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Supporting Information

Cu/TEMPO catalyzed dehydrogenative 1,3-dipolar cycloaddition for the synthesis of spirooxindoles as potential antidiabetic agents.

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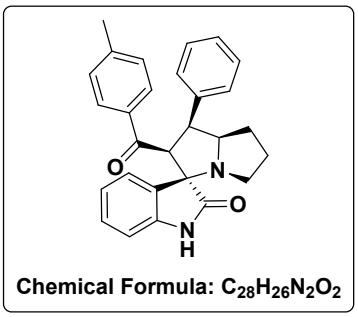
Characterization data for the synthesized compounds

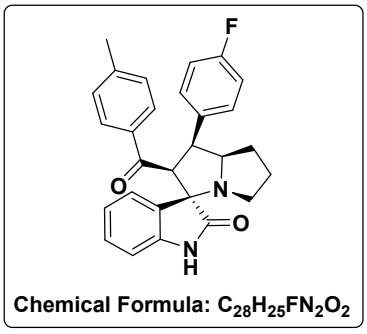
2'-benzoyl-1'-(p-tolyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4aa):



Chemical Formula: $C_{28}H_{26}N_2O_2$

Light brown solid, Mp: 134-136 °C, 2h, 85% yield (179 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.40 (t, *J* = 7.5 Hz, 4H), 7.34 – 7.24 (m, 2H), 7.12 (q, *J* = 6.7 Hz, 5H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 7.7 Hz, 1H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.22 (m, *J* = 9.8, 6.2 Hz, 1H), 3.93 – 3.84 (t, 1H), 2.74 – 2.57 (m, 2H), 2.29 (s, 3H), 2.03 (dt, *J* = 12.0, 6.8 Hz, 1H), 1.96 – 1.83 (m, 2H), 1.75 (dt, *J* = 13.1, 7.4 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 181.3, 140.7, 137.0, 136.7, 136.5, 132.8, 129.3, 128.5, 128.5, 128.0, 127.9, 127.8, 127.4, 125.1, 122.2, 110.1, 73.8, 72.0, 64.4, 52.6, 48.2, 30.7, 27.2, 21.0 ppm, IR (neat): ν = 3184, 2976, 2866, 1737, 1467, 752, 692 cm^{-1}. LC-MS calcd for $C_{28}H_{26}N_2O_2$ m/z 422.19 [M+], found 423.2 [M+].

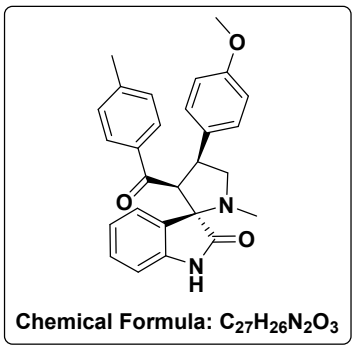
1'-(4-fluorophenyl)-2'-(4-methylbenzoyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4ab):



Chemical Formula: $C_{28}H_{25}FN_2O_2$

Off-white solid, Mp: 124-126 °C, 2h, 87% yield (191 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.49 – 7.42 (m, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.1 Hz, 3H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 8.2 Hz, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.27 – 4.17 (m, 1H), 3.89 (t, *J* = 10.6 Hz, 1H), 2.74 – 2.56 (m, 2H), 2.28 (s, 3H), 2.02 (dt, *J* = 18.6, 6.4 Hz, 1H), 1.95 – 1.83 (m, 2H), 1.74 (td, *J* = 13.3, 6.9 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 181.4, 166.7, 164.2, 140.7, 136.6, 136.6, 133.5, 133.5, 130.6, 130.5, 129.4, 129.4, 127.9, 127.5, 125.1, 122.3, 115.3, 115.1, 110.2, 73.8, 72.0, 64.4, 52.6, 48.2, 30.7, 27.3, 21.0 ppm, IR (neat): ν = 3196, 2922, 2866, 1730, 1465, 1230, 732 cm^{-1}. LC-MS calcd for $C_{28}H_{25}FN_2O_2$ m/z 440.19 [M+], found 439.2 [M+].positive mode

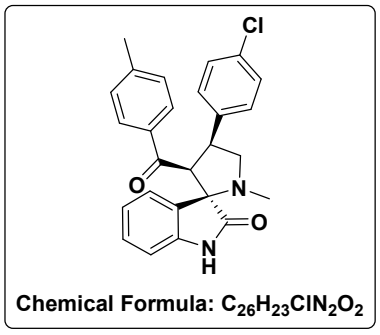
4'-(4-methoxyphenyl)-1'-methyl-3'-(4-methylbenzoyl)spiro[indoline-3,2'-pyrrolidin]-2-one (4ba):



Chemical Formula: $C_{27}H_{26}N_2O_3$

White solid, Mp:165-167 °C, 2h, 82% yield (174 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.50 – 7.38 (m, 4H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.01 (td, *J* = 7.7, 1.2 Hz, 1H), 6.92 (td, *J* = 7.6, 0.9 Hz, 1H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.56 (t, *J* = 5.8 Hz, 2H), 4.58 – 4.51 (m, 2H), 3.69 – 3.62 (m, 1H), 3.60 (s, 3H), 3.49 – 3.43 (m, 1H), 2.27 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 180.7, 163.2, 140.7, 138.5, 136.3, 130.3, 130.0, 129.3, 129.0, 128.0, 127.2, 126.9, 122.9, 113.3, 109.5, 74.0, 62.2, 60.5, 55.2, 44.3, 35.0, 21.0 ppm, IR (neat): ν = 3267, 2933, 2841, 1666, 1597, 1255, 1170, 748 cm^{-1}. LC-MS calcd for $C_{27}H_{26}N_2O_3$ m/z 426.19 [M+], found 427.2 [M+]. positive mode

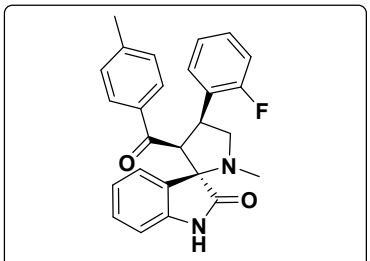
4'-(4-chlorophenyl)-1'-methyl-3'-(4-methylbenzoyl)spiro[indoline-3,2'-pyrrolidin]-2-one (4bb):



Chemical Formula: $C_{26}H_{23}ClN_2O_2$

Brown solid, Mp:143-145 °C, 2h, 86% yield (184 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.11 (dd, *J* = 12.8, 8.1 Hz, 5H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 4.54 – 4.45 (m, 2H), 3.66 (dd, *J* = 12.2, 5.7 Hz, 1H), 3.49 – 3.42 (m, 1H), 2.29 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 180.3, 140.5, 139.1, 138.2, 136.5, 135.6, 129.4, 129.2, 129.1, 128.3, 128.0, 126.9, 126.8, 123.0, 109.5, 73.7, 62.9, 60.5, 44.1, 35.0, 21.0 ppm, IR (neat): ν = 3138, 3028, 2920, 1703, 1467, 1089, 746 cm^{-1}. LC-MS calcd for $C_{26}H_{23}ClN_2O_2$ m/z 430.14 [M+], found 431.3 [M+]. positive mode

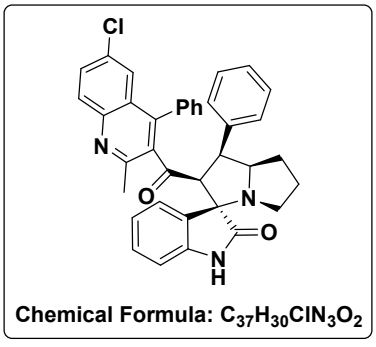
4'-(2-fluorophenyl)-1'-methyl-3'-(4-methylbenzoyl)spiro[indoline-3,2'-pyrrolidin]-2-one (4bc):



Chemical Formula: $C_{26}H_{23}FN_2O_2$

White solid, Mp:136-138 °C, 2h, 80% yield (165 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.50 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.05 – 6.88 (m, 6H), 6.58 (d, *J* = 7.7 Hz, 1H), 4.54 (dt, *J* = 27.6, 9.2 Hz, 2H), 3.64 (t, *J* = 9.1 Hz, 1H), 3.52 – 3.42 (m, 1H), 2.22 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 180.5, 162.9, 160.5, 143.6, 140.7, 137.3, 134.6, 129.6, 129.5, 129.4, 129.1, 128.8, 128.7, 127.8, 126.9, 126.8, 122.9, 115.5, 115.3, 109.5, 73.7, 62.6, 60.4, 43.8, 34.9, 21.4 ppm, IR (neat): ν = 3165, 3028, 2845, 1681, 1602, 1467, 1224, 750 cm^{-1}. LC-MS calcd for $C_{26}H_{23}FN_2O_2$ m/z 414.17 [M+], found 414.9 [M+].

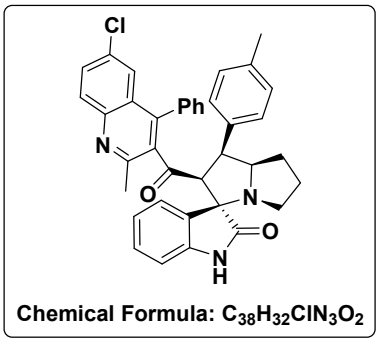
2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro-



Chemical Formula: $C_{37}H_{30}ClN_3O_2$

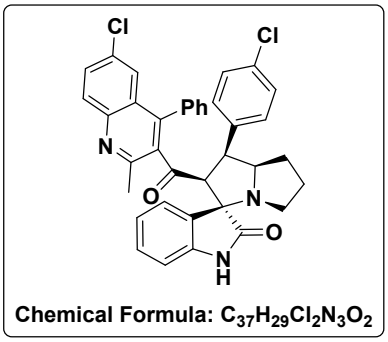
[indoline-3,3'-pyrrolizin]-2-one (5a): Brown solid, Mp: 190-192 °C, 2h, 81% yield (236 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.73 – 7.66 (m, 1H), 7.64 – 7.53 (m, 4H), 7.47 (d, J = 2.2 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.28 (dd, J = 5.6, 3.0 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.87 (t, J = 7.6 Hz, 2H), 6.67 (d, J = 7.6 Hz, 2H), 6.54 (d, J = 7.7 Hz, 1H), 4.68 (dd, J = 12.4, 8.2 Hz, 1H), 3.70 (d, J = 12.5 Hz, 1H), 3.04 (dt, J = 9.8, 5.0 Hz, 1H), 2.85 (dd, J = 15.3, 8.2 Hz, 1H), 2.66 (dd, J = 12.4, 5.1 Hz, 1H), 1.91 (s, 3H), 1.88 – 1.78 (m, 2H), 1.54 – 1.48 (m, 1H), 1.36 (dt, J = 12.1, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 200.7, 178.6, 156.4, 147.2, 145.9, 141.3, 138.9, 134.5, 132.3, 131.3, 131.1, 131.0, 130.5, 130.2, 130.0, 129.8, 129.2, 128.6, 128.5, 127.9, 127.3, 126.4, 125.9, 125.5, 125.3, 123.0, 111.3, 73.3, 72.5, 68.3, 51.7, 46.5, 31.7, 28.1, 22.3 ppm. IR (neat): ν = 3176, 3061, 2916, 2850, 1712, 1467, 1178, 698 cm^{-1}. HRMS calcd for $C_{37}H_{30}ClN_3O_2$ m/z 583.2027 [M+], found 583.2024 [M+].

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(p-tolyl)-1',2',5',6',7',7a'-exahydrospiro-[indoline-3,3'-pyrrolizin]-2-one (5b): Pale brown solid, Mp: 205-207 °C, 2h, 84% yield (250 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.75 (t, J = 7.4 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.40 – 7.30 (m, 2H), 7.15 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 7.8 Hz, 3H), 6.90 (s, 1H), 6.81 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 7.6 Hz, 1H), 4.27 (d, J = 11.6 Hz, 1H), 3.77 – 3.60 (m, 2H), 2.51 – 2.43 (m, 1H), 2.33 (s, 3H), 2.23 – 2.14 (m, 1H), 1.91 – 1.82 (m, 1H), 1.82 – 1.73 (m, 2H), 1.52 (s, 3H), 1.50 – 1.43 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 21.0, 22.3, 28.1, 31.6, 46.5, 51.4, 68.1, 72.4, 73.2, 111.2, 123.0, 125.4, 125.6, 125.9, 127.4, 127.7, 128.6, 129.1, 129.2, 129.7, 130.0, 130.3, 130.4, 130.9, 131.1, 131.4, 132.3, 134.5, 135.8, 135.9, 141.2, 145.9, 147.1, 156.4, 178.4, 200.7 ppm. IR (neat): ν = 3242, 3055, 2916, 2850, 1728, 1467, 1176, 704 cm^{-1}. HRMS calcd for $C_{38}H_{32}ClN_3O_2$ m/z 597.2183 [M+], found 597.2180 [M+].



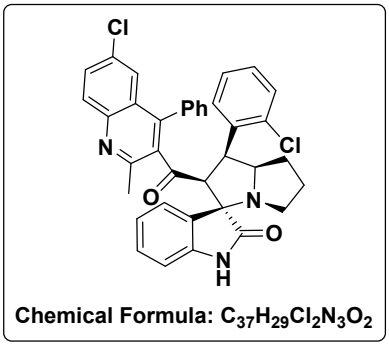
Chemical Formula: $C_{38}H_{32}ClN_3O_2$

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(4-chlorophenyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5c): Pale yellow solid, Mp: 248-250 °C, 3h, 75% yield (231 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.9 Hz, 1H), 7.73 (dd, J = 11.0, 5.7 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.55 (d, J = 7.1 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.38 (d, J = 3.1 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.30 (s, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.07 (dd, J = 14.0, 7.1 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 5.1 Hz, 1H), 6.61 – 6.55 (m, 2H), 4.59 (dd, J = 12.3, 8.3 Hz, 1H), 3.68 (d, J = 12.2 Hz, 1H), 3.03 (dt, J = 9.7, 7.6 Hz, 2H), 2.68 (t, J = 7.4 Hz, 1H), 2.13 (s, 3H), 1.88 (s, 1H), 1.79 – 1.70 (m, 1H), 1.45 – 1.34 (m, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 206.9, 178.7, 155.9, 145.6, 145.0, 141.0, 134.9, 134.6, 134.0, 133.1, 132.4, 131.3, 130.6, 130.3, 129.9, 129.5, 129.4, 129.4, 129.2, 128.9, 128.6, 127.5, 126.3, 126.2, 125.0, 124.6, 121.5, 109.5, 75.5, 65.0, 58.1, 53.1, 50.2, 30.3, 28.3, 23.4 ppm. IR (neat): ν = 3302, 3228, 2914 cm^{-1}. HRMS calcd for $C_{37}H_{29}Cl_2N_3O_2$ m/z 617.1637 [M+], found 617.1635 [M+].



Chemical Formula: $C_{37}H_{29}Cl_2N_3O_2$

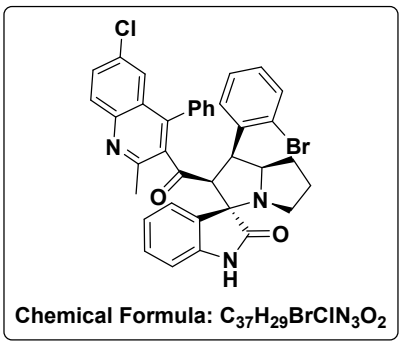
2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-chlorophenyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5d): Pale yellow solid, Mp: 234-236 °C, 3h, 72% yield (222 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.5 Hz, 1H), 7.88 – 7.78 (m, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.57 (dd, J = 9.0, 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.1 Hz, 2H), 7.14 (ddd, J = 25.1, 15.5, 7.6 Hz, 4H), 6.92 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 7.5 Hz, 1H), 5.93 (d, J = 7.3 Hz, 1H), 4.50 – 4.39 (m, 2H), 3.53 (d, J = 6.3 Hz, 1H), 2.44 (ddd, J =



Chemical Formula: $C_{37}H_{29}Cl_2N_3O_2$

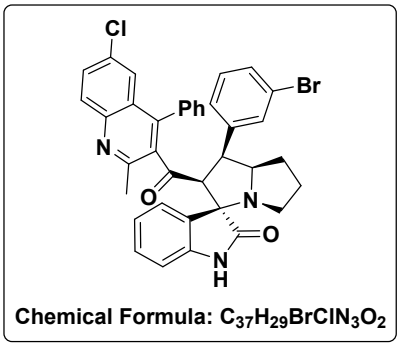
10.1, 7.6, 4.3 Hz, 1H), 2.17 (dd, J = 16.6, 7.8 Hz, 1H), 1.89 – 1.78 (m, 2H), 1.70 (ddd, J = 24.1, 15.6, 7.2 Hz, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 200.1, 178.2, 156.4, 147.0, 145.8, 141.3, 136.6, 134.9, 134.4, 132.4, 131.4, 131.3, 130.6, 130.0, 130.0, 129.3, 129.0, 128.9, 127.5, 127.3, 127.2, 127.1, 125.9, 125.4, 125.3, 123.3, 111.3, 72.9, 67.7, 46.4, 45.9, 31.1, 29.7, 28.1, 22.2 ppm. IR (neat): ν = 3074, 2914, 1714, 1469, 1193, 752 cm^{-1}. HRMS calcd for $C_{37}H_{29}Cl_2N_3O_2$ m/z 617.1637 [M+], found 617.1633 [M+].

1'-(2-bromophenyl)-2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5e): Brown solid, Mp: 194-196 °C, 2h, 76% yield (251 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.8 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.49 (dd, J = 8.9, 4.9 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.17 (dt, J = 22.6, 7.5 Hz, 2H), 7.05 – 6.94 (m, 2H), 6.90 (s, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 5.90 (d, J = 7.0 Hz, 1H), 4.50 – 4.39 (m, 2H), 3.51 (dd, J = 13.2, 6.5 Hz, 1H), 2.45 (ddd, J = 9.9, 6.3, 3.9 Hz, 1H), 2.21 – 2.11 (m, 1H), 1.82 (dt, J = 16.1, 7.0 Hz, 2H), 1.76 – 1.69 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 206.9, 178.7, 155.9, 145.6, 145.0, 141.0, 134.9, 134.6, 134.0, 133.1, 132.4, 131.3, 130.6, 130.3, 129.9, 129.5, 129.4, 129.4, 129.2, 128.9, 128.6, 127.5, 126.3, 126.2, 125.0, 124.6, 121.5, 109.5, 75.5, 65.0, 58.1, 53.1, 50.2, 30.3, 28.3, 23.4 ppm. IR (neat): ν = 3211, 2916, 2850, 1716, 1469, 1176, 702 cm^{-1}. HRMS calcd for $C_{37}H_{39}BrClN_3O_2$ m/z 661.1132 [M+], found 661.1129 [M+].



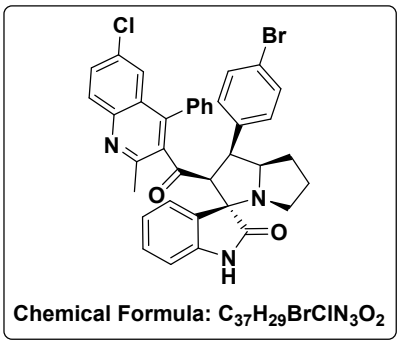
Chemical Formula: $C_{37}H_{29}BrClN_3O_2$

1'-(3-bromophenyl)-2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5f): Brown solid, Mp: 170-175 °C, 2h, 70% yield (231 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.68 – 7.62 (m, 3H), 7.53 – 7.48 (m, 2H), 7.40 (s, 2H), 7.32 (d, J = 7.5 Hz, 1H), 7.17 (dd, J = 15.9, 8.1 Hz, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.78 (t, J = 7.9 Hz, 1H), 6.74 (s, 1H), 6.59 (d, J = 7.7 Hz, 2H), 4.46 (dd, J = 12.2, 8.4 Hz, 1H), 3.63 (d, J = 12.2 Hz, 1H), 3.15 (dd, J = 15.6, 8.6 Hz, 1H), 3.01 (td, J = 9.5, 6.6 Hz, 1H), 2.67 (t, J = 7.6 Hz, 1H), 2.20 (s, 3H), 1.89 (dd, J = 12.7, 5.9 Hz, 1H), 1.72 (dd, J = 21.6, 10.1 Hz, 2H), 1.61 – 1.51 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 200.6, 178.2, 156.4, 147.2, 145.9, 141.4, 141.2, 134.2, 132.4, 131.5, 131.1, 131.0, 130.8, 130.6, 130.0, 129.8, 129.6, 129.4, 128.5, 127.3, 127.2, 125.7, 125.4, 125.3, 123.1, 122.5, 111.3, 73.3, 72.1, 68.5, 51.1, 46.4, 31.8, 28.2, 22.2 ppm. IR (neat): ν = 2978, 2850, 1712, 1471, 1382, 1155, 910, 727 cm^{-1}. HRMS calcd for $C_{37}H_{29}BrClN_3O_2$ m/z 661.1132 [M+], found 661.1130 [M+].



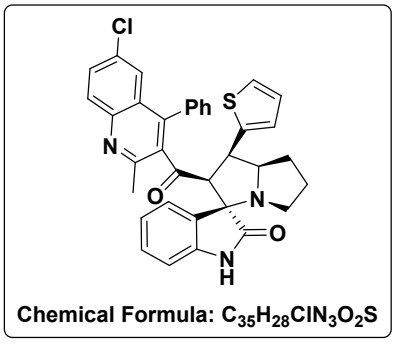
Chemical Formula: $C_{37}H_{29}BrClN_3O_2$

1'-(4-bromophenyl)-2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5g): Brown solid, Mp: 180-182 °C, 2h, 75% yield (247 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.75 (t, J = 7.3 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.50 (d, J = 2.2 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.19 – 7.12 (m, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.93 (s, 1H), 6.82 (dd, J = 5.7, 2.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 7.6 Hz, 1H), 4.25 (d, J = 11.3 Hz, 1H), 3.75 – 3.61 (m, 2H), 2.49 – 2.42 (m, 1H), 2.18 (dt, J = 9.8, 7.6 Hz, 1H), 1.91 – 1.75 (m, 3H), 1.48 (s, 3H), 1.46 – 1.41 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 200.5, 178.1, 156.4, 147.2, 145.9, 141.2, 138.1, 134.6, 132.5, 131.6, 131.5, 131.1, 130.9, 130.6, 130.0, 130.0, 129.7, 129.6, 129.3, 128.7, 127.3, 125.9, 125.4, 125.3, 123.1, 120.2, 111.3, 73.2, 72.2, 68.4, 51.0, 46.5, 31.7, 28.1, 22.21 ppm. IR (neat): ν = 3250, 2916, 2850, 1724, 1469, 1178, 748 cm^{-1}. HRMS calcd for $C_{37}H_{29}BrClN_3O_2$ m/z 661.1132 [M+], found 661.1131 [M+].



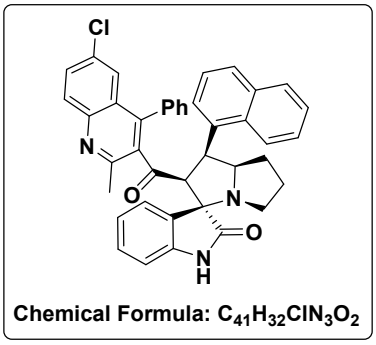
Chemical Formula: $C_{37}H_{29}BrClN_3O_2$

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(thiophen-2-yl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5h): Pale brown solid, Mp: 210-212 °C, 2h, 69% yield (203 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 1H), 7.80 – 7.72 (m, 1H), 7.72 – 7.54 (m, 5H), 7.51 (s, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.20 (td, J = 7.7, 1.1 Hz, 1H), 7.07 (dd, J = 7.6, 6.8 Hz, 1H), 6.86 (dd, J = 5.1, 1.0 Hz, 1H), 6.66 – 6.56 (m, 2H), 6.35 (d, J = 3.4 Hz, 1H), 4.65 (dd, J = 12.2, 8.3 Hz, 1H), 3.98 (d, J = 12.3 Hz, 1H), 3.04 (td, J = 9.8, 5.8 Hz, 1H), 2.87 (dd, J = 15.2, 7.9 Hz, 1H), 2.75 – 2.63 (m, 1H), 2.08 (s, 3H), 1.92 – 1.79 (m, 2H), 1.55 – 1.49 (m, 1H), 1.34 (dd, J = 10.8, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 208.2, 178.4, 156.0, 145.7, 144.8, 141.9, 136.8, 135.3, 134.8, 132.4, 131.3, 130.8, 130.4, 129.9, 129.5, 129.5, 129.3, 126.6, 126.3, 126.0, 125.7, 124.9, 124.6, 122.1, 109.9, 75.3, 65.1, 57.9, 53.7, 50.3, 28.0, 26.1, 23.3 ppm. IR (neat): ν = 3302, 3226, 2914, 2848, 1728, 1467, 1176, 702 cm^{-1}. HRMS calcd for $C_{35}H_{28}ClN_3O_2S$ m/z 589.1591[M+], found 589.1588 [M+].



Chemical Formula: $C_{35}H_{28}ClN_3O_2S$

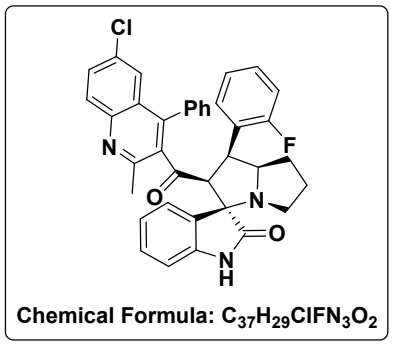
2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(naphthalen-1-yl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5i): White solid, Mp: 254-256, °C, 3h, 70% yield (221 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 8.6 Hz, 1H), 8.21 (d, J = 6.4 Hz, 1H), 7.96 – 7.80 (m, 4H), 7.72 – 7.62 (m, 2H), 7.54 – 7.43 (m, 4H), 7.38 (t, J = 7.6 Hz, 1H), 7.05 (td, J = 7.7, 1.1 Hz, 2H), 6.88 (td, J = 7.7, 2.6 Hz, 2H), 6.50 (d, J = 7.7 Hz, 2H), 4.69 (d, J = 3.6 Hz, 1H), 3.62 (p, J = 9.0 Hz, 2), 2.61 (td, J = 8.6, 2.6 Hz, 2H), 2.13 (dd, J = 16.2, 8.5 Hz, 2H), 1.89 (dd, J = 13.9, 5.2 Hz, 2H), 1.49 (s, 3H).). ^{13}C NMR (100 MHz, CDCl3) δ 176.3, 156.5, 145.8, 141.5, 140.7, 132.3, 131.3, 131.2, 130.6, 130.0, 129.0, 128.9,



Chemical Formula: $C_{41}H_{32}ClN_3O_2$

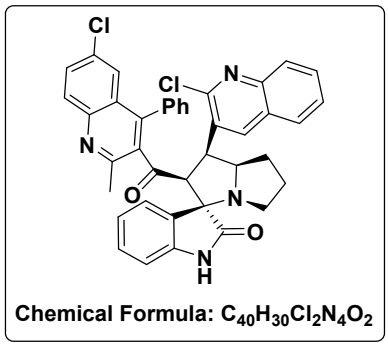
127.3, 126.5, 126.3, 126.2, 126.1, 125.9, 125.4, 125.3, 123.2, 123.0, 123.0, 122.1, 108.9, 74.4, 68.8, 68.7, 59.1, 47.6, 27.4, 22.3, 20.9 ppm. IR (neat): ν = 3176, 2918, 1701, 1467, 1180, 748 cm^{-1}. HRMS calcd for $C_{41}H_{32}ClN_3O_2$ m/z 633.2183 [M+], found 633.2180 [M+].

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-fluorophenyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (5j): White solid, Mp: 199-201 ◦C, 2h, 75% yield (225 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.65 (s, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 10.6 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.99 – 6.92 (m, 1H), 6.85 (t, J = 7.9 Hz, 2H), 6.60 (d, J = 7.6 Hz, 1H), 6.20 (t, J = 7.3 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.08 (dd, J = 11.8, 9.4 Hz, 1H), 3.66 (dd, J = 15.2, 8.3 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.17 (dd, J = 16.8, 8.2 Hz, 1H), 1.86 (dd, J = 10.7, 4.9 Hz, 1H), 1.82 – 1.70 (m, 2H), 1.57 (dd, J = 18.6, 10.3 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 207.0, 178.9, 155.6, 145.6, 144.9, 141.2, 134.9, 134.6, 132.5, 132.5, 131.3, 130.6, 130.3, 130.1, 129.5, 129.5, 129.4, 128.9, 128.8, 127.1, 126.2, 125.5, 125.0, 125.0, 124.0, 121.9, 115.2, 109.6, 75.0, 64.9, 56.4, 50.2, 46.6, 28.4, 26.2, 23.4 ppm. IR (neat): ν = 3201, 2916, 2850, 1712, 1616, 1469, 1178, 752 cm^{-1}. HRMS calcd for $C_{37}H_{29}ClFN_3O_2$ m/z 601.1932 [M+], found 601.1930 [M+].



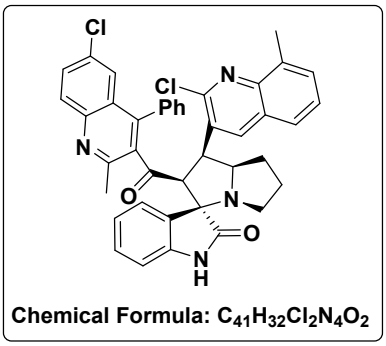
Chemical Formula: $C_{37}H_{29}ClFN_3O_2$

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-chloroquinolin-3-yl)-1',2',5',6',7',7a'-hexa-hydrospiro[indoline-3,3'-pyrrolizin]-2-one (6a): Brown solid, Mp: 205-207 ◦C, 3h, 70% yield (233 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 1H), 8.03 (dd, J = 8.6, 4.2 Hz, 1H), 7.90 (dd, J = 16.8, 8.3 Hz, 2H), 7.75 – 7.61 (m, 4H), 7.58 – 7.51 (m, 2H), 7.49 (d, J = 7.4 Hz, 1H), 7.44 (s, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 6.99 (s, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 6.5 Hz, 1H), 4.62 (dd, J = 11.8, 9.4 Hz, 1H), 4.39 (d, J = 11.9 Hz, 1H), 3.72 – 3.58 (m, 1H), 2.55 – 2.45 (m, 1H), 2.21 (dd, J = 16.3, 8.1 Hz, 1H), 1.89 – 1.82 (m, 2H), 1.77 (dd, J = 15.7, 7.9 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 178.2, 156.5, 151.8, 146.8, 146.4, 146.0, 141.4, 134.6, 132.4, 131.6, 131.4, 131.4, 131.3, 130.9, 130.1, 130.0, 129.7, 129.6, 129.4, 128.6, 128.4, 127.6, 127.2, 127.0, 126.7, 125.5, 125.2, 125.1, 123.5, 122.4, 111.6, 73.1, 68.2, 46.4, 31.2, 30.3, 29.7, 28.2, 22.1 ppm. IR (neat): ν = 2922, 2852, 1718, 1467, 1188, 750 cm^{-1}. HRMS calcd for $C_{40}H_{30}Cl_2N_4O_2$ m/z 668.1746 [M+], found 668.1744 [M+].



Chemical Formula: $C_{40}H_{30}Cl_2N_4O_2$

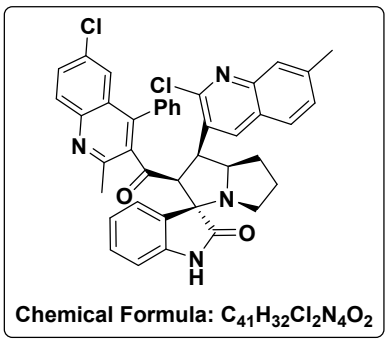
2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-chloro-8-methylquinolin-3-yl)-



Chemical Formula: $C_{41}H_{32}Cl_2N_4O_2$

1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (6b): Brown solid, Mp: 228-230 °C, 3h, 68% yield (231 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.6 Hz, 1H), 7.88 (dd, J = 7.9, 4.3 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.57 (s, 2H), 7.50 (d, J = 3.8 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.14 (s, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.92 – 6.83 (m, 2H), 6.67 (t, J = 7.5 Hz, 1H), 6.50 (dd, J = 14.4, 7.6 Hz, 2H), 4.66 – 4.57 (m, 1H), 4.36 (d, J = 11.9 Hz, 1H), 3.63 (d, J = 4.9 Hz, 1H), 2.79 (s, 3H), 2.61 (dd, J = 11.7, 5.8 Hz, 1H), 2.49 (dd, J = 11.5, 5.4 Hz, 1H), 2.24 – 2.10 (m, 2H), 1.88 – 1.82 (m, 2H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 199.9, 178.1, 156.5, 146.8, 146.0, 141.3, 136.6, 134.6, 132.4, 132.3, 131.6, 131.5, 131.2, 130.9, 130.2, 129.7, 129.5, 128.6, 128.0, 127.3, 127.0, 126.5, 125.5, 125.2, 125.1, 123.5, 122.4, 111.5, 73.0, 46.4, 31.2, 30.3, 29.7, 28.2, 22.2, 21.8 ppm. IR (neat): ν =3211, 2916, 2850, 1697, 1467, 1178, 750 cm^{-1}. HRMS calcd for $C_{41}H_{32}Cl_2N_4O_2$ m/z 682.1902 [M+], found 682.1899 [M+].

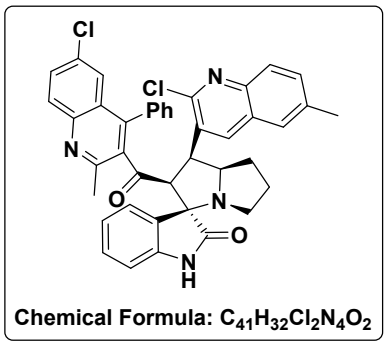
2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-chloro-7-methylquinolin-3-yl)-



Chemical Formula: $C_{41}H_{32}Cl_2N_4O_2$

1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (6c): Pale brown solid, Mp: 226-228 °C, 3h, 65% yield (221 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 1H), 7.89 (dd, J = 14.4, 7.7 Hz, 2H), 7.78 (d, J = 10.4 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.50 – 7.42 (m, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.5 Hz, 2H), 6.92 (d, J = 9.1 Hz, 1H), 6.86 (t, J = 6.4 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 7.4 Hz, 1H), 4.59 (t, J = 10.4 Hz, 1H), 4.37 (d, J = 11.9 Hz, 1H), 3.62 (d, J = 6.0 Hz, 1H), 2.59 (s, 3H), 2.55 – 2.44 (m, 2H), 1.87 – 1.83 (m, 1H), 1.73 (s, 2H), 1.66 – 1.61 (m, 1H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 199.9, 178.1, 156.5, 146.8, 146.0, 141.3, 136.6, 134.6, 132.4, 132.3, 131.6, 131.5, 131.2, 130.9, 130.2, 129.7, 129.5, 128.6, 128.0, 127.3, 127.0, 126.5, 125.5, 125.2, 125.1, 123.5, 122.4, 111.5, 73.0, 46.4, 31.2, 30.3, 29.7, 28.2, 22.2, 21.8 ppm. IR (neat): ν = 2920, 1705, 1469, 1192, 705 cm^{-1}. HRMS calcd for $C_{41}H_{32}Cl_2N_4O_2$ m/z 682.1902 [M+], found 682.1900 [M+].

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-chloro-6-methylquinolin-3-yl)-

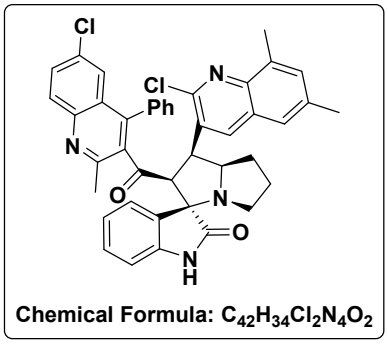


Chemical Formula: $C_{41}H_{32}Cl_2N_4O_2$

1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (6d): Pale brown solid, Mp: 220-222 °C, 2h, 72% yield (245 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.6 Hz, 1H), 7.91 (dd, J = 17.5, 6.8 Hz, 3H), 7.76 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 11.9 Hz, 3H), 7.48 (d, J = 7.7 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 6.2 Hz, 1H), 6.89 (s, 1H), 6.86 – 6.81 (m, 1H), 6.70 (t, J = 7.6 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 4.59 (t, J = 10.6 Hz, 1H), 4.38 (d, J = 11.9 Hz, 1H), 3.62 (d,

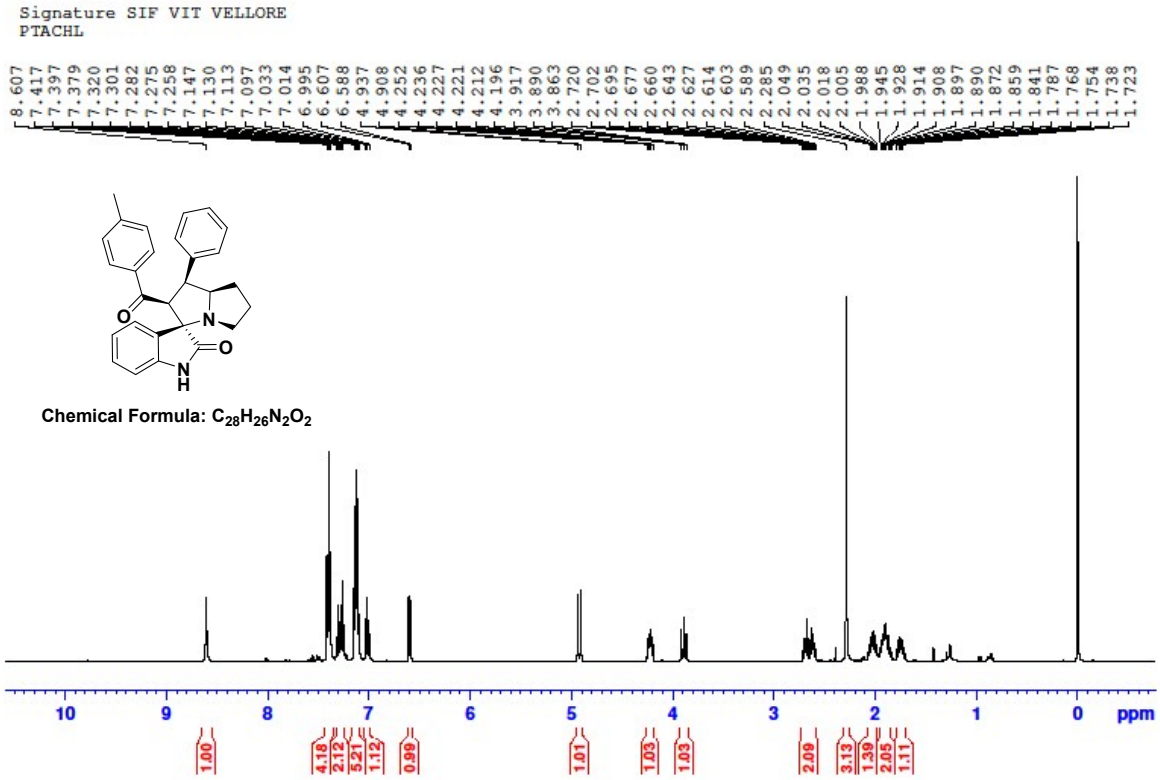
J = 6.5 Hz, 1H), 2.65 (s, 3H), 2.51 (t, J = 13.4 Hz, 2H), 2.20 (dd, J = 16.3, 8.1 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.79 – 1.73 (m, 1H), 1.51 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 199.9, 178.1, 156.5, 146.8, 146.0, 141.3, 136.6, 134.6, 132.4, 132.3, 131.6, 131.5, 131.2, 130.9, 130.2, 129.7, 129.5, 128.6, 128.0, 127.3, 127.0, 126.5, 125.5, 125.2, 125.1, 123.5, 122.4, 111.5, 73.0, 46.4, 31.2, 30.3, 29.7, 28.2, 22.2, 21.8 ppm. IR (neat): ν =3302, 2916, 1728, 1467, 1176, 705 cm^{-1}. HRMS calcd for $C_{41}H_{32}Cl_2N_4O_2$ m/z 682.1902 [M+], found 682.1904 [M+].

2'-(6-chloro-2-methyl-4-phenylquinoline-3-carbonyl)-1'-(2-chloro-6,8-dimethylquinolin-3-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (6e):



Chemical Formula: $C_{42}H_{34}Cl_2N_4O_2$

Brown solid, Mp: 230-232 ◦C, 2h, 70% yield (243 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.6 Hz, 1H), 7.89 (t, J = 9.2 Hz, 2H), 7.58 (dd, J = 12.3, 3.6 Hz, 3H), 7.51 – 7.45 (m, 1H), 7.45 (s, 1H), 7.41 – 7.35 (m, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.52 (d, J = 7.5 Hz, 1H), 4.63 – 4.55 (m, 1H), 4.35 (d, J = 11.9 Hz, 1H), 3.62 (d, J = 5.4 Hz, 1H), 2.74 (s, 3H), 2.59 (s, 3H), 2.48 (dd, J = 10.2, 4.0 Hz, 1H), 2.24 – 2.10 (m, 2H), 1.88 – 1.82 (m, 2H), 1.80 – 1.75 (m, 1H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 177.9, 175.9, 156.6, 146.7, 146.0, 144.3, 141.2, 140.6, 136.1, 136.1, 134.6, 132.4, 132.3, 131.4, 130.8, 130.1, 129.5, 129.0, 128.6, 127.3, 127.1, 126.4, 125.5, 125.3, 125.2, 124.4, 123.5, 122.1, 111.4, 108.8, 73.0, 59.1, 47.6, 46.4, 31.1, 28.2, 22.2, 21.7, 20.9, 17.7 ppm. IR (neat): ν = 3196, 2958, 2918, 1716, 1469, 1193, 707 cm^{-1}. HRMS calcd for $C_{42}H_{34}Cl_2N_4O_2$ m/z 696.2059 [M+], found 696.2057 [M+].



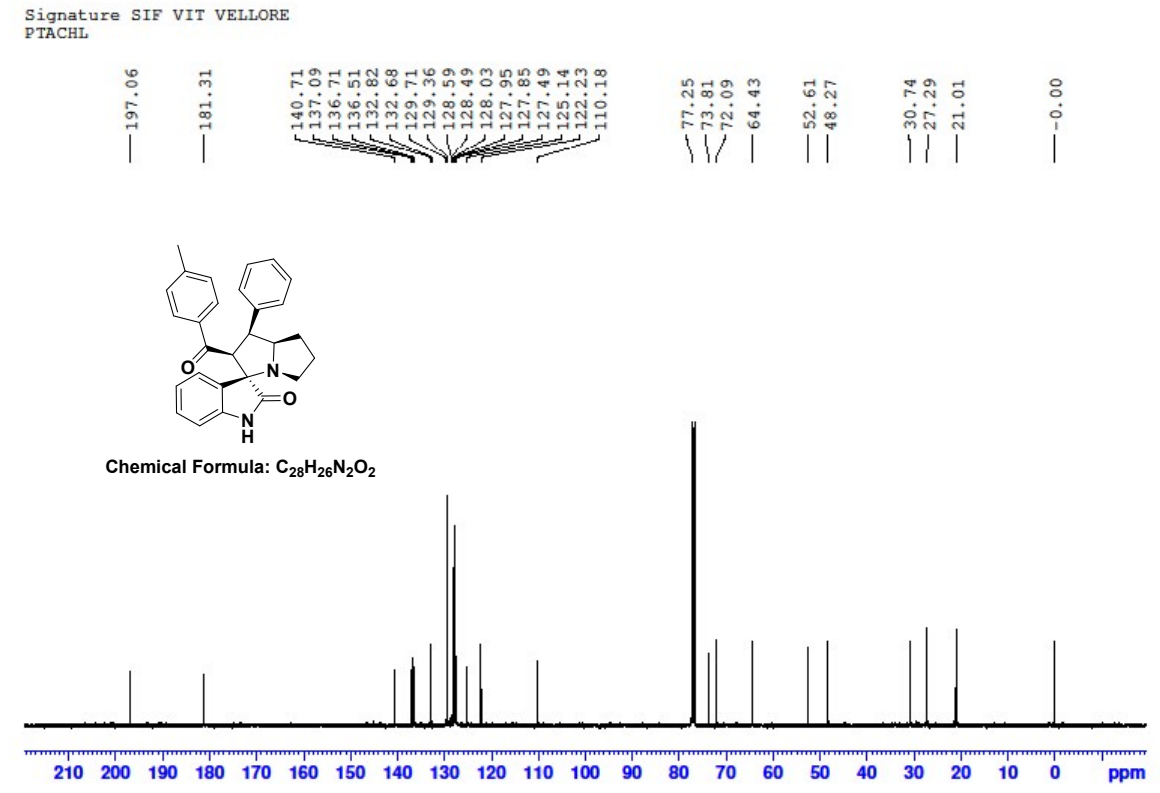
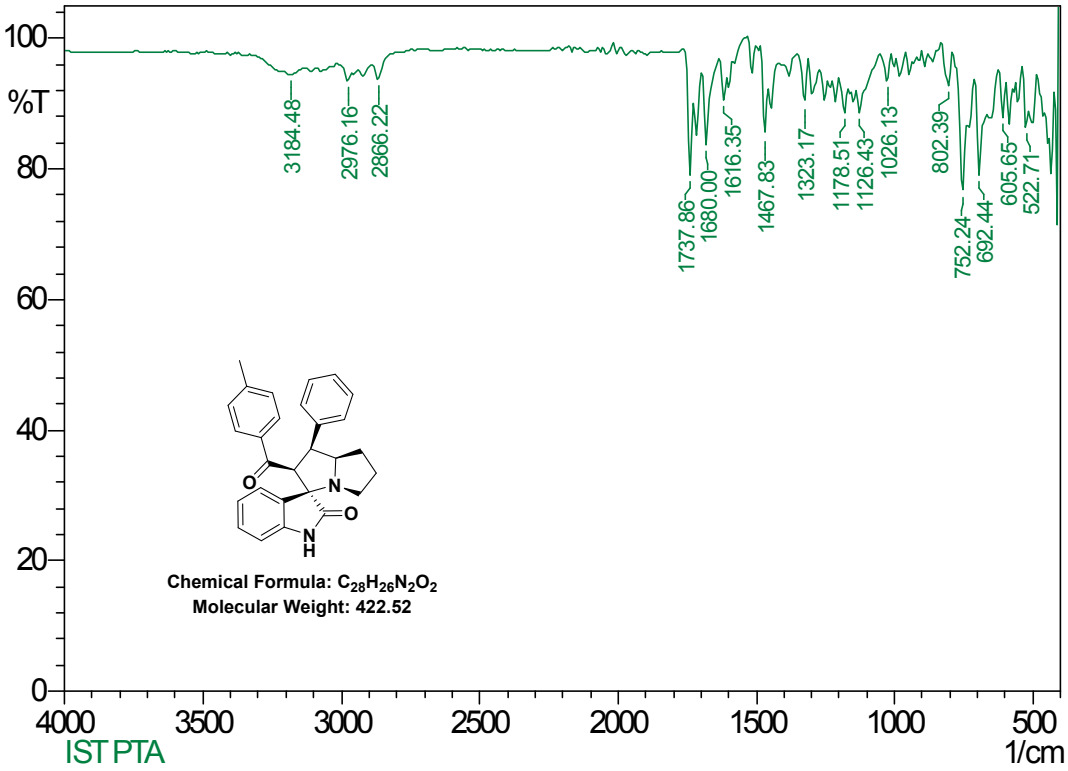


Figure S1: ^{1}H and ^{13}C NMR spectra of compound **4aa** in $CDCl_3$



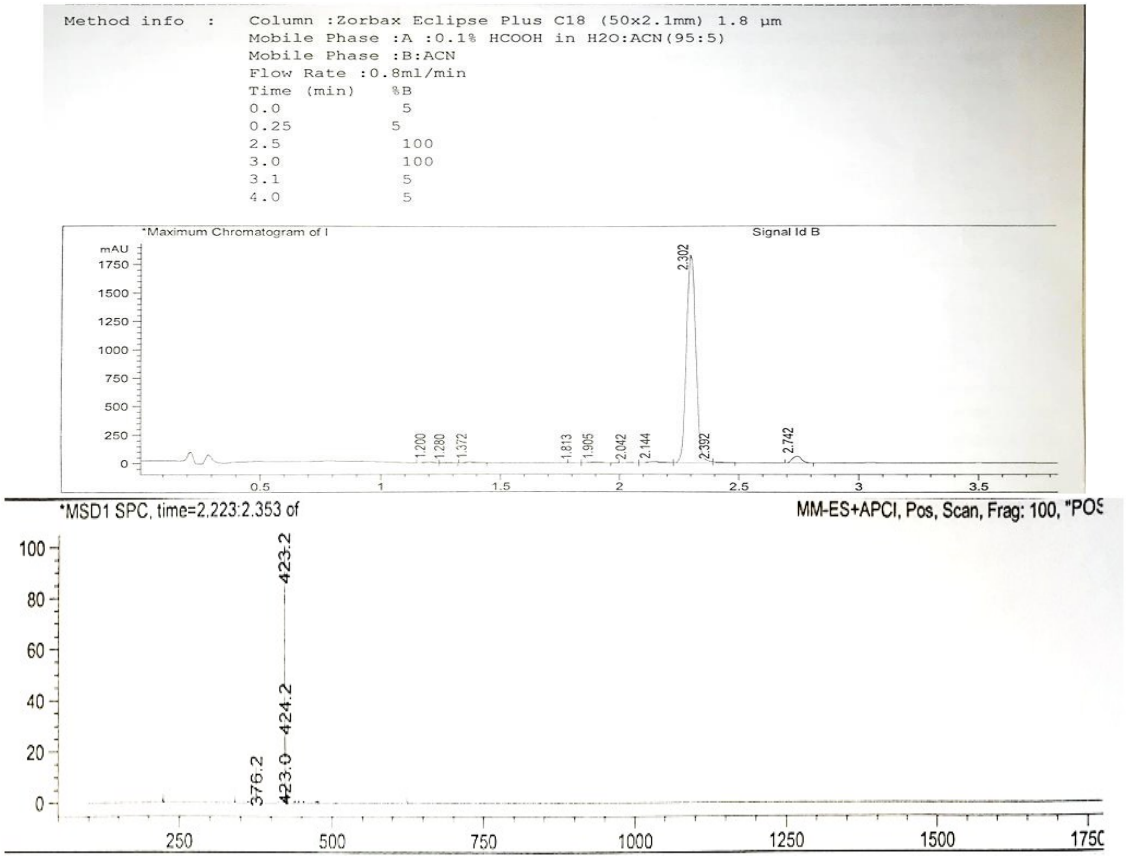
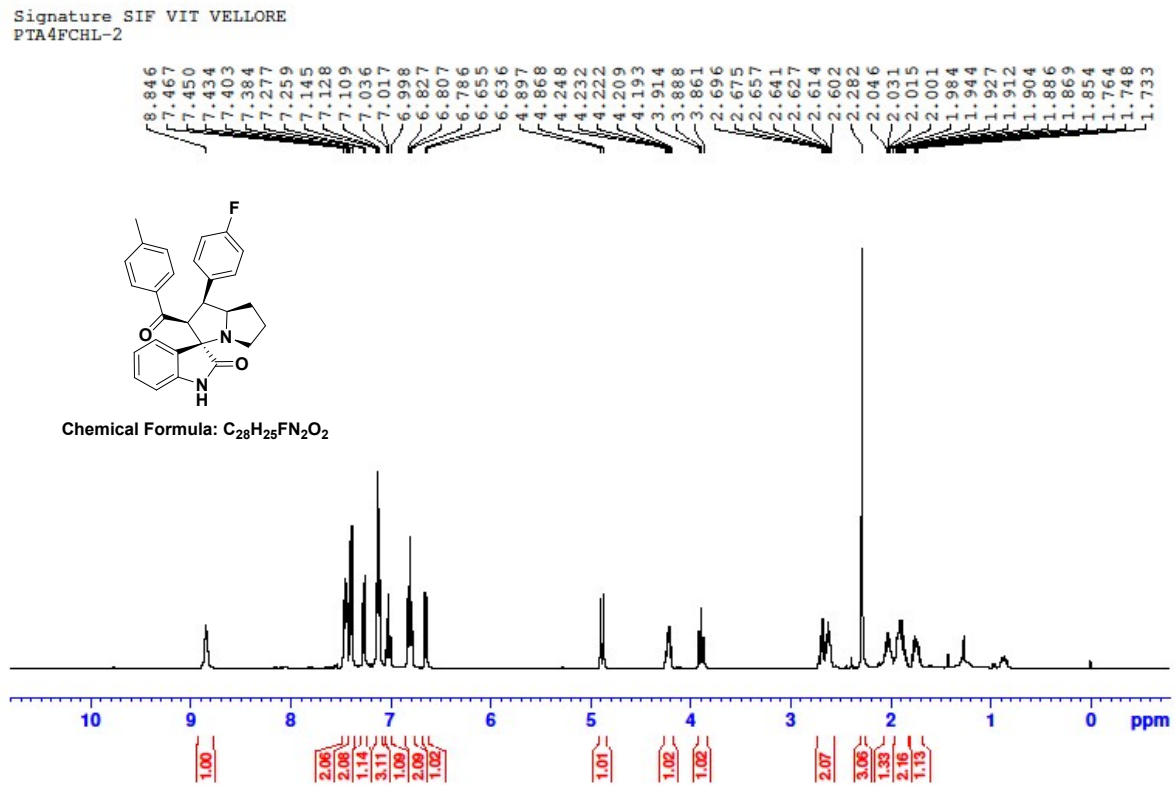


Figure S2: FT-IR and LC-MS spectra of compound **4aa**



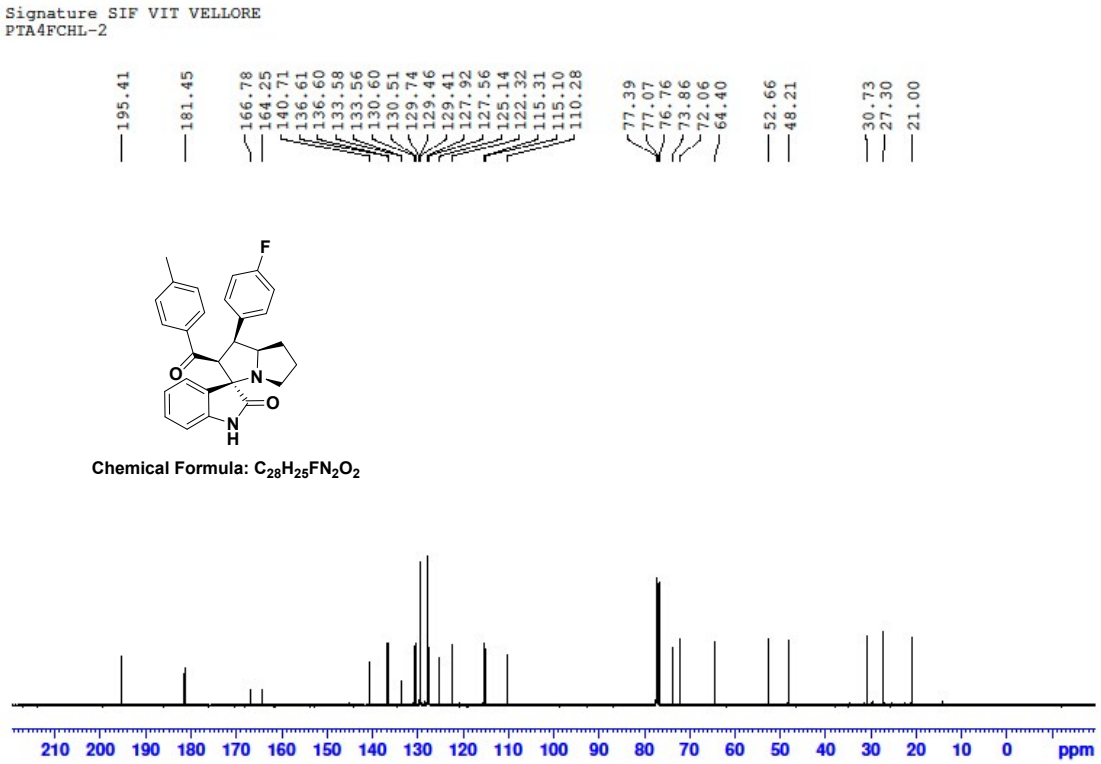


Figure S3: ^{1}H and ^{13}C NMR spectra of compound **4ab** in $CDCl_3$

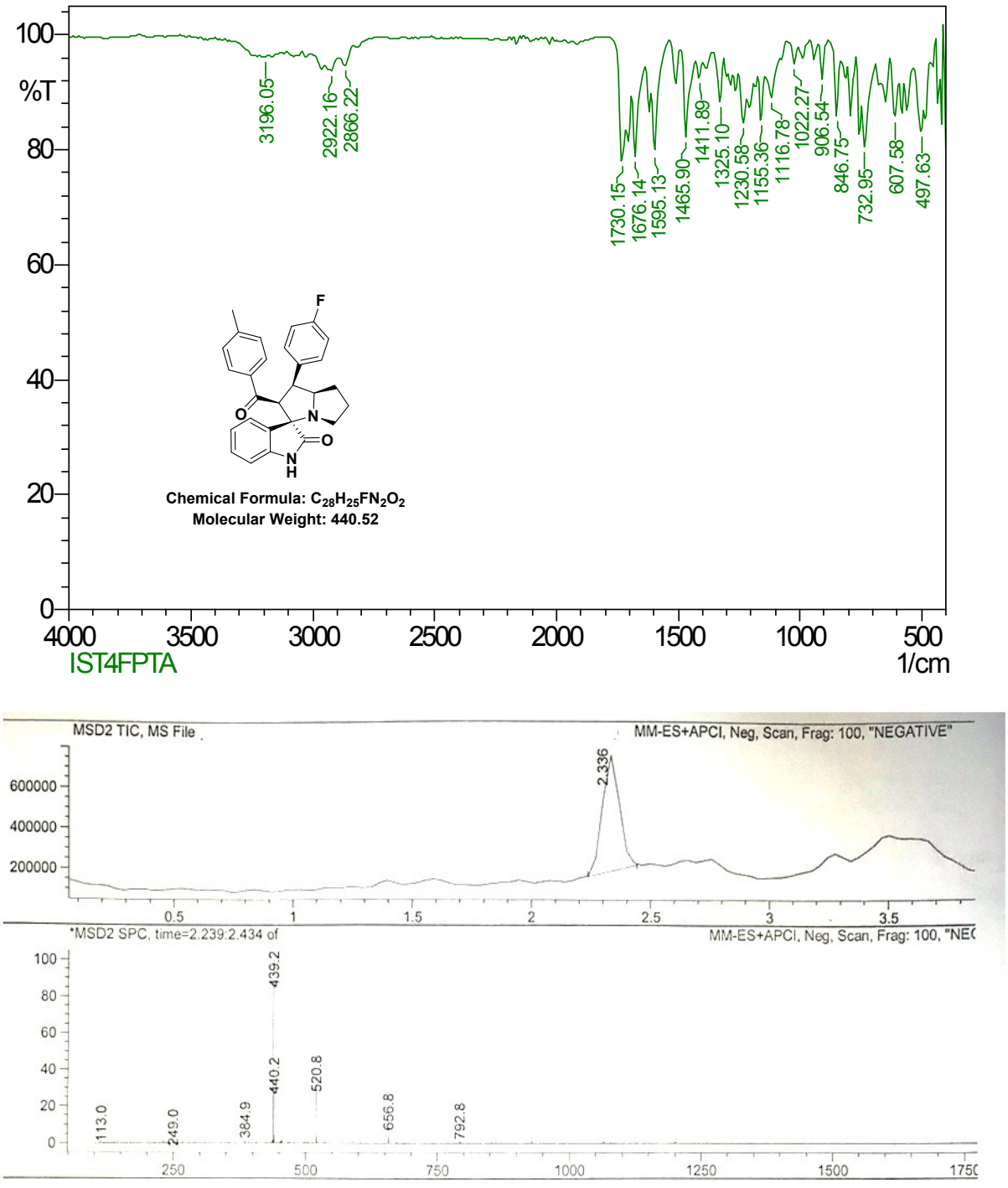
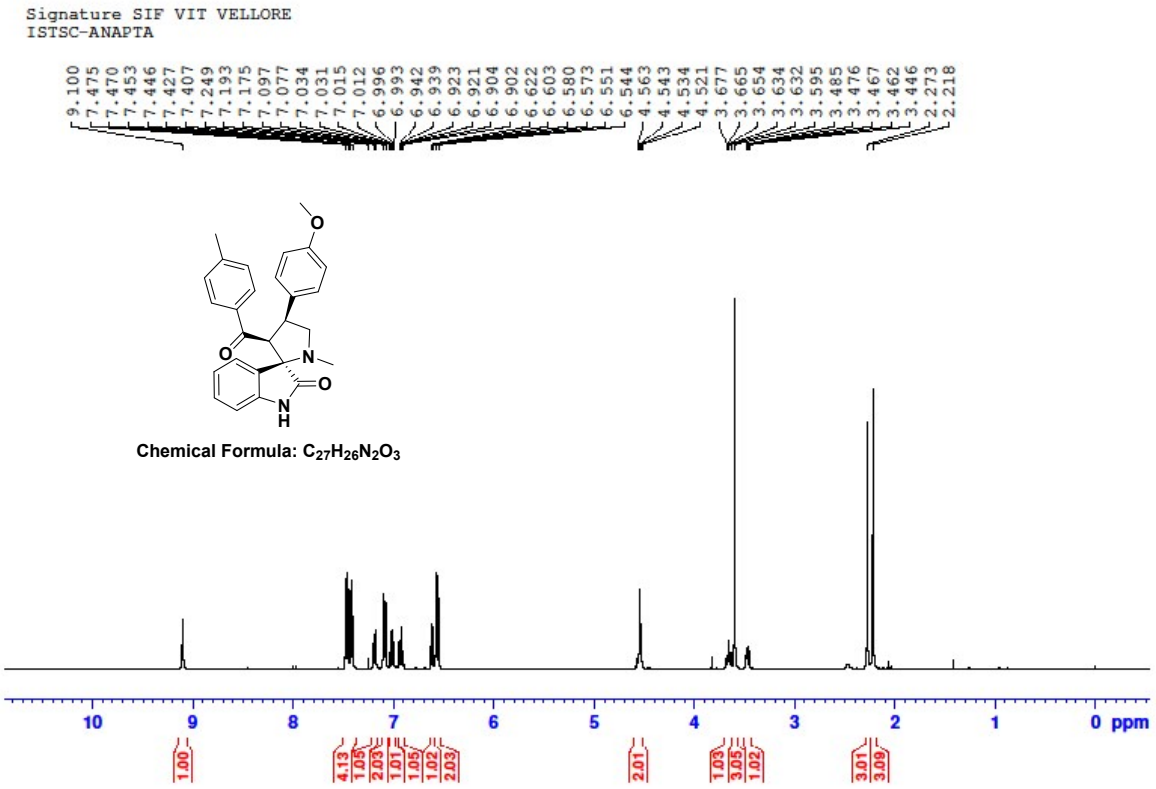


Figure S4: FT-IR and LC-MS spectra of compound **4ab**



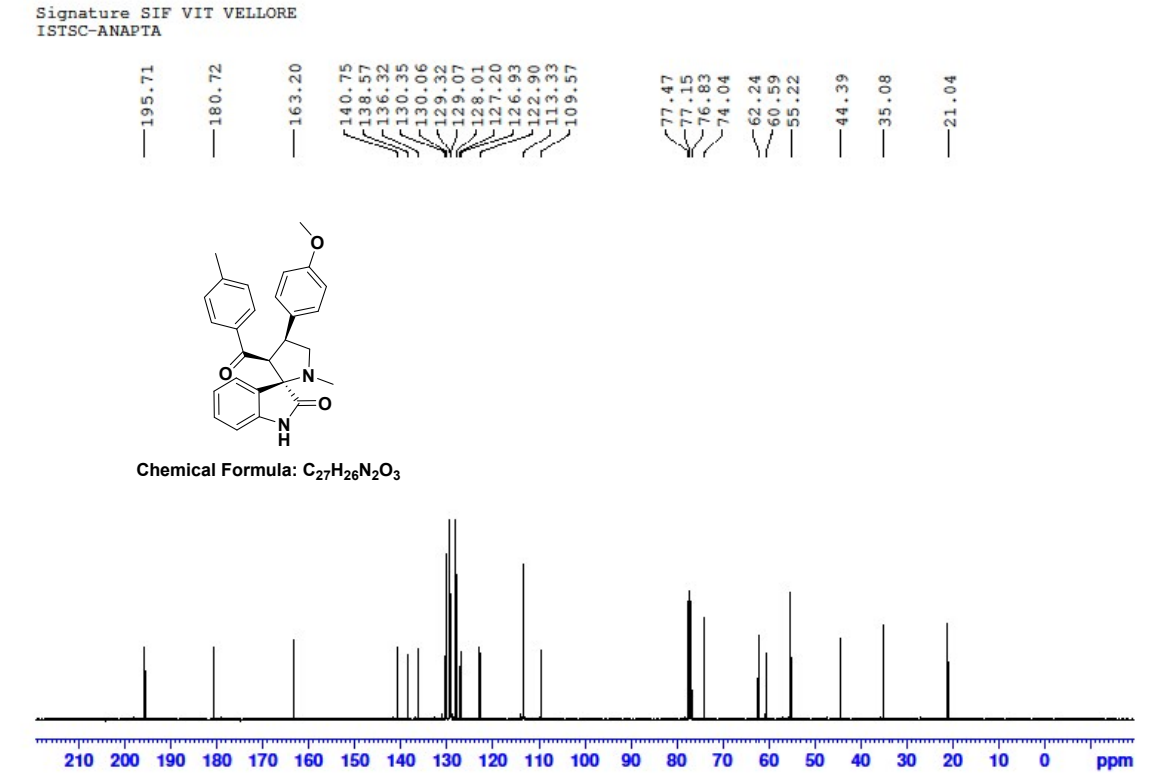
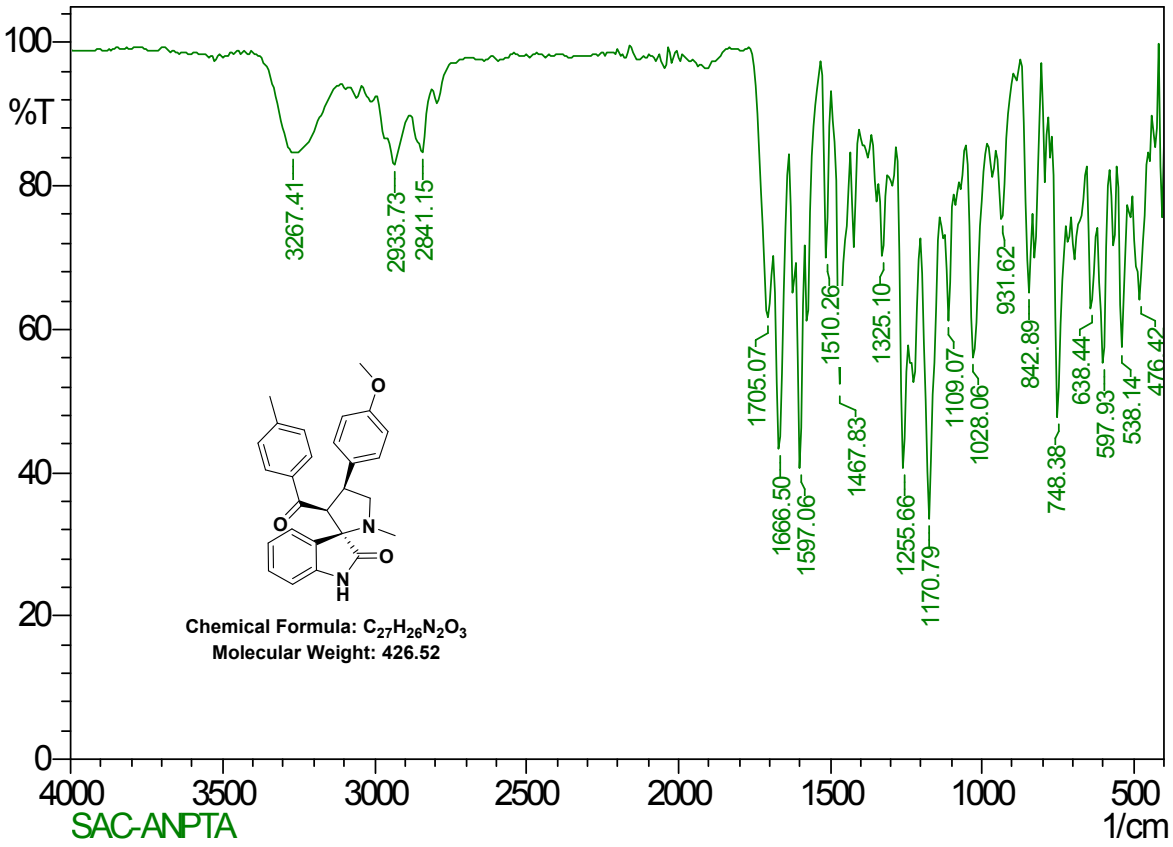


Figure S5: ^{1}H and ^{13}C NMR spectra of compound **4ba** in $CDCl_3$



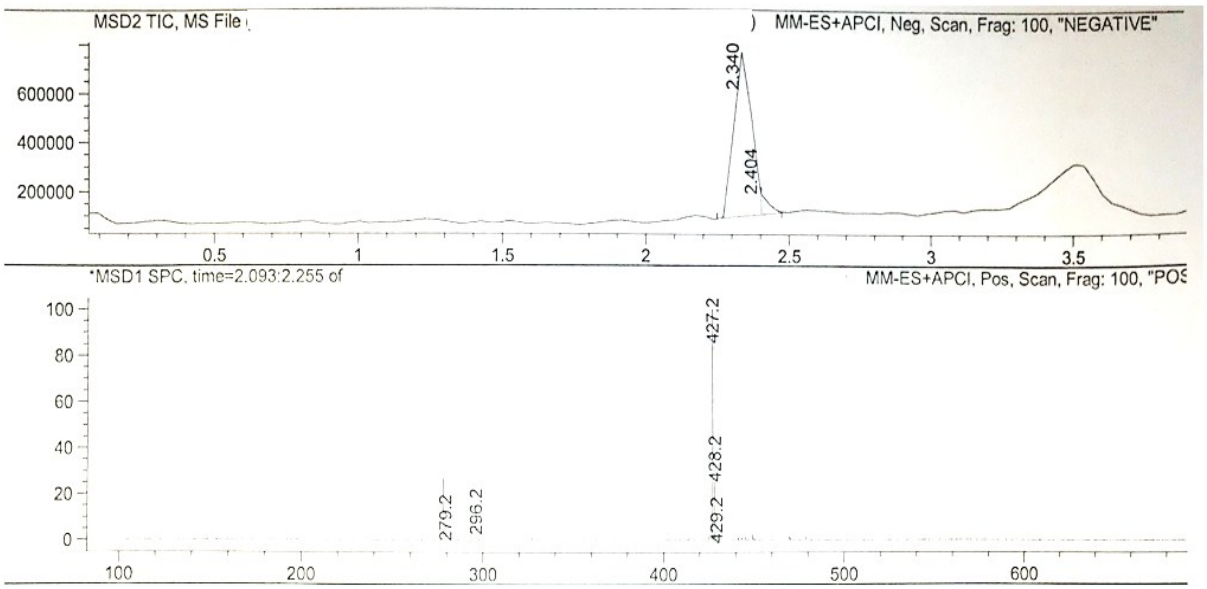
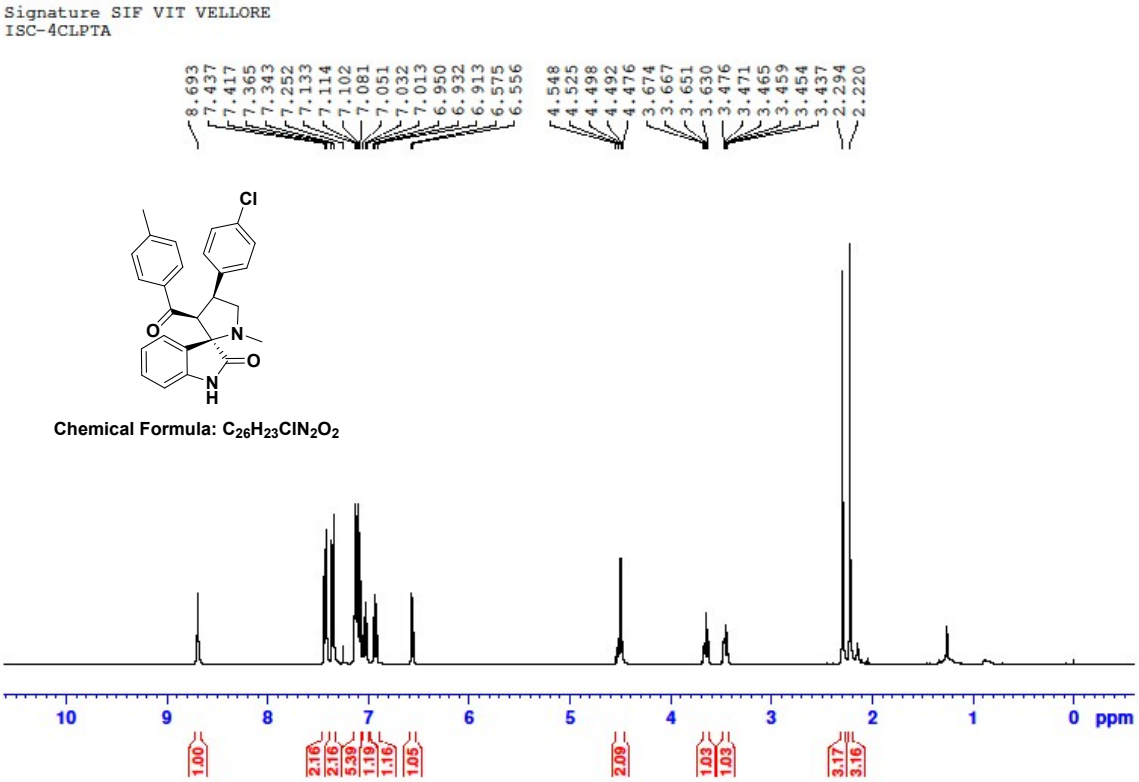


Figure S6: FT-IR and LC-MS spectra of compound **4ba**



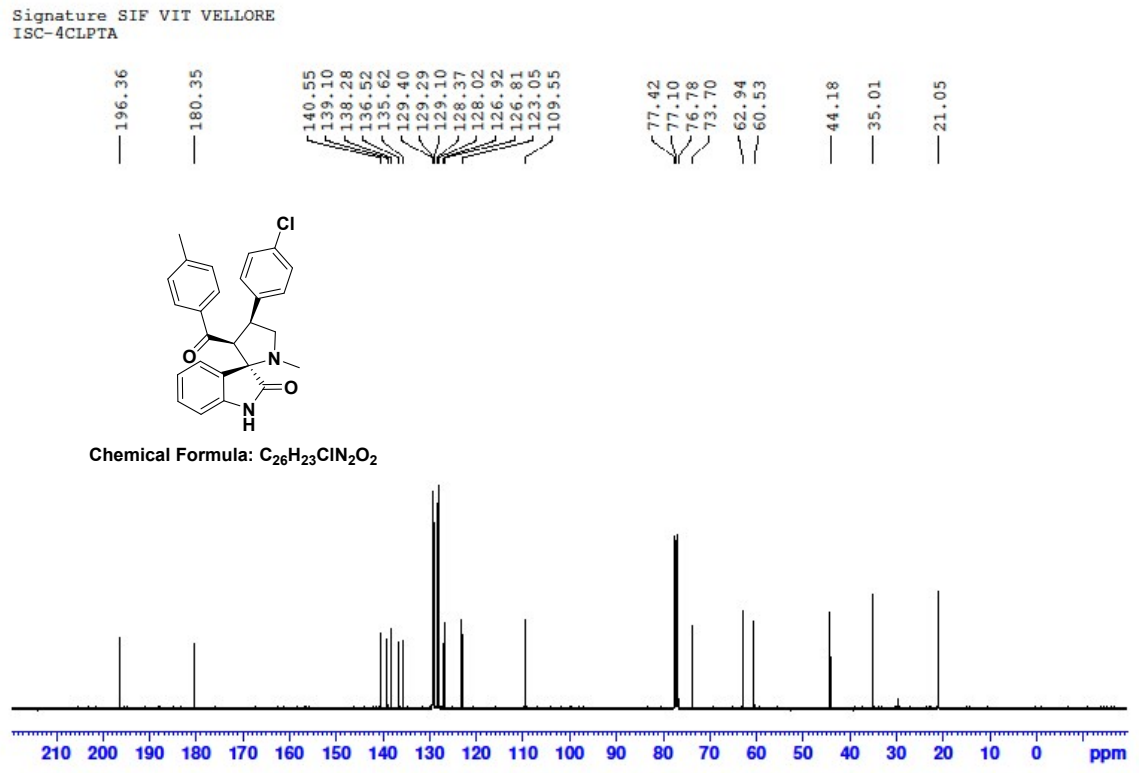
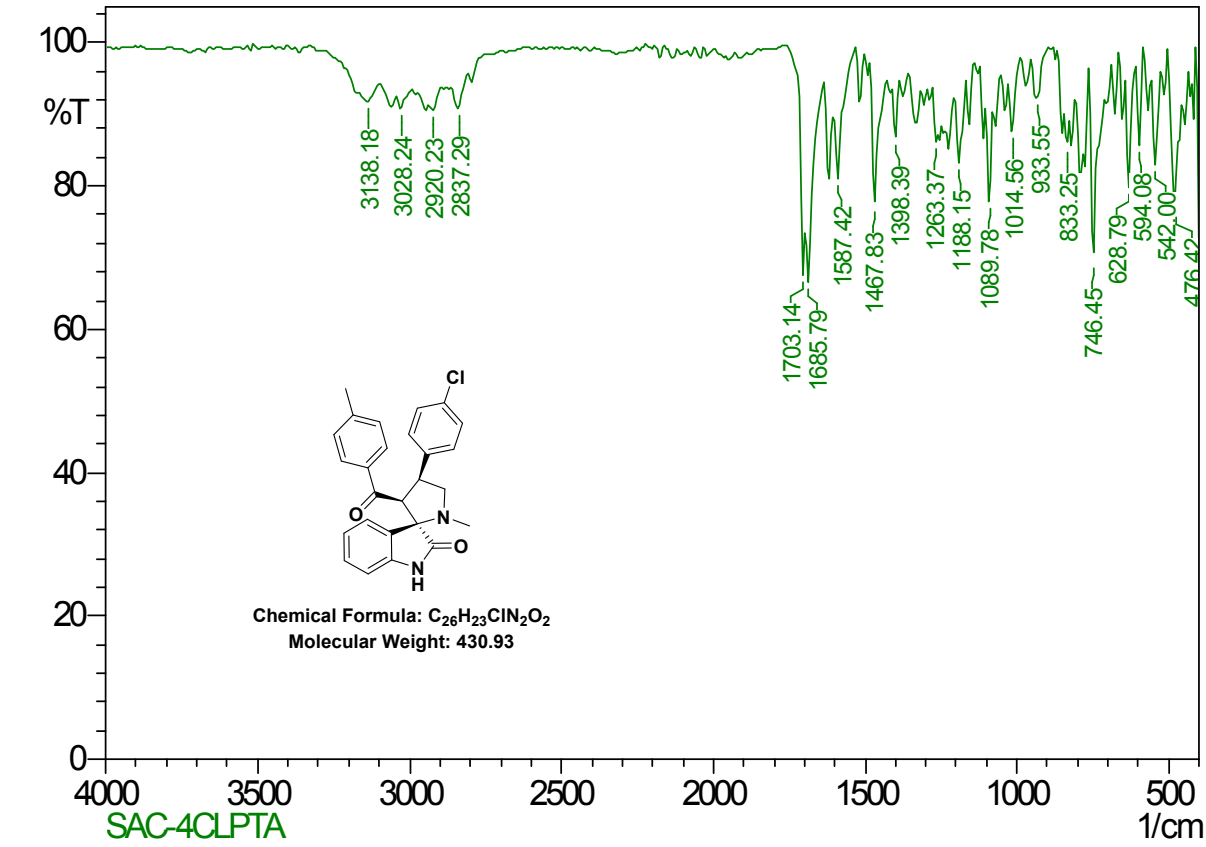
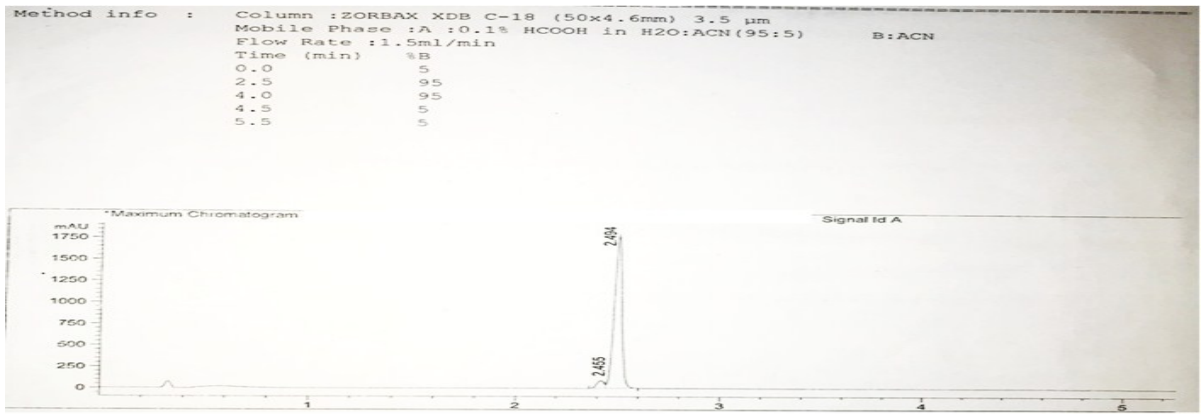


Figure S7: ^{1}H and ^{13}C NMR spectra of compound **4bb** in $CDCl_3$





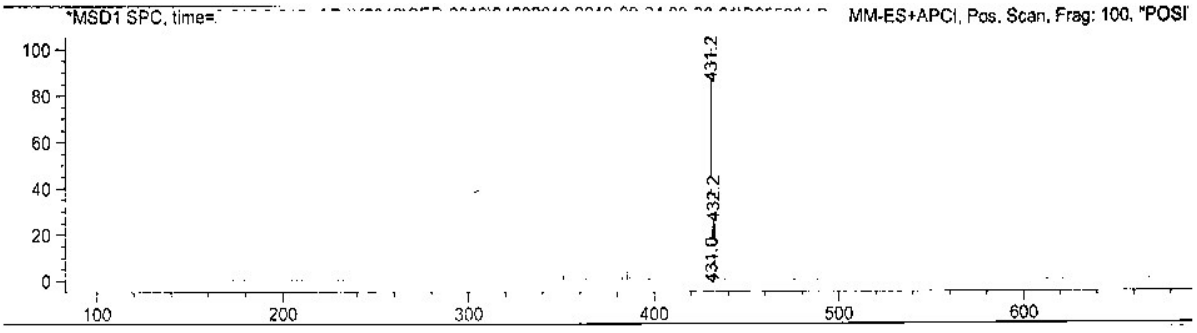
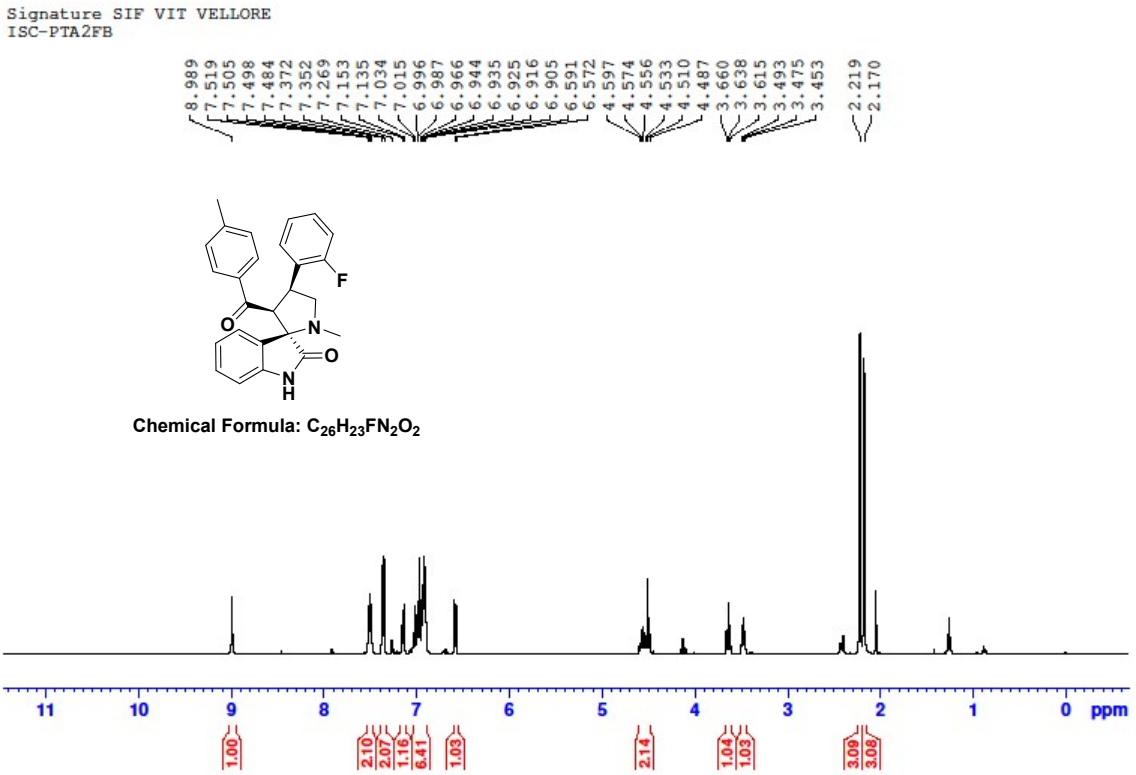


Figure S8: FT-IR and LC-MS spectra of compound **4bb**



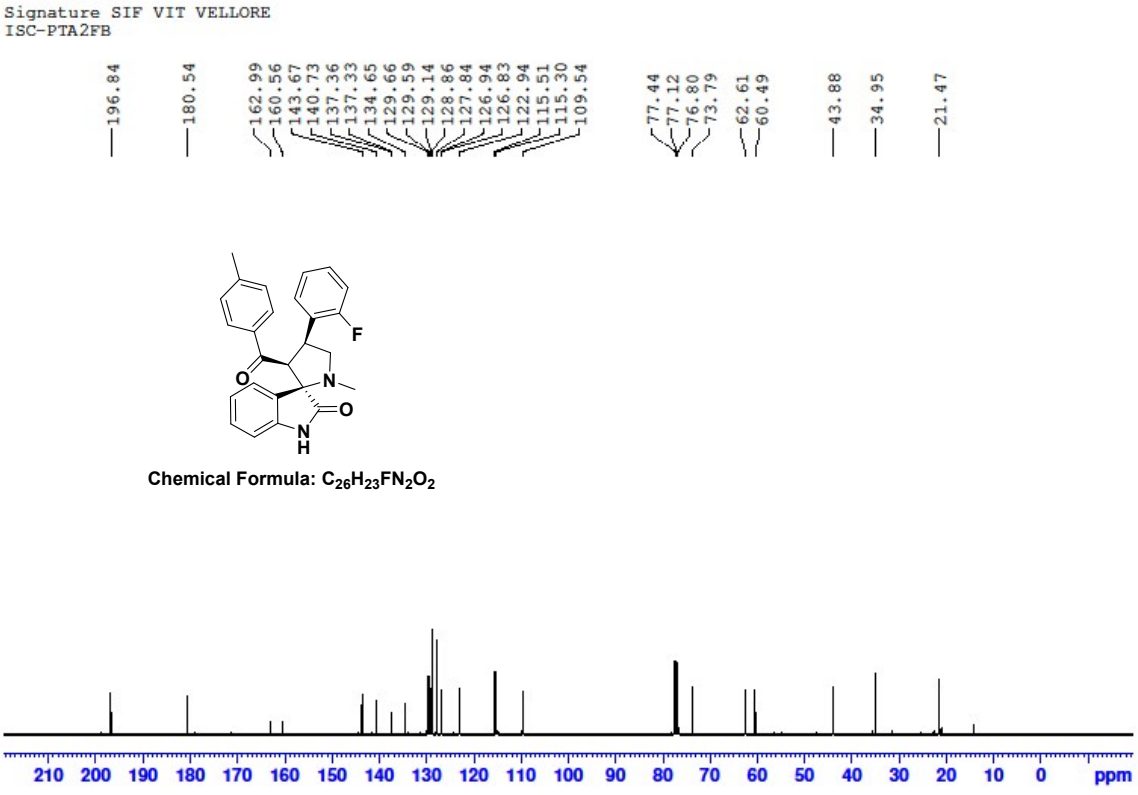


Figure S9: ^{1}H and ^{13}C NMR spectra of compound **4bc** in $CDCl_3$

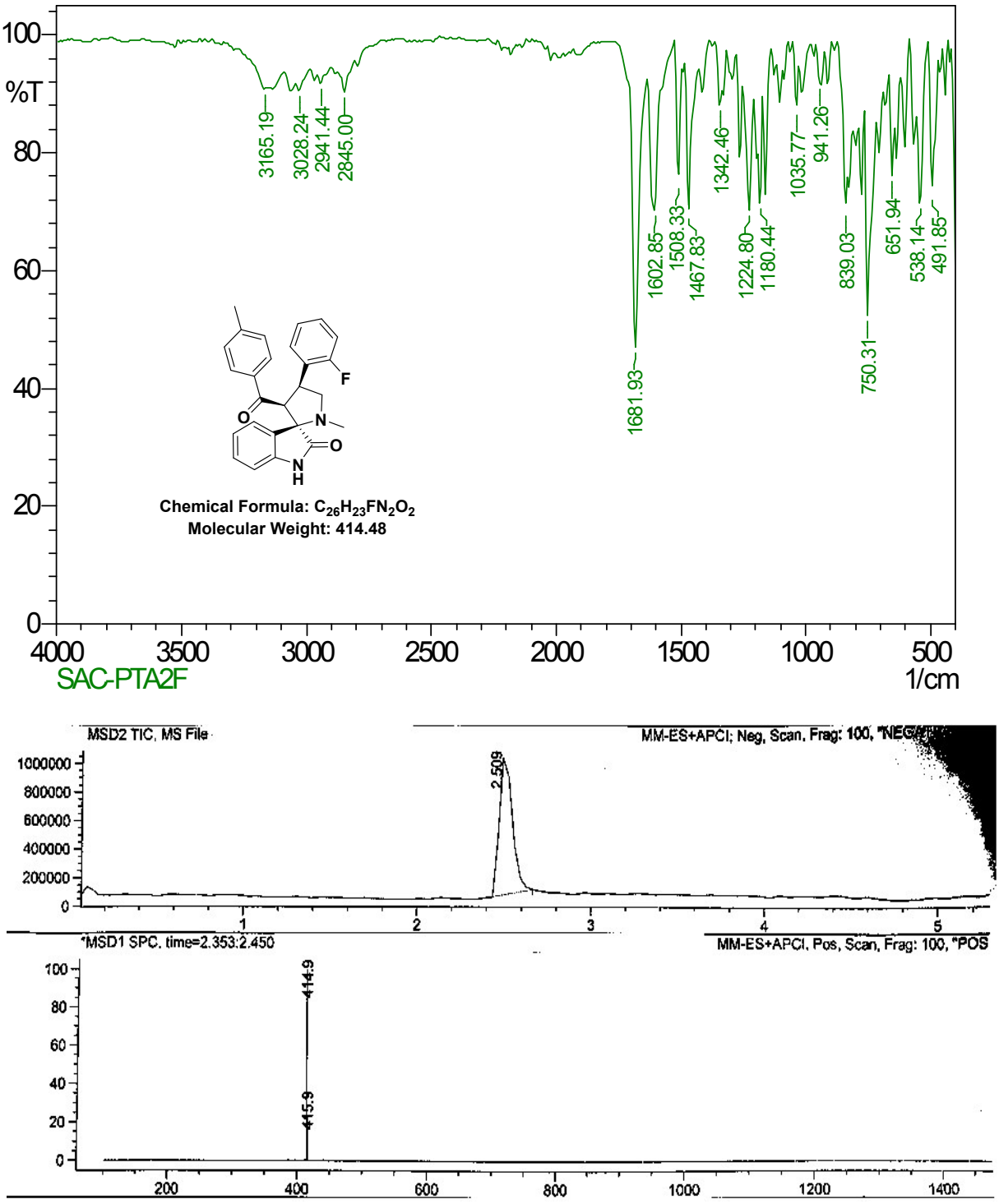
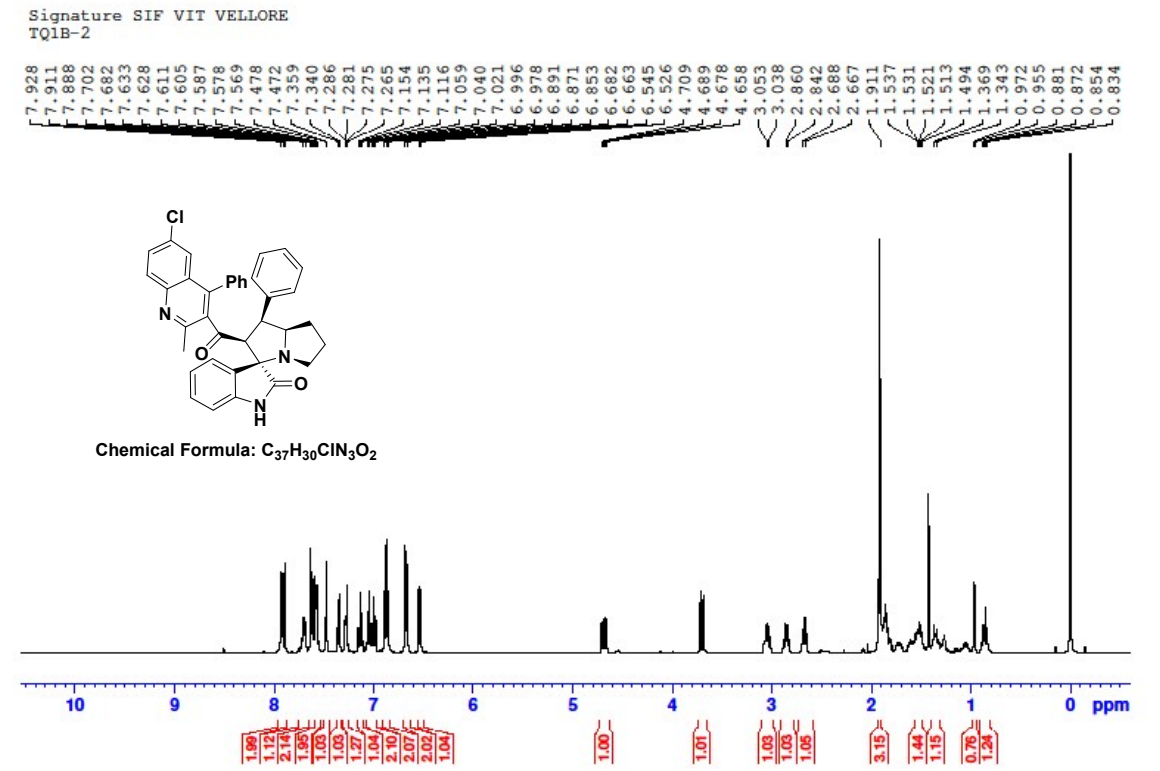


Figure S10: IR spectra of compound **4bc**



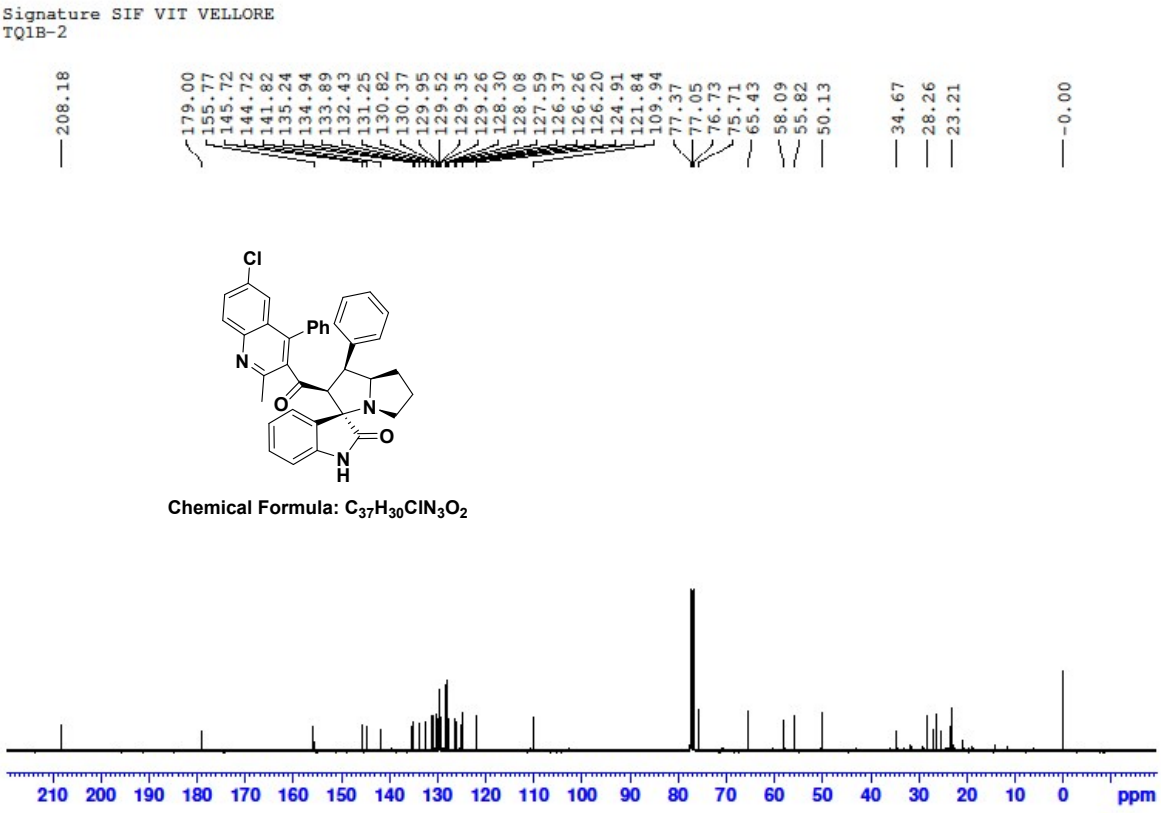
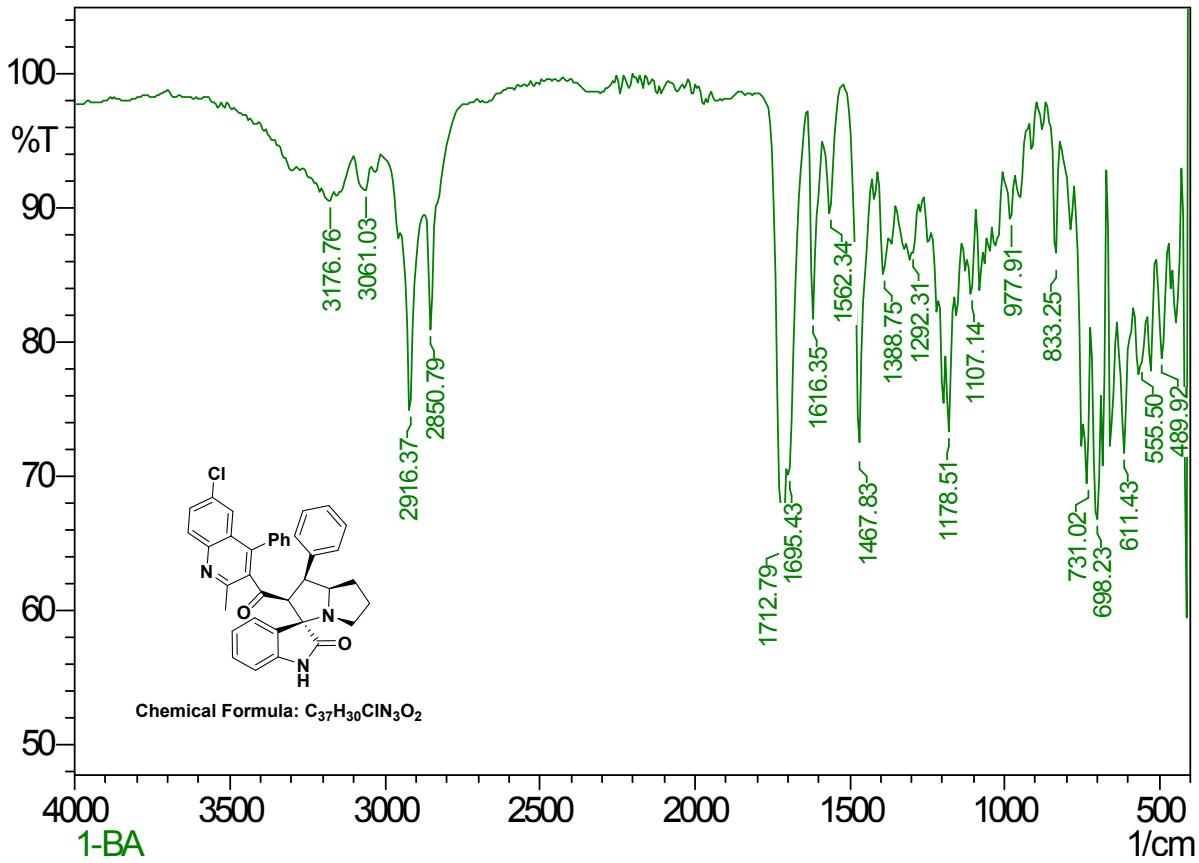


Figure S11: ^{1}H and ^{13}C NMR spectra of compound **5a** in $CDCl_3$



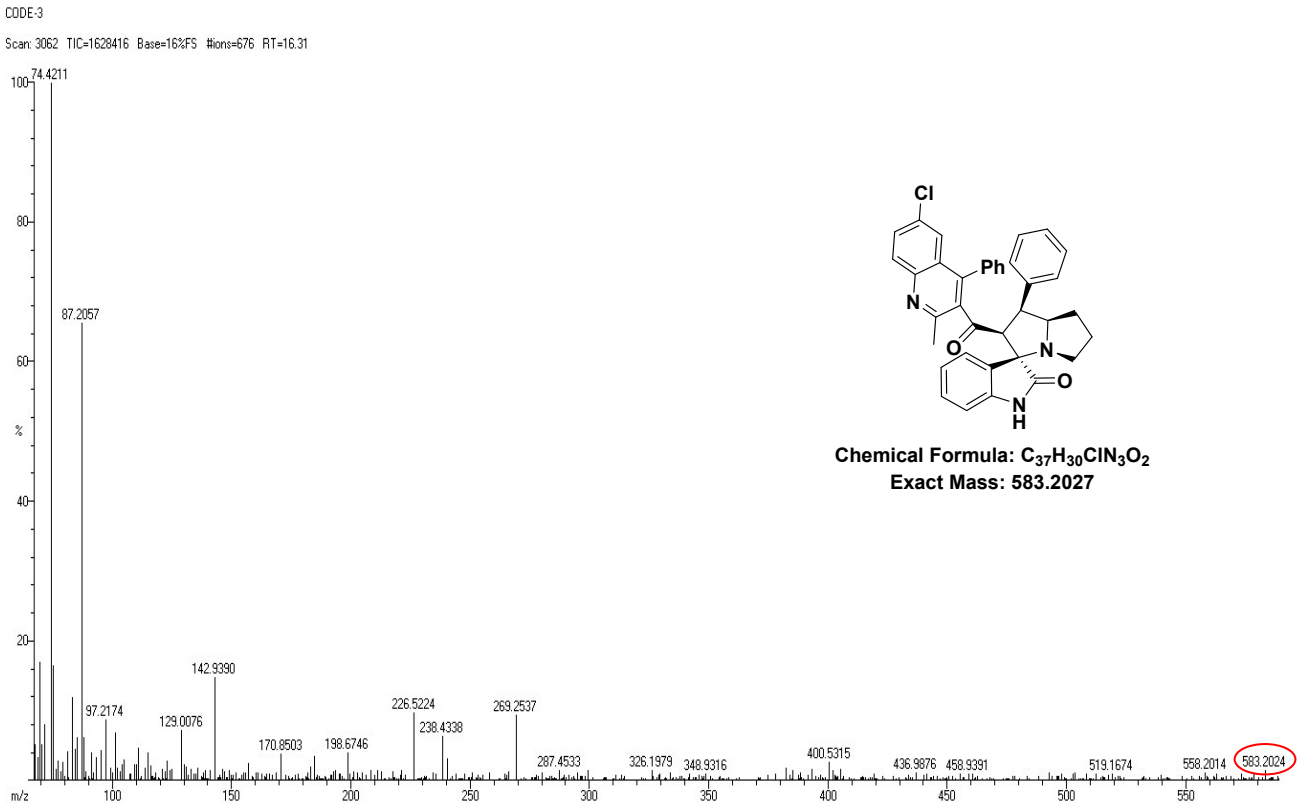


Figure S12: FT-IR & HRMS spectra of compound **5a**

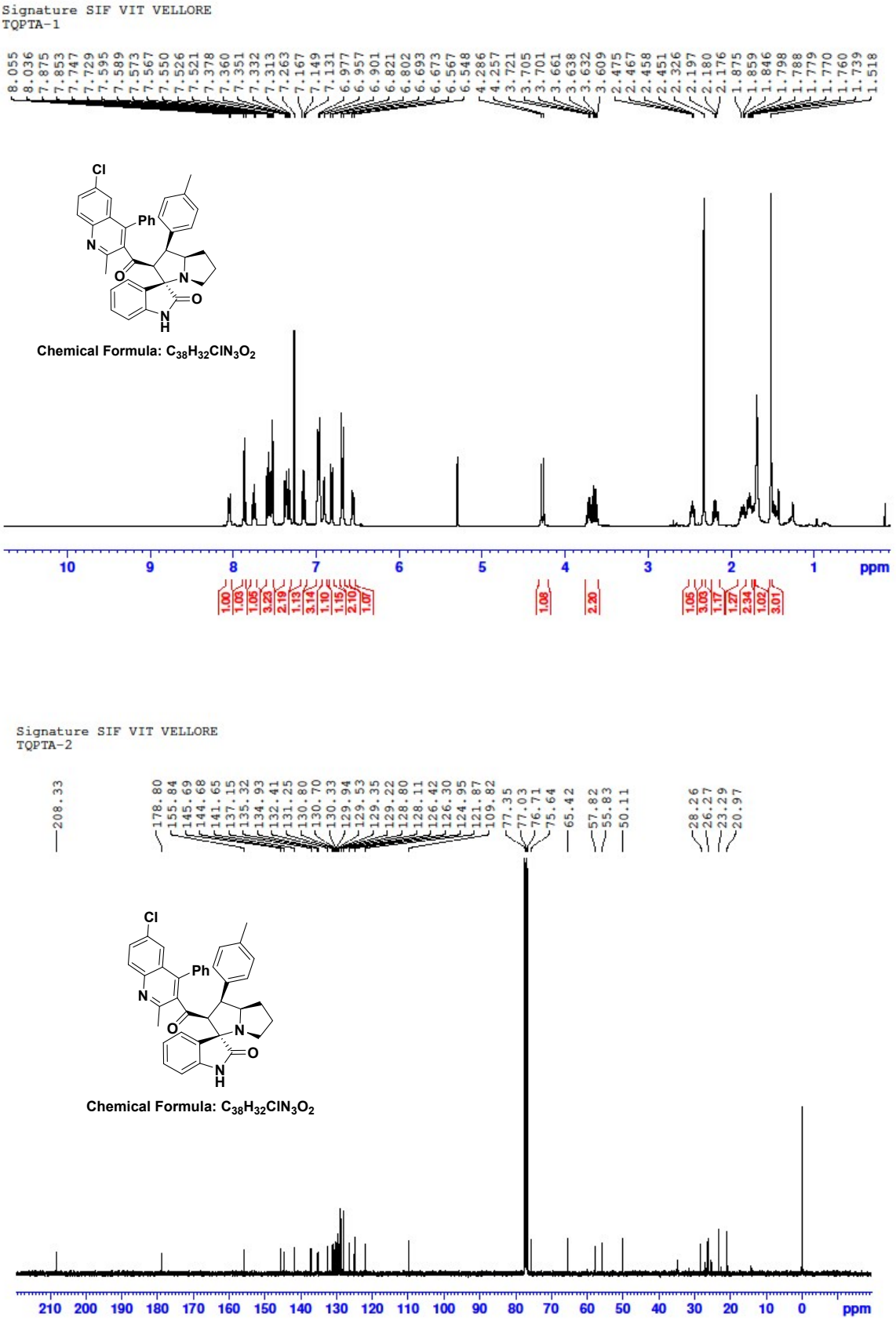
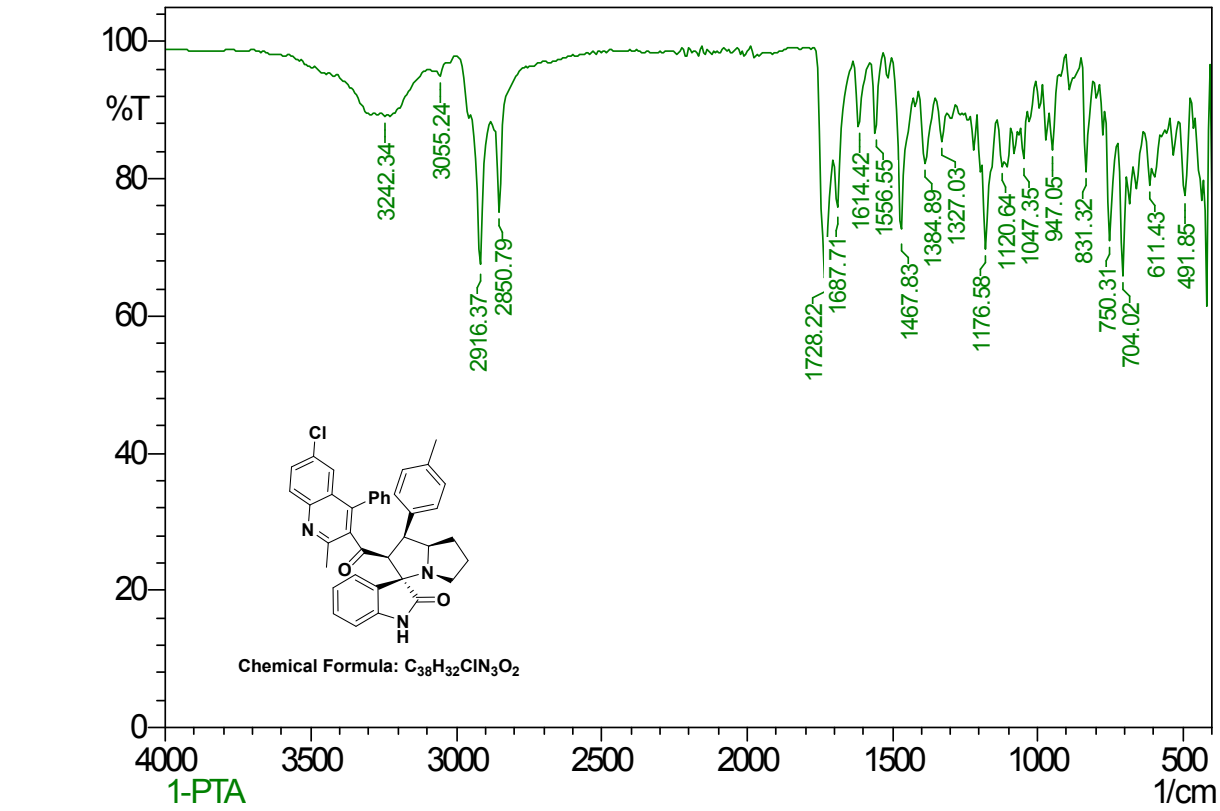


Figure S13: ^{1}H and ^{13}C NMR spectra of compound **5b** in $CDCl_3$



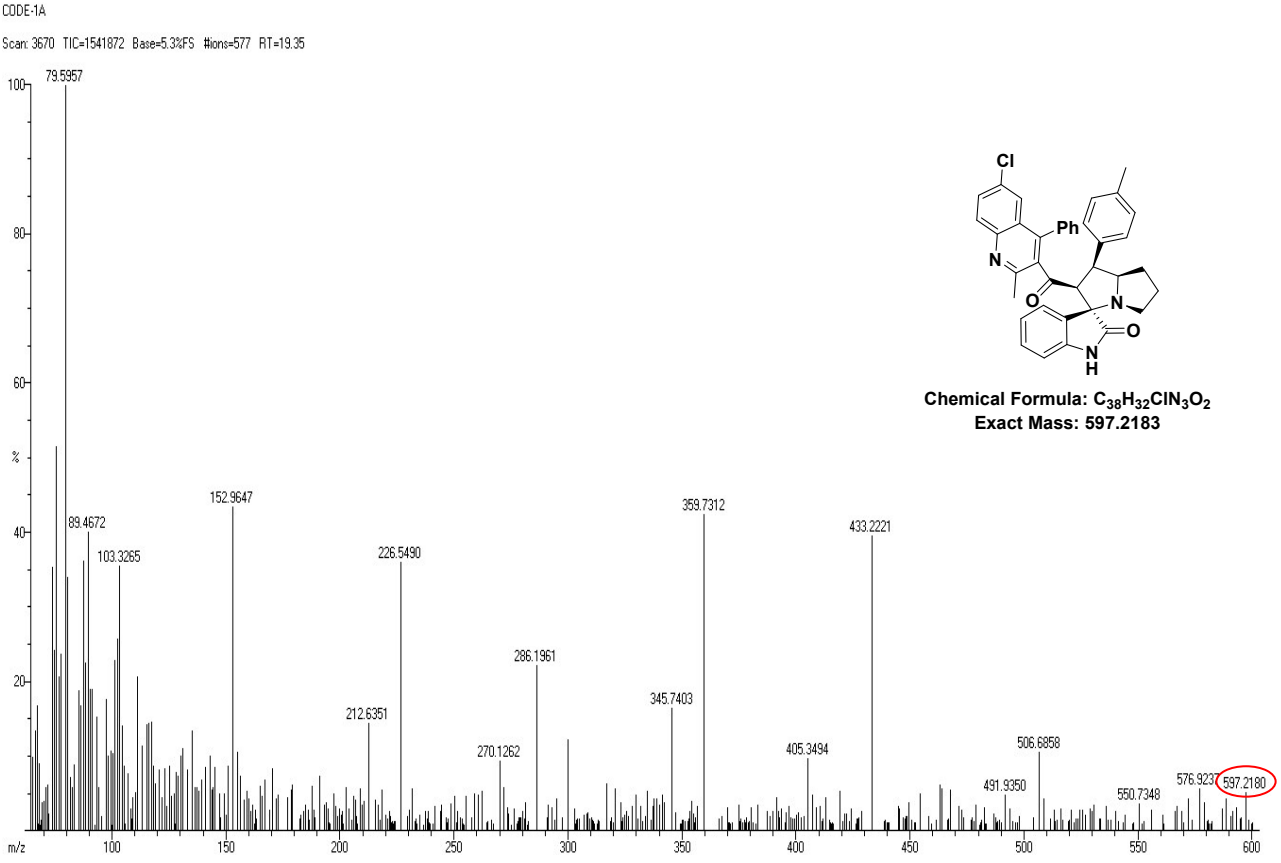
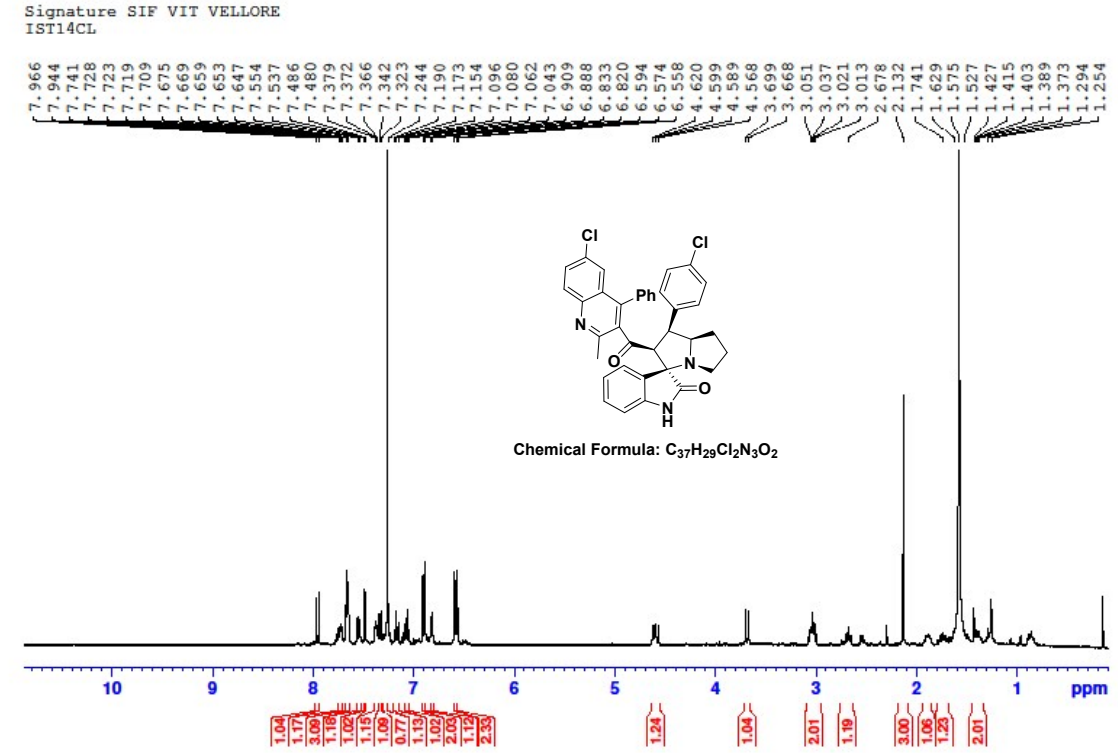


Figure S14: FT-IR & HRMS spectra of compound **5b**



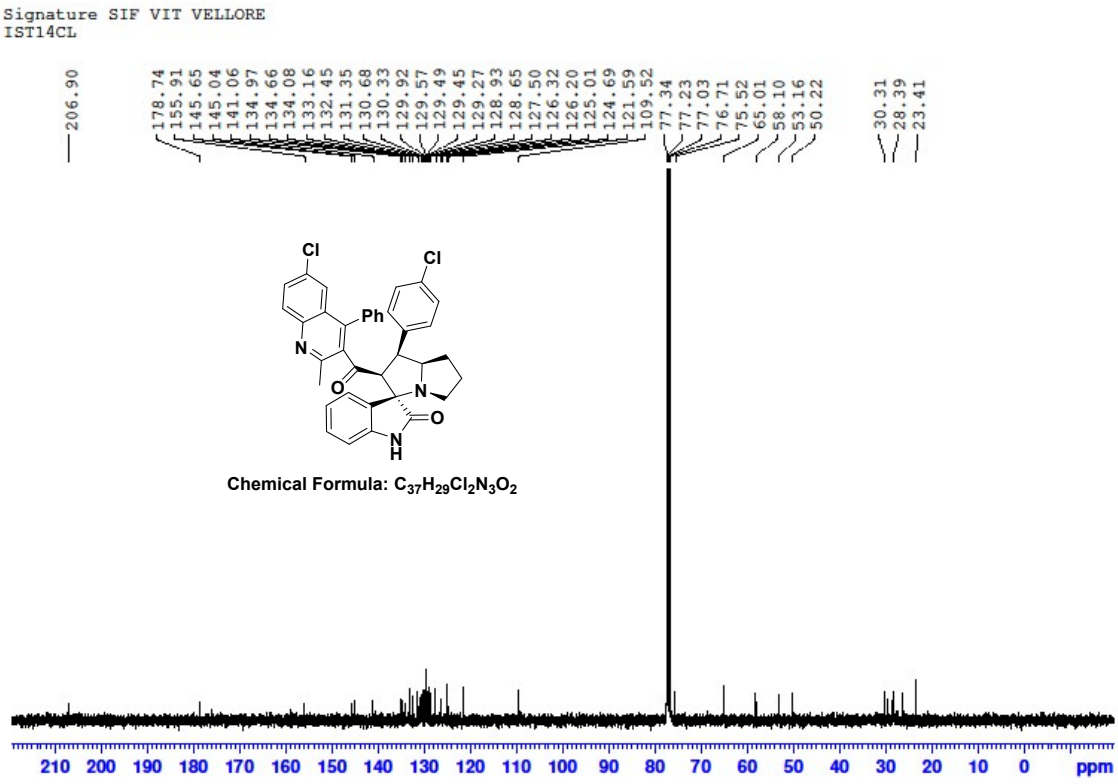
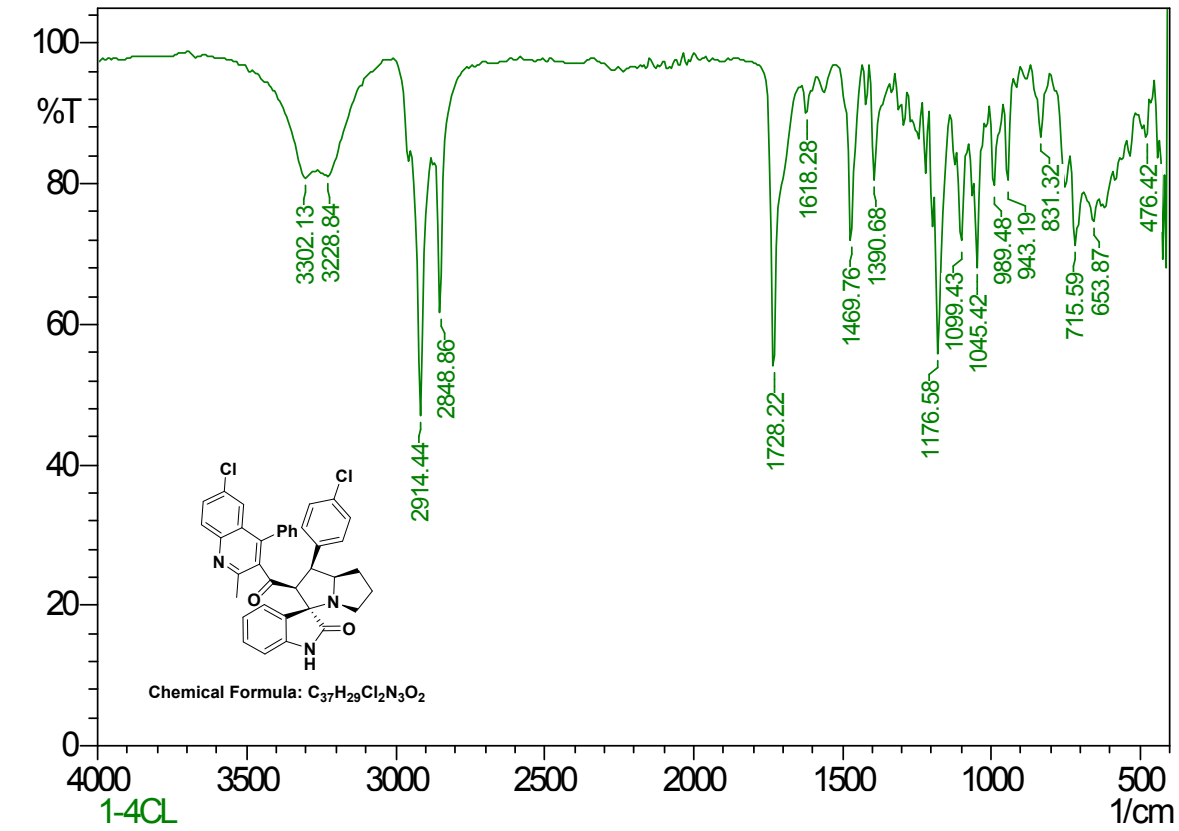


Figure S15: ^{1}H and ^{13}C NMR spectra of compound **5c** in $CDCl_3$



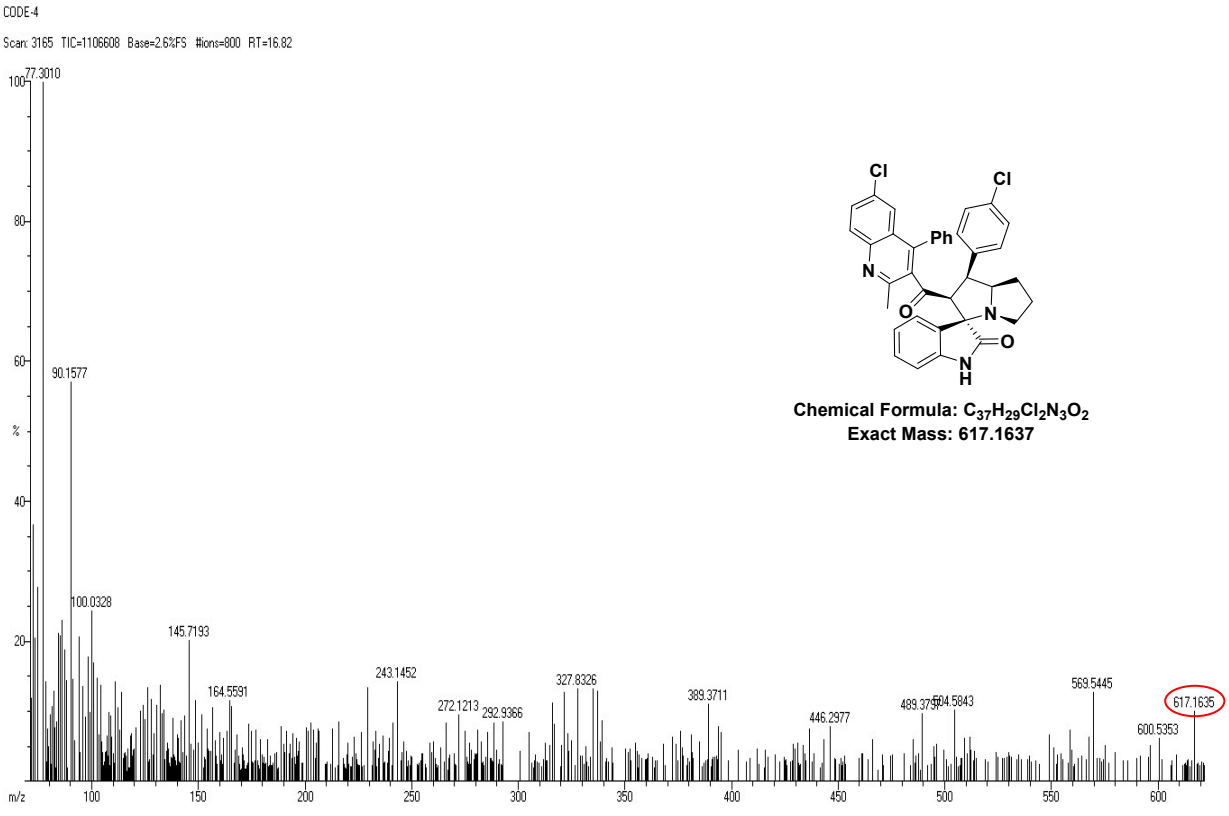
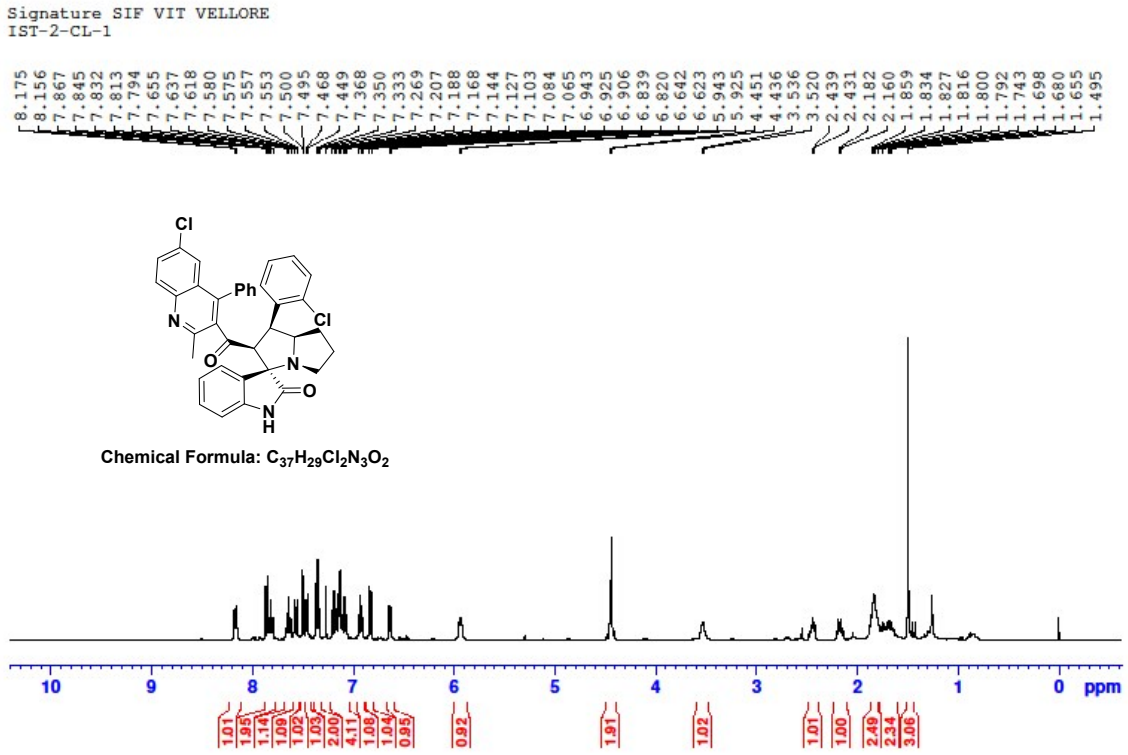


Figure S16: FT-IR & HRMS spectra of compound **5c**



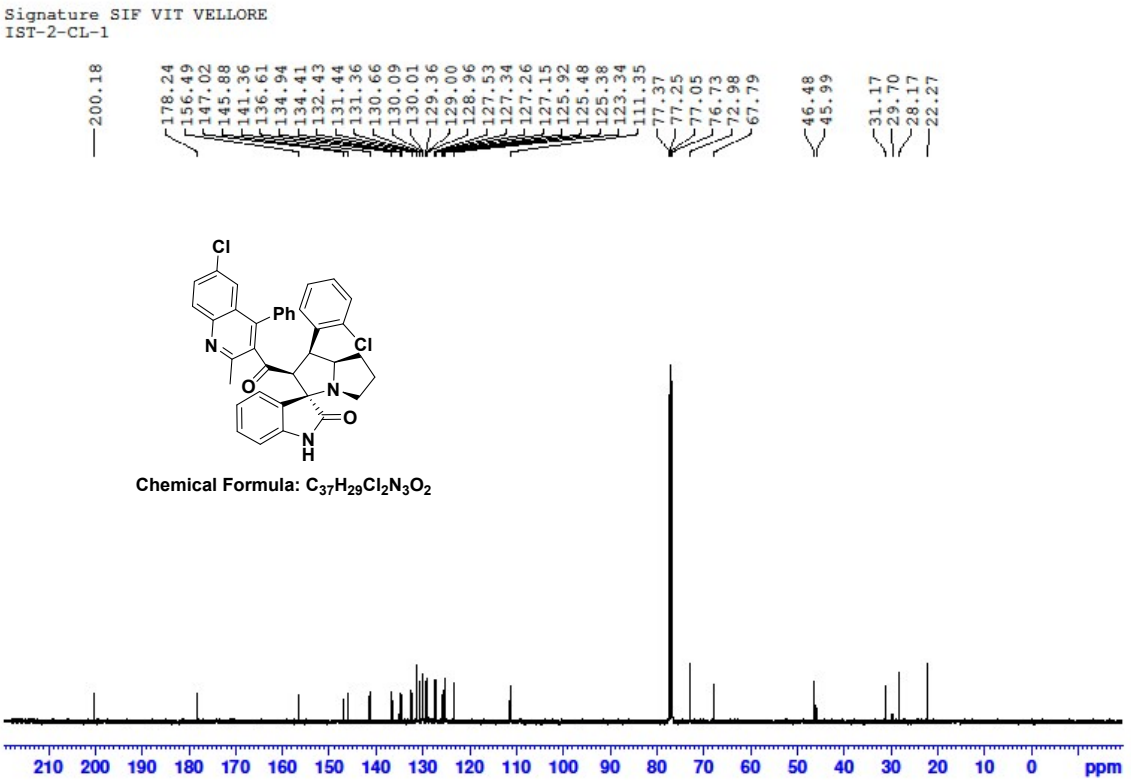
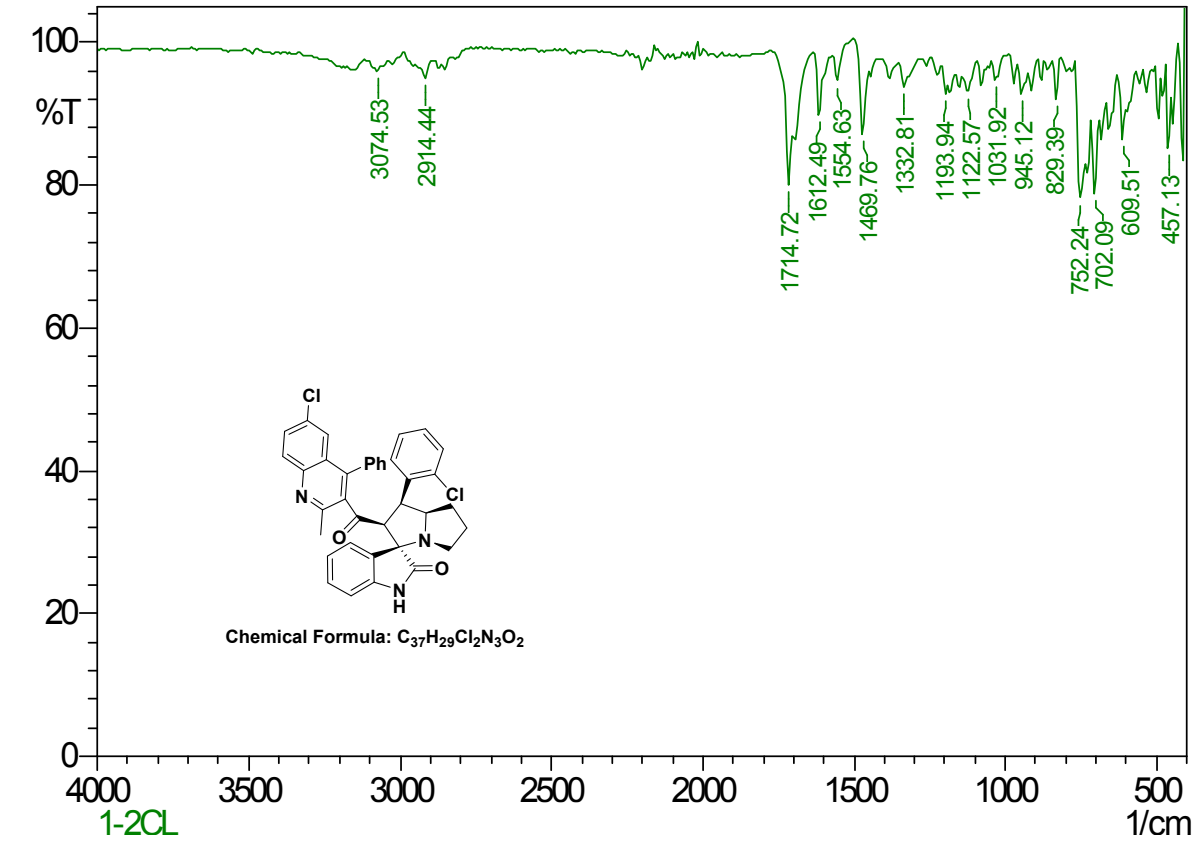


Figure S17: ^{1}H and ^{13}C NMR spectra of compound **5d** in $CDCl_3$



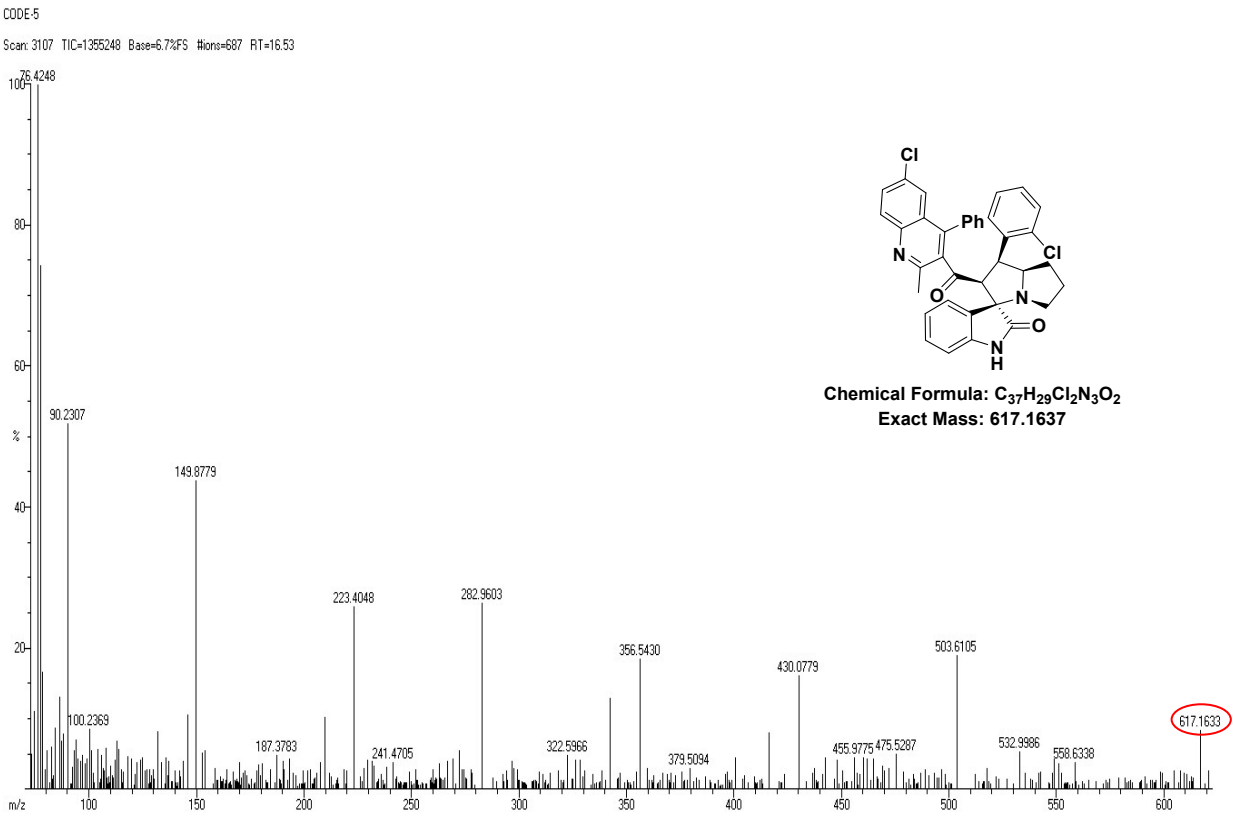
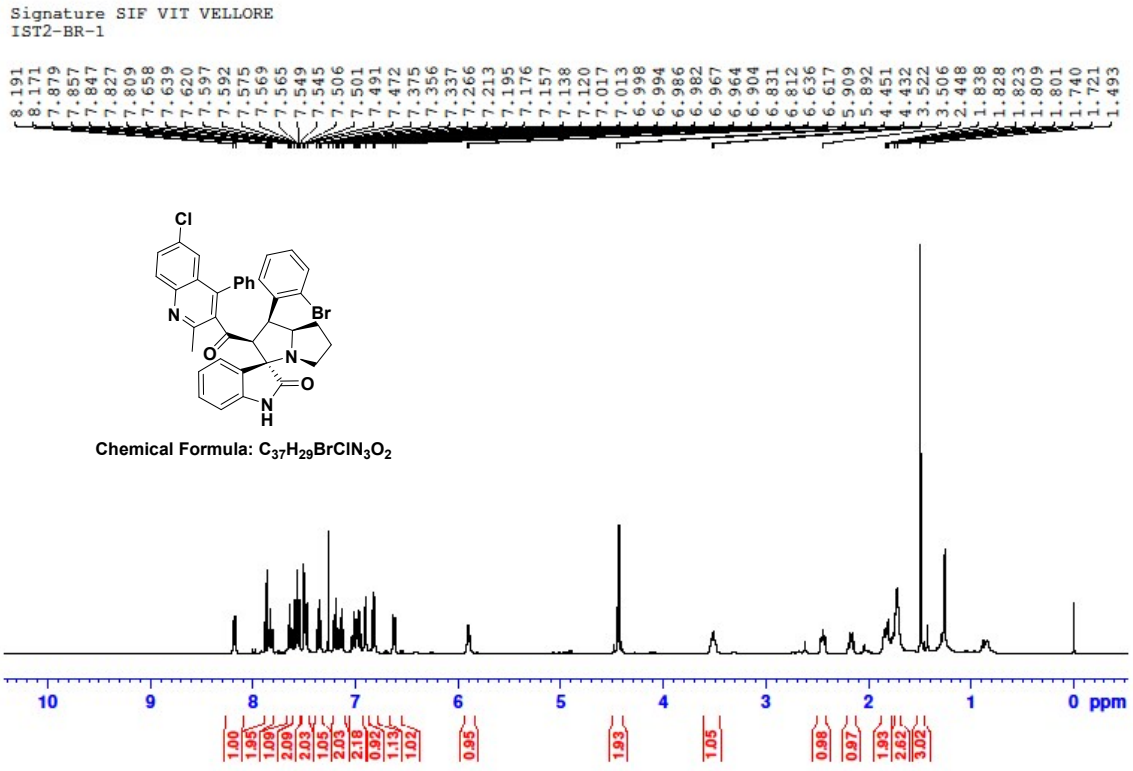


Figure S18: FT-IR & HRMS spectra of compound **5d**



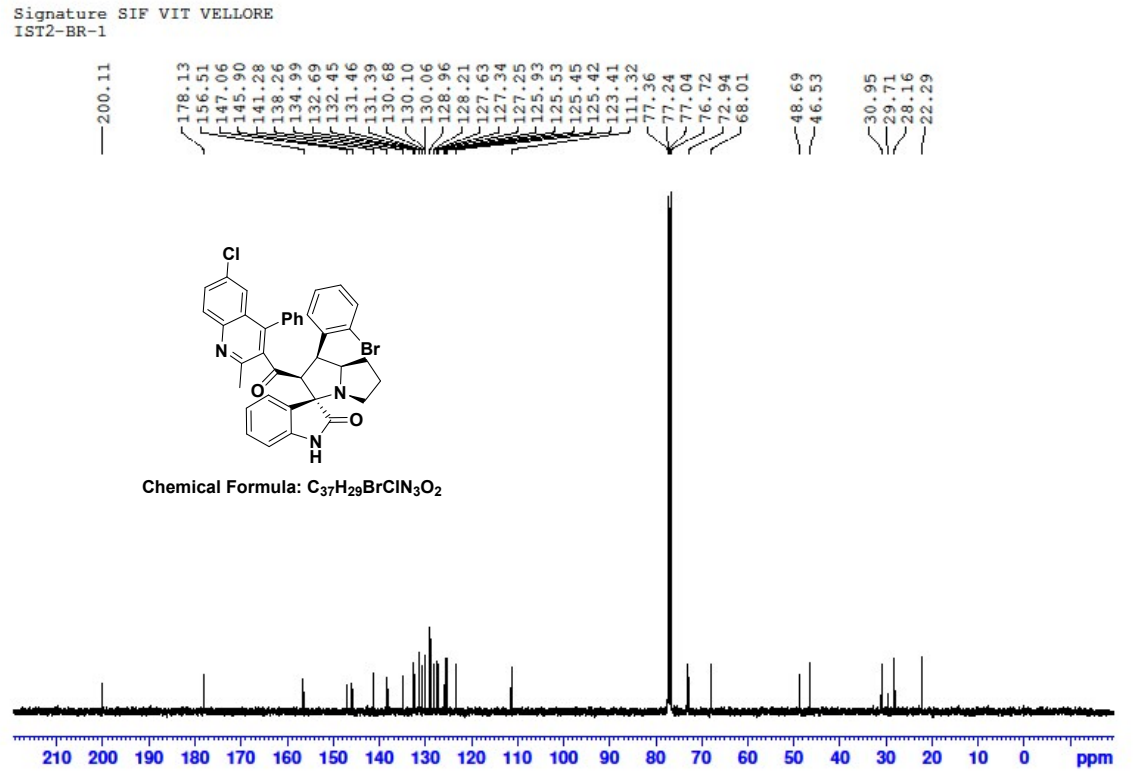
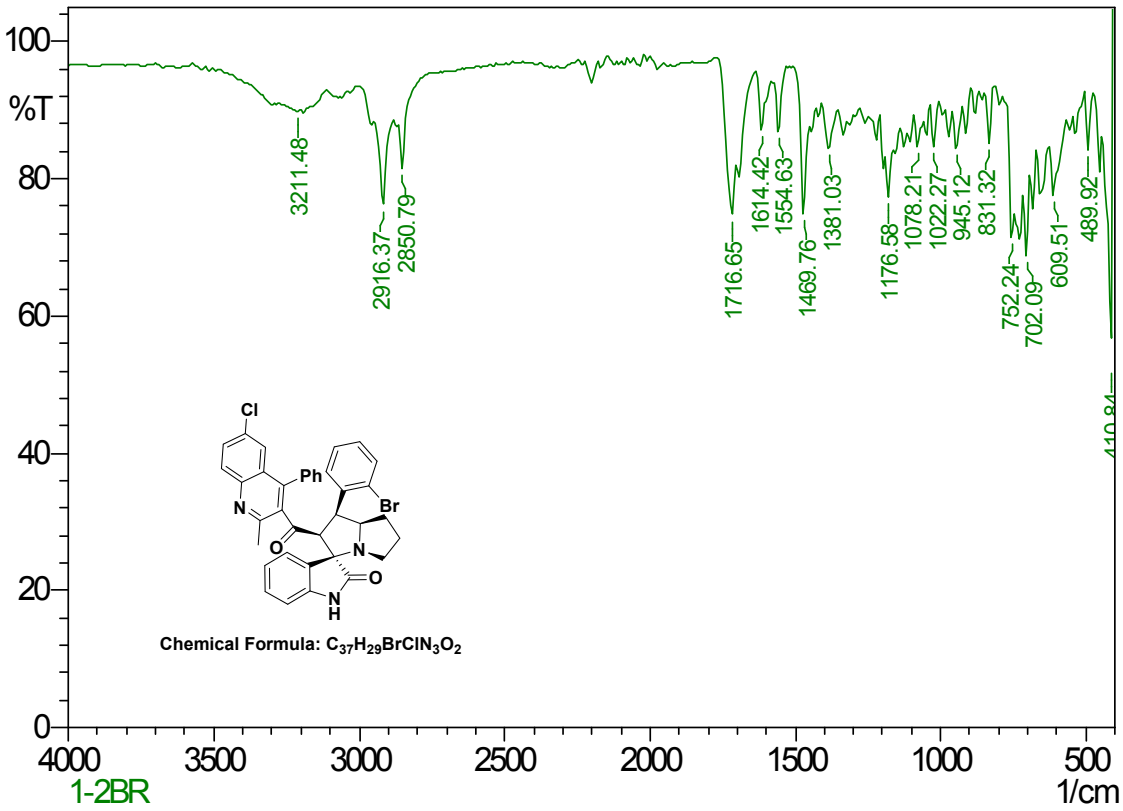


Figure S19: ^{1}H and ^{13}C NMR spectra of compound **5e** in $CDCl_3$



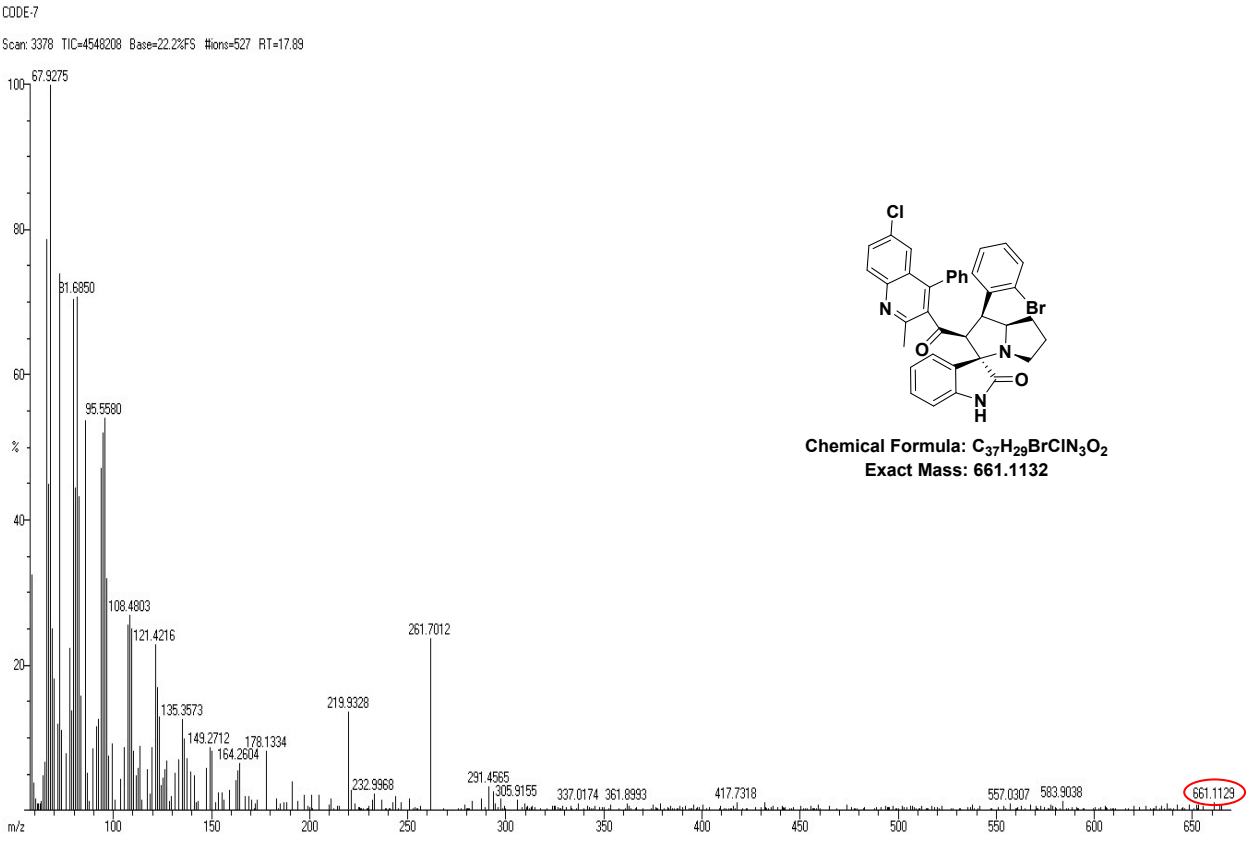


Figure S20: FT-IR & HRMS spectra of compound **5e**

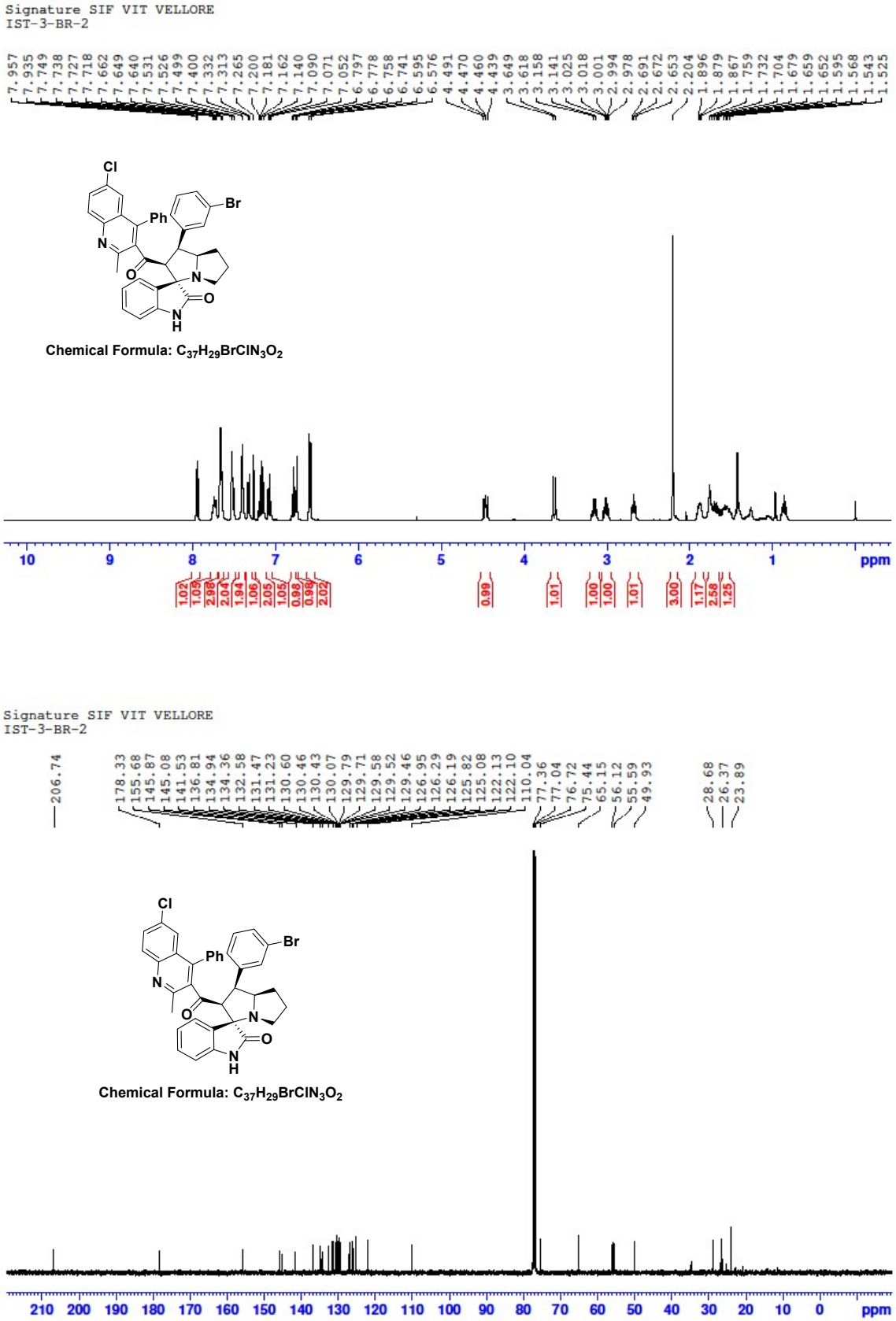
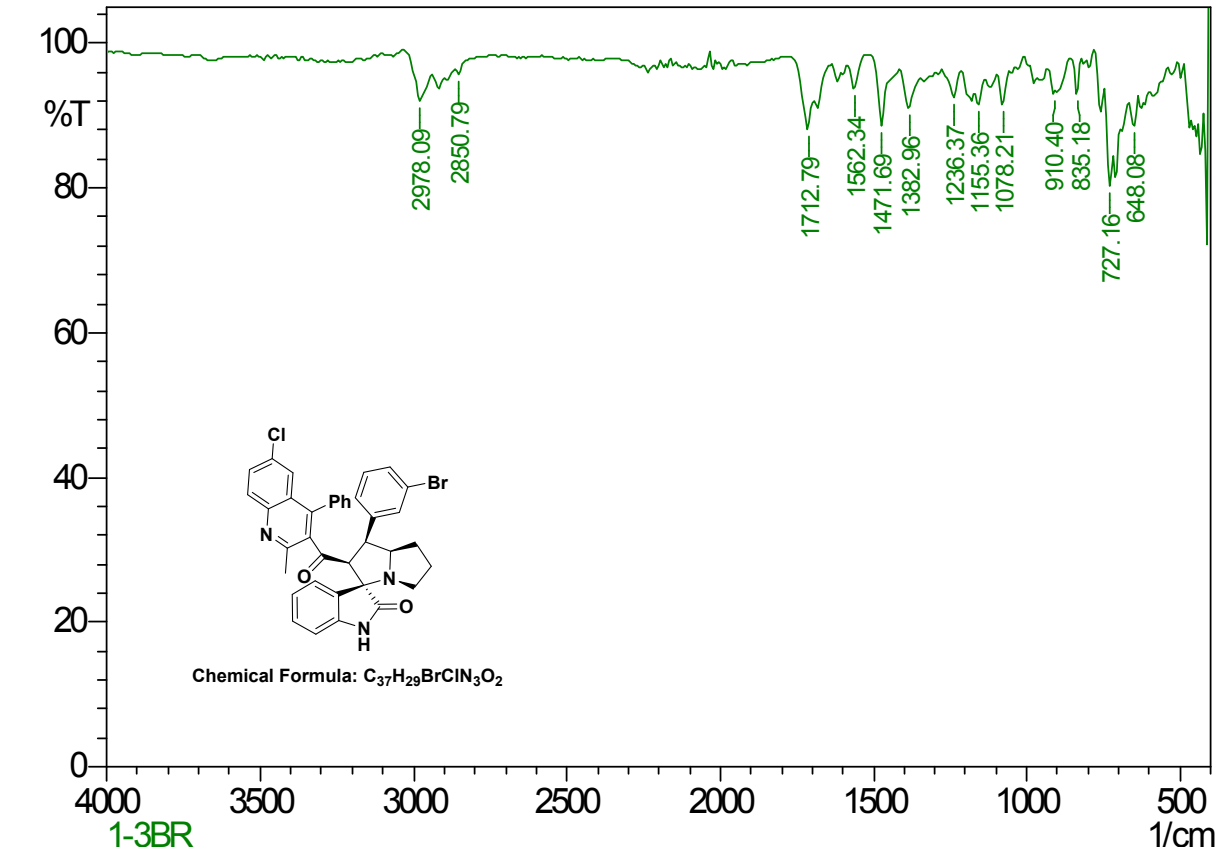


Figure S21: ^{1}H and ^{13}C NMR spectra of compound **5f** in $CDCl_3$



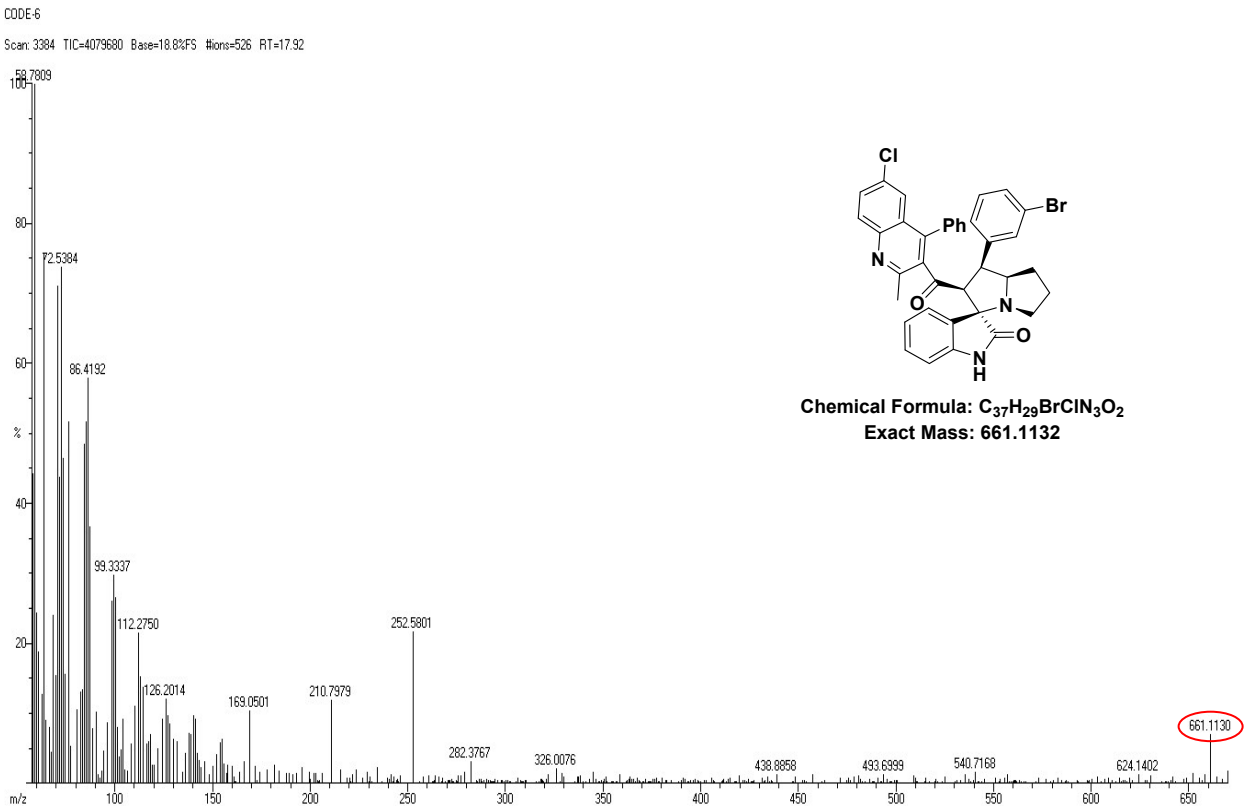
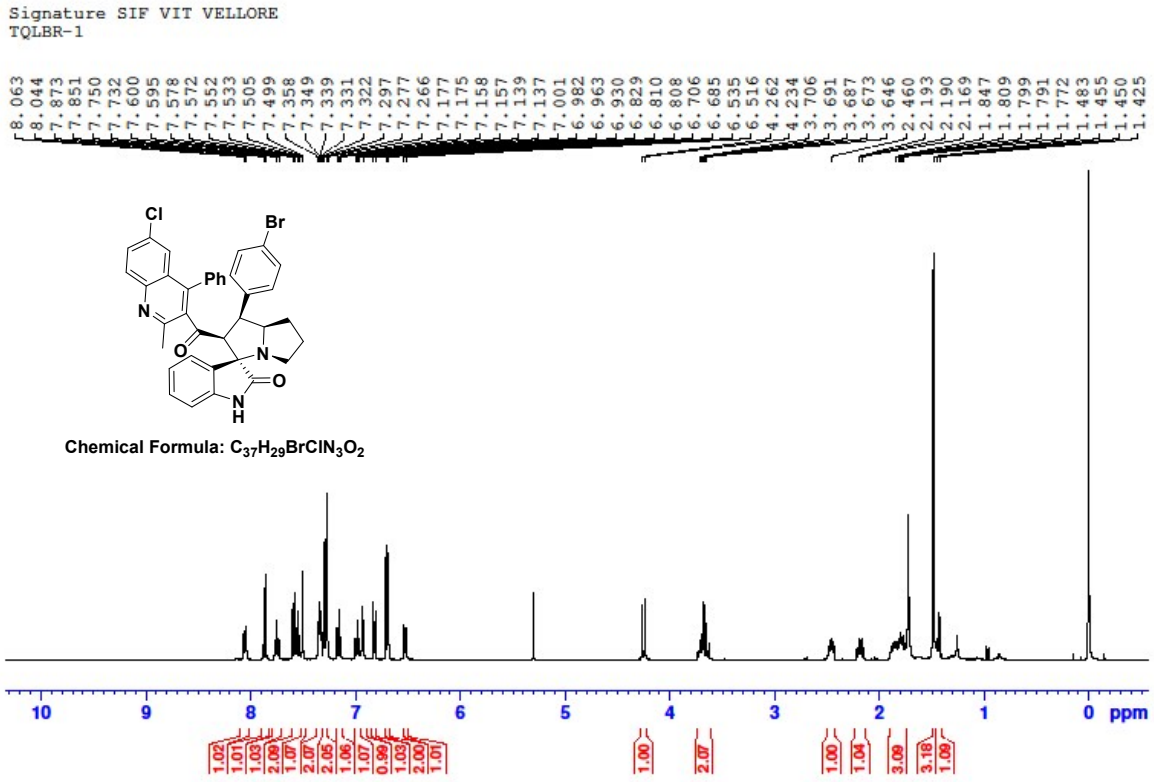


Figure S22: FT-IR & HRMS spectra of compound **5f**



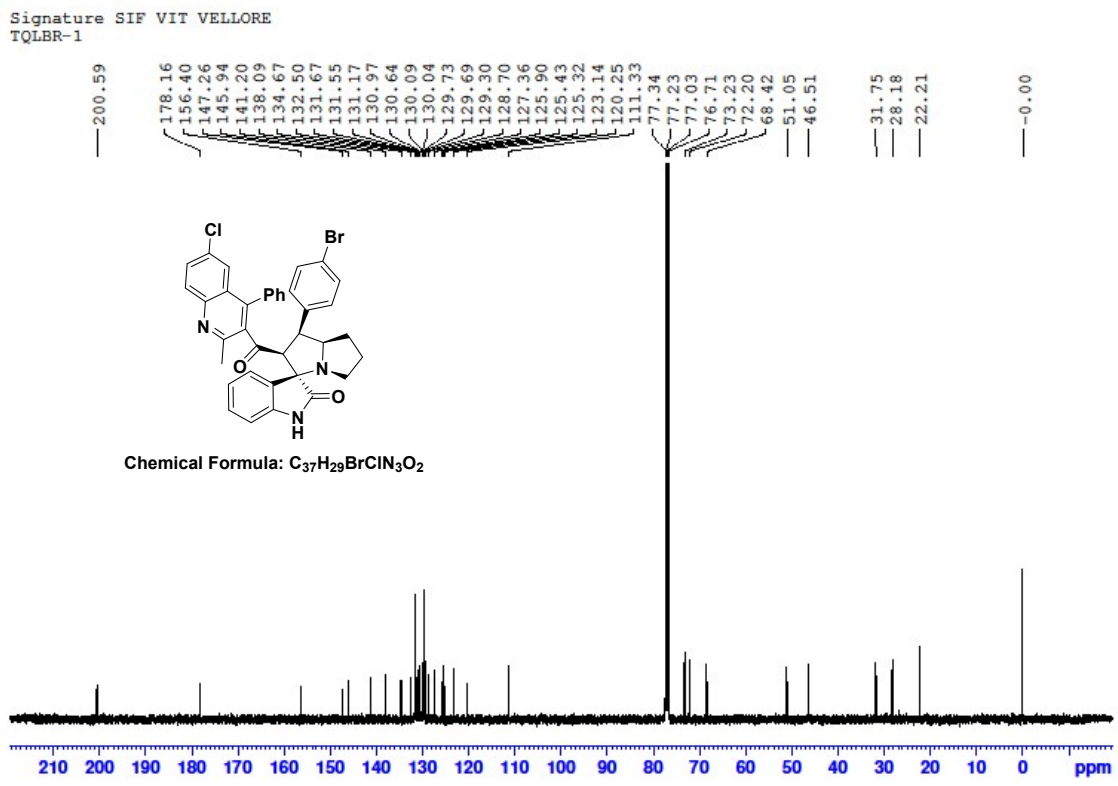
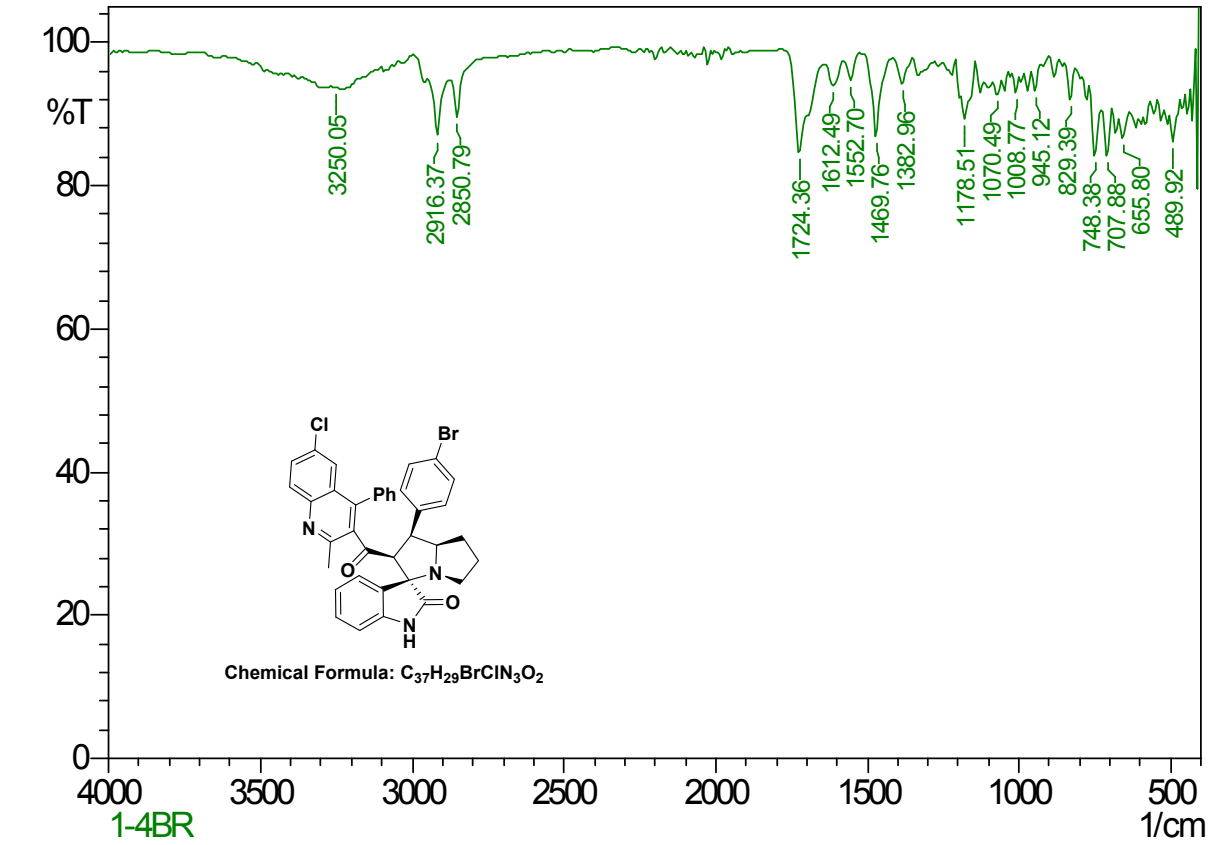


Figure S23: ^{1}H and ^{13}C NMR spectra of compound **5g** in $CDCl_3$



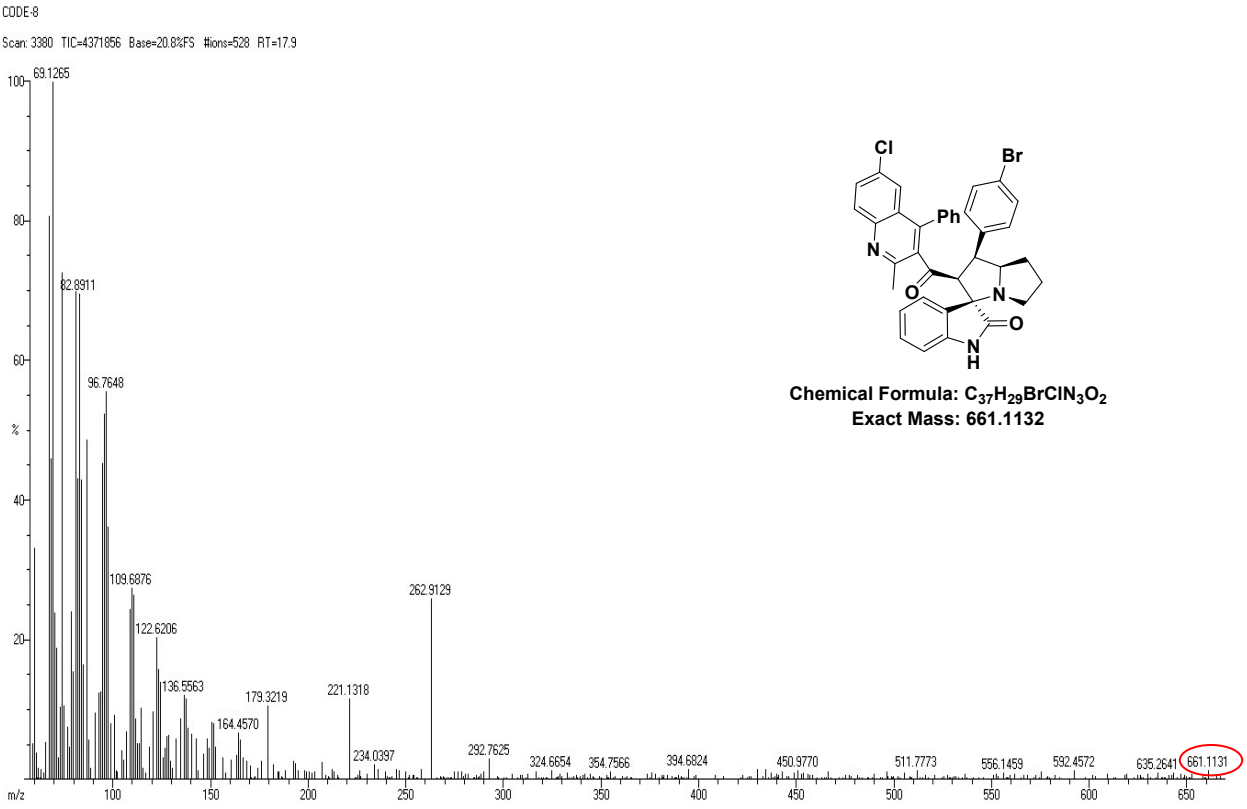
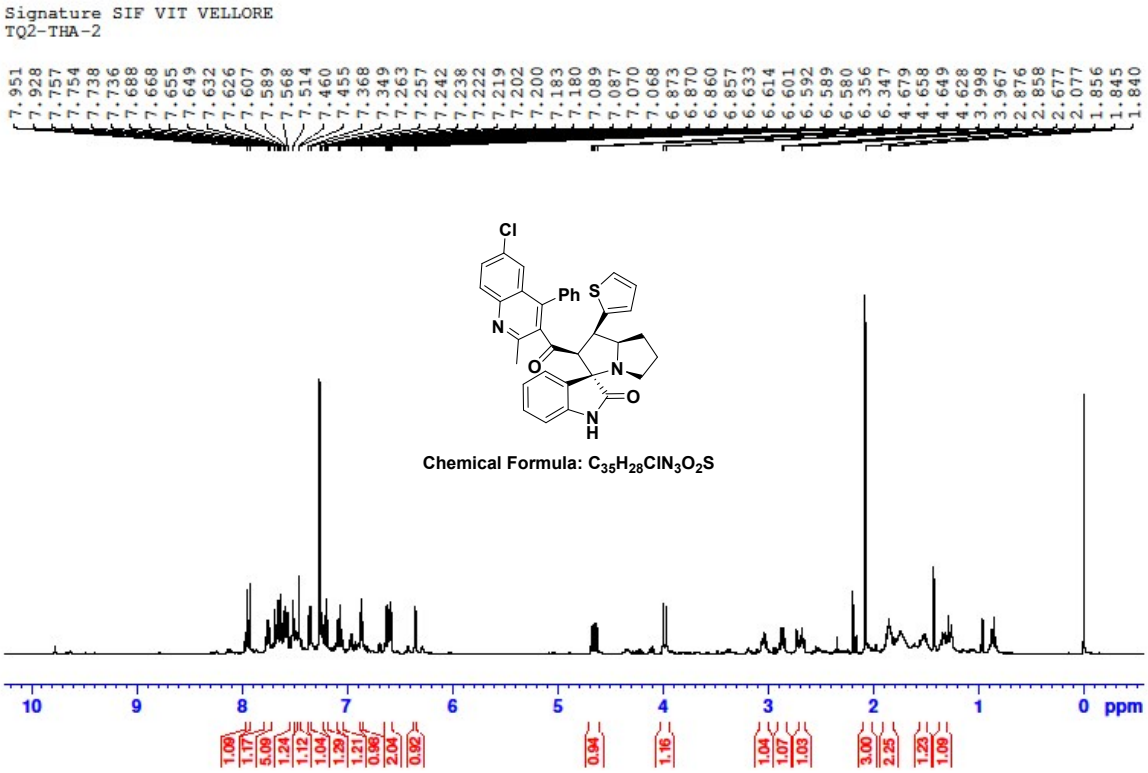


Figure S24: FT-IR & HRMS spectra of compound **5g**



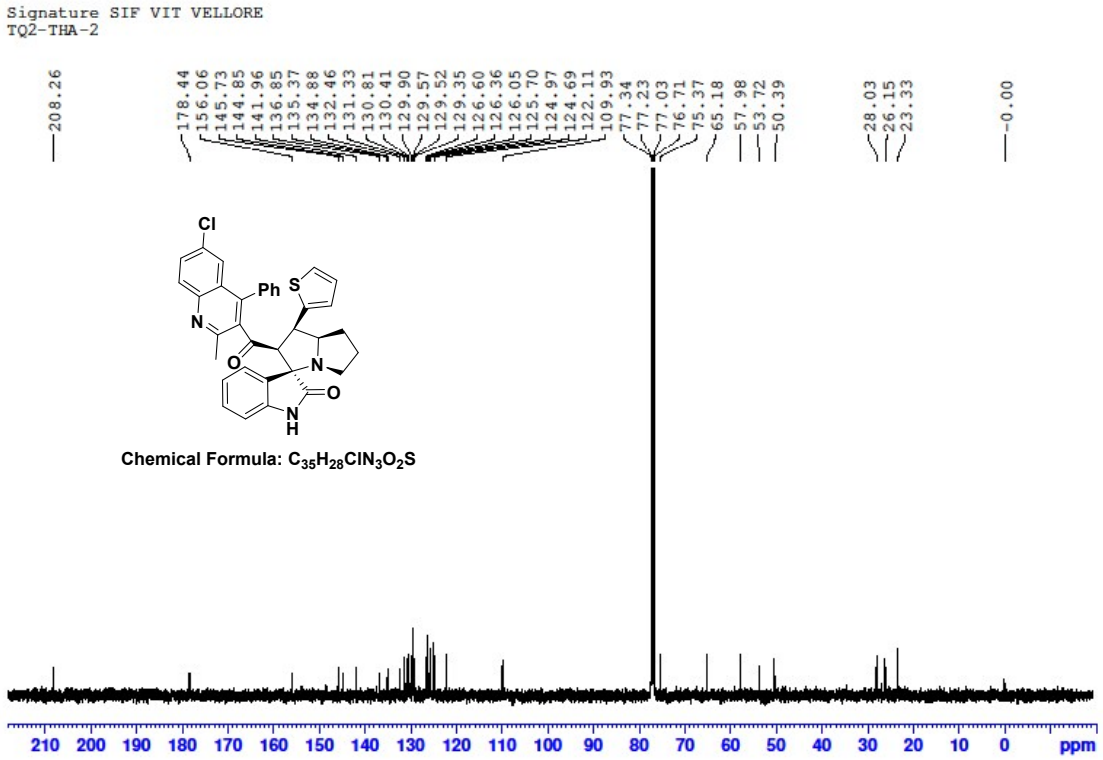
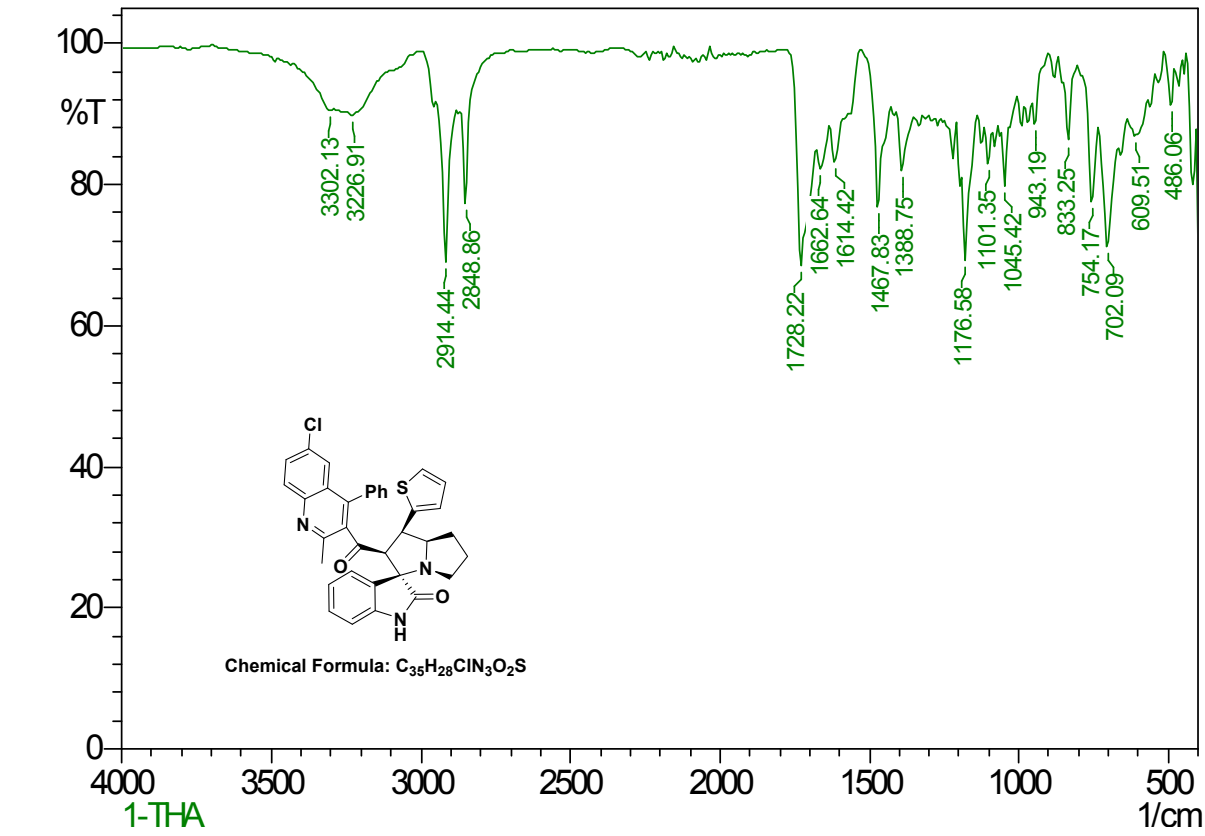


Figure S25: ^{1}H and ^{13}C NMR spectra of compound **5h** in $CDCl_3$



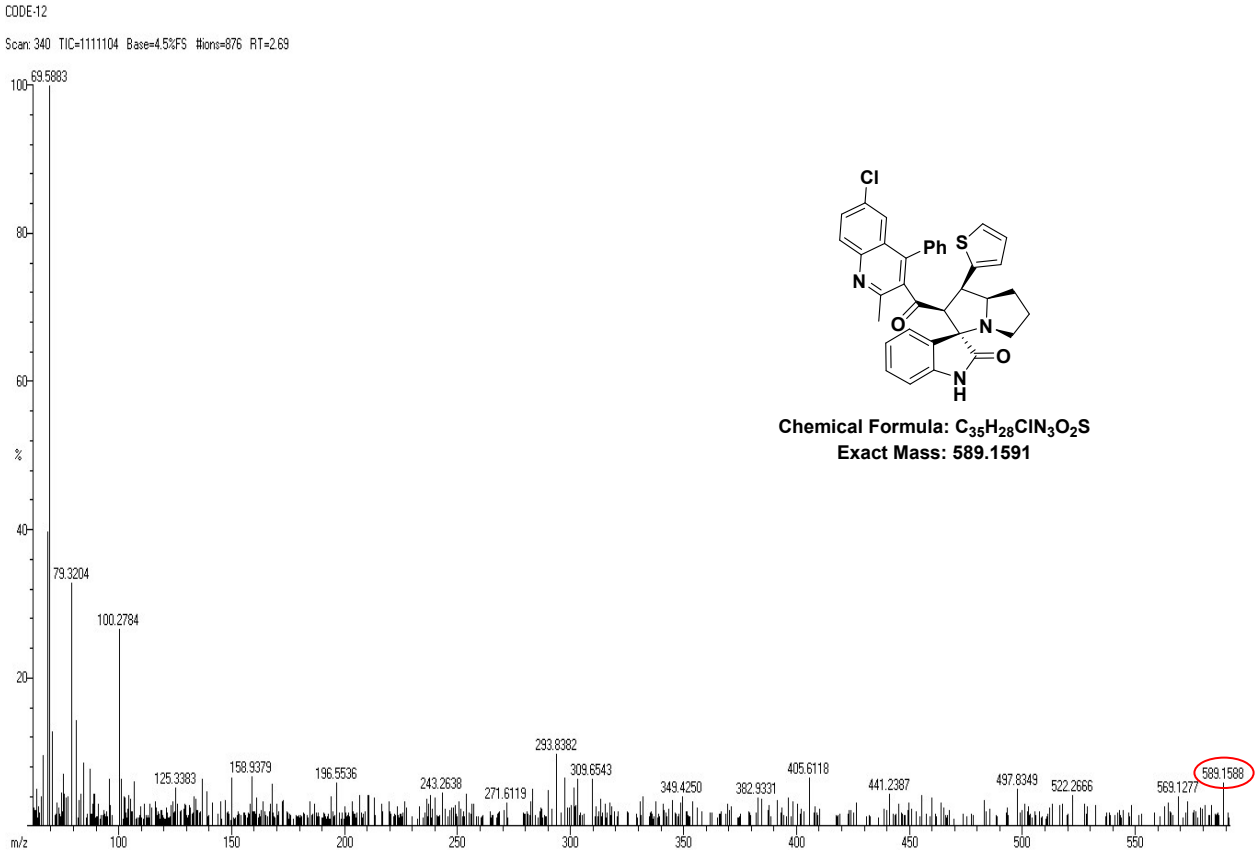
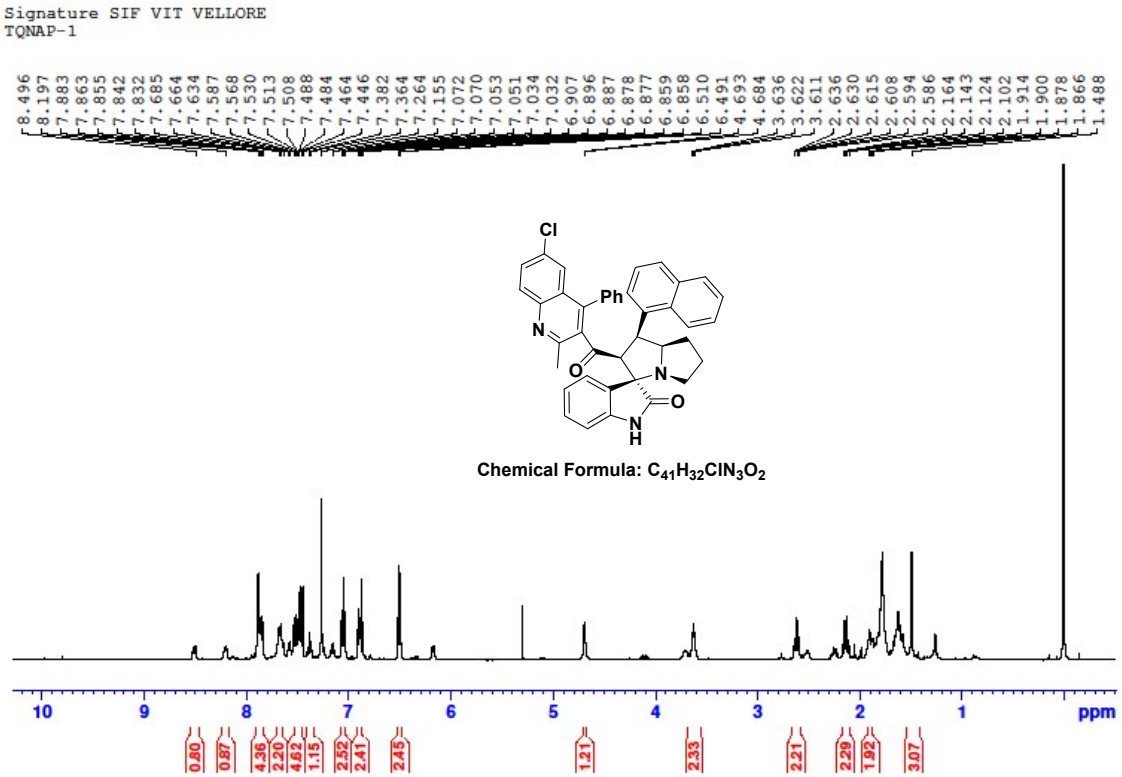


Figure S26: FT-IR & HRMS spectra of compound **5h**



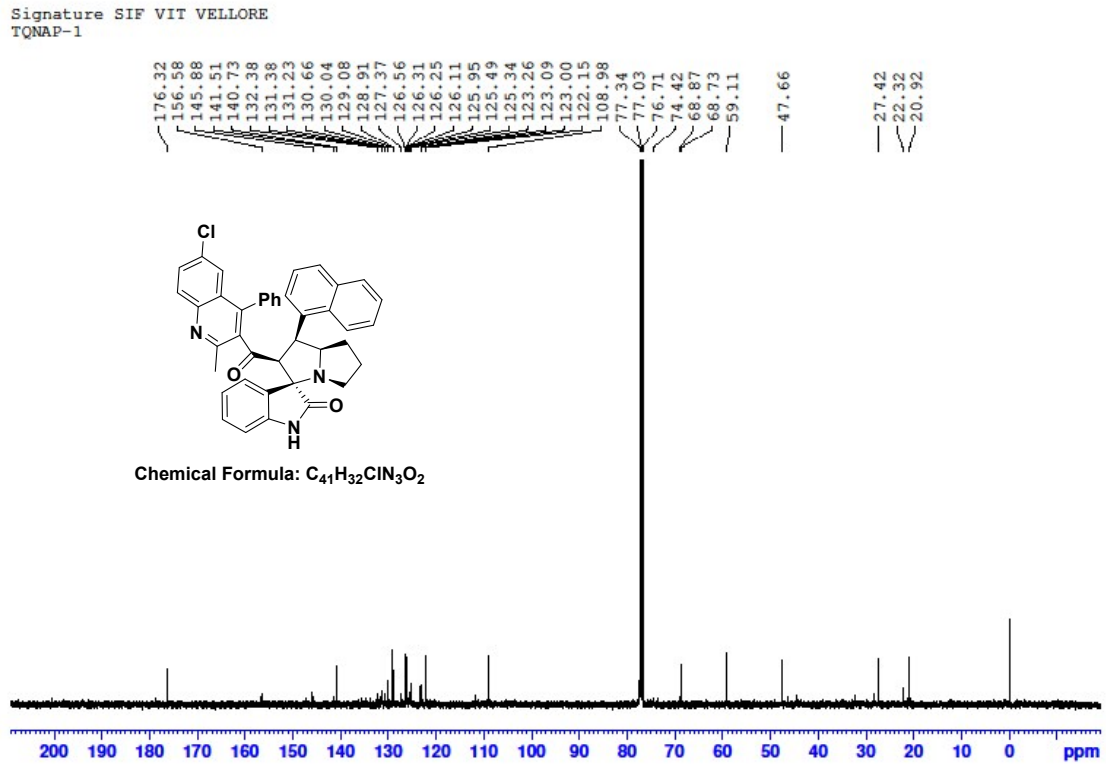
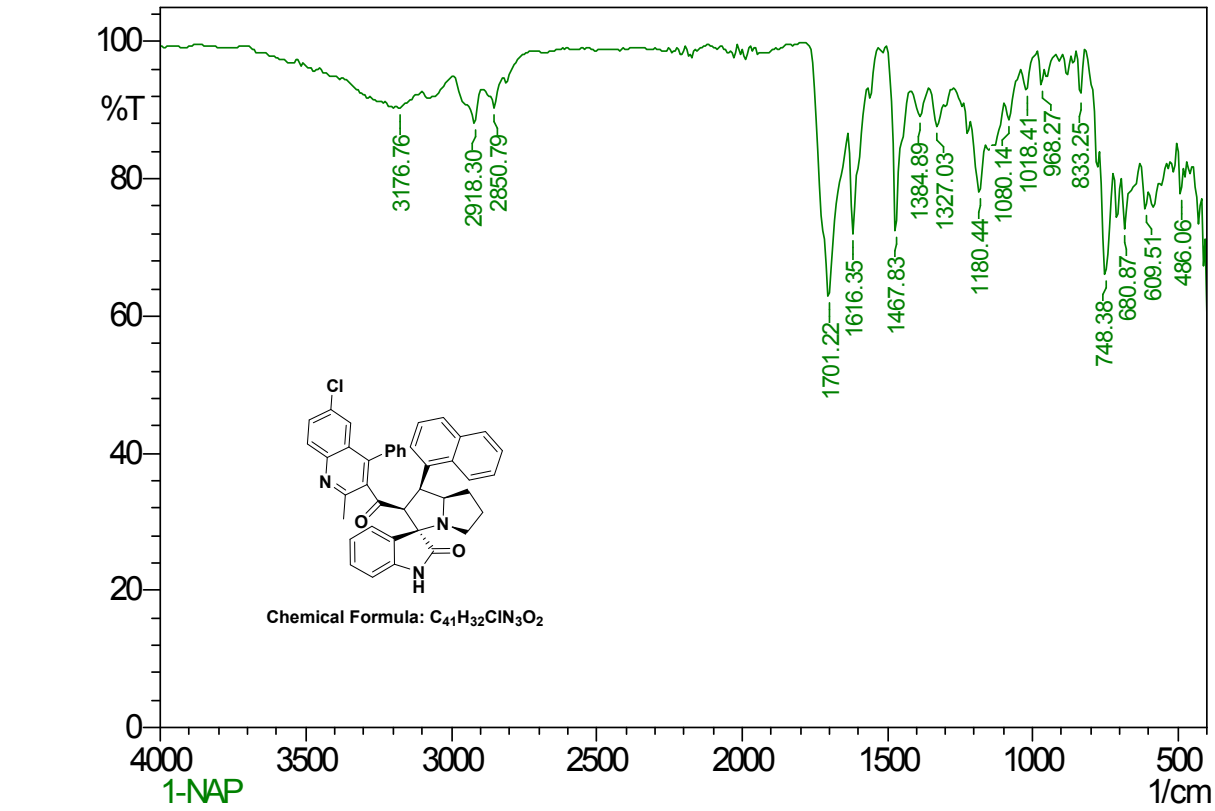


Figure S27: ^{1}H and ^{13}C NMR spectra of compound **5i** in $CDCl_3$



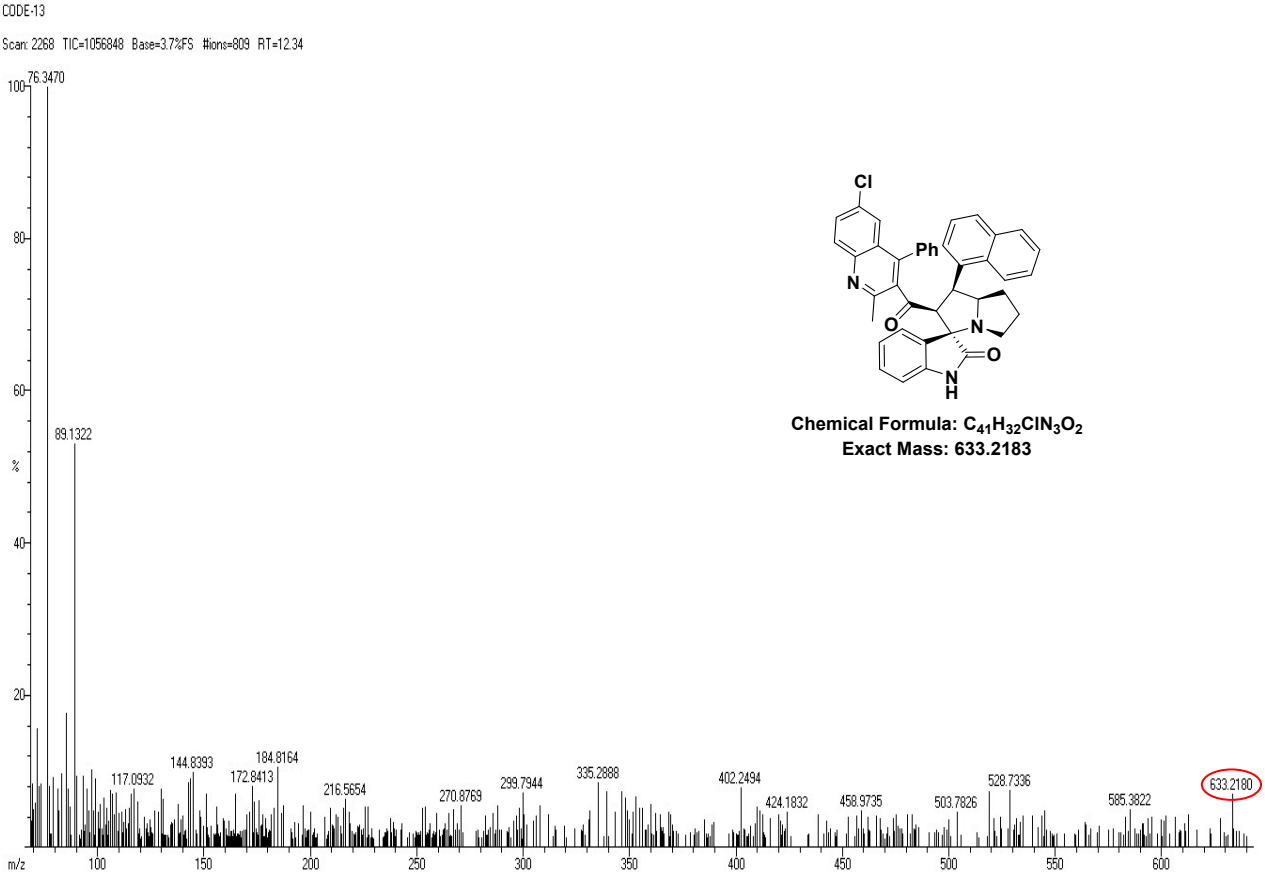
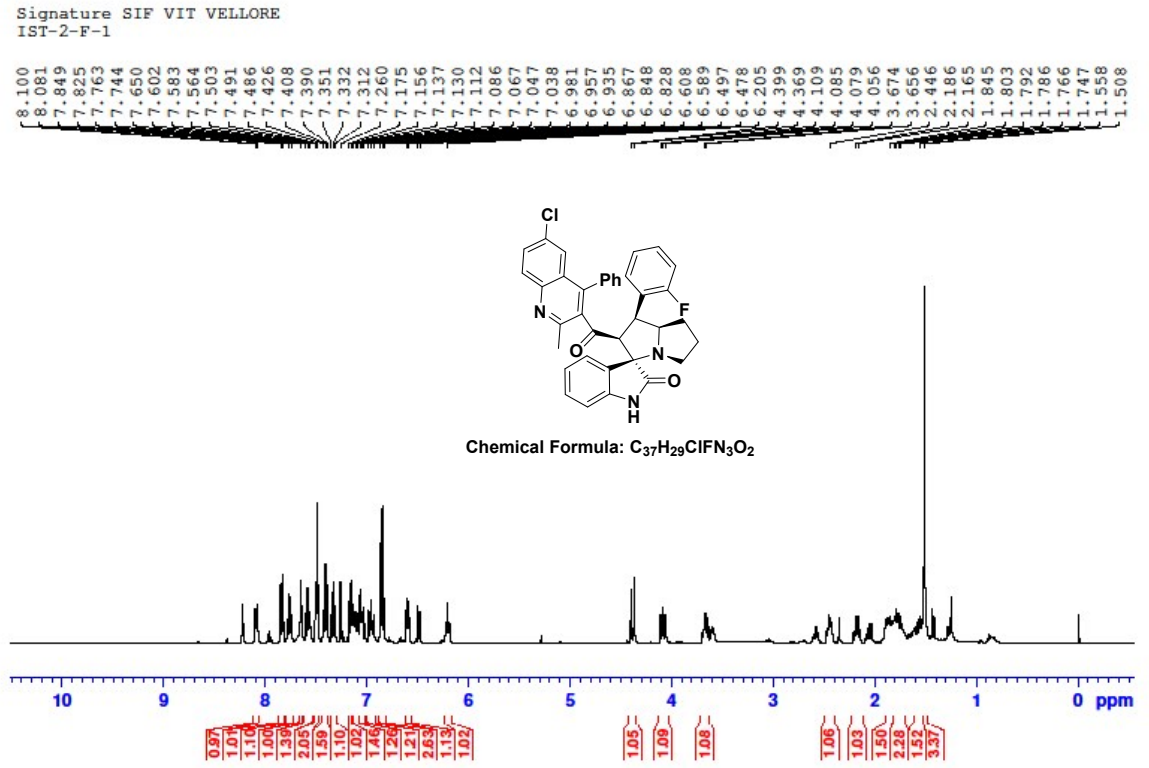


Figure S28: FT-IR & HRMS spectra of compound **5i**



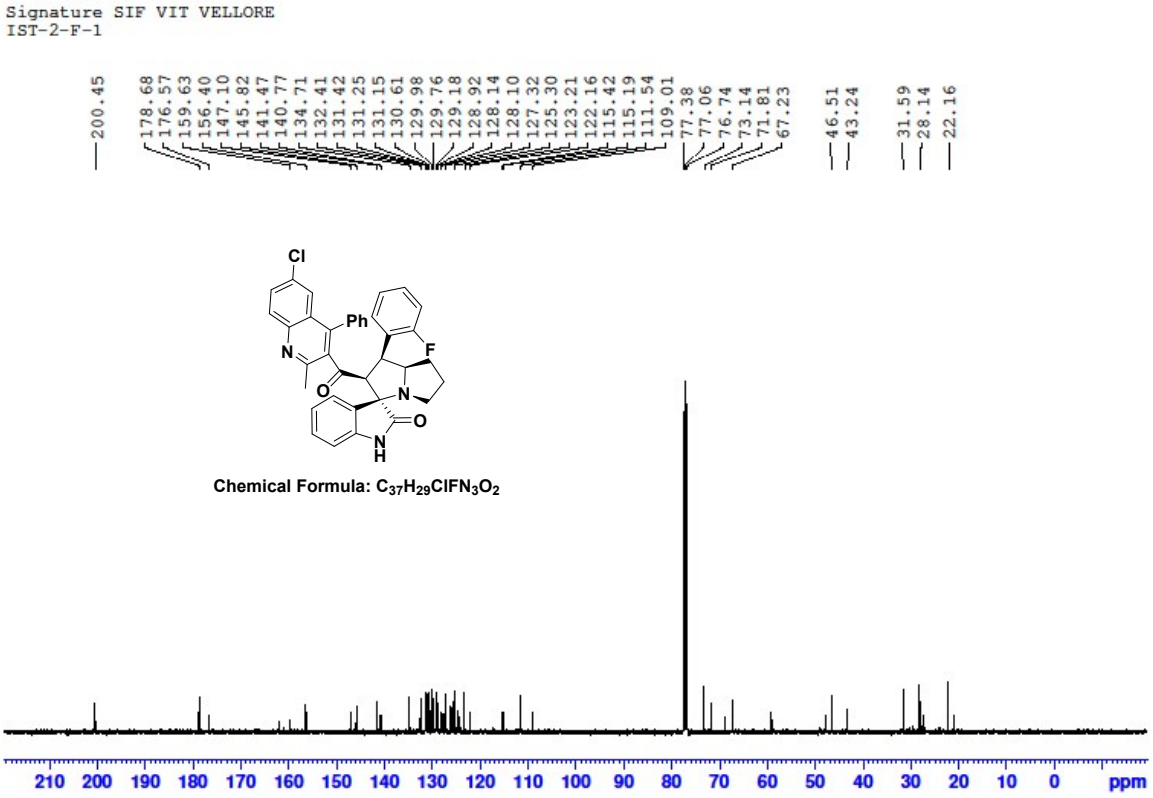
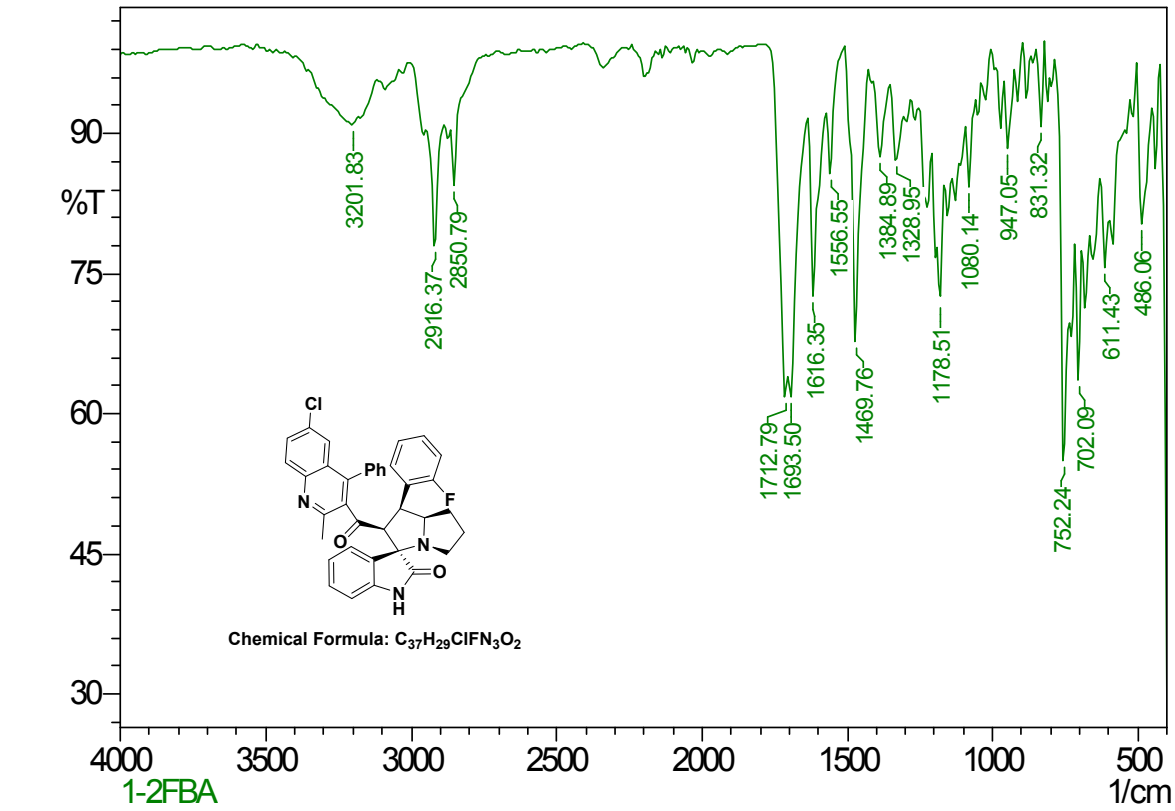


Figure S29: ^{1}H and ^{13}C NMR spectra of compound **5j** in $CDCl_3$



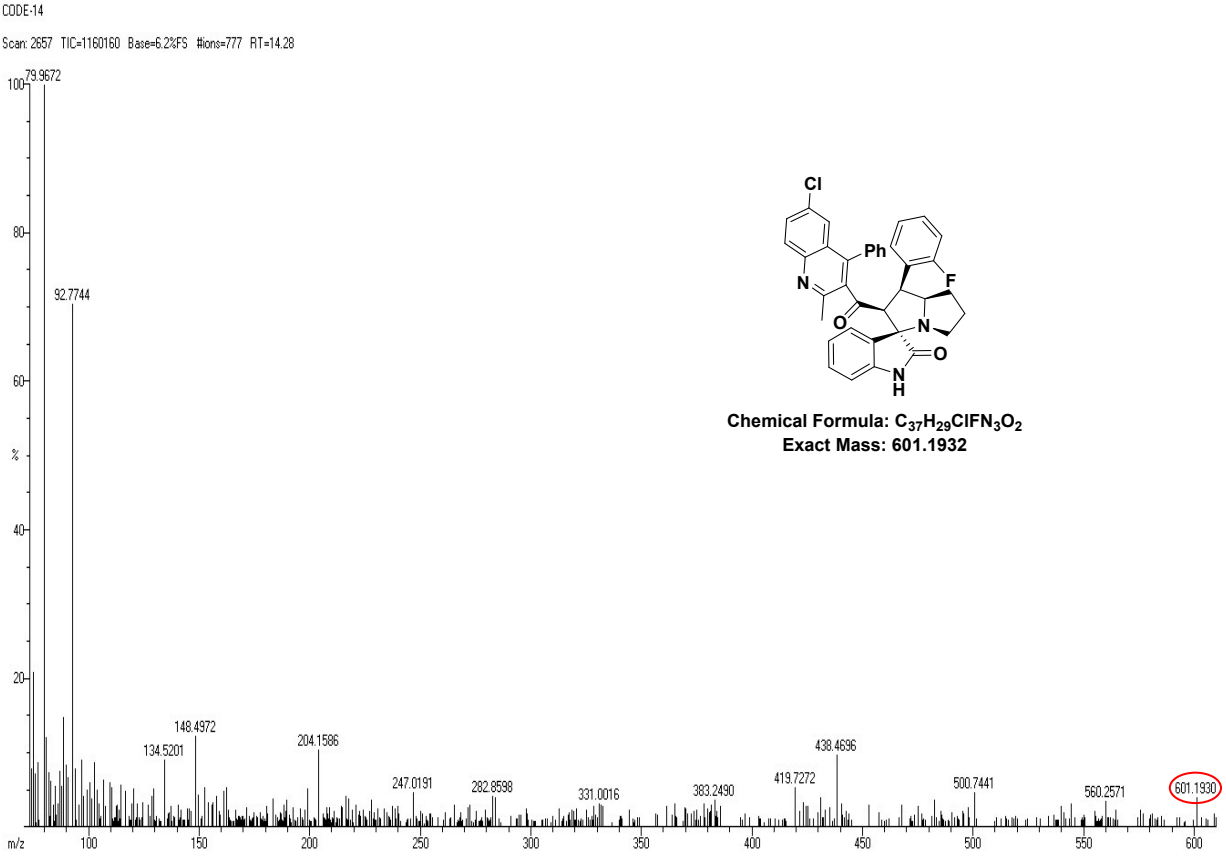
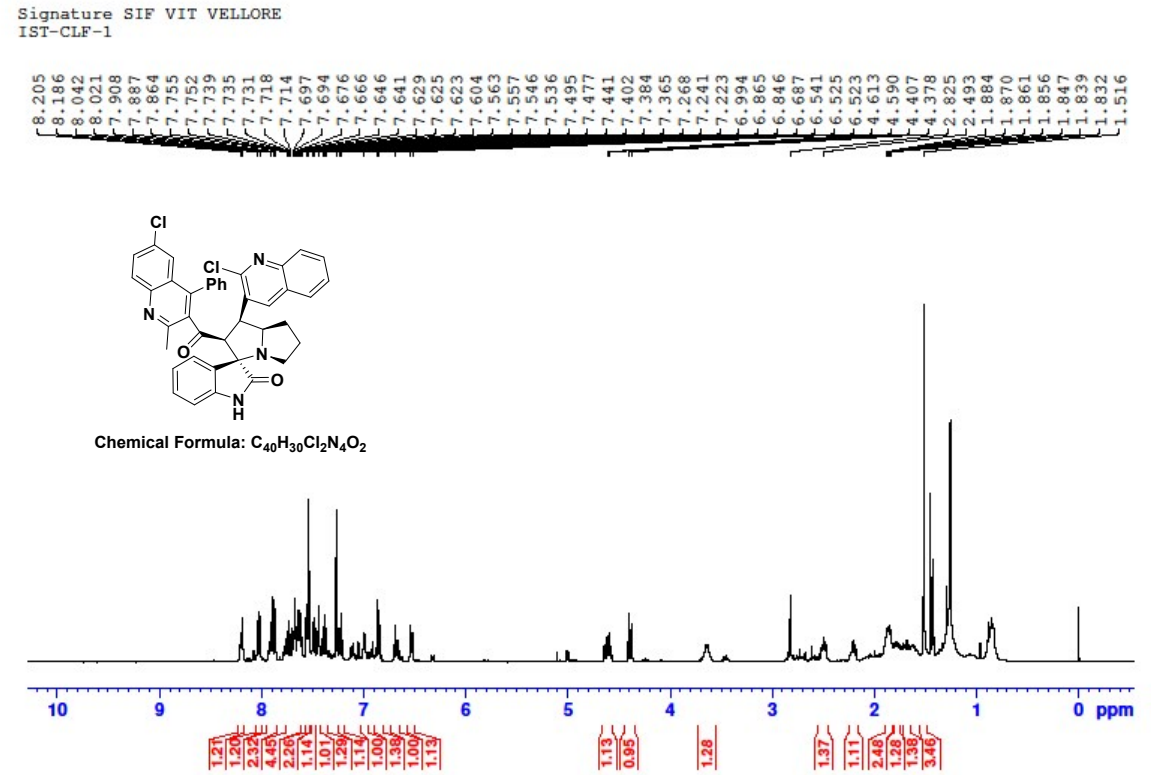


Figure S30: FT-IR & HRMS spectra of compound **5j**



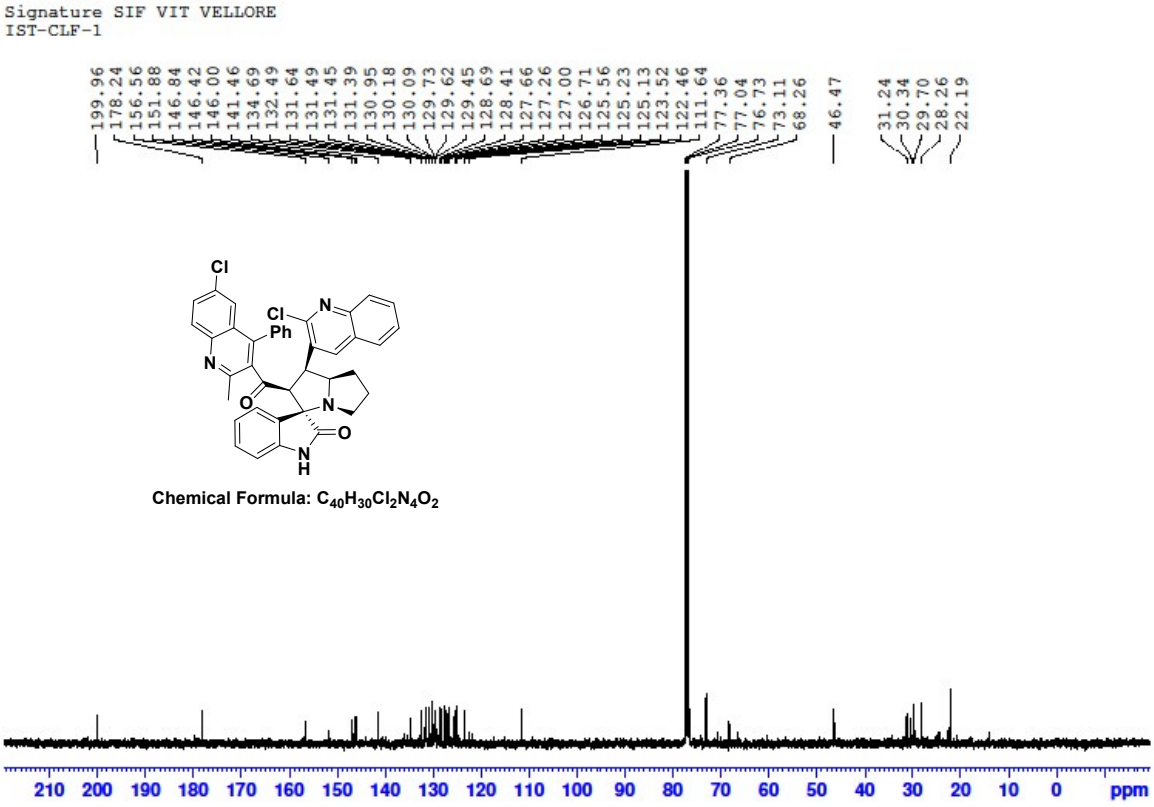
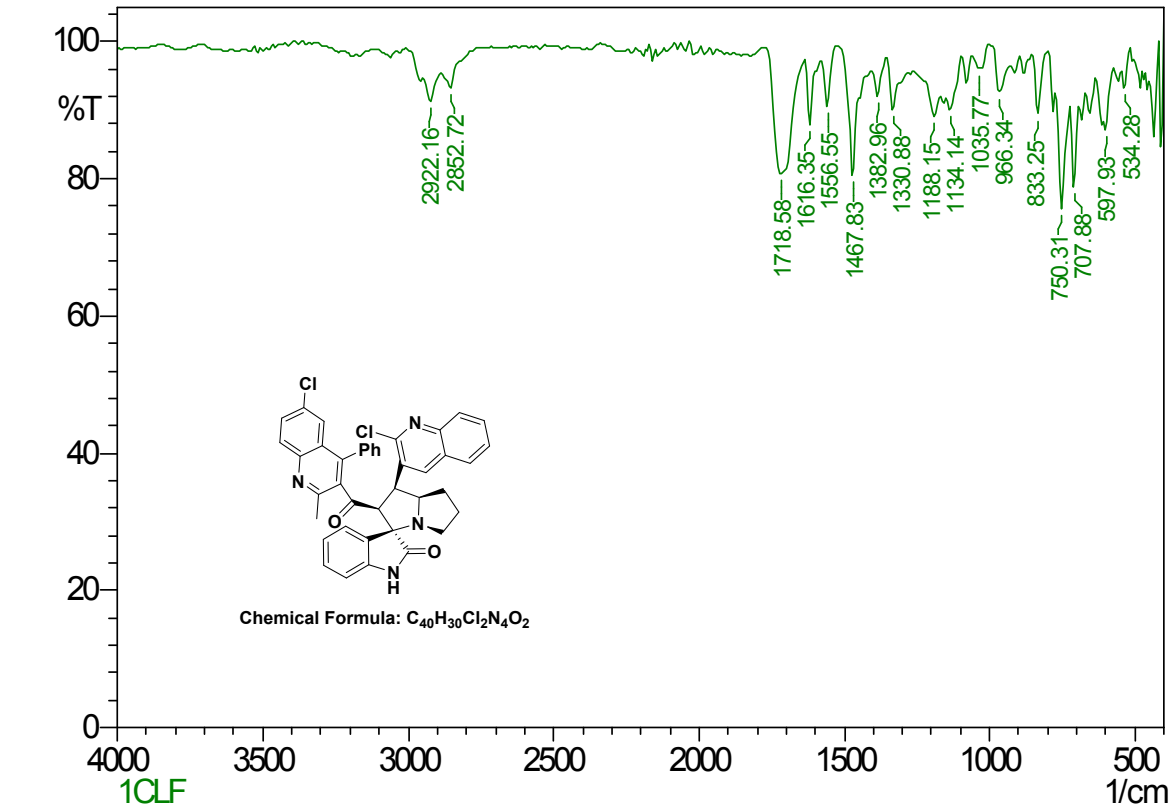


Figure S31: ^{1}H and ^{13}C NMR spectra of compound **6a** in $CDCl_3$



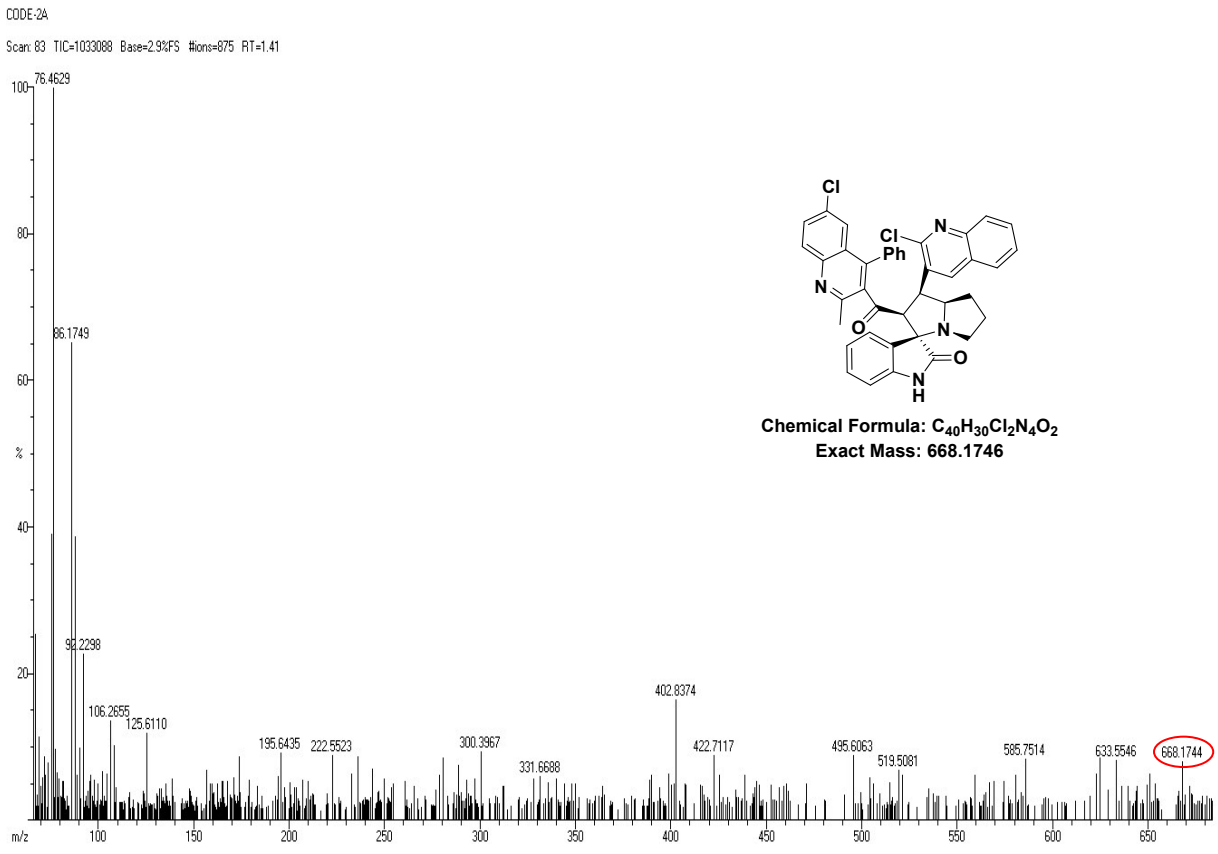
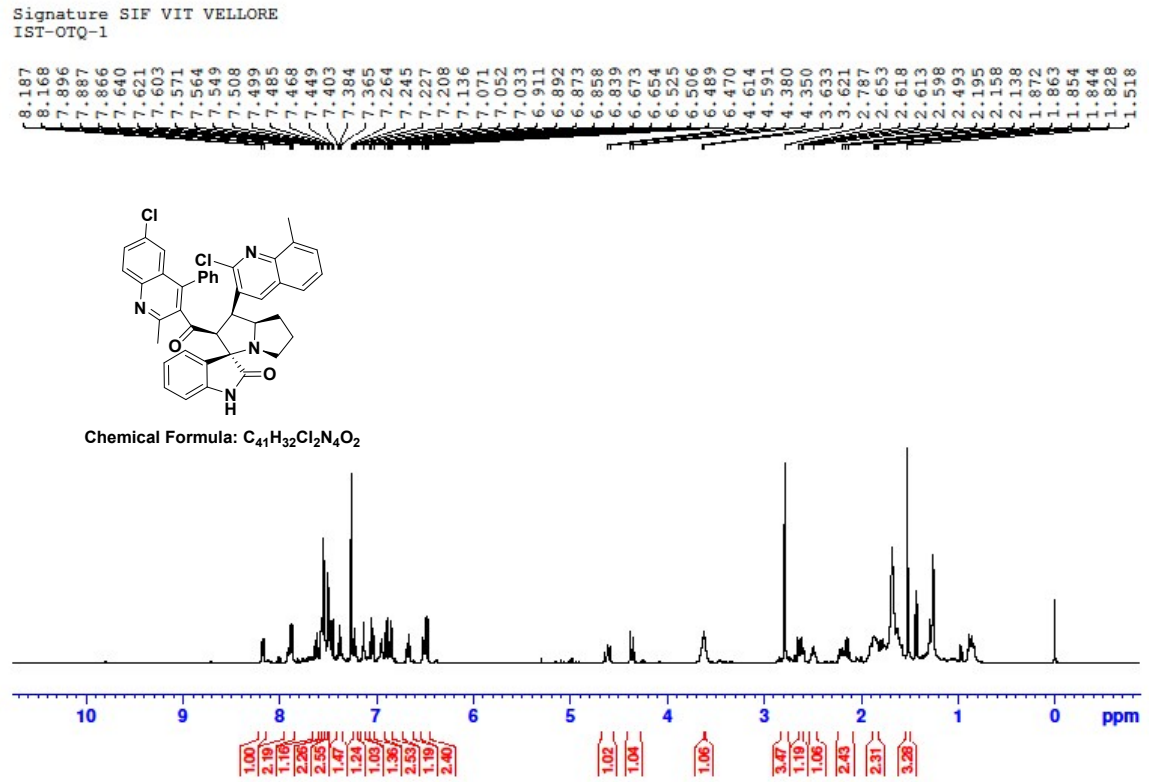


Figure S32: FT-IR & HRMS spectra of compound **6a**



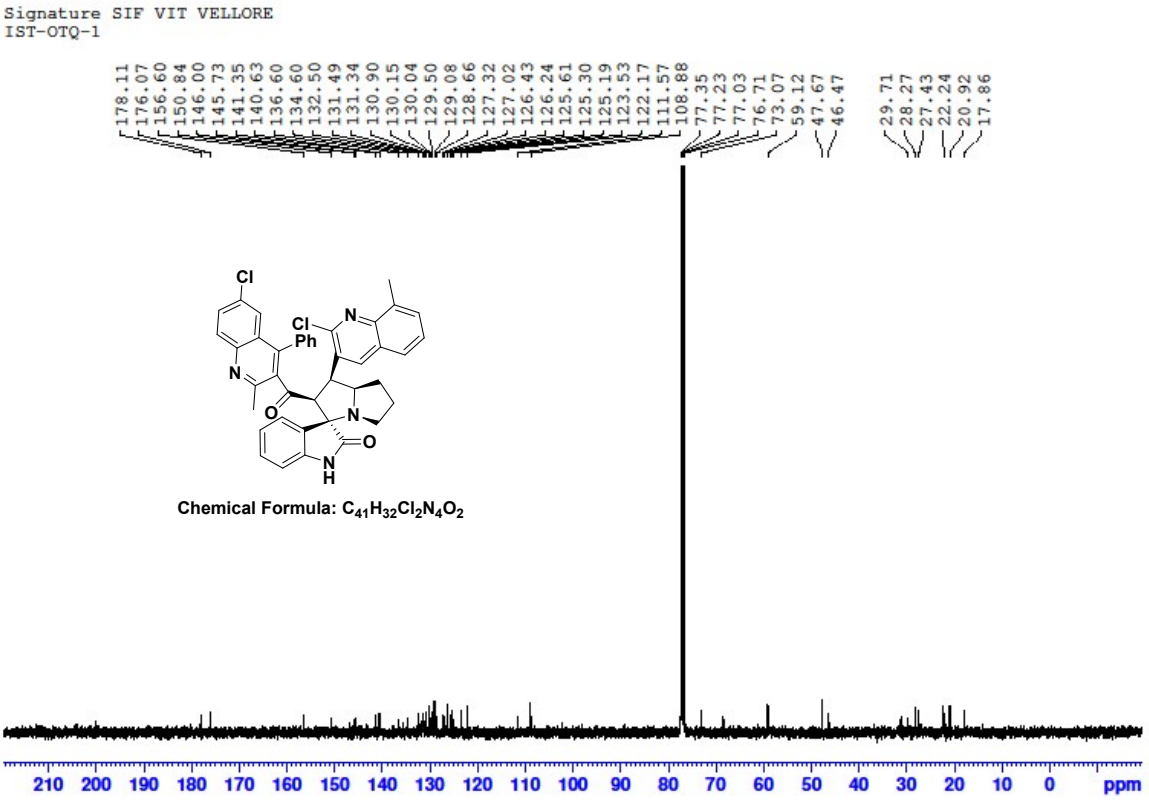
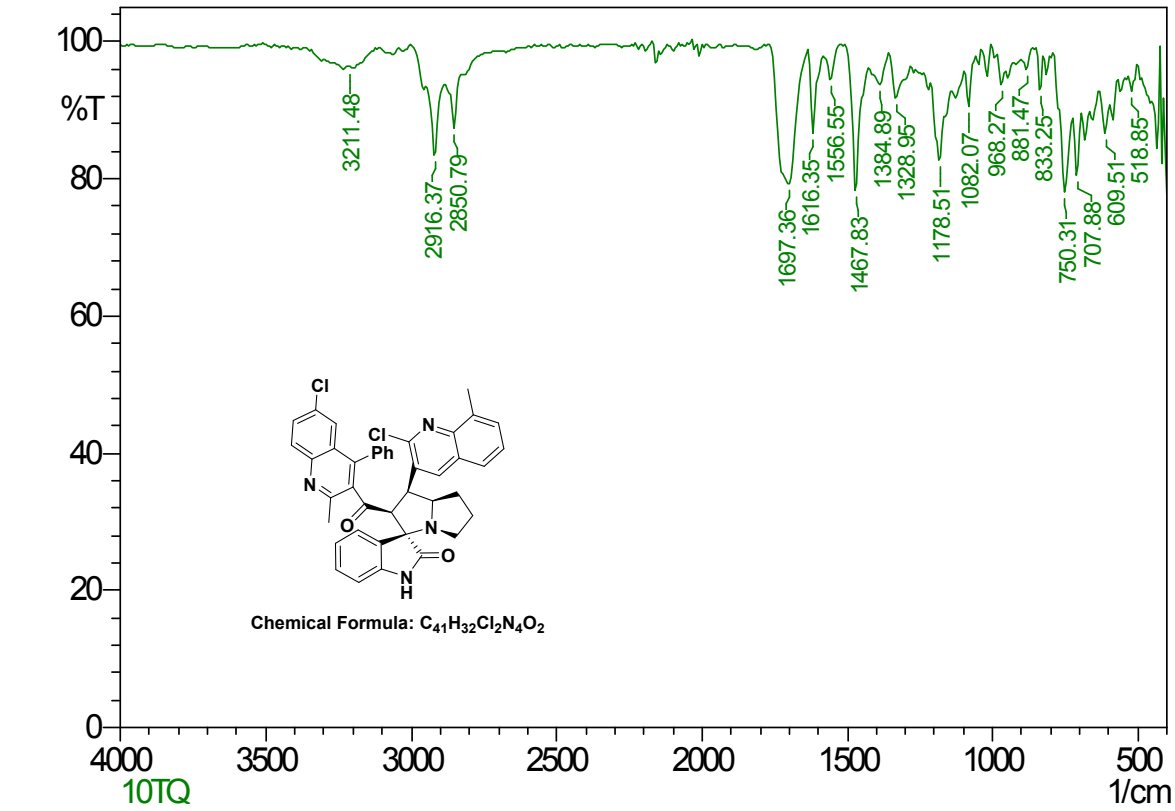


Figure S33: ^{1}H and ^{13}C NMR spectra of compound **6b** in $CDCl_3$



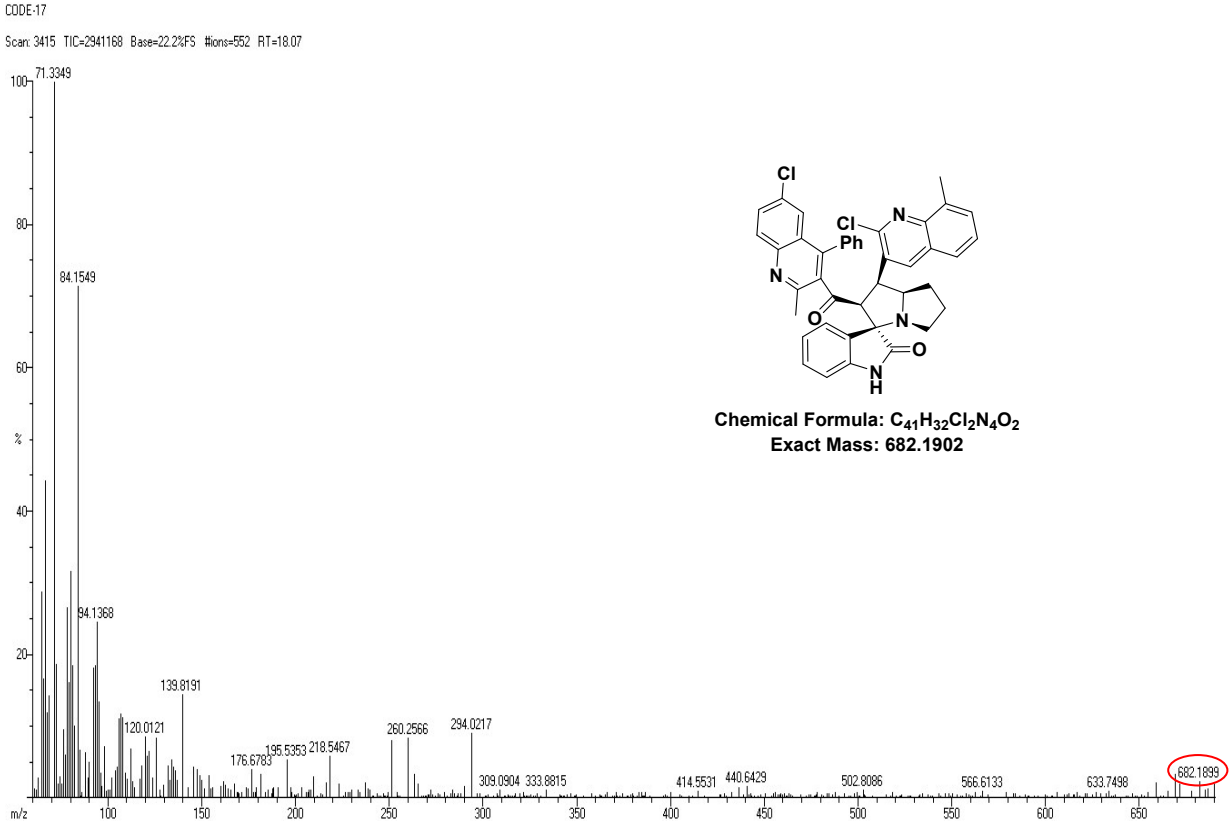
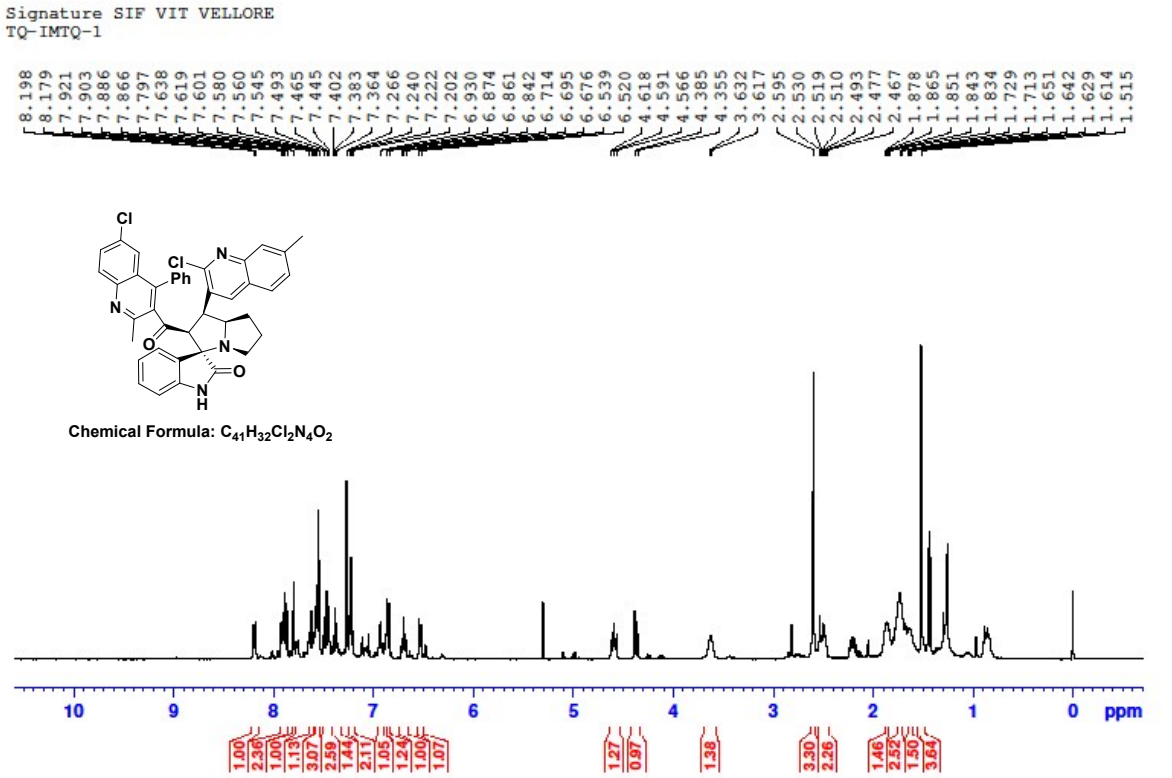


Figure S34: FT-IR & HRMS spectra of compound **6b**



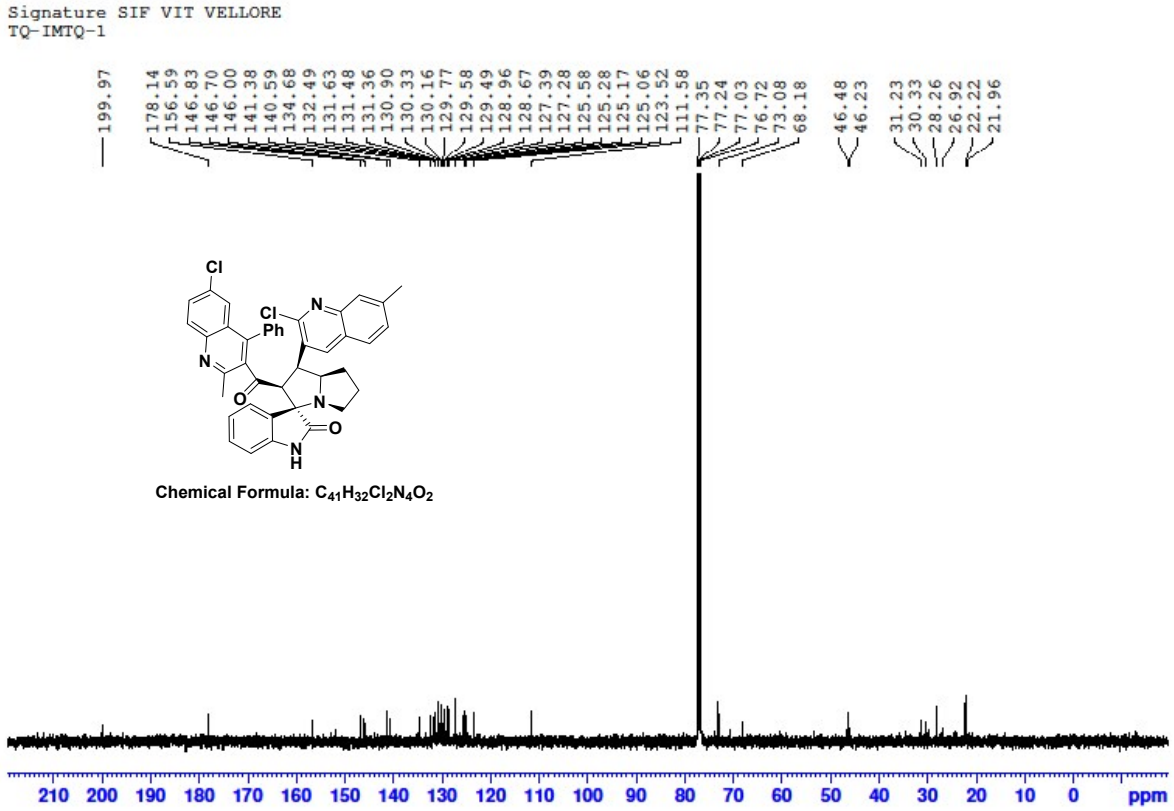
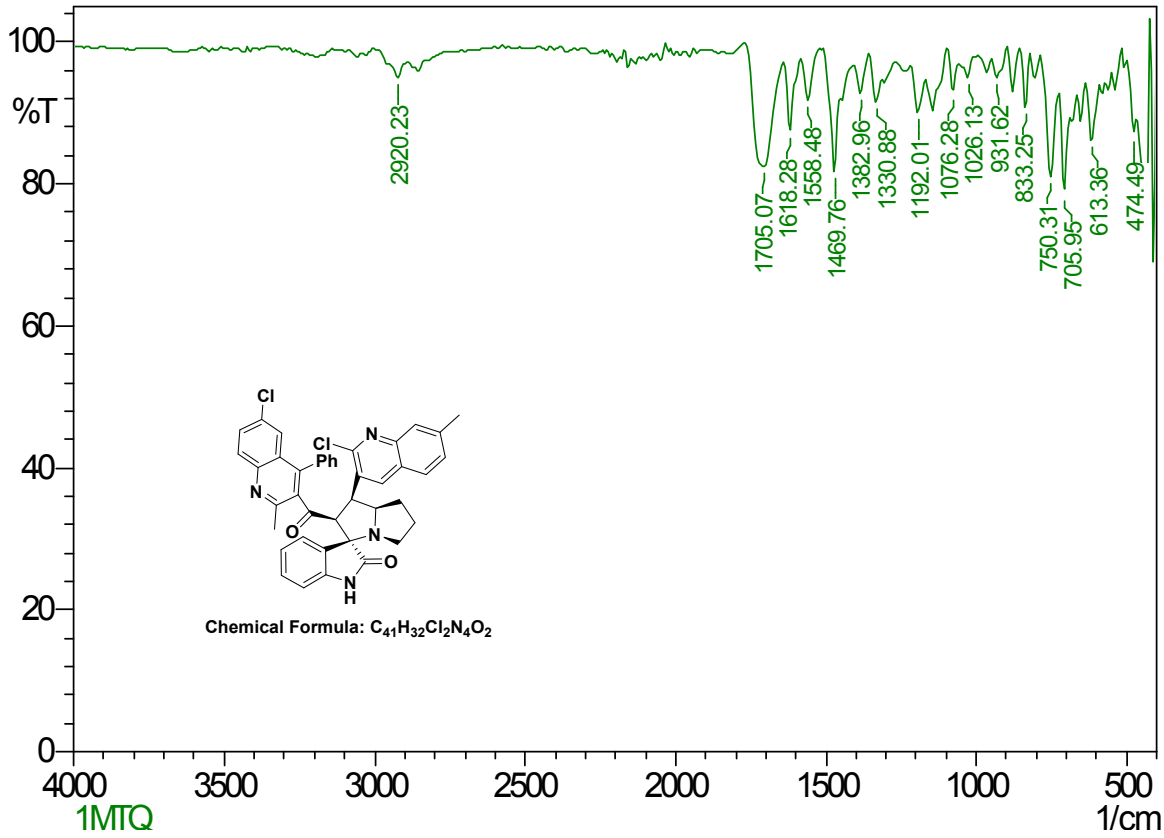


Figure S35: ^{1}H and ^{13}C NMR spectra of compound **6c** in $CDCl_3$



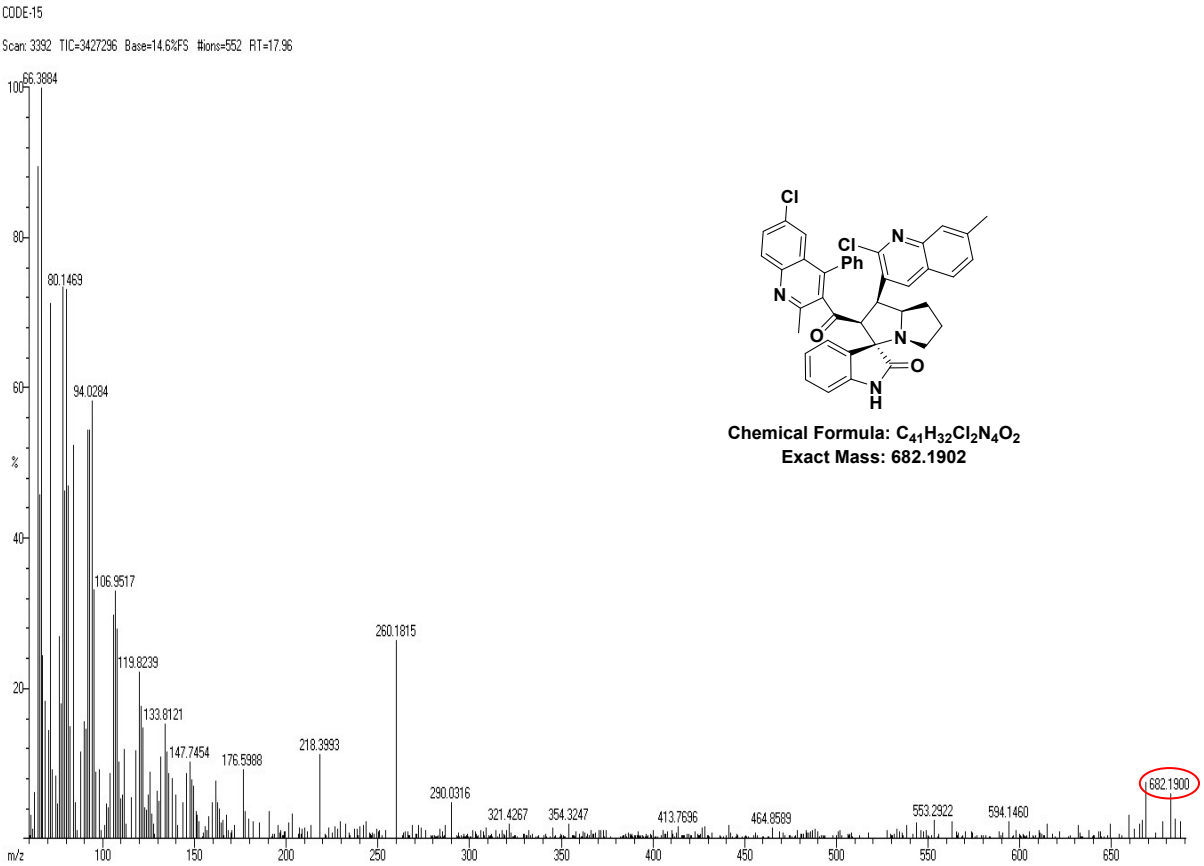


Figure S36: FT-IR & HRMS spectra of compound **6c**

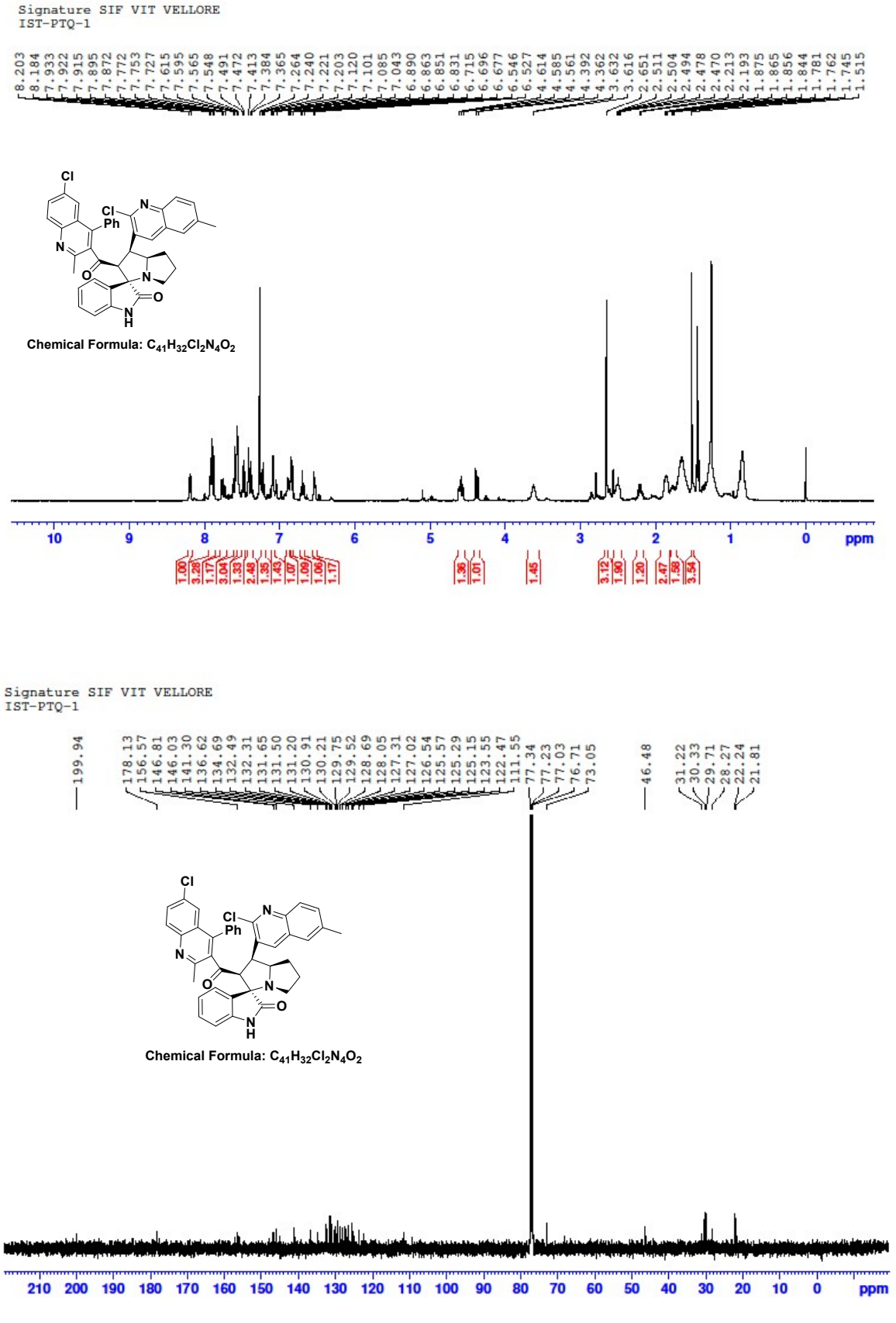
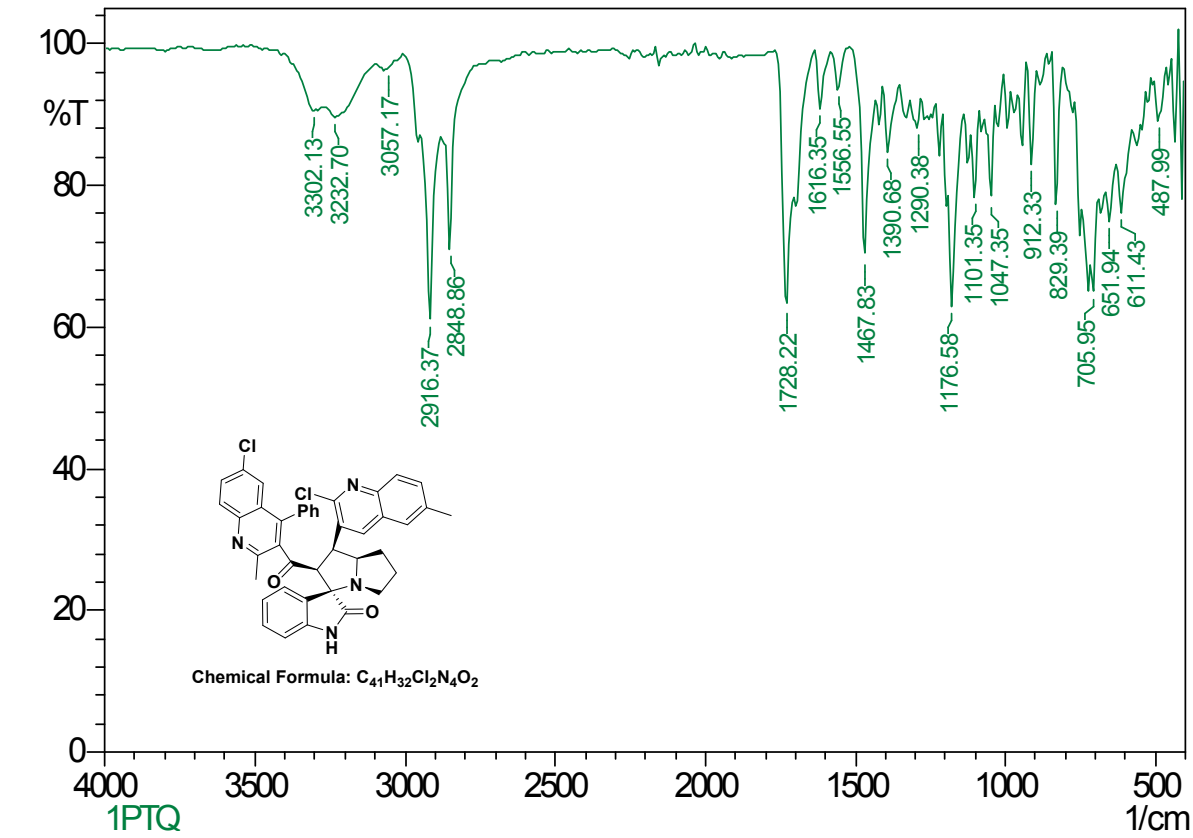


Figure S37: ^{1}H and ^{13}C NMR spectra of compound **6d** in $CDCl_3$



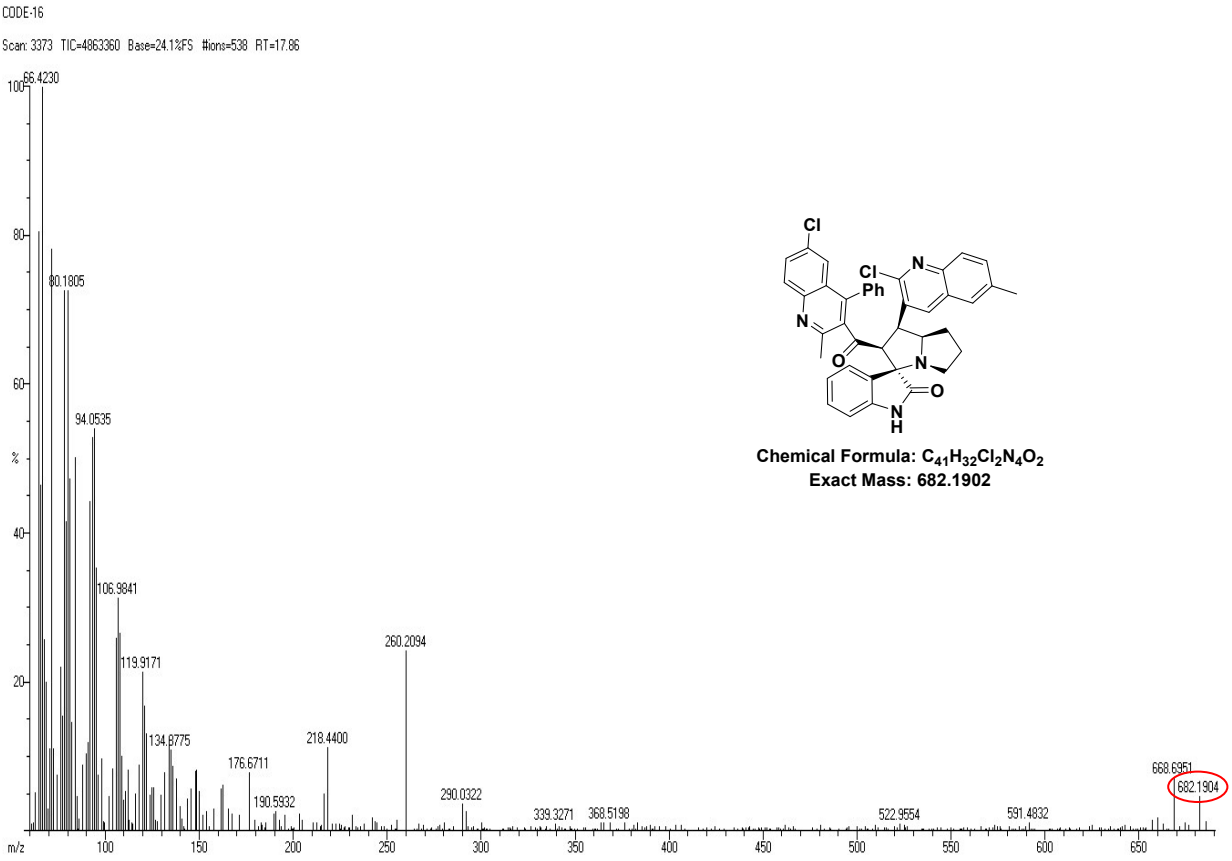
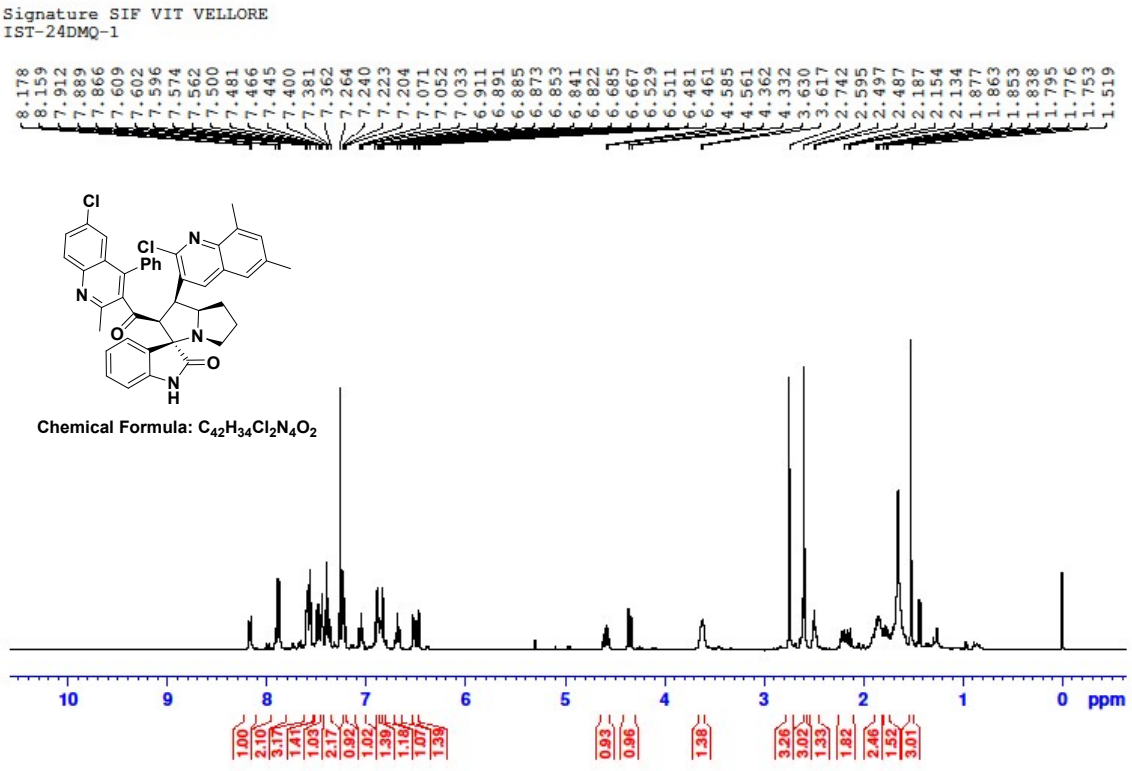


Figure S38: FT-IR & HRMS spectra of compound **6d**



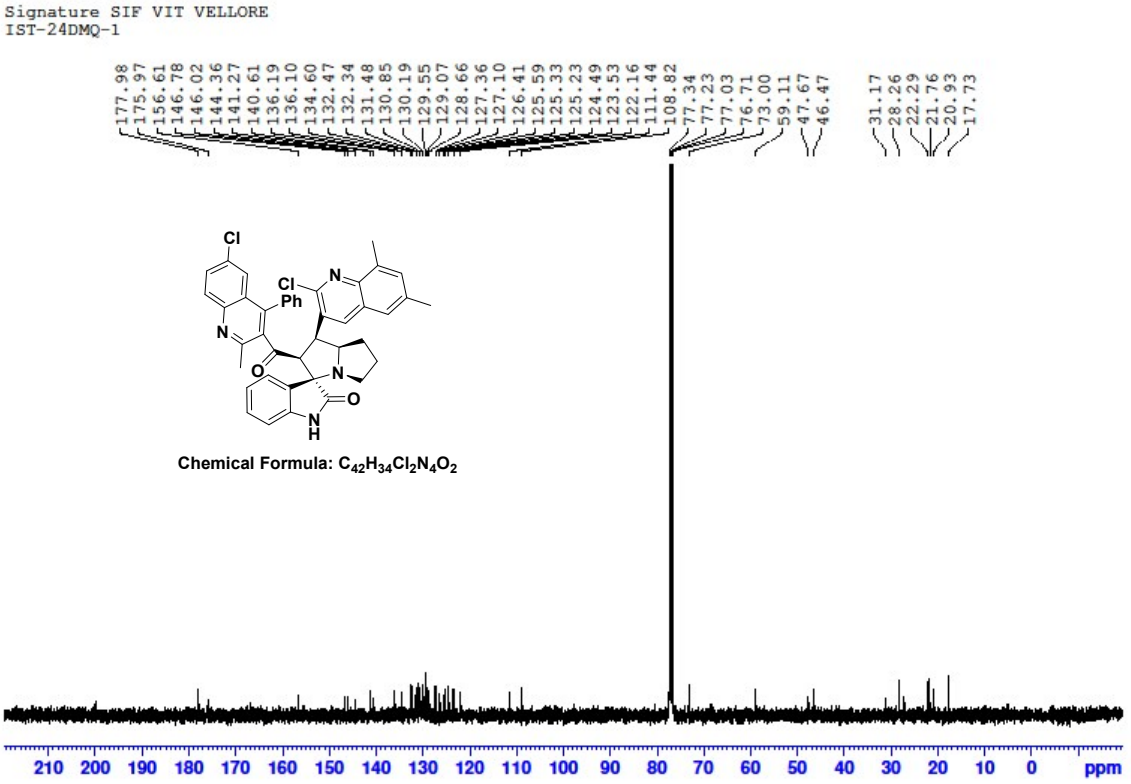
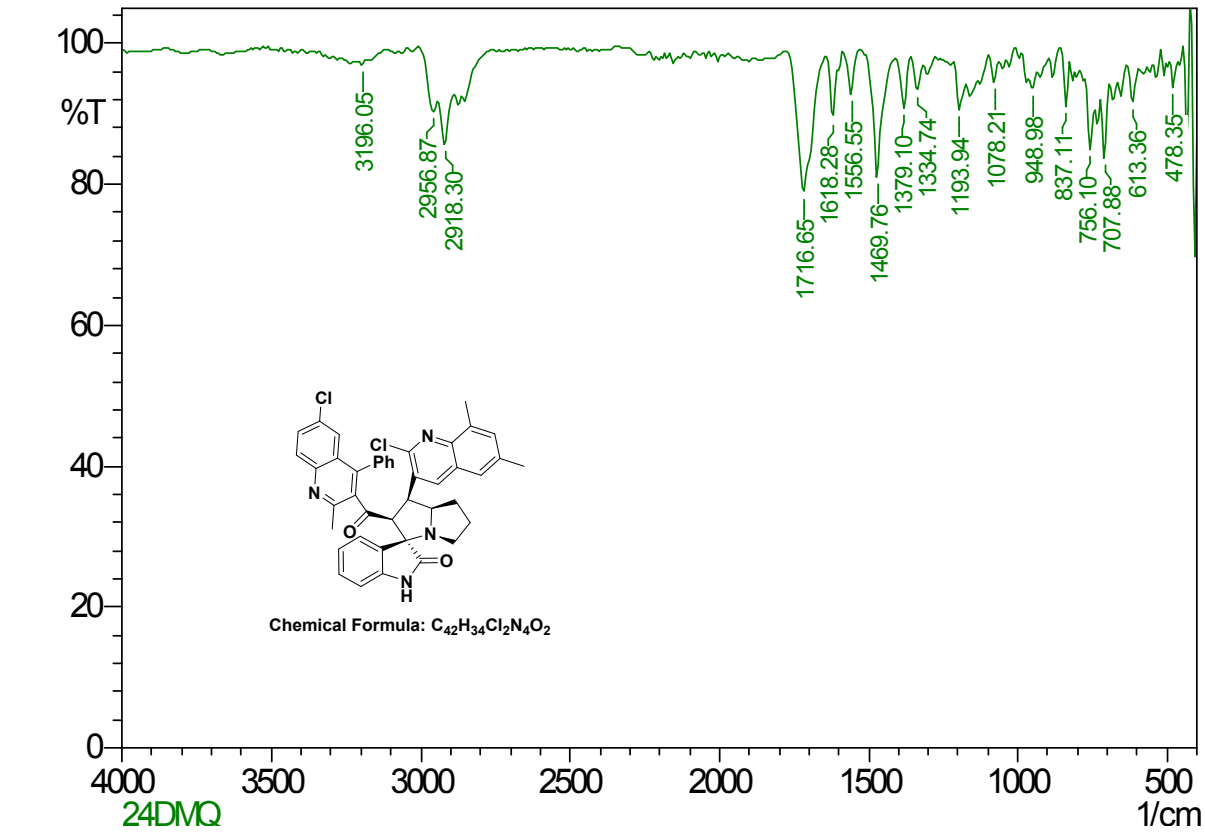


Figure S39: ^{1}H and ^{13}C NMR spectra of compound **6e** in $CDCl_3$



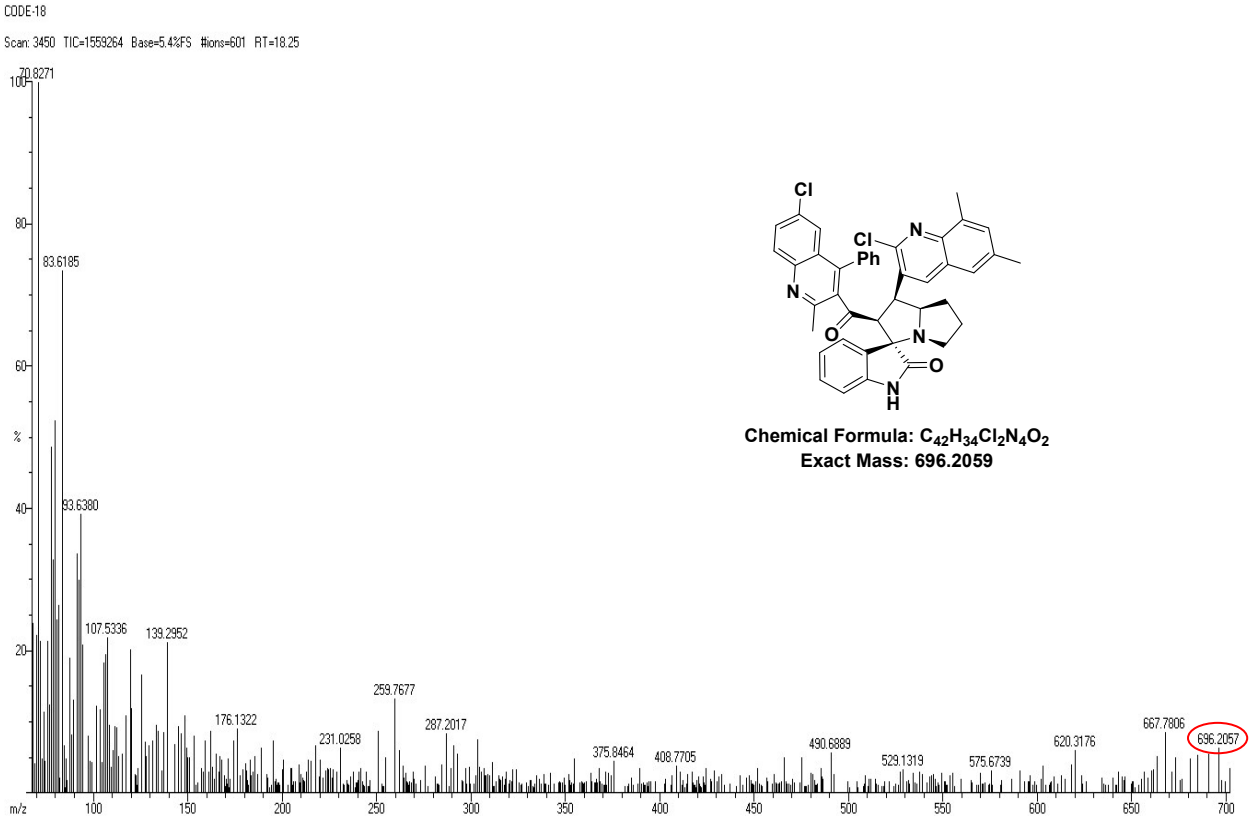


Figure S40: FT-IR & HRMS spectra of compound **6e**

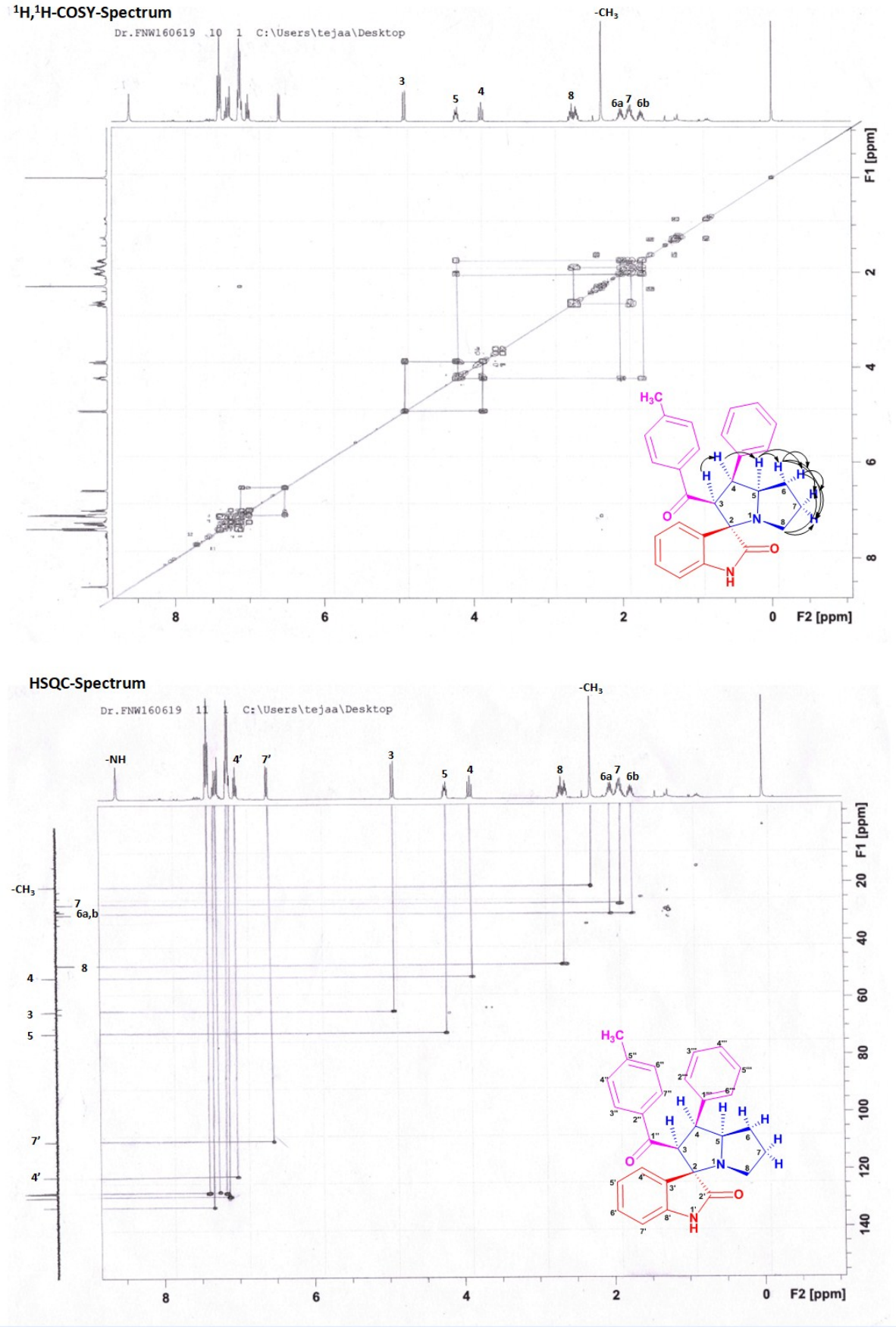


Figure S41: Plotted ^{1}H, ^{1}H-COSY, HSQC-NMR Spectrum of **4aa**

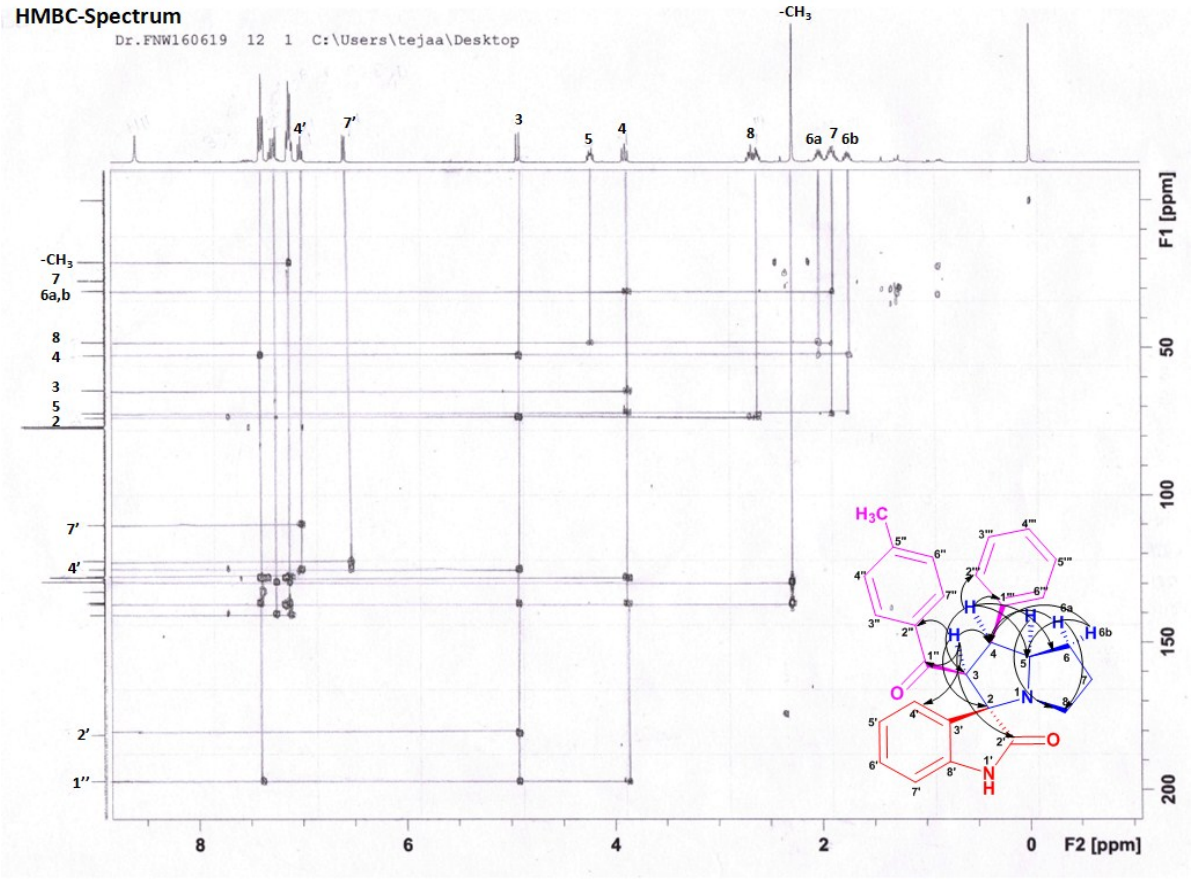


Figure S42: HMBC-NMR Spectrum of **4aa**

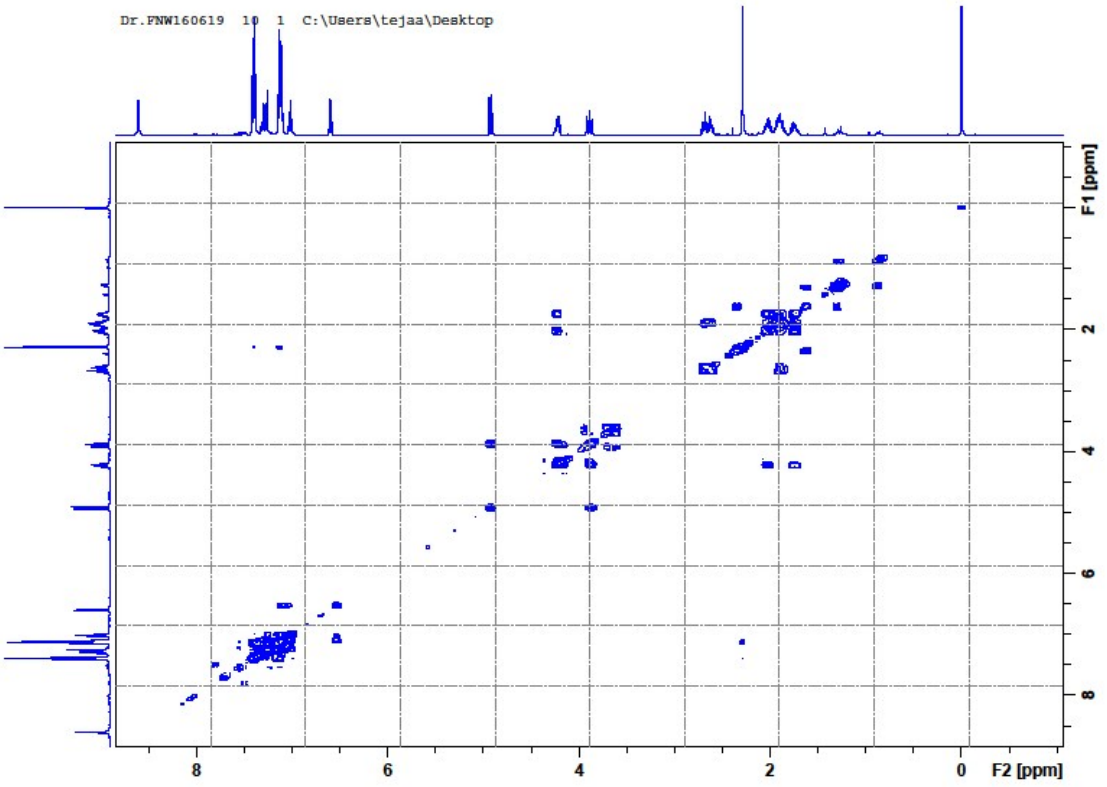


Figure S43: ^{1}H, ^{1}H-COSY NMR Spectrum of **4aa**

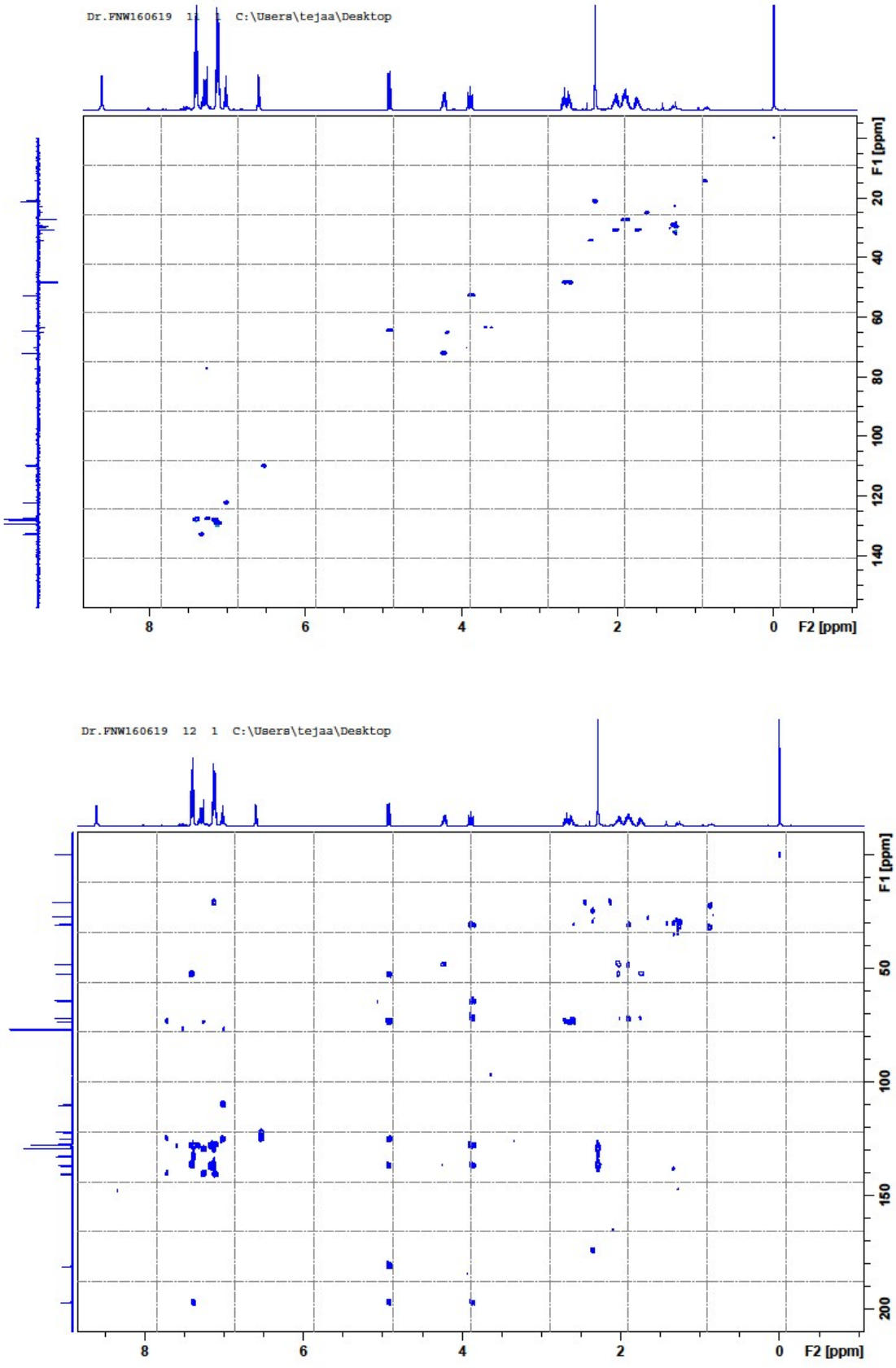


Figure S44: HSQC and HMBC NMR Spectrum of **4aa**

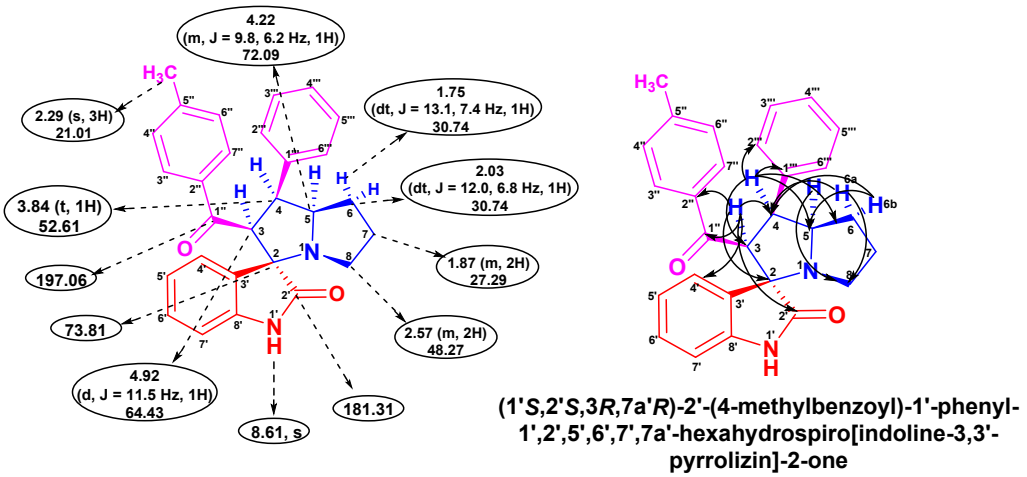


Figure S45: ^{1}H, ^{13}C NMR chemical shifts along with selected HMBC correlations.

2D-NMR Spectroscopic studies:

The structures of **4, 5 and 6** were identified using ^{1}H, ^{13}C, and 2D-NMR spectroscopic studies, as mentioned the illustrative representative example **4aa Fig. 4,** from HSQC (Heteronuclear single quantum coherence) spectrum (see supporting file page no-51, 52&53) of **4aa** shows sharp singlet at 2.28 ppm. Which correlates with peak at 21.01 ppm assigned to benzoyl group of $–CH_3$, A sharp doublet proton at 4.92 ppm correlates with 64.43 ppm assigned to C-3 at pyrrolizine ring, as well as, two methine protons as triplet at 3.84-3.93 ppm and multiplet at 4.21-4.23 ppm correlates with 52.61 and 72.09 ppm, are assigned to C-4 and C-5 carbons at pyrrolizine ring. Two protons of methylene at 1.73-1.76 and 2.00-2.03 ppm as two multiplets due to internal cross-couplings, which correlates with 30.74 ppm, are assigned to C-6. A multiplet of two protons around 1.87-1.92 ppm correlates with 27.29 ppm are assigned to C-7, another two protons of methylene as multiplets around 2.57-2.74 ppm correlates with 48.27 ppm, are assigned to C-8 carbon. From $^{1}H–^{1}H$ COSY spectrum, A sharp doublet proton at C-3 carbon in pyrrolizine ring correlates with C-4 proton, Possibly C-5 multiplet proton correlates with C-4, Also separately correlates with two protons at C-6. There is an internal cross-coupling that appears between C-6 carbon, The multiplet two protons at C-7 cross peak correlation with C-8, also an internal cross-coupling from two protons at C-8. Further, From the HMBC (Heteronuclear Multiple Bond coherence) spectrum, C-3 proton correlates with 52.61 ppm (C-4), 73.81 ppm (C-2), 125.14 ppm (C-4'), 137.09 ppm (C-2''), 181.31 ppm (C-2'), and 197.06 ppm (C-1''). C-4 proton correlates with 30.74 ppm (C-6), 64.54 ppm (C-3), 72.09 ppm (C-5), 127.95 ppm (C-2'''), 136.71 ppm (C-1'''), and 197.06 ppm (C-1''). C-5 proton correlates with 48.27 ppm (C-8). C-6a proton correlates with 48.27 ppm (C-8) and 52.61 ppm (C-4), C-6b proton correlates with 52.61 ppm (C-4) and 72.09 ppm (C-5). C-7 proton correlates with 30.74 ppm (C-6), 48.27 ppm (C-8) and 72.09 ppm (C-5). C-8 proton correlates with 73.81 ppm (C-2). In addition, the ^{1}H NMR spectrum showed singlet at 8.60 ppm which can be attributed to amide –NH proton in the isatin substitution. Hence from ^{1}H, ^{13}C, $^{1}H–^{1}H$ COSY, HSQC and HMBC NMR studies, we have confirmed the structure, regio and stereo-chemistry of the compound **4aa**.

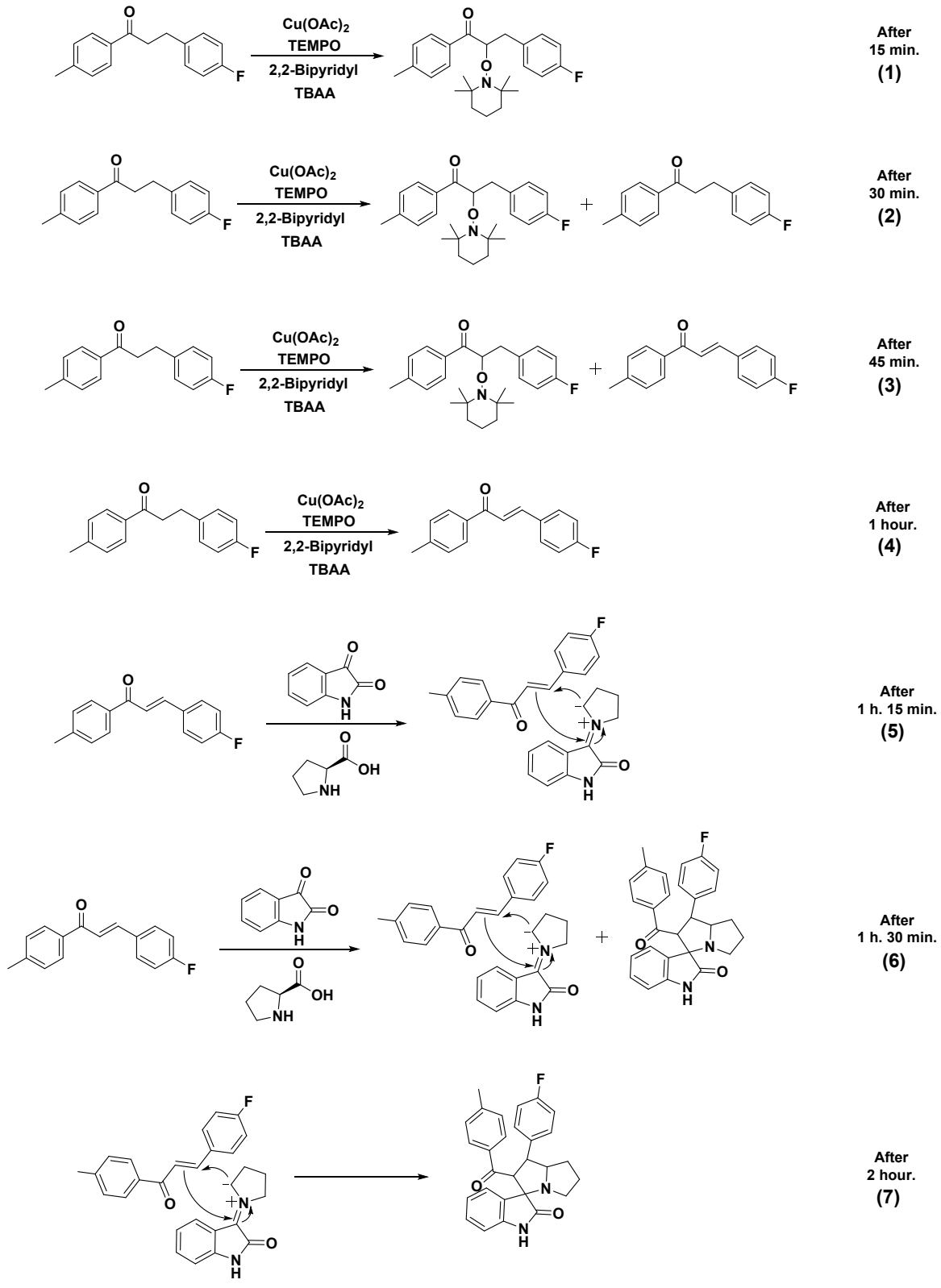


Figure S46: Control experimental studies for detection of reaction mechanism

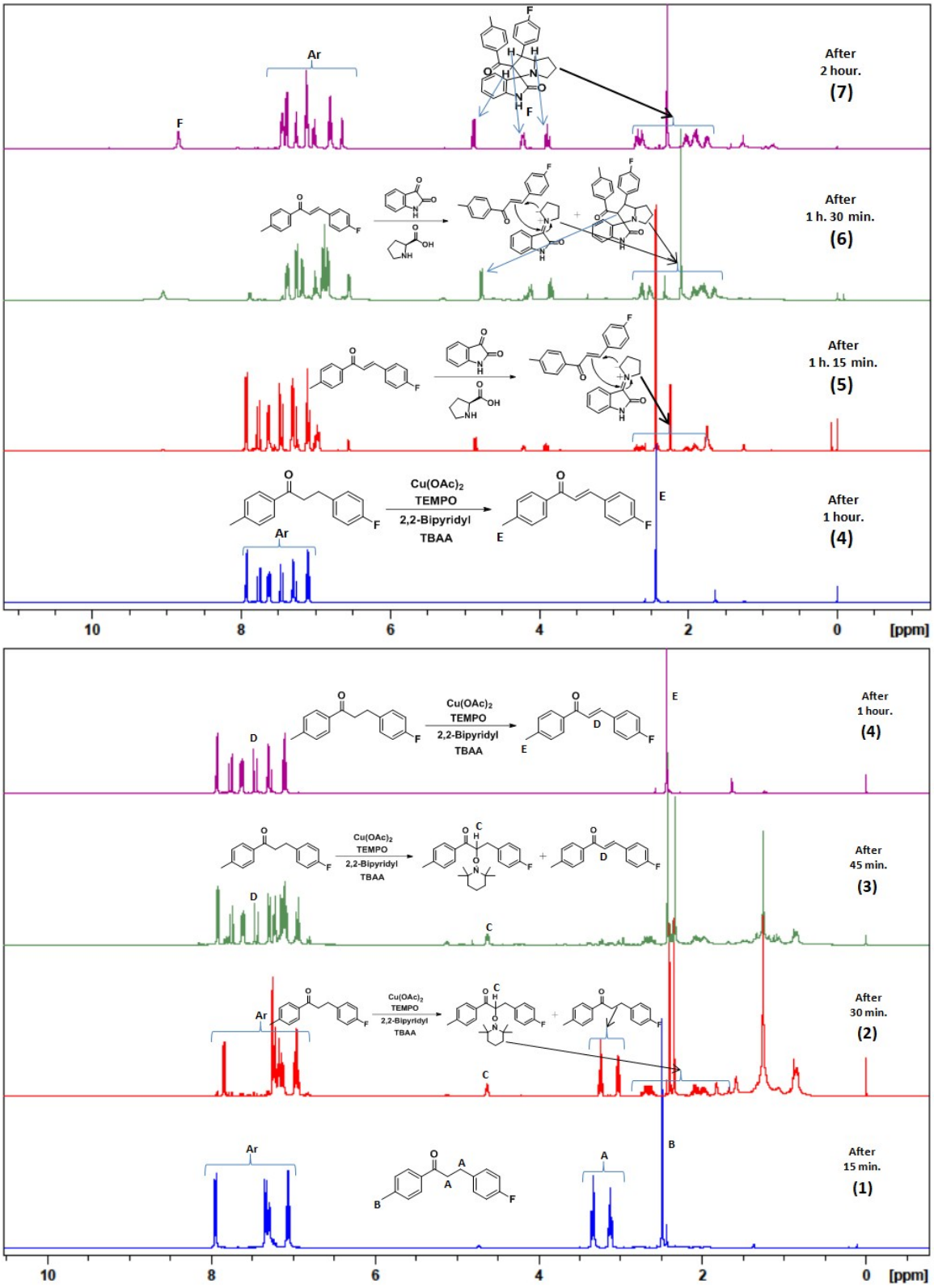
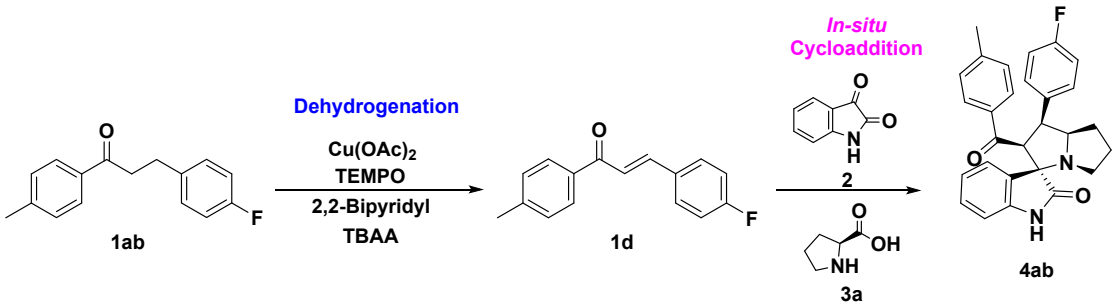


Figure S47: The ^{1}H NMR spectra of control experimental studies **(1)** Pure 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one **(2)** Mixture of 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one 7, with α-TEMPO-adducted 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one **(3)** mixtures of -TEMPO-adducted 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one with (E)-3-(4-fluorophenyl)-1-(p-tolyl)prop-2-en-1-one (chalcone) isolated from the reaction **(4)** Pure (E)-3-(4-fluorophenyl)-1-(p-tolyl)prop-2-en-1-one **1d** (chalcone). **(5)** Reaction mixture of chalcone, Isatin and L-proline (Azomethine ylide) **(6)** Mixture of Azomethine ylide, chalcone and desired product **4ab**. **(7)** Desired (1'-(4-fluorophenyl)-2'-(4-methylbenzoyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one) spirane product.

Monitoring the reaction by ^{1}H NMR analysis (Mechanistic studies)

Additionally, the more solid evidence for the reaction pathway was observed by monitoring the reaction with ^{1}H-NMR analysis. **Fig S46. Spectra-(1)** Shows the ^{1}H NMR spectra of pure alkylated ketone product; After 15 min., time interval, in that ^{1}H-NMR spectra, **A** shows the α,β-saturated-CH_2 protons around 3-3.5 ppm, and **B** shows -CH_3 2.5ppm. From **spectra-(2) Fig 3.** After 30 min. Interval, which shows the mixture of 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one (Alkylated product), with *α*-TEMPO-adducted 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one, In that **C** Shows *α*-TEMPO-adducted C-H proton at 4.6ppm according to previous literature report[1] Weiping Su *et al.* propose the mechanism for dehydrogenation using Cu-TEMPO catalyst. **Spectra-(3)** After 45min. The ^{1}H NMR spectra shows, The mixtures of α-TEMPO-substituted ketone with (E)-3-(4-fluorophenyl)-1-(p-tolyl)prop-2-en-1-one (chalcone), In that **C** Shows *α*-TEMPO-adducted C-H proton at 4.6ppm., along with **D** α-CH proton of chalcone, Which confirms that the formation of enone (chalcone) formation through *α*-TEMPO-substituted ketone.[1] From **spectra-(4)** After 1 h time interval the reaction mixture was analyzed by ^{1}H NMR-Spectroscopy, which shows the pure α,β-unsaturated enone (chalcone) **1d**. From **spectra-(5)** In the sequential addition of isatin and L-proline under the same reaction medium, after 1 h 15 min. the formation of azomethine ylide along with chalcone. **Spectra-(6)** the same reaction was analysed after 1 h 30 min., NMR spectra show the mixture of azomethine ylide, chalcone and desired spirane product. **Spectra-(7)** shows the pure product of (1'-(4-fluorophenyl)-2'-(4-methylbenzoyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one) spirooxindole after 2 h. the doublet proton of chiral –CH comes around 4.9 ppm., and other chiral protons comes around 4-4.5 ppm., and **F** shows the amide-NH proton around 9 ppm.

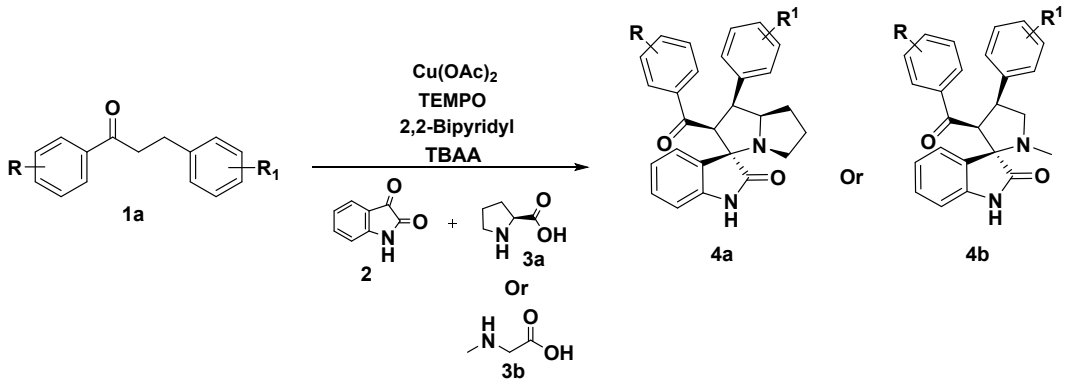
Table S1. Optimization studies for preparation of spirooxindolopyrrolizidines[a,b]

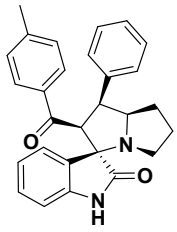


Entry	Cat. (mol %)	Additives		Solvent	Temp in °C	Time (hrs)	Yield %[b]
1	$Mn(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	9 h	56
2	$Co(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	8 h	43
3	$Ni(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	12 h	45
4	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	6 h	65
5	$Zn(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	10 h	50
6	$Pd(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	13 h	55
7	Ag_2O	TEMPO	2,2′-Bipyridyl	DMF	100	12 h	-
8	$CuSO_4$	TEMPO	2,2′-Bipyridyl	DMF	100	20 h	-
9	$CuCl_2$	TEMPO	2,2′-Bipyridyl	DMF	100	18 h	-
10	$CuBr_2$	TEMPO	2,2′-Bipyridyl	DMF	100	18 h	-
11	$Cu(OTf)_2$	TEMPO	2,2′-Bipyridyl	DMF	100	10 h	15
12	$Cu(OAc)_2$	TEMPO	1,10-phenanthroline	DMF	100	8 h	43
13	$Cu(OAc)_2$	TEMPO	DBU	DMF	100	15 h	35
14	$Cu(OAc)_2$	TEMPO	DABCO	DMF	100	18 h	25
15	$Cu(OAc)_2$	TEMPO	pyridine	DMF	100	12 h	15
16	$Cu(OAc)_2$	NHPI	2,2′-Bipyridyl	DMF	100	10 h	15
17	$Cu(OAc)_2$	tBuOOH	2,2′-Bipyridyl	DMF	100	15 h	15
18	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	1,4-Dioxane	100	10 h	40
19	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	DMSO	100	8 h	52
20	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	Toluene	100	16 h	35
21	**$Cu(OAc)_2$**	**TEMPO**	**2,2′-Bipyridyl**	**TBAA (1 eq.)**	**80**	**2 h**	**85**
22	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	**TMAB**	**80**	2 h	60
23	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	**TEAB**	**80**	2 h	63
24	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	**TBAB**	**80**	3 h	70
25	$Cu(OAc)_2$	TEMPO	2,2′-Bipyridyl	**TBAI**	**80**	4 h	68
26	**$Cu(OAc)_2$**	**TEMPO**	**2,2′-Bipyridyl**	**TBAA (0.5 eq.)**	**80**	**2 h**	**82**
27	**$Cu(OAc)_2$**	**TEMPO**	**2,2′-Bipyridyl**	**TBAA (0.25 eq.)**	**80**	**3 h**	**70**

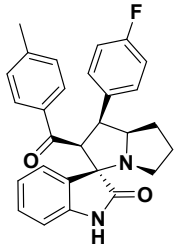
[a]**Reaction Conditions:** Saturated ketone, **1aa** (0.5 mmol), $Cu(OAc)_2$ (10 mol%), TEMPO (0.1 mmol) and 2,2-Bipyridyl (0.1 mmol), in 2 ml of solvent at 100 °C. after sequential addition of Isatin, **2** (0.5 mmol), L-proline **3a** or Sarcosine **3b** (0.6 mmol). [b]TBA-ionic-liquid (1eq) at 80 °C for 1 hour. [c]Isolated yields

Table S2. Substrate scope with alkylated saturated ketones[a,b].

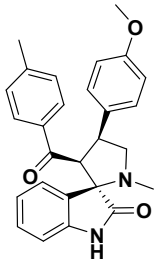




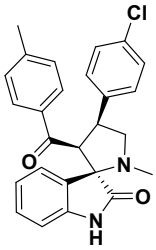
4aa, 2h, 85%



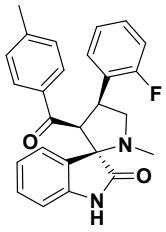
4ab, 2h, 87%



4ba, 2h, 82%



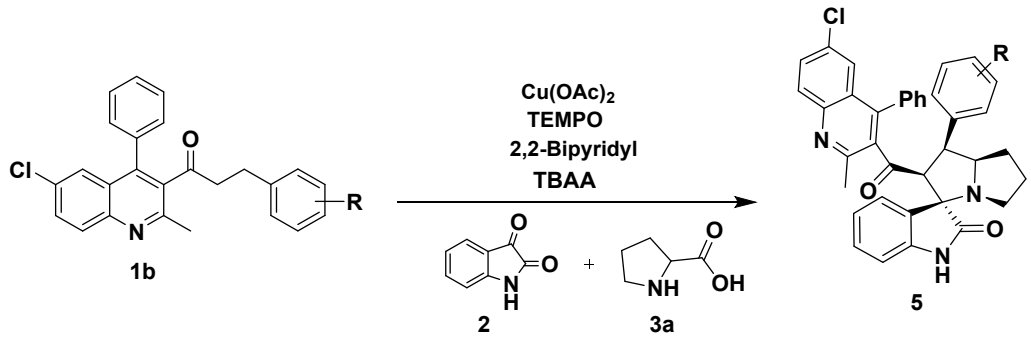
4bb, 2h, 86%

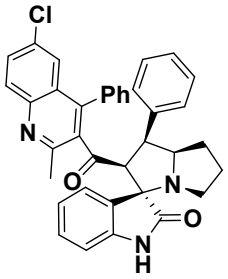


4bc, 2h, 80%

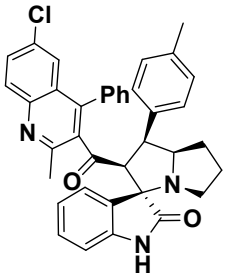
[a]**Reaction Conditions:** Alkylkated ketone, **1a** (0.5 mmol), $Cu(OAc)_2$ (10 mol%), TEMPO (0.1 mmol) and 2,2′-Bipyridyl (0.1 mmol), in TBAA (1eq) at 80 °C for 1 h, sequential addition of Isatin, 2 (0.5 mmol), L-proline **3a** or Sarcosine **3b** (0.6 mmol) at 80 °C for another 1 h, [b]Isolated yields.

Table S3. Substrate scope with Qinolinyl-keto alkanes[a,b].

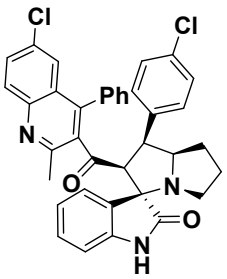




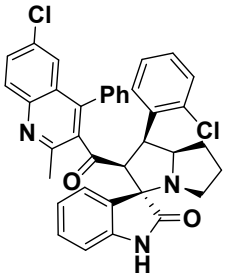
5a, 2h, 81%



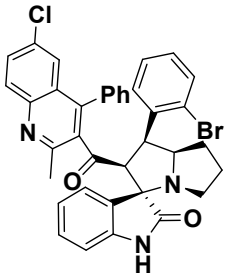
5b, 2h, 84%



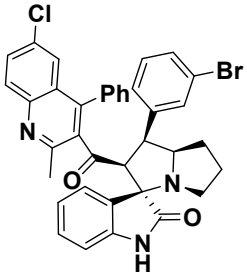
5c, 3h, 75%



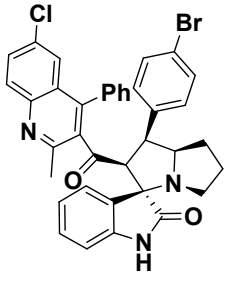
5d, 3h, 72%



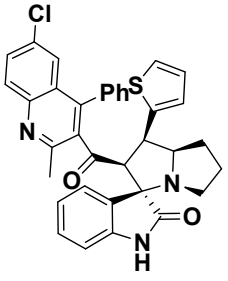
5e, 2h, 76%



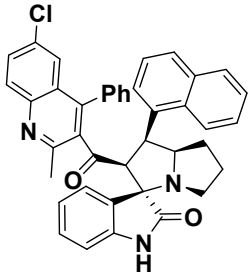
5f, 2h, 70%



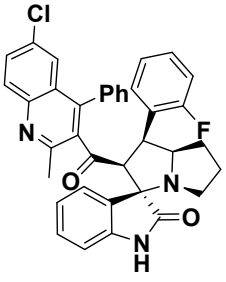
5g, 2h, 75%



5h, 2h, 69%



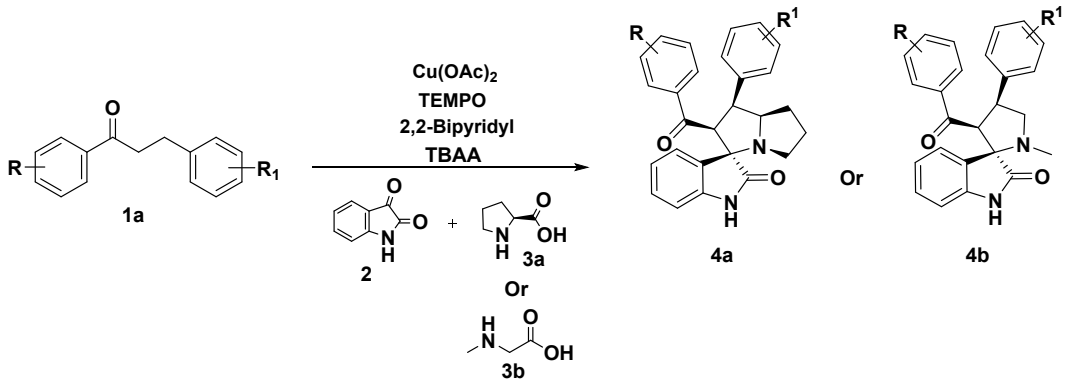
5i, 3h, 70%

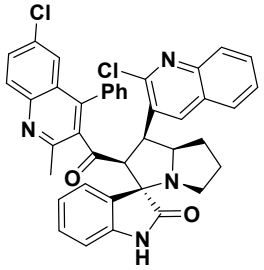


5j, 2h, 75%

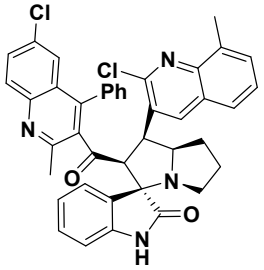
[a]**Reaction Conditions:** Quinolinyl-alkylkated ketone, **1b** (0.5 mmol), $Cu(OAc)_2$ (10 mol%), TEMPO (0.1 mmol) and 2,2′-Bipyridyl (0.1 mmol), in TBAA (1eq) at 80 °C for 1 h, Sequential addition of Isatin, **2** (0.5 mmol), L-proline **3a** or Sarcosine **3b** (0.6 mmol) at 80 °C for another 1 h. [b]Isolated yields.

Table S4. Substrate scope with Qinolinyl-keto alkanes[a,b].

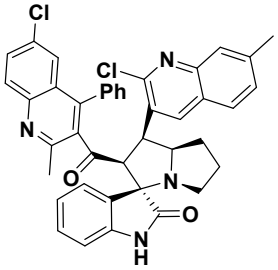




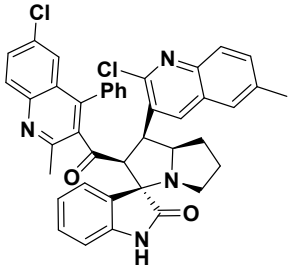
6a, 3h, 70%



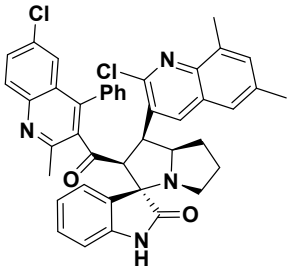
6b, 3h, 68%



6c, 3h, 65%



6d, 2h, 72%



6e, 2h, 70%

[a]**Reaction Conditions:** Quinolinyl-alkylkated ketone, **1c** (0.5 mmol), $Cu(OAc)_2$ (10 mol%), TEMPO (0.1 mmol) and 2,2′-Bipyridyl (0.1 mmol), in TBAA (1eq) at 80 °C for 1 hour., Sequential addition of Isatin, **2** (0.5 mmol), L-proline **3a** or Sarcosine **3b** (0.6 mmol) at 80 °C for another 1 h. [b]Isolated yields

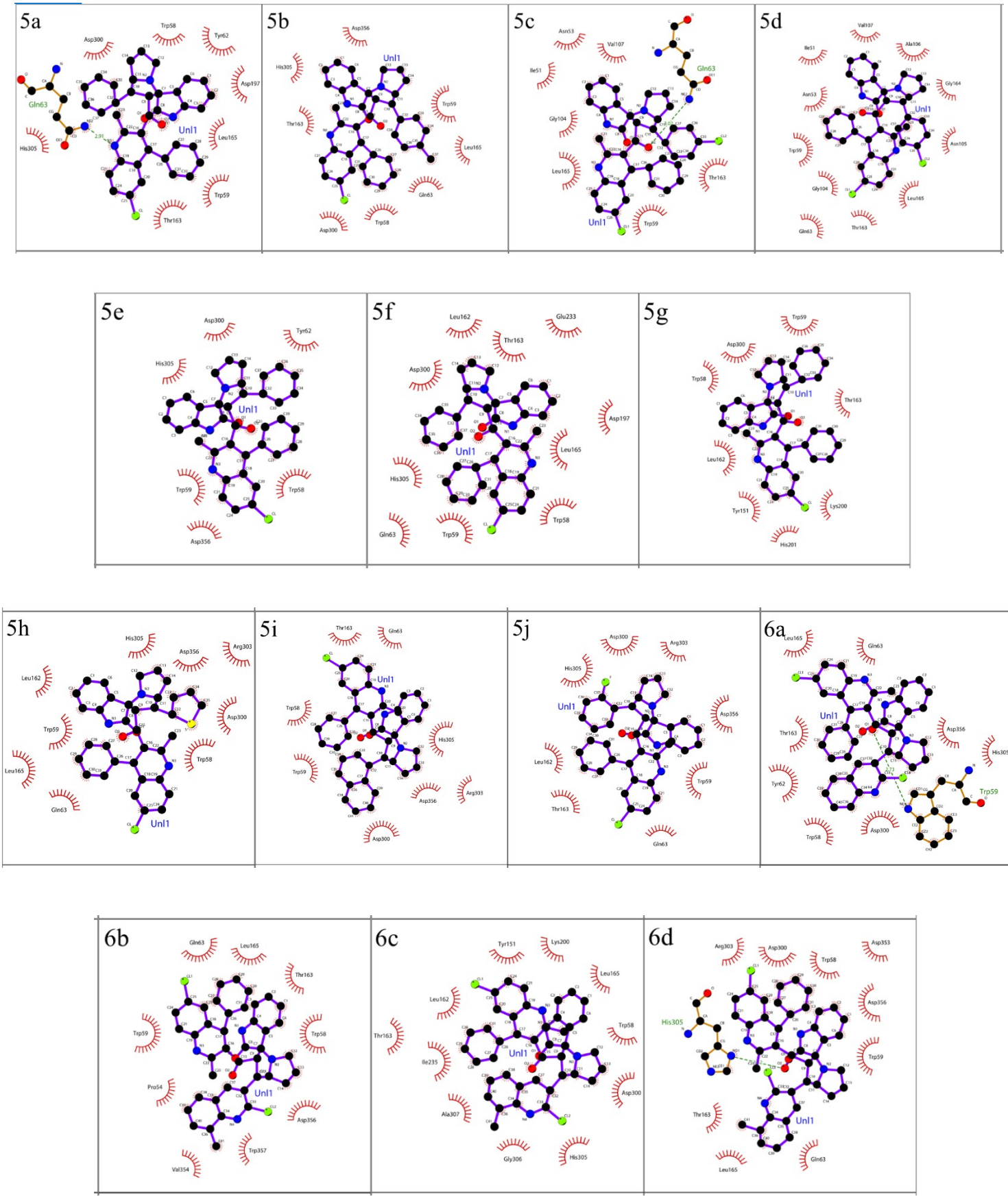
Table S5: Binding Energy Of The Synthesized Compounds Interactions Obtained From AutoDock Analysis.

S.No	Compound Name	Binding Energy (kcal/mol)		
		Alpha Amylase	Alpha Glucosidase	GLP-1
1	**5a**	-8.15	-8.64	-9.51
2	**5b**	-7.3	-8.08	-9.47
3	**5c**	-7.76	-8.66	-8.31
4	**5d**	-7.78	-8.27	-7.46
5	**5e**	-7.78	-7.6	-8.11
6	**5f**	-8.47	-7.23	-8.21
7	**5g**	-7.9	-7.61	-8.15
8	**5h**	-9.29	-7.28	-8.39
9	**5i**	-8.57	-8.73	-8.4
10	**5j**	-8.13	-7.91	-8.55
11	**6a**	-9.51	-9.29	-8.85
12	**6b**	-9.16	-9.77	-7.56
13	**6c**	-9.61	-7.07	-8.6
14	**6d**	-8.74	-7.44	-10.2
15	**6e**	-9.24	-8.71	-8.95
16	**4aa**	-7.81	-7.62	-7.65
17	**4ab**	-6.95	-7.04	-7.47
18	**4ba**	-6.77	-6.85	-6.66
19	**4bb**	-7.79	-7.14	-6.87
20	**4bc**	-7.78	-6.57	-7.31
21	**Standard Drug**	-0.74	0.32	37.44

2.2.1 Molecular docking studies

α-amylase and α-glucosidase are two vital enzymes present in the digestive system involved in the conversion of carbohydrates into glucose which in turn increases the blood glucose levels. Inhibiting these enzymes can help lower blood glucose level which can be administered for diabetic conditions. **GLP-1** is an incretin that induces the beta cells of the pancreas to produce insulin which helps in the reduction of the blood glucose level. While inhibiting the α-amylase and α-glucosidase can help in lowering the glucose levels enhancing **GLP-1** can also help in the management of diabetes which in turn can help in the management of diabetes. The result obtained has inferred that the synthesized compounds have inhibiting activity against the digestive enzymes and could act as a potential drug for diabetes management.

Figure S48: Interactions of Alpha Amylase with synthesized compounds.



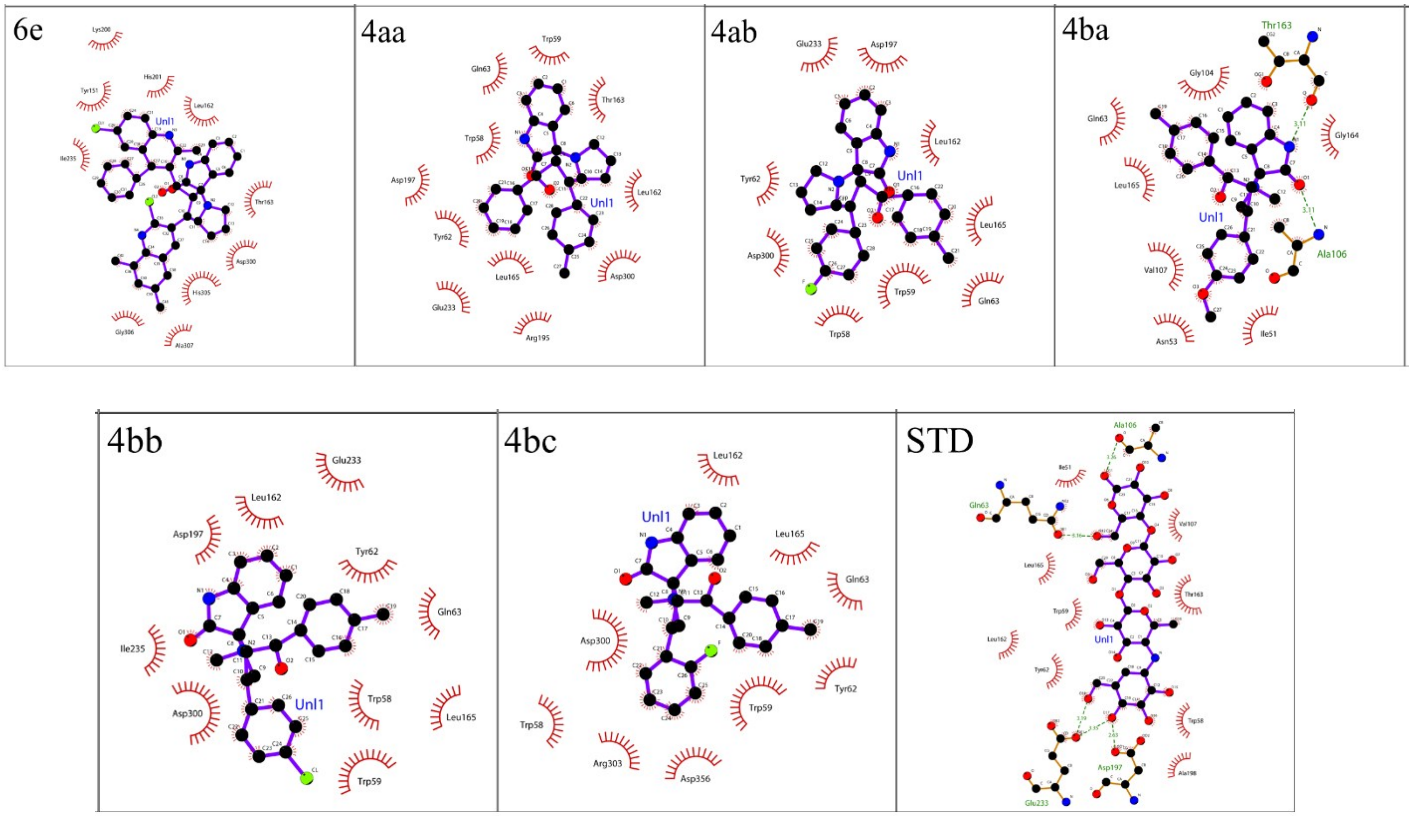
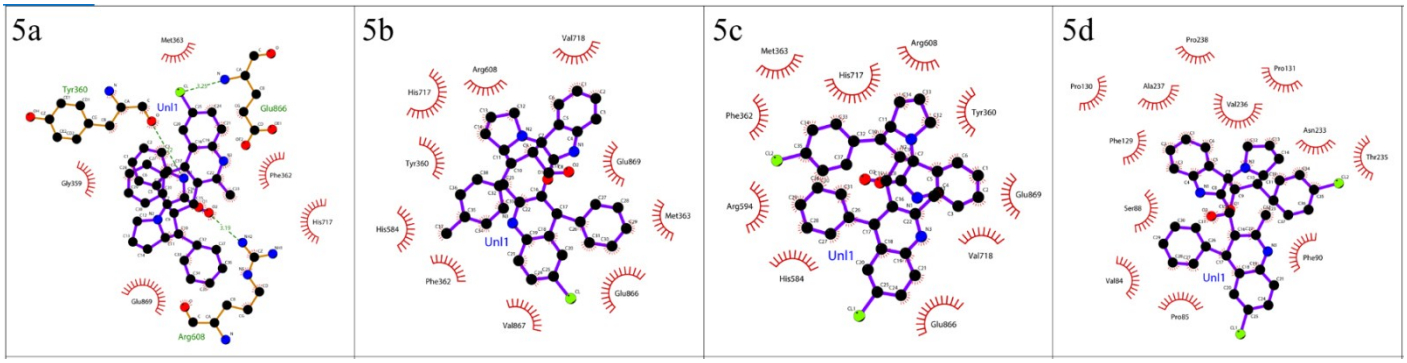
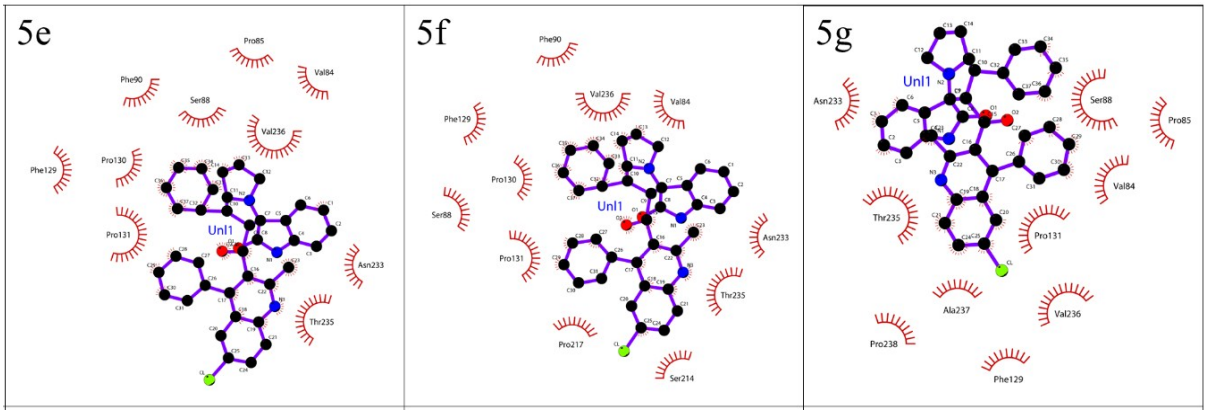
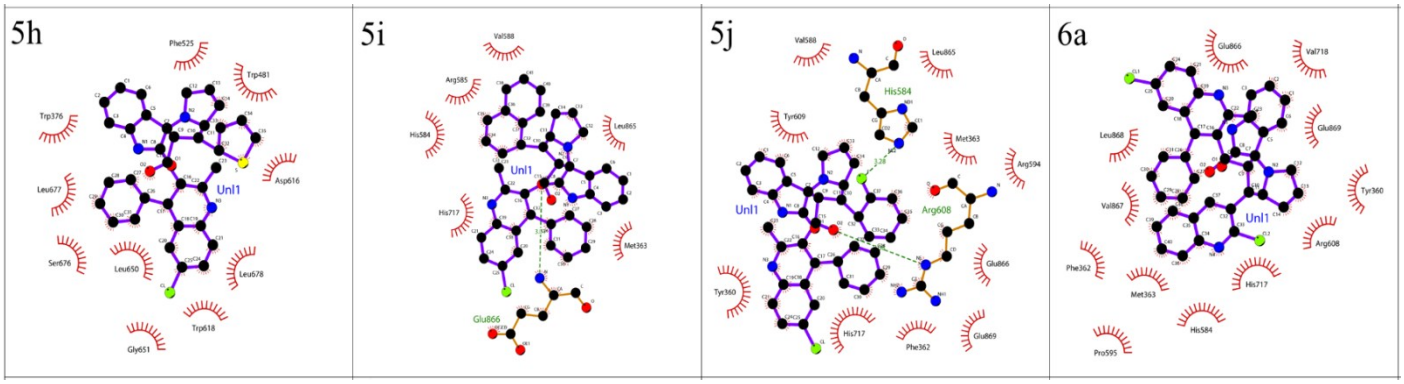


Figure S49: Interactions of Alpha Glycosidase with synthesized compounds.



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Unl1
Leu677
Ser676
Leu650
Leu678
Trp618
Gly651
5i
Val588
Arg585
His584
Leu865
Unl1
His717
Met363
Glu866
5j
Val588
Leu865
His584
Tyr609
Met363
Arg594
Unl1
Arg608
Glu866
Tyr360
His717
Phe362
Glu869
6a
Glu866
Val718
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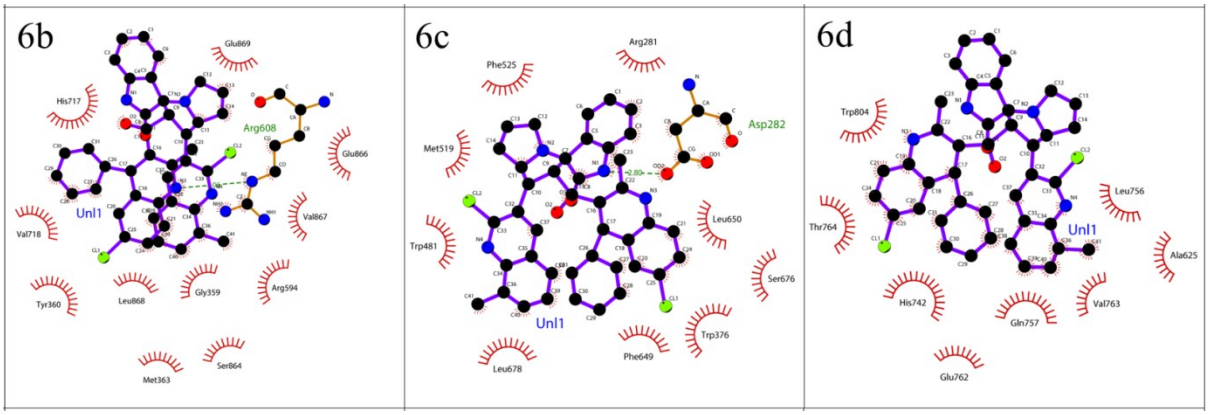
Leu868
Tyr360
Val867
Unl1
Arg608
Phe362
Met363
His717
His584
Pro595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His717
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Glu866
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Met363
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Arg281
Phe525
Asp282
Met519
Unl1
Leu650
Trp481
Ser676
Trp376
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6d
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Leu756
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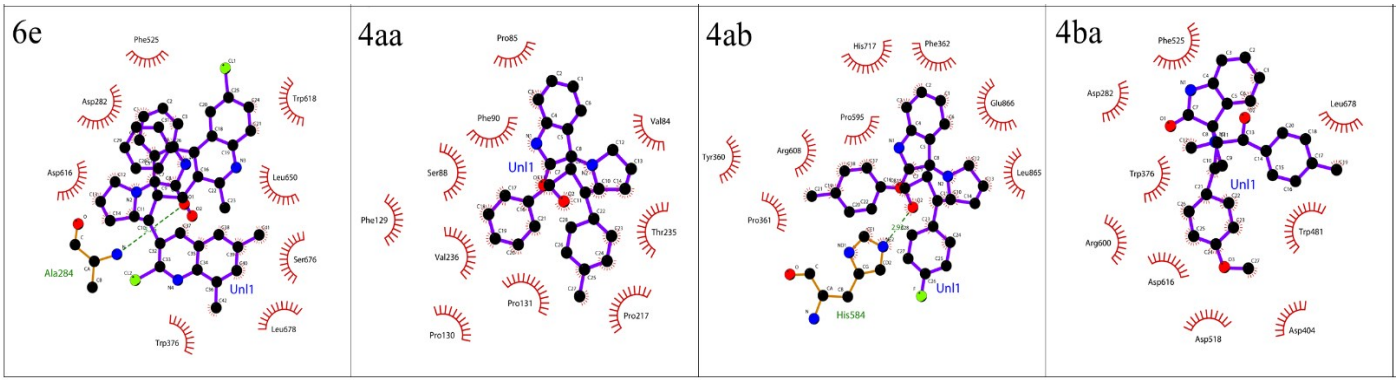
Unl1
Ala625
His742
Gln757
Val763
Glu762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Unl1
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Val84
Ser88
Unl1
Phe129
Thr235
Val236
Pro131
Pro217
Pro130
4ab
His717
Phe362
Glu866
Pro595
Tyr360
Arg608
Leu865
Pro361
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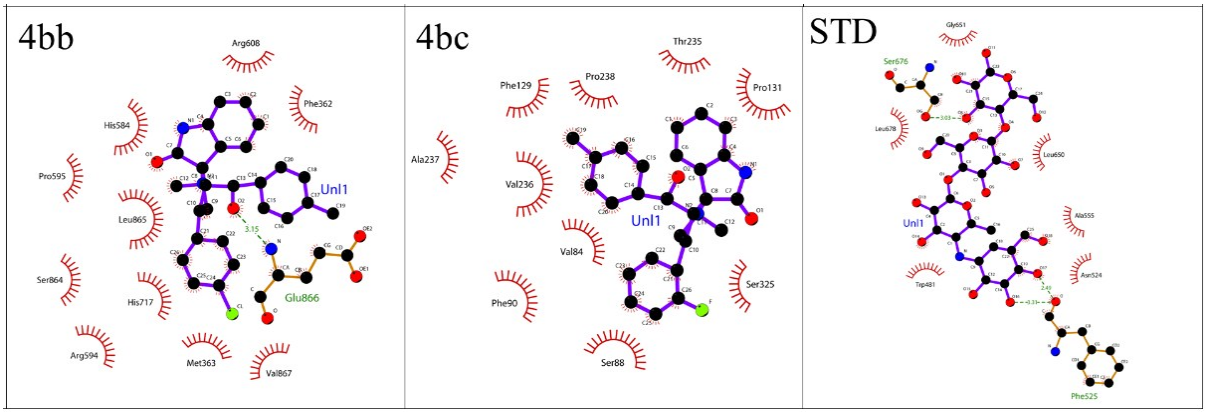
Arg600
Asp616
Asp518
Asp404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Ser88
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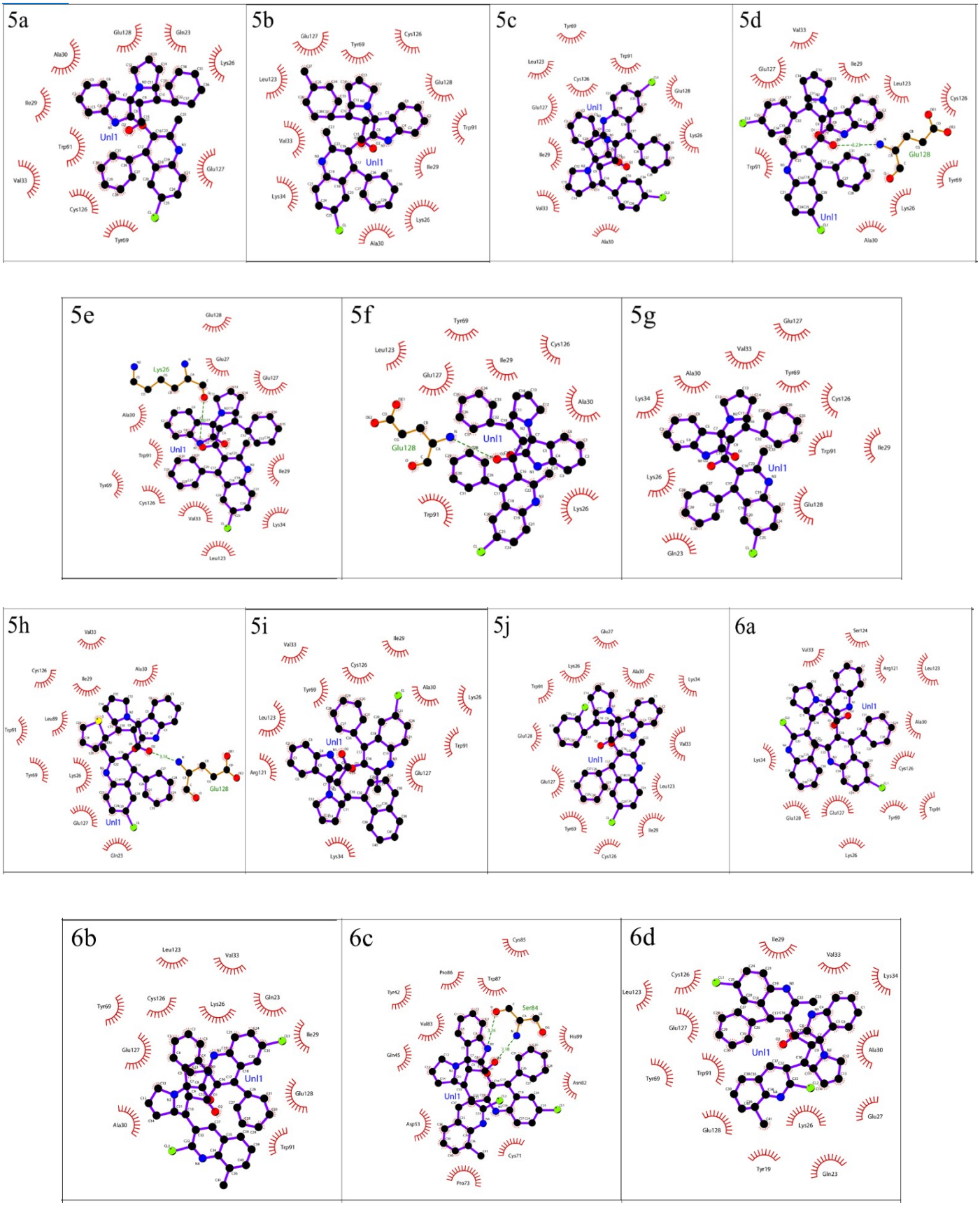
Figure S50: Interactions of GLP-1 with synthesized compounds.



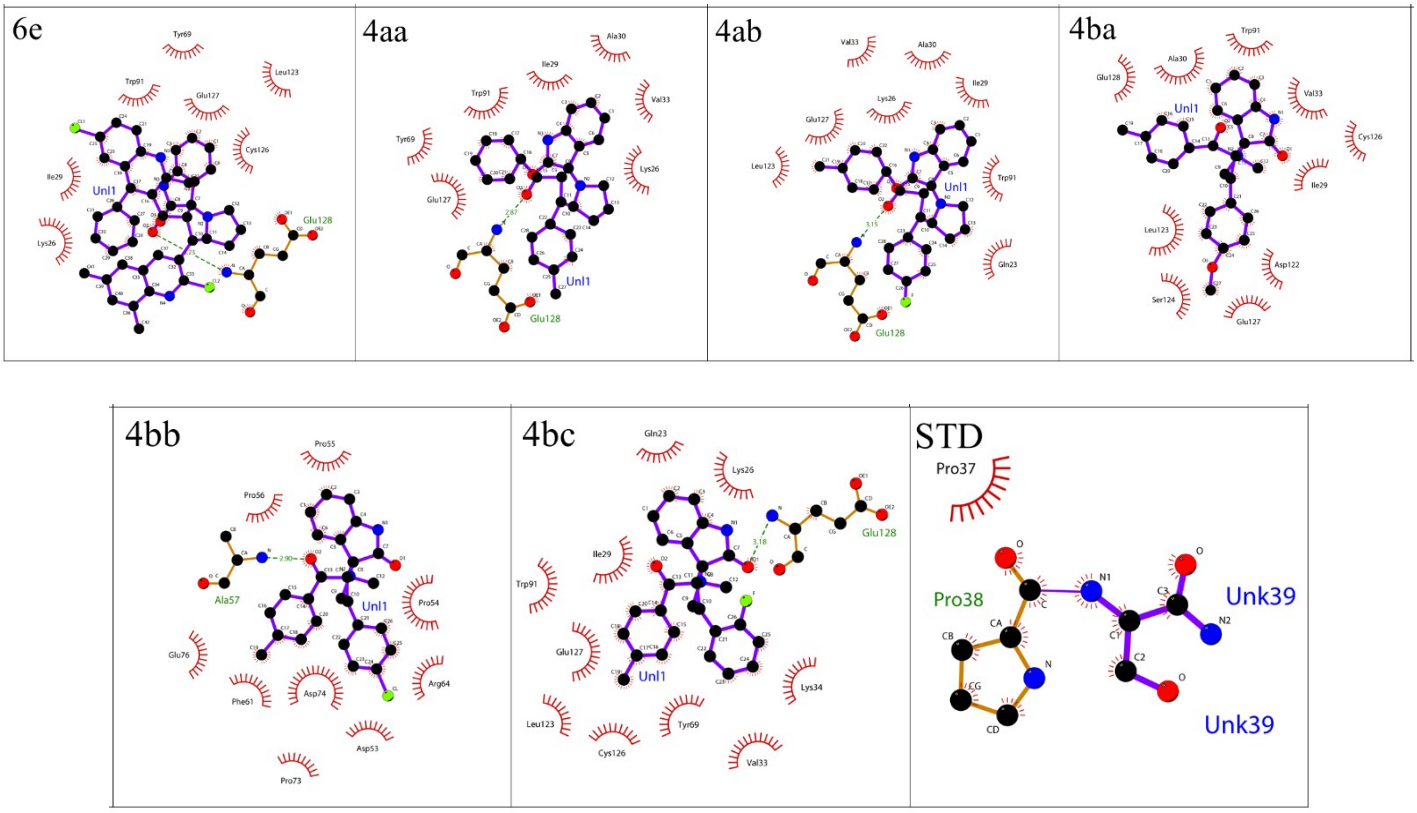


Table S6. Anti oxidant and anti-diabetic assay of the synthesised derivatives

S.no	Compound name	ABTS	DPPH	Metal chelating	H_2O_2	α-amylase	α-Glucosidase
1	**4aa**	1.62±0.21	1.46±0.21	0.96±0.23	0.63±0.12	1.47±0.27	1.48±0.32
2	**4ab**	1.54±0.30	1.22±0.34	6.91±1.10	6.15±1.12	1.11±0.41	1.52±0.35
3	**4ba**	2.70±0.60	1.23±0.39	3.21±0.76	0.88±0.06	0.99±0.06	1.25±0.24
4	**4bb**	1.42±0.31	0.80±0.07	0.46±0.08	0.41±0.04	0.98±0.25	1.46±0.31
5	**4bc**	1.50±0.45	1.68±0.34	0.86±0.09	1.16±0.35	1.52±0.40	2.22±0.57
6	**5a**	3.25±0.47	2.26±0.13	0.93±0.11	0.92±0.09	NA	0.51±0.19
7	**5b**	0.49±0.32	0.55±0.04	0.81±0.06	0.79±0.02	NA	2.73±0.52
8	**5c**	1.57±0.12	1.62±0.43	0.92±0.04	0.85±0.07	NA	0.50±0.03
9	**5d**	1.11±0.36	1.28±0.32	1.16±0.31	1.50±0.35	NA	1.02±0.34
10	**5e**	0.79±0.43	0.88±0.09	6.00±0.75	0.21±0.03	NA	0.74±0.13
11	**5f**	0.55±0.20	0.50±0.06	1.40±0.62	1.52±0.32	NA	0.30±0.05
12	**5g**	2.72±0.54	2.79±0.32	0.69±0.05	1.27±0.32	NA	0.58±0.06
13	**5h**	0.41±0.06	0.49±0.03	1.04±0.08	0.78±0.06	0.54±0.14	0.35±0.05
14	**5i**	0.86±0.09	0.92±0.05	0.77±0.22	0.57±0.09	0.28±0.07	0.31±0.07
15	**5j**	3.03±0.65	2.09±0.34	0.38±0.07	0.35±0.04	NA	1.12±0.15
16	**6a**	2.75±0.58	2.71±0.43	0.43±0.04	1.05±0.27	NA	0.41±0.04

17	**6b**	0.43±0.05	0.44±0.08	0.46±0.08	0.68±0.06	NA	0.26±0.06
18	**6c**	0.34±0.09	0.36±0.02	0.99±0.09	0.59±0.03	NA	0.32±0.07
19	**6d**	0.28±0.03	0.34±0.06	0.37±0.03	0.33±0.04	NA	0.24±0.05
20	**6e**	6.04±0.54	6.98±0.75	0.31±0.02	0.32±0.07	NA	0.27±0.02
21	**Ascorbic acid**	0.006±0.002	NA	0.0073±0.002		NA	NA
22	**Gallic acid**	NA	0.0055±0.001	NA	0.0045±0.001	NA	NA
23	**Acarbose**	NA	NA	NA	NA	0.058±0.012	0.046±0.023

2.2.4 QSAR-Studies (quantitative structure-activity relationships)

2.2.4.1 Physicochemical and Pharmacokinetic properties.

Generally, the ability of a drug after oral administration to reach its site of action depends on the drug dissolution in the GIT followed by absorption into systemic circulation, and also on the other pharmacokinetic properties such as distribution, metabolism, and elimination. Nevertheless, the poor pharmacokinetic property of the drug candidate is the main reason for most of the drug discovery failures. Hence, it is worthwhile to predict these properties to identify potential compounds for the next step of drug discovery. The advancement of computer-aided drug design tools give the opportunity to calculate number of physicochemical properties of enormous number of compound libraries and predict the ADMET properties and make decisions faster in identifying potential compound without any tubersome experiments. Recently, several standalone software and online application are growing enormously and some of these prediction tools are also approved by various regulatory agencies in new drug discovery.[2, 3]

Table S7. Physicochemical properties of the synthesized spirooxindole derivatives

Comp	MW (g/mol)	TPSA	mlogPb	n-ON	n-OH/NH	n-Viol	n-RotB	Vol
4aa	422.53	49.41	5.27	4	1	1	3	391.44
4ab	440.52	49.41	5.44	4	1	1	3	396.37
4ba	426.52	58.64	4.94	5	1	0	4	393.96
4bb	430.94	49.41	5.56	4	1	1	3	381.95
4bc	414.48	49.41	4.53	4	1	0	3	373.35
5a	584.12	62.30	7.88	5	1	2	4	516.22
5b	598.15	62.30	8.28	5	1	2	4	532.78
5c	618.56	62.30	8.44	5	1	2	4	529.76
5d	618.56	62.30	8.03	5	1	2	4	529.76
5e	663.01	62.30	8.15	5	1	2	4	534.11
5f	663.01	62.30	8.51	5	1	2	4	534.11

5g	663.01	62.30	8.52	5	1	2	4	534.11
5h	590.15	62.30	7.30	5	1	2	4	506.93
5i	634.18	62.30	8.45	5	1	2	4	560.21
5j	602.11	62.30	7.52	5	1	2	4	521.15
6a	669.61	75.19	8.30	6	1	2	4	569.59
6b	683.64	75.19	8.56	6	1	2	4	586.15
6c	683.64	75.19	8.58	6	1	2	4	586.15
6d	683.64	75.19	8.58	6	1	2	4	586.15
6e	697.67	75.19	8.77	6	1	2	4	602.72
Acarbose	**645.61**	**321.16**	**-5.51**	**19**	**14**	**3**	**9**	**544.93**

Table S8. Pharmacokinetic properties of the synthesized spirooxindole derivatives

	Absorption		**Distribution**	**Toxicity**	
COMP	**Water Solubility** Log mol/L	**Intestinal absorption** % absorbed	**BBB permeability** Log BB	**AMES Toxicity**	**Hepato toxicity**
4aa	-3.223	92.734	-0.081	Yes	No
4ab	-3.317	92.776	-0.106	Yes	Yes
4ba	-3.321	94.527	-0.249	Yes	Yes
4bb	-3.242	92.029	-0.11	Yes	No
4bc	-3.423	93.579	-0.285	No	No
5a	-3.336	92.963	-0.287	No	Yes
5b	-3.329	92.987	-0.301	No	Yes
5c	-3.313	91.529	-0.314	No	No
5d	-3.335	91.604	-0.333	No	No
5e	-3.331	91.537	-0.334	No	No
5f	-3.338	92.257	-0.306	No	No
5g	-3.309	91.462	-0.315	No	No
5h	-3.402	91.366	-0.31	No	Yes
5i	-3.027	92.803	-0.294	No	No
5j	-3.138	93.08	-0.685	No	Yes
6a	-3.083	92.353	-0.626	No	Yes
6b	-3.11	93.166	-0.637	No	No
6c	-3.081	93.022	-0.632	No	No

6d	-3.104	92.401	-0.637	No	No
6e	-3.129	92.755	-0.644	No	No
Acarbose	**-1.99**	**6.22**	**-2.712**	**No**	**No**

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