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RESEARCH ARTICLE

Some 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptor Ligands as Atypical Antipsychotic: *In Silico* Pharmacological Evaluation with ADME Predictions and Molecular Docking Techniques

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Some 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptor Ligands as Atypical Antipsychotic: In Silico Pharmacological Evaluation with ADME Predictions and Molecular Docking Techniques

SUMMARY

Serotonin (5-HT) and its receptors are involved in various neuropsychiatric disorders, and altered serotoninergic neurotransmission and interactions between the 5-HT and dopamine (DA) systems contribute to the pathophysiology of psychotic disorders. Interactions with 5-HT receptors may contribute to the elucidation of the properties of modern antipsychotic drugs, whose long-term effects on 5-HT receptors have not yet been adequately evaluated. Many people in society show at least one of the symptoms of psychotic disorder, and the mortality rate is twice as high as that of a healthy person. In this study, we revealed the molecular docking results of some drug molecules defined as atypical antipsychotics on 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$. We aimed to contribute to the development of new compounds that may be useful in the treatment of psychotic disorders by trying to demonstrate the relationship between their computational inhibitory activities and their structural properties. Docking study showed that Lurasidone (e) was one drug molecule with the best docking scores on the receptors. Also, it showed that Risperidone (h), Paliperidone (f), and Brexpiprazole (b) were one drug molecules with the best pose on the receptors. Considering ADME predictions, all drug molecules (a-j) had good pharmacokinetic profiles, but Lurasidone was found to have some disadvantages. It seems that the use of Paliperidone and Risperidone may be more valuable, especially in the treatment of psychotic patients such as schizophrenia.

Key Words: *Atypical antipsychotics, molecular docking, ADME predictions, 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2C}$*

Atipik Antipsikotik Bazı 5-HT$_{1A}$, 5-HT$_{2A}$ ve 5-HT$_{2C}$ Reseptör Ligandları: In Silico Farmakolojik Etkilerinin Moleküler Yerleştirme Teknikleriyle Değerlendirilmesi ve ADME Tahminleri

ÖZ

Serotonin (5-HT) ve reseptörleri çeşitli nöropsikiyatrik bozukluklarda rol oynamakta ve 5-HT ile dopamin (DA) sistemleri arasındaki değişen serotoninerjik nörotransmisyon ve etkileşimler, psikotik bozuklukların patofizyolojisine katkıda bulunmaktadır. 5-HT Reseptörleriyle etkileşimlerin araştırılması, 5-HT reseptörleri üzerindeki uzun vadeli etkileri henüz yeterince değerlendirilmemiş olan modern antipsikotik ilaçların özelliklerinin aydınlatılmasına katkıda bulunabilir. Toplumda psikotik bozukluk semptomlarından en az birini gösteren çok sayıda kişi vardır ve ölüm oranı sağlıklı bir kişiye göre iki kat daha yüksektir. Bu çalışmada, atipik antipsikotik olarak tanımlanan bazı ilaç moleküllerinin 5-HT$_{1A}$, 5-HT$_{2A}$ ve 5-HT$_{2C}$ üzerindeki moleküler yerleştirme sonuçlarını ortaya koyduk. Hesaplamalı inhibe edici aktiviteleri ile yapısal özellikleri arasındaki ilişkiyi ortaya koymaya çalışarak psikotik bozuklukların tedavisinde yararlı olabilecek yeni bileşiklerin geliştirilmesine katkıda bulunmayı amaçladık. Yerleştirme çalışması, Lurasidon'un (e) reseptörler üzerinde en iyi yerleştirme skorlarına sahip ilaç moleküllerinden biri olduğunu gösterdi. Ayrıca, Risperidon (h), Paliperidon (f) ve Brekspiprazol'ün (b) reseptörler üzerinde en iyi poza sahip ilaç moleküllerinden biri olduğunu gösterdi. ADME tahminleri göz önüne alındığında, tüm ilaç moleküllerinin (a-j) iyi farmakokinetik profilleri vardı, ancak Lurasidon'un bazı dezavantajları olduğu bulundu. Paliperidon ve Risperidon kullanımının, özellikle şizofreni gibi psikotik hastaların tedavisinde daha değerli olabileceği anlaşılmaktadır.

Anahtar Kelimeler: *Atipik antipsikotikler, moleküler yerleştirme, ADME tahminleri, 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2C}$*

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INTRODUCTION

Serotonin (5-hydroxytryptamine) has been found to play a substantial role in many basic physiological and pathophysiological processes, including mood and emotions, aggression and anxiety, circadian rhythms, sleep regulation, sexual behavior, memory and learning processes, thalamic blood pressure and nociception (Barnes & Sharp, 1999; Fiorino et al., 2017). 5-hydroxytryptamine (5-HT), one of the oldest known neurotransmitters, plays a role in the etiology of numerous disease states such as depression, anxiety, schizophrenia, social phobia, obsessive-compulsive disorder, and panic disorder; as well as hypertension, migraine, eating disorders, vomiting and irritable bowel syndrome (Hoyer, Hannon, & Martin, 2002). It is observed that the mortality rate of people with psychotic disorders is twice as high as that of healthy people, and the average life expectancy is 20 years less. Although these symptoms are observed at a rate of 3% in society, the rate of people showing at least one of the disorder's symptoms are relatively high in the general population (Moreno et al., 2013; Nuevo et al., 2012).

5-HT_{1A}, the first 5-HT receptor to be fully elucidated, is found in the body, meanly around the brain, particularly in the hippocampus and cortical areas. At the cellular level, *in situ* hybridization and immunocytochemical studies also demonstrate the presence of 5-HT_{1A} at receptors in pyramidal and granular neurons of the hippocampus. The pharmacological effects of 5-HT_{1A} differ from those of other 5-HT_1 and 5-HT receptors. The 5-HT_{1A} receptor agonists obtained in the first years were not selective, but over the years, selective agonists began to be obtained. The 5-HT_{1A} receptor is known to have a neurotrophic role in the young brain and possibly in adults. Recent studies have highlighted that 5-HT_{1A} receptor antagonists facilitate the effects of 5-HT reuptake inhibitors, monoamine oxidase inhibitors, and antidepressant (some tricyclics) drugs on 5-HT release. (Azmitia, Gannon, Kheck, & Whitaker-Azmitia, 1996; Fletcher et al., 1993; Kobilka et al., 1987; Sharp & Hjorth, 1990).

5-HT_{2A} was initially known as the 5-HT_2 receptor; it was later divided into a separate classification. The human 5-HT_{2A} receptor is located on chromosome 13q14-q21 and is highly identical to the human 5-HT_{2C} receptor. The 5-HT_{2A} receptor is known to have potential sites for palmitoylation, phosphorylation, and glycosylation. Several recent studies have investigated the cellular location of the 5-HT_{2A} receptor in the brain. Studies conducted so far have found 5-HT_{2A} immunoreactivity in neurons. 5-HT_2 receptor antagonists such as Ritanserin have high affinity for various 5-HT_2receptors. Ketanserin and Spiperon are approximately two orders of magnitude more selective for 5-HT_{2B} receptors than 5-HT_{2A}, while these drugs have an affinity for other monoamine receptors. Agonist action at 5-HT_2 receptors has been considered to be involved in hallucinogenic mechanisms because of their proximity to 5-HT_2 binding sites and the close relationship between the human hallucinogenic potential of 5-HT_2 receptor agonists (Baxter, Kennett, Blackburn, & Blaney, 1995; Boess & Martin, 1994; Glennon, 1990).

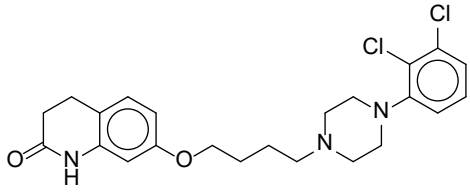
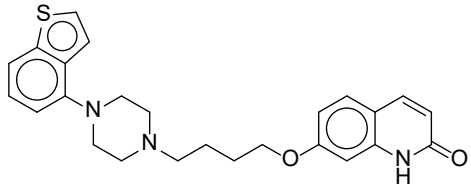
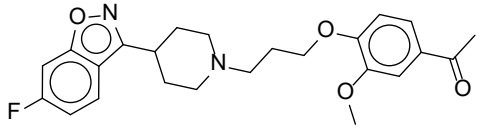
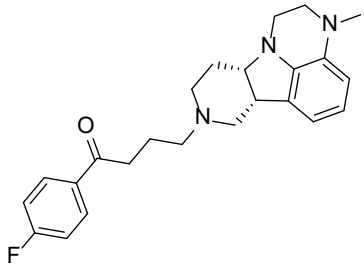
5-HT_{2C} receptors are predominantly localized in the brain, and their dysregulation can lead to increased anxiety and depression. The fact that various psychotropic agents such as fluoxetine, clozapine, and tricyclic antidepressants have significant affinity for the 5-HT_{2C} receptor has increased the interest in selective and high-affinity 5-HT_{2C} receptor ligands. Recent studies have shown that 5-HT_{2C} receptor agonists can reduce feeding when administered acutely to rats or mice and can also reduce body weight when administered to obese animals for a long time without causing tolerance. There are also reports that 5-HT_{2C} antagonists increase the release of norepinephrine and dopamine (Bickerdike, 2003; Jenck et al., 1998; Millan, Dekeyne, & Gobert, 1998).

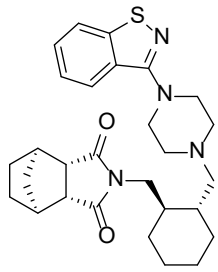
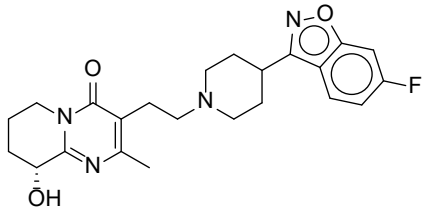
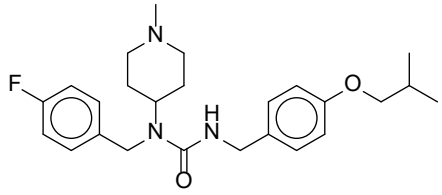
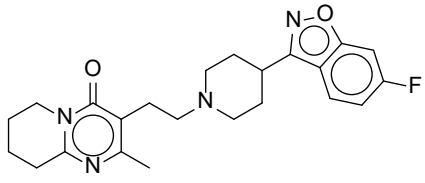
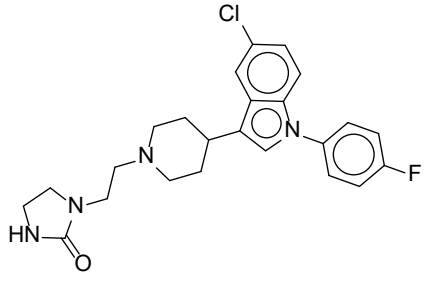
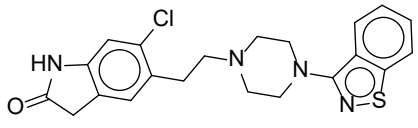
Known as a pharmacologically heterogeneous group of compounds, antipsychotics all act as D2

dopamine receptor antagonists. Atypical antipsychotic medications were developed in response to patients' failure to respond to typical psychotic problems with typical agents, including lack of effectiveness with the medications, lack of improvement in symptoms, and troublesome side effects, especially extrapyramidal symptoms. Atypical antipsychotic agents are often considered first-line agents in the treatment of schizophrenia. They are also seen as an area open to development as they are seen as agents that may be effective in other psychiatric and neurological conditions. Atypical antipsychotics are increasingly being used in the treatment of mania and depression as well as schizophrenia (Jibson & Tandon, 1998; Mackin & Thomas, 2011; Meltzer, 2013).

In this study, we revealed the molecular docking results of some drug molecules (Table 1.) characterized as atypical antipsychotic on 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}. Since ideal pharmacokinetic properties, high pharmacological activity, and low toxicity are expected in drugs, so ADME predictions were also evaluated. In this context, the evaluation was made by comparing the molecular docking results and ADME predictions. We also aim to help reveal the relationship between their computational inhibitory activities and structural properties, contributing to the development of new compounds that may be useful in the treating of psychotic disorders.

Table 1. Chemical Structure of some atypical antipsychotic drug compounds

Compounds		Chemical Structure
Code	**Name**	
a	**aripiprazole**	
b	**brexpiprazole**	
c	**iloperidone**	
d	**lumateperone**	

e	**lurasidone**	
f	**paliperidone**	
g	**pimavanserin**	
h	**risperidone**	
i	**sertindole**	
j	**ziprasidone**	

MATERIAL AND METHODS

Molecular docking studies

The compounds analyzed in this study were selected with preference given to drugs that have received regulatory approval from the US Food and Drug Administration (FDA) or other regulators and have entered clinical practice globally. The chemical structures of all selected compounds (**a**-**j**) used as ligands were carried out on a 64-bit operating system with Windows 11 Pro edition. The chemical structures of the compounds used as ligands, whose structures have been previously described in the literature (https://pubchem.ncbi.nlm.nih.gov/, access date: 23.09.2024), were created with the ChemDraw

2D program using their SMILES and their energy minimization was carried out with the ChemDraw 3D program. 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} crystal structures were taken from protein data bank (Kimura et al., 2019; Peng et al., 2018; Xu et al., 2021). The grid boxes were positioned according to the previously determined regions for the active sites of the macromolecules, with dimensions of 40x40x40 $Å^3$ and a spacing of 0.375Å. The Pdb files of the macromolecules were optimized using Maestro Version 6.4.135, Release 2023-4 (Uslu et al., 2023). At least 50 runs were performed for each selected compounds while using standard settings for 5-HT_{1A} receptor (PDB ID: 7E2Z), 5-HT_{2A} receptor (PDB ID: 6A93), and 5-HT_{2C} receptor (PDB ID: 6BQH). Lamarckian Genetic Algorithm was preferred in all studies; detailed results such as docking scores were obtained using both AutoDock 4.2 (Morris et al., 2009) and AutoDock Vina programs (Trott & Olson, 2010), and are presented. For docking validation, co-crystallized ligands were re-docked onto target sites of macromolecules, and RMSD values have been determined to be for existing ligand Aripiprazole (PDB ID: 9SC) as 1.88, existing ligand Risperidone (PDB ID: 8NU) as 0.79 and ligand Ritanserin (PDB ID: E2J) as 0.40, respectivly for 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} (Table 2-4).

ADME predictions

The SwissADME online tool was used to calculate the pharmacokinetic and physicochemical properties of some selected atypical antipsychotic ligands (**a**-**j**) and compare the results (Table 5-6.) (http://www.swissadme.ch/, access date: 23.09.2024) (Daina, Michielin, & Zoete, 2014, 2017; Daina & Zoete, 2016).

RESULT AND DISCUSSION

Molecular docking studies

The interaction domain of 5-HT_{1A} was determined previously. Weak hydrogen bonding with PHE362 and the chlorine attached to the 3rd position of the phenyl ring of Aripiprazole and van der Waals interaction with the phenyl ring were observed. A weak polar bond was observed between SER199 and the chlorine attached to the 3rd position of the phenyl ring, and weak polar and van der Waals interactions were observed with the phenyl ring. It has been observed that PHE361 forms hydrogen and weak polar bonds between chlorine attached to the second position of the phenyl ring. Hydrogen bonding and van der Waals interaction were observed between CYS120 and the piperazine ring. Weak hydrogen and weak polar bonding were observed between THR121 and the phenyl ring. Van der Waals interaction, weak polar and ionic bonding was observed between ASP116 and the piperazine ring. Weak hydrogen bonding was observed between ASP116 and the methylene group. Van der Waals interactions and weak polar bonding were observed between ASN386 and methylene groups. Van der Waals interactions and weak polar bonding were observed between TYR390 and the methylene group. A weak polar bond was observed between PHE112 and the oxygen atom. Weak hydrogen bonding and van der Waals interaction were observed between TYR96 and the dihydroquinolinone ring. It was observed that ALA93, GLN97, VAL117, ILE189, THR200, ALA203 and THR379 made hydrogen bonds with the compound (Figure 1.) (https://www.ebi.ac.uk/pdbe/entry/pdb/7e2z/bound/9SC#501R, access date: 23.09.2024) (Xu et al., 2021).

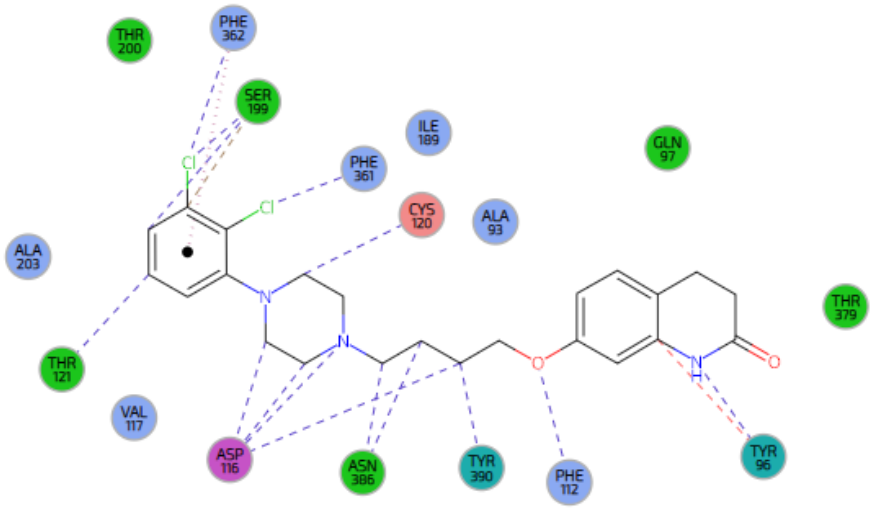


Figure 1. Interactions between aripiprazole (9SC) and 5-HT$_{1A}$ (quoted from the https://www.ebi.ac.uk/pdbe/entry/pdb/7e2z/bound/9SC#501R)

Table 2. Molecular docking scores, binding types, and estimated inhibition constants of some drug compounds on 7E2Z (5-HT$_{1A}$)

Comp.	Based on Visual Results Interacting Residues			Autodock Results		Vina Results
	Hydrogen bond	Halogen Bond	Pi-Pi interaction	Estimated inhibition Constant, Ki	The best docking score	The best docking score
a	ASN386	THR379	-	117.04 nM	-9.46	-8.7
b	CYS187	-	PHE362	66.01 nM	-9.80	-9.4
c	SER199	-	PHE112 TRP387	133.98 nM	-9.38	-8.2
d	-	-	-	592.23 nM	-8.50	-7.7
e	-	-	TYR390	2.97 nM	-11.63	-10.2
f	-	-	PHE362 TRP358	42.05 nM	-10.06	-9.7
g	-	-	-	862.78 nM	-8.27	-8.8
h	-	-	PHE362	15.60 nM	-10.65	-9.4
i	ILE189	ASN386	PHE361	92.54 nM	-9.60	-9.4
j	-	-	-	125.87 nM	-9.41	-9.4

pM: picomolar, nM: nanomolar, Docking Score: Estimated Binding Free Energy (kcal/mol)

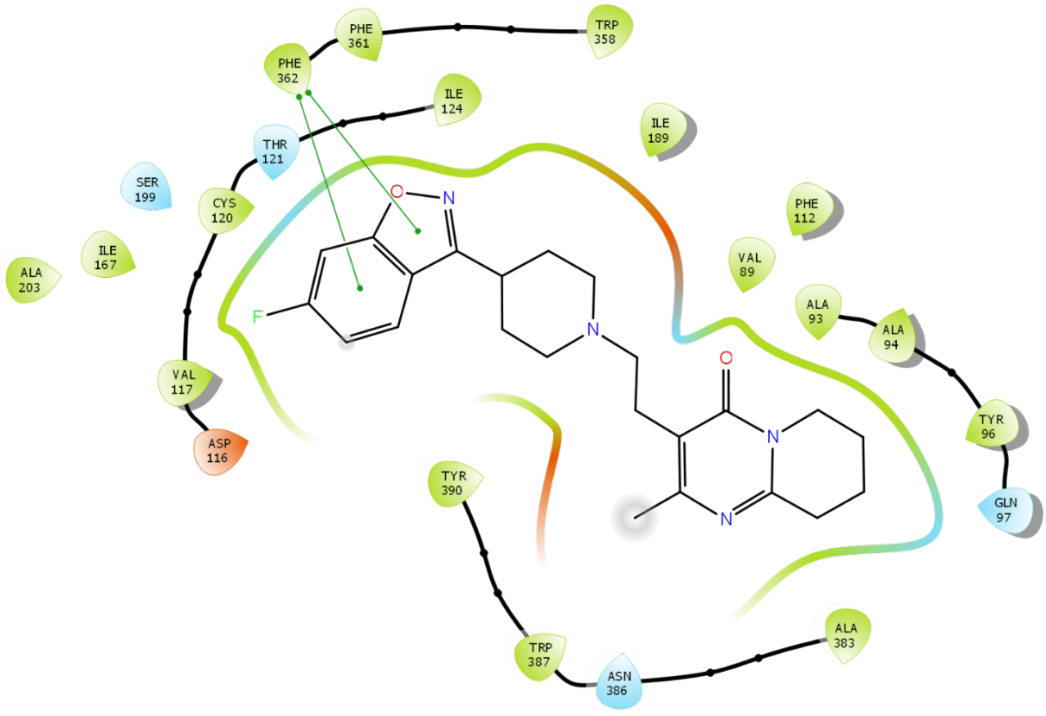


Figure 2. 2D interaction diagram with 5-HT$_{1A}$ (7E2Z) for Risperidone (**h**).

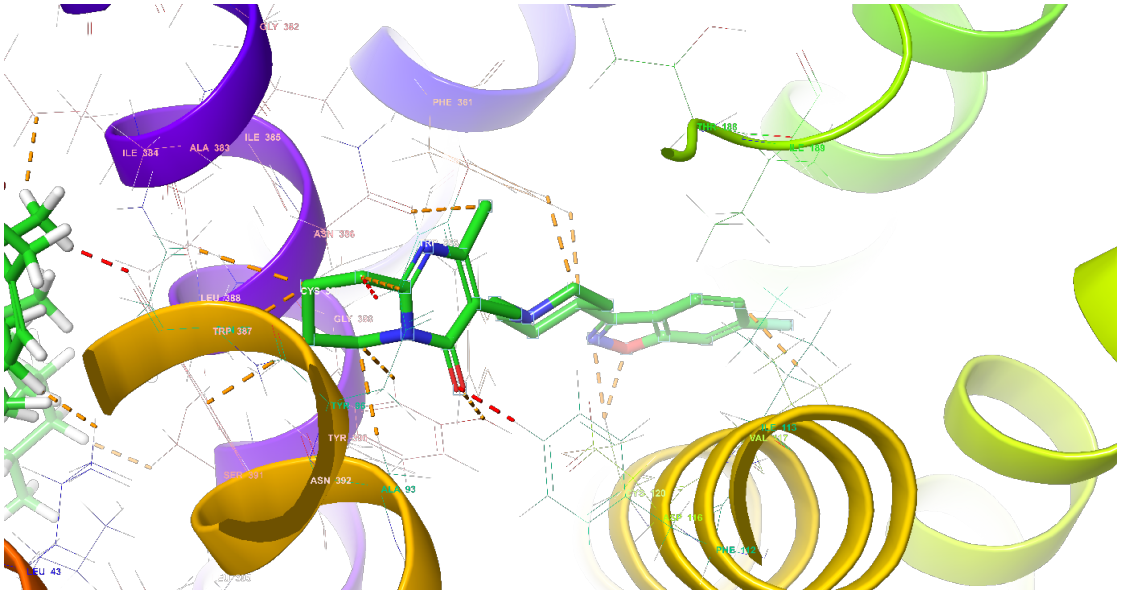


Figure 3. 3D interaction diagram with 5-HT$_{1A}$ (7E2Z) for Risperidone (**h**).

When the docking poses of Risperidone (**h**) were examined, it was seen that it had interaction such as pi-pi interaction. The pi-pi interactions were detected in the benzothiophene ring of Brexpiprazole (**b**) and PHE362 (Figure 2-3.). In this study, it was determined that Risperidone (**h**) with these residues of 5-HT_{1A} in a similar way. All these interactions enabled Risperidone (**h**) to bind strongly to the active site, explaining why it exhibited a more robust inhibition profile (Table 2.).

The interaction domain of 5-HT_{2A} was determined previously. One weak polar bond and one carbon-π bond were observed between LEU228 and the pyrimidine ring. A carbon-π bond was observed between VAL366 and the pyrimidine ring. Weak polar bond and van der Waals interaction were observed between SER131 and the methyl ring attached to pyrimidine. Van der Waals interaction was observed between TRP151 and the methyl ring attached to pyrimidine. Van der Waals interaction, weak hydrogen bond, and weak polar bond were observed between ASN363 and the tetrahydropyrido ring. A weak hydrogen bond was observed between TYR370 and the methylene group, and a weak polar bond was observed with the piperidine ring. One weak polar bond and one van der Waals interaction were observed between ASP155 and methylene groups. Ionic bond, weak polar bond, and van der Waals interaction were observed between ASP155 and the pyrimidine ring. A weak polar bond was observed between SER159 and the pyrimidine ring. Two van der Waals interactions and two carbon-π bonds were observed between SER159 and the benzoxazole ring. An aromatic hydrogen bond and a van der Waals interaction were observed between TRP336 and the benzoxazole ring. An aromatic hydrogen bond and a van der Waals interaction were observed between PHE340 and the benzoxazole ring. A weak polar bond was observed between PHE332 and the fluorine attached to the benzoxazole ring. A weak polar bond was observed between PHE243 and the fluorine attached to the benzoxazole ring. A weak polar bond was observed between ILE163 and the fluorine attached to the benzoxazole ring. Weak hydrogen bonding was observed between SER242 and the benzoxazole ring. It was observed that TYR139, LEU362, PHE339, and VAL156 made hydrogen bonds with the compound (https://www.ebi.ac.uk/pdbe/entry/pdb/6a93/bound/8NU#3001A, access date: 23.09.2024) (Figure 4.) (Kimura et al., 2019).

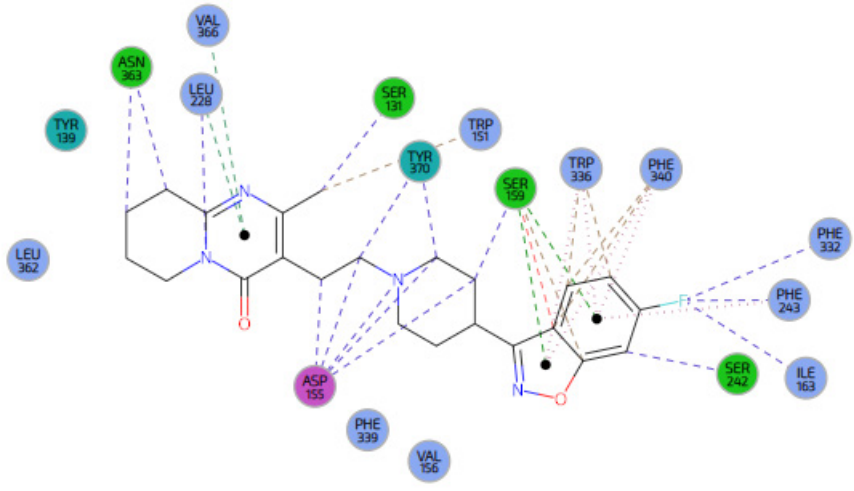


Figure 4. Interactions between risperidone (8NU) and 5-HT_{2A} (quoted from the https://www.ebi.ac.uk/pdbe/entry/pdb/6a93/bound/8NU#3001A)

Table 3. Molecular docking scores, binding types, and estimated inhibition constants of some drug compounds on 6A93 (5-HT_{2A})

Comp.	Based on Visual Results Interacting Residues		Autodock Results		Vina Results
	Hydrogen bond	Pi-Pi interaction	Estimated inhibition Constant, Ki	The best docking score	The best docking score
a	A: LEU329	A: PHE340	14.31 nM	-10.70	-10.2
b	A: ASN343 A: LYS223	A: PHE243 A: TRP:336 A: PHE340	2.27 nM	-11.79	-10.3
c	A: ASN343	A: PHE340 A: TRP336	4.86 nM	-11.34	-10.5
d	-	A: PHE340 A: TRP336	38.28 nM	-10.12	-10.5
e	-	A: PHE340 A: TRP336	202.04 pM	-13.23	-11.8
f	A: ASN343 A: LEU229	A: PHE243 A: TRP:336 A: PHE340	692.56 pM	-12.50	-11.8
g	A: ASN343	A: PHE340 A: TRP336	15.45 nM	-10.66	-9.5
h	A: ASN343	A: PHE340 A: TRP336	1.04 nM	-12.26	-11.8
i	A: CYS227	A: PHE340 A: PHE339 A: TRP336	9.91 nM	-10.92	-11.1
j	A: LYS223	A: PHE340 A: TRP336	5.10 nM	-11.31	-10.2

When the docking poses of Paliperidone (**f**) were examined, it was seen that it had pi-pi interactions and hydrogen bonds. The pi-pi interactions were detected in the benzoxazole ring of Paliperidone (**f**) and PHE243, TRP336, and PHE340. Also, there were H-bond interactions between the pyrimidin-4-one and LEU229 and ASN343 (Figure 5-6.). In this study, it was determined that Paliperidone (**f**) with these residues of 5-HT_{2A} in a similar way. All these interactions enabled Paliperidone (**f**) to bind more vital to the active site, explaining why it exhibited a more robust inhibition profile (Table 3.).

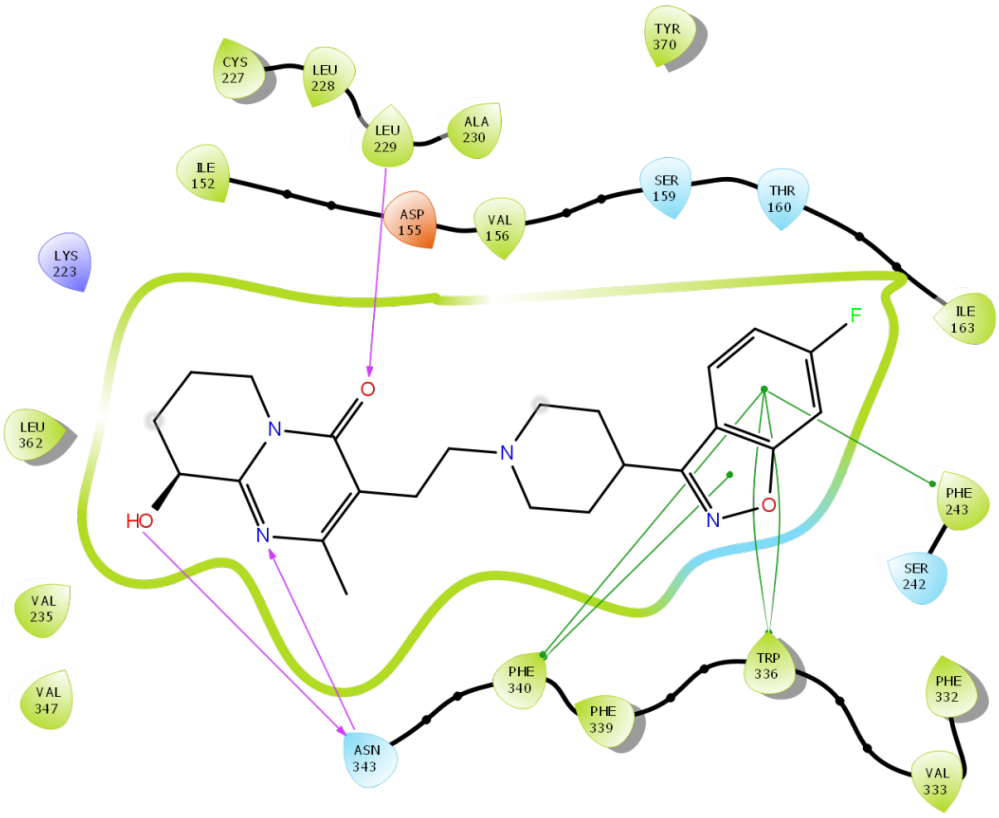


Figure 5. 2D interaction diagram with 5-HT$_{2A}$ (6A93) for Paliperidone (**f**).

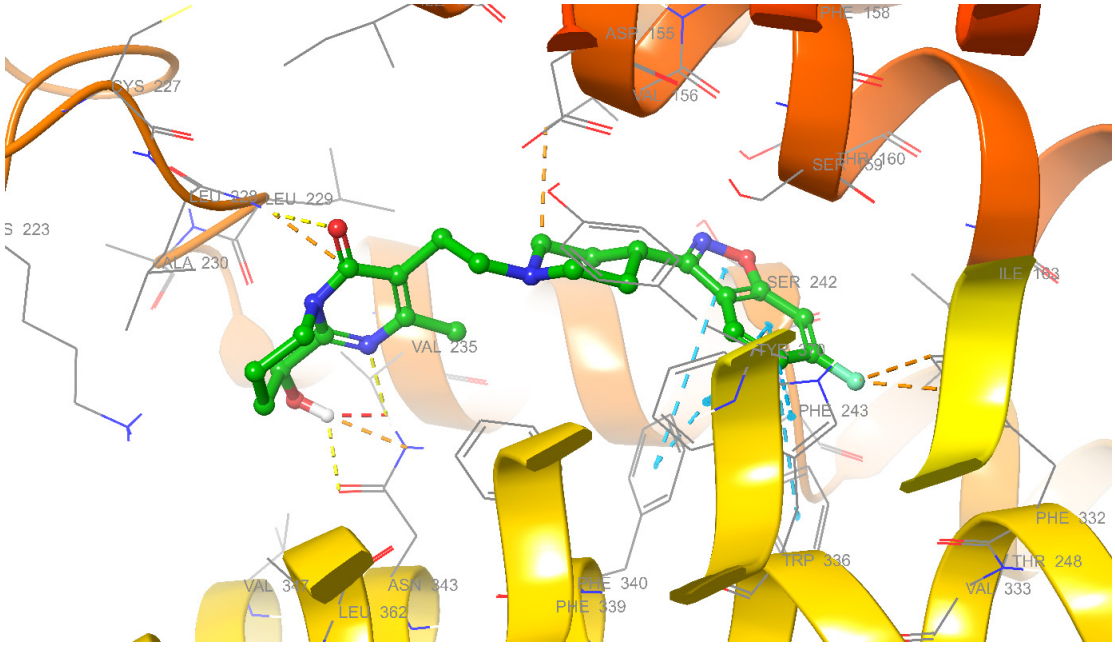


Figure 6. 3D interaction diagram with 5-HT$_{2A}$ (6A93) for Paliperidone (**f**).

The interaction domain of 5-HT_{2C} was determined previously. A weak polar bond was observed between GLY218 and the fluorophenyl ring. A weak polar bond was observed between SER219 and the fluorophenyl ring. Weak hydrogen bonding was observed between SER219 and the fluorophenyl ring. A weak polar bond was observed between ILE142 and the fluorophenyl ring. A weak polar bond was observed between PHE223 and the fluorophenyl ring. A weak polar bond was observed between PHE320 and the fluorophenyl ring. Aromatic hydrogen bonding was observed between PHE328 and the phenyl ring. One weak polar bond and one carbon-π bond were observed between SER138 and the phenyl ring. A weak polar bond was observed between SER138 and the piperidine ring. A weak polar bond was observed between TYR358 and the thiazolopyrimidine ring. A weak polar bond and carbon-π bond were observed between VAL354 and the thiazolopyrimidine ring. Two carbon-π bonds were observed between VAL208 and the thiazolopyrimidine ring. Weak polar bonding and van der Waals interaction were observed between ASN351 and the thiazolopyrimidine ring. Weak polar bond, ionic bond, and van der Waals interaction were observed between ASP134 and the piperidine ring. Weak polar bonds and van der Waals bonds were observed between ASP134 and methylene groups. Hydrogen bonding was observed between HOH1301 and the piperidine ring, methylene group and the oxygen atom. Amiding bonds were observed between ALA222 and the fluorophenyl ring. Amiding bonds were observed between LEU350 and the thiazolopyrimidine ring. It was observed that VAL135 and TRP324 made hydrogen bonds with the compound (https://www.ebi.ac.uk/pdbe/entry/pdb/6bqh/bound/E2J#1201A, access date: 23.09.2024) (Figure 7.) (Peng et al., 2018).

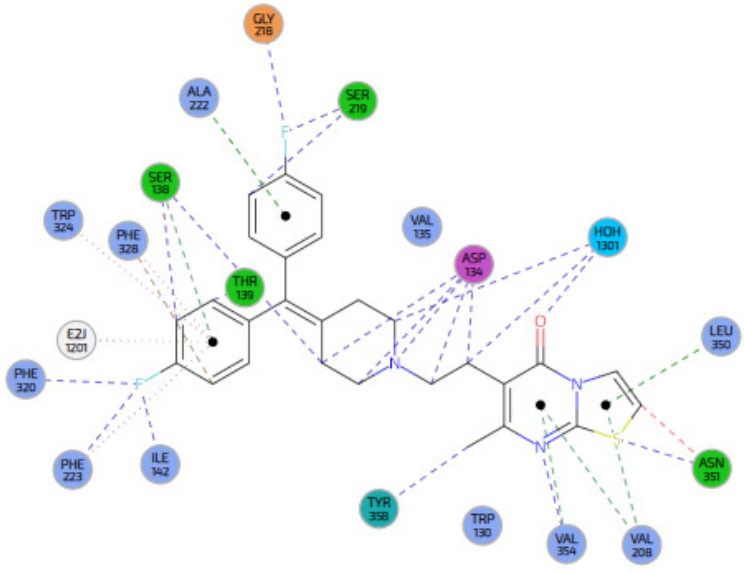


Figure 7. Interactions between ritanserin (E2J) and 5-HT_{2C} (quoted from the https://www.ebi.ac.uk/pdbe/entry/pdb/6bqh/bound/E2J#1201A)

Table 4. Molecular docking scores, binding types, and estimated inhibition constants of some drug compounds on 6BQH (5-HT_{2C})

Comp.	Based on Visual Results Interacting Residues			Autodock Results		Vina Results
	Hydrogen bond	Halogen Bond	Pi-Pi interaction	Estimated inhibition Constant, Ki	The best docking score	The best docking score
a	LEU209	ALA222	TRP324 PHE328	51.17 nM	-9.95	-10.2
b	SER219	-	PHE223 TRP324 PHE328	3.88 nM	-11.48	-10.5
c	ASN331	-	PHE223 TRP324 PHE328	32.79 nM	-10.21	-10.8
d	-	-	PHE223 TRP324 PHE327 PHE328	134.18 nM	-9.38	-9.8
e	-	-	TRP130	204.48 pM	-13.22	-11.4
f	LEU209 ASN331	-	PHE223 TRP324 PHE328	7.06 nM	-11.12	-11.4
g	ASP134 LEU209	-	PHE223 TRP324 PHE328	51.99 nM	-9.94	-9.4
h	LEU209	-	PHE223 TRP324 PHE328	9.97 nM	-10.92	-11.3
i	LEU209	PHE214	PHE223 TRP324 PHE328	17.03 nM	-10.60	-11.4
j	VAL215	-	PHE223 TRP324 PHE328	11.13 nM	-10.85	-10.2

When the docking poses of Brexpiprazole (**b**) were examined, it was seen that it had pi-pi interactions and hydrogen bonds. The pi-pi interactions were detected in the benzothiophene ring of Brexpiprazole (**b**) and PHE223, TRP324, and PHE328. Also, there was a H-bond interaction between the quinolin-2-one and SER219 (Figure 8-9.). In this study, it was determined that Brexpiprazole (**b**) with these residues of 5-HT_{2C} in a similar way. All these interactions enabled Brexpiprazole (**b**) to bind more potent to the active site, explaining why it exhibited a more robust inhibition profile (Table 4.).

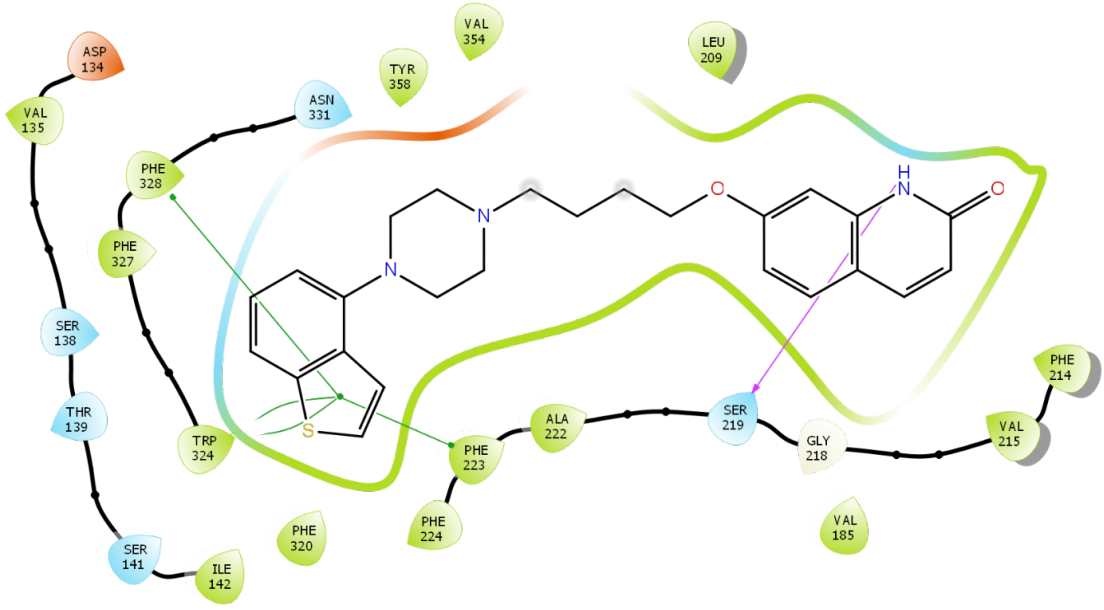


Figure 8. 2D interaction diagram with 5-HT$_{2C}$ (6BQH) for Brexpiprazole (**b**).

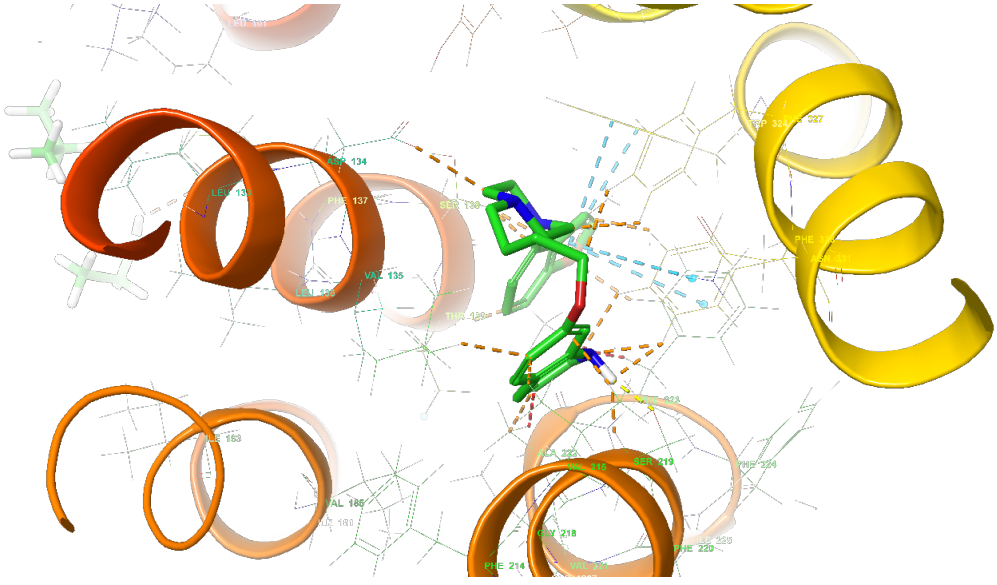


Figure 9. 3D interaction diagram with 5-HT$_{2C}$ (6BQH) for Brexpiprazole (**b**).

ADME predictions

The software, known as SwissAdme, facilitates this process while providing some preliminary research results on turning molecules into drugs (Daina et al., 2014, 2017; Daina & Zoete, 2016). The physicochemical and pharmacokinetic properties of all synthesized compounds were evaluated appropriately to become drug candidates. Log S values of the compounds are between -3.95 and -6.13, and their solubility is estimated to be between poorly and soluble. The F value, which indicates the oral bioavailability of the compounds, is 0.55 and is the most ideal (Table 5.). It was observed that all drug molecules were in full compliance with the Lipinski, Egan, and Veber rules. It was observed that all drug compounds except Lurasidone (**e**) complied

with Muegge's rules. The model that provides critically important information on passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeability estimation is the Boiled Egg model from the SwissAdme software. All drug compounds are in the white region. This shows that they can pass through the gastrointestinal system. Except for compounds **e** and **f**, all other compounds can easily cross the blood-brain barrier. This type of medicine is affect the central nervous system so this results are predictable. While the Total polar surface area (TPSA) values were found to be in the range of 26.79-84.99, the Consensus Log P (cLogP) values, which are the average of five predictions, were found to be in the range of 2.96-4.41 (Table 6., Figure 11.).

Table 5. Druglikeness, water solubility, and pharmacokinetic properties of some drug compounds.

Comp.	Druglikeness					Water Solubility		Pharmacokinetics	
Lipinski	Ghose	Veber	Egan	Muegge	LogS	Class	GI abs.	F	
a	+	-	+	+	+	-5.38	Moderately	High	0.55
b	+	-	+	+	+	-5.46	Moderately	High	0.55
c	+	+	+	+	+	-4.90	Moderately	High	0.55
d	+	+	+	+	+	-4.63	Moderately	High	0.55
e	+	-	+	+	-	-6.13	Poorly	High	0.55
f	+	+	+	+	+	-3.95	Soluble	High	0.55
g	+	+	+	+	+	-4.97	Moderately	High	0.55
h	+	+	+	+	+	-4.20	Moderately	High	0.55
i	+	-	+	+	+	-5.17	Moderately	High	0.55
j	+	-	+	+	+	-5.17	Moderately	High	0.55

LogS: ESOL, Class: -6 <Moderately <-4 GI abs: Gastrointestinal absorption, F: Bioavailability score.

Table 6. The physicochemical and lipophilicity properties of some drug compounds.

Comp.	Physicochemical Properties							Lipophilicity
	MW	Fsp3	RB	HBA	HBD	MR	TPSA	cLogP
a	448.39	0.43	7	3	1	133.26	44.81	4.21
b	433.57	0.32	7	3	1	136.65	76.81	4.41
c	426.48	0.42	8	7	0	119.98	64.80	4.20
d	393.50	0.46	5	3	0	124.68	26.79	3.56
e	492.68	0.68	5	4	0	151.55	84.99	4.14
f	426.48	0.52	4	7	1	118.87	84.39	2.96
g	427.55	0.48	10	4	1	126.21	44.81	4.29
h	410.48	0.52	4	6	0	117.71	64.16	3.62
i	440.94	0.38	5	3	1	133.17	40.51	4.00
j	412.94	0.33	4	3	1	125.48	76.71	3.57

Comp: Compounds, MW: Molecular weight, Fsp3: Fraction Csp3, RB: Number of rotatable bonds, HBA: Number of hydrogen bond acceptors, HBD: Number of hydrogen bond donors, MR: Molar refractivity, TPSA: Total polar surface area, cLogP: Consensus Log P (average of five predictions)

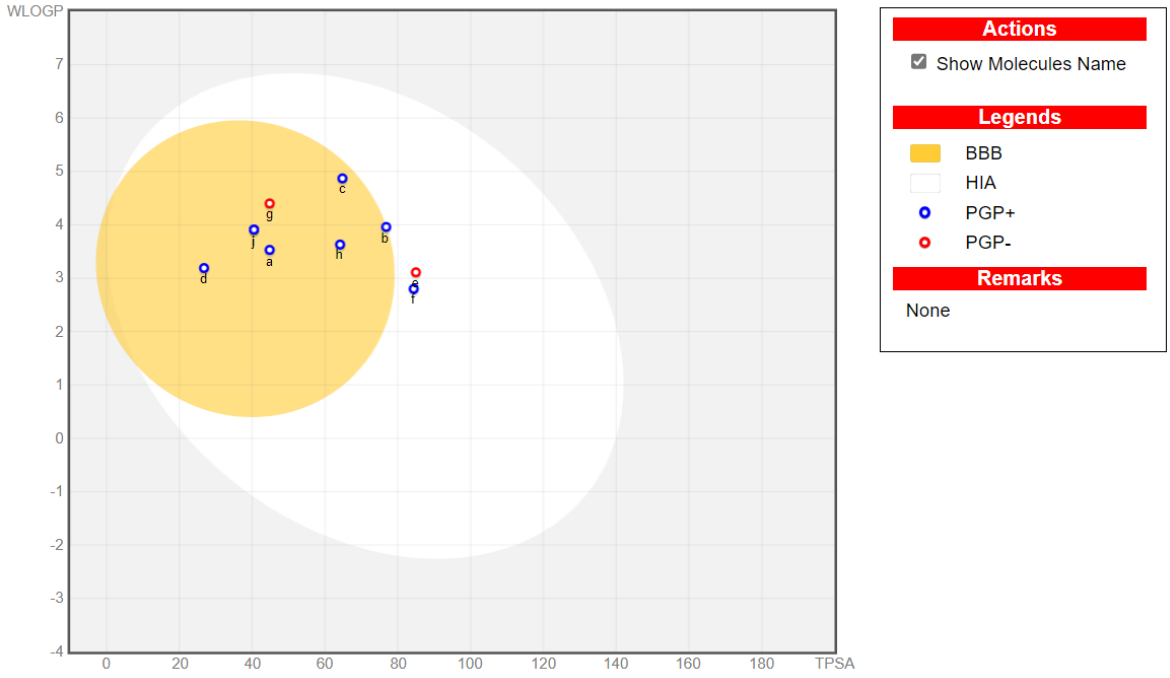


Figure 11. The BOILED-Egg model of some drug compounds

CONCLUSION

As a result of the study, molecular docking and ADME studies of some atypical antipsychotic molecules were performed on 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}, which are indicated as prominent receptors in psychotic disorders. Especially when the dock scores of Lurasidone (**e**) were examined, it was perceived to have the highest affinity for the mentioned receptors. However, when the poses and interaction types were examined, it was revealed that Risperidone (**h**) for 5-HT_{1A}, Paliperidone (**f**) for 5-HT_{2A}, and Brexpiprazole (**b**) for 5-HT_{2C} may have higher affinity. Considering ADME predictions, all compounds (**a**-**j**) had good pharmacokinetic profiles, but Lurasidone (**e**) was found to have poorer druglikeness properties and have poorer BBB crossing. It was observed that all drug molecules fully complied with the Lipinski, Egan, and Veber rules, and especially all drug compounds except Lurasidone (**e**) complied with the Muegge rules. Considering the calculated Ki values, it was predicted that the selected atypical antipsychotics would have nanomolar effects on 5-HT_{1A} and picomolar effects on 5-HT_{2A} and 5-HT_{2C}. In light of the data in this study, it seems that the use of Paliperidone (**f**) and Risperidone (**h**) may be more valuable, especially in the treatment of psychotic patients such as schizophrenia.

AUTHOR CONTRIBUTION STATEMENT

Writing-original draft, Methodology, Investigation, Formal analysis, Software, Conceptualization, Resources, Writing-review & editing, Supervision (H.U).

CONFLICT OF INTEREST

The author declared that there is no conflict of interest.

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