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International Journal of Pharmaceutical and Phytopharmacological Research

(ICV-5.09)

ISSN (Online) 2249 – 6084

ISSN (Print) 2250 – 1029

Int.J.Pharm.Phytopharmacol.Res. 2012, 2(3): 202-208

(Research Article)

Virtual Screening Tool Based Designing and Evaluation of Novel Sulfonamide Derivatives as Anticonvulsant Agent – A Pharmacophoric Approach

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Received on: 25/12/2012 ***Accepted on:*** 31/12/2012

ABSTRACT

This work has been presented for suggesting the novel sulfonamide derivatives as potent anticonvulsant agents on the basis of finding the pharmacophoric pattern of well known anticonvulsants agents of different classes. For the stated purpose we used docking as virtual screening method and it is also the basis for pharmacophoric pattern determination. We used the AutoDock software as virtual screening tool. On the basis of pharmacophoric pattern we suggested the new anticonvulsant agents. These agents were then screened on the basis of docking procedures and further in-silico evaluation of novel agents has been performed. The docking analysis has revealed that the novel agent CS shows binding with voltage gated sodium channel, GABA aminotransferase and also with voltage gated calcium channel but after comparing the number of hydrogen bonds and binding affinity, CS is supposed to be bind perfectly with GABA aminotransferase with 7 hydrogen bonds and -6.8 Kcal/mol of binding energy. The other novel agents DPS, SRS and TS do not shows any binding with GABA aminotransferase while they shows binding with voltage gated sodium and calcium channels.

Key Words: Sulfonamide derivative, Anticonvulsant agent, In-silico, Docking, AutoDock, ADMET.

INTRODUCTION

Epilepsy is a neurological disorder recognized by the onset of frequent convulsant and non-convulsant seizures that result from hypersynchronous neuronal firing and neuronal hyperexcitability. Over 50 million people worldwide are affected by epilepsy. Resistance to antiepileptic drugs (AEDs) and the side effects associated with the current AEDs are the most serious problems in the current treatment pattern of epilepsy[1–6]. So, there is a need to design anticonvulsants for the development of more effective and safer AEDs[7–9].

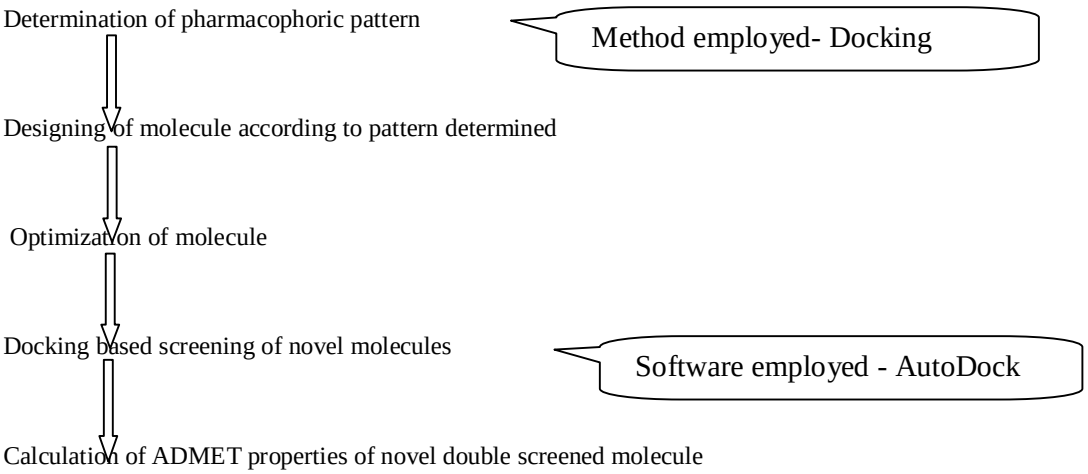


Fig.1: Complete flow chart of the work presented

The present work reports the prediction of novel sulfonamide derivatives which are supposed to act as potent anticonvulsant agents. This prediction was based on the finding the pharmacophoric pattern and designing the novel sulfonamide derivatives as anticonvulsant. This predictive work has been further proven by docking analysis, in-silico ADME properties determination and in-silico toxicity determination. However, in this work, docking has also been used for the determination of pharmacophoric pattern which is key factor.

This concept of pharmacophoric pattern has been used in the previously published research work by Laxmi Tripathi *et. al.* 2012[10]. However, we obeyed this concept by implementing the docking analysis as the method of finding the pharmacophoric pattern.

A whole flow chart of this study is given in Figure 1 in order to actually understand the work performed here.

MATERIALS AND METHOD

Determination of Pharmacophoric Pattern- Data and Database

For the determination of pharmacophoric pattern various potent pre existing anticonvulsant agents are docked with their corresponding protein or binding site and analysis of docking results suggests the pharmacophoric pattern. For this purpose the SDF files of ligands such as Phenytoin (CID 1775), Phenobarbital (CID 4763), Ethosuximide (CID 3291), Carbamazepine (CID 2554) and Clonazepam (CID 2802) are downloaded from website of NCBI (www.ncbi.nlm.nih.gov/). The corresponding proteins were downloaded from Protein Data Bank as PDB files. They are voltage gated sodium channel (PDB ID 2KAV), GABA aminotransferase (PDB ID 1OHW) and voltage gated calcium channel (PDB ID 1T0J).

Structure Designing, Structure Optimization and Modeling Parameters - Tools

The 2D structure construction, energy minimization and geometry optimization of the novel derivatives were carried out by using ChemDraw Ultra 7.0 and Chem3D Pro 7.0 (CambridgeSoft Corporation, 100 CambridgePark Drive, Cambridge MA, 02140 USA) on an Intel(R) Core(TM)2 Duo Central Processing Unit T6670 @ 2.20 GHz and 4.00 GB of RAM, running the Windows 7 Home Basic, 64-bit compatible operating system. The energy minimization was carried out to minimum RMS Gradient of 0.100, with step interval of 2.0 Fs and frame interval of 10 Fs.

Screening and Evaluation of Novel Sulfonamide Derivatives as Anticonvulsant Agent - Docking

Docking has been performed with AutoDock docking software[11]. It is avirtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets. It enables medicinal chemists to run virtual screening form any platform and helps users in every steps of this process- from data preparation to job submission and analysis of the results. For screening process, all the novel molecules has been docked with all the 3 different proteins/binding sites of previously well-known anticonvulsant agents which were also used for the determination of pharmacophoric pattern[12].

Docking Analysis

Now, the docked poses of the novel molecules are analysed for the binding energy, number of hydrogen bonds and binding pattern such as element, type of bond, atom number and residue at binding site.

Calculation ADMET Properties

All the ADMET properties have been calculated using the PaDEL-Descriptor software[13].

RESULTS AND DISCUSSION

The determined pharmacophoric pattern is shown in Fig. 2.

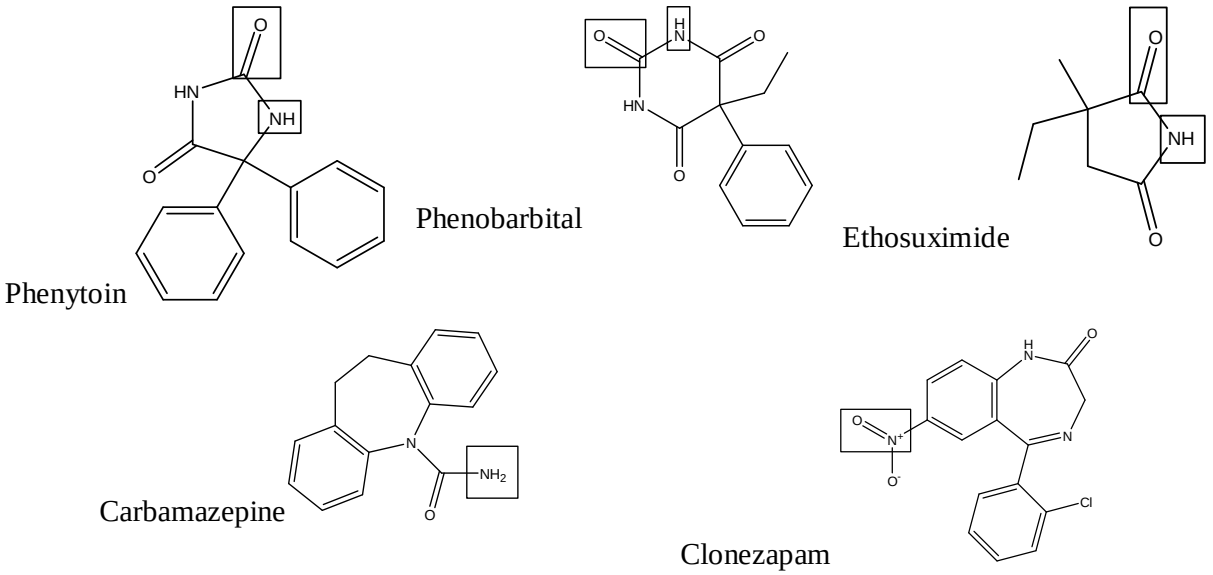
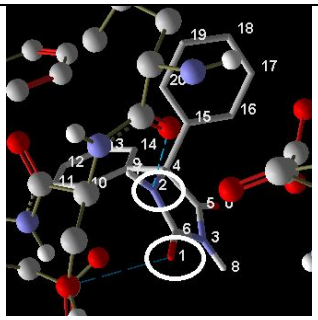
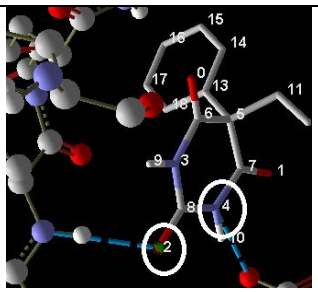
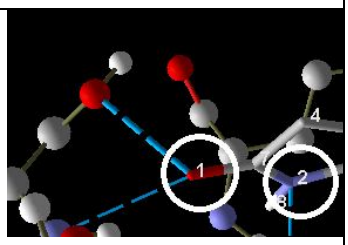
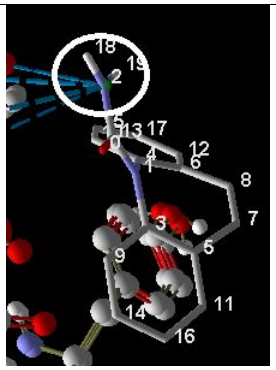
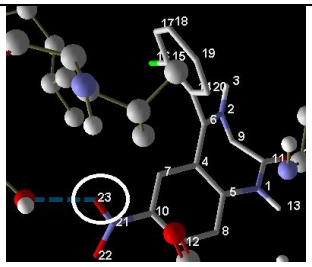


Fig. 2. Pharmacophoric pattern of known anticonvulsants

Docking is used as tool for pharmacophoric pattern determination and its result has been shown in Table 1 with binding detail and docked photo graphs.

Table-1: Docking analysis for determination of pharmacophoric pattern

Ligand	Receptor	H-bond	H-binding Ligand			Docked view, binding atom in circle
			Element	Atom no.	Type	
Phenytoin	2KAV	2	N	02	Donor	
			O	01	Acceptor	
Phenobarbitone	1OHW	2	N	04	Donor	
			O	02	Acceptor	
Ethosuximide	1T0J	3	N	02	Donor	
			O	01	Acceptor	
			O	01	Acceptor	
Caebamazepine	2KAV	6	N	02	Donor	
Clonazepam	1OHW	1	O	23	Acceptor	

Designed pharmacophore of sulfonamide as anticonvulsant is shown in Figure-3 along with the pharmacophoric pattern.

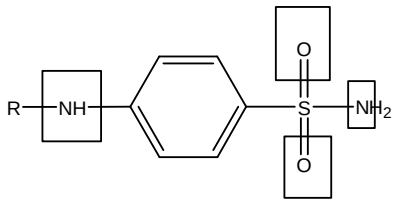


Fig. 3: Pharmacophore of sulfonamide derivative as anticonvulsant

Novel Designed Molecules of Sulfonamide Moiety as Anticonvulsants

All the novel designed molecules are shown in Fig. 4.

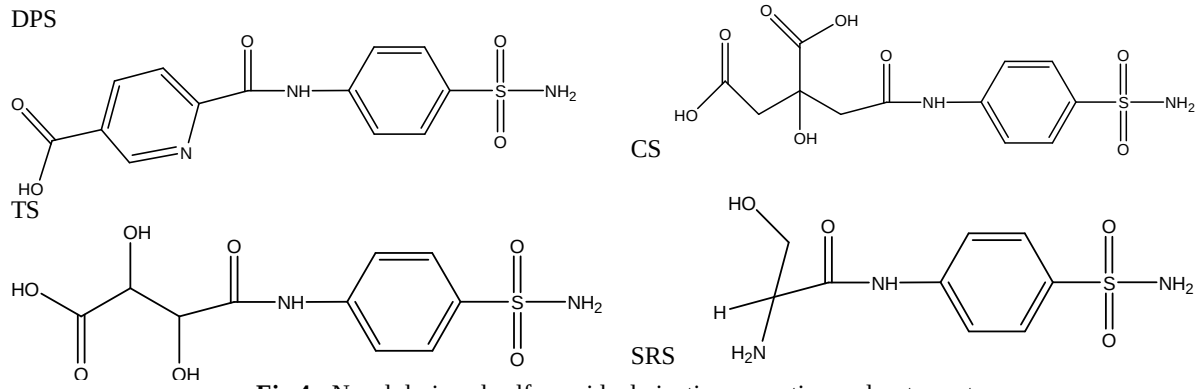


Fig.4 : Novel designed sulfonamide derivatives as anticonvulsant agent

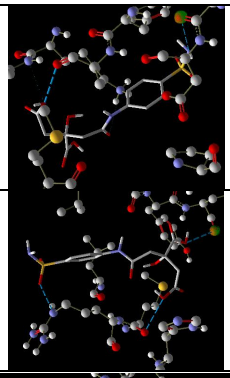
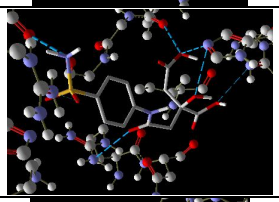
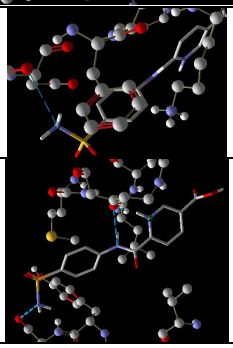
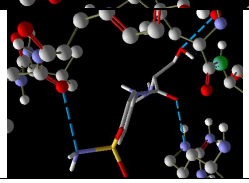
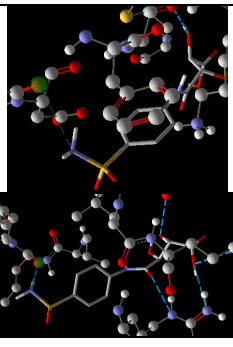
Docking Based Screening of Novel Molecules

Now, the novel molecules have been kept for the virtual docking based screening. The results of docking based screening are shown in Table 2 and their docked photographs are shown in Table 3.

Table – 2: Docking results novel sulfonamide derivatives

Ligand	Recept.	H- bonds	H- Binding Ligand			H- Binding Receptor			
			Elem.	Atom No.	Type	Residue	Elem.	Atom No.	Type
CS	2KAV	4	O	15	Both	ARG	N	1363	Donor
			O	15	Both	ALA	O	1300	Acceptor
			O	02	Acceptor	LYS	N	1349	Donor
			N	26	Donor	LEU	O	1211	Acceptor
	1T0J	3	O	24	Acceptor	ARG	N	690	Donor
			O	15	Both	MET	O	678	Acceptor
			O	10	Both	SER	O	234	Acceptor
	1OHW	7	O	15	Both	HIS	N	250	Acceptor
			O	15	Both	LEU	O	3311	Acceptor
			O	10	Both	ARG	N	3271	Donor
			O	06	Both	HIS	N	250	Acceptor
			O	02	Acceptor	ARG	N	3210	Donor
			N	26	Donor	GLU	O	2011	Acceptor
			O	24	Acceptor	ARG	N	1394	Donor
DPS	2KAV	1	N	13	Donor	LEU	O	1211	Acceptor
	1T0J	3	N	13	Donor	SER	O	234	Acceptor
			N	01	Donor	LEU	O	653	Acceptor
			N	21	Donor	LEU	O	653	Acceptor
	1OHW	0	-	-	-	-	-	-	-
SRS	2KAV	2	N	20	Donor	ASP	O	1230	Acceptor
			N	20	Donor	ASP	O	1233	Acceptor
	1T0J	4	N	20	Donor	ARG	O	211	Acceptor
			O	08	Acceptor	ARG	N	690	Donor
			O	15	Both	PRO	O	630	Acceptor
			O	15	Both	GLU	N	658	Donor
	1OHW	0	-	-	-	-	-	-	-
TS	2KAV	2	O	22	Both	ALA	O	1300	Acceptor
			N	13	Donor	LEU	O	1211	Acceptor
	1T0J	5	O	22	Both	PRO	O	630	Acceptor
			O	02	Acceptor	ARG	N	690	Donor
			O	20	Both	ARG	N	693	Donor
			O	20	Both	GLU	O	665	Acceptor
			N	13	Donor	ARG	O	211	Acceptor
	1OHW	0	-	-	-	-	-	-	-

Table- 3: Docked photographs of novel sulfonamide derivatives

Ligand	Receptor	Docked photographs
CS	2KAV	
	1T0J	
	1OHW	
DPS	2KAV	
	1T0J	
	1OHW	-
SRS	2KAV	
	1T0J	
	1OHW	-
TS	2KAV	
	1T0J	
	1OHW	-

Docking Analysis

On docking of the novel sulfonamide derivatives with the well known receptors recognized for the antiepileptic action, we found some very interesting points. Firstly, I docked the ligand **CS** with voltage gated sodium (PDB ID 2KAV) for its inhibition, then, it results with the 4 hydrogen bonds with binding affinity of -5.8 Kcal/mol. The residues to which they bind are Arg, Ala, Leu and Lys. In the same way ligand CS have been docked with voltage gated calcium channel and GABA aminotransferase with the 3 hydrogen bonds of 3 and 7 with -6.5 Kcal/mol and -6.5Kcal/mol respectively with residues Arg, Met, Ser, His, Glu and Leu.

In the same way, ligands DPS, SRS and TS have been docked with all the receptors individually in order to find the most appropriate binding. All the results have been shown previously in Table 2.

Calculation of ADME Properties

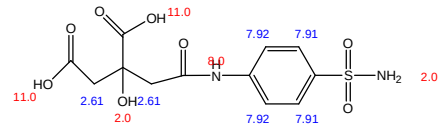
All the calculated ADMET properties of the novel agents have been listed in Table 4.

Table- 4: ADME properties of novel sulfonamide derivatives

	CS	DPS	SRS	TS
ALOGP	-2.2167	-1.0423	-2.4172	-2.5361
Fragment complexity	863.11	694.09	628.08	644.1
Hbond acceptor count	10	8	7	9
Hbond donor count	5	3	4	5
Largest chain	23	22	17	20
Largest Pi system	13	22	13	13
Longest aliphatic chain	5	6	4	4
Mannhold LogP	1.57	1.9	1.57	1.46
McGowan volume	2.2655	2.1355	1.7938	1.968
Petitjean number	0.5	0.46	0.5	0.45
Rotatable bonds count	8	5	5	6
Rule of five	0	0	0	0
TPSA	328.604	299.98	250.67	366.25
VadjMa	5.52	5.45	5.08	5.32
Molecular Weight	346.047	321.041	259.062	304.036
XlogP	-2.929	-1.68	-2.472	-2.92
Zagreb index	114	112	82	98

In-silico Evaluation of Novel Designed Molecules

Strutures and calculated H-1 NMR of novel predicted molecules are given below (Fig. 5 to Fig. 8)



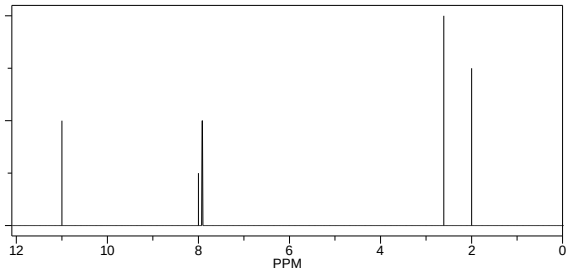
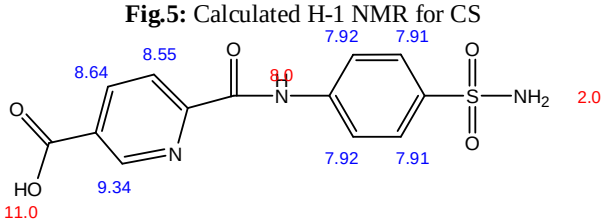


Fig.5: Calculated H-1 NMR for CS



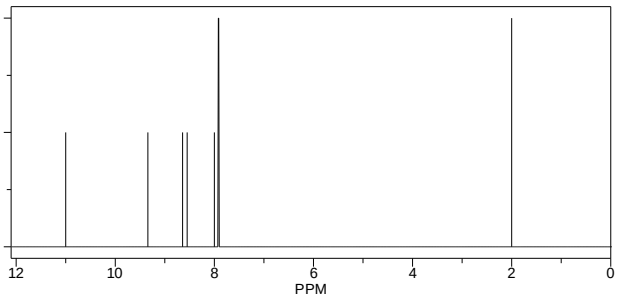
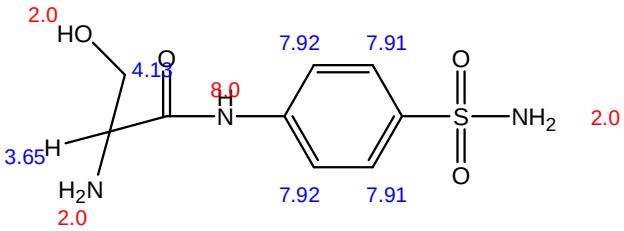


Fig.6: Calculated H-1 NMR for DPS



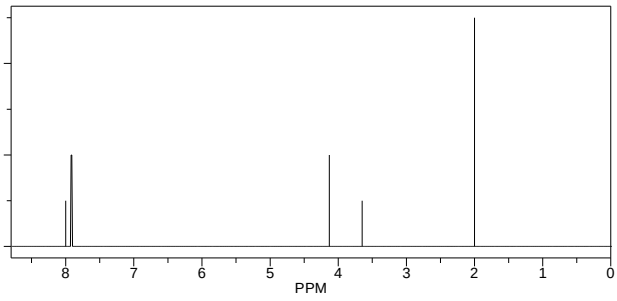


Fig.7: Calculated H-1 NMR for SRS

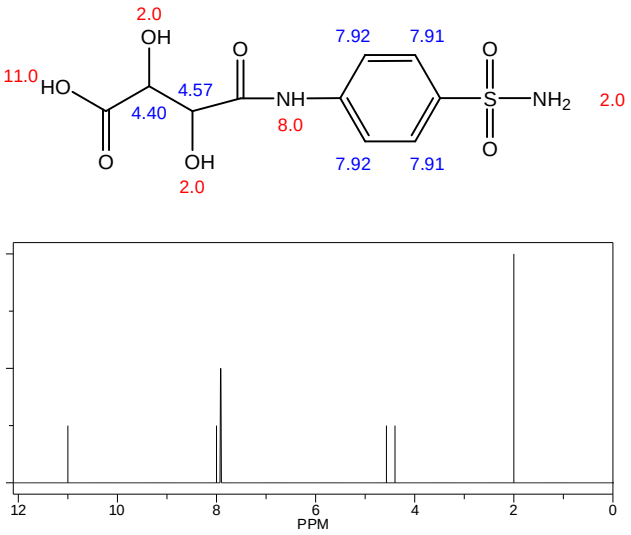


Fig. 8 : Calculated H-1 NMR for TS

CONCLUSION

With deluged data of virtual docking base screening and in-silico calculation of the ADMET properties of novel suggestion of sulfonamide derivatives, we could draw a number of conclusions. On the basis of results given earlier, we fetched that the novel molecule with code CS shows binding with all the three receptors used but on the basis of the number of hydrogen bonding and binding affinity CS is supposed to perfectly bind with GABA transferase (PDB ID 1OHW) with number of hydrogen bonding of 7 and bonding affinity of -6.8 Kcal/mol.

Turning direction towards the binding of the ligand DPS, a very interesting finding came into light that it shows no bonding with GABA aminotransferase, however it shows binding with voltage gated sodium channel (PDB ID 2KAV) with binding affinity of -6.5 Kcal/mol and voltage gated calcium channel (PDB ID 1T0J) with binding affinity of -7.6 Kcal/mol.

When we analyzed the docking results of other ligands named as SRS and TS, we observed that these two follows the same pattern of binding as that of DPS. SRS and TS do not shows any binding with GABA transferase but in comparison to voltage gated sodium channel, it shows better binding with calcium channel.

After such findings, finally we could conclude that the suggested novel sulfonamide derivatives can be further synthesize in laboratory and proceed for the further trial as in-silico evaluation suggest them to have antiepileptic activities.

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