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Extra Precision Docking and ADME Simulation Studies on Novel Analogues of Pyrazoles as Anticancer Leads

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Research Article

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Abstract

In the present study, a novel series of 15 pyrazole derivatives bearing oxime and chalcone hybrids were designed. Molecular docking studies were carried out on the designed analogues. The molecular docking studies revealed that the compound CF-4 and CF-8 possessed comparable docking scores with that of the crystal ligand.

Key words: ADME, Anticancer, GLIDE, Lung cancer, Oxime, Pyrazole, QIKPROP

Introduction

Cancer, also known as malignant neoplasm, is a group of diseases characterized by unregulated cell growth. In cancer, cells split and proliferate exponentially resulting in the formation of malignant tumours. It could escalate to more distant parts of the body through the lymphatic system or bloodstream. Further, it originates from a single abnormal cell having an altered DNA sequence caused by mutation and uncontrolled proliferation of these cells occur which leads to clinically significant stages. There are more than 200 different known cancers clinically reported till date [1].

In the past few decades, several hallmarks of cancer have been identified. According to a previous review, the hallmarks of cancer" consist of six biological capabilities which encompass sustaining proliferation, evading apoptosis, resistance to natural cell death mechanisms, attaining replicative immortality, promotion of angiogenesis and capacity of invasion and metastasis [2].

There is a concern regarding the major public health in the world owing to the emergence of cancer due to ecological imbalance set. In the past few decades, much of the attention has drawn towards heterocyclic agents for their cytotoxic activity. Out of many number of heterocyclic systems, the pyrazole and its derivatives have attracted many researchers owing to its extensive range of biological activities. Thousands of researchers utilize molecular modelling as a tool for designing novel heterocyclic analogues like pyrazoles targeting many cancer targets including protein kinase, tyrosine kinase, and vascular endothelial growth factor (VEGF), BRAF gene, cyclin dependent kinase (CDK) and tumour growth factor (TGF) [3].

They are the important members of heterocyclic family with two neighbouring nitrogens, among which one is basic and the other is neutral in a five-membered ring system. These are aromatic molecules for their requisite planar conjugated ring structures having six delocalized π-electrons. Pyrazoles possess antimicrobial, analgesic, anticancer, anti-tubercular, anti-inflammatory, antidepressant, anticonvulsant, antihyperglycemic, antipyretic, anthelmintic, antioxidant and herbicidal properties [4]. They are

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multifunctional lead compounds that has evolved into therapeutically active agents. Various synthetic pathways are conceded for the evolution of pyrazole restraining reactions to impart novel and potent molecule having extensive opportunity in the area of medicinal chemistry [5]. The pyrazole moiety is present as the core in a variety of leading anticancer drugs such as Ruxolitinib (blood cancer), axitinib (renal cancer), crizotinib (lung cancer) etc. With this background, it was thought to design and to perform computational studies on pyrazole analogues

Experimental Procedures

a. Computational studies

Schrodinger molecular modelling software was used on a Maestro interface to run all the simulation.

b. Molecular Docking studies

Molecular docking was performed using MAESTRO 11.8 software (a graphical user interface of Schrodinger). Various pyrazole derivatives were drawn using chemdraw software and their binding affinity was calculated.

Molecular docking process involves major four critical steps that include, ligand preparation, protein preparation, GRID generation and molecular docking

Ligand preparation was done using the application "lig prep" available in the Schrodinger module. This module performs energy minimization, identifies minimum energy conformer and generates ionization states at a given pH.

The protein preparation wizard is used in the preparation of protein. The Protein Data Bank (PDB) protein structures are not suitable to be used for the docking process due to missing hydrogens and some important amino acid residues. The protein preparation wizard adds hydrogens, missing residues, caps terminals and deletes additional water molecules at the ligand binding site.

In the GRID generation step, a cube of 10x10x10 dimension is created and the interaction of the molecule at each GRID point is calculated and computed.

In the ligand docking process, the energy minimized ligands were docked into the active site of the receptor and their docking scores were computed based on their interactions at the active site.

The docking process was validated by calculating RMSD values by overlapping actual pose with the generated pose and it should have values below 2 angstrom units [7].

Table1: Docking scores of the designed analogues of pyrazole

Ligand	GScore	Dock score	Lipophillic EvdW	Phob En	HBond	Electro	Sitemap	LowMW	Penalties	RotPenal
CF-1	-6.2	-6.2	-3.4	-2.7	0.0	-0.1	-0.3	0.0	1.0	0.2
CF-2	-7.8	-7.8	-4.0	-1.9	-0.9	-0.5	-0.5	-0.3	0.0	0.3
CF-3	-6.4	-6.4	-4.1	-2.7	0.0	-0.3	-0.4	0.0	1.0	0.1
CF-4	-8.8	-8.8	-4.3	-2.5	-1.0	-0.6	-0.5	-0.2	0.0	0.2
CF-5	-7.2	-7.2	-4.5	-1.8	-0.1	-0.3	-0.4	-0.4	0.0	0.3
CF-6	-6.2	-6.2	-3.3	-2.7	0.0	-0.1	-0.3	-0.0	0.0	0.2
CF-6-2	-5.9	-3.6	-3.0	-2.7	0.0	-0.1	-0.3	-0.1	0.0	0.2
CF-8	-8.2	-8.2	-4.2	-1.8	-1.4	-0.2	-0.5	-0.4	0.0	0.3
CF-8-2	-7.4	-5.1	-4.6	-1.8	-0.6	0.1	-0.4	-0.4	0.0	0.3
CF-9	-4.1	-4.1	-3.5	-0.8	-0.4	-0.3	-0.4	0.0	1.0	0.2
CF-10	-7.0	-7.0	-3.1	-2.5	-0.7	-0.4	-0.3	-0.3	0.0	0.3

Ligand	GScore	Dock score	Lipophillic EvdW	Phob En	HBond	Electro	Sitemap	LowMW	Penalties	RotPenal
CF-12	-6.0	-6.0	-3.6	-1.3	-0.7	-0.3	-0.3	0.0	0.0	0.2
CF-13	-7.2	-7.2	-4.1	-2.7	0.0	-0.2	-0.3	0.0	0.0	0.1
CF-14	-6.6	-6.6	-4.4	-2.7	0.0	-0.3	-0.4	0.0	1.0	0.2
CF-15	-4.5	-4.5	-3.2	-1.9	0.0	-0.3	-0.3	0.0	1.0	0.2
4C9W- minimi zed ligand	-9.345	-9.345	-3.9	-0.2	-1.8	-1.9	-0.3	-0.2	0.0	0.2

Results and Discussions

Molecular Docking

The synthesized test molecules that belongsto pyrazole series were docked with target protein (PDB code 4C9W) and their docking score and glide score were estimated.

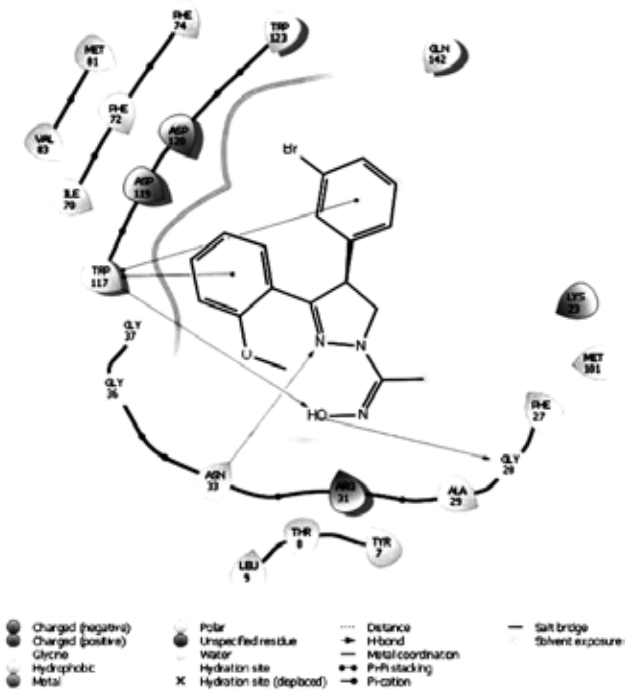


Figure 1: 2D interactions of the compound CF-4 at the active site of 4C9W

Among the series of 15 pyrazole analogs designed, the analogues namely **CF-4**, and **CF-8** were found to have good docking score in comparison to the co-crystallized ligand structure (dock score: -9.345) at the active site. The docking score of **CF-4** is **-8.8,** which consists of -4.3 **Lipophilic EvdW** which pertains to the hydrophobic interactions of receptor with ligand atoms, -2.5 **PhobEn** scored for hydrophobic atoms on the protein that enclose hydrophobic groups on the ligand,-1.0 HBond, -0.5 **Sitemap** and 0.2 **Rotational penalties**. The docking score of **CF-8** is **-8.2** which consists of -4.2 **Lipophilic EvdW** [8] which pertains to the hydrophobic interactions of receptor with ligand atoms, -1.8 **PhobEn** scored for hydrophobic atoms on the protein that enclose hydrophobic groups on the ligand,-1.4 **HBond**, -0.5**Sitemap** and 0.3 rotational penalties as shown in Table 1.

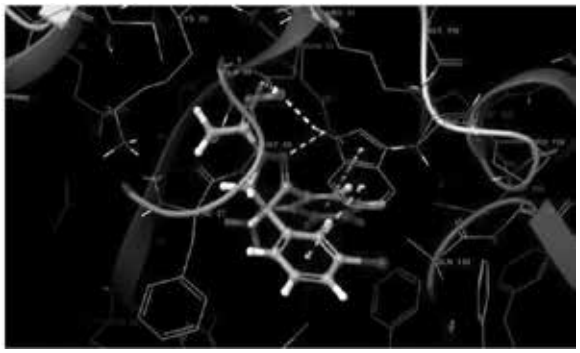


Figure 2: 3D interactions of the compound CF-4 at the active site of 4C9W

These interactions are depicted in Fig 1, Fig 2, Fig 3 and Fig 4. Table 2 shows the important interaction of the compounds at the active site. Out of the 15 compounds designed, the compounds namely CF-4 and CF-8 exhibited comparable docking scores with that of the crystal ligand. The initial design strategy to incorporate oxime functional group was found to be successful. Both CF-4 and CF-8 contains oxime functional groups and have the potential to be developed as lead compounds.

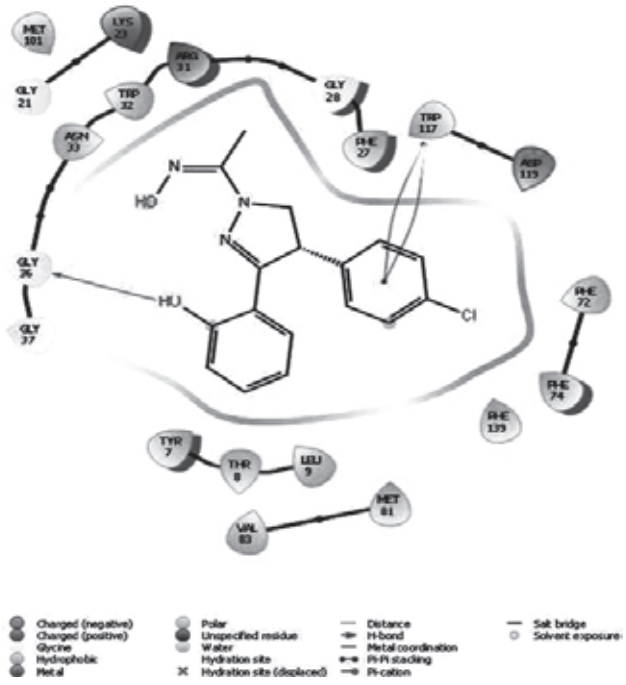


Figure 3: 2D interactions of the compound CF-8 at the active site of 4C9W

Absorption, Distribution, Metabolism, Elimination, Toxicity (ADMET)

Qikprop [9] tool was used to assess the druggable and safety profile of the synthesized pyrazole analogs. During this, various descriptors were calculated to assess the ADME prediction of the compounds, tabulated in Table 4. The values of all the descriptors for the synthesized compounds lied with in the acceptable range suggested that the compounds have good safety profile.

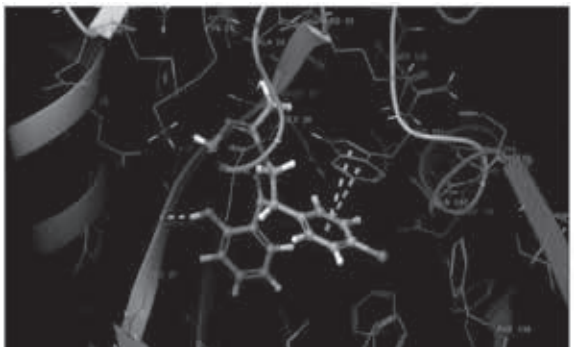


Figure 4: 3D interactions of the compound CF-8 at the active site of 4C9W

Table 2: Various interactions of the compounds CF-4 and CF-8 at the active site

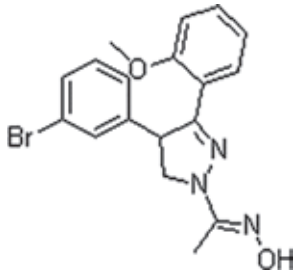
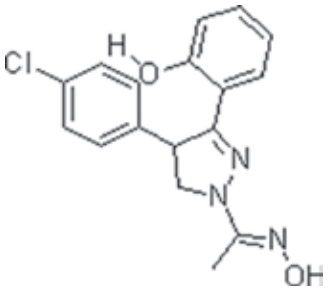
Compounds		Interactions		
Name	Structure	H-Bond	Π-Π	Hydrophobic
CF-4		a. Between ASN33 amino acid residue of 4C9W and N group of pyrazole moiety of CF-4 b. Between GLY28 and TRP117 amino acid residue of 4C9W and -OH group hydroxamic acid of CF-4	Between TRP117 and phenyl rings of CF-4 adjacent to the pyrazole moiety	These are responsible for the following amino acid residues which includeVAL83, ME T81, ILE70, PHE72, PHE74, TRP117, T RP123, LEU9, TYR7, ALA 29, PHE27, MET101
CF-8		Between GLY36 and OH group of phenol ring adjacent to the pyrazole moiety	Between TRP117 and phenyl rings of CF-4 adjacent to the pyrazole moiety	These Are responsible for the following amino acid residues which include VAL85 , MET81, PHE72, PHE74, TY R7, TRP32, LEU9, P HE139, MET101

Table 3: ADME data for the designed pyrazole analogues

Title	MW	HB^d	HB^a	$QlogP_{o/w}$	QPlogHERG	QPlogS	QPP Caco	%Human oral Absorption	PSA	Rule of Five
CF-1	451.35	0.0	4.25	6.561	-6.605	-7.728	3272.118	100	46.236	1
CF-2	343.81	1.0	4.45	3.971	-5.658	-5.658	1116.486	100	68.601	0
CF-3	495.80	0.0	4.25	6.538	-6.760	-7.918	2373.935	100	52.022	1
CF-4	388.26	1.0	4.45	4.239	-5.404	-5.530	1122.805	100	69.742	0
CF-5	327.81	1.0	3.70	4.297	-5.513	-5.652	1562.983	100	59.516	0
CF-6	437.32	1.0	4.25	6.041	-6.679	-7.369	2204.822	100	59.816	1
CF-6-2	437.32	1.0	4.25	5.928	-6.419	-7.309	2227.944	100	55.642	1
CF-8	329.78	2.0	4.45	3.421	-5.339	-4.769	894.762	100	80.575	0
CF-8	329.78	2.0	4.45	3.434	-5.430	-4.843	860.262	100	77.978	0
CF-9	455.94	1.0	4.25	6.507	-7.359	-8.380	1662.784	100	64.979	1
CF- 10	353.42	1.0	5.20	3.938	-4.831	-4.566	1391.971	90	73.438	0
CF-12	452.46	0.0	6.75	3.918	-7.202	-7.484	51.938	80	124	0
CF- 13	485.79	0.0	4.25	7.054	-6.831	-8.885	2201.323	100	52.250	1
CF- 14	496.34	0.0	5.25	5.796	-6.847	-8.134	252.051	100	96.214	1
CF- 15	476.36	0.0	5.75	6.507	-6.868	-8.815	665.909	100	73.514	1

Conclusions

A series of novel pyrazole analogues were designed and further subjected for the computational studies. The molecular docking studies revealed compound CF-4 and CF-8 possess comparable docking scores with that of the crystal ligand. ADME studies were conducted and all the compounds were shown to exhibit appreciable pharmacokinetics. The oxime bearing analogues have shown appreciable docking scores that is comparable to the crystal ligand. In our future studies, these potent analogues will be further modified so as to increase binding affinity as well as to improve their pharmacokinetic profile.

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