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Research Article

Insilico and Pharmacoknetic of Piperazine Sulfonyl Amine Derivatives

Design and In-silico Molecular Docking of NMDA NR2B Receptor Antagonist and Pharmacokinetic Prediction of Some Piperazine Sulfonyl Amine Derivatives for Alzheimer's Disease

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Abstract: Alzheimer's disease is a rare and progressive neurologic disease caused by degeneration of neurons within the brain that causes the brain to shrink (atrophy) and brain cells to die. In the US, approximately 5.5 million people are affected, and the prevalence worldwide is estimated to be as high as 24 million. Treatment is available to reduce the symptoms but no permanent cure. NMDA receptors play a crucial role in the treatment of Alzheimer's. Our aim and objective of the present work are to design some piperazine sulfonyl amine derivatives for treating Alzheimer's disease. To achieve this objective, we have docked the designed ligands with NMDA receptors. In our study, we have designed some piperazine sulfonyl amine derivatives, which were then subjected to virtual screening. The three-dimensional crystal structure of the selected protein NMDA receptor subunit NR2B (PDB Id: 3JPW) was retrieved from the RCSB Protein Data Bank (PDB). The ligands that showed low binding energy were further predicted for pharmacokinetic properties, and Lipinski's rule of 5 and the results are discussed. The final 19 compounds were used to develop a pharmacophore. The finalized 19 compounds were subjected to various in silico screening processes like drug-likeness, ADME properties and toxicity prediction. All 19 compounds exhibited good draggability nature, while ligands SE-B-15 and SE-B-12 were carcinogenic and SE-E-2 and SE-E-13 were prone to cause immunotoxicity. Ligands SE – C – 13 and SE – B – 2 exhibited good docking scores and best pharmacokinetic properties.

Keywords: Alzheimer's disease, N-methyl d-aspartate (NMDA) receptor, piperazine sulfonyl amine derivatives, Molecular docking, Pharmacokinetics, toxicology prediction.

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1. INTRODUCTION

Alzheimer's disease is the leading cause of dementia, characterized by a decline in thinking and independence in daily activities.[1] In the US, approximately 5.5 million people are affected, and the prevalence worldwide is estimated to be as high as 24 million. The exact origin of AD is ambiguous and combinatorial reasons such as genetic, lifestyle, and environmental factors are involved in the onset and progression of the disease. Formation of toxic amyloid beta (Aβ) protein in the brain, tau protein hyperphosphorylation and aggregation, bio metals dysfunction (ions; copper, iron, and zinc), alteration of calcium homeostasis, inflammation and oxidative stress due to generation of reactive oxygen species (ROS), and deficits in the cholinergic transmission have been considered as the leading causes of AD. Although several single-factor theories have been suggested for AD, no one led to a definite treatment. Even more recent pathological hallmarks of AD related to the accumulation of neurofibrillary tangles and amyloid plaques have failed in clinical trials. Up to now, only temporary symptomatic relief has been obtained from FDA-approved anti-cholinesterase (ChE) drugs via improving the cholinergic neurotransmitter systems. There are currently only two classes of approved Alzheimer's drugs: cholinesterase inhibitors and NMDA antagonists, both of which treat symptoms but do not cure or prevent the disease.[2-4] NMDARs are glutamate-gated ion channels that play an essential role in neuronal communication.[5] NMDARs are tetrameric complexes composed of multiple homologous subunits. The composition of NMDAR subunits is flexible, resulting in a large number of receptor subtypes. Because each receptor subtype has distinct biophysical, pharmacological, and signaling properties, determining whether individual subtypes perform specific functions in the CNS in both normal and pathological conditions is critical. In this study, we developed some piperazine sulfonyl amine derivatives that target the NMDA receptor to treat Alzheimer's disease. [6,7]

2. MATERIALS AND METHODS

Software, tools, and web servers used in the present study are Chemsketch, Schrodinger suit, and Swiss ADME. This study used a PC with Intel CORE i3-7100U CPU @ 2.40 GHz processor and 4 GB RAM running Windows 10 Operating System.

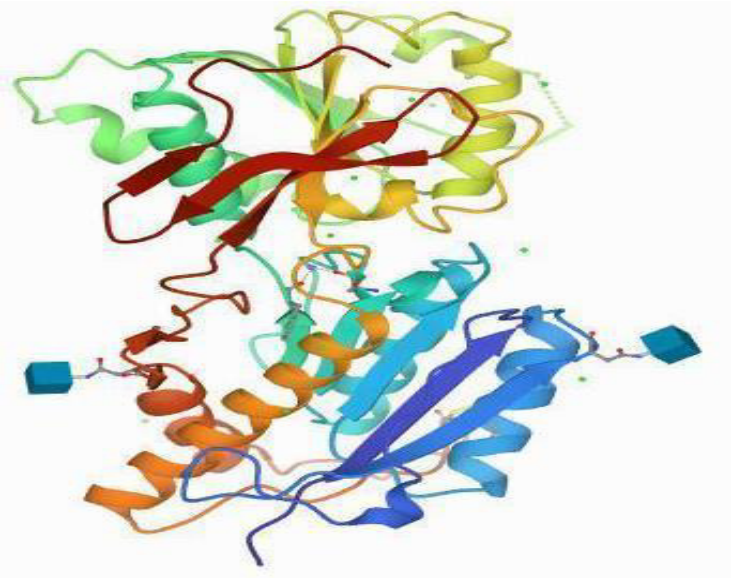

Fig 1: Structure of NMDA receptor subunit NR2B (3JPW)

2.1 Molecular Docking Studies

2.1.1 In-Silico Molecular Docking

A total of 150 designed ligands were drawn using ACD Labs ChemSketch, and further, they were saved in mol format, and the designed ligands were prepared using Ligprep. The target proteins were obtained in their 3D forms from the RCSB PDB. The designed piperazine sulfonyl amine binding affinities as ligand molecules to the selected protein target were evaluated.[8,9]

2.1.2 Therapeutic Target Identification

The first step of the methodology included a collection of the receptor protein. The subunit N-methyl-D-aspartate receptor subtype 2B (NR2B) is the chief excitatory neurotransmitter receptor in the mammalian brain. This allows for a transmembrane ion flow through the receptor to increase the neuron's action potential. This characteristic makes the synapsis among these neurons the central memory storage unit and associates them with learning and memory. As the structure of NMDA receptors in humans is unavailable, the structure of NMDAR in *Rattusnorvegicus* (brown rat) has been used for this work. The structure of NMDA receptor subunit NR2B (PDB id: 3JPW) was retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB).[10]

2.1.3 Active Site Prediction

Site Map was used with the default settings to identify ligand-binding sites for the selected proteins. The only difference was that six sites were chosen instead of the default setting of 5 sites for Site Map's site-point group reporting. The choice was made to improve the chances of finding more ligand binding sites, which were referred to as site-point groups in the SiteMap software component. The top-ranked site was used to generate a grid. All ligands were first subjected to high throughput virtual screening (HTVS), then

standard precision (SP), and finally extra precision (XP) docking. These three docking modes were applied in this order to all docking in this project. The first docking mode used to reduce the number of intermediate conformations throughout the docking funnel was HTVS docking. The SP mode was used to screen ligands with acceptable HTVS Glide scores as determined by the user. XP mode was created to screen for false positives and active compounds that could bind to a specific conformation of the receptor using top-scoring ligand poses.[11-18]

2.2 Drug Likeness Properties and Toxicity

Swiss ADME (http://www. swissadme.ch/) was used to make this prediction.[18] Lipinski's oral drug-likeness properties were predicted using the following parameters: I Molecular weight (500 Daltons), ii) the number of hydrogen bond donors (5), iii) the number of hydrogen bond acceptors (10), iv) Log P (5) and v) Molecular refractivity (140).[20-21] The toxicity properties of ligands were evaluated using the ProtoxII web server (https://tox-new.charite.de/protox II/). All of the ligands' pharmacokinetic properties were predicted.[22]

3. RESULTS AND DISCUSSION

All 150 ligands were subjected to molecular docking through three phases, viz. high throughput virtual screening (HTVS) docking initially, followed by standard precision (SP) and then extra precision (XP) docking. The initial screening was done in the first and second phases, using high throughput virtual screening (HTVS) and standard precision (SP) docking to eliminate any false results. We have chosen 90 ligands for the third phase, that is, extra precision (XP) docking, and finally, 19 ligands (in Table. No:1) with good docking scores were used for further computational studies. From work, the designed piperazine sulfonyl amine derivatives have shown promising activity against NMDA receptor subunit NR2B. The 2D interaction diagram shows significant interaction with receptor residues in the present study. Out of the designed compounds, SE – C - 13 had the best binding conformation with a g Score of – 8.145 kcal/mol, followed by SE – B – 2, SE – B – 8, and SE – B – 12 with -7.523, -7.246 and -7.166 respectively (Table No. 1). Lesser the binding energy, the greater the binding efficiency, hence augmented inhibition. The compound SE – C - 13 interacted with 13 amino acid residues in the active site of the NRB2 with two hydrogen bonds with amino acid residues ASP 58 (Figures 5 and 6). More significant the number of hydrogen bonds, the higher the binding efficiency. Despite a higher number of hydrogen bonds(four), ligand SE – B - 2 showed less docking score. Figure 7 denotes the 3D image active site cleft of the NR2B with SE – B - 2 bound to it. Ligand SE – B – 8 AND SE – B – 12 3c have interacted with 15 and 10 amino acids in the active site, respectively.[23]

Table. No: 1 - The designed ligands' docking scores (Glide Scores).

Title	Smile	docking score	glide evdw	glide ecoul	glide energy	glide e internal	glide e model	XP H Bond
SE - C - 13	O=S(=O)(Nc1ccc(cc1O)C(=O)O)N1CCN(Cc2ccccc2)CC1	-8.145	-27.373	-13.124	-40.497	3.980	-56.865	-0.970
SE - B - 2	O=S(=O)(Nc1ccccc1O)N1CCN(Cc2ccc(O)cc2)CC1	-7.523	-26.086	-16.640	-42.726	9.302	-51.284	-2.800
SE - B - 8	O=S(=O)(Nc1cccc(O)c1)N1CCN(Cc2ccc(O)cc2)CC1	-7.246	-27.615	-12.954	-40.569	6.140	-48.235	-2.800
SE - B - 12	O=S(=O)(Nc1ccc(C(=O)O)c(O)c1)N1CCN(Cc2ccc(O)cc2)CC1	-7.166	-27.458	-10.598	-38.056	4.715	-42.866	-1.274
SE - G - 2	O=S(=O)(Nc1ccc(cc1O)C(=O)O)N1CCN(Cc2ccc(O)cc2)CC1	-6.197	-30.925	-9.522	-40.447	8.515	-48.835	-1.951
SE - F - 8	O=S(=O)(NC(Cc1ccccc1O)C(=O)O)N1CCN(Cc2ccc(O)cc2)CC1	-5.514	-30.158	-7.587	-37.745	8.101	-41.273	-0.171
SE - B - 11	O=S(=O)(Nc1nc2ccccc2[NH]1)N1CCN(Cc2ccc(O)cc2)CC1	-5.400	-29.596	-11.820	-41.416	10.545	-52.303	-2.294
SE - A - 8	O=S(=O)(NCc1nc2ccccc2[NH]1)N1CCN(Cc2ccc(O)cc2)CC1	-5.327	-24.827	-9.113	-33.940	4.070	-41.405	-1.506
SE - B - 14	O=S(=O)(Nc1nc2cc(O)ccc2[NH]1)N1CCN(Cc2ccc(O)cc2)CC1	-5.234	-31.122	-10.278	-41.400	10.809	-47.480	-1.330
SE - D - 2	O=S(=O)(Nc1nc2ccccc2n1C)N1CCN(Cc2ccc(O)cc2)CC1	-5.231	-26.221	-12.712	-38.933	9.421	-50.456	-1.890
SE - B - 3	O=S(=O)(NC(Cc1cccc(O)c1)C(=O)O)N1CCN(Cc2ccc(C)cc2)CC1	-5.229	-32.187	-13.893	-46.080	7.429	-57.214	-0.925
SE - D - 8	O=S(=O)(NCc1nc2ccccc2[NH]1)N1CCN(Cc2ccc(C)cc2)CC1	-5.224	-32.578	-7.733	-40.311	3.929	-50.426	-1.890
SE - B - 15	O=S(=O)(Nc1ccccc1O)N1CCN(Cc2ccc(OC)cc2)CC1	-5.221	-32.987	-5.662	-38.650	4.432	-47.899	-0.700
SE - B - 7	O=S(=O)(Nc1ccc(cc1O)C(=O)O)N1CCN(Cc2ccc(OC)cc2)CC1	-5.176	-29.154	-9.570	-38.724	2.012	-47.078	-1.180
SE - B - 13	O=S(=O)(NC(Cc1ccccc1O)C(=O)O)N1CCN(Cc2ccc(OC)cc2)CC1	-5.136	-32.091	-10.754	-42.845	4.460	-54.728	-1.119
SE - E - 13	O=S(=O)(Nc1ccccc1O)N1CCN(Cc2ccc(OC)c(OC)c2)CC1	-5.069	-36.615	-7.734	-44.350	2.434	-57.499	-0.700
SE - D - 11	O=S(=O)(NCc1nc2ccccc2[NH]1)N1CCN(Cc2ccc(OC)c(OC)c2)CC1	-5.065	-28.783	-12.686	-41.469	20.733	-47.389	-1.384
SE - C - 9	O=S(=O)(Nc1ccc(cc1O)C(=O)O)N1CCN(CC1)C(=O)c1ccccc1	-5.022	-30.610	-9.947	-40.557	5.814	-53.626	-1.554
SE - E - 2	O=S(=O)(Nc1ccccc1O)N1CCN(CC1)C(=O)c1ccc(O)cc1	-5.008	-33.921	-9.555	-43.477	6.803	-52.484	-1.890

Table 1 Docking score and other metrics by Glide (Schrodinger Suit) to success the binding affinity of the designed ligands with NMDA NR2B receptor.

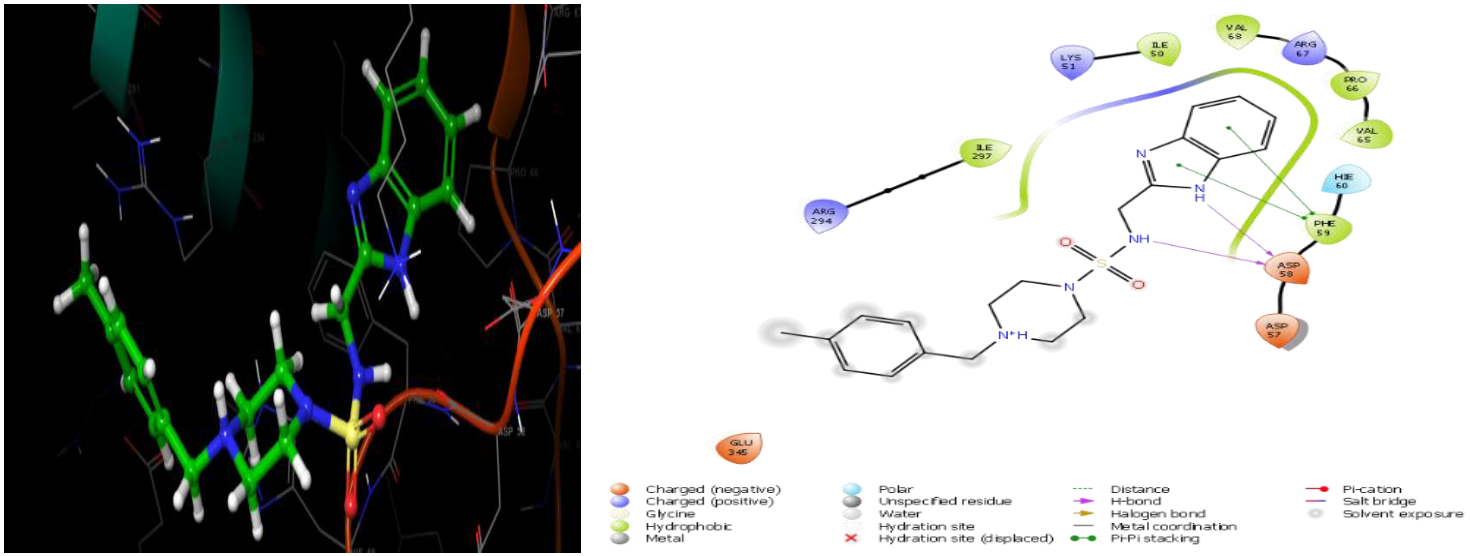

Fig 2: 2D and 3D diagram of compound SE – C - 13 showing interactions with the binding site at best pose

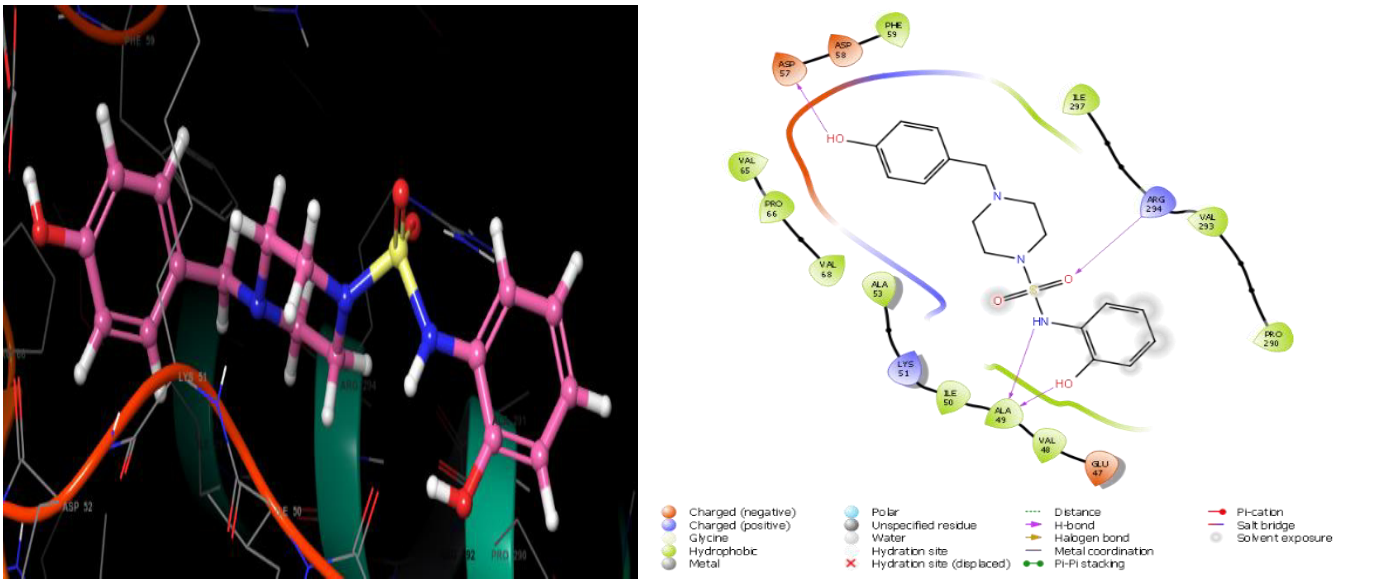

Fig 3: 2D and 3D diagram of compound SE – B - 2 showing interactions with the binding site at best pose

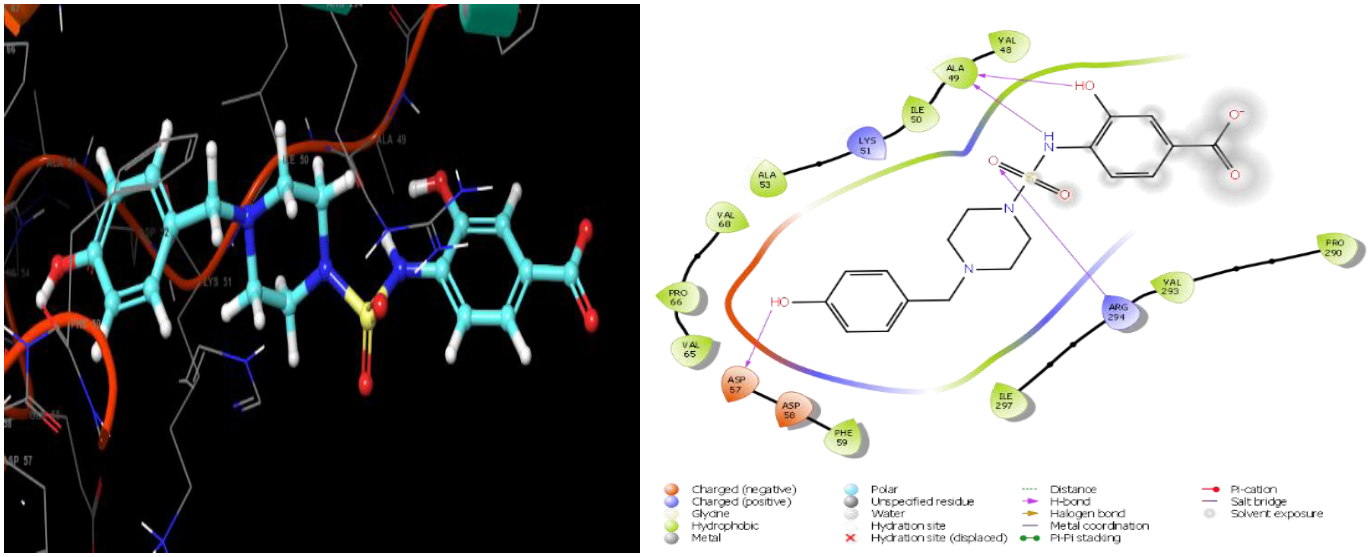

Fig 4: 2D and 3D diagram of compound SE – B - 8 showing interactions with the binding site at best pose

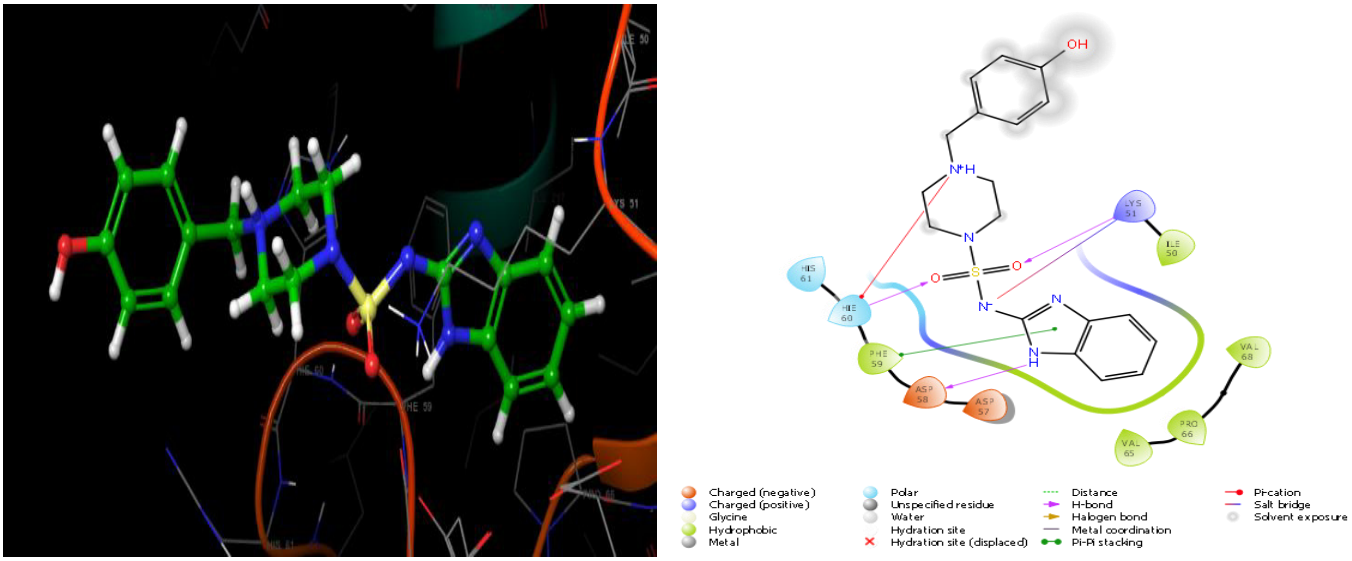

Fig 5: 2D and 3D diagram interactions with the binding site at best pose

3.1 Drug Likeness Properties and Toxicity

All the designed derivatives satisfied their properties according to Lipinski's rule of 5 (Table No.2). Lipinski rule is considered one of the essential criteria to predict the oral drug-likeness of a drug. None of the derivatives have violated the Lipinski rule. To enhance the predictions of drug-likeness, Ghose, Veber, Egan, and Muegge filters have been used in the study. All the designs obeyed Lipinski, Veber, Egan, and Muegge, whereas compounds SE – B -7, SE – B -8, SE – B - 11, and SE – F 8 did not satisfy Gosh filters. Out of all the designed derivatives, SE - E – 2, SE - E – 13, SE - C – 13, SE - D – 2, and SE - B - 15 showed good oral absorption, while SE - D – 11, SE - G – 2, SE - B – 2, SE - B – 12, SE - B – 13, SE - C – 9, SE - B – 3, and SE - B - 14 had moderate oral absorption and SE - F – 8, SE - B – 11, SE - D – 8, SE - A – 8, SE - B – 7, and SE - B - 8 exhibited poor oral absorption. Whereas all the compounds were shown to cross the blood-brain barrier.[24-27]

Table. No: 2 – Draggability of the designed ligands.

S.No	Ligand	Lipinski (No. of Violations)	Ghose	Egan	Verber	Muegge	Bioavailability
1	SE - A - 8	Yes (0)	Yes	Yes	Yes	Yes	0.55
2	SE - B - 2	Yes (0)	Yes	Yes	Yes	Yes	0.55
3	SE - B - 3	Yes (0)	Yes	Yes	Yes	Yes	0.55
4	SE - B - 7	Yes (0)	Yes	No	Yes	Yes	0.55
5	SE - B - 8	Yes (0)	Yes	No	Yes	Yes	0.55
6	SE - B - 11	Yes (0)	Yes	No	Yes	Yes	0.55
7	SE - B - 12	Yes (0)	Yes	Yes	Yes	Yes	0.55
8	SE - B - 13	Yes (0)	Yes	Yes	Yes	Yes	0.55
9	SE - B - 14	Yes (0)	Yes	Yes	Yes	Yes	0.55
10	SE - B - 15	Yes (0)	Yes	Yes	Yes	Yes	0.55
11	SE - C - 9	Yes (0)	Yes	Yes	Yes	Yes	0.55
12	SE - C - 13	Yes (0)	Yes	Yes	Yes	Yes	0.55
13	SE - D - 2	Yes (0)	Yes	Yes	Yes	Yes	0.55
14	SE - D - 8	Yes (0)	Yes	Yes	Yes	Yes	0.55
15	SE - D - 11	Yes (0)	Yes	Yes	Yes	Yes	0.55
16	SE - E - 2	Yes (0)	Yes	Yes	Yes	Yes	0.55
17	SE - E - 13	Yes (0)	Yes	Yes	Yes	Yes	0.55
18	SE - F - 8	Yes (0)	Yes	No	Yes	Yes	0.55
19	SE - G - 2	Yes (0)	Yes	Yes	Yes	Yes	0.55

Table 2 Various drug ability parameters such as Lipinski, Ghose, Egan, Verber, and Muegge were predicted, and all the finalized ligands were found to have good draggability and good bioavailability scores.

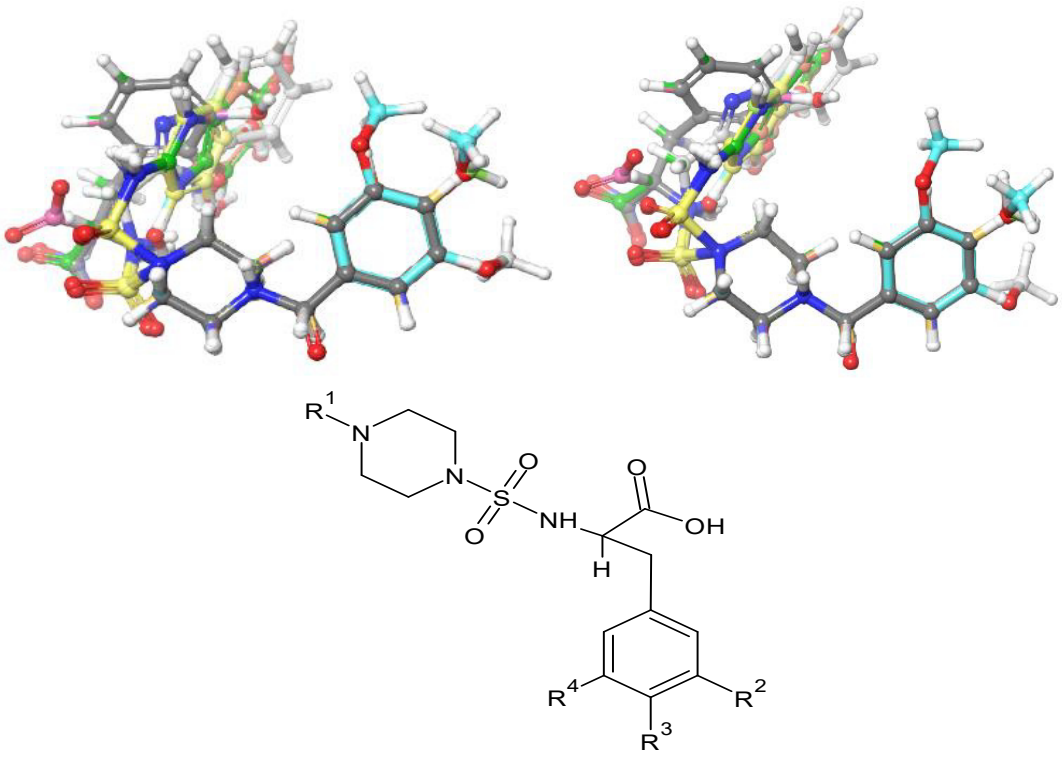

Fig 6: The Pharmacophore generated by aligning the best 19 ligands selected from XP docking

3.2 ADME Prediction

ADME of the selected drugs was done using QikProp in Schrodinger suit and ADMET Lab, an online server. Blood-Brain Barrier (BBB) penetration, HOA (Human Oral Absorption), solubility parameters, metabolism, and excretion were estimated. Currently, many approaches exist to assess a compound drug-likeness based on topological descriptors, fingerprints of molecular drug-likeness structure keys, clogP and molecular weight. Based on the predicted values, all the selected ligands can penetrate BBB, the expected site of action, and have good oral absorption.[28-31]

Table. No: 3 – ADME properties of the selected ligands.

S.No	Ligand	Absorption		Distribution	Metabolism	Excretion
		Solubility QPlogS	% Human Oral Absorption	BBB perm. QPlogBB		Total Clearance (Log mL/min/kg)
1	SE - B - 2	-1.931	74.553	-0.460	CYP3A4-inhibitor, CYP3A4-substrate, CYP2D6-inhibitor,	1.039
2	SE - A - 8	-2.725	44.140	-0.987	CYP3A4-substrate, CYP2D6-inhibitor,	0.348
3	SE - B - 3	-2.014	70.378	-0.666	CYP3A4-inhibitor, CYP3A4-substrate, CYP2D6-inhibitor,	1.094
4	SE - B - 7	-2.803	33.798	-1.597	CYP2D6-inhibitor,	0.542
5	SE - B - 8	-2.588	31.061	-1.593	CYP2D6-inhibitor,	1.116
6	SE - B - 11	-3.065	52.085	-1.319	CYP3A4-inhibitor, CYP2C9-substrate, CYP2D6-inhibitor,	1.172
7	SE - B - 12	-2.414	74.236	-0.534	CYP3A4-inhibitor, CYP2D6-inhibitor,	1.555
8	SE - B - 13	-1.843	73.710	-0.550	CYP3A4-inhibitor, CYP2D6-inhibitor,	1.491
9	SE - B - 14	-2.282	61.158	-1.139	CYP3A4-inhibitor, CYP2D6-inhibitor,	1.498
10	SE - G - 2	-3.132	77.979	-1.187	CYP3A4-inhibitor,	1.216
11	SE - F - 8	-3.246	58.501	-1.723		1.09
12	SE - E - 2	-2.497	89.415	-0.026	CYP1A2-substrate, CYP3A4-inhibitor, CYP3A4-substrate, CYP2C9-substrate, CYP2C19-substrate, CYP2D6-inhibitor, CYP2D6-substrate	1.41
13	SE - E - 13	-2.341	88.395	-0.131	CYP1A2-substrate, CYP3A4-inhibitor, CYP3A4-substrate, CYP2C19-substrate, CYP2D6-inhibitor, CYP2D6-substrate	1.53
14	SE - D -11	-3.451	78.653	-0.787	CYP3A4-inhibitor, CYP3A4-substrate, CYP2C9-substrate, CYP2D6-inhibitor, CYP2D6-substrate	1.17
15	SE - D - 8	-2.890	44.449	-1.090	CYP3A4-substrate, CYP2C19-substrate, CYP2D6-inhibitor, CYP2D6-substrate	1.29
16	SE - D - 2	-2.253	87.992	0.040	CYP1A2-substrate, CYP3A4-inhibitor, CYP3A4-substrate, CYP2C9-substrate, CYP2C19-substrate, CYP2D6-inhibitor, CYP2D6-substrate	1.553
17	SE - C- 13	-2.379	88.068	0.000	CYP1A2-substrate, CYP3A4-inhibitor, CYP3A4-substrate, CYP2C19-inhibitor, CYP2C19-substrate, CYP2D6-inhibitor,	1.794
18	SE - C - 9	-3.490	73.019	-0.924	CYP3A4-inhibitor, CYP2C9-substrate, CYP2D6-inhibitor,	1.286
19	SE - B - 15	-2.576	81.115	-0.217	CYP1A2-substrate, CYP3A4-inhibitor, CYP3A4-substrate, CYP2C19-substrate, CYP2D6-inhibitor,	1.604

Table 3 ADME parameters solubility, penetration, human oral absorption, blood-brain barrier, metabolism, and excretion were predicted for the selected compounds, and all the ligands were found to cross BBB and have good oral absorption.

3.3 Toxicity Prediction

Structure-based design is now fairly routine, but many potential drugs fail to reach the clinic because of ADME/Tox liabilities. Toxicity risks (Hepatotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity, and Cytotoxicity) of selected compounds were calculated by the Protox II web server, and their results are shown in Table 4. The present study studied drug-likeness properties and toxicity, revealing that ligands SE-B-15 and SE-B-12 have carcinogenicity and SE-E-2 and SE-E-13 have immunotoxicity. All other ligands were indicated with no Toxicity risks.[32-35]

Table. No: 4 - Predicted toxicity properties generated by Swiss ADME

S.No	Ligand	Predicted Toxicity Class	Predicted LD 50 (mg/kg)	Hepato toxicity	Carcino genicity	Immuno toxicity	Muta genicity	Cyto toxicity
1	SE - A - 8	4	1800	Inactive	Inactive	Inactive	Inactive	Inactive
2	SE - B - 2	5	2300	Inactive	Inactive	Inactive	Inactive	Inactive
3	SE - B - 3	5	2300	Inactive	Inactive	Inactive	Inactive	Inactive
4	SE - B - 7	4	1000	Inactive	Inactive	Inactive	Inactive	Inactive
5	SE - B - 8	4	1800	Inactive	Inactive	Inactive	Inactive	Inactive
6	SE – B-11	5	2500	Inactive	Inactive	Inactive	Inactive	Inactive
7	SE - B - 12	3	245	Inactive	Active	Inactive	Inactive	Inactive
8	SE - B - 13	4	1000	Inactive	Inactive	Inactive	Inactive	Inactive
9	SE - B - 14	4	1200	Inactive	Inactive	Inactive	Inactive	Inactive
10	SE - B - 15	4	330	Inactive	Active	Inactive	Inactive	Inactive
11	SE - C - 9	4	2000	Inactive	Inactive	Inactive	Inactive	Inactive
12	SE - C - 13	4	1000	Inactive	Inactive	Inactive	Inactive	Inactive
13	SE - D - 2	4	750	Inactive	Inactive	Inactive	Inactive	Inactive
14	SE - D - 8	4	1000	Inactive	Inactive	Inactive	Inactive	Inactive
15	SE - D - 11	4	800	Inactive	Inactive	Inactive	Inactive	Inactive
16	SE - E - 2	4	310	Inactive	Inactive	Active	Inactive	Inactive
17	SE - E - 13	4	740	Inactive	Inactive	Active	Inactive	Inactive
18	SE - F - 8	4	1800	Inactive	Inactive	Inactive	Inactive	Inactive
19	SE - G - 2	4	1800	Inactive	Inactive	Inactive	Inactive	Inactive

- Class I: fatal if swallowed (LD50 ≤ 5)
- Class II: fatal if swallowed (5 < LD50 ≤ 50)
- Class III: toxic if swallowed (50 < LD50 ≤ 300)
- Class IV: harmful if swallowed (300 < LD50 ≤ 2000)
- Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000)
- Class VI: non-toxic (LD50 > 5000)

4. CONCLUSION

Today treating Alzheimer's is an excellent task for physicians, leading to research on developing lead molecules and precursors. The present research aimed to discover piperazine sulfonyl amine-containing compounds that could potentially treat Alzheimer's by acting through NMDA receptor subunit NR2B (PDB Id: 3JPW). One hundred fifty compounds were designed and subjected to virtual screening using three phases to take 19 potent compounds. First, the active site of the DNA gyrase was determined using the Site Map. Then, molecular docking was done using Glide, and the interactions between the ligands and protein were predicted. Ligands SE – C – 13 and SE – B – 2 with -8.145 and -7.523 as docking scores were very effective. Pharmacokinetics and toxicity properties of designed compounds were studied and reported. On the whole, ligands SE – C – 13 and SE – B – 2 of the designed pyrazole derivatives were very potent against NMDA receptors and showed better drug-likeness and pharmacokinetic properties. Hence one could prevent infections using these. Furthermore, this research could act as a road map for discovering compounds for Alzheimer's. Thus, in-silico studies provided rapid and comprehensive insights into results in screening compounds.

5. AUTHORS CONTRIBUTION STATEMENT

Mr.Sachin Kumar gathered the data and performed complete docking studies. Dr.A. ElphinePrabahar and Mr. Rajesh Kumar Sharma analyzed the data and helped in framing the manuscript.

6. LIMITATION AND FUTURE SCOPE

The drug discovery informatics market is growing every year and may continue expanding. On the other hand, the need for drug therapy for Alzheimer's disease is also mounting. NMDA receptors play a crucial role in the treatment of Alzheimer's. So, future research on this topic will open new horizons in the treatment of Alzheimer.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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