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MOLECULAR DOCKING STUDIES FOR ADME, TOXICITY PARAMETER OF THIAZOLE DERIVATIVE FOR ANTIMICROBIAL ACTIVITY

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ABSTRACT

The aim of this study was to examine the correlation between Antimicrobial activity, Docking studies and Molecular properties of the Thiazole derivatives in search of a lead compound through Molinspiration Cheminformatics software. Molecular docking is a well established computational technique which predicts the interaction energy between two molecules. Molecular docking studies are used to determine the interaction of two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy. Seven synthetic derivative of Thiazole derivative were selected for bioactivity prediction and Drug likeness score on the basis of Lipinski's rule. Structure-based drug design by use of structural biology remains one of most logical and aesthetically pleasing approaches in drug discover paradigms. From the docking studies for antimicrobial protein shows, out of 14 ligand compound 1,2,3,8, 9, 11,12, 13 and 14 very well packed in to active site of the protein like the Thiazole derivative. On the basis of structure-based drug design, new lead structure were discovered for rational drug designing of Antimicrobial compounds and it will help full for further modification to obtained clinically useful novel entities for Antimicrobial drugs

KEYWORDS: Drug designing, Docking, Antimicrobial activity, Lipinski's, Molinspiration, Thiazole derivatives and Protein ID -1TPY, 2V0J.

INTRODUCTION

Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules.[23] Molinspiration is a web based software used to obtain parameter such as MiLogP, TPSA, drug likeness, MiLogP is calculated by the methodology developed by molinspiration has a sum of fragment based contribution and correction factors. MiLogP parameter is used to check a good permeability across the cell membrane. TPSA is related to hydrogen bonding potential of compound. Calculation of volume developed at molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailability of drugs. Through drug likeness data of molecule, it can be checked molecular properties and structure future is respective to known drugs.[22] Antimicrobials are the substances which destroys or inhibiting the growth of micro- organism. Several natural and synthetic compounds possess antimicrobial activity.[25] An antimicrobial is an agent that kills microorganism or stop their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria and antifungals are used against fungi.[25] In response, further advancements in antimicrobial technologies have results in solutions that can go beyond simply inhibiting microbial growth instead, certain types of porous media have been developed to kill microbes on contact.[24] Thiazole and related compound are called 1, 3- azoles (nitrogen and one other heteroatom in a five membered ring a heterocyclic compound featuring both a nitrogen atoms and sulfur atom (aromatic five membered ring). They are isomeric with the 1, 2- azoles, the nitrogen and sulfur compound being called Isothiazole.[12]

Therefore, in the present study the series of newly designed heterocyclic compounds of Thiazole derivatives were selected based on their molecular properties and drug likeliness score and further investigated for its binding efficiency to evaluate their ADME parameters.

MATERIALS AND METHODS

Structure of all the selected Thiazole derivatives were drawn by using ACD labs Chemsketch version 12.0 and their SMILES notation were generated. Smiles notation of the selected compound were fed in the online molinspiration software version 2016.10

(www.molinspirstion.com) for calculation of molecular properties (Logp, Total polar surface area, numbers of the hydrogen bond donors and acceptors, molecular weight, number of atom, number of rotatable bonds etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitor, ion channel modulators, enzymes and nuclear. Docking is done by using ARGUS LAB software.

***In silico* molecular docking studies**

Preparation of Protein structure

Protein target was downloaded from data base [Protein Data Bank (PDB). PDB id target protein Antibacterial Proteins1 TPY(Structure of the cyclopropane synthatase MmA2 from Mycobacterium tuberculosis). 2V0J (Characterization of the substrate binding and catalysis of the potential antibacterial target N-Acetyl glucosamine 1-phosphate uridyltransferase (GLMU)). All water molecules were removed and on final stage hydrogen atoms were added to receptor molecule.

Protein details

1. 1TPY

Classification : TRANSFERASE
Deposited : 2004-06-16
Released : 2004-10-19
Deposition author(s) : Smith, C.V., Sacchettini, J.C.
Organism : Mycobacterium tuberculosis

2. 2V0J

Classification : TRANSFERASE
Deposited : 2007-05-14
Released : 2008-01-15
Deposition author(s) : Mochalkin, I., Lightle, S., Ohren, J.F., Chirgadze, N.Y
Organism : Haemophilus influenza

Preparation of Ligands

Review of Literature shows that Thiazoles [13-16] contains wide spectrum of anti-microbial activity. Hence it was decided to design a newer heterocyclic compound of seven containing Thiazoles. The ligands were drawn in Chem sketch freeware assigned with proper 2D orientation and they are converted in to three – Dimensional structure using CORINA Classic.

TABLE-1.

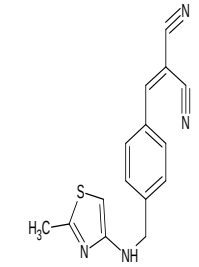
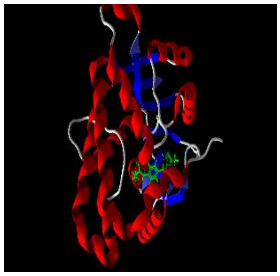
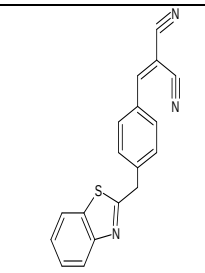
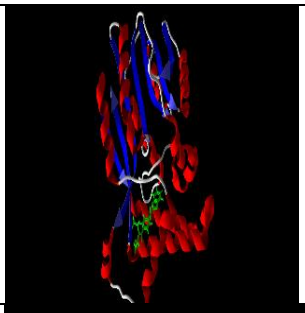
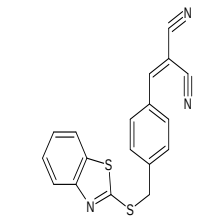
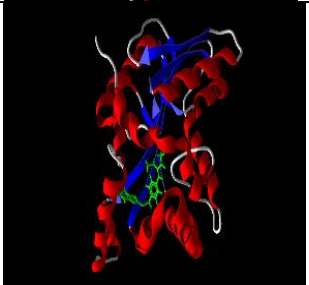
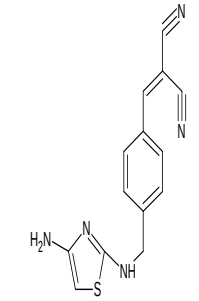
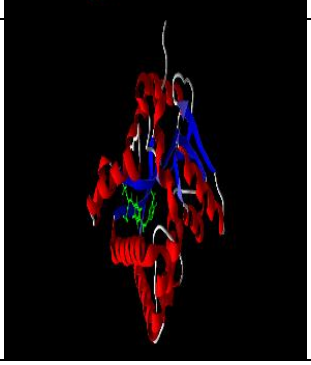
S. NO	NAME OF STRUCTURE	MOL. FORMULA	MOL. WEIGHT	COMPOSITION	MOLAR REFRACTIVE	PARACHOR	DENSITY
1.	(4-{[(2-methyl-1,3-thiazol-4-yl) amino] methyl} benzylidene) propane dinitrile	C_{15} H_{12} N_4 S	280.347	C- 64.26% H- 4.31% N-19.98% S- 11.44%	81.84 ± 0.3 Cm^3	608.7 ± 4.0 Cm^3	1.318 ± 0.06 g/Cm^3
2.	[4-(1,3-benzothiazol-2-ylmethyl)benzylidene]propanedinitrile	C_{15} $H_{11}N_3$ S	301.365	C- 71.74% H- 3.68% N- 13.94% S- 10.64%	229. 7 ± 3.0 Cm^3	654.9 ± 4.0 Cm^3	1.311 ± 0.06 g/Cm^3
3.	{4-[(1,3-benzothiazol-2-ylsulfanyl)methyl] benzylidene}propane dinitrile	C_{15} $H_{11}N_3S_2$	333.430	C- 64.84% H- 3.33% N- 12.60% S- 19.23%	95.68 ± 0.4 Cm^3	716.3 ± 6.0 Cm^3	1.37 ± 0.1 g/Cm^3
4.	(4-{[(4-methyl-1,3-thiazol-2-yl)oxy] methyl}benzylidene) propanedinitrile	C_{15} H_{11} N_3 O S	281.332	C- 64.04% H- 3.94% N- 14.94% O- 5.69% S- 11.40%	78.91 ± 0.3 Cm^3	606.5 ± 4.0 Cm^3	1.295 ± 0.06 g/Cm^3
5.	(4-{[(4-amino-1,3-thiazol-2-yl) amino] methyl}benzylidene) propanedinitrile	C_{14} H_{11} N_5 S	281.335	C- 59.77% H- 3.94% N- 24.89% S- 11.40%	81.25 ± 0.3 Cm^3	596.9 ± 4.0 Cm^3	1.416 ± 0.06 g/Cm^3
6.	{4-[(5-methyl-1,3-thiazol-2-yl) methyl] benzylidene} propanedinitrile	C_{15} H_{11} N_3 S	265.332	C- 67.90% H- 4.18% N- 15.84% S- 12.08%	77.05 ± 0.3 Cm^3	588.7 ± 4.0 Cm^3	1.252 ± 0.06 g/Cm^3
7.	{4-[(5-nitro-1,3-thiazol-2-yl) methyl] benzylidene} propanedinitrile	C_{14} H_8 N_4 O_2 S	296.303	C- 56.75% H- 2.72% N- 18.91% O- 10.80% S- 10.82%	78.78 ± 0.3 Cm^3	606.9 ± 4.0 Cm^3	1.428 ± 0.06 g/Cm^3

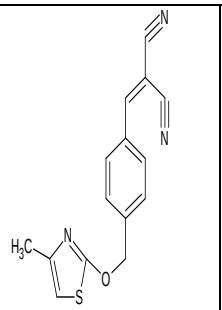
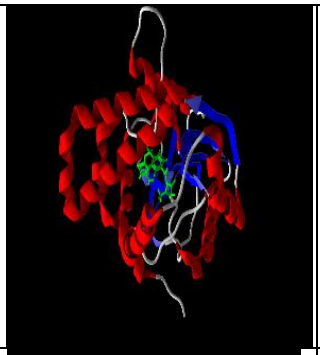
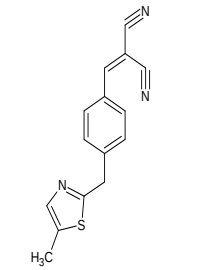
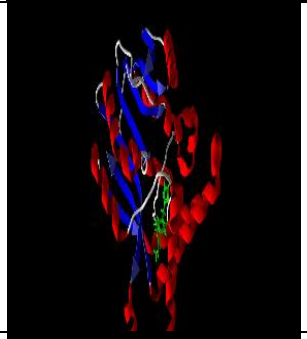
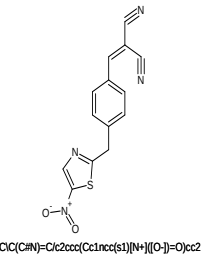
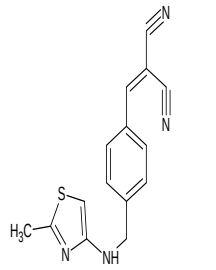
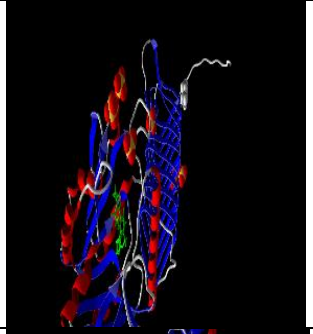
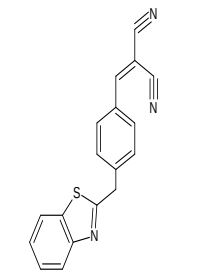
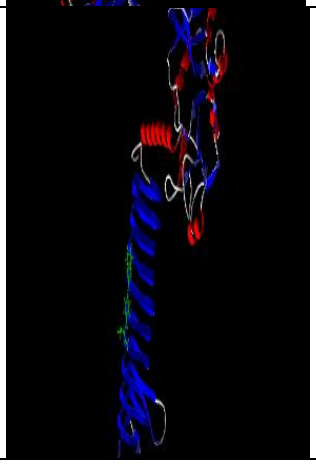
RESULT AND DISCUSSION

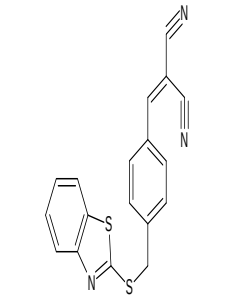
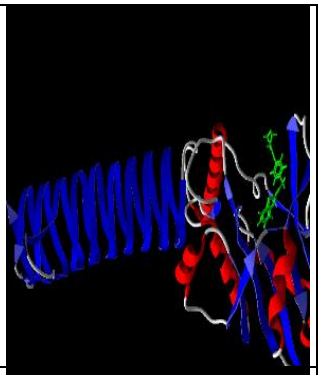
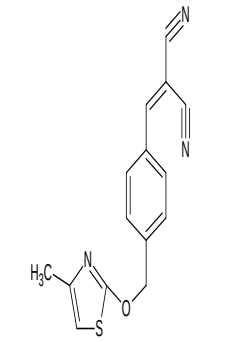
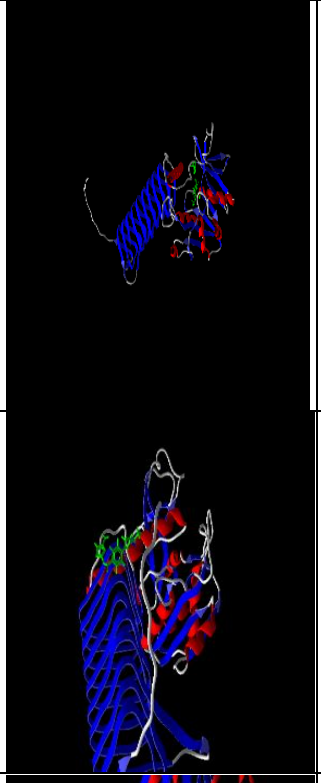
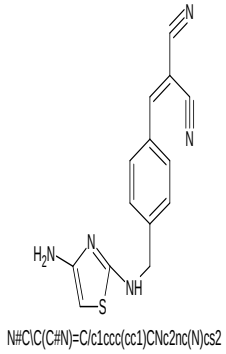
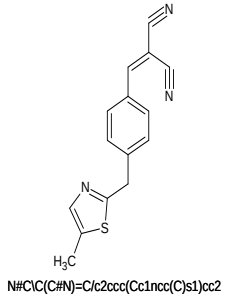
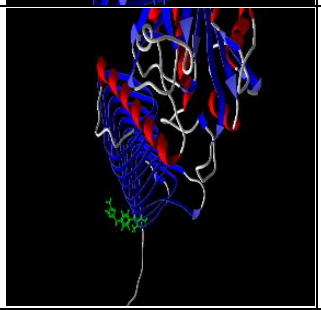
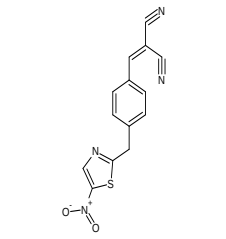
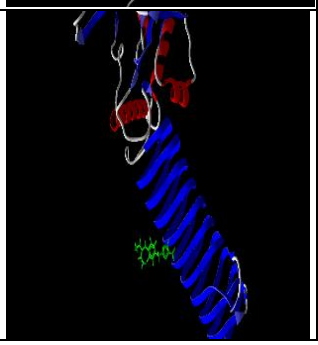
The antibacterial protein selected for the proteomic studies of Thiazole derivatives Constituent are 1TPY (Structure of the cyclopropane synthatase MmaA2 from Mycobacterium tuberculosis) and 2V0J (characterization of the substrate binding and catalysis of the potential antibacterial target N-Acetyl glucosamine-1-phosphate uridyl transferase (GLMU)). From the docking studies for antimicrobial protein shows, out of 14 ligand compound 1,2,3,8, 9, 11,12, 13 and 14 very well packed in to active site of the protein like the Thiazole derivative.

Table -2 Potential binding sites of the compound.

THIAZOLE DERIVATIVES (TABLE-2).

S. NO	PROTEIN NAME	CHEMICAL NAME	STRUCTURE	CAPTURE	FINAL ENERGY	VDW RADIUS
1	1TPY	(4-{[(2-methyl-1,3-thiazol-4-yl) amino]methyl}benzylidene) propanedinitrile	 Cc2nc(NCc1ccc(/C=C(\C#N)C#N)cc1)cs2		-9.3430 k cal/mol	1.7Å
2	1TPY	[4-(1,3-benzothiazol-2-ylmethyl) benzylidene] propanedinitrile	 N#C\C(C#N)=C/c1ccc(cc1)Cc2nc3ccccc3s2		-8.3265 K cal/mol	1.55Å
3.	1TPY	{4-[(1,3-benzothiazol-2-ylsulfanyl) methyl] benzylidene} propanedinitrile	 N#C\C(C#N)=C/c1ccc(cc1)CSc2nc3ccccc3s2		-95875 K cal/mol	1.7Å
4.	1TPY	(4-{[(4-methyl-1,3-thiazol-2-yl)oxy] methyl} benzylidene) propanedinitrile	 N#C\C(C#N)=C/c1ccc(cc1)CNc2nc(N)cs2		-10.5274 K cal/mol	1.7 Å

5.	1TPY	(4-{[(4-amino-1,3-thiazol-2-yl) amino] methyl} benzylidene) propanedinitrile	 N#C/C(C=N)=C/c1ccc(cc1)COc2nc(C)cs2		-10.5733 K cal/mol	1.55Å
6	1TPY	{4-[(5-methyl-1,3-thiazol-2-yl) methyl] benzylidene} propanedinitrile	 N#C\C(C#N)=C/c2ccc(Cc1ncc(C)s1)cc2		-7.5877 K cal/mol	1.7 Å
7	1TPY	{4-[(5-nitro-1,3-thiazol-2-yl)methyl] benzylidene} propanedinitrile	 N#C\C(C#N)=C/c2ccc(Cc1ncc(s1)[N+](=O)[O-])cc2		-10.2258 K cal/mol	1.55 Å
8	2V0J	(4-{[(2-methyl-1,3-thiazol-4-yl)amino] methyl}benzylidene) propanedinitrile	 Cc2nc(NCc1ccc(/C=C(\C#N)C#N)cc1)cs2		-8.5429 K cal/mol	1.7 Å
9	2V0J	[4-(1,3-benzothiazol-2-ylmethyl) benzylidene] propanedinitrile	 N#C\C(C#N)=C/c1ccc(cc1)Cc2nc3ccccc3s2		-9.7768 K cal/mol	1.55 Å

10.	2V0J	{4-[(1,3-benzothiazol-2-ylsulfanyl) methyl] benzylidene} propanedinitrile	 N#C\C(C#N)=C/c1ccc(cc1)CSc2nc3ccccc3s2		-10.5936 K cal/mol	1.7 Å
11.	2V0J	(4-{[(4-methyl-1,3-thiazol-2-yl)oxy] methyl}benzylidene) propanedinitrile	 N#C/C(C=N)=C/c1ccc(cc1)COc2nc(C)cs2		-9.2279 K cal/mol	1.55 Å
12.	2V0J	(4-{[(4-amino-1,3-thiazol-2-yl)amino] methyl}benzylidene) propanedinitrile	 N#C\C(C#N)=C/c1ccc(cc1)CNc2nc(N)cs2		-8.53946 Kcal/mol	1.7 Å
13.	2V0J	{4-[(5-methyl-1,3-thiazol-2-yl) methyl] benzylidene} propanedinitrile	 N#C\C(C#N)=C/c2ccc(Cc1ncc(C)s1)cc2		-9.49202 K cal/mol	1.55 Å
14.	2V0J	{4-[(5-nitro-1,3-thiazol-2-yl)methyl] benzylidene} propanedinitrile	 N#C\C(C#N)=C/c2ccc(Cc1ncc(s1)[N+](O-])=O)cc2		-9.1548 K cal/mol	1.7 Å

Bioactivity score of the compounds

The bioactive score of the compound on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor are mentioned in the below table. As a general rule, larger is the bioactivity score, higher is the probability that investigated compound will be active. Therefore, a molecule having bioactivity score more than 0.00 is mostly likely to possess considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is presumed to be inactive. The results of the present study demonstrated that the investigated compounds are biologically active molecules and will produce the physiological actions by interacting with GPCP ligands, nuclear receptor ligands and inhibit protease and other enzymes. Though bioactivity score for GPCR ligand is found to be -0.50 to 0.00 for all tested compounds 1-7 respectively, suggest moderate interaction with this target. Bioactivity score for ion channel modulator activity was in between 0.00 and -0.50 for all tested compounds 1, 2, 4, 5, 6 and 7 are moderately active and 3 compounds are less than 0.50 are inactive towards this drugs target. Similar results are obtained for kinase inhibitor and only compounds 0.00 and -0.50 the tested compound 1, 2, 3, 4, 6 and 7 are moderately active and 5 compounds are more than 0.00 is biologically active. Bioactivity scores for nuclear receptor ligands was found to be in the range of 0.00 and -0.50 the tested compounds 3,4 are moderately active and 1, 2, 5, 6 and 7 compounds less than- 0.50 are inactive towards this drugs target. Bioactivity scores for protease inhibitor were found to be in the range of 0.00 and -0.50 the tested compounds 2, 3, 4 and 6 are moderately active and 1, 5 and 7 compounds less than -0.50 are inactive towards this drugs target. Bioactivity score for enzyme inhibitor was found to be in the range of 0.00 and -0.50 suggest their moderate interaction with this target.

Table-3.

COMPOUND NUMBER	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INKIBITOR
1.	-0.38	-0.46	-0.12	-0.84	-0.56	-0.25
2.	-0.23	-0.30	-0.01	-0.69	-0.30	-0.10
3.	-0.50	-1.06	-0.30	-0.34	-0.44	-0.31
4.	-0.30	-0.10	-0.38	-0.37	-0.18	-0.15
5.	-0.38	-0.46	+0.12	-0.84	-0.56	-0.25
6.	-0.34	-0.32	-0.21	-0.58	-0.48	-0.16
7.	-0.44	-0.36	-0.04	-0.63	-0.54	-0.17

PHYSIOCHEMICAL PROPERTIES

The Physiochemical properties as melting point, Solubility of the compounds (1-7) are summarized in table 4.

DRUG LIKENESS CALCULATION ON THE BASIS OF LIPINSKI RULE OF FIVE

The drug likeness score was calculated according to Lipinski's rule of five, a candidate molecular is more likely to be

a) The molecular weight is under 500,
b) The calculated octanol/water partition coefficient (log p) is less than 5,
c) These are not more than 5 hydrogen bond donors (OH and NH groups),
d) These are not more than 10 hydrogen bond acceptors (notably N and O).

Partition coefficient or Log P is an important parameter used in rational drug design to measure molecular hydrophobicity. Hydrophilic/ lipophilic nature of drug molecule affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as well as their toxicity. Log P values of Thiazole derivatives compounds were found to be in the range of below 5 so it as obey the Lipinski rule. This implies that these compounds will have good permeability across cell membrane.

All the structure can carried out the oral absorption, bioavailability and permeability in the tested compound were found to be within Lipinski's rule. Low molecular weight drugs molecular (<500) are easily transported, diffuse and absorbed in the tested compound were found to be within Lipinski's rule. Numbers of hydrogen bond acceptor (O and N atoms) in the tested compound were found to be Lipinski's rule. Number of hydrogen bond donors (NH and OH) compounds 2, 3, 4, 6, 7 they do not obey Lipinski's rule and only 1, 5 tested compounds were found to be within Lipinski's rule. Total polar surface area (TPSA) is closely related to the hydrogen bonding potential of a molecular and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood brain barrier penetration etc. TPSA of thiazole derivatives was found to be range of 60.48-106.30 and is well below the 160 A^{o} limit.

Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs. Among all the screened compounds 2 and 6 were flexible (3 rotatable bonds) and compounds 1, 3, 4, 5 and 7 were rigid as they do not have any rotatable bonds.

Table -4.

CPD.NO	miLog P	TPSA	ni atom	Mol.wt	Non	nOHNH	n violation	N rot b	volume
1.	2.09	98.53	20	281.34	5	3	0	4	243.64
2.	4.30	60.48	22	301.37	3	0	0	3	263.14
3.	4.92	60.48	23	333.44	3	0	0	4	282.06
4.	3.10	69.71	20	281.34	4	0	0	4	245.49
5.	2.09	98.55	20	281.34	5	3	0	4	243.64
6.	3.02	60.48	19	265.34	3	0	0	3	236.51
7.	2.88	106.30	21	296.31	6	0	0	4	243.28

SUMMARY AND CONCLUSION

On the basis of studies concluded drug design, new lead structure were discovered for rational drug designing for thiazole derivatives and it will helpful for further modification (molecular modeling) to obtain clinically useful novel entities for Antimicrobial drugs. It can be concluded that thiazole derivatives are biologically important molecules and posses desirable molecular properties for drug likeness, but bioactivity score of compounds is moderately active drugs. In case of some modifications in structure, it can be produced active drug to produce antimicrobial activity. The drug discovery and pharmacophore site should be evaluated in future experiments as continuation of these investigations on this series.

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