Synthesis，Spectroscopic and Antimicrobial Investigations of Scandium(Ⅲ) Complexes with Four Kinds of Sulfa Drugs

Moamen S. Refat[1,2*]，Abeer A. El-Habeeb[3]

1. Chemistry Department，Faculty of Science，Taif University，P.O. Box 888，Al-Hawiah，Taif 21974，Saudi Arabia
2. Department of Chemistry，Faculty of Science，Port Said，Port Said University，Egypt
3. College of Science，Princess Nourah Bint Abdulrahman University，Department of Chemistry，KSA

Abstract Herein，this article was focused on the synthesis and discussed the spectroscopic characterizations of four new scandium(Ⅲ) sulfa-drug complexes. The nomenclature and symbols of these drugs were sulfadimidine (sulp-1)，sulfanilamide (sulp-2)，sulfamethoxazole (sulp-3) and sulfadiazine (sulp-4). The microanalytical and spectroscopic analyses which utilized in this study were micro-analyses，magnetic，FT-IR，UV-Vis techniques. The mid infrared spectra deduced that the four sulfa-drug chelates acts as a bidentate chelates with scandium(Ⅲ) ion via two nitrogen atoms of $—NH_2$-Ar and $—NH-SO_2$ groups. Also，the FTIR spectra of Sc^{3+} complexes referred to the existed of new medium weak bands in the range of 500～400 cm^{-1} due to stretching vibration bands of ν(M—N). The elemental analysis technique confirmed the 1∶2 stoichiometry between Sc^{3+} ions and sulp ligand with molecular formula $[Sc(sulp)_2(Cl)_2]\cdot Cl$. At room temperature，the results of magnetic measurements for the Sc(Ⅲ) complexes indicated that all of the synthesized complexes have a diamagnetic character with octahedral configuration. The electronic spectra of the free sulfa-drug ligands shows band at 275 and 310 nm which are intraligand charge transfer band. The electronic sbsorption spectra of the Sc^{3+} complexes were recorded using DMSO solvent. The spectra of complexes display bands within 275～388 nm，which attributed to $\pi—\pi^*$，$n—\pi^*$ and charge-transfer M-L_{CT} electronic transitions，which strongly favors the octahedral geometry around Sc(Ⅲ) metal ions. ^{1}HNMR spectra of complexes referred to the downfield proton shifts of the $—NH_2$ and $NHSO_2$ groups，which supported the place of coordination. The half maximal inhibitory concentration (IC_{50}) of the $Sc^{Ⅲ}$ complexes was assessed against the human hepato cellular carcinoma (HepG-2) tumor cell line.

Keywords Sulfa-drugs；$Sc^{Ⅲ}$；Spectroscopic；Chelation；Nano-particles；Antimicrobial

中图分类号：O433 **文献标识码**：A **DOI**：10.3964/j.issn.1000-0593(2020)03-0985-06

Introduction

Sulfonamides $—NHSO_2$ received much attention because of their tendency to attached with different drugs as a medicinal drugs against bacterial infections and serious diseases in humans[1-2]. Although sulfonamides are old drugs，they are still considered useful in some therapeutic areas especially in the case of eye infections as well as urinary，gastrointestinal infections[3-4] and the complex composition of metal ions and sulfa-drugs themselves constitute an important area of research[5]. Moreover，sulfa drugs and their metal complexes have many applications，as well as antibacterial activity such as diuretics，anti-glaucoma or antiepileptic，among other things[6]，such as antifungal activity[7]，and in many cases，metal compound activity is much better than ligand alone[7]. Fox et al.[8]，was discussed number of different metal sulfa drug complexes and their antimicrobial activities. Silver(Ⅰ)，

Received：2019-08-31；**accepted**：2019-12-26

* Corresponding author e-mail：msrefat@yahoo.com

zinc(Ⅱ) and cerium(Ⅲ) sulfadiazine complexes were synthesized, characterized and they were found a distinguish properties as a burn treatment[9]. Srivastava et al.[10], have been reported the synthesis and spectroscopic investigations of the coordination between sulphaguanidine ligand and different metal ions like Fe^{2+}, Cu^{2+}, Cd^{2+}, V^{4+}, Mo^{5+}, Pb^{2+}, Se^{4+}, and Sn^{4+} ions have been synthesized and investigated. The rare earth mixed ligand complexes with sulfamethoxy as a primary and pyridazine as a secondary chelates were synthesized and spectroscopically studied[11], while Gupta and Jha[12] have been characterized an antimony(Ⅲ) complexes with different kinds of sulfa drugs[13]. The complexation between two sulfa drugs (sulphisoxazole and sulfamethoxazole) ligands and first series of transition metal ions have been synthesized and characterized by Kanagaraj and Rao authors[13].

In literature survey, our group were prepared and discussed some of transition (Mn(Ⅱ), Hg(Ⅱ), Cr(Ⅲ), ZrO(Ⅱ), VO(Ⅱ)) and rare earth metal (Y(Ⅲ), Ce(Ⅲ), Gd(Ⅲ), Nd(Ⅲ), Tb(Ⅲ), Er(Ⅲ)) complexes with sulfasalazine drug ligand[14]. These complexes were spectroscopy characterized and biologically screened against bacteria, fungi and cancer cell lines. In literature survey, there is no work appears to have been done on the chelation between sulfa-drug with $Sc^{Ⅲ}$ ion. It should be noted that the medicinal properties of scandium metal is now recognized, and the scandium has been of interest because of its possible use as an adjunct to ^{67}Ga survey of cancer patients[15]. It was therefore thought to be useful to assemble some Sc^{3+} sulfa drugs for the first time. The main objective of this work is to prepare and spectroscopic characterize scandium complexes (Ⅲ) with sulp-1, sulp-2, sulp-3 and sulp-4 sulfa drugs and to determine coordination sites, antimicrobial and anti-cancer assessment.

1 Experimentals

1.1 Chemicals

There are pure grade and used as received, the name of chemicals, exporting company and their purpose can be listed as follows:

Chemicals	Company	Purpose
Sulfadimidine Sulfanilamide Sulfamethoxazole Sulfadiazine $ScCl_3$	Sigma-Aldrich, USA	Chemical Synthesis
DMSO	Sigma-Aldrich, USA	Chemical analysis
Crystal violet Trypan blue dye Fetal Bovine serum EMEM RPMI-1640 HEPES buffer solution L-glutamine Gentamycin 0.25% Trypsin-EDTA	Sigma (St. Louis, Mo., USA) Lonza Group AG, Switzerland	Biological analysis

1.2 Synthesis of scandium(Ⅲ) sulfa-drug complexes

A 1.0 mmol (152 mg) of $ScCl_3$ and 2.0 mmol from sulfadimidine (557 mg), sulfanilamide (345 mg), sulfamethoxazole (507 mg), or sulfadiazine (501 mg) were separately dissolved in methanol (25 mL), then mixed and refluxed for 6 hrs, yielding a white solution which was concentrated and left for three days yielding a white precipitate then filtered and washed with hot methanol solvent. The resulting solid precipitates were dried in a dessicator for seven days to afford the desired solid complexes. The elemental, physical and microanalytical data are summarized in Table 1.

1.3 Instrumentals

1.3.1 Instrument

Perkin Elmer CHN 2400; Jenway 4010 conductivity meter; Bruker FTIR Spectrophotometer; UV2 Unicam UV/Vis Spectrophotometer; Magnetic balance, Sherwood Scientific, Cambridge, England, at Temp 25 ℃; Varian mercury VX-300 NMR Spectrometer.

1.3.2 Measurement

Contents C, H and N; Electrolytic or non-electrolytic character; IR measurements; Electronic spectra; Magnetic moments; ^{1}H-NMR spectrum.

1.4 Antimicrobial and anticancer assessments

Antimicrobial activity was performed dependent on modified Kirby-Bauer disc diffusion method[16]. The tested species of bacteria and fungi are Escherichia coli, Pseudomonas

aeruginosa, Bacillus subtilis, Staphylococcus aureus, Aspergillus flavus and Candida albicans. The cytotoxicity of samples was screened against human Hepatocellular carcinoma (HepG-2) using viability assay[17].

Table 1　Elemental and physical data of sulfa drugs scandium(Ⅲ) complexes

Complexes	Color	Content[(calculated) found]				Λ_M/ ($\Omega^{-1}\cdot cm^2\cdot mol^{-1}$)	Yield /%
		%C	%H	%N	%M		
$[Sc(sulp\text{-}1)_2(Cl)_2]\cdot Cl$, (1)	white	(40.72) 40.34	(3.99) 3.78	(15.83) 15.69	(6.35) 6.21	40	63
$[Sc(sulp\text{-}2)_2(Cl)_2]\cdot Cl$, (2)	white	(29.07) 29.02	(3.25) 3.19	(11.30) 11.22	(9.07) 9.02	45	64
$[Sc(sulp\text{-}3)_2(Cl)_2]\cdot Cl$, (3)	white	(36.51) 36.25	(3.37) 3.32	(12.77) 12.63	(6.83) 6.71	38	60
$[Sc(sulp\text{-}4)_2(Cl)_2]\cdot Cl$, (4)	white	(36.85) 36.81	(3.09) 3.04	(17.19) 17.03	(6.90) 6.64	34	62

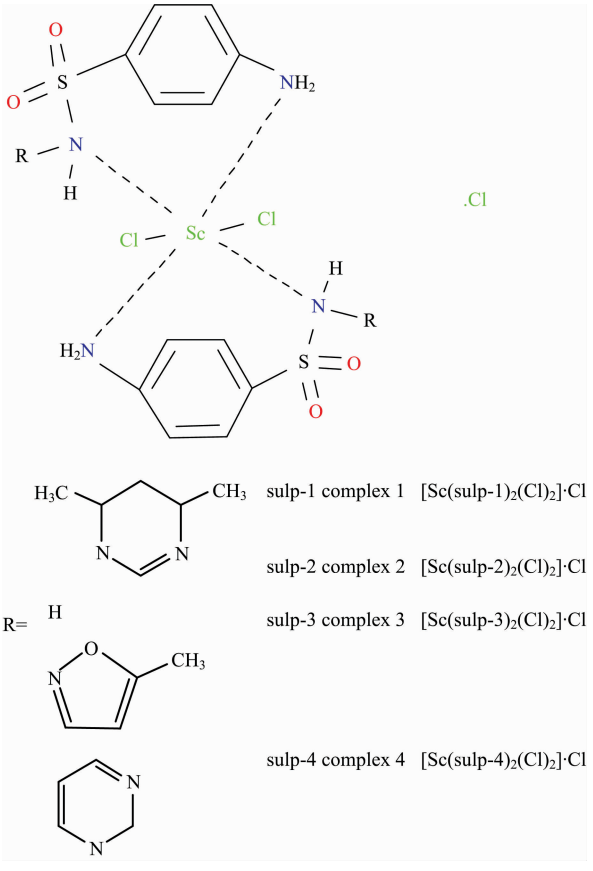


Fig. 1　Suggested structural formulas of Sc^{Ⅲ} sulf-drug complexes

2　Results and discussion

2.1　Structural characterization of the Sc(Ⅲ) sulfa-drug complexes

2.1.1　Stoichiometric and molar conductance results

The micro analytical data of the synthesized Sc^{3+} complexes are in agreement with 1∶2 stoichiometry (Sc∶sulp) as refereed in experimental section. The white scandium(Ⅲ) complexes are stable in static air with highly melting points (>300 ℃), insoluble in H_2O and slightly soluble in DMSO and DMF solvents with gently heating. The Sc^{Ⅲ} complexes have an slightly electrolytic nature[18] with molar conductance values within 34～45 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$ range, this is due to the presence of one chloride ion outside the coordination sphere. The Sc^{Ⅲ} complexes have a diamagnetic state with an octahedral geometry[19] as shown in Fig. 1.

2.1.2　Infrared spectral assignments

FTIR spectra of Sc^{Ⅲ} sulfa-drug complexes are displayed in Fig. 2(a) and the distinguish peaks are assigned in Table 2. Regarding free sulfa-drug ligands, there are observed bands at 3 479～3 423 and 3 379～3 343 cm^{-1} due to asymmetric and symmetric stretching vibratioo bands —(NH) of aniline group —NH_2[20]. The bands presence at 3 290～3 242 cm^{-1} are assigned to —NH stretching vibration of (SO_2NHR) sulfonamide group[20]. Concerning of Sc^{Ⅲ} complexes, the ν_{as}(NH) of aniline group is existed at 3 461～3 420 cm^{-1} and the ν_s(NH) band is exhibit at 3 370～3 340 cm^{-1}, These shifts to lower frequencies are due to the involved in coordination toward Sc^{Ⅲ} ions. Moreover, tie bending —(NH_2) vibration of —NH_2 group take place at 1 652～1 619 cm^{-1} for the free sulfa-drugs compounds is shifted to lower wavenumbers after complexity with Sc^{Ⅲ} ions to became at 1 611～1 645 cm^{-1}. On the other hand, the —NH band of —SO_2NH group was exhibited at 3 290～3 242 cm^{-1} in case of free sulfa-drugs, this is shifted to lower wavenumbers by 5～24 cm^{-1} upon complexation[20]. These FTIR results are supported the involvement of both —NH_2 and —NH groups in the coordination toward scandium(Ⅲ) ions. The strong-to-very strong bands placed at 1 325～1 303 cm^{-1} and 1 165～1 145 cm^{-1} in the free sulfa-drugs are attributed to asymmetric and symmetric stretching vibrations of the —SO_2 sulfonyl group, respectively. In case of Sc(Ⅲ) complexes, it's found that, these presented bands are located at the same place or shifted to slightly higher wavenumbers. These data reveal that the sulfonyl group doesn't involved in the coordination[20]. The absent of any bands in case of Sc(Ⅲ) complexes at ～3 500 cm^{-1} are due to absence of

coordinated or uncoordinated water molecules, so the complexes are fouod in the anhydrous form. The new medium-to-weak bands observed in the infrared spectra for all $Sc^{Ⅲ}$ complexes within the range of 500～400 cm^{-1} are attributed to ν(M—N) bands [see Fig. 2(b)][20].

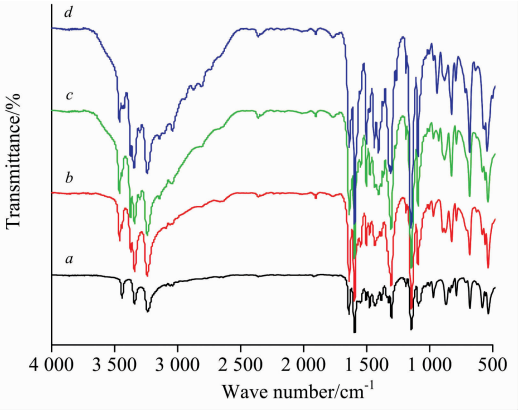


Fig. 2(a) FTIR spectra of $Sc^{Ⅲ}$ sulfa-drug complexes

a: Sulp-1; *b*: Sulp-2; *c*: Sulp-3; *d*: Sulp-4

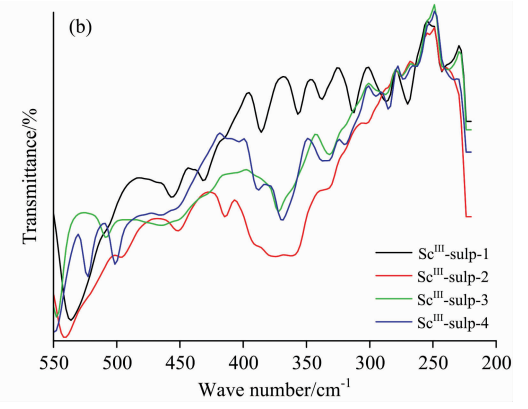


Fig. 2(b) Far-IR spectra of $Sc^{Ⅲ}$ sulfa-drug complexes

Table 2 FT-IR spectral frequencies (cm^{-1}) of sulfa-drugs and its $Sc^{Ⅲ}$ complexes

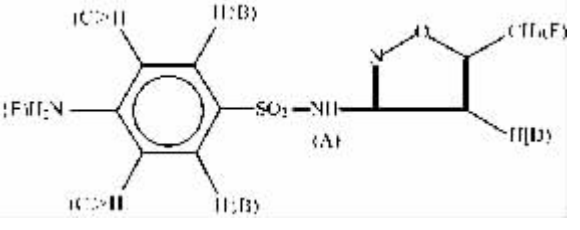
Compounds	Anilino group (—NH_2)			Sulfonamido group (—SO_2NH)		
	ν_{as}(NH)	ν_s(NH)	$\delta(NH_2)$	ν(NH)	$\nu_{as}(SO_2)$	$\nu_s(SO_2)$
sulp-1	3 442	3 343	1 640	3 242	1 303	1 147
sulp-2	3 479	3 374	1 630	3 269	1 312	1 148
sulp-3	3 467	3 379	1 619	3 290	1 305	1 145
sulp-4	3 423	3 355	1 652	3 258	1 325	1 156
Complex 1	3 438	3 340	1 635	3 235	1 303	1 146
Complex 2	3 461	3 369	1 626	3 245	1 313	1 145
Complex 3	3 460	3 370	1 611	3 285	1 311	1 157
Complex 4	3 420	3 345	1 645	3 250	1 325	1 155

2.1.3 Electronic and magnetic measurements

An electronic spectra of sulfa-drugs ligands and their Sc (Ⅲ) complexes were scanned within 200～800 nm range. These spectra have two absorption bands at 275 and 310 nm that attributed to π—π^* transition of the aromatic rings[21] and n—π^* transition of the anilino —NH_2 and sulfonamido —$NHSO_2$ groups. The electronic spectra of the four scandium (Ⅲ) complexes have different electronic transitions of the π—π^*, n—π^* and charge-transfer M-LCT are presence at (277, 315, 388 nm), (275, 295, 309 and 372 nm), (276, 281, 297, 298 and 312 nm) and (277, 312, 322 and 326 nm) for the $Sc^{Ⅲ}$ complexes of sulp-1, sulp-2, sulp-3 and sulp-4, respectively. These bands have be relocate rather than free ligands because of binding to the central metal ions. In case of octahedral statement of Sc(Ⅲ) complex, the charge-transfer transition band is often occur at low energy[21]. The scandium (Ⅲ) sulfa-drug complexes have μ_{eff} within the range of 0.43～0.69 BM, this is assigned to a diamagnetic octahedral geometry[19].

2.1.4 ^{1}H NMR assignments

^{1}H-NMR spectra of the sulp-3 drug and its [Sc(sulp-3)$_2$(Cl)$_2$]·Cl complex, were scanned. In Table 3, the signals of sulp-3 drug and its $Sc^{Ⅲ}$ complex with significant shifts are assigned. These results supported the site of coordination between the sulp-3 ligand and $Sc^{Ⅲ}$ metal ions. 1H signals of sulp-3 spectrum (scheme 1) comparing with the spectrum of scandium(Ⅲ) complex, it is clearly that they are relevant displacement shifted towards downfield when the sulp-3 ligand is coordinated to Sc(Ⅲ), especially those assigned to 2H; (NH_2), that is presented at 6.10 ppm for the free ligand, and at 6.45 ppm in the complex and ^{1}H; ($NHSO_2$) from 10.95 to 11.00, supported that the sulp-3 ligand is chelated *via* the NH_2 anilino nitrogen atom and the —NH sulfonamido nitrogen groups.



Scheme 1 Numerical protons of sulp-3 free ligand

2.1.5 Antimicrobial and Anticancer assessments

The antimicrobial activities of the free sulfa-drugs com-

Table 3　^{1}H-NMR proton signals of the sulp-3 ligand and Sc(Ⅲ) complex

δ ^{1}H	A	B	C	D	E	F
sulp-3	10.95	7.49	6.60	6.11	6.10	2.29
Sc(Ⅲ)	11.00	7.54	6.70	6.10	6.45	2.29

plexes (sulp-1, sulp-2, sulp-3 and sulp-4) and their Sc(Ⅲ) complexes have biologically assessed *in vitro* against bacteria and fungi species (Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Aspergillus flavus and Candida albicans). The zones of inhibition produced by the test compounds are summarized in Table 4. It is observed that:

(1) $[Sc(sulp\text{-}1)_2(Cl)_2]\cdot Cl$ complex has a significant inhibition against *E. coli*, *B. subtilis*, *S. aureus* and *Candida albicans* in comparable with free sulp-1 drug.

(2) $[Sc(sulp\text{-}2)_2(Cl)_2]\cdot Cl$ complex has a significant inhibition against *P. aeruginosa*, *B. subtilis*, *S. aureus*, *A. flavus* and *Candida albicans* in comparable with free sulp-2 drug.

(3) $[Sc(sulp\text{-}3)_2(Cl)_2]\cdot Cl$ complex has a significant inhibition against *E. coli*, *B. subtilis*, *S. aureus*, *Aspergillus flavus* and *Candida albicans* in comparable with free sulp-3 drug.

(4) $[Sc(sulp\text{-}4)_2(Cl)_2]\cdot Cl$ complex has a significant inhibition against *E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus* and *Candida albicans* in comparable with free sulp-4 drug.

On complexity, the polarity of the metal ion is greatly reduced due to the partial sharing of a positive charge of the metal ion interfering with the donor groups. Increased lipophilicity promote the penetration of complexes in lipid membranes and block mineral binding sites on microorganism enzymes[22].

In *vitro* cytotoxicity assessment of the $[Sc(sulp\text{-}4)_2(Cl)_2]\cdot Cl$ complex was performed on human hepatocellular carcinoma (HepG-2) tumor cell line. The results evaluated upon the determination of inhibitory concentration of 50% (IC_{50}), the data was listed in Table 5. The $[Sc(sulp\text{-}4)_2(Cl)_2]\cdot Cl$ complex has IC_{50} equal $>1\ 000\ \mu g\cdot mL^{-1}$ for HepG-2 cell line. From this data, it is deduced that $[Sc(sulp\text{-}4)_2(Cl)_2]\cdot Cl$ complex has an efficient appropriate against HepG-2 cell line.

Table 4　Inhibition zone diameter of sulfa-drugs and their Sc(Ⅲ) complexes against bacteria and fungi species

Sample		Inhibition zone diameter (mm · mg^{-1} sample)					
		Bacillus subtilis (G+)	*Escherichia coli* (G−)	*Pseudomonas aeruginosa* (G−)	*Staphylococcus aureus* (G+)	*Aspergillus flavus* (Fungus)	*Candida albicans* (Fungus)
	Control: DMSO	0.0	0.0	0.0	0.0	0.0	0.0
Standard	Tetracycline Antibacterial agent	34	32	34	30	—	—
	Amphotericin B Antifungal agent	—	—	—	—	18	19
	sulp-1	12	16	14	16	11	0.0
	Sc-sulp-1	19	22	11	20	3	17
	sulp-2	12	10	5	0.0	0.0	0.0
	Sc-sulp-2	22	9	22	14	12	21
	sulp-3	15	12	10	0.0	0.0	0.0
	Sc-sulp-3	29	15	10	19	10	12
	sulp-4	2	16	4	0.0	8	0.0
	Sc-sulp-4	10	22	9	20	2	19

Note: −G: Gram reaction; Solvent: DMSO

Table 5　Inhibitory efficiency against HepG-2 cell lines for the $[Sc(sulp\text{-}4)_2(Cl)_2]\cdot Cl$ complex

Con in $\mu g\cdot mL^{-1}$	Inhibitory activities against HepG-2 cell line								
	Ab	%C	Ab	%C	Ab	%C	Abs Av	Ave % C	SE
0	0.453	97.419 35	0.476	102.365 6	0.466	100.215 1	0.465	100	1.431 899
0.1	0.431	92.688 17	0.415	89.247 31	0.423	90.772 53	0.423	90.967 74	0.995 42
1	0.425	91.397 85	0.422	90.752 69	0.418	89.892 47	0.421 667	90.681	0.436 04
10	0.418	89.892 47	0.414	89.032 26	0.417	89.677 42	0.416 333	89.534 05	0.258 462
100	0.395	84.946 24	0.399	85.806 45	0.392	84.301 08	0.395 333	85.017 92	0.436 04
1 000	0.257	55.268 82	0.275	59.139 78	0.266	57.204 3	0.266	57.204 3	1.117 452

References

[1] Arshia F Begum, Almandil N B,et al. Bioorganic & Medicinal Chemistry, 2019, 27(6): 1009.
[2] Kausar N, Muratza S, Raza M A, et al. Journal of Molecular Structure, 2019, 1185: 8.
[3] Barnhart E R(Ed.). Physician_s Desk Reference, PDR, 43rd ed., Medical Economics, New York, 1989.
[4] García-Raso A, Fiol J J, Rigo S, et al. Polyhedron, 2000, 19: 991.
[5] Alzuet G, Ferrer-Llusar S, Borrás J, et al. J. Inorg. Biochem., 1999, 75: 189.
[6] Scozzafava A, Menabuoni L, Mincione F, et al. J. Med. Chem., 1999, 42: 2641.
[7] Briganti F, Scozzafava A, Supuran C T. Eur. J. Med. Chem., 1997, 32: 901.
[8] Fox C L, Modak S, Stanford J W, et al. Scand. J. Plast. Reconsre. Surg., 1979, 13(1): 89.
[9] Lippincott J P. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, (8th Edn); Philadelphia, 1982. 162.
[10] Srivastava S P, Gupta V K, Gupta K, et al. Synth. React. Inorg. Met.-Org. Chem., 1987, 17(8-9): 801.
[11] Gu S X, Deng R W, Wu J G. Chem. J. Chin. Univ., 1987, 8(7): 575.
[12] Gupta J K, Jha N K. Ind. J. Chem., 1987, 26A: 529.
[13] Kanagaraj G, Rao G N. Ind. J. Chem., 1993, 32A: 594.
[14] Abd El-Wahed M G, El-Megharbel S M, El-Sayed M Y, et al. Bulg. Chem. Commun., 2015, 47(3): 895.
[15] Koumarianou E, Loktionova N S, Fellner M, et al. Applied Radiation and Isotopes, 2012, 70: 2669.
[16] Bauer A W, Kirby W A, Sherris C, et al. Am. J. Clin. Pathology, 1996, 45: 493.
[17] Mosmann T. J. Immunol. Methods, 1983, 65: 55.
[18] Refat M S. J. Mol. Struct., 2007, 842(1-3): 24.
[19] Cotton S A. Polyhedron, 1999, 18: 1715.
[20] Nakamoto K. Infrared Spectra of Inorganic and Coordination Compounds, Wiley Interscience, John Wiley & Sons, New York, NY, USA, 2nd edition, 1970.
[21] Chittilappilly P S, Yusuff K K M. Indian J. Chem., 2008, 47A: 848.
[22] Dharmaraj N, Viswanathamurthi P, Natarajan K. Trans. Met. Chem., 2001, 26: 105.