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La(III) and Ce(IV)Complexes of Novel Azo-Theophylline Ligand :Structural Analysis and Biological Effectiveness

Mohnned Hamady Manulla, Alyaa Khider Abbas*

Department of Chemistry, College of Science, University of Baghdad ,Baghdad

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Abstract

A novel compound, 8-[(E)-(3-hydroxyphenyl)diazenyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (PAT), was synthesized *via* the diazotization and coupling reaction of m-amino phenol with theophylline. In addition, complexes of the ligand (PAT) with [Ce (IV) and La (III)] were synthesized. The structural features of the synthesized compounds were examined using several spectroscopic techniques including elemental analyses [CHN], Fourier transform infrared spectroscopy (FTIR), UV-Visible spectroscopy (UV-Vis) and proton nuclear magnetic resonance spectroscopy (^{1}H NMR). Other characterization techniques employed were magnetic measurement, molar conductance data, thermal analysis (thermogravimetric analysis, TGA), inductive coupled plasma (ICP), and scanning electron microscopy (SEM). Through the FTIR study, it was found that the PAT ligand behaves as a neutral N,N- bidentate ligand and that the two complexes have octahedral coordination geometry with six coordination sites. The ligand and its complexes were assessed as antioxidant by DPPH free radical scavenging with ascorbic acid as a positive control for comparative with the synthesized compounds which were appeared good activities, also all compounds were tested for their antibacterial activity *via* disk diffusion method (MIC) at two concentration (50 mg/ml and 100 mg/mol) they had varying effectiveness compared to amoxicillin as reference

Keywords: antibacterial, antioxidant, theophylline, m-amino phenol, complexes.

معقدات La(III) و Ce (IV) لليكند ازو- ثيوفلين الجديد :تحليل الصيغة التركيبية والفعالية البيولوجية

مهند حمادي مان الله ، علياء خضر عباس*

قسم الكيمياء ، كلية العلوم ،جامعة بغداد، بغداد، العراق

الخلاصة

تم تحضيرمركب جديد 8-[(E)-(3-hydroxyphenyl)diazenyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (PAT) بواسطة الديدزة والازدواج ل m-amino phenol و theophylline. وكذلك ايضا حضرت معقدات الليكاند PAT مع [(Ce (IV) و (La (III)] تم فحص السمات الهيكلية للمركبات المحضرة باستخدام العديد من التقنيات الطيفية بما في ذلك التحليلات الأولية (CHN) ، وتقنيات التحليل الطيفي [FTIR ، و UV-Vis و HNMR] ،قياسات المغناطيسية ونتائج التوصيل المولاري ، والتحليل الحراري (TGA), والبلازما الحثية (ICP) والمسح المجهري الإلكتروني SEM.من خلال دراسة FTIR وجد ان الليكند PAT يسلك كليكند متعادل N,N- ثنائي السن يرتبط عن

*Email: aligggaa36@gmail.com

طريق ذرتي نيتروجين والمعقدين ذات شكل هندسي ثماني السطوح وتناسق سداسي. الليكند ومعقداته تم فحصهم كمضاد للأكسدة باستخدام طريقة DPPH واستخدام حمض الأسكوربيك للمقارنة مع المركبات المحضرة والتي اظهرت فعالية مضادة للأكسدة جيدة وكذلك تم اختبار الفعالية المضادة للبكتريا بطريقة (MIC) وبتركيزين هما (50 مجم / مل و 100 مجم / مول) لجميع المركبات المحضرة حيث كانت لهم فعالية متباينة مقارنة مع الاموكسيلين كمرجع .

1.Introduction

Azo compounds are organic compounds have the ability to colorize other substances[1]. They have multiple strong electron-withdrawing groups in their structures, which can produce dark colored compounds and improve color fastness[2]. Azo compounds are the most widely used and oldest family of industrially produced organic dyes because of their numerous applications including coloring paper, leather, and textiles[3]. The heterocyclic azo compounds show various medical and biological applications such as antimicrobial[4], biological [5, 6],anti-inflammatory, antioxidant[7,8], anticancer activity[9, 10]. Synthetic dyes have found widespread use as pharmaceutical ingredients and in cosmetics because they are more stable than natural colors[8]. In addition they have been used as indicators [11] and also they used at chemosensors, electro-optical devices, liquid crystal displays, optical memory storage systems [12]. Theophylline(THP) is a naturally occurring plant alkaloid (1,3-dimethylxanthine)[13]. THP molecules can split into the proton tautomers N9H and N7H. In aqueous solution, N7H is more stable than N9H[14].Theophylline and its complexes are interesting antibiotic against *Staphylococci. aureus, Escherichia coli* [15]. Additionally, azo dyes containing heterocyclic nuclei have received much research due to their better medicinal qualities, including their effectiveness against bacteria, viruses, fungi, and free radicals as well as their calorific and aesthetic performance[16]. The optical and magnetic properties of lanthanide complexes are of significant research interest in materials science. Of particular interest are complexes where the ligands intrinsically function as sensitizers for lanthanide-based luminescence within the same molecule[17,18]. In the present study, we report the synthesis of a novel ligand (PAT) and its subsequent complexation with La(III) and Ce(IV) ions, forming the corresponding lanthanide complexes. They were identified by spectroscopic method [FTIR,HNMR,UV-VIS]TGA, molar conductance, elemental analysis and magnetic measurement the biological activities have also been tested (antioxidant and antibacterial activities) .

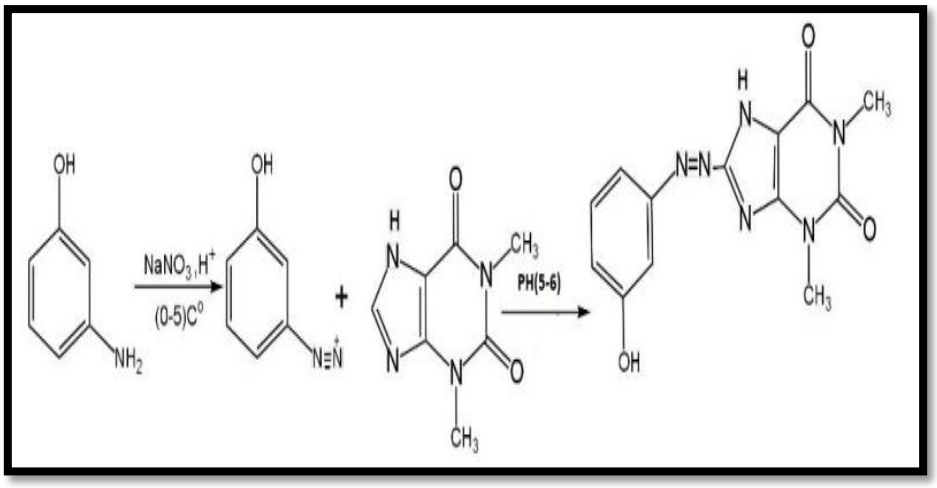
2.Experimental

2.1 Instruments and Materials

Reagents and solvents of high purity were used. The ligand constituents and its complexes were analyzed using elemental analysis (Euro EA 3000 elemental analyzer) for carbon, hydrogen, nitrogen and sulfur content. A Nova 350 spectrophotometer and Flame Atomic Absorption Spectrophotometer (Flame AA) were utilized. Fourier transform infrared (FTIR) spectroscopy was carried out for all compounds using a Shimadzu FTIR 8400S spectrophotometer to acquire spectra. Ultraviolet-visible (UV-Vis) spectra were obtained on a Shimadzu 1800 spectrophotometer in the range of 190-1100 nm employing a concentration of 10-4 M solutions. Thermogravimetric analysis (TGA) was performed using a SDT Q600 V20.9 instrument to determine the metal content of the synthesized ligands and complexes. The melting points of each compound were calculated utilizing Stuart melting point apparatus. The chloride content of the samples analyzed was ascertained using mohr method. To determine the magnetic susceptibility of the complexes at room temperature the (model - M.S.B. the Auto Apparatus) was used. However, the HNMR spectra confirmed by using (NMR Spectrometer 400 MHz, Advance III 400 Bruker, Germany).

2.2 synthesis of novel ligand (PAT)

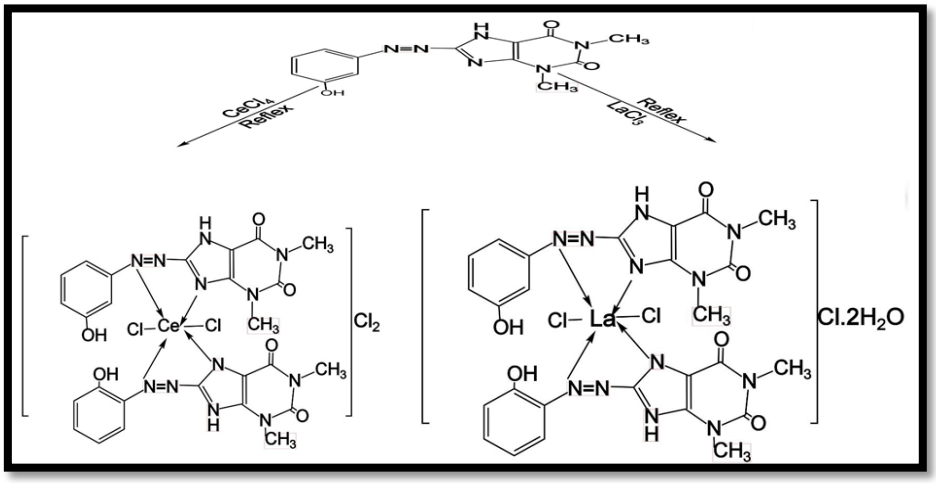
According to the literature [19], the diazonium salt was prepared by dissolving m-amino phenol (0.01 mol, 1.091 gm) in an ice-cold acidic solution containing 10 ml deionized distilled water and 10 ml concentrated acetic acid. Sodium nitrite solution (10%, 10 ml) was added dropwise at 0-5°C to the mixture with stirring for 30 minutes, yielding the cold diazonium salt solution. Separately, a solution of theophylline (0.01 mole, 1.8016 gm) was prepared in 14 ml of 10% NaOH in ethanol. The resulting diazonium salt solution was then carefully added to the theophylline solution with stirring to obtain the final product. After that, the resulting mixture was brought to pH(5-6) and neutralize with acetic acid or sodium hydroxide then it was left to precipitate. The orange precipitate was filtered, washed with [water : ethanol] [1:1], collected, and dried. Equation 1 shows the synthesis of the ligand.



Equation1.Synthesis path of ligand(PAT).

2.3 Synthesis of lanthanide complexes

An aqueous solution of ($LaCl_3$ and $CeCl_4$) [1 mole, 0.245gm and 0.2819 gm] respectively were poured into aqueous solution of [2mmol ,0.6005gm]of the ligand (PAT).The mixture was reflux for (3hours) and the reaction was followed up with a TLC technique [20] using a solvent system of methanol: ammonia: butanol (0.8 ml methanol ,1.2ml of ammonia and 4ml of butanol). The colored product was filtered and washed with a 1:1 mixture of ethanol and distilled water. It was then dried and collected. Scheme 2 outlines the synthesis of the complexes.



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Equation 2:Synthesis of the complexes.

2.4Antibacterial

The study employed two different bacterial strains: Escherichia coli (E. coli), a Gram-negative-bacteria, and Staphylococcus aureus (S. aureus), a Gram-positive-bacteria. E. coli and S. aureus were selected to represent the major classes of bacteria-Gram-negative and Gram-positive, respectively. Water was used as the solvent for the ligand (PAT) and its complexes, as well as a control, to account for any biological inhibition of the synthesized compounds. Meanwhile, amoxicillin served as the reference antibiotic. Klebsiella, another Gram-negative bacterium, was also included in the study. These bacteria were personated and cultured on nutrient agar medium to use in the experiment. Through measuring the holes process by (MIC) method, which defies *in vitro* levels of capability of bacterial strains to selected antibiotic, the biological inhibition of the distinct bacteria for the ligand (PAT) and its complexes were examined. This procedure involved filling the holes with two concentrations (50 and 100) microgram/ml of the specified complexes and ligand, allowing them to diffuse on the medium for around 15 minutes, and then incubating them at (37 C^o) for (24) hours. The deactivation diameters estimated utilizing the first basis were taken into account for this decision.

2.5Antioxidant

The ligand (PAT) and its complexes were examined the anti-oxidant activity in laboratory using DPPH radical scavenging activity[21].

3.Result and Discussion:

The ligand PAT was synthesized using the classical diazotization-coupling method, which involves the reaction of theophylline as the nucleophilic coupling component with the diazonium salt derived from m-amino phenol as the primary amine substrate. Table 1 shows the physicochemical characteristic and analytical results of the synthesized ligand (PAT)and its complexes, which was carried out in a molar ratio(1:2)(M:L) for all complexes as well as the findings obtained results from elemental analysis are agreement with calculated values. The proposed molecular structure identified and formulated by subsequent spectral, magnetic moment as well as molar conductance tests proved that complexes La(III) and Ce(IV) have electrolyte properties with chloride ion as counter ion .

Table 1: Physical and analysis properties of the ligand (PAT) and its complexes

Compounds (M.wt) (gm/mol)	**M:L**	**Color λ (nm)**	**% Experimental % (Theoretical)**					Λm(S.mol^1.cm^2)
			C	H	N	M	Cl	
PAT($C_{13}H_{12}N_6O_3$) (300.29)	----	Dark orange (436)	52.2 51.9	3.4 3.9	27.2 27.9	——	——	136
[La($C_{13}H_{12}N_6O_3$)$_2$$Cl_2$]Cl.2$H_2O$ (881.45)	1:2	Orange (465)	35.5 35.3	2.9 2.7	19.2 19.0 5	16.2 15.7	12.06 12.2	250
[Ce($C_{13}H_{12}N_6O_3$)$_2$$Cl_2$]$Cl_2$. (882.69)	1:2	Greenish yellow (627)	35.3 35.8	2.5 2.7	19.7 19.3	15.7 15.97	16.6 16.4	84

3.1 The FT-IR spectra

FTIR spectrum of the azo ligand (PAT) Figure 1 is complicated related to the large number of moieties , which overlapping regions ,while some bands are chosen in order to prove the coordination. The main bands of the free ligand (PAT) and its lanthanide complexes are tabulated in Table 2. The spectrum of the ligand (PAT) was appeared a

stretching frequency of υ (OH)Phenol, υ (N-H)imidazole and υ (C=O)pyrimidine. These bands remained unchanged in the complexes spectra, indicating that there is no coordination with these groups sometimes these bands were appeared slight changes in the intensity or position upon complexation[22]. The characteristic bands of an azo compound, namely the υ (-N=N-) and υ (-C-N=N-C-) stretches, were observed at 1421 cm-1 and 1334 cm-1 respectively in the ligand spectrum. These bands exhibit shifts to higher wavenumbers in the spectra of the complexes due to involvement in coordination to the metal centers *via* the azo nitrogen atoms. Another band was noticed in the spectrum of the free ligand (PAT), which related to υ (C=N)for imine in imidazole moiety of theophylline where also is affected by coordination between the ligand and lanthanide ions ,in terms of shape and displacement [23] as was shown in the Figures1, 2 and3. As well as new bands were appeared in the complex's spectra due to complexation, and bonds between the ligand and the chloride ion Table 2.

Table 2: The FTIR spectrum bands of PAT ligand and its Complexes.

Com.	υ(OH)	υ(C=O) pyrm.	υ(C=N) imd.	υ N=N	υ(-CN=NC-)	υ(M-N) imd.	(M-N) azo	υ(M-Cl)	υ(H_2O)
PAT	3442 d 3423 ST	1701 uw	1639 1575 d,st	1421 m	1334w	---	---	----	-----
$[La(PAT)_2Cl_2]Cl.2H_2O$	3429 3342 t 3228st	1697 vw	1645 1600 d,st	1521 1506 1461 t ,st	1388m	686w	642w	372vw	995}d 950} w
$[Ce(PAT)_2Cl_2]Cl_2$	3425 3394t 3228st	1697 vw	1645 1620 1602 t,st	1506 1460 1415 t,st	1388 m	686w	605v w	350vw	------

st=strong, , br.= broad , s= strong , m= medium , w= weak,pyrm=pyrmidine,imd=imidazole

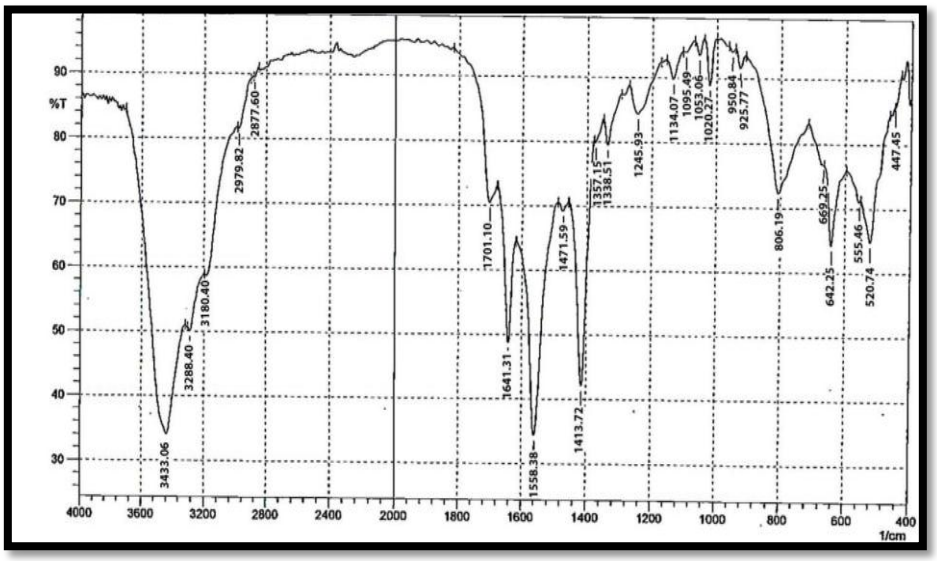


Figure 1: FTIR spectrum of the ligand (PAT).

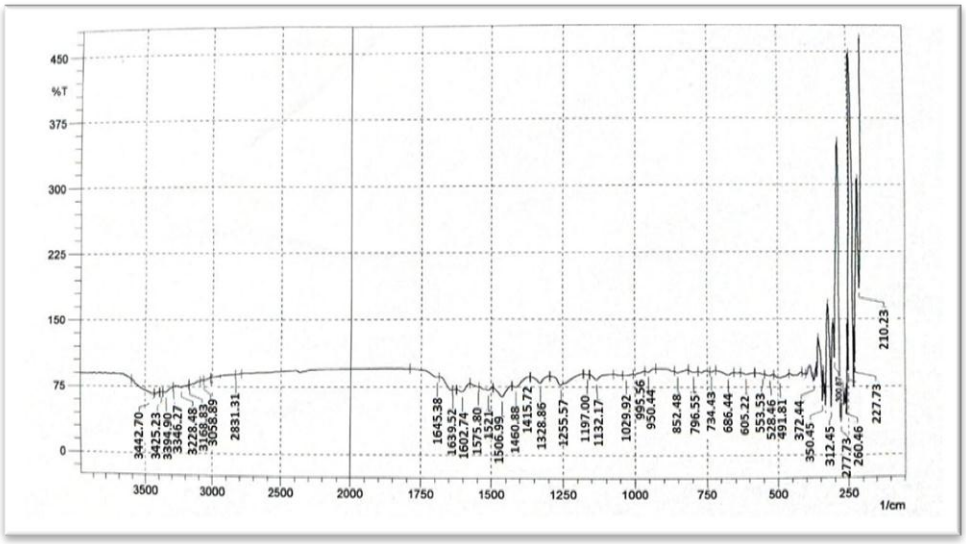


Figure 2: FTIR spectrum of $[Ce(PAT)_2Cl_2]\ Cl_2$.

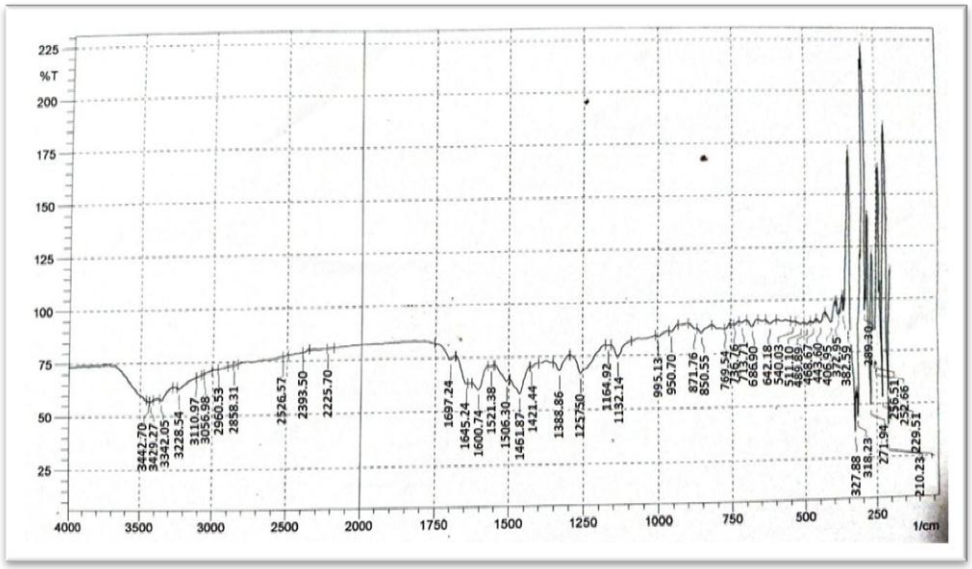


Figure 3: FTIR spectrum of$[La(PAT)_2Cl_2]Cl.2H_2O$

3.2Thermo gravimetric Analysis (TGA)

TGA assays showed that PAT ligand is thermally degradable and its complexes were also tested at (25-1000) C^o in argon. Table 3 limited the mass loss, stages, and TGA range of the decomposition, The TGA thermograms are displayed in Figures 4 and 5. The proposed formula was validated using thermal analysis, which was also used to examine the thermal stability of the ligand PAT and its complexes. Metal nitrogen residues were observed as the final products of thermolysis for all complexes. The percentage of metal nitrogen residues indicates the relative stability of the compounds in the following order: $[Ce(PAT)_2Cl_2]Cl_2$ < $[La(PAT)_2Cl_2]Cl.2H_2O$ < PAT, with PAT being the most stable based on having the lowest percentage of metal nitrogen residues remaining after thermolysis [24].For the La-complex was displayed in the first decomposition step at the range (25-150)c^o and weight loss (7.6090)is due to the loss of lattice water molecules[25].

Table3: thermal analyses data of the ligand (PAT) and its Complexes.

Com. Sym	Molecular Formula (molecular Weight) g/mole	Steps	TG. Range of the decomposition (°C)	Suggested Assignment	%Mass loss Calculate %	%Mass loss Found %
PAT	$C_{13}H_{12}N_6O_3$	1	25-165C^0	C_2H_{12}	11.98	11.80
		2	165 -380C^0	C_{25}	9.99	10.01
		3	380-850C^0	$C_{6.5}$	25.97	25.50
		4	849-1000C^0	$C_{1.25}$	4.99	5.02
		5	>1000	$C_{0.75}N_6O_3$	46.54	46.54
$[La(PAT)_2Cl_2]Cl.2H_2O$		1	25-150C^0	$(H_2O)_2Cl_{0.88}$	7.57	7.60
		2	150-300C^0	ClH_2	4.19	4.14
		3	300 - 460	$Cl_{1.12}C_2H_2$	7.39	7.43
		4	460 -600	C_4H_9	6.50	6.50
		5	600-750	C_8H_4	11.34	11.40
		6	750 -950	$C_{8.75}$	11.92	12.01
		7	>1000	$C_4N_{12}O_6La$	50.91	51.90
$[Ce(PAT)_2Cl_2]Cl_2$		1	25-150	C_2Cl_4	18.58	18.51
		2	150-350	C_6H_5	8.72	8.81
		3	350-650	C_4H_9	6.45	6.45
		4	>1000	$C_{14}H_{10}N_{12}O_6Ce$	66.05	66.24

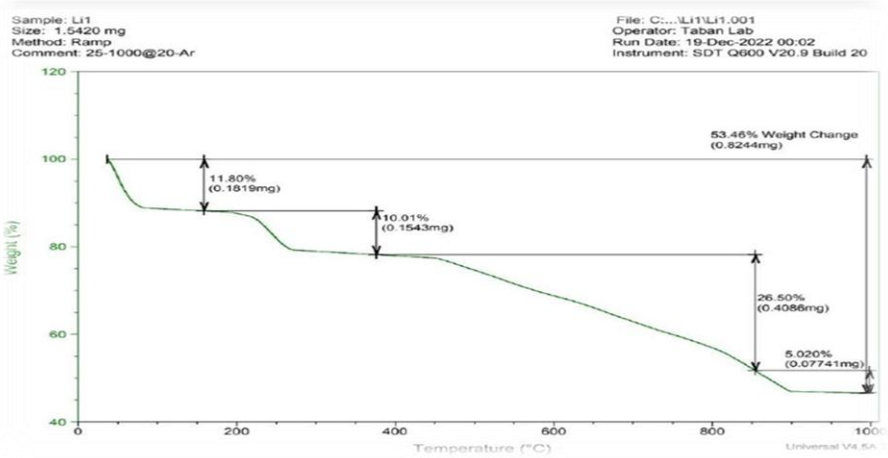


Figure 4 : pyrolysis scheme of the (PAT) ligands

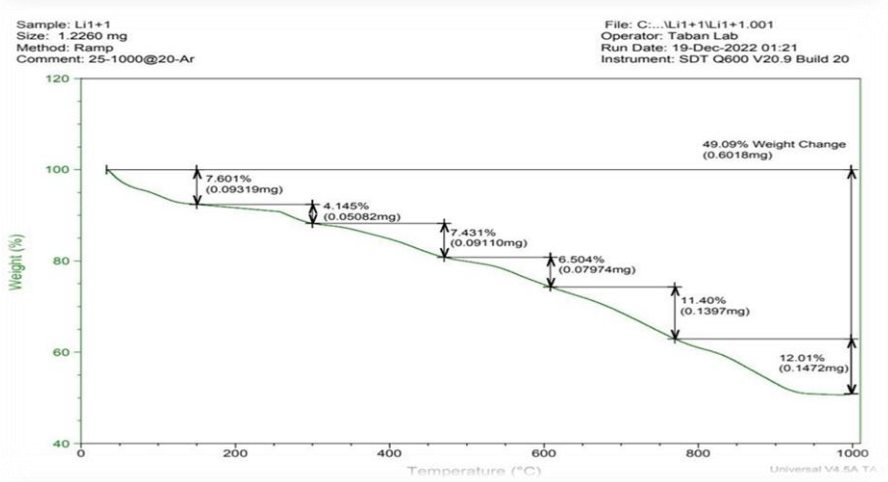


Figure 5: pyrolysis scheme of the $[La(PAT)_2Cl_2]Cl.2H_2O$ complex.

3.3 H-NMR spectrum

The ^{1}HNMR spectrum of the ligand was compared using TMS as an internal standard and chemical shift data (δ) in ppm for various proton types. The ^{1}H NMR spectrum was obtained in DMSO-d6 solution. As shown in Table 4, a singlet signal appeared at 14.5 ppm belonging to the 1H attached to the N-H group of the imidazole moiety in theophylline within the PAT ligand. All peaks were referenced to the residual DMSO solvent peak observed at 2.5 ppm [26].Two signals are shown by the free ligand (PAT) at (3.36 and 3.48) ppm can be attributed to the protons of ($N\text{-}CH_3$,6H) of pyrimidine in theophylline moiety [27] and a singlet signal at (7.8)ppm belong to (OH,H)of phenol moiety. The multiple signals at (9.4)ppm which related to benzene ring[27] .Figure 6.

Table 4:1HNMR signals of PAT ligand[(δ) ppm.

Compound	N-CH,6H imd.	N-H	Ar-H ,4H	OH,H
PAT	3.35 3.41	14.5	6.74 6.67	9.45

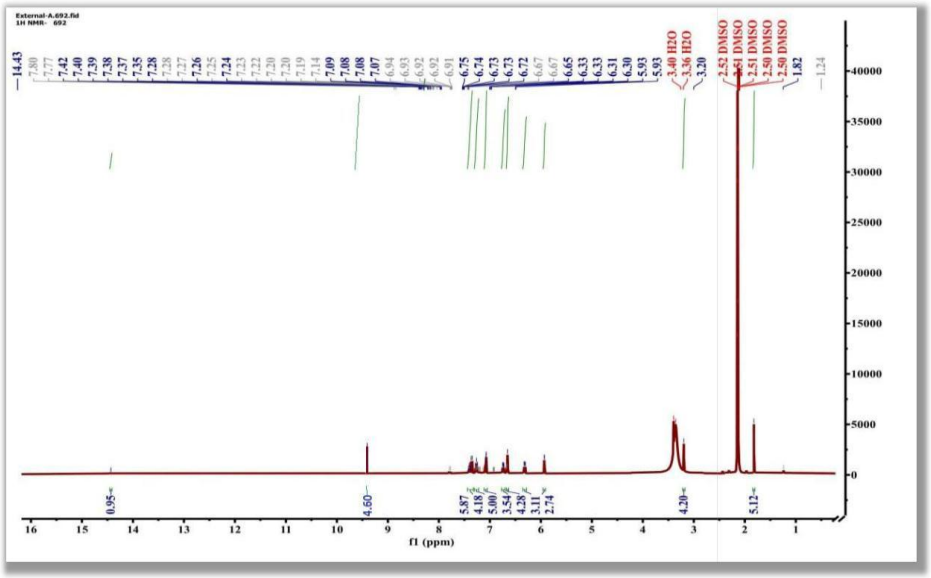


Figure 6: ^{1}HNMR Spectrum for the (PAT) ligand**.**

3.4UV-Vis spectra and magnetic properties.

Ultraviolet-visible (UV-Vis) spectroscopy is one of the most widely used techniques for characterizing metal complexes. In this study, the ligand PAT and its complexes were examined using UV-Vis spectroscopy over a wavelength range of 190-1100 nm at a concentration of 10-4 M. The results are presented in Table 5 and Figures 8-10. The electronic absorption spectrum of the PAT ligand exhibits two bands at 436 nm (22935 cm-1) and 286 nm (37037 cm-1). The lower energy band corresponds to an intraligand charge transfer transition (n→π*) involving the carbonyl and azo moieties as intermediaries. This provides information about the electronic properties and transitions within the ligand. Moreover, the inter molecular transition [inter CT] for the pyrimidine, imidazole and benzene moieties of the second band in the UV area was represented transition (π→π*)[29]. The electronic spectra of La (III)and Ce(IV) complexes ($4d^{10}$) with diamagnetic properties shows abroad band at (465nm22779cm^{-1}) and (627nm,15948cm^{-1}) respectively due to charge transfer (CT) [30].Figures 7,8and 9.

Table 5: Electronic transition, data of the ligand (PAT)and its complexes.

Compounds	ג nm	Wave number (cm^{-1})	Assignment
PAT Dark orange	436 286	22935 34965	$n\rightarrow\pi^*$ $\pi\rightarrow\pi^*$
$[La(PAT)_2Cl_2]Cl.2H_2O$ orange	465	22779	CT
$[Ce(PAT)_2Cl_2]Cl_2$ Greenish yellow	627	15948	CT

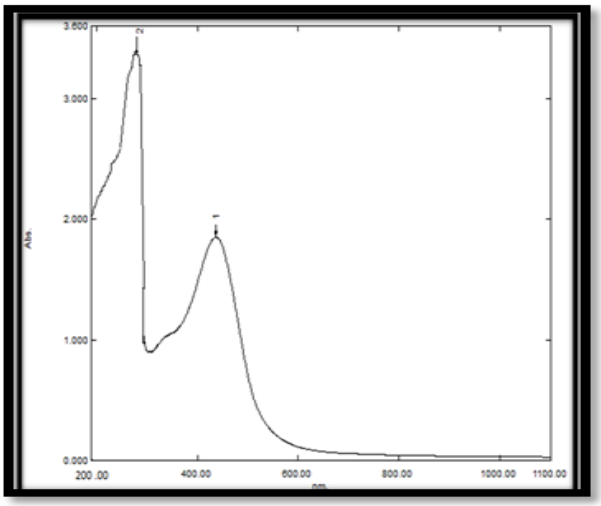


Figure 7: UV-Vis Spectrum for the PAT ligand

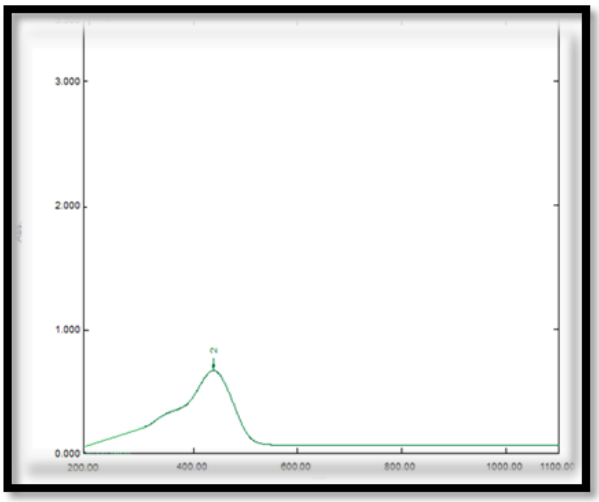


Figure 8: UV-Vis Spectrum for the $[La(PAT)_2Cl_2]Cl.2H_2O$ complex.

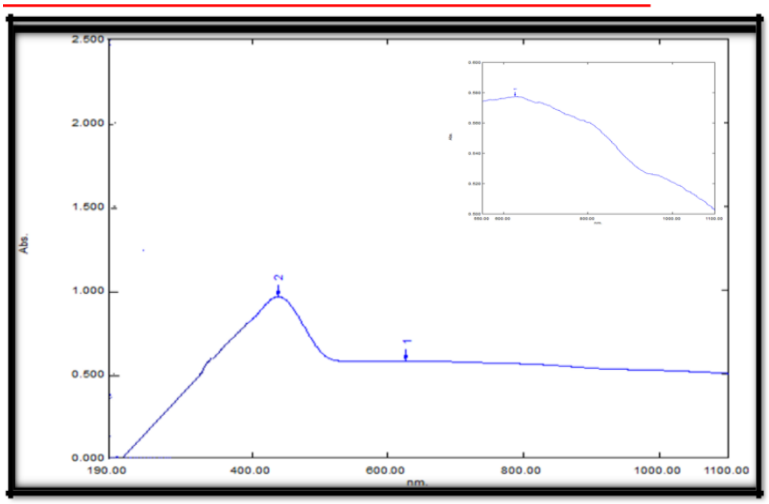


Figure 9: UV-Vis Spectrum for the $[Ce(PAT)_2Cl_2]Cl_2$ complex.

3.5 Scanning Electron microscopy Analysis (SEM)

The surface morphology is examined via SEM analysis[31]. Different crystal line structures and surface homogeneities may be seen in the morphology of the ligand (PAT)and in their complexes. SEM procedure was accredited for a cross section's area (100nm) and expanding power (Mag=60.00KX) as displayed in Figures 10. The SEM pictures demonstrated heterogeneous surfaces with various forms that vary with various compounds and change in particle volume Table 6.

Table 6: SEM data of the ligand(PAT) and its complexes.

Compounds	Average radii (nm)	shape
PAT	133.6	Coral
La(PAT)	73.54	Spherical

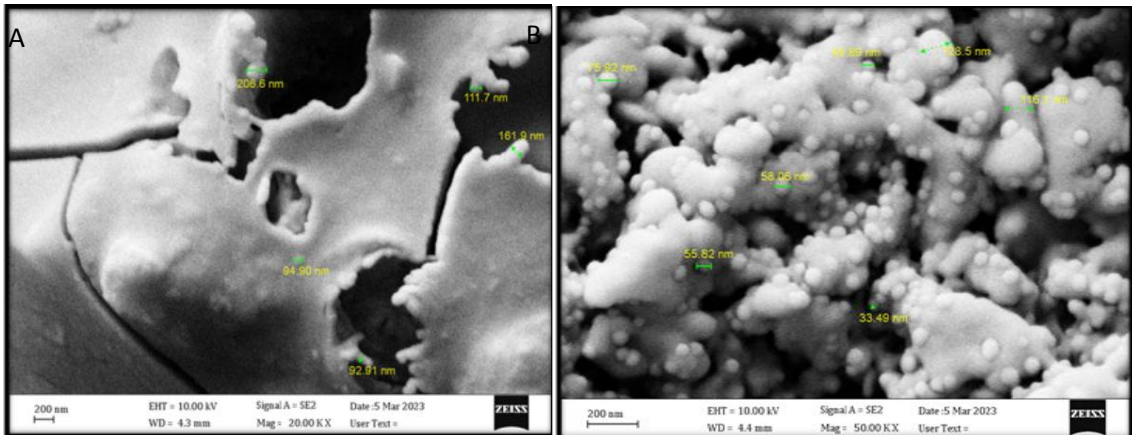


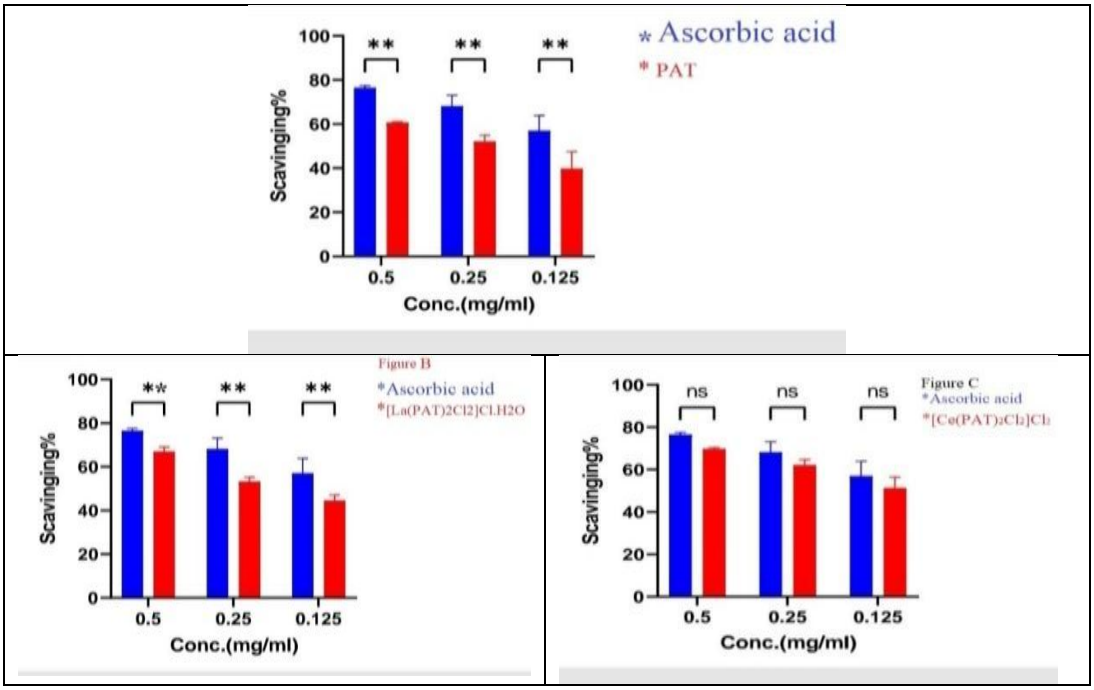
Figure 10: SEM analysis for the (A)PAT ligand and (B) $La(PAT)_2Cl_2]Cl.2H_2O$ Complex.

3.6 Anti-oxidant and Radical Scavenging Activity

An examination was carried out in the laboratory for testing antioxidant activity of the ligand PAT and its complexes with DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging which was utilized. Ascorbic acid was utilized as a positive control. The results of the antioxidant activity assay are presented in Table 7 and Figure 11. These results allow us to conclude that the susceptibility of the synthesized compounds to act as antioxidants when compared to vitamin C at a concentration of 0.125 mg/ml. The data show the effectiveness of the different compounds in quenching the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), with vitamin C serving as a positive control for antioxidant activity. The Ce(IV) has high antioxidant activity than the ligand (PAT) and La(III) complex and the ability of the tested compounds as antioxidant were dependent on their concentration.

Table7: DPPH radical scavenging activity of the ligand (PAT) and its complexes with vitami C.

The compound	**Concentration (mg/ml)**	**DPPH Radical Scavenging Activity (Mean ± SD; %)**	
		The compound	**(Vitamin C)**
$[Ce(PAT)_2Cl_2]Cl_2$	0.5	69.77±0.6	76.500±1.04
	0.25	62.18±2.49	68.23±4.90
	0.125	51.25±5.23	57.033±6.58
$[La(PAT)_2Cl_2]Cl.2H_2O$	0.5	67.01±1.99	76.500±1.04
	0.25	53.26±1.90	57.033±6.58
	0.125	44.63±2.44	68.23±4.90
PAT	0.5	60.69±0.36	76.500±1.04
	0.25	52.14±2.77	68.23±4.90
	0.125	39.81±7.63	57.033±6.58



Figures 11: DPPH radical scavenging activity of the ligand and its complexes.

3.7Antibacterial Activity of the ligand and its complexes

To prevent contamination, sickness, damage, and infection brought on by microbes, microbe control is essential. Two pathogenic bacteria were used to test the antimicrobial effectiveness of the novel azo ligand (PAT) and its complexes *in vitro* using the disk diffusion method at (50mg/ml and 100 mg/mol). Bacteria was used to cause numerous diseases in living systems that are life-threatening, been used gram –negative bacteria specie *(E.coli)* and gram- Positive bacteria specie (*Staphylococcus).* The results of the antimicrobial screening are reported in Table 8. Most of the compounds tested exhibited moderate to good antimicrobial efficacy. The complexation of the metal ions with the ligand donor atoms results in charge delocalization around the ring structure through sharing of positive charge between the metal and ligand. This increases the lipophilicity of the chemical entities, allowing better permeation of microbial cell membranes and eliciting antimicrobial action. The obstruction of metal binding sites on microbial enzymes will result in an increase in the penetration of metal ions complexes into lipid membranes. In addition, bacterial cell wall damage will cause the bacteria to die and stop the organism's growth, these compounds interfere with the cell's respiration process, preventing the production of protein[32].

Table 8: Antibactiral activity of the ligand(PAT) and its complexes.

Compounds	Gram(-) Negative *Escherichia Coli (E-Coli)*		Gram(+) Positive *Staphylococcus aureus*	
	con. 100mg/ml	con. 50mg/ml	con. 100mg/ml	con. 50mg/ml
Amoxicillin	20	16	18	14
PAT	6	4	14	12
$[La(PAT)_2Cl_2]Cl_2H_2O$	10	7	15	13
$[Ce(PAT)_2Cl_2]Cl.$	13	14	12	12

4.Conclusion

By using the diazotization-coupling process, the ligand (PAT) was synthesized, functioning as a chelating ligand for neutral N, N-bidentates bonds to the metal ions through

the nitrogen of the azo moiety and nitrogen of imine moieties in the theophylline, to complexes form a pentagonal chelating ring with octahedral geometry of La(III) and Ce(IV). Thermal analysis using TGA is used to further demonstrate the produced compounds' thermal stability. It was determined whether the ligand and its complexes have good antibacterial and antioxidant properties.

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