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MOLECULAR DOCKING AND ADMET STUDIED OF NOVEL PYRIDOPYRIMIDINE DERIVATIVES

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Abstract: In this study novel Pyridopyrimidine derivatives were designed. Designed derivative compounds against 3PBL molecular docking stimulation was carried out with MCULE and insilico ADMET prediction procedures. The results of docking study revealed that the binding profile for designed compounds PPD-III-FPB.HCl and PPD-IV-FPB.HCl was found significant interactions with 3PBL when compared with Paliperidone. The further scope of synthesized derivatives of novel Pyridopyrimidine derivatives need to evaluation of various *in vivo* pharmacological Studies to bring potentially active molecules.

Keywords: Pyridopyrimidine, ADMET prediction, PPD-III-FPB.HCl, PPD-IV-FPB.HCl, MCULE, 3PBL, Paliperidone.

INTRODUCTION

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.

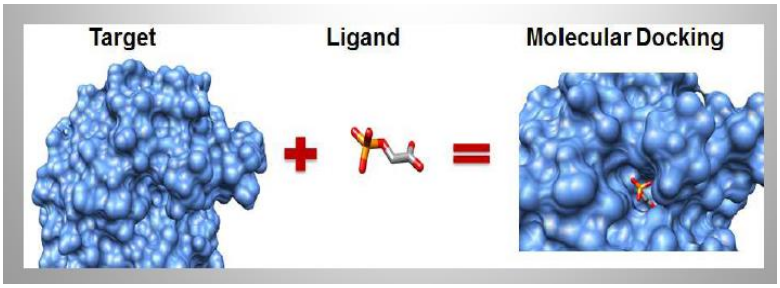


Figure 1

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 Dopamine 3, molecular docking simulation was carried out with **MCULE DOCKING**.

The crystal structure of Dopamine 3 (code ID: 3PBL; resolution 2.89-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.

3D structures of the Dopamine 3, synthesized compounds(8 compounds), standard drug (Paliperidone) were generated and energy optimized by Discovery Studio 2.5 package (Accelrys Inc., San Diego, CA) employing CHARMm force field. Full hydrogens were added to the ligands and Gasteiger-Marsili partial atomic charges were caculated using the BABEL-2.2.338 program and saved in the PDBQT format for further analysis. All possible rotatable bonds of the resultant ligand molecules were defined by using standerd protocol.

The docking simulation was performed using the Lamarckian Genetic Algorithm.

Finally, the top-posed docking conformations were submitted to post docking energy minimization on Discovery Studio 2.5. The resultant structure files were evaluated using PyMOL visualization program.

PROTIEN DATA

To understand the binding interactions and selectivity of our compounds against to Dopamine 3 receptor.

The crystal structure of Dopamine 3 (code ID: 3PBL; resolution 2.89-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.

TABLE 1: Synthesized Derivative Compounds

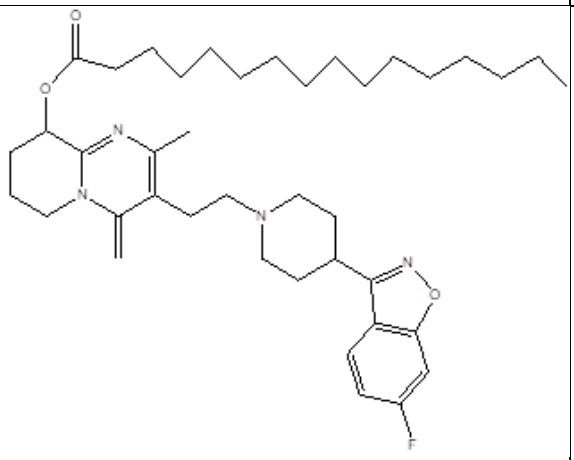
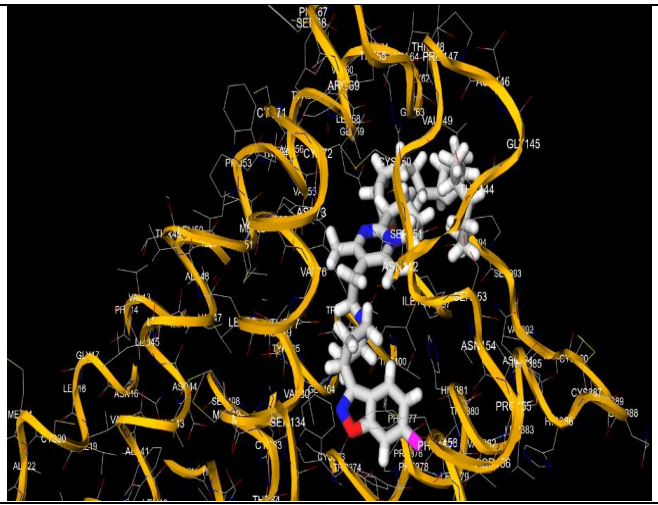
CODE	COMPOUND	BINDING INTERACTION
PALIPERIDONE		

Figure:2-Binding interaction of PALIPERIDONE with 3pbl

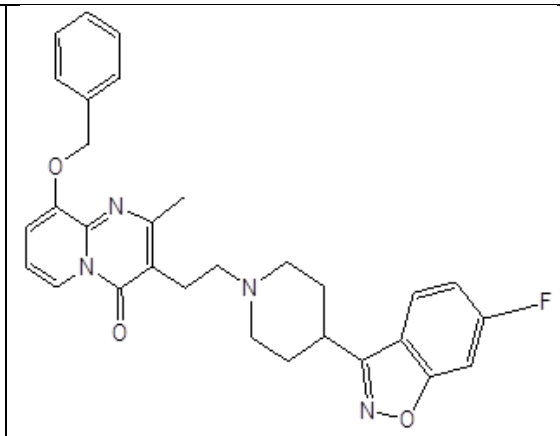
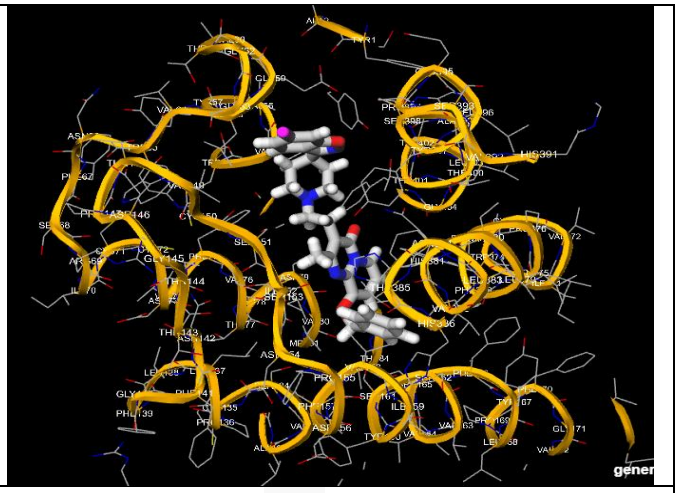
PD-III-FPB.HCL		

Figure:3-Binding interaction of PPD-III-FPB.HCL with 3pbl

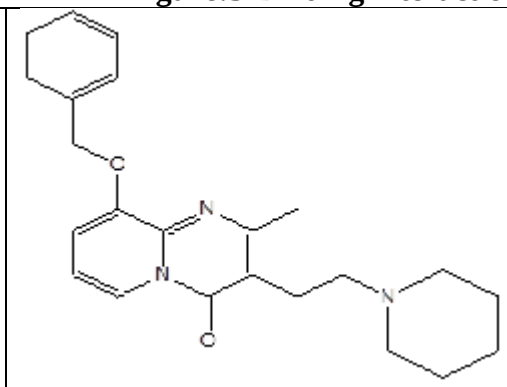
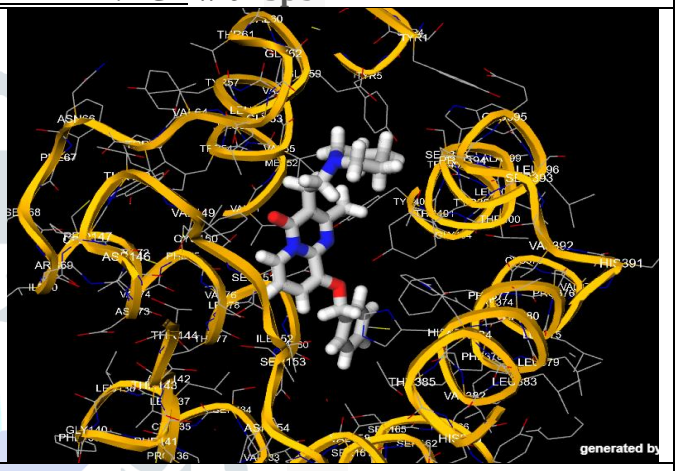
PPD-III-PIPERIDINE		

Figure:4-Binding interaction of PPD-III-PIPERIDINE with 3pbl

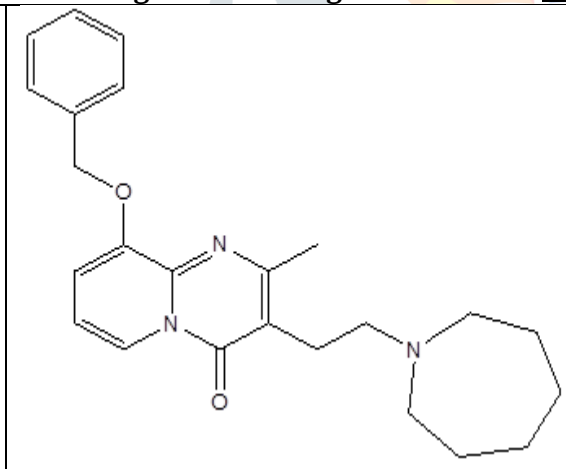
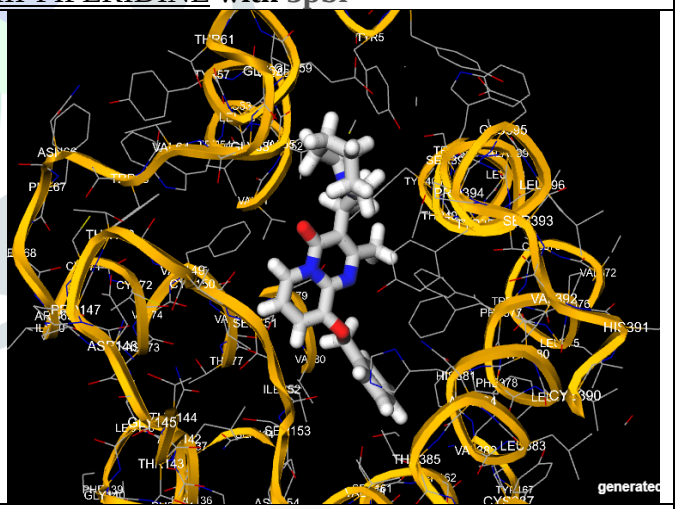
PPD-III-AZEPINE		

Figure: 5-Binding interaction of PPD-III-AZEPINE with 3pbl

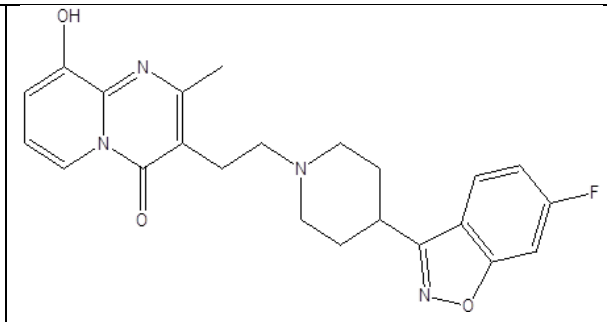
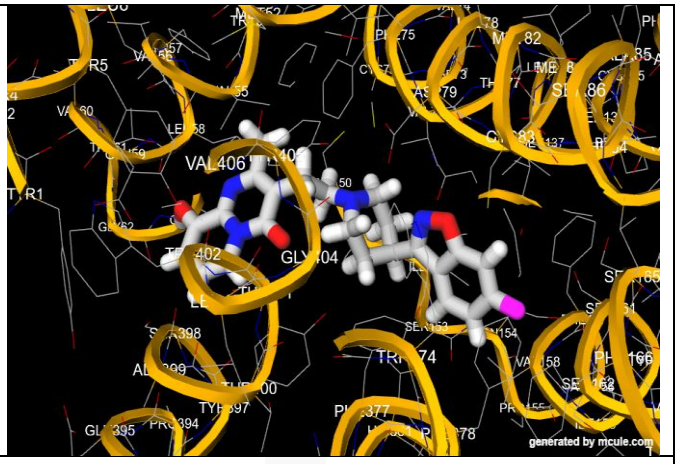
PPD-IV-FPB.HCL		

Figure:6-Binding interaction of PPD-IV-FPB.HCL with 3pbl

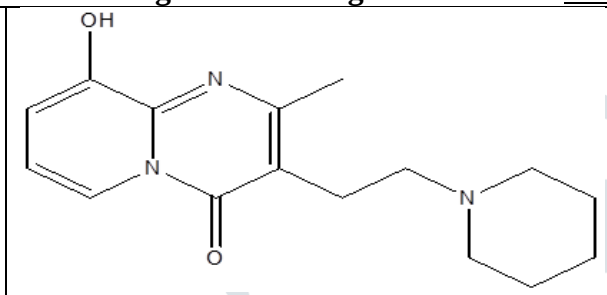
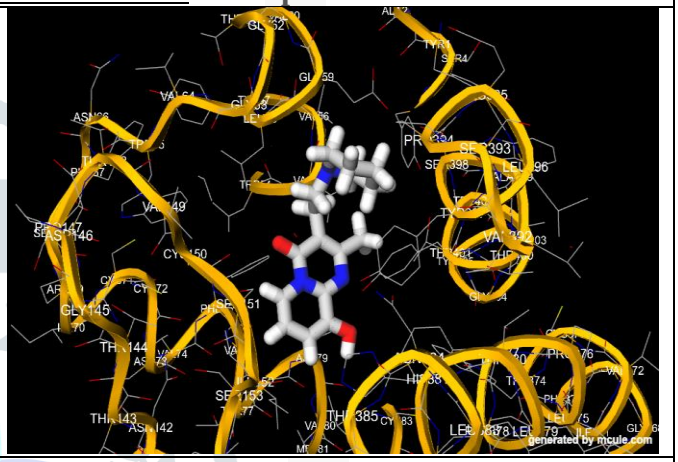
PPD-IV-PIPERIDINE		

Figure:7-Binding interaction of PPD-IV-PIPERIDINE with 3pbl

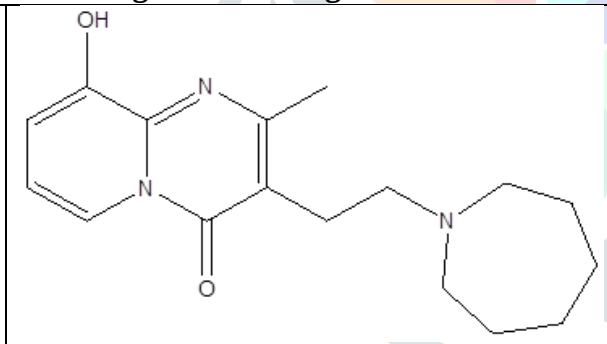
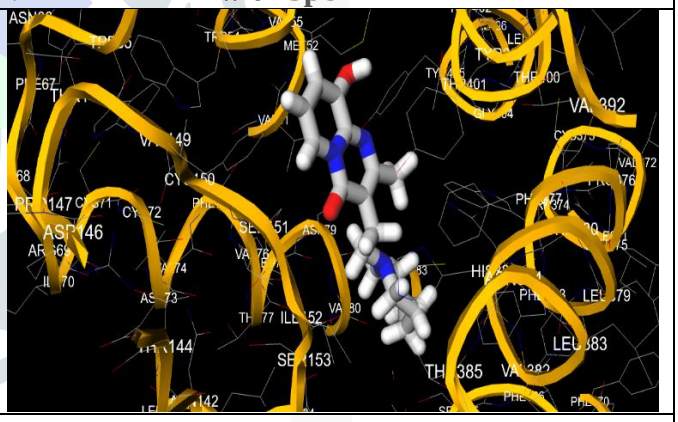
PPD-IV-AZEPINE		

Figure: 8-Binding interaction of PPD-IV-PIPERIDINE with 3pbl

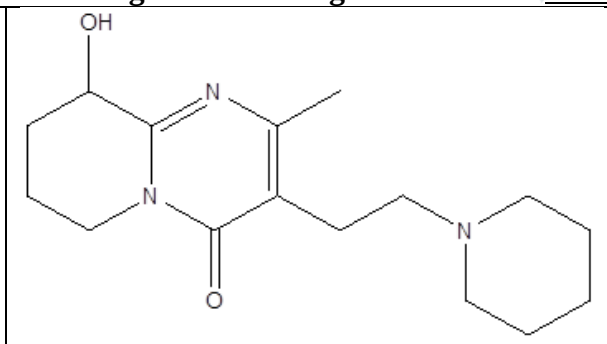
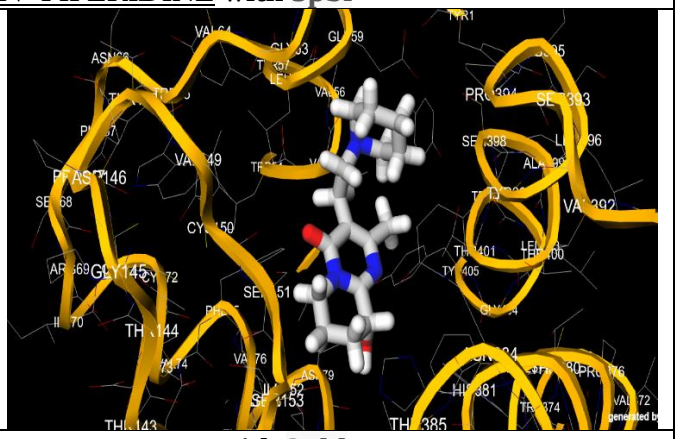
PPD-V-PIPERIDINE		

Figure:9-Binding interaction of PPD-V-PIPERIDINE with 3pbl

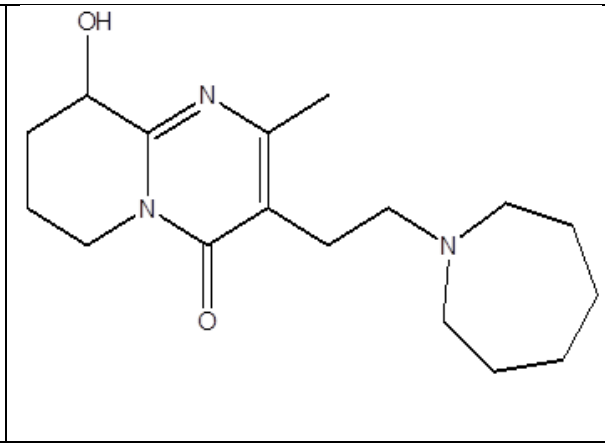
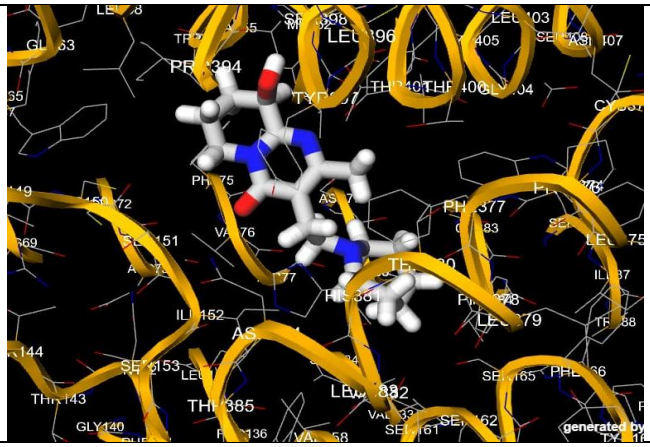
PPD-V-AZEPINE		

Figure:10-Binding interaction of PPD-V-AZEPINE with 3pbl

RESULTS

The results of designed molecules with **3pbl** were obtained as docking score and Hydrogen bond interactions are mentioned in following table.

The entire designed molecules have shown a good binding affinity with **3pbl** in comparison with standard Paliperidone.

TABLE 2: Docking Results of the Designed Compounds with 3pbl

S. No.	Comp. Code	Docking Score Kcal/Mole			
		1	2	3	Avg
1	Paliperidone	7.0	7.0	6.5	6.8
2	PPD-III-FPB.HCL	10.9	10.7	10.4	10.6
3	PPD-III-PIPERIDINE	9.5	9.3	9.1	9.3
4	PPD-III-AZEPINE	10.0	9.7	9.4	9.7
5	PPD-IV-FPB.HCL	10.4	10.3	10.2	10.3
6	PPD-IV-PIPERIDINE	7.6	7.4	6.9	7.3
7	PPD-IV-AZEPINE	8.2	8.0	7.6	7.9
8	PPD-V-PIPERIDINE	7.6	7.6	7.4	7.5
9	PPD-V-AZEPINE	8.5	8.0	7.9	8.1

TABLE 3: *In-Silico* Absorption Studies of Designed Derivative Compounds

Comp. Code	ABSORPTION		
	Human Intestinal (HIA) (1.0000)	Aqueous Solubility (logS) (1-7.5)	CaCO-2 Permeability (LogP, cm/s) (1.0000)
PALIPERIDONE	1.0000	-2.3000	0.5496
PPD-III-FPB.HCL	1.0000	-3.5088	0.5333
PPD-III-PIPERIDINE	1.0000	-2.9968	0.5393
PPD-III-AZEPINE	0.9973	-3.1752	0.5147
PPD-IV-FPB.HCL	1.0000	-3.1598	0.5496
PPD-IV-PIPERIDINE	0.9950	-2.8309	0.5000
PPD-IV-AZEPINE	1.0000	-3.5959	0.5805
PPD-V-PIPERIDINE	0.9961	-2.8165	0.5000
PPD-V-AZEPINE	0.9944	-2.9646	0.5167

TABLE 4: In silico Distribution studies of Designed Derivative Compounds

DISTRIBUTION					
Comp. Code	Plasma Protein Binding (PPB)	P-glycoprotein Substrate		P-glycoprotein Inhibitor	Blood Brain Barrier Penetration (BBB) (1.0000)
		Substrate	Inhibitor		
PALIPERIDONE	-	0.7449	0.7011	0.8229	0.7928
PPD-III-FPB.HCL	_	0.8063	0.9724	0.9931	0.9537
PPD-III-PIPERIDINE	_	0.6978	0.8598	0.9416	0.9842
PPD-III-AZEPINE	_	0.7186	0.8855	0.9350	0.9850
PPD-IV-FPB.HCL	_	0.7449	0.7011	0.8229	0.7928
PPD-IV-PIPERIDINE	_	0.7180	0.6215	0.8085	0.9071
PPD-IV-AZEPINE	_	0.6031	0.6614	0.8733	0.9731
PPD-V-PIPERIDINE	_	0.7701	0.7518	0.7467	0.6399
PPD-V-AZEPINE	_	0.7872	0.7931	0.6974	0.6851

TABLE 5: In-silico Metabolism Studies Designed Derivative Compounds

Comp. Code	CYP450 Substrate			CYP450 Inhibitor				
	2C9	2D6	3A4*	1A2	2C9	2D6	2C19*	3A4
PALIPERIDONE	0.7721	0.5131	0.7154	0.7379	0.7395	0.5326	0.7851	0.6468
PPD-III-FPB.HCL	0.8542	0.6496	0.6627	0.5883	0.6550	0.7736	0.5680	0.5055
PPD-III-PIPERIDINE	0.7090	0.5231	0.6762	0.6743	0.8556	0.8600	0.5816	0.5639
PPD-III-AZEPINE	0.6856	0.5287	0.7064	0.5976	0.8648	0.8306	0.5924	0.5522
PPD-IV-FPB.HCL	0.7721	0.5131	0.7154	0.7379	0.7395	0.5326	0.7815	0.6468
PPD-IV-PIPERIDINE	0.6275	0.5229	0.6558	0.7203	0.9312	0.7975	0.8015	0.6795
PPD-IV-AZEPINE	0.6272	0.7141	0.6464	0.8881	0.5261	0.8923	0.7468	0.8529
PPD-V-PIPERIDINE	0.6558	0.5506	0.6842	0.8075	0.9558	0.7850	0.7923	0.8625
PPD-V-AZEPINE	0.6319	0.5553	0.7095	0.8031	0.9496	0.7523	0.7820	0.8376

***In-Silico* Excretion and Toxicity Studies Designed Derivative Compounds**

Comp. Code	Human Ether-a-go-go-Related Gene (hERG) Inhibitor	AMES Toxicity (non toxic)	Carcinogens (non-carcinogenic)	Tetrahymena Pyriformis Toxicity (Pigc50,ug/L)	Honey Bee Toxicity (HBT)	Biodegradation	Acute oral toxicity	Rat acute toxicity (LD50, mol/kg)	Fish Toxicity (pLC50, mg/L)
PALIPERIDONE	0.7061	0.518	0.7995	-	-	0.9908	-	3.7859	-
PPD-III-FPB.HCL	0.8254	0.5933	0.8995	0.6626	0.6662	1.0000	0.5484	2.7192	0.8345
PPD-III-PIPERIDINE	0.7334	0.5718	0.9469	0.2584	0.8296	0.7893	0.6499	2.6874	1.4942
PPD-III-AZEPINE	0.8206	0.6111	0.9513	0.2784	0.8176	0.8560	0.6473	2.6670	1.4196
PPD-IV-FPB.HCL	0.8366	0.5180	0.7995	0.4925	0.8526	0.9908	0.7737	3.7859	1.2890
PPD-IV-PIPERIDINE	0.8200	0.6017	0.9505	0.2928	0.8496	0.9107	0.5198	2.8456	1.5375
PPD-IV-AZEPINE	0.9546	0.5272	0.9253	0.4753	0.8117	0.9650	0.6613	2.5743	1.2623
PPD-V-PIPERIDINE	0.7778	0.6779	0.9351	0.2261	0.8523	0.8470	0.5122	2.8165	1.6396
PPD-V-AZEPINE	0.8534	0.6955	0.9396	0.2481	0.8408	0.8974	0.5421	2.7724	1.5558

CONCLUSION:

All the synthesized compound derivatives of Novel Pyridopyrimidine derivative compounds were evaluated with computational analysis by appropriate 3PBL were compared with Paliperidone analog standard drugs respectively.

The results of docking study revealed that the binding profile for synthesized derivative compounds PPD-III-FPB.HCl and PPD-IV-FPB.HCl was found significant interactions with 3PBL due to hydrogen bond, hydrophobic interactions like π–π Stacking interaction and π-alkyl stacking interactions with 3PBL.

The predicted ADMET properties revealed that all compounds fulfil drug-like criteria and could be considered as good candidate for drug development. All the synthesized compound derivatives have Standard Drug (Paliperidone) like ADMET properties.

The further scope of synthesized derivatives of novel Pyridopyrimidine derivatives need to evaluation of various *in vivo* pharmacological Studies to bring potentially active molecules.

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