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RESEARCH ARTICLE

ORGANOTIN BIS-COMPLEXES: Synthesis, Characterization, antimicrobial activity and Anticancer (computational) studies

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Abstract

The synthesis of new Organotin (IV) based complexes were reported as well as charecterization by several spectrocopic techniques. The stannanes were successfully synthesized in high yield and based on the ligands, tin complexes were prepared and characterized. A possible structure of novel complexes has been proposed as evident from spectral studies. The complexes were tested against subsequent bacterial strains **Staphylococus aureus** (gram positive) and **Escherichia coli 1610**(gram negative) and their antifungal activity was evaluated against two fungal strains of **Fusarium** and **Aspergillus niger.** Synthesized organotin (IV) complexes had revealed good antibacterial and antifungal activities. Further, computational study of synthesized stannanes was performed using iGEMDOCK software. In which complex A was found to inhibit the B-RAF Kinase activity and therefore it could be a potential pharmaceutical drug which can be advantageous for melanoma patients.

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INTRODUCTION

Organometallic chemistry is a field which involves the study of compounds possessing at least one metal-carbon bond. These organotin compounds are also known as stannanes, having tin with hydrocarbon substituent. Organotin compounds also known as stannane have a wide range of applications (Tian L.L et al 2005) including biological activity as potential antineoplastic and anti-tuberculosis agents (Yousif E, et al 2009), (Y. Win et al 2012). Stannanes are commercially applied as a hydrochloric acid scavenger i.e. heat stabilizer in Poly Vinyl Chloride and also as a biocide. Other known applications are as wood preservatives, marine anti-biofouling agents, for the

production of tin dioxide layer on glass bottles, as bactericides and fungicides, as miticides, acaricides (killing mites and ticks), in anticancer therapy and as antifungal agents in paints. They are also used as intermediates in chemical reactions and as catalysts (Warren T. P., 1973).Numerous stannanes can be prepared using multiple mechanisms of action that can prevent the development of drug resistance, which was the major side effect in case of ‘cisplatin’. A wide variety of other industrial and agricultural applications are known to us. As the biocidal action of stannanes is no doubt understood, it may have both helpful and additionally unsafe impacts as a potential ecological toxicant. It targets insects, pests, ticks and flies but it may also target a variety of cellular structures and enzymatic systems. (Biunden S.J., 1984), (Cima F., 2003).

Stannane are receiving increasing interest because of their potential biological and pharmaceutical applications as anticancer agents (Davies A.G. et al 2008), (M. Gielen, Tiekink E.R.T., 2005). Large number of synthesized Organotin (IV) compounds have been found to be better an anticancer agent as compared to traditional heavy metal

based anticancer drugs (Beltran H.I. et al, 2007), (Crowe A.J., 1993) (Gleeson B. et al, 2008), (Muhammad N. et al, 2009), (Tabassum S., Pettinari C., 2006).

2.1 MATERIAL

All the chemicals used were of Analytical Grade and obtained from commercial sources(MERK SPECIALITICS ,SPECTROCHEM,QUALIGEN AND FISCHER SCIENTIFIC). Standard procedure for drying the Solvents was followed (Ramappa P.G., Somashekarappa 1994) the instrument used was Rotatory Vaccum Evaporator (KHERA INSTRUMENTS PVT .LTD.(pressure range 0-30 in Hg/0 to -760 mmHg). The UV visible spectra studies were measured using UV instrument SHIMADZU UV 1800 ,200-600 in ethanol. The ^{1}H NMR spectras (in DMSO –d^6 solution, usedTMS as internal standard) were recorded on a JEOL ECX-400P NMR spectrophotometer at 400 MHz and 100 MHz, at USIC, University of Delhi,.All the NMR spectra were processed by NMR data processing software JEOL Delta^{TM}. Computational study was carried out using software iGEMDOCK (Generic Evolutionary Method for molecular Docking). The instrument used for sterilizing purpose in Antimicrobial and antifungal study was KHERA LABORATORY AUTOCLAVE, KHERA INSTRUMENTATION (pressure range 0-30 lb/in 2 or 0-2.1 kg/cm 2) and Incubator used was ORBITAL SHAKER, PSN INTRUMENTATION PVT LTD.

2.2 METHOD

A stoichiometric amount of ligand (2 mmol) was dissolved in solution of dry benzene (30 ml) and absolute ethanol (10 ml). Dibutyltin(IV) oxide(DBTO) (1 mmol) was then added in the above mixture as required for 1:2 (metal: ligand) molar ratio . The reaction mixture was then refluxed azeotropically with a Dean Stark separator over the heating mantle. Dibutyltin (IV) oxide goes in to solution within 10-15 minutes until clear solution was obtained. Refluxing was further proceeded for 5-6 hours at room. Excess of solvent was removed under reduced pressure by a rotator evaporator to leave behind a solid complex. The solid product obtained was filtered and washed with chloroform and dried in vacuum. Recrystallisation was further done from ethanol. (Jose, S., 2004), (Mala Nath et al, 2003)(refer figure 1 for the reaction sequence).

2.2.1 ANTIBACTERIAL TEST

Agar well diffusion method was carried out to check the antibacterial activity of the stannanes synthesized. **Staphylococcus aureus** (gram-positive) and **Escherichia coli 1610** (gram-negative) bacteria were cultivated in nutrient agar on petri dishes. The 6mm well was dug in the media using sterile metallic borer, after that 18-24 h bacterial inoculums (0.165 8 OD) was spread on the nutrient agar surface using a sterilized cotton swab. The sample of different concentration of 0.002 g/100 mL in ethanol was introduced into the respective wells. Other wells containing Ethanol and the reference antibacterial drug (Chloramphenicol) served as our negative and positive controls respectively. Immediately the plates were incubated for 18-24 h at 37℃ . The antibacterial activity of different concentrations were determined by measuring the diameter of the inhibition zone (in mm) and also compared with reference. Calculated the MIC (Minimum Inhibitory Concentration) of stannane with sample concentration of 0.002 g/100 mL, 0.001 g/100 mL, 0.0005 g/100 mL, 0.00025 g/100 mL and 0.000125 g/100mL in ethanol. (Mala Nath,1999), (Mala Nath, 1997) a, (Mala Nath, 1997) b, (Tushar, S., Baul, B., 2008)a.

2.2.2 ANTIFUNGAL ACTIVITY

Agar well diffusion method was carried out to check the antifungal activity of the stannanes synthesized. The plates were prepared using the nutrient Czapak medium. The 6mm well was dug in the media using sterile metallic borer. The fungal strains of **Fusarium** and **Aspergillus niger** was streaked on the different plates .The sample in the concentration of 0.002 g/100 mL in ethanol was introduced into the respective wells. Immediately the plates were incubated at 32 ℃ for 72 h. (Ruzicka, A., 2002).

3. RESULTS AND DISCUSSION

3.1 PHYSICAL PROPERTIES

Complex A: (5,5′-((dibutylstannanediyl)bis(oxy))bis(4-formyl-6-methylpuridine-5,3-diyl)bis(methylene) -bis(dihydrogenphosphate)

After the process of synthesis ,the complex was obtained in **good yield (0.4571 g, 78 %) and was lightbrown coloured solid soluble in dimethyl sulphoxide and ethanol.**

Analysis(%),calculated for [$C_{24}H_{36}N_2O_{12}P_2Sn$] (726.07):C,39.75; H,5.00;N,3.86;O,26.47;P,8.54;Sn,16.37.

COMPLEX B: (2E, 2′E, 4E, 4′E)-dibutylstannanediylbis(hexa-2,4-dienoate)

After the process of synthesis, the complex was obtained in **good yield (0.4224 g, 92.9 %) and was yellow coloured viscous semi solid, soluble in dimethyl sulphoxide and ethanol.**

Analysis(%),calculated for[$C_{20}H_{32}O_4Sn$] (456.13):C,52.77;H,7.09;O,14.00;Sn,26.08.

Refer Figure 3.1for the proposed 3D structure of Complex A and Complex B

3.2 ANTIBACTERIAL ACTIVITY.

All the synthesized stannanes showed better antibacterial result against two types of bacteria **Staphylococcus aureus** (gram-positive) and **Escherichia coli** 1610(gram-negative) as compared to their respective ligands.(refere table 1.1 for inhibition zone data and table 1.2 for Minimum Inhibition Concentration of complex A and B). Graphs showing Inhibition zone of ligand and its corresponding stannanes are depicted in Figure 2.

The growth of microorganisms was inhibited by the synthesized stannane, it was assumed that the production of an enzyme is being affected by the complex, consequently the microbes were not able to metabolize the nutrients and hence their development ceased. The enzymes whose activity was depended on the free sulfydryl groups (-SH) were found to be susceptible to deactivation by ions of the complex (Tushar, S., Basu Baul, 2008) [a]. **The order of antimicrobial action was found to be Complex B>Complex A that is Complex B was found to be a better antibacterial agent as compared to complex A** (refer the graph in Figure 2.3)

A possible explanation for the antimicrobial action of the synthesized stannane could be: i) the effect of metal ions on the enzymes that are required for the normal cell process, ii) after chelation the polarity of metal ions were considerably reduced due to partial sharing of its positive charge with a donor groups and iii) delocalization of π-electron over the entire molecule. These factors could have made them a good pharmacophore ,hence increased the lipophilic character of the stannane by facilitating its penetration across the microorganism cell wall leading to the breakdown of permeability barrier of the cells and hence resulted in the hindrance in the normal cell process (Ramappa, P.G., Somashekarappa, 1994). This could be better understood according to Chelation theory (Srivastava, R.S., 1981) which states that the decrease in in polarizability of the metal could enhance the lipophilicity of the complexes (Sari, N. et al 2003).

Antibacterial agents act selectively on vital microbial functions, with minimal or no effect on host function. Different agents act differently; their mode of action can be categorized on the basis of their structure or on the function that they affect (Hawkey, P., Lewis, D., 1994), (Tenover, F., 2006), (Yeaman, R., Yount, N. 2003).

3.3 ANTIFUNGAL ACTIVITY

According to the in vitro antifungal results (MIC) against the two fungal strains used Fusarium and Aspergillus niger it was found that the synthesized stannane exhibited better results as compared to their respective ligands. **The MIC was found to be 10 ppm to 20 ppm..**

3.4 ELECTRONIC ABSORPTION SPECTRA

The electronic spectra analyses of ligands and its corresponding organotin(IV) complexes were carried out in ethanol at room temperature(**SHIMADZU UV 1800)** and its baseline correction was done before scanning.. **Complex A - (5,5′-((dibutylstannanediyl)bis(oxy))bis(4-formyl-6-methylpuridine-5,3-diyl)bis(methylene)bis(dihydrogenphosphate) and Complex B -(2E,2′E,4E,4′E)-dibutylstannanediylbis(hexa-2,4-dienoate):** The Ultraviolet-visible spectra depicted a bathochromic shift/ Red shift (wavelength value shifted to higher λ_{max} and Absorbance value) from the electronic transitions taking place in ligand due to its coordination to DBTO(Table 2.1 and Table 2.2). New peaks in the higher range λmax (Redshift) in the stannanes are attributed to the n--**π*** transition of band which is referred to the ligand metal charge transfer (LCMT) (Leovac et al, 2007), (Norrihen, S. 2012).

3.4. 1. ^{1}H NMR SPECTRA

The ^{1}H NMR spectras (in DMSO –d^6 solution, usedTMS as internal standard) were recorded on a JEOL ECX-400P NMR spectrophotometer at 400 MHz and 100 MHz, at USIC, University of Delhi

3.4.1a. Complex A

The Organotin complex showed resonance signals δ(ppm): 11.98 (OH, alcohol), 8.77 (CH, 2-pyridine), 1.63 (CH_2, methylene), 9.73 (CH,aldehyde), 5.29 (CH_2,methylene), 2.53 (CH_3,methyl), 1.26 (CH_2,metylene), 0.90 (CH_3,methyl)

3.4.1b. Complex B

The Organotin complex showed resonance signals δ(ppm): 1.61 (CH_2 attached to Sn-O,methylene of n-butyl group), 1.28 (CH_2,methylene of n -butyl group), 2.10 (CH_3,methyl of n butyl group), 0.91 (CH_3,methyl of n- butyl group), the other peaks for the 1-ethylene group were observed at δ :5.32 , 7.50, 6.27 , 5.72 respectively. The absence of -OH group in ^{1}H NMR spectra confirms the complexation of ligand with Dibutyl tin oxide.

3.4.2. ^{13}C NMR SPECTRA

The ^{13}C NMR spectra (in DMSO –d^{6}solution) of Organotin (IV) complexes were registered on JEOL ECX-400P NMR spectrometer at University of Delhi. TMS was used as internal standard. Total number of peaks are found same as the number of non-equivalent carbon atoms.

3.4.2a.Complex A

The Organotin complex showed resonance signals δ(ppm):13.59(CH_3, methyl carbon of n –butyl group), 18.60(CH_3, methyl carbon attached to2-pyridine group), 26.87(CH_2, methylene carbon of n –butyl group(β substituted), 27.38(CH_2, methylene carbon of n –butyl group), 30.59(CH_2, methylene carbon attached to Sn-O of n -butyl group(α substituted)),192.88 (1- carbonyl attached to 2-pyridine group)other peaks for aromatic carbon of 2-pyridine group were observed at 152.89,143.01,149.00.128.49,125.97 respectively

3.4.2b. Complex B

The Organotin complex showed resonance signals δ(ppm):13.49 (CH_3, methyl carbon of n –butyl group), 19.27(CH_3, methyl carbon of 1-ethylene), 26.30 (CH_2, methylene carbon of n –butyl group), 27.65(CH_2, methylene carbon of n –butyl group), 30.75(CH_2, methylene carbon attached to Sn-O of n -butyl group),171.5(for 1-carbonyl carbon),others peaks for 1-ethylene were observed at 117.38,147.37,129.95,137.21 respectively.

3.5 COMPUTATIONAL STUDY

3.5.1. The term **2XRG** stands for autotaxin in complexed form. Autotaxin generates the lipid mediator lypophosphatidic acid (LPA), a mutagen and chemo-attractant for many cell types. It is involved in various pathologies including tumor progression and inflammation. . For Interaction of complex A with PDB 2XRG refer figure 3.1. The data of interaction energy of complex A with PDB 2XRG is mentioned in Table 3.1 and Table 3.2.

3.5.2. The term **3OG7** stands for B-Raf kinase and in human cancers it is the most frequently mutated protein kinase. The oncogenic mutations in BRAF are common in melanoma, followed by the demonstration that these tumors are dependent on the RAF/MEK/ERK pathway, thus offered hope that inhibition of B-RAF Kinase activity could benefit melanoma patients. For Interaction of complex A with PDB 3OG7 refer figure 3.2.The data of interaction energy of complex A with with PDB 3OG7 is mentioned in Table 4.1 and Table 4.2.

3.5.3. The software **IGEMDOCK** (Generic Evolutionary Method for molecular Docking) (Yang and Chen, 2004), which was a program used for computing a ligand conformation and orientation relative to the active site of the target protein. This software uses an empirical scoring function and an evolutionary approach. The GEMDOCK energy function consists of electrostatic, steric, and hydrogen-bonding potentials. The latter two terms use a linear model that is simple and recognizes potential complexes rapidly. The core idea of this evolutionary approach is to design multiple operators that cooperate using a family competition paradigm that is similar to a local search procedure. The interactive forces between a ligand and a biomolecule (protein) might involve hydrophobic forces, electrostatic interactions, van der Waals interactions, and hydrogen bonds. Different organic molecules have different types of interactions toward proteins. The negative value of binding energy change (ΔG) reveals that the binding process is spontaneous. Ross et al have characterized the sign and magnitude of the thermodynamic parameter, which are associated with various individual kinds of interactions that take place in protein association process.

TABLE 1.1DIAMETER OF INHIBITION ZONE AND ITS INTERPRETATION

INHIBITION ZONE	INTERPRETATION
Less than 10 mm (< 10 mm)	Weak
Larger than 10 mm but less than 16 mm(<10 ,>16)	Moderate
Larger than 16 mm	Active

SAMPLE	INHIBITION ZONE (mm) BACTERIA – E. coli 1610	Conclusion	INHIBITION ZONE (mm) BACTERIA-S. aureus	Conclusion
Control Chloramphenicol	21	Active	16	moderate
Ligand(Vitamin B6)	4	Weak	4	Weak
Complex 1 CD1	15	Moderate	14	Moderate
CD2	13	Moderate	10	Moderate
CD3	10	Moderate	8	Weak
CD4	0	Nil	0	Nil
CD5	0	Nil	0	Nil
Sorbic Acid	5	Weak	10	Moderate
Complex 4 CD1	21	Active	17	Active
CD2	12	Moderate	-	Nil
CD3	-	Nil	-	Nil
CD4	-	Nil	-	Nil
CD5	-	Nil	-	Nil

(*CD1-Complex Dilution 1-(0.002 g/100 mL), CD2 Complex Dilution 2-(0.001 g/100 mL), CD3 -Complex Dilution 3-(0.0005g/100 mL), CD4- Complex Dilution- 4(0.00025g/100mL) ,CD 5- Complex Dilution 5-(0.000125g/100mL)

Table 1.2 MINIMUM INHIBITION CONCENTRATIONS (MIC*)

	COMPLEX A		COMPLEX B	
	g/100 mL	ppm	g/100 mL	ppm
E. coli 1610	0.0005	5	0.001	10
S. aureus	0.0005	**5**	0.002	20

(*MIC refers to the lowest conc. of antibacterial agent required to inhibit the visible growth of microbes)

TABLE 2.1 THE ELECTRONIC SPECTRA ANALYSES OF LIGAND AND COMPLEX A

Sample	Wavelength (nm)	Absorbance
Ligand	289.00 204.00 256.00	3.600235 0.016815 0.946762
Organotin Complex A	292.00 259.00	2.091965 0.19531
Organotin Complex A (dilution 1*)	264.00 290.00 259.00	0.050598 1.848114 0.171570
Organotin Complex A(dilution 2)	290.00 259.00	0.729538 0.171570
Organotin Complex A (dilution 3)	290.00 259.00	0.297668 0.070618

(*Dilution 1-(0.002 g/100 mL), Dilution 2-(0.001 g/100 mL), Dilution 3-(0.0005g/100 mL)

TABLE 2.2 THE ELECTRONIC SPECTRA ANALYSES OF LIGAND AND COMPLEX B

Sample	Wavelength (nm)	Absorbance
Ligand	238	4.000
Organotin Complex B(Dilution 1)	244.00	3.996338
Organotin Complex B(Dilution 2)	244.00	1.898987
Organotin Complex B (Dilution 3)	244.00	0.290000

(*Dilution 1-(0.002 g/100 mL),Dilution 2-(0.001 g/100 mL), Dilution 3-(0.0005g/100 mL)

Table 3.1. Total energy, Vander-Waal interaction, Hydrogen bonding, electrostatic of complex A and B on interaction with PDB 2XRG

Complex	Total Energy	VDW	H-Bond	Electrostatic
Complex A	-129.965	-85.5209	-38.8741	-5.56964
Complex B	-93.8605	-74.7167	-19.1438	0

Table 3.2. Amino acid involved in the docking of the complex A and B on interaction with PDB 2XRG

Complex	Energy	H-S-SER-224	H-S-ASN-524	H-M-NAG-1860	V-S-TYR-221	V-M-PRO-522	V-M-ASN-523	V-S-ASN-524	V-S-LEU-745	V-S-HIS-831	V-M-NAG-1860	V-M-NAG-1860
A	-130	0	0	-4.27893	-1.49945	-5.23256	-5.98487	-7.51093	-6.17317	-16.684	-5.53727	-6.4264
B	-93.9	-3.42611	-5.74128	-3.97641	-5.84336	-4.5315	-5.56852	-7.86409	-2.4171	-1.20101	-4.34951	-4.86167

Table 4.1. Total energy, Vander-Waal interaction, Hydrogen bonding, electrostatic energy compounds A and B on interaction with PDB 3OG7.

Complex	Total Energy	VDW	H-Bond	Electrostatic
A	-142.457	-121.406	-22.8196	1.76873
B	-121.366	-104.657	-16.7095	0

Table 4.2. Amino acid involved in the docking of the Complex A and B on interaction with PDB 3OG7

Complex	Energy	H-S-LYS-483	H-M-CYS-532	H-M-ASP-594	V-S-VAL-471	V-S-LYS-483	V-S-LEU-505	V-S-TRP-531	V-M-CYS-532	V-S-PHE-583	V-M-GLY-593	V-M-ASP-594
A	-142.5	-6.4374	-3.5	-3.5	-5.05739	-4.8195	-5.9143	-3.96181	-3.13759	-14.9378	-4.4264	-9.45443
B	-121.4	-8.48415	0	-4.7253	-3.18111	-9.53611	-8.27708	-1.15623	-0.99628	-7.73161	-4.04721	-5.52531

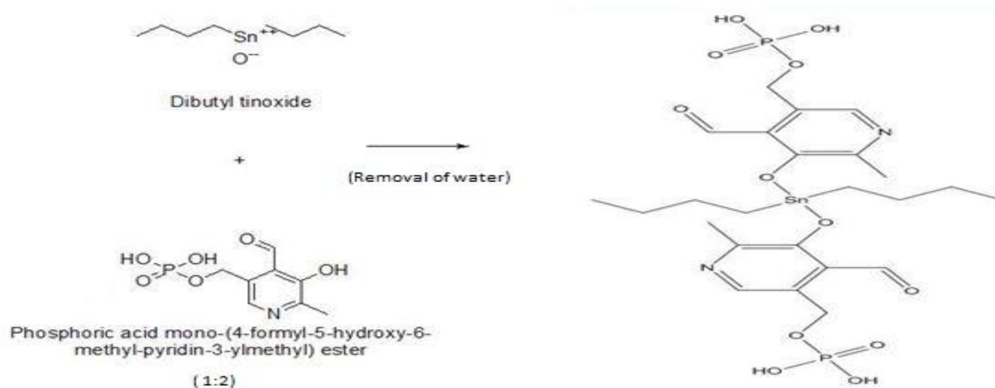


FIGURE 1 (Scheme 1.1): Reaction pathway for the formation of dibutyltin (IV) complex A.

The above reaction was found to be facile and was completed within 5-6 hours of refluxing.

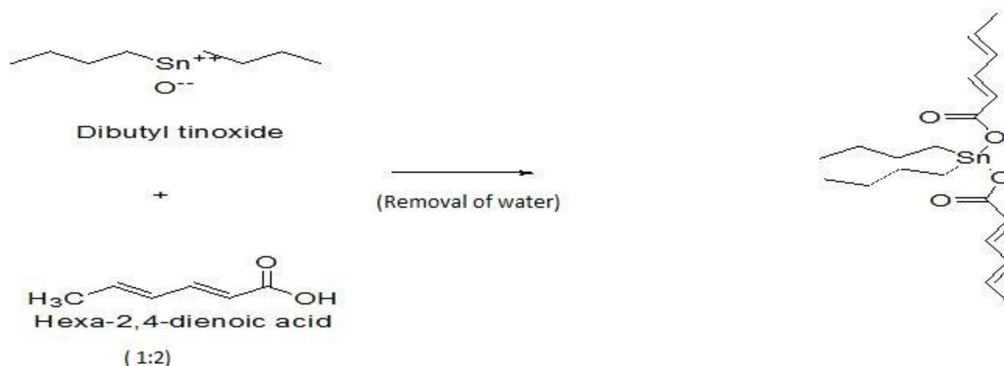
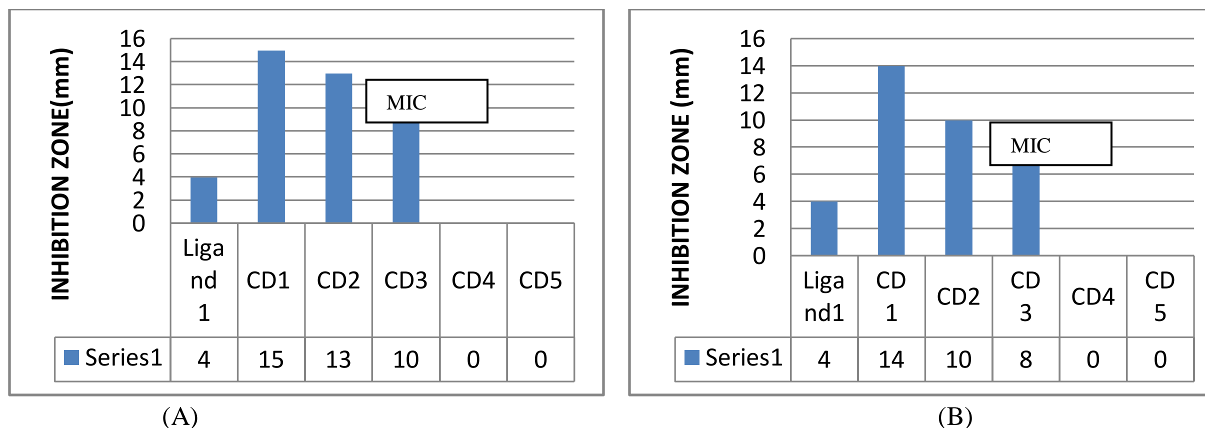


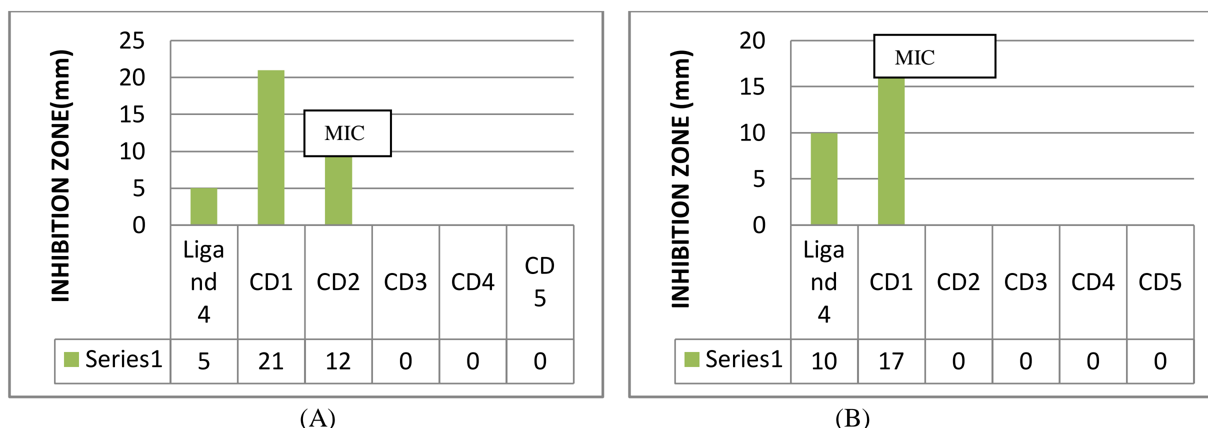
FIGURE 1(Scheme 1.2) : Reaction pathway for the formation of dibutyltin (IV) complex B

The above reaction was found to be facile and was complete within 5-6 hours of refluxing.



(A) (B)

Figure 2.1: Graph Showing Inhibition zone of Complex A against (A) Escherichia coli 1610(gram negative),(B) Staphylococus aureus (gram positive)



(A) (B)

Figure 2.2: Graph Showing Inhibition zone of Complex B against (A) Escherichia coli 1610(gram negative),(B) Staphylococus aureus (gram positive)

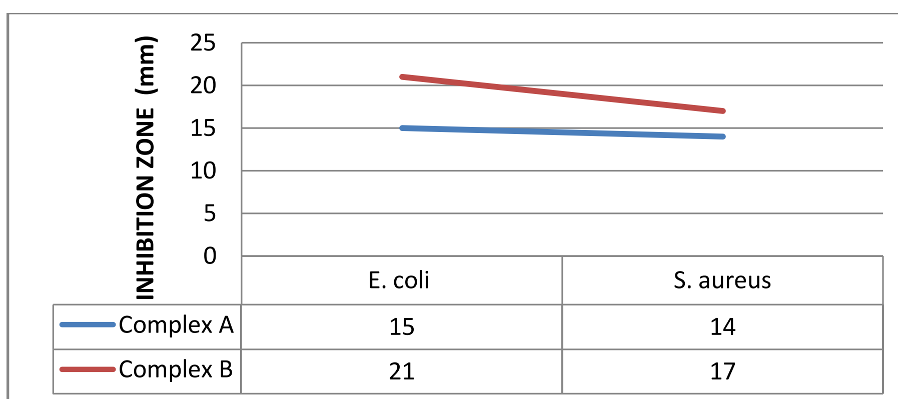


Figure 2.3: Graph showing the Antimicrobial action against different strains, complex concentration used 0.002 g/100 mL

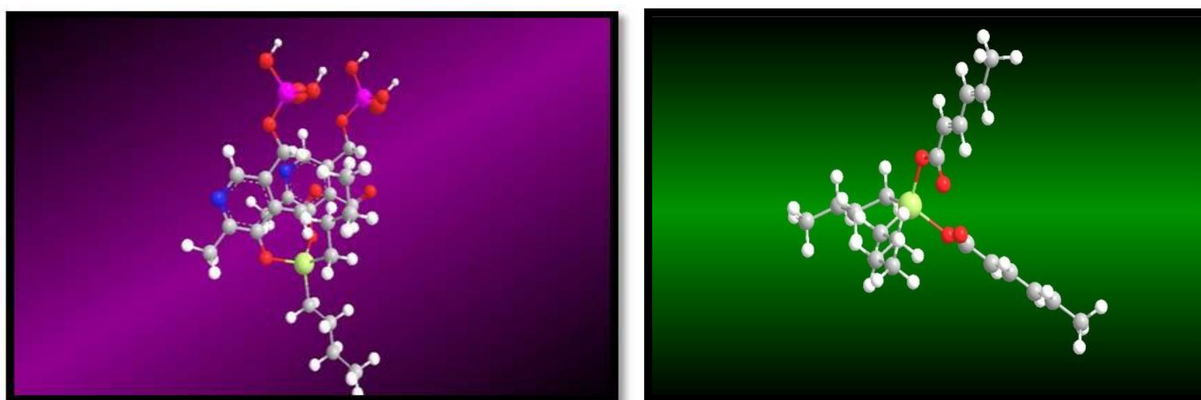


Figure 3.1: Proposed 3D structure of Complex A and Complex B (SOFTWARE USED Chem Bio 3D Ultra 13.0 and Chem Draw Pro 13.0.)

Different colors indicate: Green – tin atom ; Blue – nitrogen atom : Red –oxygen atom ; pink – phosphorus atom ;Grey –carbon atom ;White –hydrogen atom.

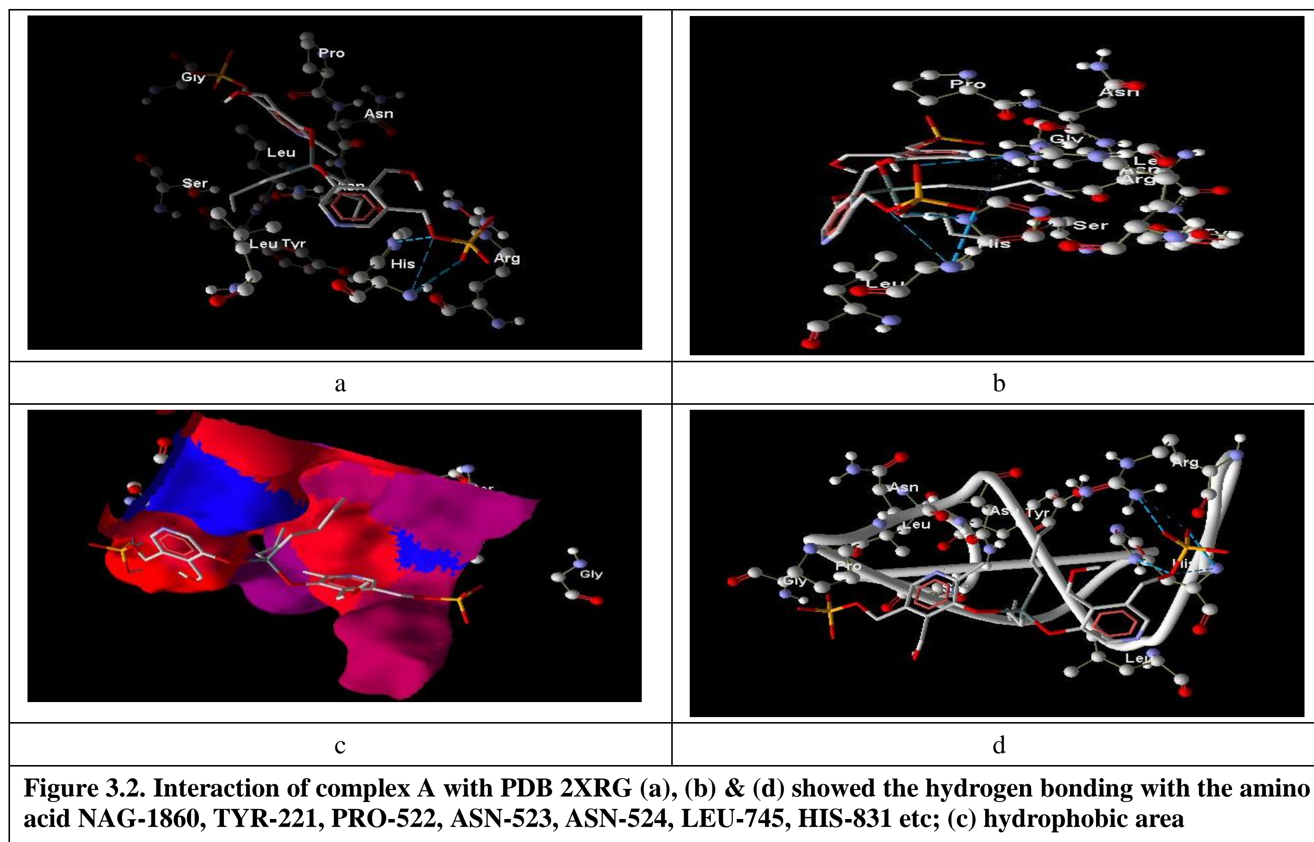
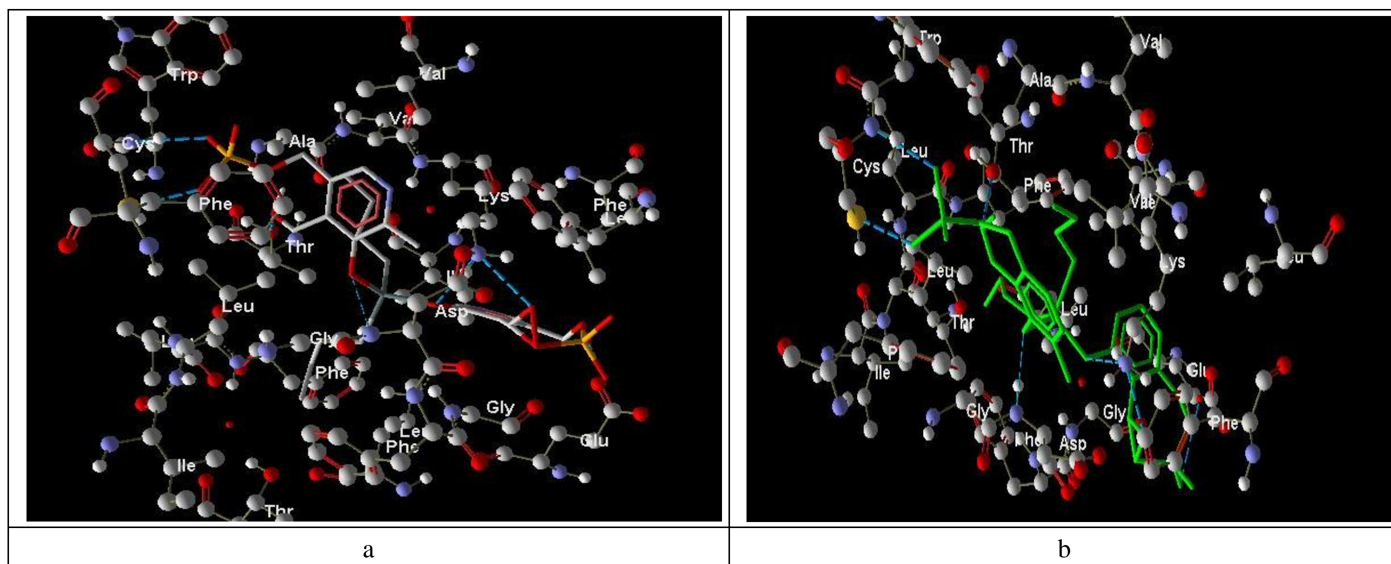
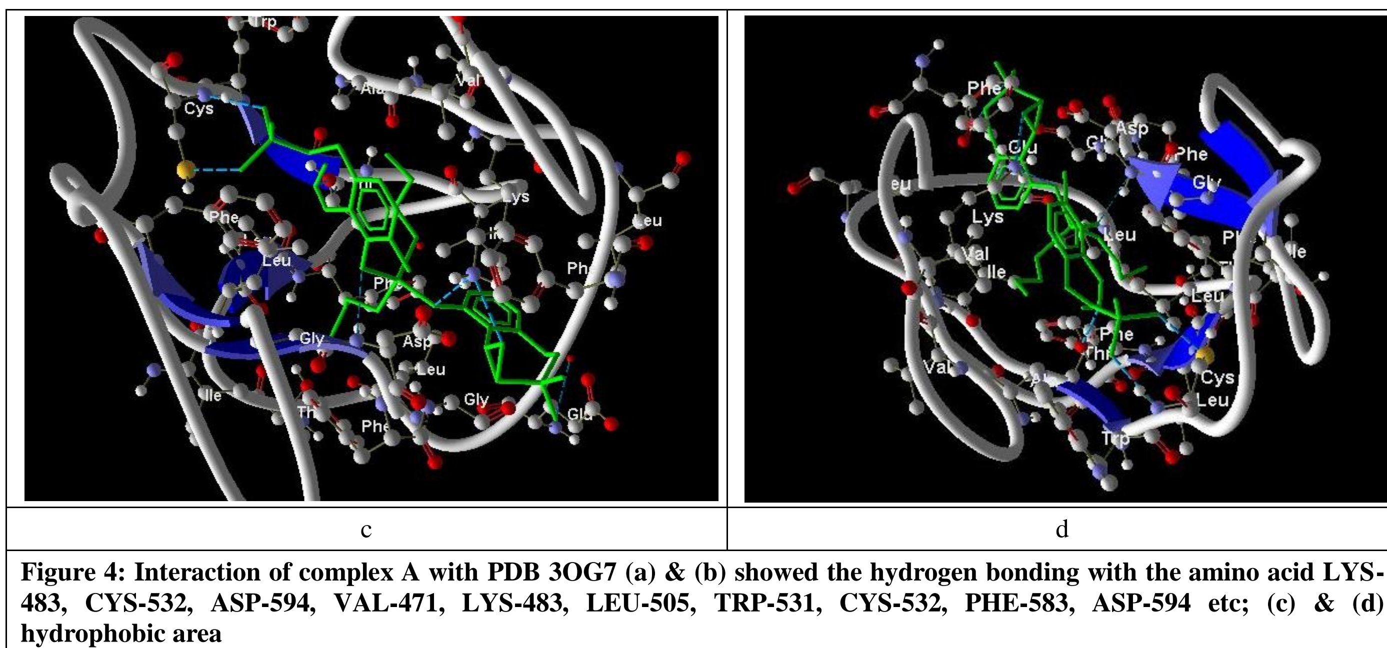


Figure 3.2. Interaction of complex A with PDB 2XRG (a), (b) & (d) showed the hydrogen bonding with the amino acid NAG-1860, TYR-221, PRO-522, ASN-523, ASN-524, LEU-745, HIS-831 etc; (c) hydrophobic area





c	d

Figure 4: Interaction of complex A with PDB 3OG7 (a) & (b) showed the hydrogen bonding with the amino acid LYS-483, CYS-532, ASP-594, VAL-471, LYS-483, LEU-505, TRP-531, CYS-532, PHE-583, ASP-594 etc; (c) & (d) hydrophobic area

CONCLUSION

The Complexes exhibited a good antimicrobial and antifungal potency higher than those of the corresponding ligands this must be due to compexation of the ligand with the parent Dibutyltinoxide. On the basis of docking of the complex A and complex B with PDB 2XRG and 3OG7, complex A gave minimum energy. Therefore, it was proven to be inhibitor for RNAse and B-Raf Kinase also has the ability to affect the antisense effect and inhibit the destroying of mRNA strand. 2XRG is involved in various pathologies including tumor progression and inflammation so via the inhibition this enzyme using compound A. Further, compound A can also inhibit the B-RAF Kinase activity and therefore, could benefit melanoma patients. These complexes have potency to use as drug.

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