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Search for Biological Active Isatins: A Short Review

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ABSTRACT
Isatin and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Isatin and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. In the past few decades, Isatin and its derivatives have received much attention due to their chemotherapeutic values. This review covers updated information on the most active isatin derivatives that have been reported to show considerable pharmacological actions such as antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic. From these results, ideas for future molecular modifications leading to compounds with greater favorable pharmacological properties may be derived.

Keywords: Isatin derivatives, antimicrobial, anticancer, antiviral, anticonvulsant, anti-HIV.

INTRODUCTION

Isatins are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry. A literature survey identified several isatin derivatives in the development phase as potential new drugs. A variety of biological activities are associated with isatin including CNS activities as potentiation of pentobarbitone induce nercosis, analgesic, anticonvulsant, antidepressant, antiinflammatory, antimicrobial, and effects on the central nervoussystem. Isatins are capable of crossing the blood–brain-barrier. Isatin, a heterocyclic compound was identified in animals as a major component of the endogenous monoamine oxidase inhibitor. The various substituents at 3rd position of the isatin which were reported various substituted phenyl ring moieties, heterocyclic rings and aliphatic system. Isatin (1*H*-Indole-2, 3-dione) is one of the most promising new class of heterocyclic molecules having many interesting activity profiles and well-tolerated in human subjects. The 2-oxoindoles derivatives of SU-5416 (semaxanib) and SU-11248 (Sunitinib) were reported having tyrosine kinase inhibitory and antiangiogenic properties. Besides, the structurally relevant SU9516 was reported a potential inhibitor of cyclin-dependent kinases (CDKs) that can induce apoptosis in colon carcinoma cells. In addition, CDK inhibitory properties in isatin derived phenylhydrazone has also been reported. On the basis of above discussions isatin can be regarded as strong candidates for future investigations.

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1. Antimicrobial Activity

Synthesis of 2-[-1-(5, 8-dihydro qinoxalino[2, 3-b] indolo acetyl)-3(1-benzofuran-2-yl)-4, 5-dihydro-1H-pyrazol-5-yl]phenyl derivatives **(1)** were reported by Manna *et al*. [1] The synthesized compounds 1a, 1b, 1c showed good antimicrobial activity and MIC were found below 10 µg/ml against *E. coli* (10.0, 5.0, and 8.0), *P. aereuginosa* (5.0, 10.0, and 9.5) and *S. aureus* (7.5, 8.5 and 2.5).

Synthesis of some new triazine derivatives **(2)** were reported by Pandeya *et al*. [2] All the synthesized compounds **2(a-f)** were tested for their antimicrobial activity against 20 strains of gram negative and gram positive bacteria. Among the compounds tested, the compound 2d and 2e showed good antimicrobial activity in comparison to the standard Suphamethoxazole. Compound 2e was found to be most active in series against *H. Pylori* with MIC 25 µg/ml.

Synthesis of several new spiro indoline–based hetrocycles **(3)** was reported by Abdel-rahman *et al*. [3] The synthesized compounds 3a, 3b, 3c, 3d showed comparable activity in which 3b, 3c revealed very high activity (Fig. 1) against *S. subtilis* (65.0, 75.0, 66.0, 42), *E. coli* (54.0, 59.0), and *A. niger* (85.0, 70.0, 63.0, 58.0) with respect to the used references Ampicillin and Chloramphenicol. Results have been given in Fig. 1.

Synthesis of new 1-alkyl/cyclohexyl-3, 3-diaryl-1'methyl-spiro [azetidine-2, 3'-indoline]-2', 4-diones **(4)** were reported by Singh *et al.* [4] The synthesized compounds 4a, 4b, 4c

showed the activity against the bacterial strains in which 4b with two 4-methyl phenyl group showed activity against bacterial strains, *B.subtilis, P. aeruginosa*, and *S. aureus.*

Synthesis of some new isatin derivatives **(5)** were reported by Bari *et al.* [5] The synthesized compounds 5(i-v) showed antimicrobial activities which were done by disc diffusion technique which is shown in Fig. 2. Among the compounds tested, the compound with 5-Br substitution showed the most favorable antimicrobial activity against *A. niger, C. albicans.*

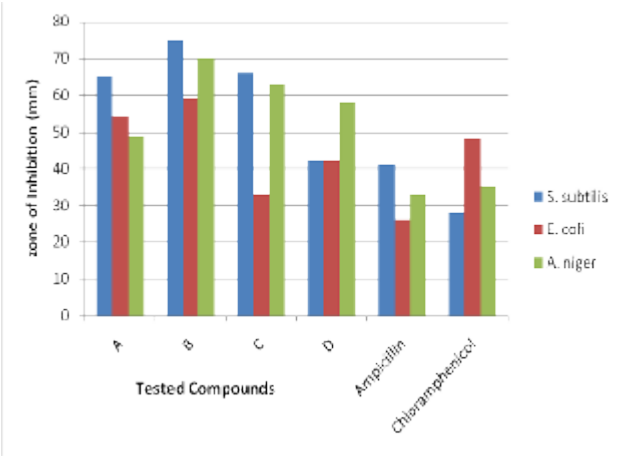


Fig. 1: The percentage inhibition of antimicrobial activity of the tested compounds (0.075-0.018 µg/ml) and standard drug ampicillin and chloramphenicol (0.2-0.3 µg/ml)

Fig. 2: By paper disc diffusion method- zone of inhibition at different concentrations (mm)

Synthesis of 3, 4'-dihydro-3-[2'-mercaptothiazolidine] indol-2-ones derivatives **(6)** were reported by Pardasani *et al.* [6] Synthesized compounds 6a, 6b, 6c showed moderate activity against *E. coli, S. facralus, R. solani* and *F. solani*.

The synthesis and antibacterial activity of two spiro[indole]thiadiazole derivatives **(7)** were reported by Olomola *et al.* [7] All the three compounds 7a, 7b, 7c were tested for antibacterial activity against gram positive and gram negative bacterial strains. 7a showed activity against 4-gram positive and 1-gram negative bacterial strains, while 7b showed activity against 3-gram positive and 2-gram negative bacterial strains. Compound 7c showed activity against 4-gram positive and 3-gram negative bacterial strains (better activity than streptomycin, the reference standard).

Synthesis of Mannich bases of norfloxacin with formaldehyde and several isatin derivatives **(8)** were reported by Pandeya *et al.* [8] The synthesized compounds 8(i-v) were evaluated for their *in vitro* antibacterial activity against many pathogenic bacterial strains (*S. typhimurium, V. parahaemolyticus, V. cholera* 0139 etc.). The compound 8-iii (3.7 times) and 8-iv (4.8 times) were more active (0.018-0.61µg/ml) to that of norfloxacin (1.22 µg/ml) against *B. subtilis*.

2. Anticancer Activity

Synthesis of substituted 1*H*-indole-2, 3 diones (isatin) **(9)** were reported by Vine *et al.* [9] The synthesized compounds 9a, 9b, 9c showed the greater selectivity towards leukemia and lymphoma cells over breast, prostate and colorectal carcinoma cell lines. The most active compound 5, 6, 7 tribromo-isatin (9c) shown antiproliferative at low micromolar concentration and also activated the effector capsases in a dose dependant manner.

Synthesis of isatin-benzothiazole analogs **(10)** were reported by Solomon *et al.* [10] The synthesized compounds 4-chloro-1-dimethylaminomethyl-3-(6-methylbenzothiazol-2-ylimino)-1, 3-dihydroindol-2-one (10c) and 4-bromo-1-diethylaminomethyl 1-H indol-2, 3-dion (10b) emerged as most active compounds. The cytotoxic effect of 10b was 10-15 folds higher on cancer than non-cancer cells.

Synthesis of a series of functionalized isoindigos structurally related to meisoindigo(1-methylisoindigo) **(11)** were reported by Wee *et al.* [11] The synthesized compounds 11a and11b [1-phenpropylisoindigo and 1-(p-methoxy-phenethyl)-isoindigo] evaluated for antiproliferative activities on a panel of human cancer cells. These compounds were more potent than meisoindigo and comparable to 6-bromoindirubin-3'oxime on leukemic K562 and liver HuH7 cell were identified.

Synthesis of 3, 5-dialkylamino substituted 8*H*, 10*H*, 15*H*, 15b(S)-2,3,6,7-tetrahydro-1,5,3-dioxazepino[3,2-c]pteridine-7-one derivatives **(12)** were reported by Ge *et al.* [12] The synthesized compounds 12a and 12b showed potential anticancer agent. Preliminary results showed that they were active as inhibitors of the growth of murine leukemia L1210 cells in vitro with IC_{50} values of 4-20µM, comparable to Ellipticine (reference drug).

3. Antiviral Activity

Synthesis of some new 6-(2-aminoethyl)-6-*H*-indolo [2, 3-b] quinoxalines **(13)** were reported by Shibinskya *et al.* [13] The synthesized compounds 13(a-f) were screened for the antiviral activity. The selective index (SI) value as the integral parameter of the antiviral effectiveness was determined as the ratio of the CC_{50} to the IC_{50} (SI =CC_{50}).

Synthesis of *N*-substituted isatin derivatives **(14)** were reported by Chen *et al.* [14] The synthesized compounds 14a, 14b, 14c and d shown as potent and selective inhibitors

against SARS Coronaviral 3CL Protease with IC_{50} values ranging from 0.95 to 17.50 μM and isatin 14a exhibited more potent inhibition for SARS Coronavirus Protease.

Synthesis of 6*H*-indolo [2, 3-b] quinoxaline derivatives **(15)** were reported by Andrien *et al.* [15] The synthesized compounds 15a, 15b, 15c and 15-i, 15-ii, 15-iii as antiviral agents and have shown to interact with the minor groove of DNA.

Synthesis of a series of benzimidazole-isatin oximes **(16)** were reported by Venables *et al.* [16] The synthesized compounds 16a, 16b and 16c showed the antiviral activity and as inhibitors of respiratory syncytial virus (RSV) replication in cell culture with EC_{50} ranging from 18 to 50 μM, with excellent HLM stability.

The synthesis of a novel series of lamivudine prodrugs involving N^4-substitution with isatin derivatives **(17)** were reported by Sriram *et al*. [17] The synthesized compounds 17a and 17b showed *in-vitro* antiretroviral activities and compound 17b was found to be equipotent to lamivudine with EC_{50} OF 0.0742 ± 0.04 μM.

Synthesis of a series of novel substituted isatin ribonucleosides **(18)** were reported by Oliveira *et al.* [18] Synthesized compounds showed antiviral activity on HSV-1 infected cells. Compounds 18a and 18c showed inhibitory activity and ribonucleoside 18c showed 66% inhibitory activity on HIV-1 reverse transcriptase.

4. Anticonvulsant Activity

Synthesis of a series of 2-aryl-2, 5 dihydropyridazino[4, 3-b]indol-3(3H)ones **(19)** were reported by Palluotto *et al.* [19] The synthesized compounds 19a, 19b, 19c and 19d showed anticonvulsant activity. The onsets of clonic and tonic seizures were significantly reduced 45 min. after ip. (intraperitoneal) administration of derivatives 19(a-d) and comparable with standard drug (Flumazenil).

Synthesis of a series of a 2-aryl -2, 5-dihydropyridazino [4, 3-b] indol-3(3H) ones **(20)** were reported by Campagna *et al.* [20] Synthesized compounds 20 a, 20b and 20c were evaluated for their good ability to prevent pentylenetetrazole (PTZ) induced seizures in mice.

Synthesis of N-aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2*H* isoindol-2-yl)butanoyl hydrazides/butanamides **(21)** were reported by Rajavendran *et al.* [21] Anticonvulsant activity was determined using four animal models of seizures which included MES, subcutaneous (sc PTZ) intraperitoneal Picritoxin (ip PIC) induced seizures threshold test. Compounds were ineffective in MES test up to 300 mg/kg and showed protection in sc PTZ screen included 21i, 21ii, and 21iii. These compounds were found to be more potent when compared to standard drug phenytoin and ethosuximide, and were effective at dose 30 mg/kg.

Synthesis of a series of N^4-(naphtha [1, 2-d] thiazol-2-yl) semicarbazides **(22)** were reported by Azam *et al*. [22] The synthesized 22a, 22b and 22c with chloro, bromo and flouro substituents respectively, showed activity at 100 mg/kg after 0.5 h in MES test is comparable to the standard drug Phenobarbital, indicating that they have rapid onset of action and shorter duration of action.

Synthesis of 3-(4-chloro-phenylimino)-5-methyl-1, 3-dihydro-indole-2-one **(23)** was reported by Sridhar *et al.* [23] The synthesized compounds 23a, 23b, 23c were active in MES test and compound 23b was found to be most active compound and showed 87% protection at 100 mg/kg dose level with an ED_{50} value of 53.61 mg/kg .

Synthesis of 3-cycloalkanone-3, 4-hydroxy-2-oxindoles derivatives **(24)** were reported by Veerasamy *et al.* [24] Synthesized compound 24a and 24b showed the MES test and PTZ test. Compound 24a was active in PTZ seizure threshold test (PTZ), thus act as a potential anticonvulsant.

5. Antiinflammatory and Analgesic Activity

Synthesis of a novel Schiff bases **(25)** were reported by Reddy *et al*. [25] The synthesized compounds were investigated for analgesic (Tail-immersion method) and anti-inflammatory (carrageenan induced paw oedema method). Among the synthesized compounds 25a-d, the compound 25 b, 25c and 25d exhibited remarkable analgesic and anti-inflammatory activity when compared with standard drug (Pentazocin, 10 mg/kg, i.p. and Indomethacin 20 mg/kg).

Synthesis of isatin derivatives **(26)** were reported by Mathues *et al.* [26] The synthesized compounds 26 a-f Inhibited the cyclooxygenase (COX-2) enzymes in RAW 264.7 activated cells. The effect of isatin derivatives on COX-2 protein expression when compared with vehicle treated groups. The incubation of cells with isatin derivatives reduced COX-2 protein expression.

6. Antiplasmodial Activity

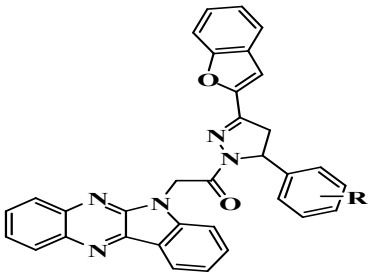
Synthesis of a new class of 4-aminoquinoline derivatives **(27)** based on the natural product isatin scaffold were reported by Clarkson *et al.* [27] The synthesized compounds were screened for biological evaluation against three strains of the malaria parasite *plasmodium falciparum*. These derivatives showed antiplasmodial IC_{50} values in the ranges of 1.3 - 0.079 and 2.0-0.050 μM against a chloroquine – sensitive (D_{10}) and two resistant (K_1 and W_2) strains of *P. falciparum*. Quinoline thiosemicarbazone derivatives [27Xa, 27Xb, 27Ya, 27Yb] showed better inhibition of falcipain-2 compared to the corresponding ketones.

7. Antitubercular Activity

Synthesis of various substituted ciprofloxacin derivatives **(28)** were reported by Sriram *et al.* [28] The synthesized compounds 28a, 28b, 28c and 28d shown better in-vivo antitubercular activity against *M. tuberculosis* than ciprofloxacin in which compound '28c' decreased the bacterial load in spleen tissue with 0.76- log10 protection and was considered to be moderately active in reducing bacterial count in spleen and compound '28d' was found to be more active compound with MIC of 1.21 μM and was five times more potent than ciprofloxacin in-vitro (6.04 μM).

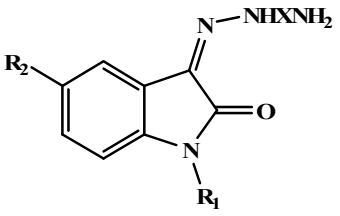
8. Antioxidant activity

Synthesis of 3, 3-bis (4-amino-2, 5-dimethoxyphenyl)-1, 3-dihydroindol-3one derivatives **(29)** were reported by Burnelli *et al*. [29] The synthesized compounds 29a-c and 29i, 29ii were evaluated with 2-methods-the Briggs-Rauscher (BR) oscillating reaction method that works in acidic conditions and the Trolox equivalent antioxidant activity (TEAC) assay working at pH=7.4 and compounds 29a-c and 29i showed good chemical antioxidant activity according to the design of these molecules that included a phenolic OH or OCH_3 groups in their structure.



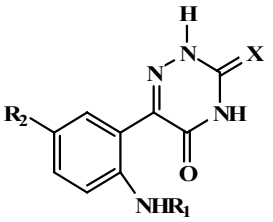
(1)

R= NO_2, OCH_3, H



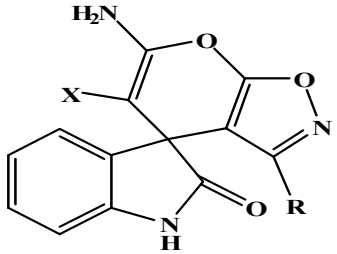
2(a-c)

R_1= H, CH_3, H, R_2= H, X= O, O, S



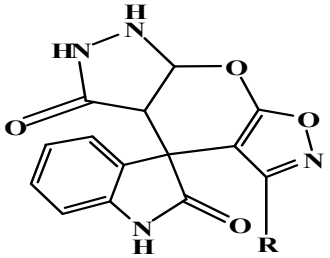
2(d-f)

R_1= H, CH_3, H, R_2= H, NO_2, H
X= O, S, S



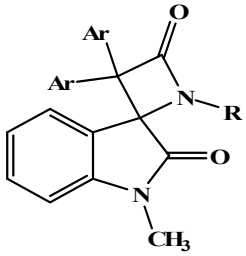
3(a,d)

R= CH_3, C_6H_5, X= $COOC_2H_5$



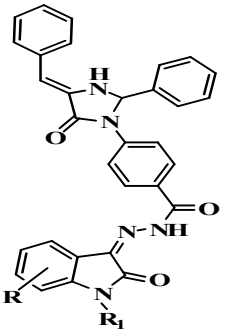
3(b,c)

R= CH_3, C_6H_5



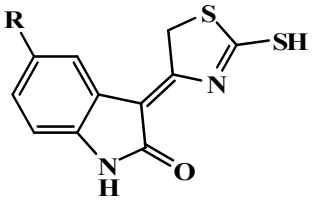
4(a-c)

R= $CH(CH_3)_2$, $CH(CH_3)_2$, $CHPh_2$,
Ar =Ph, 4-$CH_3C_6H_4$, Ph



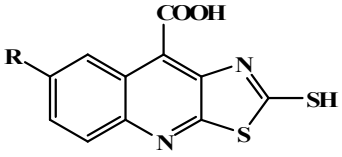
5(i-v)

R= H, 5-Cl, 5-F, 5-Br, 5-CH_3, R_1= H



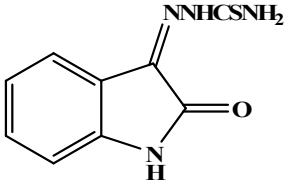
6a

R= H, Br, NO_2

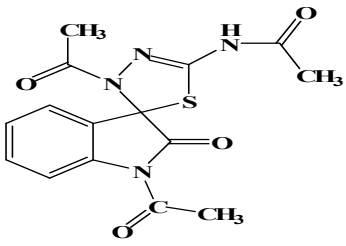


6b

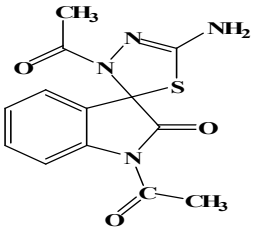
R= H, Br, NO_2



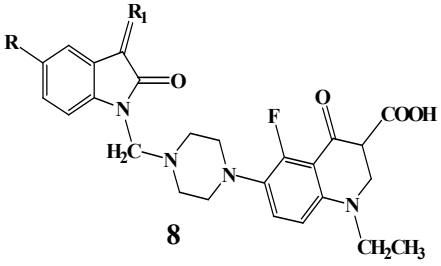
7a



7b



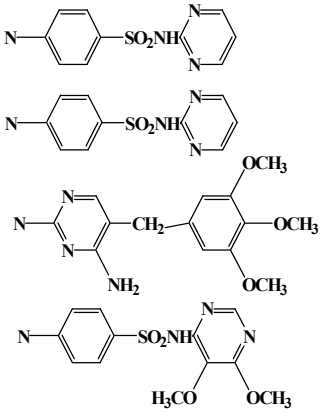
7c

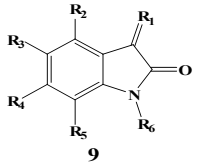


8

R= H, Cl, Br, H, Cl

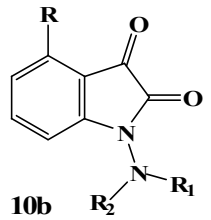
R_1 =





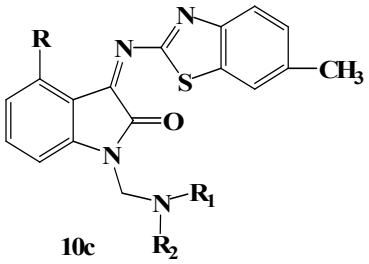
9

	R_1	R_2	R_3	R_4	R_5	R_6
9a	O	H	Br	H	Br	H
9b	O	H	Br	H	NO_2	H
9c	O	H	Br	Br	Br	H



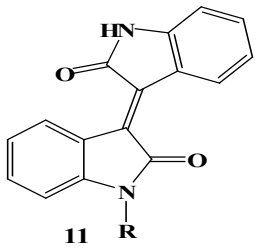
10b

R = Br,
R_1, R_2 = CH_2CH_3



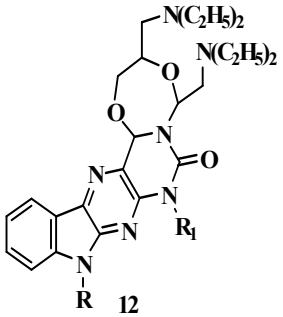
10c

R = Cl
R_1, R_2 = Morpholinyl



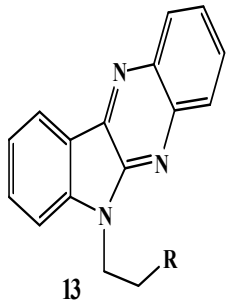
11

11a, R = $(CH_2)_3C_6H_5$
11b, R = $(CH_2)_2C_6H_4$(p- OCH_3)



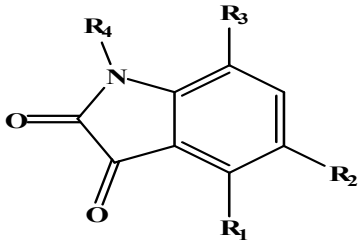
12

R = H, CH_3,
R_1 = triethylamine, 1,4-dimethylpiperazine, triethylamine



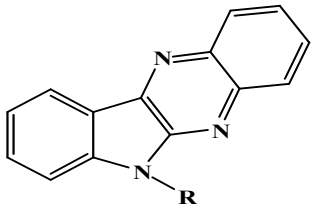
13

R= trimethylamine, pyrrolidine, 1-methylpiperazine, 1-methylpiperidine, morpholine



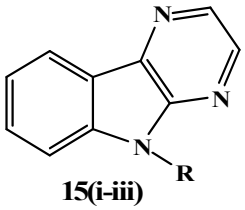
14

R_1=R_3= H
R_2= $CONH_2$, CN, I, NO_2
R_4= 3,4,5-trimethylisoxazole, 2-methylbenzothiophene, 2-methylbenzofuran



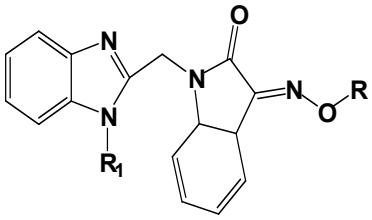
15(a–c)

R= CH_3, $CH_2CH_2N(CH_3)_2$, H



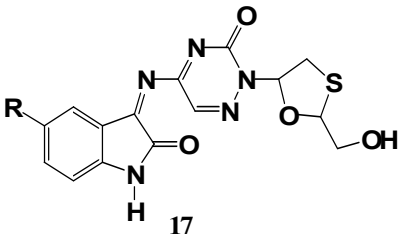
15(i–iii)

R= CH_3, $CH_2CH_2N(CH_3)_2$, H



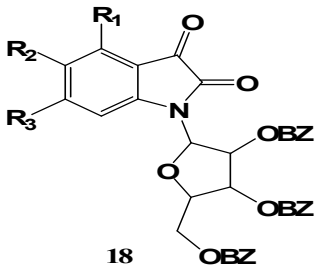
16

R=CH_2CH_2F, CH_2CF_3, CH_2CH_2F
R= $(CH_2)_4OH$, $(CH_2)_4OH$, $(CH_2)_3SO_2CH_3$



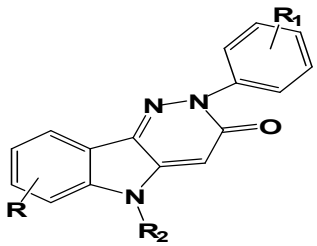
17

R = H, F



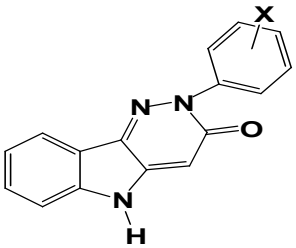
18

a= R_1= R_2= R_3 = H
b= R_1=R_3=H, R_2=CH_3
C= R_1=R_3=Br, R_2=H
OBZ=o-benzoyl-D-ribofuranose



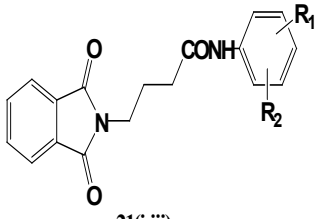
19

R=H, R_1= p-Cl, p-Br, p-OCH_3, p-Cl
R=H, CH_3



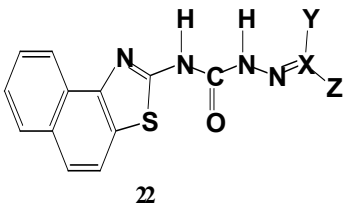
20

X= H, Cl, Br



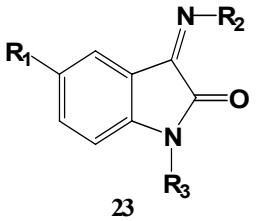
21(i-iii)

R_1=2-CH_3, 3-Cl, R_2 = 4-CH_3, 2-CH_3
R_3 =CH_3, R_4 = 4-CH_3-C_6H_4



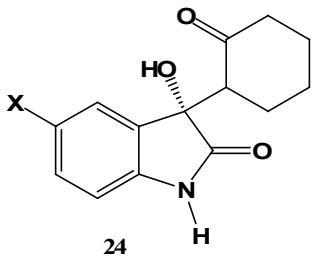
22

X=C, Y=H, Z=4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4



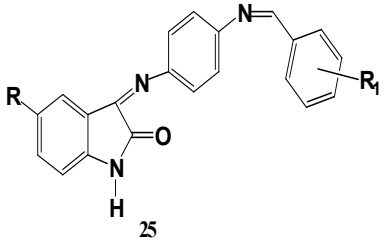
23

R_1 = H, CH_3, CH_3, 4-methylphenyl, 4-chlorophenyl, 1-naphthyl,
R_3 = H



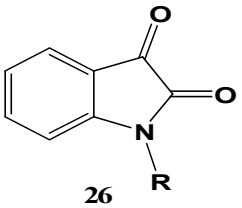
24

X = Br, Cl



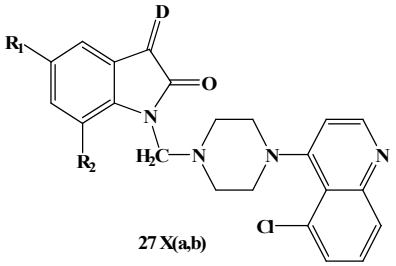
25

R = H, F, Cl, OCH_3
R_1 = Cl, OCH_3, NO_2, OH



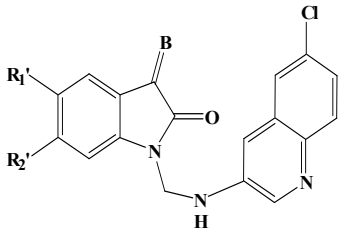
26

R = H, 5-F, 6-Cl, 7-Cl, 4-Br, 5-I, 5-CH_3



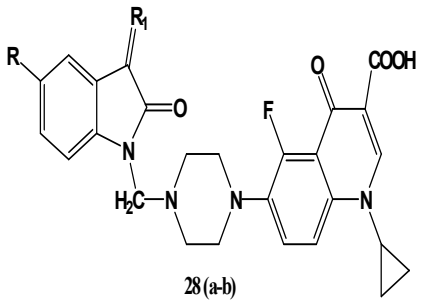
27 X(a,b)

R_1 = H, F
R_2 = H,H
D= NNHC(S)NH_2



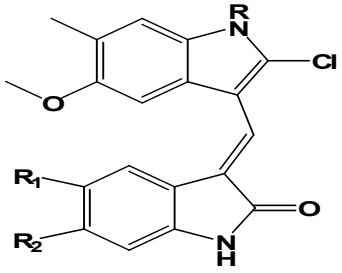
27 Y(a,b)

R_1'= H,CH3
R_2'= H,H
B= NNHC(S)NH_2



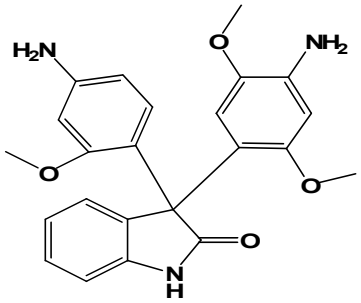
28 (a-b)

R= H, Cl, CH_3, Br
R_1= NNHCONH$_2$

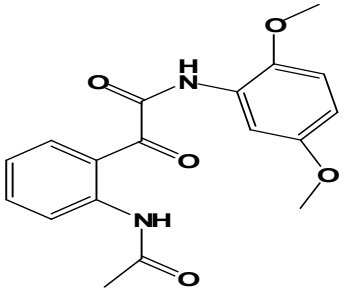


29(a-b)

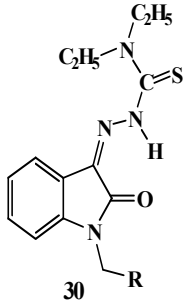
R= CH_3, CH_3, 1-Chlro-4-ethylbenzene
R_1= OH
R_2= CH_3, H, CH_3



29(i)

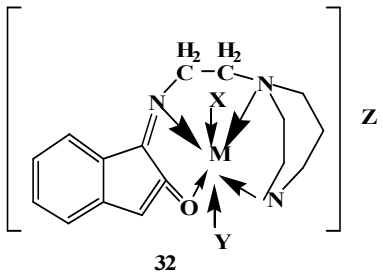


29(ii)



30

R = *N*-benzyl-*N*-methyl(phenyl)methanamine, dimethylamine, 4-methylpiperazine, 4-ethyl-7-fluoro-1,4-dihydro-6-(4-methylpiperazin-1-yl) -1-oxonaphthalene-2-carboxylic acid, 4-(4-nitrophenyl)piperazine, 1-(3-(trifluoromethyl)phenyl)piperazine



32

a- M=Cu, X=H_2O, Y=Cl and Z=$Cl2H_2O$
b- M=Co, X=Y=Cl and Z= --
c- M=Zn, X=Y=Cl and Z= $2H_2O$

9. Anti- HIV Activity

Synthesis of a series of isatin β-thiosemicarbazone derivatives **(30)** were reported by Bal *et al.* [30] The synthesized compounds 30iii, 30iv, 30vi showed significant anti-HIV activity in HTLV-III_B strain in the CEM line whereupon compound 30vi was found to be the most active compound with an EC_{50} value of 2.62 μM and selectivity index of 17.41.

Synthesis of some new isatin analoges **(31)** for effective treatment of AIDS were reported by Pawar et al. [31] The synthesized compounds 31a, 31b and 31c were found to be comparable with standard indicated that isatin analoges have

good binding affinity for Non-Nucleoside Binding Pocket (NNBP).

10. Anthelmintic Activity

Synthesis of a new series of tetradentate Schiff bases **(32)** were reported by Reddy *et al*. [32] The synthesized ligand and metal complexes 32a, 32b, 32c were screened for anthelmintic activity against earthworm (*peretima posthuma*) using 5 µg/ml concentration. The graphical representation of synthesized compounds showed the anthelmintic activity in Fig. 3.

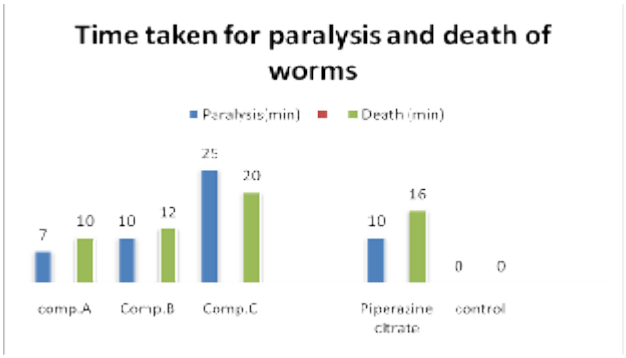


Fig. 3: The anthelmintic activity of the tested compounds (5µg/ml) and standard drug piperazine citrate (1mg/0.02ml).

It has been observed so far, that the alterations on isatin moiety displayed valuable biological activities and these alterations can be utilized to develop potentially active agents in future investigations. Thus, the search to explore many more modifications on isatin moiety needs to be continued.

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