Research Article

Docking Studies Of Some *E*-2-Phenyl-4-(2-Phenylhydrazineylidene)Oxazol-5(4H)-One Derivatives As A Potential Caspase-8 Inhibitor

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Abstract
Hydrazone and Oxazlone are important groups and have various biological activities such as antifungal, antibacterial, anti-inflammatory, antimalarial, anticonvulsant, analgesic, antiplatelets, antituberculosis, anticancer activities anti-diabetic, and other uses. So we decided to gather the two groups to form *E*-2-Phenyl-4-(2-Phenylhydrazineylidene) Oxazol-5(4*H*)-One derivatives followed by docking study their inhibitory against caspase-8 using MOE version 2014.09 software. The results of docking study would be a representative of their apoptotic inhibition activity. Compounds **4**, **8** and **21** showed the best binding to the catalytic site Cys360 and other amino acids when measured at the lowest S_score, that encourage further study as potential caspase-8 inhibitory agents.
Keywords: Hydrazone and Oxazlone, biological activities, *E*-2-Phenyl-4-(2-Phenylhydrazineylidene

Introduction
Hydrazones are a special group of compounds in the Schiff base family characterized by the presence of CH=N-N=C[1]. In recent years, a number of hydrazone compounds have been synthesized and investigated for their biological properties such a antifungal[2], antibac-terial[3], anti-inflammatory[4], antimalarial[5], anticonvulsant[6], analgesic[7], antiplatelets[8], antituberculosis[9], and anticancer activities[10].

Oxazoloneis a chemical compound with the molecular formula $C_3H_3NO_2$. It was named in-line with the Hantzsch–Widman nomenclature and is part of a large family of oxazole based compounds (fig.1).

They are present in many biologically active natural products and are valuable synthetic precursors and pharmaceuticals. They are reported to possess anti-diabetic[11], anti-microbial[12], and other uses.

Here, we fused the two important groups to obtain (*E*)-2-phenyl-4-(2-phenylhydrazineylidene) oxazol-5(4*H*)-one derivatives (**Fig. 1**) with *Para* R substitution, which are chosen according to their electronic effect, and study their effectiveness on caspase-8 as inhibitors by using docking studies.

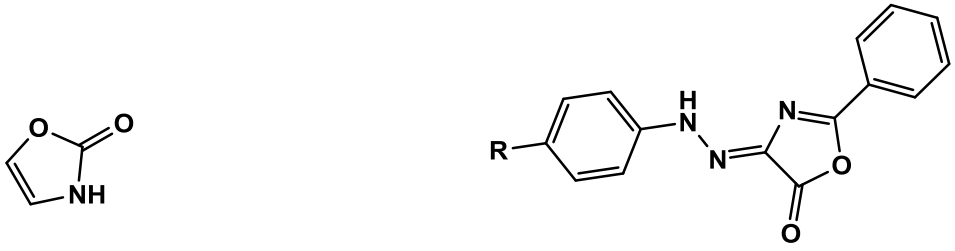

Fig. 1. The structures of oxazolone and *E*-2-phenyl-4-(2-phenylhydrazineylidene)oxazol-5(4*H*)-one derivatives

Docking study

Using Molecular Operating Environment (MOE®) version 2014.09; molecular docking study was carried outusing caspase-8, PDB: 2C2Z from Protein Data Bank.

Table 1 : The results are obtained as shown in

No.	Substitution (R)	S_score	Receptor amino acid	Bond	Distance A	Binding Energy (Kcal/mol)
1	$N(CH_3)_2$	-4.5117	No interactions	----	----	----
2	NH_2	-4.4897	No interactions	----	----	----
3	OH	-4.4963	Lys253	H- acceptor	3.65	-0.7
4	**OCH_3**	-4.4393	Cys360	H- donor	3.53	-1.3
			Ile257	Pi- H	3.93	-0.7
5	$NHCOCH_3$	-4.5457	Arg258	H- acceptor	3.26	-0.9
6	$OCOCH_3$	-4.4689	No interactions	----	----	----
7	CH_3	-4.5328	No interactions	----	----	----
8	Phenyl	-5.3601	Cys360	H- donor	3.47	-1.1
			Ile257	Pi- H	3.94	-0.7
			Arg270	Pi-cation	4.68	-1.1
9	F	-4.3737	No interactions	----	----	----
10	Cl	-4.4914	No interactions	----	----	----
11	Br	-4.2269	Ile257	Pi- H	4.46	-0.7
12	I	-4.4720	No interactions	----	----	----
13	CHO	-4.6304	His317	H- Pi	4.35	-0.7
			Arg260	Pi- H	4.08	-0.6
14	$COCH_3$	-4.4856	Arg258	H- acceptor	3.28	-1.0
			Ile257	Pi- H	4.42	-0.7
15	$COOCH_3$	-4.6998	His317	H- Pi	4.33	-0.8
			Arg260	Pi- H	4.12	-0.6
16	$COOC_2H_5$	-5.3026	Gly318	H- donor	2.94	-4.7
17	COOH	-4.6171	Gly318	H- donor	2.93	-3.3
			Lys253	H- acceptor	3.83	-1.0
18	CF_3	-4.6060	No Interactions			
19	CN	-4.3261	Lys253	H- acceptor	3.46	-1.4
20	SO_3H	-4.8536	Asp319	H-donor	2.87	-10.7
			Lys253	H- acceptor	2.97	-6.1
21	SO_2NH_2	-4.5515	Cys360	H- donor	3.63	-3.9
			Asn261	H- acceptor	3.30	-0.8
			Arg260	H- acceptor	3.29	-1.5
			Arg260	H- acceptor	2.97	-4.4
			Gln358	H- acceptor	3.20	-2.2
			Arg258	Pi- H	4.47	-0.8
22	NO_2	-4.4546	His317	H- Pi	4.45	-0.6

Table 1: shows the docking results

We chose the results of docking according to the lowest docking score (s_score). The data in the table shows that compound (4),(8),(21) have inhibitory activity toward caspase-8, as they have hydrogen bond interaction with Cys360 beside other

interaction, as any ligand can bind to Cys, can act as a caspase inhibitor[13]. As shown in below.

1- Docking of (E)-4-(2-(4-methoxyphenyl)hydrazineylidene)-2-phenyloxazol-5(4H)-one (4).

There is a binding interaction between 2 enzyme amino acids and compound in case of the lowest S_score = -4.4393as following: hydrogen bond donor with the catalytic amino acid CYS360 with E binding = -1.3 Kcal/mol in adistance = 3.53^{o} A and Pi bond with ILE257 with binding energy = -0.7 Kcal/mol in a distance = 3.93 as showing in **Fig. 2**

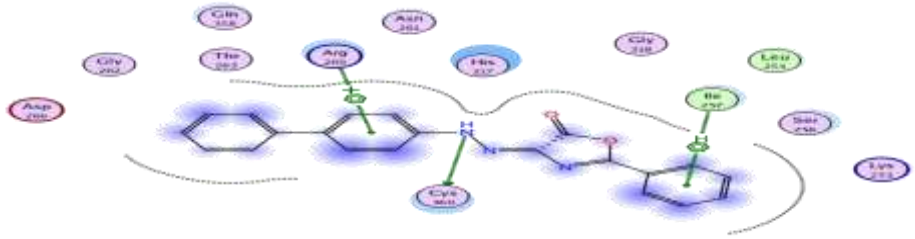

Fig. 2: 2D of compound 4 in 2C2Z

2- Docking of (Z)-4-(2-([1,1'-biphenyl]-4-yl)hydrazineylidene)-2-phenyloxazol-5(4H)-one(8)

There is a binding interaction between 3 enzyme amino acids and compound in case of the lowest S_score = -5.3601 as following : hydrogen bond donor with the catalytic amino acid Cys360 with E binding = -1.1 Kcal/mol in a distance = 3.47^{o} A, Pi-H bond with ILE257 with binding energy = -0.7 Kcal/mol in a distance = 3.94^{o} A and Pi-cation bond with Arg270 with E binding = -1.1 in a distance = 4.68^{o} A as showing in **Fig. 3**

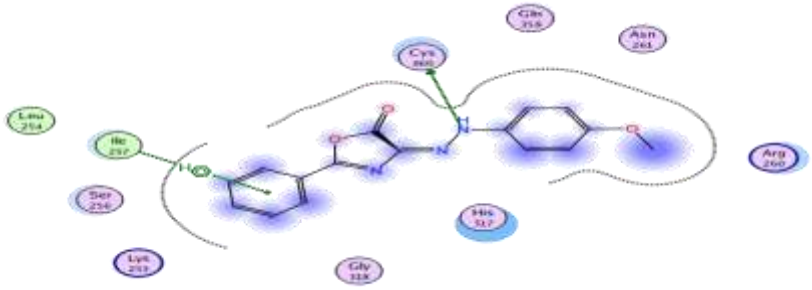

Fig. 3 : 2D of compound 8 in 2C2Z

3- Docking of (Z)-4-(2-(5-oxo-2-phenyloxazol-4(5H)ylidene) hydrazineyl) benzenesulfonamide (21).

There is a binding interaction between 5 enzyme amino acids and compound in case of the lowest S_score = -4.5515 as following : hydrogen bond donor with the catalytic amino acid Cys360 with E binding = -3.9 Kcal/mol in a distance = 3.63^{o} A, two hydrogen bond acceptor with Arg260 with binding energy = -1.5, -4.4 Kcal/mol in a distance = 3.29, 2.97^{o}, respectively, hydrogen bond acceptor with Gln358 with E binding = - 2.2 in a distance 3.20^{o}
A, Pi- H bond with Arg258 with E binding -0.8 in a distance 4.47^{o} A and hydrogen bond acceptor with Asn261 with E binding = -0.8 in a distance = 3.30 as showing in **Fig. 4**

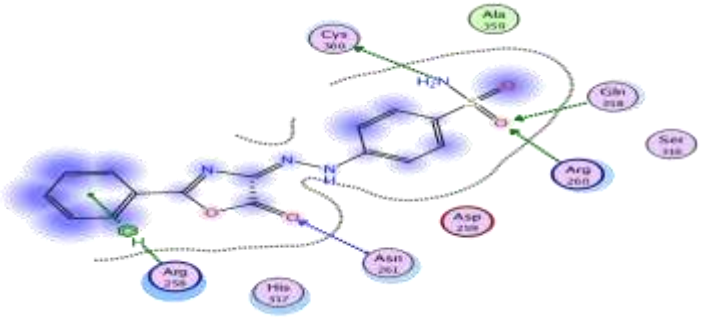

Fig. 4 : 2D of compound 21 in 2C2Z

Conclusion

The docking studies results indicated that some compounds have a good binding for caspase-8, which can obviously explain the enzyme inhibitory effect. The type of substitution in the *p*-substitution of aniline ring affect the binding affinity and the order of better substitution *p*-sulfamoyl group > *p*-phenyl group > *p*-methoxy group.

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