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Original Review Article

BIOLOGICAL IMPORTANCE OF THE INDOLE NUCLEUS IN RECENT YEARS: A COMPREHENSIVE REVIEW

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Abstract

Indole nucleus showed clinical and biological applications. Indole scaffold has been found in many of the important synthetic drug molecules which gave a valuable idea for treatment and binds with high affinity to the multiple receptors helpful in developing new useful derivatives. Indole derivative possess various types of biological activities i.e., antiviral, anti-inflammatory, anti-cancer, anti-HIV, antioxidant, antimicrobial, anti-tubercular activities, etc. This review created interest among researchers to synthesize a variety of indole derivatives. Literature data revealed that the indole derivatives have exhibited diverse biological activities and also have immeasurable potential to be explored for newer therapeutic possibilities.

Keywords: Indole, anti-viral, anti-inflammatory, anti-cancer, anti-malarial, anti-HIV, antioxidant, anti-tubercular, antimicrobial, antipyretic, antiserotonin, analgesic, Alzheimer's, Parkinson's and Huntington's diseases, antidibetic activities

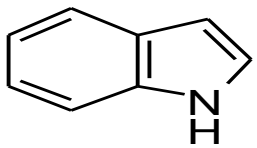
Introduction

Indole and its derivatives have occupied a unique place in the chemistry of nitrogen heterocyclic compounds [1]. The indole derivatives were known for their dying properties. Many compounds having structural resemblance to the ancient dye indigo are known. A large number of naturally occurring compounds, like alkaloids, were found to possess indole nucleus. The recognition of the plant growth hormone, heteroauxin [2] and the essential amino acid, tryptophan [3] as derivatives of indole have added stimulus to this research. Significant contribution of many derivatives of indole in the development of medicinal chemistry should be recognized. Serotonin or 5-hydroxy

tryptamine known for its vasoconstrictor principle [4], plays a vital role as neurotransmitter and psychosis. The discovery of psilocin and psilocybin [5] as the important psychotomimitic indoles have led to extensive research on derivatives of indole-3-ethylamine (tryptamine). Several derivatives of tryptamine are reported to exhibit central nervous system (CNS) depressants. Anti-inflammatory [6] activity was found to be associated with many derivatives of indoles e.g., indomethacine. The spectroscopic data collected [7] on the newer derivatives of indoles, isolated from various natural sources, have immensely helped in their structure elucidation. Because of this, good number of minor alkaloids containing indole nucleus are reported in the literature. A great deal of chemistry of indole and its derivatives have thus been accumulated and many monographs [8-10] on indole have already been published in the literature. Today the scope of indole research is multifarious extending from rather simple parent molecule to highly complex molecules.

Indole

Indole or benzo[b]pyrrole (1) is a planar heteroaromatic molecule in which the benzene ring is fused to position 2 and 3 of the pyrrole ring. This nucleus has ten π-electrons which are free to circulate throughout the molecule. Two of these electrons originate from nitrogen atom and each of the eight carbon atoms contributes one electron to π-cloud. Since these ten electrons are distributed over nine ring atoms, indole is an electron rich or π-excessive system. Since the ring nitrogen atom contributes two electrons to the overall π-system, it is a very weak base [9].



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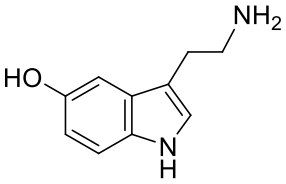
The aromatic character9 of indole is explained on the basis of its ring current effect in PMR spectra and its appreciable resonance energy (47 K cal/mole). Indole is highly reactive towards electrophilic substitution reactions, position 3 being the most preferred place for substitution. The high reactivity of position-3 is due to □-electron density [10] and localization energy [11]. In presence of acids, indole is protonated at position-3, which seldom results in dimerisation or polymerization. However, indole has appreciable stability in concentrated acids, where it is completely protonated [12]. The NH group of indole is relatively acidic and forms anion in presence of strong base [13].

Indole is widely distributed in nature [14], viz., in essential oils, coal tar, molasses tar and also it is found along with pus, in liver, pancreas, brain and bile. Human and animal faeces are found to contain indole and skatole. This nucleus is present in a number of physiologically significant compounds like serotonin, tryptophan, indole-3-acetic acid, gramine, abrine, reserpine, yohimbine, physostigmine, lysergic acid diethylamide and also in important antibiotics like mitomycin and gliotoxin. In the light of these considerations many attempts were made for the synthesis, characterization and biological activity studies of indole analogues.

Indole and its derivatives of biological interest

Serotonin or 5-hydroxy tryptamine (2) is widely distributed in animal and plant kingdom [15]. Serotonin is found to be present in salivary glands and gastrointestinal tissue of mammals and in mammalian brain16. Its highest concentration being found in basal ganglia [17, 18] and pineal glands [19]. Serotonin, known for its vasoconstrictor principle [20], plays a vital role as neurotransmitter and in psychosis. Tryptophan was first

hydroxylated to 5-hydroxytryptophan and in presence of an enzyme tryptophan-5-hydroxylase then it is decarboxylated [21] to serotonin by the action of 5-hydroxytryptophan decarboxylase. Normally in mammals, about 2% of tryptophan in the diet is converted to serotonin [22]. Interest in the psychopharmacological activity of serotonin aroused when it was found to be antagonized [23,24] by lysergic acid diethylamide (**3**) at low concentration.



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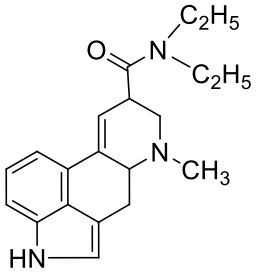

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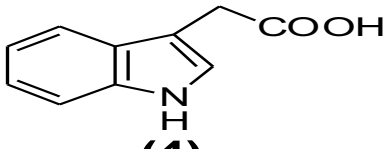
Woolley and Shaw [25] have reported that some synthetic analogues of 5-hydroxytryptamine caused behavioral changes in man and animals. Some naturally occurring alkaloids viz., ergot alkaloids and related compounds possessing psychomimitic activities also exhibit antiserotonin activity similar to lysergic acid diethylamide. The past few decades have brought an increasing awareness of serotonin's role in behavioral changes. The development of drugs acting on the serotonergic system of brain that allow for the treatment of depression, anxiety, appetite regulation and post-traumatic stress disorders has focused a great deal of attention on the role of serotonin involved in the process of emotional states [26]. The lysergic acid diethylamide [27] (3) was synthesized in 1938. This compound was found to be most potent hallucinogen, known to man.

Indole-3-acetic acid (4) also known as heteroauxin is a naturally occurring plant growth hormone and is important derivative of indole. Various structural analogues of this hormone such as indole-3-propionic acid, indole-3-butyric acid and indole-3-pyruvic acid have been synthesized and tested for their phytoharmonal activity. The 4-chloroindole-3-pyruvic acid [28] was found to have considerable activity against A. coleoptile. Indole-3-acetic acid [29] and some of its derivatives have recently been found to be active against number of human cancer cell lines [30].



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The 2(3)-carboxy(alkyl)-2, 3-disubstituted indole derivatives have been reported to be efficient glycine/NMDA [31], non-peptide endothelin antagonist [32]. The above indole carboxylic acids are also found to be cyclooxygenase [33], thromboxane synthase [34], steroid 5□-reductase [35] and phospholipase-A2 [36] inhibitors.

Bz-nitro substituted indole-3-acetic acid derivatives were prepared by Hiremath and Siddappa [37]. Amongst them, 7-nitroindole-3-acetic acid was reported to be mutagenic and its activity [38] was found to be more than heteroauxin itself. Shen and Sarett [39] have shown that indole-3-acetic acid and propionic acids possess antipyretic and anti-inflammatory activity.

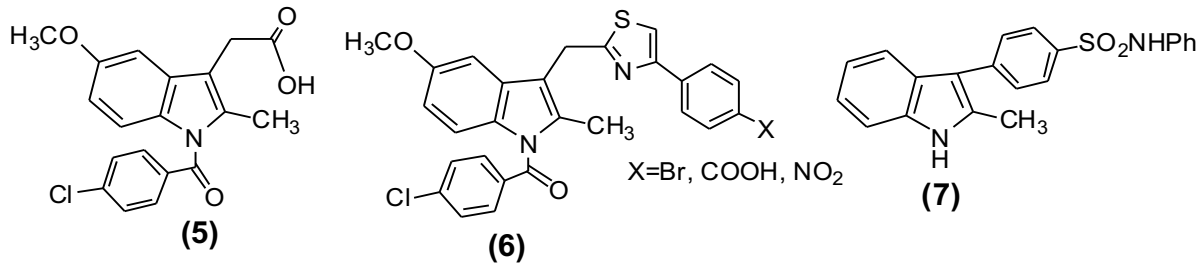
Indomethian relieves the inflammation and pain associated with rheumatoid arthritis (rheumatism), osteoarthritis, spondylitis and gout. It has been administrated antenatially for the prevention of preterm labour [40]. Indomethacin is used in closing a patent ductus arteriosus (PDA) in a premature infant, was first described in 1976 [41]. The safety of selective COX-2 (cyclooxygenase) inhibitors and their usefulness in the prevention of preterm delivery has recently been suggested [42] but at least neonatal renal dysfunction has been shown even after COX-2 inhibition [43]. Non-steroidal anti-

inflammatory drugs (NSAIDs) remain among the most widely prescribed drugs worldwide for the treatment of inflammation including pain-releasing, antipyretic and rheumatoid arthritis. The biological activities depend on the type of groups in these positions and the substituent's can be aromatic, straight chains and non-aromatic rings. 2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid (indomethacin) (5), a 5-methoxy indole nucleus which contains an acetic acid moiety at position-3 and a methyl substituent at position 2 has shown biological activities. Position-1 is occupied by 4-chlorobenzoyl group which also contributes to the observed properties. Indomethacin is a potent non-steroidal anti-inflammatory agent used primarily in the treatment of rheumatoid arthritis and has potential for use in uveitis, a common disease responsible for blindness. Indomethacin may also be used in the management of cystoids macular edema (CME), a disease characterized by a build-up of serous fluid in the extracellular space in the retina caused by a disruption of the blood-retinal barrier [44].

Keith W. Woods et al [45] reported several derivatives of indomethacin (6) these compounds are selective COX-2 inhibitors. An example of a synthetic NSAID is 2-phenyl-3-phenylsulfonamide-1H indole (7), was found to be more potent and selective against COX-2 than COX-1[46].

The heterocycle indole as anchored in tryptophan (8) and its derivatives constitutes an important structural element in peptides and peptido-mimetics as well as in alkaloids, is usually difficult to replace by other heterocycles without losing the desired biological activity.

Tryptophan is not synthesized in the animal body hence must be supplied through diet. Deficiency of tryptophan causes characteristic syndrome in animals. The metabolic pathway of tryptophan indicates that, it can substitute for nicotinic acid in higher animals [47]. A large number of alkyl substituted tryptophans have been synthesized and screened for their biological activity. Anderson [48] has synthesized and reported that 5-methyltryptophan inhibits the growth of E. coli. Hiremath and Siddappa [49] reported the synthesis of Bz-nitro, methylnitro, methoxynitro tryptophans.

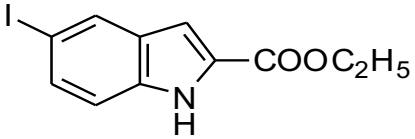


(5) (6) (7)

Indole esters

Indole carboxylic acid esters are biologically important systems. These have been found to inhibit a number of copper enzymes which are important in the biological systems. Ethyl 5, 6-dimethoxy-3-methyl indole-2-carboxylate was found to be a good inhibitor of tyrosinase showed good activity against *M. laprae* [50]. Gray et al [51] have reported that indole-2-carboxylates and its derivatives are therapeutically effective in the treatment of CNS disorders resulting from neurotoxin damage or neurodegenerative diseases. In an attempt to prepare an effective anti-inflammatory agent and at the same time, better define the hypothetical receptor proposed by Shen[39] for anti-inflammatory compounds related to

indomethacin, a series of indolyl esters and amides are synthesized by Marnett et al [52]., and reported that neutralization of the carboxylic acid moiety in indomethacin to esters or amides afforded selective COX-2 inhibitors. However, the discovery of a second COX gene, COX-2 provides important insights into NSAID (Nonsteroidal anti-inflammatory drugs) side effects like, gastric side effects that translated into more effective drugs [53]. Preclinical and clinical studies suggest that COX-2 inhibitors are highly promising agents for the treatment of pain, inflammation and for the prevention of cancer [54]. Beshore et al [55]., have reported the novel route for the synthesis of 5-iodo-1*H*-indole-2-carboxylate **(9)**.



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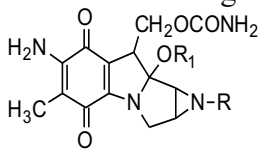
Indole fused with other heterocycles

Some antibiotics which are derived from microbial sources are also known to possess indole nucleus, e.g. mitomycin antibiotics [56] (10), and gliotoxin [57] (11) which are isolated from fungi.



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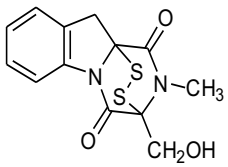

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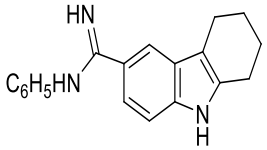
Tetrahydrocarbazole derivatives **(12)** are in use as a hypotensive drug [58]. The physostigmine **(13)** an alkaloid possess a property of acetyl cholinesterase blocking activity [59].



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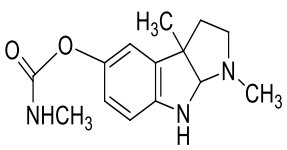

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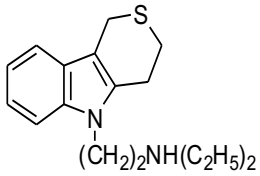
Tetrahydrothiopyranoindole **(14)** which is a potent drug for antidepressant activity [60]. For the treatment of CNS disorders, including anxiety, depression and aggression or in diseases related to cardiovascular, renal and gastrointestinal systems, several piperazinyl indole derivatives [61] **(15)** are used.



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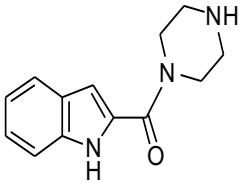


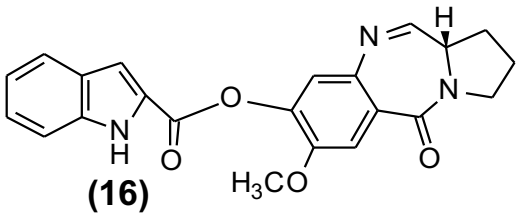
(15)

Girard et al [62]., have synthesized 2, 3-dihydro-1-hydroxyamino-1H-pyrrolo[1,2-a] indole which inhibited synthesis, action and release of SRS-A or leukotrienes in mammals and were found to be useful for treating asthma and inflammatory diseases. Furanyl indole-3-methylamines were found to be useful as antidiabetic, antiobesity and antiartherosclerotic agent [63].

Biological importance of 2-substituted indoles

2-Substituted indoles can have complex structures and interesting biological activities, but not all compounds having the indole skeleton exhibit biological importance. For example, compounds (16) and (17) both possessing a substituents at the 2-position of indole nucleus were tested for in vitro and in-vivo cytotoxic effects. These compounds have been used as highly potent broad-spectrum anticancer agents to inhibit the growth of a variety of cancer cell lines [64]. Another example is compound (18) was tested for the inhibition of the cleavage activity [65] of restriction endonuclease BamHI. Evaluation of the growth-inhibitory properties of the novel quinol (**19**), 4-(1-phenyl sulfonyl-1H-6-fluoroindol-2-yl)-4-hydroxycyclohexa-2,5-dienone (20) was the most potent against the cell lines with the mean GI50 value of 16

nM and mean LC50 value of 2.2 Mm [63]. Finally in this section, compound (21) was examined for in vitro inhibitory effects towards the lipid peroxidation induced by free radicals in a rat brain homogenate and (1,1-diphenyl-2-picrylhydrazyl) radicals and it showed antioxidative activity [64] while bis(1H-2-indolyl)methanone (21) caused a strong inhibition of PDGF receptor activity with IC50 value of 1 Mm [65].



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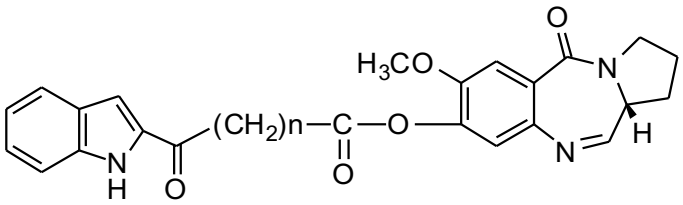

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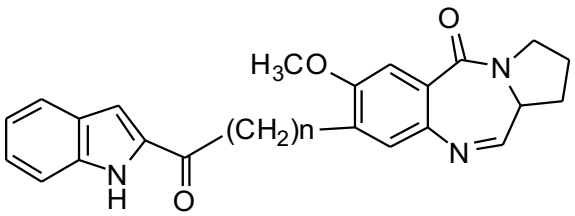

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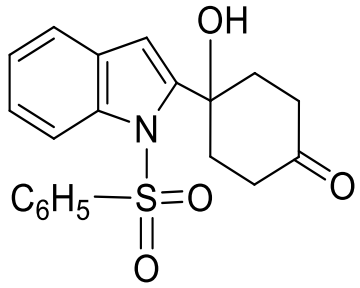

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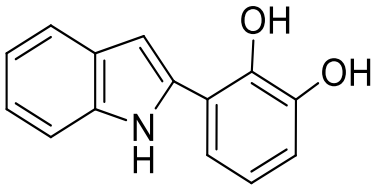

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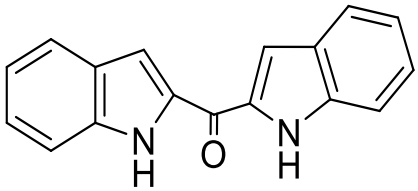

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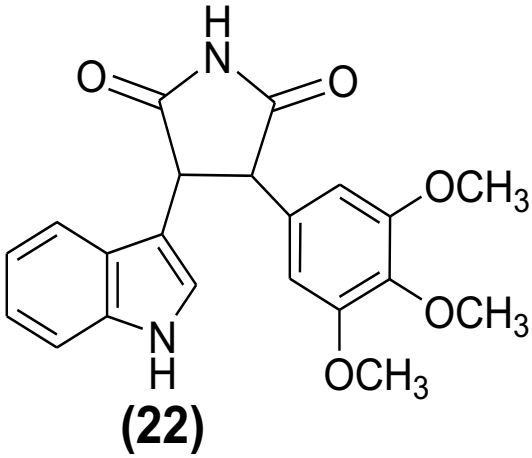
Biological importance of 3-substituted indoles

Many indoles substituted at C-3 have been found to be biologically active. Most of the active 3-substituted indoles were found to be anticancer agents and kinase inhibitors. Many have been synthesized but some are also found in Nature. Compound (22) was found to have strong potency against vessel growth in vivo chick embryo assay with 82% inhibition of vessel area after 24 hours incubation by application of 10 µg per pellet and it was also found to be active against the kinase involved in the angiogenic process resulting in in vivo activity [66].



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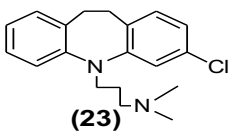
Uptake into the presynaptic neuron is the principal mechanism for the rapid inactivation of released biogenic amines in the neural synapse. The tricyclic antidepressant agents inhibit to a varying extent the uptake of noradrenaline (NA) and 5-hydroxytryptamine (5-HT). Clomipramine (23), was the most selective inhibitor of 5-HT uptake in vitro, but the selectivity was greatly reduced in vivo due to the biotransformation into chlordesipramine (24) an NA uptake inhibitor. In more detailed in vivo studies, indalpine (25) was shown to be the most potent and the most selective inhibitor of 5-HT and it was found to be the most active 5-hydroxytryptophan (5-HTP) potentiator [67]. Indole-3-carbinol (26) is a naturally occurring anticancer agent and has entered clinical trials for cancer prevention. It is a dietary component found exclusively in cruciferous vegetables and known to suppress proliferation and induce apoptosis of various cancer cells, including breast, ovarian, lung, cervical, colon, prostate and liver.



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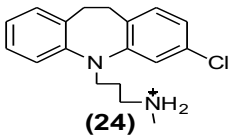

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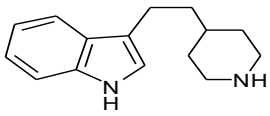

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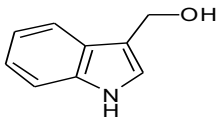

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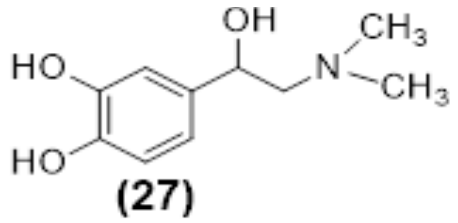
Adrenaline (27) or noradrenaline (28) are prominent in the cardiovascular system, acting through α- and β-adrenergic receptors, which exists as a number of subtypes. Many common drugs are simple carbocyclic analogues of adrenaline but few of the important compounds are heterocyclic. One of them is indoramin (29) which is used for the treatment of hypertension and benign prostatic hypertrophy [68].



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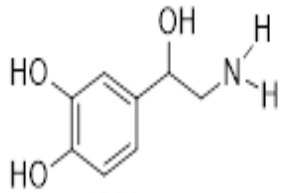

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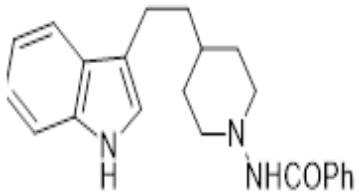

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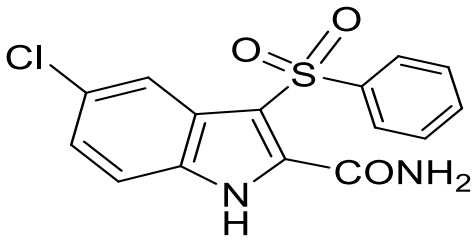
Biological importance of 2, 3-disubstituted indoles

William et al [69]., have reported that indole-2-carboxamides (31) and their analogues are HIV reverse transcriptase inhibitors and claimed for treatment of AIDS and ARC.



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Anti-HIV-1 activity

Romano Silvestri et al [70] have reported for the first time synthesis of novel indolyl aryl sulfones (IASs) and evaluated them in vitro anti-HIV-1 activity. Their study clearly demonstrated that the position of both benzenesulfonyl and carboxyamide moieties on the indole nucleus were crucial for the anti-HIV-1 activity.

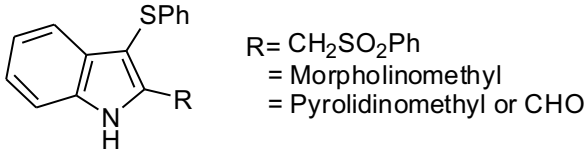
Anticancer activity

5-Bromo-3-(3,5-dimethylphenylsulfonyl) indole-2-carboxamide (32) was tested against HIV-1 in acutely infected MT-4 cells. It showed to be very potent and selective anti-HIV-1 activity not only on wild type strains, but also against mutants

carrying NNRTI-resistance mutations [71]. Compounds that interfere with the microtubule-tubulin equilibria in cells were useful in the treatment of human disease. [2-(3-Hydroxy-4-methoxyphenyl)-6-methoxy-indol-3-yl](3,4,5-trimethoxyphenyl) methanone (32) showed good activity as tubulin polymerase inhibitors and was further evaluated for inhibitory effect on the binding of [3H]colchicine to tubulin and cytotoxicity against MCF-7 human breast carcinoma cells. However, (33) was found to be less potent than combretastatin A-4 (CA-4) (34) as an inhibitor of [3H]colchicine binding to tubulin and as cytotoxins against MCF-7 human breast carcinoma cells and its cytotoxicity was less compared to CA-4.

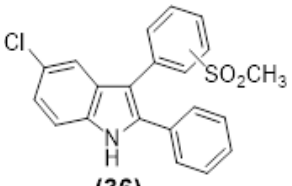
Anti-HIV activity

Greenlee and srinivasan [72] prepared several indole derivatives (35) from ethyl indole-2-carboxylates by the series of reaction sequence, which inhibited HIV reverse transcriptase activity.

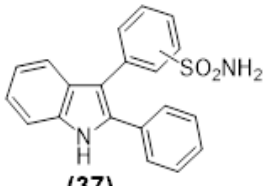


(35)

Wenhui Hu and coworkers [73] synthesized highly potent selective COX-2 inhibitors, compounds (36) and (37) possesses higher activity than celecoxib.



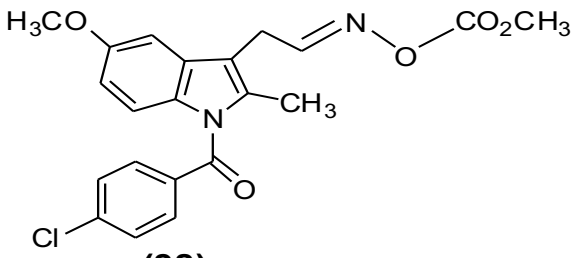
(36)



(37)

Analgesic and anti-inflammatory activities

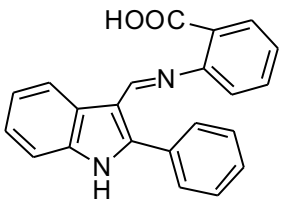
Abele et al [74] synthesized isatin and indole oximes and carried out the chemical reactions and biological activities of the synthesized compounds where the compound (38) was found to be most active analgesic and anti-inflammatory agent.



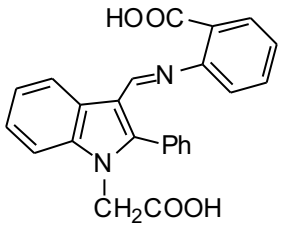
(38)

Anti-inflammatory activity

Amir et al 75., synthesized 2-phenyl-3-(2'-carboxyphenyliminomethyl)-indole (39) and 2-phenyl-3-(2'-carboxyphenyliminomethyl)-indol-1-acetic acid (40) and found that these compounds exhibited promising anti-inflammatory activity.



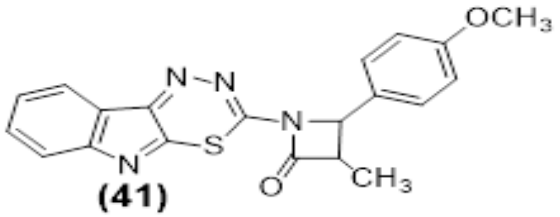
(39)



(40)

Antibacterial activity

Panwar et al [76] synthesized substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents. The compounds (41) and (42) were found to exhibit maximum inhibitory effect against E.coli and S. aureus.



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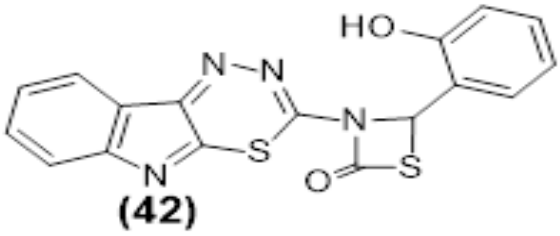
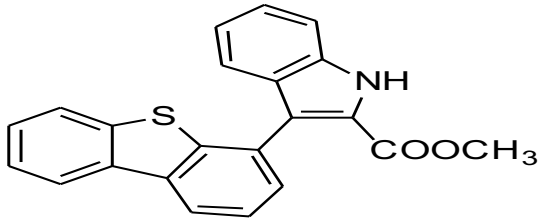


(42)

Anticancer activity

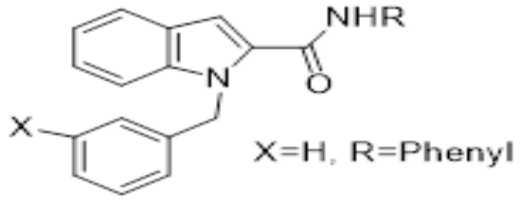
Queiroz et al [77] studied the inhibitory activity of the heteroarylindoles and phenylbenzothienoindole on the growth of human tumor cell lines. Their results showed that the methyl 3-(dibenzothien-4-yl)indole-2-carboxylate (43) had most potent growth inhibitory activity in all the tumor cell lines tested (with GI50 values ranging from 11 to 17 μM).



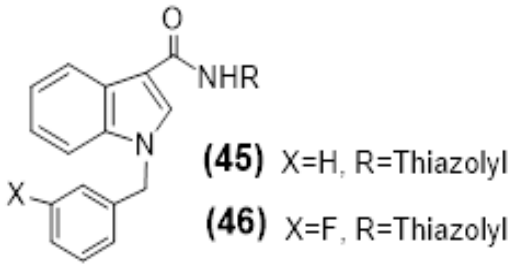
(43)

Antioxidant activity

A series of indole derivatives were synthesized and biologically evaluated by Enien et al78., found that indole-2 and 3-carboxamides were having antioxidant properties by chemoluminesence and electron spin resonance trapping. They further reported that the derivatives (44) and (45) have strongest scavenging effect on OH radicals, i.e., quenching >30% and the derivatives (45) and (46) have strongest effect on scavenging of superoxide radicals.

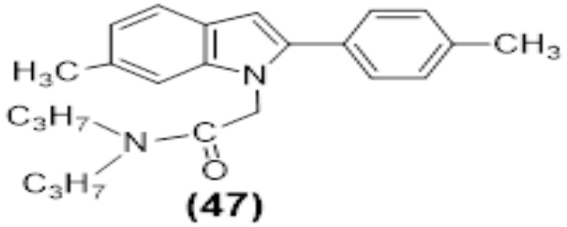


(44)

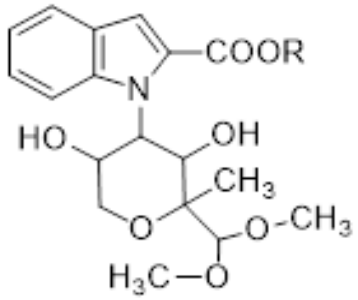


Anticancer activity

A series of N-substituted indoles were synthesized by Falco et al [79] and screened them for in vitro and in vivo spontaneous motor activity in mice and reported that compound (47) was most potent in vivo induction of sedation. A number of benzopyranyl indoline and indole analogs were synthesized and evaluated for cardioselective anti-ischemic ATP-sensitive potassium channel (KATP) opener activity by Lee et al80. The compounds (48) and (49) showed the best cardioprotective activity.



(47)

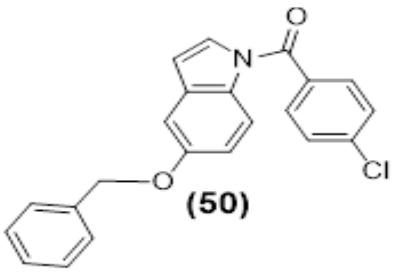


(48) (2-S, 3-R, 4-S, 2'-S)=R=Ethyl

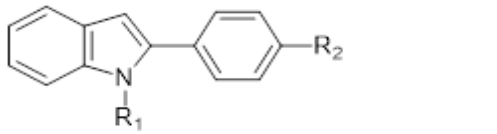
(49) (2-R, 3-S, 4-R, 2'-R)=R=Ethyl

Antidiabetic activity

Some of the indole derivatives were evaluated for their insulin sensitizing and glucose lowering effects by Li et al [81]. The indole derivative (50) showed increase in activity of PPARc agents, which showed decreased serum glucose and contributing to antidiabetic activity. A series of 2-aryl-N-acyl indole derivatives were synthesized and biologically evaluated as liver X receptor (LXR) agonists by Kher et al [82]. The compound (51) was found to be most active with EC50=0.012 μM.

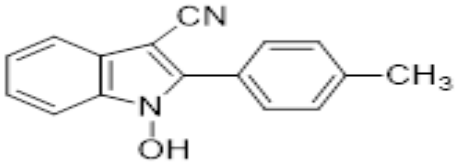


(50)

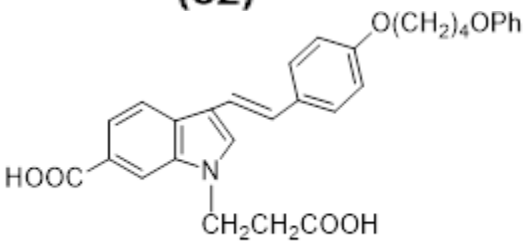


(51) R_1=COPh, R_2=$(CH_2)_2CN$

Schleigh et al [83] reported the synthesis of compound (**52**) which has a good agrochemical fungicidal activity. Butler and coworkers[84] showed that the indole derivative (**53**) has activity as leakotriene receptor blockers i.e., it is potential agent for the treatment of allergic or inflammatory diseases.



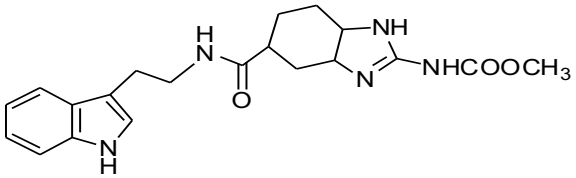
(52)



(53)

Anthelmintic activity

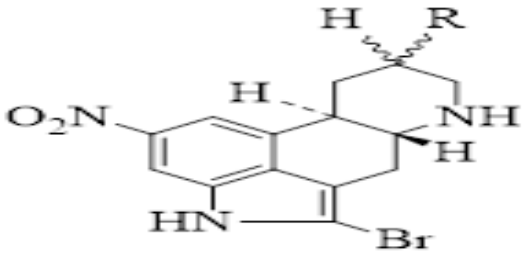
Agarwal and coworkers [85] prepared several indole derivatives and screened them for their anthelmintic activity, but the only compound (54) exhibited reduction of adult worms by 79.4% at a concentration 50 mg/kg (i.p) and 44% at 100 mg/kg (oral route) against Brugai malayi infection in mistomys natalensis.



(54)

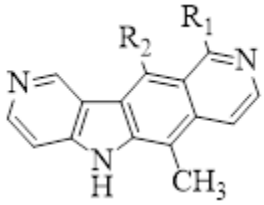
Alzheimer's, Parkinson's and Huntington's activities

Forbes and coworkers [86] synthesized several pyridyl indolyl ureas (55) and showed that N-(1-methyl-5-indolyl)-N-(3-pyridyl)urea hydrochloride (55) is selective 5-HT1c receptor antagonists. This compound (55b) showed >348 fold selectivity in ligand binding studies for 5-HT1c over the 5-HT2, 5-HT1D, 5-HT3, adrenergic α1, α2A, β1, β2 dopaminergic D1 and D2 receptors. Compound (55b) is silent competitive antagonist identified that (59) selectively inhibits neutral nitric oxide synthase (bNOS) and very useful in the treatment of Alzheimer's, Parkinson's and Huntington's diseases.



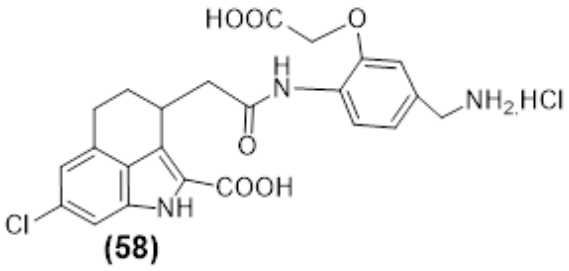
R = a-NHCONEt$_2$, b-CH_2Me

(56)

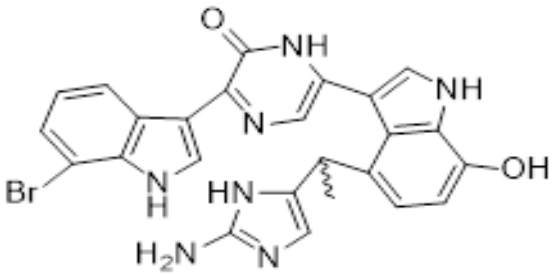


R_1 = H, OH, C1-6-alkyl, alkylthio, alkoxy, haloges, substituted/unsubstituted amino.
R_2 = H or C1-4-alkyl.

(57)



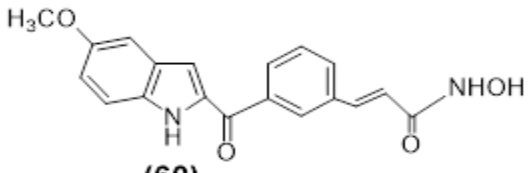
(58)



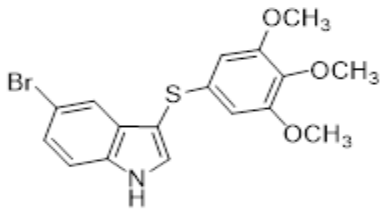
(59)

Anticancer activity

Mahboobi et al [91] showed that the indole derivatives (60) is new class of Histone deacetylase (HDAC) inhibitor which is considered as a drug for targeted cancer therapy. Regina et al92., showed the aryl thioindole derivative (61) as an inhibitor of MCF-7 cell growth in tubulin polymerization i.e. breast cancer cells.

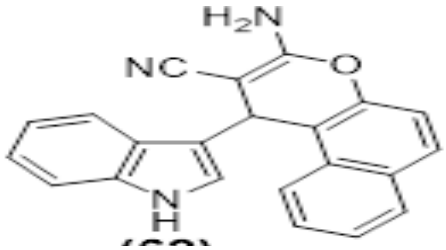


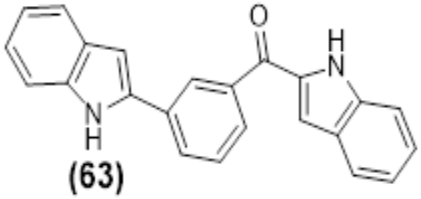
(60)



(61)

Gnanamathi and coworkers [93] synthesized indolyl chromenes (62), which showed excellent reducing power and free radical scavenging activity at a concentration of 0.125 g/L when compared with standards 2-tertiary butyl-4-methoxyphenol (butylated hydroxy anisole) (BHA), and 2-(1,1-dimethylethyl)-1,4-benzenediol (2-tertiary butyl hydroquinone) (BHT). Recently, Sunjoo et al [94] prepared 3-(1H-indol-2-yl)phenyl(1H-indol-2-yl)methanone (63) as a good antitumor agent in prostate cancer.

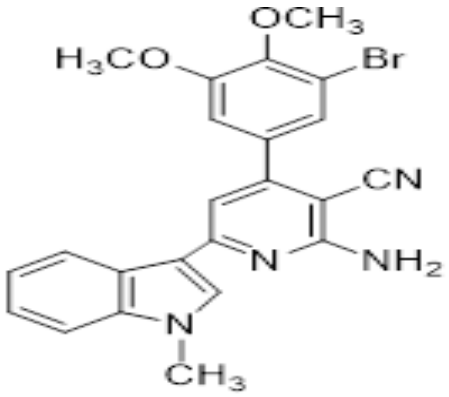




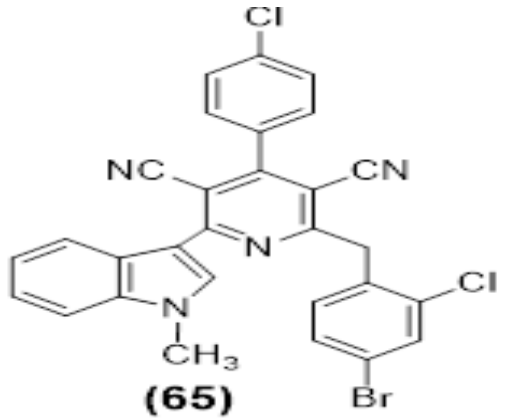
(63)

Anti-tumor activity

Fan et al [95] synthesized 2-amino-3-cyano-6-(1H-indol-3-yl)-4-phenylpyridine derivatives and screed them for their anti-tumor activity against A549, H460, HT-29 and SMMC-7721 cell lines, compound (64) showed strong anti-tumor activity. Prakash et al [96] were synthesized 3-indolyl pyridine derivative (65) and screened them for their anti-inflammatory activity.



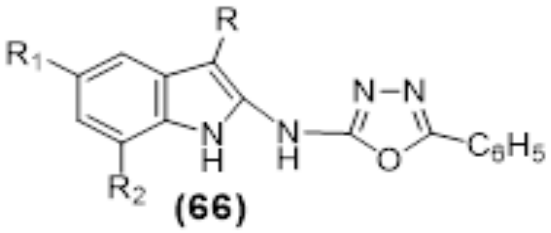
(64)



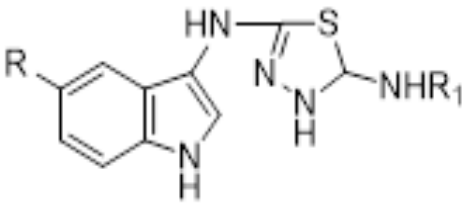
(65)

Antibacterial activity

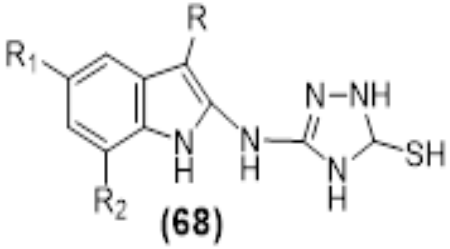
Hiremath et al [97] synthesized various indole analogues linked with different heterocyclic moieties, and studied their biological properties. Indole nucleus attached to the oxadiazole through an amino bridge (66) substituted with various functional groups and indole linked to thiadiazole (67) and triazole (68) have been synthesized by these workers [98].



(66)

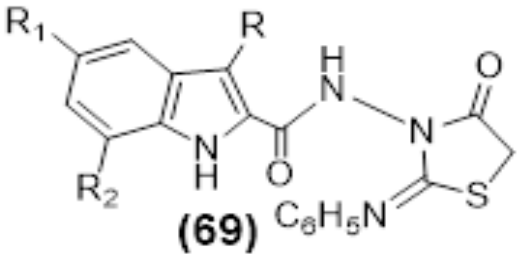


(67)

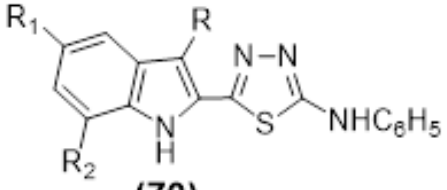


(68)

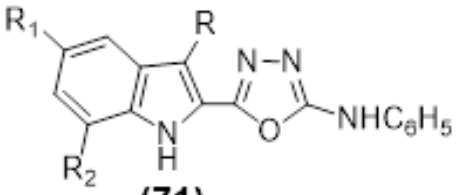
Several indole derivatives possessing thiazolidinone (69), thiadiazole (70), oxadiazole (71) and triazole (72) have been prepared and screened for their antimicrobial activities. Some of the compounds showed good activity against E. coli [99].



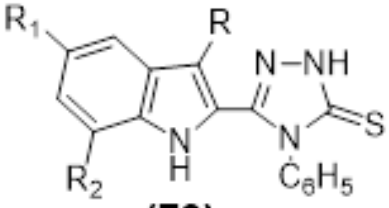
(69)



(70)



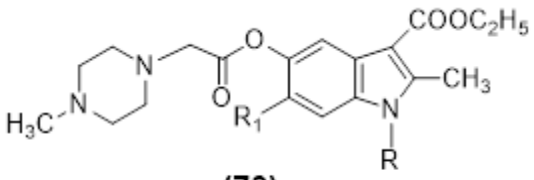
(71)



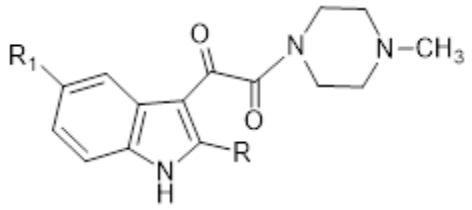
(72)

Anti-serotonin activity

Hiremath et al [100] have reported the synthesis of ethyl 5-O-(4-methyl piperazin-1-ylacetyl)-2-methyl indole-3-carboxylates (73) and 3-(4-methyl-1-piperazinyl glyoxylyl) indoles (74) and screened them for their anti-serotonin activity. Some of them found to be 5-HT2 antagonist.



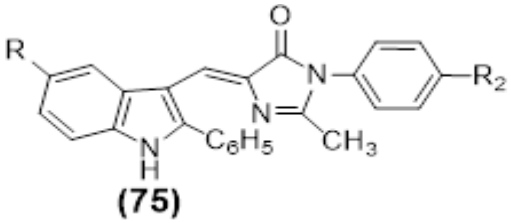
(73)



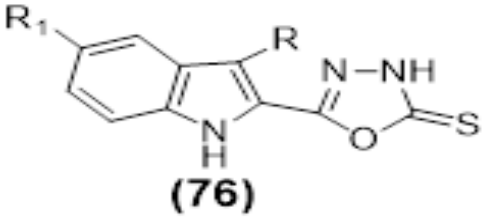
(74)

Analgesic and anti-inflammatory activity

Hiremath et al [101] have developed new method for the synthesis of diazepinoindoles where in diazepino nucleus is fused across C and D sides of indole. Further they have extended this work wherein ethyl 2-methyl-5-hydroxy-6-substituted-indole-3-carboxylate was subjected to Vielsmeier-Haack formylation to obtain 4-formyl derivatives, which on reaction with hydrazine hydrate yielded the 5-substituted-1-carbethoxy-3,7-dihydro-2-methyl pyrano [3,2-c]indol-7-ones (coumarinoindoles). Biradar et al [102]., have reported the synthesis of 1,2-disubstituted-4-[5'-substituted 2'- phenyl indol-3'-yl methyl-one]imidazolin-5-(4H)-ones (75) and 3, 5-disubstituted-2-(5'-thioxo-1',3',4'-oxadiazol-4'-ethylacetate-2'-yl)indoles (76) and evaluated for their antimicrobial activity.

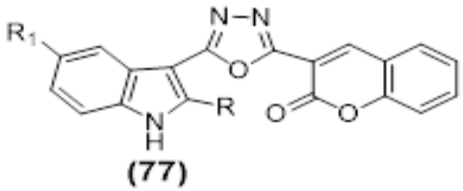


(75)

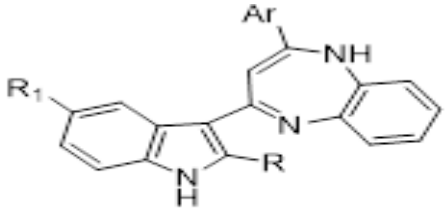


(76)

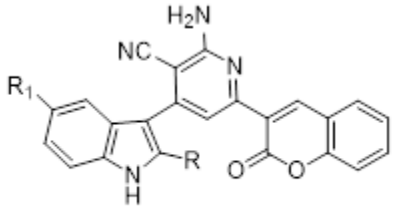
Same workers synthesized 2-(5'-chloro-2'-phenyl indol-3-yl)-5-(coumarin-3"-yl)-1,3,4-oxadiazole (77) and 4-substituted phenyl--(5'-substituted-2'-phenyl indole-3'-yl) 1, 4-benzo(b)diazepines (78) and screened them for their analgesic, anti-inflammatory and locomotor activities [103,104]. They have also synthesized 2-amino-4-(5', 2'-disubstituted-1H-indol-3'-yl)-6-(2"-oxo-chromen-3"-yl)pyridine-3-carbonitriles (79) and their derivatives as biologically active agents[105].



(77)



(78)



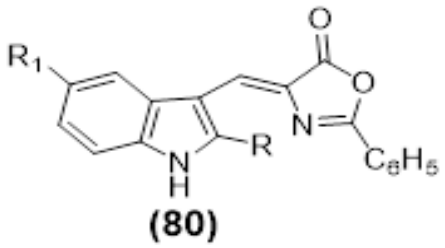
(79)

Antimicrobial activity

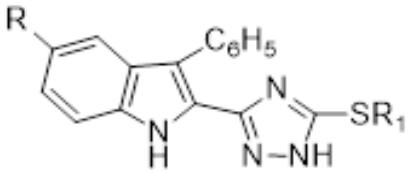
Purohit et al [106, 107] reported the synthesis and antimicrobial activity of some new 4-[(substituted-2-phenyl indol-3-yl)methylene]oxazolinones (80) and 5-substituted-3-phenyl indole-2-(1,2,4-triazole) derivatives (81).

Antimicrobial and antioxidant activities:

Saundane et al [108] have synthesized indole derivative containing pyridopyridine (82) and pyrazolopyridine (83) and tested them for their antioxidant and antimicrobial activities.

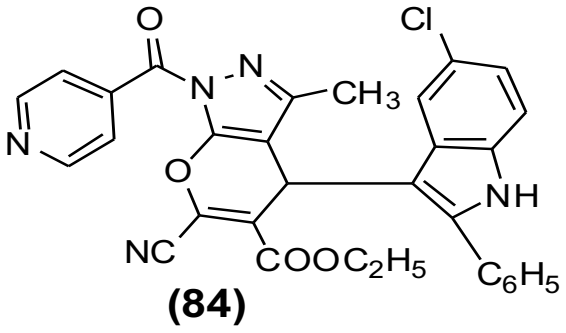


(80)



(81)

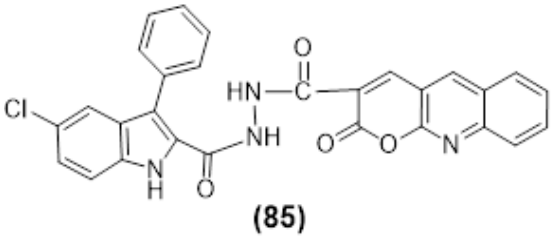
Saundane et al [109] have also synthesized ethyl 4-(5-chloro-2-phenyl-1H-indol-3yl)-6-cyano-1-isonicotinoyl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate **(84)** and tested them for their antioxidant and antimicrobial activity.



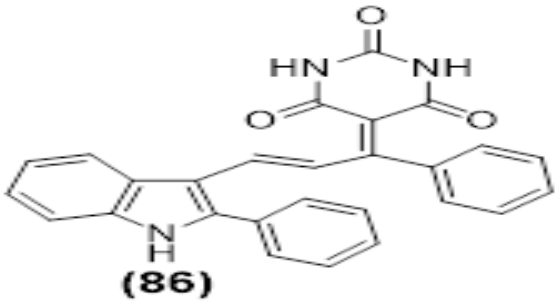
(84)

Tuberculosis activity

Basavaraj et al [110] have synthesized 5-chloro-Nβ-(2-oxo-2H-pyrano[2,3-b]quinoline-3-carbonyl)-3-phenyl-1H-indol-2-carbohydrazide (83) and screened for their antitubercular activity, which showed good activity against M. tuberculosis (H37Rv). Biradar et al [111] have synthesized 3-(2-phenyl-1H--indol)-1-phenylallylidene)pyrimidine (84) and screened for their antioxidant and DNA cleavage activities. Indole ring containing drug molecules [112] (table-1), Drugs with their mechanism of action [113] (table-2).



(85)



(86)

CONCLUSIONS

Indole derivatives are very important heterocyclic compounds in the drug discovery studies. They represent a very important class of molecules that play a major role in cell biology and are potential naturally occurring compounds. There has been an increasing interest in the use of indole derivatives as bioactive molecules against microbes, cancer cells, and various kinds of disorder in the human body. Indole derivatives have attracted the attention of researchers in the discovery of novel chemical entities. These chemical entities may be safer and effective drugs for. Summarizing the literature reports described above, we can say that indole display a diverse spectrum of biological activities. Indole has an immense potential to investigate for newer therapeutic possibilities. Chemistry of indole derivatives described in this review would help the researchers worldwide in the design and synthesis of novel useful in mitigation of various disorders. This review paper would help us to understand current status and recent studies of biologically important indole derivatives in expanding.

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