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Review Article

Indole–Pyrazole Conjugates: Synthetic Approaches And Therapeutic Potential

Vidya V L* and Anoopa John L
Department of Pharmaceutical Chemistry, The Dale View College of Pharmacy and Research Centre, Punalal, Thiruvanathapuram, Kerala, India.

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***Corresponding Author:**
Ms. Vidya V L
Email : vidyareji85@gmail.com
Phone : +9198954 54471

ABSTRACT
Indole-pyrazole hybrids represent a unique class of molecular frameworks that merge two pharmacologically privileged scaffolds into a single entity, offering broad-spectrum therapeutic potential. The indole nucleus, frequently found in bioactive natural products and neurotransmitters, provides excellent bioavailability and biological compatibility, while the pyrazole ring contributes electronic richness, stability, and versatile reactivity. Their conjugation has yielded derivatives with enhanced potency, selectivity, and multi-target activity. This review highlights recent advances in synthetic methodologies, ranging from classical approaches, such as the Fischer and Bartoli reactions, to environmentally benign strategies, including one-pot, microwave-assisted, and solvent-free techniques. Structural modifications at key positions of both indole and pyrazole rings, as well as linker variations, are critically examined for their role in optimizing pharmacological properties. A comprehensive account of the pharmacological activities of indole–pyrazole conjugates is presented, with significant evidence of anti-inflammatory, analgesic, antioxidant, antimicrobial, antidiabetic, and anticancer potential, supported by both in vitro and in vivo studies. Collectively, the indole–pyrazole framework offers a fertile platform for rational drug design, and ongoing research integrating synthetic innovation with biological evaluation may pave the way for the development of clinically relevant therapeutics.

1. INTRODUCTION

Heterocycles represent a fundamental and distinctive class of compounds when compared to more than half of the known organic compounds. Heterocyclic compounds are organic chemical compounds that have a ring structure, which includes heteroatoms such as nitrogen, oxygen, or sulphur. Heterocyclic compounds form a core structure for enormous biologically active molecules. Most of the drugs synthesised nowadays belong to heterogeneous compounds. They play a significant role in the metabolism of living organisms. The heterocyclic compounds differ from each other in the presence of five-membered or six-membered rings and also the presence of one or three hetero atoms in the ring (Al-Mulla, 2017; Saini et al., 2013). Among heterocyclic compounds, five-membered ring-containing nitrogen atoms form a vast and diverse group with remarkable biological activities. The five-membered ring category includes pyrazole, imidazole, oxazole, triazole, tetrazole, oxadiazole, thiazoles, etc. (Al-Mulla, 2017;

Ebenezer et al., 2022). Some of the heterocyclic compounds commonly incorporated in medicines are amino acids and vitamins. Other physiologically active heteroatoms are purines, pyrimidines, pyrimidine, as well as trinitrons (Saini et al., 2013). Biological molecules, such as chlorophyll, haemoglobin, DNA, and RNA, contain heterocyclic atoms in their vital ring structures (Al-Mulla, 2017). Thus, heterocyclic compounds are commonly found in many novel drugs, enhancing the relationship between biology and chemistry (Kumar et al., 2020). Heterocyclic compounds exhibit a range of activities, including antifungal, antioxidant, antibacterial, anti-inflammatory, anticancer, and antileprotic properties (Kabir and Uzzaman, 2022).

2. METHODOLOGY

The information presented in this review was collected from multiple scientific sources, including peer-reviewed journal articles, published books, conference proceedings, and reputable online databases such as PubMed, ScienceDirect, SpringerLink, and Wiley Online Library. Recent publications up to 2025 were carefully analysed to cover both synthetic methodologies and pharmacological evaluations of indole–pyrazole derivatives. Keywords such as indole–pyrazole hybrids, synthesis, pharmacological activity, green chemistry, and structure–activity relationship (SAR) were used to retrieve relevant literature. References were cross-checked to ensure accuracy and authenticity. Emphasis was placed on articles that discussed the design, synthesis, biological evaluation, and structure modifications of indole–pyrazole hybrids to provide a comprehensive and up-to-date overview.

3. IMPORTANCE OF INDOLE -PYRAZOLE MOIETY

The indole-pyrazalone moiety is a fused heterocyclic system that has gained significant attention in medicinal chemistry due to its diverse and varied pharmacological activities. This particular backbone combines the properties of both the indole and pyrazole rings. Therefore, it is crucial to comprehend the diverse synthetic strategies for indole-pyrazole hybrids. The hybrids are further categorized into two types: direct-linked and spacer-linked, and are again classified based on the position of the pyrazole group on the indole key nucleus (Fabitha et al., 2022).

4. RATIONALE OF THE STUDY

In 2020, lung cancer was the leading cause of cancer-related death, next to colon and rectal cancer. Due to the high mortality rates associated with cancer, there is an urgent need for novel anticancer drugs. Indole-containing compounds exhibit distinct biological activities, including antimicrobial, antifungal, anticancer, anti-inflammatory, analgesic, antidiabetic (Gharge et al., 2024), and anti-HIV properties. It is taken as a central nucleus for the synthesis of novel anticancer drugs (Mohamed et al., 2023). Fan Zhang et al reported that 2-amino-3-cyano-6(1H-indol-3-yl)-4-phenylpyridine derivatives indicate amiable anti-tumour activity against four human cell lines (H460, A549, HT-29, SMMC-7721) (Mohamed et al., 2023). The structural significance of the indole-pyrazole moiety was well explained in a recent study (Fabitha et al., 2022) (Figure 1).

5. SYNERGISTIC BIOACTIVE FRAMEWORKS

The indole-pyrazole hybrid incorporates two pharmacologically rich cores. The indole nucleus is frequently found in natural products and neurotransmitters, such as tryptophan and serotonin. They show excellent bioavailability and biological compatibility. The combination leads to enhanced conjugation. It helps to improve the potency, selectivity, or multi-target action.

Hybrid molecules have demonstrated the ability to display synergistic or complementary pharmacological effects compared to compounds featuring each separate pharmacophore. Numerous novel drug delivery systems have been developed using indole-3-acetic acid in combination with layered metal hydroxide nanohybrids (Yang et al., 2007). Given the varied biological effects of indole- and pyrazole-based compounds, scientists worldwide have documented their research on the creation and biological assessment of indole-pyrazole combinations using the molecular hybridization approach. Nonetheless, a limited number of evaluations emphasized the creation of distinct derivatives that contain indole and pyrazole, as acknowledged by us. There are currently no reviews available on the chemical synthesis of indole-pyrazole hybrids. Hybrid molecules composed of indole and pyrazole can typically be divided into two types: direct-linked hybrids and hybrids linked by spacers. Both classes can be further divided according to the substitution position of the pyrazole on the indole. The subgroups consist of indole-C2 pyrazole hybrids, indole-C3 pyrazole derivatives, and indole-C4/5/6/7 pyrazole hybrids. This review will focus on the synthetic advancements of directly connected and spacer-connected indole-pyrazole hybrids due to their

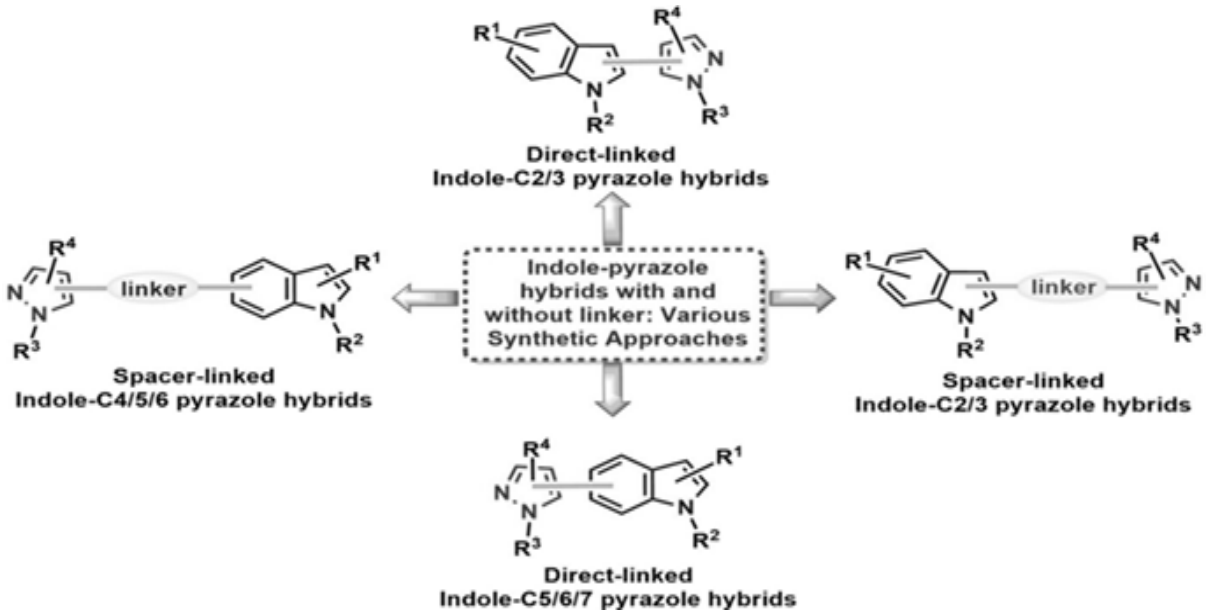

Figure 1: Structural Significance of Indole-Pyrazole Moiety.

extensive diversity.

6. STRUCTURAL MODIFICATIONS AND THE IMPORTANCE OF PHARMACOLOGICAL ACTIVITY

In the development of indole–pyrazole hybrid molecules, several key structural positions are routinely modified to optimize biological activity, pharmacokinetics, and target specificity. One prominent site is the N-1 position of the indole ring, which is often substituted with alkyl, aryl, or acyl groups to improve lipophilicity and enhance blood-brain barrier (BBB) permeability, a property that is especially useful in targeting the central nervous system (CNS) (Majola et al., 2024). The C-3 position of the indole is another crucial point, commonly used for attaching pyrazole rings, hydrazone linkers, or pharmacophores like carboxylic acids and amides. This region is considered vital for interacting with biological targets and maintaining receptor affinity.

On the pyrazole ring, substitutions at the C-3 and C-5 positions with aryl, halogen, nitro (NO_2), or trifluoromethyl (CF_3) groups have been shown to significantly influence bioactivity, enhancing cytotoxicity, anti-inflammatory effects, or enzyme inhibition. Additionally, the linker between the indole and pyrazole moieties, which can include -CH_2-, -CO-, or -NH-, plays a critical role in adjusting the spatial orientation and conformational flexibility of the molecule, which in turn affects binding to target enzymes or receptors. Lastly, incorporating electron-donating or electron-withdrawing groups (such as -OH, -OMe, -NO_2, -Cl, or -F) on the aromatic rings modulates solubility, metabolic stability, and receptor selectivity, as supported by SAR analyses presented in the 2025 Future Journal of Pharmaceutical Sciences review. These modifications are strategically employed to design molecules with enhanced pharmacological profiles across therapeutic areas, including anticancer, anti-inflammatory, and antimicrobial domains (Nehra et al., 2025).

A comprehensive explanation of how to synthesize fused indole-pyrazole derivatives in a single pot using a 3+2 annulation technique was reported by Majola et al. Compound 4a showed potent anticancer activity against A549 and HepG2 cancer cell lines, with IC_{50} values of 18.70 μg/mL and 50.07 μg/mL, respectively. The compounds also showed dual biological activities. On the other hand, compound demonstrated potent inhibition of the α-amylase and α-glucosidase enzymes, making it a highly effective antidiabetic drug. These results demonstrate the potential of this fused scaffold for creating multipurpose medications.

An ACS study from 2021 utilized isatin or indole-3-carbaldehyde intermediates to synthesize pyrazole–indole hybrids (Hassan et al., 2021). The anticancer potential of these hybrids was assessed against a variety of cell lines. Some compounds showed effectiveness against HepG2 cells, exceeding the reference medication doxorubicin, with IC_{50} values of 6.1 ± 1.9 μM and 7.9 ± 1.9 μM, respectively. These

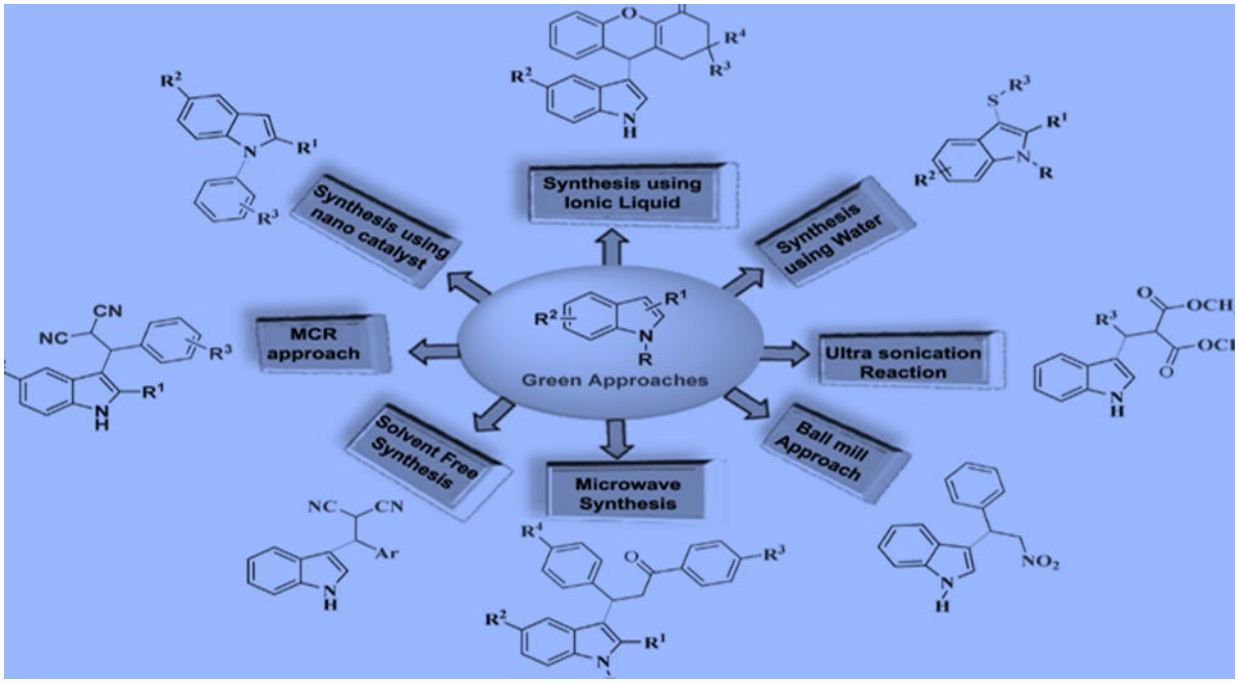

Figure 2: Green Chemistry Method for the Synthesis of Indole Derivatives.

substances are promising kinase inhibitors, as demonstrated by molecular docking, which verified significant binding associations with the CDK-2 enzyme.

The anti-inflammatory and analgesic qualities of indole-pyrazole compounds were the subject of another critical investigation. Twelve compounds with indole, pyrazole, and oxadiazole moieties were synthesized as part of the project. Carrageenan-induced paw edema was strongly inhibited in the *in vivo* tests, and docking investigations confirmed that it selectively inhibited COX-2 (Kaur et al., 2018).

Babijczuk et al. (2025) highlighted the structure–activity relationships (SAR) of indole–pyrazole hybrids in the design of anticancer drugs. They reported that stiff linkers and electron-withdrawing groups significantly improved cytotoxicity. Compounds synthesized via palladium-catalysed cross-coupling, displayed vigorous inhibitory activity against melanoma cell lines, indicating the potential of this scaffold in oncological applications.

Kumar et al. (2020) investigated the cytotoxic effects of benzene–indole–pyrazolyl-substituted amides on different cancer cell lines. Their results showed that aryl substitution on the pyrazole ring substantially enhanced potency and selectivity, emphasizing the role of steric and electronic factors in rational anticancer drug design.

Abdelgawad et al. (2017) synthesized a series of pyrazole–hydrazone derivatives that notably inhibited both 5-lipoxygenase (5-LOX) and COX-1/COX-2. With fewer gastrointestinal adverse effects than standard NSAIDs, this dual inhibitory mechanism facilitates the development of indole–pyrazole analogues for anti-inflammatory applications.

7. SYNTHESIS AND CHEMICAL APPROACHES

7.1 Conventional methods of synthesis of indole derivatives.

The literature has detailed a variety of indole synthesis techniques, such as the Fischer Indole Synthesis, 2-Alkynylaniline Cyclization, Reductive Cyclization, heteroannulations, and other various procedures (Mondal et al., 2020). To overcome the drawbacks of traditional procedures, academic researchers and the pharmaceutical industry are now employing green methods for the synthesis of molecules containing indole (Bedlovičová, 2022). Ultrasound, multicomponent reactions, microwave irradiation, deep-eutectic liquids, ionic liquids, water, green solvents, nano catalysts, solvent-free reactions, and other greener techniques are all utilized in various ways. Green synthesis is an environmentally friendly process that utilizes eco-friendly solvents, eliminates hazardous waste, and requires less energy (Soltys *et al*., 2021). The goal of "green" chemistry is to create technology for safer and more effective chemical

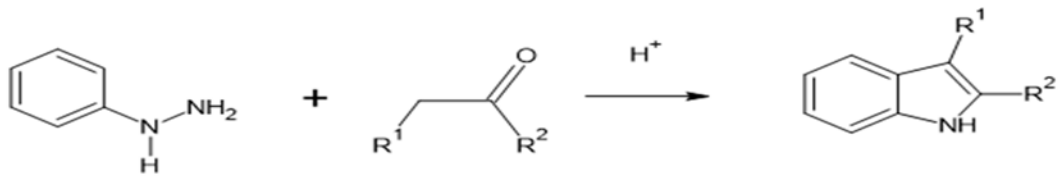

Figure 3: Reactions involved in the Fischer Indole synthesis.

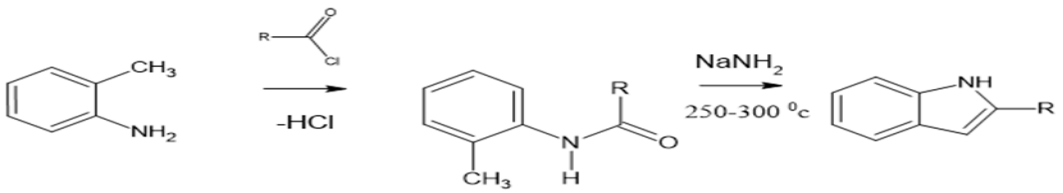

Figure 4: Madelung method of indole Synthesis.

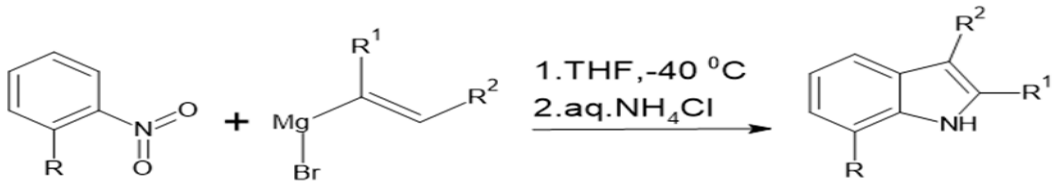

Figure 5: Bartoli synthesis of indole derivatives.

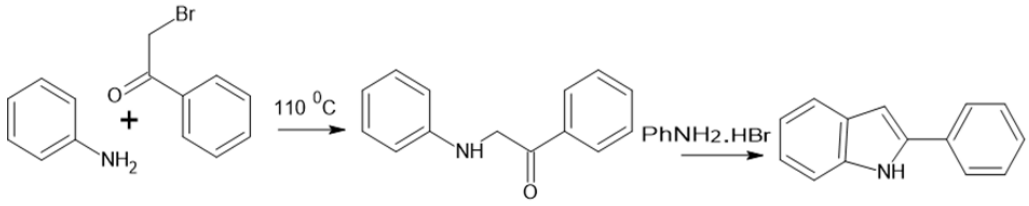

Figure 6: Bichler-Mohlau synthesis of indole derivatives.

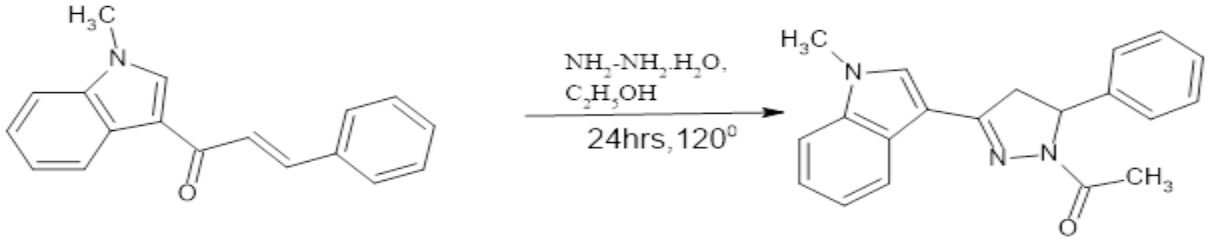

Figure 7: Reactions involved in the synthesis of indole-pyrazole derivatives.

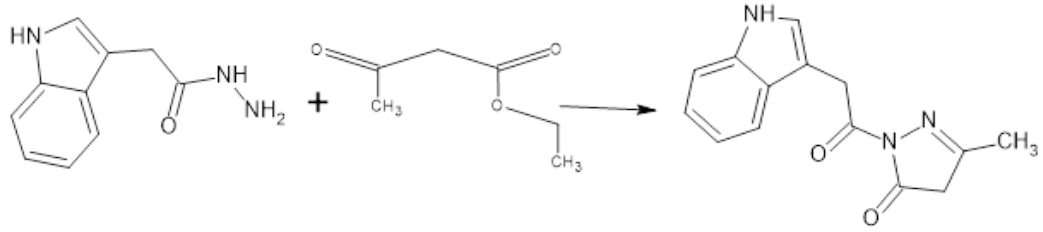

Figure 8: Describes the reaction of ethyl acetoacetate with inodol-3-yl Acetohydrazide

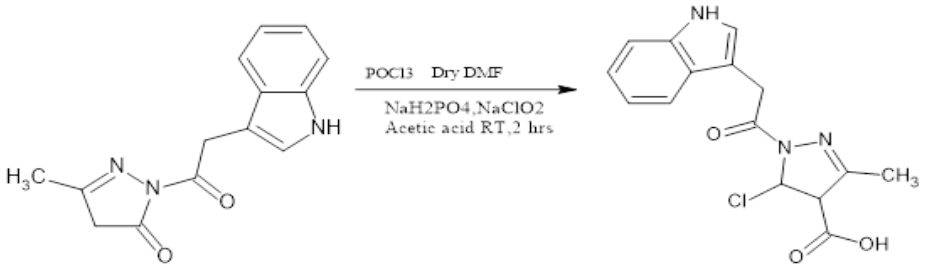

Figure 9: Synthesis of 3-(1H-indol-3-yl)pyrazole-5-carboxylic acid using acetic acid

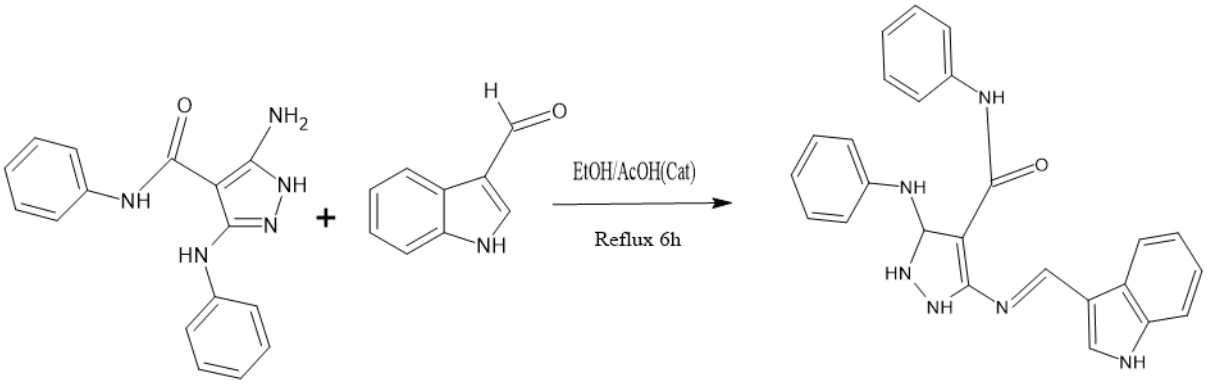

Figure 10: Reactions involved in the synthesis of Pyrazole–Oxindole hybrids.

reactions. Figure 2 illustrates the 12 guiding concepts of green chemistry (Anastas and Eghbali, 2010).

7.1.1 Fischer Indole synthesis

The Fischer indole synthesis is a well-established chemical reaction used to construct the indole ring system, a key structural component in numerous natural compounds and pharmaceutical agents. This reaction proceeds through an acid-catalyzed cyclization of a phenylhydrazone intermediate, which is generated by the condensation of phenylhydrazine with a carbonyl compound, such as an aldehyde or ketone (Taber and Tirunahari, 2011). The reactions are shown in Figure 3.

7.1.2 Madelung Synthesis

The base-catalyzed cyclization of 2-(acylamino) toluenes occurs under extremely harsh conditions, typically involving strong bases such as sodium amide or potassium tert-butoxide at high temperatures ranging from 250 to 300°C (Gribble, 1994). This method is generally restricted to the synthesis of simple indole derivatives, such as 2-methylindoles, and is not suitable for substrates containing sensitive functional groups due to the severe reaction conditions. The reactions are shown in Figure 4.

7.1.3 Bartoli indole synthesis

Bartoli indole synthesis is the method of synthesizing substituted indoles by the reaction of ortho-substituted nitro arenes with vinyl Grignard reagents (Dalpozzo and Bartoli, 2005). The reactions are shown in Figure 5.

7.1.4 Bichler-Mohlau synthesis

This method involves the cyclization of arylamino ketones and excess anilines to form 2-arylindoles (Black et al., 1980). The reactions are shown in Figure 6.

7.2 Green chemistry method of synthesis

Numerous conventional and environmentally friendly synthetic methods have been developed for the synthesis of indole derivatives, owing to their extensive use in medicinal chemistry. High yields, quick reaction times, low-cost reagents, and environmental friendliness are just a few of the many benefits of green technology over traditional techniques (Mondal et al., 2020). To overcome the shortcomings of conventional methods, researchers in the pharmaceutical and academic sectors are developing various green methodologies for the chemical synthesis of molecules based on the indole structure. The development of greener approaches for the synthesis of indole derivatives over the past decade is reflected in these low-cost reagents, and environmental friendliness is just one of the many benefits of green technology over traditional techniques.

8. SYNTHESIS OF INDOLE-PYRAZOLE DERIVATIVES

The synthesis involved the reaction of indole with benzaldehyde in a methanol solvent, resulting in the formation of an indole-chalcon derivative (Hassan and Abdulkarim, 2023). The next step involved the reaction of this chalcol derivative with aqueous hydrazine to form a pyrazole derivative in the presence of an ethanol solvent. The reactions are shown in Figure 7.

8.1 Synthesis of 3-(1H-indol-3-yl)pyrazole-5-carboxylic acid

Cyclocondensation of hydrazine on a 1,3-dicarbonyl precursor - indol-3-yl-substituted 1,3-dicarbonyl reacts with hydrazine (or substituted hydrazines) to form pyrazole-5-carboxylate and then hydrolysis to the acid (for example, by acylation/Claisen of an indole-3-derived synthon). After formation of an indol-3-yl enone, pyrazoles are obtained via [3+2] annulation with hydrazine derivatives, followed by oxidation/hydrolysis to yield 5-carboxylic acid (Originally diversified at N-/C-positions, it was widely used for indole–pyrazole hybrids.) (Betcke et al., 2024; Sapkota and Faizi, 2025). Both reactions are shown in Figures 8 and 9, respectively.

8.2 Synthesis of Pyrazole–Oxindole Hybrids

Synthesis of pyrazole-indole hybrid by refluxing indole carbaldehyde with pyrazole amine derivatives in the presence of ethanol and acetic acid as a catalyst (Hassan et al., 2021). The reactions are shown in Figure 10.

9. PHARMACOLOGICAL ACTIVITIES

The indole-pyrazole moiety exhibits a vast range of pharmacological activities. The indole-based pyrazole ring exhibits potent anti-inflammatory and antioxidant properties (Hassan et al., 2021; Sharath et al., 2013). Over the past few decades, isatin derivatives have gained significant attention as a vital scaffold, exhibiting a broad range of pharmacological applications, including antimicrobial, antitumor, antiviral, antitubercular, and enzyme-inhibitory activities (Hassan et al., 2021). Those compounds with isatin-indole combinations were screened for their cytotoxicity on human cancer types. A large variety of indole-pyrazole analogues have been reported, exhibiting the best antimicrobial activity, especially as antifungal agents (Fabitha et al., 2022).

9.1 Anti-inflammatory effect

The anti-inflammatory and analgesic properties of indole-functionalized pyrazoles were well explained by Devendra Kumar and his coworkers (Kumar et al., 2021). Inflammation is a protective mechanism that safeguards the human body from cellular injury or damage caused by harmful foreign particles or stimuli (Grivennikov et al., 2010). The significant signs of inflammation include pain, heat, swelling, and redness, all of which ultimately impair normal tissue function (Takeuchi and Akira, 2010). During this process, several microcirculatory events occur, including the recruitment of white blood cells, changes in vascular permeability, the production and release of pro-inflammatory mediators, and tissue destruction (Medzhitov, 2010). Anti-inflammatory agents exert their effects primarily by inhibiting the COX-1, COX-2, and 5-LOX enzymes, making them valuable therapeutic targets for the management of inflammation (Naglah et al., 2025). Many studies have been conducted on animals regarding the anti-inflammatory activity. One of the critical investigations was done by Kumar et al. (2021).

The induction of inflammation was assessed along with the percentage inhibition of rat paw edema by the test compounds. Statistical comparisons among control, reference, and test groups were performed using the F-test (ANOVA) followed by a post hoc analysis. The results revealed significant inhibition of edema after 4 hours. The tested molecule with indole-pyrazole demonstrated notable anti-inflammatory activity (% edema reduction = 74.07%), which was comparable to that of indomethacin (92.59%) and superior to the remaining compounds (Kumar et al., 2021; Naglah et al., 2025). Interestingly, after one hour of administration, compounds with an indole-oxadiazole structure and an electron-withdrawing group at the aryl ring exhibited the highest percentage inhibition of paw edema; however, no substantial improvement was observed at 2 hours. This inhibition suggests that the compound may have undergone rapid inactivation or metabolism. The unsubstituted aryl ring present in 15b may make it more susceptible to metabolic degradation, which could explain its reduced activity after four hours (Kumar et al., 2021). The anti-inflammatory activity of indole-based scaffolds was also clearly demonstrated by V. Sharath and his coworkers. Among the series of indole-pyrazole derivatives, replacement of the –OMe group on the phenyl ring attached to the pyrazoline moiety at the C-5 carbon atom, either by an oxygen atom or a halogen like a Cl substituent group, resulted in a dramatic drop in inhibitory activity, as observed in the

compound (Sharath et al., 2013).

9.2 Analgesic activity

The tail-flick method was employed to evaluate the analgesic potential of the synthesized compounds. Administration of the test compounds resulted in a significant reduction in the painful sensation induced by tail immersion in warm water. The effect became more prominent after a latency period of 2 h. Notably, some compounds exhibited a marked increase in reaction time, indicating potent analgesic activity. The analgesic evaluation was conducted at the same dose used for the anti-inflammatory study (Kumar et al., 2021; Varga et al., 2006).

9.3 Antioxidant activity

The synthesized compounds demonstrated varying capacities to scavenge free radicals in the DPPH assay. The activity was influenced by the type of substitutions present on the aryl ring attached to the oxadiazole/pyrazole nucleus. Compounds bearing halogen or methoxy substituents showed superior antioxidant activity compared to the other derivatives (Ali et al., 2013). This enhanced effect can be attributed to the electron-rich aryl rings, which readily donate electrons to stabilize DPPH radicals. In contrast, the free radical scavenging activity observed in compounds lacking methoxy substitution is primarily attributable to the oxadiazole nucleus itself. Hydrogen donation from this moiety leads to stabilization of the radical species. In their radical form, the compounds attain structural stability through electronic conjugation, which facilitates the reaction. The IC_{50} values of the synthesized derivatives were also determined, and compounds emerged as the most effective antioxidant agents.

9.4 Anticancer activity

Numerous traditional and more recent anticancer drugs target microtubules, which are crucial for various cellular functions, including intracellular transport, endothelial cell biology, cell division, and cell shape (Patel and Rajak, 2016). A new series of 2-amino-3,4,5-trimethoxyaroylindole derivatives was synthesized, demonstrating strong cytotoxic effects against the MCF-7 and colon HT-29 cell lines, with slightly greater potency compared to Combretastatin A-4. Molecular docking analysis further confirmed the anticancer potential, revealing favorable ligand–receptor interactions.

The sulforhodamine B assay was used to design, manufacture, and assess the antiproliferative activity of structurally varied indole-3-pyrazole-5-carboxamide analogues against three cancer cell lines (Huh7, MCF-7, and HCT116). Several of the compounds exhibited anticancer properties against cancer cell lines that were comparable to or superior to those of sorafenib (Hawash et al., 2023). 2,4-Bis(3'-indolyl)thiazoles, 3,5-bis(3'-indolyl)-2(1H)pyrazinone, and 3,6-bis(3'-indolyl)pyrazine were synthesized and evaluated for cytotoxic activity against diverse human cancer cell lines by the National Cancer Institute. These compounds demonstrated significant inhibitory effects on the growth of various cancer cell lines. 2,4-Bis(3'-indolyl)thiazole exhibited selective cytotoxicity against certain leukemia cell lines, with GI50 values in the low micromolar range. In contrast, the substituted derivatives showed a broad spectrum of cytotoxic activity. 3,5-Bis(3'-indolyl)-2(1H)- pyrazinone and 3,6-bis[3'-(N-methyl-indolyl)]pyrazine exhibited potent inhibitory activity against a wide range of human tumor cell lines (Jiang and Gu, 2000).

10. CONCLUSION

Indole-pyrazole derivatives constitute a promising scaffold in drug discovery, combining the favorable properties of both indole and pyrazole moieties to produce molecules with broad-spectrum biological activity. Structural modifications, including substitutions at key positions and variations in linker design, enable the fine-tuning of pharmacological properties, thereby enhancing potency, selectivity, and bioavailability. Advances in synthetic methodologies, including environmentally friendly and one-pot strategies, have facilitated the rapid construction of diverse indole-pyrazole hybrids. Pharmacological studies demonstrate significant anti-inflammatory, analgesic, antioxidant, antimicrobial, and anticancer activities, validating the therapeutic potential of these hybrids. Overall, the indole-pyrazole scaffold provides a valuable framework for the design of novel multi-targeted agents, and continued research integrating synthetic innovation, SAR analysis, and biological evaluation is expected to yield clinically relevant drug candidates.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Abbreviations

ATP – Adenosine Triphosphate
CNS – Central Nervous System
COX – Cyclooxygenase
DNA – Deoxyribonucleic Acid
DPPH – 2,2-Diphenyl-1-picrylhydrazyl (free radical scavenging assay)
ED_{50} – Median Effective Dose
EGFR – Epidermal Growth Factor Receptor
GABA – Gamma-Aminobutyric Acid
HPLC – High-Performance Liquid Chromatography
HRMS – High-Resolution Mass Spectrometry
IC_{50} – Half Maximal Inhibitory Concentration
IL – Interleukin
IR – Infrared Spectroscopy
LD_{50} – Median Lethal Dose
MIC – Minimum Inhibitory Concentration
MTT – 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NMR – Nuclear Magnetic Resonance
NOAEL – No Observed Adverse Effect Level
NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
PDB – Protein Data Bank
QSAR – Quantitative Structure–Activity Relationship
RNA – Ribonucleic Acid
ROS – Reactive Oxygen Species
SAR – Structure–Activity Relationship
TNF-α – Tumor Necrosis Factor-Alpha
UV–Vis – Ultraviolet–Visible Spectroscopy
VEGF – Vascular Endothelial Growth Factor

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