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A mini review diverse biological activities of heterocyclic indole analogues

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Abstract
Various heterocyclic analogues were found to possess promising pharmacological activities. Various indole analogues are also attracted the attention of researchers because of the diverse biological activities. Indole nucleus is present in many natural as well as synthetic products. Due to its wider applications the indole analogues, they will replace many existing heterocyclic based pharmaceutical products. Now days, various drugs are in market and several are in clinical trials. Various indole analogues were identified as a privileged structure of pharmacophore and possess broad spectrum of biological and pharmaceutical activities such as anticancer, antihypertensive, antidepressant, antipsychotic, anti-inflammatory, antiemetic, analgesic, anti-asthmatic, antiviral, anti-arrhythmic, β-blocker, inhibitor of RNA polymerase-11, agonist for the cannabinoid receptor, non- nucleoside reverse transcriptase inhibitor, opioid agonist and sexual dysfunction etc. Indole derivatives have been special interest to organic and medicinal chemists.

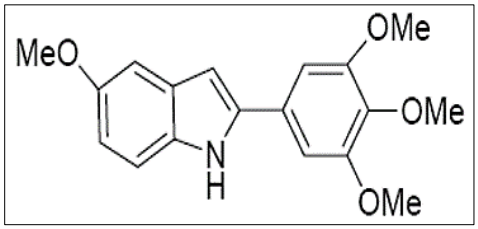
Keywords: Indole, anti-inflammatory, antimicrobial, anticonvulsant, anticancer, antihistaminic, diagnostic agents

Introduction

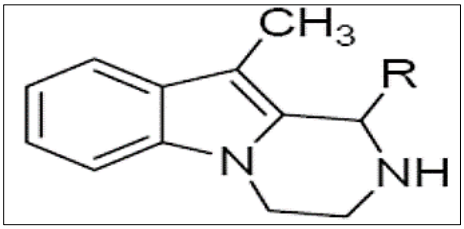
Medicinal chemistry is concerned with determining the influence of chemical structure on biological activities. The organic synthesis of new compounds based on the modifications of structures and then discovery, development, interpretation and identification of mechanism of action of pharmacological active compounds. Various pharmacologically active compounds have five-member nitrogen-containing heterocyclic ring in their structures [1]. The heterocyclic ring comprises of very core of the active pharmacophore and about half of the therapeutic agents consist of heterocyclic compounds [2]. Indoles are important class of aromatic heterocyclic compounds with many potent biological activities. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is component of fragrances and the precursor to many pharmaceutical products. Compounds that contain an indole ring are called indoles. Indolic amino acid tryptophan is the precursor of the neurotransmitter serotonin. Indole is present in various marine or terrestrial natural compounds with useful biological properties. Various alterations conducted on indole ring containing few important marketed drugs and their associated biological activities. Indole and its analogs constitute the active class of compounds possessing wide range of pharmacological activities. Various indole analogues have been exhibited antibacterial, antiplatelet, antiulcerative, antiviral, anti-inflammatory, analgesic, antileishmanial, antimalarial, anticancer, immunomodulator, inhibition of chemical mediator's release, antioxidant, antitubercular and inhibition of leukotriene B_4 inhibition of tyrosinase inhibition of aldose-reductase activities [3-12].

Pharmacological activities on indole and their analogues

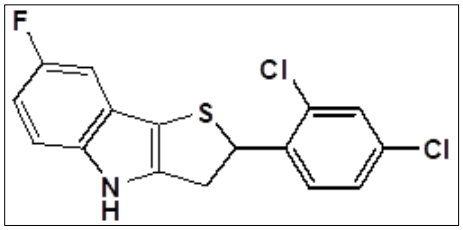
Antibacterial activity: Infections caused by pathogenic bacteria are of major health concern and new antibacterial drugs are needs to treat infections. The heterocyclic Schiff bases derived from the condensation reactions of indole 3-carboxaldehyde with different amino acids (histidine, aspartic acid, glutamic acid, valine, leucine) and some aminophenols were tested as antimicrobial agents and showed moderate to good bacterial and fungal activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas fluorescence*, *Aspergillus niger*, *Candida albicans* and *Trichophyton rubrum* [13]. The 1, 3, 4, 5-tetrahydropyrano [4, 3-b] indoles were tested for their antimicrobial activity. The compound (I) exhibited the most significant activity (3.9µg/ml) against the Gram-positive microorganism *B. cereus* [14]. A series of substituted 1, 2, 3, 4-tetrahydropyrazino indole derivatives have been tested against bacterial strain namely *S. aureus* (MTCCB 737), *S. typhi* (MTCCB 733), *P. aeruginosa* (MTCCB 741), *Streptomyces thermonitrificans* (MTCCB 1824) and *E. coli* (MTCCB 1652). All the compounds were showed mild to moderate activity. However, compounds (IIa-b) were found potent activity against pathogenic bacteria. Their MIC ranged from 3.75 to 60µg/disc [15]. A series of 2-aryl-3, 4-dihydro-2*H* thieno [3, 2b] indoles has been synthesised regioselectivity in good yields from the reaction of 5-aryldihydro-3(2*H*)-thiophenones and arylhydrazine hydrochloride. The thieno [3, 2-b] indoles were evaluated for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv and multi-drug resistant *M. tuberculosis* (MDR-TB) and screened [2-(2, 4-dichlorophenyl)-7-fluoro-3,4-dihydro-2*H*-thieno [3, 2-b] indole] (III) and was found to the most active compound with MIC of 0.4 lg/mL against MTB and MDR-TB [16].



I

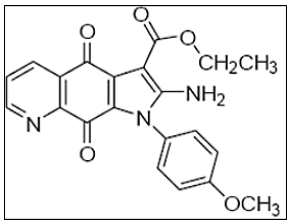


IIb R=p-$CH_3C_6H_4$ **IIa** R = p-FC_6H_4

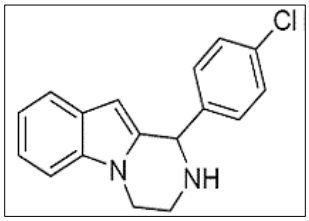


III

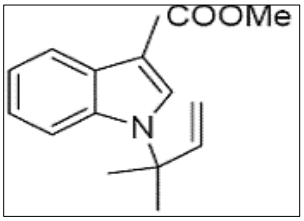
Antifungal activity: Invasive fungal infections, particularly in immunosuppressed patients, are still difficult to diagnose clinically. This need for advent of safe, novel and effective antifungal drugs. Compound 4,9-dioxo-4,9-dihydro-1H-benzo[f]indoles (IV) was found to be potent *In vitro* antifungal against fungi [17]. A series of substituted-10-methyl-1,2,3,4-tetrahydropyrazino [1,2-a] indole derivatives have been tested for their activity against pathogenic strains of *Aspergillus fumigatus* (ITCC 4517), *A. flavus* (ITCC 5192) *A. niger* (ITCC 5405) and *C. albicans* (ITCC No 4718). The most active 1-(4-chlorophenyl)-10-methyl-1, 2, 3, 4-tetratetrahydropyrazino [1, 2-a] indole (V) exhibited a MIC value of 5.85 µg/disc against *A. fumigatus* and 11.71 µg/disc against *A. flavus* and *A. niger*. Anti-*Aspergillus* activity of active compound was found to be 15.62µg/ml in case of *A. fumigatus* and 31.25 µg/ml with *A. flavus* and *A. niger*. The MIC_{90} value of the most active compound was found to be 15.62 to 250µg/ml against *A. fumigates*. The *in vitro* toxicity of most active compound was found to be non-toxic to human erythrocytes up to 312.50µg/ml. The standard drug amphotericin B exhibited 100% lysis at 37.5µg/ml [18]. Two antifungal alkaloids (VI) and (VII) and the N-isoprenyl-indole brominated key-intermediate (VIII) were inhabited fungus *Aporpium caryae* [19].



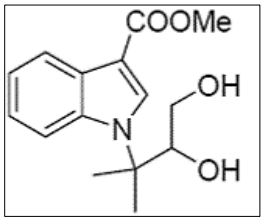
IV



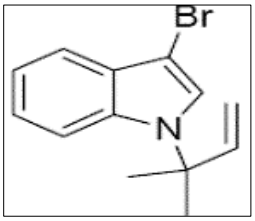
V



VI

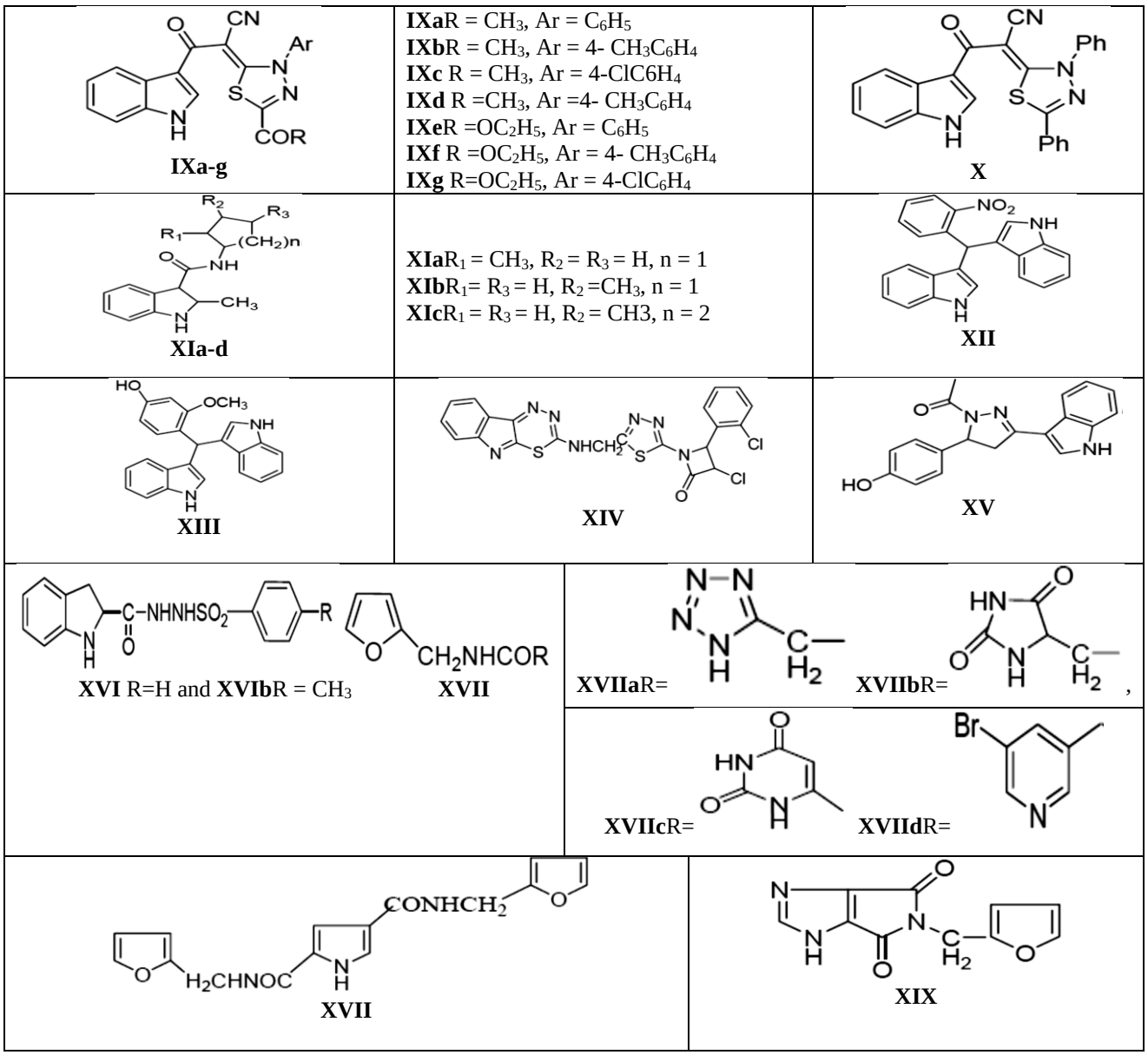


VII

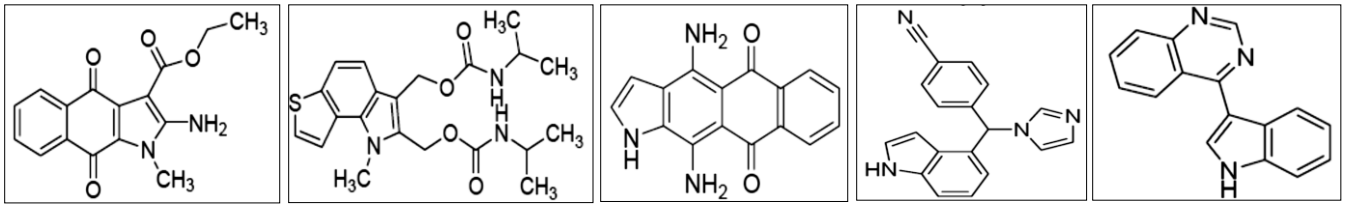


VIII

Anti-inflammatory activity: Acute and chronic inflammation and various type of arthritis are the inflammatory disorders, newer non-steroidal anti-inflammatory drugs is the only way to strengthen against this dreadful threat. The thioacetanilide derivatives with hydrazonoyl chlorides afforded the 1, 3, 4-thiadiazole derivatives (IXa-g) and X). These compounds were found to possess potential anti-inflammatory and analgesic activities [20]. a series of indole-3-carboxamides derivatives were tested for their analgesic and anti-inflammatory activities and their gastrointestinal irritation liability. Indomethacin was used as reference drug. Compounds (XIa-d) were found to be the most active anti-inflammatory activity, with dose-dependent effect [21]. Acute toxicity, analgesic, anti-inflammatory and ulcerogenic activities of the bis (indolyl) methanes were evaluated *in vivo* in comparison to standard drugs (ibuprofen and indomethacin). In acute toxicity study, no mortality is observed in the tested compounds and all the tested compounds were showed significant analgesic and anti-inflammatory activity without an ulcerogenic activity the most active compounds of this series were (XII) and (XIII) [22]. The 3-chloro-4-aryl-1-{5-[{[1, 3, 4] thiadiazinoindol-3-ylamino]methyl]-1, 3, 4-thiadiazol-2-yl} azetidin-2-one were tested for their anti-inflammatory, ulcerogenic and analgesic activities. Compound (XIV) has shown most active anti-inflammatory and analgesic activities with better ulcerogenic activity than phenylbutazone [23]. Chalcones of indole and their derivatives were tested for their anti-inflammatory activity at a dose of 50 mg/kg oral. The active compound was 3-[1-acetyl-5-(*p*-hydroxyphenyl)-2-pyrazolin-3-yl] indole (XV) was found to be most potent, which has shown higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than phenylbutazone [24]. Indole-2-carboxylic acid on condensation with benzene sulfonyl hydrazide and p-toluene sulfonyl hydrazide give the condensation products (XVIa) and (XVIb). 1*H*-Tetrazole-5-acetic acid, hydantoin-5-acetic acid, orotic acid, 5-bromo nicotinic acid and indole 2-carboxylic acid has been condensed with furfuryl amine to give corresponding condensation products (XVIIa-d) 3, 5-pyrazole dicarboxlic acid 4,5-imidazole dicarboxylic acid and 3-carboxy-1, 4-dimethyl pyrole-2-acetic acid on condensation with furfuryl amine was given compounds (XVIII) and (XIX). All compounds have been tested for anti-inflammatory and analgesic activity. Compounds (XVIIa) and (XIX) exhibit good anti-inflammatory and (XVIIa), (XVIIc) and (XIX) exhibit good analgesic activities [25].

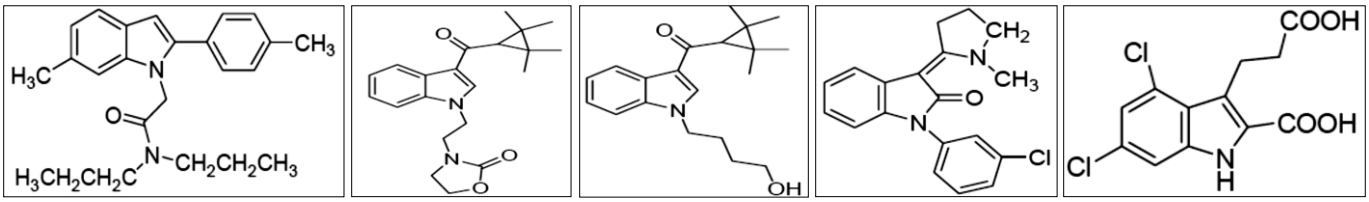


Anticancer activity: Cancer is a major threat to the public health. In the challenge to improve cancer chemotherapy, the search for new drugs with both higher therapeutic index and low induce resistance, an active field of investigation. The 2-amino-3-ethoxycarbonyl-N-methyl benz[f]indole-4, 9-dione (SME-6) (XX) was showed a potent growth inhibition of a panel of human cancer cell lines. The mechanism of action revealed that the growth inhibitory effect of SME-6 was highly related to the induction of G2/M cell cycle arrest and apoptosis in human lung cancer cells (A549) [26]. The cytotoxicity of the bis [*N*-(2-propyl) carbamates] which were linked to thienoindole scaffolds through methylene bridges as thiophene analogues of prototype. Compound (XXI) the thieno indole bis-carbamate, possessed significant (MG-MID $\log_{10}$ GI=−4.89) and selective cytotoxicity against NCI–HOP92 (non-small cell lung), MALME 3M (melanoma) and IGROV 1 (ovarian) cancer cell [27]. The 4, 11-diaminonaphtho indole-5, 10-dione tested for their cytotoxicity for human tumor cells that express major determinants of altered anticancer drug response. The cytotoxicity of compound (XXII) for multidrug resistant, P-glycoprotein-expressing tumor cells was highly dependent on the N-substituent at the terminal amino group of the ethylenediamine moiety [28]. Two series of benzonitrile derivatives on position 6 or 4 of indole ring, all compounds were evaluated *in vitro* on the inhibition of aromatase (CYP19) and 17α-hydroxylase-C17, 20-lyase (CYP17). The racemate, 4-[(1*H*-imidazol-1-yl) (1*H*-indol-4-yl) methyl] benzonitrile (XXIII) showed high level of inhibitory activity toward CYP19 (IC50 = 11.5 nM) [29]. The epidermal growth factor (EGF) family of membrane receptors has been identified as a key element in the complex signaling network that is utilized by various classes of cell-surface receptors. The pharmacological results of 4-(indole-3-yl) quinazolines (XXIV) were described these compounds were new high potent EGFR-tyrosine kinase inhibitors with excellent cytotoxic properties at different cell lines [30].

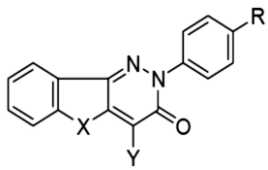


XX **XXI** **XXII** **XXIII** **XXIV**

Anticonvulsant activity: Epilepsy has been recognized as a neurological disorder affecting a large section of people both male and female. Many patients have seizures that are resistant to the available medical therapies. This necessitated the development of a new logical and scientific approach in the discovery of a new drug. Some non-benzodiazepine derivatives and the compound (XXV) 2-(6-methyl-2-p-tolyl-1*H*-indol-1-yl)-*N, N*-dipropyl acetamide is good *in vitro* affinities for the α_1-$GABA_A$ receptor and potent *in vivo* induction of sedation [31]. A series of aminoalkylindoles and found that several substituted aminoethyl derivatives have high affinity for the CB2cannabinoid receptor. Several polar side chain (alcohols, oxazolidinone) (XXVI) were well tolerated for CB2 receptor activity [32]. The compound (Dimethylamino) methy1]-4, 5, 7, 8, 9, l0-hexahydroindolo-indole (XXVII) were found to poses good anticonvulsant activity [33]. A series of l-aryl-3-(aminoalkylidene) oxindoles, compound (XXVIII) was found to be potent enhancers of benzodiazepine binding and they antagonize cyclic GMP elevations induced by isoniazid and have potential therapeutic utility as anticonvulsants or anxiolytics [34]. Tested as an antagonist for the strychnine-insensitive glycine binding site of the N-methyl-D-aspartate (NMDA) receptor, Chlorine and other small electron-withdrawing substituents in the 4 and 6 positions of the indole ring greatly enhanced binding and selectivity for the glycine site over the glutamate site of the NMDA receptor; one of the most potent compounds was 3-(4,6-dichloro-2-carboxyindol-3y1) propionic acid (XXIX) (ICm = 170 nM, >2100-fold selective for glycine) [35]. Large number of pyridazino [4, 3-b] indoles and indeno pyridazines were evaluated for their binding affinities at both central (CBR) and peripheral (PBR) benzodiazepine receptors. Relatively good PBR binding affinities were found for ligands belonging to the 3-arylmethyloxy-pyridazinoindole series, whereas only 2-aryl-indenopyridazines (XXXa-e) exhibits a weak binding affinity for CBR. The structural determinants affecting PBR affinity, a molecular modeling study based on the comparative analysis of the three-dimensional properties of four properly selected derivatives (XXXd, e) and (XXXIa, b] with those of highly active and selective PBR ligands, taken as reference [36]. The identification of GV150526, the indole-2-carboxylate template was further explored in order to identify novel potential anti-stroke agents. The SAR of the side chain present at the C-3 position of the indole nucleus was studied. The pharmacological profile of a further class of conformationally restricted analogues of GV150526 as *in vitro* and *in vivo* potent glycine antagonists ware reported. In particular, pyrazolidinone derivatives [XXXII] and were identified as a potent neuroprotective agent in animal models of cerebral ischaemia [37].

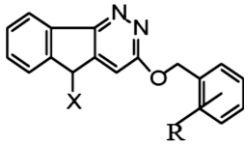


XXV **XXVI** **XXVII** **XXVIII** **XXIX**

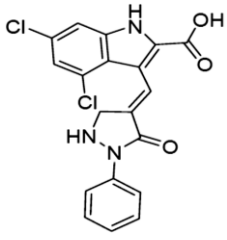


XXXa-e
XXXa X=CH_2, Y = H, R=H,
XXXb X=CO, Y= H, R=H

XXXc X=CH_2, Y=$CO_2C_2H_5$, R=H
XXXd X=NH, Y=CO_2C2H_5, R=4-Cl
XXXe X=CH_2, Y=$CO_2C_2H_5$, R=4-Br
XXXe X=CH_2, Y=$CO_2C_2H_5$, R=4-Br



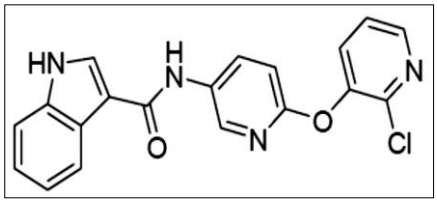
XXXIa X=2-methyl-3-indolyl methyl, R= phenyl
XXXIb X=2-methyl-3-indolyl methyl, R= p-tolyl



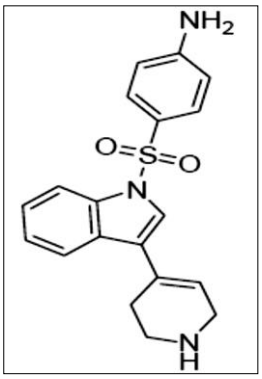
XXXII

Antihistaminic activity: For antihistaminic activity various indole derivatives were evaluated and found to possess significant activity. The 1*H*-indole-3-carboxylic acid [6-(2-chloro-pyridin-3-yloxy)-pyridin-3-yl]-amide (XXXIII) exhibits the highest affinity (IC_{50} =0.5 nM) with an excellent selectivity (>2000 times) over other serotonin (5-HT_{1A}, 5-HT_{2A}, and 5-HT_6) and dopamine (D_2-D_4) receptors [38]. A series of N_1-arylsulfonyl-3-(1, 2, 3, 6-tetrahydropyridin-4-yl) indole derivatives were shown to have high affinity for the 5-HT6 receptor [39]. Two analogs, 4-[3-(1, 2, 3, 6-tetrahydropyridin-4-yl)-1*H*-indole-1-sulfonyl]-phenylamine (XXXIV) and 4-[3-(1, 2, 3, 6-tetrahydropyridin-4-yl)-5-methoxy-1*H*-indole-1-sulfonyl]-

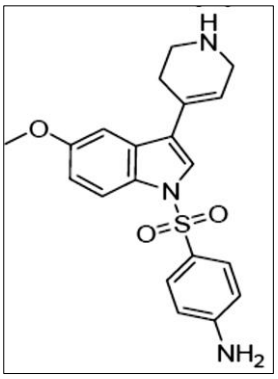
phenylamine (XXXV) had 0.4 and 3.0nM affinity respectively, and antagonized the production of adenylate cyclase at sub-nanomolar concentrations. A series of related arylpiperazin-4-yl-cyclohexyl indole analogs were evaluated as 5-HT transporter inhibitors and 5-HT_{1A} receptor antagonists. The investigation revealed the optimal pharmaco-phoric elements required for activities in this series. The best example from their study, 5-(piperazin-1-yl) quinoline analog (XXXVI) exhibited equal binding affinities at 5-HT transporter (Ki=4.9 nM), 5-HT_{1A} receptor (Ki=6.2 nM) and functioned as a 5-HT_{1A} receptor antagonist [40]. Compounds N-(3-Fluorophenyl)-2-methyl-2, 3, 4, 5-tetrahydro-1*H*-pyrido [4, 3-b] indole-8-sulfonamide hydrochloride HCl (XXXVII) and 2, 5-Dimethyl-8-(phenylsulfonyl)-2, 3, 4, 5-tetrahydro-1 *H*-pyrido [4,3-b] indole hydrochloride HCl (XXXVIII) was reported their ability to interact with 5-HT_6 receptors evaluated in cell-based and radioligand binding assay. Amongst evaluated THPIs, have been identified as the most potent 5-HT_6 receptor antagonists with Ki values equal to 2.1 nM and 5.7 nM and IC_{50} values equal to 15 nM and 78 nM, respectively and Affinities of these two compounds for several serotonin receptors in competitive radioligand binding [41].



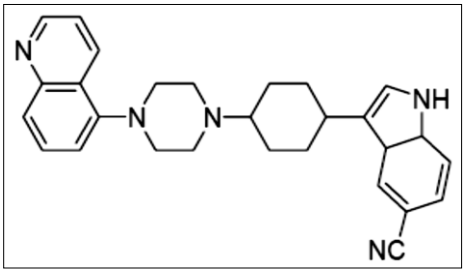
XXXIII



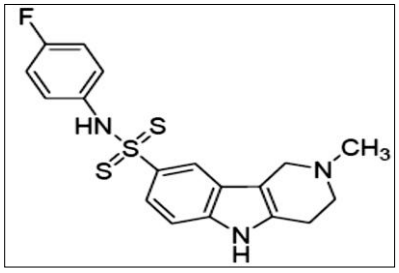
XXXIV



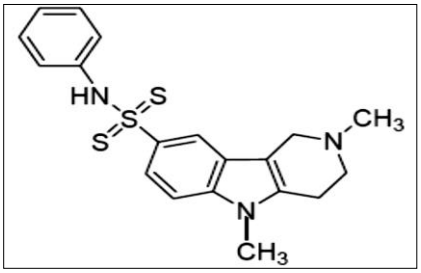
XXXVI



XXXVI

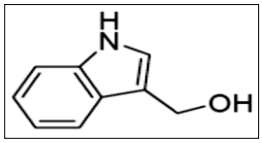


XXXVII

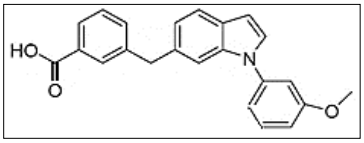


XXXVIII

Current aspects of indole: Indole-3-carbinol (XXXIX) has anti-tumor effects in various cancer cell lines. However, the anti-tumor effect of (XXXIX) on human lung cancers has been rarely reported [41]. The anti-tumor effects on human lung carcinoma A549 cell line. Treatment of the A549 cells with significantly reduced cell proliferation, increased formations of fragmented DNA and apoptotic body, and induced cell cycle arrest at G0/G1 phase increased not only the protein levels of cyclinD1, phosphorylated p53, and p21 but also the expression of Fas mRNA. Cleavage of caspase-9, -8, -3 and PARP also was increased by I3C. Treatment with wortmannin significantly suppressed both induced Ser15 phosphorylation and accumulation of p53 protein. The inhibition of caspase-8 by z-IETD-FMK significantly decreased cleavage of procaspase-8,-3 and PARP in I3C-treated A549 cells. These results demonstrate that induces cell cycle arrest at G0/G1 through the activation of p-p53 at Ser 15 and induces caspase-8 mediated apoptosis via the Fas death receptor. This apoptotic effect of on A549 lung carcinoma cells suggested that (30) may be a preventive and therapeutic agent against lung cancer. Indole ring containing compounds were designed based on the structure of the gp41 complex in the region of the hydrophobic pocket**.** These compounds were evaluated using a fluorescence binding assay and cell–cell fusion assay [42]. The inhibition constant of compound 3-((*E*)-4-methoxyhexa-1, 3, 5-trien-2yl)-1*H*-indol-6-yl) methyl) benzoic acid (XXXX) was 2.1 lM, and the IC50 for cell–cell fusion inhibition was 1.1 lM.

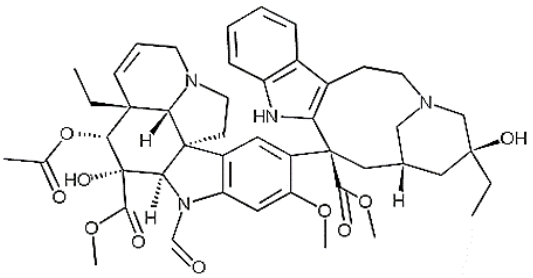
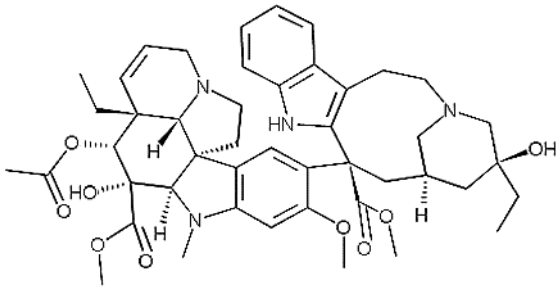
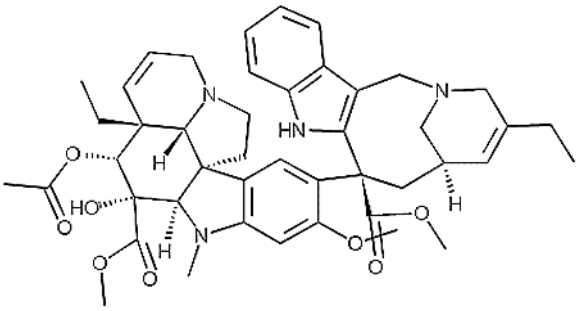
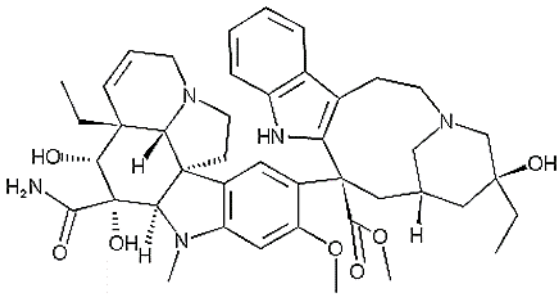
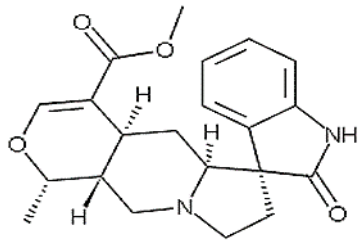
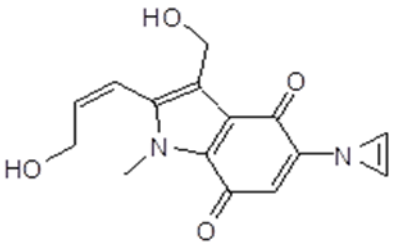
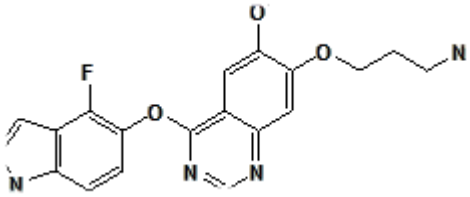
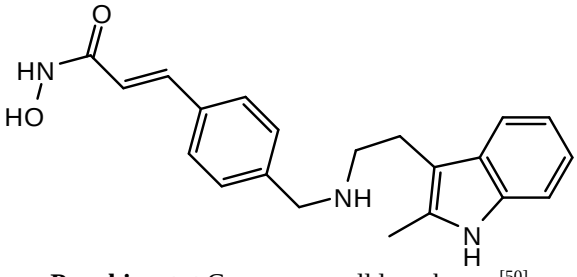
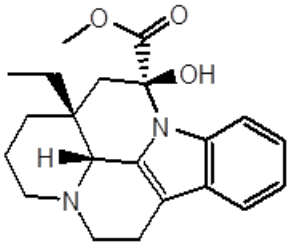
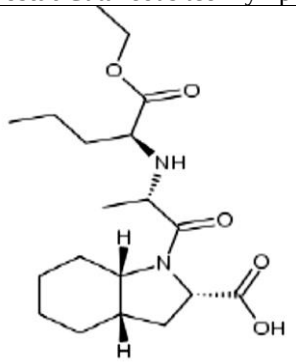


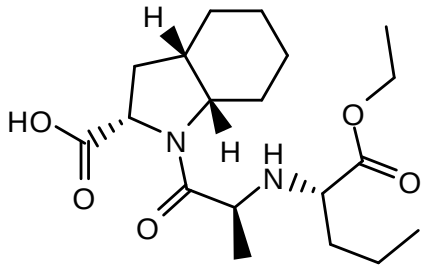
XXXIX



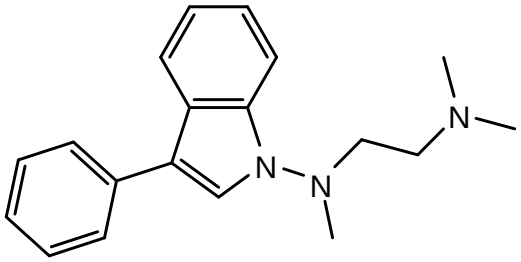
XXXX

Table 1: Indole ring containing few marketed drug shows various biological activities

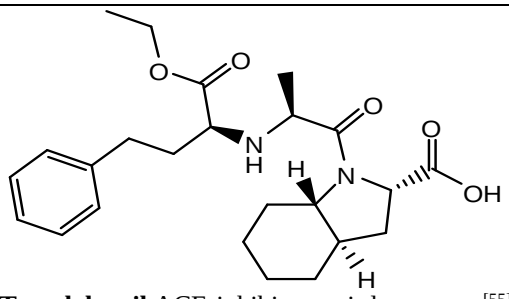
Compound name use references	Compound name use references
 **Vincristine** Anticancer [44]	 **Vinblastine** Anticancer [45]
 **Vinorelbine** Anticancer [45]	 **Vindesine** Anticancer [46]
 **Mitraphylline (**Mitraphylline) Anticancer [47]	 **Apaziquone** Anti-microbial [48]
 **Cediranib** potent inhibitor of VEGF receptor tyrosine kinases [49]	 **Panobinostat** Cutaneous tcell lymphoma [50]
 **Vincamine** Anti-hypertensive [51]	 **Reserpine** Anti-hypertensive [52]



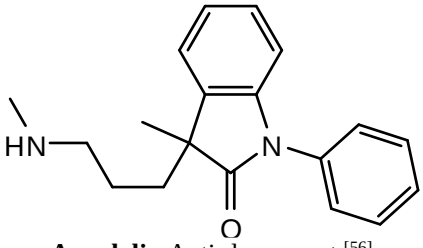
Perindopril ACE Inhibitor and anti-hypertensive [53]



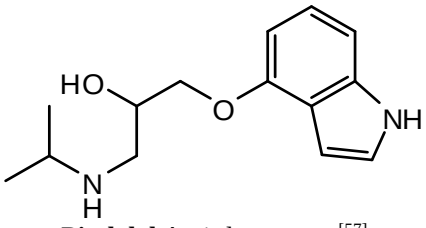
Binedaline Anti-depressant [54]



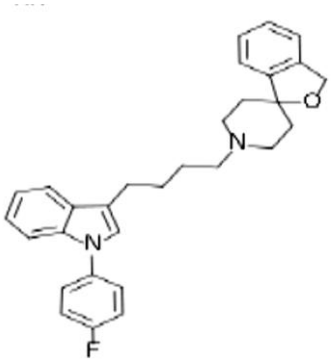
Trandolapril ACE-inhibitor anti-depressant [55]



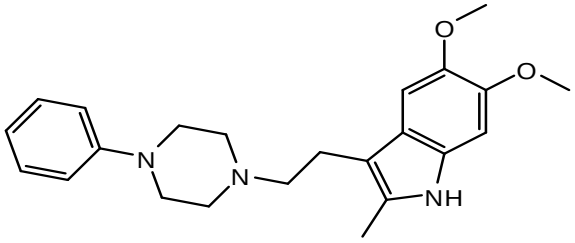
Amedalin Anti-depressant [56]



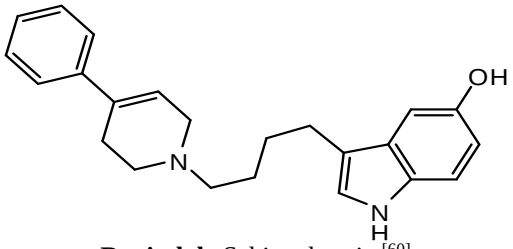
Pindolol Anti-depressant [57]



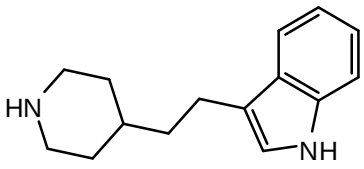
Siramesine Anxiolytic and antidepressant [58]



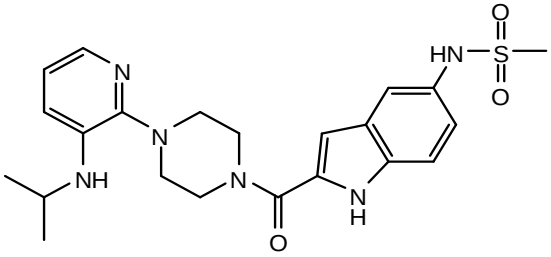
Oxypertine Anti-psychotic agents [59]



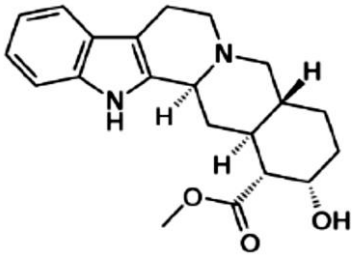
Roxindole Schizophrenia [60]



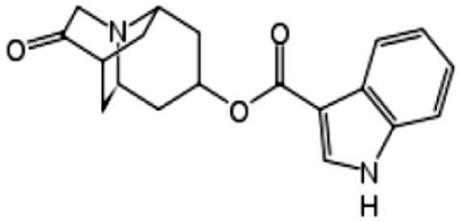
Indalpine Serotonergic antidepressant [61]



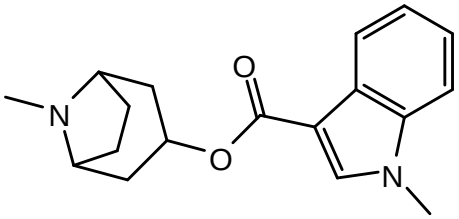
Delavirdine Non- nucleoside reverse transcriptase inhibitor [62]



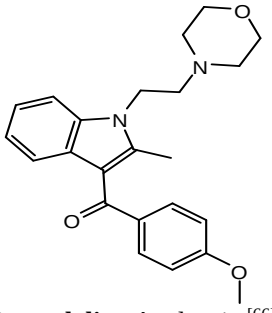
Yohimbine Sexual dysfunction [63]



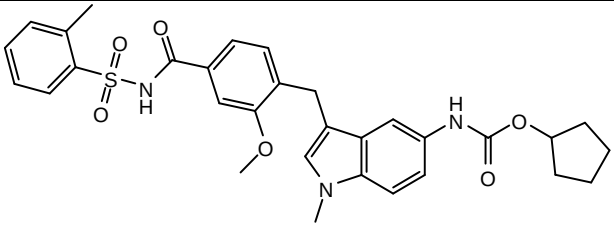
Dolasetron Anti emetic [64]



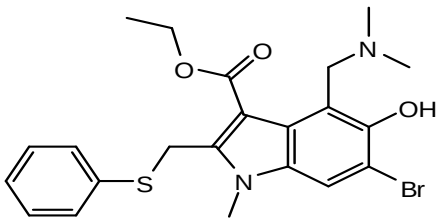
Tropisetron Anti emetic [65]



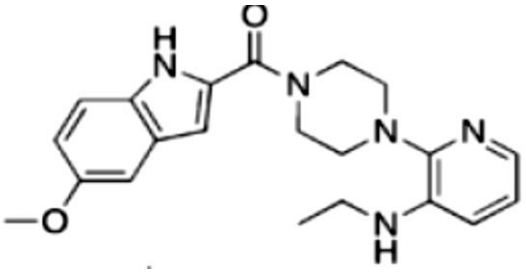
Pravadoline Analgesic [66]



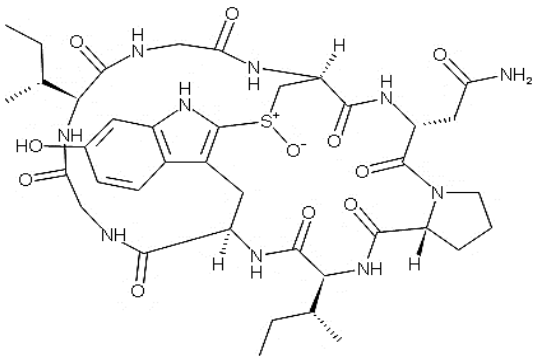
Zafairlukast Antiasthmatic [67]



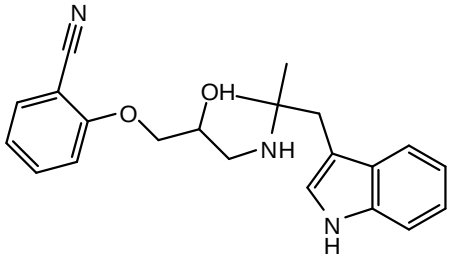
ARBIDOL Anti-viral [68]



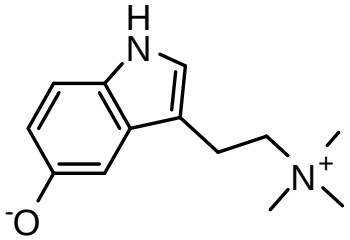
Ateviridine Non-nucleoside reverse transcriptase inhibitor [69]



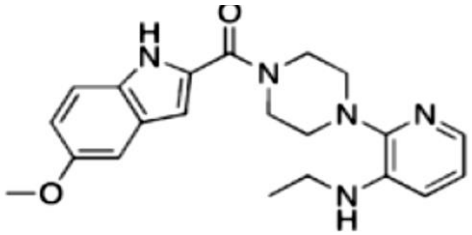
Proamanullin Inhibitor of rna polymerase-11 [70]



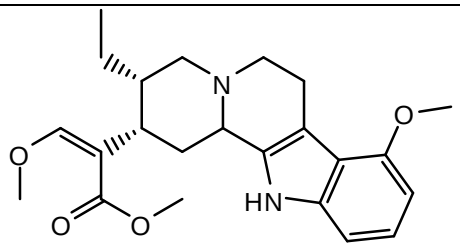
Bucindolol β-Blocker [71]



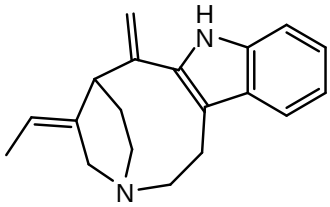
Bufotenidine (Toxins) [72]



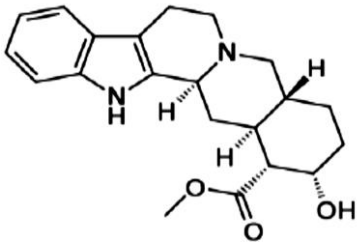
Ateviridine Anti-HIV [73]



Mitragynine (Opioid agonist) [74]



Pericine (Opioid agonist) [75]



Yohimbine (Sexual dysfunction) [76]

Conclusion

The indole moiety has shown a wide spectrum of biological activities. The indole moiety has valuable biological activities and can be used for as an intermediate for synthesizing various heterocyclic moieties. Compounds with electron releasing groups such as methoxy and hydroxyl group showed good anti-inflammatory and antimicrobial activity than those which do not have such groups. Compounds having pharmacophore such as chloro, fluoro, and bromo groups have exhibited best anti-convulsants, antitubercular, anti-inflammatory, anticancer, and antimicrobial activity. From the above discussions it may be concluded that the modifications in indole moiety displayed valuable biological activities and these modifications can be utilized to develop potentially active agents in future [79,80]. The various substituted indole derivatives having significant antibacterial, analgesic, anti-inflammatory, antipyretic, anti-tumor activity. Some effective substituted indole derivative which presently leading drug in the market. some modified indole are found to be effective as anti-hypertensive, antidepressant, opoid antagonist and antiemetic agent, whereas some of the derivatives of indole are found to show the anti-asthmatic, antiviral, anti-HIV action. Yohimbine acts as a potent drug in sexual dysfunction. Some of the important marketed drugs those contain indole nucleus having different pharmacological activities. The indole nucleus-based compounds are rapidly becoming very important class of therapeutic agents and are likely to replace many existing organic drugs in the very near future. The indole-based pharmaceuticals will be produced on a large scale by modern drug discovery by different research and development processes and will become available commercially for therapeutic use. The biological profiles of this new generation of indole represent much progress with regard to the older compounds.

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