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The Diverse Pharmacological Importance of Indole Derivatives: A Review

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ABSTRACT:

Small bicyclic molecules are frequently found in nature and are attracting increased attention from organic and pharmaceutical chemists. Heterocyclic compounds are acquiring more importance in recent years because of their broad pharmacological activities. Nitrogen, sulpher or oxygen containing five or six membered heterocyclic compound has occupied enormous significance in the field of medicinal chemistry. Indole is a bicyclic heterocycle consisting of a six membered benzene ring fused to a five membered nitrogen containing pyrrole ring. Indoles are an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, but also because they have a wide range of biological activities. Hence, it is not surprising that indoles act as lead compounds and are key building blocks in numerous pharmaceuticals. Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including antihypertensive, antiproliferative, antiviral, antitumor, analgesic, anti-inflammatory, antimicrobial, antifungal activities, etc. Although indole moiety is very small but is fascinated by scientists because of the diverse biological activities by not only indole but its various substituted derivatives as well. This review represents some synthesized indole derivatives and their pharmacological profiles which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines.

KEYWORDS: Indole, Antihypertensive, Antiproliferative, Antiviral, Antitumor.

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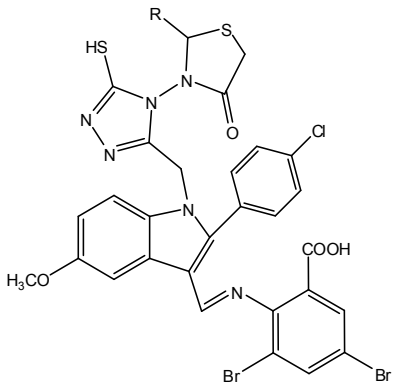
1. INTRODUCTION:

The name *indole* is portmanteau of the words ***ind****igo* and ***ole****um*, since indole was first isolated by treatment of the indigo dye with oleum. Indole chemistry began with the study of the dye indigo. Indole is an aromatic heterocyclic nucleus. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen containing pyrrole ring through the 2- and 3-positions of the pyrrole nucleus. Indole is called as benzopyrrole. The indole ring is also found in many natural products such as the vinca alkaloids, fungal metabolites and marine natural products.[1] Indole is a popular component of fragrances.[2] Indoles are a pervasive class of compounds found in abundance in biologically active compounds such as pharmaceuticals, agrochemicals and alkaloids. Since the first synthesis of indole in 1866, a number of synthetic methods for the construction of the indole nucleus have been devised. Indole myriad derivatives have, therefore, captured the attention of organic synthetic chemists. Medicine and biochemistry are also interested in many aspects of the indole chemistry.[3]

2. PHARMACOLOGICAL ACTIVITIES OF INDOLE DERIVATIVES:

2.1 ANTI-INFLAMMATORY ACTIVITY:

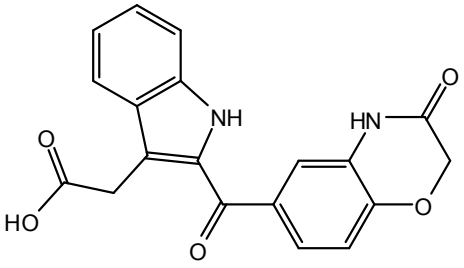
- **Ashok Kumar *et al*** synthesized a series of novel substituted indole derivatives and were evaluated for their *in vitro* anti-inflammatory activity. It was found that the compound *2-(p-chlorophenyl)-1-[4-(2-(p-chorophenyl)-4-oxo-thiazolidin-3-yl]-5-mercapto[1,2,4,]-trizole-3-yl-methyl]-3[4,6-dibromo-2-carboxyphenyliminomethyl]-5-methoxyindole* had shown prominent anti-inflammatory activity at the three graded dose of 25, 50 and 100mg/kg p.o.[4]



R= chlorobenzylideneamino

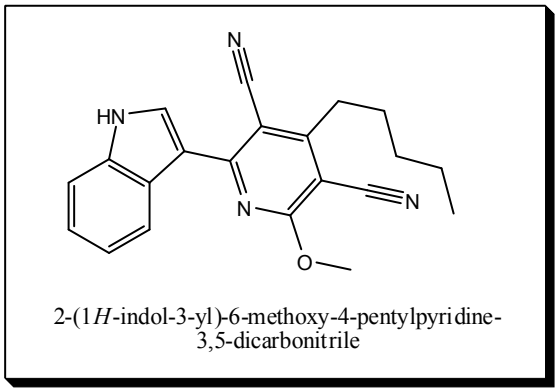
2-(4-Chlorophenyl)-1-{4'-(4-chlorobenzylidine)amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenylimino methyl }-5-methoxy-indole

- **Dubey *et al*** synthesized a series of novel [2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-carbonyl)-1H-indol-3yl]aceticacid derivatives and evaluated for their anti-inflammatory activity. It was found that the compounds had shown prominent COX-2 inhibitor properties.[5]



[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-carbonyl)-1H-indol-3yl]acetic acid

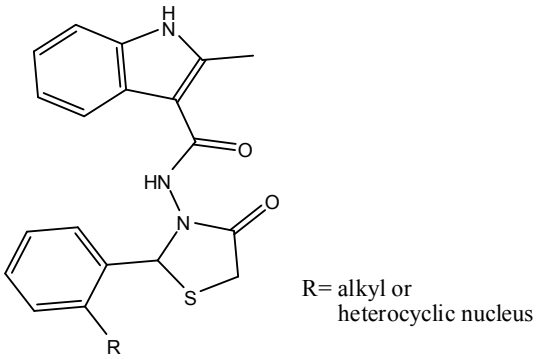
❖ **Thirumurugan prakasam *et al*** synthesized a various 2-(1H-indol-3-yl)-6-methoxy-4-pentylpyridine-3,5-dicarbonitrile derivatives and was screened for their anti-inflammatory activity. Most of the compounds had shown potent anti-inflammatory activity.[6]



2-(1*H*-indol-3-yl)-6-methoxy-4-pentylpyridine-3,5-dicarbonitrile

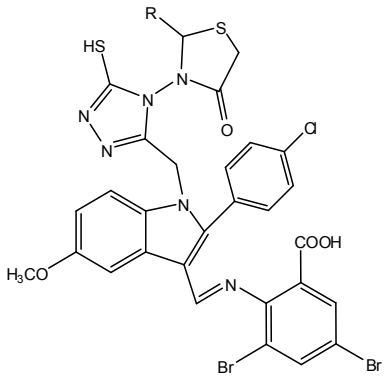
2.2 ANALGESIC ACTIVITY:

❖ **Rapolu Manish *et al*** synthesized a series of novel 2-methyl-1H-indole-3-carboxylic acid[2-(2-substitutedphenyl)-4-oxo-thiazolidin-3-yl]amide derivatives and evaluated for their analgesic activity by using hot plate latency and acetic acid induced writhing test. Most of the compounds which are having two hydroxyl group and one methoxy group on the phenyl ring had shown excellent analgesic activity.[7]



2-methyl-1H-indole-3-carboxylic acid[2-(2-substitutedphenyl)-4-oxo-thiazolidin-3-yl]amide

❖ **Kumar Ashok *et al*** synthesized a series of novel substituted indole derivatives and were evaluated for their analgesic activity. It was found that the compound *2-(p-chlorophenyl)-1-[4-(2-(p-chorophenyl)-4-oxo-thiazolidin-3-yl]-5-mercapto[1,2,4,]-trizole-3-yl-methyl]-3[4,6-dibromo-2-carboxyphenyliminomethyl]-5-methoxyindole* had shown prominent analgesic activity at the three graded dose of 25, 50 and 100mg/kg p.o.[8]

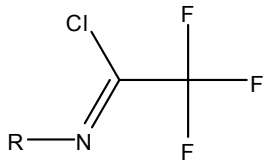


R= chlorobenzylideneamino

2-(4-Chlorophenyl)-1-{4'-(4-chlorobenzylidine)amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenylimino methyl }-5-methoxy-indole

2.3 ANTIMICROBIAL ACTIVITY:

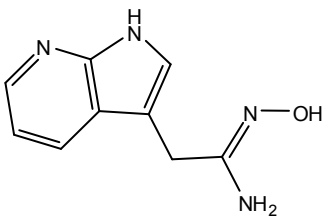
- **Darehkordi Ali *et al*** synthesized a series of novel 2,2,2-trifluoro-N-arylacetimidoylchloride derivatives and it was found that some compounds had shown prominent antibacterial activity.[9]



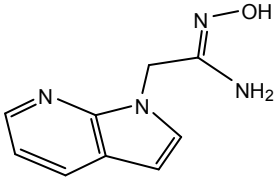
R= different aromatc or heterocyclic rings

2,2,2-trifluoro-N-arylacetimidoylchloride

- **Mehta DS *et al*** synthesized a series of novel 1-aryl-2-methyl-3-carboethoxy-5-hydorxy indole derivatives and evaluated their antimicrobial activity against B. mega , B. subtilis bacteria.[10]

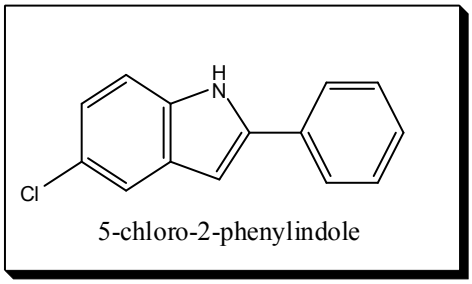


7-azaindole-3-acetamidoxime



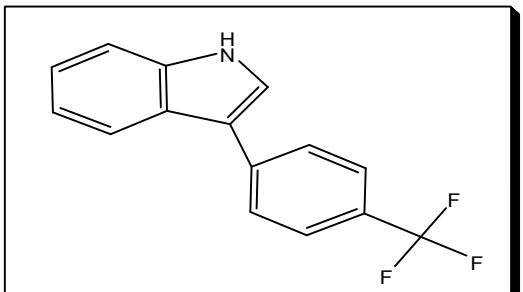
7-azaindole-1-acetamidoxime

- **Kumar Dharmendra *et al*** synthesized 5-chloro-2-phenylindole derivative and shown significant activity against P. aeruginosa and S. thermonitrificans bacteria. Most of the compounds had shown significant antibacterial activity.[11]



5-chloro-2-phenylindole

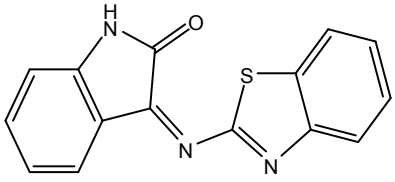
- **Hiari-Al M. Yusuf *et al*** synthesized 3-(4-trifluoromethylphenyl)indole derivative and were evaluated for their antimicrobial activity against Escherichia coli and Staphylococcus bacteria. All of the synthesized compounds had shown antibacterial activity.[12]



3-(4-trifluoromethylphenyl)indole

2.4 ANTICONVULSANT ACTIVITY:

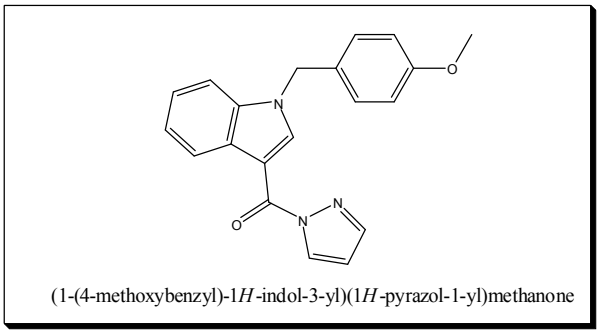
- **Sharma Prince P *et al*** synthesized a series of various 3-(1,3-benzothiazol-2-ylimino)-1,3-dihydro-2H-indol-2-one derivatives and it was found that compounds had shown prominent anticonvulsant activity.[13]



3-(1,3-benzothiazol-2-ylimino)-1,3-dihydro-2H-indol-2-one

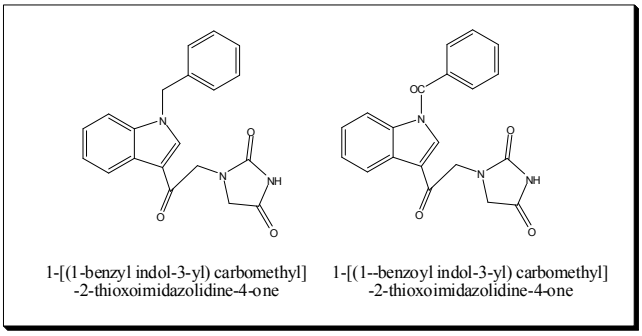
2.5 ANTITUMOR ACTIVITY:

- **Farghaly AR** synthesized a series of novel [1-(4-methoxybenzyl)indol-3-yl](1*H*-pyrazol-1-yl)methanones and 1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-3-subsituted-1*H*-pyrazol-5(4H)-one derivatives and all synthesized target compounds were tested *in vitro* for antitumor activity using the Alamar Blue assay on a panel of five human tumor cell lines. The cytotoxicity was evaluated on five different cell lines, cervix cancer (KB/HELA), ovarian carcinoma (SK-OV-3), brain cancer (SF-268), nonsmall-cell lung cancer (NCl-H460) and adenocarcinoma colon cancer (RKOP-27) and it was observed that these compounds had shown prominent antitumor activity.[14]



(1-(4-methoxybenzyl)-1*H*-indol-3-yl)(1*H*-pyrazol-1-yl)methanone

- **SAWY-EL Eslam *et al*** synthesized a series of novel 1-benzyl-3-heterocyclicindole and 1-benzoyl-3-heterocyclicindole derivatives. All the synthesized compounds were initially screened for *in vitro* anticancer activity at a concentration of 10^{-7} mol L^{-1} against two human cancer cell lines, OVCAR3 and BG-1, compared to vitamin D [1,25(OH)2D3] (10^{-7} mol L^{-1}) using the MTT assay. The growth inhibition action of the tested compounds was reported after 24 and 48 h for each cell line. Some compounds were found to be the most cytotoxic, with growth inhibition of 98.5 ± 1.2, 97 ± 0.6 and 96.14 ± 0.5 %, respectively, after treatment for 24 h and 99.9 ± 1.5, 98.6 ± 0.6 and 97.6 ± 0.6, respectively, compared to vitamin D (43.9 ± 7.8 and 59.8 ± 5.3 %) against OVCAR3.[15]

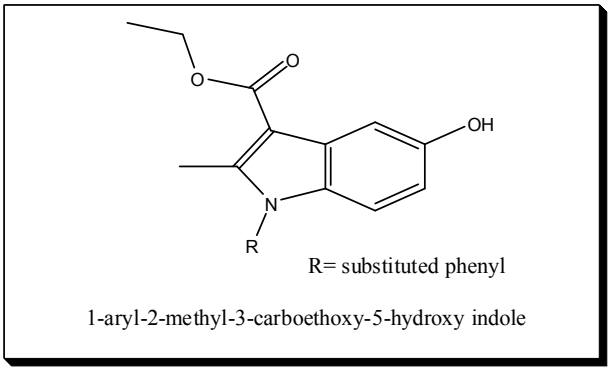


1-[(1-benzyl indol-3-yl) carbomethyl] -2-thioxoimidazolidine-4-one

1-[(1--benzoyl indol-3-yl) carbomethyl] -2-thioxoimidazolidine-4-one

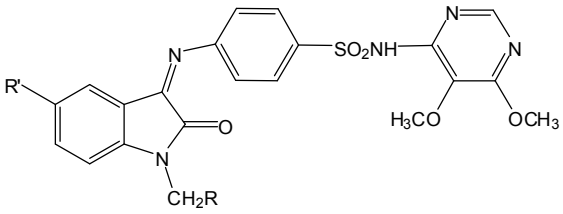
2.6 ANTIFUNGAL ACTIVITY:

- **Mehta DS *et al*** synthesized a series of 1-aryl-2-methyl-3-carbethoxy-5-hydroxyindole derivatives and evaluated their antifungal activity against A. awamori and A. arogens. Some compounds had shown remarkable antifungal activity.[16]



1-aryl-2-methyl-3-carboethoxy-5-hydroxy indole

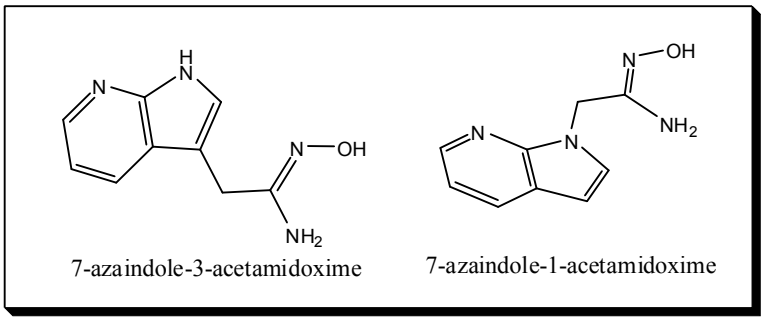
- **Pandeya *et al*** synthesized schiff bases of isatin and 5-methyl isatin with sulphadoxine and were evaluated for their *in vitro* antifungal activity against various fungal strains viz. Candida albicans, Candida neoformis, Histoplasma capsulatum, Microsporum audounii and Trichophyton mentagrophytes. It was found that the piperidino methyl compounds have shown prominent antifungal activity.[17]



R=-N $(CH_3)_2$, N$(C_2H_5)_2$, 1-piperidyl, 1-pyrrolidinyl, 4-morpholinyl, etc.
R'= -CH_3

2.7 ANTIHYPERTENSIVE ACTIVITY:

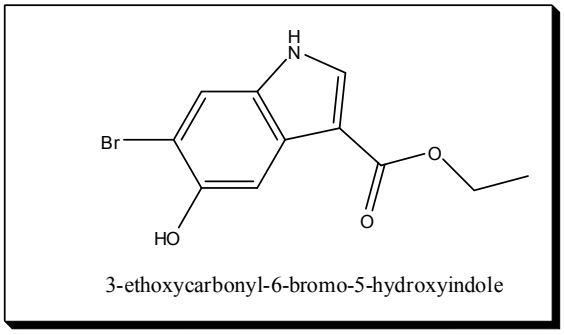
- **Bell MR *et al*** synthesized a series of novel 7-azaindole-3-acetamidoxime and 7-azaindole-1-acetamidoxime and evaluated for its antihypertensive activity. These compounds have shown prominent antihypertensive properties.[18]



7-azaindole-3-acetamidoxime　　7-azaindole-1-acetamidoxime

2.8 ANTIVIRAL ACTIVITY:

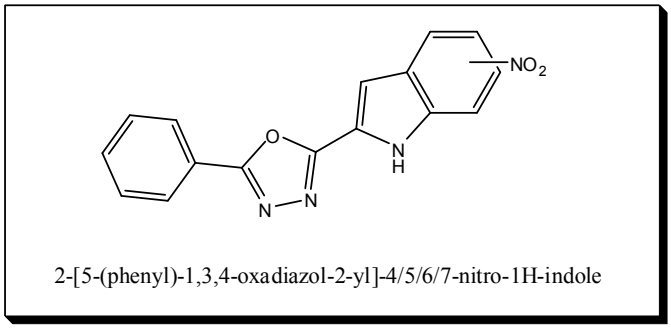
- **Wang Dun *et al*** synthesized various 2-arylthiomethyl-4-tertiary amino methyl substituted derivatives of 6-bromo-3-ethoxycarbonyl-5-hydroxyindole and evaluated their *in vitro* antiviral activity against laboratory-passaged isolates of human influenza A3 and respiratory syncytial virus (RSV) respectively in MDCK cell culture and HeLa cell culture with virus cytopathic effect assay in comparison with amantadine and Abidol. The 50% inhibitory concentration (IC_{50}) and the minimum inhibitory concentration (MIC) for the tested compouds against the above two virus were calculated with Reed and Muench Method and therapeutic index (TI) was obtained. Some compounds had shown significant antiviral activity.[19]



3-ethoxycarbonyl-6-bromo-5-hydroxyindole

2.9 ANTI-PROLIFERATIVE ACTIVITY:

- **Narayana B *et al*** synthesized a series of novel 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-4/5-6/7-nitro-1H-indole derivatives and evaluated for their *in vitro* anti-proliferative activity.[20]



2-[5-(phenyl)-1,3,4-oxadiazol-2-yl]-4/5/6/7-nitro-1H-indole

3. CONCLUSION

Indole is a unique template that is associated with several biological activities. Due to the diverse and versatile biological properties of indole derivatives, they are of great interest to the research community. In particular, their physiological, bacteriostatic, antitumor, antioxidant and anti-inflammatory activities makes these compounds attractive candidates not only for the microbe borne diseases but also for the several other conditions like Alzheimer's disease and others where oxidative stress and inflammation is involved. This review has presented comprehensive details of indole analogues, potent compounds reported for particular biological activity. More research must be carried out to evaluate the therapeutic efficacy of indole derivatives for many other untreatable diseases like AIDS, hepatitis and cancer.

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