Available online on 15.08.2024 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access

Research Article

In-Silico Design of Thiadiazole Derivatives as Anticonvulsant Agents

Vani V, Sreeja S , Fathimathul Nafiya, Harshad A, Mahima Krishnan M M, Naisam N , Sneha Saji

Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy, Alathara, Sreekariyam, Thiruvananthapuram Kerala.

A B S T R A C T

This study focuses on the *in-silico* design and molecular docking of thiadiazole and its derivatives to evaluate their potential as anticonvulsant agents.Thiadiazoles are heterocyclic compounds known for their diverse biological activities, including anticonvulsant properties.The molecular structures were subjected to various *in-silico* screening methods to predict their drug-like properties and pharmacokinetic profiles. Molecular docking studies were performed to assess the binding affinity and interactions of the designed compounds with key targets associated with anticonvulsant activity, particularly the voltage-gated sodium channels and GABA receptors.The docking results revealed that several thiadiazole derivatives exhibited strong binding affinities towards the targeted proteins, with favourable binding energies and significant interactions at the active sites.

KEYWORDS: Convulsion, *In-silico*, Chemsketch, Molinspiration, Docking, Autodock, Py MOL.

A R T I C L E I N F O: Received 12 March 2024; Review Complete 21 June 2024 ; Accepted 05 August 2024; Available online 15 August 2024

Cite this article as:
Vani V, Sreeja S , Fathimathul N, Harshad A, Mahima Krishnan M M, Naisam N , Sneha S, *In-Silico* Design of Thiadiazole Derivatives as Anticonvulsant Agents, Asian Journal of Pharmaceutical Research and Development. 2024; 12(4):85-91,
DOI: http://dx.doi.org/10.22270/ajprd.v12i4.1445

*Address for Correspondence:
Vani V, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy, Alathara, Sreekariyam, Thiruvananthapuram Kerala

INTRODUCTION

Drug discovery is a crucial and complex process in biomedical research, aimed at identifying new therapeutic compounds that can prevent, treat, or cure diseases. This multi-disciplinary endeavour involves biology, chemistry, pharmacology, and various other scientific fields, and is vital for the development of new medications to address unmet medical needs. Recent advancements in revolutionizing drug discovery include Genomics and Personalized Medicine,Artificial Intelligence and Machine Learning, CRISPR and Gene Editing.[1,2,3]

Convulsions, commonly referred to as seizures, are sudden, uncontrolled electrical disturbances in the brain. Convulsions are rapid, involuntary muscle contractions that results in uncontrollable shaking and limb movement.It produce marked changes in behaviour, movements, feelings, and levels of consciousness. Convulsions, or seizures, can be classified into focal (partial) and generalized types based on their origin and characteristics. Focal seizures are further divided into focal aware (simple partial) seizures, where consciousness is maintained, and focal impaired awareness (complex partial) seizures, where consciousness is altered or lost. Generalized seizures affect both sidesof the brain from the onset which include tonic-clonic (grand mal) seizures, absence (petit mal) seizures, myoclonic seizuresatonic (drop attacks) seizures.It is necessary to have a knowledge to understand the type of convulsion ,which iscrucial for accurate diagnosis and effective treatment.Convulsions can affect people of all ages and can be a one-time occurrence or a chronic condition requiring ongoing medical attention.[4]

1, 3, 4-Thiadiazole is a five membered heterocyclic ring with two nitrogen atoms and one sulphur atom with lone pair of electrons. Its molecular formula is $C_2H_2N_2S$ and it has a molecular weight of 86.115684 g.[5,6]

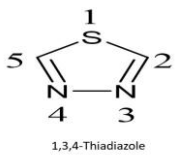


Figure 1: Structure of 1, 3, 4- thiadiazole

$GABA_A$ (G-Amino Butyric Acid) agonist the major inhibitory neurotransmitter receptors belonging to ligand gated ion

channel. GABA is synthesised in presynaptic neurons catalysed by L-glutamic acid decarboxylase and acts on the postsynaptic receptors upon release from the synaptic vesicles. The 5 subunits of $GABA_A$ are arranged around the channel in counter-clockwise pattern. Each subunit has transmembrane spanning domains of 20 amino acids. The binding pocket for GABA is located at the interface between the alpha and the beta subunit.

GABAergic neurons release GABA, which binds to $GABA_A$ receptors on the postsynaptic neuron. This binding opens chloride ion channels, allowing chloride ions to enter the neuron, leading to hyperpolarization (making the neuron less likely to fire an action potential).1,3,4-thiadiazole derivatives prevents neurons from firing in the brain by releasing the chloride ions due to $GABA_A$ pathway. [7]

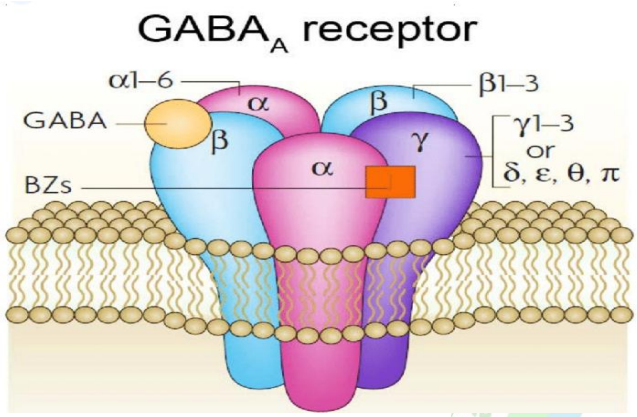


Figure 2: Structure of GABA receptor

In this study, we have designed and docked a series of new thiadiazole derivatives in search of potent anticonvulsant agents through *in-silico* studies using AutoDock4.

MATERIALS AND METHODS

In-silico screening

In-silico screening is a computational technique used in drug discovery and development to predict the binding affinity of small molecules to a target protein or receptor. It involves the use of computer algorithms and molecular modelling techniques to virtually screen large libraries of chemical compounds and identify potential drug candidates.

In-silico screening of all proposed structures of novel thiadiazole derivatives were carried out using various computational chemistry softwares such as ACD Lab/Chem Sketch 12.0, Molinspiration, PASS and Auto Dock 4.

ACD/Chemsketch

ACD/Chemsketch is a free chemical software, which is a molecular modelling program, used to generate and modify images of chemical structures.

ACD/Chemsketch provide the following features:

- Structure Mode, which isrequired for drawing chemical structures and calculating their properties.
- Draw Mode, which is required for text and graphics processing.
- Calculation of Molecular Properties for estimation of percentage composition, formula weight, molar refractivity, molar volume, density, polarizability, dielectric constant, surface tension. [8,9]

Molinspiration

Molinspiration is an independent research organization provides broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, calculation of various molecular properties needed in QSAR, molecule fragmentation, molecular modelling and drug design. The drug likeness property calculations were also be carried out in Molinspiration analysis.

All the designed compounds were then subjected to Lipinski rule analysis using Molinspiration software to identify the biologically active compounds. Lipinski rule is also known as ‘Pfizer rule of five’ or ‘Lipinski’s rule of five’. The rule was formulated by a medicinal chemist Christopher.A. Lipinski.

The Lipinski rule of five states that an orally active drug should satisfy the following criteria in that it will have:

1. Not more than five hydrogen bond donors
2. Not more than ten hydrogen bond acceptors
3. Molecular weight less than 500 Daltons
4. An octanol-water partition coefficient of log P not greater than five
5. Not more than five rotatable bond.[10]

PASS (Prediction of Activity Spectra for Substances)

PASS predicts biological activity profiles of designed chemical compounds in standardized manner.Using structural formula of a drug-like substance as input, its estimated biological activity profile obtained as output. The predicted biological activity list consists of the names of the probable activities with two probabilities: Pa –belonging to the class of “Actives” and Pi –belonging to the class of “Inactives”.

PASS is produced by the statistical software company NCSS LLC.PASS is a growing sample size software for pharmaceutical, medical and many other research areas,clinical trials etc.

Docking

Molecular docking is a computational tool used to predict the structure of the complex formed between two moleculesi.e,the complex between protein and ligand. The small designed molecule known as ligand usually interacts with protein’s binding sites and results in formation of complex with the ligands. Several possible conformations obtained when binding occur and they are commonly known as binding modes. It also aids in predicting the strength of the binding, the energy of the protein-ligand complex, and calculate the binding affinity between two molecules using scoring functions. [11,12]

Auto Dock

AutoDock consist of following programs:

- AutoTors, which smoothens the input of ligand

- Auto Grid, which calculates interaction energy based on macromolecular coordinates
- Auto Dock, which performs the docking.

The ligand traverse six spatial degrees of freedom-rotation and translation. Auto Dock successfully reproduces crystallographically determined positions of ligands with up to about eight degrees of torsional freedom. For molecules with more degrees of freedom, the simulated annealing search does not adequately sample the possible conformational space.[13,14]

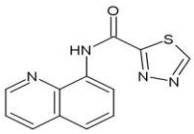
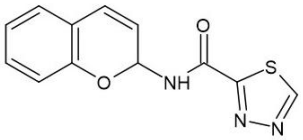
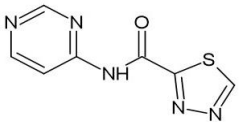
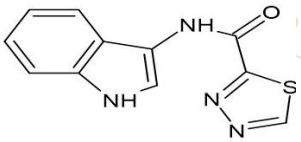
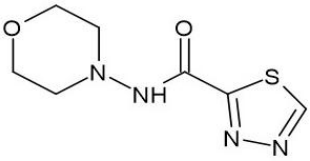
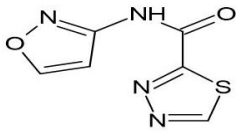
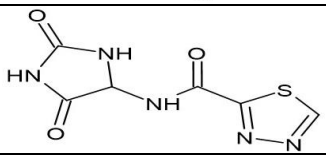
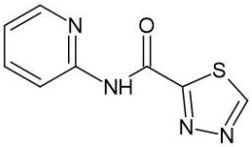
Protein Data Bank

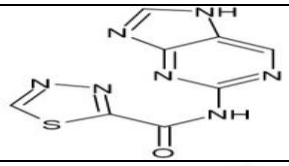
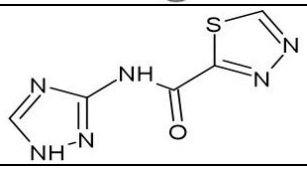
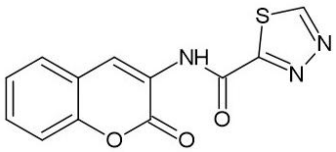
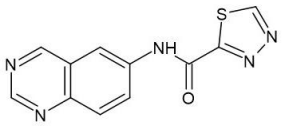
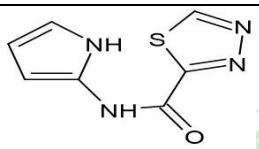
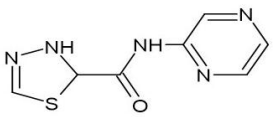
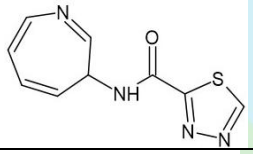
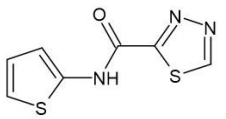
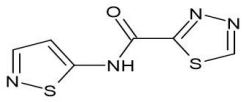
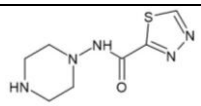
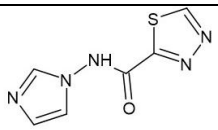
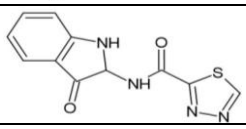
The protein data bank is a database for the three-dimensional basic structural data of largebiological molecules, such as nucleic acids and proteins. The information, usually obtained by X-ray crystallography, NMR spectroscopy, cryo-electron microscopy, and submitted by biologists and organic chemists from around the world, are open availably on the internet through the websites of its member organizations such as PDBe, PDBj ,RCSB, and BMRB. The PBD is directed by an organization called the Worldwide Protein Data Bank, wwPDB .The PDB is a key in zones of structural biology, such as structural genomics. [15 ,16]

RESULT AND DISCUSSION

Calculation of Molecular Properties for estimation of percentage composition, formula weight, molar refractivity, molar volume, density, polarizability, dielectric constant, surface tension. Lipinski rule analysis using Molinspiration software. From the Lipinski rule analysis, twenty compounds were selected for further studies, since these compounds did not show any violations from the Lipinski rule of five.

Table: 1 Structure and name of designed derivatives

SI.NO:	STRUCTURE	IUPAC NAME
1.		*N*-(quinolin-8-yl)-1,3,4-thiadiazole-2-carboxamide
2.		*N*-(2*H*-1-benzopyran-2-yl)-1,3,4-thiadiazole-2-carboxamide
3.		*N*-(pyrimidin-4-yl)-1,3,4-thiadiazole-2-carboxamide
4.		*N*-(1*H*-indol-3-yl)-1,3,4-thiadiazole-2-carboxamide
5.		*N*-(morpholin-4-yl)-1,3,4-thiadiazole-2-carboxamide
6.		*N*-(1,2-oxazol-3-yl)-1,3,4-thiadiazole-2-carboxamide
7.		*N*-(2,5-dioxoimidazolidin-4-yl)-1,3,4-thiadiazole-2-carboxamide
8.		*N*-(pyridin-2-yl)-1,3,4-thiadiazole-2-carboxamide

9.		*N*-(7*H*-purin-2-yl)-1,3,4-thiadiazole-2-carboxamide
10.		*N*-(1*H*-1,2,4-triazol-3-yl)-1,3,4-thiadiazole-2-carboxamide
11.		*N*-(2-oxo-2*H*-1-benzopyran-3-yl)-1,3,4-thiadiazole-2-carboxamide
12.		*N*-(quinazolin-6-yl)-1,3,4-thiadiazole-2-carboxamide
13.		*N*-(1*H*-pyrrol-2-yl)-1,3,4-thiadiazole-2-carboxamide
14.		*N*-(pyrazin-2-yl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxamide
15.		*N*-(3*H*-azepin-3-yl)-1,3,4-thiadiazole-2-carboxamide
16.		*N*-(thiophen-2-yl)-1,3,4-thiadiazole-2-carboxamide
17.		*N*-(1,2-thiazol-5-yl)-1,3,4-thiadiazole-2-carboxamide
18.		*N*-(piperazin-1-yl)-1,3,4-thiadiazole-2-carboxamide
19.		*N*-(1*H*-imidazol-1-yl)-1,3,4-thiadiazole-2-carboxamide
20.		*N*-(3-oxo-2,3-dihydro-1*H*-indol-2-yl)-1,3,4-thiadiazole-2-carboxamide

Based on the docking score, from the twenty designed derivatives, thirteen were selected as anticonvulsant agents. The docking score of selected thirteen derivatives are shown in table no:2.

Table 2: Docking score of selected thirteencompounds

Compound Code	Compound Name	Docking Score
1	N-(quinolin-8-yl)-1,3,4-thiadiazole-2-carboxamide	-7.5
3	N-(pyrimidin-4-yl)-1,3,4-thiadiazole-2-carboxamide	-6.1
6	N-(1,2-oxazol-3-yl)-1,3,4-thiadiazole-2-carboxamide	-6.3
7	N-(2,5-dioxoimidazolidin-4-yl)-1,3,4-thiadiazole-2 – carboxamide	-6.6
8	N-(pyridin-2-yl)-1,3,4-thiadiazole-2-carboxamide	-6.3
11	N-(2-oxo-2H-1-benzopyran-3-yl)-1,3,4-thiadiazole-2-carboxamide	-7.7
12	N-(quinazolin-6-yl)-1,3,4-thiadiazole-2-carboxamide	-7.4
13	N-(1H-pyrrol-2-yl)-1,3,4-thiadiazole-2-carboxamide	-6.0
14	N-(pyrazin-2-yl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxamide	-6.0
15	N-(3H-azepin-3-yl)-1,3,4-thiadiazole-2-carboxamide	-6.7
16	N-(thiophen-2-yl)-1,3,4-thiadiazole-2-carboxamide	-5.5
17	N-(1,2-thiazol-5-yl)-1,3,4-thiadiazole-2-Carboxamide	-5.7
18	N-(piperazin-1-yl)-1,3,4-thiadiazole-2-carboxamide	-6.0
	Acetazolamide	-6.0

The docked images of standard drug and selected thirteen derivatives were shown in figure:

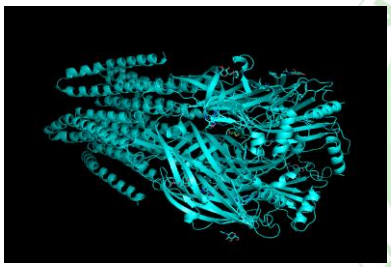


Figure 3: Acetazolamide with 4BHQ

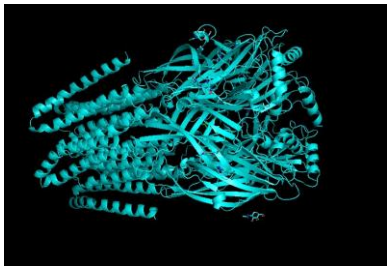


Figure 4: Compound 1 with 4BHQ

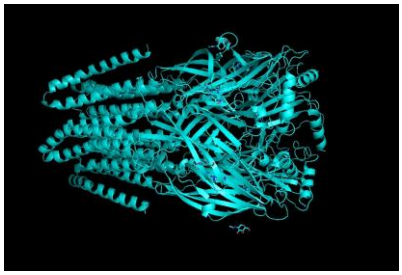


Figure 5: Compound 3 with 4BHQ

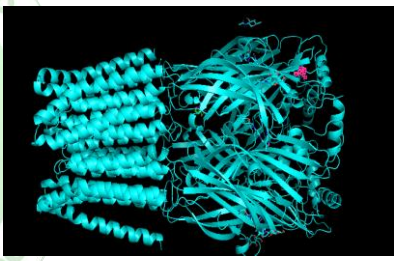


Figure 6: Compound 6 with 4BHQ

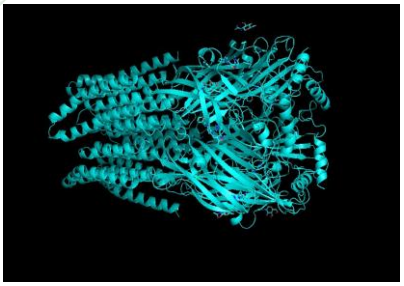


Figure 7: Compound 7 with 4BHQ

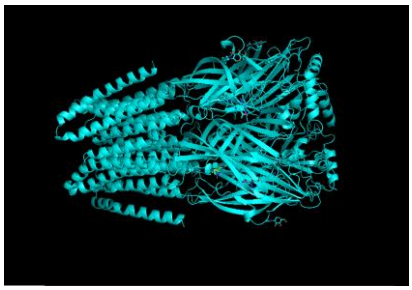


Figure 8: Compound 8 with 4BHQ

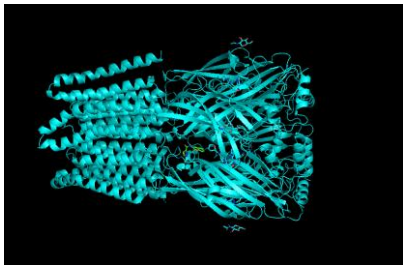


Figure 9: Compound 11 with 4BHQ

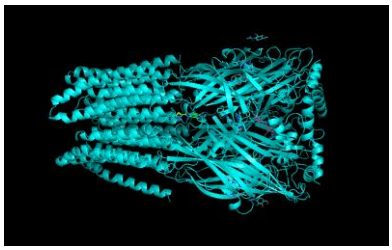


Figure 10: Compound 12 with 4BHQ

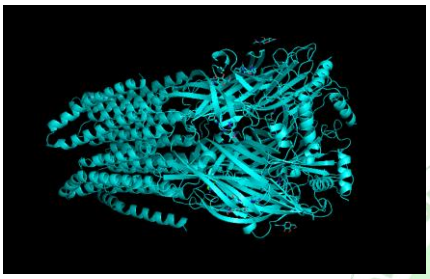


Figure 11: Compound 13 with 4BHQ

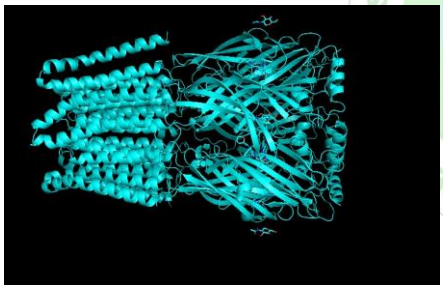


Figure 12: Compound 14 with 4BHQ

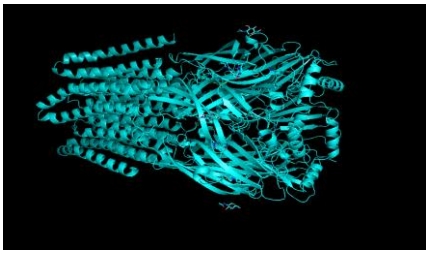


Figure 13: Compound 15 with 4 BHQ

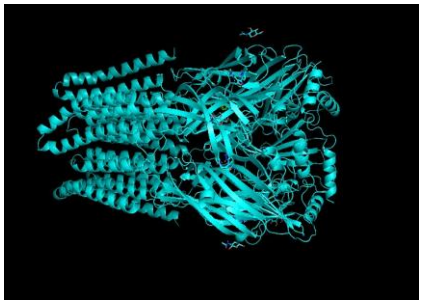


Figure 14: Compound 16 with 4BHQ

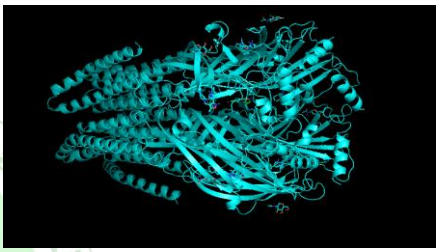


Figure 15: Compound 17 with 4BHQ

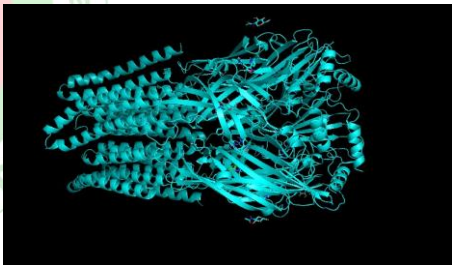


Figure 16: Compound 18 with 4BHQ

CONCLUSION

The investigation that has been carried out in the present project, the results obtained for the same and the corresponding observations made were in accordance with the objectives laid down during commencement of the work.

Based on the literature survey, it was revealed that thiadiazole derivatives can exert anticonvulsant activity. So fifty novel hybrid molecules withthiadiazole nucleus were designed using the ACD Lab ChemSketch 12.0 software. All the designed compounds were then subjected to Lipinski rule analysis using Molinspiration software to identify the theoretically active compounds. In the present study, thirteen theoretically active lead compounds were identified.

The identified compounds were subjected to docking studies against the selected target proteins, $GABA_A$ receptor (4BHQ) for anticonvulsant activity. From the docking results, compounds which had thedocking scores ranging from -7.7 to -6.0.

Majority of the designed derivatives possess similar and greater docking score than that of the standard drug .From the results obtained,we can propose the designed derivatives as promising anticonvulsant agents for future investigations in anticonvulsant therapy.

ACKNOWLEDGEMENT

We are highly indebted to our esteemed guideAssociateProf. VANI V, M Pharmand co-guide Associate Prof. SREEJAS, M Pharm,Ph.D. fortheirsupport,unending encouragement and advice, which helped us for the successful completion of this article.

REFERENCE

1. Amol B Deore, Jayprabha R Dhumane, Hrushikesh V Wagh, The stages of drug discovery and development process; Asian Journal of Pharmaceutical Research and Development.7;2019; 62-67.
2. Mithun Rudrapal, Dipak Chetia; Virtual Screening, Molecular Docking and QSAR Studies in Drug Discovery and Development Programme Journal of Drug Delivery and Therapeutics 2020; 10(4):225-233.

3. L. Scotti, F.J.B. Mendonca Junior , H. Ishiki, F.F. Ribeiro , Rajeev K Singla , J.M. Barbosa Filho , M.S. Da Silva and M.T. Scotti Docking Studies for Multi-Target Drugs 2016;17(16) ;1-13
4. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. The Lancet. 2019 Feb 16;393(10172):689-701.
5. Abhishek Kumar Jain, Simant Sharma , Ankur Vaidya , Veerasamy Ravichandran and Ram Kishore Agrawal; 1,3,4-Thiadiazole and its Derivatives: A Review on Recent Progress in Biological Activities ;Chem Biol Drug Des 2013; 81: 557–576.
6. Yijing Li, Jingkun Geng, Yang Liu, Shenghui Yu, Prof. Guisen Zhaothiadiazole—A Promising Structure In Medicinal Chemistry;2013;8(1);27-41.
7. Goetz T, Arslan A, Wisden W, Wulff P. GABAA receptors: structure and function in the basal ganglia. Progress in brain research. 2007 Jan 1;160:21-41.
8. Osterberg T, Norinder U; Prediction of drug transport processes using simple parameters and PLS statistics the use of ACD/logP and ACD/ChemSketch descriptors. European journal of pharmaceutical sciences. 2001 Jan 1;12(3):327-37.
9. Kwan EE. ACD/spectrus processor review. Journal of chemical information and modeling. 2012 Jul 23;52(7):1898-900.
10. B Fernandes T, CF Segretti M, C Polli M, Parise-Filho R. Analysis of the applicability and use of lipinski rule for central nervous system drugs. Letters in Drug Design & Discovery. 2016 Dec 1;13(10):999-1006.
11. Kitchen DB, Decornez H, Furr JR, Bajorath.J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nature reviews Drug discovery. 2004 Nov;3(11):935-49.
12. Jakhar R, Dangi M, Khichi A, Chhillar AK. Relevance of molecular docking studies in drug designing. Current Bioinformatics. 2020 May 1;15(4):270-8
13. Goodsell DS, Morris GM, Olson AJ. Automated docking of flexible ligands: applications of AutoDock. Journal of molecular recognition. 1996 Jan;9(1):1-5.
14. Morris GM, Huey R, Olson AJ. Using autodock for ligandreceptor docking. Current protocols in bioinformatics. 2008 Dec;24(1):8-14.
15. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The protein data bank. Nucleic acids research. 2000 Jan 1;28(1):235-42.
16. Berman HM, Battistuz T, Bhat TN, Bluhm WF, Bourne PE, Burkhardt K, Feng Z, Gilliland GL, Iype L, Jain S, Fagan P. The protein data bank. Acta Crystallographica Section D: Biological Crystallography. 2002 Jun 1;58(6):899-907.