Research Article

Molecular Docking Studies of 1,3,4-Thiadiazoles as Novel Peptide Deformylase Inhibitors as Potential Antibacterial Agents

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ABSTRACT

To counter increasing levels of pathogen resistance new classes of antibiotics are needed without delay. The metalloenzyme peptide deformylase (PDF) correspond to one of the most promising bacterial targets in the search for novel mode of antibiotics action and was selected as a specific bacterial target. Binding modes of a series of 1,3,4-Thiadiazoles as Peptide Deformylase inhibitors have been identified by molecular modeling techniques. We performed Insilco molecular docking using Schrodinger LLC., software (GLIDE XP) we performed rescoring of the GLIDE scores using PRIME MM-GBSA module of Schrodinger LLC. This study also helped us to understand the inhibitor mechanisms of PDF structure. The results indicate that 1,3,4-Thiadiazoles for addition to hydrogen bonding interactions, Gly45, Gly89, Glu95, Cys90, Leu91, Leu46, Met 38, Ile44 and Ile128 amino acid residues of PDF are responsible for governing inhibitor potency of the compounds. The docked values for Glide using XP were –7.1 and -6.8 K cal/mol for molecule B12 and B8. The corresponding rescored values (binding energy) values were -71 K cal/mol in XP for B12 and the molecule B8 showed values of -76 K cal/mol in XP scores. ADME predictions of compounds were done with Qikprop 3.2 tool available in Schrödinger 9.0 ver. The information generated from the present study should be useful in the design of more potent Peptide deformylase inhibitors as antibacterial agents.

Keywords: PDF, ADME predictions, antibacterial agents.

INTRODUCTION

For a long time, it has been widely established that eukaryotes have no peptide deformylase. Since this enzyme is essential in bacteria and in several human parasites, peptide deformylase (PDF) was then acknowledged as an exceptional target for the design of new antibacterial[1] and antiparasitic agents[2]. Several studies of PDFs in complex with an inhibitor have given guidelines for the design of high affinity PDF inhibitors[3]. Though recent studies have led to the identification of peptide deformylase in eukaryotes, these enzymes are targeted to the plastids and mitochondria of plants and to animal mitochondria. Likewise the process of deformylation has been shown to be an essential process in eukaryotes[4]. Docking plays an important role in the rational design of drugs[5]. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking. Effectively, several studies estimating and comparing the accuracies of protein-ligand programs like Auto dock, ICM and Gold have been reported[6].

Bioinformatics tools and computer aided drug design process have a great potential in not only reducing the cost but also the efficiency with which they can be designed. Several novel tools and techniques in the recent past have helped in the speeding up of drug discovery process such as molecular docking, linear interaction energy methods, pharmacophore designing and QSAR. This approach helps the scientist to predict the activities of a series of newly designed drugs before making a decision whether or not to synthesize them and assay them. It also helps in identification of key structural features and help in the assessment of their biological activity.

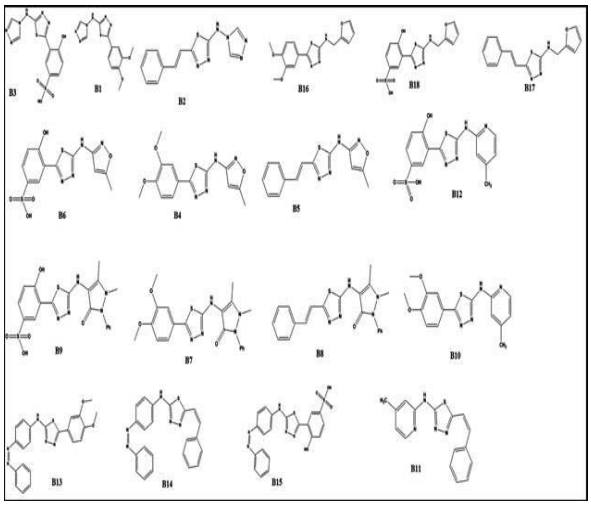
The present study was to search for potential ligands for we chose the best molecular docking programs available currently being used widely such as GLIDE and applied the linear interaction energy model (MM-GB/SA) for rescoring of the docked ligands to find out the best free energy of binding for these ligands.

MATERIALS AND METHODS

PDF protein has more than 60 structures in the PDB database in different resolutions. We chose the structure of 1G27 based on the sequence Similarity, resolution (2.1A^0). The initial X-ray crystallographic coordinates of PDF (PDB ID: 1G27) were downloaded from Protein Data Bank (http://www.rcsb.org). This protein was subjected to the protein preparation wizard of Schrodinger software in the Maestro interface 12. A small but promising group of 18 compounds database consisting of thiadiazole scaffold[6]. The ligands were subjected to ligand preparation using the ligand preparation wizard (Lprep) of Schrodinger software in the Maestro interface 12. The process of receptor grid generation is done by the Glide® of Maestro 9.9 molecular modeling suite. This software helps the identification of receptor grid according to our needs. The site map application was used to find, visualize and evaluate protein binding sites. We are

calculating their docking scores, binding free energies and ADMET properties.

Set of Compounds



The IC50 values of the 18 ligands were collected along with their structures in the beginning of our work in nanomolar units. These IC50 values can't be used for the statistical analysis; hence these values will be converted into pIC50 values which are otherwise called as activity values.

$$\text{Activity} = \text{pIC50} = 1/\log \text{IC50} = -\log \text{IC50}$$

Glide (Schrodinger, Inc.) Methodology

In order to understand the nature of interactions of these ligands, we carried out molecular docking between all compounds and the active site of peptide deformylase (PDF) kinase (1G27.pdb) and compared with the prototype of PDF inhibitor. The molecular docking studies were performed using glide (Maestro, 2013) module (extra precision) of with default docking parameter settings, the docking scores summarized in Table 2 with glide score ranging from -7.0 to -4.0 and all the molecules binding pose in the site is shown in the Fig. 3.

Prime MM-GBSA Methodology

This application calculates the free energy binding between the receptor and a ligand in its complex. The protein-ligand binding free energies during the last 2 ns were calculated using the Prime/MM-GBSA module of Schrödinger suite [Suite 2012] to get the averaged binding property.

Residues in binding pockets of the protein were treated as flexible and the ligand partial charges were assigned by the initial charges. The binding free energy ΔGbind was estimated using the equation[7].

$$\Delta G\text{bind} = G\text{complex} - (G\text{protein} + G\text{ligand})$$

ADME/T Properties

The ADME/T properties of all the ligands were calculated from the Qikprop 2.3 module of the Schrödinger suite 16[8]. Qikprop settings determine which molecules are flagged as being dissimilar to other 95% of the known drugs. The Qikprop helps us in analyzing the pharmacokinetics and pharmacodynamics of the ligands by accessing the drug like properties Predicted significant ADME/T properties such as permeability through MDCK Cells (QPlogMDCK)[9], Qik Prop predicted log IC50 value for blockage of K+ channels (QPlogHERG), Qikprop predicted gut-blood barrier (QPPCaco)[10] and violations of the Lipinski's rule of five (LROF)[11]. The molecular properties are provided in Table 1 and Glide and Prime MM-GBSA. Rescoring values are listed in Table 2. The ADME properties were predicted so as to calculate oral bioavailability, dermal penetration, CNs penetration, metabolism and Toxicity. The results are shown in the Table 3.

RESULTS AND DISCUSSION

In order to understand the nature of interactions of these ligands, we carried out molecular docking between all compounds and the active site of peptide deformylase (PDF) kinase (1G27.pdb) and compared with the prototype of PDF inhibitor.

The molecular docking studies were performed using glide (Maestro, 2013) module (extra precision) of with default docking parameter settings, the docking scores summarized in Table 2 with glide score ranging from -7.0 to -4.0 and all the molecules binding pose in the site is shown in the Fig. 1.

Among the docked compounds B6, B12 and B8 were found to have good binding affinity. The hydroxyl groups and oxygen present in the compounds formed hydrogen bonds with Gly45, Gly89 and Glu95. Hydrophobic interactions were found with Cys90, Leu91, Leu46, Met 38, Ile44 and Ile128.

The output of the Prime / MM-GBSA contains complex energy, ligand energy, receptor energy, MMGBSA DG binding energy. Compound B13, B8 and B18 showed maximum binding affinity above -71 K cal/mol. The designed compounds satisfied the Lipinski rule of 5 and rule of 3. Nearly all the compounds showed good compatibility with reference.

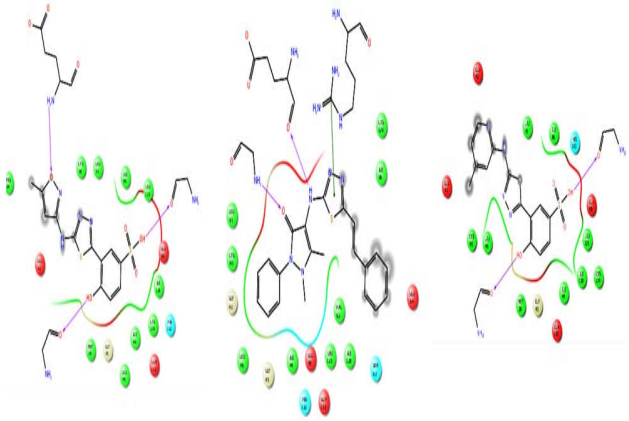


Figure 4: Docked poses of ligands B6, B12 and B18 respectively showing their positions in the active site of the protein molecule 1G27.

Table 1: Binding Database index of Molecules along with their Molecular properties, Molecular formula, Molecular weight, Activity IC50 values in micro molar units taken from Binding databank site, their PIC50 values calculated and their IUPAC nomenclature.

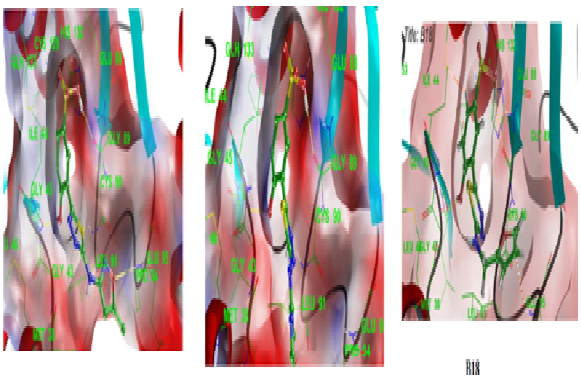
Sample	Molecular Formula	MW	IC_{50} (µm)	p IC_{50}	IUPAC
B1	$C_{12}H_{12}N_6O_2S$	340.32	97.22	1.538	5-(3,4-dimethoxyphenyl)-N-(4H-1,2,4-triazol-4-yl)-1,3,4-thiadiazol-2-amine
B2	$C_{12}H_{10}N_6S$	270.31	22.4	1.62	(E)-5-styryl-N-(4H-1,2,4-Triazol-4-yl)-1,3,4-thiadiazol-2-amine
B3	$C_{10}H_8N_6O_4S_2$	340.33	99.48	1.602	3-(5-((4H-1,2,4-triazol-4-yl)amino)-1,3,4-thiadiazol-2-yl)-4-hydroxy benzenesulphonic acid
B4	$C_{14}H_{14}N_4O_3S$	318.35	91.5	1.854	N-(5-(3,4-dimethoxy phenyl)-1,3,4-thiadiazol-2-yl)-5-methylisoxazol-3-amine
B5	$C_{14}H_{12}N_4OS$	284.33	28.39	1.602	E)-5-methyl-N-(5-styryl-1,3,4-thiadiazole-2-yl)isoxazol-3-amine
B6	$C_{12}H_{10}N_4O_5S_2$	354.35	103.52	1.886	4-hydroxy-3-(5-((5-methylisoxazol-3-yl)amino)-1,3,4-thiadiazol-2-yl)benzenesulphonic acid
B7	$C_{21}H_{21}N_5O_3S$	423.49	304.28	1.638	4-((5-(3,4-dimethoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one
B8	$C_{21}H_{19}N_5OS$	389.47	25.87	1.745	(E)-1,5-dimethyl-2-phenyl-4-((5-styryl-1,3,4-thiadiazol-2-yl)amino-1,2-dihydro-3H-pyrazole-3-one
B9	$C_{19}H_{17}N_5O_5S_2$	459.49	275.31	1.796	3-(5-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino-1,3,4-thiadiazol-2-yl-2-yl)-4-hydroxybenzenesulphonic acid
B10	$C_{16}H_{16}N_4O_2S$	328.39	172.5	1.658	5-(3,4-dimethoxyphenyl)-N-(4-methylpyridine-2-yl)-1,3,4-thiadiazol-2-amine
B11	$C_{16}H_{14}N_4S$	294.37	27.66	1.602	(Z)-N-(4-methylpyridine-2-yl)-5-styryl-1,3,4-thiadiazol-2-amine
B12	$C_{14}H_{12}N_4O_4S_2$	364.39	127.87	1.638	4-hydroxy-3-(3-(5-((4-methylpyridin-2-yl)amino)-1,3,4-thiadiazol-2-yl)benzenesulphonic acid
B13	$C_{22}H_{19}N_5O_2S$	417.48	206.05	1.699	Z)-5-(3,4-dimethoxyphenyl)-N-(4-(phenyl diazenyl) phenyl)-1,3,4-thiadiazol-2-amine
B14	$C_{22}H_{17}N_5S$	383.47	16.51	1.62	N-(4-((Z)-phenyldiazenyl) phenyl)-5-((Z)-styryl-1,3,4-thiadiazol-2-amine
B15	$C_{20}H_{15}N_5O_4S_2$	453.49	322.98	1.678	(Z)-4-hydroxy-3-(5-((4-(phenyldiazenyl) phenyl) amino)-1,3,4-thiadiazol-2-yl)benzene sulfonic acid
B16	$C_{15}H_{15}N_3O_3S$	317.36	274.33	1.699	5-(3,4-dimethoxyphenyl)-N-(furan-2-ylmethyl)-1,3,4-thiadiazol-2-amine
B17	$C_{15}H_{13}N_3OS$	283.34	65.24	1.745	(E)-N-(furan-2-ylmethyl)-5-styryl-1,3,4-thiazol-2-amine
B18	$C_{13}H_{11}N_3O_5S_2$	353.36	481.91	1.854	3-(5-((furan-2-ylmethyl)amino)-1,3,4-thiadiazole-2-yl)-4-hydroxybenzenesulphonic acid

Table 2: Binding Database index along with Glide scores in XP and Prime MM-GBSA rescoring values in XP.

ligand	GScore	Dock Score	Lipophilic EvdW	HBond	Electro	Site map	Low MW	Expos Penal	Rot Penal	Prime Energy	MMGBSA dG Bind
B6	-7.13	-7.13	-3.63	-1.63	-1.56	0	-0.32	0	0	-7538.8	-65.496
B12	-6.93	-6.93	-3.43	-1.63	-1.6	0	-0.29	0	0	-7537.2	-57.492
B18	-6.8	-6.8	-4.54	-1.27	-0.67	0	-0.32	0	0	-7521.6	-71.69
B15	-6.61	-6.61	-3.83	-0.78	-2	0	0	0	0	-7500.3	-68.992
B8	-6.58	-6.58	-4.37	-0.77	-1.24	0	-0.2	0	0	-7474.3	-76.078
B3	-6.14	-6.14	-3.51	-1.49	-0.77	0	-0.37	0	0	-7499.9	-63.485
B7	-5.93	-5.93	-4	-0.7	-1.13	0	-0.09	0	0	-7459.1	-68.061
B10	-5.9	-5.9	-4.54	-0.7	-0.26	0	-0.41	0	0	-7527.9	-69.54
B16	-5.79	-5.79	-4.08	-1.16	-0.1	0	-0.44	0	0	-7488.9	-60.977
B17	-5.56	-5.56	-4.02	-0.7	-0.34	0	-0.5	0	0	-7498.4	-62.568
B9	-5.47	-5.47	-3.42	-0.96	-1.09	0	0	0	0	-7485.2	-68.399
B4	-5.07	-5.07	-3.88	-0.67	-0.09	0	-0.44	0	0	-7511.6	-63.006
B14	-4.75	-4.75	-2.75	-0.7	-1.08	0	-0.22	0	0	-7466.9	-51.898
B11	-4.46	-4.46	-3.86	0	-0.1	0	-0.5	0	0	-7532.7	-68.166
B5	-4.46	-4.46	-2.8	-0.13	-1.02	0	-0.5	0	0	-7510.7	-59.299
B2	-4.26	-4.26	-2.74	-0.7	-0.32	0	-0.5	0	0	-7469.6	-51.852
B1	-4.22	-4.22	-2.95	-0.7	-0.08	0	-0.49	0	0	-7465.1	-52.714
B13	-4.01	-4.01	-3.85	0	-0.06	0	-0.11	0	0	-7487.7	-78.848

Table 3: ADME properties of 1,3,4 thiadiazoles

ID	CIlogSwat	% Human oral abs	R of 3	QPPCaCo	logS	QPLog Khsa	LogKp	QplogBB	MDCK	QPlogHERG	metab	Stars
B1	-3.032	73.936	0	351.307	-4.38	-0.68	-3.314	-1.074	216.715	-5.037	3	1
B2	-2.955	84.448	0	529.258	-4.83	-0.548	-2.356	-0.912	450.343	-5.802	1	0
B3	-2.659	30.139	1	3.066	-4.38	-1.184	-5.982	-2.603	1.911	-3.407	2	1
B4	-4.459	94.908	0	853.918	-4.52	0.045	-2.625	-0.735	571.97	-5.266	4	0
B5	-4.354	100	0	842.567	-4.99	0.171	-2.094	-0.749	748.567	-5.884	2	0
B6	-3.93	41.839	1	4.604	-4.50	-0.68	-5.773	-2.575	2.675	-3.572	3	0
B7	-6.181	100	1	1377.079	-6.04	0.412	-1.777	-0.562	1147.187	-6.418	4	0
B8	-6.125	100	1	1366.183	-6.52	0.606	-1.195	-6.108	1261.64	-7.097	2	0
B9	-5.657	53.819	1	6.843	-6.02	-0.301	-4.966	-2.606	4.812	-4.726	3	0
B10	-4.914	100	0	1225.518	-4.98	0.281	-2.138	-0.586	807.363	-5.557	6	0
B11	-4.806	100	0	1836.642	-5.45	0.42	-1.19	-0.407	1734.43	-6.339	4	0
B12	-4.348	53.646	1	11.074	-4.97	-0.508	-4.794	-2.159	7.64	-3.877	5	0
B13	-6.681	100	1	1460.013	-7.49	0.705	-0.948	-0.738	986.66	-7.493	4	2
B14	-6.59	100	1	1452.113	-7.97	0.855	-0.363	-0.78	1091.19	-8.175	2	2
B15	-6.04	63.154	1	12.396	-7.47	-0.172	-3.672	-2.538	8.639	-5.78	3	1
B16	-4.826	100	0	3148.614	-3.98	0.193	-1.155	-0.151	2775.842	-5.435	5	1
B17	-4.711	100	0	3136.279	-4.45	0.317	-0.57	-0.195	3080.97	-6.141	3	0
B18	-4.256	53.118	1	18.105	-3.66	-0.563	-4.204	-1.887	14.099	-3.721	4	0
Range	**-6.5 – 0.5**	**<80%H >25%L**	**Max 3**	**<25 p, >500 great**	**-1 to -5**	**-1.5 to +1.5**	**–8.0 to –1.0**	**-3 to 1.2**	**<25 poor,>500 great**	**Concern below-5**	**1-8**	**1-4**



Of all the compounds docked B8 was found to have good pharmacokinetic parameters, dock score of -6.8 and good binding affinity of -76 Kcal/mol.

CONCLUSION

The molecules showing promise (B6, B12 and B8) require further studies to be carried by taking more structural derivatives of these molecules by pharmacophoric mapping and screening. The work shows that hydrogen bonding plays a very important role in structure and function of biological molecules and especially in inhibition of a complex. We could also identify that rescoring of the docking values gives the best prediction of ligands about their interaction with protein and helps us in sorting them and choosing the best one out of a group or library of ligands. MMGB/SA based method is one of the best techniques for prioritization of lead molecules while screening compound databases using molecular docking protocols. Further studies on these molecules using pharmacophore and QSAR methods hold promise for further development of the leads into drugs.

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