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Article

Molecular Modeling Studied for Inhibition of Calcium Channel Receptor: A Strategy for the development of new Antiepileptic Drug

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ABSTRACT

Epilepsy is a common brain disease that is characterized by recurrent and spontaneous seizures that result from abnormal and excessive synchronization of neuronal activity. Whereas, accumulation of Ca++ in presynaptic terminals, leading to improved neurotransmitter release. In additional, depolarization-induced inauguration of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca++ influx and neuronal activation. The main aim of this study to focus on the deactivation of Ca++ influx and prevent the augmentation of neuron activation. However, we performed molecular modeling of novel 1,3,4-thiadiazole derivatives keeping in view structural requirement of pharmacophore and Quantitative structure activity relationship (QSAR) and evaluated in silico anticonvulsant activity. Docking procedures allow virtually screening a database of compounds and predict the strongest binder based on various scoring functions. In the docking study, targeted ligand produced significantly affinity with the calcium channel receptor which is slightly higher than the phenytoin drug. A computational study was also carried out including prediction of pharmacokinetic properties, toxicity and bioactivity studies. All above parameter was calculated which exhibited slightly excellent compared than standard Phenytoin drug. The above observation suggested that these compounds would serve as better lead for anticonvulsant screening for future drug design perspective.

Keywords: 1, 3, 4 Thiadiazole derivatives, Anticonvulsant activity, Computational study, ADMET and Bioactivity Prediction

INTRODUCTION

Epilepsy, derived from Greek word epilambanein, which means to attack or seize. It is collective term that includes over 40 different types of human seizure disorders, Approximately 1% of the world population at any one time (50 million people worldwide) is affected with this neurological disorder (McNamara, 2001)[1]. Which are evoked by unexpected, high-level neuronal discharges in brain (Loscher, 1998) [2]. Current drug therapy for epilepsy, nearly 95% of clinically drugs are available. It is roughly estimated that up to 28-30 % epilepsy are inadequately controlled by medication (Chang and Lowenstein, 2003) [3]. These drugs however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia (Schmidt *et al*., 2009; Perucca et al., 1996; Zhaiwei et al., 1997) [4-6] and lifelong medication may be required. These facts necessitate the search for the development of novel anticonvulsant drug with greater efficacy and fewer side effects.

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Pandeya (Pandeya *et al.*,2002) [7] has proposed the identifiable features for anticonvulsant activity as (i) hydrophobic aryl ring (Ar), (ii) a hydrogen bonding domain (HBD), (iii) an electron-donor group (D) and (iv) another distal hydrophobic site which are evident in the existing anticonvulsant drugs.

Thiadiazole moiety acts as "hydrogen binding domain" and "two-electron donor system". It also acts as a constrained pharmacophore. Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamethazole,etc. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphar atom. They occur in nature in four isomeric forms viz. 1, 2, 3-thiadiazole; 1, 2, 5-thiadiazole; 1, 2, 4-thiadiazole and 1, 3, 4-thiadiazole (Can*et al.,* 2012) [8]. The literature review of thiadiazole nuclei have exhibit following activity example, antimicrobial (Demirbas*et al.,* 2004 and Karegoudar*et al.,* 2008) [9-10], anticancer (Chou *et al.,* 2003) [11], antianxiety, anti-depressant (Cleici *et al.,* 2001) [12], anti-oxidant properties (Martinez *et al.,* 1999) [13] and anticonvulsant activity (Mohammad *et al.,* 2013) [14], antitubercular (Shankar *et al.,* 2012) [15] etc. 1, 3, 4-Thiadiazole exhibit diverse biological activities, possibly due the present of =N-C-S moiety (Oruc *et al.,* 2004) [16].

Docking techniques have been used in modern drug designing to understand drug-receptor interaction. It has been shown in the literature that computational procedures may strongly support and help the design of new, more potent drugs by revealing the mechanism of drug-receptor interaction (Srivastava *et al.,* 2008) [17].

MATERIAL AND METHODS

For carrying out this, National centre for Biotechnology Information (NCBI) website and Protein Data Bank (PDB) website were used as chemical sources.

For designing the derivatives: Chemdraw Ultra 10.0

For optimizing the geometry of derivatives: Argus Lab software

For docking studies: Molegro Virtual docker and autodocking software

For characterization of the derivatives: Molinspiron software toolkit, Med Chem Designer and EPA DSSTox Structure Browser v2.0 service.

Phenytoin structure data file was drawn by Chemdraw Ultra 10.0 and protein target was downloaded from Protein Data Bank with PDB id (4HKS).

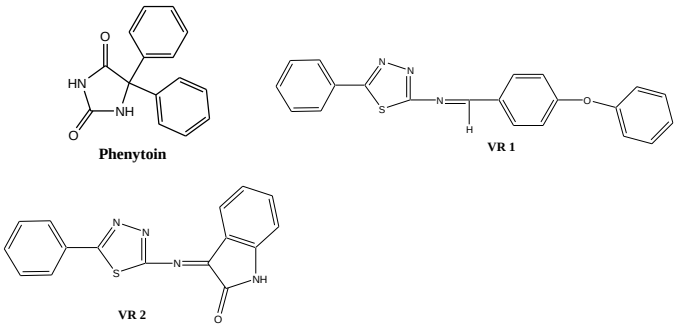

Figure 1. Show the chemical structure of standard Phenytoin drug and 1, 3, 4-thiadiazole derivatives (VR 1 and VR 2).

Computational Study

A computational study of all compounds was performed for prediction of ADME properties such as absorption (%ABS), polar surface area (TPSA), miLog P etc by using Molinspiration property calculation toolkit. Active site of protein was detected with the CASTp online server (Figure 2). Docking study of titled compounds was performed with established anticonvulsant molecular targets, namely calcium channel receptor (4MS2), by using Autodock 4.0 and Argus lab software along with its LGA algorithm for automated flexible ligand docking and affinity (Kcal/mol).

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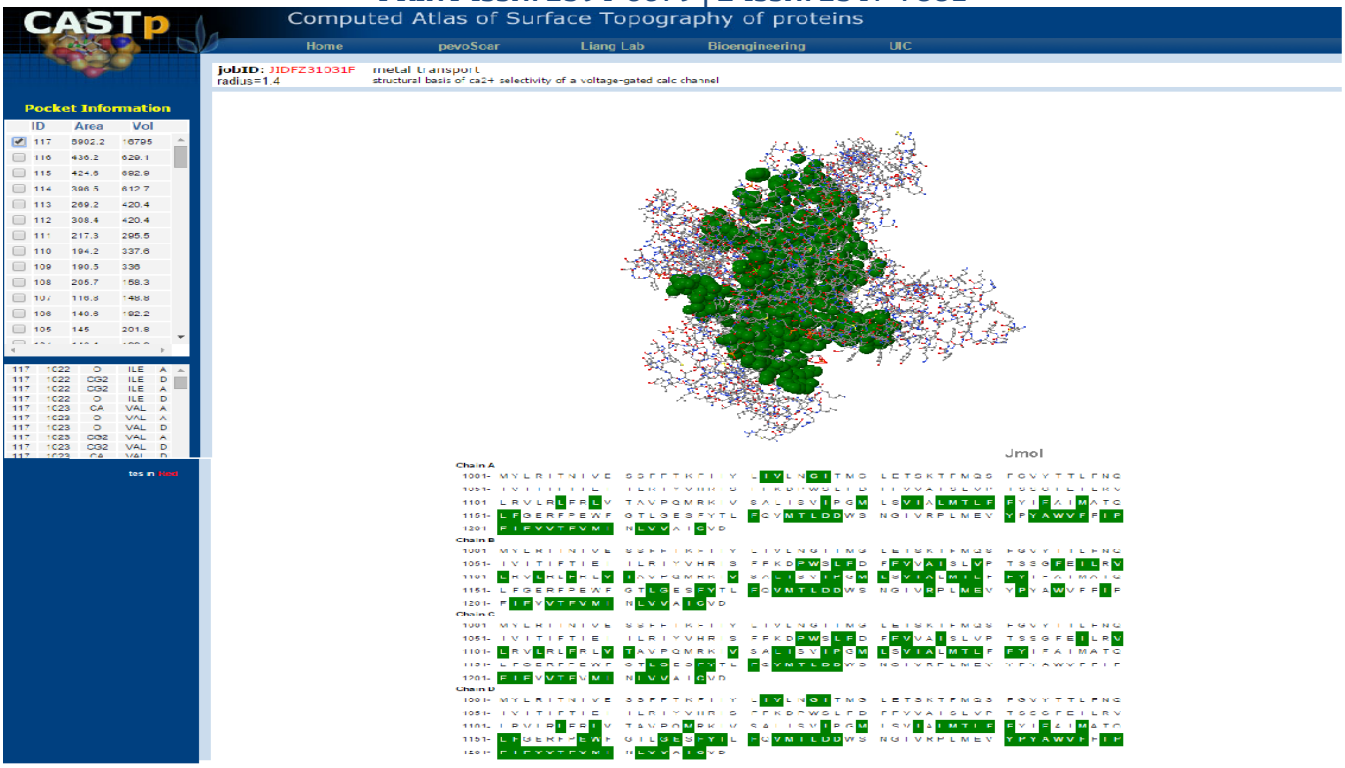

Figure 2. Amino acid present in the active site are labeled with green

Prediction of ADME properties

A computational study for prediction of ADME properties of titled compounds was performed. The percentage of absorption was calculated using TPSA. From all these parameters, it can be observed that all titled compounds exhibited a great %ABS ranging. These all parameters were calculated using Molinspiration property calculation toolkit (Bratislava, 2010) [18]. The results are shown in Table 2. Absorption (%ABS) was calculated by:

% ABS = 109-(0.345×TPSA). (Zhao *et al.,* 2002) [19]

Docking study

In this study, we have used Auto Dock 4.0 along with its LGA algorithm for automated flexible ligand docking of compounds VR 1 and VR 2 and Phenytoin drug with one established convulsant molecular targets namely calcium channel receptor, and evaluated docking affinity (Kcal/mol) and count of probable hydrogen bonds. All compounds have exhibited good binding properties (the comparison of protein-ligand interaction energy, much lower interaction energy is being associated with higher stability) compared than Phenytoin with receptor. The docking images are given in Figure 3. The results are shown in Table 1.

Bioactivity prediction and Toxological comparative studies

The designed derivatives and original drug bioactivity predictions have been compared along with some selected activity GPCR (G-Protein coupled receptor) etc. The score of bioactivity prediction of Phenytoin and 1, 3, 4-thiadiazole derivatives (VR 1and VR 2) are show in Table 3. The score of Toxological comparative studies of Phenytoin and 1, 3, 4-thiadiazole derivatives (VR 1and VR 2) are shown in Table 4. These all parameters were calculated using Molinspiration property calculation toolkit and EPA DSSTox Structure Browser v2.0 service.

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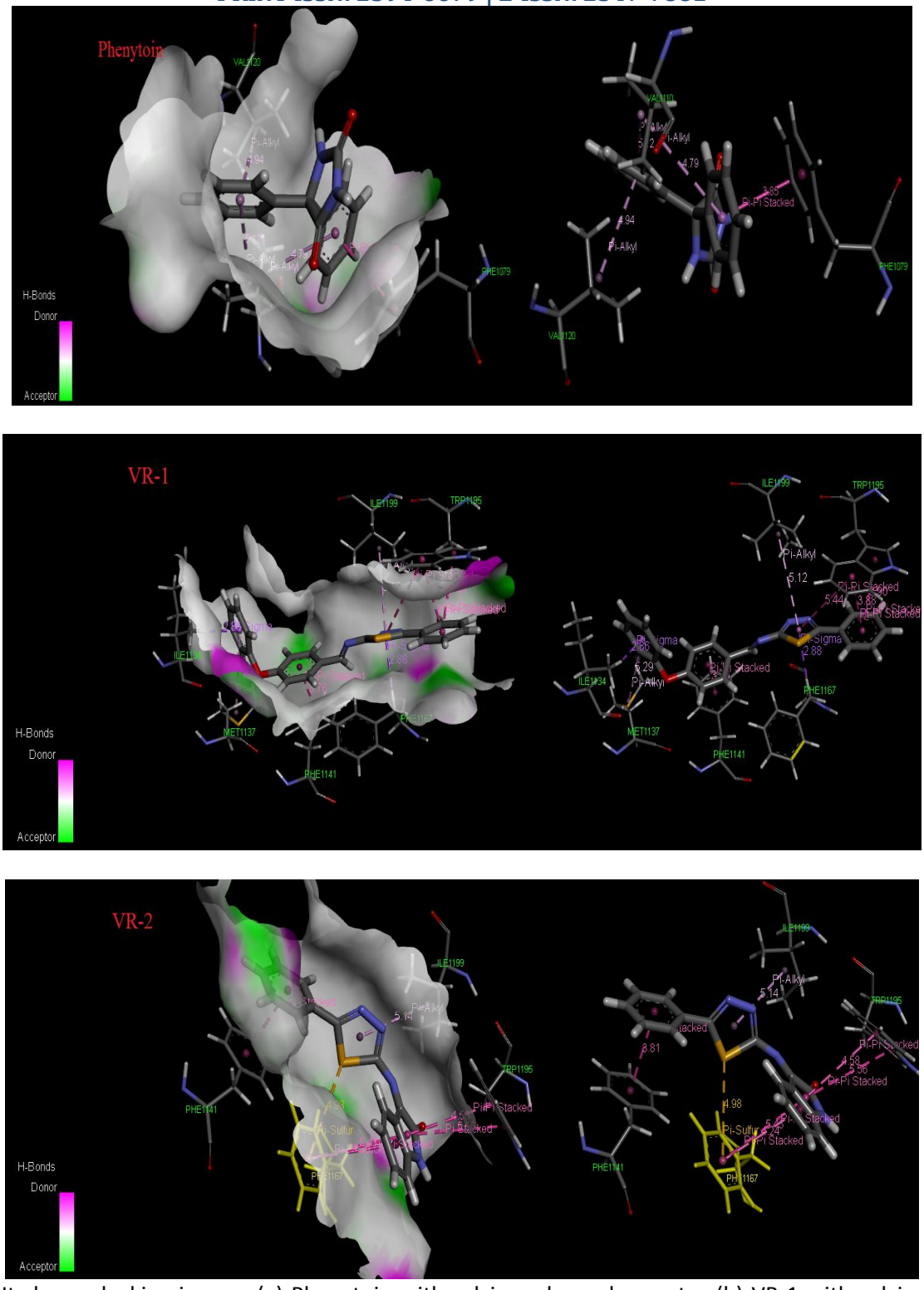

Figure 3. It shows docking images (a) Phenytoin with calcium channel receptor (b) VR 1 with calcium channel receptor and (c) VR 2 with calcium channel receptor

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Ligand	Receptor	Affinity (Kcal/Mol)	Amino acids involved in interactions	H-bonds	Pi bonds
Phenytoin	Calcium channel receptor	-8.5	TRP A 1076, PHE A 1079, PHE A 1107, ARG A 1108, VAL A 1110, THR A 1111, VAL A 1120, ILE A 1124, LEU C 1136, PHE C 1140 ,VAL C 1204	0	4
VR1	Calcium channel receptor	-11.0	ILE C 1134, MET C 1137, THR C 1138, PHE C 1141, GLY C 1164, PHE C 1167, TYR C 1168, PHE C 1171, MET C 1174, MET C 1209, LEU C 1212, TRP D 1195, ILE D 1199, PHE D 1203	0	88
VR2	Calcium channel receptor	-9.1	MET A 1137, THR A 1138, PHE A 1141, GLY A 1164, PHE A 1167, TYR A 1168, PHE A 1171, MET A 1174, TRP C 1195, ILE C 1199, PHE C 1203	0	7

Table 1. Table shows Protein-Ligand interaction Energy standard Phenytoin drug and 1, 3, 4-Thiadiazole derivatives VR 1& VR 2 with calcium channel receptor (4MS2).

S.No.		Rule	Phenytoin	VR1	VR2
1.	S+ log P	–	2.170	4.679	2.454
2.	S +log D	–	2.076	4.679	2.454
3.	M logP	–	2.201	3.987	2.585
4.	T_PSA	–	58.200	47.370	67.240
5.	n-OHNH donor	<5	2.000	0.000	1.000
6.	M_NO.	–	4.000	4.000	5.000
7.	Rule of 5	≤ 1	0.000	0.000	0.000
8.	%ABS(% of absorption)	–	88.921	92.66	85.81
9.	MV	–	223.886	329.474	253.064
10.	n-ON acceptor	<10	4	4	5
11.	n-ROTB	–	2	5	2
12.	M. Wt.	< 500	252.273	371.465	306.35

Table 2. Table shows ADME Properties Prediction of standard Phenytoin drug and Thiadiazole derivatives, VR 1& VR 2

S.No.	Receptors	Phenytoin	VR 1	VR 2
1.	GPCR ligand	0.07	-0.55	-0.48
2.	Ion channel Modulator	-0.14	-0.85	-0.90
3.	Kinase inhibitor	-0.47	-0.17	0.04
4.	Nuclear receptor ligand	-0.32	-0.40	-0.74
5.	Protease inhibitor	0.01	-0.54	-0.94
6.	Enzyme inhibitor	-0.02	-0.28	-0.32

Table 3. Table shows score of bioactivity prediction of Phenytoin and Thiadiazole derivatives, VR 1 & VR 2.

S.No.	DSSTox toxicity	Phenytoin	VR 1	VR 2
1.	DSSTox Carcinogenic Potency DBS MultiCellCall: non-carcinogen	0.0305	0.0136	0.00723
2.	DSSTox Carcinogenic Potency DBS Mutagenicity: non-mutagenic	0.519	0.101	0.00723
3.	DSSTox Carcinogenic Potency DBS Rat: non-carcinogen	0.085	0.0614	0.0495
4.	Kazius-Bursi Salmonella mutagenicity: non-mutagenic	0.0548	0.0335	0.0419
5.	FDA v3b Maximum Recommended Daily Dose mmol: 0.0152722115276765	0.138	0.106	0.0884
6.	DSSTox Carcinogenic Potency DBS SingleCellCall: non-carcinogen	0.0855	0.0463	0.0131

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7.	EPA v4b Fathead Minnow Acute Toxicity LC50_mmol: 0.00359162218026281	0.167	0.184	0.19
8.	DSSTox ISSCAN v3a Canc: carcinogen	0.024	0.0861	0.000
9.	DSSTox Carcinogenic Potency DBS Hamster: non-carcinogen	0.166	0.237	0.131
10.	DSSTox Carcinogenic Potency DBS Mouse: non-carcinogen	0.419	0.0146	0.0692

Table 4. Table shows score of Toxological comparative studies of Phenytoin and Thiadiazole derivatives, VR 1 & VR 2

RESULTS AND DISCUSSION

Docking study

In this study, we have used Autodock 4.0 along with its LGA algorithm for automated flexible ligand docking of compounds VR 1 and VR 2 with one established anticonvulsant molecular target namely calcium channel receptor (4MS2) and evaluated docking affinity (Kcal/mol). Compounds VR 1 and VR 2 have exhibited good binding properties with calcium channel receptor (affinity -11.0 kcal/mol and -9.1 kcal/mol respectively) which is better than the standard anticonvulsant phenytoin drug (affinity value -8.5 kcal/mol). The docking images are given in Figure 3 and the docking results are shown in Table1.

Prediction of ADME properties

A computational study for prediction of ADME properties of titled compounds was performed. The percentage of absorption (%ABS) was calculated using TPSA. From all these parameters, it can be observed that all titled compounds exhibited a great %ABS ranging 92.66 and 90.07s and compared than standard anticonvulsant phenytoin drug as %ABS 88.92 (Table 2). None of the compounds violated Lipinski's parameters, making them potentially promising agents for epilepsy therapy.

Bioactivity prediction and Toxological comparative studies

In this study, for prediction of Bioactivity and Toxological properties of titled compounds was carried out. From all calculated parameters, it can be observed that all titled compounds compared than standard Phenytoin drug shown less affinity with GPCR(G-Protein coupled receptor) ligand, Ion channel Modulator, Kinase inhibitor, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor and the toxological comparative studies of all titled compounds compared than standard Phenytoin drug having very less toxicity effect such as acute toxicity to fish (lethality), carcinogenicity, mutagenicity and repeated dose toxicity that mean these compounds can be make good bioactivity and minor toxicity drug compared than standard Phenytoin drug for epilepsy. The Bioactivity and Toxological data are given in Table 3-4.

CONCLUSION

From the above observation of result as compared with standard epileptic drug shown significant affinity with calcium channel receptor which indicated that both designed compounds of a series of novel 1, 3, 4-thiadiazole derivatives would be lead to the treatment of epilepsy. However, other computational parameters were also carried out including docking studies, ADME, bioactivity and toxicity prediction which also supported our hypothesis. The docking study data strongly supported the assumption that 1, 3, 4-thiadiazole derivatives may be involved as prolong deactivation of calcium channel to prevent the neuron activation in epilepsy. However, further studies need to be carried out to synthesis, *in-vivo* evaluation of pharmacological activity and ascertain the precise mechanism of action of anticonvulsant activity of these compounds. These titled compounds emerged as a lead in this series and making them potentially promising agents for epilepsy therapy.

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