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Research Article

EVALUATION OF ANTAGONIST ACTIVITY OF IFENPRODIL AND THEIR ANALOGOUS AGAINST GLUN1/GLUN2B USING *IN SILICO* MOLECULAR DOCKING AND ABSORPTION-DISTRIBUTION-METABOLISM-EXCRETION TOXICITY

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ABSTRACT

Objectives: High Ca^{2+} permeability represents a characteristic feature of N-methyl-D-aspartate (NMDA) receptors that in extreme amounts affects physiological functions such as reduced neural development, synaptic plasticity, and learning and memory. The study aims to elucidate the potent inhibitory ifenprodil and their eleven analogues, retrieved from the PubChem database, which act as ligands to the target Glun1/GluN2B subunit of the NMDA receptor.

Methods: *In silico* methods such as molecular docking performed using AutoDock Vina and absorption-distribution-metabolism-excretion-toxicity (ADMET) were SwissADME and OSIRIS carried out to elucidate the potent antagonist ligand against the target.

Results: Molecular docking showed that six of the compounds had significant binding affinities (7.8–9.0 kcal/mol) for the target. The ADMET study revealed that three (PubChemID: 12613159, 12613162, and 6604117) of six compounds with good binding affinity obeyed Lipinski's rule of five.

Conclusion: This study revealed three good antagonists of GluN1/GluN2B, namely, 4- [(1R, 2R)-2-(4-benzylpiperidin-1-yl)-1- hydroxy propyl] phenol (A2), 4-[2-(4-benzylpiperidin-1-yl)-1-hydrooxypropyl] phenol hydrobromide (A4), and 4- [(1R, 2S)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol (A7) that can be further exploited for wet lab studies.

Keywords: Ifenprodil and analogous, molecular docking, Absorption-distribution-metabolism-excretion-toxicity, GluN1/GluN2B.

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INTRODUCTION

Ionotropic glutamate receptors are cationic Na^+, K^+, and Ca^{2+} channels that are divided into three subtypes based on preferential synthetic agonists as N-methyl-D-aspartate (NMDR), α-amino-3-hydroxy-5-methyl-4-isoxazo-le propionic acid, and kainite (structural analog of glutamate) [1-4]. Overload of Ca^{2+} ions in the cells causes secondary neurotoxic events [5,6] such as cerebral ischemia, epilepsy, Parkinson's disease, and amyotrophic lateral sclerosis (Alzheimer's). The NMDA receptor consists of four subunits, that form a heterotetramer [7]. In humans, seven subunits were identified, named GluN1, GluN2A-D, and GluN3A-D. since GluN3 subunits predominantly expressed in embryonic brain, thus functional NMDA receptor typically consists of two GluN1 and two GluN2 subunits [8-10]. Synaptic plasticity, network development, and information storage in the brain, critically dependent on these receptors [11-13].

The single subunit consists of four domains: The C terminal domain, the transmembrane domain, the ligand binding domain, and the N terminal domain (NTD). The NTD is located extracellularly far away from the ion channel pore for several non-competitive positive and negative allosteric modulators, including polyamines, ifenprodil, Zn^{2+}, NO, and protons [9,10]. Recent studies have shown that the ifenprodil binding site is located at the interface between GluN1 and GluN2B, as determined by X-ray crystal structure analysis [14-17]. Ifenprodil binding site has potential for the treatment of neurodegenerative and neurological diseases by acting as negative allosteric modulators of GluN2B NMDA receptors and could be used to treat depression, cerebral ischemia, stroke[18], Parkinson's, Alzheimer's, and Huntington's disease [19-24].

Given the foregoing, we chose ifenprodil and its analogous (Table 1) for docking studies with the GluN1/GlunN2B receptors ligand complex to model interactions. *In silico* studies have been conducted to elucidate the antagonist to GluN1/GluN2B. Molecular docking simulations were performed with reliable ligands to elucidate efficient compounds, followed by ADMT studies to study the toxicology of all ligands.

METHODS

Protein preparation

The crystal structure of GluN1/GluN2B is retrieved from the RCBS PDB (www.rcbs.org) (PDB ID: 5EWL) and optimized by removing existing ligands, water molecules, heteroatoms, and cofactors using the drug discovery studio. The missing atoms, bonds, charges, and polar hydrogen atoms are added through the AutoDock version 4.2 program at Scripps Research Institute [25] and subsequently saved in PDBQT format for docking studies. Dimensions are kept at X=64, Y=44, and Z=72 and Grid center X=−16.266951, Y=−14.836195, and Z=23.759171, as determined in the drug discovery studio.

Ligand preparation

The 3D structures of antagonist ifenprodil (3689) and their analogous (23615771, 12613158, 6455334, 12613162, 11771731, 11198145, 6604117, 60703, 660488, 9826324, and 3359) are retrieved from NCBI PubChem [26] in SDF format and thereafter converted into PDB format to create ligand binding groups using open Babel [27]. Further, processing of ligands, which includes setting of torsional bonds, steric hindrances, and proper bond orders to define binding sites using AutoDock tools [28,29].

ADME study and toxicity prediction

The most accept of drug development is the elucidation of pharmacologically active substances, as predicted by *in silico* ADMET (adsorption, distribution, metabolism, excretion, and toxicity) studies performed using Swiss ADME [30-32]. The OSIRIS property

explorer (https://www.organic-chemistry.org/prog/peo/), US evaluated toxicity prediction properties evaluated such as irritation, mutagenicity, tumorigenicity, and reproductive development toxicity.

RESULTS AND DISCUSSION

Docking results

All the ligands and their interactions with the bonding site of GluN1/GluN2B are explained and displayed in Table 2 and Figs. 1 and 2. All

Table 1: Accession ID, international union of pure and applied chemistry name, chemical formula of ifenprodil, and respective analogous

Compound	PubChem ID	IUPAC name	Formula
Ifenprodil	3689	4-[2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}NO_2$
A1	23615771	4-[2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol; (2R: 3R)-2,3-dihydroxybutanedoic acid	$C_{25}H_{33}N_{08}$
A2	12613159	4-[(1R,2R)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}N_{02}$
A3	6455334	(2S,3S,4S,5R,6S)-6-[4-[2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenoxy]-3,4,5-trihydroxyoxane-2-carboxylic acid	$C_{27}H_{35}N_{08}$
A4	12613162	4-[2-(4-benzylpiperidin-1-yl)-1-hydrooxypropyl] phenol; hydrobromide	$C_{21}H_{28}BrN_{02}$
A5	11771731	4-[(1S,2S)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	C21H27N$_{02}$
A6	11198145	4-[(1S,2R)-2-(4-benzylpiperidine-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}NO2$
A7	6604117	4-[(1R,2S)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}N_{02}$
A8	60703	1-(4-chlorophenyl)-2-[4[4 (4-flurophenyl) methyl] piperidin-1-yl] ethanol	$C_{20}H_{23}ClFNO$
A9	6604887	4-[(1R,2S)-3-(4-benzylpiperidin-1-yl]-1-hydroxy-2-methyl propyl] phenol	$C_{22}H29N_{02}$
A10	9826324	1-[(1S,2S)-1-hydroxy-1-(4-hydroxyphenol) propan-2-yl] 4-phenylpiperidin-4-ol; methane sulfonic acid, trihydrate	$C_{21}H_{35}NO_9S$
A11	3359	N, N'-bis[2-(10-methoxy-7H-pyrido[4,3-c] carbazole-2-ium-2-yl) ethyl] hexane-1,6-diamine	$C_{42}H_{46}N_6O_{2+2}$

*A1-11 are analogous of ifenprodil and ifenprodil as reference compound. IUPAC: International union of pure and applied chemistry (https://iupac.org/)

Table 2: The docking scores of the tittle compounds possessing best *in vitro* inhibition activity and their interactions with the active site of GluN1/GluN2B crystal structure (ID: 5EWL)

Compound	B.A. kcal/mol	H-bond	C-H bond	Electrostatic interactions		Hydrophobic interactions				Halogen	Unfavoured bond	Π- Π T-stand
				Π-cation	Π-anion	Π-sigma	Π-alkyl	Π-amide	Alkyl			
Ifenprodil	−7.8	HIS B 273 ILE A 238	HIS B 273	LYS B 143	GLU B 230	THR A 241	ALA B 227	-	-	-	-	-
A1	−7.7	HIS B 273 ILE A 238	-	LYS B 143 ARG B 287	GLU B 230	THR A 241	ALA B 227	-	-	-	-	-
A2	−7.8	ARG B 287	-	ARG B 287	ASP B 282	THR A 241	-	-	-	-	-	-
A3 (1)	−9.0	LE A 238 ALA A 240 LYS B 143 ILE A 238 ASP B 238	TYR A 237 GLU A 132	-	-	-	ILE A 238 ALA A 216	-	-	-	MET B 278	-
A3 (2)	−9.0	LYS B 143 ASP B 282	-	-	GLU A 132	LEU A 279	ALA A 216	-	-	-	ARG B 248 GLU A 132	-
A4	−8.2	PHE B 138 ILE B 136	ASP A 259 ASP A 259	-	ASP A 259	-	VAL A 128 LYS A 255	-	LYS A 255 ARG A 256	-	-	-
A5	−7.6	-	ARG B 287 GLU B 279	-	-	THR A 241	TYR A 237	GLY A 236	-	-	LYS B 143	-
A6	−7.5	-	-	ARG B 287	GLU B 230	-	ARG B 287	-	-	-	-	-
A7	−8.1	THR A 241 LYS B 143	-	-	--	THR A 241	VAL B 286 ARG B 287	-	-	-	-	-
A8	−7.8	LYS B 143 THR B 144	-	LYS B 143 LYS B 143	GLU B 230 ASP B 282	-	ALA B 227	-	VAL B 286	PHE B 142 MET B 278 ASP B 282	-	-
A9	−7.6	ASP B 282 GLU B 279	-	ARG B 287	-	THR A 241		-	ILE A 238	-	LYS B 143	-
A10	−8.2	ALA A 240 HIS B 273 GLU A 132	GLU A 132 THR A 241	ARG B 287	-	THR A 241	-	GLY A 236		-	-	-
A11	−7.2	HIS B 13 VAL B 88	SER B 206 PRO B 48	-	-	-	-	ASP B 90	PRO B 53	-	-	HIS B 13

*A3 ligand exhibited two poses of same docking scores. B.A: Binding affinity, H bond: hydrogen bond, C-H: Carbon hydrogen bond, pi(Π)-cation, pi(Π)-anion, pi(Π)-sigma, pi(Π)-amide, pi(Π)-alkyl, pi(Π)-pi(Π)-T-Stand

the compounds (12 ligands) A1, A2, A3 (1), A3 (2), A4, A5, A6, A7, A8, A9, A10, and A11 were selected based on their remarkable docking scores of −7.7, −7.8, −9.0, −9.0, −8.2, −7.6, −7.5, −8.1, −7.8, −7.6, −8.2, and −7.2 kcal/mol, respectively, for 5EWL compared to the reference compound's ifenprodil of −7.8 kcal/mol (Table 2).

The reference compound ifenprodil forms a conventional hydrogen bond with HIS B273 and ILE A238 and a single carbon hydrogen bond with HIS B273. Electrostatic interactions with LYS B143 (Π-Cation), GLU B230 (Π-Anion) and hydrophobic interactions with THR A241 (Π-Sigma) and ALA B227 (Π-Alkyl). A1 forms conventional hydrogen bonds with HIS B273 and ILE A238. Carbon-hydrogen bonds form between TYR A237 and GLU A132. Electrostatic interactions with LYS B143, ARG B287 (Π-Cation); GLU B230 (Π-Anion) and hydrophobic interactions with THR A241 (Π-Sigma); ALA B227 (Π-Alkyl). A2 forms a conventional hydrogen bond with ARG B287. Electrostatic interactions with ARG B287 (Π-Cation); THR A282 (Π-Anion) and hydrophobic interactions with THR A241 (Π-Sigma); VAL B286, ARG B287 (Π-Alkyl).

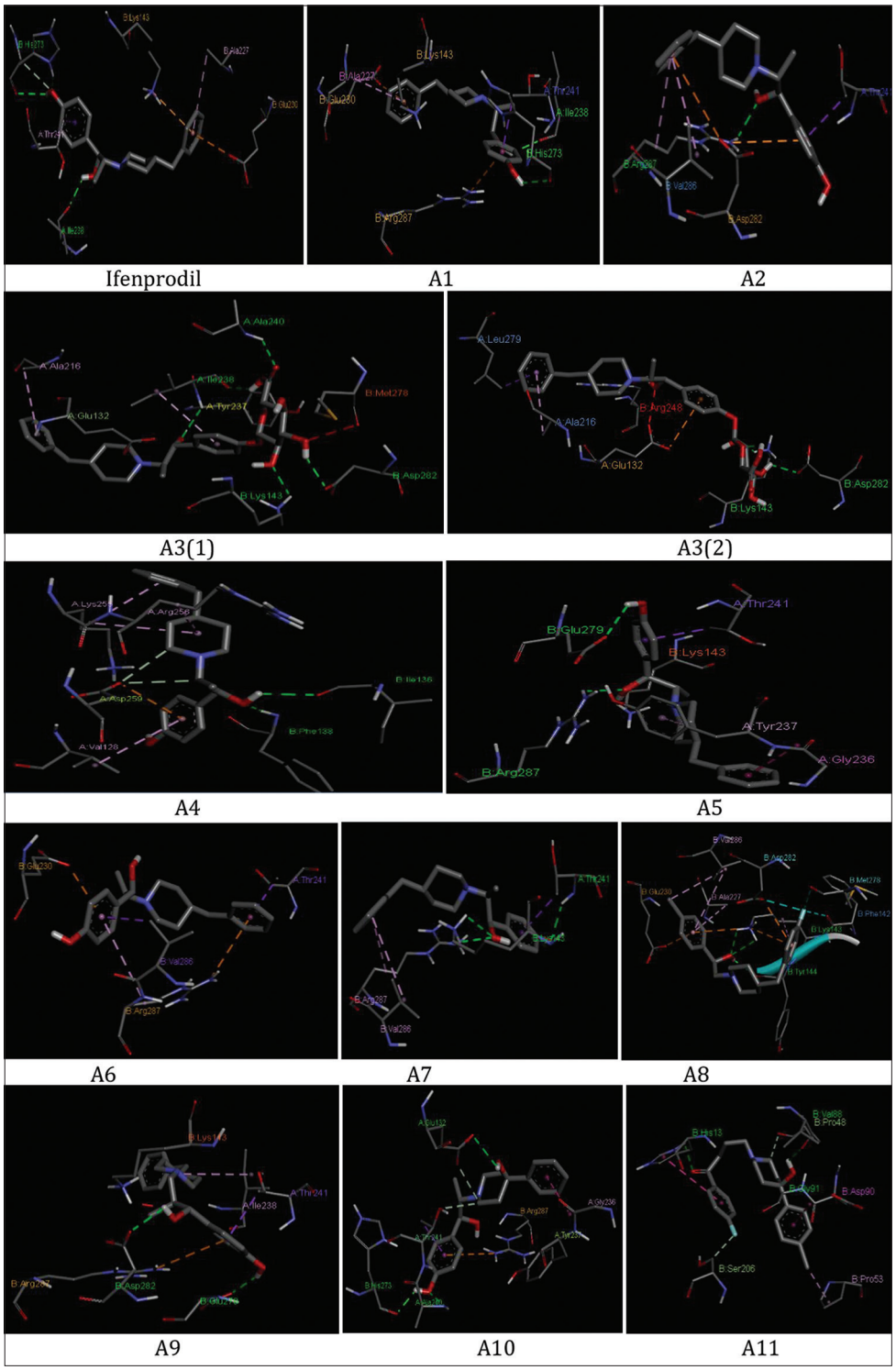

Fig. 1: Compound Ifenprodil, A1, A2, A3(1), A3(2), A4, A5, A6, A7, A8, A9, A10, and A11 and their 3D interactions with the active site of GluN1/GluN2B. *A3 ligand exhibited two poses of same docking score.

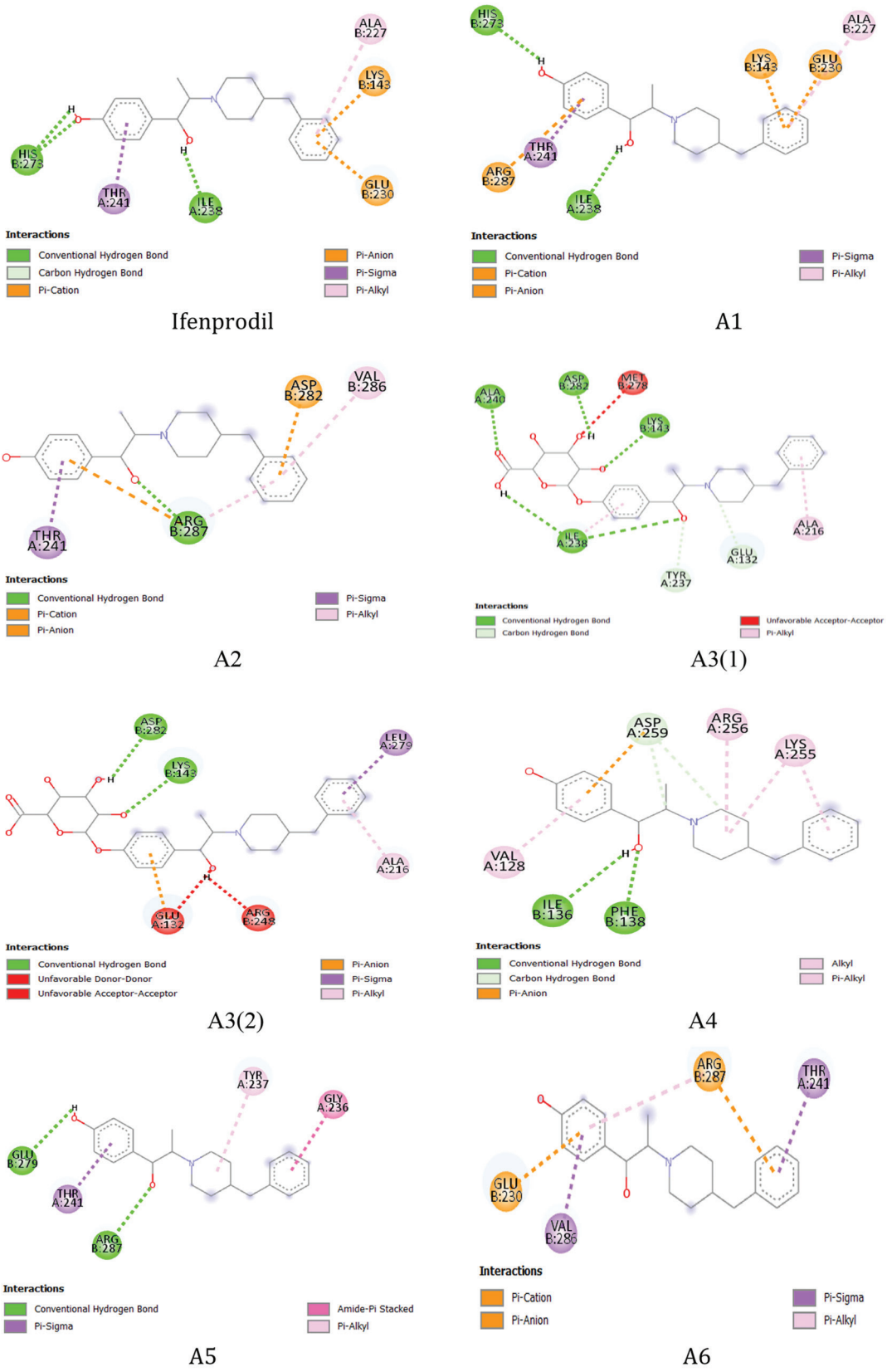

Fig. 2: ***(Continued)***

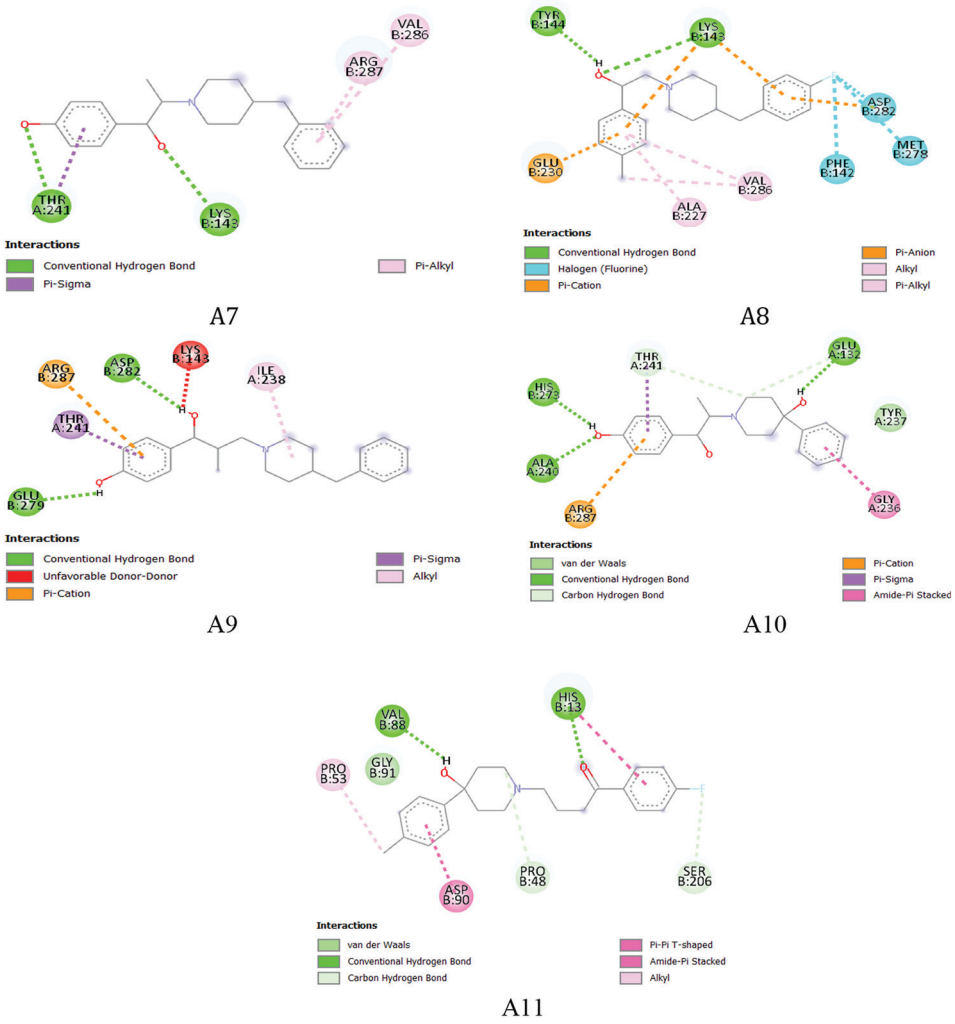

Fig. 2: Compound ifenprodil, A1, A2, A3(1), A3(2), A4, A5, A6, A7, A8, A9, A10, and A11 and their 2D interactions with the active site of GluN1/GluN2B. **A3 ligand exhibited two poses of same docking scores*.

A3 of pose 1 forms conventional hydrogen bond with ILE A238, ALA A240, LYS B143, ILE A238, and ASP B232. Hydrophobic interactions with ILE A238 and ALA A216 (Π-Alkyl). A single unfavorable bond was observed at the MET B278 amino acid residue. A3 of pose 2 forms as conventional hydrogen bonds with LYS B 143 and ASP B232. Electrostatic interactions with GLU A132 (Π-Anion). Hydrophobic interactions with LEU A279 (Π -Sigma) and ALA A216 (Π-Alkyl). Double unfavorable bond was observed at ARG B248 and GLU A132 amino acid residues. A4 forms conventional hydrogen bonds with PHE B138 and ILE B136. Carbon hydrogen bonds with ASP A259 and ASP A259. Electrostatic interactions with ASP A259 (Π-Anion) and hydrophobic interactions with VAL B286 and ARG B287 (Π-Alkyl); LYS A255 and ARG A 256 (Alkyl). A5 forms a carbon hydrogen bond with ARG B287 and GLU B279. Electrostatic interactions with ARG B287 (Π-Cation); THR A282 (Π-Anion) and hydrophobic interactions with THR A241 (Π-Sigma); GLY A236 (Π-Amide) and TYR A237 (Π-Alkyl). A single unfavorable bond at LYS B143. A6 forms conventional electrostatic interactions with ARG B287 (Π-Cation); and GLU B230 (Π-Anion) and hydrophobic interactions with THR A241, VAL B286 (Π-Sigma); and ARG B287 (Π-Alkyl). Conventional hydrogen bonds with THR A241 and LYS B143 in A7. Hydrophobic interactions with THR A241 (Π-Sigma); VAL B286, ARG B287 (Π-Alkyl). A8 forms a carbon hydrogen bond with LYS B143 and TYR B144. Electrostatic interactions with LYS B143 (Π-Cation); GLU B230, ASP B282 (Π-Anion) and hydrophobic interactions with ALA B227 (Π-Alkyl); VAL B286 (Alkyl). Halogen atoms interact with PHE B142, MET B278, and ASP B282. A9 forms a carbon hydrogen bond with ASP B282 and GLU B279. Electrostatic interactions with ARG B287 (Π-Cation) and hydrophobic interactions with THR

Table 3: The analysed descriptors related to absorption-distribution-metabolism-excretion properties of the compounds

Serial number	Descriptor	Optimal range
1	MW	150–500
2	HBD	≤5
3	HBA	≤10
4	log Po/W	−2–5
5	TPSA	<120 $[A^0]^2$/mol - orally active<100 $[A^0]^2$/mol - brain penetration
6	log S	−6.5–0.5
7	Apparent MDCK cell permeability (PMDCK)	<25 poor; >500 great
8	log P	−8.0–1.0

MW: Molecular weight, HBD: Hydrogen bond donors, HBA: Hydrogen bond acceptors, log Po/W: Octane/water partition coefficient, TPSA: Topological polar surface area, PMDCK: Permeability Maden Darby Canine kidney, log S: Apparent solubility, log P: Skin permeability

Table 4: Prediction of absorption-distribution-metabolism-excretion properties of the title compounds using Swiss absorption-distribution-metabolism-excretion

Compound	MW (g/mol)	HBA	HBD	TPSA ([A⁰]²/mol)	Log P_o/W	Log S	PMDCK	Violation	log P (cm/s)
Ifenprodil	325.44	3	2	43.70	3.41	−4.51	High	0	−5.52
A1	475.53	9	6	158.76	1.49	−2.59	Low	1	−9.40
A2	325.44	3	2	43.70	3.42	−4.51	High	0	−5.52
A3	501.57	9	5	139.92	0.98	−2.54	High	1	−9.32
A4	406.36	3	2	43.70	3.20	−5.51	High	0	−5.33
A5	325.44	3	2	43.70	3.39	−4.51	High	0	−5.52
A6	325.44	3	2	43.70	3.36	−4.51	High	0	−5.52
A7	325.44	3	2	43.70	3.40	−4.51	High	0	−5.52
A8	347.85	3	1	23.47	4.39	−4.76	High	1	−5.20
A9	339.47	3	2	43.70	3.67	−4.48	High	0	−5.35
A10	477.57	10	7	154.37	0.88	−0.46	Low	1	−10.81
A11	666.85	4	4	81.86	4.51	−9.10	Low	1	−5.01

MW: Molecular weight, HBD: Hydrogen bond donors, HBA: Hydrogen bond acceptors, log Po/W: Octane/water partition coefficient, TPSA: Topological polar surface area, PMDCK: Permeability Maden Darby Canine kidney, log S: Apparent solubility, log P: Skin permeability

A241 (Π-Sigma); ILE A238 (Alkyl). A single unfavorable bond at LYS B143. Compound A10 forms a carbon hydrogen bond with ALA A240, HIS B273, and GLU A132. Electrostatic interactions with ARG B287 (Π-Cation) and hydrophobic interactions with THR A241 (Π-Sigma); GLY A236 (Π-Amide). A11 forms a carbon hydrogen bond with HIS B13 and VAL B88 and a double carbon hydrogen bond with SER B206 and PRO B48. Hydrophobic interactions with ASP B90 (Π-Amide) and PRO B53 (Alkyl). A single pi-pi T-stand at HIS B13.

***In silico* ADME study and toxicity prediction**

Nine descriptors related to the ADME characteristics of the compounds were calculated using Swiss ADME (http://www.swissadme.ch/). The evaluated properties and the optimal range values of the descriptors are stated in Table 3. The values belonging to predicted ADME descriptors of the compounds are displayed in Table 4. The properties are based on Lipinski's rule of five, that is, molecular weight [MW] <500, hydrogen bond acceptor [HBA] ≤5, hydrogen bond donors [HBD] ≤10, and log Po/W −2–5 [32,33]. Topological polar surface area (TPSA) value <120 [A^0]²/mol] is orally active drug transport root, TPSA of <100 [A^0]²/mol] is good brain penetration of CNS drug [35]. Apparent solubility (log S) ranges from −6.5–0.5 [36]. Apparent Permeability Maden Darby Canine Kidney (PMDCK), values <25 are with poor cell permeability and >500 exhibits high cell permeability.

The MW of the compounds was between 666.85 (A11) and 325.44 (A2, A5, A6, A7). Ifenprodil, A1, A2, A4, A5, A6, A7, A8, A9, and A10 were <500 and matched Lipinski's rule of five. Compounds A3 (501.57) and A11 (666.85) both violates Lipinski's rule of five. The hydrogen bond acceptors of the compounds were between 10 (A11) and 3 (A2, A5, A6, A7, A8, and A9). The HBA of ifenprodil was determined as 3. Besides, all the compounds matched Lipinski's rule of five.

The hydrogen bond donors of the title compounds were between 7 (A10) and 1 (A8). Compounds A1 (6) and A10 (7) violate Lipinski's rule of five (HBD ≤ 5). HBD of Ifenprodil was determined as 2 and matched to Lipinski's rule of five. Topological polar surface area values that are elucidated range between 154.37 [A^0]²/mol (A10) and 23.47 [A^0]²/mol (A8). The determined values of compounds A2, A4, A5, A6, A7, and A9 are 43.70[A^0]²/mol; A8 (23.47 [A^0]²/mol) and A11 (81.86 [A^0]²/mol) are orally active and good brain penetration compounds. TPSA of ifenprodil was 43.70(81.86 [A^0] ²/mol). High TPSA compounds A1 (158.76 [A^0]²/mol) and A10 (154.37 [A^0]²/mol) exhibit less permeability.

The log Po/W value ranges between 4.51 (A11) and 0.88 (A11). A11 (0.88), A3 (0.98), and A1 (1.49) were below the optimal range. The rest of the compounds A11 (4.51), A8 (4.39), A9 (3.67), A2 (3.36), A7 (3.40), A5 (3.39), A6 (3.36), and A4 (3.20) were in the optimal range. Ifenprodil, a reference compound valued at 3.41 and matched to the values of drug likeness.

The log S values of the compounds were between −5.51 (A4) and −2.54 (A3). Furthermore, the reference compound, ifenprodil, had a value of −4.51 and matched the values for drug likeness. The PMDCK values of title compounds were determined to be high (> 500) for A2-9. The results of A1, A10, and A11 shown low (< 25) PMDCK. Reference compound PMDCK value was good.

A Log P value ranges from −10.81 (A10) to −5.20 (A8). Compounds A10 (−10.81), A3 (−9.32), were not in the optimal range, A2, A5, A6, A7 (−5.52), A9 (−5.35), A4 (−5.33), and A8 (−5.20). Furthermore, the log P of ifenprodil was determined as −5.52. The OSIRIS server identified that all the compounds are non-mutagenic, non-irritant, non-tumorigenic, and they do not exhibit any reproductive toxicity.

CONCLUSION

The present study aimed to identify inhibitors against the GluN1/GluN2B. Eleven diverse analogous were assigned to elucidate potential inhibitor compounds selected from the PubChem database. Among all ligands, six compounds A2, A3 (1) (2), A4, A7, and A10 showed higher binding affinity than reference compound ifenprodil. A8 exhibits equal inhibitory effect as like Ifenprodil. A3 (1), (2), and A10 displayed more remarkable antagonist activities than ifenprodil but violated Lipinski's rule of five. Ligands A2,4-[(1R,2R)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol, A4,4-[2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol; hydrobromide and A7, 4-[(1R,2S)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol shown better inhibitory and ADMET results. However, further studies are necessary to elucidate the potent antagonist ligands against GluN1/GluN2B.

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CONFLICTS OF INTEREST

No conflicts of interest

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