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Original Article

Novel Pyrimidine Derivatives: Microwave-Assisted Synthesis and Computational Insights Toward Anti-Inflammatory Activity

Vinayak Madhukar Gaware* , Kiran Bhausaheb Dhamak, Vikas Damu Kunde, Mayur Trimbak Gaikar

Department of Pharmaceutical Chemistry, College of Pharmacy (For Women) Chincholi, Nashik, Maharashtra, INDIA.

ABSTRACT

Aim/Background: This study focuses on the synthesis and evaluation of novel pyrimidine derivatives as potential anti-inflammatory agents. **Materials and Methods:** The compounds were synthesized via a two-step process: condensation of acetophenone with aromatic aldehydes yielded substituted chalcones, which were then cyclized with guanidine hydrochloride using Microwave-Assisted Organic Synthesis (MAOS). This green chemistry method afforded high yields (70-90%) in short reaction times (10-15 min). The synthesized derivatives were characterized using FT-IR, ^{1}H-NMR, TLC, elemental analysis, and melting point determination. PASS prediction and molecular docking indicated promising anti-inflammatory potential via inhibition of Taurine dehydrogenase. **Results:** *In vivo* evaluation using the Carrageenan-Induced Rat Paw Edema model, with Nimesulide as reference, confirmed significant anti-inflammatory activity in several compounds. **Conclusion:** These findings demonstrate a correlation between structural features and biological activity. The integration of green synthesis, *in silico* modeling and pharmacological testing supports the development of pyrimidine derivatives as promising anti-inflammatory candidates.

Keywords: Pyrimidine derivatives, Anti-inflammatory activity, Microwave-assisted synthesis, Molecular docking, PASS prediction.

Correspondence:
Dr. Vinayak Madhukar Gaware
Associate Professor, Department of Pharmaceutical Chemistry, College of Pharmacy (For Women) Chincholi, Nashik-422101, Maharashtra, INDIA.
Email: vinayak.gaware@pravara.in

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INTRODUCTION

Inflammation is a critical physiological response triggered by harmful agents such as pathogens, toxins, and damaged tissues. It is part of the innate immune defense system designed to eliminate the injurious stimuli and initiate the healing process. While acute inflammation is protective and short-lived, aiding in tissue repair and pathogen clearance, chronic inflammation is persistent and pathological, contributing to the development of several serious diseases such as rheumatoid arthritis, atherosclerosis, type 2 diabetes, Alzheimer's disease, and various types of cancer (Medzhitov, 2008; Libby, 2007). Commonly used anti-inflammatory therapies, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and corticosteroids, are effective but often associated with adverse outcomes. Prolonged use of NSAIDs can result in gastrointestinal ulcers, renal impairment, and increased cardiovascular risk, whereas corticosteroids may cause immune suppression and hormonal imbalance (Vane, 1998; Rainsford, 2007). These drawbacks underscore the necessity to develop safer and more selective anti-inflammatory drugs with minimal side effects. With recent progress in computational biology and molecular modeling, drug discovery processes have become more efficient and targeted. In particular, molecular docking has emerged as a valuable *in silico* approach that allows researchers to study the interaction of bioactive compounds with specific molecular targets. Docking simulations help predict how small molecules bind to the active sites of key enzymes or receptors involved in inflammation, estimating binding affinity, interaction types, and binding conformations. These insights support the virtual screening and rational design of potential therapeutic agents before experimental validation (Kitchen *et al*., 2004; Lionta, 2014). Several biomolecular targets are widely recognized in the regulation of inflammatory responses:

- Cyclooxygenase-2 (COX-2), a key enzyme in prostaglandin synthesis involved in pain and swelling.
- 5-Lipoxygenase (5-LOX), important in leukotriene formation contributing to allergic and chronic inflammatory responses.
- Nuclear factor kappa B (NF-κB), a transcription factor regulating pro-inflammatory gene expression.

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- Inducible Nitric Oxide Synthase (iNOS), which produces nitric oxide in inflammatory tissues.
- Tumor Necrosis Factor-alpha (TNF-α), a central cytokine mediating systemic inflammation (Lawrence, 2009; Singh and Agrawal, 2008).

The integration of computational drug discovery tools such as docking, pharmacophore modeling, and virtual screening accelerates the identification of novel lead molecules with potential anti-inflammatory effects. This study aims to explore the anti-inflammatory activity of selected natural and/or synthetic compounds by conducting molecular docking against well-characterized pro-inflammatory targets. The results from this computational evaluation will provide valuable insights into binding mechanisms, interaction patterns, and their possible therapeutic relevance in treating inflammatory diseases.

Objectives

To synthesize and characterize a series of 4, 6-diphenylpyrimidin-2-amine derivatives, evaluate their potential anti-inflammatory activity through *in silico* molecular docking studies against key pro-inflammatory targets such as Taurine dehydrogenase, and validate their anti-inflammatory efficacy using the carrageenan-induced rat paw edema model.

MATERIALS AND METHODS

Materials

All reagents, solvents, and synthetic starting materials used in the study were of analytical grade and obtained from commercial sources without further purification. The synthesis and characterization of the target compounds were performed using the following standard analytical techniques:

- Determination of physical constants (melting point),
- Thin-Layer Chromatography (TLC),
- Elemental analysis,
- Fourier-Transform Infrared (FT-IR) spectroscopy,
- Proton Nuclear Magnetic Resonance (^{1}H NMR) spectroscopy,
- Mass Spectrometry (MS).

Microwave-assisted synthesis was carried out using a scientific microwave synthesizer (RAGA Model No. RG34L4R).

Melting Point Determination

Melting points of the synthesized compounds were determined using the open capillary tube method with a liquid paraffin bath. The values reported are uncorrected. A sharp and consistent melting point was indicative of the compound's purity.

Thin-Layer Chromatography (TLC)

TLC was employed to monitor reaction progress and assess compound purity. The separation was based on differential adsorption on a stationary phase. R_f values were calculated to identify the formation of the target compounds and assess their purity.

Fourier-Transform Infrared (FT-IR) Spectroscopy

FT-IR spectra were recorded using an Agilent FT-IR spectrophotometer via the Potassium Bromide (KBr) disc method. The resulting data were analyzed to confirm the presence of functional groups through characteristic absorption bands.

Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy

^{1}H NMR spectra were recorded on a Bruker 500 MHz spectrometer using Tetramethylsilane (TMS) as the internal standard. The spectra provided detailed information on proton environments, supporting structural elucidation of the synthesized molecules.

Mass Spectrometry (MS)

Mass spectra of the proto compounds were recorded to confirm molecular mass and assess the fragmentation pattern. The results further corroborated the molecular structure proposed for the synthesized compounds.

Synthesis of Pyrimidine Derivatives

Synthesis of Chalcones 3(a-h)

Equimolar amounts of acetophenone (0.001 mol) and the corresponding substituted aromatic aldehyde 2(a-h) (0.001 mol) were dissolved in ethanol (7.5 mL) and stirred at room temperature. To this solution, a 50% aqueous potassium hydroxide solution (7.5 mL) was added dropwise with continuous stirring. The resulting reaction mixture was allowed to stand at room temperature for 24 hr. After completion (monitored by TLC), the reaction mixture was acidified with a 1:1 v/v mixture of concentrated hydrochloric acid and distilled water, leading to the precipitation of the crude chalcone. The solid was filtered under vacuum, washed with cold distilled water, and purified by column chromatography using silica gel and ethyl acetate: hexane as the eluent. Final purification was carried out by recrystallization from an ethyl acetate: hexane mixture to afford pure chalcone derivatives 3(a-h) (Phan, 2025).

Synthesis of 4, 6-Diphenylpyrimidin-2-amines 4(a-h)

A solution of chalcone 3(a-h) (0.001 mol) and guanidine hydrochloride (0.001 mol) in absolute ethanol (10 mL) was subjected to microwave irradiation using a scientific microwave synthesizer for 5 min. Upon completion of the reaction (as confirmed by TLC), the solvent was evaporated under reduced pressure. The resulting solid was poured onto crushed ice with vigorous stirring to yield a bright yellow precipitate. The crude

product was filtered under vacuum, washed with distilled water, dried, and recrystallized to obtain the corresponding 4,6-diphenylpyrimidin-2-amine derivatives 4(a-h) as pale-yellow crystalline solids (Tables 1 and 2).

Pyrimidine Scheme

Spectral Data

Compound 4a

- **IR (cm^{-1}) (Major Functional Groups):** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), C-NH_2.
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (aromatic NH_2).
- **MS (m/z) (% Relative Abundance):** 248 (M+1), 249 (M+2).

Compound 4b

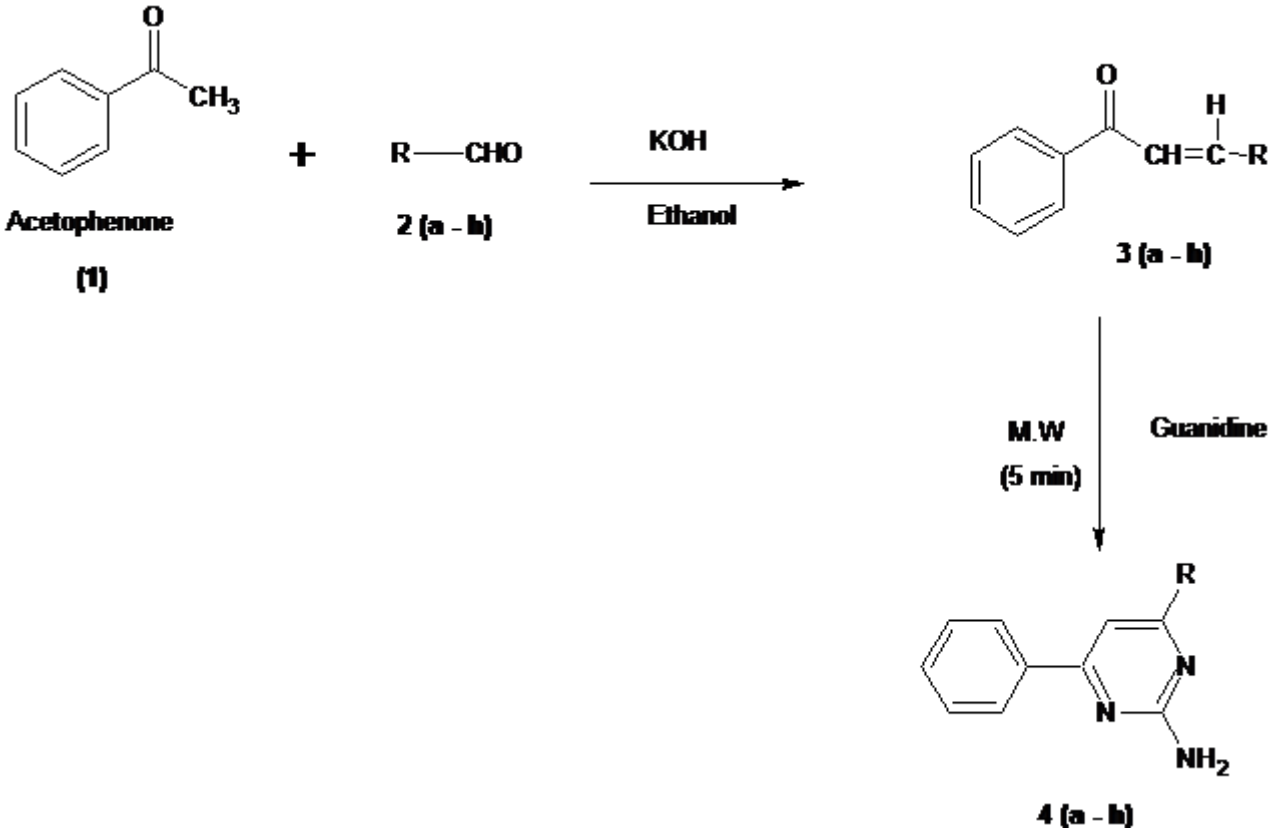
- **IR (cm^{-1}) (Major Functional Groups):** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), C-NH_2, 1200-1020 (C-OH).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 2.59 (COOH).
- **MS (m/z) (% Relative Abundance):** 264 (M+1), 265 (M+2).

Compound 4c

- **IR (cm^{-1}) (Major Functional Groups:** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), 3000-3700 (C-NH_2, C-OH).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 2.34 (COOH).
- **MS (m/z) (% Relative Abundance):** 264 (M+1), 265 (M+2).

Compound 4d

- **IR (cm^{-1}) (Major Functional:** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), 3000-3700 (C-NH_2), 600-800 (C-Cl).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 2.34 (COOH).
- **MS (m/z) (% Relative Abundance):** 282 (M+1), 283 (M+2).



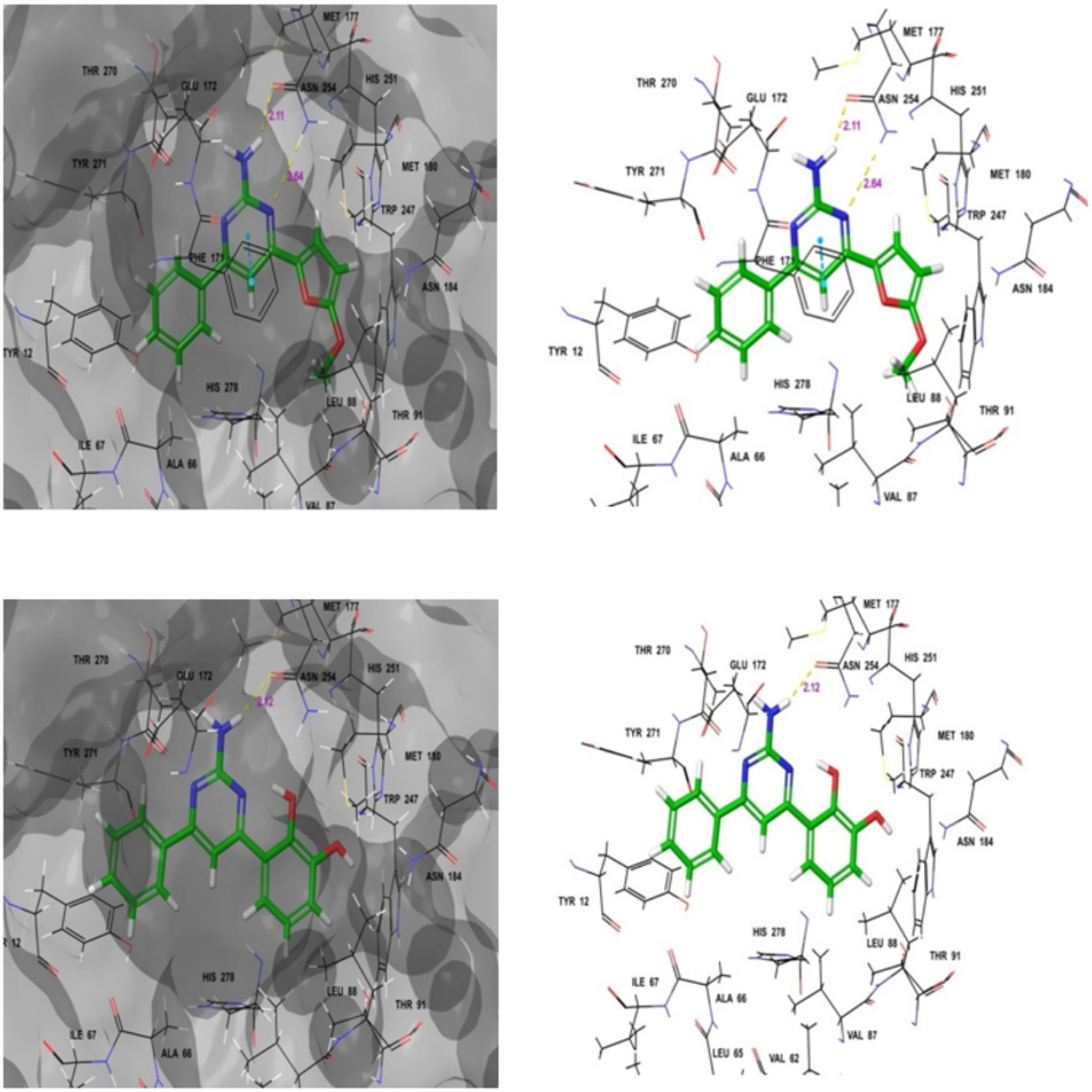


Figure 1: Graphical illustration of predicted binding mode of Pyrimidine Derivatives with active sites of Taurine dehydrogenase.

Compound 4e

- **IR (cm^{-1}) (Major Functional:** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), 3000-3700 ($C-NH_2$), 2815-2832 ($C-OCH_3$).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 2.34 (COOH), 3.39 (CH_3), 3.65 (OH).
- **MS (m/z) (% Relative Abundance):** 278 (M+1), 279 (M+2).

Compound 4f

- **IR (cm^{-1}) (Major Functional:** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), 3000-3700 ($C-NH_2$), 900-1300 (C-O).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 7.86 (2-furan CH).
- **MS (m/z) (% Relative Abundance):** 238 (M+1), 239 (M+2).

Compound 4g

- **IR (cm^{-1}) (Major Functional:** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), 3000-3700 ($C-NH_2$), 1300-1540 ($C-NO_2$).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 2.34 (CH_3).
- **MS (m/z) (% Relative Abundance):** 292 (M+), 293 (M+1).

Compound 4h

- **IR (cm^{-1}) (Major Functional:** 800-1200 (C-C), 2700-3300 (C-H), 1360-1250 (C-N), 1600-1700 (C=N), 3000-3700 ($C-NH_2$), 600-800 (C-Cl).
- **^{1}H-NMR (δ, ppm) (Key Proton Signals):** 7.85 (2-pyrimidine CH), 7.79 (benzene CH), 6.99 (NH_2), 2.59 (CH_3).
- **MS (m/z) (% Relative Abundance):** 316 (M+), 317, 318, 319, 320.

Docking Studies

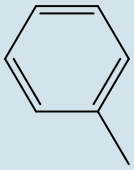
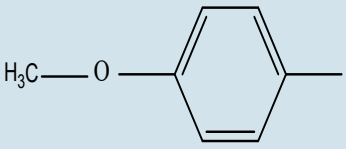
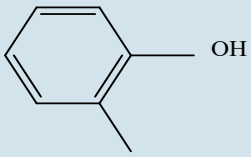
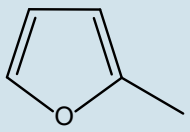
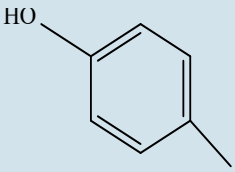
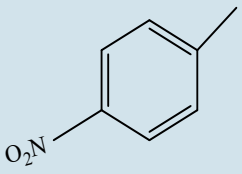
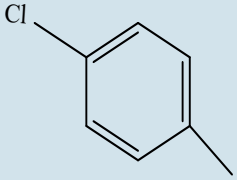
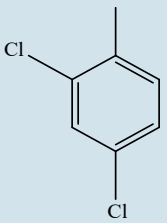
PASS Prediction of Biological Activity

Prediction of Activity Spectra for Substances (PASS) was utilized to evaluate the biological activity profile of the synthesized pyrimidine derivatives. PASS is an advanced computational tool designed to predict the biological activity spectrum of drug-like molecules based solely on their chemical structure. The system employs Multilevel Neighbourhoods of Atoms (MNA) descriptors and robust Structure-Activity Relationship (SAR) algorithms to deliver Probable activity (Pa) and Probable inactivity (Pi) scores. The biological activities of the proposed compounds were predicted using PASS Online (Version 2.0) developed by the Department of Bioinformatics, Institute of Biomedical Chemistry, Moscow. Structures were input via MOL files and processed online. Compounds showing Pa >0.7 were considered biologically significant. Results indicated high probability scores for anti-inflammatory action, particularly through inhibition of Taurine dehydrogenase, suggesting potential utility in inflammation-related pathologies.

Molecular Docking Studies

Software and Tools Molecular docking simulations were conducted using the Small-Molecule Drug Discovery Suite 2017-1 (Schrödinger, LLC, New York, NY). The docking protocol followed industry-standard practices using Glide (v7.4) and post-docking MM-GBSA calculations.

Table 1: For Compounds: 4(a-h).

COMP.CODE	R	COMP.CODE	R
4a		4e	
4b		4f	
4c		4g	
4d		4h	

Ligand Preparation

Ligands were prepared using LigPrep:

- Conversion from 2D to 3D structures,
- Generation of ionization states (pH 7.0±0.5),
- Tautomer and stereoisomer enumeration,
- Geometry optimization using the OPLS3 force field.

Protein Preparation

Target protein (Taurine dehydrogenase) was retrieved from the Protein Data Bank and processed using Protein Preparation Wizard in Maestro:

- Bond order assignments and hydrogen addition,
- Removal of crystallographic water molecules,
- Protonation state assignment using Epik at pH 7.0,
- Loop and side-chain completion using Prime,
- Optimization of H-bond networks.

Grid Generation

Receptor grids were generated based on co-crystallized ligand centering:

- Grid box defined for ligand sizes ≤ 20 Å,
- Van der Waals radius scaling factor set to 0.7 for partial atomic charges < 0.25,
- Constraints included key residues such as Asn184, Thr270, His251, and His278.

Docking Procedure

Docking was carried out using Glide XP (Extra Precision) mode:

- Flexible ligand sampling,
- Consideration of ring conformations, nitrogen inversion, and amide planarity,
- Epic penalties, intramolecular H-bond rewards, and π-conjugation planarity were incorporated,
- Constraint satisfaction with at least one key interaction was enforced.

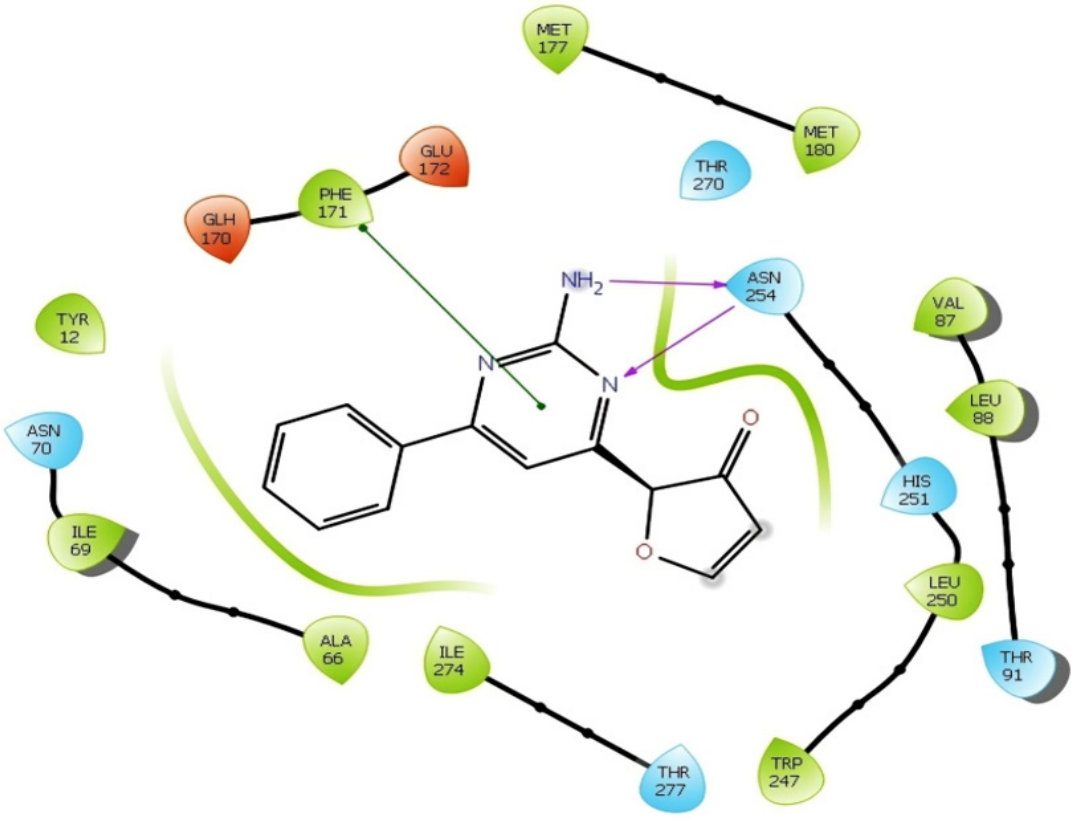


Figure 2: 2D Graphical illustration of predicted binding mode of Pyrimidine Derivatives with active sites of Taurine dehydrogenase.

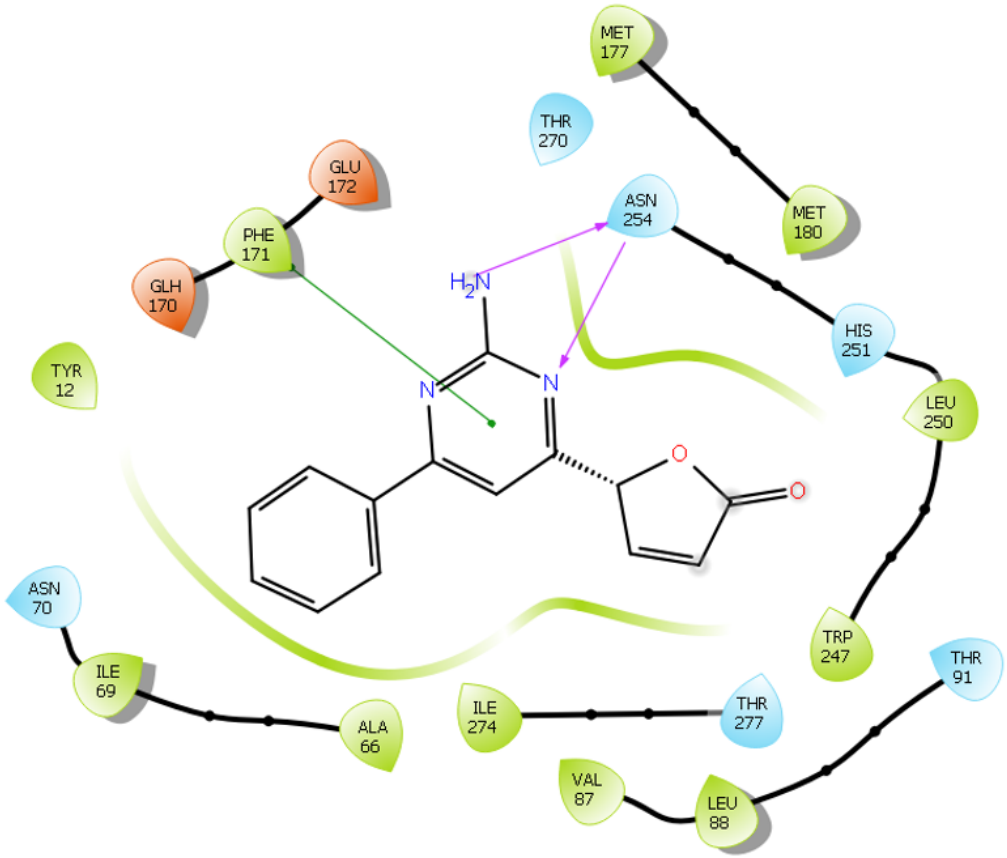


Figure 3: 2D Graphical illustration of predicted binding mode of Pyrimidine Derivatives with active sites of Pterine dehydrogenase.

Docking Validation

Protocol validation was performed by re-docking the native ligand, yielding an RMSD of 1.80 Å, confirming the reliability of the docking method (Wang *et al.*, 2019).

Binding Free Energy Calculations (MM-GBSA)

Post-docking MM-GBSA binding free energy calculations were performed using the Prime module:

- ΔG_bind = E_complex - E_ligand - E_receptor.
- Additional calculations included ligand/receptor strain energies and strain-free binding energy (ΔG_bind (NS)).
- The docking results suggested strong binding affinity of the lead pyrimidine compounds to the active site of Taurine dehydrogenase, supported by key hydrogen bonding and hydrophobic interactions (Figure 1, Table 3).

Visualization

Graphical visualizations illustrated key binding site interactions, showing consistent H bonding and π-π stacking with residues like Thr270, His251, Met180, and Tyr12. Selected figures demonstrated the stable and favourable binding orientation of synthesized pyrimidine derivatives within the enzyme's active pocket (Figures 2 and 3).

Evaluation of Anti-Inflammatory Activity of Synthesized Compounds

Materials

The anti-inflammatory activity of the synthesized pyrimidine derivatives was evaluated using the Carrageenan-induced rat hind paw edema model. Type IV λ-carrageenan (from Sigma Laboratories) was used as the phlogistic agent. Paw volumes were measured using a digital Plethysmometer based on the water displacement principle. Instrument calibration was performed using a standardized probe prior to experimentation. Nimesulide (50 mg/kg), procured from Lincoln Pharmaceuticals Ltd., Ahmedabad, was used as the standard anti-inflammatory drug.

Method: Carrageenan-Induced Rat Hind Paw Edema

Adult Wistar albino rats (120-150 g) were randomly divided into three groups (n=6 per group):

- **Control group:** Received 1% w/v sodium Carboxymethylcellulose (CMC) suspension (vehicle).
- **Standard group:** Received Nimesulide at 50 mg/kg body weight.
- **Test group:** Received synthesized pyrimidine derivatives at 200 mg/kg body weight.

All test and standard substances were suspended in 0.5% sodium CMC and administered orally. After 30 min of drug administration, inflammation was induced by sub plantar injection of 0.1 mL of 1% λ-carrageenan solution into the right hind paw of each rat (Kalcic, 2020).

Paw volume was measured using the Plethysmometer at 0 hr (baseline) and at 1, 2, 3, and 4 hr post-carrageenan injection. The difference in paw volume at each time point from the baseline reading indicated the extent of edema formation.

Calculation of Anti-inflammatory Activity

The percentage (%) inhibition of edema is calculated using the formula:

$$\% \text{ inhibition} = To - Tt / T0 \times 100$$

Where,

Tt is the thickness of paw of rats given test extract at corresponding time.

To is the paw thickness of rats of control group at the same time.

RESULTS

Interpretation of Results

The control group exhibited a steady increase in paw volume, reaching 1.83±0.02 mL at the 4th hr, indicating progressive inflammation. Nimesulide significantly reduced paw edema (1.25±0.02 mL) with 31.69% inhibition.

Among the test compounds

- Compound 4b and 4e exhibited the highest inhibition of inflammation (90.54%), closely matching or even exceeding the standard drug.
- Compound 4h also showed strong activity with 89.94% inhibition, followed by 4d (87.81%) and 4c (85.79%).

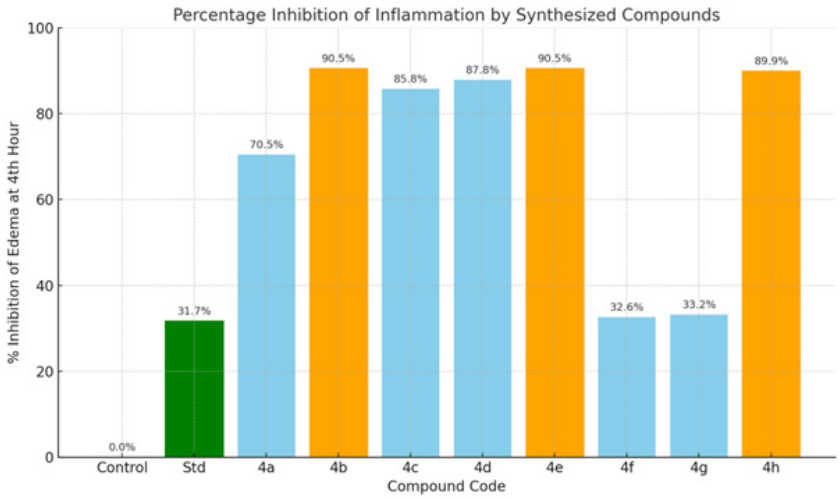


Figure 4: Percentage Inhibition of Inflammation by Synthesized Compounds.

Table 2: Analytical Physicochemical data of the synthesized Pyrimidine derivatives 4(a-h).

Comp no.	Mol. Formula	Mol. Wt. (gram)	M.P. (°C)	Yield %	Elemental analysis calculated		
					C	H	N
4a	$C_{16}H_{13}N_3$	247.29	126	66	77.71	5.30	16.99
4b	$C_{16}H_{13}N_3O$	263.29	138	53	72.99	4.98	15.96
4c	$C_{16}H_{13}N_3O$	263.29	135	57	72.99	4.98	15.96
4d	$C_{16}H_{12}ClN_3$	281.74	169	65	68.21	4.29	14.91
4e	$C_{17}H_{15}N_3O$	277.32	173	71	73.63	5.45	15.15
4f	$C_{14}H_{11}N_3O$	237.26	133	52	70.87	4.67	17.71
4g	$C_{16}H_{12}N_4O_2$	292.29	152	64	65.75	4.14	19.17
4h	$C_{16}H_{11}C_{l2}N_3$	316.18	111	69	60.78	3.51	13.29

Table 3: Docking Result of Pyrimidine Derivatives.

Title	Docking score	MMGBSA dG Bind	Complex Energy	Receptor Energy	Ligand Energy	MMGBSA dG Bind (NS)	Lig Strain Energy	Rec Strain Energy
PDB: 6D9H								
Adenosine (Inbound Ligand)	-9.312	-57.6	-10708.37499	-10661.83122	11.055259	-60.7	2.818108	0.287618
4a.mol	-6.922	-48.68	-10750.36977	-10676.73	-24.954776	-51.67	1.849749	1.133744
4b.mol	-8.634	-47.92	-10765.85411	-10676.73	-41.199761	-53.9	2.814803	3.16567
4c.mol	-7.741	-43.67	-10774.34943	-10676.73	-53.94546	-54.85	2.234104	8.944923
4d.mol	-6.785	-49.09	-10757.73626	-10676.73	-31.917345	-60.4	1.828541	9.486257
4e.mol	-7.06	-52.25	-10765.93525	-10676.73	-36.95597	-64.28	2.160639	9.865344
4f.mol	-6.547	-45.91	-10750.37378	-10676.73	-27.732234	-50.09	2.111817	2.067577
4g.mol	-6.454	-49.07	-10746.26513	-10676.73	-20.468405	-60.31	2.351563	8.890267
4h.mol	-6.605	-46.59	-10753.6589	-10676.73	-30.341235	-61.48	3.429705	11.465776

Table 4: Anti-inflammatory activity of Pyrimidine derivatives (4a-4h).

Compound code	Mean paw edema volume±SE					% Inhibition at 4th hr
	0 hr	1 hr	2 hr	3 hr	4 hr	
Control.	1.21±0.03	1.45±0.05	1.59±0.02	1.77±0.02	1.83±0.02	
Std. Nimesulide	1.13±0.03	1.15±0.02**	1.23±0.02**	1.37±0.02**	1.25±0.02**	31.69
4a	1.06±0.02	0.2137±0.021	0.1897±0.016**	0.47±0.02**	0.54±0.02**	70.49
4b	1.06±0.02	0.1932±0.005*	0.170±0.006**	0.1922±0.021**	0.173±0.021**	90.54
4c	1.06±0.02	0.183±0.181*	0.272±0.005	0.246±0.081	0.260±0.051	85.79
4d	1.06±0.02	0.1963±0.0012	0.2015±0.006	0.2517±0.021	0.223±0.06	87.81
4e	1.06±0.02	0.1893±0.02**	0.1763±0.006**	0.190±0.017**	0.173±0.025**	90.54
4f	1.36±0.02	1.301±0.02	1.262±0.006**	1.241±0.021**	1.235±0.025**	32.62
4g	1.38±0.02	1.312±0.02	1.276±0.006**	1.239±0.021**	1.223±0.025**	33.16
4h	1.06±0.02	0.1889±0.02**	0.1772±0.006**	0.1991±0.017**	0.1841±0.025**	89.94

One way ANOVA followed by Dunnett's't' test *p<0.05, **p<0.01-Significant.

- Compound 4a displayed moderate activity (70.49%).
- In contrast, compounds 4f and 4g demonstrated minimal activity (32.62% and 33.16%, respectively), comparable to the standard but significantly lower than the most potent test compounds (Figure 4).

These results suggest that structural features such as hydroxyl, methoxy, and halogen substituents on the aromatic ring strongly influence anti-inflammatory activity. Especially, electron-donating groups such as -OH and -OCH_3 at para or meta positions, as in 4b, 4c, and 4e, enhanced activity significantly. The presence of -NO_2 or -Cl groups also showed variable activity depending on their position.

DISCUSSION

Anti-inflammatory Activity

The anti-inflammatory potential of the synthesized pyrimidine derivatives 4a-4h was evaluated using the carrageenan-induced rat hind paw edema model. Nimesulide was used as the reference standard. Paw volumes were recorded at 0, 1, 2, 3, and 4 hr post-carrageenan injection. The results are summarized in Table 4.

CONCLUSION

The study successfully synthesized and characterized novel pyrimidine derivatives with confirmed purity and structure. Compounds 4b, 4e, and 4h showed significant anti-inflammatory activity in the carrageenan-induced rat paw edema model, comparable to or better than Nimesulide.

Molecular docking studies supported their strong binding affinity to inflammation-related targets. These findings suggest that the synthesized compounds have promising potential as anti-inflammatory agents. However, further studies are needed to explore their mechanism of action and assess *in vivo* toxicity to establish their safety and therapeutic applicability.

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ABBREVIATIONS

MAOS: Microwave-Assisted Organic Synthesis; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **FT-IR:** Fourier Transform Infrared Spectroscopy; **^{1}H-NMR:** Proton Nuclear Magnetic Resonance; **TLC:** Thin Layer Chromatography; **PASS:** Prediction of Activity Spectra for Substances; **MM/PBSA:** Molecular Mechanics/Poisson-Boltzmann Surface Area; **MM/GBSA:** Molecular Mechanics/Generalized Born Surface Area; **COX:** Cyclooxygenases; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **mPGES-1:** Microsomal Prostaglandin E Synthase-1; **PGE_2:** Prostaglandin E_2; **RSC:** Royal Society of Chemistry; **ED_{50}:** Effective Dose for 50% of the Population; **DMSO:** Dimethyl Sulfoxide; **SD Rats:** Sprague-Dawley Rats.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

All animal experiments were conducted in accordance with the ethical standards and guidelines for the care and use of laboratory animals as prescribed by the relevant institutional and national animal ethics committee. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of PRES's, College of Pharmacy (For Women) Chincholi Nashik, under approval number Reg.1345/PO/Re/S/10/CPCEA. The experimental procedures complied with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Efforts were made to minimize the number of animals used and to reduce their suffering. The carrageenan-induced paw edema model was selected as a well-established and minimally invasive method for assessing acute inflammation.

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