TRINUCLEAR Ce(IV) SALEN CAPPED COMPLEXES WITH BRIDGING 2, 4, 6-TRIS (4-CARBOXYPHENYLIMINO-4^1-FORMYLPHENOXY)-1, 3, 5-TRIAZINE AND 2,4,6-TRIS(4-CARBOXYBENZIMINO)-1,3,5-TRIAZINE: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES

Oruma*, U. S., Ukoha, P. O., and Ezeorah, C. J.

Coordination Chemistry and Inorganic Pharmaceuticals Unit, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, 410001, Nigeria.

*e-mail: susan.oruma@unn.edu.ng, Tel: +2348061222297

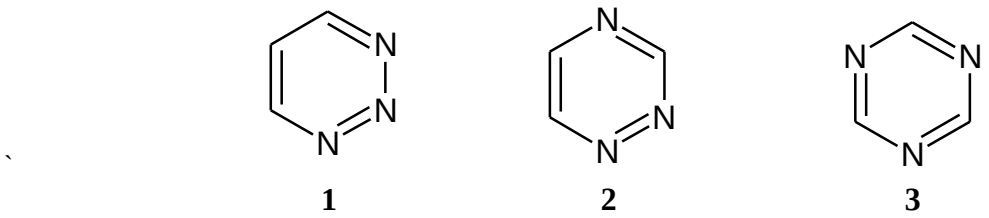
ABSTRACT

Trinuclear Ce(IV) salen capped complexes of 2,4,6-tris(4-carboxyphenylimino-4^1-formylphenoxy)-1,3,5-triazine (H_3CT) and 2,4,6-tris(4-carboxybenzimino)-1,3,5-triazine(H_3MT) were synthesized. These were characterized using UV-Visible, IR, ^{1}H and ^{13}C NMR spectroscopies, elemental analysis and molar conductivity measurements. The spectral studies indicate that both ligands are hexadentate and coordinates to the Ce(IV) ions through the oxygen atoms of the carboxylic group. The trinuclear Ce(IV) salen capped complexes were characterized as being bridged by carboxylate anions to the Ce(IV) salen centres and displays a coordination number of eight by involving two hydroxyl groups in the coordination sphere. The in vitro antimicrobial activities of the ligands and their Ce(IV) salen capped complexes were investigated against Gram-negative bacteria: Escherichia coli (ATCC 6749) and Pseudomonas aeruginosa (ATCC 9027), Gram-positive bacteria: Staphylococcus aureus (ATCC 6538P) and Bacillus cereus (ATCC 14579), and fungi: Candida albicans and Aspergillus niger by the agar well diffusion technique. In vitro antimicrobial test indicate that the tripodal ligand, H_3MT is more potent against the test micro-organisms relative to H_3CT, [{Ce(OH)$_2$(salen)}$_3$(CT)].3H_2O and [{Ce(OH)$_2$(salen)}$_3$(MT)].3H_2O. The MIC of H_3MT against Candida albicans is comparable to that of gentamycin. Amongst the Ce(IV) salen capped complexes, [{Ce(OH)$_2$(salen)}$_3$(MT)].3H_2O is more potent.

Keywords: *S*-triazine; salen; Trinuclear Ce(IV) Complexes; Antimicrobial activity.

INTRODUCTION

Triazines are six – membered aromatic heterocycles analogous to benzene, but having three carbon atoms being replaced by three nitrogen atoms. They exist in three isomeric forms namely: 1,2,3-triazines (**1**), 1,2,4-triazines (**2**) and 1,3,5-triazines (s-triazines, (**3**)[1]. The 1,3,5-triazines are the oldest and most extensively studied of the isomeric forms [2,3]. The 1,3,5 –triazine isomer is also referred to as *s*-triazine because of its symmetrical nature.



1 **2** **3**

Fig. 1: Structures of isomers of triazine

S-triazine derivatives have been reported in literature to exhibit interesting pharmacological properties such as antimalarial[4-7], antimicrobial[8-10], antiviral[11], anticancer[12-17], antituberculosis[18-20], anti-HIV[21-25], antileishmanial[26-29], anti-inflammatory agents[30-31], insecticidal[32], herbicidal[32-33]. Hence, they have found widespread applications in the pharmaceutical [34-35], plastic [36-37], textile [38-39] and rubber industries [40]. They have also been used as P13K [41-43] and mTOR [44-47] inhibitors, pesticides [48], dyestuffs [49- 50], optical bleaches [51], explosives and surface active agents [52 - 54]. 1,3,5-Triazine are used to design polydentate ligands. These polydentate ligands serve as chelating agents for the synthesis of many metal complexes with interesting molecular and supramolecular structure[55]. *S*-triazine scaffolds containing lanthanide metal complexes have been reported in literature [56- 58]. Lanthanides complexes with various organic ligands exhibit a wide range of pharmacological properties such as antimicrobial[59], anticancer [60], cytotoxic and cytostatic activities[61-63] and antitumor activity [64]. To the best of our knowledge, there is no report of tripodal trinuclear s -triazine cored lanthanide salen Schiff base complexes. There is also no report on their applications in biological studies.

Cerium is one of the lanthanides and has electronic configuration of [Xe] $4f^1 5d^1 6s^2$. It has many industrial applications in the areas of lightning and television, metallurgy, glass and ceramics [65]. Literature review has shown that cerium complexes with various organic ligands possess interesting properties such as catalytic property [66-67], antitumor and antimicrobial activities[63, 68-72]. Hence, the need to study the biological activities of s -triazine cored Ce(IV) salen capped complexes. Our research group has synthesized, characterized and evaluated the antimicrobial activity of trinuclear Ce(IV) Salen Capped Complex with 5-amino-2,4,6-tris(4-carboxybenzimino)-1,3-pyrimidine[73].

This present manuscript reports the synthesized, characterized and antimicrobial studies of trinuclear Ce(IV) salen capped complex with two *s*- triazine ligands namely:

2,4,6-tris (4-carboxyphenylimino-4[1]-formylph-enoxy)-1, 3, 5- triazine and 2,4,6-tris(4-carboxybenzimino)-1,3,5-triazine.

MATERIALS AND METHODS

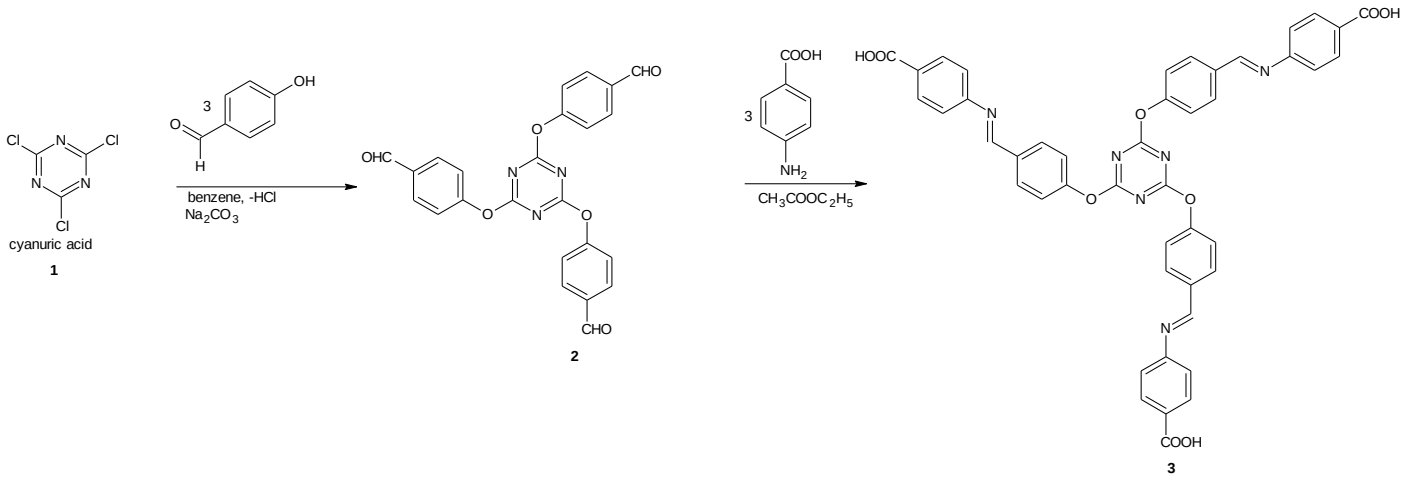
Materials and measurements

All the chemicals used were of analytical reagent grade, purchased from Zayo–Sigma and were used as supplied without further purification. The melting points of the compounds were determined using Fischer Jones melting point apparatus and were uncorrected. Molar conductance measurements were carried out by dissolving 10^{-4} mol/L solutions of the complex in methanol at room temperature and measured with WTW-LF 90 conductivity meter. Electronic spectra in dimethyl sulphoxide (DMSO) were recorded on UV-Vis 1800 SHIMADZU spectrophotometer. Infrared spectra of the compounds were performed using KBr discs on a Perkin–Elmer (Waltham, Massachusetts, USA) 100 series version 10.03.08 FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra of the compounds were recorded on a Bruker (Billerica, Massachusetts, USA) DPX 300 spectrometer in DMSO- d_6 at 300.13MHz and 75.47MHz respectively. Elemental analysis for C, H and N were carried out using LECO – CHN – 932analyzer.

Synthesis of 2, 4, 6-tris (p-formylphenoxy)-1, 3, 5-triazine (2)

The method reported by Tahmassebi and Sasaki[74] was modified and adopted. *P*–hydroxybenzaldehyde (3.20 g, 0.026 mol) and 2,4,6-trichloro-1,3,5-triazine(**1**) (1.20g, 0.0065 mol) were added to a suspension of Na_2CO_3 (20 g) in 50 mL of benzene as shown in Scheme 1. The mixture was refluxed with stirring at 70 °C for 7 h and left stirring overnight. During this time, the colour of the Na_2CO_3 changed from white to brown. The mixture was filtered and the residue washed with hot ethyl ethanoate (20 mL) twice and both filtrates were mixed. The filtrate was divided into two and one part was placed in a separating funnel and 10 mL of 10 % Na_2CO_3 (2 g of Na_2CO_3 made up to 20 mL) was poured into it, shaked properly and allowed to stand. Two layers were formed: a pink aqueous layer (below) and a golden organic layer (on top). The aqueous layer was discarded and the organic layer was further extracted with 10 mL of 10 % Na_2CO_3. The filtrate was extracted with water once. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated. The white fluffy precipitate was recrystallized from ethyl acetate (20 mL), air dried and stored over $CaCl_2$. This gave 2, 4, 6-

tris (*p*-formylphenoxy)-1, 3, 5-triazine (**2**). See Scheme 1.



Scheme 1: Synthesis of 2, 4, 6-tris (4-carboxyphenylimino-4[1]-formylphenoxy)-1, 3, 5-triazine (H_3CT) (3)

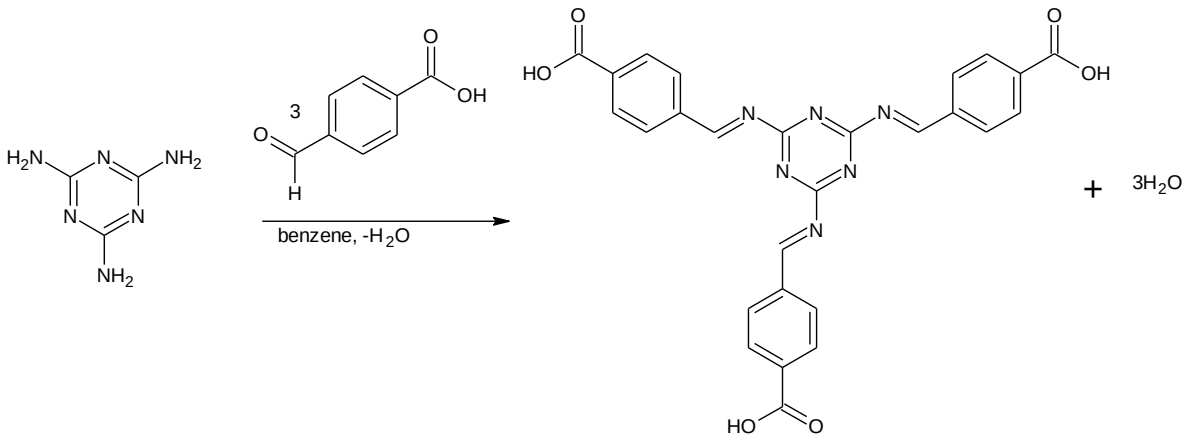
Synthesis of 2, 4, 6-tris (4-carboxyphenylimino-4[1]-formylphenoxy)-1, 3, 5-triazine (H_3CT) (3)

The method reporetd by Koc and Ucan[75] was adopted. Solid K_2CO_3 (1.55 g, 25 % excess of 0.009 mol) was added to a solution of 4-aminobenzoic acid (0.003 mol, 0.51 g) in 20 mL of ethyl ethanoate with stirring. Then the suspension of compound (**2**) (0.44 g, 0.001mol) in 10 mL of ethyl ethanoate was added dropwise with stirring. This is displayed in Scheme 1.The mixture was then boiled under reflux for 24 h. The reaction solution was left stirring overnight. Water was added to the mixture and filtered to remove some insoluble impurities. HCl (0.5 N) was added to the solution until the pH of 5 was attained and the mixture was filtered. The filtrate was evaporated slowly over the day and yellow crystals were precipitated. The yellow crystals (**3**) obtained were recrystallized from absolute ethanol, dried and stored in a desiccator over $CaCl_2$.

Synthesis of 2, 4, 6-tris (4-carboxybenzimino)-1, 3, 5-triazine (H_3MT)

The method reported by Uysal and Ucan (2009)[76] was adopted. Melamine (0.63 g, 0.005 mol) was dissolved in benzene (5 cm^3) stirred for 1 h, then 4-carboxybenzaldehyde (2.25 g, 0.015 mole) added and refluxed for 4 h. A white precipitate was obtained, filtered and recrystallized from a mixture of methanol and

water, dried and stored over $CaCl_2$. See Scheme 2.



Scheme 2: Synthesis of 2,4,6-tris(4-carboxybenzimino)-1,3,5-triazine(H_3MT)

Synthesis of the Trinuclear Ce(IV) Salen Capped Complexes of H_3CT and H_3MT

This involves synthesis of:

1. $salenH_2$
2. Ce(IV) salen complex
3. Ce(IV) ligand complex
4. Ce(IV) Salen Capped Complex of H_3CT and H_3MT

Synthesis of $salenH_2$

$SalenH_2$ was synthesized by modifying the method reported by Sathe *et al*., (2013)[77]. To a solution of ethylenediamine (3.35 mL, 0.05 mol) in 50 ml of methanol in a round bottom flask, salicylaldehyde (10.47 mL, 0.1 mol) was added. The yellow crystalline solid produced was filtered and recrystallized from absolute ethanol (50 mL) at 80 °C.

Ce(IV) salen complex

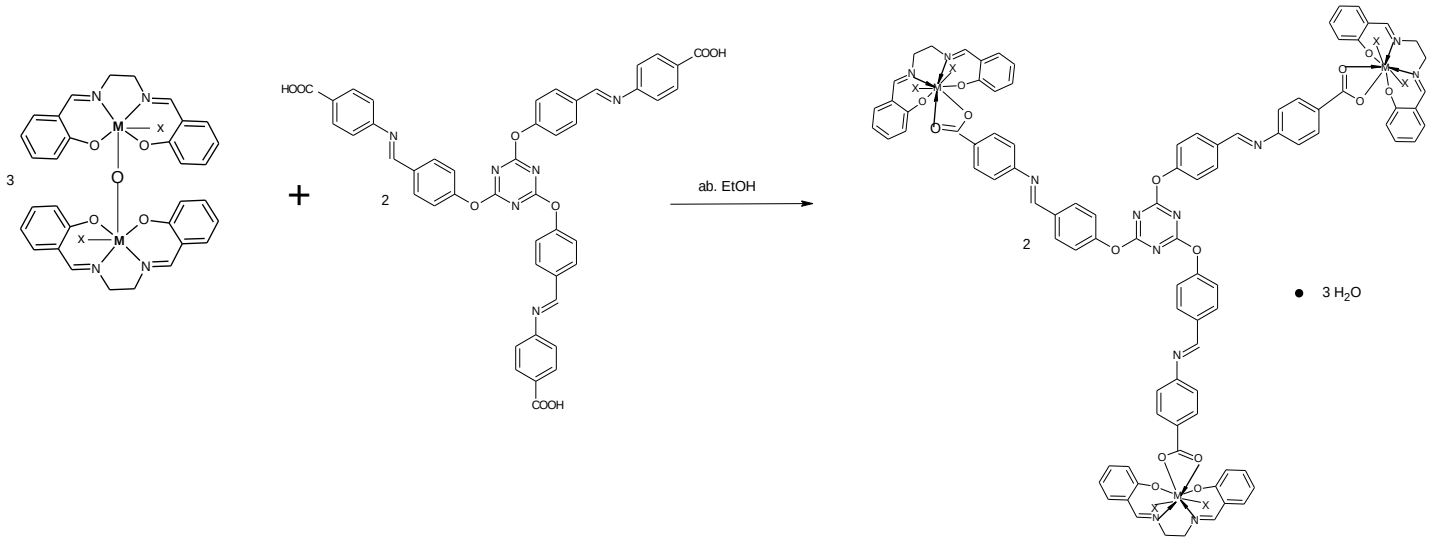
The method reported by Gembickỳ *et al.*, (2000)[78] was modified and adopted for synthesis of salen complexes. To a hot methanolic solution (40 mL) of $salenH_2$ (1.34 g, 0.005 mol), a hot aqueous solution (50 mL) $Ce(SO_4)_2$ (1.65 g, 0.005 mol) was added. The mixture was stirred at 50 °C for 30 minutes. A light brown precipitate was formed, and then triethylamine (0.02 mol, 4 mL) was added. On adding triethylamine, the light brown precipitate turned reddish brown. The resulting solution was stirred at 50 °C for 2 hours and after cooling, a reddish brown precipitate was obtained. The precipitate was washed with methanol and diethyl ether and dried over $CaCl_2$.

Synthesis of Ce(IV) ligand complex, Ce(IV)LC

The ligand complexes were prepared by modifying the method reported by Kopel *et al.*, (1998)[79] and Uysal and Koc (2010)[80]. A solution of Ce(IV) salen complex (0.50g, 10^{-3} mol) in absolute ethanol (20 mL) was stirred at 50 °C for 15 minutes. Excess concentrated ammonia solution (1 mL at a time) was added and stirred. The pH of the solution was monitored with the aid of a pH meter until the pH of 12. A brown precipitate was formed, filtered and dried over $CaCl_2$.

Synthesis of Ce(IV) Salen Capped Complex of H_3CT, $[\{Ce(OH)_2(salen)\}_3(CT)].3H_2O$

Ce(IV)LC (0.53 g, 0.00062 mol) was suspended in hot absolute ethanol (25 mL) and a solution of H_3CT (0.33 g, 0.00041 mol) in absolute ethanol was added while stirring. The reaction mixture was boiled under reflux for 4 h. The brick red solid formed was dried over $CaCl_2$. See Scheme 3.

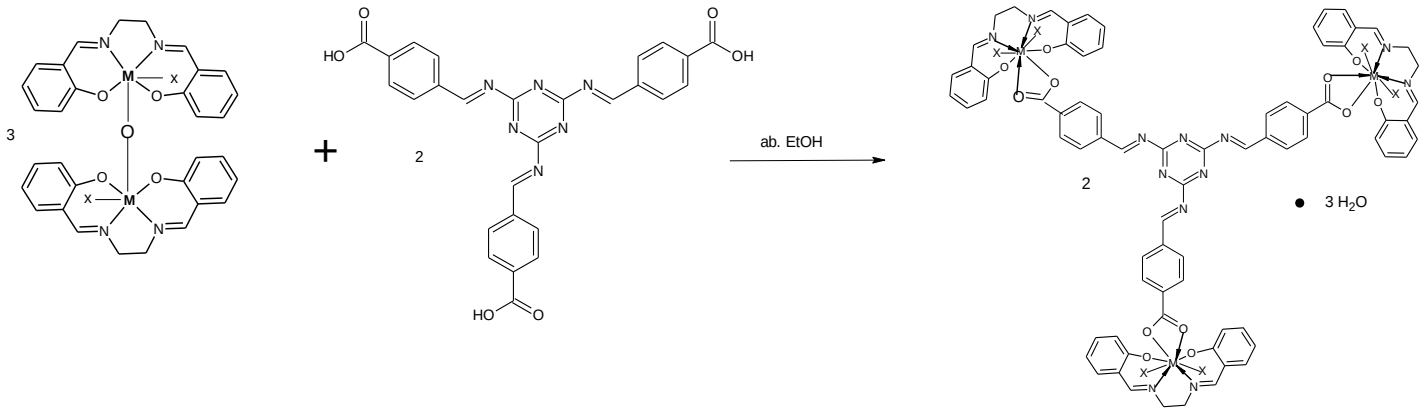


X = OH

Scheme 3: Synthesis of $[\{Ce(OH)_2(salen)\}_3(CT)].3H_2O$ M= Ce

Synthesis of Ce(IV) Salen Capped Complex of H_3MT, $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$

Ce(IV)LC (0.32 g, 0.00037 mol) was suspended in hot absolute ethanol (25 mL) and a solution of H_3MT (0.13 g, 0.00025 mol) in absolute ethanol was added while stirring. The reaction mixture was boiled under reflux for 4 h. The light yellow solid formed was dried over $CaCl_2$. See Scheme 4.



X = OH

Scheme 4: Synthesis of [{Ce(OH)$_2$(salen)}$_3$(MT)].3H$_2$O M= Ce

In vitro antimicrobial activity

The ligands and their trinuclear Ce(IV) salen capped complex were tested *in vitro* for their antimicrobial activities against American Type Culture Collection (ATCC) bacteria strains obtained from Rockville, MD, USA, by the Department of Microbiology, University of Nigeria, Nsukka while the fungi strains were isolated under clinical conditions. The typed bacteria culture comprises Gram-positive bacteria: *Staphylococcus aureus* (ATCC 6538P) and *Bacillus cereus* (ATCC 14579); Gram-negative bacteria: *Escherichia coli* (ATCC 6749) and *Pseudomonas aeruginosa* (ATCC 9027). The fungi strains used were *Candida albicans* and *Aspergillus niger*. The bacteria strains were tested for sterility on nutrient agar and then grown in nutrient broth at 37 °C for 24 hours while the fungal strains were tested on Sabourand Dextrose Agar (SDA) and cultured in Sabourand Dextrose Liquid medium at 25 °C for 24 hours. The overnight cultures were subsequently diluted and suspensions were made in normal saline and adjusted to 0.5 McFarland standards [81].

Antimicrobial assay

The antimicrobial activities of all the synthesized compounds were determined by the agar cup diffusion technique[82]. The nutrient agar and SDA plates were inoculated with 0.1 mL broth culture of the test bacteria or fungi. Using a sterile cork borer, wells (5 mm in diameter and 2.5 mm deep) were bored into the inoculated agar. Fresh stock solutions (1000 µg/mL) of the synthesized compounds were prepared in DMSO. The stock solution was further diluted with sterilized distilled water to 12.5, 25, and 50 µg/mL for antimicrobial

evaluation. The wells were filled with 100 µL of the test compounds by means of a sterile micropipette. Standard antibiotics namely: ciprofloxacin, tetracycline, gentamycin and fluconazole were used as positive control while sterile DMSO served as negative control. Subsequently, 12.5, 6.25, and 3.125 µg/mL of each positive control were prepared in DMSO. The bacteria plates were incubated at 37 ^{o}C for 24 hours while fungal plates were incubated at 25 ^{o}C for 24 hours. Inhibition zone diameter (IZD) around each well was measured in millimeter and recorded. The graph of IZD^2 against the log of concentration was plotted for each plate containing a specific compound and a microorganism. The anti-log of the intercept on *x*-axis is the MIC.

RESULTS AND DISCUSSION

Trinuclear Ce(IV) salen capped complexes of H_3CT and H_3MT were obtained in good yield. These complexes are stable at room temperature and have high decomposition temperatures of 343 and 345 °C respectively. They are soluble in DMSO, DMF, ethylacetate, and methanol but insoluble in water.

Table 1: Elemental and physical data of H_3CT, H_3MT and their Ce(IV) salen capped complexes

Compound	Colour	Λ_m ($\Omega^{-1}cm^2mol^{-1}$)	Yield g (%)	M.p. (°C)	Molar mass (g/mol)	Elemental analysis % calc. and found					
						C		**H**		**N**	
						Calc.	**Found**	**Calc.**	**Found**	**Calc.**	**Found**
$C_{45}H_{30}N_6O_9$ (H_3CT)	Yellow	-	0.47 (58.75)	282	798	67.67	67.50	3.76	3.60	10.53	10.70
$C_{27}H_{18}O_6N_6$ (H_3MT)	White	-	(2.25) 86.21	346[a]	522	62.07	61.95	3.45	3.40	16.09	15.90
[{Ce(OH)$_2$(salen)}$_3$(CT)]. 3H$_2$O	Brick red	25	(0.30) 35.29	343a	2,169.35	51.44	51.70	3.73	3.79	7.74	7.56
[{Ce(OH)$_2$(salen)}$_3$(MT)] .3H$_2$O	Red	19	(0.33) 73.33	345[a]	1,893.35	47.53	47.77	3.64	3.80	8.87	8.65

[a] = decomposition temperature

The analytical data of trinuclear Ce(IV) salen capped complexes of H_3CT and H_3MT are in good agreement with the proposed molecular formula as shown in Table 1. Molar conductivity measurements in methanol at room temperature indicate that the compounds are neutral[83].

Synthesis of the precursors

$SalenH_2$ was synthesized in high yield. The UV, IR and elemental analysis data are presented below while the UV and IR spectra are presented in supplementary materials (Figure S1 and S8). Yield = 11.14 g (83 %); mp of 109– 110 °C; UV (λ nm) (DMSO) (ε): 316 (1.91×10^4), 404 (0.41×10^4); IR (KBr): 3441 (br) ((O-H) Phenolic), 1608 (s) (C═N), 1287(m) (C–O), 751 (m) (C–H) cm^{-1}; Anal. calcd for $C_{16}H_{16}O_2N_2$ (268): C, 71.64; H, 5.97; N, 10.45. Found: C, 71.60; H, 6.00; N, 10.30.

Synthesis of Ce(IV) salen complex was achieved in moderate yield. The UV, IR and elemental analysis data are presented below while the UV and IR spectra are presented in supplementary materials (Figure S2 and S9). Yield = 1.48 g (49.33 %); mp of 102^a °C (a = decomposition temperature); UV (λ nm) (DMSO) (ε): 232 (1.75×10^4), 269 (7.04×10^4); IR (KBr): 3419 (br) (O–H Phenolic), 1637 (s) (C═N), 1420 (m), 1121 (br) (SO_4^{2-}), 629 (m) (C–H), 494 (m) (Ln-O), 412 (w) (Ln-N) cm^{-1}; Anal. calcd for $[Ce(SO_4)_2salenH_2]$ (600): C, 32.00; H, 2.67; N, 4.67. Found: C, 32.20; H, 2.70; N, 4.40.

Ce(IV) ligand complex was obtained in moderate yield. Ligand complex is one which acts as a ligand by being able to coordinate to another ligand. This is the first example of a ligand complex bearing Ce(IV) ion. The UV, IR and elemental analysis data are presented below while the UV and IR spectra are presented in supplementary materials Figure S3 and S10). Yield = 0.43 g (63.77 %); mp of 318– 320 °C; UV (λ nm) (DMSO) (ε): 260 (8.61×10^3), 307 (5.20×10^3); IR (KBr): 3250 (br) (O – H), 1631(s) (C═N), 1546(s) (C═C), 1199(m) (C–O), 907(s), 752(s) (C–H), 600 (s) (M-O-M), 580(m) (Ln-O), 455(m) (Ln-N) cm^{-1}; Anal. calcd for $[\{Ce(OH)(salen)\}_2O]$ (862): C, 44.55; H, 3.48; N, 6.50. Found: C, 44.65; H, 3.70; N, 6.60.

Electronic Spectra

The UV/Vis absorption spectra of the ligands and Ce(IV) complexes (10^{-4} $moldm^{-3}$) were carried out in DMSO at room temperature. The spectral values of the absorption wavelength and the corresponding molar absorptivities (ε) are given in Table 2. The absorption spectra are displayed in supplementary materials (Figures S4- S7). The absorption spectrum of H_3CT and H_3MT show two peaks each at 230, 283 and 233, 291 nm respectively. These were assigned

to π – π* transitions of the conjugated phenyl ring. In the Ce(IV) complexes, these bands are red shifted, supporting the coordination of ligands to the Ce(IV) ions.

Table 2: Electronic absorption data of H_3CT, H_3MT and their Ce(IV) salen capped complexes

Compound	λ_{max}		ε x10^3($mol^{-1}dm^3cm^{-1}$)	Band assignment
	nm	**cm^{-1}**		
$C_{45}H_{30}N_6O_9$ (H_3CT)	230	43478	6.93	π–π*
	283	35336	5.85	π–π*
$C_{27}H_{18}O_6N_6$ (H_3MT)	233	42918	2.88	π– π*
	291	34364	1.82	π– π*
[{Ce(OH)$_2$(salen)}$_3$(CT)].3H_2O	240	41667	14.30	π– π*
[{Ce(OH)$_2$(salen)}$_3$(MT)].3H_2O	314	31847	5.83	π– π*

Infrared Spectra

The relevant stretching frequencies of the ligands and Ce(IV) salen capped complex are shown in Table 3 while the spectra are presented in supplementary materials (Figures S11 – 14). The infrared spectrum of H_3CT displayed a broad band at 3239 cm^{-1} assigned to vibrations of O-H of carboxylic group. This band was absent in the spectra of H_3MT and the Ce(IV) complexes. The disappearance of this band in the complexes suggests deprotonation of the carboxylic OH and subsequent chelation of oxygen to the Ln metal. The absorption band due to the carboxylic acid C = O, was observed at 1674 cm^{-1} in H_3MT[84]. This band shifted to higher frequencies of about 12 cm^{-1} in [{Ce(OH)$_2$(salen)}$_3$(MT)].3H_2O suggesting coordination of the ligand complexes via the carboxylic acid C = O of H_3MT. This was further supported by the vibrations of the COO^- group observed at 1392 cm^{-1} in [{Ce(OH)$_2$(salen)}$_3$(MT)].3H_2O and at 1391 cm^{-1}in H_3MT[80]. The absorption bands due to C = N(a) and C = N(b) for H_3CT and H_3MT were observed at 1546, 1594 and 1501, 1573cm^{-1} respectively. However, in the complexes, three bands were observed: C = N (a) bands at 1593 and 1595 cm^{-1}, C = N (b) bands at 1628 cm^{-1}

and C = N(c) bands at 1545 cm^{-1}. The C = N(a) and C = N(b) stretching vibration in the complexes shifted to higher wavenumber in comparison to the same transition in the ligand. Bands in the range of 599 -580 cm^{-1} in the Ce(IV) trinuclear complexes were assigned to **ν** (Ln –O)[59-85] while bands in the range of 496 - 453 cm^{-1} were assigned to **ν** (Ln –N) [85].

Table 3: IR band assignments for H_3CT, H_3MT and their Ce(IV) salen capped complexes

Compound	ν (O –H)b	ν (C-H)ar	ν C =O	ν C =N	ν C – C	ν COO^-	ν C –N	ν Ln –O	ν Ln- N
$C_{45}H_{30}N_6O_9$ (H_3CT)	3239(br)	-	-	1546(s)a 1594(s)b	1480	1394(s) 1384(s) 1367(s)	1111	-	-
$C_{27}H_{18}O_6N_6$ (H_3MT)	-	-	1674(s)	1501(m)a 1573(m)b	1422(m)	1391(m)	1168(m)	-	-
[{Ce(OH)$_2$(salen)}$_3$(CT)].3H_2O	-	-	-	1595(s)a 1628(s)b 1545(s)c	1468	1391(s) 1340(m) 1324(m)	1147(s) 121(m)	599(m) 580(m)	496(m) 456(m)
[{Ce(OH)$_2$(salen)}$_3$(MT)].3H_2O	-	3110(br)	1686(m)	1593(m)a 1628(s)b 1545(m)c	1468(m) 1443(s)	1392(m)	1147(m) 1120(m)	599(m) 580(m)	496(m 453(m)

Where C = N(b) = from azomethine linkage, C = N(c) = from salen, C = N(a) = from pyrimidine ring.

^1H and ^{13}C NMR Spectra

The ^1H and ^{13}C NMR spectra of H_3CT, H_3MT and their Ce(IV) salen capped complexes are presented in Tables 4 and 5 while the spectra are presented in supplementary materials (Figures S15 – S22). The ^1H NMR spectrum of H_3MT revealed a singlet peak at 10.17 ppm due to carboxylic proton. This peak disappeared in the complexes. The signal due to azomethine protons was observed between 9.77 – 8.30 ppm in the compounds. The signals in the range 6.03 – 7.99 ppm in the compounds were assigned to aromatic protons. The signal due to ethylene protons appeared only in the complexes at 4.41 ppm. The spectra revealed the presence of uncoordinated water in the complexes.

The ^{13}C NMR spectrum of H_3CT showed only two signals due to phenyl carbons at 112.54 and 130.65 ppm. The ^{13}C NMR spectrum of $[\{Ce(OH)_2(salen)\}_3(CT)].3H_2O$ exhibited 9 carbon signals comprising of azomethine carbons at 166.14 and 164.10 ppm, carbons on triazine ring at 134.39 and 133.84 ppm, carbons on phenyl ring at 123.66, 117.46, 116.67 ppm, ethylene carbons at 62.95 ppm[86]. The ^{13} C NMR of H_3MT gave signal at 193.47 ppm attributed to carboxylic carbon[87]. This signal did not appear in the spectra of $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$. The signal due to azomethine carbon was observed at 165.75 and 167.47 ppm in H_3MT but shifted upfield in $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$ at 166.14 and 164.11 ppm[86]. The signal at 139.07 and 136.98 ppm in H_3MT has been assigned to carbons on triazine ring. This signal shifted upfield in $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$ at 134.39 and 133.83 ppm. Carbons on benzene ring are present at 130.32 and 129.92 ppm in H_3MT, but shifted upfield in $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$ at 123.66, 117.46 and 116.68 ppm.

Table 4: ^{1}H NMR Data of H_3CT, H_3MT and their Ce(IV) salen capped complexes

Compound	OH $_{Carboxylic}$	CH = N	$H_{aromatic}$	CH_2 = CH_2	$H_2O_{uncoordinated}$	DMSO
$C_{45}H_{30}N_6O_9$ (H_3CT)	-	8.30(1H,s)	6.12 – 6.55(4H,d) 7.47 – 7.63(4H,d)	-	3.34	2.5
$C_{27}H_{18}O_6N_6$ (H_3MT)	10.17(1H,s)	9.77(1H,s) 8.29(1H,s)	7.99 - 6.25(4H,m)	-	-	2.50
$[\{Ce(OH)_2(salen)\}_3(CT)].3H_2O$	-	8.68(1H,s)	6.03(7H,d), 6.44(1H,t), 7.08(1H,t), 7.26(3H,d)	4.41(4H,s)	3.34	2.5
$[\{Ce(OH_2)(salen)\}_3(MT)].3H_2O$	-	8.68(1H,s)	7.27(2H,d),7.08(1H,t) 6.44(1H,t),6.18(2H,s), 6.03(4H,d)	4.41(4H,s)	3.34(2H,s)	2.50

.

Table 5: ^{13}C NMR Data of H_3CT, H_3MT and their Ce(IV) salen capped complexes

Compound	Carboxylic carbon	Azomethine carbon	Carbons on triazine ring	Aromatic carbons	DMSO peak	Ethylene carbons
$C_{45}H_{30}N_6O_9$ (H_3CT)	-	-	-	130.65, 112.54	39.91	-
$C_{27}H_{18}O_6N_6$ (H_3MT)	193.47	167.47, 165.75	139.07, 136.98	130.32, 129.92	39.89	-
[{Ce(OH)$_2$(salen)}$_3$(CT)].3H$_2$O	-	166.14, 164.10	134.39, 133.84	123.66, 117.46, 116.67	39.91	62.95
[{Ce(OH)$_2$(salen)}$_3$(MT)].3H$_2$O	-	166.14, 164.11	134.39, 133.83	123.66, 117.46, 116.68	39.91	-

In vitro antimicrobial activity

The results of the *in vitro* antimicrobial screening carried out on the compounds are recorded in Table 6. Ciprofloxacin, tetracycline, gentamicin and fluconazole were used as positive control while sterile DMSO served as negative control. These drugs have been chosen because they have same mechanism of action, which is by inhibiting nucleic acid synthesis[88]. The structures of these drugs are shown in supplementary materials (Figure S23). Ciprofloxacin ($C_{17}H_{18}FN_3O_3$) belongs to fluoroquinolnes and inhibits bacteria growth by preventing deoxyribonucleic acid (DNA) synthesis before mitosis. Tetracycline ($C_{22}H_{24}N_2O_8$) inhibits the multiplication of bacteria by binding to a subunit of the ribosomes, thereby inhibiting protein and nucleic acid synthesis and consequent death of the bacterium[89-90]. Gentamycin ($C_{21}H_{43}N_5O_7$) belongs to the class of aminoglycosides and acts by preventing protein synthesis, thereby inhibiting the synthesis of nucleic acids (DNA replication or RNA synthesis) and causes death of the bacterium. Fluconazole is an antifungal drug ($C_{13}H_{12}F_2N_6O$) and belongs to synthetic triazoles. Fluconazole inhibits fungal cytochrome P –450, an enzyme responsible for fungal sterol synthesis, thereby causing fungal cell walls to weaken[90].

The results obtained (Table 6) show that the compounds inhibited the growth of *Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida*

albicans, and *Aspergillus niger* with inhibition zone diameter (IZD) in the range of 2 – 11, 1 – 15, 2 – 12, 1 – 6, 2 – 31, 5 –21 mm respectively. This reflects that the compounds exhibit higher activity against fungi (*Candida albicans* and *Aspergillus niger*) relative to the bacteria strains used. Among the test bacteria, the compounds were most active against *Staphylococcus aureus* followed by *Pseudomonas aeruginosa.*

It was observed from the results (Table 6) that the activity of H_3MT is higher than that of H_3CT and the trinuclear Ce(IV) complexes. Hence, it could be inferred that the activity of the trinuclear complexes was not enhanced after anion coordination.

Table 6: Inhibition zone diameter (IZD in mm) of the compounds against typed strains (ATCC CULTURES) microorganisms

Compound	*B.c*(ATCC 14579)	*S.a*(ATCC 6538P)	*P.a*(ATCC 9027)	*E.c*(ATCC 6749)	*C.a*	*A.n*
50 µg/mL						
$C_{45}H_{30}N_6O_9$ (H_3CT)	11	2	3	4	-	9
$C_{27}H_{18}O_6N_6$ (H_3MT)	5	15	12	6	31	21
[{Ce(OH)$_2$(salen)}$_3$(CT)].3H$_2$O	-	-	-	2	-	7
[{Ce(OH)$_2$(salen)}$_3$(MT)].3H$_2$O	-	1	2	1	3	5
25 µg/mL						
$C_{45}H_{30}N_6O_9$ (H_3CT)	2	-	-	-	-	-
$C_{27}H_{18}O_6N_6$ (H_3MT)	-	10	7	2	19	15
[{Ce(OH)$_2$(salen)}$_3$(CT)].3H$_2$O	-	-	-	-	-	-
[{Ce(OH)$_2$(salen)}$_3$(MT)].3H$_2$O	-	-	-	-	2	-
12.5 µg/mL						
$C_{45}H_{30}N_6O_9$ (H_3CT)	-	-	-	-	-	-
$C_{27}H_{18}O_6N_6$ (H_3MT)	-	5	3	3	6	10
[{Ce(OH)$_2$(salen)}$_3$(CT)].3H$_2$O	-	-	-	-	-	-
[{Ce(OH$_2$(salen)}$_3$(MT)].3H$_2$O	-	-	-	-	-	-

Key:*B.c = Bacillus cereus, S.a = Staphylococcus aureus, P.a = Pseudomonas aeruginosa, E.c = Escherichia coli, C.a = Candida albicans.A.n = Aspergillus niger,* (-) = no zone of inhibition observed.

The inhibition zone diameter (IZD in mm) of the controls is displayed in supplementary materials (Table S1). From Table S1, the inhibition zone diameters (IZD) of the controls are higher than that of the compounds.

The minimum inhibitory concentration (MIC) of the compounds and controls against *Bacillus cereus, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Candida albicans,* and *Aspergillus niger* are displayed in Table7. From Table 7, the MIC of the compounds is found to be in the range 25 - >50 for *Bacillus cereus***,** 5.57 – >50 for *Staphylococcus aureus,* 6.27 – >50 for *Pseudomonas aeruginosa,* 7.3 – 50 for *Escherichia coli,* 2.6 – >50 for *Candida albicans* and 2.3 –50 for *Aspergillus niger***.**

Table 7: Minimum inhibitory concentration (MIC) of the compounds and controls against test bacteria and fungi

	MIC (µg/mL)					
Compound	***B.c*(ATCC 14579)**	***S.a*(ATCC 6538P)**	***P.a*(ATCC 9027)**	***E.c*(ATCC 6749)**	***C.a***	***A.n***
$C_{45}H_{30}N_6O_9$ (H_3CT)	25	50	50	50	>50	50
$C_{27}H_{18}O_6N_6$ (H_3MT)	50	5.57	6.27	7.3	2.6	2.3
[{Ce(OH)$_2$(salen)}$_3$(CT)].3 H_2O	>50	>50	>50	50	>50	50
[{Ce(OH)$_2$(salen)}$_3$(MT)].3 H_2O	>50	50	50	50	25	50
	Controls					
T	1.90	1.80	0.63	2.15	2.10	0.58
F	6.25	6.25	6.25	2.80	0.64	0.74
CP	1.50	0.70	0.92	0.65	2.00	6.25
G	1.40	2.70	0.71	2.60	2.50	0.64

Legend: **T** = Tetracycline, **F** = Fluconazole, **CP** = Ciprofloxacin, **G** = Gentamycin.

From Table 7, the MIC of the controls is found to be in the range 1.4 – 6.26 for *Bacillus cereus***,** 0.70 **–** 6.25 for *Staphylococcus aureus,* 0.63 – 6.25 for *Pseudomonas aeruginosa,* 0.65 – 2.80 for *Escherichia coli,* 0.64 – 2.50 for *Candida albicans* and 0.58 – 6.25 for *Aspergillus niger***.**

The MIC of H_3MT against *Staphylococcus aureus* was 5.57 mg/ml while that of gentamycin was 2.70 mg/ml. The MIC of H_3MT against *Candida albicans* is comparable to that of gentamycin. Amongst all the test compounds, H_3MT was found to be the most active against *Candida albicans* and *Aspergillus niger* (MIC = 2.60 and 2.30 mg/ml respectively). However, the standard antifungal drug, Fluconazole was more active against *Candida albicans* and *Aspergillus niger* (MIC = 0.64 and 0.74 mg/ml respectively) relative to H_3MT. Amongst the Ce(IV) Salen Capped Complexes, $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$ is more potent.

CONCLUSION

Novel trinuclear Ce(IV) Salen Capped Complexes derived from *s*-triazine were synthesized and characterized. Based on analytical and spectral data, the ligands were found to be hexadentate and coordinate to Ce(IV) ions through the oxygen atoms of the carboxylic group. The trinuclear Ce(IV) salen capped complex was characterized as being bridged by carboxylate anions to the Ce(IV) salen centres and displays a coordination number of eight by involving two hydroxyl groups in the coordination sphere. *In vitro* antimicrobial test indicate that the tripodal ligand, H_3MT is more potent against the test micro-organisms relative to H_3CT, $[\{Ce(OH)_2(salen)\}_3(CT)].3H_2O$ and $[\{Ce(OH)_2(salen)\}_3(MT)].3H_2O$. The MIC of H_3MT against *Candida albicans* is comparable to that of gentamycin. Amongst the Ce(IV) Salen Capped Complexes, $[\{Ce(OH)_2(salen)\}_3$-$(MT)].3H_2O$

is more potent.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. Klaus Jurkschat of Technische Universität, Fakultät für Chemie und Chemische Biologie, D-44221 Dortmund, Germany for helping with the spectral analyses. We also acknowledge the support received from the African-German Network of Excellence in Science (AGNES), the Federal Ministry of Education and Research (BMBF) and the Alexander von Humboldt Foundation (AvH).

REFERENCES

1. Kumar, R., Singh, A. D., Singh, J., Singh, H., Roy, R. K. and Chaudhary, A. (2014) 1,2,3-Triazine Scaffold as a Potent Biologically Active Moiety: A Mini Review. *Mini-Reviews in Med. Chem.*, 14, 72-83.

2. Hatfield, S. E. (2007). Applications of Triazine Chemistry: Education, Remediation, and Drug Delivery. Thesis, Submitted to the Office of Graduate Studies of Texas A&M University, TX, USA.

3. Neunhoeffer, H. and Wiley, P. F. Chemistry of 1,2,3-Triazines and 1,2,4-Triazines,
Tetrazines, and Pentazines, Vol. 33, P. 1335, John Wiley & Sons, Inc., New York, 1978.

4. Agarwal, A., Srivastava, K., Puri, S. and Chauhan, P. (2005). Syntheses of 2, 4, 6-trisubstituted triazines as antimalarial agents. *Bioorg. Med. Chem. Lett.* 15(3), 531–533.

5. Ojha, H., Gahlot, P., Tiwari, A. K., Pathak, M. and Kakkar, R. (2011). Quantitative structure activity relationship study of 2, 4, 6-trisubstituted-*s*-triazine derivatives as antimalarial inhibitors of *Plasmodium falciparum* dihydrofolate reductase. *Chem. Biol. Drug Des.* 77(1), 57–62.

6. Kumar, A., Srivastava, K., Raja Kumar, S., Puri, S. and Chauhan, P. (2009). Synthesis of 9-anilinoacridine triazines as new class of hybrid antimalarial agents. *Bioorg. Med. Chem. Lett.* 19(24), 6996–6999.

7. Gravestock, D., Rousseau, A. L., Lourens, A. C., Moleele, S. S., Van Zyl, R. L.and Steenkamp, P. A. (2011). Expeditious synthesis and biological evaluation of novel 2,N6-disubstituted 1,2-dihydro-1,3,5-triazine-4,6-diamines as potential antimalarials. *Eur. J. Med. Chem.* 46(6), 2022–2030.

8. Modh, R. P., De Clercq, E., Pannecouque, C. and Chikhalia, K. H. (2013). Design, synthesis, antimicrobial activity and anti-HIV activity evaluation of novel hybrid quinazoline-triazine derivatives. *J. Enzyme Inhib. Med. Chem.* 29(1), 100–108.

9 Modh, R. P., Patel, A. C., and Chikhalia, K. H. (2013). Design, synthesis, antibacterial, and antifungal studies of novel 3-substituted coumarinyl-triazine derivatives. *Heterocycl. Commun.* 19(5), 343–349.

10. Bhat, H. R., Pandey, P. K., Ghosh, S. K. and Singh, U. P. (2013). Development of 4-aminoquinoline-1,3,5- triazine conjugates as potent antibacterial agent through facile synthetic route. *Med. Chem. Res.* 22, 5056–5065.

11. Maarouf, A. R., Farahat, A.A., Selim,

K.B. and Eisa, H. M. (2012). Synthesis and

antiviral activity of benzimidazolyl-and

triazolyl-1, 3, 5-triazines. *Med. Chem. Res.*

21(6), 703–710.

12. Machakanur. S. S., Patil, B. R., Badiger, D. S., Bakale, R. P., Gudasi, K. B.and Annie Bligh, S. (2012). Synthesis, characterization and anticancer evaluation of novel tri-arm star shaped 1, 3, 5-triazine hydrazones. *J. Mol. Struct.* 1011, 121–127.

13. Cascioferro, S., Parrino, B., Spanò, V., Carbone, A., Montalbano, A., Barraja, P., Diana, P. and Cirrincione. G.(2017). 1,3,5-Triazines: A promising scaffold for anticancer drugs development. *Eur. J. Med. Chem*. 2017, 142:523-549.

14. Patel, R. V., Kumari, P., Rajani, D. P. and Chikhalia, K. H. (2011). Synthesis and studies of novel 2-(4-cyano-3-trifluoromethyl phenyl

amino)- 4-(quinoline-4-yloxy)-6-(piperazinylpiperidinyl)-*s*-triazines as potential antimicrobial, antimycobacterial and anticancer agents. *Eur. J. Med. Chem.* 46(9), 4354–4365.

15. Kumar, G. J., Bomma, H.V. S.S., Srihari, E., Shrivastava, S., Naidu, V. G. M., Srinivas, K. and Rao, V. J. (2013). Synthesis and anticancer activity of some new *s*-triazine derivatives. *Med. Chem. Res.* 22(12), 5973–5981.

16. Sonikan, J., Pankaj, K. J., Shalu, S., Devarapalli, K. and Jaya, D. (2020). Anticancer s-triazine derivatives: A synthetic attribute. *Mini-Reviews in Organic Chemistry* 17, 10.2174/1570193X17666200131111851.

17. Demirci, S., Dogan, A., Turkmen, N.B., Telci, D., Rizvanov, A.A. and Sahin, F. (2017). Schiff base-Poloxamer P85 combination demonstrates chemotherapeutic effect on prostate cancer cells in vitro. *Biomed. Pharmacother*., 86, 492–501.

18. Patel, A. B., Patel, R. V., Kumari, P., Rajani, D. P. and Chikhalia, K. H. (2013). Synthesis of potential antitubercular and antimicrobial *s*-triazine-based scaffolds via Suzuki cross-coupling reaction. *Med. Chem. Res.* 22(1), 367–381.

19. Patel, R. V., Kumari, P., Rajani, D. P. and Chikhalia, K. H. (2011). Synthesis, characterization and pharmacological activities of 2-[4-cyano-(3- trifluoromethyl)phenyl amino)]-4-(4- quinoline/coumarin-4-yloxy)-6-(fluoropiperazinyl)-*s*-triazines. *J. Fluorine Chem.* 132(9), 617–627.

20. Sunduru, N., Gupta, L., Chaturvedi, V., Dwivedi, R., Sinha, S.and Chauhan, P. (2010). Discovery of new 1,3,5-triazine scaffolds with potent activity against *Mycobacterium tuberculosis* H37Rv. *Eur. J. Med. Chem.* 45(8), 3335–3345.

21. Jorgensen, W. L., Bollini, M., Thakur, V.V., Domaoal, R.A., Spasov, K. A. and Anderson, K. S. (2011). Efficient discovery of potent anti-HIV agents targeting the Tyr181Cys variant of HIV reverse transcriptase. *J. Am. Chem. Soc.* 133(39), 15686–15696.

22. Lozano, V., Aguado, L., Hoorelbeke B., Renders, M., Camarasa, M-J., Schols, D., Balzarini, J., San-Felix, A. and Perez-Perez, M-J. (2011). Targeting HIV entry through interaction with envelope glycoprotein 120 (gp120): synthesis and antiviral evaluation of 1, 3, 5-triazines with aromatic amino acids. *J. Med. Chem.* 54(15), 5335–5348.

23. Xiong, Y.-Z., Chen, F. –E., Balzarini, J., De Clercq, E. and Pannecouque, C. (2009). Non-nucleoside HIV-1 reverse transcriptase inhibitors. Part 13. *Chem. Biodivers.* 6(4), 561–568.

24. Liu, B., Lee, Y., Zou, J., Petrassi, H. M., Joseph, R. W., Chao, W., Michelotti, E. L., Bukhtiyarova, M., Springman, E. B. and Dorsey, B. D. (2010). Discovery and SAR of a series of 4, 6-diamino-1, 3, 5-triazin-2-ol as novel non-nucleoside reverse transcriptase inhibitors of HIV-1. *Bioorg. Med. Chem. Lett.* 20(22), 6592–6596.

25. Venkatraj, M., Ariën, K. K., Heeres, J., Joossens, J., Messagie, J., Michiels, J., Veken, P. V., Vanham, G., Lewis, P. J. and Augusty, K. (2012). Synthesis, evaluation and structure–activity relationships of triazine dimers as novel antiviral agents. *Bioorg. Med. Chem. Lett.* 22, 7174–7178.

26. Sharma, M., Chauhan, K., Shivahare, R., Vishwakarma, P., Suthar, M. K., Sharma, A., Gupta, S., Saxena, J. K., Lal, J., Chandra, P.,

Kumar, B. and Chauhan, P. M. S. (2013). Discovery of a new class of natural product-inspired quinazolinone hybrid as potent antileishmanial agents. *J. Med. Chem.* 56, 4374–4392.

27. Gupta, L., Sunduru, N., Verma, A., Srivastava, S., Gupta, S., Goyal, N. and Chauhan, P. M. (2010). Synthesis and biological evaluation of new [1,2,4] triazino[5,6-b] indol-3-ylthio-1,3,5-triazines and [1,2,4] triazino [5,6-b] indol-3-yl thio-pyrimidines against *Leishmania donovani. Eur. J. Med. Chem.* 45(6), 2359–2365.

28. Sunduru, N., Agarwal, A., Katiyar, S. B., Goyal, N., Gupta, S. and Chauhan, P. (2006). Synthesis of 2, 4, 6-trisubstituted pyrimidine and triazine heterocycles as antileishmanial agents. *Bioorg. Med. Chem.* 14(23), 7706–7715.

29. Sunduru, N., Palne, S., Chauhan, P. and Gupta, S. (2009). Synthesis and antileishmanial activity of novel 2, 4, 6-trisubstituted pyrimidines and 1, 3, 5-triazines. *Eur. J. Med. Chem.* 44(6), 2473–2481.

30. Dianzani, C., Collino, M., Gallicchio, M., Fantozzi, R., Samaritiani, S., Signore, G. and Menicagli, R. (2006). Evaluation of *in vitro* anti-inflammatory activity of some 2-alkyl-4, 6-dimethoxy-1, 3, 5-triazines*. J. Pharm. Pharmacol.* 58(2), 219–226 (2006).

31. Leftheris, K., Ahmed, G., Chan, R., Dyckman, A. J., Hussian, Z., Ho, K., Hynes, J., Letourneau, J., Li, W., Lin, S., Metzger, A., Moriarty, K. J., Riviello, C., Shimshock, Y., Wen, J., Wityak, J., Wrobleski, S. T., Wu, H., Wu, J., Desai, M., Gillooly, K. M., Lin, T. H., Loo, D., McIntyre, K. W., Pitt, S., Shen, D. R., Shuster, D. J., Zhang, R., Dieller, D., Doweyko, A., Sack, J., Baldwin, J., Barrish, J., Dodd, J., Henderson, I., Kanner, S., Schieven, G. and Webb, M. (2004). The discovery of orally active triaminotriazine aniline amides as inhibitors of p38 MAP kinase. *J. Med. Chem.* 47(25), 6283–6291.

32. Zhao, H., Liu, Y., Cui, Z., Beattie, D., Gu, Y.and Wang, Q. (2011), Design, synthesis, and biological activities of arylmethylamine substituted chlorotriazine and methylthiotriazine compounds. *J. Agric. Food. Chem.* 59(21), 11711–11717.

33. Niyaz, N., Guenthenspberger, K., Hunter, R., Brown, A. and Nugent, J., EP2481730 A1 (2012).

34. Koc, Z. E. and Ucan, H. I. (2007). Complexes of Iron(III) Salen and Saloph Schiff Bases with Bridging 2,4,6-Tris(2,5-dicarboxyphenylmino-4-formylphenoxy)-1,3,5-Triazine and 2,4,6-Tris(4-carboxyphenylimino-4^1-formylphenoxy)-1,3,5-Triazine.*Transition. Met. Chem.*, 32, 597-602.

35. Klenke, B.,Stewart, M., Barrett, M. P., Brun, R. and Gilbert, H. I. (2001). Synthesis, Biological evaluation of s-triazine substituted polyamines as potential new antitrypanosomal drugs. *J. Med. Chem.* 44, 3440, doi:10.1021/jm010854.

36. Horacek, H. and Pieh, S. (2000). The Importance of intumescent systems for fire protection of plastic materials. *Polym. Int*. 49(10), 1106–1114.

37. Uysal, S. and Koc, Z. E. (2010). Synthesis and Characterization of Dendrimeric Melamine Cored [salen/salophenFe(III)] and [salen/salophenCr(III)] Capped Complexes and Their Magnetic Behaviors. *J. of Hazardous Materials*, 175, 532-539.

38. Wu, J., Chen, L., Fu, T., Zhao, H., Guo, D., Wang, X.and Wang, Y. (2018). New application for aromatic Schiff base: high efficient flameretardant and anti-dripping

action for polyesters. *Chem. Eng. J*., 336, 622–632.

39. Agathian, K., Kannammal, L., Meenarathi, B., Kailash, S. and Anbarasan, R. (2018). Synthesis, characterization and adsorption behavior of cotton fiberbased Schiff base. *Int. J. Biol. Macromol.,* 107, 1102–1112.

40. Shah, D., Modh, R. P. and Chikhalia, K. H. (2014). Privileged s- triazines: Structure and pharmacological applications. *Future Med. Chem.*, 6(4), 463-477.

41. Miller, M. S., Pinson, J-A., Zheng, Z., Jennings, I. G. and Thompson, P. E. (2013). Regioselective synthesis of 5-and 6-methoxybenzimidazole-1, 3, 5-triazines as inhibitors of phosphoinositide 3-kinase. *Bioorg. Med. Chem. Lett.* 23, 802–805.

42. Rewcastle, G. W., Gamage, S. A., Flanagan, J. U., Kendall JD, Denny WA, Baguley BC, Buchanan CM, Chao M, Kestell P, Kolekar S, Lee WJ, Lill CL, Malik A, Singh R, Jamieson SMF, Shepherd PR (2013). Synthesis and biological evaluation of novel phosphatidylinositol 3-kinase inhibitors: solubilized 4-substituted benzimidazole analogs of 2-(difluoromethyl)- 1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]- 1*H*-benzimidazole (ZSTK474). *Eur. J. Med. Chem.* 64, 137–147.

43. Norman, M. H., Andrews, K. L., Bo, Y. Y., Booker, S. K., Caenepeel, S., Cee, V. J., D'Angelo, N. D., Freeman, D. J., Herberich, B. J., Hong, F-T., Jackson, C. L.M., Jiang, J., Lanman, B. A., Liu, L., McCarter, J. D., Mullady, E. L., Nishimuram N., Pettus, L. H., Reed, A. B., Miguel, T. S., Smith, A. L., Stec, M. M., Tadesse, S., Tasker, A., Aidasani, d., Zhu, X., Subramanian, R., Tamayo, N. A., Wang, L., Whittington, D. A., Wu, B., Wu, T., Wurz, R. P., Yang, K., Zalameda, L., Zhang, N. and Hughes, P. E.(2012). Selective class I phosphoinositide 3-kinase inhibitors: optimization of a series of pyridyltriazines leading to the identification of a clinical candidate, AMG 511. *J. Med. Chem.* 55(17), 7796–7816.

44. Tanneeru, K., Reddy, B.M. and Guruprasad, L. (2012). Three-dimensional quantitative structure– activity relationship (3D-QSAR) analysis and molecular docking of ATP-competitive triazine analogs of human mTOR inhibitors. *Med. Chem. Res.* 21(7), 1207–1217.

45. Wurz, R. P., Liu, L., Yang, K., Nishimura, N., Bo, Y., Pettus, L. H., Caenepeel, S., Freeman, D. J., McCarter, D. J., Mullady, E. L., Miguel, T. S., Wang, L., Zhang, N., Andrews, K. L., Whittington, D. A., Jiang, J., Subramanian, R., Hughes, P. E., Norman, M. H. (2012). Synthesis and structure–activity relationships of dual PI3K/ mTOR inhibitors based on a 4-amino-6- methyl-1, 3, 5-triazine sulfonamide scaffold. *Bioorg. Med. Chem. Lett.* 22, 5714–5720.

46. Richard, D. J., Verheijen, J. C., Yu, K. and Zask, A. (2010). Triazines incorporating (*R*)-3- methylmorpholine are potent inhibitors of the mammalian target of rapamycin (mTOR) with selectivity over PI3Ka. *Bioorg. Med. Chem. Lett.* 20(8), 2654–2657.

47. Verheijen, J. C., Richard, D. J., Curran, K., Kaplan, J., Yu, K. and Zask, A. (2010). 2-Arylureidophenyl-4-(3- oxa-8-azabicyclo [3.2.1] octan-8-yl) triazines as highly potent and selective ATP competitive mTOR inhibitors: optimization of human microsomal stability. *Bioorg. Med. Chem. Lett.* 20(8), 2648–2653.

48. De Hoog, P., Gamez, P., Driessen, W. L. and Reedijk, J. (2002). New polydentate and polynucleating N-donor ligands from amines and 2, 4, 6-trichloro-1, 3, 5-triazine. *Tetrahedron Lett.* 43(38), 6783-6786.

49. Naz, A., Arun, S., Narvi, S.S., Alam, M.S., Singh, A., Bhartiya, P. and Dutta, P.K. (2018). Cu(II)-carboxymethyl chitosan-silane schiff basecomplex grafted onnano silica: structural evolution, antibacterial performance and dyedegradation ability. *Int. J. Biol. Macromol.* 110, 215–226.

50. Al-Hamdani, A.A.S., Balkhi, A.M., Falah, A. and Shaker, S.A. (2016). Synthesis and investigation of thermal properties of vanadyl complexes with azo-containing Schiff-base dyes. *J. Saudi Chem. Soc.* 20, 487–501.

51. Hunger, K., Industrial Dyes: Chemistry, Properties, Applications. P. 117 – 18, John Wiley & Sons, 2007.

52. Baraka, A., Hall, P. J. and Heslop, M. J. (2007). Preparation and Characterization of Melamine–formaldehyde–DTPA Chelating Resin and its Use as an Adsorbent for Heavy Metals Removal from Wastewater. *Reactive & Functional Polymers,* **67(7),** 585 – 600.

53. Diem, H. and Matthias, G., Amino Resins: In Ullmann's Encyclopedia of Industrial Chemistry, 7th ed., P. 1-20, Wiley-VCH: Weinheim, Germany, 2006.

54. Lu, F. and Astruc, D. (2018). Nanomaterials for removal of toxic elements from water. *Coord. Chem. Rev*., 356, 147–164.

55. Tekin, O. and Uysal, S. (2019). Synthesis and Characterizations of *s*-Triazine Polymeric Complexes Including Epoxy Groups: Investigation of Their Magnetic and Thermal properties. *J. of inorganic and organometallic polymers and materials,* 29(5), 1701-1715. DOI: 10.1007/s10904-019-01132-0

56. Ilmi, R. and Iftikhar, K. (2012). Luminescent nine-coordinate lanthanide complexes derived from fluorinated *β*-diketone and 2,4,6-*tris*(2-pyridyl)-1,3,5-triazine. J. Coord. Chem., 65(3), 403-419.

57. Pavelek, L., Ladányi, V., Nečas, M., Moravec, Z. and Wichterle, K.(2016). Synthesis and characterization of lanthanide complexes with a pentadentate triazine-based ligand. Polyhedron 119,134-141.

58. Therrien, B. (2011). Coordination chemistry of 2,4,6-tri(pyridyl)-1,3,5-triazine ligands. *J.Org. Chem.*, 696(3), 637-651.

59. Taha, Z. A., Ajlouni, A. M., Al-Hassan, K. A., Hajazi, A. K. and Faiq, A. B. (2011). Synthesis, Characterization, Biological Activity and Fluorescence Properties of Bis-(salicylaldehyde)-1,3-propylenediimine Schiff base Ligand and Its Lanthanide Complexes. *Spectrochim. Acta*, Part A, 81, 317-323.

60. Dalla Cort, A., De Bernardin, P., Forte, G.and Mihan,F. Y. (2010). Metal–salophen-based receptors for anions. *Chem. Soc. Rev*., 39(10), 3863-3874.

61. Manolov, I., Kostova, I., Konstantinov, S. and Karaivanova, M. (1999). Synthesis, physicochemical characterization and cytotoxic screening of new complexes of cerium, lanthanum and neodymium with Niffcoumar sodium salt. *Eur. J. Med. Chem.*, 34(10), 853-858.

62. Kostova, I., Manolov, I., and Momekov, G. (2004). Cytotoxic activity of new neodymium (III) complexes of bis-coumarins. *Eur. J. Med. Chem.*, 39(9), 765-775.

63. Kostova, I., Manolov, I., Momekov, G., Tzanova, T., Konstantinov, S. and Karaivanova, M. (2005). Cytotoxic activity of new cerium (III) complexes of bis-coumarins. *Eur. J. Med. Chem.*, 40(12), 1246-1254.

64. Kostova, I., Manolov, I., Nicolova, I., Konstantinov, S. and Karaivanova, M. (2001). New lanthanide complexes of 4-methyl-7-

hydroxycoumarin and their pharmacological activity. *Eur. J. Med. Chem.*, 36(4), 339–347.

65. Sang, Y. –L., Lin, X.-S., Li, X.-C., Liu, Y.-H. and Zhang, X.-H. (2015). Synthesis, crystal structure and antibacterial activity of a novel phenolato- and peroxo-bridged dinuclear cerium(IV) complex with tripodal Schifff bases. *Inorg. Chem. Comm.*, 62, 115-118.

66. Yuan, F. G., Li, T.T., Zhang, M.M. and Qian, H. (2013). Synthesis and crystal structure of tri(pyrithione) cerium complex and its catalytic property for oxidation of benzoin to benzyl. *Synth. React. Inorg. Met-Org. Nano-Met. Chem.*, 43, 1510-1513.

67. Li, L., Yuan, F. G., Li, T.T., Zhou, Y. and Zhang, M.M. (2013). Synthesis and crystal structure of cerium (IV) complexes with 8-quinolinolate and amine bis(phenolate) ligands. *Inorg. Chim. Acta*., 397, 69-74.

68. Chen, Z. –F., Wei, J. –H., Liu, Y. –C., Liu, M., Gu, Y.-Q., Huang, K. –B., Wang, M. and Liang, H. (2013). High antitumor activity of 5, 7-dihalo-8-quinolinolato cerium complexes. *Eur. J. Med. Chem.* 68, 454-462.

69. Alghool, S., Abd El-Halim, H. F., Abd El-Sadek, M. S., Yahia, I. S. and Wahab, L. A.(2013). Synthesis, thermal characterization and antimicrobial activity of Lanthanum, cerium and thorium complexes of amino acid Schiff base ligand. *J. Therm. Anal. Calorim.*, 112, 671-681.

70. Abd El-Wahab, Z.H. (2008). Mixed ligand complexes of nicke (II) and cerium(III) ions with 4-(-3-methoxy-4-hydroxybenzylideneamino)-1,3-dimethyl-2,6-pyrimidine-dione and some nitrogen/oxygen donor ligands. *J. Coord. Chem.*, 61, 3284-3296.

71. Kostova, I. and Momekov, G. (2007). Synthesis, characterization and cytotoxicity evaluation of new cerium(III), lanthanum(III) and neodymium(III) complexes. *Appl. Organomet. Chem.*, 21, 226-233.

72. Kostova, I. and Momekov, G. (2008). New cerium(III) complexes of coumarins-synthesis, characterization, and cytotoxicity evaluation. *Eur. J. Med. Chem.*, 43, 178-188.

73. Oruma, U. S., Ukoha, P.O. and Obasi, L. N. (2020). Synthesis, Characterization and Biological studies of Trinuclear Ce(IV) salen capped complex with 5-amino-2,4,6-tris(4-carboxybenzimino) -1,3-pyrimidine. *Communication in Physical Sciences* 5(3), 403-417.

74. Tahmassebi, D. C.and Sasaki, T. (1994). Synthesis of a new trialdehyde template for molecular imprinting. *J. Org. Chem*., 59(3), 679-681.

75. Koc, Z. E.and Ucan, H. I. (2007). Complexes of iron(III) salen and saloph Schiff bases with bridging 2,4,6-tris(2,5-dicarboxyphenylmino-4-formylphenoxy)-1,3,5-triazine and 2,4,6-Tris (4-carboxyphenylimino-4^{1}-formylphenoxy)-1,3,5-triazine. *Transition. Met. Chem.*, 32(5), 597-602.

76. Uysal, S. and Uçan, H. I. (2009). The synthesis and characterization of melamine based Schiff bases and its trinuclear [salen/salophenFe (III)] and [salen/salophenCr (III)] capped complexes. *J. Incl. Phenom. Macrocycl. Chem.*, 65(3-4), 299-304.

77. Sathe, G. B., Vaidya, V.V., Deshmukh, R. G., Kekare, M. B., Kulkarni, V. S. and Chasker, A. C. (2013). Synthesis of Novel C2-symmetric Salen Molecules. *J. Applicable Chem.*, 2(3), 433-437.

78. Gembicky, M., Boca, R. and Renz, F. (2000). A Heptanuclear Fe(III)-Fe(III)6 System

with Twelve Unpaired Electrons. *Inorg. Chem. Comm.*, 3, 662-665.

79. Kopel, P., Sindelar, Z. and Klicka, R. (1998). Complexes of Iron(III) Salen and Saloph Schiff Bases with Bridging Dicarboxylic and Tricarboxylic Acids. *Transition. Met. Chem.*, 23, 139-142.

80. Uysal, S. and Koc, Z. E. (2010). Synthesis and Characterization of Dendrimeric Melamine Cored [salen/salophenFe(III)] and [salen/salophenCr(III)] Capped Complexes and Their Magnetic Behaviors. *J. of Hazardous Materials*, 175, 532-539.

81. Cheesbrough, M., District laboratory practice in tropical countries, P. 393 – 394, Cambridge university press, 2006.

82. Alli, A., Ehinmidu, J. and Ibrahim, Y. (2011). Preliminary phytochemical screening and antimicrobial activities of some medicinal plants used in Ebiraland. *Bayero J. of Pure and Applied Sci.*, 4(1), 10-16.

83. Ali, I., Wani, W. A. and Saleem, K. (2013). Empirical formulae to molecular structures of metal complexes by molar conductance. *Syn. React. Inorg Met.-Org and Nano-Met Chem.*, 43(9), 1162-1170.

84. Uysal, S. and Koc, Z. E. (2016). Synthesis and characterization of dopamine substitute tripodal trinuclear [(salen/salophen/salpropen) M] (M = Cr(III), Mn(III), Fe(III) ions) capped S-triazine complexes: Investigation of their thermal and magnetic properties. *J. Mol. Struct.*, 1109, 119-126.

85. Lekha, L., Raja, K. K., Rajagopal, G. and Easwaramoorthy, D. (2014). Synthesis, spectroscopic characterization and antibacterial studies of lanthanide (III) Schiff base complexes containing N, O donor atoms. *J. Mol. Struct.*, 1056, 307-313.

86. Ukoha, P. O. and Oruma, U. S. (2014). Synthesis and Antimicrobial Studies of N, N^1-Bis(4- Dimethylaminobezylidene)ethane-1,2-diamine (DAED) and its Nickel(II) and Platinium(IV) complexes . *J. Chem. Soc. Nigeria*, 39(2), 102-107.

87. Silverstein, R. M., Webster, F. X. and Kiemle, D. J., Spectrometric Identification of Organic Compounds, edn. 7, P. 106, 153, 200, 228, John wiley & Sons, Inc, Hoboken,2005.

88. Oruma, U.S., Ukoha, P.O., Rhyman, L., Elzagheid, M. I., Obasi, L. N., Ramasami, P. and Jurkschat, K.(2018). Synthesis, Characterization, Antimicrobial Screening, and Computational
Studies of a Tripodal Schiff Base Containing Pyrimidine Unit. *J. Heterocyclic Chem.*, 55, 1119- 1129.

89. Obasi, L. N., Oruma, U. S., Al-Swaidan, I. A., Ramasami, P., Ezeorah, C. J., A.E. Ochonogor, A. E. (2017). Synthesis, Characterization and Antibacterial Studies of N-(Benzothiazol-2-yl)-4-chlorobenzenesulphonamide and Its Neodymium (III) and Thallium (III) Complexes. *Molecules*, 22(2), 153, 1-11.

90. Wolters, K., Clinical Pharmacology made Incredibly Easy, 3rd ed., P. 285, 286, 239, 247, 256, Lippincott, W and Wilkins, USA, 2009.