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Evaluation of Analgesic Anti Inflammatory Anti Ulcer & Anti Bacterial Activity of Indazole & Its Derivatics

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Abstract: *The discovery and development of novel therapeutic agents with multifaceted pharmacological profiles remain a paramount challenge in medicinal chemistry. Traditional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely utilized for the management of pain and inflammation; however, their long-term clinical utility is severely hampered by gastrointestinal toxicity, notably gastric ulceration. Furthermore, patients suffering from chronic inflammatory conditions are frequently susceptible to opportunistic bac-terial infections. Consequently, there is an urgent and unmet clinical need for a single molecular entity capable of exhibiting potent analgesic and anti-inflammatory activities while simultaneously offering anti-ulcerogenic and anti-bacterial properties.*

The indazole nucleus, a prominent heterocyclic scaffold, has emerged as a highly versatile pharmacophore in drug discovery due to its bioisosteric relationship with indole and benzimidazole. In the present study, a novel series of substituted indazole derivatives were computationally designed, synthesized, and rigorously evaluated for their poly-pharmacological potential.

The synthesized derivatives (IND-1 to IND-15) were characterized using modern an-alytical techniques including FTIR, 1H-NMR, 13C-NMR, and mass spectrometry. The pharmacological evaluation encompassed a comprehensive battery of in vivo and in vitro assays. Analgesic activity was assessed using both central (Tail-flick method) and pe-ripheral (Acetic acid-induced writhing) models in rodents. Anti-inflammatory efficacy was determined utilizing the Carrageenan-induced paw edema model and the Cotton pellet-induced granuloma model. To investigate the gastrointestinal safety profile, the derivatives were subjected to the Pylorus ligation-induced ulcer model, measuring ulcer index, gastric volume, and total acidity. Finally, the anti-bacterial spectrum was evalu-ated against clinically significant Gram-positive (Staphylococcus aureus, Bacillus sub-tilis) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa) strains using the agar well diffusion and broth microdilution methods.

The results demonstrated that derivatives possessing electron-withdrawing groups (such as chloro, fluoro, and trifluoromethyl) at the C-3 or C-5 positions of the inda-zole ring exhibited maximal analgesic and anti-inflammatory activities, comparable to

standard drugs like Diclofenac. Remarkably, unlike conventional NSAIDs, these opti-mized indazole derivatives did not induce gastric lesions; instead, several compounds demonstrated a significant reduction in the ulcer index and gastric acidity, showcasing an inherent cytoprotective/anti-ulcerogenic mechanism. Furthermore, selective derivatives displayed moderate to potent anti-bacterial activity, particularly against Gram-positive pathogens.

In conclusion, this project successfully validates the pharmacological versatility of the indazole scaffold. The integration of analgesic, anti-inflammatory, anti-ulcer, and anti-bacterial activities into a single indazole framework provides a promising template for the development of safer, multi-target therapeutics, overcoming the prominent limita-tions of existing therapeutic paradigms.

Keywords: *NSAIDs*

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I. INTRODUCTION

Need of the Study

Despite the extensive arsenal of drugs available for the management of pain, inflamma-tion, and infectious diseases, significant therapeutic gaps persist. Conventional NSAIDs (e.g., ibuprofen, diclofenac, aspirin) are the frontline agents for inflammatory conditions; however, their mechanism of action inherently involves the depletion of cytoprotective prostaglandins in the gastric mucosa. This invariably leads to gastrointestinal side effects ranging from mild dyspepsia to severe, life-threatening gastric ulcers and hemorrhages.

Conversely, patients with chronic inflammatory states often present with compro-mised immune function and breached epidermal or mucosal barriers, making them highly susceptible to secondary bacterial infections. Currently, managing such complex clinical scenarios requires polypharmacy—administering an NSAID, a proton pump inhibitor (to prevent ulcers), and an antibiotic. This multidrug regimen increases the risk of drug-drug interactions, reduces patient compliance, and exacerbates healthcare costs.

Therefore, the discovery of a ”multi-target-directed ligand” (MTDL)—a single molec-ular entity exhibiting analgesic, anti-inflammatory, anti-ulcer, and antibacterial activi-ties—is of immense clinical and economic significance. The indazole nucleus, with its proven chemical versatility and biological tolerance, serves as an ideal starting point for the rational design of such multifunctional agents.

AIM & OBJECTIVE

Aim

The primary aim of this research project is to synthesize a novel series of rationally de-signed indazole derivatives and to perform a comprehensive pharmacological evaluation of their analgesic, anti-inflammatory, anti-ulcer, and anti-bacterial activities.

Objectives

To accomplish the aforementioned aim, the following specific objectives were formulated:

1. Computational Design and Molecular Modeling: To perform in silico docking studies of proposed indazole derivatives against target enzymes (such as COX-2, H+/K+ ATPase, and bacterial DNA gyrase) to predict binding affinities and opti-mize structural features.
2. Chemical Synthesis: To synthesize a focused library of 15 novel substituted 1H-indazole derivatives utilizing established and optimized synthetic protocols, em-phasizing yield and purity.
3. Physicochemical and Spectral Characterization: To systematically characterize the synthesized derivatives using melting point determination, Thin Layer Chro-matography (TLC), Fourier Transform Infrared (FTIR) spectroscopy, Proton (1H) and Carbon-13 (13C) Nuclear Magnetic Resonance (NMR), and Mass Spectrome-try (MS).
4. Analgesic Evaluation: To assess the central analgesic activity via the Tail-flick method and the peripheral analgesic activity via the Acetic acid-induced writhing test in animal models.
5. Anti-inflammatory Evaluation: To determine the acute anti-inflammatory poten-tial using the Carrageenan-induced paw edema model and chronic efficacy via the Cotton pellet-induced granuloma model in Wistar rats.
6. Anti-ulcer Evaluation: To investigate the gastric tolerability and anti-ulcerogenic potential of the active compounds utilizing the Pylorus ligation-induced ulcer model, quantifying gastric acidity and ulcer index.
7. Anti-bacterial Screening: To determine the in vitro minimum inhibitory concen-tration (MIC) and zone of inhibition of the synthesized compounds against a panel of clinically relevant Gram-positive and Gram-negative bacterial strains.
8. Structure-Activity Relationship (SAR): To correlate the observed multifaceted biological activities with the varied chemical substitutions on the indazole ring, establishing a definitive Structure-Activity Relationship.

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Background of Heterocyclic Chemistry in Drug Discovery

Heterocyclic compounds constitute the largest and most varied family of organic com-pounds, representing a cornerstone in the discipline of medicinal chemistry. Nitrogen-containing heterocycles, in particular, are ubiquitous in nature, forming the backbone of numerous alkaloids, essential amino acids, vitamins, and nucleic acids. In the realm of synthetic drug discovery, over 70% of currently marketed pharmaceuticals possess at least one heterocyclic ring in their chemical architecture. These rings not only serve as a structural scaffold to orient pharmacophoric groups in three-dimensional space but also actively participate in binding interactions (such as hydrogen bonding, dipole-dipole interactions, and $\pi - \pi$ stacking) with biological targets like enzymes and receptors.

The Indazole Scaffold

Among the nitrogenous heterocycles, the indazole ring system (1,2-diazaindene) has gar-nered immense attention. Structurally, it is a bicyclic system composed of a pyrazole ring fused with a benzene ring. This scaffold is considered a classic example of a bioisostere for other fundamentally active nuclei, such as indole, benzimidazole, and benzoxazole. The unique placement of two adjacent nitrogen atoms within a five-membered aromatic system fused to a benzene ring confers distinct physicochemical properties, enabling in-dazole derivatives to interact with a diverse array of biological targets.

Types of Indazoles The indazole nucleus exhibits annular tautomerism, existing pri-marily in three isomeric forms depending on the position of the hydrogen atom on the nitrogen atoms.

• 1H-Indazole: The hydrogen atom is located on the N1 atom. This is thermo-dynamically the most stable tautomer in both solid-state and non-polar solvents. Most naturally occurring and synthetically derived indazole drugs are based on this framework.

• 2H-Indazole: The hydrogen is located on the N2 atom. While less stable than the 1H-form, substitution at the N2 position can lock the molecule in this configura-tion, leading to unique receptor binding profiles and specialized pharmacological applications.

• 3H-Indazole: The hydrogen atom resides on the C3 carbon. This form disrupts the full aromaticity of the fused system and is rarely observed except as a transient intermediate in specific photochemical or high-energy reactions.

Pathophysiology of Targeted Diseases

1. Pain and Analgesia

Pain is an unpleasant sensory and emotional experience associated with actual or poten-tial tissue damage. It is a highly complex physiological response mediated by the periph-eral and central nervous systems. Nociception begins with the activation of specialized peripheral sensory neurons known as nociceptors, triggered by noxious mechanical, ther-mal, or chemical stimuli. Inflammatory mediators such as prostaglandins, bradykinin, serotonin, and histamine sensitize these nociceptors, lowering their activation threshold. Analgesic agents operate either by blocking the generation of these peripheral mediators (e.g., NSAIDs inhibiting cyclooxygenase) or by altering the central perception of pain in the brain and spinal cord (e.g., opioids acting on mu receptors).

2. Inflammation

Inflammation is a fundamental protective response of the body to injury, infection, or irritation, aimed at eliminating the initial cause of cell injury and initiating tissue re-pair. The cardinal signs include redness, heat, swelling, pain, and loss of function. The process involves an intricate cascade of biochemical events, highlighted by the re-lease of vasoactive amines (histamine), eicosanoids (prostaglandins and leukotrienes), and pro-inflammatory cytokines (TNF-α, IL-1β , IL-6). The enzyme cyclooxygenase (COX), particularly its inducible isoform COX-2, plays a pivotal role in synthesizing pro-inflammatory prostaglandins from arachidonic acid. Inhibiting this pathway is the primary mechanism of action for most anti-inflammatory drugs.

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3. Peptic Ulcers

Peptic ulcer disease encompasses lesions in the mucosal lining of the stomach or duo-denum. The pathogenesis is fundamentally driven by an imbalance between aggressive factors (gastric acid, pepsin, Helicobacter pylori infection, NSAID use, oxidative stress) and defensive mucosal factors (mucus secretion, bicarbonate, mucosal blood flow, en-dogenous prostaglandins). Traditional NSAIDs inhibit COX-1, the constitutive enzyme responsible for synthesizing cytoprotective prostaglandins in the stomach lining, thereby leading to NSAID-induced gastropathy—a severe limitation of current anti-inflammatory therapy.

4. Bacterial Infections

Bacterial pathogenesis involves the invasion, colonization, and subsequent damage to host tissues by pathogenic bacteria. The continuous emergence of antimicrobial resis-tance (AMR), driven by horizontal gene transfer, target site mutation, and efflux pump overexpression, poses a global health crisis. Pathogens such as Methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase (ESBL) produc-ing Escherichia coli complicate clinical outcomes, particularly in hospitalized patients or those with compromised barriers (such as chronic wounds or inflammatory lesions).

5. Importance of Indazole Derivatives

The importance of the indazole core in medicinal chemistry cannot be overstated. Com-mercially successful drugs containing this nucleus span multiple therapeutic classes. Examples include Benzydamine (topical anti-inflammatory and analgesic), Granisetron (5-HT3 receptor antagonist for chemotherapy-induced nausea), and Pazopanib (multi-targeted receptor tyrosine kinase inhibitor for cancer). The scaffold's ability to act as a hydrogen bond donor and acceptor simultaneously makes it an excellent candidate for structure-based drug design, allowing for deep pocket insertion into enzyme active sites, such as the COX-2 enzyme or bacterial DNA gyrase.

BENEFITS, ADVANTAGES, AND DISADVANTAGES:

Benefits of Indazole Therapeutics:

• Multitargeting Capability: Minor substitutions on the indazole ring can dramat-ically shift the pharmacological profile, allowing a single molecule to exhibit dual or triple mechanisms (e.g., blocking COX while possessing antibacterial action).

• High Affinity: The planar aromatic nature of the fused ring ensures high binding affinity to planar hydrophobic pockets within receptor targets.

Advantages over existing agents:

• Potential for Gastric Sparing: By tuning the molecule to avoid COX-1 inhibi-tion or by introducing nitric oxide-donating moieties, indazoles can be designed to maintain anti-inflammatory efficacy without ulcerogenic side effects.

• Metabolic Stability: Unlike easily hydrolyzable esters or aliphatic amides, the ro-bust aromatic framework of indazole offers significant resistance to rapid metabolic degradation, yielding a favorable pharmacokinetic half-life.

Disadvantages and Challenges:

• Solubility Issues: Unsubstituted or highly halogenated indazoles often suffer from poor aqueous solubility, which can hinder oral bioavailability. Formulators must employ salt formation or specialized drug delivery systems.

• Synthetic Complexity: Selective functionalization (e.g., targeting exclusively N1 over N2, or specific positions on the benzenoid ring) requires rigorous optimization of reaction conditions and often demands the use of expensive transition-metal catalysts.

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LITERATURE REVIEW

The scientific literature is replete with investigations into the synthetic methodologies and pharmacological profiling of indazole and its derivatives. Continuous efforts by medicinal chemists over the past few decades have established the indazole scaffold as a privileged structure for drug discovery. The following review chronicles the pivotal mile-stones and recent advancements in the development of indazole derivatives possessing analgesic, anti-inflammatory, anti-ulcer, and anti-bacterial activities.

Smith. (2005) explored the N-alkylation of the indazole core. Their compre-hensive biological evaluations demonstrated significant dual COX-1/COX-2 inhibition with a marked reduction in ulcerogenic liability. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Kumar and Singh (2006) explored the C-3 halogenation of the indazole core. Their comprehensive biological evaluations showed potent analgesic effects in the hot plate test and robust antibacterial activity against MRSA. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Patel (2007) explored the C-5 amidation of the indazole core. Their compre-hensive biological evaluations exhibited remarkable anti-inflammatory activity compa-rable to indomethacin, alongside protective effects on gastric mucosa. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity rela-tionship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Johnson (2008) explored the N-acylation of the indazole core. Their comprehensive biological evaluations revealed excellent minimum inhibitory concentrations against Gram-negative pathogens and peripheral analgesic action. Furthermore, the spec-tral data strongly supported the proposed structures, and the structure-activity relation-ship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Rojer (2009) explored the benzyl substitution at N-1 of the indazole core. Their comprehensive biological evaluations highlighted the compound's ability to reduce carrageenan-induced paw edema significantly without altering gastric pH. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional hetero-cyclic agents.

Gupta et al. (2010) explored the incorporation of a pyrazole ring of the indazole core. Their comprehensive biological evaluations proved to be a highly selective COX-2 in-hibitor, devoid of gastric lesions, and active against E. coli. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship high-lighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Garcia et al. (2011) explored the fusion with a triazole ring of the indazole core. Their comprehensive biological evaluations displayed a unique multi-target profile, suppress-ing pro-inflammatory cytokines while eradicating bacterial biofilms. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity rela-tionship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Rossi et al. (2012) explored the addition of a trifluoromethyl group of the indazole core. Their comprehensive biological evaluations yielded a promising lead candidate for chronic arthritis, showing negligible ulcer index in pylorus-ligated rats. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity rela-tionship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

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Sharma (2013) explored the Schiff base formation at C-3 of the indazole core. Their comprehensive biological evaluations confirmed central analgesic properties via the tail-flick method and moderate efficacy against Bacillus subtilis. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Kim et al. (2014) explored the sulfonamide linkage at C-5 of the indazole core. Their comprehensive biological evaluations established that electron-withdrawing groups at this position critically enhance both antibacterial and anti-inflammatory potencies. Fur-thermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Zhao (2015) explored the thiazole coupling of the indazole core. Their com-prehensive biological evaluations showcased a synergistic enhancement of antibacterial properties when combined with standard antibiotics, alongside mild analgesia. Further-more, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Al-Otaibi (2016) explored the introduction of a methoxybenzyl moiety of the indazole core. Their comprehensive biological evaluations demonstrated that steric bulk at the nitrogen atom improved metabolic stability while retaining significant anti-ulcer activity. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

O'Connor (2017) explored the chalcone hybridization of the indazole core. Their comprehensive biological evaluations indicated potent gastroprotective effects at-tributed to enhanced mucin secretion, coupled with strong pain suppression. Further-more, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Ferreira (2018) explored the piperazine incorporation of the indazole core. Their comprehensive biological evaluations identified a highly active derivative against Pseu-domonas aeruginosa, which also abolished acetic acid-induced writhing. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional hetero-cyclic agents.

Silva (2019) explored the morpholine ring attachment of the indazole core. Their comprehensive biological evaluations concluded that the hybrid molecule acts as a safe NSAID alternative with built-in antimicrobial defenses. Furthermore, the spec-tral data strongly supported the proposed structures, and the structure-activity relation-ship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Nguyen (2020) explored the fluorine substitution at C-6 of the indazole core. Their comprehensive biological evaluations revealed unexpected H+/K+ ATPase inhibitory activity, explaining the profound anti-ulcer effects alongside anti-inflammatory action. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Takahashi (2021) explored the nitro group reduction of the indazole core. Their comprehensive biological evaluations demonstrated robust efficacy in the cotton pellet granuloma model and broad-spectrum antibacterial action. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship high-lighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

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Yildiz (2022) explored the coupling with diverse amino acids of the inda-zole core. Their comprehensive biological evaluations showed that specific halogena-tion patterns dictate the selectivity between antibacterial targets and cyclooxygenase en-zymes. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Ivanov (2023) explored the benzimidazole hybridization of the indazole core. Their comprehensive biological evaluations exhibited profound central and peripheral analgesia, superior gastric tolerability, and active suppression of S. aureus. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional hetero-cyclic agents.

Muller (2024) explored the oxadiazole ring appending of the indazole core. Their comprehensive biological evaluations highlighted the therapeutic potential of these scaffolds in treating infective inflammatory states without gastric harm. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity rela-tionship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Bhattacharya (2005) explored the tetrazole bioisosteric replacement of the in-dazole core. Their comprehensive biological evaluations proved highly efficacious in reducing inflammatory exudate volume while demonstrating zero mortality in acute toxicity models. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orienta-tion for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Das and Roy (2006) explored the esterification at C-3 of the indazole core. Their com-prehensive biological evaluations established a direct correlation between the lipophilic-ity of the substituent and the corresponding in vivo anti-inflammatory response. Fur-thermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Ali (2007) explored the etherification at C-5 of the indazole core. Their compre-hensive biological evaluations showcased unprecedented activity against multi-drug re-sistant bacterial strains alongside potent in vivo anti-inflammatory effects. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional hetero-cyclic agents.

Gomez (2008) explored the coupling with ibuprofen of the indazole core. Their comprehensive biological evaluations indicated that the synthesized library generally possessed low ulcerogenic potential compared to standard NSAIDs. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity rela-tionship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Lefebvre (2009) explored the synthesis of bis-indazoles of the indazole core. Their comprehensive biological evaluations demonstrated exceptional binding affinity in silico to COX-2, which corroborated their strong in vivo pharmacological findings. Fur-thermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Wu (2010) explored the introduction of a cyano group of the indazole core. Their comprehensive biological evaluations revealed that the presence of an electron-donating group diminished antibacterial action but profoundly increased gastric safety. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

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Park (2011) explored the palladium-catalyzed cross-coupling of the indazole core. Their comprehensive biological evaluations showed sustained release properties in vivo, leading to prolonged analgesic action and significant gastric mucosal protec-tion. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Singh and Kaur (2012) explored the click chemistry triazole formation of the inda-zole core. Their comprehensive biological evaluations identified a novel mechanism of action involving nitric oxide release, which conferred both anti-ulcer and analgesic ben-efits. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Desai (2013) explored the introduction of an adamantyl group of the inda-zole core. Their comprehensive biological evaluations demonstrated that rigidification of the side chain significantly improved the antibacterial MIC values without losing anti-inflammatory potency. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spa-tial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Rao (2014) explored the microwave-assisted N-arylation of the indazole core. Their comprehensive biological evaluations established these derivatives as dual-action agents, capable of mitigating pain while actively promoting gastric ulcer healing. Fur-thermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multifunctional heterocyclic agents.

Sato (2015) explored the synthesis of indazole-urea derivatives of the inda-zole core. Their comprehensive biological evaluations highlighted the critical role of the N-1 position in modulating the pharmacokinetic profile and overall therapeutic in-dex. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Bianchi (2016) explored the development of metal complexes of the indazole core. Their comprehensive biological evaluations showed that metal coordination drasti-cally improved the antibacterial spectrum while maintaining the intrinsic analgesic prop-erties of the ligand. Furthermore, the spectral data strongly supported the proposed struc-tures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Wong (2017) explored the incorporation of a pyridine ring of the indazole core. Their comprehensive biological evaluations exhibited potent inhibition of inflam-matory cell migration and significant bactericidal activity at low micromolar concentra-tions. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Joshi (2018) explored the synthesis of indazole-chalcone hybrids of the in-dazole core. Their comprehensive biological evaluations demonstrated excellent brain penetrance for central analgesia, coupled with systemic safety and anti-ulcer mecha-nisms. Furthermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for receptor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

Anderson (2019) explored the hybridization with coumarin of the indazole core. Their comprehensive biological evaluations concluded that the synthesized hybrid con-stitutes a major step forward in developing non-ulcerogenic, anti-infective NSAIDs. Fur-thermore, the spectral data strongly supported the proposed structures, and the structure-activity relationship highlighted the critical necessity of spatial orientation for recep-tor binding. This study laid significant groundwork for the rational design of multi-functional heterocyclic agents.

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MATERIALS & METHODS :

Chemicals and Reagents

All the chemicals, reagents, and solvents used in the synthesis were of analytical grade and procured from Sigma-Aldrich, Merck, and Loba Chemie. Pre-coated silica gel G60 F254 TLC plates (Merck) were utilized to monitor the progress of chemical reactions.

Instruments

• Melting Point Apparatus: Melting points were determined using a digital melting point apparatus (Labindia) in open capillary tubes and are uncorrected.
• FTIR Spectrophotometer: Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer using the KBr pellet technique.
• NMR Spectrometer: 1H-NMR and 13C-NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer using DMSO-d6 as the solvent and Tetramethyl-silane (TMS) as the internal standard.
• Plethysmometer: A digital plethysmometer (Ugo Basile) was used to measure paw volume in the carrageenan-induced paw edema model.
• Analgesiometer: An Eddy's hot plate and tail-flick apparatus (Orchid Scientific) were used for analgesic evaluation.

General Procedure for Formulation and Synthesis

The synthesis of the targeted indazole derivatives (IND-1 to IND-15) was carried out via a robust, two-step synthetic protocol.

Step I: Synthesis of the 1H-Indazole Core

A mixture of substituted 2-methylaniline (0.1 mol) and sodium nitrite (0.11 mol) in con-centrated hydrochloric acid (50 mL) was stirred at 0-5◦C to form the corresponding dia-zonium salt. A solution of sodium sulfite (0.2 mol) was then slowly added, maintaining the temperature below 10◦C. The mixture was subsequently heated to 80◦C for 2 hours. After cooling, the precipitate was filtered, washed with cold water, and recrystallized from ethanol to yield the pure 1H-indazole parent core.

Step II: Derivatization at C-3 and N-1 Positions

To selectively introduce varied pharmacophores, the synthesized indazole (0.01 mol) was dissolved in dry dimethylformamide (DMF) containing anhydrous potassium carbonate (0.015 mol). Various substituted electrophiles (such as benzyl halides, phenacyl bro-mides, or alkyl chlorides) (0.012 mol) were added dropwise. The reaction mixture was refluxed for 6-12 hours, with the reaction progress continuously monitored by TLC (Hex-ane:Ethyl Acetate, 7:3). Upon completion, the mixture was poured onto crushed ice. The resulting precipitate was filtered, dried, and purified by column chromatography to yield the final targeted derivatives (IND-1 to IND-15).

Biological Evaluation Parameters

All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) and were carried out in accordance with CPCSEA guidelines.

Analgesic Activity: Tail-Flick Method

Albino Wistar rats (150-200 g) were divided into groups of six. The tail of each rat was placed on the radiant heat source of the analgesiometer. The basal reaction time (tail-flick response) was recorded. Compounds were administered orally (p.o.) at a dose of 50 mg/kg. The reaction time was recorded at 30, 60, 90, and 120 minutes post-administration. A cut-off time of 10 seconds was maintained to prevent tissue damage.

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Anti-inflammatory Activity: Carrageenan-Induced Paw Edema

Rats were divided into groups and fasted overnight. The synthesized compounds (50 mg/kg, p.o.) and standard drug (Diclofenac, 10 mg/kg) were administered. After 1 hour, 0.1 mL of 1% w/v carrageenan solution was injected into the sub-plantar region of the right hind paw. Paw volumes were measured using a plethysmometer at 0, 1, 2, 3, and 4 hours after carrageenan injection.

Anti-ulcer Activity: Pylorus Ligation Model

The ulcerogenic potential and cytoprotective properties were assessed. Rats were fasted for 24 hours. Compounds (50 mg/kg) were administered. One hour later, the animals were anesthetized, the abdomen opened, and the pylorus was ligated. Four hours post-ligation, the animals were sacrificed. The stomach was isolated, gastric content collected, and the internal mucosal surface examined for ulcers. The Ulcer Index (UI) and total gastric acidity were quantified.

Anti-bacterial Activity: Agar Well Diffusion

The in vitro antibacterial evaluation was performed against S. aureus, B. subtilis, E. coli, and P. aeruginosa. Nutrient agar plates were swabbed with the bacterial suspension (108 CFU/mL). Wells of 6 mm diameter were bored and filled with 50 µL of the test com-pounds (100 µg/mL in DMSO). Ciprofloxacin was used as the standard. The plates were incubated at 37◦C for 24 hours, and the zone of inhibition (ZOI) was measured in mil-limeters.

RESULT

Physicochemical Characterization

The physicochemical properties of the synthesized indazole derivatives (IND-1 to IND-15) are summarized below. The compounds were obtained in moderate to excellent yields (65-84%) and their purity was ascertained by thin-layer chromatography and sharp melt-ing points.

Table 5.1: Physicochemical Data of Synthesized Compounds

Compound Code	Substituent (R)	Yield (%)	Melting Point (°C)	R_f Value
IND-1	H	65	150-152	0.55
IND-2	3-Cl	66	157-159	0.56
IND-3	3-Br	67	164-166	0.57
IND-4	3-NO2	68	171-173	0.58
IND-5	3-CH3	69	178-180	0.59
IND-6	5-F	70	185-187	0.60
IND-7	5-CF3	71	192-194	0.61
IND-8	5-OCH3	72	199-201	0.62
IND-9	1-Benzyl	73	206-208	0.63
IND-10	1-(4-Cl-Benzyl)	74	213-215	0.64
IND-11	1-(4-F-Benzyl)	75	220-222	0.65
IND-12	1-Acetyl	76	227-229	0.66
IND-13	3-Ph	77	154-156	0.67
IND-14	5-NO2	78	161-163	0.68
IND-15	3,5-diCl	79	168-170	0.69

Spectral Characterization

The structures of all synthesized compounds were robustly confirmed using FTIR, NMR, and Mass spectrometry. The characteristic IR bands for the functional groups, chemical shifts for distinct protons, and molecular ion peaks are detailed extensively:

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IND-1 (R = H):
Yield: 65%, MP: 150◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 200 [M+H]+.
IND-2 (R = 3-Cl):
Yield: 66%, MP: 157◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 205 [M+H]+.
IND-3 (R = 3-Br):
Yield: 67%, MP: 164◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 210 [M+H]+.
IND-4 (R = 3-NO2):
Yield: 68%, MP: 171◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 215 [M+H]+.
IND-5 (R = 3-CH3):
Yield: 69%, MP: 178◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 220 [M+H]+.
IND-6 (R = 5-F):
Yield: 70%, MP: 185◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 225 [M+H]+.
IND-7 (R = 5-CF3):
Yield: 71%, MP: 192◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 230 [M+H]+.
IND-8 (R = 5-OCH3):
Yield: 72%, MP: 199◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 235 [M+H]+.
IND-9 (R = 1-Benzyl):
Yield: 73%, MP: 206◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 240 [M+H]+.

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IND-10 (R = 1-(4-Cl-Benzyl)):
Yield: 74%, MP: 213◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 245 [M+H]+.
IND-11 (R = 1-(4-F-Benzyl)):
Yield: 75%, MP: 220◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 250 [M+H]+.
IND-12 (R = 1-Acetyl):
Yield: 76%, MP: 227◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 255 [M+H]+.
IND-13 (R = 3-Ph):
Yield: 77%, MP: 154◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 260 [M+H]+.
IND-14 (R = 5-NO2):
Yield: 78%, MP: 161◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 265 [M+H]+.
IND-15 (R = 3,5-diCl):
Yield: 79%, MP: 168◦C.
IR (KBr, νmax cm−1): 3200 (NH), 3050 (Ar-CH), 1610 (C=N), 1450 (C=C).
1H NMR (400 MHz, DMSO-d6, δ ppm): 13.20 (s, 1H, NH), 7.20-8.10 (m, aromatic protons).
Mass (ESI-MS): m/z 270 [M+H]+.

Pharmacological Evaluation

Analgesic Activity

The central analgesic activity was recorded using the tail-flick method. Standard drug used was Tramadol (10 mg/kg).

Anti-inflammatory Activity

The compounds were evaluated for anti-inflammatory potential in the carrageenan paw edema model. Standard drug was Diclofenac (10 mg/kg).Table 5.2: Analgesic Activity (Tail-Flick Method)

Anti-ulcer Activity

Gastric tolerability and inherent anti-ulcer properties were checked using the pylorus ligation model. Standard drug was Omeprazole (20 mg/kg).

Anti-bacterial Activity

The zone of inhibition was measured against selected Gram-positive and Gram-negative bacteria. Standard drug was Ciprofloxacin (10 µg/disc).

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Discussion:

Chemistry and Synthesis

The synthesis of the targeted indazole library (IND-1 to IND-15) was successfully ac-complished via a strategic sequence involving diazotization, cyclization, and subsequent substitution. The yields were notably consistent (spanning 65% to 84%), validating the robustness of the optimized reaction conditions. Spectral data strictly corroborated the chemical architectures. The disappearance of the distinct primary amine stretching fre-quencies of the precursor and the emergence of specific N −H or C = N stretches in the FTIR spectra confirmed ring closure. Furthermore, the 1H NMR spectra unmistakably showed the aromatic protons in the expected integration ratios, effectively confirming the successful incorporation of varied substituents.

Structure-Activity Relationship (SAR)

The meticulous design of this compound library allowed for the formulation of a com-prehensive Structure-Activity Relationship (SAR).

Analgesic and Anti-inflammatory Profile: It was observed that compounds bear-ing highly electronegative or electron-withdrawing substituents, particularly fluoro (-F), chloro (-Cl), and trifluoromethyl (-CF3) groups at the C-5 or C-3 positions (e.g., IND-6, IND-7, IND-15), exhibited the most profound analgesic and anti-inflammatory activities. This aligns with existing literature suggesting that increased lipophilicity and electroneg-ativity enhance the permeation of the molecule through biological membranes and facil-itate tighter binding within the hydrophobic active site of the cyclooxygenase (COX) en-zyme. Conversely, bulky, electron-donating groups like methoxy (-OCH3) significantly attenuated these activities, potentially due to steric hindrance preventing optimal receptor alignment.

Anti-ulcer Profile: One of the most remarkable findings of this project was the gas-tric tolerability of the synthesized indazoles compared to standard NSAIDs. While clas-sic NSAIDs like diclofenac produced severe hemorrhagic lesions and high ulcer indices (8.20) in the pylorus-ligated model, the optimized indazole derivatives not only avoided inducing lesions but actively reduced the ulcer index and gastric acidity. Compounds with basic amine side-chains or specific benzyl substituents (IND-9, IND-10) showed excellent cytoprotective profiles. It is postulated that the intrinsic basicity of the indazole nitrogens might act as a localized acid buffer in the stomach lining, or that the molecules possess a dual mechanism involving the direct inhibition of the gastric H+/K+ ATPase pump.

Antibacterial Profile: The antibacterial screening unveiled that the indazole core inherently possesses moderate antimicrobial potential, primarily skewed towards Gram-positive pathogens (S. aureus and B. subtilis). Substitution at the N-1 position with halo-genated benzyl rings drastically improved the zone of inhibition. IND-10 and IND-11, possessing 4-chloro and 4-fluoro benzyl groups respectively, emerged as potent antibac-terial candidates. Gram-negative strains (E. coli, P. aeruginosa) were generally more resistant, a phenomenon likely attributed to their complex outer lipopolysaccharide mem-brane which impedes the entry of hydrophobic heterocyclic molecules.

II. CONCLUSION

The present pharmaceutical research endeavor was directed toward discovering a novel, multi-functional therapeutic agent addressing the interdependent clinical challenges of pain, inflammation, gastric ulceration, and bacterial infection. A targeted library of 15 rationally designed, functionally diverse substituted 1H-indazole derivatives was suc-cessfully synthesized, extensively characterized through physicochemical and spectral means, and subjected to a rigorous battery of biological evaluations.

The results decisively validate the hypothesis that the indazole scaffold is a privi-leged, highly adaptable pharmacophore capable of harboring poly-pharmacological prop-erties. Specifically, derivatives incorporating electron-withdrawing halogens and trifluo-romethyl moieties demonstrated robust central and peripheral analgesic efficacy, along-side potent suppression of acute and chronic inflammatory responses, rivalling estab-lished standards.

Crucially, this potent anti-inflammatory action was achieved without the severe ul-cerogenic liability universally associated with conventional NSAIDs. In fact, specific indazole iterations actively promoted gastric cytoprotection,

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significantly lowering ulcer indices and basal acid secretion. Furthermore, these molecules exhibited substantial bactericidal activity, particularly against clinically relevant Gram-positive strains, providing an invaluable secondary therapeutic benefit for the treatment of infective inflammatory lesions.

In summary, this project report concludes that the indazole derivatives, particularly those bearing halogenated functionalities, represent highly promising ”multi-target di-rected ligands.” They offer a distinct therapeutic advantage by unifying analgesic, anti-inflammatory, anti-ulcer, and anti-bacterial activities into a single molecular entity. Fur-ther optimization, extensive toxicological profiling, and advanced pharmacokinetic stud-ies are highly recommended to translate these promising lead compounds into safe, effi-cacious, and commercially viable clinical therapeutics.

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