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Microwave-assisted synthesis, spectroscopy and biological aspects of binuclear titanocene chelates of isatin-2,3-bis(thiosemicarbazones)

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The reactions of bis(cyclopentadienyl)titanium(IV) chloride with a new class of bis(thiosemicarbazones) (H_2L), derived by condensing isatin with different N(4)-substituted thiosemicarbazides, have been studied both by a conventional stirring method and also using microwave technology. Binuclear products of type [{(η^5-$C_5H_5)_2TiCl$}$_2$(L)] have been isolated in both cases. Tentative structural conclusions are drawn for the reaction products based upon analysis, electrical conductance, magnetic moment and spectral (UV-visible, IR, ^{1}H NMR and ^{13}C NMR) data. FAB mass spectra of these compounds were also recorded to confirm the binuclear structures. Studies were conducted to assess the growth inhibiting potential of the ligands and complexes against various fungal, viral and bacterial strains.

Keywords: titanium(IV); bis(thiosemicarbazones); IR; NMR; fungicidal; viricidal and bactericidal

Introduction

The potential antitumour, antibacterial, antiviral, fungicidal, antimalarial and anticancer activities of thiosemicarbazones and their metal complexes have encouraged the study of the coordination chemistry of these ligands.[1–8] Heterocyclic thiosemicarbazones exercise their beneficial therapeutic properties in mammalian cells by inhibiting *ribonucleotide reductase*, a key enzyme in the synthesis of DNA precursors.[9] Their ability to provide this inhibitory action is thought to be owing to coordination of iron via their N–N–S tridentate ligating system, either by a preformed iron complex binding to the enzyme, or by the free ligand complexing with the iron-charged enzyme. Studies of iron and copper complexes have shown that they can be more active in cell destruction, as well as in the inhibition of DNA synthesis, than the uncomplexed thiosemicarbazones. Recent developments in the structural nature of metal complexes of heterocyclic thiosemicarbazones, depicted below, are correlated with their biological activities.

$$=N-NH-C(S)-NR_2$$

It has been suggested that the stereochemistries and activities of metal complexes often depend upon the anion of metal used, the nature of N(4)-substituents and the groups attached to N(1).[1–3,9]

A number of papers have appeared on coordination behavior of isatin-3 and isatin-2-thiosemicarbazones.[10–15] Their coordination behavior depends upon the pH of the medium, the nature of the substituents and the nature of the metal ion. However, very few reports are available on coordination behavior of isatin-2,3-bis(thiosemicarbazones). Casas *et al*. reported reactions of diorganotin(IV) oxides with isatin-2,3-bis(thiosemicarbazones).[12] These ligands might have interesting ligational features, since they contain additional donor sites, for example, azomethine nitrogen and thione sulfur.

The present paper describes the synthesis, characterization and biological aspects of bis(cyclopentadienyl)titanium(IV) derivatives with isatin-2,3-bis(thiosemicarbazones). The structures of isatin-2,3-bis(thiosemicarbazones), used for the present study, are shown in Fig. 1.

Experimental

All glass apparatus with interchangeable quick fit joints was used throughout. Precautions were taken to exclude moisture. Tetrahydrofuran was dried by distilling it over sodium wire or pieces. Bis(cyclopentadienyl)titanium(IV) chloride was purchased from Aldrich Chemical co. The details of elemental analysis and physical measurements were the same as described earlier.[11] 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. The isatin-2,3-bis(thiosemicarbazones) were prepared by the general method of condensation of isatin with different N(4)-substituted thiosemicarbazides as reported.[12]

Synthesis of complexes

The complexes were prepared by two different routes.

(1) In microwave-assisted synthesis, the complexes were prepared by irradiating the reaction mixture of titanocene

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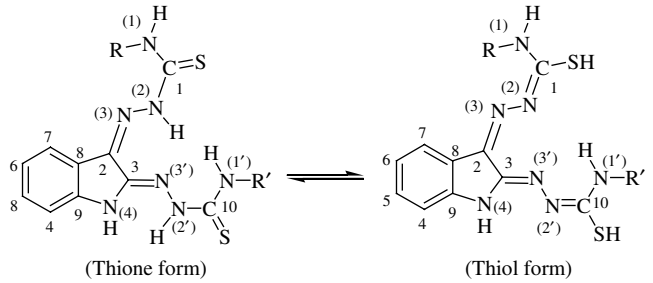

Figure 1. Structures of isatin-2,3-bis(thiosemicarbazones), where, R = H, R′ = $C_6H_4CH_3(o)$ (H_2L_1); R = $C_6H_4CH_3(o)$, R′ = $C_6H_4CH_3(o)$ (H_2L_2); R = $C_6H_4CH_3(p)$, R′ = $C_6H_4CH_3(p)$ (H_2L_3); R = C_6H_4, R′ = C_6H_4 (H_2L_4); and R = $C_6H_4OCH_3$, R′ = $C_6H_4OCH_3$ (H_2L_5).

(6 mmol) and respected isatin-2,3-bis(thiosemicarbazone) (3 mmol) in tetrahydrofuran using triethylamine (6 mmol) as hydrogen chloride acceptor for 10–15 min. The products were recovered from the microwave oven and dissolved in a few milliliters of dry tetrahydrofuran, where the precipitate of triethylamine hydrogen chloride formed during the course of reaction was removed by filtration and the filtrate was dried under reduced pressure. The resulting compounds were washed and recrystallized with tetrahydrofuran–petroleum ether (1 : 1 mixture). They were further subjected to checking of their purity by TLC using silica gel G.

(2) A mixture of Cp_2TiCl_2 (60 mmol) and appropriate isatin-2,3-bis-(thiosemicarbazone) (30 mmol) was dissolved in dry tetrahydrofuran (60 mmol). To the resulting clear solution, Et_3N (60 mmol) was added and the mixture was stirred for *ca* 10–12 h at room temperature. Precipitated $Et_3N{\cdot}HCl$ was removed by filtration and the volume of the solution was reduced to *ca* 15 cm^3 under reduced pressure. The coloured complexes so obtained were recrystallized from a tetrahydrofuran–petroleum ether (1 : 1) mixture.

The comparison between stirring method and microwave-assisted method is presented in Table 1.

The details of the complexes reported in this paper are given below. The analytical data are for compounds prepared under the microwave method. The analytical data for compounds prepared under stirring method deviate by ±0.02–0.06.

[{(η^5-C_5H_5)TiCl}$_2$(L_1)]

Yellow solid; yield(%): 60 (stirring method), 72 (microwave method); analyses (%) found (calcd for $C_{37}H_{35}Cl_2N_7S_2Ti_2$); C 54.90 (54.97), H 4.35 (4.36), Cl 8.65 (8.77), N 12.18 (12.13), Ti 12.0(11.84); mol. wt found (calcd) 808(808.5); UV–vis (nm): 459, 290; IR (cm^{-1}): 3300m ($\nu N^{(1/1')}$–H), 3150 (νN–H, isatin),1615 w,1580s (νC=N), 620 (νC–S), 460m (νTi–N), 380m (νTi–S), 3000m, 1415m, 1000 w, 810m (η^5-C_5H_5); ^{1}HNMR (δ): 6.75m (s, η^5-C_5H_5), 10.60 (s, $N^{1/1'}$–H), 4.25 (s, N–H isatin), 7.75–7.92 (m, phenyl ring); ^{13}CNMR (δ): 115.8 (η^5-C_5H_5), 165(C-10), 155, 150 (C-2 and C-3), 147.2, 140.1, 134.5, 131.6, 125.8, 126.2, 125.2, 124.4, 120.4, 118.6, 116.0, 115.5 (phenyl ring).

[{(η^5-C_5H_5)$_2$TiCl}$_2$(L_2)]

Brown solid; yield (%): 65 (stirring method), 78 (microwave method); analyses (%) found (calcd for $C_{44}H_{41}Cl_2N_7S_2Ti_2$): C 58.75 (58.81), H 4.55 (4.60), Cl 7.70 (7.89), N 10.80 (10.91), Ti 10.60 (10.65); mol. wt found (calcd): 898(898.6); UV–vis (nm): 221 500, 312; IR (cm^{-1})3300 ($\nu N^{1/1'}$–H), 3165 (νN–H isatin), 1620 w, 1570s (νC=N), 615 (νC–S), 455m (νTi–N), 375m (νTi–S), 3010m, 1420m, 1010 w, 815m (η^5-C_5H_5); ^{1}HNMR (δ): 10.65 (s,$N^{1/1'}$–H), 6.80 (s, η^5-C_5H_5), 4.20 (s, N–H isatin), 7.70–7.80 (m, phenyl ring); ^{13}C NMR (δ): 116.2 (η^5-C_5H_5),160 (C-10), 154, 152 (C-2 and C-3), 148.2, 140.5, 135.6, 130.8, 130.2, 129.8, 125.2, 124.8, 120.4, 117.5, 115.6 (phenyl ring), 13.4 (CH_3).

[{(η^5-C_5H_5)$_2$TiCl}$_2$(L_3)]

Brown solid, yield (%): 62 (stirring method), 75 (microwave method); analyses (%) found (calcd for $C_{44}H_{41}Cl_2N_7S_2Ti_2$): C 58.70 (58.81), H 4.57 (4.60), Cl 7.72 (7.89), N 10.78 (10.91), Ti 10.65 (10.65); mol. wt found (calcd): 898 (898.6); UV–vis (nm): 458, 307; IR (cm^{-1}): 3290m ($\nu N^{1/1'}$–H), 3160m (νN–H isatin), 1620 w, 1580s (νC=N), 610m (νC–S), 460m (νTi–N), 380m (νTi–S), 3005m, 1425m, 1015 w, 810 w (η^5 C_5H_5);[1]H NMR (δ): 6.82 (s,η^5-C_5H_5),10.60 (s,$N^{1/1'}$–H), 4.28 (s, N–H isatin), 7.68–7.78 (m, phenyl ring); ^{13}C NMR (δ): 115.5 (η^5-C_5H_5), 162 (C-10),156,154 (C-2 and C-3), 147.8, 136.2, 133.8, 131.5, 129.8, 129.5, 125.2,124.2, 120.6, 118.6, 117.8, 115.2 (phenyl ring), 20.8(CH_3).

[{(η^5-C_5H_5)$_2$TiCl}$_2$(L_4)]

Yellow solid, yield (%): 60 (stirring method), 70 (microwave method); analyses (%) found (calcd for $C_{42}H_{37}Cl_2N_7S_2Ti_2$): C 57.62(57.95), H 4.20(4.28), Cl 8.05(8.14), N 11.16 (11.26), Ti 10.86 (11.0); mol. wt found (calcd): 870 (870.7); UV–vis (nm): 438, 286; IR (cm^{-1}): 3295m ($\nu N^{1/1'}$–H), 3155m (νN–H isatin), 1625 w, 1575 (νC=N), 615m (νC–S), 450m (νTi–N), 385 (νTi–S); ^{1}HNMR (δ): 6.85 (s,η^5-C_5H_5),10.70 (s,$N^{1/1'}$–H), 4.25 (s, N–H isatin), 7.70–7.80 (m, phenyl ring); ^{13}C NMR (δ): 116.2 (η^5-C_5H_5), 165.0 (C-10), 150.1, 152.8 (C-2 and C-3), 146.8, 139.2, 134.5, 131.5, 129.8, 128.7, 125.3, 123.2, 120.5, 118.8, 117.5, 115.0 (phenyl ring).

Table 1. Comparision between stirring and microwave method

	Yield (%)		Solvent (cm^3)		Time	
Compound	Stirring	Microwave	Stirring	Microwave	Stirring (h)	Microwave method (min)
[{(η^5-C_5H_5)$_2$TiCl(L_1)}]	60	72	60	5	10	10
[{(η^5-C_5H_5)$_2$TiCl(L_2)}]	65	78	60	5	12	15
[{(η^5-C_5H_5)$_2$TiCl(L_3)}]	62	75	60	5	12	15
[{(η^5-C_5H_5)$_2$TiCl(L_4)}]	60	70	60	5	12	12
[{(η^5-C_5H_5)$_2$TiCl(L_5)}]	64	72	60	5	12	12

[{(η^5-C_5H_5)$_2$TiCl}$_2$(L$_5$)]

Yellow solid; yield (%): 64 (stirring method), 72 (microwave method); analyses (%) found (calcd for $C_{44}H_{41}Cl_2N_7O_2S_2Ti_2$): C 56.70(56.79), H 4.38(4.44), Cl 7.55(7.62), N 10.46(10.54), Ti 10.20(10.29); mol. wt found (calcd): 930(930.6); UV–vis (nm): 450, 292; IR (cm^{-1}): 3300 m (νN$^{1/1'}$–H), 3140 m (νN–H isatin), 1620 w, 1570s (νC=N), 610m (νC–S), 455 (νTi–N), 380 (νTi–S); ^{1}H NMR (δ): 6.70 (s, η^5-C_5H_5), 10.62 (s, N$^{1/1'}$–H), 4.15 (s, N–H isatin), 7.62–7.78 (m, phenyl ring), 3.80 (s, O–CH$_3$); ^{13}C NMR (δ): 116.2 ($\eta^5C_5H_5$), 164.8 (C-10), 151.6, 153.4 (C-2 and C-3), 158.8, 148.2, 135.2, 131.6, 129.8, 126.3, 125.8, 123.2, 121.0, 118.5, 117.8, 115.2 (phenyl ring), 56.0 (O–CH$_3$).

Results and Discussion

A systematic study of the reaction of bis (cyclopentadienyl) titanium(IV) dichloride with isatin-2.3-bis(thiosemicarbazones) (molar ratio 2 : 1, respectively) in anhydrous tetrahydrofuran in the presence of Et$_3$N may be represented by the following reaction:

$$2(\eta^5 - C_5H_5)_2TiCl_2 + H_2L + 2Et_3N \xrightarrow{THF} [\{(\eta^5 - C_5H_5)_2TiCl\}_2L] + 2Et_3N{\cdot}HCl$$

The complexes are soluble in THF, DMF and DMSO. The electrical conductance measurements show that the complexes are non-electrolytes. Magnetic susceptibility measurements show that they are diamagnetic.

Electronic spectra

The electronic spectra of all the complexes showed a single band in the region of 465–438 nm, which was assigned to the charge transfer band and is in accordance with an $(n-1)d^0\,ns^0$ electronic configuration.[10] One more band was observed at *ca* 286–312 nm, which may be due to intra-ligand transition.

Infrared spectra

Isatin-2,3-bis(thiosemicarbazones) can exist either as thione or thiol tautomeric forms or as an equilibrium mixture of both forms, since they have a thioamide, –NH–C(=S) function. The infrared spectra of thiosemicarbazones in the solid state do not show any ν(S–H) band but exhibit a medium ν(N–H) [at (2) or (2′)] band at *ca* 3200 cm^{-1}, indicating that, in the solid state, they remain mainly in the thione form.[16,17] However, in solution (basic medium) they readily convert to the thiol tautomeric form with concomitant formation of the Ti(IV) complexes of the protonated mercapto form of the ligands. This is indicated by the absence of–NH band in the complexes. The IR spectra of the complexes also show a new band at *ca* 620 cm^{-1}, owing to the conversion of C=S to C–S. The band in the complexes at *ca* 375–385 cm^{-1} assigned[11] to ν(Ti–S) and shows that sulfur is bonded to the metal atom. The ν(C=N) shift of the thiosemicarbazone ligands from 1585–1600 cm^{-1} to lower energy in the spectra of the complexes indicates[18] the coordination of two imine nitrogens (3 and 3′). However, the N$^{(2/2')}$–H from the two thiosemicarbazone moieties, by thione thiol tautomerism, produces an additional carbon–nitrogen double bond, N$^{(2/2')}$=C(S), indicated by the appearance of a weak band at *ca* 1615 cm^{-1} in the spectra of the complexes. Bands in the 450–465 cm^{-1} region are assigned to ν(Ti–N) and support coordination of both the imine nitrogens.[11] In addition, the spectra of thiosemicarbazones show a band at *ca* 3150 cm^{-1}, assignable to ν(N–H) of isatin moiety. This band remains almost at the same position in the spectra of the complexes, suggesting non-coordination of isatin (N–H) group to metal ion. H_2L_1 shows one medium band at *ca* 3300 cm^{-1} assignable to ν(N$^{(1or1')}$–H), which remains at the same position in its corresponding complex, indicating that the (N$^{(1or1')}$–H) nitrogen atom of H_2L_1 is not coordinated to the metal.

Absorption bands occurring at *ca* 3000 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 ring. These bands are similar to those reported for bis(cyclopentadienyi)titanium(IV)dichloride and their appearance indicates that the (η^5-C_5H_5) group persists in the complexes.[19]

^{1}H NMR spectra

The ^{1}H NMR spectra of the complexes have been recorded in DMSO-d$_6$. Coupling between various groups complicates the spectra, but a comparison of the spectra of ligands with those of the complexes can lead to the following conclusions:

(1) The δ 6.65–6.80 signals may be assigned to the cyclopentadienyl ring protons and indicate the rapid rotation of the ring about the metal ring axis.
(2) The signal of N$^{(2)}$H is seen at δ *ca* 7.0 , in isatin-2,3-bis(thiosemicarbazones), which disappears in their corresponding complexes.
(3) The signal due to – NH proton of isatin ring appears at δ *ca* 4.2 in the ligands, which also persists in the complexes.
(4) The chemical shift due to aromatic ring appears at *ca* 7.6–8.0 ppm, which slightly shifts downfield in the complexes. This may be due to decrease in electron density after forming the complex.

^{13}C NMR spectra

The ^{13}C NMR spectra of [{(η^5-C_5H_5)$_2$TiCl}$_2$] type complexes were recorded in DMSO-d$_6$. The following are the salient features:

(1) The peak due to cyclopentadienyl groups appears at *ca* 116 (relative to TMS).
(2) The ligands show thioamide – C signal at *ca* δ 180.0. In the complexes, this signal is at significantly higher field which is due to enolization of thione group and formation of new azomethine linkage.
(3) The ligands show signals at *ca* δ 150 and δ 145 due to two azomethine–Cs (C-2 and C-3) in the ligands. These signals undergo downfield shift, indicating coordination of both the azomethine nitrogens to metal.
(4) For aromatic ring, a number of signals appear.

Thus, the above studies suggest that two thiol sulfur atoms and two azomethine nitrogen atoms of the ligands are involved in chelation. Casas *et al*. studied[12] the reactions of $SnMe_2O$ with identical isatin 2,3-bis(thiosemicarbazone) ligands (H_2L) and reported spectral features for [$SnMe_2$(L)] complexex. X-ray diffraction shows that one thiosemicarbazone chain is bound to the metal through the sulfur atom and the azomethine nitrogen atom, forming a five-membered metallacycle. The other thiosemicarbazone chain coordinates through the nitrogen of the hydrazine group following its deprotonation. However, in the complexes reported in this paper, coordination of all the donor

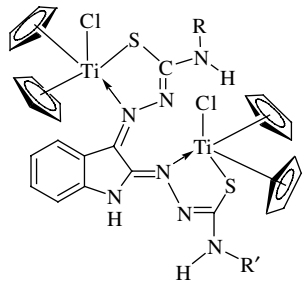

Figure 2. Structures of titanocene complexes.

atoms with single metal atom seems unlikely for steric reasons and also because of the 18-electron rule. It can be possible for one sulfur atom and one azomethine nitrogen to coordinate to one Ti(IV) ion, while the second sulfur atom and second azomethine nitrogen of the same ligand coordinate to another metal atom, leading to a binuclear structure (Fig. 2). The molecular weight determination by FAB-mass spectra further supports the proposed structure. Attempts are being made to develop single crystals suitable for X-ray structure, but so far no success has been achieved.

Antifungal activity

The fungicidal activity of isatin-2,3-bis(thiosemicarbazones) and their corresponding complexes were evaluated (Table 2) in DMF against *Aspergillus niger*, *Aspergillus fumigate* and *Helminthosporium oryzae* by the agar plate technique[20] at 1000, 100 and 10 ppm concentrations with triplicate determination in each case. The average percentage inhibition was calculated using the expression (%) = 100 $(C - T)/C$ where C and T are the diameters of the fungus colonies in control and test plates, respectively. The compounds showed significant toxicity at 1000 ppm concentration against all species of fungi. However, the complexes were more toxic than isatin-2,3-bis(thiosemicarbazones), which may be due to their chelation and the presence of the sulfur atom. For a particular species of ligands, the compounds with R = $C_6H_4{\cdot}OCH_3$, i.e. ligands derived from N(4)-methoxy thiosemicarbazide, showed better activity as compared with compounds with ligands containing other substituent at the N(4) position. The variation in the effectiveness of different biocidal agents against different organisms as suggested by Lawrence *et al*. depends upon the permeability of the cells or differences in ribosomes of antimicrobial agents.[21]

Antiviral activity

The antiviral activity was evaluated by noting the reduction in number of local lesions by cucumber virus in *Chenopodium amaranticolor* when mixed with the chemical. Standard extracts of the virus were mixed in an equal quantity of solution of isatin-2,3-bis-(thiosemicarbazones) and their Ti(IV) complexes. Inoculations were made by the leaf rubbing method. One-half of each leaf was inoculated with inoculum containing the virus and chemical, and the remainder was inoculated with the standard virus extracts. Infections on different samples were calculated on the basis of local lesions produced by each treatment, and percentage inhibition was calculated from the expression below:

$$\% \text{ inhibition} = \frac{(\text{No. of local lesions by control} - \text{No. of lesions by treatment})}{\text{No. of lesions by control}} \times 100$$

All compounds displayed a weak antiviral activity (Table 3); however, the thiosemicarbazone ligands were less active than their corresponding Ti(IV) compounds.

Antibacterial activity

The antibacterial activity of the complexes together with the parent ligands was screened against Gram-positive *Bascillus subtitis* and Gram-negative *Escherichia coli* at 1000 ppm concentration. Gram-positive and Gram-negative bacteria differ markedly in their cell wall composition and nature. Gram-negative forms are usually pathogenic whereas Gram-positive forms have association with decay or organic wastes in nature. The cell wall of Gram-positive forms is mostly peptitoglycan or murein, whereas Gram-negative bacteria possess only 20–25% peptitoglycan.

The results (Table 4) show that activity increases on chelation. The activity of the ligands is affected by the nature of the substituents; this in relation to the liophilicity of the ligands and

Table 2. Antifungal activity of titanocene chelates

	Average percentage inhibition after 96 h								
	A. niger			*A. fumigate*			*H. oryzae*		
Compound	1000	100	10	1000	100	10	1000	100	10
H_2L_1	42.4	28.6	21.6	36.8	24.0	20.8	35.6	22.5	16.2
$[\{(\eta^5\text{-}C_5H_5)_2TiCl(L_1)\}]$	62.1	48.0	30.6	58.9	38.6	26.8	57.8	36.1	28.2
H_2L_2	52.6	40.8	36.2	50.5	38.1	31.6	50.9	40.0	32.8
$[\{(\eta^5\text{–}_5H_5)_2TiCl\}_2(L_2)]$	70.6	56.2	44.8	68.8	51.6	40.5	69.1	51.9	42.5
H_2L_3	50.8	36.2	31.8	44.6	30.2	28.5	43.6	32.6	30.8
$[\{(\eta^5\text{–}_5H_5)_2TiCl\}_2(L_3)]$	69.8	55.8	41.6	64.2	48.6	38.2	65.1	48.8	39.6
H_2L_4	49.2	32.8	30.2	41.6	28.2	26.1	38.9	25.6	22.5
$[\{(\eta^5\text{–}_5H_5)_2TiCl\}_2(L_4)]$	65.6	50.2	36.8	61.6	42.8	32.1	60.5	40.2	32.8
H_5L_5	58.6	42.5	38.6	56.8	40.2	32.6	57.1	40.8	35.2
$[\{(\eta^5\text{–}_5H_5)_2TiCl\}_2(L_5)]$	78.5	62.4	50.8	72.6	60.8	48.2	75.3	62.0	51.6

Table 3. Antiviral activity of titanocene (IV) chelates

Compound	Organism – cucumber mosaic virus Host plant – *Chenopodium amaranticolor* Concentration – 1000 ppm Inhibition (%)
H_2L_1	4
$[\{(C_5H_5)_2TiCl\}_2(L_1)]$	10
H_2L_2	8
$[\{(C_5H_5)_2TiCl\}_2(L_2)]$	20
H_2L_3	10
$[\{(C_5H_5)_2TiCl\}_2(L_3)]$	22
H_2L_4	6
$[\{(C_5H_5)_2TiCl\}_2(L_4)]$	18
H_2L_5	12
$[\{(C_5H_5)_2TiCl\}_2(L_5)]$	25

Table 4. Antibacterial activity of titanocene chelates

Compound	Diameter of inhibition zone (mm)	
	B. subtilis (Gram +ve)	*E. coli* (Gram -ve)
H_2L_1	0	3
$[\{(C_5H_5)_2TiCl\}_2(L_1)]$	4	7
H_2L_2	3	5
$[\{(C_5H_5)_2TiCl\}_2(L_2)]$	6	10
H_2L_3	4	7
$[\{(C_5H_5)_2TiCl\}_2(L_3)]$	8	11
H_2L_4	4	6
$[\{(C_5H_5)_2TiCl\}_2(L_4)]$	7	10
H_2L_5	5	8
$[\{(C_5H_5)_2TiCl\}_2(L_5)]$	9	13
Streptomycin (standard)	17	30

their membrane permiabilities, a key factor in determining the entry inside the cell. The complexes are slightly more toxic than the parent ligands. The presence of methoxy substituent at phenyl ring of R increases the antibacterial activity. The compounds exhibit a better effect on the Gram-negative form.

Conclusion

Bis(cyclopentadienyl) titanium(IV) complexes of isatin-2,3-bis(thiosemicarbazone) have been synthesized by both conventional thermal method and by the use of microwaves. The principal frequencies of microwave heating are between 900 and 2450 MHz. The major advantages of microwaves for industrial processing are rapid heat transfer and volumetric and selective heating.[22] For the microwave-assisted synthesis, 10–15 min were required to complete the reactions, while in the conventional method 20–38 h were required. The yield of the products was also less in the conventional method as compared with that obtained by the microwave synthesis. The structures of the complexes were established by analyses and spectral studies. Antifungal, antiviral and antibacterial activity of the ligands and the complexes were also evaluated and showed that activity increases on chelation.

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