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Study of novel triazolo-benzodiazepine analogues as antidepressants targeting by molecular docking and ADMET properties prediction

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ABSTRACT

In this study, we have selected a series of a new family of molecules bearing Triazolo-benzodiazepines, an eleven membered heterocyclic ring has been studied for antidepression activity. Docking studies suggested that all the eleven ligands interacted well within active site of Drosophila melanogaster dopamine transporter (dDAT) (PDB ID: 4M48). Most ligands formed H-bond with amino acid Phe43, Asp46, Asp475, Tyr123, Ser421 and/or Gln316 and also exhibited Pi and Pi-Pi interactions with amino acid residues Tyr124, Phe319, Phe43, Phe325, Ala479 and Val120. In silico ADME evaluations of compounds showed more than 96% intestinal absorption for all compounds. During in vitro Toxicity properties prediction, the Triazolo-benzodiazepines derivatives: M_1, M_2, M_3 and M_{11} showed less toxicity than the other studied molecules against algae, for daphnia the molecules M_1, M_2, M_3, M_8, M_{10} and M_{11} showed less toxicity than the reference molecule (Nortriptyline).

1. Introduction

Diazepines are a well-known class of heterocycles and they have gained importance since 1957, when the chlordiazepoxide (first benzodiazepine) was synthesized and studied in terms of psychotropic activity [1, 2, 3]. Actually, they possess a wide spectrum of biological activity including anxiolytic, hypnotic, sedative, anticonvulsant, skeletal, amnestic and muscle relaxant properties [4, 5, 6, 7].

Triazolo-benzodiazepines analogues are a key structural motif in numerous therapeutics that have sedative, muscle relaxant, and antitumor activities [8, 9]. Alprazolam, adinazolam and estazolam are commercially available chemical drugs based on triazolo-benzodiazepine scaffold that widely used as anxiolytic and sedative agents [10, 11, 12, 13]. Some triazolo-benzodiazepine derivatives have been reported to be weakly bound to the benzodiazepine receptor and prevent serine protease [14, 15].

So, due to the therapeutic and biological applications of this class of compounds, the study of type of interactions between these molecules and protein targetingby molecular docking methods for the prediction of the activity is definitely of great importance.

Molecular docking turns out to be a reliable method for preliminary evaluation of binding affinity and prediction of intermolecular interactions of novel compounds with receptors [16]. Nowadays, this method has become indispensable for studying protein-ligand interactions. Docking method can produce significant knowledge for complex systems, which complements experimentally achievable data. Molecular docking simulations have found widespread application for virtual screening and pose prediction of new or non-synthesized compounds [17, 18, 19, 20].

Molecular docking studies were focused on the dopamine trans-porter (DAT). This transmembrane protein is responsible for reup-take of dopamine from the synaptic cleft. DAT inhibitors are used in the treatment of depression due to the increased level of dopamine in the synaptic cleft as well as in adjuvant therapy of Parkinson's Disease (PD) [21].

In this paper, a new family of Triazolo-benzodiazepines (Fig. 1) was docked to neurotransmitter trans-porter (DAT). We predict and interpret thebinding affinity and intermolecular interactions of complexes formed by docking of these molecules on DAT protein, so as to gain insight if those newly synthesized compounds could be of use as therapeutics in medicine.

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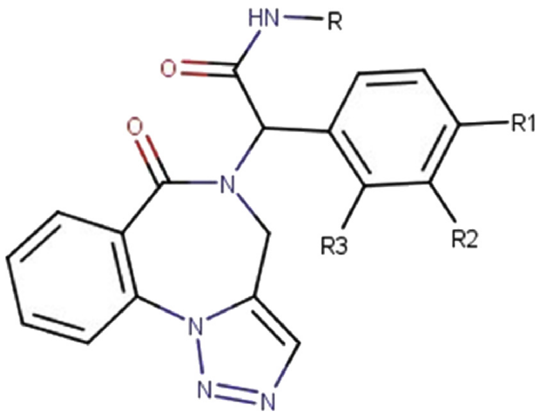

Fig. 1. Chemical structures of studied compounds.

2. Material and methods

2.1. Data collection

2.1.1. Ligands

In the present study, a series of 11 selected Triazolo-benzodiazepines derivatives were taken from literature (Table 1) [22], these molecules were considered to molecular docking study. The selected Triazolo-benzodiazepines were prepared by Asgari et al. from simple methods and substrates [22].

2.1.2. Receptor: dopamine transporter DAT

The dopamine trans-porter (DAT) is transmembrane protein. Drosophila melanogaster dopamine transporter (dDAT) is a proven model of DAT, which is 50% similar to mammalian DAT sequence, and is used in research into the mechanism of action of many compounds. Thus, in our docking studies we made use of the X-ray structure of dDAT in complex with the tricycilcanitide-pressant nortriptyline, which indicate primary binding site (PDB code: 4M48) [16].

Table 1
Chemical structures of the 11 selected Triazolo-benzodiazepines derivatives.

N°	R	R_1	R_2	R_3
1	Cyclohexyl	O–CH_3	H	H
2	Cyclohexyl	O–CH_3	O–CH_3	H
3	Cyclohexyl	Cl	H	H
4	*t*-Butyl	CH_3	H	H
5	*t*-Butyl	H	H	CH_3
6	*t*-Butyl	O–CH_3	H	H
7	*t*-Butyl	O–CH_3	O–CH_3	H
8	*t*-Butyl	Cl	H	H
9	*t*-Butyl	H	H	F
10	Cyclohexyl	F	H	H
11	1,1,3,3-tetramethyl-butyl	F	H	H

2.2. Molecular docking studies

Molecular docking turns out to be a reliable method for pre-liminary evaluation of binding affinity and prediction of intermolecular interactions of novel compounds with receptors. We decided to use neurotrans-mitter transporters (DAT) for docking study. In general, our research is based on crystal structures of receptors with bound ligand molecules. This structure has been obtained from X-ray crystal data of RCSB Protein Data Bank (PDB). In the majority of selected structures, co-crystallized ligand molecules are known drugs with proven action, and thus determine the binding site location in DAT as well as serve as references in our considerations.

In this research space, a docking process is launched for each studied molecule; the bioactive conformations were simulated using Autodock vina and Autodock tools 1.5.6 [23]. The results were analyzed using Discovery studio 2016 [24] and PyMol [25] softwares.

2.3. ADME and toxicity prediction

Absorption, distribution, metabolism, excretion and toxicity are predicted for the 11 selected Triazolo-benzodiazepines derivatives using Pre ADMET predictor server [26, 27].

3. Results and discussion

3.1. Molecular docking

The top-scoring pose of each molecule is selected according to the best interaction energy with the Drosophila melanogaster dopamine transporter (dDAT) (Table 2).

The best energies of interaction with the Drosophila melanogaster dopamine transporter (dDAT) (lowest energy level) are observed for the ligand M_{10}, whereas the ligand M_6 is the least stable ligand in the list of studied molecules (Table 2). We can also observe that all complex formed by studied compounds and dDAT are more stable than the complex formed with the reference molecule (Nortriptyline) except for two studied molecules: M_2 and M_6.

The result of the re-docked Nortriptyline molecule and its position in the PDB structure of protein dDAT is shown in Fig. 2.

Nortriptyline is involved in Pi-Pi T-shaped interactions with Tyr124 as well as alkyl and Pi-alkyl interactions with Ala479, and Pi-sigma interactions with Val120. The N-methylpropanamine chain of nortriptyline enables formation of carbon hydrogen bonds with Asp46, Ser421 and Phe319, while conventional hydrogen bon and Pi-donor hydrogen bond are created only with Phe43 because nitrogen atom (N) is present in this position. The Van der Waals interactions are observed with Ile 483, Tyr

Table 2
Comparison of Autodock score (kcal/mol) of the 9 best poses obtained by docking of 11 selected Triazolo-benzodiazepines derivatives and the re-docking of reference molecule (Nortriptyline) with dDAT.

Ligands	1	2	3	4	5	6	7	8	9
Ref: Nortriptyline	-10.0	-9.3	-9.2	-9.0	-8.8	-8.7	-8.7	-8.5	-8.0
M_1	-10.0	-9.8	-9.2	-9.1	-9.0	-8.9	-8.8	-8.7	-8.7
M_2	-9.9	-9.5	-9.4	-9.2	-9.1	-8.9	-8.9	-8.8	-8.7
M_3	-10.6	-10.0	-10.0	-9.9	-9.8	-9.6	-9.5	-9.4	-9.4
M_4	-10.5	-9.4	-9.3	-9.3	-9.3	-9.2	-9.2	-9.1	-8.8
M_5	-10.4	-9.3	-9.3	-9.3	-9.1	-8.7	-8.7	-8.7	-8.6
M_6	-9.6	-9.2	-9.1	-9.1	-9.0	-9.0	-8.9	-8.9	-8.7
M_7	-10.0	-9.9	-9.5	-9.5	-9.4	-9.2	-9.0	-9.0	-8.9
M_8	-10.4	-9.8	-9.5	-9.4	-9.4	-9.3	-9.3	-9.2	-8.9
M_9	-10.3	-9.4	-9.4	-9.3	-9.3	-9.1	-9.0	-8.9	-8.8
M_{10}	-12.3	-10.6	-10.5	-10.3	-10.0	-10.0	-9.8	-9.6	-9.5
M_{11}	-10.1	-10.1	-9.9	-9.5	-9.3	-9.1	-8.8	-8.8	-8.7

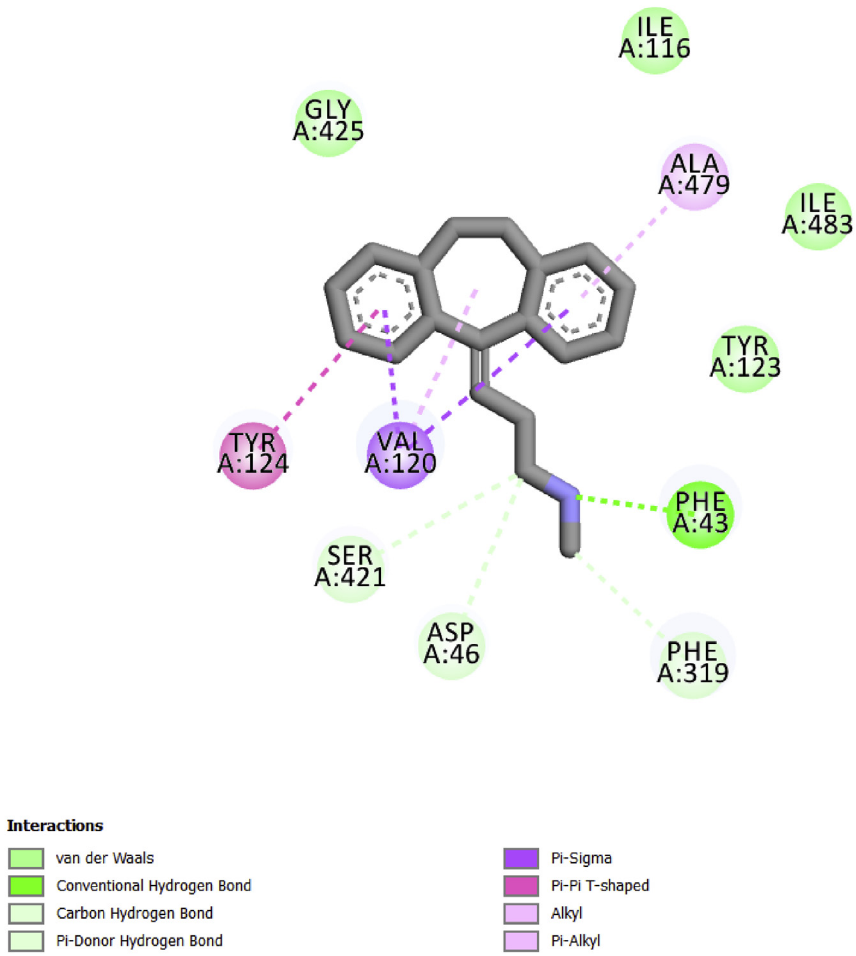

Fig. 2. Types of interactions between the dDAT (PDB code: 4M48) and Nortriptyline.

123 and Gly 425 amino acids.

The docking result of 11 selected Triazolo-benzodiazepines derivatives and dDAT is shown in Fig. 3. And the comparison of these results and the result of the re-docked Nortriptyline molecule and its position in the PDB structure of protein dDAT is shown in Table 3.

Visual inspection of the docked poses of molecule M_{11} clearly indicates similarity between binding modes and interactions of this molecule and the reference molecule (Nortriptyline) with dDAT. Both of them form carbon hydrogen bonds with Asp46, while conventional hydrogen hydrogen bond is formed with Phe43. Moreover, Tyr124 is bonded with M_3, M_4, M_5, M_7, M_8, M_9 and M_9 by Pi-Pi interactions, which play a similar role in the binding of docked Nortriptyline molecule. All orientations of the discussed Triazolo-benzodiazepines derivatives are stabilized in the dDAT cavity by weak hydrophobic interactions with Val120 and Ala479 in a similar manner to docked Nortriptyline except the two molecules M_5 and M_9.

The similarities between interactions of 11 Triazolo-benzodiazepines derivatives and reference molecule are retained to usas therapeutics in medicine to treat the depression.

3.2. ADME, toxicity and drug likeness prediction

Absorption, distribution, metabolism, excretion, toxicity and drug likeness are predicted for the 11selected Triazolo-benzodiazepines derivatives using Pre ADMET predictor server, and the results are presented in Tables 4 and 5.

The analysis of predicted ADME properties results (Table 4) shows that: the eleven molecules have different predicted in vivo blood-brain barrier penetration, the molecules M_1, M_2, M_3 and M_{10} have highest penetration (0.318, 0.320, 0.340 and 0.331, respectively) in comparison with the other molecules, whereas the molecule M_4 has a very low permeability (0.122). All these values are largely insufficient; in fact blood-brain barrier penetration of antidepressant molecules can reach for example in Nortriptyline 13.406.

All the molecules can't inhibit or be substrate for cytochromes CYP_2C19, CYP_2C9 and CYP_2D6 while they inhibit and substrate cytochrome CYP_3A4. These molecules have a high absorption which can exceed 96% for all the molecules, which is important for oral administration. A percent of plasma proteinbinding more than 80% is noted for all molecules which mean that 20% of the fraction of these molecules can actually give the pharmacological effect. This doesn't prevent that protein binding can influence the drug's biological half-life. The bound portion may act as a reservoir or depot from which the drug is slowly released as the unbound form.

The results of the prediction of the toxicity presented in Table 5 show that these molecules show a very low toxicity on the algae and daphnia, and a negative toxicity according to the four Ames tests (in vitro Ames test in TA100 strain (Metabolic activation by rat liver homogenate), in vitro Ames test in TA100 strain (No metabolic activation), in vitro Ames test in TA1535 strain (Metabolic activation by rat liver homogenate), in vitro Ames test in TA1535 strain (No metabolic activation)) except M_4, M_5, M_6, M_7, M_8 and M_9 whom has a positive toxicity on in vitro Ames test in TA100 strain (Metabolic activation by rat liver homogenate).

The Ames's mutagenicity test that uses several strains of the bacterium Salmonella typhimurium that carry mutations in genes involved in histidine synthesis, so that they require histidine for growth show that the molecule M_2 can induce mutations, and none of these molecules present a risk of carcinogenicity neither in the rat nor in the mouse, and

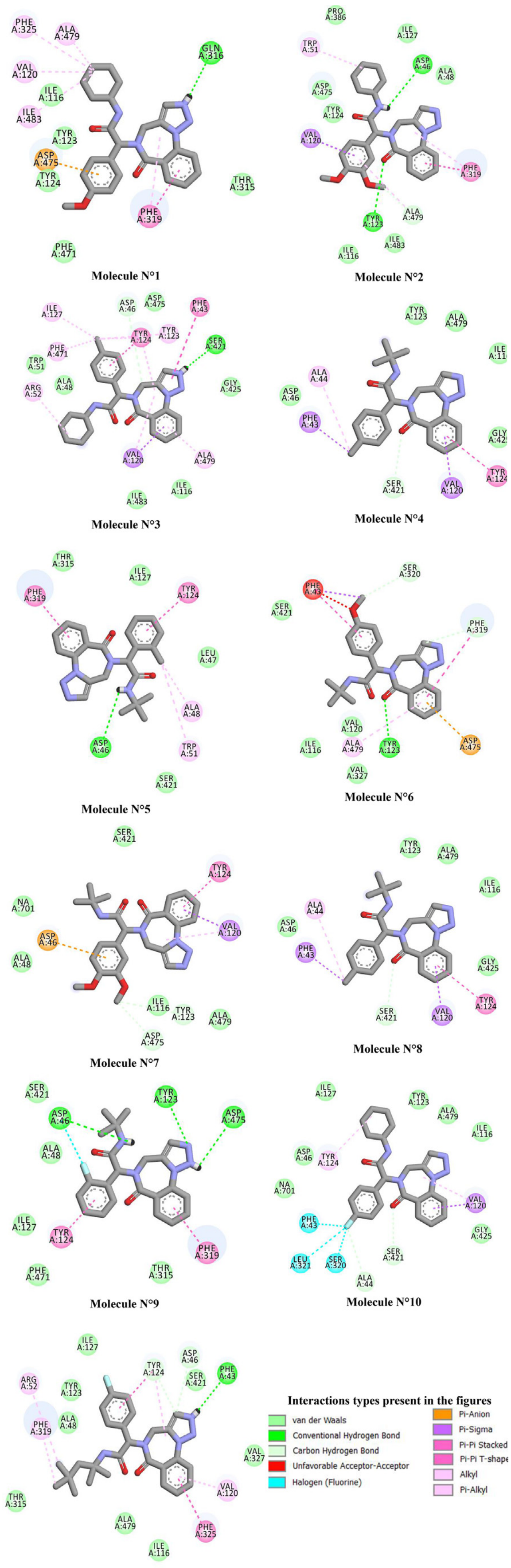

Fig. 3. Types of interactions between the dDAT (PDB code: 4M48) and the 11 selected Triazolo-benzodiazepines derivatives.

Table 3
Comparison of interactions formed by docking of 11 selected Triazolo-benzodiazepines derivatives and the re-docking of reference molecule (Nortriptyline) with dDAT.

Type of interactions		Residues	Molecules											
			Ref: Nortriptyline	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}	M_{11}
Hydrogen Bonds	Conventional H-Bond	PHE43	X											X
		GLN316		X										
		ASP46			X			X				X		
		TYR123			X				X			X		
		SER421				X								
		ASP475										X		
	Carbon -H-Bond	SER421	X				X				X		X	
		ASP46	X			X								X
		PHE319	X						X					
		ALA479			X									
		SER320							X					
		ASP475								X				
		TYR123								X				
		ALA44											X	
		SER124												X
	Pi-Donor-H-Bond	PHE43	X											
Hydrophobic interactions	Pi-Pi	TYR124	X			X	X	X		X	X	X		X
		PHE319		X	X			X	X			X		
		PHE43				X			X					
		PHE325												X
	Alkyl	VAL120	X	X		X				X			X	
		ALA479		X										
		ILE483		X										
		ILE127				X								
		ARG52				X								X
		ALA44					X				X			
		ALA48						X						
		TYR124								X				
	Pi-Alkyl	ALA479	X		X	X			X					
		PHE319		X	X									X
		PHE325		X										
		TRP51			X			X						
		TYR123				X								
		TYR124				X							X	X
		PHE471				X								
		VAL120												X
	Pi-Sigma	VAL120	X		X	X	X			X	X		X	
		PHE43							X		X			

Table 4
Predicted ADME properties of the 11 studied compounds in comparison with the reference drug.

	Ref	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}	M_{11}
BBB	13.406	0.318	0.320	0.340	0.122	0.159	0.245	0.197	0.277	0.180	0.331	0.246
BS	66.488	93.970	52.011	59.350	247.204	77.602	326.688	181.526	206.459	368.859	189.694	157.659
CYP_2C19_inhibition	Inhibitor	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
CYP_2C9_inhibition	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
CYP_2D6_inhibition	Inhibitor	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
CYP_2D6_substrate	Substrate	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
CYP_3A4_inhibition	Non	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
CYP_3A4_substrate	Non	Weakly	Substrate	Weakly	Substrate	Substrate	Substrate	Substrate	Substrate	Substrate	Weakly	Substrate
HIA	100	96.828	97.356	96.548	96.466	96.466	97.004	97.525	96.457	96.506	96.438	96.440
MDCK	96.879	1.121	0.143	3.675	24.933	112.593	6.772	1.476	9.663	27.802	2.223	0.043
Pgp_I	Inhibitor	Non	Inhibitor	Inhibitor	Non	Non	Inhibitor	Inhibitor	Inhibitor	Non	Non	Inhibitor
PPB	100	90.524	89.190	91.919	88.306	87.741	83.385	80.719	87.854	88.330	89.897	89.716
PWS	2.941	2.472	1.721	0.520	9.662	18.801	22.013	15.382	4.624	21.762	1.755	0.514
SKlogD_value	3.500	3.554	3.5489	4.269	3.407	3.3850	2.876	2.872	3.592	3.046	3.735	4.600
SKlogP_value	4.844	3.554	3.5489	4.269	3.407	3.3850	2.876	2.872	3.592	3.046	3.735	4.600
SKlogS_buffer	-3.621	-3.676	-3.961	-3.880	-3.213	-3.716	-3.109	-3.394	-3.312	-3.043	-3.359	-3.468
SKlogS_pure	-4.975	-5.256	-5.441	-5.938	-4.621	-4.332	-4.280	-4.466	-4.962	-4.272	-5.393	-5.955

BBB = in vivo blood-brain barrier penetration (C.brain/C.blood), BS = Buffer Solubility (mg/l), CYP2C19 = cytochrome P4502C19, CYP2C9 = cytochrome P4502C9, CYP3A4 = cytochrome P4503A4, CYP2D6 = cytochrome CYP2D6, PgP I = P-glycoprotein inhibition, PPB = Plasma Protein Binding %, PWS = Pure Water Solubility (mg/l), HIA = Human intestinal absorption %, MDCK = in vitro MDCKcellpermeability (Mandin Darby Canine Kidney (nm/sec)).

Table 5
Toxicity predicted of the 11 studied compounds in comparison with the reference drug.

ID	Ref	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}	M_{11}
algae_at	0.008	0.019	0.013	0.011	0.053	0.064	0.055	0.040	0.037	0.076	0.025	0.011
Ames_test	Mutagen	Mutagen	Non-mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen	Mutagen
Carcino_Mouse	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Carcino_Rat	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
daphnia_at	0.030	0.024	0.022	0.009	0.0434	0.044	0.078	0.070	0.029	0.059	0.020	0.012
hERG_inhibition	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk	Medium_risk
TA100_10RLI	Negative	Negative	Negative	Negative	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Negative
TA100_NA	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
TA1535_10RLI	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
TA1535_NA Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	

all present a medium risk to inhibit HERG (Human ether-a-go-go related gene channel). It should be noted that all these values are predicted.

4. Conclusion

In this study, the docking study was performed to elucidate the type of interactions between 11 selected Triazolo-benzodiazepines derivatives and Drosophila melanogaster dopamine transporter (dDAT), the results show that all the eleven ligands interacted well within active site of dDAT (PDB ID: 4M48); the molecules showed promising in silico results as indicated by their high protein–ligand interaction energy. The studied compounds are screened by ADME and Toxicity properties; these molecules are predicted to have more than 96% intestinal absorption for all compounds. During in vitro Toxicity properties prediction, the Triazolo-benzodiazepines derivatives: M_1, M_2, M_3, M_8, M_{10} and M_{11} showed less toxicity than the reference molecule (Nortriptyline) against daphnia.

A deep investigation of in vitro activity supported by docking results and in silico ADMET results clearly suggested that these molecules could be of use as therapeutics in medicine to treat the depression.

Declarations

Author contribution statement

Mohammed Bouachrine, Assia Belhassan, Hanane Zaki, Mohamed Benlyas, Tahar Lakhlifi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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