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In silico investigation and molecular docking study of 1,2,4-triazole derivatives for antifungal activity

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Abstract

The development of novel antifungal agents is therefore urgently needed. Many fungicidal treatments have become ineffective due to development of resistance, a range of undesirable effects, and excess toxicity. Hence, the need to synthesize and develop some sort of new antifungal drugs. 1,2,4-triazole is one of the most important pharmacophore systems of five-membered heterocycles. The nitro-containing heterocycle demonstrated a potential antifungal activity in its structure-activity relationship (SAR).

A wide variety of classes of antifungal agents contain the 1,2,4-triazole core as part of their nucleus. Due to their strongest and broad spectrum activity, triazoles are clinically important moieties. The purpose of this article is to review the advances in the synthesis and SAR of 1,2,4-triazole as a potential fungicide.

Keywords: 1;2;4-triazoles; Antifungal; Synthesis; 1Q6S Receptor; Ethanol; Pharmacology; Fungal

1. Introduction

Heterocyclic organic chemistry is one of the most important subgroups of organic and medicinal chemistry [1–4]. Azoles are nitrogen-containing heterocyclic compounds with five members [5, 6]. Nitrogen is the key component that controls biological activity of heterocycles. Recently, azole compounds have received international attention [2, 7]. The most stable compounds between the azoles + heterocyclic compounds are 1,2,4-triazole derivatives with the molecular formula C2H3N3[8].

1,2,4-triazoles showed many biological effects, such as Antimalarial [9], Antiurease [10], Antiviral [11], Anticonvulsant [12], Antioxidant [13], Antifungal [14]. Various Triazole scaffolds which are also being exploited in cyproconazole, triadimefon, metconazole, tebuconazole, propiconazole, epoxiconazole and prothioconazole plant medicines exhibits antifungal activity [15]. Invasive fungal infections globally result in an estimated 1.7 million deaths per year [16], [17], [18], making it an important public health problem. The discovery of novel 1,2,4-triazoles with low toxicity is crucial globally since the emergence of synthetic drug resistance to different fungal infections is one of the most important problems [17]. A key enzyme in the manufacture of ergosterol in fungi, lanosterol 14α-demethylase (CYP51), is a cytochrome P450-dependent enzyme that is inhibited by this class of bioactive chemicals[18]. Azoles inhibit the fungal ergosterol biosynthesis by binding to iron in porphyrins, which cause the accumulation of 14-demethylated sterols[19]. Nowadays, the new 1,2,4-triazole compounds were synthesized and evaluated for fungicidal activity, and some of them seemed to be influenced against certain fungi. Two years ago, a recent review about the importance of 1,2,4-triazoles as powerful antifungal and antibacterial agents was published, where it was stated that there were several reports and patents published on this topic in the last few years [20–31]. As a potential new target for rational design of antifungal activity 1,2,4-triazole derivatives the enzyme Protein Tyrosine phosphatase, non-receptor

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type-1 have been suggested. While the bioanalytical and biochemically related aspects of process pharmacology are central to the field, chemists must work collaboratively with scientists from other disciplines.

The process of developing novel medications is intricate. It requires skills of the individuals who works in a variety of disciplines, including pharmacology, pharmacy, molecular biology, physiology, biochemistry, and chemistry. Drug characteristics including physiochemical characteristics, size, shape, and rational movement can all be correctly detected by molecular modeling software. Consequently, chemists have a strategic position at the intersection of biology and chemistry [32-34].

1.1. Experimental

1.1.1. General Method for Synthesis Of Ester

For four hours, 0.3 moles of acid, 0.3 moles of 100% ethanol, and 0.15 milliliters of concentrated sulfuric acid were refluxed.

1.1.2. General Method for synthesis of POTASSIUM SALT OF DITHIOCARBAZINATE (II)

75 milliliters of ethanol were used to dissolve 0.01 moles of potassium hydroxide. After stirring and cooling in ice, 0.01 mole of acid hydrazide (II) was added to the above mentioned solution. 10 milliliters were added in a tiny amount to this carbon disulphide. For four to six hours, the reaction mixture was refluxed. The separated potassium dithiocarbazinate was filtered, repeatedly cleaned with ether, and vacuum-dried. A qualitative yield was obtained for the dithiocarbazinates. Since the majority of potassium salts of dithiocarbazinates were sensitive to moisture, they were used straight away to prepare aminomercaptothiazoles without additional purification.

1.1.3. General Method for synthesis of ACID HYDRAZIDE (V)

50 milliliters of 95% ethanol were used to reflux a mixture of 0.01 moles of ester and 0.2 moles (10 milliliters) of hydrazine hydrate for two hours. The final combination was chilled, condensed, and then poured over crushed ice pieces. The resulted solid mass was then filtered, dried, refined by recrystallizing it from ethanol.

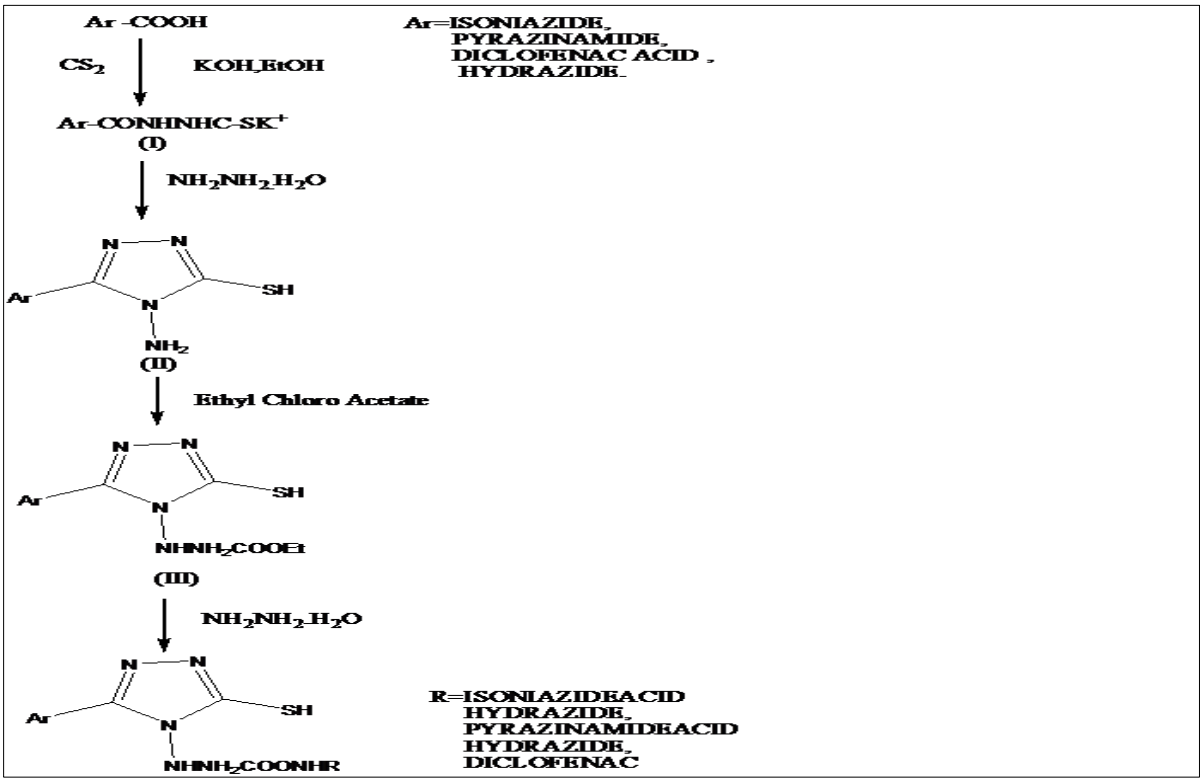


Figure 1 Synthesis Scheme of 1,2,4- triazole derivative

2. Results and discussion

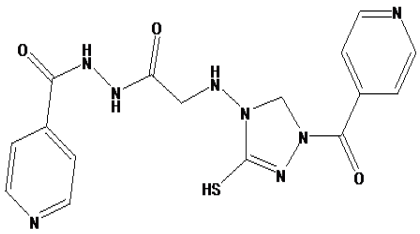
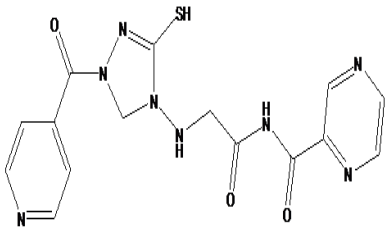
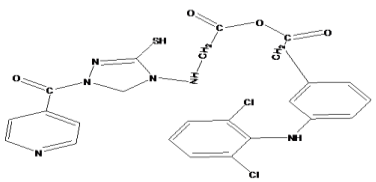
1,2,4-triazole hybrids are becoming increasingly popular in the fields of chemical and medicinal chemistry, thanks to their impressive antifungal properties. These compounds, along with their derivatives, play a essential role in the search for new medications that can deliver a range of biological effects. One of the reasons for their diverse biological activity is their small, stable cyclic ring structure. This structure allows nitrogen atoms to act as both hydrogen bond donors and acceptors at the active site of receptors. What's more, the pentacyclic triazole ring is quite flexible, providing multiple binding sites that enable the development of various derivatives. Given its versatility, this strong scaffold is poised to be a key player in future drug development. In the coming years, one of the coolest tools in medicinal chemistry is going to be the various methods for making 1,2,4-triazole scaffolds in a selective way. Based on Lipinski's "five rules," if we want oral meds to do their thing, they need to have (a) a molecular weight of less than 500 Daltons, (b) be moderately lipophilic (you know, logP ≤ 5), (c) include around five hydrogen bond donors, and (d) have no more than ten hydrogen bond acceptors. But it's not just the stuff in Lipinski's list; other factors have also been tossed in as filters for figuring out oral and liquid absorption.

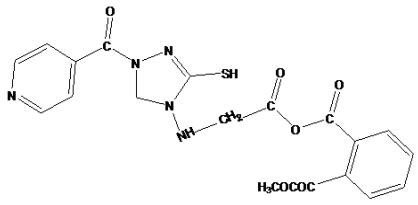
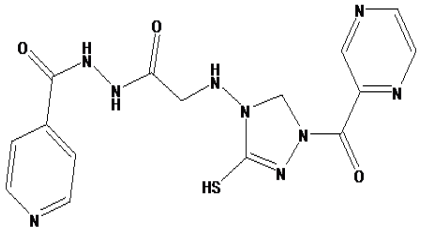
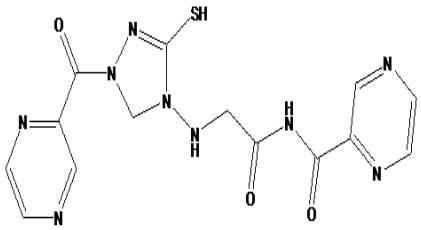
In Table No. 1 the targeted compounds with IUPAC name are shown. Results are presented in Table No. 2 shows the exception of the parameters. In this study, we checked out lipophilicity, melting point, molecular weight, and toxic hazards all in one go. This info can really help us get a good sense of how a drug performs overall.

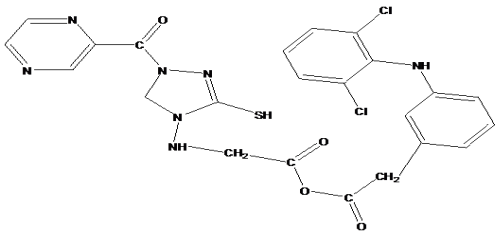
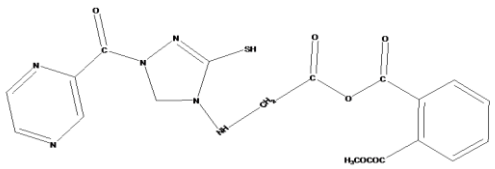
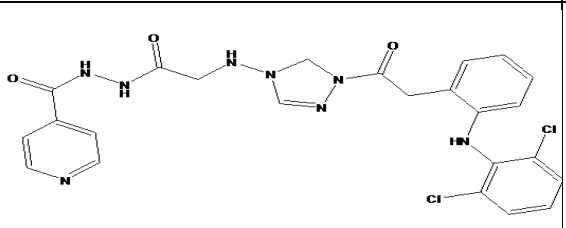
2.1. A stronger binding affinity is indicated by a more negative docking score.

So, about the docking study I mentioned earlier, we're looking at how these proposed chemicals interact with the enzyme Protein-tyrosine phosphatase non-receptor type-1 (check out figures 2-4 for that). We used the 1 Click Docking software to compare the documents. The enzyme we found is listed in Table No. 2, and it shows a negative amount of free energy, which is pretty interesting. It’s worth noting that the compounds like A3, C1, C2, and C4 have a much better fit for the binding ligand. Compounds such as A3, B3, C1, C2 and C4 shows great antifungal activity. Among them, C2 compound shows the high intimacy with the native ligand and exerts great antifungal activity.

Table 1 Name Of the Compounds

Comp. Name	Structure	IUPAC Name	Mol. Formula
A1		N'-(2-(1-isonicotinoyl-3-mercapto-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)isonicotinohydrazide	C16H16N8O3S
A2		N-(2-(1-isonicotinoyl-3-mercapto-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)pyrazine-2-carboxamide	C15H14N8O3S
A3		2-(3-(2,6-dichlorophenylamino)phenyl)acetic2-(1-isonicotinoyl-3-mercapto-1H-1,2,4-triazol-4(5H)-ylamino)acetic anhydride	C24H20Cl2N6O4S

A4		2-(1-isonicotinoyl-3-mercapto-1H-1,2,4-triazol-4(5H)-ylamino)acetic 2-(2-oxopropanoyl)benzoic anhydride	C20H17N5O6S
B1		N'-(2-(3-mercapto-1-(pyrazine-2-carbonyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)isonicotinohydrazide	C15H15N9O3S
B2		N-(2-(3-mercapto-1-(pyrazine-2-carbonyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)pyrazine-2-carboxamide	C14H13N9O3S

Comp. Name	**Structure**	**IUPAC Name**	**Mol. Formula**
B3		2-(3-(2,6-dichlorophenylamino)phenyl)acetic 2-(3-mercapto-1-(pyrazine-2-carbonyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetic anhydride	C23H19Cl2N7O4S
B4		2-(3-mercapto-1-(pyrazine-2-carbonyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetic 2-(2-oxopropanoyl)benzoic anhydride	C19H16N6O6S
C1		N'-(2-(1-(2-(2-(2,6-dichlorophenylamino)phenyl)acetyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)isonicotinohydrazide	C24H22Cl2N8O3

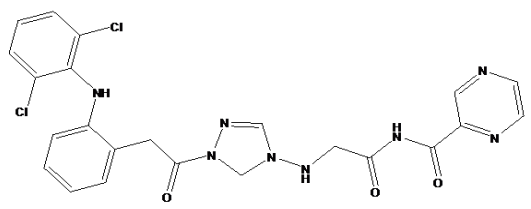
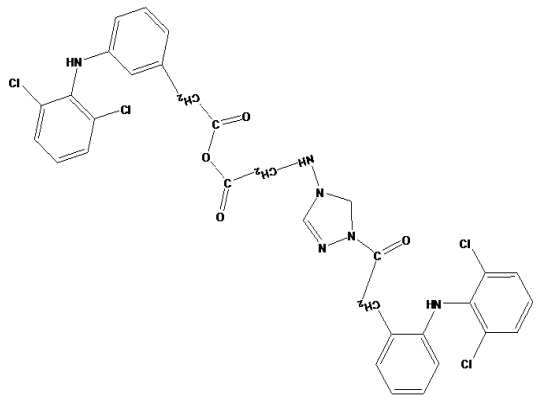
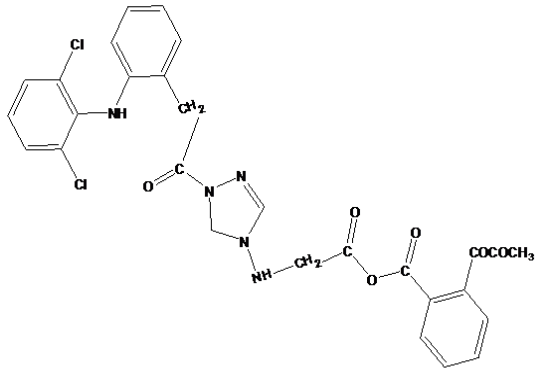
C2		N-(2-(1-(2-(2-(2,6-dichlorophenylamino)phenyl)acetyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)pyrazine-2-carboxamide	C23H10Cl2N8O3
C3		2-(3-(2,6-dichlorophenylamino)phenyl)acetic 2-(1-(2-(2-(2,6-dichlorophenylamino)phenyl)acetyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetic anhydride	C32H26Cl4N6O4
C4		2-(1-(2-(2-(2,6-dichlorophenylamino)phenyl)acetyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetic 2-(2-oxopropanoyl)benzoic anhydride	C32H26C4N6O4

Table 2 Drug Likeness Properties of the Target Compounds Predicted by Swiss ADME and 1 Click Docking Score of the Compounds

CO.	MW	HBA	HBD	Log P	Docking Score (1Q6S)		
	<500	<10	<5	<5	1	2	3
A1	400.42	7	3	1.98	-8.1	-7.6	-7.5
A2	386.39	8	2	0.71	-8.2	-7.9	-7.9
A3	559.42	7	2	2.46	-9.3	-8.0	-8.0
A4	471.44	10	1	2.48	-7.9	-7.8	-7.5
B1	401.4	8	3	1.14	-7.9	-7.8	-7.5
B2	387.38	9	2	-0.01	-8.0	-7.2	-7.1
B3	560.41	8	2	3.09	-9.1	-8.7	-8.7
B4	471.44	11	1	1.72	-8.1	-7.5	-7.5

C1	541.39	6	4	2.64	-9.4	-9.0	-8.5
C2	527.36	7	3	1.88	-9.8	-8.5	-7.6
C3	700.4	6	3	3.9	-8.7	-6.9	-6.8
C4	612.42	9	2	3.51	-9.2	-8.6	-8.6

Table 3 Analytical Data of the Synthesized Compounds

Comp.	**Mol. Formula**	**Mol. Wt**	**M.P**	**% Yield**	**Elemental analysis/ calcd (found)**		
					C%	**H%**	**N%**
A1	C16H16H8O3S	400.42	108	78	47.99 (48)	4.03 (4.06)	27.98 (27.96)
A2	C15H14N8O3S	386.39	110	92	46.63 (46.60)	3.65(3.67)	29.00(29.04)
A3	C24H20Cl2N6O4S	559.42	118	68	51.53	3.60	15.02
A4	$C_{20}H_{17}N_5O_6S$	471.44	102	69	52.74	3.76	15.38
B1	$C_{15}H_{15}N_9O_3S$	401.4	109	62	44.88(44.90)	3.77 (3.81)	31.40 (31.38)
B2	$C_{14}H_{13}N_9O_3S$	387.38	103	92	43.41	3.38	32.54
B3	$C_{23}H_{19}Cl_2N_7O_4S$	560.41	112	68	49.29	3.42	17.50
B4	$C_{19}H_{16}N_6O_6S$	471.44	122	80	50.00(50.01)	3.53 (3.50)	18.41 (18.38)
C1	$C_{24}H_{22}Cl_2N_8O_3$	541.39	120	70	53.24	4.10	20.70
C2	$C_{23}H_{10}Cl_2N_8O_3$	527.36	115	72	52.38 (52.35)	3.82 (3.85)	21.25(21.23)
C3	$C_{32}H_{26}Cl_4N_6O_4$	700.4	108	59	54.87	3.74	12.00
C4	$C_{32}H_{26}C_4N_6O_4$	612.42	104	68	54.87 (54.89)	3.74 (3.72)	12.00(12.03)

Table 4 Thin Layer Chromatographic Data of Synthesized Compounds

Compound	Solvent system and proportion of solvent	Rf Value
A1	Ethyl acetate : Hexane (1:3)	0.56
A2	Ethyl acetate : Hexane (1:3)	0.65
A3	Ethyl acetate : Hexane (1:3)	0.56
A4	Ethyl acetate : Hexane (1:3)	0.52
B1	Ethyl acetate : Hexane (1:3)	0.66
B2	Ethyl acetate : Hexane (1:3)	0.54
B3	Ethyl acetate : Hexane (1:3)	0.63
B4	Ethyl acetate : Hexane (1:3)	0.66
C1	Ethyl acetate : Hexane (1:3)	065
C2	Ethyl acetate : Hexane (1:3)	0.55
C3	Ethyl acetate : Hexane (1:3)	0.60
C4	Ethyl acetate : Hexane (1:3)	0.54

Table 5 Receptor Ligand Interaction Structures generated by 1 Click Docking

2D structures of the Targeted Compounds	3D Sructure of the Targeted Compounds

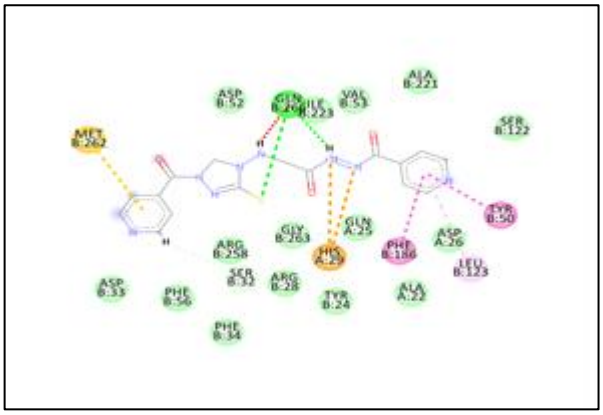
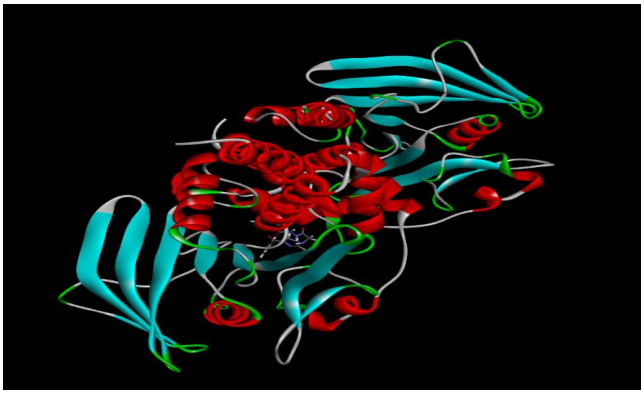

	

Figure 2 A1-1Q6S Receptor-Ligand 2D Diagram	**Figure 2A: A1-1Q6S Receptor-Ligand Interaction**

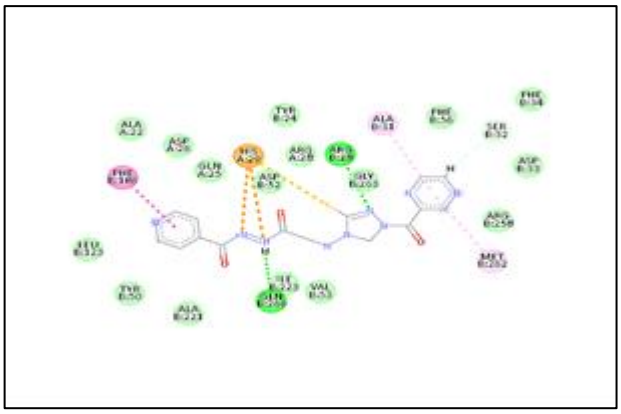
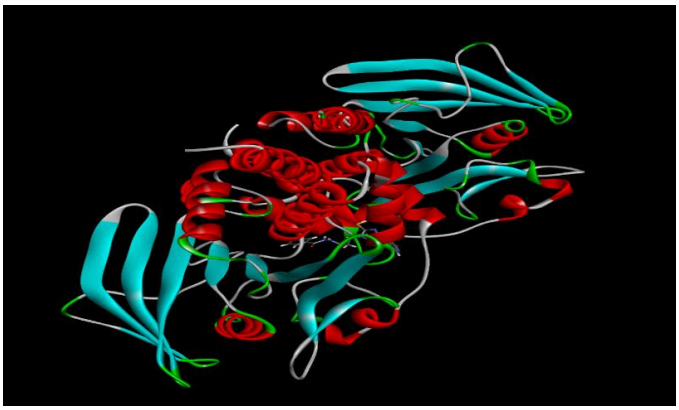

	

Figure 3 B1- 1Q6S Receptor-Ligand 2D Diagram	**Figure** 3A: B1-1Q6S Receptor-Ligand Interaction

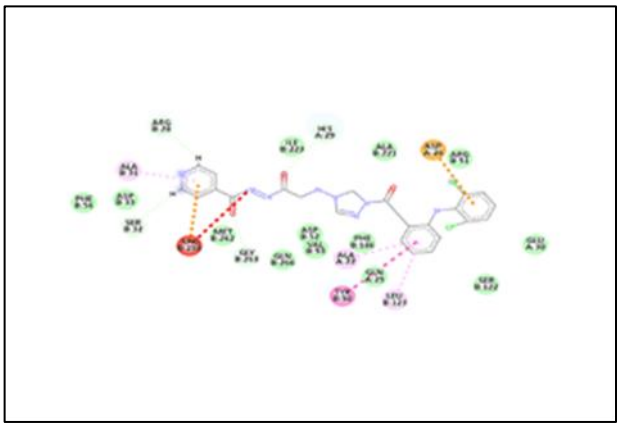
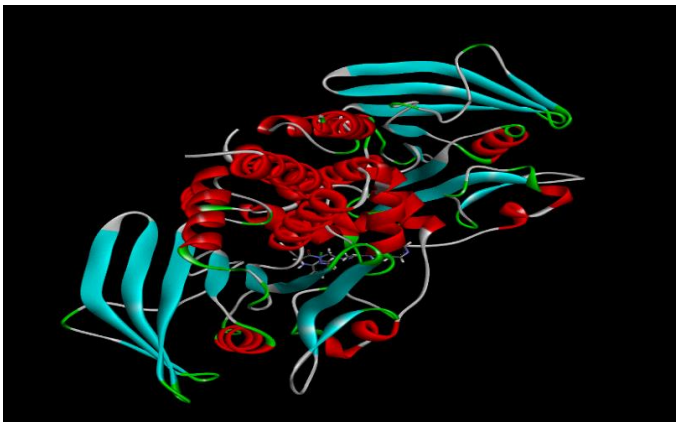

	

Figure 4 C1- 1Q6S Receptor-Ligand 2D Diagram	**Figure 4A:** C1- 1Q6S Receptor-Ligand Interaction

3. Conclusion

Researchers have been exploring both traditional and innovative methods for creating derivatives of 1,2,4-triazoles. Recent docking studies have emphasized N-(2-(1-(2-(2-(2,6-dichlorophenylamino)phenyl)acetyl)-1H-1,2,4-triazol-4(5H)-ylamino)acetyl)pyrazine-2-carboxamide [C2], a promising derivative of 1,2,4-triazole, as a potential antifungal agent. It's clear that with the right modifications, these compounds could show even better antifungal properties in the

future. The encouraging antifungal potential seen in these compounds is certainly worth considering for drug development and discovery. Plus, the more negative docking scores of these derivatives suggest they might be effective against various fungal infections.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

Regarding the manuscript, there are no disclosures or conflicts of interest.

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