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VIRTUAL SCREENING OF NEWER POTENTIAL COLONY STIMULATING FACTOR 1 INHIBITORS AS POTENT ANTIEPILEPTIC AGENTS

R. Priyadharsini * A. Dharuman, P. Nithya, P. Shalini and G. Sumithra

College of Pharmacy, Madras Medical College, Chennai - 600003, Tamil Nadu, India.

Keywords:

Epilepsy, CSF1R inhibitors, ADMET properties, Docking studies

Correspondence to Author:
Dr. R. Priyadarsini

Assistant Professor,
College of Pharmacy,
Madras Medical College, Chennai - 600003, Tamil Nadu, India.

E-mail: rpdharsinimpharam@yahoo.co.in

ABSTRACT: Background: Epilepsy is a chronic disorder that causes unprovoked, recurrent seizures like a sudden rush of electrical activity in the brain. Neuronal hyperexcitability in epilepsy is due to an imbalance between glutamate-mediated excitation and GABA-mediated inhibition. **Aim:** This prompted us to design newer CSF1R inhibitors as efficient therapeutic drugs for the treatment of epilepsy. **Materials and Methods:** Based on the common pharmacophoric features for the inhibition of CSF1R inhibitors, a series of leads were designed using computational methods. A virtual library consisting of newly designed 60 molecules as CSF¬1R inhibitors were constructed .Based on these facts, a virtual library has been generated with 60 newly designed ligands containing imidazole, benzo pyrrole, quinoline, oaxzole, quinoxaline, benzimidazole, heterocyclic nucleus as CSF1R inhibitors (60). The binding mechanism of newly designed ligands with target enzymes CSF1R inhibitors was studied using Auto dock tools 1.5.6. **Conclusion:** The designed compounds were subjected and filtered by applying ADMET properties. In comparison with docking scores of standard antiepileptic drugs vigabatrin (GABA-2.14, CSF1R-1, 31) and sodium valproate (GABA-3.19, CSF1R-3.6) and the newly designed ligands, CS1 (-6.61), CS3 (-6.22), CS14 (-6.04) were found to be highly active hits than that of standards.

INTRODUCTION: The word Epilepsy means "seizure disorders", the fourth most common neurological disorder which affects people of all ages. Epilepsy is a chronic disorder that causes unprovoked, recurrent seizures like a sudden rush of electrical activity in the brain [1]. For 6 in 10 people, the cause of a seizure can't be determined. Between 15 to 30 percent of children with intellectual disabilities have epilepsy. Between 30 and 70 percent of people who have epilepsy also have depression, anxiety, or both. Neuronal hyperexcitability in epilepsy is due to an imbalance between glutamate-mediated excitation and GABA-mediated inhibition.

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The symptoms of epilepsy are seizures, staring blankly, unresponsiveness, performing repetitive movements, biting of the tongue, loss of consciousness. Colony-stimulating factor 1 receptor (CSF1R), also known as macrophage Colony-stimulating factor receptor (M-CSFR) is a cell-surface protein encoded in humans, by the CSF1R gene (also known as c-FMS). It is a receptor for a cytokine called colony-stimulating factor 1. The main aim of the study is to identify novel, safe and effective newer antiepileptic agents with good predicted capability to inhibit the Colony Stimulating Factor 1 Receptor using Computational Drug Designing methods.

MATERIALS AND METHODS:

Selection of Target: Approximately one in three epilepsy patients are resistant to all currently available antiepileptic drugs (AED_S) and none of the current drugs are disease-modifying or curative which targets cell membrane receptors.

In order to connect module expression to cell membrane receptors, the colony-stimulating factor 1 receptor was identified as a novel therapeutic target for the treatment of epilepsy. The targets creating the greatest enthusiasm at this time for the treatment of epilepsy include colony-stimulating factor 1 receptor. Some of the recent and efficient PDB file receptors for the treatment of Epilepsy with low resolution were selected and further evaluated by their resolution value (R-value), optimized crystal ligand, and interaction details. Some of the selected receptors listed below from which the highlighted best PDB target was selected for the present study.

The active amino acid binding sites for the selected PDB (3BEA) of the CSF1R target were identified by reviewing the journals.

TABLE 1: LIST OF PDB FOR CSF1R TARGET FOR EPILEPSY

S. no.	Code	Resolution (A^o)	S. no.	Code	Resolution (A^o)
1	4R7H	2.8001	9	3LCO	3.4
2	4R7I	2.75	10	4HW7	2.9
3	3BEA	2.02	11	2OGV	2.7
4	3KRL	2.4	12	3EJJ	2.4
5	3DPK	1.95	13	4DKD	3.0
6	3KRJ	2.1	14	4EXP	2.8
7	2I1M	1.8	15	4WRL	2.8
8	3LCD	2.5	16	4WRM	6.85

TABLE 2: ACTIVE AMINO ACID SITE OFCSF1R TARGET

Receptor	PDB Code	Active Amino Acid Binding Sites
CSF1R	3BEA	Cys 666 (A), Glu 664 (A), Ala 614 (A), Leu 588 (A), Asp 802 (A), Arg 801(A), His 899 (A), Lys 586 (A), Tyr 665 (A), Gln 547 (A), Arg 816 (A), Gln 920 (A), Lys 883 (A), Pro 882 (A), Gln 913 (A), Phe 563 (A), Thr 562 (A), Asp 565 (A), Tyr 561 (A), Cys 666 (A), Lys 574 (A), Val 811 (A), Val 861 (A), His 757 (A), Tyr 575 (A), Leu 649 (A), Gln 642 (A), Gln 576 (A), Leu 650 (A), Arg 801 (A), Gln 904 (A), Ala 767 (A), Phe 903 (A), Glu 884 (A), Thr 563 (A), Asp 570 (A), Arg 816 (A), Gln 547 (A), Leu 799 (A), Thr 833 (A), Tyr 546 (A).

Pharmacophoric Identification: A Pharmacophore is defined as a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity [38]. Hence, all these chemical features were used as 3D structural query to screen the chemical database for retrieving new potent CSF1R inhibitors.

Database Screening: Based on the above quoted literature facts in designing potent CSF1R inhibitors, the target screening library was designed by using molecular fragments from a relatively narrow and low molecular weight range (300-5000D), selected diversity at both the putative "scaffold" core.

The analogue library was generated by modifying the respective functional groups with sterically and conformationally allowed substituent's using the reagent database and a computational design model.

Virtual Library: A virtual scaffold library consisting of newly designed 60 molecules has *CSF1R* inhibitors has been constructed.

Lead Optimisation:

Drug Likeness Screening: Drug likeness is a qualitative concept used in drug design for how a drug-like substance is to be an effective drug. Drug likeness properties were performed for all the newly designed CSF1R inhibitors using different online software like Lipinski's rule of five, Osiris online software, Mol inspiration software, and the results tabulated.

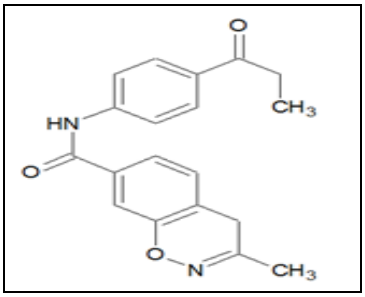
Docking Studies: All the designed ligands were subjected to docking studies using Auto dock tools *1.5.6* software, and the results were discussed below. Auto dock tools 1.5.6 are a molecular modeling simulation, especially effective for protein-ligand docking.

RESULTS AND DISCUSSION: In search of new and potent CSF_1R inhibitors as antiepileptic agents, a virtual scaffold library of 60 molecules was constructed using chem sketch by reviewing efficient articles and journals and based on features such as HBA, HBD, and HYP Pharmacophoric features.

TABLE 3: PHARMACOPHORIC FEATURES USED IN CONSTRUCTION OF LIBRARY OF CSF1R INHIBITORS

HBD	HBA	HYP
Imidazole, Thiadiazole, Benzimidazole, Aminothiazole, Phenolic-OH, Aniline, Alkyl amines, Oxazole, Morpholine.	C=O of aliphatic and aromatic amides, C=O of aromatic ketones, C=O of diamide	Phenyl, Biphenyl, Diazole, Pyridine, Triazole, Quinaxoline, Tolyl, Dimethyl benzene

VIRTUAL LIBRARY OF CSF1R INHIBITORS



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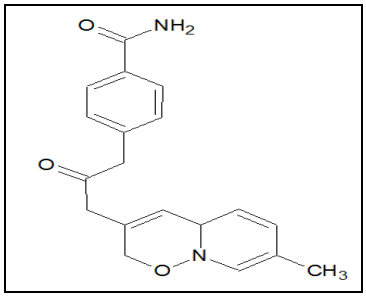

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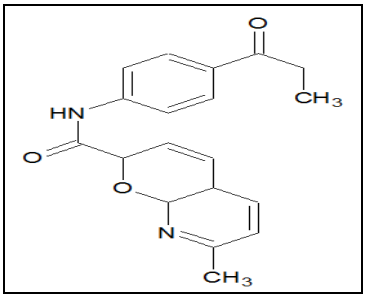

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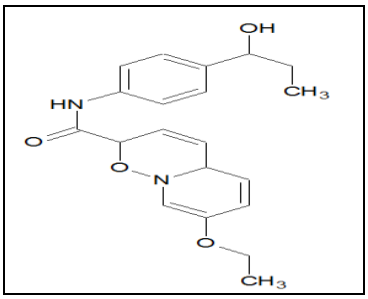

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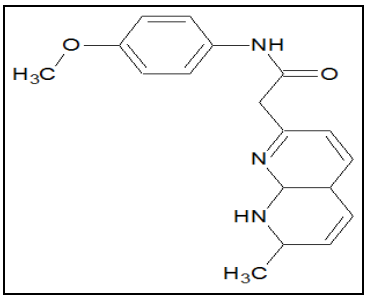

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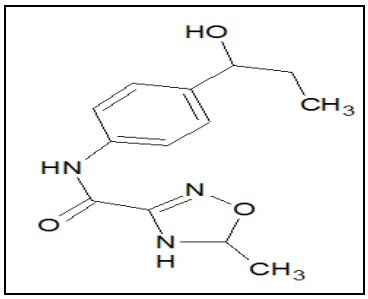

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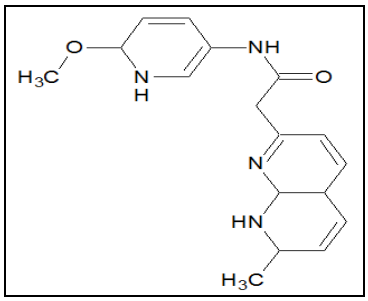

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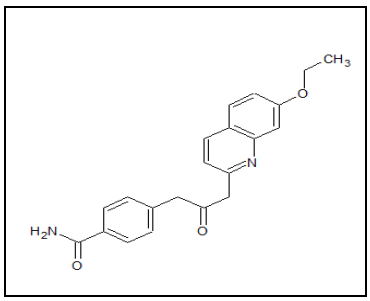

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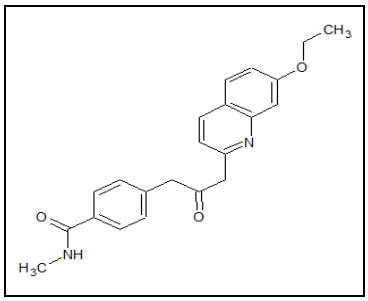

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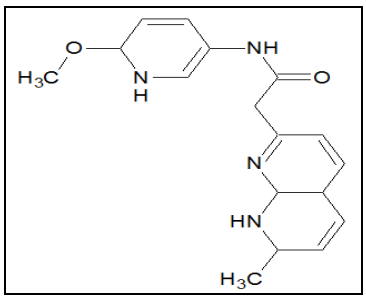

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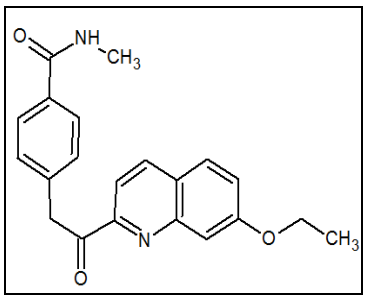

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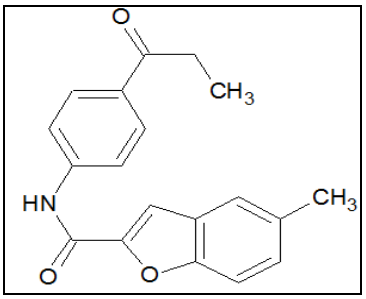

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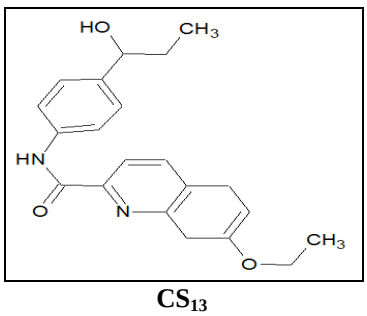

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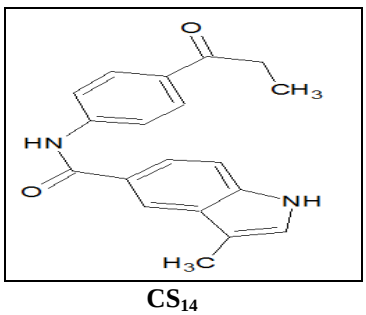

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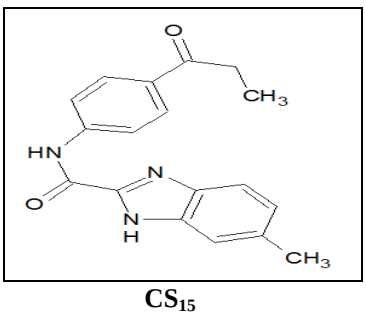

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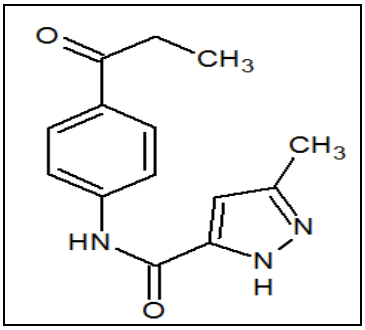

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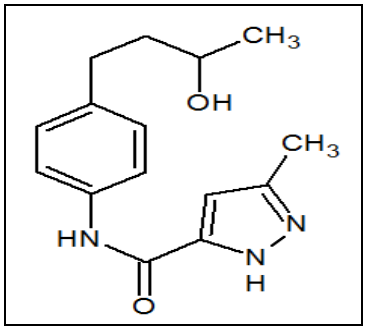

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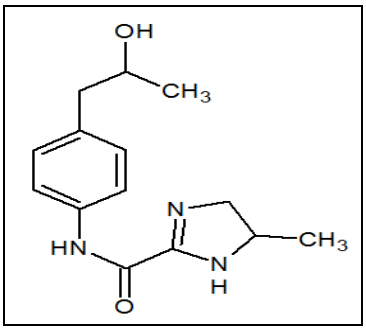

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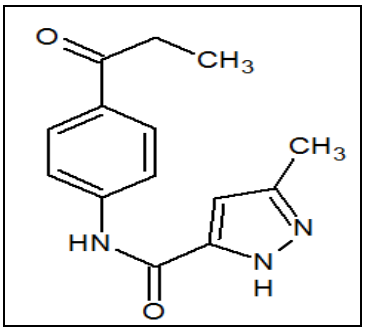

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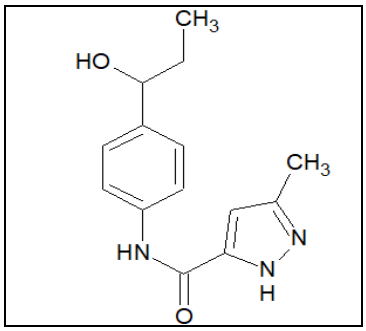

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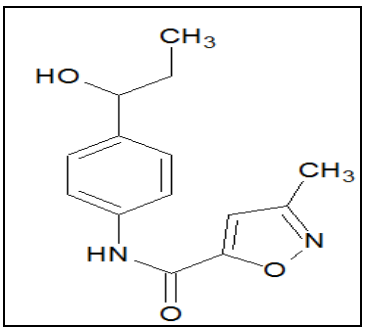

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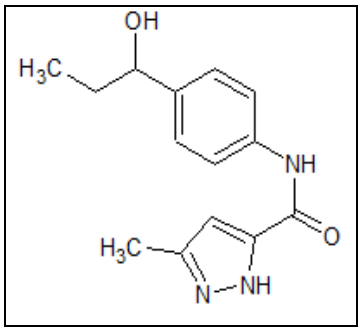

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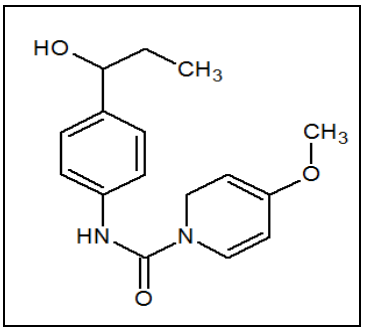

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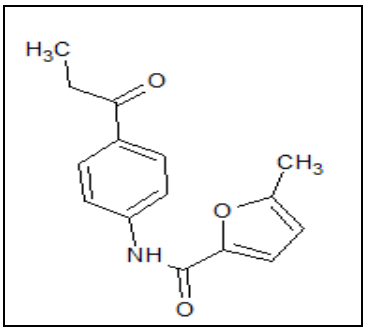

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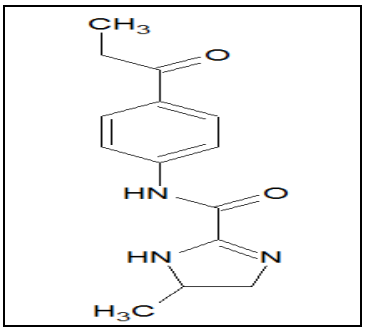

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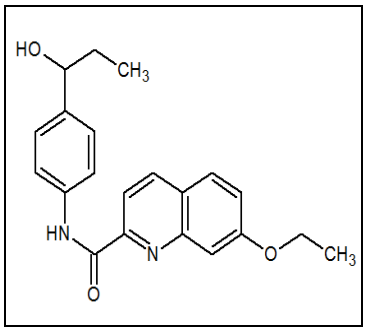

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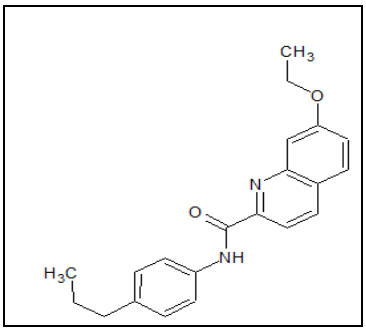

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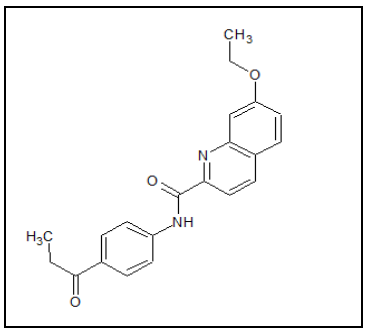

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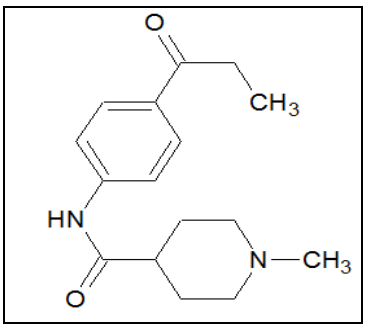

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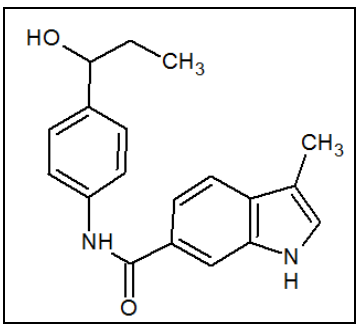

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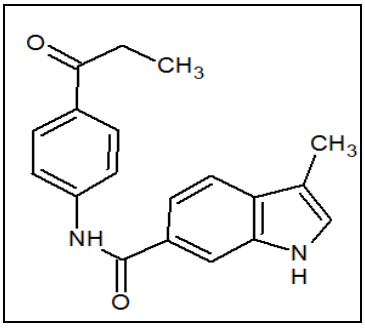

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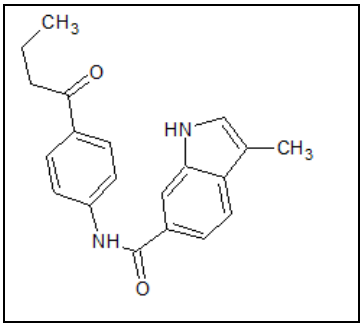

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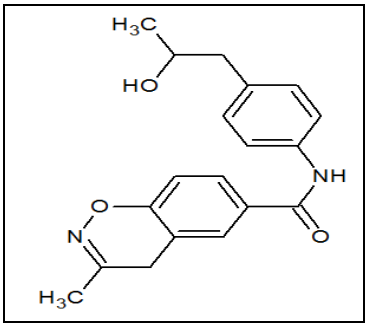

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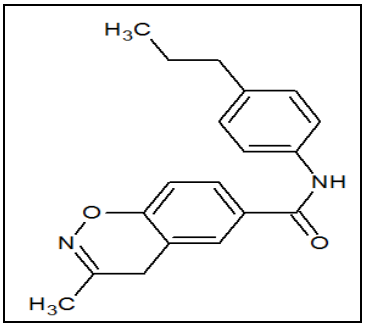

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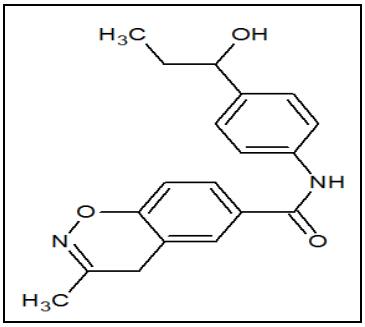

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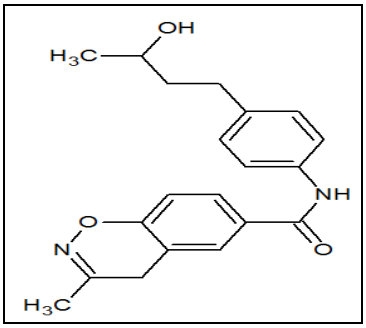

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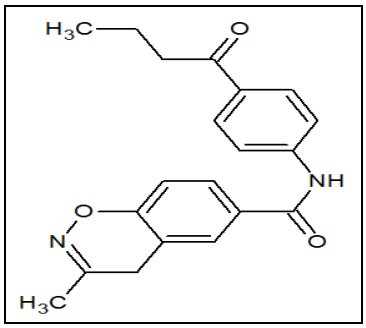

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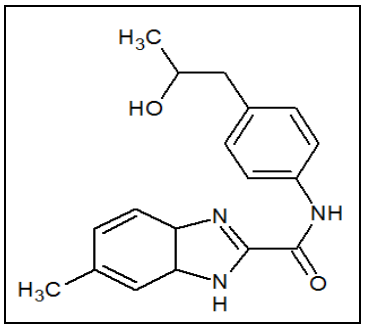

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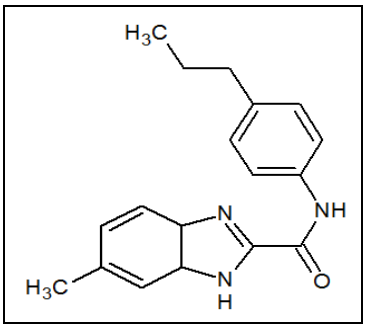

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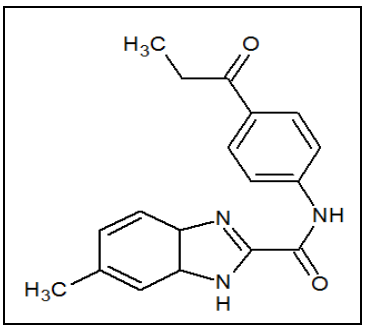

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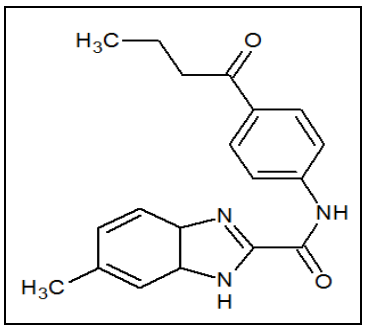
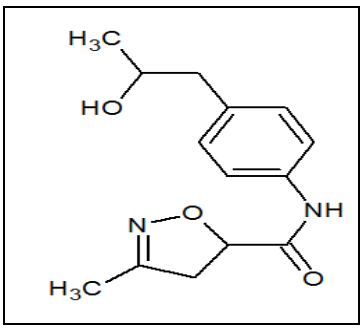
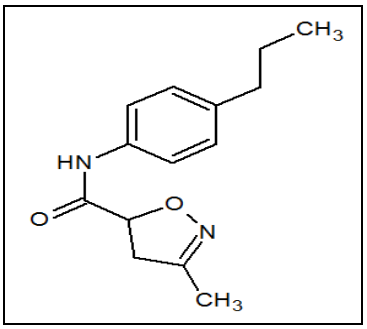


CS_{41}



CS_{42}



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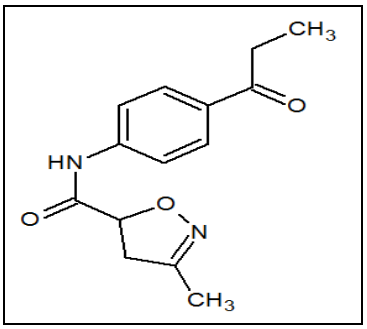

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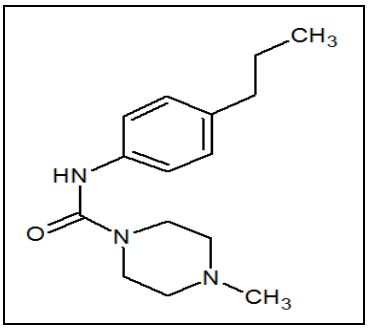

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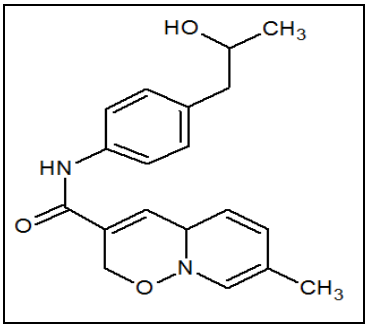

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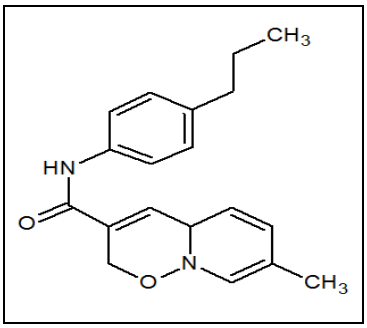

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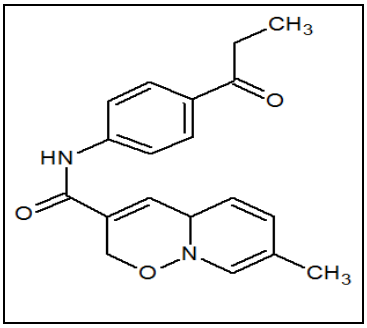

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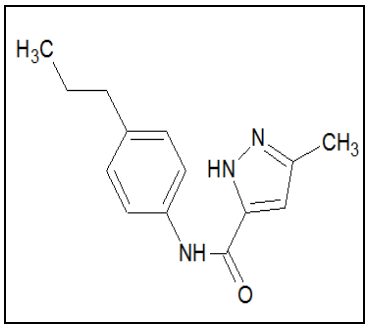

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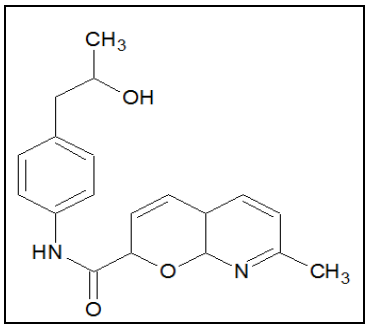

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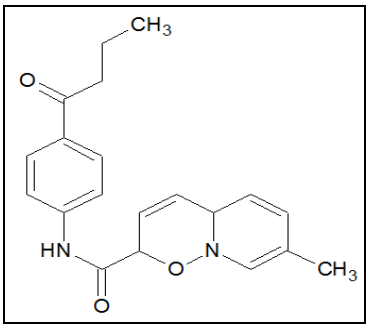

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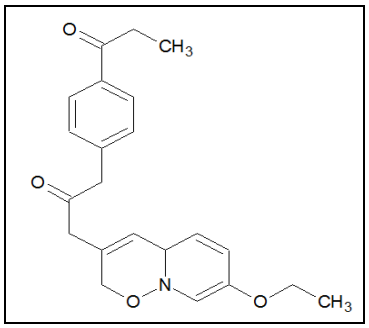

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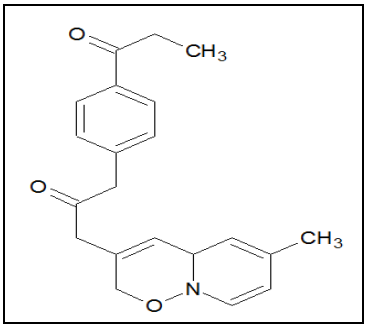

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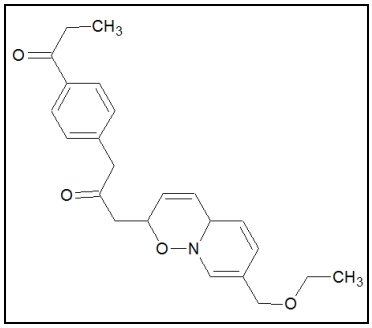

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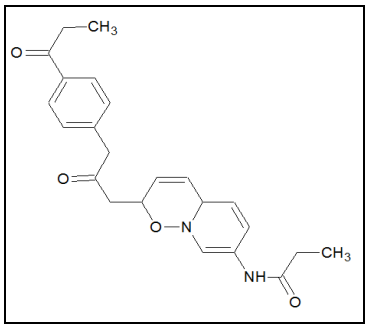

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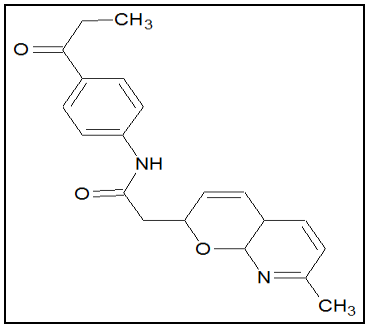

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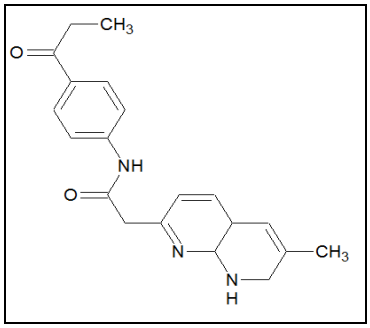
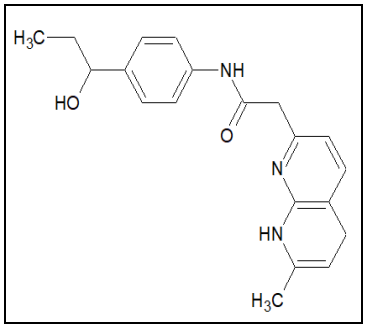


CS57



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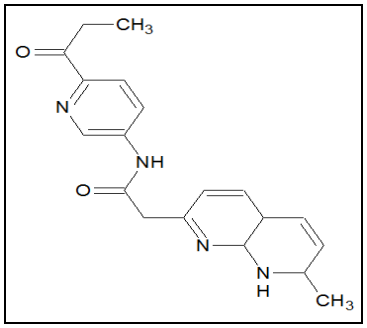

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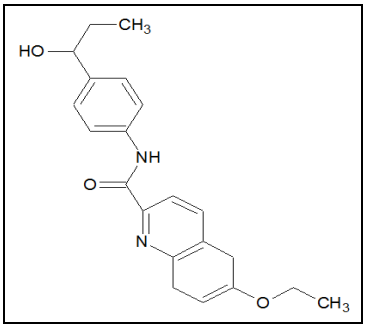


CS60

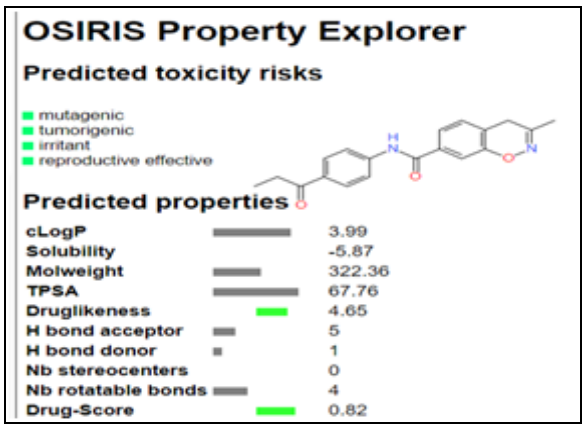
Drug Likeness Screening: The newly designed ligands were subjected to molecular docking, ADMET properties, and Lipinski rule of five, toxicity prediction. Through this, the newly generated ligands are filtered and refined, which constitutes optimization of leads. The compounds having better-estimated activity value and drug-like properties are filtered and considered for further molecular docking.

TABLE 4: LIPINSKI, S RULE OF FIVE FOR THE CSF1R INHIBITORS

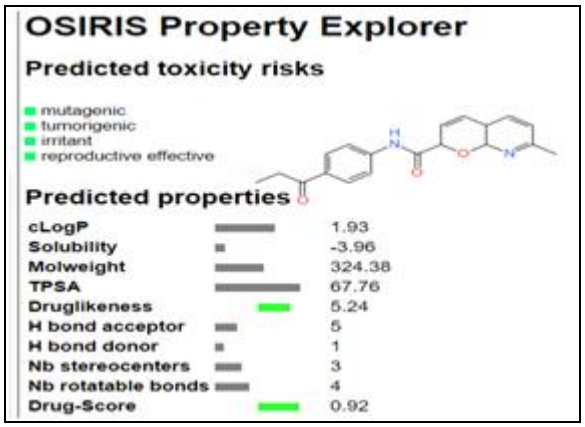
Compound	Log P	Mol. Wt	Tpsa	Nohnh	Non	No. of Rotatable Bonds	No. of Violations
Cs_1	3.54	322.4	67.77	1	5	4	0
Cs_2	1.78	324.38	72.64	2	5	5	0
Cs_3	1.94	324.38	67.77	1	5	4	0
Cs_4	2.74	356.42	71.03	2	6	6	0
Cs_5	1.98	311.38	62.72	2	5	4	0
Cs_6	1.06	263.30	82.95	3	6	4	0
Cs_7	0.72	314.39	74.75	3	6	4	0
Cs_8	2.39	348.40	82.29	2	5	7	0
Cs_9	2.77	362.43	68.30	1	5	7	0
Cs_{10}	2.94	348.40	68.30	1	5	6	0
Cs_{11}	1.60	269.30	71.95	1	5	4	0
Cs_{12}	4.22	307.35	59.31	1	4	4	0
Cs_{13}	3.38	350.42	71.45	2	5	6	0
Cs_{14}	3.80	306.37	61.96	2	4	4	0
Cs_{15}	3.25	307.35	74.85	2	5	4	0
Cs_{16}	2.07	257.29	74.85	2	5	4	0
Cs_{17}	2.10	273.34	78.01	3	5	5	0
Cs_{18}	1.05	259.31	78.01	3	5	4	0
Cs_{19}	2.10	271.32	74.85	2	5	5	0
Cs_{20}	1.74	259.31	78.01	3	5	4	0
Cs_{21}	1.84	260.29	75.36	2	5	4	0
Cs_{22}	1.74	259.31	78.01	3	5	4	0
Cs_{23}	1.31	288.35	61.80	2	5	4	0
Cs_{24}	2.71	257.29	59.31	1	4	4	0
Cs_{25}	1.42	259.31	70.56	2	5	4	0
Cs_{26}	3.38	350.42	71.45	2	5	6	0
Cs_{27}	4.62	334.42	51.22	1	4	6	0
Cs_{28}	3.71	348.40	68.30	1	5	6	0
Cs_{29}	2.32	274.36	49.41	1	4	4	0
Cs_{30}	3.47	308.38	65.12	3	4	4	0
Cs_{31}	3.80	306.37	61.96	4	2	4	0
Cs_{32}	4.36	320.39	61.96	2	4	5	0
Cs_{33}	3.05	324.38	70.92	2	5	4	0
Cs_{34}	4.45	308.38	50.70	1	4	4	0
Cs_{35}	3.21	324.38	70.92	2	5	4	0
Cs_{36}	3.57	338.41	70.92	2	5	5	0
Cs_{37}	4.10	336.39	67.77	1	5	5	0
Cs_{38}	2.76	309.37	78.01	3	5	4	0
Cs_{39}	4.16	293.37	57.78	2	4	4	0
Cs_{40}	3.25	307.35	74.85	2	5	4	0
Cs_{41}	3.81	321.38	74.85	2	5	5	0
Cs_{42}	1.42	262.31	70.92	2	5	4	0
Cs_{43}	2.81	246.31	50.70	1	4	4	0
Cs_{44}	1.91	260.29	67.77	1	5	4	0
Cs_{45}	2.89	261.37	35.57	1	4	3	0
Cs_{46}	2.43	326.40	61.80	2	5	4	0
Cs_{47}	3.82	310.40	41.57	1	4	4	0
Cs_{48}	1.58	259.31	78.01	3	5	4	0
Cs_{49}	2.98	243.31	57.78	2	4	4	0
Cs_{50}	2.48	326.40	61.80	2	5	4	0
Cs_{51}	3.53	338.41	58.64	1	5	5	0

Cs_{52}	3.52	367.44	55.85	0	5	8	0
Cs_{53}	3.41	337.42	46.61	0	4	6	0
Cs_{54}	3.16	381.47	55.85	0	5	9	0
Cs_{55}	2.95	394.47	75.71	1	6	8	0
Cs_{56}	2.21	338.41	67.77	1	5	5	0
Cs_{57}	2.68	337.42	70.56	2	5	5	0
Cs_{58}	1.98	337.42	70.56	2	5	5	0
Cs_{59}	0.98	338.41	83.45	2	6	5	0
Cs_{60}	3.38	350.42	71.45	2	5	6	0

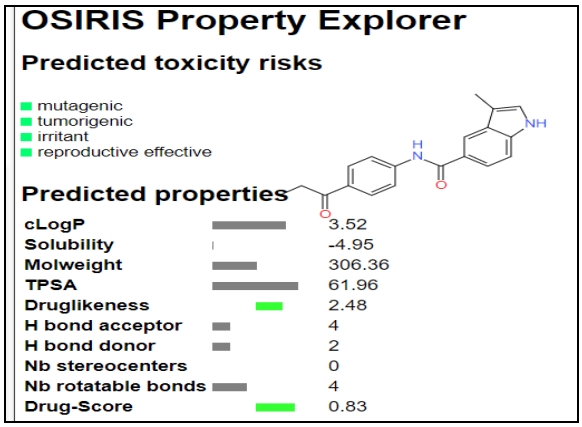
Toxicity: Thus, all newly designed ligands (CSF1R inhibitors) have satisfied all the above filtering method of good predictive activity with good docking scores and also drug-likeness properties confirming that these molecules are accepted to be orally bioavailable.



CS_1



CS_3



CS_{14}

Docking Results:

Docking Studies: Auto dock tools 1.5.6 is a molecular modeling simulation, especially effective for protein-ligand docking. Based on docking scores, all the newly designed ligands were categorized as highly active, moderately active, and low active hits as below. Based on docking scores, all the newly designed ligands were categorized as highly active, moderately active, and low active hits as below.

TABLE 4: LIST OF DOCKING SCORE FOR DESIGNED CSF1RLIGANDS (AUTODOCK 1.5.6)

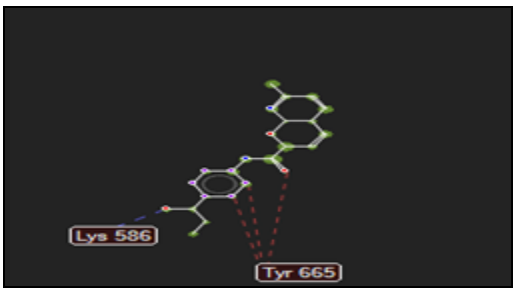
Ligand	Docking Score	No. of Interactions	Hydrogen Bond Interaction
CS_1	-6.61	7	i) Nitrogen of benzoxazine group with Cys666.
CS_2	-4.12	1	i) Nitrogen of benzamide group with His899.
CS_3	-6.22	4	i) Oxygen of carbonyl group with Lys586.
CS_4	-4.41	2	i) NH group with Gln547. ii) Oxygen of carbonyl group with Arg816
CS_5	-4.62	2	i) Oxygen of methoxy group with Gly605. ii) NH group with Lys574.

CS_6	-5.07	3	i) Oxygen of hydroxyl group with Ala800 ii) Oxygen oxadiazole group with Cys666.
CS_7	-4.92	4	i) Oxygen of methoxy group of Lys883. ii) Oxygen of carbonyl group with Gln913.
CS_8	-3.34	5	i) Oxygen of carbonyl group with Asp565 ii) Quinoline group with Tyr561
CS_9	-3.5	4	i) Nitrogen group of Methyl benzamide group with Lys574
CS_{10}	-5.05	2	i) Oxygen of carbonyl group with Tyr665
CS_{11}	-4.38	6	i) Nitrogen of pyridazine group with Cys883
CS_{12}	-4.44	1	i) Oxygen of Benzofuran group with Lys574
CS_{13}	-4.28	3	i) Hydroxyl group with Glu554 ii) NH group with Leu588
CS_{14}	-6.04	4	i) N of Indole group with Glu664
CS_{15}	-4.73	6	i) NH group with Gly603
CS_{16}	-3.38	5	i) Oxygen of carbonyl group with Val834 ii) Nitrogen of pyrazole group with Glu554
CS_{17}	-3.19	7	i) NH group with Lys574 ii) Nitrogen of pyrazole group with Glu554
CS_{18}	-3.38	3	i) Nitrogen of pyrazole group with Arg801
CS_{19}	-3.15	2	i) Nitrogen of pyrazole group with Val811 ii) Oxygen of carbonyl group with Val811
CS_{20}	-4.29	5	i) Oxygen of carbonyl group with Ser632 ii) Hydrogen group with Arg549
CS_{21}	-3.53	3	i) Hydrogen group with Glu554 ii) Oxygen of carbonyl group with Lys551
CS_{22}	-3.75	3	i) Hydroxyl group with Arg816 ii) N of pyrazole group with Val861
CS_{23}	-3.55	4	i) NH group with Gly789
CS_{24}	-3.72	3	i) NH Group with Ala879
CS_{25}	-3.92	5	i) Oxygen of carbonyl group with Ala592 ii) Nitrogen of pyrazole group with Arg816
CS_{26}	-4.34	3	i) Hydroxyl group with Ser555 ii) Hydroxyl group with Asn773
CS_{27}	-4.38	3	i) NH group with Phe880
CS_{28}	-4.96	4	i) Ethoxy group with Tyr665
CS_{29}	-4.28	5	i) NH group with Ala767 ii) Oxygen of carbonyl with Phe903
CS_{30}	-5.3	4	i) Hydroxyl group with Asp670
CS_{31}	-4.68	2	i) Oxygen of carbonyl group with Glu858
CS_{32}	-4.42	6	i) Oxygen of carbonyl group with Gly858 ii) Hydrogen of Indole group with Val861
CS_{33}	-4.93	5	i) Hydroxyl group with Arg816 ii) Oxygen of carbonyl group with Gln574
CS_{34}	-4.75	4	i) Nitrogen and Oxygen of Benzoxazine group with Tyr556
CS_{35}	-4.75	7	i) NH group with Gln835 ii) Oxygen of benzoxazine group with Tyr833
CS_{36}	-5.03	6	i) Hydroxyl group with Tyr556 ii) Oxygen and Nitrogen of benzoxazine group with Gln904
CS_{37}	-4.83	2	i) Oxygen of benzoxazine group with Lys606 ii) Oxygen of carboxyl group with Thr787
CS_{38}	-4.64	6	i) Hydroxyl group with Cys666 ii) Nitrogen of benzimidazole group with Leu588
CS_{39}	-4.86	5	i) Oxygen of carbonyl group with Tyr668
CS_{40}	-4.85	4	i) Nitrogen of benzimidazole group with Asn814
CS_{41}	-4.4	4	i) Oxygen of carbonyl group with Glu835 ii) Nitrogen of benzimidazole group with Glu835
CS_{42}	-4.1	5	i) Hydroxyl group with Gln642 ii) Nitrogen and Oxygen of oxazole group with Gls605
CS_{43}	-4.95	4	i) Oxygen and Nitrogen of oxazole group with Asp802 ii) NH group with Ala800

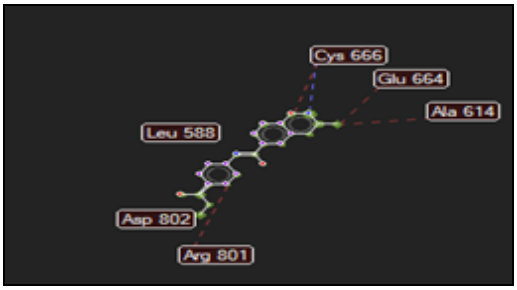
CS_{44}		-5.38	5	i) Nitrogen of oxazole group with Asp802
CS_{45}		-4.23	2	i) NH group with Glu576
CS_{46}		-4.82	3	Hydroxyl group with Asp802
CS_{47}		-5.13	3	i) NH group with Ala800
CS_{48}		-5.73	3	i) NH group with Ala800
CS_{49}		-4.34	1	i) Nitrogen of pyrazole group with Leu588
CS_{50}		-4.47	4	i) Oxygen of carbonyl group with Lys793 ii) NH group with Glu664
CS_{51}		-4.91	3	i) Oxygen of carbonyl group with Lys586
CS_{52}		-4.13	3	i) Oxygen of pyridoxazine group with Lys678
CS_{53}		-4.37	3	i) Oxygen of carbonyl group with Val811 ii) Oxygen of pyridoxazine group with Lys820
CS_{54}		-4.18	3	i) Oxygen of carbonyl group with Lys574
CS_{55}		-4.65	5	i) Nitrogen of pyridoxazine group with Lys574
CS_{56}		-4.44	4	i) Oxygen of pyrazole group with Gls605
CS_{57}		-5.6	*5*	i) *Oxygen of carbonyl group with Lys616* ii) *Nitrogen of Naphthyridine group with Leu588*
CS_{58}		-4.71	*4*	i) *Nitrogen atom with Gln 904*
CS_{59}		-4.83	6	i) Nitrogen of naphthyridine group with Lys574 ii) NH group with Lys574
CS_{60}		-4.26	2	i) Oxygen of carbonyl group with Gln835
Sodium Valproate	GABA	-3.19	9	i) Keto group with Lys 48 ii) OH group with Leu 50
	CSF1R	-3.6	2	i) keto group with Arg 777 ii) OH group with Arg 649
Vigabatrin	GABA	-2.14	4	i) NH_2 Group with Glu 17 ii) NH_2 Group with Tyr 5
	CSF1R	-1.31	2	i) NH_2 Group with Glu 554

TABLE 5: DOCKING RESULTS OF CSF1R INHIBITORS USING AUTODOCK TOOLS 1.5.6

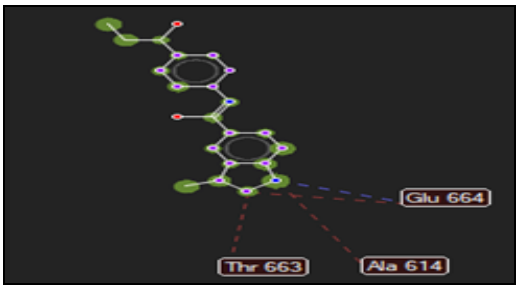
S. no.	Receptor	Highly Acting (>6)	Moderately Acting (4-6)	Low Acting (<4)
1.	CSF1R Inhibitors	CS_1,CS_3,CS_{14}	CS_2, CS_4, CS_5, CS_6, CS_7, CS_{10}, CS_{11}, CS_{12}, CS_{13}, CS_{15}, CS_{20}, CS_{26}, CS_{27}, CS_{28}, CS_{29}, CS_{30}, CS_{31}, CS_{32}, CS_{33}, CS_{34}, CS_{35}, CS_{36}, CS_{37}, CS_{38}, CS_{39}, CS_{40}, CS_{41}, CS_{42}, CS_{43}, CS_{44}, CS_{45}, CS_{46}, CS_{47}, CS_{48}, CS_{49}, CS_{50}, CS_{51}, CS_{52}, CS_{53}, CS_{54}, CS_{55}, CS_{56}, CS_{57}, CS_{58}, CS_{59}, CS_{60}	CS_8, CS_9, CS_{16}, CS_{17}, CS_{18}, CS_{19}, CS_{21}, CS_{22}, CS_{23}, CS_{24}, CS_{25}



CS1



CS3



CS14

CONCLUSION: Virtual screening of the Molecular chemical database has revealed that all the 60 newly designed CSF1R inhibitors containing hydrogen bond acceptor lipid (HBAL), hydrogen bond donor (HBD), hydrophobic (HYP) features have a crucial role in the treatment of epilepsy. Nearly 20 proposed ligands were found to be effective in inhibiting *CSF1R* by exhibiting two hydrogen bond interactions. In comparison with docking scores of standard antiepileptic drugs Vigabatrin (GABA-2.14,CSF1R-1.31) and Sodium valproate (GABA-3.19, CSF1R -3.6) and the newly designed ligands, CS_1 (-6.61), CS_3 (-6.22), CS_{14} (-6.04) were found to be highly active hits than that of standard. Hence, we propose that the final lead compounds like CS_1 (3-methyl-N-(4-propanoyl-phenyl) - 4H - 1, 2-benzoxazine-7-carboxamide), CS_3(7-methyl-N-(4-propanphenyl)-4a-8a-dihydro 2H-pyrano[2,3-b] pyridine-3-carboxamide), CS_{14} (3-methyl – N - (4 - propanoylphenyl) - 1H - indole-5 carboxamide) as a possible virtual leads to design novel *CSF1R* inhibitors which can be synthesized and evaluated for *in-vitro* and *in-vivo* antiepileptic screening further, in future studies.

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CONFLICTS OF INTEREST: Nil

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