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Virtual Screening of Thymol Thiophenol Analogues for Antiepileptic Activity

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Abstract

Epilepsy is a chronic neurological disorder which affects people of almost all age group. It is mainly recognized by brief episodes of recurrent seizures which involves either a part of body or as whole body and sometimes in epilepsy patient is unconscious. Although various drugs are available in market for treatment of epilepsy but still there is a need to develop new drug because every drug has its own limitations. For developing new drug there is need of huge money and it is time consuming process but molecular docking is one of the important methods by which we can do that work and estimate the probability of developing new drug on the basis of dock score and glide energy. So, in our work we take thymol which is dietary monoterpenoid and have potent neuroprotective activity, we make derivatives of thymol with thiophenol group and then docking was done with suitable receptors for antiepileptic property. The thymol thiophenol derivatives were designed using ChemDraw software and were docked with PDBID 5HVX and 3F8E protein receptors using Schrodinger software. Thymol thiophenol derivatives bind more efficiently than standard drug ethosuximide with protein receptors which is observed because the docking score and the glidant energy of the thymol thiophenol derivatives is much better than standard drug ethosuximide, which may conclude that thymol derivatives have potent anti-epileptic potential when bind to these receptors PDBID 5HVX and 3F8E.

Keywords: Thymol thiophenol; Molecular docking; Ethosuximide; Neurological disorder; Epilepsy

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Introduction

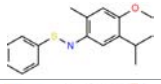
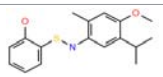
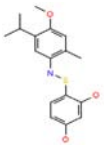
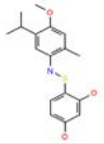
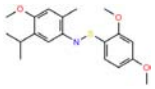
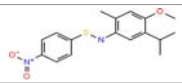
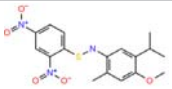
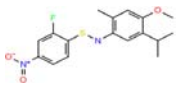
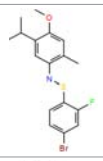
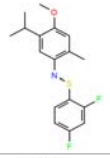
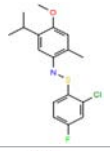
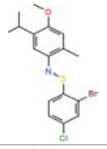
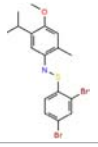
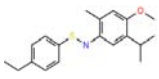
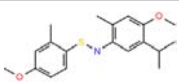
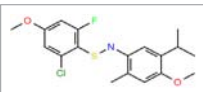
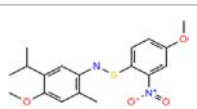
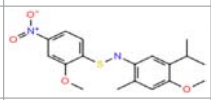
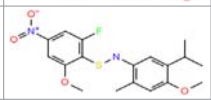
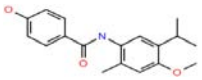
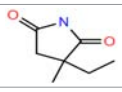
In neurological disorders mortality rate is being increased greatly throughout the last few decades [1]. Epilepsy is one these of neurological disorders which expanded their scope widely in a significant time interval [2]. Epilepsy consists of a frequent seizure's activity without any specific pattern [3]. The seizures growth and frequency can be interrupted and they can become severe through any external as well as internal injury [4]. The reason for this severity of seizures is the extensive and non-homogenized neurological activity in the cerebellar cortex [5]. Throughout time a number of drugs marketed for their significant antiepileptic activity [6]. However, with the current state new antiepileptic drugs are required and the best way to discover the potential of new antiepileptic drugs is via in silico method [7]. The molecular docking acquires significant characteristics and can help to elucidate antiepileptic results [8]. Various antiepileptic drugs like Phenytoin, Ethosuximide and Vigabatrin etc. are potential candidate which target the specific protein site with their unique mechanism. Eugenol exerted the strongest protection against seizures therefore, derivatives of thymol have been design using ChemDraw and evaluated in the comparison to marketed drugs. The structures of these drugs help to insulate their activity as per their docking score and binding energy. In this research, we introduced a thymol derivative i.e., thymol thiophenol in a set of specific molecules and docked for specific protein PDBID 5HVX and 3F8E [9,10].

Material and Methods

Molecular docking

The different compounds were formed by incorporating thymol origin derivatives thymol thiophenol with them (Table 1). These compounds were designed with the help of Insilico method i.e., Schrodinger (A1-A12). The process of formation of these compounds covers the use of ChemDraw 12.0 and the docking of these compounds with protein was done via Schrodinger suite v 18.1.

Table 1: Structure and IUPAC name of different derivatives of thymol thiophenol.

S.NO	Molecule	Structure	IUPAC Name
1	A		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-phenylthiohydroxylamine
2	B		2-(((5-isopropyl-4-methoxy-2-methylphenyl)amino)thio) phenol
3	C		4-(((5-isopropyl-4-methoxy-2-methylphenyl)amino)thio) benzene-1,3-diol
4	D		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-(4-methoxyphenyl) thiohydroxylamine
5	E		S-(2,4-dimethoxyphenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
6	F		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-(4-nitrophenyl) thiohydroxylamine
7	G		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-(4-nitrophenyl) thiohydroxylamine
8	H		S-(2-fluoro-4-nitrophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
9	I		S-(4-bromo-2-fluorophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
10	J		S-(2,4-difluorophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
11	K		S-(2-chloro-4-fluorophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
12	L		S-(2,4-dichlorophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
13	M		S-(2-bromo-4-chlorophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
14	N		S-(2,4-dibromophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
15	O		S-(4-ethylphenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
16	P		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-(4-methoxy-2-methylphenyl) thiohydroxylamine
17	Q		S-(2-chloro-6-fluoro-4-methoxyphenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
18	R		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-(4-methoxy-2-nitrophenyl)thiohydroxylamine
19	S		N-(5-isopropyl-4-methoxy-2-methylphenyl)-S-(2-methoxy-4-nitrophenyl)thiohydroxylamine
20	T		S-(2-fluoro-6-methoxy-4-nitrophenyl)-N-(5-isopropyl-4-methoxy-2-methylphenyl) thiohydroxylamine
21	Ethosuximide		(RS)-3-Ethyl-3-methyl-pyrrolidine-2,5-dione

Protein preparation

The molecular docking runs on algorithms which have some requirements i.e., for docking the molecule must have a charge on each atom with its coordinates which can give information about its properties yet the most proficient source to get protein structure i.e., PDB protein structure fails to give information to such extent. To fulfill these requirements, we have to prepare protein as well as ligand file which include all the required information with their atomic coordination. The protein of specific characteristics was required and that can be acquired through RCSB protein data bank. The target protein for epilepsy acquired from RCSB protein (i.e., PDB 5HVX and 3F8E) of greater resolution. The preparation of respective protein

Table 2: Docking score and glide energy of molecule with PDBID 5HVX.

S. no	Molecule Name	Docking Score	Glide energy (Kcal/mol)
1	A	-3.765	-20.450
2	B	-3.029	-19.831
3	C	-7.380	-13.873
4	D	-3.219	-20.309
5	E	-3.284	-23.414
6	F	-3.647	-21.008
7	G	-3.257	-23.382
8	H	-3.723	-22.870
9	I	-3.506	-21.222
10	J	-3.319	-20.946
11	K	-3.703	-21.733
12	L	-2.840	-22.035
13	M	-3.042	-22.843
14	N	-5.773	-15.706
15	O	-3.476	-22.368
16	P	-2.927	-23.006
17	Q	-3.560	-24.937
18	R	-3.310	-20.946
19	S	-3.080	-23.997
20	T	-6.416	-19.305
21	Ethosuximide	-4.159	-16.412

Table 3: Docking score and glide energy of molecules with PDBID 3F8E.

S. no	Molecule Name	Docking score	Glide Energy (Kcal/mol)
1	A	-3.075	-24.781
2	B	-6.972	-16.661
3	C	-7.205	-14.139
4	D	-3.068	-26.546
5	E	-3.272	-28.428
6	F	-3.346	-29.108
7	G	-3.408	-30.108
8	H	-3.335	-27.375
9	I	-2.867	-26.273
10	J	-3.111	-25.134
11	K	-3.621	-28.798
12	L	-2.782	-26.928
13	M	-2.725	-28.764
14	N	-3.049	-25.895
15	O	-3.248	-27.665
16	P	-3.013	-26.754
17	Q	-3.574	-30.171
18	R	-3.513	-29.952
19	S	-3.389	-29.965
20	T	-6.019	-11.228
21	Ethosuximide	-4.776	-17.423

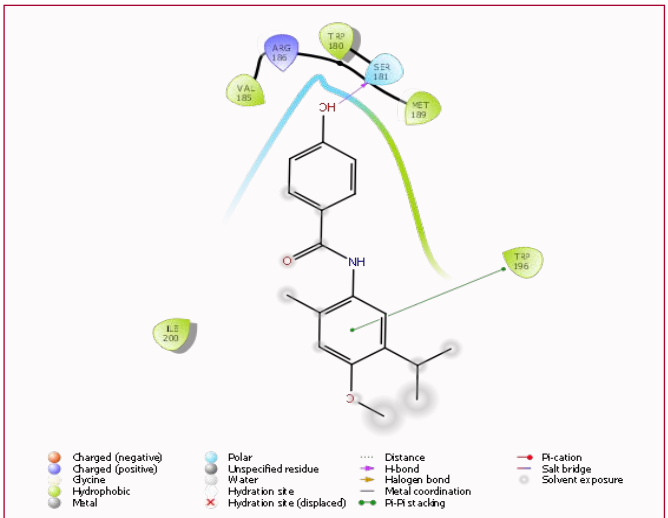
was performed in protein preparation wizard of the Schrodinger suite and preceded for further studies. In between docking process, the electrostatic treatment was done with the help of hydrogen atoms. Later on, the water molecules were separated and formed the bond order [11]. The possible factor for unstable atoms could be steric hinderance which was stabilized by optimization of charges and by controlling protein energy *via* OPLS force field [12].

Ligand preparation

The first step for ligand preparation is to know about their interaction with specific protein through which their potential for anti-epileptic activity can be measured. It can be achieved by preparing 3D ligands *via* Mol2 file. Various number of thymol derivatives were prepared via using maestro module after a significant study of literature. The respective 3D mol files were converted with the help of software Maegz file in LigPrep. After which selection of ligands as per criteria was done with help of OPLS force field module [13,14]. The docking process search algorithm and the energy score function was required and they perform the evaluation of ligand poses throughout the receptor binding site [15].

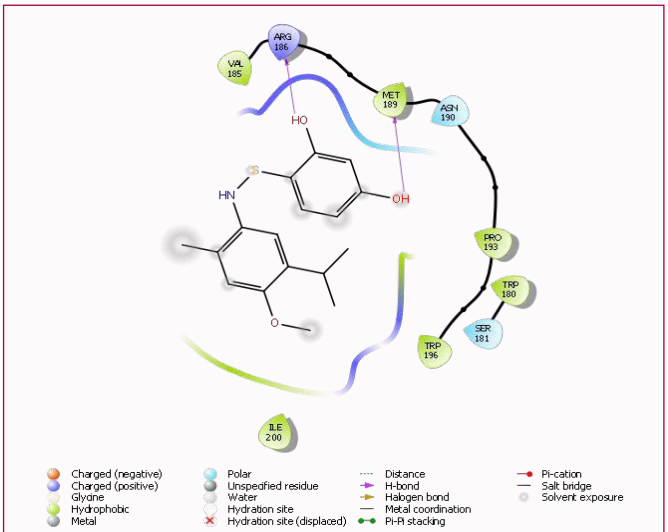
Grid generation and molecular docking

The grid generation of protein includes formation of grip at the prominent active site using certain tool i.e., site map tool. The process was further proceeded with prepared ligands to the receptor generated by the grid i.e., active site of protein. After that docking was performed with Standard Precision (SP) which helped to generate the dock scores values for a suitable protein ligand conformational complex [13]. All the thymol derivatives have their antiepileptic activities which were selected by literature survey and categorized through their docking scores performed *via* Schrodinger v 18.1, using PDB 5HVX and 3F8E (Table 2, 3) with respect to standard drug



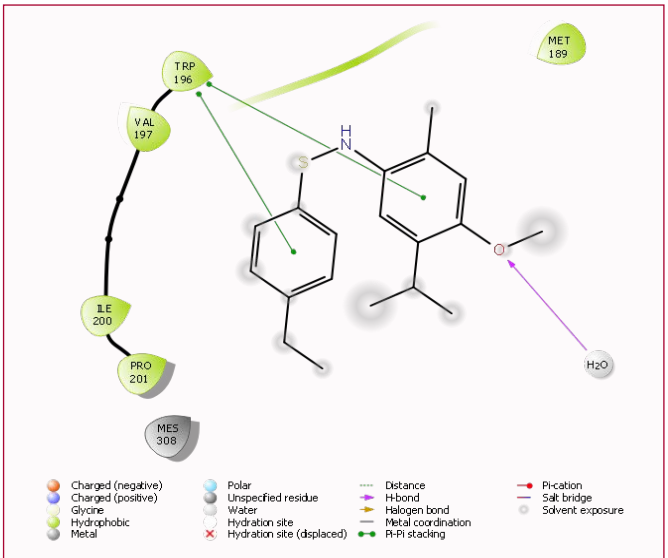
MOLECULE T

Figure 1: 2D ligand interaction of molecule T with PDBID 5HVX.



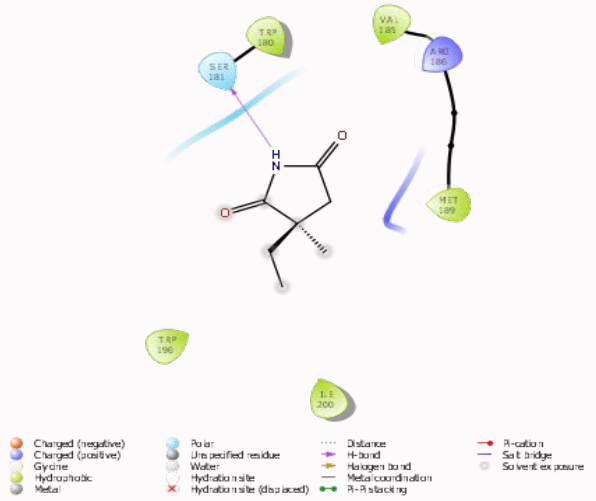
MOLECULE C

Figure 2: 2D ligand interaction of molecule C with PDBID 5HVX.



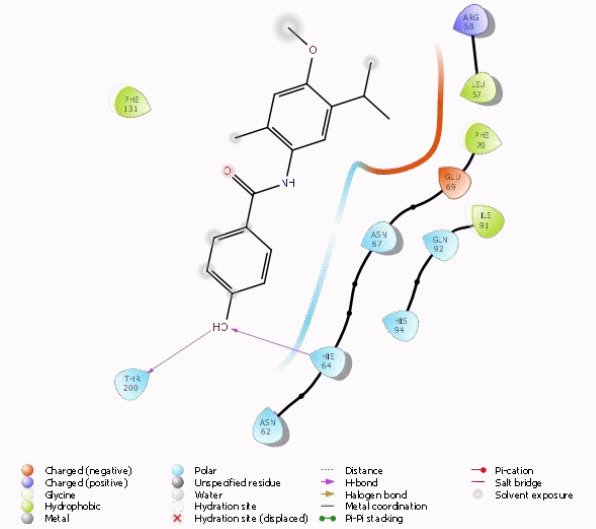
MOLECULE N

Figure 3: 2D ligand interaction of molecule N with PDBID 5HVX.



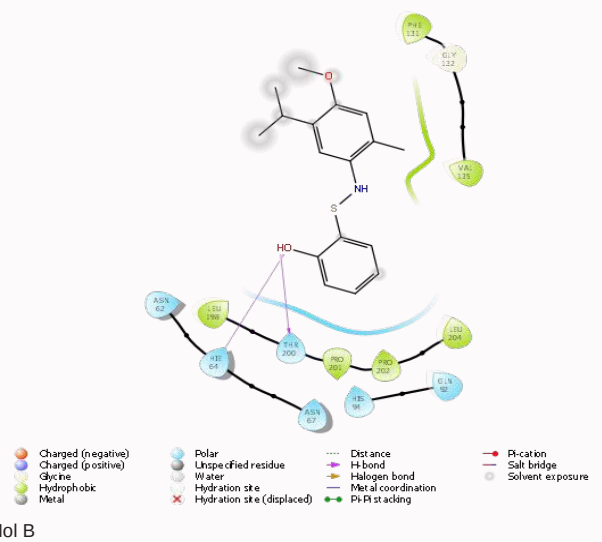
Ethosuximide

Figure 4: 2D ligand interaction of ethosuximide with PDBID 5HVX.



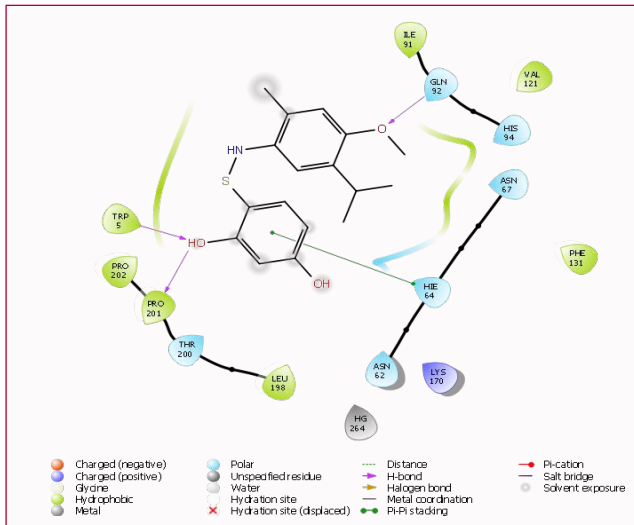
Mol T

Figure 5: 2D ligand interaction of molecule T with PDBID 3F8E.



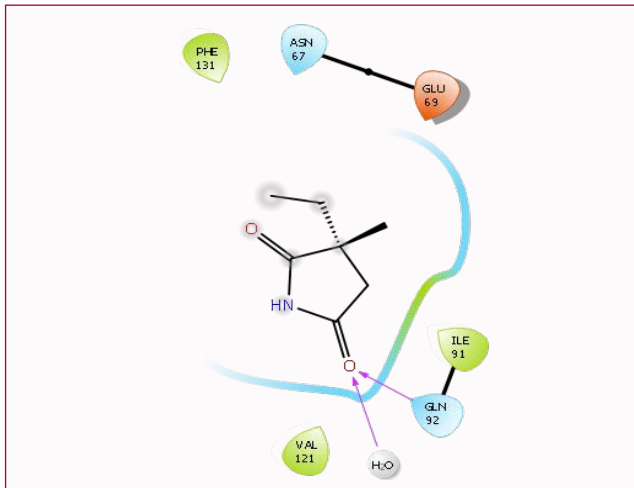
Mol B

Figure 6: 2D ligand interaction of molecule B with PDBID.



MOL C

Figure 7: 2D ligand interaction of molecule C with PDBID.



ETHOSUXIMIDE (standard)

Figure 8: 2D ligand interaction of ethosuximide with PDBID 3F8E.

ethosuximide. The docking scores of compounds was the screening factor for synthesis of those compounds with respect to the standard drug.

Results

The molecular protein docking of the thymol thiophenol derivatives for the evaluation of anti-epileptic potential have been studied in this study. The Table 2 demonstrated the docking score and glide energy of molecules which bind with 5HVX receptor from which molecule C (-7.380 dock score and -13.873 kcal/mol glide energy), N (-5.773 and -15.706 kcal/mol), and T (-6.416 and -19.305 kcal/mol) have much better dock score and glide energy as compared to standard drug ethosuximide (-4.159 and -16.412 kcal/mol). Similarly, Table 3 also shown the docking score and glide energy of molecules that bind with 3F8E receptor from which molecule B (-6.972 and -16.661), C (-7.205 and -14.139 kcal/mol) and T (-6.019 and -11.228 kcal/mol) have good dock score and glide energy as compared to standard drug ethosuximide (-4.776 and -17.423). The results of docking studies clearly shown that some derivatives of thymol thiophenol which mention above will be valuable finding of this work and if we synthesize them, then they will be more potent in

treating convulsion (Figures 1-8).

Conclusion

Thymol thiophenol derivatives designed in this study bind with both the receptors 5HVX and 3F8E efficiently which was observed on the basis of potent docking score and glide energy. Therefore, it can be concluded that some thiophenol derivatives of thymol show significant antiepileptic activity *via* these molecular receptors used in this study. The standard drug ethosuximide was less potent in treating epilepsy in comparison with some thymol thiophenol derivatives on the basis of dock score and glide energy.

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