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A RECENT SURVEY ON CHEMICAL AND BIOLOGICAL SIGNIFICANCE OF ISATIN DERIVATIVES

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Keywords:

Isatin derivatives, Anticancer, Antibacterial, Antitubercular, Anti-inflammatory

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ABSTRACT: Isatin, a heterocyclic moiety, is a significant scaffold in medicinal chemistry. Isatin contains a nitrogen atom at position 1 and two ketone groups at positions 2 and 3. It consists of two cyclic rings, one of which is a six-membered ring, and the other is a five-membered ring. It is a resourceful nucleus for the synthesis of several pharmacologically active molecules. Isatin itself acquires an extensive range of biological activities. Currently, the design of unique isatin derivatives as potent drugs is the key role of the researchers. The focus of this present study is to overview the recent literature published on isatin derivatives. In this review, some of the pharmacological activities of isatin derivatives such as anticancer, antibacterial, antiviral, antifungal, antioxidant, antitubercular, anti-malarial, antidiabetic, anticonvulsant, analgesic, and anti-inflammatory activities were reported. From these studies, isatin has been established as the more promising candidate for further research and investigations in many fields.

INTRODUCTION: To design and develop safe and effective drugs is very much essential in order to overcome the various diseases emerging day by day. Synthesis of novel medicinal compounds with diverse biological activities is the prerequisite for medicinal chemists. Isatin, a heterocyclic moiety, is regarded AS a significant scaffold in medicinal chemistry to achieve a wide range of pharmacological activities. Isatin contains a nitrogen atom at position one and two ketone groups at positions 2 and 3 **Fig. 1**. It consists of two cyclic rings, one of which is a six-membered ring, and the other is a five-membered ring.

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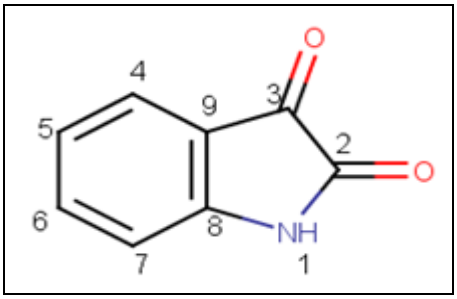
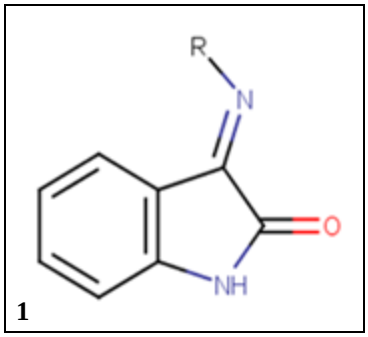


FIG. 1: STRUCTURE OF ISATIN

Isatin (1H-indole-2,3-dione) was obtained by Erdman and Laurent in 1841 as an oxidation product of indigo by nitric acids and chromic acids [1]. It also occurs naturally in plants. It is also found in humans as a metabolic derivative of the hormone adrenaline. An extensive literature survey pinpointed that is a tin derivative is a promising precursor for the development of novel drugs. Isatin derivatives have acquired a prominent interest in recent years because of their medicinal properties like anticancer, antibacterial, antiviral,

antifungal, antioxidant, antitubercular, antimalarial, antidiabetic, anticonvulsant, analgesic, and anti-inflammatory. In this present study, some of the biological activities of isatin derivatives published in past two decades were discussed.

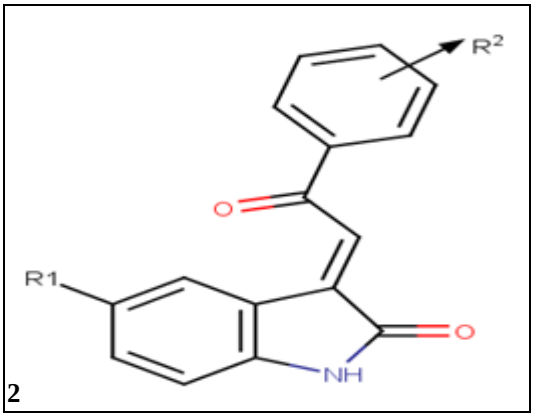
1. Anticancer Activity: A set of novel Schiff bases of Isatin derivatives (1) were synthesized by reaction of Isatin with various aromatic or heterocyclic primary amines. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. Cytotoxic activities for some of the synthesized compounds were evaluated by MTT assay in three human cancer cell lines (HeLa, LS180 and Raji). Among the tested compounds, 3-(2-(4-nitrophenyl) hydrazono) indolin-2-one (1b) was found to be the most potent molecule (IC_{30} =12.2 ± 3.1 µM in HeLa cells). Docking studies of 3-substituted indolin-2-one scaffolds on vascular endothelial growth factor receptor 2 (VEGFR-2) involved in cell proliferation and angiogenesis was performed (PDB Code: 2OH4). 3-(naphthalen-1-ylimino) indolin-2-one (1j) and 3-(2-(4-nitrophenyl) hydrazono)indolin-2-one (1b) exhibited higher docking binding energies such as -9.20 and -7.89 kcal/mol among other synthesised compounds. The compound 1b interacts with amino acids Glu915, Asn921 and Arg1049 to obtain key hydrogen bonds with the receptor [2].



1

R: 1a = 2-phenylhydrazone, 1b = 2-(4-nitrophenylhydrazone), 1c = phenyl, 1d = p-tolyl, 1e = o-tolyl, 1f = 4-chlorophenyl, 1g = 4 hydroxyphenyl, 1h = 4-nitrophenyl, 1i = 4-chloro-2-methylphenyl, 1j = naphthyl, 1k = 6-chloro-2-methyl-pyrimidine, 1l = dihydrothiazole, 1m = 5-chloropyridine, 1n = benzimidazole, 1o = benzothiazole, 1p = 4-chlorothiazole, 1q = 4-methylisoxazole, 1r = 5-methylisoxazole.

A novel series of 3-(2-oxo-2-phenylethylidene) indolin-2-ones (2) incorporating pharmacophoric elements of isatins and chalcones were designed and synthesised by one pot sequential addition of isatin and substituted acetophenones in the presence of dimethylamine, glacial acetic acid, and concentrated HCl. The compounds were evaluated for anticancer activity against three breast cancer cell lines MDA-MB468 (EGFR positive breast adenocarcinoma cell line), MDA-MB321 (estrogen receptor-negative, basal-like breast cancer), and MCF7 (invasive ductal breast carcinoma). Compound 2m containing 5-chloro substituents in the benzo ring of the isatin moiety and 3,4-dimethoxy substituents in the phenyl ring was reported as the most active in the series with GI_{50} values of 8.54, 4.76, and 3.59 against MDA-MB231, MDA-MB468 and MCF7 cells, respectively [3].

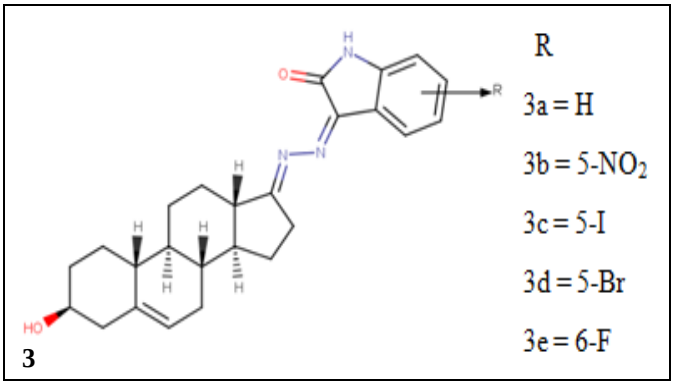


2

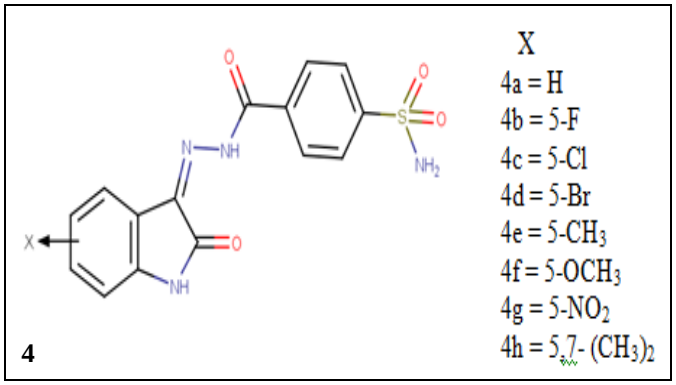
R^1: 2a = H, 2b = H, 2c = H, 2d = H, 2e = H, 2f = H3-$NO_2$2m = Cl, 2g = H; R^2: H, 2h = H, 2-OCH_3, 4-F2i = H, 3,4-OCH_3, 4-Cl, 2j = H, 4-CH_3, 4-Br, 2k = Cl, H, 4-$NO_2$2l = Cl, 4-F, 3,4-OCH_3, 4-$OCH_3$2n = Br, H

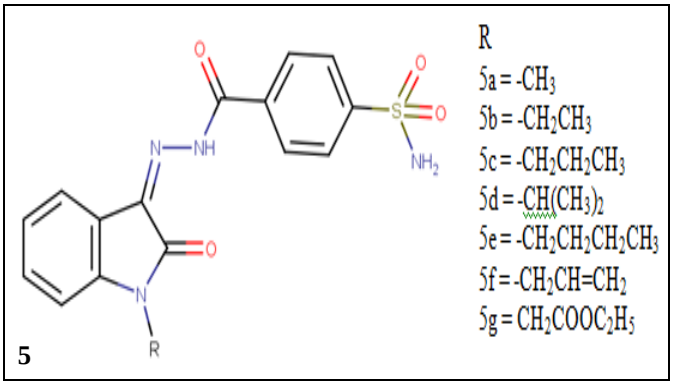
In a recent study, a series of isatin-dehydro-epiandrosterone hybrids (3) were synthesized *via* the condensation of dehydroepianderosterone and isatin through the =N-N= bridge and which were evaluated for their potential anticancer activities against HepG2 (Human hepatocellular liver carcinoma), Huh-7 (human hepatoma), A875 (human melanoma) and BEL-7402 (5-fluorouracil resistant human hepatocellular carcinoma) cell lines by MTT assay.

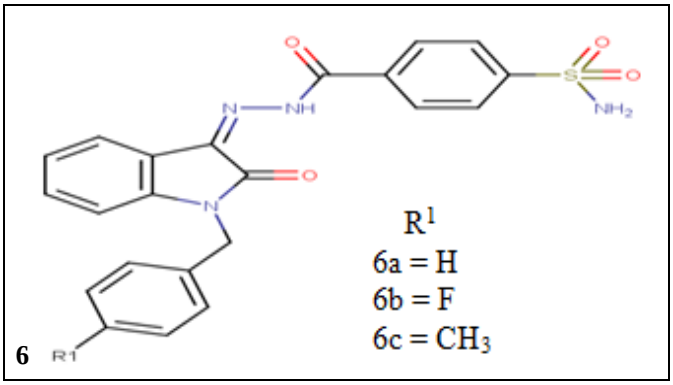
Results showed that all the target compounds displayed good antitumor activities when compared to 5-flurouracil (positive control). Especially compound 3d exhibited significant inhibition activities (IC_{50}= 5.97 ± 2.67 µM) against BEL-7402/5-FU cell lines that resistant to 5-FU, which might be developed as a novel lead scaffold for anticancer agents [4].



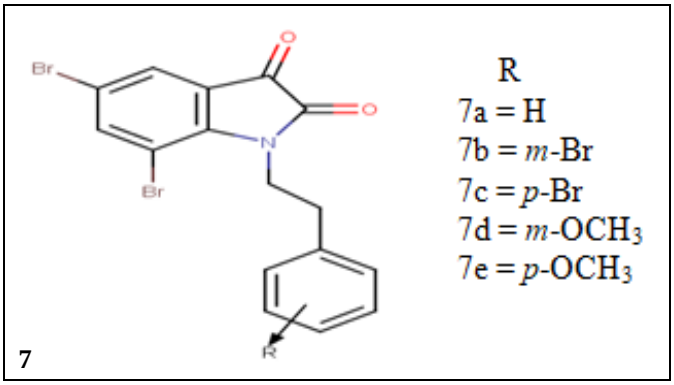
In another study, the development of novel carbonic anhydrase inhibitors based on the isatin moiety, reported the synthesis and biological evaluation of novel sulfonamides (4a-h, 5a-g and 6a-c) incorporating substituted 2-indolinone moiety (as tail) linked to benzenesulfonamide (as zinc anchoring moiety) through a hydrazide linker. The synthesized sulfonamides were evaluated *in vitro* inhibitory activity against the following human carbonic anhydrase (hCA) isoforms- hCA I, II, IX, and XII. Human CA isozymes IX and XII are two tumor-associated proteins being overexpressed in many tumors and involved in serious processes related to cancer progression and response to therapy. These two CA isozymes had been the recent target for anticancer drugs. The results revealed that compound 5b emerged as a single-digit nanomolar hCA IX and XII inhibitor (8.9 and 9.2 nM, respectively). Molecular docking studies were carried out for compound 5b within the hCA II, IX, and XII active sites, allowed to rationalize the obtained inhibition results [5].

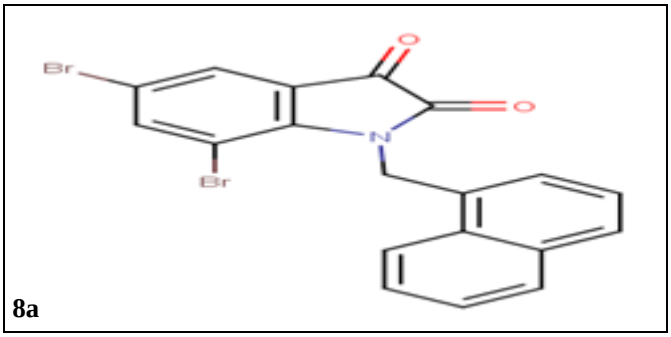




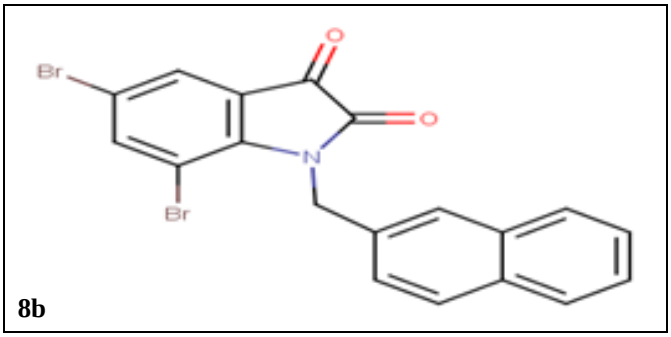


Synthesis of N-phenethyl (7a-e) and N-(1-and 2-naphthylmethyl) derivatives (8a-b) of 5,7-dibromoisatin by N-alkylation reactions were reported [6]. Their activity against human monocyte-like histiocytic lymphoma (U937), leukemia (Jurkat) and breast carcinoma (MDA-MB-231) cell lines were assessed. The results allowed further development of structure-activity relationships. The compound 5,7-dibromo-N-(1-naphthylmethyl)-1H-indole-2,3-dione (8a) was the most potent against U937 cells with an IC_{50} value of 0.19 µM.



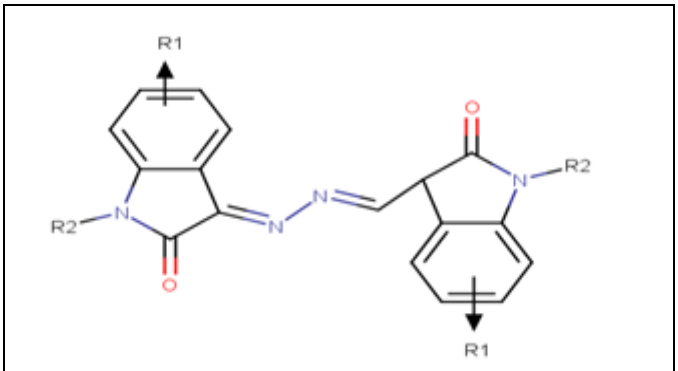


8a



8b

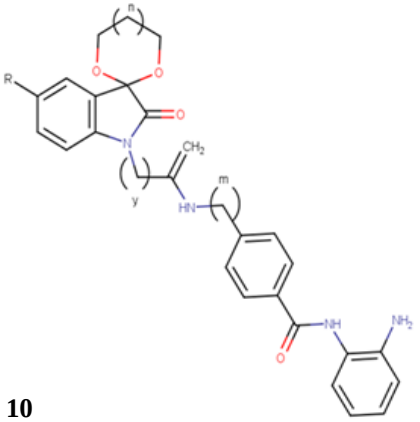
In a recent study, a series of eighteen symmetrical bis-Schiff base derivatives of isatin (9) were synthesized by condensation of the isatins with hydrazine and were evaluated for their in vitro and *in-vivo* antitumor activities. More than half of the obtained compounds showed potent cytotoxicity according to the MTT assay on five different human cancer cell lines such as HeLa, SGC-7901, HepG2, U251, and A549. The results showed that 3,3´-(hydrazine-1,2diylidene)bis (5-methylindolin-2-one) (9b) was the most potent compound on HepG2 (IC_{50} = 4.23 µM). 3b was also found to be able to inhibit the tumor growth substantially on the HepS-bearing mice at a dose of 40 mg/kg. The real-time live-cell imaging and tracking in the H2B labelled HeLa cells revealed that 3b could induce mitosis interference and apoptosis-associated cell death [7].



R^1	R^2	R^1	R^2
9a = H	H	9j = H	Et
9b = 5-Me	H	9k = 5-Me	Et
9c = 5-Br	H	9l = 5-F	Et
9d = 5-F	H	9m = H	Bn
9e = 5-Cl	H	9n = 5-Me	Bn
9f = 5-OMe	H	9o = 5-F	Bn
9g = 7-F	H	9p = H	i-Pr
9h= 6-Cl	H	9q = 5-Me	i-Pr
9i = 6-F	H	9r = 5-F	i-Pr

9

Design and synthesis of a novel series of compounds with isatin-based caps and *o*-phenylenediamine-based zinc-binding groups (10) as Histone deacetylases (HDAC) inhibitors were reported recently[8]. HDACs as novel targets for the discovery of anticancer agents is a series of enzymes that regulate histone deacetylation, which may be the best-understood type of epigenetic modifications. All synthesized target compounds were evaluated for their HDAC inhibition using HeLa nuclear extract. Among these compounds, the most potent compound 10n exhibited better HDAC inhibition and antiproliferative activities against multiple tumor cell lines with IC_{50} values of 0.032, 0.256, and 0.311 µM for HDAC 1, 2, and 3 respectively when compared with the positive control entinostat (MS-275). Compounds 10h and 10n were docked into the active site of HDAC1 (PDB code 5ICN), and hence the binding modes of these compounds in HDACs were explored.

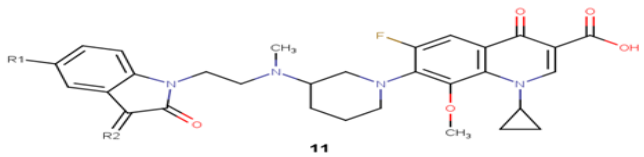


R	n	m	y
10a = Br	1	0	1
10b = Cl	1	0	1
10c = F	1	0	1
10d = Br	0	0	1
10e = Cl	0	0	1
10f = F	0	0	1
10g = Br	1	1	1
10h = Cl	1	1	1
10i = F	1	1	1
10j = Br	0	1	1
10k = Cl	0	1	1
10l = F	0	1	1
10m = Br	1	0	2
10n = Cl	1	0	2
10o = Cl	1	1	2

10

2. Antitubercular Activity: A series of novel balofloxacin ethylene isatin derivatives (11) with remarkable improvement in lipophilicity as compared to the parent compound balofloxacin were designed and synthesized. All of the synthesized compounds were less active than balofloxacin against M. phlei CMCC 93201 and M.

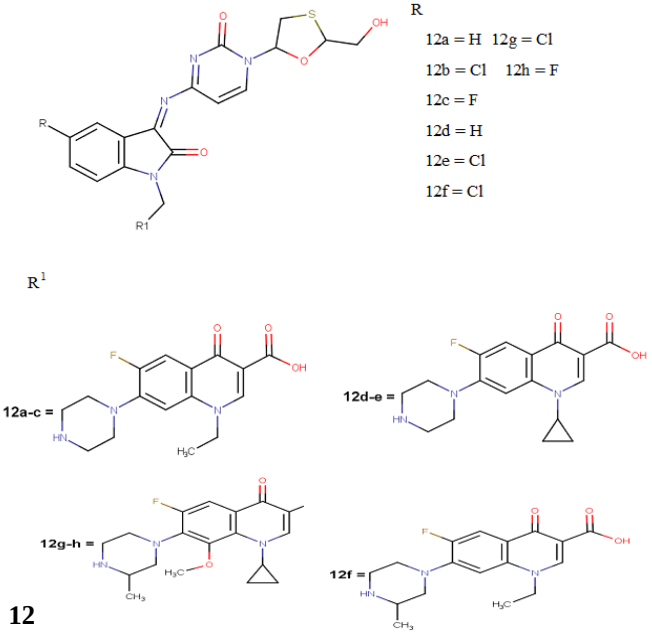
smegmatis CMCC 93202, but compounds 11g-j (MIC: <0.5e8 mg/mL) were more potent than balofloxacin (MIC:16 mg/mL) against MTB09710. In particular, compound 11h (MIC =< 0.5 mg/mL) was found to be comparable to moxifloxacin and ≥32 fold more potent than balofloxacin against MTB09710 and MTBH37Rv ATCC27294 [9].



11

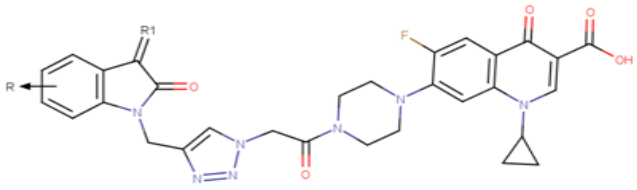
R_1		R_2	
11a = H	O	11h = F	$NOCH_2CH_3$
11b = F	O	11i = H	$NNHCSNH_2$
11c = H	NOH	11j = F	$NNHCSNH_2$
11d = F	NOH	11k = H	$NNHCONH_2$
11e = H	$NOCH_3$	11l = F	$NNHCONH_2$
11f = F	$NOCH_3$	11m = H	$NNHC_6H_5$
11g = H	$NOCH_2CH_3$	11n = F	$NNHC_6H_5$

In another study, the synthesis of a novel series of lamivudine prodrugs involving Schiff and Mannich reaction with isatin derivatives (12) was reported[10]. The synthesized compounds were screened against *Mycobacterium tuberculosis* strain H37Rv, and all the Mannich bases (12a–h) were found to be most active with 92–100% inhibition. In particular, the compound 12c showed 100% inhibition against *Mycobacterium tuberculosis* and concluded as a beneficial candidate for the treatment of tuberculosis.



12

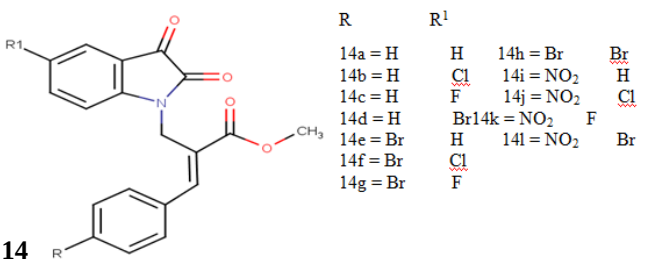
A class of novel amide tethered ciprofloxacin-1,2,3-triazole-isatin hybrids (13) were designed, synthesised and the *in-vitro* anti-mycobacterial activity against both drug-susceptible MTB H37Rv and MDR-MTB strains. The result revealed that the most active hybrid 13a (MIC MTB H37Rv = 0.5 µg/mL and MIC MDR-MTB = 0.12µg/mL) had the activity in the same level with the first-line anti-tubercular agents isoniazid (MIC = 0.12 µg/mL) and rifampicin (MIC = 0.25 µg/mL) and it was 2-fold more active than the parent ciprofloxacin (MIC = 1.0 µg/mL) against MTB H37Rv and ≥16 folds more potent than ciprofloxacin (MIC = 2.0 µg/mL), isoniazid (MIC= >64 µg/mL) and rifampicin (MIC =>64 µg/mL) against MDRMTB [11].



13

R	R^1		
13a = H	=O	13g = 5-Me	NOMe
13b = 5-F	=O	13h = 7-F	NOMe
13c = 5-Me	=O	13i = H	NOEt
13d = 7-F	=O	13j = 5-F	NOEt
13e = H	NOMe	13k = 5-Me	NOEt
13f = 5-F	NOMe	13l = 7-F	NOEt

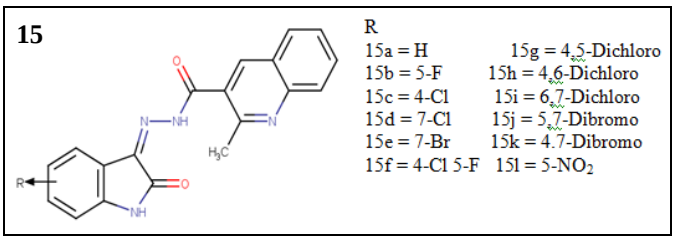
A series of new Baylis–Hillman adduct-derived N-cinnamyl-substituted isatin derivatives (14) were synthesized from a starting material 5-halo isatin in a simple and efficient manner. All the synthesized compounds were evaluated for their *in-vitro* antitubercular activity against *Mycobacterium tuberculosis* H37RV strain ATCC 27294, which is susceptible to control drugs (Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide) using the agar dilution method. These compounds have inhibited Mycobacterium strains, especially compounds 14j–l have shown overall good activity with MIC = 1.56 µg/mL on *M. tuberculosis* H37Rv strain ATCC27294 [12].



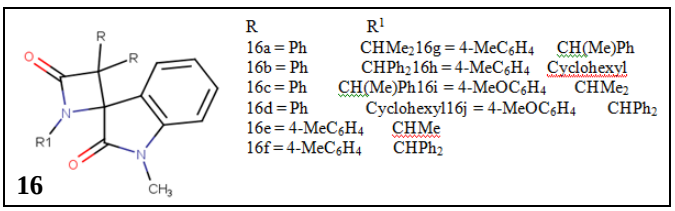
14

R	R^1		
14a = H	H	14h = Br	Br
14b = H	Cl	14i = NO_2	H
14c = H	F	14j = NO_2	Cl
14d = H	Br	14k = NO_2	F
14e = Br	H	14l = NO_2	Br
14f = Br	Cl		
14g = Br	F		

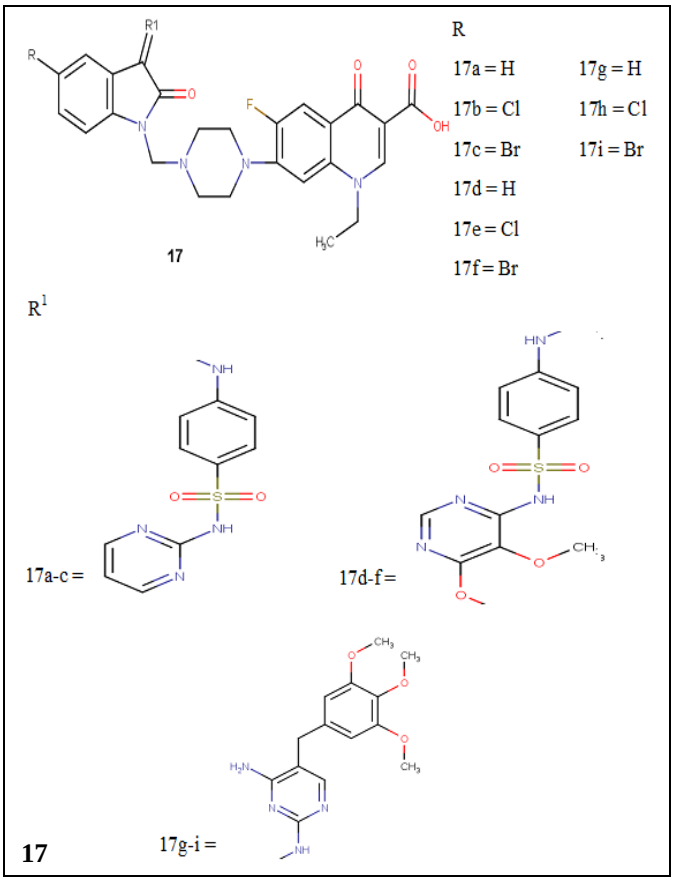
In another work, a set of novel analogs of isatin-quinoline hybrids (15) were designed and synthesized by a hybrid pharmacophore approach. The preliminary antitubercular screening of the test compounds was predicted against enoyl-ACP reductase enzyme (PDB ID: 4TZK) by using molecular docking studies. The compound 15h has the highest binding affinity with a binding energy of -9.08 kcal/mol, and the predicted inhibition constant is 221.75 nanomolar. This compound exhibited well-established hydrophobic bonds with amino acid Tyr 158 and the cofactor NAD 500 in the receptor active pocket. Further, *in-vitro* antitubercular activity was performed for all the hybrids against drug-resistant strains of *Mycobacterium tuberculosis* using microdilution assay, and their minimum inhibitory concentration was determined. Compound 15h has the good inhibitory (0.09 µM) activity as compared to the reference drug, isoniazid (0.03 µM) [13].



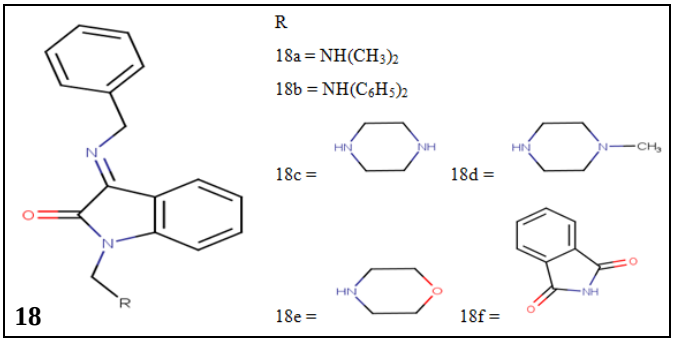
3. Antibacterial Activity: Synthesis of new 1-alkyl/cyclohexyl- 3, 3- diaryl- 10- methylspiro [azetidine-2, 30-indoline]-20,4-diones (16) from the reactions of the 2-diazo-1,2-diarylethanones with 1-methyl-3-(alkyl/ cyclohexylimino)indolin-2-ones were reported [14]. All the synthesized compounds were screened for their antibacterial activity against the bacterial strains Gram-(+) *Bacillus subtilis*, *Staphylococcus aureus* and Gram-(-) *Escherichia coli* and *Pseudomonas aeruginosa*. The results revealed that four compounds showed activity on *E. coli* (16d: MIC =100 µgmL^{-1}, 16e: MIC =10 µgmL^{-1}, 16h: MIC =100 µgmL^{-1}, 16j: MIC =50 µgmL^{-1}) whereas only one compound showed activity on *P. aeruginosa* (16e: MIC =50 µgmL^{-1}).



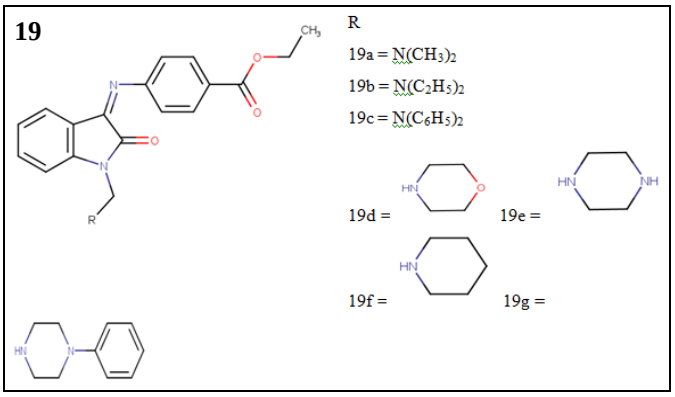
In another study, Mannich bases of norfloxacin (17) were synthesized by reacting them with formaldehyde and several isatin derivatives. The synthesized compounds were investigated for *in vitro* antimicrobial activity by the agar dilution method against many pathogenic bacteria. Among them, compounds 17d (3.7 times) and 17i (4.8 times) were more active (MIC:0.018 and 0.61µg/ml respectively) to than of norfloxacin (MIC: 1.22 µg/ml) against *B. subtilis* [15].



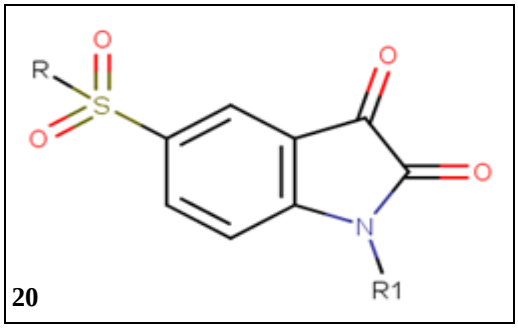
Synthesis of benzylimino isatin Mannich bases (18) by the simple Mannich reaction was reported[16]. The *in-vitro* antibacterial activities were screened with gram +ve as well as gram -ve bacteria by disc diffusion method. Especially, compound 18d showed better activity with 19, 17, 17 and 11mm zone of inhibition against *S. aureus*, *B. subtilis*, *P. eruginosa*, and *E. Coli*, respectively, compared to standard fluoroquinolone antibacterial Ciprofloxacin (30 mm zone of inhibition in *B. subtilus* and *P. eruginosa*). Molecular docking studies were carried out for the better active compound 19d with DNA gyrase enzyme (PDB Code: 1kzn) protein in order to determine the probable binding model into the active site of 1kzn with the compound 18d.

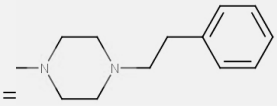
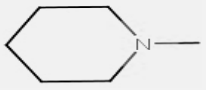
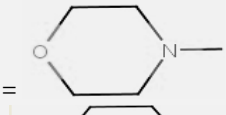
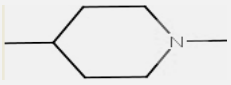
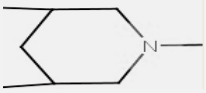


In another work, a series of novel Schiff bases of isatin were synthesized by refluxing isatin with p-aminoethyl benzoate. Further Mannich bases of isatin (19) were synthesized *via* Mannich reaction with various secondary amines. All the synthesized compounds were screened for antimicrobial activities by turbidity method using Ampicillin as standard against gram-positive and gram-negative bacteria. The results revealed that all compounds showed significant activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris* and *Escherichia coli*. Notably Compound 19a showed excellent activity against all gram-positive organisms (*Bacillus subtilis* MIC =12.5 µg/mL and *Staphylococcus aureus* MIC = 12.5 µg/mL) and gram-negative organisms (*Escherichia coli* MIC =12.5 µg/mL and *Proteus vulgaris* MIC =25 µg/mL) [17].

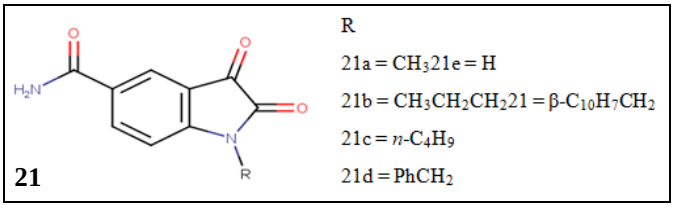


4. Antiviral Activity: A series of 5-sulfonyl isatin derivatives (20) as SARS-CoV chymotrypsin-like protease inhibitors ($3CL^{pro}$) were designed, synthesized, and evaluated by *in-vitro* protease assay using fluorogenic substrate peptide, in which several compounds showed potent inhibition against the $3CL^{pro}$. Structure-activity relationship was analyzed and possible binding interaction modes were proposed by molecular docking studies (PDB Code: 1uk4). Among all compounds, 20j showed the most potent inhibitory activity against $3CL^{pro}$ (IC_{50} = 1.04 µM). These results indicated that these inhibitors could be potentially developed as anti-SARS drugs[18].



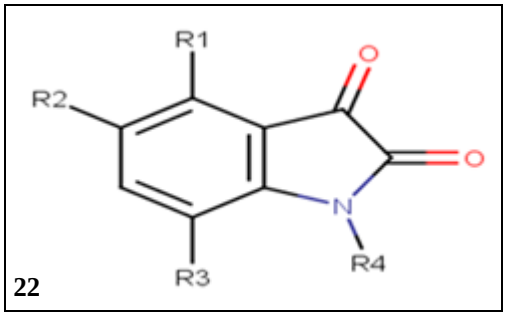
R	R^1
20a-20c= 	20a = CH_3 20b = $PhCH_2$ 20c = β-$C_{10}H_7CH_2$
20d = 	20d =CH_3
20e = 	20e = CH_3 20f = $PhCH_2$
20f = 	
20g-i =	20g = CH_3 20h = $PhCH_2$ 20i = β-$C_{10}H_7CH_2$
20j-l = 	20j = CH_3 20k = $PhCH_2$ 20l= β-$C_{10}H_7CH_2$
20m-n = 	20m = CH_3 20n = $PhCH_2$

In another study, a series of N-substituted isatin derivatives (21) were synthesized and tested against SARS CoV 3C-like protease using a colorimetric assay and confirmed by HPLC. The compounds were shown to be noncovalent, reversible inhibitors of SARS CoV 3C-like protease. The C-5 position was found to favor a carboxamide group and the N-1 position to favor large hydrophobic substituents. The results showed that compound 21f shows significant inhibition with an IC_{50} of 0.37 µM [19].

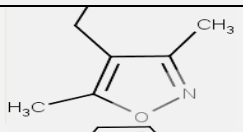
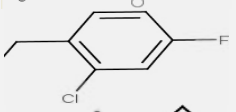
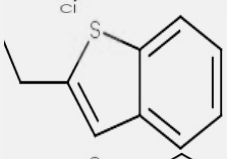
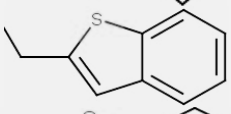
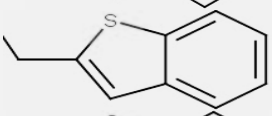
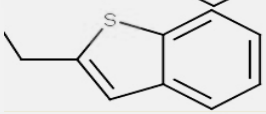
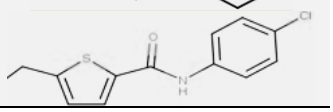


A series of N-substituted isatin derivatives (22) were synthesized from isatin, sodium hydride and

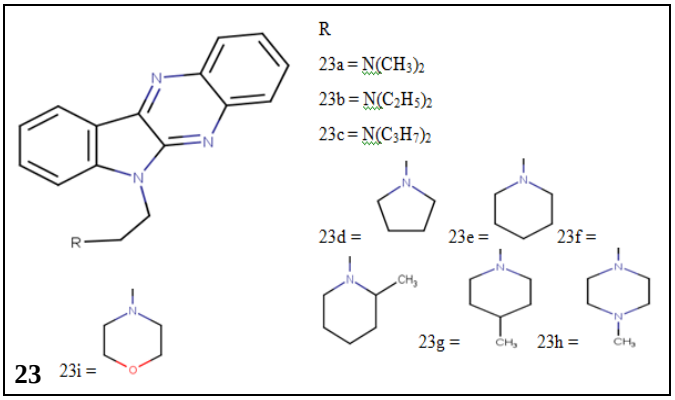
various bromide derivatives. The inhibition activities of these compounds against SARS CoV 3CL^{pro} were assessed by fluorescence resonance energy transfer (FRET) method and confirmed via HPLC analysis. The IC_{50} values demonstrated that these isatin derivatives inhibited SARS CoV 3CL^{pro} in low micromolar range (0.95–17.50 µM). In particular, compound 22f with IC_{50} = 0.95 µM was reportedasone of the most potent and selective SARS CoV 3CL^{pro}inhibitors [20].



22

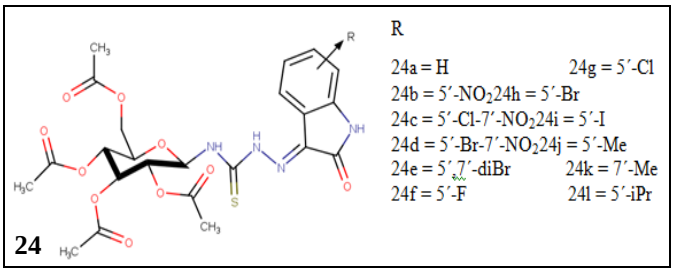
R^1	R^2	R^3	R^4
22a = H	CN	H	
22b = H	I	H	
22c = H	H	NO_2	
22d = H	H	Br	
22e = H	F	H	
22f = H	I	H	
22g = H	I	H	

Synthesis of new 6-(2-aminoethyl)-6H-indolo[2,3-b]quinoxalines(23) using bromoethylisatin and 6-(2-bromoethyl)- 6H- indolo[2, 3-b]quinoxaline as starting materials were reported [21]. These compounds were screened for antiviral activity against vesicular stomatitis virus (VSV). It was shown that compounds 23d and 23f demonstrate the maximal antiviral activity against L929 cells (-lg IC_{50}= 5.65 and -lg IC_{50}= 5.72, respectively).



23

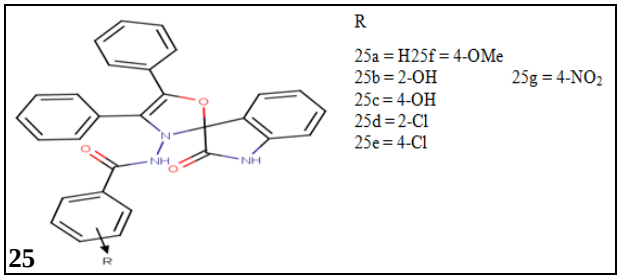
5. Antifungal Activity: Some novel series of isatin N-(2, 3, 4, 6-tetra-O-acetyl-b-Dglucopyranosyl) thiosemicarbazones (24) with different substituents at 1-, 5- and 7-positions of isatin ring were synthesized by reaction of N-(2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyl)thiosemicarbazide with substituted isatins. All the compounds were evaluated for their *in-vitro* antifungal activity against *Aspergillus niger* (439), *Candida albicans* (ATCC 7754), *Fusarium oxysporum* (M42) and *Saccharomyces cerevisiae* (SH20). The results revealed that compound 24e with two bromine atoms at 5th and 7th positions is most active amongst these thiosemicarbazones with MIC = 3.12 µM and MIC = 6.25µM against *Aspergillus niger* and *Candida albicans*, respectively [22].



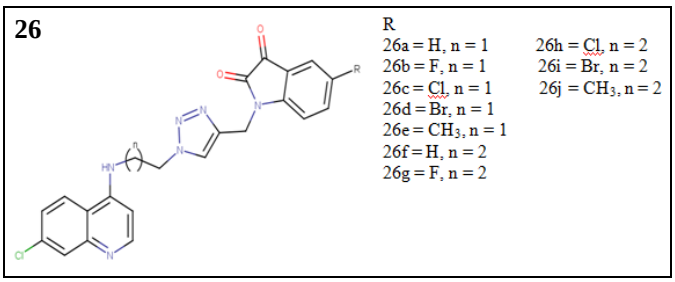
24

In another study, two series of new 2,3-dihydrooxazole-spirooxindole derivatives (25) were efficiently synthesized and screened for antifungal activity against different pathogenic strain of fungi.

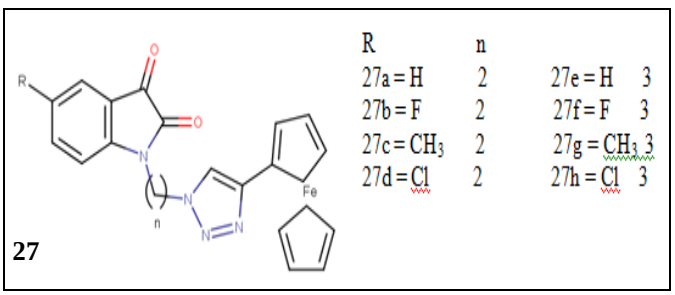
The minimum fungicidal concentration (MFC) was determined for the test compounds against *Pyricularia oryzae, Pseudo-perenospora cubensis, Sphaerotheca fuliginea* and *Phytophthora infestans* through the disc diffusion method. The results showed that compounds 25f have displayed better antifungal activity with MIC = 8 µg/mL against *S. fuliginea* [23].



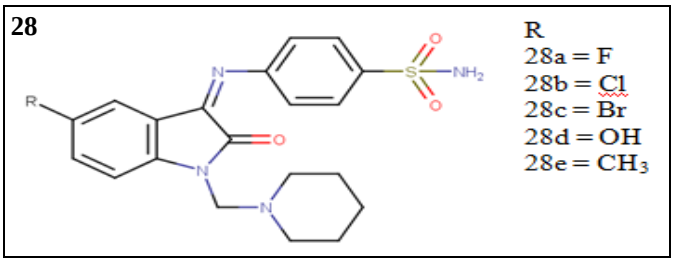
6. Antimalarial Activity: The synthesis of 1H-1, 2,3-triazole tethered isatin-7-chloroquinoline hybrids (26) along with evaluation of their anti-plasmodial activity against the CQ resistant W2 strain of *P. falciparum* were reported [24]. The activity profiles showed dependence on the substituents at the C-5 position of isatin as well as the length of the alkyl chain. Especially, Compound 26 h containing longer alkyl chain length and a chloro substituent at the C-5 position of the isatin ring, with IC_{50} =1.21µM, displayed the best activity among the test compounds when compared to Chloroquine (IC_{50} =0.099 µM).



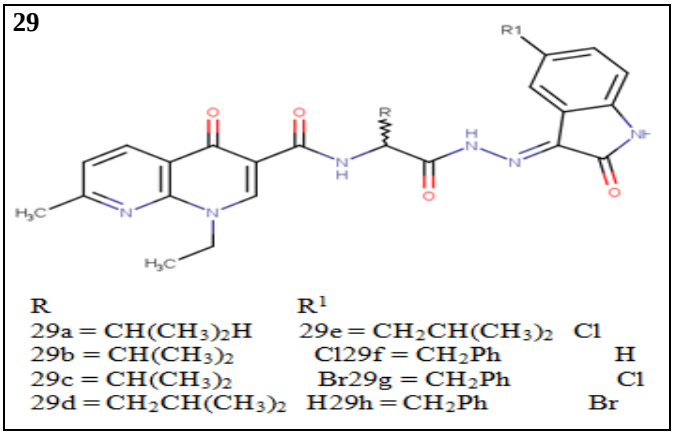
In another study, 1H-1,2,3-triazole tethered isatin-ferrocene conjugates (27) were synthesized and evaluated for their antiplasmodial activities against chloroquine-susceptible (3D7) and chloroquine-resistant (W2) strains of *Plasmodium falciparum*. The results showed that compound 27f and 27h with an optimum combination of electron withdrawing halogen substituent at C-5 position of isatin ring and a propyl chain, introduced as linker, proved to be most potent among the series with IC_{50} values of 3.76µM and 4.58 µM against 3D7 and W2 strains respectively [25].



7. Anti-Inflammatory and Analgesic Activity: In recent study, synthesis of some new Mannich bases of isatin derivatives (28) was reported. These compounds were evaluated for their *in-vivo* anti-inflammatory activities by Cotton pellet-induced granuloma method. The results showed that compounds 28c, 28e, and 28f were the most potent derivatives with percentage inhibition values of 55.44%, 52.58%, and 55.36%, respectively as compared to reference drug Indomethacin (56.82%) [26].

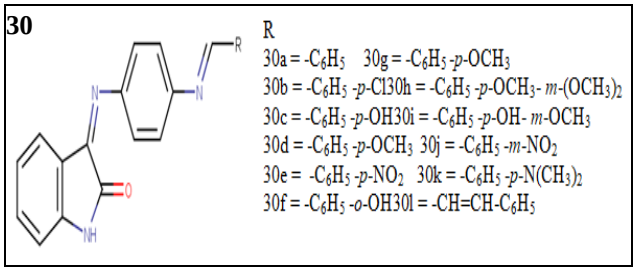


In another work, a series of new Schiff bases (29) by condensations of isatins with the nalidixic acid-L-amino acid hydrazides through a peptide linkage were synthesized. The anti-inflammatory activity of these Schiff bases was evaluated via measurement of the expressed inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in the lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells model. The Schiff bases (29g and 29h) exhibited a significant dual inhibitory effect against the induction of the pro-inflammatory iNOS and COX-2 proteins. Notably, they strongly down-regulated the iNOS expression to the level of 16.5% - 42.2% compared to the effect on COX-2 expression (<56.4% inhibition) at the same concentration (10 µM) [27].



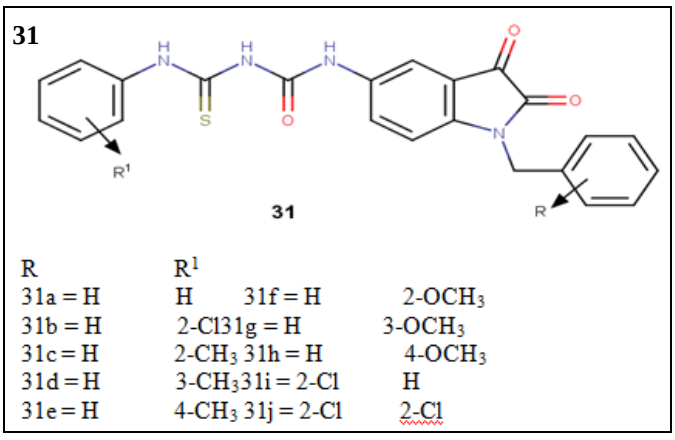
A series of novel Schiff bases of isatin (30) were synthesized by condensation of imesatin with

different aromatic aldehydes. These compounds were screened for the *in-vivo* analgesic activity by the tail-immersion method at a dose of 200 mg/kg body weight. Among the tested compounds, 30i exhibited better analgesic activity with a percentage analgesic activity of 62.62% at 180 minutes when compared to standard Pentazocine (66.11%). The analgesic activity results showed that Schiff bases bearing electron-donating substituents produced significant activity [28].

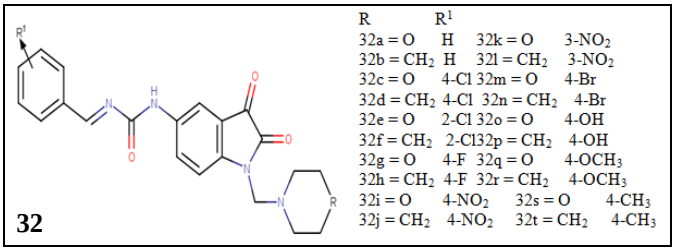


8. Anticonvulsant Activity: A new 1-(amino-N-arylmethanethio)- 3- (1- substituted benzyl-2, 3-dioxoindolin-5-yl)urea (31) were designed and synthesized from 5-Nitroindoline-2, 3-dione. Their *in vivo* anticonvulsant screenings were performed by two most adopted seizure models: maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ).

The results revealed that compound 31f was found active in MES screening while compounds 31h, 351, 31k and 31l showed significant anticonvulsant activity in both the screenings and were devoid of any neurotoxicity. Compound 31h and 31i showed marked protection at 300 mg/kg against MES and scPTZ screening [29].

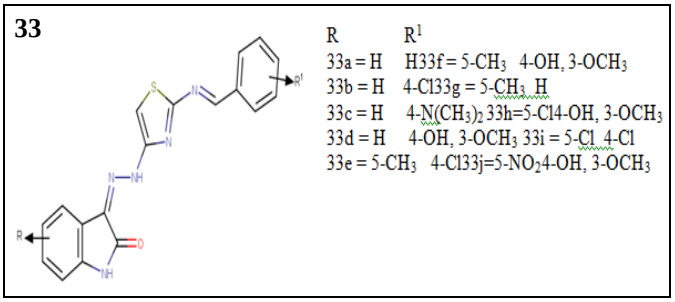


In another study, design and synthesis of novel 1-(substituted benzylidene)- 3- (1 (morpholino / piperidino methyl)-2, 3-dioxoindolin- 5- yl) urea derivatives (32) were reported. All the compounds were screened for anticonvulsant activity using Maximal Electroshock Seizure (MES) test and Subcutaneous pentylenetetrazole (scPTZ) seizures tests. The neurotoxicity was determined by rotorod test. In the preliminary screening, compounds 32c, 32g, 32j, and 32n were found active in MES model, while 32o showed significant anticonvulsant activity in scPTZ model. Among these compounds, 32c revealed protection in MES at a dose of 30 mg/kg and 100 mg/kg 0.5 h and 4 h after i.p. administration, respectively [30].



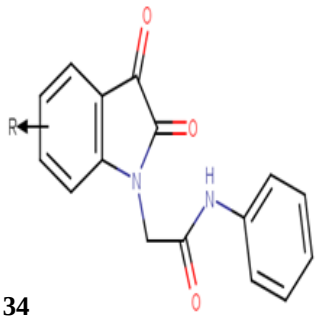
Synthesis of some new isatin-3-[N2-(2-benzal-aminothiazol-4-yl)] hydrazones (33) and their anticonvulsant activity were reported. Anti-convulsant effect was performed by MES and PTZ models.

It is evident that 33b, 33e, 33h, 33i, and 33j showed anticonvulsant effect at the dose levels of 10 and 100mg/kg in the MES test and except 33j, all other derivatives exhibited anticonvulsant effect at 10 and 100mg/kg in PTZ induced convulsions test. They significantly possess anti-convulsant activity by restoring the GABA levels in mice brain was studied [31].



In another work, a series of novel isatin-1-N-phenylacetamide derivatives (34) were synthesized and screened for their *in-vivo* anticonvulsant activity against maximal electroshock test and evaluated for their neurotoxicity by the rotarod test at the same dose levels. The results showed that 34b was found to be the most potent compound of the series with an ED_{50} of 91.3 mg/kg and TD_{50} of

>1,000 mg/kg than the reference drug phenobarbital (ED_{50} = 21.8 mg/kg and TD_{50} = 69 mg/kg) [32].



R
34a = H
34b = *o*-CH_3
34c = *m*-CH_3
34d = *p*-CH_3
34e = *o*-F
34f = *m*-F
34g = *o*-Cl
34h = *m*-Cl
34i = *p*-Cl
34j = *o*-Br
34k = *m*-Br
34l = *p*-Br
34m = 2,4-Br
34n = *p*-NO_2

34

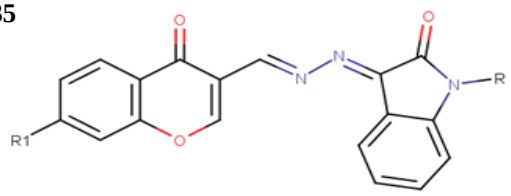
9. Anti-Diabetic Activity: A novel series of chromone-isatin derivatives (35) were synthesized and their *in-vitro* α-glucosidase inhibitory activity was evaluated.

All the synthesized compounds shown excellent to potent inhibitory activity in the range of IC_{50} = 3.18 ± 0.12–16.59 ± 0.17 µM as compared to the standard drug acarbose (IC_{50} = 817.38 ± 6.27 µM).

In particular, compound 35j (IC_{50} = 3.18 ± 0.12 µM) with a hydroxyl group at the 7-position of chromone and a 4-bromobenzyl group at the N1-positions of isatin, was found to be the most active compound.

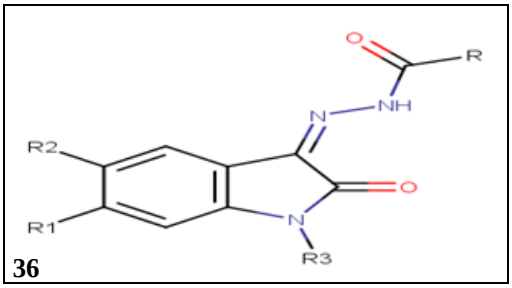
A molecular docking study was also investigated to define the possible binding mode of compounds with the active site of Saccharomyces cerevisiae α-glucosidase [33].

35

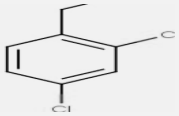
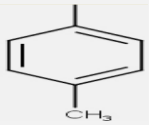
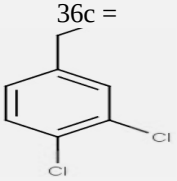
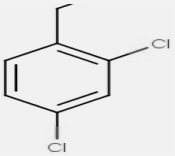
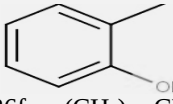


R	R^1		
35a = 4-bromobenzyl	H	35i = 2,4-dichlorobenzyl	OH
35b = methyl	H	35j = 4-bromobenzyl	OH
35c = 4-chlorobenzyl	H	35k = 4-chlorobenzyl	OH
35d = H	H	35l = 3-fluorobenzyl	OH
35e = 3-fluorobenzyl	H	35m = 2-fluorobenzyl	OH
35f = 2-fluorobenzyl	H	35n = 4-fluorobenzyl	OH
35g = 4-fluorobenzyl	H	35o = 2-bromobenzyl	OH
35h = 2-chlorobenzyl	H	35p = 2-chlorobenzyl	OH

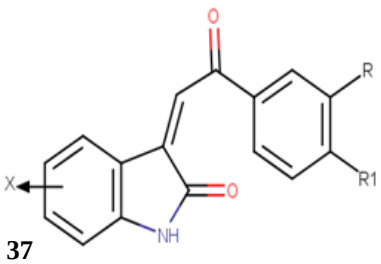
In another study, Synthesis of isatin based Schiff bases (36) in three steps, *via* an esterification by reacting different carboxylic acid with methanol were reported [34]. The synthesized compounds were evaluated for α-glucosidase inhibition. Among the series, compound 36d having IC_{50} value of 2.2 ± 0.25 µM) showed excellent inhibitory potential many fold better than the standard acarbose (IC_{50} = 840 ± 1.73 µM). The binding interaction of these active compounds was confirmed through molecular docking study (PDB Code: 3AJ7).



36

R	R^1	R^2	R^3
36a = 	H	H	$-CH_2CH_2CH_3$
36b = 	Cl	H	H
36c = 	H	Br	H
36d = 	H	Br	H
36e = 	H	Br	H
36f = $-(CH_2)_{10}-CH_3$	H	H	H

10. Antioxidant Activity: A series of new 1, 3-dihydro-3-(2-phenyl-2-oxoethylidene)-2H-indol-2-ones (37) were synthesized and their *in-vitro* antioxidant activity was determined by 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay. The results showed that the majority of compounds with halogen substitution at position 5 of isatin ring exhibited good antioxidant activity within a concentration range of 5-100 µg/ml [35].



X	R	R^1
37a = H	H	H
37b = 5-F	H	H
37c = 5-Cl	H	H
37d = 5-Br	H	H
37e = 5-CH_3	H	H
37f = H	H	OH
37g = H	OH	H

37

CONCLUSION: The basic core of the isatin molecule is prone to several structural modifications and thus intensified its chemical and biological significance towards drug design. Isatin derivative is an excellent candidate having a broad spectrum of activities against various emerging diseases. Hence isatin, a prominent nucleus, should be used as a promising precursor for novel drug development strategies.

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