PROTEIN-NUCLEIC ACID INTERFACE (PNAI) INHIBITOR DRUG MOLECULES FOR SARS-COV-2

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1. Abstract

In this research we used the structure of SARS-CoV-2 related, recently mapped, atomic structure of nsp10/16 proteins for docking with some known drug molecular structures at pH 7 and 5. Chosen molecules were azo -N=N- and -COOH derivatives. It was revealed that the molecules showed good binding energy with nsp10/16 protein at both pH. These molecules can act as protein-nucleic acid interface (PNAI) inhibitor drug molecules. Such molecules can be used in combination with polymerase and protease inhibitors for treatment of SARS-CoV-2.

Keywords: PNAI; Drug; SARS-CoV-2; Docking; NSP10/16

2. Introduction

SARS-COV-2 is a single positive strand RNA virus [1]. So far, the strategies to develop potent drugs against the SARS-COV-2 virus included inhibition of RNA dependent RNA polymerase (RdRp), angiotensin-converting enzyme II (ACE2) entry receptor and protease. Some of the identified RdRp molecular inhibitors targeting ACE2 have showed less specificity with side effects [2][3]. Protease (Mpro) proteins also act as drug targets for protease inhibitor molecules [4][5][6][7]. Recently, X-ray crystal structure of the SARS-COV-2 Mpro has been determined which provides an opportunity for structure-based protease inhibitor drug molecular designing [8]. Covalent binding protease inhibitors have shown side effects as well [9-14], while noncovalent protease inhibitors showed fewer side effects. Recent research work being done is focusing on known and clinically approved drug molecules [15-17]. In this research we used the same strategy of using known structures.

Recently Scientists from Northwestern University Feinberg School of Medicine have mapped the atomic structure of two critical proteins joined together in a complex, nsp10/16 [18]. The nsp10/16 protein is

known as RNA methyltransferase or MTase. SARS-CoV-2 lacks replicase and transcriptase components. In order to replicate itself, the viral RNA reaches the cytoplasm of the human cell transcriptase and replicase components are synthesized as a result. These components include nonstructural viral proteins (nsp) which aid the virus to replicate. Hence, nsp proteins serve as potential SARS-CoV-2 target sites for anti-viral molecules. nsp10 plays a vital role in viral RNA synthesis where as nsp 16 aids in cap formation. Thus, to resist the viral replication, nsp10/16 should be inhibited by protein-nucleic acid interface (PNAI) inhibitors [19].

In this research, we used already known drug molecules so that other molecular and drug related properties are already known. This research can lead to further development of PNAI inhibitor drug molecules for binding with nsp10/16 proteins.

3. Experimental

Docking simulations were performed using MOE2015.10 software. Structures of all drug molecules were downloaded from PubChem website in .sdf format. By using Open Babel software [20] all structures were converted to. mol2 format. For preparation of receptor, the structure of PDB 6W4H (resolution 1.80 Å) was obtained from the Protein Data Bank [21] in .pdb format. Docking simulations were performed using MOE2015.10 software at pH 7 and 5.

4. Results and Discussion

Docking analysis on nsp10/16 was done on the basis of hydrogen bonding, Van der Waals forces and π-stacking interactions. Binding energies of proposed protein-nucleic acid interactions (PNAI) inhibitors **(1-10)** are given in **Table**-1. Ligand and receptor interaction details are given in **Table** 2.1 and 2.2. Some of the selected molecules **(1-2)** are known PNAI inhibitors against SARS-COV Nsp15 [22]. Benzopurpurin B (**1**) has recently been tested on SARS-COV-2 infected patients [23]. (**4-6**) were selected based on their similar structure to the known PNAI inhibitor molecules (**1-2**). We also used aurintricarboxylic acid (ATA) (**3**) for docking with PNAI. This molecule was used in previous studies as selective inhibitor of nsp16 for SARS-COV [24].

The virus-infected cells produce ATP during oxidative metabolism and also by glycolysis. Glycolysis converts glucose ($C_6H_{12}O_6$) into pyruvate ($CH_3COCOO^- + H^+$) which further converts into lactate. Because of high rates of glycolysis and synthesis of lactate, pH of the cell turns acidic [25]. In this research work, we checked the binding of the selected molecules (**1-10**) at both neutral and slightly acidic pH.

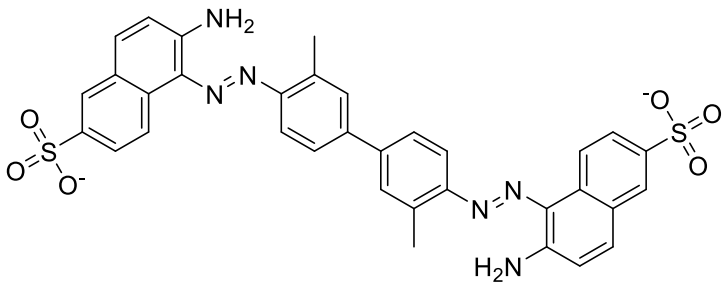
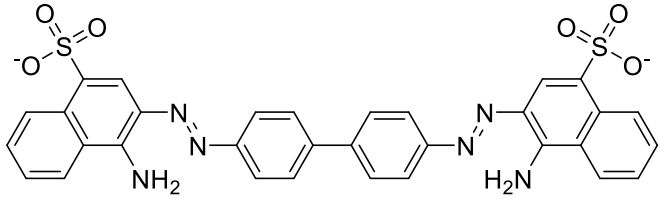
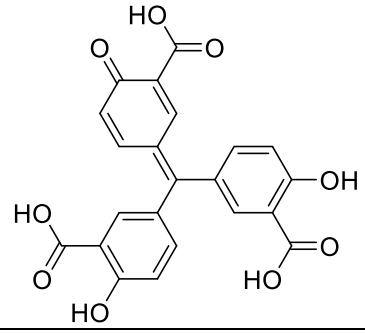
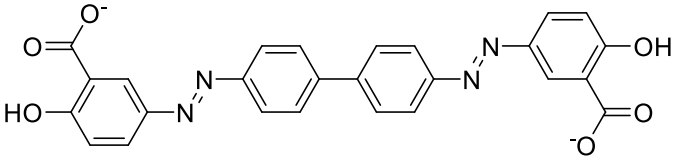
Data from **Table**-1 demonstrates that all the selected protease inhibitors **(1-10)** bind with energy in between 5.6-10.1 -kcal/mol. At pH 5, highest binding was showed by molecule (**9**) (**Figure**-1) while at pH 7, (**5**) gave the highest binding energy (**Figure**-2). Almost all selected molecules showed least differential in the binding energies with changing pH except (**5**).

5. Conclusion

We used protein-nucleic acid interface (PNAI) as a receptor site for binding with selected -N=N and -COOH based (PNAI) inhibitors **(1-10)** at pH 7 and 5. It has been found that selected molecules showed fair level binding energies towards protein-

nucleic acid interface (PNAI). The molecules we used for docking such as (**1-3**) are commercially available and have been proven effective in inhabiting replication of SARS-CoV. Hence, these molecules can lead to further development of protein-nucleic acid interface (PNAI) inhibitor drug molecules for SARS-CoV-2. Our group is working on further deep docking (DD) structural searches for more PNAI inhibitors for SARS-CoV-2 virus. PNAI inhibitors along with protease and polymerase inhibitors can be used to treat SARS-CoV-2.

Table 1: Binding energy evaluation data of molecules (**1-10**) with 6W4H (PNAI).

	PubChem code	**Structure**	**Binding Energy Kcal/mol**	
			pH 5	**pH 7**
1	CID 428775		-8.698	-8.571
2	CID 11314		-8.076	-8.244
3	CID 2259		-7.025	-6.281
4	CID 160843		-7.798	-7.682

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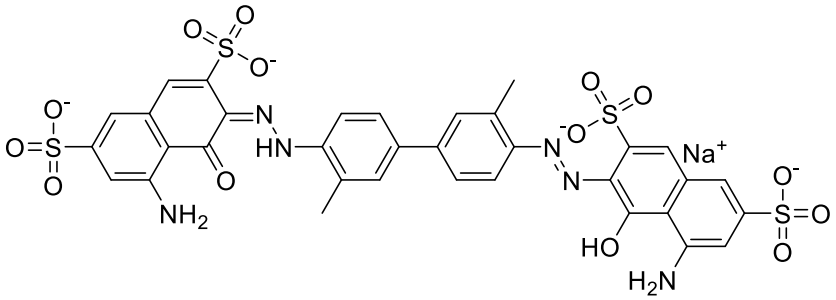
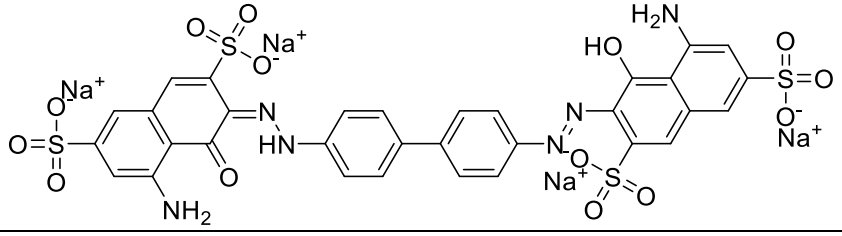
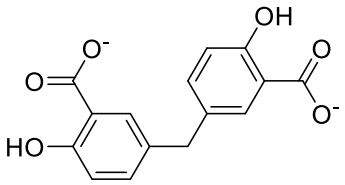
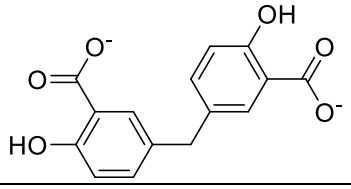
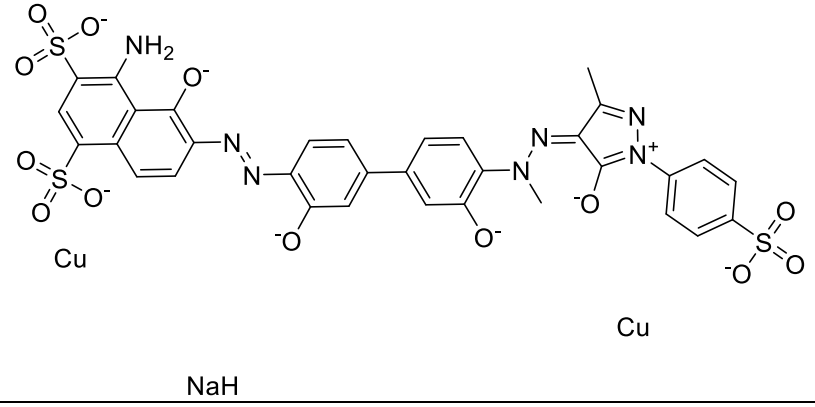
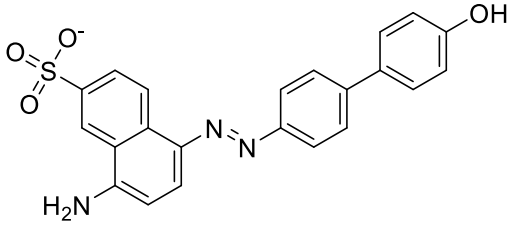
5	CID 135903069		-8.591	-10.109
6	CID 17449		-9.147	-9.316
7	CID 67145		-5.998	-5.655
8	SID 349765978		-9.385	-8.595
9	CID 138395300		-9.613	-9.380
10	CID 414983		-6.462	-7.056

Docking of (PNAI) inhibitor molecules for SARS-COV-2

Table 1.2: Details of ligand and receptor interaction of molecules (**1-10**) with 6W4H (PNAI) at pH 7.

S.no.	PubChem code	Total Binding Energy Kcal/mol	Ligand	Receptor	Interaction	Distance
1	CID 428775	-8.57129	N 14	O CYS 4294 (B)	H-donor	3.01
			O 6	ND2 ASN 6996 (A)	H-acceptor	2.99
			O 6	OG SER 6999 (A)	H-acceptor	3.16
			O 8	NZ LYS 4296 (B)	H-acceptor	3.47
			O 4	NZ LYS 6836 (A)	ionic	3.00
			O 5	NZ LYS 6844 (A)	ionic	2.94
			O 5	NZ LYS 6968 (A)	ionic	3.53
			O 7	NZ LYS 6836 (A)	ionic	2.84
			O 7	NZ LYS 4296 (B)	ionic	2.94
			O 8	NZ LYS 4296 (B)	ionic	3.47
			6-ring	MET 6839 (A)	Π-H	4.07
			6-ring	N MET 6840 (A)	Π-H	3.98
			6-ring	NZ LYS 6844 (A)	Pi cation	4.73
			6-ring	NZ LYS 4296 (B)	pi-cation	4.53
2	CID 11314	-8.24403	O 5	SD MET 6929 (A)	H-donor	2.87
			O 6	SD MET 6929 (A)	H-donor	3.03
			N 9	O TYR 6930 (A)	H-donor	3.05
			O 5	N CYS 6913 (A)	H-acceptor	3.09
			O 8	NZ LYS 6968 (A)	H-acceptor	3.13
			6-ring	CD2 LEU 6898 (A)	Π-H	3.71
			6-ring	ND2 ASN 6996 (A)	Π-H	4.34
			6-ring	ND2 ASN 6996 (A)	Π-H	3.88
3	CID 2259	-6.28164	O 1	ND2 ASN 6996 (A)	H-acceptor	3.08
			O 3	NZ LYS 6874 (A)	H-acceptor	2.97
			O 4	NZ LYS 6968 (A)	H-acceptor	3.10
			O 5	CA SER 6872 (A)	H-acceptor	3.31
			O 5	N ASP 6873 (A)	H-acceptor	3.14
			O 6	N MET 6840 (A)	H-acceptor	3.08
			O 7	ND2 ASN 6996 (A)	H-acceptor	3.05
			O 7	OG SER 6999 (A)	H-acceptor	2.94
			O 9	N ASN 6841 (A)	H-acceptor	2.99
			O 4	NZ LYS 6844 (A)	ionic	3.88

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			O 4	NZ LYS 6968 (A)	ionic	3.10
			O 6	NZ LYS 6874 (A)	ionic	3.78
4	CID 160843	-7.68205	O 3	N CYS 6913 (A)	H-acceptor	3.09
			O 5	NZ LYS 6874 (A)	H-acceptor	2.97
			O 7	N MET 6840 (A)	H-acceptor	3.16
			O 8	N GLY 6869 (A)	H-acceptor	3.12
			O 5	NZ LYS 6874 (A)	ionic	2.97
			O 7	NZ LYS 6874 (A)	ionic	3.58
5	CID 135903069	-10.1096	O 14	SG CYS 4294 (B)	H-donor	3.31
			O 7	NZ LYS 6968 (A)	H-acceptor	2.93
			O 13	NZ LYS 6935 (A)	H-acceptor	2.91
			O 14	N CYS 4294 (B)	H-acceptor	3.25
			O 15	N SER 7000 (A)	H-acceptor	3.13
			O 15	OG SER 7000 (A)	H-acceptor	2.74
			O 7	NZ LYS 6968 (A)	ionic	2.93
			O 10	NZ LYS 6844 (A)	ionic	2.96
			O 10	NZ LYS 6968 (A)	ionic	3.58
			O 11	NZ LYS 6874 (A)	ionic	3.14
			O 13	NZ LYS 6935 (A)	ionic	2.91
6	CID 17449	-9.31642	O 16	SG CYS 4294 (B)	H-donor	3.49
			O 12	NZ LYS 6968 (A)	H-acceptor	2.90
			O 14	N SER 7000 (A)	H-acceptor	2.91
			O 14	OG SER 7000 (A)	H-acceptor	2.70
			O 16	N CYS 4294 (B)	H-acceptor	3.10
			O 17	NZ LYS 6935 (A)	H-acceptor	2.79
			O 7	NZ LYS 6874 (A)	ionic	2.86
			O 8	NZ LYS 6844 (A)	ionic	2.95
			O 8	NZ LYS 6968 (A)	ionic	3.69
			O 12	NZ LYS 6968 (A)	ionic	2.90
			O 17	NZ LYS 6935 (A)	ionic	2.79
			6-ring	N MET 6840 (A)	Π-H	3.84
7	CID 67145	-5.65501	O 1	NZ LYS 6844 (A)	H-acceptor	3.05
			O 5	NZ LYS 6968 (A)	H-acceptor	3.27
			O 7	NZ LYS 6968 (A)	H-acceptor	2.96
			O 8	OH TYR 6930 (A)	H-acceptor	3.06

			O 5	NZ LYS 6844 (A)	ionic	2.96
			O 5	NZ LYS 6968 (A)	ionic	3.27
			O 7	NZ LYS 6968 (A)	ionic	2.96
			6-ring	NZ LYS 6935 (A)	pi-cation	3.94
8	SID 349765978	-8.59571	O 2	NZ LYS 6968 (A)	H-acceptor	2.98
			O 7	N CYS 6913 (A)	H-acceptor	3.17
			O 7	SG CYS 6913 (A)	H-acceptor	3.32
9	CID 138395300	-9.38083	O 8	NZ LYS 6836 (A)	H-acceptor	2.92
			O 15	NZ LYS 6935 (A)	H-acceptor	3.47
			O 16	OG SER 7000 (A)	H-acceptor	2.94
			O 8	NZ LYS 6836 (A)	ionic	2.92
			O 8	NZ LYS 4296 (B)	ionic	3.87
			O 10	NZ LYS 6836 (A)	ionic	3.52
			O 11	NZ LYS 6844 (A)	ionic	3.76
			O 13	NZ LYS 6874 (A)	ionic	2.80
			O 15	NZ LYS 6935 (A)	ionic	3.47
			5-ring	NZ LYS 6968 (A)	pi-cation	4.26
10	CID 414983	-7.05687	O 2	O GLY 6871 (A)	H-donor	3.12
			O 4	ND2 ASN 6841 (A)	H-acceptor	2.99
			6-ring	CD2 PHE 6947 (A)	П-H	3.95

Docking of (PNAI) inhibitor molecules for SARS-COV-2

Table 1.2: Details of ligand and receptor interaction of molecules (**1-10**) with 6W4H (PNAI) at pH 5.

S.no.	PubChem code	Total Binding Energy Kcal/mol	Ligand	Receptor	Interaction	Distance
1	CID 428775	-8.57129	N 13	O CYS 4294 (B)	H-donor	3.04
			N 14	OG SER 6831 (A)	H-donor	3.22
			O 7	NZ LYS 6968 (A)	H-acceptor	3.45
			O 8	ND2 ASN 6996 (A)	H-acceptor	3.03
			O 8	OG SER 6999 (A)	H-acceptor	3.10
			O 3	NZ LYS 6836 (A)	ionic	2.95
			O 5	NZ LYS 6836 (A)	ionic	2.84
			O 5	NZ LYS 4296 (B)	ionic	2.97
			O 6	NZ LYS 4296 (B)	ionic	3.63
			O 7	NZ LYS 6844 (A)	ionic	2.99
			O 7	NZ LYS 6968 (A)	ionic	3.45
			6-ring	CA MET 6839 (A)	Π-H	4.04
			6-ring	N MET 6840 (A)	Π-H	3.90
			6-ring	NZ LYS 6844 (A)	pi-cation	4.65
			6-ring	NZ LYS 4296 (B)	pi-cation	4.58
2	CID 11314	-8.24403	N 9	O CYS 4294 (B)	H-donor	3.35
			O 3	NZ LYS 4296 (B)	H-acceptor	3.54
			O 4	ND2 ASN 6996 (A)	H-acceptor	2.93
			O 4	OG SER 6999 (A)	H-acceptor	3.09
			O 8	NZ LYS 6844 (A)	H-acceptor	3.08
			O 3	NZ LYS 4296 (B)	ionic	3.54
			O 8	NZ LYS 6844 (A)	ionic	3.08
			6-ring	CA MET 6839 (A)	Π-H	3.91
			6-ring	N MET 6840 (A)	Π-H	4.65
			6-ring	N MET 6840 (A)	Π-H	4.11
3	CID 2259	-6.28164	O 3	SG CYS 6913 (A)	H-acceptor	3.51
			O 9	N CYS 6913 (A)	H-acceptor	2.90
			6-ring	CA ASP 6931 (A)	Π-H	4.35
4	CID 160843	-7.68205	O 3	N CYS 6913 (A)	H-acceptor	3.15

Docking of (PNAI) inhibitor molecules for SARS-COV-2

			O 8	N GLY 6869 (A)	H-acceptor	3.09
			6-ring	N ASN 6841 (A)	Π-H	4.65
5	CID 135903069	-10.1096	N 2	OD1 ASN 4293 (B)	H-donor	2.88
			O 5	NZ LYS 6874 (A)	H-acceptor	3.23
			O 9	NZ LYS 6844 (A)	H-acceptor	2.92
			O 9	ND2 ASN 6996 (A)	H-acceptor	3.07
			O 12	NZ LYS 6968 (A)	H-acceptor	3.14
			O 15	OH TYR 6930 (A)	H-acceptor	3.06
			O 18	N HIS 6972 (A)	H-acceptor	3.19
			O 19	CD2 HIS 6972 (A)	H-acceptor	3.43
			O 9	NZ LYS 6844 (A)	ionic	2.92
			O 12	NZ LYS 6968 (A)	ionic	3.14
			O 19	NZ LYS 6935 (A)	ionic	3.65
			6-ring	N SER 7000 (A)	Π-H	4.29
6	CID 17449	-9.31642	O 18	SG CYS 4294 (B)	H-donor	3.29
			N 23	O GLY 6837 (A)	H-donor	3.02
			O 8	NZ LYS 6844 (A)	H-acceptor	3.01
			O 10	NZ LYS 6844 (A)	H-acceptor	2.96
			O 14	N SER 7000 (A)	H-acceptor	3.37
			O 16	NZ LYS 6935 (A)	H-acceptor	2.82
			O 17	N SER 7000 (A)	H-acceptor	3.33
			O 17	OG SER 7000 (A)	H-acceptor	2.82
			O 8	NZ LYS 6844 (A)	ionic	3.01
			O 9	NZ LYS 6874 (A)	ionic	2.92
			O 10	NZ LYS 6844 (A)	ionic	2.96
			O 16	NZ LYS 6935 (A)	ionic	2.82
			6-ring	NZ LYS 6874 (A)	pi-cation	4.67
			6-ring	ND2 ASN 6996 (A)	Π-H	4.22
7	CID 67145	-5.65501	O 5	N CYS 6913 (A)	H-acceptor	3.14
			6-ring	N TYR 6930 (A)	Π-H	4.61

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8	SID 349765978	-8.59571	N 11	OD1 ASP 6897 (A)	H-donor	3.33
			O 1	N TYR 6930 (A)	H-acceptor	2.93
			O 2	NZ LYS 6968 (A)	H-acceptor	2.91
			O 6	NZ LYS 6844 (A)	H-acceptor	3.01
			O 8	N GLY 6869 (A)	H-acceptor	3.02
			O 6	NZ LYS 6844 (A)	ionic	3.01
			6-ring	ND2 ASN 6996 (A)	Π-H	4.79
9	CID 138395300	-9.38083	O 4	ND2 ASN 6996 (A)	H-acceptor	2.92
			O 4	OG SER 6999 (A)	H-acceptor	3.28
			O 5	N GLY 6829 (A)	H-acceptor	3.31
			O 8	NZ LYS 6935 (A)	H-acceptor	2.77
			O 9	NZ LYS 6935 (A)	H-acceptor	3.50
			O 10	OG SER 7000 (A)	H-acceptor	3.05
			O 12	CA SER 6872 (A)	H-acceptor	3.17
			O 12	N ASP 6873 (A)	H-acceptor	3.16
			O 13	NZ LYS 6844 (A)	H-acceptor	2.75
			O 14	CA ASP 6912 (A)	H-acceptor	3.34
			O 15	SG CYS 6913 (A)	H-acceptor	3.23
			O 8	NZ LYS 6935 (A)	ionic	2.77
			O 9	NZ LYS 6935 (A)	ionic	3.50
			O 13	NZ LYS 6844 (A)	ionic	2.75
			N 18	OD1 ASP 6897 (A)	ionic	3.28
			N 18	OD2 ASP 6897 (A)	ionic	3.38
10	CID 414983	-7.05687	O 3	NZ LYS 6968 (A)	H-acceptor	2.94
			O 4	NZ LYS 6844 (A)	H-acceptor	2.92
			O 3	NZ LYS 6844 (A)	ionic	3.80
			O 3	NZ LYS 6968 (A)	ionic	2.94
			O 4	NZ LYS 6844 (A)	ionic	2.92
			6-ring	CB LEU 6898 (A)	Π-H	3.57
			6-ring	N TYR 6930 (A)	Π-H	4.91

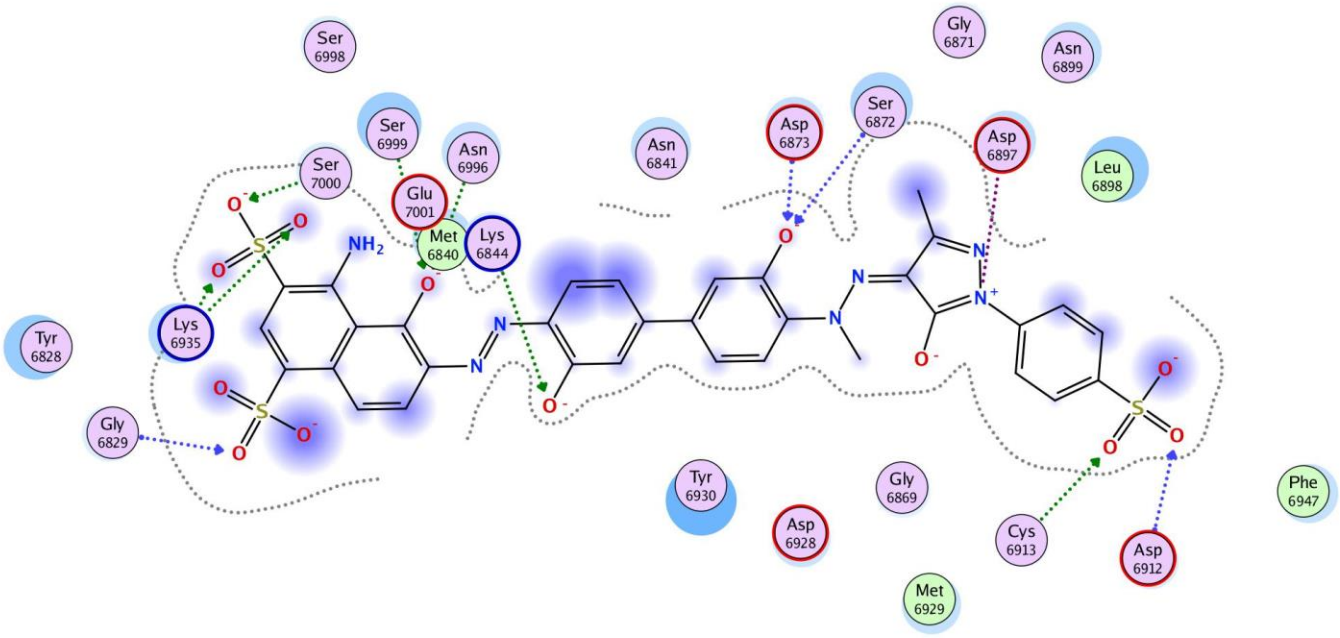

Figure-1. Binding interactions of (**9**) with 6W4H PNAI at pH 5.

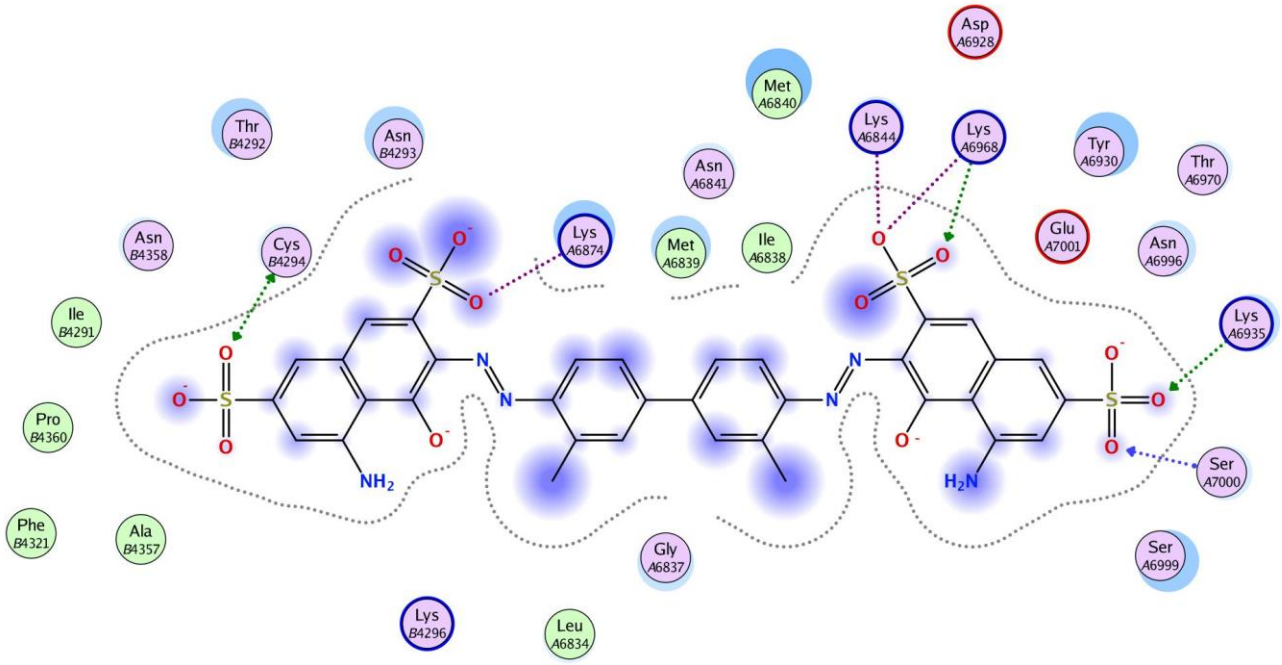

Figure-1. Binding interactions of (**5**) with 6W4H PNAI at pH 7.

Reference

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