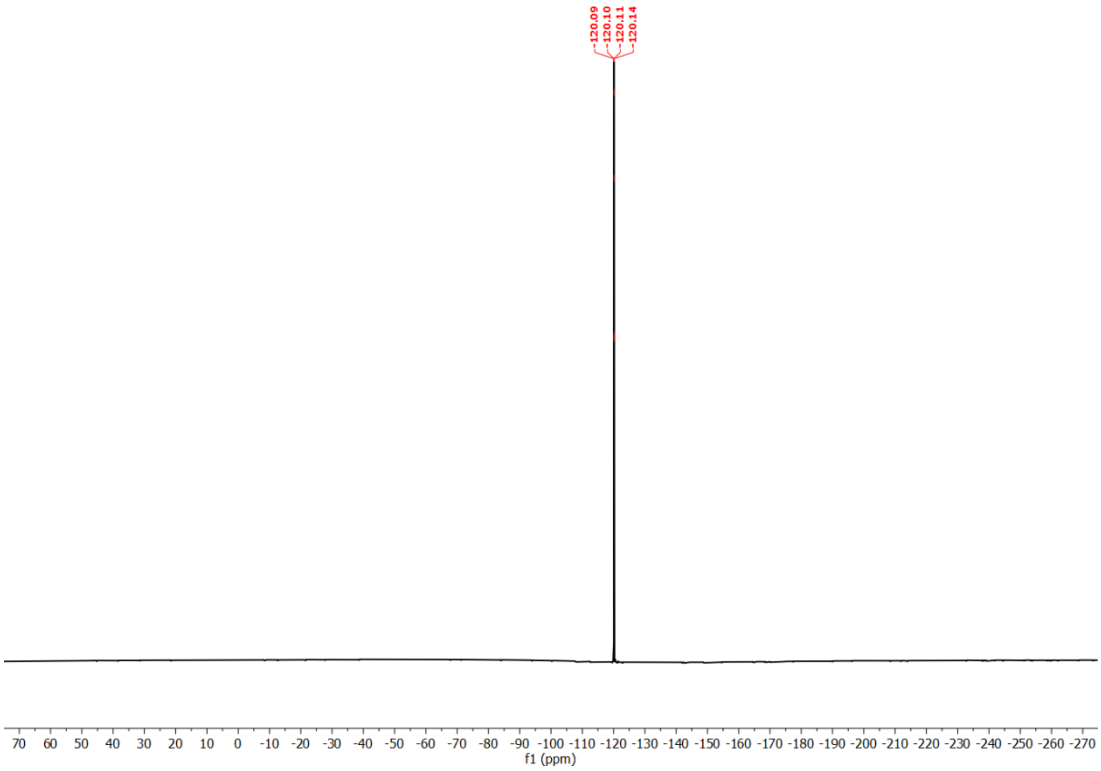


Figure SI-99: ^{19}F NMR spectrum of compound **4f**

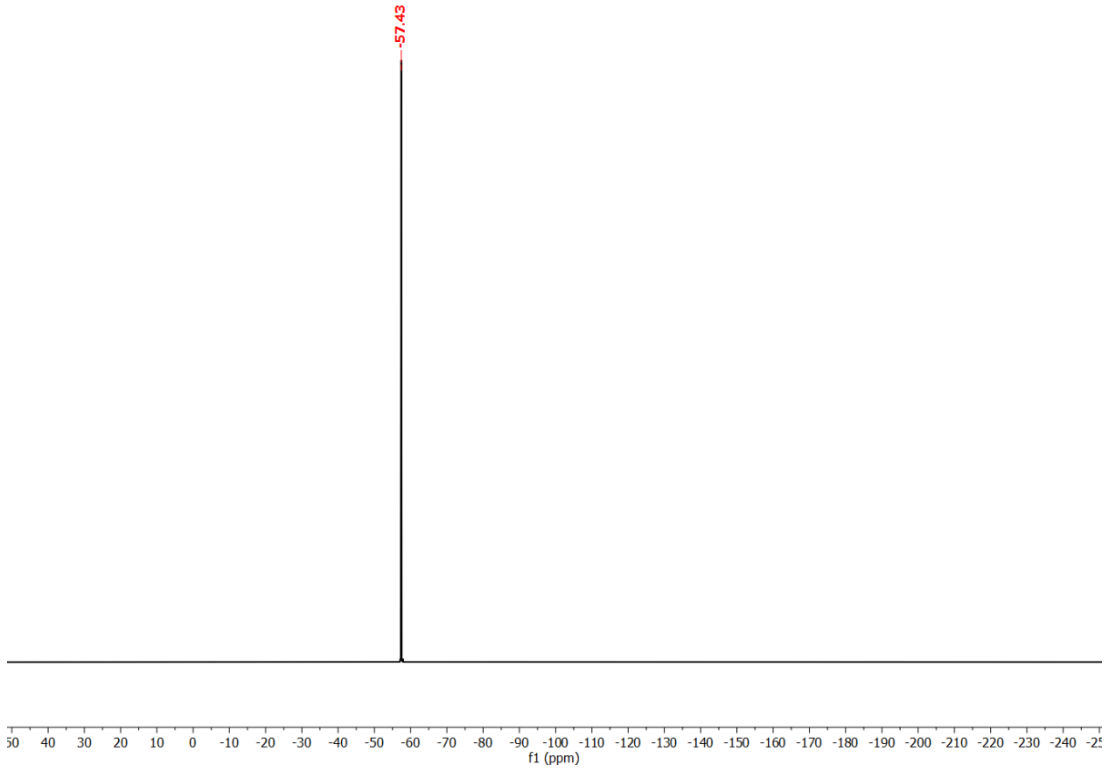


Figure SI-100: ^{19}F NMR spectrum of compound **4m**

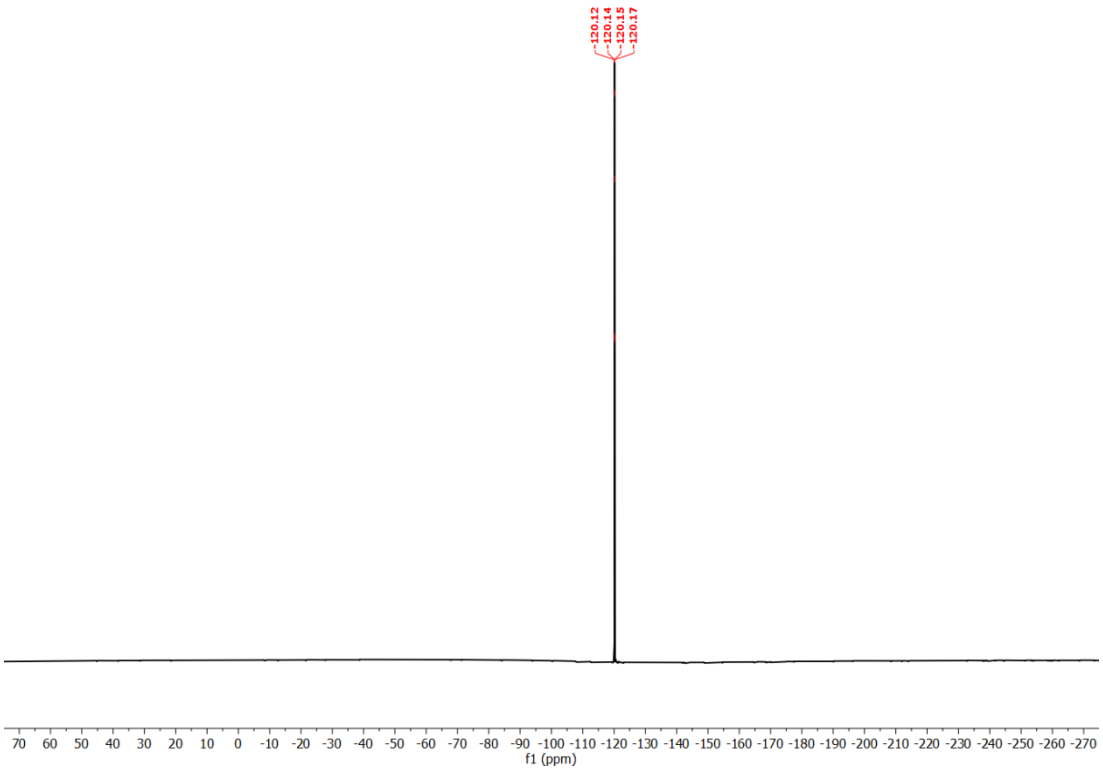


Figure SI-101: ^{19}F NMR spectrum of compound **4p**

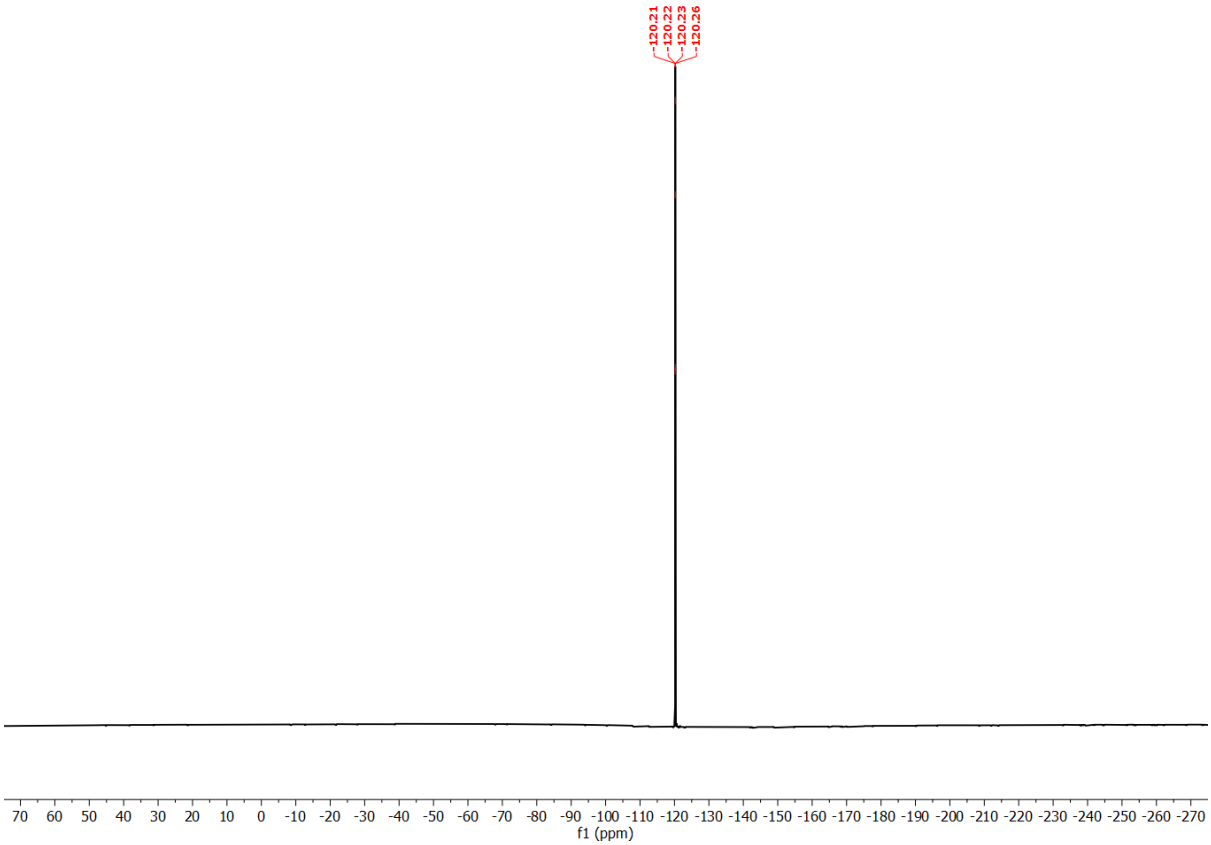


Figure SI-102: ^{19}F NMR spectrum of compound **4v**