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Supplementary Material

DABCO Promoted Regioselective Synthesis of New Diversely Functionalized 3-Hydroxy-2-Oxindole Scaffolds

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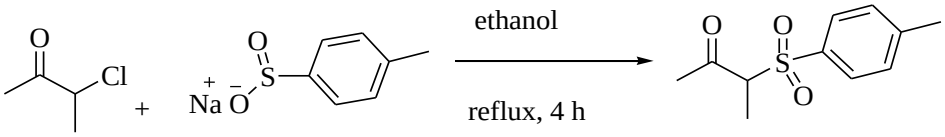
General Information

All materials used in this study were obtained from commercial supplier and used without further purification as received. Reaction involving moisture and/or air sensitive reagents was performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Tetrahydrofuran (THF) was distilled over Na/Ph_2CO under nitrogen atmosphere. Commercial grade solvents and reagents were used without further purification. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates (AL SIL G/UV, aluminum back) and One or more of the following methods were used for visualization: 254 nm UV light fluorescence quenching; iodine staining; anisaldehyde stain (ethanol (135 mL)/H_2SO_4 (5 mL)/AcOH (1.5 mL)/p-anisaldehyde 3.7 mL). Evaporation of solvents was performed at reduced pressure on a BUCHI rotary evaporator. Column chromatography was carried out with acme's silica gel grade 60–120 and 100–200 mesh. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Ethyl acetate and hexane were the common eluents used. All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO d_6/ $CDCl_3$+DMSO d_6 on Gemini 200, Avance 300 or Inova 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to either residual $CHCl_3$ (^1H: δ 7.26 ppm, ^{13}C: δ 77.00 ppm) or DMSO d_6 (^1H: δ 2.50 ppm, ^{13}C: δ 39.43 ppm) as an internal reference. The number of protons (n) for a given resonance is indicated by nH.Coupling constants (*J*) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet), dd (doublet of doublets) and br s (broad singlet). Melting points were measured on a BUCHI melting point machine. IR spectra were recorded on Thermo Nicolet FT/IR-5700 spectrometer. Mass spectra were recorded using Waters Mass spectrometers. High resolution mass spectrums (HRMS) were recorded using Applied Bio-Sciences HRMS spectrometers.

Experimental section

1. Preparation of reagents:

(a) Synthesis of 3-[(4-methylphenyl)sulfonyl]butan-2-one

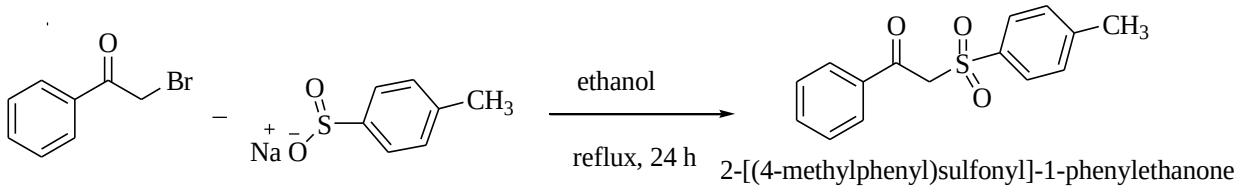


3-[(4-methylphenyl)sulfonyl]butan-2-one

3-[(4-methylphenyl)sulfonyl]butan-2-one was prepared by using reported method[1]. 3-chlorobutan-2-one (10 mmol) and sodium 4-methylbenzenesulfinate (10 mmol) were mixed in 30 mL ethanol and refluxed for about 4 h. The reaction mixture was allowed to cool. The crude solid obtained was filtered and washed with cold ethanol. The part of the product was purified by column chromatography and used for reaction.

White solid, MP 62-64 °C. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO d_6): δ 7.69 (d, *J* = 8.30 Hz, 2H), 7.39 (d, *J* = 8.30 Hz, 2H), 3.96-3.64 (m, 1H), 4.27 (q, *J* = 6.98 Hz, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 1.36 (d, *J* = 6.98 Hz, 3H) ppm.

(b) Synthesis of 2-[(4-methylphenyl)sulfonyl]-1-phenylethanone:

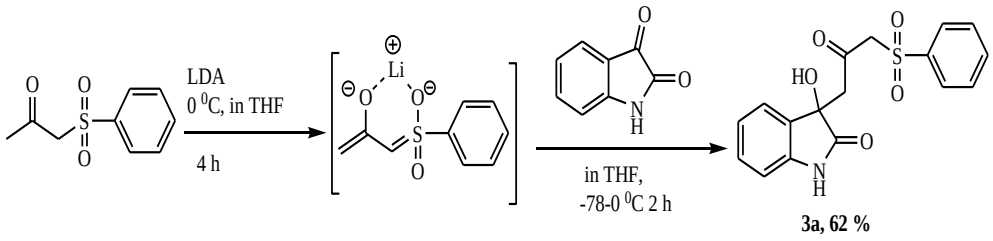


2-[(4-methylphenyl)sulfonyl]-1-phenylethanone

2-[(4-methylphenyl)sulfonyl]-1-phenylethanone was prepared by using reported method[1]. Phenacyl bromide (10 mmol) and sodium 4-methylbenzenesulfinate (10 mmol) were mixed in 30 mL ethanol and refluxed for about 24 h. The reaction mixture was allowed to cool. The crude solid obtained was filtered and washed with cold ethanol. The part of the product was purified by column chromatography and used for reaction.

Light brown solid, MP 107-109 °C. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO d_6): δ 7.81 (d, *J* = 6.9 Hz, 2H), 7.65 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 6.9 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 4.76 (s, 2H), 2.32 (s, 3H) ppm.

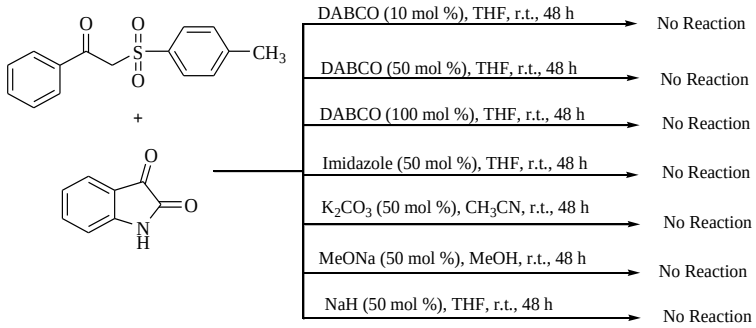
2. Reaction of isatin under dianion method[2]



Reaction of isatin with 1-(phenylsulfonyl) propan-2-one under dianion method:

To a solution of LDA prepared from diisopropylamine (0.336 g, 3.6 mmol) and butyllithium (in hexane. 2.32 mL, 3.6 mmol) at -78 °C in THF (2 mL) was added 1-phenylsulfonylpropanone (0.297 g, 1.5 mmol) in THF (2 mL) under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 4 h. To the resulting THF suspension of the dianion was added isatin (0.265 g, 1.8 mmol dissolved in 2 mL THF) dropwise at 0 °C. After stirred at 0 °C for 2h, the mixture was acidified with 1 M HCl. The THF was removed in vacuum and the aqueous residue was extracted with ethyl acetate (5 mL x 3). The combined extracts were dried (Na_2SO_4) and evaporated in vacuum to obtain the crude product. Part of crude reaction mixture was subjected for ^{1}H NMR analysis and remaining was further purified by column chromatography on silica gel with 1:1 EtOAc-hexane as eluents to afford pure product **3a** (0.200 g. 58%).

3. Reaction[a] of isatin with those β-keto esters having no enolizable protons at γ-position:

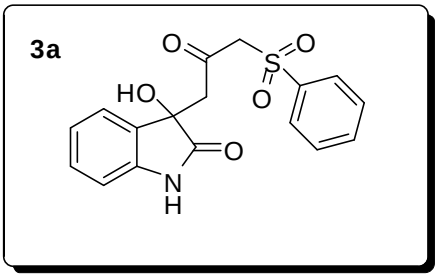


Scheme 3. Reaction of isatin with 2-[(4-methylphenyl)sulfonyl]-1-phenylethanone; Reaction conditions: isatin (1 mmol), β-keto sulfone (1 mmol) in 5 mL solvent at room temperature.

General Procedure for the DABCO Catalyzed Regioselective γ-Addition of β-Keto Sulfones to Isatins:

To the stirred solution of β-keto sulfone (1.0 mmol) and DABCO (30 mol %) in 5 mL THF was added isatin (1mmol). The mixture was then stirred at room temperature for stipulated time (Table 2). After completion of reaction as indicated by TLC, the solvent was removed at reduced pressure on a BUCHI rotary evaporator. The residue was then purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1-1:1) to afford the desired product.

Spectral Characterization Data for products 3a-3p:



3-hydroxy-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2*H*-indol-2-one (**3a**, Table 2): Yield 88 %, 0.303 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.10, Pale yellow solid, MP 62-64 $^{\circ}$C.

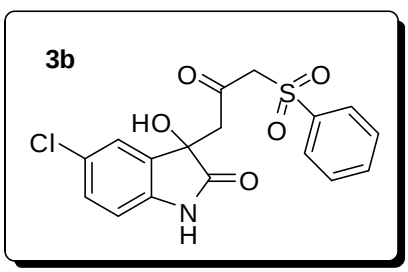
^{1}H NMR (300 MHz, $CDCl_3$+DMSO d_6): δ 10.09 (br s, 1H), 7.80-7.61(m, 3H), 7.57-7.46 (m, 2H), 7.25-7.17 (m, 2H), 6.95 (t, *J*=7.6 Hz, 1H), 6.83 (d, *J*=7.6 Hz, 1H), 6.2 (br s, 1H), 4.55 (d, *J*=13.6 Hz, 1H), 4.32 (d, *J*=13.6 Hz, 1H) 3.45 (d, *J*=16.6 Hz, 1H), 3.21 (d, *J*=16.6 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 194.42, 177.18, 141.09, 137.42, 132.98, 129.53, 128.40, 128.07, 127.09, 122.98, 120.84, 109.15, 72.28, 65.66, 50.10 ppm.

IR (KBr) ν = 3329, 2927, 1723, 1622, 1473, 1317, 1153, 1081, 1032, 753, 687, 529 cm^{-1}.

MS (ESI) *m/z* 368 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{17}H_{15}O_5NSNa[M+Na]^+$=368.05631, found 368.05582.



5-chloro-3-hydroxy-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2*H*-indol-2-one (**3b**, Table 2): Yield 94 %, 0.356 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.25, White solid, Mp 137-139 °C.

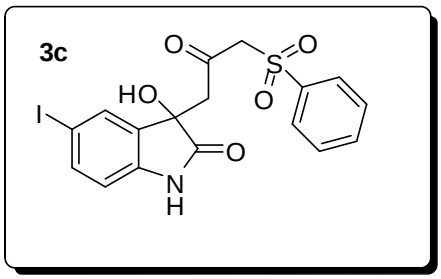
^{1}H NMR (200 MHz, $CDCl_3$+DMSO d_6): δ 10.22 (br s, 1H), 7.73 (d, *J*=7.4 Hz, 2H), 7.66 (t, *J*=7.4 Hz, 1H), 7.52 (t, *J*=7.7 Hz, 2H) 7.21 (d, *J*=1.7 Hz, 1H), 7.17 (dd, *J*=8.1, 1.7 Hz, 1H), 6.77 (d, *J*=8.3 Hz, 1H), 6.29 (br s, 1H), 4.52 (d, *J*=13.6 Hz, 1H), 4.32 (d, *J* =13.6 Hz, 1H), 3.50 (d, *J*= 17.2 Hz, 1H), 3.26 (d, *J*=17.2 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$+DMSO d_6): δ 194.06, 176.76, 139.93, 137.28, 132.81, 131.34, 127.87, 127.78, 126.79, 125.12, 123.11, 109.93, 71.84, 65.33, 49.66 ppm.

IR (KBr) ν = 3378, 3274, 2994, 2898, 1761, 1712, 1621, 1482, 1317, 1160, 1025, 882, 745, 528 cm^{-1}.

MS (ESI) *m/z* 380 $[M+H]^+$.

HRMS (ESI): *m/z* calcd. for $C_{17}H_{15}ClNO_5S[M+H]^+$= 380.03595, found 380.03611.



3-hydroxy-5-iodo-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2*H*-indol-2-one (**3c**, Table 2): Yield 84 %, 0.395 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.13, Yellow solid, Mp 102-104 °C.

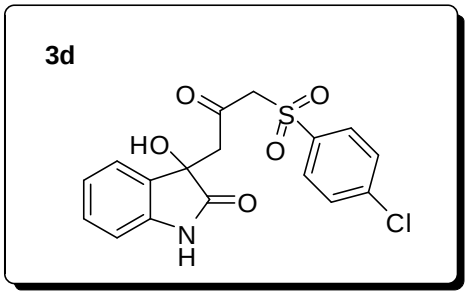
^{1}H NMR (200 MHz, $CDCl_3$+DMSO d_6): δ 9.98 (br s, 1H), 7.94-7.78 (m, 1H), 7.58-7.48 (m, 6H), 7.45 (br s, 1H), 6.62 (d, *J*=8.1 Hz, 1H), 4.43 (d, *J*=13.4 Hz, 1H), 4.20 (d, *J*=13.3 Hz, 1H), 3.47 (d, *J*=16. 8 Hz, 1H), 3.25 (d, *J*=16.8 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 194.71, 177.03, 141.50, 137.62, 132.55, 132.24, 128.70, 128.55, 127.70, 112.03, 82.71, 72.69, 66.45, 50.48 ppm.

IR (KBr) ν = 3316, 2927, 2856, 1724, 1614, 1474, 1310, 1149, 1080, 731, 687, 527 cm^{-1}.

MS (ESI) *m/z* 494 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. For $C_{17}H_{14}O_5NISNa[M+Na]^+$=493.95296, found 493.95346.



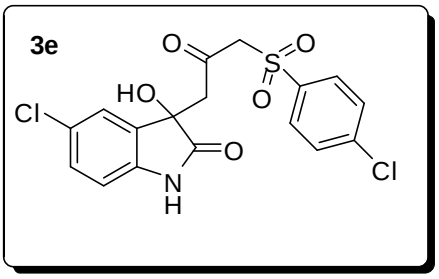
3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3d**, Table 2): Yield 91 %, 0.345 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.13, Pale yellow solid, Mp 132-134 °C. ^{1}H NMR (500 MHz, $CDCl_3$+DMSO d_6): δ 9.78 (br s, 1H), 7.66 (d, *J*=8.5 Hz, 2H), 7.44 (d, *J*=8.5 Hz, 2H), 7.26 (d, *J*=7.4 Hz, 1H), 7.22 (t, *J*=7.4 Hz, 1H), 6.98 (t, *J*=7.4 Hz, 1H), 6.85 (d, *J*=7.4 Hz, 1H), 5.95 (br s, 1H), 4.53 (d, *J*=14.9 Hz, 1H), 4.31 (d, *J*=13.8 Hz, 1H) 3.41 (d, *J*=17.0 Hz, 1H), 3.22 (d, *J*=16.0 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 195.01, 177.82, 141.34, 139.86, 136.18, 129.75, 129.38, 129.03, 128.71, 123.50, 121.55, 109.83, 72.93, 66.06, 50.56 ppm.

IR (KBr) ν = 3359, 3093, 2927, 1723, 1621, 1579, 1475, 1394, 1324, 1154, 1086, 1034, 761, 654, 559, 467 cm^{-1}.

MS (ESI) *m/z* 402 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{17}H_{14}O_5NClSNa[M+Na]^+$=402.01734, found 402.01675.



5-chloro-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3e**, Table 2): Yield 92 %, 0.382 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.22, White solid, Mp 161-163 °C.

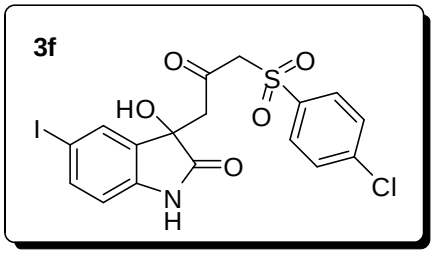
^{1}H NMR (300 MHz, $CDCl_3$+DMSO d_6): δ 10.24 (br s, 1H), 7.70 (d, *J*=9.1 Hz, 2H), 7.50 (d, *J*=8.3 Hz, 2H), 7.26-7.13 (m, 2H), 6.79 (d, *J*=8.30 Hz, 1H), 6.32 (br s, 1H), 4.56 (d, *J*=13.6 Hz, 1H), 4.39 (d, *J*=14.4 Hz, 1H), 3.48 (d, *J*=17.4 Hz, 1H), 3.26 (d, *J*=17.4 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 193.95, 175.73, 139.65, 137.92, 135.64, 131.04, 128.15, 127.44, 127.10, 124.05, 122.44, 109.24, 70.96, 64.13, 48.91 ppm.

IR (KBr) ν = 3429, 3236, 2898, 1714, 1621, 1475, 1393, 1328, 1153, 1089, 1037, 822, 767, 648, 553 cm^{-1}.

MS (ESI) *m/z* 436 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{17}H_{13}O_5NCl_2SNa[M+Na]^+$=435.97837, found 435.97803.



3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-iodo-1,3-dihydro-2*H*-indol-2-one (**3f**, Table 2): Yield 88 %, 0.444 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.30, Brown solid, Mp 67-69 °C.

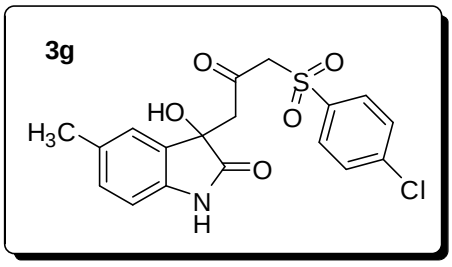
^{1}H NMR (200 MHz, $CDCl_3$+DMSO d_6): δ 10.25 (br s, 1H), 7.69 (d, *J*=8.5 Hz, 2H), 7.61-7.42 (m, 4H), 6.65 (d, *J*=8.7 Hz, 1H), 6.29 (br s, 1H), 4.55 (d, *J*=14.0 Hz, 1H), 4.36 (d, *J*=14.0 Hz, 1H), 3.48 (d, *J* = 17.18 Hz, 1H), 3.27 (d, *J*=17.2 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 194.10, 175.95, 141.01, 138.76, 136.44, 135.59, 132.05, 131.20, 128.58, 127.92, 110.95, 82.47, 71.39, 64.96, 49.51 ppm.

IR (KBr) ν = 3376, 3272, 2929, 1755, 1716, 1612, 1472, 1319, 1154, 1083, 1021, 818, 761, 642, 529, 464 cm^{-1}.

MS (ESI) *m/z* 506 $[M+H]^+$.

HRMS (ESI): *m/z* calcd. $C_{17}H_{14}ClINO_5S[M+H]^+$=505.93259, found 505.93336.



3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-methyl-1,3-dihydro-2*H*-indol-2-one (**3g**, Table 2): Yield 81 %, 0.318 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.26, Light orange solid, Mp 65-67 °C. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO d_6): δ 9.64 (br s, 1H), 7.65 (d, *J*=8.5 Hz, 2H) 7.44 (d, *J*=8.7 Hz, 2H), 7.07 (s, 1H), 7.03 (d, *J*=7.9 Hz, 1H), 6.74 (d,

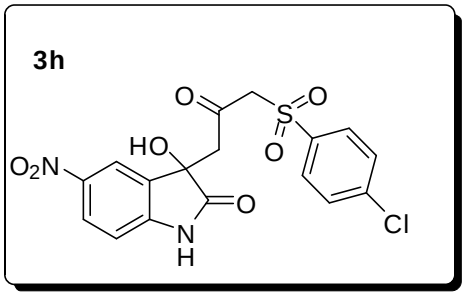
J=7.9 Hz, 1H), 5.90 (br s, 1H), 4.53 (d, *J*=13.8 Hz, 1H), 4.31 (d, *J*=13.8 Hz, 1H) 3.38 (d, *J*=16.1 Hz, 1H), 3.21 (d, *J*=16.1 Hz, 1H), 2.29 (s, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$+DMSO d_6): δ 195.11, 177.95, 139.89, 138.73, 136.25, 131.09, 129.75, 129.38, 129.33, 128.78, 124.27, 109.65, 73.15, 66.14, 50.54, 20.44 ppm.

IR (KBr) ν = 3364, 2923, 1721, 1627, 1493, 1322, 1154, 1087, 1033, 821, 764, 559, 468 cm^1.

MS (ESI) *m*/*z* 416 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{18}H_{16}ClNO_5SNa[M+Na]^+$=416.03354, found 416.03421.



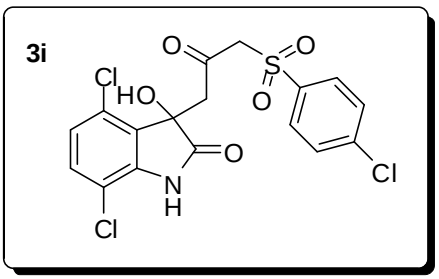
3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-nitro-1,3-dihydro-2*H*-indol-2-one (**3h**, Table 2): Yield 94 %, 0.398 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.13, White solid, Mp 176-178 °C.

^{1}H NMR (500 MHz, DMSO d_6): δ 10.64 (br s, 1H), 8.20-8.12 (m, 2H), 7.71 (d, *J*=8.3 Hz, 2H), 7.48 (d, *J*=8.3 Hz, 2H), 6.95 (d, *J*=9.3 Hz, 1H), 6.36 (br s, 1H), 4.41 (d, *J*=13.5 Hz, 1H), 4.34 (d, *J*=14.5 Hz, 1H), 3.57 (d, *J*=17.6 Hz, 1H), 3.43 (d, *J*=17.6 Hz, 1H) ppm.

^{13}C NMR (75 MHz, DMSO d_6): δ 194.72, 177.68, 148.17, 142.06, 139.99, 136.25, 129.16, 128.77, 128.05, 125.85, 119.36, 109.43, 72.10, 65.90, 50.27 ppm.

IR (KBr) ν = 3359, 3128, 2927, 1717, 1623, 1522, 1471, 1334, 1161, 1094, 835, 795, 744 cm^{-1}. MS (ESI) *m*/*z* 447 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{17}H_{13}ClN_2O_7SNa[M+Na]^+$=447.00242, found 447.00258.



4,7-dichloro-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3i**, Table 2): Yield 96 %, 0.429 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.33,

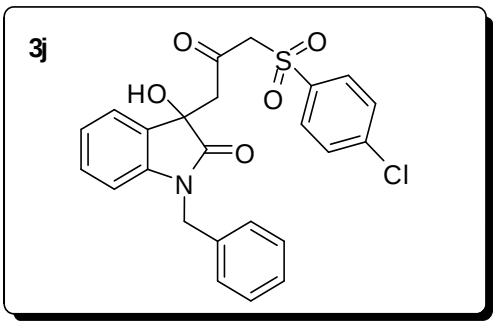
White solid, Mp 180-182 °C. ^{1}H NMR (500 MHz, $CDCl_3$+DMSO d_6): δ 10.35 (br s, 1H), 7.75 (d, *J*=7.2 Hz, 2H), 7.49 (d, *J*=7.2 Hz, 2H), 7.15 (d, *J*=9.6 Hz, 1H), 6.85 (d, *J*=7.2 Hz, 1H), 6.31 (br s, 1H), 4.46 (d, *J*=14.3 Hz, 1H), 4.35 (d, *J*=14.3 Hz, 1H), 3.74 (d, *J*=16.7 Hz, 1H), 3.58 (d, *J*=16.7 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 194.16, 175.77, 140.88, 138.87, 135.90, 129.17, 128.58, 128.03, 127.63, 126.96, 122.10, 112.26, 73.06, 64.76, 48.02 ppm.

IR (KBr) ν = 3484, 3218, 3089, 2925, 1731, 1612, 1470, 1322, 1156, 1089, 1032, 943, 765, 621, 562 cm^{-1}.

MS (ESI) *m*/*z* 448 $[M+H]^+$.

HRMS (ESI): *m/z* calcd. for $C_{17}H_{13}O_5NCl_3S[M+H]^+$= 447.95745, found 447.95776.



1-benzyl-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3j**, Table 2): Yield 87 %, 0.408 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.38, Orange viscous liquid.

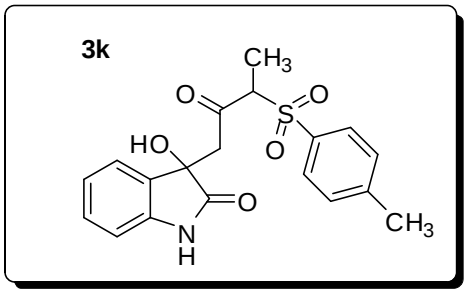
^{1}H NMR (500 MHz, $CDCl_3$+DMSO d_6): δ 7.56 (d, *J*=7.1 Hz, 2H), 7.39-7.27 (m, 5H), 7.28-7.18 (m, 3H), 7.14 (t, *J*=7.1 Hz, 1H), 6.98 (t, *J*=7.1 Hz, 1H), 6.62 (d, *J*=7.1 Hz, 1H), 6.16 (br s, 1H), 4.70 (d, *J*=15.3 Hz, 1H), 4.76 (d, *J*=15.3 Hz, 1H), 4.44 (d, *J*=13.3 Hz, 1H), 4.27 (d, *J*=13.3 Hz, 1H), 3.58 (d, *J*=17.3 Hz, 1H), 3.42 (d, *J*=17.3 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6): δ 194.83, 176.04, 142.50, 139.95, 135.92, 134.98, 129.43, 129.30, 129.00, 128.71, 128.05, 126.90, 126.63, 123.31, 122.07, 108.83, 72.46, 66.09, 50.76, 43.12 ppm.

IR (KBr) ν = 3420, 2925, 2854, 1720, 1614, 1580, 1491, 1469, 1357, 1325, 1282, 1156, 1087, 1065, 761, 701, 564 cm^{-1}.

MS (ESI) *m*/*z* 492 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{24}H_{20}O_5NClSNa[M+Na]^+$=492.06429, found 492.06387.



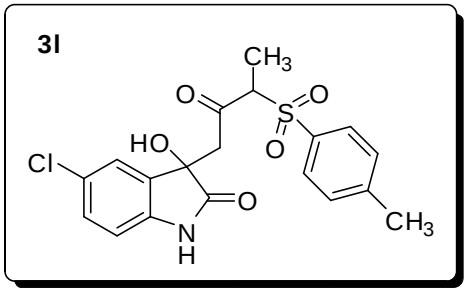
3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3k**, Table 2): Yield 89 %, 0.332 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.13, White solid, Mp 171-173 °C.

^{1}H NMR (300 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 57:43, * denotes minor diastereomer peaks): δ 9.85* (br s, 1H), 9.79 (br s, 1H), 7.71-7.51* (m, 4H), 7.49-7.38* (m, 2H), 7.36-7.24 (m, 4H), 7.20-7.15 (m, 2H), 7.04 (t, *J*=7.6 Hz, 1H), 6.97* (t, *J*=7.6 Hz, 1H), 6.89 (d, *J*=7.7 Hz, 1H), 6.85* (d, *J*=7.7 Hz, 1H), 5.95 (br s, 1H), 5.92* (br s, 1H), 4.50 (q, *J*=6.8 Hz, 1H), 4.38* (q, *J*=6.8 Hz, 1H), 3.73 (d, *J*=17.4 Hz, 1H), 3.65* (d, *J*=15.5 Hz, 1H), 3.47 (d, *J*=17.5 Hz, 1H), 3.18* (d, *J*=15.5 Hz, 1H), 2.43* (s, 3H), 2.40 (s, 3H), 1.27 (d, *J*=8.5 Hz, 3H), 1.23* (d, *J*=6.8 Hz, 3H) ppm.

^{13}C NMR (75 MHz, DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 57:43, * denotes minor diastereomer peaks): δ 198.10*, 197.96, 177.16, 177.08*, 143.98*, 143.83, 141.41, 140.97*, 131.99, 131.13, 130.98*, 129.88*, 129.70, 129.31*, 128.45*, 128.19, 128.12, 127.91*, 127.45, 122.92*, 122.88, 120.58*, 120.50, 108.95*, 108.90, 72.48*, 72.01, 68.98*, 67.60, 50.54, 49.50* 20.32*, 20.28, 10.44, 10.03* ppm.

IR (KBr) ν = 3475, 3415, 3205, 2922, 1715, 1623, 1475, 1298, 1144, 1074, 749, 715, 656, 573 cm^{-1}. MS (ESI) *m*/*z* 396 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{19}H_{19}O_5NSNa[M+Na]^+$=396.08761, found 396.08691.



5-chloro-3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3l**, Table 2): Yield 91 %, 0.370 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.29, White solid, Mp 85-87 °C.

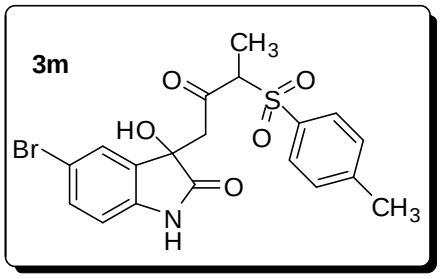
^{1}H NMR (500 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 56:44, * denotes minor diastereomer peaks): δ 9.91* (br s, 1H), 9.87 (br s, 1H), 7.60-7.53 * (m, 3H), 7.42-7.36 (m, 3H), 7.30* (d, *J*=8.7 Hz, 2H), 7.25 (dd, *J*=8.7, 1.7 Hz, 1H), 7.22 (d, *J*=7.8 Hz, 2H), 7.17* (dd, *J*=8.7, 2.3 Hz, 1H), 6.82 (d, *J*=8.7 Hz, 1H), 6.79* (d, *J*=,8.7 Hz, 1H), 6.00 (br s, 1H), 5.94* (br s, 1H), 4.45 (q, *J*=7.0 Hz, 1H), 4.35* (q, *J*=7.0 Hz, 1H), 3.70 (d, *J*=17.4 Hz, 1H), 3.62* (d, *J*=16.5 Hz, 1H), 3.46 (d, *J*=17.4 Hz, 1H), 3.27* (d, *J*=16.5 Hz, 1H), 2.43* (s, 3H), 2.41 (s, 3H), 1.26* (d, *J*=6.9 Hz, 3H), 1.25 (d, *J*=6.9 Hz, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 56:44, * denotes minor diastereomer peaks): δ 197.94*, 197.74, 176.60*, 176.53, 143.90*, 143.86, 140.28, 139.86*, 131.74*, 131.54, 131.29*, 131.10, 129.78, 128.35*, 128.16, 127.94, 127.83*, 127.71*, 127.66, 127.37, 125.05, 123.27*, 123.10, 109.86, 72.17*, 71.77, 68.69*, 67.47, 50.26, 49.00*, 20.27*, 20.25, 10.27, 9.97* ppm.

IR (KBr) ν = 3327, 2925, 2859, 1727, 1622, 1477, 1311, 1143, 1077, 1010, 817, 722, 653, 580 cm^{-1}.

MS (ESI) *m/z* 408 $[M+H]^+$.

HRMS (ESI): *m/z* calcd. for $C_{19}H_{19}O_5NClS[M+H]^+$= 408.06670, found 408.06650.



5-bromo-3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3m**, Table 2): Yield 88 %, 0.417 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.19, Brown solid, Mp 170-172 °C.

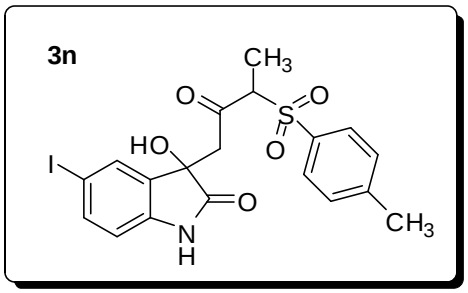
^{1}H NMR (500 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 55:45, * denotes minor diastereomer peaks): δ 10.92* (br s, 1H), 10.67 (br s, 1H), 7.72-7.66 * (m, 3H), 7.43-7.37 (m, 3H), 7.29* (d, *J*=8.6 Hz, 2H), 7.26 (dd, *J*=8.6, 1.7 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 2H), 7.18* (dd, *J*=8.6, 2.3 Hz, 1H), 6.73 (d, *J*=8.7 Hz, 1H), 6.69* (d, *J*=,8.7 Hz, 1H), 6.01 (br s, 1H), 5.95* (br s, 1H), 4.46 (q, *J*=7.0 Hz, 1H), 4.34* (q, *J*=7 Hz, 1H), 3.71 (d, *J*=17.4 Hz, 1H), 3.63* (d, *J*=16.5 Hz, 1H), 3.47 (d, *J*=17.4 Hz, 1H), 3.27* (d, *J*=16.5 Hz, 1H), 2.43* (s, 3H), 2.41 (s, 3H), 1.27* (d, *J*=6.9 Hz, 3H), 1.25 (d, *J*=6.9 Hz, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 55:45, * denotes minor diastereomer peaks): δ 198.27, 198.05*, 176.81*, 176.88, 144.50*, 144.25, 140.81*, 140.44, 132.06*, 131.85, 131.05, 130.71*, 128.90*, 128.66, 128.47*, 128.38, 128.09, 128.01*, 126.32, 126.15*, 124.82*, 124.32, 123.13, 112.98*, 110.88, 72.54, 72.11*, 69.45, 68.90*, 50.48*, 49.19* 20.05, 19.96*, 10.53*, 10.24 ppm.

IR (KBr) ν = 3383, 3245, 2925, 1748, 1619, 1480, 1304, 1142, 1068, 1009, 830, 720, 650, 581 cm^{-1}.

MS (ESI) *m/z* 474 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{19}H_{18}BrNO_5SNa[M+Na]^+$=473.99868, found 473.99929.



3-hydroxy-5-iodo-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3n**, Table 2): Yield 86 %, 0.429 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.31, Yellow solid, Mp 216-218 °C.

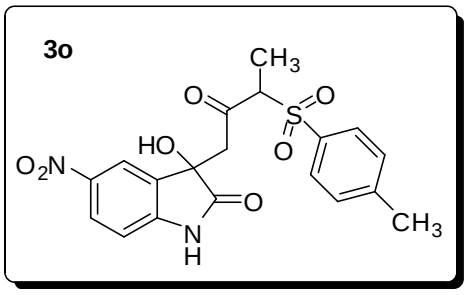
^{1}H NMR (200 MHz, DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 59:41, * denotes minor diastereomer peaks): δ 10.06* (br s, 1H), 10.04 (br s, 1H), 7.68* (d, *J*=1.0 Hz, 2H), 7.59-7.50 (m, 4H), 7.39-7.28* (m, 4H), 7.23 (d, *J*=8.1 Hz, 2H), 6.68 (d, *J*=8.3 Hz, 1H), 6.65* (d, *J*=8.3 Hz, 1H), 6.15 (br s, 1H), 6.10* (br s, 1H), 4.50-4.43 (m, 1H), 4.37-4.30* (m, 1H), 3.73 (d, *J*=17.5 Hz, 1H), 3.63* (d, *J*=16.6 Hz, 1H), 3.44 (d, *J*=17.5 Hz, 1H), 3.27* (d, *J*=16.6 Hz, 1H), 2.44* (s, 3H), 2.42 (s, 3H), 1.34* (d, *J*=6.8 Hz, 3H), 1.24 (d, *J*=6.8 Hz, 3H) ppm.

^{13}C NMR (50 MHz, DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 59:41, * denotes minor diastereomer peaks): δ 199.14*, 199.06, 177.04*, 176.92, 144.91, 142.54, 142.31*, 137.49, 133.65, 133.55*, 132.92, 132.23, 129.55*, 129.35, 128.95, 128.85*, 112.01, 119.95*, 83.86*, 83.78, 72.46*, 72.12, 68.76*, 67.93, 51.08, 50.08* 21.08, 11.19, 10.86* ppm.

IR (KBr) ν = 3382, 3236, 2988, 1740, 1615, 1477, 1387, 1305, 1212, 1140, 1066, 1005, 828, 716, 646, 578 cm^{-1}.

MS (ESI) *m/z* 517 $[M+ NH_4]^+$.

HRMS (ESI): *m/z* calcd. For $C_{19}H_{22}IN_2O_5S[M+NH_4]^+$=517.02941, found 517.02999.



3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-5-nitro-1,3-dihydro-2*H*-indol-2-one (**3o**, Table 2): Yield 83 %, 0.347 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.30, Pale yellow solid, Mp 199-201 °C.

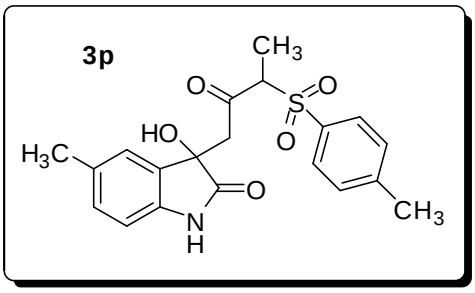
^{1}H NMR (500 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 59:41, * denotes minor diastereomer peaks): δ 10.65 (br s, 1H), 10.64* (br s, 1H), 8.29-8.21* (m 2H), 8.20-8.13 (m, 2H), 7.57* (d, *J*=7.8 Hz, 2H), 7.4 (d, *J*=7.8 Hz, 2H), 7.30* (d, *J*=7.8 Hz, 2H), 7.21 (d, *J*=7.8 Hz, 2H), 6.99 (d, *J*=8.8 Hz, 1H), 6.97* (d, *J*=8.8 Hz, 1H), 6.34 (br s, 1H), 6.30* (br s, 1H), 4.49-4.39 (m, 1H), 4.38-4.31* (m, 1H), 3.80 (d, *J*=18.5 Hz, 1H), 3.73* (d, *J*=16.5 Hz, 1H), 3.54 (d, *J*=17.5 Hz, 1H), 3.52* (d, *J*=17.5 Hz, 1H), 2.43* (s, 3H), 2.41 (s, 3H) 1.32* (d, *J*=6.8 Hz, 3H), 1.26 (d, *J*= 6.8 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 59:41, * denotes minor diastereomer peaks): δ 197.86*, 197.81, 176.94*, 176.82, 147.95, 147.78*, 143.81, 143.76*, 140.92*, 140.88, 131.53*, 131.32, 130.47, 130.40*, 128.20*, 128.05, 127.63*, 127.50, 124.91, 118.48, 108.37, 108.32*, 71.20*, 71.01, 68.08*, 67.17, 49.90, 48.97*, 20.03*, 19.99, 10.02, 9.85* ppm.

IR (KBr) ν = 3289, 2931, 1715, 1624, 1520, 1456, 1327, 1141, 1006, 909, 715, 640 cm^{-1}.

MS (ESI) *m*/*z* 441 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. For $C_{19}H_{18}N_2O_7SNa[M+Na]^+$=441.07324, found 441.07398.



3-hydroxy-5-methyl-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3p**, Table 2): Yield 81 %, 0.313 g, Time 8 h, *Rf*(50% EtOAc/hexanes) 0.19, Brown solid, Mp 80-82 $^{\circ}$C.

^{1}H NMR (300 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 63:37, * denotes minor diastereomer peaks): δ 9.72* (br s, 1H), 9.67 (br s, 1H), 7.53-7.41* (m, 3H), 7.27-7.18 (m, 3H), 7.15 (d, *J*=7.6 Hz, 1H), 7.10 (d, *J*=8.1 Hz, 2H), 6.98* (d, *J*=6.8 Hz, 2H), 6.92* (d, *J*=7.6 Hz, 1H), 6.68 (d, *J*=7.9 Hz, 1H), 6.64* (d, *J*=7.9 Hz, 1H), 5.90 (br s, 1H), 5.84* (br s, 1H), 4.45 (q, *J*=6.8 Hz 1H), 4.32* (q , *J*=6.8 Hz 1H), 3.58* (d, *J* = 15.5 Hz, 1H), 3.53 (d, *J*=17.2 Hz, 1H), 3.37 (d, *J*=17.2 Hz, 1H), 3.05* (d, *J*=15.5 Hz, 1H), 2.08 (s, 3H), 2.08* (s, 3H), 2.08 (s, 3H), 2.08* (s, 3H) 1.19* (d, *J*=6.9 Hz, 3H), 1.14 (d, *J*=6.9 Hz, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$+DMSO d_6) (inseparable diastereomeric ratio, *major:minor*, 63:37, * denotes minor diastereomer peaks): δ 198.71*, 198.41, 177.84, 177.70*, 144.71*, 144.26, 139.03, 138.57*, 132.28*, 131.37, 130.46, 130.20*, 129.91, 129.57*, 128.97*, 128.82, 128.54, 128.33*, 124.01, 109.26, 73.22*, 72.70, 69.58*, 68.12, 50.87, 49.75*, 22.02*, 21.72*, 20.73, 20.19, 10.81, 10.42* ppm.

IR (KBr) ν = 3331, 2924, 1721, 1628, 1494, 1318, 1146, 1082, 817, 718, 656 cm^{-1}.

MS (ESI) *m/z* 410 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd. for $C_{20}H_{21}O_5NSNa[M+Na]^+$=410.10326, found 410.10248.

References:

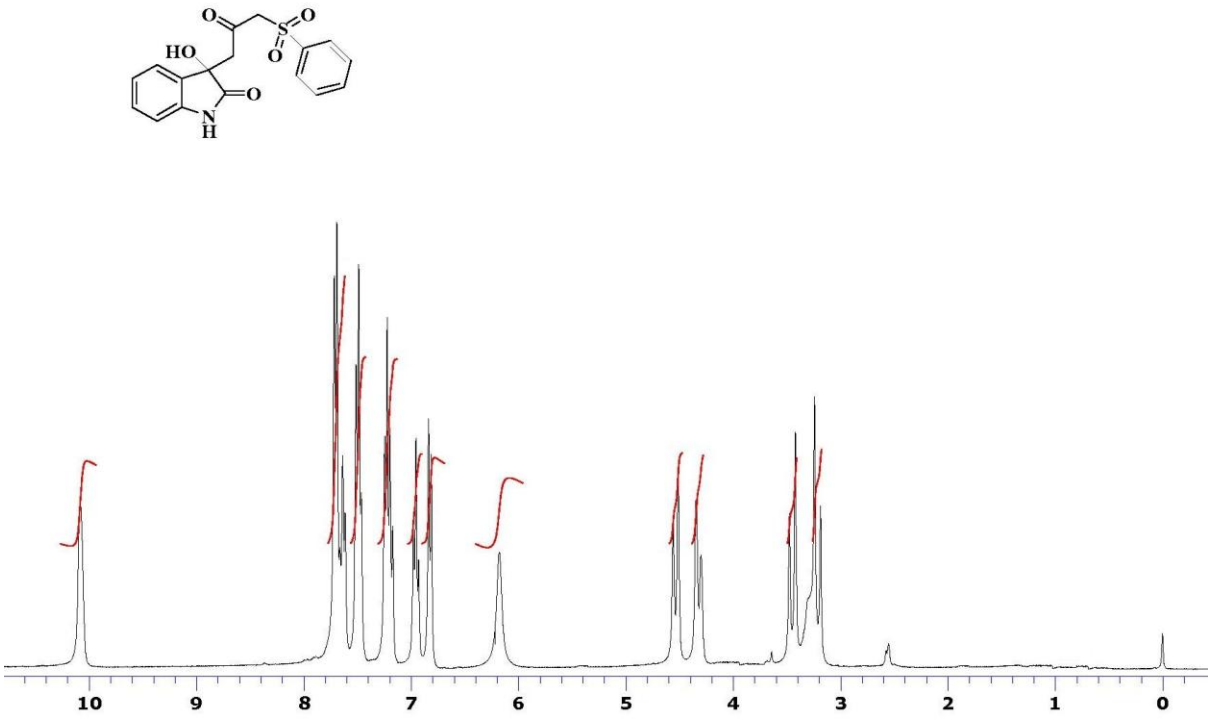
1. Newman, M.; Magerlein, B.; Wheatley, W. *J. Am. Chem. Soc.* **1946**, *68*, 2112.

2. (a) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc*. **1974**, *96*, 1082. (b) Xu, C. F.; Yuan, C. Y. *Tetrahedron* **2005**, *61*, 2169.

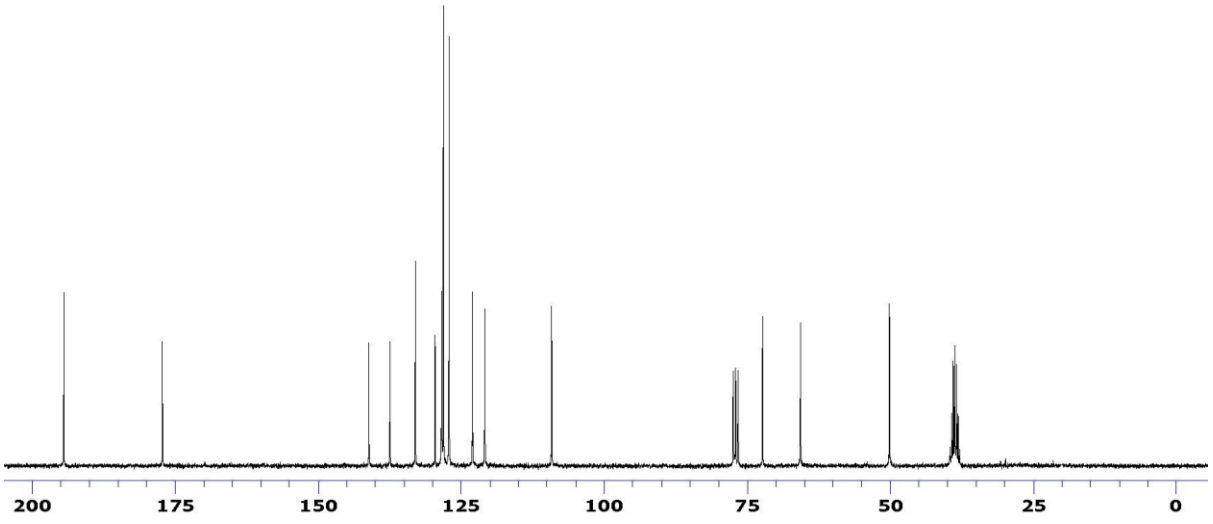
Copies of ^{1}H and ^{13}C NMR spectra for compound 3a-3p:

3-hydroxy-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2*H*-indol-2-one (**3a**, Table 2)

^{1}H NMR, 300 MHz, $CDCl_3$+DMSO d_6

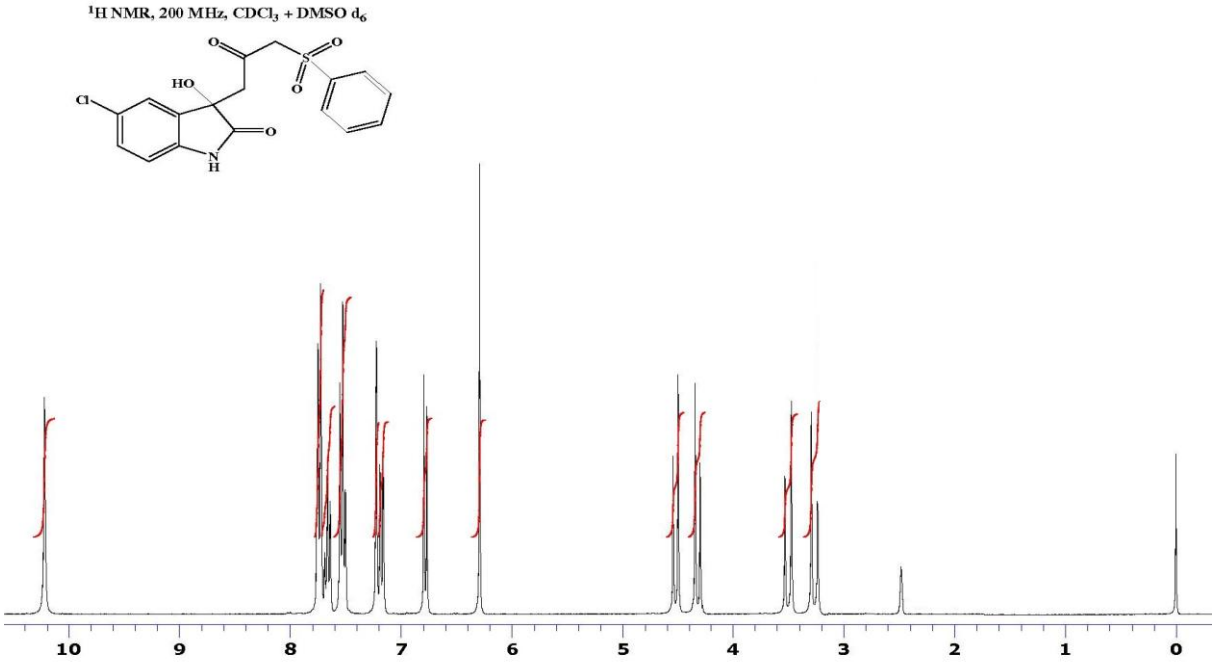


^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6

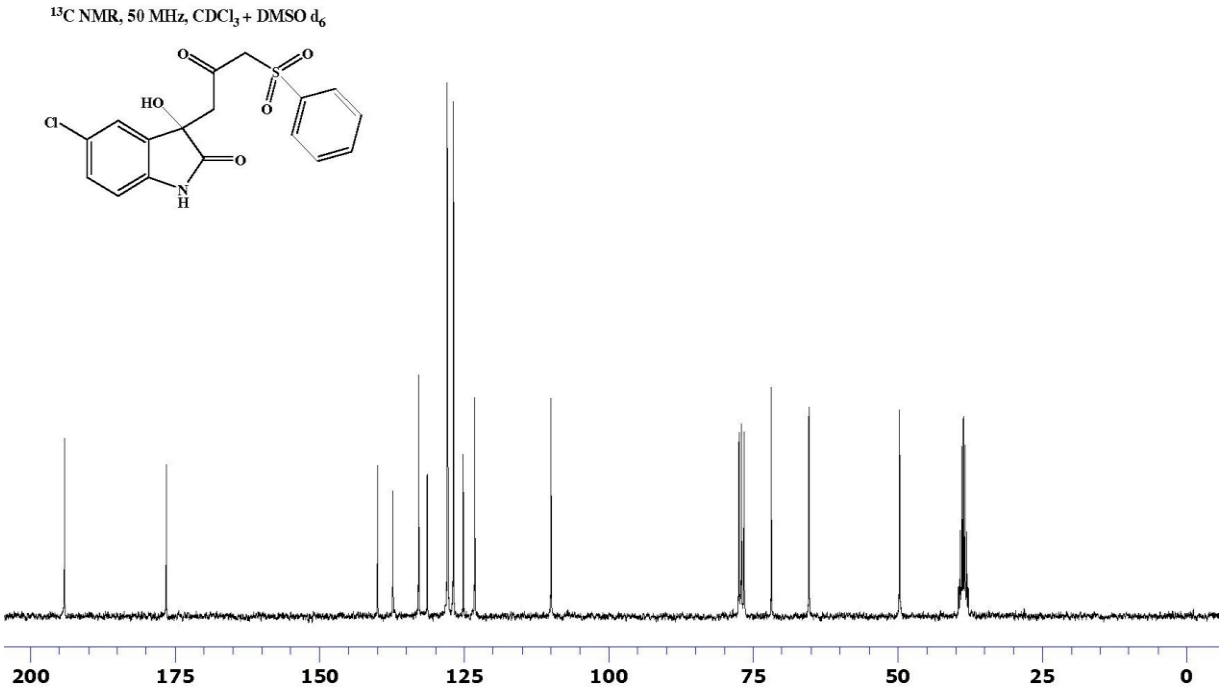


5-chloro-3-hydroxy-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2*H*-indol-2-one (**3b**, Table 2)

^{1}H NMR, 200 MHz, $CDCl_3$ + DMSO d_6

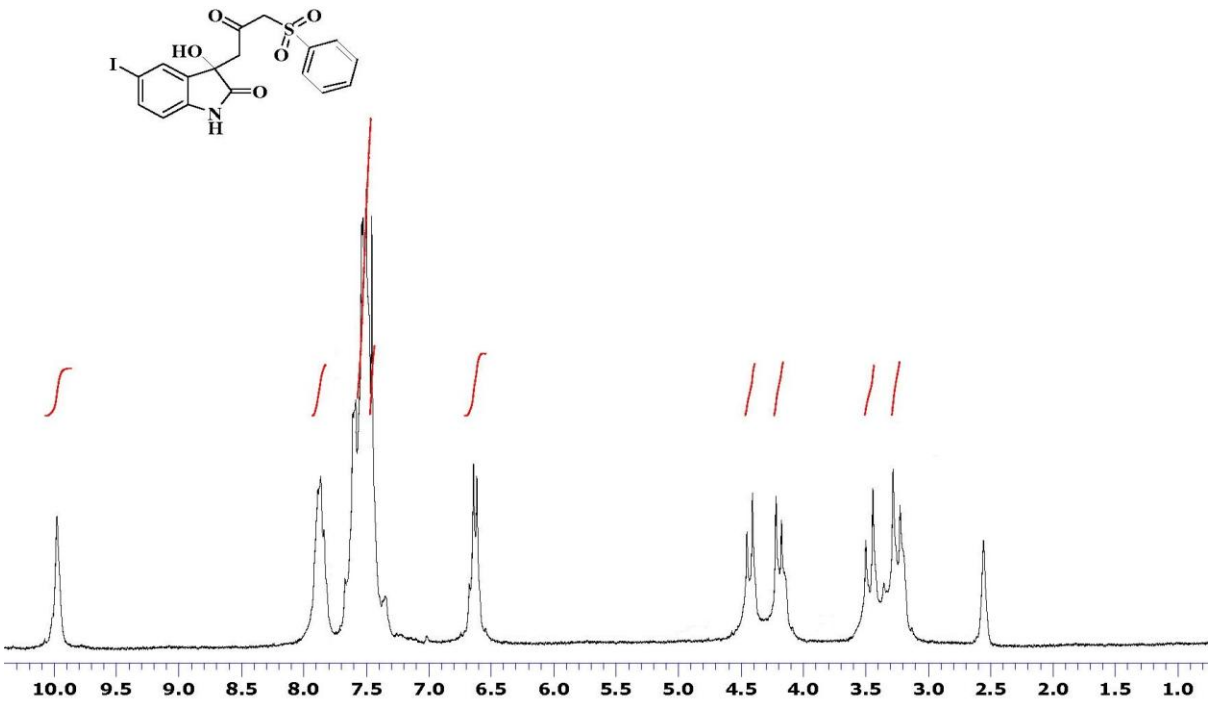


^{13}C NMR, 50 MHz, $CDCl_3$ + DMSO d_6

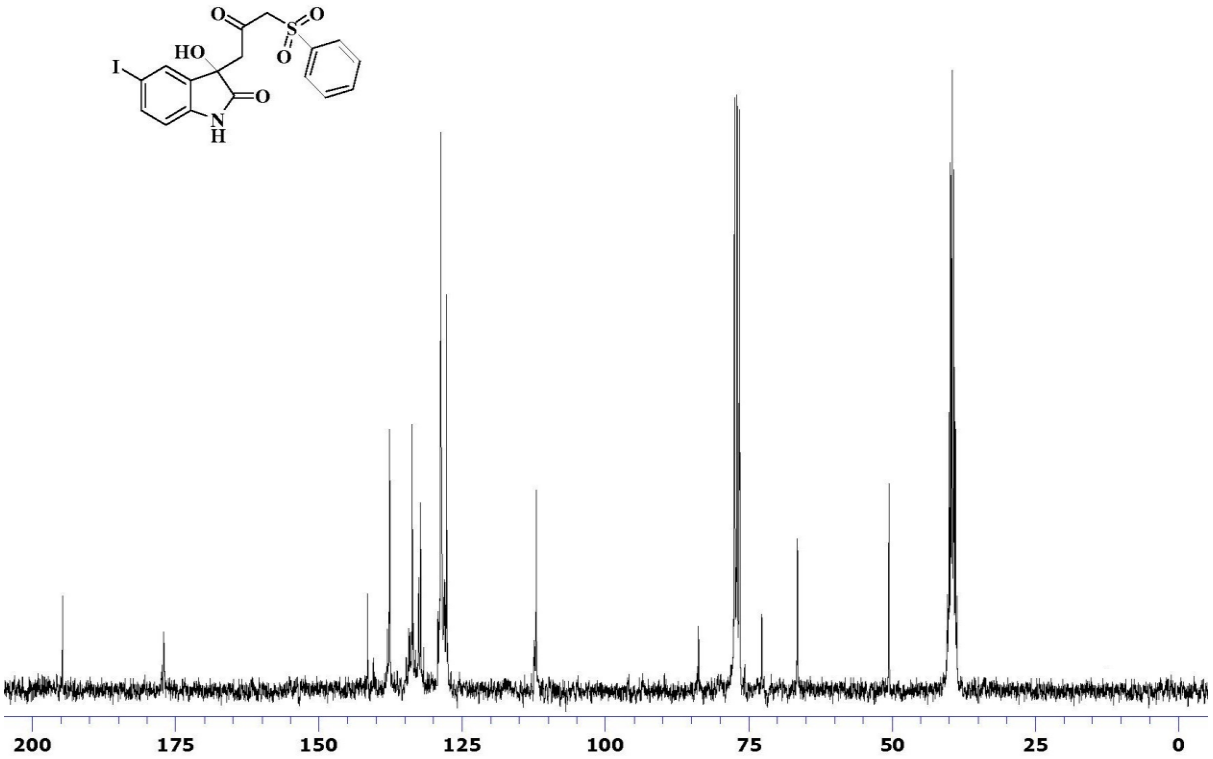


3-hydroxy-5-iodo-3-[2-oxo-3-(phenylsulfonyl)propyl]-1,3-dihydro-2*H*-indol-2-one (**3c**, Table 2):

^{1}H NMR, 300 MHz, $CDCl_3$+DMSO d_6

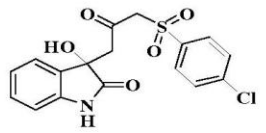


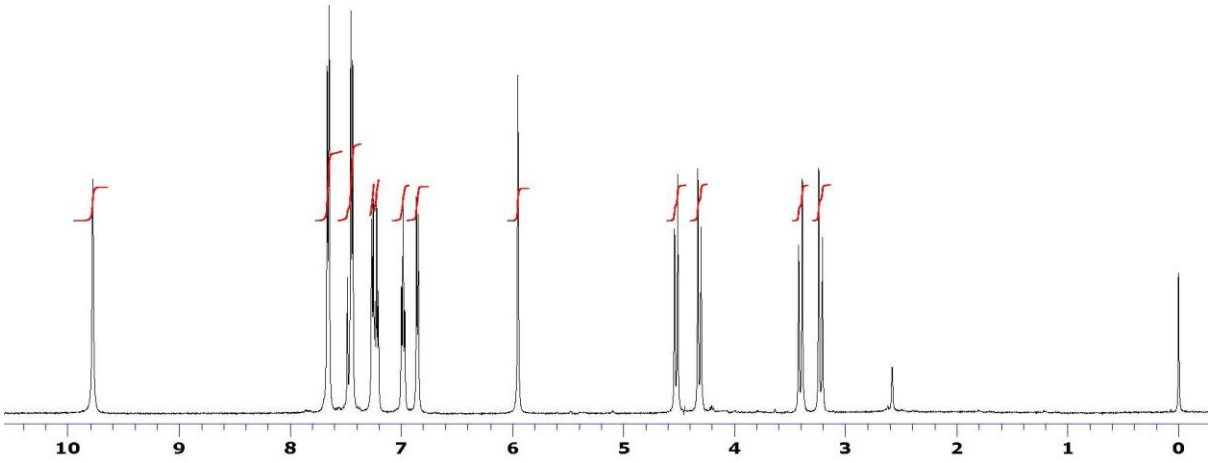
^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6



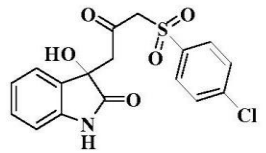
3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3d**, Table 2)

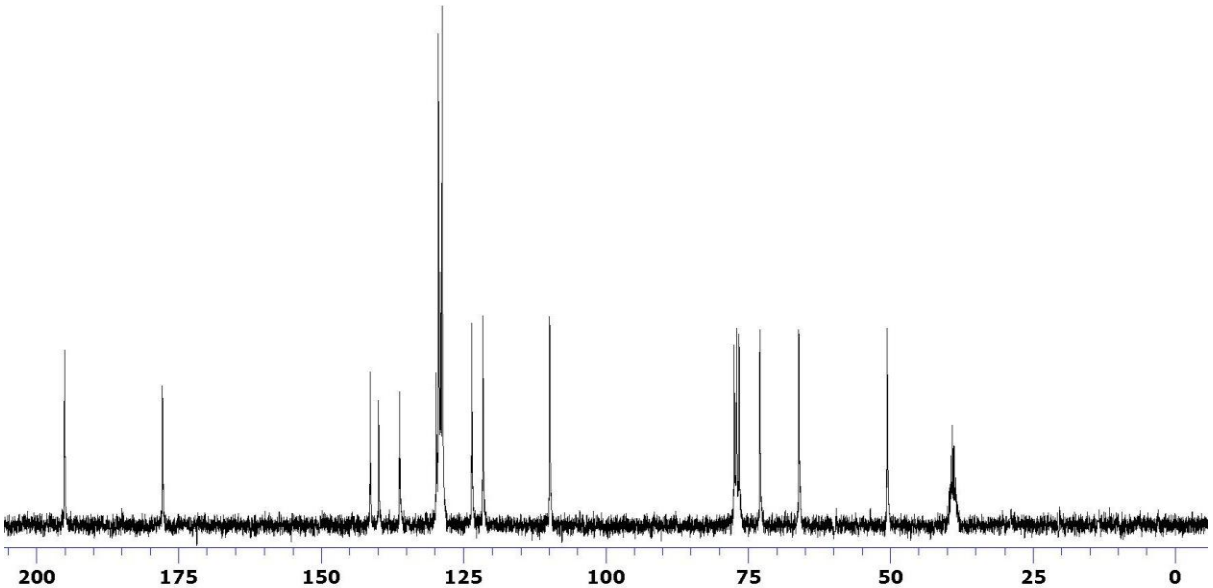
^{1}H NMR, 500 MHz, $CDCl_3$+DMSO d_6





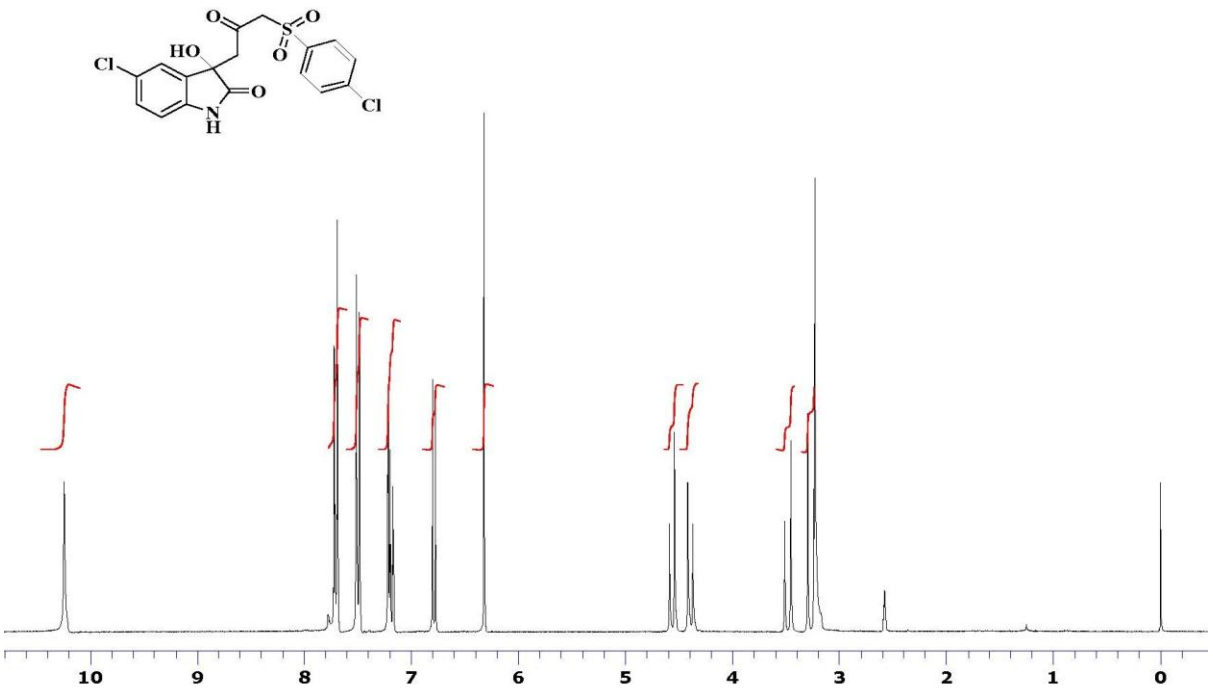
^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6



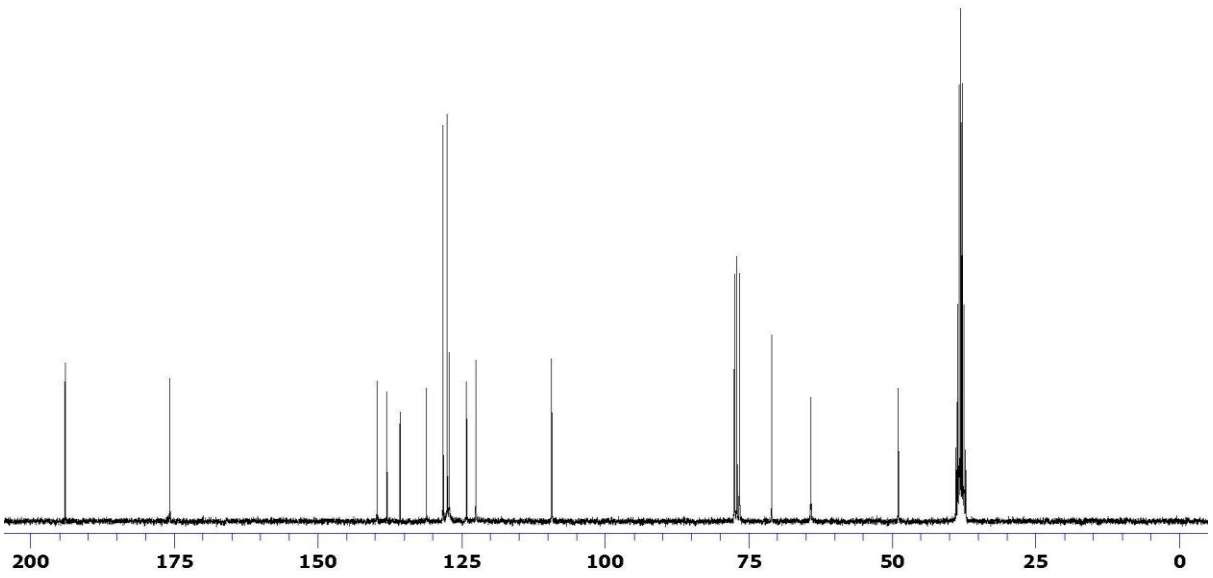


5-chloro-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3e**, Table 2)

^{1}H NMR, 300 MHz, $CDCl_3$+DMSO d_6

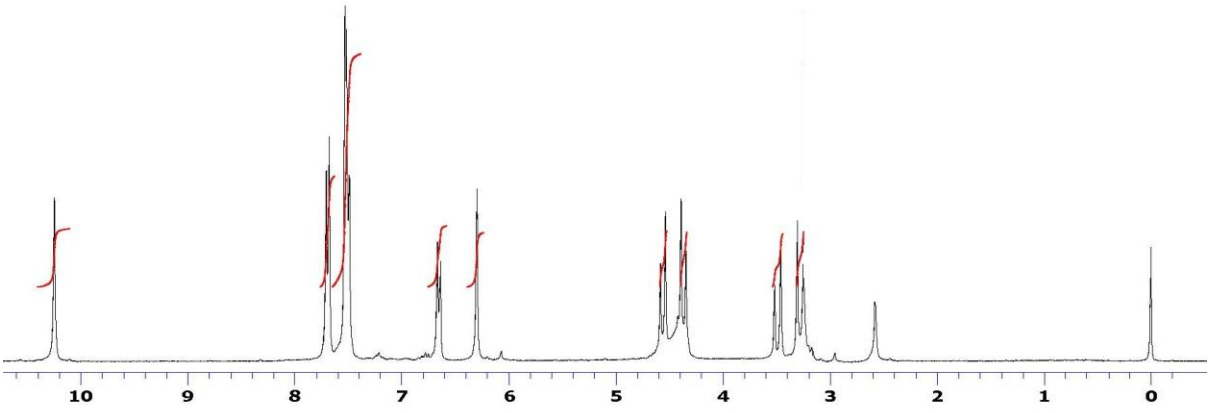


^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6

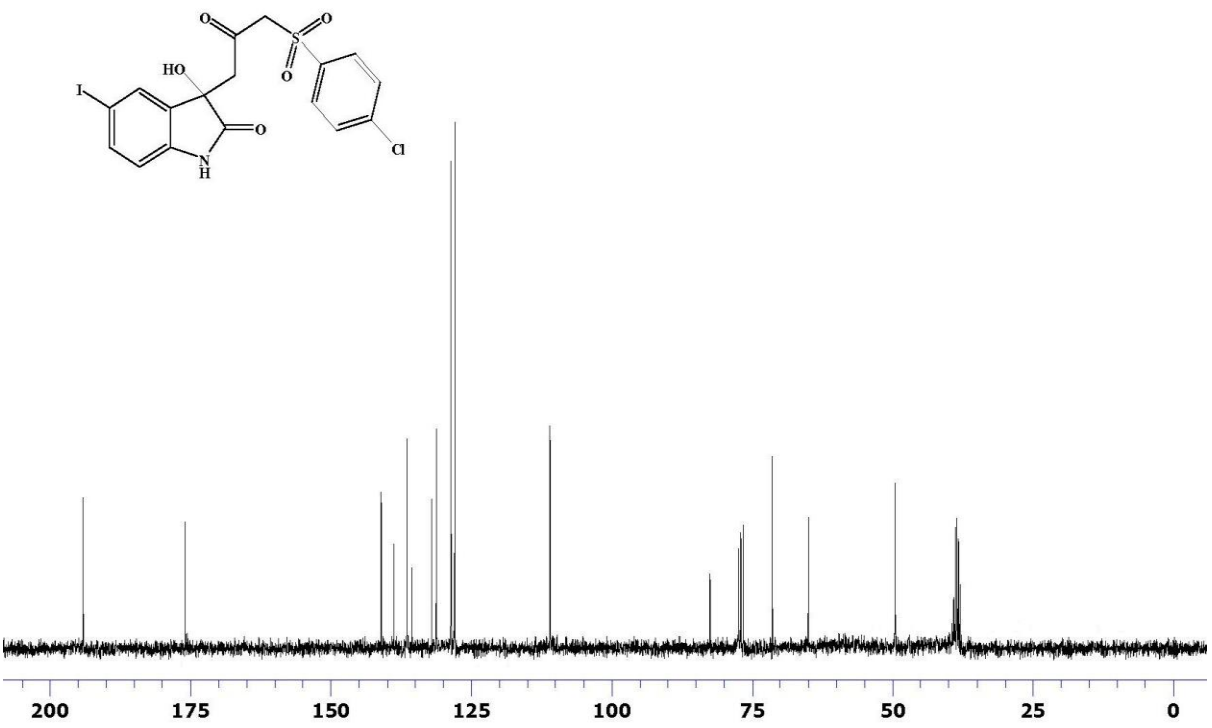


3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-iodo-1,3-dihydro-2*H*-indol-2-one (**3f**, Table 2)

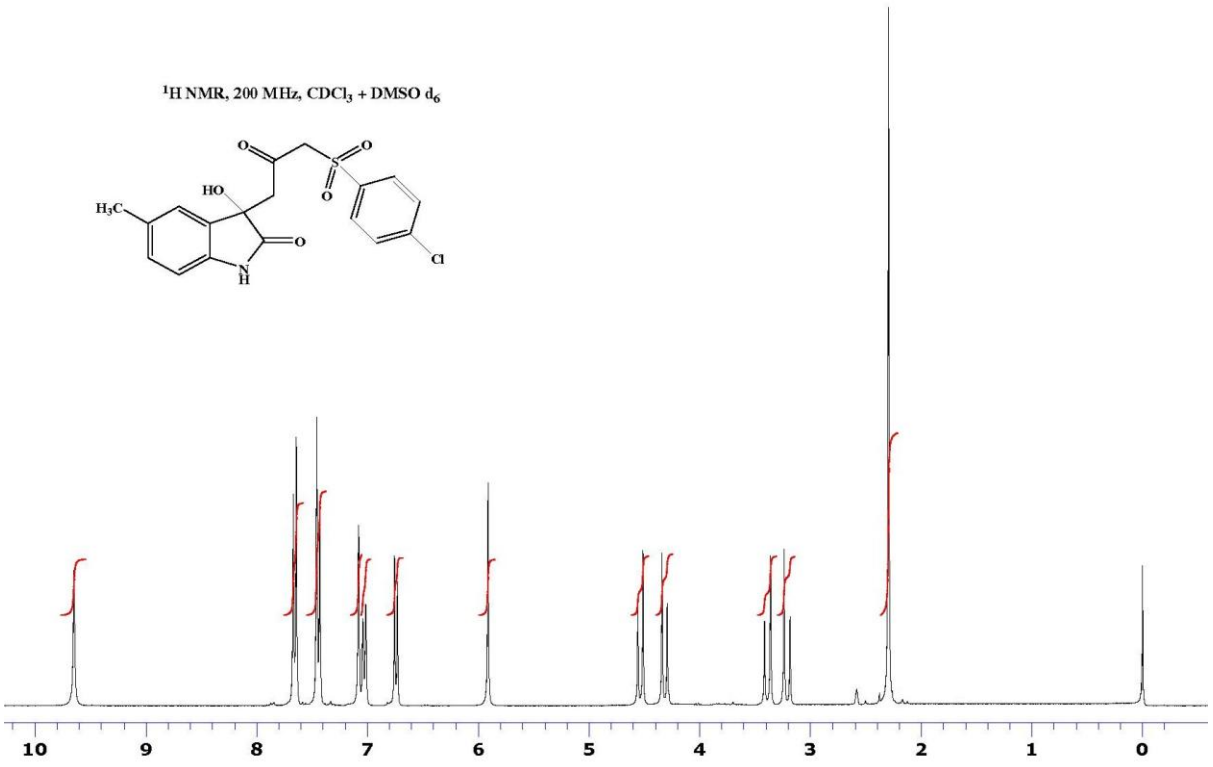
^{1}H NMR, 200 MHz, $CDCl_3$ + DMSO d_6

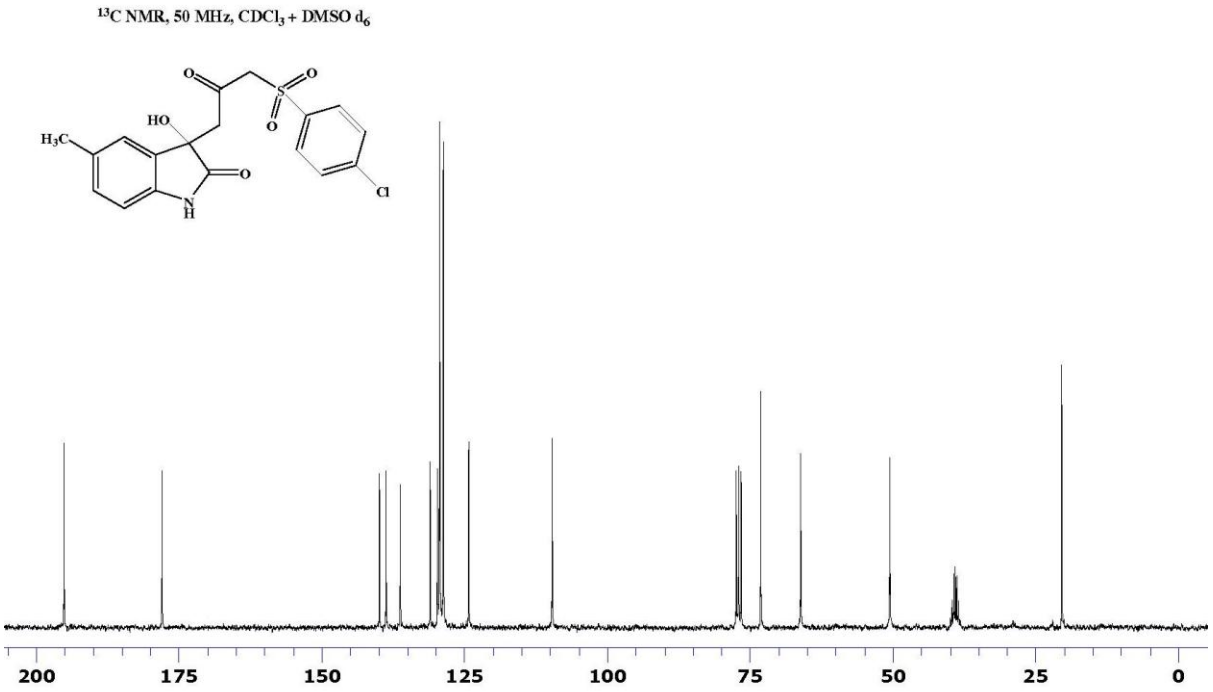


^{13}C NMR, 75 MHz, $CDCl_3$ + DMSO d_6



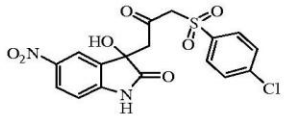
3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-methyl-1,3-dihydro-2*H*-indol-2-one (**3g**, Table 2)

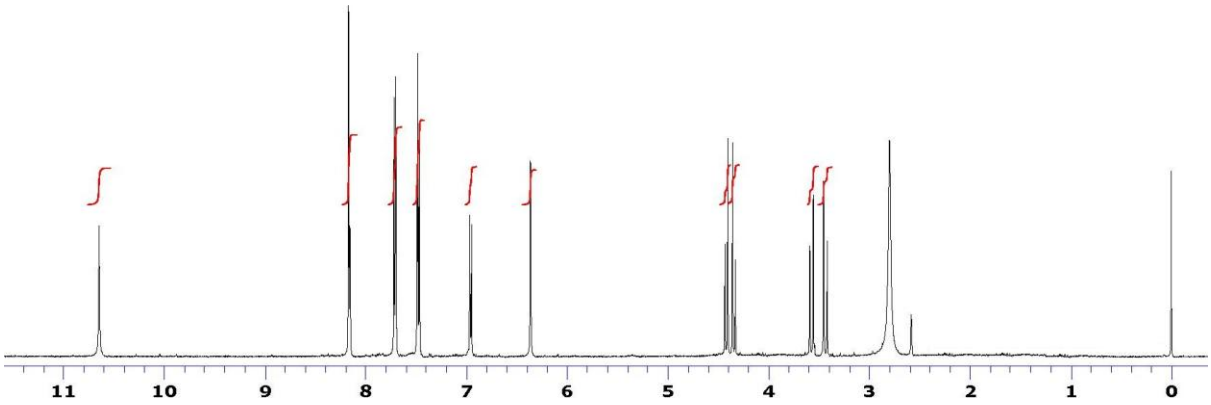




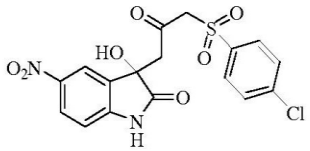
3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-5-nitro-1,3-dihydro-2*H*-indol-2-one (**3h**, Table 2)

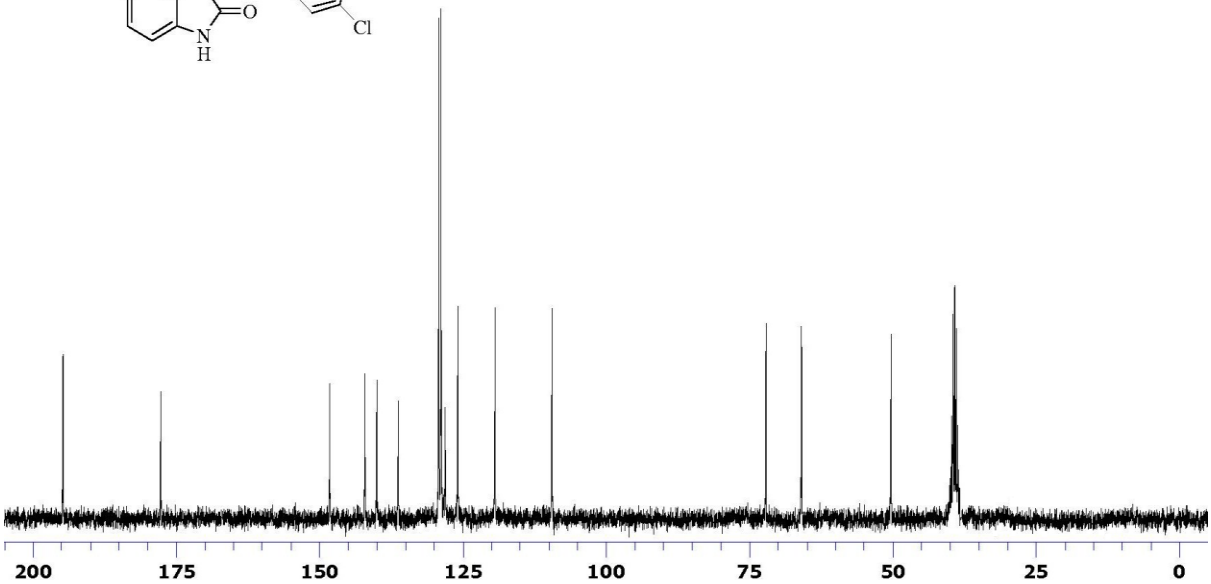
^{1}H NMR, 500 MHz, DMSO d_6





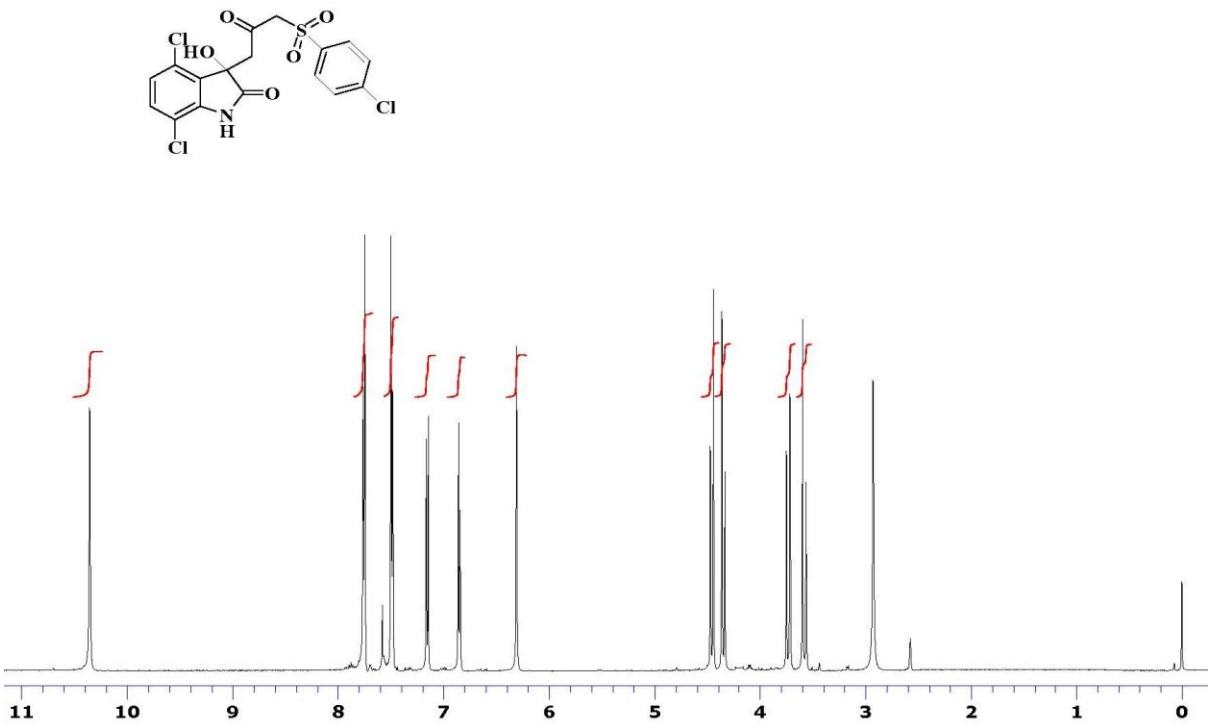
^{13}C NMR, 75 MHz, DMSO d_6



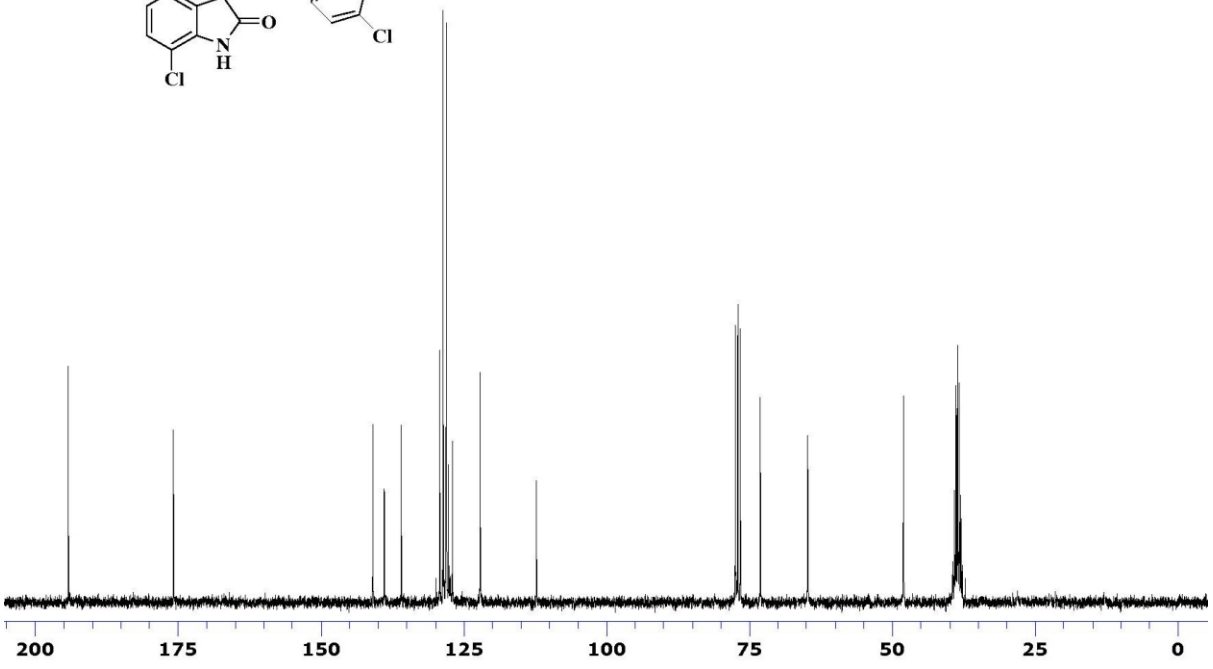


4,7-dichloro-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3i**, Table 2)

^{1}H NMR, 500 MHz, $CDCl_3$+DMSO d_6

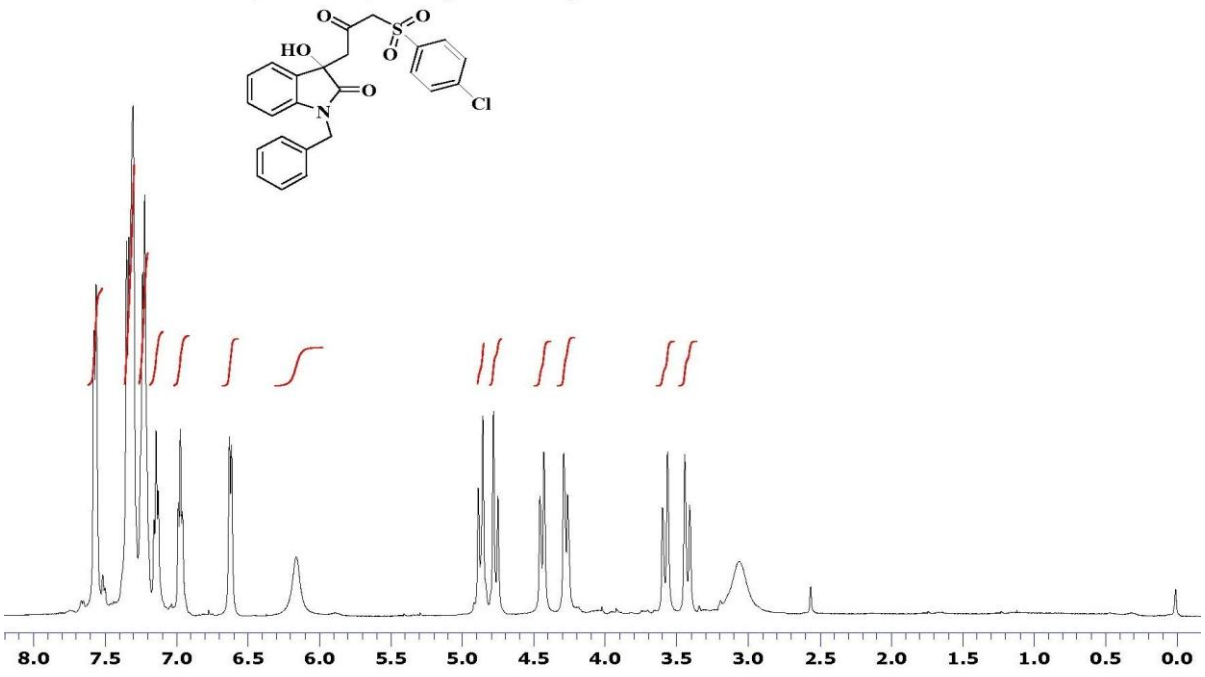


^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6

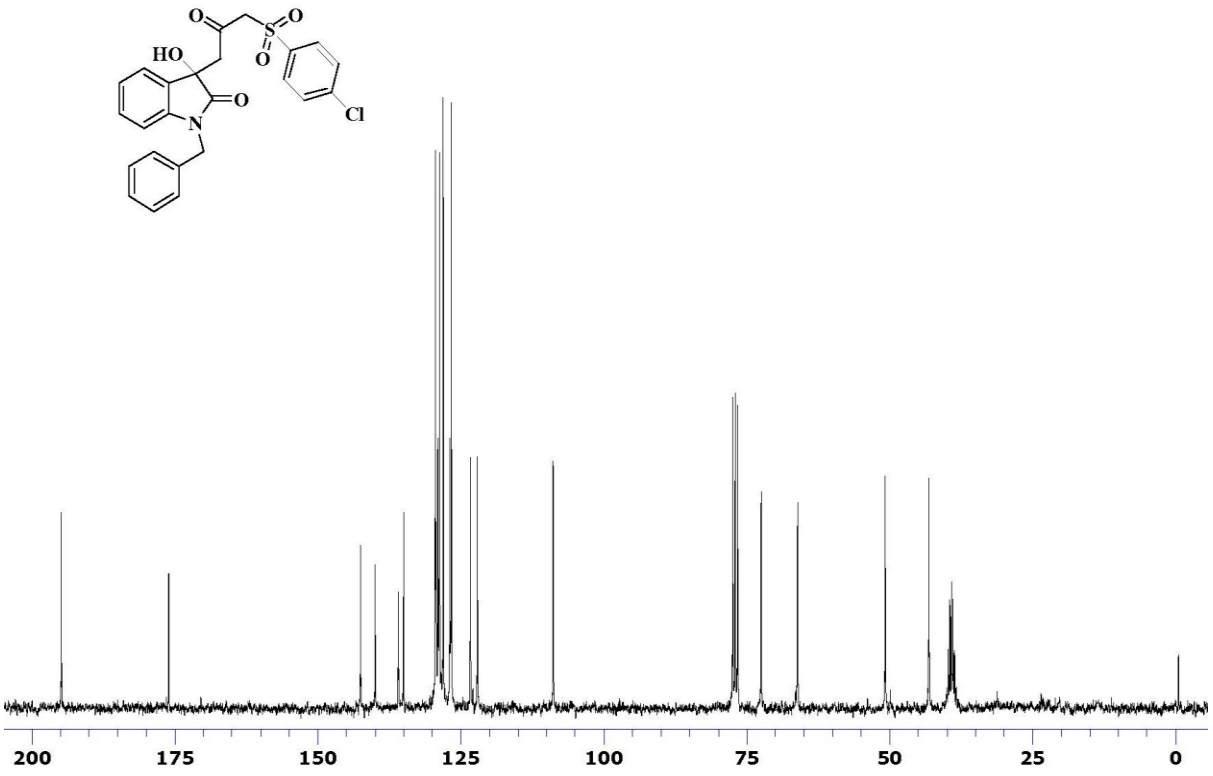


1-benzyl-3-{3-[(4-chlorophenyl)sulfonyl]-2-oxopropyl}-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (**3j**, Table 2)

^{1}H NMR, 500 MHz, $CDCl_3$+DMSO d_6

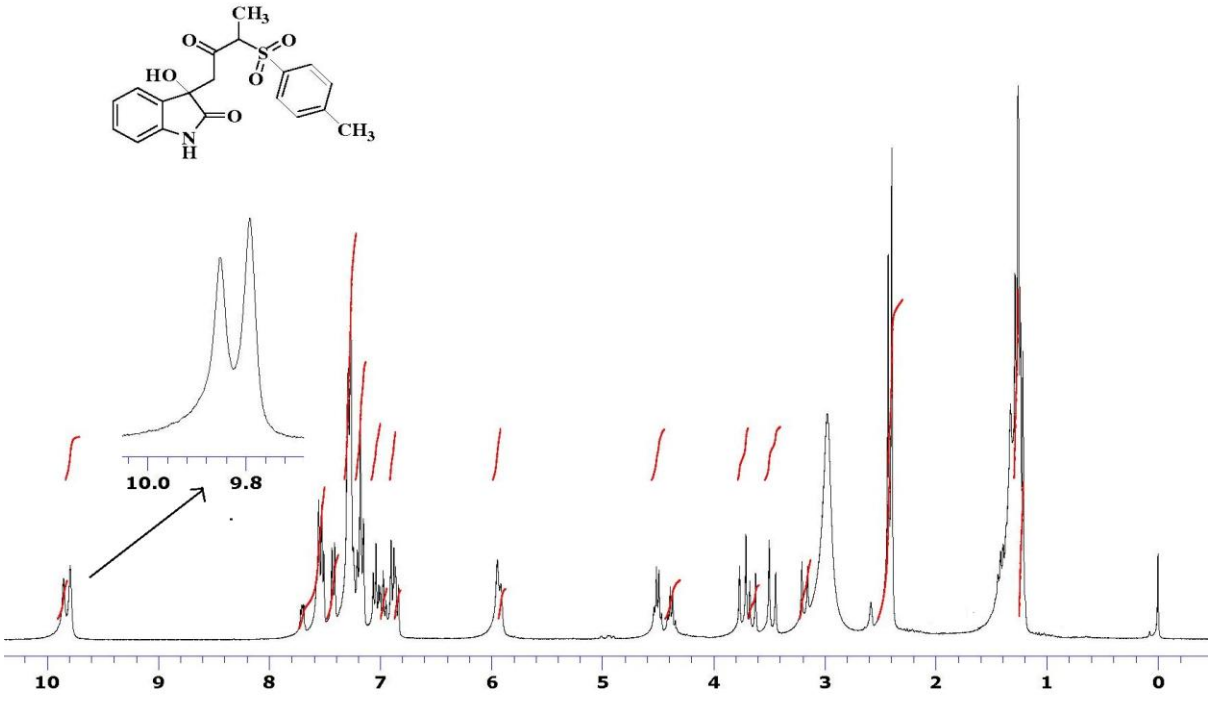


^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6

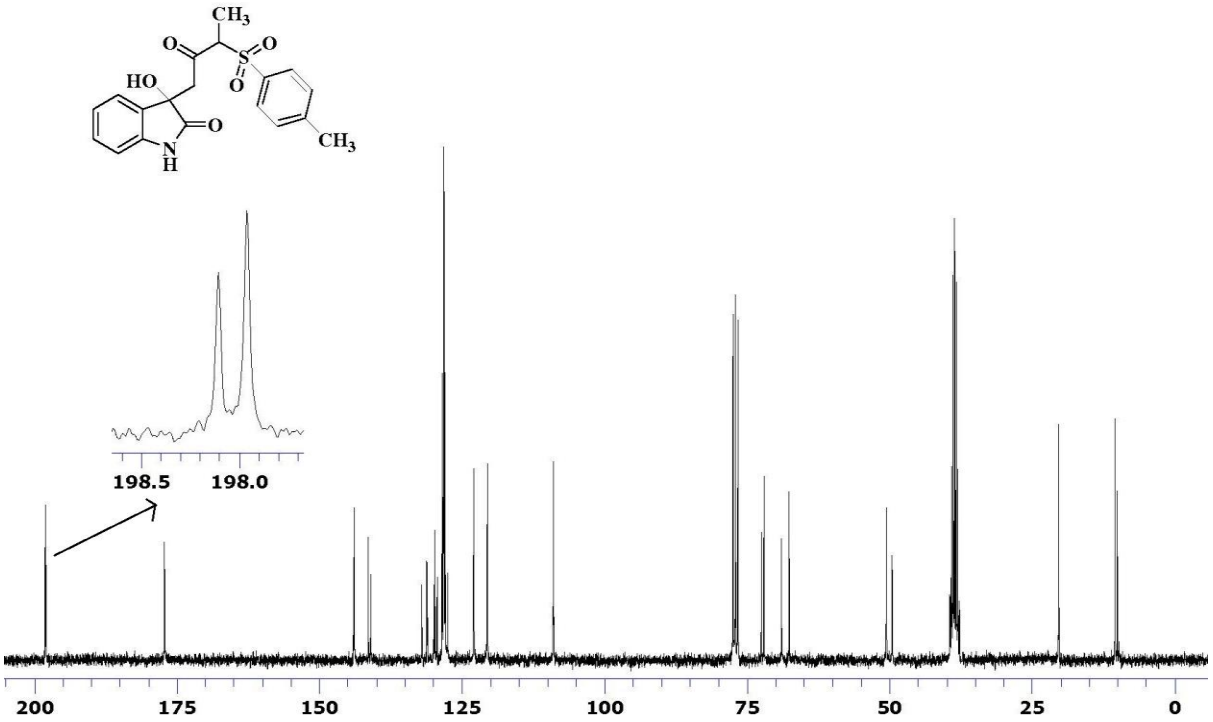


3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3k**, Table 2)

^{1}H NMR, 300 MHz, $CDCl_3$+DMSO d_6

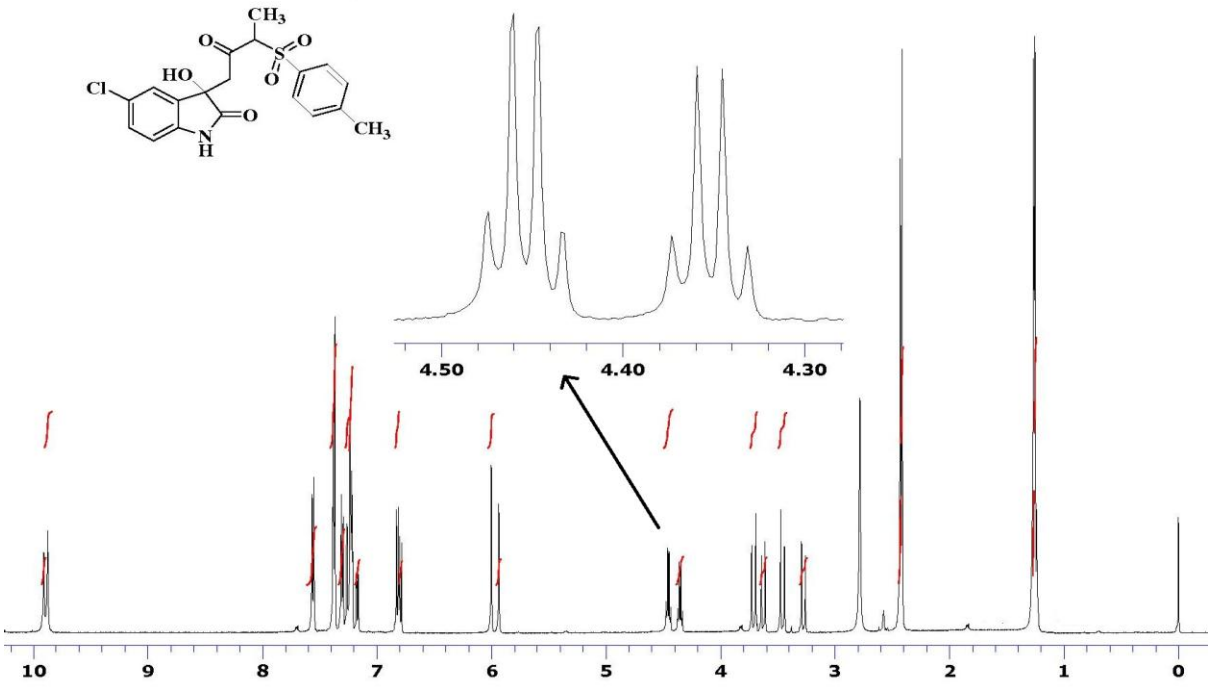


^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6

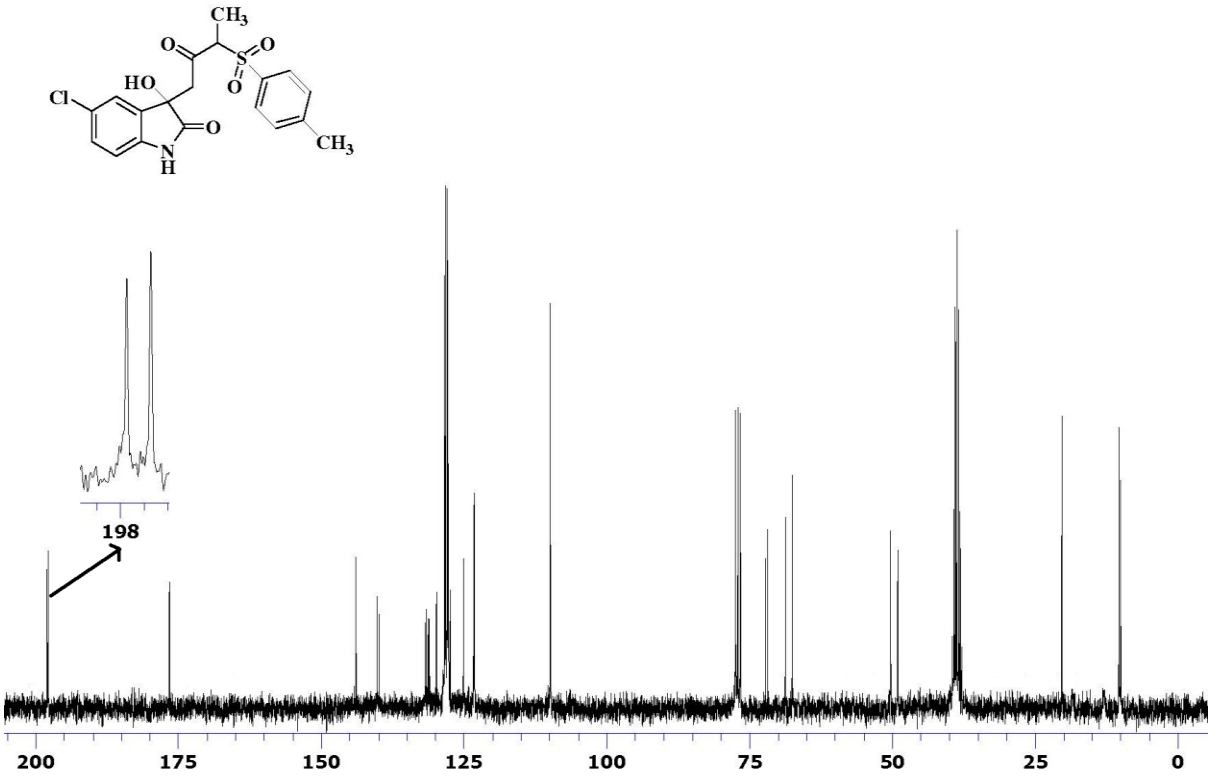


5-chloro-3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3l**, Table 2)

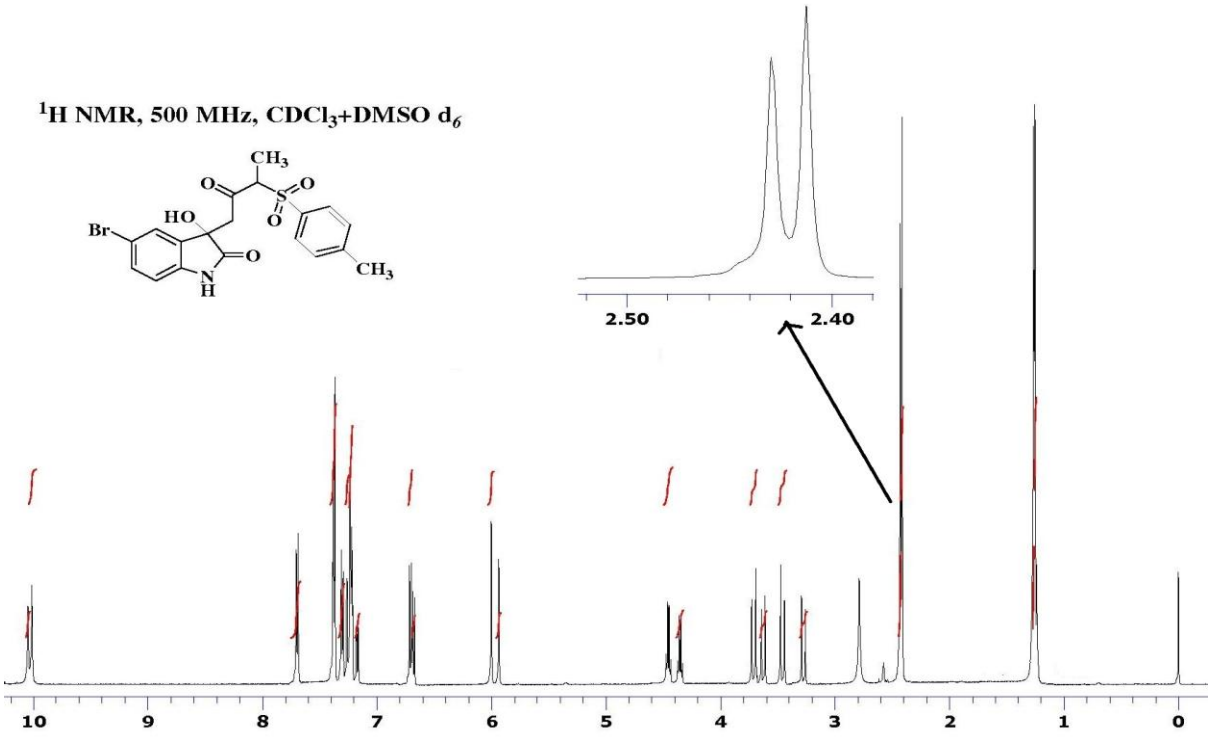
^{1}H NMR, 500 MHz, $CDCl_3$+DMSO d_6

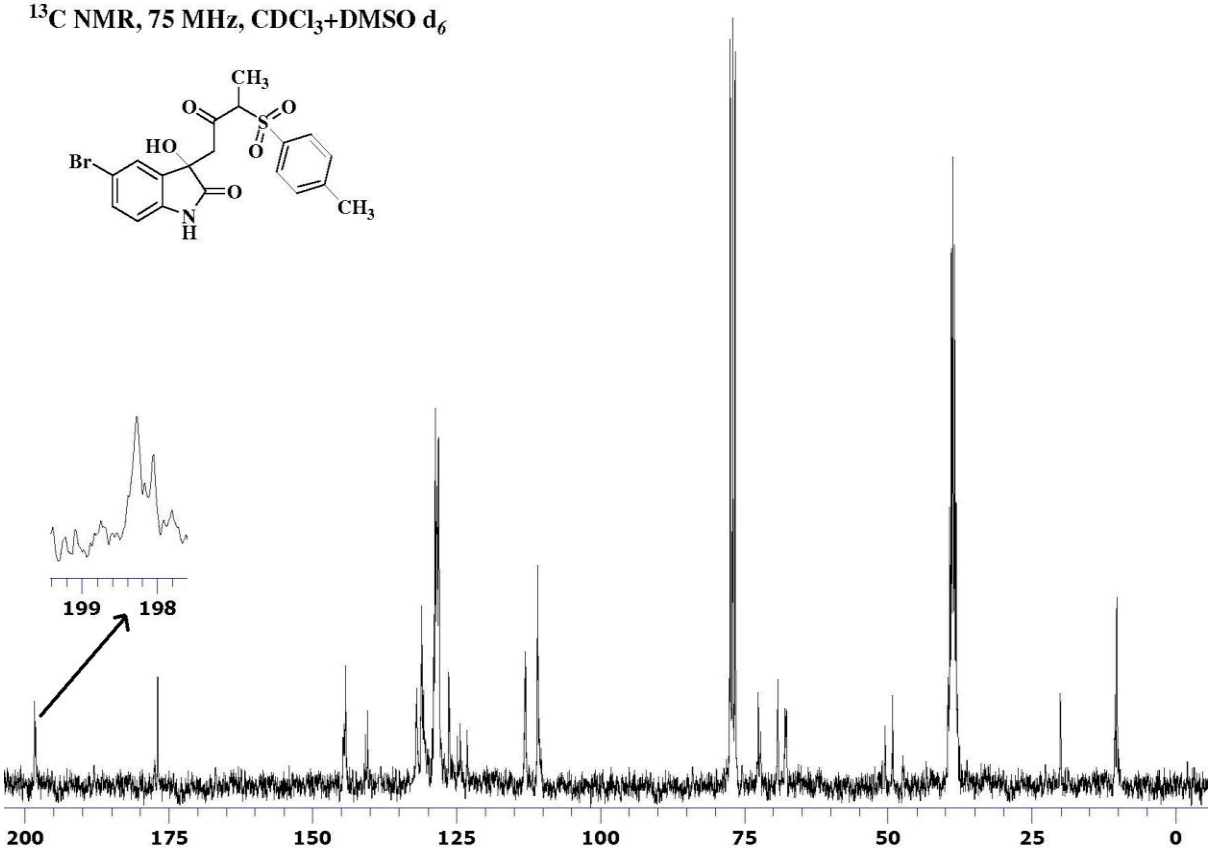


^{13}C NMR, 75 MHz, $CDCl_3$+DMSO d_6

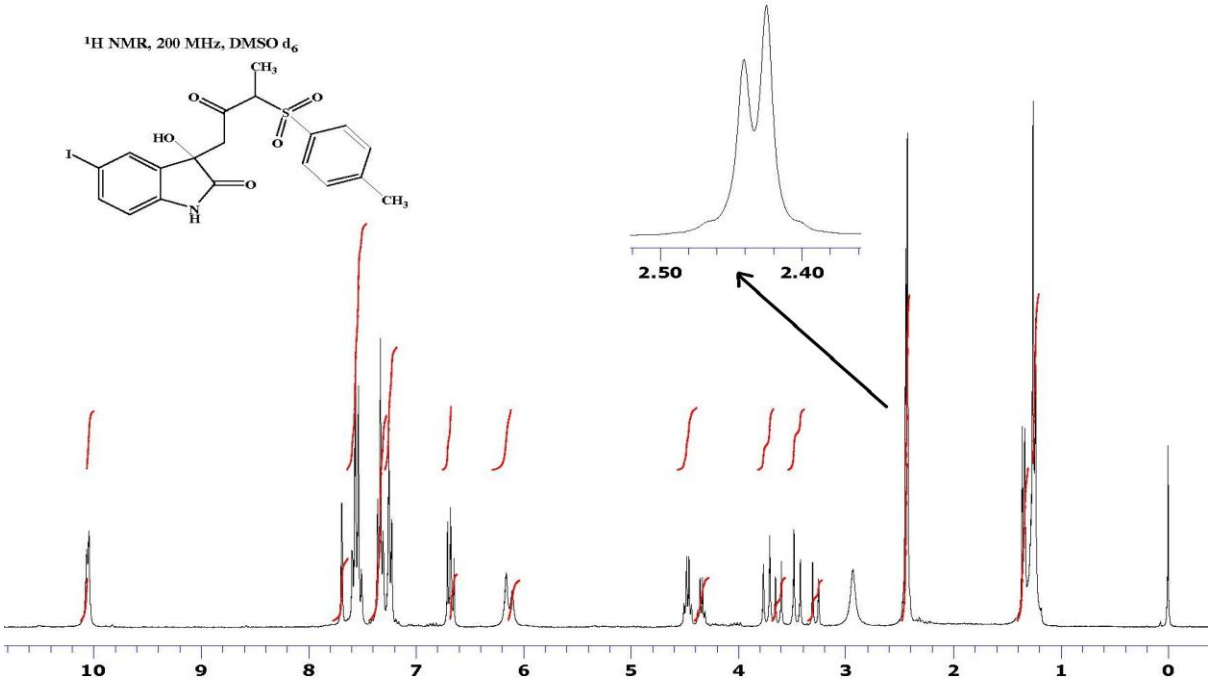


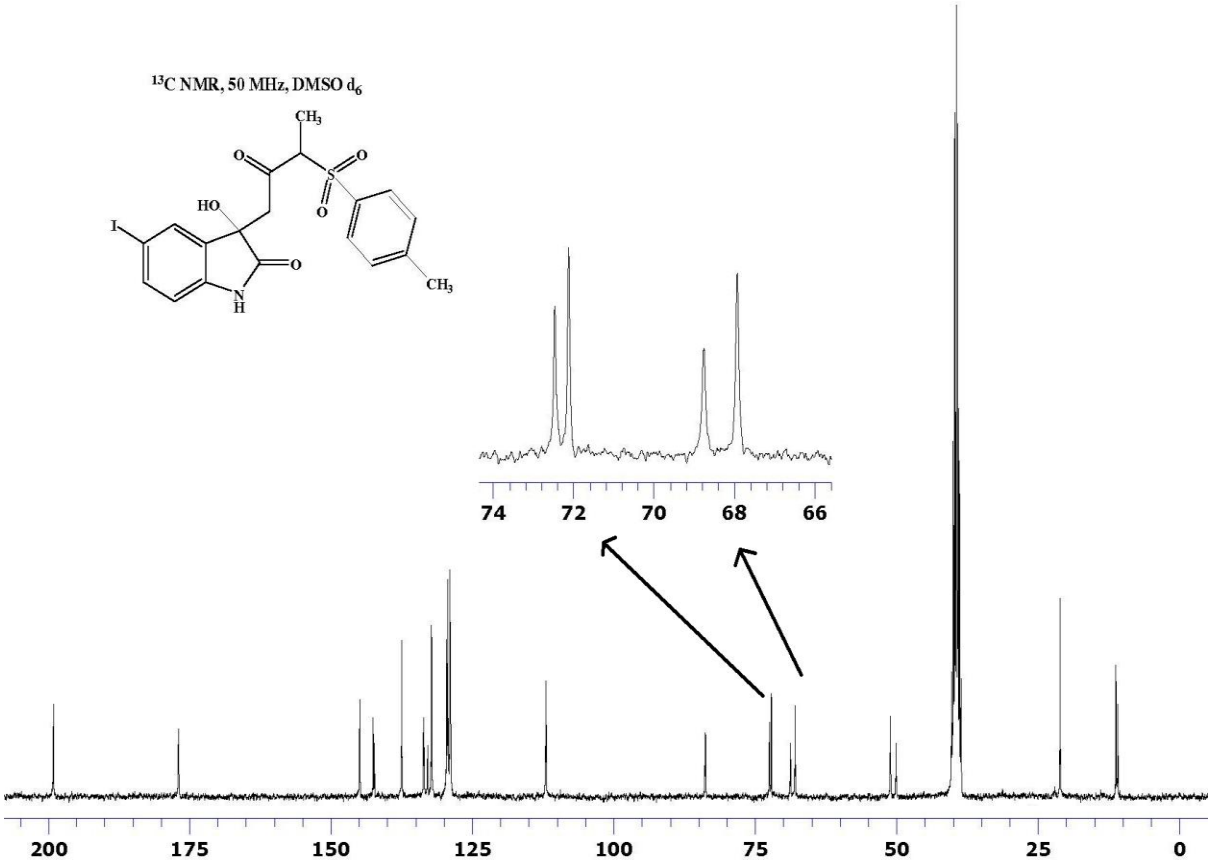
5-bromo-3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3m**, Table 2)



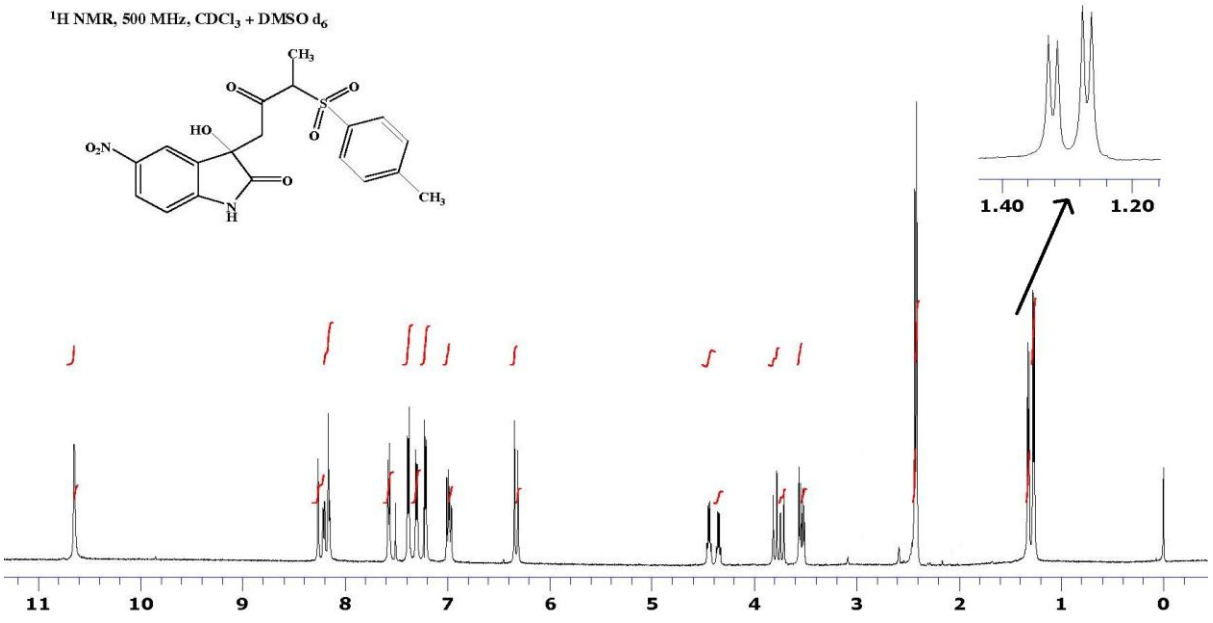


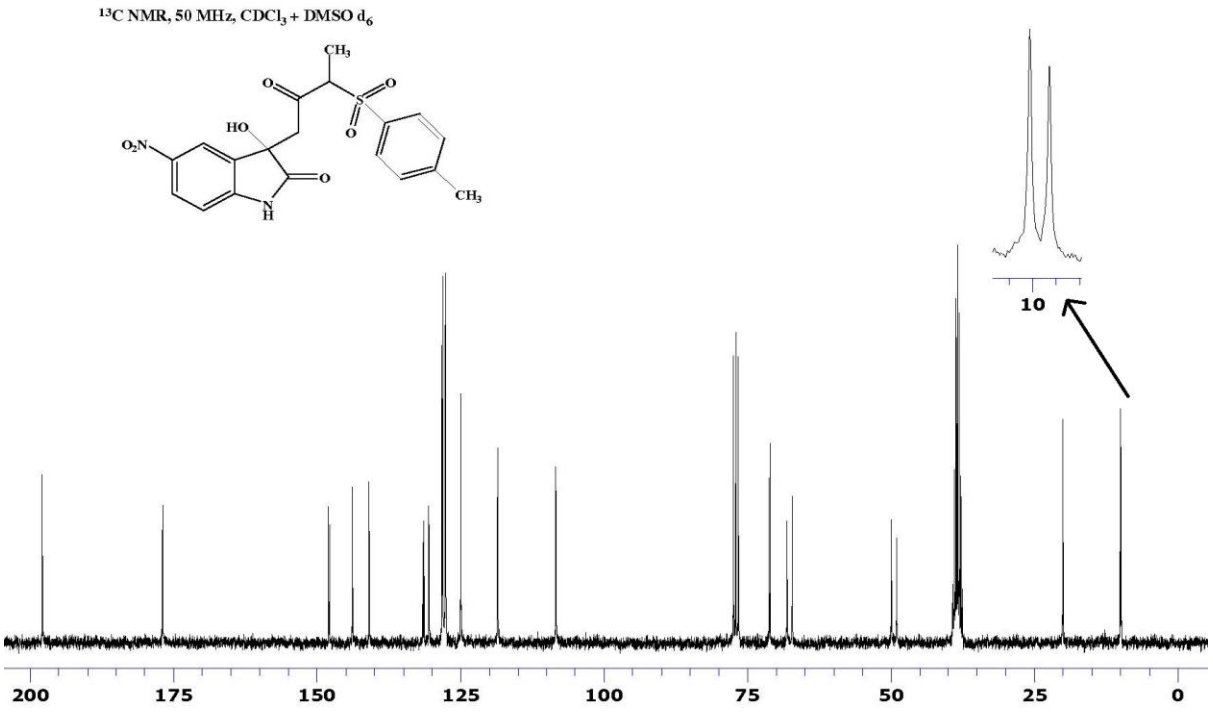
3-hydroxy-5-iodo-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3n**, Table 2)



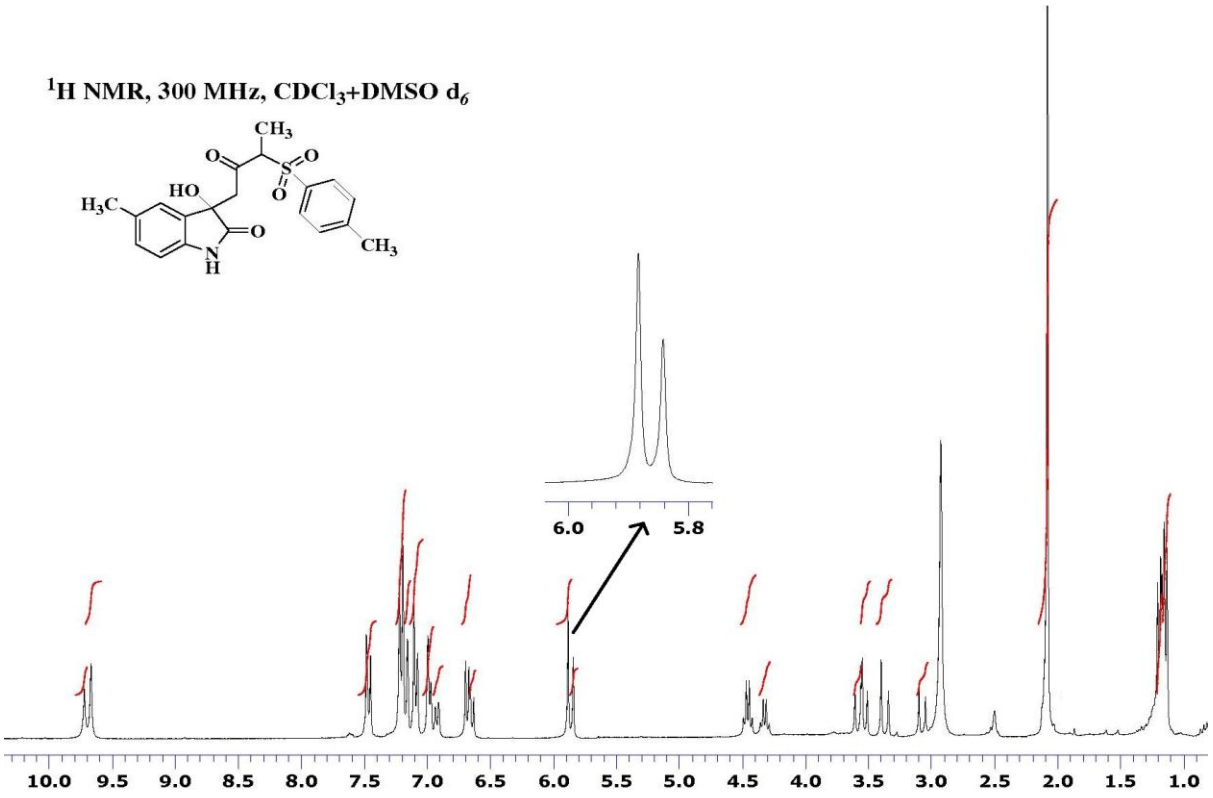


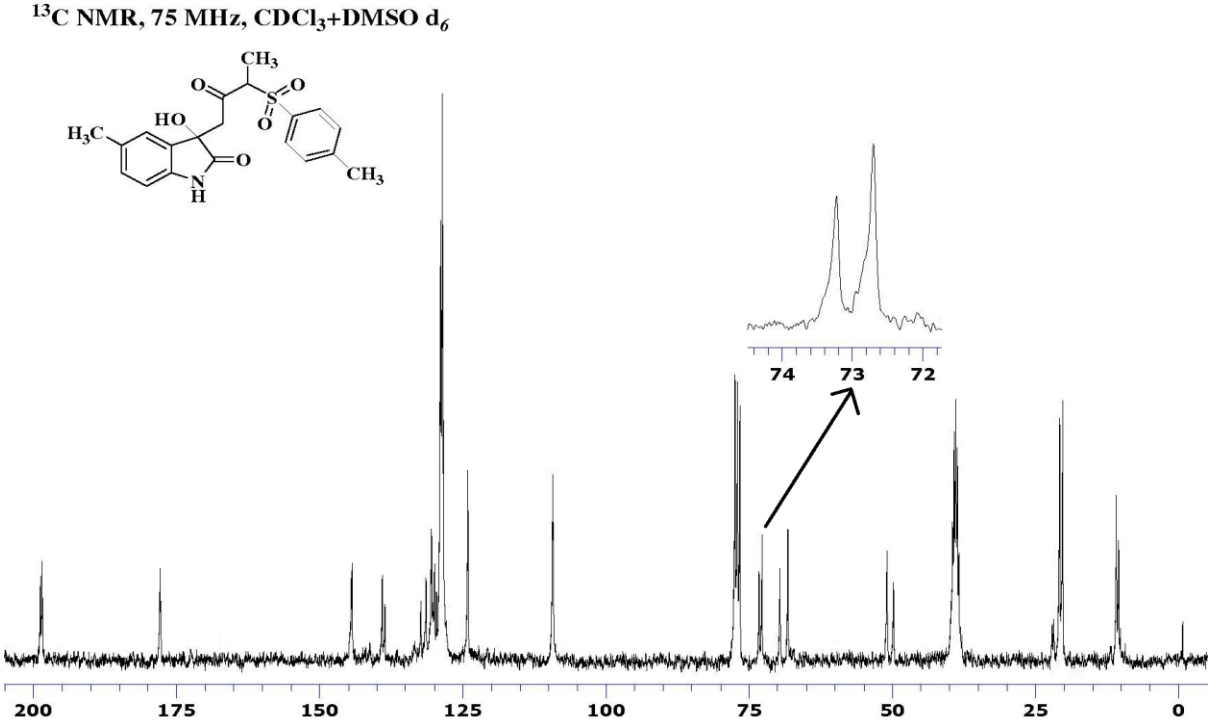
3-hydroxy-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-5-nitro-1,3-dihydro-2*H*-indol-2-one (**3o**, Table 2)





3-hydroxy-5-methyl-3-{3-[(4-methylphenyl)sulfonyl]-2-oxobutyl}-1,3-dihydro-2*H*-indol-2-one (**3p**, Table 2)





X-ray crystallographic data for compound 3i:

X-ray data for the compound **4,7-dichloro-3-(3-(4-chlorophenylsulfonyl)-2-oxopropyl)-3-hydroxyindolin-2-one** (**3i**, Table 2) was collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method.[1] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 5373 reflections for AP65 data. Integration and scaling of intensity data were accomplished using SAINT program.[1] The structures were solved by Direct Methods using SHELXS97[2] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[2] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}$ (C) or $1.5U_{eq}$ for methyl atoms.

X-ray Crystallographic Data for compound 4,7-dichloro-3-(3-(4-chlorophenylsulfonyl)-2-oxopropyl)-3-hydroxyindolin-2-one (**3i**, Table 2):

$C_{17}H_{12}NO_5Cl_3S$, M = 448.69, Compound **3i** crystallized as colorless long needles. One crystal was selected and was cut prior to mounting on the Goniometer. The diffraction data was collected on a crystal of 0.41 × 0.33 × 0.17 mm^3 size, monoclinic, space group $P2_1/c$ (No. 14), a = 12.3354(11), b = 8.2343(8), c = 18.3236(17) Å, β = 104.167(2)°, V = 1804.6(3) $Å^3$, Z = 4, D_c = 1.651 g/cm^3, F_{000} = 912, CCD area detector, MoKα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 50.0º, 14142 reflections collected, 3170 unique (R_{int} = 0.0197). Final *GooF* = 1.038, *R1* = 0.0280, *wR2* = 0.0766, *R* indices based on 2958 reflections with I >2σ(I) (refinement on F^2), 252 parameters, μ = 0.654 mm^{-1}. CCDC 916506 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk]

1. SMART & SAINT. Software Reference manuals. Versions 6.28a & 5.625, Bruker Analytical X-ray Systems Inc., Madison, Wisconsin, U.S.A., 2001.

2. Sheldrick, G. M. SHELXS97 and SHELXL97, Programs for crystal structure solution and refinement; University of Gottingen: Germany, 1997.

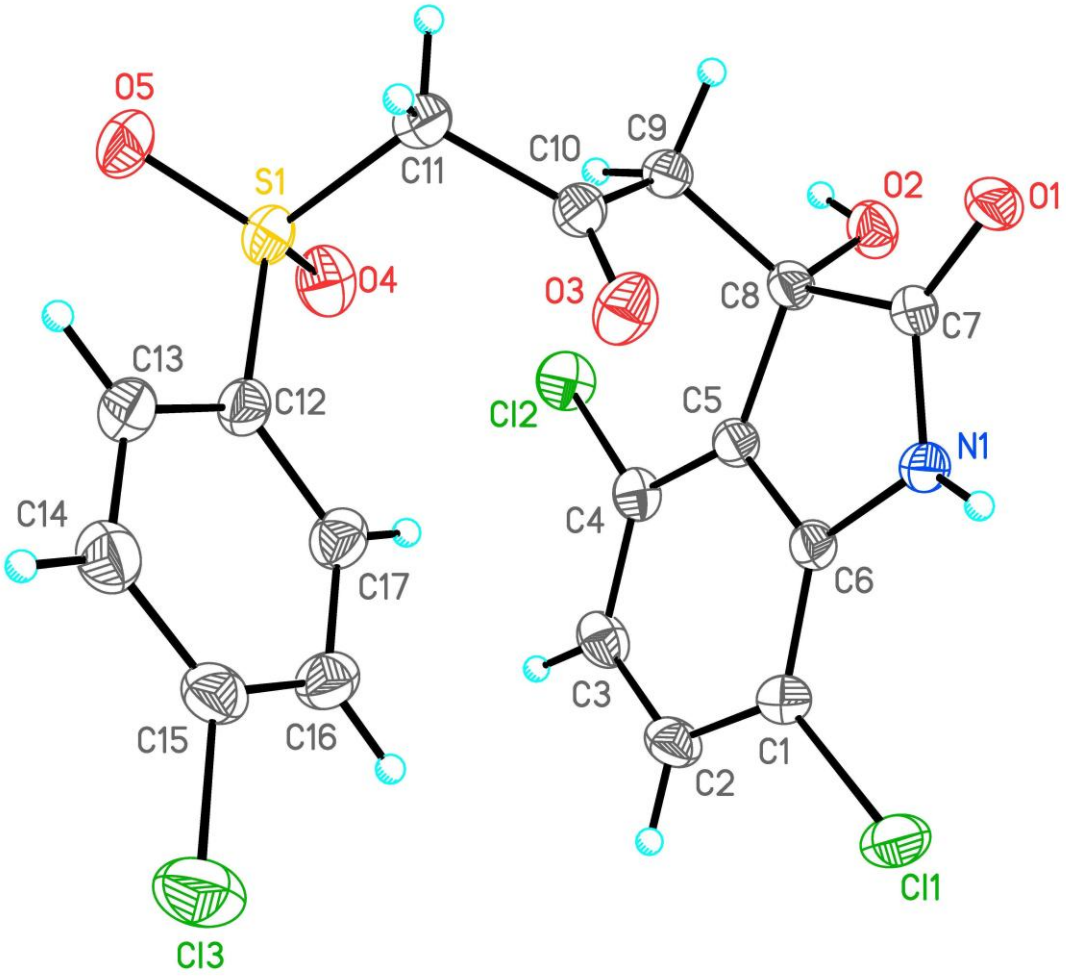


Figure caption: The molecular structure of AP65, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.