Original Article

Recent Advances, Future Challenges, Sar And Antimicrobial Activities Of Isatin: A Breaf Review

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Abstract

Isatin (2, 3-dioxindate), a very potent scaffold has been developed due to its clinical significance concerned in organic & medicinal chemistry with varied pharmacological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. Present review gives significance details to chemistry, synthesis, biological and pharmacological activity, SAR, and advance applications of isatin moiety. The advances in the use of isatins for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported along with supplementary information.

KEYWORDS: Isatin, heterocyclic synthesis, analgesic, anti-inflammatory activity, eco-friendly.

1. Introduction

Recently, heterocyclic compounds form a bridge between the natural and the purely synthetic compounds have been found to occur widely in nature and have proved to be of an enormous significance to life. [1]. Isatin or 1H-indole-2, 3-dione is an indole derivative and first organic compound to be synthesized, characterised by Bayer, Erdman and Laurent in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids which resulted in bright orange colored monoclinic crystals of isatin as a product. Naturally, isatin is also found in plants of genus Isatis [2].

Other Names of Isatin:
1H-indole-2,3-dione
Indole-2,3-dione
Indole-2,3-dione
Indoline-2,3-dione
2, 3-Dihydro-1H-indole-2,3-dione

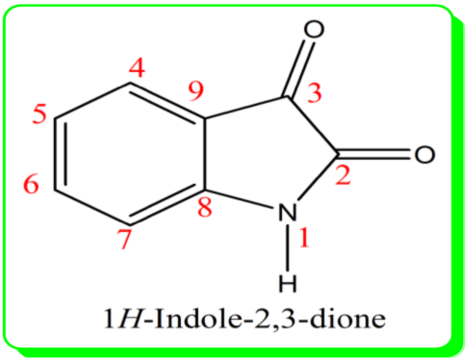


Figure-1 Chemical structure of isatin.

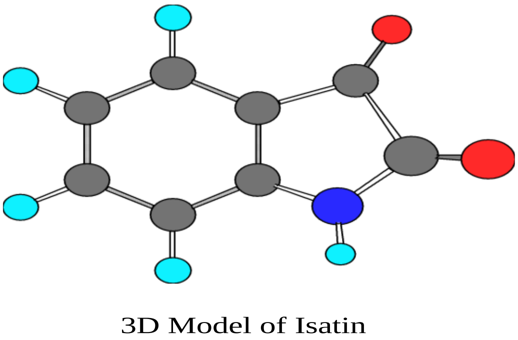


Figure-2

Figure-3 bright orange power of isatin

Figure-4 Plant Couroupita guianensis Aubl[6.1]

Figure-5 Plant Isatis tinctoria

Figure-6 Toad Bufo melanostrictus [7.1]

Figure-7 Toad Bufo gargarizans [7.2]

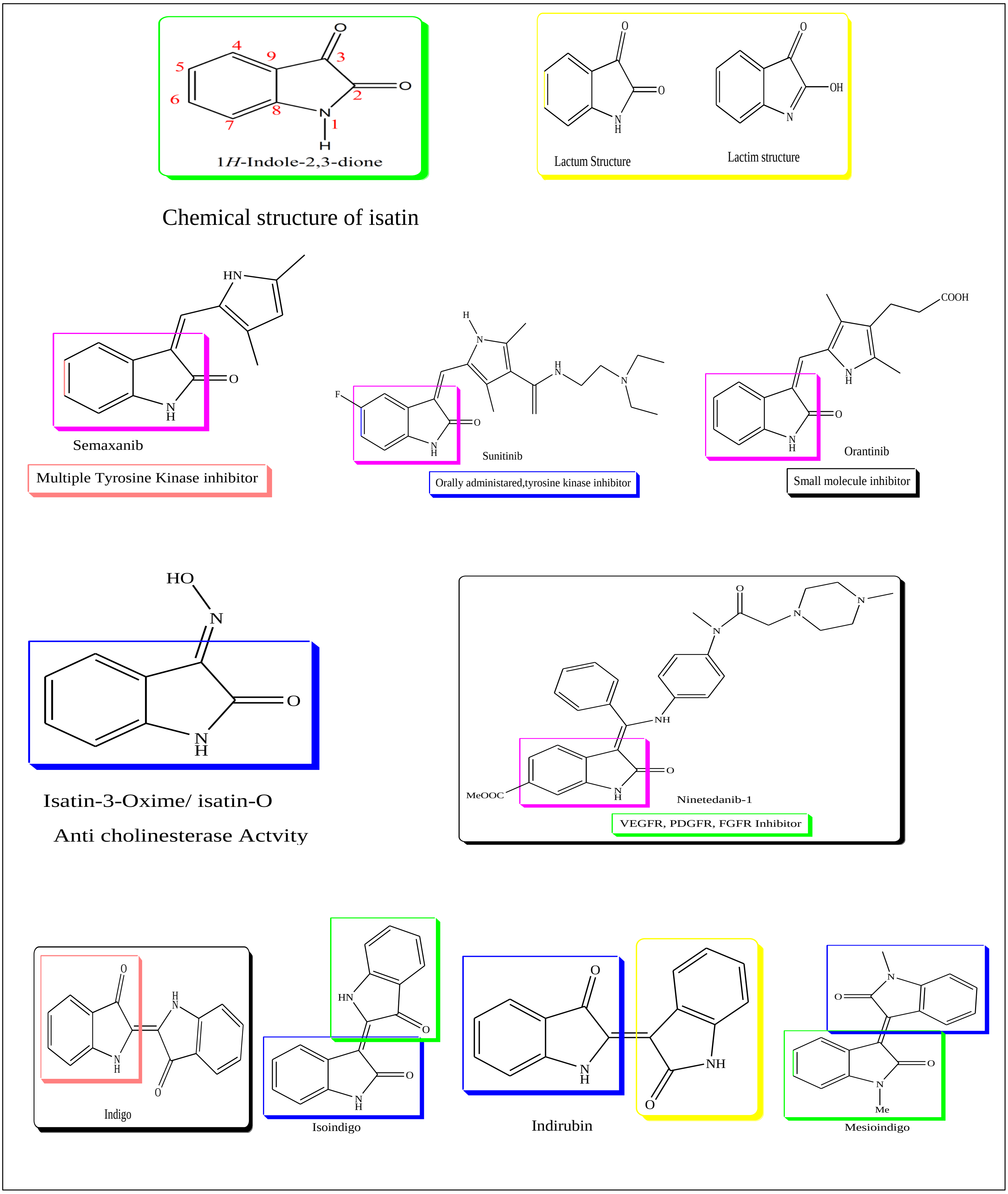
Figure-8 Marine mollusc Dicathais orbita [7.3]

Figure (1-8) Flora and fauna containing isatin and its derivatives.
Figure-1 Chemical structure of isatin
Figure-2 3-D Model of isatin
Figure-3 bright orange power of isatin
Figure-4 Plant Couroupita guianensis Aubl[6.1]
Figure-5 Plant Isatis tinctoria

Figure-6 Toad Bufo melanostrictus [7.1]
Figure-7 Toad Bufo gargarizans [7.2]
Figure-8 Marine mollusc Dicathais orbita[7.3]

Three reviews have been published regarding the chemistry of this compound: first by Sumpter in 1954, second by Popp in 1975 and third on the utility of isatin as a precursor for the synthesis of other heterocyclic compounds. In nature, isatin is found in plants of the genus Isatis, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant Melochia tomentosa [3- 4] in Calanthe discolour LINDL [5], and in Couroupita guianensis AubL[6, 6.1] and has also been found as a component of the secretion from the parotid gland of Bufo frogs [7,7.1,7.2] and in humans as a metabolic derivative of adrenaline.[8-10] It is also isolated from fungi: 6-(3'-methylbuten- 2'-yl) isatin was isolated from Streptomyces albus, 5- (3'-methylbuten-2'-yl)isatin from Chaetomium globosum and Marine mollusc Dicathais orbita[7.3] . Isatin has also been found to be a component of coal tar and further known to be a colour reagent for the amino acid proline, forming a blue derivative. [11-12] Mammalian tissues and rat brain (mainly in hippo- campus and cerebellum) can be the sourse of isatin, where it functions as a modulator of biochemical processes [13].

Isatin and its derivatives have been reported highly efficient during in vitro studies against genotoxic and mutagenic diseases, but during in vivo, the genotoxic and mutagenic potential of isatin is not well established and reported. Isatin was first reported as "Tribulin" and was identified as a selective inhibitor of monoamine oxidase (MAO) [14]. Structurally, isatin is a fusion of six-membered benzene ring and five-membered ring containing nitrogen. Both rings lie in the same plane, but one is aromatic and another is anti-aromatic [15]. The isatin's reported different substituents at the 1st and 3rd positions include phenyl ring moieties, heterocyclic rings, and aliphatic systems. Isatin is one of the most exciting new groups of heterocyclic compounds, with a variety of fascinating activity profiles and good human tolerance [16]. This study aims to compile a collection of all publications that mention isatin, its synthesis, chemical reactivity, and pharmacological properties and were published between 2010 and 2022. The biological and pharmacological information obtained from the scientific literature is summarised in Electronic Supplementary Information (ESI).



The first and most used technique for synthesising isatin was created by Sandmeyer. It may be made by cyclizing the aniline, chloral hydrate, and hydroxylamine hydrochloride condensation result in aqueous sodium sulphate to create an isonitrosoacetanilide, which, following separation and treatment with concentrated sulfuric acid, yields isatin in an overall yield of greater than 75%. The technique works well with certain heterocyclic amines, such as 2-aminophenoxathine, and anilines having electron-withdrawing substituents. [17-18].

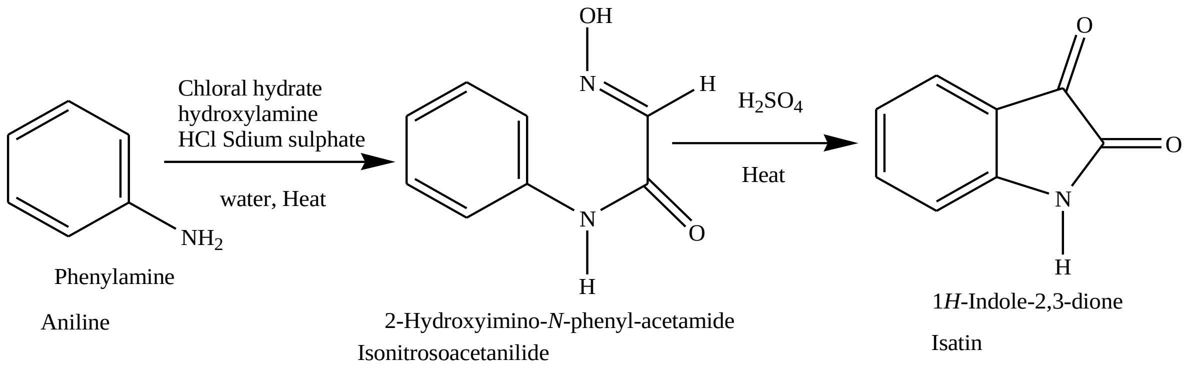


Figure-10 Sandmeyer isatin synthesis

2.2. The Stolle isatin synthesis

Stolle's approach is the most significant substitute for Sandmeyer's method. In this procedure, anilines and oxalyl chloride combine to generate an intermediate chlorooxalylanilide, which may then be cyclized in the presence of a Lewis acid, often aluminium chloride or BF3. TiCl4 has also been used to produce the equivalent isatin, although Et2O is the preferred method [19-20].

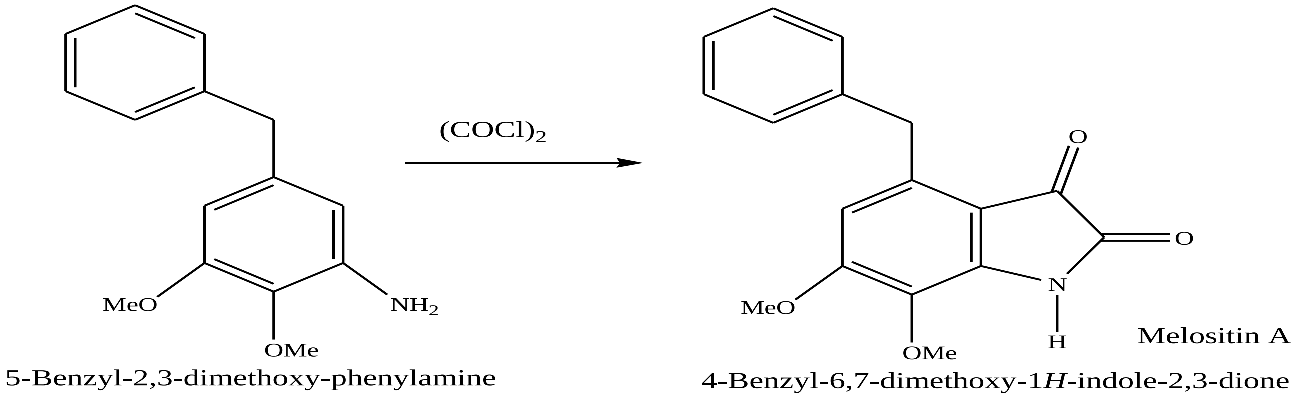


Figure-11 Stolle isatin synthesis

2.3. The Martinet method includes reacting an aminoaromatic molecule with either an oxomalonate ester or its hydrate in the presence of an acid to produce a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative, which upon oxidative decarboxylation results in the appropriate isatin. In contrast to the less successful utilisation of 2,4-dimethoxyaniline, this approach was successfully used to synthesise 5,6-dimethoxyisatin from 4-aminoveratrole. [21].

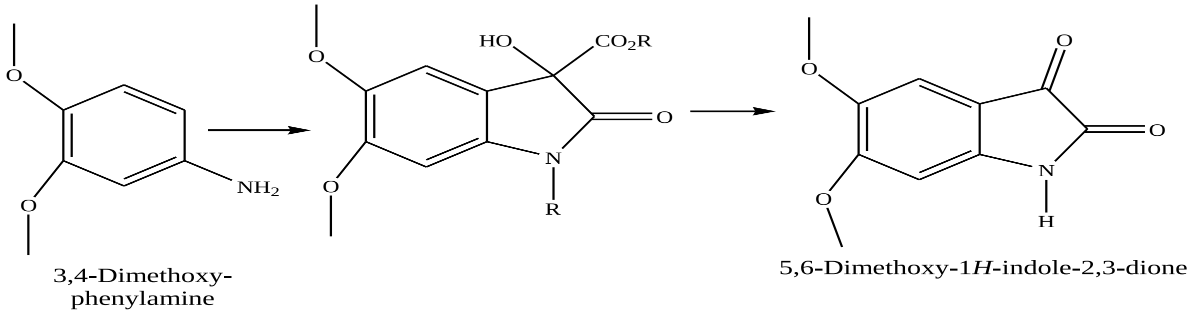


Figure-12 Martinet isatin synthesis

2.4. **The Gassman isatin synthesis** another method for the synthesis of isatins was created by Gassman, and it is fundamentally distinct and general. This approach involves creating an intermediate 3-methylthio2-oxindole44–46 and then oxidising it to produce the corresponding substituted isatins with a 40–81% yield. The development of two complementary methods for the synthesis of the 3-methylthio-2-oxindoles depends on the electronic effects of the substituents bound to the aromatic ring. The oxindole derivative can be made when electron-withdrawing groups are present by using an N-chloroaniline intermediate, which then reacts with a methylthioacetate ester to produce an azasulfonium salt. The N-chloro intermediate is destabilised by electron-donating groups, which results in lower yields of the azasulfonium salt [22].

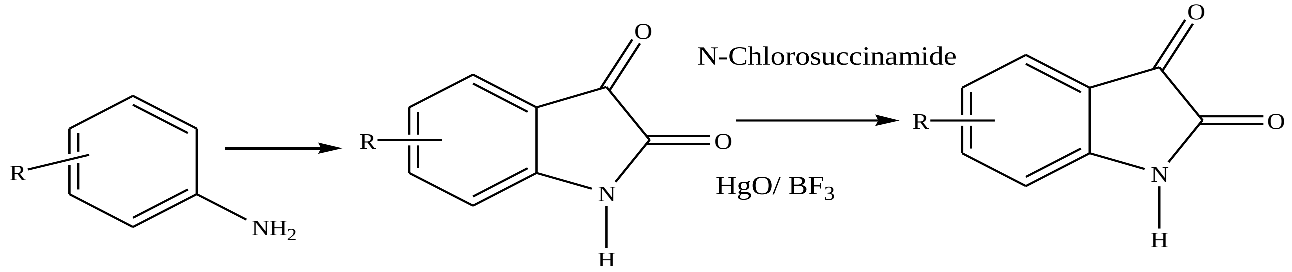


Figure-13 Gassman isatin synthesis

2.5. Metalation of anilide isatin synthesis The recent method for synthesis of isatin is based on ortho-metalation (DoM) of N-pivaloyl- and N-(t-butoxycarbonyl)-anilines. The dianions are treated with diethyl oxalate and then isatins are obtained after deprotection and cyclisation of the intermediate a-ketoesters. The advantage of this method is being regioselective for the synthesis of 4-substituted isatins from meta-substituted anilines [23].

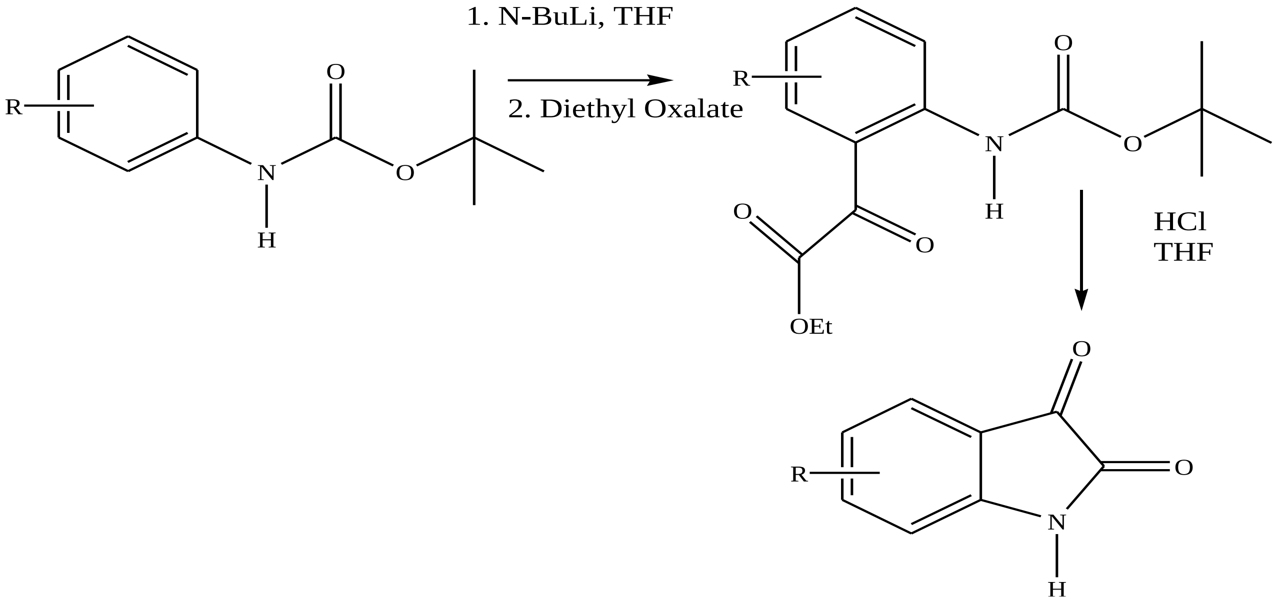
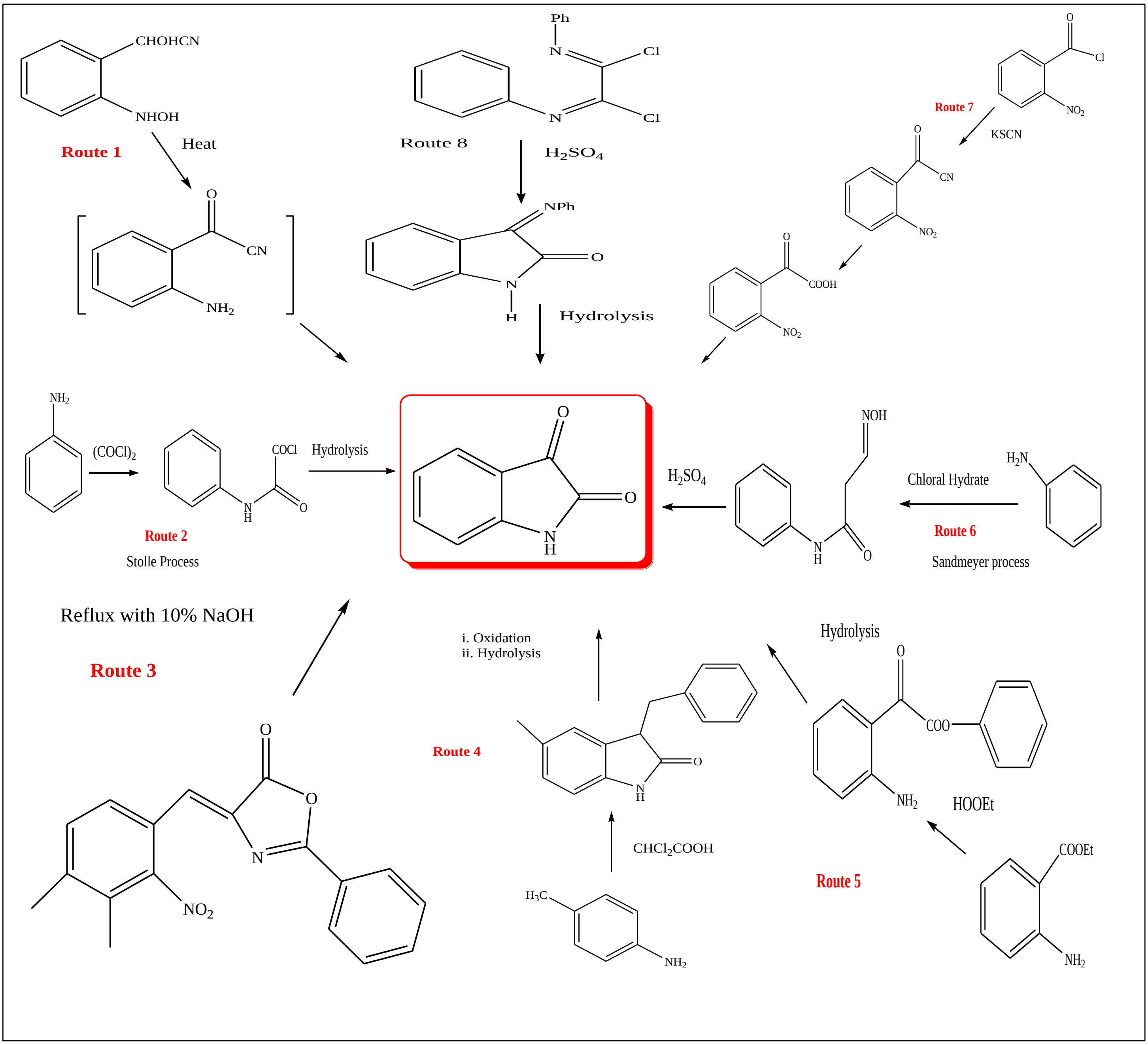


Figure-14 Metalation of anilide isatin synthesis



3. Chemistry of Isatin (1H-indole-2,3-dione) derivatives
   The transformation of isatins into other heterocyclic systems has been described using a variety of synthetic techniques. [24] The following tactics can be applied to this chemistry.
   a. Partial or complete reduction of the heterocyclic ring, resulting in indoles and their derivatives.
   b. Heterocyclic ring oxidation. For instance, the transformation of isatin into isatoic anhydride, followed by the formation of additional heterocyclic systems, as seen in Figure 15.

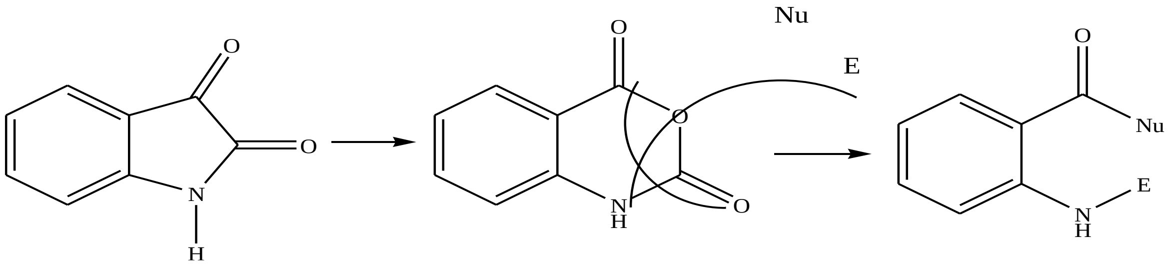


Figure-15

C. Nucleophilic addition at position C-3, which is then followed by a cyclization procedure, with or without the cleavage of the N1-C2 bond (Figure 2); or by a spiro- annelation at position C-3, as shown in Figure 16.

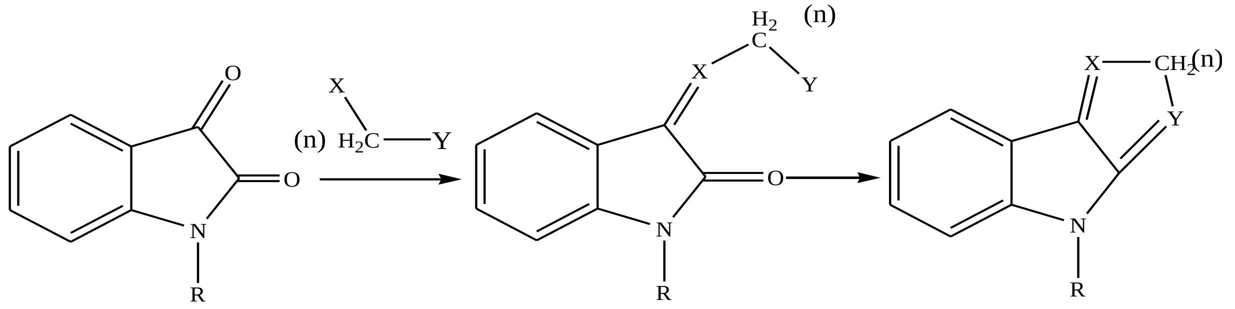


Figure-16

D. A nucleophilic substitution at position C-2 that causes the heterocyclic ring to open. Exo-trig cyclization may occur intramolecularly or intermolecularly as seen in Figures 17 and 18.

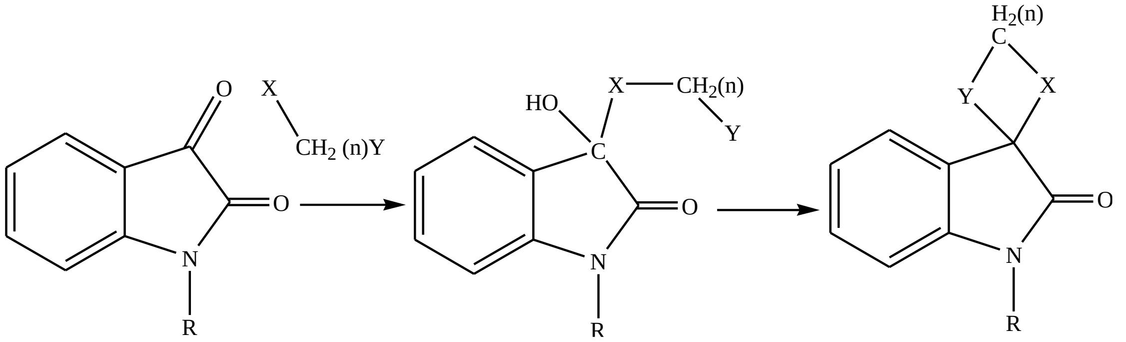


Figure-17

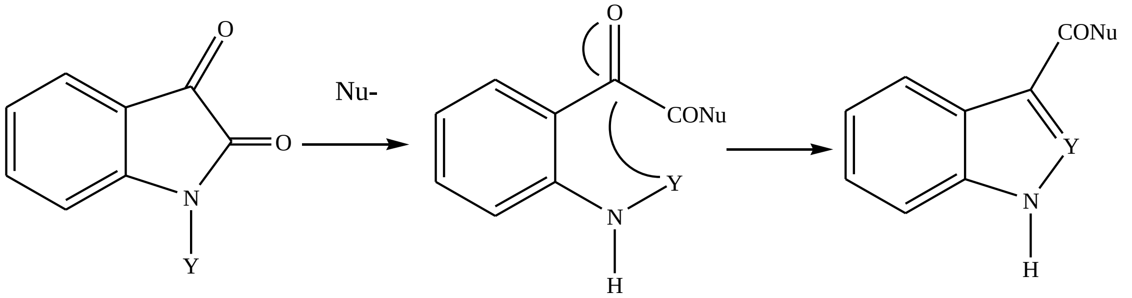


Figure-18

Isatin ring system consists of pyrrole ring fused with benzene ring. Pyrrole ring is a five-membered ring containing one nitrogen in the ring system[25]. It was the first compound to exhibit the phenomenon of tautomerism. It is an example of lactam-lactim tautomerism system; the two forms are (**Figure-19**
) :

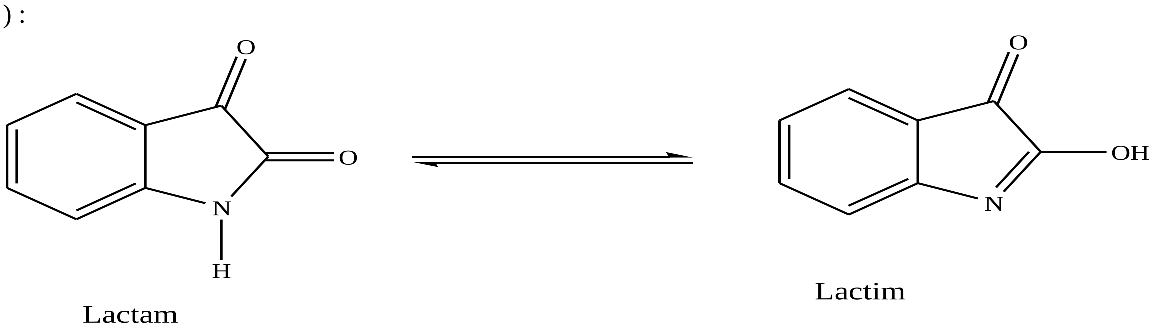


Figure-19

The existence of the above tautomeric system in isatin is proved by the formation of N- and Oalkyl isatins. The former is formed by treating the sodium salt of isatin with methyl iodide whereas the latter is formed by treating the silver salt of isatin with methyl iodide **Figure-20** [26].

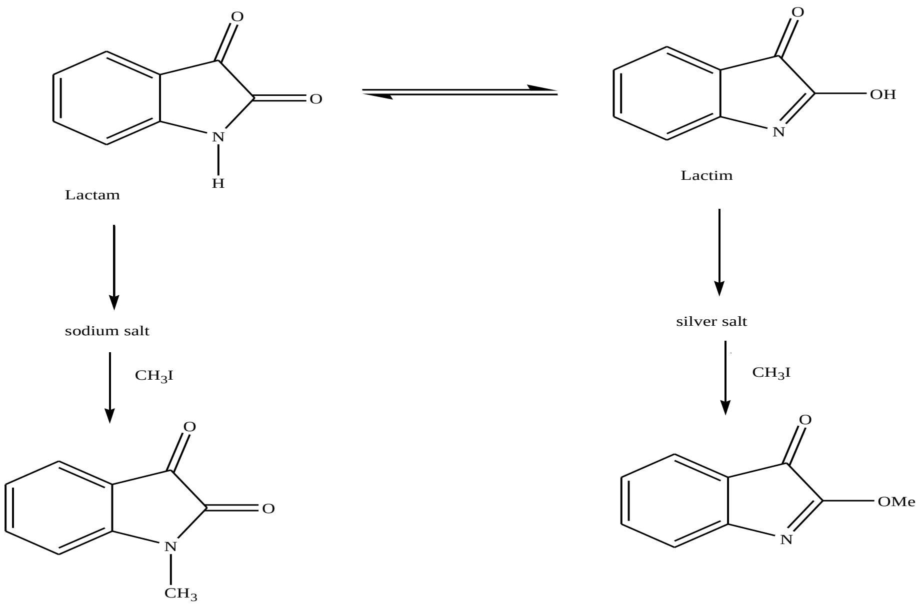
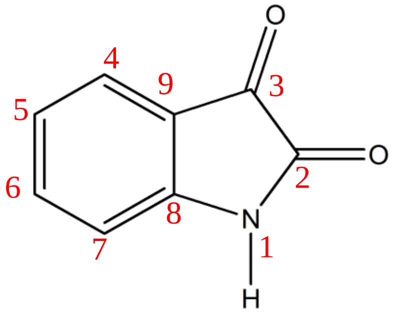


Figure-20

4. ACTION MECHANISM:- ISATIN

In 1988, isatin was shown to be a key component of tribulin, a low-molecular-weight inhibitor of MAO type B (MAO-B). In addition, urine isatin concentrations in people with Parkinson's disease tend to rise in correlation with disease severity [27] These findings imply that urinary isatin may develop into a diagnostic biomarker for the clinical severity of Parkinson's disease and that endogenous isatin, a novel biological modulator, may contribute to the control of the brain's ACh levels by raising DA levels under stressful situations [28]. Tribulin may include isatin metabolites or other similar endogenous substances [29]. Isatin and tribulin are yet unknown in terms of their physiological and pathological functions. Exercise [30]and aging [31] both cause tribulin levels in people to rise. Comparison to males, females excrete much more Tribulin [32]. Kumar et al., reported reported that the rat brain and erythrocytes' ability to produce acetylcholine esterase (AChE) is inhibited by isatin [33]. The levels of acetylcholine (ACh), choline (Ch), and dopamine (DA) in rat tissues at 2 hours after isatin administration (50 or 200 mg/kg, i.p.) were used to clarify the physiological role of isatin in the regulation of ACh levels in the rat brain. The group that received isatin experienced significantly higher levels of ACh and Ch. After receiving isatin therapy, striatum DA levels also rose. That is to say, isatin elevated ACh and DA levels in the WKY striatum at the same time, at a single dosage. In our in vitro work, isatin at 10.4 M caused a 93% to 5% inhibition of MAO and a 5% inhibition of AChE in the rat brain. It is obvious that isatin prefers MAO to AChE as its preferred target molecule. Ch, an AChE metabolite of ACh, was likewise elevated after isatin injection in several brain areas. These findings showed that isatin enhanced ACh levels through a different method than that which AChE activity inhibition would have done [34]. Isatin has a broad range of biological characteristics: its physiological functions safeguard against anxiety and certain infections; The central nervous system is impacted by it. Isatin has a wide range of biological effects, including acting as a stress and anxiety marker, an inhibitor of several enzymes, an anti-seizure drug, an agonist at the 5-HT3 receptors, an inhibitor of benzodiazepine receptors, among other things.

STRUCTURE ACTIVITY RELATIONSHIP OF ISATIN



1*H*-Indole-2,3-dione

Figure-21

1. Substitution at position 5, 6 and 7 improves the CNS activity [35-36].
2. Nitration at C5 enhanced the anticancer activity by a factor 4, while the addition of a methoxy group mildly increases the cytotoxicity [37].
3. Halogenation yielded most active compounds with 5-bromo, 5-iodo, 5-fluoro isatin being 5-10 times more active than the unsubstituted parent compound[38].

5. formation of Schiff base on reaction with aromatic amine leads to formation of compound with anticonvulsant activity.[39]
6. Little variation at position 2, 3 produce different degree of biological activity [39]
7. N-alkylation and acylation can be done on position 1[40]
8. If substituted phenyl ring is substituted at position 3, then it enhances antimicrobial activity.[40]
9. Bond acceptor at the position (3)
10. Free rotation bond O#H
11. Bond donor at position 1.
12. Polar surface area-37.38

The carbonyl group at position-2 is adjacent to the hetero atom and is stabilized by resonance, thus it behaves as typical amide in its properties. It readily undergoes aromatic substitution reaction at C- 5, N-alkylation via anions, and ketonic reaction at the C-3 carbonyl groups. If the 5th position is already occupied then electrophilic attack takes place at 7th position. Isatin and its derivatives can confort nucleophilic attack at positions C-2 and/or C-3. The chemo-selectivity of these reactions depends on the nature of nucleophile, substituent, solvent and temperature employed. Nucleophilic substitution at position C-2 in isatin, leads to the opening of the heterocyclic ring. This process may be followed by an intra-molecular or by an inter-molecular cyclization. The initial products obtained can relieve further reaction in the presence of a second nucleophilic group to give cyclization products [41]

5. Biological activity of Isatin

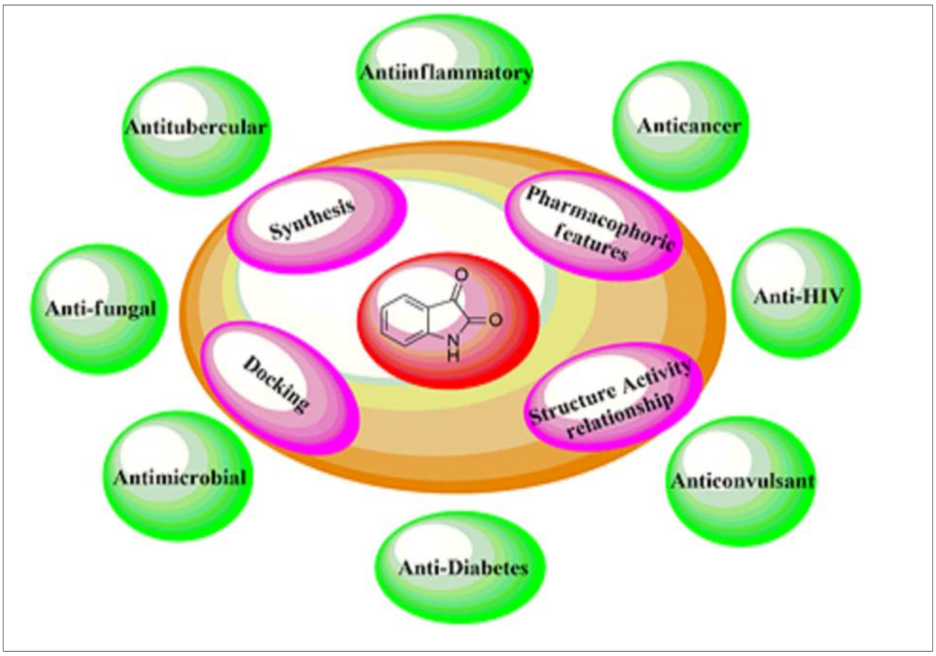


Figure-22

5.1. Antimicrobial Activity

Elmongy et al., (2022) reported new synthesis of Isatin–Quinoline Conjugates against Multidrug-Resistant Bacterial Pathogens along with their In Silico Screening activity. All synthesized conjugates were evaluated and displayed activity higher than the first line antibiotics ampicillin and chloramphnicol used in this study. In addition, the synthesized conjugates exhibited well to excellent bactericidal and anti-biofilm activity[42].

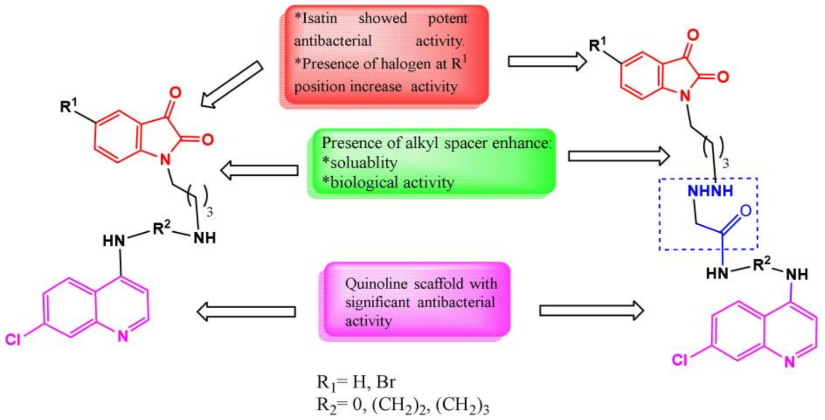


Figure-23

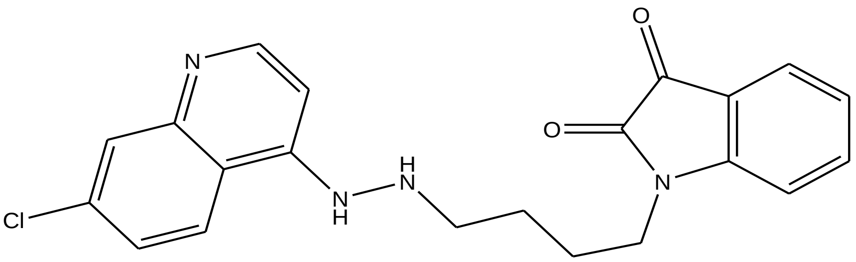


Figure-24

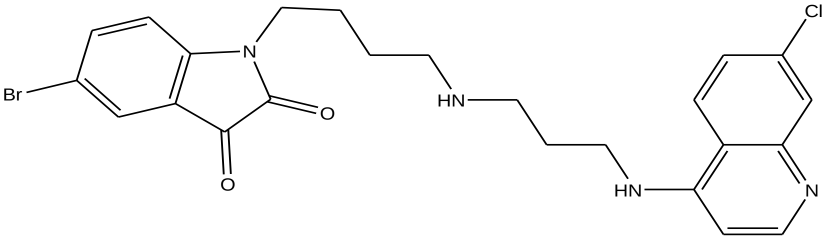


Figure-25

Bonvicini et al., (2022) A small library of 18 isatin hybrids was synthetized and evaluated for their antimicrobial potential on three reference strains: S. aureus, E. coli, both important human pathogens infamous for causing community- and hospital-acquired severe systemic infections; and C. albicans, responsible for devastating invasive infections, mainly in immunocompromised individuals. The study highlighted lead compounds,1-(4-chlorobenzyl)-3,3-bis(6-chloroimidazo[2,1-b]thiazol-5-yl)indolin-2-one **25,** endowed with inhibitory activity against S. aureus at very low concentrations (39.12 and 24.83g/mL, respectively).

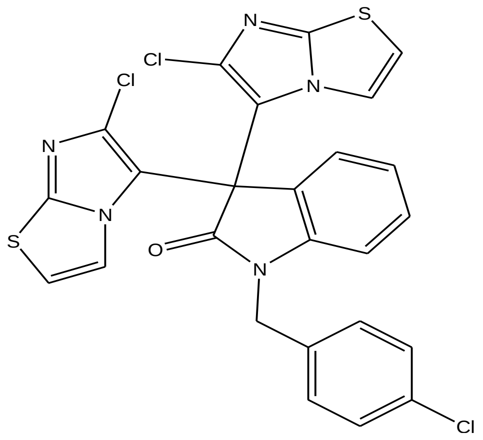


Figure-26

Trivedi et al., (2021) reported that a triazole moiety connects two isatin2,4-thiazolidinedione molecules that have ferrocene attached to them. All of the new compounds demonstrated significant and enhanced antibacterial activity against a variety of gram-positive and gram-negative infections [45].

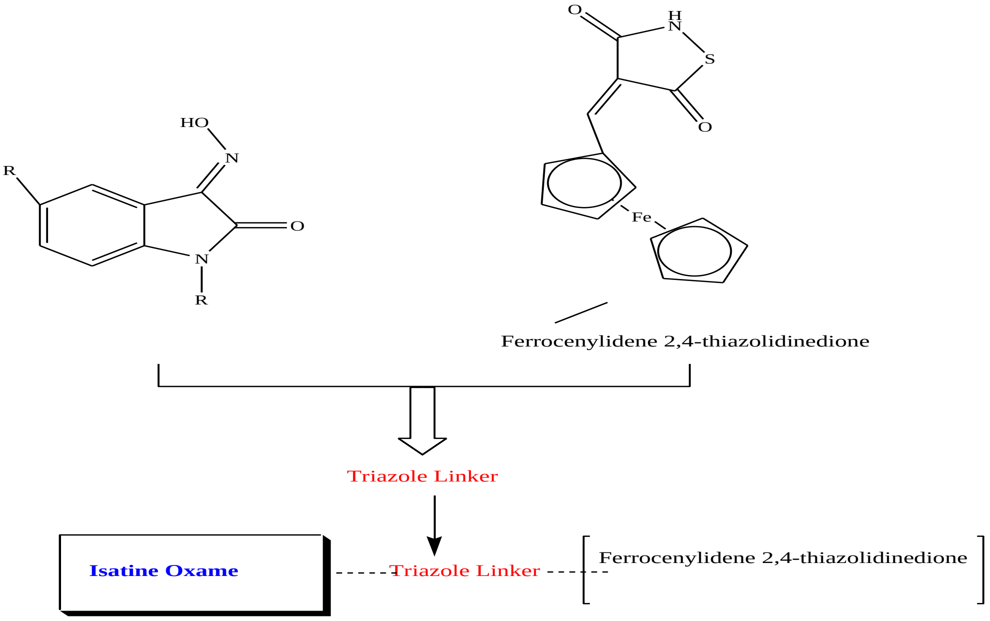
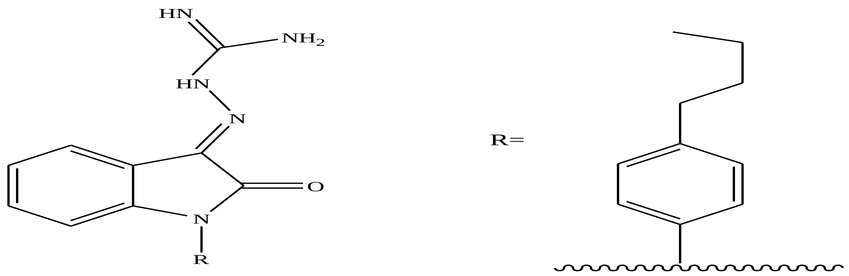
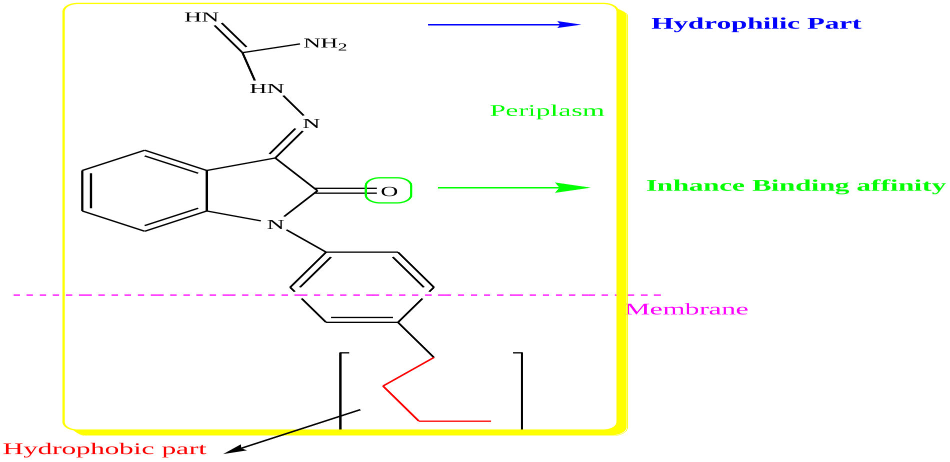


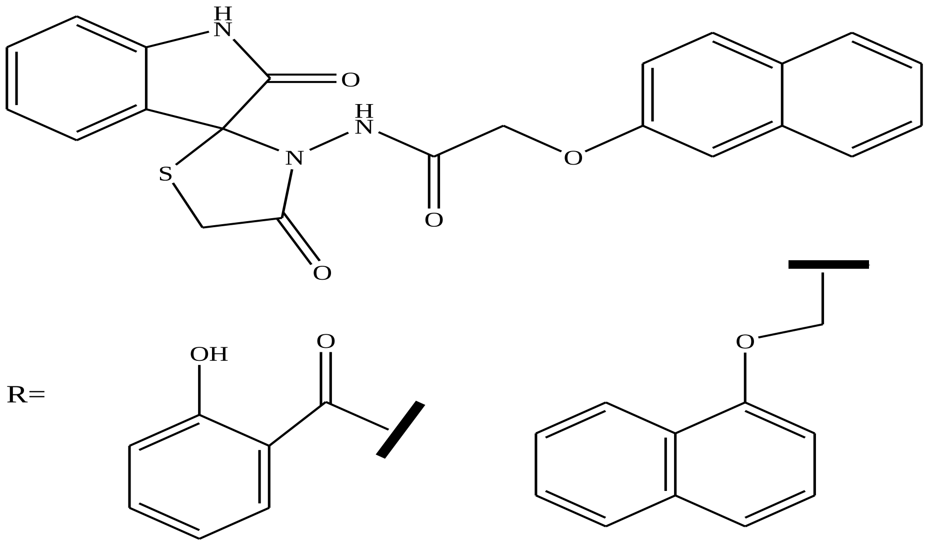
Figure-27

Wang et al., in (2020) reported a number of new antimicrobial medications were produced as a consequence of the addition of the natural chemical moenomycin A, which inhibits the peptido glycan transferase (PGT) enzyme. The most efficient molecule was (V), with MIC values of 6 g/mL for MSSA, MRSA, B. subtilis, and 12 g/mL for E. coli protein (PBP-1b). The chemical's hydrophilic component interacts with the enzyme's active site, while the hydrophobic component interacts with the enzyme's trans membrane portion in the cell wall [46].

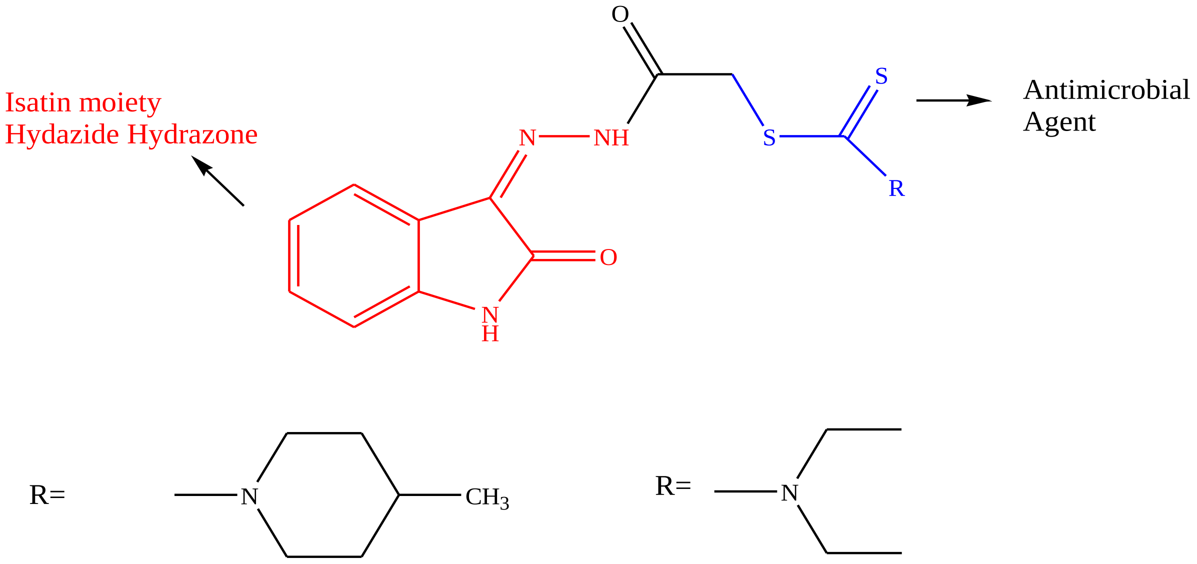




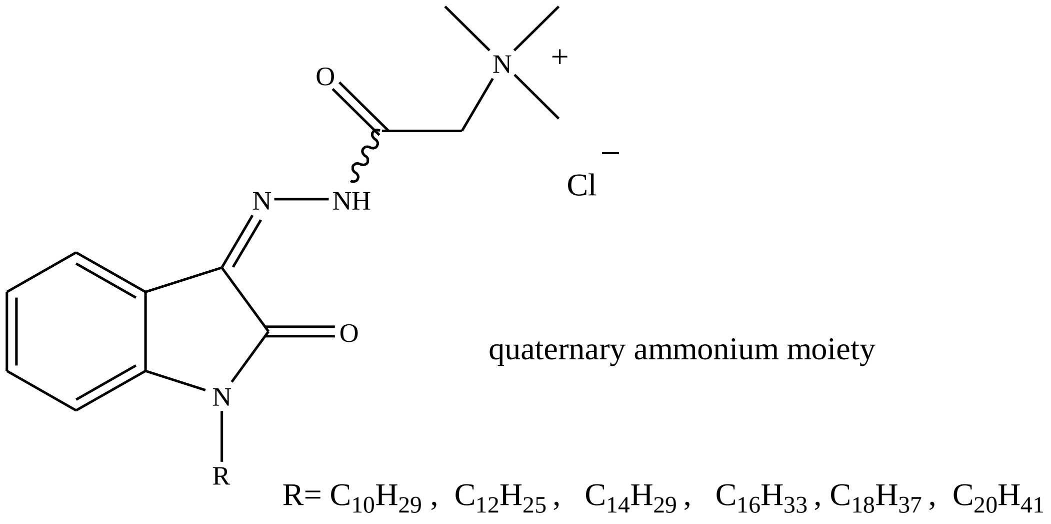
Bakht et al., (2020) also discuss about synthesis of isatin-thiazolidine hybrids which was carried out using a graphene oxide (GO) catalyst in deep eutectic solvent (DES) as a green medium. All generated compounds underwent in vitro testing for their antibacterial and cytotoxic characteristics. He found substances with greater antibacterial action against Gram-positive bacteria than Gram-negative bacteria. He also noticed that compounds with electron-withdrawing groups, such as bromo, fluoro, and nitro, had a better ability to inhibit bacteria than those with electron-donating substituents, such as methyl and hydroxyl groups[47]



Mangasuli et al., (2020) Synthesized named compounds, such as isatin-dithiocarbamate hybrids, have become serious contenders for use as antibacterial agents. He found that the majority of the compound exhibited high antibacterial activity against the bacterial strains A. flavus, T. harzianum, P. chrysogenum, and Candida albicans. The substance (3e) has displayed outstanding antifungal efficacy when compared to the widely used drug Fluconazole. Both traditional irradiation techniques and microwave irradiation were used to generate these compounds. The microwave method is cost-effective in addition to other advantages including mild reaction conditions, excellent product yields in a shorter reaction time, and a rapid workup procedure [48]

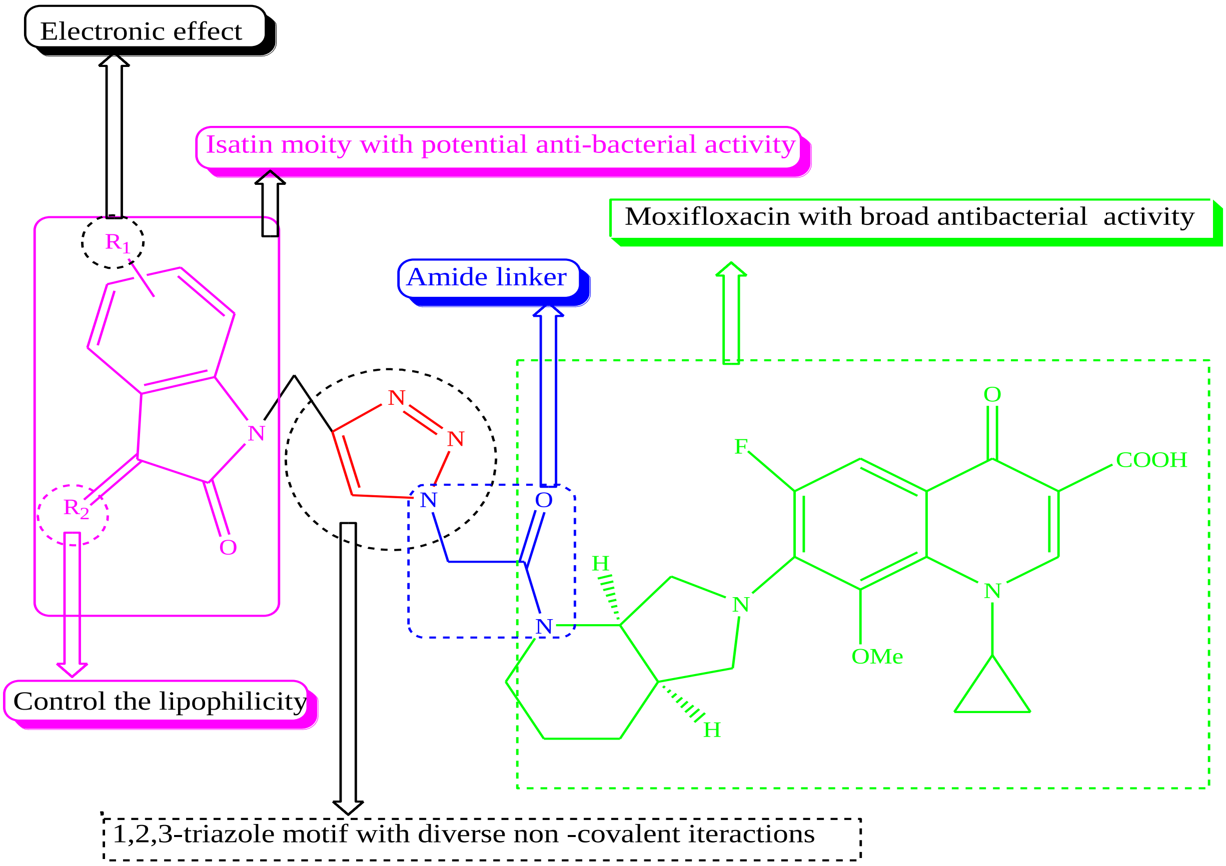


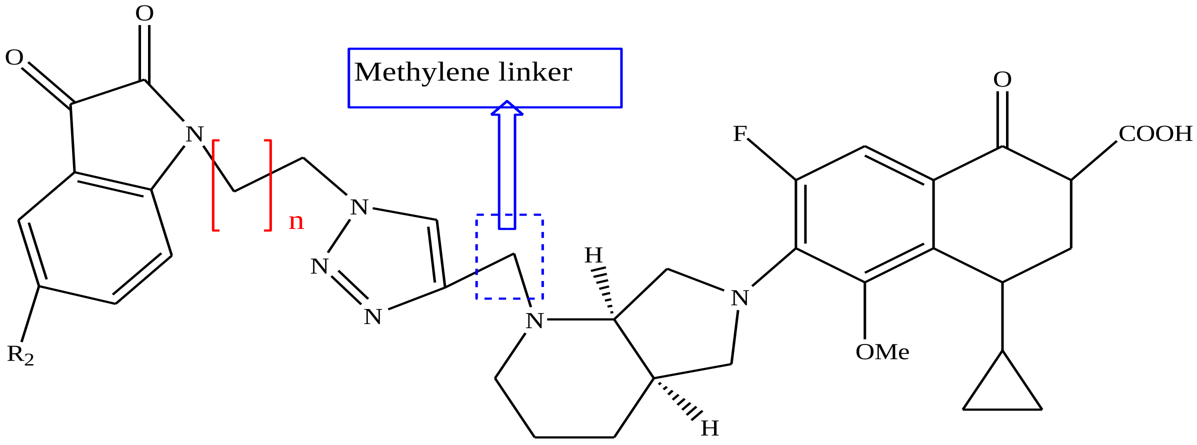
Pashirova et al., (2019) reported the synthesis of isatin-3-acylhydrazones with quaternary ammonium moiety of tunable hydrophobicity. -Amphiphiles' hydrophilic-lipophilic ratio and solvent polarity both have an impact on biological activity. Low hazardous ammonium salts shown specific antibacterial activity against Candida albicans 855-653 and Gram-positive bacteria (S. aureus 209p and B. cereus 8035). For newly created 1-dodecylisatin compounds with a quaternary ammonium component, and especially for drugs with the potential for stacking interactions, antimicrobial agents and drug solubilization may be advised [49]



Gao et al., (2019) The synthesis of novel moxifloxacin-amide-1,2,3-triazole-isatin hybrids has been completed. All generated compounds were tested for their in vitro antibacterial activity against Gram-positive and Gram-negative bacteria, as well as against illnesses with treatment resistance. All of the hybrids shown appreciable efficacy against the pathogens investigated, with MIC values ranging from 0.03 to 128 g/mL. Investigating the links between structure and cytotoxicity and structure was also shown to

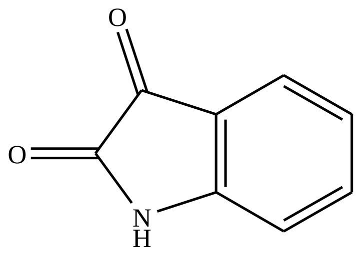
1. R1 position substitutes significantly affected activity.
2. Methyl that donated electrons outperformed fluoro that received electrons.
3. The phenyl ring's substituents had a comparable impact on the antibacterial activity.
4. When compared to their C-7 counterparts, substituted analogues at the C-5 position were more potent.
5. While ethyloxime was discovered to be harmful to activity generally, the addition of methyloxime (R2) to the C-3 position of the isatin moiety may increase activity to some extent.[50]





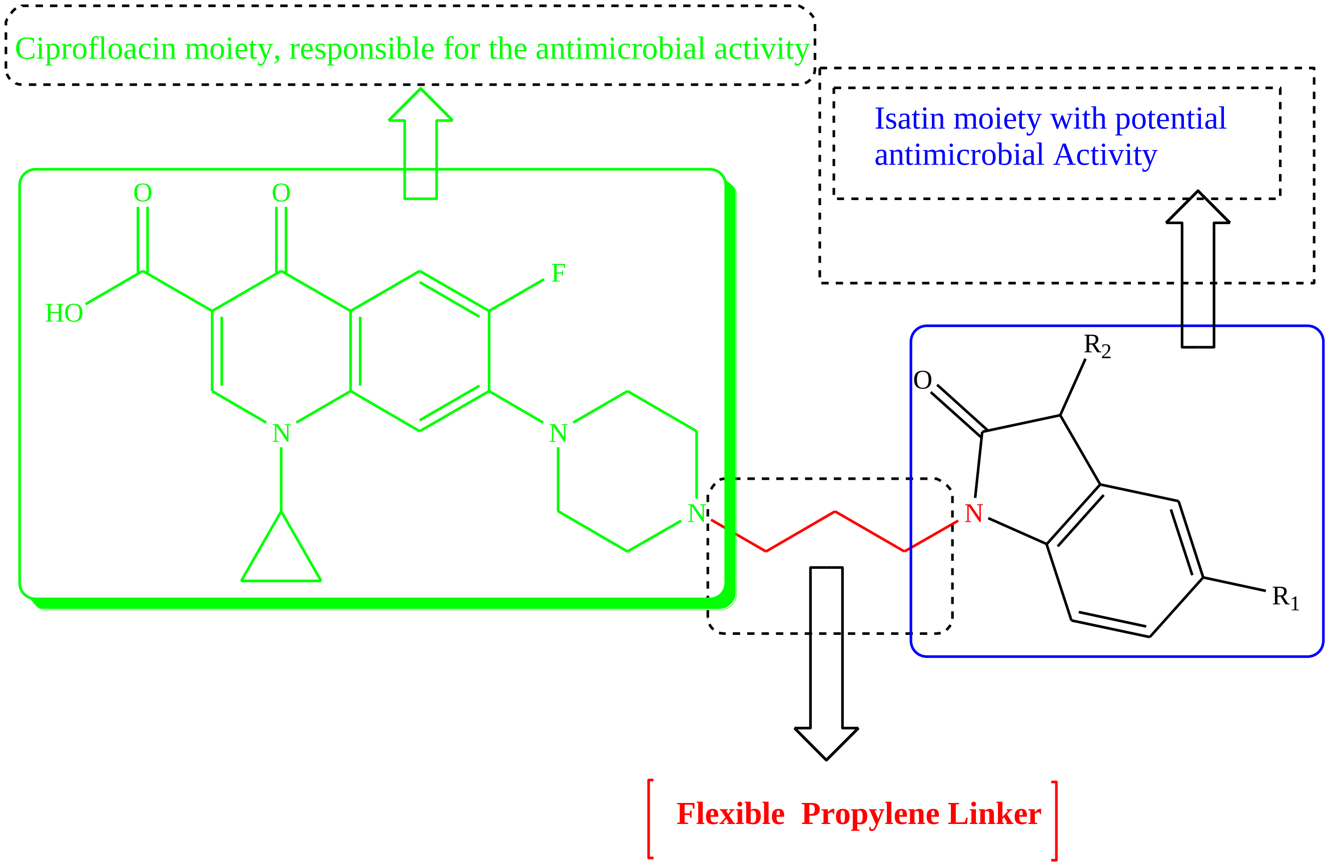
R1= H, 5-F, 5-Me,7-F
R2= O, NOMe, NOEt

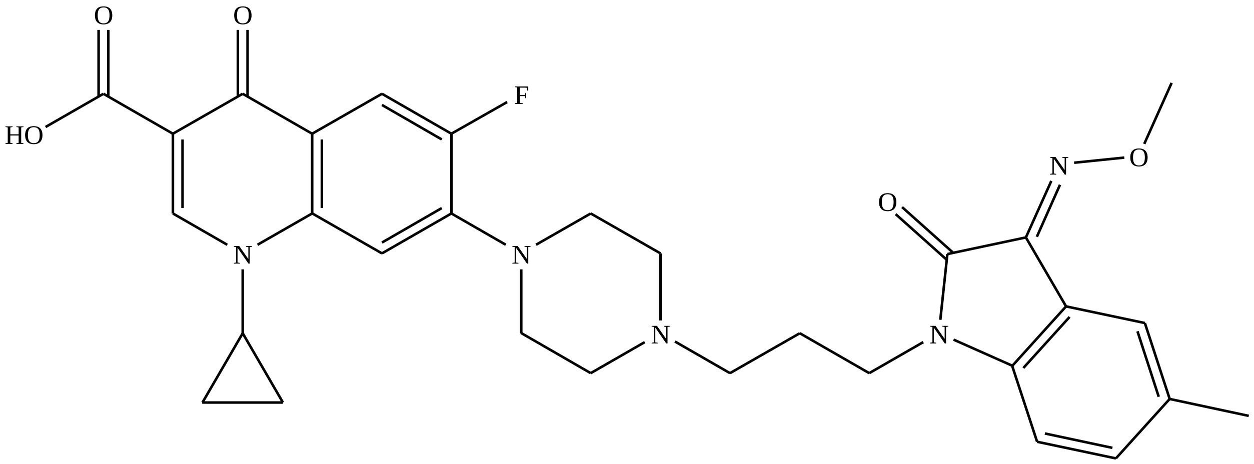
Ganim et al., (2018) reported the synthesis of isatin and thiosemicarbazone derivatives, which were then examined for their ability to attach to DNA, including DNA protection assays using plasmid DNA (pUC19) and DNA interaction tests using calf thymus DNA (CT-DNA). Additionally, they conducted an in vitro experiment to evaluate the antibacterial abilities of several hazardous bacterial species. All isatin and thiosemicarbazone derivative compounds exhibited DNA protection activities ranging from 23.5 to 59.5 percent. I3-(N-2-MP)-TSC had the strongest DNA-protective action of the group. Isatin thiosemicarbazone derivatives had significant and focused antibacterial activity at low doses. These substances largely worked against Gram-positive bacteria, but not P. vulgaris or E. coli. The Gram-positive MRSA strain of S. aureus ATCC 43300 was most affected by these compounds [51]



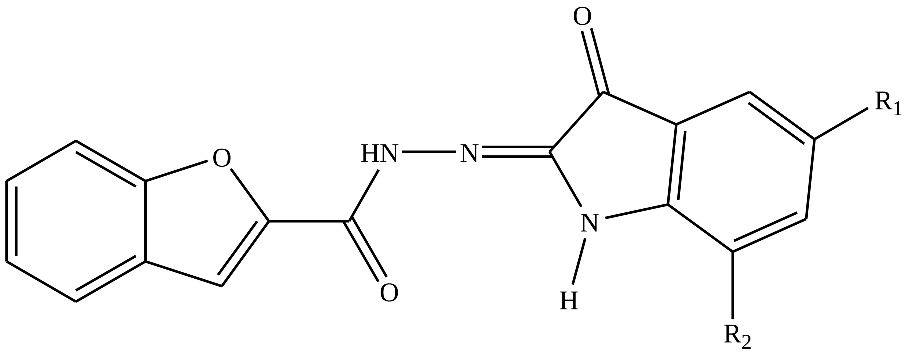
Isatin

Wang et al., (2018) reported twelve ciprofloxacin-isatin hybrids with propylene tethers were synthesised in an original manner, and all of the hybrids underwent in vitro testing for antibacterial activity against illnesses caused by Gram-positive, Gram-negative, and mycobacterial bacteria. He found that all mono-isatin-ciprofloxacin hybrids exhibited excellent antibacterial activity against the majority of the pathogens tested, with MICs ranging from 0.03 to 0.5 mg/mL. The ciprofloxacin-isatin hybrid (3d) was as effective as or more effective than the parent ciprofloxacin and the standard of care levofloxacin against all Gram-positive and Gram-negative bacteria tested, including clinically important drug-resistant infections.[52]



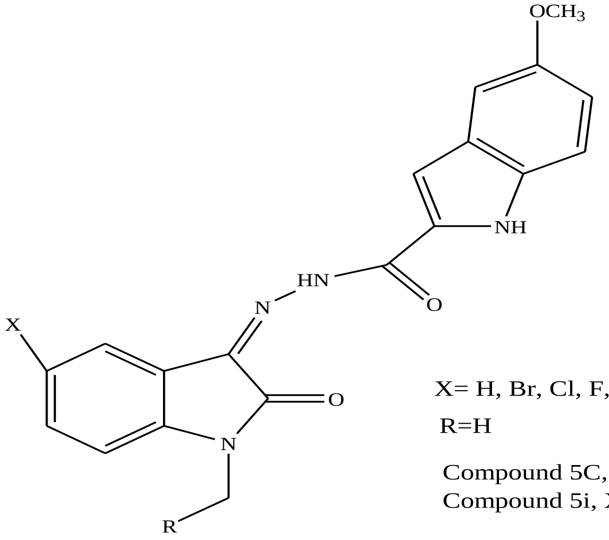


Ugale et al., (2017) reported that N-(5 or 7 substituted-2-oxoindolin-3-ylidene)benzofuran-2-carbohydrazides existed. Testing all of the generated compounds for antibacterial activity revealed that 3o was efficient against Escherichia coli and Pseudomonas vulgaris while 3p was effective against Bacillus subtilis, E. coli, and Pseudomonas vulgaris. Additionally, it was shown that 3o and 3p have antifungal action against Aspergillus niger.[53]



3O = R_1=H, R_2=NO_2 3P = R_1=H, R_2=F

Almutairi et al., (2017) synthesized new indole-isatin molecular hybrids as new antimicrobial agents against a panel of Gram positive bacteria, Gram negative bacteria, and moulds. In this compound **5c** emerged as the most active congener towards Ps. aeruginosa with MIC value of 3.9 µg mL-1. Whereas, compound **5i** is the most active congener against A. niger



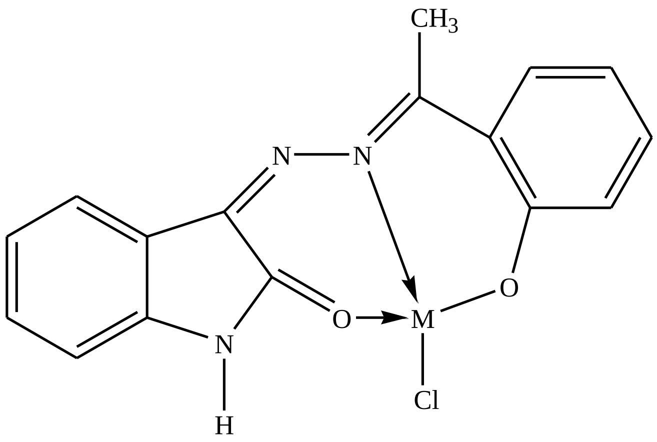
X= H, Br, Cl, F, OCH_3
R=H

Compound 5C, X= Cl and X=H
Compound 5i, X=F and X= 4F-C_6H_4

5C, N'-[(3Z)-5 Chloro-1-methyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene]-5-methoxy-1Hindole-2-carbohydrazide

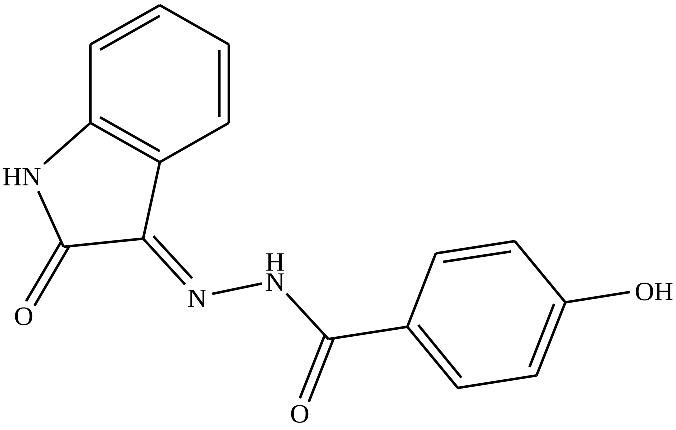
M.S. Almutairi, A.S. Zakaria, P.P. Ignasius, R.I. Al-Wabli, I.H. Joe, M.I. Attia, Synthesis, spectroscopic investigations, DFT studies, molecular docking and antimicrobial potential of certain new indole-isatin molecular hybrids: Experimental and theoretical approaches, Journal ofMolecular Structure (2017), doi: 10.1016/j.molstruc.2017.10.025.

Swathy et al (2016). Reported Manganese(II), cobalt(II), nickel(II), copper(II), and zinc are metals with which isatin complexes may be made, according to a description of the process (II). All the complexes exhibit a higher activity against E. coli than S. typhi and S. aureus. [CuLCl] > [NiLCl] > [MnL2] > [ZnLCl] > [CoL2] > L. Antibacterial activity hierarchy [CuLCl] follows [NiLCl] and [MnL2] follows [ZnLCl] and [CoL2] L. A chemical's antifungal activity increases by a factor of five when it is combined with metal. Ni(II), Co(II), Mn(II), Zn(II), and L come after Cu(II). Following is a list of the ligands and complexes in order of their activity: Ni(II), Co(II), Mn(II), Zn(II), and L come after Cu(II). According to the comparison of activities, the copper complex is more effective than the ligand against R. stolonifer.[54]



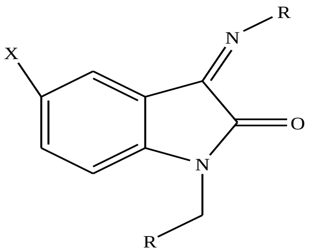
M= Ni (II) & Cu (II)

Konstantinovic et al., (2015) Described isatin-3-(4-hydroxy) benzoylhydrazone's synthesis. He found that the C-3 position in isatin is particularly susceptible to attack by nucleophiles, whereas C-2 only reacts with nucleophiles under specific circumstances because of the adverse inductive effect of the amido group. Staphylococcus aureus, Serratia marcescens, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, and Candida albicans were tested for antimicrobial activity against all compounds produced [55-60].



isatin-3-(4`-hydroxy)benzoylhydrazone

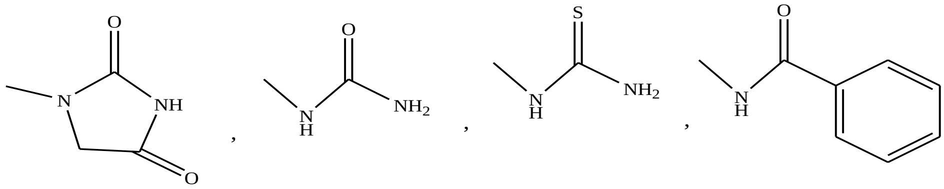
Tehrani et al., (2015) synthesized 5-substituted isatins with bioactive amines/hydrazides and evaluated using a microtiter plate method on a series of gram positive and gram negative bacterial strains for antimicrobial activity of the synthesized derivatives. The bacterial strains included P. aeruginosa (ATCC 27853), E. coli (ATCC 25922), E. faecalis (ATCC 29212), S. aureus (ATCC 25923) and Methicillin resistant Staphylococcus aureus (MRSA, ATCC 43300)[45].



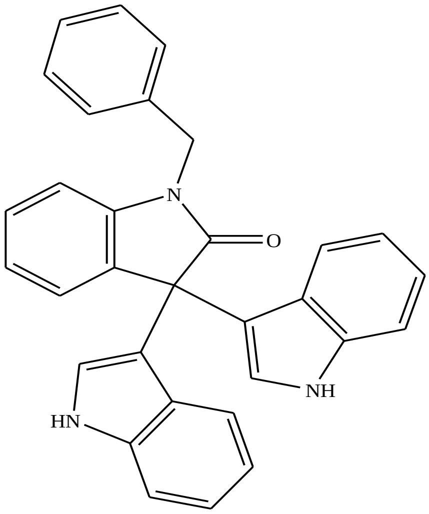
X= H, F, Cl, F, Me

Compound 2d, X= Me
Compound 3b, X=F
Compound 5c, X=Cl

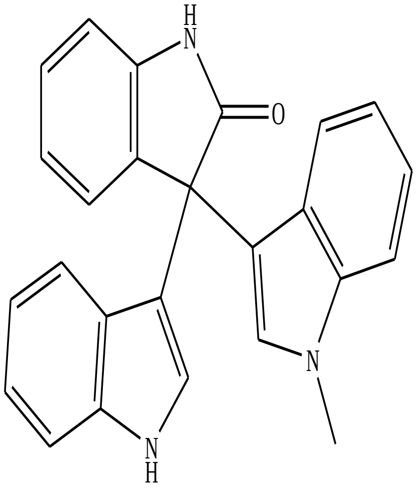
R=



Ziarani et al., (2015) synthesized novel class of symmetrical 3,3-di(indolyl)indolin-2-ones with excellent yields by green and effective solid acid catalyst in reaction of isatin with indoles under mild reaction conditions. The antimicrobial activities of synthesized compounds have been tested. Antimicrobial tests showed that the MIC value of compound **3e** against B. subtilis was equal to that of Chloramphenicol[61].

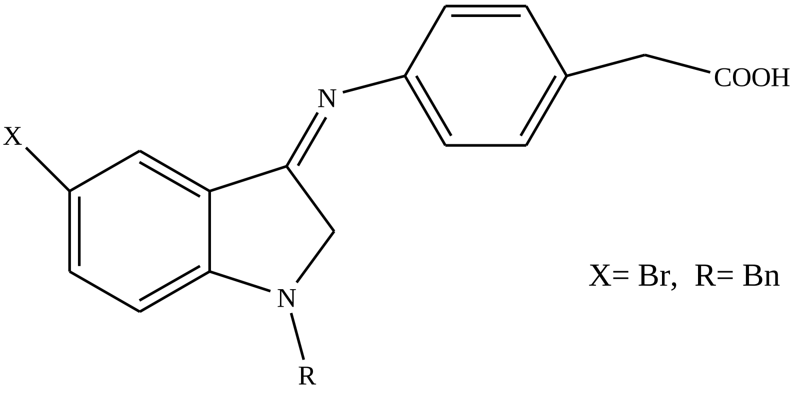


Compound 3 e, 3,3-Di(1H-indol-3-yl)-1-benzyl-indolin-2-one



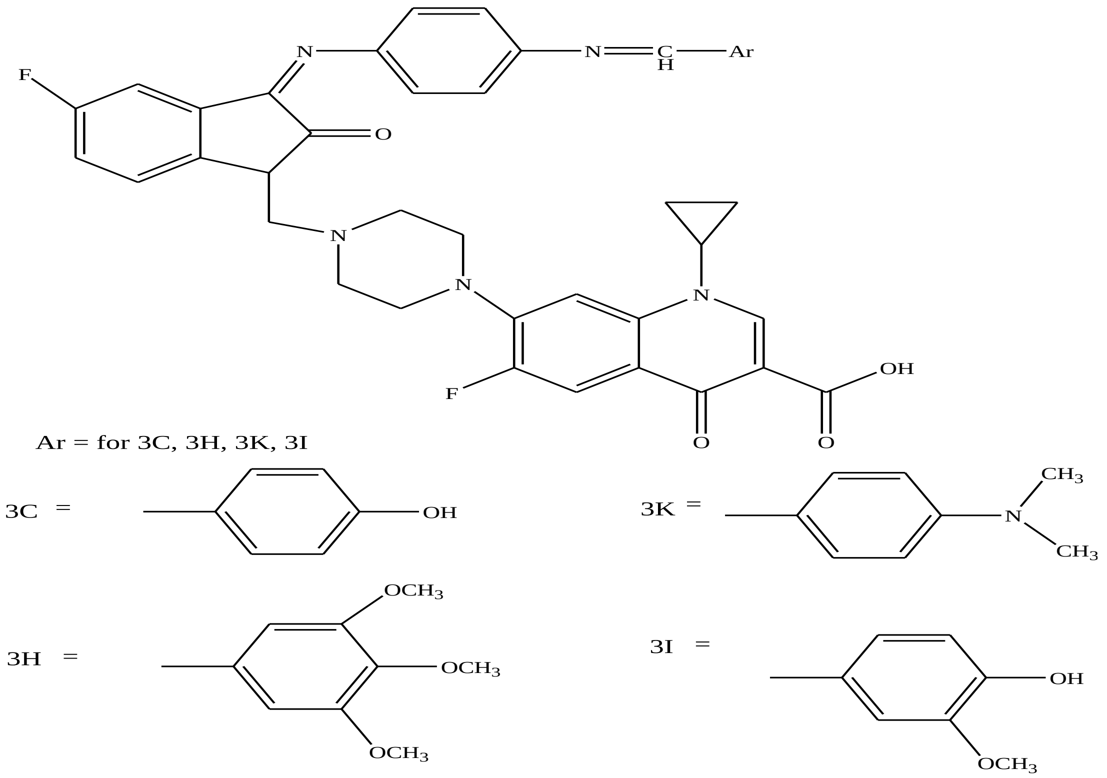
3-(1H-Indol-3-yl)-3-(1-methyl-1H-indol-3-yl)indolin-2-one

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 imino isatin 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.

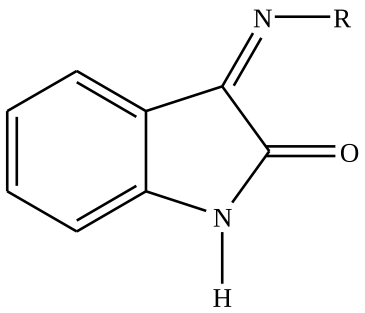


X= Br, R= Bn

Prakash et al., (2013) A number of new Schiff and mannich bases of the isatin derivative (I) were created by replacing different aromatic aldehydes at the third position and joining ciprofloxacin at the N1 position with formalin. Compounds 3c, 3k, 3h, and 3i shown remarkable antibacterial properties against all microbes with the exception of B. cereus ATCC 11778. seven bacteria (four gram-positive and three gram-negative) and two fungus strains were tested for in vitro antibacterial activity. It has been demonstrated that electron donating group substituted derivatives have stronger antibacterial properties than electron withdrawing substances[63].

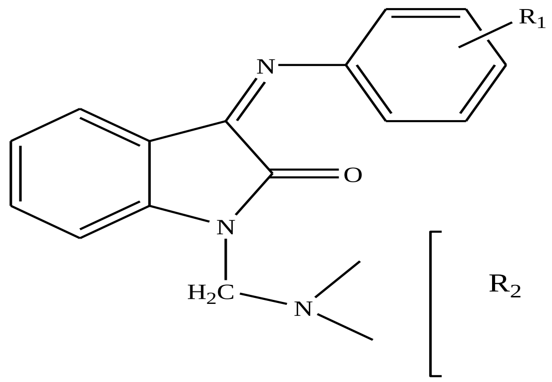


Pandey et al., (2013) Isatin derivatives was synthesized using microwave heating method. Schiff base of Isatin were synthesized by condensation of the keto group of Isatin with different aromatic primary amines. Antibacterial Study. The synthesized compounds were screened in-vitro for their antibacterial activities against Staphylococcus aureus (MTCC-87), Escherichia coli (MTCC- 40), Staphylococcus epidermidis (MTCC-2639), Pseudomonas aeruginosa (MTCC-424), and Proteus vulgaris (MTCC 426) using cup plate method[62].



2a phenyl
2b 2-nitrophenyl
2c 3-nitrophenyl
2d 4-nitrophenyl
2e 3-chlorophenyl
2f 4-chlorophenyl
2g 4-bromophenyl
2h 4-fluorophenyl
2i 3-Cl-4-F-phenyl
2j 2,6-dichlorophenyl

1. **Chaluvaraju et al., (2011)** discussed a series of isatin derivatives by using Schiff's and Mannich reactions. Investigation of antimicrobial properties was done against S.aureus, B.subtilis, S.typhi E.coli, A.niger and C.albicans by cup-plate method using amoxacillin and fluconazole as standard drugs. All the tested compounds shown moderate activity.



R_1= p - Br, Cl,o- NO_2, 4-OCH_3 p- OCH_3

Chaluvaraju K C, Zaranappa. Synthesis and Biological Evaluation of some Isatin derivatives for Antimicrobial Properties, Research Journal of Pharmaceutical, Biological and Chemical Sciences (2011) 2 1. 541- 46.

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6. Conclusion

Structural changes in the basic structure of isatin, allowed the emergence of new derivatives with a broad spectrum of biological activity. Thus, the most important structural changes concern the substituents at positions 1, 3 and of the bicyclic system. Bibliographical studies have shown that the structural change on the different positions of the base molecule improves its pharmacological profile conferring sedative, anticonvulsant, anxiolytic, anti-microbial, anti-HIV and anti-cancer and inhibitor of corrosion.

Given the biological activities associated with these molecules, the goal of our work is devoted to the synthesis and reactivity of new compounds derived from isatin, and the study of their biological activities, as well as industrial uses. We must always continue to search for drugs which exhibit clear advantages over the already existing respective drugs. Such advantages may be:(1) A qualitative or quantitative improvement in activity, (2) a partial or total absence of undesirable side effects, (3) a lower toxicity, (4) more neutritive value, (5) improved stability and (6) a decrease in production cost. Heterocycles are considered “versatile” due to their properties of possessing specific chemical reactivity and therefore have always attracted the attention of scientists working in both the area of natural products and synthetic organic chemistry.

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