10.1071/CH14239_AC



Australian Journal of Chemistry 2015, 68(3), 453-460

# Supplementary Material

## "An exploration of organocatalyst DABCO in the direct regioselective and chemoselective γ-addition of β-keto amide on isatin to affords structurally diverse molecular frameworks"

Pramod B Thakur[A] and Harshadas H Meshram[A, B]

[A]Medicinal Chemistry and Pharmacology Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India

[B]Corresponding author. Tel.: +91-40-27191643, Fax: +91-40-27193275.

E-mail address: *hmmeshram@yahoo.com*

## Table of contents

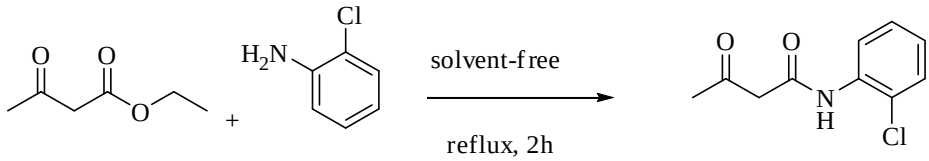
# General Information

All materials used in this study were obtained from commercial supplier and used without further purification as received. All β-keto amides used in this study were prepared by reported methods. 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 $^{1}H$ 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 $CHCl_3$ ($^{1}H$: δ 7.26 ppm, $^{13}C$: δ 77.00 ppm) or DMSO $d_6$ ($^{1}H$: 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 doublet) 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 β-keto amides:**

**(a) Synthesis of *N*-(2-chlorophenyl)-3-oxobutanamide (2a):**

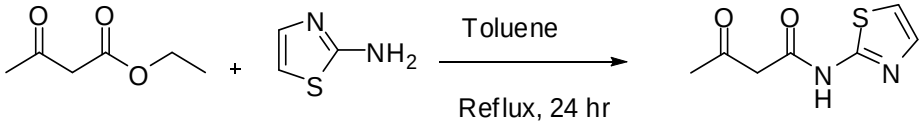



N-(2-chlorophenyl)-3-oxobutanamide (**2a**)

*N*-(2-chlorophenyl)-3-oxobutanamide (**2a**) was prepared as per reported method[1]. Ethyl acetoacetate (10 mmol) and o-chloroaniline (10 mmol) were mixed and refluxed for about 2 h under solvent free conditions. The yellowish liquid formed was then heated on a water bath for 30 min. The reaction mixture was allowed to cool. The crude solid obtained was filtered and washed with ether. The part of product was purified by column chromatography and used for reaction.

White solid, **Mp** 105-106 °C [1C]. **$^1$H NMR** (200 MHz, $CDCl_3$+DMSO $d_6$): δ 9.96 (br s, 1H), 8.09 (d, *J* = 9.25 Hz, 1H), 7.38 (d, *J* = 9.25 Hz, 1H), 7.25 (t, *J* = 8.30 Hz, 1H), 7.08 (t, *J* = 8.30 Hz, 1H), 3.68 (s, 2H), 2.31 (s, 3H) ppm.

**(b) Synthesis of 3-oxo-*N*-(thiazol-2-yl)butanamide (2b):**



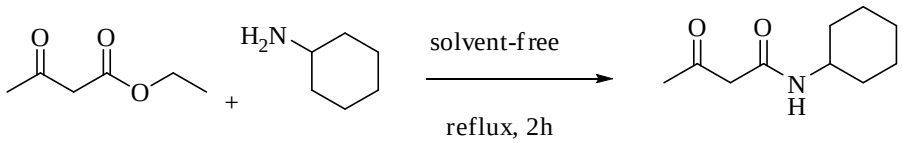

3-oxo-*N*-(thiazol-2-yl)butanamide (**2b**)

3-oxo-*N*-(thiazol-2-yl)butanamide **(2b)** was prepared by using same method. Ethyl acetoacetate (10 mmol) and 2-aminothiazole (10 mmol) were mixed in 20 ml Toluene and refluxed for about 24 h. The reaction mixture was allowed to cool. The crude solid obtained was filtered and

washed with ether. The part of product was purified by column chromatography and used for reaction.

Pale yellow solid, **Mp** 160-162 °C. **$^1$H NMR** (300 MHz, $CDCl_3$ + DMSO $d_6$): δ 7.41 (d, *J* = 3.6 Hz, 1H), 7.00 (d, *J* = 3.6 Hz, 1H), 3.68 (s, 2H), 3.29 (br s, 1H), 2.19 (s, 3H) ppm.

**(c) Synthesis of *N*-cyclohexyl-3-oxobutanamide (2c):**

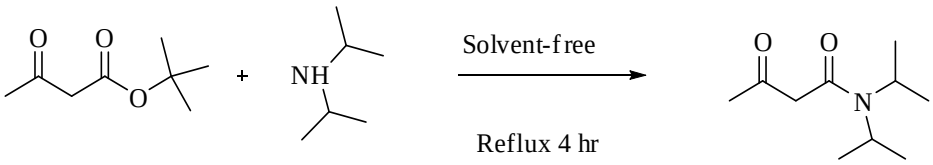



N-cyclohexyl-3-oxobutanamide (**2c**)

*N*-cyclohexyl-3-oxobutanamide (**2c**) was prepared by using same reported method[1]. Ethyl acetoacetate (10 mmol) and cyclohexanamine (10 mmol) were mixed and refluxed for about 2 h under solvent free conditions. The pale yellowish liquid formed was then heated on a water bath for 30 min. The reaction mixture was allowed to cool. The crude solid obtained was filtered and washed with ether. The part of product was purified by column chromatography and used for reaction.

White solid, **Mp** 58-60 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): δ 6.83 (br s, 1H), 3.96-3.64 (m, 1H), 3.39 (s, 2H), 2.27 (s, 3H), 1.91-1.68 (m, 4H), 1.63-1.12 (m, 6H) ppm.

**(d) Synthesis of *N,N*-diisopropyl-3-oxobutanamide (2d):**



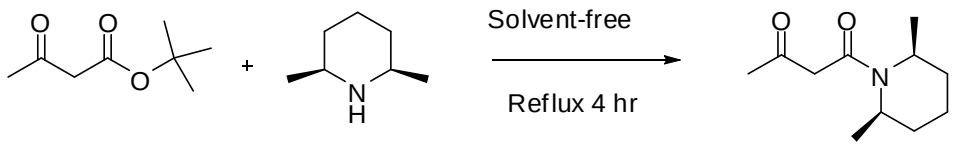

*N,N*-diisopropyl-3-oxobutanamide (**2d**)

***N,N*-diisopropyl-3-oxobutanamide (2d)** was prepared by using same method. *Tert*-Butyl acetoacetate (10 mmol) and diisopropyl (10 mmol) were mixed and refluxed for about 4 h under

solvent free conditions. The reaction mixture was allowed to cool. Solvent was removed under reduced pressure. The crude viscous yellow oil obtained was purified by column chromatography to get pure *N*,*N*-diisopropyl-3-oxobutanamide (**2d**) as pale yellow viscous oil.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 3.62-3.56 (s, 2H), 3.53-3.50 (m, 1H), 3.42-3.38 (m, 1H), 2.22 (s, 3H), 1.34 (d, *J* = 5.5 Hz 6H), 1.03 (d, *J* = 5.8 Hz 6H) ppm.

**(e) Synthesis of 1-((2R,6S)-2,6-dimethylpiperidin-1-yl)butane-1,3-dione (2e):**

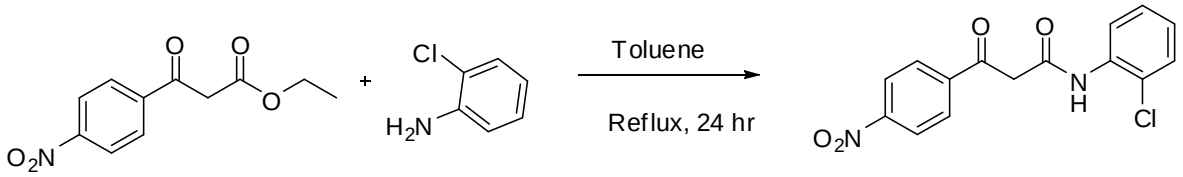



1-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)butane-1,3-dione (**2e**)

**1-((2R,6S)-2,6-dimethylpiperidin-1-yl)butane-1,3-dione (2e)** was prepared by using same reported method[1]. *Tert*-Butyl acetoacetate (10 mmol) and (2S,6R)-2,6-dimethylpiperidine (10 mmol) were mixed and refluxed for about 4 h under solvent free conditions. The reaction mixture was allowed to cool. Solvent was removed under reduced pressure. The crude viscous yellow oil obtained was purified by column chromatography to get pure 1-((2R,6S)-2,6-dimethylpiperidin-1-yl)butane-1,3-dione **(2e)** as pale yellow viscous oil.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 4.78-4.64 (m, 1H), 3.97-3.78 (m, 1H), 3.50 (s, 2H), 2.24 (s, 3H), 1.65-1.48 (m, 6H), 1.20-1.17 (m, 6H) ppm.

**(F) Synthesis of N-(2-chlorophenyl)-3-(4-nitrophenyl)-3-oxopropanamide:**

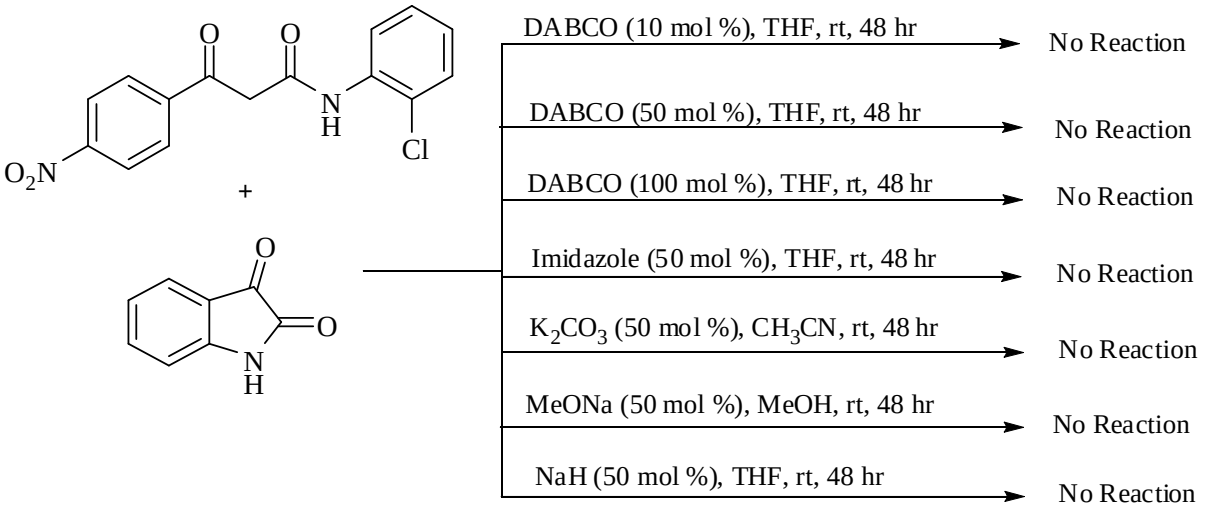



*N*-(2-chlorophenyl)-3-(4-nitrophenyl)-3-oxopropanamide

**N-(2-chlorophenyl)-3-(4-nitrophenyl)-3-oxopropanamide** was prepared by using reported method. Ethyl 3-(4-nitrophenyl)-3-oxopropanoate (10 mmol) and 2-aminothiazole (10 mmol) were mixed in 20 ml Toluene and refluxed for about 24 h. The reaction mixture was allowed to cool. The crude solid obtained was filtered and washed with ether. The part of product was purified by column chromatography and used for reaction.

**$^1$H NMR** (300 MHz, $CDCl_3$+ DMSO $d_6$): δ 9.16 (br s, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.51(d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.85-6.81 (m, 2H), 6.66 (d, *J* = 7.5 Hz, 1H), 3.85 (s 2H)

**2. Reaction[a] of isatin with β-keto amide having no enolizable protons at γ-position:**

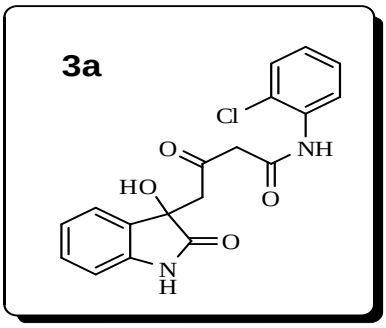



**Scheme 3:** Reaction of isatin with *N*-(2-chlorophenyl)-3-(4-nitrophenyl)-3-oxopropanamide; Reaction conditions: isatin (1 mmol), *N*-(2-chlorophenyl)-3-(4-nitrophenyl)-3-oxopropanamide (1 mmol) in 5 mL solvent at room temperature.

## General Procedure for the DABCO Catalyzed Chemoselective and Regioselective γ-Addition of β-Keto Amides to Isatins:

To the stirred solution of β-keto amide (1.0 mmol) and DABCO (0.3 mmol) in 5 mL THF was added isatin (1mmol). The mixture was then stirred at room temperature for stipulated time. 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 = 4:3-1:1) to afford the desired product.

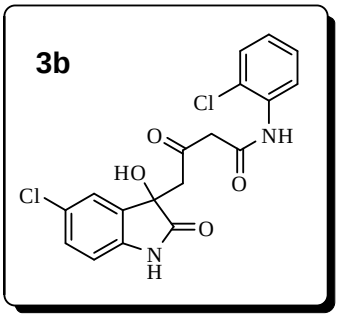
## Spectral data for synthesized compounds (3a-3r):




***N*-(2-chlorophenyl)-4-(3-hydroxy-2-oxoindolin-3-yl)-3-oxobutanamide**, (**3a**, Table 2, entry 1):

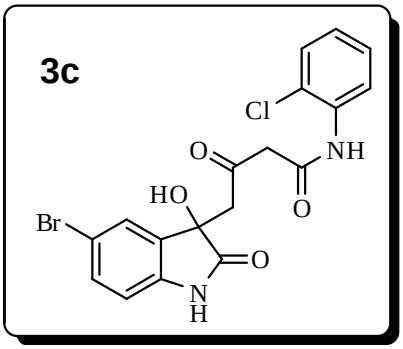
Yield: 81 %, Time, 12 h, *Rf*(50% EtOAc/hexanes, 2 times run) 0.16.Yellow solid, **Mp** 72-74 °C. **$^{1}$H NMR** (500 MHz, $CDCl_3$+DMSO $d_6$): δ 9.98 (br s, 1H), 9.36 (br s, 1H), 8.14 (d, *J*=6.9 Hz, 1H), 7.37 (d, *J*=7.9 Hz, 1H), 7.32 (d, *J*=6.9 Hz, 1H),7.25 (t, *J*=6.9 Hz, 1H), 7.19 (t, *J*=6.9 Hz, 1H), 7.07 (t, *J*=6.9 Hz, 1H), 6.96 (t, *J*=7.9 Hz, 1H), 6.87 (d, *J*=7.9 Hz, 1H), 6.03 (br s, 1H), 3.84 (d, *J*=16.7 Hz, 1H), 3.76 (d,*J*= 16.7 Hz, 1H), 3.26 (d, *J*=15.7 Hz, 1H), 3.18 (d, *J*=15.7 Hz, 1H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 202.21, 177.78, 163.84, 141.03, 133.82, 129.98, 128.73, 128.41, 126.52, 124.51, 123.64, 123.17, 122.62, 121.37, 109.56, 72.99, 50.53, 49.51

ppm. **IR (KBr)** ν=3268, 2924, 1722, 1620, 1531, 1472, 1300, 1183, 1032, 750, 654 $cm^{-1}$. **MS (ESI)** *m/z* 381 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{15}O_4N_2ClNa$ $[M+Na]^+$=381.06180, found 381.06246.



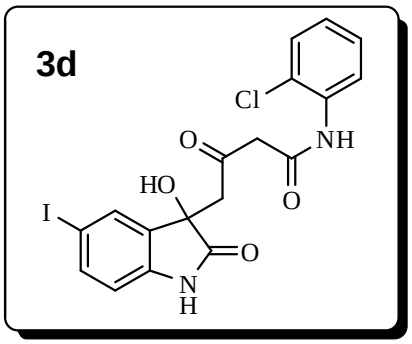

**4-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)-N-(2-chlorophenyl)-3-oxobutanamide** (**3b**, Table 2, entry 2):

Yield 86 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, 2 times run) 0.32, White solid, **Mp** 138-140 °C. **$^1$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 10.35 (br s, 1H), 9.56 (br s, 1H), 7.88 (d, *J*=7.9 Hz, 1H), 7.39 (d, *J*=7.7 Hz, 1H), 7.30-7.23 (m, 2H), 7.17-7.08 (m, 2H), 6.81(d, *J*=8.3 Hz, 1H), 6.25 (br s, 1H), 3.75-3.63 (m, 2H), 3.45 (d, *J*=17.0 Hz, 1H), 3.24 (d, *J*=17.0 Hz, 1H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 200.19, 176.40, 163.33, 139.73, 133.07, 131.61, 127.75, 127.32, 125.66, 124.57, 124.20, 123.82, 123.17, 122.69, 109.54, 71.54, 49.81, 48.24 ppm. **IR (KBr)** ν=3274, 2925, 2854, 1722, 1621, 1590, 1532, 1477, 1441, 1304, 1180, 1063, 1033, 818, 751 $cm^{-1}$. **MS (ESI)** *m/z* 393 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{15}O_4N_2Cl_2$ $[M+H]^+$=393.04034, found 393.04071.



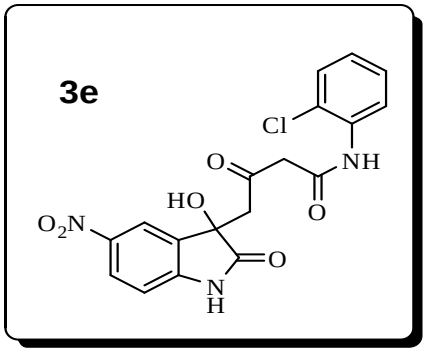

**4-(5-Bromo-3-hydroxy-2-oxoindolin-3-yl)-*N*-(2-chlorophenyl)-3-oxobutanamide, (3c,** Table 2, entry 3):

Yield: 84 %, Time, 12 h, *Rf*(50% EtOAc/hexanes, 2 times run) 0.20. Pale yellow solid, **Mp** 144-146 °C. **$^{1}$H NMR** (200 MHz, $CDCl_3$+DMSO $d_6$): δ 10.12 (br s, 1H), 9.32 (br s, 1H), 8.19 (d, *J*=7.8 Hz, 1H), 7.69 (s, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.45 (d, *J*=7.8 Hz, 1H), 7.29 (t, *J*=7.8 Hz, 1H), 7.11 (t, *J*=7.8 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 1H), 6.18 (br s, 1H), 3.88 (d, *J*=17.2 Hz, 1H), 3.64 (d, *J*=17.2 Hz, 1H) 3.32 (d, *J*=17.2 Hz, 1H), 3.14 (d, *J*=17.2 Hz, 1H) ppm. **$^{13}$C NMR** (50 MHz, $CDCl_3$+DMSO $d_6$): δ 201.49, 177.20, 163.80, 140.41, 133.60, 132.26, 131.17, 128.34, 126.39, 126.30, 124.61, 123.93, 123.01, 113.35, 111.07, 72.60, 50.33, 49.14 ppm. **IR (KBr)** ν=3219, 2924, 2855, 1723, 1645, 1539, 1442, 1298, 1061, 744, 533 $cm^{-1}$. **MS (ESI)** *m/z* 439 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. For $C_{18}H_{15}O_4N_2BrCl$ $[M+H]^+$=438.99037, found 438.99109.



***N*-(2-chlorophenyl)-4-(3-hydroxy-5-iodo-2-oxoindolin-3-yl)-3-oxobutanamide,** (**3d**, Table 2, entry 4):

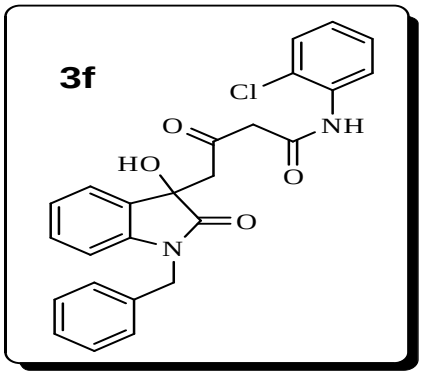
Yield: 83 %, Time, 12 h, *Rf*(50% EtOAc/hexanes, 2 times run) 0.25. White solid, **Mp** 153-155 °C. **$^{1}$H NMR** (200 MHz, $CDCl_3$+DMSO $d_6$): δ 10.29 (br s, 1H), 9.47 (br s, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 7.37 (d, *J*=7.8 Hz, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 7.08 (t, *J*=7.8 Hz, 1H), 6.68 (d, *J*=9.0 Hz, 1H), 6.24 (br s, 1H), 3.76 (d, *J*=16.8 Hz, 1H), 3.67 (d, *J*=16.8 Hz, 1H) 3.39 (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 200.50, 176.32, 163.46, 140.92, 136.35, 133.21, 132.48, 131.12, 127.91, 125.85, 124.28, 123.81, 123.11, 110.95, 82.65, 71.59, 49.98, 48.49 ppm. **IR (KBr)** ν=3256, 1699, 1616, 1592, 1529, 1440, 1347, 1184, 1033, 828, 749, 577, 530 $cm^{-1}$. **MS (ESI)** *m/z* 507 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{14}O_4N_2ClINa$ $[M+Na]^+$=506.95845, found 506.95921.




**N-(2-chlorophenyl)-4-(3-hydroxy-5-nitro-2-oxoindolin-3-yl)-3-oxobutanamide** (**3e**, Table 2, entry 5):

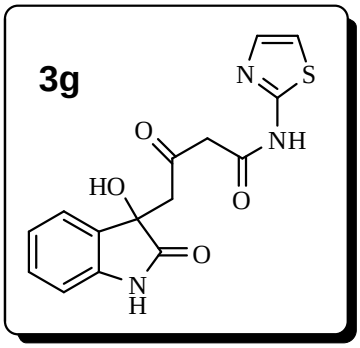
Yield: 92 %, Time, 12h, *Rf*(50% EtOAc/hexanes, 2 times run) 0.26. Pale yellow solid, **Mp** 140-142 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 10.91 (br s, 1H), 9.49 (br s, 1H), 8.21-8.12 (m, 2H), 7.54 (t, *J*=9.01 Hz, 1H), 7.37 (d, *J*=7.9 Hz, 1H), 7.36 (t, *J*=7.4 Hz, 1H), 7.09 (t, *J*=7. 2 Hz, 1H), 6.98 (d, *J*=8.5 Hz, 1H), 6.42 (br s, 1H), 3.89-3.59 (m, 4H) ppm. **$^{13}$C NMR** (75 MHz,

$CDCl_3$+DMSO $d_6$): δ 200.27, 176.51, 164.32, 144.71, 132.06, 130.60, 126.74, 126.31, 124.67, 123.58, 123.21, 122.81, 122.18, 121.71, 110.52, 70.94, 49.30, 47.98 ppm. **IR (KBr)** ν=3278, 2927, 2851, 1723, 1629, 1598, 1536, 1471, 1339, 1309, 1187, 1061, 1037, 821, 752 $cm^{-1}$. **MS (ESI)** *m/z* 426 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd. For $C_{18}H_{14}O_6N_3ClNa$ $[M+Na]^+$=426.04688, found 426.04721.



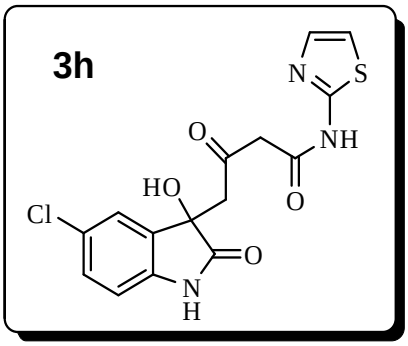

**4-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-N-(2-chlorophenyl)-3-oxobutanamide** (**3f**, Table 2, entry 6):

Yield 82 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, 2 times run) 0.32, Yellow viscous oil. **$^1$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 9.84 (br s, 1H), 9.24-8.65 (m, 13 H), 8.30 (br s, 1H), 5.54-5.17 (m, 2H), 3.91-3.46 (m, 4H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 203.33, 176.66, 163.75, 142.55, 135.04, 134.09, 129.78, 128.90, 128.52, 127.17, 126.90, 124.88, 123.52, 122.94, 122.28, 109.55, 73.50, 60.12, 50.16, 49.86 ppm. **IR (KBr)** ν=3255, 1698, 1617, 1597, 1532, 1440, 1345, 1187, 1039, 829, 752, 579, 539 $cm^{-1}$. **MS (ESI)** *m/z* 449 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{25}H_{22}O_4N_2Cl[M+H]^+$=449.12626, found 449.12573.




**4-(3-hydroxy-2-oxoindolin-3-yl)-3-oxo-N-(thiazol-2-yl)butanamide** (**3g**, Table 2, entry 7):

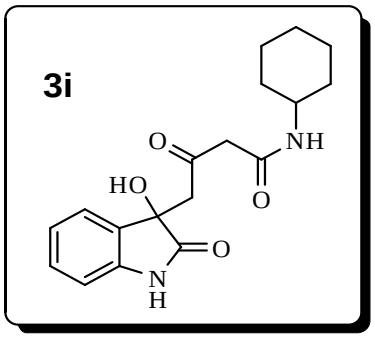
Yield 82 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, 2 times run) 0.12. White solid, **Mp** 168-170 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 10.11 (br s, 1H), 7.45-7.36 (m, 1H), 7.32-7.23 (m, 1H), 7.22-7.10 (m, 1H), 7.02-6.89 (m, 2H), 6.88-6.78 (m, 1H), 6.07 (br, s 1H), 3.84-3.58 (m, 2H), 3.43-3.22 (m, 2H), 2.83 (br s, 1H) ppm. **$^{13}$C NMR** (100 MHz, $CDCl_3$+DMSO $d_6$): δ 200.43, 177.99, 164.27, 157.58, 142.29, 130.90, 128.91, 123.56, 121.24, 109.50, 72.57, 50.58, 49.65 ppm. **IR (KBr)** ν=3391, 3182, 3073, 3027, 2964, 1736, 1712, 1649, 1623, 1570, 1474.1428, 1337, 1286, 1192, 1026, 756 $cm^{-1}$. **MS (ESI)** *m/z* 332 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. $C_{15}H_{14}O_4N_3S[M+H]^+$=332.06995, found 332.06958.




**4-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)-3-oxo-N-(thiazol-2-yl)butanamide** (**3h**, Table 2, entry 8):

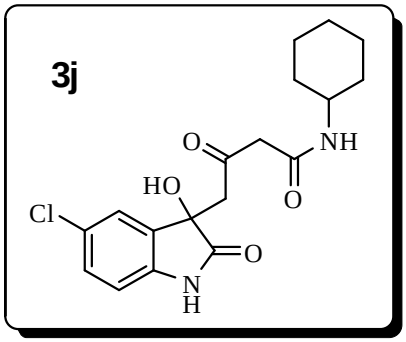
Yield 84 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, , 2 times run) 0.12. White solid, **Mp** 162-164 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ12.07 (br s, 1H), 10.24 (br s, 1H), 7.62-6.58 (m,

5H), 6.15 (br s, 1H), 4.02-3.61 (m, 2H), 3.45-3.18 (m, 2H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 199.13, 176.55, 162.99, 156.43, 139.87, 136.07, 131.61, 127.44, 124.74, 122.77, 111.67, 109.65, 71.54, 49.26, 48.30 ppm. **IR (KBr)** ν=3394, 3207, 1720, 1677, 1621, 1560, 1478, 1355, 1324, 1190, 1164, 1036, 826, 725 $cm^{-1}$. **MS (ESI)** *m/z* 366 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{15}H_{13}O_4N_3ClS$ $[M+H]^+$=366.03098, found 366.03125.



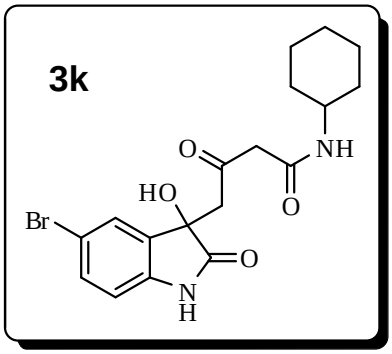

**N-cyclohexyl-4-(3-hydroxy-2-oxoindolin-3-yl)-3-oxobutanamide** (**3i**, Table 2, entry 9):

Yield 79 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, , 2 times run) 0.12. White solid, **Mp** 58-60 °C. **$^1$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 10.04 (br s, 1H), 7.48 (br s, 1H), 7.37-7.11 (m, 2H), 7.03-6.77 (m, 2H), 6.06 (br s, 1H), 3.81-3.53 (m, 1H), 3.49-3.22 ( m, 4H), 1.95-1.61 (m, 4H), 1.45-0.98 (m, 6H ) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 201.42, 177.83, 164.14, 141.48, 129.88, 128.36, 122.87, 121.03, 109.27, 72.49, 50.27, 48.67, 47.28, 31.51, 24.38, 23.76 ppm. **IR (KBr)** ν=3302, 2931, 2855, 1722, 1644, 1548, 1474, 1342, 1190, 752 $cm^{-1}$. **MS (ESI)** *m/z* 353 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{22}O_4N_2Na$ $[M+Na]^+$=353.14773, found 353.14822.



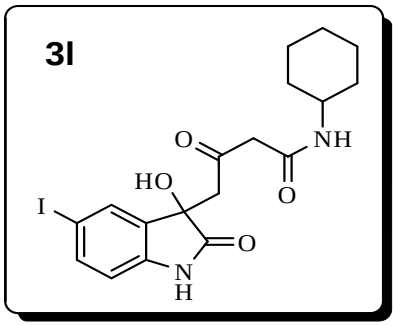

**4-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)-N-cyclohexyl-3-oxobutanamide** (**3j**, Table 2, entry 10):

Yield 81 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, 2 times run) 0.12. Brown solid, **Mp** 68-70 °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$+DMSO $d_6$): δ 10.28 (br s, 1H), 7.69 (br d, *J*=7.5 Hz, 1H), 7.25 (d, *J*=1.7 Hz, 1H), 7.16 (dd, *J*=8.3, 1.7 Hz, 1H), 6.82 (d, *J*=8.3 Hz, 1H), 6.21 (br s, 1H), 3.71-3.55 (m, 1H), 3.48 ( d, *J*=17.2 Hz, 1H), 3.35-3.27 (m, 2H), 3.20 ( d, *J*=17.4 Hz, 1H), 1.98-1.59 (m, 4H), 1.36-1.01 (m, 6H ) ppm. **$^{13}$C NMR** (125 MHz, $CDCl_3$+DMSO $d_6$): δ 200.57, 176.94, 163.60, 139.95, 131.78, 127.63, 125.13, 122.89, 109.92, 71.90, 50.07, 48.18, 46.95, 31.24, 24.11, 23.46 ppm. **IR (KBr)** ν=3294, 2929, 2854, 1723, 1617, 1559, 1446, 1256, 1072, 816, 646 $cm^{-1}$. **MS (ESI)** *m/z* 365 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{22}O_4N_2Cl$ $[M+H]^+$=365.12626, found 365.12628.



**4-(5-Bromo-3-hydroxy-2-oxoindolin-3-yl)-*N*-cyclohexyl-3-oxobutanamide**, (**3k**, Table 2, entry 11):

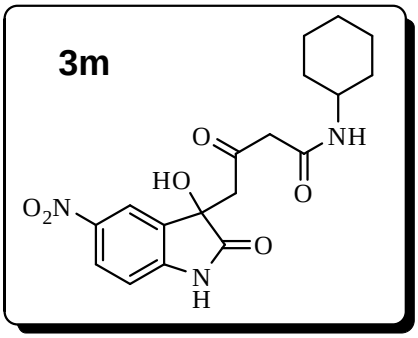
Yield 78 %, Time, 12 h, *Rf*(50% EtOAc/hexanes, 2 times run) 0.13. Yellow solid, **Mp** 92-94 °C. **$^{1}$H NMR** (200 MHz, $CDCl_3$+DMSO $d_6$): δ 10.23 (br s, 1H), 7.57 (br d, *J*=7.4 Hz, 1H), 7.36 (d, *J*=1.1 Hz, 1H), 7.29 (dd, *J*=8.1, 1.1 Hz, 1H), 6.76 (d, *J*=8.1 Hz, 1H), 6.19 (br s, 1H), 3.67-3.56 (m, 1H), 3.47-3.20 (m, 4H), 1.90-1.68 (m, 4H), 1.37-1.08 (m, 6H) ppm. **$^{13}$C NMR** (50 MHz, DMSO $d_6$): δ 199.89, 177.21, 163.66, 141.68, 133.39, 131.74, 126.11, 113.48, 111.69, 71.81, 50.13, 48.21, 46.71, 31.11, 23.97, 23.34 ppm. **IR (KBr)** ν=3319, 2930, 2854, 1725, 1643, 1543, 1475, 1345, 1184, 817, 535 $cm^{-1}$. **MS (ESI)** *m/z* 409 $[M+H]^+$. HRMS (ESI): *m/z* calcd. for $C_{18}H_{22}O_4N_2Br[M+H]^+$=409.07629, found 409.07681.




***N*-cyclohexyl-4-(3-hydroxy-5-iodo-2-oxoindolin-3-yl)-3-oxobutanamide**, (**3l**, Table 2, entry 12):

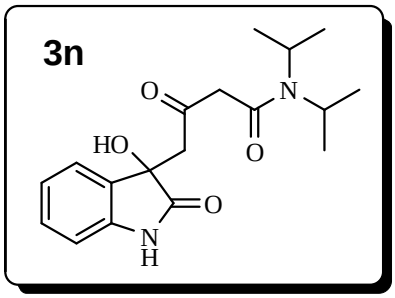
Yield 80 %, Time, 12 h, *Rf*(50% EtOAc/hexanes, 2 times run) 0.13. White solid, **Mp** 96-98 °C. **$^{1}$H NMR** (200 MHz, $CDCl_3$+DMSO $d_6$): δ 10.22 (br s, 1H), 7.56 (br d, *J*=7.6 Hz, 1H), 7.54 (d, *J*=1.5 Hz, 1H), 7.47 (dd, *J*=8.1, 1.5 Hz, 1H), 6.67 (d, *J*=8.1 Hz, 1H), 6.17 (br s, 1H), 3.71-3.52 (m, 1H), 3.49-3.24 (m, 4H), 1.94-1.62 (m, 4H), 1.33-1.13 (m, 6H) ppm. **$^{13}$C NMR** (50 MHz, $CDCl_3$+DMSO $d_6$): δ 200.29, 176.31, 163.26, 141.09, 136.18, 132.60, 130.89, 110.79, 82.39, 71.41, 50.03, 48.02, 46.69, 31.12, 23.97, 23.32 ppm. **IR (KBr)** ν=3331, 2927, 2853, 1725, 1640,

1543, 1472, 1306, 1182, 817, 635, 569 $cm^{-1}$. **MS (ESI)** *m/z* 479 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{21}O_4N_2INa$ $[M+Na]^+$=479.04437, found 479.04503.



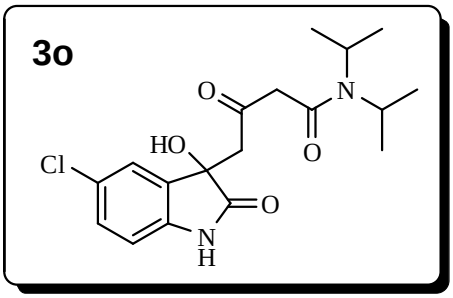

**N-cyclohexyl-4-(3-hydroxy-5-nitro-2-oxoindolin-3-yl)-3-oxobutanamide** (**3m**, Table 2, entry 13):

Yield 81 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, , 2 times run) 0.15. Brown solid, **Mp** 180-182 °C. **$^1$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ10.78 (br s, 1H),8.39-8.04 (m, 2H), 7.52 (br d, *J*=6.3 Hz, 1H), 6.97 (d, *J*=8.1 Hz, 1H), 6.30(br s, 1H), 3.79-3.34 (m, 5H), 1.19-1.58 (m, 4H), 1.41-1.19 (m, 6H) ppm. **$^{13}$C NMR** (75 MHz, DMSO $d_6$): δ 201.93, 178.24, 164.16, 149.43, 141.84, 132.40, 126.34, 119.28, 109.49, 71.92, 50.85, 49.09, 48.47, 32.16, 25.10, 24.36 ppm. **IR (KBr)** ν=3290, 2929, 2854, 1736, 1624, 1525, 1452, 1338, 1257, 1108, 1071, 838, 753, 550 $cm^{-1}$. **MS (ESI)** *m/z* 376 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{22}O_6N_3$$[M+H]^+$=376.15031, found 376.15033.



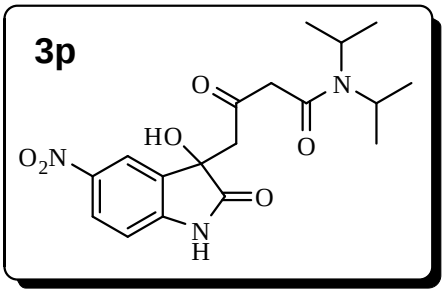

**4-(3-hydroxy-2-oxoindolin-3-yl)-N,N-diisopropyl-3-oxobutanamide** (**3n**, Table 2, entry 14):

Yield 82 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, , 2 times run) 0.15. Brown solid, **Mp** 118-120 °C. **$^1$H NMR** (500 MHz, $CDCl_3$+DMSO $d_6$) δ10.03 (br s, 1H), 7.28 (d, *J*=7.2 Hz, 1H), 7.18 (t, *J*=6.9 Hz, 1H), 6.94 (t, *J*=7.0 Hz, 1H), 6.84 (d, *J*=7.8 Hz, 1H), 6.01 (br s, 1H), 3.57-3.53 (m, 1H), 3.50-3.48 (m, 2H), 3.42-3.38 (m, 1H), 3.32 (d, *J*=15.9 Hz, 1H), 3.10 (d, *J*=16.0 Hz, 1H), 1.33 (d, *J*=5.5 Hz, 6H), 1.05 (d, *J*=6.4 Hz, 3H), 1.01 (d, *J*=6.4 Hz, 3H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 200.43, 177.40, 164.10, 141.14, 129.78, 128.20, 122.68, 120.66, 109.00, 72.31, 51.14, 48.65, 48.43, 44.47, 19.30, 19.23 ppm. **IR (KBr)** ν=3195, 3010, 2976, 2934, 1725, 1705, 1618, 1475, 1349, 1302, 1198, 1119, 1043, 754, 651 $cm^{-1}$. **MS (ESI)** *m/z* 333 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{25}O_4N_2[M+H]^+$=333.18088, found 333.18024.



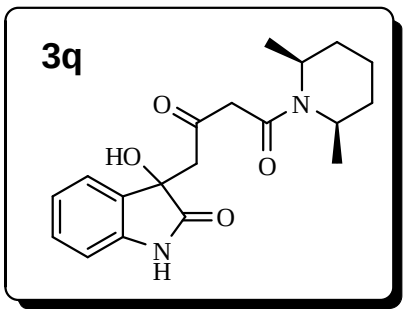

**4-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)-N,N-diisopropyl-3-oxobutanamide** (**3o**, Table 2, entry 15):

Yield 84 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, , 2 times run) 0.12. Brown solid, **Mp** 66-68 °C. **$^1$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 10.1 (br s, 1H), 7.20-6.98 (m, 2H), 6.80 (s, 1H), 6.06 (br s, 1H), 3.78-3.41 (m, 4H), 3.35 (d, *J*=16.1 Hz, 1H), 3.15 (d, *J*=16.1 Hz, 1H), 1.34 (d, *J*=6.1 Hz, 6H), 1.05 (d, *J*=6.1 Hz, 6H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 200.56, 177.38, 164.27, 140.11, 131.88, 128.15, 125.77, 123.30, 110.42, 72.52, 51.14, 48.97, 48.41, 44.82, 19.48, 19.41 ppm. **IR (KBr)** ν=3247, 2970, 2931, 1722, 1619, 1478, 1447, 1346, 1197, 1042, 820, 756, 601 $cm^{-1}$. **MS (ESI)** *m/z* 367 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. for $C_{18}H_{24}O_4N_2Cl[M+H]^+$=367.14191, found 367.14178.



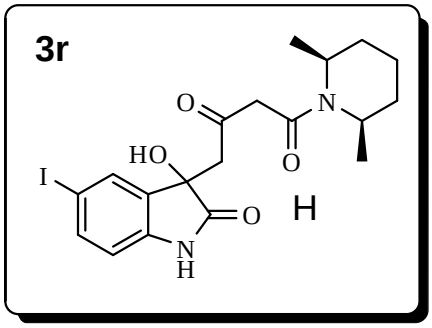

**4-(3-hydroxy-5-nitro-2-oxoindolin-3-yl)-N,N-diisopropyl-3-oxobutanamide** (**3p**, Table 2, entry 16):

Yield 84 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, , 2 times run) 0.19. Pale yellow solid, **Mp** 144-146 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$+DMSO $d_6$): δ 10.70 (br s, 1H), 8.23-8.13 (m, 2H), 6.96 (d, *J*=8.6 Hz, 1H), 6.31 (br s, 1H), 3.72-3.61 (m, 1H), 3.60-3.53 (m 2H), 3.46-3.34 (m, 1H), 3.28 (d, *J*=17.1 Hz, 1H), 2.28 (d, *J*=15.3Hz, 1H), 1.35 (d, *J*=6.4 Hz, 6H), 1.08 (d, *J*=6.6 Hz, 3H), 1.04 (d, *J*=6.6 Hz, 3H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 200.72, 177.89, 164.17, 148.25, 141.79, 131.22, 125.50, 119.10, 109.04, 72.01, 50.88, 48.96, 48.63, 45.00, 19.68, 19.54 ppm. **IR (KBr)** ν=3207, 2972, 2931, 1767, 1720, 1622, 1516, 1480, 1343, 1125, 1079, 836, 735, 574 $cm^{-1}$. **MS (ESI)** *m/z* 378 $[M+ H]^+$. **HRMS (ESI)**: *m/z* calcd. For $C_{18}H_{24}N_3O_6$ $[M+H]^+$=378.16596, found 378.16592.




**1-((2R,6S)-2,6-dimethylpiperidin-1-yl)-4-(3-hydroxy-2-oxoindolin-3-yl)butane-1,3-dione** (**3q**, Table 2, entry 17):

Yield 81 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, 2 times run) 0.15, Brown solid, **Mp** 68-70 °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$+DMSO $d_6$) (inseparable diastereomers, spectral data is given only for major isomer): δ 10.23 (br s, 1H), 7.40-7.25 (m, 1H), 7.19 (t, *J*=7.6 Hz, 1H), 7.99-7.93(m, 1H), 6.85 (d, *J*=7.6 Hz, 1H), 4.66 (br s 1H), 4.55-3.80 (m, 4 H), 3.66-3.50 (m, 1H), 3.46-3.24 (m, 1H), 1.68-1.41 (m, 4H), 1.35-1.24 (m, 2H), 1.23-1.11 (m, 6H) ppm. **$^{13}$C NMR** (125 MHz, $CDCl_3$+DMSO $d_6$): δ 200.12, 176.86, 164.20, 140.86, 129.48, 127.66, 122.31, 120.08, 108.40, 71.74, 51.18, 48.61, 48.17, 46.51, 41.90, 28.51, 19.87, 18.88, 12.02 ppm. **IR (KBr)** ν=3255, 2939, 1722, 1618, 1474, 1340, 1237, 1190, 1120, 1060, 753, 633, 551 $cm^{-1}$. **MS (ESI)** *m/z* 345 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. For $C_{19}H_{25}O_4N_2[M+H]^+$=345.18143, found 345.18211.




**1-((2R,6S)-2,6-dimethylpiperidin-1-yl)-4-(3-hydroxy-5-iodo-2-oxoindolin-3-yl)butane-1,3-dione** (**3r**, Table 2, entry 18):

Yield 79 %, Time 12 hr, *Rf*(50% EtOAc/hexanes, 2 times run) 0.19. White solid, **Mp** 94-96 °C. **$^{1}$H NMR** (500 MHz, $CDCl_3$+DMSO $d_6$) (inseparable diastereomers, spectral data is given only for major isomer): δ 10.20 (br s, 1H), 7.58 (s, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 6.67 (d, *J*=7.8 Hz, 1H), 6.14 (br s, 1H), 3.88-3.31 (m, 4H), 3.05-2.98 (m, 1H), 2.80-2.74 (m, 1H), 1.64-1.46 (m, 6H), 1.18-1.15 (m, 6H) ppm. **$^{13}$C NMR** (75 MHz, $CDCl_3$+DMSO $d_6$): δ 200.41, 176.64, 164.44, 141.01, 136.69, 132.09, 131.31, 111.25, 82.85, 76.37, 51.68, 48.90, 48.30, 47.18, 42.55, 29.62,

21.93, 18.85, 12.41 ppm. **IR (KBr)** ν=3257, 2941, 1729, 1621, 1479, 1339, 1241, 1189, 1118, 1058, 756, 638, 549 $cm^{-1}$. **MS (ESI)** *m/z* 471 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd. For $C_{19}H_{24}O_4N_2I$ $[M+H]^+$=471.07808, found 471.07781.

**References:**

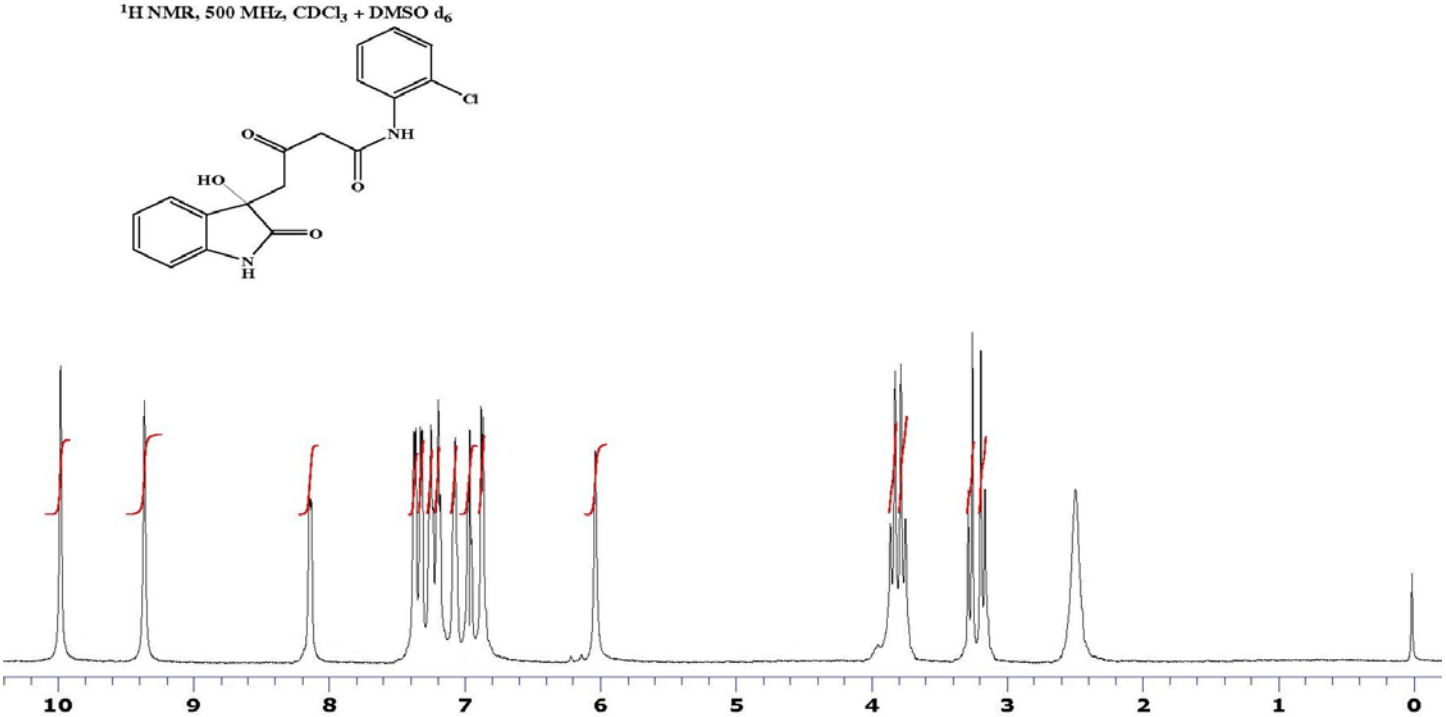

1. (a) G.V.J. Jadhav, J. Indian Chem. Soc. 7 (1930) 669;

(b) K.B.R. Prashantha, S. Yuvaraj, A. Srivastava, V. Chaturvedi, Y.K. Manju, B. Suresh, M.J. Nanjan, Lett. Drug Des. Discovery 5 (2008) 7-14;

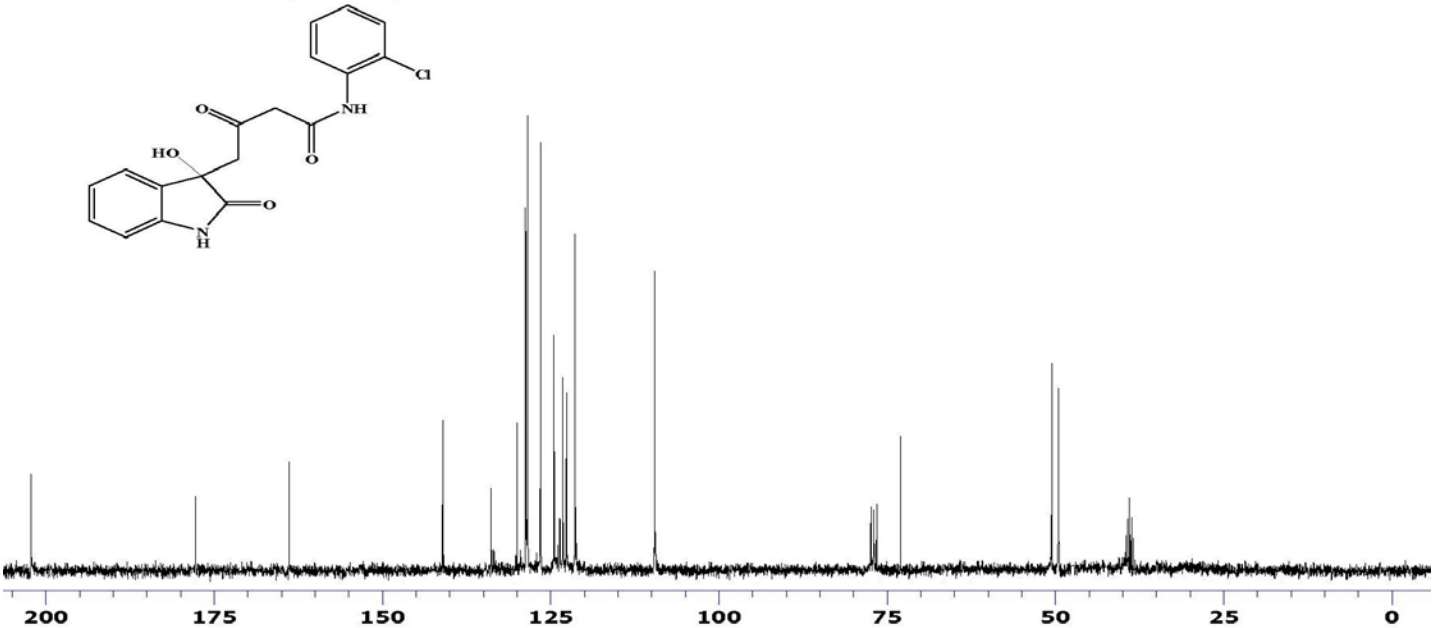
(c) K.B.R. Prashantha, S. Gopu, B.R.B. Nasir, C. Srinivasan, Eur. J. Med. Chem. 44 (2009) 4192-4198.

# $^{1}$H and $^{13}$C NMR spectra

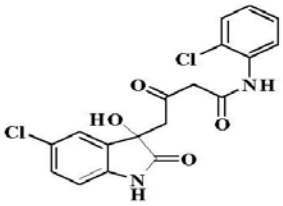
$^{1}$H NMR, 500 MHz, $CDCl_3$ + DMSO $d_6$

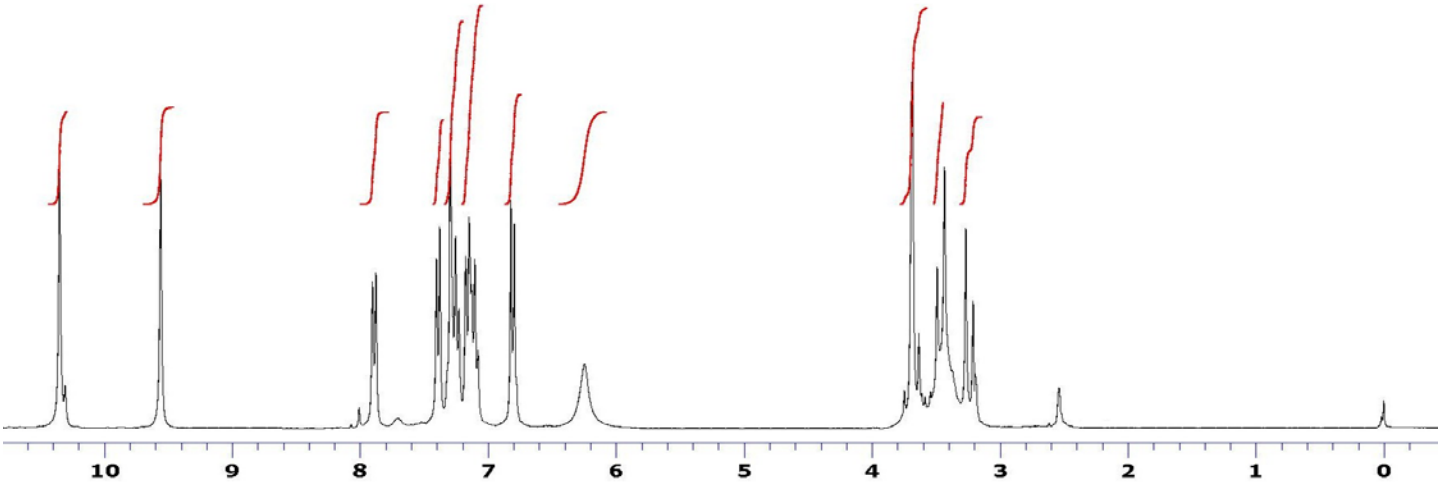



$^{13}$C NMR, 75 MHz, $CDCl_3$ + DMSO $d_6$

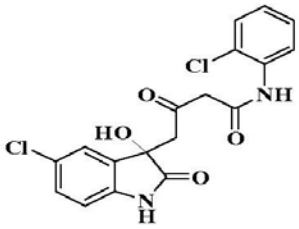


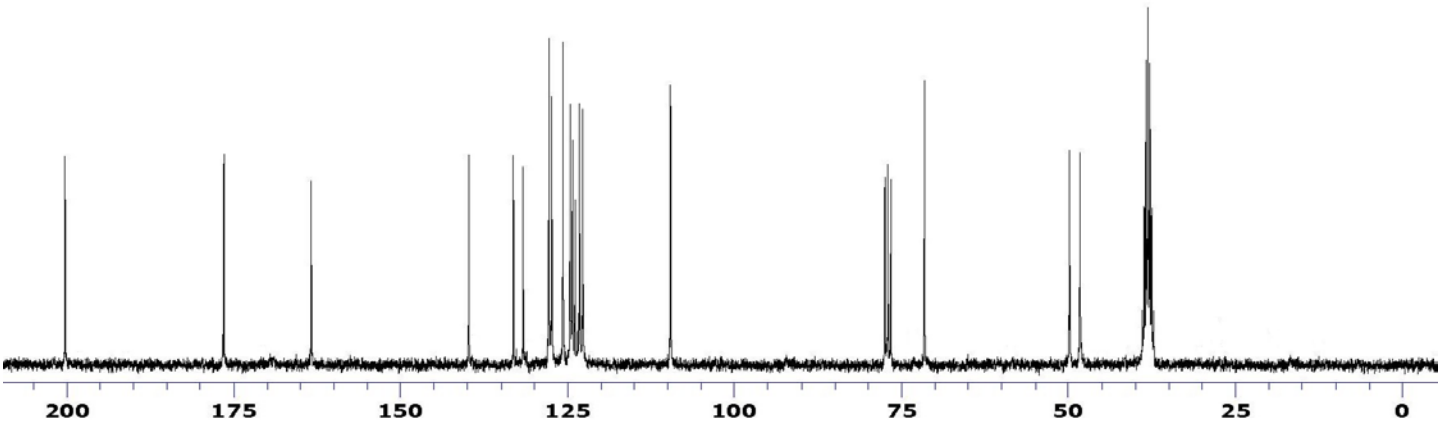
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



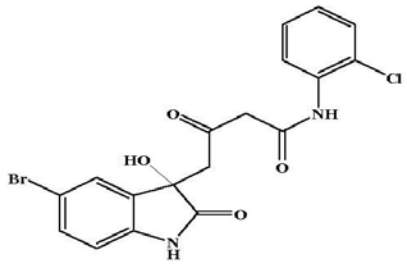



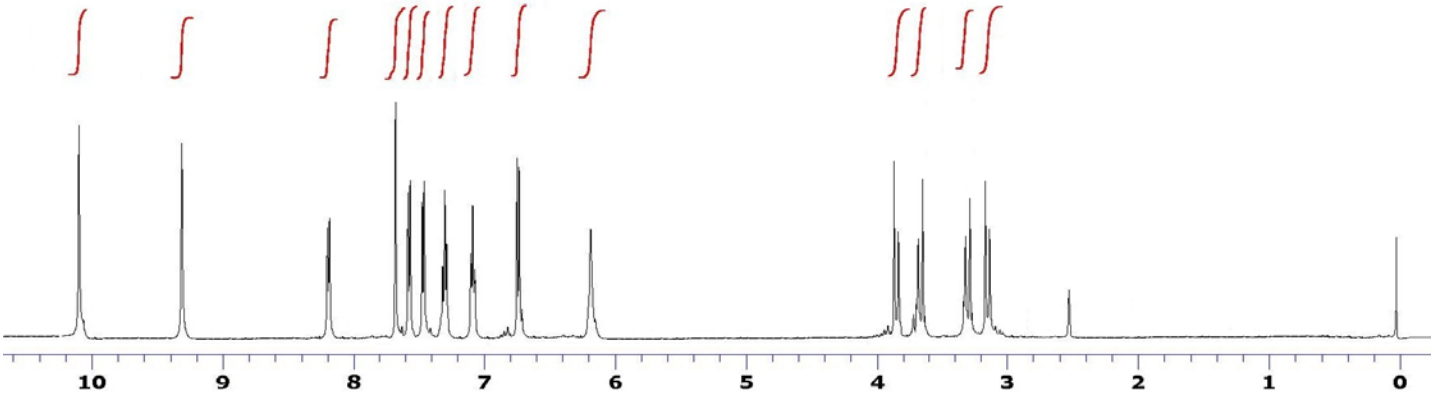

**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**



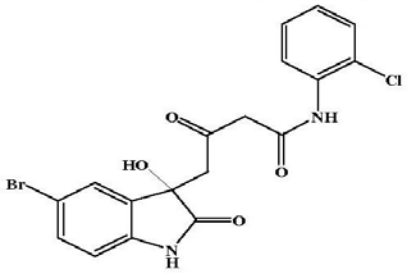



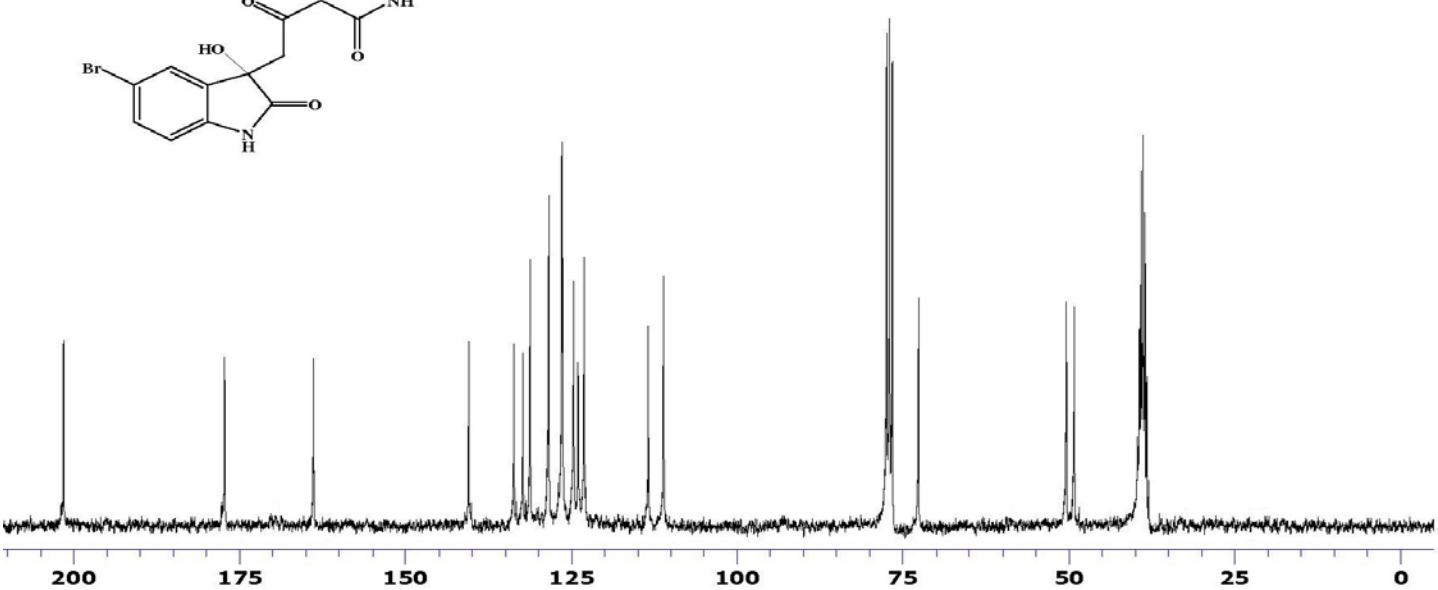
$^{1}H$ NMR, 200 MHz, $CDCl_3$ + DMSO $d_6$



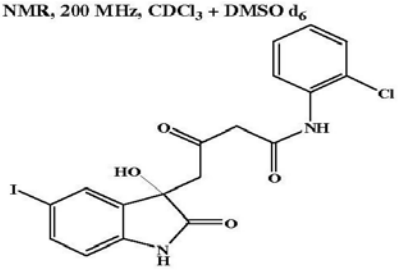



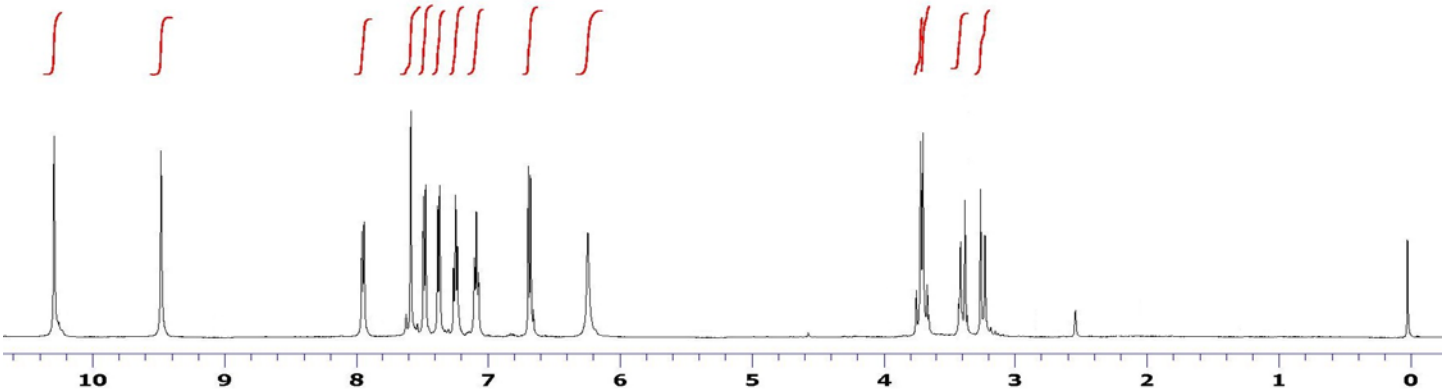

$^{13}C$ NMR, 50 MHz, $CDCl_3$ + DMSO $d_6$



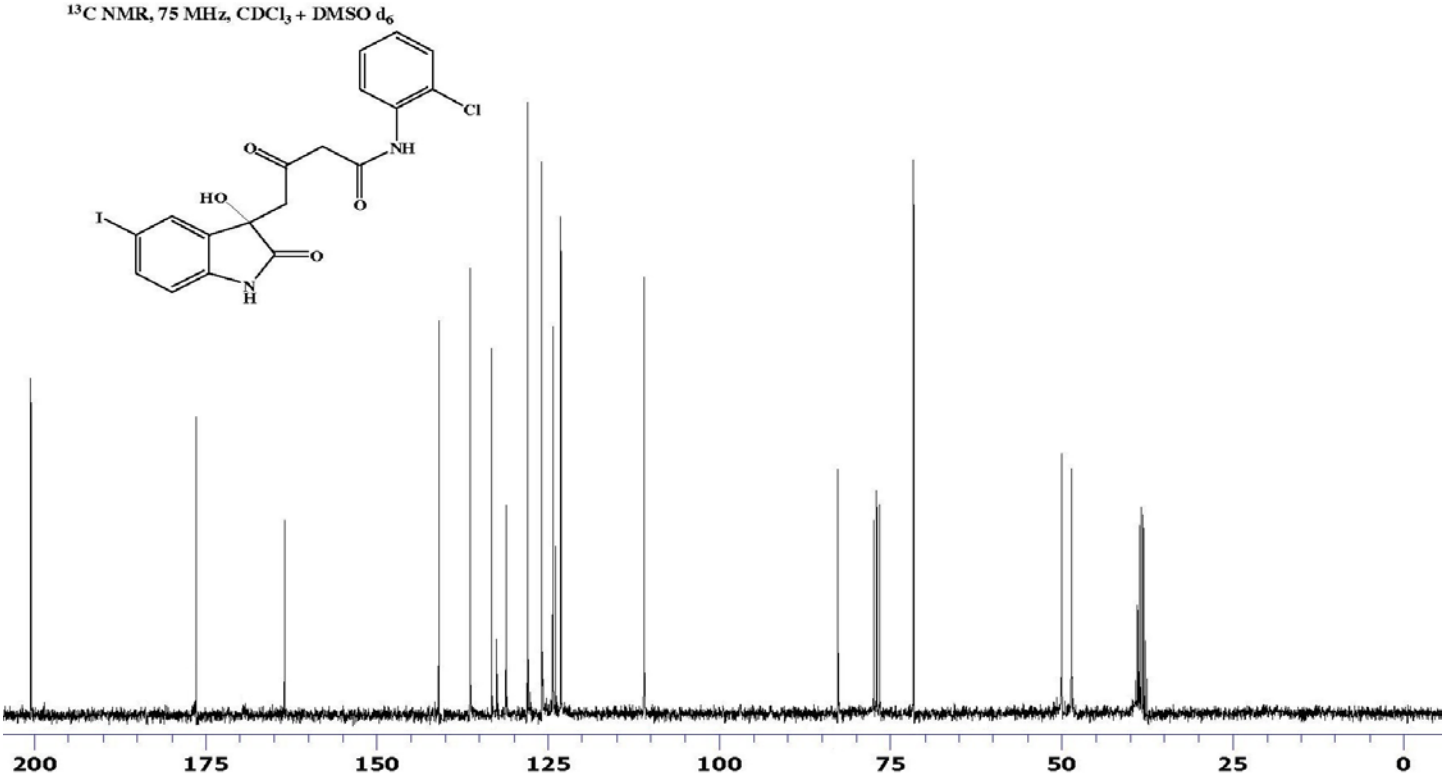
$^{1}H$ NMR, 200 MHz, $CDCl_3$ + DMSO $d_6$



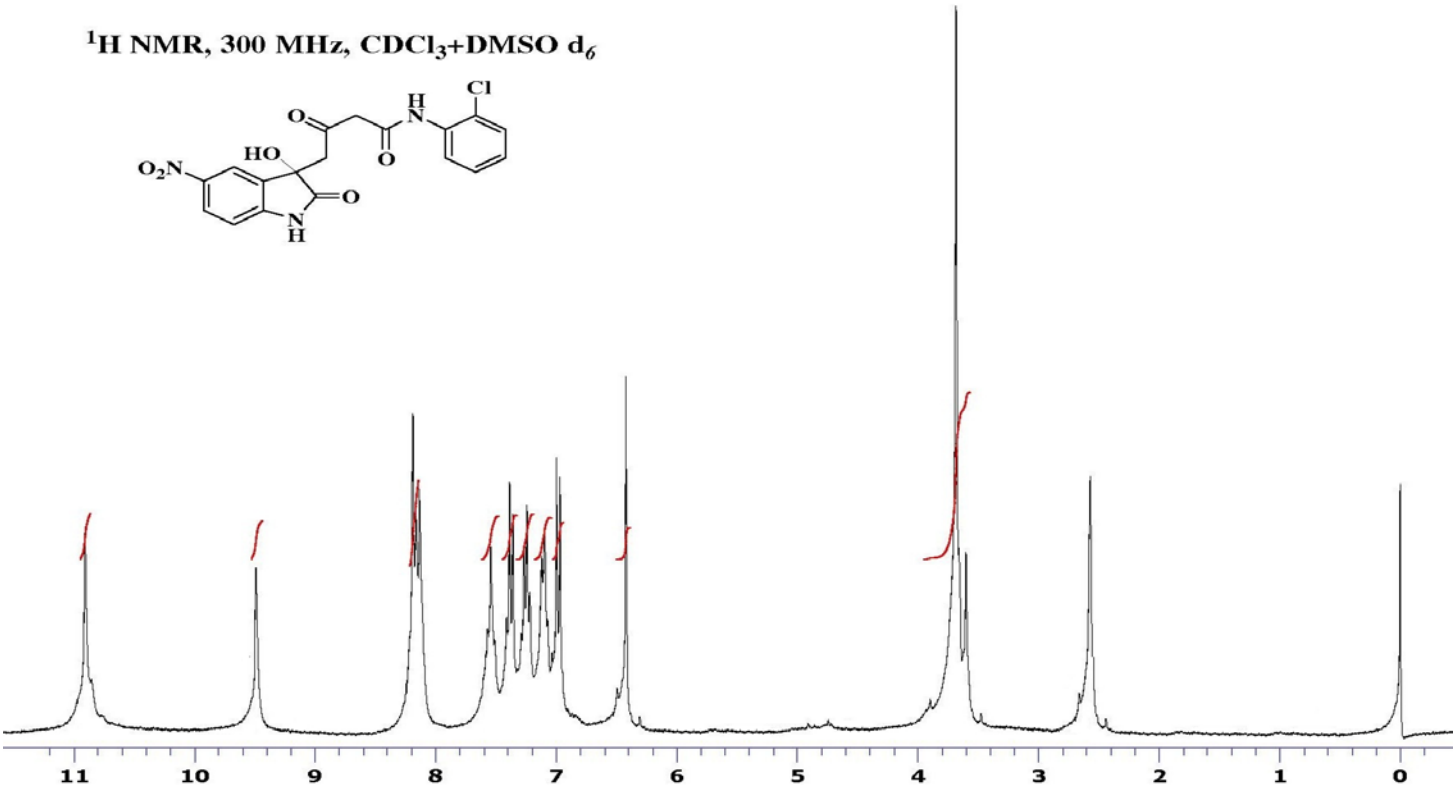

$^{13}C$ NMR, 75 MHz, $CDCl_3$ + DMSO $d_6$



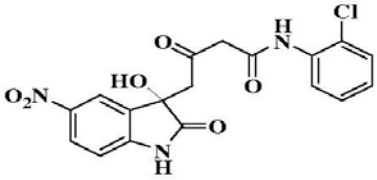



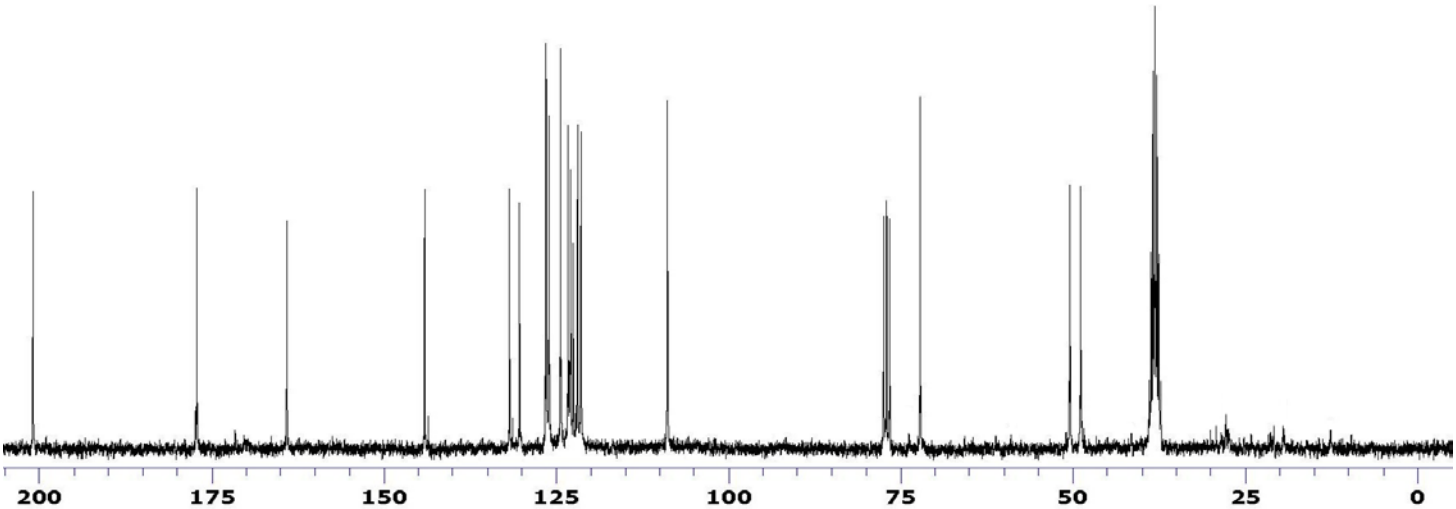
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



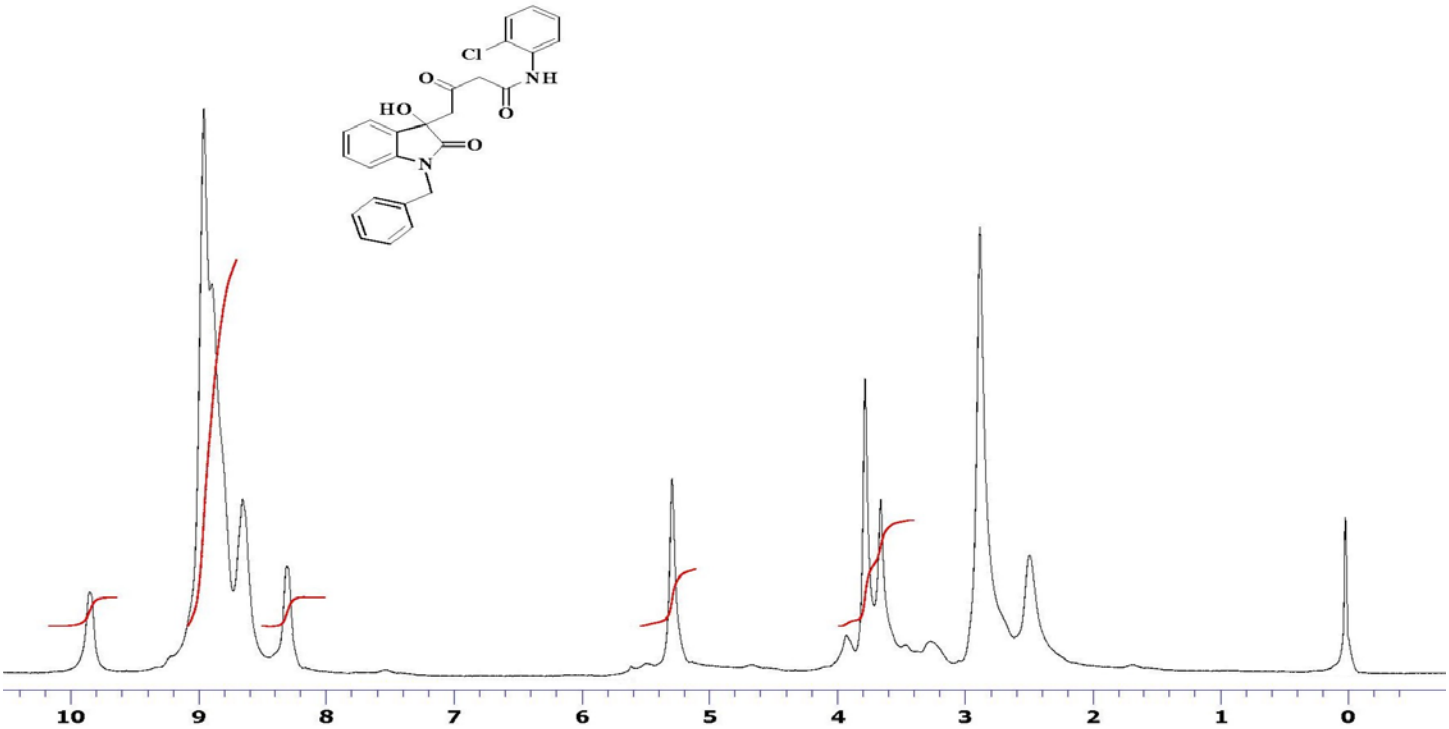




**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**

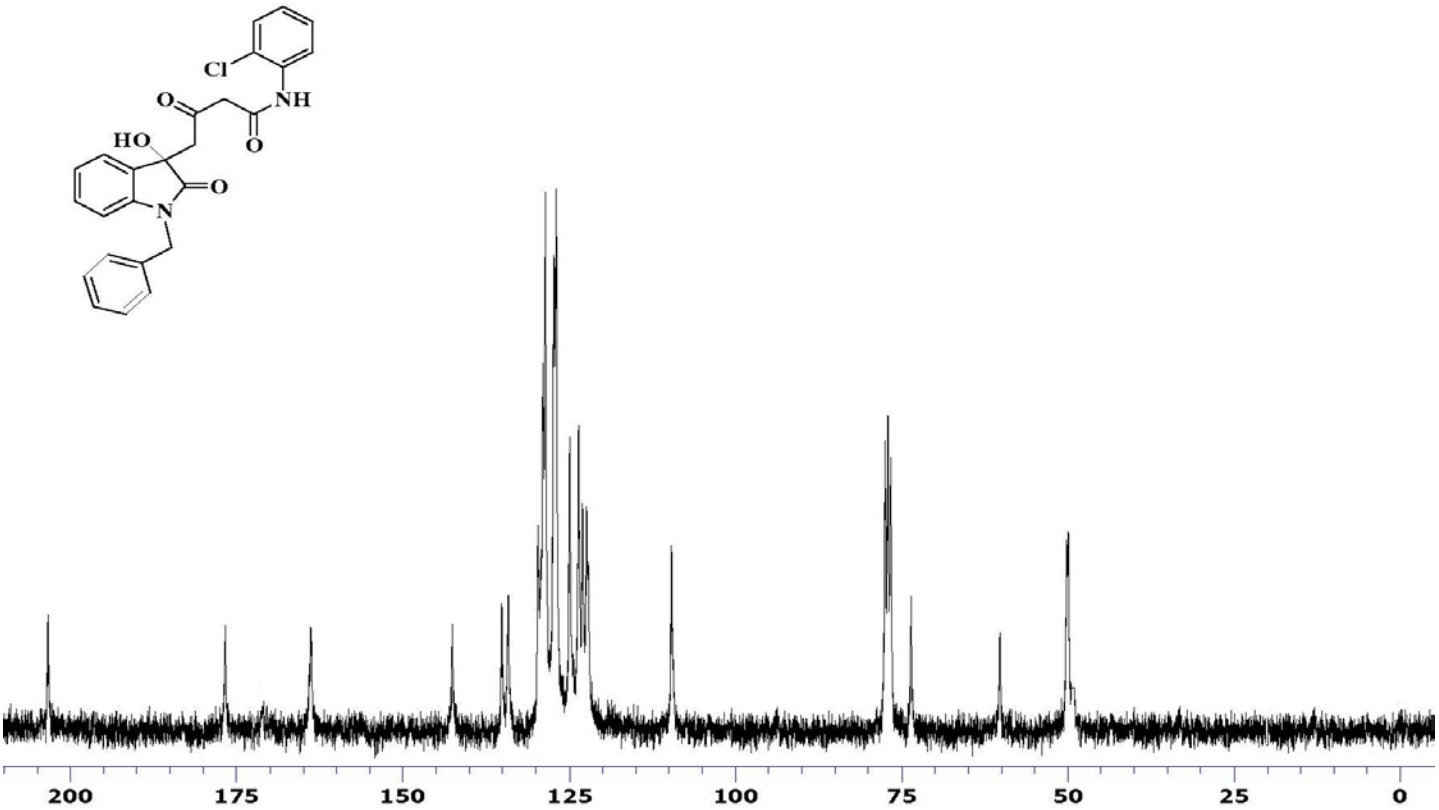


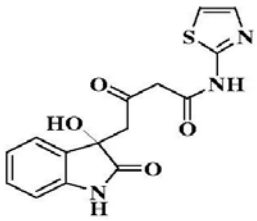
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**

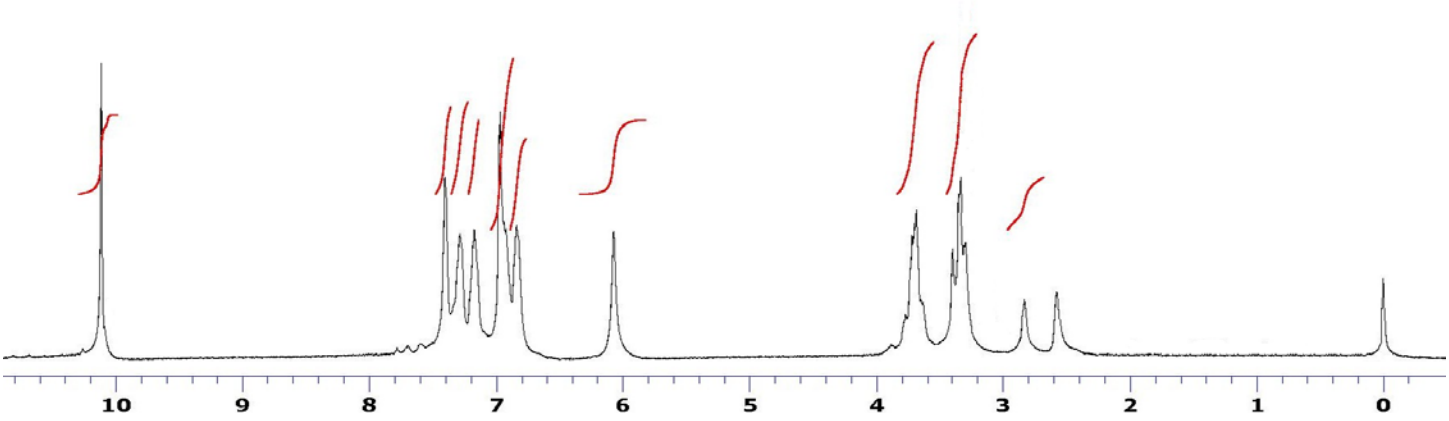



**$^{13}$C NMR, 75 MHz, $CDCl_3$**

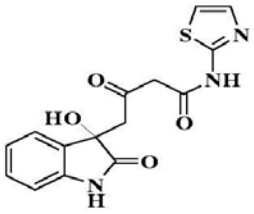


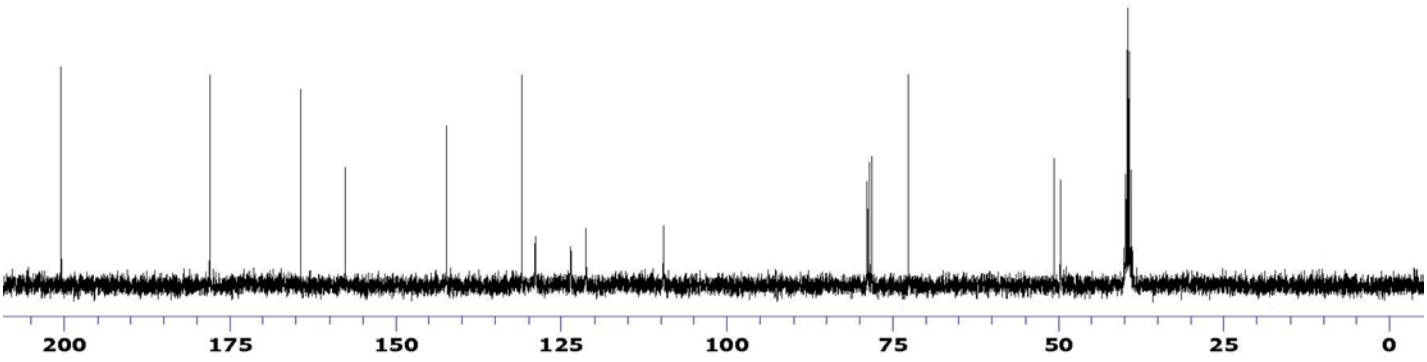
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



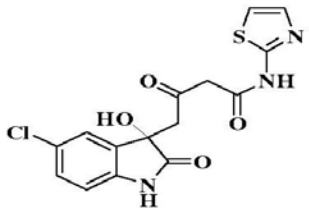



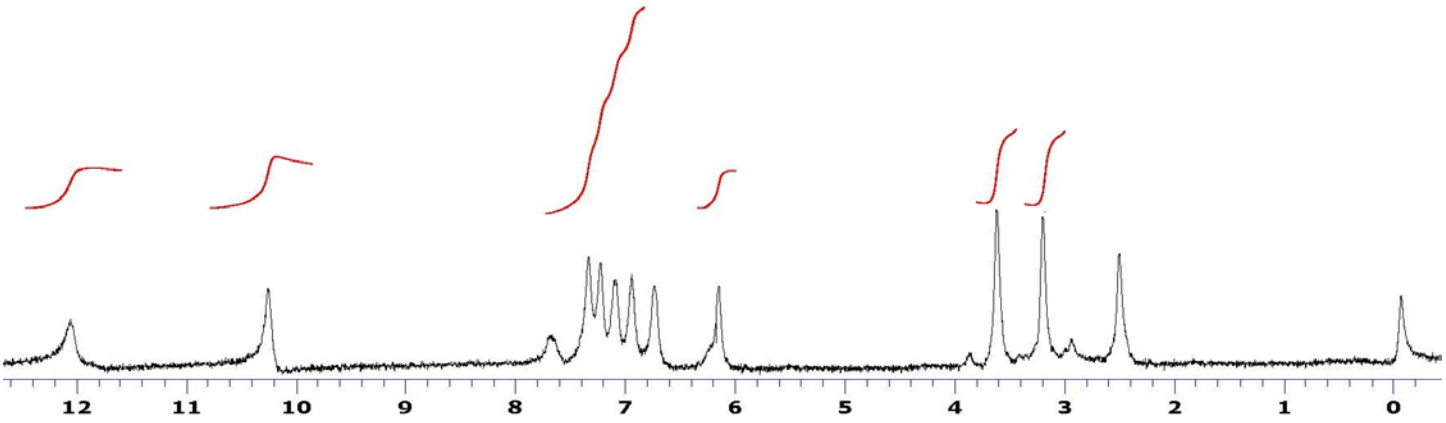

**$^{13}$C NMR, 100 MHz, $CDCl_3$+DMSO $d_6$**



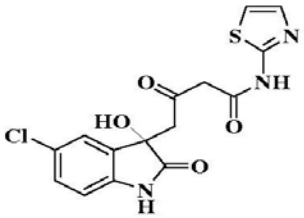



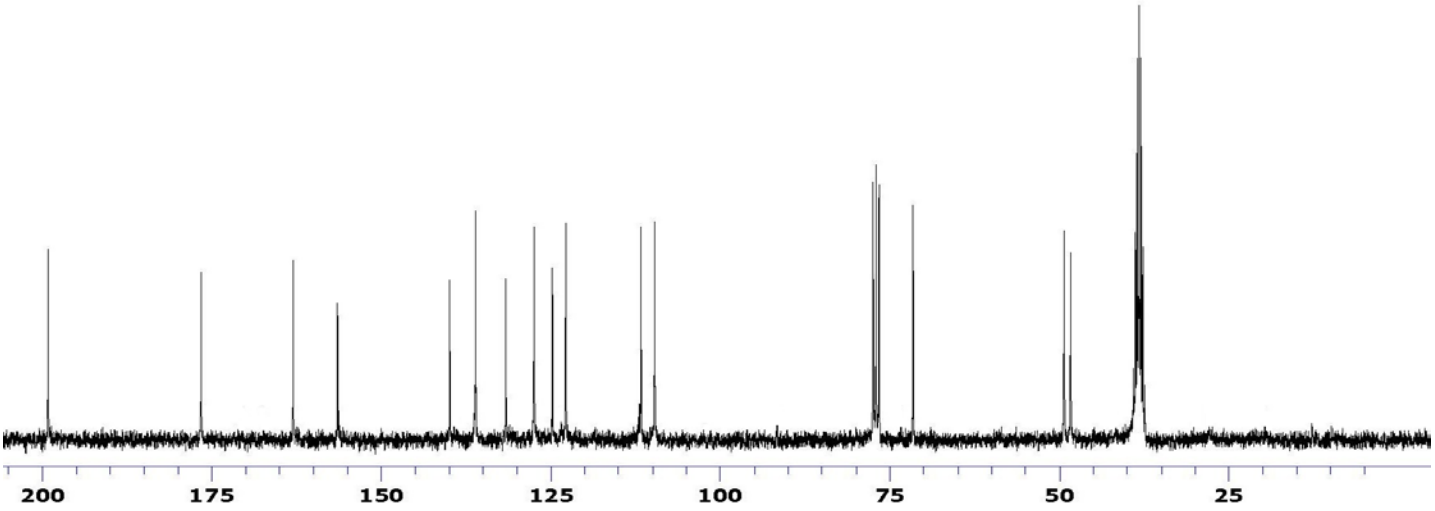
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



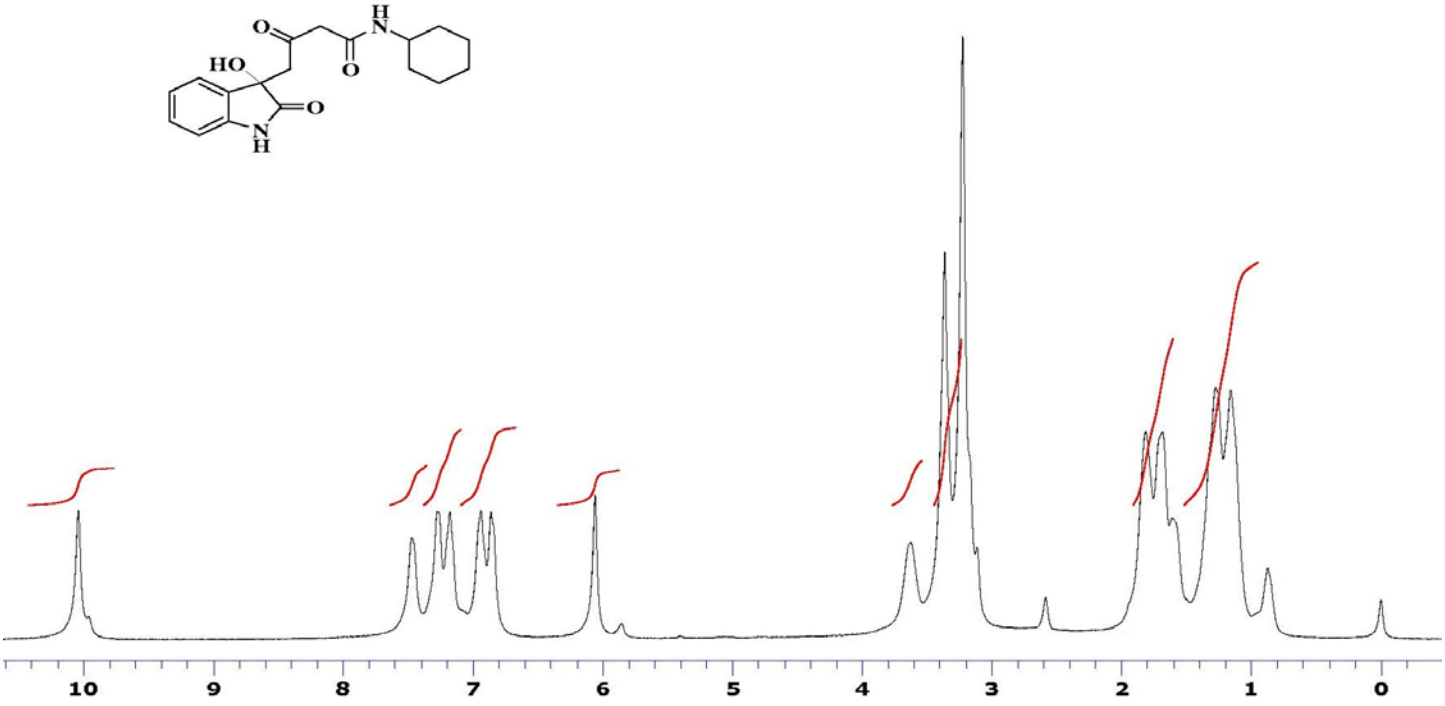




**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**

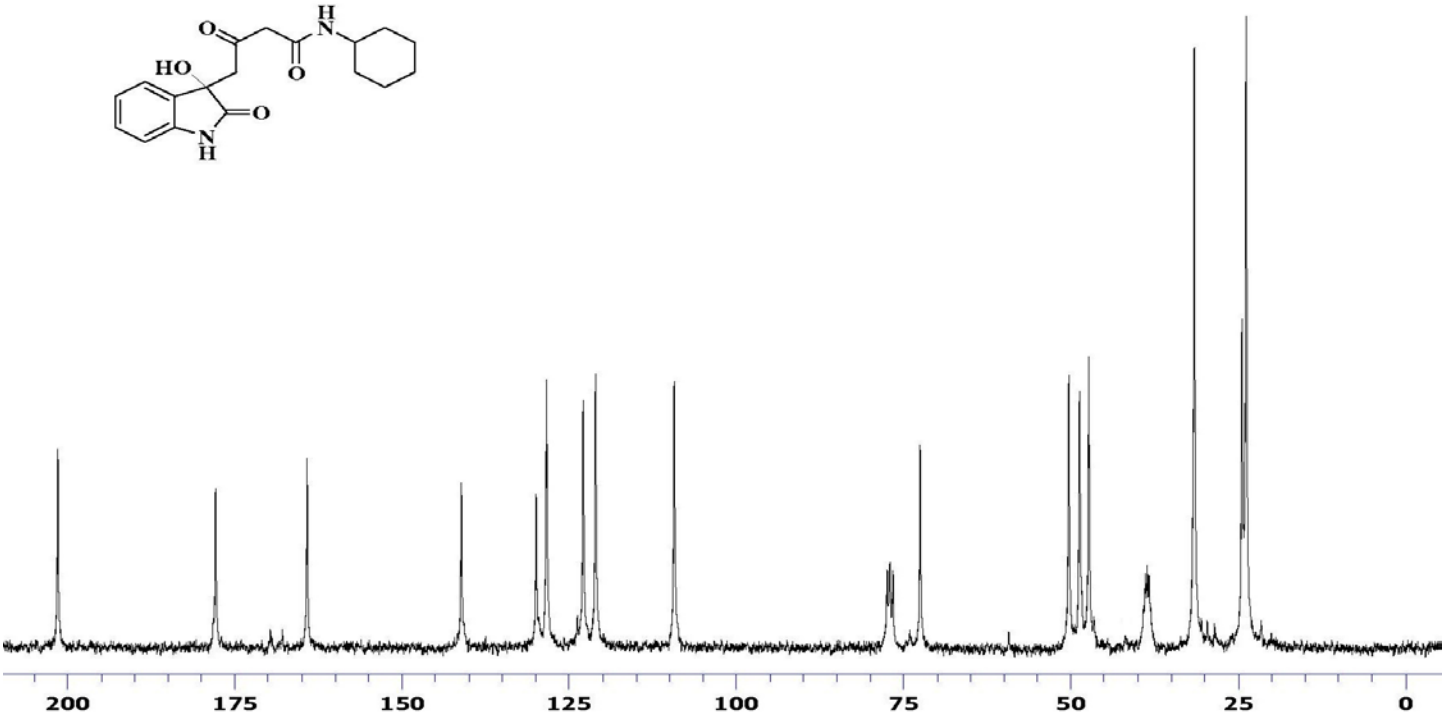


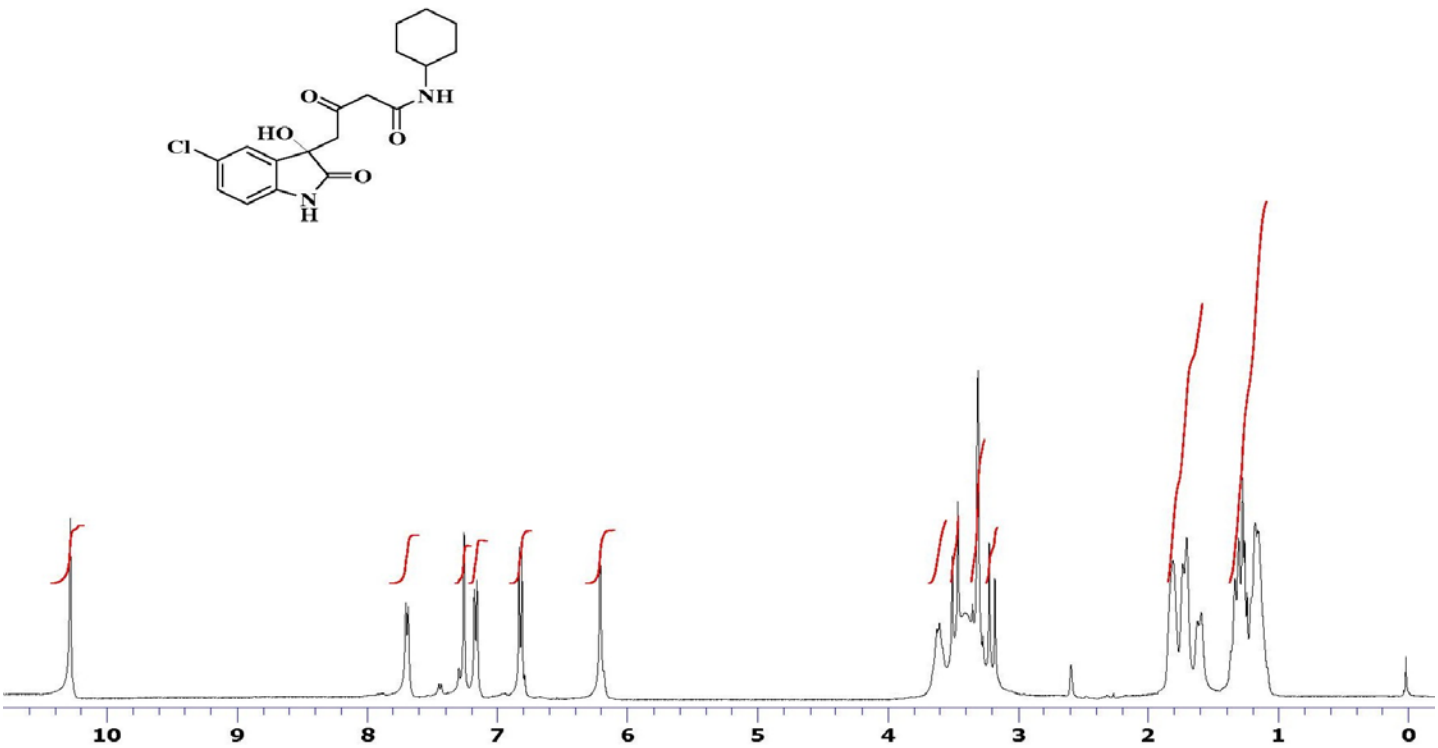
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



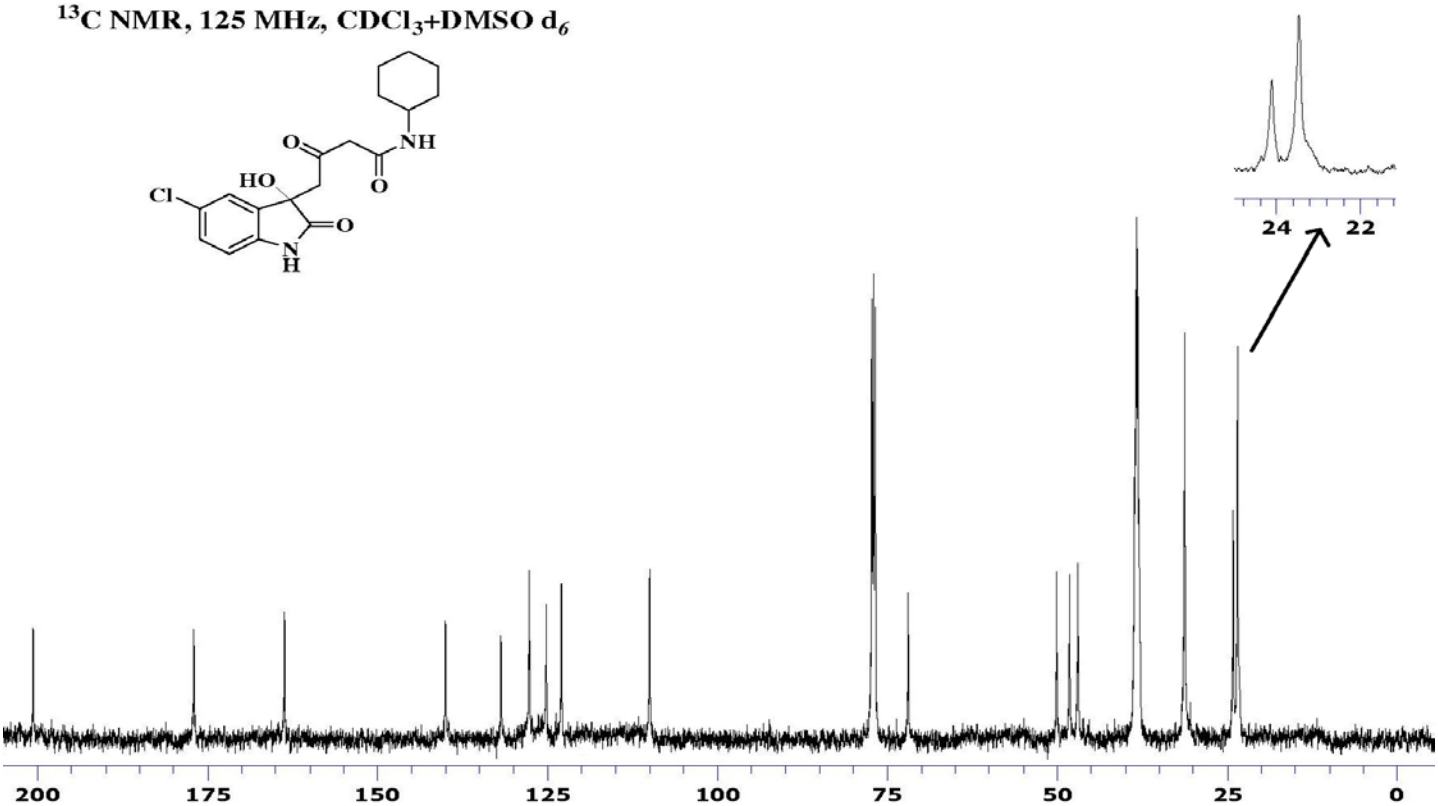

**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**



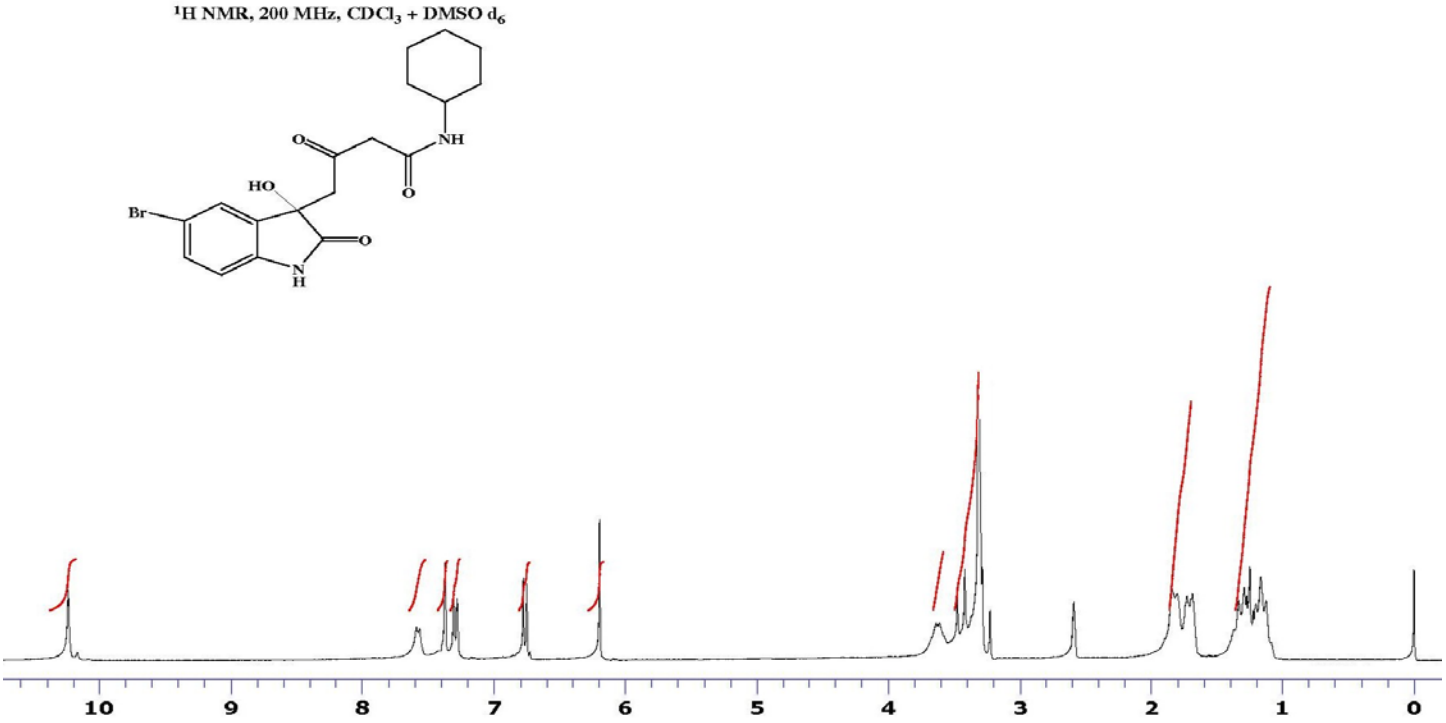
**$^{1}$H NMR, 400 MHz, $CDCl_3$+DMSO $d_6$**



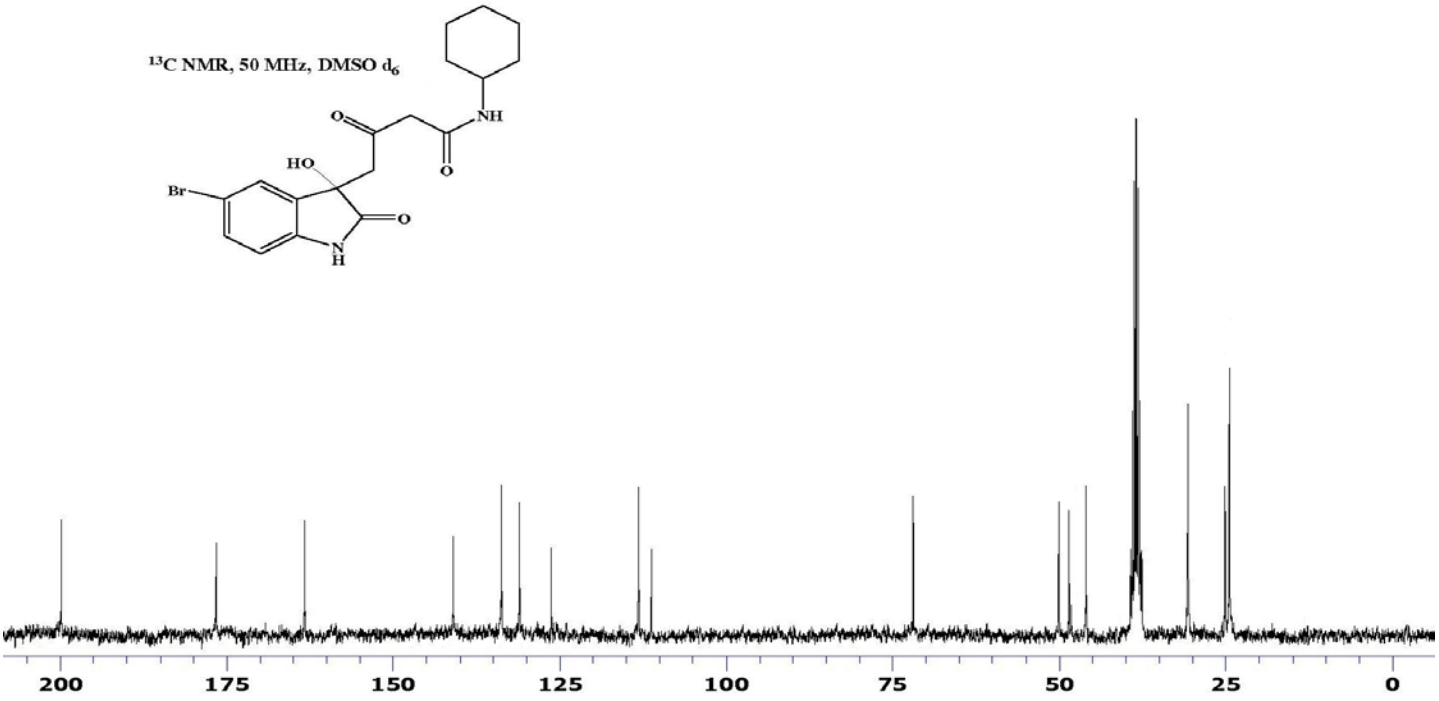

**$^{13}$C NMR, 125 MHz, $CDCl_3$+DMSO $d_6$**



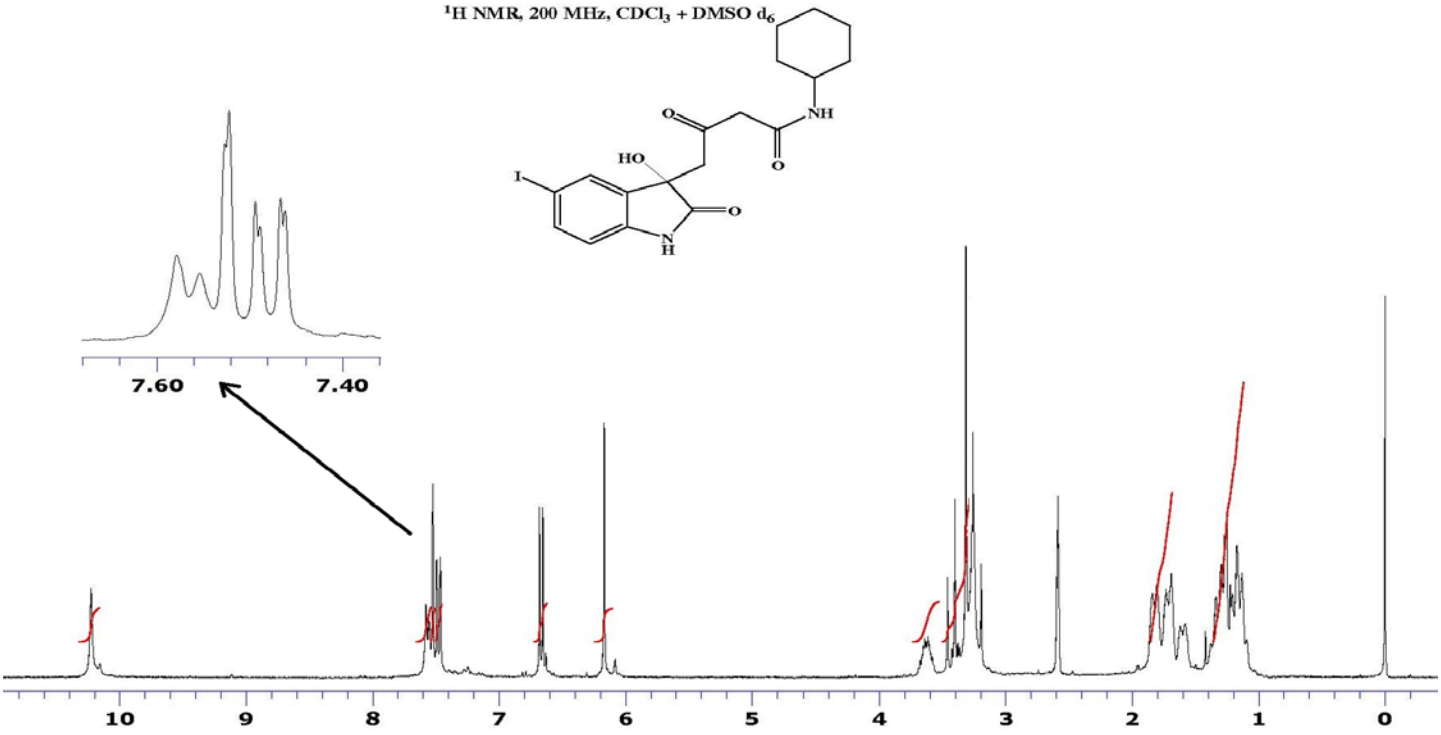
$^{1}$H NMR, 200 MHz, $CDCl_3$ + DMSO $d_6$



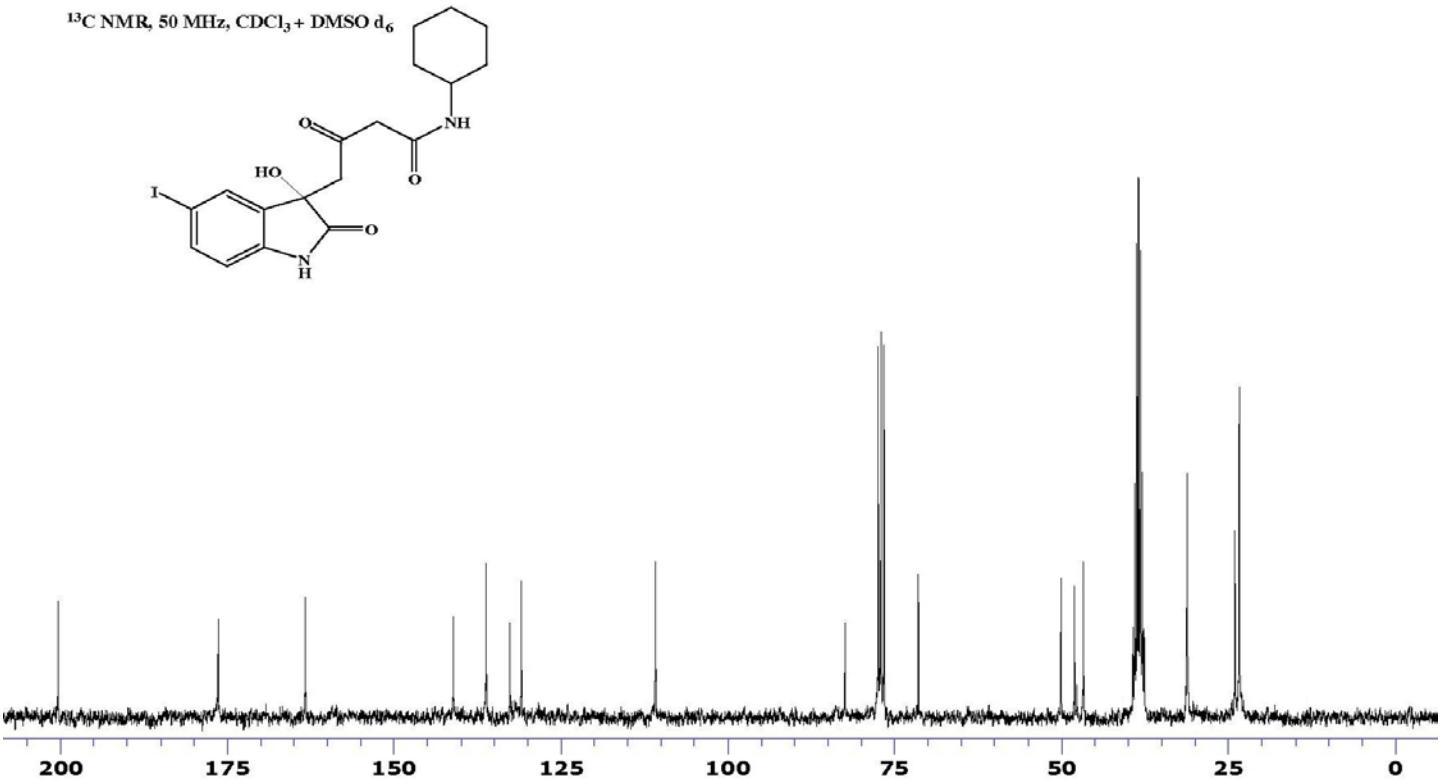

$^{13}$C NMR, 50 MHz, DMSO $d_6$



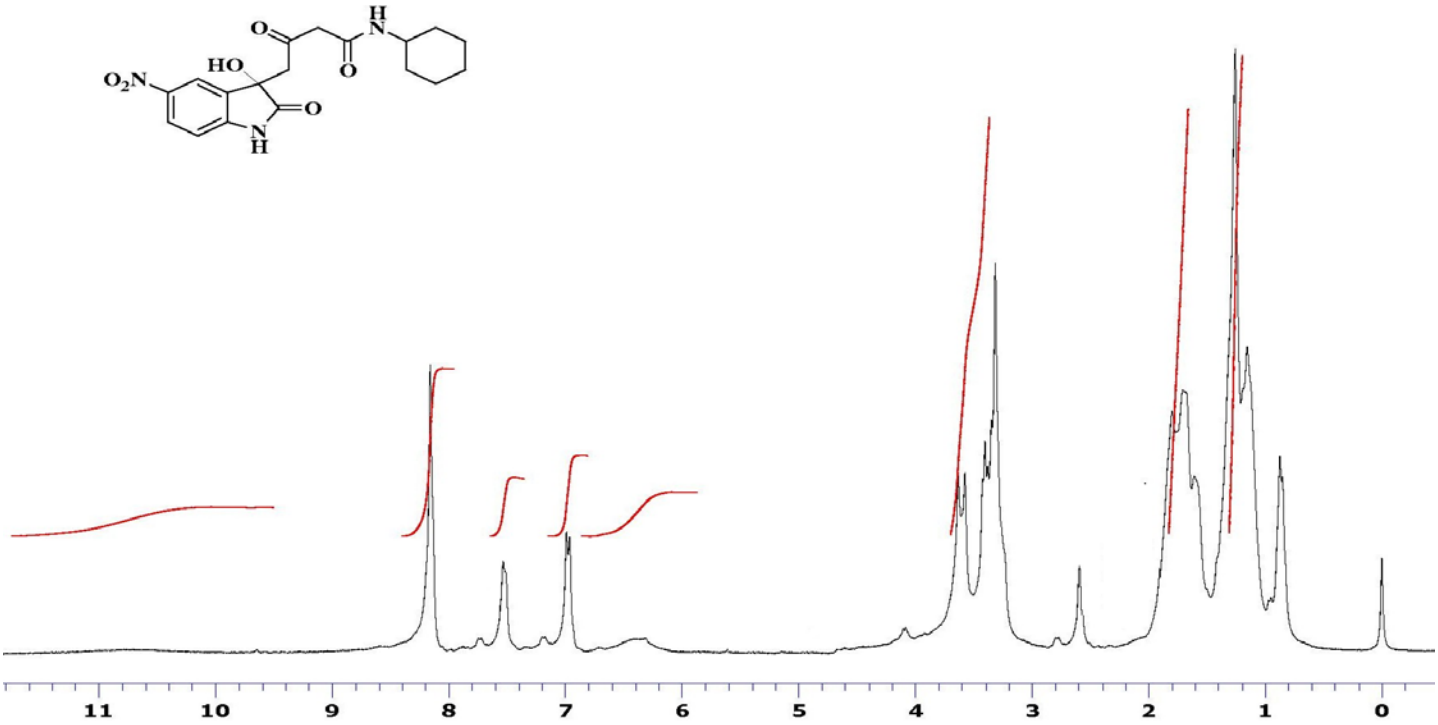
$^{1}H$ NMR, 200 MHz, $CDCl_3$ + DMSO $d_6$



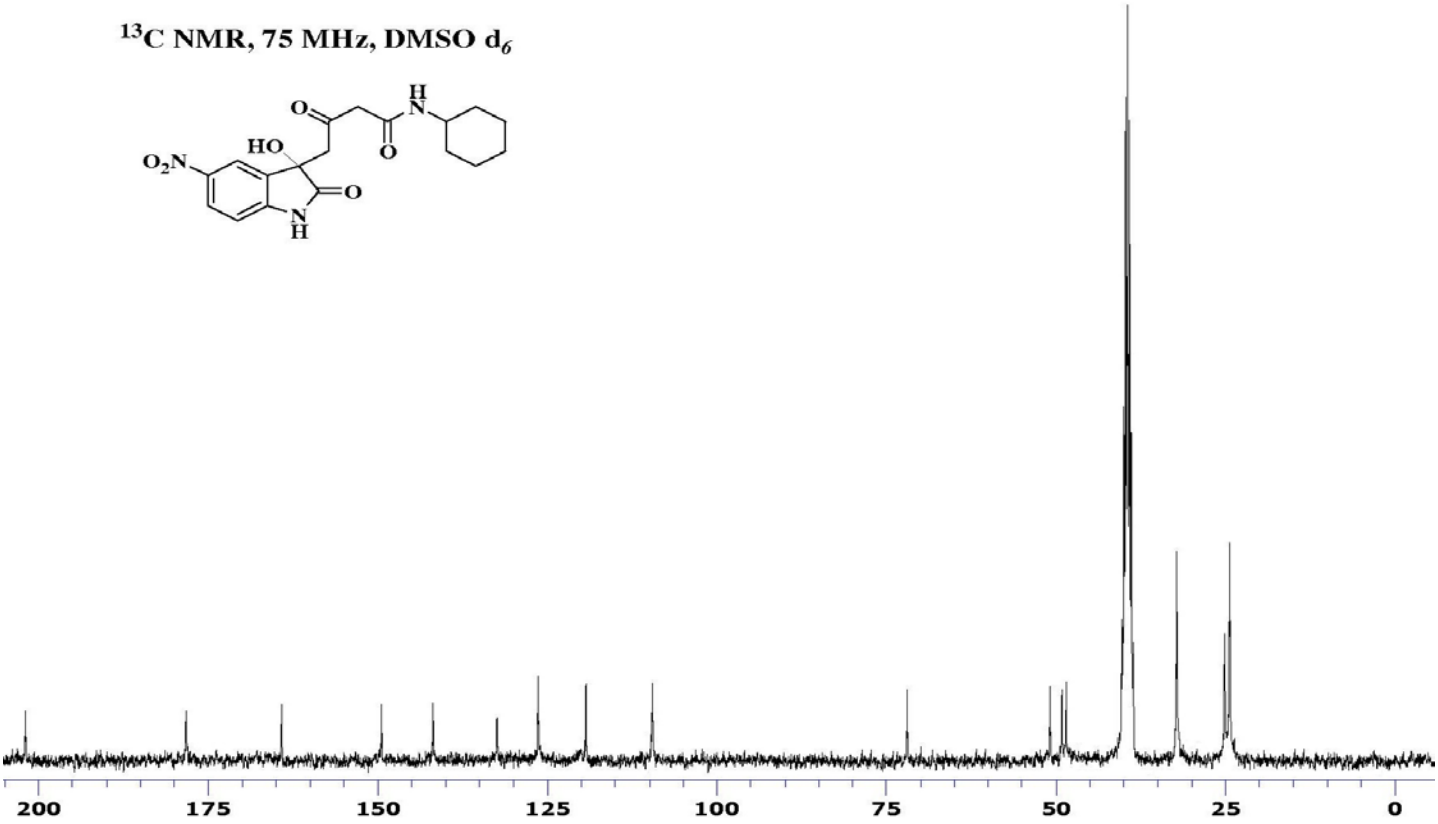

$^{13}C$ NMR, 50 MHz, $CDCl_3$ + DMSO $d_6$



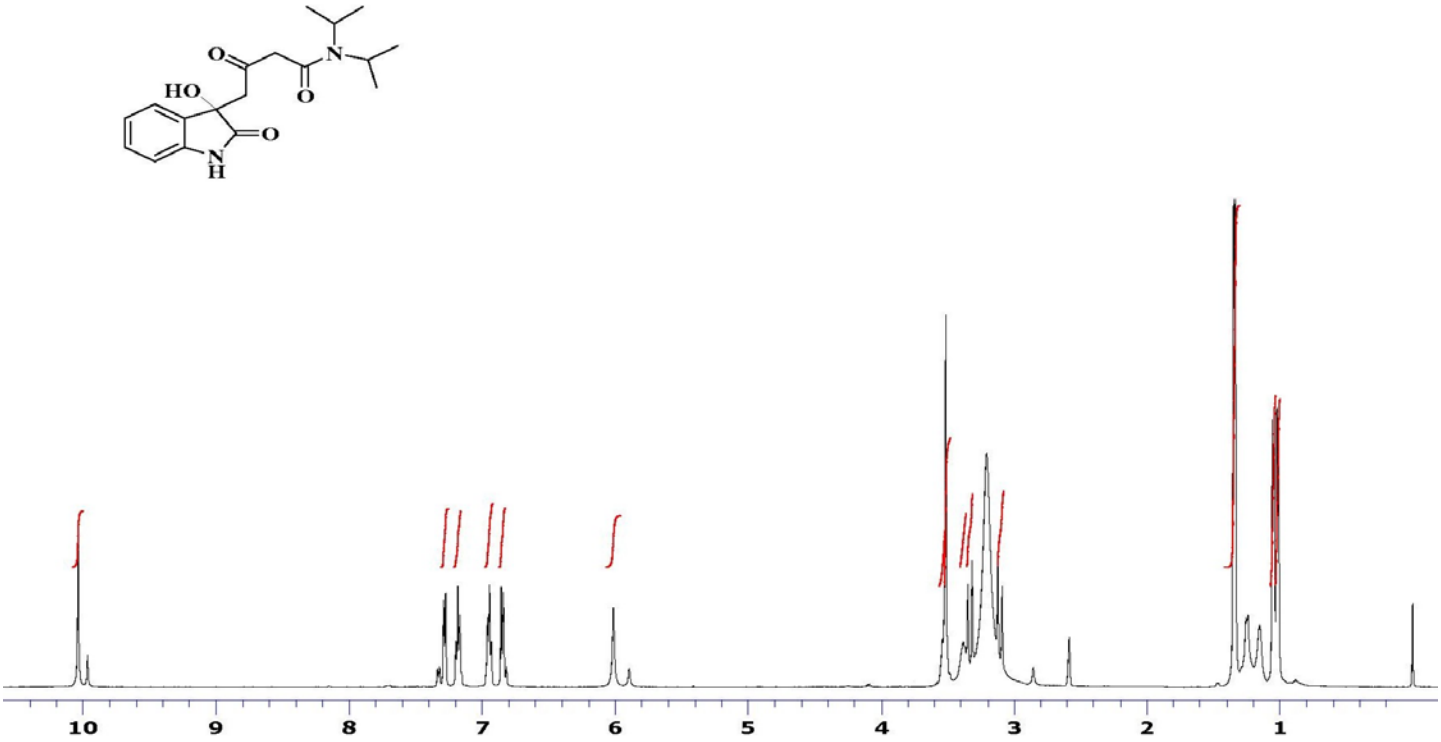
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



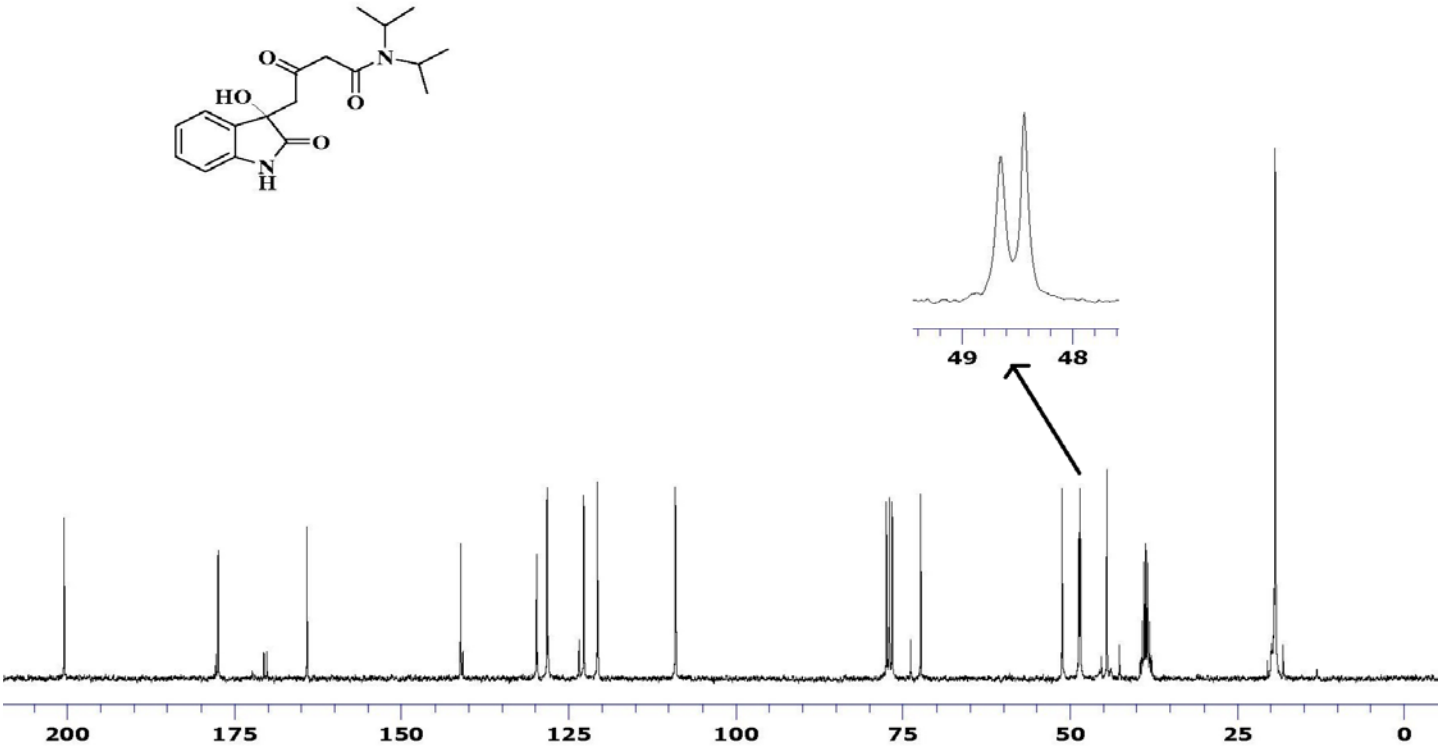

**$^{13}$C NMR, 75 MHz, DMSO $d_6$**



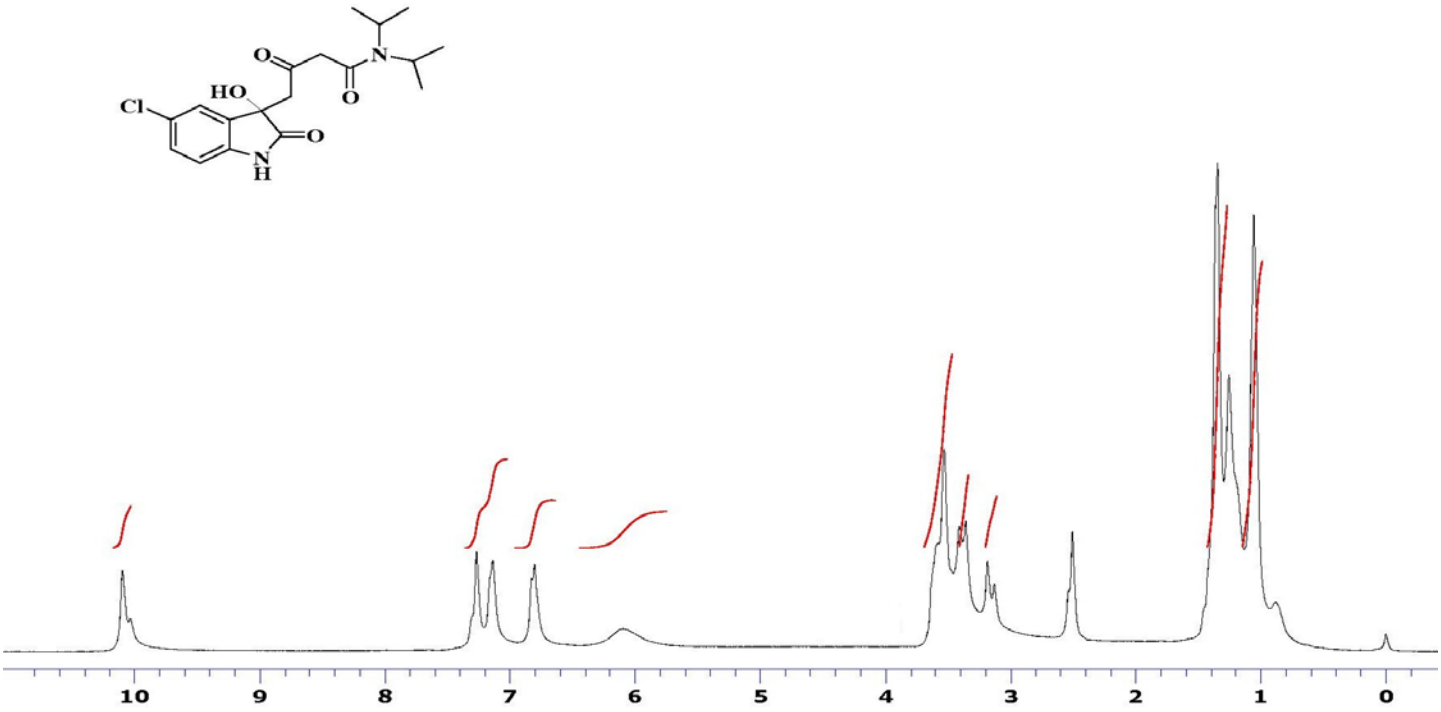
**$^{1}$H NMR, 500 MHz, $CDCl_3$+DMSO $d_6$**



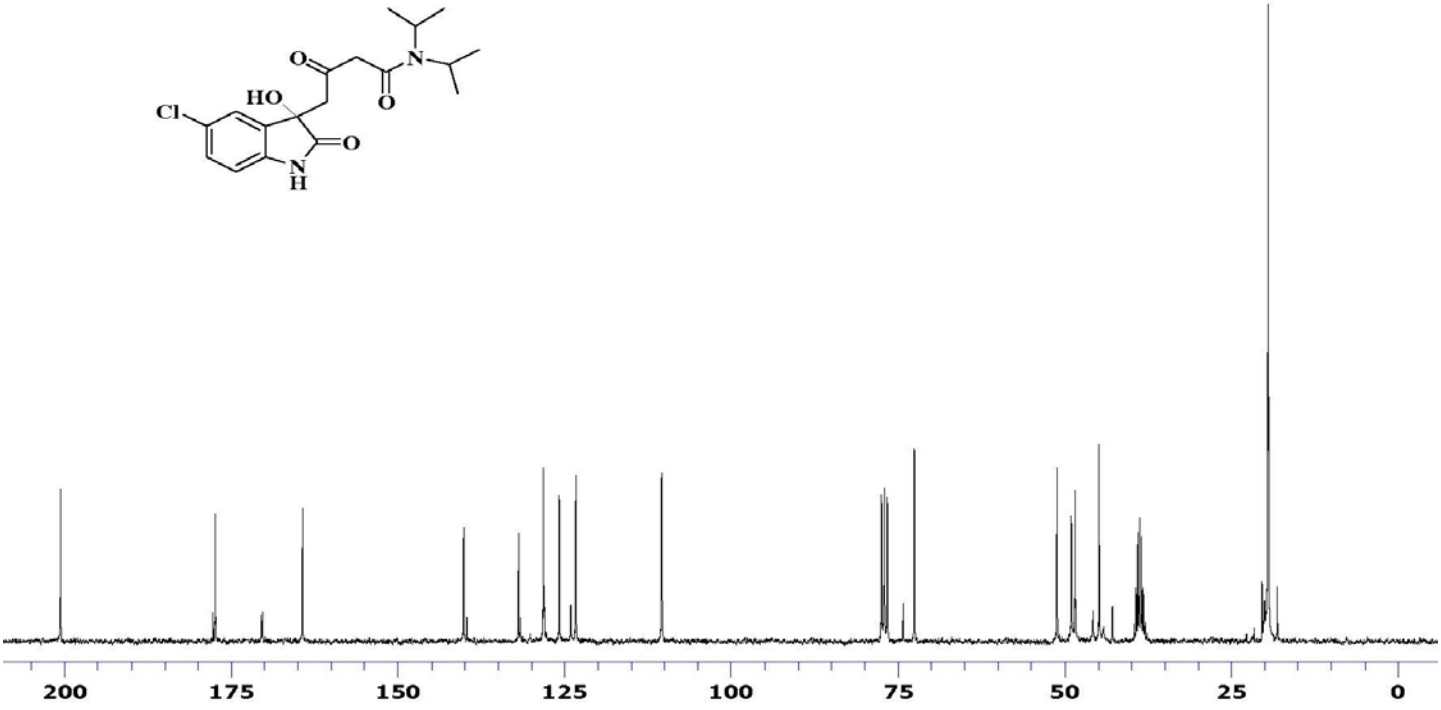

**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**



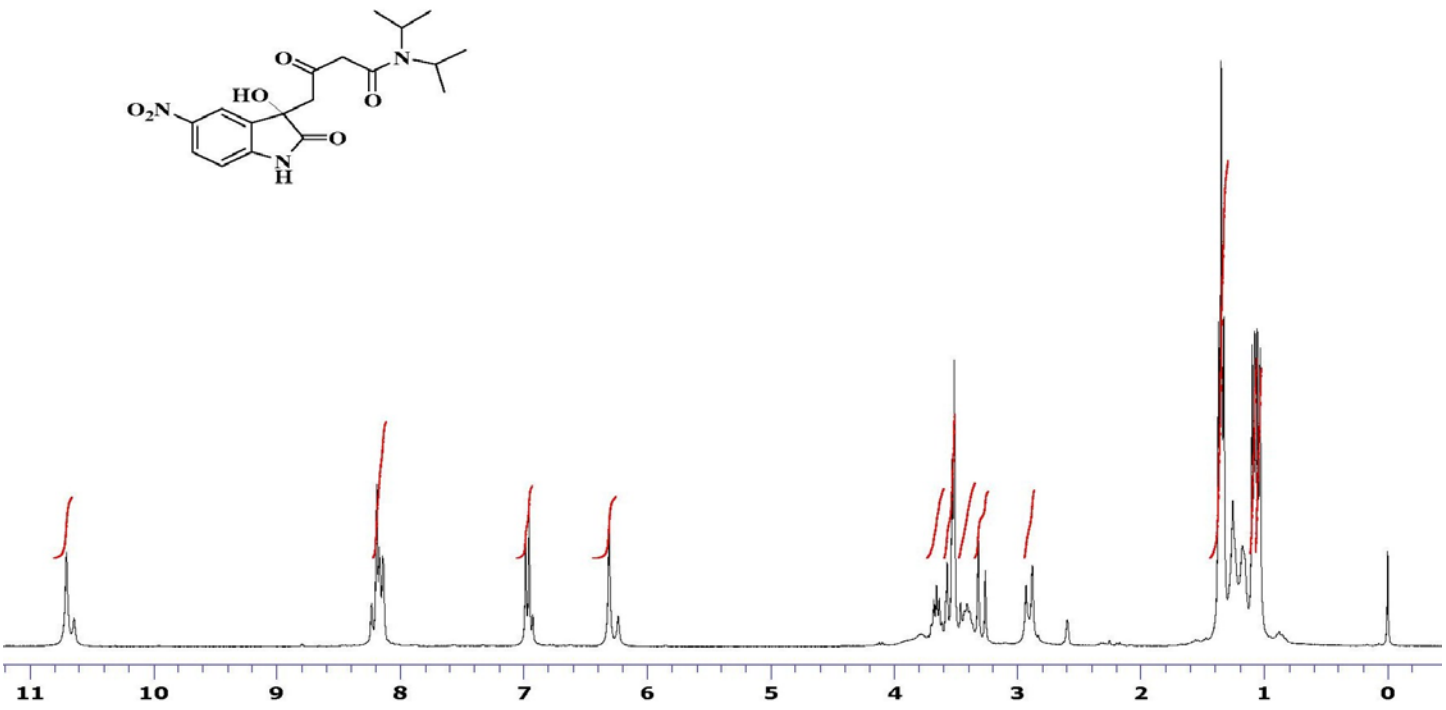
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



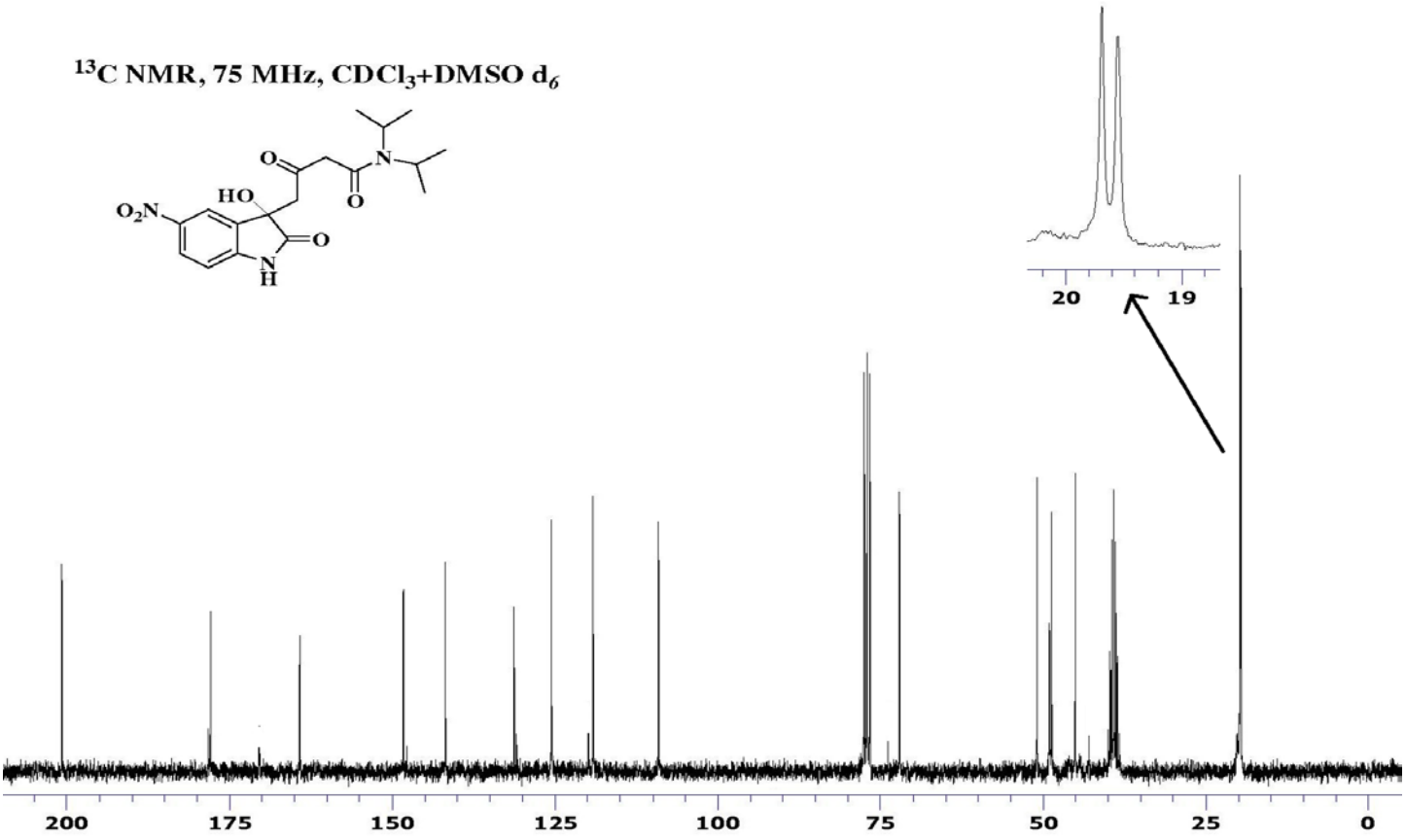

**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**



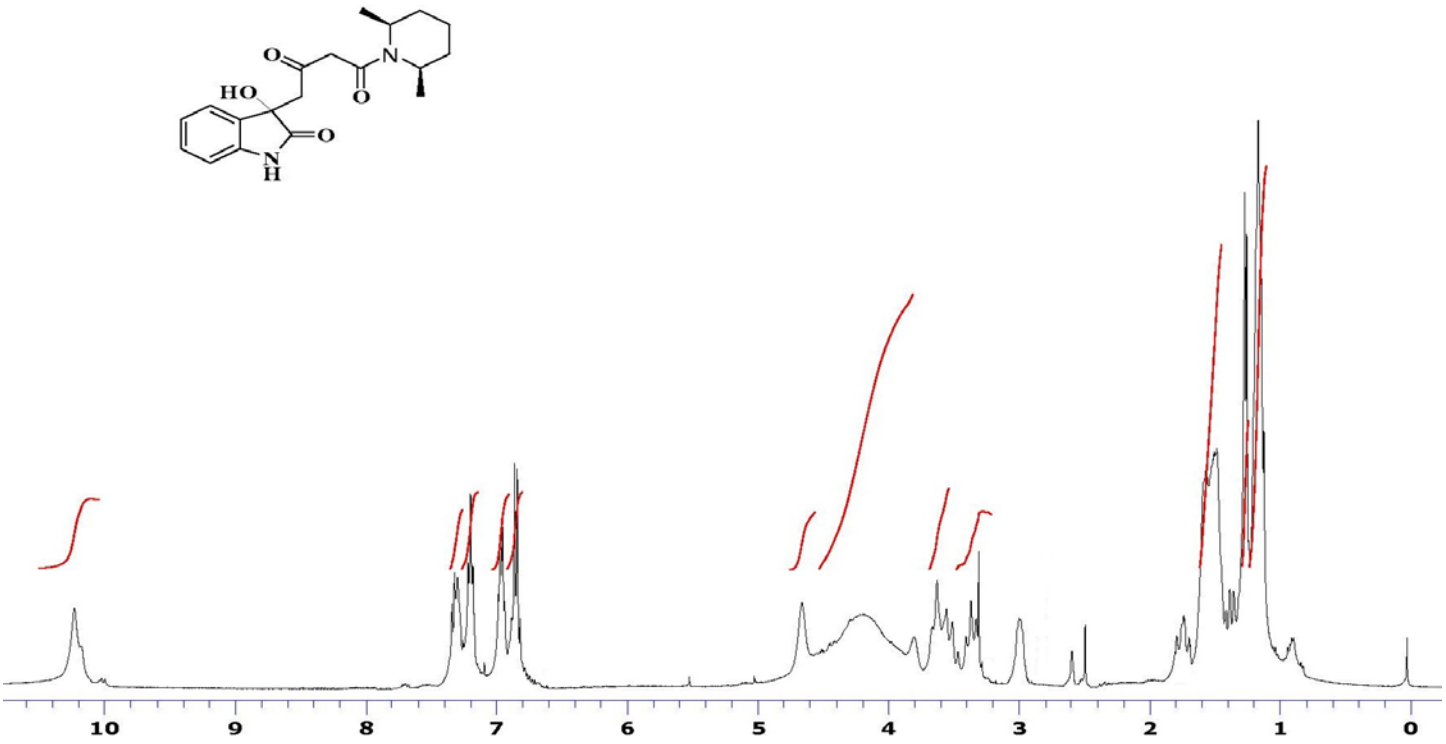
**$^{1}$H NMR, 300 MHz, $CDCl_3$+DMSO $d_6$**



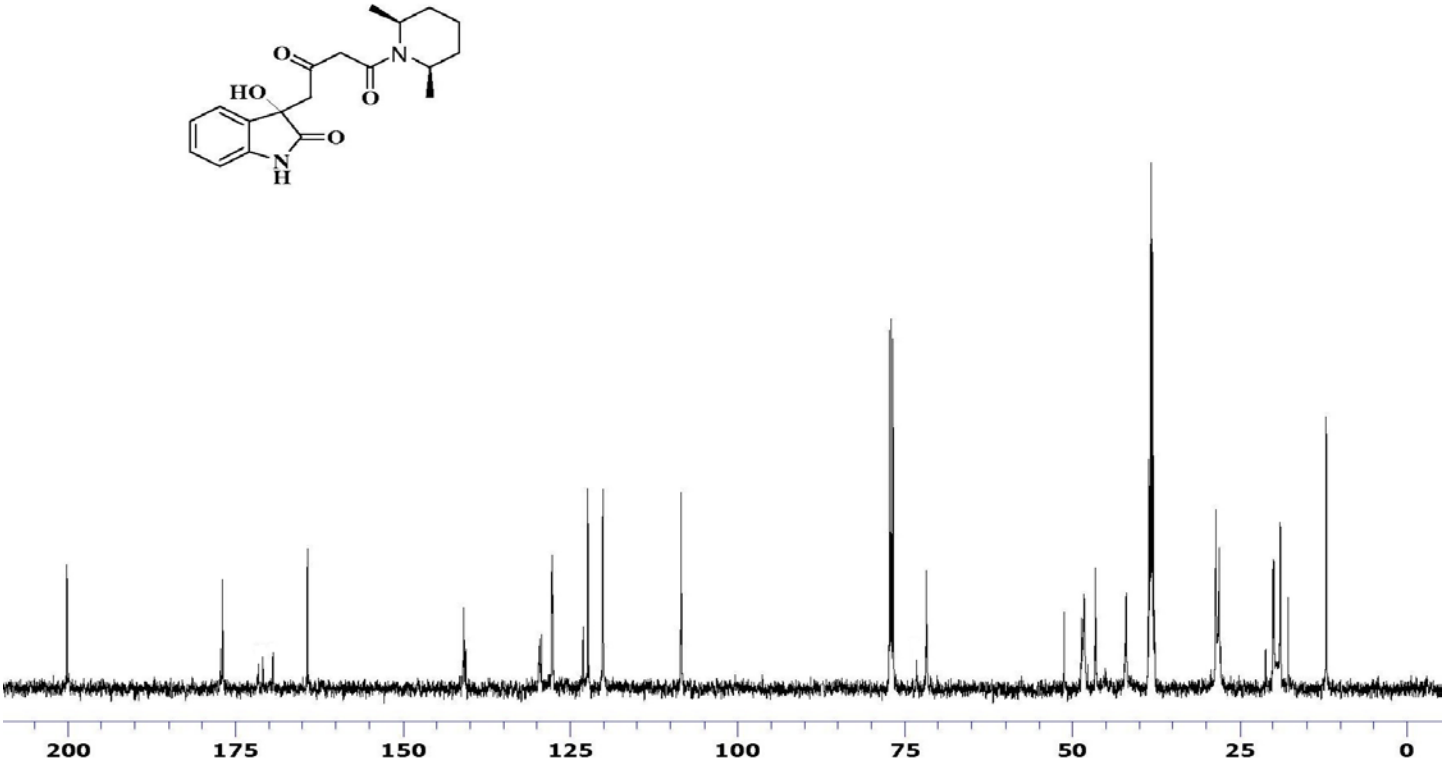

**$^{13}$C NMR, 75 MHz, $CDCl_3$+DMSO $d_6$**



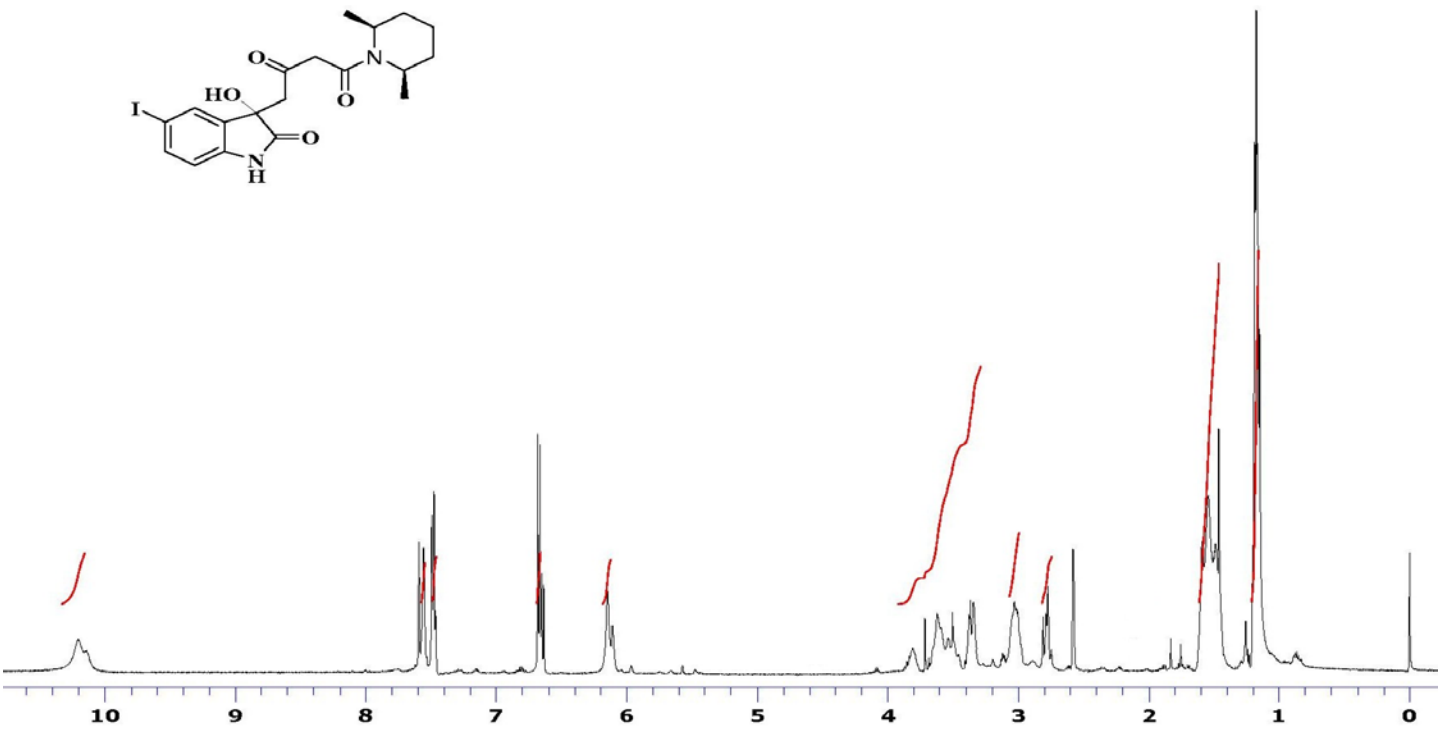
**$^{1}$H NMR, 400 MHz, $CDCl_3$+DMSO $d_6$**




**$^{13}$C NMR, 125 MHz, $CDCl_3$+DMSO $d_6$**



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




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