Supporting Information

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Synthesis and molecular docking studies of dispiropyrrolidine oxindole derivatives as a therapeutics agent against methicillin-resistant *Staphylococcus aureus* (MRSA)

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Supplementary information

Characterisation data and NMR Spectrum for compounds **3** and **5a-g**

Phenethyl-4-piperidinone (**3**)

Dark brown crystal. (1.1 g, 57%), m.p 58-62 °C, FTIR (ATR, cm^{-1}): 2928 (C-H), 1710 (C=O), 1218 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.48 (t, J=6.0 Hz, 4H, H8), 2.71-2.74 (m, 2H, H1), 2.81-2.86 (m, 6H, H2 & H7), 7.21-7.22 (m, 3H, H5 & H6), 7.28-7.31 (m, 2H, H4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.1 (C2), 41.2 (C7), 53.1 (C1), 59.3 (C8), 128.2 (C6), 128.5 (C4), 128.7 (C5), 140.0 (C3), 209.2 (C9). HRMS (ESI): *m/z* 204.1336 (MH^+ $C_{13}H_{18}NO^+$ requires 204.1338).

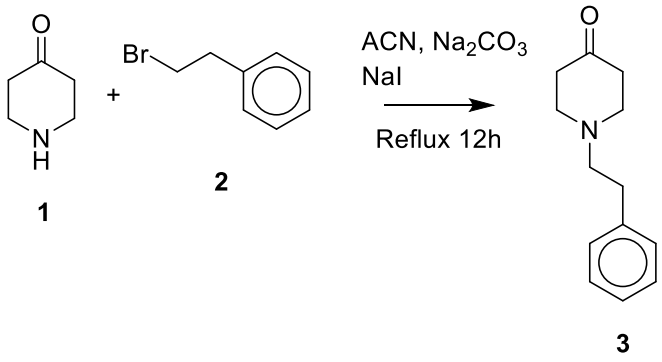

Figure S1: Reaction scheme of compound **1**

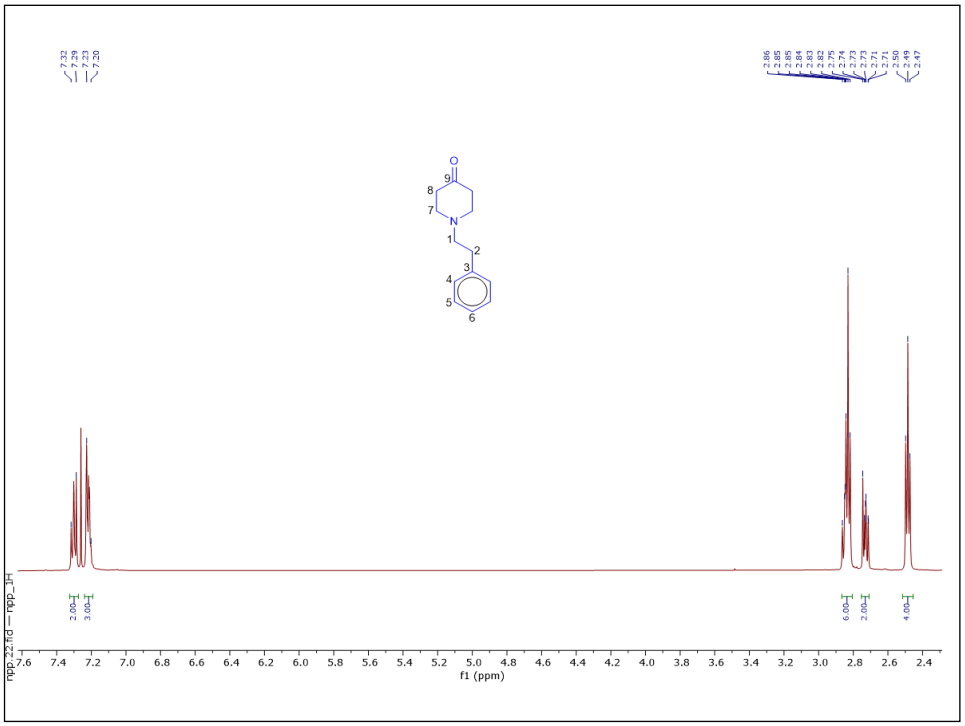

Figure S2: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **1**

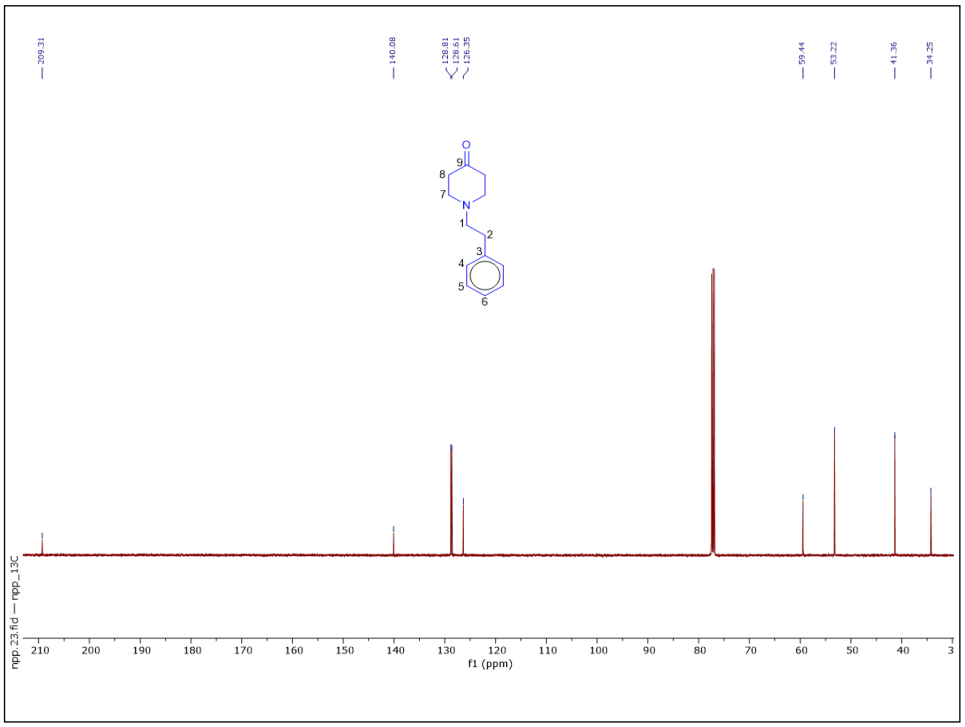

Figure S3: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **1**

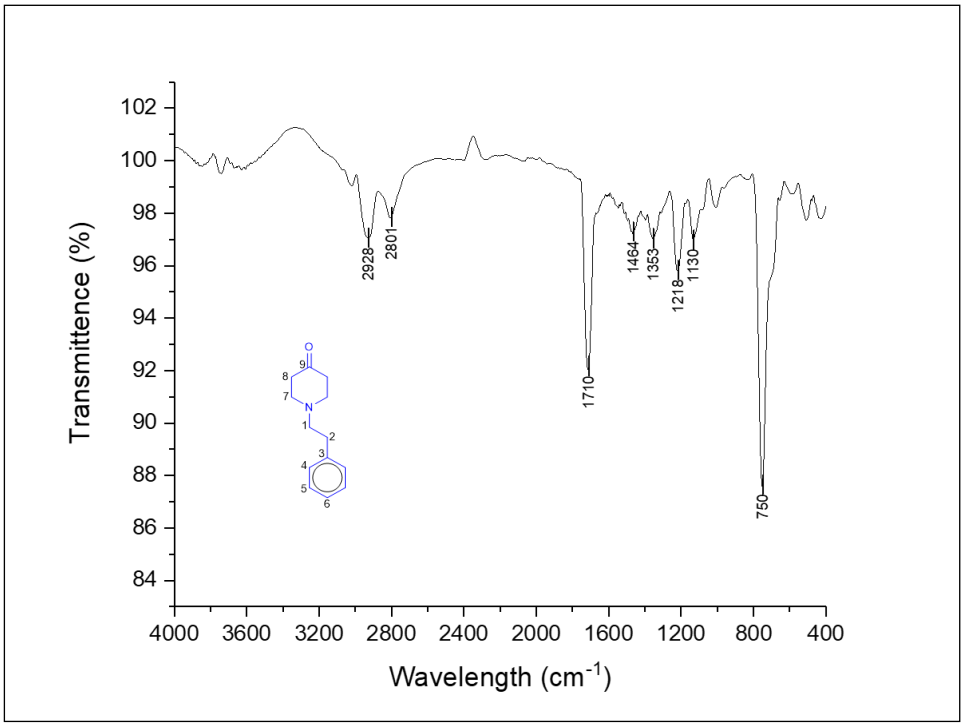

Figure S4: FT-IR spectrum of compound **1**

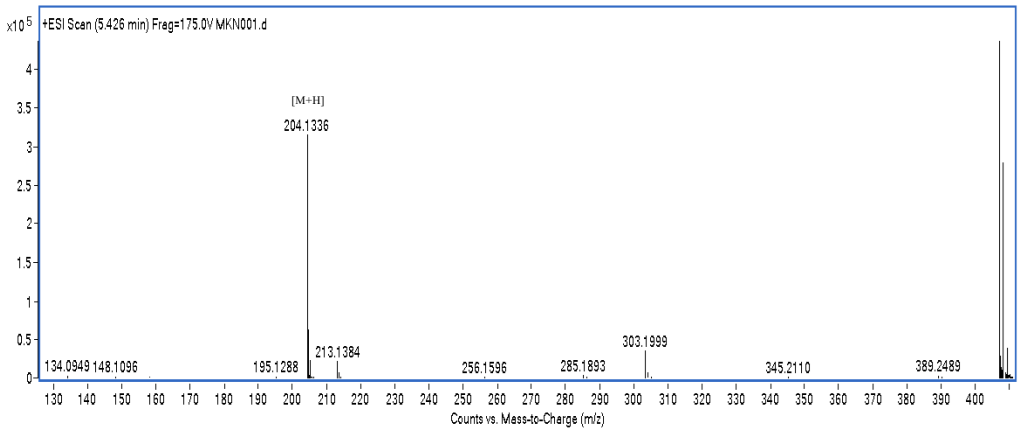

Figure S5: HRMS spectrum for compound **1**

(3*E*,5*E*)-3,5-bis(benzylidene)-1-phenylethyl-4-piperidone (**5a**)

Yellow solid. (0.33 g, 88%), m.p 116-118 °C, FTIR (ATR, cm-1): 3034 (w, C-H), 1672 (s, C=O) 1598 (s, C=C), 1176 (s, C-N). 1H NMR (500 MHz, CDCl3):δ 2.72-2.75 (m, 2H, H2), 2.81-2.84 (m, 2H, H1), 3.91 (s, 4H, H7), 7.11-7.13 (m, 3H, H4 & H6), 7.22-7.26 (m, 2H, H5), 7.37-7.43 (m, 10H, H12-H14), 7.84 (br s, 2H, H10).13C NMR (125 MHz, CDCl3): δ 34.2 (C2), 54.9 (C7), 58.8 (C1), 126.3 (C6), 128.5 (C4), 128.7 (C5), 128.8 (C13), 129.2 (C14), 130.5 (C12), 133.3 (C8), 135.2 (C11), 136.8 (C10), 139.9 (C3), 187.6 (C9). HRMS (ESI): m/z 380.1985 (MH+ C27H26NO + requires 380.2014).

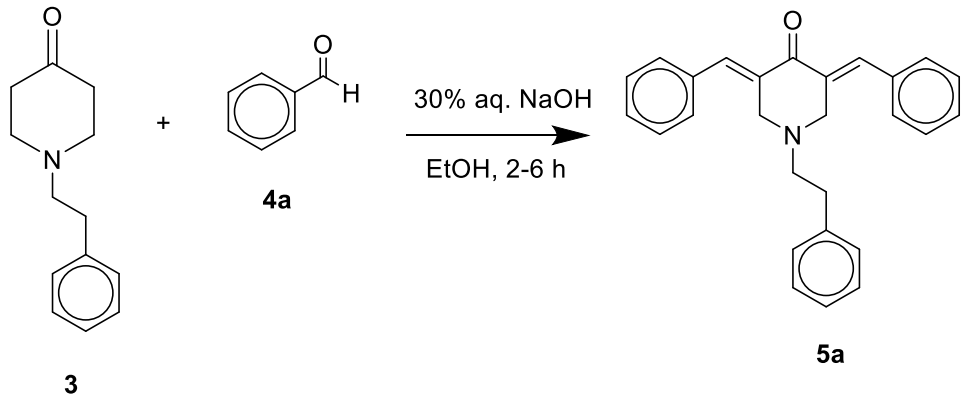

Figure S6: Reaction scheme of compound **5a**

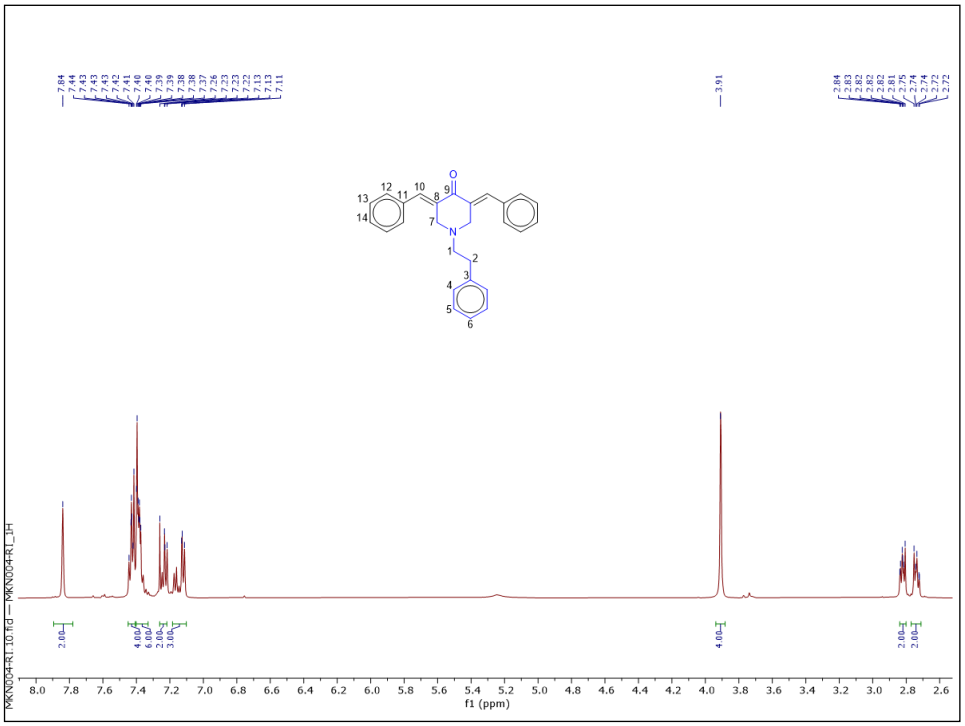

Figure S7: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5a**

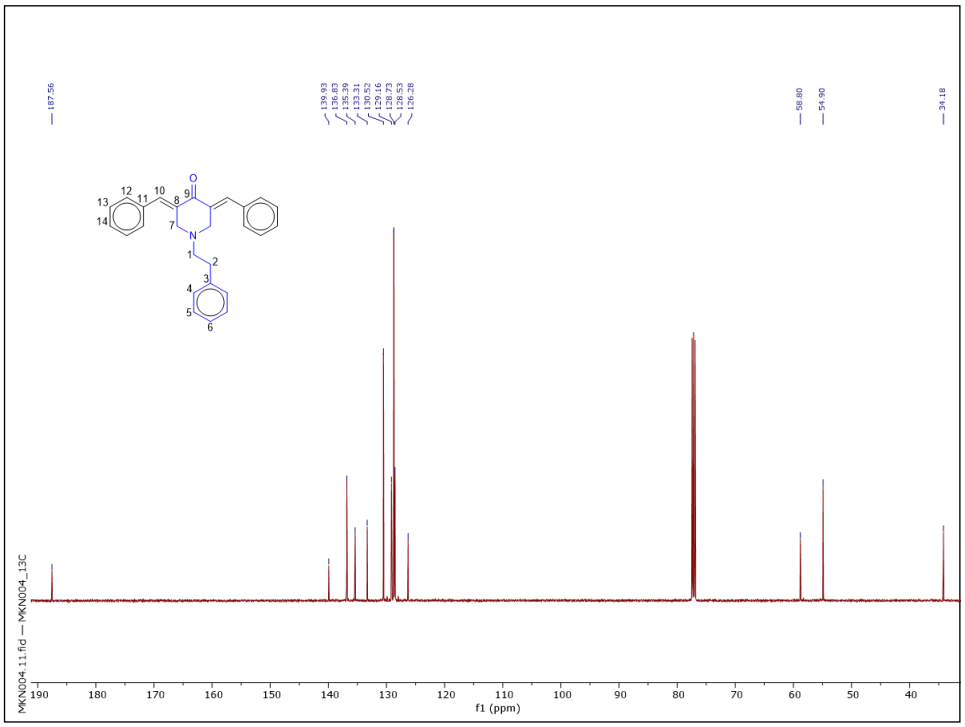

Figure S8: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5a**

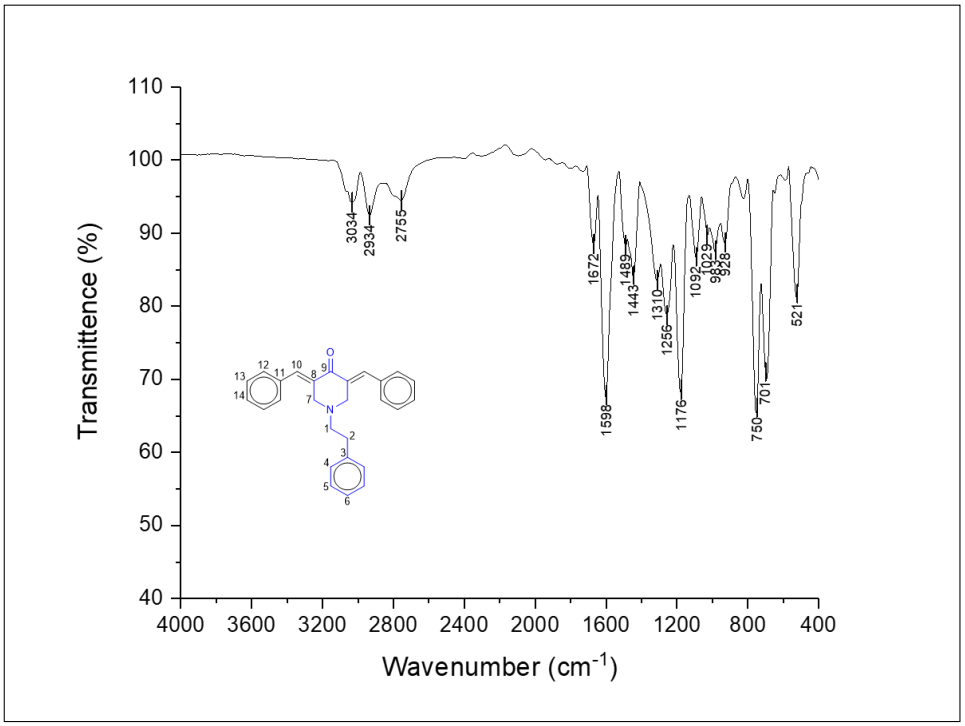

Figure S9: FT-IR spectrum of compound **5a**

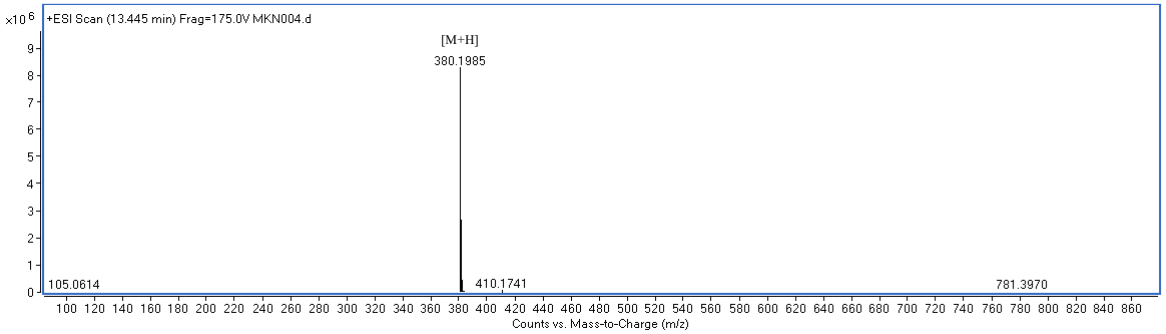

Figure S10: HRMS spectrum for compound **5a**

(3*E*,5*E*)-3,5-bis(4-methylbenzylidene)-1-phenylethyl-4-piperidone (**5b**)

Yellow solid. (0.37 g, 90%), m.p 120-124 °C, FTIR (ATR, cm^{-1}): 3022 (w, C-H), 1667 (m, C=O) 1601 (s, C=C), 1190 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (s. 6H, H15), 2.73-2.77 (m, 2H, H2), 2.81-2.84 (m, 2H, H1), 3.91 (s, 4H, H7), 7.12-7.15 (m, 2H, H4), 7.16-7.18 (m, 1H, H6), 7.22-7.25 (m, 6H, H5 & H13), 7.29 (d, *J*= 8.0 Hz, 4 H, H12), 7.81 (br s, 2 H, H10). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9 (C15), 34.5 (C2), 55.3 (C7), 59.3 (C1), 126.6 (C6), 128.9 (C4), 129.1 (C5), 129.8 (C13), 131.0 (C12), 132.8 (C11), 132.9 (C8), 134.2 (C10), 139.8 (C14), 140.3 (C3), 187.9 (C9). HRMS (ESI): *m/z* 408.2214 (MH^+ $C_{29}H_{30}NO^+$ requires 408.2327).

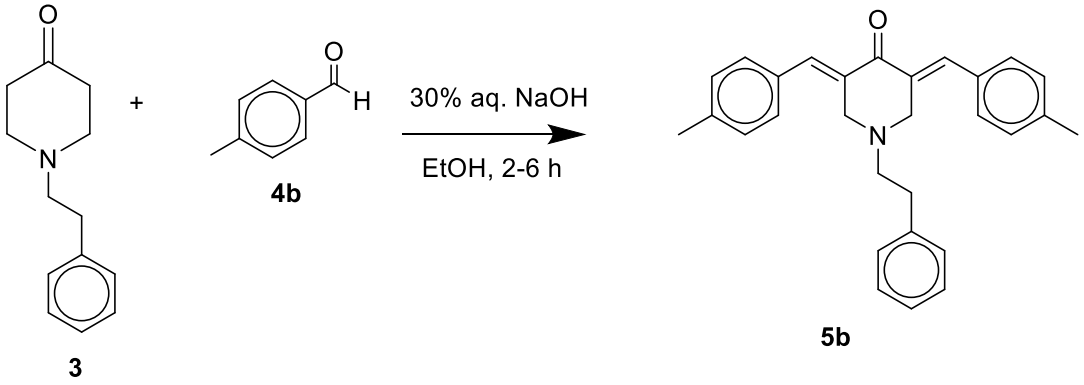

Figure S11: Reaction scheme of compound **5b**

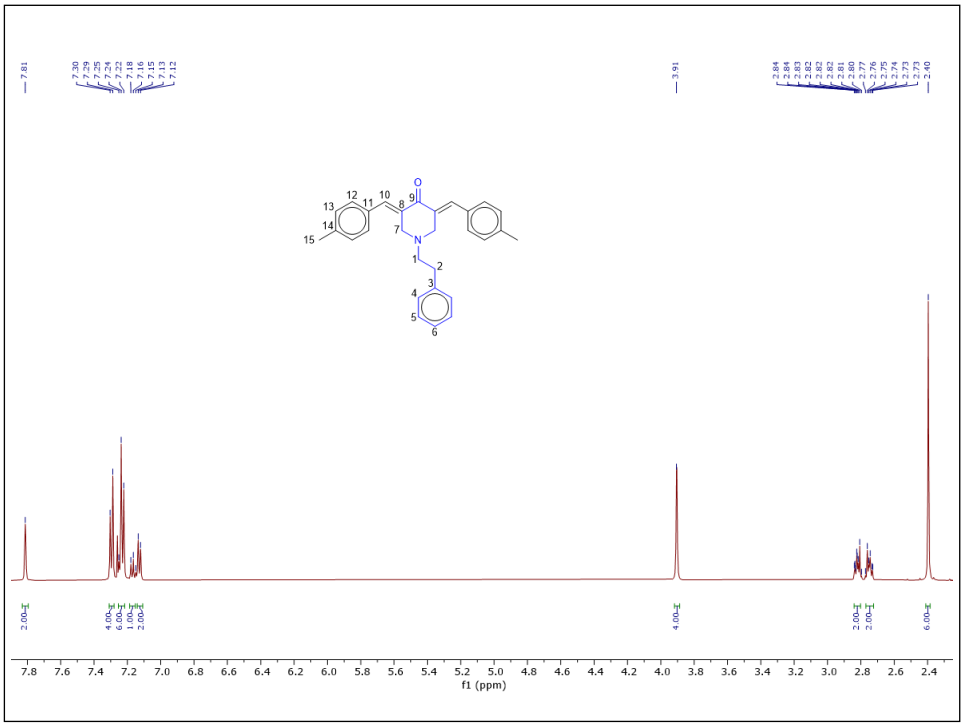

Figure S12: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5b**

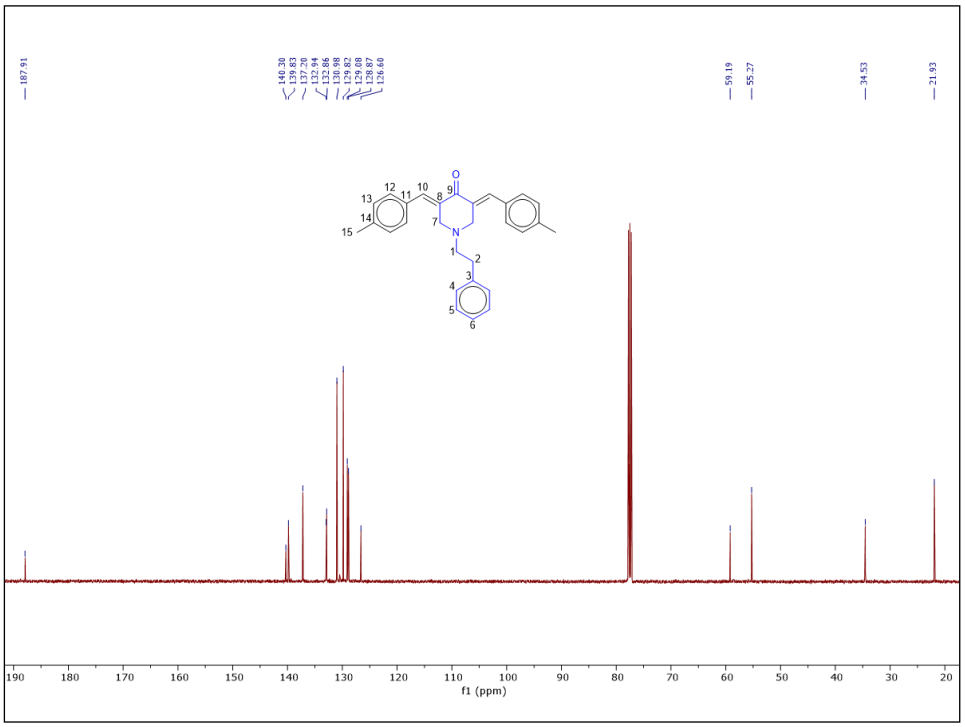

Figure S13: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5b**

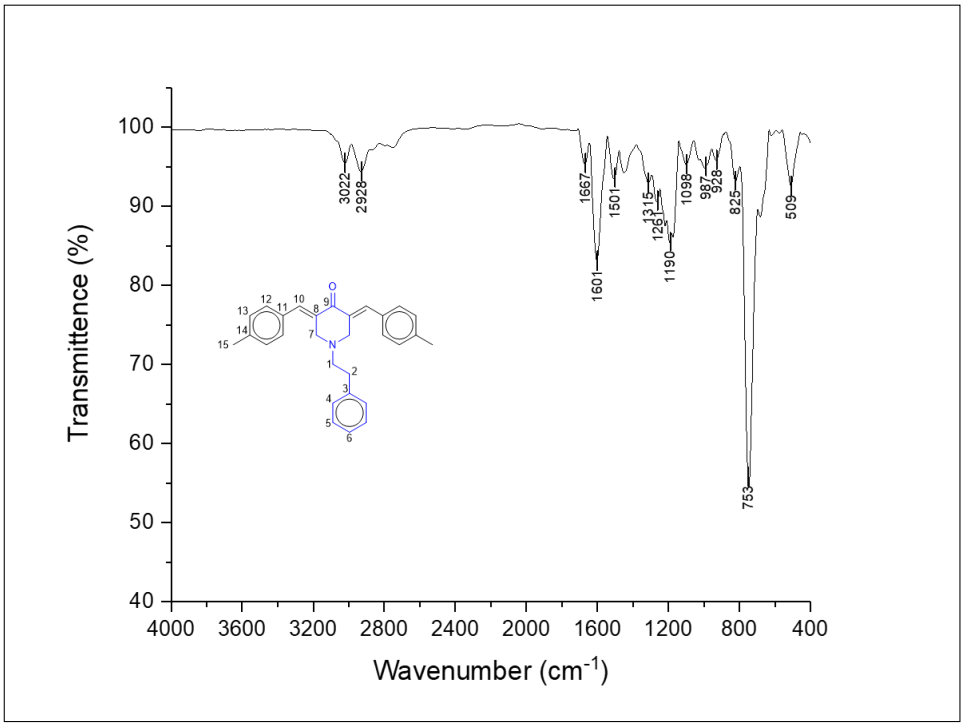

Figure S14: FT-IR spectrum of compound **5b**

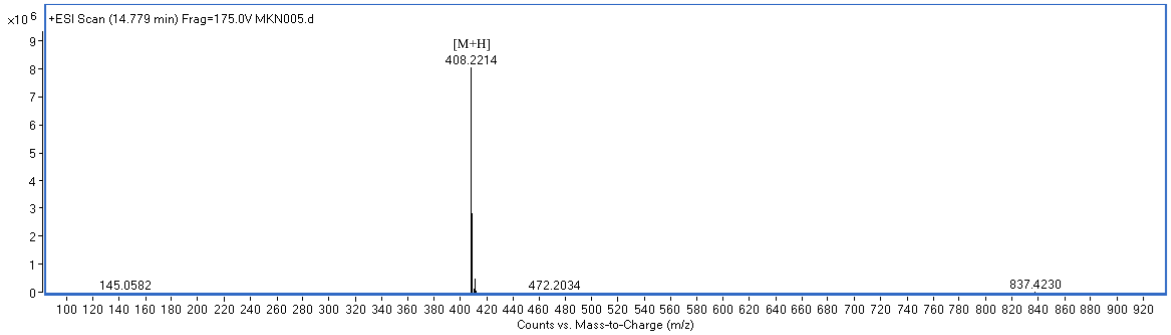

Figure S15: HRMS spectrum for compound **5b**

(3*E*,5*E*)-3,5-bis(4-methoxybenzylidene)-1-phenylethyl-4-piperidone (**5c**)

Yellow solid. (0.36 g, 83%), m.p 148-152 °C, FTIR (ATR, cm^{-1}): 3015 (w, C-H),1664 (m, C=O), 1586 (m, C=C), 1248 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.75-2.78 (m, 2H, H2), 2.83-2.86 (m, 2H, H1), 3.86 (s, 6H, H15), 3.90 (br s, 4H, H7), 6.95 (d, *J*=8.5 Hz, 4H, H12), 7.14-7.18 (m, 3H, H4 & H6) 7.23 (br t, *J*=8.5 Hz, 2H, H5), 7.23-7.26 (m, 2H, H5), 7.36 (d, *J*=8.5 Hz, 4H, H13), 7.79 (br s, 2H, H10). ^{13}C NMR (125 MHz, $CDCl_3$,): δ 34.3 (C2), 55.0 (C7), 55.5 (C15), 58.9 (C1), 114.3 (C13), 126.3 (C6), 128.2 (C8), 128.6 (C4), 128.8 (C5), 131.5 (C11), 132.5 (C12), 136.44 (C10), 140.1 (C3), 160.4 (C14), 187.4 (C9). HRMS (ESI): *m/z* 440.2139 (MH^+ $C_{29}H_{30}NO_3^+$ requires 440.2226).

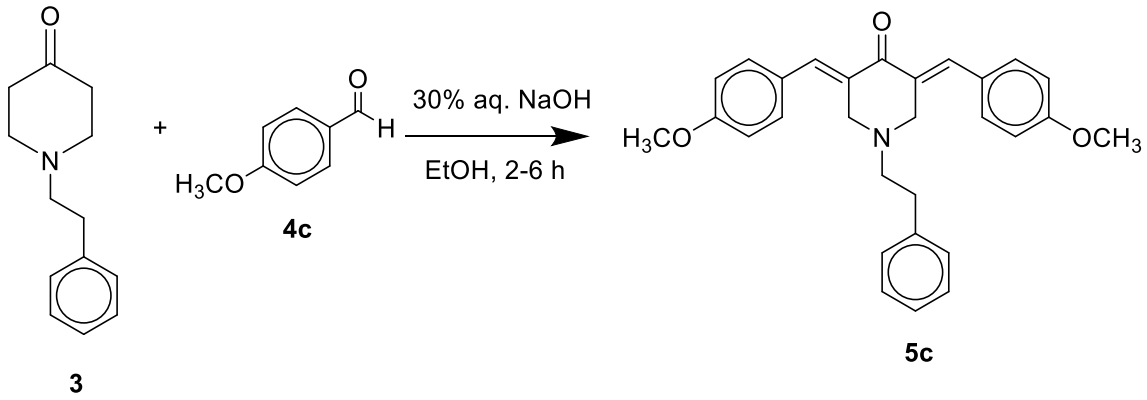

Figure S16: Reaction scheme of compound **5c**

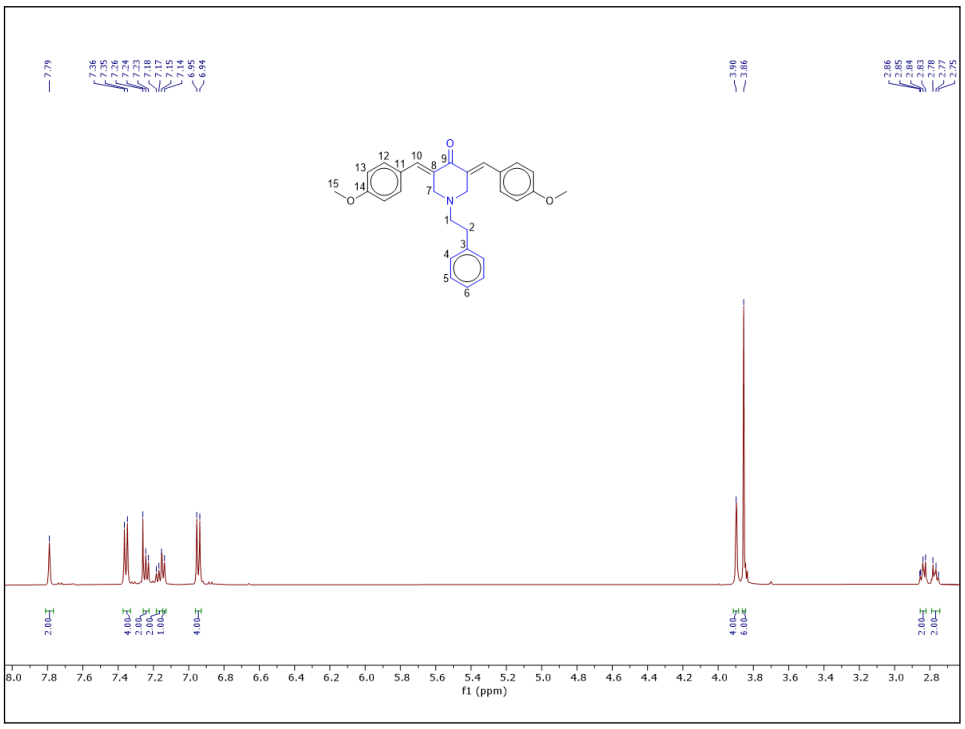

Figure S17: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5c**

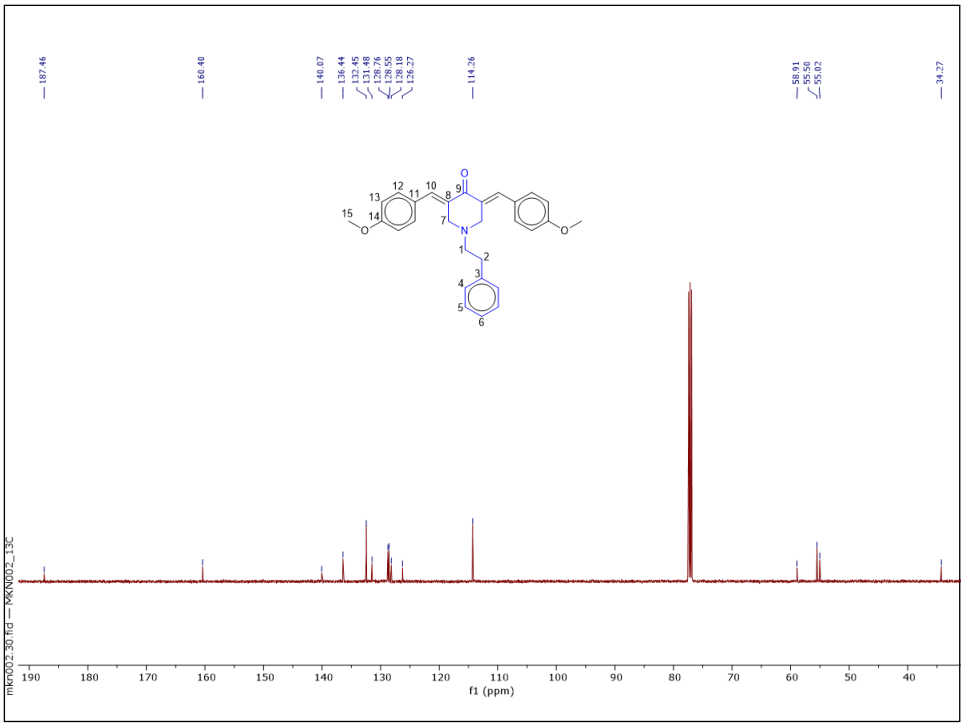

Figure S18: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5c**

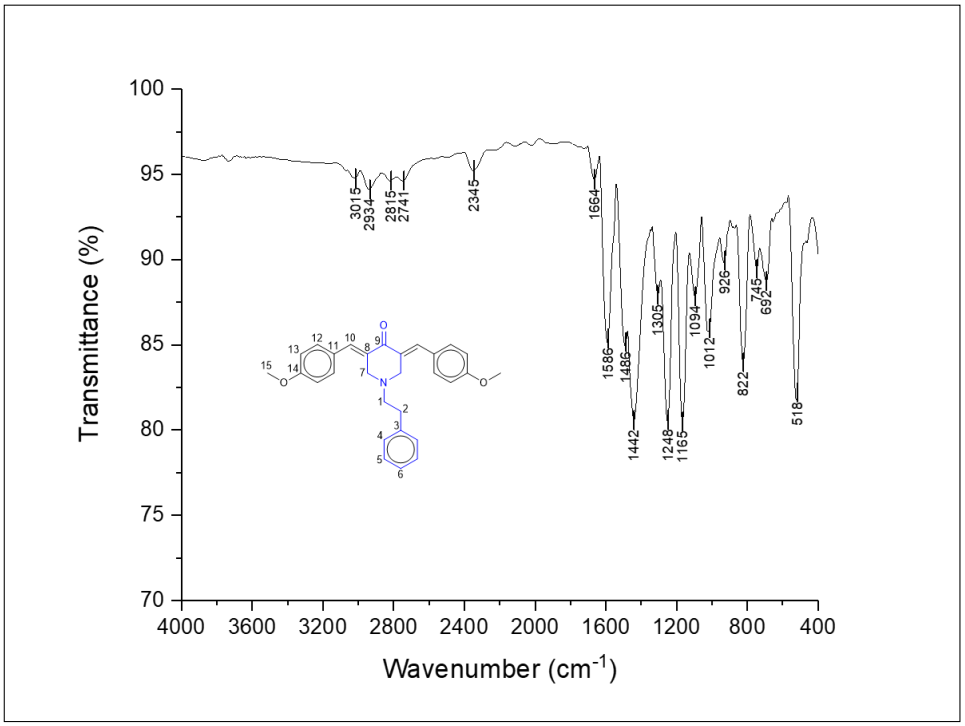

Figure S19: FT-IR spectrum of compound **5c**

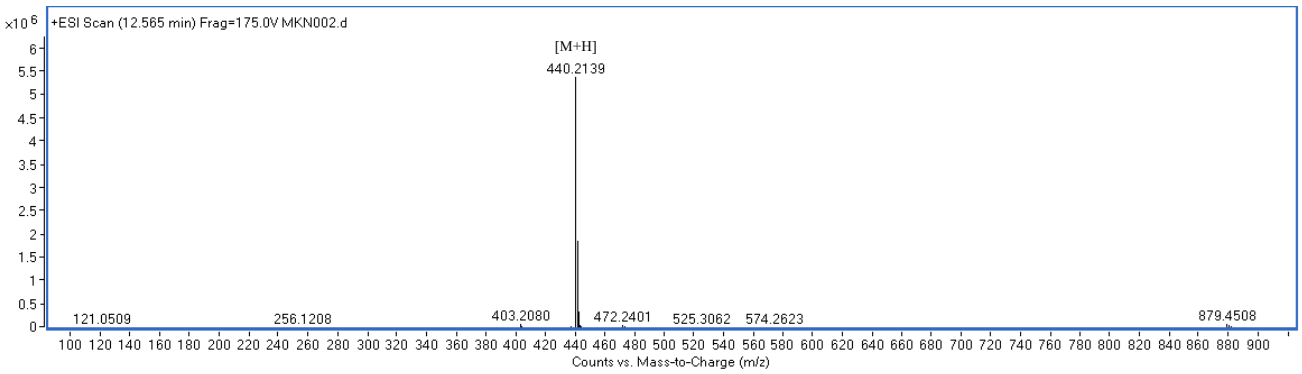

Figure S20: HRMS spectrum for compound **5c**

(3*E*,5*E*)-3,5-bis(2-methoxybenzylidene)-1-phenylethyl-4-piperidone (**5d**)

Yellow solid. (0.36 g, 83%), m.p 148-152 °C, FTIR (ATR, cm^{-1}): 2945 (w, C-H),1660 (m, C=O), 1589 (m, C=C), 1236 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$) : δ 2.61-2.65 (m, 2H, H2), 2.71-2.74 (m, 2H, H1), 3.83 (br s, 4H, H7), 3.86 (s, 6H, H13), 6.92 (d, *J*=8.0 Hz, 2H, H17), 6.97 (t, *J*=8.0 Hz, 2H, H15), 7.06 (d, *J*=8.0 Hz, 2H, H4), 7.13 (t, *J*=8.0 Hz, 1H, H6), 7.18 (dd, *J*=8.0, 2.0 Hz, 2H, H14), 7.20 (t, *J*=8.0 Hz, 2H, H5), 7.34 (dt, *J*=8.0, 2.0 Hz, 2H, H16), 8.08 (s, 2H, H10). ^{13}C NMR (125 MHz, $CDCl_3$,): δ 34.2 (C2), 54.7 (C7), 55.6 (C13), 58.1 (C1), 110.9 (C14), 120.2 (C16), 124.6 (C8), 126.2 (C6), 128.4 (C4), 128.7 (C5), 130.41 (C11), 130.6 (C15), 133.1 (C10), 133.2 (C17), 140.1 (C3), 158.6 (C12), 187.7 (C9). HRMS (ESI): *m/z* 440.2040 (MH^+ $C_{29}H_{30}NO_3^+$ requires 440.2226).

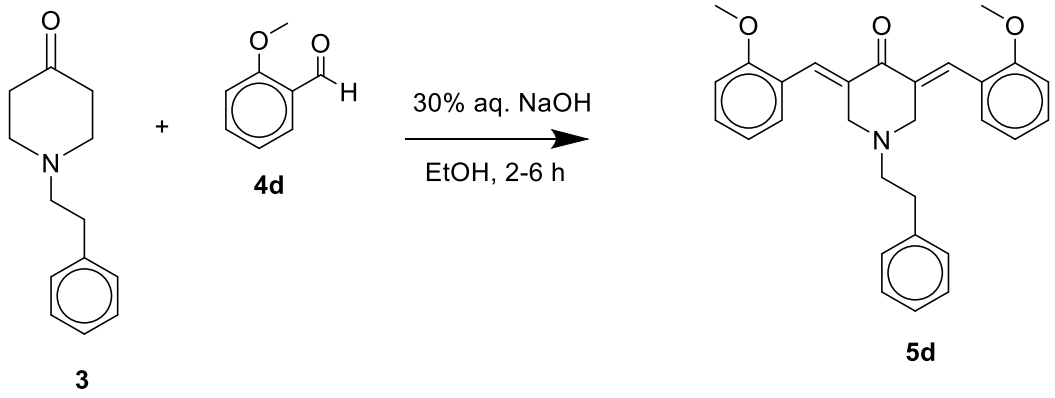

Figure S21: Reaction scheme of compound **5d**

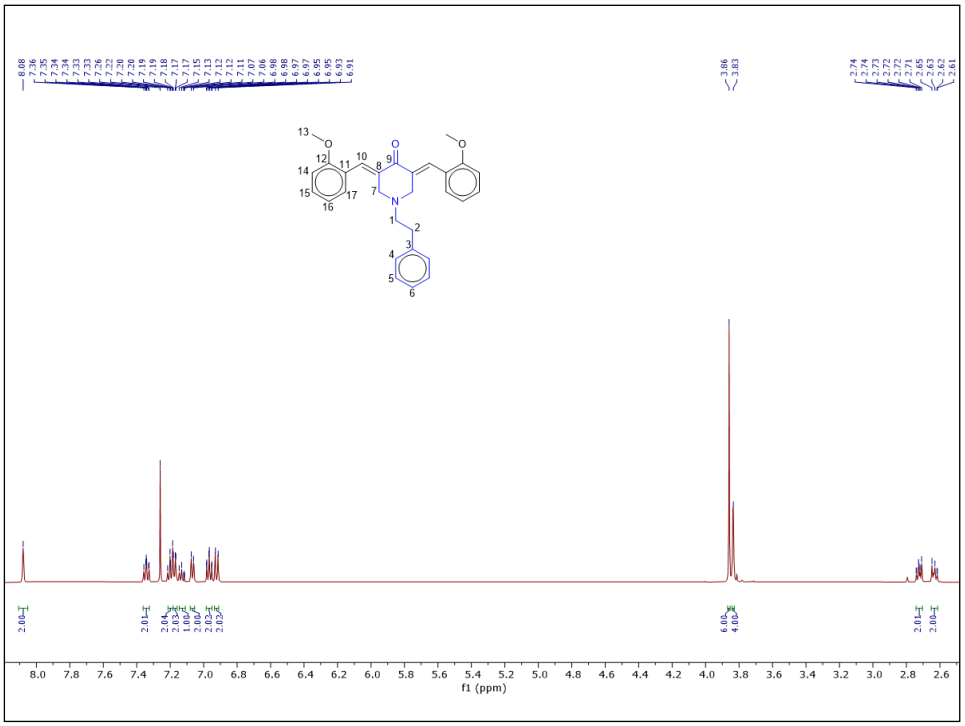

Figure S22: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5d**

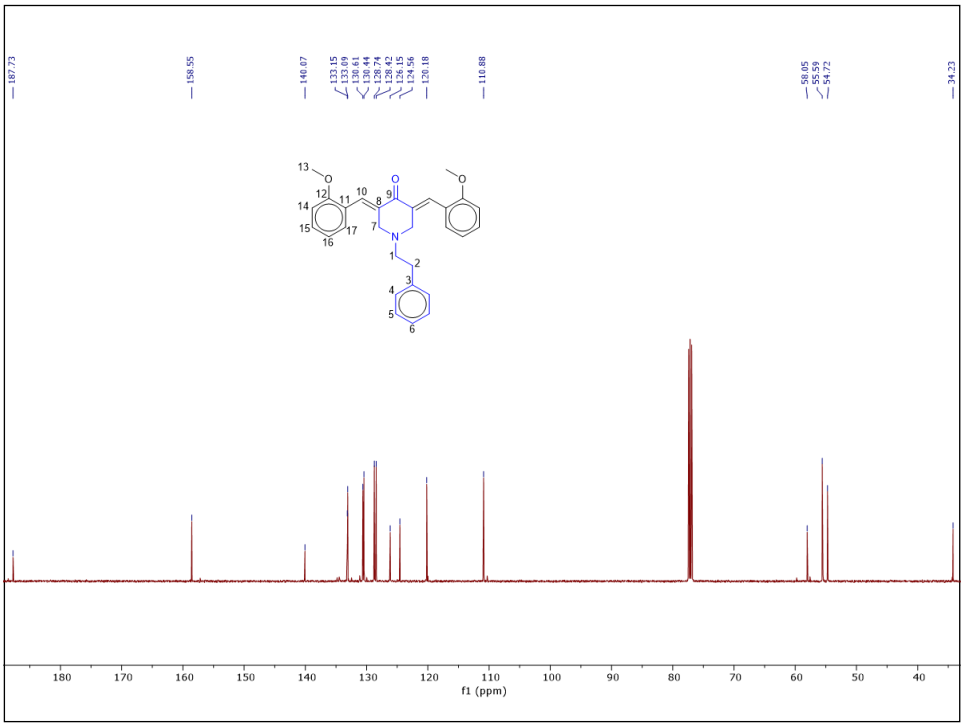

Figure S23: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5d**

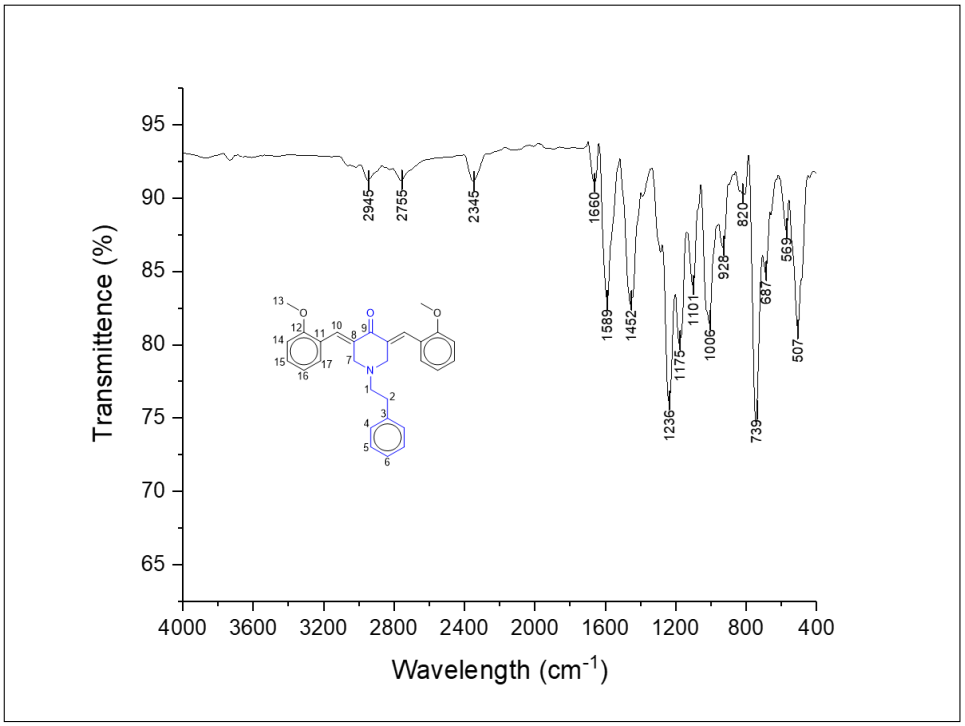

Figure S24: FT-IR spectrum of compound **5d**

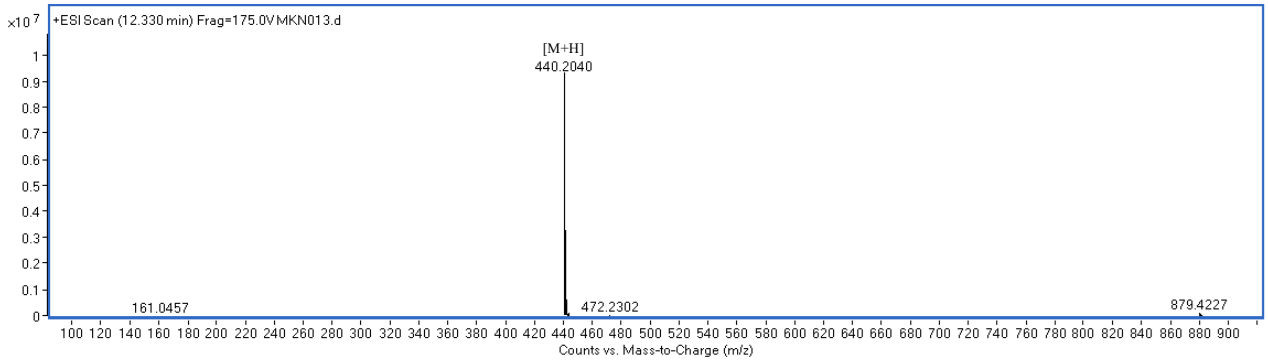

Figure S25: HRMS spectrum for compound **5d**

(3*E*,5*E*)-3,5-bis(2,4-methoxybenzylidene)-1-phenylethyl-4-piperidone (**5e**)

Yellow solid. (0.43 g, 96%), m.p 128-132 °C, FTIR (ATR, cm^{-1}): 3006 (w, C-H), 1728 (m, C=O), 1455(m, C=C), 1236 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64-2.68 (m, 2H, H2), 2.73-2.76 (m, 2H, H1), 3.84 (s, 12H, H13 & H16), 3.85 (s, 4H, H7), 6.47 (d, *J*=2.0 Hz, 2H, H14), 6.50 (dd, *J*=8.0, 2.0 Hz, 2H, H18), 7.08-7.15 (m, 5H, H4, H5, H6), 7.21 (d, *J*=8.0 Hz, 2H, H17), 8.06 (br s, 2H, H10). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.2 (C2), 55.0 (C7), 55.6 (C16), 55.7 (C13), 58.3 (C1), 98.5 (C14), 104.6 (C17), 126.2 (C6), 128.4 (C4), 128.5 (C5), 128.8 (C18), 128.9 (C8), 131.4 (C10), 132.2 (C11), 140.1 (C3), 160.1 (C15), 162.1 (C12), 187.6 (C9). HRMS (ESI): *m/z* 500.2320 (MH^+ $C_{31}H_{34}NO_5^+$ requires 500.2437).

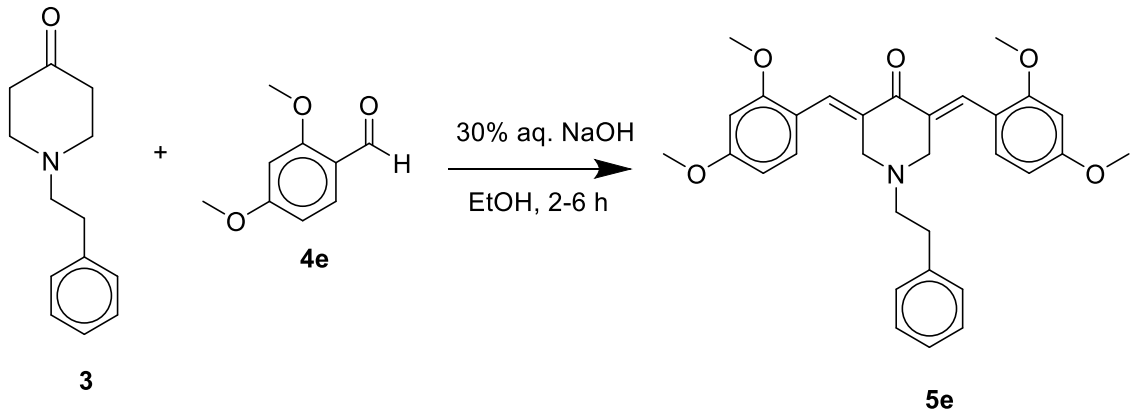

Figure S26: Reaction scheme of compound **5e**

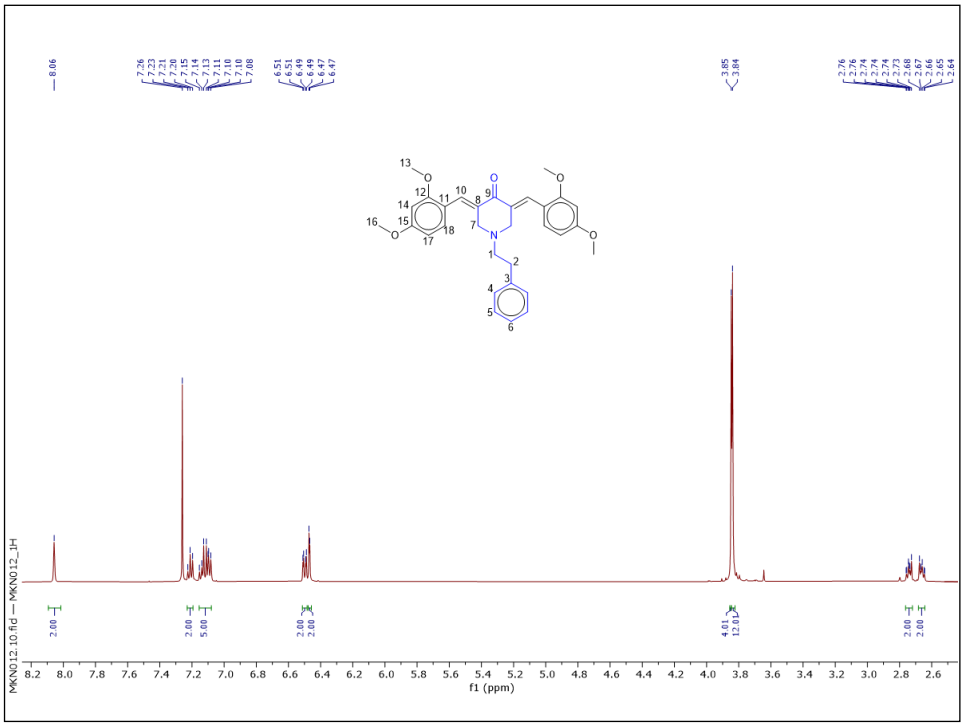

Figure S27: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5e**

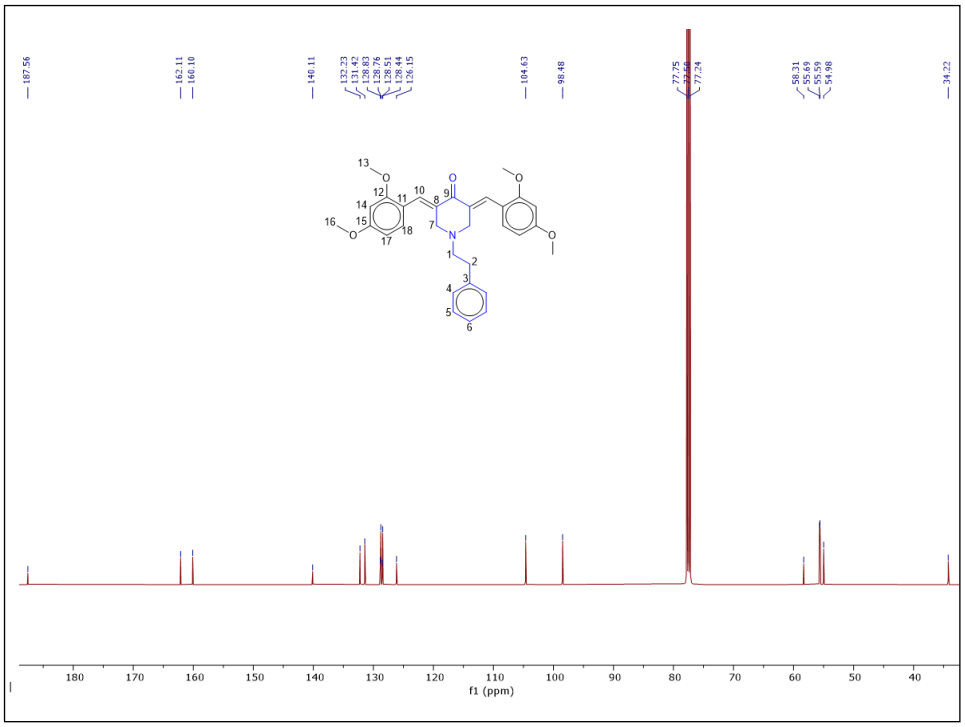

Figure S28: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5e**

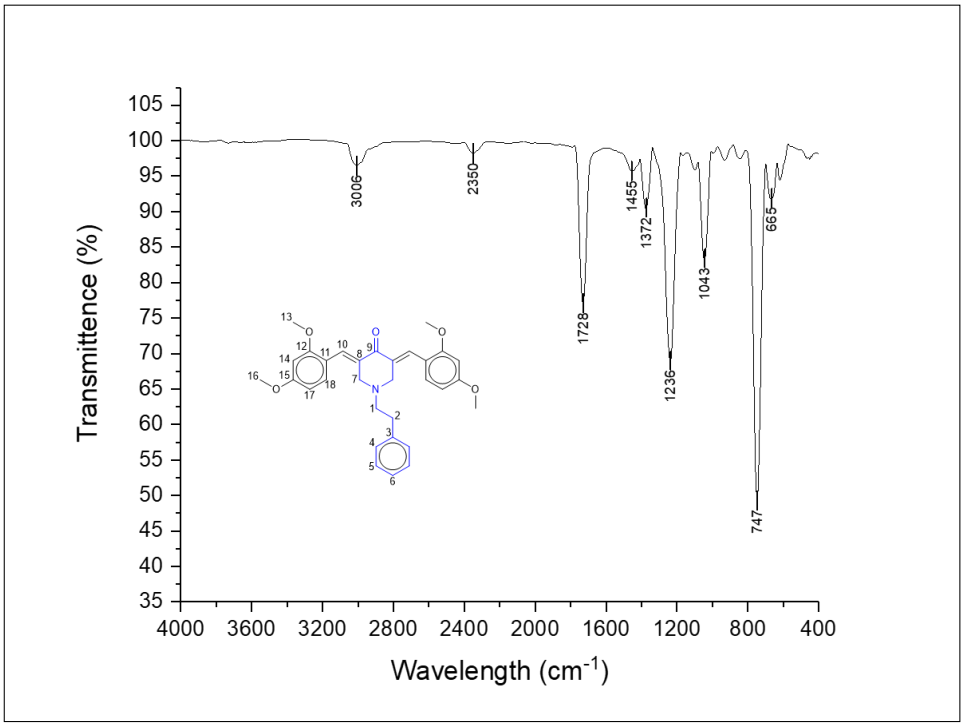

Figure S29: FT-IR spectrum of compound **5e**

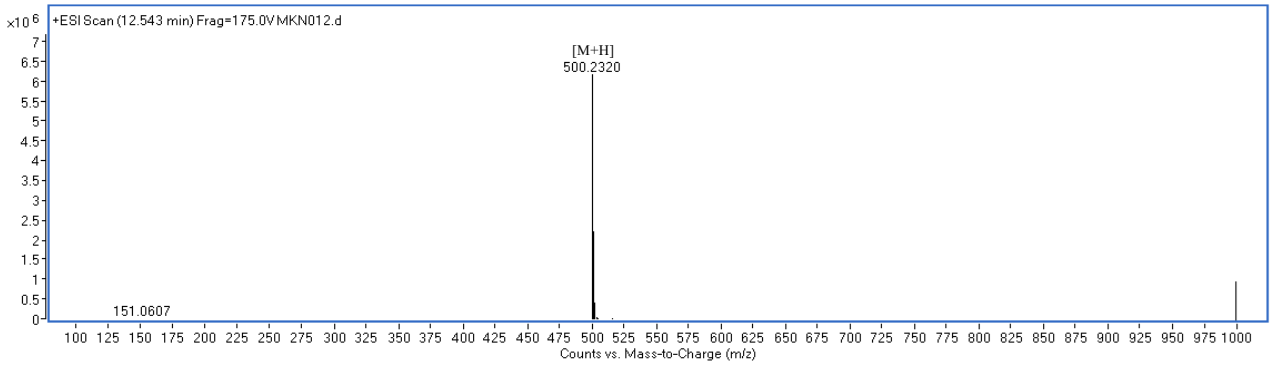

Figure S30: HRMS spectrum for compound **5e**

(3*E*,5*E*)-3,5-bis(4-chlorobenzylidene)-1-phenylethyl-4-piperidone (**5f**)

Yellow solid. (0.41 g, 96%), m.p 128-132 °C, FTIR (ATR, cm^{-1}): 3038 (w, C-H), 1663 (m, C=O), 1588 (m, C=C), 1269 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.73-2.76 (m, 2H, H2), 2.81-2.84 (m, 2H, H1), 3.84 (s, 4H, H7), 7.11-7.13 (m, 2H, H5), 7.16-7.18 (m, 1H, H6), 7.22 (m, 2H, H4), 7.29 (m, 4H, H13), 7.38-7.40 (m, 4H, H12), 7.75 (br s, 2H, H10). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.6 (C2), 55.2 (C7), 59.1 (C1), 126.7 (C6), 128.5 (C4), 128.9 (C5), 129.0 (C13), 129.4 (C12), 132.1 (C8), 133.9 (C11), 135.6 (C10), 135.9 (C14), 140.2 (C3), 187.5 (C9). HRMS (ESI): *m/z* 448.1188 (MH^+ $C_{27}H_{24}{}^{35}Cl_2NO^+$ requires 448.1235).

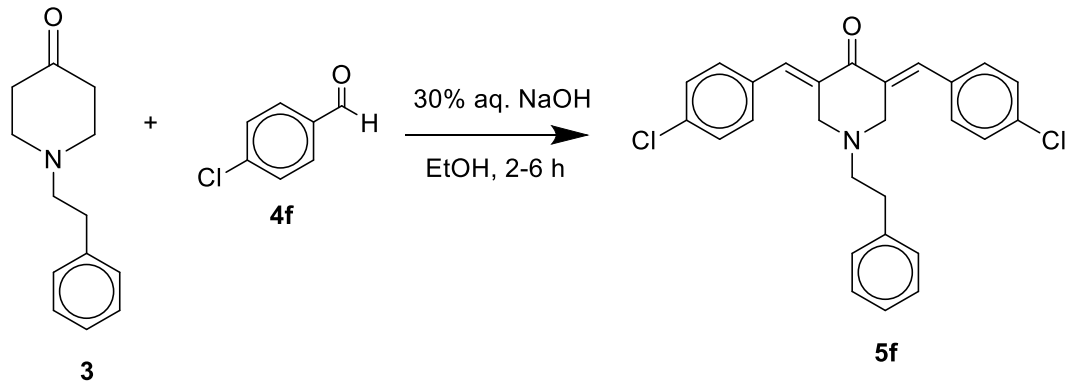

Figure S31: Reaction scheme of compound **5f**

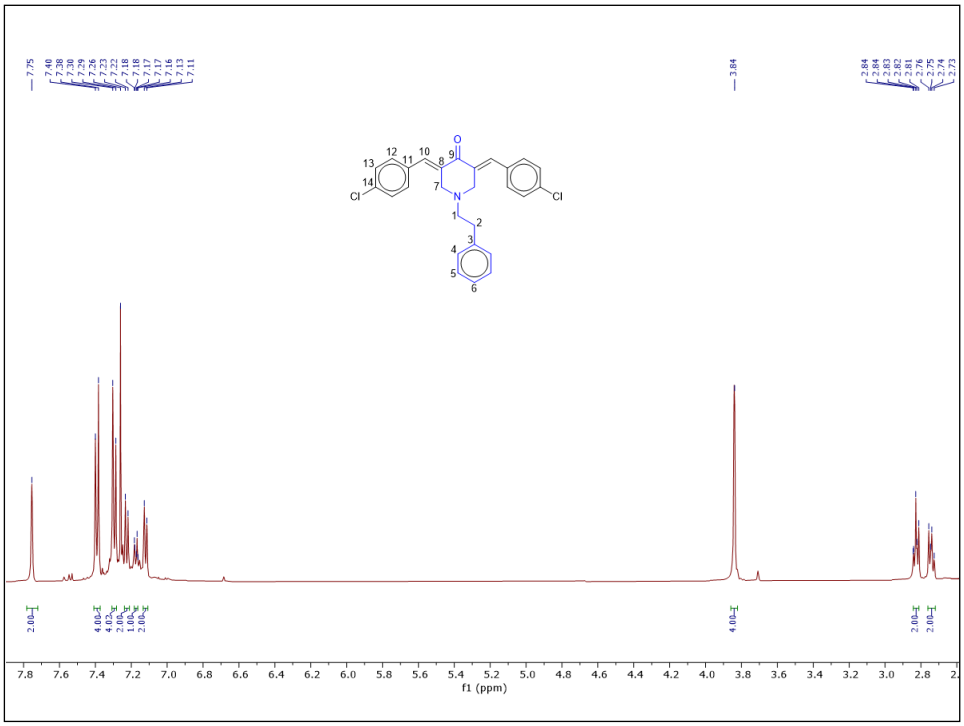

Figure S32: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5f**

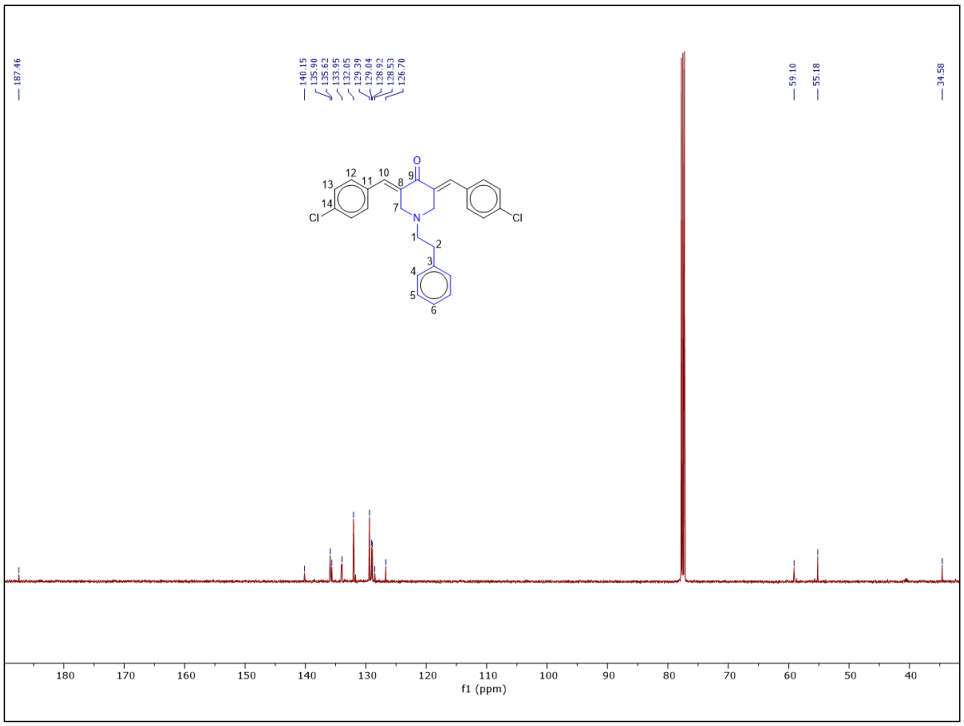

Figure S33: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5f**

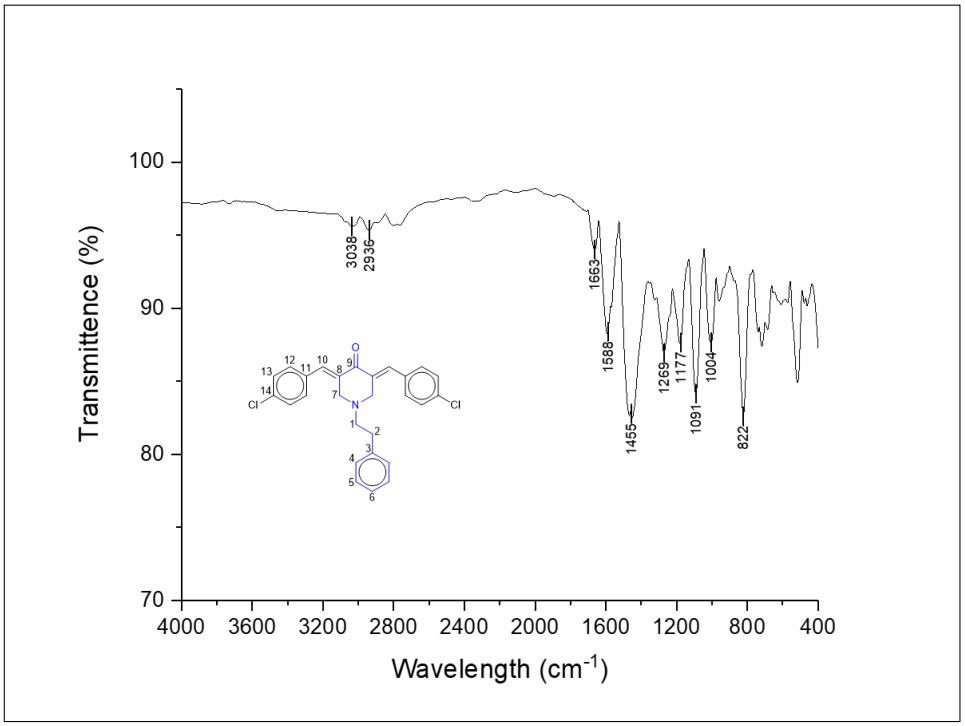

Figure S34: FT-IR spectrum of compound **5f**

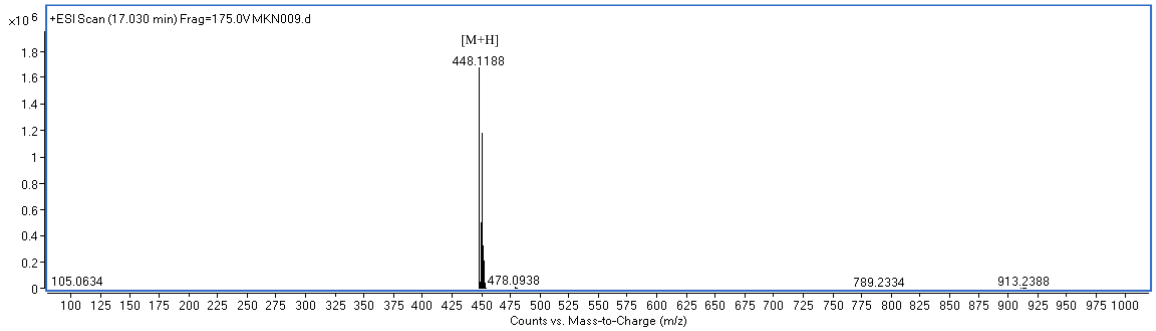

Figure S35: HRMS spectrum for compound **5f**

(3*E*,5*E*)-3,5-bis(4-bromobenzylidene)-1-phenylethyl-4-piperidone (**5g**)

Yellow solid. (0.48 g, 89%), m.p 130-134 °C, FTIR (ATR, cm^{-1}): 3022 (w, C-H), 1673 (m, C=O), 1602 (m, C=C), 1205 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72-2.75 (m, 2H, H2), 2.81-2.84 (m, 2H, H1), 3.83 (s, 4H, H7), 7.11-7.13 (m, 2H, H5) 7.17-7.18 (m, 1H, H6), 7.20-7.25 (m, 6H, H4 & H13), 7.55 (d, *J*=8.0 Hz, 4H, H12), 7.73 (br s, 2H, H10). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.3 (C2), 54.9 (C7), 58.8 (C1), 123.7 (C14), 126.4 (C6), 128.6 (C4), 128.7 (C5), 131.9 (C13), 132.0 (C12), 133.7 (C8), 134.2 (C11), 135.6 (C10), 139.8 (C3), 187.1 (C9). HRMS (ESI): *m/z* 537.9303 (MH^+ $C_{27}H_{24}{}^{79}Br^{81}BrNO^+$ requires 538.0146).

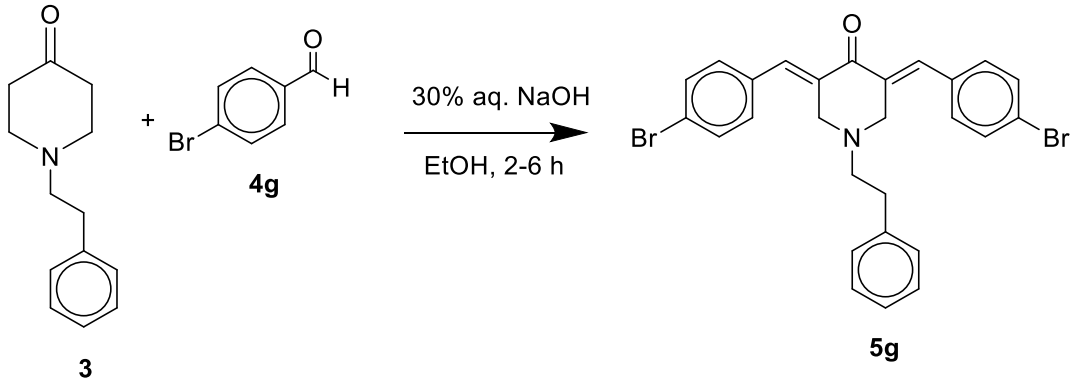

Figure S36: Reaction scheme of compound **5g**

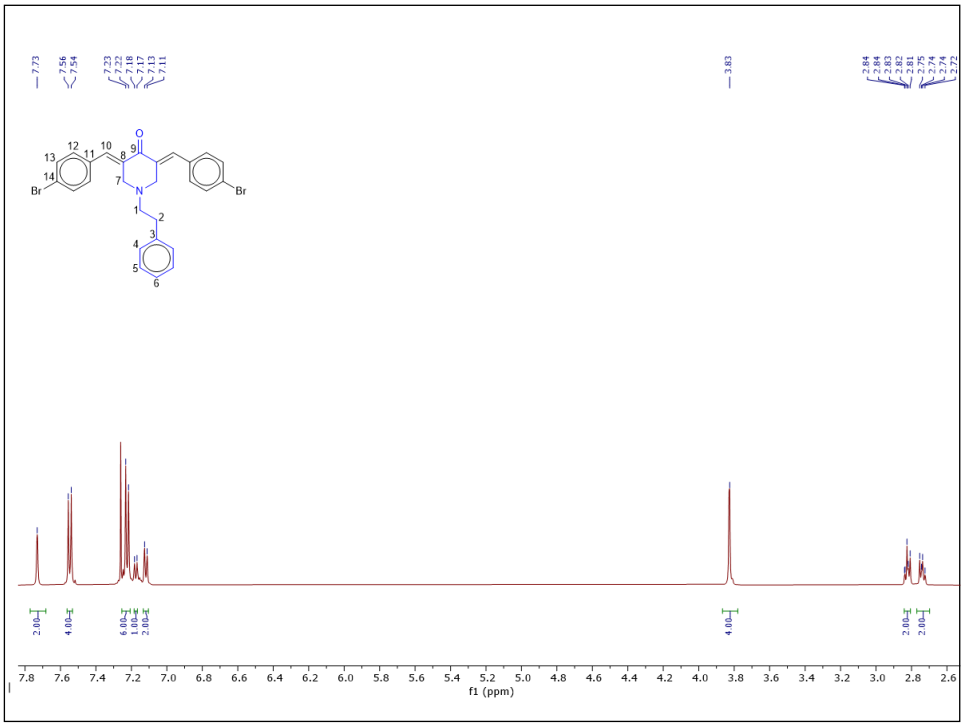

Figure S37: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5g**

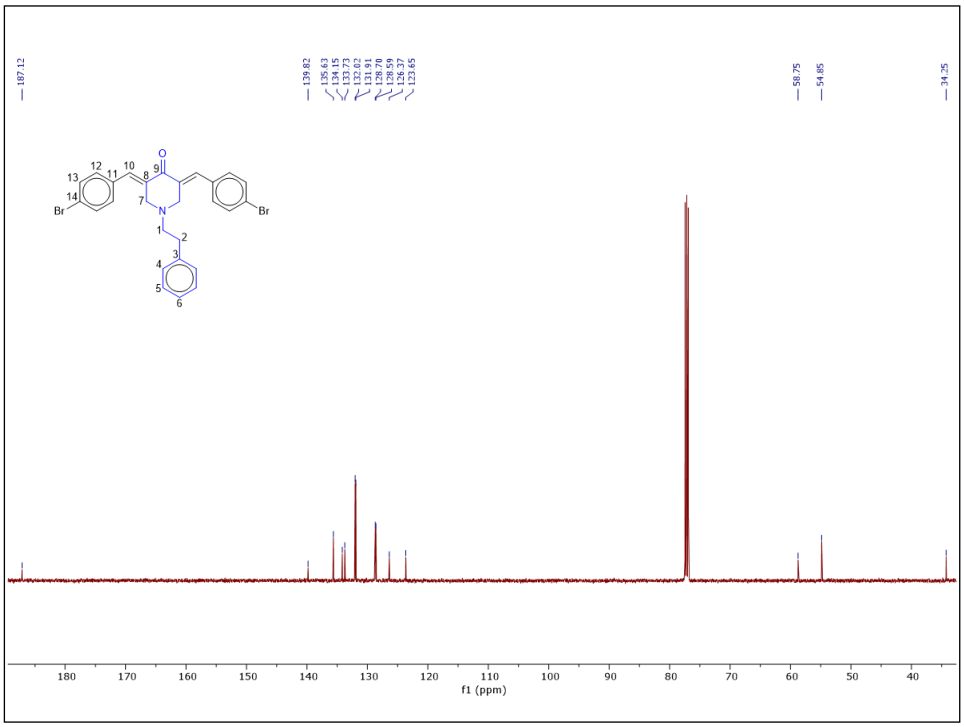

Figure S38: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5g**

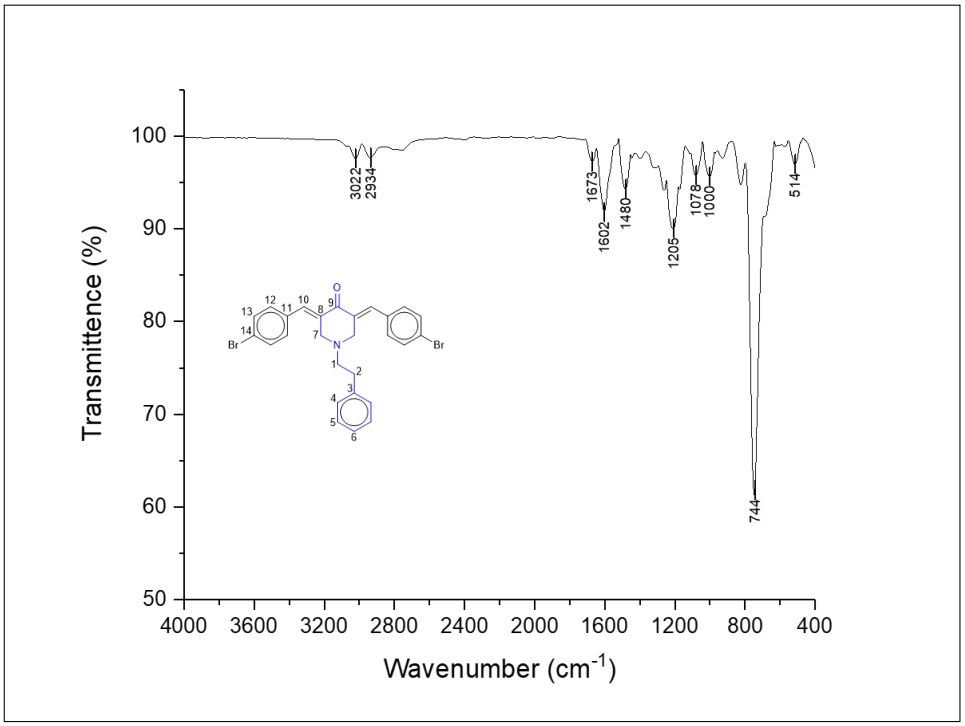

Figure S39: FT-IR spectrum of compound **5g**

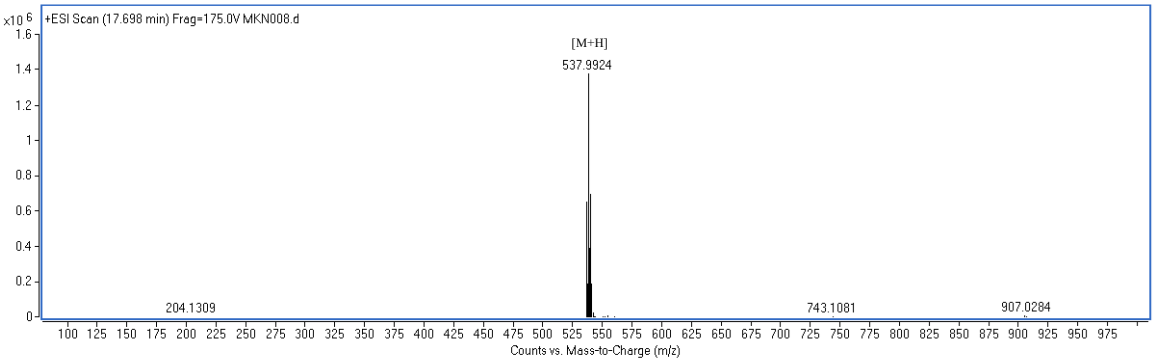

Figure S40: HRMS spectrum for compound **5g**

(3*E*,5*E*)-3,5-bis(4-fluorobenzylidene)-1-phenylethyl-4-piperidone (**5h**)

Yellow solid. (0.34 g, 81%), m.p 134-136 °C, R_f=0.81 [UV-active, *n*-hex:EtOAc 60%], FTIR (ATR, cm^{-1}): 3019 (w, C-H), 1599 (m, C=O), 1504 (m, C=C), 1216 (s, C-N). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.73-2.76 (m, 2H, H2), 2.82-2.85 (m, 2H, H1), 3.85 (s, 4H, H7), 7.10-7.13 (m, 6H, H4 & H13), 7.17 (t, *J*=8.0 Hz, 1H, H6), 7.22 (t, *J*=8.0 Hz, 2H, H5), 7.34-7.37 (m, 4H, H12), 7.78 (br s, 2H, H10). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.6 (C2), 55.1 (C7), 59.1 (C1), 116.3 (d, *J*=21.7 Hz, C13), 126.9 (C6), 128.9 (C4), 129.0 (C5), 131.9 (d, *J*=8.5 Hz, C12), 132.8 (d, *J*=2.5 Hz, C11), 133.3 (C8), 136.0 (C10), 140.2 (C3), 163.4 (d, *J*=252.0 H z, C14), 187.6 (C9). HRMS (ESI): *m/z* 416.1894 (MH^+ $C_{27}H_{24}F_2NO^+$ requires 416.1826).

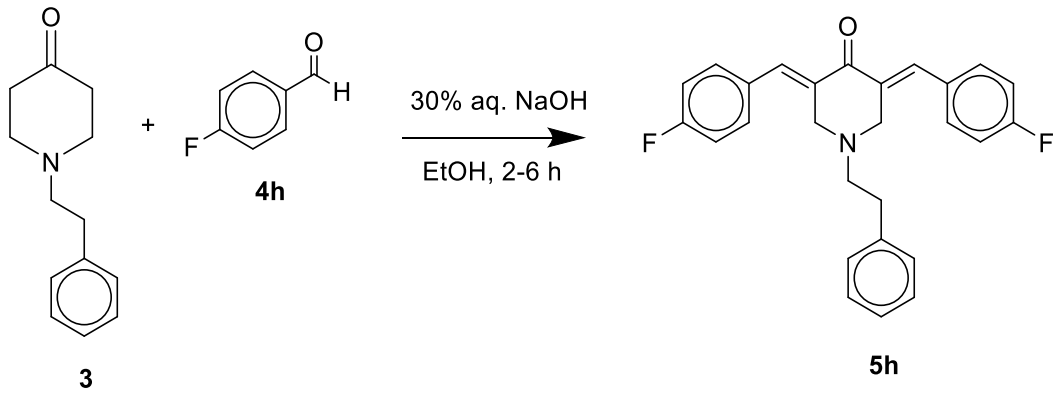

Figure S41: Reaction scheme of compound **5h**

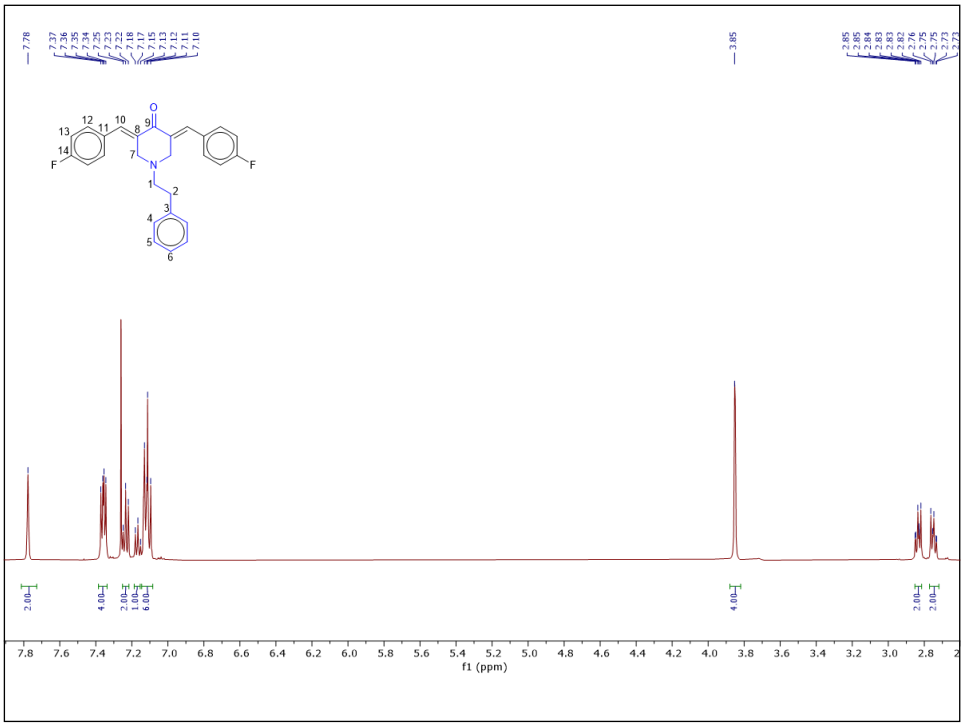

Figure S42: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5h**

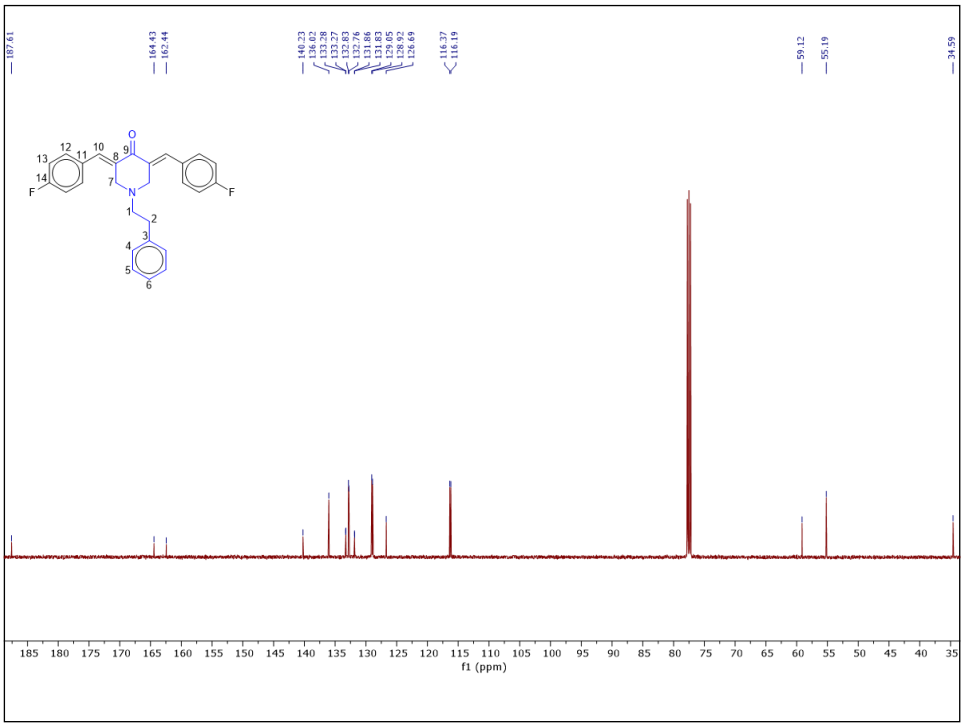

Figure S43: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound **5h**

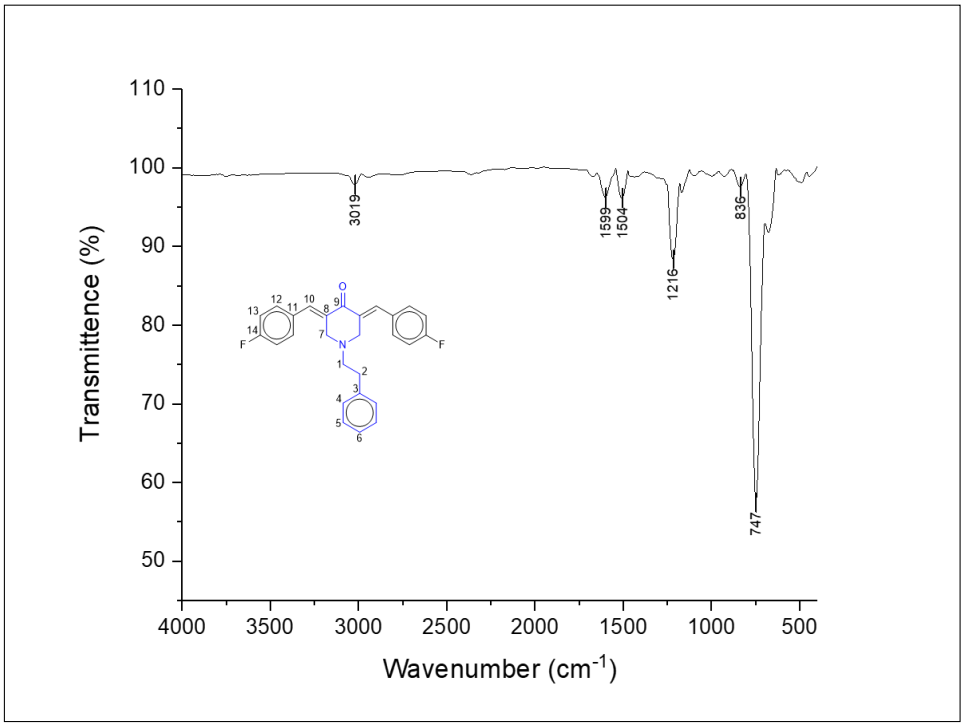

Figure S44: FT-IR spectrum of compound **5h**

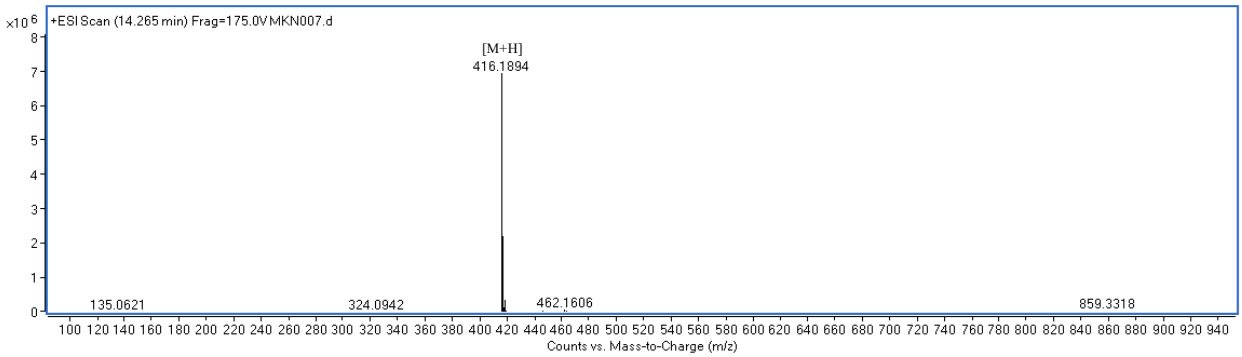

Figure S45: HRMS spectrum **5h**

Characterisation data and NMR Spectrum for compounds **8a-10h**

1-methyl-4(phenyl) pyrrolo-(spiro [2.3'‘] oxindole)-spiro [3.3']-5'-(phenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8a**)

White powder. m.p. 120-124 °C. FTIR (ATR): 3259 (w, N-H), 1699 (s, C=O), 1607 (m, C=C), 1173 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (1H, d, *J*=15.0 Hz, H11a), 1.99 (3H, s, H22), 2.26-2.38 (2H, m, H2), 2.40-2.47 (1H, m, H1), 3.05 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.18 (1H, d, *J*=15.0 Hz, H11b), 3.23 (1H, dd, =12.0, 8.0 Hz, H13a), 3.34 (1H, d, *J*=15.0 Hz, H7b), 3.84 (1H, dd, *J*=12.0, 3.0 Hz, H13b), 4.64 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.64 (1H, d, *J*=8.0 Hz, H19), 6.87-6.88 (2H, m, H16, H17), 7.05 (1H, t, *J*=8.0 Hz, H18), 7.08-7.10 (5H, m, H4, H29, H27), 7.14-7.15 (2H, m, H26 & H6), 7.20-7.23 (4H, m, H5, H24), 7.30-7.36 (5H, m, H25, H30, H31), 10.39 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.1 (C2), 34.2 (C22), 45.3 (C12), 54.1 (C7), 56.3 (C11), 56.4 (C13), 59.2 (C1), 64.7 (C10), 75.3 (C14), 108.8 (C19), 120.8 (C17), 125.9 (C6), 126.8 (C16), 126.9 (C15), 127.0 (C26), 128.3 (C4), 128.4 (C25), 128.5 (C5), 128.6 (C30), 128.7 (C18), 129.1 (C31), 129.3 (C24), 130.2 (C29), 133.0 (C8), 134.6 (C28), 136.8 (C27), 138.5 (C23), 140.1 (C3), 143.5 (C20), 176.7 (C21), 198.3 (C9). HRMS (ESI): *m/z* 554.2784 (MH^+ $C_{37}H_{36}N_3O_2^+$ requires 554.2808)[10].

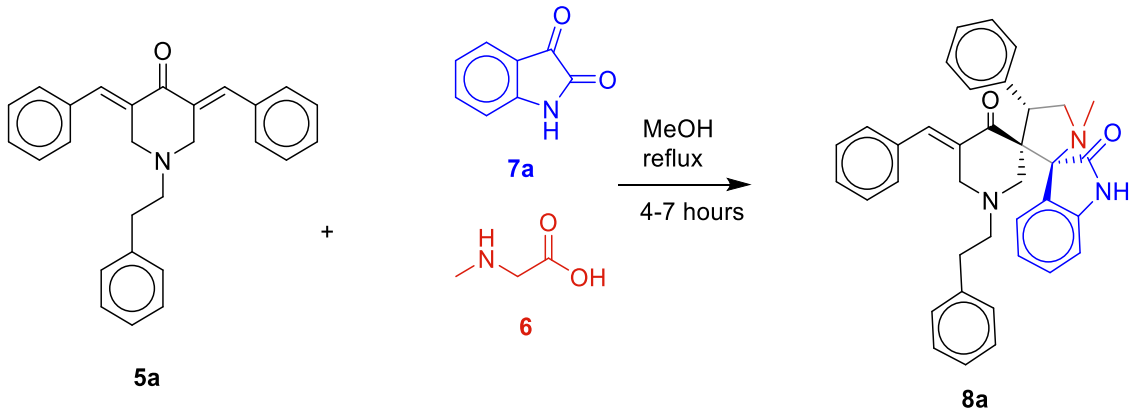

Figure S46: Reaction scheme of compound **8a**

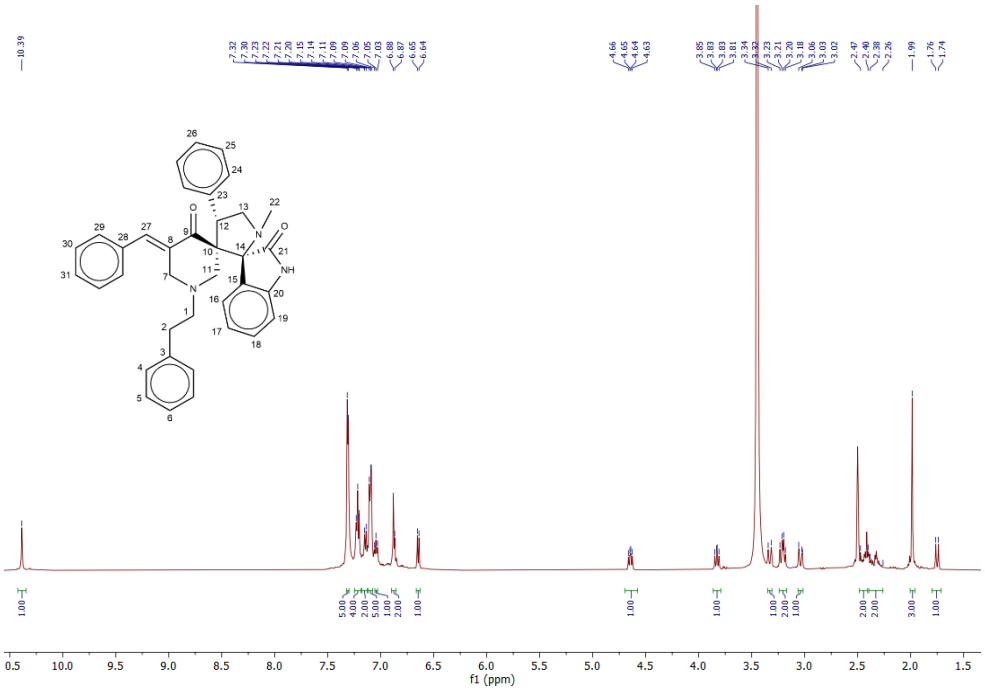

Figure S47: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8a**

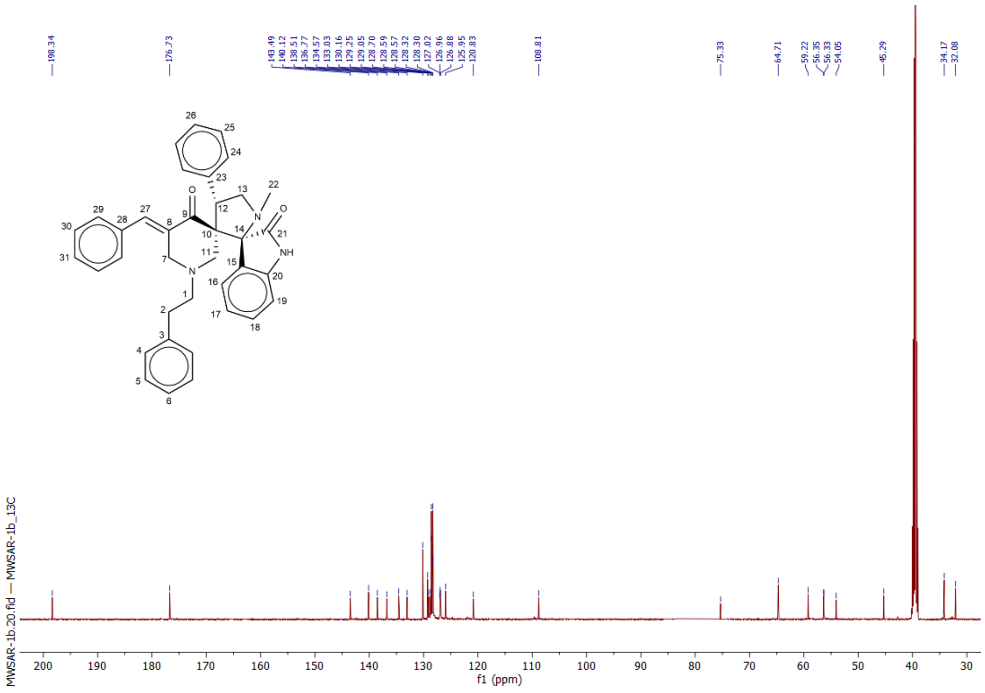

Figure S48: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8a**

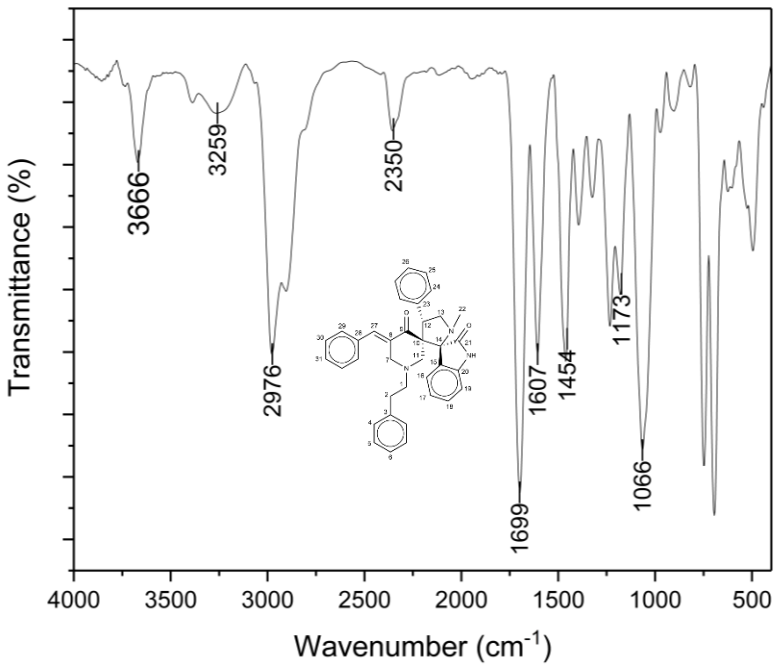

Figure S49: FT-IR spectrum of compound **8a**

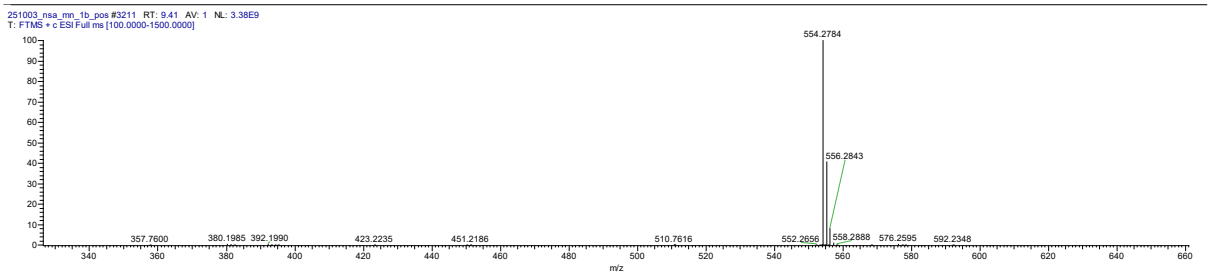

Figure S50: HRMS spectrum for compound **8a**

1-methyl-4(4-methylphenyl) pyrrolo-(spiro [2.3''] oxindole)-spiro [3.3']-5'-(4-methylphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8b**)

White powder. m.p. 114-118 °C. FTIR (ATR): 3278 (w, N-H), 1696 (s, C=O), 1599 (m, C=C), 1176 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.26 (3H, s, H27), 2.27 (3H, s, H33), 2.32-2.48 (4H, m, H1 & H2), 3.03 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.16 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.20 (1H, d, *J*=15.0 Hz, H11b), 3.32 (1H, d, *J*=15.0 Hz, H7b), 3.79 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.60 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.62 (1H, d, *J*=8.0 Hz, H19), 6.83-6.87 (2H, m, H16, H17), 7.00-7.04 (1H, m, H18 & H30), 7.07 (1H, d, *J*=2.0 Hz, H28), 7.10-7.16 (7H, m, H4, H6, H25, H31), 7.20 (2H, d, *J*=8.0 Hz, H24), 7.24 (2H, t, *J*=8.0 Hz, H5), 10.37 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.7 (C27), 20.9 (C33), 32.1 (C2), 34.1 (C22), 44.8 (C12), 54.1 (C7), 56.3 (C11), 56.4 (C13), 59.2 (C1), 64.5 (C10), 75.3 (C14), 108.6 (C19), 120.7 (C17), 125.8 (C6), 126.9 (C16), 127.0 (C15), 128.2 (C4), 128.3 (C25), 128.5 (C5), 128.8 (C18), 129.0 (C31), 129.1 (C24), 130.2 (C30), 131.8 (C29), 132.2 (C8), 135.4 (C23), 135.7 (C26), 136.7 (C28), 138.9 (C32), 140.1 (C3), 143.4 (C20), 176.6 (C21), 198.2 (C9). HRMS (ESI): *m/z* 582.3105 (MH: $C_{39}H_{40}N_3O_2^+$ requires 582.3120)[10].

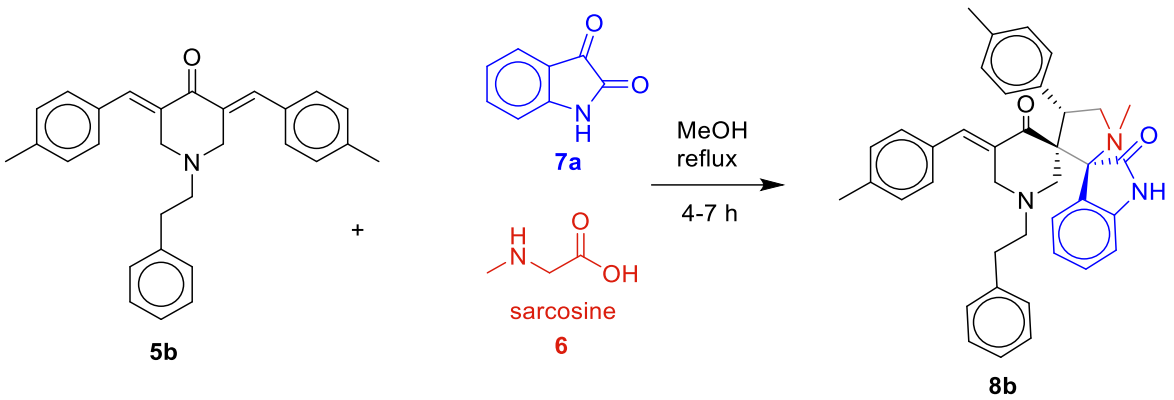

Figure S51: Reaction scheme of compound **8b**

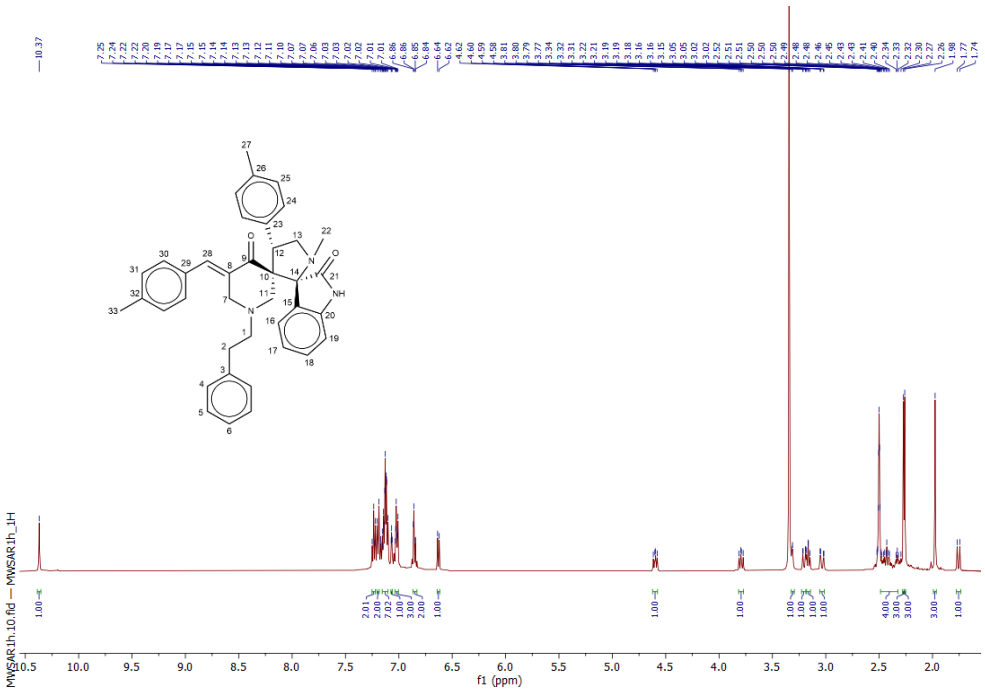

Figure S52: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8b**

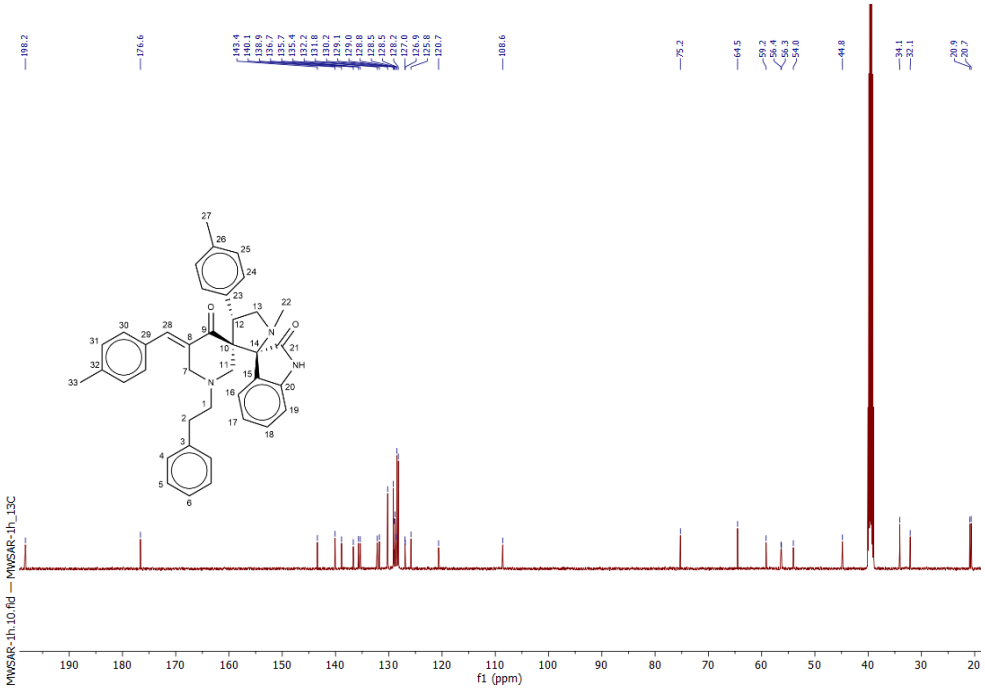

Figure S53: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8b**

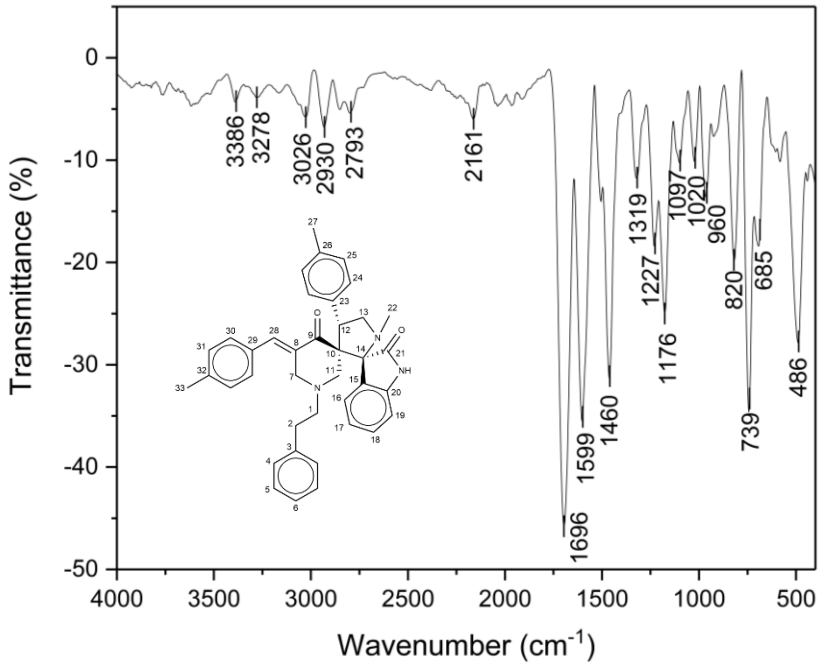

Figure S54: FT-IR spectrum of compound **8b**

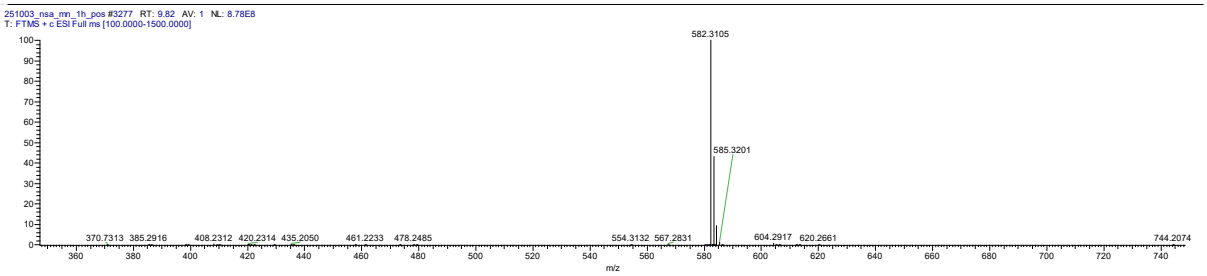

Figure S55: HRMS spectrum for compound **8b**

1-methyl-4(4-methoxyphenyl) pyrrolo-(spiro [2.3''] oxindole)-spiro [3.3']-5'-(4-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8c**)

Pale yellow powder, m.p. (114-118 °C). FTIR (ATR): 3217 (w, N-H), 1699 (s, C=O), 1598 (m, C=C), 1175 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (1H, d, *J*=15.0 Hz, H11a), 1.97 (3H, s, H22), 2.30-2.49 (4H, m, H1 & H2), 3.03 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.12-3.19 (2H, m, H11b & H13a), 3.31 (1H, d, *J*=15.0 Hz, H7b), 3.71 (3H, s, H27), 3.74 (3H, s, H33), 3.75-3.80 (1H, m, H13b), 4.58 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.64 (1H, d, *J*=8.0 Hz, H19), 6.81 (1H, d, *J*=8.0 Hz, H17), 6.85-6.89 (5H, m, H16, H30, H31), 7.02 (1H, t, H18), 7.10-7.18 (6H, m, H4, H6, H25, H28), 7.21-7.26 (4H, m, H5 & H24), 10.37 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.2 (C2), 34.1 (C22), 44.6 (C12), 54.3 (C7), 55.0 (C27), 55.3 (C33), 56.3 (C11), 56.7 (C13), 59.4 (C1), 64.4 (C10), 75.5 (C14), 108.7 (C19), 113.6 (C25), 114.1 (C31), 120.7 (C17), 125.9 (C6), 126.9 (C16), 127.1 (C15), 127.2 (C29), 128.3 (C4), 128.4 (C18), 128.5 (C5), 130.2 (C24), 130.4 (C30), 130.8 (C23), 132.3 (C8), 136.6 (C28), 140.2 (C3), 143.5 (C20), 158.1 (C26), 159.9 (C32), 176.8 (C21) 198.2 (C9). HRMS (ESI): *m/z* 614.2997 (MH^+ $C_{39}H_{40}N_3O_4^+$ requires 614.3019).

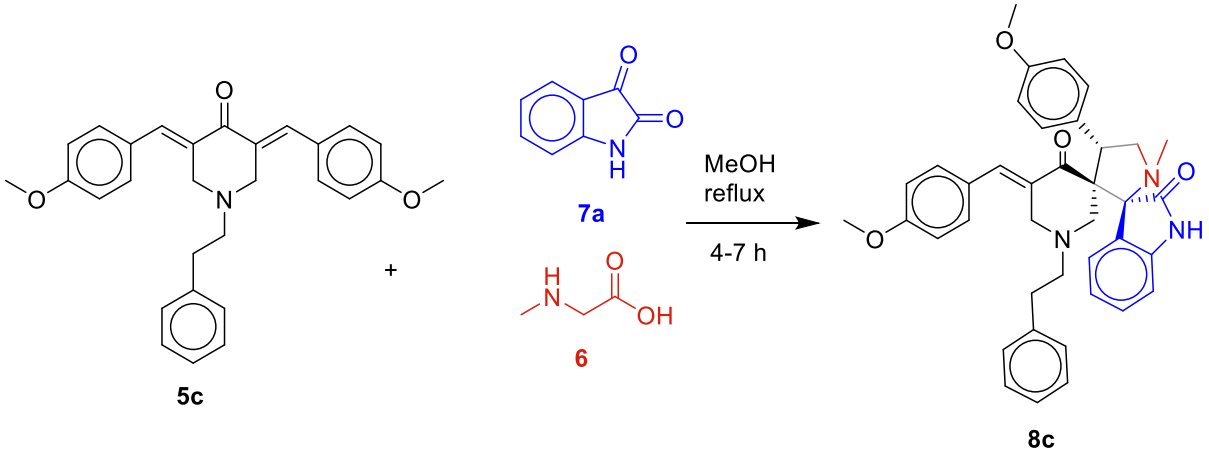

Figure S56: Reaction scheme of compound **8c**

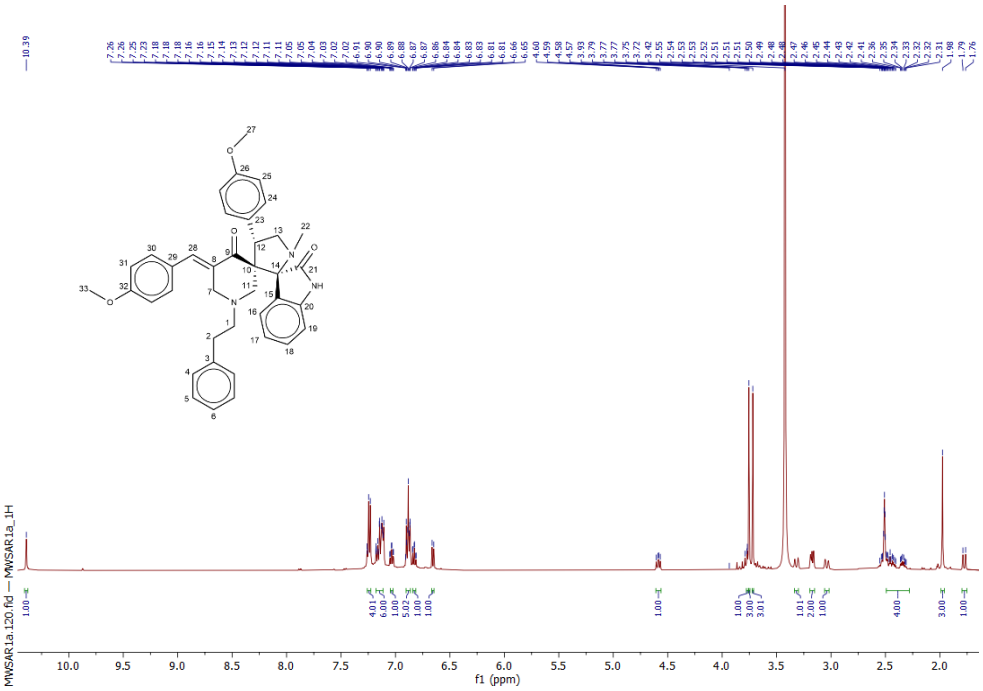

Figure S57: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8c**

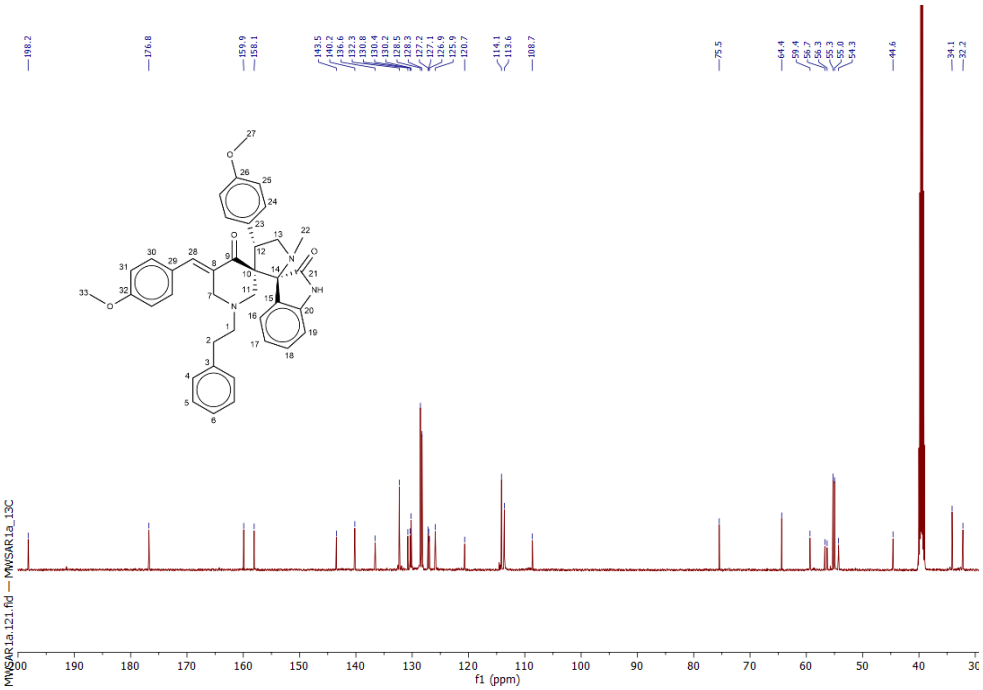

Figure S58: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8c**

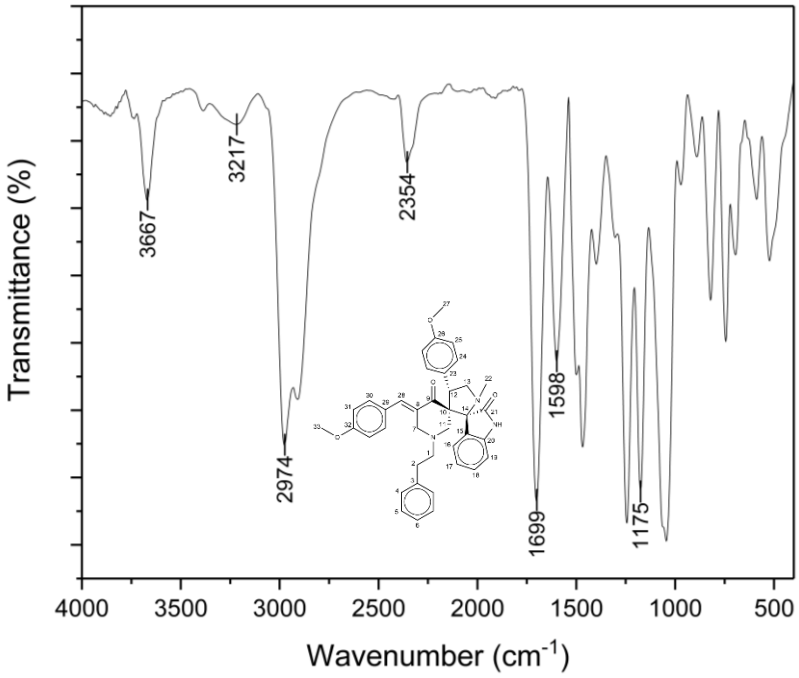

Figure S59: FT-IR spectrum of compound **8c**

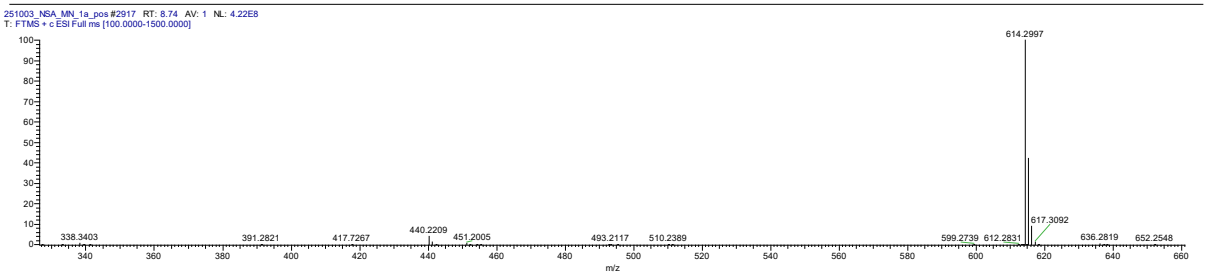

Figure S60: HRMS spectrum for compound **8c**

1-methyl-4(2-methoxyphenyl) pyrrolo-(spiro [2.3"] oxindole)-spiro [3.3']-5'-(2-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8d**)

Pale yellow powder, m.p. (110-114 °C). FTIR (ATR): 3220 (w, N-H), 1699 (s, C=O), 1598 (m, C=C), 1175 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (1H, d, *J*=15.0 Hz, H11a), 1.97 (3H, s, H22), 2.19-2.30 (2H, m, H2), 2.35-2.44 (2H, m, H1), 2.88-2.96 (2H, m, H7a & H11b), 3.14 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.21 (1H, d, *J*=12.0 Hz, H7b), 3.62 (3H, s, H24), 3.83 (3H, s, H32), 3.95 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.67 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.68 (1H, d, *J*=8.0 Hz, H19), 6.82 (1H, td, *J*=8.0, 2.0 Hz, H17), 6.85-6.87 (2H, m, H16 & H37), 6.89-6.92 (2H, m, H27 & H28), 6.96 (1H, t, *J*=8.0 Hz, H18), 7.01 (1H, d, *J*=8.0 Hz, H26), 7.05 (2H, d, *J*=8.0 Hz, H4), 7.09 (1H, d, *J*=8.0, H29), 7.12 (1H, t, *J*=8.0 Hz, H6), 7.19 (2H, t, *J*=8.0 Hz, H5), 7.22 (1H, d, *J*=8.0 Hz, H34), 7.29-7.33 (1H, m, H35), 7.51 (1H, d, *J*=8.0 Hz, H29), 7.58 (1H, d, *J*=2.0 Hz, H30), 10.47 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.3 (C2), 34.2 (C22), 38.8 (C12), 54.6 (C7), 54.9 (C32), 55.1 (C24), 55.5 (C11), 55.7 (C13), 59.7 (C1), 62.4 (C10), 76.1 (C14), 108.5 (C19), 110.3 (C28), 111.2 (C26), 120.0 (C27), 120.1 (C34), 120.8 (C17), 123.4(C23), 125.8 (C6), 127.0 (C16), 127.1 (C15), 127.2 (C36), 127.6 (C31), 128.1 (C29), 128.2 (C4), 128.3 (C18), 128.4 (C5), 129.5 (C37), 130.6 (C35), 131.1 (C30), 132.2 (C8), 140.0 (C3), 143.6 (C20), 157.7 (C25), 157.9 (C33), 176.7 (C21), 197.0 (C9). HRMS (ESI): *m/z* 614.2995 (MH^+ $C_{39}H_{40}N_3O_4^+$ requires 614.3019).

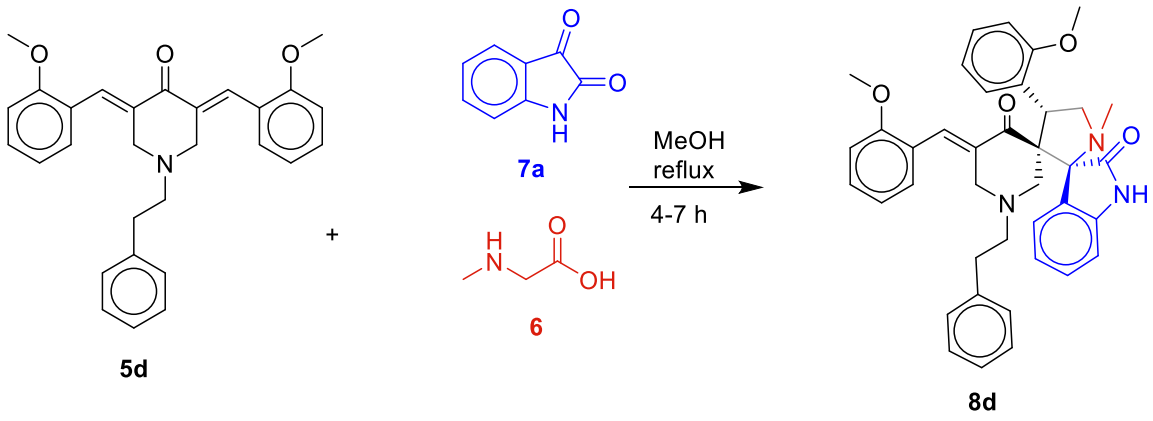

Figure S61: Reaction scheme of compound **8d**

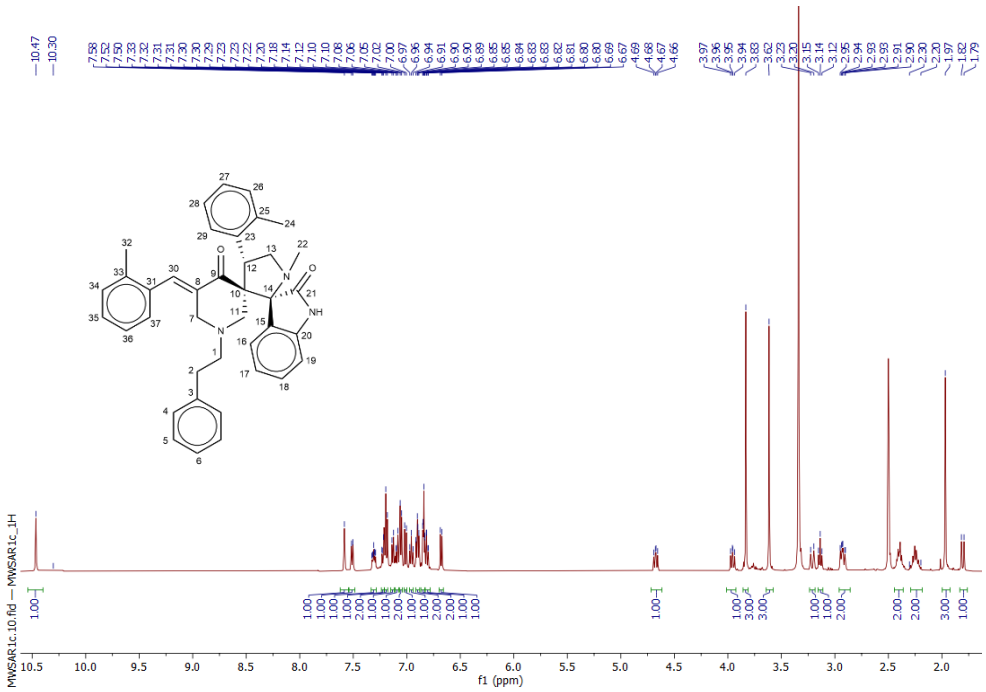

Figure S62: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8d**

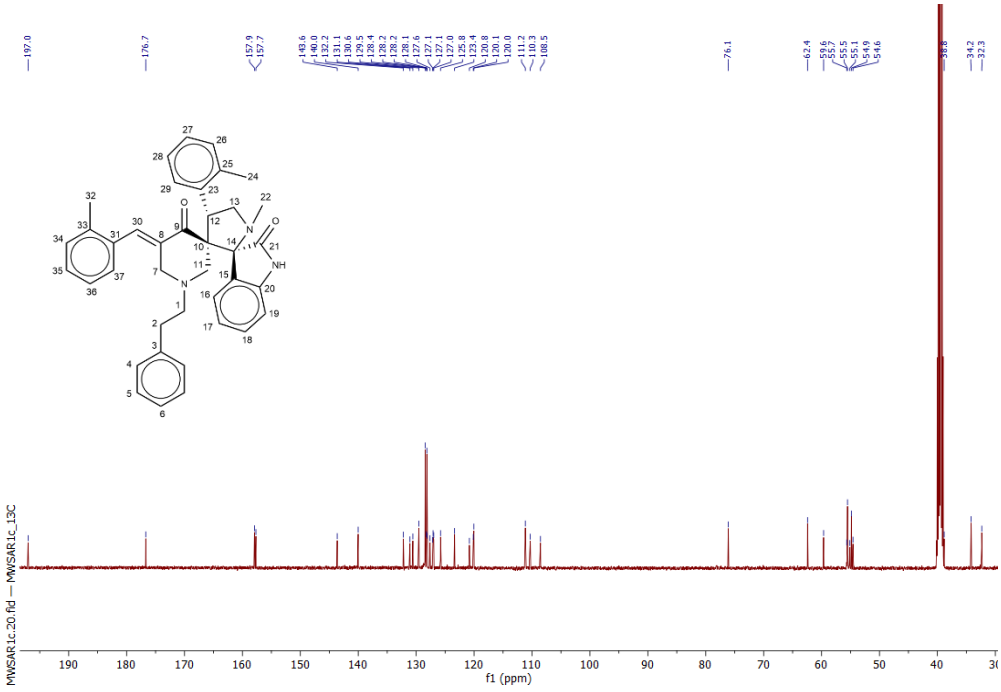

Figure S63: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8d**

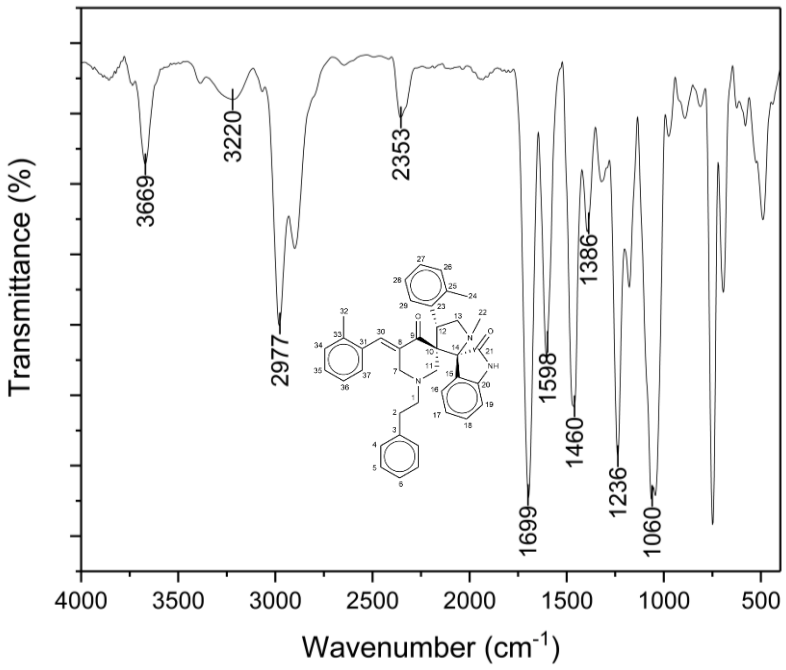

Figure S64: FT-IR spectrum of compound **8d**

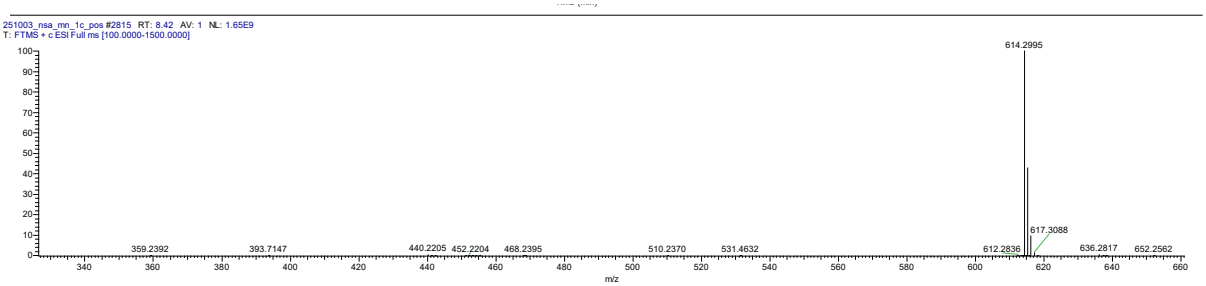

Figure S65 HRMS spectrum for compound **8d**

1-methyl-4(2,4-methoxyphenyl) pyrrolo-(spiro [2.3"] oxindole)-spiro [3.3']-5'-(2,4-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8e**)

Pale yellow powder, M.p. (114-118 °C). FTIR (ATR): 3214 (w, N-H), 1696 (m, C=O), 1597 (s, C=C), 1208 (m, C-N) cm^{-1}. ^{1}H NMR(500 MHz, DMSO-d_6): δ 1.80 (1H, d, *J*=15.0 Hz, H11a), 1.95 (3H, s, H22), 2.20-2.33 (2H, m, H2), 2.37-2.45 (2H, m, H1), 2.89 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 2.93 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.10 (1H, t, *J*=15.0 Hz, H11b), 3.20 (1H, d, *J*=12.0 Hz, H7b), 3.58 (3H, s, H25), 3.73 (3H, s, H34), 3.84 (3H, s, H37), 3.89 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.60 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.42 (1H, dd, *J*=8.0, 3.0 Hz, H38), 6.44 (1H, d, *J*=3.0 Hz, H26), 6.52 (1H, dd, *J*=8.0, 3.0 Hz, H29), 6.89 (1H, d, *J*=8.0 Hz, H16), 7.05 (1H, dd, *J*=8.0, 2.0 Hz, H18), 7.07-7.10 (2H, m, H5), 7.12-7.16 (1H, m, H6), 7.19-7.23 (2H, m, H4), 7.41 (1H, d, *J*=8.0 Hz, H30), 7.57 (1H, d, *J*=2.0 Hz, H31). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.5 (C2), 34.2 (C22), 38.4 (C12), 54.9 (C7), 55.0 (C25), 55.1 (C28), 55.4 (C34), 55.5 (C13), 55.7 (C37), 55.8 (C11), 59.8 (C1), 62.5 (C10), 76.2 (C14), 98.1 (C26), 98.3 (C35), 104.2 (C29), 105.1 (C38), 108.5 (C19), 116.3 (C32), 119.3 (C23), 120.8 (C17), 125.8 (C6), 127.0 (C16), 127.1 (C15), 128.2 (C18), 128.4 (C4), 128.5 (C5), 128.7 (C30), 130.3 (C8), 130.5 (C31), 130.8 (C39), 140.2 (C3), 143.6 (C20), 158.6 (C24), 159.1 (C27), 159.7 (C36), 161.6 (C33), 176.8 (C21), 197.3 (C9). HRMS (ESI): *m/z* 674.3204 (MH^+ $C_{41}H_{44}N_3O_6^+$ requires 674.3230).

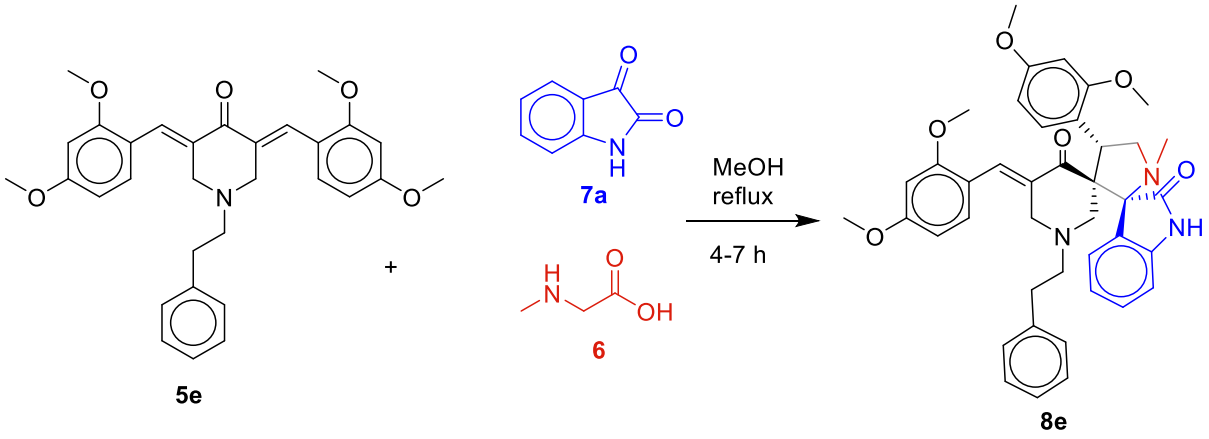

Figure S65: Reaction scheme of compound **8e**

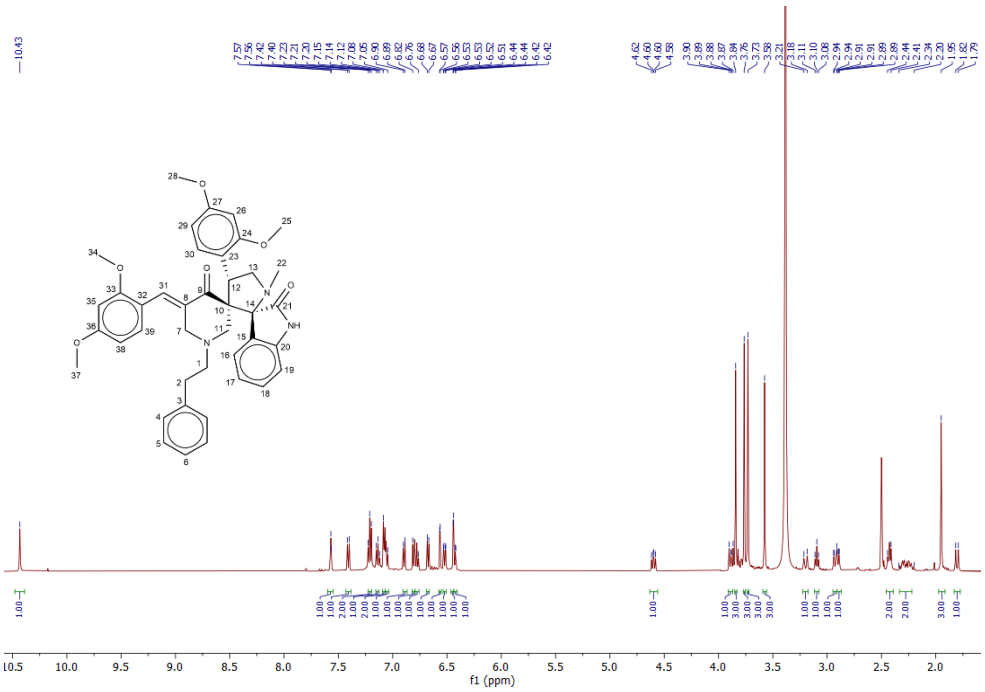

Figure S66: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8e**

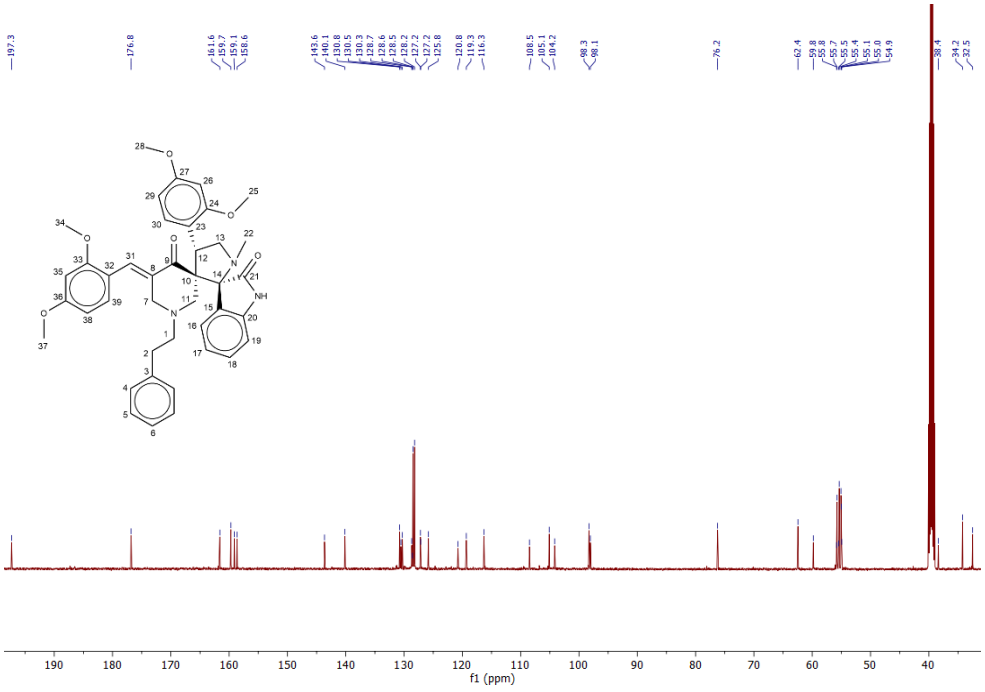

Figure S67: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8e**

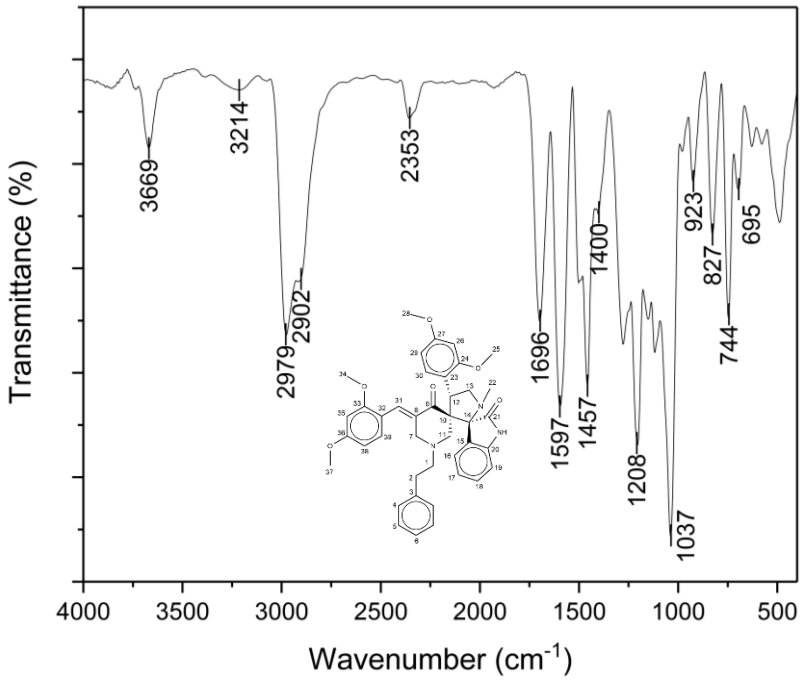

Figure S68: FT-IR spectrum of compound **8e**

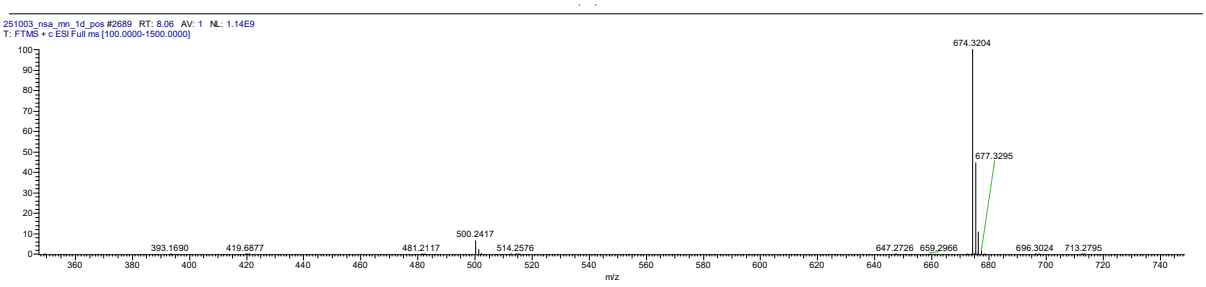

Figure S69: HRMS spectrum for compound **8e**

1-methyl-4(4-chlorophenyl) pyrrolo-(spiro [2.3"] oxindole)-spiro [3.3']-5'-(4-chlorophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8f**)

White powder, m.p. (124-128 °C). FTIR (ATR): 3224 (w, N-H), 1701 (m, C=O), 1604 (s, C=C), 1205 (m, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.79 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.30-2.47 (4H, m, H1, H2), 3.09 (1H, dd, *J*=12.0 & 2.0 Hz, H7a), 3.14 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.22 (1H, t, *J*=15.0 Hz, H11b), 3.27 (1H, d, *J*=12.0 Hz, H7b), 3.76 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.61 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.68 (1H, d, *J*=8.0 Hz, H19), 6.85-6.90 (2H, m, H16 & H17), 7.03-7.07 (2H, m, H18 & H27), 7.09-7.16 (5H, m, H4, H6 & H29), 7.22 (2H, t, *J*=8.0 Hz, H5), 7.33-7.40 (6H, m, H24, H25 & H30), 10.43 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.0 (C2), 34.1 (C22), 44.7 (C12), 53.8 (C7), 56.2 (C11), 56.4 (C13), 59.0 (C1), 64.5 (C10), 75.2 (C14), 108.8 (C19), 120.8 (C17), 125.8 (C6), 126.6 (C16), 126.9 (C15), 128.2 (C4), 128.3 (C18), 128.5 (C5), 128.6 (C25), 128.7 (C24), 131.1 (C29), 131.4 (C28), 131.8 (C30), 133.0 (C26), 133.3 (C8), 133.6 (C31), 135.3 (C27), 137.5 (C23), 140.0 (C3), 143.6 (C20), 176.5 (C21), 197.1 (C9). HRMS (ESI): *m/z* 622.2009 (MH^+ $C_{37}H_{34}{}^{79}Cl_2N_3O_2^+$ requires 622.2028).

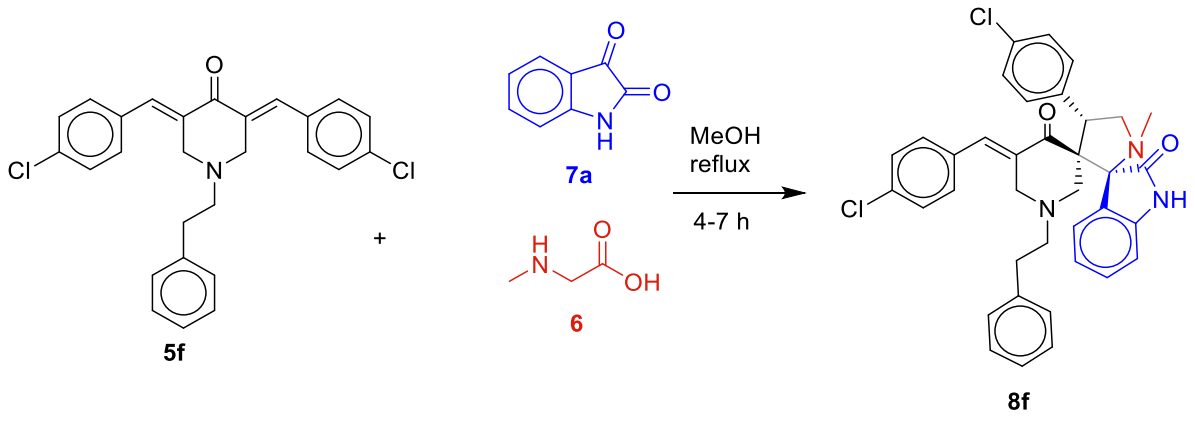

Figure S70: Reaction scheme of compound **8f**

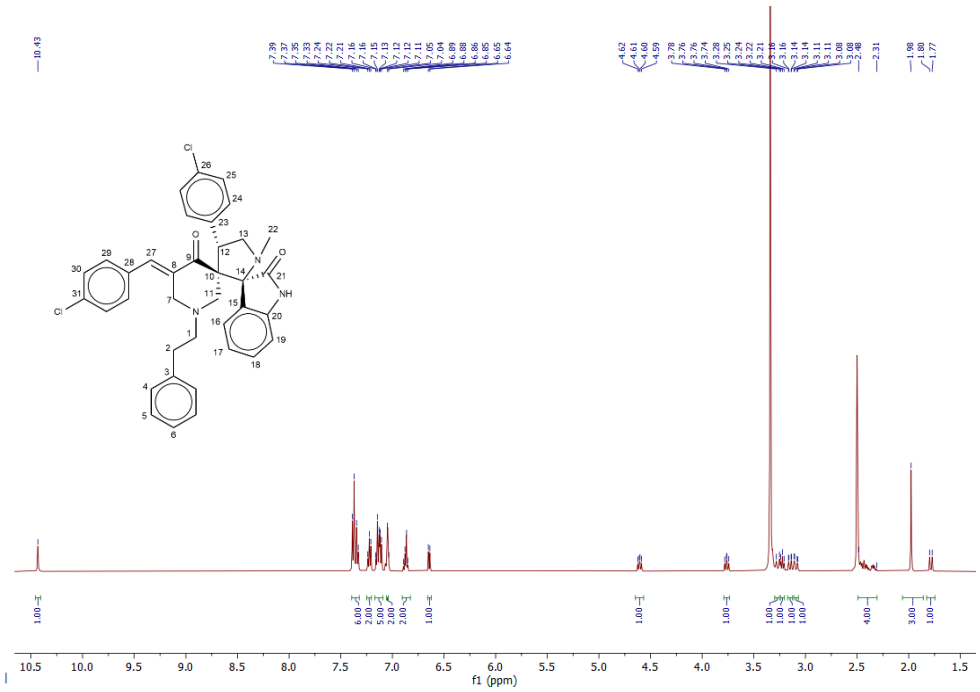

Figure S71: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8f**

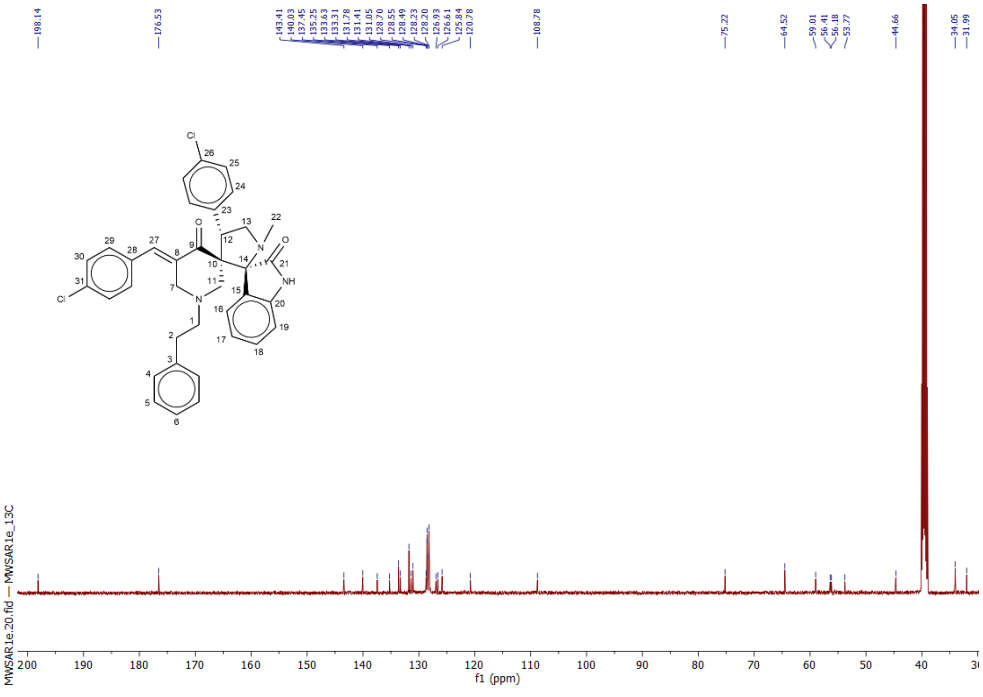

Figure S72: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8f**

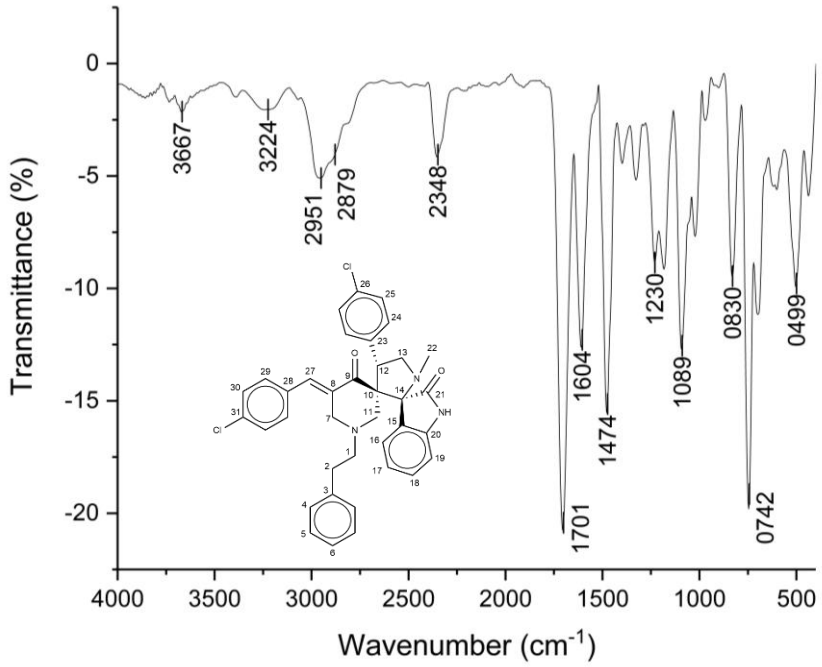

Figure S73: FT-IR spectrum of compound **8f**

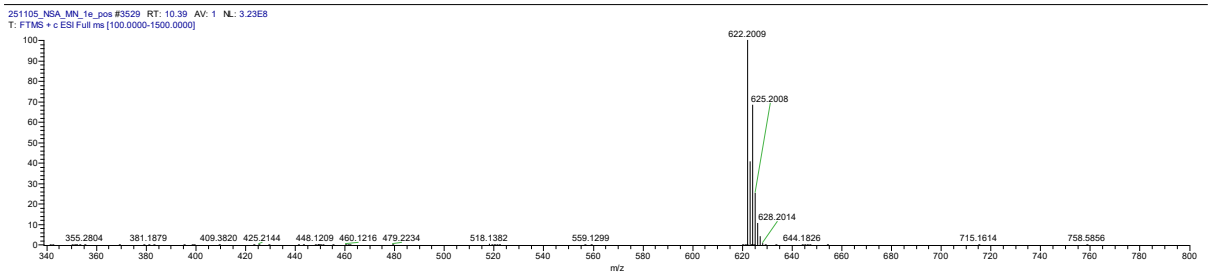

Figure S74: HRMS spectrum for compound **8f**

1-methyl-4(4-bromophenyl) pyrrolo-(spiro [2.3"] oxindole)-spiro [3.3']-5'-(4-bromophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8g**)

White powder, m.p. (125-129 °C). FTIR (ATR): 3183 (w, N-H), 1696 (m, C=O), 1595 (s, C=C), 1178 (m, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.79 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.31-2.47 (4H, m, H1 & H2), 3.08 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.15 (1H, d, *J*=15.0 Hz, H11b), 3.22 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.26 (1H, d, *J*=15.0 Hz, H7b), 3.76 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.59 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.65 (1H, d, *J*=8.0 Hz, H19), 6.84-6.89 (2H, m, H16, H17), 7.02 (1H, d, *J*=2.0 Hz, H27), 7.04-7.08 (3H, m, H18 & H29), 7.11 (2H, d, *J*=8.0 Hz, H4), 7.15 (1H, t, *J*=8.0 Hz, H6), 7.22 (2H, d, *J*=8.0 Hz, H5), 7.28 (2H, d, *J*=8.0 Hz, H24), 7.47-7.53 (4H, m, H25 & H30), 10.43 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.2 (C2), 34.1 (C22), 44.7 (C12), 53.7 (C7), 56.2 (C11), 56.3 (C13), 59.0 (C1), 64.5 (C10), 75.2 (C14), 108.8 (C19), 120.0 (C26), 120.8 (C17), 122.5 (C31), 125.8 (C6), 126.6 (C16), 126.9 (C15), 128.2 (C4), 128.5 (C5), 128.7 (C18), 131.1 (C25), 131.4 (C24), 131.5 (C30), 132.0 (C29), 133.6 (C8), 133.7 (C28), 135.3 (C27), 137.9 (C23), 140.0 (C3), 143.4 (C20), 176.5 (C21), 198.1 (C9). HRMS (ESI): *m/z* 710.0846 (MH^+ $C_{37}H_{34}{}^{79}Br_2N_3O_2^+$ requires 710.1018).

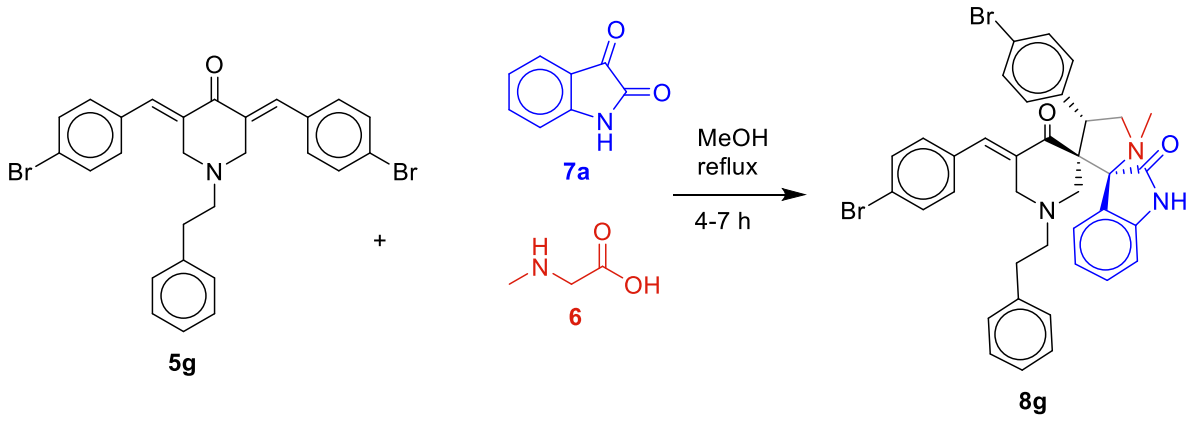

Figure S75: Reaction scheme of compound **8g**

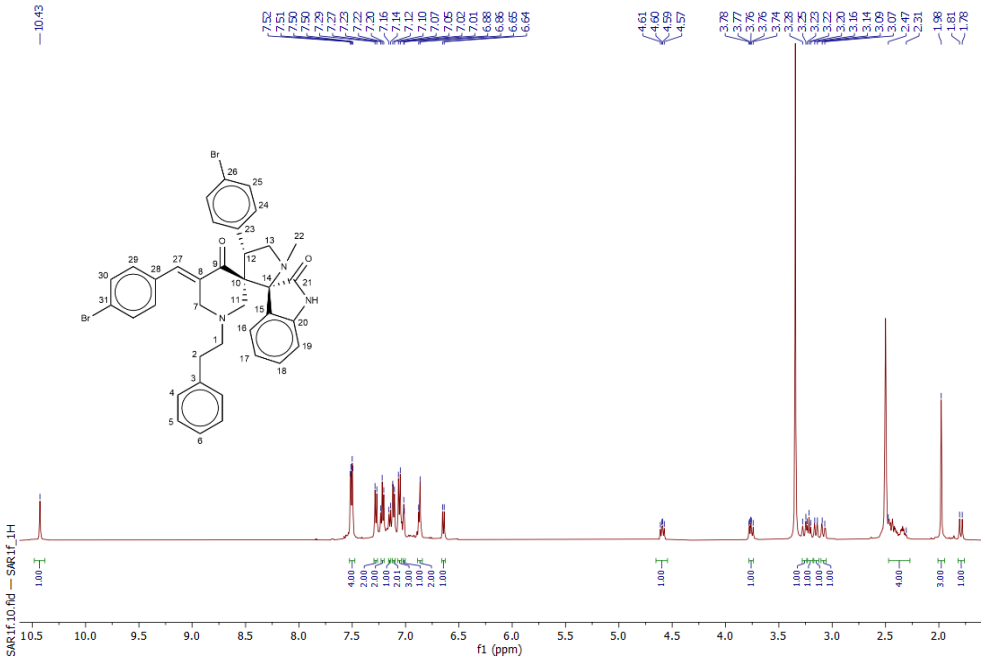

Figure S76: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8g**

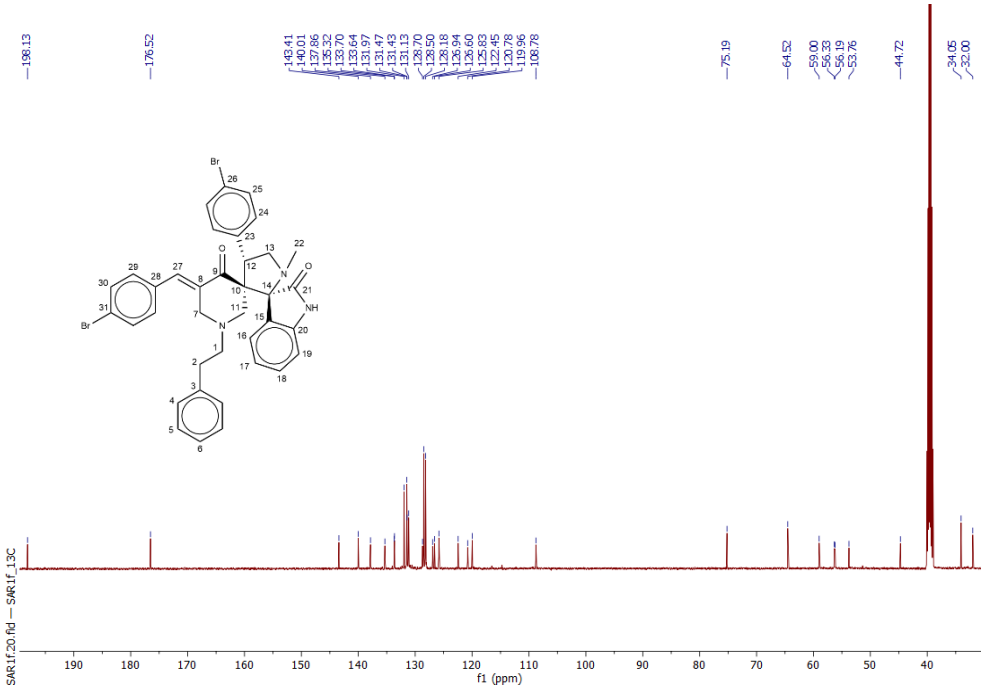

Figure S77: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8g**

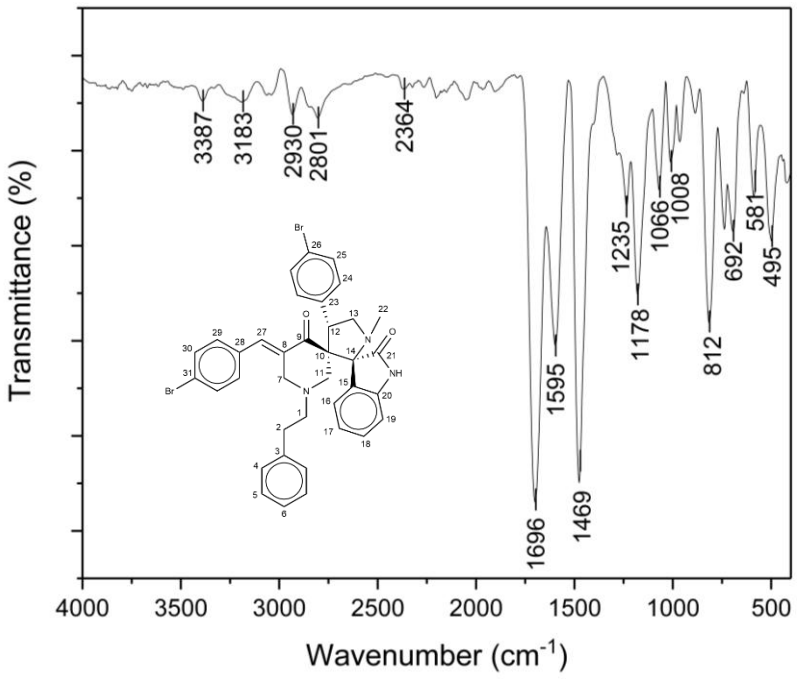

Figure S78: FT-IR spectrum of compound **8g**

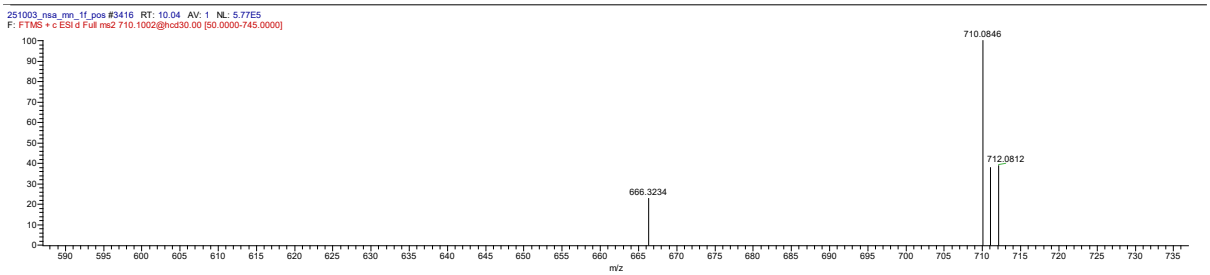

Figure S79: HRMS spectrum for compound **8g**

1-methyl-4(4-fluorophenyl) pyrrolo-(spiro [2.3''] oxindole)-spiro [3.3']-5'-(4-fluorophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**8h**)

White powder, m.p. (106-110 °C). FTIR (ATR): 3254 (w, N-H), 1696 (m, C=O), 1599 (s, C=C), 1170 (m, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.78 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.29-2.48 (4H, m, H1 & H2), 3.07 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.16 (1H, d, *J*=15.0 Hz, H11b), 3.23 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.28 (1H, d, *J*=15.0 Hz, H7b), 3.76 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.62 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.65 (1H, d, *J*=8.0 Hz, H19), 6.85-6.89 (2H, m, H16, H17), 7.02-7.07 (1H, m, H18), 7.08 (1H, d, *J*=2.0 Hz, H27), 7.10-7.19 (9H, m, H4, H6, H25, H29, H30), 7.23 (2H, t, *J*=8.0 Hz, H5), 7.36 (2H, dd, *J*=8.0, 3.0 Hz, H24), 10.43 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.2 (C2), 34.0 (C22), 44.5 (C12), 53.9 (C7), 56.2 (C11), 56.7 (C13), 59.0 (C1), 64.4 (C10), 75.3 (C14), 108.7 (C19), 115.0 (d, *J*=20.7 Hz, C25), 115.5 (d, *J*=20.7 Hz, C30), 120.7 (C17), 125.8 (C6), 126.6 (C16), 126.9 (C15), 128.2 (C4), 128.5 (C5), 128.6 (C18), 131.0 (d, *J*=8.5 Hz, C24), 131.1 (C8), 132.4 (d, *J*=8.5 Hz, C29), 132.8 (d, *J*=2.5 Hz, C23), 134.6 (d, *J*=2.5 Hz, C28), 135.5 (C27), 140.1 (C3), 143.4 (C20), 161.1 (d, *J*=242 Hz, C26), 162.1 (d, *J*=242 Hz, C31), 176.6 (C21), 198.2 (C9). HRMS (ESI): *m/z* 590.2598 (MH^+ $C_{37}H_{34}F_2N_3O_2^+$ requires 590.2619).

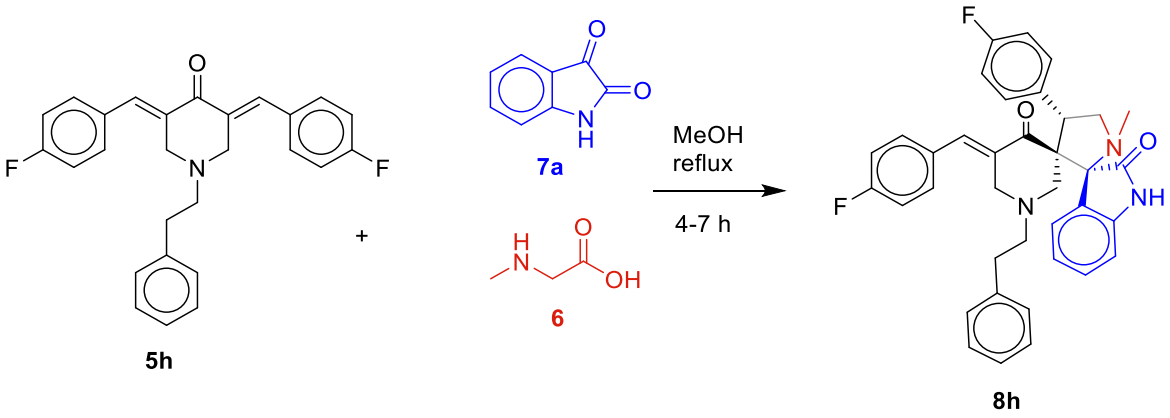

Figure S80: Reaction scheme of compound **8h**

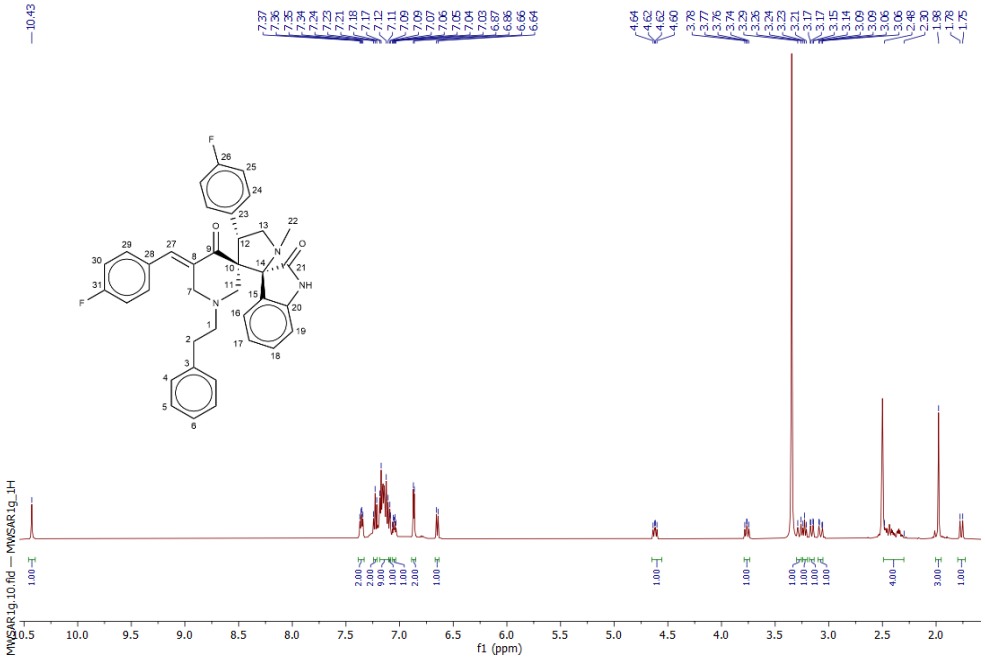

Figure S81: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **8h**

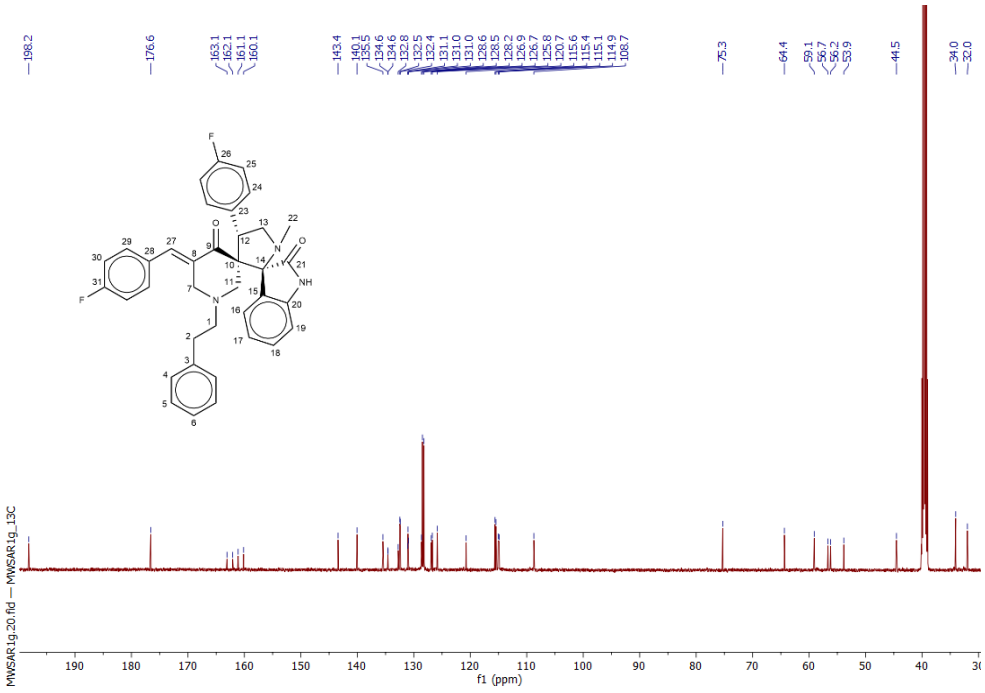

Figure S82: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **8h**

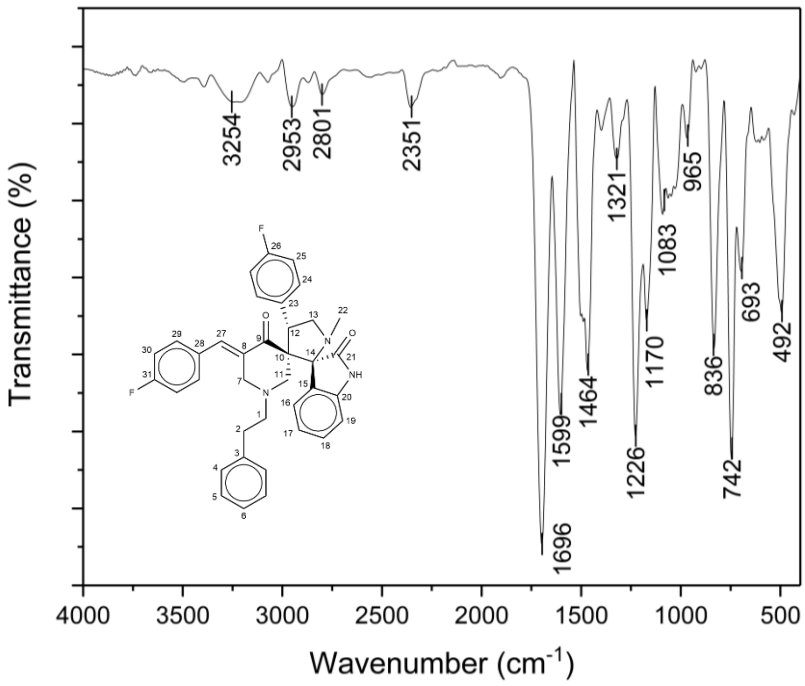

Figure S83: FT-IR spectrum of compound **8h**

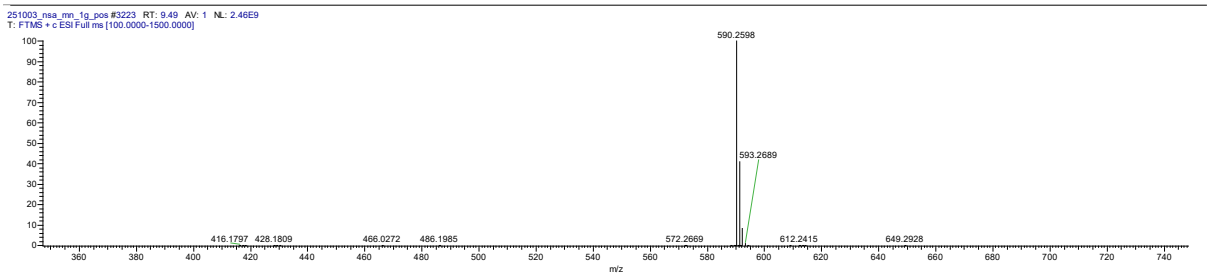

Figure S84: HRMS spectrum for compound **8h**

1-methyl-4(phenyl) pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(phenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9a**)

White powder, m.p. (118-122 °C). FTIR (ATR): 3216 (w, N-H), 1710 (m, C=O), 1598 (s, C=C), 1172 (m, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.35-2.48 (4H, m, H1 & H2), 3.06-3.13 (2H, m, H7a & H13a), 3.21-3.24 (2H, m, H7b & H11b), 3.81 (1H, dd, *J*=8.0, 2.0 Hz, H13b), 4.65 (1H, dd, *J*=8.0, 2.0 Hz, H12), 6.61 (1H, d, *J*=8.0 Hz, H19), 6.93 (1H, d, *J*=2.0 Hz, H16), 7.11-7.15 (5H, m, H4, H6, H26, H27), 7.20 (1H, dd, *J*=8.0, 2.0 Hz, H18), 7.23-7.26 (4H, m, H5 & H9), 7.31-7.37 (7H, m, H24, H25, H30, H31), 10.57 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.9 (C2), 34.2 (C22), 45.0 (C12), 54.0 (C7), 56.3 (C11), 56.4 (C13), 59.1 (C1), 65.1 (C10), 75.1 (C14), 110.8 (C19), 112.7 (C17), 125.9 (C6), 126.9 (C26), 128.2 (C4), 128.3 (C25), 128.4 (C5), 128.6 (C30), 129.1 (C31), 129.2 (C24), 129.5 (C15), 129.6 (C16), 130.1 (C29), 131.3 (C18), 133.1 (C8), 134.5 (C28), 137.1 (C27), 138.1 (C23), 139.9 (C3), 143.7 (C20), 176.1 (C21), 198.2 (C9). HRMS (ESI): *m/z* 632.1879 (MH^+ $C_{37}H_{35}{}^{79}BrN_3O_2^+$ requires 632.1912).

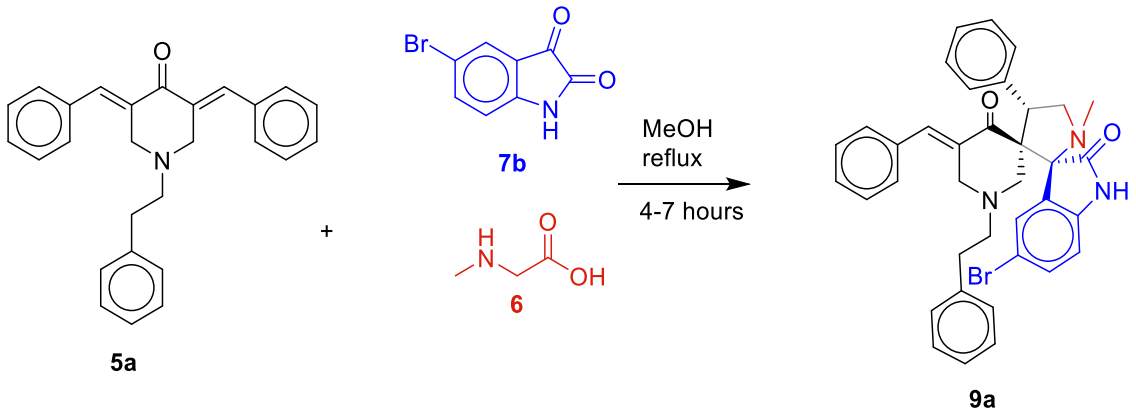

Figure S85: Reaction scheme of compound **9a**

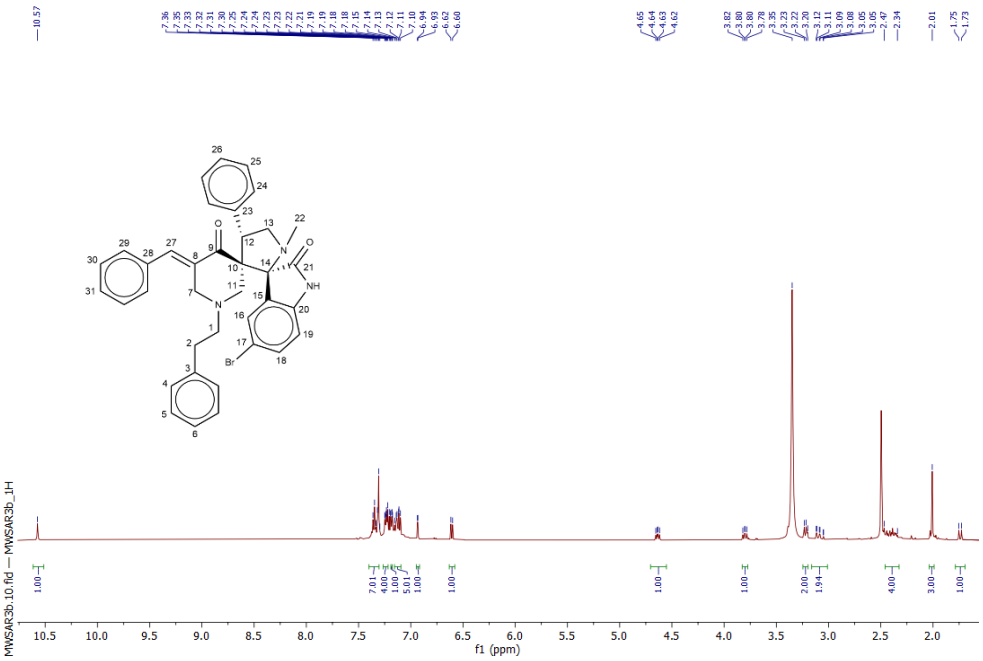

Figure S86: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9a**

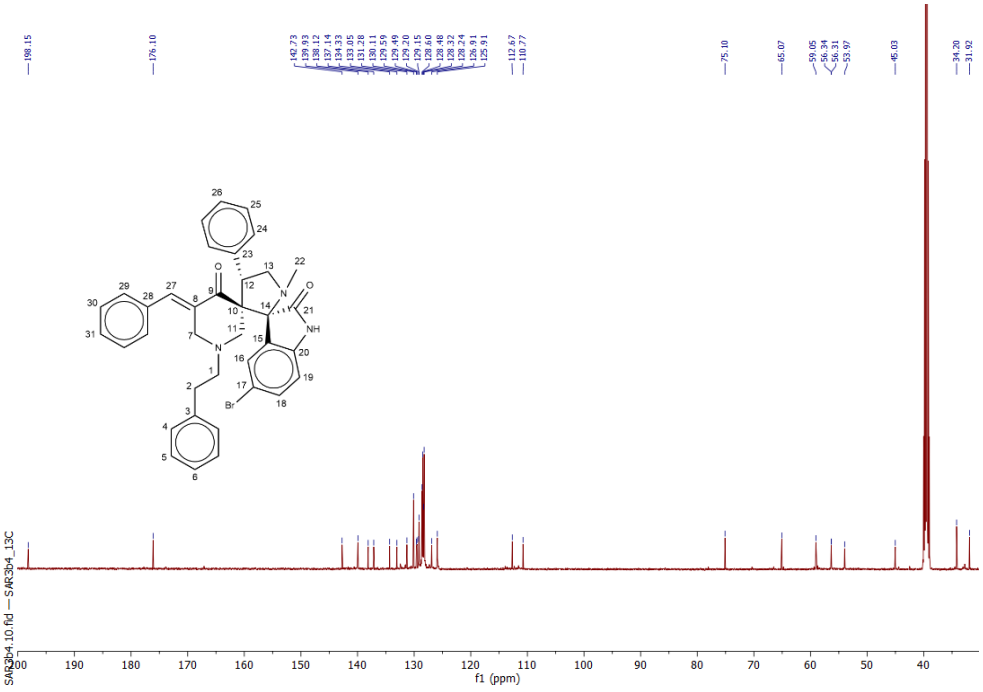

Figure S87: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9a**

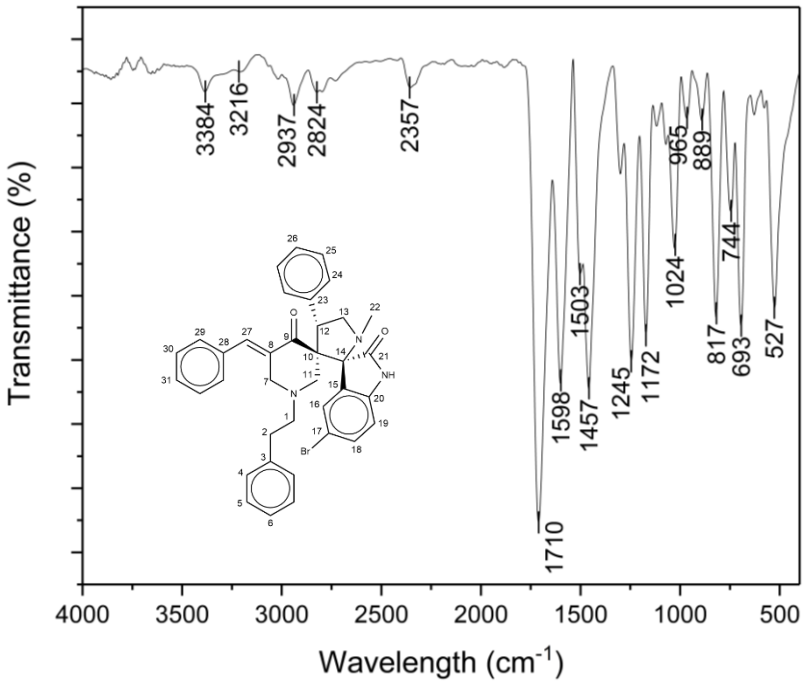

Figure S88: FT-IR spectrum of compound **9a**

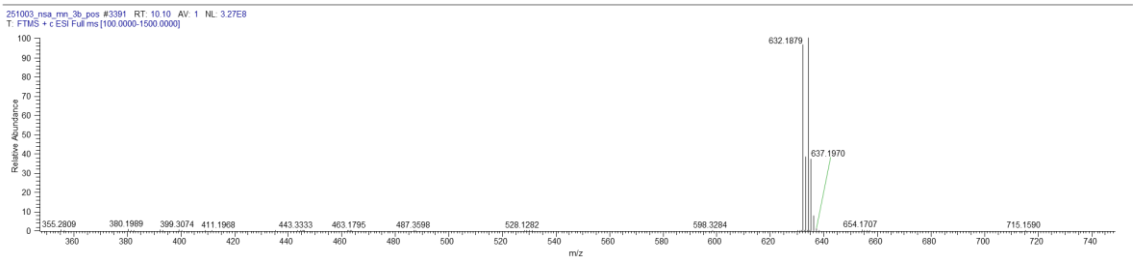

Figure S89: HRMS spectrum for compound **9a**

1-methyl-4(4-methylphenyl) pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(4-methylphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9b**)

White powder, m.p. (120-124 °C). FTIR (ATR): 3215 (w, N-H), 1709 (m, C=O), 1599 (s, C=C), 1176 (m, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (1H, d, *J*=15.0 Hz, H11a), 2.00 (3H, s, H22), 2.27 (3H, s, H27), 2.29 (3H, s, H33), 2.33-2.49 (4H, m, H1 & H2), 3.08 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.16-3.22 (2H, m, H11b & H13a), 3.37 (1H, d, *J*=15.0 Hz, H7b), 3.77 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.60 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.61 (1H, d, *J*=8.0 Hz, H19), 6.93 (1H, d, *J*=2.0 Hz, H16), 7.09 (1H, d, *J*=2.0 Hz, H28), 7.10-7.14 (6H, m, H4, H25, H30), 7.16-7.19 (5H, m, H6, H24, H31), 7.21-7.25 (3H, m, H5 & H18), 10.57 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.7 (C27), 21.0 (C33), 32.1 (C2), 34.2 (C22), 44.7 (C12), 54.1 (C7), 56.4 (C11), 56.5 (C13), 59.1 (C1), 65.0 (C10), 75.2 (C14), 110.7 (C19), 112.7 (C17), 125.9 (C6), 128.3 (C4), 128.5 (C25), 128.9 (C5), 129.0 (C31), 129.3 (C24), 129.6 (C15), 129.7 (C16) 130.3 (C30), 131.3 (C18), 131.6 (C29), 132.3 (C8), 135.1 (C23), 135.9 (C26), 137.2 (C28), 139.2 (C32), 140.0 (C3), 142.7 (C20), 176.2 (C21), 198.2 (C9). HRMS (ESI): *m/z* 660.2208 (MH^+ $C_{39}H_{39}{}^{79}BrN_3O_2^+$ requires 660.2226)[10].

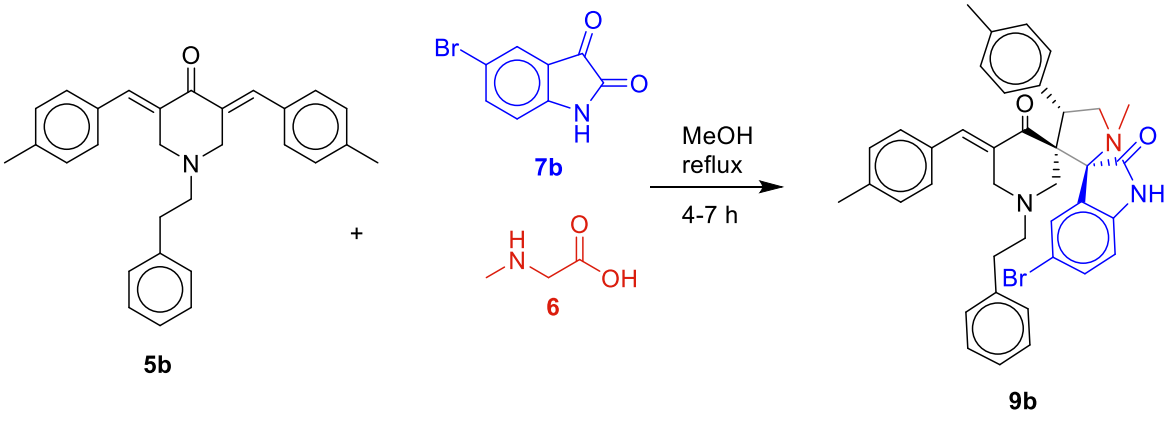

Figure S90: Reaction scheme of compound **9b**

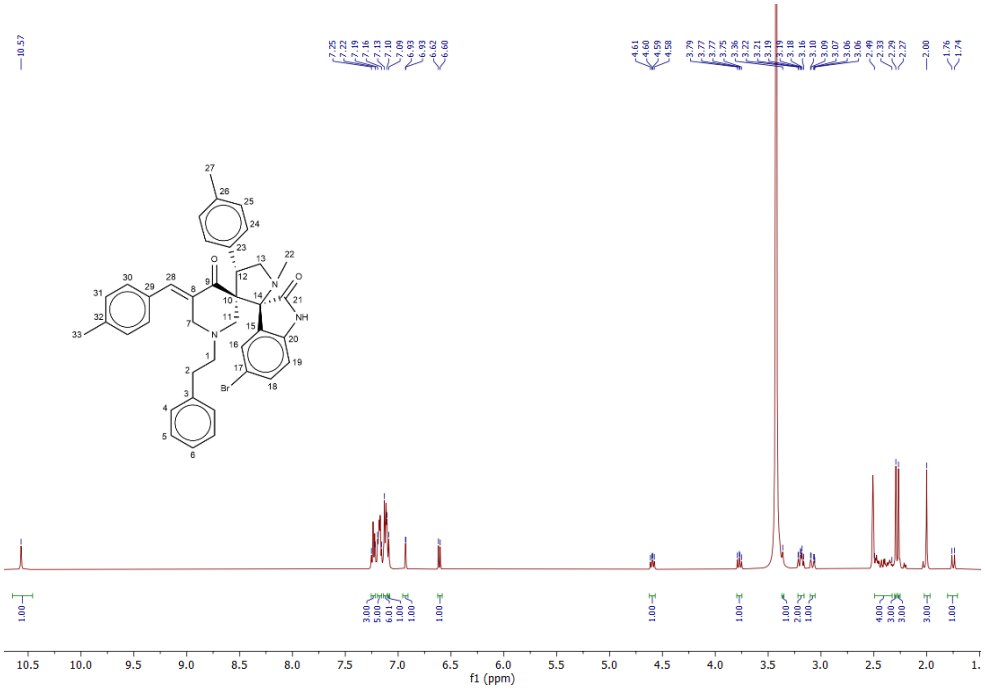

Figure S91: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9b**

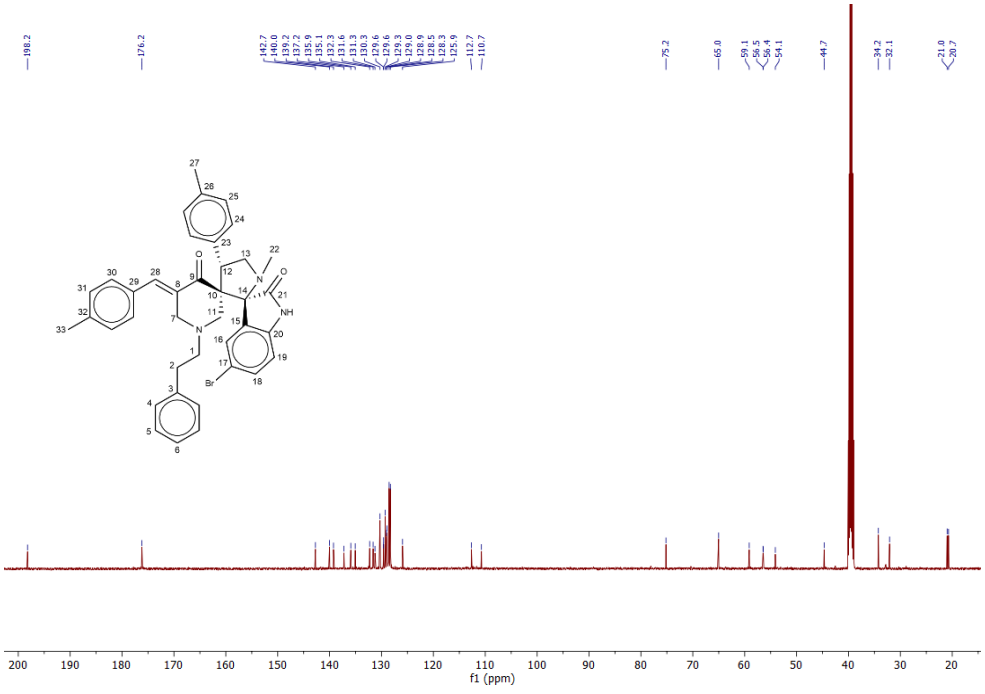

Figure S92: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9b**

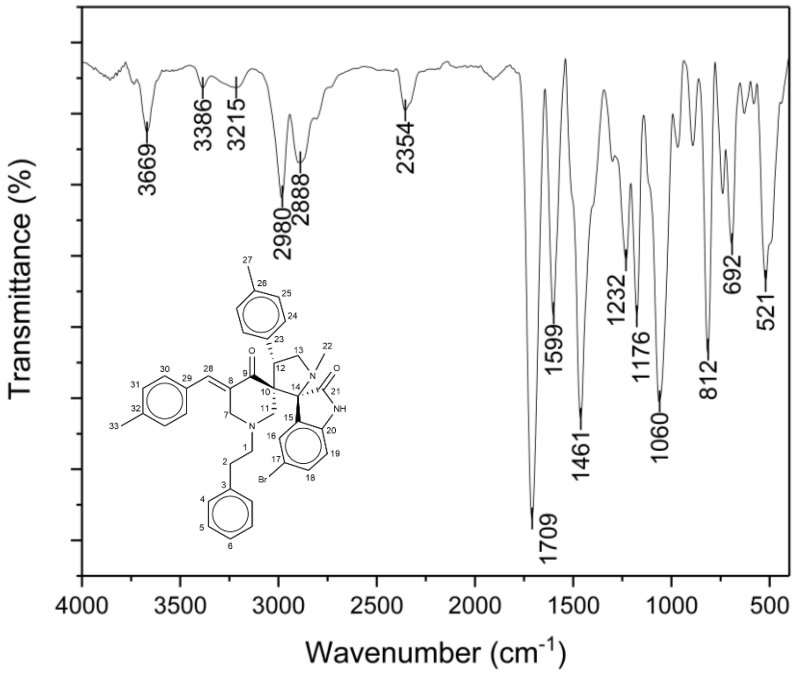

Figure S93: FT-IR spectrum of compound **9b**

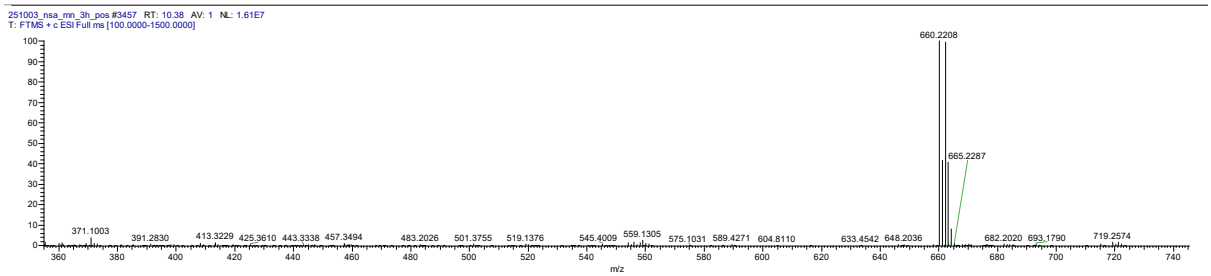

Figure S94: HRMS spectrum for compound **9b**

1-methyl-4(4-methoxyphenyl) pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(4-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9c**)

Pale yellow powder, m.p. (112-116 °C). FTIR (ATR): 3252 (w, N-H), 1715 (m, C=O), 1595 (s, C=C), 1162 (s, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74 (1H, d, *J*=15.0 Hz, H11a), 1.99 (3H, s, H22), 2.30-2.50 (4H, m, H1 & H2), 3.07 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.12-3.20 (2H, m, H11b & H13a), 3.33 (1H, d, *J*=15.0 Hz, H7b), 3.71 (3H, s, H27), 3.72-3.73 (1H, m, H13b), 3.77 (3H, s, H33), 4.56 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.60 (1H, d, *J*=8.0 Hz, H19), 6.87 (1H, d, *J*=8.0 Hz, H16), 6.91-6.94 (3H, m, H18, H31), 7.11-7.14 (3H, m, H6, H28), 7.16-7.19 (4H, m, H4, H25), 7.20-7.26 (4H, m, H5 & H24), 10.57 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.1 (C2), 34.2 (C22), 44.4 (C12), 54.3 (C7), 55.0 (C27), 55.3 (C33), 56.4 (C11), 56.7 (C13), 59.3 (C1), 64.8 (C10), 75.3 (C14), 110.7 (C19), 112.7 (C17), 113.7 (C25), 114.2 (C31), 126.0 (C6), 127.2 (C29), 128.3 (C4), 128.6 (C5), 129.6 (C15), 130.0 (C16), 130.2 (C24), 130.3 (C30), 130.9 (C23), 131.2 (C18), 132.3 (C8), 137.3 (C28), 140.5 (C3), 143.2 (C20), 158.9 (C26), 160.6 (C32), 176.8 (C21) 198.5 (C9). HRMS (ESI): *m/z* 692.2088 (MH^+ $C_{39}H_{39}{}^{79}BrN_3O_4^+$ requires 692.2123).

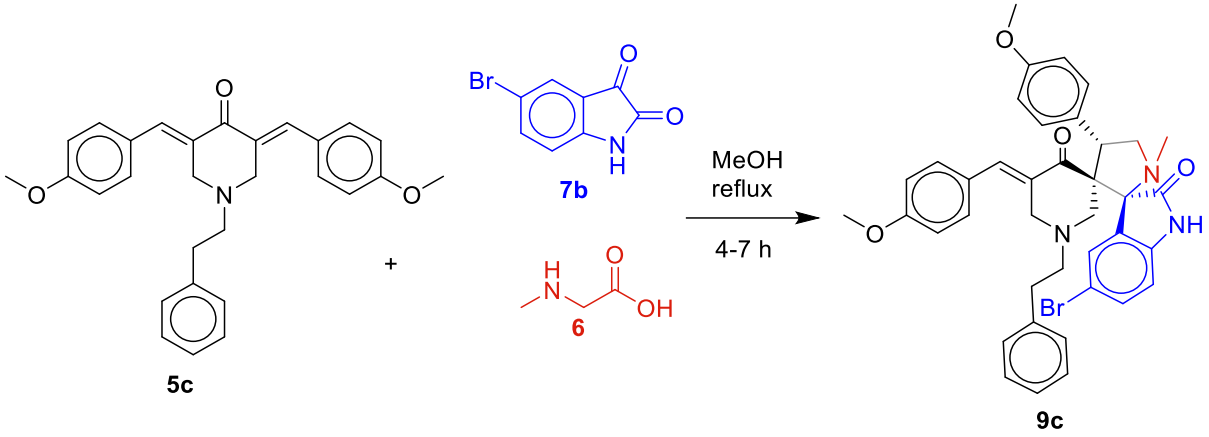

Figure S95: Reaction scheme of compound **9c**

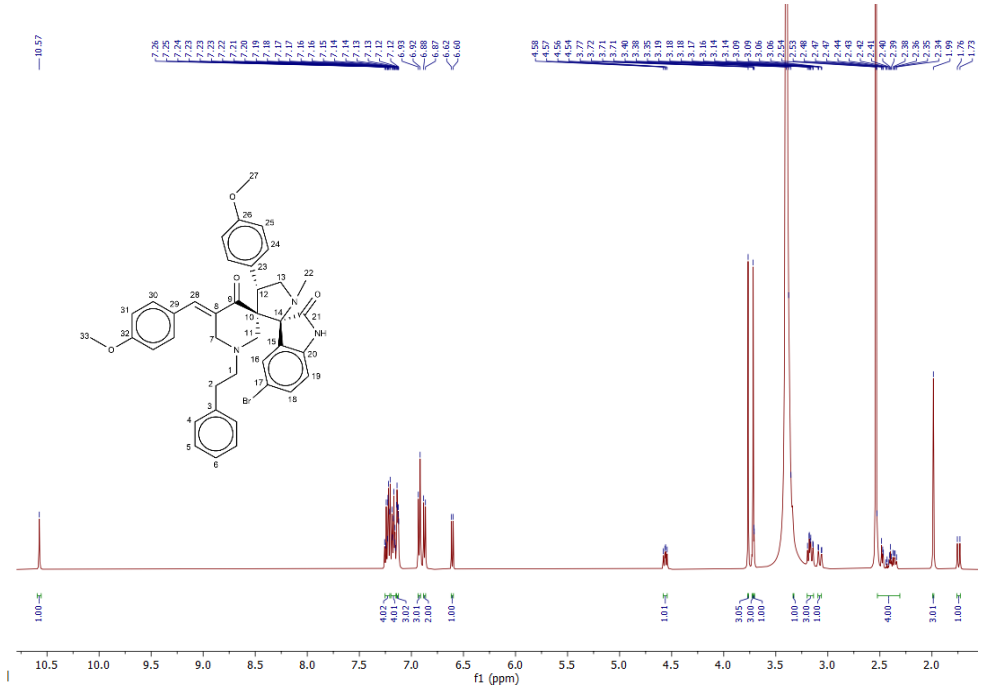

Figure S96: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9c**

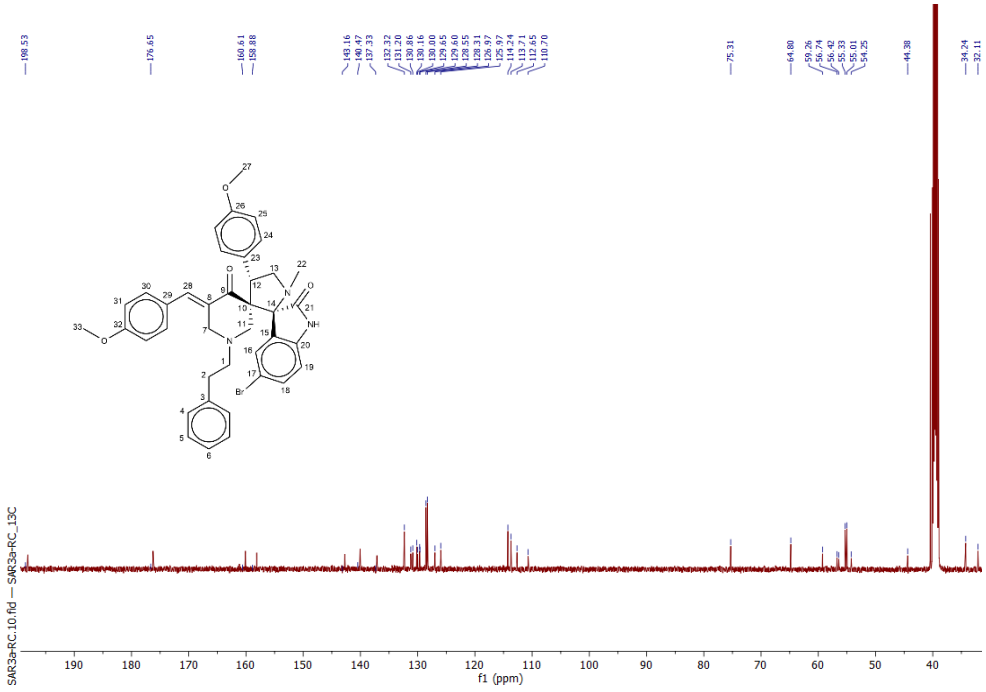

Figure S97: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9c**

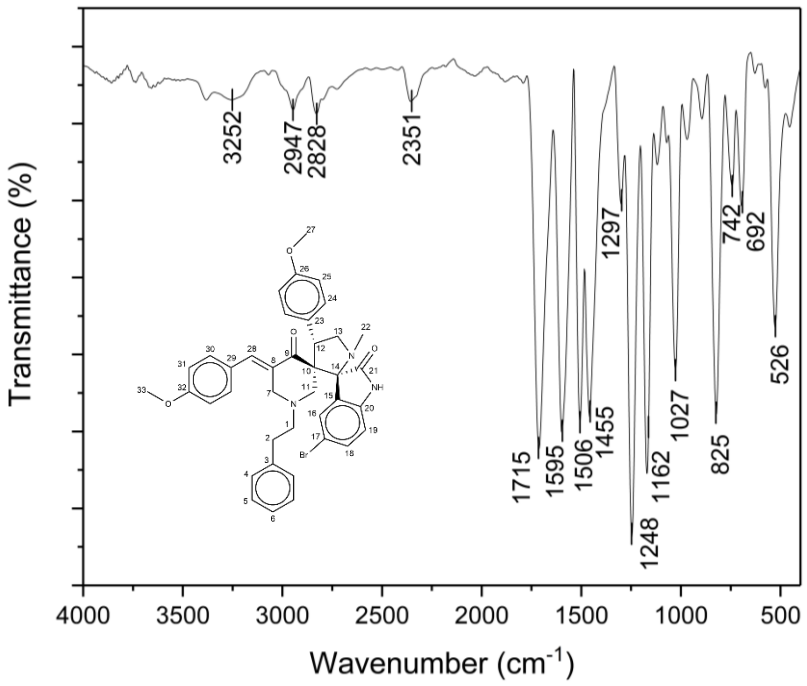

Figure S98: FT-IR spectrum of compound **9c**

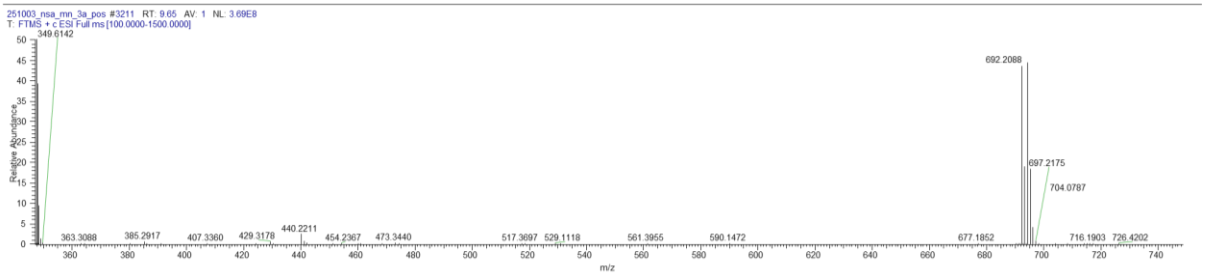

Figure S99: HRMS spectrum for compound **9c**

1-methyl-4(2-methoxyphenyl)pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(2-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9d**)

Pale yellow powder, m.p. (128-132 °C). FTIR (ATR): 3200 (w, N-H), 1701 (m, C=O), 1599 (s, C=C), 1176 (s, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.18-2.31 (2H, m, H2), 2.35-2.42 (2H, m, H1), 2.95 (1H, dd, *J*=15.0 & 2.0 Hz, H7a), 3.11-3.18 (2H, m, H11b & H13a), 3.28 (1H, d, *J*=15.0 Hz, H7b), 3.60 (3H, s, H24), 3.83 (3H, s, H32), 3.93 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.62 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.67 (1H, d, *J*=8.0 Hz, H19), 6.85-6.91 (2H, m, H28 & H36), 6.92-6.97 (2H, m, H27 & H37), 6.99 (1H, d, *J*=2.0 Hz, H16), 7.00-7.06 (3H, m, H4 & H26), 7.11 (1H, t, *J*=8.0 Hz, H6), 7.19 (2H, t, *J*=8.0 Hz, H5), 7.23 (1H, d, *J*=8.0 Hz, H34), 7.28 (1H, d, *J*=2.0 Hz, H18), 7.33 (1H, t, *J*=8.0 Hz, H35), 7.44 (1H, d, *J*=8.0 Hz, H29), 7.65 (1H, d, *J*=2.0 Hz, H30), 10.63 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.5 (C2), 34.5 (C22), 38.5 (C12), 54.9 (C7), 55.0 (C32), 55.2 (C24), 55.8 (C11), 55.9 (C13), 59.7 (C1), 63.2 (C10), 76.1 (C14), 110.5 (C19), 110.8 (C28), 111.3 (C26), 113.1 (C17), 120.3 (C27), 120.4 (C34), 123.4 (C23), 126.0 (C6), 127.0 (C36), 128.0 (C31), 128.1 (C29), 128.4 (C4), 128.6 (C5), 129.7 (C15), 129.8 (C16), 130.2 (C37), 131.0 (C35), 131.2 (C18), 131.8 (C30), 132.1 (C8), 140.0 (C3), 143.1 (C20), 157.8 (C25), 158.2 (C33), 176.8 (C21), 197.2 (C9). HRMS (ESI): *m/z* 692.2087 (MH^+ $C_{39}H_{39}{}^{79}BrN_3O_4^+$ requires 692.2124).

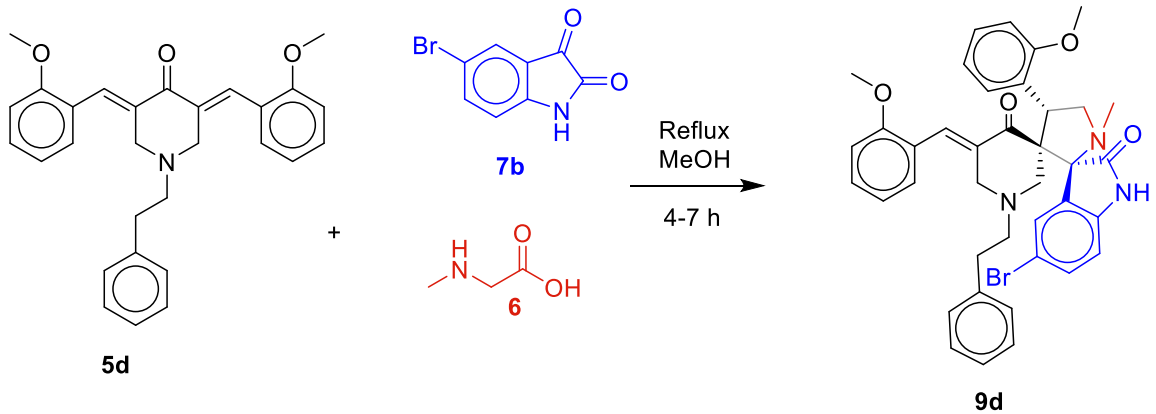

Figure S100: Reaction scheme of compound **9d**

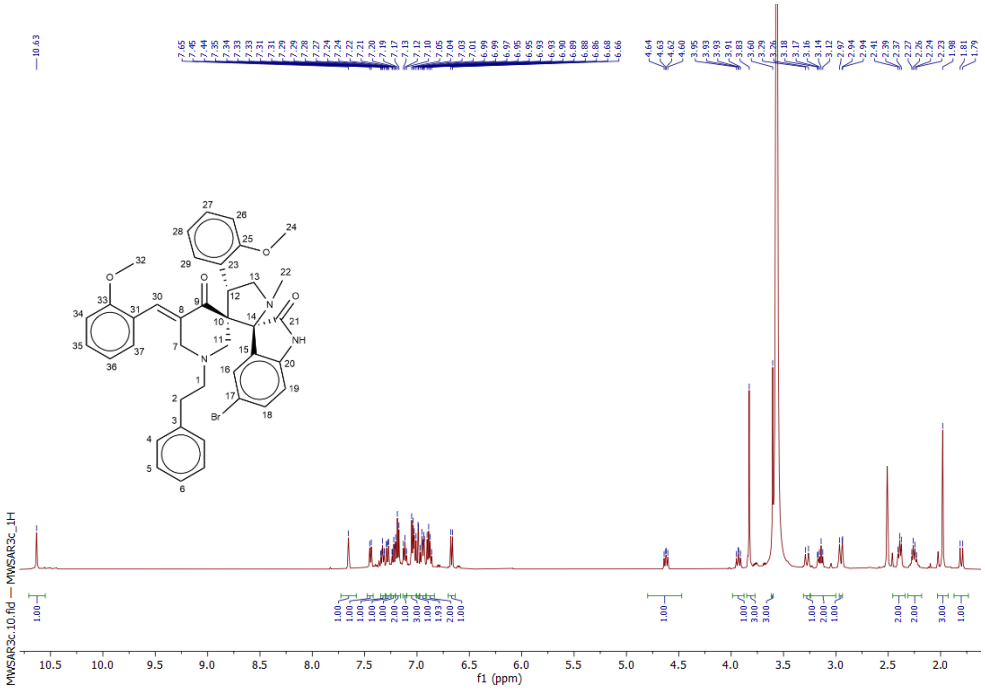

Figure S101: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9d**

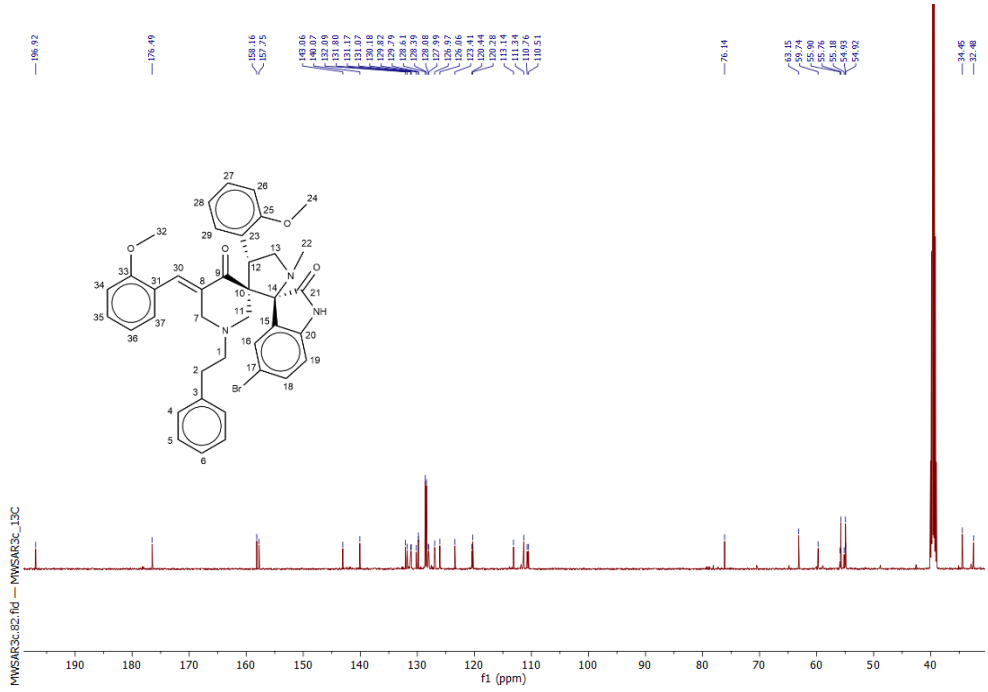

Figure S102: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9d**

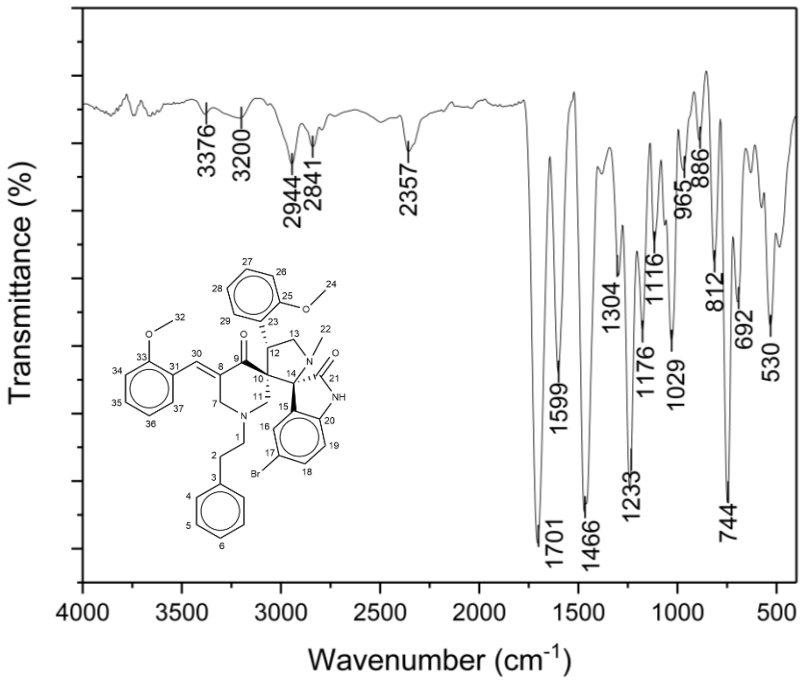

Figure S103: FT-IR spectrum of compound **9d**

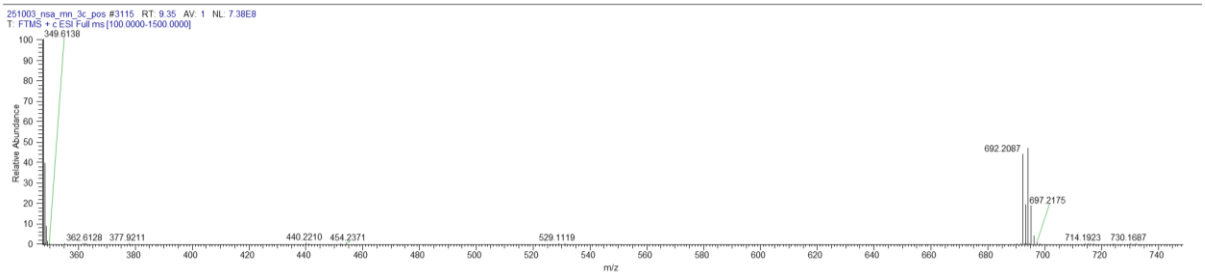

Figure S104: HRMS spectrum for compound **9d**

1-methyl-4(2,4-methoxyphenyl) pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(2,4-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9e**)

Pale yellow powder, m.p. (122-126 °C). FTIR (ATR): 3193 (w, N-H), 1709 (m, C=O), 1593 (s, C=C), 1204 (m, C-N) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 1.79 (1H, d, *J*=15.0 Hz, H11a), 1.96 (3H, s, H22), 2.25-2.44 (4H, m, H1, H2), 2.92 (1H, dd, *J*=12.0 & 2.0 Hz, H7a), 2.97 (1H, d, *J*=15.0 Hz, H11b), 3.10 (1H, t, *J*=8.0, 7.5 Hz, H13a), 3.28 (1H, d, *J*=12.0 Hz, H7b), 3.58 (3H, s, H25), 3.73 (3H, s, H37), 3.78 (1H, s, H28), 3.82 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 3.85 (3H, s, H34), 4.57 (1H, dd, *J*=7.5, 3.0 Hz, H12), 6.45-6.48 (2H, m, H26, H38), 6.52 (1H, dd, *J*=8.0, 2.0 Hz, H29), 6.58 (1H, d, *J*=2.0 Hz, H35), 6.63 (1H, d, *J*=8.0 Hz, H19), 6.92 (1H, d, *J*=8.0 Hz, H39), 6.97 (1H, d, *J*=2.0, H16), 7.08 (2H. d, *J*=8.0 Hz, H5), 7.11-7.15 (m, H6), 7.21 (2H, d, *J*=8.0 Hz, H4), 7.25 (1H, dd, *J*=8.0, 2.0 Hz, H18), 7.35 (1H, d, *J*=8.0 Hz, H30), 7.65 (1H, d, *J*=2.0 Hz, H31), 10.59 (1H, s, NH). ^{13}C NMR (125 Mhz, DMSO-d_6): δ 32.4 (C2), 34.3 (C22), 38.5 (C12), 54.9 (C7), 55.1 (C25), 55.4 (C28), 55.7 (C34), 55.8 (C13), 55.9 (C37), 56.0 (C11), 59.7 (C1), 62.9 (C10), 76.0 (C14), 98.1 (C26), 98.2 (C35), 104.2 (C29), 105.1 (C38), 110.4 (C19), 112.8 (C17), 116.2 (C32), 119.0 (C23), 125.8 (C6), 128.2 (C4), 128.4 (C5), 128.5 (C30), 129.8 (C15), 129.9 (C16), 130.0 (C8), 130.9 (C31), 131.0 (C18), 132.4 (C39), 140.0 (C3), 142.9 (C20), 158.5 (C24), 159.8 (C27), 159.2 (C36), 161.8 (C33), 176.3 (C21), 196.8 (C9). HRMS (ESI): *m/z* 752.2309 (MH^+ $C_{41}H_{43}{}^{79}BrN_3O_6^+$ requires 752.2335).

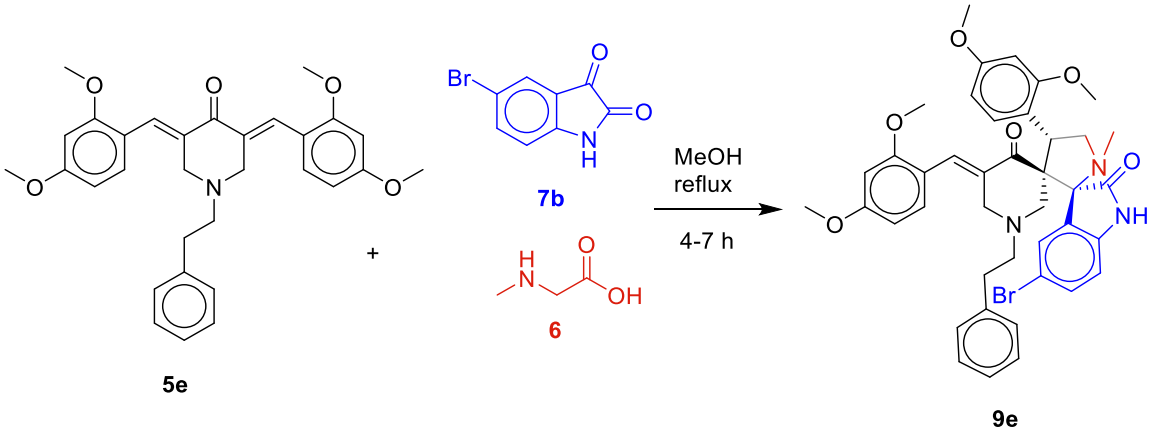

Figure S105 Reaction scheme of compound **9e**

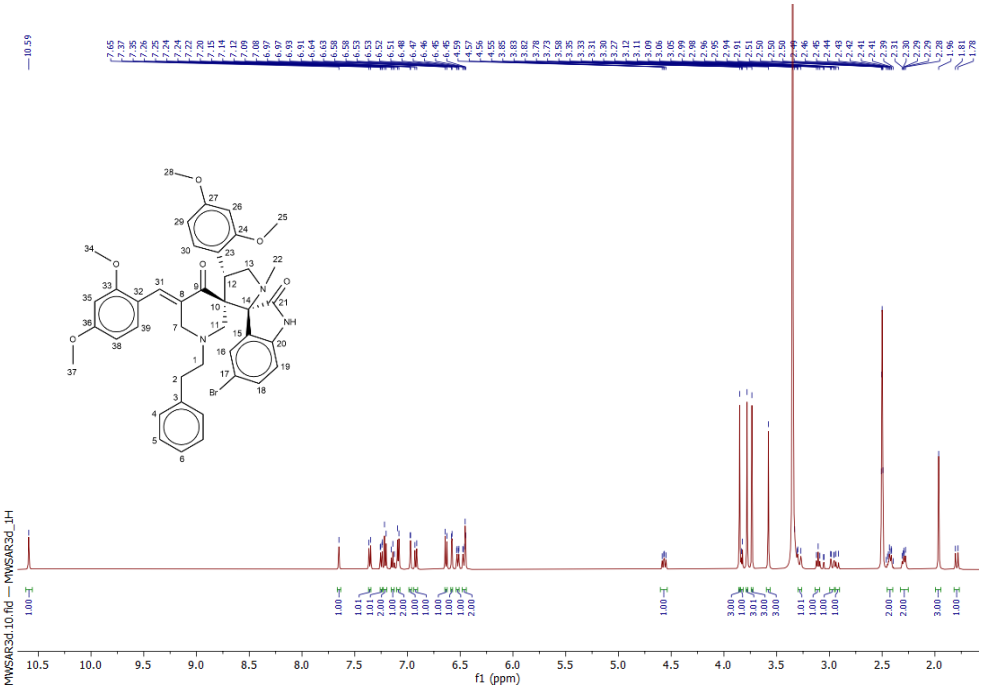

Figure S106: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9e**

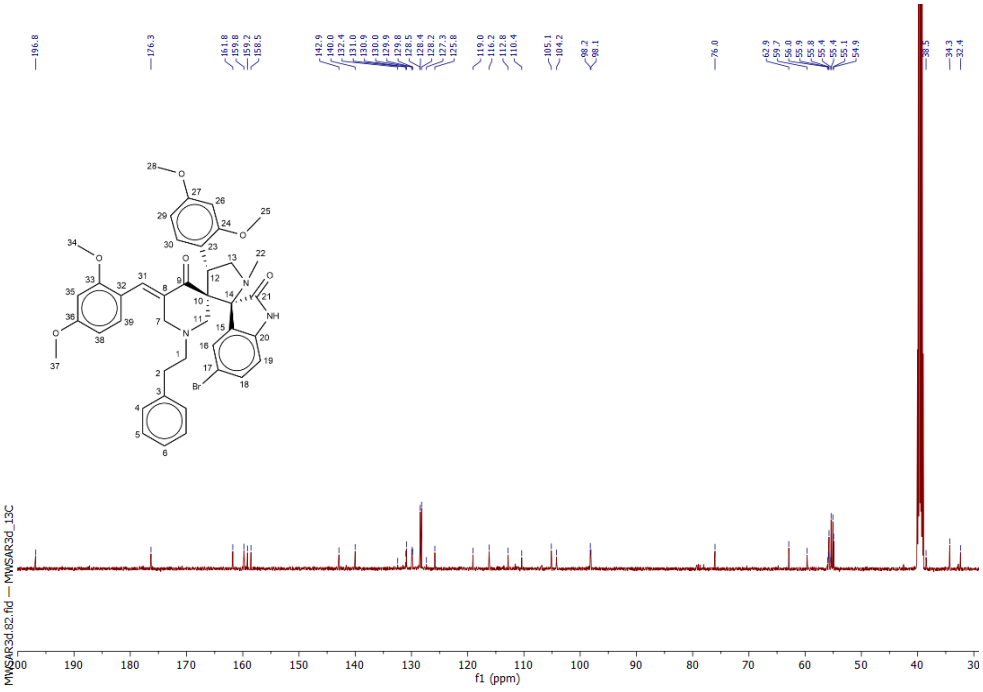

Figure S107: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9e**

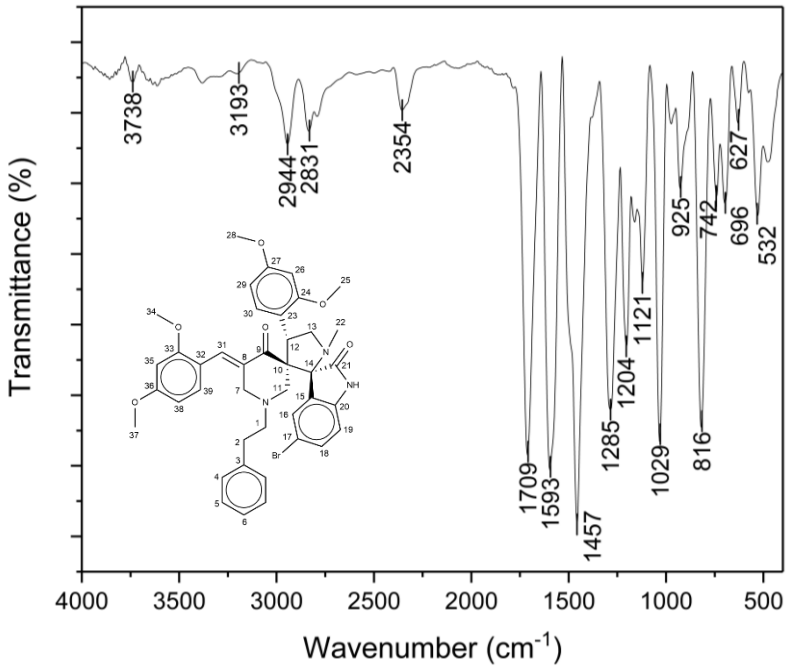

Figure S108: FT-IR spectrum of compound **9e**

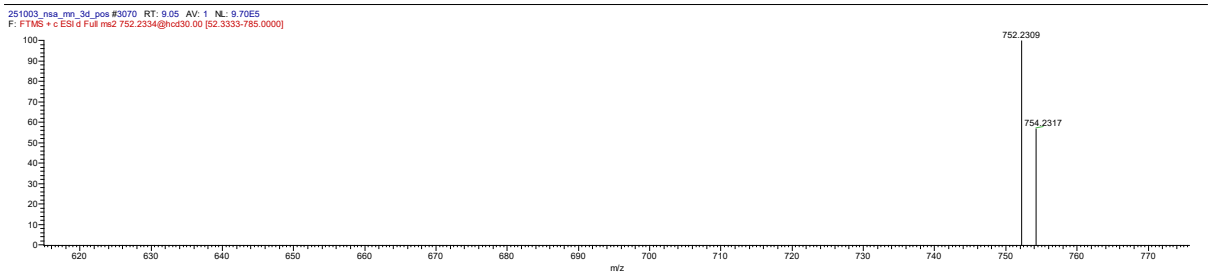

Figure S109: HRMS spectrum for compound **9e**

1-methyl-4(4-chlorophenyl) pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(4-chlorophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9f**)

White powder, m.p. (121-125 °C). FTIR (ATR): 3194 (w, N-H), 1713 (m, C=O), 1599 (s, C=C), 1181 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76 (1H, d, *J*=15.0 Hz, H11a), 2.00 (3H, s, H22), 2.32-2.46 (4H, m, H1, H2), 3.10-3.17 (2H, m, H7a & H11b), 3.23 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.31 (1H, d, *J*=12.0 Hz, H7b), 3.74 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.61 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.62 (1H, d, *J*=8.0 Hz, H19), 6.91 (1H, m, H16), 7.08-7.16 (3H, m, H4 & H27), 7.18-7.26 (6H, m, H5, H6, H18, H29), 7.32 (2H, d, *J*=8.0 Hz, H24), 7.38 (2H, d, *J*=8.0 Hz, H25), 7.42 (2H, d, *J*=8.0 Hz, H30), 10.63 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.9 (C2), 34.1 (C22), 44.5 (C12), 53.8 (C7), 56.2 (C11), 56.5 (C13), 58.9 (C1), 65.0 (C10), 75.1 (C14), 110.8 (C19), 112.6 (C17), 125.9 (C6), 128.2 (C4), 128.3 (C5), 128.5 (C25), 128.7 (C24), 129.3 (C15), 129.5 (C16), 131.1 (C29), 131.4 (C28), 131.5 (C30), 131.8 (C18), 133.0 (C26), 133.7 (C8), 133.9 (C31), 135.6 (C27), 137.1 (C23), 139.9 (C3), 142.7 (C20), 176.0 (C21), 198.0 (C9). HRMS (ESI): *m/z* 700.0960 (MH^+ $C_{37}H_{33}{}^{79}Br^{37}Cl_2N_3O_2^+$ requires 700.1133).

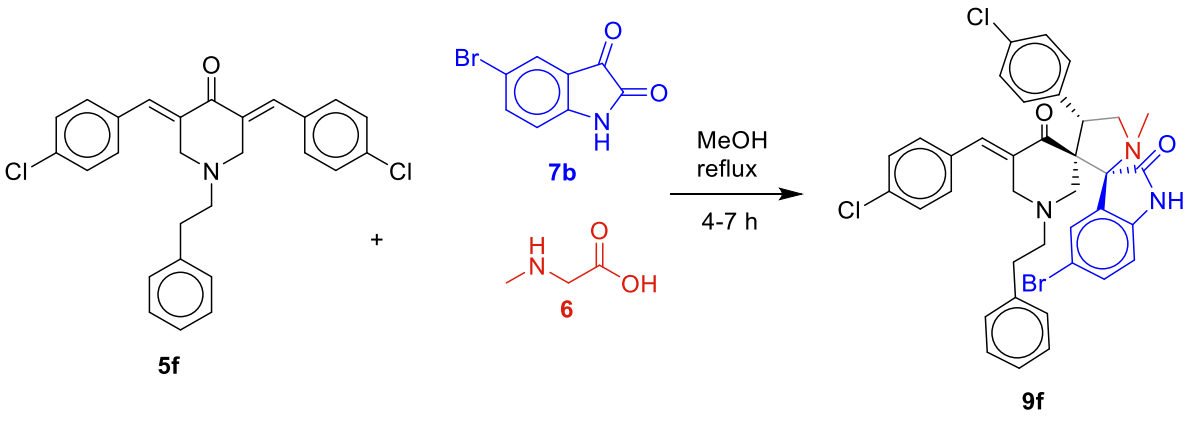

Figure S110: Reaction scheme of compound **9f**

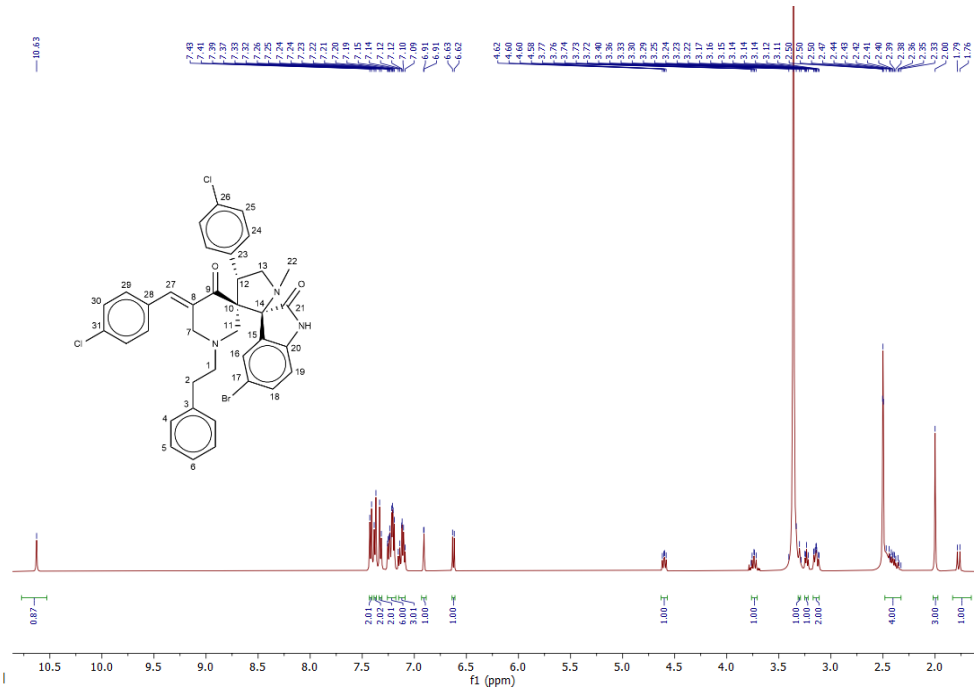

Figure S111: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9f**

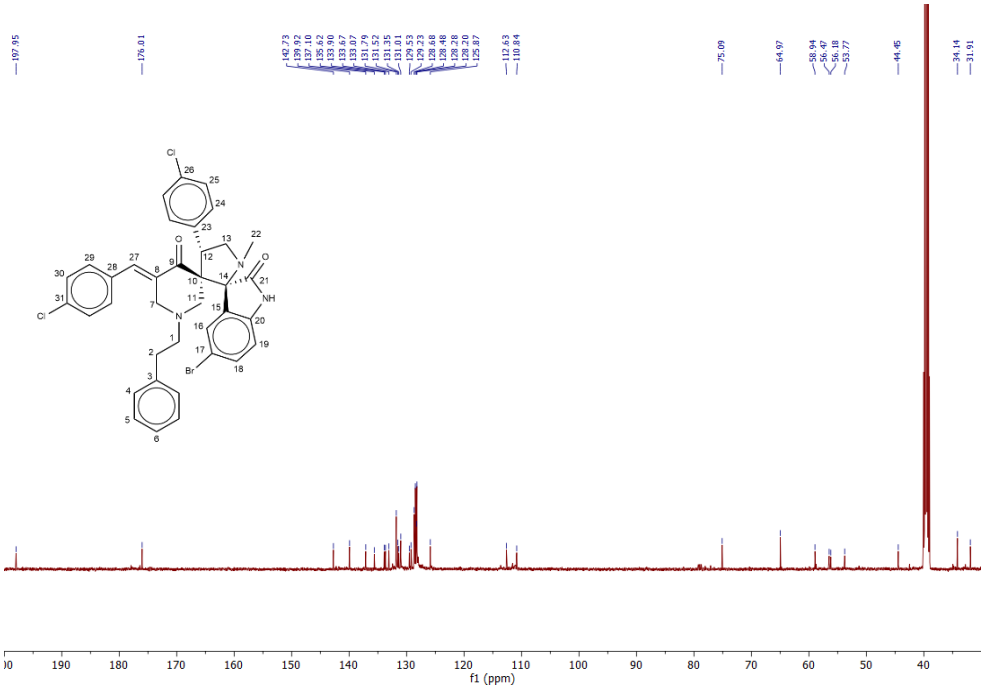

Figure S112: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9f**

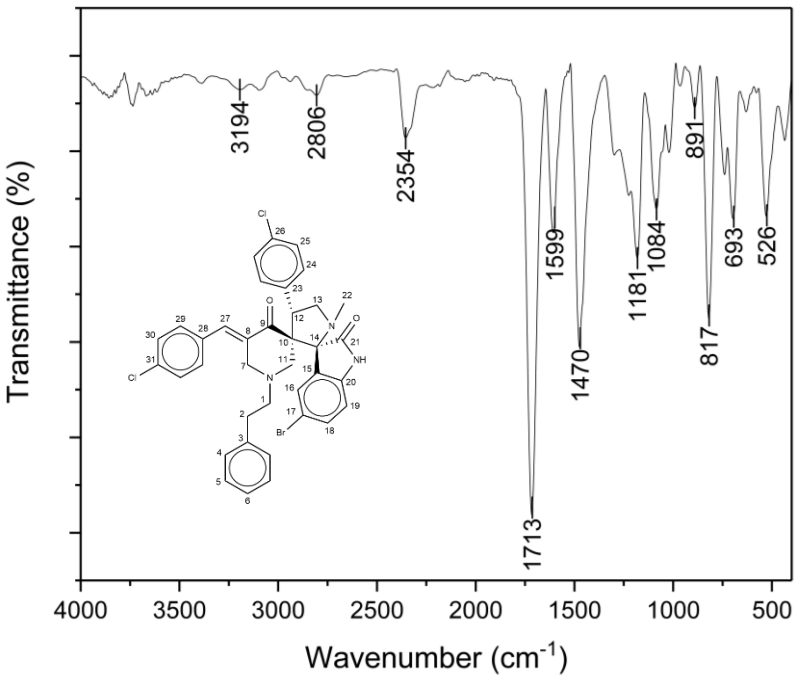

Figure S113: FT-IR spectrum of compound **9f**

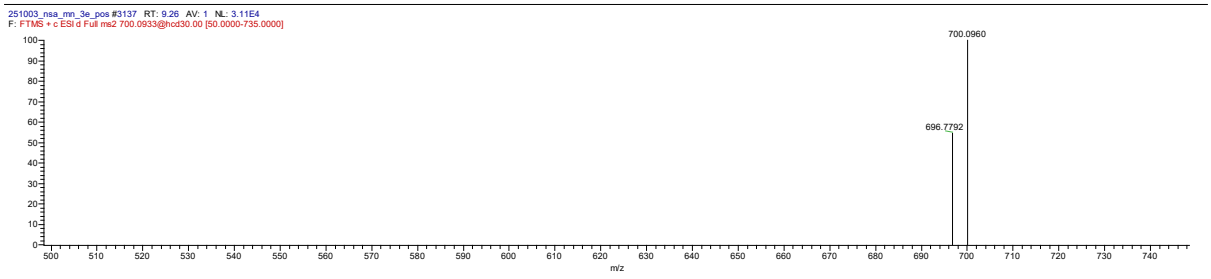

Figure S114: HRMS spectrum for compound **9f**

1-methyl-4(4-bromophenyl) pyrrolo-(spiro [2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(4-bromophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9g**)

White powder, m.p. (124-128 °C). FTIR (ATR): 3193 (w, N-H), 1704 (m, C=O), 1607 (m, C=C), 1181 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.78 (1H, d, *J*=15.0 Hz, H11a), 2.00 (3H, s, H22), 2.30-2.43 (2H, m, H1 & H2), 3.10-3.17 (2H, m, H7a & H11b), 3.23 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.30 (1H, d, *J*=15.0 Hz, H7b), 3.73 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.58 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.62 (1H, d, *J*=8.0 Hz, H19), 6.90 (1H, d, *J*=2.0 Hz, H16), 7.06 (1H, s, H27), 7.08-7.14 (5H, m, H4, H18, H29), 7.20-7.27 (5H, m, H5, H6, H24), 7.50-7.56 (4H, m, H25, H30), 10.62 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.9 (C2), 34.1 (C22), 44.5 (C12), 53.8 (C7), 56.2 (C11), 56.4 (C13), 58.9 (C1), 65.0 (C10), 75.0 (C14), 110.9 (C19), 112.6 (C17), 120.0 (C26), 122.7 (C31), 125.9 (C6), 128.1 (C4), 128.2 (C5), 129.2 (C15), 129.5 (C16), 131.2 (C25), 131.3 (C24), 131.4 (C18), 131.6 (C30), 132.0 (C29), 133.4 (C8), 133.7 (C28), 135.7 (C27), 137.5 (C23), 139.9 (C3), 142.7 (C20), 176.0 (C21), 198.0 (C9). HRMS (ESI): *m/z* 790.0090 (MH^+ $C_{37}H_{33}{}^{79}Br_2{}^{81}BrN_3O_2^+$ requires 790.0122).

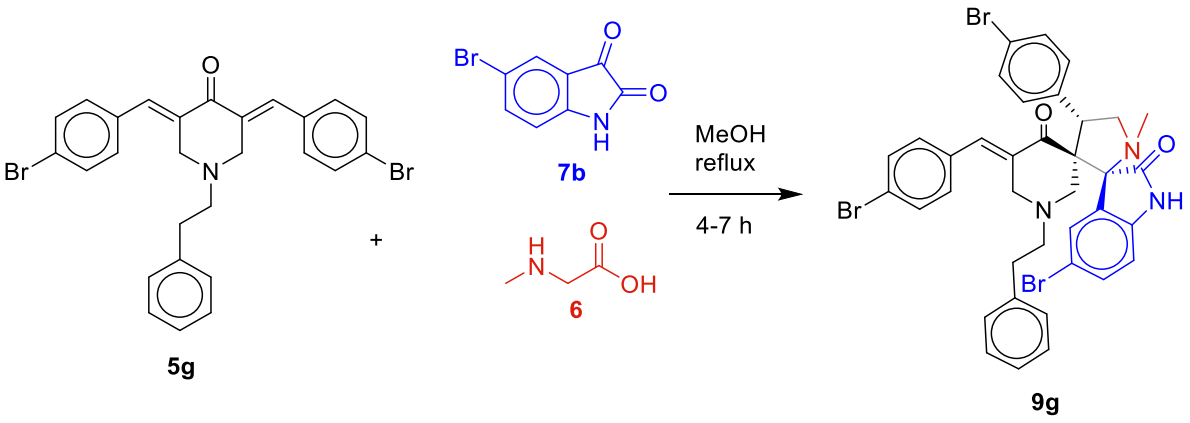

Figure S115: Reaction scheme of compound **9g**

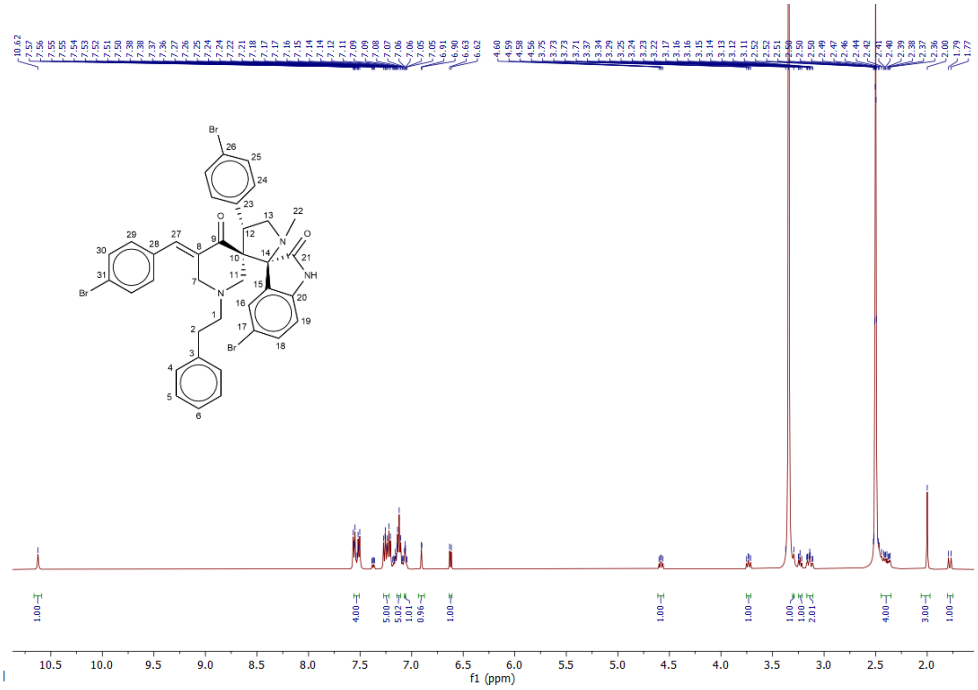

Figure S116: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9g**

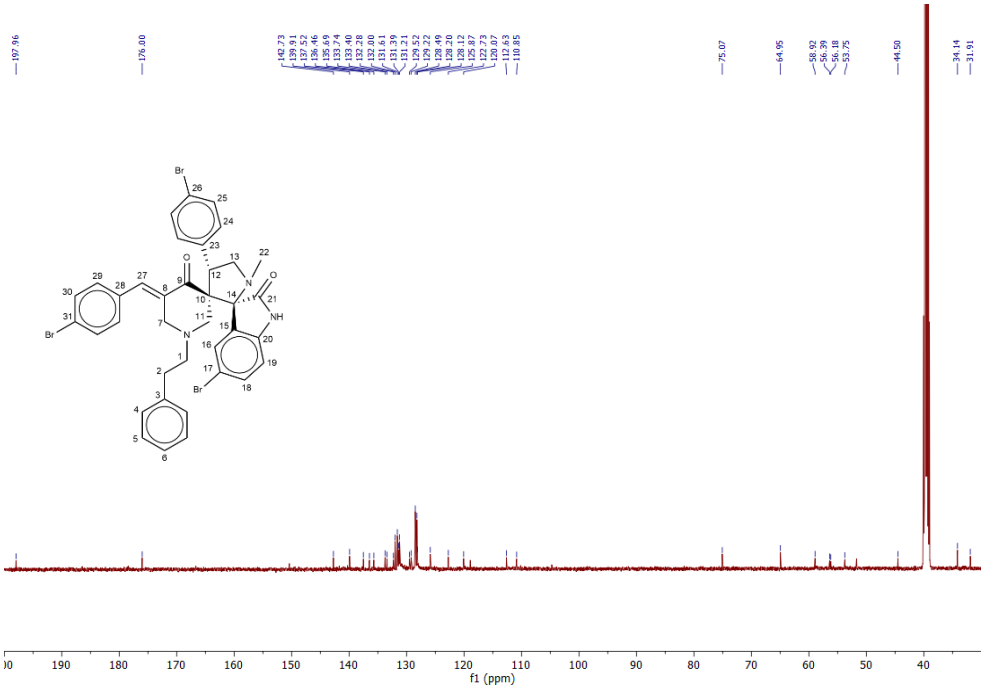

Figure S117: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9g**

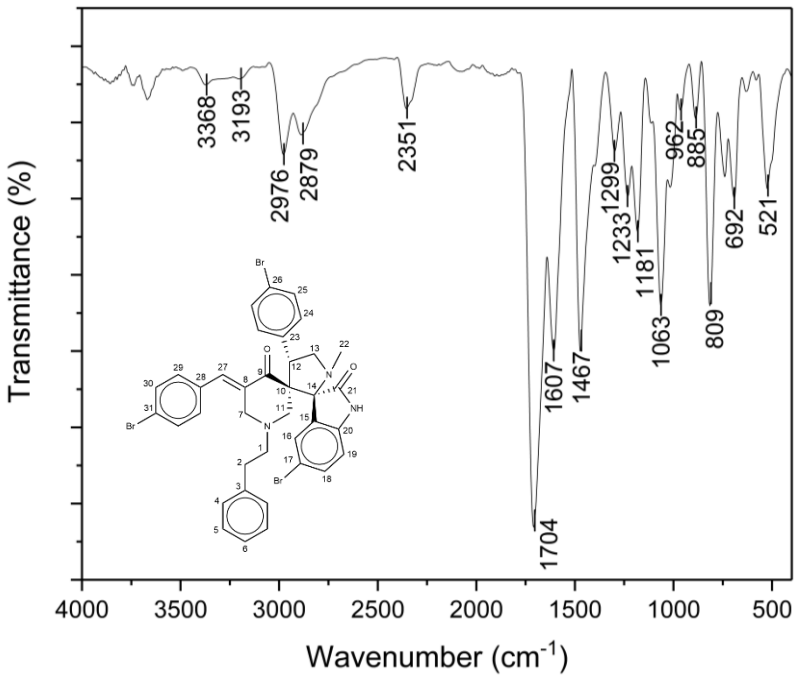

Figure S118: FT-IR spectrum of compound **9g**

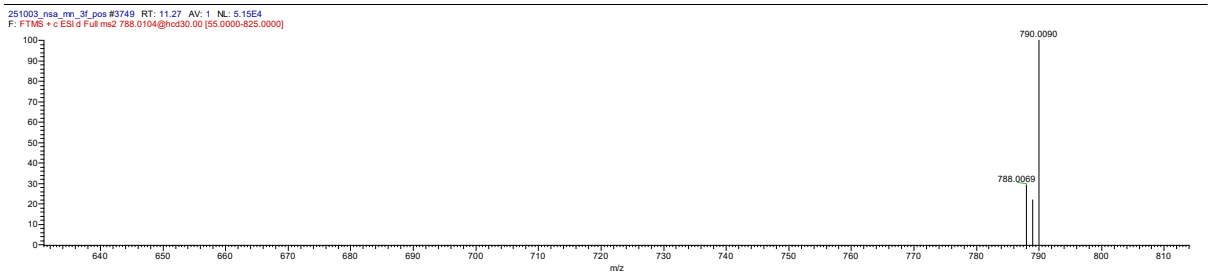

Figure S119: HRMS spectrum for compound **9g**

1-methyl-4(4-fluorophenyl) pyrrolo-(spiro[2.3"]-5"-bromooxindole)-spiro [3.3']-5'-(4-fluorophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**9h**)

White powder, m.p. (116-120 °C). FTIR (ATR): 3257 (w, N-H), 1709 (m, C=O), 1599 (m, C=C), 1167 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (1H, d, *J*=15.0 Hz, H11a), 2.00 (3H, s, H22), 2.33-2.49 (4H, m, H1 & H2), 3.09-3.18 (2H, m, H7a & H11b), 3.24 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.32 (1H, d, *J*=15.0 Hz, H7b), 3.74 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.61 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.62 (1H, d, *J*=8.0 Hz, H19), 6.91 (1H, d, *J*=2.0 Hz, H16), 7.10 (1H, s, H27), 7.11-7.17 (5H, m, H4, H18, H25), 7.18-7.27 (7H, m, H5, H6, H29, H30), 7.35 (2H, dd, *J*=8.0, 3.0 Hz, H24), 10.61 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.9 (C2), 34.1 (C22), 44.3 (C12), 53.8 (C7), 56.2 (C11), 56.7 (C13), 59.0 (C1), 64.8 (C10), 75.2 (C14), 110.8 (C19), 112.6 (C17), 115.0 (d, *J*=20.7 Hz, C25), 115.6 (d, *J*=20.7 Hz, C30), 125.9 (C6), 128.2 (C4), 128.5 (C5), 129.3 (C15), 129.5 (C16), 130.8 (d, *J*=8.5 Hz, C24), 131.0 (d, *J*=8.5 Hz, C29), 131.1 (C18), 132.5 (d, C24*J*=2.5 Hz, C23), 132.8 (C8), 134.2 (d, *J*=2.5 Hz, C28), 135.9 (C27), 139.9 (C3), 142.7 (C20), 161.1 (d, *J*=242 Hz, C26), 162.1 (d, *J*=242 Hz, C31), 176.1 (C21), 198.0 (C9). HRMS (ESI): *m/z* 668.1736 (MH^+ $C_{39}H_{39}{}^{79}BrN_3O_2^+$ requires 668.1724).

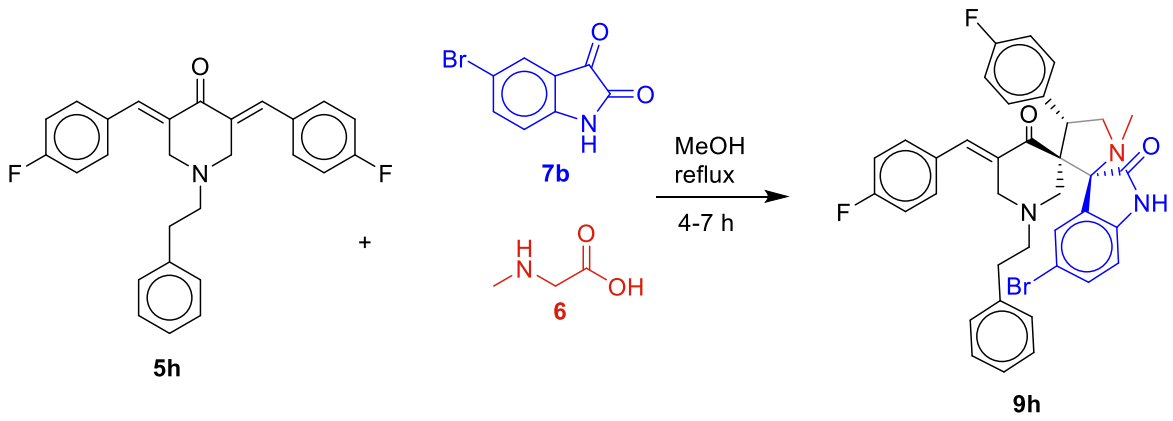

Figure S120: Reaction scheme of compound **9h**

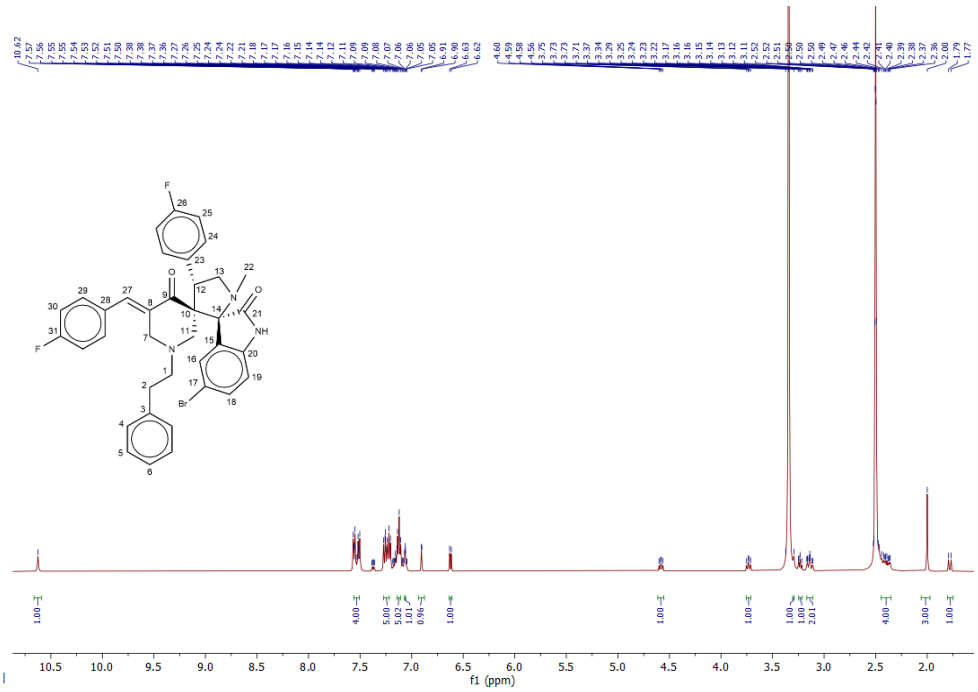

Figure S121: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **9h**

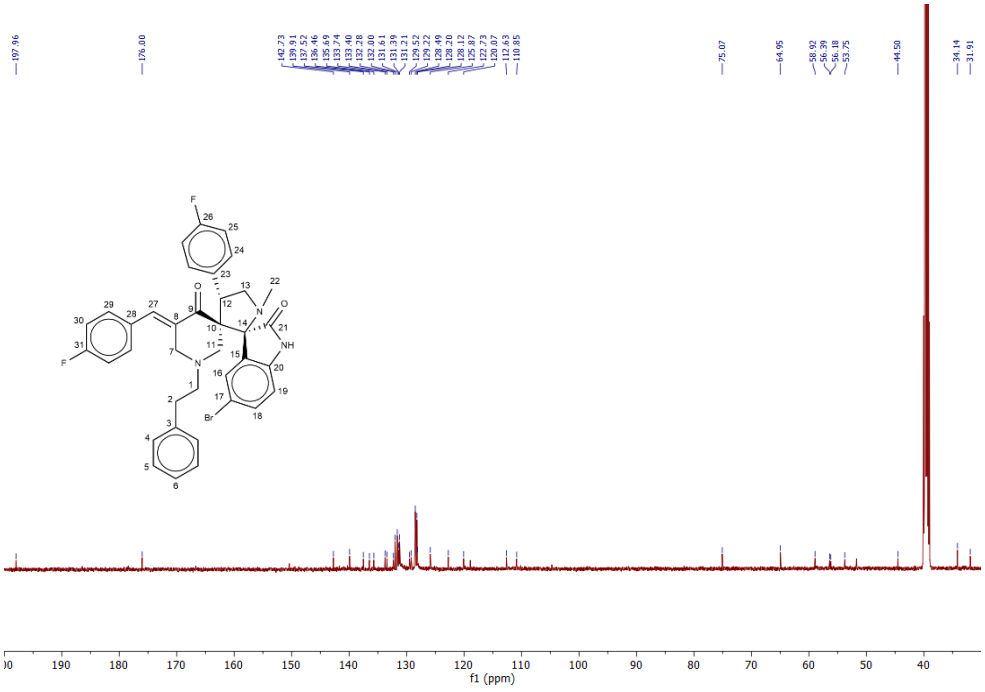

Figure S122: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **9h**

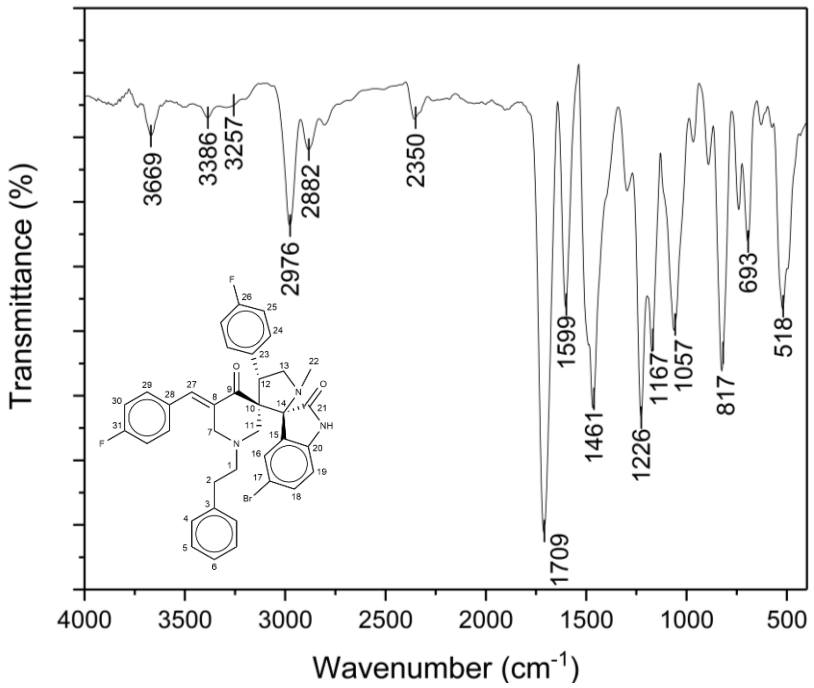

Figure S123: FT-IR spectrum of compound **9h**

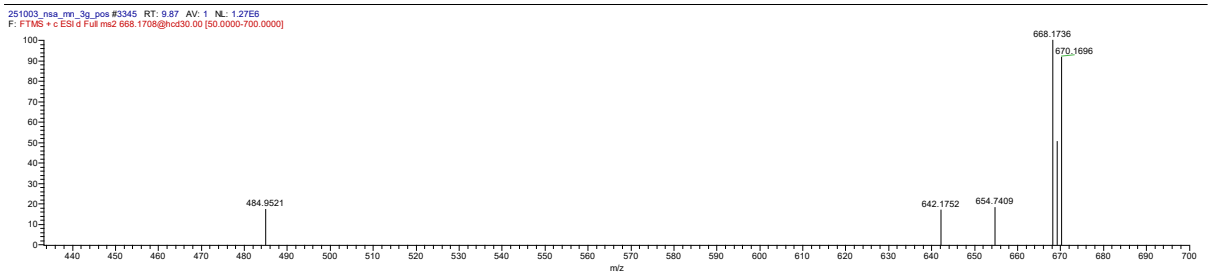

Figure S124: HRMS spectrum for compound **9h**

1-methyl-4(phenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(phenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10a**)

White powder, m.p. (104-108 °C). FTIR (ATR): 3220 (w, N-H), 1699 (s, C=O), 1599 (m, C=C), 1184 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (1H, d, *J*=15.0 Hz, H11a), 2.01 (3H, s, H22), 2.32-2.46 (4H, m, H1, H2), 3.07 (1H, dd, *J*=15.0, 2.0 Hz, H7a), 3.20-3.25 (2H, m, H11b & H13a), 3.34-3.36 (1H, m, H7b)*, 3.82 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.63 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.60-6.66 (2H, m, H16 & H19), 6.90 (td, *J*=8.0, 2.0 Hz, H18), 7.09-7.12 (3H, m, H4 & H26), 7.13-7.16 (3H, m, H6 & H27), 7.20-7.24 (4H, m, H5 & H29), 7.30-7.37 (7H, m, H24, H25, H30, H31), 10.48 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.0 (C2), 34.2 (C22), 45.2 (C12), 54.0 (C7), 56.3 (C11), 56.5 (C13), 59.2 (C1), 65.0 (C10), 75.5 (C14), 109.5 (d, *J*=7.5 Hz, C19), 114.2 (d, *J*=20.5 Hz, C16), 114.9 (d, *J*=20.5 Hz, C18), 125.9 (C6), 126.9 (C26), 128.3 (C4), 128.4 (C25), 128.5 (C5), 128.7 (C30), 128.8 (C31), 128.9 (C24), 129.0 (d, *J*=7.5 Hz, C15), 130.1 (C29), 133.0 (C8), 134.3 (C28), 137.1 (C27), 138.2 (C23), 139.7 (d, *J*=2.0 Hz, C20), 140.0 (C3), 157.5 (d, *J*=248 Hz, C17), 176.7 (C21), 198.2 (C9). HRMS (ESI): *m/z* 572.2696 (MH^+ $C_{37}H_{35}FN_3O_2^+$ requires 572.2713). * This signal was buried in the peak of water. However, its location and coupling pattern could be deduced from 2D NMR experiments and other relevant ^{1}H signals.

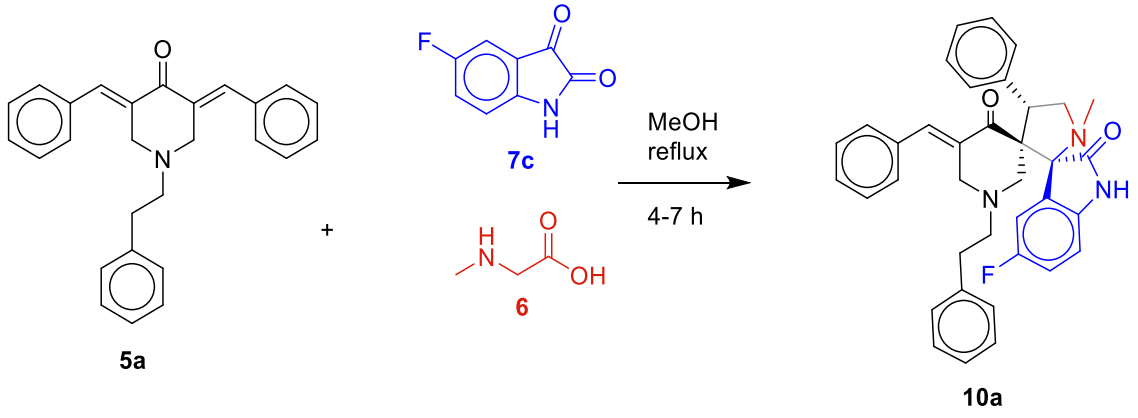

Figure S125: Reaction scheme of compound **10a**

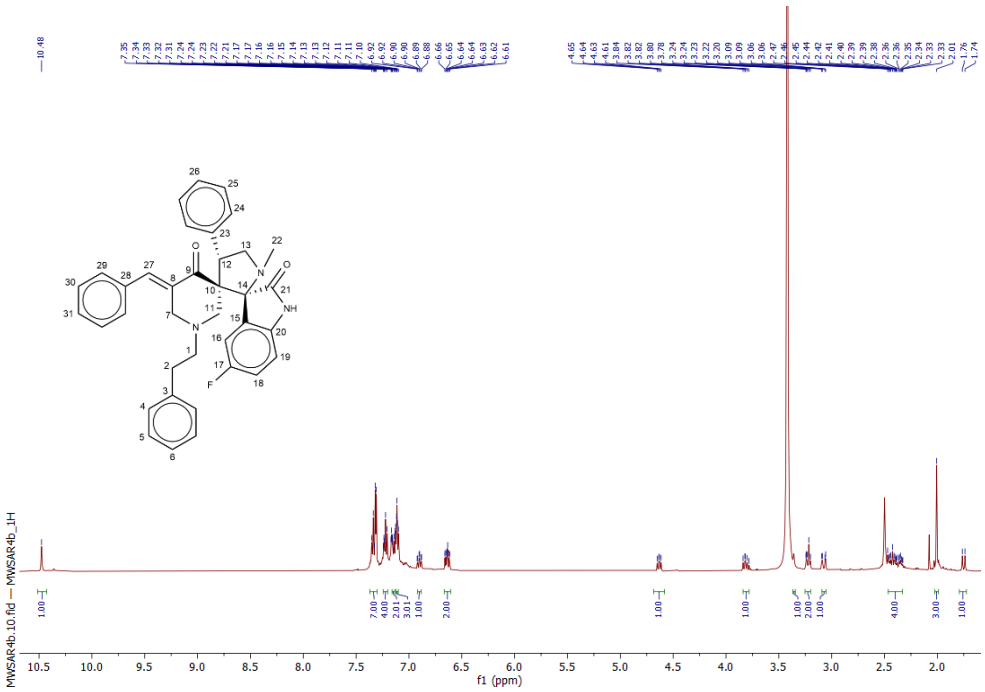

Figure S126: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10a**

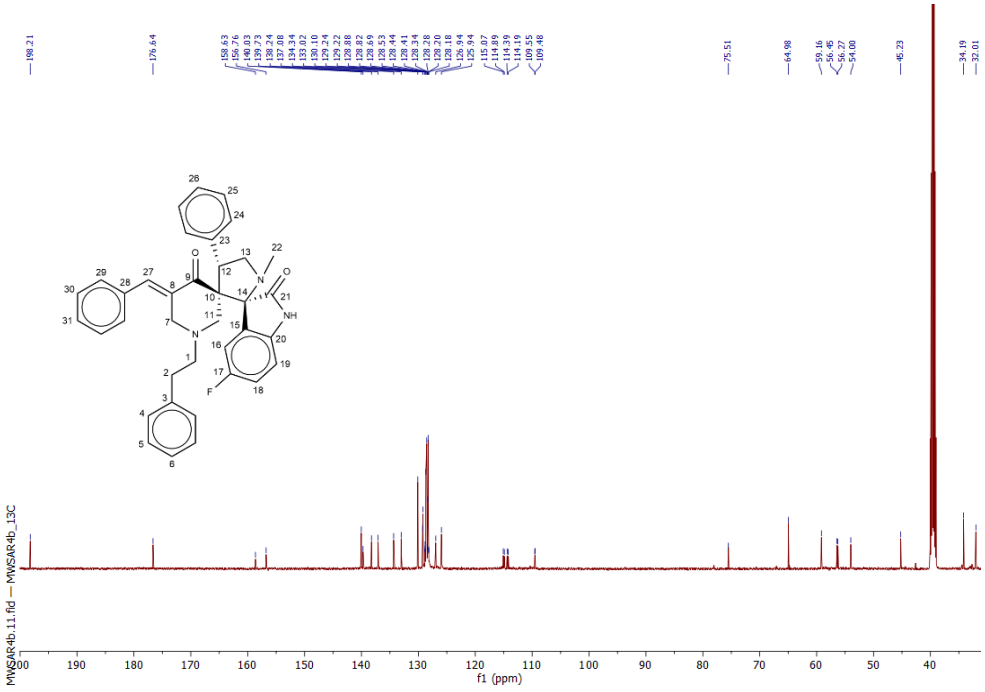

Figure S127: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10a**

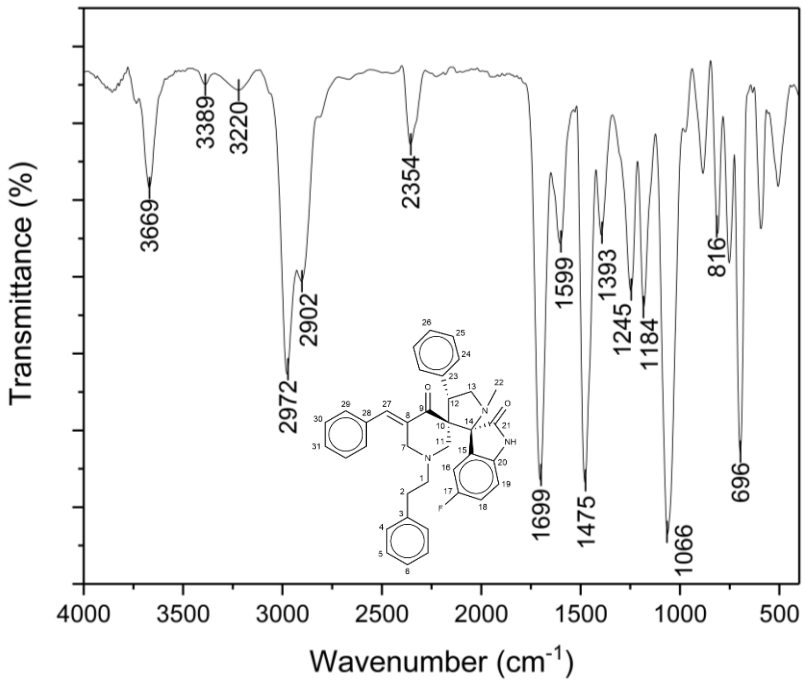

Figure S128: FT-IR spectrum of compound **10a**

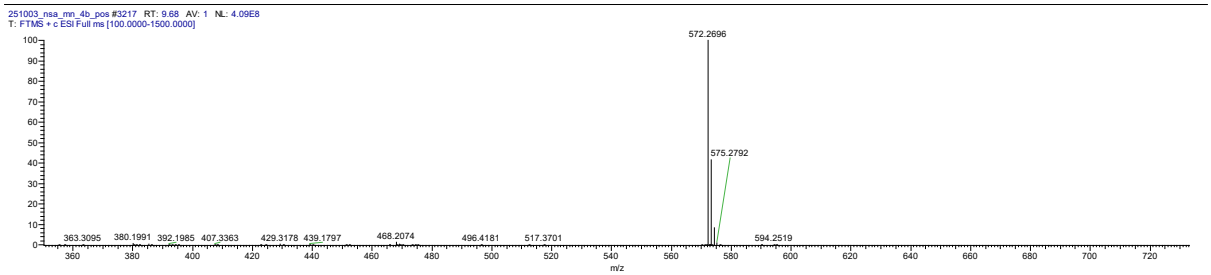

Figure S129: HRMS spectrum for compound **10a**

1-methyl-4(4-methylphenyl) pyrrolo-(spiro[2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(4-methylphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10b**)

White powder, m.p. (110-114 °C). FTIR (ATR): 3214 (w, N-H), 1699 (s, C=O), 1592 (m, C=C), 1180 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (1H, d, *J*=15.0 Hz, H11a), 1.99 (3H, s, H22), 2.26 (3H, s, H27), 2.28 (3H, s, H33), 2.33-2.49 (4H, m, H1 & H2), 3.06 (1H, d, *J*=15.0 Hz, H7a), 3.16-3.22 (2H, m, H11b & H13a), 3.36 (1H, d, *J*=15.0 Hz, H7b), 3.77 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.58 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.61 (1H, dd, *J*=8.0, 3.0 Hz, H16), 6.62-6.65 (1H, m, H19), 6.88 (1H, td, *J*=8.0, 3.0 Hz, H18), 7.03 (1H, d, H30), 7.10-7.13 (5H, m, H4, H27, H28), 7.15-7.20 (5H, m, H6, H24, H31), 7.23 (2H, t, H5), 10.45 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.7 (C27), 21.0 (C33), 32.1 (C2), 34.2 (C22), 44.8 (C12), 54.1 (C7), 56.3 (C11), 56.5 (C13), 59.2 (C1), 64.9 (C10), 75.5 (C14), 109.4 (d, *J*=8.5 Hz, C19), 114.2 (d, *J*=20.7 Hz, C16), 114.9 (d, *J*=20.7 Hz, C18), 125.9 (C6), 128.3 (C4), 128.5 (C25), 128.9 (C5), 129.1 (d, *J*=7.5 Hz, C15), 129.3 (C31), 129.6 (C24), 130.2 (C30), 131.6 (C29), 132.2 (C8), 135.1 (C23), 135.9 (C26), 137.1 (C28), 139.2 (C32), 139.7 (d, *J*=2.5, C20), 140.1 (C3), 157.6 (d, *J*=248 Hz, C17), 176.6 (C21), 198.2 (C9). HRMS (ESI): *m/z* 600.3012 (MH^+ $C_{39}H_{39}FN_3O_2^+$ requires 600.3026)[10].

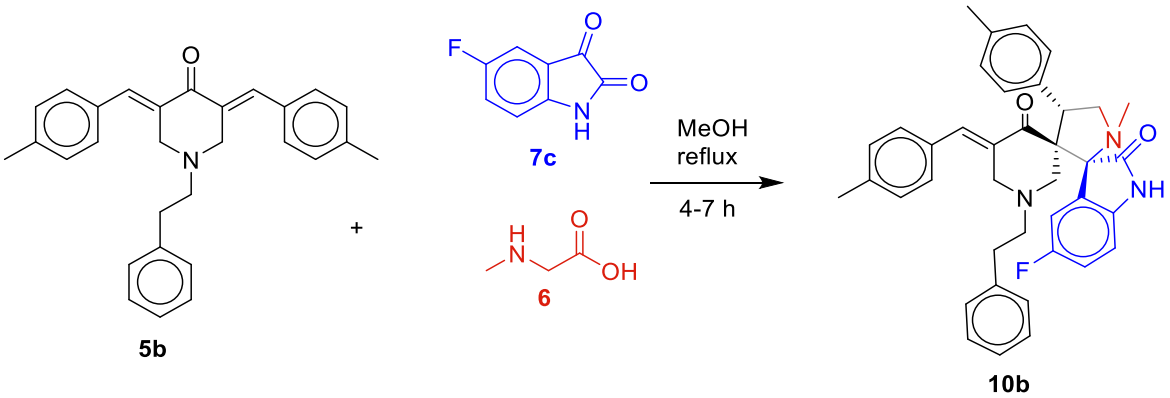

Figure S130: Reaction scheme of compound **10b**

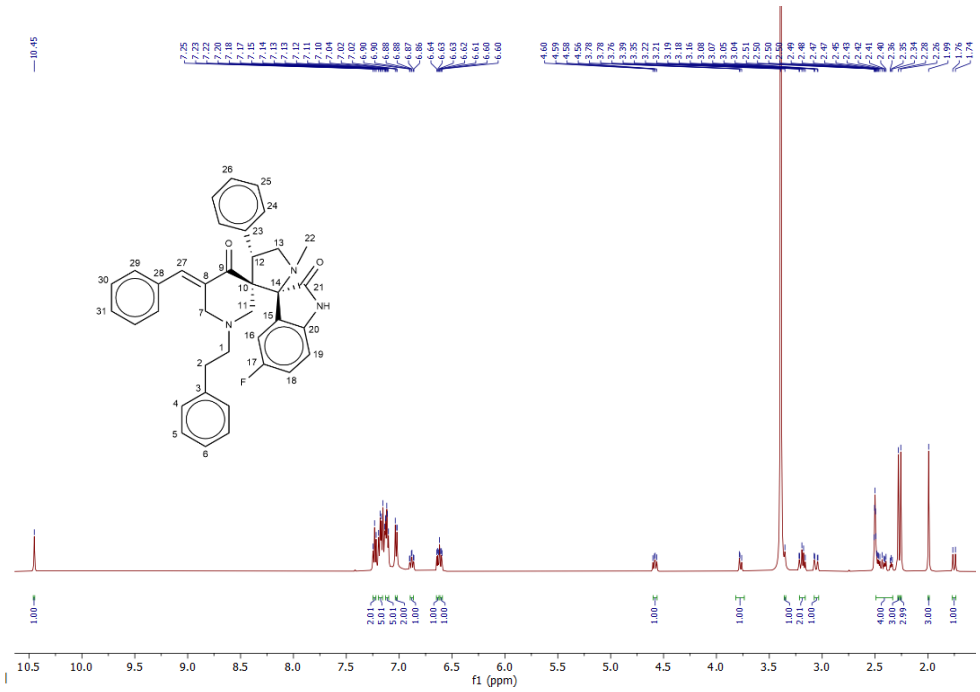

Figure S131: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10b**

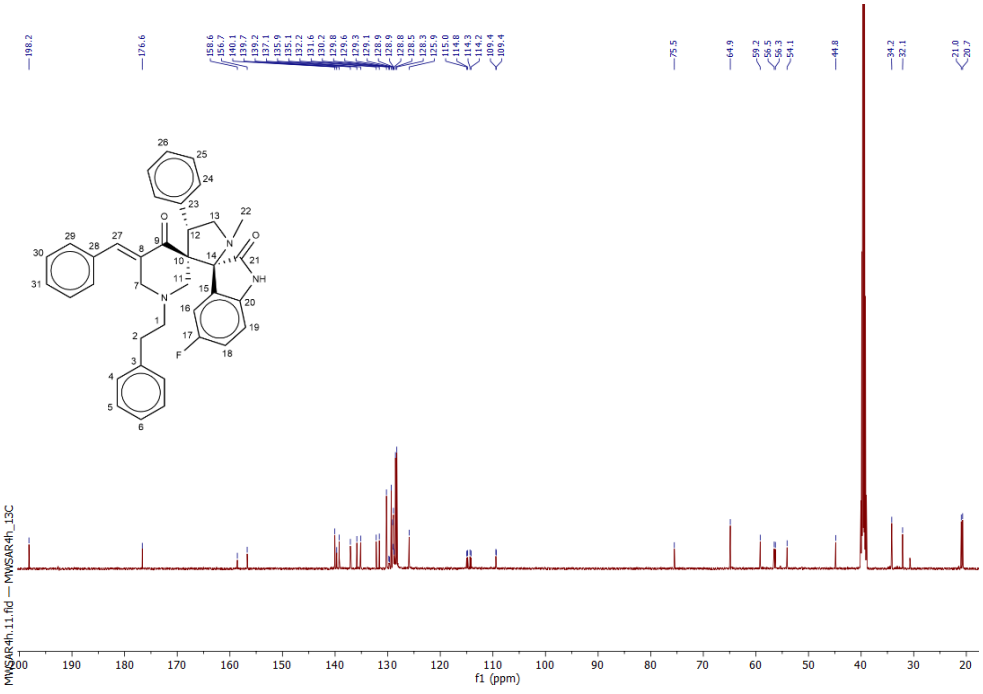

Figure S132: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10b**

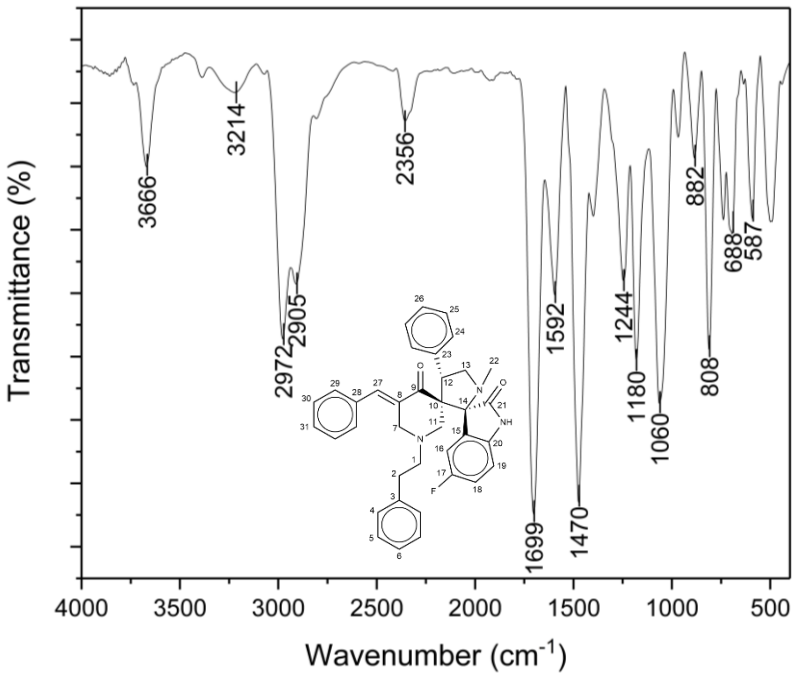

Figure S133: FT-IR spectrum of compound **10b**

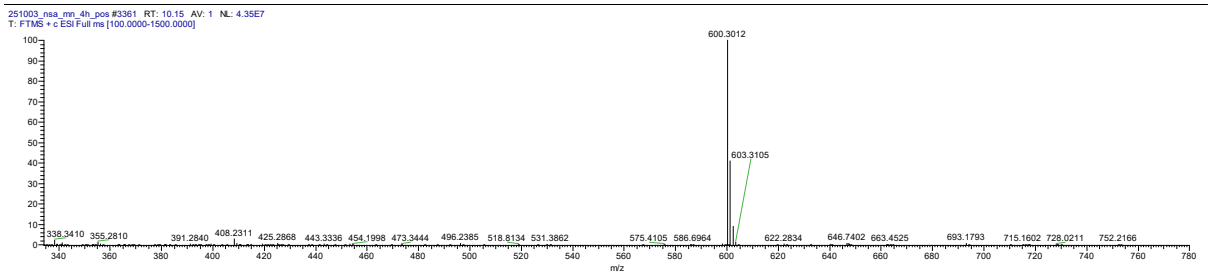

Figure S134: HRMS spectrum for compound **10b**

1-methyl-4(4-methoxyphenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(4-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10c**)

Pale yellow powder, m.p. (104-108 °C). FTIR (ATR): 3214 (w, N-H), 1709 (s, C=O), 1593 (m, C=C), 1170 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76 (1H, d, *J*=15.0 Hz, H11a), 1.99 (3H, s, H22), 2.31-2.54 (4H, m, H1 & H2), 3.06 (1H, dd, *J*=15.0, 2.0 Hz, H7a), 3.14-3.20 (2H, m, H11b & H13a), 3.35 (1H, m, H7b)*, 3.71 (3H, s, H27), 3.75-3.77 (4H, m, H13b & H33), 4.55 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.60 (1H, dd, *J*=8.0, 3.0 Hz, H16), 6.63-6.65 (1H, m, H19), 6.85-6.89 (3H, m, H18, H31), 6.91 (2H, d, *J*=8.0 Hz, H30), 7.12-7.15 (4H, H4, H25), 7.16-7.18 (2H, m, H6, H28), 7.21-7.27 (4H, m, H5 & H24), 10.47 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.1 (C2), 34.2 (C22), 44.5 (C12), 54.3 (C7), 55.0 (C27), 55.3 (C33), 56.3 (C11), 56.8 (C13), 59.3 (C1), 64.6 (C10), 75.6 (C14), 109.3 (d, *J*=8.5 Hz, C19), 113.7 (C25), 114.2 (d, *J*=20.7, C16), 114.3 (C31), 114.8 (d, *J*=20.7 Hz, C18), 126.0 (C6), 128.3 (C4), 128.6 (C5), 129.0 (d, *J*=7.5 Hz, C15), 130.0 (C24), 130.2 (C30), 130.7 (C23), 131.2 (C29), 132.3 (C8), 137.3 (C28), 139.7 (d, *J*=2.0 Hz, C20), 140.1 (C3), 157.6 (d, *J*=248 Hz, C17), 158.1 (C26), 160.1 (C32), 176.7 (C21) 198.1 (C9). HRMS (ESI): *m/z* 632.2902 (MH^+ $C_{39}H_{39}FN_3O_4^+$ requires 632.2925). *This signal was buried in the peak of water. However, its location and coupling pattern could be deduced from 2D NMR experiments and other relevant ^{1}H signals.

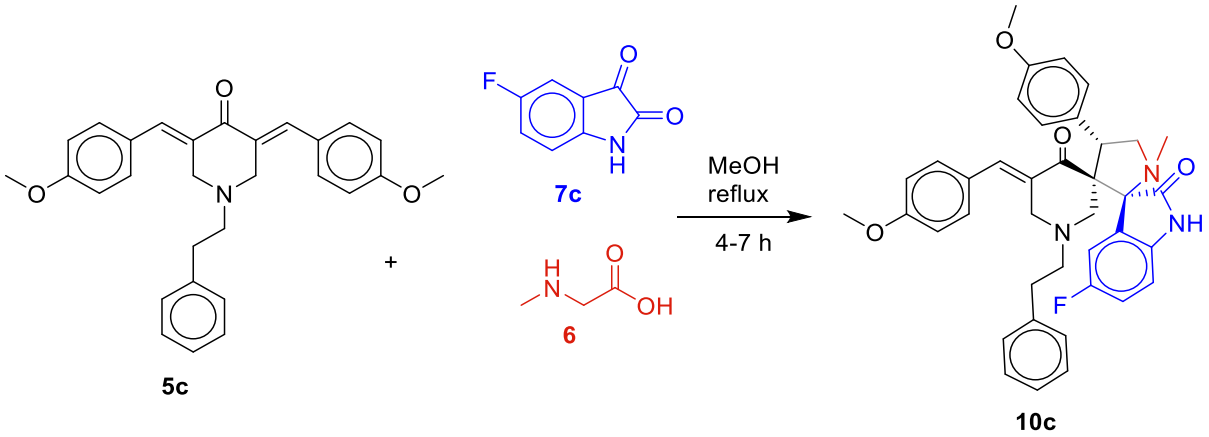

Figure S135: Reaction scheme of compound **10c**

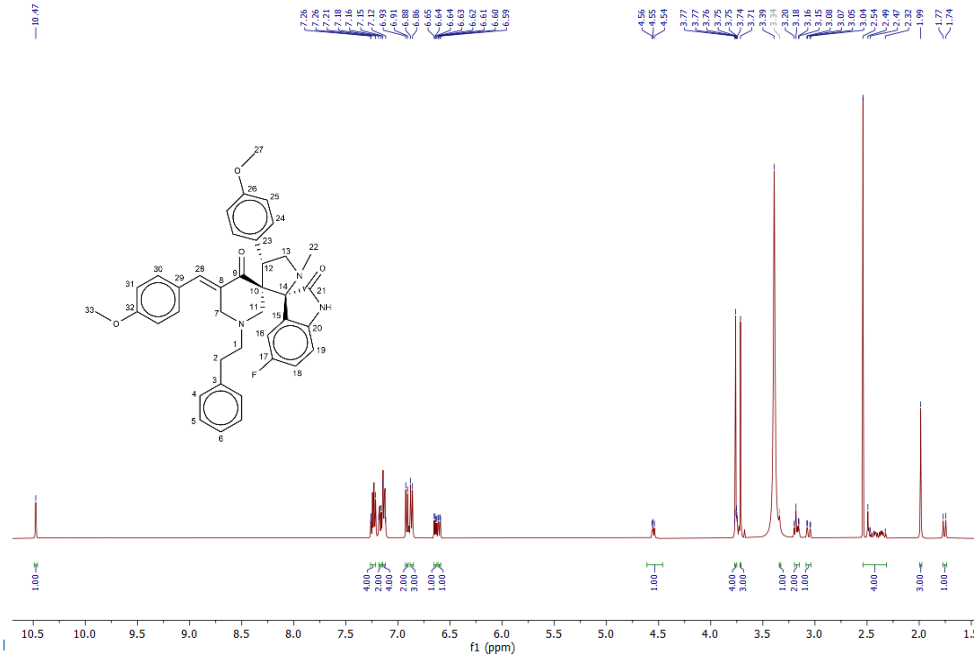

Figure S136: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10c**

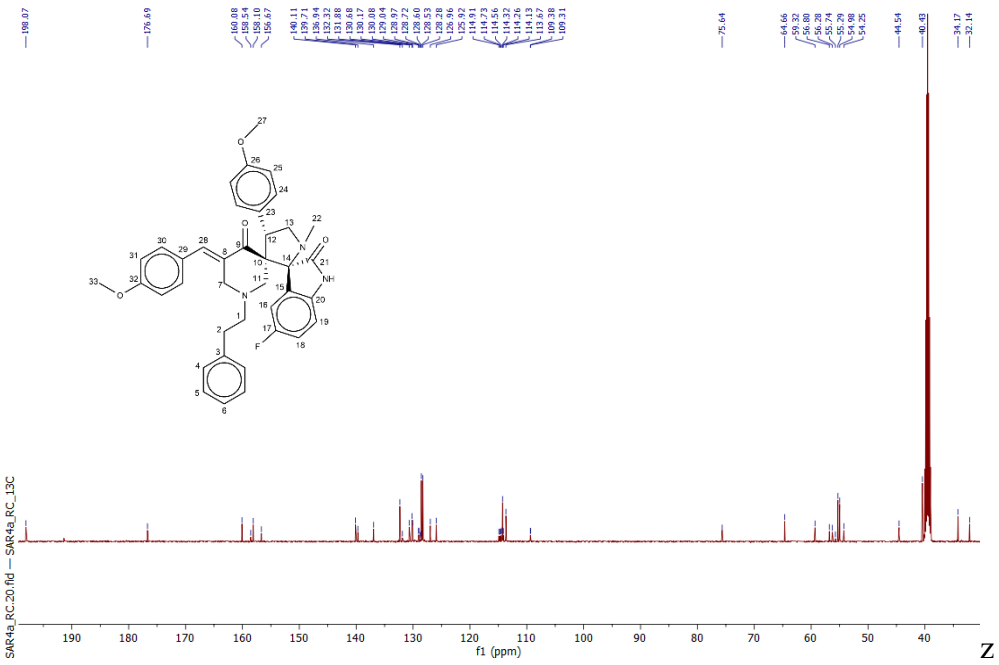

Figure S137: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10c**

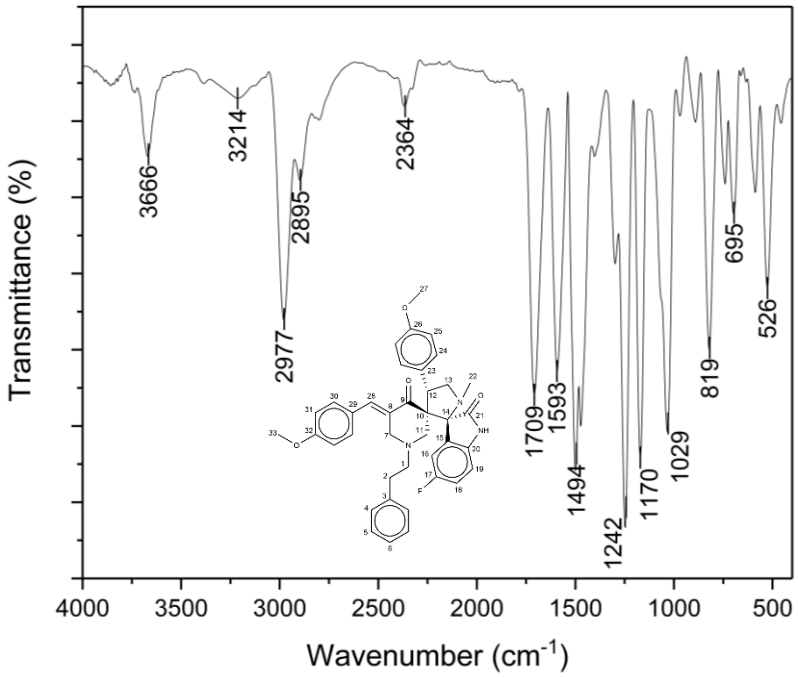

Figure S138: FT-IR spectrum of compound **10c**

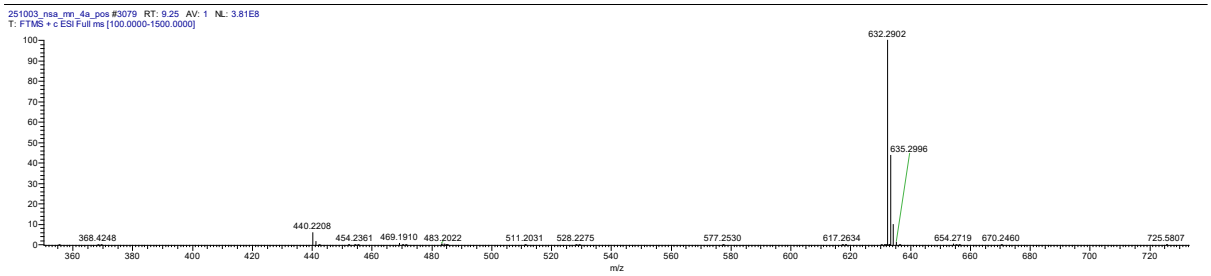

Figure S139: HRMS spectrum for compound **10c**

1-methyl-4(2-methoxyphenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(2-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10d**)

Pale yellow powder, m.p. (121-125 °C). FTIR (ATR): 3217 (w, N-H), 1669 (s, C=O), 1590 (m, C=C), 1180 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (1H, d, *J*=15.0 Hz, H11a), 1.98 (3H, s, H22), 2.22-2.30 (2H, m, H2), 2.37-2.45 (2H, m, H1), 2.95-3.00 (2H, m, H7a & H11b), 3.14 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.28 (1H, d, *J*=12.0, H7b), 3.62 (3H, s, H24), 3.81 (3H, s, H32), 3.94 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.65 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.63-6.68 (2H, m, H16 & H19), 6.86 (1H, t, *J*=8.0 Hz, H18), 6.89-6.98 (4H, m, H27, H28, H36, H37), 7.01 (1H, d, *J*=8.0 Hz, H26), 7.05 (2H, d, *J*=8.0 Hz, H4), 7.12 (1H, t, *J*=8.0 Hz, H6), 7.19 (2H, t, *J*=8.0 Hz, H5), 7.23 (1H, d, *J*=8.0 Hz, H34), 7.32 (1H, t, *J*=8.0 Hz, H35), 7.46 (1H, d, *J*=8.0 Hz, H29), 7.58 (1H, d, *J*=2.0 Hz, H30), 10.50 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.3 (C2), 34.3 (C22), 39.0 (C12), 54.7 (C7), 54.9 (C32), 55.1 (C24), 55.5 (C11), 55.8 (C13), 59.6 (C1), 62.9 (C10), 76.2 (C14), 109.2 (d, *J*=7.5 Hz, C19), 110.4 (C28), 111.2 (C26), 114.5 (d, *J*=20.5 Hz, C16), 114.7 (d, *J*=20.5 Hz, C18), 120.1 (C27), 120.3 (C34), 123.3 (C23), 125.9 (C6), 126.9 (C36), 127.8 (C31), 128.0 (C29), 128.2 (C4), 128.5 (C5), 129.0 (d, *J*=7.5 Hz, C15), 129.6 (C37), 130.4 (C35), 131.7 (C30), 132.1 (C8), 139.9 (d, *J*=2.0 Hz, C20), 140.0 (C3), 157.7 (C25), 157.8 (d, *J*=248 Hz, C17), 158.0 (C33), 176.8 (C21), 197.0 (C9). HRMS (ESI): *m/z* 632.2902 (MH^+ $C_{39}H_{39}FN_3O_4^+$ requires 632.2924).

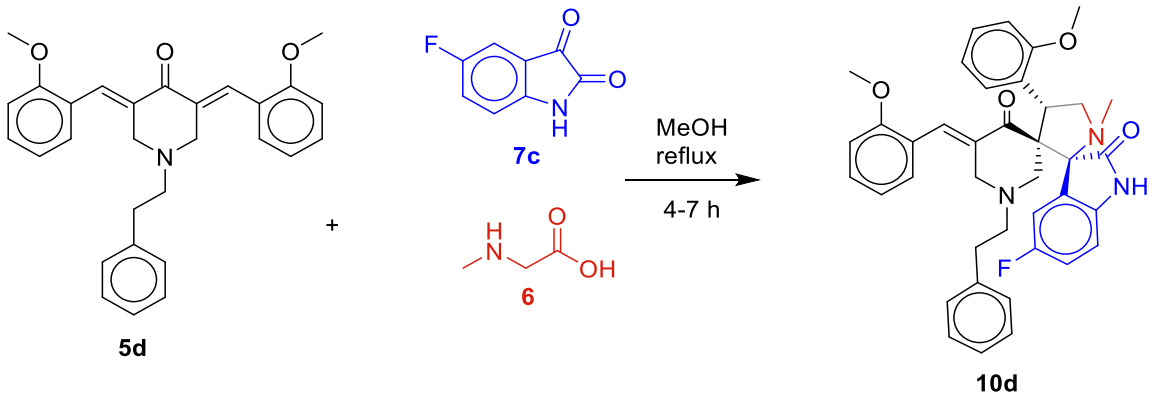

Figure S140: Reaction scheme of compound **10d**

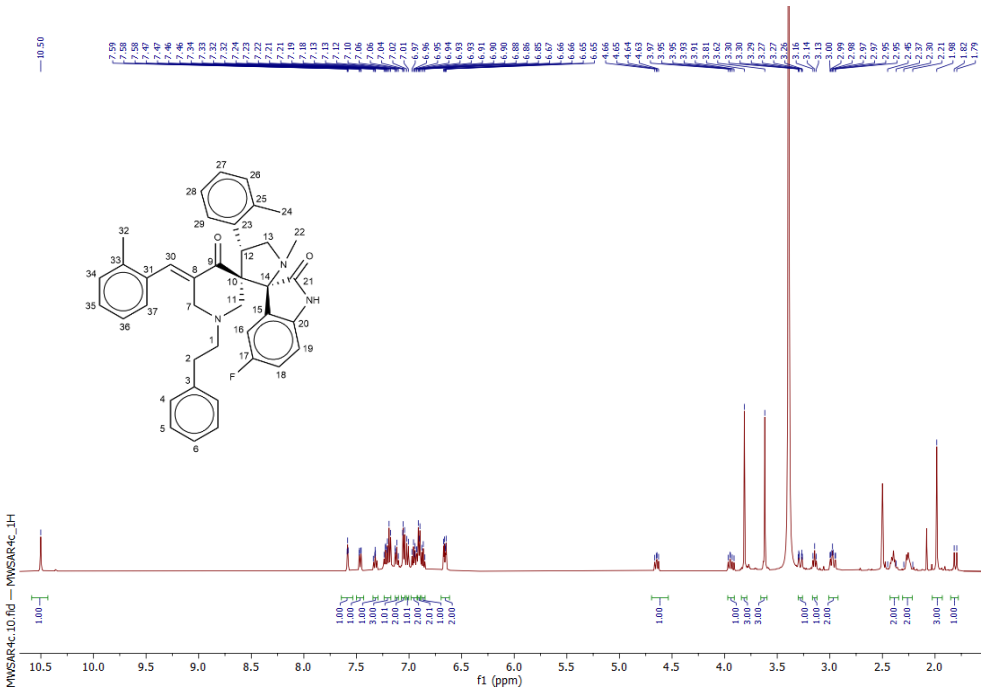

Figure S141: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10d**

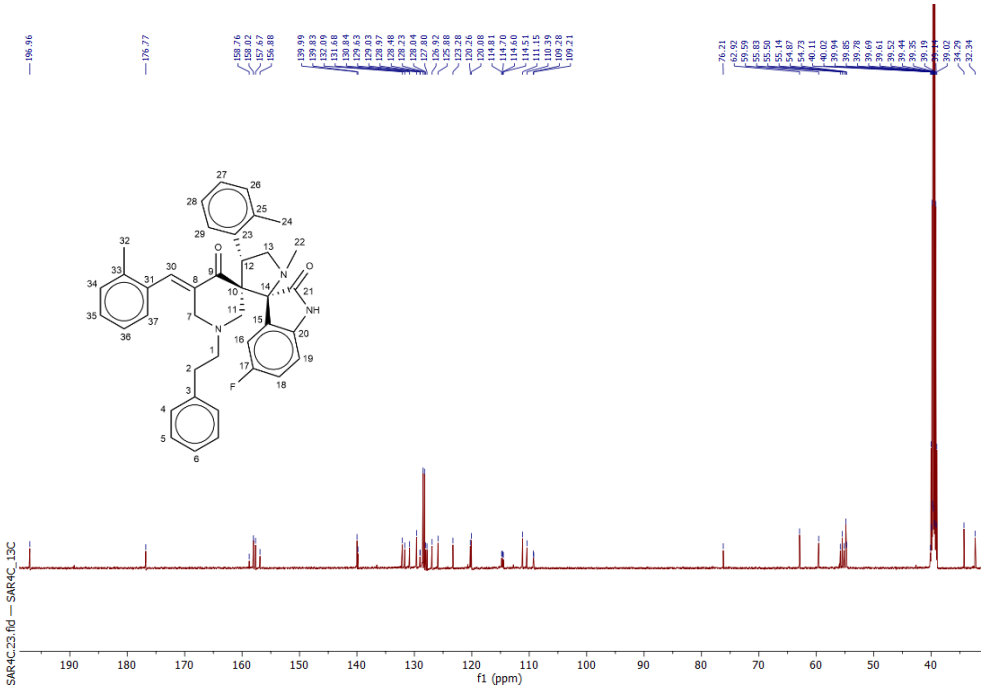

Figure S142: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10d**

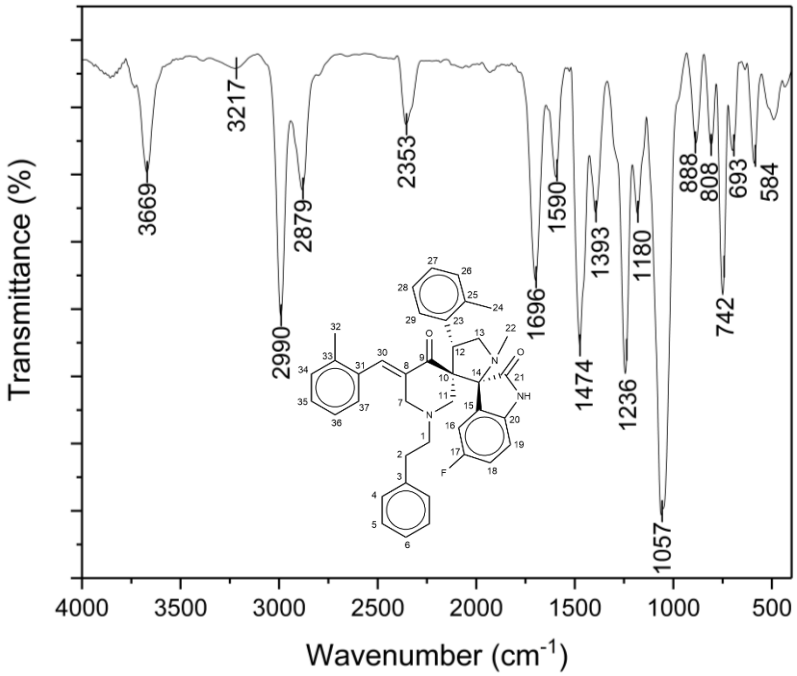

Figure S144: FT-IR spectrum of compound **10d**

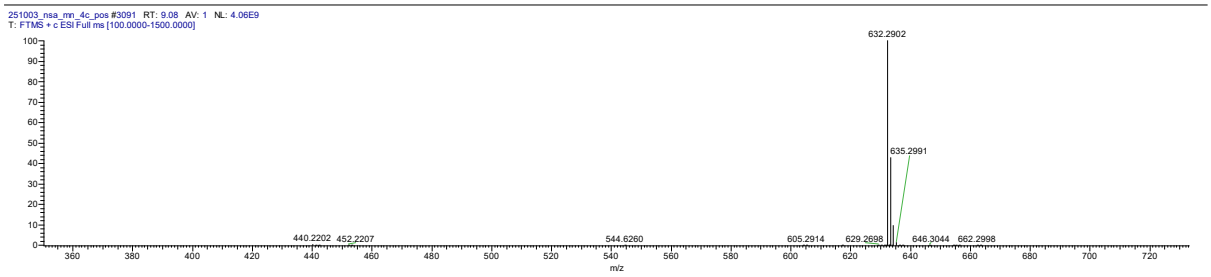

Figure S143: HRMS spectrum for compound **10d**

1-methyl-4(2,4-methoxyphenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(2,4-methoxyphenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10e**)

Pale yellow powder, m.p. (124-128 °C). FTIR (ATR): 3233 (w, N-H), 1710 (s, C=O), 1592 (m, C=C), 1201 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (1H, d, *J*=15.0 Hz, H11a), 1.96 (3H, s, H22), 2.23-2.31 (2H, m, H2), 2.40-2.46 (2H, m, H1), 2.91-3.00 (2H, m, H7a & H11b), 3.10 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.27 (1H, d, *J*=15.0 Hz, H7b), 3.58 (3H, s, H25), 3.73 (3H, s, H37), 3.77 (1H, s, H28), 3.83 (3H, s, H34), 3.86 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.57 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.45 (1H, dd, *J*=8.0, 3.0 Hz, H38), 6.46 (1H, d, *J*=2.0 Hz, H26), 6.52 (1H, dd, *J*=8.0, 2.0 Hz, H29), 6.57 (1H, d, *J*=2.0 Hz, H35), 6.62-6.67 (2H, m, H16 & H19), 6.87 (1H, d, *J*=8.0 Hz, H39), 6.90 (1H, td, *J*=8.0, 2.0 Hz, H18), 7.08 (2H, d, *J*=8.0 Hz, H4), 7.11-7.16 (1H, m, H6), 7.20 (2H, t, *J*=8.0 Hz, H5), 7.36 (1H, d, *J*=8.0 Hz, H30), 7.65 (1H, d, *J*=2.0 Hz, H31), 10.47 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.4 (C2), 34.3 (C22), 38.6 (C12), 55.0 (C7), 55.1 (C25), 55.4 (C28), 55.5 (C34), 55.7 (C13), 55.8 (C37), 55.9 (C11), 59.7 (C1), 62.9 (C10), 76.3 (C14), 98.1 (C26), 98.2 (C35), 104.2 (C29), 105.1 (C38), 109.1 (d, *J*=7.5 Hz, C19), 114.5 (d, *J*=20.5 Hz, C16), 114.7 (d, *J*=20.5 Hz, C18), 116.2 (C32), 119.1 (C23), 125.8 (C6), 128.2 (C4), 128.5 (C5), 128.6 (C30), 129.2 (d, *J*=7.5 Hz, C15), 130.2 (C8), 130.8 (C31), 131.1 (C39), 139.8 (d, *J*=2.0 Hz, C20), 140.1 (C3), 156.8 (d, *J*=248 Hz, C17), 158.6 (C24), 159.2 (C27), 160.7 (C36), 161.8 (C33), 176.8 (C21), 197.2 (C9). HRMS (ESI): *m/z* 692.3113 (MH^+ $C_{41}H_{43}FN_3O_6^+$ requires 692.3136).

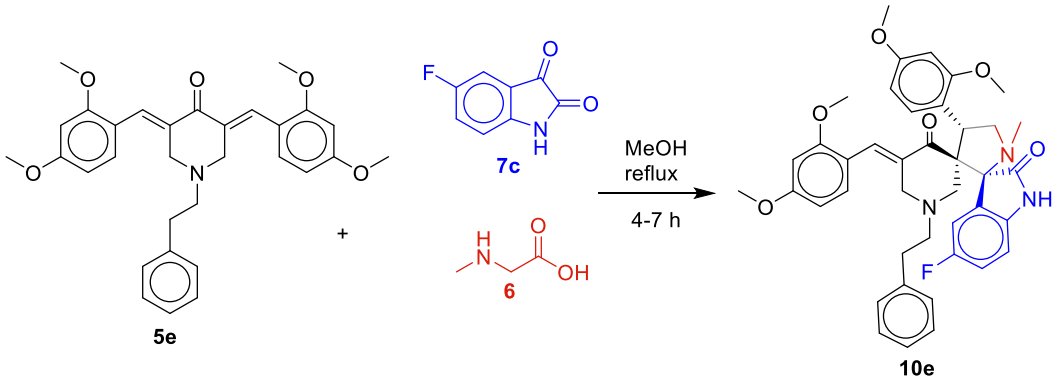

Figure S144: Reaction scheme of compound **10e**

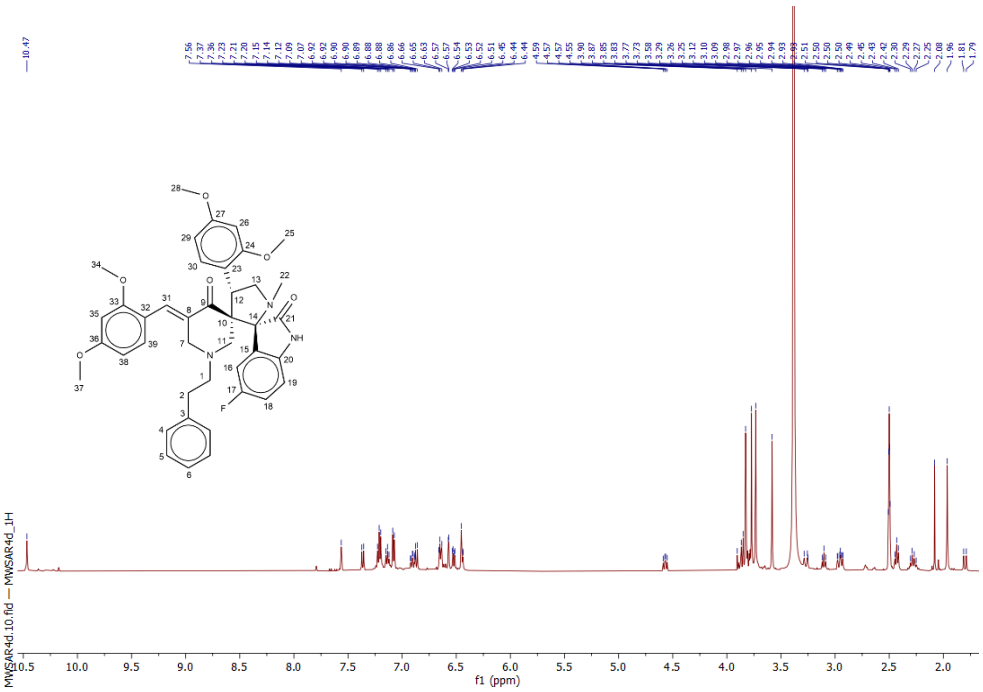

Figure S145: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10e**

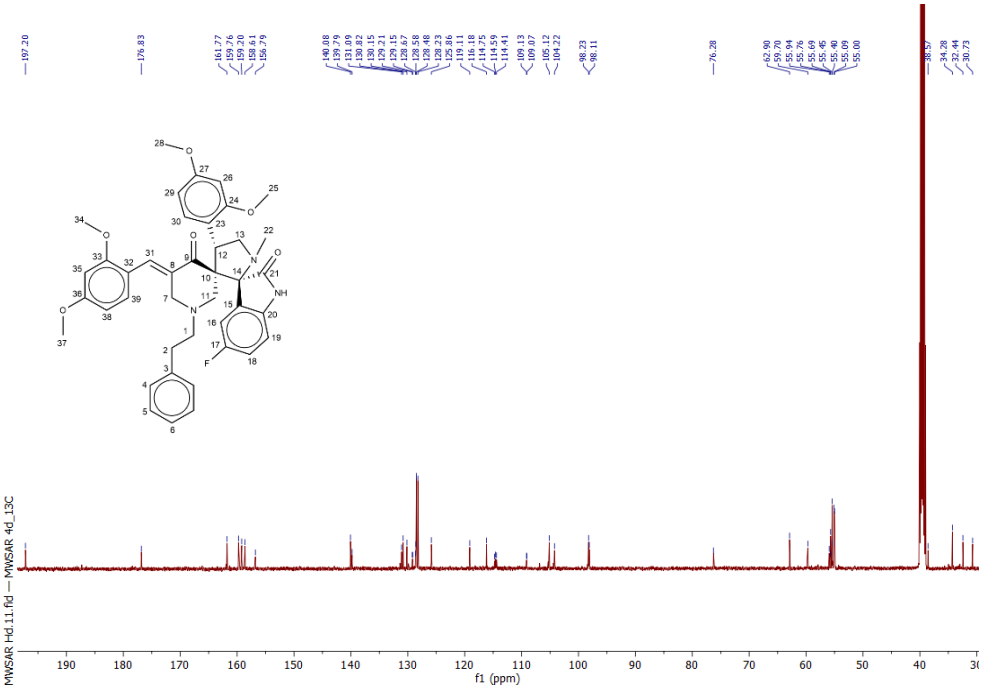

Figure S146: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10e**

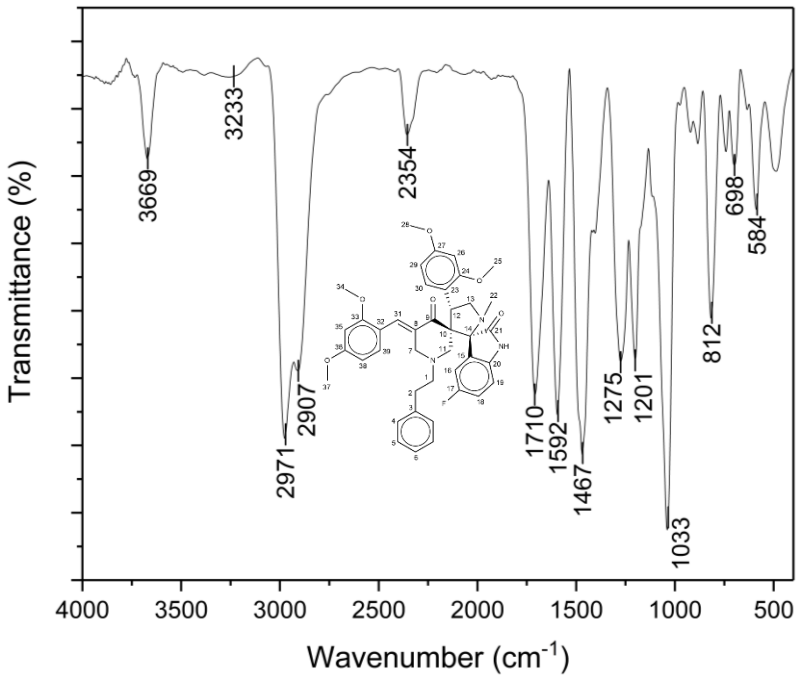

Figure S147: FT-IR spectrum of compound **10e**

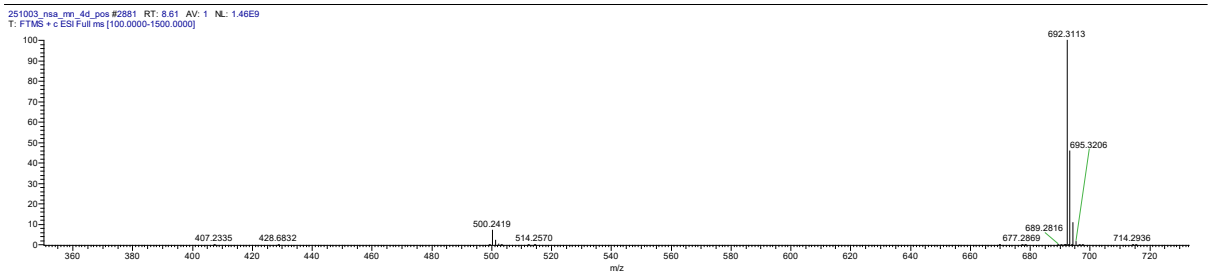

Figure S148: HRMS spectrum for compound **10e**

1-methyl-4(4-chlorophenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(4-chloro phenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10f**)

White powder, m.p. (116-120 °C). FTIR (ATR): 3220 (w, N-H), 1701 (s, C=O), 1593 (m, C=C), 1248 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.78 (1H, d, *J*=15.0 Hz, H11a), 2.00 (3H, s, H22), 2.29-2.48 (4H, m, H1, H2), 3.09-3.19 (2H, m, H7a & H11b), 3.25 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.33 (1H, d, *J*=12.0 Hz, H7b), 3.76 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.60 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.60 (1H, dd, *J*=8.0, 3.0 Hz, H16), 6.64-6.68 (1H, m, H19), 6.90 (1H, td, *J*=8.0, 3.0 Hz, H18), 7.11 (1H, d, *J*=2.0, H27), 7.12-7.17 (5H, m, H4, H6, H29), 7.23 (2H, t, *J*=8.0 Hz, H5), 7.34 (2H, d, *J*=8.0 Hz, H24), 7.39 (2H, d, *J*=8.0 Hz, H25), 7.42 (2H, d, *J*=8.0 Hz, H30), 10.53 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.0 (C2), 34.2 (C22), 44.7 (C12), 53.8 (C7), 56.2 (C11), 56.5 (C13), 59.0 (C1), 64.9 (C10), 75.5 (C14), 109.6 (d, *J*=7.5 Hz, C19), 114.2 (d, *J*=20.5 Hz, C16), 115.1 (d, *J*=20.5 Hz, C18), 125.9 (C6), 128.2 (C4), 128.3 (C5), 128.5 (d, *J*=7.5 Hz, C15), 128.6 (C25), 128.8 (C24), 131.1 (C29), 131.5 (C28), 131.8 (C30), 132.1 (C26), 133.6 (C8), 133.9 (C31), 135.6 (C27), 137.7 (C23), 139.7 (d, *J*=2.0 Hz, C20), 140.0 (C3), 157.7 (d, *J*=248 Hz, C17), 176.6 (C21), 198.1 (C9). HRMS (ESI): *m/z* 640.1927 (MH^+ $C_{37}H_{33}{}^{79}Cl_2FN_3O_2^+$ requires 640.1934).

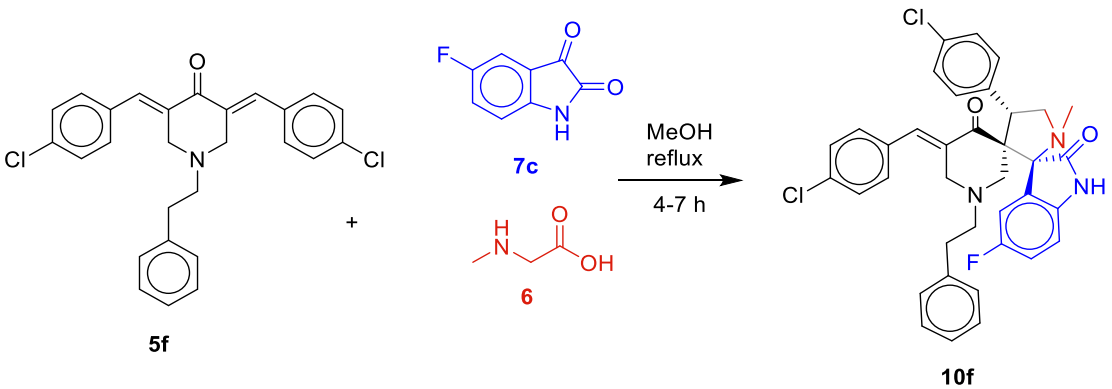

Figure S149: Reaction scheme of compound **10f**

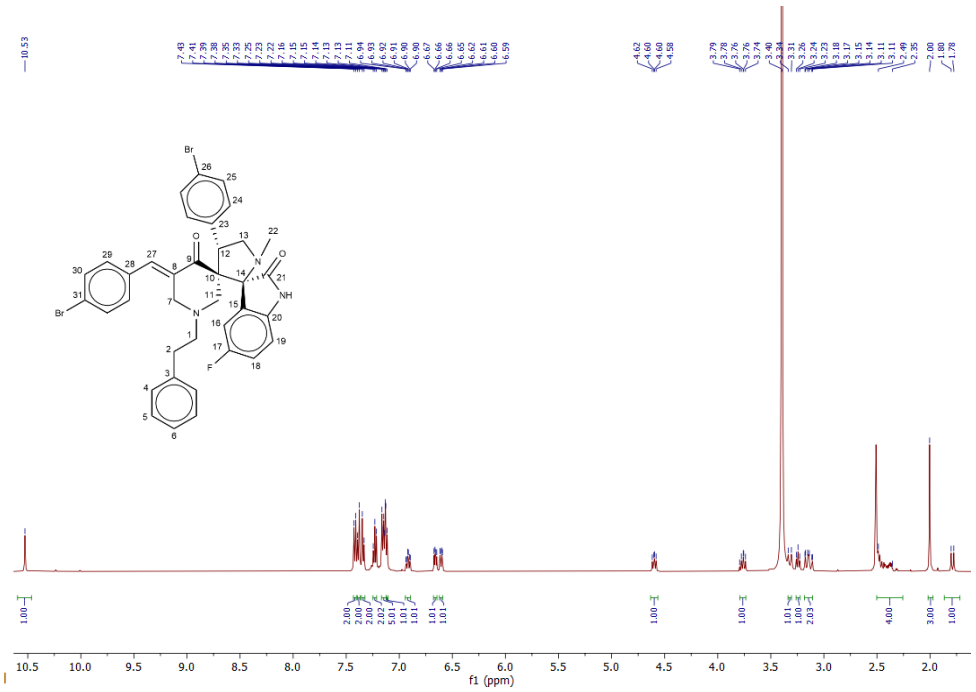

Figure S150: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10f**

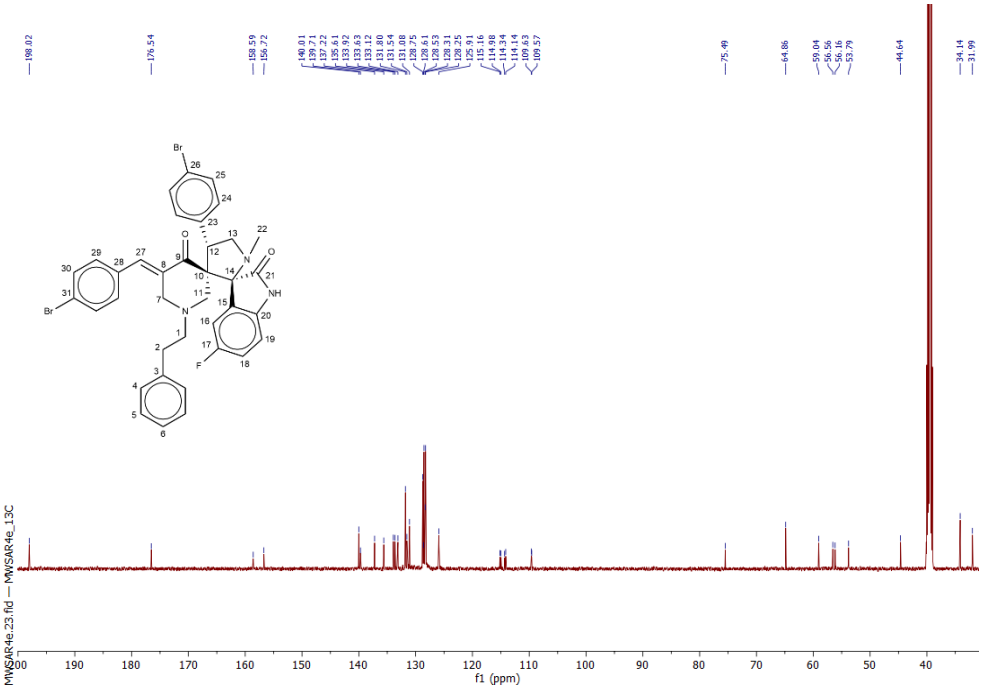

Figure S151: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10f**

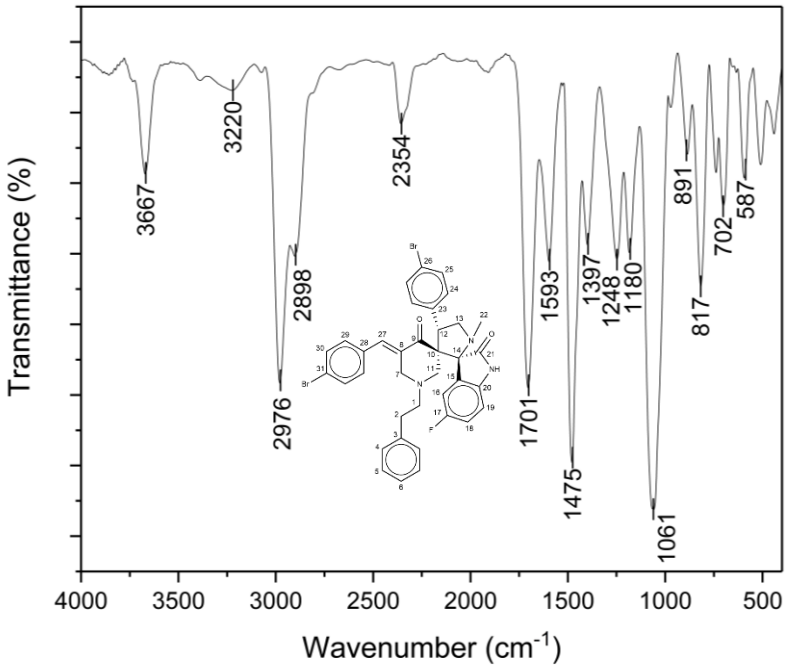

Figure S152: FT-IR spectrum of compound **10f**

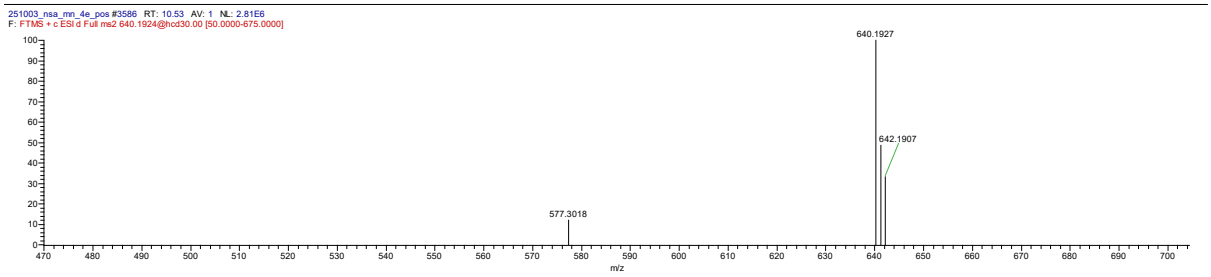

Figure S153: HRMS spectrum for compound **10f**

1-methyl-4(4-bromophenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(4-bromo phenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10g**)

White powder, m.p. (140-144 °C). FTIR (ATR): 3215 (w, N-H), 1704 (s, C=O), 1598 (m, C=C), 1239 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.79 (1H, d, *J*=15.0 Hz, H11a), 2.00 (3H, s, H22), 2.35-2.48 (2H, m, H1 & H2), 3.11 (1H, d, *J*=15.0 Hz, H11b), 3.16 (1H, d, *J*=12.0, 2.0 Hz, H7a), 3.23 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.30 (1H, d, *J*=12.0 Hz, H7b), 3.75 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.58 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.60 (1H, dd, *J*=8.0, 3.0 Hz, H16), 6.63-6.66 (1H, m, H19), 6.91 (1H, td, *J*=8.0, 3.0 Hz, H18), 7.06 (1H, d, *J*=2.0 Hz, H27), 7.08-7.15 (5H, m, H4, H6, H29), 7.22 (2H, t, *J*=8.0 Hz, H5), 7.27 (2H, d, *J*=8.0 Hz, H24), 7.50 (2H, d, *J*=8.0 Hz, H25), 7.55 (2H, d, *J*=8.0 Hz, H30), 10.51 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.0 (C2), 34.2 (C22), 44.7 (C12), 53.8 (C7), 56.2 (C11), 56.5 (C13), 59.0 (C1), 64.9 (C10), 75.5 (C14), 110.6 (d, *J*=8.5 Hz, C19), 114.2 (d, *J*=20.5 Hz, C16), 115.1 (d, *J*=20.5 Hz, C18), 120.1 (C26), 122.8 (C31), 125.9 (C6), 128.2 (C4), 128.5 (C5), 128.6 (d, *J*=8.5 Hz, C15), 131.2 (C25), 131.4 (C24), 131.7 (C30), 132.0 (C29), 133.5 (C8), 133.7 (C28), 135.7 (C27), 137.7 (C23), 139.7 (d, *J*=2.5 Hz, C20), 140.0 (C3), 157.7 (d, *J*=248 Hz, C17), 176.6 (C21), 198.1 (C9). HRMS (ESI): *m/z* 728.0750 (MH^+ $C_{37}H_{33}{}^{79}Br_2FN_3O_2^+$ requires 728.0924).

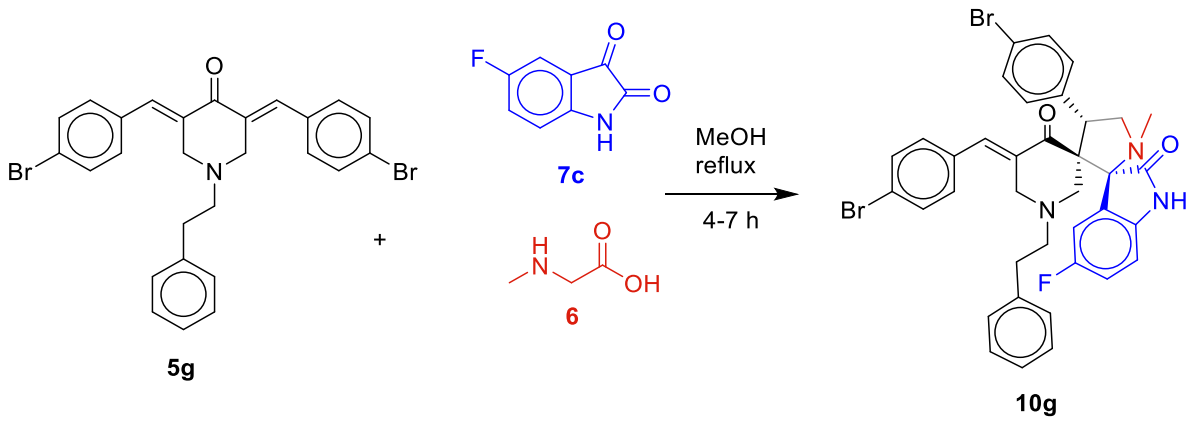

Figure S154: Reaction scheme of compound **10g**

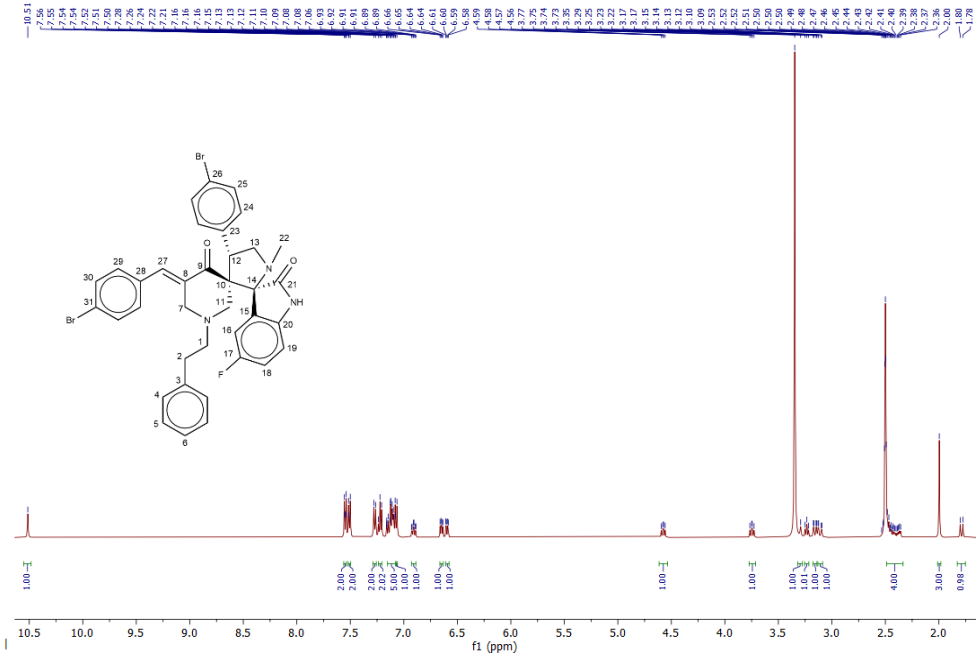

Figure S155: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10g**

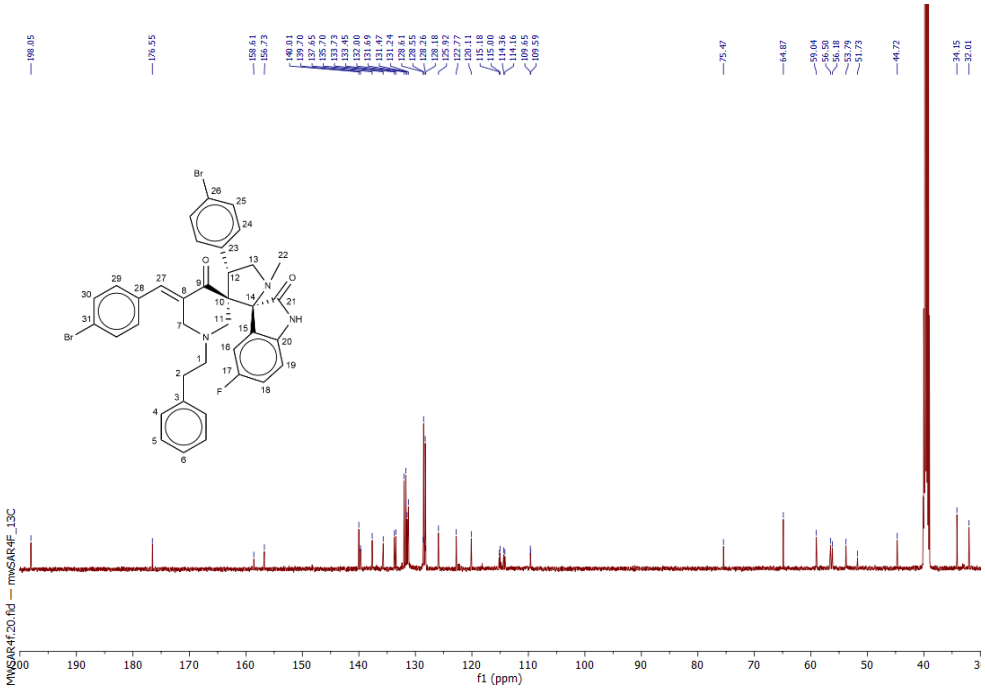

Figure S156: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10g**

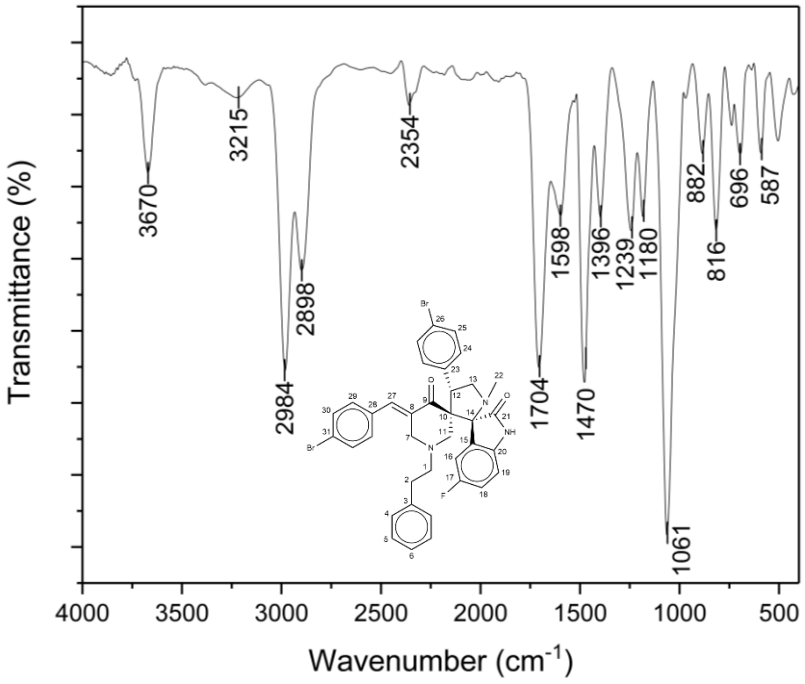

Figure S157: FT-IR spectrum of compound **10g**

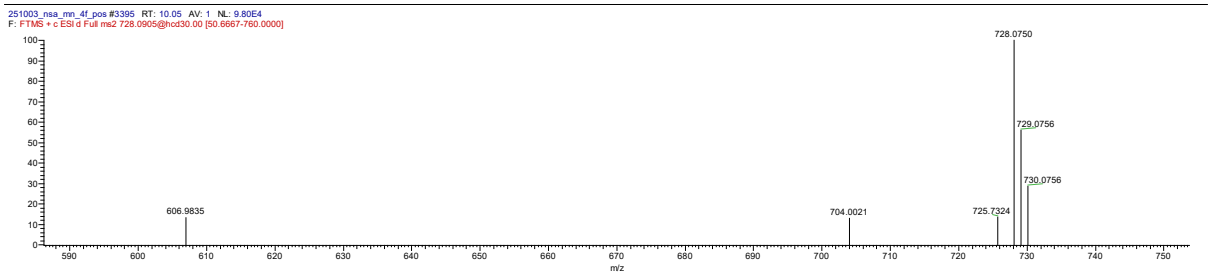

Figure S158: HRMS spectrum for compound **10g**

1-methyl-4(4-fluorophenyl) pyrrolo-(spiro [2.3"]-5"-fluorooxindole)-spiro [3.3']-5'-(4-fluorophenylmethylidene)-1'-phenylethyl-4'-piperidinone (**10h**)

White powder, m.p. (112-116 °C). FTIR (ATR): 3214 (w, N-H), 1699 (s, C=O), 1592 (m, C=C), 1244 (m, C-N) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76 (1H, d, *J*=15.0 Hz, H11a), 1.99 (3H, s, H22), 2.31-2.48 (4H, m, H1 & H2), 3.10 (1H, dd, *J*=15.0, 2.0 Hz, H7a), 3.16 (1H, d, *J*=15.0 Hz, H11b), 3.24 (1H, dd, *J*=8.0, 8.0 Hz, H13a), 3.32 (1H, d, *J*=15.0 Hz, H7b), 3.75 (1H, dd, *J*=8.0, 3.0 Hz, H13b), 4.60 (1H, dd, *J*=8.0, 3.0 Hz, H12), 6.60 (1H, dd, *J*=8.0, 3.0 Hz, H16), 6.64-6.67 (1H, m, H19), 6.90 (1H, td, *J*=8.0, 3.0 Hz, H18), 7.10-7.13 (3H, m, H4, H27), 7.14-7.20 (7H, m, H5, H6, H25, H29, H30), 7.35 (2H, dd, *J*=8.0, 3.0 Hz, H24), 10.51 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.0 (C2), 34.1 (C22), 44.5 (C12), 53.9 (C7), 56.2 (C11), 56.8 (C13), 59.1 (C1), 64.7 (C10), 75.6 (C14), 109.6 (d, *J*=8.5 Hz, C19), 114.2 (d, *J*=20.7 Hz, C16), 114.9 (d, *J*=20.7 Hz, C25), 115.1 (d, *J*=20.7 Hz, C18), 115.7 (d, *J*=20.5 Hz, C30), 125.9 (C6), 128.3 (C4), 128.7 (d, *J*=8.5 Hz, C15), 130.8 (d, d, *J*=8.5 Hz, C24), 131.0 (d, *J*=8.5 Hz, C29), 132.5 (d, *J*=2.5 Hz, C23), 132.8 (C8), 134.4 (d, *J*=2.5 Hz, C28), 135.9 (C27), 139.7 (C3), 140.0 (C20), 157.6 (d, *J*=242 Hz, C17), 161.2 (d, *J*=242 Hz, C26), 162.2 (d, *J*=242 Hz, C31), 176.6 (C21), 198.1 (C9). HRMS (ESI): *m/z* 608.2507 (MH^+ $C_{37}H_{33}F_3N_3O_2^+$ requires 608.2524).

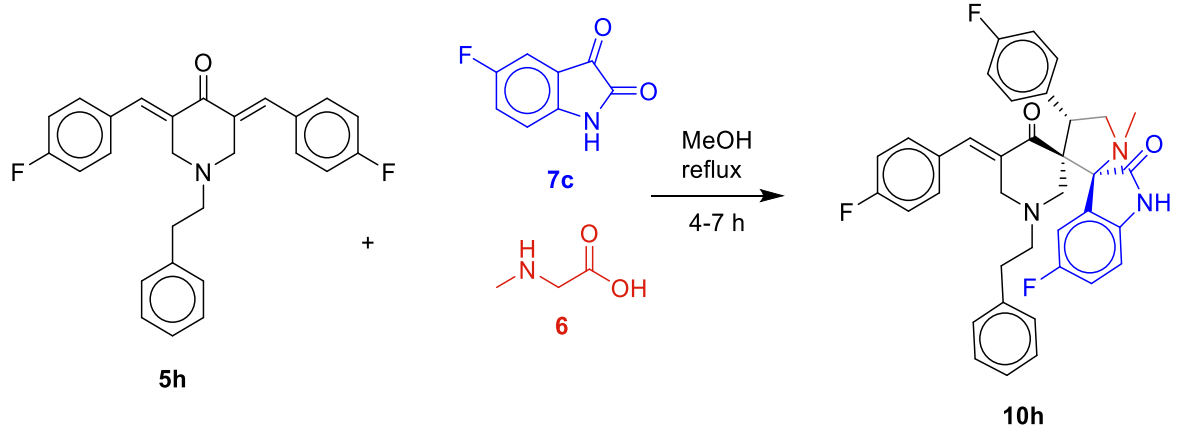

Figure S159: Reaction scheme of compound **10h**

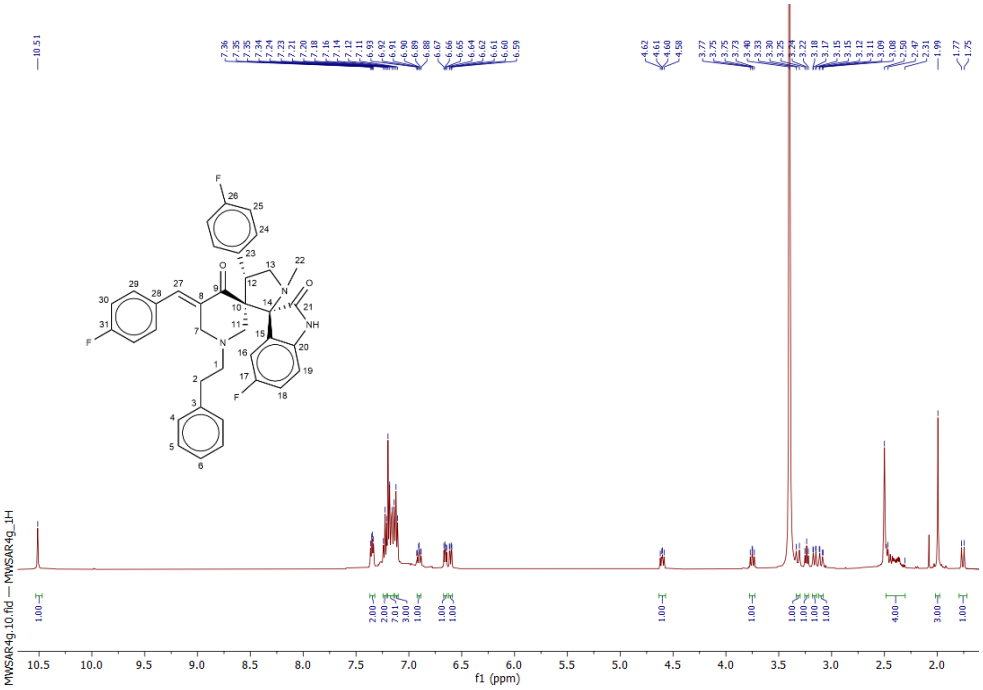

Figure S160: ^{1}H NMR spectrum (DMSO-d$_6$, 500 MHz) of compound **10h**

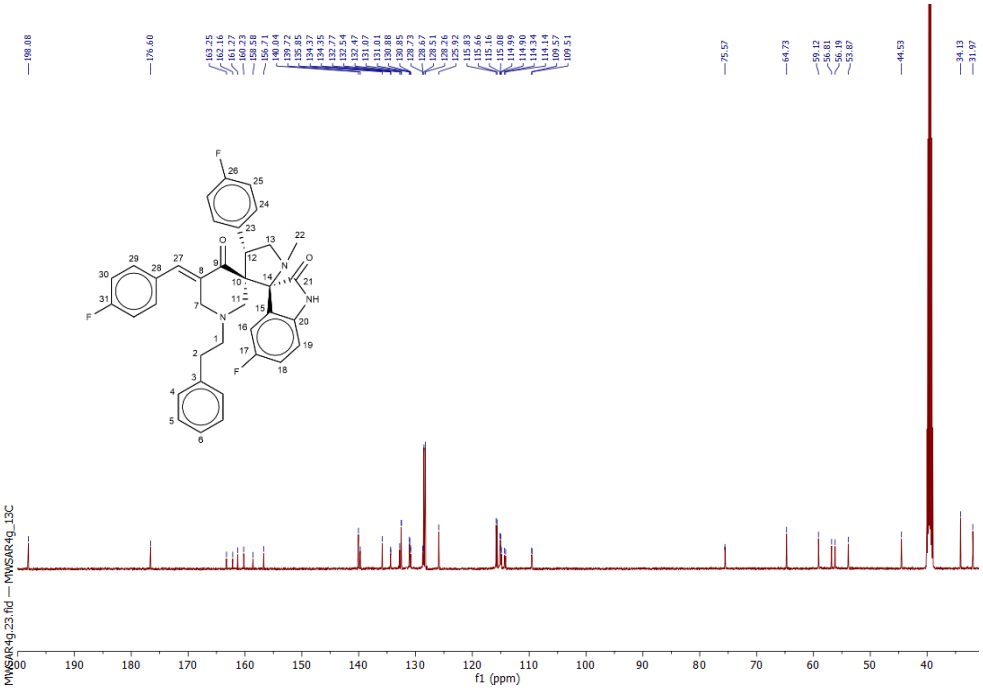

Figure S161: ^{13}C NMR spectrum (DMSO-d$_6$, 125 MHz) of compound **10h**

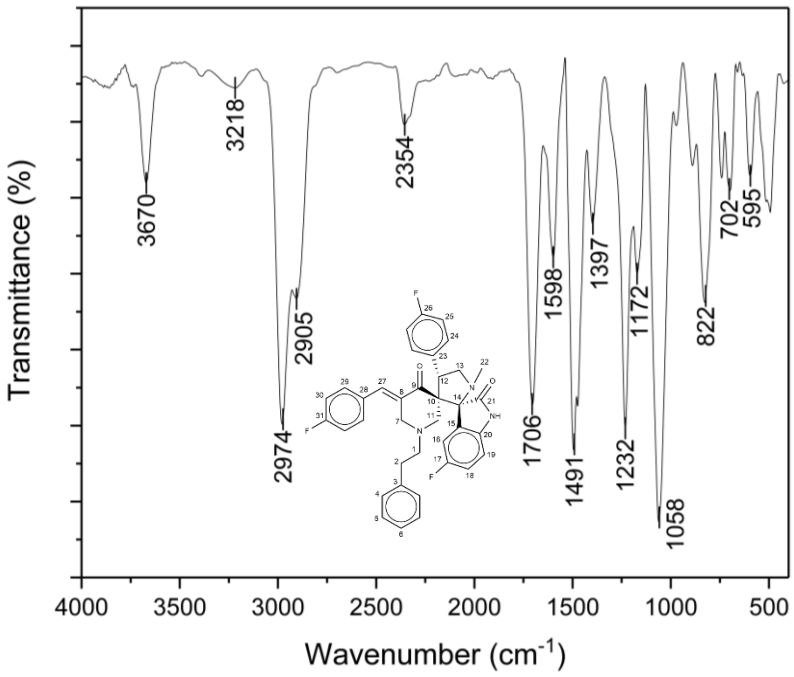

Figure S162: FT-IR spectrum of compound **10h**

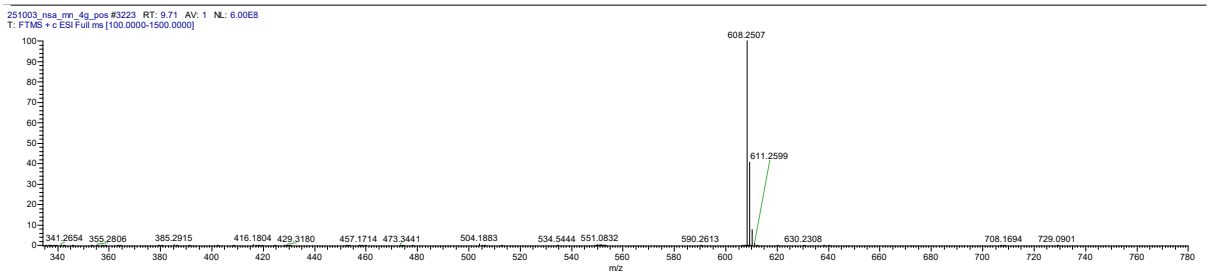

Figure S163: HRMS spectrum for compound **10h**