Review Article

A Comprehensive Review on Indole Derivatives as Privileged Scaffolds in Drug Discovery

Karthika S[1], R Aravindh[2], M Mohamed Syed[2], M Nandhini[2], B Rajalaksmi[2], R Yuvaraj[2], S Anbazhagan[1]

From, [1]Department of Pharmaceutical Chemistry, [2]UG Students, Surya School of Pharmacy, Vikravandi, Affiliated to The Tamil Nadu Dr.MGR Medical University, Guindy, Chennai, India.

ABSTRACT

Background: Indole derivatives are an important class of heterocyclic compounds containing a fused benzene and pyrrole ring system. They are widely distributed in nature, particularly in plants, microorgan-isms, and marine organisms, and many naturally occurring indole alkaloids are biosynthesized from tryp-tophan. Due to their unique structural features and ability to interact with multiple biological targets, in-dole derivatives are recognized as privileged scaffolds in medicinal chemistry. **Objective:** To review the synthetic approaches, biological activities, and recent advancements in the de-velopment of indole derivatives, highlighting their significance in pharmaceutical and medicinal research. **Methods:** A literature-based review was conducted on the synthesis and pharmacological applications of indole derivatives. Various synthetic methods, including Fischer indole synthesis, Madelung synthesis, Bartoli reaction, metal-catalyzed cyclization, microwave-assisted synthesis, and solvent-free reactions, were examined for their efficiency and applicability. **Results:** Numerous synthetic strategies have been successfully employed for the preparation of indole derivatives, with the Fischer indole synthesis being the most widely utilized method. Modern techniques such as microwave-assisted and solvent-free reactions have improved reaction efficiency, selectivity, and sustainability. Indole derivatives have demonstrated diverse biological activities, including anticancer, antimicrobial, antifungal, anti-inflammatory, antioxidant, and neuropharmacological properties, making them valuable intermediates in the development of therapeutic agents. **Conclusion:** Indole derivatives continue to play a pivotal role in drug discovery and medicinal chemistry due to their structural versatility and broad spectrum of biological activities. Ongoing research is focused on the development of environmentally friendly synthetic methodologies and the exploration of struc-ture–activity relationships to optimize their therapeutic potential and facilitate the discovery of novel bio-active compounds..

Key words: Indole derivatives, Fischer indole synthesis, Pharmacological importance, Bioactive compounds, Greener synthetic methods, Structure–activity relationship

Indole is an aromatic heterocyclic organic compound in which a benzene ring is fused with a pyrrole ring (Figure 1). Having molecular formula of $C_8H_7N_1$**.** Indole and its derivatives are used in organic synthesis. They are used in evaluating a new product that possesses different physical activities such as anticonvulsant, anti-HIV, antitubercular, antidiabetic, antimalarial, antimicrobial, anticancer, antioxidant, antifungal, anti-inflammatory, etc. [1]. Indole has a variety of biological applications in medicinal chemistry (Figure 2). Indole occurs in both natural and synthetic. The indole ring system represents one of the most abundant and important heterocycles in nature. Found in a hugely diverse array of biologically significant natural compounds, from simple derivatives such as the neurotransmitter serotonin to complex alkaloids such as the clinically used anticancer agents vinblastine and mitomycin C, and the antihypertensive alkaloid reserpine (Figure 3), the importance of indoles to biological chemistry cannot be overstated. Additionally, several important synthetic drugs contain an indole motif, including sumatriptan, tadalafil, rizatriptan, and fluvastatin [2] (Figure 4).

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1.2 SYNTHESIS OF INDOLE

1.2.1 Fischer Indole Synthesis

Emil Fischer and Jourdan first reported the synthesis of indoles. In this reaction, arylhydrazones derived from aromatic hydrazines react with aldehydes or ketones in the presence of a

Correspondence to: Dr. Karthika S, Professor, Department of Pharmaceutical Chemistry, Surya School of Pharmacy, Vikravandi, Villupuram – 605652

Email:karthikaselvam1990@gmail.com

Lewis or mineral acid, resulting in the formation of indole derivatives. Over time, various catalysts such as cation-exchange resins, toluene sulfonic acid, phosphorus trichloride, and acidic clays have been employed to improve the efficiency of the cyclization at different temperatures in the Fischer indole synthesis. The reaction's rate is influenced by the substituents on the benzene ring: electron-donating groups accelerate the reaction, while electron-withdrawing groups slow it down [3].

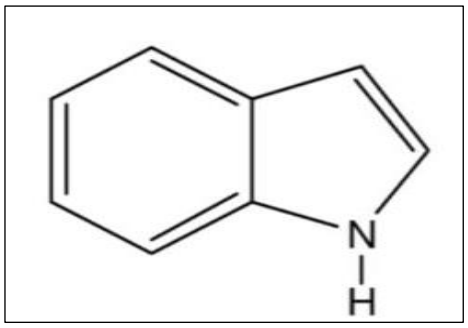


Figure. 1: Structure of Indole

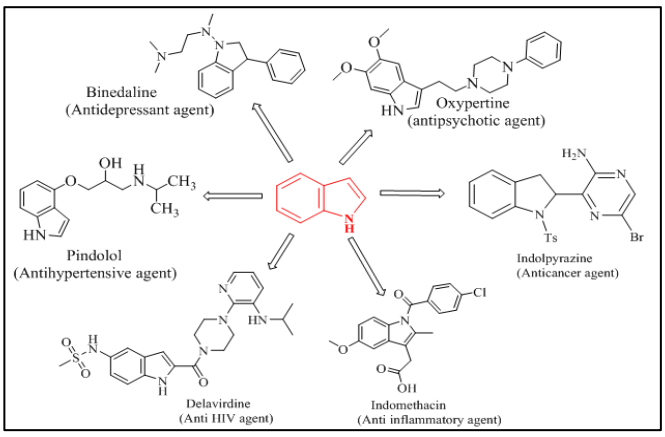


Figure. 2: Biological application of Indole nucleus in medicinal chemistry

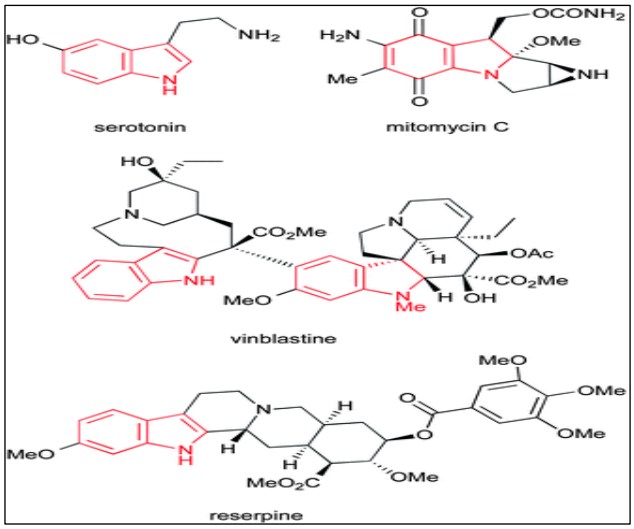


Figure. 3: Naturally occurring indoles

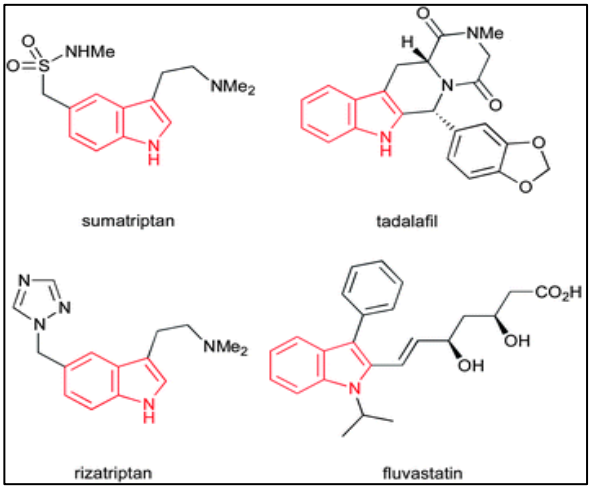
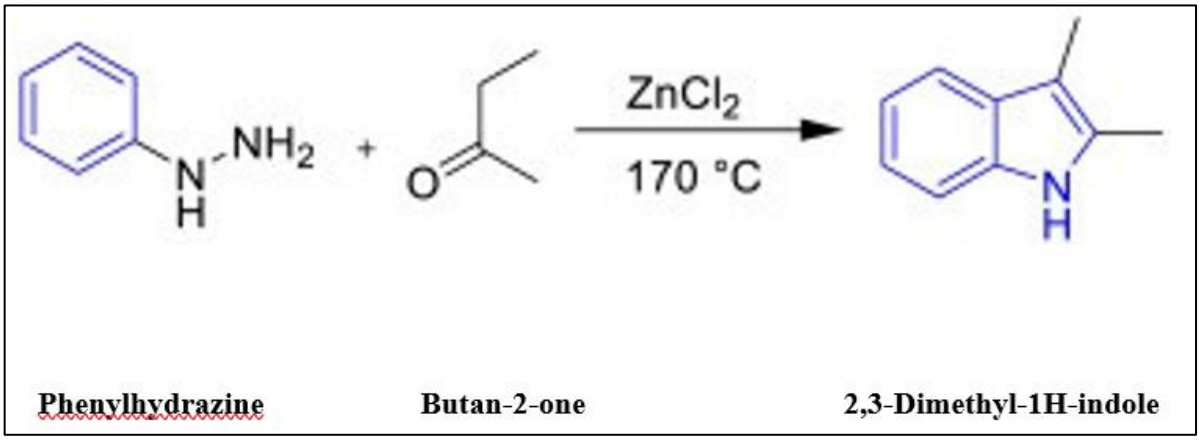


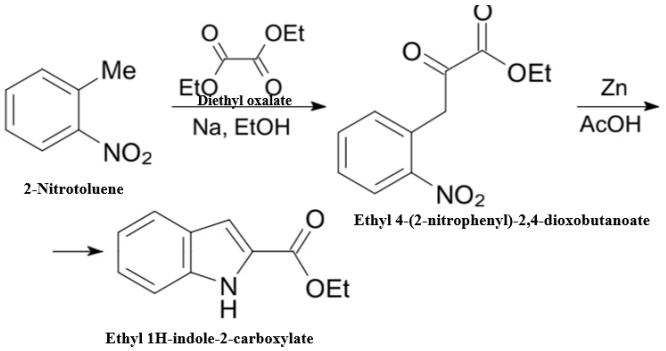
Figure. 4: Clinically used indoles



Scheme 1. Phenylhydrazone and an aldehyde or ketone

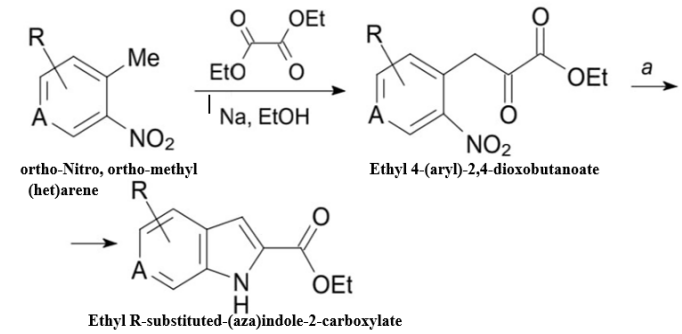
1.2.2 Reissert Indole Synthesis

The first step of the classical Reissert indole synthesis comprises the condensation of o-nitrotoluenewithdiethyl oxalate to give ethyl o-nitrophenylpyruvic acid. The subsequent reduction of the nitro group leads to spontaneous cyclization, giving esters of indole-2-carboxylic acid [4] (Scheme 2).



Scheme 2: Cyclization and esters of indole-2-carboxylicacid.

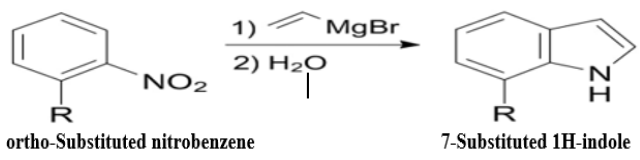
A modern version of the Reissert synthesis includes catalytic hydrogenation in a continuous-flow reactor (H-Cube continuous-flow hydrogenation reactor), the yields are given according to the HPLC data with UV detection. The best results were attained in the synthesis of 2-ethoxycarbonylindole (93%yield) at a hydrogen pressure of 1 bar in an ethyl acetate ± ethanol mixture (1:1) at a flow rate of 1ml min $^{-1}$ and at 20 C [5] (Scheme 3).



Scheme 3: Reissert indole synthesis

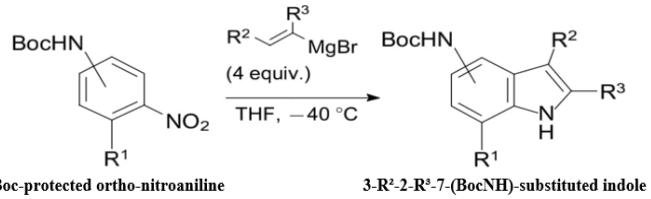
1.2.3 Bartoli Indole Synthesis

The classical Bartoli indole synthesis involves the preparation of 7-substituted indoles by the reaction of ortho-substituted nitroarenes with vinyl Grignard reagents (Scheme 4).



Scheme 4: Cyclization and aromatization of the indole ring.

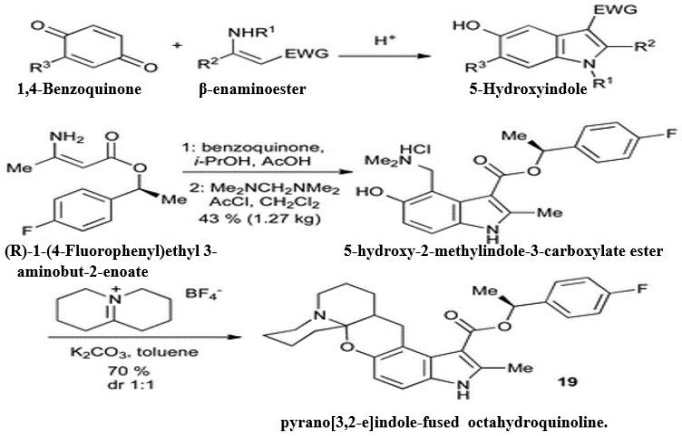
Substituted nitroanilines were used for the first time instead of nitrobenzene for the Bartoli indole synthesis; this resulted in the development of a new route to substituted amino indoles, promising building blocks for fine organic and pharmaceutical chemistry. However, this approach was applicable only to a rather narrow range of substrates and Grignard reagents [6] (Scheme 5).



Scheme 5: Bartoli indole synthesis.

1.2.4 Nenitzescu Synthesis

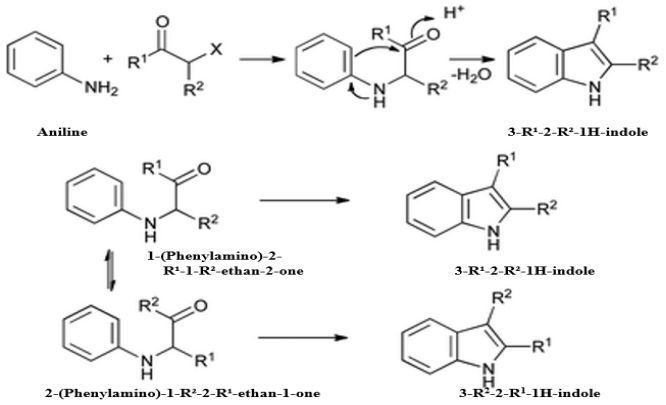
5-Hydroxyindoles can be accessed in a convergent manner through the Nenitzescu reaction of enamines with quinones [7]. (The regiochemistry is usually as shown, except where R3 is an electron-withdrawing group, in which case a 4-substituted indole is the main product. The Nenitzescu reaction has been plagued by poor yields, but its inexpensive starting materials and scalability have allowed it to be used in the large-scale synthesis of relatively simple indole building blocks. For example, a kilogram-scale Nenitzescu reaction was reported in the synthesis of the chemokine receptor antagonist [8] (Scheme 6).



Scheme 6: The Nenitzescu Indole synthesis and its application.

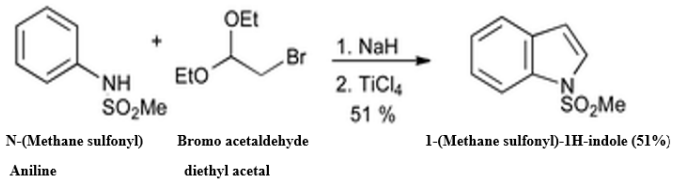
1.2.5 The Bischler Indole Synthesis And Modern Variants

First reported in 1892, the Bischler indole synthesis involves alkylation of an aniline with an α-haloketone, followed by acid-catalyzed ring closure. Although rather limited in scope due to the harsh reaction conditions required, it circumvents the problems associated with arylhydrazines and has found widespread application in the synthesis of relatively simple indole derivatives. It can be complicated by rearrangements of the α-anilinoketone intermediate under acidic conditions if the aniline is not protected before cyclization, giving isomeric mixtures of products in some cases [9] (Scheme 7).



Scheme 7: The Bischler indole synthesis.

A useful variation on the Bischler reaction is the use of α-haloaldehyde acetals, which permits access to 3-unsubstituted indoles [10] (Scheme 8).



Scheme 8: Nordlander and Sundberg modification of the Bischler indole synthesis

2. REVIEW OF LITERATURE

2.1 Antiviral Activity

Xue et al., 6-Amino-4-substitutedalkyl-1H-indole-2-substituted carboxylate derivatives were prepared and reported as antiviral agents. In all tested compounds, compound methyl 6-amino-4-isobutoxy-1H-indole-2-carboxylate showed inhibitory activity against influenza A with an IC50 of 7.53 gmol/L and the highest selectivity index (SI) value of 17.1 against CoxB3 virus [11] (Figure 5).

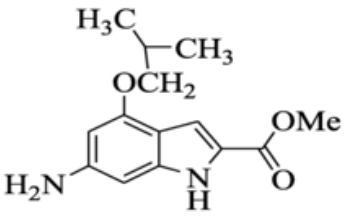


Figure 5. Chemical structure of methyl 6-amino-4-[(isopropoxy)methoxy]-1H-indole-2-carboxylate.

4 - Alkyl - 1 - (5 - fluoro - 3 - phenyl - 1H - indole - 2 - carbonyl) thiosemicarbazide derivatives of indole were prepared and investigated in vitro for antiviral activity in a broad range of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses by Cihan-Üstündag et al. Compound (5-fluoro-3-phenyl-1H-indole2 -carbonyl) -4-methylthiosemicarbazide, 4-ethyl-1-(5-fluoro-3-phenyl-1H-indole- 2carbonyl)thiosemicarbazide, 1-(5-fluoro3-phenyl-1H-indole-2-carbonyl)- 4propylthiosemicarbazide and 4-butyl-l(5-fluoro-3-phenyl-1H-indole- 2carbonyl)thiosemicarbazide are potent antiviral agents with IC50 values ranging from 0.4 to 2.1 µg/mL against Coxsackie B4 virus [12] (Figure 6).

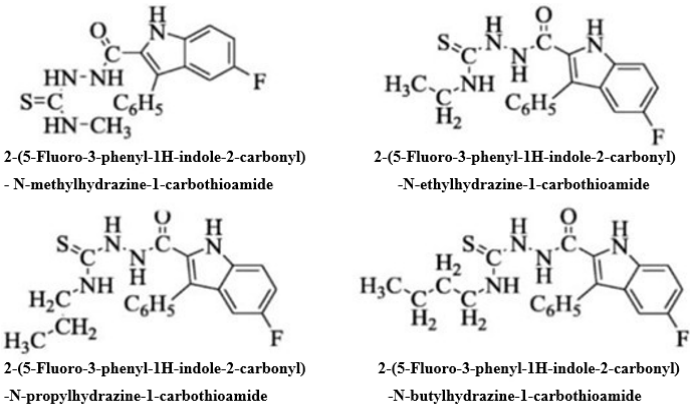


Figure 6. Chemical structures of 2-(5-fluoro-3-phenyl-1H-indole-2-carbonyl)-N-methyl-, N-ethyl-, N-propyl-, and N-butylhydrazine-1-carbothioamides.

2.2 Anti-Inflammatory And Analgesic Activities

Ozdemir et al. reported indole-based chalcone derivatives as COX-1 and COX-2 inhibitor Compound (5-Bromo-1H-indol-3-yl)-1-(4- cyanophenyl) prop-2-en-1-one and compound (5-methoxy-1H-indol-3-yl)-1(4-methylsulfonylphenyl)prop-2-en-1-one were found to demonstrate significant activity [13]. Sarva et al. carried out a solvent-free reaction in a microwave between indole and substituted aldehydes. The product, bis(indolyl)methane, is bioactive. The anti- inflammatory activity was shown by most of the compounds, but compounds 3,3'-([1,1'-biphenyl]-4- ylmethylene)bis(1H-indole), 3,3'-((1H-imidazol-2-yl)methylene)bis(1H-indole), 3,3'-((5-methylpyridin-2-yl)methylene)bis(1H-indole), and 3,3'- (thiophen-2-ylmethylene)bis(1H-indole)) were the most potent [14] (Figure 7).

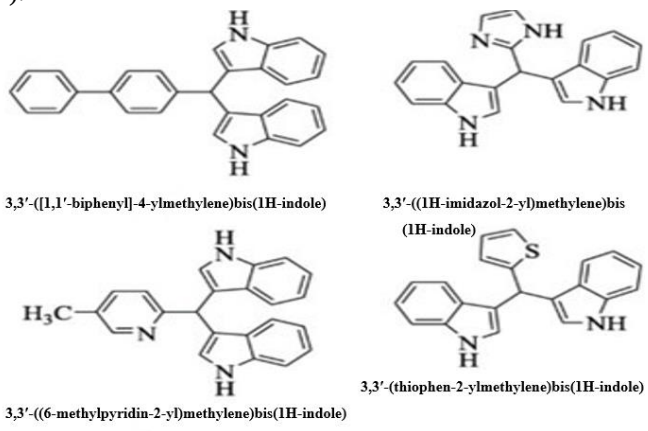


Figure 7. Chemical structures of bis(indolyl)methane derivatives

Anti-inflammatory activities of chalcones of indole were elaborated by Rani et al. against carrageenan-induced edema in albino rats. The most effective compound of this series was found to be 4-(3-(1H- indol-3-yl)-4, 5- dihydro-1H- pyrazol-5-yl) phenol [15] (Figure 8).

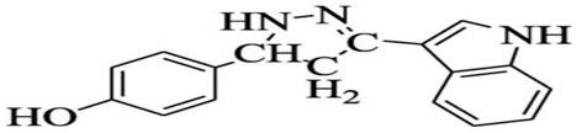


Figure 8. Chemical structure of 4-[3-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-5-yl]phenol.

2.3 Anticancer Activity

Hong et al, the series of various tricyclic and tetracyclic indoles for their anticancer activity, where the compounds were found to exhibit the highest in vitro activity against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) cell lines [16] (Figure 9).

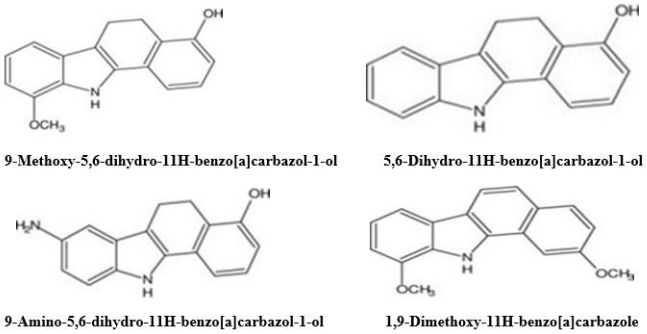


Figure 9. Chemical structures of tricyclic and tetracyclic indole derivatives evaluated for anticancer activity against HONE-1 and NUGC-3 cell lines.

The compound synthesized by Abele et al. was reportedly showing the highest anticancer activity [17] (Figure 10).

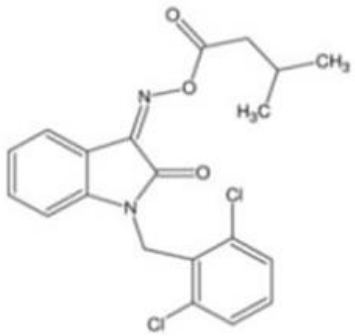


Figure 10. Chemical structure of [1-(2,6-dichlorobenzyl)-2-oxoindolin-3-ylidene]amino 3-methylbutanoate.

Garcia et al. synthesized pyrrolo[2,3-e]indole derivatives and evaluated them for possible in vitro cytotoxic activity. The most active compound was found to be the compound shown in Figure 11, which showed activity against the PC-3 (prostate) cell line [18].

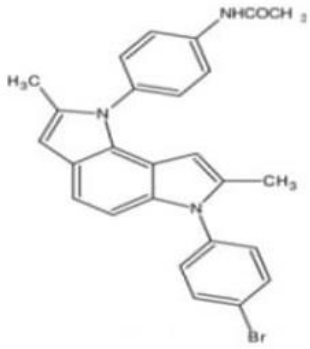


Figure 11. Chemical structures of pyrrolo[2,3-e]indole derivatives evaluated for in vitro cytotoxic activity against the PC-3 prostate cancer cell line.

A series of halogenated indole-3-acetic acids as oxidatively activated prodrugs with potential for targeted cancer therapy were reported by Rossiter et al. These derivatives were oxidized by horseradish peroxidase (HRP), and toxicity against V79 Chinese hamster lung fibroblasts was determined; the compound was found to possess the highest cytotoxicity, and it was the best drug for targeted cancer therapy [19] (Figure 12).

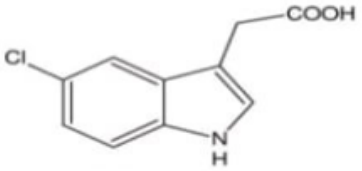


Figure 12. Chemical structure of 2-(5-chloro-1H-indol-3-yl) acetic acid.

Queiroz et al. studied the inhibitory activity of the heteroarylindoles and of the phenylbenzothienoindole on the growth of human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer). The results showed that methyl 3-(dibenzothien-4-yl)indole-2-carboxylate had the most potent growth-inhibitory activity in all the tumor cell lines tested (with G150 values ranging from 11 to 17µM) [20] (Figure 13).

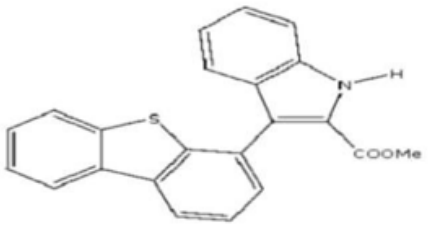
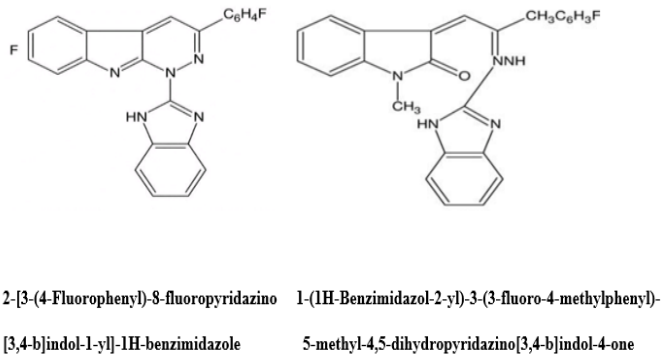


Figure 13. Chemical structures of heteroarylindole and phenylbenzothienoindole derivatives evaluated for in vitro anticancer activity against MCF-7, NCI-H460, and SF-268 cell lines.

2.4 Insecticidal Activity

Sharma et al. investigated the insecticidal activity of synthesized novel indole derivatives. The compounds exhibited promising results against *Spodoptera liture* (eighth instar larvae) and *Heliothis armigera* [21] (Figure 14).



2-[3-(4-Fluorophenyl)-8-fluoropyridazino [3,4-b]indol-1-yl]-1H-benzimidazole

1-(1H-Benzimidazol-2-yl)-3-(3-fluoro-4-methylphenyl)-5-methyl-4,5-dihydropyridazino[3,4-b]indol-4-one

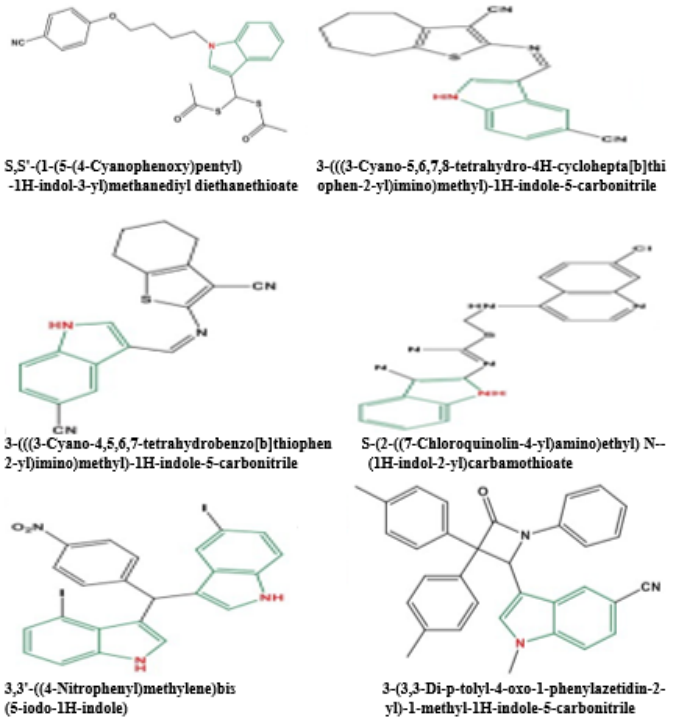
Figure 14. Chemical structures of novel indole derivatives evaluated for insecticidal activity against *Spodoptera litura* and *Heliothis armigera*.

2.5 Anti-Leishmanial Activity

Porwal et al. (2017) designed and synthesized gem-dithioacetylated indole analogs and investigated them against Leishmania donovani. The compound (% inhibition of 96-99%) revealed higher potency [22]. In 2016, Felix and colleagues designed and investigated thiophene-indole hybrids and tested them on L. donovani. The prepared compound (ICg=3.2 µg/mL, SI>124.6) has shown good potency, as equated to the reference drug amphotericin B (ICg=0.2 µg/mL, SI>124.5) [23]. Sharma and colleagues (2014) synthesized and investigated triazine indole- quinoline hybrid derivatives and treated them against L. donovani. The compound (ICg =0.36µM) has revealed higher potency as equated to the reference drug miltefosine (IC_{50}=8.10 µM) [24]. Bharate and colleagues (2013) synthesized and evaluated 3.3-diindolylmethane for anti-leishmanial activity on L. donovani. The synthesized compounds (IC_{50}<7.17 µM) and (IC_{50}<8.39 µM) have shown higher potency as equated to the reference drug amphotericin B(IC_{50}<0.17µM) and pentamidine (IC_{50} <8.39 µM) [25]. Singh et al. (2012) synthesized and investigated azetidine-indole analogues and screen for L.promastigotes. The compound (056±0.001µM/ml) [26] the indole derivatives based anti-leishamanial active compound structure (Figure 15).

2.6 Antioxidant Activity

Silveira et al. prepared and evaluated di (1H-indol-3-yl) sulfane derivatives as antioxidant agents. The compound di(1H-indol-3- yl)sulfane exhibited antioxidant activity in ferric reducing ability of plasma (FRAP), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and 2,2'-Azino-bis(3-ethylbenzothiazoline-6- sulfonic acid) (ABTS) assays at micromolar concentrations [27] (Figure 16).



S,S'-(1-(5-(4-Cyanophenoxy)pentyl) -1H-indol-3-yl)methanediyl diethanethioate

3-(((3-Cyano-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl)imino)methyl)-1H-indole-5-carbonitrile

3-(((3-Cyano-4,5,6,7-tetrahydrobenzo[b]thiophen 2-yl)imino)methyl)-1H-indole-5-carbonitrile

S-(2-((7-Chloroquinolin-4-yl)amino)ethyl) N--(1H-indol-2-yl)carbamothioate

3,3'-((4-Nitrophenyl)methylene)bis (5-iodo-1H-indole)

3-(3,3-Di-p-tolyl-4-oxo-1-phenylazetidin-2-yl)-1-methyl-1H-indole-5-carbonitrile

Figure 15. Chemical structures of indole-based anti-leishmanial derivatives evaluated against *Leishmania donovani*.

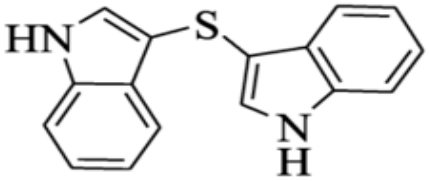


Figure 16. Chemical structure of di(1H-indol-3-yl)sulfane evaluated for antioxidant activity in FRAP, DPPH, and ABTS assays.

2.7 Antimicrobial Activity

Xu et al, Indole[1,2-c]-1,2,4- butylnitrite benzotriazine derivatives were prepared using Sandmeyer reaction and screened them for antifungal activity. The indole[1,2- c]-1,2,4-butylnitrite benzotriazine was the most potent derivative [28] (Figure 17).

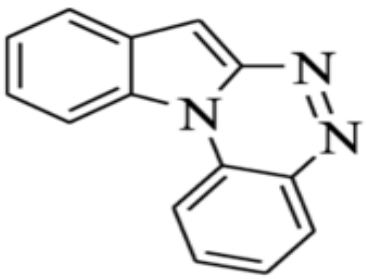
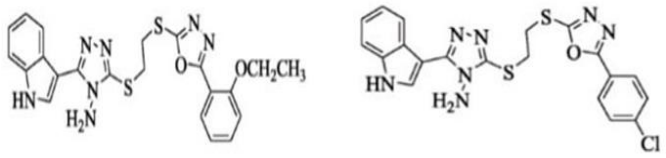


Figure 17. Chemical structures of indole[1,2-c]-1,2,4-benzotriazine derivatives evaluated for antifungal activity.

3-(2-(5-(substituted phenyl)- 1,3,4-oxadiazol-2-ylthio) ethylthio) -5- (1H-indol-3-yl)- 4H-1,2,4-triazol-4-amines were prepared by Shi et al. using a special technique, i.e., ultrasonic. (2-(5-(2- ethoxyphenyl)-1,3,4- oxadiazol-2- ylthio)ethylthio)-5-(1H-indol-3-yl)-4H1,2,4-triazol-4-amine (126), and 3-(2-(5-(4- chlorophenyl)-1,3,4-oxadiazol-2- ylthio)ethylthio)-5-(1H-indol-3- yl)-4H1,2,4-triazol-4-amine exhibited excellent activity against *Staphylococcus aureus* and *Escherichia coli* strains [29] (Figure 18).

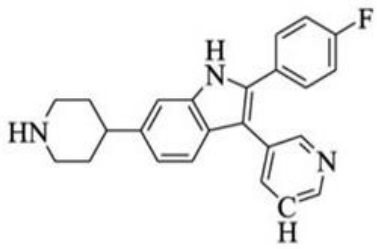


4-Amino-3-(1H-indol-3-yl)-5-({2-[(5-(2-ethoxyphenyl)-1,3,4-oxadiazol-2-yl)thio]ethyl}thio)-4H-1,2,4-triazole

4-Amino-3-(1H-indol-3-yl)-5-({2-[(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio]ethyl}thio)-4H-1,2,4-triazole

Figure 18. Chemical structures of substituted 3-(2-(5-(substituted phenyl)-1,3,4-oxadiazol-2-ylthio)ethylthio)-5-(1H-indol-3-yl)-4H-1,2,4-triazol-4-amine derivatives evaluated for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

3-Diarylindole derivatives containing an amine substituent at the 5 and 6 positions of indole were prepared and screened as anticoccidial agents by Scribner et al. (4-fluorophenyl)-6-(piperidin-4-yl)-3-(pyridin-3-yl)- 1H-indole showed the best activity [30] (Figure 19).

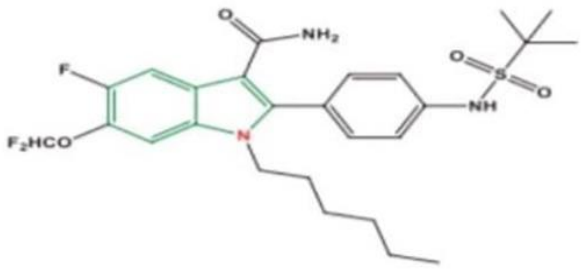


2-(4-Fluorophenyl)-3-(pyridin-4-yl)-6-(piperidin-4-yl)-1H-indole

Figure 19. Chemical structures of 3-diarylindole derivatives bearing amine substituents at the 5- and 6-positions of the indole nucleus, evaluated for anticoccidial activity.

2.10 Hepatitis C Virus Activity

Zhang et al., 2005, reported and prepared a new series of indole derivatives (2- (4-sulfonamidophenyl)- indole-3-carboxamides) and evaluated them on the HCV genotype 1b replicon. The synthesized compound exhibits good potency. The indole derivatives are hepatitis C virus active compounds [31] (Figure 20).



6-(Difluoromethoxy)-5-fluoro-2-{4-[(2-methylpropane-2-sulfonyl)amino]phenyl}-1-hexyl-1H-indole-3-carboxamide

Figure 20. Chemical structures of 2-(4-sulfonamidophenyl)-1H-indole-3-carboxamide derivatives evaluated for anti-hepatitis C virus (HCV) activity against the HCV genotype 1b replicon.

CONCLUSION

Indole derivatives are recognized as privileged scaffolds in medicinal chemistry due to their unique structural framework, remarkable chemical versatility, and broad spectrum of biological activities. The indole nucleus is present in numerous natural products, neurotransmitters, and clinically important drugs, highlighting its significance in both nature and pharmaceutical science. Owing to its ability to interact with diverse biological targets, the indole scaffold has beend extensively explored for the development of anticancer, antimicrobial, antiviral, anti-inflammatory, antidiabetic, and neuroprotective agents.

Researchers have demonstrated that strategic substitution at different positions of the indole ring can significantly enhance pharmacological activity, selectivity, and safety profiles, enabling the design of molecules capable of addressing complex and emerging diseases. Furthermore, advances in synthetic methodologies, including green chemistry approaches and sustainable catalytic processes, have facilitated the efficient and environmentally friendly synthesis of novel indole derivatives.

Beyond their therapeutic applications, indole-based compounds also play important roles in agriculture, biotechnology, and materials science. Their structural resemblance to biologically relevant molecules allows them to interact effectively with proteins, enzymes, receptors, DNA, and other biomolecular targets. As a result, indole derivatives continue to serve as valuable lead compounds in drug discovery and development. Continued research focusing on rational drug design, molecular modeling, and eco-friendly synthetic strategies is expected to further expand the therapeutic potential of indole derivatives and maintain their prominence in the development of safer, more potent, and highly targeted medicines.

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