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A BRIEF REVIEW ON BIOLOGICAL POTENTIAL OF INDOLE DERIVATIVES

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ABSTRACT

Indole is a heterocyclic (bicyclic) molecule, various bioactive indole containing compound showed clinical and biological applications like anticancer, anticonvulsant, anti-inflammatory, antimicrobial, anti-platelet, anti-tubercular, anti-malarial, antiviral, anti-diabetic and other miscellaneous activities which have been investigated. Indole scaffold found in many drug and it act as a key pharmacophore in synthesizing the most potent biological agents. It's a superb moiety in drug development having the only feature of imitating much protein structure.

KEYWORDS: Indole derivatives, substituted, anti-inflammatory, anticancer, antiviral.

INTRODUCTION

Indole, a bicyclic heterocyclic structure found in a variety of physiologically essential compounds, is one of them. Indole, also known as benzo [b] pyrrole, is an organic chemical molecule with the formula C8H7N that has a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring and is employed as a building block in medicinal chemistry.

In 1886 the indole was created by Adolf von Baeyer by reducing oxindole. Indole is non-basic nitrogenous compound because of delocalization of the nitrogen lone-pair into the electronic system, which is free to circulate across the indole ring. Indole contains benzene ring fused to a pyrrole nucleus at 2, 3 position of pyrrole ring.[1-8]

It undergoes all types of reaction protonation, sulfonation, and acylation. Oxidation electrophilic substitution reaction cycloadditions carbon lithiation, this reaction occurs particularly at C-3 position. Indole can be substituted at the N-1, C-2 through C- 6, or C-7

positions with a variety of substituent to create a variety of Indole scaffolds. This knowledge is used to make indole derivatives that are versatile.[9]

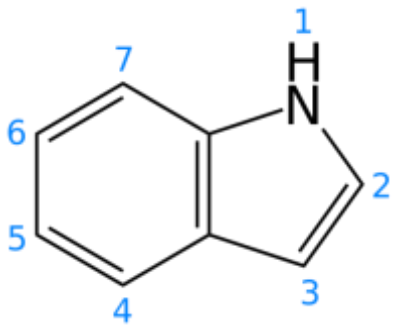


Fig.1 Illustration of the structure of indole.

Indole is a crystalline white solid that melts at 52°C and is soluble in alcohol, benzene, and ether. Water can be used to recrystallize it. It is found naturally in human feces and provides a fecal odor. At lesser concentrations, however, it has a floral odor and is acomponent of many flower smells, perfumes, and coal tar and can be produced by the bacteria as a degradation product of tryptophan.[10]

Here we have attempted to summarize the key pharmacological properties of indole derivatives.

PHARMACOLOGICAL APPLICATIONS OF INDOLE DRIVATIVES

Anti-Inflammatory and Analgesic Activity

Inflammation is the body's complicated response to damaging stimuli such as bacteria, damaged cells, and irritants. Tissue healing is complicated by inflammation. However, it has harmful consequences on the body when it is persistent. Anti-inflammatory drugs reduce swelling and discomfort by treating inflammation. The indole has been discovered to be a powerful cyclooxygenase inhibitor.[11]

In 2020, Deepmala and co-worker synthesized 1, 5-disubstituted derivatives of indole, all the newly synthesized compounds characterized by spectroscopic ally and analytically. The entire compounds were screen for the anti-inflammatory activity. The pharmacological screening of synthesized compound ranges from 12.12-65.51%. From the synthesized derivatives compound 1 found to be more potent than Indomethacin standard drug. Compound 4 & 5 showed more potent activity than 1, 2 & Indomethacin.[12]

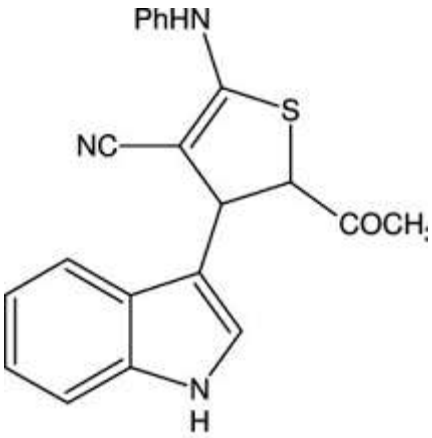
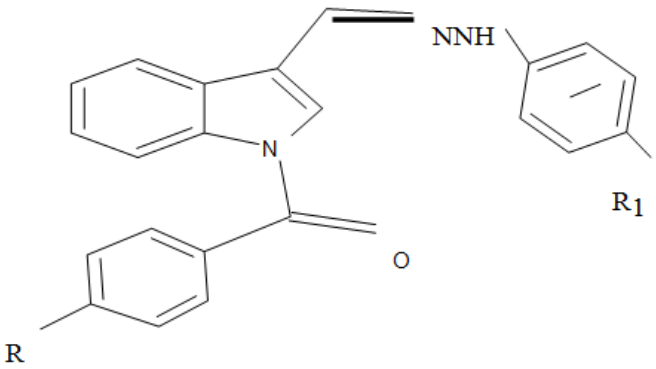


Fig.2: Chemical structure of indole derivatives having anti-inflammatory activity.

1= R=CH3CO, **2**=R=C6H5CO **3**=R=C2H5C6H4CO **4**=R=NO2C6H4CO **5**=R=BrC6H4CO.

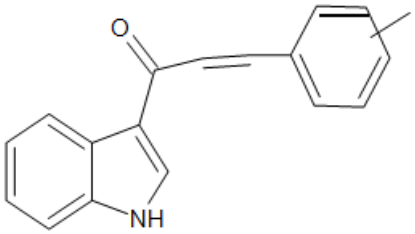
In 2017 Khaled R. A. Abdellatif and colleague synthesized, Through N-benzoylation of indole-3-cabaldehyde with the suitable benzoyl fragment followed by reaction with substituted phenyl hydrazine, a novel group of (4- substituted phenyl) (3-((2-(4- substituted phenyl) hydrazono) methyl)-1H-indol-1- yl) methanone derivatives 13a-f as indomethacin analogue In contrast to the parent medicine indomethacin, all of the synthesized compounds were tested in vitro for COX-1/COX-2 inhibitory action and in vivo for anti-inflammatory efficacy. Compounds 6a, b, d, e, which include SO2Me or SO2NH2 as a COX-2 pharmacophore, showed the highest anti-inflammatory and selectivity actives, thus they were further tested by calculating their ED50 percent dosages and ulcerogenic indices to assure their stomach safety margin compared to indomethacin.[13-17]



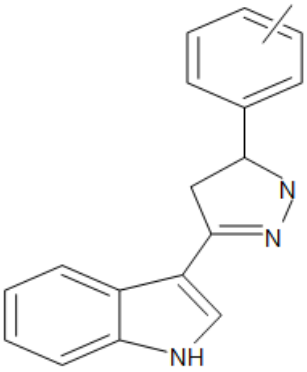
6a, R=H, R1=SO2CH3, **6b,** R=H, R1=SO2NH2, **6d,** R=Cl, R1=SO2CH3,
6e, R=Cl, R1=SO2NH2

Fig.3: Chemical structure of indole derivatives having anti-inflammatory activity.

In 2014 Mayura A. Kale and coworker did treatment of 3- acetyl indole (1) with different aromatic aldehydes (2) yielded the matching 3- chalconylindoles 7a-e, allowing for easy synthesis of certain new anti-inflammatory and analgesic medicines. The pyrazoline derivatives 8a-e was obtained by treating these products 7a-e with hydrazine hydrate. When pyrazoline indoles 8a-e was reacted with the diazotized salt of aniline, azo derivatives of pyrazoline indoles 9a-e were formed. These newly synthesized compounds were tested forthe mentioned activities and found to have promising anti-inflammatory and anti-pain properties.[18-20]



7a= p-CH_3, **7b**= p-Cl, **7c**=p-F, **7d**=m-NO_2, **7e**= m, p-$(CH_3)_2$



8a= p-CH_3, **8b**= p-Cl, **8c**=p-F, **8d**=m-NO_2, **8e**= m, p-$(CH_3)_2$

Fig.4: Chemical structure of indole derivatives having anti-inflammatory activity.

Antiviral Activity

When pathogenic viruses and infectious virus particles enter the body, they spread a viral infection. Various antiviral medications for HIV, Herpes, and Hepatitis B & C viruses are available on market. Viruses are the fastest spreading of all illnesses, causing 60% of sickness in developed nations.[21]

As antiviral drugs, Scuotto et al. (2016) developed a variety of new multi-target indole-3-carboxylate derivatives. A CPE reduction assay was used to test all of the produced compounds against Chikungunya virus in Vero cell culture. According to SAR research, the hydroxyl group at the fifth position is the most beneficial. Compound 10 (Fig.5) was shown to be the most active (EC 50 = 6.5 1), ten times greater than the conventional medication arbidol. The crystal structure of the CHIKV glycoprotein complex was also used to conduct further docking investigations. Maximum derivatives entered into the active site's lateral sites, but in compound 10 (Fig.5), indole was deeply inserted into the cavity and the thiophenol ring occupied solvent exposed parts, resulting in the highest solvent exposure.

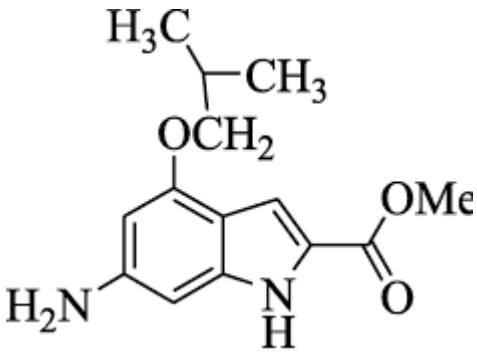


Fig.5: Chemical structure of indole derivative having antiviral activity.

Xue et al. synthesized and reported 6-amino-4-substituted alkyl-1H-indole-2-substituted carboxylate derivatives as antiviral agents. The chemical methyl 6-amino-4-isobutoxy-1H indole-2-carboxylate (11), with an IC50 of 7.53μmol/L and the greatest selectivity index (SI) of 17.1 to C, demonstrated inhibitory action against influenza A with highest selectivity index (SI) value 17.1 to CoxB3 virus.

Anti-cancer

Atanasova et al synthesized galantamine derivatives with indole moiety in the side chain which were 11-95 times more active than galantamine. Compound (**22**) (4aS, 6R, 8aS)-11-(6-(4-((1H-Indol-5- ylamino) methyl) phenoxy) hexyl)-3-methoxy-5, 6, 9, 10, 11, 12-hexahydro-4aH-benzo [2, 3]-benzofuro [4,3- cd] azepin-6-ol, (**23**) (4aS, 6R, 8aS)-11-(6-(1H-Indol-5-yloxy) hexyl)-3-methoxy-5, 6, 9, 10, 11, 12-hexa hydro-4aH-benzo [2, 3] benzo-furo [4,3-cd] azepin-6-ol and (**24**) N-(1H-Indol-5-yl)-6-((4aS, 6R, 8aS)-6-hydroxy-3-methoxy- 5,6,9,10-tetrahydro-4aH-benzo [2, 3]-benzo furo [4, 3-cd] azepin-11(12H)-yl) hexanamide were found to be most potent.[22-24]

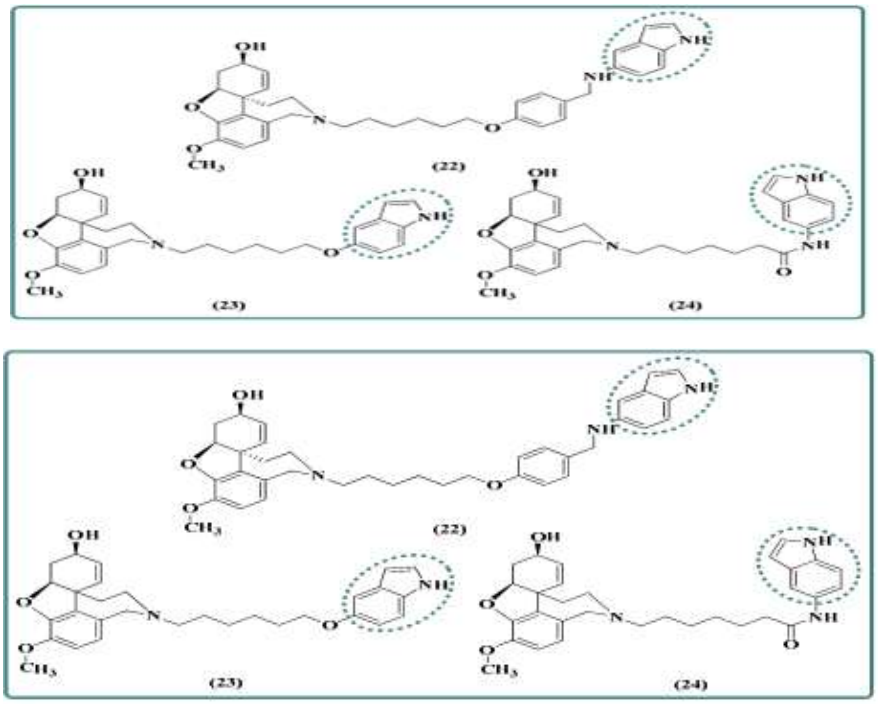


Fig.6: chemical structure of indole derivative having Anti-cancer activity.

CONCLUSION

Indole is a plentiful heterocycle that is frequently included in medicines, agrochemicals, and naturally occurring compounds that are pharmacologically active. Researchers became interested in using indole derivatives as bioactive compounds against many diseases because of their diverse biological profile. According to this assessment, indole's recent advances serve as a crucial scaffold for the creation of new drugs. The focus of the paper is on several morpholine derivative targets that can be investigated with various inhibitors/activators for improved therapy of lifestyle disorders.

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