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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF BIS (CYCLOPENTADIENYL) TITANIUM (IV) COMPLEXES

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Abstract

Titanium (IV) complexes of type [(η^5-C_5H_5)$_2$ TiCl(L)] have been synthesized by the reactions of bis(cyclopentadienyl)titanium(IV)dichloride with Schiff bases (LH) derived by the condensation of 5-(substituted aryl)-2-hydrazino-1,3,4-thiadiazole and indoline-2,3-dione in dry tetrahydrofuran in the presence of triethylamine. The complexes were characterized by elemental analyses, electrical conductance, magnetic susceptibility, UV-Vis, IR, ^{1}H NMR, ^{13}C NMR, XRD and SEM spectral techniques.In vitro antifungal activity of synthesized compounds was evaluated against fungi Aspergillus niger, Aspergillus flavus, Candida albicans and In vitro antibacterial activity was determined by screening the compounds against gram negative (P.aeruginosa, S.typhi) and gram positive (S. aureus and B. subtilis) bacterial strains using MIC method by serial dilution technique. The titanocene(IV) complexes have higher antimicrobial effect than the parent Schiff bases.

***Keywords**: Titanocene, Schiff bases, NMR, Antimicrobial*

Introduction

Titanium and its derivatives are extensively used as disinfectant [Tsuang *et al.*], antibiotic [Brabec and Novakova], biological sensor [Stefanou *et al.*], tumor cell killing agent [Zhang and Sun] and gene targeting device [*Sang et al.*]. It is an effective antimicrobial agent that kill bacterial cell in water due to the generation of reactive oxygen species [Verdiere *et al.*] which decomposes the cell of bacteria, fungi, algae and viruses due to the oxophilic nature and formation of strong bonds with various biological molecules. On the other hand, thiadiazole ring is reported to display various medicinal property by virtue of –N=C-S- linkage, which is a possible toxophore in many medicinal drug. This heterocyclic moiety is responsible for a broad spectrum of biological activities, antimicrobial [Akhtar *et al.*],

antidepressant [Bahadur and Singh], antitubercular [Bauer *et al*.], pesticides, herbicidal [Srivastava *et al*.; Xin and Huaxue].

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

Experimental

Materials and Reagents

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 [Vogel]. Bis(cyclopentadienyl)titanium(IV) dichloride was purchased from Aldrich. The ligands were prepared as reported in literature [Mishra *et al*.].

Instruments

Elemental analysis was measured with Elementar Vario 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 Whatmann filter paper no. 41, washed with distilled water and ignited in a silica crucible to TiO_2.^{1}H and ^{13}CNMR spectra were recorded by a BrukerAvanceIII, 400MHz. Chemical shifts are reported in ppm and are referenced to TMS. Infrared spectra (4000-200cm^{-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 vapour. The magnetic susceptibility at room temperature was measured by Gouy's method using $Hg[Co(NCS)_4]$ as callibrant. Electronic spectra of the complexes were recorded on Beckmann DU-2 spectrophotometer and Cϕ10 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. XRD of complexes recorded on BrukerAXS D8 Advance X-ray powder diffractometer.

Synthesis of titanium(IV) complexes

A mixture of bis(cyclopentadienyl)titanium(IV) dichloride (60 mmol) and appropriate Schiff base, derived from 5-(substituted aryl)-2-hydrazino-1,3,4-thiadiazoleand indoline-2,3-dione,(60mmol) was dissolved in dry tetrahydrofuran (30 cm^3). To the resulting clear

solution, triethylamine (60 mmol) was added and the mixture was refluxed for *ca*10-12 h at room temperature. The coloured complexes, so obtained, were recrystallized from a dimethylformamide and ether mixture anddried in vacuo.

The synthetic route for the preparation of ligands and their corresponding bis(cyclopentadienyl)titanium(IV)complexes is given in **(Figure.1)**

Biological activity study

Bio safety during the antibacterial and antifungal activity

The antimicrobial properties of the Schiff bases (L^1H–L^5H) and there titanium(IV) complexes were tested against three fungal strains *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans* and four bacteria namely *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Streptococcus aureus*. 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% isopropenol/water followed by bleach. The work area was also sterilized with70% isopropenol/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.

Antimicrobial studies

Antibacterial screening

The antibacterial properties of the ligands and their corresponding titanocene complexes were evaluated *In vitro* against (i) Gram-positive bacteria, *S.aureus, B.subtilis* and (ii) Gram-negative bacteria, *P. aeruginosa, S.typhi* by disk diffusion method. The bacterial strains were subculture in broth agar and incubated for 18 h at37˚C, and then freshly prepared bacterial cells were spread onto nutrient agar plate in a laminar flow cabinet. Sterilized paper disks (6.0mm in diameter) were placed on the nutrient agar plates. Five milligrams of each test compounds were dissolved in 1mL of DMSO separately to prepare stock solution. From stock solution, different concentrations 100, 50, 25, 12.5, 6.25, 3.12 and 1.625 µg/mL of eachcompound were prepared. Thus, proper amounts of the different concentrations of compounds were pipetted on the blank disks, which were placed on the plates. The plates were incubated at 37˚C for 24 h. The MICs, the lowest concentration (µg/mL) of the

testcompound that result no visible growth on the plate, were recorded. DMSO was used as a solvent control to ensure that the solvent had no effect on bacterial growth. Ciprofloxacin was designated in our experiment as a control drug.

Antifungal screening

The ligands and their corresponding titanocene complexes were screened for their antifungal activity against *Aspergillus niger, Aspergillus flavus and Candida albicans* (recultured) in DMSO by serial plate dilution method. Test compound (5µg) were dissolved in 1mL of DMSO, and solutionwas diluted with water (9mL). Further progressive dilutions withmelted Mueller-Hinton agar were performed to obtain required concentrations of 100, 50, 25, 12.5, 6.25, 3.12 and 1.625µg/mL. Petri disheswere inoculated with 1.5×10^{-4} colony forming units (CFU) and incubated at 37˚C for 26 h. The MICs in µg/mL were noted. Toensure that solvent had no effect on fungal growth, a control testwas performed with test mediumsupplemented with DMSO at the same dilutions as used in the experiment. Fluconazole was used as a standard drug.

Chemistry

$[(\eta^5\text{-}C_5H_5)_2TiCl(L^1)]$

Yellow color solid; M.P(˚C): 186, yield (%):66 (stirring method) 12h,conductance ($Ohm^{-1}cm^2mole^{-1}$): 7.3; analyses (%) found (calcd for $C_{26}H_{19}N_6O_3TiCl$): C-54.04(54.06), H-3.36 (3.39), N-14.56 (14.60), Ti-8.18(8.23); M.W. found (calcd): 577.37(577.69); Conductance ($Ohm^{-1}cm^2mole^{-1}$) 7.3; IR(KBr, cm^{-1}): 2978m (C-H aromatic), 1610s (ν C=N ring), 3274s (ν N-H group), 500m (ν Ti-O), 463m (ν Ti-N), 1330s (ν C-O), 1054s (C-S-C), 3022m, 1420m, 1015m, 810m(η^5-C_5H_5); ^{1}HNMR(300MHz, DMSO-d_6, δ, ppm): 6.93(s η^5 - C_5H_5), 7.53 - 7.62m (phenyl ring), 12.33s (NH); ^{13}CNMR(DMSO-d_6, δ, ppm): 116.4 (η^5 - C_5H_5), 130.1-152.7(aromatic ring), 156.2(C=N), 175.9, 174.7(thiadiazole ring).

$[(\eta^5\text{-}C_5H_5)_2TiCl(L^2)]$

Light orange color solid; M.P(˚C): 144, yield (%):62 (stirring method) 11h,conductance ($Ohm^{-1}cm^2mole^{-1}$): 9.4; analyses (%) found (calcd for $C_{26}H_{19}N_5SOTiCl_2$): C-55.14(55.16), H-3.35 (3.39), N-14.36 (14.38), Ti-8.30 (8.36); M.W. found (calcd): 566.37(566.69); IR(KBr, cm^{-1}): 2967m (C-H aromatic), 1608s (ν C=N ring), 3260s (ν N-H group), 493m (ν Ti-O), 458m (ν Ti-N), 1326s (ν C-O), 1052s (C-S-C), 3018m, 1420m, 1017m, 815m(η^5-C_5H_5); ^{1}HNMR(300MHz, DMSO-d_6, δ, ppm): 6.90(s η^5 - C_5H_5), 7.52 - 7.59m (phenyl ring), 12.31s (NH); ^{13}CNMR(DMSO-d_6, δ, ppm): 116.1 (η^5 - C_5H_5), 126.2-149.3(aromatic ring), 153.9(C=N), 175.5, 174.3(thiadiazole ring).

[(η^5-C_5H_5)$_2$TiCl(L^3)]

Brown color solid; M.P(˚C): 182, yield (%):69 (stirring method) 11h,conductance ($Ohm^{-1}cm^2mole^{-1}$): 6.7; analyses (%) found (calcd for $C_{27}H_{19}N_5SOTiCl$): C-59.34(59.35), H-4.03 (4.09), N-12.82 (12.85), Ti-8.60 (8.65); M.W. found (calcd): 546.37(546.69); IR(KBr, cm^{-1}): 2946m (C-H aromatic), 1600s (ν C=N ring), 3238s (ν N-H group), 480m (ν Ti-O), 446m (ν Ti-N), 1312s (ν C-O), 1042s (C-S-C), 2096m, 1420m, 1007m, 807m(η^5-C_5H_5); ^{1}HNMR(300MHz, DMSO-d_6, δ, ppm): 6.80(s η^5 - C_5H_5), 7.35 - 7.40m (phenyl ring), 1.07(CH_3), 12.18s (NH); ^{13}CNMR(DMSO-d_6, δ, ppm): 115.2 (η^5 - C_5H_5), 120.3-142.2(aromatic ring), 150.7(C=N), 173.1, 171.5(thiadiazole ring).

[(η^5-C_5H_5)$_2$TiCl(L^4)]

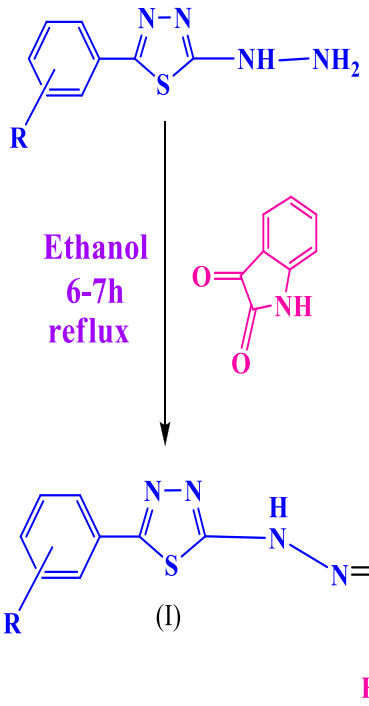
Light brown color solid; M.P(˚C): 151, yield (%):54 (stirring method) 12h,conductance ($Ohm^{-1}cm^2mole^{-1}$): 3.0; analyses (%) found (calcd for $C_{26}H_{19}N_5OTiCl_2$): C-59.34(59.35), H-4.07 (4.09), N-12.87 (12.88), Ti-8.62 (8.69); M.W. found (calcd): 546.49(546.82); IR(KBr, cm^{-1}): 2953m (C-H aromatic), 1602s (ν C=N ring), 3240s (ν N-H group), 484m (ν Ti-O), 452m (ν Ti-N), 1316s (ν C-O), 1047s (C-S-C), 3008m, 1420m, 1012m, 809m(η^5-C_5H_5); ^{1}HNMR(300MHz, DMSO-d_6, δ, ppm): 6.85(s η^5 - C_5H_5), 7.42 - 7.47m (phenyl ring), 1.09(CH_3), 12.23s (NH); ^{13}CNMR(DMSO-d_6, δ, ppm): 115.7 (η^5 - C_5H_5), 124.5-149.6(aromatic ring), 150.7(C=N), 174.6, 172.6(thiadiazole ring).

[(η^5-C_5H_5)$_2$TiCl(L^5)]

Brown color solid; M.P(˚C): 167, yield (%):78 (stirring method) 11h,conductance ($Ohm^{-1}cm^2mole^{-1}$): 5.2; analyses (%) found (calcd for $C_{26}H_{20}N_5SOTiCl$): C-58.63(58.69), H-3.76 (4.09), N-13.19 (13.59), Ti-8.82 (8.85); M.W. found (calcd): 546.49(546.82); IR(KBr, cm^{-1}): 2962m (C-H aromatic), 1605s (ν C=N ring), 3248s (ν N-H group), 489m (ν Ti-O), 453m (ν Ti-N), 1316s (ν C-O), 1050s (C-S-C), 3012m, 1420m, 1005m, 802m(η^5-C_5H_5); ^{1}HNMR(300MHz, DMSO-d_6, δ, ppm): 6.89(s η^5 - C_5H_5), 7.49 - 7.58m (phenyl ring), 12.27s (NH); ^{13}CNMR(DMSO-d_6, δ, ppm): 115.9 (η^5 - C_5H_5), 124.8-149.2 (aromatic ring), 151.9(C=N), 175.1, 173.4(thiadiazole ring).

Results and Discussion

5-(Substituted aryl)-2-hydrazino-1,3,4-thiadiazoles react with indoline-2,3-dionein ethanol in acidic medium to give Schiff base ligands (LH) (I). These ligands react with bis(cyclopentadienyl)titanium(IV) dichloride in dry tetrahydrofuran in presence of triethylamine to give coloured amorphous products of type [(η^5-C_5H_5)$_2$TiCl(L)], (II) as shown in Figure 1.



R = NO_2 (L^1H), R = Cl (L^2H), R = 2-CH_3 (L^3H)
R = 4-CH_3 (L^4H), R = H (L^5H)

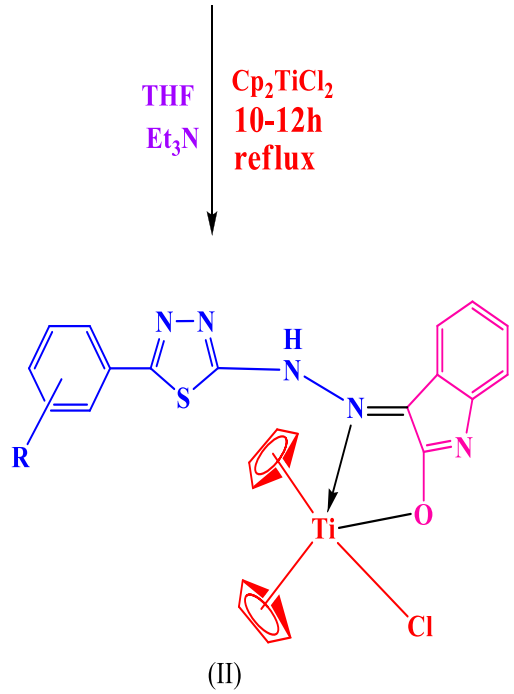


Figure.1 Reaction scheme for the preparation of Schiff bases (I) and their corresponding titanium(IV) complexes (II).

The complexes are soluble in nitrobenzene, dimethylformamide and dimethylsulphoxide. The molar conductance values in DMF are in range of 4-16 $ohm^{-1}cm^2$ mol^{-1} indicating nonelectrolyte behaviour in solution. Magnetic susceptibility measurement shows their diamagnetic nature.

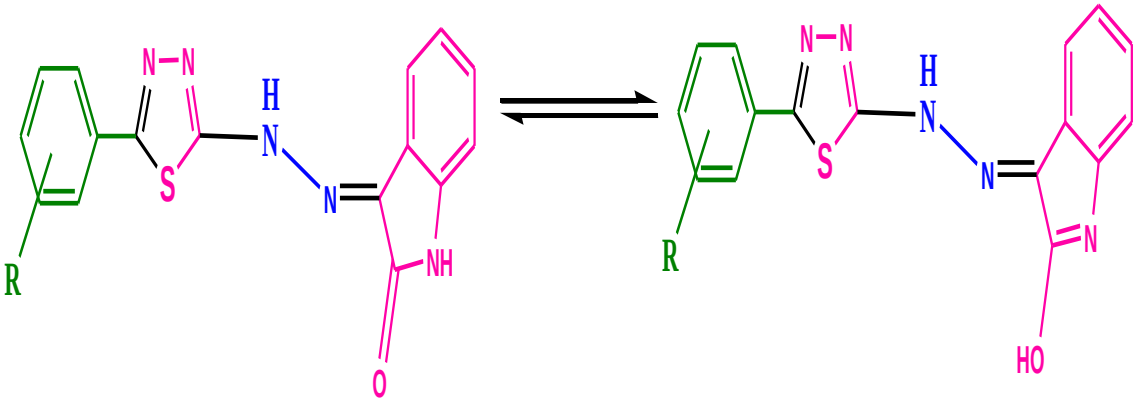
Electronic spectra

The electronic spectra of all the complexes showed a single band in the region of 428 - 475 nm, which was assigned to the charge transfer band and is in accordance with an $(n-1)d^0$ ns^0 electronic configuration [Rai *et al*.]. One more band was observed at ca 283-315 nm, which may be due to intra-ligand transition.

Infrared spectra

The IR spectra provide valuable information regarding the nature of the functional group attached to the metal atom. Schiff bases appear to exist in both keto and enol tautomeric forms **(Figure.2)** suggested by a broad band (solution spectra) at 2600 cm^{-1}, due to intramolecular H-bonded OH group which disappears in their corresponding Ti(IV) complexes indicating the coordination of phenolic oxygen to titanium metal ion through deprotonation. This is further supported by shift in phenolic (C-O) band from 1285 cm^{-1} (in the free ligand) to 1311-1330 cm^{-1} in the complexes. The coordination through phenolic oxygen further confirmed by the appearance of band at 479-500cm^{-1} assignable [Swamy and Pola]to ν(Ti-O). The spectra of Schiff bases show a medium band at 3238-3274 cm^{-1} due to ν(N–H) which remains almost at the same position in complex indicating the non-involvement of N–H group in bond formation. The ν(C-S-C) vibration appears as a strong band at ca.1050 cm^{-1} in the free ligands type (L^1H–L^5H). The position of which also remains the same in their corresponding complexes, indicating non-coordination of thiadiazole ring sulphur to metal atom. The ligands show one medium intensity band at 1630 cm^{-1} assignable [Banerjee *et al*.] to ν(C=N) which shifts to 1610-1600 cm^{-1} in the complexes. This shift indicates the coordination of azomethine nitrogen to metal ion. The bands at 452-463 cm^{-1} are assigned [Vatsa *et al*.] to ν (Ti-N). Absorption bands occurring at ca 2996-3022 cm^{-1} for ν(C–H), ca 1420 cm^{-1} for ν(C–C) and ca 1010 and 810 cm^{-1} for (C–H out-of-plane deformation) in the complexes are due to the cyclopentadienyl rings. These bands are similar to those reported for bis(cyclopentadienyl)titanium(IV) dichloride and their appearance indicates that the (η^5-C_5H_5) group persists in the complexes [Srivastava *et al*.].

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



[Keto form] **[Enol form]**

Figure.2 Synthesized Schiff bases in tautomer forms

^{1}H NMR spectra

The proton magnetic resonance spectra of ligands and their corresponding complexes were recorded in DMSO-d_6. 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. Schiff bases derived from indoline-2,3-dione of type (L^1H-L^5H) exhibit signals at δ5.52-5.60 ppm due to an indoline-2,3-dione NH proton. In titanium(IV) complexes [(η^5-$C_5H_5)_2$TiCl(L^1)] to [(η^5-$C_5H_5)_2$TiCl(L^5)] indoline-2,3-dione NH peak disappears. This confirms that the enol form (OH) of Schiff base reacted with metal ion via deprotonation. Multiplet is observed at δ 7.39 -7.62 ppm due to aromatic protons in the Schiff bases and their corresponding titanium(IV) complexes. Schiff bases and their corresponding titanium(IV) complexes also exhibit a signal at δ 1.03–1.09 ppm due to methyl protons. The ^{1}H NMR spectra of Schiff bases of type (L^1H-L^5H) exhibit signals at δ12.18-12.33 ppm due to NH of azomethine. In titanium(IV) complexes this signal shifts downfield. The downfield shift indicates the deshielding effect due to the coordination of azomethine nitrogen to central metal ion.

^{13}C NMR spectra

The ^{13}C NMR spectra recorded in DMSO-d6 of these complexes were given in experimental section (2.6) in DMSO-d_6. Schiff bases show signals at δ159.5-147.4 for their azomethine carbons and they shift downfield in their corresponding titanium(IV) complexes due to the coordination through azomethine nitrogen [Singh *et al*.]. For methyl carbon a signal appears at δ 9.5-10.8 in ligands (L^3H, L^4H) and their corresponding complexes. Schiff bases of type (L^1H-L^5H) and their corresponding titanium(IV) complexes show signals at about ca.δ169.4-175.5 assignable for thiadiazole ring carbons. These signals remain unchanged in their corresponding complexes indicating that thiadiazole ring nitrogen is not participated in bond formation. All complexes show peak at δ 115.2-116.4 ppm due to cyclopentadienyl group [Srivastava *et al*.]. The signal observed in the region δ 120.3-152.7 ppm as a multiplet could be assigned to aromatic carbons of ligands and their corresponding complexes.

Antimicrobial activity

The Schiff bases are found to be biologically active and their corresponding titanium(IV) complexes show significantly enhanced antibacterial (**Table. 2**) antifungal(**Table. 3**) (**Figures 3 and 4**). As chelation increases, bacterial and fungal growth inhibition also increases. Actual mechanism of increased activity of complexes is not certain but factors like solubility, dipole moment and cell permeability mechanism and their enzymatic action may be the possible reason. According to Overtone's concept of cell permeability, the lipid membrane surrounding the cell favours the passage of lipid-soluble materials, making the solubility an important factor controlling the antimicrobial activity [Parekh *et al*.]. Tweedy chelation theory the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the hetero chelates. The increased lipophilicity enhances the penetration of the hetero chelates into lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. These hetero chelates also disturb the respiration process of the cell and block the synthesis of proteins, which actually restricts further growth of the organisms. Furthermore ,the mode of action comprising the compounds may involve the formation of hydrogen bond through the azomethine/carbonyl/amine group with the active centre of cell constituents and interferences forced with the normal cell process [40].

Conclusion

Schiff bases (L^1H–L^5H) are monobasic, bidentate 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, ^{13}C NMR). All these data puts together leads us to propose the structure of titanium(IV)complexes shown in **Figure. 1.** Antifungal and antibacterial activities of the ligands and corresponding complexes have also been evaluated which showed that the activities increase on chelation.

Acknowledgements

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Table. 1: Antibacterial Activity of bis(cyclopentadienyl)titanium(IV) complexes with Schiff bases derived by the condensation of 5-(substituted aryl)-2-hydrazino-1,3,4-thiadiazole and indoline-2,3-dione

S. N.	Complexes	Antibacterial (MIC, $\mu g/ml$			
		S. aureus	B. subtilis	P. aeruginosa	S. typhi
1	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^1)]$	3.12	3.12	12.5	6.25
2	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^2)]$	1.62	3.12	3.12	6.25
3	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^3)]$	3.12	6.25	6.25	25
4	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^4)]$	6.25	12.5	12.5	12.5
5	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^5)]$	6.25	12.5	25	12.5
6	Ciprofloxacin	6.25	6.25	6.25	6.25

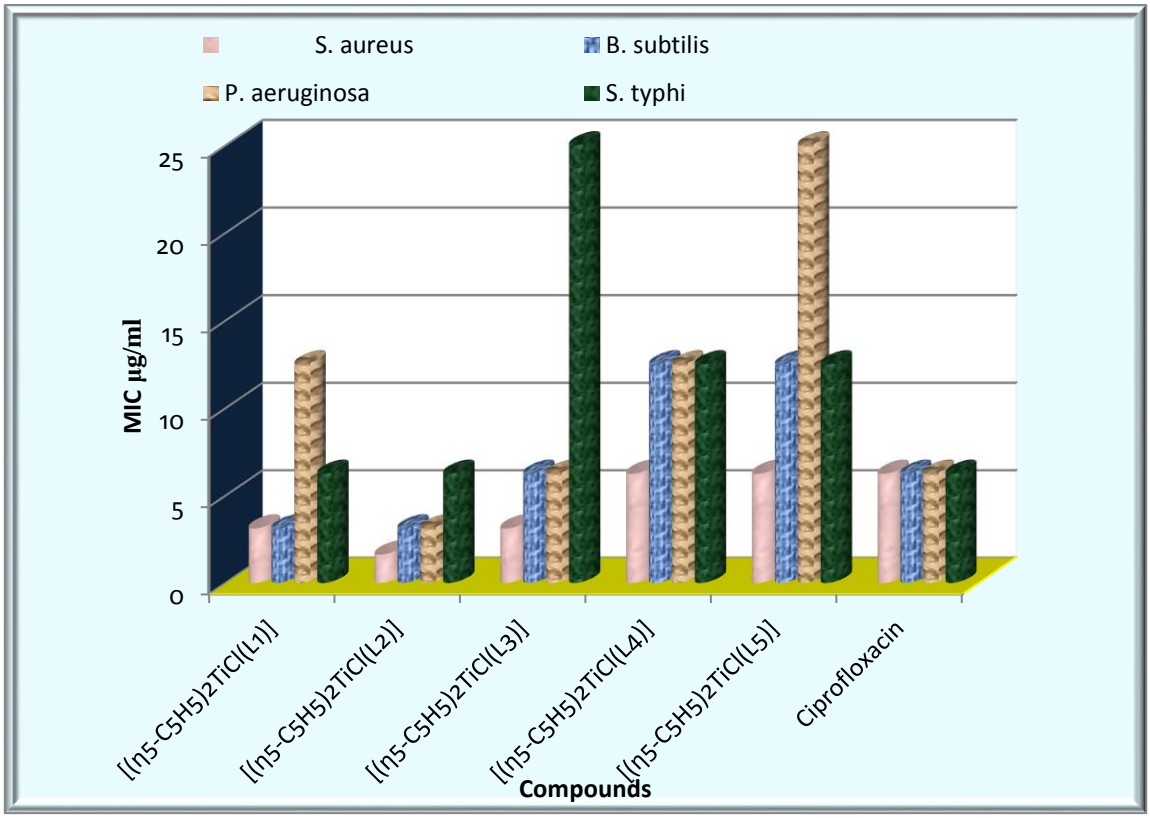

Figure. 3: Antibacterial activity of synthesized compounds and standard drug

Table. 2 : Antifungal Activity of bis(cyclopentadienyl)titanium(IV) complexes with Schiff bases derived by the condensation of 5-(substituted aryl)-2-hydrazino-1,3,4-thiadiazole and indoline-2,3-dione

S.N.	Complexes	Antifungal(MIC,$\mu g/ml$)		
		A. flavus	*A.niger*	*C. albicans*
1	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^1)]$	6.25	6.25	3.12
2	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^2)]$	3.12	3.12	1.62
3	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^3)]$	6.25	6.25	3.12
4	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^4)]$	12.50	3.12	3.12
5	$[(\eta^5\text{-}C_5H_5)_2TiCl(L^5)]$	12.50	6.25	6.25
6	fluconazole (standard)	3.12	3.12	3.12

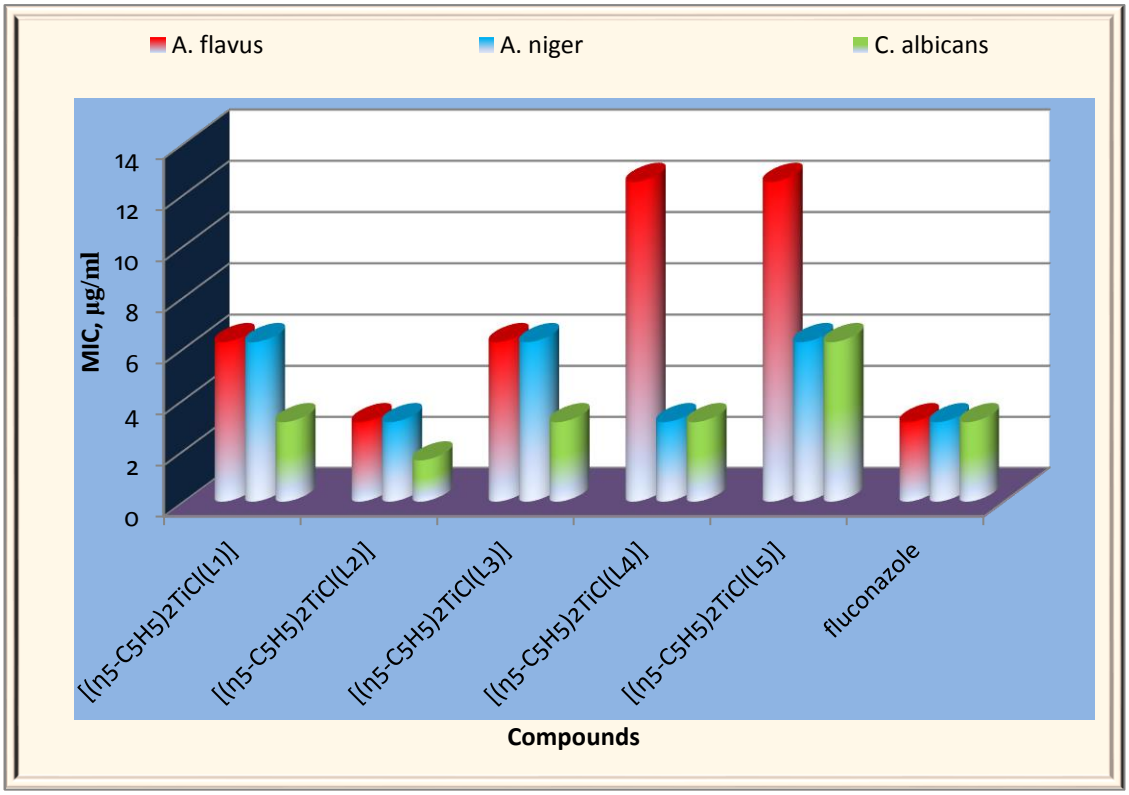

Figure. 4: Antifungal activity of synthesized compounds and standard drug.

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