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A REVIEW: PHARMACOLOGICAL 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, antiplatelet, anti-tubercular, antimalarial, antiviral, antidiabetic 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

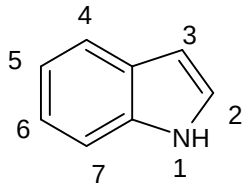
1. INTRODUCTION

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 C_8H_7N 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[1].

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, 2, 8]. It undergoes all types of reaction protonation, sulfonation, and acylation [1]. Oxidation [3] electrophilic substitution reaction [4] cycloadditions [5] carbon lithiation [6, 7] 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.



1H-indole

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 [2]. It is found naturally in human feces and provides a fecal odor. At lesser concentrations, however, it has a floral odor and is a

component of many flower smells, perfumes, and coal tar[1,2] and can be produced by the bacteria as a degradation product of tryptophan[8].Here we have attempted to summarize the key pharmacological properties of indole derivatives .

2. PHARMACOLOGICAL APPLICATIONS OF INDOLE DRIVATIVES

2.1 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 [10].

In 2020, Deepmala and coworker 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 [2].

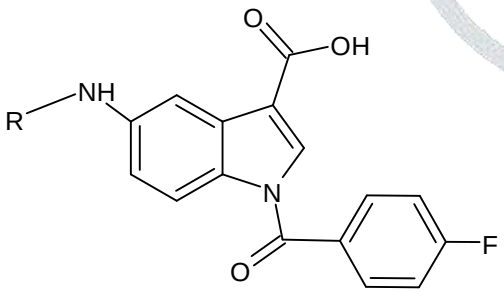
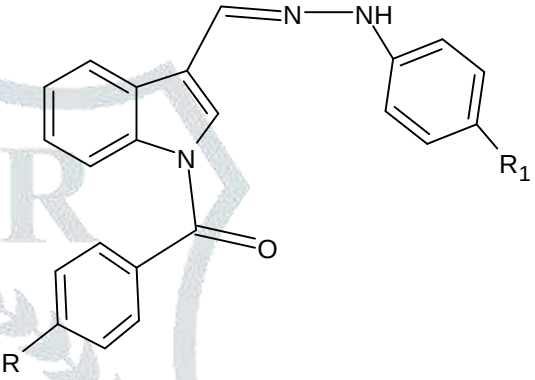


Fig.2 Chemical structure of indole derivatives having anti-inflammatory activity

1= R=CH_3CO, **2**=R=C_6H_5CO

3=R=$C_2H_5C_6H_4CO$ **4**=R=$NO_2C_6H_4CO$ **5**=R=BrC_6H_4CO. 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-substitutedphenyl)(3-((2-(4-substitutedphenyl)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[11].



6a, R=H, $R_1=SO_2CH_3$

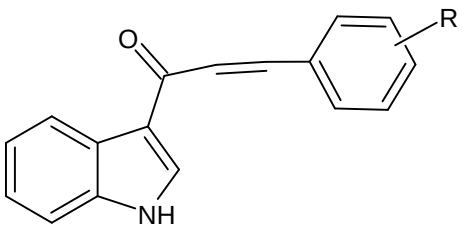
6b, R=H, R1=SO_2NH_2

6d, R=Cl, R1=SO_2CH_3

6e, R=Cl, R1=SO_2NH_2

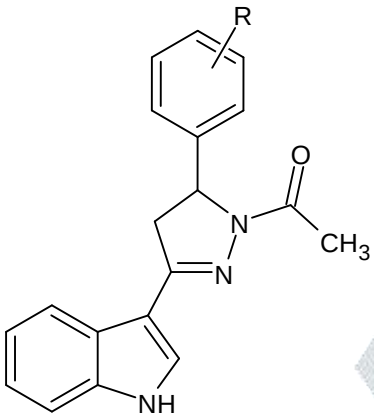
Fig. 3. Chemical structure of indole derivatives having anti-inflammatory activity

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 were 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 for the mentioned activities and found to have promising anti-inflammatory and anti-pain properties[12].



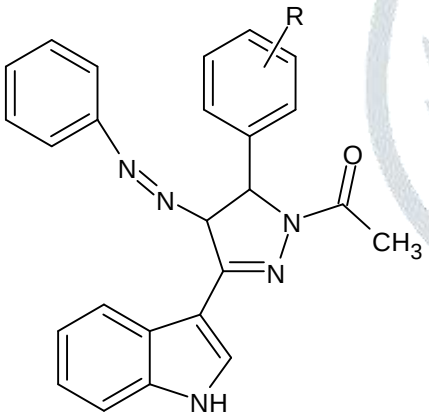
7a= p-CH_3, **7b**= p-Cl, **7c**=p-F, **7d**=m-NO_2

7e= m, p-$(CH_3)_2$



8a= p-CH_3, **8b**= p-Cl, **8c**=p-F, **8d**=m-NO_2

8e= m, p-$(CH_3)_2$



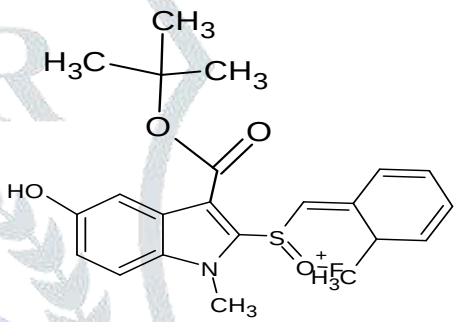
9a= p-CH_3, **9b**= p-Cl, **9c**=p-F, **9d**=m-NO_2 9e= m, p-$(CH_3)_2$

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

2.2 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 and C viruses are available on the market. Viruses are the fastest spreading of all illnesses, causing 60 percent of sickness in developed nations [1].

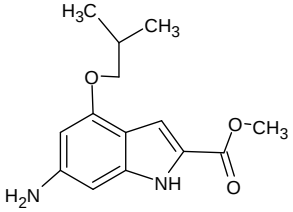
As antiviral drugs, Scuotto et al. (2016) developed a variety of new multi-target indole-3- carboxylate derivatives. A CPE reduction assay was used to test all of the produced compounds against Chikungunya virus in Vero cell culture. According to SAR research, the hydroxyl group at the fifth position 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 [13].



(10)

Fig.5 chemical structure of indole derivative having antiviral activity

Xue et al. synthesized and reported 6-amino-4-substitutedalkyl-1H-indole-2-substitutedcarboxylate derivatives as antiviral agents. The chemical methyl 6-amino-4-isobutoxy-1*H* indole-2-carboxylate (11), with an IC50 of 7.53 μmol/L and the greatest selectivity index (SI) of 17.1 to C, demonstrated inhibitory action against influenza Awith highest selectivity index (SI) value 17.1 to CoxB3 virus[14].



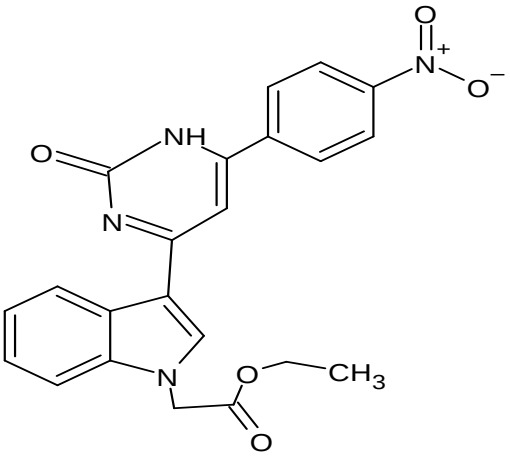
(11)

Fig.6 chemical structure of indole derivative having antiviral activity

7-Ethoxy-1-methyl-4, 9-dihydro-3H-pyrido [3, 4-b] 7-Ethoxy-1-methyl-4, 9-dihydro-3H-pyrido El-sawy

et al. identified indole derivatives as anti-Herpes Simplex Virus-1 (HSV-1) drugs, and derivatives ethyl 2-(3-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro1H-pyrazol-3-yl)-1H-indol-1-yl)acetate (12), ethyl 2-(3-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-indol-1-yl)acetate (13), ethyl 2-(3-(6-(4-nitrophenyl)-2- thioxo-1,2-dihydropyrimidin-4-yl)-1H-indol-1-yl)acetate (14) and ethyl 2-(3-(6-(4-chlorophenyl)-2-imino-1,2-dihydropyrimidin-4-yl)-1H-indol-1-yl)acetate (15) exhibited significant antiviral activity, with IC50 values ranging between 5 and 6 g/ml and therapeutic indices (TI) of 80 and 83[15].

(12)



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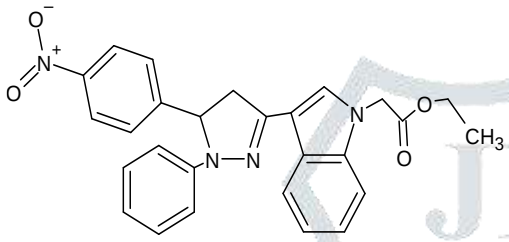

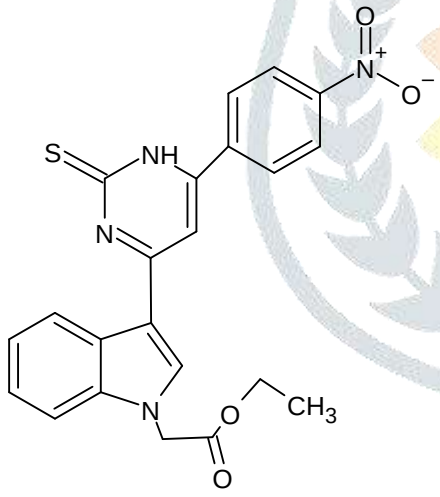

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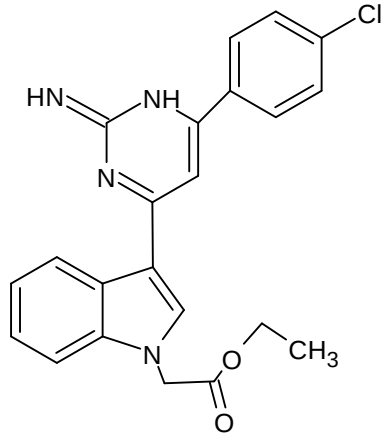

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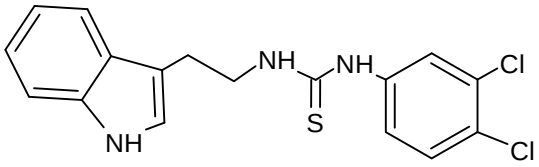
Fig.7 chemical structure of indole derivative having antiviral activity

2.3 Antimicrobial Activity

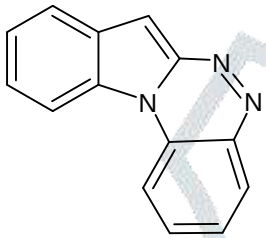
Since the first antimicrobial drugs were introduced into clinical usage in the 1940 antimicrobial resistance has been a problem. To prevent the formation and spread of antimicrobial resistance, present antimicrobials must be preserved through proper usage, as well as new agents must be discovered and developed. A higher rate of mortality and cost is observed in the treatment of microbial disease and that further amplified with an increase in antimicrobial resistance [16]. Sanna and colleagues described the synthesis of indole-thiourea hybrids, which they tested against a group of microorganisms that included both Gram-positive and Gram-negative bacteria. When compared to the typical medication ciprofloxacin (MIC 1.0 g/mL), compound 16 (MIC 12.5 g/mL) (Fig. 8) was shown to be significantly powerful [17].Thiazolidine is also recognized for its antibacterial properties. Several researchers are attempting to combine the thiazolidine moiety with others in order to develop effective antibacterial drugs[18].



(16)

Fig.8 chemical structure of indole derivative having antimicrobial activity

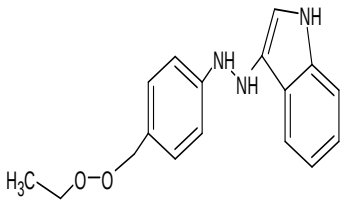
Indole[1,2-c] Xu et al. synthesized -1,2,4-butylnitrite benzotriazine derivatives utilizing the Sandmeyer process and tested them for antifungal activity. 1, 2-c compound indole The derivative -1, 2, 4-butylnitrite benzotriazine (17) was more powerful [19].



(17)

Fig.9 chemical structure of indole derivative having antimicrobial activity

Ozturk et al. created an azo dye of indoles that was tested in vitro against yeast Saccharomyces cerevisiae, Gram (+), and Gram (-) bacteria. The compounds (E)-ethyl 4-((1H-indol-3-yl) diazenyl) benzoate (17), (E)-ethyl 4-((1-methyl-1H-indol-3-yl) diazenyl) benzoate (18), and (Z)-1- (4-methoxyphenyl)-2-(3-methyl-1H-indol-2-yl) diazene (18) [20].

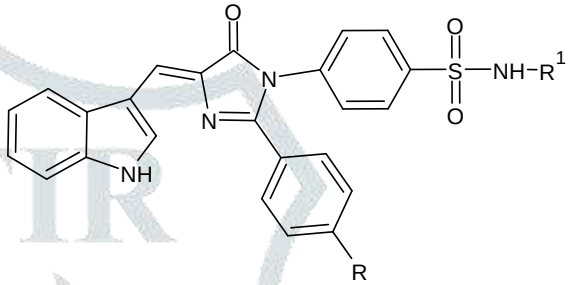


(18)

Fig.10 chemical structure of indole derivative having antimicrobial activity

2.4 Anticancer Activity

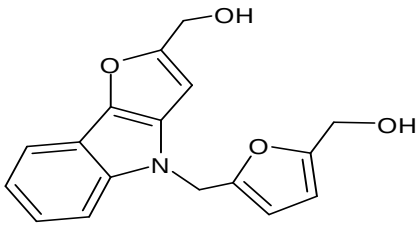
Hanaa M. Roaiah and coworker work on a panel of 60 tumor cell lines was used to investigate the cytotoxic activity of a series of novel indole derivatives 19-36. Additionally, using sorafenib's as a reference VEGFR-2 inhibitor, molecular docking was used to investigate their binding pattern and affinity in the VEGFR-2 active site. Compounds 23a, 23b, 24, 25, 32b, 36b, and 36c were chosen to be tested for their VEGFR-2 inhibitory action based on the molecular docking data. On 47 cell lines, compound 36b showed broad-spectrum anti-proliferative action, with GI percent ranging from 31 to 82.5 percent. Furthermore, compound 18b was the most effective VEGFR-2 inhibitor, with an IC50 of 0.07 M, which was higher than sorafenib's (0.09 M) [21].



(36b)

Fig.11 chemical structure of indole derivative having anticancer activity

Zhuang et al. reported a series of 2, 4-disubstituted furo [3, 2-b] indoles for anticancer activity against the (human NCI-60) tumor cell lines. Among the tested compounds, compound (5-((2-(hydroxymethyl)-4H-furo [3, 2-b] indol-4-yl) methyl) furan-2- yl) methanol (37) demonstrated the best anticancer activity. The analysis of results suggests that the fingerprint of the compound 48 is similar NSC754549 [22].

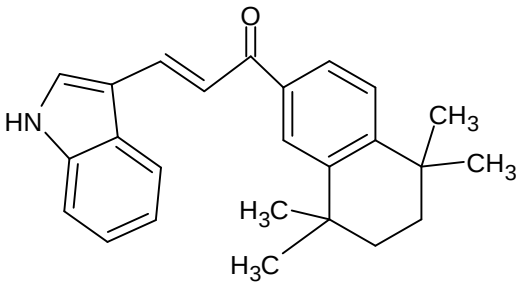


(37)

Fig.12 chemical structure of indole derivative having anticancer activity

(E)-3-novel (E)-3-novel (E) (5-substituted-1H-indol-3-yl) Gurkan-Alp et al. developed and tested -1-(5, 5, 8, 8-tetramethyl-5, 6, 7, 8-tetrahydronaphthalen-2-yl) prop-2-en-1-one derivatives for anticancer activities.

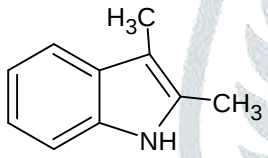
Compound \s(E)-3-(1H-indol-3-yl) The most active compound was determined to be -1-(5, 5, 8, 8-tetramethyl-5, 6, 7, 8-tetrahydronaphthalen-2-yl) prop-2-en-1-one (38) [23].



(38)

Fig.13 chemical structure of indole derivative having anticancer activity

Kumar et al. found that 2, 3-dimethylindoles and tetrahydrocarbazoles had anticancer activities against cancer cell lines such as MCF10A, Calu1, HCT116, Panc1, ACHN, and H460 using a propidium iodide (PI) staining test. 2, 3-dimethyl-1H-indole (39) and 5-fluoro-2, 3-dimethyl-1H-indole (40) have been discovered to be cytotoxic to cancer cell lines [24].



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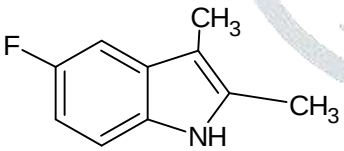
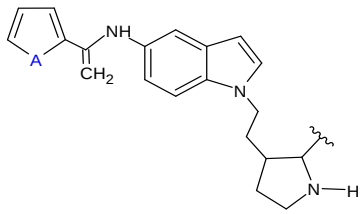


(40)

Fig.14 chemical structure of indole derivative having anticancer activity

2.5 Antioxidant Activity

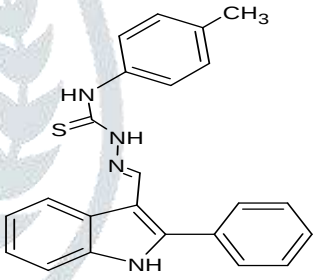
A series of 1, 5-disubstituted indole derivatives were developed, produced, and tested as nitric oxide synthase inhibitors. At the 1-position of the indole ring, a range of flexible and limited basic amine side chain replacements were investigated while the amidine group remained fixed at the 5-position. N-(1-(2-(1-methylpyrrolidin-2-yl) ethyl-and N-(1-(1-methylazepan-4-yl)- side chains. The most potent compound of the series for human nNOS (IC50 = 0.02 lM) (S)-41 showed very good selectivity over the eNOS (eNOS/nNOS = 96-fold) and iNOS (iNOS/nNOS = 850-fold) isoforms [25].



(40)

Fig.15 chemical structure of indole derivative having anticancer activity

Bakherad et al. produced (E)-1-((2-Phenyl-3H-inden-1-yl) methylene)-4-substituted thiosemicarbazides, a novel family of antioxidant drugs with improved anti-oxidant properties. (E)-1-((2-phenyl-3H-inden-1-yl) methylene) (E)-1-((2-phenyl-3H-inden-1-yl) methylene) (E)-1-((2-phenyl.The chemical -4-ptolylthiosemicarbazide (41) was discovered to be the most effective [26].



(41)

Fig.16 chemical structure of indole derivative having anticancer activity

Conclusion

The indole moiety can be found in a wide range of compounds with biological uses. The indole nucleus is a component of the pharmacophore structure of many synthetic drug compounds, and it aids in the attachment of pharmaceuticals to the residues of the binding site of targeted targets.

Biological actions of derivatives containing the indole core include anticancer, antiviral, anti-inflammatory, antioxidant, antimicrobial etc. properties. Indole has drawn the attention of

researchers interested in the discovery of new chemical entities as a result of these actions. These chemical entities might be more effective and safer medications for a variety of illnesses. Based on the preceding literature findings, we may conclude that indole has a wide range of biological functions. Indole offers a lot of promise for further research into novel medicinal options. The chemistry of indole derivatives detailed in this study will aid researchers all around the world in the design and synthesis of innovative medications that may be used to treat a variety of diseases.

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