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Original Research Article

Design, molecular docking studies and ADME prediction of 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives as CYP51 inhibitor for antimicrobial activity

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ABSTRACT

The 1, 3, 4-Oxadiazole nucleus offers a wide range of applications in hetero cyclic chemistry, including antimicrobial medicine. A series of the 2, 5-disubstituted 1, 3, 4-Oxadiazole derivatives were designed and *in silico* study was performed against the ergosterol biosynthesis as an antimicrobial target. The drug-likeness properties of the designed compounds were predicted. All the designed compounds showed good *in silico* ADME properties and investigated for CYP51 inhibitory activity. According to molecular docking studies, all compounds showed better interaction with target protein and could be the potent inhibitor of ergosterol biosynthesis. The designed 2, 5-disubstituted 1, 3, 4-Oxadiazole derivatives analogs could be safer and more or equivalent effective antimicrobial agents.

1. Introduction

Treatment for bacterial infections is becoming complicated day by day due to the ability of bacteria to develop resistance to antimicrobial agents,[1] Microorganisms have become resistant to currently used antibiotics due to over-prescription of antibiotics, and their inappropriate use by patients. This challenges the treatment even though previously used antibiotics or antimicrobial drugs are no longer effective, and infections become progressively difficult to treat.[2] Hence, it is essential to design and discover new and safer as well as more effective antimicrobial drugs,[3] Literature survey revealed that 1, 3, 4-oxadiazole possess diverse pharmacological activities such as anticancer,[4] antimicrobial,[5,6] anti-hypertensive,[7] anticonvulsant,[8] antimalarial,[9] antiviral,[10] anti-inflammatory.[11] Some of 2, 5-disubstituted 1, 3, 4-oxadiazole based entities have emerged as most potent antimicrobial activities.[12–14] CYP51 is one of the key enzyme of ergosterol biosynthesis in different biological kingdoms and is found in eukaryotes (including humans). Inhibition of ergosterol synthesis, as the new structures fit very well in the active site of the lanosterol 14α-demethylase enzyme. It takes part in the synthesis of ergosterol, the main sterol component of the fungal cell membrane and serves the metabolic function such as membrane permeability, membrane fluidity, enzyme activity, cell morphology, and cell cycle progression. Inhibition of this enzyme causes loss of cell continuity and cell dysfunction.[15] 1, 3, 4-Oxadiazole block the 14α-demethylation of lanosterol into ergosterol, which is a major component of fungal cytoplasmic membranes and a bioregulator of membrane asymmetry, fluidity and integrity.[16–25]

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2. Materials and Methods

2.1. In silico ADME (Absorption, Distribution, Metabolism and Excretion Studies)

ADME describes the pharmacokinetics of the molecules within the body of organisms. It evaluates the risk of a pharmacological compound being administered to the human body or other organisms. These pharmacokinetic properties are identified in silico using an online tool such as SwissADME (http://www.swissadme.ch/),[24] preADMET (https://preadmet.bmdrc.kr/). According to the Lipinski's rule of 5, the two or more violation makes the molecules orally inactive. Drug likeness is the complicated balance of multiple chemical characteristics and structure features that determines whether a molecule is similar to the medications that are already on the market. These properties include hydrophobicity, hydrogen bonding characteristics, electronic distribution, flexibility, molecule size, and the presence of several pharmacophoric features all influence a molecule's behavior in a living organism, including transport properties, bioavailability, reactivity, affinity to proteins, toxicity, metabolic stability, and many other factors.[20]

2.2. Molecular docking studies

To predict the binding interaction of designed 2,5 disubstituted 1,3,4-Oxadiazole derivatives with targeted protein, molecular docking is performed. The targeted protein is the CYP51 (PDB ID: 6AYC). Molecular docking is performed using Autodock Vina software. Before docking, the protein was prepared using the Discovery visual studio tool. The protein is downloaded from PDB and the unwanted atoms such as water molecules, hetero atoms, unwanted chains, cofactors are removed, making the protein ready for interaction. The designed 2, 5 disubstituted 1, 3, 4-Oxadiazole derivatives are optimized by using Chem 3D software to minimize the energy of the structure.

3. Result and Discussion

To be a successful medicine, the chemical must have high biological activity at low effective concentrations, low toxicity, and the ability to remain active until the intended result occurs. As the 1, 3, 4-Oxadiazole nucleus is reported widely to treat microbial infection, new derivatives containing 2, 5 disubstituted 1, 3, 4-Oxadiazole are designed for its antimicrobial activity, targeting the ergosterol biosynthesis inhibitor activity. From the Pass online (http ://way2drug.com/PassOnline/predict.ph). All the designed compounds are given in Diagram 1. It was found that the designed compound shows ergosterol biosynthesis inhibitor activity with a minimal adverse drug reaction.

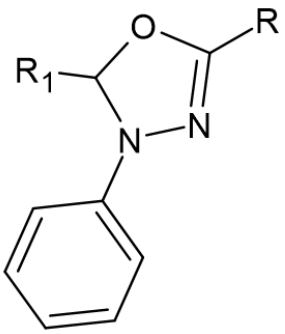
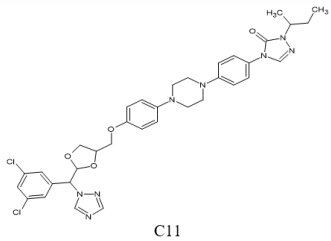


Fig. 1: Designed 2, 5 disubstituted 1,3,4-Oxadiazole derivatives.

Derivatives	R Group	R1 Group
C1		-CH3
C2		-CH3
C3		
C4		
C5		
C6		
C7		
C8		
C9		
C10		

Diagram 1: Derivatives of designed compound



C11

Fig. 2: Structure of standard Itroconazole

3.1. Absorption, distribution, metabolism and excretion (ADME results)

All the designed compounds violate only one rule, so we can say that the molecules are orally active. The results of ADME studies are given in Tables 1 and 2. From the designed compounds follow the rule of 5 having octanol-water partition coefficient (mol log P) not greater than 5 except C4 and C6,[24]

Table 1: Druglikeness analysis of designed 2, 5 disubstituted 1,3,4-Oxadiazole derivatives

Compounds	Molecular Weight	CMC Rule Violation	Lipinski's rule violation	Mol Log P	H-bond donor	H-bond acceptor	No. of Rotatable bonds	TPSA(Å2)
C1	238.28	0	0	3.48	0	2	2	24.83
C2	272.73	0	0	3.99	0	2	2	24.83
C3	300.35	0	1	4.71	0	2	3	24.83
C4	334.8	1	1	5.6	0	2	3	24.83
C5	326.39	1	1	4.81	0	2	4	24.83
C6	360.84	1	1	5.7	0	2	4	24.83
C7	316.35	0	0	4.13	1	3	3	45.06
C9	350.8	0	1	4.62	1	3	3	45.06
C9	344.36	0	1	4.26	1	4	4	62.13
C10	378.81	0	1	4.74	1	4	4	62.13

Table 2: In silico ADME properties of 2, 5 disubstituted 1,3,4-Oxadiazole designed derivatives.

Comp	Absorption		Distribution			Metabolism			
	Caco2	Intestinal absorpation (%absorbed)	BBB Perm.(log BB)	BBB permeant	PPB (%)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6
C1	55.5244	High	1.76127	Yes	92.73	Yes	Yes	Yes	No
C2	55.2623	High	0.61500	Yes	89.51	Yes	Yes	Yes	No
C3	55.5777	High	1.77748	Yes	97.69	Yes	Yes	Yes	No
C4	56.4348	High	1.18389	Yes	98.44	Yes	Yes	Yes	No
C5	54.1999	High	1.58087	Yes	100	Yes	Yes	Yes	No
C6	56.931	High	1.68276	Yes	97.38	Yes	Yes	Yes	No
C7	51.4554	High	1.59199	Yes	92.78	Yes	Yes	Yes	Yes
C8	39.2712	High	2.64081	Yes	100	Yes	Yes	Yes	No
C9	23.5578	High	4.54256	Yes	92.84	No	Yes	Yes	No
C10	25.4542	High	0.601595	Yes	100	No	Yes	Yes	No

Table 3: Docking study of the designed2, 5 disubstituted 1,3,4-Oxadiazole derivatives.

Comp.	Binding Affinity (kcal/mol)	Binding Constant (Ki) (nM)	Interacting Amino Acid Hydrophobic Interaction	Distance	Hydrogen Bonds	Distance
C1	13.1657	-8.9	LEU467	3.63765	-	-
			PHE53	4.82166		
			PHE216	5.22713		
			ALA54	4.87982		
			PRO57	5.25823		
			PRO213	4.95128		
C2	13.7172	-8.8	LEU467	3.61086	-	-
			PHE53	4.8416		
			PHE216	5.46117		
			TYR107	4.41613		
			PHE109	4.74541		
			ALA54	4.86547		
			PRO57	5.29111		
			PRO213	4.93923		
C3	10.3517	-8.9	TYR107	3.80725		
			ILE361	4.54583		
			ALA293	4.11265	-	-
C4	10.9145	-8.8	TYR107	3.80553	TYR120	2.73813
			ILE361	3.99089		
			PHE94	5.44064		
			ILE361	4.76548		
			MET110	5.13972		
			ALA293	4.24122		
			LEU358	5.46755		
C5	15.7589	-8.4	MET362	3.81233	-	-
			LEU467	3.97853		
			TYR107	4.01724		
			PHE216	5.07628		
			ALA293	4.66649		
			LEU358	5.02032		
C6	16.3187	-9.5	LEU467	3.66563	-	-
			TYR107	4.02047		
			UNL1	3.82428		
			PHE216	5.16666		
			PHE216 :CL	4.69912		

Continued on next page

Table 3 continued

			ALA293	4.54972		
			LEU358	5.00921		
C7	8.1309	-8.5	TYR107	3.91713	-	-
			ALA293	4.2378		
			ILE361	4.4369		
C8	8.6638	-8.7	TYR107	3.82282	TYR120	2.78335
			ILE361	3.99909		
			PHE94	5.42586		
			ALA293	4.25718		
			LEU358	5.40895		
C9	27.1817	-8.9	TYR107	4.27086	TYR107	2.57296
			ALA293	4.99474	HIS428	1.97642
			ILE361	4.03364		
C10	27.9346	-9.3	LEU358	3.68783		
			LEU467	3.55247	-	-
			TYR107	4.63635		
			PHE216	5.24933		
			PRO213	4.94516		
			PHE216	5.07169		
			MET110	5.34765		
			LEU358	4.98145		
			LEU467	5.22268		
			ILE361	5.43969		
C11	87.7771	-10.5	ALA54	3.94	ARG363	2.98
						2.69
						3.28
						2.82
						3.15
			ALA293	3.76	TYR107	2.96
						3.36

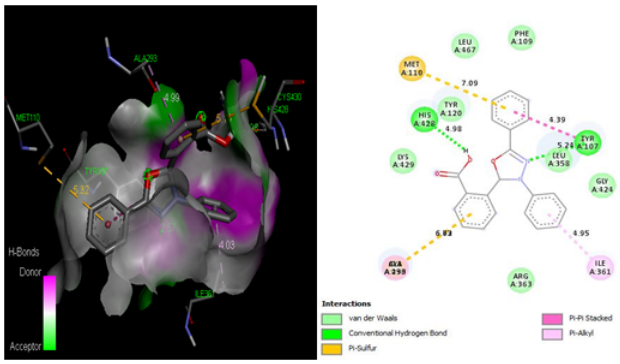


Fig. 3: Binding interaction of C9 with 6AYCprotein.

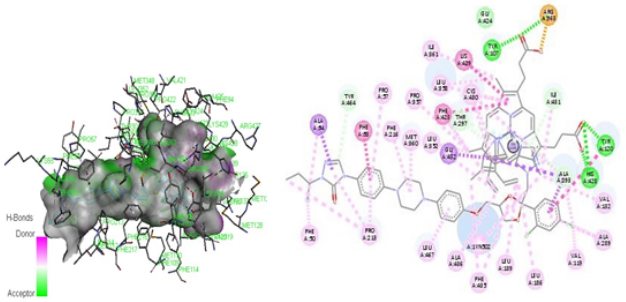


Fig. 4: Binding interaction of C11(Standard) with 6AYC protein.

it is predicted that the molecules have good oral bioavailability. (Table 1) The water solubility is given as the logarithm of molar concentration. The water solubility of designed compounds is typically in the range of -5.00 to -6.00. (Table 1) Because of the presence of lipophilic functionalities aimed at improving cell permeability, the designed compounds are moderately water-soluble. The percent absorption of the compounds was calculated since the absorption of an orally administered medication occurs mostly through the small intestine. Because Caco2 cells from human colon cancer resemble intestinal epithelial cells, their permeability can predict drug intake. The compound having high permeability should have Papp > 8 x10-6 246 cm/s. Interestingly, all the designed compounds show high Caco-2 permeability. Also, all the compounds showed high intestinal absorption. (Table 2)

The distribution of the drug in the body was predicted using a volume of distribution (VDss), blood-brain barrier permeability, and fraction unbound. Higher value VDss implies better drug distribution in the tissues than in plasma, and Log VDss> 0.45 suggests more tissue distribution. All the compounds show the moderate distribution in tissues. The percent bound efficacy of medicine suggests that it is less bound to blood proteins and hence more free to distribute. The plasma protein binding model predicts whether a substance will bind strongly to blood carrier proteins. The percent PPB of the designed compound ranges from 92 to 100%. As a result of the designed compound, there's a high probability of these compounds can reach the desired targets. SwissADME and preADMET tools were used to calculate the permeability of the blood-brain barrier (BBB). All the designed compounds interact with cytochromes either as substrates or as inhibitors. The compounds are likely to have hepatotoxicity hence further study is necessary to determine the hepatotoxic dose level. All the designed compounds have good ADME and toxicity properties and can be considered as the probable lead candidate.

3.2. Molecular docking results

Molecular docking is a method for predicting the major binding mode of a ligand with a target protein of known 3D structure, which is an important tool in structure-based computer-assisted drug design.[25] The designed 2, 5 disubstituted 1,3,4-Oxadiazole derivatives are docked well into the active site of the target protein (PDB ID: 6AYC) using autodock software. The designed compound C4, C8, C9 shows appropriate binding to the target protein by hydrogen bond and hydrophobic interaction whereas C1, C2, C3, C5, C6, C7, C10 shows hydrophobic bonding. Among this, C3, C7, C8, and C9 shows other interaction. The interactions established by the active compounds were within the 5 Å radius to the binding site of CYP51 protein. Almost all the compounds were active and C9 is the most active compound with minimum binding affinity are selected as potent inhibitors. Hydrophobic interaction of C9 with TYR, ILE and ALA are distinguished. There is also the formation of the hydrogen bonds between molecules TYR and HIS are fully recognized as indicated which have observed Tables 2 and 3. Docking studies revealed that the binding mode of the most active compounds with designed compound and target protein.

4. Conclusion

The 2, 5 disubstituted 1,3,4-Oxadiazole derivatives were designed and it's *in silico* parameter was studied. According to ADME studies all the designed compounds can be considered as lead molecules. Among the derivatives, C9 show the most potent inhibitor according to a molecular docking study. They interact with TYR, ILE and ALA to form hydrophobic interaction and with TYR and HIS form hydrogen bonding. The ADME study of these compounds reveals that they are suitable for drug-likeness. These derivatives have good PPB and intestinal absorption properties. Overall, the studies reveal that C9 compounds show potent inhibitors against CYP51 as an antimicrobial agent.

5. Source of Funding

None.

6. Conflict of Interest

None.

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