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Indole-Based Scaffolds in Medicinal Chemistry: Recent Advances and Perspectives

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ABSTRACT

Indole-based scaffolds remain a cornerstone in medicinal chemistry due to their privileged structural framework and capacity for diverse molecular interactions. Recent advances in synthetic methodologies, including metal-catalyzed reactions, multicomponent strategies, and green chemistry approaches, have enabled the efficient generation of indole derivatives with enhanced structural complexity and drug-like features. Parallel pharmacological studies have highlighted their broad therapeutic relevance, ranging from anticancer and antimicrobial agents to modulators of neurological and inflammatory pathways. This review focuses on the synthesis of indole derivatives, their pharmacological evaluation, and emerging medicinal applications. By integrating synthetic innovation with pharmacological insights, indole scaffolds continue to provide a versatile foundation for modern drug discovery and hold significant potential in addressing unmet clinical challenges.

Keywords: Drug Discovery; Indole; Medicinal Chemistry; Pharmacological Evaluation; Synthesis.

1. INTRODUCTION

Indole remains a privileged heterocyclic scaffold in medicinal chemistry, combining a benzene ring fused to a pyrrole ring that grants exceptional structural versatility and biological relevance. Its prevalence in natural products and therapeutic agents underscores its importance in drug discovery [1]. As classical synthetic methods like Fischer, Reissert, and Bartoli syntheses continue to evolve, novel and more sustainable techniques have emerged, expanding access to complex indole derivatives [2].

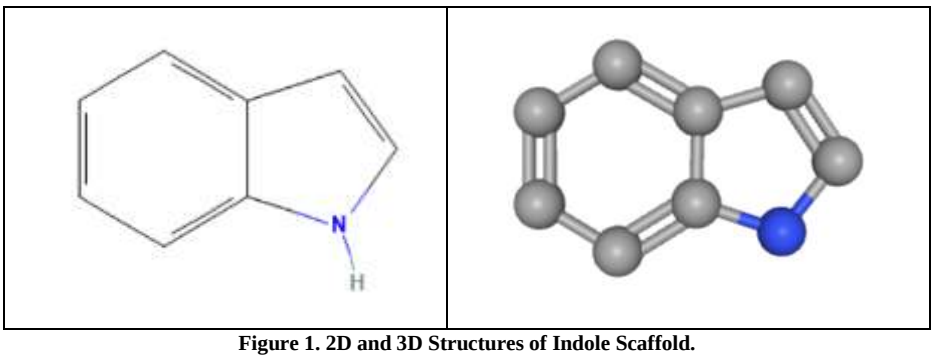


Figure 1. 2D and 3D Structures of Indole Scaffold.

The therapeutic potential of indoles is rapidly expanding, with growing evidence of their effectiveness in cancer, infectious diseases, inflammatory disorders, metabolic regulation, and neurological conditions. This review focuses on recent advancements in the synthesis of indole scaffolds and their pharmacological evaluation.

2. SYNTHESIS OF INDOLE SCAFFOLDS

2.1 Classical Nitroarene to Indole Methods:

Bartoli, Reissert, Cadogan, and Leimgruber-Batcho approaches remain foundational for indole formation from ortho-substituted nitroarenes.

2.2 One-Pot/Tandem Redox-Hydrogenation:

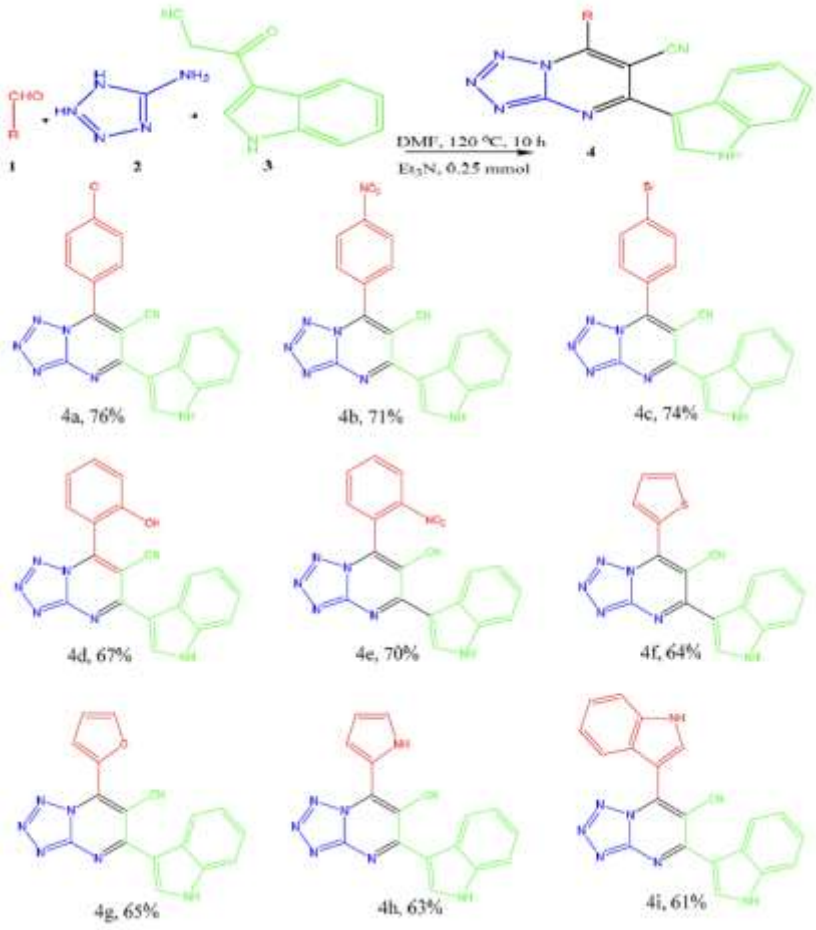
New integrated protocols facilitate streamlined conversion of nitroarenes into functionalized indoles via combined redox and hydrogenation sequences.

2.3 Photochemical & Electrochemical Routes:

These emerging strategies enable selective, green synthesis of indoles with tailored substitution patterns [3].

2.4 Multicomponent Reactions (MCRs):

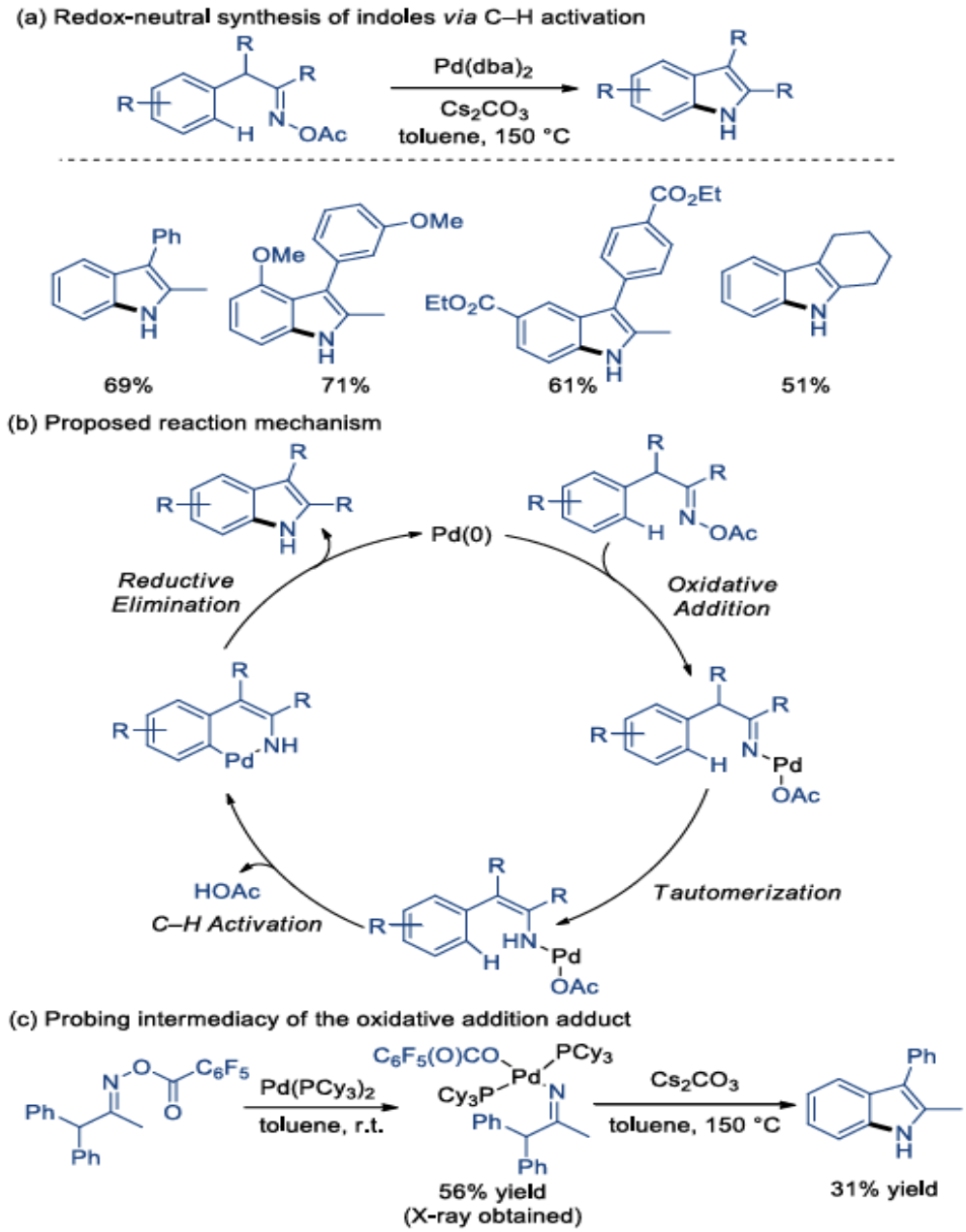
Efficient assembly of complex indole-based tetrazolopyrimidine frameworks was recently achieved through a one-pot three-component reaction of aldehydes, 1H-tetrazole-5-amine, and 3-cyanoacetyl indole under mild base-catalyzed conditions. This method provided rapid access to structurally diverse indole derivatives, several of which (notably compounds 4h, 4b, 4c, 4i, and 4a) exhibited significant anticancer activity against HCT-116, MCF-7, MDA-MB-231, and A549 cell lines. This demonstrates the utility of MCRs in simultaneously incorporating multiple reactants to generate biologically relevant fused indole scaffolds with therapeutic potential (**Scheme 1**) [4].



Scheme 1. Multi-component synthesis of 7-substituted-5-(1H-indol-3-yl)tetrazolopyrimidine-6 carbonitrile. Reaction conditions: aldehyde 1 (1 mmol), 1H-tetrazole-5-amine 2 (1 mmol), 3 cyanoacetyl indole 3 (1 mmol), Et3N (0.25 mmol), in dimethylformamide (DMF) at 120 °C, and about 10h reaction time.

2.5 Transition-Metal Catalysis:

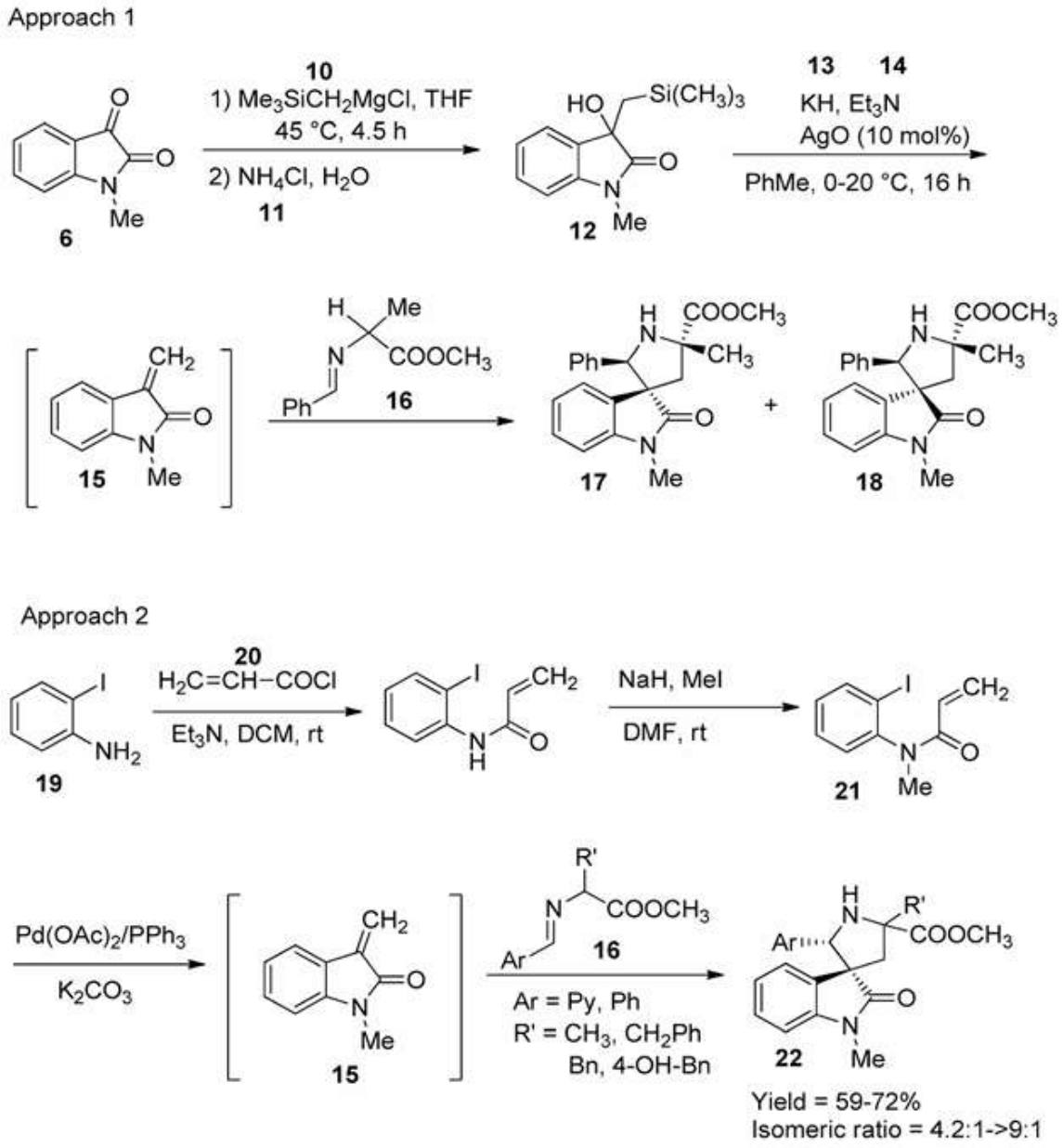
Palladium-catalyzed C-H activation offers a green and efficient route to construct indole frameworks directly from simple arene precursors. This strategy circumvents the need for extensive pre-functionalization, facilitating "green synthesis" and enabling access to indoles, indolines, and carbazoles under milder, more sustainable conditions (**Scheme 2**) [5].



Scheme 2. Redox-neutral intramolecular synthesis of indoles from oxime esters.

2.6 Spirofused Indole Hybrids via Green Synthesis:

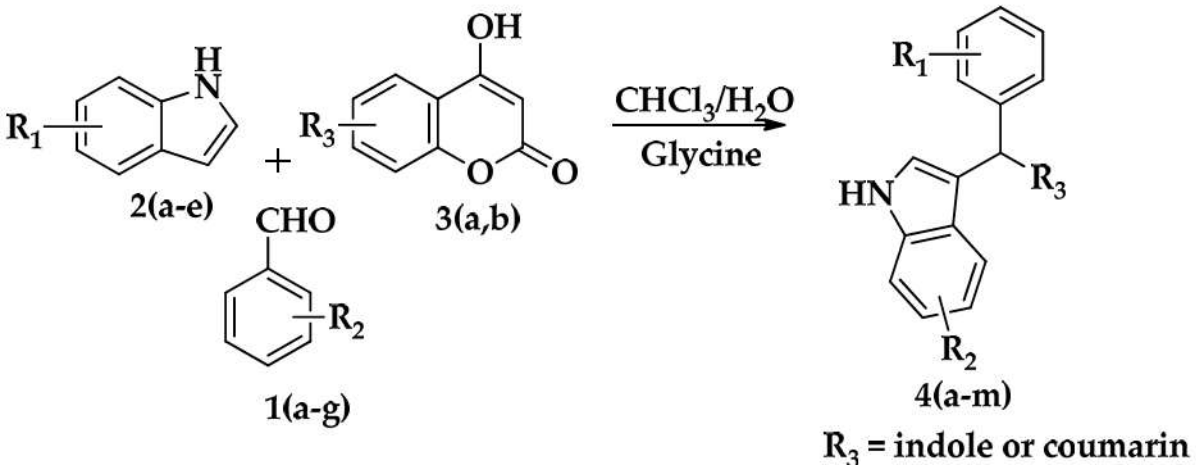
Eco-friendly, one-pot and cascade protocols (including metal-free multicomponent and [3+2] annulation approaches) have been developed for the synthesis of spiro-oxindole and other spiro-indole frameworks from isatin/indole derivatives and active methylene partners. These methods proceed under mild conditions, often with high diastereo- and chemoselectivity, and afford diverse libraries of spiro-indole scaffolds that have shown antiproliferative and antiparasitic activity in cell-based assays (**Scheme 3**) [6].



Scheme 3. Synthesis of Spiro oxindole via Peterson olefination/1,3 dipolar cycloaddition and intramolecular Heck/1,3-dipolarcycloaddition.

2.7 Suzuki Coupling-Based Indole-Coumarin Hybrids:

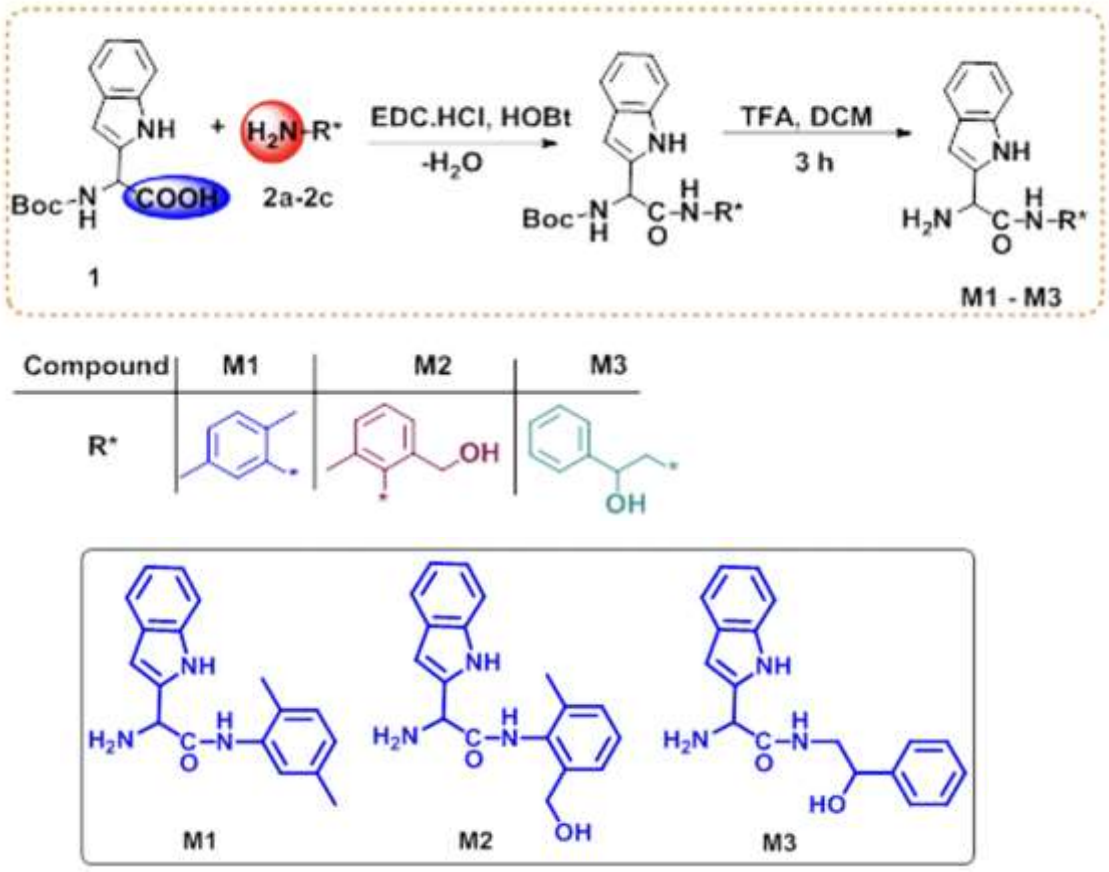
A sustainable Suzuki-Miyaura cross-coupling protocol was developed to create **indole–coumarin hybrid molecules** by coupling 4-bromobenzaldehyde with various boronic acids, followed by condensation with indole and coumarin derivatives in aqueous glycine-chloroform (1:1) at 70 °C. This one-pot strategy afforded a library of hybrid compounds (notably 4a-4m) in good yields. Substituent effects on the indole core influenced product distribution, where electron-donating groups favoured formation of bisindole derivatives (e.g., 4c and 4m), whereas heteromeric indole–coumarin hybrids formed preferentially in other cases. Some of these compounds (such as 4b and 4e) exhibited potent antibacterial activity against *Staphylococcus aureus*, with in silico docking studies suggesting binding to bacterial histidine kinase targets (**Scheme 4**) [7].



Scheme 4. Synthesis of bisindoles and heterodimers of indole-clubbed coumarin derivatives 4(a-m).

2.8 Pseudo-Peptide Indole Acetamides:

The synthesis and theoretical profiling of novel indole-based pseudo-peptides were accomplished via acetamide linkages derived from 2-amino-2-(1H-indole-2-yl) acetamides. Researchers prepared three pseudo-peptide analogues (M1–M3), characterized them using ^1H- and ^13C-NMR and mass spectrometry, and then conducted computational analyses exploring their electronic structure, reactive hotspots, solvent-dependent optical behaviour, and potential pharmacological relevance, including drug-like stability and autoxidation sensitivity. These insights suggest they may serve as promising lead scaffolds in drug design (**Scheme 5**) [8].



Scheme 5. General synthetic pathway of pseudo-peptides M1-M3.

3. PHARMACOLOGICAL APPLICATIONS OF INDOLE DERIVATIVES

3.1 Anticancer via Apoptosis Induction and EGFR Inhibition:

Isatin-derived indole spirooxindoles exhibited sub-10 μM IC_{50} values against multiple cancer lines, inducing cell-cycle arrest and outperforming Lapatinib in EGFR inhibition (0.019–0.026 μM vs 0.028 μM) [9].

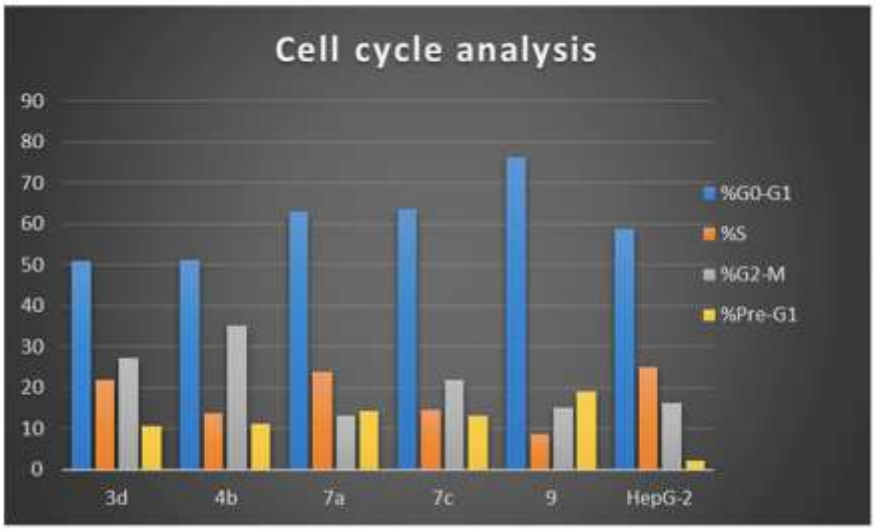
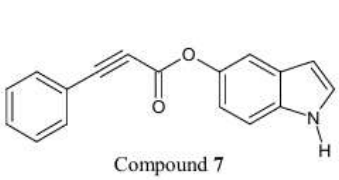


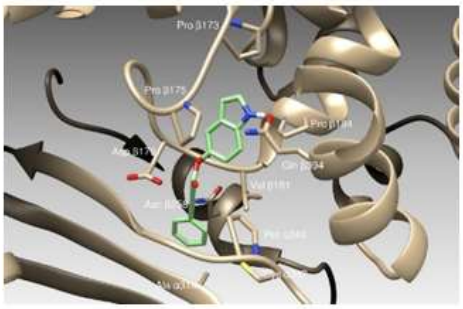
Figure 1. Cell cycle analysis and apoptosis effect in HepG2 cells treated with compounds 4 b,7a,7cand9.

3.2 Tubulin Polymerization Inhibition in Cancer:

Novel indole/pyranoindole derivatives effectively inhibited tubulin polymerization, with compound 7 demonstrating potent cytotoxicity in HeLa cells (IC_{50} = 3.6 ± 0.5 μM). Notably, this compound triggered apoptosis without compromising the viability of normal cells, underscoring its selective anticancer potential. Additional evaluations revealed that compound 7 also reduced menadione-induced reactive oxygen species (ROS) levels in 3T3-L1 fibroblasts, indicating a concurrent antioxidant effect that may mitigate oxidative stress during therapy. In silico docking studies confirmed strong binding affinity of compound 7 to the colchicine-binding site on tubulin, reinforcing its mechanistic relevance. This dual functionality—anticancer efficacy combined with ROS modulation—positions compound 7 as a compelling lead for further exploration [10].



Compound 7



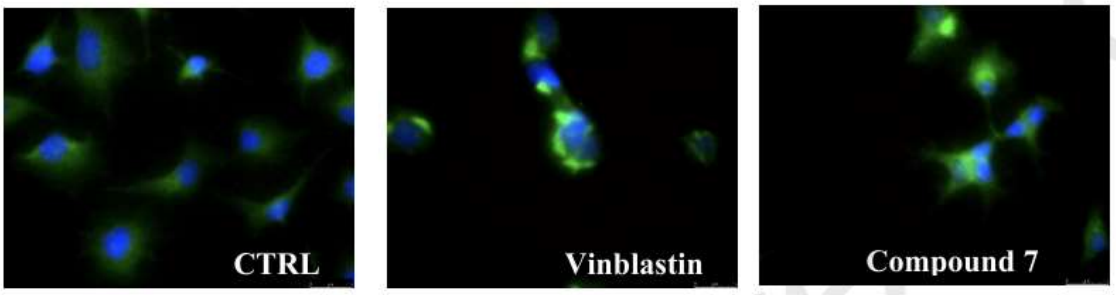


Figure 2. Tubulin Polymerization Inhibition of Compound 7.

3.3 Antibacterial Agents Targeting Histidine Kinase in S. aureus:

Novel indole-coumarin and bisindole derivatives synthesized via Suzuki coupling demonstrated significant antibacterial activity against *Staphylococcus aureus*. Docking studies suggest these compounds act by targeting bacterial histidine kinase, a key regulator in two-component systems [7].

Table 1. Zone of inhibition (ZOI) of the synthesized compounds 4b and 4e against S. aureus in mm [7].

Compound	Diameter of Zone of Inhibition (ZOI) (mm)
	S. aureus
4b (350 µg/mL)	8.0 mm
4e (160 µg/mL)	7.2 mm
Negative control (1:1) Ethanol:distilled water	-
Tetracycline (30 µg/disc)	16.25 mm

3.4 Indole-Based Agents Against Extensive Fungal and Bacterial Strains:

Indole derivatives fused with 1,2,4-triazole and 1,3,4-thiadiazole moieties were tested across a range of pathogens (*S. aureus*, MRSA, *E. coli*, *B. subtilis*, *C. albicans*, *C. krusei*). Compound 3d stood out with multi-pathogen efficacy, including fungal and antibiotic-resistant targets [11].

Table 2. MIC values (µg/mL) of tested indole derivatives

3a-h	*S. aureus*	MRSA	*E. coli*	*B. subtilis*	*C. albicans*	*C. krusei*
3a	50	25	25	25	12.5	3.125
3b	25	12.5	25	25	3.125	3.125
3c	25	50	25	3.125	3.125	3.125
3d	6.25	3.125	50	25	3.125	3.125
3e	50	25	25	25	6.25	3.125
3f	25	25	25	25	12.5	12.5
3g	25	12.5	25	50	6.25	3.125
3h	12.5	6.25	25	12.5	6.25	3.125

3.5 Indole-Based Compounds for Neurodegenerative Disorders:

A recent open-access study characterized a series of synthetic indole-phenolic hybrids for their neuroprotective capabilities. These compounds showed robust antioxidant activity and metal-chelating properties, particularly against copper ions, mitigating oxidative stress induced by amyloid-β ($A\beta_{(25-35)}$) in SH-SY5Y neuroblastoma cells. Treatment elevated cell viability by ~25% and normalized ROS levels. Additionally, they facilitated the disassembly of Aβ aggregates, indicating potential in counteracting amyloid pathologies [12].

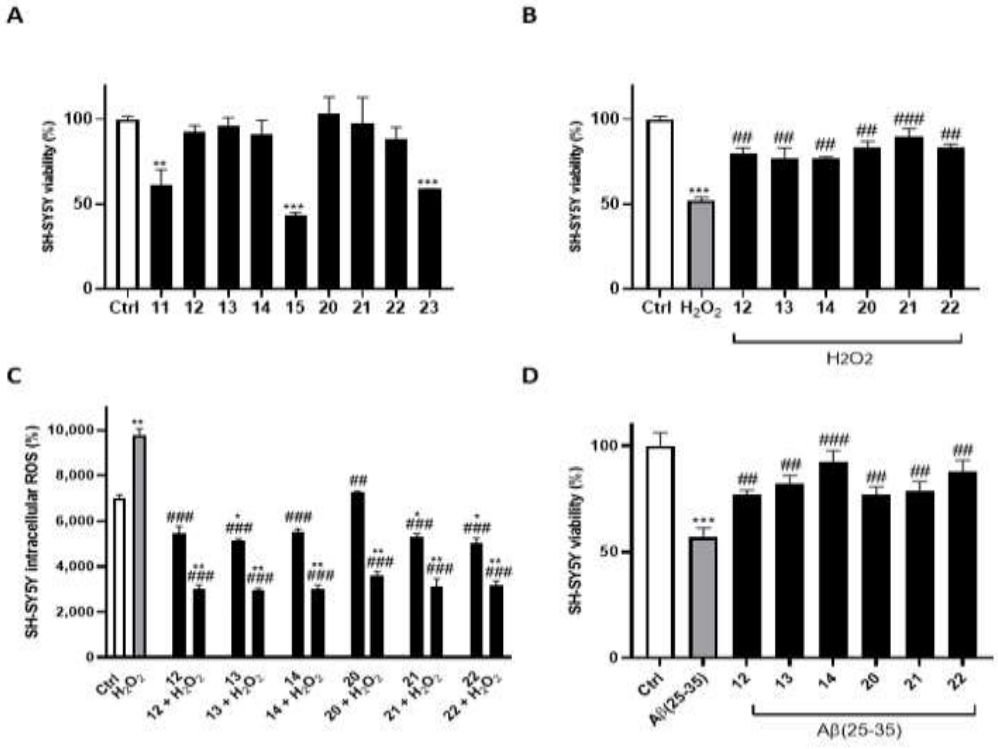


Figure 3. Neuroprotective activity of compounds [12].

Table 3 highlights a selection of recently approved and investigational indole-based drug candidates that demonstrate the structural versatility and therapeutic potential of the indole scaffold. These compounds span diverse pharmacological classes, ranging from neurotransmitter receptor modulators and opioid receptor agonists to mitochondrial metabolism disruptors and psychedelic-inspired therapeutics. Notably, indole derivatives are being pursued not only for classical applications such as pain and cancer but also for emerging areas like anxiety, post-traumatic stress disorder, and postpartum depression.

The inclusion of both clinically approved agents, such as ***Maritupirdine,*** and late-stage investigational drugs illustrates the ongoing translation of indole chemistry from bench to bedside. Collectively, these examples reinforce the enduring relevance of indole scaffolds in modern medicinal chemistry and drug discovery pipelines.

Table 3. Recently approved and investigational indole-based drugs.

Drug Name	Status	Indication / Mechanism	References
Maritupirdine (Aviandr)	Approved (2023, Russia)	5-HT$_6$ receptor antagonist for generalized anxiety disorder	[13]
Cebranopadol	Investigational (Phase III)	Dual μ-opioid/NOP receptor agonist for acute pain	[14]
Linrodostat (BMS-986205)	Investigational (Phase II/III)	IDO1 inhibitor under study in bladder and melanoma cancers	[15]
Devimistat (CPI-613)	Investigational (Phase III)	Targets mitochondrial TCA cycle in metastatic pancreatic cancer	[16]
Luvesilocin (RE-104)	Investigational (Phase II)	Psychedelic prodrug for rapid-acting postpartum depression treatment	[17]
Soclenicant (BNC210)	Investigational (Phase II)	α$_7$-nAChR negative allosteric modulator for anxiety and PTSD	[18]

4. CONCLUSION

Indole scaffolds remain central to medicinal chemistry due to their structural flexibility and wide pharmacological relevance. Advances in synthetic methods and hybrid designs have expanded their therapeutic potential across cancer, infections, neurological, and inflammatory diseases. With ongoing innovations in green chemistry and computational drug design, indole-based frameworks are poised to play an even greater role in developing next-generation medicines.

5. ACKNOWLEDGMENT

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6. CONFLICT OF INTEREST

All authors declare there are no conflicts of interest.

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