THE FEATURES OF PROTEIN BINDING BY RUTHENIUM COMPLEXES: DOCKING, FORCE FIELD AND QM/MM STUDIES

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ABSTRACT

The ruthenium complexes are known for their anticancer property. Some ruthenium complexes can bind with protein that may be related to the anticancer activity. The protein binding features of few ruthenium complexes have been analyzed to understand the amino acid selectivity within protein sequences. The docking, Molecular mechanics and QM/MM methods are used to predict the binding sites of these ruthenium complexes. The fluorinated ruthenium pyridocarbazole is a protein binding complex. The cis-chlorodimethylsulphoxide-S-bis(1,10-phenanthroline) ruthenium (II) chloride [RuN(B)], trichlorodimethylsulphoxide-S-(1,10-phenanthroline) ruthenium (III) [RuN(C)] and cis-dichlorotetrakis(dimethylsulphoxide) ruthenium (II) [RuN(D)] complexes can bind perfectly within fluorinated ruthenium pyridocarbazole is binding region. The complexes are found selective of certain amino acids, and the formation hydrogen bonds within the complex bonded region are found.

Keywords: *Ruthenium complexes, protein, anticancer activity*.

1. INTRODUCTION

The emerging interests on the metal complexes by many researchers have been found in literatures because of the wide spread anticancer activity of these complexes. However, the toxicity of these complexes may result negative impact on the useful properties [1-3]. The actual interactions between the metal complexes and macromolecules, like DNA or proteins are subject of further investigation to precisely understand the features of ligand interaction as well as metal coordination, which are not fully understood. The binding of metal complexes within certain regions of DNA, may be related to the various ligands attached to the metal. Most promising ruthenium complexes usually contain certain aromatic rings, which are important for anticancer activity [6-10]. The planar aromatic ligand present in the metal complexes may be responsible for stacking interactions with the aromatic molecules present in biological system [4-5]. On the other hand, the complexes may be stabilized through hydrogen bonds to associate with the surrounding amino acids of proteins [11-15]. There are several protein binding metal complexes. The binding features of some complexes are already reported, which may be relevant to the medicinal properties [16-24]. The present study focuses on the amino acid selectivity of these complexes within the binding sites, and subsequently the binding ability of various complexes may be investigated. Hence, the molecular docking procedure used for analyzing the binding of different ruthenium complexes within the active sites of proteins may provide insight into the sequence selectivity of these complexes.

Computational methods are important tools in the process of drug discovery W. L. Jorgensen *et al.* [1]. Starting with a structure of protein, these methods can help to filter number of possible compounds that need to be tested from large compound libraries. With molecular docking protocol, the compounds are positioned in the unoccupied active sites of a target protein. Within the energy-based framework, molecular mechanics (MM) force fields are commonly used, as they are fast to evaluate and the terms involved can be derived easily. Parameters for these terms (charges, well depths, etc.) are included in the force field methods, such as CHARMM or AMBER [6-7]. A better estimate of the electronic interactions can be obtained by using a quantum mechanics/molecular mechanics (QM/MM) hybrid method that refits the ligand's partial charges in a field of static MM charges inside the protein to allow polarization effects from the protein [8-12]. For the QM part, there are many density functional theories (DFT) that provide approximate qualitatively reliable results without imposing crippling computational costs**.** The popular B3LYP functional may be useful for such systems [13-14]. The DFT method is well-known for application to several systems, perhaps the most serious problem is for its inability to account for dispersion interactions. It has been successfully used in hydrogen bonded system [15-18].

2. METHODOLOGY

The Receptor-Ligand docking protocol was used to carry out a molecular docking analysis of few ruthenium complexes with proteins N. Pagano *et al.* [20]. The studies were carried out based on the structures and positions of the complexes within the protein, which was obtained from the available Protein data bank. The docking protocol

implemented in Discovery studio was used to reproduce the position of complex [Ru(A)] inside the protein. Subsequently, the most favored ligand docked proteins was minimized with CHARMm, and the interaction energies, both from the electrostatic and van der Waals energies were calculated. In order to estimate the intermolecular interactions between ruthenium complexes and the amino acid sequences of protein accurately, further calculations were carried out with QM/MM method. Here, the most preferred position of fluorinated ruthenium pyridocarbazole [Ru(A)] within the protein obtained from docking study was selected, and the complex (ligand) was selected as QM region, where the protein (receptor) was taken as MM region. Several hydrogen bonded interactions were included in the calculations. The B3LYP method with the fine basis sets was used for QM region. The dielectric constant for water (80) was taken for solvent medium.

The electrostatic stabilization energies of other protein bonded complexes were also studied with CHARMm Force field method. The most favored docked structures were selected and the minimized completely using CHARMm Force field. The electrostatic and van der Waals stabilization energies were calculated from these structures. The electrostatic and van der Waals stabilization energies are computed from the following equation,

$$\Delta E = E_{COM} - (E_{NU} + E_{PR})$$

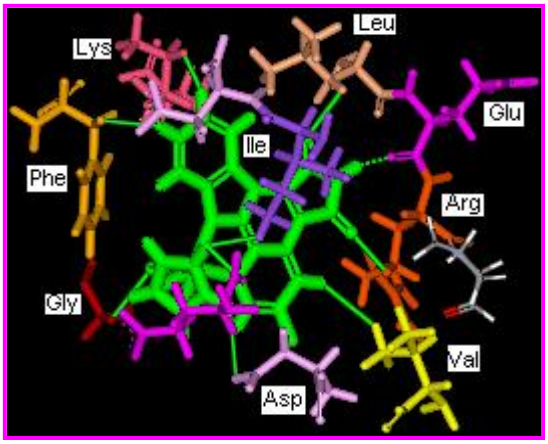
$E_{COM.}$ $E_{NU.}$ and E_{PR} are the corresponding energies of complex-protein, protein and complex. For all energy minimization procedure, the steepest decent technique up to energy convergence of 0.1 kcal/mole was used. Subsequently, the QM/MM calculations were carried out for these ruthenium complexes [RuN(B), RuN(C) and RuN(D)].

3. RESULTS AND DISCUSSION

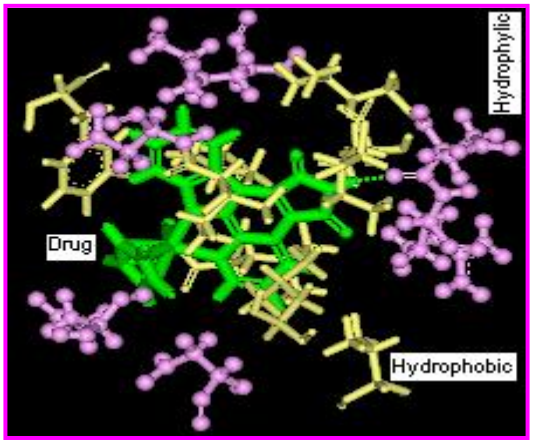
The internal energies of docked complexes within the various active sites are calculated by using Receptor-Ligand docking protocol (Table 1). The molecular docking studies of fluorinated ruthenium pyridocarbazole [Ru(A)] was studied on the basis of the protein bonded structures of this complex collected from crystal structure N. Pagano *et al.* [20]. Initially, the Ru(A) bonded structure within protein has been analyzed, and the features of protein bonding at the active site obtained from the crystal structure can be compared with that of docked structures. Table 1 summarizes the docking scores and corresponding internal energies of Ru(A) at several active sites. Some binding sites gain low scores as well as small internal energies, and the maximum score is expected for the binding site indicated in crystal and more internal energy (-ve) is found compared to other sites. The optimum docked position is found very close to the position of this complex in the crystal structure (Fig. 1). The docking data are based on the displacement of the complex related to the thermodynamically favorable process, since the maximum internal energies (-ve) is considered for the most favored site.

Table 1. Docking scores and internal energies of docked Ru complexes.

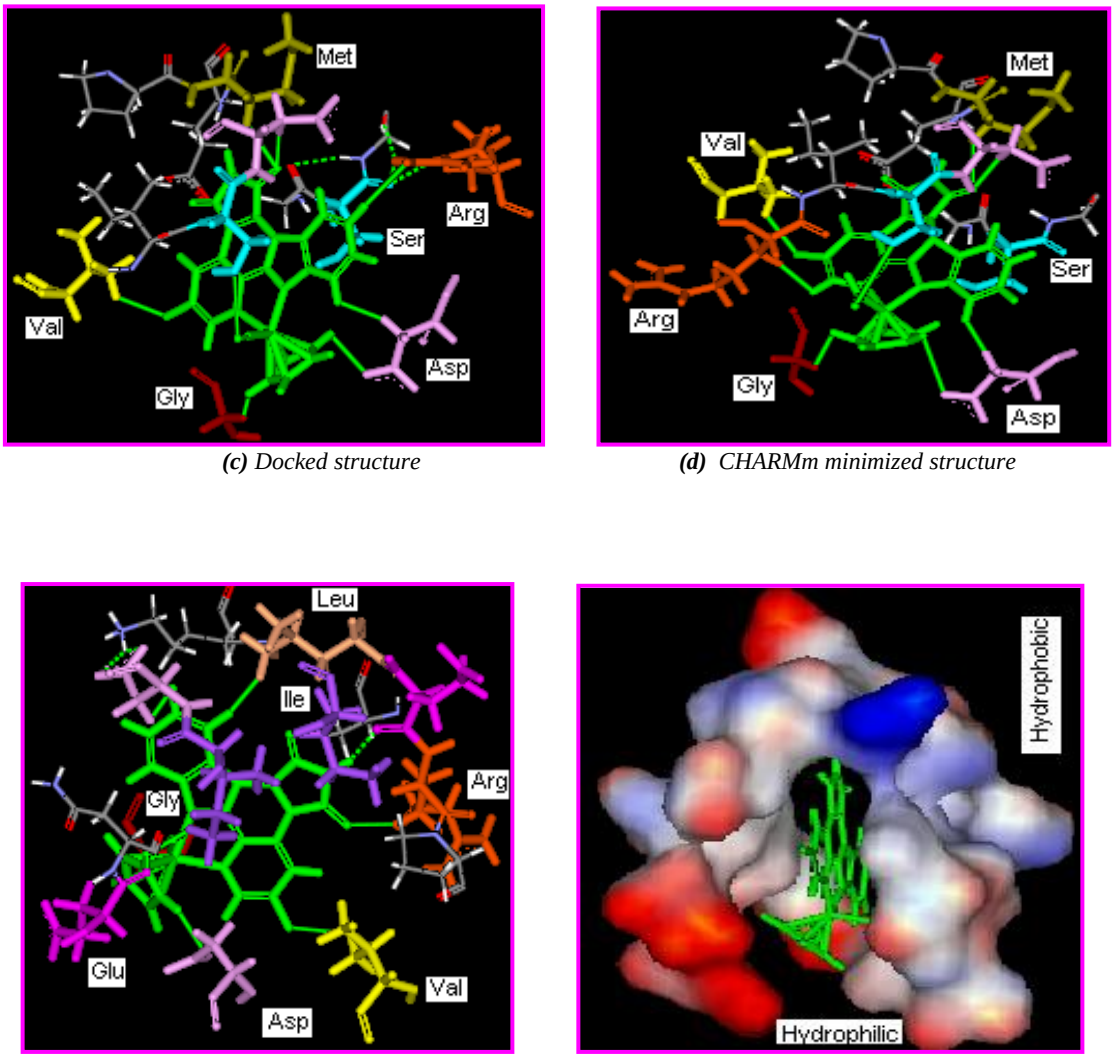
Name of complexes	LigScore1 Dreiding	LigScore2 Dreiding	-PLP1	-PLP2	Dock score	-PMF	Internal energies
Ru(A)	4.02	6.33	119.46	106.79	80.435	-27.98	-7.50
	2.77	4.89	94.82	84.54	56.538	-24.94	-7.51
	2.32	4.14	95.42	84.72	49.404	-26.40	-7.51
	2.29	4.64	92.70	99.52	47.242	-27.23	-7.50
	2.30	4.64	91.11	98.66	46.941	-25.01	-7.51
	1.61	3.42	72.76	74.22	37.607	-12.72	-7.50
RuN(B)	0.54	2.10	56.10	68.09	113.434	-2.49	-9.44
	-0.20	0.81	64.24	64.31	103.617	-1.75	-11.23
	0.37	1.66	63.01	66.4	103.193	-0.83	-6.50
	-0.16	0.61	62.99	63.15	99.389	-2.44	-11.23
	-0.54	0.59	59.10	67.03	93.198	-5.53	-13.15
	-0.65	-1.30	20.93	36.15	91.039	-5.00	-12.10
	0.42	2.24	55.78	67.74	107.691	1.53	-9.44
	0.36	1.60	64.57	66.01	104.912	-2.13	-6.50
	-0.39	0.48	53.93	61.62	90.425	-1.76	-11.23
RuN(C)	1.35	3.81	48.82	41.87	88.151	10.52	-1.74
	1.12	3.24	51.21	42.41	82.549	2.26	-3.59
	1.64	4.00	51.84	46.49	81.697	-1.56	-3.53
	1.37	3.62	52.01	47.91	81.079	2.50	-3.67
	1.05	3.45	28.86	29.03	80.453	-2.16	-1.74
	1.70	4.10	51.79	42.23	78.208	7.81	-3.18
	1.84	3.47	36.67	38.07	26.862	44.09	-3.38
	1.78	3.81	35.27	38.46	26.347	47.04	-3.28
	1.89	3.51	28.85	32.90	24.657	40.58	-3.37
	1.59	3.65	33.94	37.35	23.366	43.91	-1.99
RuN(D)	2.20	2.39	29.10	32.55	13.681	-18.89	5.43
	0.46	2.08	10.77	16.33	7.797	-12.53	7.14
	0.79	2.91	17.88	17.34	1.948	2.80	2.21



(a) *Crystal structure of Ru(A)*



(b) *Hydrophobic and hydrophilic residues*



(c) *Docked structure* ***(d)*** *CHARMm minimized structure*

(e) *QM/MM minimized structure* ***(f)*** *Hydrophobic and hydrophilic regions*

Figure 1. Different binding sites for Ru(A) complex with the nearest amino acid residues.

Similar docking studies have been carried out for the other synthesized complexes (RuN(B), RuN(C) and RuN(D)). On the average, the difference of internal energies from the least bonded active sites to strongest active sites complex is 0.03 kcal/mole (Table 1). The displacement of Ru(A) from its position shown in crystal structure is clearly indicated in Fig. 1. In order to probe the stabilization of Ru(A) within the predicted sites of protein accurately, the QM/MM studies were carried out. The chosen functional (DFT) may be useful to estimate the strength of the intermolecular interactions through hydrogen bonding as well as dipole-dipole interactions of Ru(A) within the binding sites. In this study, full optimization of the Ru(A)-protein was carried out with QM/MM calculation. Table 3 shows the interaction energies for QM and MM regions. As detected from the docked structure of the complex, and the interaction of the Ru(A) complex with certain amino acids are found prominent (Fig. 1). The hydrogen bond distances and the feature of Ru(A) towards the interaction sites (only for close contacts) are shown in Table 4. The minimized docked structure of Ru(A) with CHARMm is shown in Fig. 1. The changes of electrostatic and van der Waals interaction energies are also tabulated in Table 2. Similar studies have been carried out for the newly synthesized complexes, RuN(B), RuN(C) and RuN(D), and the results are examined to understand the favorable interactions of these ruthenium complexes within amino acid sequences.

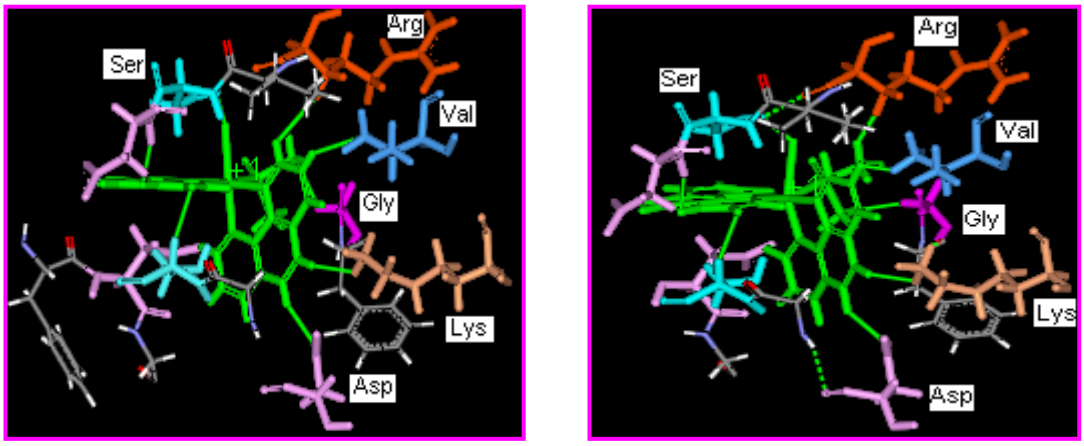
The QM/MM calculations for the structures predicted by docking studies were carried out. In certain cases, the orientations of the docked complexes within protein predicted by docking studies are somewhat compliment to QM/MM calculations, since interaction energies (-ve) are large. The orientation of Ru(A) is slightly different from that of crystal structure (Fig. 1). Similarly, the docked and QM/MM minimized structures of other Ru complexes are shown in Figs. 2, 3 and 4. The electrostatic and van der Waals interactions energies and the QM/MM energies are shown in Table 3.

Table 2. The van der Waals and electrostatic interaction energies along with RMS gradient of the complexes are obtained from CHARMm minimization.

Name of complexes	ΔE (kcal/mol)		RMS gradient (kcal/mol× Angstrom)
	Van der waals energies	Electrostatic energies	
1.Ru(A)	-33.57	-40.43	0.585
2.RuN(B)	-20.984	-5.43	0.589
3.RuN(C)	-16.821	-8.26	0.598
4.RuN(D)	-7.651	-5.31	0.594

Table 3. The van der Waals, electrostatic energies and interaction energies of the complexes are obtained from QM/MM minimization.

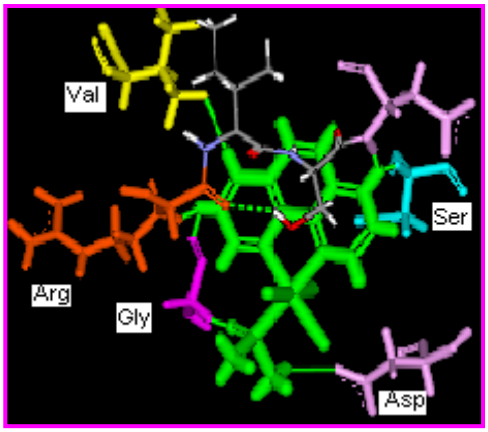
Name of complexes	Electrostatic interaction energies (kcal/mol)	Van der Waals interaction energies (kcal/mol)	Interaction energies (kcal/mol)
1.Ru(A) (crystal)	-92.294	-35.584	-127.88
2. Ru(A) (docked)	-37.99	-32.01	-70.30
3. RuN(B)	-64.84	-28.54	-93.38
4. RuN(C)	-61.20	-17.39	-76.95
5. RuN(D)	-63.62	-11.82	-75.44



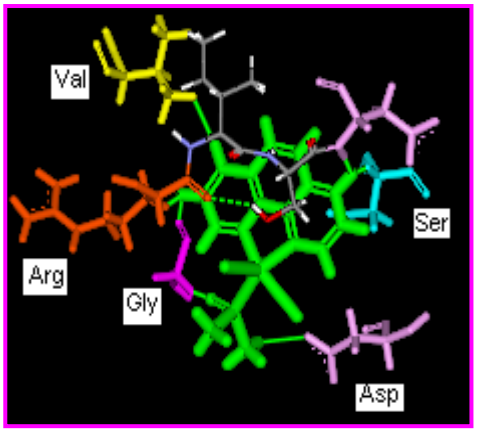
(a) *Docked structure* ***(b)*** *CHARMm minimized*

(c) *QM/MM minimized structure* ***(d)*** *Hydrophobic and hydrophilic regions*

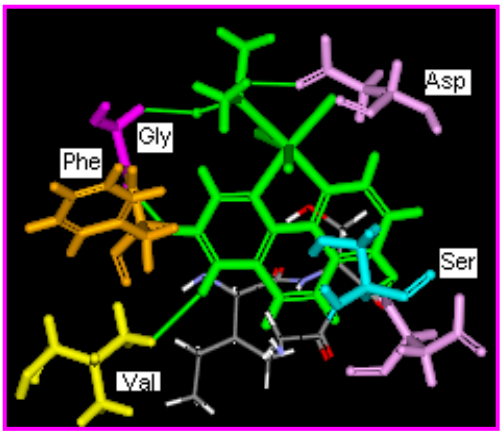
Figure 2. Different binding sites for RuN(B) complex with the nearest amino acid residues.



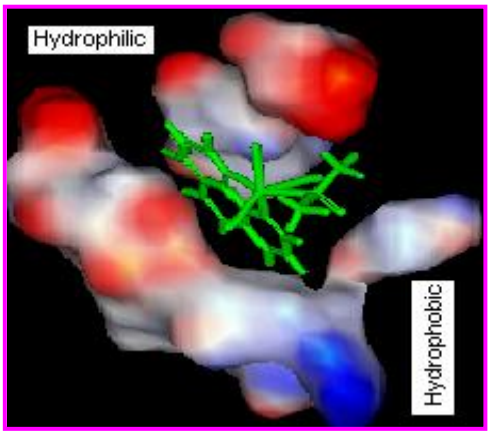
(a) *Docked structure*



(b) *CHARMm minimized structure*

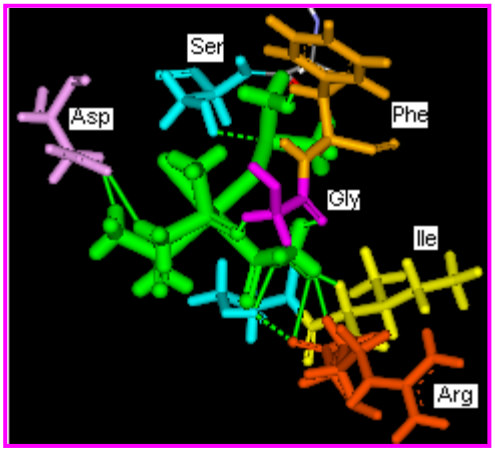


(c) *QM/MM minimized structure*

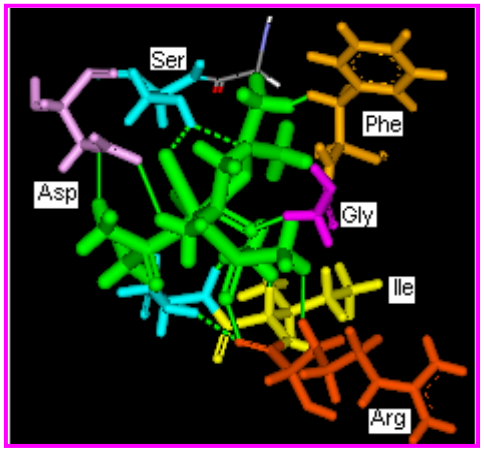


(d) *Hydrophobic and hydrophilic regions*

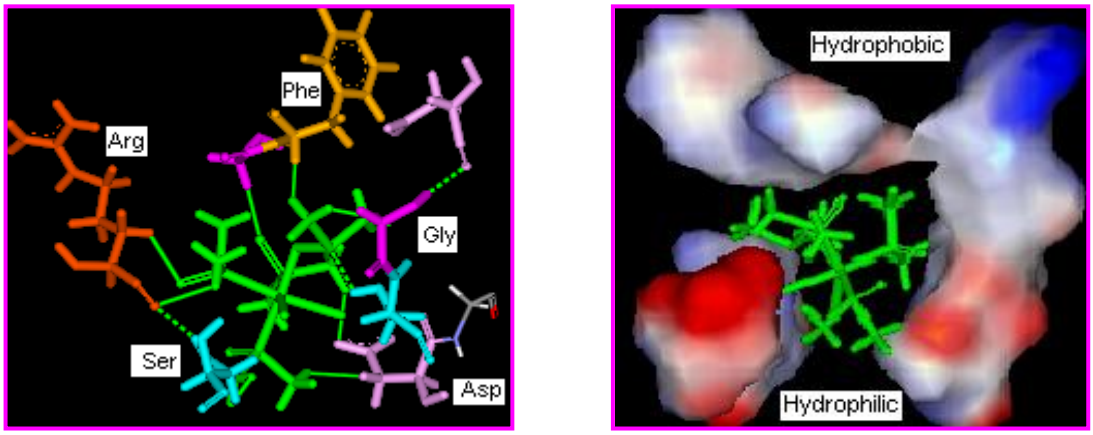
Figure. 3. Different binding sites for RuN(C) complex with the nearest amino acid residues.



(a) *Docked structure*



(b) *CHARMm minimized structure*



(c) *QM/MM minimized structure* ***(d)*** *Hydrophobic and hydrophilic cavity*

Figure 4. Different binding sites for RuN(D) complex with the nearest amino acid residues.

The interactions of other complexes with the surrounding amino acids can be monitored to tract the selectivity of certain amino acids located in close vicinity along the protein chain. The observed cluster of amino acids around the Ru(A) complex can be visualized in Figure 1. It consists of several amino acids within certain region in the helical turns of protein, which are not exactly similar to the other ruthenium complexes (Fig. 2, 3 and 4). As we can see, in Fig. 1, the Ru(A) is stabilized with the combination of amino acid residues, Gly, Asp, Ser, Val, Arg, Ile, Pro and Met, in the ratio of 3:2:2:1:1:1:1:1:1. One can further look insight into the formation of any non covalent interactions with these amino acids. The closest distances measured between amino acid residues and Ru(A) complex as depicted in Figure 1 are shown in Table 4. The respective amino acids combinations of RuN(B), are also shown in Table 5, and Figure 2 indicates the amino acid residues Gly, Asp, Ser, Val, Arg, Ile, Phe and Lys in the ratio of 3:3:2:1:1:1:1:1:1. Similarly, for RuN(C) and RuN(D) the amino acids combinations are shown in Tables 6 and **7**,

Table 4. Interaction distances (Å) of Ru(A) complex with the nearest amino acid residues.

In Docked structure		In CHARMm minimized structure		In QM/MM minimized structure	
Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)
F(RC)-H(Val)	2.34	F(RC)-H(Val)	2.42	F(RC)-H(Val)	2.62
H(RC)-O(Asp)	2.43	H(RC)-O(Asp)	3.46	H(RC)-O(Asp)	2.23
H(RC)-H(Asp)	2.91	H(RC)-H(Asp)	2.60	H(RC)-H(Asp)	2.49
O(RC)- H(Asp)	2.45	O(RC)- H(Asp)	2.37	H(RC)- H(Leu)	2.02
H(RC)-H(Arg)	2.69	H(RC)-H(Arg)	2.56	O(RC)-H(Arg)	2.32
O(RC)-O(Ser)	2.97	O(RC)-O(Ser)	3.47	O(RC)-N(Gly)	2.82
H(RC)-H(Ser)	2.37	H(RC)-H(Ser)	2.38	H(RC)-O(Glu)	2.26
O(RC)-H(Met)	2.38	O(RC)-H(Met)	2.52	H(RC)-O(Glu)	1.86
H(RC)-H(Gly)	2.32	H(RC)-H(Gly)	2.62	O(RC)-H(Ile)	2.50
				H(RC)-H(Ile)	2.70

Table 5. Interaction distances (Å) of RuN(B) complex with the nearest amino acid residues.

In Docked structure		In CHARMm minimized structure		In QM/MM minimized structure	
Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)
H(RC)-O(Asp)	1.91	H(RC)-O(Asp)	2.26	H(RC)-O(Asp)	2.32
H(RC)-O(Asp)	2.15	H(RC)-O(Asp)	2.28	H(RC)-O(Asp)	2.45
H(RC)-H(Asp)	2.05	H(RC)-H(Asp)	1.98	H(RC)-H(Asp)	2.13
H(RC)-H(Ser)	2.49	H(RC)-H(Ser)	2.67	H(RC)-H(Ser)	2.43
Cl(RC)-H(Ser)	2.52	H(RC)-H(Ser)	2.98	H(RC)-H(Ser)	3.12
H(RC)-H(Val)	2.60	H(RC)-H(Val)	2.38	H(RC)-H(Val)	2.39
H(RC)-H(Gly)	2.28	H(RC)-H(Gly)	2.03	H(RC)-H(Gly)	2.22
H(RC)-H(Lys)	2.32	H(RC)-H(Lys)	2.37	H(RC)-H(Phe)	2.65
H(RC)-H(Arg)	2.85	H(RC)-H(Arg)	2.62	H(RC)-O(Arg)	2.80

Table 6. Interaction distances (Å) of RuN(C) complex with the nearest amino acid residues.

In Docked structure		In CHARMm minimized structure		In QM/MM minimized structure	
Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)
O(RC)-H(Gly)	2.39	O(RC)-H(Gly)	2.39	O(RC)-H(Gly)	2.28
H(RC)-O(Gly)	2.40	H(RC)-O(Gly)	2.34	H(RC)-O(Gly)	2.30
H(RC)-H(Val)	2.38	H(RC)-H(Val)	2.28	H(RC)-H(Val)	2.84
H(RC)-H(Arg))	2.25	H(RC)-H(Arg))	2.30	H(RC)-H(Phe)	2.68
H(RC)-O(Asp)	2.32	H(RC)-O(Asp)	2.38	H(RC)-O(Asp)	2.26
H(RC)-H(Asp)	2.60	H(RC)-H(Asp)	2.58	H(RC)-H(Asp)	2.02
H(RC)-H(Ser)	2.02	H(RC)-H(Ser)	2.04	H(RC)-H(Ser)	2.67

Table 7. Interaction distances (Å) of RuN(D) complex with the nearest amino acid residues.

In Docked structure		In CHARMm minimized structure		In QM/MM minimized structure	
Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)	Interacting atoms	Distances(Å)
O(RC)-H(Gly)	1.99	O(RC)-H(Gly)	2.66	O(RC)-H(Gly)	2.35
H(RC)-O(Asp)	2.33	H(RC)-O(Asp)	2.35	H(RC)-H(Gly)	2.12
H(RC)-H(Asp)	2.00	H(RC)-H(Asp)	2.13	H(RC)-O(Asp)	2.39
H(RC)-H(Ser)	2.20	H(RC)-H(Ser)	2.12	H(RC)-H(Asp)	2.28
H(RC)-H(Ser)	2.07	H(RC)-H(Ser)	2.22	H(RC)-H(Ser)	2.54
H(RC)-H(Arg))	1.84	H(RC)-H(Arg))	2.02	H(RC)-H(Ser)	2.11
H(RC)-O(Arg)	2.53	H(RC)-O(Arg)	2.66	H(RC)-H(Arg)	2.19
H(RC)-H(Ile)	1.88	H(RC)-H(Ile)	1.94	H(RC)-O(Arg)	2.49
H(RC)-H(Phe)	1.86	H(RC)-H(Phe)	1.96	H(RC)-H(Phe)	1.97

and Figs. 3 and 4 show the presence of the amino acid residues, Gly, Asp, Ser, Val, Arg and Ile around RuN(C) in the ratio 2:2:2:1:1:1. Figure 4 shows for RuN(D) with Gly, Asp, Ser, Arg, Ile and Phe in the ratio of 2:1:2:1:1:1 respectively.

At the most, the folding and unfolding of proteins is also likely to be a secondary process that may occur due to complex and protein interactions. Here, several mechanisms cannot be studied simultaneously, since the structure of Ru(A) under study is collected from the crystal structure. The differences in the amino acid sequence selectivity as well as the interaction distances of amino acids and Ru complexes usually give certain information of the protein interactions with these complexes. Another distinguishable characteristic of complex and protein interactions can be inferred from the location of the complex between alpha and beta helical protein chains (Fig. 1). In all cases, it has been seen that the binding of the complex is contributed from both the two protein strands. It might be due to the specificity of the complexes for some amino acids present within the binding sites, which is again involved from both the protein chains. The other possibility is the selectivity of the hydrophobic regions located at the adjoint of the two α and β protein chains (Figs. 1-4). On the other hand, the binding of complex with a particular protein chain might usually induce conformation of the other protein chain, and thereby strengthen the double helical alpha and beta protein chains. There may be other reasonable explanation of the feature of complex binding within protein as a result of the interactions with basic or acidic sites of proteins. The distances between the acidic or basic site of protein and the complementary sites of the complex that can interact through hydrogen bonds are shown in Table 4. Apparently, the formation of hydrogen bonds with these sites may be one of the factors for the stabilization of the complexes within the protein.

The molecular structures predicted by docking studies of Ru(A) are shown in Fig.1, where the combinations of amino acids as well as the positions of drug inside the vicinity of active sites are clearly shown. The hydrogen bond between hydrogen atom of complex and oxygen of glutamic acid at distances of 1.68 Å is visible, and the other amino acids are not involved in crystal structure. The drug binding active site obtained from the crystal structure has been usually chosen for docking studies, which in fact is predicted as the most favored active site for complex binding. The docking scores obtained from various scoring functions are shown in Table 1, where the active site obtained from the crystal structure is found the best position for drug binding. However, the hydrogen bonds and the position of Ru(A) at this site is not exactly similar to that of crystal structure (Fig. 1). The hydrogen bond between hydrogen atom of complex and oxygen atom of glutamic acid occur at a distance of 1.86 Å, and the interaction energies of docked and crystal structures are found – 70.30 kcal/mole and -127.88 kcal/mole respectively (Table 3).

The drug bonded structure results considerable change after minimization, and the hydrogen bonds formed in the structure is shown in Fig. 1 and Table 4. The existence of these non bonded weak interactions in both the crystal and minimized structures depend on the location of hydrogen bonding sites of the complex towards the amino acids. It is obvious that the crystal structure cannot be exactly equal to the theoretically predicted structures because of the participations of many other parameters. However, it has been found that the drug occupy at the same cavity as in the crystal structure (Fig. 1). As expected the interaction energies, electrostatic and van der Waals energies of these structures vary significantly, which depend on the type and hydrogen bond strength of Ru(A) within the regions. Similarly, the structures of other complexes predicted by docking studies, and the corresponding minimized structures are shown in Figs. 2, 3 and 6.4. Tables 2 and 3 show the differences of interaction energies, electrostatic and van der Waals energies. The results may be useful for comparing protein binding ability of these complexes.

The intermolecular hydrogen bonds between the amino acids of protein and complex contribute to the stabilization of these complexes inside the cavity. The stability can be predicted from the interaction energies that may be contributed partially from the hydrogen bonds and donor-acceptor interactions. In order to take into account these

interactions, QM/MM calculations on the docked structures were carried out. In some cases, the hydrogen bonding directions are different from that of MM studies, which can be visualized from the QM/MM optimized structures. The hydrogen bonds formed between complexes and proteins are shown in Tables 4-7. Significant variation of hydrogen bond lengths and the interaction energies are found. The shortening of certain hydrogen bond lengths after QM/MM optimization of the MM minimized structures are found (Table 4). So, the pattern of hydrogen bonding with amino acids may be related to the difference of interaction energies of these Ru complexes.

It should be noted that the hydrophobic and hydrophilic regions are present inside the cavity of binding sites. The hydrophilic regions usually occur within the hydrogen bonding region and the hydrophobic amino acid chain falls within certain sequences (Fig.1 and Table 4). The contributions of hydrophobic and hydrophilic interactions to the stabilization of these complexes are given in Table 3. The Ru(A) is found covered by hydrophilic chain of amino acids, Lys, Glu, Asp and Arg, and the amino acids, Ile, Leu, Val, Phe and Ala are found within the hydrophobic region. It has been found that significant differences of the energy terms due hydrophilic and hydrophobic stabilization of these complexes are shown in Table 3. So the stabilization of these complexes may be assessed from the hydrophobic and hydrophilic interactions inside the protein cavity.

4. CONCLUSION

The binding energies of ruthenium complexes are significantly different. The docking studies are useful for locating the most favored site for binding of RuN(B), RuN(C) and RuN(D) complexes in protein. These complexes preferably bind within the region where Ru(A) is found in crystal structure. The binding energies of these ruthenium complexes are -70.30 kcal/mol, -93.38 kcal/mol, -76.95 kcal/mol and -75.44 kcal/mol respectively. The recognition of certain amino acid combination by these complexes has been found. The formation of hydrogen bonds among the amino acids and Ru complexes are distinct.

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6. REFERENCES

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