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Syntheses and Biological screening of Schiff base complexes of Titanium(IV)

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The novel titanium(IV) complexes of composition $[TiCl_2(SB)_2]$ have been synthesized by reacting $TiCl_4$ and Schiff bases (SBs) where (SBs = A1(tetracycline hydrochloride schiffs base) ;B1(Streptomycin schiffs base) ;C1(Ceffixime schiffs base) ;D1(ampicillin schiffs base) in fixed molar ratio 1:2. Titanium and chlorine estimation were estimated by gravimetrical and Volhard method respectively. These were characterized by Mass, IR, UV- Visible, ^{1}H-NMR spectral techniques. The synthesized complexes were screened/tested for their antimicrobial activity against pathogenic bacterial strains i.e. Bacillus cereus MTCC 6728, Micrococcus luteus MTCC 1809, Staphylococcus aureus MTCC 3160, Staphylococcus epidermidis MTCC 3086, Aeromonas hydrophila MTCC 1739, Aclaligenes faecalis MTCC 126, Shigella sonnei MTCC 2957, Klebsiella pneumoniae MTCC 3384, Pseudomonas aeruginosa MTCC 1035, and Salmonella typhimurium MTCC 1253. It was found that metal complexes have more antimicrobial activity than their parent Schiff bases.

1. Introduction

Metal complexes have powerful antimicrobial such as silver bandages for treatment of burns, zinc antiseptic creams, bismuth drugs for the treatment of ulcers and metal clusters as anti-HIV drugs (Joseyphus and Nair, 2008). Metal complexes treatments as an antimicrobial agent (Scozzafava et al., 2011) is of great importance with the evolution of drug-resistant bacteria. Metal coordination complexes have been widely studied for their antimicrobial (Kamalakannan and Venkappayya, 2002) and anticancer (Aderoju et al., 2012) properties. Schiff's bases complexes continues to attract many researchers because of their wide application in food industry, dye industry, analytical chemistry, catalysis, amtimicrobial activity and pharmacological application like antitumoral, antifungal, antibacterial, antimicrobial etc. Schiff bases(SBs) are important intermediates for the synthesis of some bioactive compounds such as *ß*-lactams (Anacona, 2006) and employed as ligands for the complexation of metal ions. Among these novel metal complexes derivatives which show considerable biological activity may represent an interesting approach for designing new antibacterial drugs. This may be due to the dual possibility of both ligands plus metal ion interacting with different steps of the pathogen life cycle. In the present paper, we herein report the syntheses, characterization and antimicrobial activities of titanium(IV) complexes of SBs(A1,B1,C1,D1) derived from fructose and antibiotic drugs tetracycline hydrochloride, Streptomycin, Ceffixime, Ampicillin respectively.

2. Experimental

2.1 Reagents

Titanium tetrachlorides, tetracycline hydrochloride, Amoxicillin trihydrate, Ceffixime, Streptomycin, Ampicillin, fructose were obtained from Aldrich and Merck products and used as such after checking their melting point/ boiling point. All reagents and solvents were of AR grade and were purified by standard procedure. Infrared spectral measurements for the free ligand and its metal complexes were recorded in KBr pellets in the region 4,000 -200 cm^{-1} using a Perkin Elmer1600 FT-IR spectrophotometer. The

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absorbance maxima (λmax) were recorded on PerkinElmerLambda750 UV-Visible spectrophotometer in the range 300- 900 nm in methanol. ^{1}HNMR was recorded on Bruker AvanceII 400 NMR spectrometer using DMSO-d_6. Mass spectra were recorded on LC-MS spectrometer having mass Range of 4,000 amu in quadruple and 20,000 amu in ToF.

2.2 Synthesis of Schiff's bases

2.2.1 Tetracycline SB [$C_{28}H_{34}N_2O_{13}$] (A1)

Methanolic solution of fructose (0.56 mmol, 0.101 gm) was added to tetracycline (0.56 mmol, 0.25 gm) dissolved in methanol (25 mL) dropwise with constant stirring. pH of the reaction mixture was adjusted between 7- 8 by the addition of 0.1 % methanolic solution of NaOH. Reaction mixture was refluxed for 12 h to ensure the completion of reaction. Schiff base (A1) was extracted by the addition of diethyl ether at room temperature. A black colour solid obtained by the removal of water as side product and then dried over anhydrous $CaCl_2$ in vacuum. Schiff's bases of streptomycin, ceffixime, ampicillin with fructose were synthesized by adopting the above mentioned procedure. The colour of Schiff's bases varies from light yellow to reddish brown respectively.

2.3 Metal complexes of Schiff bases

2.3.1 Synthesis of [$Ti(A1)_2Cl_2$] ($TiCl_2C_{56}H_{66}N_4O_{26}$)

To a solution of $TiCl_4$ (0.28 mmol, 0.053 gm) in toluene was added dropwise into 20 mL methanolic solution of the SB (A1) (0.56 mmol, 0.34 gm) with continous stirring. After addition, the reaction mixture was refluxed for 10hrs. Completion of reaction was established by ceasation of evalution of HCl gas and reaction mixture concentrated to one-third volume through distillation. A dark black colored product was isolated by the addition of diethyl ether which was then filtered, washed with methanol and then dried over vacuum. Recrystallization of compound was done in methanol.

Yield 71.85 %, mp 300^{o}C; % Ti exp(cal.) 6.3(6.6); % Cl exp(cal.) 9.5(9.78); UV (MeOH) λ_{max} 235,281 nm; IR (KBr) v_{max} (3,408 cm^{-1}) –OH stretch intermolecular hydrogen bonding, (2961 cm^{-1}) aliphatic C-H stretch, (1604 cm^{-1}) –C=N stretch, (1,424 cm^{-1}) C=C ring stretch, (1266 cm^{-1}) C-O stretching and O-H in-plane bending vibration, (626 cm^{-1}) M-N stretch, (473 cm^{-1}) M-O stretch; ^{1}HNMR (DMSO-d_6, 400MHz) δ(ppm) =7.55(^{1}H,=CH), 15.5(-C=C-OH,s), 6-7(Phenolic - OH, broad ,1.5- 2.5(-CH_3); LC-MS Mass m/z = [M+H – H_2O]$^+$(427), [M+H-NH_3]$^+$(410), [M+H-NH_3-H_2O]$^+$ (392), [M+H-NH_3-H_2O-CO]$^+$(364), [M+H-NH_3-H_2O-CH_3]$^+$(377), [M+H-(CH_3)NH]$^+$(365), [M+H-(CH_3)NH-CO]$^+$(337).

Same procedure will be followed for the synthesis of titanium(IV) complexes with other Schiff bases i.e. [$Ti(B1)_2Cl_2$]:($TiCl_2C_{54}H_{96}N_{14}O_{34}$), [$Ti(C1)_2Cl_2$]:($C_{22}H_{36}N_5O_{12}S_2$), [$Ti(D1)_2Cl_2$]:($C_{22}H_{28}N_3O_9S$).

2.3.2 Synthesis of [$Ti(B1)_2Cl_2$] ($TiCl_2C_{54}H_{96}N_{14}O_{34}$)

Yield 85 %, mp >300^{o}C; % Ti exp(cal.) 6.4(6.7); % Cl exp(cal.) 8.9(9.5); UV (MeOH) λ_{max} 235-281nm; IR(KBr)v_{max} (3384 cm^{-1}) –OH stretch intermolecular hydrogen bonding, (1623 cm^{-1}) -C=N stretch (1459 cm^{-1}) -C-N stretch, (1369 cm^{-1}) -C-H bending, (626 cm^{-1}) -M-N, (1142 cm^{-1}) C-O stretching and O-H in-plane bending vibration; ^{1}HNMR (DMSO-d_6,400MHz) δ(ppm) = 2.5(-CH-OH), 3.4 - 4(-OH); LC-MS Mass m/z = [M+H-($C_6H_{12}O_5$)]$^+$(401), [M+H-($C_6H_{12}O_5$)-2CH_3]$^+$(371), [M+H-($C_6H_{12}O_5$)-2CH_3-N=C(NH_2)$_2$]$^+$(313), [M+H-($C_6H_{12}O_5$)-2CH_3-N=C(NH_2)$_2$-OH] (284).

2.3.3 Synthesis of [$Ti(C1)_2Cl_2$] ($C_{22}H_{36}N_5O_{12}S_2$)

Yield 87 %, mp 330^{o}C; % Ti exp(cal.) 5.9 (6.07); % Cl exp(cal.) 8.6 (9.0); UV (MeOH) λ_{max} 235,281 nm; IR (KBr) v_{max} (3440cm^{-1}) -OH stretch, (2942cm^{-1}) C-H stretch, (1618 cm^{-1}) C=N stretch, (1430 cm^{-1}) C-H def , (1066 cm^{-1}) C-N stretch, (666 cm^{-1}) M-N ,(486 cm^{-1}) M-O stretch; ^{1}HNMR (DMSO-d_6,400MHz) δ(ppm) =8.12 (-N-H,s), 3.4(-OH,s), 2.5(=CH_2 ,s) ; LC-MS Mass m/z = C_7 H_5O_3SN (187)

2.3.4 Synthesis of [$Ti(D1)_2Cl_2$] ($C_{22}H_{28}N_3O_9S$)

Yield 67 %, mp >300^{o}C; % Ti exp(cal.) 6.8(7.6); % Cl exp(cal.) 10.5(11.2); UV (MeOH) λ_{max} 235,281 nm; IR (KBr) v_{max} (3407 cm^{-1}) O-H group, (1648cm^{-1}) C=N stretch (1259cm^{-1}) C-O stretch, (1453cm^{-1}) C-H def , (1011cm^{-1}) C-N stretch , (676cm^{-1}) M-N stretch ,(468 cm^{-1}) M-O stretch; ^{1}HNMR (DMSO-d_6,400MHz) δ(ppm) = 8.2(H-N-C=O,s),8.2 (Ar-H), -OH (3.3,s), 2.5 (C-H); LC-MS Mass m/z = $C_{17}H_{17}N_3O_4S$ (360), $C_{17}H_{17}N_3O_4S$-CH_3 (345), $C_{13}H_{18}O_5N$ (268), C_9H_8ON (146).

2.4 Antibacterial activity

Antibacterial activity was determined by the Agar well diffusion method (Parekh et al., 2005). The investigated microorganisms were Bacillus cereus MTCC 6728, Micrococcus luteus MTCC 1809, Staphylococcus aureus MTCC 3160, Staphylococcus epidermidis MTCC 3086, Aeromonas hydrophila MTCC 1739, Aclaligenes faecalis MTCC 126, Shigella sonnei MTCC 2957, Klebsiella pneumoniae MTCC 3384, Pseudomonas aeruginosa MTCC 1035, and Salmonella typhimurium MTCC 1253. The compounds were dissolved in DMF solvent to obtain a final concentration 1mg/1mL. A loop full of the given test strain was inoculated in 25 mL of N-broth (nutrient broth) and incubated for 24 h in an incubator at 37 ºC in order to activate the bacterial strain. 28–30 mL of the nutrient agar media was added into a 100 mm diameter Petri-plate. Inoculation was done by the Pour-plate technique. 0.1 mL of the activated strain was inoculated into the media when it reached a temperature of 40 - 45 ºC. The complete procedure of the plate preparation was done in a laminar airflow to maintain strict sterile and aseptic condition. The medium was allowed to solidify. After solidification of the media, a well was made in the plates with the help of a cup-borer (0.85 cm), which was then filled with one of the test sample solutions. Controls were run (for each bacterial strain and solvent), where pure solvent was inoculated into the well. The plates were incubated for 24 h at 37 ºC. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds. The mean value obtained for two individual replicates was used to calculate the zone of growth inhibition of each sample.

3. Results and discussion

The analytical data of the complexes correspond well with the general formula $[ML_2Cl_2]$, where M = Ti(IV) ; L = Deprotonated Schiff bases. Schiff's bases complexes of titanium (IV) have been synthesized by reaction of $TiCl_4$ and Schiff's bases of corresponding antibiotic in a fixed 1:2 molar ratio in methanol with contnous stirring followed by refluxing. It can be rationalized in terms of following chemical equation:

$$TiCl_4 + 2\,SB \xrightarrow[\text{Reflux 16hrs.}]{\text{MeOH}} TiCl_2(SB)_2 + HCl\uparrow$$

3.1 UV-Visible Spectra

The UV-Visible spectra of Schiff's bases and their copper complexes were recorded in methanol solution at 300 K. The UV-VIS spectra of ligands showed two bands between 300-350 nm and 310-365 nm. The first band may be due to Π–Π* transition within the aromatic ring. The second band would be due to n-Π* transition within –C=N group. Due to complex with the metal n- π* transition shift to lower value indicating the coordination of ligand to metal. Since metal ion has d^0 configuration, so there is no possibility of d-d transition. The broadness of the band can be taken as an indication of distortion from perfect octahedral geometry

3.2 FTIR Spectra

FTIR spectra of complexes have provided the valuable information about the nature of binding mode and functional group(s) attached to the metal ion.. The IR spectra of the ligands showed a weak broad band at 1,690 cm^{-1} which are assigned to enolic –C=O group of SB(A1) moiety. Disappearance of this band in complexes has indicated that coordination through carbonyl group. The IR spectrum of SB(B1) has showed primary amine coupled doublet due to $–NH_2$ group at 3,370 cm^{-1}. Absence of band at 3,370 cm^{-1} further confirmed that coordination is through $–NH_2$ group. FTIR spectra of ligand C1 and D1 show a band in the region 1,725-1,730 cm^{-1} and 1,248-1,254 cm^{-1} assignable to the -COOH group. The absence of these bands in metal complexes revealed that the deprotanation of the –COOH group on complexation .IR spectra of all compounds showed a strong band at 3,600 – 3,300 cm^{-1} region which can be assigned to phenolic -OH group of ligand. It indicates that phenolic – OH group does not involved in coordination with metal ion. In the spectra of all the Schiff bases, there are strong bands at 1,630 cm^{-1} and 1,650 cm^{-1} due to -C=N groups. These bands were observed at 1,594 – 1,614 cm^{-1} region in complexes due to possible drift of the lone pair electron density towards the metal ion on coordination. In the synthesized complexes, there were appearance of new wide and strong peaks at 425-440 cm^{-1} and 320-385 cm^{-1} due to M-N, and M-Cl bonds (Prasad et al., 2011).

3.3 ^{1}H NMR spectra

^{1}H NMR spectra of the Schiff bases and their metal complexes were recorded in DMSO-d_6 solution. In the spectrum of metal complexes with A1, signal corresponding to phenolic protons at 9.5 ppm and enolic signal at 15 ppm are present indicating absence of participation of the phenolic oxygen at C-10 and enolic oxygen at C-12 of the ligand A1. In the spectrum of metal complexes with B1, signal corresponding to –

NH_2 protons at 2.2-2.9 ppm were get shifted to downfield 3.4 ppm indicating the presence of the participation of $–NH_2$ protons. In the spectrum of metal complexes with C1and D1, signal in the downfield region to the proton of the –OH group was absent indicating the deprotonation of the –COOH group and involvement of the oxygen atom in complexation. Complex formation further established by integration of signal in NMR spectrum.

3.4 Mass spectra of the Titanium(IV) complexes

The mass spectrum of titanium complex $[TiCl_2(A1)_2]$ gives peaks at m/e = 427, 410, 392,364, 377, 365, 337 and were assigned as $[M+H –H_2O]^+$, $[M+H\text{-}NH_3]^+$, $[M+H\text{-}NH_3\text{-}H_2O]$, $[M+H\text{-}NH_3\text{-}H_2O\text{-}CO]^+$, $[M+H\text{-}NH_3\text{-}H_2O\text{-}CH_3]^+$, $[M+H\text{-}(CH_3)NH]^+$, $[M+H\text{-}(CH_3)NH\text{-}CO]^+$ fragments respectively. The mass spectrum of $[TiCl_2(B1)_2]$ complex gives a peak at m/e = 401, 371 ,313 ,284, and were assigned for $[M+H\text{-}(C_6H_{12}O_5)]^+$, $[M+H\text{-}(C_6H_{12}O_5)\text{-}2CH_3]^+$, $[M+H\text{-}(C_6H_{12}O_5)\text{-}2CH_3\text{-}N{=}C(NH_2)_2]^+$, $[M+H\text{-}(C_6H_{12}O_5)\text{-}2CH_3\text{-}N{=}C(NH_2)_2\text{-}OH]$ fragments respectively. The mass spectrum of titanium complex $[TiCl_2(C1)_2]$, $[TiCl_2(D1)_2]$ gives peaks at m/e= 187 due to $C_7H_5O_3SN$ fragment and 360 ($C_{17}H_{17}N_3O_4S$), 345 ($C_{17}H_{17}N_3O_4S\text{-}CH_3$), 268 ($C1_3H_{18}O_5N$), 146 (C_9H_8ON, base peak) fragments respectively. MS-data of synthesized metal complexes were given in Table 1.

Table 1 Mass-Spectrometry Data Of titanium(IV) complexes with their Schiff bases

Sr.No.	Metal Complexes	Major Peaks (m/e)
1.	$Ti(A1)_2Cl_2$	$C_{22}H_{23}N_2O_7$(427), $C_{22}H_{21}N\ O_7$(410), $C_{22}H_{19}NO_6$ (392), $C_{21}H_{19}NO_5$((364), $C_{21}H_{16}NO_6$(377), $C_{20}H_{14}O_7$ (365), $C_{19}H_{14}O_6$ (337)
2.	$Ti(B1)_2Cl_2$	$C_{15}H_{27}N_7O_{12}$(401),$C_{13}H_{21}N_7O_{12}$(371), $C_{12}H_{17}N_4O_{12}$(313), $C_{15}H_{16}N_7O_{11}$ (284)
3.	$Ti(C1)_2Cl_2$	$C_7\ H_5O_3SN$(187), $C_7N_2H_5O_4S$(214+ ^{13}C or ^{15}N), $C_{16}H_{15}N_5O_7S_2$(453), $C_{16}H_{13}N_4O_7S_2$(436), $C_{16}H_{13}N_5O_7S_2$(451), $C_{17}H_{13}N_5O_7S_2$(463), $C_{18}H_{16}N_5O_8S_2$ (494),$TiCl_2$(118)
4.	$Ti(D1)_2Cl_2$	$C_{17}H_{17}N_3O_4S$(360) , $C_{17}H_{17}N_3O_4S\text{-}CH_3$(345) , $C_{13}H_{18}O_5N$(268), C_9H_8ON(146)

Table 2. Antibacterial activity of titanium (IV) complexes with Schiff bases

Sr.No.	Microbial Species	Zone of Inhibition (mm)			
		$[TiCl_2(A1)_2]$	$[TiCl_2(B1)_2]$	$[TiCl_2(C1)_2]$	$[TiCl_2(D1)_2]$
1.	*S. typhimurium*	14.5	9.5	7	10.5
2.	*B. cereus*	9.5	10	5	6.4
3.	*S. epidermidis*	10	7	5	5
4.	*A. faecalis*	11	7	6.5	6
5.	*S. aureus*	14.5	10.5	7	6.6
6.	*M. luteus*	15.5	9.5	6	6
7.	*A. hydrophila*	12	16.5	7	5.5
8.	*K. pneumoniae*	6.5	12.5	6	6.5
9.	*P. aeroginesa*	11.5	9.5	6.5	6.5
10.	*S. sonnei*	5.5	7	5	6.5

3.5 Antibacterial activity

In vitro biological screening of the complexes was tested against bacterial strains i.e. Bacillus cereus MTCC 6728, Micrococcus luteus MTCC 1809, Staphylococcus aureus MTCC 3160, Staphylococcus epidermidis MTCC 3086, Aeromonas hydrophila MTCC 1739, Aclaligenes faecalis MTCC 126, Shigella sonnei MTCC 2957, Klebsiella pneumoniae MTCC 3384, Pseudomonas aeruginosa MTCC 1035, and Salmonella typhimurium MTCC 1253. The zone of inhibition in mm of the novel investigated titanium(IV) complexes against the growth of organisms were summarized in Table 2. A comparative study of ligands and their metal complexes showed that they exhibit higher antibacterial activity than uncomplexed ligands.

The results are promising compared with the previous studies. Such increased activity of metal chelate can be explained on the basis of the overtone concept and chelation theory. According to the overtone concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid-soluble materials in which liposolubility is an important factor that controls the antimicrobial activity. On chelation the polarity of the metal ion will be reduced to a greater extent due to overlap of ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of p-electrons over the whole chelate ring and enhances the lipophilicity of complexes Jelokhani-Niaraki et al., 2009, Moradell et al., 2004).This increased lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism.

Table 3: Minimum inhibitory concentration (MIC) values of Schiffs bases complexes of titanium(IV)

Sr. No.	Microbial Species	Minimum Inhibitory Concentration ((µg/mL)			
		$[TiCl_2(A1)_2]$	$[TiCl_2(B1)_2]$	$[TiCl_2(C1)_2]$	$[TiCl_2(D1)_2]$
1.	*S. typhimurium*	62.5	250	500	250
2.	*B. cereus*	500	500	1000	500
3.	*S. epidermidis*	500	500	1000	1000
4.	*A. faecalis*	15.6	500	1000	500
5.	*S. aureus*	15.6	500	500	250
6.	*M. luteus*	31.2	500	1000	250
7.	*A. hydrophila*	31.2	31.2	500	1000
8.	*K. pneumoniae*	1000	62.5	500	500
9.	*P. aeroginesa*	125	125	500	1000
10.	*S. sonnei*	1000	1000	1000	500

The minimum inhibitory concentration (MIC) values of the titanium(IV) complexes were summarized in Table3.A comparative study of the ligand and its complexes (MIC values) indicates that complexes exhibit higher antibacterial activity than the free ligand. From the MIC value(s), it was found that the complexes, $[Ti(A1)_2Cl_2]$ was more potent against *A.facalis, S.aureus*, $[Ti(B1)_2Cl_2]$ was more potent against *K. pneumonia,* $Ti(C1)_2Cl_2]$ was more potent against *S. typhimurium and* $[Ti(D1)_2Cl_2]$ was more potent against *S. typhimurium, S. aureus, M. luteus* than the other bacterial strains respectively.

4. Conclusions

It is concluded that, metal complexes have been prepared in ethanol using Schiff bases derived from Fructose and antibiotic drug. FAB-Mass, IR, UV-Visible, NMR spectral techniques were used to confirm their formation. Based upon spectroscopic investigation, octahedral geometry of complexes may be proposed. The in-vitro biological evaluation of complexes against various pathogenic bacterial strains shows that metal complexes exhibited higher antimicrobial activity than free ligands.

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