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Review: Isatin (1H-Indole-2,3-dione) a versatile heterocyclic molecule

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ABSTRACT

Isatin is a versatile byclic heterocyclic molecule.Isatin possess active functional groups because of which isatin deployed for many drug and dye synthesis reactions. In synthesis reactions isatin molecule were used as a precursor. Isatin molecule has high therapeutic value and numerous molecules were synthesized and tested for for biological activities. In current review we have summarized reported biological activities shown by isatin and its heterocyclic derivatives.

Keywords: Isatin, Therapeutic value, Antimicrobial activity

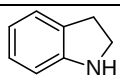
INTRODUCTION

Heterocyclic compounds are of very much interest in our daily life, because these compounds occur widely in nature and are essential to life. Most notably heterocyclic rings compose the core structures of mono and polysaccharides and the four DNA bases that establish the genetic code. Many of alkaloids, antibiotics, essential amino acids, hemoglobin, vitamins, hormones and many synthetic drugs and dyes contains heterocyclic ring systems. Heterocyclic compounds are also used as vehicles in the synthesis of other organic compounds chlorophyll-photosynthesizing and hemoglobin-oxygen transporting pigments are also heterocyclic compounds.

Carboxylic compounds are another important type, where they can be converted into a heterocyclic analogs by replacing one or more carbon atom present in the ring by hetero atom like nitrogen, sulfur or oxygen.

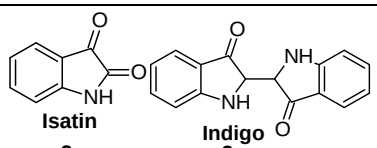
METHODS

Polycyclic compounds incorporating one or more heterocyclic rings are well known to us.Nitrogen-containing compounds have been known to have a tremendous potential in various fields of chemistry. In nitrogen containing heterocyclic compounds indole is the most important fused ring heterocyclic moiety.



Indole
1

An oxidized derivative of indole is known as Isatin (1*H*-indole-2,3-dione), which was first discovered by Erdmann and Laurent as a product in 1840 while oxidation of indigo using nitric and chromic acid[1-2].

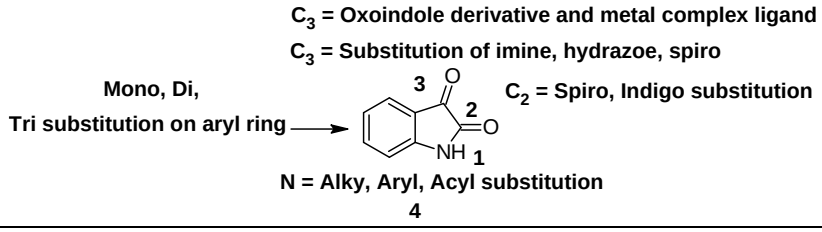


2 **3**

For almost 140 years isatin compound was considered as synthetic until it was found in plants and animals[3-14]. It was found in plants from *Isatis*genus, fruits of the cannon ball tree and in secretions from the parotid gland of the *Bufo* frog, fungi, symbiotic bacteria and marine mollusks. 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 synthesized *in vivo* from tryptophan-rich foods such as meat, dairy and whole grains.

Isatinis a syntheticallyversatile substrate that can be used to prepare a huge variety of heterocyclic compounds. Synthetic chemists and industries draw on more attention on various functionalisable groups of Isatin and which has led Isatin as a precursor molecule for organic synthesis.



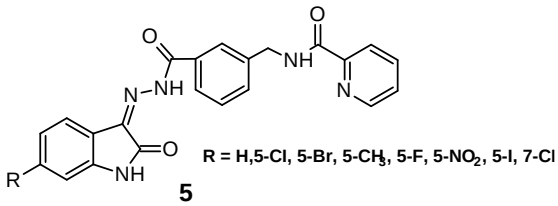
Various literature survey identified severalisatin derivatives in the development phase as potential newdrugs. More recently, reviews have focused on the biological role of endogenous Isatin[15-17] and the diverse range of biological activities displayed by assorted isatins and isatin derivatives[18-24]including oxindoles and their coppercomplexes.[25-26]
Most recently, isatin derivatives have received considerable attention due to their potent anticanceractivities.[27]

It is marked from literature, that isatin derivatives are known to be associated with broad spectrum of biological activities like Antimicrobial, Anticancer, Anticonvulsant, Anti-inflammatory, Analgesic, Antioxidant, Anthelmintic, Antiviral, Antiplasmodial, Antitubercular, Antioxidant, Anti- HIV, Antifungal and Ulcerogenic activity.

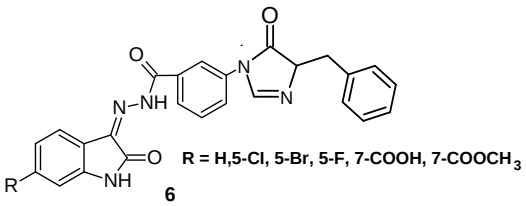
Here in, report describes broad spectrum of various biological activities that are mentioned above and associated with indole and indole derivatives.

- **Antimicrobial activity**

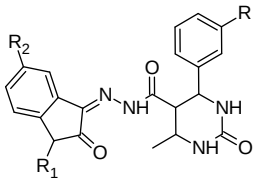
Nathani*et al*.,[28]has reported synthesis of *N*-[3-(2-oxo-1, 2-dihydro-indol-3-ylidene-hydrazinocarbonyl) benzyl] nicotinamide derivativesdifferent derivatives of isatin by condensation with *N*-(3-hydrazinocarbonylbenzyl) nicotinamide. Among all the synthesized molecules compound with 5-F, 5-CH3 substitution showed the most favorable antimicrobial activity.



Synthesis of 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4*H*-imidazol-4-one-3-(4-bezoyl hydrazono)]-indole-2-ones derivatives were reported by Patel *et al*.,[29]The synthesized compound tested against *S.aureus* and *B.subtilis.*



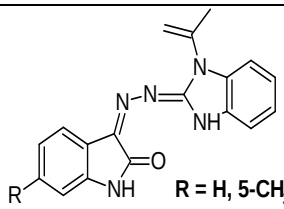
Pandeya*et. al.*[30]were reported Synthesis of 6-methyl-2-oxo-4-phenyl (substituted)- 1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid (2-oxo-1,2-dihydro (1,5-sustituted) -indol-3-ylidene)-hydrazide. Compounds were tested for antibacterial sensitivity against 24 strains at 5000 µg/mL. was the most active antibacterial agent having MIC 3.92 µg/mL against *V. parahaemolyticus* and *E. faecalis*.



R = 3,5-Dichloro, p-Cl R_1 = H, Br R_2 = H, CH_3

7

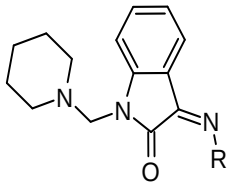
Synthesis of 3-[(1-isopropenyl-1, 3-dihydrobenzimidazol-2-ylidine]-1,3-dihydro-indol-2-ones were reported by Madhu *et al*.,[31]It has been synthesized from different isatinhydrazones by condensing with 1-isopropenyl-1,3-dihydro-*2H*-benzimidazol-2-ones. Antimicrobial activity was tested using disc diffusion method and against bacterial strain *S. aureus* good result observed.



R = H, 5-CH_3, 5-Br, 5-Cl, 5-NO_2, 7-NO_2

8

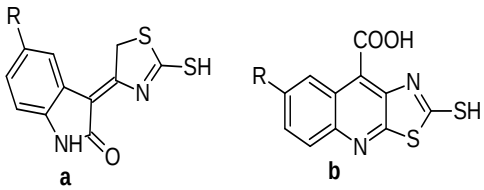
Synthesis of *1H*-Indole-2,3- dione derivativeswere reported by Patro*et al.*, [32] Investigation of antimicrobial activity of the mannich bases was done by cup plate method against pathogenic bacteria and fungi. Among the tested compounds, chloro substitution showed the most favorable antimicrobial activity.



R = Phenyl, 2-nitrophenyl, 3-chlorophenyl, 4-bromopheny
4-Flurophenyl, 2,6-dichlorophenyl, 3-chloro-4-flurophenyl
4-chloro-2-nitrophenyl

9

Synthesis of 3, 4-dihydro-3-[2-mercaptothiazolidine] indol- 2-ones derivatives were reported by Pardasani*et al.*, [33] Synthesized compounds 11a, 11b, showed moderate activity against *E coli, S. facralus, R. solani*and *F. solani*.



a
R = H, Br, NO_2

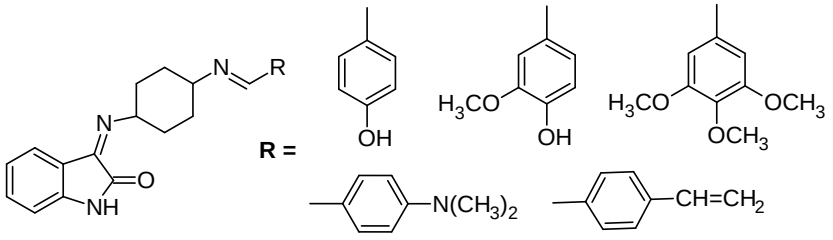
b
R = H, Br, NO_2

10

- **Anticonvulsant Activity**

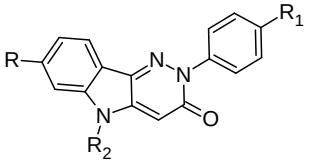
Prakash *et al.*,[34]reported condensation of isatin with various aromatic aldehydes to synthesize novel schiff base of isatin derivatives which was then characterized. Synthesized molecules were tested for anticonvulsant activities.

Among the compounds synthesized 3-(4-(3, 4, 5,-trimethoxy benzylideneamino) phenylimino) indoline-2-one showed excellent anticonvulsant activity with lower dose in MES as well as in ScMet methods.



11

Synthesis of a series of 2-aryl-2, 5 dihydropyridazino[4, 3-b]indol-3(3H)ones were reported by Palluotto*et al.*[35]The synthesized compounds showed anticonvulsant activity.



R = H, R_1 = p-Cl, p-Br, p-OCH_3, p-Cl

R_2 =H, CH_3

12

Synthesis of N-aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2*H* isoindol-2-yl)butanoyl hydrazides/butanamides were reported by Rajavendran*et al.*[36] Anticonvulsant activitywas determined using four animal models of seizures which included MES, subcutaneous (sc PTZ) intraperitoneal Picritoxin (ip PIC) induced seizures threshold test. Obtained derivatives found to be more potent as compared to standard drug ethosuximide and phenytoin.

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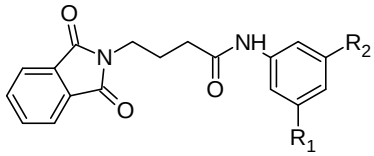
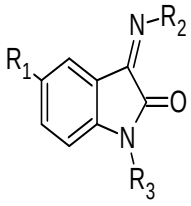


R_1 = 2-CH_3, 3-Cl R_2 = 2-CH_3, 4-CH_3

13

Synthesis of 3-(4-chloro-phenylimino)-5-methyl-1, 3-dihydro-indole-2-one was reported by Sridhar *et al.*[37]The synthesized compounds were active inMES test and compound 23b was found to be most activecompound and showed 87% protection at 100 mg/kg doselevel with an ED50 value of 53.61 mg/kg.



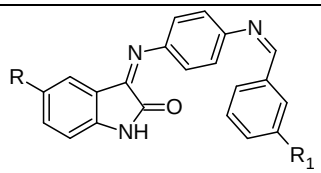
R_1 = H, CH_3, 4-methylphenyl R_2 = 4-Chlorophenyl, 1-naphthyl

R_3 = H

14

- **Anti- inflammatory**

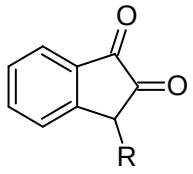
Synthesis of a novel Schiff bases were reported by Reddy *et al.*[38]The synthesized compounds were investigated for analgesic and anti-inflammatory. Synthesized compounds exhibited remarkable anti-inflammatory activity when compared with standard drug (Pentazocin, 10 mg/kg, i.p. and Indomethacin 20 mg/kg).



R = H, OCH_3, F, Cl R_1 = Cl, OCH_3, NO_2, OH

15

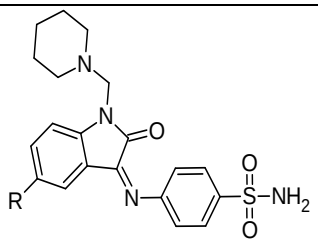
Mathues*et al.* [39]reported synthesis of isatin derivatives, synthesized compounds Inhibited the cyclooxygenase (COX-2) enzymes in RAW 264.7 activatedcells. The effect of isatin derivatives on COX-2 protein expression when compared with vehicle treated groups. COX-2 protein expression is reduced on incubation of cells with isatin derivatives.



R = H, 5-F, 6-Cl, 7-Cl

16

Synthesis, characterization and anti-inflammatory activity of isatin derivatives reported by Prasad *et al.*,[40]It has been synthesized from isatin& different p-substitute aniline. Obtained derivatives were established by author on the basis of spectral techniques. All the synthesized isatin derivatives have been investigated for their anti-inflammatory activity.



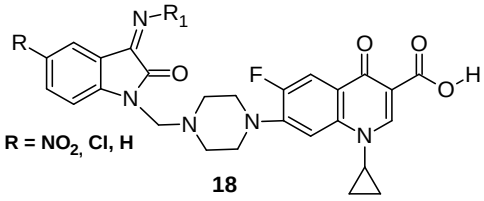
R = F, Cl, Br, CH_3, OCH_3, NO_2, NH_2

17

- **Analgesic Activity**

Synthesis, analgesic and ulcerogenic evaluation of some novel schiff and mannich bases of isatin derivatives were reported by Ramachandran *et al*., [41] Novel schiff and mannich bases of isatin derivatives were synthesized.

All the compounds were evaluated for analgesic and ulcerogenic activities. Majority of the synthesized derivatives shown significant analgesic activity and ulcerogenic activity when compared with standard drugs.

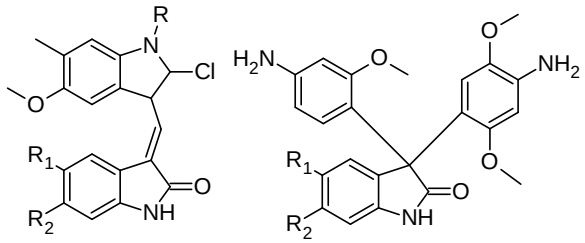


R = NO_2, Cl, H

18

- **Antioxidant activity**

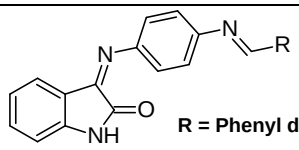
Synthesis of3, 3-bis (4-amino-2, 5-dimethoxyphenyl)-1, 3-dihydroindol-3one derivatives were reported by Burnelli*et al*.[42]The synthesized compounds showed good chemical antioxidant activity.



R = CH_3, 1-Chloro-4-ethylbenzene R_1 = OH R_2 = CH_3, H,

19

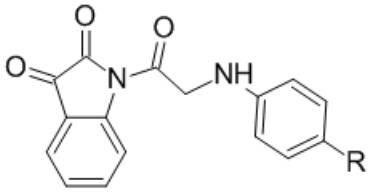
Synthesis and evaluation of antioxidant activities of some novel isatin derivatives and analogs were reported by Prakash *et al.*,[43]These compounds were screened for antioxidant activity by DPPH radical scavenging activity. In this method, the compound 3-(4-(4-dimethylaminobenzylideneamino) phenylimino) indoline-2-one showed highest antioxidant activity because of the presence of electron donating group.



R = Phenyl derivatives

20

Synthesis and evaluation of antioxidant potential of novel isatin analogues were reported by Naik *et al.*,[44]A series of novel isatin conjugated with aniline and substituted anilines were synthesized and examined for their antioxidant activity. Compounds displayed good antioxidant properties, whereas, compound displayed superior antioxidant activity relative to other examined analogues and also exhibit more activity than the standard, butylated hydroxy anisole (BHA).

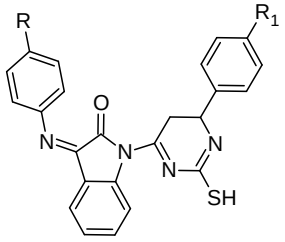


R = H, OH, OCH_3, Br, NO_2

21

Synthesis of novel mercapto-pyrimidine and amino-pyrimidine derivatives of indoline-2-one as potential antioxidant & antibacterial agents were reported by Mondal *et al.*,[45]It was synthesized from different substituted chalconised Indole 2,3 dione.

Synthesized compounds were tested for antioxidant activity and in vitro antimicrobial activity. Derivatives show significant enhancement in antioxidant and antibacterial activity.

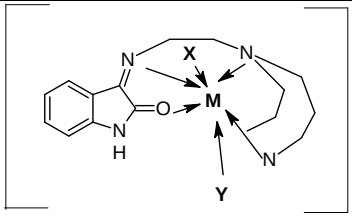


R = Cl, NO_2 R_1 = OH, OCH_3, NO_2

22

- **Anthelmintic Activity**

Synthesis of a new series of tetradentate Schiff bases were reported by Reddy *et al*.,[46]The synthesized ligand and metal complexes 32a, 32b, 32c were screened for anthelmintic activity against earthworm (*peretimaposthuma*) using 5 µg/ml concentration.

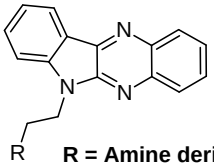


a - M = Cu, X = H_2O, Y = Cl, Z = Cl_2H_2O
b - M = Co, X = Y = Cl
c - M = Zn, X=Y=Cl, Z = $2H_2O$

23

- **Antiviral Activity**

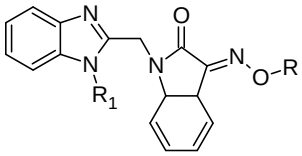
Synthesis of some new 6-(2-aminoethyl)-6-*H*-indolo [2, 3-b] quinoxalines were reported by Shibinskya*et al.*[47]The synthesized compounds 13(a-f) were screened for the antiviral activity.



R = Amine derivative

24

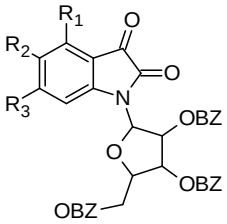
Synthesis of a series of benzimidazole-isatin oximes were reported by Venables *et al.*[48]The synthesized compounds 16a, 16b and 16c showed the antiviral activity.



R = CH_2F, CH_2CF_3, R = $(CH_2)_4OH$, $(CH_2)_3SO_2CH_3$

25

Synthesis of a series of novel substituted isatinribonucleosides were reported by Oliveira *et al.*[49]Synthesized compounds showed antiviral activity.



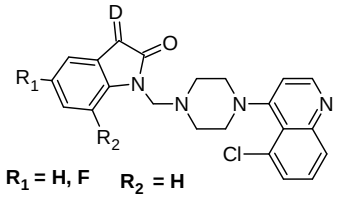
a = R_1=R_2=R_3=H b = R_1=R_2=R_3=CH_3

c = R_1=R_3=Br,R_2=H

26

- **Antiplasmodial Activity**

Synthesis of a new class of 4-aminoquinoline derivatives based on the natural product isatin scaffold were reported by Clarkson *et al.*[50]The synthesized compounds were screened for biological evaluation against strains of the malaria parasite *plasmodium falciparum.* and resistant (K1 and W2) strains of *P. falciparum.*

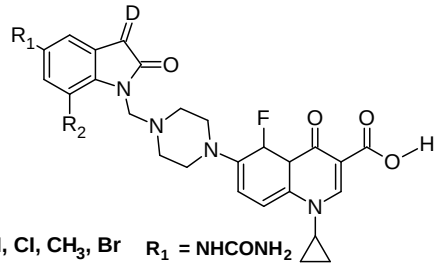


R_1 = H, F R_2 = H

27

- **Antitubercular Activity**

Synthesis of various substituted ciprofloxacin derivatives were reported by Sriram *et al.*[51]The synthesized compounds shown better in-vivo antitubercular activity against *M. tuberculosis* than ciprofloxacin

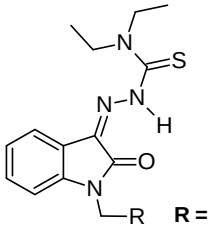


R = H, Cl, CH_3, Br R_1 = $NHCONH_2$

28

- **Anti- HIV Activity**

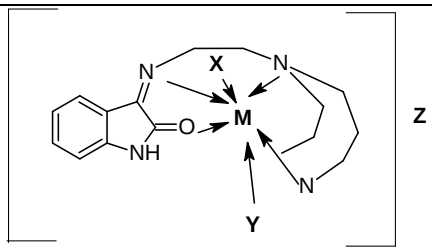
Isatin derivatives were reported by Bal *et al.*[52]The synthesized compounds showed significant anti-HIV activity .



R = Amine derivatives

29

Synthesis of some new isatinanalogs for effective treatment of AIDS were reported by Pawar *et al.*[53]The synthesized compounds were found to becomparable with standard.



a - M = Cu, X = H_2O, Y = Cl, Z = Cl_2H_2O

b - M = Co, X = Y = Cl c - M = Zn, X=Y=Cl, Z = $2H_2O$

30

- **Antifungal activity**

R. Anisetti and M. S. Reddy[54]reportedsynthesis of novel spiro(imidazo[4′,5′: 4,5′]benzo[1,2-*e*][1,4]thiazepine)-9,3′-indolines from 5-amino-2-mercapto benzimidazole, istains and mercapto acetic acid. Compounds were characterized by IR, ^{1}HNMR, ^{13}C NMR and mass spectral data. Obtained compound were tested by author for antifungal activity.

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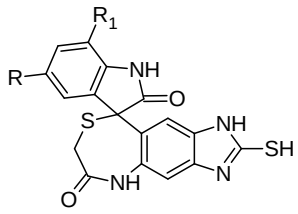


R = H, Cl, Br, CH_3 R_1 = H, Cl

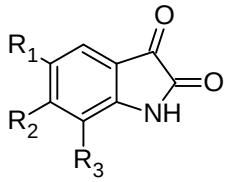
31

- **Anticancer activity**

Current literature describing the cytotoxic and anticancer activities of isatin analogues derived from either mono-, di-, and tri-substitution of the aryl ring and those obtained by derivatisation of the isatin nitrogen and C2/C3 carbonyl moieties.

❖ **Mono-, di- and tri-substituted aromatic isatin derivatives:**

Vine *et. al.*[55]eported the synthesis of substituted derivatives of Isatin which showed anticancer activity.

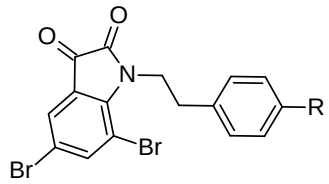


R_1 = H, F, Br, NO_2, OCH_3

32

❖ ***N*-Alkyl substituted isatin derivatives**

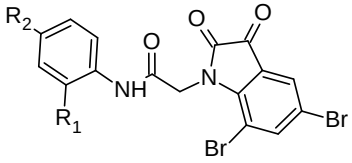
In 2008 Matesic*et al.*[56]synthesised a family of *N*-phenethyl derivatives (low to sub-micromolar cytotoxic activity against a panel of human leukemic, lymphoma and or *para* position yielded the most active compounds.



R- a=H, b=m-Br, c=p-me, d=m-OCH_3, e=p-OCH_3

33

N-phenylacetamide derivatives prepared by Modi *et al.*[57]were also shows anticancer activity.

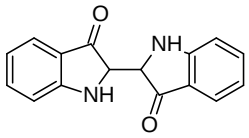


R_1, R_2 = H, CH_3, NO_2

34

2-Substituted isatin derivatives

The most famous of the C2-substituted isatins are the widely employed indigo pigments used since ancient times. This class includes indigo carmine (5,5'-indigodisulfonic acid sodium salt), an extensively used non-toxic, inexpensive stain for chromo-colonoscopy diagnosis and management of early colorectal cancer.[58-61]The best known cytotoxic C2-substituted isatins derivative is indirubin, the red component of indigo pigments. This compound is found in plants belonging to the genii *Indigofera*, *Isastis*and *Polygonum*, and in marine molluscs of the *Murex* genus.[62]

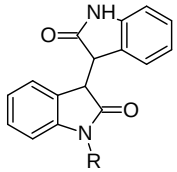


indirubin

35

- **C3-Substituted isatin derivatives**
  - **3-Arylidene derivatives**

Synthesis of a series of functionalized isoindigos structurally related to meisoindigo(1-methylisoindigo) were reported by Wee *et al*.[63]The synthesized compounds [1- phenpropylisoindigo and 1-(p-methoxy-phenethyl)-isoindigo] evaluated for antiproliferative activities on a panel of human cancer cells.



R = $(CH_2)_3C_6H_5$, $(CH_2)_2C_6H_4(_P\text{-}OCH_3)$

36

CONCLUSION

From all above reference material, we can conclude thatisatin has proven to be an excellent scaffold for both the natural and synthetic construction of molecules with interesting biological activities.New derivatives of isatin are continuously discovered and developed by researcher which show novel bioactivities. Newly synthesized isatin biomolecules are treated or fused with drug fragments to enhance or to develop new biological activity. Though isatin has proven itself a highly efficient heterocyclic molecule in medicinal chemistry still lot more possibilities are there to explore other useful activities of isatin and its derivatives.

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