In Silico Designing And Admet Study Of 1,5-Benzodiazepine As An Antidepressants

Deepak S. Musmade[1*], Bhagwat H. Garje[2], Sharav A. Desai[3], Suvarna M. Bhadane[4], Rupali P. Yevale[5], Sanjay Y. Garje[6], Vijay K. Patel[7], Ankita S. Patel[8]

Abstract

The study carried out in this research is based on selection of new scaffold for its effectiveness in treatment of depression. The novel derivatives from the 1,5-Benzodiazepine class were selected. The selected series of 1,5-Bnezodiazepines was then subjected for molecular docking studies on (PDB ID :3GWV). Most ligands show van der Waals interaction with amino acids as well as Pi-Pi interactions with amino acid residues Phe494, Arg487, Ilu491, Trp406 and Ala329. In silico ADME evaluations of compounds showed high GI absorption and BBB permeability for all compounds. During in vitro Toxicity properties prediction the 1,5-Benzodiazepines shows no Mutagenicity,Irrirtant and effect on reproductive system as compared to lead Fluoxetine. The in silico bioavailability of the compounds was found to be 0.55.

[1*]Department of Pharmaceutical Chemistry, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423601

[2]Department of Pharmacology, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423601

[3]Department of Pharmaceutics, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423601

[4]Department of Pharmaceutics, Ideal College of Pharmacy and Research, Kalyan E, MS, India-421306

[5]Department of Pharmaceutical Chemistry, K.G.Rahul Dharkar College of Pharmacy and Research Institute, Karjat, MS, India- 410201

[6]Department of Pharmaceutics, College of pharmaceutical science & research Center, Kada, MS, India-414202

[7]Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar (Gujarat), India.

[8]Department of Pharmaceutical Chemistry, Sharda School of Pharmacy, Pethapur, Gandhinagar (Gujarat), India.

***Corresponding Author: Mr. Musmade Deepak S.**

*Department of Pharmaceutical Chemistry, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423601, E-mail: Deepak.musmade@gmail.com

1. INTRODUCTION

Since 1957, when the first benzodiazepine, chlordiazepoxide, was created and its psychotropic action was investigated, the diazepines have become a well-known class of heterocycles [1]. In reality, they have a wide range of biological effects, including skeletal, amnestic, hypnotic, sedative, anticonvulsant, and muscle relaxant qualities [2]. An important structural theme in several treatments with sedative, muscle-relaxant, and anticancer effects is 1,5-benzodiazepine analogues [3]. Commercially accessible chemical medicines based on the triazolo-benzodiazepine scaffold, alprazolam, adinazolam, and estazolam, are frequently utilised as sedative and anxiolytic agents [4]. According to several studies, some 1,5-benzodiazepine derivatives poorly bind to the benzodiazepine receptor and inhibit serine protease [5].

Consequently, the study of the types of interactions between these molecules and protein targeting by molecular docking methods for the prediction of the activity is unquestionably of great importance because of the therapeutic and biological applications of this class of compounds. The preliminary assessment of binding affinity and the forecasting of intermolecular interactions of new drugs with receptors both show promise for molecular docking [6]. These days, this approach is required for researching protein-ligand interactions. For complicated systems, the docking method can generate important knowledge that supplements experimentally obtainable data. For virtual screening and posture prediction of novel or non-synthesized molecules, molecular docking simulations have found extensive use [7]. Dopamine trans-porter investigations using molecular docking were the primary subject. The reuptake of dopamine from the synaptic cleft is carried out by this transmembrane protein. Due to the elevated levels of dopamine in the synaptic cleft inhibitors are sometimes utilised as adjuvant therapy for Parkinson's disease (PD) [8]. In this study, PDB ID:3GWV was docked to a novel family of 1,5-benzodiazepines (Fig. 1). In order to determine whether the recently synthesised chemicals could be used as medicines, we forecast and evaluate the binding affinity and intermolecular interactions of complexes generated by docking these molecules on PDB ID:3GWV.

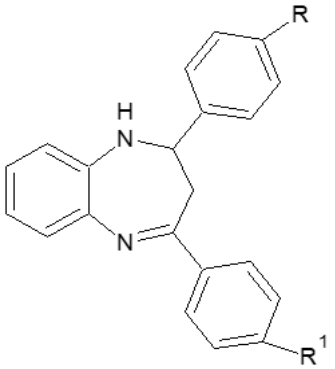


Fig. no. 01: Structure of 1,5-Benzodiazepine

2. Material and methods

2.1. Data collection

2.1.1. Ligands

In the current work, a number of carefully chosen 1,5-benzodiazepine derivatives were collected from the literature [9] and subjected to molecular docking analysis. Simple techniques and substrates were used to manufacture the chosen 1,5-benzodiazepine [9].

2.1.2. Leucine transporter LeuT in complex with R-fluoxetine

Selective serotonin reuptake inhibitors (SSRIs), such as sertraline and fluoxetine, are frequently given to treat depression. They work by preventing the presynaptic plasma membrane serotonin transporter (SERT) from doing its job. All SSRIs contain halogen atoms at particular locations, which play a crucial role in determining the drugs' SERT specificity. However, it is unclear what structural factors contribute to the SERT protein's SSRI specificity. Here, we provide the crystal structures of sertraline, R-fluoxetine, or S-fluoxetine complexed with LeuT, a bacterial SERT homolog. All of the SSRI halogens bind to the exact identical place in LeuT. The affinity of the SERT transporter for SSRIs is significantly decreased by mutation at this halogen-binding pocket (HBP), but not for tricyclic antidepressants. In contrast, the affinities for all three SSRIs increase evenly when the sole nonconserved HBP residue in the norepinephrine and dopamine transporters is changed into that found in SERT. Therefore,

the interaction of the drug's halogens with the protein's HBP plays a significant role in the specificity of SERT for SSRIs. PDB ID 3GWV.

2.2. Molecular docking studies

The preliminary assessment of binding affinity and the forecasting of intermolecular interactions of new drugs with receptors both show promise for molecular docking. For the docking study, we chose to use the leucine transporter LeuT in complex with R-fluoxetine. Typically, the crystal structures of receptors with bound ligand molecules serve as the foundation for our research. This structure was discovered using RCSB Protein Data Bank (PDB) X-ray crystallographic data. The bulk of the chosen structures have cocrystallized ligand molecules that are well-established pharmaceuticals that help us locate the binding site in DAT as well as serve as references for our deliberations. Each molecular target is docked in this research environment; Autodock vina and Autodock were used to mimic the bioactive conformations.

2.3. ADME and toxicity prediction

Pre ADMET predictor server is used to forecast absorption, distribution, metabolism, excretion, and toxicity for the chosen 1,5-benzodiazepine derivatives [10].

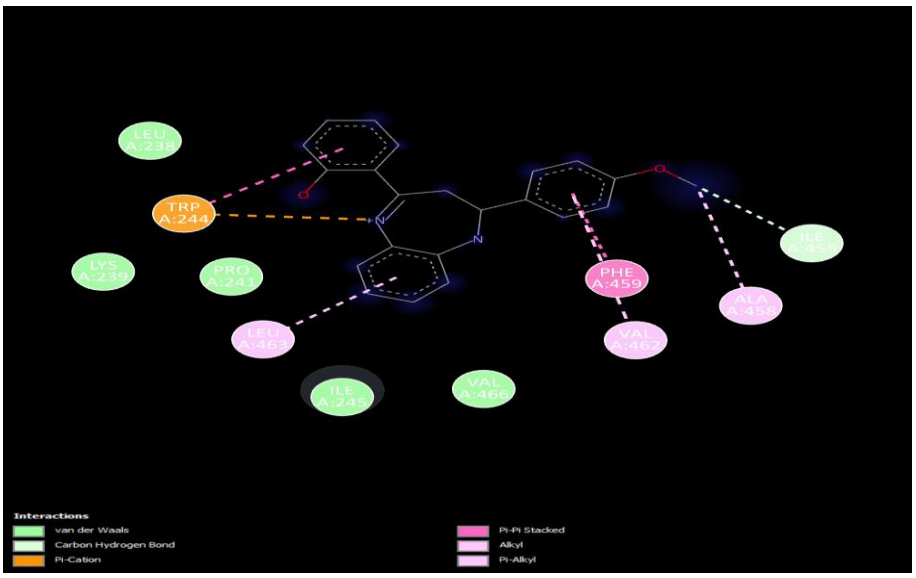
Table no. 01: Chemical structure of selected 1,5-Benzodiazepine derivatives

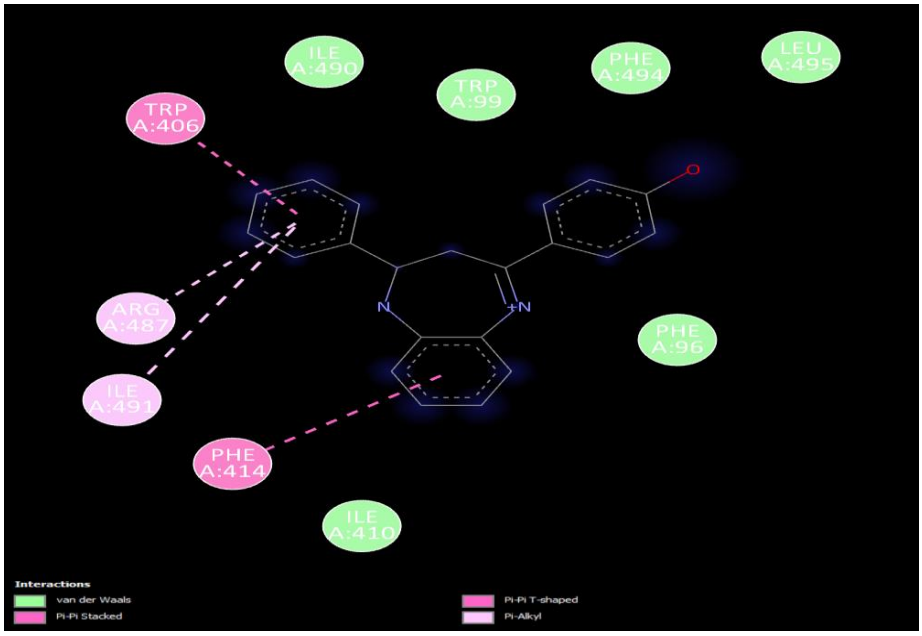
Comp. Code	-R	-R^1
A_1	Ortho-OH	Para-OCH_3
A_2	Para-OH	
A_3	-H	
A_4	Ortho-OH	-H
A_5	Para-OH	
A_6	-H	

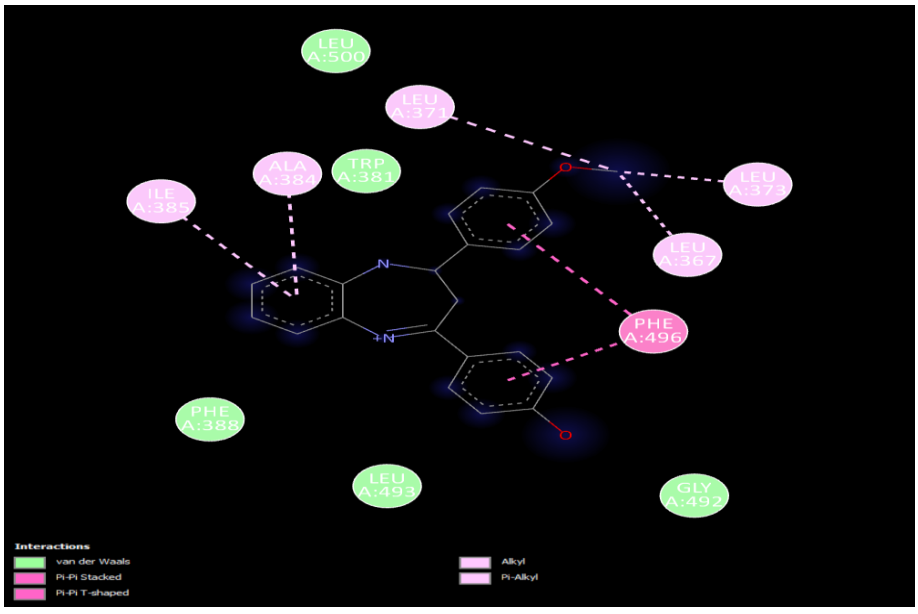
3. Results and discussion

3.1. Molecular docking

The optimum interaction energy with the Leucine Transporter LeuT in complex with R-fluoxetine determines which posture of each molecule receives the highest score (Table 2). While ligand A4 is the least stable ligand among the molecules under study, ligand A6 exhibits the best energies of interaction with the Leucine Transporter LeuT in complex with R-fluoxetine (lowest energy level) (Table 2). We can also see that, with the exception of two analysed molecules, A2 and A6, every complex generated by the investigated chemicals and the leucine transporter LeuT in association with R-fluoxetine are more stable than the complex formed with the reference molecule (fluoxetine). Figure 2 depicts the outcome of the re-docked fluoxetine molecule and its location within the protein structure of the leucine transporter LeuT in association with R-fluoxetine. Fluoxetine participates in alkyl and Pi-alkyl interactions with Phe494, Pi-sigma interactions with Ile491, and Pi-Pi T-shaped interactions with Arg487. Trp406, Ala329, and Thr135 amino acids exhibit the Van der Waals interactions. As seen in Fig. 2, the docking outcome of six chosen 1,5-benzodiazepine derivatives and the leucine transporter LeuT in complex with R-fluoxetine. Additionally, Table 3 compares these outcomes with the outcome of the re-docked nortriptyline molecule and its location in the protein structure of the leucine transporter LeuT in complex with R-fluoxetine. A4's docked poses make it obvious that this molecule and the reference molecule (fluoxetine), which is in complex with the leucine transporter LeuT, interact in binding modes and ways that are similar to each other Asp46 and Phe43 create carbon hydrogen bonds between the two of them, whereas Asp46 and Asp43 create typical hydrogen hydrogen connections. Additionally, Pi-Pi interactions, which are also involved in the docked Fluoxetine molecule's binding, link Tyr124 to A1-A6. Similar to docked fluoxetine, all orientations of the described 1,5-benzodiazepine derivatives are stabilised in the cavity of the leucine transporter LeuT in association with R-fluoxetine by weak hydrophobic interactions with Val120 and Ala479.


LEU A:238
TRP A:244
LYS A:240
PRO A:241
LEU A:463
ILE A:245
VAL A:466
PHE A:459
ALA A:458
VAL A:462
Interactions
van der Waals
Carbon Hydrogen Bond
Pi-Cation
Pi-Pi Stacked
Alkyl
Pi-Alkyl


ILE A:490
TRP A:99
PHE A:494
LEU A:495
TRP A:406
ARG A:487
ILE A:491
PHE A:414
ILE A:410
PHE A:96
Interactions
van der Waals
Pi-Pi Stacked
Pi-Pi T-shaped
Pi-Alkyl


LEU A:500
LEU A:373
ALA A:384
TRP A:381
ILE A:385
LEU A:373
LEU A:367
PHE A:496
PHE A:388
LEU A:493
GLY A:492
Interactions
van der Waals
Pi-Pi Stacked
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

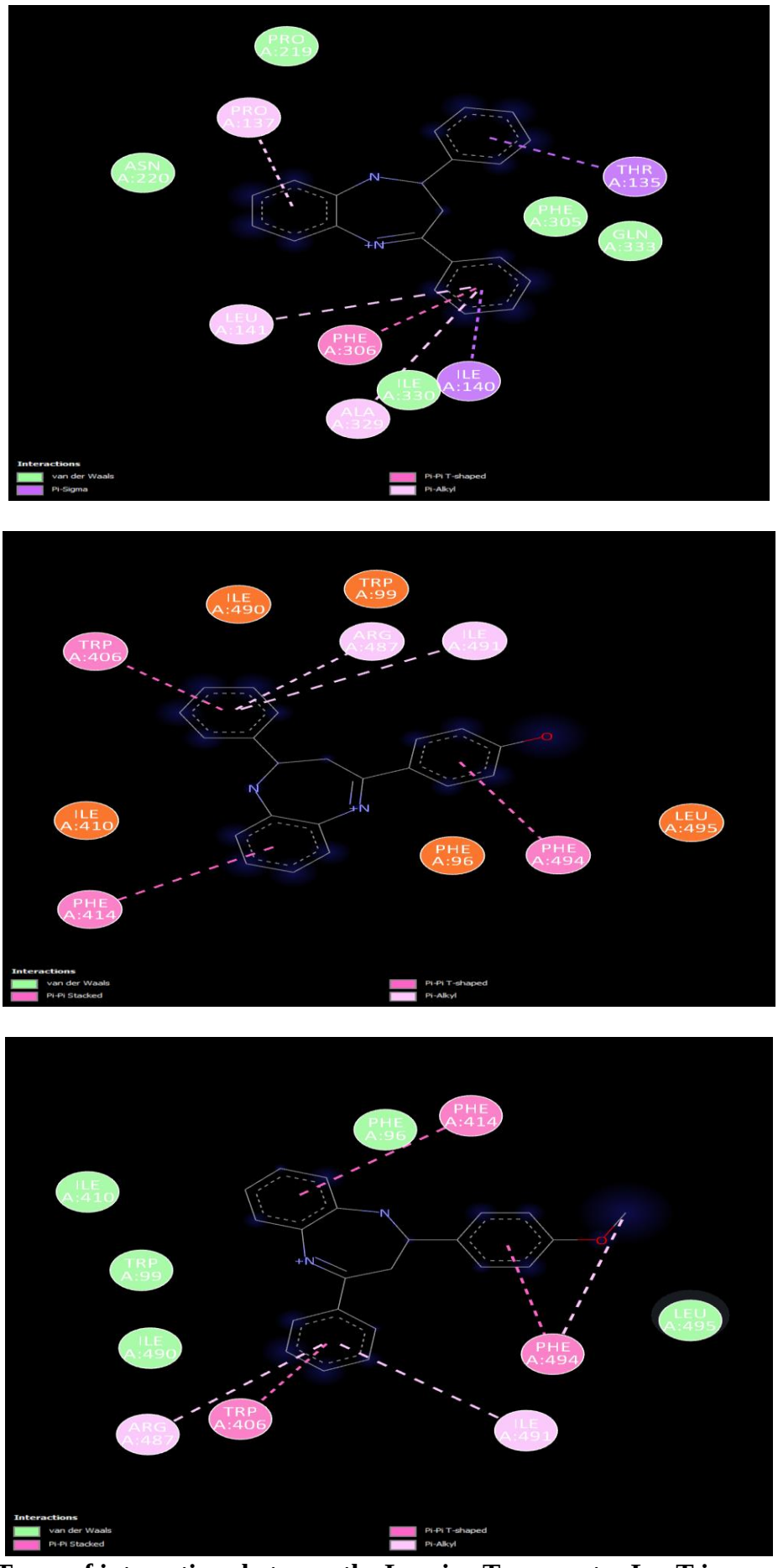


Fig. no. 02: Types of interactions between the Leucine Transporter LeuT in complex with R-fluoxetine (PDB code: 3GWV) and the six selected 1,5-benzodiazepines derivatives

Table no. 02: Auto dock score of six derivatives of 1,5-Benzodiazepines wit reference to reference drug Fluoxetine

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
A1	-8.2	50.6	47.63
A2	-8.1	21.835	18.264
A3	-7.9	19.75	18.42
A4	-7.7	16.752	14.096
A5	-7.7	20.412	16.275
A6	-7.4	28.566	25.313

3.2. ADME, toxicity and drug likeness prediction

Using the Pre ADMET predictor software, the six chosen 1,5-benzodiazepine derivatives had their absorption, distribution, metabolism, excretion, toxicity, and drug similarity predicted. The results are shown in Tables 3. Table 3's study of anticipated ADME qualities reveals that only a few compounds exhibit good blood-brain barrier penetrations in contrast to the other molecules, while one molecule has a very low permeability. All of these numbers are largely insufficient; in actuality, antidepressant molecules can penetrate the blood-brain barrier as far as Fluoxetine (11.456), for instance. While they inhibit and substrate cytochrome CYP_3A4, all molecules cannot substrate or inhibit cytochromes CYP_2C19, CYP_2C9, or CYP_2D6. For oral delivery, these compounds' high absorption—which can surpass 96% for all of them—is crucial. All molecules have a plasma protein binding percentage greater than 80%, meaning that only 20% of these molecules can have a pharmacological effect. This does not stop protein binding from affecting the biological half-life of the medication. The bound portion might serve as a store or reservoir from which the drug's unbound form is gradually released.

Table no. 03: Predicted ADME properties of the six studied compounds in comparison with the reference drug

	MR	MLOGP	GI absorption	BBB permeant	log Kp (cm/s)	Bioavailability Score	Druglikeness	Mutagenic
A1	102.88	3.92	High	Yes	-4.89	0.55	0.52187	N
A2	104.91	3.31	High	Yes	-5.24	0.55	0.47567	N
A3	104.91	3.31	High	Yes	-5.24	0.55	0.47567	N
A4	109.38	3.53	High	Yes	-5.09	0.55	0.505	N
A5	111.4	2.94	High	Yes	-5.44	0.55	0.52946	N
A6	111.4	2.94	High	Yes	-5.44	0.55	0.52946	N

4. Conclusion

All six ligands interacted well within the active site of Leucine transporter LeuT in complex with R-fluoxetine (PDB ID: 43GWV), according to the results of a docking study that was conducted in this study to clarify the type of interactions between selected 1,5-benzodiazepine derivatives and LeuT in complex with R-fluoxetine. The molecules displayed promising in silico results as evidenced by their high protein-ligand interaction energy. These molecules are estimated to have more than 96% intestinal absorption for all compounds when the examined compounds are evaluated for ADME and Toxicity characteristics. The 1,5-benzodiazepine derivatives A1, A2, A4, and A5 shown lower toxicity than the reference drug (Fluxetin) against depression during in vitro Toxicity characteristics prediction.

5. References

1. S.M. Hanson, C. Czajkowski, Structural mechanisms underlying benzodiazepine modulation of the GABAA receptor, J. Neurosci. 28 (2008) 3490–3499.
2. P.J. Snyder, J. Werth, B. Giordani, A.F. Caveney, D. Feltner, P. Maruff, A method for determining the magnitude of change across different cognitive functions in clinical trials: the effects of acute administration of two different doses

alprazolam, Hum. Psychopharmacol. Clin. Exp. 20 (2005) 263–273.
3. M. Watanabe, K. Maemura, K. Kanbara, T. Tamayama, H. Hayasaki, GABA and GABA receptors in the central nervous system and other organs, in: K.W. Jeon (Ed.), Int. Rev. Cytol., Academic Press, 2002, pp. 1–47.
4. J. Levine, D.P. Cole, K.N.R. Chengappa, Anxiety disorders and major depression, together or apart, Depress. Anxiety 14 (2001) 94–104.
5. L. Bertelli, G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, C. Martini, G. Giannaccini, L. Trincavelli, P.L. Barili, 1,2,3-Triazolo[1,5-a][1,4]- and 1,2,3-triazolo[1,5-a][1,5]benzodiazepine derivatives: synthesis and benzodiazepine receptor binding, Il Farmaco 53 (1998) 305–311.
6. D.K. Mohapatra, P.K. Maity, M. Shabab, M.I. Khan, Click chemistry based rapid one pot synthesis and evaluation for protease inhibition of new tetracyclic triazole fused benzodiazepine derivatives, Bioorg. Med. Chem. Lett 19 (2009) 5241–5245.
7. A. Adamski, D. Kruszka, Z. Dutkiewicz, M. Kubicki, A. Gorczynski, V. Patroniak, Novel family of fused tricyclic [1, 4] diazepines: design, synthesis, crystal structures and molecular docking studies, Tetrahedron 73 (2017) 3377–3386.
8. N. Mobaraki, B. Hemmateenejad, T.R. Weikl, A. Sakhteman, On the relationship between docking scores and protein conformational changes in HIV-1 protease, J. Mol. Graph. Model. 91 (2019) 186–193.
9. D.B. Kitchen, H. Decornez, J.R. Furr, J. Bajorath, Docking and scoring in virtual screening for drug discovery: methods and applications, Nat. Rev. Drug Discov. 3 (2004) 935.
10. Z. Gaieb, S. Liu, S. Gathiaka, M. Chiu, H. Yang, C. Shao, V.A. Feher, W.P. Walters, B. Kuhn, M.G. Rudolph, D3R Grand Challenge 2: blind prediction of protein–ligand poses, affinity rankings, and relative binding free energies, J. Comput. Aided Mol. Des. 32 (2018) 1–20.
11. S. Gathiaka, S. Liu, M. Chiu, H. Yang, J.A. Stuckey, Y.N. Kang, J. Delproposto, G. Kubish, J.B. Dunbar, H.A. Carlson, D3R grand challenge 2015: evaluation of protein–ligand pose and affinity predictions, J. Comput. Aided Mol. Des. 30 (2016) 651–668.