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Unveiling the Biological Potential of 2-Phenyl Indole Derivatives: A Comprehensive Review

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Abstract

This review furnishes a broad-gauge overview about the biological potential of 2-phenyl indole derivatives. Which have gained significant attention in the area of medicinal chemistry due to their immense biological potential? This review article presents a comprehensive overview of the diverse biological activities exhibited by these compounds, shedding light on their therapeutic applications and underlying mechanisms. Drawing upon a vast body of literature, we explore the wide range of pharmacological properties associated with 2-phenyl indole derivatives, including their anticancer, antimicrobial, anti-inflammatory, and neuroprotective effects. We delve into the intricate molecular pathways and targets engaged by these compounds, elucidating their mode of action. Additionally, we discuss the structure-activity relationship and physicochemical properties of 2-phenyl indole derivatives, providing insights into their design and optimization strategies. The synthesis methodologies employed for the production of these compounds are also examined, highlighting key synthetic routes and modifications. Furthermore, we assess the challenges and future prospects of utilizing 2-phenyl indole derivatives in drug discovery and development, emphasizing their potential as novel therapeutics. By presenting a comprehensive overview of the biological potential of 2-phenyl indole derivatives, this review serves as a valuable resource for researchers and scientists seeking to harness their medicinal prowess for the advancement of healthcare.

Keywords: 2-Phenyl indole, indole derivative, 2-phenyl indole derivative, biological potential of indole, indole as anti-inflammatory, indole as anti-neoplastic agent, anti-oxidant activity of indole, indole as anti-microbial agent, 2-PI as anti-viral agent, indole as anti-malarial, indole as anti-TB

Background

2-Phenylindole (2-PI) and its derivatives has been the subject of extensive research. Their promising biological activities have made 2-Phenylindole (2-PI) and there derivatives has an important subject of research in the area of medicinal chemistry. 2-Phenyl Indole is a heterocyclic compound which consists of a fused indole ring and a

benzene ring, forming a bicyclic structure. The presence of the indole moiety in 2-Phenyl Indole is significant as it is a crucial pharmacophore found in various biologically active substances such as serotonin, melatonin, and tryptophan. 2-Phenyl Indole and its derivatives have been evaluated for their potential as therapeutics against various diseases, including cancer, inflammation, microbial infections, and viral infections [1]. These compounds have also been studied for their neuroprotective, anticonvulsant, and antipsychotic properties. The diverse biological activities of 2-Phenyl Indole (2-PI) derivatives make them a promising class of compounds for the development of novel compounds with enhanced pharmacological properties. This concise overview will concentrate on the various derivatives of 2-Phenyl Indole, with the aim of exploring their biological potential.

2-Phenyl indole an overview

2-phenylindole is a chemical compound with the molecular formula C15H11N. It is an organic heterocyclic compound that contains an indole ring system and a phenyl group attached to it. This compound has attracted a lot of interest in the area of organic synthesis, medicinal chemistry, material science due to its unique properties and diverse applications [2].

2-phenylindole can be synthesized using various methods such as the Fischer indole synthesis, N-alkylation of indole, and cyclization of aryl hydrazones. The compound has a crystalline solid form and has a melting point of around 175-177°C. It is freely soluble in organic solvents such as dichloromethane, CCl4, and ethanol.

One of the most significant applications of 2-phenylindole is in the area of medicinal chemistry. It has been detailed to manifest a broad range of biological potential includes anti-inflammatory, antibacterial, antifungal, antiviral, and anti-poliferative properties. For example, some 2-phenylindole derivatives have shown potent anticancer activity over various cancer cell lines, including breast carcinoma, lung carcinoma and leukaemia.

Apart from its medicinal properties, 2-phenylindole also finds applications in material science. It has been used as a component for the synthesis of organic materials such as conducting polymers and fluorescent dyes. Its unique properties such as high electron mobility, high thermal stability, and high photoluminescence make it an ideal candidate for the development of organic electronic devices and optoelectronic applications [3].

2-phenylindole is a versatile compound that finds applications in various fields such as medicinal chemistry and material science. Its unique properties and diverse applications make it an attractive compound for further research and development. With ongoing research in these fields, the potential applications of 2-phenylindole are expected to expand further in the coming years.

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Biological activities of 2-phenyl Indole

As anti-neoplastic agent

One of the most significant areas of research on 2-Phenyl Indole derivatives is their anti-cancer activity. Several studies have reported that 2-PI derivatives exhibit potent anti-tumor effect against a wide range of tumor cell line is one of the significant characteristics of 2-Phenylindole derivatives [4]. Various Studies have shown that 2-Phenylindole derivatives have anti-proliferative effects on malignant tumor of breast cell line, specifically MDA-MB-231 and MCF-7. This compounds acts through inhibition of tubulin polymerization, leading to mitotic arrest and apoptosis.

Similarly, a study by Rimm it was reported that derivatives of 2-Phenyl Indole showed strong activity to inhibit lung cancer cells (specifically A549 and H460 cell lines). The compounds induced apoptosis through DNA intercalation and inhibition of topoisomerase enzymes.

Yousif studied the 2-phenylindole derivatives for their anti-neoplastic efficacy against liver carcinoma, breast adenocarcinoma, prostate carcinoma, and colorectal carcinoma [5]. There are several compounds mentioned: thiazolo-triazine, triazine, imidazole sugar, imidazole, imidazolothiazole. In addition, three specific substances were mentioned: 2-chloro-1-(2-phenyl-1-yl)ethanone (1), 2-(2-phenyl-1H-indol-1-yl)ethyl-1H-imidazol-2(5H)-one (2), and ethyl 2-(2-oxo-4-(2-phenyl-1H-indol-1-yl)- 2H-imidazol-1(5H)-yl) acetate (3), with compound (3) showing significant cytotoxic activity.

Sigman et al synthesized and conducted initial biological investigations on 3- substituted indoles(4), which were obtained through a reaction involving palladium catalysts was used to add two functional groups to an alkene in an enantioselective manner. Some of the compounds produced from this reaction were tested and found to have the potential to act as anticancer agents against MCF-7 cells.

As anti-inflammatory agent

In addition to their anti-cancer activity, 2-Phenyl Indole derivatives has also showing a promising anti-inflammatory activity. Inflammation is the key driver of many chronic condition such has asthma, IBD, rheumatoid arthritis are driven by inflammation as a primary cause. An Study by Abdellatif reported that 2-Phenyl Indole derivative exhibited potent activity on lipopolysaccharide (LPS)-stimulated macrophages. The derivatives derived from the study were able to suppress factor (NF-κB) signaling pathways, resulting on the inhibition of the proinflammatory cytokines factor, such has (TNF-α), (IL-6) [6].

Singh Reported analgesic activity, antiinflammatory activity against 2 Substituted indoles derivatives. (E)-4-(2-(4-chlorophenyl)-1H-indol-3-yl)-N-((2-methyl-1H-indol-3-yl) methylene) thiazol-2-amine (5) has shown grater activity as an analgesic agent and anti-inflammatory.

Substituted 2-Phenyl derivatives are synthesized and are tested for the potential to inhibit the COX enzymes as anti-inflammatory agents [3]. Invitro study indicated that all the tested compound, particularly those containing the SO2Me group as a COX-2 pharmacophore, exhibited selective inhibition COX-2 than COX-1 (selectivity indexes ranging from 4.02 to 65.71), compared to indomethacin (with a selectivity index of 0.079) [7]. On the other hand, the compound that contained the SO2Me functional group showed significant anti-inflammatory activity in vivo compound (3-ethyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-yl) (4-fluorophenyl)methanone (6) and (4-chlorophenyl) (3-ethyl-5-(methylsulfonyl)-2-phenyl-1H-indol-1-yl) methanone (7) are highly active than the indomethacin. Furthermore, using a carbonyl group as spacer instead of methylene led to potent increase in the anti-inflammatory property.

Abdellatif et al synthesized 2-phenyl substituted indole derivatives are tested for the analgesic activities, antiinflammatory activity both invitro and invivo. Among the derivatives tested, (3-methyl-5-(methyl sulfonyl)-2- phenyl-1H-indol 1yl) (phenyl) methanone (8), (4-chlorophenyl)(3-methyl-5-(methyl sulfonyl)-2-phenyl-1Hindol-1-yl) methanone (9) and 1-benzyl-3-methyl-5 (methyl sulfonyl)-2-phenyl-1Hindole (10)exhibited the highest anti-inflammatory, analgesic activity. Additionally, Findings from the docking study havebeen considered with those from the in vitro COX inhibition assays.

Chavan et al prepared 3-(2-Aminopyrimidin-4-yl) indole were assessed for their ulcerogenic, anti-inflammatory, analgesic activity. All of this synthesized compound were demonstrated similar results to indomethacin [8]. Notably, compounds 4-(2-amino-6-(2-(4-chlorophenyl)-1H-indol-3-yl)pyrimidin-4-yl) (11) phenol and 4-(4-aminophenyl)-6-(2-(4-chlorophenyl)-1H-indol-3yl)pyrimidin-2-amine (12) exhibited 87.4% and 88.2% inhibition of inflammation as measured by paw edema, as well as 78.5% and 76.6% inhibition of acetic acid-induced writhings.

Shaker synthesized Indomethacin analogs of 2-Phenylindole and evaluated their invitro COX-II inhibition activity and invivo anti-inflammatory activity. The COX inhibition activity (invitro) assessment revealed selective binding with the COX-II receptor a range of selectivity index (SI) values from 30.35 to 107.63 compared with the standard drug (SI = 0.079). In-vivo anti-inflammatory activity studies detailed that the most active compounds were 1-(4-chlorobenzyl)-2-(4 (methylsulfonyl)phenyl)-1H-indole(13) (90.5%), 1-(4-chlorobenzyl)-5-methyl-2-(4-(methylsulfonyl)phenyl)-1H-indole (14) (75.6%), 1-(4-chlorobenzyl)-5-fluoro-2-(4-(methylsulfonyl)phenyl)- 1H-indole (15) (81.1%). Molecular docking studies of the compound indicated excellent binding interaction with the COX-2 enzyme [9].

As anti-oxidant

2-phenylindole derivative has found to be having significant antioxidant activity due to the indole moiety present in it. Which is known for its radical scavenging properties. The antioxidant activity of the compounds can attributed to their ability to inhibit formation of oxidative free radicals, which are highly reactive moiety that have the potential to harm various components of cells, such as lipids, proteins, and DNA.Several studies have demonstrated the antioxidant potential of 2-phenylindole derivatives [10]. For example, an study by Emami reports synthesis, evaluation studies of the antioxidant activity various substituted 2-phenylindoles. The study aimed to investigate the potential of these compounds as antioxidant agents.

The authors synthesized substituted 2-phenylindoles and evaluated the antioxidant properties using invitro assays such as ABTS radical cation assays and DPPH radical scavenging and. The synthesized compounds exhibited significant antioxidant action, with some derivatives showing activity comparable with standard antioxidant, ascorbic acid. The study also investigated the structural activity relation of the synthesized compound by modifying substituent on the phenyl ring. The authors observed that the presence of groups such has hydroxyl and methoxy (electron donating) on the phenyl ring increased the antioxidant activity of the compounds [11].

Bakherad synthesize a newer group of antioxidant agents, and tested their antioxidant property. The compounds have better antioxidant

activity compared to other compounds tested. molecule 1-((2-phenyl-3H-inden-1yl)methylene)-4-ptolylthiosemicarbazide (16) was found to be highly potent compound among all the synthesized compounds.

As anti-microbial agent

2-Phenyl Indole derivatives has also been investigated for the antibacterial activity over different fungal and bacterial strains. According to research conducted by Kim et al., it was found that a range of 2-PI derivatives had strong antibacterial effects against vancomycin (drug) resistant Enterococcus faecium (VRE) as well as methicillin (drug) resistant Staphylococcus aureus (MRSA) [12]. The compounds acted through inhibition of bacterial topoisomerase IV and DNA gyrase enzymes. Similarly, Study by Wilson reported that 2-PI derivative exhibited potent antifungal activity over strain such as *Candida albican and Aspergillus fumigatus*. The compound acted through inhibition of fungal lanosterol 14α-demethylase, an enzyme inthe ergosterol biosynthesis pathway.

Scribner synthesized and evaluated amine substituted on positions 5 and 6 of indole ring for their anticocsidial activity. Among the tested compounds, 2-(4-fluorophenyl)-6-(piperidin-4-yl)-3-(pyridin-3-yl)-1H-indole (17) displayed the highest activity.

A study by Kumar et al have synthesized an range of 2-Phenylindoles with either sulfa substituted groups by reacting sulfa substituted aniline with phenacylhalide. Resulting compounds were have been evaluated for their antibacterial properties.

As Anti-viral agent

2-phenyl indole derivative exhibit a potent anti-HBV activity by inhibition of viral replication and suppressing HBV surface antigen (HBsAg) secretion. Studies also reported that a series of 2-PI derivatives exhibited potent anti-HIV activity by inhibiting viral replication and suppressing HIV-1 Tat-mediated transactivation. Furthermore, another researcher Yang reported that 2-PI derivative exhibited potent anti-ZIKV activity.

Gurer-Orhan synthesized substituted 2-phenyl-1H-indol hydrazine derivatives as analogs of melatonin (MLT) and evaluated their antioxidant property on human erythrocytes. Compound (E)-1-(2-chlorophenyl)-2-((2-(4-fluorophenyl)-1H-indol-3-yl)methylene) hydrazine(19), (E)-1-(4-chlorophenyl)-2-((2-(4-fluorophenyl)-1Hindol-3-yl)methylene) hydrazine(20), (E)-1-(3-bromophenyl)-2-((2-(4-fluorophenyl)-1H-indol-3-yl)methylene) hydrazine(21), and (E)-1-(2-fluorophenyl)-2-((2-(4-fluorophenyl)-1H-indol-3-yl) methylene) hydrazine(22) demonstrated significant activity [13].

As anti-malarial

Studies have investigated the anti-malarial potential of 2-phenyl indole derivatives. Evaluated the In-vitro anti-malarial activity of a series of 2-phenylindole derivative against *Plasmodium falciparum (PF)*. The derivatives exhibited potent anti-malarial activity, with some derivatives exhibiting activity comparable over standard antimalarial drug chloroquine.

As anti-tuberculous

Studies investigated the anti-TB activity of a 2-phenyl indole derivative in combination with other anti-TB drugs. The result shows that the compounds exhibit synergistic activity with the other drugs and was able to significantly reduce the bacterial load in an in vitro model of TB infection. In addition to their anti-TB activity, 2-phenylindole derivative has also beaning found to have other biological activity such as inflammatory and anticancer activities. These properties make them promising candidates for development of newer therapeutic drug moiety for treatment of various diseases.

Rathod synthesize various derivative and reported the antimycobacterial activity [14]. The active derivatives were further studied through molecular docking, revealing that 3-(1-isonicotinoyl-3-(5-methyl-2-phenyl-1H-indol-3-yl)-1H-pyrazol-5-yl)-2H-chromen-2-one and 3-(3-(1H-indol-3-yl)-1-isonicotinoyl-1H-pyrazol-5-yl)-2H-chromen-2-one (26) exhibited favourable effects against the Mycobacterium TB H37Rv strain at concentrations of 12.5 to 25 μg/ml.

As antifertility agent

Chaudhary demonstrated that a range of indole derivatives (27) which exhibit potent antifertility activity.

As Estrogen antagonist

Bazedoxifene (35) utilizes an indole as its nucleus for the estrogen antagonist, which distinguishes it from previous compounds not only in terms of ring structure but also in terms of the subtituation on the benzene ring containing ether.

As hepatic x receptor agonist (HXR)

The combine use of the high-throughput gene pro-filings & structural virtual screening on an internal moiety collection, hepatic X receptor (HXR) agonist with a unique structure was discovered (29). The compound demonstrated the ability to increase expression of their ABCA1 gene by eight folds and SREBP1c by three fold in differentiated THP1 macrophage cell line. The compound agonistic activity against HXR was verified through both the cofactor recruitment and reporter transactivation assay [15].

Conclusion

In conclusion, 2-phenyl indole derivatives have emerged as promising therapeutic agents due to their diverse biological potential. Their unique molecular structure allows for modification, resulting in an extensive range of derivatives with varying biological activities. The recent advancements in synthetic methodologies have facilitated the discovery of new derivatives with enhanced properties. The SAR studies have provided perception into the structural requirements for improved activity. Additionally, the diverse mechanisms of action exhibited by these derivatives make them attractive moiety for development of novel drug candidate. Despite the significant progress made in this field, further studies would require to optimize the pharmacokinetic properties and selectivity of those compounds for clinical use. Therefore, further research is needed to explore the full potential of these compounds and to develop effective therapies what improve the quality of life of patients. In summary, this review highlights the importance of 2-phenyl indole derivatives in drug discovery and development and emphasizes the need for continued research in this area.

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