World Journal of
Pharmacy and Medical Science

ISSN: 3049-3501
Impact Factor: 3.2
CODEN (USA): WJPMAA

Research Article
2025 Volume 1, Issue 4
Page No.: 23-34

MOLECULAR DOCKING - GUIDED SYNTHESIS AND EVALUATION OF NOVEL COUMARIN DERIVATIVES FOR ANTI-INFLAMMATORY ACTIVITY

Dr. M. Rajasekaran[*1], N. Yuvashree[2], P. Yogalakshmi[2], K. Yukesh[2] and P. Yuvaresh[2]

[*1]Professor Cum HOD Department Of Pharmaceutical Chemistry, Aadhibhagawan College of Pharmacy, Rantham.
[2]B.Pharmacy Final Year Student, Aadhibhagawan College of Pharmacy, Rantham.

Article Received: 07 August 2025 Article Review: 28 August 2025 Article Accepted: 18 September 2025

[*]**Corresponding Author: Dr. M. Rajasekaran**
Professor Cum HOD Department Of Pharmaceutical Chemistry, Aadhibhagawan College of Pharmacy, Rantham.
DOI: https://doi.org/10.5281/zenodo.17235843

How to cite this Article: Dr. M. Rajasekaran, N. Yuvashree, P. Yogalakshmi, K. Yukesh and P. Yuvaresh (2025). MOLECULAR DOCKING - GUIDED SYNTHESIS AND EVALUATION OF NOVEL COUMARIN DERIVATIVES FOR ANTI-INFLAMMATORY ACTIVITY. World Journal of Pharmacy and Medical Science, 1(4): 23-34. https://doi.org/10.5281/zenodo.17235843

Copyright © 2025 Dr. M. Rajasekaran | World Journal of Pharmacy and Medical Science
This is an open-access article distributed under creative Commons Attribution-NonCommercial 4.0 International license (CC BY-NC 4.0)

ABSTRACT
A novel series of coumarin derivatives were synthesized and evaluated for their anti-inflammatory potential. The synthesis pathway involved the preparation of intermediates like 3-acetyl-2H-chromen-2-one, chromene-3-carbonyl chloride, and 3-(2-aminooxazol-4-yl)-2H-chromen-2-one, followed by final coupling with benzoic acid and 4-amino benzoic acid to yield compounds A and B, respectively. These compounds were characterized using physical methods (melting point, solubility, TLC), and confirmed through spectral analysis (IR, NMR, UV). Their anti-inflammatory activity was assessed via the egg albumin protein denaturation assay, with compound A showing a maximum inhibition of 73.94% at 300 mg/mL, surpassing the standard diclofenac sodium. Molecular docking studies against COX-2 revealed strong binding affinities, with compound A showing the lowest binding energy (-10.74 kcal/mol), indicating potent COX-2 inhibition. These results suggest that the synthesized compounds, particularly compound A, may serve as promising leads for the development of anti-inflammatory agents.

KEYWORDS: Coumarin derivatives, Oxazole, Anti-inflammatory activity, COX-2, Molecular docking, Protein denaturation.

1. INTRODUCTION

Medicinal chemistry is a branch of science that combines principles from chemistry, biology, and pharmacology to design, develop, and optimize compounds used as drugs. It primarily focuses on understanding the relationship between the chemical structure of a substance and its biological activity, which is essential for creating effective and safe medications. Medicinal chemists play a vital role in the drug discovery process by identifying potential therapeutic targets, designing new drug molecules, and modifying chemical structures to enhance their efficacy, reduce toxicity, and improve pharmacokinetic properties such as absorption, distribution, metabolism, and excretion (ADME). The field involves not only the synthesis of bioactive compounds but also the study of how these compounds interact with biological systems at the molecular level. With the aid of modern techniques like computational modeling and structure-activity relationship (SAR) analysis, medicinal chemistry has contributed significantly to the development of treatments for various diseases, including cancer, infectious diseases, neurological disorders, and cardiovascular conditions. As an interdisciplinary field, medicinal chemistry continues to be at the forefront of pharmaceutical innovation, aiming to improve human health and quality of life through the discovery of new and more effective therapeutic agents.

Fig. 1: Medicinal Chemistry.

1.1 Drug Design

Drug design is a crucial aspect of medicinal chemistry that involves the process of discovering and developing new medications based on the knowledge of a biological target, such as a protein or enzyme involved in a disease. The goal of drug design is to create molecules that can interact specifically and effectively with the target to produce a desired therapeutic effect. There are two main approaches to drug design: structure-based drug design, which relies on the 3D structure of the target obtained through techniques like X-ray crystallography or molecular modeling, and ligand-based drug design, which uses the information from known active compounds to develop new ones. During the design process, scientists aim to optimize the compound's binding affinity, selectivity, potency, and pharmacokinetic properties, while minimizing toxicity and side effects. Modern drug design often involves computer-aided techniques such as molecular docking, quantitative structure-activity relationships (QSAR), and virtual screening to predict how well a molecule will interact with its target. Overall, drug design is an iterative and multidisciplinary process that plays a key role in creating new therapies for a wide range of diseases.

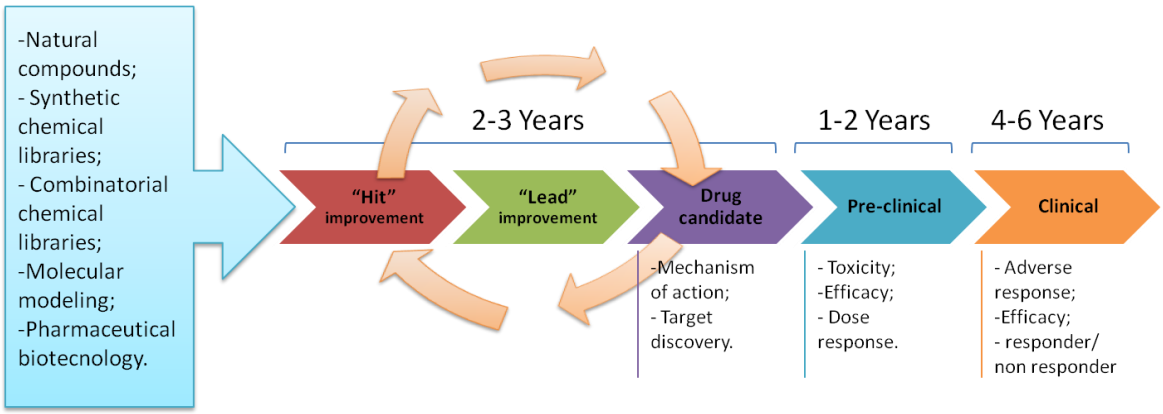


Fig. 2: Drug Design.

1.2 Molecular Docking Study

Molecular docking study is a computational technique used in drug discovery and design to predict the interaction between a small molecule (ligand) and a biological target, usually a protein or enzyme. The main goal of molecular docking is to determine the best binding orientation and conformation of a ligand within the active site of the target, which helps in understanding how the drug might inhibit or activate the target's function. This method provides insights into the strength and nature of the binding interactions, such as hydrogen bonding, hydrophobic interactions, and van der Waals forces. Docking studies are often used to screen large libraries of compounds to identify potential drug candidates before conducting laboratory experiments, saving time and resources. The results of a molecular docking study are typically evaluated using a docking score or binding energy, which estimates how strongly the ligand binds to the target. By predicting the most favorable binding poses, molecular docking helps medicinal chemists in rational drug design, lead optimization, and understanding structure-activity relationships (SAR). It is a valuable tool in modern pharmaceutical research, often used alongside other computational and experimental methods.

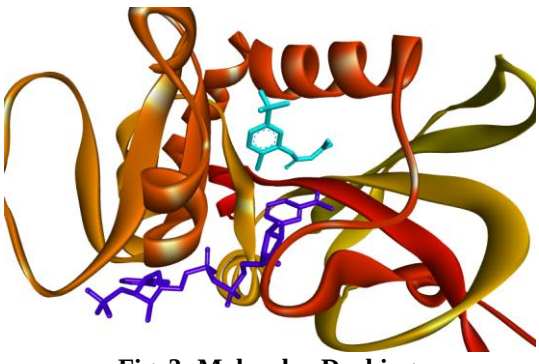


Fig. 3: Molecular Docking.

1.3 Heterocyclic Chemistry

Heterocyclic chemistry is the branch of organic chemistry that deals with the study of heterocyclic compounds, which the cyclic compounds that contain atoms of at least two different element as members. Heterocyclic chemistry deals with compounds containing rings with atoms other than carbon. A heterocyclic

compound is any ring structure that contains at least one atom other than carbon within the ring. Coumarin is a heterocyclic compound. Coumarin is a natural organic compound consisting of a benzene ring fused to a pyrone ring, also known as alpha-benzopyrone, due to it's oxygen containing fused ring system.

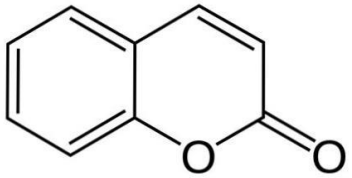


Fig. 4: Chemical Structure of Coumarin.

- Molecular formula: $C_9H_6O_2$
- Molecular weight : 145.15g/mol
- Appearance : white crystals or a crystalline powder
- Melting point : 68-73 degree Celsius
- Boiling point : 291 degree Celsius
- Odour : pleasant
- Taste : bitter
- Solubility : acetone

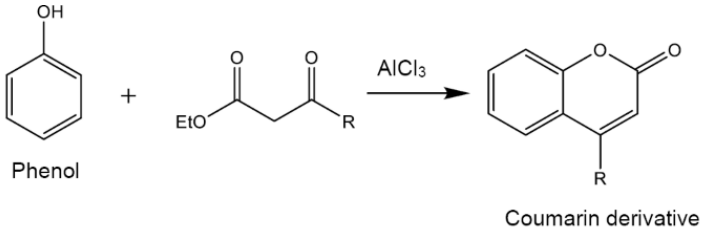


Fig. 5: Synthesis of Coumarin.

2. SCHEME OF WORK

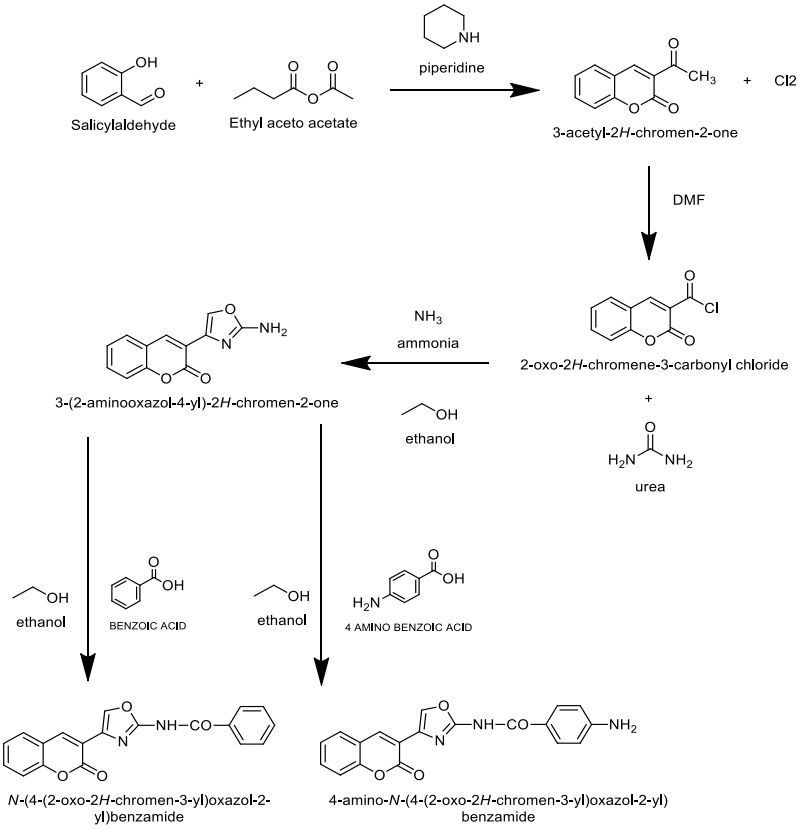


Fig: 6 Scheme of Work.

Fig. 7: Synthesis.

2.1 Synthesis Procedure

Synthesis of 3-acetyl-2H-chromen-2-one

The solution was made up of 25.65mL (0.1mol) ethyl acetoacetate and 21.29mL (0.1mol) salicylaldehyde. In an ice bath, it was chilled. Rapid stirring was used to add 2ml (0.02mol) of piperidine to the liquid. The reaction mixture was held at a low temperature. The yellowish material was separated after 20 minutes, filtered, and washed with ethanol thereafter. It was recrystallized from ethanol from ethanol: water (7:3).

Synthesis of 2-oxo-2H-chromene-3-carbonyl chloride

4.7gm (0.025mol) 3-acetycoumarin was taken in a beaker and dissolved in 20 ml of chloroform. 4gm (0.05mol) chloride was taken in the round bottom flask. 13 ml of chloroform was added to it. The two mixtures were mixed by slowly stirring and refluxing for 1hr. After 1hr reaction mixture was cooled, filtered and washed with petroleum ether. It was recrystallized from ethanol: chloroform (2:1).

Synthesis of 3-(2-aminooxazol-4-yl)-2H-chromen-2-one

1gm of 3-chloro acetyl coumarin (1mol) and 1gm (1mol) of urea were taken in 250 ml of round bottom flask and dissolved in 20 ml of ethanol by slowly stirring for 15min. After 15 min 0.5ml of ammonia was added to it. The reaction mixture was heated under the reflux for 30min. After 30min the reaction mixture was poured in ice cold water (50ml), filtered and dried. It was recrystallized from ethanol.

Synthesis of N-(4-(2-Oxo-2H-Chromen-3-yl)oxazol-2-yl)benzamide

In round bottom flask, 0.7gm (0.005mole) of 3-(2-aminooxazol-4-yl)-2H-chromen-2-one one, 0.5gm and 2ml of benzoic acid added with slowly stirring. The reaction mixture was refluxed for 1-2hr. After 2hr the reaction mixture was evaporated. The resulting solid was washed with cold water and dried. It was recrystallized from ethanol: water (80:20).

Synthesis of 4-amino-N-(4-(2-Oxo-2H-Chromen-3-yl)oxazol-2-yl)benzamide

In round bottom flask, 0.7gm (0.005mole) of 3-(2-aminooxazol-4-yl)-2H-chromen-2-one one, 0.5gm and 2ml of 4-amino benzoic acid added with slowly stirring. The reaction mixture was refluxed for 1-2hr. After 2hr the reaction mixture was evaporated. The resulting solid was washed with cold water and dried. It was recrystallized from ethanol: water (80:20).

Fig. 8: Final Product.

3. MATERIALS AND METHODS

3.1 PHYSICAL CHARACTERIZATION

- Appearance
- Melting Points
- Solubility
- Thin Layer Chromatography

3.2 SPECTRAL CONFIRMATION

- IR Spectrum Analysis
- NMR Spectrum Analysis
- UV Spectrum Analysis

3.3 BIOLOGICAL SCREENING

Anti – Inflammafory Activity: (Egg Albumin Assay)

The anti-inflammatory activity of unknown crude extracts can be determined in vitro for inhibition of the denaturation of egg albumin (protein).

- 0.2 mL of 1-2% egg albumin solution (from fresh hen's egg/ or commercially available egg albumin powder), 2 mL of sample extract or standard (Diclofenac sodium) at varying concentrations, and 2.8 mL of phosphate buffered saline (pH 7.4) were mixed to form a reaction mixture of a total volume of 5 mL.
- A total volume of 5 mL of the control was created by combining 2 mL of triple-distilled water, 0.2 mL of 1-2% egg albumin solution, and 2.8 mL of phosphate-buffered saline.
- The reaction mixtures were then incubated at 37±2°C for 30 min and will be heated in a water bath at 70±2°C for 15 min.
- After cooling, the absorbance was measured at 280 nm by a suitable UV/Vis spectrophotometer using triple distilled water as the blank.[1]
- The following equation was used to determine the % inhibition of protein denaturation.

Percentage of inhibition

Absorbance of control -Absorbance of test sample/Absorbance of control ×100

3.4 Molecular Docking

3.4.1 Protein: cox2

COX-2 (Cyclooxygenase-2) is an enzyme that plays a major role in inflammation and pain processes in the body. It's one of two main isoforms of cyclooxygenase, the other being COX-1**.** COX-2, or Cyclooxygenase-2, is an enzyme that plays a crucial role in the body's inflammatory response. It is one of two main isoforms of cyclooxygenase, the other being COX-1. Unlike COX-1, which is produced continuously in most tissues and is responsible for maintaining normal physiological functions such as protecting the stomach lining and supporting platelet function, COX-2 is inducible and is produced in response to inflammation, injury, or infection. Its primary function is to convert arachidonic acid into prostaglandins, which are lipid compounds involved in promoting inflammation, pain, and fever. Because of its role in inflammation, COX-2 has become a key target in the development of anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and aspirin, inhibit both COX-1 and COX-2, which can relieve pain but may also cause gastrointestinal side effects due to COX-1 inhibition. To reduce these side effects, selective COX-2 inhibitors like celecoxib were developed, although some, such as rofecoxib (Vioxx), were later withdrawn from the market due to increased cardiovascular risks. Beyond inflammation, COX-2 is also implicated in several diseases, including arthritis, certain types of cancer, and neurodegenerative disorders, where its overexpression contributes to disease progression. The gene encoding COX-2 is known as *PTGS2* and is located on chromosome 1. Given its central role in mediating inflammation and pain, COX-2 remains a significant focus in both basic research and drug development.

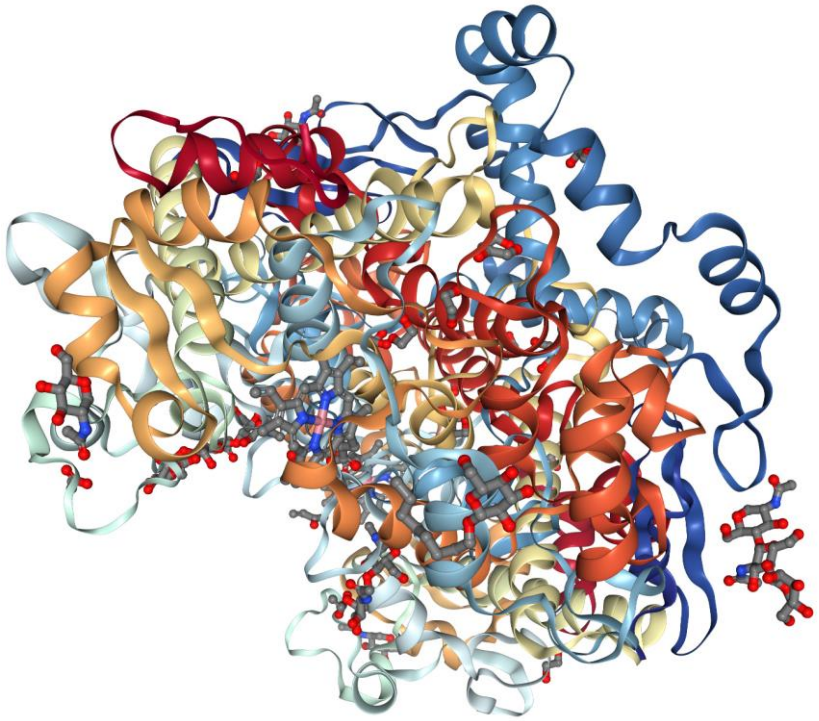


Fig. 9: COX 2 Protein.

3.4.2 Procedure

Molecular docking using AutoDock is a computational technique that predicts the interaction between a small molecule (ligand) and a target protein (receptor), helping researchers understand binding affinity and pose. The process begins with the preparation of the receptor, usually a protein structure obtained from the Protein Data Bank (PDB). In this step, water molecules and unnecessary ligands are removed, and polar hydrogens along with Kollman charges are added. The prepared receptor is then saved in PDBQT format. The ligand, which can be drawn or downloaded from chemical databases like PubChem, is also prepared by optimizing its geometry, adding hydrogens and Gasteiger charges, and defining rotatable bonds before saving it in PDBQT format as well.

After preparation, the next step involves defining the binding site using a grid box in AutoDock Tools. The grid box is positioned over the active site of the protein, and its dimensions are adjusted to cover the region of interest. This setup is saved in a Grid Parameter File (GPF), which is used to run AutoGrid. AutoGrid calculates the interaction energy maps for each atom type

present in the ligand, which guides the docking algorithm during the docking process.

Following this, a Docking Parameter File (DPF) is created, where the user specifies parameters such as the number of docking runs and the search algorithm, typically the Lamarckian Genetic Algorithm. The docking is then executed using the AutoDock software via the command line, producing a Docking Log File (DLG) containing the docking results. These results are analyzed using AutoDock Tools, where different docking poses are evaluated based on binding energy and root mean square deviation (RMSD). The best binding pose, usually the one with the lowest binding energy, is selected for further analysis.

Finally, the docked complex can be visualized using molecular visualization tools such as PyMOL, Discovery Studio, or LigPlot+ to examine hydrogen bonding, hydrophobic interactions, and other key contacts. This molecular docking workflow in AutoDock provides essential insights for drug discovery and rational drug design by predicting how potential drug molecules may interact with target proteins such as COX-2.

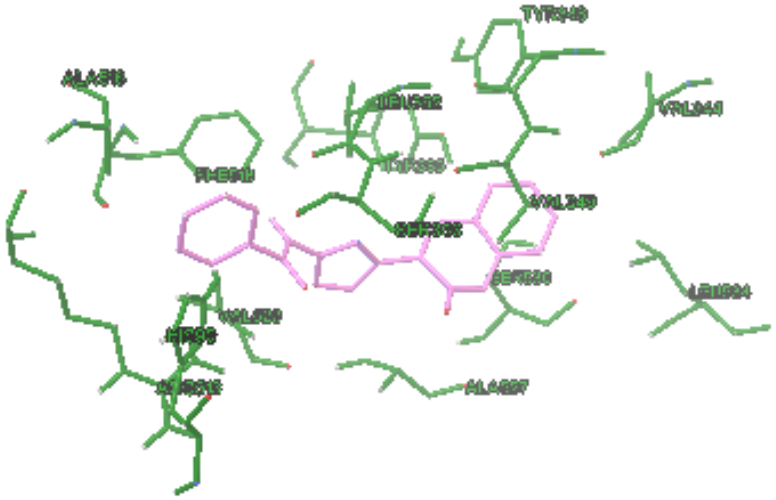


Fig: 10 COX 2 Targeted.

4. RESULTS AND DISCUSSION

4.1 Physical Characterization

Table 1: Physical Characterization.

S. No.	Code	Molecular Formula	Molecular weight	Color	Nature	Percentage yield
1	1	$C_7H_6O_2$	122.12	White	Powder	-
2	2	$C_{11}H_8O_3$	188.18	Yellow	Crystal	96.22%
3	3	$C_{10}H_5ClO_3$	208.60	Yellow	Crystal	95.35%
4	4	$C_{12}H_8N_2O_3$	228.20	Yellow	Crystal	91.31%
5	A	$C_{19}H_{12}N_2O_4$	332.31	Light Yellow	Crystal	90.99%
6	B	$C_{19}H_{13}N_3O_4$	347.32	Dark Yellow	Crystal	91.17%

Fig: 11 Compound A & B.

4.2 Physical Properties

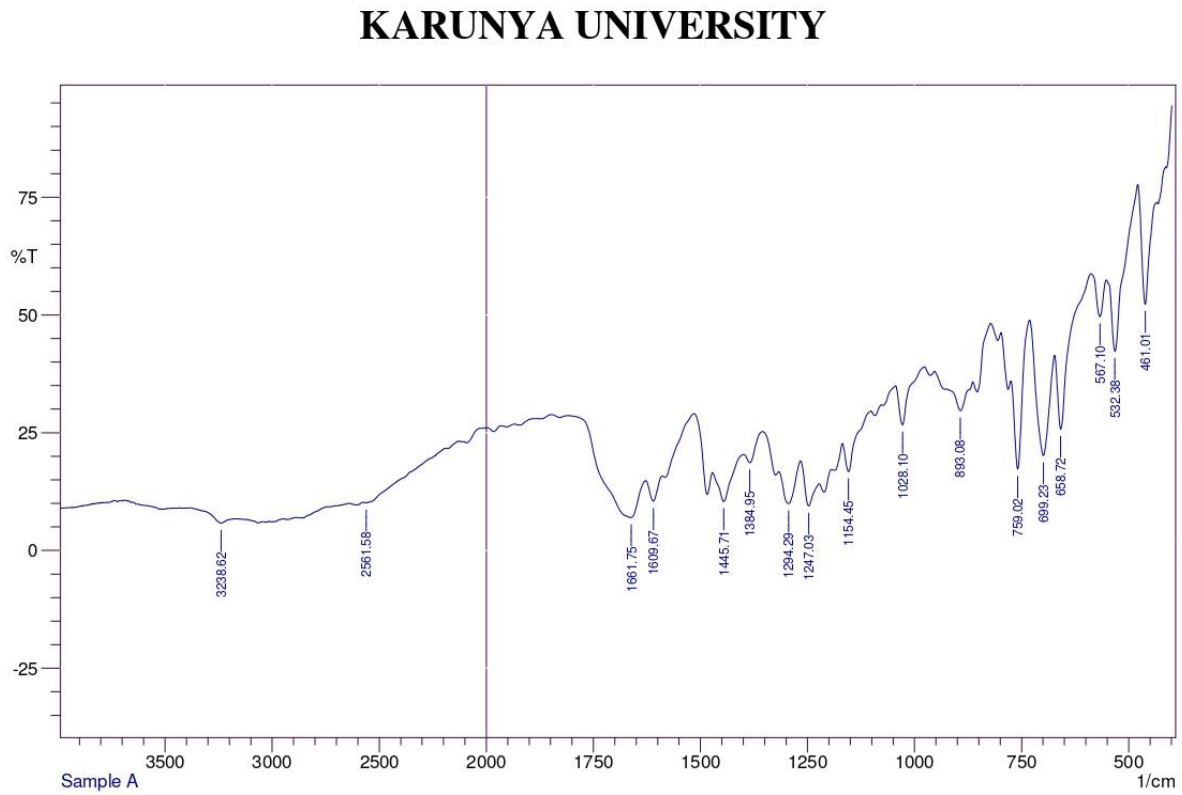
Table 2: Physical Properties.

Code	Melting Point	RF value	Methanol	Ethanol	Chloroform	DMF	DMSO
1	75-80	0.56	+	+~	+~	+	+
2	112-115	0.63	+	+	+	+	+
3	130-135	0.65	+~	+~	+~	+~	+~
4	190-195	0.70	+~	+~	+~	+~	+~
A	270-275	0.71	+~	+	+~	+	+
B	280- 285	0.73	+~	+	+~	+	+

Where
+ → soluble,
- → insoluble,
~ +→ slightly soluble

4.3 Spectral Conformation

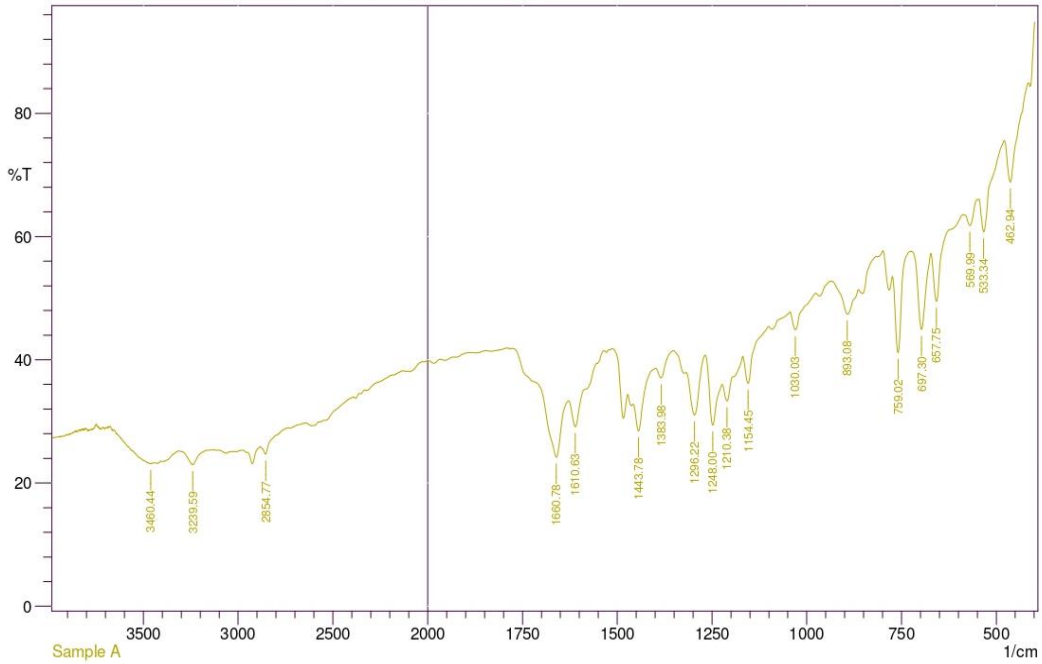
4.3.1 IR Spectrum Analysis



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	461.01	52.293	23.893	479.33	433.04	8.566	2.988
2	532.38	42.329	20.487	551.67	479.33	16.957	4.274
3	567.1	49.67	8.31	587.35	551.67	9.473	1.049
4	658.72	25.765	18.584	673.19	587.35	30.42	4.077
5	699.23	20.145	24.651	731.05	673.19	29.803	9.744
6	759.02	17.277	23.288	774.45	731.05	22.086	5.708
7	893.08	29.683	5.372	924.91	864.15	29.478	1.784
8	1028.1	26.701	9.255	1044.5	976.99	31.854	2.649
9	1154.45	16.761	7.366	1167.95	1102.37	41.388	2.949
10	1247.03	9.453	7.393	1266.32	1222.92	38.826	4.749
11	1294.29	9.948	7.807	1317.44	1266.32	44.796	6.513
12	1384.95	18.612	3.287	1398.45	1355.05	29.128	1.167
13	1445.71	10.398	7.506	1471.75	1398.45	60.309	6.355
14	1609.67	10.469	4.834	1627.99	1589.41	34.384	2.953
15	1661.75	6.992	0.898	1665.6	1627.99	37.344	0.153
16	2561.58	10.121	0.534	2576.04	2187.37	317.479	-3.87
17	3238.62	5.827	1.628	3382.32	3172.07	238.699	5.734

Fig. 12: IR Spectrum of Compound A.

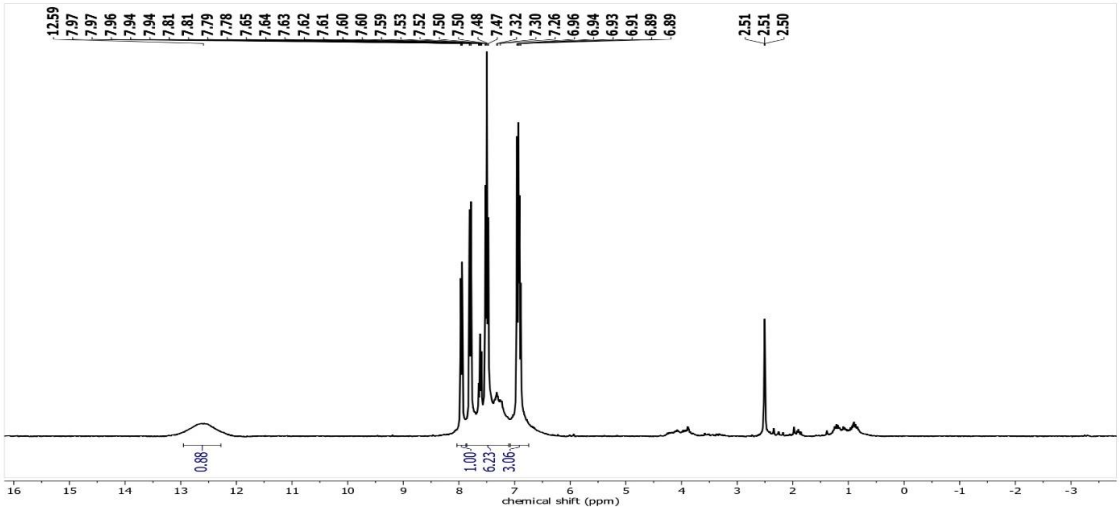
KARUNYA UNIVERSITY



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	462.94	68.855	9.173	479.33	416.64	7.439	1.402
2	533.34	60.774	6.954	544.91	479.33	10.799	0.906
3	569.99	61.798	2.922	588.31	549.74	7.623	0.346
4	657.75	49.487	8.872	672.22	588.31	19.597	1.185
5	697.3	44.917	12.512	726.23	672.22	15.248	2.243
6	759.02	41.171	13.583	773.49	726.23	13.932	1.852
7	893.08	47.388	4.551	935.52	864.15	21.452	1.223
8	1030.03	44.871	3.501	1043.53	976.02	21.517	0.761
9	1154.45	36.184	5.405	1168.91	1101.4	25.815	1.007
10	1210.38	33.335	3.72	1222.92	1168.91	23.576	1.008
11	1248	29.41	9.227	1268.25	1222.92	21.171	2.282
12	1296.22	31.044	8.159	1318.4	1268.25	22.68	2.361
13	1383.98	37.072	2.471	1399.42	1351.19	19.624	0.45
14	1443.78	28.438	5.798	1458.25	1399.42	27.575	1.184
15	1610.63	29.153	5.603	1627.99	1553.73	34.781	2.057
16	1660.78	24.204	10.27	1712.86	1627.99	44.221	5.293
17	2854.77	24.676	1.802	2883.7	2737.11	83.055	0.553
18	3239.59	22.984	2.276	3313.85	3161.47	93.316	2.26
19	3460.44	23.133	0.238	3493.24	3445.01	30.516	0.128

Fig. 13: IR Spectrum of Compound B.

4.3.2 NMR Spectrum Analysis



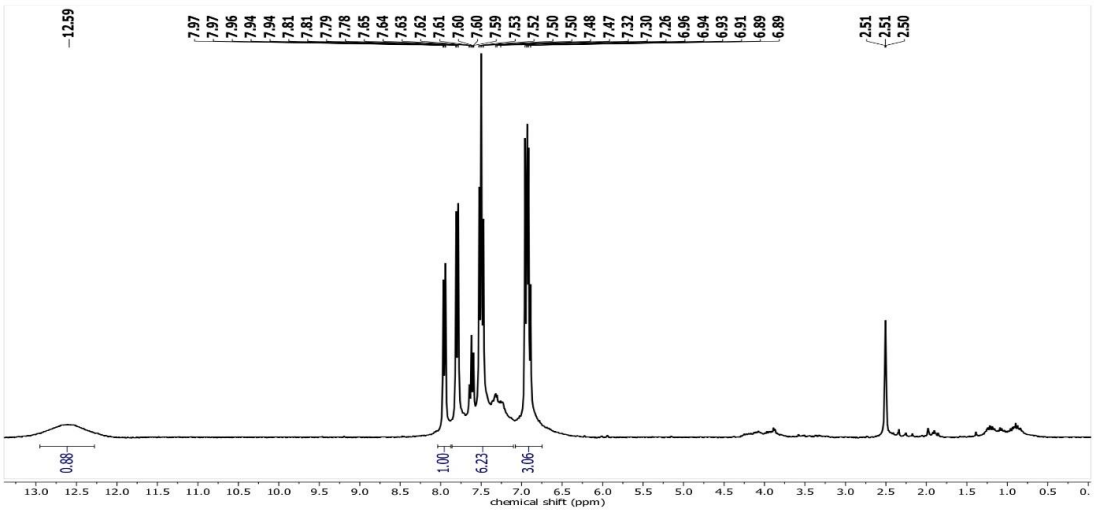
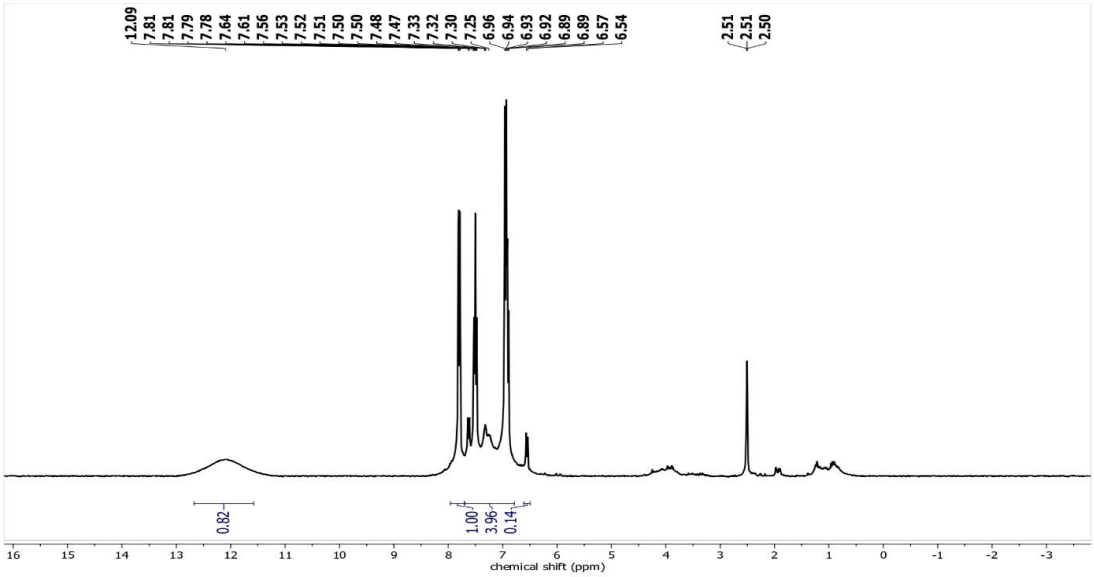


Fig. 14: NMR Spectrum of Compound A.



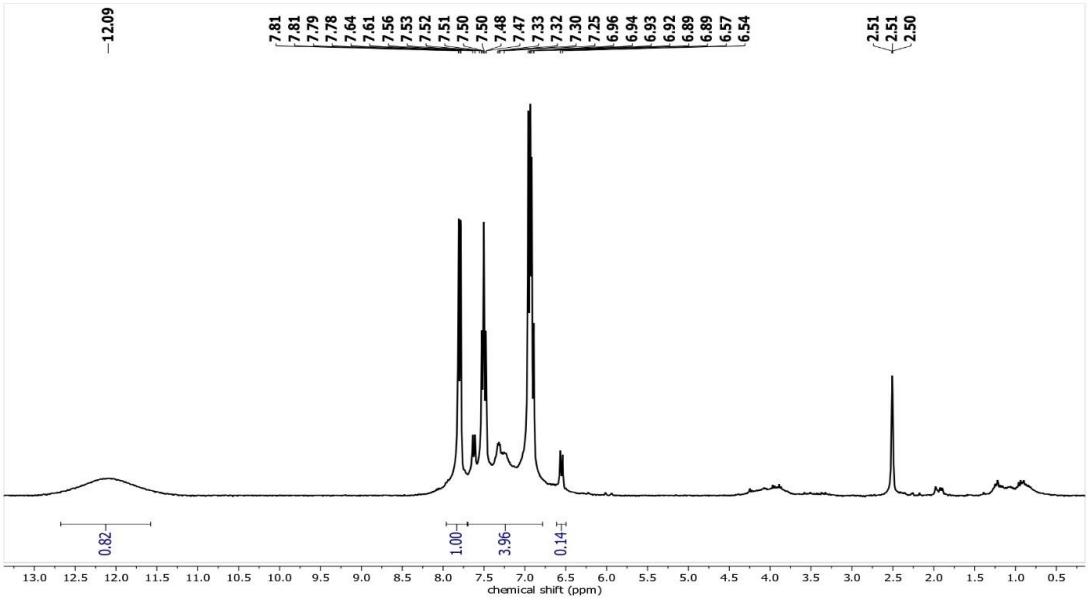


Fig. 15: NMR Spectrum of Compound B.

4.4 Anti – Inflammatory Activity

Table 3: Anti – Inflammatory activity For Compound A.

S. No.	Sample - A	OD Value	% of Inhibition
1	Distilled Water	0.00	-
2	Control	0.449	-
3	Standard	0.146	67.48
4	100 mg	0.129	71.26
5	200 mg	0.123	72.60
6	300mg	0.117	73.94

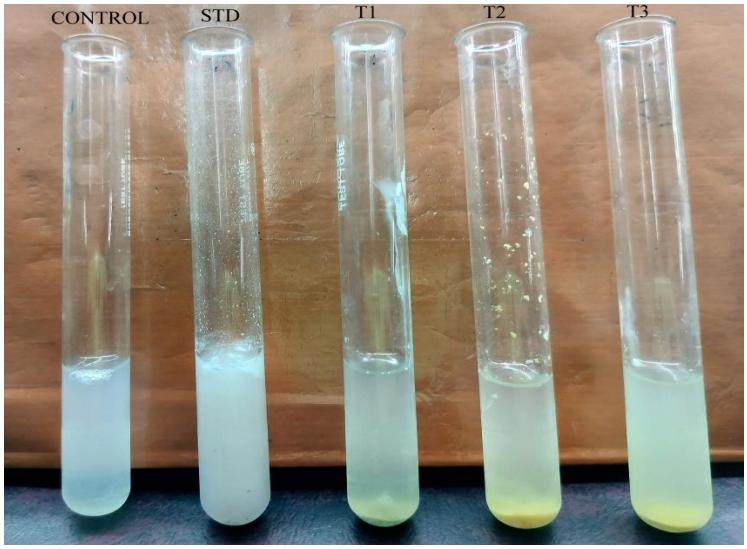


Fig. 16: Anti – Inflammatory activity For Compound A.

Table 4: Anti – Inflammatory activity For Compound B.

S. No	Sample- B	OD Value	% of Inhibition
1	Distilled Water	0.00	-
2	Control	0.449	-
3	Standard	0.146	67.48
4	100 mg	0.185	58.79
5	200 mg	0.179	60.13
6	300mg	0.173	61.46

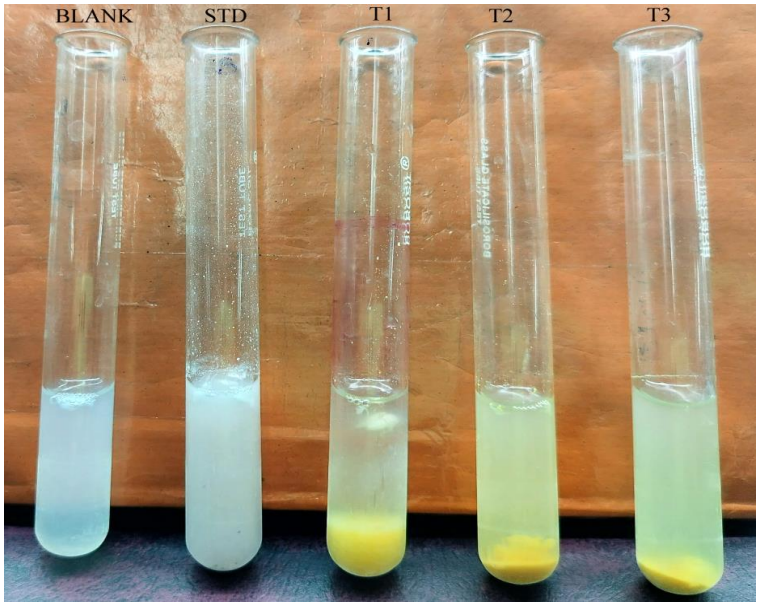


Fig. 17: Anti – Inflammatory activity For Compound B.

4.5 Molecular Docking Study

Table 5: Molecular Docking Data Analysis.

S. No	Parameters	COX - 2	
		Compound A	Compound B
1	Binding Energy	-10.74	-8.95
2	Kl	13.42Nm	275.02Nm
3	Intermolecular Energy	-11.63	-10.14
4	Internal Energy	-0.36	-0.28
5	Torsional Energy	0.89	1.19
6	Unbound Extended Energy	-0.36	-0.28
7	Cluster RMS	0.0	0.0
8	Ref RMS	38.14	38.24

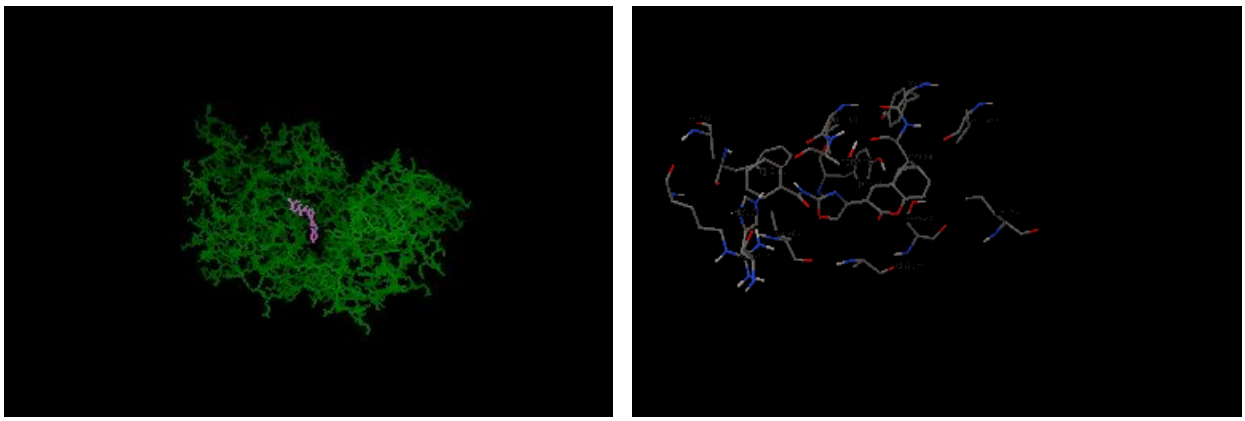


Fig. 18: Docking For Compound A.

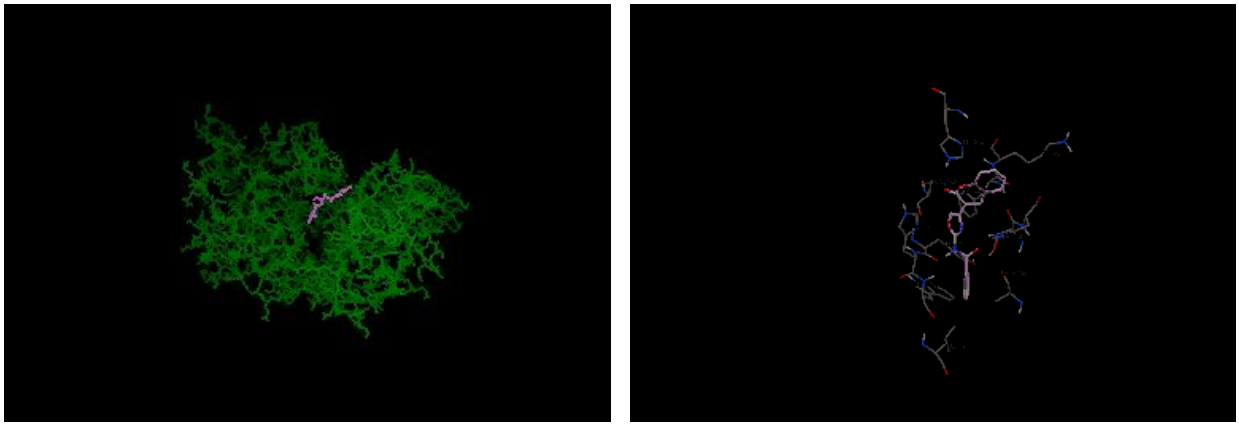


Fig. 19: Docking For Compound B.

5. DISCUSSION

1) **Synthesis Strategy:** The synthesis followed a multi-step process starting from the condensation of ethyl acetoacetate and salicylaldehyde to yield 3-acetyl-2H-chromen-2-one, followed by chlorination and reaction with urea to form an oxazole intermediate. This intermediate was then functionalized using benzoic acid and 4-amino benzoic acid to yield final compounds A and B, respectively. The process was efficiently designed, with high yields in all key steps, demonstrating good reaction control and purification strategies (e.g., recrystallization in ethanol: water or chloroform mixtures).
2) **Physical Characterization and Properties:** Compounds A and B appeared as light and dark yellow crystals with high yields (90.99% and 91.17%). Their high melting points (270–285°C) and consistent Rf values suggest high purity and good stability. Solubility patterns indicated moderate-to-good solubility in polar organic solvents (methanol, ethanol, DMF, DMSO), making them suitable for biological and spectral testing.
3) **Spectral Confirmation:** IR and NMR spectral analysis confirmed the expected structures. The IR spectra displayed characteristic functional group peaks (carbonyl, amide, aromatic, oxazole), while NMR data revealed proton and carbon signals consistent with the coumarin-oxazole skeleton, validating the structural identity of both compounds.
4) **Biological Screening: Anti-inflammatory Activity:** Using egg albumin denaturation assay**,** Compound A demonstrated stronger anti-

inflammatory activity than both Compound B and the standard drug (Diclofenac Sodium). Compound A reached 73.94% inhibition at 300 mg, while Compound B reached only 61.46% at the same concentration. The inhibition trend was dose-dependent in both compounds. This indicates that the presence of a plain benzoic acid moiety (in A) enhances anti-inflammatory potential compared to the amino-substituted benzoic acid (in B).

5) **Molecular Docking:** Docking with COX-2 (a key inflammation mediator) revealed stronger binding affinity for Compound A (Binding Energy: -10.74 kcal/mol) than for Compound B (-8.95 kcal/mol). Lower torsional and internal energy in Compound A indicates a more stable binding conformation. Both compounds showed ideal RMSD values (0.0), confirming docking reliability. The docking results align with the biological data, reinforcing Compound A's superior anti-inflammatory activity.

6. CONCLUSION

The research successfully synthesized and characterized two coumarin–oxazole derivatives through a strategic, high-yielding synthesis pathway. Compound A emerged as the most promising anti-inflammatory agent, as evidenced by its strong inhibition of protein denaturation and superior COX-2 binding affinity in molecular docking studies. The alignment between experimental (biological) and computational (docking) results confirms its potential as a lead compound for anti-inflammatory drug development. Future directions should include in vivo validation**,** toxicity profiling, and structure-activity relationship (SAR) studies.

7. REFERENCES

1. Sharma, Dhayalan, Manikandan & Dandela – *Recent Methods for Synthesis of Coumarin Derivatives and Their New Applications*; covers name reactions, metal- and metal-free catalysis IntechOpen, 2022.
2. Szwaczko – *Coumarins Synthesis and Transformation via C–H Bond Activation*; comprehensive methods using C–H functionalization MDPI, 2022.
3. J. Pharma Insights and Research – *A Review of Synthesis and Therapeutic Applications of Coumarin Derivatives*; modern synthetic routes and green protocols jopir.in, 2024.
4. PMC - *Recent Advances in the Synthesis of Coumarin Derivatives from Different Starting Materials*; conventional and green methods comparison PubMed Central, 2022.
5. PMC – *Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds*; includes silver-mediated radical cyclizations PubMed Central, 2018.
6. Molecules – *Coumarin and Its Derivatives—Editorial*; synthesis and applications overview MDPI, 2021.
7. RSC – *Coumarin Heterocyclic Derivatives: Chemical Synthesis and Biological Activity*; review covering 2000–2014 RSC Publishing.
8. Yan et al. – silver-mediated radical cyclization of alkynoates → 3-aroyl coumarins under mild aqueous conditions PubMed Central.
9. Metal-free radical cyclization using tert-butyl hydroperoxide for coumarin synthesis PubMed Central.
10. Sugino & Tanaka – solvent-free Pechmann and Knoevenagel methods for greener coumarin synthesis organic-chemistry.org, 2001.
11. Sonochemical synthesis – active methylene + 2-hydroxybenzaldehydes under ultrasonic conditions organic-chemistry.org.
12. Moazzam et al. – Direct arylation/aroylation of coumarins with glyoxals, metal-free cross-coupling organic-chemistry.org, 2022.
13. Wikipedia – *Pechmann Condensation*; classic acid-catalyzed method using phenols & β-keto esters Wikipedia.
14. Wikipedia – *Perkin Reaction*; aldehyde + acid anhydride condensation route to coumarins and cinnamic acids Wikipedia.
15. Gadamsetti et al. – room-temperature Pd(OAc)\₂-mediated intramolecular cyclization and solvent-free routes ResearchGate, 2024.
16. Continued from above – palladium-catalyzed oxidative Heck coupling for coumarin frameworks ResearchGate.
17. Wikipedia – *Kostanecki Acylation*; acylation of O-hydroxyaryl ketones leading to coumarins/chromones Wikipedia.
18. Wikipedia – *Auwers Synthesis*; historical route forming flavonols from coumarone derivatives Wikipedia.
19. Chandra S, Chatterjee P, Dey P, Bhattacharya S., Evaluation of In Vitro Anti-Inflammatory Activity of Coffee against the Denaturation of Protein. Asian Pac J Trop Biomed, 2012; 2(1): 178-180.
20. Sen S, Chakraborty R, Maramsa N, Basak M, Deka S, et al., In vitro anti-inflammatory activity of amaranthus caudatus L. Leaves. Indian J Nat Prod Resour, 2015; 6(4): 326-329.
21. Chandra S, Chatterjee P, Dey P, Bhattacharya S., Evaluation of In Vitro Anti-Inflammatory Activity of Coffee against the Denaturation of Protein. Asian Pac J Trop Biomed, 2012; 2(1): 178-180.
22. Sen S, Chakraborty R, Maramsa N, Basak M, Deka S, et al., In vitro anti-inflammatory activity of amaranthus caudatus L. Leaves. Indian J Nat Prod Resour, 2015; 6(4): 326-329.
23. Azmir J, Zaidul ISM, Rahman MM, Sharif KM, Mohamed A, et al., Techniques for extraction of bioactive compounds from plant materials: A review. J Food Eng., 2013; 117(2013): 426-436.
24. Burn JH, Medical Pharmacology. BMJ, 1961; 1961(2): 11.