Int.J.Curr.Microbiol.App.Sci (2022) *11*(01): 61-77

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 11 Number 01 (2022)**
Journal homepage: http://www.ijcmas.com

Review Article https://doi.org/10.20546/ijcmas.2022.1101.009

Isatin: A Short Review of their Antimicrobial Activities

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Keywords

Isatin, heterocyclic synthesis, analgesic, anti-inflammatory activity, eco-friendly

Article Info

Received:
08 December 2021
Accepted:
31 December 2021
Available Online:
10 January 2022

A B S T R A C T

Isatin(2, 3-dioxindate), a particularly effective scaffold with a variety of pharmacological actions, has been developed due to its therapeutic significance in organic and medicinal chemistry. Many researchers have been drawn to this skeleton because of its diverse biological response profile and its multiple possibilities against a variety of activities. Sandmeyer's and Stolle processes are two typical ways for synthesizing isatin derivatives. Many researchers have taken advantage of the isatin moiety by using NH at the first position, C2 and C3 carbonyl positions for the creation of numerous derivatives with varying biological activities. Design strategies for the synthesis of isatin-containing heterocyclics have been discussed in this review paper using several approaches. The chemistry, synthesis, biological and pharmacological action, SAR, and advanced uses of the isatin moiety are all covered in this paper. The progress in the use of isatins for organic synthesis over the previous twenty-five years, as well as a study of their biological and pharmacological properties, are given, together with supplemental data.

Introduction

In modern environment, microbial infections are a major cause of a variety of health problems. Heterocyclic compounds, which cross the gap between natural and synthetic, have recently been discovered to occur abundantly in nature and have proven to be extremely important to life (Elleby *et al.*, 2001). Isatin, also known as 1H-indole-2, 3-dione, is an indole derivative and the first organic compound to be synthesised. It was discovered in 1841 by Bayer, Erdman, and Laurent as a product of the oxidation of indigo dye with nitric acid and chromic acids, resulting in bright orange coloured monoclinic crystals of isatin. Isatin is naturally present in plants of the genus Isatis. (Joaquim *et al.*,

2001) Sumpter published the first overview of this compound's chemistry in 1954, followed by Popp in 1975 and a third review on the use of isatin as a precursor for the synthesis of other heterocyclic compounds in 1975. Isatin can be found in nature in plants of the genus Isatis, such as the melosatin alkaloids (methoxy phenylpentylisatins) obtained from the Caribbean tumorigenic plant Melochiatomentosa (Rastogi *et al.,* 2011; Prasad, 2012), in Calanthe discolour LINDL (Varvounis *et al.,* 2004) and in Couroupitaguianensis AubL (Silva *et al.,* 2011), as well as in the secretion of the parotid gland (Yoshikawa *et al.,* 1998; Ischia *et al.,* 1988) 6-(3'-methylbuten-2'-yl) isatin was recovered from Streptomyces albus, and 5-(3'-methylbuten-2'-yl) isatin was isolated from *Chaetomium globosum*.

Isatin is also a component of coal tar and is used as a colour reagent for the amino acid proline, resulting in a blue derivative (Elliott and Gardner, 1976; 2012). Isatin can be found in mammalian tissues and the rat brain (mostly in the hippocampus and cerebellum), where it acts as a biochemical modulator (Hou *et al.,* 2008). In vitro research have shown that isatin and its derivatives are extremely effective against genotoxic and mutagenic disorders, although the genotoxic and mutagenic potential of isatin has not been thoroughly proven or documented in vivo. Isatin was first identified as a selective inhibitor of monoamine oxidase (MAO) and was given the name "Tribulin" (Gang *et al.,* 2011). Isatin is made up of a six-membered benzene ring and a nitrogen-containing five-membered ring. Although both rings are in the same plane, one is aromatic while the other is anti-aromatic.

Synthesis of Isatin derivatives

Sandmeyer isatin synthesis

The Sandmeyer method for isatin synthesis is the most ancient and widely used method for isatin synthesis. It's made by cyclizing aniline's condensation product with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulphate to produce an isonitrosoacetanilide, which is then isolated and treated with concentrated sulphuric acid to give isatin in >75 percent of the time. Anilines having electron-withdrawing substituents, such as 2-fluoroaniline, and some heterocyclic amines, such as 2-aminophenoxathine, are good candidates for the procedure (Johansson *et al.,* 2013; Anne *et al.,* 2009).

The Stolle isatin synthesis

The Stolle approach is the most prominent alternative to Sandmeyer's procedure. Anilines are reacted with oxalyl chloride to produce an intermediate chlorooxalylanilide, which can be cyclized in the presence of a Lewis acid, typically aluminium chloride or BF3. Et2O has been used to make the equivalent isatin, but TiCl4 has also been employed (Loloiu and Maior, 1997).

The Martinet isatin synthesis

Isatin is made by reacting an amino aromatic molecule with an oxomalonate ester or its hydrate in the presence of an acid to produce a 3-(3-hydroxy-2-oxindole) carboxylic acid derivative, which can then be further oxidatively decarboxylated to produce isatin (Gassman *et al.,* 1977).

The Gassmanisatin synthesis

The synthesis and subsequent oxidation of an intermediate 3- methylthio-2- oxindole leads to the creation of substituted isatin (40-81 percent yield) (David *et al.,* 2007).

Metalation of anilideisatin synthesis

The ortho-metalation (DoM) of N-pivaloyl- and N-(t-butoxycarbonyl)-anilines is a new method for synthesising isatin. After deprotection and cyclization of the intermediate a-ketoesters, thedianions are treated with diethyl oxalate, and isatins are produced. For the synthesis of 4-substituted isatins from meta-substituted anilines, this approach has the advantage of being regioselective (Nataša *et al.,* 2013).

Chemistry of Isatin derivatives

The pyrrole ring is fused with the benzene ring in the isatin ring system. The pyrrole ring is a five-membered ring with one nitrogen in its ring structure. (Prasad, 2012) It was the first chemical to display the tautomerism phenomena. It is a lactam-lactim tautomerism system in which the two forms are:

The production of N- and O alkyl Isatins proves the existence of the aforementioned tautomeric system in isatin. The former is made by reacting methyl iodide with the sodium salt of isatin, whereas the latter is made by reacting methyl iodide with the silver salt of isatin (Pal *et al.,* 2011; Aggarwal, 2009).

Synthetic methodologies of Isatin (1H-indole-2,3-dione)

For the conversion of Isatins to other heterocyclic methods, numerous synthetic techniques have been outlined. One of the following strategies can be used to generalise this method.

Indoles and derivatives are formed by total or partial reduction of the heterocyclic ring. Heterocyclic ring oxidation, such as the conversion of isatin to isatoic anhydride, followed by conversion to various heterocyclic systems, as shown in Figure 1. Nucleophillic addition at position C-3, followed by a cyclization process (figure 2), with or without N1-C2 bond cleavage, or spiroannelation at position C-3, as shown in figure 2. A nucleophillic substitution at position C-2 causes the heterocyclic ring to open. As shown in Figures 3 and 4, this process can be followed by intramolecular or intermolecular exo-trig cyclization.

Antimicrobial

Trivedi *et al.,* (2021) The production of a ferrocene-appended isatin 2,4-thiazolidinedione molecular hybrid connected by a triazole moiety has been reported. Against a number of gram-positive and gram-negative pathogens, all of the novel compounds showed considerable and improved antimicrobial efficacy (Trivedi *et al.,* 2021).

Wang *et al.,* in 2020 The inclusion of the natural substance moenomycin A, which inhibits the peptidoglycan transferase (PGT) enzyme, resulted in a variety of novel antimicrobial drugs. The most effective molecule was (V), which had MIC values of 6 g/mL for MSSA, MRSA, B. subtilis, and 12 g/mL for E. coli protein (PBP-1b). The hydrophilic part of the chemical interacts with the enzyme's active site, whereas the hydrophobic part interacts with the enzyme's transmembrane region in the cell wall (Wang *et al.,* 2020).

Mangasuli *et al.,* (2020) Synthesized named compounds including Isatin-dithiocarbamate hybrids have emerged as a viable antimicrobial agent contender. He discovered that the majority of Compound had potent antibacterial action against *A. flavus, T. harzianum, P. chrysogenum,* and *Candida albicans* bacterial strains. In comparison to the commonly used Fluconazole, the chemical (3e) has showed excellent antifungal activity. These chemicals were created using both conventional and microwave irradiation methods. In addition to additional benefits such as gentle reaction conditions, high yields of products in a shorter reaction time, and a quick workup procedure, the microwave approach is cost-effective (Mangasuli *et al.,* 2020).

Bakht *et al.,* (2020) Graphene oxide (GO) catalyst in deep eutectic solvent (DES) as a green media was used to synthesise isatin-thiazolidine hybrids. Antibacterial and cytotoxic properties of all produced compounds were tested in vitro.

Compounds with higher antibacterial activity against Gram-positive bacteria than Gram-negative bacteria, he discovered. He also observed that chemicals with electron-withdrawing groups like bromo, fluoro, and nitro had stronger bacterial suppression than those with electron-donating substituents like methyl and hydroxyl groups. (Bakht *et al.,* 2020)

Pashirova *et al.*, (2019) described the synthesis of Isatin-3-acylhydrazones with variable hydro-phobicity quaternary ammonium moiety. The hydrophilic-lipophilic balance of -amphiphiles, as well as solvent polarity, influenced biological activity. Low hazardous ammonium salts showed selective antibacterial action against Gram-positive bacteria (*S. aureus* 209p and *B. cereus* 8035) and the fungus *Candida albicans* 855–653.

Antimicrobial agents and drug solubilization may be indicated for newly produced 1-dodecylisatin derivatives having a quaternary ammonium component, particularly for medications capable of -stacking interactions (Pashirova *et al.*, 2019).

Gao *et al.*, (2019) Novel moxifloxacin-amide-1,2,3-triazole-isatin hybrids have been synthesised. In vitro antibacterial activity against Gram-positive and Gram-negative bacteria, as well as drug-resistant diseases, was assessed for all produced compounds.

With MIC values ranging from 0.03 to 128 g/mL, all hybrids exhibited significant activity against the pathogens studied. The structure-activity and structure-cytotoxicity relationships were also investigated, and it was discovered that (Gao *et al.*, 2019).

Substituents in the R1 position had a significant impact on activity.

Electron-donating methyl performed better than electron-receiving fluoro.

The antibacterial activity was similarly influenced by substituents on the phenyl ring.

Substituted analogues at the C-5 position were more powerful than analogues at the C-7 position.

The addition of methyloxime (R2) to the C-3 position of the isatin moiety could improve activity to some extent, however ethyloxime was found to be deleterious to activity in general.

Fig.1

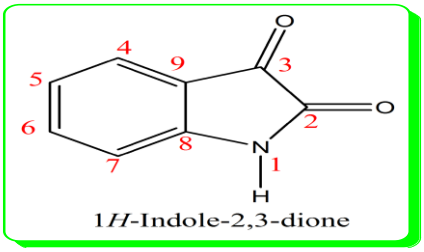


Fig.2 (a)4-Thiazolidinone 3D Model, (b) 4-Thiazolidinone's structure

a

b

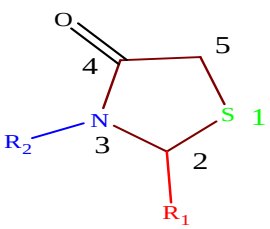


Fig.3 Isatin moiety structure, marketable medicines, and dyes.

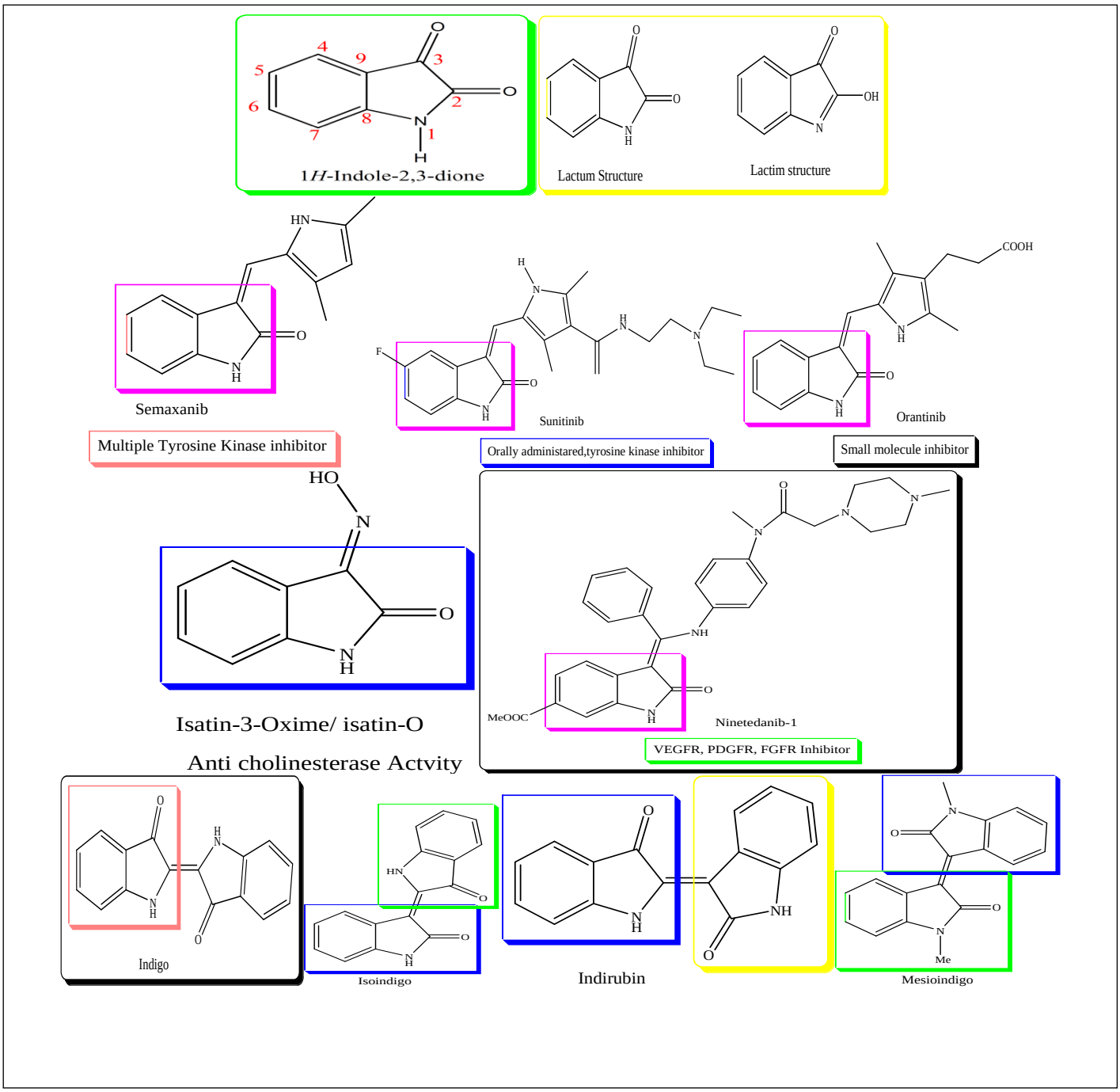


Fig.4 Sandmeyer isatin synthesis

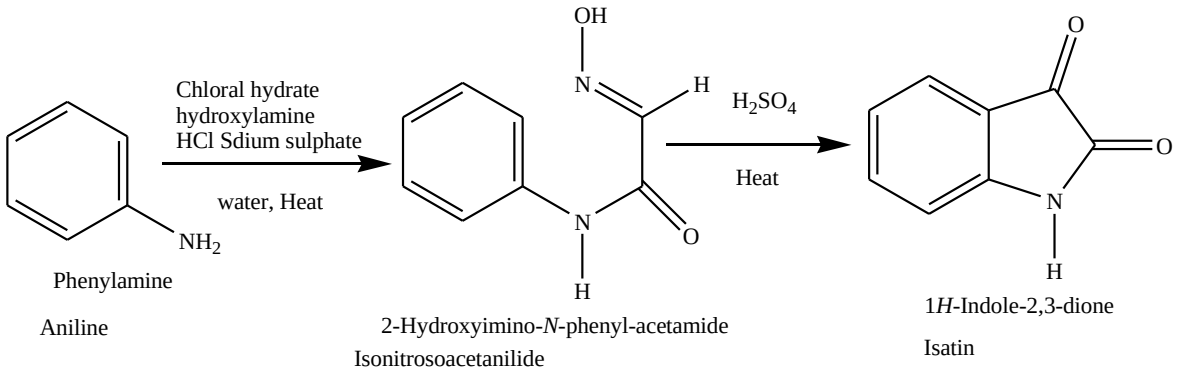


Fig.5 Common Routes to Synthesis of Substituted Isatin Derivatives

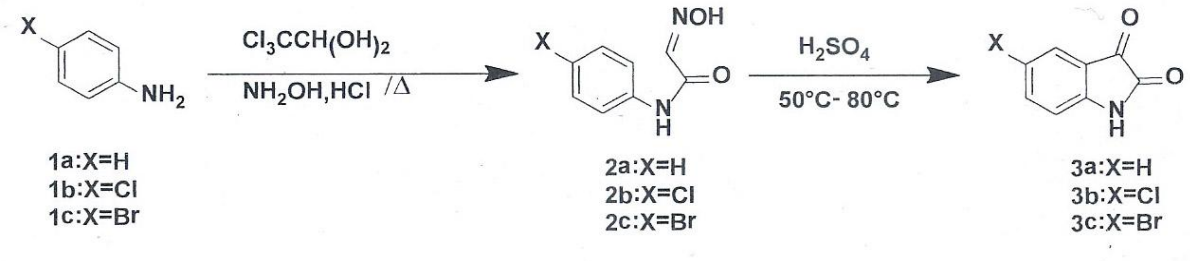


Fig.6 Stolle isatin synthesis

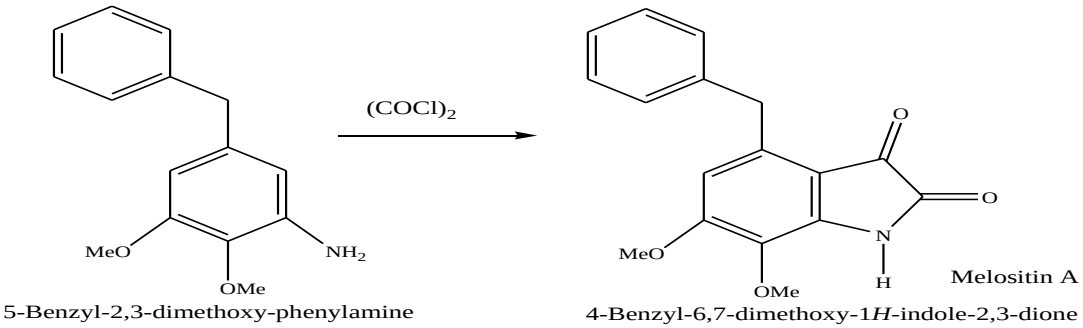


Fig.7 Martinet isatin synthesis

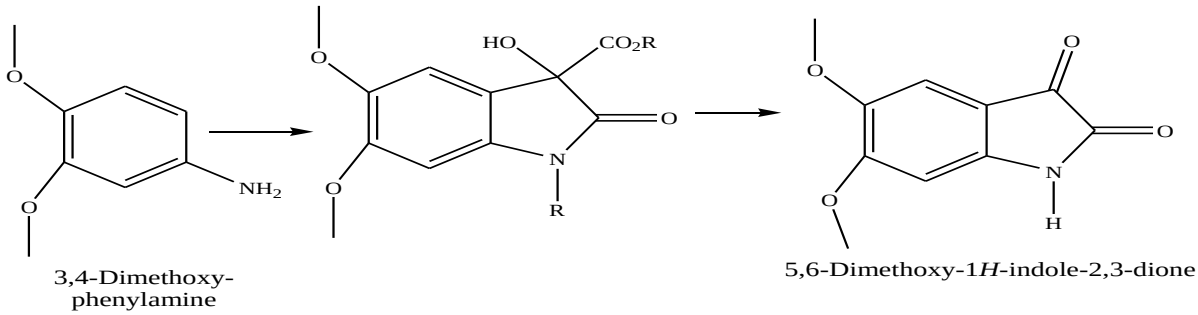


Fig.8 Gassmanisatin synthesis

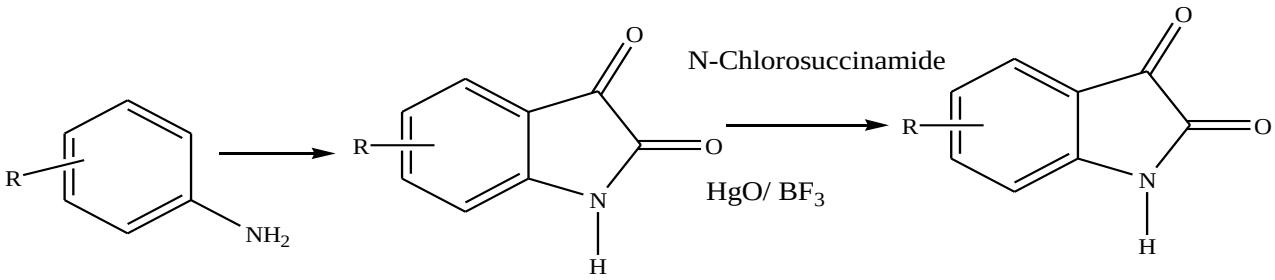


Fig.9 Metalation of anilideisatin synthesis

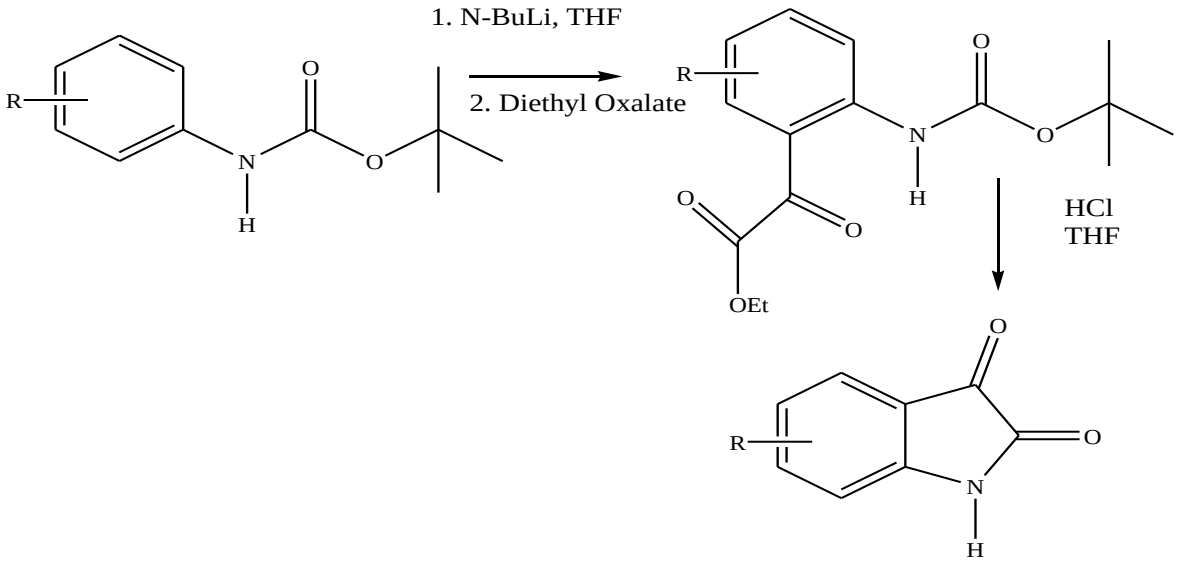


Fig.10 Lactam-lactim tautomerism

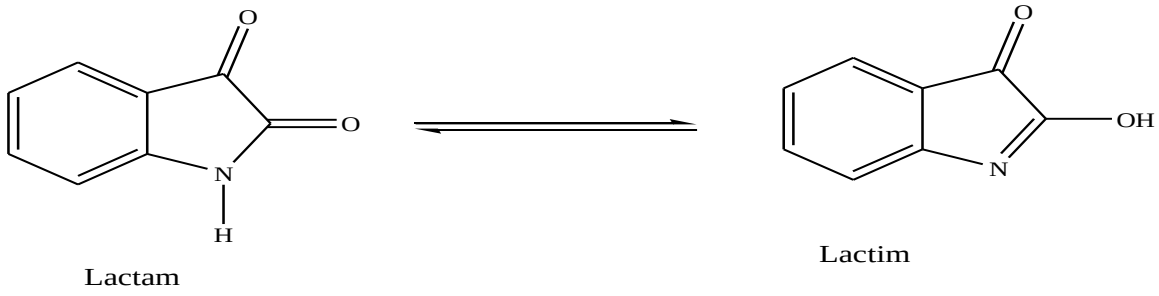
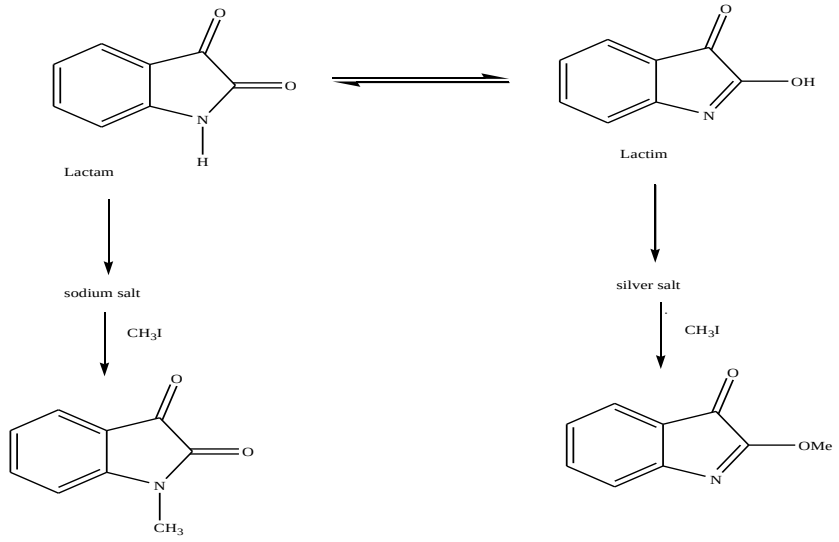


Fig.11 Tautomeric system in Isatin



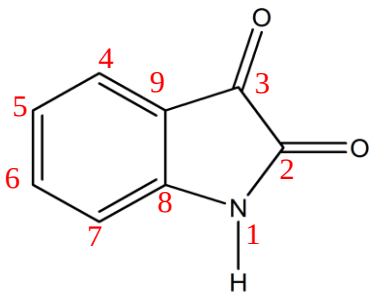


Fig.12

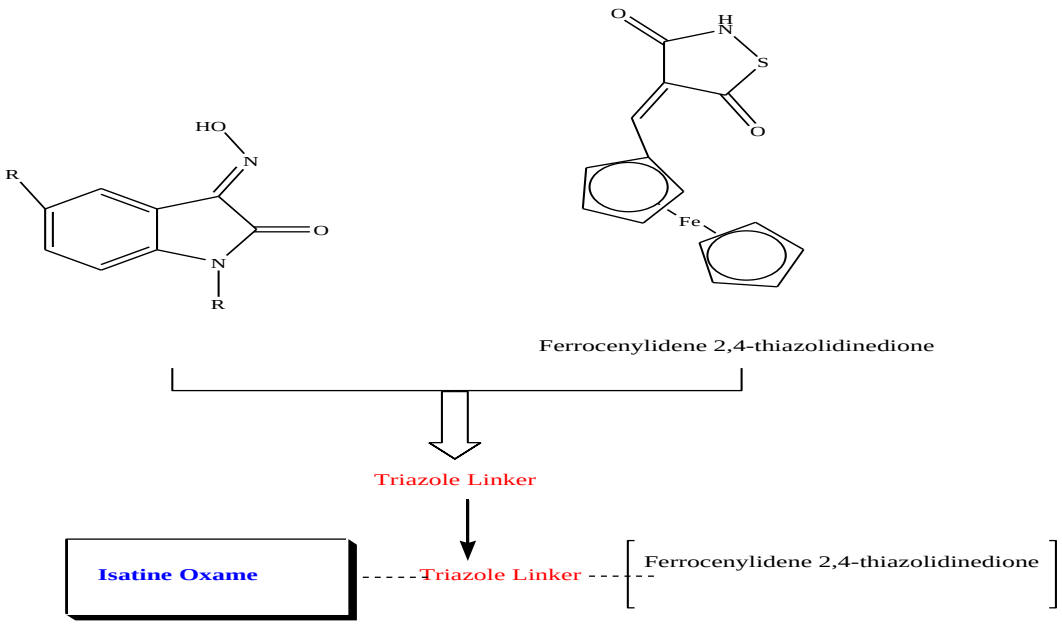


Fig.13

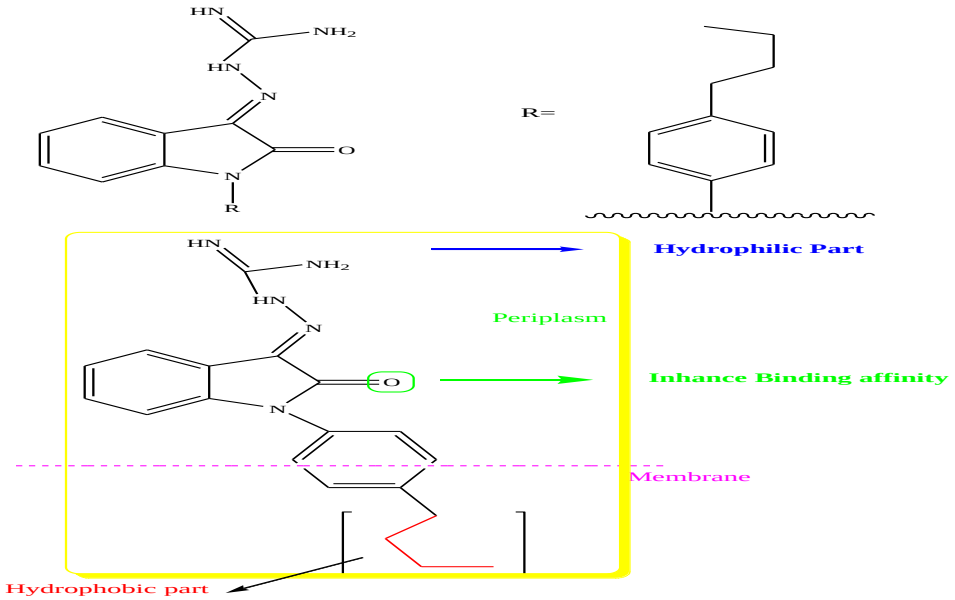
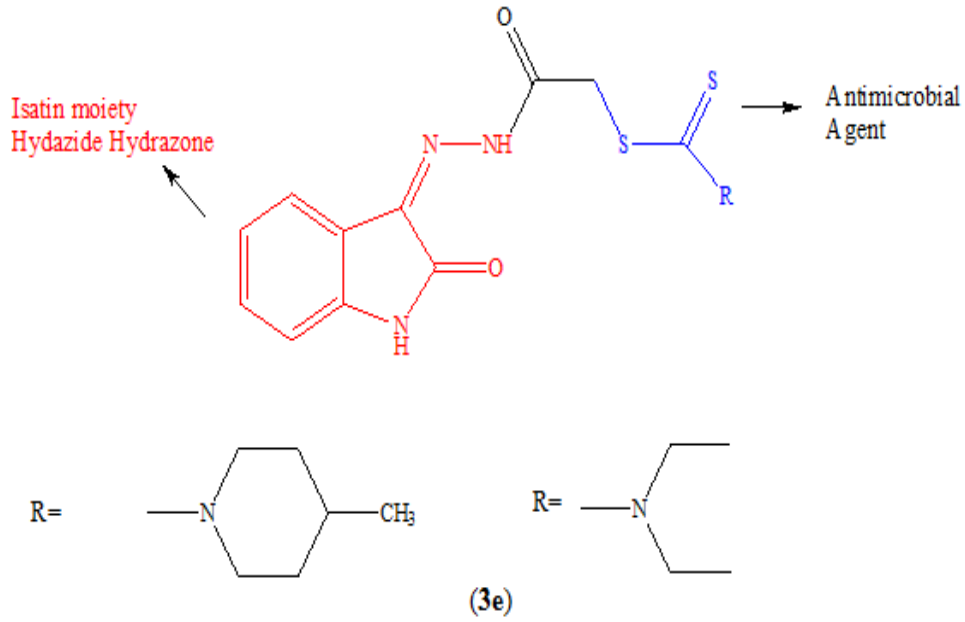


Fig.14



(3e)

Fig.15

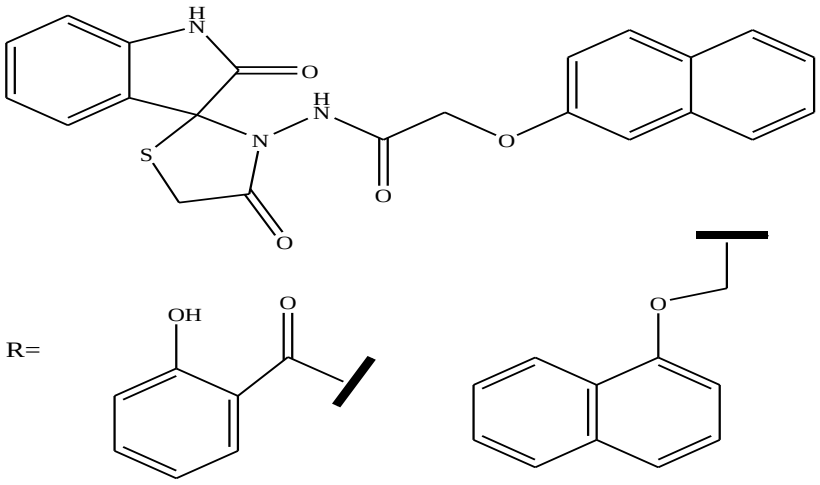
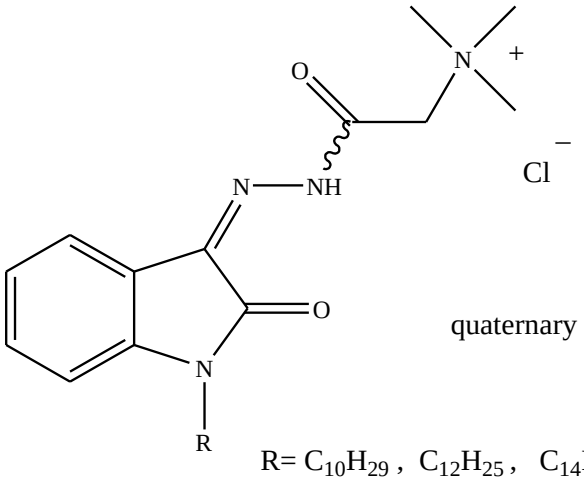


Fig.16



quaternary ammonium moiety

R= $C_{10}H_{29}$, $C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$, $C_{18}H_{37}$, $C_{20}H_{41}$

Fig.17

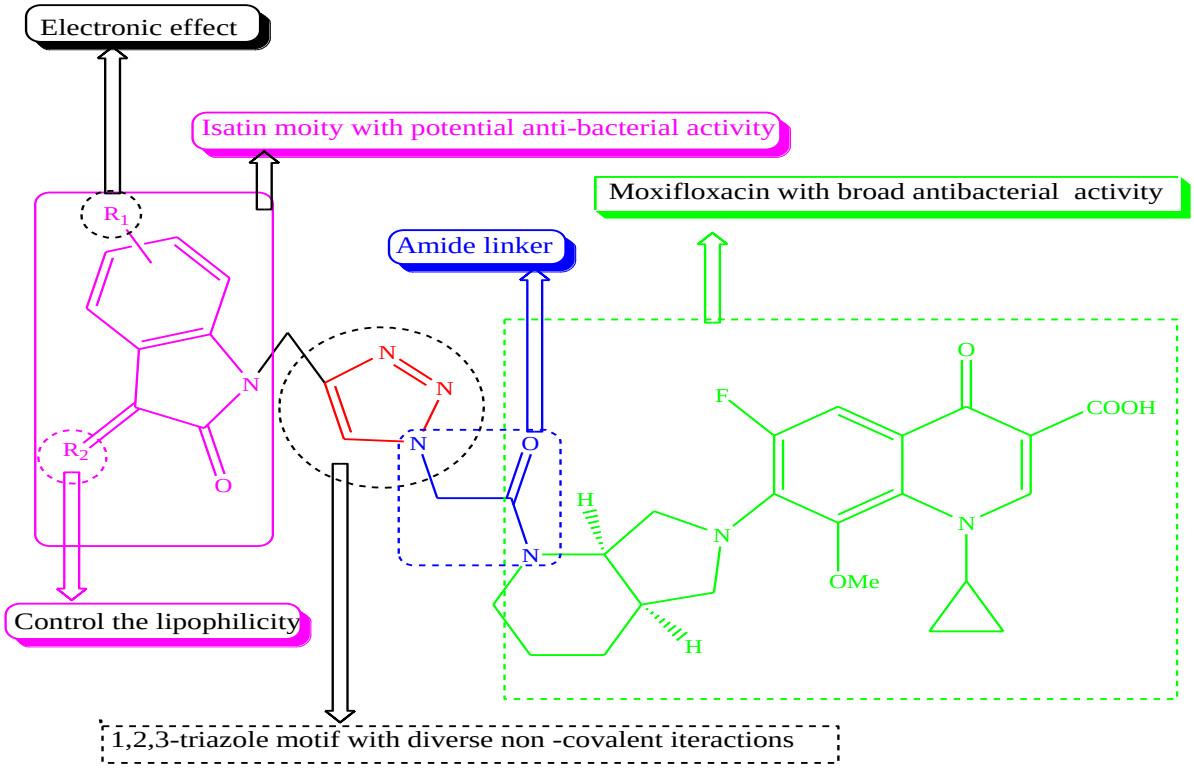
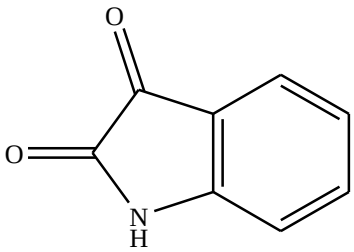
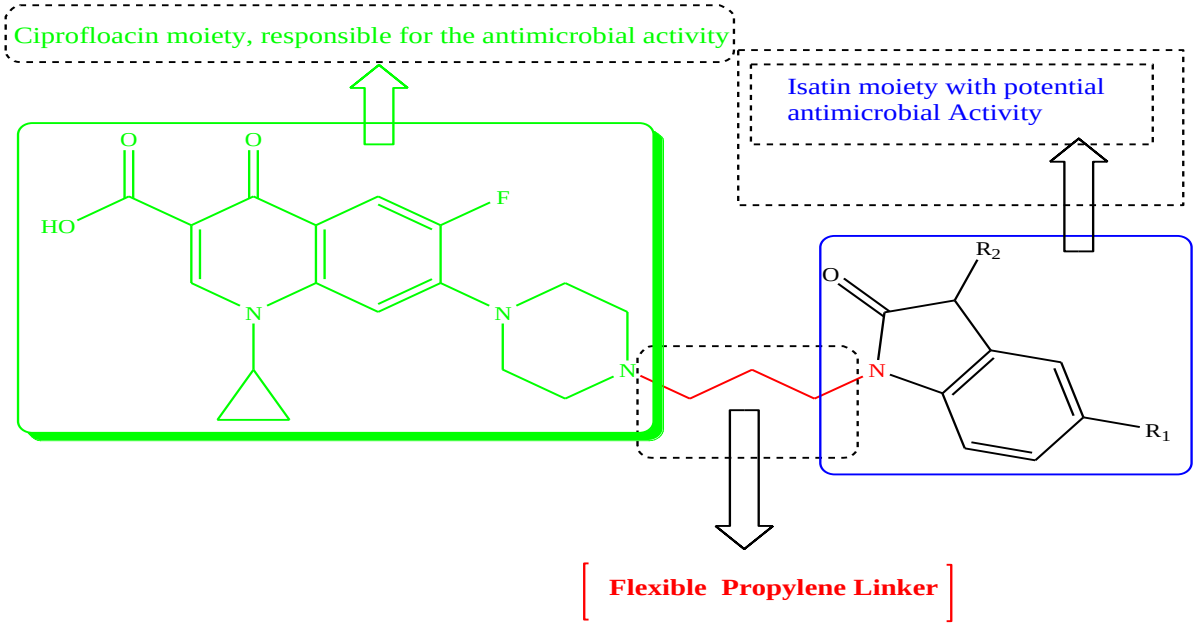


Fig.18



Isatin

Fig.19


Ciprofloacin moiety, responsible for the antimicrobial activity
Isatin moiety with potential antimicrobial Activity
Flexible Propylene Linker

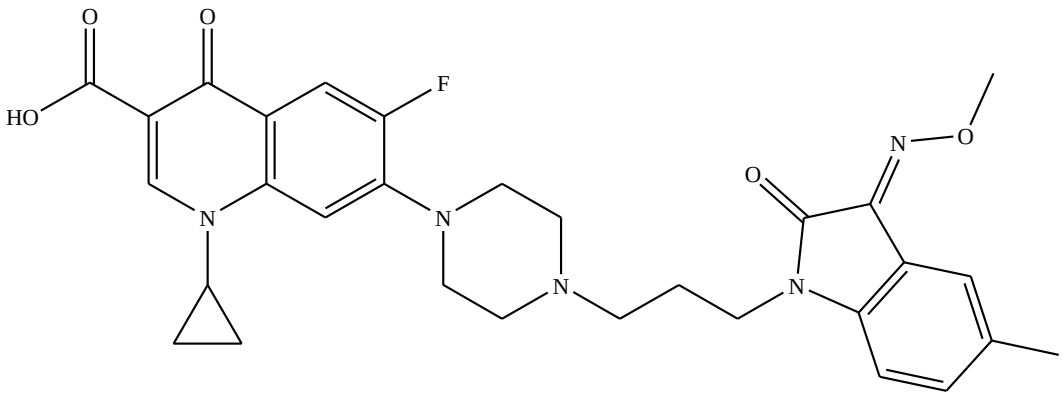


Fig.20

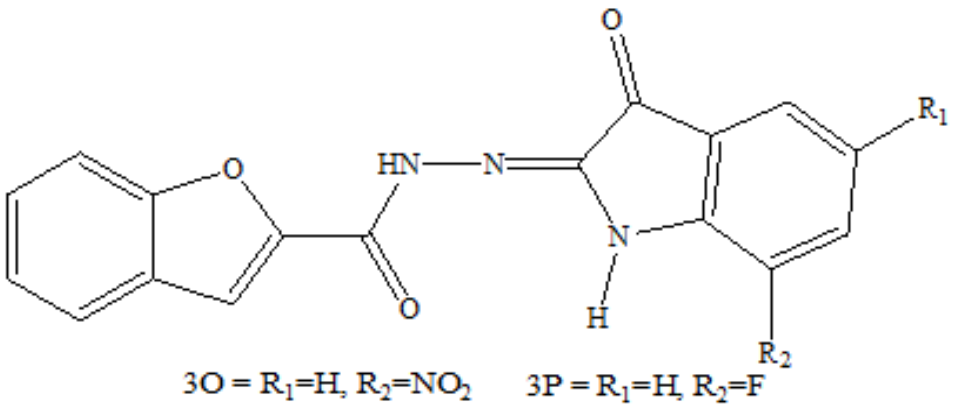
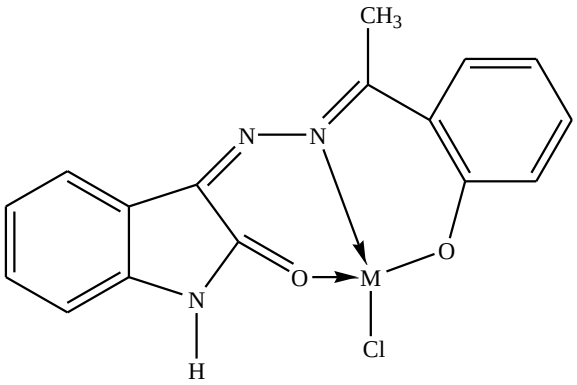
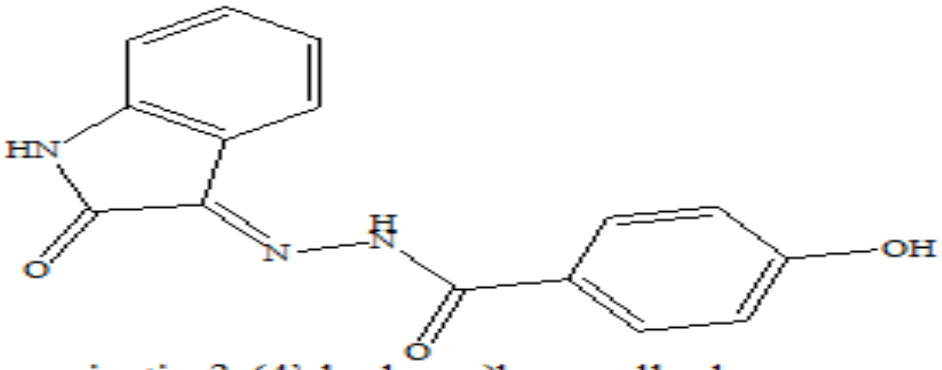

3O = R1=H, R2=NO2
3P = R1=H, R2=F

Fig.21



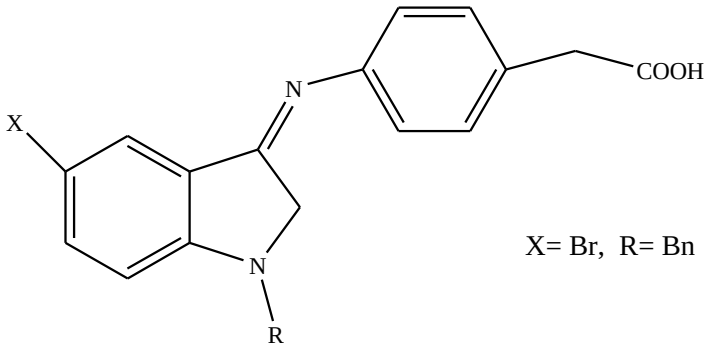
M= Ni (II) & Cu (II)

Fig.22



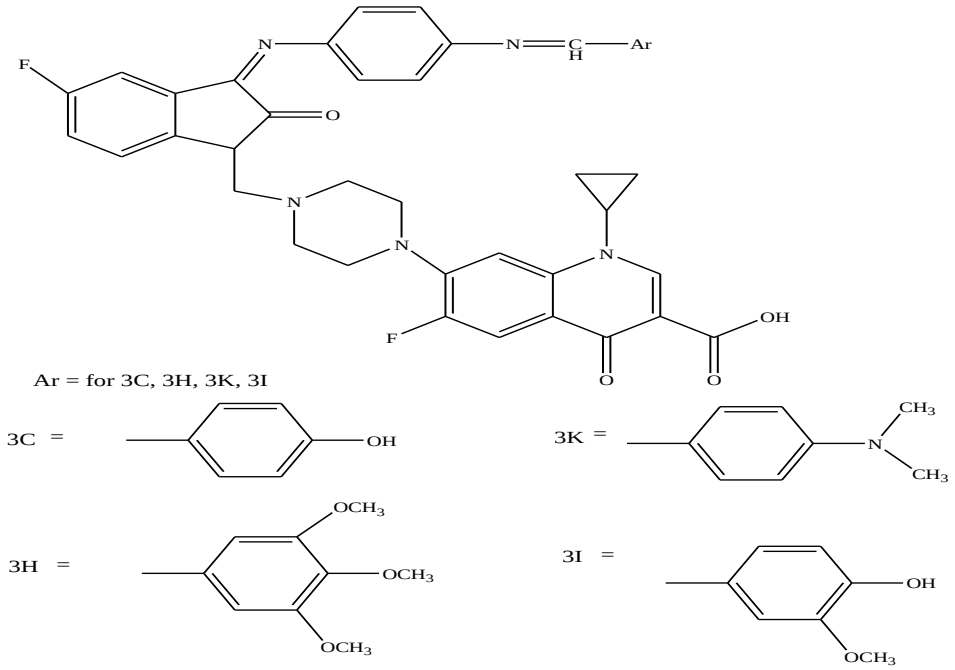
isatin-3-(4`-hydroxy)benzoylhydrazone

Fig.23



X= Br, R= Bn

Fig.24



Ganim *et al.,* (2018) described the synthesis of isatin and thiosemicarbazone derivatives, which were then tested for DNA binding, including DNA protection studies using plasmid DNA (pUC19) and DNA interaction experiments with calf thymus DNA (CT-DNA). They also used an in vitro experiment to test drugs' antibacterial properties against a variety of harmful bacterial species. DNA protection activity ranged from 23.5 to 59.5 percent in all isatin and thiosemicarbazone derivative compounds. The DNA-protective activity of I3-(N-2-MP)-TSC was the highest among them. With low concentrations, derivatives of isatin thiosemicarbazone showed substantial and specific antibacterial action. These chemicals were mostly efficient against Gram-positive bacteria, but not against *P. vulgaris* or *E. coli*. These chemicals had the greatest impact on the Gram-positive methicillin-resistant *S. aureus* ATCC 43300 (MRSA) strain. The methyphenyl group at isatin was discovered to be critical for its antibacterial action against MRSA (Ganim *et al.,* 2018).

Wang *et al.,* (2018) A unique synthesis of twelve propylene-tethered ciprofloxacin-isatin hybrids was reported, and all hybrids were tested in vitro for antibacterial activity against Gram-positive, Gram-negative, and mycobacterial infections. He discovered that all mono-isatin-ciprofloxacin hybrids had outstanding antibacterial activity against majority of the pathogens tested, with MICs ranging from 0.03 to 0.5 mg/mL. Ciprofloxacin-isatin hybrid (3d) was very effective against all Gram-positive and Gram-negative microorganisms tested, including clinically significant drug-resistant infections, and was comparable to or more effective than the parent ciprofloxacin and the reference levofloxacin (Wang *et al.,* 2018).

Ugale *et al.,* (2017) N-(5 or 7 substituted-2-oxoindolin-3-ylidene) benzofuran-2-carbohydrazides were discovered. All of the produced compounds were tested for antimicrobial activity, and he discovered that 3o was effective against *Escherichia coli* and *Pseudomonas vulgaris*, while 3p was effective against *Bacillus subtilis*, *E. coli* and *Pseudomonas vulgaris*. Antifungal activity of 3o and 3p against *Aspergillus niger* was also observed (Ugale *et al.,* 2017).

Swathy *et al.,* (2016) studied the synthesis of isatin complexes with manganese(II), cobalt(II), nickel(II),

copper(II), and zinc has been described (II). In comparison to *S. typhi* and *S. aureus*, all of the complexes have increased activity against E. coli. (CuLCl) > (NiLCl) > (MnL2) > (ZnLCl) > (CoL2) > L. Antibacterial activity order (CuLCl) > (NiLCl) > (MnL2) > (ZnLCl) > (CoL2) > L. When a chemical is coordinated with metal, its antifungal activity is increased by several times. Cu(II) > Ni(II) > Co(II) > Mn(II) > Zn(II) > L. The activity of these complexes and ligands is in this order: Cu(II) > Ni(II) > Co(II) > Mn(II) > Zn(II) > L. The copper complex is more active against *R. stolonifer* than the ligand, according to the comparison of activities. (Swathy *et al.,* 2016). The synthesis of isatin-3-(4-hydroxy) benzoylhydrazone was described by. He discovered that the C-3 position in isatin is particularly vulnerable to nucleophilic assault, whereas C-2 only reacts with nucleophiles under precise conditions due to the amido group's negative inductive impact. Antimicrobial activity was tested against *Staphylococcus aureus, Serratia marcescens, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis* and *Candida albicans* in all produced compounds (Sandra *et al.,* 2015; El-Faham *et al.,* 2015).

Faham *et al.,* (2015) Microwave irradiation was used to synthesise three isatin derivatives (3-hydrazino, 3-thiosemicarbazino, and 3-imino carboxylic acid). He tested all of the produced chemicals for antibacterial activity and discovered that the N-alkyl isatin derivatives were physiologically active. He also discovered that iminoisatin carboxylic acid derivatives (2-(4-(1-benzyl-5-bromo-2-oxoindolin-3-ylideneamino) phenyl) acetic acid, 5d) were effective against all Gram-positive bacterial and fungal pathogens tested (Faham *et al.,* 2015).

Prakash *et al.,* (2013) by substituting various aromatic aldehydes at the 3rd position and connecting Ciprofloxacin at the N1 position with formalin, a series of novel Schiff and mannich bases of isatin derivative (I) were produced. Except for *B. cereus* ATCC 11778, compounds 3c, 3k, 3h, and 3i showed excellent antibacterial capabilities against all microorganisms. *In vitro* antimicrobial activity against seven bacteria (four gramme positive and three gramme negative) and two fungal strains The antibacterial capabilities of electron donating group substituted derivatives were shown to be superior to those of electron withdrawing compounds (Prakash *et al.,* 2013).

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How to cite this article:

Ashutosh Pathak, P. Malairajan, Arti Gautam and Shibu Das. 2022. Isatin: A Short Review of their Antimicrobial Activities. *Int.J.Curr.Microbiol.App.Sci.* 11(01): 61-77.
doi: https://doi.org/10.20546/ijcmas.2022.1101.009