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DESIGN AND SYNTHESIS OF INDOLE DERIVATIVES AS COX-2 INHIBITORS FOR ANTI- INFLAMMATORY ACTIVITY

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ABSTRACT

Indole-based compounds have gained considerable attention in medicinal chemistry due to their broad spectrum of biological activities and structural versatility. In the present study, a series of novel indole–pyrimidine derivatives (SIPA1–SIPA10) were designed, synthesized, and evaluated for their potential anti-inflammatory activity as cyclooxygenase-2 (COX-2) inhibitors. The design strategy focused on combining the indole and pyrimidine scaffolds to enhance biological activity and selectivity toward the COX-2 enzyme. The synthesized compounds were characterized using standard analytical techniques such as TLC and IR spectroscopy. In silico ADME analysis was performed using the SwissADME tool to evaluate physicochemical and pharmacokinetic properties, including molecular weight, lipophilicity, hydrogen bonding capacity, and drug-likeness based on Lipinski, Ghose, and Veber rules. Most of the synthesized compounds showed acceptable drug-like characteristics with no rule violations. The anti-inflammatory activity was assessed using the carrageenan-induced rat paw edema model, and the percentage inhibition of inflammation was measured at different time intervals. Among the tested compounds, SIPA2 and SIPA4 exhibited significant anti-inflammatory activity, showing inhibition levels comparable to the standard drug indomethacin after 4 hours. These findings suggest that the incorporation of indole and pyrimidine moieties may enhance COX-2 inhibitory activity and support further development of these derivatives as potential anti-inflammatory agents.

KEYWORDS: Indole derivatives, COX-2 inhibitors, Pyrimidine scaffold, Anti-inflammatory activity, Carrageenan-induced paw edema.

INTRODUCTION

Cyclooxygenase-2 (COX-2) inhibitors represent a critical class of therapeutic agents designed to manage inflammation while minimizing adverse effects associated with traditional nonsteroidal anti-inflammatory drugs. The continuing need for safer anti-inflammatory drugs has driven research toward the development of compounds that selectively target COX-2, reducing the risks linked to nonselective inhibition of cyclooxygenase isoforms. Within this context, the indole scaffold has gained recognition in medicinal chemistry due to its versatile chemical structure and its capacity to serve as a foundation for bioactive molecules. This research paper focuses on the exploration of indole-based COX-2 inhibitors, highlighting their design principles, synthetic strategies, and biological profiles. Its scope encompasses the detailed examination of structure-activity relationships, the assessment of anti-inflammatory activities of newly synthesized derivatives, and a discussion of the challenges and future prospects in the field.

Indole Scaffold and Its Relevance in Drug Design

The indole scaffold occupies a distinguished position in medicinal chemistry due to its chemical adaptability and widespread occurrence in both natural and synthetic bioactive compounds. Its core structure forms the basis of several endogenous molecules—including tryptophan, serotonin, and melatonin—which perform essential roles in physiological regulation and cellular communication (Drăgoi et al., 2026). Notably, indole derivatives are found in numerous therapeutic agents targeting diverse medical needs, such as oncology, central nervous system disorders, and inflammatory diseases, underscoring their capacity to interact effectively with enzymes, G-protein-coupled receptors, and nuclear receptors (Teraiya et al., 2023). The synthetic versatility of the indole ring further allows medicinal chemists to generate tailored molecules, optimizing binding interactions and pharmacokinetics for specific therapeutic targets. As a result, the indole scaffold remains a cornerstone in the rational design of drug candidates, particularly when selective inhibition of enzymes like COX-2 is desired, setting the stage for innovative approaches to anti-inflammatory therapy.

INDOLE

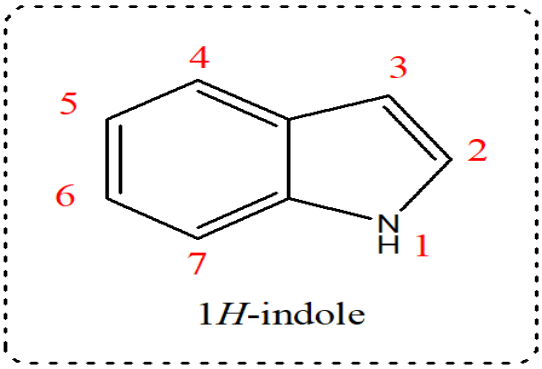

Fig. 1: Structure of Indole.

Fig. 1 illustrates the chemical structure of 1H-indole, a bicyclic heterocyclic compound consisting of a fused benzene ring and pyrrole ring system. Indole and its derivatives represent an important structural motif in medicinal chemistry because they are widely found in natural products, pharmaceuticals, and biologically active molecules, contributing significantly to drug discovery and development due to their versatile pharmacological properties

Physical Properties of Indole nucleus

Chemical Formula	: C_8H_7N
IUPAC Name	: 1H- indole
Molecular Weight (Molar mass)	: 117.15 g/mol
Appearance	: Colorless crystalline Solid
Odour	: Pleasant and flowery smell
Density	: 1.1747 g/cm³
Melting Point	: 52-55 °C
Boiling Point	: 253 to 254 °C
Solubility	: Sparingly soluble in cold water, but soluble in hot water and most organic solvents like chloroform, methanol, and DMSO
Hydrogen Bond Acceptor	: 0
Hydrogen Bond Donor	: 1
Lipinski Rules (drug-likeness)	: Yes, Zero violations
Xlogp3 (cLogP)	: 2.05 (Moderately lipophilic)
Molecular Shape	: Planar

Indole is an aromatic fused heterocyclic organic compound with a bicyclic structure, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery.

The Indole basic structure composed of a six membered benzene ring fused with a five-membered pyrrole ring. The two rings fused together to constitute the basic nucleus 1H-indole.

Indole exhibits diverse biological activities, making it a significant scaffold in medicinal chemistry for developing pharmaceuticals with anticancer, anti-inflammatory, antimicrobial, antiviral, and antidiabetic properties, among others. Its core structure is found in various natural compounds, including neurotransmitters like serotonin and hormones like indole-3-acetic acid (IAA).

PYRIMIDINE

Pyrimidine (1,3-diazinine) is an aromatic, heterocyclic organic compound with a six-membered ring containing four carbon and two nitrogen atoms at positions 1 and 3. The atoms are arranged with alternating single and double bonds, which creates a stable, planar ring structure. Pyrimidine is weakly basic organic compound with the formula $C_4H_4N_2$ that is a crucial building block for DNA and RNA, with the pyrimidine bases cytosine, thymine, and uracil being key components. It is also used in the manufacturing of pharmaceuticals, agrochemicals, and dyes, and exhibits a wide range of biological activities, such as antimicrobial, antiviral, and anticancer properties. Fig. 2 shows the chemical structure of **pyrimidine**, a six-membered aromatic heterocyclic compound containing two nitrogen atoms at positions 1 and 3 of the ring. Pyrimidine forms an important structural framework in many biologically significant molecules, including nucleic acid bases such as cytosine, thymine, and uracil, and it also serves as a key scaffold in the design of various pharmaceutical agents due to its diverse biological and pharmacological activities.

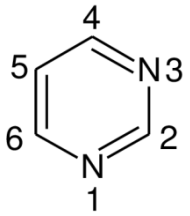

Fig. 2: Structure of Pyrimidine.

Physical Properties of Pyrimidine nucleus

Chemical Formula	: $C_4H_4N_2$
Molecular Weight (Molar mass)	: 88.08 g/mol
Appearance	: Colorless crystalline Solid
Odour	: Penetrating odor
Density	: 1.02 g/cm³
Melting Point	: 22 °C
Boiling Point	: 123 °C
Solubility	: Soluble in water
Hydrogen Bond Acceptor	: 2
Hydrogen Bond Donor	: 0
Lipinski Rules (drug-likeness)	: Yes, Zero violations
Xlogp3 (cLogP)	: 0.36 (lipophilic)

Pyrimidine derivatives comprise a diverse and interesting group of drugs which are extremely important for their biological activities. Many pyrimidine scaffolds were developed and utilized by medicinal chemists to design novel therapeutics with a broad range of pharmacological activities including anti-proliferative, antiviral, antitumor, anti-inflammatory, antibacterial, antifungal, anti-Alzheimer, and anti-tubercular properties.

COX Enzymes and the Need for Selectivity

Understanding the distinct biological roles of cyclooxygenase isoforms is crucial for appreciating the therapeutic objectives behind selective COX-2 inhibition. Cyclooxygenase-1 (COX-1) performs homeostatic functions, such as gastric protection and platelet aggregation, while cyclooxygenase-2 (COX-2) is primarily induced in response to inflammatory stimuli and mediates pro-inflammatory prostaglandin synthesis (Ferrer et al., 2019). Consequently, traditional non-selective NSAIDs that inhibit both enzymes offer effective symptom relief but are associated with gastrointestinal and renal side effects due to the disruption of COX-1 functions. The development of COX-2 selective inhibitors aims to provide targeted anti-inflammatory benefits while minimizing harm to physiological pathways governed by COX-1, although their use has raised concerns regarding cardiovascular risks linked to a biochemical imbalance in prostanoid synthesis (Arora et al., 2020). This duality highlights the ongoing challenge in anti-inflammatory drug development, where maximizing therapeutic efficacy must be carefully balanced with mitigating off-target adverse effects.

Design Strategies for Indole-Based COX-2 Inhibitors

Advances in rational drug design have enabled the strategic development of indole-based derivatives that display enhanced selectivity for COX-2 inhibition. Incorporating common pharmacophore models, medicinal chemists often focus on introducing electron-withdrawing or hydrophobic substituents at specific positions on the indole ring, which improves binding within the unique secondary pocket of the COX-2 active site (Shah et al., 2024). Structural considerations such as the accommodation of bulkier side chains and fine-tuning of hydrogen bond donors or acceptors further differentiate COX-2 selective inhibitors from those affecting COX-1 (Chahal et al., 2023). Computer-aided drug design, including quantitative structure-activity relationship (QSAR) models, molecular docking, and molecular dynamics simulations, has accelerated the identification of suitable molecular features that optimize isoform selectivity. Such approaches allow for the iterative refinement of candidate molecules, driving the discovery of indole derivatives with favorable COX-2 affinity and reduced potential for off-target toxicity.

Synthetic Approaches to Indole Derivatives

In parallel with the rational design of COX-2 selective molecules, the advancement of synthetic methodologies for indole derivatives has become essential for introducing structural diversity and functionality. Classical approaches, such as the Fischer indole synthesis and the Bischler indole synthesis, have historically provided reliable routes to the indole nucleus and remain foundational in medicinal chemistry (De Moraes et al., 2025). More recently, attention has shifted to modern techniques that prioritize sustainability and efficiency, including metal-free organophotoredox catalysis and electrochemical synthesis, which facilitate the introduction of pharmacologically relevant substituents with minimal environmental impact (De Moraes et al., 2025). There is also a rising emphasis on green chemistry protocols and atom-economic processes, enabling the scalable production of complex indole frameworks while reducing hazardous waste and resource consumption (Bugaenko et al., 2018). These innovations collectively empower researchers to fabricate functionally diverse indole scaffolds tailored for COX-2 inhibition, supporting ongoing drug discovery and optimization efforts.

Structure-Activity Relationships and Potency Modulation

Distinct patterns emerge when analyzing how structural modifications to the indole scaffold affect COX-2 inhibitory activity and selectivity. Introducing bulky hydrophobic substituents—such as di-tert-butyl groups—has been shown to favor interactions with the expanded active-site cavity of COX-2, especially at residues like Arg513 and Val523, thereby enhancing enzyme selectivity (Ahmadi et al., 2022). Moreover, compounds with increased lipophilicity exhibit improved inhibitory potency, as demonstrated by correlations with higher log P values in structure-activity studies (Ribeiro et al., 2019). Flexible linkers or additional aromatic moieties attached to the indole core also play a central role in optimizing spatial orientation, which can maximize both affinity and selectivity against COX-2 over COX-1. Therefore, the modulation of key physicochemical and steric features in the indole framework continues to be a critical approach for advancing indole-based COX-2 inhibitors with favorable selectivity and pharmacological profiles.

General Procedure

Synthesis of N-(indole-3-yl) acetamide

To a solution of indole-3-amine (0.01mole) in chloroform (dry, 100ml), acetyl chloride (0.02 mole) is added drop wise at 0-5^{0}C with constant stirring. The reaction mixture was stirred for 2 hrs by magnetic stirrer. The excess solvent was distilled of and the separated mass was poured into ice water and recrystallised from methanol. The recrystallised

product purity was checked by TLC by using solvent system Ethanol, Dichloromethane (1:2) ratio. The synthesized compound functional group was confirmed by IR spectral analysis.

Synthesis of N-(indole-3-yl)-3-aryl acryl amide derivatives

To a mixture of N-(indole-3-yl)acetamide (0.01 mole) in methanol (50ml) appropriate aromatic aldehydes (0.01mole) are added in the presence of 2% NaOH solution (5ml). The reaction mixture is stirred for 10 hrs at room temperature and then refluxed for 6 hrs. The excess solvent was distilled off and poured into ice water. The resulting solid thus seperatered, is filtered, washed with water and recrystallised from ethanol. The recrystallised product purity was checked by TLC by using solvent system Ethanol, Dichloromethane (1:2) ratio. The synthesized compound functional group was confirmed by IR spectral analysis.

Synthesis of 2-amino-4-[3-indole amino]-6-phenyl pyrimidine derivatives

To a mixture of N-(indole-3-yl)-3-aryl acryl amide derivatives (0.01 mole) in absolute ethanol (50ml, dry), guanidine nitrate (0.01 mole) and solid NaOH (0.4 g) are added. The reaction mixture was refluxed for 5 hrs and poured into ice water. The solid thus separated was filtered, washed with water and re-crystallized from acetone. The recrystallised product purity was checked by TLC by using solvent system Ethanol, Dichloromethane (1:2) ratio. The proposed reactions are shown below fig. 3.

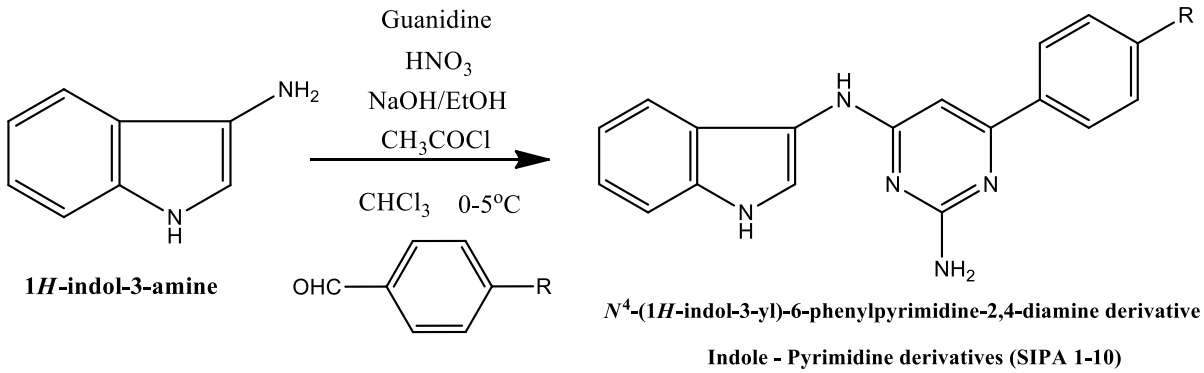

Fig. 3: Synthetic work and design of scheme-1 (SIPA1-10).

For the calculation of ADME properties, SMILES notations of synthesized compounds are submitted as input to the Swiss ADME online programme to calculate molecular parameters. Along-with molecular docking, it is better to conduct ADME studies before in vivo and in vitro studies to save cost and time. Biopharmaceutical properties determine the drug-like behaviour of synthesized compounds. In the reported study, the Swiss ADME online programme was used to calculate molecular parameters that were in accordance with Lipinski's rule.

The ADME/Tox properties are closely related to physico-chemical descriptors such as lipophilicity (logP), molecular weight, polar surface area, and water solubility.

Study of ADMET Properties

Table 1: Physiochemical and ADMET Properties of Titles Compounds (SIPA 1-10).

Compound ID	Molecular Formula	Mol. Wt. (g/mol)	No. of Rotatable bonds	No of H-bond acceptors	No of H-bond donors	ClogP	PSA	Solubility	Druglikeness (Lipinski / Ghose/ Veber) Follow / Violations	Bioavailability
SIPA-1	$C_{18}H_{15}N_5O$	**317.34**	**3**	**3**	**4**	2.53	97.74	Poorly Soluble	Yes / 0	0.55
SIPA-2	$C_{18}H_{14}ClN_5$	**335.79**	**3**	**2**	**3**	3.15	76.92	Poorly Soluble	Yes / 0	0.55
SIPA-3	$C_{18}H_{14}BrN_5$	**380.24**	**3**	**2**	**3**	3.60	76.92	Poorly Soluble	Yes / 0	0.55
SIPA-4	$C_{18}H_{14}FN_5$	**319.34**	**3**	**3**	**3**	3.29	76.92	Poorly Soluble	Yes / 0	0.55
SIPA-5	$C_{19}H_{17}N_5O$	**331.37**	**4**	**3**	**3**	2.97	85.85	Poorly Soluble	Yes / 0	0.55
SIPA-6	$C_{18}H_{14}N_6O_2$	**346.34**	**4**	**4**	**3**	2.26	119.75	Poorly Soluble	Yes / 0	0.55
SIPA-7	$C_{18}H_{16}N_6$	**316.34**	**3**	**2**	**4**	2.43	103.46	Poorly Soluble	Yes / 0	0.55
SIPA-8	$C_{19}H_{15}N_5O_2$	**345.35**	**4**	**4**	**4**	2.56	115.04	Poorly Soluble	Yes / 0	0.55
SIPA-9	$C_{18}H_{15}N_5O_3S$	**381.41**	**4**	**5**	**4**	1.94	132.34	Poorly Soluble	Yes / 0	0.55
SIPA-10	$C_{18}H_{13}ClN_6O_2$	**380.79**	**4**	**4**	**3**	2.72	119.75	Poorly Soluble	Yes / 0	0.55
AMPICILIN	$C_{16}H_{19}N_3O_4S$	**349.40**	**5**	**5**	**3**	0.18	115.42	Soluble	Yes / 0	0.55
INDOMETHACIN	$C_{19}H_{16}ClNO_4$	**357.79**	**3**	**4**	**1**	3.12	68.42	Soluble	Yes / 0	0.55
5-FU	$C_4H_3FN_2O_2$	**130.08**	**2**	**3**	**2**	0.89	58.02	Soluble	Yes / 0	0.55

Table-1 explore the physicochemical and drug-likeness properties of the synthesized compounds (SIPA-1 to SIPA-10) along with reference drugs are presented in the table. Parameters such as molecular weight, rotatable bonds, hydrogen bond donors and acceptors, ClogP, polar surface area (PSA), solubility, and bioavailability were evaluated to assess their suitability as potential drug candidates. All compounds satisfied the major criteria of Lipinski, Ghose, and Veber rules with no violations, indicating favorable drug-likeness and acceptable pharmacokinetic properties, although most synthesized derivatives showed poor aqueous solubility compared with standard drugs such as ampicillin, indomethacin, and 5-fluorouracil.

Anti-Inflammatory Activity

Cyclooxygenase (COX) is the key enzyme which catalyses the conversion of arachidonic acid to prostaglandins and thromboxanes. There are two types of cyclooxygenase enzymes, COX-1 and COX-2. COX-1 is a constitutive enzyme, produced in many tissues such as the kidney and the gastrointestinal tract, while COX-2 is inducible and is expressed during inflammation at a site of injury. Prostaglandins made by COX-1 enzyme are protective prostaglandins, the presence of which leads to normal renal function in the kidneys, whereas, prostaglandins made by COX-2 cause inflammation. Currently available NSAIDs (Nonsteroidal antiinflammatory drugs) inhibit both COX-1 and COX-2 enzymes. Inhibition of COX-1 reduces the basal production of cytoprotective PGE2 and PGI2 and hence causes ulceration. Therefore complete inhibition of COX-1 is not preferred and drugs that inhibit the COX- 2 enzyme are better anti-inflammatory agents.

Carrageenan induced paw edema

Carrageenan induced inflammation is a biphasic phenomenon. The first phase of edema is attributed to release of histamine and 5-Hydroxy tryptamine, plateau phase is maintained by kinin like substances and second accelerating phase of swelling is attributed to prostaglandin-like substances. The knowledge of these mediators involved in different phases is important for interpreting mode of drug action.

Carrageenan induced paw edema is a classical model for determination of acute phase inflammation. The rat paw edema was provoked by sub plantar injection 0.1 ml of 1% w/v of carrageenan in 0.9 % saline in right hind paw. The hind paw volume was measure by dipping the foot in Digital plethysmometer up to the lateral malleolus (Winter et. al. 1962). The displacement of sodium chloride solution was measure in the plethysmometer. The initial paw volume was

measure and recorded; it was considered as 0h reading. The drug or test substances like Indomethacin and various test compound doses were administered orally 60 min before administration of carrageenan. 0.1 ml of 1% w/v of carrageenan in saline was injected into the right hind paw of rats. The hind paw volume was measured at 1h internal up to 4thhour of experiment. The difference between paw volumes at various time intervals indicated the edema volume due to inflammation. The percentage inhibitions produced by the drug and test compounds were calculated by following formula:

$$\text{Percentage inhibition of paw edema (\%)} = ((\text{Control} - \text{Treated}) / \text{Control}) \times 100$$

The percentage inhibition of carrageenan-induced paw edema for the synthesized compounds (SIPA1–SIPA10) was evaluated at different time intervals (1, 2, 3, and 4 hours) and compared with the standard drug indomethacin. The results indicate that several compounds exhibited moderate to significant anti-inflammatory activity over time. Among the synthesized derivatives, SIPA2 and SIPA4 showed comparatively higher inhibition percentages at the 4-hour interval, approaching the activity of the reference drug, suggesting their potential as promising anti-inflammatory agents shown in below table-2.

Table 2: Percentage inhibition of paw volume of synthesized compounds by carrageenan induced rat paw edema method.

Compounds	TIME			
	1hr	2hr	3hr	4hr
Carraggenan	NA	NA	NA	NA
Indomethacin	58.18	60.18	72.53	80.11
SIPA1	4.36	17.71	35.97	51.28
SIPA2	19.23	29.82	46.23	71.65
SIPA3	4.12	18.23	32.14	48.25
SIPA4	20.21	39.25	48.91	74.58
SIPA5	16.79	27.17	33.33	38.09
SIPA6	6.56	12.98	29.81	55.97
SIPA7	5.23	16.21	38.26	49.16
SIPA8	3.96	14.32	34.51	55.23
SIPA9	7.12	20.98	30.82	48.91
SIPA10	5.72	11.81	27.17	50.24

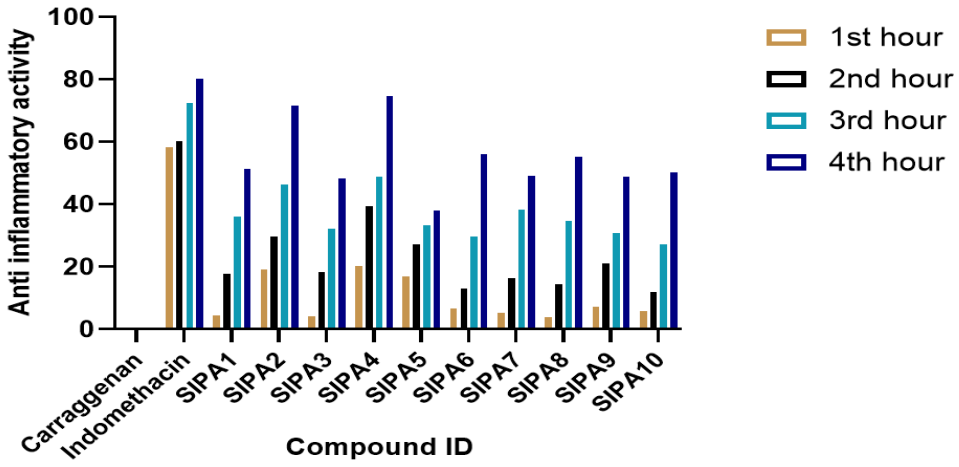

Fig. 4: Percentage inhibition of paw volume of synthesized compounds by carrageenan induced rat paw edema method.

The compounds under study are tested for acute anti-inflammatory activity by the carrageenan-induced paw edema method. The percentage of inflammation was calculated at high (180 mg) and low doses (45 mg) of synthesized compounds and at regular intervals of time, i.e. 2 hours, 3 hours, and 4 hours. Compounds SIPA4, SIPA2 showed the greatest inhibition after 4 hours, with a significant decrease in paw volume. The above acute model result was indicate that synthetic compounds at the dose levels of 45, 90, 135 and 180 mg/kg showed reduction in paw edema volume at all time intervals as compared to carrageenan control but significant reduction in paw edema volume was noticed in 45 mg/kg at 1stand 4thhour observation 24.13 % and 23.71 % respectively. The groups treated with synthesized compounds at the dose levels of 45, 90, 135 and 180 mg/kg showed reduction in paw edema volume at all time intervals as compared to carrageenan control but significant reduction in paw edema volume was noticed in 180 mg/kg body weight at 1st and 4thhour observation 20.21 % and 74.58 % respectively.

The synthesized compounds were (45, 90, 135 and 180 mg/kg) screened for anti-inflammatory activity by carrageenin-induced paw edema method. Compared to standard drug (Indomethacin) Compounds SIPA4, SIPA2 and SIPA6 & SIPA8 were found to exhibit good anti-inflammatory activity. Indole and pyrimmidine substitution favour the anti-inflammatory activity as observed in potent compounds. However, medium inhibition was shown by compounds SIPA1, SIPA3, SIPA7, SIPA9, SIPA10 at similar doses (Table 3).

Table 3: Anti-inflammatory activity of synthesized derivatives measured by carrageenan induced paw edema.

Compounds	TIME			
	1hr	2hr	3hr	4hr
Carraggenan	NA	NA	NA	NA
Indomethacin	58.18 ± 3.1	60.18 ± 3.7	72.53 ± 4.2	80.11 ± 5.4
SIPA1	4.36 ± 0.8	17.71 ± 2.5	35.97 ± 3.1	51.28 ± 4.6
SIPA2	19.23 ± 4.0	29.82 ± 3.9	46.23 ± 2.8	71.65 ± 7.0*
SIPA3	4.12 ± 1.0	18.23 ± 3.0	32.14 ± 3.4	48.25 ± 4.2
SIPA4	20.21 ± 3.6	39.25 ± 4.7	48.91 ± 3.2	74.58 ± 6.1*
SIPA5	16.79 ± 3.3	27.17 ± 4.1	33.33 ± 4.6	38.09 ± 5.2
SIPA6	6.56 ± 1.4	12.98 ± 2.1	29.81 ± 3.8	55.97 ± 6.5
SIPA7	5.23 ± 0.9	16.21 ± 3.2	38.26 ± 4.7	49.16 ± 5.3
SIPA8	3.96 ± 0.6	14.32 ± 2.5	34.51 ± 3.9	55.23 ± 6.1
SIPA9	7.12 ± 1.7	20.98 ± 3.8	30.82 ± 4.0	48.91 ± 5.0
SIPA10	5.72 ± 1.3	11.81 ± 2.3	27.17 ± 3.5	50.24 ± 5.8

Note: Values are expressed as Mean ± SD, N = 5 animals in each group. One-way ANOVA followed by Turkey‟s multiple comparisons were made between:

a: Disease Control Vs Standard, synthesized compounds (SIPA1-10).

b: Symbols represent statistical significance: *P<0.001 (Highly significant)

Challenges and Future Perspectives in Indole-Based COX-2 Inhibitor Design

Nevertheless, despite noteworthy progress in the development of indole-based COX-2 inhibitors, several persistent limitations continue to constrain their clinical utility. Chief among these concerns is the cardiovascular toxicity resulting from a disruption in the balance between prostacyclin and thromboxane, as selective COX-2 inhibition can elevate the risk of serious cardiovascular events such as heart attack and stroke (Arora et al., 2020). Additional challenges include the emergence of off-target toxicities, incomplete selectivity, and the potential for adaptive resistance in inflammatory and oncogenic contexts, which may reduce long-term therapeutic efficacy or lead to adverse outcomes (Shah et al., 2024). Addressing these multifaceted hurdles will require greater emphasis on integrating structural, pharmacokinetic, and systems-level data—an approach that could facilitate the rational innovation of novel

scaffolds or hybrid molecules with improved safety and functional profiles. Future research directions should also prioritize the evaluation of cardiotoxicity mechanisms and the development of lead compounds that exhibit precise selectivity without compromising safety, thereby ensuring sustained therapeutic benefit across diverse indications.

CONCLUSION

A comprehensive evaluation of indole-based COX-2 inhibitors highlights substantial advances in the rational design, synthetic innovation, and functional assessment of these compounds. Iterative optimization of the indole scaffold, through the integration of structural and physicochemical modifications, has generated derivatives with high selectivity and promising anti-inflammatory efficacy. The synthesis and biological characterization of these molecules confirm their therapeutic potential, especially in addressing the limitations of traditional nonsteroidal anti-inflammatory drugs. Importantly, studies consistently demonstrate that careful modulation of structure-activity relationships enhances both safety and pharmacological profiles, positioning indole-based inhibitors as a promising direction in anti-inflammatory therapy. Continued research in this area is essential, as it will support the refinement of molecular architectures and ensure the emergence of safer agents that meet the evolving challenges of clinical drug development.

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