Impact Factor (SJIF): 6.092 E-ISSN: 2583-1615

International Journal of Research in Academic World

Received: 24/May/2023 IJRAW: 2023; 2(6):106-114 Accepted: 27/June/2023

Computational Analysis of Novel Piperazine Derivatives with 4TRJ Protein along with ADMET Studies

[*1]Chukka Ajay Kumar, [2]Kosuru Sai Srinivas, [3]Badduri Sathwika, [4]Boddu Ramya Rani, [5]Gade Anantha Lakshmi, [6]Chinthapalli Venkanna Babu and [7]Dr. JN Suresh Kumar

[*1]Associate Professor, Department of Pharmaceutical Chemistry, Narasaraopeta Institute of Pharmaceutical Sciences, Kotappakonda Road. Yellamanda, Narasaraopet, Palnadu, Andhra Pradesh, India.

[2, 3, 4, 5, 6]IV B. Pharmacy, Narasaraopeta Institute of Pharmaceutical Sciences, Kotappakonda Road. Yellamanda, Narasaraopet, Palnadu, Andhra Pradesh, India.

[3]Principal, Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Kotappakonda Road. Yellamanda, Narasaraopet, Palnadu, Andhra Pradesh, India.

Abstract

In this study novel piperazine derivatives were designed. Piperazine is a vital organic scaffold that consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring and also posse's four carbon atoms. Designed derivative compounds against Enoyl-ACP reductase (4TRJ) molecular docking stimulation was carrier out with MCULE and insilico ADMET prediction procedures. The results of docking study revealed that the binding profile for designed compounds was found significant interactions with 4TRJ when with isoniazid, Thiocarlide, Megazole. The scope of the synthesized derivatives of novel pipe4erazine derivatives need for evaluation of various pharmacological studies to bring potentially active molecules. Molecular docking is used to find the best matching between two molecules i.e. target and ligand. In this procedure we can use enoyl-ACP reductase as a protein. This Protein help to catalyze the last step of elongation cycle in fatty acid synthesis. It is a key enzyme of type II fatty acid synthesis (FAS) system. ADMET properties of a compound deal with the absorption, distribution, metabolism, excretion and toxicity in and through the human body. ADMET which constitutes the pharmacokinetic profile of drug molecule is very essential in evaluating the pharmacodynamic activities. In ADMET studies we have used SWISS ADME and ADMETSAR prediction tools.

Keywords: Piperazine derivatives, Molecular docking, 4TRJ, isoniazid, thiocarlide, megazole, ADMET prediction, MUCLE

Introduction

Piperazine is an organic compound it consist of six membered ring containing two opposite nitrogen atoms. Firstly it used as a solvent in uric acid, the use of anthelmintic property was introduced in the year 1953.piperazine is a GABA receptor agonist. Piperazine binds directly and selectively to muscle membrane GABA receptor, presumably causing hyperpolarization of nerve endings, while the worm is paralysed, it is dislodged live form the body by normal intestinal peristalsis.

The 1, 3, 4-thiadiazole nucleus is one of the most important and well known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as antitubercular, antimalarial, antiviral, antineoplastic, anti-inflammatory, antiepileptic, antineoplastic, analgesic agents.

Molecular Docking: Docking is an attempt to find the best matching between two molecules. Docking is a method which predicts the preferred orientation of one ligand when bound in an active site to form a stable complex. Lock and key finding the correct relative orientation of the “key” which will open up the “lock”. On the surface of the lock is the key hole in the direction to turn the key after it is inserted. The protein can be thought of the “lock” and the ligand can be thought of as a “key”. To achieve an optimized conformation for both receptor and ligand and the relative orientation between protein and ligand such that the free energy of the overall system is minimized. Successful docking methods search high dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings.

***Corresponding Author:** Chukka Ajay Kumar

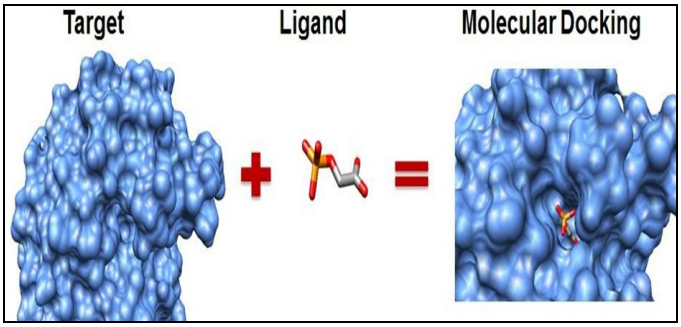


Fig 1: Molecular docking between target and ligand

Stages of Docking

i). **Pose Generation:** Place the ligand in the binding site generally well solved. Rigid docking with a series of conformers most techniques use this approach and then techniques will generate the conformers internally rather than using conformers as inputs. Incremental construction (Flexx): Split ligand into base fragment and side-chains place base add side chains to grow, scoring as you grow. In general, uses a very basic vdw shape function often see variability with input conformers.

ii). **Pose Selection/Scoring:** Where most of the current research focused more sophisticated scoring functions take longer. Balance need for speed vs. need for accuracy. Virtual screening needs to be very fast. Studies on single compounds can be much slower. It can do multi stage studies.

Molecular Docking Procedure

To understand the binding interactions and selectivity of our compounds against to enoyl-ACP reductase, molecular docking simulation was carried out with MCULE DOCKING. The crystal structure of enoyl reductase (code ID: 4TRJ; resolution 1.75 Å) used in the docking study were obtained from the Protein Data Bank (http://www.rcsb.org/pdb). The original inhibitor, hetero atoms and water molecules in the PDB files were eliminated in the beginning of docking study. The enzyme was set up for docking with standard protocol. Add polar hydrogen atoms to amino acids residues and for assigning Gasteiger charges to all atoms of the enzyme.

Admet Prediction

ADMET properties of a compound deal with its absorption, distribution, metabolism, excretion, and toxicity in and through the human body. ADMET, which constitutes the pharmacokinetic profile of a drug metabolism, is very essential in evaluating its pharmacodynamic activities. Today a lot of online tools and offline software programs are available which helps us in predicting this behaviour of candidate. I have used the SWISS adme, ADMET prediction tools (http://Immd.ecust.edu.cn:8000/).

Protein Data

To understand the binding interactions and selectivity of our compounds against to enoyl reductase receptor. The crystal structure of Dopamine 3 (code ID: 4TRJ; resolution 1.75-Å) used in the docking study were obtained from the Protein Data Bank (http://www.rcsb.org/pdb).

Enoyl-ACP reductase (ENRs) are enzymes that catalyse the last step of the alongation cycle during fatty acid synthesis.

Fatty acid biosynthesis is essential for survival in mammals, plants, fungi and bacteria.

InhA, the enoyl acyl carrier protein reductase of the key enzymes involved in the type-2 fatty acid biosynthesis pathway of mycobacterium tuberculosis.

General Function

Enoyl-ACP reductase of the type-2 fatty acid synthase (FAS-2) system, which is involved in the biosynthesis of mycolic acid, a major component of mycobacterial cell walls. Catalyzes the NADH dependent reduction of the double bonds of 2-trans-enoyl/(aceyl/carrier protein), an essential step in the fatty acid elongation cycle of the FAS to pathway. Shows preference for long chain fatty acid acyl thioester substrates (>c16), and can also use 2-trans-enoyl-COAS as alternative substrates.

The mycobacterial FAS-2 system utilizes the products of the FAS-1 system as primers to extend fatty acyl chain lengths upto C56, forming the meromycolate chain that serves as the precursor for final mycolic acids.

Table 1: Synthesized Derivative Compounds

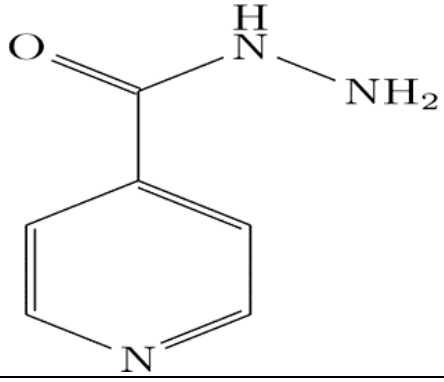
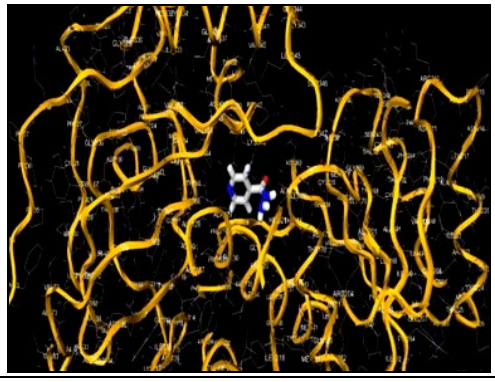
Code	Compound	Binding Interactions
Isoniazid		

Fig 2: Binding interaction of ISONIAZID with 4TRJ

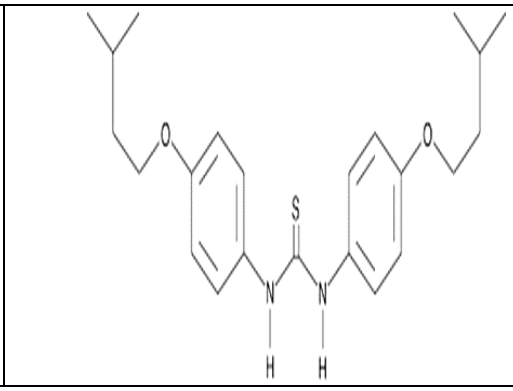
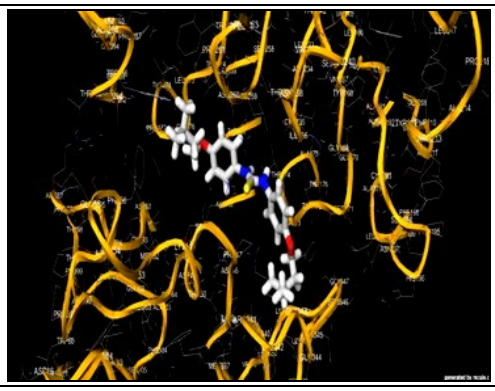
		

Fig 3: Binding interaction of THIOCARLIDE with 4TRJ

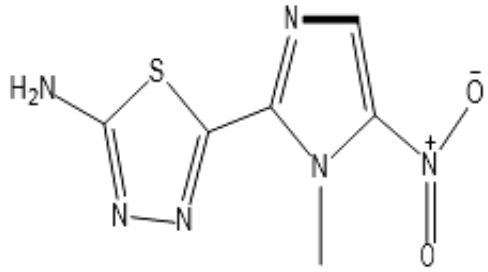
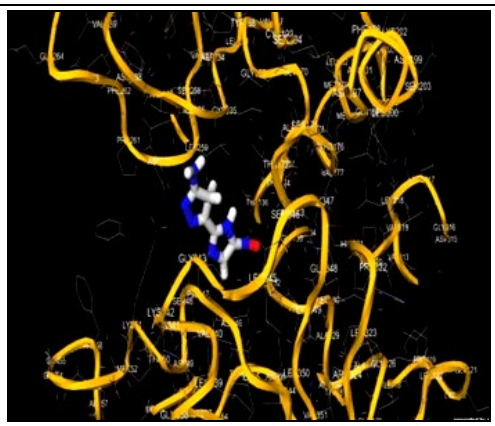
Megazole		

Fig 4: Binding interaction of MEGAZOL with 4TRJ

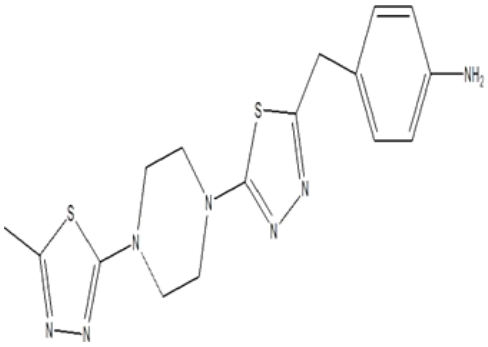
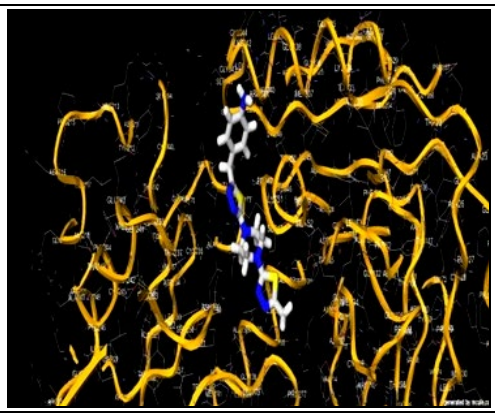
Compound 1		

Fig 5: Binding interaction of COMPOUND 1 with 4TRJ

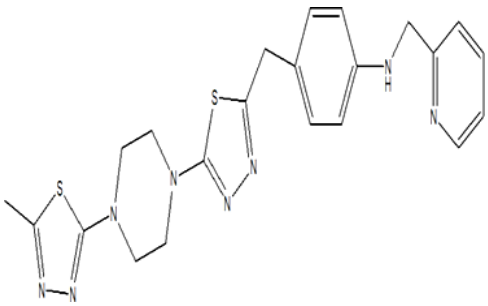
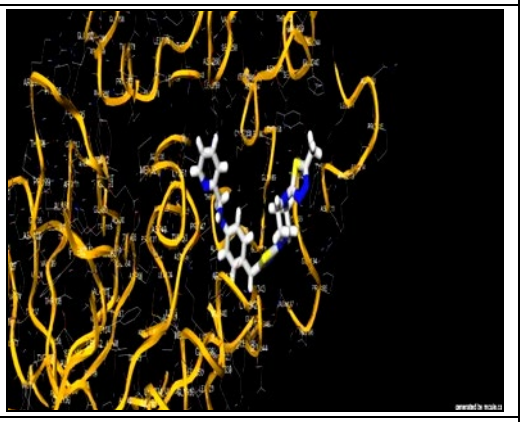
Compound 2		

Fig 6: Binding interaction of COMPOUND 2 with 4TRJ

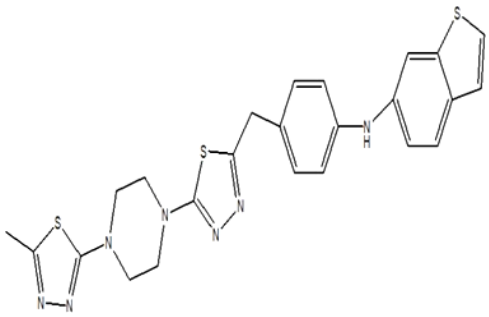
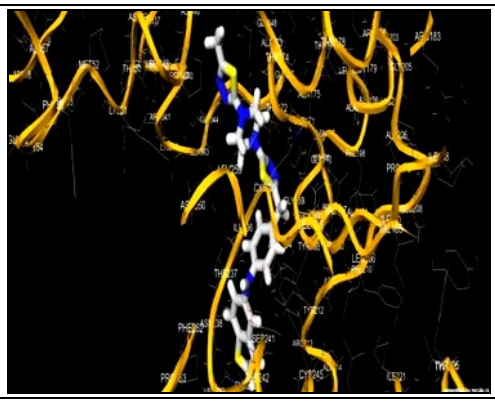
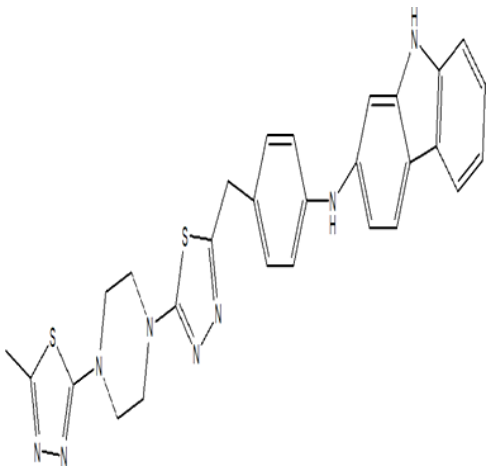
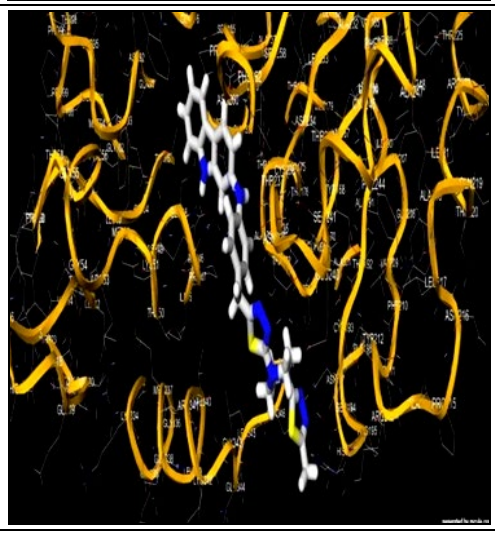
Compound 3		
Compound 4		

Fig 8: Binding interaction of COMPOUND 4 with 4TRJ

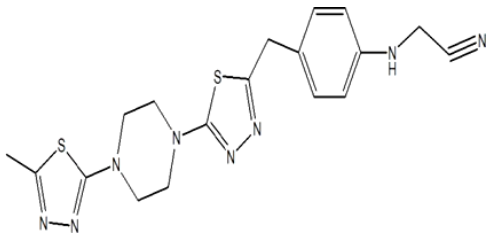
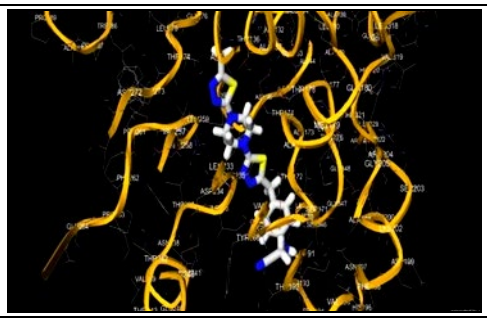
Compound 5		

Fig 9: Binding interaction of COMPOUND 5 with 4TRJ

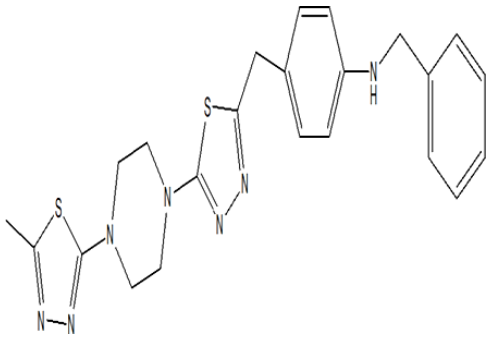
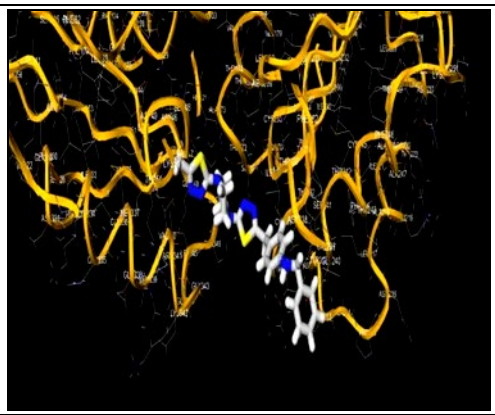
Compound 6		

Fig 10: Binding interaction of COMPOUND 6 with 4TRJ

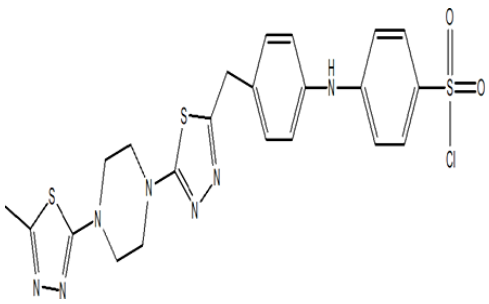
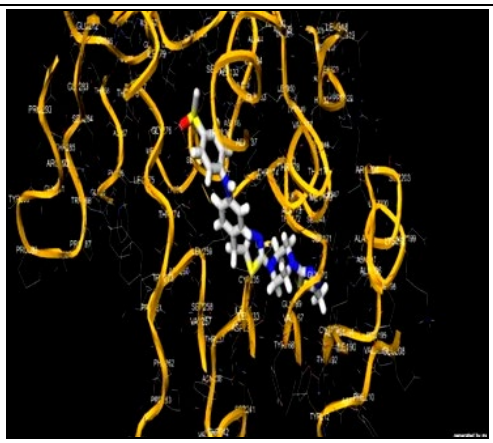
Compound 7		

Fig 11: Binding interaction of COMPOUND 7 with 4TRJ

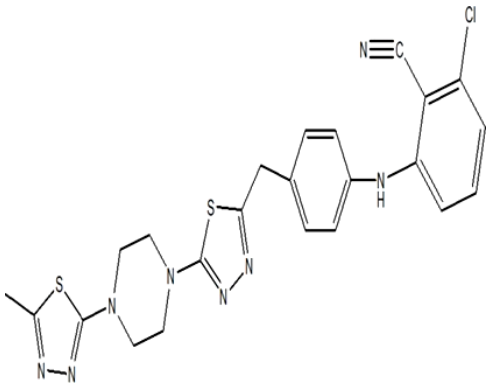
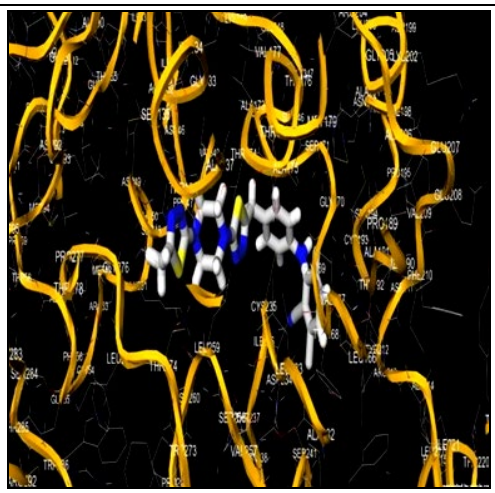
Compound 8		

Fig 12: Binding interaction of COMPOUND 8 with 4TRJ

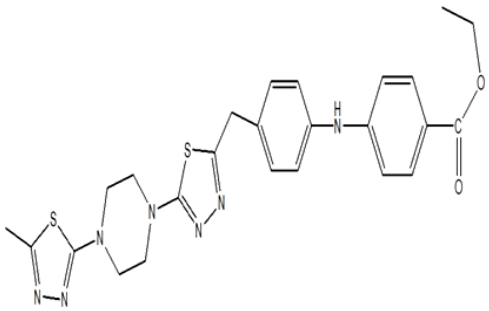
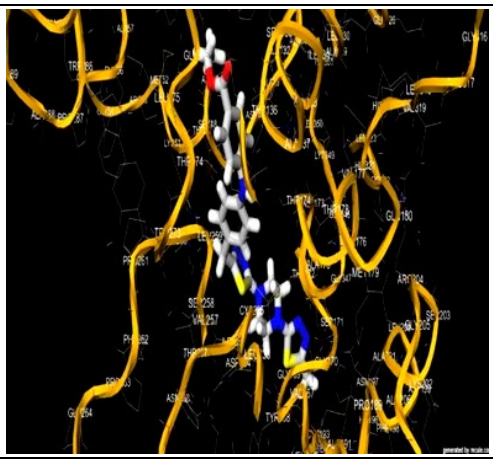
Compound 9		

Fig 13: Binding interaction of COMPOUND 9 with 4TRJ

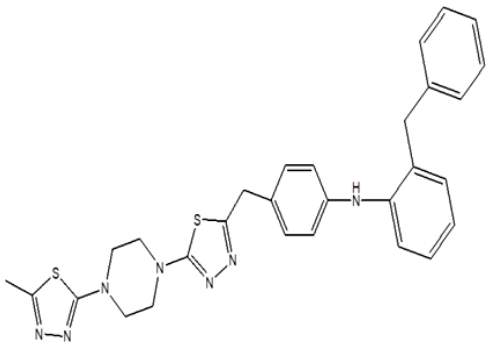
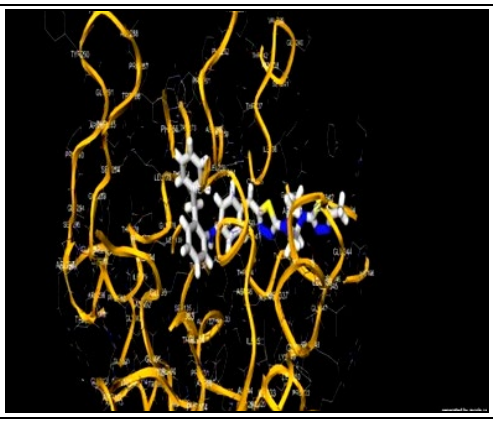
Compound 10		

Fig 14: Binding interaction of COMPOUND 10 with 4TRJ

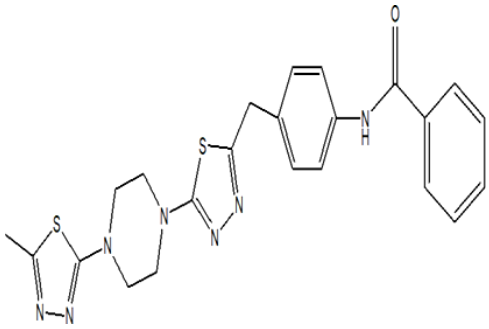
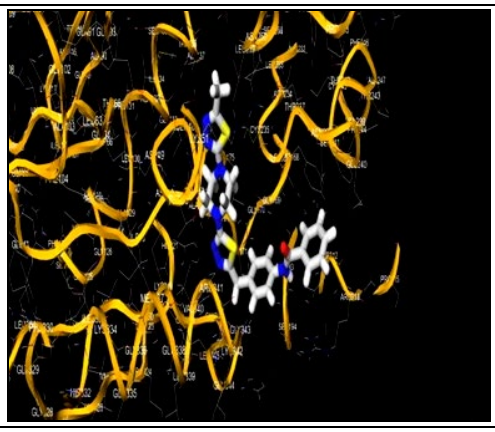
Compound 11		

Fig 15: Binding interaction of COMPOUND 11 with 4TRJ

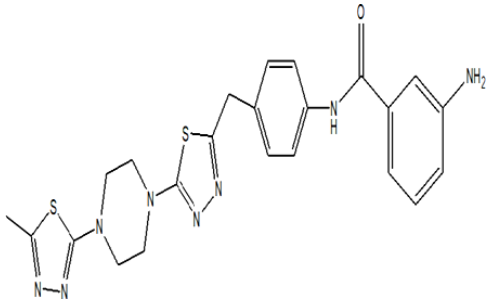
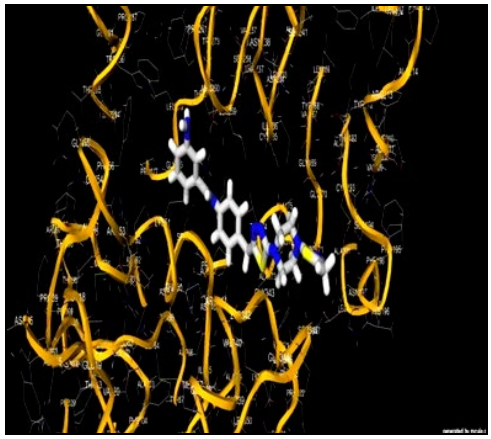
Compound 12		

Fig 16: Binding interaction of COMPOUND 12 with 4TRJ

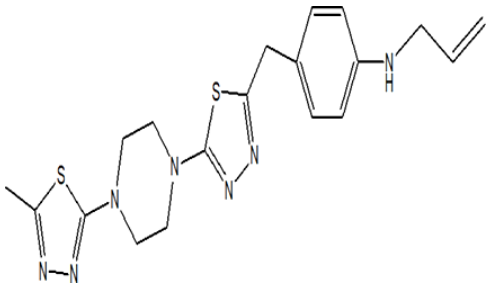
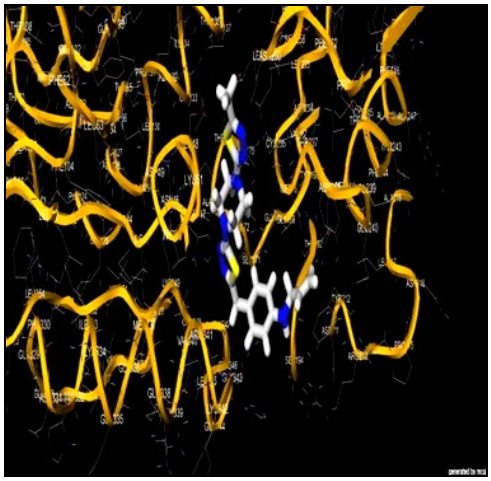
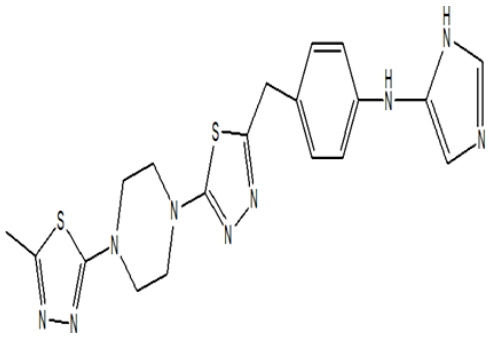
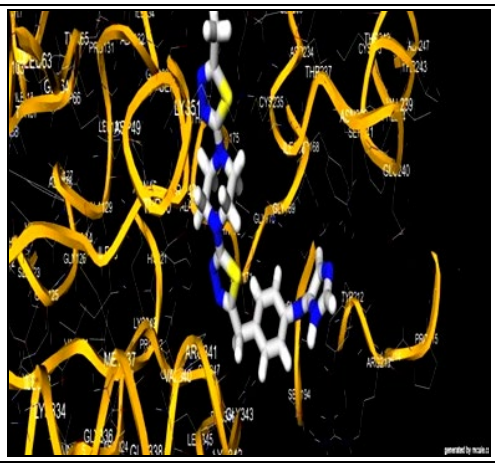
Compound 13		
Compound 14		

Fig 18: Binding interaction of COMPOUND 14 with 4TRJ

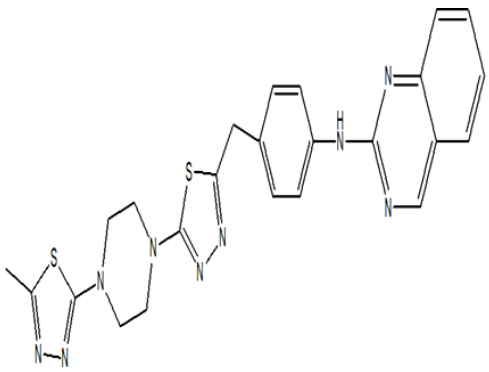
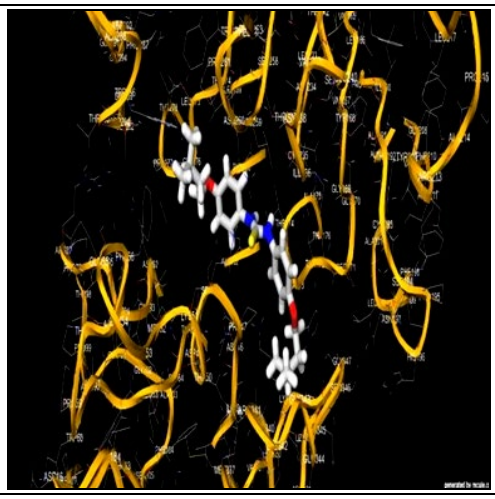
Compound 15		

Fig 19: Binding interaction of COMPOUND 15 with 4TRJ

Results

i). The results of designed molecules with 4TRJ were obtained a docking score and hydrogen bond interaction are mentioned in following table.

ii). The entire designed molecules have shown a good binding affinity with 4TRJ in comparision with standard Isoniazid, Thiocarlide, Megazol.

Table 2: Docking Results of the Designed Compounds with 4TRJ

S. No.	Comp. Code	Docking Score Kcal/Mole				
		1	2	3	4	Avg.
1	ISONIAZID	5	5	4.9	4.9	4.95
2	THIOCARLIDE	7.5	7.4	7.3	7.0	7.3
3	MEGAZOL	6.3	6.2	5.9	5.9	6.0
4	Compound 1	8.5	8.3	8.2	7.9	8.2
5	Compound 2	9.0	8.7	7.6	7.4	8.1
6	Compound 3	9.8	9.2	8.8	8.6	9.1
7	Compound 4	10.1	9.8	9.6	9.3	9.7
8	Compound 5	8.1	7.3	7.2	7.2	7.4
9	Compound 6	9.4	9.2	8.1	7.7	8.6
10	Compound 7	9.6	9.2	8.3	8.2	8.8
11	Compound 8	9.3	8.8	8.3	8.0	8.6
12	Compound 9	8.9	8.8	8.2	7.8	8.4
13	Compound 10	9.9	9.6	9.0	8.6	9.2
14	Compound 11	9.5	8.8	7.7	7.3	8.3
15	Compound 12	8.9	8.9	8.9	8.3	8.7
16	Compound 13	8.7	8.3	8.3	8.1	8.3
17	Compound 14	9.2	8.3	8.2	8.2	8.4
18	Compound 15	10.0	9.9	8.8	8.6	9.3

Table 3: In-Silico Absorption studies of Designed Derivative Compounds

Comp. Code	Absorption		
	Blood Brain Barrier (BBB)	Human Intestinal Absorption (HIA)	CaCO-2 Permeability
ISONIAZID	0.9168	0.9744	0.6822
THIOCARLIDE	0.8378	0.9518	0.5150
MEGAZOL	0.7500	0.9733	0.5628
1	0.9536	0.9945	0.5275
2	0.9579	0.9907	0.5180
3	0.9579	0.9973	0.5117
4	0.9261	0.9954	0.5274
5	0.9399	0.9953	0.5000
6	0.9556	0.9959	0.5172

7	0.9144	0.9866	0.6257
8	0.9028	0.9936	0.5300
9	0.9215	0.9968	0.5470
10	0.9502	0.9958	0.5724
11	0.9627	0.9950	0.5498
12	0.9382	0.9927	0.5182
13	0.9615	0.9951	0.5000
14	0.9241	0.9918	0.5181
15	0.9402	1.0000	0.5098

Table 4: In-Silico Distribution studies of Designed Derivative Compounds

Distribution	
Comp. Code	**Subcellular Localization (Mitochondria)**
ISONIAZID	0.9260
THIOCARLIDE	0.7487
MEGAZOL	0.5680
1	0.5121
2	0.5485
3	0.5242
4	0.5365
5	0.4842
6	0.5377
7	0.3383
8	0.5454
9	0.6802
10	0.6755
11	0.4143
12	0.6540
13	0.4355
14	0.5787
15	0.5694

Table 5: In-silico Metabolism Studies Designed Derivative Compounds

Comp. Code	**CYP450 Substrate**			**CYP450 Inhibitor**				
	2C9	**2D6**	**3A4**	**1A2**	**2C9**	**2D6**	**2C19**	**3A4**
ISONIAZID	0.9260	0.8551	0.7732	0.6354	0.6821	0.7902	0.7632	0.7209
THICARLIDE	0.6609	0.6772	0.5108	0.8078	0.6683	0.8233	0.8453	0.5183
MEGAZOL	0.7806	0.9056	0.5453	0.5502	0.6377	0.8706	0.6922	0.9340
1	0.8290	0.7652	0.6378	0.5703	0.5149	0.5561	0.8313	0.8323
2	0.7747	0.7420	0.6164	0.6495	0.6471	0.5193	0.7837	0.6559
3	0.7965	0.7125	0.5634	0.7309	0.5240	0.5114	0.8774	0.7178
4	0.8143	0.7264	0.5834	0.6739	0.5000	0.5094	0.8635	0.6578
5	0.7708	0.7503	0.6214	0.6927	0.5147	0.6324	0.8387	0.6552
6	0.7678	0.7369	0.6363	0.7238	0.5435	0.5156	0.8661	0.7199
7	0.6977	0.7755	0.5195	0.5645	0.5643	0.8162	0.7797	0.5110
8	0.7782	0.7937	0.5398	0.8293	0.8681	0.5375	0.9226	0.6201
9	0.8429	0.7930	0.5779	0.5432	0.8624	0.8423	0.8785	0.8631
10	0.7881	0.7362	0.5565	0.6000	0.7337	0.6829	0.9038	0.6538
11	0.7643	0.7188	0.5379	0.8647	0.5716	0.8203	0.7006	0.8458
12	0.8314	0.7433	0.5213	0.8701	0.5839	0.8312	0.6696	0.8570
13	0.7742	0.7469	0.6256	0.6699	0.5325	0.5956	0.8663	0.7079
3	0.7965	0.7125	0.5634	0.7309	0.5240	0.5114	0.8774	0.7178
4	0.8143	0.7264	0.5834	0.6739	0.5000	0.5094	0.8635	0.6578

Table 6: *In-Silico* Excretion and Toxicity Studies Designed Derivative Compounds

Comp. Code	Human Ether-a-go-go-Related Gene (hERG) Inhibitor	AMES Toxic_ _ity (nontoxic)	Carci_ _nogen s (non-carcin) ogenic)	Tetrahy_mena Pyriformis Toxicity (Pigc50,u g/L)	Honey Bee Toxicity (HBT)	Biod_egrad ation	Acute oral toxicity	Rat acute toxicit y (LD50, mol/kg)	Fish Toxicity (pLC50 ,mg/L)
STD 1	0.9114	0.6676	0.6735	-0.1297	0.6382	1.0000	0.5967	2.5133	1.3968
STD2	0.7004	0.7446	0.7964	1.2527	0.6267	0.9959	0.7056	2.5039	0.8739
STD 3	0.7793	0.9800	0.8400	-	0.9169	0.8250	0.4877	-	0.4002
1	0.6236	0.5992	0.8631	0.6878	0.8303	1.0000	0.4848	2.6289	0.4955
2	0.7662	0.5562	0.8405	0.6933	0.8096	0.9896	0.5403	2.6338	1.5437
3	0.7704	0.6613	0.8829	0.7365	0.7847	1.0000	0.4713	2.7041	1.3818
4	0.7344	0.5717	0.8675	0.7004	0.7908	1.0000	0.4594	2.6963	1.4746
5	0.7924	0.5667	0.8471	0.6920	0.8112	1.0000	0.5049	2.6489	1.4868
6	0.7664	0.5492	0.8429	0.7240	0.8202	0.9945	0.5036	2.6430	1.4460
7	0.5481	0.5808	0.6708	0.6345	0.8264	0.8143	0.5900	2.5386	1.4313
8	0.8220	0.5081	0.8412	0.8710	0.8843	1.0000	0.4937	2.5925	1.2576
9	0.5727	0.5552	0.8195	0.6749	0.7961	0.9677	0.4704	2.6856	1.3615
10	0.7022	0.5000	0.8907	0.7154	0.8506	0.9940	0.4771	2.6530	1.4789
11	0.5845	0.5583	0.8413	0.6184	0.8640	0.9776	0.5800	2.6562	1.6013
12	0.7484	0.5842	0.8247	0.4812	0.8679	0.9897	0.5886	2.6126	1.7316
13	0.8102	0.5056	0.8309	0.7149	0.7871	1.0000	0.5401	2.5813	1.2473
14	0.5949	0.5501	0.8742	0.6979	0.8286	1.0000	0.5317	2.5894	1.5360
15	0.7791	0.6449	0.8892	0.7116	0.7743	1.0000	0.4767	2.6864	1.4021

Conclusion

All the synthesized compound derivatives of novel piperazine compounds were evaluated with computational analysis by appropriate 4TRJ were compared with piperazine analogue standard drug respectively.

The results of docking study revealed that the binding profile for synthesized derivative compound-4, compound-5, compound-10 and compound-3 was found significant interactions with 4TRJ due to hydrogen bond, hydrophobic interaction like π-π stacking interaction and π-alkyl stacking interactions with 4TRJ.

The predicted ADMET properties revealed that all compounds fulfill drug-like criteria and could be considered as good candidate for drug (piperazine) like ADMET properties.

The further scope of synthesized derivatives of novel piperazine derivatives need to evaluation of various in-vivo pharmacological studies to bring potentially active molecules

References

1. Mohammed Al-Ghorbani, Bushra Begum A, Zabiulla, Mamatha S. V. and Shaukath Ara Khanum, *"Piperazine and Morpholine: Synthetic Preview and Pharmaceutical Applications", J Chem. Pharma. Res*. 2015; 7(5):281-301.
2. Kuldeep Singh, H.H Siddiqui, Pragati Shakya, Paramdeep bagga, Arun Kumar, M.Khalid, M.Arif and Shashi Alok. ''Piperazine-a biologically active scaffold "*IJPSR*. 2015; 6(10):1547-1548.
3. Jose´ M. Quintela, Carlos Peinador, Liliana Gonza´lez, Rau´l Iglesias, Anabel Parama, Francisca A´ lvarez, Manuel L. Sanmart´ın, Ricardo Riguera. Piperazine N-Substituted Naphthyridines, pyridothienopyrimidines and pyriodothienotriazines: new antiprotozoals active against philasterides dicentrarchi" *European Journal of Medicinal Chemistry*. 2003; 38:265 275.
4. Durand C, Szostak M. Recent Advances in the Synthesis of Piperazines: Focus on C-H Functionalization" Functionalization. *Organics* 2021; 2:337-347.
5. Betül Kaya, Yusuf Özkay, Halide Edip Temel, and Zafer AsJm KaplancJklJ. ¨Synthesis and Biological Evaluation of Novel Piperazine Containing Hydrazone Derivatives" Hindawi Publishing Corporation Journal of Chemistry volume 2016; A:1341-1349.
6. Tomar Amita, Mall Mridula, Verma Manju "The Molecule of Diverse pharmacological importance "*IJPRA*. 2011; 2:1547-1548.
7. Sait SARI, Mehmet Yilmaz. "Synthesis and characterization of piperazine-substituted dihydrofuran derivatives viaMn(OAc)3 mediated radical cyclizations" Truk j chem journal of chemistry, 1303-1313.
8. G.I. Regnierr and J. Canevari, *"Synthesis and Vasodilator Activity of New Piperazine Derivatives',* Chem. Res. Div. 1968; 11:1151-1155.
9. Chaudhary P, Kumar R, Verma AK, Singh D, Yadav V, Chhillar AK, Chandra R. *"Synthesis and Antimicrobial Activity of N-Alkyl and N-Aryl Piperazine Derivatives",* Bioorg. Med. Chem. 2006; 14(6):1819-1826.
10. Amani M, *"Synthesis and Biological Activity of Piperazine Derivatives of Phenothiazine",* Drug Res. 2015; 65:5-8.