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Indoles: Role in Diverse Biological Activities

Nadeem Siddiqui*, Bishmillah Azad, M Shamsher Alam, Ruhi Ali

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, New Delhi 110062, India

ABSTRACT
In recent years, indole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities. It is well known fact that the indole nucleus is present as a structural unit in many natural products. Synthesis and biological evaluation of indole derivatives have been a topic of special interest to organic and medicinal chemists. A number of indole derivatives have been reported and widely identified as a privileged structure of pharmacophore with representation in over 3000 natural isolates and are known to possess broad spectrum of biological and pharmaceutical activities.

Keywords: Indole, Anti-inflammatory, Antibacterial, Antifungal, Anticonvulsant, Antitubercular, Anticancer, Antihistaminic and Diagnostic agents.

INTRODUCTION

Indoles are important class of heterocyclic compounds, found in many potent biological activities. Indole and its analogs constitute the active class of compounds possessing wide spectrum of biological activities. A number of indole derivatives have been reported to exhibit antibacterial, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, immunomodulator, inhibition of chemical mediator's release and inhibition of leukotrieneB_4 inhibition of tyrosinase inhibition of aldose - reductase activity. Some of these compounds are also known to possess anti- inflammatory and analgesic properties. [1-10]

BIOLOGICAL ACTIVITIES ON INDOLE AND THEIR DERIVATIVES

Anti-inflammatory activity

Acute and chronic inflammation and different type of arthritis are the inflammatory disorders, which are a big blow to humanity and continual search for newer non-steriodal anti-inflammatory agents is the only way to fortify against this awful threat. Radwan *et al* [11] were reported the treatment of 3-cyanoacetyl indole with the diazonium salts of 3-phenyl-5-aminopyrazole and 2-aminobenzimidazole afforded the corresponding hydrazones. 3-Cyanoacetyl indole reacted with phenylisothiocyanate to give the corresponding thioacetanilide derivatives. Treatment of thioacetanilide derivatives with hydrazonoyl chlorides afforded the corresponding 1, 3, 4-thiadiazole derivatives **[1a-g]** and **[2]**. The newly synthesized compounds were found to possess potential anti-inflammatory and analgesic activities.

Polamba *et al* were reported a series of indole-3-carboxamides derivatives and evaluated for their analgesic, anti-inflammatory activities as well as for their gastrointestinal irritation liability. [12] Indomethacin was used as reference drug in both tests. Compounds **[3a-d]** were found to be the most active anti-inflammatory activity by rat paw edema inhibition test, with a sharply dose-dependent effect.

Sujatha *et al* have synthesized a series of bis (indolyl) methanes by stirring a mixture of indole and aldehydes in methanol:water (1:1 v/v) containing catalytic amount of sodium bisulphite at RT. Acute toxicity, analgesic, anti-inflammatory and ulcerogenic activities of the prepared bis(indolyl)methanes [13] 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 show significant analgesic and anti-inflammatory activity without an ulcerogenic activity the most active compounds of this series were **[4]** and **[5]**

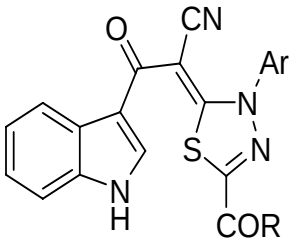
Bhati *et al* have synthesized 3-chloro-4-aryl-1-{5-[{[1,3,4] thiadiazino indol-3-ylamino]methyl]-1,3,4-thiadiazol-2-yl}azetidin-2-one and were also evaluated for their anti-inflammatory, ulcerogenic and analgesic activities. [14] Compound **[6]** has shown most active anti-inflammatory and analgesic activities with better ulcerogenic activity than phenylbutazone.

Rani *et al* were reported chalcones of indole and their corresponding products [15] and evaluated for their anti-inflammatory activity against carrageenan induced oedema in albino rats at a dose of 50 mg kg^{-1} oral. The active compound

***Corresponding author: Prof. Nadeem Siddiqui,** Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, New Delhi 110062, India; **Tel.:** +91-11-26059688 Extn 5639; **E-mail:** nadeems_03@yahoo.co.in, nadeems_03@rediffmail.com

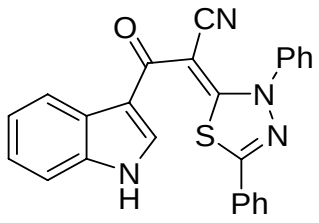
of this series was 3-[1-acetyl-5-(*p*-hydroxyphenyl)-2-pyrazolin-3-yl] indole **[7]** was found to be most potent, which has shown higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than the standard drug phenylbutazone.

Sondhi *et al* were reported Indole-2-carboxylic acid on condensation with benzene sulfonyl hydrazide and p-toluene sulfonyl hydrazide [16] and it was given the condensation products **[8a]** and **[8b].** 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 **[9a-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 **[10]** and **[11].** All compounds have been characterized by spectroscopic means and have been screened for anti-inflammatory and analgesic activity. Compounds **[9a]** and **[11]** exhibit good anti-inflammatory and **[9a], [9c]** and **[11]** exhibit good analgesic activities.

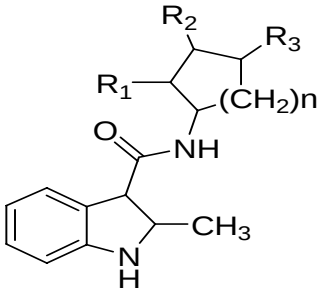


[1a-g]

[1a]; R = CH_3, Ar = C_6H_5
[1b]; R = CH_3, Ar = 4-MeC_6H_4
[1c]; R = CH_3, Ar = 4-ClC_6H_4
[1d]; R = CH_3, Ar =4-MeC_6H_4
[1e]; R = OC_2H_5, Ar = C_6H_5
[1f]; R = OC_2H_5, Ar = 4-MeC_6H_4
[1g]; R = OC_2H_5, Ar = 4-ClC_6H_4

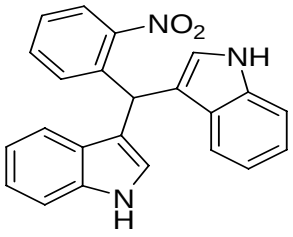


[2]



[3a-d]

[3a]; R_1 = CH_3, R_2 = R_3 = H, n = 1
[3b]; R_1 = R_3 = H, R_2 = CH_3, n = 1
[3c]; R_1 = R_3 = H, R_2 = CH_3, n = 2
[3d]; R_1 = R_2 = H, R_3 = CH_3, n = 2



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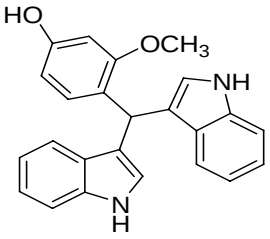

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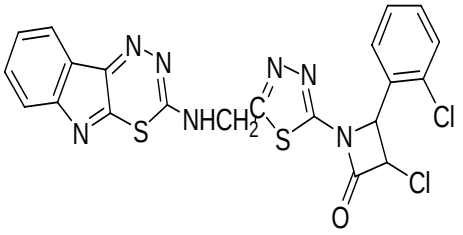

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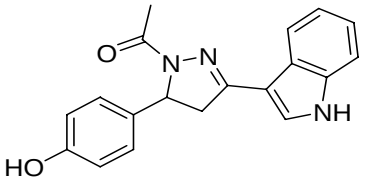

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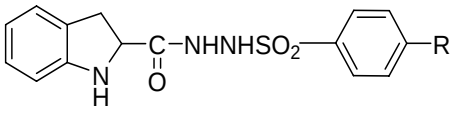
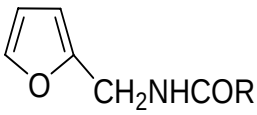
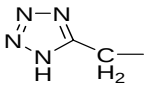
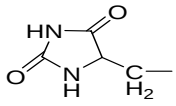


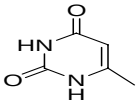
[8a]; R = H and [8b]; R = CH_3

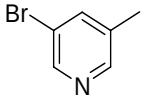


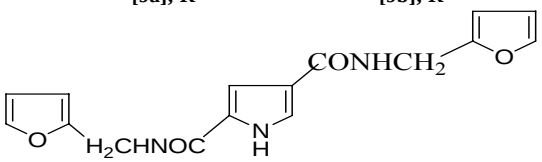
[9a-d]

[9a]; R = 

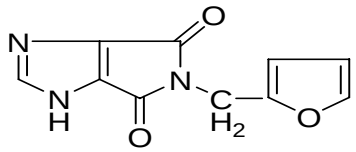
[9b]; R = 

[9c]; R = 

[9d]; R = 



[10]



[11]

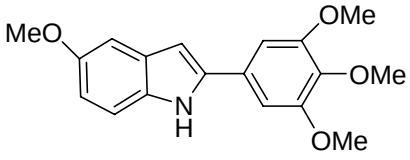
Antibacterial activity

Infections caused by multi-drug resistant bacteria are of major health concern worldwide, new antibacterial agents is need to treat infections. Sinha *et al* have prepared eight novel heterocyclic Schiff bases derived from the condensation reactions of indole 3-carboxaldehyde with different L-amino acids (histidine, glutamic acid, aspartic acid, leucine, valine) as well as with some aminophenols. [17] Antimicrobial activity of all the tested compounds showed moderate to good bacterial inhibition, these Schiff base compounds were evaluated against *Bacillus subtilis*, *Pseudomonas fluorescence*, *Staphylococcus aureus*, *Aspergillus niger*, *Candida albicans* and *Trichophyton rubrum*.

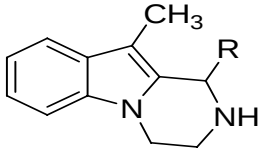
Leboho *et al* were reported 1, 3, 4, 5-tetrahydropyrano [4, 3-b]indoles and screened for their antimicrobial activity. [18] The compound **[12]** displaying the most significant activity (3.9 lg/mL) against the Gram-positive micro-organism *Bacillus cereus*.

Tiwari *et al* were reported a series of substituted 1, 2, 3, 4-tetrahydropyrazino indole derivatives [19] have been synthesized and tested against the Gram positive and Gram negative strains of bacteria namely *Staphylococcus aureus*

(MTCCB 737), *Salmonella typhi* (MTCCB 733), *Pseudomonas aeruginosa* (MTCCB 741), *Streptomyces thermonitrificans* (MTCCB 1824) and *Escherichia coli* (MTCCB 1652). All the synthesized compounds showed mild to moderate activity. However, compounds **[13a-c]** were found to have potent activity against pathogenic bacteria used in the study. Their MIC ranged from 3.75 to 60 1g/disc. In vitro toxicity tests demonstrated that toxicity of was not significantly different than that of gentamycin. However, at higher concentration (1000–4000 lg/ml) difference was highly significant.



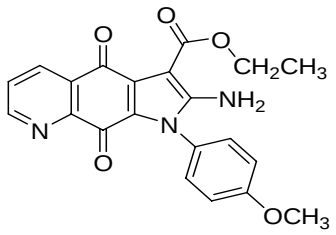
[12]



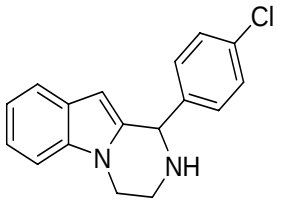
[13]
[13a]; R = p-FC_6H_4
[13b]; R = p-$CH_3C_6H_4$
[13c]; R = p-$NO_2C_6H_4$

Antifungal activity

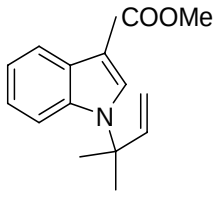
Invasive fungal infections, particularly in immunosuppressed patients, have continued to increase in incidence during the past 20 years. Although invasive fungal diseases are still difficult to diagnose clinically. This situation highlights the need for advent of safe, novel and effective antifungal compounds. Ryu *et al* were reported and tested for *in vitro* antifungal activity [20] against fungi. Among them the compound 4, 9-dioxo- 4, 9-dihydro-1H-benzo[f]indoles **[14]** was found to be potent antifungal activity.



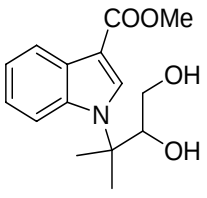
[14]



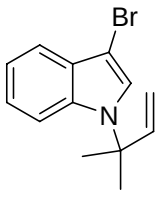
[15]



[16]



[17]



[18]

Tiwari *et al* were reported a series of substituted-10-methyl-1, 2, 3, 4-tetrahydropyrazino [1, 2-a] indoles derivatives [21] have been synthesized and examined for their activity against pathogenic strains of *Aspergillus fumigatus* (ITCC 4517), *Aspergillus flavus* (ITCC 5192) *Aspergillus niger* (ITCC 5405) and *Candida albicans* (ITCC No 4718). The most active 1-(4-chlorophenyl)-10-methyl-1, 2, 3, 4-tetra tetrahydropyrazino[1,2-a]indole **[15]** exhibited a MIC value of 5.85 µg/disc against *A. fumigatus* and 11.71 µg/disc against *A. flavus* and *A. niger* in disc diffusion assay. Anti-*Aspergillus* activity of active compound by microbroth dilution assay 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 by percent germination inhibition assay was found to be 15.62 to 250µg/ml against *A. fumigates*. The in vitro toxicity of the most active was evaluated using haemolytic assay, in which the compound was found to be non-toxic to human erythrocytes up to a concentration of 312.50µg/ml. The standard drug amphotericin B exhibited 100% lysis at a concentration of 37.5µg/ml.

Della Sala *et al* have reported [22] the synthesis of two antifungal alkaloids **[16]** and **[17]** is described. It involves the N-isoprenyl-indole brominated key-intermediate **[18]** prepared by introduction of the isoprenyl group on the indole from the woodinhabiting fungus Aporpium caryae.

Anticonvulsant activity

Epilepsy has been recognized as a neurological disorder affecting a large section of people both male and female across the world. Every year approximately 2, 50, 000 new cases are added to this figure. 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. Falco *et al* were reported some new non-benzodiazepine derivatives [23] and the compound **[19]** 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.

Frost *et al* were synthesized a series of aminoalkylindoles and found that several substituted aminoethyl derivatives [24] have high affinity for the CB_2 cannabinoid receptor. Several polar side chain (alcohols, oxazolidinone) were well tolerated for CB_2 receptor activity **[20]** and **[21].**

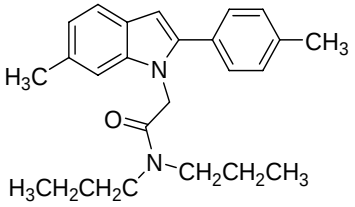
Stanton *et al* were reported a series of newly synthesized compounds and tested for their anticonvulsant activity. [25] The newly synthesized compound (Dimethylamino) methy1]-4, 5, 7, 8, 9, l0-hexahydroindolo-indole **[22]** were found to poses good anticonvulsant activity.

Sarges *et al* reported a series of l-aryl-3-(aminoalkylidene) oxindoles. [26] The compound **[23]** 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.

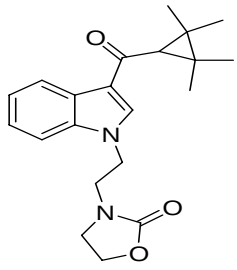
Salituro et al have been synthesized and tested as an antagonist for the strychnine-insensitive glycine binding site of the NMDA receptor. [27] Chlorine and other small electron-withdrawing substituents in the 4th and 6th positions of the indole ring greatly enhanced binding and selectivity for the glycine 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 **[24]** (ICm = 170 nM, >2100-fold selective for glycine)

Campagna *et al* have synthesised a large number of pyridazino [4, 3-b] indoles and indeno pyridazines and evaluated their binding affinities at both central (CBR) and peripheral (PBR) benzodiazepine receptors. [28] Relatively good PBR binding affinities were found for ligands belonging to the 3-arylmethyloxy-pyridazinoindole series, whereas only 2-aryl-indenopyridazines **[25a-c]** display a weak binding affinity for CBR. To find out the main structural determinants affecting PBR affinity, a molecular

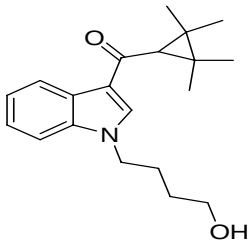
modeling study based on the comparative analysis of the three-dimensional properties of four properly selected derivatives **[25d,e]** and **[26a,b]** with those of highly active and selective PBR ligands, taken as reference. Fabio *et al* were reported after the identification of GV150526, the indole-2-carboxylate template was further explored in order to identify novel potential anti-stroke agents. [29] In particular, the SAR of the side chain present at the C-3 position of the indole nucleus was widely studied. The synthesis and 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 **[27]** and were identified as a potent neuroprotective agent in animal models of cerebral ischaemia.



[19]



[20]



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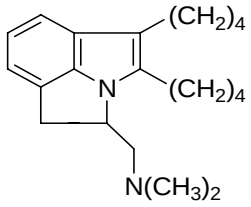
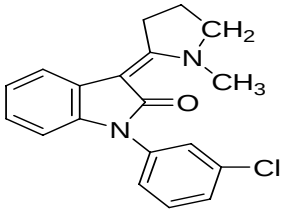
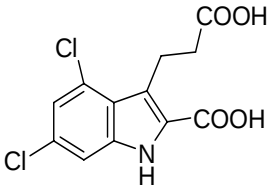


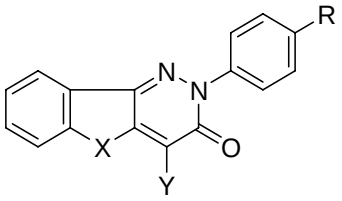
[22]



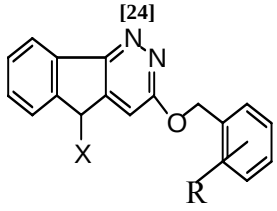
[23]



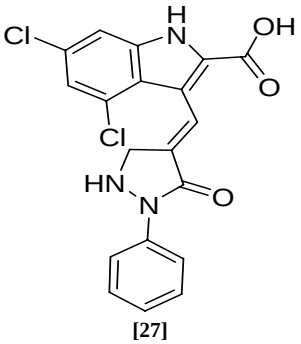
[24]



[25a]; X = CH_2, Y = H, R = H
[25b]; X = CO, Y = H, R = H
[25c]; X = CH_2, Y = $COOC_2H_5$, R = H
[25d]; X = NH, Y = $COOC_2H_5$, R = 4-Cl
[25e]; X = CH_2, Y = $COOC_2H_5$, R = 4-Br



[26a]; X = 2-methyl-3-indolylmethyl, R= phenyl
[26b]; X = 2-methyl-3-indolylmethyl, R= p-tolyl



[27]

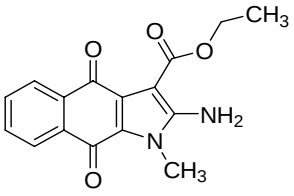
Antitubercular activity

Among the synthetic methodologies reported so far for the preparation of the indole analogs, the Fischer indole synthesis still maintains its prominent role for the large scale production of biologically active compounds. Karthikeyan *et al* were reported. [30] A series of novel 2-aryl-3, 4-dihydro-2*H* thieno **[3,2b]** indoles has been synthesised regioselectively in good yields from the reaction of 5-aryldihydro-3(2*H*)-thiophenones and arylhydrazine hydrochloride. This reaction was found to be assisted by microwaves. The thieno[3,2-b]indoles were evaluated for their in vitro activity against Mycobacterium tuberculosis H37Rv (MTB) 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] **[28]** and was found to the most active compound with MIC of 0.4 lg/mL against MTB and MDR-TB.

Anticancer activity

Cancer remains a major threat to the public health. In the challenge to improve modern cancer chemotherapy, the search for new drugs with both higher therapeutic index and lower capacity to induce resistance is, therefore, an active field of investigation in medicinal chemistry. Lee *et al* have synthesized 2-amino-3-ethoxycarbonyl-N-methylbenz[f]indole-4, 9-dione (SME-6) **[29]** and showed a potent growth inhibition of a panel of human cancer cell lines. [31] The mechanism of action study 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).

Pirici *et al* were reported the cytotoxicity of the bis [*N*-(2-propyl) carbamates] which were linked to thienoindole scaffolds through methylene bridges were studied as thiophene analogues of prototype. Compound **[30]** the thieno indole bis-carbamate, possessed only significant (MG-MID log10 GI50=−4.89) and selective cytoxicity against NCI–HOP92 (non-small cell lung), MALME 3M (melanoma) and IGROV 1 (ovarian) cancer cell. [32]



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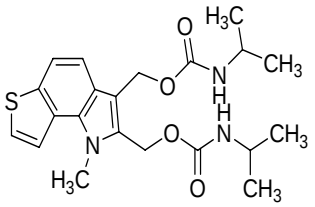

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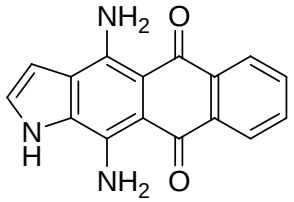

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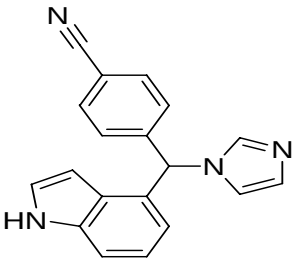

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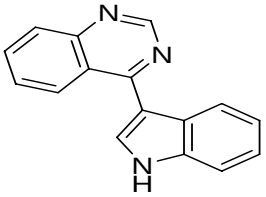


[33]

Shchekotikhin *et al* were described the synthesis of derivatives [33] of 4, 11-diaminonaphtho indole-5, 10-dione and their cytotoxicity for human tumor cells that express major determinants of altered anticancer drug response. The cytotoxicity of novel compounds **[31]** for multidrug resistant, P-glycoprotein-expressing tumor cells was highly dependent on the N-substituent at the terminal amino group of the ethylenediamine moiety.

Lézé *et al* were reported two new series of benzonitrile derivatives [34] on position 6 or 4 of indole ring were successfully synthesized *via* a Leimgruber-Batcho reaction. All the 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 **[32]** showed high level of inhibitory activity toward CYP19 (IC50 = 11.5 nM).

A Luth and W Lo were reported 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. [35] The synthesis and pharmacological results of 4-(indole-3-yl) quinazolines **[33]** were described. The synthesized compounds were new high potent EGFR-tyrosine kinase inhibitors with excellent cytotoxic properties at different cell lines.

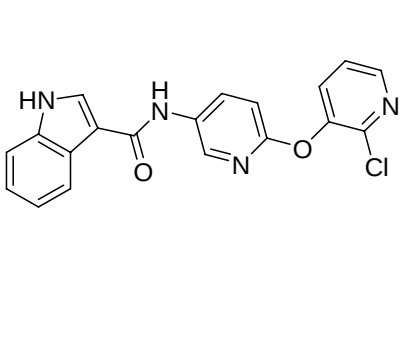
Antihistaminic activity

For antihistaminic activity a large number of indole derivatives were evaluated and found to possess significant a ctivity. Park *et al* have synthesized 1*H*-indole-3-carboxylic acid [6-(2- chloro-pyridin-3-yloxy)-pyridin-3-yl]-amide **[34]** 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. [36]

Cole et al were reported a series of N_1-arylsulfonyl-3-(1, 2, 3, 6-tetrahydropyridin-4-yl) indole derivatives were designed and synthesized. These compounds were shown to have high affinity for the 5-HT6 receptor. [37] Two analogs, 4-[3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-1-sulfonyl]-phenylamine **[35]** and 4-[3-(1,2,3,6-tetrahydropyridin-4-yl)-5-methoxy-1*H*-indole-1-sulfonyl]-phenylamine **[36]** had 0.4 and 3.0nM affinity respectively, and antagonized the production of adenylate cyclase at sub-nanomolar concentrations.

Zhou *et al* were reported a series of related arylpiperazin-4-yl-cyclohexyl indole analogs were synthesized then evaluated as 5-HT transporter inhibitors and 5-HT_{1A} receptor antagonists. [38] The investigation of the structure–activity relationships revealed the optimal pharmacophoric elements required for activities in this series. The best example from their study, 5-(piperazin-1-yl) quinoline analog **[37]** 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.

Ivachtchenko *et al* have synthesized the compounds N-(3-Fluorophenyl)-2-methyl-2, 3, 4, 5-tetrahydro-1*H*-pyrido [4, 3-b] indole-8-sulfonamide hydrochloride HCl **[38]** and 2,5-Dimethyl-8-(phenylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole hydrochloride HCl **[39]** and 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 (functional assay) equal to 15 nM and 78 nM, respectively. Affinities of these two compounds for several serotonin receptors in the competitive radioligand binding. [39]



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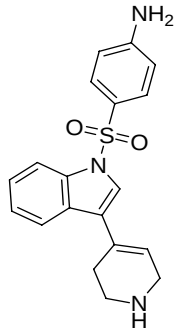

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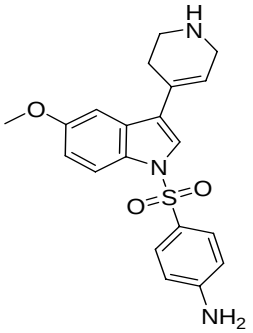

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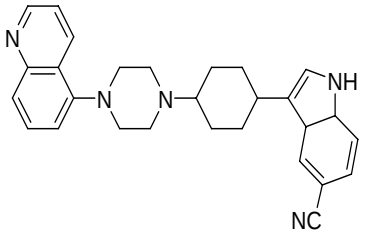

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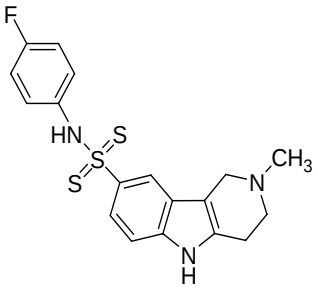

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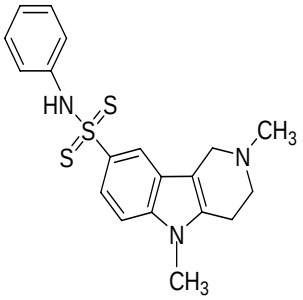
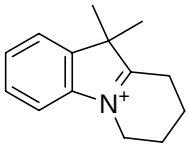


[39]

Diagnostic agents

Andrii *et al* were reported the electronic absorption spectra of merocyanines and symmetric cationic polymethine dyes based on 10, 10-dimethyl-7, 8, 9, 10-tetrahydro-6*H*-pyrido [1, 2-*a*] indolium **[40]** have been investigated in a wide range of solvent polarity. [40] An important feature of these compounds was a cyclic group connecting the nitrogen atom of indole nucleus with the polymethine chain. The explored cationic cyanine dyes in comparison with the derivatives of 3*H*-indoles are characterized by less bond order and charge alternation in their chromophore in the ground state. The synthesized merocyanines get the greater dipolarity of the ground state, as compared to their non-cyclic analogues. It leads to a color deepening and an increase of the absorption band intensity.



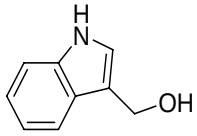
[40]

Current Aspects of Indole

Choi *et al* were reported Indole-3-carbinol **[41]** has anti-tumor effects in various cancer cell lines. However, the anti-

tumor effect of **[41]** on human lung cancers has been rarely reported. [41] They investigated the anti-tumor effects and its mechanism of **[41]** on human lung carcinoma A549 cell line. Treatment of the A549 cells with **[41]** significantly reduced cell proliferation, increased formations of fragmented DNA and apoptotic body, and induced cell cycle arrest at G0/G1 phase **[41]** increased not only the protein levels of cyclin D1, 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 **[41]** 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. Taken together, these results demonstrate that **[41]** 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 molecular mechanism for apoptotic effect of **[41]** on A549 lung carcinoma cells may be a first report and suggest that **[41]** may be a preventive and therapeutic agent against lung cancer.

Zhou *et al* synthesized indole ring containing compounds and were designed based on the structure of the gp41 complex in the region of the hydrophobic pocket **[Fig].** These compounds were synthesized using a Suzuki Coupling reaction, and evaluated using a fluorescence binding assay and cell–cell fusion assay. [42] The observed inhibition constant of compound 3-((*E*)-4-methoxyhexa-1, 3, 5-trien-2yl)-1*H*-indol-6-yl) methyl) benzoic acid **[42]** was 2.1 lM, and the IC50 for cell–cell fusion inhibition was 1.1 lM.



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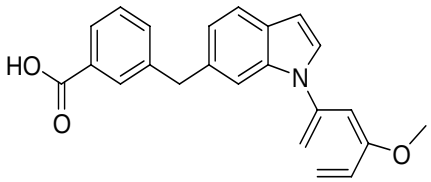

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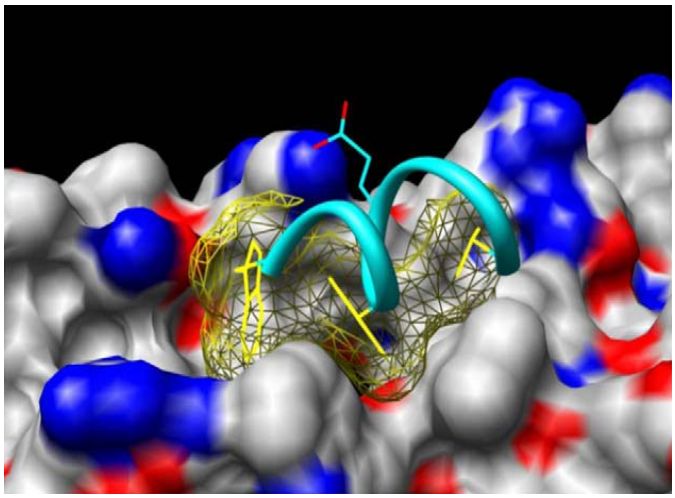

Fig: The hydrophobic pocket of gp41 (Molecular dynamics—simulated structure (R. Rizzo, personal communication), starting with PDB 1IF$_3$). The segmentof the CHR containing hydrophobic (Trp628, Trp631and Ile635, in yellow) and charged (Asp632 in cyan) residues is shown interacting in the pocket. Residue numbering is based on Genbank accession number AAK49977.

CONCLUSION

The survey of literature revealed that 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, anti-inflammatory, anticancer, antitubercular 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.

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