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1. Evaluation of antagonist activity of Ifenprodil and their analogous against GluN1/GluN2B using *In-Silico* Molecular docking and ADME Toxicity

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ABSTRACT

High Ca^{2+} permeability represents a characteristic feature of NMDA receptors on extreme amounts effects physiological functions like reduce neural development, synaptic plasticity and learning and memory. The study aims to elucidate the potent inhibitory Ifenprodil and their eleven analogues were retrieved from PubChem database which acts as ligands to the target Glun1/GluN2B subunit of NMDA receptor. In silico methods like 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 target. Molecular docking results showed that six of compounds had remarkable binding affinities (-7.8 to -9.0 kcal/mol) for target. ADMET study revealed that three (PubChemID:12613159, 12613162 and 6604117 of six compounds with good binding affinity and obeyed Lipinski's rule of five. Hence, they were compounds with inhibitory functions. Therefore, this study revealed three good antagonists of GluN1/GluN2B viz. 4-[(1R,2R)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] 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, ADMET, GluN1/GluN2B.

Introduction

Ionotropic glutamate receptors were cationic channels of Na^+, K^+ and Ca^{2+}, have been classified 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 (AMPA) and kainite (structural analogue of glutamate [1] [2] [3] [4].Overload of Ca^{2+} ions in the cells causes secondary neurotoxic events [5] [6]such as Cerebral Ischemia, Epilepsy, Alzhemier's and Parkinson's disease and Amyotrophic lateral scelerosis. NMDA receptor consists of four subunits, which forms a heterotetramer [7]. In humans, seven subunits were identified named as GluN1, GluN2A-D, and GluN3A-D. since GluN3 subunits were predominantly expressed in embryonic brain, thus functional NMDA receptor usually consists of two GluN1 and two GluN2 subunits [8] [9] [10]. These receptors were critically dependent for synaptic plasticity, network development and information storage in the brain [11] [12] [13].

Single subunit consists of four domains namely C terminal domain (CTD), transmembrane domain (TMD), ligand binding domain(LBD) and N-terminal domain(NTD). NTD located extracelluar far away from 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 was located at the interface between the GluN1 and Glun2B, determined by X-ray crystal structure analysis [14] [15] [16] [17].Ifenprodil binding site have potential for the neurodegenerative and neurological diseases which acts as negative allosteric modulators of GluN2B NMDA receptors could be exploited for the treatment of Depression, Cerebral Ischmia, Stroke,Parkinson's, Alzheimer's and Huntington's disease [18] [10] [19] [20] [21] [22] [23].

In the light of above observations, we choose Ifenprodil and their analogous (table 1) for docking studies with the GluN1/GlunN2B to model interactions in the receptors ligand complex. In silico studies have been conducted to elucidate the antagonist to GluN1/GluN2B. Molecular docking simulations were performed by reliable ligands to elucidate efficient compound followed by ADMT studies to study toxicology of all ligands

Table 1: Accession ID, IUPAC 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	$C_{25}H_{33}NO_8$
A2	12613159	4-[(1R,2R)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}NO_2$

Compound	PubChem ID	IUPAC name	Formula
A3	6455334	(2S,3S,4S,5R,6S)-6-[4-[2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenoxy]-3,4,5-trihydroxyoxane-2-carboxylic acid	$C_{27}H_{35}NO_8$
A4	12613162	4-[2-(4-benzylpiperidin-1-yl)-1-hydrooxypropyl] phenol; hydrobromide	$C_{21}H_{28}BrNO_2$
A5	11771731	4-[(1S,2S)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}NO_2$
A6	11198145	4-[(1S,2R)-2-(4-benzylpiperidine-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}NO_2$
A7	6604117	4-[(1R,2S)-2-(4-benzylpiperidin-1-yl)-1-hydroxypropyl] phenol	$C_{21}H_{27}NO_2$
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	$C_{22}H_{29}NO_2$
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.

2. Materials and Methods:

2.1. Protein Preparation:

The crystal structure of GluN1/GluN2B was retrieved from RCBS PDB (www.rcbs.org) (PDB ID:5EWL) and optimized by removing existing ligand, water molecules, heteroatoms, and co-factors using Drug Discovery Studio. The missing atoms, bonds, charges and polar hydrogen atoms were added through AutoDock version 4.2 program, Scripps Research Institute[24]and subsequently saved in pdbqt format for docking studies. Dimensions were kept at X=64, Y=44, Z=72 and Grid centre X=-16.266951, Y=-14.836195, Z=23.759171, determined in Drug Discovery Studio.

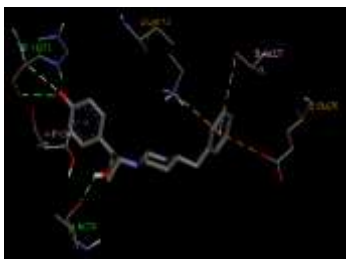
2.2. Ligand Preparation

The 3D structures of antagonist Ifenprodil (3689) and their analogous (23615771, 12613158, 6455334, 12613162, 11771731, 11198145, 6604117, 60703, 660488, 9826324, 3359) were retrieved from NCBI PubChem [25]in sdf format thereafter converted into pdb format to create ligand binding groups using open babel [26]. Further processing of ligands which includes setting of torsional bonds, steric hinderances and proper bond orders to define binding site using AutoDock tools [27] **[28]**

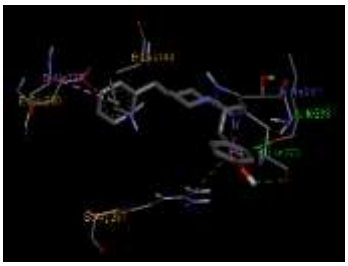
2.3. In-silico ADME study and Toxicity prediction

Elucidation of pharmacologically active substances in drug development is most important aspect, predicted by in silico ADMET (adsorption, distribution, metabolism, excretion and toxicity) studies performed using Swiss ADME [29] [30] [31]. OSIRIS property explorer(https://www.organic-chemistry.org /prog/peo/),US Food and Drug administration toxicity prediction properties evaluated such as irritation, mutagenicity, tumorigenicity and reproductive development toxicity.

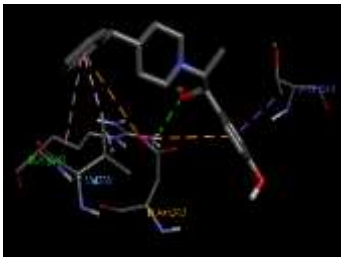
Figure 1. Compound Ifenprodil, A1, A2, A3(1), A3(2), A4, A5, A6, A7, A8, A9, A10, A11 and their 3D interactions with the active site of GluN1/GluN2B. **A3 ligand exhibited two poses of same docking score.*



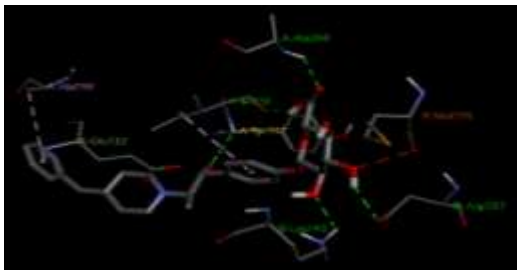
Ifenprodil



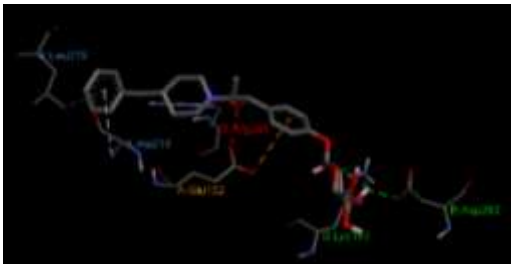
A1



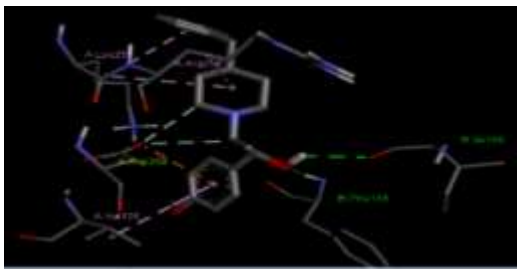
A2



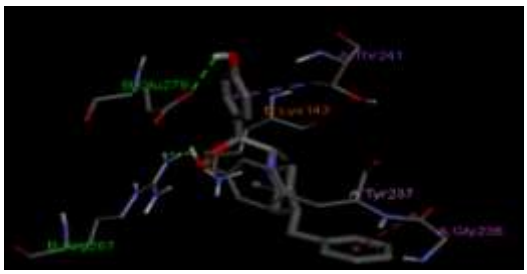
A3(1)



A3(2)



A4



A5

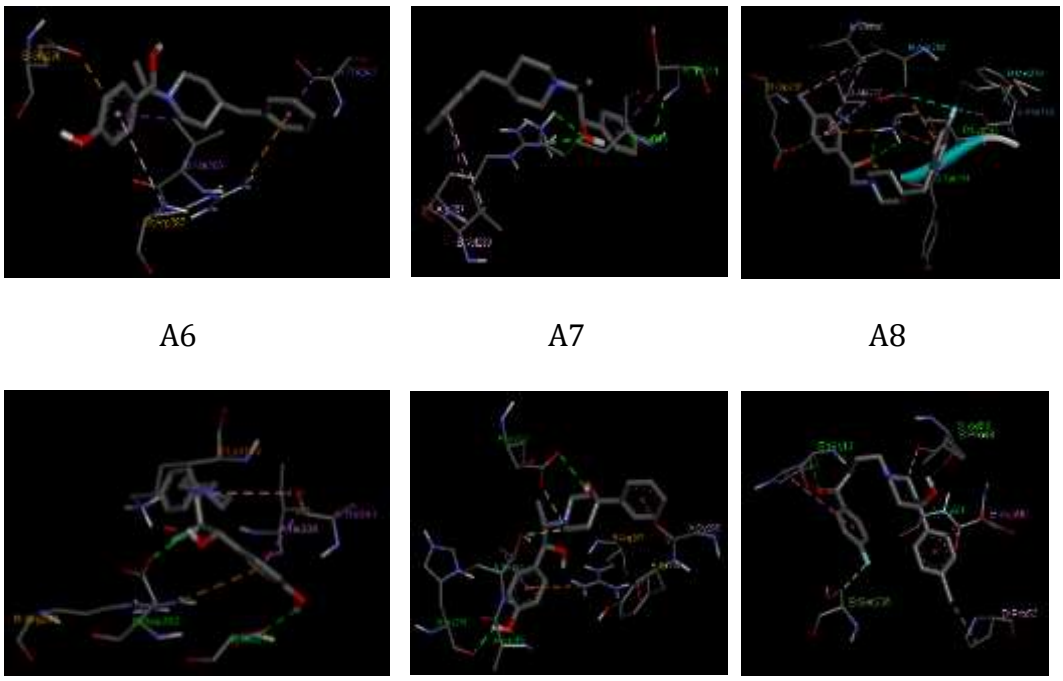
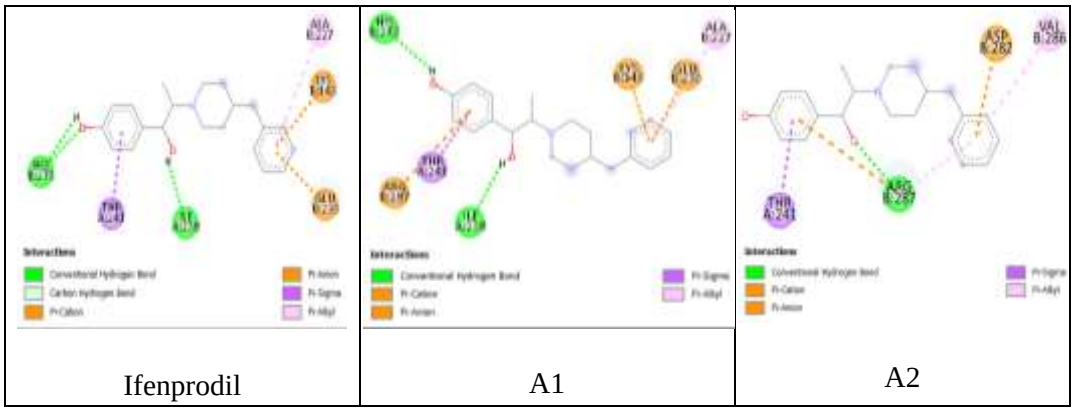
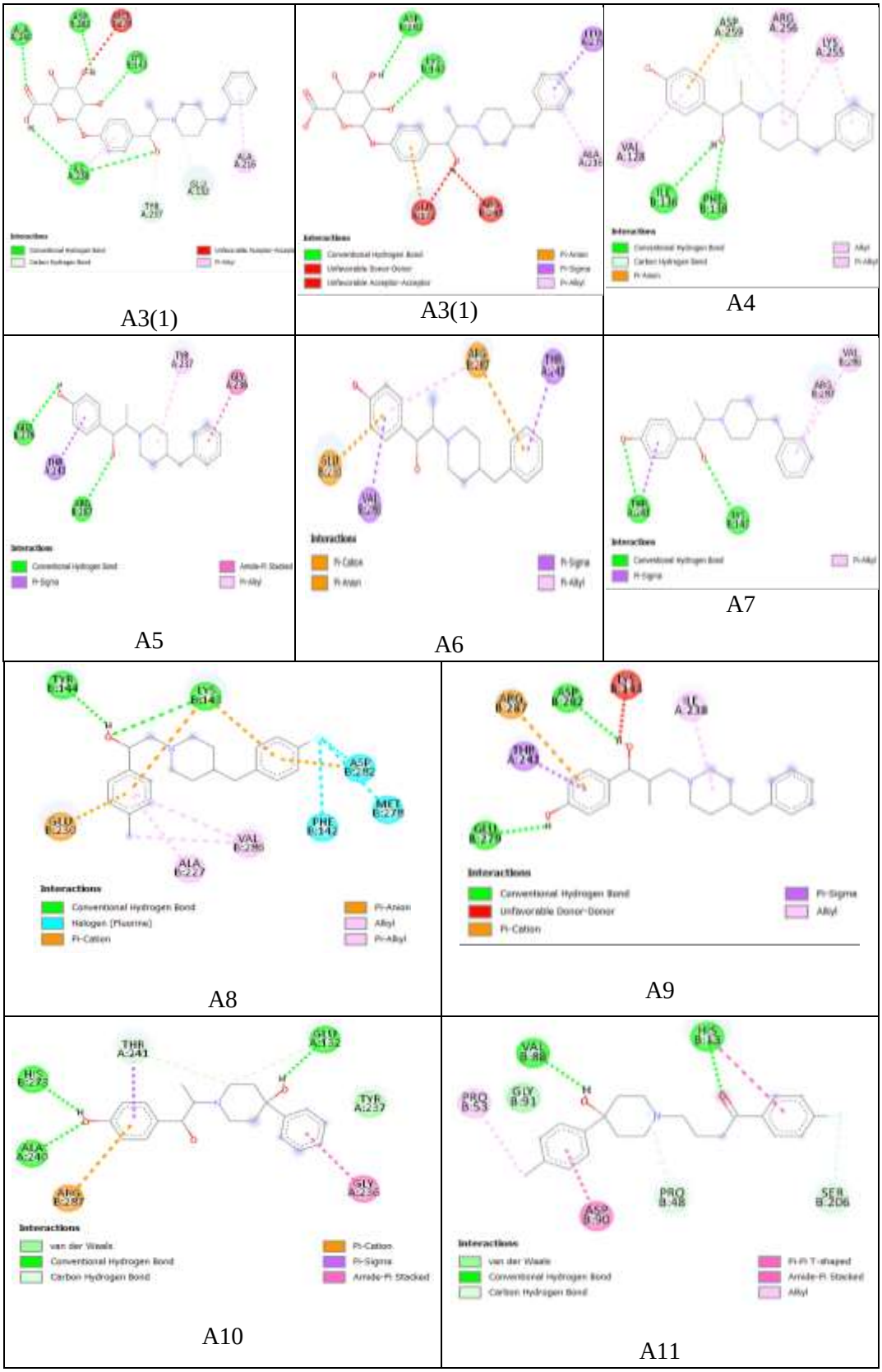


Figure 2. Compound Ifenprodil, A1, A2, A3(1), A3(2), A4, A5, A6, A7, A8, A9, A10, A11 and their 2D interactions with the active site of GluN1/GluN2B. **A3 ligand exhibited two poses of same docking scores*




A3(1)
A3(1)
A4
A5
A6
A7
A8
A9
A10
A11

3. RESULTS AND DISCUSSION:

3.1 Docking Results:

All the ligands and their interactions with bonding site of GluN1/GluN2B were explained and displayed in table 2, figure 1 and figure 2. All the compounds (12ligands) **A1, A2, A3 (1), A3(2), A4, A5, A6, A7, A8, A9, A10, 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 conventional hydrogen bond with HIS B273 and ILE A238 along 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 bond with HIS B273 and ILE A238.Carbon-hydrogen bond with 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 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*).* **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 unfavourable bond was observed at MET B278 amino acid residue. **A3**of pose **2** forms conventional hydrogen bond 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 unfavourable bond was observed at ARG B248 and GLU A132 amino acid residues. **A4**forms conventional hydrogen bond with PHE B138 and ILE B136.Carbon hydrogen bond with ASP A259 and ASP A259. Electrostatic interactions with ASP A259(Π-Anion) and hydrophobic interactions with VAL B286, ARG B287(Π-Alkyl) and LYS A255, ARG A 256(Alkyl). **A5**forms 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 unfavourable bond at LYS B143.

A6forms conventional electrostatic interactions with ARG B287(Π-Cation); GLU B230 (Π-Anion) and hydrophobic interactions with THR A241, VAL B286(Π-Sigma); ARG B287(Π-Alkyl). **A7** forms conventional hydrogen bond with THR A241 and LYS B143. Hydrophobic interactions with THR A241(Π-Sigma); VAL B286, ARG B287(Π-Alkyl). **A8** forms 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). ssHalogen atoms interacts at PHE B142, MET B278 and ASP B282. **A9** forms carbon hydrogen bond with ASP B282 and GLU B279. Electrostatic interactions with ARG B287(Π-Cation) and hydrophobic interactions

with THR A241(Π-Sigma); ILE A238(Alkyl). A single unfavourable bond at LYS B143. Compound **A10** forms 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 carbon hydrogen bond with HIS B13 and VAL B88. 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.

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 (PDB ID: 5EWL)

Compound	B.A. kcal/mol	H-bond	C-H bond	Electrostatic interactions		Hydrophobic interactions				Halogen	Unfav-oured bond	Π- Π T-stand
				Π-Cation	Π-Cation	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 28	ASP B 282	THR A 241	-	-	-	-	-	-
A3(1)	-9.0	ILE 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 225	-	LYS A 225 ARG A 256	-	-	-
A5	-7.6	-	ARG B 287 GLU B 279-	-	-	THR A 241	THR A 237	GLY A 236	-	-	LYS B 225	-
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	-	-	-	-

Compound	B.A. kcal/mol	H-bond	C-H bond	Electrostatic interactions		Hydrophobic interactions				Halogen	Unfav-oured bond	Π- Π T-stand
				Π-Cation	Π-Cation	Π-sigma	Π-alkyl	Π-amide	Alkyl			
A11	-7.2	HIS B 13 VAL B 88	SER B 206 PRO B 48	-	-	-	-	ASP B 90	PRO B 53	-	-	HIS B 13

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

3.2. 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 were stated in table 3. The values belonging to predicted ADME descriptors of the compounds were displayed in table 4. The properties based on Lipinski's rule of five i.e. (MW<500, HBA≤5, HBD≤10, log Po/W -2 to 5) [32] [33]. TPSA of <120[A^{0}] ^{2}/mol] are orally active drugs transport root, <100 [A^{0}] ^{2}/mol] are good brain penetration of CNS drugs [34]. Apparent solubility (log S) ranges -6.5 to 0.5 [35]. Apparent Permeability Maden Darby Canine Kidney (PMDCK), value ranges <25 poor cell permeability and >500 exhibits high cell permeability.

The MW of the compounds were 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 the Lipinski's rule of five. Hydrogen bond acceptors of the compounds were between 10(**A11**) and 3(**A2**, **A5**, **A6**, **A7**, **A8**, **A9**). HBA of **Ifenprodil** was determined as 3. Besides all the compounds matched to Lipinski's rule of five. Hydrogen bond donor of title compounds were between 7(**A10**) and 1(**A8**). Compounds **A1** (6) and **A10**(7) violates Lipinski's rule of five (HBD≤5). Besides HBD of **Ifenprodil** was determined as 2 and matched to Lipinski's rule of five.

Topological polar surface area values that are elucidated ranges between 154.37 $[A^{0}]^{2}$/mol (**A10**) and 23.47 $[A^{0}]^{2}$/mol (**A8**). Compounds **A2**, **A4**, **A5**, **A6**, **A7** and **A9** determined value was 43.70$[A^{0}]^{2}$/mol; **A8**(23.47$[A^{0}]^{2}$/mol), **A11**(81.86$[A^{0}]^{2}$/mol) were 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) exhibits 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. Rest of 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 optimal range. **Ifenprodil**, reference compound valued 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**). Also, reference compound, **Ifenprodil** value was -4.51 and matched the values for drug likeness. The PMDCK values of title compounds were determined high (>500) for **A2-9**. **A1**, **A10** and **A11** results shown low (<25) PMDCK. Reference compound PMDCK value was good. Log P value ranges -10.81(**A10**) and -5.20 (**A8**). Compounds **A10**(-10.81), **A3**(-9.32), were not

in optimal range. Compounds **A2**, **A5**, **A6**, **A7**(-5.52), **A9**(-5.35), **A4**(-5.33) and **A8**(-5.20). Also, log P of **Ifenprodil** was determined as -5.52. OSIROS server identified that all the compounds are non-mutagenic, non-irritant, non-tumorigenic and they do not exhibit any reproductive toxicity.

Table 3: The analysed descriptors related to ADME properties of the compounds

Sr. No	**Descriptor**	**Optimal range**
1.	Molecular weight (MW)	150 to 500
2.	Hydrogen bond donors (HBD)	≤ 5
3.	Hydrogen bond acceptors (HBA)	≤10
4.	Octane/water partition coefficient (log Po/W)	-2 to 5
5.	Topological polar surface area (TPSA)	<120 $[A^{0}]^{2}$/mol- orally active <100 $[A^{0}]^{2}$/mol – brain penetration
6.	Apparent solubility (log S)	-6.5 to 0.5
7.	Apparent MDCK cell permeability (PMDCK)	<25 poor; >500 great
8.	Skin permeability (log P)	-8.0 to 1.0

Table4: Prediction of ADME properties of the title compounds using Swiss ADME

Compound	**MW (g/mol)**	**Hydrogen bond acceptor**	**Hydrogen bond donor**	**TPSA ($[A^{0}]^{2}$/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

ADME-Absorption, Distribution, Metabolism and Excretion, PMDCK-Permeability Maden Darby Canine Kidney.

4. 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** shown high binding affinity than reference compound Ifenprodil. **A8** exhibits equal inhibitory effect as like **Ifenprodil**. **A3**(**1**), (**2**) and **A10** displayed 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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