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Review Article

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Isatin: A Versatile Heterocyclic Compound a Review

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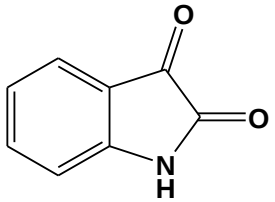
Abstract In medicinal chemistry, Isatin is an important scaffold it is an indole derivative heterocyclic compound having a benzene ring fused with a five-membered pyrrole ring. It is a versatile nucleus use for the synthesis of several pharmacologically active molecules in medicinal chemistry. Isatin express an excessive range of biological activities such as anti-oxidant, anti-proliferative, anti-bacterial, anticancer, anticonvulsant, antimicrobial, anti-inflammatory, anti-fungal and analgesic etc. As various diseases are emerging day by day so, design and development of novel Isatin derivatives as an effective drug is the key role to researchers. This review explains the recent work on Isatin derivatives.

Keywords Isatin; Biological action; Schiff base; catalysis

Introduction

There are different heterocyclic compounds but there is a special place for five and six membered heterocyclic compounds in organic chemistry as these compounds have versatile nature and diversified biological activities [1,2]. Isatin is a fused, indole derivative heterocyclic compound. Isatin and its synthesized derivatives show wide range of biological activities and they are frequently employed as starting material for drug synthesis. Formally, Isatin was first synthesize by Laurent and Erdman (1841). By oxidation of indigo dye in the presence of chromic acid and nitric acid [3]. It is isolated as red-orange powder from the Isatin tinctoria as natural alkaloid the plant is found in the Europe and China [4]. It's also a metabolic byproduct of the hormone adrenaline in humans [5,6,7].



Isatin

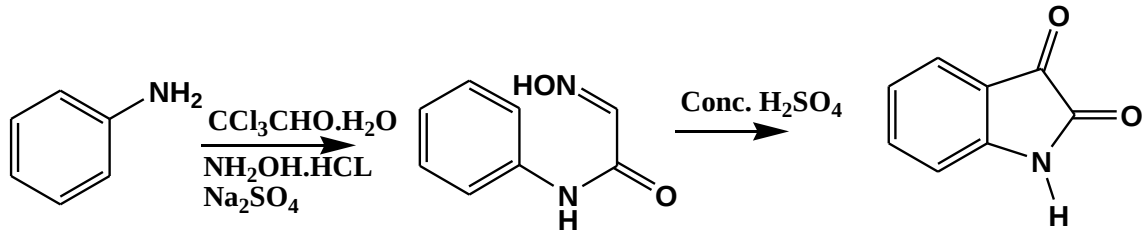
A literature survey determined that Isatin and its derivatives can be use as promising precursor for discovery and development of new drugs. A recent search in 2020 on SciFinder release data that more than Ten thousand articles including review has published since 1951 containing Isatin as keyword. [8] In medicinal chemistry Isatin derivatives have shown excellent interest as they express anticancer, antibacterial, antiviral, Anti-inflammatory,

antioxidant, antimalarial, antifungal, anti-tubercular, anticonvulsant, analgesic, antidiabetic and anti-inflammatory activity.

1. General methods for synthesis of Isatin.

a) Sandmeyer method

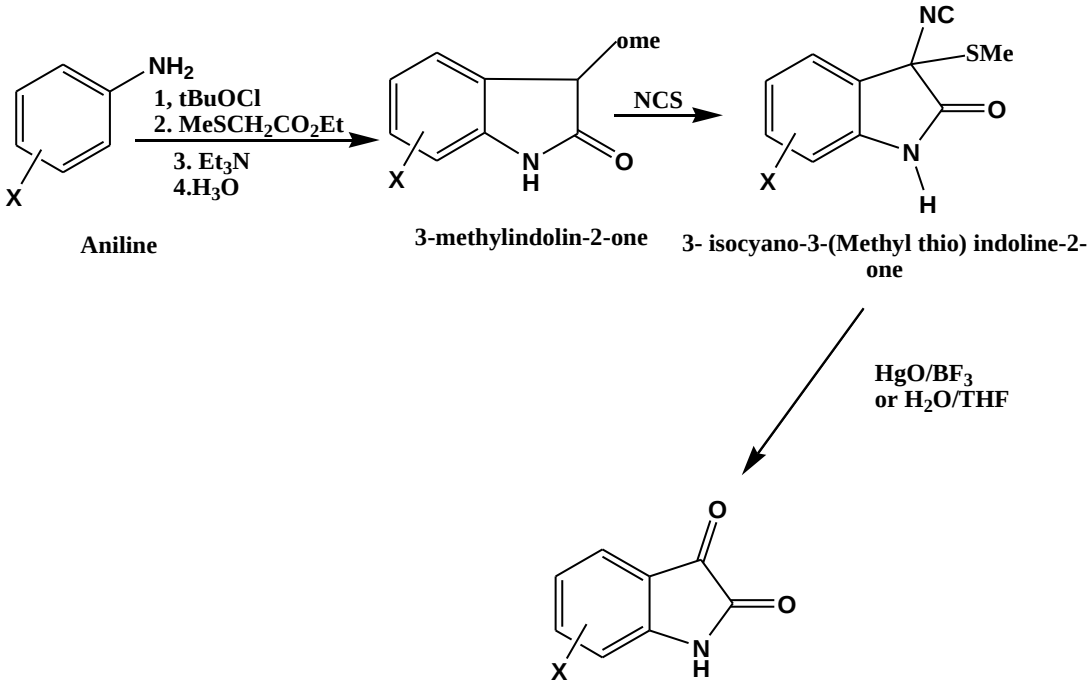
In this reaction aniline was refluxed with chloral hydrate in the presence of hydroxyl amine and sodium sulphate to form an intermediate 2-(hydroxyimino)-N-phenylacetamide for cyclization of 2-(hydroxyimino)-N-phenylacetamide compound we use strong acid (sulfuric acid) and get good yield of Indoline-2,3-dione [9].



Aniline **2-(hydroxyimino)-*N*-phenylacetamide** **1H-indole-2,3-dione**

b) Grassman method

In this reaction aniline was used as starting material to get 3-methylindoline-2-one as intermediate product. For cyclization of intermediate product N-chlorosuccinimide was use, a 3-isocyano-3-(Methyl thio) indoline-2-one was obtained. It was further reacted with mercury(II) oxide/ boron trifluoride etherate get 1H-indole -2,3 –dione [10,11].

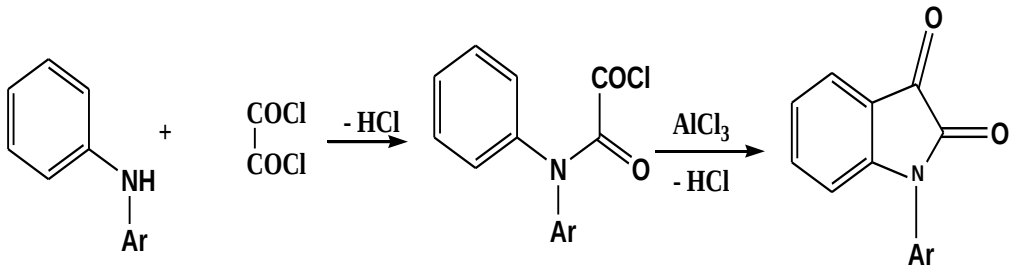


Aniline **3-methylindolin-2-one** **3- isocyano-3-(Methyl thio) indoline-2-one**

1H-indole -2,3 -dione.

c) Stole method

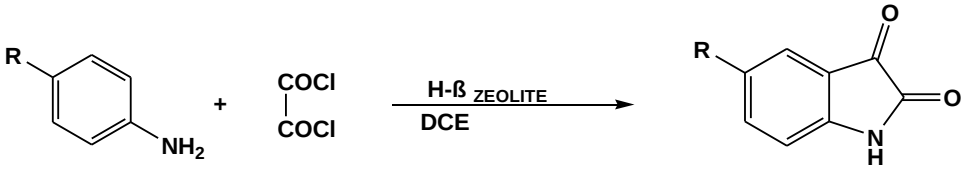
This method utilizes primary and secondary aryl-amine along with oxyl chloride to form an chlorooxalyl anilide as intermediate product. By using aluminum tri-chloride or other Lewis bases cyclization of the intermediate is performed to form 1-aryl-indole -2,3 –dione [12].



Aryl-Amine **oxyl chloride** **chlorooxalyl anilide** **1-aryl-indole -2,3 - dione.**

d) One-Pot Synthesis method

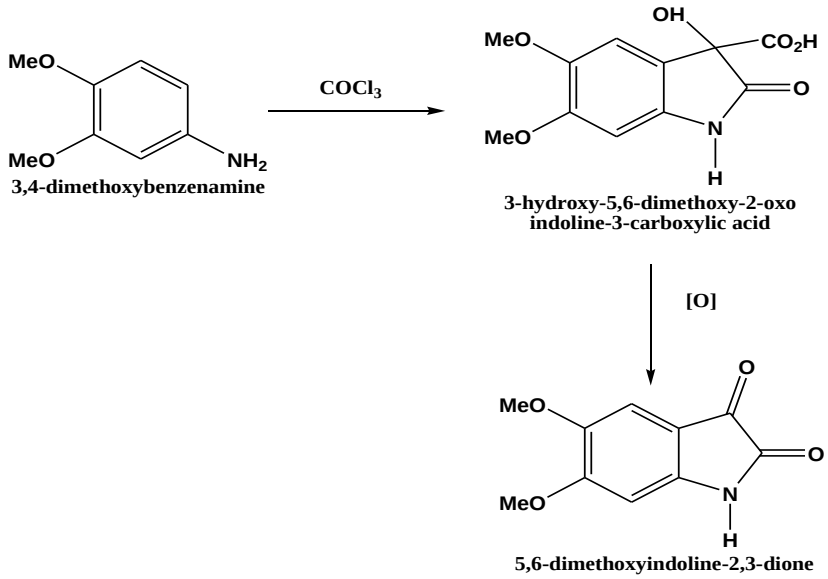
In this reaction aniline is refluxed in the presence of oxalyl chloride and H-β as catalyst to get good yield of 1H-indole-2,3-dione [13].



Aniline **oxalyl chloride** **1H-indole -2,3 - dione.**

e) Martinet method

In this method aminoaromatic or oxamalonate esters are refluxed in the presence of cobalt chloride an intermediate substance 3-(3-hydroxy-2-oxindole) carboxylic acid derivative is form. This intermediate product is oxidised to get 5,6-dimethoxyindoline-2,3-dione [14].



3,4-dimethoxybenzenamine

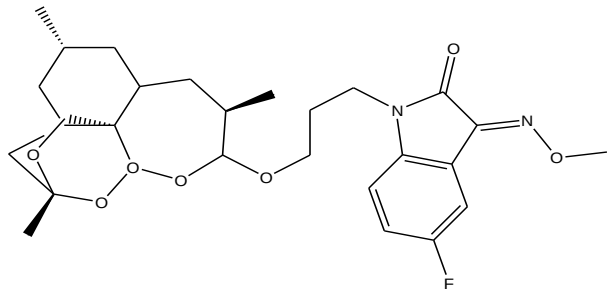
3-hydroxy-5,6-dimethoxy-2-oxo indoline-3-carboxylic acid

5,6-dimethoxyindoline-2,3-dione

2. Biological activity.

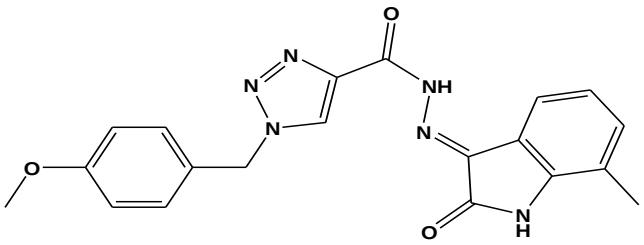
Anticancer activity:

Zhang, Zhe, *et al* 2022 reported synthesis of nineteen synthesized propylene tethered dihydroartemisinin-isatin hybrids of Isatin. All the final compounds were tested there *in vitro* antiproliferative activity against A549, A549/DOX and A549/DDP lung cancer cell lines, cell lines. Compound (**1a)** expressed excellent effects [15].



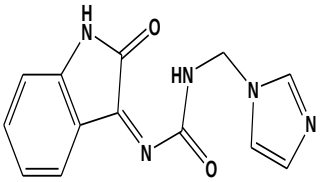
1a

Aneja babita *et al* synthesized nine derivatives of isatin-triazole hydrazones and tested anticancer activity against MCF-7 cells, HepG2cells and MDA-MB-435s HepG2 cells. One compound **(1b)** has expressed excellent activity against the tested cell lines. [16]



1b

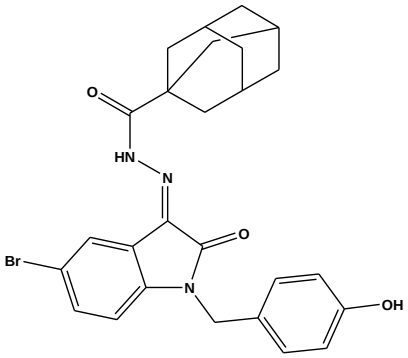
Rajesh Kumar M *et al* reported the synthesis of benzotriazole (BTA) Isatin and imidazole by using multicomponent reaction. p-TSA.H_2O used as acid catalyst during experiment. Compounds were examined for activates like Antioxidant, anti-breast cancer and anti-inflammatory for all thirteen newly synthesized compounds. they tested their compounds for anti-inflammatory against cyclooxygenase-2 (COX-2) enzyme and for anticancer phosphoinositide-3 kinase (PI3K) breast cancer cell line in vitro. They found that compound **(1c)** were exhibit excellent anti-inflammatory and anti-cancer activity [17].



1c

Anticonvulsant activity:

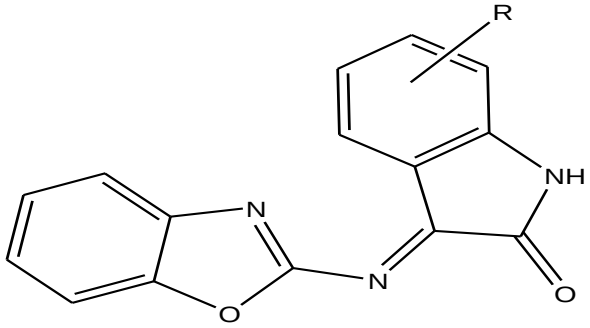
Hind M. Osman *et al* 2021 six Schiff bases synthesis starting from Isatin and adamantane-1-carbohydrazide. By using pentylenetetrazole- (PTZ-) they tested the compounds for anticonvulsant activity. It was found that compound **(2a)** express major protecting effect against PTZ-induced seizure [18].



2a

Antimicrobial activity:

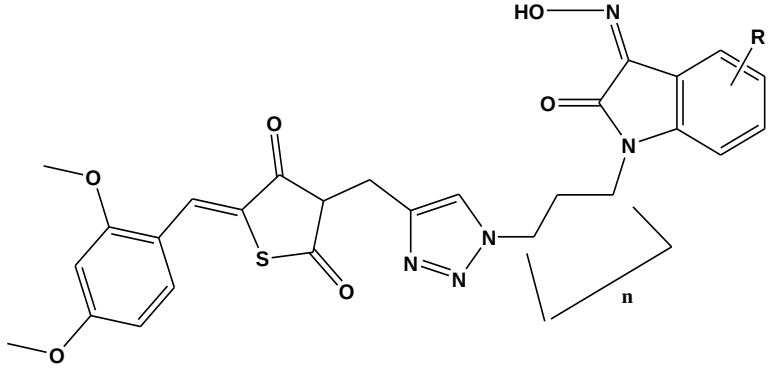
Susithra, E *et.al* 2021 were reported the synthesis of new series of compounds. By reacting 2-amino benzoxazole with 5 or 7 substituted Isatin. All the synthesized compound was tested for *in vitro* cytotoxic and also antimicrobial activities. Mild to potent effects was observed from all compounds tested for antibacterial activity. Two Compounds **(3a & 3a1)** expressed excellent antimicrobial activity among all the synthesized compounds [19].



3a1 R= Cl

3a2 R= Br

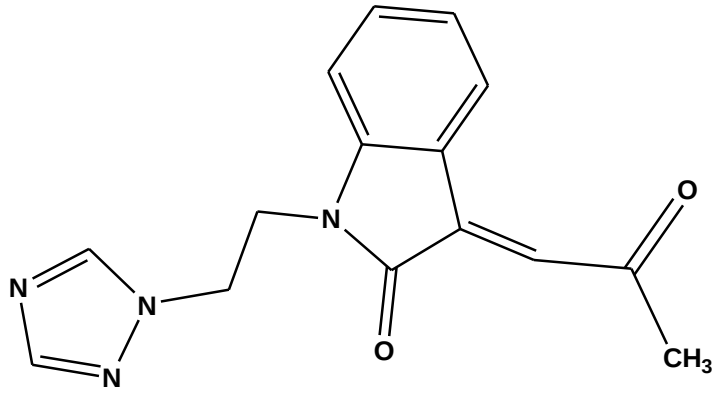
Yagnam, Swetha *et al* reported synthesis of triazole moiety linked with hybrid molecule of isatin−2,4-thiazolidinedione by using1,3-dipolar cycloaddition reaction. Copper was used as catalyst. All the compounds were tested for Antimicrobial activity at few specific gram-positive and also gram-negative strains. Similar antimicrobial activity results were revealed by compounds **(3b1-3b4)** [20].



3b1-3b4

Compound	N	R
3b1	3	CH_3
3b2	3	OCH_3
3b3	4	Cl
3b4	4	F

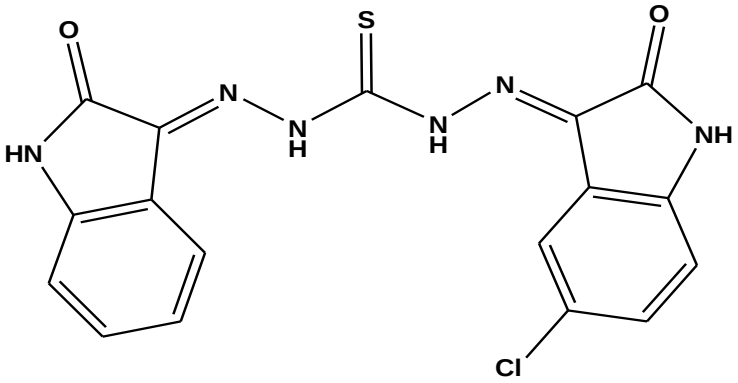
Tangadanchu, Vijai Kumar Reddy *et al* reported synthesis of Isatin-derived azoles as novel and effective agents for antimicrobial activity. All the compounds were tested against E. coli (ATCC 25,922). Compound **(3c)** has expressed the maximum activity against E. coli bacterial stain. It was found that the tested compound was more potent than the standard compound (Norfloxacin) [21].



3c

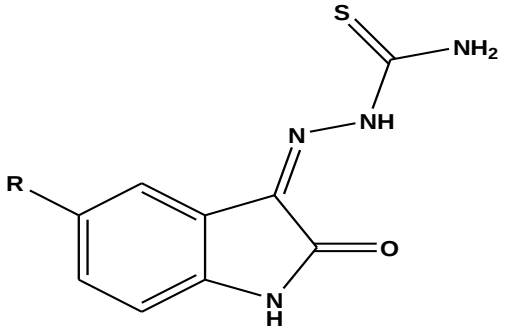
Anti-oxidants activity:

Yakan, Hasan *et al*reported synthesis of eight bis-Isatin derivatives compounds having urea/thiourea moiety. Newly synthesized compound were investigated for anti-oxidant activity, by using CUPRAC and ABTS. It was observed the bis-Isatin to release CUPRAC activity at a minimum micro molar stage. One compound **(4a)** had the expressed effective CUPRAC activity [22].



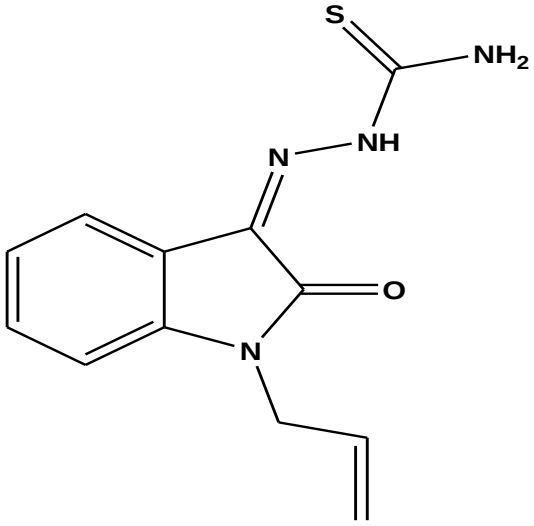
4a

Sivaraj Saranya *et al* reported synthesis of Isatin thiosemicarbazone compounds. All the synthesized compounds were tested for *in vitro* antioxidant property and breast cancer cell lines. It was observed that few compounds **(4b1-4b3)** have expressed excellent anti-oxidant activity [23].



4b1= NO_2

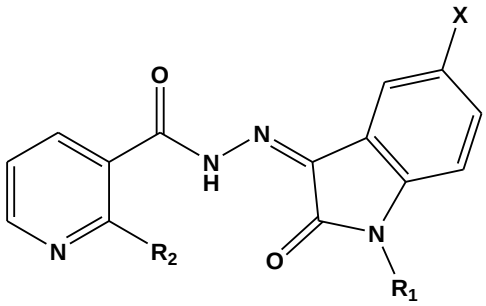
4b2 = OC_3H



4b3

Antibacterial activity:

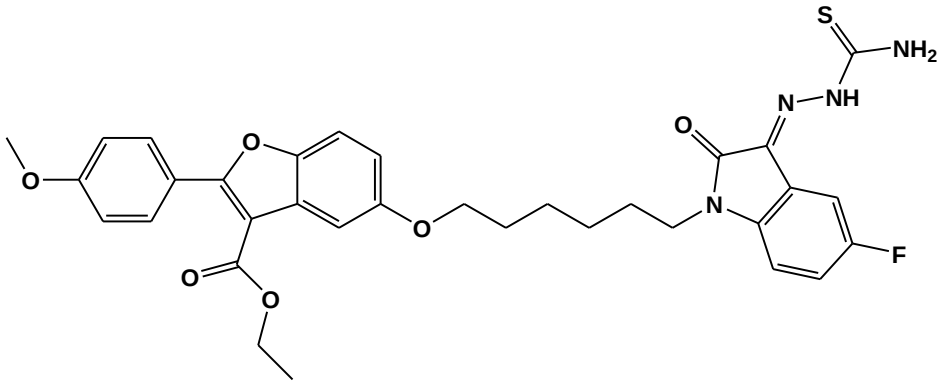
Elsayed, Zainab M *et al* were reported synthesis of sixteen Isatin-nicotinohydrazide hybrids compounds. All the synthesized compounds were tested for anti-tubercular and antibacterial activity. ATCC 27294 stains was used for anti-tubicular and antibacterial activity. Three compounds **(5a1-5a3)** expressed potent activity and it was also evaluated against M. Tuberculosis Isoniazid/ Streptomycin resistant strain [24].



Compound	R_1	X	R_2
5a1	H	H	Benzyl
5a2	H	Br	Propyl
5a3	H	Br	isobutyl

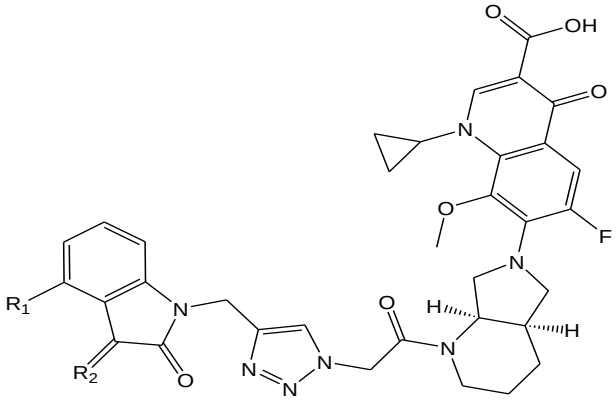
5a1-5a3

Gao, Feng *et al* reported synthesis of benzofuran-Isatin hybrids linked with alkyl group. Compounds were tested against two multi-drug resistant strains, *in vitro* for anti-mycobacterial activity. Tuberculosis (mycobacterium tuberculosis) is a kind of bacteria that causes tuberculosis (MDR-MTB). After testing it was found that one compound **(5b)** has expressed excellent activity against the tested cell lines [25].



5b

Gao Feng *et al* reported the synthesis fourteen new moxifloxacin-acetyl-1,2,3-1*H*-triazole-methylene-isatin hybrids and tested biologically against anti-tubercular agents. Synthesized compounds were tested against both multidrug-resistant and rifampicin-resistant Mycobacterium tuberculosis strains. It was found that two compounds **(5c1-5c2)** were relieved excellent activity against Mycobacterium tuberculosis strains [26].

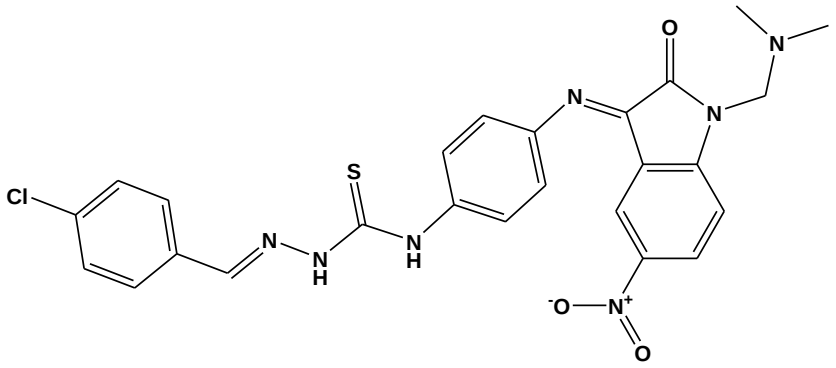


Compound	R_1	R_2
5c1	H	NOMe
5c2	H	$NNHCSNH_2$

5c1-5c2

Analgesic activity:

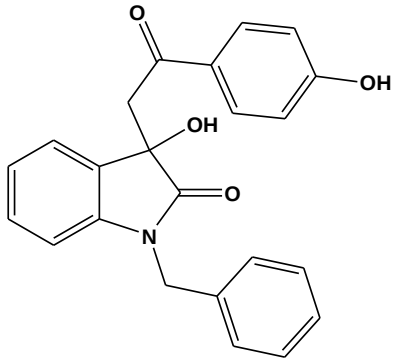
Lahari, Kosaraju, *et al* reported synthesis of Isatin derivatives compounds as a powerful anti-inflammatory, analgesic and antimicrobial drug. carrageenan-induced foot paw edema method and agar streak dilution technique were used for evaluation of *in vitro* activities for the synthesized compounds of drugs. Compound (**6a)** was found as potent derivatives [27].



6a

Antidepressant activity

Tripathi, R. K. *et al* reported synthesis of a series of 3-hydroxy-3-phenacyloxindole analogues of Isatin and evaluated *in vitro* for anti-depressants activity toward monoamine oxidase (MAO) A and B. it was found that one compound **(7a)** has expressed potent and selective inhibitors at MAO-A [28].



7a

Conclusion

In medicinal chemistry or in drug discovery and drug development the fused bicyclic indole derivative Isatin moiety with one nitrogen atom at first position and two oxygen attached outside the ring has great use in pharmaceutical industry. substitution of different groups at various positions of the ring result in the development of potent compounds with antimalarial, antiviral anticancer, anticonvulsant, antifungal, and bacterial activities, but it also resulted in the development of potent compounds with anticancer, antiviral, antifungal, and antibacterial activities. Further efficient optimization of Isatin derivatives with numerous biological activities could lead to the development of promising poly-functional medicines for the treatment of a variety of disorders and dis-function. It is envisaged that future study will disclose interesting properties of Isatin as a flexible moiety.

Acknowledgement

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