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The DNA binding features of ruthenium complexes compared with cisplatin : docking, force field and QM/MM studies

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Abstract

The binding of cisplatin with DNA is considered as one of the factors for acquiring anticancer activity. Some ruthenium complexes are also known for their anticancer activity. The DNA binding features of cis-chlorodimethylsulphoxide-S-bis (1,10-phenanthroline) ruthenium (II) chloride, trichlorodimethyl sulphoxide-S-(1,10-phenanthroline) ruthenium (III) and cis-dichlorotetrakis (dimethylsulphoxide) ruthenium (II)complexes within cisplatin bonded region of DNA are studied with molecular docking, MM and QM/MM studies. The DNA binding ability of cis-chlorodimethylsulphoxide-S-bis (1,10-henanthroline) ruthenium (II) chloride is similar to that of cisplatin, but other two ruthenium complexes bind less effectively. These complexes bind selectively within the cisplatin occupied region of DNA.

Keywords : Ab initio, DNA, Cisplatin, Ruthenium, DNA binding features.

1. Introduction

The binding of clinically important drugs with DNA through covalent or non covalent bond is the major factor for acquiring biological activity (Peng Z, Jie C, Yi Liang *et al.,* 2010. Acta Biochim Biophys Sin., 42 : 440-4491). It is essential to elucidate the mechanism of drug action as well as drug recognition for certain sequences of DNA. It may be an important basis in the development of new cancer drugs. The drug may bind within the major or minor groove of DNA through covalent or non covalent bond, and some of them intercalate within the sequences (Eric. D S, James M. B, Stephen B. H *et al.,* 1999, Molecular Pharmacology, 56, 633-643; Michael E B, Ulrich B, Rebecca W A *et al.,* 2005, Biochemistry, 44 : 11262-11268; Kuo L.Y, Kanatzidis M G, Sabat M, Tipton A L, Marks T J *et al.,* 1991, J. Am. Chem. Soc., 113 : 9027-9045; Japeck T, 2006, Langmuir, 22 : 4699-4709). Certain drugs may be highly sequence specific, and others may not produce sequence specificity in DNA binding. At the molecular level, the contribution of covalent, hydrogen bonding, electrostatic and vander Waals interactions in drug-DNA binding may be analyzed (Japeck T, 2006, Langmuir, 22 : 4699-4709; Philip W, Veronica G, Martin R G, Harry A, Anthony J H M M, Mike P W, James A T *et al.,* 2010, Chem. E J, 16 : 2407-2417; Fehmida F, Fazlul H, Jun Q Y, Philip B, *et al.,* 2009, J. Biol. Inorg. Chem., 14 : 175-184.). Cisplatin is a very important metal complex, and the recent emerging metal complexes are not superior in biological activity than this drug (Michele B, Jaroslav M, Jana K, Viktor B, Giovanni N, *et al.,* 2002, Metals Toxicity, 110 : 779-782; Diana C F M, Roger M. P, Benjamin D C, Jake F, Charlotte E. W, *et al.,* 2012, Dalton Trans., 41 : 3720-3725). Similarly, the DNA binding of several new complexes may be looked

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to analyze the relevant biological activity of the complexes. The strong anionic behavior along the phosphate chain can also contribute effective binding of drug within DNA. So, it is rather important to analyze the importance of various interactions and energies in the overall binding of complexes. There are many reports on the drug and DNA interactions, and the requirement of theoretical studies for analyzing at the molecular level has also been known. The QM/MM studies may be taken as reliable technique for such large molecules than the MM computational studies to understand the structural features and contacts, and also to estimate the extent of interactions between drug and component of DNA (Mark D T, David M W, Holmes R J, Denny W A, Murray V, *et al.,* 2000, Biochemistry, 39: 5593-5599; Mutter S T, Platts J A, 2011, J. Phys. Chem., *et al.,* 115 : 11293-11302; Christian G, Ivano T, Ursula R, *et al.,* 2008, J. Am. Chem. Soc. 130 : 10921-10928; Antonella C, Samuel G, *et al.,* 2011, J. Comput. Aided Mol. Des., 25 : 729-742).The interest on platinum complexes in medicine and coordination chemistry has been increasing since the discovery of cisplatin (Antonella C, Samuel G, *et al.,* 2011, J. Comput. Aided Mol. Des., 25 : 729-742). The binding of these metal complexes is another area of investigation for assessing the anticancer activities. Moreover, structural characterization of complexes within the binding sites with respect to the ligands attached to the metal complexes may give a comprehensive and detailed report on the biological/anticancer properties of these complexes (Fehmida F, Fazlul H, Jun Q Y, Philip B, *et al.,* 2009, J. Biol. Inorg. Chem., 14 : 175-184; Loeher P J, Einhorn L H, *et al.,* 1984, Ann. Intern. Med., 100, 704-713). Most of the potential anticancer complexes of platinum contain various types of ligands, and the activities of these compounds largely depend on the property of the attached ligands (Fatma G, Gokcen E, Leyla A, Ayten C, Fatma O, Sukran Y, Rahsan I S, Sibel G, Aykut O, A E, Yalcin E, *et al.,* 2009, J. Med. Chem., 52:1345-1357; Malina J, Hofr C, Maresca L, Natile G, Brabec V, *et al.,* 2000, J. Bio.Phys., 78:2008-2021; Irena K, 2006, Recent Patents on Anti-Cancer Drug Discovery, 1 : 1-22). In that case, the binding mode of complexes as a whole may be analyzed to know the DNA sequence specificity of complexes (Wang F, Bella J, Parkinson J A, Sadler P J *et al.* 2005, J. Biol. Inorg. Chem., 10:147-155; Chen H, Parkinson J A, Morris R E, Sadler P J *et al.*, 2003, J. Am. Chem. Soc., 125:173-186; Wang F, Xu J, Habtemariam A, Bella J, Sadler P J *et al.,* 2005, J. Am. Chem. Soc., 127, 17734-17743). There are other few platinum complexes, but the study will focus on cisplatin for comparison with Ru complexes. The structure of cisplatin bonded DNA is further analyzed to examine the nature of DNA binding as well as the stabilization within DNA. The coordination ability of Pt with guanine nucleobases of DNA present in the binding region is very important (Wang F., Xu J., Habtemariam A., Bella J. *et al.,* Sadler P. J., 2005, J. Am. Chem. Soc., 127: 17734-17743; Zhao G., Lin H., 2005, Curr. Med. Chem. Anticancer Agents, 5: 137-147; Adnan S, Abu-Surrah, Mika K *et al.,* 2006, Current Medicinal Chemistry, 13 : 1337-1357; Sudeshna R, Katharine D.H, Dr. Palanisamy U M, Dr.Martin L, Prof. A L. Spek, Prof. Jan R, Dr. Gilles P. van W *et al.,* 2008, chem. med. chem., 3:1427-1434). Several components of interactions can be analyzed to elucidate binding ability of cisplatin. As a whole, it may be useful for differentiating the sequence selective binding of DNA by cisplatin from the other ruthenium complexes.

2. Methodology

Two different methods have been chosen in the present study. The MM and QM/MM calculations have been used to calculate the drug interactions with DNA. In the MM calculation, the CHARMm protocol was used, and the QM/MM studies were carried out with discovery studio, where the QM region is calculated with quantum mechanical program package (Dmole). The stabilization energies of cisplatin were determined for both the regions. The differences in the DNA binding of Ru complexes from that of cisplatin can be studied, which is essential for distinguishing cisplatin and Ru complexes. The coordination of Pt is the major basis in DNA binding of cisplatin, whereas the contribution of additional ligand is possible for Ru complexes. In order to understand the binding of these complexes, the molecular docking studies within

DNA were performed. The complexes were docked within DNA, and the binding energies were computed with QM/MM calculations. Initially, docking studies were carried out for cisplatin within DNA, and the most favorable structure was selected from the minimum internal energy and highest score. The structures were reoptimized with QM/MM calculations.

QM/MM and MM calculations were performed with CHARMm programme. In the MM calculation, the CHARMm force field with dielectric constant C = 80 (for water environment) was used. The steepest descent minimization algorithm was chosen for energy minimization. The CDocker protocol implemented in CHARMm package was used for docking studies. The cisplatin bonded DNA is obtained from the crystal structure (Patricia M T, Amy C. R, Christin A. F, Stephen J L *et al.,* 1995, Nature, 377, 649-652). In the QM/MM calculations, the QM region is calculated with DFT method by using coarse, medium and fine basis sets. The MM minimization steps were chosen as 1000. The close contacts were considered within the distance <3 Å, and hydrogen bonds contacts were taken within the distance ~2.5 Å, where the contacts within the distance >3.5 Å were also analyzed as van der Waals contacts. The charge neutralization of the phosphate group of DNA was performed by adding H atom at the anionic oxygen atoms. The docking studies were analyzed based on the flexibility of the complex within the active sites, whereas all the atoms of DNA were kept fixed.

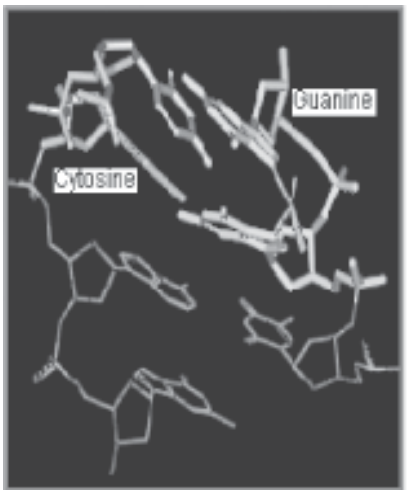
Interaction energy = $E_{Complex} - E_{Ru} - E_{DNA}$

$E_{Complex}$, E_{Ru} and E_{DNA} are the energies of the drug-DNA, drug and DNA of the structures obtained from different methods and minimization.

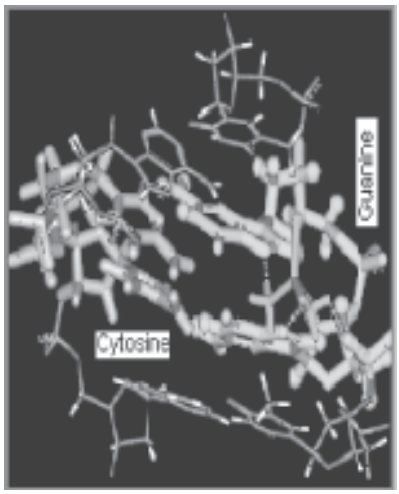
3. Results and Discussions

The DNA binding ability of cisplatin as indicated in the crystal structure depend on the covalent bond formation within two guanine nucleobases (Fig.1a). However, subsequent studies may be taken up how the ruthenium metal complexes occupy this region to form a stable complex. So, we have carried out docking studies of these ruthenium complexes within the cisplatin bonded region of DNA, and comparison has been made with the docked structure of cisplatin. The optimized geometry of the cisplatin was initially docked within the binding region shown in the crystal structure, and the docking scores are analyzed from various scoring functions (Table 1). The highest score and the lowest internal energies (-ve) obtained from the docking studies are given in Table 1 and the corresponding structure is shown in Fig. 1.

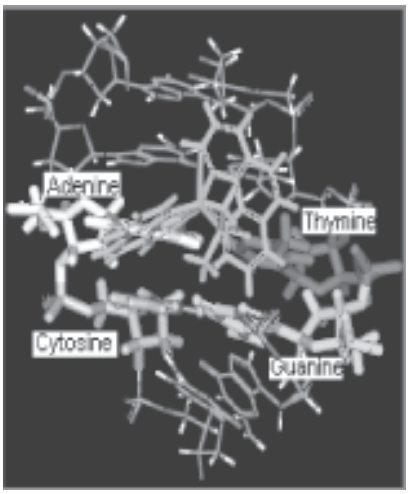
It should be noted that the covalent bonding ability cannot be studied in the docking studies, and the binding of cisplatin as a whole within this region can be understood from the internal energy. However, certain intermolecular interactions of cisplatin within the binding region can be explored by minimizing the structure with CHARMm (Fig.1).



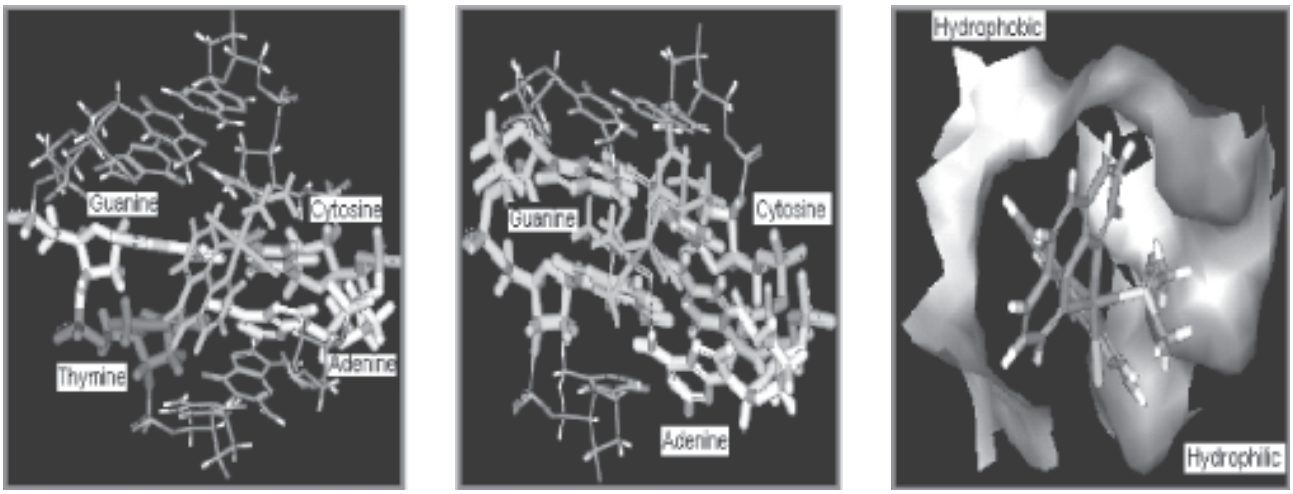
1 (a) Crystal cisplatin



1 (b) Docked cisplatin

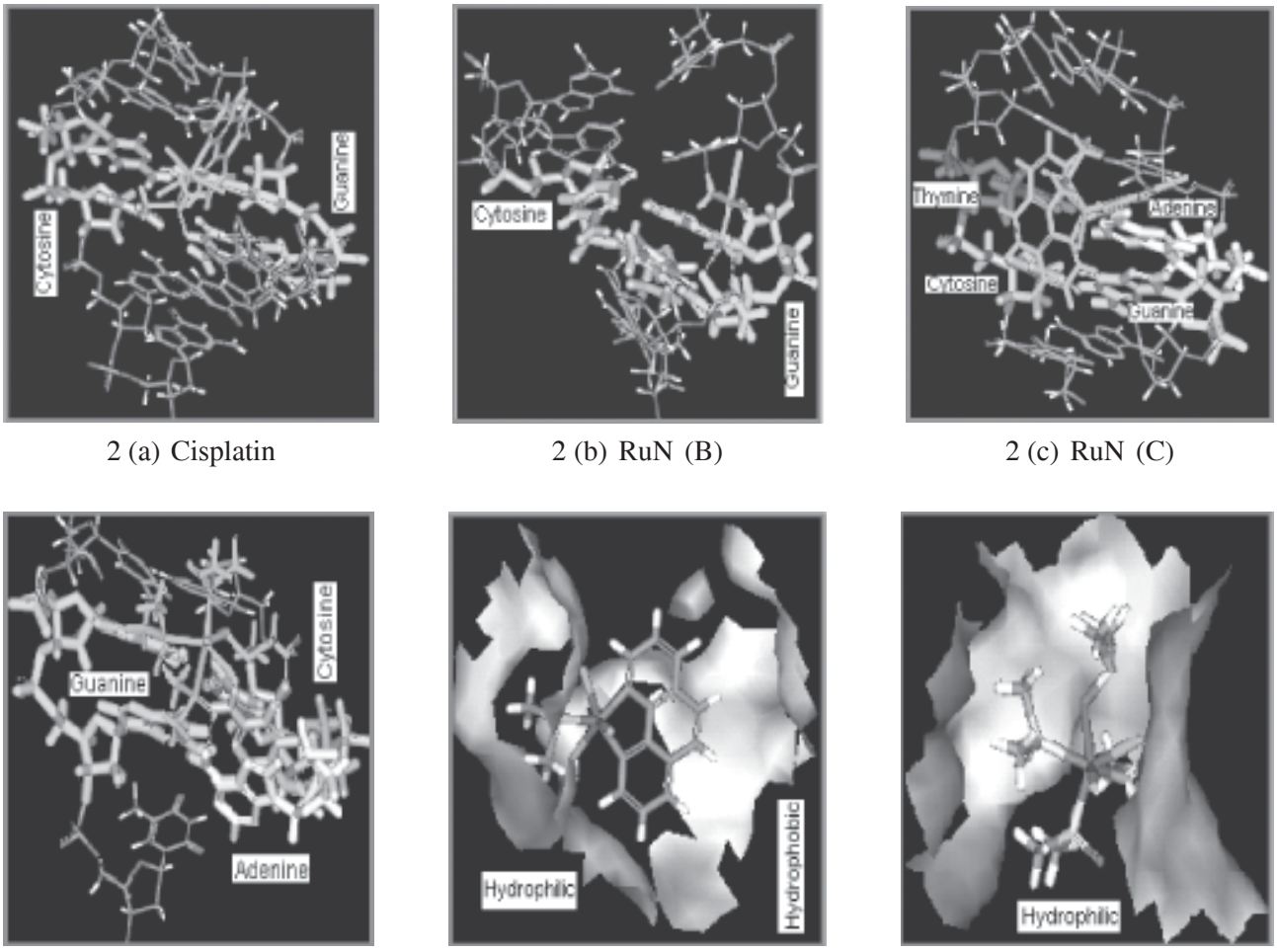


1 (c) RuN (B)



1 (d) RuN (C) 1 (e) RuN (D) 1 (f) RuN (B)

Fig. 1 : CHARMm minimized structures of cisplatin and synthesized Ru complexes, **(f)** is the hydrophobic (blue) and hydrophilic regions (red) of docked RuN (B) within DNA.



2 (a) Cisplatin 2 (b) RuN (B) 2 (c) RuN (C)

2 (d) RuN (D) 2 (e) RuN (C) 2 (f) RuN (D)

Fig. 2 : QM/MM minimized structure of cisplatin and synthesized Ru complexes, **(e)** and **(f)** are the hydrophobic (blue) and hydrophilic regions (red) of docked RuN (C) and RuN (D) within DNA.

Table - 1 : CDocker energies and interaction energies for the Ru complexes along with docked cisplatin

Cisplatin		RuN (B)		RuN (C)		RuN (D)	
Cdocker energies	Cdocker interaction	Cdocker energies	Cdocker interaction	Cdocker energies	Cdocker interaction	Cdocker energies	Cdocker interactio
-430.028	42.888	-270.188	1.926	-176.541	1.860	-213.078	1.756
-402.780	42.510	-270.234	1.708	-176.511	1.775	-213.643	1.693
-402.099	42.562	-270.422	1.853	-176.473	1.454	-213.089	1.689
-401.943	42.522	-270.542	1.655	-176.362	1.851	-213.758	1.623
-401.281	42.339	-270.735	1.384	-176.178	1.716	-213.390	1.610
-401.207	42.658	-270.815	1.501	-175.985	1.865	-213.464	1.370
-400.976	41.925	-270.870	1.128	-175.723	1.889	-213.703	1.235
-400.759	42.541	-270.927	1.195	-175.878	1.764	-213.692	1.209
-400.737	42.648	-270.931	1.075	-176.098	1.653	-214.546	0.612
-400.682	42.551	-270.976	1.257	-177.010	1.667	-214.451	0.556
-400.400	42.666	-271.041	0.942	-176.216	1.603	-214.422	0.351
-400.284	42.566	-271.123	1.091	-176.036	1.405	-214.314	0.498
-400.275	42.605	-271.232	0.866	-177.156	1.249	-214.313	0.507
-400.229	42.562	-271.275	0.871	-177.177	1.213	-214.157	0.801
-400.193	42.639	-271.379	0.887	-176.701	1.383	-214.088	0.894
-399.988	42.597	-271.405	0.708	-177.017	0.483	-214.048	0.767

Table - 2 : The Van der Waals energies, electrostatic energies (kcal/mol) and RMS gradient of Ru complexes and cisplatin obtained from CHARMm calculations.

Name of Complexes	ΔE (mcal/mol)		RMS gradient (kcal/mol × Angstrom)
	Van der Waals energies	Electrostatic energies	
1. Cisplatin	-6.221	059.656	2.223
2. RuN (B)	-18.084	-6.592	3.672
3. RuN (C)	-28.191	-2.826	2.340
4. RuN (D)	-27.031	-4.793	2.376

Where RuN (B), RuN (C) and RuN (D) are cis-chlorodimethylsulphoxide-S-bis (1, 10-phenanthroline) ruthenium (II) chloride, trichlorodimethylsulphoxide-S-(1, 10-phenanthroline) ruthenium (III) and cis-dichloro tetrakis (dimethylsulphoxide) ruthenium (II) complexes with cisplatin bonded DNA having sequence CCTCTGGTCTCC respectively. RuN donotes newly synthesized complexes.

Table - 3 : The van der Waals and electrostatic interaction energies (kcal/mol) for Ru complexes and cisplatin obtained from QM/MM calculations

Name of complexes	Basis Sets	QM/MM Electrostatic interaction energies (kcal/mol)		QM/MM Vander Waals interaction energies (kcal/mol)		QM/MM interaction energies (kcal/mol)	
		BLYP	PBE	BLYP	PBE	BLYP	PBE
1. Crystal cisplatin	Coarse	-7.14	-7.21	-1.07	-1.07	-8.22	-8.28
	Medium	-7.73	-7.73	-1.07	-1.07	-8.81	-8.80
	Fine	-7.96	-7.91	-1.07	-1.07	-9.03	-8.986
1. Docked cisplatin	Coarse	-76.82	-77.29	-2.43	-2.43	-79.24	-79.71
	Medium	-76.69	-76.95	-2.43	-2.43	-79.11	-79.38
	Fine	-78.06	-78.18	-2.43	-2.43	-80.48	-80.61
3. RuN(B)	Coarse	-49.13	-48.23	-23.92	-23.92	-73.05	-72.15
	Medium	-50.57	-49.66	-23.92	-23.92	-74.50	-73.59
	Fine	-51.86	-50.87	-23.92	-23.92	-75.78	-74.79
4. RuN(C)	Coarse	-38.43	-38.23	-21.72	-21.72	-61.86	-61.25
	Medium	-40.27	-39.96	-21.72	-21.72	-63.02	-62.59
	Fine	-41.88	-41.05	-21.72	-21.72	-63.78	-63.09
5. RuN(D)	Coarse	-25.28	-25.10	-16.07	-16.07	-41.35	-41.06
	Medium	-25.33	-25.07	-16.07	-16.07	-41.40	-41.13
	Fine	-26.29	-25.96	-16.07	-16.07	-42.36	-42.03

Table - 4 : Torsion angles (º) of the Ru complexes and cisplatin obtained from CHARMm and QM/MM minimization after docked within DNA of CCTCTGGTCTCC sequence

Sites of DNA	Torsion Angles (º)							
	Cisplatin		RuN (A)		RuN (B)		RuN (C)	
	CHARMm	QM/MM	CHARMm	QM/MM	CHARMm	QM/MM	CHARMm	QM/MM
G6	1.012	-0.096	0.896	0.216	0.833	-0.314	0.858	0.596
G7	-0.574	-0.457	0.940	0.004	1.148	-0.834	0.939	-1.306
C18	178.71	-179.03	178.91	-179.74	179.07	178.79	178.94	178.83
C19	0.541	-0.394	0.443	-0.103	0.438	0.354	0.426	0.685

(Torsion angles for G6, G7, C18 and C19 are -0.230, 0.004, 0.179 and -0.125 respectively of free DNA).
( ) Bracketed values obtained from QM/MM minimization.

Table - 5 : Distances (Å) between the GC and AT base pairs after the Ru complexes and cisplatin docked within the DNA of CCTCTGGTCTCC sequence

Distances (Å)									
DNA		Cisplatin		RuN(A)		RuN(B)		RuN(C) (Å)	
G6-G7	C18-C19	G6-G7	C18-C19	G6-G7	C18-C19	G6-G7	C18-C19	G6-G7	C18-C19
3.598	4.174	4.234	4.798	4.151	4.822	4.170	4.780	4.145	4.800
		(3.573)	(4.841)	(4.073)	(4.701)	(3.790)	(4.067)	(3.622)	(4.627)

Table - 6 : Hydrogen bonding distances (Å) of cisplatin and other Ru complexes with CHARMm and QM/MM minimization after docked within the DNA

Cisplatin (Å)			RuN(D) (Å)		
Interacting atoms	CHARMm	QM/MM	Interacting atoms	CHARMm	QM/MM
(Guanine) N-H(Cisplatin)	1.86		(Adenine)N-H(RuN(D))	2.12	2.28
(Guanine) N-H(Cisplatin)	1.84				
(Phosphate) O-H(Cisplatin)	1.85	2.31, 1.77			

The vander Waals and electrostatic interaction energies are shown in **Table 2.** Similarly, docking studies were carried out for the ruthenium complexes. The interaction energies of Ru complexes are found significantly less from that of cisplatin **Tables 2** and **3** show the hydrogen bonds and other close contacts of donor-receptor sites that contribute to the stabilization of these complexes.

Perhaps the area where the complexes occupy should be well characterized to quantify its impact on the binding sites accurately. So, we focus on the computation of the interaction energies with QM/MM method rather than MM method. In this study the interaction energies (electrostatic and van der Waals) of cisplatin and other ruthenium complexes are computed **(Table 3)**, but the values (-ve) are not more than that of cisplatin. The binding region and the interaction sites are shown in **Fig. 2,** which may be relevant to the DNA binding ability as well as anticancer properties of these complexes.

The analysis of close contacts, between complex and DNA were performed for the minimized structures of QM/MM, MM and the crystal structure. In order to differentiate the interaction of cisplatin from the Ru complexes, the close contacts were analyzed from the most favored docked structures of cisplatin and ruthenium complexes. As we know that cisplatin forms intra-strand covalent binding with two guanine nucleobases after dissociation of two chlorine atoms, but this model study does not incorporate the covalent binding for comparison with ruthenium complexes, since the exact covalent bond characteristics are not known for 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)]. The docked structures within the cisplatin bonded region are taken for QM/MM studies and the respective energies are given in **Table 3.** It is important to understand the characteristics of ruthenium binding within the active sites that lead to preferred binding region.

The hydrophobic and hydrophilic regions within the binding sites are shown in **Fig. 1,** and **2.** The phen ligand of RuN(B) is found towards

hydrophobic region whereas the other groups may contribute to DNA binding resulting the relative changes of the interactions energies are shown in **Fig. 1.** Although, the ruthenium complex can bind preferably within GC base pairs, the complex as a whole occupy selectively within AT and GC sequences in the docked structure **(Fig. 1** and **2),** and **Table 2** shows the van der Waals and electrostatic interaction energies of CHARMm minimized cisplatin and other Ru complexes. The changes of torsion angles may be due to the deformation of DNA due to the binding with complexes (Table 4), and QM/MM minimized structures also produces significant induction to DNA structure **(Fig. 2** and **Table 3).** The values of CHARMm and QM/MM minimization are quite different, but the trend of torsion angles is similar. Such changes are relevant to the variation of interaction energies computed by using QM/MM with coarse, medium and fine basis sets. The result shows that RuN(B) and RuN(C) may bind more strongly than the RuN(D), but not stronger than cisplatin. The sequential arrangement of base pairs within the binding region is also affected to a large extent compared to the distant base pairs **(Table 5).** The number of hydrogen bonds and the value of van der Waals interaction energies are shown in **Tables 3** and **6.** It appears that hydrogen bond formation is one of the major factors for the stabilization of complexes within DNA.

4. Conclusion

The RuN(B), RuN(C) and RuN(D) complexes can bind favorably within the cisplatin bonded sequences of DNA, but the binding energies are not more than that of cisplatin. The phen ligand is found well embedded within hydrophobic region, whereas the DMSO groups occupy the hydrophilic regions. The binding energies of RuN(B) is very close to that of cisplatin.

5. Acknowledgement

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