MOLECULAR DESIGN AND SYNTHESIS OF THIAZOLE-BASED COMPOUND WITH POTENTIAL ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

Inflammation is a complex biological response to harmful stimuli and is closely associated with the progression of various chronic diseases, including cancer, cardiovascular disorders, and autoimmune conditions. Despite the availability of conventional anti-inflammatory drugs, their long-term use is often limited due to adverse side effects, creating a need for safer and more effective alternatives. The present study aims to design, synthesize, and evaluate novel 2-aminothiazole derivatives for their potential anti-inflammatory activity.

A series of 2-aminothiazole derivatives were synthesized using standard chemical methods and characterized by physicochemical and spectral techniques such as infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS). Molecular docking studies were carried out using PyRx software against the DNA gyrase receptor (PDB ID: 4PS8) to predict the binding affinity and interaction patterns of the synthesized compounds. The docking results demonstrated favorable binding energies ranging from –7.9 to –8.6 kcal/mol, indicating strong interactions with the active site of the target protein. Among the synthesized compounds, Compound 7 exhibited the highest binding affinity, suggesting superior binding stability and potential biological activity.

Furthermore, ADMET analysis using pkCSM and Swiss ADME tools revealed that most compounds possess good pharmacokinetic properties, including high intestinal absorption, acceptable distribution, low toxicity, and compliance with Lipinski's Rule of Five, indicating good drug-likeness and oral bioavailability.

In conclusion, the synthesized 2-aminothiazole derivatives demonstrated promising anti-inflammatory potential supported by molecular docking and computational studies. These compounds may serve as potential lead molecules for the development of safer and more effective anti-inflammatory drugs, warranting further experimental validation through in vitro and in vivo studies.

Keywords

2-Aminothiazole, Anti-inflammatory activity, Molecular docking , ADMET analysis PyRx Drug-likeness,

DNA gyrase (4PS8) ,Swiss ADME , pkCSM

CHAPTER NO1:-INTRODUCTION

1. Inflammation:

The term "inflammation" was first used to describe the common symptoms of inflammation, which include heat, pain, swelling (edema), redness (erythema), and decreased function or mobility. According to current knowledge, inflammation is a dynamic biological reaction of bodily tissues to damage. Hazardous substances, exposure to the environment, physical damage, overuse, or infections can all cause these ailments. Because the yaid in the healing of wounds and the management infections , inflammatory reactions canbe advantageous. They might, however, accelerate the course of some chronic illnesses. Inflammation is a key component of disease and serves as a secondary defensive mechanism against pathogenic pathogens. Many inflammatory disorders have the suffix "-itis" at the end. Inflammation requires both cellular and antibody-mediated immune responses. Furthermore, inflammation has been connected to significant severe health problems like cancer and cardiovascular disease, which are the world's top causes of death.

1.1 Pathogenesis

Pain development is intimately linked to chronic inflammation, which is a major contributing factor to many diseases. It results from the body's inflammatory reaction brought on by a number of factors ,such as exposure to dangerous chemicals or radiation, physical injuries like cuts or foreign objects, and pathogens like bacteria ,viruses ,or fungi .There are three phases to the inflammatory process: acute, sub-acute, and chronic (sometimes called proliferative). This process involves specialized immune cells known as inflammatory cells. The hallmark appear during the acute phase, which typically lasts one to three days. The immune system's activity in reaction to various stimuli causes inflammation. Prolonged or chronic inflammation can impair normal immunological tolerance and cause major alterations in tissues and organs, although short-term inflammation is beneficial. In people of all ages, this can impede regular cellular processes and raise the risk of chronic non-communicable diseases. Persistent inflammation can harm healthy tissues and organs over time, resulting in scarring (fibrosis), cell death, and damage to DNA. A significant percentage of deaths globally are caused by chronic inflammatory diseases, which constitute a serious global health concern.

1.2 Types of Inflammation

Acute Inflammation:

The body's temporary reaction to damage, infection, or damaging stimuli is known as acute inflammation. When germs cause harm or infection to the body. White blood cells swiftly traveltothesiteofaninfectioncausedbypathogenslikebacteriaorviruses in order to defend and restore tissues. Redness, heat, swelling, and pain are typical symptoms. Depending on how severe the disease is, this reaction

typically goes away in a few hours or days.

B. Chronic Inflammation:

A persistent inflammatory reaction that can happen even in the absence of an obvious injury is known as chronic inflammation. Persistent inflammation results from the body's constant warnings that something is wrong. It involves immune cells including monocytes, lymphocytes, and macrophages and has a more complicated structure than acute inflammation. Additionally, it is linked to the development of new connective tissue andblood vessels. In general, chronic inflammation lasts longer and is less uncomfortable than acute inflammation in many cases.

1.2 Treatment:

Improved prevention and treatment of inflammation can be achieved by comprehending the molecularmechanismsandbiologicalpathwaysinvolved.Aveterinarian'sclinicaljudgmentis frequently used to diagnose animals. Typical therapies consist of: Corticosteroids: By lowering immunological reactions and managing tissue inflammation, these medications have anti-inflammatory properties. They are frequently used to treat illnesses like respiratory infections. Immuno suppressants: By lowering immune system activity, these drugs lessen inflammation brought on by an over active immunological response.

1.4 Diagnosis:

Serum Protein Electrophoresis (SPEP):

Serum protein electrophoresis, is a trustworthy diagnostic technique for identifying persistent inflammation. It helps detect anomalies by measuring several blood proteins. Any protein level imbalance may be a sign of underlying medical conditions.

B.C-reactive protein(CRP):

The liver responds to inflammation by producing C-reactive protein (CRP). An elevated CRP level in the blood indicates the existence of inflammatory diseases including tissue damage or infections. Despite being a very sensitive indicator, CRP's levels rise in both acute and chronic inflammation, making it difficult to discern between the two. However, CRP values can aid physicians in making a precise diagnosis when they are considered in conjunction with clinical symptoms

C. Erythrocyte sedimentation rate(ESR)

An indirect indicator of inflammation is the erythrocyte sedimentation rate (ESR), sometimes referred to as the sedimentation rate test. This test measures the rate at which red blood cells sink to the bottom of a blood-filled test tube. Ahigher degree of inflammation in the body is typically indicated by a faster settling rate. Infections, autoimmune diseases, and some types of cancer can all be linked to elevated ESR levels. As a result, this test is frequently used in conjunction with other diagnostic instruments to evaluate a patient's general health and spot any possible underlying problems.

D. Other blood tests

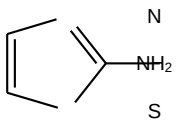
If the doctor believes that a bacteria or virus is the source of the inflammation, they might perform another specific test. The doctor can discuss what to expect in this case.

E. Other diagnostic tests

In some cases, imaging techniques may be necessary to assess specific symptoms. For instance, if a patient has long-term diarrhoea or facial numbness, doctors might recommend scans to evaluate relevant organs or the brain. To diagnose inflammatory conditions in the gastrointestinal tract, doctors often perform procedures that provide direct visualization ofthe digestive system. Common methods include

Colonoscopy- which examines the entire colon, and Sigmoidoscopy- which focuses on the lower part ofthe colon.

2.12-Aminothiazoleanditsderivatives



thiazol-2-amine

2.1. Basic structure and properties of 2- aminothiazole: A heterocyclic amine with a thiazolecoreis called aminothiazole. It mayalso be regarded as a cyclicthiourea. It is soluble in water, alcohols, and diethyl ether and smells like pyridine. 2-With very few exceptions, aminothiazole itself is primarily of academic interest. 2-aminothiazole is a useful building block in the synthesis of numerous bioactive compounds, despite its few practical uses. Its potential in medicinal chemistry is still being investigated by researchers, especially for the creation of novel medications.

2.2Structure-Activity Relationship (SAR):2-aminothiazole derivatives ishighly dependent on the specific biological target(e.g., anti-tubercular, anticancer, antiproton). Generally, the central **thiazole ring and its 4-position substituent are crucial** for activity and often intolerant to modification, while the **N-2 amino position offers significant flexibility** for chemical modification to optimize potency and pharmacokinetic properties.

2.3Central Thiazole Ring: The fundamental**2-aminothiazole core is essential**for activity and generally cannot be replaced by other heterocycles (e.g., thiophene, oxazole) without significant loss of potency. The 2-amino group is crucial and often participates in key interactions, such as hydrogen bonding within the target protein's binding site.

2.4Substituent at the 4-Position (C-4): The nature of the substituent at C-4 is a critical determinant of activity. For many targets (e.g., ant tubercular, antiproton, Src/Abl kinase inhibitors), a **2-pyridyl ring at the**

2.5C-4 positionis required Ring: for potent activity .Other aromatic or hetero aromatic rings can be tolerated,

but often result in reduced potency compared to the 2-pyridyl group. Alkyl groups at this position are generally less effective or inactive. The co-planar arrangement of the C-4 aryl/heteroaryl ring and the thiazole ring often appears important for activity.

2.6 Substituent at the 2-Amino Position (N-2): This position exhibits high flexibility and isa primarysite for structural modification to improve activity, selectivity, and pharmacokinetic profiles (e.g., metabolic stability, brain penetration).

2.7 Acylation (forming an amide): Of theN-2amineisacommon and effective modification that can dramatically increase potency. The nature of the acyl group (aliphatic vs. aromatic, size, electronic properties) influences activity, with specific groups being optimal for different targets. For antitubercular activity, *m*-chlorobenzyl groups were highly effective.

For anticancer activity (e.g., as PI3K inhibitors), the linker length and specific substituents (e.g., certain proline amides or acyclic chains) are critical for binding affinity and selectivity.

Modifications at this position can also influence the molecule's interaction with metabolizing enzymes, allowing for the tuning of metabolic stability and reduction of potential toxicity.

2.8 Substituent at the 5-Position (C-5): The C-5 position can be modified, though its impact varies. In some cases (e.g., certain anticancer agents), lipophilic or specific functional groups (likeisothiocyanatomethyl) at C-5 are important for activity. In other instances, substitution at the C-5 position can lead to a loss of activity or altered activity profiles.

3. Molecular docking:-

The appropriate orientation of a ligand molecule that allows it to interact with a receptor and form a stable complex is known as molecular docking. This technique is widely used to predict binding affinity and evaluate the strength of interactions between ligands and protein targets through scoring functions. Molecular docking also helps in understanding drug–receptor interactions and predicting the biological activity of molecules.

3.1 Types of Molecular Docking

Rigid Docking: In rigid docking, both the receptor and ligand molecules are treated as fixed structures. No conformational changes are allowed during the docking process, and the interaction is evaluated based on their static geometries.

Flexible Docking: In flexible docking, either the ligand, the receptor, or both are allowed to undergo conformational changes. The molecules can rotate and adjust their structures, and the energy of each conformation is calculated. Surface interactions and occupancy are evaluated for different conformations, and the most energetically favourable binding pose is selected.

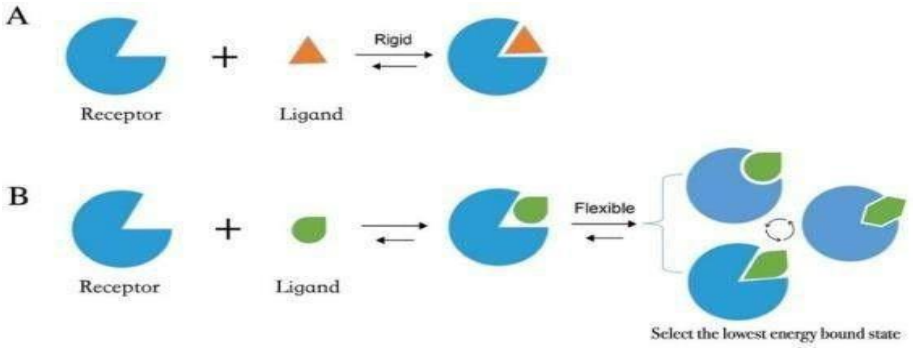


Fig.1.RigidandFlexibleDocking

3.2Molecular docking mechanics steps: Molecular docking is anin-silico technique used to study intermolecular interactions between drug molecules and biological targets. In this process, the protein receptor acts as a macromolecule, while the ligand acts as a small molecule that may function as an inhibitor or activator. The following steps are involved in the molecular docking process:

Step I: Preparation of Protein: The three-dimensional structure of the target protein is obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB**)**. The downloaded protein structure is then pre-processed by removing water molecules, stabilizing charges, correcting missing residues, adding hydrogen atoms, and generating side chains. This preparation ensures proper docking conditions.

Step II: Ligand Preparation: Ligand molecules can be obtained from databases such as ZINC and Pub chem. alternatively; ligand structures may be drawn using chemical drawing software such as Chem Sketch. The prepared ligands are then optimized, and drug-likeness properties are evaluated using Lipinski's Rule of Five. This rule helps in identifying compounds with better pharmacokinetic properties and increases the probability of successful drug development.

Step III: Grid generation defines the binding region of the protein where docking will occur. Parameters such as rotatable bonds, excluded volumes, and constraints are specified. Binding cavity prediction is performed to determine the active region of the protein.

Step IV: Active Site Prediction of the protein is identified before docking. During protein preparation, water molecules and heteroatoms present in the binding cavity are removed to improve docking accuracy.

Step V: Docking: Docking is performed to analyse ligand-protein interactions. Multiple conformations are generated, and docking scores are calculated. The best binding pose withthe lowest energy and highest docking score is selected for further analysis.

3.3PyRx Software: - PyRx virtual screening tool software was used in the molecular docking studies along with the Graphical User Interface (GUI) to build a grid, create a dock score and evaluate conformers. PyRx is a virtual a screening tool for computational drug discovers and property that can be used to check compound libraries against desired target for drugs. This software helps to decrease time and resources which are required to test the whole database

Experimental by selecting most promising ones only. Docking based virtual screening (DBVS) method helps to find out the binding behaviour of small molecules to targets and also helps in selection of best interaction of molecule for testing.

3.4pKCSM Analysis

PKCSM is a computational method that uses graph-based signatures to predict the pharmacokinetic and toxicity characteristics of small molecules.By training predictive models on molecular features, such as atomic Pharmacophore and molecular properties like lipophilicity and molecular weight, it covers important ADMET (absorption, distribution, metabolism,excretion,andtoxicity)properties.Indrugdiscovery,pkCSMisusedtominimize late-stage failures and quickly screen compounds for favourable ADMET profiles. This approach allows researchers to identify promising candidates early in the development process, ultimately leading to more efficient and cost-effective drug design. By leveraging advanced machine learning techniques, pkCSM can adapt to new data, improving its predictive accuracy and enhancing the overall success rate of new pharmaceuticals.

3.5Swiss ADME Analysis: Swiss ADME Analysis: Swiss ADME is a free online tool that evaluates a compound's medicinal chemistry friendliness, drug-likeness, and several ADME properties. It offers approximations for pharmacokinetics (including P), water solubility,

CHAPTER NO.3: OBJECTIVES

1. To study the biological mechanism and mediators involved in the process of inflammation.

2. To design and synthesize novel compounds with potential anti-inflammatory activity.

3. To evaluate the synthesized compounds for their effectiveness in reducing inflammation.

4. To compare the activity of the new compounds with standard anti-inflammatory drugs.

5. To identify compounds with improved efficacy and fewer side effects for future therapeutic use

CHAPTER NO.4: NEED OF INVESTIGATION

1. Chronic inflammation causes major diseases

Such as cancer, diabetes, arthritis, asthma, cardiovascular and neurodegenerative disorders. Better drugs are needed to prevent and manage these conditions.

2. Limitation so fexisting drugs

NSAID sand corticosteroids, though effective, are not suitable for long-term use due to serious side effects like gastric ulceration, renal failure, liver toxicity, hormonal imbalance, and increased infection risk.

3. Drug resistance and reduced efficacy

Patients may develop poor response or intolerance to current therapy, demanding new alternatives.

4. Need for targeted therapy

Modern research aims to specifically block inflammatory pathways (e.g., cytokines, COX-2, NF-κB) to improve effectiveness without disturbing normal immune functions.

5. Demand for safer long-term medications

Chronic diseases require continuous treatment, so drugs with better safety profiles are necessary.

6. Exploration of natural and green alternatives

Medicinal plants, phytochemicals, and eco-friendly synthesized compounds offer potential candidates with fewer adverse effects.

7. Improvement in patient quality of life

Reducing side effects and increasing effectiveness enhances therapy outcomes and patient compliance

CHAPTER NO.5: MATERIAL SANDMETHOD

TableNo.1. Software's used in Docking Study and their Company names.

Softwares	Company Name
ChemDraw	Cheminformatics
ChemSketch	ACD/Labs
BIOVIA Discovery Studio	Dassault Systems
PyRx0.8 program	SourceForge

TableNo.2.Chemicals Used in Synthesis and Their Company Names.

Chemicals	Company Name
Hydroxybenzaldehyde	LOBA Chemicals
Thiourea(0.01mol)	LOBA Chemicals
Ethanol(15–20 mL)	LOBA Chemicals
Glacialaceticacid(2–3 drops)	LOBA Chemicals
p-Nitrobenzaldehyde	LOBA Chemicals
2-Hydroxybenzaldehyde	LOBA Chemicals

TableNo.3.Instruments

NameOf Method	Instrument Used
Melting Point	Thie's Tube
IR	FT-IR(Shimadzu)

Method:-PKCSM

Is a useful drug discovery tool that assesses the pharmacokinetic and toxicity profiles of small molecules using graph-based signatures ?It efficiently evaluates key ADMET characteristics,

such as absorption, distribution, metabolism, excretion, and toxicity, by utilizing predictive models based on molecular features. By reducing late-stage failures and speeding up the screening of possible compounds, this approach improves the drug development process. Promising candidates can be swiftly identified by researchers, resulting in more effective and successful drug discovery outcomes. All things considered, pkCSM is essential to contemporary pharmacology because it enables researchers to make well-informed choices earlyin the development process. Its capacityto forecast molecular interactions and behaviors facilitates a more efficient transition from the lab to the marketplace.

Swiss Analysis of ADME

Swiss ADME Analysis: Swiss ADME is a free online tool that evaluates a compound's medicinal chemistry friendliness, drug-likeness, and several ADME properties. It offers approximations for pharmacokinetics (including P), water solubility, lipophilicity, and physicochemical characteristics. Water solubility, lipophilicity, physiochemical characteristics, and synthetic accessibility. Swiss ADME is designed to help drug discovery medicinal chemists choose compounds for synthesis and additional testing. It is based on robust machine learning models and a fragment-based scoring system for synthetic accessibility.

Ligand preparation: ACD/ChemDraw software was used to create the designed compounds' chemical structures and SMILES notations. BIOVIA Discovery Studio was then used to protonate the generated structures in order to guarantee appropriate tautomeric and ionization states. Using the Avogadro software, the prepared structures' energy was minimized. In order to achieve stable conformations, the developed compounds were further optimized using Chem3D Ultra. Table 1 displayed the newly designed ligands' structures.

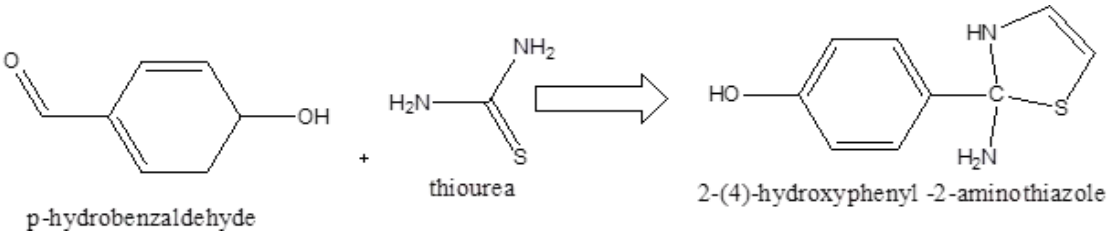
Protein Preparation: The RCSB Protein Data Bank provided the crystal structure of DNA gyrase in an incredibly open clamp conformation (PDB ID: 4PS8) with a resolution of 2.6 Å. To create a clean receptor model, the protein structure was stripped of all heteroatoms and water molecules. For the amino acid residues to be properly protonated, polar hydrogen atoms were added. BIOVIAD iscovery Studio was used to prepare and refine protein structures.

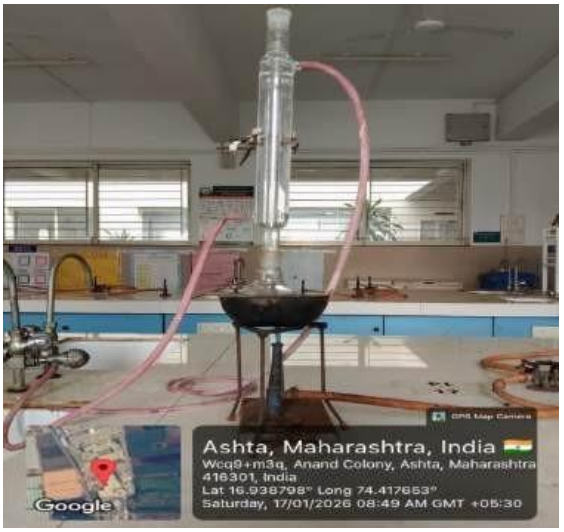
Molecular Docking: The docking procedure was performed using the PyRx 0.8 program. Using PyRx 0.8's AutoDockVina wizard unit, prepared protein and ligand structures were imported and chosen .The blind docking protocol was used to examine docked molecules'

Capacity to bind to the entire protein surface. The grid box's dimensions were selected to be X: X: X: 103.8633, 113.4580, and80, and Z: 146.6926, and its center coordinates were X: 96.8294, Y: -10.041, and Z: 308.5555. The default setting for exhaustiveness was 8. Each compound's docked pose with the highest negative binding affinity was saved in pdb format, and BIOVIADiscovery Studio was used to examine additional binding interactions.

Procedure:

Derivative1. Synthesisof–2-(4-Hydroxyphenyl)-2-aminothiazole





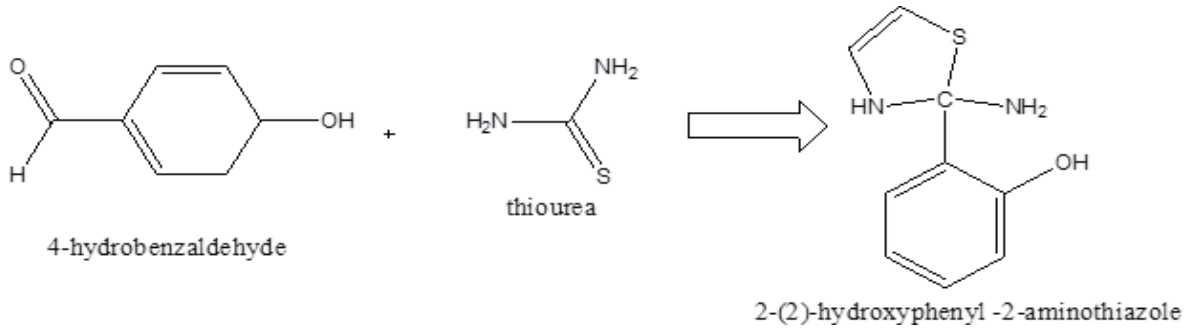
With constant stirring,0.01mol hydroxybenzaldehyde was dissolved in15–20mLofethanol. After that, 0.01 mol of thiourea was gradually added to the mixture and stirred until it completely dissolved. As a catalyst to encourage condensation, two to three drops of glacial acetic acid were added to this reaction mixture.

For two to four hours, the reaction mixture was either gently heated at40 to 50 °C or stirredat room temperature. Schiff base formation was the first step, and then slow cyclization produced derivatives of 2-substituted-2-aminothiazole.

The mixture was left to stand at room temperature for the entire night after the reaction was finished, during which time the solid product progressively separated out. To finish the precipitation process, the reaction

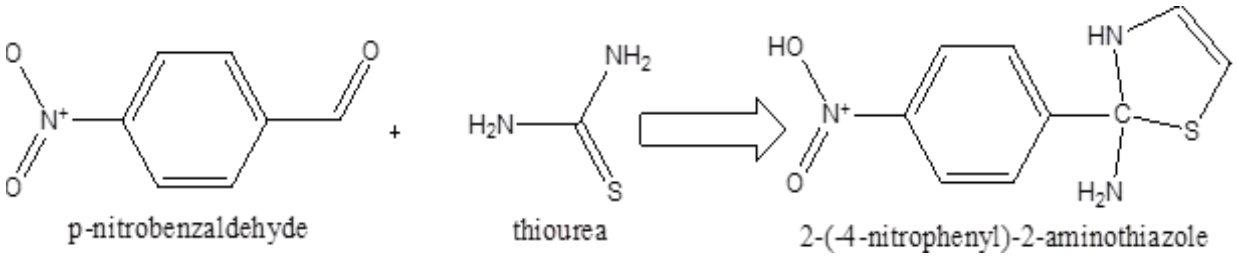
mixture was then added to ice-cold water.

Derivative2. Synthesis of 2-(2-hydroxyphenyl)-2-aminothiazole.



Ethanol (15–20 mL) was mixed with 0.01mol of 4-hydroxybenzaldehyde while being constantly stirred. After adding thiourea (0.01mol) to the mixture gradually, two to three drops of glacial acetic acid were added as a catalyst. After stirring the reaction mixture at room temperature or slowly heating it to 40–50°C for two to four hours, the separated solid product was added to ice-cold water to finish precipitating. To obtain pure 2-(2-hydroxyphenyl)-2-aminothiazole, the precipitate was filtered, cleaned with cold water, dried at 50–60°C, and then recrystallized from ethanol.

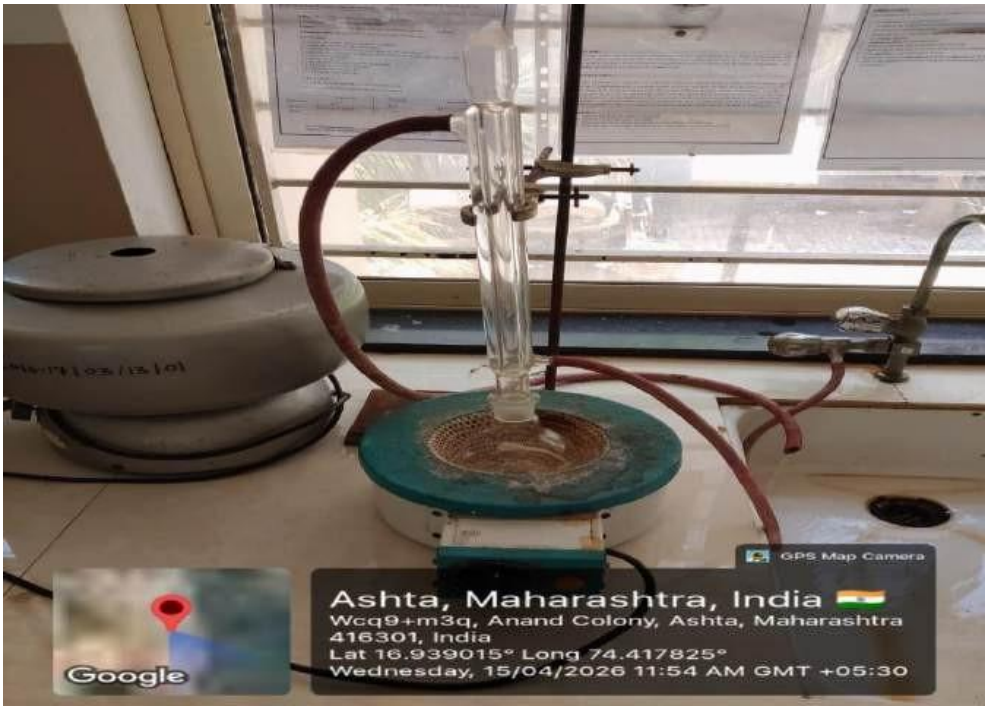
Derivative3.Synthesis-2-(4-Nitrophenyl)-2-aminothiazole



With constant stirring, p-nitro benzaldehyde (0.01 mol) was dissolved in 15–20 mL of ethanol. After adding thiourea (0.01 mol) to the mixture gradually, two to three drops of glacial acetic acid were added as a catalyst. For two to four hours, the reaction mixture was either gently heated at 40 to 50 °C or stirred at room

temperature.

The mixture was left to stand at room temperature for an entire night after the reaction was finished. To finish the precipitation process, the separated solid product was added to ice-cold water. To obtain pure 2-(4-nitrophenyl)-2-aminothiaz, the precipitate was filtered, cleaned with cold water, dried at 50–60 °C, and then recrystallized from ethanol. The final product was characterized using various analytical techniques to confirm its identity and purity. These methods included NMR spectroscopy and mass spectrometry, which provided insight into the molecular structure and confirmed the successful synthesis of the compound.



Method In vitro anti-inflammatory activity by Protein Denaturation Method

The reaction mixture (10 mL) consisted of 0.4 mL of egg albumin (from fresh hen's egg), 5.6 mL of phosphate buffered saline (PBS, pH 6.4) and 100 µL of different concentration sample. Similar volume of double-distilled water served as control. Then the mixtures were incubated at (37^0c ±2) in a incubator for 15 min and then heated at 70ºC for 5 min. After cooling, their absorbance was measured at 660 nm by using vehicle as blank. Diclofenac sodium at the concentration was used as reference drug and treated similarly for determination of absorbance. The percentage inhibition of protein denaturation was calculated by using the following formula,

% Inhibition = C -T/ C

Were,

T = absorbance of test sample C = absorbance of control

CHAPTER NO.6:-RESULT AND DISCUSSION

The results of the present study demonstrated that the synthesized 2-aminothiazole derivatives possess promising anti-inflammatory potential based on molecular docking, ADMET profiling, and physic chemical evaluation .Molecular docking studies against the DNA gyrase receptor **(PDB ID: 4PS8)** showed that all eight compounds exhibited favorable binding affinities ranging from **–7.9 to –8.6 kcal/mol**, indicating strong interaction with the active site of the target protein. Among them, Compound 7 showed the highest binding

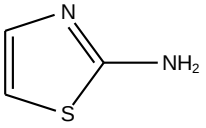
affinity **(–8.6 kcal/mol),** followed by **Compound 1 (–8.4 kcal/mol), Compound 8 (–8.3 kcal/mol**), and **Compound 5 (–8.2 kcal/mol),** suggesting strong and stable binding behavior. Thecom pounds formed important interactions such as conventional hydrogen bonds, carbon-hydrogen bonds, π-alkyl, π-sigma,π-sulfurinter actions, and π–πstacking with keyamino acid residues**likeARG550,ASP841,TYR867,VAL882,LEU838,andLYS833**.ADMET

Analysis using pkCSM revealed that most compounds showed highintest in al absorption bove **70%**, with **Compounds 1, 4, 5, 6, 7, and 8** showing excellent absorption above **90%**, along with good distribution, low **CNS permeability, non-mutagenic nature (AMES negative**), and non-hepatotoxic behavior, indicating a favorable safety profile. **Compounds 4, 5, 6, and8** demonstrated the most balanced pharmacokinetic properties. Swiss ADME analysis further confirmed that all compounds followed **Lipinski's Rule of Five** without any **Ghose or Veber** violations, indicating good drug-likeness and oral bioavailability. Physicochemical characterization showed thatDerivatives1 and 2 had the same molecular formula($C_9 H_8 N_2$ OS) and molecular weight **(192.24 g/mol)** with melting points of **197°C and 190°C** respectively, whileDerivative3 had a molecular formula of **$C_9 H_7 N_3$ OS**, molecular weight of **221.24 g/mol,** and melting point **o**f **154°C**, confirming structural differences and successful synthesis. IR, NMR, and MS spectral studies further validated the identity and purity of the synthesized compounds. Overall, the results suggest that 2-aminothiazole derivatives, especially **Compound 7,** represent promising lead molecules for the development of safer and more effective anti-inflammatory drugs and warrant further in vitro and in vivo biological evaluation

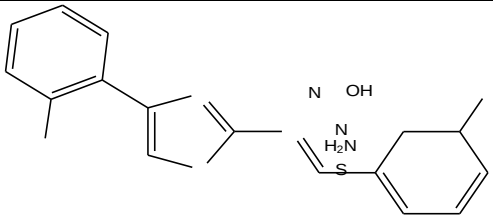
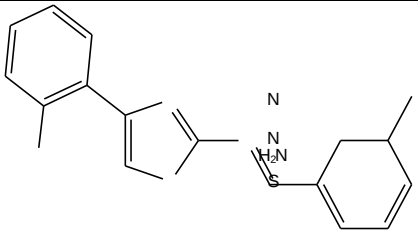
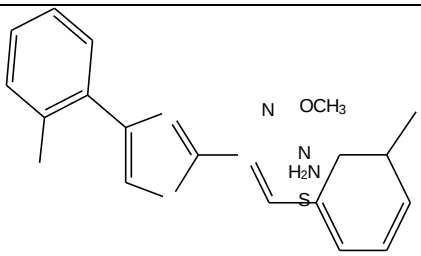
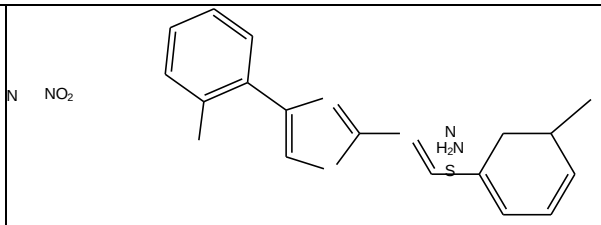
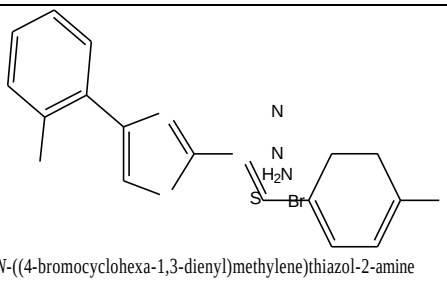
The study confirms that 2-aminothiazole derivatives are promising lead molecules for anti-inflammatory drug development. Among all evaluated compounds, Derivative 1 (biological activity) and Compound 7 (docking study) emerged as the most promising candidates.

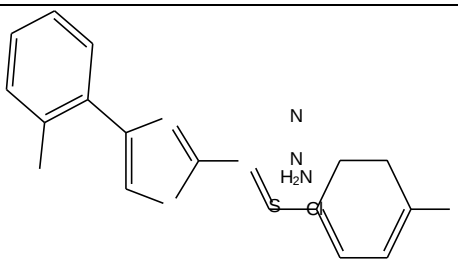
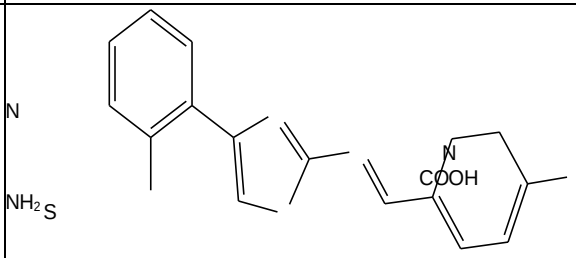
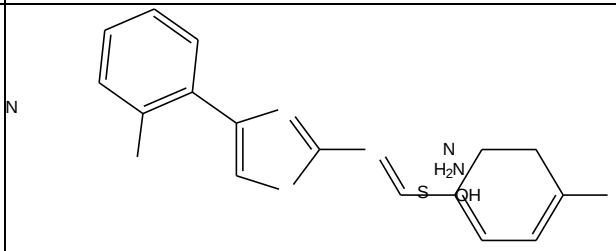
Table No-4:Newly designed2- Aminothiazole

General structure



thiazol-2-amine

Compound code	Compound structure
1	 (*E*)-5-((4-(2-aminophenyl)thiazol-2-ylimino)methyl)cyclohexa-2,4-dienol
2	 (*E*)-4-(2-aminophenyl)-*N*-((5-methylcyclohexa-1,3-dienyl)methylene)thiazol-2-amine
3	 (*E*)-4-(2-aminophenyl)-*N*-((5-methoxycyclohexa-1,3-dienyl)methylene)thiazol-2-amine
4	 (*E*)-4-(2-aminophenyl)-*N*-((5-nitrocyclohexa-1,3-dienyl)methylene)thiazol-2-amine
5	 (*E*)-4-(2-aminophenyl)-*N*-((4-bromocyclohexa-1,3-dienyl)methylene)thiazol-2-amine

6	 (*E*)-4-(2-aminophenyl)-*N*-((4-chlorocyclohexa-1,3-dienyl)methylene)thiazol-2-amine
7	 (*E*)-4-((4-(2-aminophenyl)thiazol-2-ylimino)methyl)cyclohexa-1,3-dienecarboxylicacid
8	 (*E*)-4-((4-(2-aminophenyl)thiazol-2-ylimino)methyl)cyclohexa-1,3-dienol

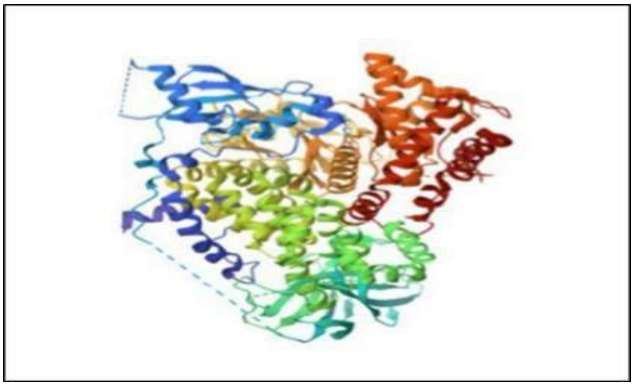
TableNo.5.Binding affinity along with binding interactions of designed compounds Against PDB 4PSD

Com. Code	PDBID	Binding Affinity Com.	Interacting residues Compound	Type of interaction Compound	Distance Com
1	4PS8	**-8.4**	ASP841 TYR867	Carbon Hydrogen bond	3.29 5.15
			LYS833 ILE881	Pi alkyl	4.72 5.05
2	4PS8	-7.9	VAL882	Conventional Hydrogen bond	4.38
			LEU838 LYS833	Pi alkyl	4.68
			ARG634	Pi-sigma	3.84

3	4PS8	**-8.1**	ARG550 TYR297 ASP348	Conventional hydrogen bond	3.19
			TYR867 ASP841	Carbon- Hydrogenbond	3.29 5.15
4	4PS8	**-7.9**	TYR845	Carbon Hydrogen bond	3.55
			ILS963	Pi-alkyl	4.60
5	4PS8	**-8.2**	VAL882	Conventional Hydrogen bond	2.92
			LYS833	Carbon Hydrogen bond	4.72
			HIS1052	Pi-sigma	3.77
			MET812 TRP812	Pi-sulfur	3.65 5.32
6	4PS8	**-8.0**	VAL882	Conventional hydrogen bond	3.19
7	4PS8	**-8.6**	TYR867 ASP842	Carbon Hydrogen bond	3.28 4.71
			LYS833 ILE881	ialkyl	5.04 5.32
8	4PS8	**-8.3**	VAL882	Conventional Hydrogen bond	3.19
			LEU838	Pi alkyl	3.80

"The molecular docking results of the synthesized compounds **(1–8)** against the target protein **(PDB ID: 4PS8**) demonstrated favourable binding affinities ranging from **−7.9 to −8.6 kcal/mol**, indicating good interaction with the active site of the protein. Among all the tested compounds,**Compound7** exhibited the **highest binding affinity (−8.6 kcal/mol),**suggesting strong binding stability and potential biological activity. Most compounds formed significant interactions such as conventional hydrogen bonds, carbon–hydrogen bonds, π–alkyl, π–sigma, andπ–sulfurinteractionswithkeyaminoacidresiduesincluding**ASP841, TYR867, LYS833, VAL882, and LEU838**. These interactions indicate that the synthesized compounds possess good binding capability with the target protein and may exhibit promising anti-inflammatory activity. Overall, the docking study

supports the potential of thiazole derivatives as effective candidates for further biological evaluation.

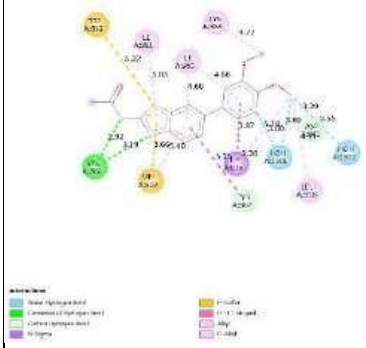
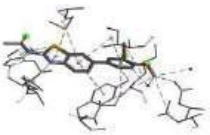
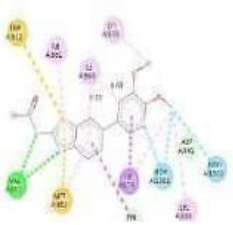
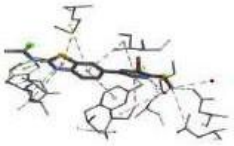


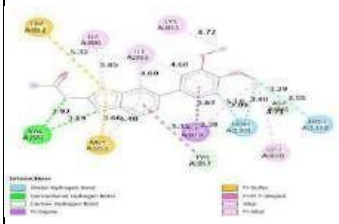
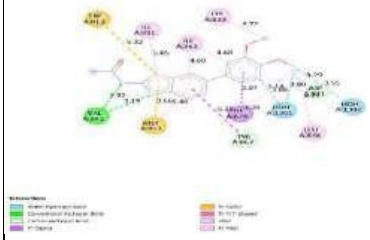
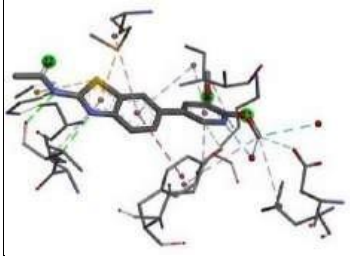
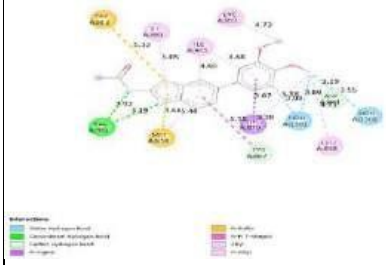
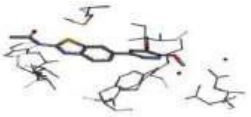
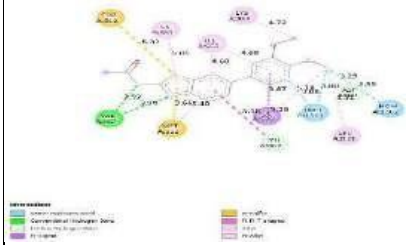
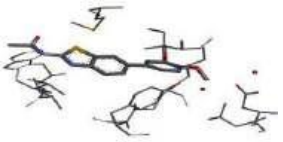
FigNo.2:PDB4PS8

CLASSIFICATION: TRANSFERASE/TRANSFERASEINHIBITOR

Organism(s): Homosapiens

TableNo.6.2D and 3D interaction diagrams of 2Aminothiazole derivative structure Against the 4PSD

Com. Code	2Dinteraction	3Dinteraction
1		
2		

3		
4		
5		
6		

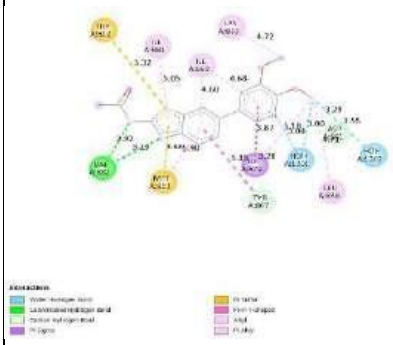
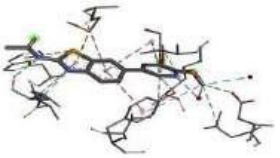
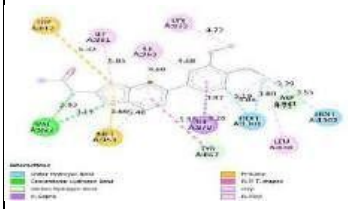
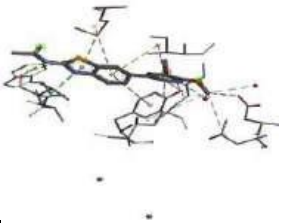
7		
8		

Table-7: Predicated ADMET Properties of the identified by using pkCSM Server

Comp. Code	Absorption	Distribution			Metabolism					Excretion	Toxicity	
	Intestinal Absorption(%Abs)	VdsPermeability (Log L/Kg)	BBB Permeability (Log BB)	CNS Permeability (Log PS)	Substratee (Yes/No)		Inhibitor (Yes/No)			Total ClearanceLog ml/min/kg	AMES Toxicityty(Yes/No)	Hepatoxicity
					2D6	3A4	1A2	2c19	3A4			
1	90.89	1.067	-0.22	-3.415	Yes	No	No	No	No	0.656	No	No
2	71.50	-0.366	-1.434	-3.715	No	No	No	No	No	0.142	No	NO
3	73.29	1.166	-0.820	-3.093	No	No	No	No	No	0.88	No	No

4	95.89	0.047	0.25	-2.493	No	No	Yes	No	No	0.171	No	No
5	93.88	0.594	0.44	-2.234	No	No	Yes	No	No	0.27	No	No
6	94.45	0.129	0.356	-2.047	No	No	Yes	No	No	0.036	No	No
7	91.59	0.619	0.308	-3.302	No	No	No	No	No	1.00	No	No
8	90.89	1.067	0.845	-2.036	No	Yes	Yes	Yes	No	0.217	No	No

He ADMET profiling of all eight compounds indicates generally favorable pharmacokinetic and safety characteristics. Most compounds exhibit **high intestinal absorption** (>70%), with Compounds **1, 4, 5, 6, 7, and 8** showing excellent absorption (>90%), suggesting good oral bioavailability.

In terms of **distribution**, the volume of distribution (Vd) values indicate moderate to good for most compounds .**BBB permeability** results show that Compounds **4,5, 6,7,and8**possess better potential for brain penetration (positive Log BB),where as Compounds **2 and 3**exhibit poor BBB permeability, indicating limited central nervous system (CNS) exposure. However, all compounds show **low CNS permeability (Log PS values)**, suggesting minimal central nervous system side effects.

Regarding **metabolism**, none of the compounds act as substrates for major metabolic enzymes, reducing the likelihood of rapid metabolic degradation. Compounds **4, 5, 6, and 8** show inhibitory activity toward certain CYP enzymes (notably CYP3A4 and CYP1A2),which may lead to potential drug–drug interactions and should be considered during further development.

The **excretion profile**, indicated by total clearance values, varies among compounds. Compounds **3 and 7** show relatively higher clearance, suggesting faster elimination, whereas Compound **6** shows very low clearance, indicating possible longer systemic retention.

From a **toxicity perspective**, all compounds are predicted to be **non-mutagenic (AMES negative)** and **non-hepatotoxic**, indicating a favorable safety profile.

Overall, **Compounds 4, 5, 6, and 8** demonstrate the most balanced ADMET properties, combininghigh absorption,acceptabledistribution,manageablemetabolism,andlowtoxicity. These compounds may be considered promising candidates for further pharmacological and preclinical evaluation, while others may require optimization to improve specific pharmacokinetic parame

TableNo8:Predicated physiochemical properties lipophilicity,solubility an ddrug likness of identified compound

Comp. No	MW (g/mol)	nRo t	mlog P	HB A	HBD	MR	TPSA	Lipi nski' s	Ghose Violat ions	Veber' sViola tions
1	362.22	4	0.65	2	1	94.79	52.65	0	0	0
2	297.65	3	-3.36	6	4	67.27	123.93	0	0	0
3	279.2	3	-4.42	7	5	64.05	144.16	0	0	0
4	340.17	4	-0.22	5	2	72.64	92.7	0	0	0
5	341.28	2	0.86	7	2	82.02	77.84	0	0	0
6	323.69	5	-2.36	6	2	74.51	109.77	0	0	0
7	413.81	6	-1.78	6	3	104.74	120.77	0	0	0
8	387.77	5	-1.88	6	4	96.57	123.93	0	0	0

All Eight Compounds Demonstrate Favorable Drug-Likeness Profiles Based On Standard Physicochemical Parameters. None Of The Compounds Violate **Lipinski's Rule Of Five**, **Ghose Filter**, Or **Veber's Criteria**, Indicating Good Potential For Oral Bioavailability. The Molecular Weight Of All Compounds Lies WithinThe Acceptable Range (<500 G/Mol), And The Number Of Rotatable Bonds (Nrot ≤ 6) Suggests Adequate Molecular Flexibility For Receptor Binding. The **Mlogp Values** Indicate That Most Compounds Are Hydrophilic To Moderately Lipophilic, Which May Support Good Solubility, Although Highly Negative Values (Compounds 2 And 3) Suggest Strong Hydrophilicity That Could Affect Membrane Permeability.Hydrogen Bond Acceptors (Hba) And Donors (Hbd) Fall Within Acceptable Limits, Supporting Favorable Interactions With Biological Targets. The **Topological Polar Surface Area (Tpsa)** Values Are Within The Permissible Range For Most Compounds (<140 Å²), Except Compound 3, Which Slightly Exceeds The Ideal Threshold, Potentially Indicating Lower Permeability. Overall, **Compounds 1, 4, And 5** Appear Most Promising Due To Balanced Lipophilicity, Moderate Tpsa, And Optimal Hydrogen Bonding Characteristics, Suggesting Better Oral Absorption And Membrane Permeability.

Compounds With Higher Tpsa And Lower Mlogp (Especially Compounds 2 And 3) May Require Structural Optimization To Improve Permeability. Thus, The Dataset Indicates That All Compounds Are Drug-Like, With A Few Candidates Showing Superior Pharmacokinetic Potential For Further Development.

ADMETLAB3.0

Comp Code	Adsorption			Distribution			Metabolism				Excretion		Toxicity	
	Caco-2 Permeability	Pg p-inhibitor	Pg p-substrate	Plasma Protein Binding	Blood Brain Barrier(BBB) Penetration	Fractin Unboun d (Fu)	CYP2C 19 substrate	CYP2D 6 substrate	CYP2C 9inhibitor	HLM Stability	CL plasm a	T1/2	AMES Mutagenicity	Human Hepatotoxicity
1	-4.846	0.705	0.003	92.022	0.995	6.805	0.001	0.44	0.417	0.555	4.88	0.838	0.359	0.571
2	-4.638	0.933	0.01	91.959	0.922	5.924	0.0	0.024	0.676	0.676	5.011	0.921	0.819	0.892
3	-4.777	0.953	0.006	96.244	0.987	2.725	0.002	0.157	0.235	0.355	4.828	1.069	0.358	0.518
4	-4.572	0.966	0.004	94.402	0.992	4.152	0.0	0.388	0.269	0.166	3.98	0.781	0.492	0.47
5	-4.879	0.507	0.083	92.48	0.783	6.574	0.437	0.223	0.658	0.962	5.217	0.629	0.517	0.599
6	-4.583	0.859	0.004	94.237	0.868	4.869	0.0	0.109	0.037	0.758	2.667	0.795	0.153	0.161
7	-5.144	0.238	0.025	89.694	0.641	6.834	0.002	0.054	0.256	0.396	4.935	0.845	0.407	0.514

8	-4.942	0.843	0.044	89.38	0.972	8.514	0.001	0.052	0.37	0.18	3.944	0.95	0.494	0.561

The ADMET profiling of compounds 1–8 indicates that most compounds exhibit acceptable pharmacokinetic properties with moderate to good absorption, distribution, metabolism, excretion, and toxicity profiles.

Regarding **absorption**, all compounds showed comparable Caco-2 permeability values, suggesting moderate intestinal absorption potential. Compounds 2, 3, and 4 demonstrated higher P-gp inhibitor probability, indicating improved membrane permeability and better absorption characteristics.

For **distribution**, high plasma protein binding **(>89%)** was observed for all compounds, indicating strong binding affinity with plasma proteins. Most compounds also showed high **BBB penetration values**, particularly **compounds 1, 3, 4, and 8,** suggesting their potential to cross the blood-brain barrier effectively.

In terms of **metabolism**, CYP enzyme interaction analysis revealed that most compounds showedlowCYP2C19andCYP2D6substrateprobabilities,suggestingareducedriskofrapid metabolic degradation. Compound 5 exhibited relatively higher **CYP2C19** substrate probability, which may influence its metabolic stability.

For **excretion**, compounds showed acceptable human liver microsomal **(HLM)** stability, plasma clearance (CL plasma), and half-life **(T1/2)** values, indicating favorable elimination profiles. Compound 2 demonstrated relatively better excretion characteristics with balanced clearance and stability.

In the **toxicity assessment**, AMES mutagenicity and human hepatotoxicity predictions were generally within acceptable limits for most compounds. **Compound 6** showed the lowest hepatotoxicity probability, indicating better safety potential, whereas compound 2 showed relatively higher toxicity concern.

Overall, **compounds 2, 4, and 8** demonstrated comparatively **better ADMET** profiles with balanced pharmacokinetic behaviour and acceptable toxicity, making them promising candidates for further biological evaluation and lead optimization studies.

TableNo9: Physiochemical scheme

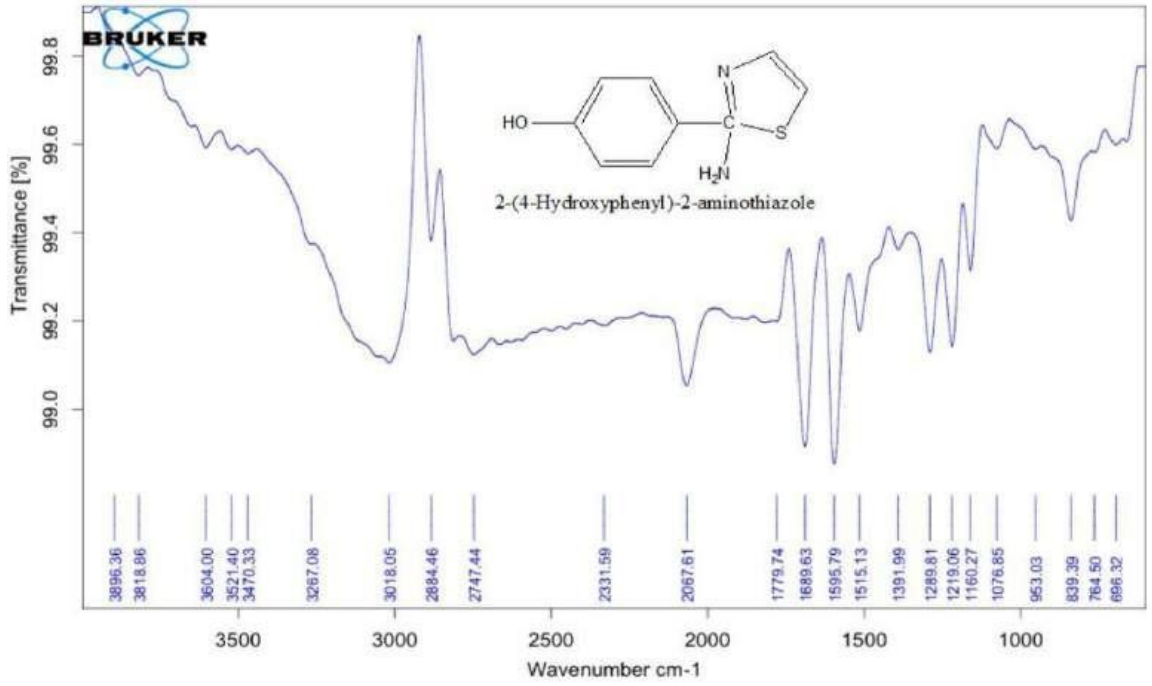
Comp. Name	Mo. Formula	Molecular weight	Melting points
Derivatives1	C9H8N2OS	192.24 g/mol	197
Derivatives2	C9H8N2OS	192.24 g/mol	190
Derivatives3	C9H7N3OS	221.24 g/mol	154

He Synthesized Derivatives Exhibit Consistent And Well-Defined Physicochemical Properties. **Derivatives 1 And 2** Share The Same Molecular Formula (**$C_9H_8N_2Os$**) And Molecular Weight (192.24 G/Mol), Indicating Structural Similarity, Which Is Also Reflected In Their Comparable Melting Points (197°C And 190°C). The Slight Variation In Melting Points Suggests Minor Differences In Purity Or Crystal Packing.

In Contrast, **Derivative 3** Possesses A Different Molecular Formula (**$C_9H_7N_3Os$**) With A Higher Molecular Weight (221.24 G/Mol), Indicating the Incorporation Of An Additional Nitrogen Atom. This Structural Modification Is Associated With A Significantly Lower Melting Point (154°C), Suggesting Reduced Intermolecular Interactions Or Altered Crystal Lattice Stability.

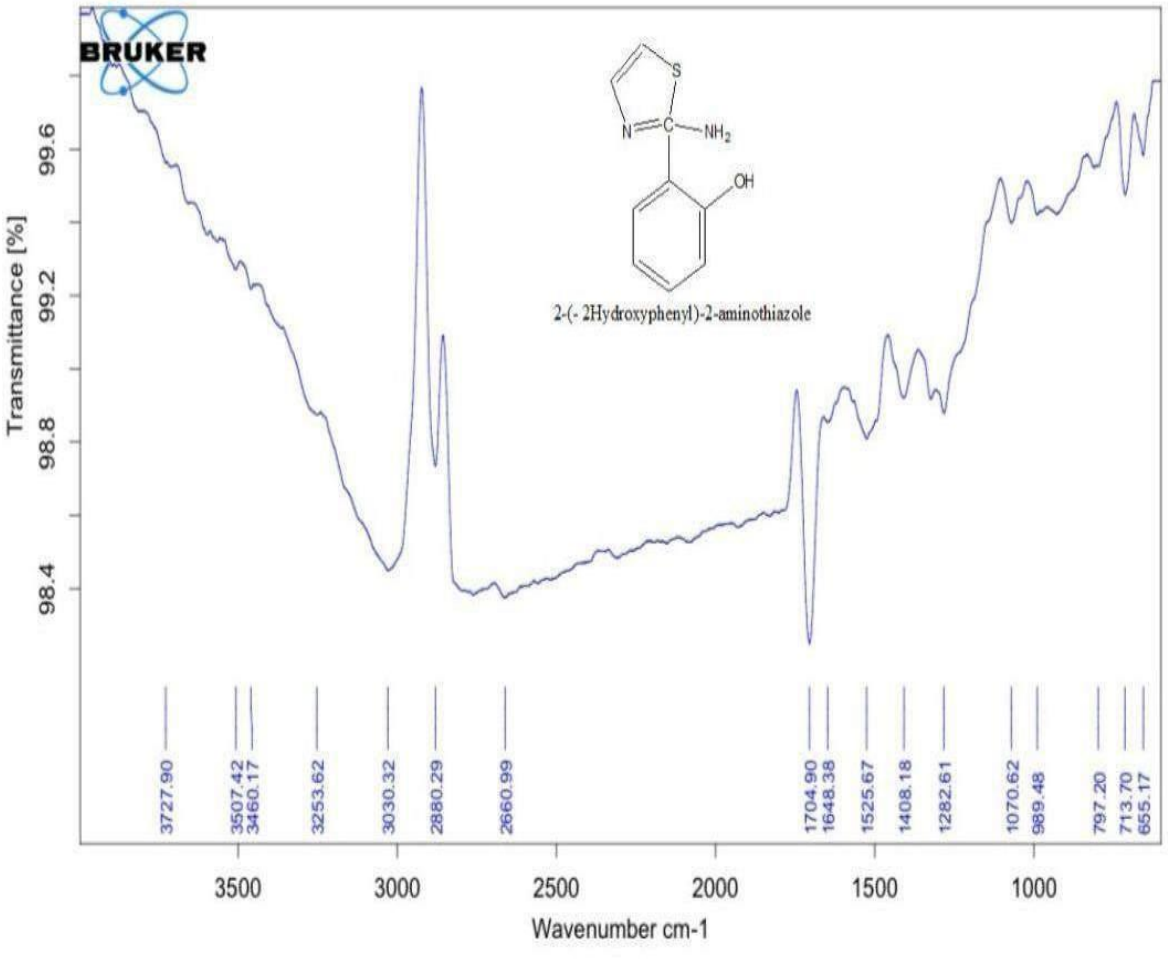
Overall, The Data Confirm The Successful Synthesis Of Distinct Derivatives With Characteristic Physicochemical Properties. The Variation in Melting Points Supports Structural Differences among The Compounds And Can Serve As An Indicate or Of Purity And Identity.

IR Spectral Analysis–



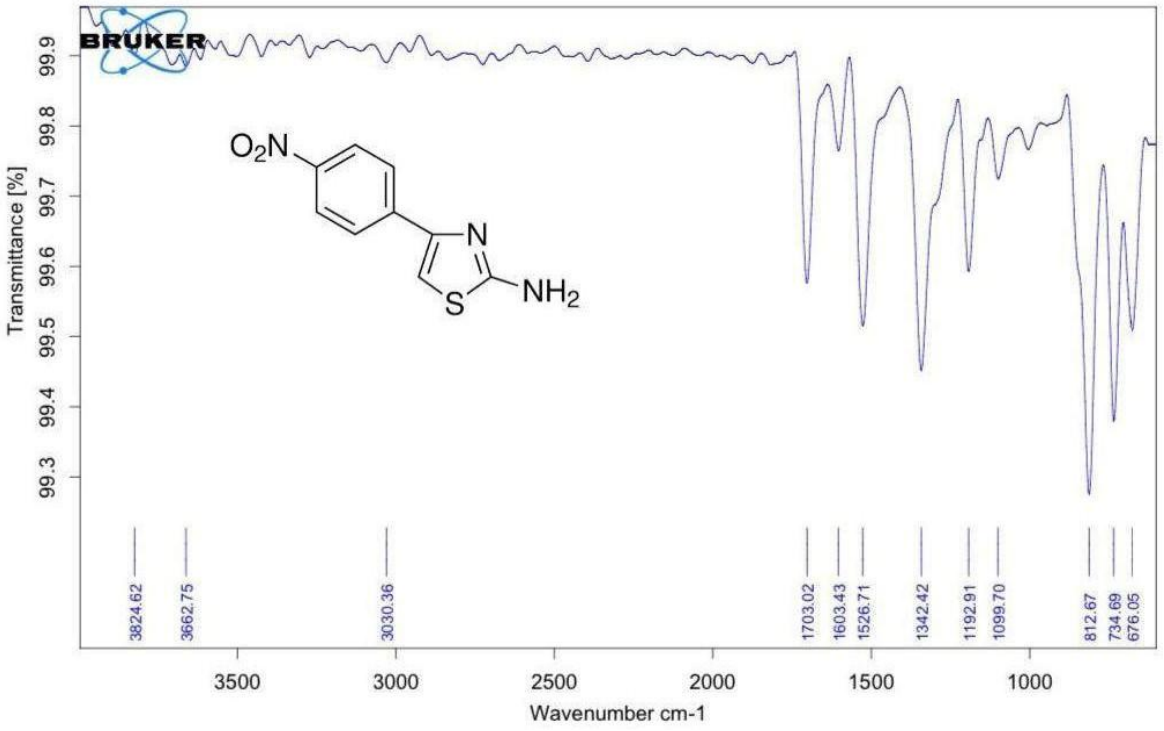
IR spectra of–2-(4-Hydroxyphenyl)-2-aminothiazole

Sr.no	Compound	Functional Group	range	Observed Frequency
1	Derivative 1	O-H Stretching	3200-3600	3260
		C-H Stretching	3100-3000	3018
		C-C Aromatic Stretching	1500-1600	1595
		C-H Bending	1200-1300	1289
		C-S Stretching	1050-1200	1099
		C=N Stretching	1600-1690	1603
		C=NH2Stretching	1450-1600	1567.71



IR spectra of–2-(2-hydroxyphenyl)-2-aminothiazole

Sr.no	Compound	Functional Group	range	Observed Frequency
2	**Derivative2**	O-H Stretching	3200-3600	3360
		C-H Stretching	3100-3000	3033
		C=C Aromatic Stretching	1500-1600	1526
		C-H Bending	1200-1300	1289
		C-S Stretching	600-700	650
		C=N Stretching	1640-1690	1620
		C=NH2	1600-1650	1580



IRSpectralDataof2-(4-nitrophenyl)-2-aminothiazole

Sr.no	Compound	Functional Group	range	Observed Frequency
3	**Derivative 3**	N-H Stretching	3500-3300	3662.75
		C-N Stretching	1650-1550	1603.43
		NO2Asymmetry	1550-1500	1526.71
		NO2 Symmetry	1250-1020	1099.70
		C-H Bending	900-600	812.63
		C-S Stretching	600-800	676.05
		Aromatic C-HStretching	3100-3000	3330.36
		C=N Stretching	1600-1690	1603
		C-CStretching	1450-1600	1567.71

NMR Analysis:

Fig. No.: NMR spectra of Derivative

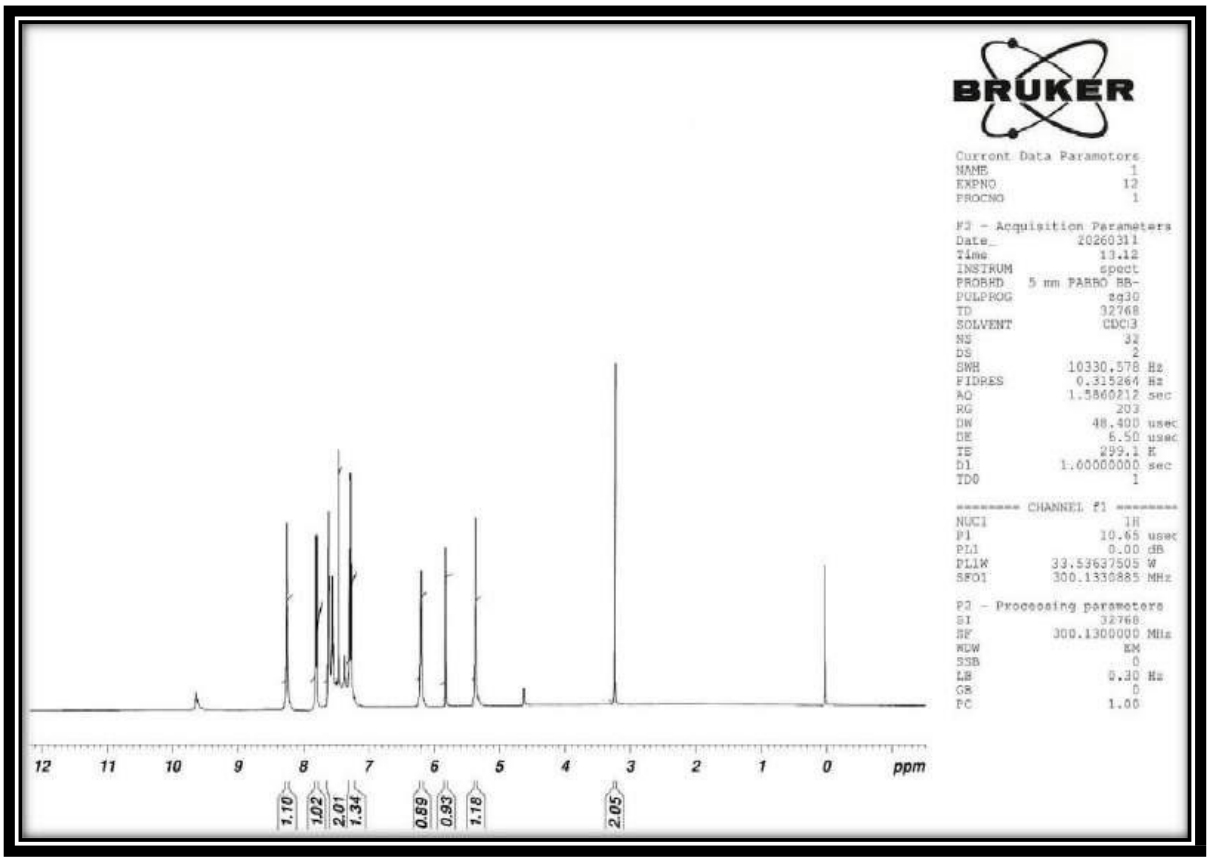


Table No.: Spectral Data of Derivative

No.	Δ (PPM)
Derivative1.	**^{1}H-NMR($CDCl_3$,300MHz)δppm: 8.25**(s.1H,NH),**7.21-7.83**(m,4H,AromaticC-H),**6.20**(d,1H, -S-CH=CH-NH-),**5.82**(d,1H,-S-CH=CH-NH-),**5.38**(s,1H,OH)**,3.24**(s,2H,NH_2).

MS Analysis:

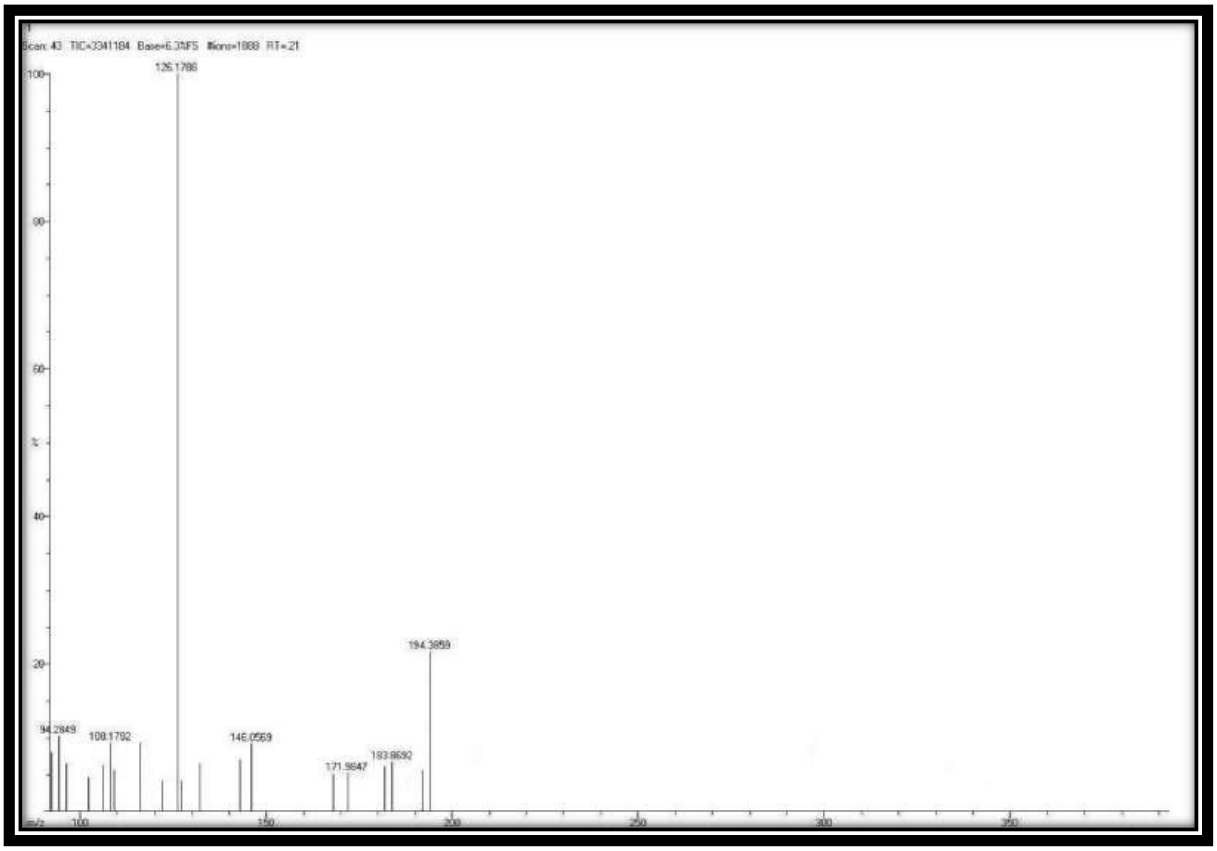


Fig. No: MS spectra Derivative Table No.: Spectral Data of Derivative

Compound	m/z(M+)	Molecular formula	Interpretation
Derivative1	194.38	C10H10O4	Likely molecular ion peak(M/z)→ gives molecular weight ≈ 194

Biological activity

The *in vitro* anti-inflammatory activity of the synthesized derivatives was successfully evaluated using the protein denaturation assay and compared with the standard drug, Diclofenac Sodium.

All tested compounds exhibited a concentration-dependent inhibition of protein denaturation in the range of 20–100 µg/mL, confirming their potential anti-inflammatory properties.

Among the derivatives:

- Derivative 1 showed the highest activity **(IC_{50} = 78.70 µg/mL),** indicating strong inhibition close to

the standard.

- Derivative 2 demonstrated moderate activity **(IC_{50} = 90.04 µg/mL).**
- Derivative 3 exhibited the least activity (**IC_{50} = 97.40 µg/mL).**

The standard drug showed maximum inhibition with an IC_{50} value of 70.89 µg/mL, confirming its superior potency.

The study confirms that 2-aminothiazole derivatives are promising lead molecules for anti-inflammatory drug development. Among all evaluated compounds, Derivative 1 (biological activity) and Compound 7 (docking study) emerged as the most promising candidates.

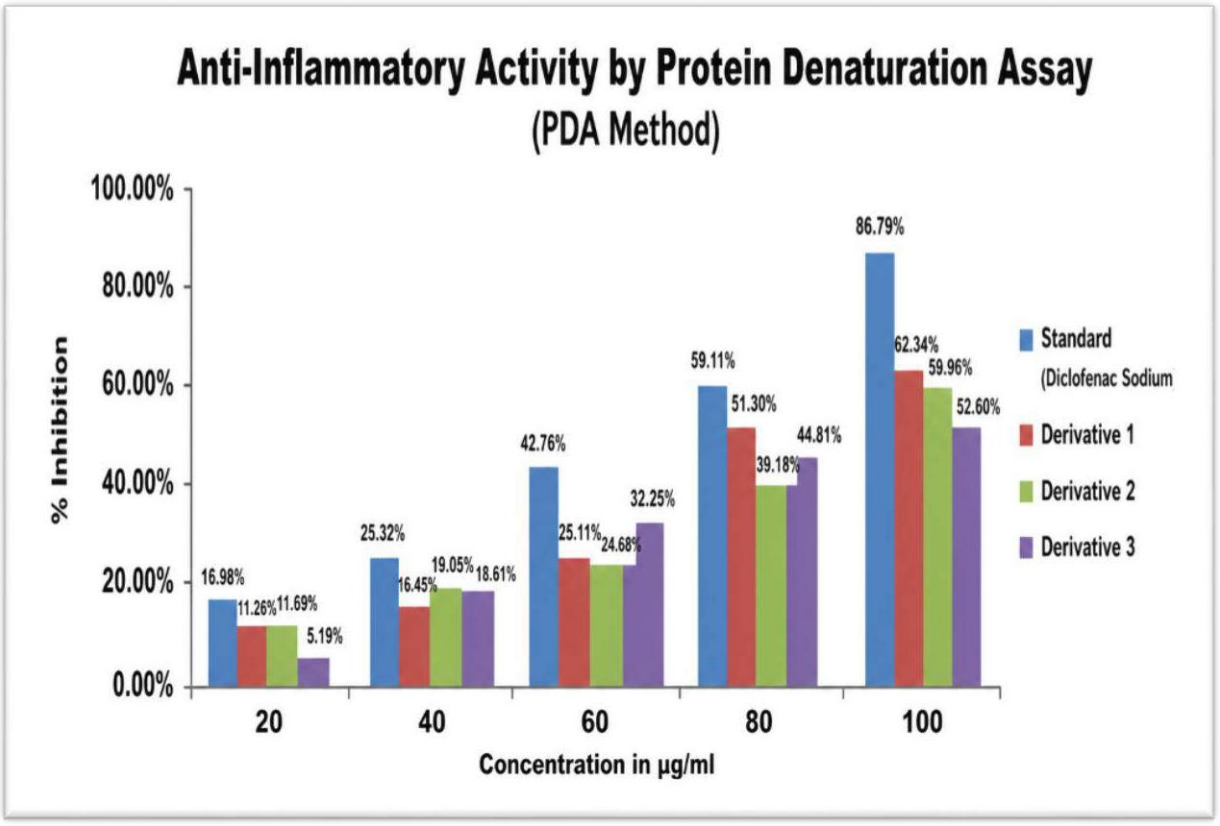


Fig no 8 -graphical representation of anti -inflammatory activity

Anti–inflammatory activity of synthesis compound

			Protein Denaturation Assay					
SR.NO	Samplecode	Concentration (µg/ml)	Absorbanceat660 nm					
			Test 1	Test 2	Test 3	Mean	%Inhibition	IC_{50} (µg/ml)
1.	Control		1.54	1.54	1.54	1.54	-	
2.	Standard (Diclofenac Sodium)	20	1.40	1.37	1.39	1.32	16.98%	

		40	1.11	1.19	1.15	**1.15**	**25.32%**	
		60	0.91	0.89	0.93	**0.91**	**42.76%**	
		80	0.67	0.65	0.63	**0.65**	**59.11%**	**70.89**
		100	0.21	0.18	0.23	**0.21**	**86.79%**	
3.	**Compound 3**	**20**	1.37	1.35	1.38	**1.37**	**11.26%**	
		40	1.29	1.27	1.30	**1.29**	**16.45%**	**78.70**
		60	1.15	1.13	1.18	**1.15**	**25.11%**	
		80	0.74	0.78	0.73	**0.75**	**51.30%**	
		100	0.58	0.56	0.60	**0.58**	**62.34%**	
4	**Derivatives –I**	**20**	1.36	1.34	1.38	**1.36**	**11.69%**	
		40	1.25	1.28	1.21	**1.25**	**19.05%**	**90.04**
		60	1.16	1.14	1.18	**1.16**	**24.68%**	
		80	0.92	0.94	0.95	**0.94**	**39.18%**	
		100	0.61	0.6	0.64	**0.62**	**59.96%**	
5	**Compound - II**	**20**	1.46	1.45	1.47	**1.46**	**5.19%**	
		40	1.23	1.25	1.28	**1.25**	**18.61%**	
		60	1.05	1.05	1.03	**1.04**	**32.25%**	
		80	0.83	0.85	0.87	**0.85**	**44.81%**	**97.40**
		100	0.76	0.72	0.71	**0.73**	**52.60%**	

CHAPTER NO.7: CONCLUSION

The present study successfully focused on the **design, synthesis, and evaluation of novel 2-aminothiazole derivatives** as potential anti-inflammatory agents. The synthesized compounds were systematically evaluated using **molecular docking, ADMET analysis, physicochemical characterization, and in vitro biological studies**.

Molecular docking studies against the DNA gyrase receptor (PDB ID: 4PS8) revealed that all compounds exhibited **favourable binding affinities (–7.9 to –8.6 kcal/mol)**, indicating strong interaction with the active site. Among them, **Compound 7 showed the highest binding affinity**, suggesting superior binding stability and promising biological potential.

ADMET analysis confirmed that most compounds possess **good intestinal absorption, acceptable distribution, low toxicity, and non-hepatotoxic nature**, indicating a favourable pharmacokinetic profile. Swiss ADME evaluation further demonstrated that all compounds obey **Lipinski's Rule of Five**, confirming good drug-likeness and oral bioavailability.

Spectral analysis (IR, NMR, and MS) and physicochemical evaluation validated the

successful synthesis and structural integrity of all derivatives.

In the **in vitro anti-inflammatory study (Protein Denaturation Assay)**, all derivatives showed **concentration-dependent inhibition**. Among them:

The study confirms that **2-aminothiazole derivatives are promising lead molecules** for anti-inflammatory drug development. Among all evaluated compounds, **Derivative 1 (biological activity) and Compound 7 (docking study)** emerged as the most promising candidates.

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