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Designing of Triazolethione Nucleus Derivatives as Gamma-Amino butyric Acid (GABA) Activators Using Pharmacophore Modeling, 2D-QSAR, and Molecular Docking Approach

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ABSTRACT

New Chemical Entities (NCEs) were designed using information from pharmacophore profile of known anticonvulsants. Binding affinities of designed NCEs were studied on gamma-aminobutyric acid (GABA-alpha) using docking studies. Two Dimensional (2D) Quantitative Structure–Activity Relationship (QSAR) studies were performed for correlating the chemical composition of triazolethione analogs and estimation of their anticonvulsant activity using Multiple Linear Regression (MLR) Analysis. ADMET properties were also predicted. These four basic strategies (pharmacophore mapping, QSAR, docking & ADMET screening) were implemented to evaluate the performance of derivatives. Although predicted Ki through QSAR model showed significant mild activity for GABA. Conclusively compounds, 2, 6, 7, 8, 9, 10, 11, and 20 were observed to be most feasible to activate GABA for anticonvulsant activity.

Keywords: ADMET; Anticonvulsant; Docking; Epilepsy; GABA; Pharmacophore; QSAR; Triazolethione.

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INTRODUCTION

Epilepsy, neurological disorder, is characterized by an enduring predisposition to generate seizures and by its neurobiological, cognitive, psychological, and social consequences [1-2]. Worldwide, nearly 50 million people are diagnosed with epilepsy, of which 90 % of the cases occur in developing countries and more than 250,000 new cases surfacing every year, as of 2013, about 22 million people have epilepsy [3-6]. In India about 10 million people are affected with epilepsy (prevalence of about 1%) [7,] this being higher in the rural (1.9%) as compared with the urban counterpart (0.6%) [8-10.] The reason behind epilepsy has been defined on the basis of single gene defect, an interaction of multiple genes as well as environmental factors [11.] Most of the interacting genes are known to be involved with ion channels, enzymes, Gamma-Amino-Butyric-Acid (GABA), and G-protein-coupled receptors [12.]The main strategy for epilepsy treatment is pharmacotherapy with antiepileptic or anticonvulsant drugs [13.]A number of anti-epileptic drugs (AEDs) such as topiramate [14], lamotrigine [15], tiagabine [16], felbamate [17,] vigabatrin [18], and zonisamide [19] have been introduced to treat epilepsy diseases. However, 20-30% of patients are failed to control seizures by current medications. At present, the most commonly used antiepilepsy/anticonvulsant therapy for synaptic transmission are through the concomitant use of drugs that belongs either to the class of GABA activator (GA), Na+/Ca++ inhibitor (NCaI), Glutamate receptor inhibitor (GRI), and PPAR-alpha activator (PPARa). GA is structurally diverse group of compounds which binds to the GABA (alpha, beta or delta), where it interacts with a specific allosteric non-substrate binding pocket site. GA non-competitively activates the GABA [20.] Currently, drugs used to treat epilepsy under GA for anticonvulsant therapy are Gabapentin, Nefiracetam, and Zolpidem etc. Triazolethione analogs, due to the importance of triazolethione backbone have shown a variety of biological activities such as anticonvulsant, anti-migraine[21-24]. Molecular modeling approach used to design novel compounds based on existing potential drugs as well as leads which opened a new prospect in the drug discovery area. The available databases and bioinformatics tools help us to determine potential leads [25- 26]. Recently, pharmacophore mapping, 2D/3D QSAR, and docking guided optimization of identification of novel compounds has been used as important strategies in the discovery of new anticonvulsants [27-29]. ADMET screening of newly designed molecules provides a pre-clinical trial scaled analysis for their bioavailability and drug-like possibilities [30-31].These approaches are inexpensive and more practical than discovering novel compounds. Recently L.Tripathi and P. Kumar have investigated differentN-(substituted)-2-[4-(substituted)benzylidene]hydrazine carbothioamides by GABAergic

neurotransmission as potential anticonvulsant compounds[32]. In the recent past S.N.Pandeya, Laxmi Tripathi and co-workers have also developed different semicarbazone as anticonvulsant compounds[33-39]. Thus we have focused our aim on computer-aided design of GA containing triazolethione nucleus with simultaneous goals of enhanced performance against GABA. For achieving this aim and optimizing the pharmacophore requirement of triazolethione nucleus for a design of potent and selective activator of GABA, pharmacophore profiling of known anticonvulsants is carried out. New Chemical Entities (NCEs) are designed using pharmacophore information from existing drugs from literature survey. In order to gain molecular interaction insights, docking studies of NCEs are carried out targeting GABA. The possible activity of NCEs was obtained from two-dimensional (2D) Quantitative Structure–Activity Relationship (QSAR) studies using Multiple Linear Regression (MLR) Analysis. ADMET properties are used to estimate the drug like a pharmacokinetic profile of the designed NCEs. The most promising compounds can be selected on the basis of results of molecular modeling studies. In the present study, triazolethione derivatives have been presented as novel anticonvulsant agents targeting GABA. After confirmation of molecular interaction, their activity and ADMET screening of derivatives were performed for cross-evaluation of their performance for identification of most possible novel compounds.

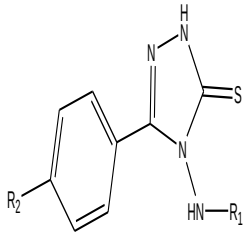


Figure 1: Scaffold used in designing of triazolethione derivatives

COMPUTATIONAL METHODS

Raw Data

Raw data for anticonvulsant activity was collected from literature as well as databases. Anticonvulsant activity was collected in terms of Ki (nM) value against GABA. Bioactivity in term of Ki nM (inhibition constant) was transformed to (natural) log Ki (nM) for normalization of a dataset. The 3D structure of GABA-alpha was modeled by homology method.

Pharmacophore profiling of compounds

Pharmacophore properties of anticonvulsant compounds were identified through literature definitions for anticonvulsant activity. The pharmacophore properties were used for designing of

triazolethione derivatives. The pharmacophore profiles of designed molecules were judged in comparison of positive control compounds.

Structural modeling and optimization

ChemBioDraw Ultra v12.0 modeling suite (CambridgeSoft Corp., UK) was used for sketching of compounds under study. Molecule's geometry cleaning and energy minimization were performed by Discovery studio 3.5 client (Accelrys USA). It was also used for conversion of 2D to a 3D structure.

Docking simulation parameters

The AutoDock Vina[40] 4.2 was used for virtual high throughput screening of compounds against glutamate receptor. Docking of known positive control was used for identification of the best possible binding site of query molecules. During docking simulation process, the ligand was set to flexible mode, while the protein set to rigid form. All other docking simulation parameters were set to default mode.

Chemical descriptors and QSAR modeling parameters

To screen out potential leads for GABA activation, a total of known anticonvulsant compounds with low to high Ki (nM) values were collected in the raw data set from PubChem database of NCBI[41]. To select the compounds for model development, pharmacophore features of control & query compounds were matched. Only best-selected compounds were used for model building. Molecular descriptors were calculated through PaDEL-Descriptors software [42.] After removing zero values descriptors, the descriptors were selected through data reduction through a removal of highly inter-correlated descriptors followed by forward selection and backward elimination procedures. Finally, a total of 14 known anticonvulsant compounds with experimental Ki and one molecular descriptor were found to be involved in the model building using multiple-linear-regression (MLR) method. The QSAR model robustness and prediction quality were represented by high regression coefficient (R^2) value. Cross-validation of QSAR model was done by LOO (Leave-one-out) approach. The applicability domain of derived QSAR model was indicated by cross-validation regression coefficient (R^2_{CV}). Evaluation of model was also performed through the residual plot.

Evaluation of pharmacokinetic behavior through Lipinski's rule of five and ADMET parameters

Potential leads may fail to clear the clinical trial approval through FDA due to unmatched standard pharmacokinetic properties. The key pharmacokinetic properties were represented by 'admetSAR' as used by Drug Bank database. Besides this, Lipinski's rules of five, [43] along with other

physicochemical properties were used to explain the pharmacokinetic behavior of compounds. TPSA and MW (cutoff= ≤500) were used to evaluate the fractional absorption of compounds. Bioavailability of compounds was evaluated by topological PSA (polar surface area) (cutoff= ≤140 $Å^2$). These descriptors also represent the passive membrane transport. For estimation of fractional absorption, a sum of H-bond donors and acceptors was used. Additionally, a number of rotatable bonds also used as a measure of bioavailability. The pharmacokinetic behavior of drug distribution depends on membrane permeability (estimated by Caco-2 cell line), blood-brain barrier and distribution (volume). Excretion ability of compounds from the body is evaluated on the basis of logP (octanol/water) and molecular weight. Renal clearance is indicated by negative lipophilicity of molecule. Metabolism of compounds in liver was evaluated on the basis of logP value (hydrophobic condition) and topological polar surface area of molecules. Lipophilicity of molecule also provided indications about absorption and metabolic process. The majority of oral bioavailable drugs (90%) follow the Lipinski's rule of five; therefore the designed molecules were also studied for oral bioavailability of active anticonvulsant drugs through a rule of five. These chemical properties for drug-likeness were calculated for triazolethione derivatives and further evaluated for compliance with the standard drug.

Pharmacophore distance map

Structure-based pharmacophore distance map was prepared for triazolethione derivatives, where it was found to be mild active against Glutamate receptor and GABA respectively. The result was showing in Figure5.

RESULTS AND DISCUSSION

Preliminary quantitative structure-activity relationship (SAR) studies revealed high structure-activity relationship (pharmacophore) features for anticonvulsant activity. Based on features identified from pharmacophore, molecules were designed on the nucleus of triazolethione. Pharmacophore features were also used for data collection for QSAR model building using multiple linear regression (MLR) methods. Since the QSAR approach is a well established as lead optimization method, therefore the designed molecules were screened through QSAR model to predict the Ki value (activation of GABA) of new anticonvulsant compounds derivatives. The binding affinity of known anticonvulsant target GABA was studied through docking simulation so that to identify a possible binding site and to explain the drug-target activity relationship by using a complex structure of GABA with known positive control. Finally, the designed molecules were processed for ADMET screening for estimate the pharmacological behavior of designed

molecules. Results of the pharmacophore, QSAR based Ki prediction, docking, and ADMET screening were analyzed to receive conclusive information to predict the possibilities about designed molecules for anticonvulsant activity.

Pharmacophore profiling for anticonvulsant activity through GABA activation

To understand the pharmacophore behavior of GABA activators for anticonvulsant activity, QSAR model building molecules were also observed. Observations were based on the sub-structural relationships considering the electron flow. It was found that the pharmacophore components those are available for anticonvulsant activity through GABA activation were as: amide group, the pyrrole ring, benzene ring, the ketone group, aromatic ring, halide linked benzene ring, the methoxy group, the nitro group and aliphatic chain. Our designed molecules also compliance with some of the known components of GABA activators. Based on pharmacophore profile, it was observed that 2, 6, 7, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22 contain a halide, RO_3=N, benzene ring, halide connected to benzene ring by single bond, benzene ring with substituent halide & an unsubstituted atom at distance of one and two bond from halide. These observations also support the potential of designed molecules for anticonvulsant activity through GABA activation.

Design of new chemical entities (NCEs) containing Quinazolinone nucleus

The findings of pharmacophore studies provided the overall substitution pattern (electrostatic, steric and hydrophobic pattern) required around the triazolethione nucleus. Hypotheses shown in literature were also considered for optimization of triazolethione derivatives. Pharmacophore features signified the importance of triazolethione nucleus for the anticonvulsant activity of compounds. This information had helped a lot in optimizing triazolethione pharmacophore and designing of NCEs. Substitution pattern around triazolethione pharmacophore showed in Figure 1 was used for the manual design of NCEs. Designed compounds were passed through Lipinski's screen to ensure drug like the pharmacokinetic profile of the designed compounds in order to improve their bioavailability. We had designed 22 compounds containing triazolethione nucleus with substitution pattern shown in Figure 2. All these compounds were subjected for further studies to sort out the compounds with good binding affinity for GABA and having good ADME properties.

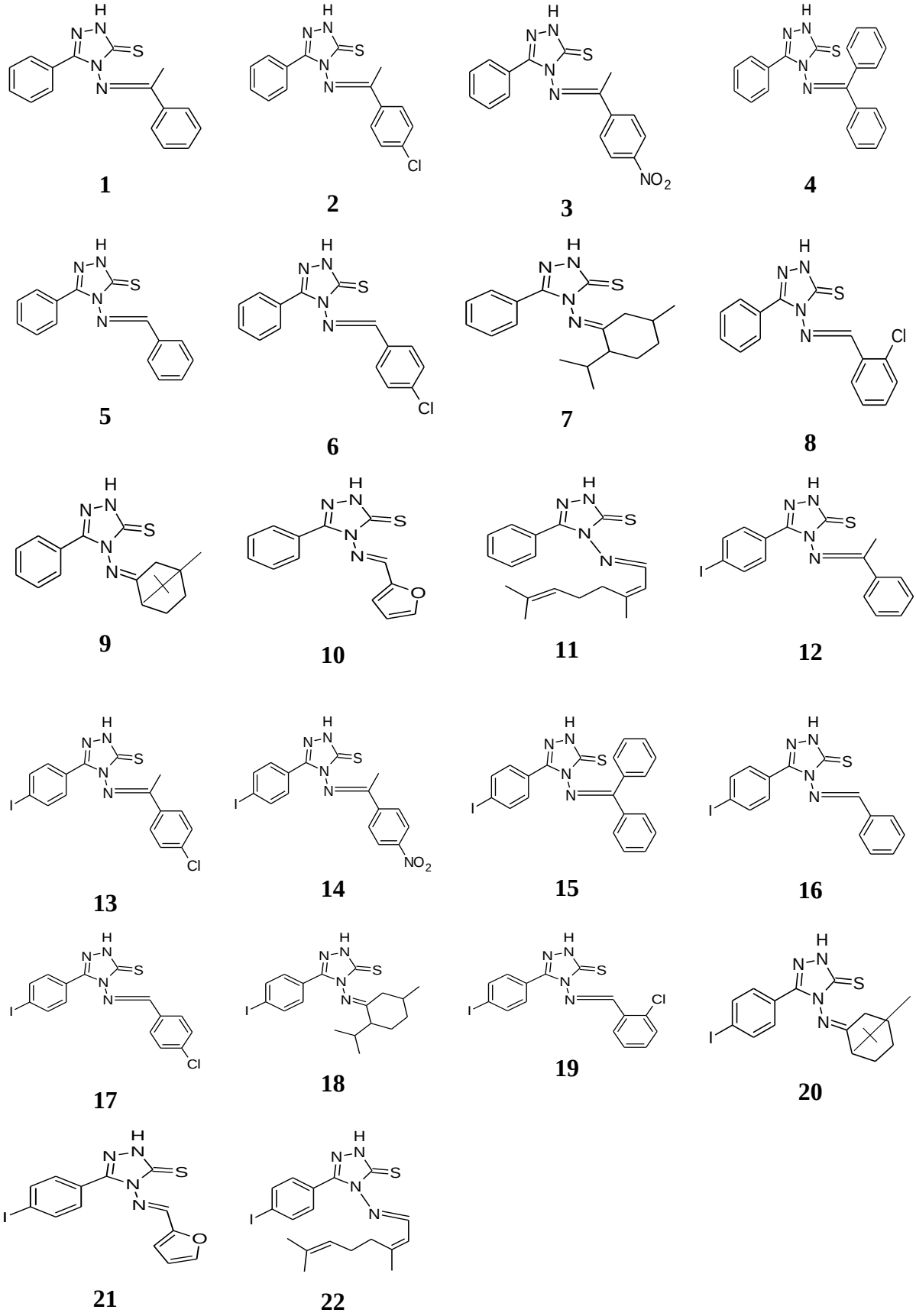


Figure 2: **Designed triazolethione derivatives**

Molecular docking studies on GABA-alpha

To understand the binding behavior of studied compounds named '1 to 22' against GABA based anticonvulsant activity was processed for docking studies. The docking studies suggested that designed compounds activated the GABA activity by equivalent binding affinity in compliance of control. Later, orientations and binding affinity of tested derivatives were explored. The binding affinity allowed the derivatives to be compared with standard control Nefiracetam shown in Figure 4

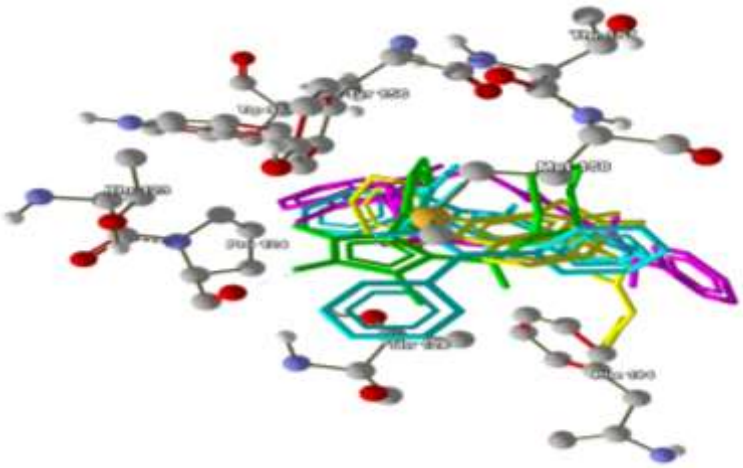
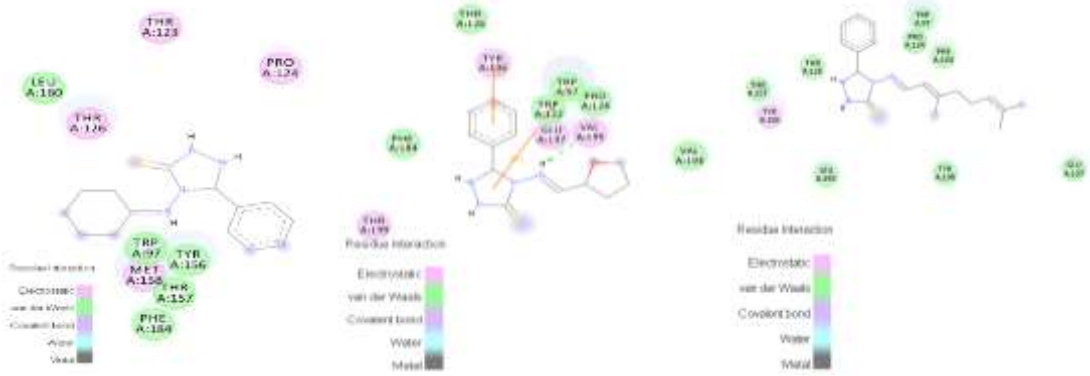
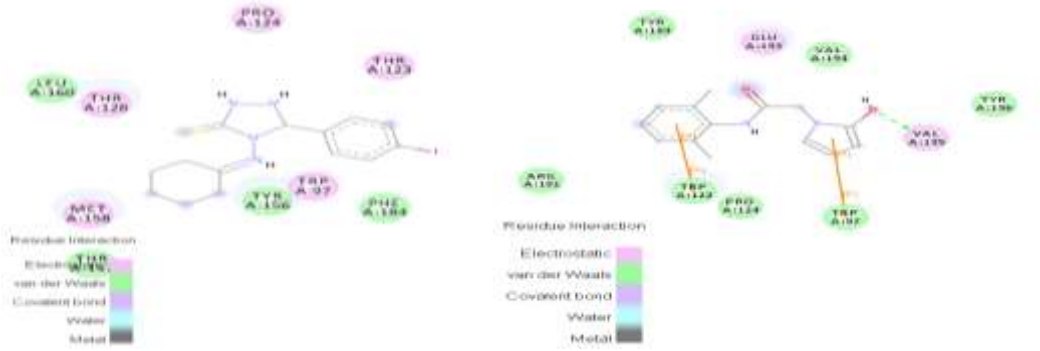


Figure 3: Docking results of triazolethione derivatives against GABA and Residual interaction of GABA-alpha with compound 9, 10, 11 & 20



Compound 9 **Compound 10** **Compound 11**



Compound 20 **Nefiracetam at GABA**

Figure 4: Compound 9 at GABA. Residual interactions are as: threonine, proline & methionine in electrostatic region Leusine, tryptophan, tyrosine & phenylalanine in Vander Waals region, Compound 10 at GABA. Residual interactions are as: Pi-bonds with tryptophan, hydrogen bond with valine, Compound 11 at GABA. Residual interactions are as: Tyrosine (electrostatic bonding), other trptophan, proline, phenylalanine, tyrosine & glutamic acid in Vander Waals bonding range, Compound 20 at GABA. Residual interactions are as: Tryptophan, proline, threonine and methionine in electrostatic interaction; and leusine, phenylalanine, threonine & tyrosine in Vander Waals interaction, Nefiracetam at GABA. Residual interactions are as: Pi-bonds with tryptophan, hydrogen bond with valine, tyrosine.

Docking studies

The molecular docking tool, AutoDock-Vina software was used for studying binding modes of the designed compounds into the binding pocket of GABA. AutoDock-Vina was found to produce the least count of wrong poses and results near to native co-crystallized structures. These studies helped to sort out the designed compounds with the good binding affinity with GABA. The docking score in terms of Kcal/mol and other results of docking studies of designed compounds of triazolethione series are presented in Table 1 and 2.

Table 1: Docking Results and Evaluation of Query Molecules in Reference of Known GABA Activator

	Compound	Binding affinity (kcal/mol)	Interacting residues	Comparison with control
Control	Nefiracetam	-6.6	Pi-bonds with tryptophan, hydrogen bond with valine, tyrosine	
Query	10	-6.6	Pi-bonds with tryptophan, hydrogen bond with valine	Equivalent binding
Query	11	-6.7	Tyrosine (electrostatic bonding), other tryptophan, proline, phenylalanine, tyrosine & glutamic acid in Vander Waals bonding range	Equivalent binding

Query	20	-6.7	Tryptophan, proline, threonine and methione in electrostatic interaction; and leusine, phenylalanine, threonine & tyrosine in Vander Waals interaction.	Equivalent binding
Query	9	-6.5	Threonine, proline & methionine in electrostatic region. Leusine, tryptophan, tyrosine & phenylalanine in Vander Waals region	Equivalent binding

Table 2: Showing Residual Interaction With Compound 9, 10, 11 & 20

Interacting Residue	ID	Residual energy (Kcal/mol)
ASP	125	-1.00315
LEU	160	-1.1599
MET	158	-11.6323
PHE	128	-0.50203
PHE	184	-4.24585
PRO	124	-15.7056
THR	123	-1.66539
THR	126	-15.9817
THR	157	-4.50578
TRP	97	-6.24914
TYR	156	-18.2325
TYR	196	-0.30033

Binding affinity

Binding affinity was shown in the negative value, which indicates the measure of the stability of ligand-Protein interaction. The binding affinity of the standard compound Nefiracetam was found to be -6.6 kcal/mol. The binding affinity of the designed NCEs "10, 11, 20, 9" was found to be '-6.6, -6.7, -6.7, & -6.5 respectively' kcal/mol respectively. The close analysis of these results suggests that the designed NCEs have the comparable binding affinity with the standard compound. Overall interacting residues can be visualized from Figure 3.

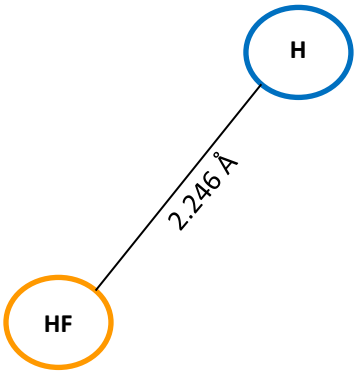


Figure 5: Two property based pharmacophore distance map of triazolethione derivatives designed molecules against GABA. Here the components are as: Hydrogen bond donor (HD) and Hydrophobic (HF). The inter-component distance has been providing in Å.

Contacts

Docking studies were analyzed in reference to known target (GABA) interacting control compound Nefiracetam. Literature based information shows that, binding pocket of control ligand at target bears aspartate, phenylalanine, glycine, alanine, threonine, valine, serine, tyrosine residues (the majority of hydrophobic nature). Control ligand binds with a binding affinity of -6.6 kcal/mol. In reference of control ligand, query compounds shared common residues valine, tyrosine & phenylalanine etc. Out of the tested ligand compounds 9, 10, 11 and 20 ligands were found to be possibly good interactivity with target GABA.

QSAR model based prediction of GABA targeted anticonvulsant activity

QSAR studies

All QSAR studies were performed in Weka software. A series of 22 compounds of triazolethione derivatives tested for their anticonvulsant activity was selected for QSAR Studies. 14 Compounds were used for model building. The model was cross evaluated with Leave-One-Out-Cross validation (LOOCV) method. Selection of molecules in the training set and their cross validation is a key and important feature of any QSAR model. Therefore the care was taken in such a way that biological activities of all compounds validation result must lie within the maximum and minimum value range of biological activities of the training set of compounds. The maximum and minimum value in training and set were compared in a way that: The maximum value of LN Ki (nM) of query compound should be less than or equal to the maximum value of LN Ki (nM) of the training set. The minimum value of LN Ki (nM) of query compound should be higher than or equal to the minimum value of LN Ki (nM) of the training set. Several 2D QSAR models were generated for a training set of 14 compounds using MLR method. The best QSAR model was selected on the basis of the value of statistical parameters like R^2 (square of the correlation coefficient for a training set of compounds), and R^2_{cv} (LOO cross-validated R^2). The QSAR model was validated through LOOCV method. Statistical results generated by 2D QSAR analysis showed that QSAR model has good cross-validation predictability. Prior studies of anticonvulsant lead identification and optimization showed an important part of QSAR application in drug discovery. Activity was predicted on the basis of derived QSAR model for newly designed triazolethione derivatives. The QSAR model development accuracy was represented by R^2 (= 0.858) (i.e., 85.8%) and activity prediction accuracy denoted by R^2_{CV} (= 0.807) (i.e., 80.7%) Table 3, 4, Figure6, 7. Single chemical descriptors namely, ATSm5 well allied with experimental anticonvulsant activity. Derived QSAR model equation was as:

Predicted LN Ki (nM) = -0.1682 * D1 + 10.4576

(Here D1: 'ATSm5', this molecular descriptor was calculated by PaDEL-Descriptor software)

[R^2 = 0.858 and R^2_{CV} = 0.807]

Where, R^2= regression coefficient and R^2_{CV}= cross-validation regression coefficient. QSAR results suggest that compound '5, 2, 8, 9, 1, 6, 7, 11, 10' possess good potency for anticonvulsant activity.

Table 3: Model Development and Loo Cross Validation (Cv)

Dataset	ID	D1	Experimental LN_Ki (nM)	Training predicted	Training error	CV LOO predicted	CV LOO error
Train	CHEMBL311249	46.47217	2.332144	2.64	0.308	2.735	0.402
Train	CHEMBL308760	46.86433	2.397895	2.574	0.176	2.633	0.235
Train	CHEMBL317815	40.79624	3.394508	3.595	0.2	3.616	0.222
Train	CHEMBL319058	42.62772	3.490429	3.287	-0.204	3.257	-0.233
Train	CHEMBL303152	43.9699	3.591818	3.061	-0.531	2.961	-0.631
Train	CHEMBL148858	40.20014	3.871201	3.695	-0.176	3.678	-0.193
Train	CHEMBL124871	32.04861	4.127134	5.066	0.939	5.195	1.068
Train	CHEMBL98509	34.40223	4.212128	4.67	0.458	4.713	0.501
Train	CHEMBL7327	35.9278	4.304065	4.414	0.11	4.423	0.119
Train	CHEMBL7953	37.21277	4.672829	4.198	-0.475	4.161	-0.512
Train	CHEMBL306310	31.87522	5.09375	5.096	0.002	5.096	0.002
Train	CHEMBL72505	29.09687	5.313206	5.563	0.25	5.623	0.31
Train	CHEMBL381131	28.70931	6.054439	5.628	-0.426	5.518	-0.536
Train	CHEMBL147868	29.87522	6.063785	5.432	-0.632	5.302	-0.762

Table 4: Query Prediction through QSAR Model

Dataset	ID	D1	Model predicted LN Ki (nM)	Calculated Ki (µM)	z-score
Query	14	49.72664	2.093	0.008109	-1.30506
Query	13	46.18382	2.689	0.014717	-0.93739
Query	18	49.73064	2.092	0.008101	-1.30567
Query	19	45.62609	2.782	0.016151	-0.88002
Query	S4644 Zolpidem	34.40884	4.669	0.106591	0.284066
Query	22	43.0659	3.213	0.024854	-0.61413
Query	12	43.23208	3.185	0.024167	-0.63141
Query	17	42.18382	3.361	0.028818	-0.52283
Query	15	54.89682	1.223	0.003397	-1.84176
Query	4	44.3309	3	0.020086	-0.74553
Query	NEURONTIN (gabapentin)	15.49111	7.852	2.570871	2.247644
Query	GABA_activator_nefiracetam	22.3252	6.702	0.814032	1.538214
Query	21	38.61936	3.961	0.05251	-0.1527
Query	3	39.16072	3.87	0.047942	-0.20883
Query	20	39.0659	3.886	0.048716	-0.19896
Query	16	39.23208	3.858	0.047371	-0.21624
Query	5	28.66616	5.635	0.280059	0.879987
Query	2	35.6179	4.466	0.087008	0.158836

Query	8	35.06017	4.56	0.095583	0.216824
Query	9	28.49998	5.663	0.288011	0.89726
Query	1	32.66616	4.963	0.143022	0.465433
Query	6	31.6179	5.139	0.170545	0.574006
Query	7	31.6179	5.139	0.170545	0.574006
Query	11	32.49998	4.99	0.146936	0.482089
Query	10	28.05344	5.738	0.310443	0.943527

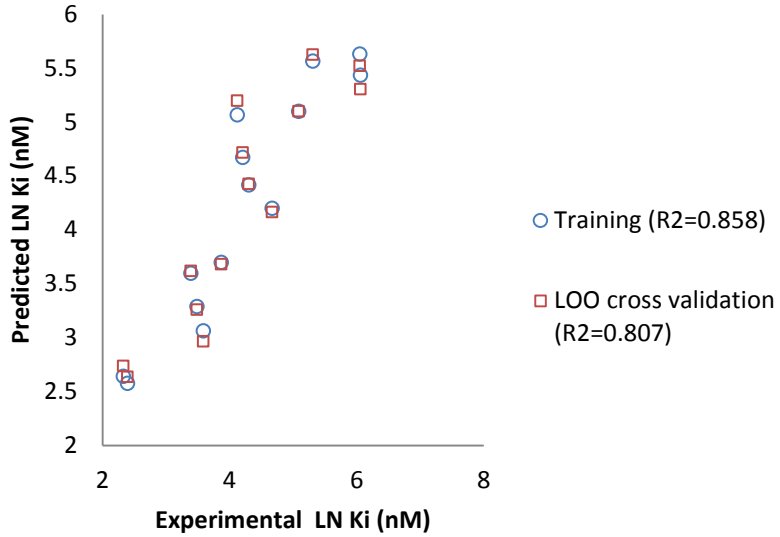


Figure 6: **Regression plots showing model training as well as cross-evaluation results through leave-one-out cross validation**

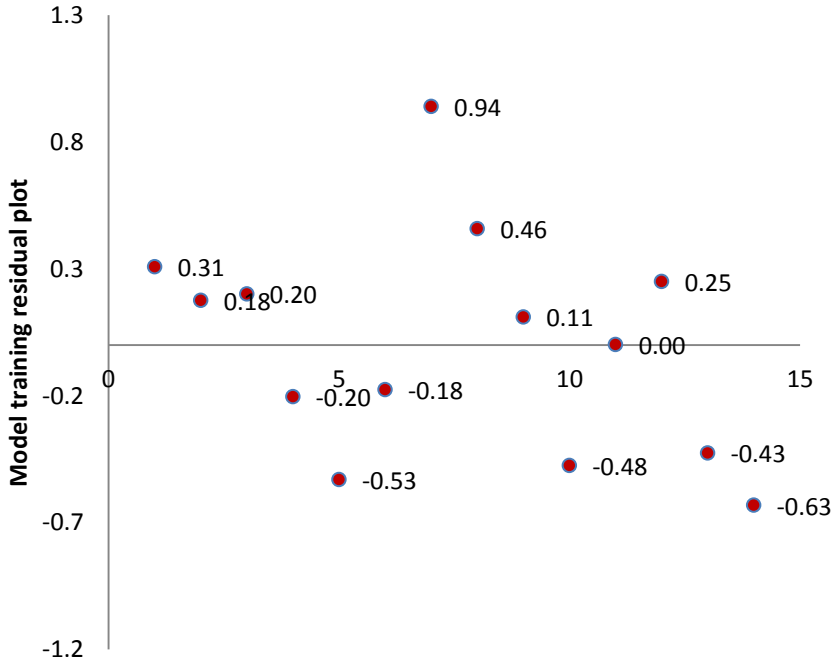


Figure 7: Residual plot of model representing error distribution of QSAR model

Compliance with pharmacokinetics properties & toxicity estimation (ADME/T)

Prediction of the ADME parameters prior to the experimental studies is one of the most important aspects of the drug discovery and development of the drug molecule. The drug may fail to reach the market phase if those properties are not fulfilled by the drug candidate. Taking into consideration the above-mentioned aspects, the ADME profile of the designed NCEs was studied using the tool. In addition to predicting molecular properties, provides the ranges for comparing the properties of the molecule with those of majority of known drugs. The range of values that cause a molecule to be flagged can be similar or dissimilar to other known drugs. Lipinski's rule of five and adme-SAR physical descriptors and pharmaceutically relevant properties of triazolethione analogs were analyzed, among which significant descriptors were reported here required for predicting the drug-like properties of molecules. These properties were given in Table 4.

GABA's known activators were observed to bear the properties of crossing the Blood-Brain-Barrier (BBB), being intestinally absorbable, easy accessibility to the cells, the non-inhibitor substrate of plasma proteins, being safe from being metabolized through CYPs and don't have carcinogenic properties. Results revealed that triazolethione derivatives followed the screening through Lipinski's rule of five for oral bioavailability, no any derivate showed violation of Lipinski's rule of five. Here, the hydrophilicity of studied compounds was measured by logP value. Rule of five screening results indicate mild hydrophilicity of triazolethione derivatives and so there is a good average possibility of absorption or membrane permeability due to their logP values less than 5 **Table 5**. LogP also associated to blood–brain-barrier used to calculate the membrane permeability. The derivatives showed less efficiency of membrane permeability than control compound. The low aqueous solubility of derivatives may significantly affect its absorption and distribution. Higher doses may be required for bioavailability. All derivatives showed higher lipo affinity than control compound. Intestinal permeability has been found to be comparatively lower than control compound.

Table 5: Lipinski's rule of five and other parameters for ADME property analysis of molecules

Name	Lipoaffinity Index	nHBAcc	nHBDon	MLogP	nRotB	Lipinski Failures	Topo PSA	MW
NEURONTI (gabapentin)	-0.18096	3	0	2.12	3	0	17.07	153.9929
Nefiracetam Control	3.379699	4	2	2.56	4	0	52.57	241.0977
1	7.422108	4	1	2.67	2	0	32.09	294.0939
10	5.461976	5	1	2.23	2	0	41.32	274.0888
11	7.483556	4	1	2.89	4	0	32.09	326.1565
12	7.803506	4	1	2.56	2	0	32.09	419.9906
13	7.927511	4	1	2.45	2	0	32.09	453.9516
14	6.359651	4	1	2.23	3	0	77.91	464.9756
15	10.18298	4	1	3.11	3	0	32.09	482.0062
16	7.540048	4	1	2.45	2	0	32.09	405.9749
17	7.670672	4	1	2.34	2	0	32.09	439.9359
18	9.349564	4	1	2.78	2	0	32.09	454.0688
19	7.635972	4	1	2.34	2	0	32.09	439.9359
2	7.546664	4	1	2.56	2	0	32.09	328.0549
20	6.702527	4	1	2.34	1	0	32.09	398.0062
21	5.862678	5	1	2.12	2	0	41.32	399.9855
22	7.864405	4	1	2.78	4	0	32.09	452.0532
3	6.066383	4	1	2.34	3	0	77.91	339.079
4	9.845715	4	1	3.22	3	0	32.09	356.1096
5	7.147513	4	1	2.56	2	0	32.09	280.0783
6	7.278689	4	1	2.45	2	0	32.09	314.0393
7	7.278689	4	1	2.45	2	0	32.09	314.0393
8	7.244151	4	1	2.45	2	0	32.09	314.0393
9	6.276882	4	1	2.45	1	0	32.09	272.1096
Zolpidem	0.067314	4	0	3.11	4	0	35.91	286.0041

Toxicity indicated by triazolethione derivatives at high doses/long term use

If administered in high doses or used therapeutically in long term, the toxicity risk assessment screening results indicated Table 6. One noticeable component is that no any derivative showed carcinogenicity. It indicates the safe trials of these compounds for further lead optimization. The prior studies related to cases of accumulation and its toxicity also supported the predicted results. Still, there is a scope for further lead optimization based on these calculated ADMET parameters.

Complete molecule evaluation profile

To evaluate the performance of compounds, four basic strategies: pharmacophore mapping, QSAR, docking & ADMET screening, were implemented. Although predicted Ki was showed mild activity against GABA, but conclusively compounds, 2, 6, 7, 8, 9, 10, 11 & 20 were observed to be most feasible to activate GABA **Table 6**.

Table 6: Complete molecule evaluation profile

Compounds	**Pharmacophore**	**QSAR**	**Docking**	**ADMET**							**Final remark**
	matched features with control	**positive z-score considered**	**Binding affinity equivalent to control**	**BBB+**	**HIA+**	**Caco+**	**pp-substrate**	**pp-non-inhibitor**	**no-easy metabolism**	**no-carcinogenicity**	
Nefiracet(Control)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**10**
1	0	1	0	1	1	1	0	0	1	1	6
2	**1**	**1**	0	1	1	1	0	0	1	1	**7**
3	0	0	0	1	1	1	0	0	1	1	5
4	0	0	0	1	1	1	0	0	1	1	5
5	0	1	0	1	1	1	0	0	1	1	6
6	**1**	**1**	0	1	1	1	0	0	1	1	**7**
7	**1**	**1**	0	1	1	1	0	0	1	1	**7**
8	**1**	**1**	0	1	1	1	0	0	1	1	**7**
9	0	**1**	**1**	1	1	1	0	0	1	1	**7**
10	0	**1**	**1**	1	1	0	0	0	1	1	**6**
11	0	**1**	**1**	1	1	0	0	1	1	1	**7**
12	1	0	0	1	1	1	0	0	1	1	6
13	1	0	0	1	1	1	0	0	1	1	6
14	1	0	0	1	1	0	0	0	1	1	5
15	1	0	0	1	1	1	0	0	1	1	6
16	1	0	0	1	1	1	0	0	1	1	6
17	1	0	0	1	1	1	0	0	1	1	6
18	1	0	0	1	1	0	0	1	1	1	6
19	1	0	0	1	1	1	0	0	1	1	6
20	**1**	0	**1**	1	1	0	0	0	1	1	**6**
21	1	0	0	1	1	0	0	0	1	1	5
22	1	0	0	1	1	0	0	1	1	1	6

CONCLUSION

In conclusion, the docking study reveals the possible role of GA in an observed anticonvulsant activity of substituted triazolethione derivatives. The results show that triazolethione derivative 9, 10, 11, and 20 lead to active anticonvulsant compounds. QSAR results suggest that compound '5, 2, 8, 9, 1, 6, 7, 11, 10' possess good potency for anticonvulsant activity. Although predicted Ki was showed mild activity against GABA, but conclusively, 2, 6, 7, 8, 9, 10, 11, and 20 were observed to be most feasible to act against GABA. Finally, these compounds were found as gamma-amino butyric acid (GABA) activators.

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