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IN-SILICO DESIGN AND DOCKING STUDY OF SOME 4-(10-ACETYL-10H-PHENO-THIAZINES-3-YL)-1-PHENYLAZETIDIN-2-ONE DERIVATIVES

Sandip Sen [*1], Bairam Ravindar [2], Sirikonda Jala [2] and Laxmi Dharabonia [2]

Department of Pharmaceutical Chemistry [1], School of Pharmacy, Gurunanak Institute Technical Campus, Ibrahimpattnam - 501506, Telangana, India.
Department of Pharmaceutical Chemistry [2], Srikrupa Institute of Pharmaceutical Sciences, Velikatta, Kondapakka, Siddipet - 502277, Telangana, India.

Keywords:

Phenothiazine, *In-silico* study, Drug likeliness, Bioactivity score, ADMET, Docking analysis, Betalactum, Anti-inflammatory

Correspondence to Author:
Dr. Sandip Sen

Associate Professor and Head, Department of Pharmaceutical Chemistry, School of Pharmacy, Gurunanak Institute Technical Campus, Ibrahimpattnam - 501506, Telangana, India.

E-mail: sandipsen2010@gmail.com

ABSTRACT: Background: The current study used computational approaches to investigate the molecular, physicochemical and drug-like properties of some 4-(10-acetyl-10H-phenothiazines-3-yl)-1-phenylazetidin-2-one derivatives. **Methods:** The structures of the compounds were drawn using Chemdraw ultra12 and smiles were generated using ACD chem sketch software. The physicochemical and molecular properties were calculated using the OSIRIS data warrior, and Toxicity potential, pharmacokinetic profile and medicinal chemistry aspects were determined by Swiss ADME tools. The docking analysis was carried out by mCule for the antimicrobial and anti-inflammatory profiles. The compounds were targeted for beta-lactamase, peptidoglycan hydroxylase, Cyclo-oxygenase-1 and 2 inhibitions. **Result:** All the compounds exhibited moderate to good drug likeliness and pharmacokinetic potential. The molecules showed good bioactivity scores against enzyme receptors. The ADMET prediction showed PGP and CYP-inhibitory effects with the least toxic profile. The docking analysis showed good binding affinity toward beta-lactamase, peptidoglycan hydroxylase and cycloxygenase-1 enzymes. **Conclusion:** The compounds showed good drug likeliness properties along with good toxicity potential and pharmacokinetic profiles. From docking analysis, it was found that all the molecules had a good binding affinity for beta-lactamase enzymes and peptidoglycan hydroxylase enzymes. The results also showed a more strong COX2 binding affinity than COX-1.

INTRODUCTION: Phenothiazine (Ptz) $S(C_6H_4)$ 2NH is a tricyclic heterocyclic compound. Berntsen, in 1883, prepared phenothiazine by condensation of diphenylamine with sulfur. In the manufacture of phenothiazine, used as a chemical stabilizer or inhibitor to prolong the storage of monomers and enhance the shelf life of products such as acryloyl chloride.

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Phenothiazine (chlorpromazine) is the most commonly used neuroleptic [1]. Chlorpromazine was one of the first compounds used as a neuroleptic to treat symptoms of psychosis. It is considered an important molecular template for developing related compounds with various biological activities.

It is used as a tranquilizer, anti-inflammatory, antimalarial, antipsychotic, antimicrobial, anti-tubercular, antitumor and antihistaminic. Analgesic agent [2]. 10 (N-10) of the tricyclic ring, with the terminal amine group in the side chain, determines the activity of Ptz against cancer cells, and the activity is more strongly bound to the type of

substituents in the phenothiazine ring than the nature of the side chain [3]. In rational drug design, a major step is identifying and characterizing bioactive molecules using advanced spectroscopic techniques like X-ray crystallography and nuclear magnetic resonance (NMR). Spectroscopy provides stereochemical information about molecules with initiating the structure-based drug design (SBDD) process.

Applying *in-silico* drug design is commonly based on experimental background information and computational methodologies [4]. Structure-based drug design describes the specificity and affinity of the interaction of a particular unknown target protein with various small molecules. The compound with the highest score, which is thought to have high binding affinity and specificity, is chosen for biochemical and biological testing [5].

The most widely used approaches are molecular docking, molecular dynamics (MD), fragment-based drug design (FBDD) , and pharmacophore modeling, which are referred to as the commonest computational SBDD methods [6]. *In-silico* approaches are utilized in ligand-based drug design. This approach is employed to spot the ligand's important structural and physicochemical properties for its interaction with the molecular target. The most widely used approaches in ligand-based drug design (LBDD) are ligand chemical similarity, binding affinity, and physicochemical properties with known active compounds.

The other is pharmacophore mapping and quantitative structure-activity relationship (QSAR) [7]. The simulation of a biomolecular interaction is often achieved by molecular docking. It provides information regarding the affinity of every ligand. The high relative molecular mass compounds exhibit unsatisfied pharmacokinetic properties because of poor solubility.

A fragment-based drug design (FBDD) approach will be applied to overcome this problem. It is based on discovering ligands (150 Da) with low molecular weight and chemical complexity that are soluble organic molecules and target subpockets within an oversized binding site. It is the starting point for hit-to-lead optimization. For a compound to be characterized as a fragment, it has to stick to the rule of three. According to this rule, fragments should have a relative molecular mass of less than 300 Da, cLogP ≤3, the number of hydrogen bond donors ≤3 and the number of hydrogen bond acceptors ≤3 [7, 8].

This research aimed to run web-based SBDD, FBDD, and LBDD designs on some synthesised 4-(10-acetyl-10H-phenothiazines-3-yl)1-phenylazetidin-2-one derivatives. The cyclization of unsymmetrical imines obtained the compounds in the presence of chloro acetyl chloride and a base catalyst triethyl amines to search for potent compounds [9]. The structures of compounds 1-11 are shown in **Table 1.**

TABLE 1: MOLECULAR LIBRARY ALONG WITH STANDARDS

Molecule no	Structure with IUPAC nomenclature	Smile notations
1	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(4-chlorophenyl)azetidin-2-one	Clc1ccc(cc1)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O
2	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(4-bromophenyl)azetidin-2-one	Brc1ccc(cc1)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O

3		[O][N+](=O)c1ccc(cc1)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O
4	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(4-nitrophenyl)azetidin-2-one	Clc1ccc(cc1Cl)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O
5	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(3,4-dichlorophenyl)azetidin-2-one	[O-][N+](=O)c1cc(ccc1Cl)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O
6	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(4-chloro-3-nitrophenyl)azetidin-2-one	COc1ccc(cc1)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O
7	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(4-methoxyphenyl)azetidin-2-one	Fc1ccc(cc1)N2C(=O)CC2c3ccc4N(c5ccccc5Sc4c3)C(C)=O
8	4-(10-acetyl-10H-phenothiazin-3-yl)-1-(4-fluorophenyl)azetidin-2-one	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O
9	Ibuprofen	NS(=O)(=O)c1ccc(cc1)n3nc(cc3c2ccc(C)cc2)C(F)(F)F
	Celecoxib	

10		CC1(C(N2C(S1)C(C2=O)NC(=O)C(C3=CC=C(C=C3)O)N)C(=O)O)C
11	Amoxicillin	CC1(C(N2C(S1(=O)=O)CC2=O)C(=O)O)C
	Sulbactam	

MATERIALS AND METHODS:

Preparation of Structure: The structures of the titled compounds were prepared by Chemdraw ultra 12.0.2. SMILES notations of the title compounds were obtained by using ACD Labs Chemsketch version 12.0.

Calculation of Molecular and Physicochemical Property and Toxicity Potential of Compounds: The smile notation of compounds 1-7 was entered into Osiris Data Warrior software and calculated molecular properties like shape index, molecular flexibility, and molecular complexity of the molecules [10]. Similarly, physicochemical properties such as molecular weight, partition coefficient (cLog P), water solubility in moles/liter (cLogS); hydrogen bond acceptors and donors, total surface area, relative polar surface area, topological polar surface area (TPSA), and violations of Lipinski's rule of five were calculated to evaluate the drug likeliness of the compounds and toxicity profiles like mutagenic, tumorigenic, reproductive effective, and irritant properties were calculated. The fraction Csp3 and the molar refractive index were calculated using the Swiss ADME online tool. The compounds' molecular, physicochemical, and toxicity potential were compared with the standard drugs. The absorption percentage (% Abs) was also determined by the reported method of Zhao *et al*. (2002) by using the following formula:

$$\% \text{ Abs} = 109 - (0.345 \times \text{TPSA})$$

Calculation of Drug Likeliness and Bioactivity score: SMILES notations of the molecules were placed in the online tool Swiss ADME (http://www.swissadme.ch/index.php) to predict drug likeliness properties like Lipinski, Ghose, Veber, Egan, Muegge, Bioavailability Score and Molinspiration software version 2011.06 (www.molinspiration.com) to calculate the score for drug targets including enzymes and nuclear receptors, kinase inhibitors, GPCR ligands, and ion channel modulators. The bioactivity radar of molecules and standards was prepared using the Swiss ADME tool[10].

Calculation of Pharmacokinetic Potential: Pharmacokinetic potential of the compounds was determined by the online tool Swiss ADME (http://www.swissadme.ch/index.php).

The Pharmacokinetic properties like GI absorption, BBB permeant, PGP substrate, a CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, Log Kp (skin permeation) were calculated. Based on the values determined, the boiled egg diagram was prepared using the SWISS ADME tool [10].

Calculation of Medicinal Chemistry Aspect: The medicinal chemistry aspects like PAINS alerts, Brenk alerts, lead likeness violations, and synthetic accessibility were determined by the Swiss ADME tool (http://www.swissadme. ch/index.php).

Docking Analysis: Docking analysis of the molecules was carried out using https://mcule.com by 1-click docking. Input the smile notation of the molecules in the structure refinery for generating an energy minimized structure for docking. The targeted proteins 3NY4 (Mycobacterium tuberculosis beta-lactamase K73A and E166A Mutant), 1PYY (beta-lactamase enzyme from Streptococcus pneumoniae strain R6), 3PBI (peptidoglycan hydrolase from Mycobacterium

tuberculosis), 3N8Z (Cyclooxygenase-1), 4COX (Cyclooxygenase-2 Prostaglandin Synthase-2) were selected from the database of the mcule library and run docking. 4 different binding scores were given. The results with more negative values were considered, and the images were downloaded to predict binding pose and binding residue.

RESULTS AND DISCUSSION:

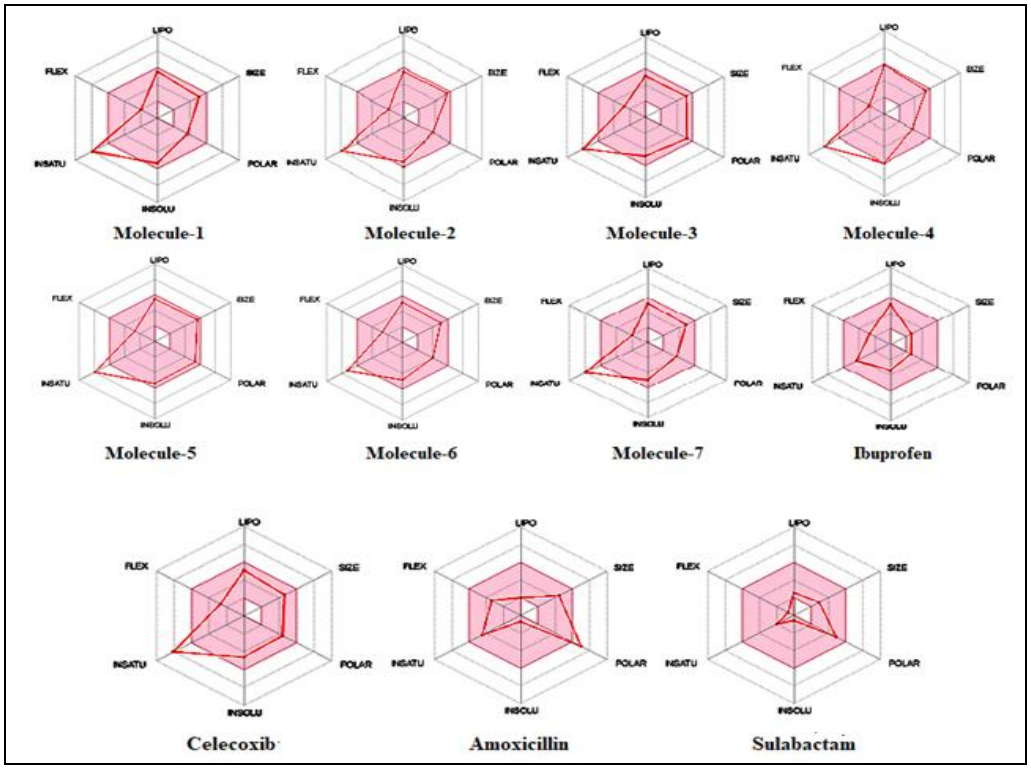
Physicochemical Properties: Physicochemical properties like molecular weight, partition coefficient, Solubility, H-Acceptors, H-Donors, Total Surface Area, Relative polar surface area, TPSA (Å²) [11], percentage of absorption, Fraction Csp3, molar refractive index [12] have great significance on biological activity and drug likeliness property of the molecules.

The physicochemical properties are shown in **Table 2**. All the molecules exhibited good drug likeliness characteristics concerning all the parameters except cLogP and Csp3. Based on the molecular and physicochemical properties, a bioactivity reader was drawn in **Fig. 1**.

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF THE COMPOUNDS

Molecules	MW[a]	cLogP[b]	cLogS[c]	H-Acceptors	H-Donors	TPSA[d](Å²)	% Abs[e]	Fraction Csp3	MR[f]
1	420.919	5.6084	-6.918	4	0	65.92	86.2576	0.13	122.48
2	465.37	5.7276	-7.016	4	0	65.92	86.2576	0.13	125.17
3	431.471	4.0808	-6.642	7	0	111.74	70.4497	0.13	126.3
4	455.364	6.2144	-7.654	4	0	65.92	86.2576	0.13	127.49
5	465.916	4.6868	-7.378	7	0	111.74	70.4497	0.13	131.31
6	416.5	4.9324	-6.2	5	0	75.15	83.07325	0.17	123.97
7	404.464	5.1032	-6.496	4	0	65.92	86.2576	0.13	117.43
Ibuprofen	206.284	3.0025	-2.895	2	1	37.3	96.1315	0.46	62.18
Celecoxib	381.377	2.5888	-4.174	5	1	86.36	79.2058	0.12	89.96
Amoxicillin	365.409	-2.0029	-1.269	8	4	158.26	54.4003	0.44	94.59
Sulbactam	233.243	-0.1556	-0.47	6	1	100.13	74.45515	0.75	54.13

a: Molecular weight (MW); b:P=[n-Octanol]/[Water]; (cLogP); c: S=Water solubility in moles/ liter at PH=7.5 (25°C) (cLogS); d: Toplogical polar surface area (TPSA); e: Percentage of absorption (%Abs); f: Molar refractive index.



The colored zone is suitable physicochemical space for oral bioavailability. LIPO (Liphophilicity): 0.7≤XLOGP3≤+5.0; SIZE: 150 g/mole ≤ MV; POLAR (Polarity): 20 Å2≤ TPSA ≤ 140 Å2; INSOLU (Insolubility): 0 ≤LOGS (ESOL)≤ 5.0; INSATU (Insaturation): 0.25 ≤Fraction Csp3≤1; FLEX (Flexibility): 0 ≤Number of rotatable bond ≤ 9

FIG. 1: BIOACTIVITY RADAR OF THE COMPOUNDS

Molecular Property: The shape index, molecular flexibility, and molecular complexity play a vital role in drug action and binding with the receptor molecules [13]. Generally, linear-shaped molecules are considered ideal for drug molecules [14]. Whereas molecules with high flexibility and low molecular complexity are considered for proper binding affinity toward the receptors [15]. The results shown in **Table 3** are that all the molecules are linear in shape. All the molecules showed low molecular flexibility and higher molecular complexity compared to the standard.

TABLE 3: MOLECULAR PROPERTIES OF THE COMPOUNDS

Molecules	Shape Index	Molecular Flexibility	Molecular Complexity	Rotatable Bonds
1	0.51724	0.32538	0.91922	2
2	0.51724	0.32538	0.91922	2
3	0.51613	0.35589	0.91714	3
4	0.5	0.33319	0.92897	2
5	0.46875	0.36967	0.93729	3
6	0.53333	0.34412	0.91408	3
7	0.51724	0.32538	0.91217	2
Ibuprofen	0.66667	0.62095	0.56446	4
Celecoxib	0.5	0.47398	0.82757	4
Amoxicillin	0.56	0.36195	0.89586	4
Sulbactum	0.4	0.21812	0.88723	1

a: Molecular shape index (Spherical ≤ 0.5 ≤ Linear); b: Molecular Flexibility (Low ≤ 0.5 ≤ High); c:Molecular Complexity (Low ≤ 0.5 ≤ High).

Druglikliness: The total drug likeliness characteristics like Drug likeness score, Lipinski, Ghose, Veber, Egan, and Muegge rule 15 [16]. The bioavailability score of all the molecules was also calculated and the results are represented in **Table 4**. All the molecules violate the drug likeliness as per Lipinski rules due to MLOGP>4.15. Ghose rules violate Molecule-5 also. But all the molecules followed Veber and Egan's rules for drug likeliness. The bioavailability score was 0.55 in respect of all the compounds. The result showed good drug likeliness characteristics in comparison to standards.

TABLE 4: DRUG LIKELINESS PROPERTIES OF THE MOLECULES

Molecules	Drug like lines	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
1	2.7178	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	Yes	0.55
2	0.86545	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	Yes	0.55
3	-2.4064	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	Yes	0.55
4	2.7178	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	Yes	0.55
5	-2.3358	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MR>130	Yes	Yes	Yes	0.55
6	2.7106	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	Yes	0.55
7	1.3155	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	Yes	0.55
Ibuprofen	0.0805	Yes	Yes	Yes	Yes	Yes	0.55
Celecoxib	-8.1085	Yes	No; 1 violation: WLOGP>5.6	Yes	Yes	Yes	0.55
Amoxicillin	9.3648	Yes	No; 1 violation: WLOGP<-0.4	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
Sulbactam	3.9525	Yes	Yes	Yes	Yes	Yes	0.55

Bioactivity Score: Based on the drug likeliness characteristics, the bioactivity score of the compounds was calculated by the mole inspiration online tool (www.molinspiration.com).

The bioactivity score was determined on the GPCR ligand (G-Protein coupled receptor), ion channel modulator, a kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor. A bioactivity score of more than 0 is considered good, -0.50 to 0 is considered moderate, and less than -0.5 is considered inactive compounds [16]. Based on the results shown in **Table 5,** the bioactivity order for the molecules with respect to target receptors are enzyme inhibitor > GCPR ligand > nuclear receptor, protease inhibitor, ion channel modulator, and kinase inhibitor.

All the molecules exhibited a moderate bioactivity score concerning different receptors.

TABLE 5: BIOACTIVITY SCORES OF THE COMPOUNDS

Molecules	GCPR	Ion Channel	Kinase Inhibitor	Nuclear Receptor	Protase Inhinitior	Enzyme Inhibitior
1	-0.1	-0.49	-0.37	-0.39	-0.44	-0.17
2	-0.18	-0.56	-0.4	-0.47	-0.5	-0.21
3	-0.21	-0.49	-0.46	-0.42	-0.49	-0.21
4	-0.09	-0.48	-0.35	-0.38	-0.45	-0.18
5	-0.22	-0.52	-0.44	-0.55	-0.57	-0.26
6	-0.13	-0.54	-0.38	-0.37	-0.43	-0.18
7	-0.09	0.5	-0.33	-0.35	-0.42	-0.16
Ibuprofen	-0.17	-0.01	-0.72	0.05	-0.21	0.12
Celecoxib	-0.06	-0.27	0.01	-0.28	-0.06	0.17
Amoxicillin	0.07	-0.42	-0.65	-0.47	0.84	0.27
Sulbactum	-0.42	-0.5	-1.19	-0.76	1.07	0.77

Toxicity Profiles: The toxicity potential of the molecules was determined for their mutagenic, tumorigenic, reproductive effects, and irritant properties. The result is shown in **Table 6,** where all the molecules have a high reproductive effect.

TABLE 6: TOXICITY PROFILES OF THE COMPOUNDS

Molecules	Mutagenic	Tumorigenic	Reproductive Effective	Irritant
1	None	none	high	none
2	None	none	high	none
3	None	none	high	none
4	None	none	high	none
5	None	none	high	none
6	None	none	high	none
7	None	none	high	none
Ibuprofen	None	none	none	none
Celecoxib	None	none	none	none
Amoxicillin	None	none	none	none
Sulbactam	None	none	none	none

Pharmacokinetics profiles: Most biomolecules are absorbed by the active or passive diffusion process. GI-absorptivity is an important parameter for oral absorption of bimolecular substances. The small intestine has the largest area for absorption of drugs in the GI tract than the stomach due to the permeability of its membrane [10].

As the intestine is considered a major absorption site, prediction of human intestinal absorption (HIA) of drug compounds is necessary [22]. The blood-brain barrier controls the entry of drug molecules into the brain. The molecules that have drug-like likeliness properties may cross the blood-brain barrier and may cause some toxic effects. So, it is important to predict the BBB penetrability and the toxicity profile of the molecules [10].

The PGP plays a vital role in the drug disposition process, like a urinary excretion mechanism and a biliary excretion mechanism. IT is also an important factor absorption barrier of oral bioavailability and the blood-brain barrier, limiting the accumulation of drugs in the brain. PGP

inhibition causes drug interactions and increases the accumulation of drugs in the brain.

Cytochrome P450 is a class of enzymes essential for the metabolism of drugs. Inhibition of cytochrome P450 (CYP) enzymes by a drug may decrease the metabolism of drugs and other metabolic processes.

The skin permeability of the drug substances is an important criterion for tropical applications. The measurement of the rate at which a molecule can cross the lipid bilayer membrane of the skin is called the skin permeation coefficient (KP). It is expressed in cm/s and equals the diffusion coefficient multiplied by the width of the membrane [10, 17]. **Table 7** and **Fig. 2** show that all the molecules have GI-absorption capacity.

The molecules 1, 2, 6, and 7 have blood-brain barrier penetrability. Similarly, for molecules 3 and 5, human intestinal absorptions (HIA) capacity is greater.

Molecules 1, 2, 4, 6, and 7 exhibited the PGP initiator effect, whereas molecules 3 and 5 exhibited the PGP inhibitory effect. All the molecules have an CYP-inhibitory impact against different CYP inhibitors. The results also reported skin permeability of the molecules in the acceptable range.

TABLE 7: PHARMACOKINETIC POTENTIALS OF THE COMPOUNDS

Molecules	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
1	High	Yes	Yes	No	Yes	Yes	No	Yes	-5.88
2	High	Yes	Yes	No	Yes	Yes	No	Yes	-6.11
3	High	No	No	No	Yes	Yes	No	No	-6.51
4	High	No	Yes	No	Yes	Yes	No	Yes	-5.64
5	High	No	No	No	Yes	Yes	No	No	-6.27
6	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-6.32
7	High	Yes	Yes	No	Yes	Yes	No	Yes	-6.15
Ibuprofen	High	Yes	No	No	No	No	No	No	-5.07
Celecoxib	High	No	No	Yes	No	Yes	No	No	-6.21
Amoxycillin	Low	No	No	No	No	No	No	No	-9.94
Sulbactam	High	No	No	No	No	No	No	No	-8.44

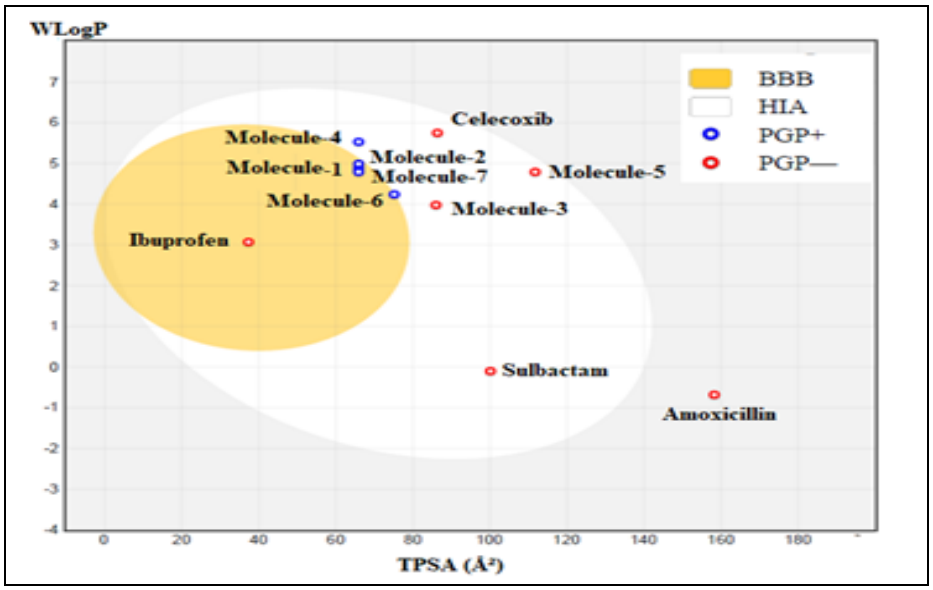


FIG. 2: BOILED EGG DIAGRAM FOR THE MOLECULES IN COMPARISON TO STANDARD

Medicinal Chemistry Acceptability: The medicinal chemistry acceptability in **Table 8** showed no pain alerts. Molecules 3 and 5 showed brank alerts due to the presence of nitro groups. There was a violation of drug likeliness due to a molecular weight of more than 350 and XLOGP3>3.5. But synthetic accessibility is good for all the compounds.

TABLE 8: MEDICINAL CHEMISTRY ASPECTS OF THE COMPOUNDS

Molecules	PAINS alerts	Brenk alerts	Lead likeness violations	Synthetic Accessibility
1	0	0	No; 2 violations: MW>350, XLOGP3>3.5	3.49
2	0	0	No; 2 violations: MW>350, XLOGP3>3.5	3.54
3	0	2 alerts: nitrogroup, oxygen-nitrogen single bond	No; 1 violation: MW>350	3.64
4	0	0	No; 2 violations: MW>350, XLOGP3>3.5	3.53
5	0	2 alerts: nitrogroup, oxygen-nitrogen single bond	No; 2 violations: MW>350, XLOGP3>3.5	3.77
6	0	0	No; 2 violations: MW>350, XLOGP3>3.5	3.6
7	0	0	No; 2 violations: MW>350, XLOGP3>3.5	3.5
Ibuprofen	0	0	No; 1 violation: MW<250	1.92
Celecoxib	0	0	No; 1 violation: MW<250	2.74
Amoxicillin	0	0	No; 1 violation: MW<250	4.17
Sulbactam	0	0	No; 1 violation: MW<250	3.84

Docking Analysis: Docking is a useful tool for predicting the predominant binding mode(s) of a ligand with a known three-dimensional structure of a protein. The majority of the molecules designed using ligand-based approaches were found to be biologically active with good pharmacokinetics and therapeutic profiles. The results in **Table 9** represent the molecules' binding energy ΔG (kcal/mol). The results show that all of the molecules have a high affinity for beta-lactamase (3NY4) and peptidoglycan hydroxylase (3PBI). The results also showed more COX2 (4COX) binding affinity than COX-1. A comparative study was carried out for all the individual compounds in comparison to standards. The binding pose and binding residue of the molecules with good binding affinity represent in **Fig. 3. 4. 5, 6** and **7** molecule-4, 7 (3NY4), molecule-5, 6 (1PYY), molecule-4, 7(3PBI), molecule-1, 4 (3N8Z) and molecule-3, 5 (4COX) have a good inhibitory action on different targeted proteins.

TABLE 9: BINDING ENERGY (ΔG KCAL/MOL) OF THE MOLECULES BY DOCKING ANALYSIS

Compound	3NY4	1PYY	3PBI	3N8Z	4COX
1	-8.5	-7.6	-8.9	-7.5	-6.6
2	-8.4	-7.2	-8.8	-1.1	-6.4
3	-8.1	-7.5	-8.2	-2.4	-9.1
4	-8.6	-7.9	-9	-7.1	-5.9
5	-8.2	-8.7	-8.9	-3.1	-9.5
6	-8.2	-8.3	-8.5	-3	-8.2
7	-8.6	-8.2	-9.9	-3.2	-5.5
Ibuprofen				-7.5	
Celecoxib					-10.2
Amoxicillin		-6.3	-8.2		
Sulbactam	-5				

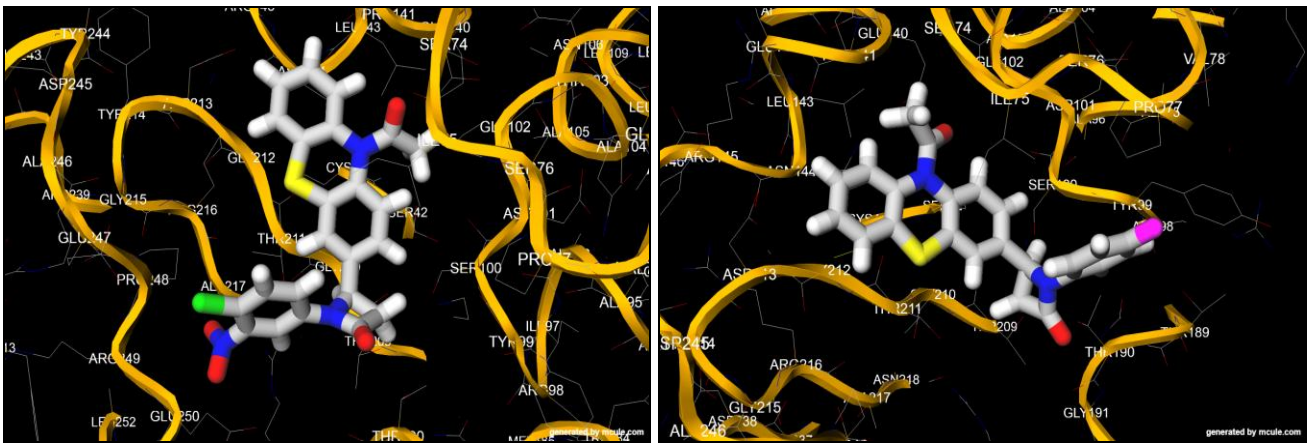


FIG. 3: BINDING POSE OF MOLECULE-4 AND 7 WITH 3NY4 ALONG WITH THE BINDING RESIDUE

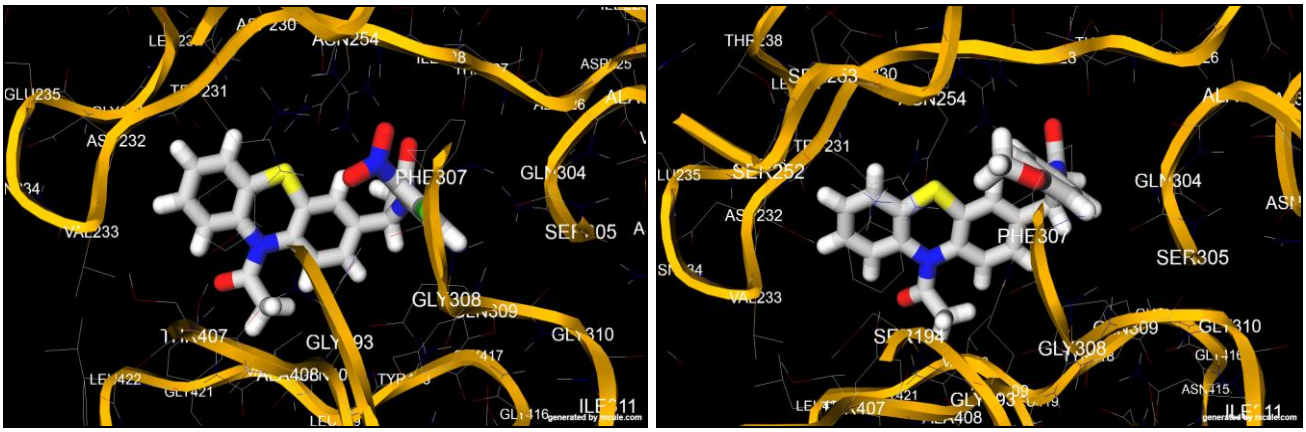


FIG. 4: BINDING POSE OF MOLECULE-5 AND 6 WITH 1PYY ALONG WITH THE BINDING RESIDUE

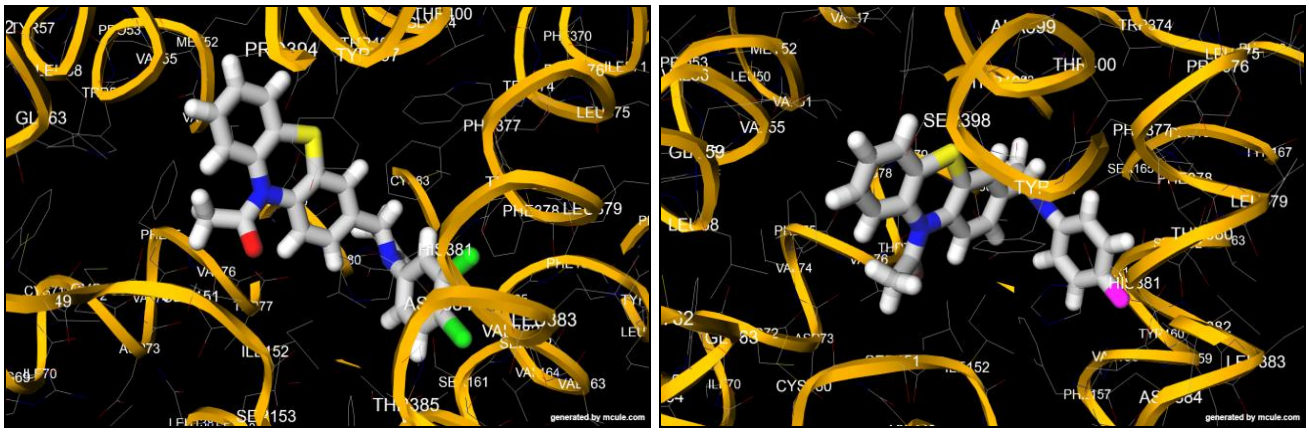


FIG. 5: BINDING POSE OF MOLECULE-4 AND 7 WITH 3PBI ALONG WITH THE BINDING RESIDUE

FIG. 6: BINDING POSE OF MOLECULE-1 AND 4 WITH 3N8Z ALONG WITH THE BINDING RESIDUE

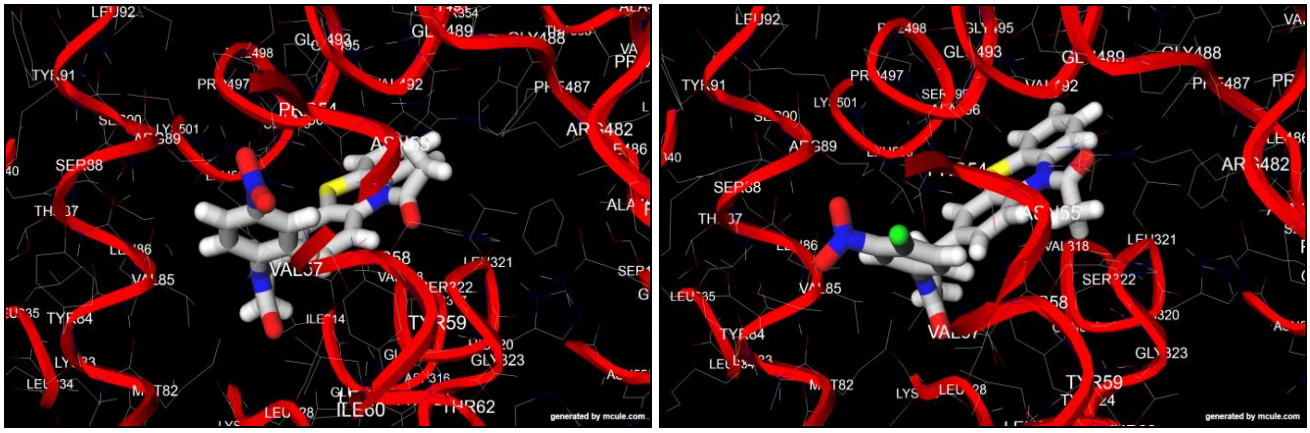


FIG. 7: BINDING POSE OF MOLECULE-3 AND 5 WITH 4COX ALONG WITH THE BINDING RESIDUE

CONCLUSION: From the detailed analysis, it was found that the compounds showed good drug likeliness properties along with good toxicity potential and pharmacokinetic profiles. But due to the PGP and CYP-inhibitory effects, some molecular development is required from a pharmaceutical point of view. In docking analysis, it was found that molecule- 7 have good binding affinity for both beta-lactamase and peptidoglycan hydroxylase enzymes. The molecule 1 have moderate binding affinity for COX-1, and molecule-5 have strong binding affinity for COX-2 enzymes. The antibacterial profile may be due to the beta-lactam ring, whereas the anti-inflammatory action may be due to the acetyl moiety and the phenyl ring.

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