Acta Poloniae Pharmaceutica – Drug Research, Vol. 63 No. 2 pp. 95–100, 2006 ISSN 0001-6837
Polish Pharmaceutical Society

DRUG SYNTHESIS

SYNTHESIS, CHARACTERIZATION, ANTIBACTERIAL AND CYTOTOXICITY STUDIES ON SOME MIXED LIGAND Th(IV) COMPLEXES

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Abstract: Mixed ligand Th(IV) complexes of the type $[M(Q)_2LNO_3 \cdot H_2O]$ have been synthesized using 8-hydroxyquinoline (HQ) as a primary ligand and N- and/or O- donor amino acids (HL) such as L-alanine, L-phenylalanine, L-serine and L-tyrosine as secondary ligands. The metal complexes have been characterized on the basis of elemental analysis, electrical conductance, room temperature magnetic susceptibility measurements, spectral and thermal studies. The electrical conductance studies of the complexes in DMF at 10^{-3} M concentration indicate their non-electrolytic nature. Room temperature magnetic susceptibility measurements revealed diamagnetic nature of the complexes. Electronic absorption spectra of the complexes show intra-ligand and charge transfer transitions, respectively. The thermal analysis data of the complexes indicate the presence of a coordinated water molecule. The tube dilution method has been used to study the antibacterial activity of the complexes against the pathogenic bacteria *S. aureus* and *E. coli*. The results have been compared against those of control tetracycline, which was screened simultaneously and indicate mild antibacterial activity of the complexes. The representative complex has been screened for cytotoxicity (IC_{50}) studies against *Ehrlich ascites* cells and *Daltons lymphoma ascites* cells and shows low cytotoxic activity.

Keywords: Mixed ligand thorium complexes; antibacterial; cytotoxicity (IC_{50}) study

It is well established that ternary complexes play a decisive role in the activation of enzymes and also in the storage and transport of active substances (1). Actinide metal ions are of great interest for the researchers because of their large size and high positive charge (2). High charge on Th(IV) along with its effective ionic size enables thorium to form complexes with high coordination number (3, 4). Biological activity of some mixed ligand complexes against pathogenic microorganisms has also been reported (5, 6). It has been found that, a majority of the metal complexes with 8-hydroxyquinoline possess biological activity (7). Amino acids are well known for their tendency to form complexes with metals having biological significance and metabolic enzymatic activities (8).

The present paper reports the synthesis and characterization of mixed ligand Th(IV) complexes prepared using 8-hydroxyquinoline as a primary ligand and some amino acids as secondary ligands. These complexes have been screened for their antibacterial and cytotoxic (IC_{50}) characteristic properties.

EXPERIMENTAL

Materials

Analytical grade thorium nitrate pentahydrate was used as received. 8-Hydroxyquinoline, L-serine and the solvents N, N-dimethylformamide and dimethyl sulfoxide were purchased from E. Merck, whereas L-alanine, L-phenylalanine and L-tyrosine were purchased from S.D. Fine Chemicals, Mumbai, India. Laboratory grade chemicals whenever used, were purified by standard procedures (9).

Preparation of mixed ligand complexes

Mixed ligand Th(IV) complexes were prepared from thorium nitrate pentahydrate, 8-hydroxyquinoline (HQ) and different amino acids (HL) such as L-alanine, L-phenylalanine, L-serine and L-tyrosine as secondary ligands.

To an aqueous solution (10 mL) of thorium nitrate pentahydrate (507 mg, 1 mmol) ethanolic solution (10 mL) of 8-hydroxy quinoline (290 mg, 2 mmol) was added. The mixture was stirred and kept in a boiling water bath for 10 minutes. To this hot

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solution an aqueous solution (10 mL) of amino acids (1 mmol) was added with constant stirring. The mixture was again heated in a water bath. The complexes were obtained by raising pH of the reaction mixture by adding diluted ammonia solution. The mixture was cooled and solid complex obtained was filtered, washed with water followed by ethanol. The complexes thus prepared were dried under vacuum.

The complex with L-tyrosine as a secondary ligand was prepared by dissolving L-tyrosine in dilute ammonia and then added to warm mixture of thorium nitrate pentahydrate and 8-hydroxyquinoline.

Instrumentation

The complexes were analyzed for C, H, and N contents on Thermo Finnigan elemental analyzer, Model No. FLASH EA 1112 Series at SAIF, I.I.T. Mumbai. Metal content was estimated gravimetrically by standard procedure (10). The molar conductance values were measured in DMF (10^{-3} M) on an Equiptronics digital conductivity meter Model No. EQ-DCM-P. Room temperature magnetic susceptibilities were measured by a Guoy balance using $Hg[Co(SCN)_4]$ as a calibrant. Electronic absorption spectra in DMF (10^{-4} M) in the ultraviolet and visible range were measured on Shimadzu UV-160A and Spectronic-20 spectrophotometers. FT-IR spectra were recorded in KBr discs on a Perkin-Elmer FT-IR spectrophotometer model 160. Thermal studies of the complexes were made on a Perkin-Elmer Diamond TG-DTA instrument at SAIF, I.I.T. Mumbai, by recording the change in weight of the complexes on increasing temperature up to 900^{0}C in the nitrogen atmosphere at the heating rate of 10^{0}C per minute.

Antibacterial screening

The antibacterial activity of the complexes was assayed against the bacteria, *S. aureus* and *E. coli* by tube dilution method (11). The solvent used was dimethyl sulfoxide (DMSO) and sample concentrations from 1 to 200 µg/mL were used.

Tube dilution method

Bacterial inoculum was prepared in sterilized Mueller Hinton broth and incubated for 4 h at 37^{0}C. Opacity was adjusted to 10^7 organisms/mL by Macfarland standard containing 0.1 mL of 1% aqueous $BaCl_2$ and 9.9 mL of 1% dil. H_2SO_4.

The complexes were dissolved in DMSO (1 mg/mL) and added into 5 mL of broth to give final concentration ranging from 1 to 200 µg/mL. To this solution 0.1 mL of inoculum of respective bacteria was added. The tubes were then kept on a rotary shaker and incubated at 37^{0}C for 24 h. On the next day the results were observed for the presence or absence of growth to estimate Minimum Inhibition Concentration (MIC).

The lowest concentration at which there was no visible growth was taken as MIC.

Cytotoxicity studies

In vitro cytotoxicity (IC_{50}) study on one representative complex, $[Th(Q)_2(Ser)NO_3{\cdot}H_2O]$ was carried out at „Amala Cancer Research Centre, Thrissure, Kerala", on established tumor cell lines *Ehrlich ascites* cells and *Daltons lymphoma ascites* cells, respectively.

The *Ehrlich ascites* cells were originally procured from Cancer Institute, Mumbai and *Daltons lymphoma ascites* cells from Cancer Institute, Adayar, Chennai. For the experiment these cells were aspirated, washed with phosphate buffered saline and made up to a concentration of 10 million/mL.

Different concentrations of the complexes (5 to 100 µg) in DMSO (20 µL) were incubated with 1 million cells in a total volume of 1 mL with phosphate buffered saline (PBS) used as a control in the experiment. Cells were incubated at 37^{o}C for 3 h.

After incubation 0.1 mL of 1% trypan blue was added and cytotoxicity was determined by counting live and dead cells using hemocytometer.

RESULTS AND DISCUSSION

Characterization of metal complexes

The synthesis of mixed ligand Th(IV) complexes may be represented as follows.

$Th(NO_3)_4{\cdot}5H_2O + 2HQ + HL \rightarrow$

$[Th(Q)_2(L)NO_3{\cdot}H_2O] + 3HNO_3 + 4H_2O$

(Where, HQ is 8-hydroxyquinoline and HL is an amino acid)

All the complexes are colored, non-hygroscopic and thermally stable solids (Table 1), indicating a strong metal-ligand bond. The complexes are insoluble in common organic solvents such as ethyl alcohol, acetone, chloroform etc. but are fairly soluble in DMF and DMSO. The elemental analysis data (Table 1) of metal complexes are consistent with their general formulation as 1:2:1, mixed ligand complexes of the type $[M(Q)_2(L)NO_3{\cdot}H_2O]$. The molar conductance values of the complexes in DMF at 10^{-3} M concentration are very low (< 1) indicating their non-electrolytic nature (12).

Magnetic studies

The magnetic moments of the complexes were calculated from the measured magnetic susceptibili-

ties after employing diamagnetic corrections and revealed their diamagnetic nature as expected for thorium metal with $5f^0$ configuration.

Electronic absorption spectra

The electronic spectra of the metal complexes in DMF were recorded in the UV-visible region. The spectra shows three transitions in the range 37037-36363 cm^{-1}, 30303-29411 cm^{-1} and 27027-26315 cm^{-1} ascribed to $\Pi \rightarrow \Pi^*$, $n \rightarrow \Pi^*$ and the charge transfer transitions from the ligands to the metal, respectively.

Infra-red spectra

The FT-IR spectra of the metal complexes were recorded for KBr discs over the range 4000-400 cm^{-1}. On the basis of the reported infra-red spectra of amino acids, 8-hydroxyquinoline and their metal complexes (13-15), some of the important bands have been assigned.

1. A broad band observed in the region between 3400-3200 cm^{-1} due to asymmetric and symmetric O-H stretching modes and a band in the range 1630-1600 cm^{-1} due to H-O-H bending vibrations, indicating presence of a coordinated water molecule (16), further confirmed by thermal studies.

2. Charles et al. (17) reported that for several metal complexes with HQ, the ν(C-O) band is observed at ~1120 cm^{-1}. The position of this band undergoes variation depending on metal complex under study. A strong ν(C-O) band observed at ~1104 cm^{-1} indicates the presence of oxine moiety in the complexes coordinated through its nitrogen and oxygen atoms as uninegative bidentate ligand (18). The ν(C=N) mode observed at 1580 cm^{-1} in the spectra of free HQ ligand is found to be shifted to lower wave number i.e. ~1500-1497 cm^{-1} in the spectra of complexes. A negative shift in this vibrational mode on complexation indicates the coordination through tertiary nitrogen donor of HQ. The in plane and out of plane ring deformations modes observed at ~554 and ~790 $cm^{-1,}$ respectively, confirm coordination through the nitrogen atom of HQ with the metal.

3. Broad bands at 3040 and 2960 cm^{-1} due to N-H (asymmetric) and N-H (symmetric) vibrations of free amino acid moiety are shifted to higher wave numbers i.e. in the range 3240-3150 cm^{-1} and 3048-3044 cm^{-1}, respectively, in the spectra of metal complexes, suggesting coordination of the amino group through nitrogen with the metal ion.

The $\nu_{asym}(COO^-)$ band of free amino acid, i.e. 1610-1590 cm^{-1} is shifted to lower wave number in the range 1570-1568 cm^{-1} and $\nu_{sym}(COO^-)$ mode observed at ~1400 cm^{-1} in the spectra of free amino acids is also shifted to lower wave numbers i.e. 1381-1378 cm^{-1} in the spectra of complexes, indicating the co-ordination of carboxylic acid group via oxygen with metal ion (14). The C-N symmetric stretching frequency observed at ~950 cm^{-1} in the spectra of free amino acids is found to be shifted to lower wave numbers, i.e. ~897-885 cm^{-1} in the spectra of complexes confirming coordination through the amino group of the amino acids.

4. An important feature of infra-red spectra of metal complexes with 8-HQ is the absence of the band at ~3440 cm^{-1} due to the O-H stretching vibration of the OH group of HQ (15). This observation leads to the conclusion that the complex formation takes place by deprotonation of the hydroxyl group of HQ moiety.

5. A band observed at ~ 3204 cm^{-1} due to the O-H stretching vibration in the spectra of metal complexes of L-tyrosine indicates that free hydroxyl group of amino acid does not take part in the coor-

Table 1. Color, decomposition temperature, molar conductance and analytical data of the complexes.

Complex	Empirical formula	Color	Elemental analysis, Found (Calculated)				Molar conductance. $Mhos.cm^2mol^{-1}$
			%M	%C	%N	%H	
$[Th(Q)_2(Ala)NO_3 \cdot H_2O]$	$ThC_{21}H_{20}O_8N_4$	Light Yellow	34.13 (33.71)	36.94 (36.65)	7.81 (8.13)	3.15 (2.90)	0.017
$[Th(Q)_2(Ph\text{-}Ala)NO_3 \cdot H_2O]$	$ThC_{27}H_{23}O_8N_4$	Light Yellow	30.90 (30.36)	41.95 (42.43)	7.23 (7.32)	3.35 (3.14)	0.042
$[Th(Q)_2(Ser)NO_3 \cdot H_2O]$	$ThC_{21}H_{20}O_9N_4$	Dark Yellow	33.16 (32.95)	35.54 (35.81)	7.43 (7.95)	3.04 (2.84)	0.051
$[Th(Q)_2(Tyr)NO_3 \cdot H_2O]$	$ThC_{27}H_{24}O_9N_4$	Light Yellow	30.44 (29.74)	41.32 (41.56)	6.89 (7.18)	3.12 (3.08)	0.008

[a] Q represents the deprotonated primary ligand 8-hydroxyquinoline, whereas Ala, Ph-Ala, Ser and Tyr represents deprotonated secondary ligands alanine, phenylalanine, serine and tyrosine, respectively.

dination. Similar band is expected for the metal complex of L-serine at about 3400 cm^{-1} but could not be interpreted because of overlapping with the bands of coordinated water molecule. Hence both ligands act as bidentate ligands.

6. The FT-IR spectra of the metal complexes show no absorption bands near 1352 cm^{-1} where ionic nitrate is known to absorb (19), indicating absence of ionic nitrate. Other bands observed at ~1463, ~1274, ~1035, and ~734 cm^{-1} corresponding to v_1, v_4, v_2 and v_3 vibrations agree with frequencies reported for bidentate nitrate group (20,21). The separation of highest frequency bands v_1 and v_4 (186-140 cm^{-1}) in the complexes favors bidentate character of the nitrate group (22).

7. Some new bands of weak intensity observed in the regions around 648-602 cm^{-1} and 529-484 cm^{-1} may be ascribed to M-O and M-N vibrations, respectively (23). It may be noted that these vibrational bands are absent in the spectra of the ligands.

Thermal studies

The TG and DTA studies of the complexes have been recorded in the nitrogen atmosphere at the constant heating rate of 10°C/min.

The TG of the complexes shows that they are thermally quite stable to varying degree. The complexes show gradual loss in weight due to decomposition by fragmentation with increasing temperature as presented in Table 2. The complexes with L-alanine, L-phenylalanine and L-serine show similar behavior in TG and DTA studies. The thermogram of these complexes shows the loss in weight corresponding to one water molecule in the temperature range ambient to ~200°C, followed by weight loss due to amino acid moiety in the range 220-350°C. The final step of the decomposition observed in the range 380-760°C corresponds to the weight loss of nitrate as well as HQ moieties present in the complexes. In case of L-tyrosine complex the first step shows a weight loss due to one water molecule in the temperature range ambient to ~ 200°C, followed by weight loss due to the decomposition of nitrate in the range 220-390°C. The final step shows a major weight loss attributed to decomposition of the amino acid along with two HQ moieties present in the complexes. This may be due to ring stacking interaction (24, 25) of the hydroxyphenyl group of L-tyrosine which gives exceptional stability to the complex.

The DTA of the complexes display an endothermic peak in the range 140-170°C, which indicates presence of coordinated water molecule. As the temperature is raised, the DTA curve shows a small exotherm in the temperature range 220-350°C, and a broad exotherm in the range 380-760°C attributed to decomposition of amino acid moiety, and nitrate along with 8-hydroxyquinoline moieties present in the complexes. The formation of a broad exotherm is possibly due to simultaneous decomposition of the ligand moieties and their subsequent oxidation to gaseous products like CO_2, H_2O, and NO_2 etc.

Like most of the metal organic complexes, these complexes also decomposes to a fine powder of metal oxide i.e. ThO_2. The constant weight plateau in TG after 760°C indicates completion of the reaction. The ThO_2 formed was confirmed by X-ray diffraction pattern of the decomposed product.

On the basis of the physico-chemical studies, the bonding and structure for the metal complexes may be represented as shown in Figure 1.

Table 2. Thermal data of the complexes.

Complex	Decomposition Temp. (°C)	Temperature range (°C)	% Weight loss		Decomposition product
			Found	Calculated	
$[Th(Q)_2(Ala)NO_3 \cdot H_2O]$	220	120-200	2.50	2.62	$[Th(Q)_2(Ala)NO_3]$
		220-350	13.2	12.78	$[Th(Q)_2NO_3]$
		380-750	44.28	46.19	$[ThO_2]$
$[Th(Q)_2(Ph\text{-}Ala)NO_3 \cdot H_2O]$	225	125-210	2.8	2.36	$[Th(Q)_2(Ph\text{-}ala)NO_3]$
		225-375	20.14	21.46	$[Th(Q)_2NO_3]$
		390-750	39.64	41.8	$[ThO_2]$
$[Th(Q)_2(Ser)NO_3 \cdot H_2O]$	220	120-210	2.85	2.56	$[Th(Q)_2(Ser)NO_3]$
		220-375	14.14	14.91	$[Th(Q)_2NO_3]$
		380-760	42.14	45.15	$[ThO_2]$
$[Th(Q)_2(Tyr)NO_3 \cdot H_2O]$	220	120-210	2.14	2.31	$[Th(Q)_2(Tyr)NO_3]$
		220-390	8.36	7.95	$[Th(Q)_2(Tyr)]$
		400-760	50.71	55.87	$[ThO_2]$

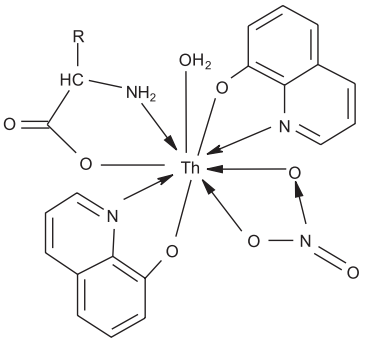

Figure 1. Proposed structures and bonding for the complexes

Antibacterial studies

The minimum inhibition concentrations (MIC) of the complexes against *S. aureus* and *E. coli* studied by tube dilution method are recorded in Table 3. All the complexes show mild antibacterial activity against the selected strains but show marginally higher activity compared to similar type of mixed ligand complexes reported (6). The complexes are more active against *S. aureus*. Compared to standard antibacterial compound, *tetracycline,* the present complexes show lesser activity against selected strains of microorganisms.

Cytotoxicity (IC_{50}) studies

The results of the *in vitro* cytotoxicity studies performed at „Amala Cancer Research Centre" Thrissur, Kerala, on one representative complex $[Th(Q)_2(Ser)NO_3{\cdot}H_2O]$ recorded in Table 4, show low cytotoxic activity of the complex even at the highest concentration that could be applied (100 µg/mL). Dose-response curves (26) were established and the concentration which is sufficient to reduce the cell number by 50% (IC_{50}) was calculated. IC_{50} value of 238 µg/mL for *Ehrlich ascites* cells and 206 µg/mL for *Dalton's lymphoma ascites* cells indicate marginally higher activity of the complex against *Ehrlich ascites* cells as compared to *Dalton's lymphoma ascites* cells. IC_{50} values of standard cytotoxic compound, curcumin, have been reported (27) as 4 µg/mL for *Ehrlich ascites* cells and 22 µg/mL for *Dalton's lymphoma ascites* cells. The IC_{50}

Table 3. Antibacterial activity (MIC µg/ml).

Complex	Antibacterial activity	
	S. aureus	*E. coli*
$[Th(Q)_2(Ala)NO_3{\cdot}H_2O]$	20	40
$[Th(Q)_2(Ph\text{-}ala)NO_3{\cdot}H_2O]$	20	20
$[Th(Q)_2(Ser)NO_3{\cdot}H_2O]$	20	40
$[Th(Q)_2(Tyr)NO_3{\cdot}H_2O]$	20	40
Tetracycline	1.5	2.5

Table 4. Cytotoxicity study.

Sample	Conc. µg/ml	Cells	No. of EA cells		% Death	No. of DLA cells		% Death
			Live	Dead		Live	Dead	
Control	-	1. $1x10^6$	100	0	0	100	0	0
		2. $1x\ 10^6$	100	0		100	0	
DMSO	20 µl	1. $1x10^6$	100	0	0	100	0	0
		2. $1x\ 10^6$	100	0		100	0	
$[Th(Q)_2(Ser)NO_3{\cdot}H_2O]$	5 µg	1. $1x10^6$	96	4	3	100	0	0
		2. $1x\ 10^6$	97	3		100	0	
		3. $1x10^6$	97			100	0	
	10 µg	1. $1x10^6$	95	5	5	94	6	5
		2.$1x\ 10^6$	95	5		95	5	
		3. $1x10^6$	95	5		95	5	
	20 µg	1. $1x10^6$	93	7	7	91	9	9
		2. $1x\ 10^6$	93	7		91	9	
		3. $1x10^6$	93	7		91	9	
	50 µg	1. $1x10^6$	87	13	13	84	16	16
		2. $1x\ 10^6$	86	14		84	16	
		3. $1x10^6$	88	12		82	18	
	100 µg	1. $1x10^6$	82	18	18	81	19	21
		2. $1x\ 10^6$	83	18		77	23	
		3. $1x10^6$	82	17		78	22	

value of the complex when compared to that of curcumin indicates low cytotoxic activity of the complex.

CONCLUSIONS

Based on the above results the following conclusions may be drawn.

The higher decomposition temperatures of the complexes indicate a strong metal-ligand bond and electrical conductance studies show non-electrolytic nature of the complexes, respectively. Magnetic studies indicate diamagnetic nature of the complexes. The IR spectra show bonding of the metal ion through N- and O- donor atoms of the two ligands. Thermal analysis confirms presence of a coordinated water molecule. On the basis of above results a nine-coordinated structure is proposed for thorium complexes.

The antibacterial studies show mild antibacterial activity of the complexes against selected strains of *S. aureus* and *E. coli*. Compared to standard antibacterial compound, *tetracycline,* the present complexes are much less active against the selected strains of microorganisms. The cytotoxicity (IC_{50}) studies on one of the representative complex show low cytotoxic activity.

Acknowledgement

The author (G.A.T.) is grateful to University Grants Commission (Western Regional Office, Pune) for the award of Teacher Fellowship under Faculty Improvement Programme and Dr. Ramadasan Kuttan, Research Director, Amala Cancer Research Centre, Thrissur, Kerala, India, for cytotoxicity study.

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Received: 21.11.2005