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Isatin – a potent anti-microbial agent

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ABSTRACT

From many years in hospitalized and ambulatory patients, it is observed that increased antibiotic resistance in both Gram-positive and Gram-negative bacteria. For global health, a significant threat was found to be quick development of resistance by various microorganisms against anti-microbial drugs. In addition, multidrug-resistant organisms also developing rapidly which further complicated the situation. Hence it is necessary to develop and find out novel anti-microbial agent urgently. In the field of organic chemistry important role was played by heterocyclic compounds. They are acquiring more importance in recent years due to their extensive pharmacological properties and wide applications in the field of chemistry. Out of many available heterocyclic compounds, isatin and various isatin analogues were found to be significant due to its broad range of biological activities. Isatin has emerged as anti-microbial agents due to its wide range of anti-microbial potency displayed in both *in-vivo* and *in-vitro* method. In this review, various anti-microbial isatins were summarised & reported. In addition, this review highlights the anti-microbial potency of isatin to the medicinal world.

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INTRODUCTION

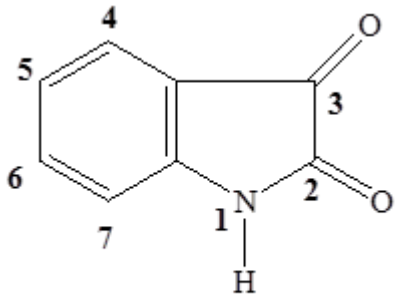
On the mucosal health of human's various parasitic bacteria like *E. coli, S. Typhimurium, S. pyogenes* & *S. aureus* have a significant impact. Life-threatening diseases are produced by *E. coli, S. Typhimurium, S. pyogenes* & *S. aureus* due to massive destruction of host tissue. In developing countries, these bacterial parasites affect millions of individuals and cause diarrhoea, rheumatic fever and food poisoning. Worldwide every year up to 1,10,000 people die and a number of infected peoples crossing fifty million. Ciprofloxacin, norfloxacin & amoxicillin are most commonly used drugs for these bacterial infections, but severe side effects associated with them are a major drawback. Gradually antibiotic resistance is increasing for many infections caused by various micro-organisms which shows significant threat and may lead to complications and treatment failures. Hence several scientists are trying to find out new anti-microbial agents by placing significant efforts (Krishnanjaneyulu *et al*., 2014).

The main aim of the pharmaceutical sciences is novel drug discovery particularly in the pharmaceutical chemistry field medicinal chemistry region. The various important studies involved in medicinal chemistry field include designing of novel drug and its synthesis & SAR study. In current decades from the discovery medicinal chemistry becomes modern and exceptionally productive due to the growth of medicinal chemistry research. At present 1 or more heterocycles are present in

many accessible drug molecules. Up to date investigation of medicinal chemistry revealed isatin and its derivatives as significant heterocycle because it possesses potent pharmacological activities (Robert, 1957; Wilson and Gisvold, 1991; Andrejus, 2003).

Originally in 1841, using nitric acid & chromic acids indigo was oxidised by Erdman & Laurent resulted in the production of 1*H*-indole-2,3-dione or isatin I. In organic synthesis isatin was extensively used due to its versatile synthetic method. To improve the various biological activities associated with isatin, several modifications are made in the structure which attracted the interest of many researchers who involved in pharmaceutical chemistry research (Saravanan *et al*., 2014). Isatin has emerged as anti-microbial agents due to its wide range of anti-microbial potency displayed in both *in-vivo* and *in-vitro* method. In this review, various anti-microbial isatins were summarised & reported. In addition, this review highlights the anti-microbial potency of isatin to the medicinal world.

Anti-microbial isatin



Isatin (I)

Pandeya *et al*. synthesized isatin Schiff and Mannich bases 1 (Figure 1) by reacting 4-(4′-chlorophenyl)-6-(4″-methyl phenyl)-2-aminopyrimidine, formaldehyde, several secondary amines & indole-2,3-dione & its analogues. Agar dilution method used to test the synthesized derivatives against thirty-six pathogenic micro-organisms. Against tested bacteria and fungi test analogs exhibited significant activity. In addition title derivatives were also tested in MT-4 cells against replication of HIV-1 (III B) to determine its anti-HIV potency (Pandeya *et al*., 1999). A series of benzothiazole, thiadiazole, thiazole, and *p*-toluenesulfonyl hydrazide moieties incorporated isatins, 2 (Figure 1) and its metal complexes are prepared and characterized by Zahid *et al*. Employing the agar well diffusion test these analogues were screened for its anti-microbial activity against *S. aureus, E. coli, P. aeruginosa, S. flexneri, B. subtillis*, *S. Typhi, C. glaberata, F. solani, A. flavus, C. albicans, M. Canis,* & *T. longifusus*. Against entire test microbial strains, metal complexes exhibited markedly enhanced activity. The title analogs, in general, displayed moderate anti-bacterial activity and good anti-fungal activity. The high potency of metal complexes is due to the existence of extra C=N bond with an aromatic /heteroaromatic ring (Zahid *et al*., 2004).

Various azlactones are treated with 3'-(substituted phenyl)-spiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-dione-1-ylacetylhydrazine to synthesize a variety of novel 1- {3'-(substituted phenyl)-spiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-dione-1'-ylacetamido]-2-phenyl-4-arylidine-5-oxoimidazolines **3** (Figure 1) by Uday *et al*. They screened these derivatives at 100 µg/ml concentration by bioassay agar cup method for its antibacterial activity against *B. subtilis, P. aeruuginosa, S. aureus* and *E. coli*. Many test compounds displayed moderate activity against various tested strains of bacteria (Uday *et al*., 2005). Ankur *et al*., synthesized few novel 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4*H*-imidazole-4-one-3-(4-bezoylhydrazono)]-indole-2-ones 4 (Figure 1) from isatinhydrazones & 2-phenyl-5-benzylidene-3-N (4-acetyl phenyl)-1,5-dihydroimidazole-4-one. Disk diffusion technique was employed to investigate its anti-microbial activity using Gentamicin as a standard drug against four strains of bacteria. In addition, using Amphotericin B, the anti-fungal activity of test analogues was studied against two pathogenic fungi. The report showed that fluorine, bromine or chlorine-substituted isatin (C-5) displayed more activity. The most potent one is 5-bromo isatin analogue (Ankur *et al*., 2006).

5-Halogenated isatin analogs were reacted with 4-(substituted-pyridine-2-yl) thiosemicarbazide to produce some novel 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl) thiosemicarbazide 5 (Figure 1) analogs by Vijey *et al*. Disc diffusion method was used to examine its anti-bacterial and anti-fungal activity (*in-vitro*) against *P. aeruginosa, E. coli, B. subtilis, S. aureus, A. niger,* and *C. albicans* using Ciprofloxacin and Ketoconazole as reference drug. Moderate to good anti-microbial activity was shown by all test analogues (Vijey *et al*., 2008).

Against four strains of fungi and seven strains of pathogenic bacteria Sandra *et al*., testes anti-microbial potency of Pd(II), Hg(II), Zn(II), Co(II), Ni(II) & Cu(II) complex of isatin-3-thiosemicarbazones 6 (Figure 1). Because of transition metal involvement in complexes, compared to ligand complexes displayed better activity. In addition, against *Entamoeba histolytica in-vitro* anti-amoebic activity was screened using Metronidazole as the reference standard. Like anti-microbial activity compared to the ligand complexes displayed better activity (Sandra *et al*., 2008).

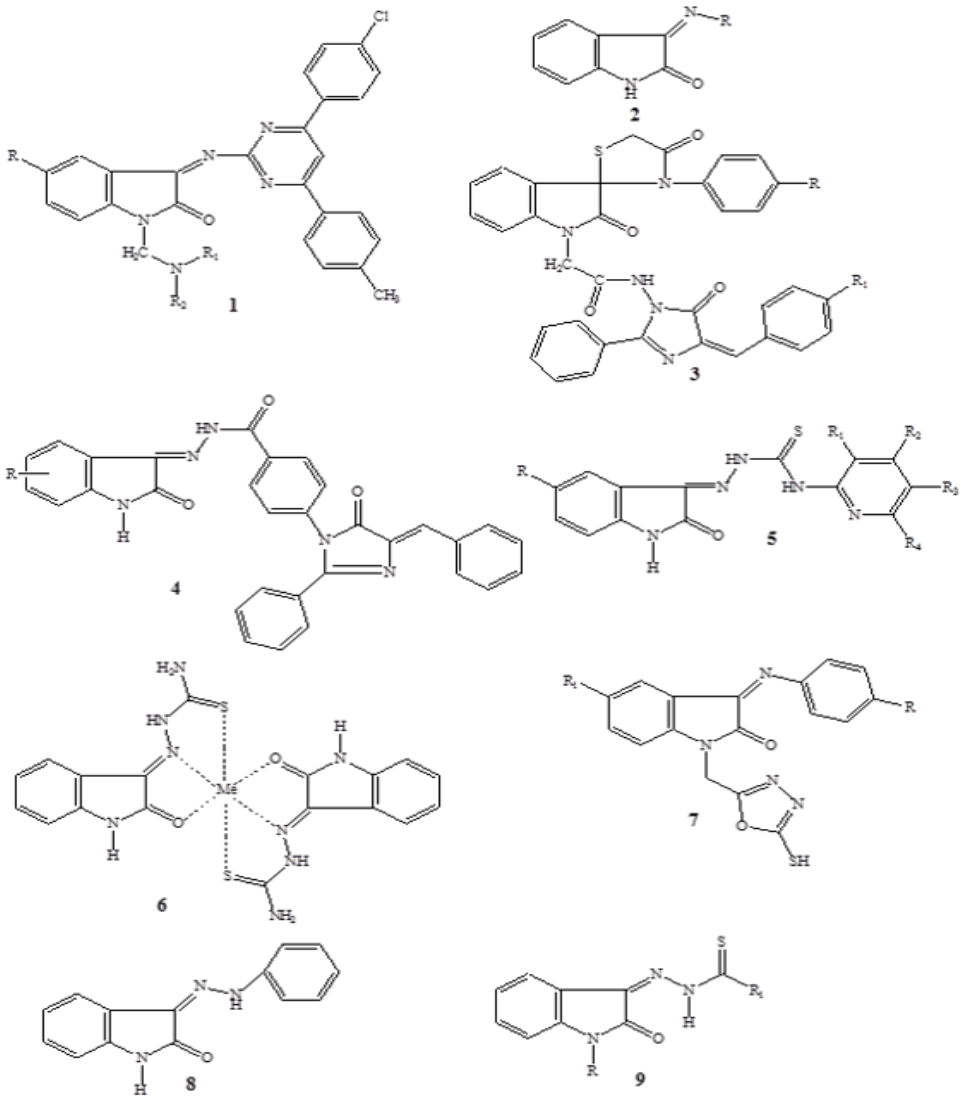


Figure 1: Structure of anti-microbial isatins (1-9)

Bari *et al*., synthesized various novel 5-substituted-3-(4-arylimino)-1-[5-mercapto(1,3,4-oxadiazolyl)]-methyl-indol-2-one 7 (Figure 1) using CS_2 and 5-substituted-3-(4-arylimino)-2-oxo-1-indole acetyl hydrazide by heterocyclization. By *in-vitro* method at 200 and 500 µg/ml concentrations, these derivatives are screened for the anti-microbial test against *Staphylococcus aureus, Bacillus subtilis*, *Escherichia coli, Proteus vulgaris*, *Candida albicans* and *Aspergillus niger*. Out of various tested compounds fluoro, methyl and bromo substituted analogs displayed potent activities (Bari *et al*., 2008). X-ray crystal structure and synthesis of isatin-3-phenylhydrazone 8 (Figure 1) was reported by Sandra *et al*. Isatin-3-phenylhydrazone analogs were examined for the anti-microbial test (*in-vitro*) against *Pseudomonas aeruginosa, Candida albicans, Proteus vulgaris, Bacillus subtilus, Escherichia coli, Staphylococcus aureus* and *Enterococcus D.* Amoxycillin and Norfloxacin was used as standard drug. They also studied the stability of isatin-3-phenylhydrazone against irradiation of UV-A and found that it undergoes bleaching following first-order kinetics (Sandra *et al*., 2008).

Complexes of three isatin 2-thiophenecarbonyl hydrazone with various metals were synthesized and characterized by Maria *et al*. Molecular structure of these three acylhydrazones 9 (Figure 1) was confirmed by X-ray. *In-vitro* anti-microbial activity of the ligands (free & its complexes) are tested against various moulds, yeasts & pathogenic Gram positive & Gram negative bacteria. *Haemophilus influenzae* was found to be more sensitive out of variously tested microorganism (Maria *et al*., 2009). From chalcone Dinesh *et al*., synthesized several new alkoxyphthalimide moieties possessing spiro-isatin-thiazolidine-pyrazoline 10 (Figure 2) by multi-step synthesis. *In-vitro* anti-microbial potency of test compounds was screened by cup and well method at a concentration of 100 µg/ml against *E. coli, K.*

Pneumonia, B. subtilis, P. mirabilis, A. fumigatus & *C. albicans*. The obtained zone of inhibition was

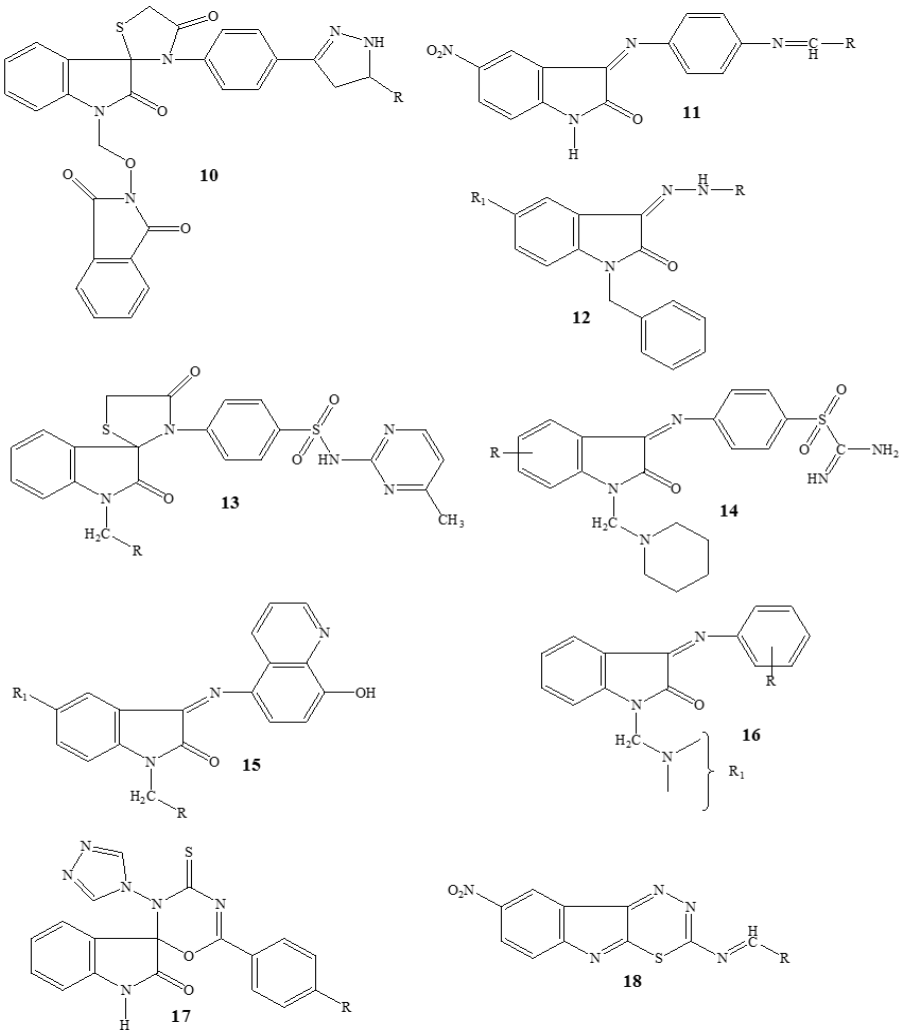


Figure 2: Structure of anti-microbial isatins (10-18)

compared with Ciprofloxacin, Roxithromycin, Amphotericin and Fluconazole (Dinesh *et al*., 2009).

Imesatin was condensed with various aromatic aldehydes by Prakash *et al*., to synthesize several Schiff bases of 5-substituted isatin 11 (Figure 2). By paper disc diffusion technique Schiff bases are screened for anti-microbial potency against *K. pneumoniae, P. aeruginosa, B. cereus, S. epidermidis, M. luteus, E. coli, S. aureus, A. fumigatus* & *A. niger*. Agar streak dilution test is employed to estimate MIC of title analogs. Among various synthesized derivatives nitro derivatives exhibited a potent activity which may be due to its electron withdrawing nature (Prakash *et al*., 2009). Various isatin and 5-halo isatins are treated to produce Mannich bases (C-N), Schiff's bases (C=N) & Friedal Craft alkylation's (C-C). The reactions take place at first & third position of isatin is confirmed from its spectral data. Various prepared compounds 12 (Figure 2) were tested for their anti-microbial activity against various strains of microorganisms (Hajare *et al*., 2009).

Monika *et al*., reported environmentally benign microwave assisted preparation of new 3'-[4'-N-{4-methyl-2-pyrimidinyl}-benzenesuphonamido]-spiro-(3*H*-indol-3,2'-thiazolidine)-1*H*-2,4'(5*H*) dione & its Mannich's bases 13 (Figure 2) were synthesized from the commercially availablesulphamerazine. *In-vitro* anti-microbial activities of sulphamerazinyl substituted [spiro-indolo-4-thiazolidinone] Mannich's bases were screened against B. substilis, E. coli, A. flavus and A. niger by agar-well assay method using Ciprofloxacin for and Fluconazole as reference drug (Monika *et al*., 2010). Initially, Schiff's base of isatins & substituted isatins is synthesized from 4-Amino-N-carbamimidoylbenzenesulfonamide. Latter using piperidine and formaldehyde the Mannich bases of above compounds 14 (Figure 2) were synthesized. Tube dilution method was used to study its anti-bacterial potency against various strains of six bacteria using 4-Amino-N-carbamimidoylbenzenesulfonamide as standard. Prepared derivatives displayed superior anti-bacterial potency compared to standard drugs. Against *C. Albicans* and *S. cerevisiae* anti-fungal activity of test derivatives are

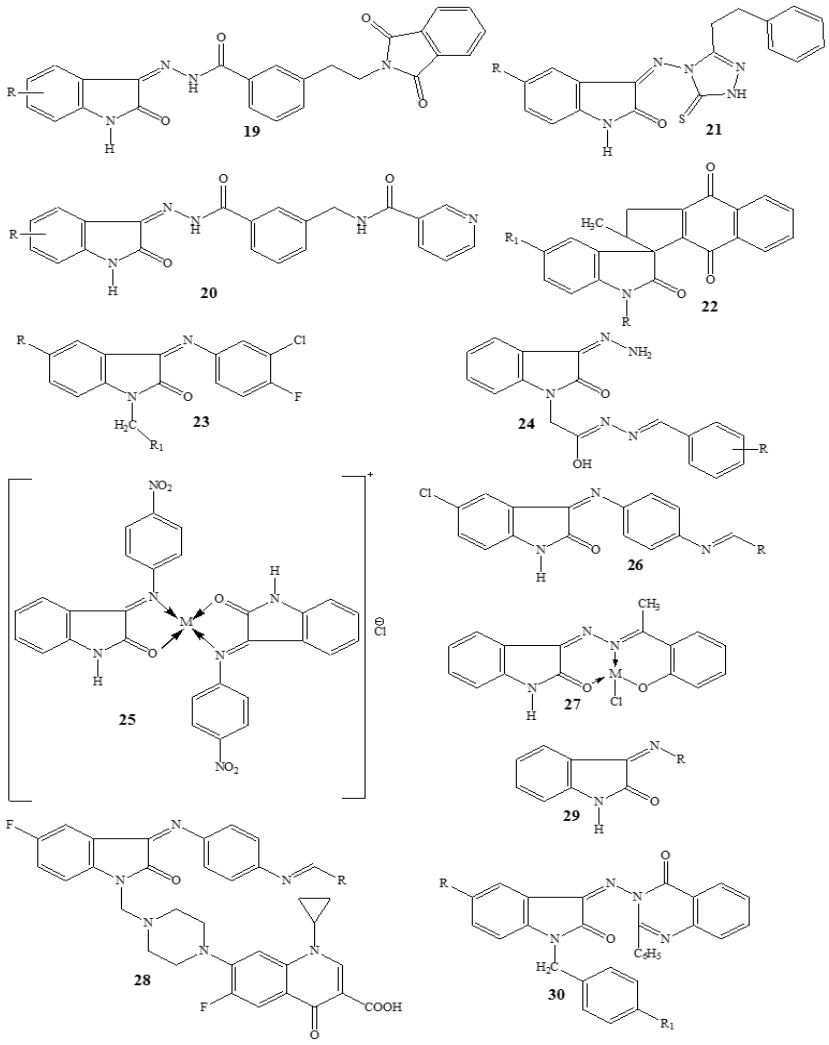


Figure 3: Structure of anti-microbial isatins (19-30)

screened and found that no one anlalog showed comparable activity with Clotrimazole. Among various tested compounds, chlorine substituted analog displayed potent anti-bacterial activity (Singh *et al*., 2010).

Several new Schiff bases of isatin and its chloro derivative 15 (Figure 2) were synthesized from 5-amino, 8-hydroxyquinoline by Chhajed *et al*. Latter *N*-Mannich bases of above analog was prepared by treating with various secondary amines and formaldehyde. Agar dilution method was used to assess its anti-microbial activity against *B. subtilis, P. aeruginosa, S. faecalis, S. aureus, E. coli, C. albicans* and *A. niger* at 250, 500 and 750 µg/ml concentrations using DMSO as a solvent. Ketoconazole and Sulphamethoxazole were used as a standard drug (Chhajed *et al*., 2011). Various novel isatin Schiff's and Mannich bases 16 (Figure 2) were reported by Chaluvaraju *et al*. *In-vitro* cup-plate agar diffusion test is employed to study the antibacterial activity of test derivatives against *E. coli, S. aureus, S. Typhi, B. subtilis, C. albicans* and *A. niger*. Results were compared against Amoxicillin and Fluconazole and found that entire tested analogs displayed gentle to reasonable activity (Chaluvaraju *et al*., 2011). Visha *et al*., synthesized several 6′-phenyl-4′-thioxo-3′-(4*H*-1,2,4-triazole-4-yl)-3′,4′-dihydro spiro [Indoline-3,2′-[1,3,5] oxadiazine]-2-one 17 (Figure 2) by multi-step synthesis from 4*H*-1,2,4-triazole-4-amine & indole-2,3-dione. The synthesized derivatives are tested for its anti-microbial activity and found that possessing fine anti-microbial activities. MIC and zone of inhibition were measured and compared with standard drug (Visha *et al*., 2011).

Various new 5-nitro satin Schiff bases 18 (Figure 2) are synthesized from thiosemicarbazide by multi-step synthesis. Anti-microbial activities (*in-vitro*) of above-prepared derivatives were done by agar cup plate test against *B. pumilus, P. aeruginosa, E. coli, P. chrysogenum* & *A. niger*. Agar streak dilution method was employed to determine its MIC. The most potent compound was found to be (6-nitro-1-thia-3,4,9-triaza-fluorene-2-yl)-naphthalene-1-yl methylene-amine and (6-nitro-1-thia-3, 4, 9-triaza-fluorene-2-yl)-pyridine-2-ylmethylene-amine (Laxmi *et al*., 2011). Bhavesh

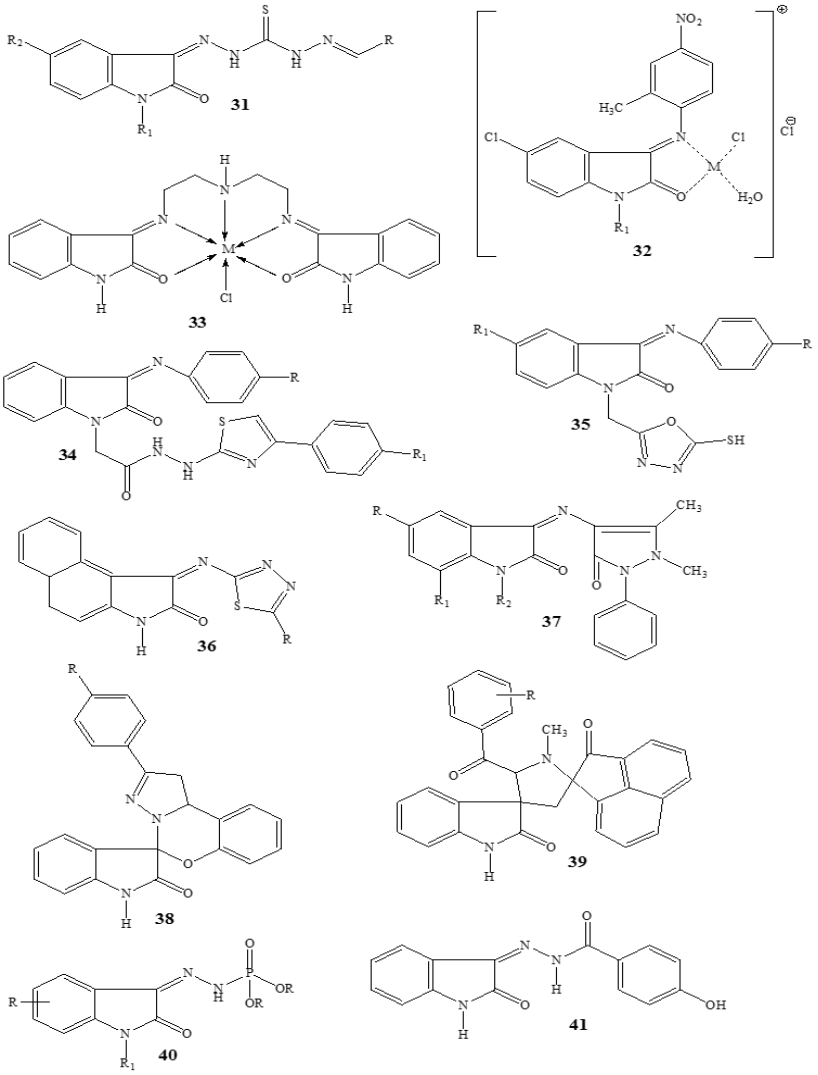


Figure 4:: Structure of anti-microbial isatins (31-41)

et al., prepared eight novel 3-[2-(1,3-dioxo-1,3-dihydro-isoindole-2-yl) ethyl] benzoic acid (2-oxo-1,2-dihydroindole-3-ylidene) hydrazide 19 (Figure 3) by treating various isatins and 3-[2-(1,3-dioxo-1,3-dihydro-isoindole-2-yl) thyl]benzoicacid hydrazide. Disk diffusion technique was employed to investigate its anti-microbial activity using Gentamicin and Amphotericin B as a standard drug against *B. subtills*. *S. aureus* and *A. niger*. The potent compounds of the series possessing chloro, nitro and iodo group at C-5 of isatin (Bhavesh *et al*., 2011).

From N-(3-hydrazino carbonyl benzyl) nicotinamide and various isatin derivatives novel N-[3-(2-oxo-1,2-dihydro-indol-3-ylidene-hydrazinocarbonyl)-benzyl]-nicotinamide 20 (Figure 3) was synthesized and reported by Bhavesh *et al*., Disk diffusion technique was used to assess its anti-microbial activity. The potent compounds of the series possessing fluoro and a methyl group at C-5 of isatin ring (Bhavesh *et al*., 2011). Yellajyosula *et al*. synthesized several new isatin Mannich & Schiff bases 21 (Figure 3) from 4-amino-5-benzyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione. Using agar dilution test synthesized compounds zone of inhibitions was determined by *in-vitro* method against *E. coli, P. aeruginoa, S. aureus* & *A. niger*. Ciprofloxacin and Fluconazole are used as a standard drug for comparison. Presence of chlorine and bromine moiety at C-5 of isatin favors anti-microbial activity. They also studied the SAR of synthesized isatin analogs (Yellajyosula *et al*., 2012).

Initially, azomethine ylide was prepared from l-proline or sarcosine, isatin & 1,4-naphthoquinone (dipolarophile) by dehydrogenation (spontaneous). Latter using the above-synthesised azomethine ylide, several novels spirooxindoles 22 (Figure 3) were prepared by 1,3-dipolar cycloaddition reaction. *In-vitro* anti-microbial activities of test compounds were evaluated against *Salmonella paratyphi*-B, *Salmonella typhimurium*, *Klebsiella pneumonia*, *Micrococcus luteus*, Enterobacter *aerogens, Proteus vulgaris*, *S. aureus* (MRSA), *Staphylococcus aureus*, *Candida albicans*, *Botyritis cinerea* and *Malassezia pachydermatis*.

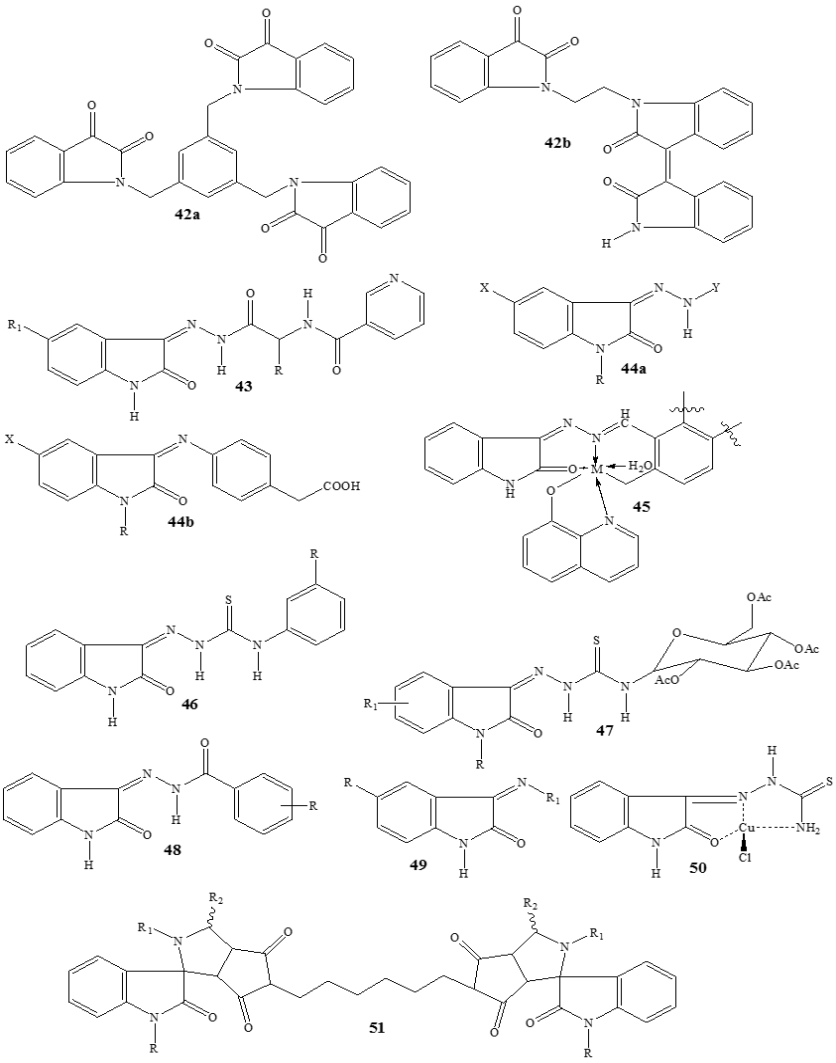


Figure 5: Structure of anti-microbial isatins (42-51)

Out of twenty-three tested analoga, the most potent one was found to be 1′-acetyl-2,5′-dimethyl-2,3-dihydrospiro[benzo[*f*]isoindole-1,3′-indoline]-2′,4,9-trione (Gangaru *et al*., 2012). Subhas *et al*., synthesized various Mannich base derivatives of 5-chloro-3-(3-chloro-4-fluorophenylimino) indolin-2-one & substituted 3-(3-chloro-4-fluorophenylimino) indolin-2-one 23 (Figure 3). Antibacterial activities of test analogs were screened against several strains of bacteria. In addition, all derivatives are tested for β-lactamase inhibitory activity. Results exposed the mild to the good activity of synthesized derivatives (Subhas *et al*., 2012).

Sallam *et al*., condensed *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and benzaldehyde with 3-hydrazono-2-oxo-2,3-dihydro indol-1-yl)-acetic acid hydrazide to synthesise several novels Schiff-bases 24 (Figure 3) using acetic acid as a catalyst in ethanol. In addition, they prepared metal complexes of the above-synthesised compounds. Chemical formulation of the complexes was confirmed from TGA and DTA. Moreover, they also evaluated its thermal decomposition. Disk diffusion test is employed to screen its anti-microbial activity of test compounds against *Proteus Vulgaris*, *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus*. Compared to free ligand, complexes displayed potent activity. Chelation theory explains the increased activity of the complexes as chelation decreases metal ion polarity. In addition, chelation also improves chelate lipophilic nature which is useful for penetration into micro-organism (Sallam *et al*., 2012).

Isatin was condensed with *p*-nitroaniline by Adebomi *et al*., to synthesize some novel Schiff base. They also synthesized its metal complexes of above ligand 25 (Figure 3). The synthesized compounds were tested for its anti-microbial potency using Sabouraud dextrose agar medium and Mueller-Hinton agar medium. The test compounds were tested against *S. Typhi, E. coli, P. aeruginosa, B. subtilis, M. luteus, S. aureus, C. albicans, A. flavus* & *A. niger*. The cobalt (II) complex showed moderate activity against bacteria whereas nickel (II) complex showed no activity. Both complexes not

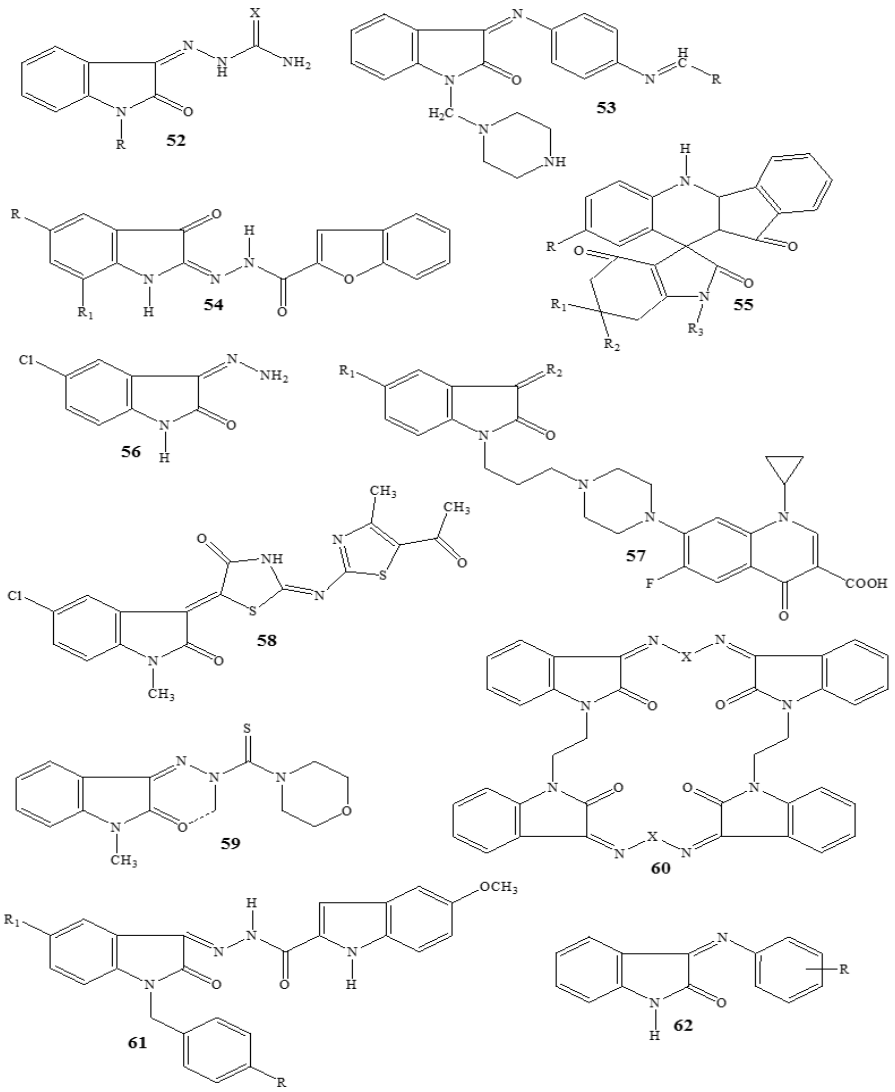


Figure 6: Structure of anti-microbial isatins (52-62)

displayed any anti-fungal activity. The reason for poor activity is deactivation of the ring system by nitro group (electron withdrawing) (Adebomi *et al*., 2012).

Joshi *et al*., condensed various aromatic aldehydes with imesatin to synthesize various new Schiff bases of isatin 26 (Figure 3). From p-phenylenediamine and isatin, imesatins are synthesized. Antimicrobial potency of test derivatives was screened *in-vitro* against various strains of fungi and bacteria. Two of the synthesised analogues displayed mild and good antibacterial activity against tested bacteria (Joshi *et al*., 2012). 2-Hydroxyacetophenone was condensed isatin monohydrazone to synthesise novel bis-hydrazone by Swathy *et al*. Latter the bishydrazole formed several complexes with metals 27 (Figure 3). Monobasic tridentate nature of the ligand was confirmed form spectral studies. Through indole-2,3-dione ring oxygen (deprotonated phenolate), nitrogen (azomethine) & oxygen (carbonyl) ligand coordinated the metal ion. From the study, it was found that entire synthesized complexes are non-electrolytes from its low molar conductance. Metal-ligand bond covalent character was indicated by EPR spectral data. XRD and ligand & its metal complex thermal decomposition data were also reported. *In-vitro* agar disc diffusion is employed to study its anti-microbial potency. While comparing MIC of the free ligand with complexes, they found that the copper complex demonstrated superior anti-microbial potency. Weight loss measurements were used to study ligand & its complex corrosion inhibitory activity in sulphuric acid (Swathi *et al*., 2012).

Various ciprofloxacin methylene isatin analogs 28 (Figure 3) were synthesized by using a variety of aromatic aldehydes as potent anti-microbial agents by Chinnasamy *et al*. They tested the *in-vitro* anti-microbial potency of above compounds by disc diffusion technique against various human pathogenic microorganisms. From the study, they found that when compared to electron withdrawing moiety substituted analogs electron donating group displayed potent anti-microbial properties. Among various synthesised derivatives *p*-hydroxy

group-containing compounds showed better activity which is higher than Ciprofloxacin and Ketoconazole (Chinnasamy *et al*., 2013). Jnyanaranjan *et al*. synthesized some novel Schiff bases of isatin 29 (Figure 3) by microwave technology. Various aromatic primary amines are treated with keto group of isatin to produce novel Schiff base of Isatin. They studied the anti-bacterial potencies (*in-vitro*) against various strains of bacteria. From the study, they observed that against entire tested microorganisms the compound with electron withdrawing substituent displayed good anti-bacterial activities (Jnyanaranjan *et al*., 2013).

Basavaraj & its co-workers described the synthesis, characterisation & anti-microbial screening of various Mannich and Schiff bases of indole-2,3-dione 30 (Figure 3). The compounds were prepared by reacting indole 2,3-dione with 4-substituted benzyl chloride to give intermediate, and also isatin reacted with morpholine to give Mannich base which was then fused with 3-amino-2-phenylquionazolin-4H-one, to give the title compound. Entire test compounds were characterised and tested for its anti-microbial potency against various microorganism (Basavaraj *et al*., 2013). *In-vitro* antioxidant and anti-microbial activity of series of β-isatin Aldehyde-N, N'-thiocarbohydrazide analogues 31 (Figure 4) were reported by Kiran *et al*. Against various tested microorganisms entire test compounds displayed a broad spectrum of activity (MIC: 12.5 - 400 μg/ml). In addition, spectrophotometrically they measured the free radical scavenging effects of synthesized derivatives against stable free radical H_2O_2 and DPPH (Kiran *et al*., 2013).

Raghavendra *et al*. synthesised Schiff base from 2-methyl-4-nitroaniline and 5-chloroisatin. Later they prepared various complexes of above Schiff base 32 (Figure 4) with metals. In co-ordination involvement of oxygen (carbonyl) & nitrogen (azomethine) of ligand confirms its bidentate nature. They proposed square planar geometry and tetrahedral geometry for Ni (II) & Cu (II) complexes and Zn (II) and Co (II) complexes, respectively. The complexes were tested for its anti-microbial activity against *E. coli, S. aureus, A. flavours* and *A. niger* (Raghavendra *et al*., 2013). Isatin was condensed with diethylenetriamine to synthesize various new Schiff base ligand bis(indoline-2-one) diethylenetriamine 33 (Figure 4). Then various metal Schiff base complexes are prepared & characterized. Anti-microbial activity of the prepared complexes was measured as resistance to anti-microbial drugs against various pathogens. From the study, they found that compared to rest of tested metal complexes, cadmium complex displayed superior anti-bacterial activity (Ddaula *et al*., 2014).

Amani *et al*. synthesized various new l-(arylimino-2-oxo-2,3-dihydro-indol-1-yl)-acetic acid N'-(4-aryl-2-yl)-hydrazides 34 (Figure 4) and characterised by spectral studies. *In-vitro* anti-microbial activities of above analogs were examined by disc diffusion technique against various human pathogenic bacteria and fungi. When compared to reference standard few of tested compounds displayed moderate to good anti-microbial activity (Amani *et al*., 2014). A series of novel N'-[{5-(4-aryl)-1,3-thiazol-2yl} carbohydrazide-methyl]-3(4-arylimino) indol-2-one analogs 35 (Figure 4) were synthesized by Suman *et al*. They synthesized title compounds from 3-(4-arylimino)-2-oxo-1-indole-acetylthiosemicarbazide in the presence of substituted / unsubstituted phenacyl bromides in ethanol. They evaluated the synthesized compounds for its anti-microbial potency against several pathogenic strains of micro-organisms by *in-vitro* method (Suman *et al*., 2014). (3)-3-Hydrazinylidine-1,3-dihydro-2h-benzo(g)indol-2-one was reacted with various thiadiazole analogues to synthesise some pharmacologically active heterocyclic compounds 36 (Figure 4) by Vasanthi *et al*. The prepared derivatives are examined for its anti-microbial activity at two dose level against various pathogenic bacteria and fungi. Entire new indole-2,3-dione analogs displayed mild to moderate activity. From the study, they found that at both tested dose levels compound possessing halogen substitution at the para position of aryl ring exhibited higher activity against *B. subtilis* & *E. coli*. In addition, it showed activity against *S. aureus* & *P. vulgaris*. The reason behind the potent activity of halogenated derivatives may be due to its favorable contribution to the inhibitory activity. In general, they found that the presence of substitution at aryl ring favors inhibitory activity (Vasanthi *et al*., 2014).

From 4-aminoantipyrine various new Schiff bases of isatin/substituted isatins 37 (Figure 4) were synthesized and examined for their anti-microbial potency by Gabriela *et al*. In order to assess their anti-microbial potency, the prepared analogs are screened against several micro-organisms *in-vitro*. In addition, using standard ascorbic acid prepared derivatives are also examined for its antioxidant potency. Anti-microbial results revealed that against tested microorganism's entire analogs displayed consistent potency. Test analogs also displayed considerable antioxidant activity (GabrielaDdaula *et al*., 2014). Mayuri *et al*., synthesized novel 2-(4-substituted phenyl)-1,10b-dihydrospiro[benzo[*E*] pyrazolo[1,5-*C*][1,3]oxazine-5,3'-indolin]-2'-ones 38 (Figure 4) by multi-step reactions from indole-2,3-dione & 2-(3-(4-substituted phenyl)-4, 5-dihydro-1*H*-pyrazole-5-yl)phenol, various 4-substituted acetophenones and *o*-

hydroxy benzaldehyde. They synthesized the spiro analogs by both conventional and microwave method. Increased % yields and less reaction time are the advantages of the microwave-assisted method, contrary to the conventional method. Entire test analogs are tested for anti-microbial activities. Few of test analogs displayed fine anti-microbial potency at 50 and 250 µg/ml concentrations (Mayuri *et al*., 2014).

Several new 3-phencyclidine-2-indolinone derivatives 39 (Figure 4) were synthesised by Ramu *et al*., from isatin and various acetophenone derivatives. Latter they synthesised novel spirooxindole derivatives by reacting 3-phencyclidine-2-indolinone derivatives with acenaphthenequinone and sarcosine. The biological activity of synthesised spiroheterocycles was tested against various micro-organisms & found the remarkable potency of tested analogues. One of the test compounds showed appreciable activity against the bacteria *Salmonella spp*. & against fungi *Penicillium spp* & *A. niger*. Spirooxindole and an aromatic ring are the major contributions for the noteworthy activity of spiro analogs (Ramu *et al*., 2014). Substituted isatins were condensed with phosphorylhydrazines by Leticia *et al*., to synthesise sixteen dialkylphosphorylhydrazones 40 (Figure 4). Against *R. solani* & *F. oxysporum* fungicidal activities of these compounds were evaluated and found that a few derivatives inhibited the growth of *R. solani* (43 %) & *F. oxysporum* (51 %) (Laticia *et al*., 2014).

Various new isatin-3-(4`-hydroxy) benzoylhydrazone 41 (Figure 4) is prepared by carbonyl amine condensation of 4-hydroxybenzoylhydrazide with isatin and characterised by Sandra *et al*. The derivatives were screened for anti-microbial activity against *K. pneumoniae, P. aeruginosa, S. marcescens, S. aureus, E. faecalis* & *C. albicans*. At 25-50 µg/cm^3 concentration against the *E. faecalis* & *C. albicans* test analogs displayed better activity (Sandra *et al*., 2015). By *N*-alkylation method Reena *et al*. synthesised two compounds 42a & 42b (Figure 5) and evaluated its biological activities. Out of that one compound shows good anti-bacterial and anti-fungal potency plus extremely minute antioxidant activity but another one displayed activity only towards negative strains of bacteria. The potent activity of one analogue is owing to aromatic ring present in test derivatives (Reena *et al*., 2015).

Using acid chloride method nicotinic acid was coupled with some L-amino acid methyl esters including phenylalanine, valine and leucine by coupling reaction. To get corresponding hydrazides, the above compound was treated with hydrazine hydrate. Finally obtained hydrazides were treated with indoline-2,3-dione to get Schiff bases 43 (Figure 5) using microwave technology. Agar diffusion test is employed to screen *in-vitro* anti-microbial potency of prepared derivatives against *B. subtilis*, *S. aureus*, *E. coli*, *C. albicans* & *A. niger*. The compounds showed a strong anti-microbial inhibitory activity. Majority of the tested analogs displayed a wide spectrum of activities (MIC: 50 - 500 μg/ml). A compound having unsubstituted isatin and phenylalanine as the bridge was found to be the most potent compound against all strains (MIC: 50 μg/ml) (Ahmed *et al*., 2015). They are using microwave irradiation Ayman *et al*., synthesised novel 3-hydrazino, 3-thiosemicarbazide, and 3-amino carboxylic acid derivatives of isatin 44a & 44b (Figure 5). Against selected bacteria and fungi, the prepared derivatives are examined for anti-microbial activity. *N*-alkyl isatin derivatives were found to be possessing a different range of anti-microbial activity.

Moreover, 3-thiosemicarbazone and 3-hydrazino isatin analogues were found to be biologically inactive, and the active compounds of these series also displayed feeble to reasonable activity mainly against Gram "+"ve bacteria. Against all tested bacteria and fungi pathogens, the 3-imino isatin carboxylic acid analogs displayed good anti-microbial activity. From the study, it was found that the potent activity was exhibited by the compounds possessing bromine or chlorine in the isatin moiety (Ayman *et al*., 2015).

Mixed ligand complexes of four different metals with a range of tridentate uninegative ligands derived from isatin monohydrazone with 8-hydroxyquinoline (heterocyclic nitrogen base) and substituted salicylaldehyde / 2-hydroxynapthaldehyde 45 (Figure 5) was synthesized by Jai *et al*. From various characterizations it was found that quinoline ring nitrogen attached to metal ion by normal or distorted octahedral geometry. Against several pathogenic bacteria and fungi, entire compounds (ligands & its complexes) was tested *in-vitro* at four different concentrations. When compared against free ligands, mixed complexes displayed potent anti-microbial activity. Out of various tested analogs, the most potent one was found to be copper(II) Cu(L_{IV})(Q) ·H_2O complex **(**Jai *et al*., 2015). In the first time Xu *et al*. reported the significant Gram-positive anti-bacterial activity of isatin-β-thiosemicarbazones 46 (Figure 5). Twenty out of fifty-one title compounds displayed 0.78 mg/L MIC against a clinical isolated MRSA strain. In addition, another twelve new derivatives showed 0.39 mg/L MIC. At similar levels, in addition, this derivative inhibited *E. faecalis* & VRE. The above results indicated that compared to vancomycin, isatin-β-thiosemicarbazones might possess a different mode of action. Further, they established CoMFA (compar-

ative field analysis) models for these isatin-β-thiosemicarbazones, to understand the SAR with the aim of design novel derivatives from electrostatic & steric contributions (Xu *et al*., 2015).

Nguyen *et al*., studied the preparation of various novel isatin *N*-(2,3,4,6-tetra-*O*-acetyl-β-d-glucopyranosyl) thiosemicarbazones 47 (Figure 5) differing in nature of substituent present at C-1, C-5 and C-7 positions of isatin ring. The title compounds were prepared by treating corresponding isatins with *N*-(2,3,4,6-tetra-*O*-acetyl-β-d-glucopyranosyl)thiosemicarbazide. *In-vitro* anti-microbial and *in-vivo* antioxidant potency of compounds were also evaluated. For Gram-positive bacteria the MIC of title compounds was found to be 1.56–6.25 μM; whereas for Gram "-"ve bacteria it is 12.5 μM. For fungi *Saccharomyces cerevisiae*, *Fusarium oxysporum*, *Aspergillus niger* the MIC were found to be 6.25–12.5 μM, 6.25–12.5 μM and 3.12–12.5 μM, respectively. Zhi *et al*., designed and characterized 7 isatin derivatives 48 (Figure 5). In molecular recognition, intermolecular and intramolecular hydrogen bonds and structural stabilization made these analogs as perfect examples (Within a single molecule possessing self-complementary donor and acceptor units). Anti-microbial activities of these compounds were also studied. To find out its possible binding models docking simulations were performed in FtsZ active site. Results revealed the anti-bacterial potency of entire test compounds. Against *Staphylococcus aureus* the IC_{50} values of two potent compounds were found to be 0.03 and 0.05 μmol/ml. Against *E. coli* and *P. aeruginosa*, another one derivatives displayed anti-bacterial activity with 0.672 and 0.830 μmol/mL IC_{50}, respectively (Zhi *et al*., 2016).

Various bioactive amines/hydrazides are reacted with several 5-substituted isatins to synthesize a number of Schiff bases 49 (Figure 5). By microtiter plate test against various bacterial strains, the antibacterial potency of the test derivatives is screened. Four of the test analogs were found to be most potent with MIC of 6.25 μg/ml against *Pseudomonas aeruginosa*. A broader spectrum of antibacterial activity exhibited by compounds possessing (thio)urea-based Schiff bases. Moreover, any detectable anti-bacterial activity was shown by compounds having high lipophilicity. From the study, they found that hydantoin derivatives of *N*-benzylisatins exhibited some anti-bacterial activity (Kamaleddin *et al*., 2016).

Mini *et al*. synthesized various novel isatin Schiff bases 50 (Figure 5) from thiosemicarbazide and isatin. In addition, they also synthesized metal complex of the above derivatives and characterized by several techniques. From the study, they found that Copper (II) ion is coordinated with Schiff base by tetradentate manner. Stoichiometry was found to be 1:1 (ligand: metal) from the elemental analysis suggestion. In the dx2-y2 orbital presence of unpaired electron are found from calculated g values of copper(II) complex. Both the Cu(II) complex and the ligand crystalline nature was revealed by XRD study. Against the selected micro-organisms both synthesised Copper(II) complex and ligand exhibited effective anti-microbial activity (Mini *et al*., 2016). Redkin *et al*. studied the interaction of 1,6-bismaleimidohexane, α-amino acids and isatins. They successfully developed thirty-six new hexamethylene-N, N'-bis-derivatives of 3a′,6a′-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[3,4-*c*] pyrrole]-2,4',6'(1*H*,3'*H*,5'*H*)-trione 51 (Figure 5) using 1,3- dipolar cycloaddition. Enhanced percentage yields, more atom economy & gentle reaction conditions are the advantages of this method. In alcoholic-water media, boiling is the most suitable conditions for this reaction. Against *Micrococcaceae* family, test compounds displayed a weak selective anti-microbial activity (Redkin *et al*., 2017).

Six novel thiosemicarbazones and nine novel semicarbazones of isatin analogues 52 (Figure 6) were synthesised (two steps) and reported by Masoumeh *et al*. In DMF using different alkyl halides, isatin ring was alkylated in the presence of Ca_2H (Step 1). Thiosemicarbazide or semicarbazide was treated with above-alkylated isatin in ethanol to synthesise corresponding thiosemicarbazones and semicarbazones, respectively. By broth microdilution method anti-microbial potency of these compounds was examined. In addition, against MDA-231iv and MCF-7iii breast cancer cell lines cytotoxicity of the synthesised derivatives was also examined using MTT methods. Test compounds exhibited notable anti-microbial potency with moderate cytotoxicity (Masoumeh *et al*., 2017). Imesatin was condensed with various aromatic aldehydes by Rani *et al*., to synthesise various novel Mannich and Schiff bases of isatin analogues 53 (Figure 6). *p*-Phenylene diamine was treated with isatin to synthesise imesatin. Piperazine and formaldehyde were treated with high Schiff base to obtain Mannich base. By cup plate method these analogues were tested for its anti-microbial potency against *P. vulgaris, K. pneumoniae, B. cereus, B. subtilis* & *A. niger*. MIC was measured using tube dilution test. Test analogues MIC was found to be between 62.5 and 125 μg/ml (Rani *et al*., 2017).

Different substituted-isatins were reacted with benzofuran-2-carbohydrazide to prepare several new *N*′-(5 or 7 substituted-2-oxoindolin-3-ylidene) benzofuran-2-carbohydrazides 54 (Figure 6) as potent microbial agent**s**. These novel compounds were tested for its anti-microbial potency. Against *Pseudomonas vulgaris* and *Escherichia coli,*

one of the test compounds displayed potent anti-bacterial activity. When compared with standards another one analogue displayed potent activity against *P. vulgaris, E. coli* and *Bacillus subtilis*. The above potent compounds also exhibited significant antifungal activity against *Aspergillus niger* when compared to fluconazole (Vinod *et al*., 2017). By one pot three component condensation highly substituted spiro[indolo-3,10′-indeno[1,2-*b*] quinolin]-2,4,11′-triones 55 (Figure 6) were synthesised from indane-1,3-dione, enaminones and isatin using ceric ammonium nitrate as a catalyst. Operational simplicity, high yield and lesser reaction time are the several advantages of this method. Against six microbial strains, these compounds were tested for anti-microbial activity. Results revealed the good anti-microbial activity of some test analogues (Kalawati *et al*., 2017).

5-Chloroisatin-3-hydrazone 56 (Figure 6) is prepared & reported by Milica *et al*. In different concentrations these 5-chloroisatin-3-hydrazones were tested against *P. vulgaris, P. aeruginosa, S. aureus, E. faecalis* & *E. coli* to determine its antibacterial potency. Entire tested concentrations 5-chloroisatin-3-hydrazone showed potent activity against *Proteus vulgaris* (Zone of inhibition: 25 mm at 500 µg/cm3). At different time intervals by UV-B and UV-C cumulatively irradiation tests photolytic stability of prepared compounds was estimated. Enhance in the rate of degradation was observed with raised incoming photons energy. Hence stability of test derivatives depends on incoming photons energy (Milica *et al*., 2018). Ruo *et al*. studied the preparation & characterisation of 12 novel propylene-tethered ciprofloxacin-isatin hybrids 57 (Figure 6). *In-vitro* anti-microbial activity of entire hybrids was screened against various Gram-positive, Gram-negative and mycobacterial pathogens. In addition, *in-vivo* pharmacokinetic properties, metabolic stability and cytotoxicity in VERO cell line were also examined. Against most of the tested strains, excellent anti-bacterial activities were displayed by mono-isatin-ciprofloxacin hybrids (MIC: ≤0.03-0.5 µg/ml). Against all tested pathogens, the most potent compound was found to be a ciprofloxacin-isatin hybrid which displayed more potent or comparable activity like reference levofloxacin and ciprofloxacin. In addition, the potent hybrids showed low cytotoxicity (CC_{50}: 64 and 256 µg/ml) with acceptable *in-vivo* pharmacokinetic properties and metabolic stability (Ruo *et al*., 2018).

Mahmoud *et al*., designed and synthesised two different series of novel indole-thiazolidinone conjugates 58 (Figure 6) and reports its anti-microbial activity. The indole-thiazolidinone conjugates were tested *in-vitro* against several human pathogens such as *M. tuberculosis*, *E. coli*, *P. aeruginosa, S. aureus*, *C. albicans* & *A. fumigatus*. To assure their safety cytotoxicity of indole-thiazolidinone conjugates was explored towards a panel of WI-38 cells, human lung fibroblast normal cell line and cancer cell lines. Potent compound of the study exhibited wide spectrum activity (MIC: 0.39–0.98 µg/ml for anti-bacterial; 0.49–0.98 µg/ml for anti-fungal). Additionally, it killed mycobacteria *M. aurum* with good therapeutic window inside an infected macrophage model. The potent compound also exhibited potent activity towards resistant bacteria strains such as MRSA (MIC: 3.90 µg/ml) & VRE (MIC: 7.81 µg/ml) (Mahmoud *et al*., 2018). Ayman *et al*. studied the coordination feature of novel N^4-morpholinyl isatin-3-thiosemicarbazone 59 (Figure 6) with various metals. Anti-microbial potency of the freshly prepared thiosemicarbazone ligand & some of its metal complex is screened against *S.s aureus, S. pneumoniae*, *P. aeruginosa*, *E. coli*, *C. albicans* &d *A. fumigatus*. Higher anti-microbial activity was noticed for all metal complexes compared with free thiosemicarbazone. The coordination and chelation of complexes make it as more controlling & potent anti-microbial drugs, as a result obstructing the growth of microorganisms. Compared to Schiff base and its metal complexes copper bromide complex displayed better anti-microbial activity (Ayman *et al*., 2018).

Five macrocyclic compounds 60 (Figure 6) are prepared & characterised by Dileepan *et al*. They investigated the capability of this derivative binding to DNA *in-vitro* by viscosity measurements circular dichroism, fluorescence & UV–Visible spectroscopy. *Via* intercalation, these analogues displayed strong DNA binding affinity. DPPH, OH and NO assays were used to determine the radical scavenging activities of synthesised analogues. These derivatives *in-vitro* arrested the growth of bacteria potentially. (Dileepan *et al*., 2018). Indole-isatin molecular hybrids 61 (Figure 6) were synthesised and characterised by Maha *et al*. Anti-microbial potency of indole-isatin molecular hybrids was tested against various micro-organisms. To perform computational investigations, they selected one compound as a representative example. DFT approach using FT-IR & FT-Raman they studied the vibrational properties of representative analogue. With the target, fungal protein binding mode of representative analogue was predicted using molecular docking (Maha *et al*., 2018).

An experimental and theoretical methodology was used to study the ratios of *E*/*Z* isomers of 16 synthesised 1,3-dihydro-3-(substituted phenylimino)-2*H*-indol-2-ones 62 (Figure 6). Kamlet-Taft equa-

tion was used to study linear solvation energy relationships (LSER). SSP is used to study LFER & analyze substituent effects. Bader's analysis was used to know electron charge density. Effect of a substituent on ICT was estimated using TD-DFT method. Broth microdilution method was used to study the anti-microbial activity. 3D QSAR modelling was employed to show the effect of molecule geometry and substituent effects on anti-microbial activity (Dominik *et al*., 2018).

CONCLUSION

Complication & treatment failures in various infections are due to increased bacterial resistance to several antibiotic drugs which is a significant threat to treat various infections. Consuming more antibiotic is the major reason behind the progress & spread of microbial resistance. Hence it is necessary to develop & discover novel drugs with an enhanced spectrum of activity to overcome the microbial resistance problem. The indole-2,3-dione ring is an important pharmacophore in modern drug discovery. In medicinal research still, the major focus is the preparation of novel isatin analogues. There is still scope for more research work to be done in this field to find a novel agent. The versatility of new generation isatin would represent a fruitful pharmacophore for further development of better medicinal agents. Therefore, this substrate has tremendous scope for the discovery of new, better, safe and more potent anti-microbial agents.

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