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RESEARCH LETTER

DMF mediated Henry reaction of isatins: an efficient synthesis of 3-hydroxy-2-oxindole

Harshadas M. Meshram*, Pramod B. Thakur, Madhu B. Bejjam and Vikas M. Bangade

Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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An efficient Henry reaction has been described for the synthesis of 3-hydroxy-3-(nitroalkyl)-2-oxindole by the reaction of isatins with nitroalkanes in N,N-dimethylformamide (DMF) under anhydrous condition. This method provides high yield of 3-hydroxy-2-oxindoles under mild reaction condition. Moreover, the procedure is environmentally benign in nature, efficient, and applicable to variety of isatins as well as nitroalkanes.

Keywords: DMF mediated reaction; Henry reaction; Isatin; Nitroalkane; 3-Hydroxy-2-oxindole

Introduction

Substituted 3-hydroxy-2-oxindoles are important structural motif (Figure 1, **A**) found in many biological active natural products (*1–4*) and pharmaceutical lead compounds (*5–12*). Particularly, chiral 3-substituted-3-hydroxyindolin-2-ones are important molecules in the field of medicinal chemistry (*13–16*) as an antibacterial, anti-inflammatory, laxative, growth hormone secretagogue agent, and new targets for cancer chemotherapy. The hydroxy indolines are also useful for the synthesis of chiral ligands which are used to obtain high enantioselectivities in numerous catalytic reactions (*17*). Additionally, 3-substituted-3-β amino-2-oxindol analogous structural motif is also found in several natural products (*18–21*) (Figure 1, **B**). These molecules not only have an interesting molecular architecture but also have a densely functionalized core and exhibit significant bioactivities (*22–28*). Because of distinct biochemical properties and important medicinal values of 3-hydroxy indolines, an efficient protocol for the synthesis of these molecules is desirable.

The Henry Reaction (*29*) is a base-catalyzed C-C bond-forming reaction between nitroalkanes and aldehydes or ketones. This reaction has been utilized (*30,31*) for the synthesis of 3-hydroxy-3-(nitroalkyl)-oxindole by the reaction of nitoalkanes with isatins in presence of diethylamine (*30*) or alkali metal halides with electrochemical setup (*31*). Recently, catalyst-free reactions have been attracting more and more attention from synthetic chemists (*32–39*). In continuation of our research work (*40–42*) on synthesis of 3-hydroxy-2-oxindoles, we envisioned that the Henry reaction between isatin and nitroalkane might be readily proceed without use of conventional base catalyst under certain appropriate reaction conditions due to the fact that the highly reactive β-carbonyl group of isatin derivatives is much susceptible to nucleophilic attack (*43,44*).

To the best of our knowledge, there is no precedent protocol of this work for the synthesis 3-hydroxy-3-(nitroalkyl)-oxindole in DMF under anhydrous condition. Herein, we wish to describe our preliminary results about DMF mediated efficient synthesis of 3-hydroxy-3 (nitroalkyl)-oxindole by the Henry reaction of isatin.

Results and discussion

Optimal reaction condition for the synthesis of 3-hydroxy-3-(nitromethyl)-2-oxindole (**3a)** was established by screening the reaction of nitromethane **2a** with free isatin **1a** (Scheme 1). As we envisioned that the reaction might proceed without use of conventional base catalyst, we began with the neat reaction of isatin with nitromethane as substrate and solvent. But the formation of desired product was not observed (Table 1, entry 1). Later, we attempted the reaction in polar aprotic solvents like dimethyl sulfoxide (DMSO) and DMF. The desired adduct **3a** was obtained in very trace amount in DMSO (Table 1, entry 2) whereas the reaction in DMF gave encouraging results (33%), (Table 1, entry 3). Next we plan to examine the reaction in detail to increase the reaction rate and yield of reaction. The drastic increase in the reaction rate and yield (92%) of **3a** was observed by adding 10 mg activated molecular sieves (*45*) (MS) 4 Å to the reaction system as an additive (Table 1, entry 4).

*Corresponding author. Email: hmmeshram@yahoo.com

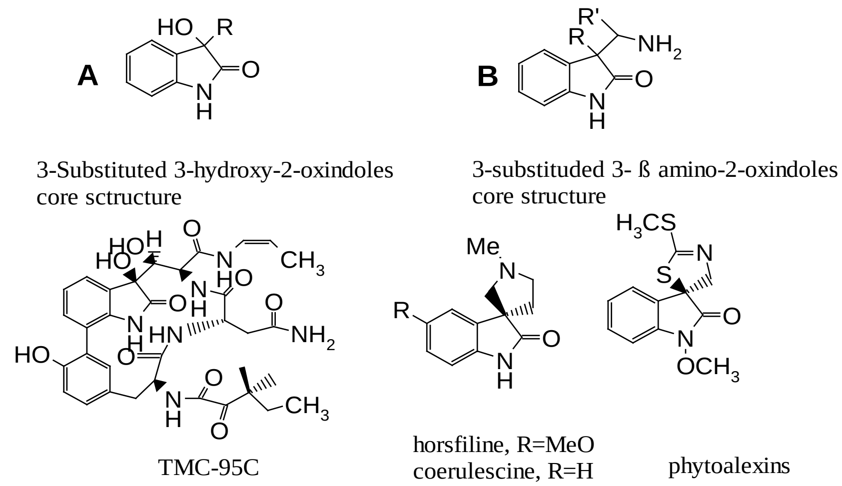
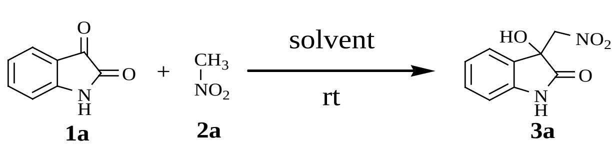


Figure 1. Representative examples of natural products containing 3-hydroxy-2-oxindoles and 3-substituted 3-β amino-2-oxindoles structural motifs.

According to the recent study (*46*), hydration reduces the nucleophilicities of aliphatic nitroalkyl anions; hence we articulate that the decrease in nucleophilicity of aliphatic nitroalkyl anion can be detained in anhydrous condition. MS may seize the decrease in nucleophilicity of anion by absorbing the small amount of moisture present in the reaction system. Hence, we observe the drastic increase in the reaction rate and yield after addition of activated molecular sieve to the reaction system. With these observations, further we planned to study the reaction in completely anhydrous condition. We have attempted the reaction of isatin **1a** with nitromethane **2a** in freshly distilled dry DMF under nitrogen atmosphere (*47*). To our surprise, reaction proceeds smoothly under anhydrous condition to give desired adduct **3a** with 95% yield in 72 min without any additional basic catalyst or additive (Table 1, entry 5).

Encouraged by these results, next we have studied the model reaction in different dry solvents under anhydrous condition. It is interesting to note that model reaction preceded very well in polar aprotic DMF solvent but worked poorly in other polar aprotic solvents like CH_3CN, tetrahydrofuran (THF), and dichloromethane (DCM) (Table 1, entry 5–9). The exact reason for this is not clear, but we assume that the DMF acts like a poor base which form and stabilize nitromethyl anions in reaction media, which might have efficiently promoted this reaction in anhydrous conditions. Similarly, unsurprising results were obtained with polar protic solvents like ethanol, n-butanol and nonpolar solvents like $CHCl_3$, toluene, dioxane, diethyl ether (Table 1, entry 10–15). This can be attributed to a less helpfulness of this solvent to form and stabilize the nitromethyl anion under catalyst-free condition. It is important to mention that the formations of any other possible by-products were not



Scheme 1. Optimization of reaction condition for the synthesis of 3 hydroxy-3-(nitroalkyl)-2-oxindole.

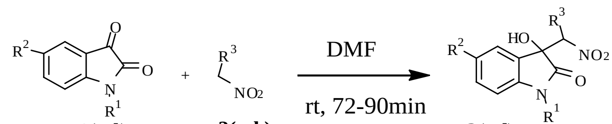
Table 1. Study towards the optimization of reaction condition for the synthesis of 3-hydroxy-3-(nitromethyl)-2-oxindole (**3a**).[a]

Entry	Solvent	Conversion[b]	Time	Yield (%)[c]
1	Neat	–	24 h	–
2	DMSO[d]	Trace	24 h	–
3	DMF[d]	33	24 h	31
4	DMF[e]	92	85 min	90
5	DMF	95	72 min	93
6	DMSO	34	24 h	32
7	CH_3CN	38	24 h	36
8	THF	35	24 h	33
9	DCM	29	24 h	27
10	Ethanol	27	24 h	25
11	*n*-Butanol	22	24 h	20
12	$CHCl_3$	24	24 h	21
13	Toluene	19	24 h	17
14	Dioxane	23	24 h	21
15	Diethyl ether	24	24 h	21

[a]Reactions condition: All reactions were performed using isatin 1a (1.0 mmol) and nitromethane 2a (2.0 mmol) in 3 ml freshly distilled dry solvent at room temperature.
[b]Conversion of isatin to 3-hydroxy oxindole was evaluated by ^{1}H NMR of crude reaction mixture.
[c]Isolated yields of purified products.
[d]Reagent grade.
[e]With 10 mg activated 4 Å moleculra sieve.

observed in present reaction condition. Accordingly, we have chosen the reaction of isatin **1a** with nitromethane **2a** in freshly distilled dry DMF under nitrogen atmosphere as an optimized condition for the synthesis of **3a,** without any additional basic catalyst at room temperature.

With a set of optimized reaction conditions in our hand, we examined the scope of the reaction with respect to the different isatin electrophiles (Scheme 2, Table 2). A wide range of free isatin derivatives bearing halogen atom (**1b, c**) underwent smooth reaction with nitromethane (**2a**) and resulted into corresponding products (**3b, c**) in very good yields (91%, 90%, respectively) within 75–90 min (Table 2, entry 2, 3). Encouraged by the aforementioned results we next studied the reactions of N-1 protected isatins (**1d, e**) with nitromethane **2a**. It was found that in all cases the



R^1 = -H, $-CH_3$, -Ph, -Bn, $-CH_2OH$; R^2 = -H, -F, -Br, -I; R^3 = -H, $-CH_3$

Scheme 2. Synthesis of 3-hydroxy-3-(nitroalkyl)-oxindole by DMF mediated Henry reaction of Isatin with nitoalkanes.

Table 2. Synthesis of 3-hydroxy-3-(nitroalkyl)-oxindole derivative by DMF mediated Henry reaction of isatins and nitroalkanes.[a]

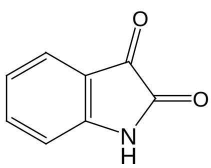
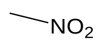
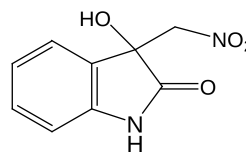
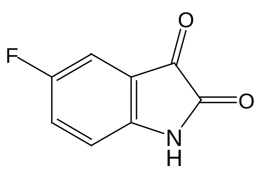
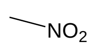
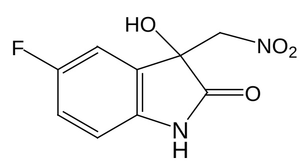
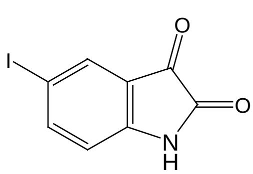
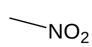
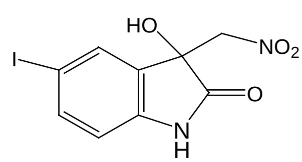
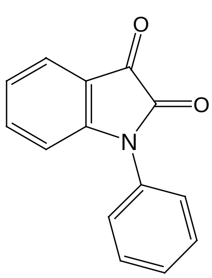
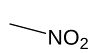
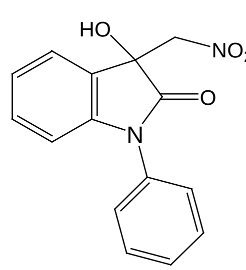
Entry	Isatin **(1a–i)**	Nitroalkane **(2a,b)**	Product	Time (min)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	72	93
2	 **1b**	 **2a**	 **3b**	75	91
3	 **1c**	 **2a**	 **3c**	90	90
4	 **1d**	 **2a**	 **3d**	85	91

Table 2 (*Continued*)

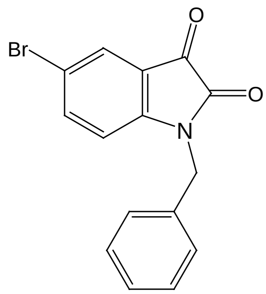
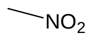
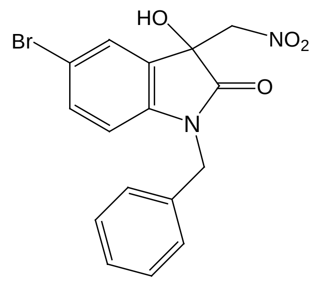
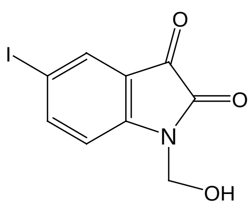
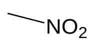
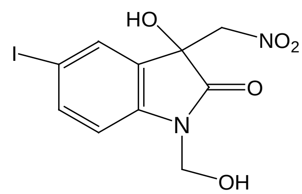
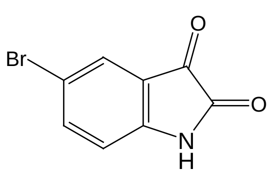
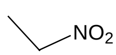
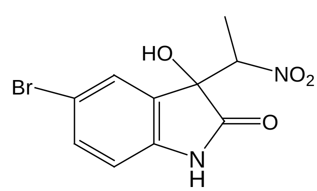
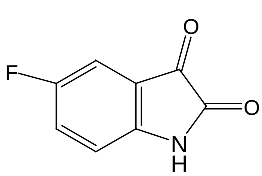
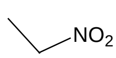
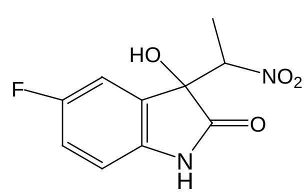
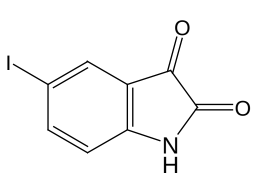
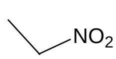
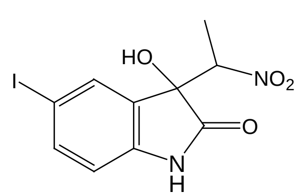
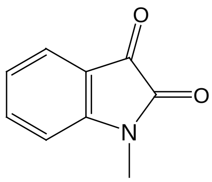
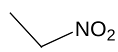
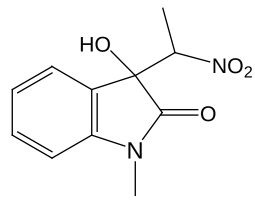
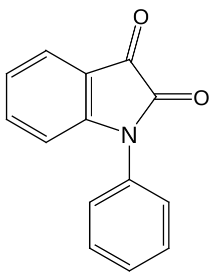
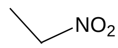
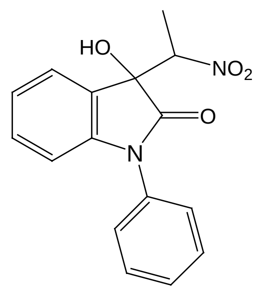
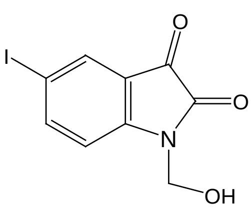
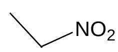
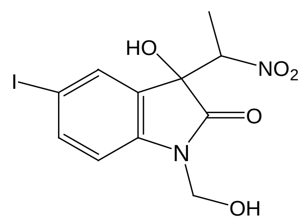
Entry	Isatin **(1a–i)**	Nitroalkane **(2a,b)**	Product	Time (min)	Yield[b] (%)
5	 **1e**	 **2a**	 **3e**	72	93
6	 1f **1f**	 **2a**	 **3f**	90	89
7	 1g **1g**	 **2b**	 **3g**	86	94 (77:29)*
8	 **1h**	 **2b**	 **3h**	90	89 (67:33)*
9	 **1i**	 **2b**	 **3i**	86	90 (91:09)*

Table 2 (*Continued*)

Entry	Isatin **(1a–i)**	Nitroalkane **(2a,b)**	Product	Time (min)	Yield[b] (%)
10	 **1j**	 **2b**	 **3j**	72	92 (67:37)*
11	 **1k**	 **2b**	 **3k**	90	89 (72:28)*
12	 **1l**	 **2b**	 **3l**	90	88 (88:12)*

[a]Reactions condition: All reactions were performed with isatins **(1a–l)** (1 mmol), nitroalkane **(2a,b)** (2 mmol) in 3 ml freshly distilled dry DMF at room temperature.
[b]Isolated yields of purified products.
*Inseparable mixture of diasteromers, threo:erythro ratio written in parentheses.

reactions preceded smoothly and provided their corresponding products in good yields (Table 2, entry 4, 5). It is worthy to mention that the *N*-hydroxymethylated adduct (**3f**) was also obtained in high yield (89%) in 90 min at room temperature with our optimized reaction condition (Table 2, entry 6).

Further as a logical extension, we explored a series of isatin derivatives with nitroethane under the optimized reaction conditions (Table 2, entries 7–12). All isatin electophiles (**1g–l**) reacted well with nitroethane (**2b**) to give the respective adduct in very high yield (88–94%) and with moderate to high diasteroselectivity (63–91%, *threo:erythro* ratio, Table 2, entries 7–12). 5-Iodo isatin (**1i**) shown highest diasteroselectivity (*threo:erythro* ratio, 91:9; Table 2, entry 9). It is noteworthy that, such high diastereoselectivity was obtained with our optimized reaction condition without using any additional base catalyst or chiral mediator. The diasteromeric ratios of products were determined by ^{1}H NMR analysis of crude product. As the reaction was performed without any chiral mediator, we proposed the thermodynamically more stable *threo* configuration for major isomer due to the possibility of formation of six member chair conformation by hydrogen bonding (Figure 2)

The tentative mechanistic pathway proposed for the DMF mediated Henry reaction of isatins is shown in Scheme 3. We reasoned that, DMF work as a solvent as well as a mild base which abstract acidic α-hydrogen of nitroalkane and efficiently form nitroalkyl anion [**A**][48]. This nitroalkyl anion (azinate) attacks on highly reactive β-carbonyl group of isatin

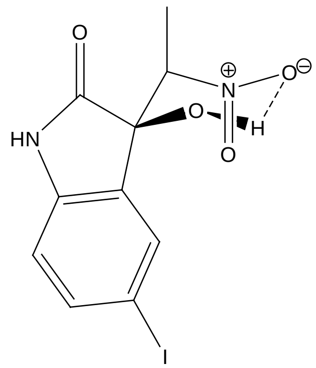
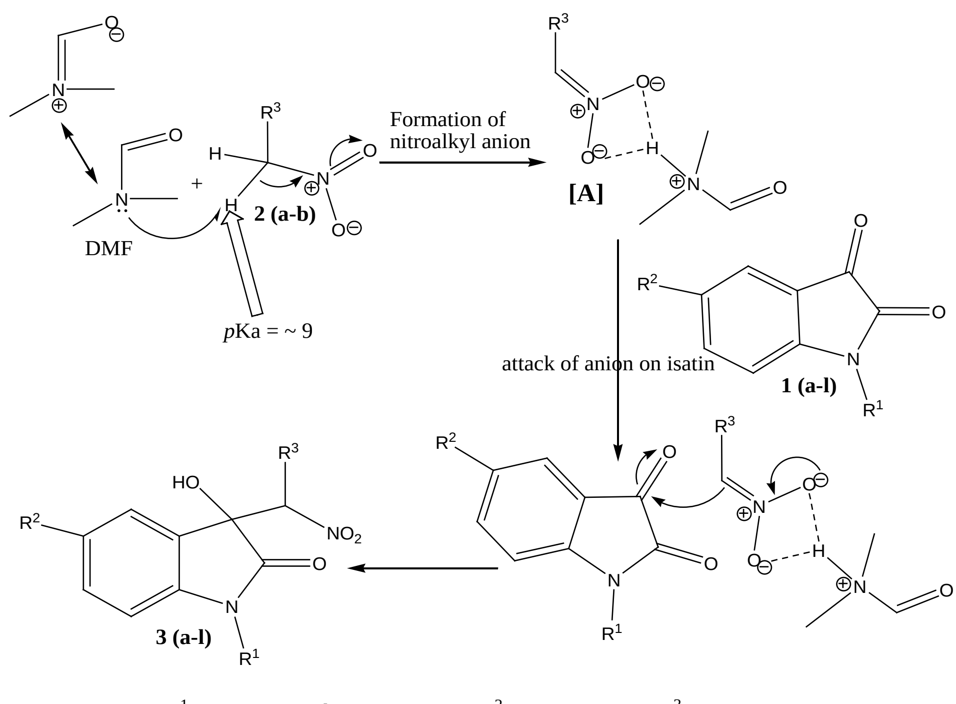


Figure 2. Illustration for the possibility of formation of six member chair conformation by hydrogen bonding in *threo* configuration.

and form desired 3-hydroxy-3-(nitroalkyl)-2-oxindole product in high yield. We found that the reaction worked very well in DMF and gave very high yields of product within shorter reaction time as compared to the other solvents. The exact reason for this is not well understood, but we assume that, due to the distinctive basicity and polarity associated with DMF, it efficiently forms and stabilize nitroalkyl anion and hence resulted in to the high yields of products. However, may be due to the very less efficiency of other solvents to form and stabilize the nitromethyl anion is resulted in to the poor yields of product even after longer reaction time.

Experimental section

All reactions were conducted under an atmosphere of nitrogen (IOLAR Grade I). DMF was dried and freshly distilled over calcium hydride before use. Progress of the reactions was monitored by TLC on Merck Silica Gel 60 F-254 pre-coated. Evaporation of solvents was performed at reduced pressure on a BUCHI rotary evaporator. Column chromatography was carried out with silica gel grade 60–120 and 100–200 mesh. Melting points were measured on a BUCHI Melting Point machine. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz in $(CD_3)_2SO$. *J* values were recorded in hertz and abbreviations used were: s, singlet; d, doublet; m, multiplet; dd, doublet of doublet; dt, doublet of triplet; and br, broad. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard in ppm. IR spectra were recorded on Thermo Nicolet FT/IR-5700. Mass spectral data were obtained using MS (ESI), One or more of the following methods were used for visualization: UV absorption by fluorescence quenching; iodine staining; anisaldehyde stain (ethanol (135 mL)/H_2SO_4 (5 mL)/AcOH



Scheme 3. Proposed mechanistic pathway for the DMF mediated Henry reaction of isatins.

(1.5 mL)/p-anisaldehyde 3.7 mL). Ethyl acetate and hexane were the common eluents used.

Typical procedure

To a solution of isatins (**1a–l;** 1.0 mmol) in freshly distilled DMF (3 mL) was added nitroalkane (**2a,b;** 2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for stipulated time (Table 2). After the complete consumption of isatins as indicated by TLC, the reaction mixture was poured on 10 ml ice cold water to obtain the crude solid products. When reaction mixture does not give solid compound after pouring on ice cold water (in case of **3d, e, j, k**), that time reaction mixture was extracted with ethyl acetate and crude products were obtained as yellow viscous liquid by evaporation of ethyl acetate under reduced pressure. The Crude products were sufficiently pure for spectroscopic analysis. However, crude products were further purified by silica gel column chromatography using ethyl acetate:hexane (1:3–1:1) as eluent to give the corresponding pure products.

All the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C NMR, IR and Mass spectroscopic techniques and spectral data are given as following:

(1) **3-hydroxy-3-(nitromethyl)indolin-2-one** (**3a**, Table 2, entry 1): Yield: 93%. *Rf*(50% EtOAc/hexanes) 0.48; white solid. M.p. 139 141°C[30, 31]; **IR (KBR, cm^{-1})**: 3264, 3157, 2922, 1726, 1734, 1621, 1550, 1468, 1377, 1186, 755. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**[31]: δ 10.36(br s, 1H), 7.34(d, 1H, $J = 7.36$ Hz), 7.22(t, 1H, $J = 7.74$, Hz), 6.96 (t, 1H $J = 7.36$ Hz), 6.87 (d, 1H, $J = 7.74$ Hz) 6.58 (br s, 1H), 4.89 (d, 1H, $J = 12.46$ Hz), 4.82 (d, 1H, $J = 12.46$ Hz) ppm.**^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 176.5, 142.7, 130.6, 127.7, 124.7, 122.4, 110.8, 78.7, 73.4 ppm. **MS(ESI)**: $m/z = 231$ $[M+Na]^+$.

(2) **5-Fluoro-3-hydroxy-3-(nitromethyl)indolin-2-one**[42] (**3b**, Table 2, entry 2): Yield: 91%. *Rf*(50% EtOAc/hexanes) 0.40; Yellow solid. M.p. 161 163°C; **IR (KBR, cm^{-1})**: 3358, 3271, 2924, 1726, 1612, 1555, 1470, 1374, 1182, 744. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 10.39(br s, 1H), 7.14(d, 1H, $J = 7.74$ Hz), 6.94(dt, 1H, $J = 9.06$, 2.26 Hz), 6.84-6.80(m, 1H), 6.69(br s, 1H), 4.90-4.82(m, 2H) ppm.**^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 179.9, 160.6, 157.4, 138.9, 129.6, 129.5, 117.5, 117.2, 113.2, 112.9, 112.1, 112.0, 78.8, 74.1 ppm. **MS(ESI)**: $m/z = 249$ $[M+Na]^+$.

(3) **3-hydroxy-5-Iodo-3-(nitromethyl)indolin-2-one**[42] (**3c**, Table 2, entry 3): Yield: 90%. *Rf*(50% EtOAc/hexanes) 0.39; White solid. M.p. 273 275°C; **IR (KBR, cm^{-1})**: 3388, 3271, 2924, 1726, 1612, 1555, 1471, 1374, 1182, 822. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 10.46(br s, 1H), 7.64(d, 1H, $J = 1.51$ Hz), 7.53(dd, 1H, $J = 8.30$, 1.70 Hz), 6.70(d, 1H, $J = 8.30$ Hz), 6.66(br s, 1H), 4.91-4.81 (m, 2H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 175.2, 142.4, 138.6, 133.1, 130.5, 112.6, 84.2, 78.1, 72.6 ppm. **MS(ESI)**: $m/z = 357$ $[M+Na]^+$.

(4) **3-Hydroxy-3-(nitromethyl)-1-phenylindolin-2-one**[42] (**3d**, Table 2, entry 4): Yield: 91%. *Rf*(50% EtOAc/hexanes) 0.65; White solid. M.p. 99 101°C; **IR (KBR, cm^{-1})**: 3328, 2933, 1709, 1617, 1559, 1467, 1389, 1090, 761. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 7.55-7.40(m, 6H), 7.29(t, 1H, $J = 7.5$ Hz), 7.08(t, 1H, $J = 7.4$ Hz), 6.91(br s, 1H), 6.75(d, 1H, $J = 7.7$ Hz), 5.11-4.92(m, 2H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 174.1, 143.7, 133.8, 129.7, 128.4, 128.1, 126.4, 125.4, 122.3, 109.1, 78.4, 72.7 ppm. **MS(ESI)**: $m/z = 307$ $[M+Na]^+$.

(5) **1-Benzyl-5-bromo-3-hydroxy-3-(nitromethyl)indolin-2-one**[42] (**3e**, Table 2, entry 5):Yield: 93%. *Rf*(50% EtOAc/hexanes) 0.43; Pale yellow solid. M.p. 121 123°C; **IR (KBR, cm^{-1})**: 3334, 2921, 1711, 1621, 1561, 1457, 1391, 1097, 757. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 7.62(s, 1H), 7.41-7.19(m, 6H), 6.95(br s, 1H), 6.66(d, 1H, $J = 8.3$ Hz), 5.05(s, 2H), 4.95(d, 1H, $J = 15.8$ Hz), 4.85(d, 1H, $J = 15.8$ Hz) ppm.**^{13}C NMR (50 MHz, $(CD_3)_2SO$)**: δ 179.2, 147.6, 140.4, 138.1, 135, 134.7, 132.7, 132.4, 120, 116.6, 101.0, 83.0, 77.7, 48.7 ppm. **MS(ESI)**: $m/z = 399$ $[M+Na]^+$.

(6) **3-Hydroxy-1-(hydroxymethyl)-5-iodo-3-(nitromethyl) indolin-2-one** (**3f**, Table 2, entry 6): Yield: 89%. *Rf*(50% EtOAc/hexanes) 0.33; White solid. M.p. 267 269°C; **IR (KBR, cm^{-1})**: 3249, 2945, 1711, 1608, 1549, 1476, 1370, 1033, 820. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 7.72(s, 1H), 7.65 (d, 1H, $J = 8.3$ Hz), 6.97(d, 1H, $J = 8.3$ Hz), 6.81(br s, 1H), 6.20(br s, 1H), 5.19-5.02(m, 2H), 4.91(s, 2H) ppm. **^{13}C NMR (75 MHz, $CD_3)_2SO$)**: δ 173.1, 142.3, 138.4, 132.8, 129.5, 112.3, 82.1, 77.9, 72.2, 62.8 ppm. **MS(ESI)**: $m/z = 387$ $[M+Na]^+$.

(7) **5-Bromo-3-hydroxy-3-(1-nitroethyl)indolin-2-one**[42] (**3g**, Table 2, entry 7): Yield: 94%. *Rf*(50% EtOAc/hexanes) 0.40; Pale yellow solid. M.p. 167 169°C; **IR (KBR, cm^{-1})**: 3356, 1729, 1628, 1572, 1558, 1487, 1371, 1161, 1091, 847. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro*, 77:29* denotes minor diastereomer peaks): δ 10.54(br s, 1H), 10.48*(br s, 1H), 7.51(d, 1H, $J = 1.7$ Hz), 7.37(d, 1H, $J = 8.1$Hz), 6.8-6.7(m, 1H), 6.74(br s, 1H), 6.72*(br s, 1H), 6.7-6.6*(m, 1H), 5.01-4.59(m, 1H), 1.76*(d, 3H, $J = 7.0$ Hz), 1.38(d, 1H, $J = 7.0$ Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 176.1, 175.8*, 142.1, 141.8*, 133.3, 132.7*, 130.7, 130.4*, 127.7, 127.2, 113.9, 113.4*, 112.4*, 112.1*, 86.2, 85.4*, 75.8, 75.9*, 13.7, 12.5* ppm. **MS(ESI)**: $m/z = 323$ $[M+Na]^+$.

(8) **5-Fluoro-3-hydroxy-3-(1-nitroethyl)indolin-2-one**[42] (**3h**, Table 2, entry 8): Yield: 89%. *Rf*(50% EtOAc/hexanes) 0.38; Pale yellow solid. M.p. 128 130°C; **IR (KBR, cm^{-1})**: 3361, 3277, 2927, 1731, 1617, 1558, 1480, 1377, 1192, 749. **^{1}H NMR (300 MHz,**

$(CD_3)_2SO$) (diastereomeric ratio, *threo:erythro*, 67:33* denotes minor diastereomer peaks): δ 10.47(br s, 1H), 10.39*(br s 1H), 7.17(d, 1H, $J=7.0$ Hz), 7.07*(d, 1H, $J=6.2$ Hz), 7.01-6.96(m 1H), 6.84-6.81(m 1H), 6.78(br s, 1H), 6.78*(br s, 1H), 5.01-4.95(m, 1H), 1.72*(d, 3H, $J=6.2$ Hz), 1.35(d, 3H, $J=6.2$ Hz) ppm. **^{13}C NMR (75 MHz, $CD_3)_2SO$)**: δ 176.28*, 175.61, 159.60, 159.51*, 156.42, 156.34*, 138.67*, 138.51, 128.81*, 128.77*, 128.41, 128.31, 116.54, 116.33*, 116.14, 116.01*, 113.71, 113.33, 112.74*, 112.41*, 111.01*, 110.91*, 110.85, 110.84, 86.38, 85.41*, 76.01, 75.21*, 13.64, 12.44 ppm. **MS(ESI)**: $m/z=263$ $[M+Na]^+$.

(9) **3-Hydroxy-5-iodo-3-(1-nitroethyl)indolin-2-one**[42] (**3i**, Table 2, entry 9): Yield: 90%. *Rf*(50% EtOAc/hexanes) 0.37; White solid. M.p. 278 280°C; **IR (KBR, cm^{-1})**: 3381, 3248, 2934, 1733, 1614, 1552, 1472, 1357, 1188, 816. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 91:9, * denotes minor diastereomer peaks): δ 10.55(br s, 1H), 10.49*(br s, 1H), 7.67(d, 1H, $J=1.5$ Hz), 7.55(dd, 1H, $J=8.1$, 1.5, Hz), 6.7(br s, 1H), 6.68(d, 1H, $J=8.1$ Hz), 4.99-4.92(m, 1H), 1.75*(d, 3H, $J=7.0$ Hz), 1.38(d, 3H, $J=7.0$ Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 175.51*, 174.83, 142.32*, 142.27, 138.38, 133.15, 132.56*, 129.80*, 129.45, 112.36*, 112.30, 86.19, 85.18*, 84, 83.6*, 75.34, 74.64*, 13.5, 12.3* ppm. **MS(ESI)**: $m/z=371$ $[M+Na]^+$.

(10) **3-Hydroxy-1-methyl-3-(1-nitroethyl)indolin-2-one** (**3j**, Table 2, entry 10): Yield: 92%. *Rf*(50% EtOAc/hexanes) 0.44; White solid. M.p. 140 142°C; **IR (KBR, cm^{-1})**: 3316, 2939, 1703, 1616, 1551, 1468, 1385, 1355, 1113, 1061, 759. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 63:37, * denotes minor diastereomer peaks): δ 7.44*(s, 1H), 7.42*(s, 1H), 7.35(s, 1H), 7.33(s, 1H), 7.12-7.0(m, 1H), 6.88(d, 1H, $J=3.5$ Hz), 6.85*(d, 1H, $J=3.2$ Hz), 6.68*(br s, 1H), 6.63(br s, 1H), 5.05-4.98(m, 1H), 3.18*(s, 3H), 3.17(s, 3H), 1.76*(d, 3H, $J=6.8$ Hz), 1.37(d, 3H, $J=6.8$ Hz) ppm. **^{13}C NMR (75 MHz, $CD_3)_2SO$)**: δ 174.83*, 174.4, 144.3*, 144.09, 130.43, 130.13*, 127.4*, 126.9, 124.24, 123.8*, 122.7, 122.3*, 108.9*, 108.57, 78.4, 77.8*, 72.75, 71.6*, 26.17, 25.3*, 13.9, 12.8* ppm. **MS(ESI)**: $m/z=259$ $[M+Na]^+$.

(11) **3-Hydroxy-3-(1-nitroethyl)-1-phenylindolin-2-one** (**3k**, Table 2, entry 11): Yield: 89%. *Rf*(50% EtOAc/hexanes) 0.43; White solid. M.p 102 105°C. **IR (KBR, cm^{-1})**: 3331, 2923, 1711, 1619, 1569, 1471, 1374, 1087, 769. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 72:28, * denotes minor diastereomer peaks): δ 7.56-7.37(m, 6H), 7.26(t, 1H, $J=7.4$ Hz), 7.19-7.15*(m, 1H), 7.10(t, 1H, $J=7.5$ Hz), 7.06-7.01*(m, 1H), 6.91(br s, 1H), 6.89*(br s, 1H), 6.74(d, 1H, $J=7.4$ Hz), 5.19-5.09 (m, 1H), 1.84*(d, 3H, $J=6.9$ Hz), 1.57(d, 3H, $J=6.9$ Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 174.4*, 173.3, 143.9*, 143.6, 133.8*, 133.7, 130.0*, 129.4, 128.2*, 128.1, 128.03, 127.9*, 126.5*, 126.3, 125.2, 124.9*, 122.92, 122.79*, 109.18*, 109.05, 86.93, 85.7*, 74.7*, 74.6, 13.58, 12.2* ppm. **MS(ESI)**: $m/z=321$ $[M+Na]^+$.

(12) **3-Hydroxy-1-(hydroxymethyl)-5-iodo-3-(1-nitroethyl)indolin-2-one** (**3l**, Table 2, entry 12): Yield: 88%. *Rf*(50% EtOAc/hexanes) 0.35; White solid. M.p. 151 153°C; **IR (KBR, cm^{-1})**: 3341, 2982, 1731, 1604, 1537, 1480, 1333, 1194, 1029, 965, 810. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 88:12, * denotes minor diastereomer peaks) δ 7.75(d, 1H, $J=7.5$ Hz), 7.66(dd, 1H, $J=8.3$, 1.7 Hz), 7.61*(dd, 1H, $J=8.3$, 1.7 Hz), 6.95(d, 1H, $J=8.1$ Hz), 6.9(br s, 1H), 6.8*(br s, 1H), 6.2(br s, 1H), 5.1(s, 2H), 5.04-4.9(m, 1H), 1.76*(d, 1H, $J=7.0$ Hz), 1.37(d, 1H, $J=7.0$ Hz). **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 173.5*, 172.9, 142.3, 138.6, 133.6, 132.7*, 129.0*, 128.6, 112.4, 86.35, 85.6, 85.4, 85.3*, 75.1, 74.6*, 62.8, 13.52, 12.4*. **MS(ESI)**: $m/z=379$ $[M+1]^+$.

Conclusions

In summary, we have developed an efficient Henry reaction of variety of isatins with nitroalkanes in DMF at room temperature. Desired products, 3-hydroxy-3-(nitroalkyl)-oxindoles, were obtained in very good to excellent yields. Mild reaction condition, high yields and wide scope of substrates are the distinct features of our protocol. This protocol may find utility in the synthesis of biologically active oxindole analogous compounds. Further investigation to develop more efficient and convenient reaction condition from a green chemistry viewpoint is under way in our laboratory.

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Supplementary information file

INDEX

EXPERIMENTAL SECTION

General remarks:

All reactions were conducted under an atmosphere of nitrogen (IOLAR Grade I). DMF was dried and freshly distilled from calcium hydride before use. Progress of the reactions was monitored by TLC on Merck Silica Gel 60 F-254 pre-coated. Evaporation of solvents was performed at reduced pressure on a BUCHI rotary evaporator. Column chromatography was carried out with silica gel grade 60–120 and 100–200 mesh. Melting points were measured on a BUCHI Melting Point machine. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz in $(CD_3)_2SO$. *J* values were recorded in hertz and abbreviations used were s—singlet, d—doublet, m—multiplet, dd—doublet of doublet, dt—doublet of triplet and br—broad. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard in ppm. IR spectra were recorded on Thermo Nicolet FT/IR-5700. Mass spectral data were obtained using MS (ESI), One or more of the following methods were used for visualization: UV absorption by fluorescence quenching; iodine staining; anisaldehyde stain (ethanol (135 mL)/H_2SO_4 (5 mL)/AcOH (1.5 mL)/p-anisaldehyde 3.7 mL). Ethyl acetate and hexane were the common eluents used.

Typical procedure for DMF mediated Henry reaction of Isatins (Table 2): To a solution of isatins (**1a-l**) (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroalkane (**2a-b**) (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for stipulated time (Table 2). After the complete consumption of isatins as indicated by TLC, the reaction mixture was poured on 10 ml ice cold water to obtain the crude products. (When reaction mixture does not give solid compound after pouring on ice cold water ((in case of **3d, 3e, 3j, 3k**), that time reaction mixture was extracted with ethyl acetate and crude products were obtained as yellow viscous liquid by evaporation of ethyl acetate under reduced pressure). Crude products were sufficiently pure for spectroscopic analysis. However, crude products were further purified by silica gel column chromatography using ethyl acetate:hexane (1:3 to 1:1) as eluent to give the corresponding pure products. The inseparable diastereomers *threo:erythro* ratio of the product was determined by ^{1}H NMR analysis of the crude reaction mixture. In ^{1}H NMR spectrum, few peaks of minor isomer were well separated from the peaks of major isomer and few peaks were merged in major isomer peaks. ^{1}H NMR peaks for minor isomer which were well separated from the peaks of major isomer are marked with asterisk (*) and written along with the peaks of major isomer in spectral data.

Detail experimental procedure and Spectraldata for compounds 3a-3l:

3-hydroxy-3-(nitromethyl)indolin-2-one (**3a**, Table 2, Entry 1): To a solution of isatin **1a** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitromethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 72 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3a** as pale yellow solid. The Crude solid of **3a** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3a**. Yield: 93%. *Rf*(50% EtOAc/hexanes) 0.48; white solid. M.p. 139 141°C [30, 31]; **IR (KBR, cm^{-1})**: 3264, 3157, 2922, 1726, 1734, 1621, 1550, 1468, 1377, 1186, 755. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**[31]: δ 10.36(br s, 1H), 7.34(d, 1H, *J* = 7.36 Hz), 7.22(t, 1H, *J* = 7.74, Hz), 6.96 (t, 1H *J* = 7.36 Hz), 6.87 (d, 1H, *J* = 7.74 Hz) 6.58 (br s, 1H), 4.89 (d, 1H, *J* = 12.46 Hz), 4.82 (d, 1H, *J* = 12.46 Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 176.5, 142.7, 130.6, 127.7, 124.7, 122.4, 110.8, 78.7, 73.4 ppm. **MS(ESI):** $m/z = 231$ $[M + Na]^+$.

5-Fluoro-3-hydroxy-3-(nitromethyl)indolin-2-one[42] (**3b**, Table 2, Entry 2): To a solution of isatin **1b** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitromethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 75 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3b** as pale yellow solid. The Crude solid of **3b** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3b**. Yield: 91%. *Rf*(50% EtOAc/hexanes) 0.40; Yellow solid. M.p. 161 163°C; **IR (KBR, cm^{-1})**: 3358, 3271, 2924, 1726, 1612, 1555, 1470, 1374, 1182, 744. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 10.39(br s, 1H), 7.14(d, 1H, *J* = 7.74 Hz), 6.94(dt, 1H, *J* = 9.06, 2.26 Hz), 6.84-6.80(m, 1H), 6.69(br s, 1H), 4.90-4.82(m, 2H) ppm.**^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 179.9, 160.6, 157.4, 138.9, 129.6, 129.5, 117.5, 117.2, 113.2, 112.9, 112.1, 112.0, 78.8, 74.1 ppm. **MS(ESI)**: $m/z = 249$ $[M + Na]^+$.

3-hydroxy-5-Iodo-3-(nitromethyl)indolin-2-one[42] (**3c**, Table 2, Entry 3): To a solution of isatin **1c** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitromethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 90 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3c** as off white solid. The Crude solid of **3c** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3c.** Yield: 90%. *Rf*(50% EtOAc/hexanes) 0.39; White solid. M.p. 273 275°C; **IR (KBR, cm^{-1})**: 3388, 3271, 2924, 1726, 1612, 1555, 1471, 1374, 1182, 822. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 10.46(br s, 1H), 7.64(d, 1H, *J* = 1.51 Hz), 7.53(dd, 1H, *J* = 8.30, 1.70 Hz), 6.70(d, 1H, *J* = 8.30 Hz), 6.66(br s, 1H), 4.91-4.81 (m, 2H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 175.2, 142.4, 138.6, 133.1, 130.5, 112.6, 84.2, 78.1, 72.6 ppm. **MS(ESI)**: $m/z = 357$ $[M + Na]^+$.

3-Hydroxy-3-(nitromethyl)-1-phenylindolin-2-one[42] (**3d**, Table 2, Entry 4): To a solution of isatin **1d** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitromethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 85 min. After then, the reaction mixture was poured on 10 ml ice cold water and extracted with ethyl acetate (10x3). The Combine organic extract was dried on Na_2SO_4 and concentrate in *Vacuo* to provide crude **3d** as pale yellow viscous liquid. The Crude **3d** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3d.** Yield: 91%. *Rf*(50% EtOAc/hexanes) 0.65; White solid. M.p. 99 101°C; **IR (KBR, cm^{-1})**: 3328, 2933, 1709, 1617, 1559, 1467, 1389, 1090, 761. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 7.55-7.40(m, 6H), 7.29(t, 1H, *J* = 7.5 Hz), 7.08(t, 1H, $J = 7.4$ Hz), 6.91(br s, 1H), 6.75(d, 1H, $J = 7.7$ Hz), 5.11-4.92(m, 2H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 174.1, 143.7, 133.8, 129.7, 128.4, 128.1, 126.4, 125.4, 122.3, 109.1, 78.4, 72.7 ppm. **MS(ESI)**: $m/z = 307$ $[M+Na]^+$.

1-Benzyl-5-bromo-3-hydroxy-3-(nitromethyl)indolin-2-one[42] (**3e**, Table 2, Entry 5):
To a solution of isatin **1e** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitromethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 72 min. After then, the reaction mixture was poured on 10 ml ice cold water and extracted with ethyl acetate (10x3). The Combine organic extract was dried on Na_2SO_4 and concentrate in *Vacuo* to provide crude **3e** as pale yellow viscous liquid. The Crude **3e** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3e**. Yield: 93%. *Rf*(50% EtOAc/hexanes) 0.43; Pale yellow solid. M.p. 121 123°C; **IR (KBR, cm^{-1})**: 3334, 2921, 1711, 1621, 1561, 1457, 1391, 1097, 757. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 7.62(s, 1H), 7.41-7.19(m, 6H), 6.95(br s, 1H), 6.66(d, 1H, $J = 8.3$ Hz), 5.05(s, 2H), 4.95(d, 1H, $J = 15.8$ Hz), 4.85(d, 1H, $J = 15.8$ Hz) ppm.**^{13}C NMR (50 MHz, $(CD_3)_2SO$)**: δ 179.2, 147.6, 140.4, 138.1, 135, 134.7, 132.7, 132.4, 120, 116.6, 101.0, 83.0, 77.7, 48.7 ppm. **MS(ESI)**: $m/z = 399$ $[M+Na]^+$.

3-Hydroxy-1-(hydroxymethyl)-5-iodo-3-(nitromethyl)indolin-2-one (**3f**, Table 2, Entry 6): To a solution of isatin **1f** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitromethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 90 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3f** as off white solid. The Crude solid of **3f** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:1) as eluent to give the pure title compound **3c**. Yield: 89%. *Rf*(50% EtOAc/hexanes) 0.33; White solid. M.p. 267 269°C; **IR (KBR, cm^{-1})**: 3249, 2945, 1711, 1608, 1549, 1476, 1370, 1033, 820. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)**: δ 7.72(s, 1H), 7.65 (d, 1H, $J = 8.3$ Hz), 6.97(d, 1H, $J = 8.3$ Hz), 6.81(br s, 1H), 6.20(br s, 1H), 5.19-5.02(m, 2H), 4.91(s, 2H) ppm. **^{13}C NMR (75 MHz, $CD_3)_2SO$)**: δ 173.1, 142.3, 138.4, 132.8, 129.5, 112.3, 82.1, 77.9, 72.2, 62.8 ppm. **MS(ESI):** $m/z = 387$ $[M+Na]^+$.

5-Bromo-3-hydroxy-3-(1-nitroethyl)indolin-2-one[42] (**3g**, Table 2, Entry 7): To a solution of isatin **1g** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 86 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3g** as yellow solid. The Crude solid of **3g** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3g.** Yield: 94%. *Rf*(50% EtOAc/hexanes) 0.40; Pale yellow solid. M.p. 167 169°C; **IR (KBR, cm^{-1})**: 3356, 1729, 1628, 1572, 1558, 1487, 1371, 1161, 1091, 847. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro,* 77:29* denotes minor diastereomer peaks): δ 10.54(br s, 1H), 10.48*(br s, 1H), 7.51(d, 1H, $J = 1.7$ Hz), 7.37(d, 1H, $J = 8.1$Hz), 6.8-6.7(m, 1H), 6.74(br s, 1H), 6.72*(br s, 1H), 6.7-6.6*(m, 1H), 5.01-4.59(m, 1H), 1.76*(d, 3H, $J = 7.0$ Hz), 1.38(d, 1H, $J = 7.0$ Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 176.1, 175.8*, 142.1, 141.8*, 133.3, 132.7*, 130.7, 130.4*, 127.7, 127.2, 113.9, 113.4*, 112.4*, 112.1*, 86.2, 85.4*, 75.8, 75.9*, 13.7, 12.5* ppm. **MS(ESI)**: $m/z = 323$ $[M+Na]^+$.

5-Fluoro-3-hydroxy-3-(1-nitroethyl)indolin-2-one[42] (**3h**, Table 2, Entry 8): To a solution of isatin **1h** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 90 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3h** as pale yellow solid. The Crude solid of **3h** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:2) as eluent to give the pure title compound **3h**. Yield: 89%. *Rf*(50% EtOAc/hexanes) 0.38; Pale yellow solid. M.p. 128 130°C; **IR (KBR, cm^{-1})**: 3361, 3277, 2927, 1731, 1617, 1558, 1480, 1377, 1192, 749. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 67:33, * denotes minor diastereomer peaks): δ 10.47(br s, 1H), 10.39*(br s 1H), 7.17(d, 1H, $J = 7.0$ Hz), 7.07*(d, 1H, $J = 6.2$ Hz), 7.01-6.96(m 1H), 6.84-6.81(m 1H), 6.78(br s, 1H), 6.78*(br s, 1H), 5.01-4.95(m, 1H), 1.72*(d, 3H, $J = 6.2$ Hz), 1.35(d, 3H, $J = 6.2$ Hz) ppm.**^{13}C NMR (75 MHz, $CD_3)_2SO$)**: δ 176.28*, 175.61, 159.60, 159.51*, 156.42, 156.34*, 138.67*, 138.51, 128.81*, 128.77*, 128.41, 128.31, 116.54, 116.33*, 116.14, 116.01*, 113.71, 113.33, 112.74*, 112.41*, 111.01*, 110.91*, 110.85, 110.84, 86.38, 85.41*, 76.01, 75.21*, 13.64, 12.44 ppm. **MS(ESI)**: $m/z = 263$ $[M+Na]^+$.

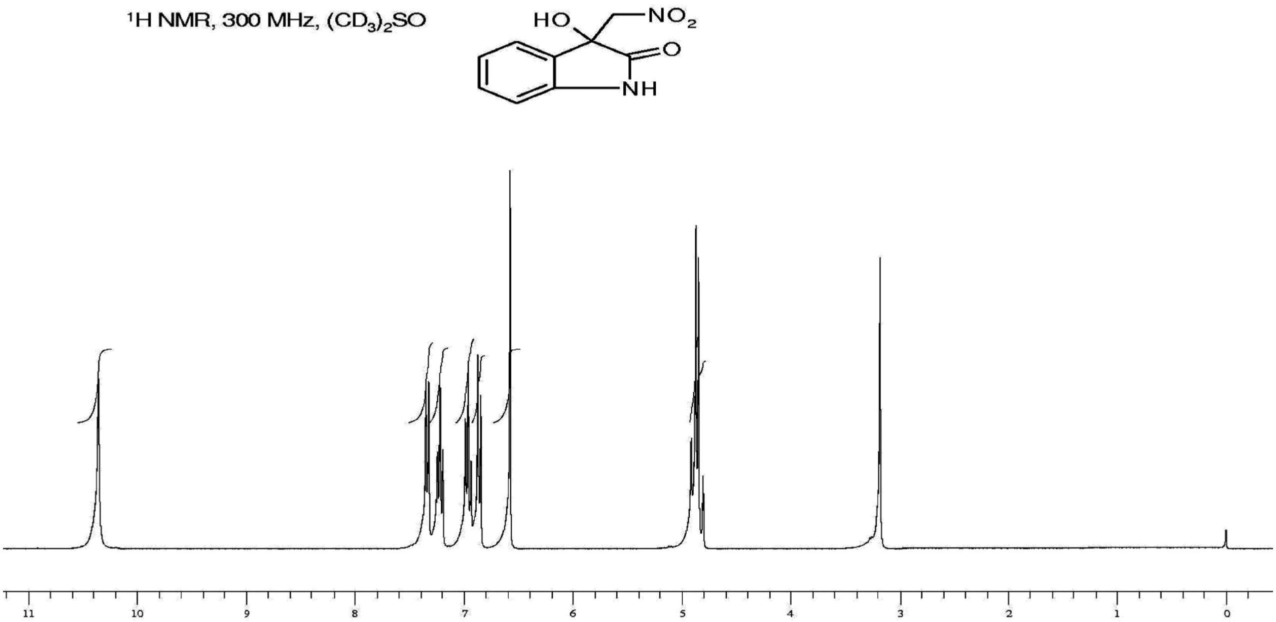
3-Hydroxy-5-iodo-3-(1-nitroethyl)indolin-2-one[42] (**3i**, Table 2, Entry 9): To a solution of isatin **1i** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 86 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3i** as off white solid. The Crude solid of **3i** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:2) as eluent to give the pure title compound **3i.** Yield: 90%. *Rf*(50% EtOAc/hexanes) 0.37; White solid. M.p. 278 280°C; **IR (KBR, cm^{-1})**: 3381, 3248, 2934, 1733, 1614, 1552, 1472, 1357, 1188, 816. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 91:9, * denotes minor diastereomer peaks): δ 10.55(br s, 1H), 10.49*(br s, 1H), 7.67(d, 1H, $J = 1.5$ Hz), 7.55(dd, 1H, $J = 8.1$, 1.5, Hz), 6.7(br s, 1H), 6.68(d, 1H, $J = 8.1$ Hz), 4.99-4.92(m, 1H), 1.75*(d, 3H, $J = 7.0$ Hz), 1.38(d, 3H, $J = 7.0$ Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 175.51*, 174.83, 142.32*, 142.27, 138.38, 133.15, 132.56*, 129.80*, 129.45, 112.36*, 112.30, 86.19, 85.18*, 84, 83.6*, 75.34, 74.64*, 13.5, 12.3* ppm. **MS(ESI)**: $m/z = 371$ $[M+Na]^+$.

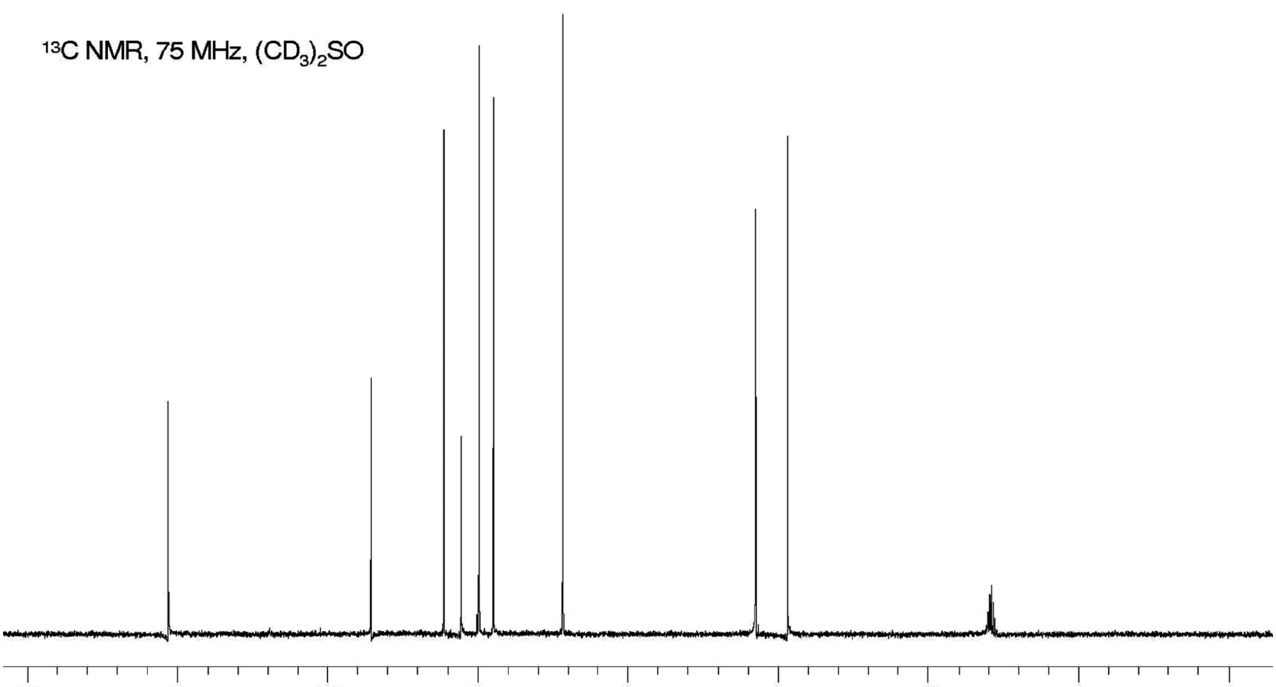
3-Hydroxy-1-methyl-3-(1-nitroethyl)indolin-2-one (**3j**, Table 2, Entry 10): To a solution of isatin **1j** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 72 min. After then, the reaction mixture was poured on 10 ml ice cold water and extracted with ethyl acetate (10x3). The Combine organic extract was dried on Na_2SO_4 and concentrate in *Vacuo* to provide crude **3j** as pale yellow viscous liquid. The Crude **3j** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3j**. Yield: 92%. *Rf*(50% EtOAc/hexanes) 0.44; White solid. M.p. 140 142°C; **IR (KBR, cm^{-1})**: 3316, 2939, 1703, 1616, 1551, 1468, 1385, 1355, 1113, 1061, 759. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 63:37, * denotes minor diastereomer peaks): δ 7.44*(s, 1H), 7.42*(s, 1H), 7.35(s, 1H), 7.33(s, 1H), 7.12-7.0(m, 1H), 6.88(d, 1H, $J=3.5$ Hz), 6.85*(d, 1H, $J=3.2$ Hz), 6.68*(br s, 1H), 6.63(br s, 1H), 5.05-4.98(m, 1H), 3.18*(s, 3H), 3.17(s, 3H), 1.76*(d, 3H, $J=6.8$ Hz), 1.37(d, 3H, $J=6.8$ Hz) ppm. **^{13}C NMR (75 MHz, $CD_3)_2SO$)**: δ 174.83*, 174.4, 144.3*, 144.09, 130.43, 130.13*, 127.4*, 126.9, 124.24, 123.8*, 122.7, 122.3*, 108.9*, 108.57, 78.4, 77.8*, 72.75, 71.6*, 26.17, 25.3*, 13.9, 12.8* ppm. **MS(ESI)**: $m/z=259$ $[M+Na]^+$.

3-Hydroxy-3-(1-nitroethyl)-1-phenylindolin-2-one (**3k**, Table 2, Entry 11): To a solution of isatin **1k** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 90 min. After then, the reaction mixture was poured on 10 ml ice cold water and extracted with ethyl acetate (10x3). The Combine organic extract was dried on Na_2SO_4 and concentrate in *Vacuo* to provide crude **3k** as pale yellow viscous liquid. The Crude **3k** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give the pure title compound **3k**. Yield: 89%. *Rf*(50% EtOAc/hexanes) 0.43; White solid. M.p 102 105°C. **IR (KBR, cm^{-1})**: 3331, 2923, 1711, 1619, 1569, 1471, 1374, 1087, 769. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 72:28, * denotes minor diastereomer peaks): δ 7.56-7.37(m, 6H), 7.26(t, 1H, $J=7.4$ Hz), 7.19-7.15*(m, 1H), 7.10(t, 1H, $J=7.5$ Hz), 7.06-7.01*(m, 1H), 6.91(br s, 1H), 6.89*(br s, 1H), 6.74(d, 1H, $J=7.4$ Hz), 5.19-5.09 (m, 1H), 1.84*(d, 3H, $J=6.9$ Hz), 1.57(d, 3H, $J=6.9$ Hz) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)**: δ 174.4*, 173.3, 143.9*, 143.6, 133.8*, 133.7, 130.0*, 129.4, 128.2*, 128.1, 128.03, 127.9*, 126.5*, 126.3, 125.2, 124.9*, 122.92, 122.79*, 109.18*, 109.05, 86.93, 85.7*, 74.7*, 74.6, 13.58, 12.2* ppm. **MS(ESI)**: $m/z=321$ $[M+Na]^+$.

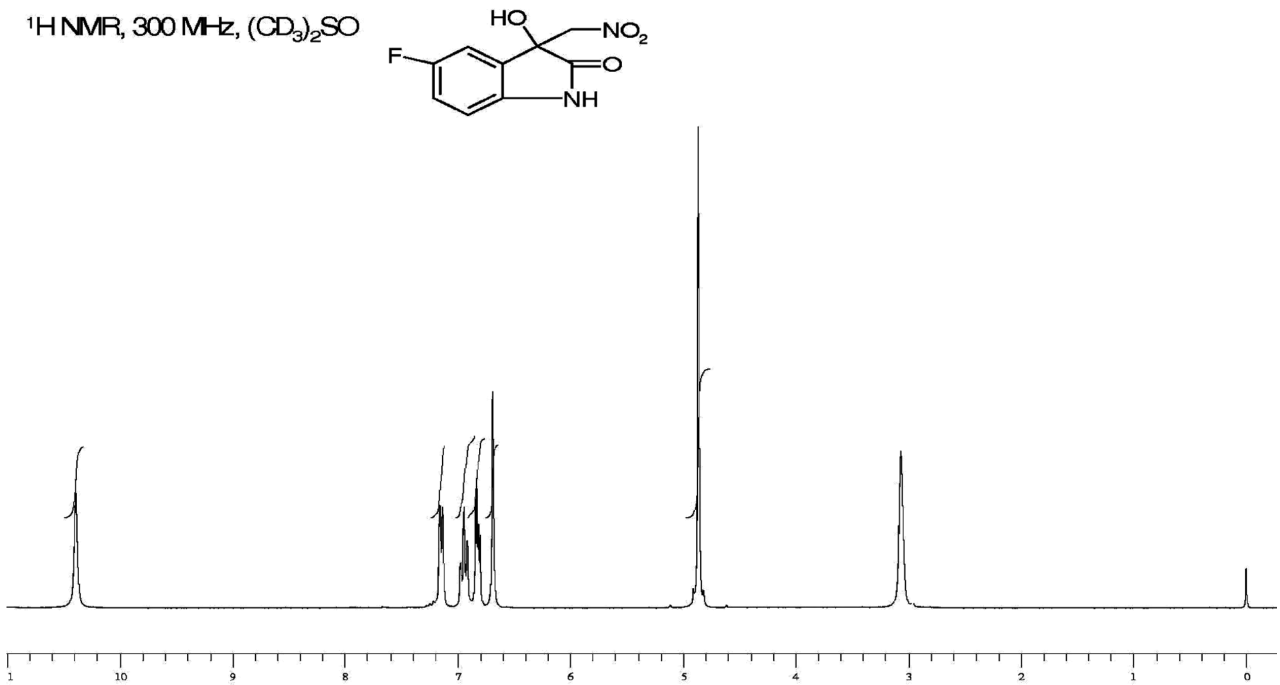
3-Hydroxy-1-(hydroxymethyl)-5-iodo-3-(1-nitroethyl)indolin-2-one (**3l**, Table 2, entry 12): To a solution of isatin **1l** (1.0 mmol) in freshly distilled DMF (3 mL) was added nitroethane (2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 90 min. After then, the reaction mixture was poured on 10 ml ice cold water to obtain the crude **3l** as off white solid. The Crude solid of **3l** was further purified by silica gel column chromatography using ethyl acetate:hexane (1:1) as eluent to give the pure title compound **3l**. Yield: 88%. *Rf*(50% EtOAc/hexanes) 0.35; White solid. M.p. 151 153°C; **IR (KBR, cm^{-1})**: 3341, 2982, 1731, 1604, 1537, 1480, 1333, 1194, 1029, 965, 810. **^{1}H NMR (300 MHz, $(CD_3)_2SO$)** (diastereomeric ratio, *threo:erythro* 88:12, * denotes minor diastereomer peaks) δ 7.75(d, 1H, $J=7.5$ Hz), 7.66(dd, 1H, $J=8.3$, 1.7 Hz), 7.61*(dd, 1H, $J=8.3$, 1.7 Hz), 6.95(d, 1H, $J=8.1$ Hz), 6.9(br s, 1H), 6.8*(br s, 1H), 6.2(br s, 1H), 5.1(s, 2H), 5.04-4.9(m, 1H), 1.76*(d, 1H, $J=7.0$ Hz), 1.37(d, 1H, $J=7.0$ Hz).**^{13}CNMR (75 MHz, $(CD_3)_2SO$)**: δ 173.5*, 172.9, 142.3, 138.6, 133.6, 132.7*, 129.0*, 128.6, 112.4, 86.35, 85.6, 85.4, 85.3*, 75.1, 74.6*, 62.8, 13.52, 12.4*. **MS(ESI)**: $m/z=379$ $[M+1]^+$.

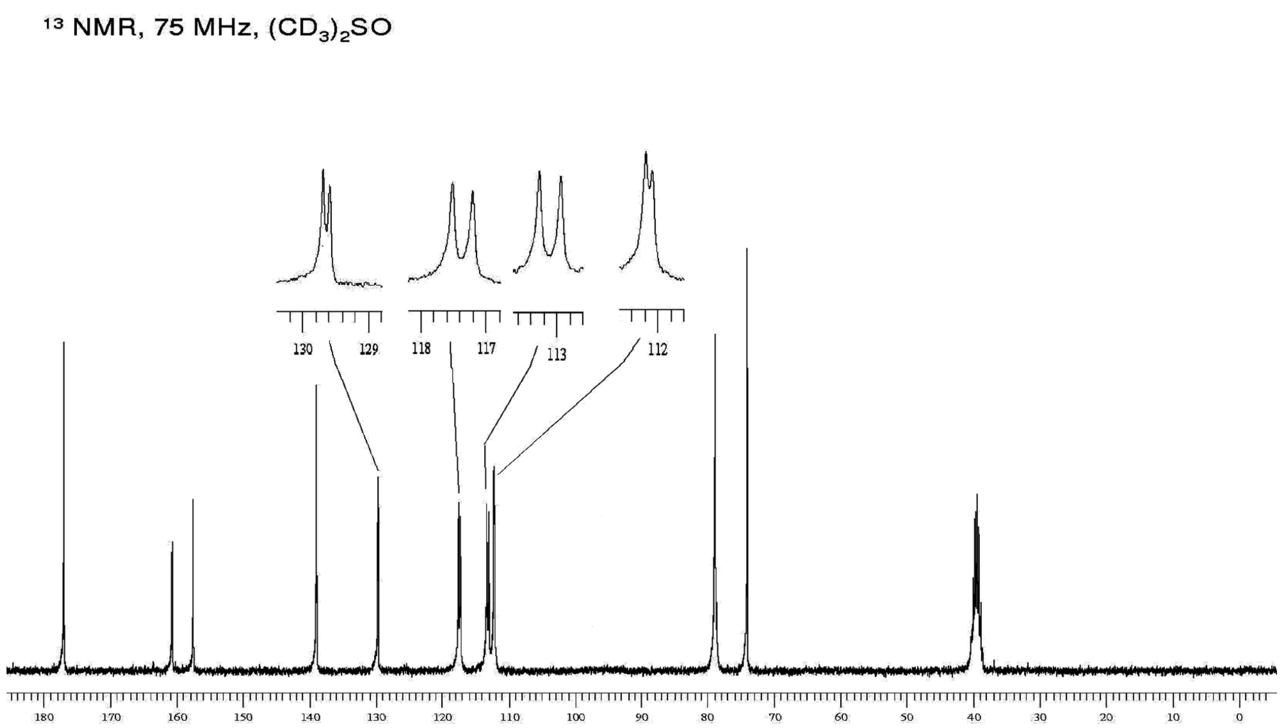
^{1}H NMR and ^{13}C NMR Spectrum of compound 3a-3l
3-Hydroxy-3-(nitromethyl)indolin-2-one (3a, Table 2, Entry 1)



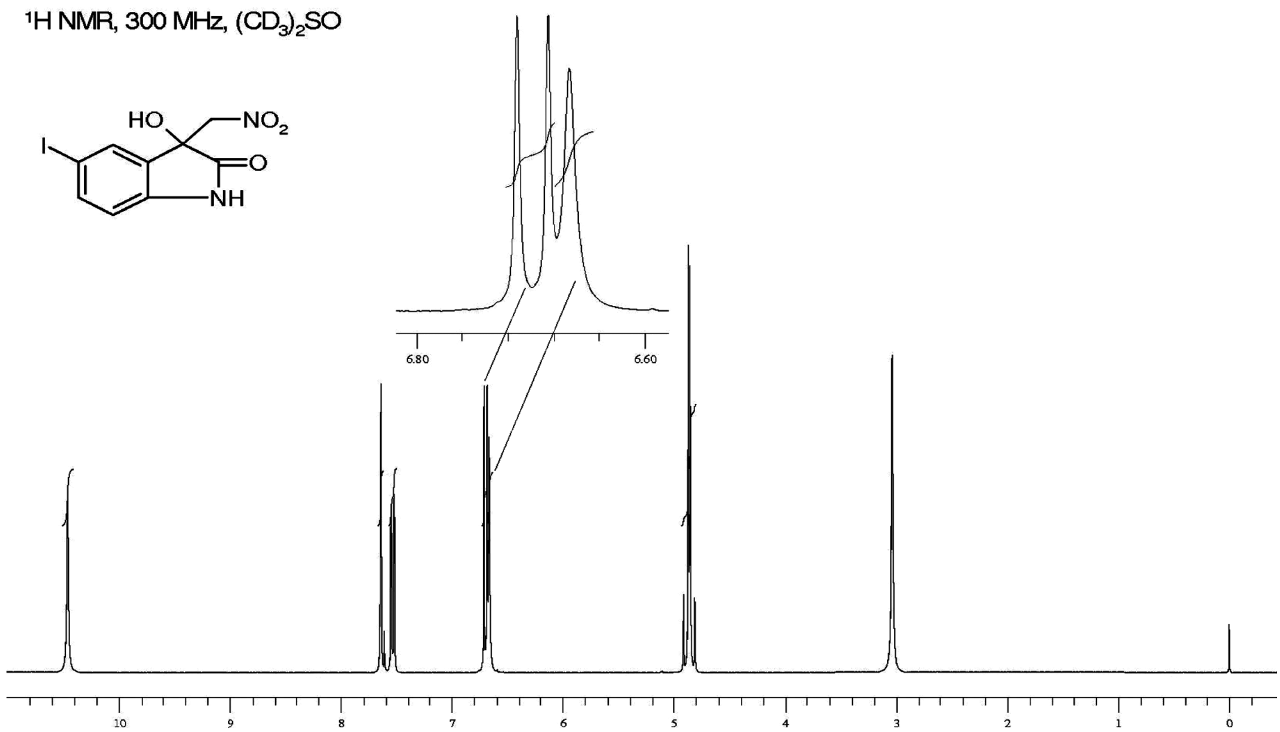


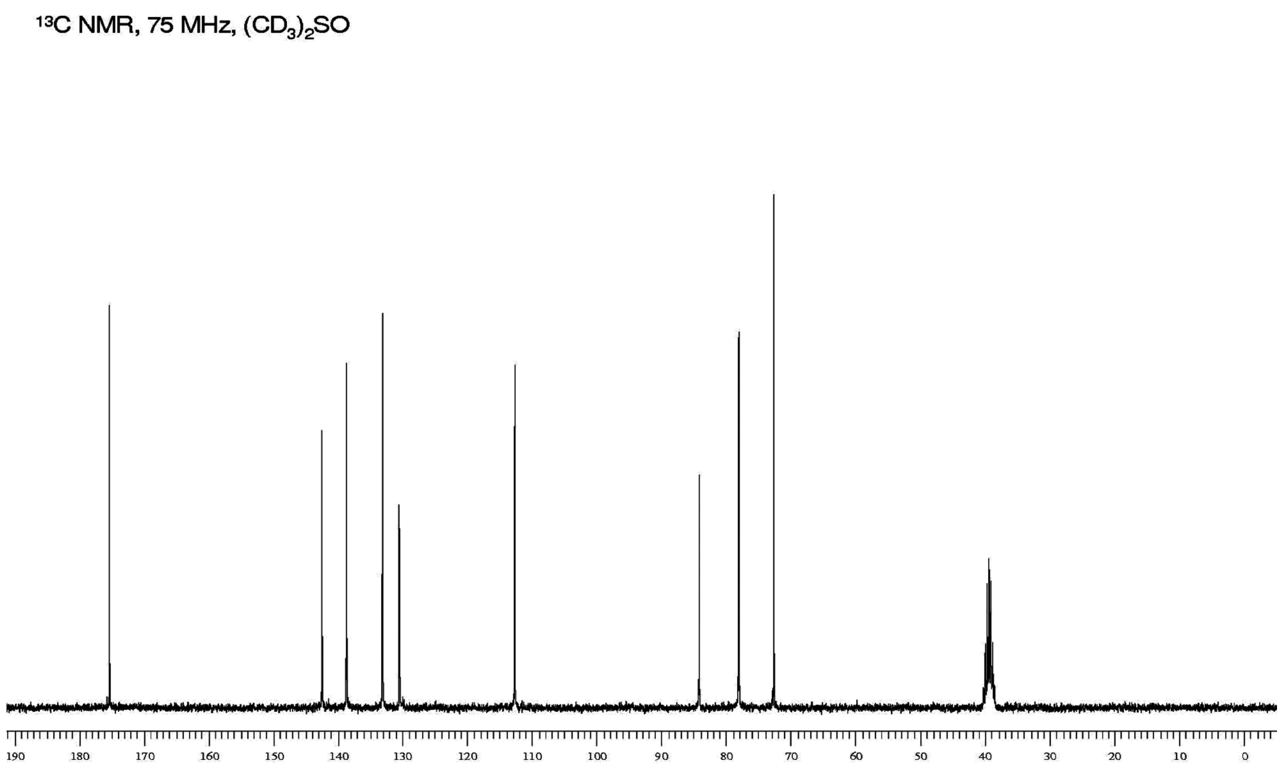
5-fluoro-3-Hydroxy-3-(nitromethyl)indolin-2-one (3b, Table 2, entry 2)





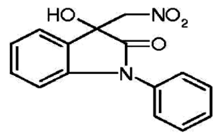
3-hydroxy-5-iodo-3-(nitromethyl)indolin-2-one (3c, Table 2, entry 3)

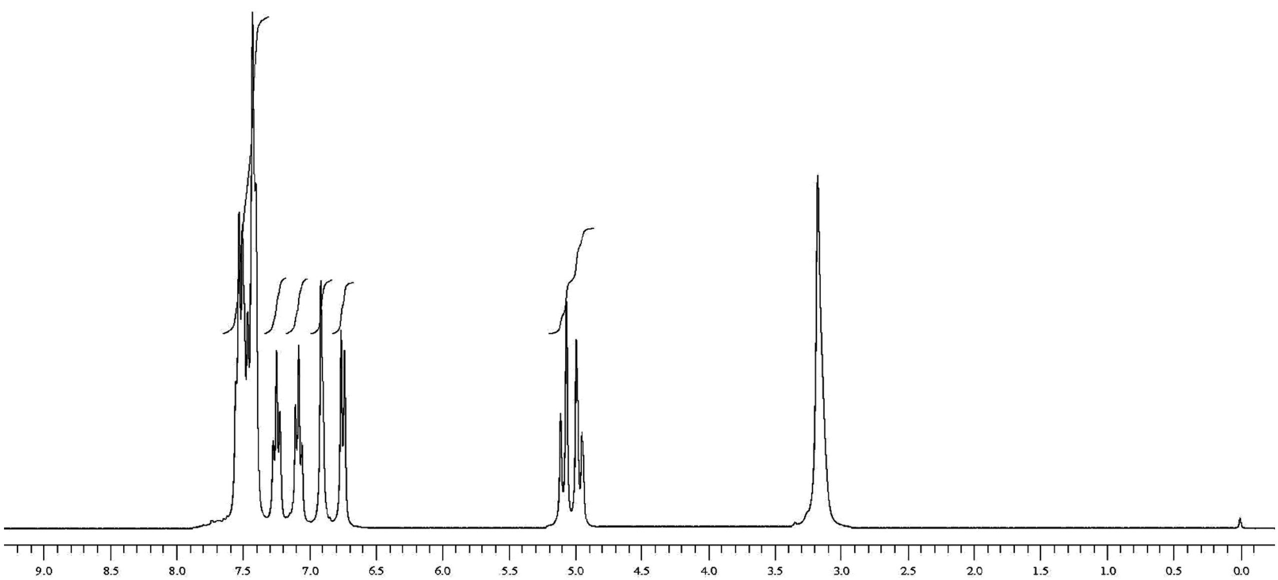




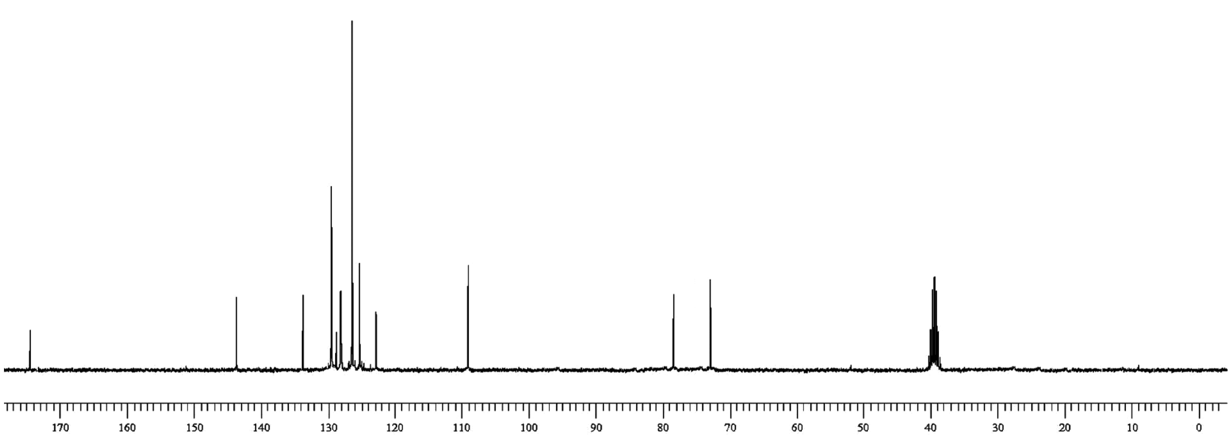
3-hydroxy-3-(nitromethyl) -1- phenylindolin-2-one (3d, Table 2, Entry 4)

^{1}H NMR, 300 MHz, $(CD_3)_2SO$

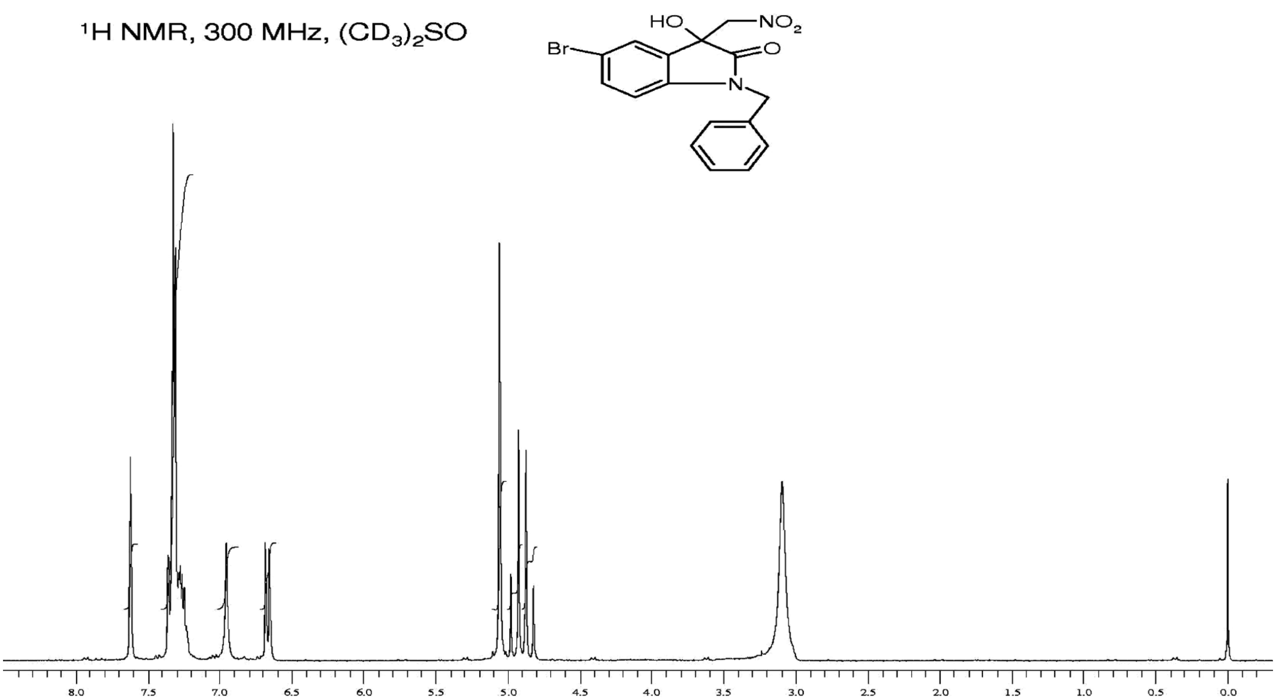


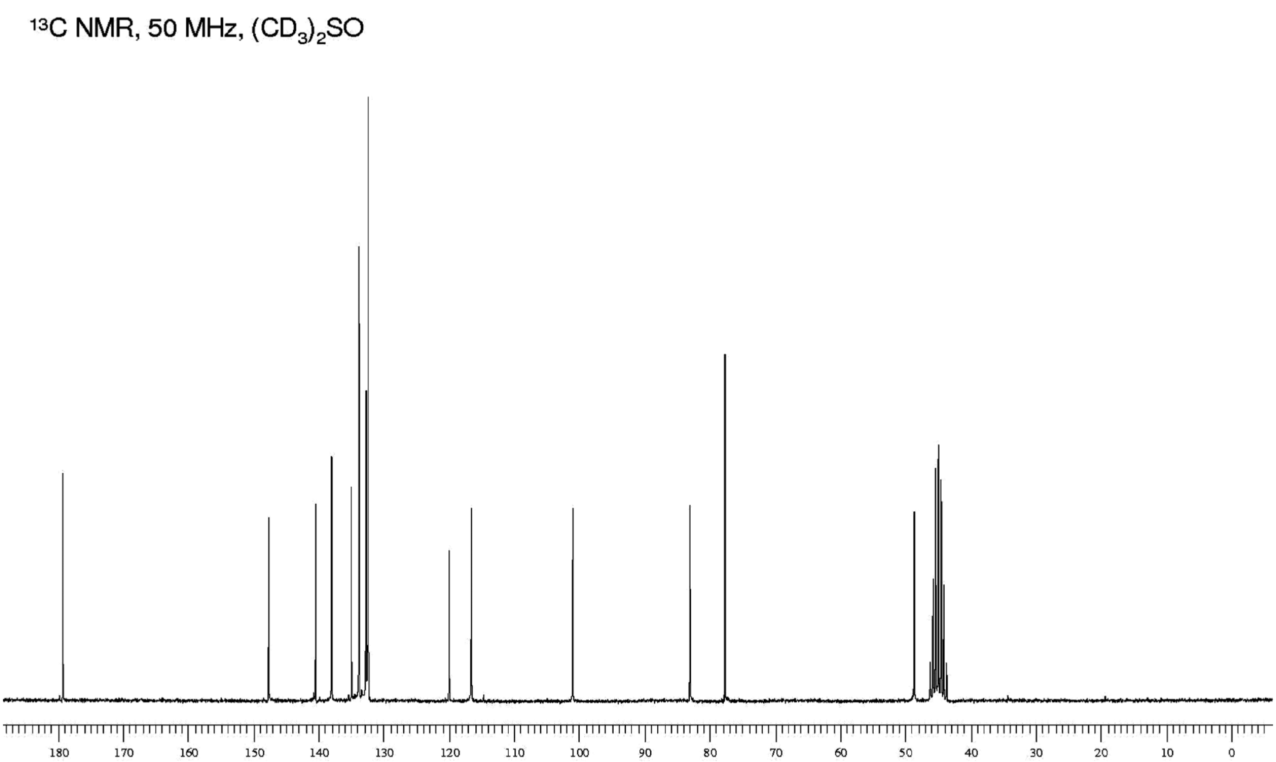


^{13}C NMR, 75 MHz, $(CD_3)_2SO$

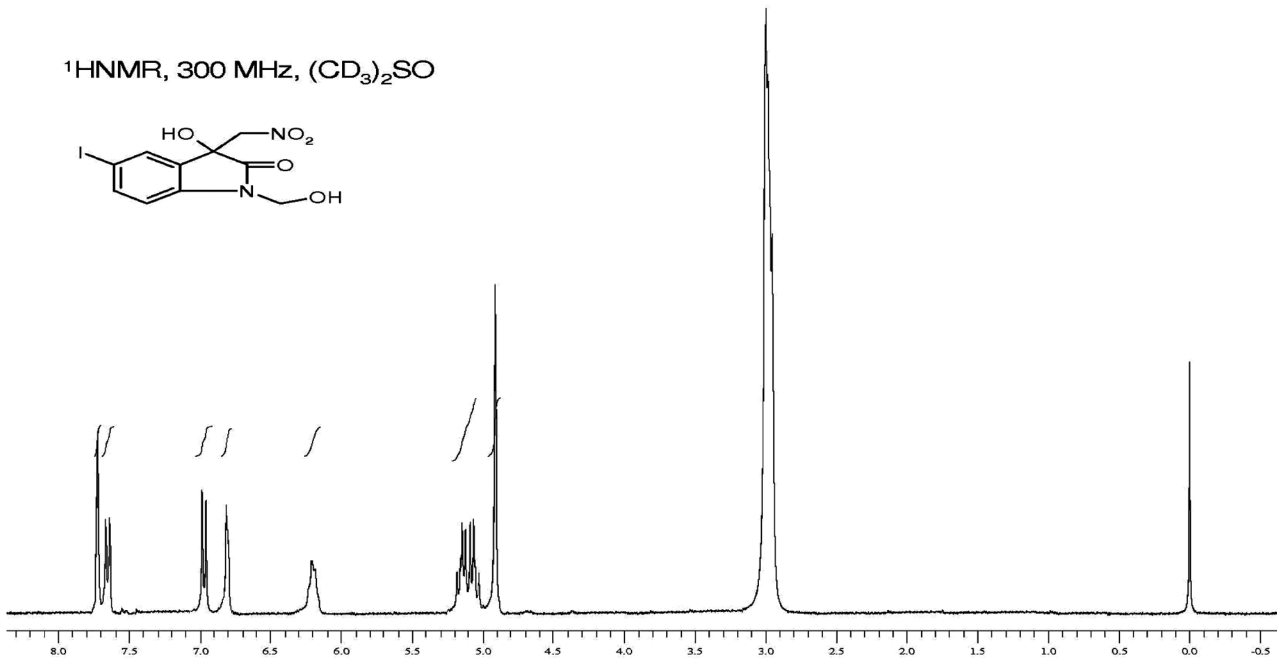


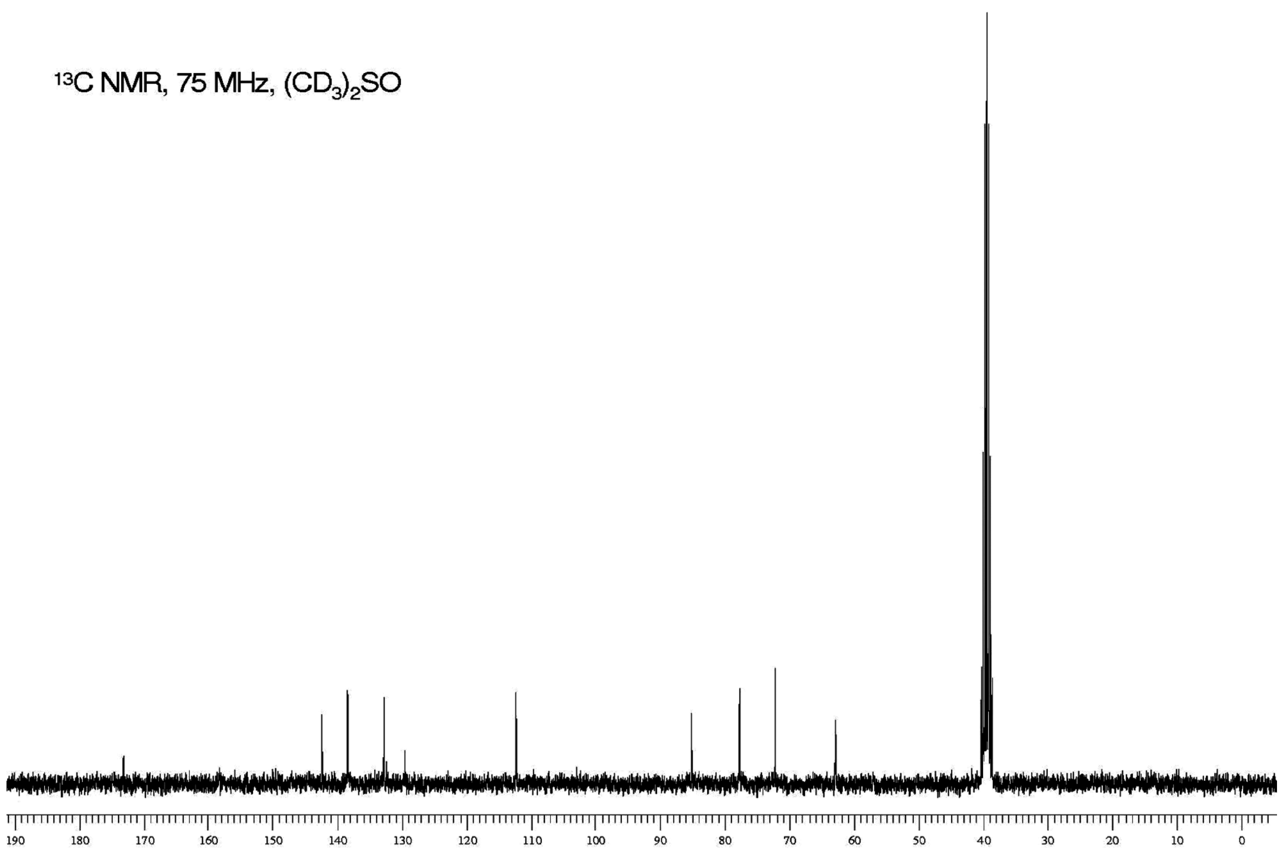
1-benzyl-5-bromo-3-hydroxy-3-(nitromethyl)indolin-2-one (3e, Table 2, Entry 5)



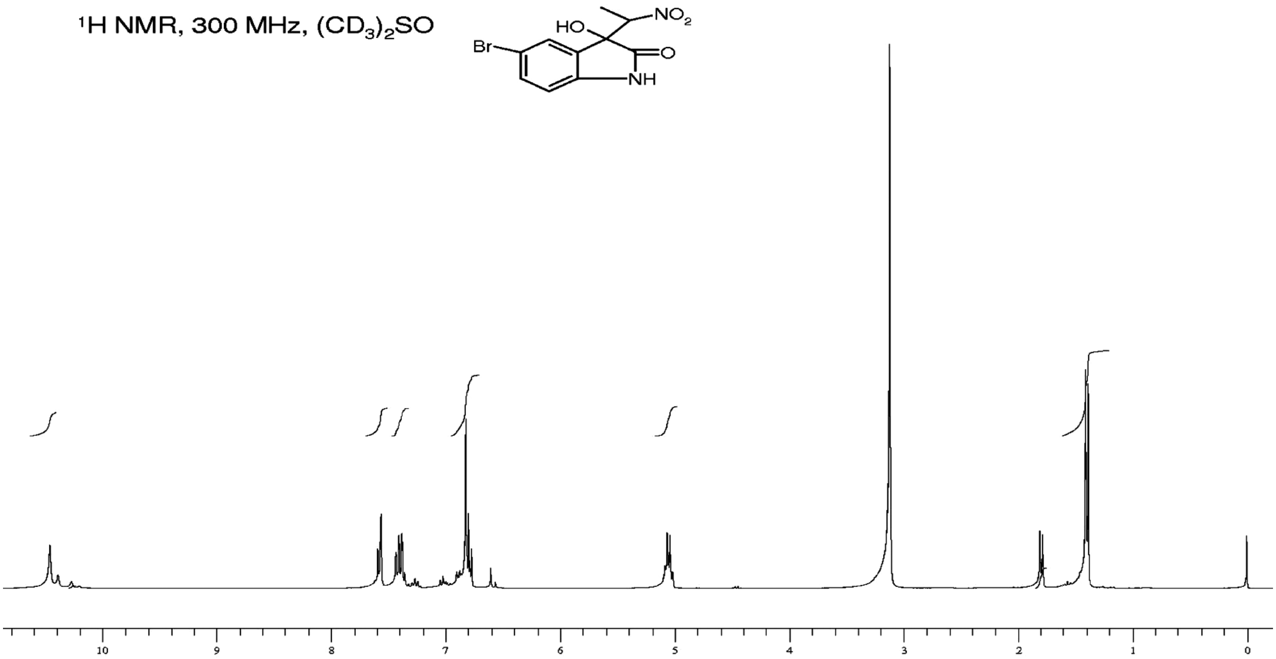


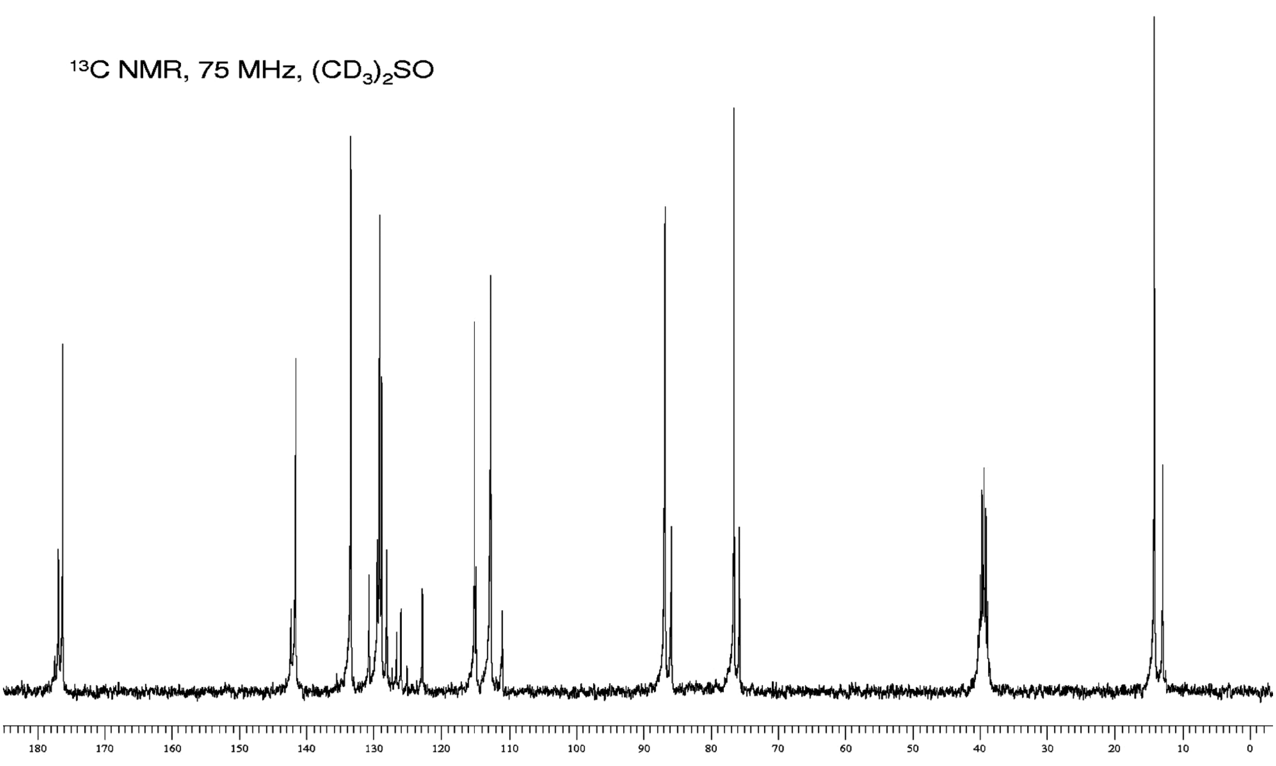
3-hydroxy-1-(hydroxymethyl)-5-iodo-3-(nitromethyl)indolin-2-one (3f, Table 2, entry 6)



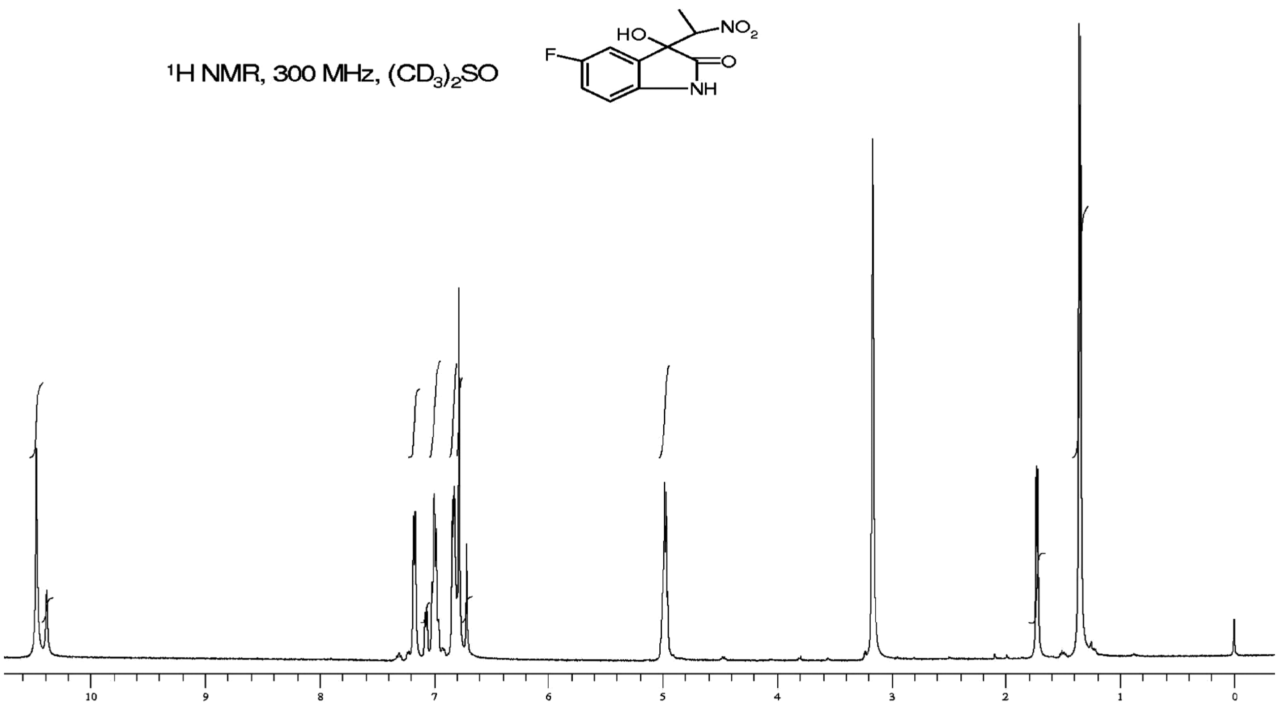


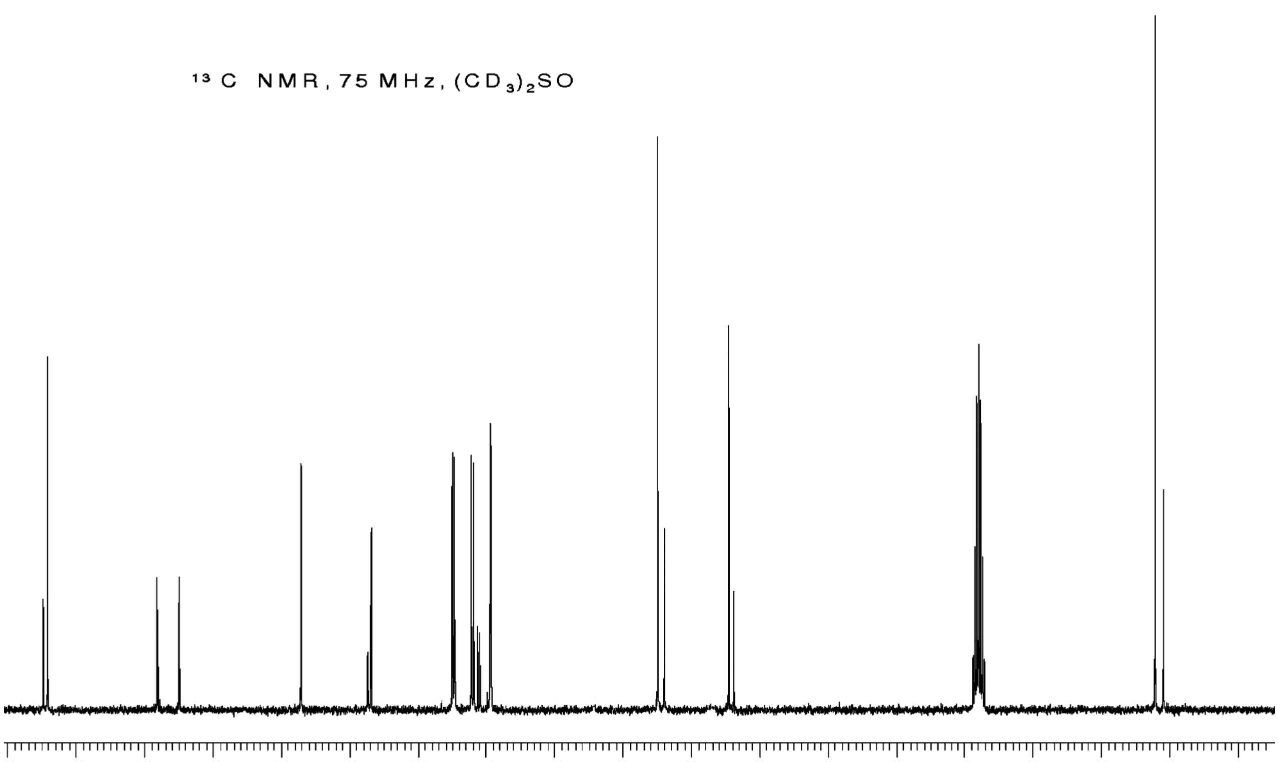
5-bromo-3-hydroxy-3-(1-nitroethyl)indolin-2-one, (3g, Table 2, entry 7)



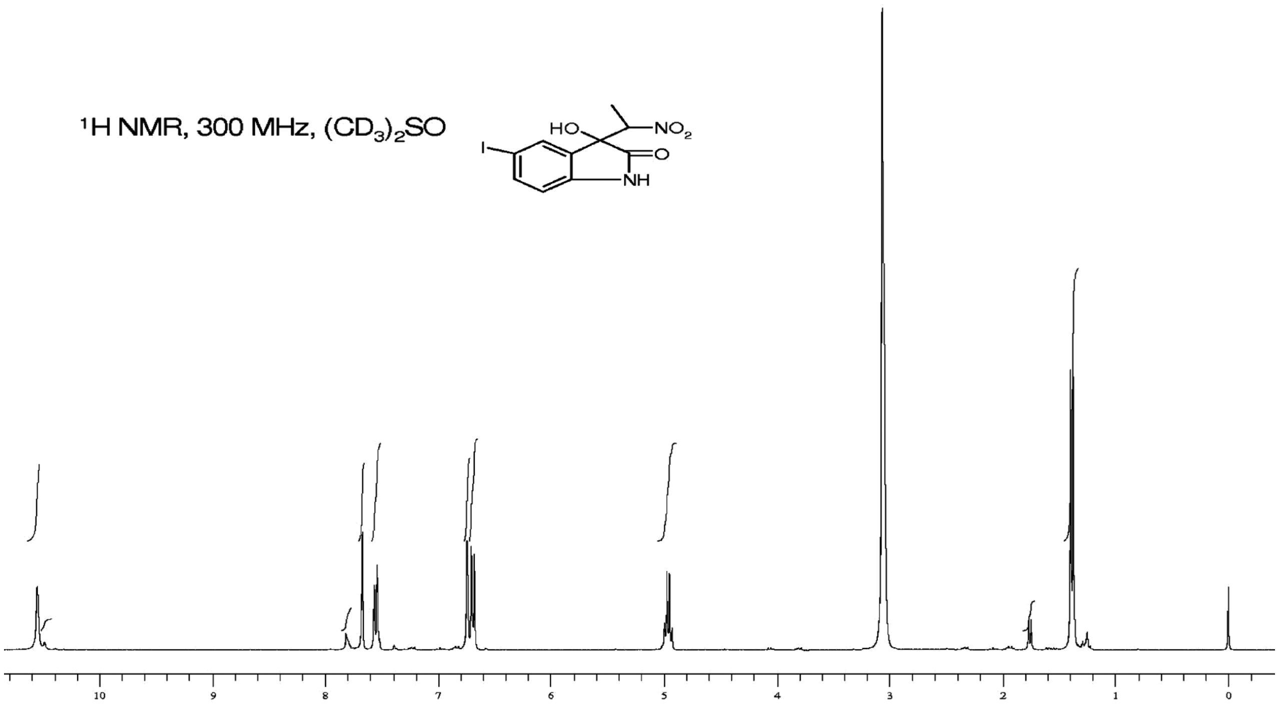


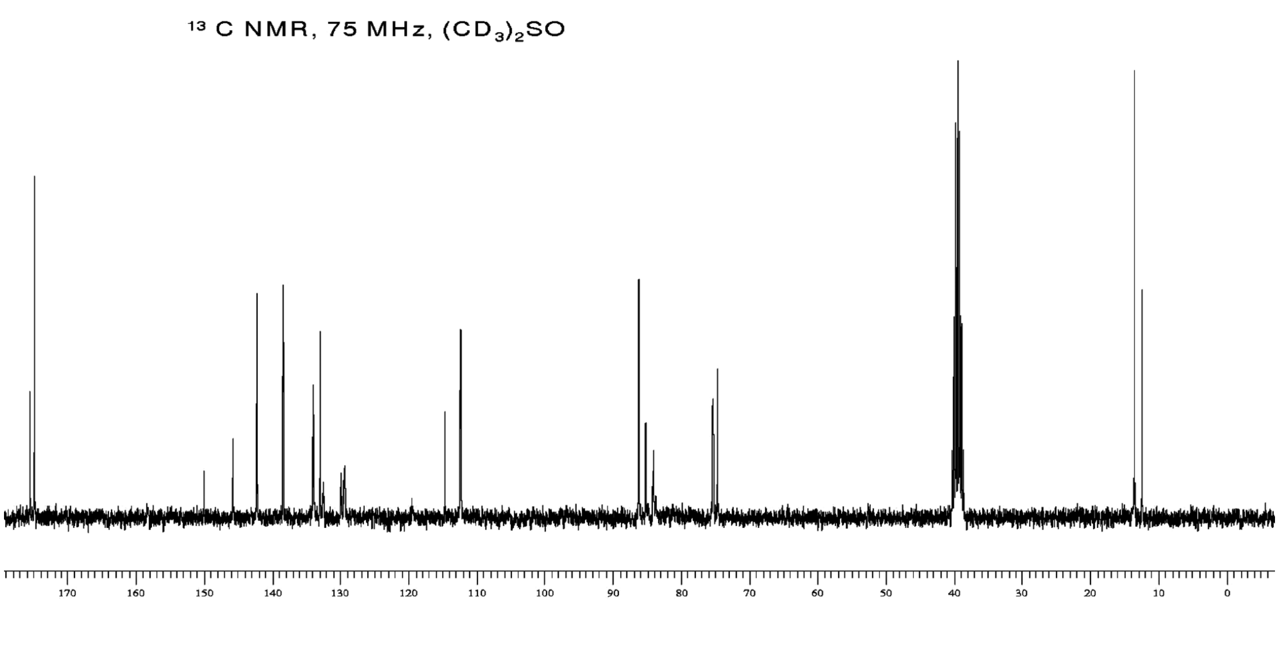
5-fluoro-3-hydroxy-3-(1-nitroethyl)indolin-2-one(3h, Table 2, entry 8)



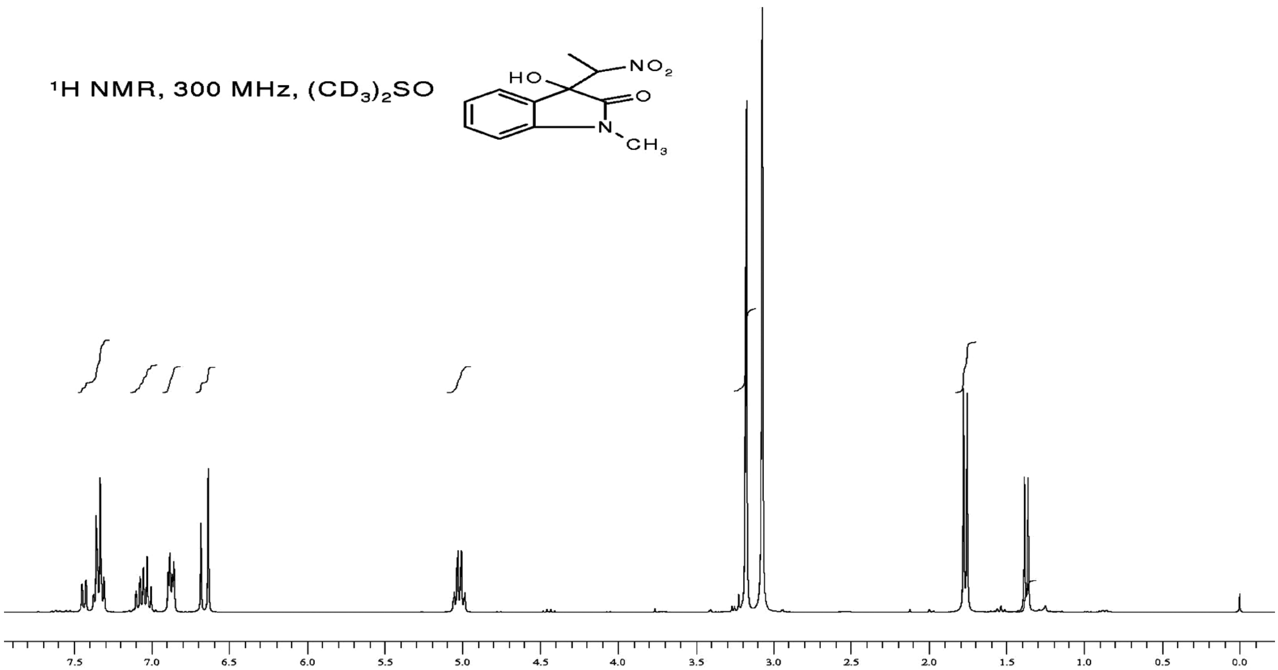


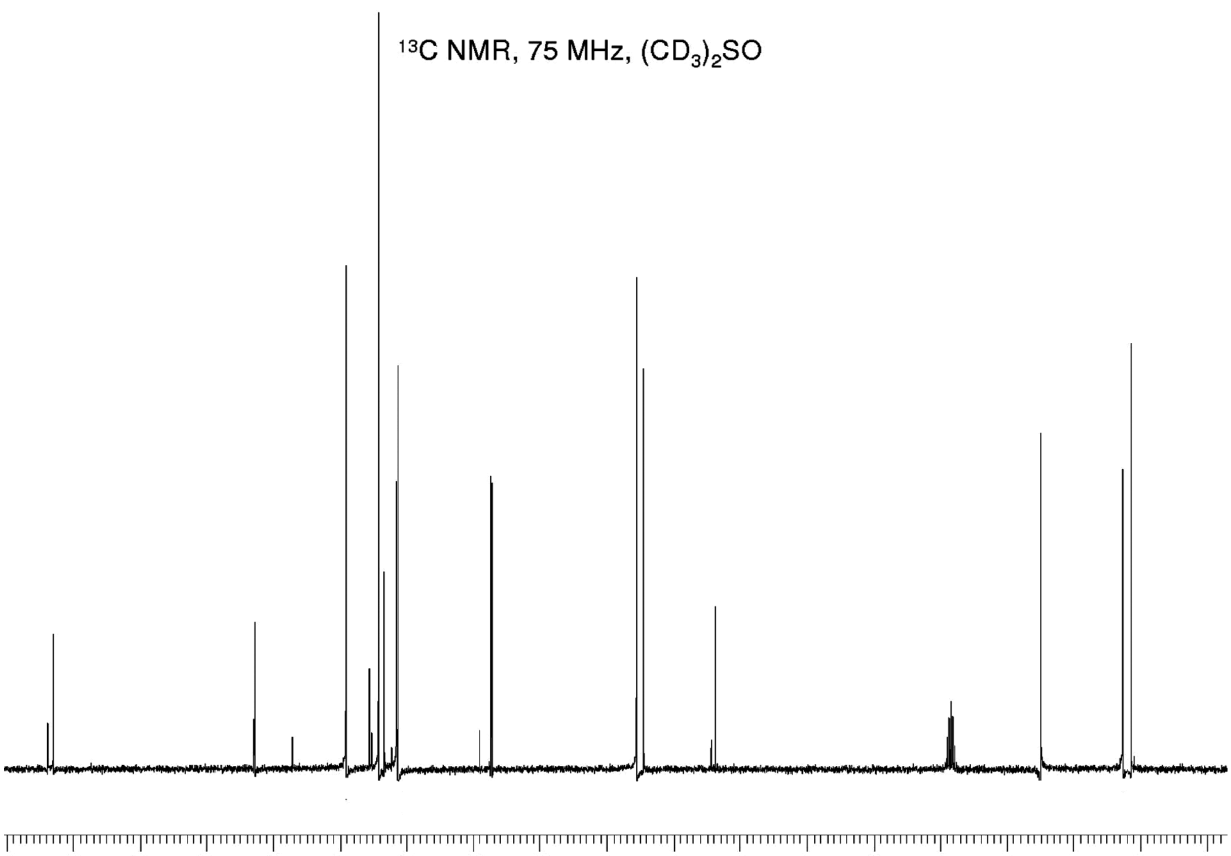
3-hydroxy-5-iodo-3-(1-nitroethyl)indolin-2-one, (3i, Table 1, Entry 9)



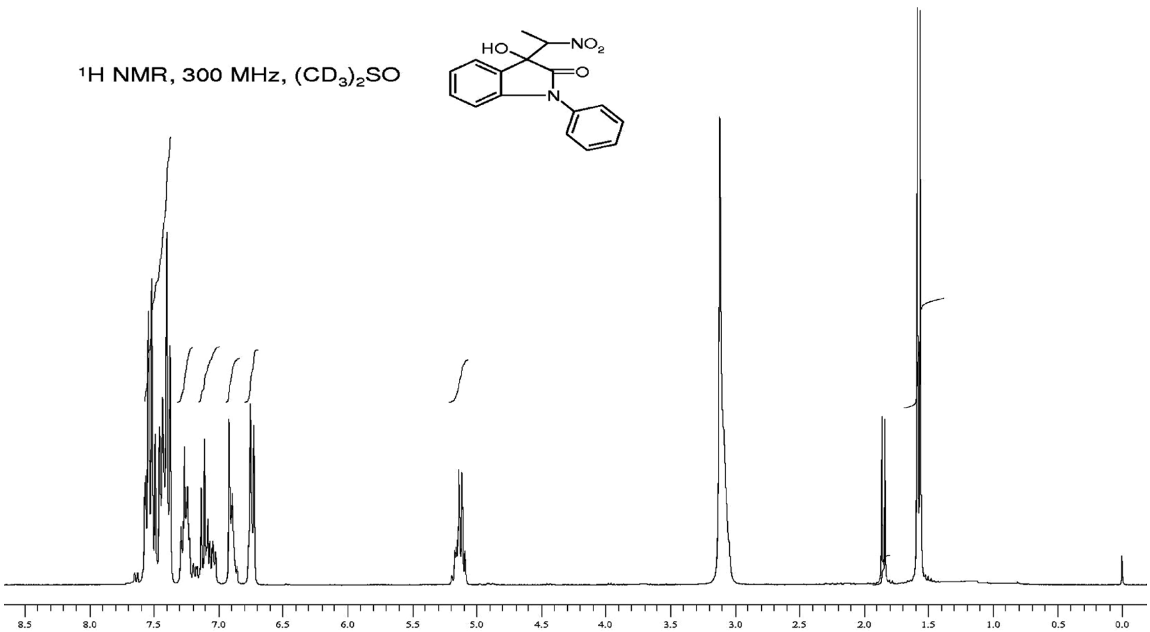


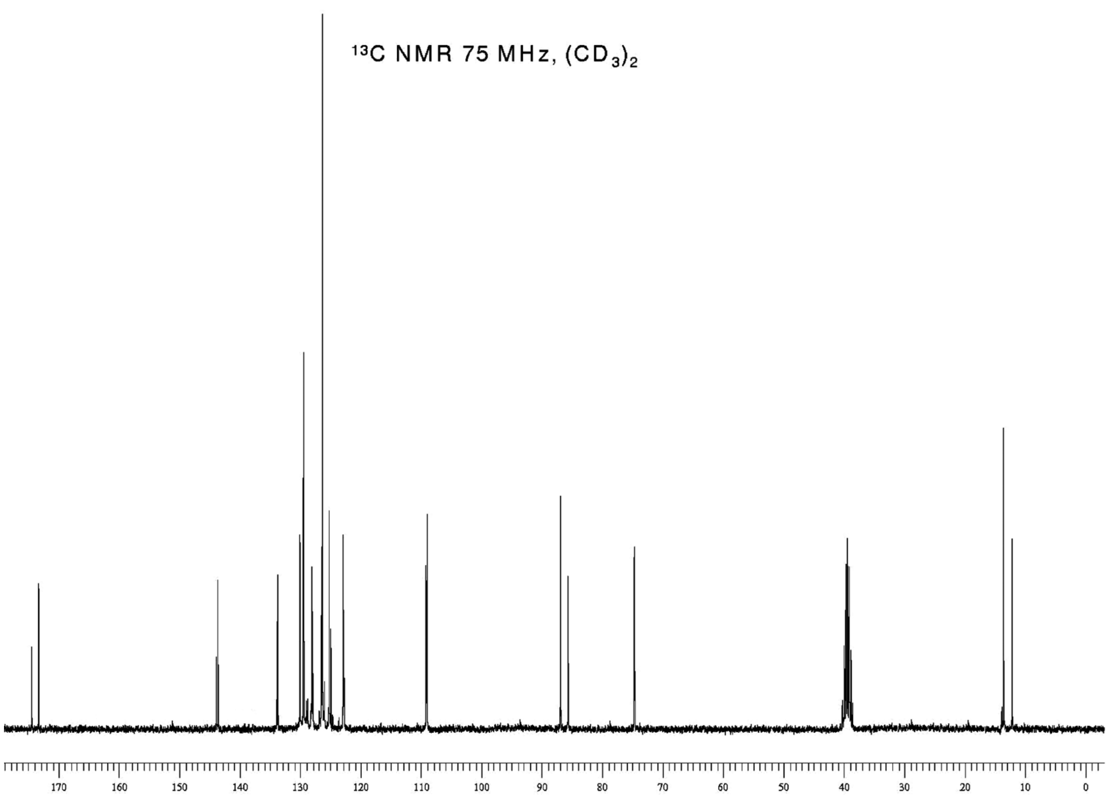
3-hydroxy-1-methyl-3-(1-nitroethyl)indolin-2-one (3j, Table 2, entry 10)





3-hydroxy-3-(1-nitroethyl)-1-phenylindolin-2-one (3k, Table 2, Entry 11)





3-hydroxy-1-(hydroxymethyl)-5-iodo-3-(1-nitroethyl)indolin-2-one, (3l, Table 2, Entry 12)