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# A Brief Review of the Medicinally Important Indole Derivatives

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**Abstract**

Indole is an exceptional heterocyclic molecule with a broad spectrum of pharmacological activity owing to various modes of action. It is also a versatile pharmacophore and a favored scaffold. For drug development, it is an excellent moiety whose only characteristic is that it resembles many protein structures. Plenty of research has been taking place in recent years to synthesize and explore the various therapeutic prospective of this moiety. This review summarizes some of the recent effective chemical synthesis (2014-2018) for indole ring. Some of the most recent efficient chemical synthesis for the indole ring (from 2014 to 2018) is compiled in this review. The structure-activity relationship (SAR) was also given a lot of weight in this review in order to pinpoint the active pharmacophores of different indole analogues that have been the subject of studies for the past five years and are responsible for a variety of effects, including antiviral, antitubercular, anticancer, and anticonvulsant ones. The goals and framework of every research issue are explained in detail to help medicinal chemists have a deeper understanding of the circumstances contextually. Researchers will undoubtedly use this review as a platform to strategically design a variety of novel indole derivatives with lower toxicity and side effects and a range of intriguing pharmacological activity.



***Keywords: Indole derivatives, medicinal importance, activity.***

## Introduction:

Indole is the primary active pharmacophore found in a wide variety of natural compounds, alkaloids, and bioactive heterocycles. These stimulate its investigation by researchers as a potential lead in the process of developing new drugs. The chemical and biological features of heterocyclic compounds are diverse and have led to their therapeutic usage. They are important in many biological processes of the human body. The most potentially pharmacologically active compound among them is indole. Indole is an organic molecule with the formula C8H7N that is heterocyclic and aromatic. Its bicyclic structure is made up of a five-membered pyrrole ring fused to a six-membered benzene ring. Numerous bacteria may make indole, which is extensively dispersed in the natural world. The bacterial physiology that includes spore generation, plasmid stability, drug resistance, biofilm development, and virulence is regulated by indole, an intercellular signal molecule [1]. Indole derivatives are widely used as anti-inflammatory, anti-microbial, anti-viral, anti-cancer,

antirheumatoidal, anti-HIV, and anti-tumour drugs, as well as corrosion inhibitors, copolymers and sanitizers. In addition to offering vital insight into the creation of a hybrid pharmacophore-based method in drug design with expanded potential, the review is created to assist researchers in selecting leads against their target. It is a valuable heterocyclic that can have a variety of biological features because therapeutic compounds incorporate an indole core, a pharmacophore that is known to biology [2]. The synthesis of various compounds containing indole is intriguing because of their importance as building blocks for bioactive molecules and as intermediates in antifungal drugs.

## 1. GENERAL SYNTHESIS:

The continued development of routes towards indoles has been a central theme in organic synthesis over the last century, in keeping with their importance [3]. On the other hand, the conveniently available chemical space still has constraints, as the contrast of naturally occurring indole medicines with synthetic ones demonstrates. Specifically, compared to naturally occurring indoles, the substitution pattern surrounding the six-membered ring in synthesized indoles is noticeably less complicated. As far as we are aware, there are currently no synthetic indoles in clinical use that have substituents at more than one benzenoid ring position. We explain this observation to the relative synthetic intractability of substantially substituted indoles rather than any apparent pharmacological drawbacks. As such, the field of indole synthesis can yet be improved.
Indole syntheses almost universally involve annelation of the five-membered ring to an existing benzene ring bearing the appropriate functionality. These can be divided into those in which two substituents in an ortho-relationship are connected together (Scheme 1A), and those in which a single substituent is cyclized directly onto the aromatic ring (Scheme 1B) (Fig.1) [3].

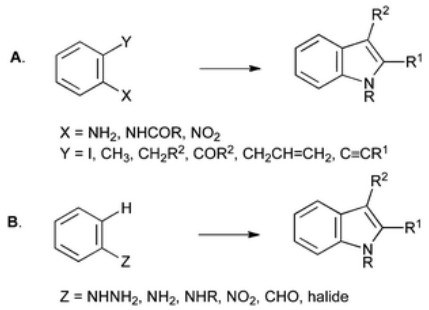



**Fig. 1:** Scheme 1A & 1B General methods for indole synthesis.

## 2. Applications of indole derivatives

Indoles are promising scaffolds in the medicinal world. Due to versatile applications of natural and synthetic indole derivatives in biological and pharmacological fields, they are being used as drugs, e.g., anti-HIV [4], anticancer [5-6], antimicrobial [7], antioxidant [8-9], anti-inflammatory [10], anticholinesterase [11], antidepressant [12], antihistaminic [13], antiparkinson [14], antitumor [15, 16], tubulin inhibitors [17] and receptor inhibitors [18].

### 3.1 Indole derivatives used as anticancer agents:

Cancer is a class of complex diseases in which cells undergo rapid, uncontrollable, and pathological proliferation by disruption of the principles of normal cell division. Cancer has been considered one of the most dangerous diseases, which threatens human lives and is the second leading cause of death globally [19].

All the nitrogen heterocycles, indole is one of the most important scaffolds, and the derivatives of it have demonstrated strong ability to induce cell death in a number of cancer cell lines. Over the last few decades, indole and its derivatives have been shown to modulate a number of biological pathways implicated in the progression of cancer [20]. Vincristine and vinblastine, the two most significant naturally occurring indole alkaloids, are used to treat melanoma, acute lymphoblastic leukaemia, and small- and nonsmall-cell Hodgkin's lymphoma, lung cancer in cells, etc. Numerous other compounds of indole, such as DIM (3, 3′- and indole-3-carbinol diindolylmethane) are effective in a variety of from cancers [21]. Some iodole-containing compounds

such as Semaxanib, Sunitinib, Nintedanib, and Vinorelbin have already been applied in clinical practice for the treatment of various cancers even drug-resistant cancer [22].

Hybridization of indole moiety with other anticancer pharmacophores is a promising approach to develop novel anticancer candidates with anti-drug-resistant cancer potential.
E.g. A. The indole-pyrrole hybrid (Fig. 2) not only exhibited potent in vitro antiproliferative and apoptosis-inducing activities in a panel of human solid tumour cell lines, including breast, cervix, prostate, colon, and non-small cell lung cancers, but also demonstrated positive activity against drug-resistant ovarian cancer cell lines [23-25]

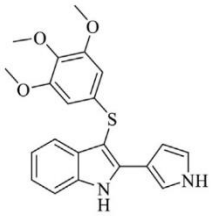


**Fig. No. 2**

B. The carboxamide-containing indole-pyrrole hybrid (Fig. 3) possessed potential activity against mutantassociated human acute myeloid leukaemia (AML) cell lines.

Several indole dimers which are exemplified by Vinblastine, Vincristine, Indirubin could exert their anticancer activity through multiple mechanisms, and have already been used in clinical practice for the treatment of cancers, including drug resistant cancers [26, 27].

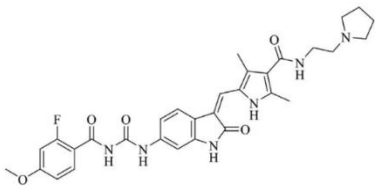


Fig. No. 3

Therefore, indole dimers are useful templates for the development of new anticancer drugs. Etc.

**3.2 Indole derivitives used as anticonvulsant agents:**
Convulsion is a central nervous system (CNS) disorder due to paroxysmal cerebral dysrhythmia with brief episodes of seizures and /or loss of consciousness. Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally [28].

Researchers have created and assessed a range of derivatives of indole as anticonvulsants.
E.g. A. Dialkylaminoalkoxy-oxindole derivatives: SAR studies suggested that semicarbazone substitution at the 3rd position of indole and alkyl substitution at the nitrogen atom present in the side chain of the iodole were favourable for the anticonvulsant activity (Fig. 4). [29] Benzohydrazide moiety exhibits a significant anticonvulsant activity by binding to GABA receptors [30].

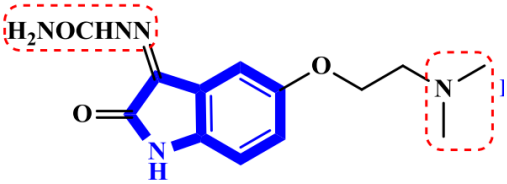
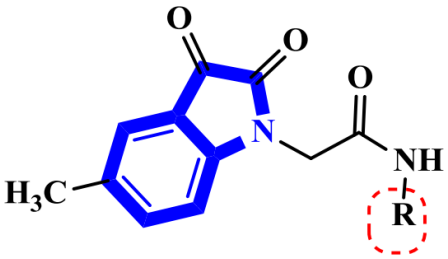


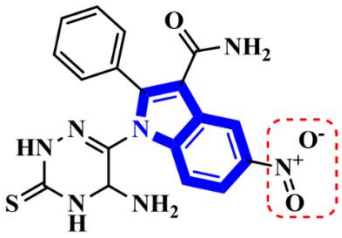

**Fig. No. 4** Dialkylaminoalkoxy-oxindole

B. Acetamide derivatives of oxindole: SAR studies concluded the role of halogen substituent for the activity. 50a and 50b were found to be highly active on comparing with standard drug carbamazepine (Fig. 5). [31]




(Fig. No. 5) Acetamide derivatives of oxindole 50a and 50b 50a = R = 2 - Br - C6H4 & 50b= R =2,3Br2C6H3

C. Indole-1, 2, 4- triazine derivatives: It is screened against maximal electroshock (MES) test and subcutaneous pentylenetetrazole (scPTZ). Electron withdrawing groups such as trifluoromethyl and chloro were more effective in modulating anticonvulsant activity as compared to electron donating groups i.e. thiomethyl and methoxy (Fig. 6) [32].

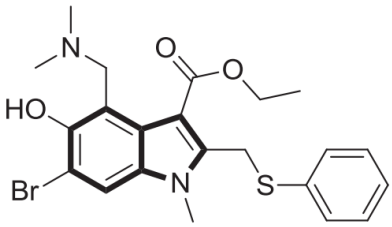



(Fig. 6) Indole-1, 2, 4- triazine

**3.3 Indole derivatives used as antiviral agents :**

Viral diseases are extremely widespread infections. Common viral illnesses include the flu, chickenpox, herpes, gastroenteritis (stomach flu), hepatitis, HIV/AIDS, and the common cold. More than 60% of illnesses that occur in developed countries are thought to be caused by viral infections. Viral diseases can result in significant, potentially fatal consequences. Indole scaffold is widely used in antiviral research. Examples of marketed indole-containing antiviral drugs include Arbidol and Delavirdine.

E.g. A. Arbidol 10: Represents one of the most highly functionalized indole-containing drugs. Arbidol is a Russian developed broad spectrum antiviral which was widely used in Russia and China since 1990s. It is used for the treatment and prophylactic prevention of influenza A and B virus, respiratory syncytial virus, and SARS. It is Arbidol demonstrated both immunomodulating and anti-influenza effects, specifically against influenza groups A and B, and SARS (Fig. 7) [33, 34]




**(Fig. 7)** Arbidol 10

B. Delavirdine 11: It is a first generation nonnucleoside reverse transcriptase inhibitor. In 1997, the FDA approved it for the treatment of HIV-1, or human immunodeficiency virus. In conjunction with highly active antiretroviral therapy, it is utilized (HAART). *(Fig. 8)*[35]

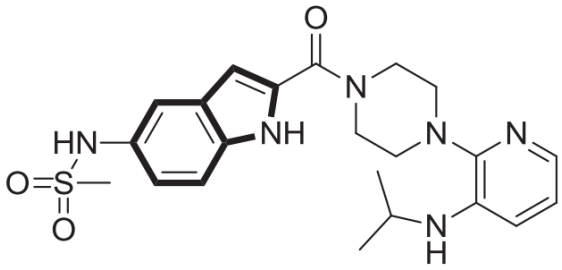


Fig. 8: Delavirdine 11

C. Atevirdine 12 is a new non-nucleoside (heteroarylpiperazine) reverse transcriptase inhibitor that has been studied for the treatment of HIV. It inhibits HIV-1 replication in infected peripheral blood leukocyte cultures it also o inhibits completely the formation of syncytia in human T-cell leukaemia virus type IIIinfected MT-2 cells (Fig. 9)

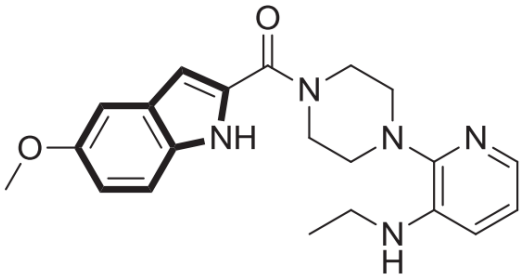


**Fig. 9**: Atevirdine 12

D. Enfuvirtide (T-20; brand name: Fuzeon) 19: The first HIV fusion/entry inhibitor approved by the U.S. FDA in 2003, is a peptide anti-HIV medicine that targets the gp41N-terminal heptad repeat (NHR). It is used to treat HIV/AIDS patients who do not react to conventional antiretroviral medications. T20 does not have a pocket-binding domain, so it has a limited half-life and little anti-HIV-1 action (Fig. 10).[36]

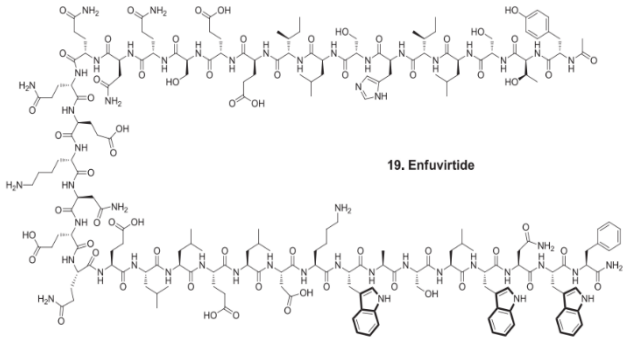



**Fig. 10**: Enfuvirtide

### 3.4 Indole derivatives used for treatment of Alzheimer Disease:

Alzheimer's disease (AD) is a neurodegenerative brain disorder that affects millions of elderly people. Researchers have discovered that patients with AD share three distinct pathological manifestations: reduced levels of tauhyperphosphorylation, β-amyloid protein aggregation, and acetylcholine. However, the pathogenesis of AD remains unclear. [37, 38, 39]

The indole nucleus is an important heterocyclic moiety found in many natural and synthetic molecules with interesting pharmacological activities. Additionally, this moiety is commonly found in the structures of inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).[40,41] Another study reported on quinoline–iodole derivatives as MTDLs for the treatment of AD.[42] These derivatives showed a variety of biological activities, such as biometal chelation, modulation of Aβ aggregation, antioxidant effect, and neurotrophic and neuroprotective qualities.

E.g. A. 8-hydroxyquinlineindole hybrids (1, 2 Fig.11) could effectively inhibit Aβ aggregation.
B. 8-hydroxyquinline-indole derivatives also presented other biological activities related to AD, such as metal ions chelation. [43]

C. Deoxyvasicinone: a naturally occurring alkaloid comprising a quinazolinone moiety fused with a pyrrolidine ring has been identified as novel cholinesterase inhibitor.

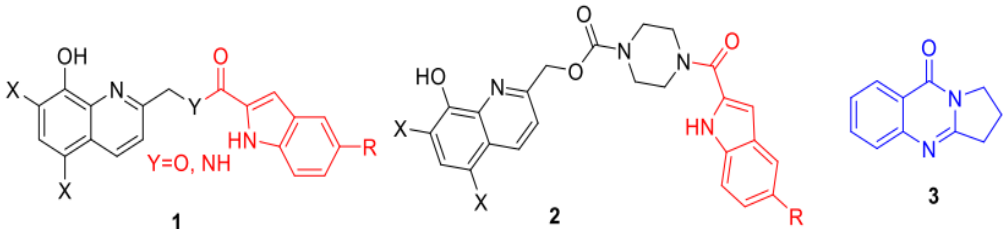



**Fig. 11**: Chemical Structures of MTDL Agents: 8-hydroxyquinline-indole, (1&2) & deoxyvasicinone (3)

In the current work, we made an effort to link deoxyvasicinone and indoles as novel, multifunctional compounds for the treatment of AD, based on the aforementioned reports. [44, 45]

### 3.5 Indole derivatives used as antifungal agents:

Fungal infection, also known as mycosis, is a disease caused by fungi.[43,44] Different types are traditionally divided according to the part of the body affected; superficial, subcutaneous, and systemic [46,47].

Some simple indole derivatives were found to possess antifungal activities against Botrytis allii, Cladosporium cucumerinum, Penicillium italicum, and Aspergillus niger. [48] The antifungal properties of nine basic indole derivatives against seven phytopathogenic fungi are reported here:

Nine indole derivatives, numbered 1 - 9, were obtained from commercial sources and possessed a purity level higher than 98%. The poisoned food technique was then used to screen compounds 1 - 9 for their antifungal activities against the phytopathogenic fungi in vitro. [49, 50, 51] Compounds 2 to 9 demonstrated greater antifungal activity against the seven phytopathogenic fungi at 100 µg/mL. Compounds 2, 5, 8, and 9 in particular showed greater than 80% inhibition rates against the tested phytopathogenic fungi.

These indole derivatives have the following structure-activity relationships.
The methyl, cyano, or nitro groups added to the indolyl ring significantly raised the corresponding compounds inhibition rates.
The position of the substituents at the indolyl ring was also essential for the activity.
The inhibition rates against the seven phytopathogenic fungus were almost 100% when the nitro group was added at the 5-position of indole, giving 5.

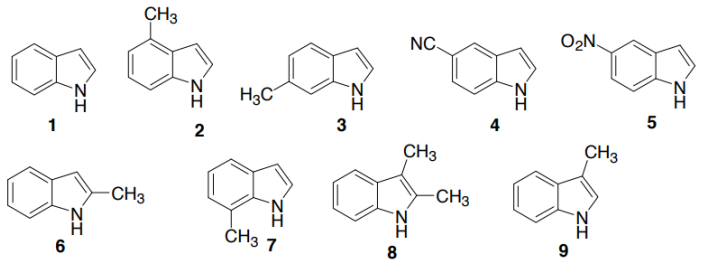



**Fig. 12:** Chemical Structure of Indole Derivative as Antifungal Agen

Especially compounds 2, 5, 8, and 9 exhibited broad-spectrum antifungal activities against the mentioned seven phytopathogenic fungi (Fig.12) [49-51].

## 3. Conclusion

The article addresses the excellent moiety in drug discovery, indole, and its many different pharmacological properties. It highlights the structure-activity relationship (SAR) of several indole analogues and provides an

overview of recent efficient chemical synthesis for the indole ring. The chemical compound indole has the formula $C_8H_7N$ and is heterocyclic and aromatic. It is widely distributed in the natural world and is employed in many medications as an anti-inflammatory, anti-microbial, and anti-cancer agent. The five-membered ring is annealed to an already-existing benzene ring with the necessary functionality to create synthetic indoles. As of right now, no synthetic indole with substituents at more than one benzenoid ring position is being used in clinical settings. Researchers can use the article as a platform to create a variety of novel indole derivatives that have less toxicity and side effects.

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