Asian Journal of Chemistry; Vol. 35, No. 4 (2023), 815-827

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.27632

REVIEW

Antibacterial Potentiality of Isatin-Containing Hybrid Derivatives

SUVAIV[1], KULDEEP SINGH[1,*], PRAVEEN KUMAR[2], SYED MISBAHUL HASAN[1], SHOM PRAKASH KUSHWAHA[1], ARUN KUMAR[1], KHATIB SAYEED ISMAIL[3], SAMAR MUJEEB[1], SHUBHAM KUMAR MAURYA[1] and SYED MEHDI HASAN ZAIDI[1]

[1]Faculty of Pharmacy, Integral University Lucknow-226026, India
[2]Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai-206130, India
[3]Department of Biology, College of Science, Jazan University, Jazan, Kingdom of Saudi Arabia

*Corresponding author: E-mail: kuldeep@iul.ac.in

Received: 15 February 2023; *Accepted*: 17 March 2023; *Published online*: 30 March 2023; AJC-21177

Antibiotics are critical in the management of a variety of bacterial infections, however, repeated infections produced by relentless bacteria are obstructing effective infection treatment and it is the most significant and vexing problem at the moment. Medicinal chemists face a difficult problem in developing appropriate lead compounds for various diseases, isatin and its hybrids would be one of them due to its versatility in many medications and its derivatives exhibit an extensive variety of structural and mechanistic properties. This review looks at the isatin hybrids that have probable antibacterial action. The structure-activity relationship (SAR) and the way of producing action are also examined in order to locate the course for the intent and expansion of isatin hybrids by means of increased efficacy, reduced toxicity and good pharmacokinetic profiles. Based on the findings, it can be inferred that 3-hydrazone, imine, spiro, oxindole, guanidino and N-alkyl, aryl, acyl substituted isatin hybrids with electronegative groups on other heterocycles have improved bactericidal activity. Furthermore, the antibacterial activity of isatin is dependent on the binding linkage, such as amide (NHCO), carbonyl (CO) or other hetero atom-containing linkers that have improved antibacterial activity. This review gives an idea and scope for the synthesis of novel isatin-containing heterocyclics with the goal of having potent bactericidal activity.

Keywords: Isatin, Antibacterial, Hybrid derivatives, SAR, Gram-positive, Gram-negative.

INTRODUCTION

Various Gram-positive and negative bacterial strains are amongst the most common and causative organisms for a variety of infectious diseases and these are found to be resistant to most of the existing antibiotics [1,2]. Bacterial strains which cause a variety of infectious diseases such as lower respiratory tract infection (LRT), urinary tract infection (UTI), intra-abdominal and skin soft tissue infections (SST) are the most common and causative organisms are found to be resistant to existing antibiotics [3-5]. The recurrent and unfortunate use of antibiotics responsible for the current status of antibiotic resistance leads to decreased effectiveness of empiric antimicrobial therapy [6-9]. The seriousness of the problem can be estimated by the latest report of the new Global Research on Antimicrobial Resistance (GRAM), which recorded deaths of people directly associated with antimicrobial resistance per year [10,11]. Resulting, drug-challenging bacteria presented a severe risk to public health, necessitating the discovery of new antimicrobial drugs that are both effective and unique [12-15].

Indole derivative, isatin (1*H*-indole-2,3-dione) having keto groups (at positions 2 and 3), the pyrrole nucleus is fused with benzene ring in the isatin ring system. Isatin was first synthesized in 1841 from the oxidation of indigo with nitric acid and chromic acids [16-18]. Many plants, including *Isatis tinctoria*, *Calanthe discolour* and *Couroupita guianensis*, contain the chemical, plants also contain substituted isatins, such as *Melochia tomentosa's* melosatin alkaloids (methoxy phenylpentyl isatins) [19-21]. Isatin is a unique scaffold with a broad array of therapeutical features [22], including antitumor, antiangiogenic [23], antiviral [24-26], antibacterial [27], anticonvulsant [28], antifungal [27], antitubercular [29] and anticancer activities [30].

An endogenous compound, isatin is present in humans, it works as a powerful natriuretic peptide receptor antagonist *in*

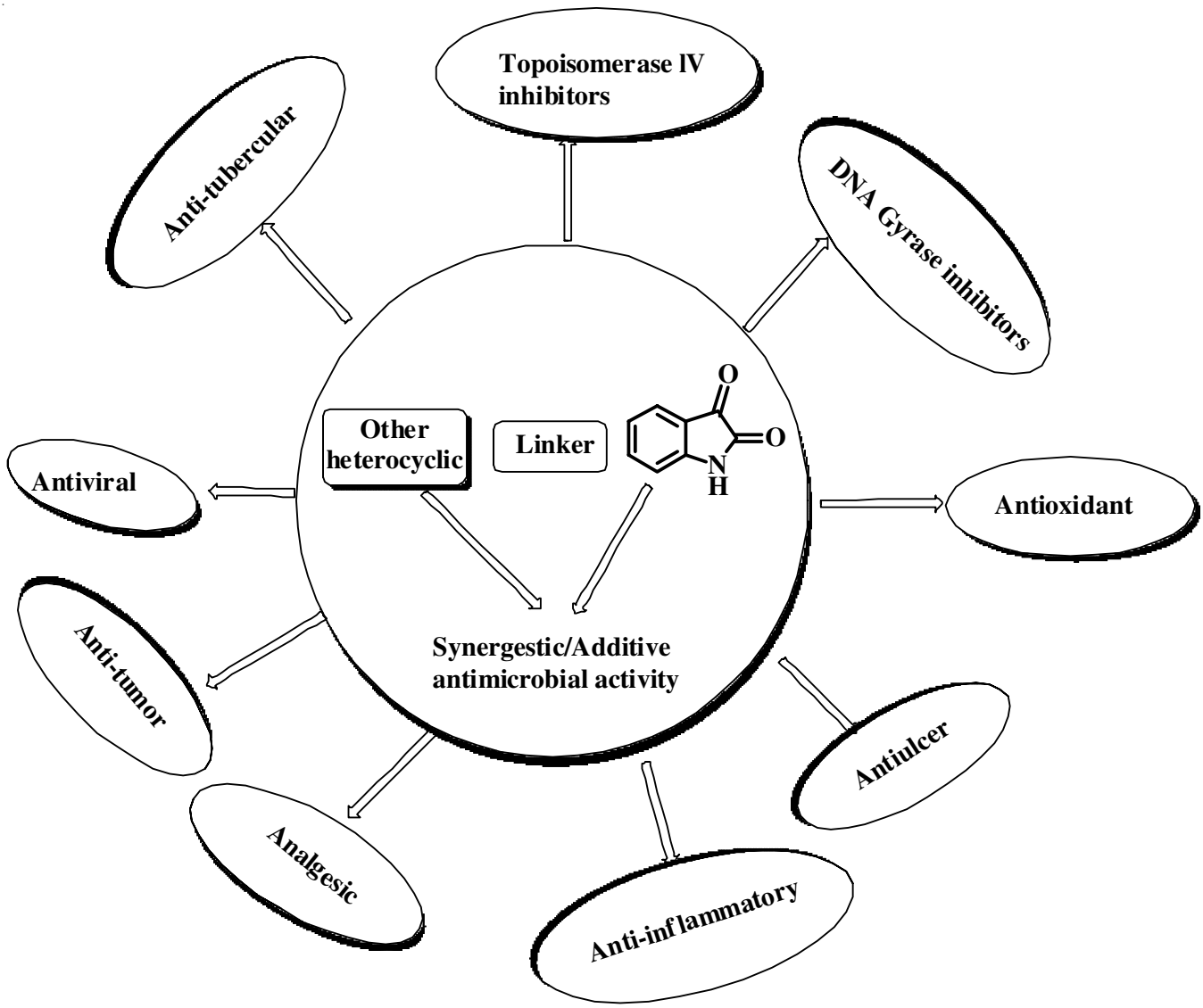


Fig. 1. Biological characteristics of benzimidazole-isatin compounds

vitro and has anxiogenic and anticonvulsant properties. Several researchers have recently investigated the use of isatin in the defense over plant pathogens and as a possible herbicide [31-33]. Isatin nucleus has a wide variety of *in vivo* and *in vitro* pharmacological activity, derivatization of different pharmacologically active compounds has been done by using isatin as an important precursor [34]. The hybrid pharmacophore method is a widely used and valuable method in the development of novel lead compounds [35-43]. This review summarizes the most recent isatin hybrids development. As potent antibacterial candidates, SARs are examined in order to offer guidance towards reasonable development of efficacious candidates (Fig. 1).

Tautomerization: Lactam (A) and lactim (B) are the two tautomeric forms of isatin formed by proton transfer between [N] and [O] atom at 2nd carbon (Fig. 2) [44-46].

Antibacterial potential of some isatin derivatives: Three series of isatin derivatives were synthesized using microwave irradiation (3-hydrazino, 3-thiosemicarbazino and 3-imino carboxylic acid derivatives) with good yields and purities and tested against pathogenic bacterial strains. Usually, *N*-alkyl substituted

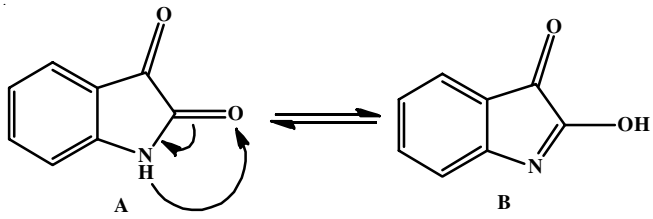


Fig. 2. Tautomerization in isatin

derivatives are found to be physiologically active, whereas a few 3-hydrazino and 3-thio semicarbazino substituted compounds were found to be active against bacterial strains. SAR revealed that the substitution of -Br or -Cl in the isatin moiety, resulting an increase in the antibacterial activity. The maximum activity was found in one derivative (imino isatin carboxylic acid) (Fig. 3) which demonstrated fine to elevated potential [47].

Antibacterial results of compounds containing electron-withdrawing groups showed considerable activity, indicating that halogen atoms engage in the recreation of antimicrobial

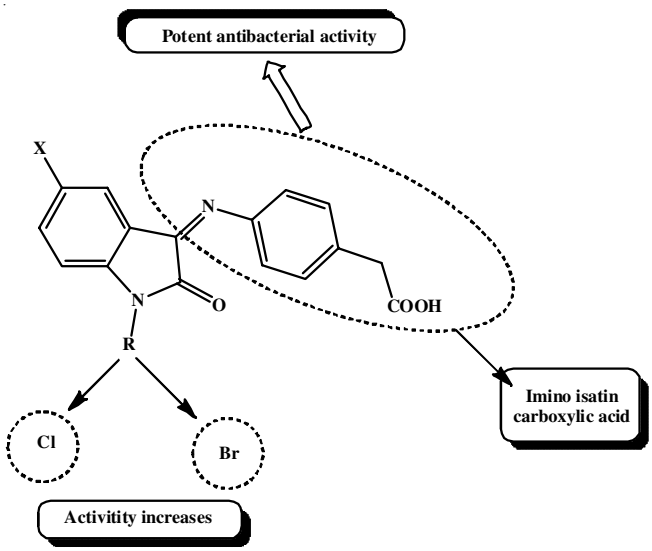
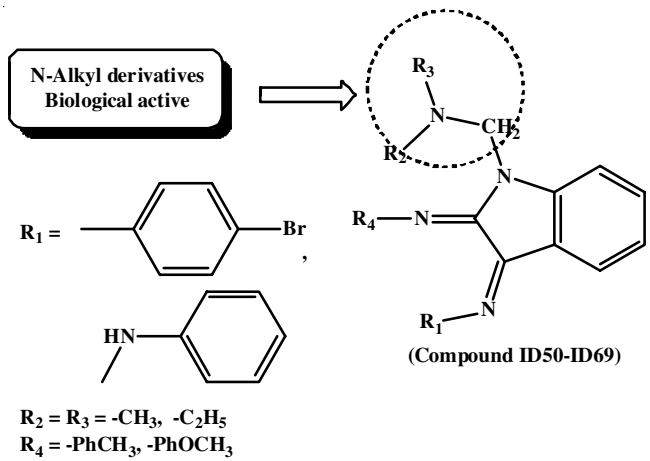


Fig. 3. Imino isatin carboxylic acid derivatives

potential. The synthetic compounds ID54, ID58, ID64 and ID67 are particularly effective against germs (Fig. 4) [48]. A group of researchers, developed novel and potent antibacterial derivatives targeting bacterial peptidoglycan glycosyltransferase and their performance was recorded against (*S. aureus* and *E. coli*) strains, MRSA (Methicillin-resistant *Staphylococcus aureus*). Amongst all compounds **70** and **71** (Fig. 5) were identified as leads for new antibacterial agents [49].



m.f: ID50: $C_{26}H_{27}N_5O_2$ ID51: $C_{25}H_{21}N_4O_4Br$
ID52: $C_{26}H_{27}N_4F$ ID53: $C_{26}H_{27}N_4Br$
ID54: $C_{33}H_{23}N_4Br_2F$ ID55: $C_{21}H_{15}N_3OBr_2$
ID56: $C_{21}H_{13}N_4O_4Br$ ID57: $C_{21}H_{13}N_3O_2Cl_2$
ID58: $C_{21}H_{15}N_3OClF$ ID59: $C_{22}H_{17}N_3Br_2$
ID60: $C_{18}H_{18}N_3Br$ ID61: $C_{21}H_{16}N_3F$
ID62: $C_{34}H_{26}N_4Br_2$ ID63: $C_{28}H_{31}N_5O_2$
ID64: $C_{24}H_{20}N_4O_2BrCl$ ID65: $C_{26}H_{27}N_4Cl$
ID66: $C_{28}H_{31}N_4Br$ ID67: $C_{27}H_{28}N_4BrCl$
ID68: $C_{37}H_{33}N_4Cl$ ID69: $C_{33}H_{23}N_4Br_2Cl$

Fig. 4. N-Alkyl derivatives of isatin

Since isatin derivatives have therapeutic importance against a wide variety of pathogenic microorganisms, scientists are investigating them for better antibacterial action. Isatin derivatives of Schiff and Mannich bases have been found to be

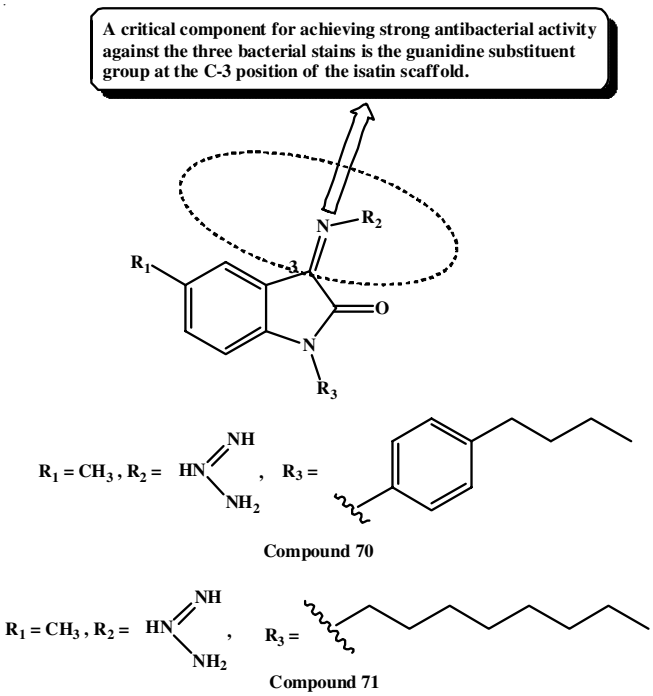


Fig. 5. Compounds differ at R_1, R_2 and R_3 with different substituents

substantial antibacterial agents [50-52]. Compounds **72** and **73** (Fig. 6) were screened for *in vitro* activity against the proposed pathogen. These compounds displayed significant antibacterial potential against tested bacterial strains [53].

Isatin and other heterocyclic hybrids (antibacterial activity): Isatin derivatives thiosemicarbazone and dispiropyrrolidine were found to suppress the growth of *Mycobacterium tuberculosis*. *In vitro* investigations have shown that isatin-3-phenylhydrazone has greater antibacterial activity as compared to control drugs amoxicillin and norfloxacin against tested strains [54-58]. The biological activity of the newly synthesized isatin-3-[N2-(benzimidazole-1-acetyl)]hydrazones (Fig. 7) was found to be outstanding against tested bacterial strains [59].

Antibacterial evaluation of acetylinic isatin hybrids: The functional groups of alkyne are stable under biological conditions due to their inner behaviour and turn into active form when needed [60-63], they are susceptible to functionalization in different pharmacologically active groups [64]. The lipophilicity of the drugs can be increased by inducing alkyne groups, which are necessary for any drug to cross biological membranes [65]. A number of substitution, addition and cycloaddition reactions are documented but still, there is a need for the development of N-substituted isatin linked to alkynes for better pharmacological activity [66,67].

Acetylinic isatin hydrazone derivatives (**74a-74n**) and (acetylinic spiroisatins) (**74o-74q**) have been synthesized and evaluated with an IC_{50} of 1.95 µM against *E. coli*. Compound **74e** was found to be the most effective antibacterial scaffold. SAR study revealed that 3′-N substituted isatin derivatives (Fig. 8) could be effective in combating bacterial infections [68].

Antibacterial potentiality of new isatin Schiff bases coupled to nicotinic acid *via* a specific amino acid linker:

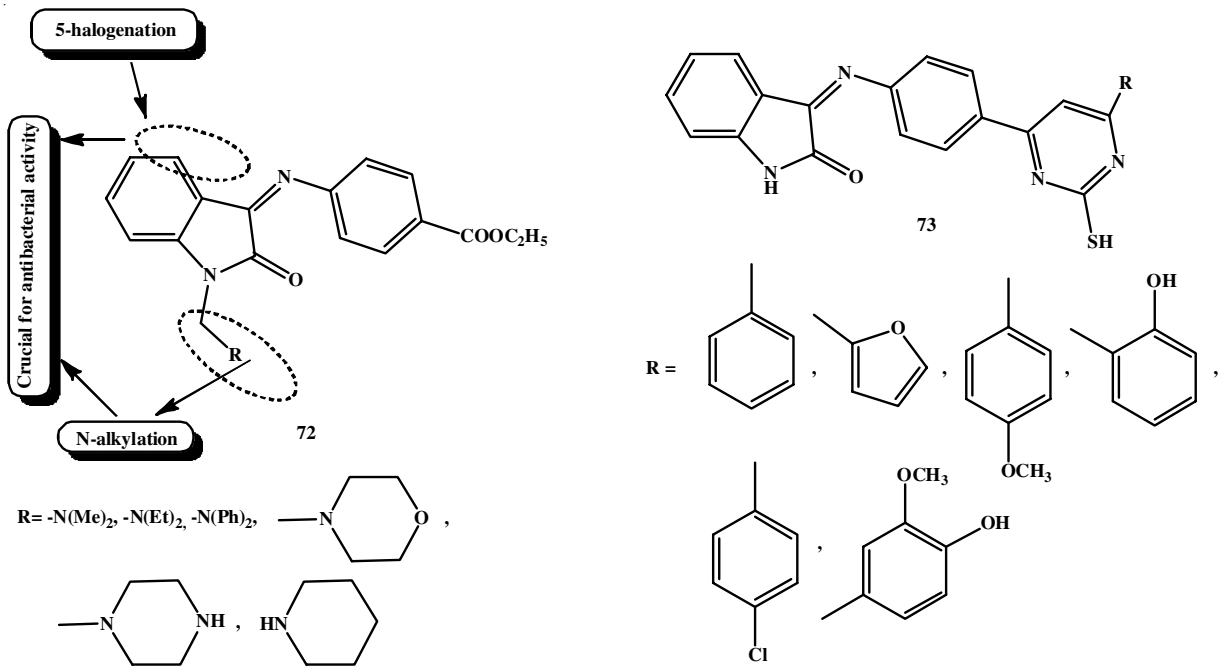


Fig. 6. Isatin derivatives of Schiff and Mannich bases

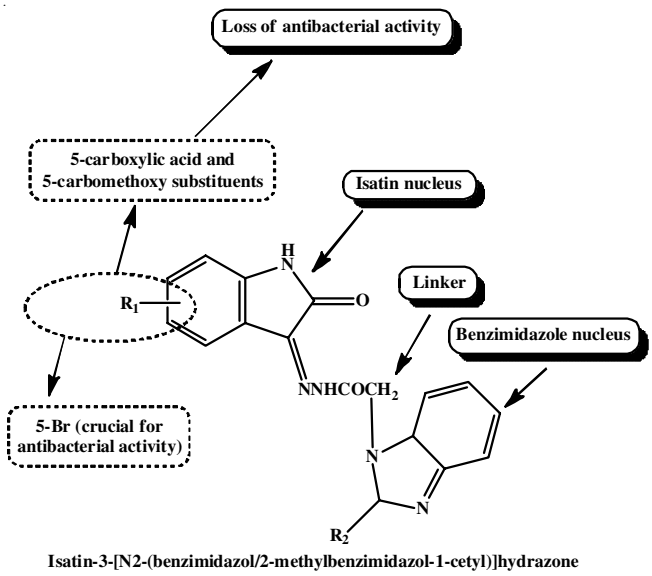


Fig. 7. Isatin-3-[N2-(benzimidazol/2-methylbenzimidazol-1-cetyl)]hydrazone

Nicotinic acid is widely distributed in various plants and animals, used as an energy source [69] and its derivatives have been documented as pharmacologically active [70,71] and employed an as important precursor in the lipids synthesis [72]. Antivirus [73], anti-inflammatory [74], enzymatic peptide [75] and antimicrobial activities of some new derivatives have been reported [76,77].

The fuctional group with (–C=N–) is known as Schiff base. Schiff bases have nitrogen atoms and a double bond in their structure, which makes them more versatile for hydrogen bonding at the active site amino acids of targeted proteins [78-80]. Due to its ability to interact with biological molecules, its derivatives possessed activities such as anti-inflammatory [81-84], analgesic [85], antimicrobial [86,87], anticonvulsant [88], antitubercular [89], anticancer [90,91], antioxidant [92], anthelmintic [93]. The hydrogen bonding of nitrogen atom present in imine coordinates various biological activities [94,95]. Other than this Schiff bases are also used as important linkers in the synthesis of various compounds they act as catalysts [96]. Metal complexes of Schiff base showed the potent inhibitory activity [97].

The antibacterial potential of synthesized Schiff bases isatin linked to nicotinic acid through a specific bridge of amino acid was evaluated *in vitro* (agar diffusion method) [98]. The majority of the test compounds (Fig. 9) had a wide range of activity, with MICs of 50 to 500 µg/mL. With a MIC of 50 µg/mL, derivative **75e** was determined as best derivative against all tested microorganisms [98].

Molecular hybrids based on monocarbonyl curcumin as effective antibacterial agents: Coumarins with benzopyrone structure have a wide range of pharmacological effects, which can interact non-covalently with a number of biological targets [99,100]. Coumarins bind to DNA gyrase's B subunit by inhibiting ATPase activity, bacteria are unable to supercoil DNA [101,102]. Many coumarin-based antibiotics, such as clorobiocin and novobiocin, have already been used in clinics to combat infections, including drug-resistant strains [103,104], coumarins' potential as putative antibiotics has been revealed. Consequently, isatin with coumarin hybrids could lead to the generation of new antibacterial agents.

The antibacterial potential of synthesized, monocarbonyl curcumin-based molecular hybrids was investigated against proposed bacterial strains. Compound **76** (Fig. 10) had the most maximum activity among all the hybrid compounds. The SAR also showed that the inclusion of electronegative atoms in the indole nucleus (at the C-5 position), additionally an alkyl short linker of alkyl groups between the 1,2,3-triazole and isatin motifs, were beneficial to the antibacterial activity [105].

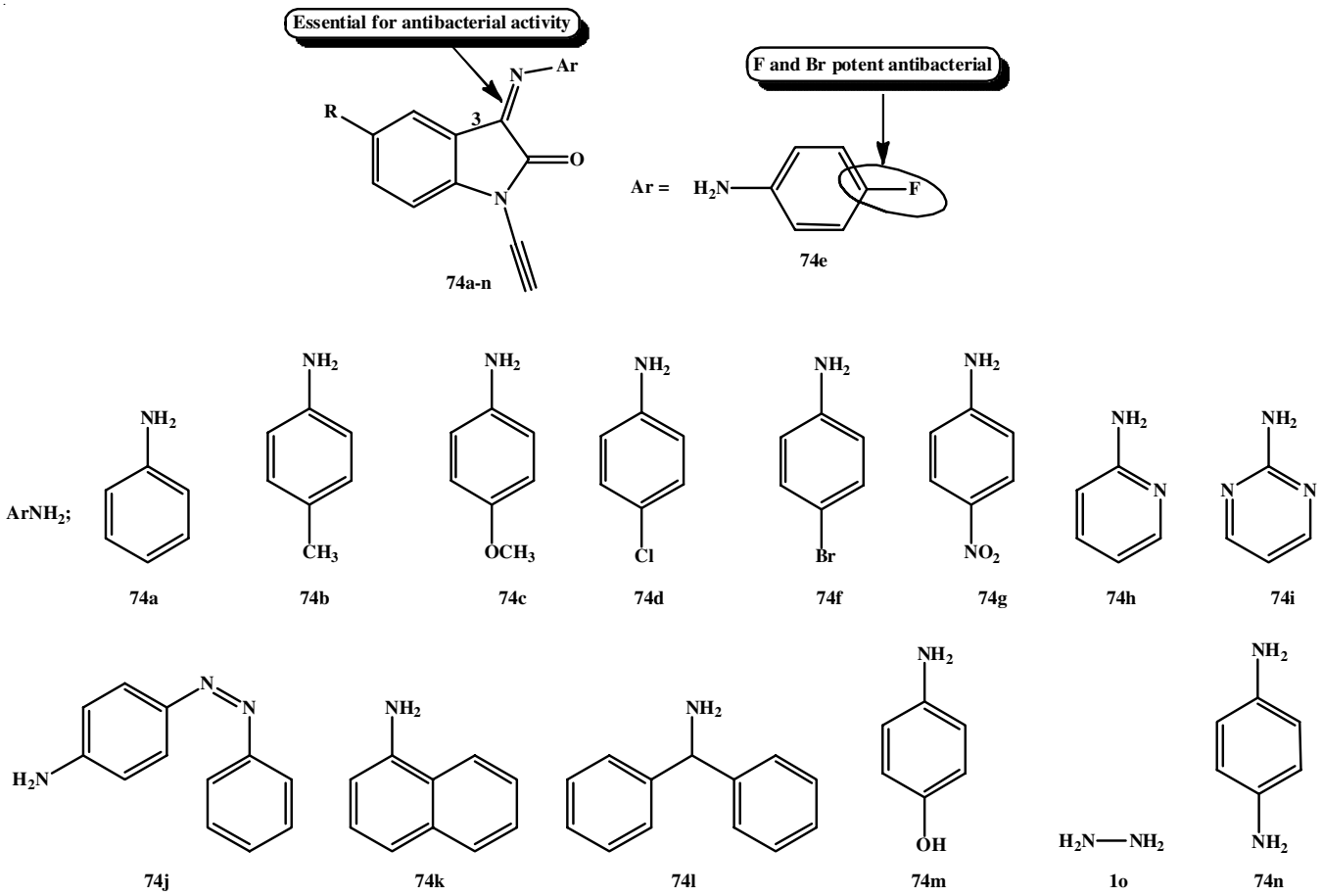


Fig. 8. Acetylinic isatin derivatives

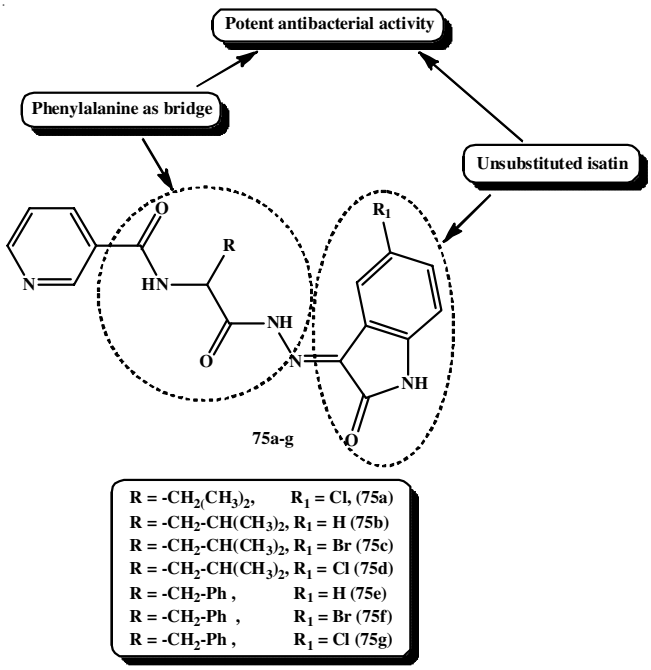


Fig. 9. Hybrids of isatin schiff bases coupled to nicotinic acid

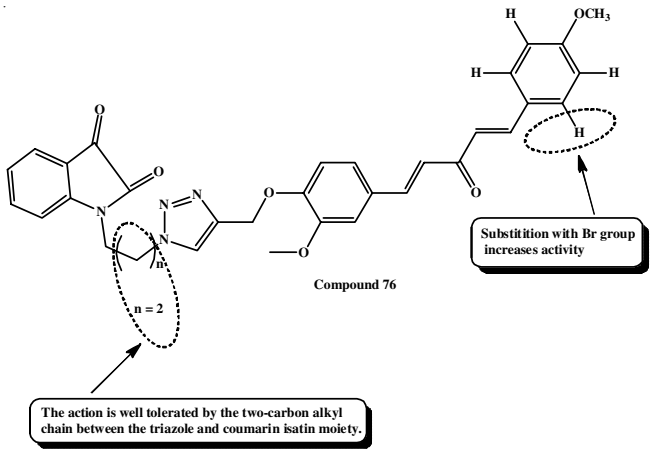


Fig. 10. Monocarbonyl curcumin hybrids with isatin

Isatin-azole hybrids as potent antibacterial agents: The azole nucleus has been demonstrated to be an extraordinarily rich source of therapeutic chemicals [106,107]. Azole derivatives may have antibacterial activity [108-114] through a variety of mechanisms, including inhibition of topoisomerase IV, DNA gyrase and efflux pumps. The combination of isatin/indole and the triazole moiety is a potential technique for developing novel antibacterial compounds [115,116].

Hybrids **77** (MIC: 15.6-38.8 µg/mL) and **78** (MIC: 7.5-35.7 µg/mL) (Fig. 11) have been found to be potent for *E. coli*, *S. epidermidis*, *B. subtilis* and *P. aeruginosa*. The SAR revealed that benzyl ring has increased activity than the phenyl moiety at the N1 position [117,118]. The activity of compound could

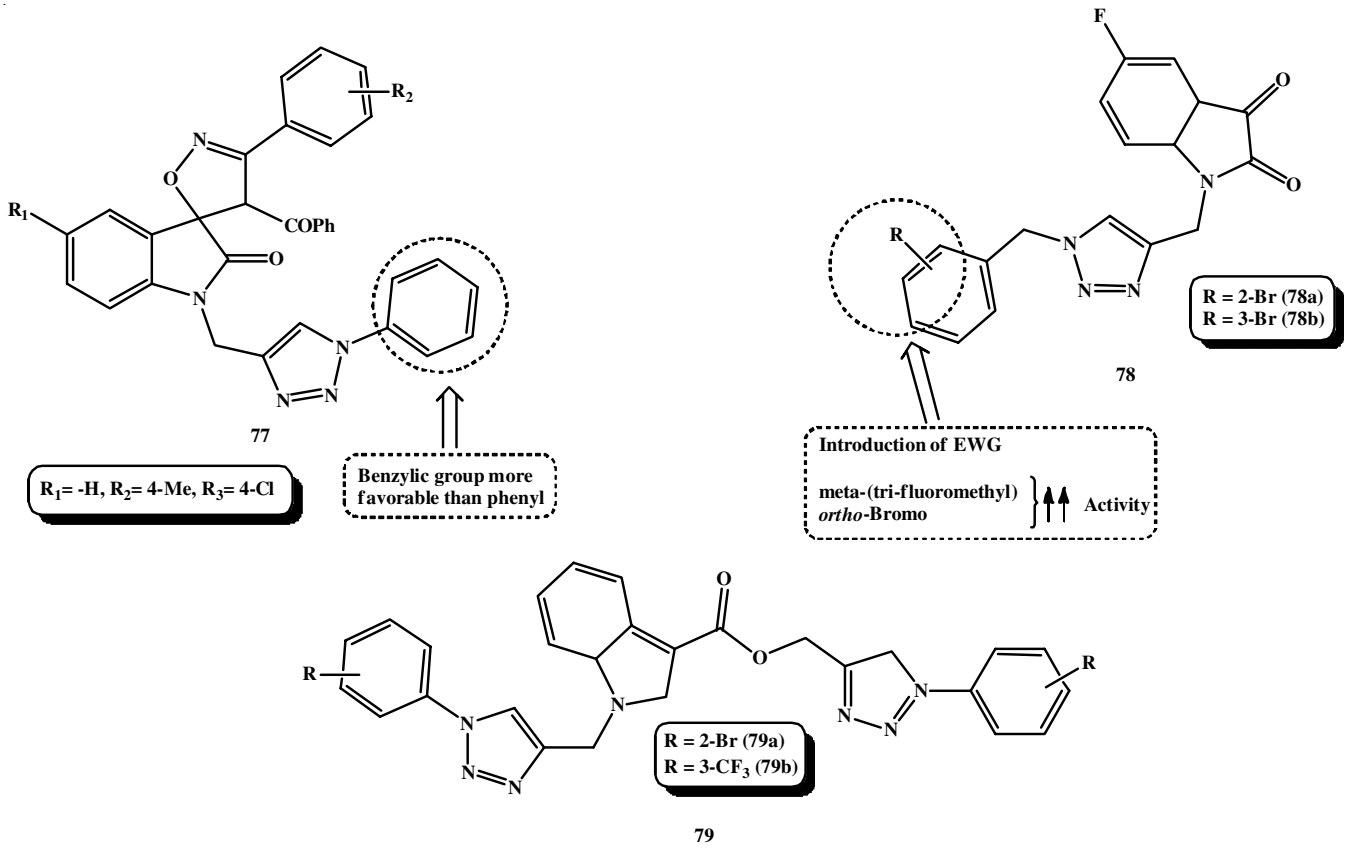


Fig. 11. Hybridization of isatin with azole derivatives

be improved by inserting an electron withdrawing group (EWG) into the phenyl ring. Ciprofloxacin (MIC: 4.7 µg/mL) was used as the reference standard and hybrid **78a** (MIC: 7.5 µg/mL) was found to be significant antibacterial efficacy [119-121]. According to the SAR study, addition of -CF_3 substituent in the phenyl moiety (at *meta*-position) and -Br group (at *ortho*-position) had a significant impact on the activity. Hybrids **78a**, **78b**, **79a** and **79b** have outstanding antibacterial action against some strains and activity outperformed streptomycin.

Isatin-pyrazole/pyrazoline hybrids as potent antibacterial agents: Pyrazole/pyrazoline derivatives are powerful therapeutic scaffolds having a broad range of biological characteristics, with antibacterial activity [122-124]. Hybridization of indole/isatin with pyrazole/pyrazoline can be used to synthesize novel and effective compounds against both drug-resistant sensitive bacteria, mainly *S. aureus*, *Listeria monocytogenes*, *E. coli*, *Salmonella*, VRSA (vancomycin-resistant *Staphylococcus*, MRSA bacteria were inhibited by derivative **80** (MIC: 0.02-99.0 µg/mL) [125]. The SAR showed electronegative groups at R_1 and R_3 and cyano at R_2 were beneficial to the antibacterial potential (Fig. 12). In comparison with the unsubstituted analogue, compound **81** showed harmful to activity by substitution at R_1 and R_2 positions as per the antibacterial SAR study [126]. The addition of a -Cl atom into the phenyl moiety might boost the antibacterial potential, although the groups of positive inductive effect (EDGs) were not beneficial for the activity, compound

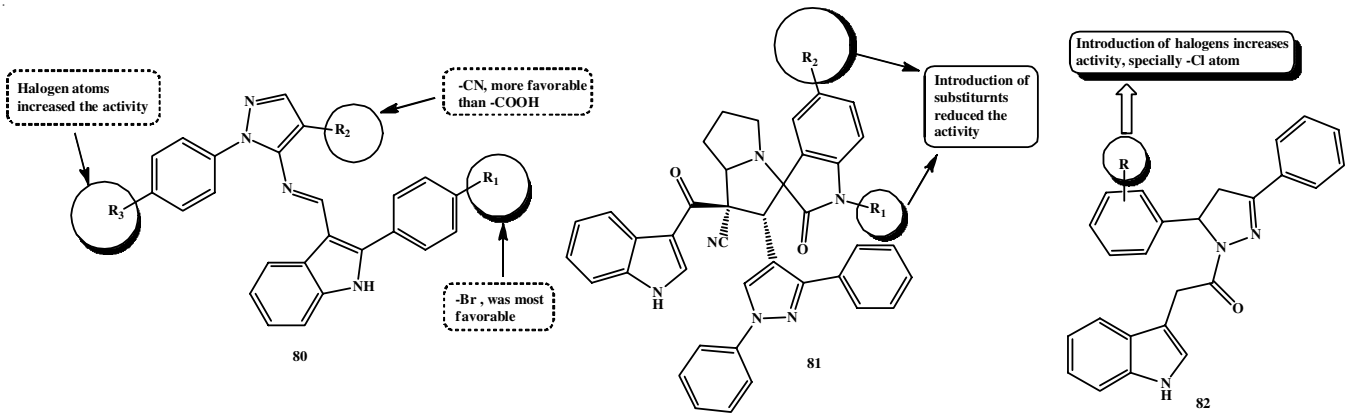


Fig. 12. Isatin-pyrazole/pyrazoline hybrids

82, showed the best antibacterial potential against *Bacillus, E. coli* and *Staphylococcus* [127].

Isatin-thiazole/thiazolidione hybrids as potent antibacterial agents: Thiazole/thiazolidione is a 5-membered heterocyclic with sulfur and (-N_2) atoms that has probable to alter the pharmacodynamics, pharmacokinetics and physicochemical action of drug molecules [128,129]. More than 18 FDA-permitted medications and additional **70** investigational compounds contain the thiazole/thiazolidione moiety, demonstrating that the compounds containing thiazole/thiazolidione moiety are an affluent cause of drug leads [130]. Because certain thiazole/thiazolidione compounds show promise against both drug-susceptible and drug-opposing bacteria [131,132] the combination of isatin and thiazole/thiazolidione could serve as a lead compound for the development of new antibacterial options that overcome drug resistance. Compound **83** (MIC: 0.49-3.90 µg/mL) (Fig. 13) showed superior activity to ciprofloxacin (MIC: 1.95-3.90 µg/mL) [133]. The -CH_3, -Cl and ketone groups at R_1, R_2 and R_3 locations were preferable to benzyl, hydrogen and ester groups revealed in SAR study. Hybrid **83b** (MIC: 0.49-0.98 µg/mL) in particular demonstrated a strong potentiality against drug-opposing bacterial strains (MIC: 3.90 and 7.81 µg/mL).

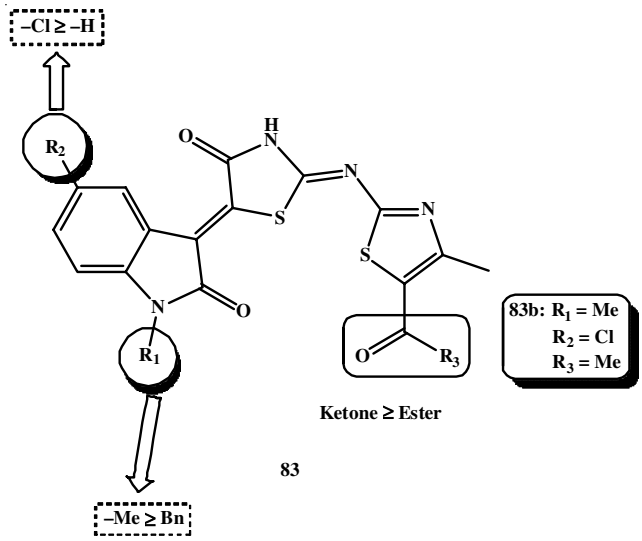


Fig. 13. Isatin-thiazole/thiazolidione hybrids

Antibacterial activity of isatin–pyrrole/furan/thiophene hybrids: The [N_2]/[O]/[S] heterocycles pyrrole/furan/thiophene derivatives are possible tyrosinase inhibitors [134], topoisomerase IV, DNA gyrase [135,136], tyrosyl-tRNA synthetase [137], efflux pumps [138]. As a result, the pyrrole/furan/thiophene compounds have good antibacterial and antifungal properties against pathogens which are responsible for various infections [139,140]. Furthermore, several pyrrole/furan/thiophene derivatives, for example, temocillin and cefoxitin, are widely clinically used, bactericidal agents [141]. As a result, isatin hybridization with the pharmacophore pyrrole/furan/thiophene could be an effective approach for obtaining the high-activity antibacterial agents.

Hybrid (isatin-furan) **84** (IZ: 8.5-14 mm at 20 µg/mL) against tested bacterial strain, has decreased activity than chloramphenicol (IZ: 15.6-26 mm, 20 µg/mL) [142]. Hybrid **85** (isatin-benzofuran) (MIC: 0.06-64 µg/mL) was shown to be a potent addition of alkyloxyimine in indole moiety (at C-3 position) possibly will enhance the antibacterial potential (Fig. 14), while 2nd furan fragment decreases the activity [143].

Isatin-imine hybrids as potent antibacterial: Imine derivatives, such as hydrazone, carbohydrazide, semicarbazone and thiosemicarbazone have a range of biological features, counting antibacterial action, making them essential scaffolds in the generation of antibacterial drugs [144]. According to SAR results, these derivatives possibly block DNA GyrB [145] and efflux pump [146] and bring DNA damage [147], therefore conjugation of isatin-imine could generate compounds with a diverse range of antibacterial activity.

Hybrids **86** (isatin-carbohydrazide, minimum inhibitory concentration: 3.9-83.3 µg/mL) had the parallel inhibitory potentiality to tetracycline against many pathogenic bacteria and the mechanistic learning revealed that the antibacterial activity of hybrid **86a** (IC_{50}: 19.3 µM) against *S. aureus* was equivalent to ciprofloxacin (IC_{50} of 26.4 µM.) used as reference drug [148]. As per structural study (Fig. 15), sulfonamide fragment at C5 was not required for the reaction. As indicated *via* the fact that hybrids **87a-b** (IC_{50}: 30 and 50 µM) have a stronger antibacterial activity than penicillin (IC_{50}: 631 µM) [149] as well as no improvement in the antibacterial activity seen with the addition of piperidin-1-ylmethyl in the indole ring (at N1 position) [150].

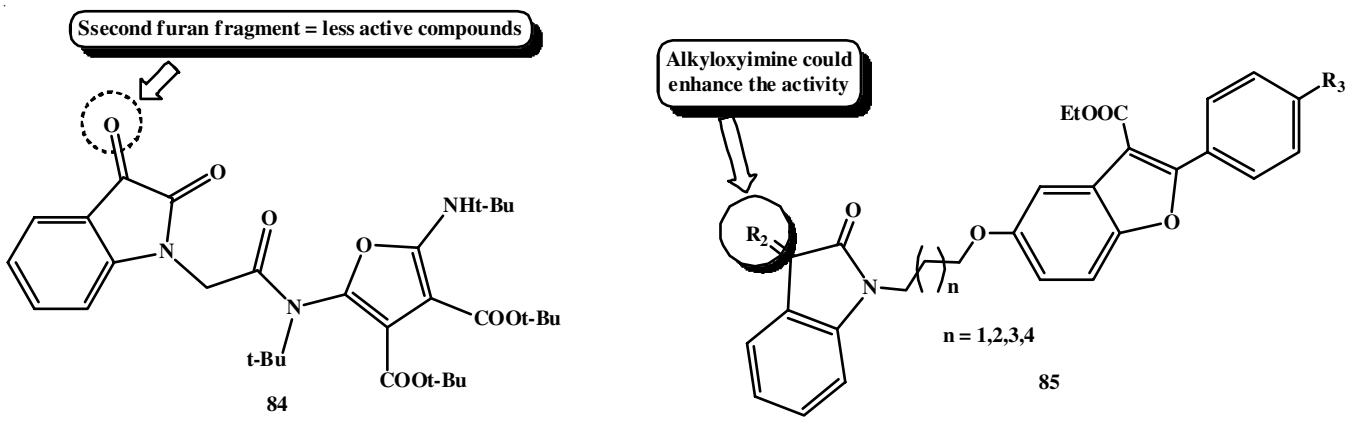


Fig. 14. Isatin-pyrrole/furan/ thiophene hybrids

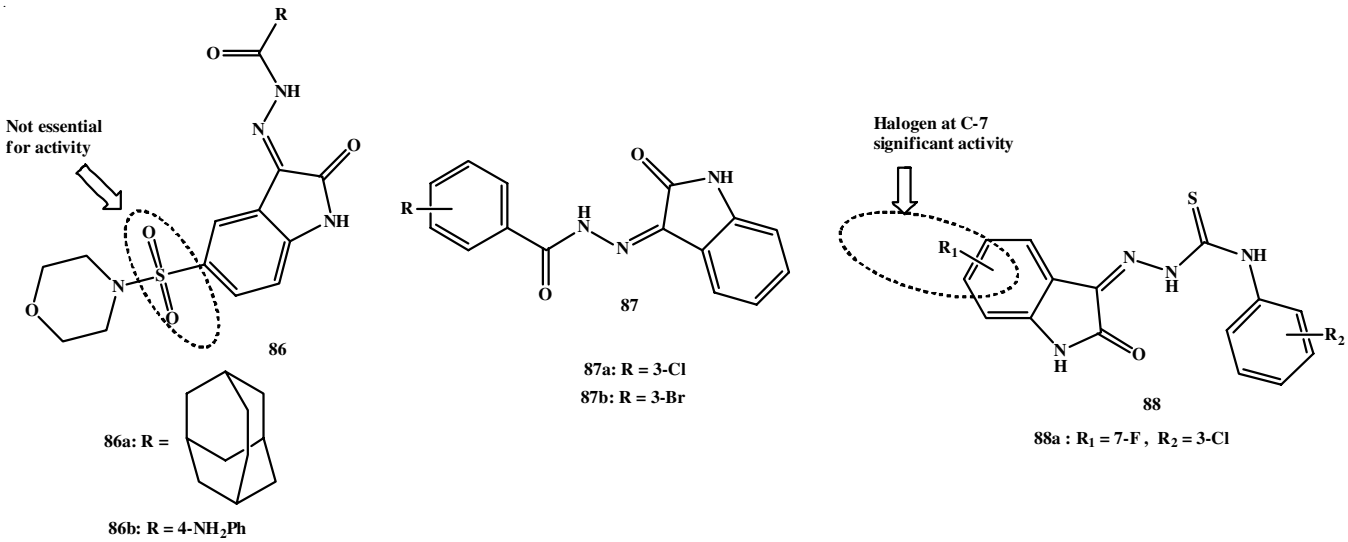


Fig. 15. Structures of isatin-imine hybrids

Hybrids **88** (MIC: 0.39-6.25 µg/mL) had outstanding Gram-positive activity, counting MRSA and VRE strains. Halogen atom in the indole moiety (at C7 position) was required to be significant for considerable action against MRSA revealed in the SAR study [151]. Hybrid **88a** (MIC: 0.39-1.56 µg/mL) was extremely potent for *E. faecalis*, VRE and MRSA strains and had better activity as compared to vancomycin (minimum inhibitory concentration: 1 to > 8 µg/mL), indicating that these hybrids have potential as putative antibacterial agents.

Hybrids of isatin-quinoline, quinolone, quinazoline and quinazolinones as potent antibacterial: Derivatives of quinoline/quinolone/quinazoline/quinazolinones are the prospective blocker of DNA gyrase and topoisomerase IV as well as potential privileged heterocyclic pharmacophore with high antibacterial action [152-155]. Moreover, norfloxacin, ciprofloxacin and other antibiotics *viz.* ofloxacin and moxifloxacin were employed in the treatment of various infections [156,157]. As a result, hybrids of isatin-quinoline/quinolone/quinazoline/quinazolinones could be used to find new inhibitors to fight both drug-resistant and drug-sensitive organisms.

In hybrids **89** and **90** (Fig. 16), the fluoroquinolone scaffold had a considerable impact on antibacterial activity, with the following comparative participation order: ciprofloxacin > gatifloxacin > 8-methoxy ciprofloxacin [158,159]. The activity of hybrids with methyl in the isatin moiety (at C5 position) and alkyloxyimine (at C3 position) could be increased. Hybrid **89a** (isatin-ciprofloxacin, MIC: 0.03-8 µg/mL) performed equally well as ciprofloxacin and levofloxacin.

Miscellaneous indole/isatin hybrids: Recent few years' developments of new isatin and indole hybrid derivatives showed that the isatin/indole nucleus has potential to serve as lead for the development novel antibacterial agents [160-163]. One of the most privileged scaffolds which have antibacterial potential along with multi-pharmacological actions is a sulfonamide [164,165]. A number of antibiotics are used clinically which has sulfonamide nucleus in their structure, due to their increased efficacy, safety and low toxicity profile they are widely used [166,167]. Hybridization of indole/isatin with sulfonamide may be the lead for medicinal chemists to develop more potent and safe antibacterial agents. Here some indole sulfonamide derivatives (Fig. 17) have been developed and shown to be potent such as compound **93** (MIC: 7.8-133.3 µg/mL) **93a-b** (MIC: 3.9-31.2 µg/mL), **92a-e** (MIC: 6.25-62.5 µg/mL) and **91a-b** (MIC: 7.8-88.3 µg/mL), shown to be potent against each tested strain and were evaluated in reference of tetracycline (MIC: 15.6-62.5 µg/mL) [168-170]. SAR studies reveal that for the antibacterial activity morpholino group was more potent as compared to the piperazinyl. Hybridization of indole with thiourea was also reported to be potent for antibacterial activity. Some of its derivatives were shown to have activity

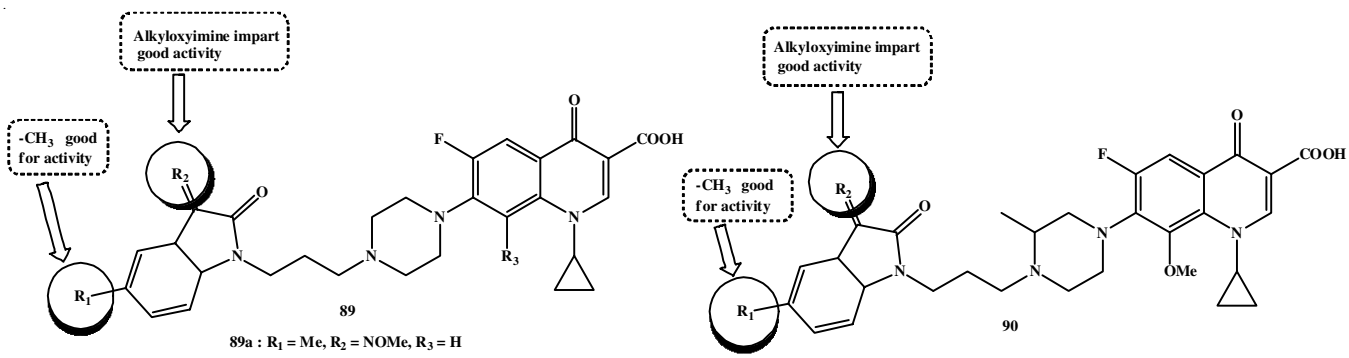


Fig. 16. Structures of isatin-quinoline, quinolone, quinazoline and quinazolinones hybrids

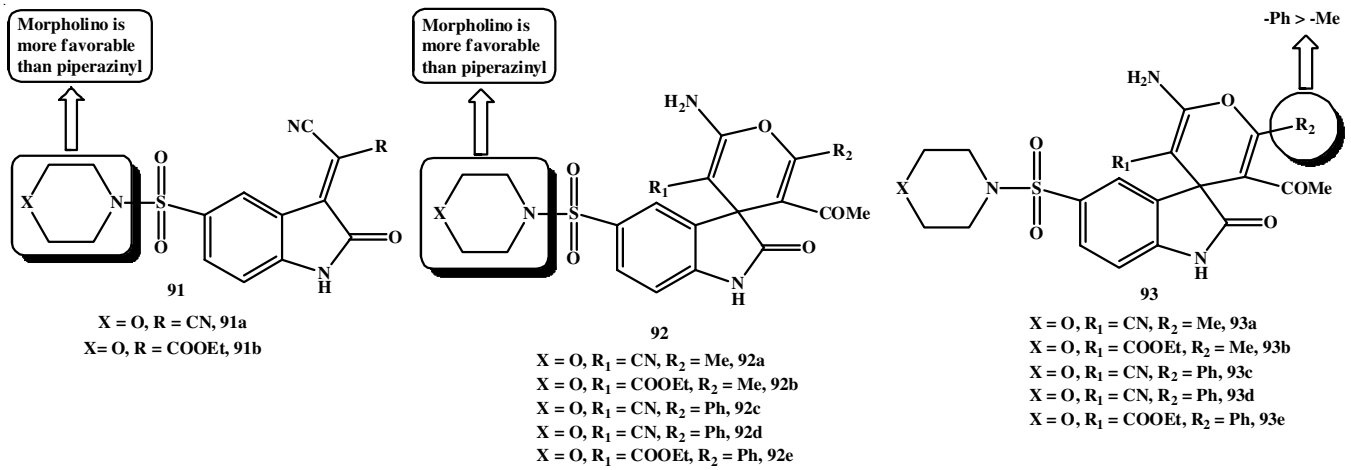


Fig. 17. Structures of miscellaneous indole/isatin hybrids

superior to the standard drugs and the modification of these derivatives may lead to the development of clinically effective antibacterial agents [171].

Hybridization of indole with 1,2,3-triazole-azithromycin (Fig. 18), compounds **94**, **95** and **96** have promised antibacterial activity the same as macrolide due to similarity in the mechanism of action they were also resistant to the same strain as macrolide [172]. Hybrid **96a** has the same MIC values against macrolide-susceptible *S. aureus* as that of the parent azithromycin. The structural modification of these compounds and hybridization with isatin instead of indole may lead to the development of more rational compounds for the antibacterial activity against macrolide-susceptible strains [173-179].

Conclusion

The isatin moiety and its derivatives is present in a wide range of pharmaceuticals display a wide range of structural and mechanistic characteristics. Isatin derivatives are crucial inhibitors of various proteins and involved in several diagnostic conditions indicating that they could be employed in mitigation of pathogenic infections. Hybridization is a popular method, it is possible that combining the isatin moiety with other antibacterial pharmacophores could boost antibacterial efficacy, defeat drug resistance, diminish adverse effects and advance pharmacokinetic characteristics. Based on the findings, it can be inferred that hybrids with electronegative groups attached on

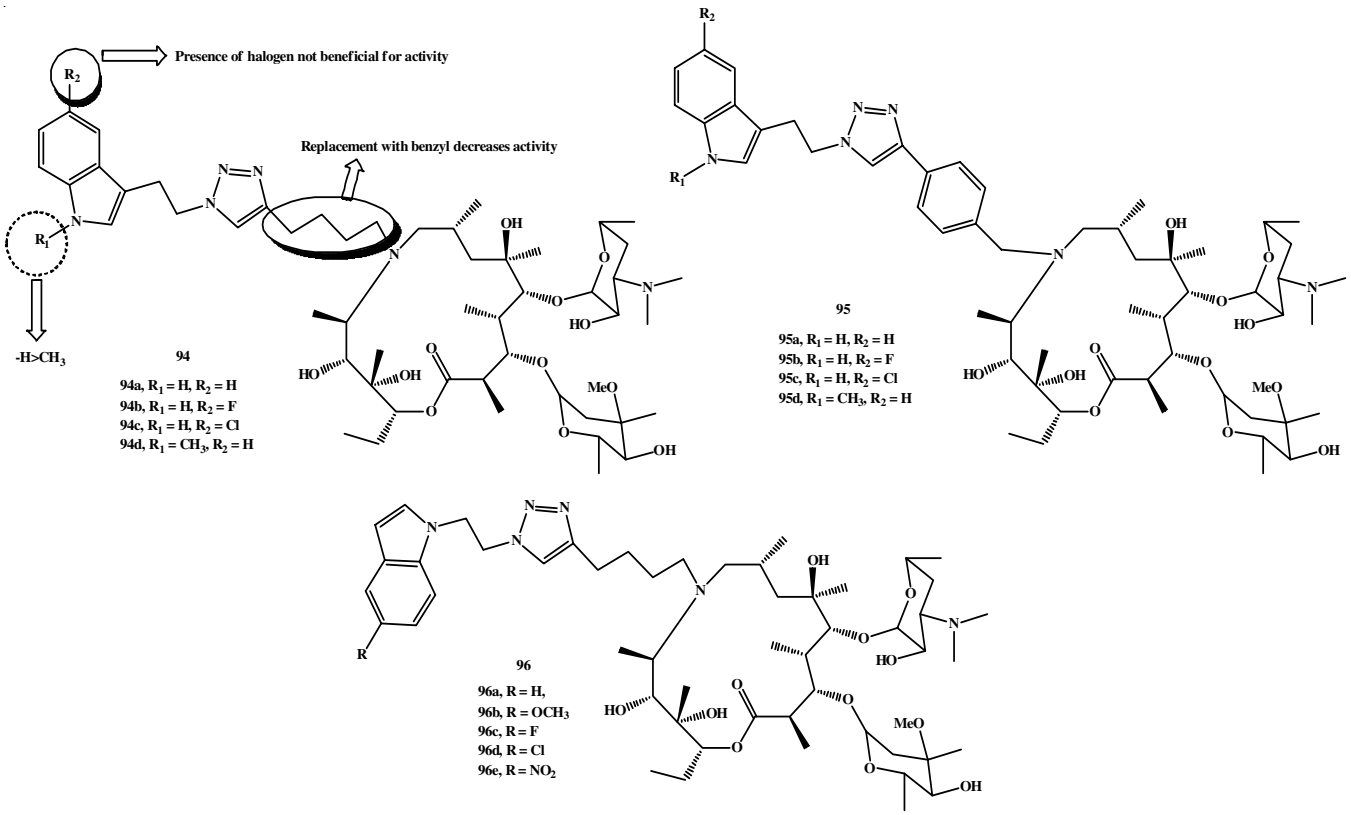


Fig. 18. Structures of indole with 1,2,3 triazole-azithromycin hybrids

substituted isatin nuclei have best antibacterial activity than unsubstituted isatins and also the role of binding linkage has been revealed, if the compound having linkers such as amide (NHCO), carbonyl (CO) or other hetero atoms, the antibacterial activity is enhanced. A review of the literature revealed that there is only one report on isatin derivatives with the benzimidazole system in the third position side chain. As a result, the hybridization of isatin with different heterocycles such as quinoline, quinolone, imine, isatin–azole, isatin-curcumin hybrids, isatin Schiff bases, isatin-benzimidazole hybrids, have an immense role and would be a lead in the development of various pharmacologically active compounds. It is believe that this review could serve as a springboard for the development of isatin hybrids as antibacterial agents with considerably superior bactericidal activity than antibiotics already in the market or in use in hospitals.

ACKNOWLEDGEMENTS

The authors thank Research and Development, Integral University, Lucknow, India for providing the research facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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