Target Diversity: Investigating Multi-receptor interactions of antipsychotic drugs through molecular docking

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Psychotic Disorders

- Mental disorders affect thinking, emotions, and behavior
- Mental disorders can be treated by the administration of antipsychotic drugs
- Chlorpromazine, discovered in 1951, was the first effective means for treating delusions and hallucinations (often referred to as positive symptoms) of schizophrenia and other psychotic disorders.
- Major issue: Extrapyramidal Side Effects (EPS)

Types of Antipsychotic Drugs

TYPICAL ANTIPSYCHOTIC DRUG

- Also known as first generation antipsychotic drug
- It was introduced between 1954 and 1975.
- High EPS

ATYPICAL ANTIPSYCHOTIC DRUG

- Second generation drugs
- Low EPS
- Better efficacy

ATYPICAL ANTIPSYCHOTIC DRUGS:

Act on

- Seratonin (5HT 2A)
- Dopamine (D2)

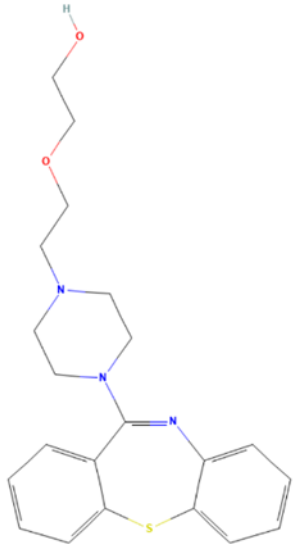
Used as:

- Monotherapy
- Combination therapy

Selected Drugs

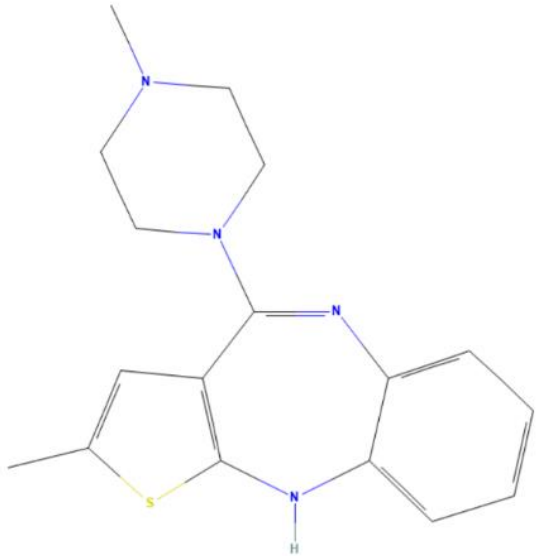
Quetiapine:

A dibenzothiazepine derivative called quetiapine (QTP) is approved for the treatment of bipolar depression



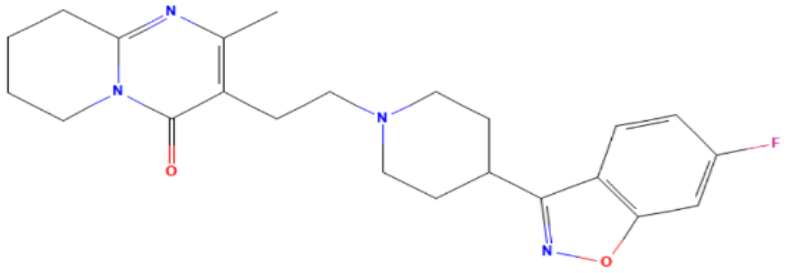
Olanzapine:

Olanzapine (OLZ), a thienobenzodiazepine derivative that exhibits structural similarities with clozapine, is useful in the treatment of acute manic episodes and schizophrenia as well as in preventing the recurrence of bipolar disorders.



Risperidone:

An authorized antipsychotic medication for the treatment of schizophrenia and the acute manic phase of bipolar disorder is risperidone (RSP). It works well for treating positive and negative symptoms of schizophrenia, has a rapid onset of action, and is beneficial in both short- and long-term therapy.



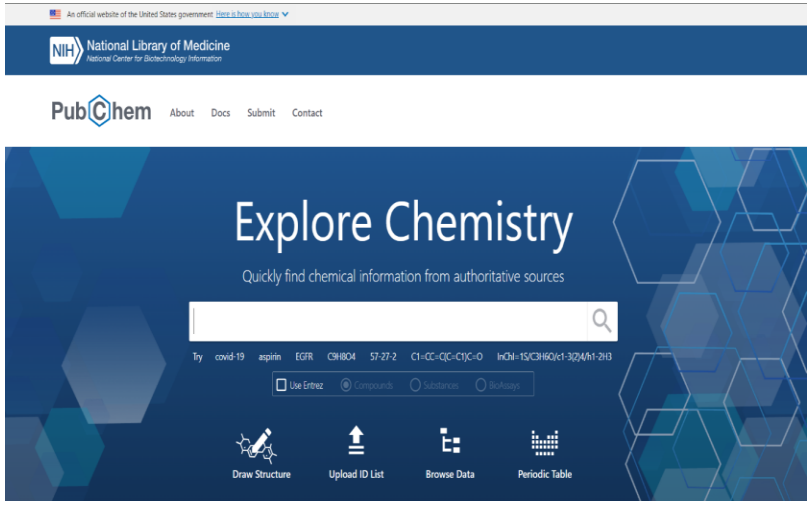
Methodology

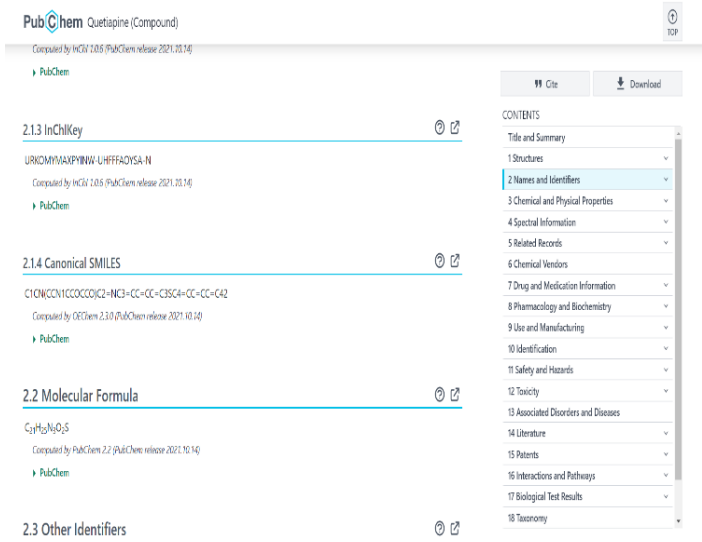
TOOLS:

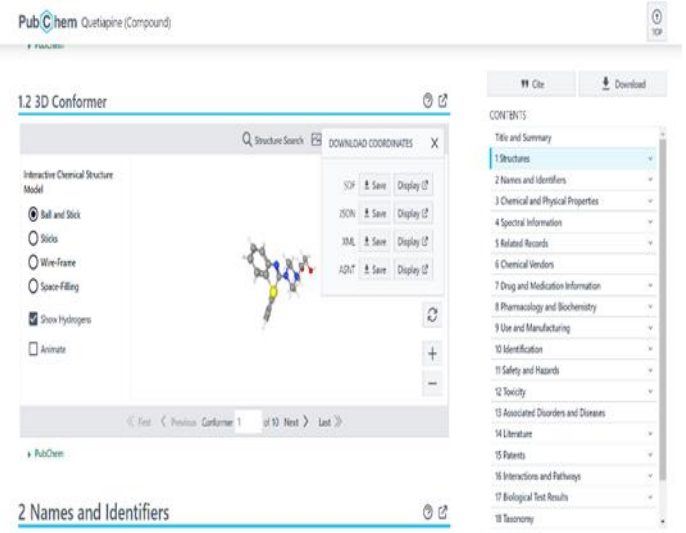
- PubChem
- Swiss ADME
- UniProt
- Maestro Schrödinger

Pubchem

The Canonical SMILE and 3D structure (in SDF format) of the drugs (Quetiapine, Olanzapine, Risperidone) is retrieved from PubChem.

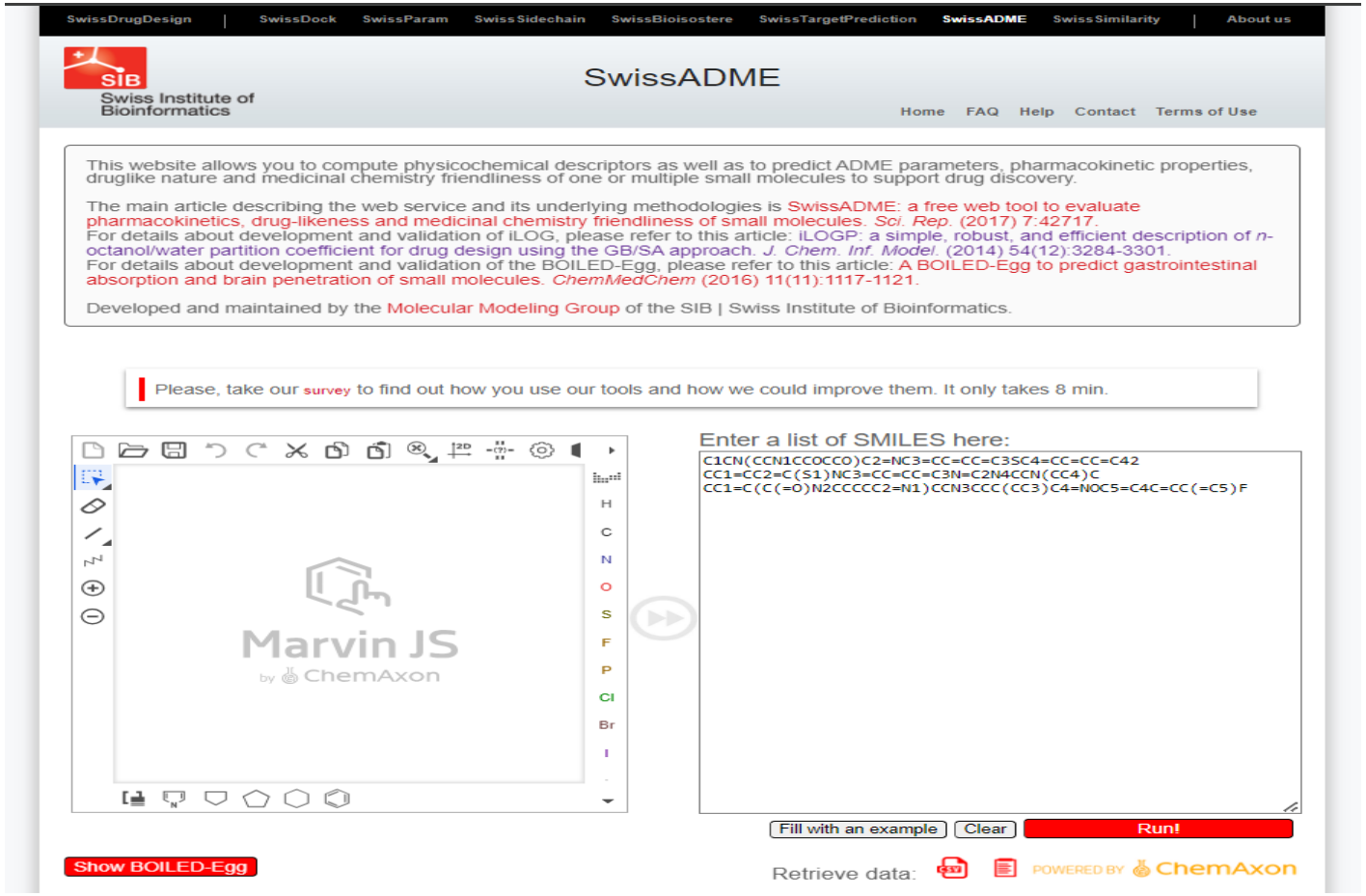






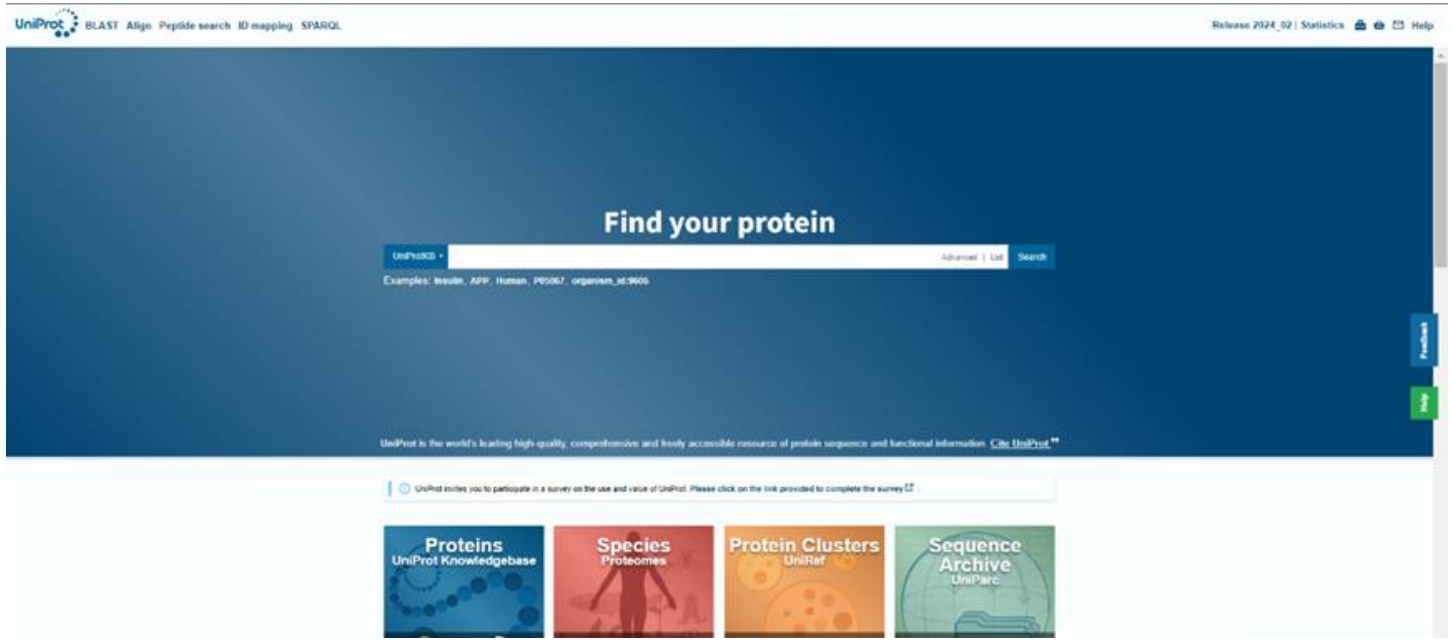
SwissADME:

- The Canonical SMILE of Quetiapine, Olanzapine, and Risperidone is imported in SwissADME to get the ADME properties of the respective drugs.



UniProt:

The Electron Microscopic structure of the receptor 5-HT1A (7E2X), 5-HT2B (7SRQ), 5HT6 (8JLZ), D1 (7JVQ), D2 (7JVR), D3 (8IRT), α2A (7EJ8), α2B (6K41), GABA subunit alpha-1 (7QNE) , H1 (7DFL), H2 (7UL3) and x-ray structure of 5-HT1B (4IAR), 5-HT2A (7WC8), GABA TYPE SUB-2 (6WIV) are retrieved from UniProt as 3D structures in pdf format.



Maestro Schrodinger

- Initially, ligand preparation was done using the Ligprep tool.
- LigPrep is designed to rapidly generate high-quality small-molecule ligand structures for structure-based virtual screening
- It functions by explaining stereoisomers, ring conformation, and tautomeric and ionization states.
- The protein (receptor) retrieved from PDB was imported and protein preparation was done by protein preparation wizard tool.
- A first-in-class, structure-based drug development effort faces several early challenges, one of which is locating druggable pockets.

- The binding sites and drugabilities of protein-protein interfaces and allosteric binding sites can be identified with the aid of the SiteMap technique.
- Grid generation must be performed before running a virtual screen with glide.
- To define the grid surrounding the ligand and retain all the functional residues within it, the receptor grid generation technique applied.
- Finally, the protein-ligand docking was done and the docking was done

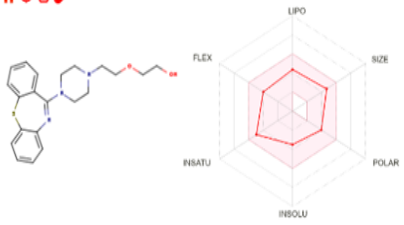
Results

- Drugs and their canonical SMILES

S.No	Name of the Drug	Drug Type and status	Canonical SMILE	Punchem ID
1.	Quetiapine	Atypical antipsychotic drug, Approved by FDA	C1CN(CCN1CCOCCO)C2=NC3=CC=CC=C3SC4=CC=CC=C42	5002
2.	Olanzapine	Atypical antipsychotic drug, Approved by FDA	CC1=CC2=C(S1)NC3=CC=CC=C3N=C2N4CCN(CC4)C	135398745
3.	Risperidone	Atypical antipsychotic drug, Approved by FDA	CC1=C(C(=O)N2CCCCC2=N1)CCN3CCC(CC3)C4=NOC5=C4C=CC(=C5)F	5073

ADME properties of Quetiapine, Olanzapine and Risperidone

Molecule 1

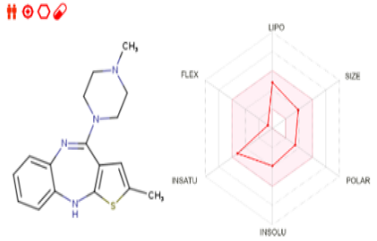


SMILES OCCOCCN1CCN(CC1)C1=Nc2ccccc2Sc2c1cccc2

Physicochemical Properties	
Formula	C21H25N3O2S
Molecular weight	383.51 g/mol
Num. heavy atoms	27
Num. arom. heavy atoms	12
Fraction Csp3	0.38
Num. rotatable bonds	6
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	119.80
TPSA	73.60 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.49
Log $P_{o/w}$ (XLOGP3)	2.14
Log $P_{o/w}$ (WLOGP)	1.71
Log $P_{o/w}$ (MLOGP)	2.93
Log $P_{o/w}$ (SILICOS-IT)	3.60
Consensus Log $P_{o/w}$	2.77

Water Solubility	
Log *S* (ESOL)	-3.50
Solubility	1.22e-01 mg/ml ; 3.17e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.32
Solubility	1.85e-01 mg/ml ; 4.81e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-5.83
Solubility	5.65e-04 mg/ml ; 1.47e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.12 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.90

Molecule 2

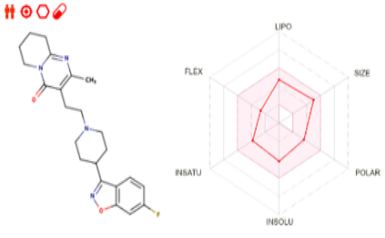


SMILES CN1CCN(CC1)C1=Nc2ccccc2Nc2c1cc(s2)C

Physicochemical Properties	
Formula	C17H20N4S
Molecular weight	312.43 g/mol
Num. heavy atoms	22
Num. arom. heavy atoms	11
Fraction Csp3	0.35
Num. rotatable bonds	1
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	107.89
TPSA	59.11 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.04
Log $P_{o/w}$ (XLOGP3)	2.86
Log $P_{o/w}$ (WLOGP)	1.92
Log $P_{o/w}$ (MLOGP)	2.88
Log $P_{o/w}$ (SILICOS-IT)	3.83
Consensus Log $P_{o/w}$	2.91

Water Solubility	
Log *S* (ESOL)	-3.88
Solubility	4.09e-02 mg/ml ; 1.31e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.76
Solubility	5.43e-02 mg/ml ; 1.74e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-5.08
Solubility	2.60e-03 mg/ml ; 8.32e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.18 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	3.86

Molecule 3

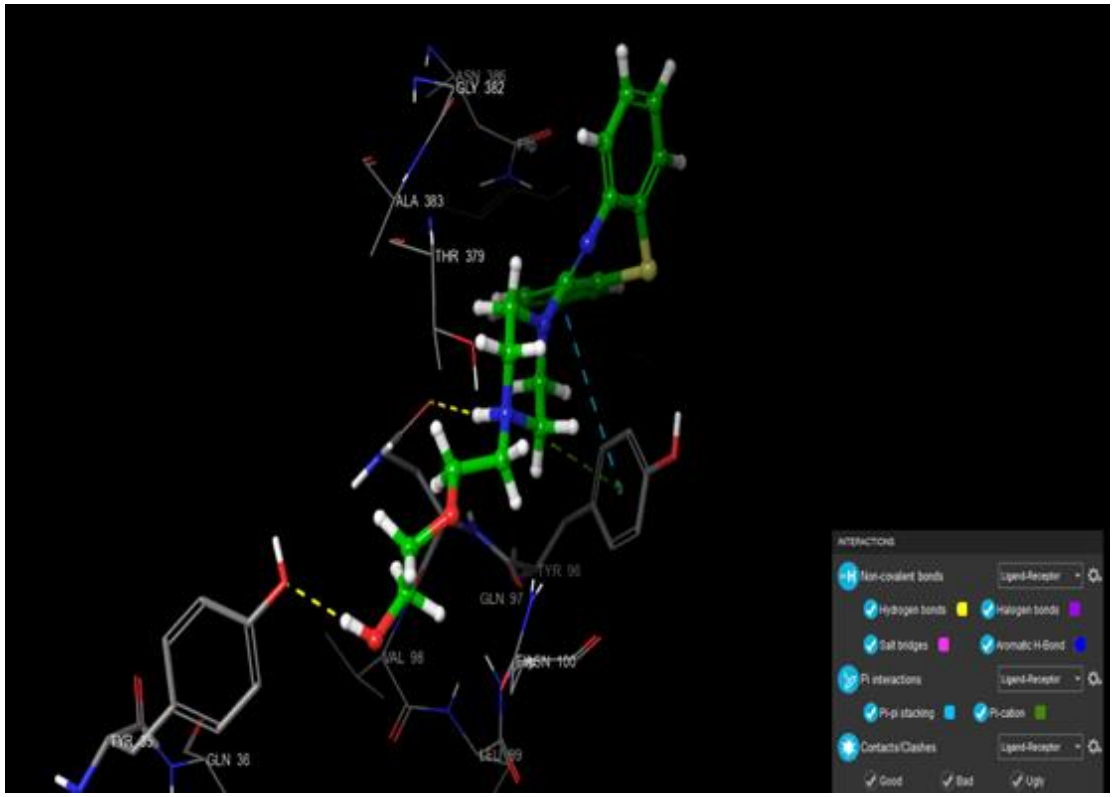


SMILES Fc1ccc2c(c1)onc2C1CCN(CC1)CCc1c(C)nc2n(c1=O)CCCC2

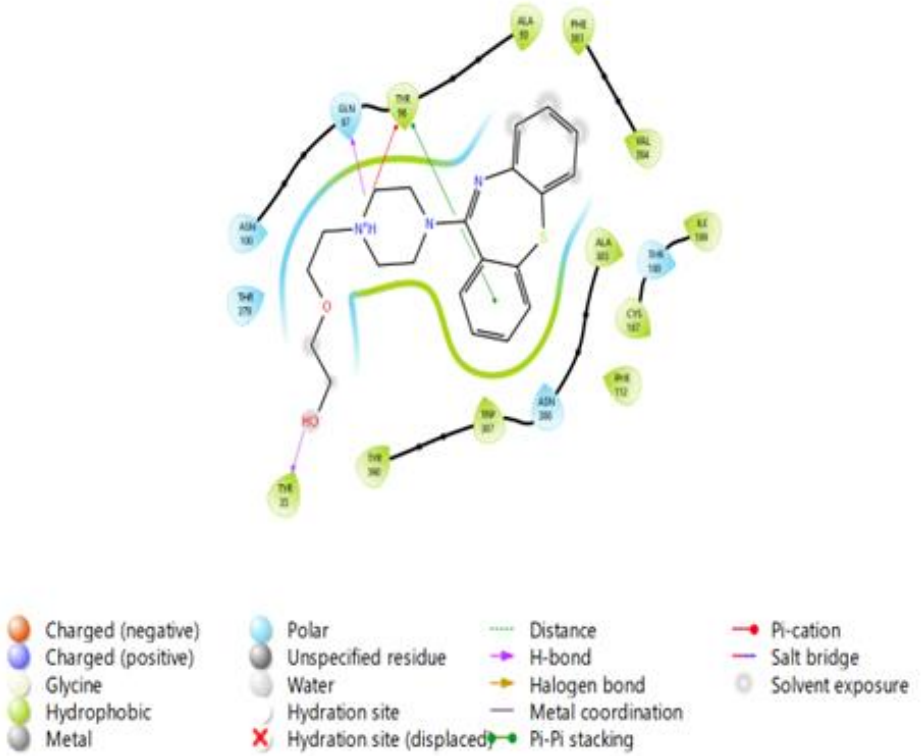
Physicochemical Properties	
Formula	C23H27FN4O2
Molecular weight	410.48 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	15
Fraction Csp3	0.52
Num. rotatable bonds	4
Num. H-bond acceptors	6
Num. H-bond donors	0
Molar Refractivity	117.71
TPSA	64.16 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.08
Log $P_{o/w}$ (XLOGP3)	2.72
Log $P_{o/w}$ (WLOGP)	3.63
Log $P_{o/w}$ (MLOGP)	3.19
Log $P_{o/w}$ (SILICOS-IT)	4.48
Consensus Log $P_{o/w}$	3.62

Water Solubility	
Log *S* (ESOL)	-4.20
Solubility	2.56e-02 mg/ml ; 6.24e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-3.72
Solubility	7.80e-02 mg/ml ; 1.90e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-6.76
Solubility	7.13e-05 mg/ml ; 1.74e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.87 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.82

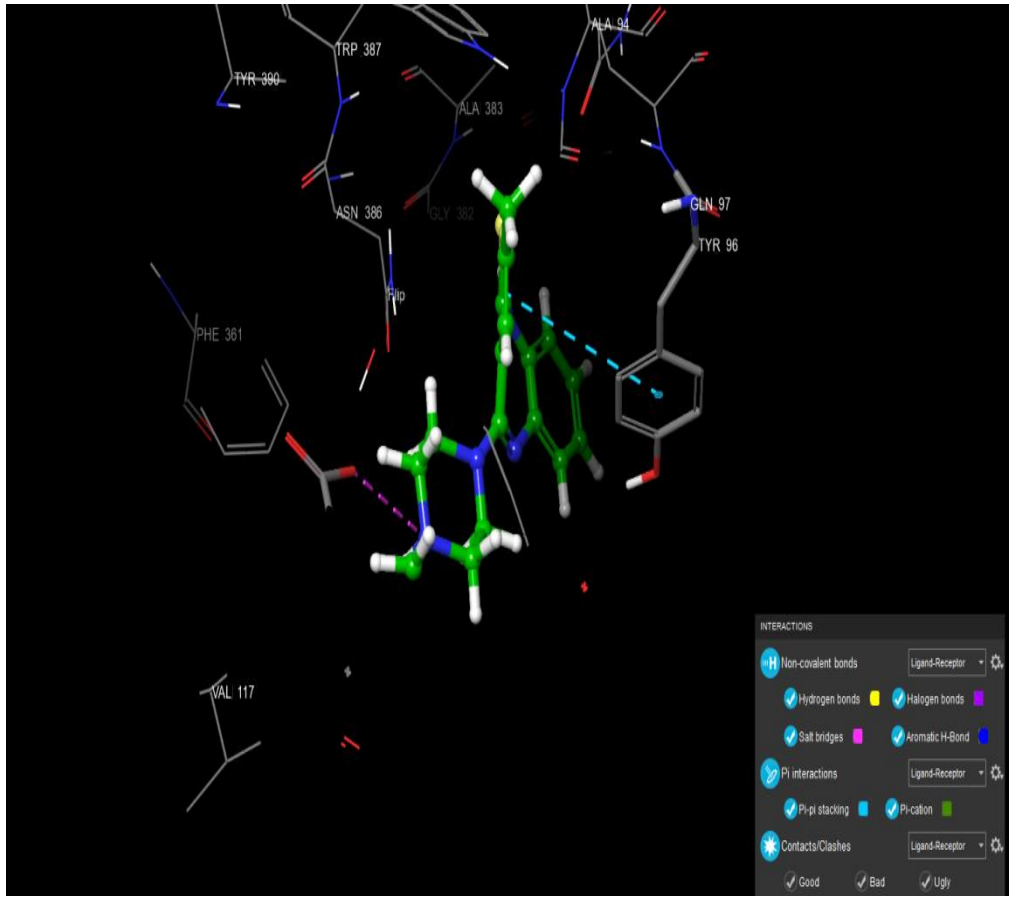
Molecular Docking of 5-HT1A with Quetiapine, Olanzapine, and Risperidone respectively



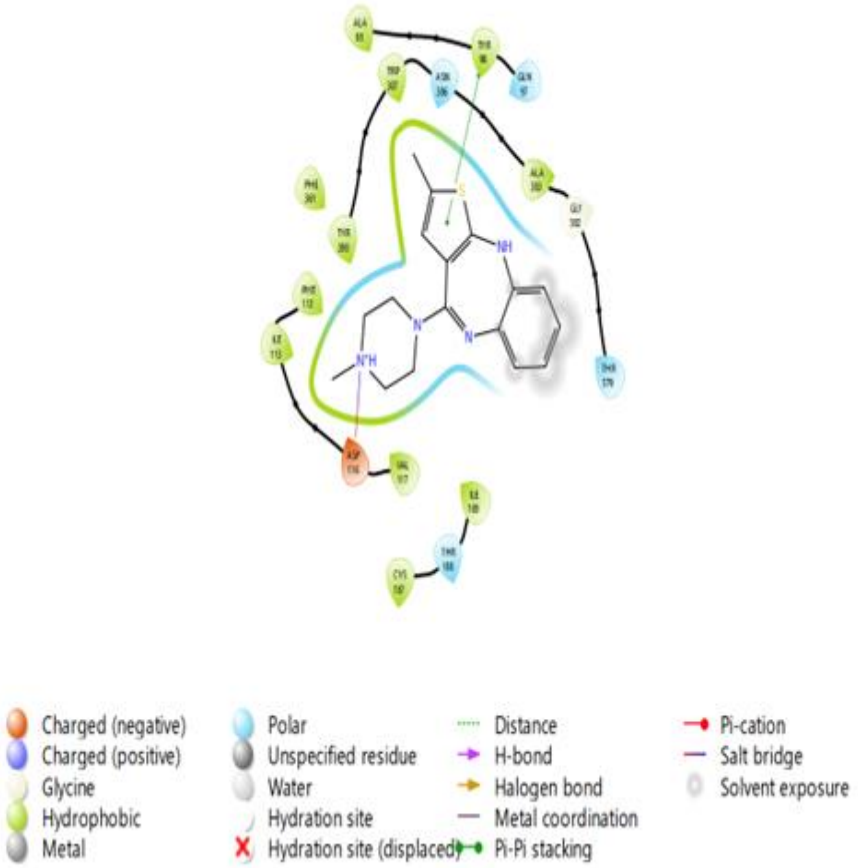
docking of Quetiapine with 5-HT1A



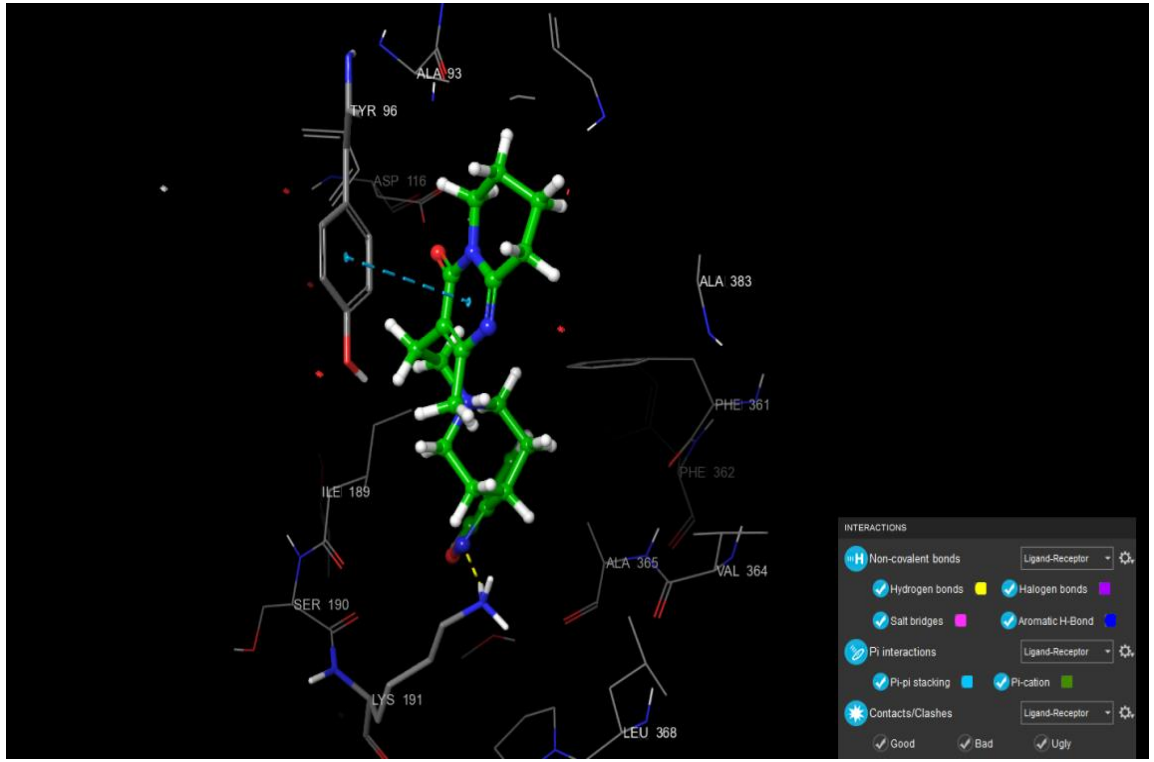
ligand interaction of Quetiapine with 5-HT1A



docking of Olanzapine with 5-HT1A



ligand interactions of Olanzapine with 5-HT1A



docking of Risperidone with 5-HT1A

ligand interaction of

Risperidone with 5-HT1A

Docking score:

- Quetiapine:

1	**5-HT1A(7E2X)**	**-5.231**	**TYR 96, GLN 97**
2	5-HT1B(4IAR)	-5.445	ASP 352
3	5-HT2A(7WC8)	-6.720	ASP 155
4	5-HT2B(7SQR)	-6.988	ASP 135, PHE 341
5	D1(7JVQ)	-5.487	SER 275, SER 147
6	α_{2A} (7EJ8)	-5.004	ASN A: 346, 347, ASP A: 262, ARG A:349
7	α_{2B}(6K41)	-5.183	ARG B: 22, GLN B: 259, LYS B: 15
8	GABA SUB α-1(7QNE)	-6.292	HIS A: 56, GLU E: 152, GLN G 53
9	H1(7DFL)	-6.565	HIS A: 218

Olanzapine:

S.No.	Recptor	Docking score Kcal/mol	Amino acids involved in interactions
1	5-HT1A(7E2X)	-5.525	ASP 116, TYR 96
2	5-HT1B(4IAR)	-7.096	ASP 129, PHE 331, SER 212
3	5-HT2A(7WC8)	-6.462	ASP 155
4	5-HT2B(7SQR)	-8.136	ASN 344, ASP 133
5	5-HT6(8LZ)	-6.706	ASP 106
6	D1(7JVQ)	-5.668	ILE 232
7	D2(7JVR)	-6.341	ASP 114
8	α_{2A} (7EJ8)	-4.809	ASN 346
9	α_{2B}(6K41)	-4.113	ASP B: 205, LYS B: 209
10	GABA SUB α-1(7QNE)	-7.689	ILE E: 47, MET A: 141

Risperidone:

S.No	Receptor	Docking score kcal/mol	Amino acids involved in interactions
1	5-HT1A(7E2X)	-7.043	LYS 191, TYR 96
2	5-HT1B(4IAR)	-7.386	ASP 129
3	5-HT2B(7SQR)	-8.657	ASP 135, PHE 341, TRP 131
4	D2(7JVR)	-6.944	ASP 114, PHE 390, TYR 408
5	α_{2A} (7EJ8)	-4.600	ASP R: 447, HIE R: 446
6	α_{2B}(6K41)	-5.523	ARG B: 19, LYS B: 209
7	GABA Type B sub-2 (6WIV)	-7.793	TYR 667
8	GABA SUB α-1(7QNE)	-8.005	MET E: 49
9	H1(7DFL)	-6.401	ARG B: 150, ASN B: 230, HIS A: 218
10	H2(7UL3)	-6.909	ASP 98, VAL 176, PHE 254, PH 251

Conclusion:

The docking between the drug and the respective receptors is done. The drugs involved in this experiment bind to multiple receptors and there are variations in binding affinity when a drug binds with different receptors. Quetiapine shows high affinity towards the receptors 5-HT2A, 5-HT28, GABRAI, and H1 with a docking score (Kcal/mol) of -6.720, -6.988, -6.292, and -6.565 respectively. Olanzapine shows high affinity towards the receptors 5-11T2A 5-HT 18 5-HT28, 5-HT6, D1, and GABRAI with a docking score of -6.462, -7.096, -8.136, -6.706,-6.341, and -7.689 respectively. Risperidone shows high affinity towards the receptors 5-HT 28-5-HTIB. GABBR2, and GABRA1 with a docking score of -7.386, -8.657, -7.793 and -8.005 respectively. Molecular docking holds great promise for accelerating the drug discovery process and addressing complex biomedical challenges. However, further in vitro, and in vivo study is important for analyzing the drug properties.