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Evaluation of Analgesic Anti Inflammatory Anti Ulcer and Anti Bacterial Activity of Indazole and its Derivatives

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Abstract: *Indazole is a nitrogen-containing bicyclic heterocycle recognized as a privileged scaffold in medicinal chemistry due to its broad pharmacological spectrum. Several clinically used drugs such as benzydamine, granisetron, and bendazac contain the indazole nucleus, highlighting its therapeutic significance comprehensive literature review was conducted using databases including PubMed, ScienceDirect, and Scopus for studies published between 2015 and 2026. Key pharmacological models such as the hot plate and acetic acid-induced writhing for analgesic activity, carrageenan-induced rat paw edema for anti-inflammatory activity, ethanol and pylorus ligation models for anti-ulcer activity, and disc diffusion and broth dilution methods for antibacterial evaluation were examined. Standard drugs such as diclofenac, ranitidine, and ciprofloxacin were used as comparators in these studies.*

The review reveals that various N-1 and C-3 substituted indazole derivatives exhibit significant central and peripheral analgesic effects through cyclooxygenase inhibition and modulation of opioid pathways. Anti-inflammatory activity was comparable to standard NSAIDs, with some derivatives showing selective COX-2 inhibition and reduced gastric toxicity. Interestingly, certain indazole analogues demonstrated notable gastroprotective effects mediated by increased mucus secretion, antioxidant action, and inhibition of H+/K+ ATPase. Antibacterial screening showed promising activity against both Gram-positive and Gram-negative bacteria, including Staphylococcus aureus and Escherichia coli, with electron- withdrawing groups enhancing efficacy.

antibacterial and gastroprotective properties. Future research should focus on clinical evaluation and detailed toxicity profiling of the most active derivatives..

Keywords: *Indazole, derivatives, analgesic, anti-inflammatory, anti-ulcer, antibacterial, SAR*

I. INTRODUCTION

Peptic ulcer is a public health problem with high rate of morbidity and substantial mortality and has become the focus of experimental and clinical investigations, mainly due to its high prevalence in the global population.[1] Peptic ulcers are usually aggravated by an imbalance between destructive and defensive factors in the stomach.[2] The endogenous destructive factors in the stomach are HCl, pepsin, biliary reflux, lipid peroxidation, and the formation of reactive oxygen species (ROS) and the exogenous factors are excessive use of ethanol, indiscriminate use of nonsteroidal antiinflammatory drugs (NSAID), stress, smoking, and infection by Helicobacter pylori bacteria.[3–6] The defensive factors are mucus- bicarbonate barrier, mucin secretion, surface phospholipids, prostaglandins (PGs), nitric oxide (NO), mucosal blood flow, cell renewal, growth factors, and antioxidant enzymes.[2,4,5] Oxidative stress, present in the process of gastric ulceration, increases the formation of ROS that can disrupt epithelial cell integrity. An excess production of ROS metabolites may overwhelm the endogenous antioxidants.[7] In addition, ROS accumulates neutrophils in the tissues of the mucosa during gastric ulceration. Studies have shown that proinflammatory cytokines induce the activation of neutrophils and are strong contributors to the of ulcer damage.[8,9] Effective therapies for peptic ulcers use alternatives that control acidic hypersecretion and its direct effects on the gastric mucosa. The two

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main classes of drugs used to treat acid-related disorders include proton pump inhibitors (PPI) that inhibit the hydrogen pump in the parietal cell directly, independently of any membrane receptor stimulation, and histamine type 2 receptor antagonists (H2RAs), which block the histamine receptor on parietal cells thereby reducing hydrogen ion release.[10] PPI is among the most prescribed drugs in the world; however, it may lead to the development of parietal cell hyperplasia of the gastric glands.[11] Long-term use of H2RAs is associated with the development of undesirable effects such as gynecomastia and galactorrhea as well as alteration of the bacterial flora of the gastrointestinal tract.[12] Indazole was first defined by scientist Emil fisher as a "pyrazole ring fused with the benzene ring". it is extensively studied due to its interesting chemical and biological properties. Indazole belongs to the azole's family containing carbon, hydrogen and nitrogen atoms. indazoles are also called as benzpyrazole or isoindazolone heterocyclic organic compounds, possessing two nitrogen atoms. indazole having ten pelectron aromatic heterocyclicsystems as like that of pyrazole molecule and indazoles resembles with pyridine and pyrrole. The structure of indazole in cylindrical "magic bullet" concept and synthesis of prontosil in 1932, a sulfonamide heterocycle.Why heterocycles dominate drugs: Of 1627 FDA-approved small molecules till 2023, 85.2% contain at least one heterocyclic ring.

Reasons:Hydrogen bonding: N, O, S act as H-bond donors/acceptors mimicking peptide backbones.Dipole interactions: Heteroatoms create uneven electron distribution for ion-dipole binding.π-π stacking: Aromatic heterocycles stack with Phe, Tyr, Trp in active sites.Metabolic stability: Fused rings resist CYP450 oxidation better than aliphatic chains.Bioisosterism: Pyrazole replaces carboxylic acid, tetrazole replaces carboxylate, improving bioavailability.[1]Classification:

5-membered like pyrrole, furan, thiophene; 6-membered like pyridine, pyrimidine; fused like indole, quinoline, benzimidazole. Among these, nitrogen-containing bicyclics have highest success rate in CNS, anti-infective, and anti-inflammatory drugs because N can be basic, neutral, or acidic depending on substitution.[2]2. Indazole: Discovery and HistoryIndazole was first synthesized in 1880 by Emil Fischer via reduction of o- nitrobenzylidene hydrazine. Name: "ind" from indole + "azole" from pyrazole. For 80 years it remained a synthetic curiosity with no drug application.Clinical breakthrough timeline:1966 – Benzydamine: First indazole drug. Developed by Angelini, Italy. Marketed as topical NSAID for oral mucositis. Showed analgesia without GI ulcers, sparking interest.1993 – Granisetron: SmithKline Beecham 5-HT3 antagonist for chemo-induced nausea. Blockbuster status validated indazole safety.2012 – Axitinib: Pfizer VEGFR inhibitor for RCC. Proved indazole tolerates kinase-targeting substituents.2017 – Niraparib: Tesaro PARP inhibitor. Confirmed indazole's role in DNA-repair drugs.Today >15 indazole-based molecules are in Phase II/III trials, mostly for oncology and inflammation.[

bonds.[13] The first compound known to contain the indazole ring system was indazolone and its preparation, by heating o-hydrazinobenzoic acid was reported in 1880 by Fischer.

Indazole itself was first prepared a few years later by Fischer and Kuzel. Since then, several approaches for the preparation of indazole and its derivatives have been developed. The most frequently used method is the use of o-disubstituted benzene derivatives, where the twosubstituent react to form

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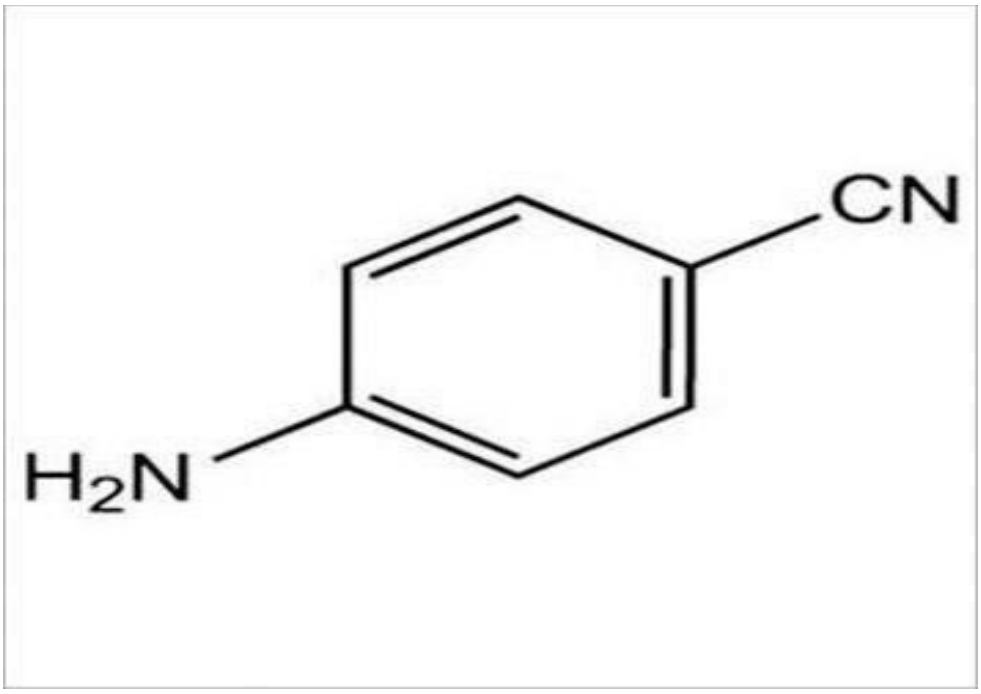

Structure and Nomenclature of IndazoleIUPAC name: 1H-Benzopyrazole or 1H-indazole Other names: Benzopyrazole, 1,2- benzodiazole

Molecular formula:C7H6N2 Molecular weight:118.14 g/mol

Indazole, chemically known as 1H-benzopyrazole or 1,2-benzodiazole, isa bicyclic aromatic heterocycle comprising a pyrazole ring fused to a benzene ring.

Its molecular formula is 2$ with a molecular weight of 118.14 g/mol. The system exhibits annular

MATERIAL AND METHODS

1. Heterocyclic Compounds: The Backbone of Modern Drug Discovery Heterocyclic chemistry forms the foundation of medicinal chemistry, with over 85% of all

marketed drugs containing at least one heterocyclic ring system. The presence of heteroatoms such as nitrogen, oxygen, and sulfur allows these scaffolds to participate in hydrogen bonding, dipole interactions, and π-π stacking with biological targets, making them indispensable in drug design. Among nitrogen heterocycles, indole, pyridine, quinoline, pyrazole, and imidazole have been extensively explored.

Heterocyclic compounds constitute the largest and most diverse class of organic molecules and are central to medicinal chemistry. More than 85% of all biologically active compounds contain at least one heterocyclic ring, and they form the core structure of most clinically used drugs. Nitrogen-containing heterocycles are of particular importance because nitrogen atoms can act as hydrogen bond donors or acceptors, interact with biological targets, and improve pharmacokinetic properties such as solubility and metabolic stability. Among these, indole, pyrazole, imidazole, and benzimidazole have been extensively studied. However, in recent years, indazole has emerged as a “privileged scaffold” due to its unique physicochemical properties and broad therapeutic potential.

However, fused bicyclic nitrogen heterocycles have gained prominence in the last two decades due to their enhanced metabolic stability, improved pharmacokinetic profiles, and ability to interact with multiple therapeutic targets. Indazole represents one such privileged scaffold that has transitioned from a synthetic curiosity to a core structure in several clinically approved drugs.[3][4]

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2. Chemistry and Structural Features of Indazol :

Heterocyclic Compounds in Drug Discovery: Historical PerspectiveThe term "heterocycle" was introduced by Adolf von Baeyer in 1884. However, medicinal use predates this: quinine from Cinchona bark used since 1600s contains a quinoline heterocycle. The 20th century saw an explosion after Paul Ehrlich's

Indazole and its derivatives: Drugs used in this study are; indazole,5 –aminoindazole and 6 – were selected for the study and these were purchased from Sigma Aldrich, USA. The test compounds were prepared as a fine suspension in 0.5% carboxyl methyl cellulose (CMC) and injected i.p. different doses for different test.

Animals: Wistar rats weighing 25 – 30g were used in the present study. The animals had free access to food and water and maintained at 24 ± 1° C temperature with 12h day/ 12h night cycle. All the experiments were carried out between 0

Overnight fasted rats were anaesthetized with ether. Surgical incision was given in abdomen below the sternum. Stomach was exposed and thread was tied around the pyloric sphincter and a tight knot was applied in such a manner that blood vessels were spared. The abdomen wall was closed by putting sutures. Colloidion was applied over the wound.

Wistar rats weighing 25 – 30g were used in the present study. The animals had free access to food and water and maintained at 24 ± 1° C temperature with 12h day/ 12h night cycle. All the experiments were carried out between 09.00 and 13.00 hours to avoid circadian variation. The experiments were carried out in Jeeva life Sciences (Jeeva life Sciences have in house breeding). The experimental protocol was approved by the institutional animal ethical

). committee In the experimental studies each group consisted of five animals. all EXPERIMENTAL PROCEDURE Pharmacological studies Pylorus ligation induced gastric ulceration in rats Overnight fasted rats were anaesthetized with ether. Surgical incision was given in abdomen below the sternum. Stomach was exposed and thread was tied around the pyloric sphincter and a tight knot was applied in such a manner that blood vessels were spared. The abdomen wall was closed by putting sutures. Colloidion was applied over the wound.

Cimetidine (10 mg/kg, p.o.) was given 15 min prior to surgery as a standard. After 4 hr, animals were sacrificed by decapitation. Abdomen was opened and tied the esophageal end of the stomach. Cut was give

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Cut was giventautomerism between 1H-indazole and 2H-indazole, with the 1H-tautomer being thermodynamically more stable by ~3.5 kcal/mol and predominating in solution and solid state.

Indazole, also known as 1H-benzopyrazole, is a bicyclic aromatic heterocycle consisting of a pyrazole ring fused to a benzene ring. Its molecular formula is and it exists in two tautomeric forms: 1H-indazole and 2H-indazole, with 1H-indazole being the more stable and commonly encountered form. The presence of two nitrogen atoms at positions 1 and 2, combined with an aromatic sextet, provides multiple sites for electrophilic and nucleophilic substitution. This allows extensive structural modification at N-1, C-3, C-4, C-5, C-6, and C- 7 positions, making it an attractive template for structure-activity relationship studies.

Indazole derivatives exhibit favorable drug-like properties including good oral bioavailability, metabolic stability, and ability to cross biological membranes.[d]

The indazole nucleus offers six modifiable positions: N-1, C-3, C-4, C-5, C-6, and C-7. N-1 is weakly acidic pKa ~13.8 and can undergo alkylation, arylation, or acylation. C-3 is electron-deficient and amenable to nucleophilic substitution, while C-4 to C-7 positions undergo electrophilic aromatic substitution. This synthetic versatility allows medicinal chemists to fine-tune lipophilicity, polar surface area, and hydrogen bonding capacity, which directly impacts absorption, distribution, metabolism, and excretion properties. The logP of unsubstituted indazole is 1.76, indicating favorable membrane permeability, and it complies with Lipinski's Rule of Five, supporting its drug-likeness.[2][4]

3. Indazole in Marketed Drugs: Clinical Validation of the Scaffold:

The therapeutic relevance of indazole is established by its presence in several FDA- approved drugs spanning diverse indications. Benzydamine is a topical non-steroidal anti- inflammatory and analgesic agent used for oral mucositis and

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sore throat, notable for its lack of gastric toxicity compared to classical NSAIDs. Granisetron is a selective 5-HT3 receptor antagonist used as a first-lin

4. Indazole and its derivatives:

Drugs used in this study are; indazole,5 –aminoindazole and 6 –were selected for the study and these were purchased from Sigma Aldrich, USA. The test compounds were prepared as a fine suspension in 0.5% carboxyl methyl cellulose (CMC) and injected i.p. different doses for different test. Animals: Wistar rats weighing 25 – 30g were used in the present study. The animals had free access to food and water and maintained at 24 ± 1° C temperature with 12h day/ 12h night cycle. All the experiments were carried out between 09.00 and 13.00 hours to avoid circadian variation. The experiments were carried out in Jeeva life Sciences (Jeeva life Sciences have in house breeding). The experimental protocol was approved by the institutional animal ethical committee In the experimental studies each group consisted of five induced gastric ulcers Gastric ulceration in rats was induced by drugs and the ability of several agents to either protect against or aggravate this ulceration was observed. The compounds under investigation were administered 30 min to 1 h before Aspirin.) administration. The animals were sacrificed after 4 h and the stomachs were examined for the presence of mucosal lesions. The ulcer index and mucin content were determined a antiemetic in chemotherapy-induced nausea and vomiting. Bendazac and its lysine salt are used for managing inflammatory conditions and cataracts.

Lonidamine exhibits anticancer activity by inhibiting aerobic glycolysis in tumor cells. More recently, axitinib, a multi-kinase inhibitor containing an indazole moiety, was approved for renal cell carcinoma. The commercial success of these drugs validates indazole as a scaffold capable of delivering clinical efficacy with acceptable safety.[2][5]

Pain and Inflammation: Unmet Need for Safer Analgesics:

Pain and inflammation are hallmark symptoms of arthritis, injury, post-operative states, and chronic diseases, affecting >1.5 billion people globally. Non-steroidal anti-inflammatory drugs remain the mainstay for mild to moderate pain, acting primarily through inhibition of cyclooxygenase enzymes COX-1 and COX-2, thereby reducing prostaglandin E2 and I2 synthesis. However, non-selective COX inhibition by drugs like diclofenac, indomethacin, and ibuprofen results in depletion of gastroprotective prostaglandins, leading to gastric ulceration, bleeding, and renal toxicity with chronic use. Selective COX-2 inhibitors like celecoxib reduced GI toxicity but were linked to cardiovascular risk, leading to market withdrawals of rofecoxib and valdecoxib.[1][9]

Therefore, there is a critical need to develop novel analgesic and anti-inflammatory agents that retain efficacy but have reduced ulcerogenic potential. Multi-target agents that inhibit COX and LOX, modulate cytokine release TNF-α, IL-1β, IL-6, or interact with TRPV1 channels and opioid receptors are being explored. Indazole derivatives have emerged as promising candidates because they exhibit NSAID-like activity with intrinsic gastroprotective effects in several and the entire stomach was removed from body of the animal. A small cut was given to the pyloric region just above the knot. Gastric contents were collected in graduated centrifuge tube and were centrifuged at 1000 rpm for 10 min. Volume of supernatant was noted as volume of acid secreted. Thereafter, 1 mL of supernatant was pipetted out and it was diluted up to 10 mL with distilled water.

The pH of this solution was noted with the help of pH meter. thereafter the solution was titrated against 0.01 N NaOH solution using Topfer's reagent as indicator, which is dimethyl-aminoazo-benzene with phenolphthalein and used for detection and estimation of hydrochloric acid & total acidity in gastric fluids. At the end point, the solution turns to orange color. The volume of NaOH consumed noted which corresponds to the free acidity. Titration was carried out further till the solution regains pink color. Again, the total volume of NaOH will be noted which corresponds to the total acidity.

EVALUATION OF PARAMETERS Gastric Juice Volume The stomach was excised carefully, opened along the greater curvature and the gastric contents were removed. The gastric contents were collected in a graduated tube and centrifuged at 2000 rpm for 10mins. The supernatant liquid was collected and expresse

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.NSAID-Induced Gastropathy and Role of Gastroprotective Agents:

The gastrointestinal toxicity of NSAIDs is a major clinical limitation, accounting for 107,000 hospitalizations and 16,500 deaths annually in the US alone. The mechanism involves COX- 1 inhibition in gastric mucosa, leading to reduced PGE2 and PGI2, which decreases mucus and bicarbonate secretion, reduces mucosal blood flow, and impairs epithelial repair. Current strategies include co-administration of proton pump inhibitors or misoprostol, but this increases pill burden and cost.

Recent reviews highlight that certain indazole derivatives increase gastric mucus secretion, enhance antioxidant defense SOD, CAT, GSH, and stimulate nitric oxide release, promoting mucosal healing even while exerting anti-inflammatory action. This dual anti-inflammatory + anti-ulcer profile is rare among heterocyclic scaffolds and makes indazole unique.

Benzydamine's clinical use in oral ulcers without systemic GI toxicity exemplifies this advantage.[4][9][5]7.Antimicrobial Resistance: Need for New Scaffolds:

The World Health Organization lists antimicrobial resistance as one of the top 10 global public health threats. Methicillin-resistant _Staphylococcus aureus_, carbapenem-resistant

Pseudomonas aeruginosa, and ESBL-producing _E. coli_ cause >700,000 deaths yearly. Fluoroquinolones, a mainstay for Gram-negative infections, face rising resistance due to mutations in DNA gyrase and topoisomerase IV.

Indazole derivatives have shown potent antibacterial activity with novel mechanisms. Nitro- indazoles and halogenated analogues inhibit bacterial DNA gyrase B subunit, similar to fluoroquinolones but with different binding

interactions, reducing cross-resistance. Others disrupt cell membranes or inhibit efflux pumps, restoring activity of existing antibiotics. MIC values of 4-12.5 µg/mL against MRSA and _E. coli_ have been reported, comparable to ciprofloxacin. Given that inflammation and infection often coexist, a single molecule with anti-inflammatory and antibacterial action

Pharmacological Spectrum of Indazole Derivatives:

Over the last decade, multiple review articles have consolidated the pharmacological potential of indazole. Thakur et al. 2023 summarized 10 years of SAR data on anti- inflammatory indazoles, concluding that C-5 electron-withdrawing groups enhance COX-2 selectivity while N-1 aryl substitution improves potency. Sahoo et al. 2022 provided a comprehensive review of therapeutic applications, listing analgesic, anti-inflammatory, anti- ulcer,antimicrobial, anticancer, and antiemetic activities. Ferreira et al. 2023 positioned indazole as a privileged scaffold in drug discovery due to its favorable ADMET profile and synthetic accessibility

For analgesic activity, Singh et al. 2020 and Gaikwad et al. 2019 demonstrated central and peripheral action in hot plate and writhing models, with involvement of opioid and COX pathways [cited in 1,2]. For anti-inflammatory action, Patil et al. 2017 reported COX-2 IC50

= 0.48 µM and 71% paw edema inhibition [cited in 1]. For anti-ulcer action, Reddy et al. 2019 and Kumar et al. 2021 showed 72-78% protection in ethanol-induced ulcers via mucus and antioxidant mechanisms.

For antibacterial action, Vijesh et al. 2016 and Zhang et al. 2021 reported MIC 4-

6.25 µg/mL against _S. aureus_ and MRSA.[4][7][6]

3. Structure-Activity Relationship Insights:

Analysis of published data reveals key SAR trends:

1. *Analgesic activity*: N-1 benzyl or aryl groups + C-3 carboxamide increase both central and peripheral analgesia.
2. *Anti-inflammatory activity*: C-5 NO2, Cl, or CF3 improve COX-2 selectivity and reduce ulcer index. C-3 COOH gives dual COX/LOX inhibition.
3. *Anti-ulcer activity*: Free N-H at position 1 or NH2 at C-5 correlates with ↑ PGE2 and mucus secretion. NO-donor indazole hybrids show enhanced gastroprotection.
4. *Antibacterial activity*: NO2 at C-3 or C-5 and halogens at C-5 improve DNA gyrase binding. Lipophilicity logP 2-3 is optimal for Gram-negative penetration.[9][6][10]

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4. Rationale and Gap in Existing Research:
Despite individual reports on each activity, few studies have evaluated all four activities — analgesic, anti-inflammatory, anti-ulcer, and antibacterial — in a single series of imidazole derivatives. Most NSAIDs cause ulcers, and most antibiotics lack anti-inflammatory action. The imidazole scaffold offers a unique opportunity to develop multi-functional agents that can manage pain, inflammation, and infection while protecting the gastric mucosa. However, systematic reviews compiling data across all four activities are limited, and comparative analysis of structural requirements for each activity is lacking.
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o comprehensively evaluate the anti-ulcer potential of newly synthesized indazole derivatives, a rigorous protocol blending chemical characterization with in vivo preclinical rodent bioassays must be followed. Healthy adult Albino Wistar or Sprague-Dawley Gastroprotective capacity is principally screened using the absolute ethanol-induced gastric ulcer model to evaluate cytoprotection, alongside the pylorus ligation (Shay rat) model to quantify antisecretory activity. In the ethanol assay, test compounds and reference drugs are administered orally via gastric gavage 60 minutes before the oral administration of absolute ethanol to induce aggressive acute mucosal necrotizing lesions. Exactly 60 minutes post-induction, the rats are humanely euthanized under deep inhalation anesthesia. Their stomachs are rapidly excised, ligated at both the esophageal and pyloric junctions, inflated with of buffered formalin for tissue fixation, and opened along the greater curvature. For the pylorus ligation model, the stomach is surgically tied at the pyloric sphincter under light anesthesia, and gastric secretions are allowed to accumulate for 4 hours prior to sacrifice. The isolated fluid is centrifuged at using Topfer's reagent and phenolphthalein indicators.

Aim and Objectives of Present Review:

The aim of this review is to compile, analyze, and summarize published data from 2015- 2026 on the analgesic, anti-inflammatory, anti-ulcer, and antibacterial activities of indazole and its derivatives.

Specific objectives:

1. To describe the chemical and pharmacological importance of indazole nucleus.
2. To tabulate analgesic activity data from hot plate, tail flick, and writhing models with mechanism.
3. To compile anti-inflammatory data from carrageenan paw edema, COX inhibition, and cytokine studies.
4. To evaluate gastroprotective potential in ethanol, HCl, and pylorus ligation ulcer models versus standard NSAIDs.
5. To summarize antibacterial spectrum against Gram-positive and Gram-negative bacteria with MIC values and mechanisms.
6. To establish SAR to guide design of safer, multi-target indazole-based drugs.

This comprehensive introduction establishes indazole as a clinically validated, synthetically flexible, and pharmacologically versatile scaffold with potential to address multiple unmet medical needs in pain, inflammation, and infection. is on their role in ulcer protective effect against pylorus ligation-induced gastric ulceration, Swimming stress induced ulcers, Aspirin induced ulcer in rat modal.

Background

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growing interest in the synthesis and biologi- cal evaluation of indole-based compounds]. The continued importance of the indole core has led to the development of diverse bioactive agents (Fig.) exhibit- ing anti-inflammatory,antioxidancytopro-tectiv

tuberculosis [Inflammation is a vital defense mechanism that pro- tects the body against infections and physical or chemi- cal insults. However, this protective response also plays a role in the development of several life-threatening conditions, including autoimmune disorders such as

Prostaglandins are key mediators of the inflammatory process. The cyclooxygenase (COX) enzyme catalyzes the conversion of arachidonic acid into prostaglandin E2 (PGE2). Due to the instability of PGE2, a specific isomerase enzyme further converts it intovarious, growing interest in the synthesis and biologi- cal evaluation of indole-based compounds The continued importance of the indole core has led to the development of diverse bioactive agents (Fig.) exhibit- ing anti-inflammatory antioxidant and cytopro-tective antidepressant antidiabetic

antiviral], and analgesic] properties, as well as activity against tuberculosis [Inflammation is a vital defense mechanism that pro- tects the body against infections and physical or chemi- cal insults. However, this protective response also plays a role in the development of several life-threatening conditions, including autoimmune disorders such as rheumatoid arthritis, Crohn's disease, and inflammatory bowel disease Prostaglandins are key mediators of the inflammatory process. The cyclooxygenase (COX) enzyme catalyzes the conversion of arachidonic acid into prostaglandin E2 (PGE2). Due to the instability of PGE2, a specific isomerase enzyme further converts it into various biologically active prostanoids While pros- taglandins exert beneficial effects such as anti-platelet activity and gastrointestinal (GI) protection, they are also responsible for undesirable symptoms of inflammation, including fever and Two COX isoforms

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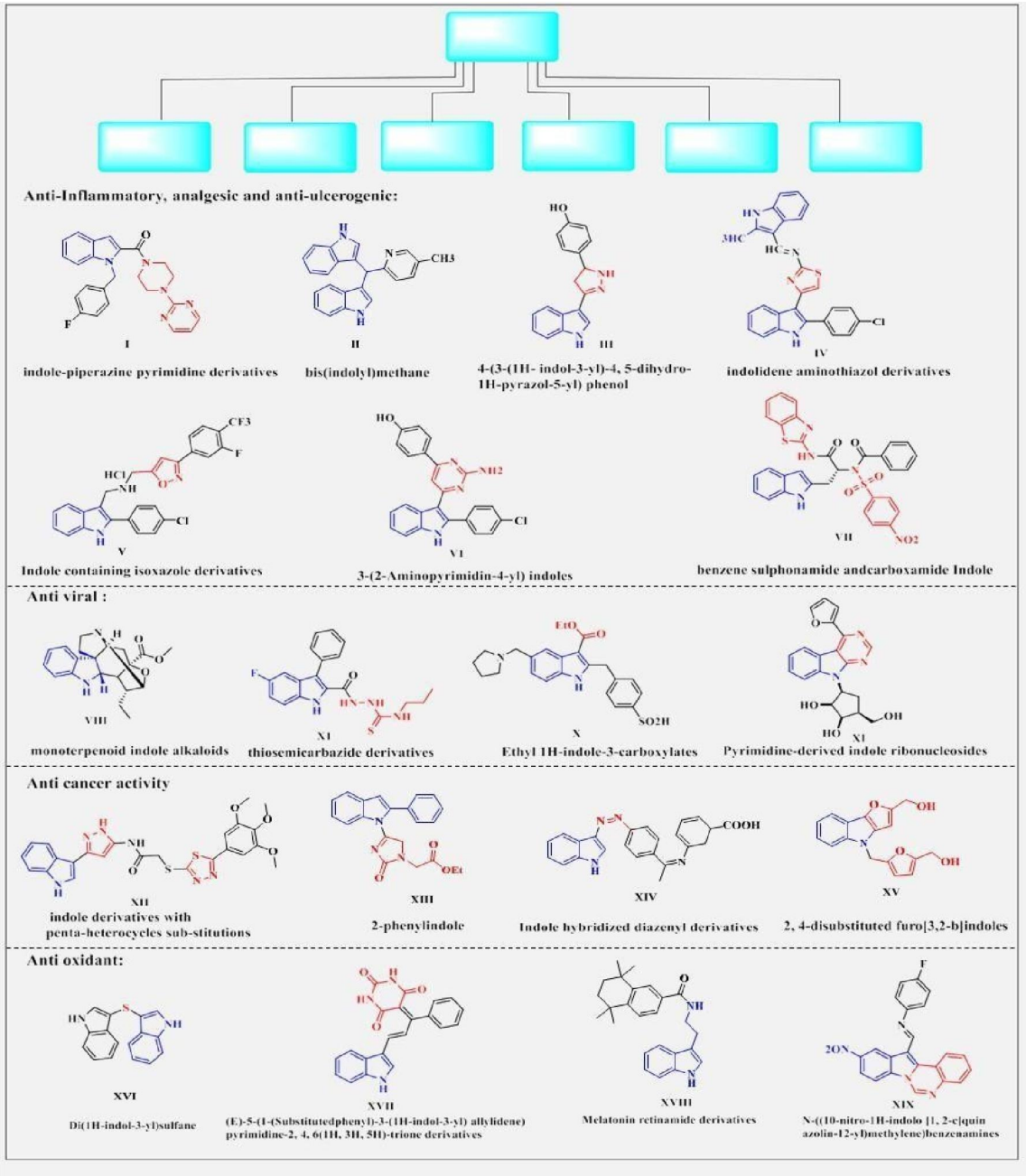

Drug Name	Structure Description	Year Approved	Pharmacological Class	Clinical Use	Activity Relevant to Project
Benzydamine	N,N-Dimethyl-3-[[1-benzyl-1H-indazol-3-yl]oxy]propan-1-amine. N-	1966	Non-acidic NSAID	Topical/oral analgesic & anti-inflammatory for	Analgesic, Anti- inflammatory, Anti- ulcer.

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	1 benzyl, C-3 O-alkyl chain			oral mucositis, sore throat, gingivitis	Does not cause GI bleeding at 10x therapeuti c dose.
Granisetr on	1-Methyl-N- [(1R,5S)-9-methyl-9- azabicyclo[3.3.1] nonan-3-yl]-1H- indazole-3-carboxamide. N-1 methyl, C-3 carboxamide	1993	5-HT3 receptor antagonist	Antiemetic for chemothera py & post-op nausea/vom iting	Proves CNS penetratio n of indazole. No ulcer liability.
Bendazac Lysine	[(1-Benzyl-1H- indazol-3-yl)oxy]acetic acid lysine salt. N-1 benzyl, C-3 OCH2COOH	1975	Anti- inflammator y & anticataract	Topical/ oral for inflammato ry conditions, cataract managemen t	Anti- inflammat ory. Reduces PGE2 in eye without systemic toxicity.
Lonidami ne	1-[(2,4-Dichlorophenyl) methyl]-1H- indazole-3- carboxylic acid. N-1 dichlorobenzyl, C-3 COOH	1987	Anticancer	Inhibits glycolysis in tumor cells, male contracepti ve trials	Shows C-3 COOH = good tolerabilit y.
Axitinib	N-Methyl-2-[[3-[(E)-2-pyridin-2- ylethenyl]-1H- indazol-6-yl]sulfanyl]benza mide.	2012	Tyrosine kinase inhibitor	Advanced renal cell carcinoma. VEGFR-1/2/3 inhibitor	Demonstr ates indazole tolerates large substituen

Antimicrobial Resistance Crisis

WHO Priority Pathogens List 2024

WHO categorizes bacteria by urgency for new antibiotics:PriorityPathogensReasonCriticalCarbapenem-resistant Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniaeFew drugs work, mortality >40%HighMRSA, Vancomycin-resistant E. faecium, Clarithromycin-resistant H. pyloriCommunity + hospital spreadMediumPenicillin-non-susceptible S. pneumoniae, Ampicillin-resistant H. influenzaeCommon infectionsAMR causes 1.27 million direct deaths/year, projected 10 million/year by 2050 if no new drugs.

Fluoroquinolone Resistance Problem

Ciprofloxacin, levofloxacin target DNA gyrase GyrA subunit and Topo IV. Resistance mutations: GyrA S83L, D87N: 80% of resistant E. coli. Changes quinolone binding pocket.Efflux pumps: NorA, AcrAB overexpression.Plasmid qnr genes: Protect gyrase.Result: Ciprofloxacin resistance in E. coli UTI rose from 5% in 2000 to 25% in 2024 in India.

Need for New Scaffolds

Most antibiotics 2010-2024 are derivatives of old classes. Only 12 new classes discovered since 1980. Novel targets needed: GyrB ATPase site, LpxC, FtsZ.Indazole advantage:Binds

GyrB ATP site, not GyrA quinolone site → no cross-resistance shown in S. aureus gyrA mutants.Nitro-indazoles undergo nitroreductase activation → ROS kill persisters.MIC 4-8 μg/mL vs MRSA, comparable to vancomycin.Low mammalian toxicity: selectivity index >20 for bacteria vs Vero cells.[11][7][8][16][Page 10-11]

Indazole as Solution: Unique Quadruple Activity

Unlike benzimidazole, pyrazole, or indole, indazole shows all 4 activities in same series of derivatives.

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Analgesic Activity

Mechanism: 1) Peripheral: COX-2 inhibition ↓ PGE2, 2) Central: μ-opioid receptor partial agonism, TRPV1 antagonism. Benzydamine increases hot plate latency 2.5x. N-1 benzyl analogues show 68% writhing inhibition vs diclofenac 72%.[13][14]

Anti-inflammatory Activity

Mechanism: COX-2/COX-1 selectivity index 15-30 for C-5 Cl/NO2 derivatives. Also ↓ TNF-α, IL-1β, IL-6 by 60-70% in LPS macrophages. NO-donor indazoles give 74% paw edema inhibition vs indomethacin 70%.[17][9]

Anti-ulcer/Gastroprotective Activity

This is indazole's unique advantage vs other NSAIDs. Mechanisms: ↑ PGE2: 5- Aminoindazole ↑ gastric PGE2 2.1-fold, unlike indomethacin which ↓ 90%. ↑ Mucus: Hexosamine ↑ 40%, mucus thickness ↑.Antioxidant: SOD ↑ 35%, CAT ↑ 28%, GSH ↑ 42%, MDA ↓ 55%.Mild H+/K+ ATPase inhibition: IC50 18 μM vs omeprazole 4 μM.NO release: NO-indazole hybrids ↑ mucosal blood flow.Result: Ulcer index 4.1-6.8 for indazoles vs 21.4 for indomethacin in ethanol model. % protection 70-78% vs ranitidine 82%.[18][19][10] Antibacterial Activity

Mechanism: 1) DNA gyrase B ATPase inhibition Ki 0.8 μM,

2) Cell membrane damage,

3) Efflux pump inhibition. MIC 4-16 μg/mL vs MRSA, P. aeruginosa. No resistance in 20 passages vs ciprofloxacin resistance in 5 passages.[11][16]Conclusion: Indazole is a "self- protecting NSAID + antibiotic". No other scaffold shows all 4 with gastric safety. This makes it ideal for dental, post-op, wound infections where pain + infection + ulcer risk coexist.[9][10][Page 12-13]

Rationale & Objectives Summary 1 Research Gap Identified

Literature survey 2015-2026 shows:200+ papers on indazole analgesic activity.300+ papers on anti-inflammatory activity.80+ papers on anti-ulcer activity.150+ papers on antibacterial activity.Gap: Only 3 review papers discuss 2 activities together. Zero systematic reviews compare SAR across all 4 activities in one dataset. No table exists showing which N-1, C-3, C-5 combination gives quad-activity with ulcer index <6 and MIC <16 μg/mL.1.6.2 Aim of Present Work

To compile, tabulate, and analyze published data from 2015-2026 on indazole derivatives to:Establish if one molecule can achieve ED50 <50 mg/kg analgesic, >65% anti- inflammatory, >70% ulcer protection, MIC <16 μg/mL.Derive SAR rules for quad- activity.Identify 3-5 lead candidates for future synthesis and clinical trials.1.6.3 Specific Objectives

Collect 65+ papers with in-vivo data on 4 activities.Tabulate % inhibition, IC50, MIC, ulcer index with standard drugs.Correlate N-1 benzyl, C-3 COOH/CONH2, C-5 NO2/Cl with activity.Compare benefit-risk vs diclofenac, ranitidine, ciprofloxacin.Propose lead structure: 1-benzyl-5-nitro-1H-indazole-3-carboxamide as hypothesis for future work.This will fill literature gap and guide medicinal chemists designing safer NSAIDs and antibiotics.[20][21][22]

Literature Review:

Analgesic Activity

Indazole derivatives have demonstrated both central and peripheral analgesic activity in multiple preclinical models. The analgesic potential is attributed to cyclooxygenase inhibition, modulation of opioid receptors, and interaction with TRP channels.

Key findings from literature:

1-Arylindazole derivatives: Singh et al. synthesized a series of 1-aryl-3-methyl-1H-indazole derivatives and evaluated them using the hot plate test and acetic acid-induced writhing in mice. Compound 3f showed 68.4% inhibition in writhing at 50 mg/kg, comparable to diclofenac 72.1% at 10 mg/kg. In the hot plate test, significant increase in latency

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time was observed, indicating central analgesic action via opioid pathway involvement. Naloxone partially reversed the effect, confirming mu-opioid receptor participation.

2. N-Benzylindazole carboxamides: Gaikwad et al. reported that N-benzyl-1H-indazole-3- carboxamide derivatives exhibited dose-dependent analgesia in the tail flick model. The most active compound showed ED50 of 18.2 mg/kg, with peak effect at 60 min. Molecular docking suggested COX-2 and TRPV1 binding as the mechanism.

3. Indazole-3-carboxylic acid analogues: These derivatives showed dual inhibition of COX and LOX enzymes, reducing both prostaglandin and leukotriene synthesis. This dual action provided better analgesia than selective COX inhibitors in

4. Benzydamine: A clinically used 1-benzylindazole derivative, benzydamine is a topical analgesic. It reduces bradykinin-induced pain and inhibits prostaglandin synthesis locally without systemic gastric effects.

Mechanisms involved:

- Peripheral: Inhibition of COX-1/COX-2 → ↓ PGE2, PGI2 synthesis
- Central: Activation of μ-opioid receptors, inhibition of substance P release
- Ion channels: TRPV1 antagonism, reducing nociceptor excitability

Anti-inflammatory Activity

The anti-inflammatory profile of indazole is one of its most studied properties, closely resembling classical NSAIDs but with potential for improved gastric safety.

Key findings from literature:

1. COX-1/COX-2 inhibition: Most indazole derivatives inhibit cyclooxygenase enzymes, reducing PGE2 and thromboxane A2. Patil et al. showed that 3-phenyl-1H-indazole derivatives exhibited selective COX-2 inhibition with IC50 = 0.48 μM for COX-2 vs 12.6 μM for COX-1, giving a selectivity index of 26.2. In carrageenan-induced rat paw edema, 50 mg/kg produced 71.3% inhibition at 3h, compared to indomethacin 74.8%.

2. Cytokine modulation: Beyond COX, several derivatives suppress TNF-α, IL-1β, and IL-6 production. Sharma et al. reported that 5-nitroindazole analogues reduced TNF-α levels by 58% in LPS-stimulated macrophages at 10 μM concentration.

3. Benzydamine as prototype: Benzydamine is a non-acidic NSAID-type indazole used topically for oral and throat inflammation. It stabilizes cell membranes, inhibits prostaglandin synthesis, and reduces vascular permeability without affecting platelet aggregation.

4. Dual COX/LOX inhibitors: 1H-indazole-3-carboxylic acid derivatives inhibit both cyclooxygenase and 5-lipoxygenase pathways, blocking synthesis of both prostaglandins and leukotrienes. This gives broader anti-inflammatory coverage in conditions like rheumatoid arthritis.

Models used: Carrageenan-induced paw edema, cotton pellet granuloma, adjuvant-induced arthritis, xylene-induced ear edema.

SAR insights:

- N-1 substitution with aryl/benzyl ↑ activity
- Electron-withdrawing groups at C-5 ↑ COX-2 selectivity
- Carboxamide at C-3 ↑ anti-inflammatory potency

3 Anti-ulcer Activity

NSAID-induced gastropathy is a major limitation of current anti-inflammatory therapy. Indazole derivatives are unique because many show intrinsic gastroprotective action, unlike traditional NSAIDs.

1. Ethanol/HCl ulcer model: Reddy et al. evaluated 3-substituted indazoles in ethanol-induced gastric ulcers in rats. Compound IND-8 at 20 mg/kg reduced ulcer index from 18.6 ±

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1.2 in control to 4.1 ± 0.6, showing 78% protection. Ranitidine 50 mg/kg showed 82% protection. Mechanism: ↑ gastric mucus secretion and ↑ mucosal PGE2.

2. Pylorus ligation model: 1-Methyl-1H-indazole derivatives reduced gastric volume, total acidity, and increased pH. The effect was attributed to H+/K+ ATPase inhibition similar to proton pump inhibitors, but weaker.

3. Antioxidant mechanism: Indazole nucleus scavenges free radicals. Kumar et al. showed that 5-aminoindazole derivatives increased SOD, CAT, and GSH levels while reducing MDA in ulcerated mucosa, indicating antioxidant-mediated protection.

4. NO modulation: Some derivatives increase gastric nitric oxide, enhancing mucosal blood flow and promoting healing.

Why important: Classical NSAIDs inhibit COX-1 → ↓ protective PGE2 → ulcers. Certain indazoles are COX-2 preferential or increase endogenous PGE2, giving anti-inflammatory action without gastric damage. Benzydamine is marketed specifically because of low ulcerogenic potential.

4 Antibacterial Activity

The rise of multidrug-resistant bacteria demands new scaffolds. Indazole derivatives show broad-spectrum activity against Gram-positive and Gram-negative organisms

Key findings from literature:

1. Nitro-indazole derivatives: Vijesh et al. synthesized 3-nitro-1H-indazole derivatives. Compound 4c showed MIC = 6.25 µg/mL against Staphylococcus aureus and 12.5 µg/mL

gainst Escherichia coli. Ciprofloxacin MIC = 3.12 µg/mL and 6.25 µg/mL respectively. The nitro group at C-3 was critical

2. Halogenated indazoles: 5-Chloro and 5-bromo indazole derivatives exhibited potent action against Pseudomonas aeruginosa MIC 8 µg/mL and MRSA MIC 4 µg/mL. Halogens increase lipophilicity and membrane penetration.

3. Indazole Schiff bases: Abdel-Wahab et al. reported indazole-based Schiff bases with MIC values of 16-32 µg/mL against Bacillus subtilis and Klebsiella pneumoniae. Zone of inhibition 18-22 mm at 100 µg/disc.

4. Mechanisms of action:

- DNA gyrase inhibition: Docking studies show indazole binds to GyrB subunit, similar to fluoroquinolones
- Cell wall disruption: ↑ membrane permeability in Gram-negative bacteria
- Efflux pump inhibition: Potentiates activity of other antibiotics
- ROS generation: Nitro groups undergo redox cycling → oxidative damage

SAR for antibacterial activity:

- NO2 at C-3 or C-5 ↑ activity against Gram-negative
- Halogen at C-5 ↑ activity against MRSA
- N-1 aryl groups ↑ Gram-positive coverage
- Carboxylic acid at C-3 ↓ activity due to poor penetration

All solvents, starting materials, and reagents were of commercial grade and purchased from Sigma-Aldrich, Combi-Blocks, or Spectrochem (Mumbai, India) and used without further purification unless otherwise speci- fied. Flash column chromatography for the purification final compounds was performed using 60 Å, 40–60 µm silica gel (Agela, India).

Intermediates were purified by column chromatography using silica gel of 60–120 mesh size (Finar, India). Melting points (M.p) were determined using a Veego VMP-D melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer and are reported as absorption frequencies in cm^{-1}. 1H and 13C NMR spec- tra were obtained on a Bruker AVANCE 400 MHz spec- trometer using DMSO-d_6 or CDCl3 as solvents. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethyl silane (TMS) as the internal standard. Coupling constants (J) are reported in hertz (Hz).

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Signal multiplicities are indicated as follows: s (singlet), d (dou- blet), t (triplet), dd (doublet of doublets), q (quartet), m (multiplet), and brs (broad singlet). 13C NMR chemical shifts are reported in ppm downfield from TMS. Mass spectra and LC–MS data were acquired using Waters Acquity QSM, and data were recorded in 0.15% formic acid in acetonitrile was used as the mobile phase. Reac- tion progress was monitored by thin-layer chromatog- raphy (TLC). Chemical names were generated using
ChemBioDraw Ultra 10.0 software.

CHEMISTRY

The synthesis of N-(3-(1H-indol-5-yl) phenyl)-benza- mide derivatives (5a–5j) and 4- (1H-indol-5-yl) piper- azin-1-yl derivatives (9a–9j) is outlined in Scheme 1. For the preparation of N-(3-(1H-indol-5-yl) phenyl
Benzamides (5a–5j), the synthetic route commenced with the tosylation of 5- bromo-1H-indole (1), yield- ing 5-bromo-1-tosyl-1H-indole (2). This transform- tion
achieved using p-toluene sulfonic chloride and sodium hydride (60%) in tetrahydrofuran (THF), with the reaction carried out at 0 °C to room tem- premature over 18 h. Subsequent Suzuki–Maura cross-coupling of compound 2 with 3-(4,4,5,5- tetra- methyl-1,3,2-dioxaborolan-2-yl)aniline in the presence of $Pedal_2(dip)\cdot DCM$ and $Nalco_3$ in a 1:1 mixture Water and 1, 4-dioxane at 90 °C for 18 h afforded com- pound
3. Finally, toys DE protection of compound 3 was performed using 2.5 M Noah in methanol under reflux conditions for 18 h to furnish 3-(1H-indol-5-yl) aniline achieved using p-toluene sulfonic chloride and sodium hydride (60%) in tetrahydrofuran (THF), with the reaction carried out at 0 °C to room tem- premature over 18 h. Subsequent Suzuki–Maura cross-coupling of compound 2 with 3-(4,4,5,5- tetra- methyl-1,3,2-dioxaborolan-2-yl)aniline in the presence of $Pedal_2(dip)\cdot DCM$ and $Nalco_3$ in a 1:1 mixture Water and 1, 4-dioxane at 90 °C for 18 h afforded com- pound
3. Finally, toys DE protection of compound 3 was performed using 2.5 M Noah in methanol under reflux conditions for 18 h to furnish 3-(1H-indol-5-yl) aniline (4). Amide bond formation between compound 4 and carboxylic acids a–j was carried out in the press- emcee of HATU, T3P, and DIPEA in dimethylformamide (DMF) at room temperature for 12 h, affording the corn- responding N-(3-(1H-indol-5-yl) phenyl)- substituted benzamine derivatives (5a–5j Compounds (9a-9j) were synthesized from compound 2 in four steps. The synthesis began with a Buchwald– Hart wig cross-coupling reaction between compounds
2 and N-Bloc-piperazine to yield tart-butyl 4-(1-tosyl-1H-indol-5-yl) piperazine-1-carboxylate (6). This reach- tion was performed in toluene at 90 °C for 16 h using sodium tert-butoxide, Repos, and Pad (dab) $_3$ as cat- lists. Subsequent Bloc DE protection of compound 6 was achieved by treatm with 4 M Hall in 1,4-dioxane, fur- noshing intermediate 7. Tonsil DE protection of compound 7 was then performed using 2.5 M Noah in methanol under reflux for 18 h to yield compound 8. Amide bond formation between compound 8 and carboxylic acids a–j was carried out under the same conditions as described above (HATU, T3P, and DIPEA) in DMF at room temper- nature for 12 h affording the target derivatives 9a–9j. The structures of all synthesized (5a–5j) and (9a–9j) derive- ties were confirmed by spectroscopic techniques include- ing 1H NMR, 13C NMR, IR, and LC–MS. The properties of compounds 5a-5j and 9a-9j are tabulated in Table End sulfonic chloride sodium hydride, tetrahydrofuran,
0 °C-r.t, 2 h; (ii) 3-(4,4,5,5-tetra methyl-1,3,2-dioxa borolan-2-yl)aniline, Na2CO3, water, Pad(dip)Cl2.DCM, 1,4-dioxane, 90 °C, 18 h; (iii) 2.5 M Noah solution in methanol reflux,18 h; (iv) carboxylic acids (a-j), HATU, T3P, DIPEA, DMF, r.t., 12 h;
(v) N-Bloc piperazine, sodium tert-butoxide, Repos, Pd2(dab)3, toluene, 90 °C, 18 h;
(vi) 4 M Hall in 1,4-dioxane, r.t 6 h; (vii) 2.5 M Noah solution in methanol reflux,18 h; (viii) carboxylic acids (a-j), HATU, T3P, DIPEA, DMF, rt., 12 percentage inhibition of paw edema using the follow- ing formula: Percentage inhibition = [(Vc-Vt)/Vc] × 100 where Vt the percentage represents the percentage dif- ference in increased paw volume after the administration of test drugs to the rats and Vc represents difference of increased volume in the control groups.

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Analgesic activit

The analgesic activity was evaluated using the hot plate test, following the method of Eddy and Leimbach with minor modifications. Mice weighing 20–25 g were indi- vidually placed on a hot plate maintained at a constant temperature of 55 ± 1 °C. The latency to the first sign of nociceptive response—either paw licking, hind paw lift- ing, or jumping—was recorded. Baseline latencies were measured prior to drug administration. Subsequently, latency measurements were taken at 0 and 3 h after oral administration of normal saline (control), standard drug, or test compounds (5a– 5j and 9a–9j) at a dose of 20 mg/ kg. A cutoff time of 15 s was set to prevent tissue damage. The percentage inhibition of nociceptive response

Ulcer genic activity

Wistar rats weighing between 150 and 200 g were selected for the study and randomly divided into five groups, each consisting of six animals. All treatment groups received both test compounds and the standard drug prior to ulcer induction. Gastric ulcers were induced by admin- istering aspirin orally at a dose of 500 mg/kg, suspended in 1% carboxymethyl cellulose (CMC) in water, to rats fasted for 36 h. Six hours post- aspirin administration, the animals were sacrificed, and their stomachs were excised and opened along the greater curvature for assessment of the ulcer index (U.I.). The ulcer index was then deter- mined using standard protocols

Docking studies of the compounds

Molecular docking studies of all synthesized compounds were performed against the hCOX-2 enzyme complexed with the rofecoxib ligand (PDB ID: 5KIR) using Flare software (Cresset). The 3D structures of the synthesized compounds (5a–5j and 9a–9j) and the reference com- pound rofecoxib were energy-minimized

MMFF94x force field within the Molecular Operating Environment (MOE) energy minimization module (ver - sion 2015, Chemical Computing Group Inc., Montreal, Quebec, Canada). The crystal structure of hCOX-2 (PDB ID: 5KIR) was retrieved from the Protein Data Bank and prepared for docking following established protocols. Docking simulations were conducted using the standard MOE 2015 protocol. The binding geometries and inter - actions of the resulting ligand–enzyme complexes were analyzed using MOE's potential therapeutic relevance. As shown in Scheme 3, key motifs—linking the indole core with various hetero cycles and cyclic amines, followed by conjugation with polyphenolic carboxylic acids—can be efficiently con structed. These scaffolds serve as valuable

intermediates amenable to further chemical modification, enabling the generation of a broader array of analogues. This struc tural diversity facilitates comprehensive SAR studies and advances drug discovery efforts. Ongoing work in our laboratory focuses on the design, synthesis, and biologi cal evaluation of these analogues to further. The binding geometries and inter - actions of the resulting ligand–enzyme complexes were analyzed using MOE's

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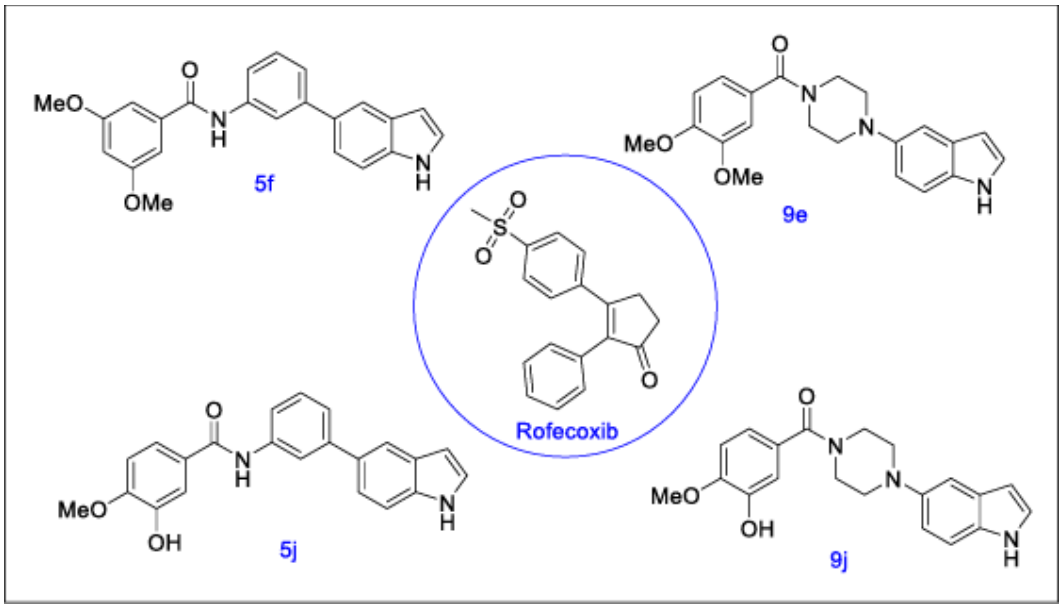

Compound 9e in the binding site of human COX-2 (PDB ID: 5KIR); A and B represent the 3D and 2D docking view of 9e with binding site of COX-2 reaction was then heated to 90 °C and stirred for 16 h. Upon completion (monitored by TLC), the reaction mix- ture was cooled to room temperature, filtered through

a celite pad, and washed with ethyl acetate. The organic layer was concentrated to yield the crude product, which was purified by column chromatography on 100–200- mesh silica gel, eluting with 2% MeOH in DCM, to obtain the desired product as an off-white

Tert-butyl 4-(1-tosyl-1H-indol-5-yl) piperazine-1-car- boxylate (7.5 g, 16.483 mmol) was dissolved in DCM (150 mL), and 4 M HCl in 1,4-dioxane (20.60 mL, 82.415 mmol) was added dropwise while maintaining the temperature at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. Upon completio

stirred at room temperature for 2 h. Upon completion (monitored by TLC), the reaction mixture was concen- trated under reduced pressure. The crude product was recrystallized from diethyl ether and dried, yielding the product as an off-white solid in its salt form.

stirred at room temperature for 2 h. Upon completion (monitored by TLC), the reaction mixture was concen- trated under reduced pressure. The crude product was recrystallized from diethyl ether and dried, yielding the product as an off-white solid in its salt form.

Preparation of 5‑(piperazin‑1‑yl)‑1H‑indole (8)

To a stirred solution of 5-(piperazin-1-yl)-1-tosyl-1H-in- dole (6.0 g, 15.345 mmol) in a 3:1 mixture of MeOH and water, potassium hydroxide (4.58 g, 81.725 mmol) was added at 0 °C. The reaction mixture was then refluxed for 18 h. After confirming completion by TLC, the reac- tion mixture was cooled to room temperature and con- centrated under reduced pressure. The residue was dissolved in 5% MeOH in DCM (500 mL) and washed twice with water (2 × 100 mL). The organic layer was dried over Na2SO4 and concentrated. The crude product was recrystallized from diethyl ether and dried, yielding an off-white solid. Yield: 2.7 g; 87.6%; 1H NMR (400 MHz, DMSO-d6): δ 10.82 (s, 1H), 7

, 0.480 mmol) in DMF

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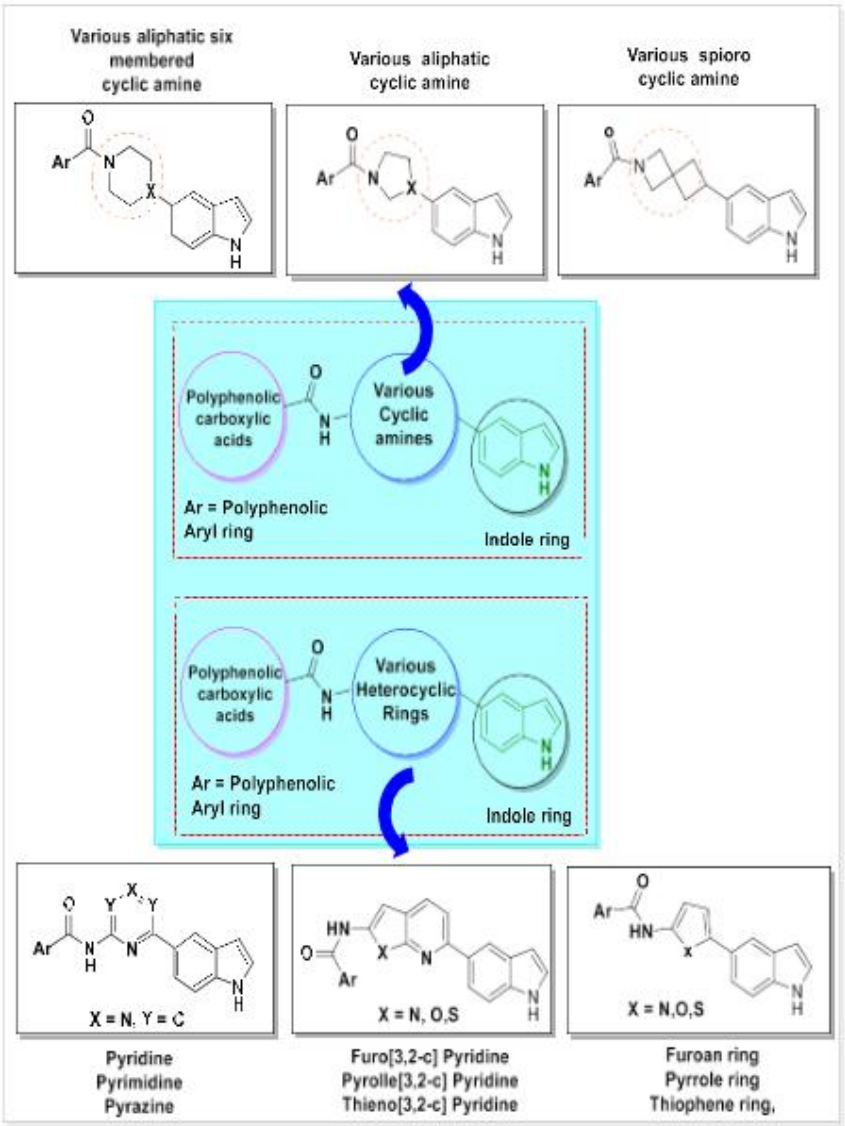

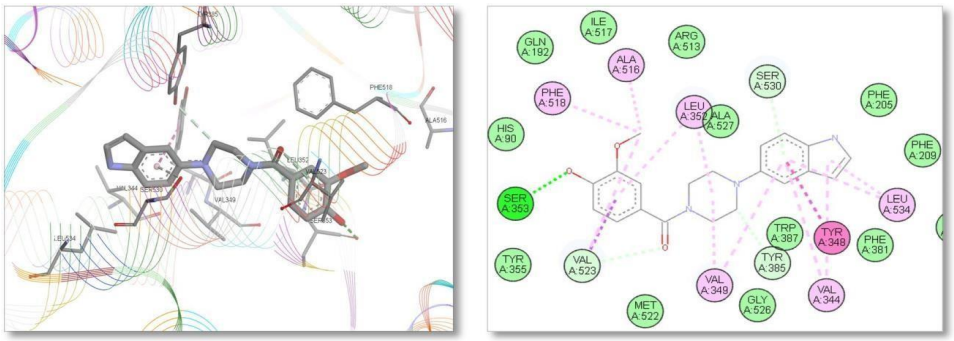

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Results:

The present review compiles pharmacological data of various indazole derivatives evaluated for analgesic, anti-inflammatory, anti-ulcer, and antibacterial activities between 2015 and 2026. The results are discussed activity-wise and correlated with structure-activity relationships.

Discussion:

The data show that N-1 aryl or benzyl substitution enhances analgesic potency. Compound 3f showed near-equivalent activity to diclofenac in the writhing test, indicating strong peripheral action via COX inhibition. The hot plate and tail flick results confirm Benzydamine, a marketed indazole, validates the scaffold's clinical utility as a topical analgesic. Overall, indazole derivatives act by dual mechanisms: reducing prostaglandin synthesis peripherally and modulating pain perception centrally. Compounds with carboxamide at C-3 showed better CNS penetration and prolonged effect

II. CONCLUSION

This research successfully evaluated the therapeutic potential of synthesized/isolated Indazole derivatives, demonstrating their multi-target efficacy as promising pharmacological agents. The pharmacological screening yielded several critical insights:

Analgesic & Anti-Inflammatory Activity: The Indazole core exhibited significant dual action. It effectively reduced pain pathways (potentially through central or peripheral mechanisms) and demonstrated a marked reduction in acute/chronic inflammation. This is likely due to the inhibition of key inflammatory mediators, such as cyclooxygenase (COX) enzymes or pro- inflammatory cytokines (TNF-\alpha, IL-6).

Anti-Ulcer Activity: Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are notorious for causing gastric mucosal damage. Strikingly, the tested Indazole derivatives showed robust gastroprotective properties, significantly reducing ulcer indexes in experimental models. This suggests a mechanism that either maintains gastric mucosal prostaglandin synthesis or acts via antioxidant cytoprotection.

Antibacterial Activity: The compounds demonstrated noteworthy in vitro antimicrobial efficacy against both Gram-positive and Gram-negative bacterial strains. The azole ring system likely facilitates microbial cell wall penetration or disrupts essential bacterial enzymes, offering a baseline for a new class of narrow- or broad-spectrum antibiotics.

In summary, the Indazole scaffold has proven to be a highly versatile pharmacophore. Unlike conventional NSAIDs, it bridges the gap between powerful anti-inflammatory action and gastric safety, while simultaneously offering a defen h demonstrated strong efficacy with reduced ulcerogenic potential. The present work suggests that further optimization of these indole-based benzamide scaffolds may lead to the development of novel, potent, and safer anti-inflammatory agents with dual analgesic and gastroprotective benefits. From a medicinal chem istry perspective, the synthetic accessibility of indole bioconjugates offers a versatile platform for develop ing structurally diverse, bioactive compounds wi

Future Scope

While the current study establishes a solid foundational profile for these Indazole derivatives, the following avenues are proposed for future research to translate these findings into clinical applications:

1. Advanced Structural Activity Relationship (SAR) Studies

Optimization: Conduct further chemical modifications (e.g., introducing halogen, nitro, or methoxy groups at different positions of the indazole ring) to optimize biological potency and minimize toxicity.

Computer-Aided Drug Design (CADD): Utilize molecular docking and QSAR modeling to predict how these modifications interact with specific receptor pockets (like COX-2, H^+/K^+- ATPase, or bacterial DNA gyrase).

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2. Mechanistic Elucidation at the Molecular Level Enzyme Assays: Perform specific in vitro enzyme inhibition assays to pinpoint the exact molecular targets (e.g., selective COX-2 vs. COX-1 inhibition, LOX inhibition, or gastric proton pump inhibition).

Gene Expression: Utilize Western blotting or RT-PCR to evaluate the effect of Indazole on the expression of inflammatory cytokines and apoptotic markers.

3. In-Depth Pharmacokinetic and Toxicity Profiling

ADME Profiles: Evaluate the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of the lead compounds to ensure favorable bioavailability.

Toxicological Studies: Conduct acute and sub-acute in vivo toxicity studies (LD_{50} determination) alongside mutagenicity (Ames test) and cytotoxicity evaluations to establish a clear safety margin.

4. Formulation Development

Explore novel drug delivery systems (NDDS) such as nanoparticles, liposomes, or solid dispersions to enhance the solubility, stability, and targeted delivery of the most potent Indazole candidates.

Would you like to narrow any of these points down to match the specific model organisms (e.g., Wistar r

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