Design and *in silico* evaluation of oxadiazole linked chromone derivatives as anti-depressant agents

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Abstract

Depression is a common CNS disorder due to disturbances in the serotonin and dopamine level within the brain. In this study, different derivatives (C1-C32) of oxadiazole-linked chromone were designed and in silico studies were performed to investigate its anti-depressant activities. Compounds were docked with 5HT1 receptors to do so and MMGBSA and ADMET properties were evaluated. Further, compounds pharmacophore modeling and antidepressant activity were calculated using the phase and PASS tools. Among 32 designed compounds, C15, C29 and C31 showed the highest docking scores of -7.617, -7.269 and -7.325 kcal/mol *and exhibited significant interaction with 5HT1 receptors compared to the standard drug imipramine. Compound C15 showed the highest binding efficiency with a binding energy of -77.79; the expected common is having a binding energy of -47.20. ADME properties show that all the designed compounds followed the rule of five.*

Further ligand-receptor complex potential interactions were evaluated using pharmacophore modeling, indicating that the compound has steric and electronic features to ensure the interaction with the selected receptor. Further, the antidepressant activity was predicted. Compounds C15 and C21 have the highest possibility of being antidepressant molecules with 0.827 and 0.833 pa values.

Keywords: Chromone, Depression, Docking Studies Oxadiazole, Pharmacophore.

Introduction

Nowadays, depression has become a severe mental problem with a high incidence of suicide and much social withdrawal. It is characterized by sadness, disturbed sleep, appetite, loss of interest, feelings of tiredness, guilt or low self-worth and poor concentration.[1] As per the World Health Organization (WHO), depression has affected 264 million people worldwide. It is also a prevalent mental condition involving complex social and psychological behaviour interactions and substantially burdens the society.[10]

This disorder is treated with antidepressant drugs by elevating mood and modifying behaviour. There are various classes of drugs used for the treatment of depression such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCA), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants[15].

However, despite so many classes of antidepressants available, the effect in the long term is still questionable**.** All these drugs have reported side effects in the long-term treatment such as changes in sleep patterns, weight increases, gastrointestinalhaemorrhagee and loss of libido[8]. Hence, finding a new molecule to treat depression is urgently needed.

Chromone is an isomer of coumarin and is also known as 1-benzopyran-4-one. It is a member of the benzopyran class and has a keto group replaced on the fourth position of the Pyran ring. Its derivatives have demonstrated various biological actions including antioxidant[3], antibacterial, anticancer, psychotropic, insecticidal, fungicidal[9] and antiviral properties[7]. A heterocyclic molecule with a five-membered ring of two nitrogen atoms and one oxygen atom is known as 1,3,4 oxadiazole. This has also demonstrated various biological effects such as anti-inflammatory[2], antimicrobial[11], antiviral and depressive properties[12].

The serotonin 5-HT1A receptor (5-HT1AR) is a G-protein coupled receptor extensively expressed in the central nervous system (CNS)[14]. It is responsible for modulating mood, emotion and depression, as well as various behavioral responses such as thermoregulation, sleep, feeding, aggression and anxiety. Of all the serotonin receptor subtypes, 5-HT1AR is the primary receptor that causes depression and it plays a massive role in many antidepressants' works.

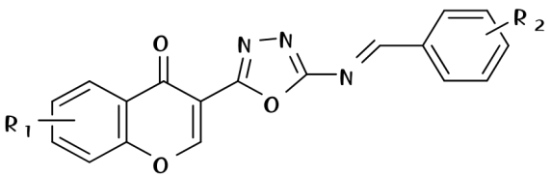
Keeping this in view, the two pharmacophores chromone and oxadiazole, were merged to form a single pharmacophore and different derivatives were further designed based on various substitutions on the main pharmacophore. Further, these designed ligands were evaluated for antidepressant activity using *in silico* studies targeting the serotonin 5-HT1A receptor (5-HT1AR).

Material and Methods

Designed compounds data: Designed compounds (C1-C32) shown in figure 1 were evaluated for anti-depressant activities using *in silico* studies.

***In silco* study:** All the computational studies were carried out on Maestro 12.3 version 25 from Schrodinger programmed on DELL 27″ computer terminal which works on Intel Core i7-7700 CPU at 3.60 GHz x8 clock speed with

the random-access memory 8 GB and 1 TB hard drive on Linux 64-bit operating system.



R_1 = H, CH_3
R_2 = 2,3-NO_2, 4-NO_2, 6-F, 4-Br, 4-OH, 2-OH, 4-OCH_3, 3-Cl, 4-Cl, 2-OCH_3, 3-OCH_3, 2,4-Cl, 4-NO_2, 2,5-OCH_3, 3,4,5-OCH_3

Figure 1: Designed Oxadiazole-linked chromone derivatives (C1-C32)

Molecular docking and MM-GBSA binding free energy: Molecular docking is significant in structural molecular biology and computer-aided drug design. Designed ligand-protein docking uses a three-dimensional enzyme to anticipate the predominant ligand binding mode(s). A structure-based drug design process called molecular docking identifies the crucial interactions between the targeted protein and produced ligands with low energy conformation. The scoring function used to predict the binding affinity with the receptor characterizes the minimum interaction of the ligands. All these designed ligands docked with 5 HT1A (PDB-ID: 7E2X) receptors and their binding affinity were assessed in terms of binding free energies (Docking score, Kcal/mol) creations on the active site of the protein and the optimal interaction of ligand molecules. Lastly, these ligands were docked using Glide enhanced precision scoring methods (XP).[6,13] Further binding efficiency receptor-ligand complexes were calculated regarding molecular mechanics-generalized born surface area (MM-GBSA).

ADMET properties and pharmacophore modelling: With the QikProp module of the Schrödinger suite 2022-4, an ADME calculation was performed for the top ten docked designed ligand and its physicochemical properties were determined such as hydrogen bond donors and acceptor and log P value; the molecules are anticipated to adhere to Lipinski's rule of five deprived of breaking. This study predicts the druggable nature of designed compounds. Further, the top ten docked designed compounds' pharmacophore modeling was performed using e - pharmacophore generation to understand the receptor's and ligand's interaction using phase pharmacophore models (Schrodinger 2020-4: Phase). This modeling shows that the minimum feature of ligand must possess functional interaction with the receptor.[4,5]

Prediction of biological activity using PASS: The top ten docked were evaluated for antidepressant activity using the online tool predicting activity spectra for substances *(*PASS). The PASS provides Pa (pharmacologically active) and Pi (pharmacologically inactive) values by uploading the canonical smiles of compounds. Pa (pharmacologically active) value is the possibility of compounds belonging to a particular class of compounds. The greater is the Pa value, the greater is the chance to belong to that compound class.[16]

Results and Discussion

Molecular docking: The prepared library of compounds (C1-C32) was docked into the active pockets of the Apo serotonin 1A (5-HT1A) receptor (PDB ID: 7E2X) and its docking score was calculated as Kcal/mol. The compound's docking score ranged from -7.617 to -4.436 kcal/mol whereas the standard drug imipramine was -5.653 Kcal/mol. Among all these, compounds C15, C31 and C29 have shown the best docking score and their binding interaction of protein (7E2X) along with imipramine respectively presented in figures 2, 3, 4 and 5.

Compounds interacted with various amino acid receptors through bonds such as π- π stacking, hydrogen bonding and hydrophobic, positive and negative interaction. Apart from compound C24, all the compounds showed polar interaction with SER199. The docking score of the designed compound (C1-C32) is shown in table 1.

Table 1
Docking scores of designed compounds (C1-C32) bounded to 7E2X receptor

Comp code	R_1	R_2	Docking score	Comp code	R_1	R_2	Docking score	Comp code	R_1	R_2	Docking score
C1	H	3NO_2	-7.161	C11	H	2OH	-7.084	C21	H	3OCH_3	-6.854
C2	CH_3	3NO_2	-4.436	C12	CH_3	2OH	-6.819	C22	CH_3	3OCH_3	-6.567
C3	H	4 NO_2	-6.544	C13	H	4-OCH_3	-6.983	C23	H	2,4 Cl	-6.787
C4	CH_3	4 NO_2	-5.106	C14	CH_3	4-OCH_3	-6.224	C24	CH_3	2,4 Cl	-5.077
C5	H	4F	-6.970	C15	H	3Cl	-7.617	C25	H	4 NO_2	-5.122
C6	CH_3	4F	-6.190	C16	CH_3	3Cl	-6.001	C26	CH_3	4 NO_2	-6.175
C7	H	4Br	-6.188	C17	H	4Cl	-6.445	C27	H	2, 5 OCH_3	-6.440
C8	CH_3	4Br	-5.194	C18	CH_3	4Cl	-6.209	C28	CH_3	2, 5 OCH_3	-5.272
C9	H	4-OH	-6.242	C19	H	2OCH_3	-5.780	C29	H	3, 4, 5 OCH_3	-7.269
C10	CH_3	4-OH	-6.226	C20	CH_3	2OCH_3	-6.099	C30	CH_3	3, 4, 5 OCH_3	-6.309
C31	H	2 Cl	-7.325	C32	CH_3	2 Cl	-6.287	Imipramine			-5.653

Table 2
The glide score of the top ten compounds docked to Apo serotonin 1A (5-HT1A) receptor

Comp code	Glide EVDW	Glide Coulombic	Glide energy
C1	-33.832	-0.651	-34.483
C5	-34.691	-0.691	-35.381
C11	-36.892	-0.802	-37.694
C12	-36.236	-3.200	-39.436
C13	-36.186	-0.785	-36.971
C15	-38.926	-0.385	-39.311
C21	-36.715	-0.301	-37.016
C23	-37.812	0.786	-37.026
C29	-39.821	0.406	-39.416
C31	-37.061	-0.659	-37.720
Imipramine	-28.846	-1.641	-38.310

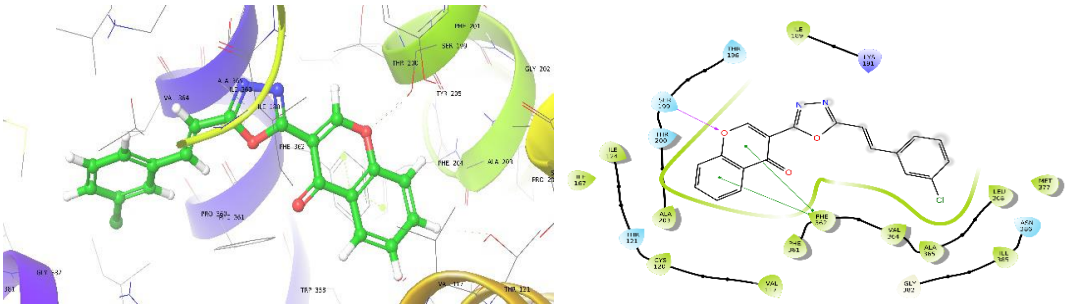


Figure 2: 3D and 2D interaction of C15 with 7E2X

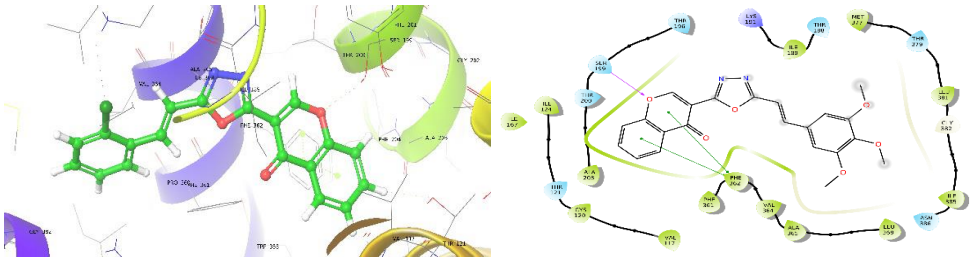


Figure 3: 3D and 2D interaction of C31 with 7E2X

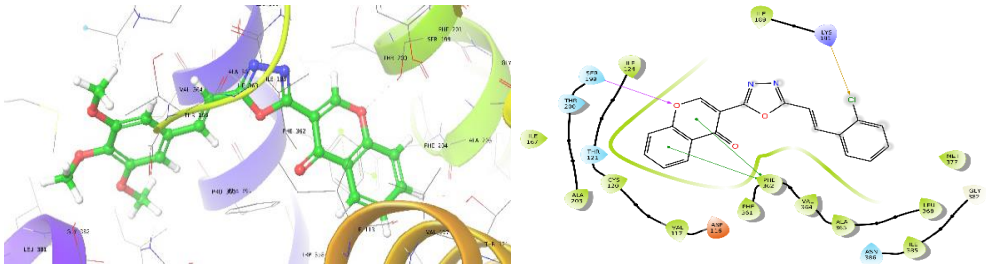


Figure 4: 3D and 2D interaction of C29 with 7E2X

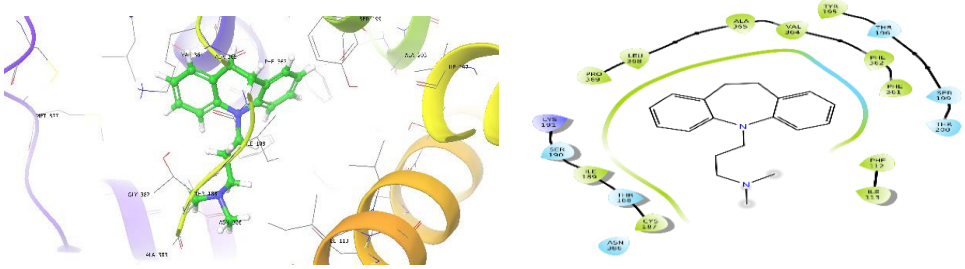


Figure 5: 3D and 2D interaction of Imipramine with 7E2X

Table 3
List of amino acids of top ten docked molecules that interacted with 7E2X receptor

Comp Code	Hydrophobic interaction	Polar interaction	H-bonding	Positively charged	Negatively Charged
C1	ILE189, ILE124, ILE176, ALA203, CYS120, VAL117, PHE361, VAL364, ALA365, ILE385, LEU368, LEU381, MET377	SER199, THR200, THR121, ASN386	SER199	LYS101	
C5	MET377, ILE189, ILE124, ILE167, CYS120, ALA203, VAL117, PHE361, PHE362, VAL364, ALA365, ILE385, LEU368	SER199, THR200, THR121, ASN386	SER199	LYS191	ASP116
C11	ILE189, ILE124, ILE167, CYS120, ALA203, VAL117, PHE361, PHE362, VAL364, ALA365, ILE385, LEU368, MET377	SER199, THR200, THR121, ASN386	SER199	LYS191	ASP116
C12	ILE189, ILE167, ALA203, CYS120, VAL117, PHE361, PHE362, VAL364, ALA365, ILE385, LEU368, MET377	SER199, THR200, THR121, ASN386	SER199	LYS191	ASP116
C13	ILE124, ILE167, ALA203, CYS120, VAL117, PHE361, PHE362, VAL364, ALA365, LEU368, MET377, PRO378, ILE385	SER199, THR200, THR121, ASN386, THR379	SER199	LYS191	
C15	ILE189, ILE124, ILE167, CYS120, ALA203, VAL117, CYS120, PHE361, PHE362, VAL364, ALA365, ILE385, LEU368	THR196, SER199, THR200, THR121, ASN386	SER199	LYS191	
C21	ILE189, ILE124, ILE167, ALA203, CYS120, VAL117, PHE361, PHE362, VAL364, ALA365, ILE385, LEU368, LEU381, MET377	THR196, SER199, THR200, THR121, ASN386	SER199	LYS191	
C23	ILE189, ILE124, ILE167, ALA203, CYS120, VAL117, PHE361, PHE362, VAL364, ALA365, LEU368, MET377	THR200, SER199, THR121, ASN386, THR196	SER199	LYS191	
C29	ILE124, ILE167, ALA203, CYS120, VAL117, PHE361, PHE362, VAL362, ALA365, LEU368, ILE385, LEU381, MET377	THR196, SER199, THR200, THR121, ASN386, THR379	SER199	LYS191	
C31	LEU368, ALA365, ILE189, PHE362, PHE361, ILE167, ALA203, TRP358, ILE124, CYS120, TYR390, VAL117, MET377	SER199, THR200, THR121, ASN386,	ASN386	LYS191	ASP116
Imipramine	CYS187, ILE189, PRO369, LEU368, ALA365, VAL364, TYR195, PHE362, PHE361, PHE112, ILE113	SER190, THR188, ASN386, THR200, SER199, THR196		LYS191	

Further analysis of compounds was done based on the docking score obtained. Among the 32 molecules designed, top ten docked molecules were selected for further research. These molecules' glide score, ADMET properties, binding energy and PASS activity were performed. The glide score of compromise of Vander Waal energy (evdw), Coulomb energy (ecoul) and glide energy is shown in table 2. Various amino acids and different bonds through which receptors and the top ten docked molecules interacted are shown in table 3.

Binding free energy calculation: Similarly, to determine the binding free energy of the top docked molecules with the target protein 7E2X, the prime MM-GBSA simulations were run. It showed that compounds binding energy ranged from-77.81 kcal/mol to -75.48 kcal/mol and standard drug imipramine had -47.20 kcal/mol. It was observed that compounds C29, C15 and C30, with the highest docking score, have the highest binding free energy. The MM/GBSA findings of the top ten docked compounds are reported in Table 4.

ADME profile: The compound's pharmacokinetics and drug-like characteristics were evaluated using the QikProp module of the Schrödinger suite 2020-4. Table 5 lists the findings of the top ten docked molecules. Based on the results, it was observed that it successfully satisfied all the parameters to be a druggable molecule. All the compounds had a molecular weight lesser than 500 Daltons and other features well within the prescribed limit to obey Lipinski's rule of five and rule of three.

Pharmacophore modelling: Further pharmacophore modeling using *e*-pharmacophore generation from the phase module was generated. It determines the compounds' steric and electronic features to show supra-interaction with receptors 7E2X. The highest dock score compound and receptor complex were selected to lead aromatic rings R8, R10 and R11. Hydrogen bond acceptor A5 and hydrophobic H6 of the compound had excellent interaction with the receptor. The distance between the rings R10 to R11 is 10.84 Å, R11 to R8 is 6.29 Å and R8 to R10 is 6.28 Å respectively. The generated Pharmacophore modeling are shown in figures 5 and 6.

Table 4
Binding free energy simulations using Prime/ MM-GBSA approach of top ten docked compounds

Comp Code	ΔG bind	ΔG bind lipo	ΔG bind coulomb	ΔG bind covalent	ΔG bind Solve GB	ΔG bind vdW
C1	-68.80	-34.03	5.90	5.13	2.52	-46.87
C5	-66.44	-33.73	-0.09	2.97	6.18	-40.38
C11	-66.74	-34.09	-1.12	3.40	8.98	-42.46
C12	-69.02	-35.16	-9.89	1.47	15.59	-40.50
C13	-68.96	-35.05	-0.16	2.66	7.62	-42.72
C15	-77.79	-42.75	1.61	2.57	6.54	-44.32
C21	-73.00	-37.61	1.19	2.72	6.89	-44.84
C23	-75.63	-43.17	3.62	3.55	6.20	-44.45
C29	-77.81	-41.08	0.29	0.89	10.93	-47.50
C31	-71.02	-36.89	0.84	2.04	6.27	-41.91
Imipramine	-47.20	-40.19	1.08	1.10	18.93	-27.40

Table 5
Predicted ADME profile of top ten docked compounds

Compound Code	Mol MW	dipole	SASA	FOSA	FISA	QPlogPw	Rule of five	Rule of three
C1	361.313	2.921	627.064	24.589	186.849	2.590	0	0
C5	334.306	6.873	597.699	24.560	89.678	3.584	0	0
C11	332.315	7.098	597.456	20.302	135.021	2.876	0	0
C12	346.342	6.763	629.591	108.457	135.081	3.179	0	0
C13	346.342	8.309	625.704	117.314	89.774	3.402	0	0
C15	350.760	5.093	612.685	24.562	89.685	3.849	0	0
C21	346.342	7.405	625.607	116.777	89.733	3.402	0	0
C23	385.206	8.470	632.218	17.555	89.776	4.297	0	0
C29	406.394	7.291	700.606	290.284	89.688	3.597	0	0
C31	350.760	8.892	608.131	17.584	89.792	3.791	0	0
Imipramine	280.412	1.471	578.771	281.577	6.800	4.420	0	0

Table 6
Predicted antidepressant PA (Pharmacologically active) value of top ten docked molecules

Compound	Pass value
C1	0.734
C5	0.779
C11	0.647
C12	0.666
C13	0.793
C15	0.827
C21	0.833
C23	0.664
C29	0.721
C31	0.611
Imipramine	0.912

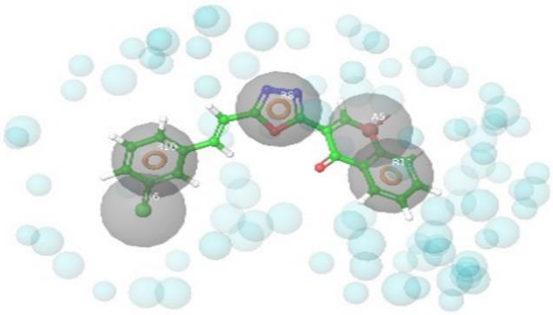


Figure 6: Alignment of compound C15 with the best common pharmacophore hypotheses

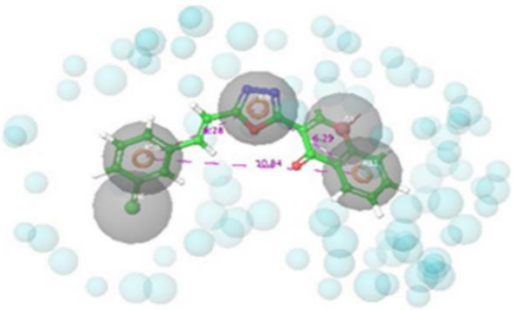


Figure 7: Pharmacophore hypothesis and angles between pharmacophoric sites

PASS predicted value: The compound's biological activity showed a superior value close to the standard drug imipramine 0.912. The predicted compounds' antidepressant activity ranged from 0.611 to 0.833. Among all these compounds, C15 and C21 showed the highest antidepressant activity with pa of 0.827 and 0.833 respectively. Pa value of predicted compounds is shown in table 6.

Conclusion

In this study, to evaluate the anti-depressant of oxadiazole-linked chromone, thirty-two different substituted compounds were designed and *in silco* studies were performed. The designed compounds' molecular docking was conducted with Apo serotonin 1A (5-HT1A) receptor (7E2X) and most of these compounds exhibited higher docking scores compared to the standard drug imipramine. Compound C15 ((E)-3-(5-(3-chlorostyryl)-1, 3, 4-oxadiazol-2-yl)-4H-chromen-4-one) showed the highest docking score of -7.617 kcal/mol. To evaluate its other properties, the top ten docked molecules were selected. ADMET studies of these compounds showed physiochemical properties well within the limit and possessed druggable properties.

The MM-GBSA of the compounds showed an excellent binding affinity with receptors, with the highest compound being C29 (77.81 kcal/mol.) The pharmacophore mapping showed electronic and aromatic features of the ligand such as potential hydrogen bond acceptor A5, hydrophobic H6 and aromatic rings R8, R10 and R11, to show excellent interaction with receptor 7E2X. The PA value from PASS predicted that these designed compounds have a greater

chance of belonging to an antidepressant class of drugs with the highest of compounds C15 and C21.

Thus, this study showed that oxadiazole-linked chromone is a potential candidate for antidepressant activity with the highest potential of compounds C15, C29 and C23. Further, these compounds should be synthesized and pharmacologically investigated to become promising leads for the treatment of depression.

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