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Molecular Docking of Dichlorodiorgano [*N*-(2-pyridylmethylene)arylamine]tin(IV) Complexes with Some Enzymes

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ABSTRACT

The molecular structures of some dichlorodiorgano[N-(2-pyridylmethylene)arylamine]tin(IV) (R_2SnCl_2.L) complexes were determined using the PM3 method and their geometries have been optimized. The Sn atom in the complexes adopt a trans-R_2Sn octahedral geometry. The mechanism for cytotoxic activities of some diorganotin(IV) compounds, R_2SnCl_2.L (R = Me (1), Et (2), Ph (4)) is discussed in relations to their docking in some of the cancer associated enzymes such as ribonucleotide reductase (RNR), thymidylate synthase (TS), thymidylate phosphorylase (TP) and topoisomerase II (topoII). The docking studies revealed that compound 1 docked in the active site of enzymes by virtue of hydrophobic interactions and comparable interactions were also noted for compound 2. On the other hand, compound 3 exhibited hydrogen bonding, hydrophobic and π-π interactions when docked to enzymes RNR, TS and topoII, respectively. None of the compounds entered the active site pocket of thymidylate phosphorylase (TP).

Keywords: diorganotin(IV), NN donor Schiff base, docking studies, enzymes

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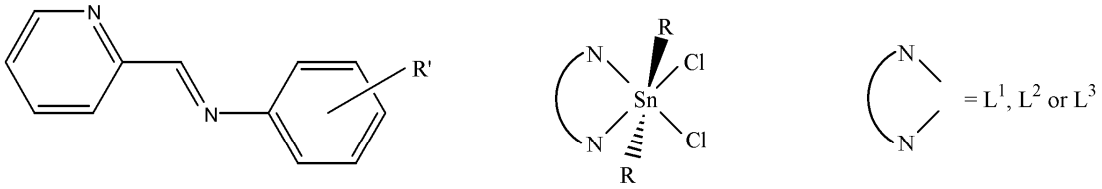
INTRODUCTION

Diorganotin(IV) compounds, R_2SnCl_2 are often tetrahedral, and when appropriate nitrogen-chelating ligands are coordinated to the central metal, octahedral complexes R_2SnCl_2·L (L = bidentate ligand) are obtained. A structural correlation with biological activity for these diorganotin(IV) complexes has shown that active species are associated with complexes having Sn–N bonds longer than 2.39 Å [1]. Based on this assumption, a series of diorganotin(IV) dichloride complexes of *N*-(2-pyridylmethylene)arylamine (N^N chelating ligands, L) have been

synthesized and characterized on the basis of IR, NMR, ^{119}Sn-Mössbauer studies [2] and a few of them were analyzed by single crystal X-ray crystallography [3,4]. In line with these developments, the anti-proliferative and cytotoxic effects of complexes $R_2SnCl_2.L$ (R = Me (**1**), Et (**2**), Bu (**3**)) have been investigated both in vivo and in vitro [2,3,5]. The data suggest that **3** shows better antiproliferative and antitumor activity than the other two but it shows higher toxicity to mice [3]. It was shown earlier that the antitumor activity of **2** was improved after depleting endogenous glutathione (GSH) by buthionine sulfoximine (BSO) [5], however, such treatment did not show any effect with **3** [3]. Further, this study was extended in combination with X-rays (1.5 Gy) in human peripheral lymphocytes and the antitumor activity was assessed in Dalton's lymphoma cells [6]. Complex **3** showed better antiproliferative and antitumor activity than **1** and **2**, both as alone and in combination with X-rays. Subsequently, the cytotoxic potential of these diorganotin(IV) complexes, $R_2SnCl_2.L$ (Fig. 1) were investigated in human tumor cell lines in vitro [7], which indicated that the high cytotoxic activity is dependent on the Sn-R groups and Sn-N bond lengths. Complex **2** was found to exhibit stronger cytotoxic activity in vitro particularly for A498 (renal cancer), IGROV (ovarian cancer), MCF-7 (breast cancer), and WIDR (colon cancer) human tumour cell lines and the results are far superior to standard reference drugs e.g., doxorubicin, cisplatin, 5-fluorouracil, methotrexate, etoposide including paclitaxel.

Recently, organotin(IV) 2-/4-[(*E*)-2-(aryl)-1-diazenyl]benzoates have shown very promising cytotoxic activities [8-10] and consequently the mechanistic role of these compounds were investigated using docking studies with some of the key enzymes, such as ribonucleotide reductase, RNR (pdb ID: 4R1R), thymidylate synthase, TS (pdb ID: 2G8D), thymidylate phosphorylase, TP (pdb ID: 1BRW) and topoisomerase II, topoII (pdb ID: 1QZR), which take part in the synthesis of raw materials for DNA and its replication [11]. The docking studies indicated that the azo group nitrogen atoms and formyl, carbonyl and ester oxygen atoms in the ligand moiety play an important role, and exhibit hydrogen bonding interactions with the active site of amino acids of the aforementioned enzymes [8-10]. In view of this and as a result of the promising cytotoxic activities of dichlorodiorgano[*N*-(2-pyridylmethylene)arylamine]tin(IV) compounds, e.g., $R_2SnCl_2.L$ (R = Me (**1**), Et (**2**), Ph (**4**)) (Fig. 1), it is planned to investigate the mechanistic role of these compounds with aforementioned enzymes using docking studies. It is should be noted that the molecular modeling by docking studies provides most detailed possible view of drug-receptor interaction and has created a new rational approach to drug design where the structure of drug is designed based on its fit to three dimensional structures of receptor site, rather than by analogy to other active structures or random leads.



[R' = 3-Me (L^1); = 4-Me (L^2); = 4-OMe (L^3)] [R = Me (**1**); = Et (**2**); = ^{n}Bu (**3**); = Ph (**4**)]

(**a**) (**b**)

Figure 1. (a) Structure of the ligands (b) Structure of the diorganotin(IV) complexes

MATERIALS AND METHODS

Computational methods

The molecular structures and geometries of the diorganotin(IV) compounds (**1**, **2** and **4**) were fully optimized using the semiempirical quantum chemistry method (PM3). Dockings of compounds **1**, **2** and **4** in the active sites of various enzymes are performed using ArgusLab 4.0.1 [12-15]. This program was also applied for visualization and molecular modeling of the compounds. The three dimensional coordinates of the enzymes such as RNR, TS, TP and topoII, were obtained through the Internet at the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank. The docking program implements an efficient grid-based docking algorithm, which approximates an exhaustive search within the free volume of the binding site cavity. The conformational space was explored by the geometry optimization of the flexible ligand (rings are treated as rigid) in combination with the incremental construction of the ligand torsions. Thus, docking occurs between the flexible ligands part of the compounds and enzymes. The ligand orientation is determined by a shape scoring function based on Ascore and the final positions are ranked by lowest interaction energy values. Prior to docking, the ground state was optimized using the PM3QM implemented in the geometry optimization module of program package to confirm that no significant divergence in the conformations of the complexes due to crystal packing effects.

Syntheses of diorganotin(IV) complexes

The synthetic details for the preparations of dichlorodiorgano[*N*-(2-pyridylmethylene)arylamine]tin(IV) compounds, e.g., $Me_2SnCl_2.L^1$ (**1**), $Et_2SnCl_2.L^2$ (**2**) and $Ph_2SnCl_2.L^3$ (**4**) are described in ref. 2.

Experimental protocol and cytotoxicity tests

The in vitro cytotoxicity test of diorganotin(IV) compounds **1**, **2** and **4** was performed using the SRB test for the estimation of cell viability [16]. Cytotoxicity studies were carried out on human tumor cell lines A498 (renal cancer), EVSA-T (mammary cancer), H226 (non-small-cell lung cancer), IGROV (ovarian cancer), M19 MEL (melanoma), MCF-7 (mammary cancer) and WIDR (colon cancer) and the results have been reported elsewhere [7].

RESULTS AND DISCUSSION

Dichlorodiorgano[*N*-(2-pyridylmethylene)arylamine]tin(IV) compounds (**1**, **2** and **4**) have been characterized earlier on the basis of IR, NMR and ^{119}Sn-Mössbauer studies [2]. Complexes **1** and **2** were also characterized by single crystal X-ray crystallography [3,4]. The crystallography results indicated that the tin atom in diorganotin(IV) complexes have a *trans*-R_2Sn octahedral geometry where the *N*-(2-pyridylmethylene)arylamine acts as bidentate ligand (Fig. 1 b). X-ray crystallography results show that the Sn–N(1) and Sn–N(2) bond lengths in structures of complexes **1** and **2** are 2.427 (8) Å and 2.500 (7) Å [4], and 2.452 (6) Å and 2.559 (6) Å [3], respectively, which are > 2.39 Å, as observed for the octahedral $R_2SnCl_2 \cdot L$ (L = α-diimine; N^N bidentate chelating ligands ligand) complexes [1]. This prompted us to carry out the molecular structure of the diphenyltin(IV) compound **4**, for which the X-ray diffraction data is not

available, using the semiempirical quantum chemistry method. In addition, the molecular structures of the other two compounds, viz., **1** and **2** were also determined using the semiempirical quantum chemistry method and the results of **2** was compared with that found from single crystal X-ray crystallography (Table 1). The structures of diorganotin(IV) complexes (**1**, **2** and **4**) were used subsequently for molecular modeling work (see below).

Quantum chemical calculations

The geometries of the diorganotin(IV) complexes (**1**, **2** and **4**) were fully optimized using the quantum mechanical method (PM3). Harmonic frequency calculations were performed for all the stationary points to characterize their nature and to ensure that the optimized structures correspond to global minima. The molecular structures of **1**, **2** and **4** are shown in Figs. 2-4 respectively, while the optimized geometric parameters are listed in Table 1.

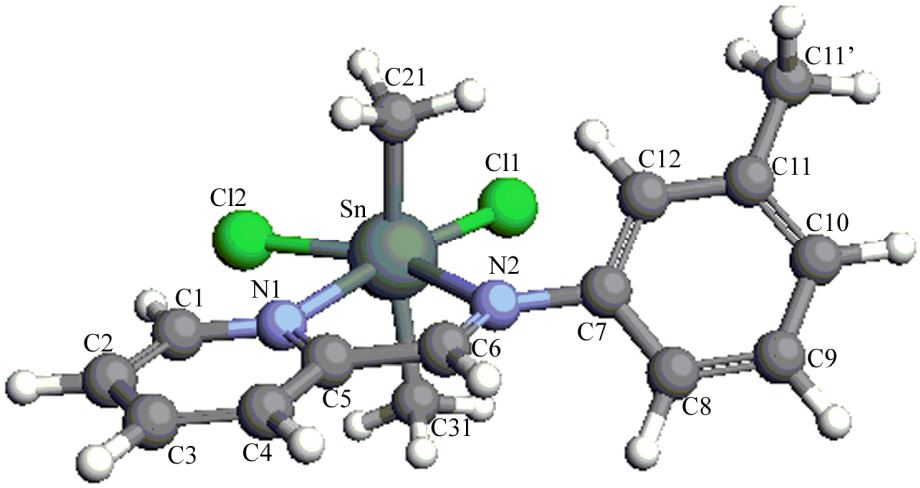


Figure 2. The structure of Me_2SnCl_2.L (1) obtained after full geometry optimization

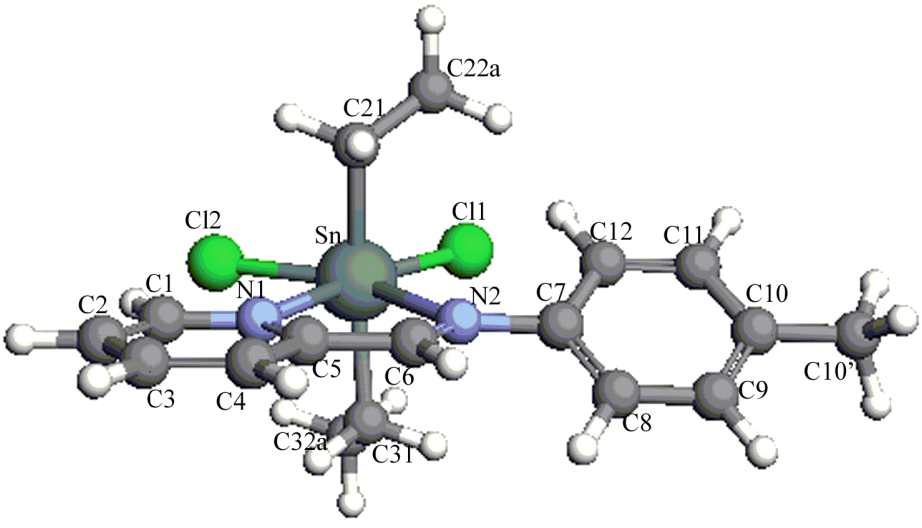


Figure 3. The structure of Et_2SnCl_2.L (2) obtained after full geometry optimization

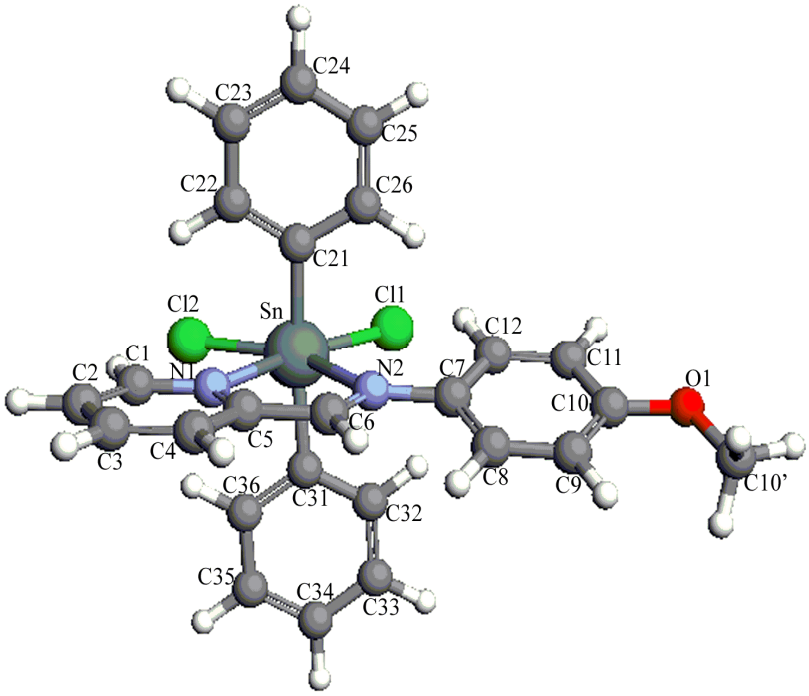


Figure 4. The structure of Ph_2SnCl_2.L (4) obtained after full geometry optimization

Table 1 Selected bond lengths (Å) and angles (º) for energy minimized structures of the diorganotin(IV) complexes 1, 2 and 4

Bond lengths (Å) and angles (°)	1	2		4
			X-ray [a]	
Sn-Cl(1)	2.402	2.413	2.516(2)	2.406
Sn-Cl(2)	2.401	2.413	2.480(2)	2.412
Sn-N(1)	2.588	2.573	2.452(6)	2.547
Sn-N(2)	2.67	2.663	2.559(6)	2.669
Sn-C(21)	2.117	2.158	2.187(9)	2.08
Sn-C(31)	2.116	2.15	2.156(8)	2.088
N(1)-C(5)	1.372	1.371	1.341(9)	1.37
N(2)-C(6)	1.298	1.3	1.276(8)	1.301
Cl(1)-Sn-Cl(2)	107.32	108.94	96.45(8)	114.89
Cl(1)-Sn-N(1)	169.77	167.06	173.0(2)	160.35
Cl(1)-Sn-N(2)	105.21	101.88	106.6(1)	95.23
Cl(1)-Sn-C(21)	92.95	95.94	94.4(3)	94.07
Cl(1)-Sn-C(31)	93.37	93.46	92.9(3)	92.53
Cl(2)-Sn-N(1)	82.83	83.99	90.2(2)	84.61
Cl(2)-Sn-N(2)	147.44	149.18	156.9(1)	149.84
Cl(2)-Sn-C(21)	98.07	94.18	96.2(3)	94.31
Cl(2)-Sn-C(31)	98	96.77	96.5(3)	94.57
N(1)-Sn-N(2)	64.68	65.19	66.8(2)	65.4
N(1)-Sn-C(21)	86.69	82.33	82.7(3)	86.45.
N(1)-Sn-C(31)	83.77	85.19	88.5(3)	83.03
N(2)-Sn-C(21)	78.81	82.61	84.0(3)	81.34
N(2)-Sn-C(31)	81.34	80.93	80.9(3)	85.23
C(21)-Sn-C(31)	160.12	162.42	164.6(4)	165.52
Sn-N(1)-C(1)	122.44	122.36	123.9(6)	121.95
Sn-N(1)-C(5)	118.09	117.96	117.5(5)	118.39
Sn-N(2)-C(6)	116.9	116.21	114.6(5)	115.39
Sn-N(2)-C(7)	122.9	123.19	127.4(4)	125.08

[a] *Data taken from ref. 3.*

The geometric parameters for **2** obtained from the X-ray diffraction technique are also included in Table 1 for comparison. The experimental geometrical parameters for **2** correspond closely with that of calculated values for **2,** as expected. Most of the geometric parameters for **1**, **2** and **4** are found to be insensitive to the nature of the substituents R' (see Fig. 1). The optimized geometrical parameters for **1**, **2** and **4** show that bond lengths, bond angles and torsion angles remain virtually unchanged. Calculated results indicate that the diorganotin(IV) complexes **1**, **2** and **4** have a six-coordinate structure where the *N*-(2-pyridylmethylene)arylamine ligand acts as bidentate chelating agents. The basal plane around the tin atom is completed by two chlorine atoms and two nitrogen atoms of the ligand while the two R groups occupy the axial positions to produce a distorted octahedral structure (Fig. 1 b; Figs. 2-4)). The R groups are approximately *trans* to each other as reflected in the bond angles (C(21)-Sn-C(31)) of **1** (R = Me; 160.12°), **2** (R = Et; 162.42°) and **4** (R = Ph; 165.52°)).

The Sn–N(1) and Sn–N(2) bond lengths in structures of complexes **1**, **2** and **4** are 2.588 Å and 2.67 Å, 2.573 Å and 2.663 Å and, 2.547 Å and 2.669 Å, respectively, which are > 2.39 Å. Since the basic structures and coordination geometry of the diorganotin (IV) complexes (**1**, **2** and **4**) are similar for the differently substituted ligands, it can be expected that the ligand properties may have direct influences on the stability of the corresponding diorganotin (IV) complexes, as well as on their cytotoxic activity (see below).

Docking study

The results of the in vitro cytotoxicity tests performed with diorganotin(IV) compounds (R_2SnCl_2.L; **1**, **2** and **4**) are already described in our earlier communication [7]. In general, the cytotoxic activities for the complexes **1**, **2** and **4** are cell lines specific. Complex **2** was found to exhibit stronger cytotoxic activity in vitro particularly for A498, IGROV, MCF-7, and WIDR human tumor cell lines and the results are far superior to standard reference drugs e.g., doxorubicin, cisplatin, 5-fluorouracil, methotrexate, etoposide including paclitaxel. Under identical conditions, the activity of **2** is more pronounced for the A498 (14 fold), IGROV (26 fold), MCF-7 (1.6 fold) and H226 (1.7 fold) cell lines compared to paclitaxel. On the other hand, **1** displayed over all very good activity and better results were noted for EVSA-T, M19 MEL and MCF-7 cell lines. The appreciable cytotoxic activity is correlated to the structural features such as Sn-N bond lengths and R group attached to tin atom [7].

The encouraging cytotoxic activity for the test compounds **1**, **2** and **4** across a panel of cell lines prompted us to perform molecular docking studies to understand the complex-protein interactions. Dockings of compounds **1**, **2** and **4** in the active sites of enzymes RNR, TS, TP and topoII have been determined since these enzymes are promising targets for cancer therapy [18-25] and the results of docking studies are shown in Figs. 5-13**.** The docking programme is validated by docking ADP in the active site of enzyme RNR, with a close overlap between the docked ligand and the native ligand being observed [9-10].

The docking studies revealed that compound **1** docked in the active site of enzymes RNR (4R1R), TS (2G8D) and topoII (1QZR) by virtue of hydrophobic interactions (Figs. 5-7). In RNR, a ligand phenyl ring is held in the hydrophobic region of L464 amino acid residue and such interactions are also noted between the ligand phenyl ring and alkyl chain (Sn-methyl) of L195 in TS while in topoII, the ligand phenyl rings of compound **1** lies in the hydrophobic sub-

pocket constituted by F121, I120, Y415 and V197 amino acid residues. Like wise, comparable interactions were noted for compound **2** and are shown in Figs. 8-10. In RNR, the ligand phenyl

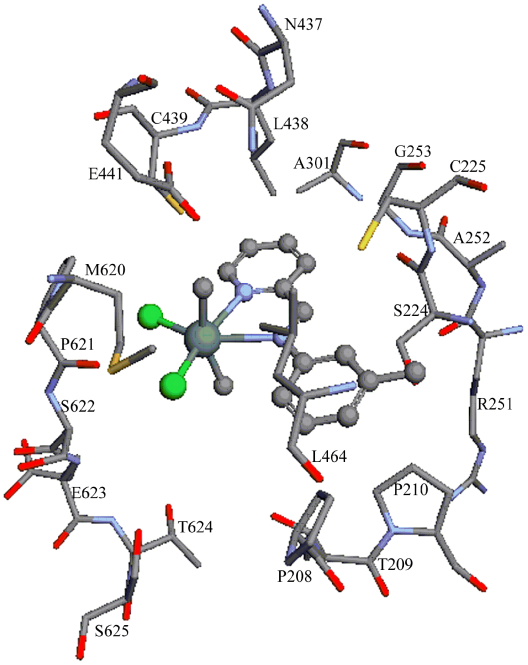


Figure 5. Me_2SnCl_2.L (1) docked into the active site of ribonucleotide reductase. One of the phenyl rings of compound 1 is held in the hydrophobic region of L464 amino acid residue.

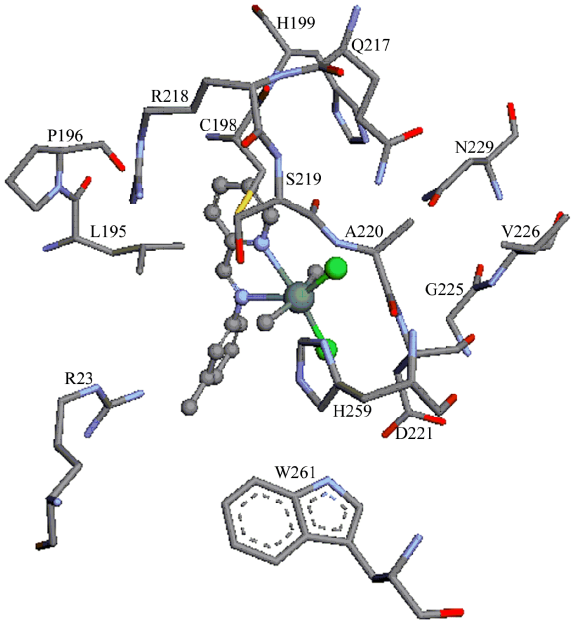


Figure 6. Me_2SnCl_2.L (1) docked in the active site of thymidylate synthase showing the hydrophobic interactions between the phenyl ring of 1 and alkyl chain of L195 amino acid residue.

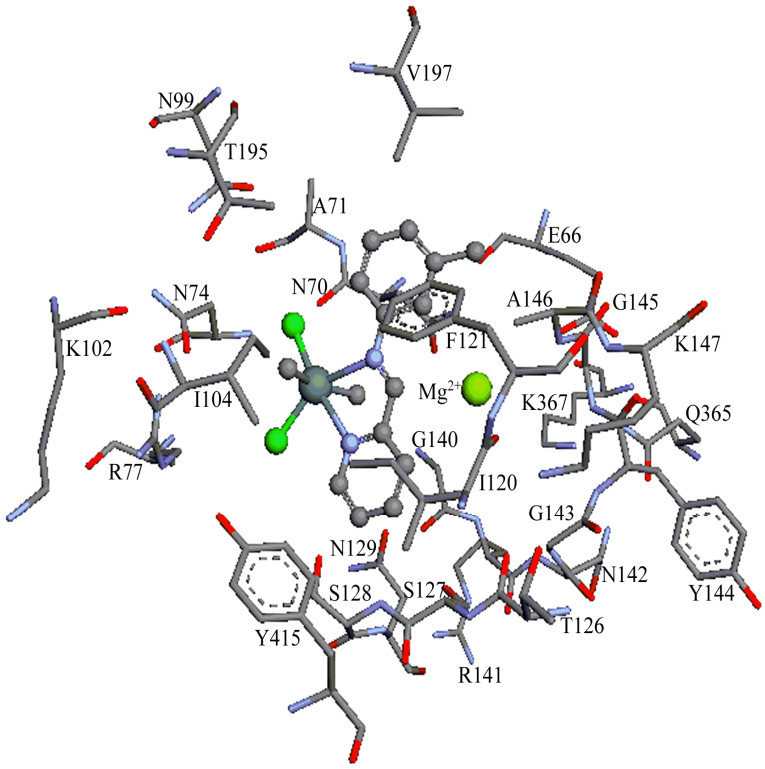


Figure 7. Me_2SnCl_2.L (1) docked into the active site of topoisomerase II. The phenyl rings of compound 1 lies in the hydrophobic sub-pocket constituted by F121, I120, Y415and V197 amino acid residues.

ring is present in the vicinity of P621 amino acid residue. The alkyl part of the L195 in TS was found to interact with the ligand phenyl ring of compound **2** whereas in topoII, the aromatic part is held in the region constituted by Y415, I120 and F121 amino acid residues. On the other hand, compound **4** exhibits hydrogen bonding, hydrophobic interactions and π-π interactions when docked to enzymes RNR, TS and topoII, respectively (Figs. 11-13). In RNR, oxygen atom of methoxy group exhibits hydrogen bonding with T209 and T624 amino acid residues while in the case of TS, one of the tin-phenyl ring of compound **4** approaches L195 amino acid residue and exhibits hydrophobic interactions. The tin-phenyl rings of compound **4** are oriented towards Y415 and F121 residues and are held by π-π interactions. However, none of the compounds enter into the active site of enzyme TP. Therefore, on the basis of docking studies, it is inferred that the anticancer activities of compounds **1**, **2** and **4** might be emanating from their interactions with

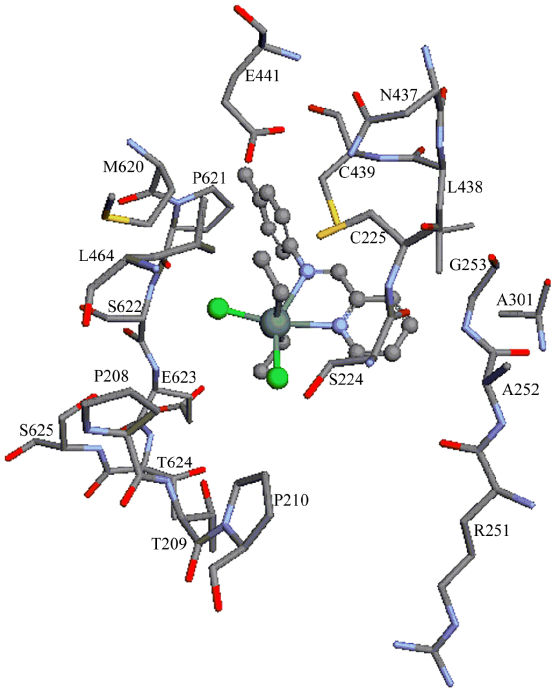


Figure 8. Et_2SnCl_2.L (2) docked into the active site of ribonucleotide reductase. The phenyl ring of compound 2 is held in the vicinity of P621 amino acid residue.

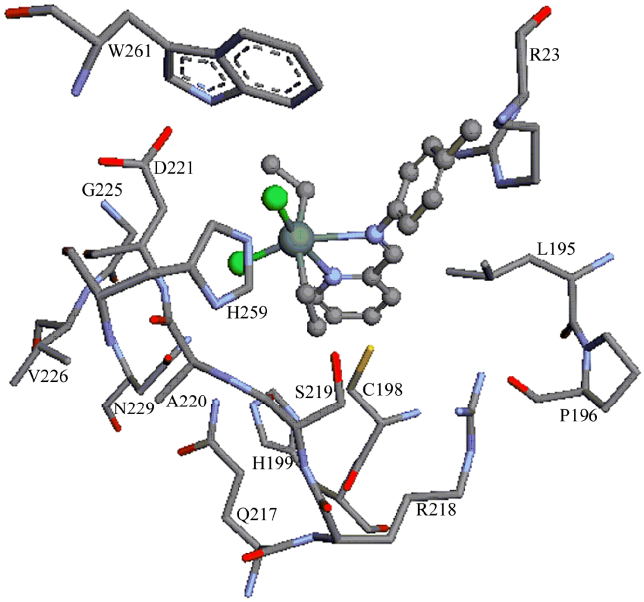


Figure 9. Et_2SnCl_2.L (2) docked into the active site of thymidylate synthase. The alkyl part of L195 is held perpendicular to the phenyl ring of compound 2.

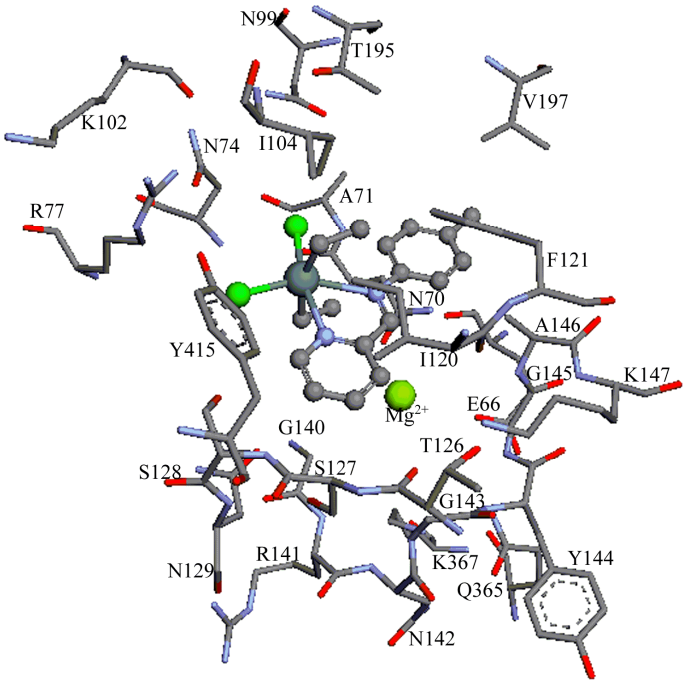


Figure 10. Et_2SnCl_2.L (2) docked into the active site of topoisomerase II. The aromatic part of compound 2 is held in the region constituted by Y415, I120 and F121 amino acid residues.

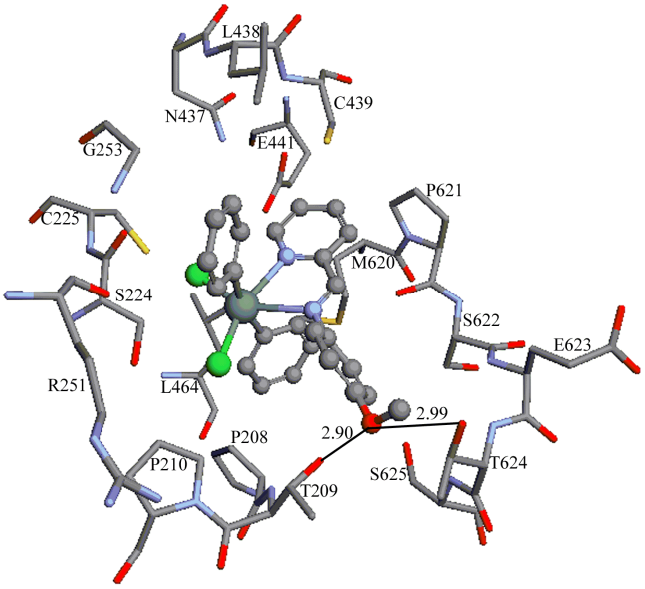


Figure 11. Ph_2SnCl_2.L (4) docked into the active site of ribonucleotide reductase. Oxygen atom of methoxy group exhibits hydrogen bonding interactions with T209 and T624 amino acid residues.

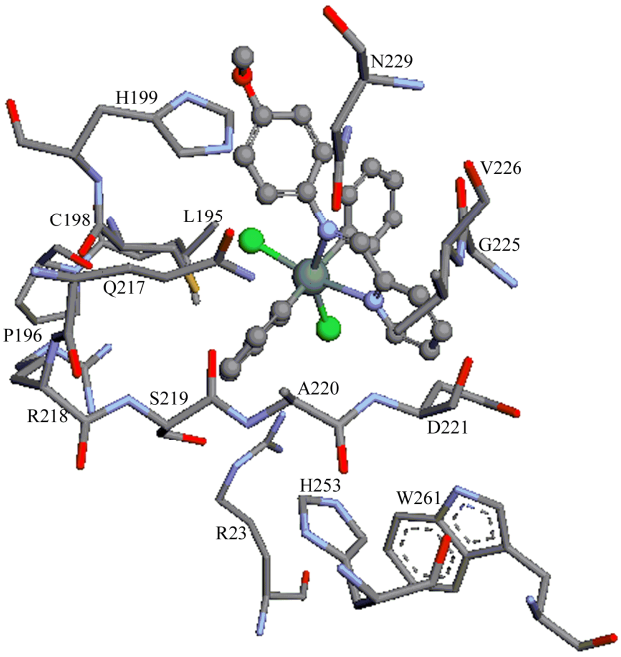


Figure 12. Ph_2SnCl_2.L (4) docked into the active site of thymidylate synthase. One of the phenyl rings of compound 4 approaches L195 amino acid residue and are held by hydrophobic interaction.

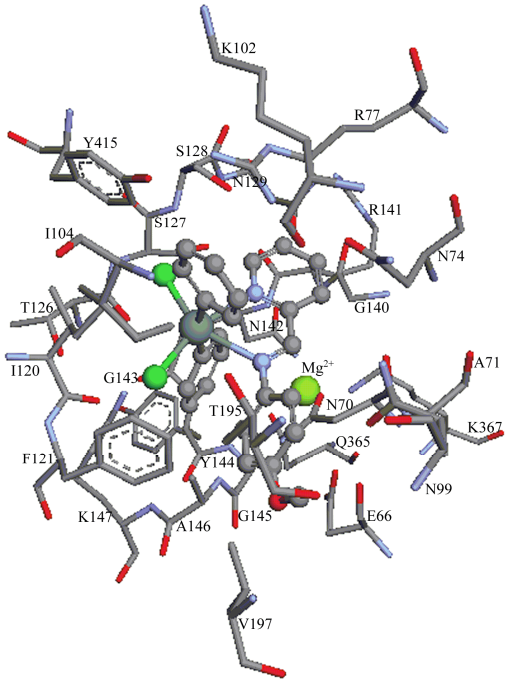


Figure 13. Ph_2SnCl_2.L (4) docked in the active site of topoisomerase II. The phenyl rings of compound 4 are oriented towards Y415 and F121 amino acid residues and are held by π-π interactions.

enzymes RNR, TS and topoII. The docking studies also indicate that the imino nitrogen atom of the ligand do not play any role during the dockings of the diorganotin(IV) compounds into the active sites of various enzymes unlike that observed for organotin(IV) complexes of arylazocarboxylates where azo group nitrogen atom(s) indicated hydrogen bonding interactions

with various amino acid residue [9,10]. This further indicate that the mechanism of action of dichlorodiorgano[*N*-(2-pyridylmethylene)arylamine]tin(IV) complexes of present investigation could be different than that of organotin(IV) arylazocarboxylates [9,10]. Nevertheless, the possibility of coordination through tin beyond the active site of the enzymes can not be ruled out completely. It is very difficult to envisage the role of such atoms in binding (interactions) proteins in relation to improved cytotoxic activity. It is well known that many drugs with anti-proliferative activity act either by interfering with the bases and/or nucleotides of the double helix of DNA or with the metalloenzymes that are necessary for the rapid growth of malignant cells [26-28]. In conclusion, these preliminary results suggest that the dichlorodiorgano[*N*-(2-pyridylmethylene)arylamine]tin(IV) compounds of the type $R_2SnCl_2.L$ merits more detailed investigation.

Acknowledgements
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