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Graphical Abstract

Synthesis of Spiroindolone scaffolds by Pictet-Spengler Spirocyclisation using *β*-cyclodextrin-SO_3H as a recyclable catalyst

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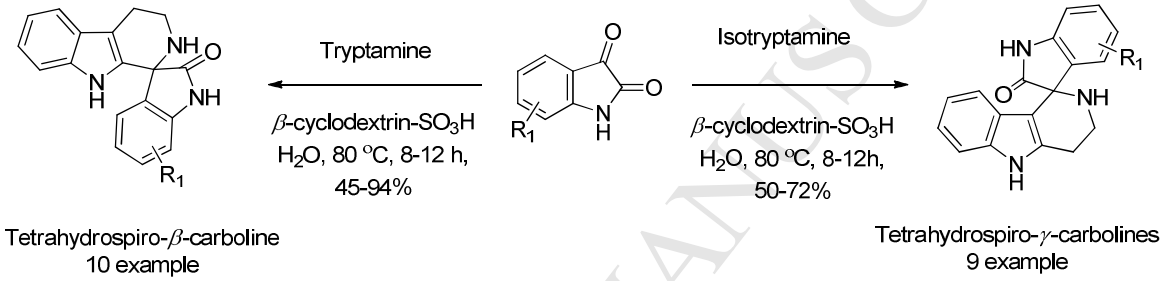

Using a recyclable catalyst, *β*-cyclodextrin-SO_3H in aqueous medium in a Pictet-Spengler spirocyclisation, the synthesis of spiroindolones (tetrahydrospiro-*β*-carbolines as well as tetrahydrospiro-*γ*-carbolines) was demonstrated. The products were obtained in good yield in an environmental friendly procedure.

Synthesis of Spiroindolone scaffolds by Pictet-Spengler Spirocyclisation using *β*-cyclodextrin-SO_3H as a recyclable catalyst

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Abstract

A recyclable catalyst, *β*-cyclodextrin-SO_3H in aqueous medium was used effectively for the synthesis of spiroindolones (tetrahydrospiro-*β*-carbolines as well as tetrahydrospiro-*γ*-carbolines) in a Pictet-Spengler spirocyclisation. The products were obtained in good yield in an environmental friendly procedure.

Keywords: Pictet-Spengler Spirocyclisation, Spiroindolone, tetrahydrospiro-*β*-carboline, tetrahydrospiro-*γ*-carboline, Green synthesis

1. Introduction

Literature survey reveals that *β*-cyclodextrin-SO_3H catalyst have gathered attention of many researcher owing to its use in aqueous media for ring closure and also for the multi-component one-pot condensation reaction.[1] *β*-Cyclodextrin-SO_3H represents a derivatized cyclodextrin which is chemically modified by replacing one of the hydroxyl group on the ring of cyclodextrin by -SO_3H group[2] and displays improved solubility in water compared to the *β*-cyclodextrin. Use of low amount of catalyst in easily available solvent like water and simple workup procedure are some of the advantages of this catalyst.

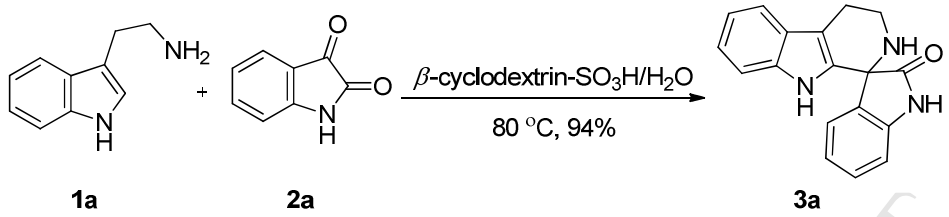
Recently, green chemistry involving development of environmentally benign chemical processes and sustainable technologies is in demand. Water is a preferred solvent as green media as it is cheapest, safest, environment friendly and non-toxic solvent.[3] As most of organic compounds are insoluble in water, the use of water as a medium for organic reactions is one of the latest challenges for modern organic chemists. Green synthesis based on water mediated reactions has attracted more attention from the scientific community[4] due to the reduction in pollution caused by organic solvents.

Spiroindolones are members of spirooxindole alkaloids and many of them are naturally occurring and bioactive molecules. Due to its interesting framework having one spiro stereocentre and various biological properties, it has gained a lot of attention. Pictet Spengler reaction is one of the commonly used[5, 6i] synthetic routes for these scaffolds. Various acids catalyst like silica gel,[6a] chiral phosphoric acid,[6b,c] carbon-SO_3H,[6d] glacial acetic acid,[6e,f] *p*-TsOH,[6g] chlorotrimethylsilane,[6h] HCl[6i] and metal catalyst like gold[6j] etc. have been implemented for the synthesis of spiroindolones. Many of these catalysts suffer drawbacks like expensive catalysts, low yields of products, environmentally hazardous and harsh reaction conditions. Nevertheless, environmental friendly approach employing aqueous phase organic synthesis can be an alternative which would overcome the difficulties related with the catalyst and organic solvents.[7] A few syntheses are reported for spirooxindoles, using Pictet Spengler reaction in aqueous medium.[8] However there is no report available for the synthesis of spiroindolones in water. Thus, we envisioned an environmental friendly synthetic approach for spiroindolones using *β*-cyclodextrin-SO_3H as a recyclable catalyst in water using Pictet-Spengler spirocyclisation reaction.

2. Result and discussions

Initially, it was planned to synthesize spiroindolone scaffold containing tetrahydrospiro-*β*-carboline unit, starting from tryptamine (**1a**) and isatin (**2a**). The required catalyst *β*-cyclodextrin-SO_3H was prepared as a white solid using the reported[2] procedure from chlorosulfonic acid and *β*-cyclodextrin in CH_2Cl_2 at 0 $^{\circ}$C. The -SO_3H contents were measured by titration method and this data was matching with the reported[2] value (0.52 mequiv.g.$^{-1}$). The starting isatins (except **2g)** were commercially available.

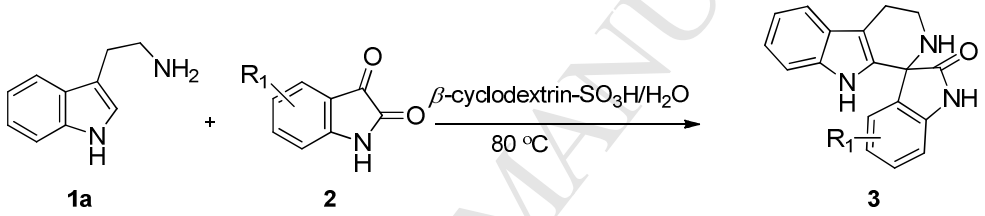
Having all starting materials in hand, the model reaction for the synthesis of tetrahydrospiro-*β*-carboline was carried out by treating tryptamine **1a** with isatin **2a** using 20 mol% *β*-cyclodextrin-SO_3H catalyst in water as a solvent. The reaction was quite sluggish at RT. However, when heated at 80 $^{\circ}$C, complete consumption of starting materials was observed within 12 h along with the formation of a new compound. The compound after subsequent purification and characterization was found to be the expected product, tetrahydrospiro-*β*-carboline i. e. 2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (**3a**) (Scheme 1). The NMR data of **3a** was well matching with the literature report.[6c]

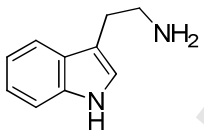
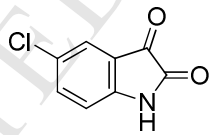
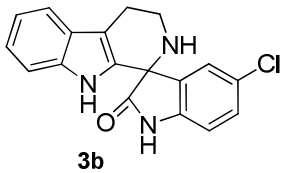
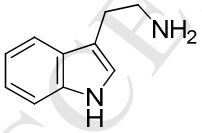
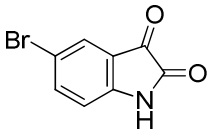
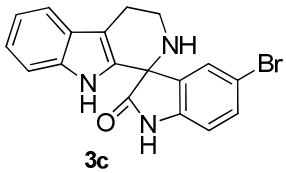
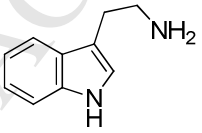
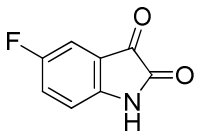
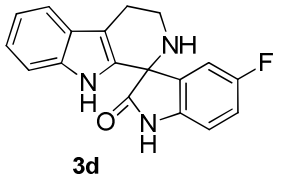


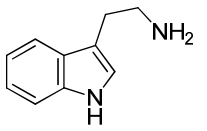
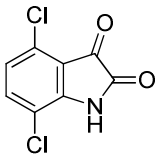
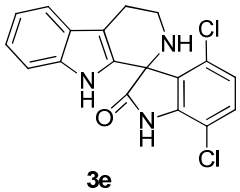
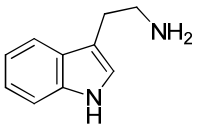
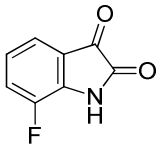
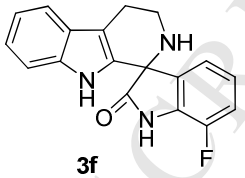
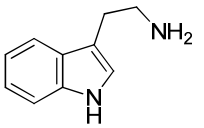
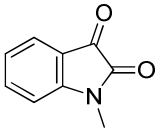
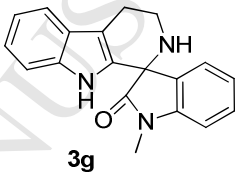
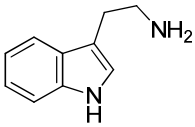
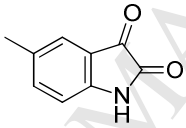
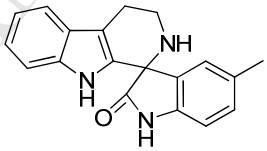
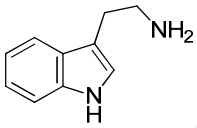
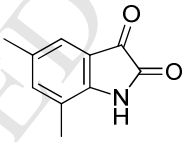
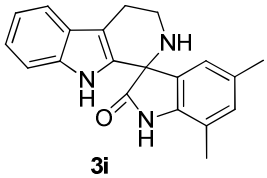
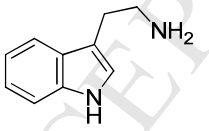
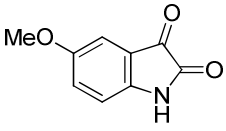
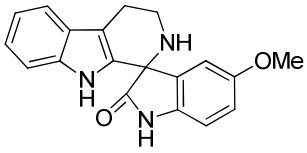
Scheme 1. Synthesis of 2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (**3a**)

The catalyst in aqueous solution after work up was directly used for the next batch of the same reaction to furnish the product in 92% yield. Even after third run, using the same catalyst in the aqueous medium, yield of the product was found to be up to 90%. This indicated that the catalyst could be recycled for three runs.

Table 1. Synthesis of tetrahydrospiro-*β*-carboline [a] (**3b-3j**)



Entry	tryptamine (1a)	isatin (2)	Product (3)	Yield[b] (%)
1				85
2				91
3				83

Entry	tryptamine (1a)	isatin (2)	Product (3)	Yield[b] (%)
4				83
	1a	2e	3e	
5				81
	1a	2f	3f	
6				74
	1a	2g	3g	
7				83
	1a	2h	3h	
8				51
	1a	2i	3i	
9				45
	1a	2j	3j	

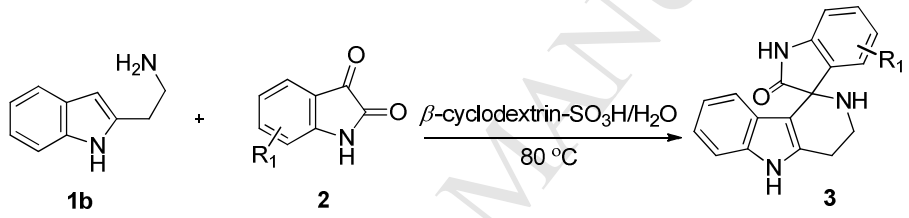
[a]Reaction condition: **1a** (0.31 mmol), **2** (0.31 mmol), were heated in presence of *β*-cyclodextrin-SO_3H (0.06 mmol) in water (5 mL) at 80 °C for 8-12 h. [b]Isolated yield.

After achieving the synthesis of **3a** using the catalyst *β*-cyclodextrin-SO_3H, the scope of the reaction was studied. The optimized protocol was employed for the reaction of tryptamine with various substituted isatins. In all the cases corresponding tetrahydrospiro-*β*-carbolines **3b-3j**

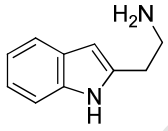
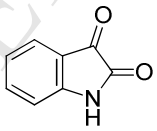
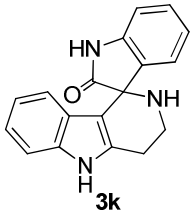
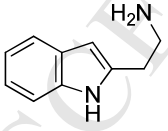
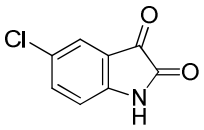
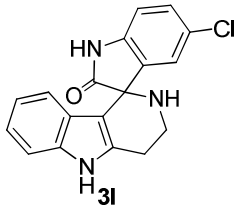
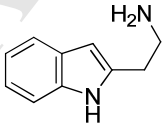
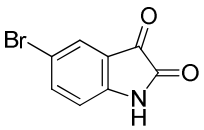
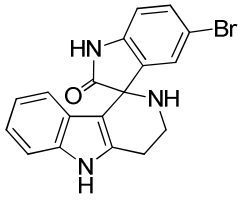
were obtained in good to excellent yields within short period of time (Table 1). The reaction was well tolerated by isatins bearing electron withdrawing groups (-F, -Cl, -Br) as well as electron donating groups (-Me, -OMe). All the synthesized tetrahydrospiro-*β*-carbolines were well characterized by analytical and spectral data which was matching with the previous literature reports.[6c, d]

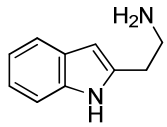
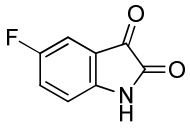
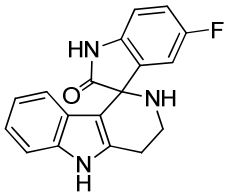
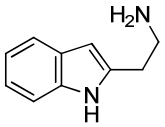
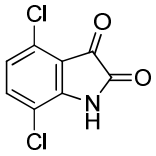
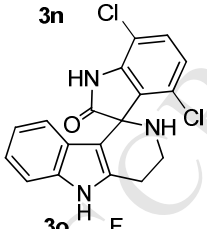
Tetrahydro-*γ*-carbolines are the precursors of naturally occurring *γ*-carbolines.[9] These are less studied than the *β*-carboline analogues though they exhibit range of biological activities.[10] Literature survey revealed that tetrahydrospiro-*γ*-carbolines are not much reported.[6j] Thus, the synthesis of tetrahydrospiro-*γ*-carbolines was undertaken by using the present protocol in which isotryptamine **1b** is used instead of tryptamine **1a** as a starting material.

Table 2. Synthesis of tetrahydrospiro-*γ*-carbolines [a] (**3k-3s**)



1b **2** **3**

Entry	isotryptamine (1b)	isatin (2)	Product (3)	Yield[b] (%)
10				68
	1b	**2a**	**3k**	
11				65
	1b	**2b**	**3l**	
12				60
	1b	**2c**	**3m**	

Entry	isotryptamine (1b)	isatin (2)	Product (3)	Yield[b] (%)
13				60
	1b	2d	3n	
14				50
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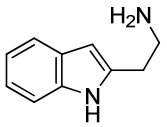
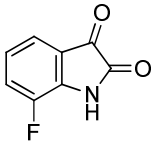
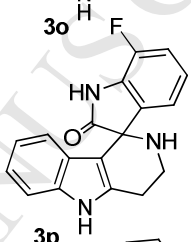
15				55
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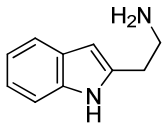
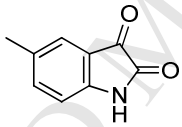
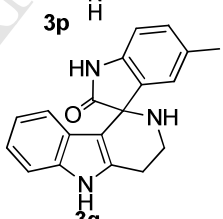
16				70
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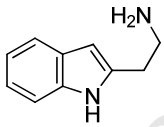
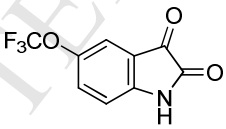
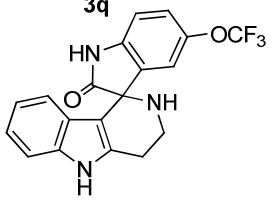
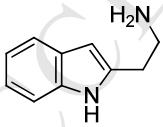
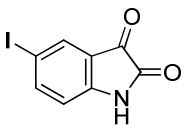
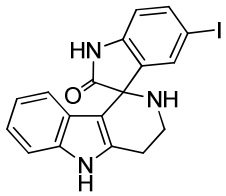
17				83
	1b	2k	3r	
18				72
	1b	2l	3s	

[a]Reaction condition: **1b** (0.31 mmol), **2** (0.31 mmol), were heated in presence of *β*-cyclodextrin-SO_3H (0.06 mmol) in water (5 mL) at 80 °C for 8-12 h. [b]Isolated yield.

Reaction of isotryptamine **1b** with various substituted isatins was carried out using the recyclable *β*-cyclodextrin-SO_3H catalyst in aqueous medium. Even in this case, the isotryptamine **1b** smoothly underwent spirocyclisation with substituted isatins using the same procedure and furnished the corresponding tetrahydrospiro-*γ*-carbolines **3k-3s** in little lower yields. The results are summarized in table 2.

The products tetrahydrospiro-*γ*-carbolines were characterized by HRMS and spectral data. Change in the substitution pattern on isatins (electron withdrawing groups like -Cl, -Br, -OCF_3, -I as well as electron donating group like -Me) did not much affect the rate and the yield of the reaction.

3. Conclusion

Synthesis of range of tetrahydrospiro-*β* as well as *γ*-carbolines have been demonstrated using recyclable *β*-cyclodextrin-SO_3H catalyst in water as a reaction solvent. Good to excellent yields of the products were obtained within short time by using this catalyst with simple starting materials. The catalyst was found to be efficient for the spirocyclisation reaction and can be recycled for three batches of the same reaction. Use of mild reaction condition along with the use of catalytic amount of cheap and easily available *β*-cyclodextrin-SO_3H in aqueous medium, makes the present protocol important from the environmental perspective.

4. Experimental

4.1 General Remarks

Chemicals and solvents received from commercial sources were used without further purification. ^1H NMR spectra and ^{13}C NMR spectra were recorded on Bruker (400 MHz and 500 MHz) spectrometer. Coupling constants (*J*) are reported in hertz (Hz) and chemical shifts are reported in parts per million (*δ*). Melting points were determined using a Thomas Hoover capillary melting point apparatus and uncorrected. Column chromatography was performed using silica gel (100-200 mesh). Exact mass measurements were performed on Bruker impact HD Q-TOF analyzer in the ESI mode. IR spectra were recorded by a Shimadzu FT-IR 8400 Spectrometer. The routine monitoring of reactions were performed using TLC (Merck kieselgel 60 0.20 mm layer, UV254).

Starting tryptamine **1a** and isatins **2** were commercially available. Isotryptamine **1b** and isatin **2g** were prepared according to the literature report.[11]

4.2 Synthetic Procedures and Characterization Data

4.2.1. General procedure for preparation of sulfonated β-cyclodextrin [2] *(β-CD-SO_3H)*

Chlorosulfonic acid (1.572 g, 13.5 mmol) was added dropwise under stirring to the mixture of *β*-cyclodextrin (7.660 g, 6.75 mmol) in CH_2Cl_2 (35 mL) and was kept at 0 °C for 3 h. Further, the mixture was stirred for 2 h at room temperature to remove HCl. Then, the mixture was filtered, washed with methanol (30 mL) and dried at RT which furnished sulfonated *β*-cyclodextrin as white powder (7.92 g, 88%). The $–SO_3H$ contents were measured by titration method and were matching with the value 0.52 mequiv.g^{-1}

*4.2.2. General procedure for spirocyclization (**A**)*

Sulfonated-*β*-cyclodextrin (*β*-CD-SO_3H) (76 mg, 0.06 mmol) was dissolved in water (5 mL) at RT by stirring to get the clear solution in 50 mL round bottom flask. Further, isatin **2** (0.31 mmol) and tryptamine **1a**/ isotryptamine **1b** (0.31 mmol) were added to the solution under constant stirring and mixture was heated at 80 °C for 8-12 h. The progress of the reaction was monitored by TLC. After completion of reaction, it was cooled to room temperature, water was added to it. The aqueous phase was extracted with ethyl acetate. The organic extracts were combined, washed with brine and dried over sodium sulfate. The solvent was evaporated in vacuo and the crude product obtained was purified by column chromatography using chloroform/methanol (99:1) as an eluent furnishing the product. The spectral and analytical data of all the reported products is consistent with the previous [6c,d,f] reports.

*4.2.3. 2',3',4',9'-Tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3a**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and isatin **2a** (46 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (85 mg, 94%); mp 178-180 (Lit. 176–177 °C); R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (br s, 1H), 8.33 (br s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.15-6.94 (m, 4H), 6.90 (t, *J* = 7.2 Hz, 2H), 6.59 (d, *J* = 7.7 Hz, 1H), 3.62-3.47 (m, 1H), 3.28-3.08 (m, 1H), 2.86 (dd, *J* = 11.4, 5.7 Hz, 2H), 2.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 140.9, 136.4, 132.1, 129.9, 129.8, 127.0, 124.9, 123.2, 122.4, 119.5, 118.5, 112.1, 111.3, 111.1, 62.1, 40.0, 22.0.

*4.2.4. 5-Chloro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3b**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 5-chloroisatin **2b** (57 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a white solid (85 mg, 85%); mp 227-229°C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.92 (br s, 1H), 7.54-7.35 (m, 1H), 7.08-7.00 (m, 3H), 7.00-6.90 (m, 2H), 6.51 (d, *J* = 8.2 Hz, 1H), 3.57 (dd, *J* = 12.4, 5.6 Hz, 1H), 3.28-3.12 (m, 1H), 2.93-2.71 (m, 2H), 1.87 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 139.1, 136.4, 133.7, 129.8, 129.0, 128.8, 127.0, 125.5, 122.9, 119.9, 118.7, 112.7, 111.8, 111.3, 62.2, 40.1, 29.8.

*4.2.5. 5-Bromo-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3c**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 5-bromoisatin **2c** (70 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (105 mg, 91%); semisolid; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 8.09 (br s, 1H), 7.62-7.39 (m, 1H), 7.26-7.22 (m, 1H), 7.20-7.14 (m, 1H), 7.12-7.06 (m, 2H), 7.04-6.99 (m, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 3.88-3.51 (m, 1H), 3.35-3.20 (m, 1H), 3.01-2.83 (m, 2H), 1.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 139.7, 136.4, 134.0, 132.7, 129.0, 128.2, 126.9, 122.9, 119.8, 118.7, 116.0, 112.6, 112.3, 111.3, 62.2, 40.1, 22.0.

*4.2.6. 5-Fluoro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3d**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 5-fluoroisatin **2d** (52 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (80 mg, 83%); mp 230-232 (lit.[7d] 229-230°C); R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (br s, 1H), 10.42 (br s, 1H), 7.52-7.42 (m, 1H), 7.24-7.14 (m, 1H), 7.14-7.00 (m, 2H), 7.00-6.84 (m, 3H), 3.63-3.53 (m, 1H), 3.16-3.06 (m, 1H), 2.88-2.76 (m, 1H), 2.77-2.67 (m, 1H) (One -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) 178.7, 158.4 (d, *J* = 238 Hz, C-F), 138.7, 136.5, 131.5, 126.8, 121.7, 118.9, 115.8 115.78 (d, *J* = 24 Hz), 112.7 112.58 (d, *J* = 24 Hz), 111.5, 111.23 (d, *J* = 7.7 Hz) 110.9, 61.93, 44.87, 21.79.

*4.2.7. 4,7-Dichloro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3e**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 4,7-dichloroisatin **2e** (67 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a white solid (93 mg, 83%); mp 264-265 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (br s, 1H), 10.58 (br s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J*

= 7.9 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 13.9, 8.0 Hz, 2H), 3.66- 3.57 (m, 1H), 3.19-3.06 (m, 1H), 2.82-2.69 (m, 2H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.7, 142.6, 136.2, 130.9, 129.9, 129.3, 128.9, 126.6, 123.8, 121.4, 118.6, 118.1, 113.2, 111.4, 111.3, 62.5, 38.9, 21.6. FTIR *v* 3033, 2922, 1627, 1032, 788, cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 358.0511, calcd for $C_{18}H_{14}Cl_2N_3O$ 358.0508.

*4.2.8. 7-Fluoro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3f**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 7-fluoroisatin **2f** (52 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a yellow solid (78 mg, 81%); mp 157-159 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (br s, 1H), 10.50 (br s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.23-7.12 (m, 2H), 7.09-6.86 (m, 4H), 3.62 (ddd, *J* = 12.6, 8.0, 4.8 Hz, 1H), 3.13 (dt, *J* = 12.4, 4.5 Hz, 1H), 2.90-2.67 (m, 2H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.7, 148.2, 136.5, 136.2 (d, *J* = 3.5 Hz), 131.7, 126.9, 122.9 (d, *J* = 5.7 Hz), 121.7, 121.1 (d, *J* = 2.8 Hz), 119.4, 118.4,(d, *J* = 17 Hz), 111.5, 110.7, 61.8, 39.4, 22.0.

*4.2.9. 1-Methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3g**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and *N*-methylisatin **2g** (51 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a yellow solid (70 mg, 74%); mp 219-221 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (br s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.12 (m, 3H), 7.05-6.92 (m, 3H), 3.16 (s, 3H), 3.16-3.13 (m, 4H), 2.72-2.78 (m, 2H), (one -*N*H and aliphatic protons was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 144.0, 136.2, 132.3, 131.7, 129.4, 126.7, 124.4, 122.7, 121.5, 118.7, 118.1, 111.3, 110.6, 109.1, 79.3, 61.1, 26.4, 21.8.

*4.2.10. 5-Methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3h**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 5-methylisatin **2h** (51 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a yellow solid (79 mg, 83%); mp 266-268 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (br s, 1H), 10.35 (br s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.09-6.93 (m, 3H), 6.91 (s, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.58 (ddd, *J* = 12.6, 7.7, 4.9 Hz, 1H), 3.14 (dt, *J* = 12.6, 4.8 Hz, 1H), 2.89-2.64 (m, 2H), 2.19 (s, 3H) (one -*N*H proton was not seen); ^{13}C NMR

(100 MHz, DMSO-d_6) δ 178.3, 139.8, 136.0, 133.0, 131.8, 130.4, 129.1, 126.5, 125.1, 121.0, 118.2, 117.6, 111.1, 110.1, 109.5, 61.2, 39.1, 21.7, 20.5.

*4.2.11. 5,7-Dimethyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3i**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 5,7-dimethylisatin **2i** (55 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a white solid (50 mg, 51%); mp 266-268 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br s, 1H), 10.36 (br s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.20-7.13 (m, 1H), 7.07-6.92 (m, 2H), 6.90-6.87 (m, 1H), 6.76-6.68 (m, 1H), 3.59 (ddd, *J* = 12.7, 7.9, 4.8 Hz, 1H), 3.13 (dt, *J* = 12.6, 4.8 Hz, 1H), 2.87-2.66 (m, 2H), 2.25 (s, 3H), 2.15 (s, 3H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.7, 138.3, 136.0, 132.6, 132.0, 130.5, 130.4, 126.5, 122.4, 120.9, 118.7, 118.2, 117.6, 111.0, 110.0, 61.4, 39.1, 21.7, 20.4, 16.4.

*4.2.12. 5-Methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-b]indol]-2-one (**3j**)*

2-(1*H*-indol-3-yl)ethan-1-amine **1a** (50 mg, 0.31 mmol) and 5-methoxyisatin **2j** (56 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a Orange solid (45 mg, 45%); mp 253-255 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (br s, 1H), 10.27 (br s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.06-6.93 (m, 2H), 6.85-6.81 (m, 2H), 6.69 (d, *J* = 1.6 Hz, 1H), 3.65-3.57 (m, 4H), 3.12 (dt, *J*= 12.5, 4.6 Hz, 1H), 2.88 (ddd, *J* = 13.5, 8.2, 5.2 Hz, 1H), 2.72 (dt, *J* = 15.1, 4.4 Hz, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.3, 154.9, 136.1, 135.5, 133.9, 131.7, 126.6, 121.1, 118.3, 117.7, 114.0, 111.1, 110.2, 61.5, 55.4, 40.1, 21.6.

*4.2.13. 2',3',4',5'-Tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3k**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and isatin **2a** (46 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (61 mg, 68%); mp 184-186 °C; R_f 0.25 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 10.39 (br s, 1H), 7.25-7.20 (m, 2H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.91-6.83 (m, 2H), 6.66 (t, *J* = 7.4 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 3.72-3.67 (m, 1H), 3.16-3.11 (m, 1H), 2.92-2.89 (m, 1H), 2.77-2.72 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.6, 141.9, 135.7, 135.3, 131.5, 128.6, 124.6, 124.3, 121.6, 120.2, 118.4, 116.8, 110.8, 109.3, 60.7, 38.5, 23.3; FTIR *v* 3033, 2922, 1627, 1032, 788, cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 290.1289, calcd for $C_{18}H_{16}N_3O$ 290.1288.

*4.2.14 5-Chloro-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3l**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 5-chloro isatin **2b** (57 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (65mg, 65%); mp 172-174 °C; R_f 0.28 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 10.54 (br s, 1H), 7.29-7.26 (m, 2H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.98-6.95 (m, 2H), 6.71 (t, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 3.70-3.64 (m, 1H), 3.16-3.11 (m, 1H), 2.95-2.91 (m, 1H), 2.78-2.75 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.5, 140.8, 136.1, 136.0, 135.3, 128.4, 125.6, 124.5, 124.2, 120.2, 118.6, 116.5, 110.9, 110.8, 106.3, 61.0, 38.5, 23.3; FTIR *v* 3272, 2922, 1616, 1454, 1088, 742 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 324.0900, calcd for $C_{18}H_{15}ClN_3O$ 324.0898.

*4.2.15 5-Bromo-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3m**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 5-bromo isatin **2c** (71 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (68 mg, 60%); mp 195-197 °C; R_f 0.48 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 10.55 (br s, 1H), 7.41 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 1.8 Hz, 1H), 6.98-6.91 (m, 2H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 3.68-3.64 (m, 1H), 3.15-3.12 (m, 1H), 2.95-2.89 (m, 1H), 2.88 -2.72 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.4, 141.2, 136.4, 136.1, 135.3, 131.2, 127.2, 124.1, 120.2, 118.6, 116.5, 113.3, 111.3, 111, 106.3, 60.9, 38.5, 23.3; FTIR *v* 2921, 1656, 1386, 1089, 771 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 368.0395, calcd for $C_{18}H_{15}BrN_3O$ 368.0393.

*4.2.16. 5-Fluoro-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3n**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 5-fluoro isatin **2d** (52 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (57 mg, 60%); mp 153-155 °C; R_f 0.47 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 10.44 (br s, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.10-7.03 (m, 1H), 6.98-6.90 (m, 2H), 6.87 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 3.71-3.66 (m, 1H), 3.24-3.05 (m, 1H), 3.00-2.84 (m, 1H), 2.78-2.63 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.9, 138.0, 136.1, 135.4, 126.8, 124.3, 120.3, 118.6, 116.6, 114.9, 112.3, 111.0, 110.1, 106.5, 61.2, 38.5, 23.3; FTIR *v* 3200, 2921, 1642, 1490, 782 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 308.1196, calcd for $C_{18}H_{15}FN_3O$ 308.1194.

*4.2.17. 4,7-Dichloro-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3o**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 4, 7-dichloro isatin **2e** (68 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (55 mg, 50%); mp 262-264 °C; R_f 0.33 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 10.99 (br s, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 6.97-6.90 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.78-6.67 (m, 1H), 6.33 (d, *J* = 7.9 Hz, 1H), 3.80-3.70 (m, 1H), 3.20-3.09 (m, 1H), 2.98-2.85 (m, 1H), 2.76-2.67 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.1, 141.6, 136.7, 135.3, 130.7, 130.1, 129.1, 124.1, 123.6, 120.1, 118.6, 115.9, 112.5, 111, 103.6, 62.2, 38.3, 23.3; FTIR *v* 3404, 2922, 1643, 1490, 742 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 358.0511, calcd for $C_{18}H_{14}Cl_2N_3O$ 358.0508.

*4.2.18. 7-Fluoro-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3p**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 7-fluoro isatin **2f** (52 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (52 mg, 55%); mp > 180 °C; R_f 0.42 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 10.90 (br s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.15 (m, 1H), 6.96-6.83 (m, 3H), 6.74-6.67 (m, 1H), 6.38 (d, *J* = 7.9 Hz, 1H), 3.75-3.60 (m, 1H), 3.16-3.08 (m, 1H), 2.97-2.86 (m, 1H), 2.81-2.70 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.6, 136.9, 136, 135.3, 124.2, 122.4, 122.4, 120.5, 120.2, 118.5, 116.5, 115.5, 115.4, 110.9, 106.5, 60.9, 38.3, 23.3; FTIR *v* 3043, 2922, 1642, 1458, 1163, 755 cm^{-1}. HRMS (ESI) $[M + H]^+$ found *m/z* 308.1196, calcd for $C_{18}H_{15}FN_3O$ 308.1194.

*4.2.19. 5-Methyl-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3q**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 5-methyl isatin **2h** (50 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (66 mg, 70%); mp 173-175 °C; R_f 0.30 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 10.30 (br s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.85-6.83 (m, 2H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 3.71-3.65 (m, 1H), 3.17-3.13 (m, 1H), 2.95-2.87 (m, 1H), 2.77-2.73 (m, 1H), 2.14 (s, 3H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.8, 139.3, 135.7, 135.3, 134.1, 130.2, 128.6, 125.0, 124.4, 120.0, 118.3, 116.8, 110.7, 108.9, 107.2, 60.8, 38.6, 23.4, 20.5.; FTIR *v* 3150,

2922, 1684, 1456, 1087, 727 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 304.1444, calcd for $C_{19}H_{18}N_3O$ 304.1444.

*4.2.20. 5-(Trifluoromethoxy)-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3r**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 5-(trifluoromethoxy) isatin **2k** (72 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (83 mg, 72%); mp 177-179 °C; R_f 0.37 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (br s, 1H), 10.58 (br s, 1H), 7.27-7.23 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 1.5 Hz, 1H), 6.95-6.88 (m, 1H), 6.73-6.65 (m, 1H), 6.35 (d, *J* = 7.9 Hz, 1H), 3.79-3.64 (m, 1H), 3.18-3.05 (m, 1H), 2.93 (m, 1H), 2.74 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.9, 143.3, 141.1, 136.2, 135.7, 135.4, 124.2, 121.7, 121.4, 120.3, 118.6, 118.0, 116.4, 111.0, 110.2, 106.2, 61.1, 38.4, 23.3; FTIR *v* 3022, 2922, 1640, 1458, 1163, 760, 655 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 374.1112, calcd for $C_{19}H_{15}F_3N_3O_2$ 374.1111.

*4.2.21. 5-Iodo-2',3',4',5'-tetrahydrospiro[indoline-3,1'-pyrido[4,3-b]indol]-2-one (**3s**)*

2-(1*H*-indol-2-yl)ethan-1-amine **1b** (50 mg, 0.31 mmol) and 5-iodoisatin **2l** (85 mg, 0.31 mmol) were reacted using the general procedure **A**. The product was obtained as a brown solid (93 mg, 72%); mp 169-171°C; R_f 0.23 ($CHCl_3$/MeOH = 99/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (br s, 1H), 10.52 (br s, 1H), 7.56 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.27-7.26 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 3.67-3.63 (m, 1H), 3.20-3.07 (m, 1H), 2.95-2.89 (m, 1H), 2.75-2.67 (m, 1H) (one -*N*H proton was not seen); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.3, 141.7, 137.0, 136.7, 136.1, 135.3, 132.7, 124.2, 120.2, 118.6, 116.5, 111.8, 110.9, 106.4, 60.7, 38.5, 23.3; FTIR *v* 3272, 2921, 1609, 1458, 1088, 737 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 416.0258, calcd for $C_{18}H_{15}IN_3O$ 416.0254.

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5. References

1. a) Wu J, Du X, Ma J, Zhang Y, Shi Q, Luo L, Song B, Yanga S, Hua D. *Green Chem.* 2014; 16:3210-3217;

b) Tayade YA, Patil DR, Wagh YB, Jangle AD, Dalal DS. *Tetrahedron Lett.* 2015; 56:666-673.

2. Asghari S, Tajbakhsh M, Kenari BJ, Khaksar S. *Chin. Chem. Lett.* 2011; 22:127-130.

3. a) Lindstrom UM. *Chem. Rev*. 2002; 102:2751-2772;

b) Hailes HC. *Org. Process Res. Dev.* 2007; 11:114-120;

c) Rueping M, Theissmann T. *Chem. Sci*. 2010; 1:473-476.

4. a) McNulty J, Velázquez CZ, McLeod D. *Green Chem.* 2013; 15:3146-3149;

b) Song J, Fan H, Ma J, Han Buxing. *Green Chem.* 2013; 15:2619-2635;

c) Elchinger P-H, Faugeras P-A, Zerrouki C, Montplaisir D, Brouillette F, Zerrouki R. *Green Chem*. 2012; 14:3126-3131;

d) Osada M, Kikuta K, Yoshida K, Totani K, Ogatab M, Usuic T. *Green Chem*. 2013; 15:2960-2966.

5. a) Abe T, Yamada K. *J. Nat. Prod.* 2017; 80:241-245;

b) Hansen CL, Ohm RG, Olsen LB, Ascic E, Tanner D, Nielsen TE. *Org. Lett.* 2016; 18:5990-5993;

c) Reddy C, Burra AG, Singarapu KK, Gree R. *Eur. J. Org. Chem.* 2016;5274-5281;

d) Shmatova OI, Khrustalev VN, Nenajdenko VG. *Org. Lett.* 2016; 18:4494-4497;

e) Stçckigt J, Antonchick AP, Wu F, Waldmann H. *Angew. Chem. Int. Ed.* 2011; 50:8538-8564;

f) Dalpozzo R. *Molecules.* 2016; 21:699-716;

g) Cox ED, Cook JM. *Chem. Rev.* 1995; 95:1797-1842;

h) Larghi EL, Kaufman TS. *Synthesis.* 2006; 2:187-220;

i) Saha B, Sharma S, Sawant D, Kundu B. *Tetrahedron Lett.* 2007; 48:1379-1383.

6. a) Khalafi-Nezhad A, Shahidzadeh ES, Sarikhani S, Panahi F *J. Mol. Catal. A: Chem.* 2013; 379:1-8;

b) Badillo JJ, Silva-Garcia A, Shupe BH, Fettinger JC, Franz AK. *Tetrahedron Lett.* 2011; 52:5550-5553;

c) Duce S, Pesciaioli F, Gramigna L, Bernardi L, Mazzanti A, Ricci A, Bartoli G, Bencivenni G. *Adv. Synth. Catal*. 2011; 353:860-864;

d) Reddy GN, Rao BM, Vijay M, Devi BLAP, Prasad RBN, Reddy BVS. *Can. J. Chem.* 2015; 93:341-347;

e) Shumaila AMA, Puranik VG, Kusurkar RS. *ARKIVOC*. 2011; 2:41-56;

f) Dawange MA, Urmode TD, Khan A, Kusurkar RS. *ChemistrySelect.* 2017; 2:2552-2555;

g) Yeung BKS, Zou B, Rottmann M, Lakshminarayana SB, Ang SH, Leong SY, Tan J, Wong J, Keller-Maerki S, Fischli C, Goh A, Schmitt EK, Krastel P, Francotte, Kuhen K, Plouffe D, Henson K, Wagner T, Winzeler EA, Petersen F, Brun R, Dartois V, Diagana TT, Keller TH. *J. Med. Chem*. 2010; 53:5155-5164;

h) Ryabukhin SV, Panov DM, Plaskon AS, Tolmachev AA, Smaliy RV. *Monatsh Chem.* 2012; 143:1507-1517;

i) Zou Bi, Yap P, Sonntag L-S, Leong SY, Yeung BKS, Keller TH. *Molecules.* 2012; 17:10131-10141;

j) Reddy BVS, Swain M, Reddy SM, Yadav JS, Sridhar B. *Eur. J. Org. Chem.* 2014;3313-3318.

7. a) Yu H, Ru S, Dai G, Zhai Y, Lin H, Han S, Wei Y. *Angew. Chem. Int. Ed.* 2017; 56:1-6;

b) Butler RN, Coyne AG, *Chem. Rev.*, 2010; 110:6302-6337;

c) Simon M-O, Li C-J. *Chem. Soc. Rev.* 2012; 41:1415-1427.

8. a) Khalafi-Nezhad A, Mohammadi S. *ACS Comb. Sci*. 2013: 15:512-518;

b) Ziarani M, Ghodsi, Aleali, Faezeh. *Iran. J. Chem. Chem. Eng*, 2016; 35:17-23.

9. a) Bridoux A, Millet R, Pommery J, Pommery N, Henichart J-P. *Bioorg. Med. Chem.* 2010; 18:3910-3924;

b) Bonjoch J, Diaba F, Pages L, Perez D, Soca L, Miralpeix M, Vilella D, Anton P, Puig C. *Bioorg. Med. Chem. Lett.* 2009; 19:4299-4302;

c) Kharkevich DA. *Farmakol. Toksikol.* 1957; 20:46-51.

10. a) Chen J, Dong X, Liu T, Lou J, Jiang C, Huang W, He Q, Yang B, Hu Y. *Bioorg. Med. Chem.* 2009; 17:3324-3331;

b) Harbert CA, Plattner JJ, Welch WM. *J. Med. Chem.* 1980; 23:635-643;

c) Henderson AJ, Guzzo PR, Ghosh A, Kaur J, Koo J-M, Nacro K, Panduga S, Pathak R, Shimpukade B, Tan V, Xiang K, Wierschke JD, Isherwood ML. *Bioorg. Med. Chem. Lett.* 2012; 22:1494-1498.

d) Ivachtchenko AV, Frolov EB, Mitkin OD, Kysil VM, Khvat AV, Okun IM, Tkachenko SE. *Bioorg. Med. Chem. Lett.* 2009; 19:3183-3187.

11. a) Reddy BVS, Dey SK, Yadav JS, Sridhar B. *Tetrahedron Lett.* 2012; 53:3676-3679;

b) Spadoni G, Balsamini C, Bedini A, Diamantini G, Giacomo BD, Tontini A, and Tarzia G. *J. Med. Chem.*1998; 41:3624-3634;

c) Carne-Carnavalet B, Krieger J-P, Folleas B, Brayer J-L, Demoute J-P, Meyer C, Janine C. *Eur. J. Org. Chem.* 2015; 1273-1282;

d) Trost BM, Zhang Y. *J. Am. Chem. Soc*. 2007; 129:14548-14549.