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EXPLORING THE ANTIMICROBIAL POTENTIAL OF ISATIN AND DERIVATIVES: A COMPREHENSIVE REVIEW

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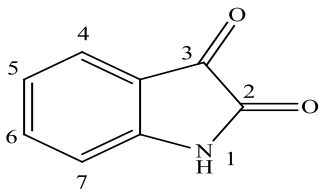
ABSTRACT

Isatin (*1H*-Indole-2, 3-dione) is a small nitrogen containing heterocyclic chemical moiety. It possesses an indole scaffold substituted with carbonyl groups at 2nd and 3rd position. It is also known as oxindole. Isatin nucleus can be modified in several ways to serve as a precursor for a large number of pharmacologically active compounds. It is a compound of significant importance in medicinal chemistry. Upon exploration of literature, it is found that several of isatin derivatives have promising pharmacological activity *viz.* antimycobacterial, anti-inflammatory, herpes simplex virus inhibitor, antiviral, antimicrobial, anticancer and anticonvulsant activities. In recent years it have attracted a great attention not only as drug candidate but also as insecticides, fungicide etc. The purpose of this review is to provide an overview of synthetic method and a detailed antimicrobial profile of isatin and analogs.

KEYWORDS: Isatin; Indole-2, 3-dione; Antimicrobial; Antibacterial; Antifungal.

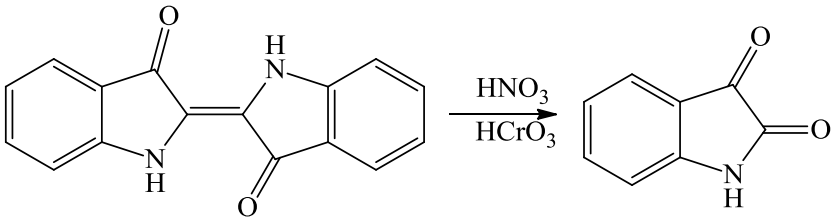
INTRODUCTION

Isatin (1H-Indole-2, 3-dione) is a small nitrogen containing heterocyclic chemical moiety. It possesses an indole scaffold substituted with carbonyl groups at 2nd and 3rd position. Isatin is yellow to red needle crystalline substance, which melt at 200 °C (392 °F; 473 K). It has variable solubility in different solvents. It is soluble in methanol, hot ethanol, ethyl ether, hot water, benzene and acetone, dissolve in alkali metal hydroxide.[1]



Isatin

In 1841, Erdman and Laurent obtained isatin as an oxidation product of indigo by nitric and chromic acid. It is also known as oxindole. It is an endogenous compound reported to be present in many organisms.[2]



Indigo Isatin

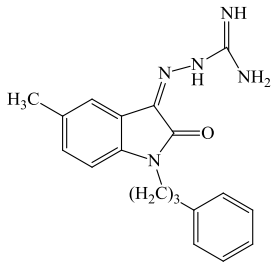
Initially isatin was supposed to be synthetic till its presence was not reported in nature. In plants isatin is reported in the genus isatis, *Calanthe (Calanthe discolor Lindl.)* and *Couroupita (Couroupita guianensis Aubl).* Substituted isatin is also found in plant *Melochia tomentosa* (alkaloids- methoxyphenylpentylisatins), fungi *Streptomyces albus* [6-(3'-methylbuten- 2'-yl) isatin] and *Chaetomium globosum* [5- (3'-methylbuten-2'-yl) isatin] and some marine mollusks. In animal the presence is reported in Bufo frog (secretions from parotid gland) while in human it is a metabolic derivative of adrenaline.[3] Isatin has also been found to be a component of coal tar.

Antimicrobial Potential of Isatin Derivatives

Isatin is a versatile chemical moiety which possesses different activity. Several of its derivatives have been reported to elicit promising pharmacological activity *viz.* antimycobacterial,[4] anti-inflammatory,[5] herpes simplex virus inhibitor,[6] antiviral,[7] antimicrobial,[8,9] anticancer,[10] anticonvulsant,[11,12] etc. In this review article a comprehensive study on antimicrobial potential of isatin and its analogues have been reported.

Analogues of isatin bearing three different substituent groups at the N-1, C-3 and C-5 positions of the isatin scaffold were synthesized to study their SAR, inhibition of bacterial

peptidoglycan glycosyltransferase (PGT) activity and antimicrobial susceptibility against *S. aureus*, *E. coli* and methicillin-resistant *Staphylococcus aureus* (MRSA (BAA41)) strains. Two compounds 1 and 2 show good antimicrobial potency (MIC = 3 μg mL^{-1} against *S. aureus* and MRSA; 12–24 μg mL^{-1} against *E. coli*.[13]



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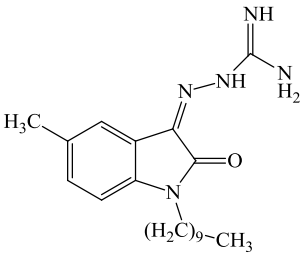

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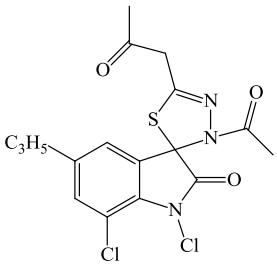

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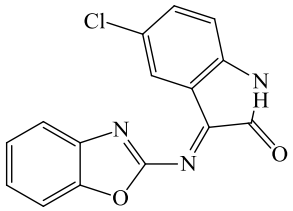

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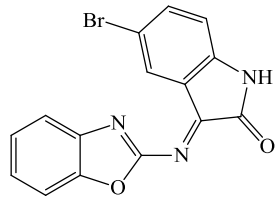
Costaa et al., showed that *spiro* 1, 3, 4-thiadiazolines from isatin-β-thiosemicarbazone acetylation have antimicrobial activity. Compound *spiro* thiadiazolines derived from allylated isatins (compound 3) have significant activity.[14] The antimicrobial study of novel benzoxazole-isatin conjugates prepared by treating 2-amino benzoxazole with 5 and 7 substituted isatin derivatives showed that among all the compounds, 4 and 5 showed good antimicrobial activity.[15[Using *in silico* structure based approach a new series of isatin Schiff base derivatives bearing imine linkage were screened for antimicrobial activity against *B. cerus*, *S. aureus*, *E. coli*, *P. aeruginosa* and antifungal activity against *A. flavus*, *F. oxysporum*, *A. niger*, *A. brassicae* were performed. The compounds 6 and 7 displayed excellent antibacterial activity compared to chloramphenicol and ciprofloxacin.[16]



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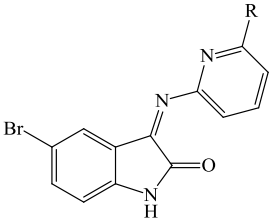
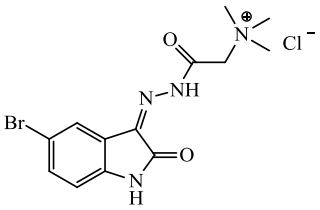


6 (R=-F), 7 (R=-OH)



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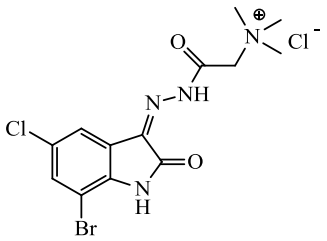

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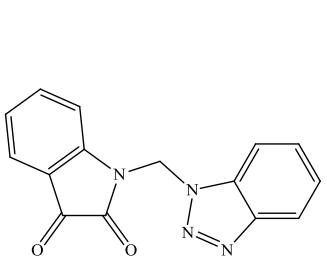
To explore antimicrobial potential Bogdanov et al., synthesised isatin-based quaternary ammonium compounds (QACs) bearing pyridinium or trimethylammonium moiety. Among twelve hydrazones of series I, two compounds 8 and 9 showed 2–5 times better activities than drug chloramphenicol while no compounds of series II exhibited any antimicrobial activity.[17] In another study, Bogdanov et al., synthesied isatins-benzotriazole hybrids.

Compound 10, 1-[(1*H*-benzo[*d*] [1, 2, 3]-triazol-1-yl) methyl] indoline-2, 3-dione (bactericidal activity in a concentration of 31.3 mg/L) was most active against *Staphylococcus aureus*, while isatins 1, 2 and acylhydrazone did not exhibit antimicrobial properties.[18] Isatin and thiosemicarbazone derivatives prepared by Ganim et al., exhibited significant antibacterial activity against Gram-positive methicillin-resistant *S. aureus* ATCC 43300(MRSA).[19]



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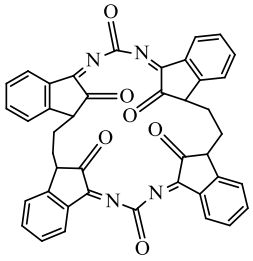

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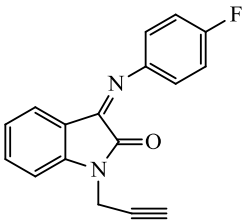

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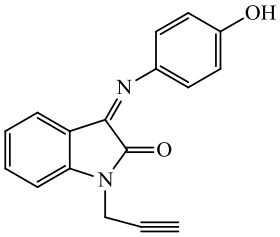

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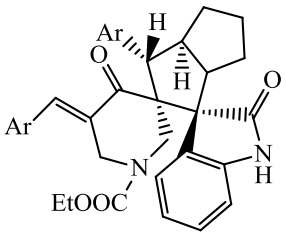
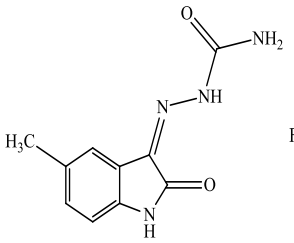
The *in vitro* and *in silico* antibacterial studies carried out by, Dileepan et al., showed that Isatin based macrocyclic schiff base, compounds 11 have the potential to inhibit the growth of both Gram-positive and Gram-negative bacteria.[20] Singh et al., designed a library of acetylinic isatin hydrazones and acetylinic *spiro*-isatins. Acetylinic isatin 12 was the most potent antibacterial scaffold with IC_{50}= 1.95 mM against *E. coli* while 13 with *bis*-isatin assembly was the active compound against *C. albicans* with IC_{50} 15.67 Mm.[21] Hassaneen and coworker synthesized new derivatives of spirooxindole-spiropiperidinone-pyrrolidines and spirooxindole-spiro piperidinone-pyrrolizines through the condensation of isatin, sarcosine, and L-proline. Compounds 14, 15, 16 exhibited the highest potency against tested organisms from the series as antibacterial and antifungal agents.[22]



14 (Ar= 4-NO_2-C_6H_4), 15 (Ar= 4-OCH_3-C_6H_4) 16 (Ar= 2, 4-F_2-C_6H_3)

A number of Schiff bases were formed by Tehrani and coworker by the reaction of isatin and bioactive amine/hydrazide. Study showed that compounds 17, 18, 19, and 20 were most

active against *Pseudomonas aeruginosa* (MIC = 6.25 mg/mL). Further, SAR study shows that (thio) urea-based Schiff bases have broader spectrum of antibacterial activity.[23]



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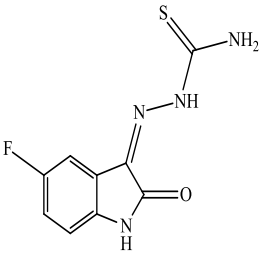

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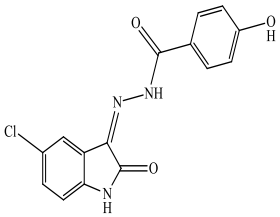

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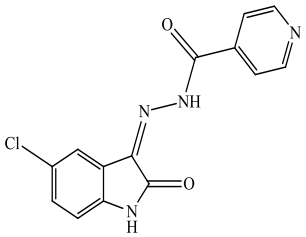

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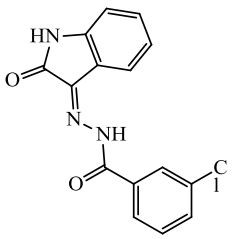
Lian et al., synthesized seven isatin derivatives. Screening of compounds against bacterial strains revealed that compounds 21 and 22 had better antimicrobial profile, with IC_{50} values of between 0.03 and 0.05 mmol/mL against *Staphylococcus aureus*, respectively.[24] In an another stidy, Synthesized 3-hydrazino, 3-thiosemicarbazino, and 3-imino carboxylic acid derivatives of isatin yielded Compound 23 i.e. (2-[4-(1-benzyl-5-bromo-2-oxoindolin-3-ylideneamino) phenyl] acetic acid, which comes out to be active against all tested Gram-positive bacteria and fungal strains.[25]



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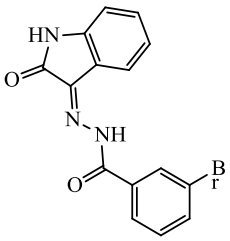

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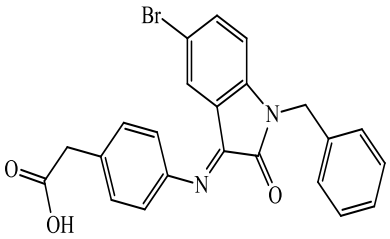
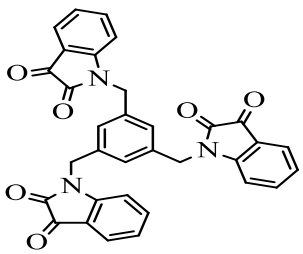


23

D Souza and Chattree prepared two isatin derivatives by *N*-Alkylation method. The synthesized derivatives were confirmed by IR, UV, Mass and ^{1}HNMR and ^{13}C NMR. The compounds were screened for antimicrobial and antioxidant activity. Compound 24 shows good antibacterial and antifungal activity with very little antioxidant property.[26]



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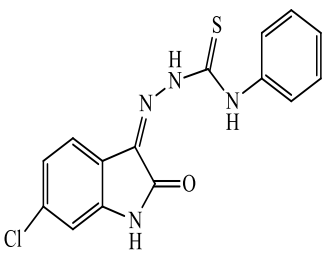

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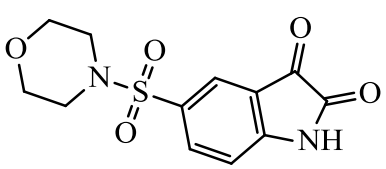

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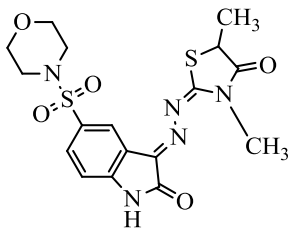
Zhang et al., synthesized isatin β- thiosemicarbazones derivative. Further compounds were tested against two resistant strain *S. aureus* (MRSA) and Enterococcus (VRE). Compound 25 displayed the potent biological activity, the MICs of which were 0.78 mg/L, 1.56 mg/L and 0.78 mg/L for MRSA, *S. aureus* and *B. subtilis*, respectively. The other nine compounds also showed good antimicrobial activities with MICs ranging from 1.56 mg/L to 25 mg/L for the tested MRSA and *Staphylococcus* strains.[8] Farag carried out the synthesis of novel 5-(Morpholinosulfonyl) isatin clubbed with thiazole moiety by two synthetic routes. Evaluation of antimicrobial activity showed that compound 26, 27 and 28 have broad spectrum of activity.[9] To find out the better antimicrobial agent, Majik et al., prepared isatin and its synthetic analogues against ecologically relevant marine microorganisms. Result reveals that although all isatin derivatives possess stronger activity compared with the parent marine natural product (isatin) against *Planococcus donghaensis, Erythrobacter litoralis, Alivibriosalmonicida, Vibrio furnisii*. The 3-acetonylidene oxindole, compound 29 was identified as the most potent with maximum antibacterial properties against fouling bacteria.[27]



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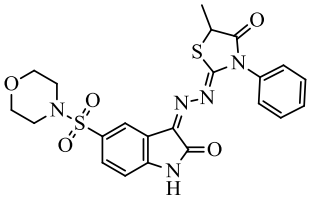

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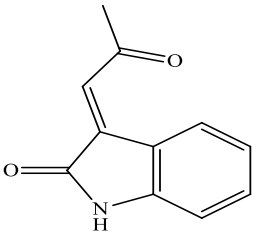

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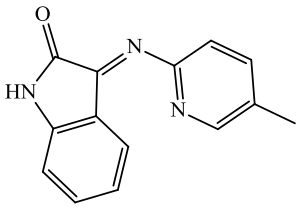
Reaction of isatin and primary amine performed by Sekularac and coworker resulted in the formation of isatin schiff bases. Screening of compounds against nine bacterial strains and one yeast strain was done. Many compounds showed activity against bacteria *S. sonei*, *Y. enterocolitica* and *P. hauseri* (Gram-negative). Compounds 30 and 31showed significant activity against Gram-negative strains compared to Gram-positive strains.[28] Using SBA-Pr-SO_3H as a green and effective solid acid catalyst Ziarani and coworker prepared 3, 3-di-(indolyl)-indolin-2-one analogue The reaction of isatin with indoles under mild reaction conditions yielded a novel class of 3, 3-di (indolyl)-indolin-2-ones in good yields. The MIC value of compound 32 against *B. subtilis* showed that the antimicrobial activity was equal to that of Chloramphenicol.[29]



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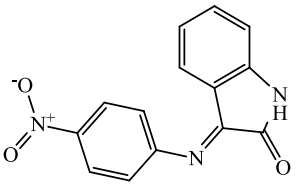

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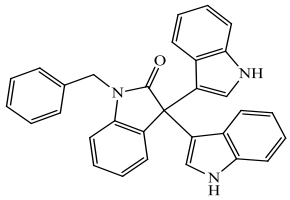

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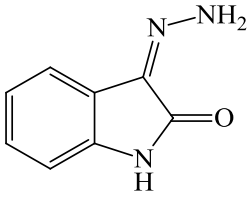

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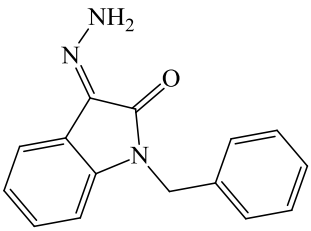
El-Faham et al., prepared silver nanoparticles (AgNPs) hydrazino-isatin derivatives using 3-hydrazino-isatin derivatives (3-hydrazino-isatin [IsH] and 1-benzyl-3-hydrazino-isatin [BIsH]) in an aqueous methanol. The compound (AgNPs) 33, as well as (BIsH) 34, showed high activity against the Gram-positive *Bacillus subtilis* and Gram-negative *Micrococcus luteus* and *Proteus vulgaris*, and antifungal against *Saccharomyces cerevisiae*.[30] Baharfar et al., synthesized novel 5-isatinylidenerhodanine-based furan derivatives *via* a multi-component reaction. The titled analogues were evaluated for antimicrobial activity against *S. aureus* and *B. subtilis* (Gram-positive) and *E. coli* and *P. aeruginosa* (Gram-negative). The results indicated that the compound 35 have high activity against *E. coli*.[31] Reaction of 2, 4-Dioxo-4-phenylbutanal and primary amine yielded four imine derivatives which subsequently converted to thiazolidinon-4-one derivative. These derivatives were further reacted with vanillin and isatin to give eight title compounds. Screening of compound for antimicrobial activity showed that compound 36 ($X=NO_2$), 37 (X=OH), 38 ($X=OCH_3$) and 39 [X= N-$(CH)_3$] have significant activity. This study was conducted by Ayalew and coworker.[32]



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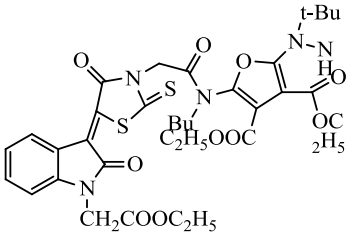

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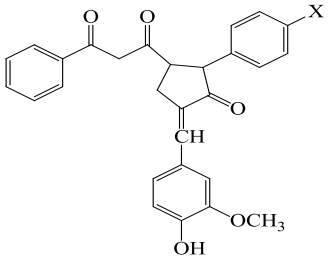
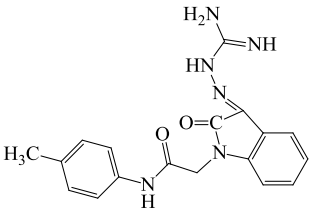


36 ($X=NO_2$), 37 (X=OH),
38 ($X=OCH_3$), 39 [X= N-$(CH)_3$

Wang et al., synthesized compound 40 and screened it for antimicrobial activity. The synthesized compound showed promising antimicrobial activities against *B. subtilis* (24 µg/mL), *S. aureus* (48µg/mL) and *E. coli* (96µg/mL). With favorable drug-like properties and small molecular weight, compound 40 comes out to be a potential candidate for further development as potent GT inhibitors.[33]The synthesis and screening of new *bis* isatin

carbohydrazone derivative for antimicrobial and antioxidant activity was done by Kirana and coworker. The result of study demonstrated that the compounds 41 (R=H) and 42 (-CHC_6H_5) both have antibacterial activity and compound 42 was also having antifungal activity.[34] Prakash et al., synthesised a series of ciprofloxacin methylene isatin analogues which were screened for antimicrobial activity. Although all compounds showed activity against several of the microorganisms but compound 43 was the most active compound.[2] Jarrahpour et al., synthesized many *bis*-Schiff bases of isatin, benzylisatin and 5-fluoroisatin using computational model. None of the compounds displayed activity against *S. cerevisiae* (ATCC28383) or *C. albicans* (CIP 1180-79).[35]



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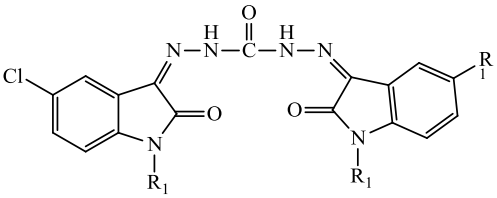
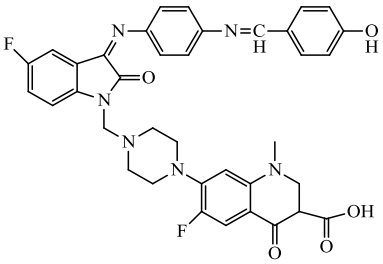
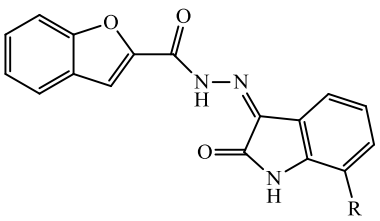


41 (R_1= H), 42 (**R_1**= -CHC_6H_5)

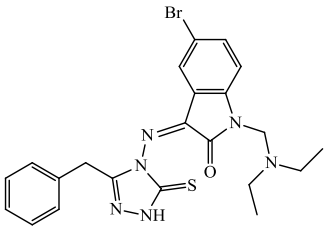


43

Synthesis of *N*-(5 or 7-substituted-2-oxoindolin-3-ylidene)-benzofuran-2-carbahydrazide by the reaction between benzofuran-2-carbohydrazide and 5 and 7 substituted-isatins was carried out by Ugale and coworker. Two analogues 44 and 45, among the series, demonstrate significant activity. Compound 44 showed activity against *E. coli* and *P. vulgaries* while compound 45 against *B. subtilis*, *E.coli* and *P. vulgaris* (31.25 mg/mL) when compared to standard. Similarly both compounds showed significant antifungal activity (31.25 µg/mL) against *Aspergillis niger* when compared to fluconazole.[36] Reaction of isatin and 4-amino-5-benzyl-2, 4-dihydro-*3H*-1, 2, 4-triazole-3-thione was reported by Murthy and coworkers to prepare schiff and mannich bases of isatin. Subsequent, antimicrobial investigation against *S. aures*, *P. aeruginoa*, and *E. coli* revealed that four compound showed good antimicrobial activity and compound 46 have equipotent activity against *A. niger*.[37]



44 (R=-NO_2), 45 (R= -F)



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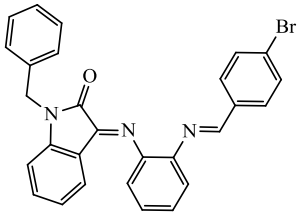
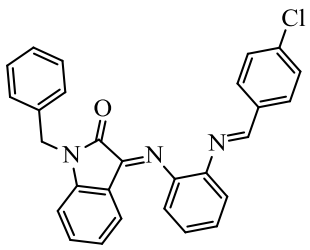
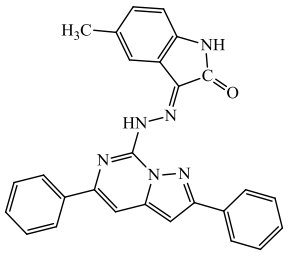


47

Murali et al., synthesized isatin derivatives which were further assessed for *in vitro* antibacterial (*S. aureus, S. epidermis, M. Luteus* and *B. cereus*) and antitubercular activity (*Mycobacterium tuberculosis* H37Rvstrain). Finding of study showed that compound 47, 3-(4-bromo-benzylidene-amino)-phenylimino)-1-benzylindolin-2-one exhibit promising antimycobacterial activity (MIC= 4.26 µg/ml) and compound 48, 3-(4-chloro-benzylideneamino) phenylimino)-1-benzylindolin-2-one possess significant antibacterial activity as compared with standard drug (Ciprofloxacin).[38] Condensation of 7-hydrazino-2, 5-diphenylpyrazolo [1, 5-*c*] pyrimidine and isatin was performed to furnish 3-{2-(2, 5-Diphenylpyrazolo-[1, 5-c] pyrimidin-7-yl) hydrazono}-indolin-2-one by Atta et al. The antibacterial activity against multidrug resistant bacteria, three Gram-positive (*B. subtilis*, *Micrococcus luteus* and *S. aureus*) and two Gram-negative (*E. coli* and *P. aeruginosa*) were performed. Six compounds were found active against *B. subtilis*, four against *M. luteus*, two against *S. aureus* and three were active against *P. aeruginosa*. Compound 49 was found to have broader antibacterial activity.[39]



48



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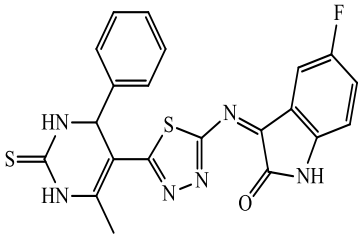
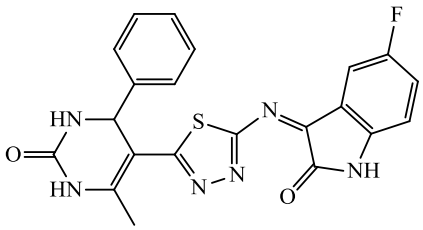
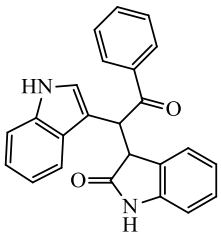


50

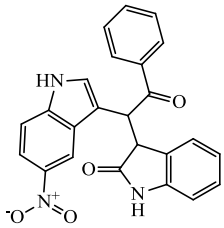
Using one pot multi component-Biginelli reaction *via* $CaCl_2$ catalyst Akhaja et al., prepared 5-substituted-3-[{5-(6-methyl-2-oxo/thioxo-4-phenyl-1, 2, 3, 4-*tetra*-hydro pyrimidin-5-yl)-1, 3, 4-thiadiazol-2-yl}imino]-1,3-dihydro-2*H*-indol-2-one derivatives. Two compounds 50 and 51 showed antimicrobial activity while compound 50 showed only antitubercular activity.[40]. Conjugate addition of indoles onto en-1, 4-dione in the presence of molecular iodine (catalytical amount) was performed to furnish 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl) indolin-2- one analogues by Reddy and coworkers. Finding of study showed that compounds 52, 53, 54, and 55 have strong antibacterial activity against *Pseudomonas aeruginosa* (9.375µg/mL).[41]



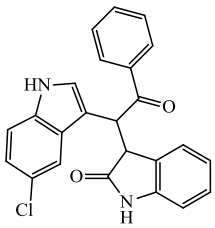
51



52

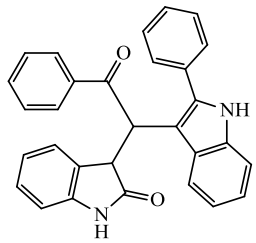


53



54

To prepare a *dispiro*-pyrrolidines Karthikeyan et al., carried out a cycloaddition reaction of an azomethine ylide, which was generated from sarcosine and isatin, and dipolarophile 3-benzylidene-1-methyl- pyrrolidine-2, 5-dione. Investigation showed that compound 56 have good antimicrobial activity while other compounds showed little activity.[42] Nandkumar and coworkers synthesised 2'-(Indol-3-yl)-2-oxospiro-(indoline-3, 4'-pyran) analogues by one-pot multicomponent synthesis. *In vitro* antimicrobial screening of the title compound against *Staphylococcus epidermidis, Staphylococcus aureus, Bacillus subtilis and Aspergillus niger* by disc diffusion method showed that compounds 57, 58, 59 and 60 have good antimicrobial activity.[43]



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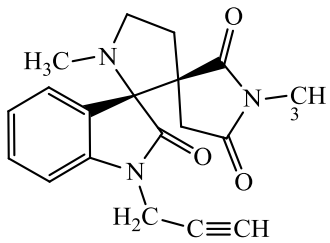
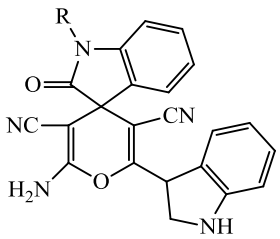
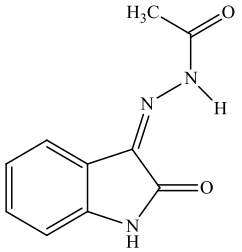


56



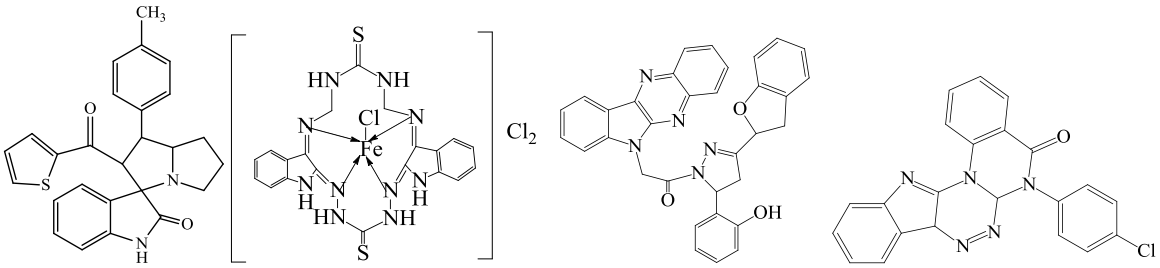
57(R= H), 58 (R=CH_3), 59($CH_2C_6H_5$), 60(Propragyl)



61

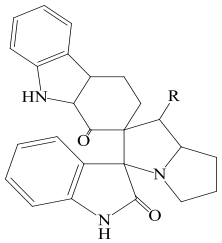
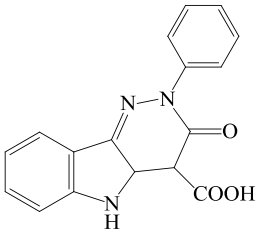
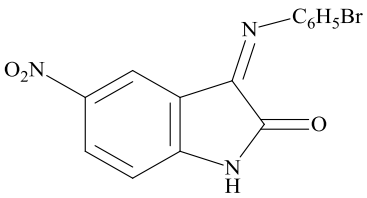
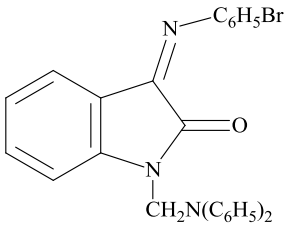
Taking adipic hydrazide, acetohydrazide, oxalyl dihydrazide Adibi et al., synthesized a new series of hydrazone and bishydrazone derivatives. These compounds were further subjected for antimicrobial evaluation against various Gram-positive and Gram-negative and antifungal against *Candida albicans* (clinical strain) by the minimal inhibitory concentration (MIC) method. Compound, N^1-(2-oxo-1, 2-dihydro-3*H*-indol-3-yliden)-acetohydrazide 61 was active against *S. dysenteriae* compared to the other compound.[44] Azomethine ylide, generated *in situ* by condensation of isatin with L-proline, was reacted with (*E*)-3-Aryl-1-(thiophen-2-yl)-prop-2-en-1-ones to furnish 1'-(Aryl)-2'-(2-thienylcarbonyl)-spiro-[3*H*-indole-3,3'-[3*H*] pyrrolizin]-2-ones. Finding of investigation showed that compound 62, 1'-(*p*-Chlorophenyl)-2'-(2-thienylcarbonyl)-*spiro*-[3*H*-indole-3, 3'-[3*H*] pyrrolizin]-2-one, have

good antimicrobial activity with MIC of 6.25-25 µg/mL.[45] Condensation of thiocarbohydrazide and isatin was used to prepare macrocyclic complexes [type M ($C_{18}H_{14}N_{10}S_2$) X] X_2 where M= Cr (III), Mn (III), Fe (III) and X= NO_3,-Cl, and acetic acid] by Singh et al. Further, antimicrobial evaluation against *S. aureus, B. subtilis, E. coli, P. aeruginosa* (bactyeria); *A. niger, C. albicans,* (fungus) *A. flavus (molds), Saccharomyces cerevisiae* (yeast) demonstrates that compound 63 was most effective against both the Gram-positive bacterial strains *i.e. S. aureus and B. subtilis.*[46]



62 63 64 65

Using microwave, a series of 2-[1-(5, 8-Dihydro quinoxalino[2,3-*b*]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]-phenyl analogues were synthesized by reaction between 2-(5, 8-Dihydro quinoxalino-[2,3-*b*]-indol-5-yl)-acetohydrazide and 1-(1-Benzofuran-2-yl)-4-phenyl-but-2-en-1-one. In series, one of the compound 64 i.e. 1-(3-(Benzofuran-2-yl)-5-(2-hydroxyphenyl)-4, 5-dihydropyrazol-1-yl)-2-(6*H*-indolo [3, 2-*b*]-quinoxalin-6-yl)-ethanone was possessing good antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. aureus* (MICs=10 µg/mL).[47] Three series of fused heterocyclic system having [1, 2, 4, 5]-tetrazino[4, 3-*a*]-quinazolin-8-one, triazolo[4, 3-*a*]-quinazolin-7-one and indolo-[2, 3-c][1, 2, 4]-triazino[4, 3-*a*]-quinazolin-8-one were prepared and evaluated for antimicrobial activity. Investigation revealed that compound, 3-(4-chlorophenyl)-indolo-[2, 3-*c*][1,2,4]-triazino[4,3-*a*]-quinazolin-8-ones, 65 was most active against tested organism.[48] An effeicient synthesis of novel dispiro-oxindolo-pyrrolizidine accomplished by 1, 3 dipolar cycloaddition reaction of azomethine ylide, generated by reaction of isatin and proline, and dipolarophile-2-arylidine-1-keto carbazole were reported by Periyasami *et al*. In the study, the cycloadducts compound 66 and 67 were possessing antibacterial and antifungal activity.[49]

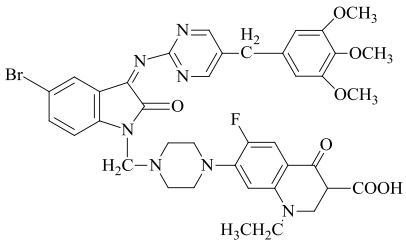





66 (R= -Cl), 67 (R= -Br) 68 69 70

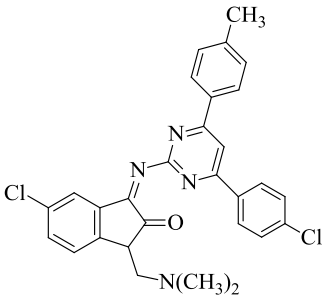
A class of novel Pyridazino-[4, 3-b]-indole-4-carboxylic acid were prepared and evaluated for antibacterial activity using different bacterial strains *viz Bacillus subtilis*, *E. faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella oxytoca* and *Pseudomonas aeruginosa* by Palluotto and coworkers. No significant activity was shown by compounds except compound 68, 2-oxo-3-phenyl-2, 3, 9, 9*a*-tetrahydro-1*H*-3, 4, 4-triaza-fluorene-1-carboxylic, which was having activity against Gram positive bacteria.[50] Sridhar et al., synthesized three different types of isatin derivatives *viz.* schiff bases, hydrazones and *N*-Mannich base. Antibacterial study was done against various bacterial strains *viz S. aureus*, *S. epidermidis*, *S. pneumonia*, *B. cereus*, *B. subtilis*, *B. pumilus*, *E. faecalis*, *E. coli*, *P. aeruginosa*, *P. vulgaris*, *S. typhi*, *S. typhimurium*, *S. dysenteriae* and *K. pneumoniae*. The study concluded that the compound 3-(4-bromo phenylimino)-5-nitro-1, 3-dihydroindol- 3-one 69 and 1-diphenyl amino-methyl-3-(4-bromo phenylimino)-1, 3-dihydro-indol-3-one, 70 were the most active member of the series. Further correlation shows that, mannich bases were more active than corresponding schiff bases.[51]

Pandeya et al., condensed norfloxacin, formaldehyde and isatin to obtain mannich bases. In *in-vitro* model, compound 71**,** namely 1-Ethyl-6-fluoro-1, 4-dihydro-4-oxo-7[(N(4)-(5'-bromo-3'-(4'-amino-5'-trimethoxybenzylpyrimidin-2'-yl)-imino-1'-isatinyl) methyl) N(1)-piperazinyl]-3-quinoline carboxylic acid (ED_{50}: 1.25 mg/kg) was more active than the standard norfloxacin (ED_{50}: 6mg/kg).[52] In another study, Pandeya and coworker reacted isatin and its derivatives with 4-(4'-chlorophenyl)-6-(4"-methyl phenyl)-2-aminopyrimidine to get schiff and the *N*-mannich bases. Investigation of antimicrobial activity against pathogenic microbes demonstrated that compound 72 i.e. 5-chloro-3-[4-(4-chloro-phenyl)-6-*p*-tolyl-pyrimidin-2-ylimino]-1-dimethylamino methyl-1, 3-dihydro-indol-2-one, was the most active among synthesized compounds.[53] A class of Schiff and mannich bases of isatin was obtained by reaction of ciprofloxacin methylene isatin and various aromatic aldehydes by Prakash and coworkers. *In vitro* antimicrobial investigation against human pathogenic microbe showed that the compound 73, 7-(4-((3-(4-(4-hydroxy benzylidene amino)-

phenylimino)-5-fluoro-2-oxindolin-1-yl) methyl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid was active.[2]



71



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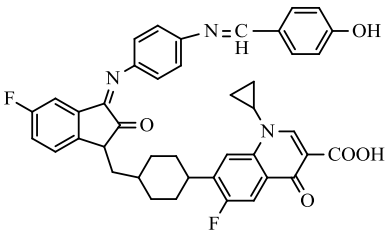
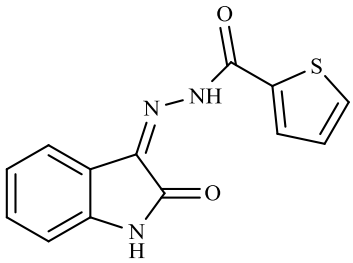


73

Metal II complex of acylhydrazones of 3-isatin and 3-(*N*-methyl)-isatin were prepared by Arguelles *et al*. which were further subjected for antimicrobial evaluation. Among the tested compound, (*Z*)-N^1-2 (2-Oxoindolin-3-ylidene)-thiophene-2-carbohydrazide 74 and its complex was most active compound against *Haemophilus influenza*.[54] Using 2-Diazo-1, 2-diaryl-1'-methylspiro-[azetidine-2, 3'-indoline]-2', 4-dione the synthesis of novel 1-Alkyl/cyclohexyl-3, 3-diaryl-1'-methylspiro-[azetidine-2, 3-indoline]-2', 4-dione were investigated by Singh and coworker. The antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Gram positive) and *Pseudomonas aeruginosa and Escherichia coli* (Gram-negative) and *Candida albicans* and *Saccharomyces cerevisiae* (fungal strain) were done. Compound 75, 1-Isopropyl-3, 3-bis-(4-methylphenyl)-1'-methylspiro[azetidine-2, 3'-indoline]-2',4-dione was most active member of series.[55] The reaction of isatin and various aromatic aldehyde to give 2-Arylquinoline-4-carboxylic acid hydrazode-hydrazone were reported by Metwally and coworkers. Antimicrobial activity was assessed against *Staphylococcus aureus, Escherichia coli* and *Candida albican*. Investigation of SAR predicted that, that compound having nitro substituents at the arylidene moiety were potent antifungal and antibacterial agents particularly against *E. coli.* Study concluded that compound 76, 6-Chloro-2-(4-methoxyphenyl)-quinoline-4-carboxylic acid (4-nitrobenzylidene)hydrazide, displays comparable antifungal activity to *nystatin.*[56] The reaction of isatin and various aromatic aldehyde to give 2-Arylquinoline-4-carboxylic acid hydrazode-hydrazone were reported by Metwally and coworkers. Antimicrobial activity was assessed against *Staphylococcus aureus, Escherichia coli* and *Candida albican*. Investigation of SAR predicted that, that compound having nitro substituents at the arylidene moiety were potent antifungal and antibacterial agents particularly against *E. coli.* Study concluded that

compound 76, 6-Chloro-2-(4-methoxyphenyl)-quinoline-4-carboxylic acid (4-nitrobenzylidene)hydrazide, displays comparable antifungal activity to *nystatin.*[56]



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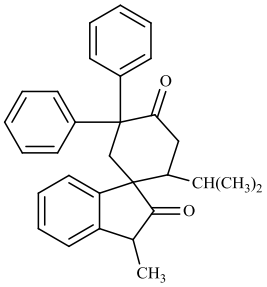

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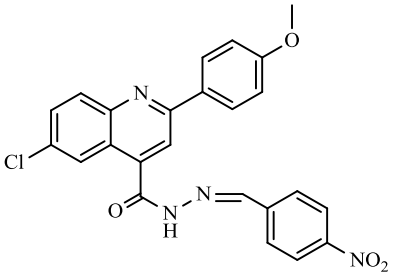
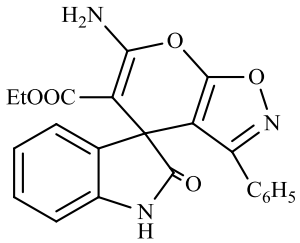


76

New *spiro* heterocycles based on indole nucleus were prepared by Rahman and coworker. The compounds were prepared by reaction of 4-(2'oxo-indol-3'-ylidene)-oxazol-5-one derivatives and indol-3-ylidene based heterocycles with activated nitrile reagents. Antimicrobial investigation against various Gram-positive (*B. subtilis* and *B. megatherium*), Gram-negative (*E. coli*) and fungi (*Aspergillus niger* and *Aspergillus oryzae*) reveals that compounds 77 and 78 were most active antibacterial and antifungal agents, respectively.[57]



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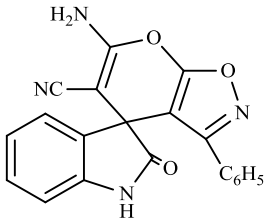

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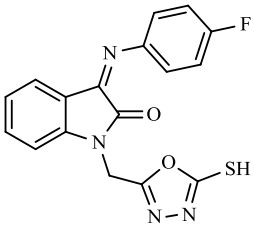

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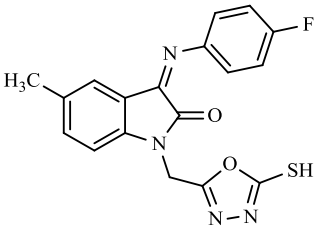
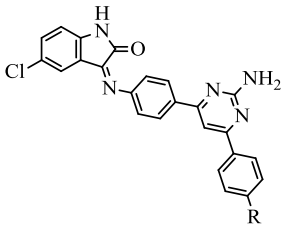


80

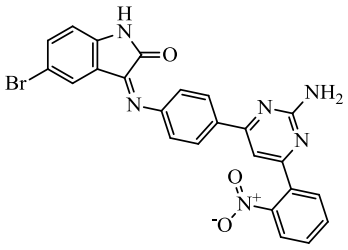
With the objective to find out antimicrobial agent, Bari et al., reacted 5-substituted-3-(4-arylimino)-2-oxo-1-indole acetylhyrazide and CS_2 in ethanolic KOH to obtain new 5-substitued-3-(4-arylimino)-1-[5-mercapto (1, 3, 4-oxadiazolyl)]-methylindol-2-one. Result of antimicrobial study against showed that compound 5-Fluoro-3-(4-fluorophenylimino)-1-(5-mercapto-1, 3, 4-oxadiazol-2-yl)-methyl)-*1H*-inden-2(3*H*)-one 79, is active against *staphylococcus aureus* and *bacillus subtills* while compound 80 showed significant activity against *candida albican* and *aspergillus niger.*[58]

Kumar et al., synthesized novel pyrimidine derivatives of 5-chloroisatin and evaluated them for their *in vitro* antimicrobial activity. In the series, compound 81(R= -Br) comes out to be most potent antimicrobial while compound 82 (R= $-NO_2$) as antifungal agent.[59] In another study Kumar and Kumar prepared a new series of 5-bromoisatin derivative clubbed with

pyrimidine i.e. 3-[4-(2-Amino-6-substituted-phenyl-pyrimidine-4-yl)-phenylamino]-5-bromo-1, 3-dihydro-indol-2-one derivatives. In this screening result showed that compound 83 was possessing antibacterial while compound 84 was having antifungal activity.[60]



81(R= -Br), 82(R= -NO_2)



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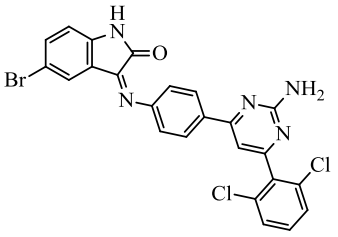
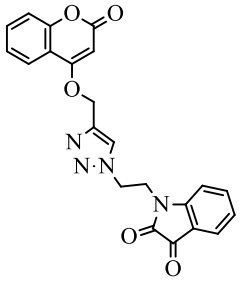


84

Bhagat et al., designed and prepared a new series of indolindione-coumarin molecular hybrids. Antimicrobial evaluation of hybrid molecules showed that among all synthetics, compounds 85 and 86 were found to be the best antimicrobial agents with the minimum inhibitory concentration values of 30 and 312µg/mL, against *Penicillium sp.* and *S. aureus*, respectively.[61]



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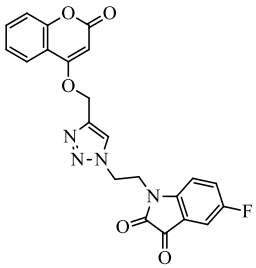

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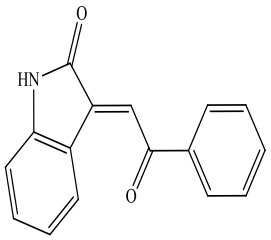

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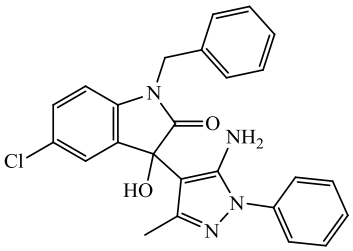
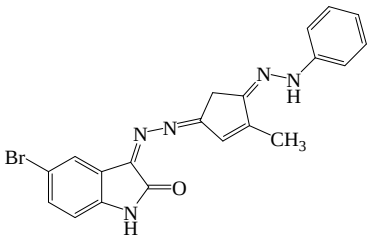


88

Dawar et al., synthesised isatin derivatives by reacting isatin with different reagents *viz* substituted acetophenones, sodium nitrate, hydroxylamine hydrochloride and hydrazine hydrate. Following characterization by spectral techniques such as IR, ^{1}HNMR, ^{13}CNMR, elemental analysis and mass spectrometry, synthesized compounds were further evaluated for their antifungal activity against *Helminthosporium oryzae*, *Rhizoctonia solani* and *Fusarium moniliforme* using poison food technique. One of the synthesized compounds, compound 87, 3-(2-Oxo-2-phenylethylidene) indolin- 2-one, showed mycelium inhibition activity against all tested fungi.[62] Konstantinovic et al., synthesized isatin-3-(4`-hydroxy)-benzoylhydrazone. Antimicrobial screening of the compounds was carried out against *Staphylococcus aureus*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Candida albicans*. Compounds showed activity against Gram-positive bacteria

Enterococcus faecalis and yeast *Candida albicans* in the concentration range of 25-50 µg-cm^3, while no significant activity was shown against Gram negative bacteria.[63] To get new oxindole derivatives, Romo et al., reacted isatin and 5-aminopyrazole in the presence of *p*-toluenesulfonic acid as catalyst. Although many compounds showed antibacterial activity but most potent activity was shown by compound 88 against vancomycin intermediate Staphylococcus aureus.[64] Isatin-decorated thiazole derivatives have shown potent antimicrobial activities against *E. coli*, a representative of gram-negative bacteria. Also,compound 89 showed the best activity against Methicillin Resistant *Staphylococcus aureus* (MRSA).[65] Isatin Bis-Indole and Bis-Imidazothiazole Hybrids were synthesized and evaluated for their antimicrobial potential on three reference strains, including S. aureus, E. coli, and C. albicans. The study delivered two lead compounds, 906k and 916m, endowed with excellent inhibitory activity against S. aureus in comparison with other isatin hybrids.[66]



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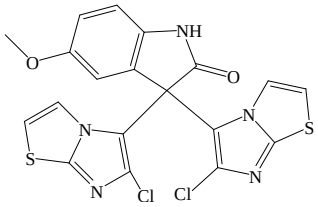

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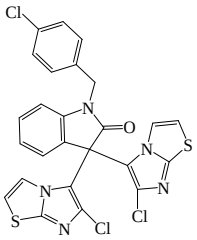
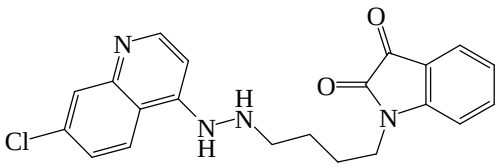


91

Isatin–Quinoline conjugates were synthesized and evaluated against Multidrug-Resistant Bacterial Pathogens. Conjugates 92 and 93 displayed the most potent activity against all clinical isolates.[67]



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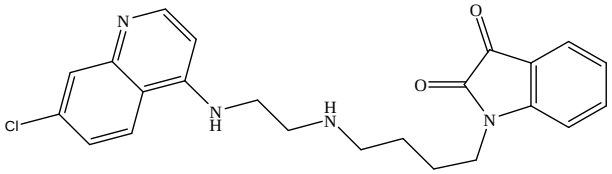

93

CONCLUSIONS

The present study shows that Isatin can be modified in different way to produce its analogues. The most important position for alteration is 1, 3 and 5th position. The study shows that isatin can be converted to different type of compounds *viz* Schiff bases, mannich bases, thiosemicarbazones, *spiro* compounds and fused heterocyclic compounds. Many of the synthesized analogues show potent antimicrobial activity. Information provided in this

review may be useful for further optimization of isatin to yield new chemical entity as potential antimicrobial agents.

Conflict of Interest

None.

ACKNOWELGEMENT

Declared none.

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