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**RESEARCH ARTICLE**

# Design, Synthesis and Biological Activities of Isatin Derivatives

REENA D SOUZA and AMIT CHATTREE

Department of Chemistry, Sam Higginbottom Institute of Agriculture, Technology & Sciences (Deemed-to-be-University), Allahabad -211007, (U.P.), India
*srreenabs@gmail.com*

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**Abstract:** Two compounds ISD-1 and ISD-2 were synthesized by *N*-Alkylation method. Synthesized compounds were characterized by IR, UV, Mass and $^{1}$H NMR and $^{13}$C NMR. The biological activities of both the compounds were evaluated. ISD-2 shows good antibacterial and antifungal activity as well as very little antioxidant property where as ISD-1 shows activity only towards negative strains of bacteria.

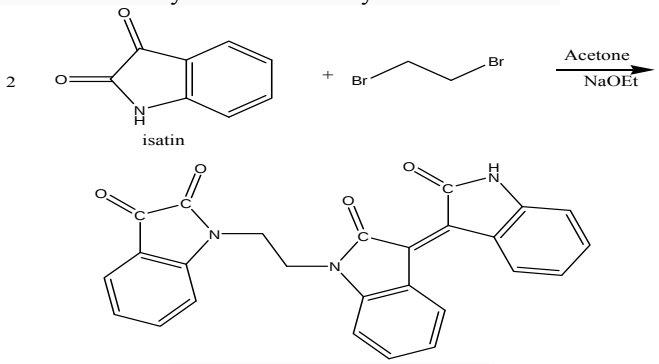
**Keywords:** Isatin, ISD-1, ISD-2, *N*-Alkylation

## Introduction

Isatin is one of the few compounds to have been synthesized before it was discovered in nature. Isatin (1-*H*-indole-2,3-dione) and its derivatives possess a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. From literature[1] we come to know that Isatin containing synthetic compounds and their derivatives are known to be associated with broad spectrum of biological activity. In humans and other mammals, isatin is found as an endogenous molecule. Although the Metabolic pathways of isatin have not yet been fully elucidated; it has been proposed that it is synthesised *in vivo* from tryptophan-rich foods such as meat, dairy and whole grains[2]. Formerly, the study of Isatin derivatives was connected with dye synthesis, but more recently these heterocycles have been shown to demonstrate antiprotozoal, antibacterial, antifungal[3-5], antiviral[6]. Anti-HIV, anticonvulsant[7], antitumoral[8], anti-inflammatory and antihelminthic activities; influence neurodegenerative diseases; participate in metabolism; acetylcholinesterase inhibitors and stimulate the growth of plants[9]. Drugs containing the Isatin skeleton are used to treat diseases such as epilepsy[10], tuberculosis[11] and bulimia[12]. The various substituents at 1$^{st}$ and 3$^{rd}$ position of the Isatin, are phenyl ring moieties, heterocyclic rings and aliphatic system. Isatin is one of the most promising new classes of heterocyclic molecules having many interesting activity profiles and well-tolerated in human[2]. Since Isatins have active area for medicinal chemistry there is a great need to create novel Isatin derivatives for emerging drug targets.

## Experimental

Isatin derivatives ISD-1 and ISD-2 were prepared according to the literature by *N*-alkylation method[13]. Synthesized derivatives were characterized by spectrometry method. UV-Vis spectra were recorded on a Shimadzu UV-2450 spectrophotometer controlled by the Win Lab Software through computer. IR spectra was recorded by Perkin-Elmer Spectrum RX-1 FT-IR spectrometer in the range 4000-400 $cm^{-1}$. Mass spectra by Bruker Micro TOF III, Analyzed in positive Mode, Source voltage: 4500 V and $^{1}H$ NMR and $^{13}C$ NMR were recorded by Bruker 400 MHz NMR spectrometer controlled by TOPSPIN software working at 400 MHz at 20 ºC. By disc diffusion method anti bacterial[8] and antifungal activity was evaluated[14]. Antioxident activity was evaluated by DPPH method[15].

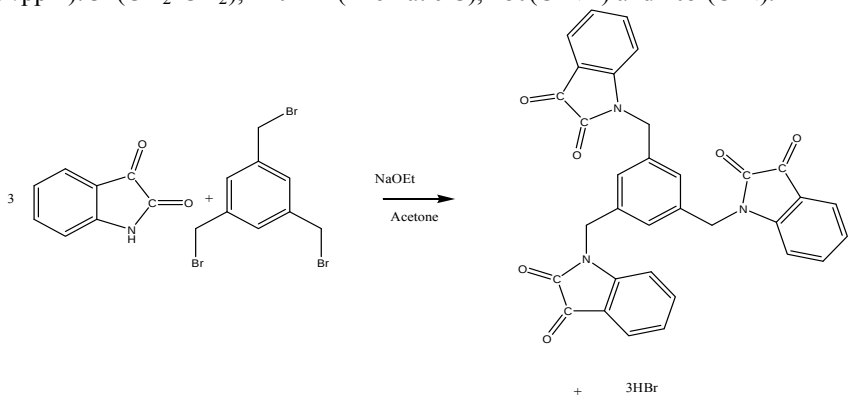



**Scheme 1.** Synthesis of ISD-1

Isatin (2.94, 10 mmol) and 1,2-dibromo ethane (0.865 g, 10 m.mol) was dissolved in 100 mL of acetone taken in a 250 mL round bottom flask. Then few drops of base (NaOEt) was added till it becomes dark green color and refluxed[13] for 2 hours at 50 ºC. Then the reaction mixture was kept for evaporation. The yellow crystals formed were filtered and air dried. Yield 52% mp 166 ºC

*2-((Z)-2-oxo-3-(2-oxoindolin-3-ylidene) indolin-1-yl) ethyl) indoline-2,3-dione. (ISD-1)*

IR (KBr $cm^{-1}$): 3059.8(aromatic C-H), 3110.6(N-H), 2888.3(-$CH_2$-$CH_2$-), 1709 (C=O), 1620 (C=C), 1333 (CN aromatic). UV (ethanol nm): 254 ($\pi \rightarrow \pi^*$ for conjugated –C=O group), 291($\pi \rightarrow \pi^*$ for unconjugated –C=O group). MS (*m/z*) 432.9. $^{1}$HNMR (400MHz DMSO /ppm): 3.2(4H in -$CH_2$-$CH_2$-), 6.5 to 8.4 (12H in ArH) and 10.2 (1H of –NH-). $^{13}C$ NMR (400MHz DMSO /ppm): 31($CH_2$-$CH_2$), 110-114(Aromatic C), 180(C-NH) and 205 (C-N).




**Scheme 2**. Synthesis of ISD-2

Isatin (4.41 g, 30 mmol) and 1,3,5-tris(bromomethyl)benzene (3.56 g, 10 m.mol) was dissolved in 100 mL of acetone taken in a 250 mL round bottom flask. Then few drops of base (NaOEt) was added till it becomes dark green color and refluxed[13] for 2 hours at 50 ºC. Then the reaction mixture was kept for evaporation. The orange red solid formed were filtered and air dried. Yield 26% mp 116 ºC.

### *1,3,5-Tris(indole 2,3 dione methyl)benzene.(ISD-2)*

IR (KBr $cm^{-1}$): 3056.8(aromatic C-H), 3110.6(N-H), 2888.3(-$CH_2$-), 1709 (C=O), 1334(CN aromatic). UV (ethanol nm): 244 ($\pi \rightarrow \pi^*$ for conjugated –C=O group), 294($\pi \rightarrow \pi^*$ for unconjugated –C=O group). MS (*m/z*) 555.98. $^1$HNMR (400MHz DMSO /ppm): 3.2(6H in -$CH_2$-), 7 -7.5 (12H in ArH of isatin) and 6.7 (3H of central aromatic ring). $^{13}$CNMR (400MHz DMSO /ppm): 40(3C of-$CH_2$-), 109-130(Aromatic C of Isatin), 140(C of mesytilene) and 180 (C-N).

## Results and Discussion

The characteristic frequency 2888.3 $cm^{-1}$ corresponds to aliphatic stretch and frequency 1470.6 $cm^{-1}$ corresponding to -$CH_2$- bending in alkanes shows that *N*-alkylation has taken place for the formation of ISD-1. Absorption maxima in the UV region 254 nm and 291 nm are assignable to $\pi \rightarrow \pi^*$ transition for conjugated and unconjugated –C=O group respectively.

EI mass spectrum was recorded gives peak at *m/z* at 432.9 is due to parent ion with the molecular mass 435 and the proton NMR of spectrum ISD-1 shows signal at 3.2 ppm assignable to proton attached with alkanes. The resonance at 7-7.5 ppm is assigned to the aromatics protons in all three rings. The $^{13}$C NMR spectrum of ISD-1 shows a signal at 31 ppm for aliphatic carbon, the resonance at 110-140 ppm is assigned to aromatic carbons, 180 ppm shows carbonyl groups attached with –NH group. 205 ppm shows carbonyl carbon attached to amide group.

The characteristic frequency 1474 $cm^{-1}$ corresponds to alkane vibration and absence of –NH vibration shows that *N*-alkylation has taken place in ISD-2. ISD-2 shows two characteristic absorption maxima in the UV region 244 nm and 294 nm are assignable to $\pi \rightarrow \pi^*$ transition for conjugated and unconjugated –C=O group respectively. EI mass spectrum was recorded gives peak at *m/z* at 555.8 which agrees with the molecular mass of the designed compound.

The proton NMR of spectrum shows signal at 3.2 ppm assignable to proton attached with alkanes. The resonance at 7-7.5 ppm is assigned to the aromatics protons in all four rings. The $^{13}$C NMR spectrum of ISD-2 shows a signal at range 39-40 ppm for aliphatic carbon, the resonance at 109-130 ppm is assigned to aromatic carbons of Isatin, resonance at 140 ppm carbons of mesitylene, 180 ppm shows carbonyl groups attached with –NH group. 205 ppm shows carbonyl carbon attached to amide group.

### *Antimicrobial activity*

*Enterobacter aerogenes* and *Yersinia enterocolitica* – ISD-1 has shown the activity towards Gram Negative bacteria. ISD-2 shows good activity towards the Gram positive bacteria, *Staphylococcus aureus, Micrococcus luteus*, Gram negative bacteria *Enterobacter aerogenes Yersinia enterocolitica*, fungal strains *Aspergillus flavus* and *Trichophyton rubrum* (Table 1). ISD-2 shows only 9.5% of free radical scavenging property (Figure 1).

**Table 1.** Antibacterial and antifungal activities of ISD-1 and ISD-2

| S.No | Pathogen | Zone inhibition, mm (mg/disc) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2.5 | | 5 | | 10 | | Control | |
| | | ISD-1 | ISD-2 | ISD-1 | ISD-2 | ISD-1 | ISD-2 | ISD-1 | ISD-2 |
| 1 | *Staphylococcus aureus (*96) | - | 12 | - | 15 | - | 17 | 22 | 19 |
| 2 | *Micrococcus luteus* (106) | - | 11 | - | 13 | - | 15 | 25 | 20 |
| 3 | *Enterobacter aerogenes* (111) | 11 | 10 | 10 | 11 | | 14 | 28 | 17 |
| 4 | *Yersinia enterocolitica* (840) | 12 | 16 | 12 | 18 | | 21 | 25 | 19 |
| 5 | *Aspergillus flavus (AF)* | - | 14 | - | 17 | - | 20 | - | - |
| 6 | *Scopulariopsis sp (101)* | - | 12 | - | 16 | - | 21 | - | - |

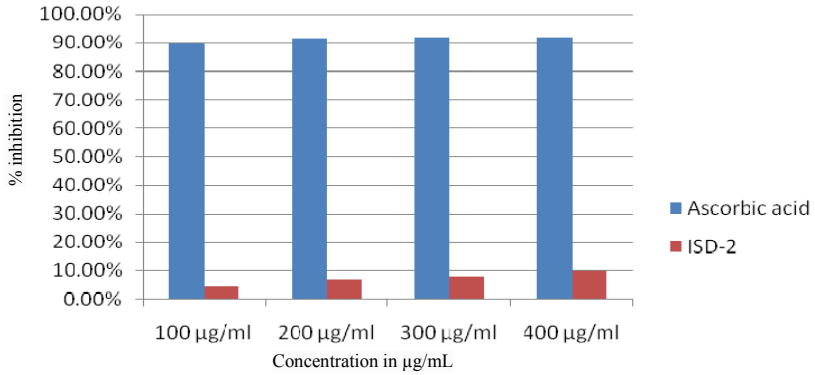



**Figure 1.** Free radical scavenging of ISD-2 derivative

## Conclusion

Thus from the study it can be concluded that among the two synthesized compounds ISD-2 shows more activity as compared to ISD-1 which may be due to presence of the aromatic ring in the structure of the isatin derivative 1,3,5-tris(indole 2,3 dione methyl)benzene. Further studies can be conducted in derivatising these compounds by substituting C2 and C3 positions, along with substitution on the aromatic ring. By this process the activities of the compounds can be enhanced. Thus these compounds provide the opportunities to design new derivatives with improved activities and applications. These compounds can be applied in medicinal chemistry as they show various biological activities.

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