ANTIMICROBIAL ACTIVITY OF ISATIN HYBRIDS: A BRIEF REVIEW

Neelima Tripathi[1], Arun Kumar[2*],Kuldeep Singh[3]

Abstract

Antibiotics are undeniably a gift to humanity, since they have prevented the loss of millions of lives due to the elimination of infectious bacteria. This review was based on the antimicrobial activity of Isatin-hybrids through extensive literature survey. Isatin, also called 1H-indol-2,3-dione, is a naturally occurring heterocyclic chemical found in several plants across the globe. The amino acid proline reacts with isatin, another component of coal tar, to produce a blue derivative. It is widely dispersed in the human CNS, peripheral tissues, and bodily fluids, and is known to be a metabolite of tryptophan or epinephrine. Recently, it has been discovered that 5,7-dibromo-N-(p-trifluoromethylbenzyl)- isatin exhibits a selective inhibitory effect against lymphoma and leukemic cancer cell lines compared to freshly separated, nontransformed human peripheral blood lymphocytes. Many researchers have shown that isatin-hybrids are active against various microbes, protozoans, parasites etc. These analogues also demonstrated significant anti-plasmodial action. Thus, it can be concluded that isatin-hybrids have numerous pharmacological potentials in terms of antimicrobial, anticancer, anthelmintic, antimalarial, anti-plasmodial etc. and such moieties are of great interest for promising researches**.**

Keywords: isatin-hybrids, 1H-indol-2,3-dione, anthelmintic, antibacterial, anti-plasmodial.

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INTRODUCTION

Antibiotics are undeniably a gift to humanity, since they have prevented the loss of millions of lives due to the elimination of infectious bacteria [1]. Over the years, many antibiotics have been utilised therapeutically. Antibiotics were heralded as a "wonder medication" in the middle of the 20th century. At the time, there was a hopeful consensus that infectious diseases were declining [2]. It was formerly believed that antibiotics could be used as a silver bullet to eradicate disease by acting only on the bacteria responsible for it. Rapid development of antibiotic resistance is quite worrisome [3]. While antibiotics have been less effective over time, many common infections like pneumonia and gonorrhoea are getting harder to treat, if not impossible, to cure. The antibacterial (antimicrobial) and antiviral activities are entirely related to molecules that kill bacteria and viruses selectively or decrease their rate of development without being harmful to nearby tissues [4].

Isatin, also called 1H-indol-2,3-dione, is a naturally occurring heterocyclic chemical found in several plants across the globe [5]. The amino acid proline reacts with isatin, another component of coal tar, to produce a blue derivative. The biochemical modulator isatin is found in mammalian tissues and the rat brain (mostly in the hippocampus and cerebellum). Although the genotoxic and mutagenic potential of isatin has not been extensively demonstrated or documented in vivo, in vitro research has shown that isatin and its derivatives are particularly efficient against genotoxic and mutagenic illnesses. Tribulin was the original name given to isatin when it was shown to be a selective inhibitor of monoamine oxidase (MAO). Isatin consists of a nitrogen-containing five-membered ring and a six-membered benzene ring. One ring is aromatic and the other is anti-aromatic, but they are on the same plane [6].

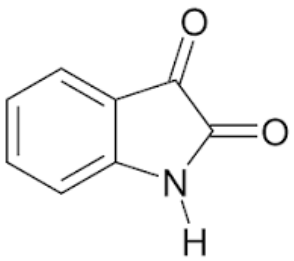

Fig 1. Structure of isatin (IUPAC name: 1H-indole-2,3-dione)

It is widely dispersed in the human CNS, peripheral tissues, and bodily fluids, and is known to be a metabolite of tryptophan or epinephrine. There are several different sources for substituted isatins, including plants like the melosatin alkaloids (methoxy phenyl isatins) isolated from the Caribbean tumour-genic plant Melochia tomentosa and fungi like the 6-(3-Methylbuten-2'-yl) isatin and 5-(3'-Methylbuten-2'-yl) isatin isolated from Streptomyces albus [7].

As a class of physiologically active scaffolds, isatin shows promise due to its human-tolerance12, as well as its utility as a platform for structural modification and derivatization. Many different biological effects can be seen in isatin derivatives, such as anticancer [8], antidepressant [9], antifungal [10], anti-HIV [11], and anti-inflammatory [12] effects. Selective cytotoxicity against gp-overexpressing tumor cells in vitro has recently been studied using isatin-thiosemicarbazones [13]. In 2006, the Food and Drug Administration (FDA) approved SU11248 (Sutent), a 5-fluoro-3-substituted isatin derivative, for the treatment of advanced renal carcinoma and gastrointestinal stromal tumors [14]. Recently, it has been discovered that 5,7-dibromo-N-(p-trifluoromethylbenzyl)- isatin exhibits a selective inhibitory effect against lymphoma and leukemic cancer cell lines compared to freshly separated, nontransformed human peripheral blood lymphocytes [15].

Antimicrobial roles of Isatin hybrids

- Thanhet et al. (2016) were synthesised a series of Isatin-N- (2,3,4,6-tetra-O-acetyl-D-glucopyranosyl) thiosemicarbazones and tested antioxidant and antibacterial efficacy in living organisms and laboratory dishes. MIC values for the produced compounds against Gram-positive bacteria ranged from 1.56-7.25 M, while against Gram-negative bacteria, they ranged from 12.5 M. Among the synthesised thiosemicarbazones, the one containing bromine at the C-5 and C-7 locations of the isatin ring was the most effective against Aspergillus niger (MIC= 3.12 M) and Bacillus subtilis (MIC= 1.56 M), Staphylococcus aureus (MIC= 1.56 M), and Staphylococcus epidermidis (MIC= 1.56 M). Furthermore, **compound 97** showed a MIC of 0.78 M against three clinical MRSA isolates and shown selective cytotoxic effects on cancer (LU-1, HepG2, MCF7, P338, SW480, KB) and normal fibroblast (NIH/3T3) cells [16].
- Lian et al. (2016) developed, synthesised and tested the efficacy of these compounds against bacteria. These ligands were docked into the FtsZ active site using computational models. Antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, and

Staphylococcus aureus was enhanced in the produced compounds. Notably, IC50 values for **compound 98a** against S. aureus were 0.03 and 0.05 mol/mL, suggesting potent antibacterial activity. In vitro, the MIC for **compound 98b** against Escherichia coli and Pseudomonas aeruginosa were 0.672 and 0.830 mol/mL, respectively [17].

- Abo-Ashouret al. (2016) synthesised a library of indole-thiazolidinones and tested their antibacterial and antifungal activities in vitro against a variety of bacteria and fungi, including S. aureus, P. aeruginosa, E. coli, Mycobacterium tuberculosis, Aspergillus fumigatus, and Candida albicans. Utilizing an integrated ex vivo drug screening model, eukaryotic cell-toxicity was used to calculate the selective therapeutic index (SI). The most effective of the synthesised series was compound 99, which showed broad-spectrum antibacterial (MIC: 0.39-0.98 g/mL), antifungal (MIC: 0.49-0.98 g/mL), and anti-TB properties. In addition, **compound 99** showed strong action against the resistant bacterial strains methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococcus (VRE), with a minimal inhibitory concentration (MIC) of 3.90 and 7.81 g/mL, respectively [18].
- Yang et al. (2019) designed a series of isatin-Schiff bases to concurrently block the survival (assistant inhibition) and replication (Gyrase inhibition) activities. With an IC50 of 0.025 M for Gyrase inhibition and an antibacterial efficacy comparable to that of the standard, Novobiocin (IC50 = 0.040 M), **compound 100** emerged as the most promising of the produced compounds. It was also shown that these compounds impede FabH activity (IC50 = 5.20 M) [19].
- Salem et al. (2020) the antibacterial efficacy of a variety of Schiff bases and hydrazones derived from isatin was investigated There were only a few number of produced compounds that showed considerable activity against both Gram-positive and Gram-negative bacteria, and only moderate antifungal activity. Research into the compounds' efficacy against a strain resistant to many antibiotics showed that they were just as effective as Norfloxacin and Tetracycline. The IC50 values for S. aureus DNA gyrase inhibition by **compounds 101a** and **101b** were 18.75 and 19.32 M, respectively, which are comparable to those of Ciprofloxacin (26.43 M) [20].
- Song et al. (2018) a variety of isatin-thiosemicarbazones were produced and tested for their ability to inhibit New Delhi metallo lactmase-1. Nearly all of the produced compounds displayed activity, with IC50 values below 10 M. The most active scaffold in the series was **compound 102**, which had an IC50 of 2.72 M and consisted of a bromo-substituted isatin ring and an m-tolyl ring [21].
- Wang et al. (2020) developed a series of isatin-based amphiphilic compounds that specifically target peptidoglycan glycosyltransferase (PGT). In order to evaluate the correlation between hydrophobicity and antibacterial action,). The inhibitory effects of the synthesised compounds on E. coli PBP1b's lipid II transglycosylation (IC50) were measured in vitro. Methicillin susceptible Staphylococcus aureus (MSSA), methicillin-resistant Staphylococcus aureus (MRSA), and Bacillus subtilis were all killed at 6 g/mL by **compound 103**, while E. coli was killed at 12 g/mL [22].
- Ma et al. (2020) produced and tested a series of di-isatin heteronuclear hybrids with propylene and butylene against bacteria. The majority of the created hybrids were effective against drug-resistant strains, while most were effective against Gram-positive bacteria as well. **Compound 104**, in instance, showed greater action than vancomycin against Gram-negative bacteria, and its inhibitory activity against E. coli DNA gyrase was greater than that of mono-isatin (MIC = 32-512 g/mL) [22].
- Ugaleet al. (2017) produced and evaluated a series of isatin-benzofuran-2-carbohydrazides for anti-bacterial potential. Antibacterial activity was high in all of the synthesised compounds, but **compound 105a, b** stood out as particularly effective, with a MIC = 31.25 g/mL against B. subtilis, E. coli, and P. vulgaris. In addition, 105a and 105b showed significant antifungal activity (MIC = 31.25 g/mL) against A. niger, which was significantly lower for fluconazole [23].
- Kandileet al. (2012) and their antibacterial and antifungal properties against a few harmful bacterial strains were investigated in vitro Recently, benzenesulphonamides based on isoxazolyl-isatin were synthesised by. Research conducted in vitro indicated that **compounds 106a** and **106b** in the synthesised series showed the most promise. The addition of chlorine to the oxindole core at position C-5 made compound 106b (MIC= 5 g/mL) more effective against fungi than 106a (MIC= 15 g/mL). The minimum inhibitory concentration (MIC) for 106b against S. dysenterie and B. cereus was 5 g/mL, which is on par with that of commonly used antibiotics such sulphamethoxazole [24].

- Faraget al. (2012) a panel of Gram-positive and Gram-negative bacteria were used to test the antibacterial effects of a series of 5-(morpholinosulfonyl)isatins and their hybrids with amino-thiazoles. 5-(morpholino-sulfony-l)isatin (107a) was one of the synthesised scaffolds that demonstrated the most activity against the screening microorganisms, with MIC values ranging from 0.007 to 0.49 g/mL. **Compound 107a** showed two times the potency of amphotricin B against A. clavatus (MIC = 0.98 g/mL) and four times the efficacy against A. fumigates (MIC = 0.24 g/mL). The most effective against the examined bacterium strains were the thiazole-linked hybrids, specifically compounds 107b (MIC = 0.03-0.12 g/mL) and 107c (MIC = 0.06-0.49 g/mL) [25].
- Zhanget al. (1015) identified a series of antibacterial isatin-thiosemicarbazones with potent inhibition against the VRE (vancomycin-resistant enterococcus) strain but poor action against a clinically isolated MRSA (methicillin-resistant Staphylococcus aureus) strain. The most promising of the synthesised series was **compound 108a**, which showed minimal inhibitory concentrations (MICs) of 0.78, 1.56, and 0.78 mg/L against methicillin-resistant Staphylococcus aureus, S. aureus, and Bacillus subtilis, respectively. It was found that the activities of the synthesised scaffolds were enhanced by the addition of a halogen atom to the C-7 position of the isatin ring (R1) H on the phenyl ring (R2). Based on this rationale, a new set of 41 isatin-thiosemicarbazones was synthesised and added to the library. Three different strains of MRSA were all killed by 0.39 milligrammes per litre of compound 108b [26].
- Yagnamet al. (2021) a ferrocene-affixed isatin-2,4-thiazolidinedione molecular hybrid coupled via a triazole moiety can be created. An isatin-coupled 2,4-thiazolidinedione moiety was produced by adding a triazole unit to an alkyne in a 1,3-dipolar cycloaddition catalysed by copper. Several Gram-positive and Gram-negative bacteria strains were tested to ensure that all of the novel entities were effective antimicrobials. Against bacterial strains, the MIC values for **compounds 109a, 109b, 109c,** and **109d** were 4 g/mL, whereas against fungal strains, they were 32 g/mL [27].
- Tehraniet al. (2016) employing a microtiter plate assay, we tested the antibacterial efficacy of a variety of N-benzylated isatin-Schiff bases against a panel of Gram-positive and Gram-negative bacterial strains. The compounds in the series **110a** and **110b** that were synthesised showed the highest activity against Pseudomonas aeruginosa (MIC = 6.25 g/ml. The SAR study found that compounds with broad-spectrum antibacterial activity might be found by including the (thio)urea-moiety. Furthermore, appropriate lipophilicity may be important for the activity of the produced compounds, as the compounds with high lipophilicity showed no detectable antibacterial activity [28].

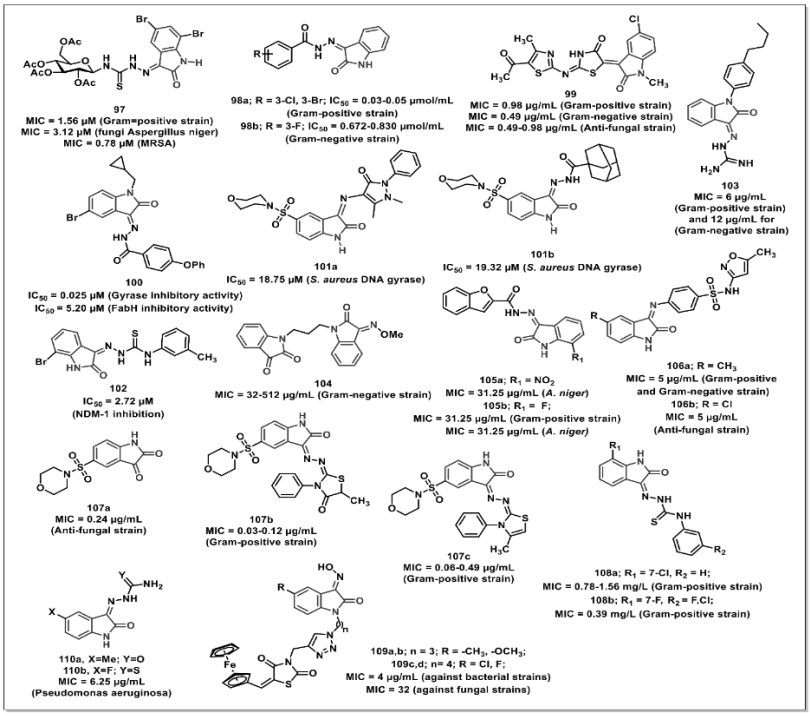

Fig 2. Isatin hybrids (compound 97-110 b) showing antimicrobial potential

- Guo et al. (2018) bactericidal activity against a panel of Gram-positive and Gram-negative pathogens, including drug-resistant bacteria, were evaluated in vitro using synthetic hybrids of 8-methoxy-ciprofloxacin (8-OMe CPFX) and isatin coupled via propylene linker. In tests against Gram-negative bacteria, the produced chemicals performed admirably. Among these, **compound 111** was the most effective hybrid, with MIC values between 0.03 and 8 g/mL, similar to those of the parent 8-OMe CPFX [29].
- Gao et al. (2019) developed a library of amide-triazole-linked moxifloxacin-isatin hybrids and tested them for antibacterial activity in vitro against a collection of Gram-positive, Gram-negative, and drug-resistant bacteria. The hybrids that were produced were quite active, having a MIC of 0.03-28 g/ml. Despite having pharmacokinetic characteristics that were inferior to moxifloxacin, the non-cytotoxic hybrids **compound 112** showed activity comparable to that of moxifloxacin (MIC: 0.03-8 g/ml) [30].

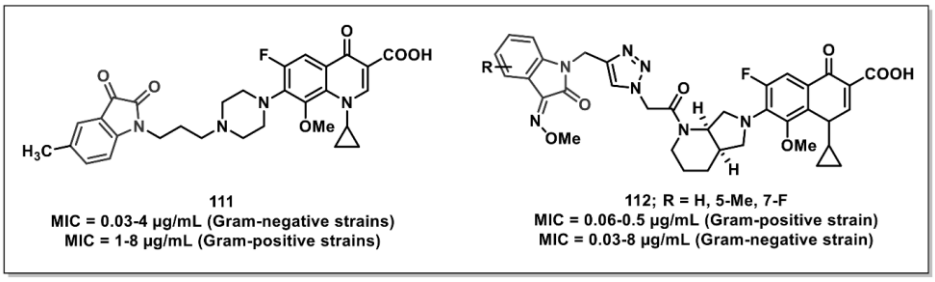

Fig 3. Isatin hybrids (compound 111 & 112) showing antimicrobial potential

- Salem et al. (2020) series of 2-oxospiro[indoline-3,4'-pyran] derivatives were synthesised by using a single pot reaction of substituted indole-2,3-diones, suitable nitriles, and -dicarbonyl compounds, and there in vitro antibacterial, antifungal, and immunomodulatory activities were assessed. Most of the synthetic compounds tested showed strong antimicrobial action, with an MBC value that was competitive with norfloxacin, and were also studied against a larger panel of multidrug-resistant bacteria. Most significantly, the series' most potent chemical, **compound 113**, showed elevated neutrophil intracellular killing activity. Results showed that the minimum inhibitory concentration (MIC) was 0.78 g/mL against S. aureus ATCC 33,591 and 1.95 g/mL against P. aeruginosa ATCC BAA-2111 [31].
- Bhagat et al. (2019) constructed a library of indolindione-coumarin hybrids and tested them for antibacterial activity against Gram-negative (E. coli and S. enterica), Gram-positive (S. aureus and M. smegmatis), and fungal strains (C. albicans, A. mali, Penicillium sp., and F. oxysporum). Antifungal activity against Penicillium sp. and Staphylococcus aureus was demonstrated by compounds 114a and 114b, with MIC values of 30 and 312 g/mL, respectively. SAR analyses showed that the antibacterial activity of the produced hybrids was significantly impacted by the electronic nature of the substituents on the isatin core and the length of the alkyl chain connecting the two pharmacophores. The mechanism of action of **compound 114b** in S. aureus dihydrofolate reductase was determined by molecular docking experiments, which demonstrated Van der Waal's - stacking and H-bonding interactions [32].
- Singh et al. (2019) antibacterial activity against Gram-positive (E. faecalis and S. aureus) and Gram-negative (P. aeruginosa and E. coli) bacterial strains using a range of 1H-1,2,3-triazole-tethered curcumin-coumarin and curcumin-isatin hybrids. When comparing the synthesised hybrids, the one with the lowest MIC (6.25) was hybrid 115. Studies on structure-activity relationships (SAR) determined that the antibacterial activity of curcumin was maximised when it contained an ethyl chain as a spacer, a bromo substituent at the C-5 position of the isatin ring, a -chloro substituent at the C-4 position of ring-A, and a -OCH3 substituent at the C-2 position of ring-B. Molecular modelling studies of **compound 115** at the DHFR active site were also performed to investigate the different binding interactions [33].
- Khatoon et al. (2021) reported the synthesis and in silico and in vitro testing of isatin hydrazones containing coumarin as antileishmanial agents. The confirmation of binding of lead compounds to the target protein was initially determined using molecular docking. High binding affinities were only found for three of the docked compounds. The IC50 values for these compounds against Leishmania tropica promastigotes and

amastigotes ranged from 0.1 to 4.13 mol/L, indicating that they have antileishmanial action. With IC50 values of 0.10 and 0.87 mol/L against L, **compound 116** was shown to be the most effective. promastigote and amastigote stages of the tropica virus [34].

- Freitas et al. (2021) phenyl- and thiosemicarbazone-derived thiazolyl-isatins were produced and tested for their ability to inhibit the growth of Trypanosoma cruzi. The trypomastigote form of T. cruzi was most sensitive to **compounds 117a** (IC50 = 4.12 M) and 117b (1.72 M), both of which had a selectivity index greater than that of benznidazole (BZN). Parasite death was confirmed by scanning electron microscopy (SEM) after treatment with **compound 117b** on T. cruzi trypomastigote cells, which caused morphological and flagellar alterations as well as surface damage. The series' strongest promastigote activity was shown by compounds 117a (IC50 = 7.36 and 7.97 M) and 117b (6.17 and 6.04 M). They also showed greater selectivity than Miltefosine [35].

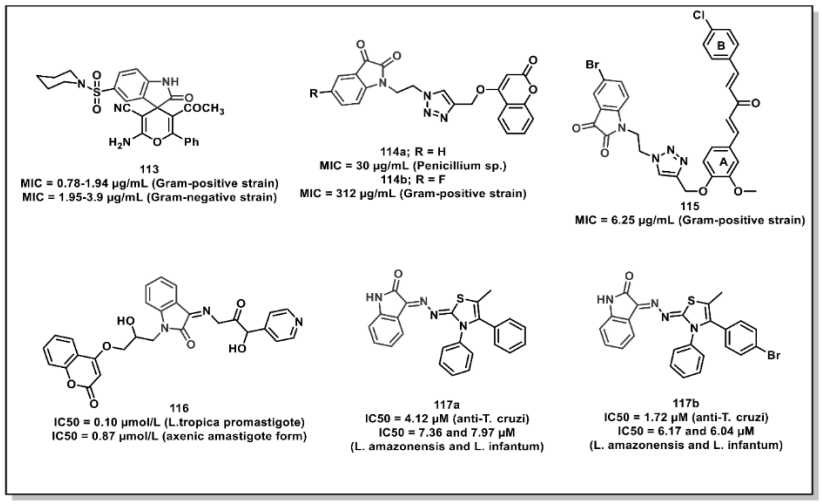

Fig 4. Isatin hybrids (compound 113-117b) showing antimicrobial potential

- Singh et al. (2018) the 1H-1,2,3-triazoletethered isatinferrocene conjugates 12 were synthesised by first base-promoted N-alkylation of isatin with dibromoalkanes at 80 °C, and then the corresponding N **alkylazidoisatins 8** were afforded by treatment with sodium azide (Scheme 2). First, ferrocene **carboxyaldehyde 9** was reduced with NaBH4 in dry tetrahydrofuran to produce **ferrocenylmethanol 10**, which was then O-propargylated to yield the second precursor, **((prop-2-yn-1-yloxy)methyl)ferrocene 11.**

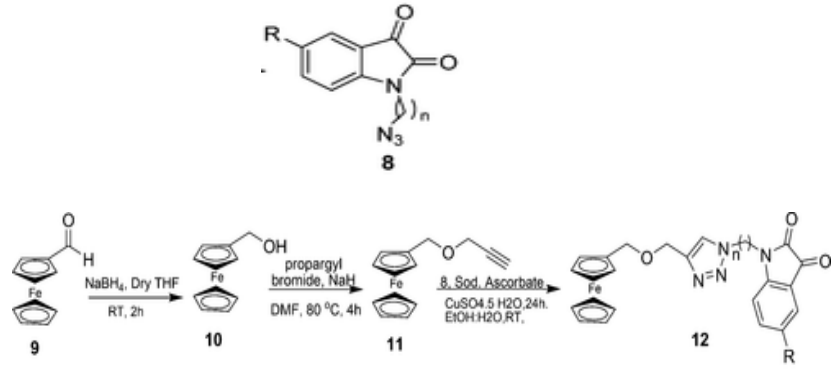

Fig 5. Isatin conjugates (8-12) showing antibacterial potential

Good to exceptional yields of **12** were obtained via the cupromoted azidealkyne cycloaddition of 8 with O-propargylated ferrocene methanol **11**. The crude product was refined using silica gel chromatography (60:120) with a methanol/ chloroform (10:90) mixture as the eluent [36].

These conjugates which were produced, were tested for their ability to inhibit T. vaginalis growth. Most of the newly synthesised isatin-ferrocene conjugates (12a-x) showed 100 percent growth inhibition, and this improvement was mostly

attributable to the inclusion of a 1H1,2,3-triazole ring [37].

- Nisha et al. (2014) developed a library of 4-aminoquinoline-isatin hybrids with different -amino alcohol linkages and tested them for antiplasmodial activity. Both hybrids **86a and 86b** showed antimalarial activity against a CQ-resistant (W2) strain of Plasmodium falciparum and negligible cytotoxicity towards normal cells (IC50 = 11.8 and 13.5 nM, respectively) [38].
- Raj et al. (2013) developed a panel of 7-chloroquinoline-isatin hybrids by synthesis and evaluated their activity against a CQ-resistant W2 strain of Plasmodium falciparum. SAR showed that the activity depends on the type of substituent put into the isatin core and the length of the alkyl chain added as a linker between the two pharmacophores. The C-5 unsubstituted hybrid performed the worst in the anti-plasmodial activity tests among the series of compounds produced. The series was topped by **compound 87**, which had the lowest IC50 (1.21) and the most potent combination of propyl chain as spacer and chloro substituent at the C-5 position of the isatin core [39].

It was shown that the anti-plasmodial activity was dependent on the length of the alkyl chain but was unaffected by the nature of the substituent at the C-5 position of the isatin or indole ring. When tested against a CQ-resistant strain of P. falciparum, the IC50 of the most powerful hybrid in the synthesised series, **88** was 69 nM [40].

- Kumar et al. (2020) 7-chloroquinoline-based hybrids with isatins/indoles/nitroimidazoles produced by Cupromoted click reaction were synthesised and evaluated for anti-plasmodial and cytotoxic activity. More potent anti-plasmodial effects were seen in the hybrids of the synthesised series with shorter alkyl chain lengths (ethyl/butyl as spacer) as opposed to those with longer chain lengths (hexyl/octyl as spacer). The most promising hybrid **90** in the synthesised series, had an IC50 of 0.33 M on the evaluated strain [41].

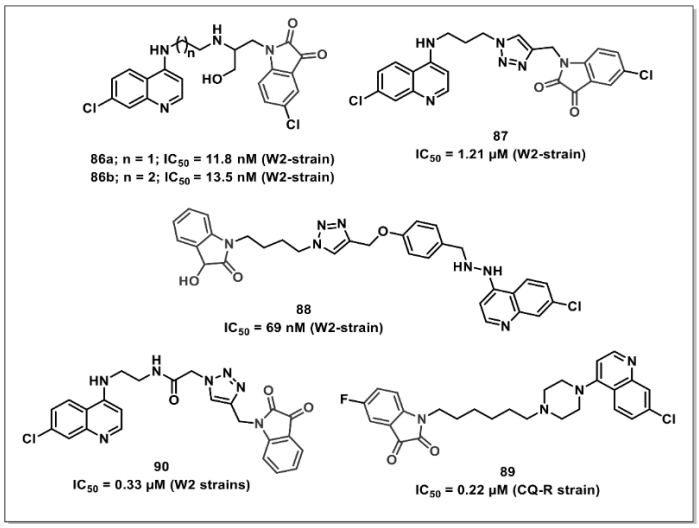

Fig 6. Isatin-hybrids (compounds 86a-89) showing antibacterial potential

- Hans et al. (2011) synthesized the tetracyclic bi-products with enhanced anti-plasmodial potential were discovered when a series of thiolactone-isatin hybrids. Through SAR analysis, the most effective compound in the series against the CQ-resistant (W2) strain of P. falciparum was determined to be **compound 94**, with an IC50 of 6.92 M [42].
- Kumar et al. (2014) Utilizing a Cu-promoted click process, we synthesised a series of 1H-1,2,3-triazole-tethered isatin-ferrocene hybrids and tested their anti-plasmodial activity against the P. falciparum 3D7 and W2 strains. The least cytotoxic and most effective of the series was hybrid **95**, which included the best mix of halogen substituents at the C-5 position of the isatin ring and a propyl chain as spacer (IC50 values of 3.76 and 5.97 M against the 3D7 and W2 strains, respectively) [43].
- Gaurav and Manish, (2018) L-proline was used as a catalyst in a three-component reaction involving substituted isatin, enaminones, and active methylene, which resulted in a variety of functionalized spiro-indolinones containing 1,2,4-triazolo [1,5-a] quinolones. The antibacterial, anti-tuberculous, and anti-plasmodial activity of the produced compounds were tested in vitro. When tested against P. falciparum,

the synthesised scaffolds showed IC50 values between 0.122 and 0.454 M. The synthesised scaffold **96** had an IC50 of 0.122 M, which was similar to CQ [44].

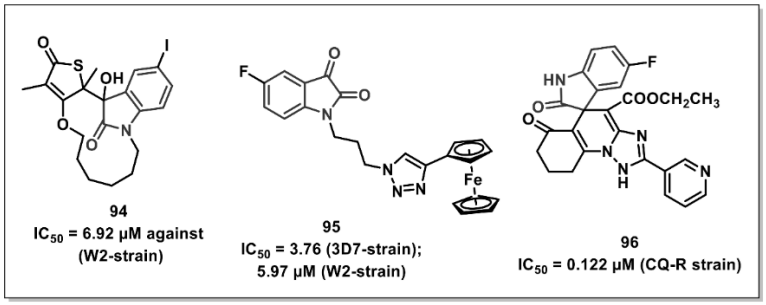

Fig 7. Isatin-hybrids (compounds 94-96) showed antimicrobial potential

- Liu et al. (2022) One of the leading causes of patient morbidity and mortality globally is bacterial infections, which can trigger a wide spectrum of host immunological diseases that ultimately result in local and systemic tissue destruction. Since resistance mechanisms are constantly being refined by bacteria, there is a pressing need for new antibacterial drugs. Since distinct pharmacophores in the hybrid compounds could control several targets and have synergistic effects, hybridization is among the most promising strategies in the creation of novel antibacterial medications with the ability to overcome drug resistance. Because of its widespread occurrence in nature, isatin has the potential to inhibit bacterial growth by interacting with a wide variety of enzymes, proteins, and receptors. The combination of isatin pharmacophores with those of other antibacterial pharmacophores in a single molecule has the potential to yield novel antibacterial candidates with broad-spectrum activity against a wide range of pathogens, including those that have developed resistance to existing antimicrobials [45].

CONCLUSION

Hybrid isatin-pharmacophore compounds may help reduce the prevalence of drug resistance while also delivering novel functional entities with improved safety profiles and various modes of action. The addition of isatin to isoniazid has not only increased the lipophilicity and activity of the hybrids, but has also reduced the occurrence of resistance in the treatment of mycobacteria. Hybrids with an isatin core and a quinoline core were more effective than CQ alone against CQ-resistant strains of P. falciparum.

Thus, it can be concluded that isatin-hybrids have numerous pharmacological potentials in terms of antimicrobial, anticancer, anthelmintic, antimalarial, anti-plasmodial etc. and such moieties are of great interest for promising researches**.**

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Nil.

CONFLICT OF INTEREST

None conflict of interest was declared by the authors.

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