



Synthesis, Spectral Characterization and Antimicrobial Activities of Binuclear Titanium (IV) Complexes With Schiff Bases Derived From 4-Amino-3-Hydrazino-6-Methyl-5-Oxo-1,2,4-Triazine

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Accepted on 20th July 2016

ABSTRACT

Titanium (IV) complexes of type $[(\eta^5-C_5H_5)_2TiCl_2(L)]$ have been synthesized by the reactions of bis(cyclopentadienyl) titanium (IV) dichloride with Schiff bases (LH_2) derived by the condensation of 4-amino-3-hydrazino-6-methyl-5-oxo-1,2,4-triazine with 2-hydroxy aldehyde/ketone in ethanol in 2:1 molar ratio in dry tetrahydrofuran in the presence of triethylamine. All these complexes are soluble in $PhNO_2$, DMF and DMSO. The complexes were characterized by elemental analyses, electrical conductance, magnetic susceptibility, and UV-Vis, IR, and 1H NMR spectral techniques. Low molar conductance values indicate that they are non-electrolytes. The spectral data indicate 5-coordinate geometry for the metal ion in all complexes. In vitro antifungal and antibacterial activities were determined by screening the compounds against the three fungi (*A.niger*, *A. fumigate* and *H. oryzae*) and gram negative (*E. coli*) and gram positive (*B. subtilis*) bacterial strain. The binuclear titanocene (IV) complexes have higher antimicrobial effect than the parent Schiff bases.

Keywords: Titanocene, Schiff base, IR, NMR, Antimicrobial.

INTRODUCTION

Over the past several years, there has been a substantial interest in the application of titanium complexes in biological applications. Titanium and its derivatives are extensively used as disinfectant [1], antibiotic [2], biological sensor [3], tumour cell killing agent [4] and gene targeting device [5]. It is an effective antimicrobial agent that kill bacterial cell in water due to the generation of reactive oxygen species [6] which decomposes the cell of bacteria, fungi, algae and viruses due to the oxophilic nature and formation of strong bonds with various biological molecules. The titanium (IV) species are also useful as anticancer agent [7].Titanocene dichloride or in its complexes Ti-Cl bond undergoes rapid hydrolysis in biological system. After hydrolysis titanocene and its derivatives interact with DNA [8-9]. Due to this type of interaction with DNA, titanocene and its derivatives form interstrand or intrastrand DNA cross-links which result DNA double strand break and lead to cell damage [10]. It was reported that photoexcited anatase TiO_2 particles could effectively induces cytotoxicity against HeLa cancer cells [11]. These photoexcited anatase TiO_2 particles will effectively damage the human colon carcinoma cell [4]. Due to the lower

toxicity and less acute side effects exhibited by the titanium (IV) materials, these are found to be highly attractive in various therapeutic applications.

On the other hand, 1,2,4-triazine are an important type of oxygen and nitrogen containing aromatic heterocyclic compounds, possess desirable electronic and charge-transport properties and the various functional groups are easily introduced into the structurally rigid triazine ring. These characteristics resulted in the extensive potential applications of triazine based derivatives in the field of medicinal chemistry. 1,2,4-triazine derivatives have been found to exhibit diverse biological activities such as antitubercular [12], anti-AIDS [13], anti-inflammatory [14], potent CRF receptor antagonists [15] anticancer [16], cathepsin K inhibitor, agriculture [17] as well as used as analytical reagent [18]. The widespread use of 1, 2, 4-triazine as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocycles.

The present paper includes the synthesis, characterization and antimicrobial activities of bis (cyclopentadienyl) titanium(IV) complexes with Schiff bases derived from 4-amino-3-hydrazino-6-methyl-5-oxo-1,2,4-triazine.

MATERIALS AND METHODS

All reactions were carried out under strictly anhydrous conditions. Glass apparatus with interchangeable quick fit joints were used throughout. THF was dried by heating under reflux over Na wire. The Et_3N was purified by published methods [19]. Bis (cyclopentadienyl) titanium (IV) chloride was purchased from Aldrich. The ligands were prepared as reported in literature [20].

Instruments: Elemental analysis was measured with ElementarVario EL III. Titanium was estimated gravimetrically as its oxide. The known weight of the compound was added in concentrated nitric acid and heated up to a small volume. Then the solution was diluted with distilled water and titanium precipitated as its hydrated oxide by adding ammonia solution. This precipitate was collected on Whatman filter paper no. 41, washed with distilled water and ignited in a silica crucible to TiO_2 . ^1H spectra were recorded by a Bruker Avance III, 400MHz. Chemical shifts are reported in ppm and are referenced to TMS. Infrared spectra ($4000\text{-}200\text{cm}^{-1}$) of the ligands and complexes were recorded as KBr pellets on a Nicolet-5700 FTIR Spectrophotometer. Progress of reaction and purity of the compounds were confirmed by pre-coated TLC plates (Merck, 60F-254) and spots were visualized using iodine vapours. The magnetic susceptibility at room temperature was measured by Gouy's method using $\text{Hg}[\text{Co}(\text{NCS})_4]$ as calibrant. Electronic spectra of the complexes were recorded on Beckmann DU-2 spectrophotometer and C ϕ 10 spectrophotometer instruments using DMSO as a solvent. Conductance measurements were recorded in DMSO using Toshniwal conductivity bridge model no. c/01/01, provided with a dip type conductivity cell fitted with Pt electrodes.

Synthesis of binuclear titanium (IV) complexes by conventional method: A mixture of bis (cyclopentadienyl) titanium(IV) chloride (60 mmol) and appropriate Schiff base derived from 4-amino-3-hydrazino-6-methyl-5-oxo-1,2,4-triazine (30 mmol) was dissolved in dry tetrahydrofuran (30 cm^3). To the resulting clear solution, triethylamine (60 mmol) was added and the mixture was refluxed for ca10–12 h at room temperature. The coloured complexes, so obtained, were recrystallized from a mixture of dimethylformamide and ether and then dried in vacuo.

Synthesis of binuclear titanium (IV) complexes by microwave assisted method: A mixture of bis (cyclopentadienyl) titanium (IV) chloride (6mmol) and appropriate Schiff base derived from 4-amino-3-hydrazino-6-methyl-5-oxo-1, 2 ,4-triazine (3 mmol) was dissolved in dry tetrahydrofuran (5 cm^3). To the resulting clear solution, triethylamine (6mmol) was added. The reaction mixture was irradiating in microwave oven for 15-20 min. The prepared complexes were recovered from microwave oven. The

coloured complexes, so obtained, were recrystallized from a mixture of dimethylformamide and ether dried in vacuo.

The synthetic route for the preparation of ligands and their corresponding binuclear titanium (IV) complexes is given in figure1. The comparison between conventional method and microwave assisted method given in table1.

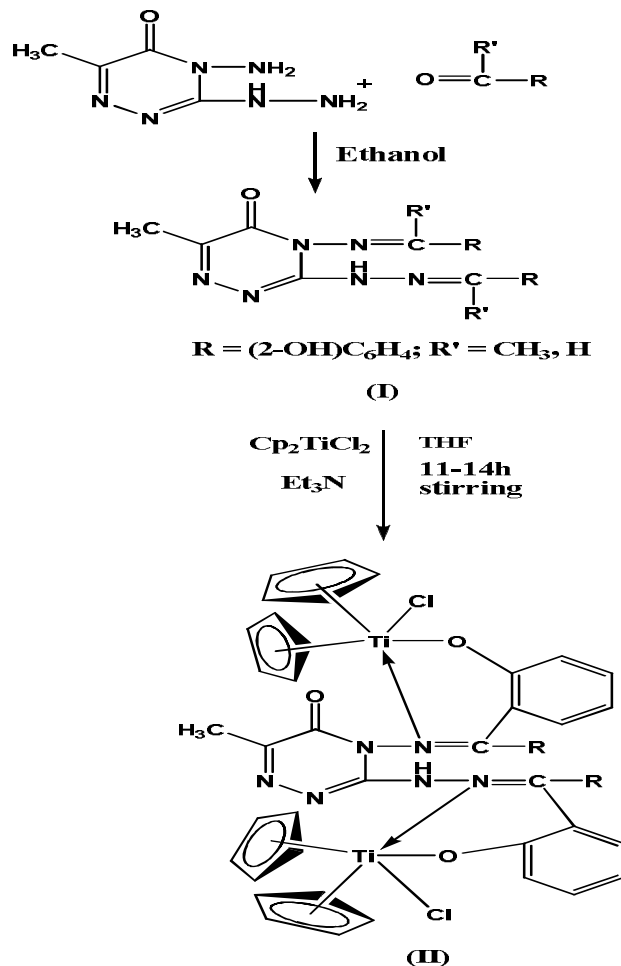


Figure.1 Reaction scheme for the preparation of Schiff bases (I) and their corresponding binuclear titanium (IV) complexes (II)

Table-1 Comparison between stirring and microwave method

Compounds	Yield (%)		Solvent		Time	
	Stirring	Microwave	Stirring	Microwave	Stirring	Microwave(min)
($\eta^5\text{-C}_5\text{H}_5$) ₂ TiCl ₂ } L ¹	61	73	60	5	12	10
[{($\eta^5\text{-C}_5\text{H}_5$) ₂ TiCl ₂ }] ₂ L ²	65	79	60	5	14	16

Biological activity study: Synthesized Schiff bases and binuclear titanium (IV) complexes were screened for their antimicrobial activity against two bacteria (*Escherichia coli* and *Bacillus subtilis*) and three fungi (*A. niger*, *A. fumigate* and *H. oryzae*).

Bio safety during the antibacterial and antifungal activity: The antimicrobial properties of the Schiff bases (L¹H₂-L²H₂) and their binuclear titanium (IV) complexes were tested against three fungal strains *A.niger*, *A. fumigate* and *H. oryzae* and two bacteria namely *B.subtilis*, and *E.Coli*. Bacteria/fungi are

potentially hazardous and care should be taken while working with them. Standard bio safety lab techniques were followed while handling bacteria /fungi and various media. Gloves were used during all experimentation, and any accidental spills were immediately sterilized using 70% isopropanol/water followed by bleach. The work area was also sterilized with 70% isopropanol/water after completion of work unused media and bacteria suspensions were first deactivated with commercial bleach for 1 h before being disposed in biosafety bags. All material that had come in contact with bacteria (pipette tips tubes, plates, etc.) was also thrown in biosafety bags in tightly closed bins. Bio safety bags were autoclaved for 2 h before final disposal.

Growth of inhibition: All Schiff bases and binuclear titanium (IV) complexes were screened for their activity against three fungal organism *A. niger*, *A. fumigate* and *H. oryzae* and two bacteria namely *E. coli* and *B. subtilis* by Petri dishes method [29]. Fungicidal and bactericidal activity of each compound was evaluated at three different concentrations 10, 100 and 1000 $\mu\text{g mL}^{-1}$. For each compound 1% standard solution was prepared and 1 mL of the solution was diluted with 9 mL of the solvent (DMSO). Petri dishes of equal diameter were sterilized at 180°C. Stock solutions of each compound were prepared for three concentration 10, 100 and 100 $\mu\text{g mL}^{-1}$. Solution of 1 mL of each concentration was poured in presterilized Petri dishes and 9 mL of agar medium was added immediately. Each dish was rotated on the table top in order to achieve thorough mixing of medium with the compound. After this, fungus and bacterial strain was inoculated in the dishes (diameter 5 mm). These set were then inoculated at 28°C. The colony diameter of the test organism was measured with mm scale after 6 days. The percentage Inhibition of the growth of the test organism was calculated by the following formula.

$$\text{Inhibition (\%)} = \frac{\text{Cd} - \text{Td}}{\text{Cd}} \times 100$$

Where Cd = colony diameter of control; Td = colony diameter of treated set.

[{ $(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}$ }]₂L¹]: Buff colour solid; yield (%): 61 (stirring method), analyses (%) found (calc. for C₄₀H₃₈N₆O₃Cl₂Ti): C- 58.07(58.89), H - 4.32 (4.80), N - 10.69 (10.92), Ti-11.95 (12.03); mol. wt found (calc.): 786 (787.46); UV- Vis (nm): 430,310; IR(cm^{-1}): 3305, (ν N-H amine), 1660s (ν C=O), 1605s (ν C=N azomethine group), 440m (ν Ti-N), 475m (ν Ti-O), 1350s (C-O phenolic), 3000m,1420m,1015m, 810w ($\eta^5\text{-C}_5\text{H}_5$); ¹HNMR(δ): 11.07 (s N-H), 6.55 (s $\eta^5\text{-C}_5\text{H}_5$), 2.18 (s CH₃ at C-6 of triazene ring), 2.95 (s CH₃ of azomethine), 7.50-7.85 (m, phenyl ring).

[{ $(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}$ }]₂L²]: Buff colour solid; yield(%): 65 (stirring method), analyses (%) found (calc. for C₄₀H₃₈N₆O₃Cl₂Ti): C-58.86 (59.02), H- 4.90 (5.07), N-10.29 (11.25), Ti-11.55(12.23); mol wt found (calc.): 816.34 (817.92); UV- Vis (nm): 427, 298; IR (cm^{-1}): 3000m, (ν N-H amine), 1658s (ν C=O), 1600s (ν C=N azomethine group), 455m (ν Ti-N), 475m (ν Ti-O), 1350s (C-O phenolic), 3000m,1415m,1020m, 800w ($\eta^5\text{-C}_5\text{H}_5$); ¹HNMR(δ): 11.05 (s N-H), 6.75 (s $\eta^5\text{-C}_5\text{H}_5$), 2.20 (s CH₃ at C-6 of triazene ring), 1.81 (s CH₃ of azomethine), 7.65-7.70 (m phenyl ring).

RESULTS AND DISCUSSION

4-Amino-3-hydrazino-6-methyl-5-oxo-1,2,4-triazine reacts with 2-hydroxyacetophenone /salicylaldehyde (1:2) in ethanol in acidic medium to give Schiff base ligands (LH₂) (I). These ligands react with bis(cyclopentadienyl)titanium(IV) dichloride in dry tetrahydrofuran in presence of triethylamine to give coloured amorphous products of type [$(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}$]₂(L), (II) as shown in fig1.

The complexes are soluble in nitrobenzene, dimethylformamide and dimethylsulphoxide. The molar conductance values in DMF are in range of 10-18 $\text{ohm}^{-1}\text{cm}^2 \text{mol}^{-1}$ indicating nonelectrolyte behaviour in solution. Magnetic susceptibility measurement shows their diamagnetic nature.

Electronic spectra: The electronic spectra of all the complexes showed a single band in the region of 410 - 430 nm, which was assigned to the charge transfer band and is in accordance with an (n-1) $d^0 \text{ns}^0$

electronic configuration [21]. One more band was observed at ca 260-310 nm, which may be due to intra-ligand transition.

Infrared spectra: The characteristic FT-IR spectral bands of the complexes are given in experimental section (2.4). The IR spectra provide valuable information regarding the nature of the functional group attached to the metal atom. Schiff bases appear suggested by a broad band (solution spectra) at 2650 cm^{-1} , due to intramolecular H-bonded OH group which disappears in their corresponding titanium (IV) complexes indicating the coordination of phenolic oxygen to titanium metal ion through deprotonation. This band is absent in their corresponding titanium (IV) complexes indicating the coordination of phenolic oxygen through deprotonation. This is further supported by the shift of phenolic C-O bond from 1280 cm^{-1} (in the free ligands) to ca. 1350 cm^{-1} in the complexes. The coordination through deprotonated phenolic oxygen is confirmed by a new band at ca $480\text{-}470\text{ cm}^{-1}$ assignable [22] to $\nu(\text{Ti-O})$. The infrared spectrum of the parent triazene shows band at 1660 cm^{-1} due to $\nu(\text{C=O})$ [23]. In the complexes, the position of $\nu(\text{C=O})$ band does not change appreciably indicating the noncoordination of carbonyl oxygen to the metal ion. The ligands also show one broad band at 3300 cm^{-1} which may be due to $\nu_{\text{sym}}(\text{NH})$ and $\nu_{\text{asym}}(\text{NH})$ vibration of the amine group. In the complexes these bands remain almost at the same position due to noncoordination of amino group to the metal. Band at ca. $1620\text{-}1605\text{ cm}^{-1}$ due to the $\nu(\text{C=N})$ vibration of the azomethine group was observed [24]. In the complexes, this band shifts to lower frequency ($15\text{-}10\text{ cm}^{-1}$) indicating the coordination of azomethine nitrogen to metal ion. This is further confirmed by the appearance of $\nu(\text{Ti-N})$ band at ca. $440\text{-}460\text{ cm}^{-1}$. The bands at 3000 cm^{-1} for $\nu(\text{C-H})$, ca. 1420 cm^{-1} for $\nu(\text{C-C})$, ca. 1015 cm^{-1} and 800 cm^{-1} for (C-H out of plane deformation) in the complexes are due to the cyclopentadienyl ring. These bands are similar to those similar for bis(cyclopentadienyl)titanium (IV) dichloride and their appearance indicates that the $(\eta^5\text{-C}_5\text{H}_5)$ group persists in the complexes [25].

On the basis of IR data, we conclude that the Schiff base ligands behave as dibasic, bidentate chelating agent having coordination sites at OH group and one azomethine nitrogen atoms.

^1H NMR spectra: The proton magnetic resonance spectra of ligands and their corresponding complexes were recorded in DMSO-d_6 . Chemical shift for proton in different environments have been given above. Coupling between various groups complicates the spectra but a comparison of spectra of ligands with those of the complexes can lead to following conclusions.

The complexes exhibit signal at δ 6.93-6.80 assigned to the cyclopentadienyl ring proton and indicate the rapid rotation of the ring about the metal axis [22]. Multiplet is observed at δ 7.39 -7.62 ppm due to aromatic protons in the Schiff bases and their corresponding binuclear titanium (IV) complexes. The ligands and the complexes show a singlet at δ ca. 11.05-11.07 due to the proton of $-\text{NH}$ group. All the ligands and complexes show a singlet at ca δ 2.2 due to three protons of methyl group attached at 6th position of triazene ring.

APPLICATIONS

Antifungal activity: The antifungal activity of the compounds was studied against three fungi *A. niger*, *A. fumigate* and *H. oryzae*. The results observed are tabulated (Table 2). The results were compared with the standard drug (Fluconazole). It has also been observed that titanium (IV) complexes have higher activity than corresponding free ligands. The binuclear titanium (IV) complexes containing ligand with 2-OH substituent shows better activity than other compounds. All complexes show slightly higher activity against *A. Niger* as compared to other fungi. It has been suggested that the ligands with N and O donor system might have inhibited enzyme production, since enzyme which requires a free hydroxyl group for their activity appears to be especially susceptible to deactivation by the ions of the complexes. Chelation reduces the polarity of central ion mainly because of partial sharing of its positive charge with donor groups and possible π -electron delocalization within the whole chelating ring. This chelation increases the lipophilic nature of the central atom which favors its permeation through lipid layer of cell membrane [26].

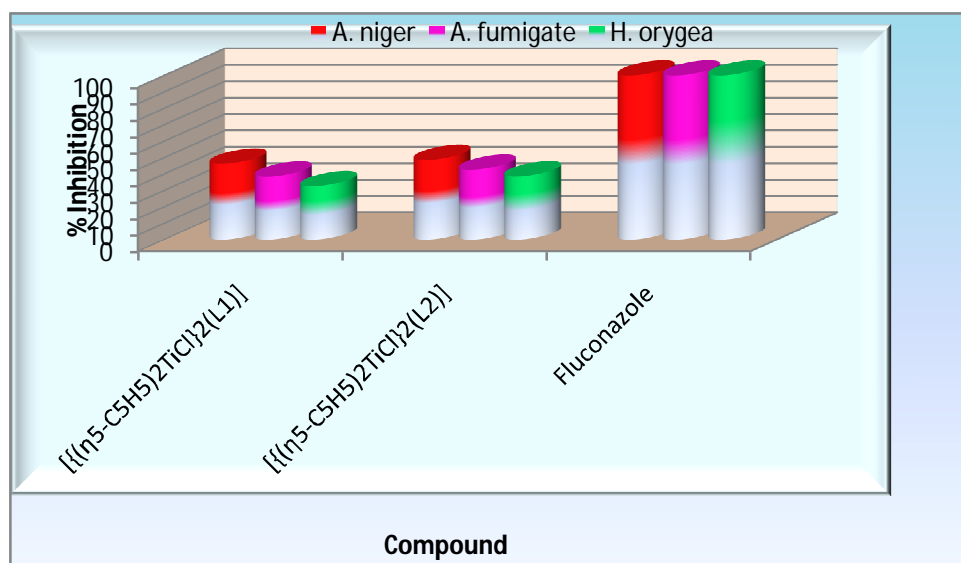
Furthermore, the mode of action of compounds may involve the formation of hydrogen bonds through the azomethine(C=N) group of complexes with the active centers of cell constituents resulting in the interference with normal cell process [27]. Though the complexes possess activity, it could hardly reach the effectiveness of the standard drug such as Fluconazole.

Some compounds are less effective, the variation in effectiveness depends on either on the impermeability of the cells of the microbes or on differences in the ribosome of microbial cells. The toxicity of compounds is directly proportional to the concentration. Antifungal activity is shown in Fig. 2.

Table-2 Antifungal Activity of titanium (IV) complexes in $\mu\text{g mL}^{-1}$

Complexes	<i>A. niger</i>			<i>A. fumigates</i>			<i>H. oryzae</i>		
	1000	100	10	1000	100	10	1000	100	10
$[(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}(\text{L}^1)]$	46.2	28.9	20.2	38.4	28.3	22.5	32.5	22.9	16.2
$[(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}(\text{L}^2)]$	48.5	26.5	26.0	42.6	27.5	20.2	38.5	21.6	14.6
fluconazole (standard)	100	100	100	100	100	100	100	100	100

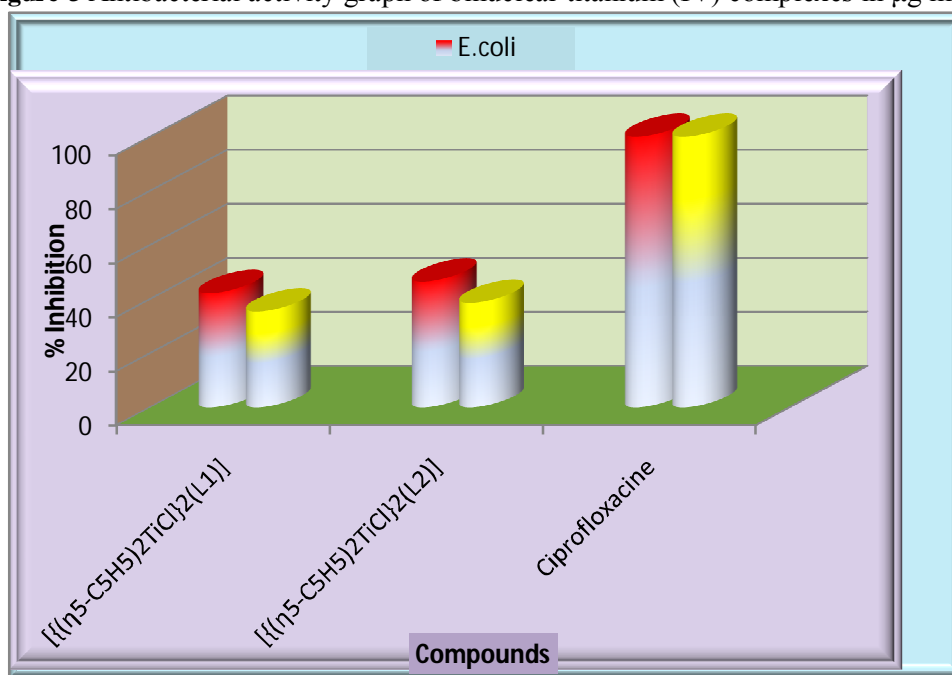
Figure-2: Antifungal activity graph of binuclear titanium (IV) complexes in $\mu\text{g mL}^{-1}$



Antibacterial activity: *In vitro* antibacterial results are reported in table 3 and shown in fig. 3. It is evident that coordination makes the ligands strong antibacterial agents and inhibits the growth of bacteria more than the parent ligand. The results were compared with those of the standard drug ciprofloxacin. All ligands and titanium (IV) complexes possess various percentage of inhibitory effects: low (upto 33%), moderate (upto 50%) and significant (above 55%). The antibacterial results of titanium (IV) complexes with ligands containing 4-OH group have greater chelating effect show significant inhibitory effect. The significant inhibition was displayed by all titanium (IV) complexes against all strains of Gram-positive bacteria. Generally it was observed that the Gram-negative bacteria were resistant to all the synthesized compounds. The extra outer layer on the cell wall of the Gram-negative bacteria acts as a barrier and needs high penetration of the compounds to reach the cell. The bacteria cell may also change the structure of its cell membrane and prevent the compound from entering into the cell of gram-negative bacteria.

Table-3 Antibacterial activity of titanium (IV) complexes in $\mu\text{g ml}^{-1}$

Complexes	1000	<i>B.subtilis</i>		<i>E.coli</i>		
		100	10	1000	100	10
$[\{(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}\}_2(\text{L}^1)]$	42.2	24.9	18.2	35.4	20.3	15.5
$[\{(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}\}_2(\text{L}^2)]$	46.5	22.5	23.0	38.6	17.5	19.2
fluconazole (standard)	100	100	100	100	100	100

Figure-3 Antibacterial activity graph of binuclear titanium (IV) complexes in $\mu\text{g mL}^{-1}$ 

CONCLUSIONS

The bis (cyclopentadienyl) titanium (IV) complexes with Schiff bases derived from 4-amino-3-hydrazino-6-methyl-5-oxo-1, 2, 4-triazine have been prepared by stirring and microwave assisted method. The frequency ranges of microwave heating are 900 and 2450 MHz. The major advantages of using microwaves for industrial processing are rapid heat transfer, and volumetric and selective heating [28]. For the microwave assisted synthesis, only 10–15 min was required to complete the reactions while in conventional method, the time required is 12–15 h. The yield of the products was also less in the conventional method as compared to that obtained by the microwave synthesis. Schiff bases ($\text{L}^1\text{H}-\text{L}^4\text{H}$) are monobasic, tetradentate ligands coordinating through azomethine nitrogen and oxygen atom (NO donor). The complexes are soluble in PhNO_2 , DMF and DMSO. The structures of Schiff bases and complexes have been established by elemental analysis and spectral studies IR, ^1H NMR. All these data puts together leads us to propose the structure of binuclear titanium (IV) complexes shown in **figure. 1**. Antifungal, antibacterial and activities of the ligands and corresponding complexes have also been evaluated which showed that the activities increase on chelation.

ACKNOWLEDGEMENTS

The authors are thankful to the SAIF STIC Cochin for providing IR, ¹HNMR. We thank the DRDO for financial support. Authors are also thankful to Department of Zoology, D.D.U Gorakhpur University, Gorakhpur for help in evaluating antibacterial studies.

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