Synthesis And Insilico Evaluation Of 2-(4-Substituted Benzylidene Amino)-4 Phenyl 1,3 Thiazole Derivatives

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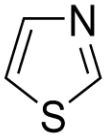
***Abstract*—Thiazole derivatives are an important class of heterocyclic compounds known for their wide range of biological and pharmacological activities such as antimicrobial, anticancer, anti-inflammatory, antioxidant, and antiviral effects. In the present study, a series of 2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives were synthesized and evaluated through in silico methods. The synthesis was carried out through a two-step reaction process involving the cyclization of acetophenone with thiourea in the presence of iodine to form 2-amino-4-phenyl thiazole, followed by condensation with different substituted aromatic aldehydes to obtain the final derivatives. The synthesized compounds were characterized by using melting point determination, thin layer chromatography (TLC), and FT-IR spectral analysis.**

The drug-likeness and molecular properties of the synthesized compounds were predicted using Molinspiration and SwissADME software tools. The results indicated that all the synthesized derivatives obeyed Lipinski's rule of five, suggesting favorable pharmacokinetic properties and good oral bioavailability. Furthermore, molecular docking studies were performed using PyRx software to evaluate the binding affinity of the compounds with the target protein. Among the synthesized derivatives, compound 4 showed the highest binding affinity, indicating better interaction with the target site. Overall, the synthesized thiazole derivatives demonstrate promising drug-like properties and may serve as potential candidates for further medicinal chemistry studies

***Index Terms*—Thiazole derivatives, Molecular docking, *Insilico* evaluation, Molinspiration, SwissADME, PyRx, Drug-likeness, Lipinski's rule of five.**

I. THIAZOLES

Thiazoles is a 5 – membered ring moiety containing nitrogen and Sulphur at position 1 and 3. The structural pattern of thiazole derivatives as active compounds is predominantly focused on the substitution of hydrogen atoms with desired moieties at position 2,4,5[1,2]. Thiazole employs both an electron donating group and electron accepting group and these create stable heterocyclic compound [3]. The thiazole nucleus serves as a fundamental structural component of vitaminB, highlighting the biological importance of this heterocyclic moiety.



Thiazole moieties occupy a prominent place in contemporary organic and medicinal chemistry owing to their wide range of pharmacological and therapeutic activities, including antimicrobial, anticancer, and antioxidant properties. The occurrence of the thiazole ring in several clinically important drugs such as penicillin, pramipexole, tiazofurin, meloxicam, and nizatidine has encouraged researchers to design and develop novel thiazole-based scaffolds. The thiazole nucleus plays a significant role in the discovery of new lead compounds and drug candidates for the treatment of various diseases. This chapter discusses the most commonly employed synthetic strategies for the preparation of substituted thiazole derivatives, outlines their key electronic characteristics, and emphasizes their important chemical reactivity. Special attention is given to the application of thiazoles in dyes, their metal complexes, and other miscellaneous uses of thiazole-based dyes. In addition, the biological activities of thiazole derivatives are comprehensively reviewed. [4]

II. AIM & OBJECTIVES

From the review of literature various biological activities were reported on Thiazoles derivatives like Anti-cancer, Anti-tumor, Anti-fungal, Anti-oxidant,

Anti-bacterial, Anti- inflammatory, Anti tuberculosis, Anti diabetic, Anti-malarial, Anti-viral.

The main objective of the present work is to synthesize and I*nsilico* evaluation of 2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives by using different online software tools like

1. Synthesis
2. Swiss ADME
3. Molinspiration
4. PyRx (Docking)

III. MATERIALS AND METHODS

Materials

The chemicals required were obtained from Hi Media Chem. Ltd, SD Fine Ltd., and Sigma Aldrich Pvt. Ltd. and were used as such. Melting points were determined using open capillary tube melting point apparatus and are uncorrected. Reaction progress was monitored by performing thin-layer chromatography on silica gel plates. After physical characterization, the compounds were subjected to spectral analysis. IR spectra were recorded on a Nicolet Summit X using KBr pellets.

Thiourea, Iodine beads, Acetophenone, Sodium thiosulphate, n- hexane, Ethanol, Benzaldehyde, Anisaldehyde, Vanillin, p- Chlorabenzaldehyde, Glacial acetic acid, Ethyl acetate, Silica gel, Nitro benzaldehyde.

Method

General procedure for the synthesis of2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives

Step – 1

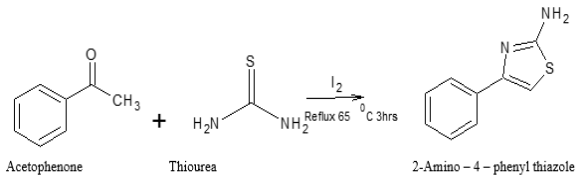
Thiourea (40 mmol, 2 molar equivalents) was combined with iodine beads (20 mmol, 1 molar equivalent) in a mortar and thoroughly ground using a pestle to obtain a homogeneous mixture. The resulting solid mixture was then transferred into a 250 mL round-bottom flask containing a magnetic stirring bar and subsequently mixed with the corresponding acetophenone (20 mmol, 1 molar equivalent). The reaction mixture was refluxed at 65 °C in heating mantle for 5 hours with continuous stirring. After completion of the reaction, a 5% aqueous solution of sodium thiosulfate pentahydrate was added with mechanical stirring to break the solid matrix and reduce the excess iodine until the brown color disappeared. The resulting suspension was then filtered and carefully washed with 20 mL of diethyl ether (note: the product is partially soluble in ether) to remove any unreacted acetophenone and its derivatives.

Step – 2:

A solution of phenyl thiazole (25mmol) and different substituted aldehydes (25mmol) were mixed in glacial acetic acid (40mL). The reaction mixture was refluxed for 5h at 65^0C. The mixture was left to stand at room temperature overnight and filtered. The residue was filtered and recrystallized with n-hexane.

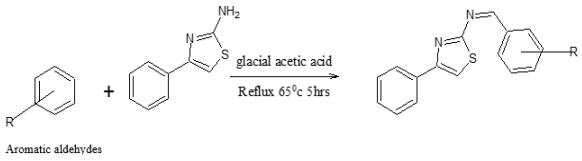
SCHEME

Step- 1



Acetophenone Thiourea 2-Amino – 4 – phenyl thiazole

Step – 2



Aromatic aldehydes

S.NO	R
1	-H
2	4-CH_3O
3	4-OH 3-CH_3O
4	4-Cl
5	3-NO_2

TABLE -2: List of substituted aromatic aldehydes

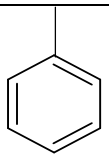
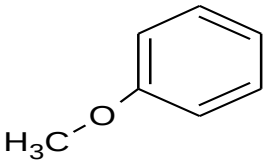
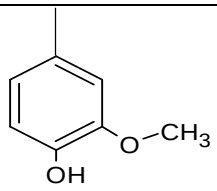
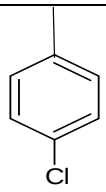
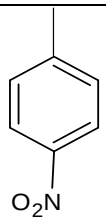
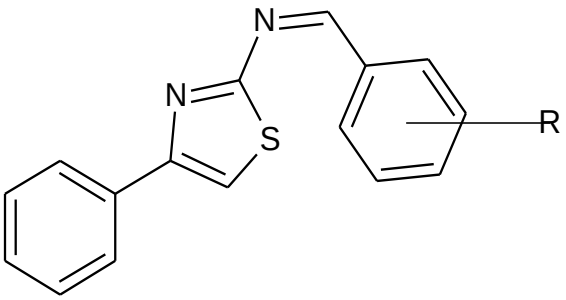
Compound	Aromatic Aldehydes	Molecular weight
1		264.35 g/mol
2		294.38 g/mol
3		310.38 g/mol
4		263.35 g/mol
5		263.35 g/mol

TABLE -3: Physical data and yields of 2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives

Compound	R	Molecular formula	Molecular weight	% Yield	Melting point	R_F Value
1.	-H	$C_{16}H_{13}N_3S$	264.35	76%	155- 158^{0}C	0.45
2.	4-CH_3O	$C_{17}H_{15}N_3OS$	294.38	78.2%	170- 174^{0}C	0.52
3.	4-OH 3-CH_3O	$C_{17}H_{15}N_3O_2S$	310.38	73%	198-202^{0}C	0.60
4.	4-Cl	$C_{16}H_{12}ClN_3S$	263.35	77%	182-186^{0}C	0.48
5.	3-NO_2	$C_{16}H_{12}N_4O_2S$	263.35	75%	188-192^{0}C	0.41



Thin layer chromatography

General procedure for thin layer chromatography

1.Preparation of TLC plate

Take a pre-coated silica gel TLC plate. Draw a light pencil line about 1 cm from the bottom to mark the baseline. Do not use ink.

2. Preparation of sample solution
Dissolve a small amount of the sample (and standard, if required) in a suitable volatile solvent such as methanol, ethanol, or ethyl acetate.

3. Spotting the sample
Using a capillary tube, apply a small, concentrated spot of the sample on the baseline. Allow the spot to dry completely.

4. Preparation of mobile phase
Prepare the mobile phase in a TLC chamber (e.g., ethyl acetate:hexane, 7:3). Close the chamber and allow it to saturate with solvent vapors for a few minutes.

5. Development of the plate
Place the TLC plate vertically in the chamber, ensuring the spot remains above the solvent level. Close the chamber and allow the solvent to rise.

6. Removal of plate
When the solvent front reaches about ¾ of the plate, remove the plate and immediately mark the solvent front with a pencil.

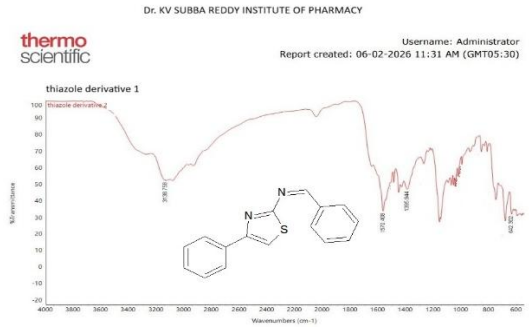
7. Drying and visualization
Dry the plate and visualize the spots under UV light or by using a spraying reagent or iodine chamber.

8. Calculation of Rf value
Measure the distance traveled by the compound and the solvent front.

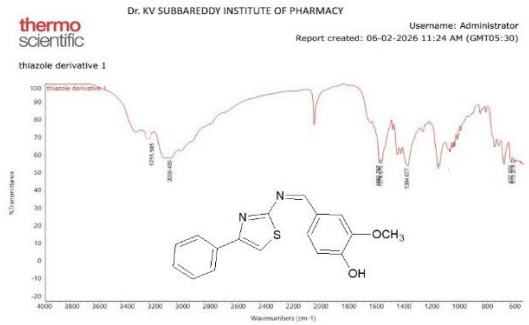
Compound: 1

Compound: 2

IR SPECTRA FOR COMPOUND – 1



IR SPECTRA FOR COMPOUND – 2



IR SPECTRA FOR COMPOUND – 3

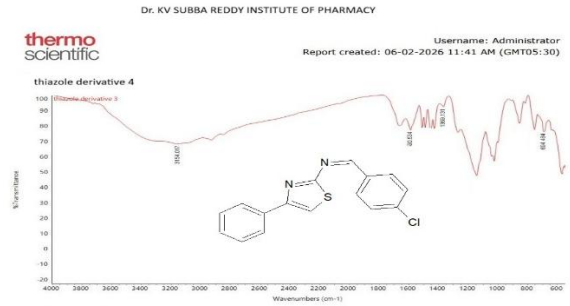


TABLE 4: FT-IR Spectral Data of Different Derivatives

Compound	FT-IR
1	Stretching 3138(C-H)1570(C=N)1395(C-S) Bending 642(C-S)
2	Stretching 3255(C-OH)3099(C-H)1589(C=N)1384(C-O)637 s Bending(C-S)
3	Stretching3154(C-H)1590(C=N)1369(s)618(C-Cl) Bending 694(C-S)

IV. MOLINSPIRATION

Molinspiration is an independent research organization focused on development and application of modern chem informatics techniques, especially in connection with the internet. Molinspiration offers broad range of chem, informatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomer's, molecule fragmentation, calculation of various molecular properties needed in OSAR, molecular modelling and drug design, high quality molecule depiction, molecular data base tools supporting substructure search or similarity and pharmacophore similarity search,

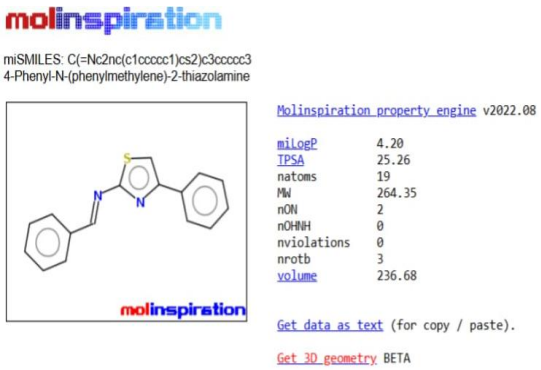
Molinspiration tools are therefore platform independent and may be run on any PC, Mac, UNIX or LINUX machine. The software is distributed in a form of toolkits, which may be used as stand-alone computational engines, used top over web-based tools, or easily incorporated into larger in-house Java applications.

Molinspiration mi screen engine allows fast prediction of biological activity- virtual screening of large collections of molecules and selection of molecules with the highest probability to show biological activity. The screening is based on identification of fragments or substructure features typical for the active molecules. The Molinspiration virtual screening is fast and therefore allows processing of very large molecular libraries. Validation tests performed by our company, as well as results of our customers on various target classes show 10 to 20-fold increase in hit rate in comparison with random selection of molecules for screening.

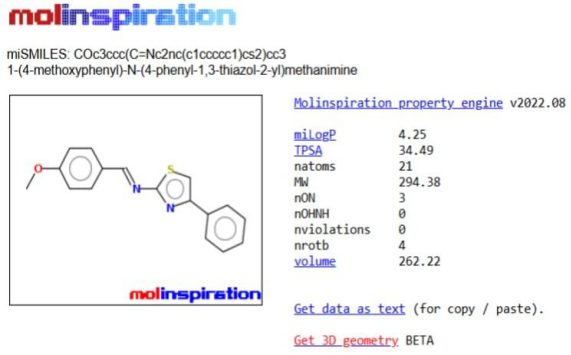
To run a virtual screening, three steps need to be performed:

1. Generation of fragments from a training set containing active and inactive molecules.
2. Development of a bioactivity model from fragment files generated in step1
3. Actual virtual screening by using the model generated in step 2[20]

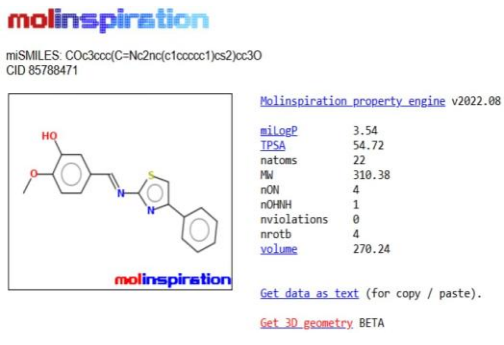
COMPOUND:1



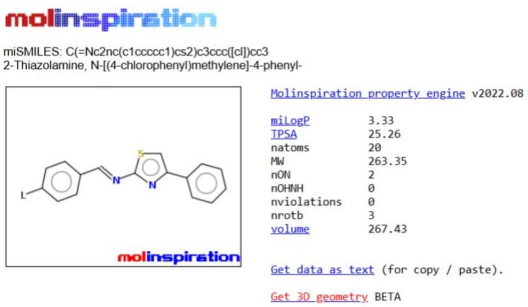
COMPOUND:2



COMPOUND:3



COMPOUND: 4



COMPOUND: 5

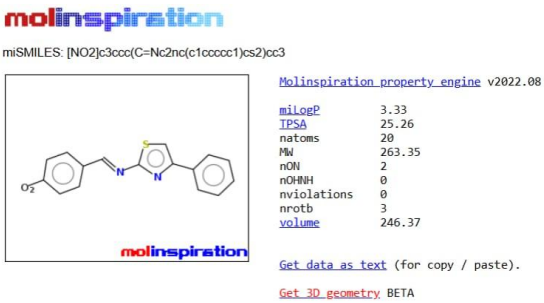
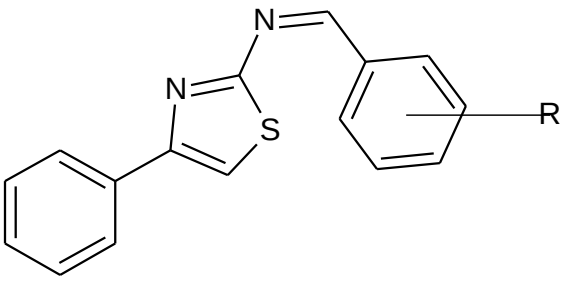


TABLE-5: Molecular properties of2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives by using Molinspiration

Compound	MiLo	TPSA	natos	MW	noN	nOHOH	nviolations	nrotd	volume
1	4.20	25.26	19	264.35	2	0	0	3	236.68
2	4.25	34.49	21	294.38	3	0	0	4	262.22
3	3.54	54.72	72	310.8	4	1	0	4	270.24
4	3.33	25.26	20	263.35	2	0	0	3	267.43
5	3.33	25.26	20	263.35	2	0	0	3	246.37

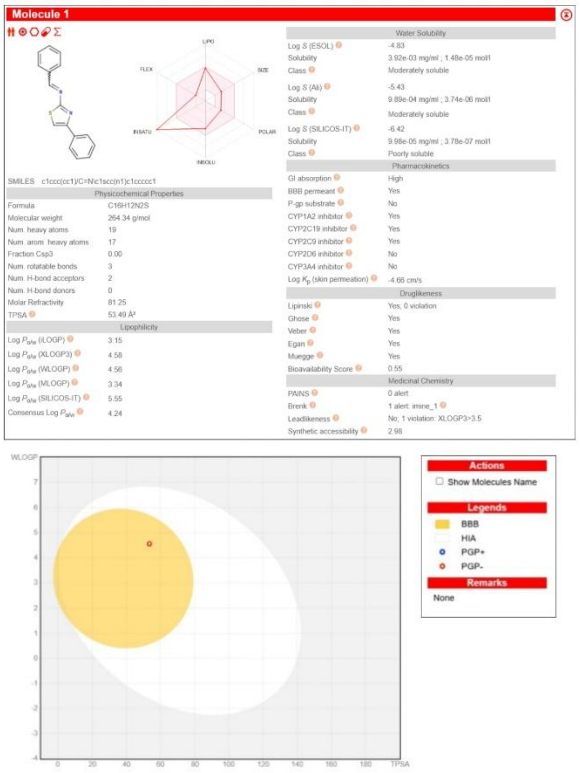


V. SWISS ADME:

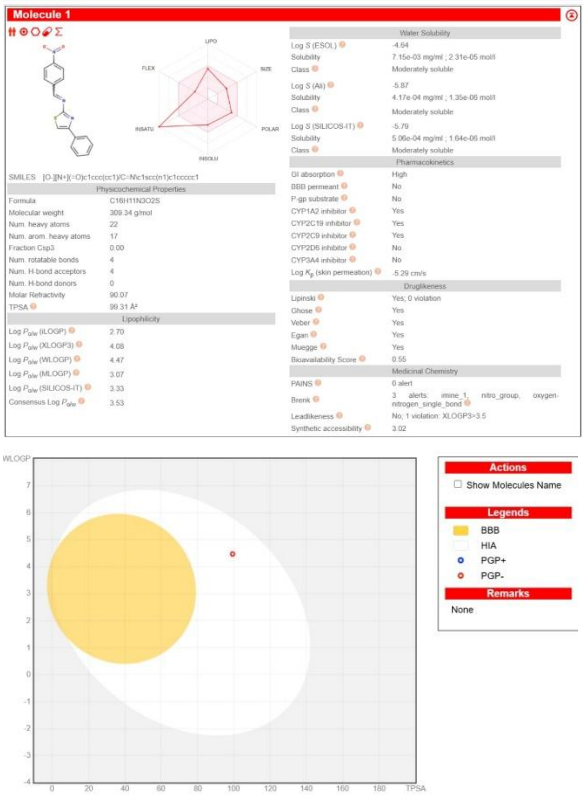
A large variety of in silico methods share the objective of predicting ADME parameters from molecular structure. Noteworthy, the pioneer work of Lipinski et al. Examined orally active compounds to define physicochemical ranges for high probability to be an oral drug. This is called Rule-of-five delineated the relationship between pharmacokinetic and physicochemical parameters. Whereas physicochemical parameters give a global description of the structure. molecules can be directly described by substructure searches. In turn, these ADME parameters can be evaluated separately by dedicated methods. It has been demonstrated that early estimation of ADME in the discovery phase reduces drastically the fraction of pharmacokinetics-related failure in the clinical phases. Computer models have been fostered as a valid alternative to experimental procedures for prediction of ADME, especially at initial steps, when investigated chemical structures are numerous but the availability of compounds is scarce. Swiss ADME is a free online web tool for predicting ADME properties, drug-likeness, and medicinal chemistry friendliness of small molecules. It is developed and maintained by the *Swiss Institute of Bioinformatics (Molecular Modeling Group). The tool computes physicochemical descriptors such as molecular weight, lipophilicity (log P), polar surface area (PSA), and solubility Lipophilicity are estimated using multiple methods (e.g., XLOGP3, iLOGP) and influences absorption and distribution. SwissADME predicts pharmacokinetic behaviors like gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation.

It includes the BOILED-Egg model for visualizing passive absorption and brain access in a simple graph. The tool can identify if a molecule is a P-glycoprotein (P-gp) substrate, which affects efflux and bioavailability. SwissADME predicts whether the compound might inhibit important Cytochrome P450 (CYP)enzymes, relevant for metabolism. It evaluates drug-likeness using filters like Lipinski's Rule of Five, Ghose, Veber, Egan, and Muegge.

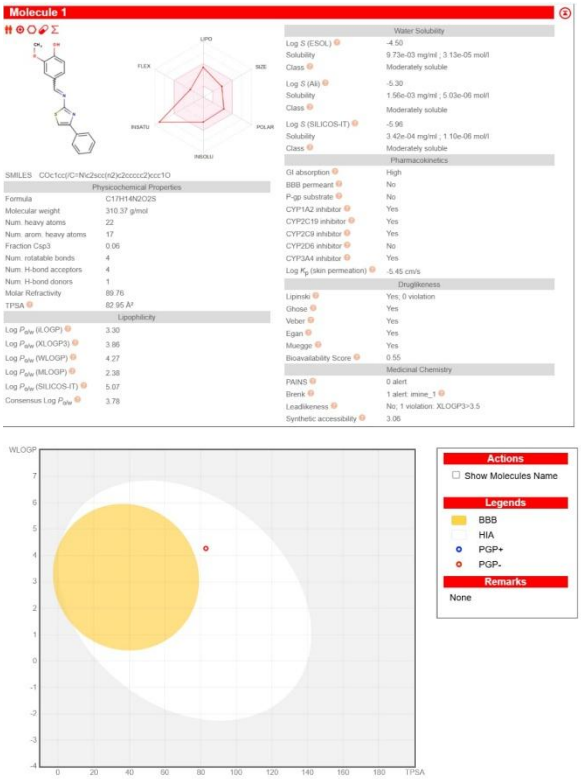
COMPOUND 1:



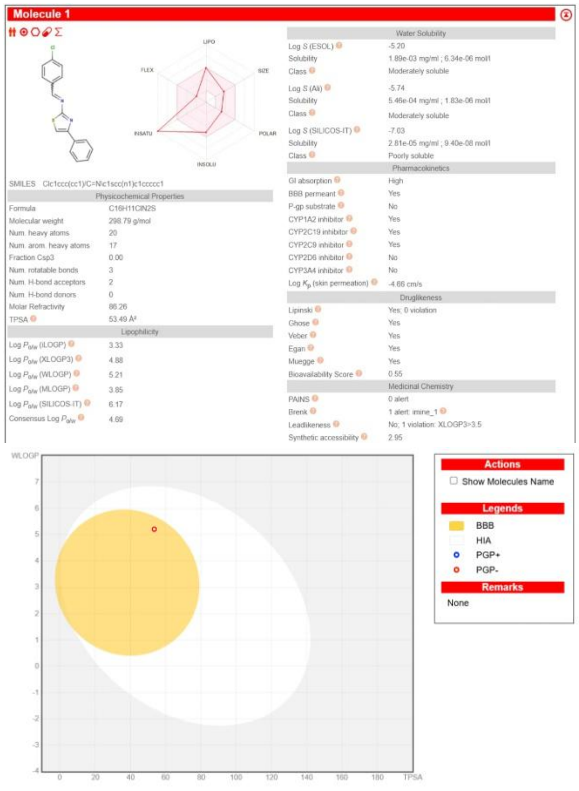
COMPOUND 2:



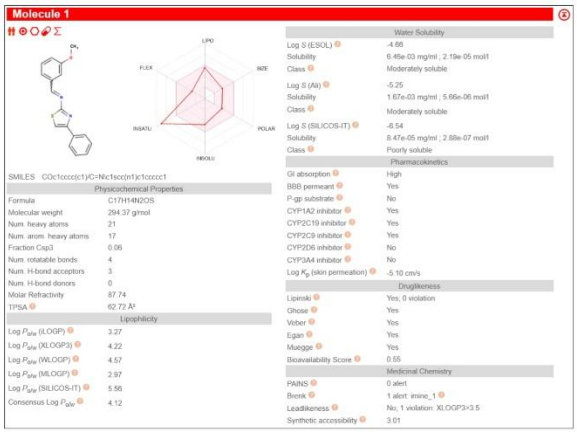
COMPOUND:3



COMPOUND:4



COMPOUND:5



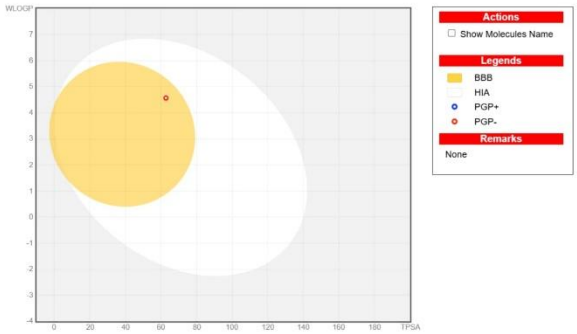
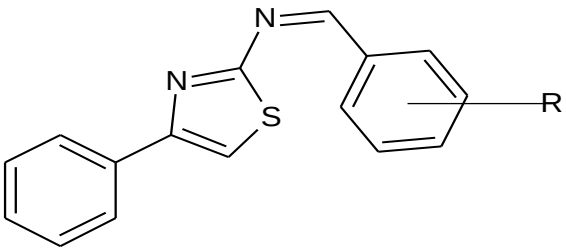


TABLE-6: Molecular properties of2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives by using Swiss ADME

Compound	R	Physico-chemical properties							Pharmacokinetics		
		No. of Heavy metals	No. of arom. heavy metals	N-Rb	NH-a	NH-d	Molar refractivity	TPSA	GI Absorption	BBB	Drug likelyness
1	-H	19	17	3	2	0	81.25	53.49 A^2	High	Yes	Yes
2	4-CH_3O	22	17	4	4	0	90.07	99.31A^2	High	No	Yes
3	4-OH 3-CH_3O	22	17	4	4	1	89.76	82.95A^2	High	No	Yes
4	4-Cl	20	17	3	2	0	86.26	53.49A^2	High	Yes	Yes
5	3-NO_2	21	17	4	3	0	87.74	62.74A^2	High	Yes	Yes



Docking by using PyRx software tool

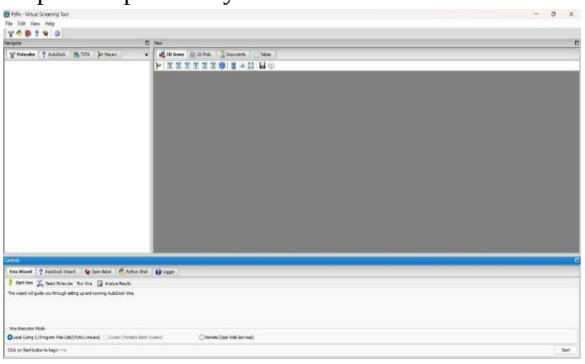
Pyrx is a type of borosilicate glass that is highly resistant to heat, thermal shock, and chemical reactions. It is commonly used in laboratories, pharmaceutical industries, and kitchenware because it does not crack easily when exposed to sudden temperature changes. It is mainly used for virtual screening and molecular docking, allowing scientists to predict the binding affinity and orientation of drug-like compounds within the active site of a target protein. PyRx provides a user-friendly graphical interface and integrates powerful tools like AutoDock and AutoDock Vina, making complex docking studies easier even for beginners. Being free and open-source,

it is commonly used in academic research for lead identification and optimization, helping to reduce time, cost, and experimental effort in drug development.

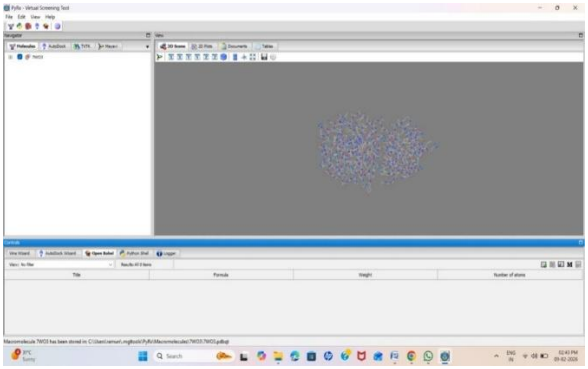
One of the major advantages of PyRx is its easy-to-use graphical interface, which reduces the need for advanced programming knowledge. It supports ligand and protein preparation, energy minimization, and file format conversion using Open Babel. Users can import compounds from databases, prepare them for docking, define the binding site using a grid box, and perform docking in a systematic manner. PyRx also provides visualization and analysis tools that help in comparing docking scores and selecting promising lead molecules. Because it is free, open source, and cross-platform, PyRx is extensively used in academic institutions and research projects for lead discovery, optimization, and validation studies, making it an important tool in modern pharmaceutical and medicinal chemistry research.

Compound: 1

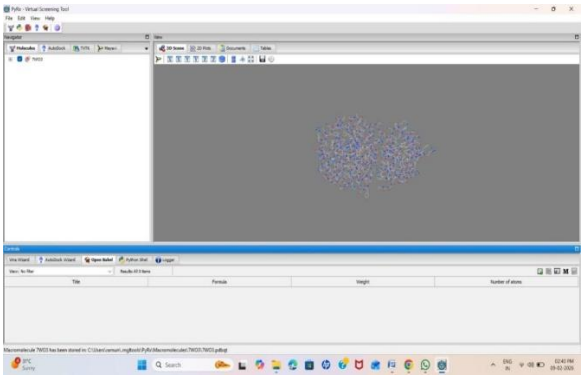
Step – 1: Open the PyRx window



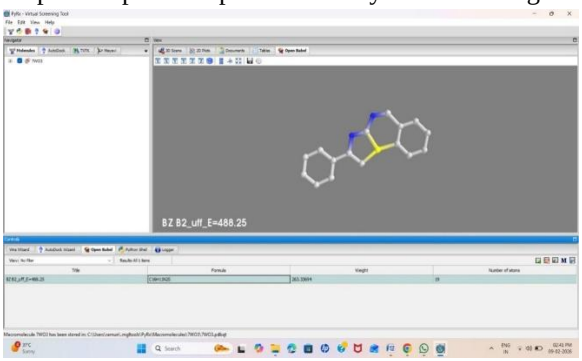
Step – 2: Insert the protein



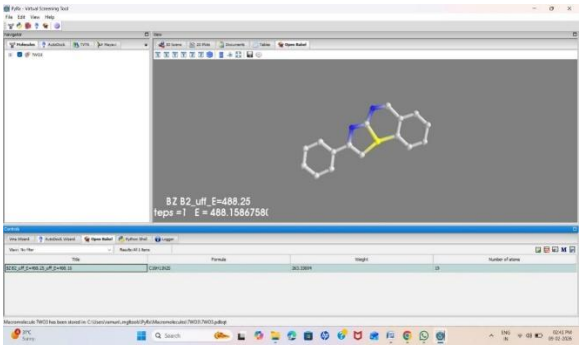
Step – 3: Make a macromolecule of a protein



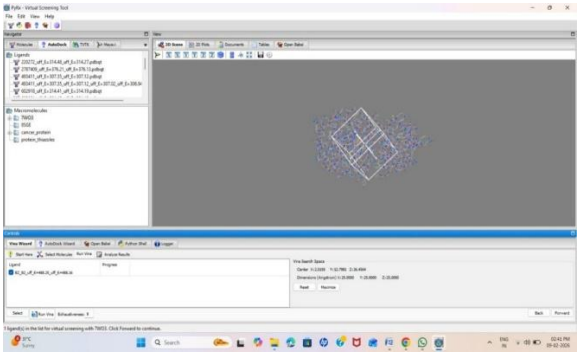
Step – 4: Open the open babel in PyRx & insert ligand



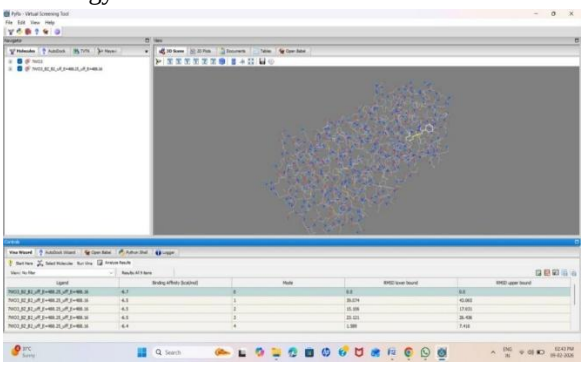
Step5: Minimize the energy



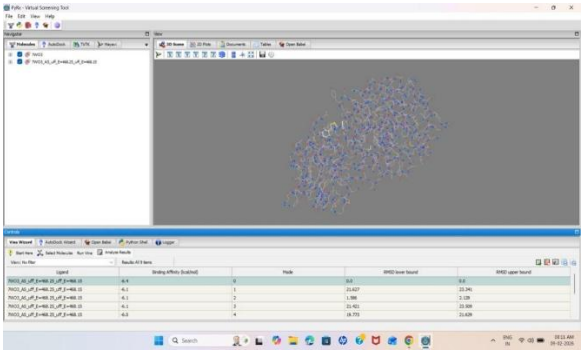
Step – 6: Set a grid box



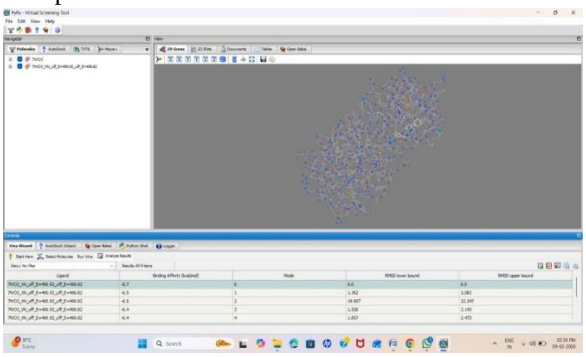
Step – 7: Docking by using autodock in PyRx, analyze the energy



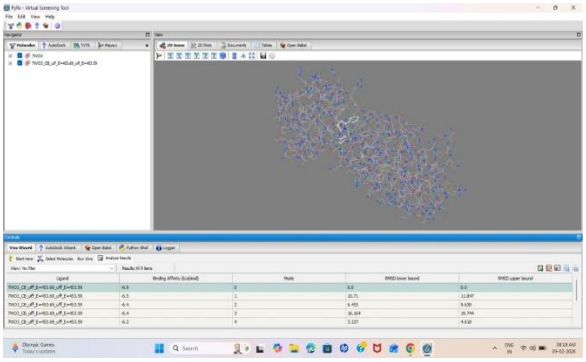
Compound: 2



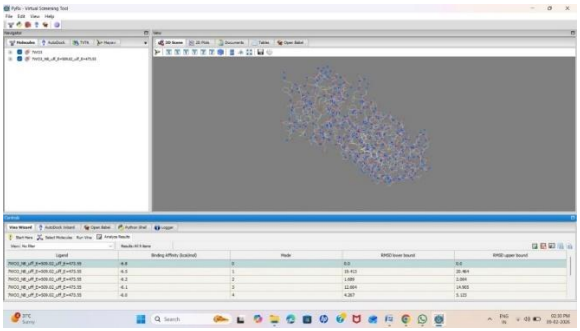
Compound: 3



Compound: 4



Compound: 5



Standard drug: Tiazofurin

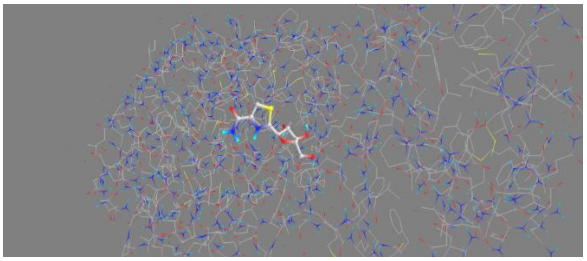


TABLE-7: Molecular binding affinity score

COMPOUND	BINDING AFFINITTY (Kcal/ mol)
1	-6.7
2	-6.4
3	-6.7
4	-6.9
5	-6.8
Standard drug: Tiazofurin	-5.5

VI. RESULTS AND DISCUSSION:

Synthesis of 2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivatives

The 2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivativeswere synthesized by using various homogenous mixtures such as Acetophenone, thiourea, iodine solution, glacial acetic acid, ethanol, sodium thiosulfate pentahydrate substituted aromatic aldehydes in which the mechanism is followed condensation process.

A series of 1 to 5 compounds were synthesized. The compounds obtained in good yield range from 60-90%. All the synthesized compounds were characterized by their TLC and IR. The physical data percentage and melting point yield and the spectral

data of the compounds were given under the physicochemical data of compounds.

The IR spectra of compounds (1-5) showed bonds such as 3099 - 3154(C-H str) 614- 698 (C-S str) observed at 1570 - 1589 (C=N str)

MOLECULAR DESCRIPTION:

The derivatives were also evaluated for its *Insilico* properties by using software programmes like Molinspiration, Swiss ADME, Molecular docking by using PyRx. Which are helpful to predict molecular general properties, drug likeness and binding affinities. All the results were tabulated and it was observed that compounds obeyed the LIPINSKI rule of five.

All the molecular properties of the synthesized derivatives were calculated by using molinspiration and swiss ADME. All the compounds obyed LIPINSKI rule of five.

Molecular properties of the title compounds include mi log p (3.33 - 4.25) TPSA (25.26 -54.72) MW (263.35-310.8) HBA (2-4) HBD (0) M violate (0) ROB (3 - 4) All the synthesized compounds showed good TPSA which represents good overall absorption and crosses blood brain barrier also n atoms represent all the derivatives are orally active. The molecular weight was less than 500 for all the synthesized compounds. Number of H bond acceptors are less than 10 and number of H bond donor are less than 5, number of violations are zero. So, all these compounds represents that all synthesized derivatives follow LIPINSKI rule of five.

All the synthesized derivatives showed good binding affinity towards the ligand. Compared to standard drug Tiazofurin. Aamong the 5 synthesized derivatives compound 4 showed good binding affinity towards the ligand.

VII. Conclusion:

A series of 2-(4-substituted benzylidene amino)-4-phenyl-1,3-thiazole derivativeswere synthesized good yield. The *Insilico* evaluate revealed that all 5 compounds adhered to LIPINSKI rule of five. Indicates favourable pharmacokinetics properties and good oral absorption potential. Molecular docking studies showed good binding interactions, particularly compound 4, which exhibited the highest binding infinity with target protein. These finding collectively highlight the multi-functional biological significance of thiazole derivatives reinforcing their values in medicinal chemistry. They serve as promising leads for further development in treating, inflammation, cancer, diabetic, tumour, fungal, Anti-viral infections some other disorders.

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