

Synthesis, Spectroscopic, Biological and DFT Studies of 2,4,6-Tris(4-Carboxyphenylimino-4¹-Formylphenoxy)-1,3,5-Triazine and its Trinuclear Dy(III) and Er(III) Salen Capped Complexes

Uchechukwu S. Oruma, Pius O. Ukoha, Collins U. Ibeji, Lawrence N. Obasi, Obinna C. Okpareke, Ebubechukwu N. Dim, Klaus Jurkschat and Ponnadurai Ramasami

Received 29 August 2021/Accepted 23 September 2021/Published online: 27 September 2021

Abstract: A tripodal Schiff base ligand, 2,4,6-tris(4-carboxyphenylimino-4¹-formylphenoxy)-1,3,5-triazine (H₃CT) and its trinuclear Dy(III) and Er(III) complexes were synthesized. Characterization of these compounds was done via UV-Visible, IR, ¹H and ¹³C NMR spectroscopies, elemental analysis and molar conductivity measurements. The spectral studies indicate that the ligand is hexadentate and coordinates to Dy/Er(III) ions through the oxygen atoms of the carboxylic group. The trinuclear complexes were characterized as being bridged by a carboxylic group to the Dy(III) and Er(III) salen centres and displays a coordination number of six. Biological studies revealed that the Dy(III) complex showed the highest activity against tested microorganisms and also gave the highest percentage parasitemia inhibition (84.0 %) relative to Artesunate (87.2 %). DFT calculations were carried out to enhance understanding of H₃CT at the molecular level based on (B3LYP)/6-31+G(d,p). The molecular docking results revealed the binding mode of H₃CT complexed with *Staphylococcus aureus*.

Keywords: Tripodal Schiff base; 1,3,5-triazine, trinuclear Dy/Er(III) complexes; antimicrobial activity; antimalarial activity; DFT, docking

Uchechukwu Susan Oruma*

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

Email: susan.oruma@unn.edu.ng

Orcid. Id: [0000-0002-9226-2512](https://orcid.org/0000-0002-9226-2512)

Communication in Physical Sciences 2020, 7(3): 182-202

Available at <https://journalcps.com/index.php/volumes>

Pius Oziri Ukoha

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

Email: pius.ukoha@unn.edu.ng

Orcid id: [0000-0003-3041-0919](https://orcid.org/0000-0003-3041-0919)

Collins U. Ibeji

Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, 410001, Nigeria.

Email: Ugochukwu.ibeji@unn.edu.ng

Orcid id: [0000-0003-4762-2256](https://orcid.org/0000-0003-4762-2256)

Lawrence Nnamdi Obasi

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

Email: nnamdi.obasi@unn.edu.ng

Orcid id: [0000-0001-9310-0825](https://orcid.org/0000-0001-9310-0825)

Obinna C. Okpareke

Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, 410001, Nigeria.

Email: Obinna.okpareke@unn.edu.ng

Ebubechukwu N. Dim

Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, 410001, Nigeria.

Email: Ebubechukwu.dim@unn.edu.ng

Klaus Jurkschat

Technische Universität, Fakultät für Chemie und Chemische Biologie, -44221 Dortmund, Germany.

Email: Klaus.jurkschat@tu-dortmunde.de

Ponnadurai Ramasami

Computational Chemistry Group, Department of Chemistry, Faculty of Science, University of Mauritius, Réduit 80837, Mauritius.

Department of Applied Chemistry, University of Johannesburg, Doornfontein, Johannesburg 2028, South Africa.

Email: ramchemi@intnet.mu

1.0 Introduction

Tripodal ligands refer to those which have three arms containing donor atoms (N, S, P, or O) through which they can bind to one or more metals. They are generally employed in coordination, bioinorganic and organometallic chemistry in building multinuclear metal complexes (Kocyigit and Guler, 2010; Kocyigit 2013). These multinuclear metal complexes are related to multimetal active sites of various metalloproteins and metallo-enzymes (Hu *et al.*, 2003). Examples of tripodal ligands are: triazine tripods, tripyridylalkylamine (TPA) tripods, polypyridylamine tripods (Kocyigit and Guler, 2010; Kocyigit 2013), tris(2-aminoethyl)amine (tren) tripods, tris(2-pyridyl) tripods and tris(pyrazolyl)borate tripods. Substituted s-triazines derivatives have been known to possess anticancer (Afonso *et al.*, 2006; Kumar *et al.*, 2010; Sączewski *et al.*, 2006), antitumor (Arya and Dandia, 2007; Bepalov *et al.*, 2011; Zheng *et al.*, 2007), antiviral (Lemke *et al.*, 2010), and antifungal activities (Milata *et al.*, 2012). They are used as bridging agents in the synthesis of herbicides, drugs or polymers (De Hoog *et al.*, 2002; Uysal and Koc, 2010).

Tripodal- trinuclear [salen metal (III)] capped complexes of some main group and d-block metals have been synthesized and characterized, but no report exists of such complexes with the lanthanides. The work done

by Koc and Ucan (Koc and Ucan, 2007) was the first reported synthesis of tripodal-trinuclear [salen metal (III)] capped complexes. There is no report on their applications in biological studies.

Salen (N,N'-bis(salicylidene)ethylenediamine) has been recognized as one of the best known tetradentate organic ligands (Chen *et al.*, 2013; Yue *et al.*, 2015) with an N₂O₂ cavity (Taha *et al.*, 2011). Salen ligand was first synthesized by Jacobsen and Katsuki in 1990 when they discovered the enantioselective epoxidation of unfunctionalized alkenes using chiral Mn(salen) complexes (Irie *et al.*, 1990; Zhang *et al.*, 1990). Salen-type ligands have been employed in the synthesis of numerous metal complexes, both with transition and non-transition metals (Chen *et al.*, 2013; DallaCort *et al.*, 2010; Fei *et al.*, 2016) and their complexes are of great interest in chemistry because of their catalytic activities in a wide range of useful organic transformations (Sathe *et al.*, 2013). Their ability to form ligand complexes has been used to obtain capped complexes (Uysal and Koç, 2016). Earlier studies (DallaCort *et al.*, 2010) implicated the metal centre of salen complexes as being responsible for most of the activities like catalysis, chiral synthesis and biological activities. Consequently, most lanthanide salen/salen-type complexes have been employed in luminescent study (Chen *et al.*, 2013; Yue *et al.*, 2015; Taha *et al.*, 2011; Cristóvão and Hnatejko, 2015) and magnetic study (Chien *et al.*, 2015; Yue *et al.*, 2015). There are also reports on the study of biological activities of lanthanide salen/salen-type complexes (Feng *et al.*, 2017; Taha *et al.*, 2011). Lanthanides have an interesting but not well-understood biological role in living organisms as trace elements (Oruma *et al.*, 2014). Reports (Kostova *et al.*, 2005; Manolov *et al.*, 1999; Kostova *et al.*, 2004; Kostova *et al.*, 2005) have shown that lanthanide(III) complexes of coumarins exhibit potent cytotoxic and cytostatic activities. Lanthanide-



salophen complexes have been reported to exhibit physiological activities for several pathological conditions including ovarian cancer (DallaCortet *et al.*, 2010). Recently, Taha *et al.*, (Taha *et al.*, 2011) reported that Nd, Dy, Sm, Pr, Gd, Tb and Er complexes with bis-(salicylaldehyde)-1,3-propylenediimine Schiff base ligand possess high antibacterial activity against *Shigelladysenteriae*, *Pseudomonas aeruginosa* and *Proteus vulgaris* (Gram-negative bacteria).

In view of the noted biological properties of s-triazines and lanthanide(III) complexes, we synthesized and characterized 2,4,6-tris(4-carboxyphenylimino-4¹-formylphenoxy)-1,3,5-triazine (**H₃CT**) and its trinuclear Dy(III) and Er(III) salen capped complexes. Their *in vitro* antimicrobial, *in vivo* antimalarial activities and acute toxicity, were investigated. The experimental work was supplemented with the density functional theory method and molecular docking.

2.0 Materials and methods

2.1 Materials and measurements

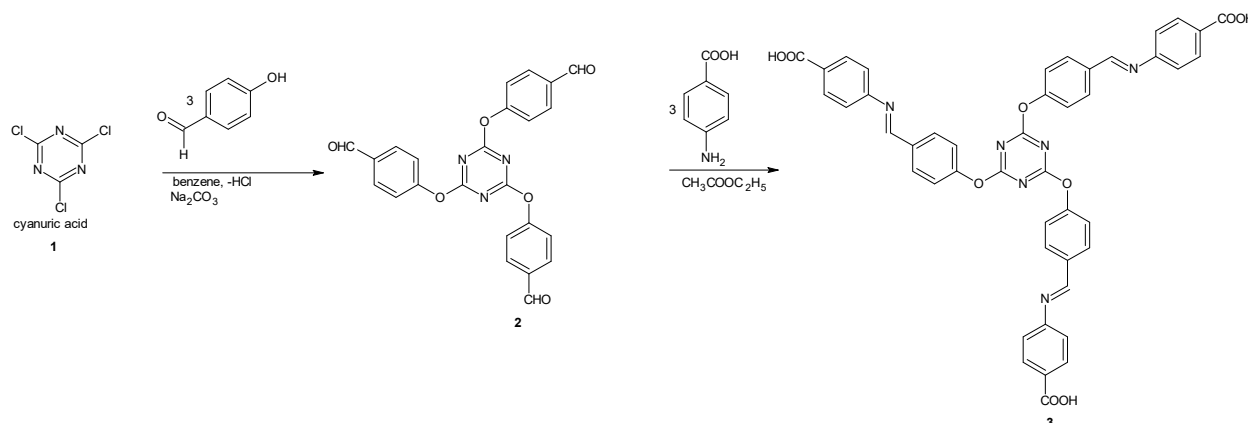
The chemicals used were of analytical reagent grade, purchased from Zayo–Sigma and were used as supplied without further purification. Fischer Jones melting point apparatus was used for the determination of melting point and values obtained were uncorrected. A 10⁻⁴mol/L solution of the complexes in methanol at room temperature was used for the determination of molar conductance using WTW-LF 90 conductivity meter. Electronic spectra (in DMSO) were recorded on UV-Vis 1800 SHIMADZU spectrophotometer. A Perkin–Elmer (Waltham, Massachusetts, USA) 100 series version 10.03.08 FTIR spectrophotometer was employed for infrared

spectra of the compounds. The ¹H and ¹³C NMR spectra of the compounds were recorded on a Bruker (Billerica, Massachusetts, USA) DPX 300 spectrometer in DMSO- d₆ at 300.13MHz and 75.47MHz respectively. LECO – CHN – 932 analyzer was used for elemental analysis for C, H and N.

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

The method reported by Tahmassebi and Sasaki (Tahmassebi and Sasaki, 1994) 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 Na₂CO₃ (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 Na₂CO₃ changed from white to brown. The mixture was filtered and the residue was 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 % Na₂CO₃ (2 g of Na₂CO₃ made up to 20 mL) was poured into it, shake 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 % Na₂CO₃. The filtrate was extracted with water once. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated. The white fluffy precipitate was recrystallized from ethyl acetate (20 mL), air-dried and stored over CaCl₂. This gave 2, 4, 6-tris (p-formylphenoxy)-1, 3, 5-triazine (**2**).





Scheme 1: Synthesis of 2, 4, 6-tris (4-carboxyphenylimino-4'-formylphenoxy)-1, 3, 5-triazine (H₃CT) (3)

2.3 Synthesis of 2, 4, 6-tris (4-carboxyphenylimino-4'-formylphenoxy)-1, 3, 5-triazine(H₃CT) (3)

The method reported by Koc and Ucan (Koc and Ucan, 2007) was adopted. Solid K₂CO₃ (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. 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 CaCl₂. Yield 0.47g (58.75 %), mp 282 °C; UV (DMSO) λ_{max} nm (ϵ): 230 (6.93 $\times 10^3$), 283 (5.85 $\times 10^3$); IR(KBr): 3239(O-H), 1594, 1546 (C=N), 1480 (C-C), 1394, 1384, 1367 (COO-), 1111 (C-N); ¹H NMR (DMSO- d₆, 300.13MHz): δ = 8.30(1H, s), 6.12 – 6.55(4H, d), 7.47 – 7.63(4H, d), 3.34(H₂O), 2.50(DMSO); ¹³C NMR (DMSO- d₆, 75.47MHz): δ = 130.65(Ar – C), 112.54(Ar – C), 39.91(DMSO); Anal. Calcd for

C₄₅H₃₀N₆O₉(798):C, 67.67; H, 3.76; N, 10.53 Found: C, 67.50; H, 3.60; N, 10.70. The UV, IR, ¹H NMR and ¹³C NMR spectra are presented in supplementary materials S6, S14, S17 and S20 respectively.

2.3 Synthesis of the trinuclearLn(III)Salen Capped Complex of H₃CT

This involves the synthesis of:

1. salenH₂
2. Dy(III) and Er(III) salen complex
3. Dy(III) and Er(III) ligand complex, ([{Dy/Er(salen)}₂O])
4. Dy(III) and Er(III) Salen Capped Complex of H₃CT, ([{Dy/Er(salen)}₃(H₃CT)]³⁺ . 3H₂O)

2.3.1 Synthesis of salenH₂

SalenH₂ was synthesized by modifying the method reported by Sathe *et al.* (Sathe *et al.*, 2013). To a solution of ethylenediamine(3.35 mL, 0.05mol) in methanol (50 mL) was added salicylaldehyde (10.47 mL, 0.1mol) in a round bottom flask. A yellow crystalline solid product was formed immediately. The yellow product was filtered and recrystallized from absolute ethanol(50 mL) at 80 °C to obtain yellow crystals. Yield = 11.14 g (83 %); mp of 109–110°C; UV(DMSO) λ_{max} nm (ϵ):316 (1.91 $\times 10^4$), 404 (0.41 $\times 10^4$);IR (KBr): 3441 (br)(O-H) Phenolic), 1608 (s) (C=N),1287(m) (C–O),751 (m)(C–H) cm⁻¹;Anal. calcd forC₁₆H₁₆O₂N₂ (268): C, 71.64; H, 5.97; N, 10.45. Found: C, 71.60; H, 6.00; N, 10.30. The



UV and IR spectra are presented in supplementary materials S1 and S9.

2.3.2(a) Synthesis of Dy(III) salen complex

The method reported by Gembický *et al.* (Gembický *et al.*, 2000) was modified and adopted for the synthesis of salen complexes. To a hot methanolic solution (40 mL) of salenH₂ (1.34g, 0.005mol), a hot methanolic solution (50 mL) of Dy(NO₃)₃ · 5H₂O (2.2 g, 0.005mol) was added. A yellow precipitate was formed. The mixture was stirred at 50 °C for 30 min., and then triethylamine (0.02mol, 4 mL) was added. The yellow precipitate dissolved and a clear solution was obtained. The resulting clear solution was stirred at 50 °C for 2h and after cooling a milk coloured precipitate was formed. The precipitate was washed with methanol and diethyl ether and dried over CaCl₂. Yield = 2.35 g (72.31 %); mp of 298^a °C (a = decomposition temperature) °C; UV (DMSO) λ_{max}nm (ε): 225 (5.44 x 10⁴), 349 (0.91 x 10⁴); IR(KBr): 3436 (O-H), 1631 (C=N), 1198 (C-O), 1458, 1041, 894, 1388 (NO₃⁻), 755 (C-H), 586 (Ln-O), 400 (Ln-N); ¹H NMR spectrum could not be taken due to their paramagnetic character; Anal. Calcd for [Dy(L)(NO₃)₂(H₂O)₂][NO₃] (650.50): C, 29.52; H, 2.77; N, 10.76. Found: C, 29.30; H, 2.90; N, 10.64. L = salen. The UV and IR spectra are presented in supplementary materials S2 and S10.

2.3.2(b) Synthesis of Er(III) salen complex

To a hot methanolic solution (40 mL) of salenH₂ (1.34g, 0.005mol), a hot methanolic solution (50 mL) of Er(NO₃)₃ · 5H₂O (2.23 g, 0.005mol) was added. The mixture was stirred at 50 °C for 30 min and a yellow product formed, then triethylamine (0.02mol, 4 mL) was added. On adding triethylamine, the yellow precipitate dissolved. The resulting clear solution was stirred at 50 °C for 2h and after cooling a milk coloured precipitate was formed. The precipitate was washed with methanol and diethyl ether and dried over CaCl₂. Yield = 2.18 g (66.56 %); mp of 350^a °C (a = decomposition temperature) °C; UV

(DMSO) λ_{max}nm (ε): 350 (3.49 x 10⁴); IR(KBr): 3434 (O-H), 1631 (C=N), 1193 (C-O), 1451, 1041, 884, 1390 (NO₃⁻), 755 (C-H), 597 (Ln-O), 417 (Ln-N); ¹H NMR spectrum could not be taken due to their paramagnetic character; Anal. Calcd for [Er(L)(NO₃)₂(H₂O)₂][NO₃] (655.26): C, 29.30; H, 2.75; N, 10.68. Found: C, 29.40; H, 2.80; N, 10.78. The UV and IR spectra are presented in supplementary materials S3 and S11.

2.3.3.(a) Synthesis of Dy(III) ligand complex, [{Dy(salen)}₂O]

The ligand complexes were prepared by modifying the method reported by Kopel *et al.* (1998) and Uysal *et al.* (2010; 2009). A solution of Dy(III) Salen complex (0.50 g, 10⁻³mol) in absolute ethanol (20 mL) was stirred at 50 °C for 15 min. 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 milk coloured precipitate was formed, filtered and dried over CaCl₂.

Yield = 0.48 g (71.64 %); mp of 275^a °C (a = decomposition temperature) °C; UV (DMSO) λ_{max}nm (ε): 263 (12.39 x 10³), 339 (4.48 x 10³); IR(KBr): 1627 (C=N), 1546 (C=C), 1272 (C-O), 887, 755 (C-H), 600 (Ln-O-Ln), 574 (Ln-O); ¹H NMR spectrum could not be taken due to their paramagnetic character; Anal. Calcd for [{Dy(salen)}₂O] (873): C, 43.99; H, 3.21; N, 6.41. Found: C, 44.10; H, 3.25; N, 6.54. The UV and IR spectra are presented in supplementary materials S4 and S12.

2.3.3.(b) Synthesis of Er(III) ligand complex, [{Er(salen)}₂O]

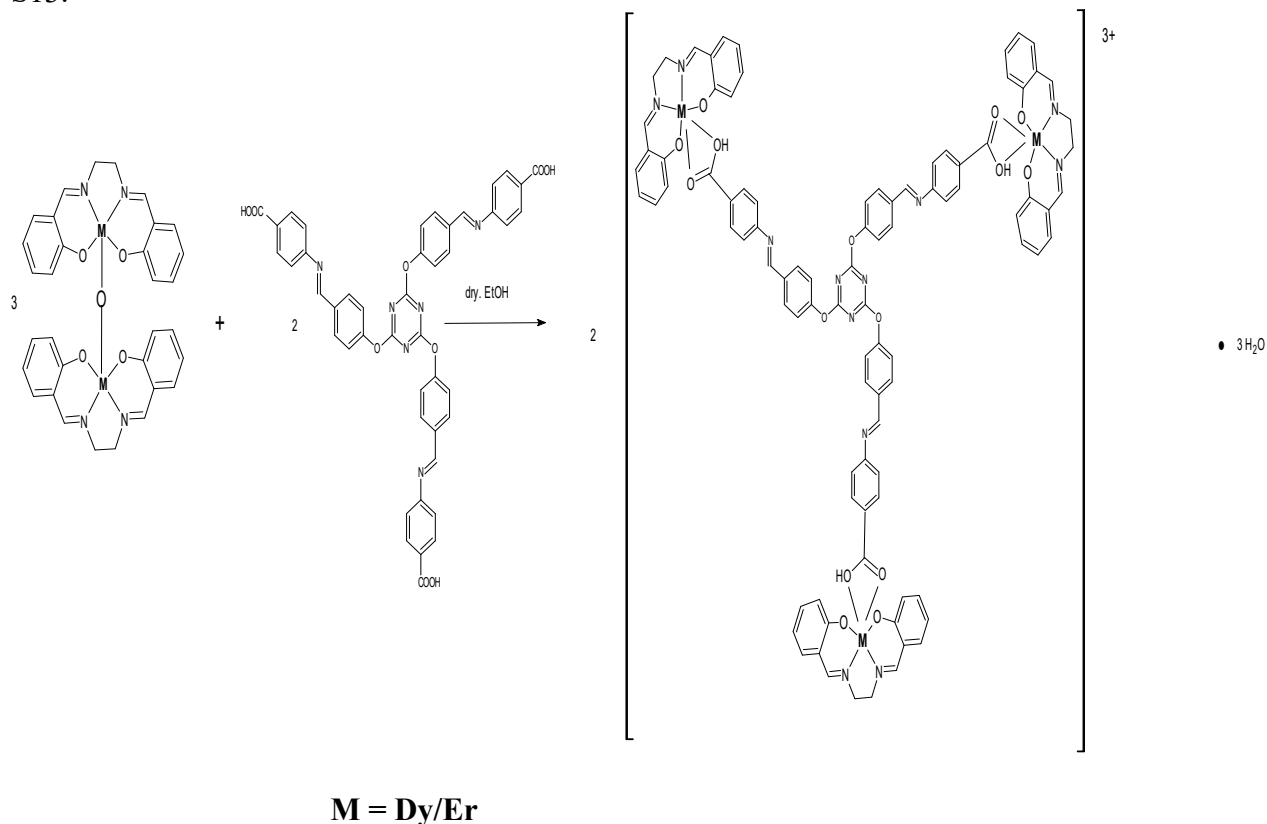
A solution of Er(III) Salen complex (0.50 g, 10⁻³mol) in absolute ethanol (20 mL) was stirred at 50 °C for 15 min. Excess concentrated ammonia solution (1 mL at a time) was added and stirred. The pH of the solution was monitored with the aid of a pH meter until the pH of 12. A pale yellow precipitate was formed, filtered and dried over CaCl₂. Yield = 0.45 g (67.16 %); mp of 275^a °C (a = decomposition temperature) °C; UV (DMSO)



λ_{\max} nm (ϵ): 264 (5.42×10^3), 348 (1.41×10^3); IR(KBr): 1625 (C=N), 1544 (C=C), 1285 (C-O), 906, 753 (C-H), 598 (Ln-O-Ln), 574 (Ln-O), 438 (Ln-N); ^1H NMR spectrum could not be taken due to their paramagnetic character; Anal. Calcd for $[\{\text{Er}(\text{salen})\}_2\text{O}]$ (882.52): C, 43.51; H, 3.17; N, 6.35. Found: C, 43.70; H, 3.20; N, 6.57. The UV and IR spectra are presented in supplementary materials S5 and S13.

2.3.4. Syntheses of the tripodal- trinuclear Dy(III) and Er(III) Salen Capped Complexes of H_3CT , $([\{\text{Dy/Er}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O})$

The trinuclear complexes were prepared by the reaction of two moles of the ligand(H_3CT) separately with three moles of $[\{\text{Dy/Er}(\text{salen})\}_2\text{O}]$ (ligand complexes(LC)) as shown in Scheme 2.



Scheme 2: Synthesis of $[\{\text{Dy/Er}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$

2.3.4.(a) Synthesis of $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$

$[\{\text{Dy}(\text{salen})\}_2\text{O}]$ (0.54 g, 0.00062 mol) was suspended in hot absolute ethanol (25 mL) and a solution of H_3CT (**3**) (0.33 g, 0.00041 mol) in absolute ethanol was added while stirring. The reaction mixture was heated at reflux for 4 h. The cream coloured solid formed was dried over CaCl_2 . Yield 0.47g (53.41 %), mp 332^a(a = decomposition temperature) $^\circ\text{C}$; UV (DMSO) λ_{\max} nm (ϵ): 346 (4.38×10^3); IR(KBr): 3024 (C-

Har), 1625, 1593, 1538 (C=N), 1467, 1448, 1432 (C-C), 1390, 1340, 1332 (COO⁻), 1144, 1121(C-N), 593, 569 (Ln-O), 456, 432 (Ln-N); ^1H NMR (DMSO- d_6 , 300.13MHz): δ = 12.98(1H, s), 8.83 (1H, s), 6.32- 6.95(4H,d), 4.12(4H, s)2.93(H₂O), 2.49(DMSO); ^{13}C NMR spectrum could not be taken due to their paramagnetic character; Anal. Calcd for $\text{C}_{93}\text{H}_{78}\text{O}_{18}\text{N}_{12}\text{Dy}_3$ (2,137.50):C, 52.21; H, 3.65; N, 7.86. Found: C, 52.43; H, 3.59; N, 7.94. The UV, IR, ^1H NMR and ^{13}C NMR spectra are



presented in supplementary materials S7, S15, S18 and S21 respectively.

23.4.(b) Synthesis of $[{\text{Er}}(\text{salen})]_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$

$[{\text{Er}}(\text{salen})]_2\text{O}$ (0.55 g, 0.00062 mol) was suspended in hot absolute ethanol (25 mL) and a solution of H_3CT (**3**) (0.33 g, 0.00041 mol) in absolute ethanol was added while stirring. The reaction mixture was heated at reflux for 4 h. The milky solid formed was dried over CaCl_2 . Yield 0.47g (51.69 %), mp 335^a(a = decomposition temperature)^oC; UV (DMSO) $\lambda_{\text{max}}\text{nm}$ (ϵ): 355 (10.30×10^3); IR(KBr): 1626, 1595, 1539 (C=N), 1468, 1448, 1432 (C-C), 1391, 1339 (COO⁻), 1147(C-N), 595, 572 (Ln-O), 456, 438 (Ln-N); ¹H NMR (DMSO-*d*₆, 300.13MHz): δ = 11.35(1H, s), 8.35(1H, s), 3.40(H₂O), 2.50(DMSO); ¹³C NMR spectrum could not be taken due to their paramagnetic character; Anal. Calcd for $\text{C}_{93}\text{H}_{78}\text{O}_{18}\text{N}_{12}\text{Er}_3$ (2,151.78):C, 51.86; H, 3.62; N, 7.81. Found: C, 51.94; H, 3.76; N, 7.99. The UV, IR, ¹H NMR and ¹³C NMR spectra are presented in supplementary materials S8, S16, S19 and S22 respectively.

2.4 In vitro antimicrobial activity

The tripodal ligand and its trinuclear complexes were tested *in vitro* for their antimicrobial activities against American Type Culture Collection (ATCC) bacteria strain 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 consists of 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 fungal strains were tested on Sabourand Dextrose Agar(SDA) and cultured in Sabourand Dextrose Liquid medium at 25 °C for 24 h while the bacteria strains were tested for sterility on nutrient agar and then grown in nutrient broth at 37 °C for 24

h. The overnight cultures were subsequently diluted and suspensions were made in normal saline and adjusted to 0.5 McFarland standards (Cheesbrough 2006).

2.5 Antimicrobial assay

The agar cup diffusion technique (Alliet *al.*, 2011) was employed in the determination of the antimicrobial activities of all the synthesized compounds. 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 using a sterile micropipette. Standard antibiotics namely: Ciprofloxacin, tetracycline, gentamycin and fluconazole served as positive control while sterile DMSO served as a 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 °C for 24 h while fungal plates were incubated at 25 °C for 24 h. Inhibition zone diameter (IZD) around each well was measured in millimeters and recorded. The graph of IZD² against the log of concentration was plotted for each plate containing a specific compound and a microorganism. The anti-log of the intercept on the *x*-axis is the MIC.

2.6 Determination of acute toxicity (LD₅₀)

Ethical approval: "All experiments involving the use of mice were conducted in compliance with NIH guidelines for care and use of animals (Council 2010)". $[{\text{Dy}}(\text{salen})]_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ was used for the test because it showed higher sensitivity against the tested micro-organisms. The oral acute toxicity of the ethanolic solutions of the samples was estimated in albino mice (100-250 g) by upper level lethal dose (LD₅₀) described



by Lorke's method (Lorke, 1983). Four mice of both sexes were employed and an acclimatization period of 24 h was allowed. The samples were weighed and dissolved in 3 % ethanol. The ethanolic solutions of the samples were administered orally at doses of 1000, 1600, 2900 and 5000 mg/kg. The animals were monitored for 24 h and the number of deaths per group was recorded. Then, the mice were observed continuously for one hour after treatment, intermittently for three hours and thereafter for 24 h. The mice were observed for gross behavioral changes such as feeding, hair erection, lacrimation, mortality and other signs of toxicity manifestation. The mice were given access to food and clean water during the study.

2.7 In vivo studies

The *in vivo* antimalarial assay was done based on a 4-day suppressive test using mice. The evaluation of the antimalarial activity against the methanolic solutions of the samples and Artesunate sensitive *Plasmodium berghei* (NK 65) was carried out according to a standard protocol of Peter's 4-day suppressive test (Peters, 1975). Each of the 12 healthy experimental mice was inoculated intraperitoneally on the first day (Day 1). The infected mice were weighed and randomly divided into four groups of three mice each and four hours post-inoculation were treated orally thereafter 24, 48 and 72 h post inoculation. For groups 1 and 2, 25 mg of sample/kg of mouse and 50 mg of sample/kg of mouse were administered orally for four consecutive days. For group 3, 5 mg of Artesunate/kg of the mouse was administered while group 4 was given 5 mL of distilled water/kg of the mouse for four consecutive days. A blood smear was taken on day 5. On day 4 post-inoculation, one drop of blood was taken from the tail of each experimental mouse and smeared on a microscope slide to make a thin film (Saidu *et al.*, 2000). The thin films were fixed with methanol, stained with 10 % Giemsa solution at pH 7.2 for 10 mins and

examined microscopically. Parasitemia level was determined by counting the number of parasitized erythrocytes out of 100 erythrocytes per field in 4 random fields under a light microscope at magnification ($\times 100$) while average percentage parasitemia suppression was determined by comparing the parasitemia in the control group with the treated group.

$$\text{Average percentage suppression} = pc - \frac{pt}{pc} \times 100 \text{ (Ukwe } et al., 2010)$$

where pc is the average parasitemia in the control group and pt average parasitemia in the treated group.

2.8 Computational method

Geometric optimization for $C_{45}H_{30}N_6O_9$, H₃CT was performed using Becke 3 Lee Yang par (Becke, 1992), (B3LYP)/6-31+G(d,p). The IR spectrum was studied by performing a frequency calculation and the electronic (UV) calculation was determined using time-dependent density functional theory (TDDFT) (Runge and Gross, 1984; Suendo and Viridi, 2011). The energy of the highest molecular orbital (HOMO) and that of the lowest molecular orbital (LUMO) (Chen *et al.*, 2009; Rauf *et al.*, 2015; Chioma *et al.*, 2018) of the ligand was estimated using 6-31+G(d,p).

Molecular docking was performed to determine the binding energies on the inhibition potentials of *Staphylococcus aureus*. The 3D PDB structures were retrieved from the Protein data bank (PDB) for *Staphylococcus aureus* access code: 3k4q (Oakley, 2010), (resolution 2.2 Å). The grid box size for the possible binding site was determined using AutoDock 1.5.4. tools (Sanner 1999) and the dimension was X= 44, Y= 42, Z= 40 with 1.00 Å as the grid spacing. Gasteiger (Yang *et al.*, 2013) charges were added using the AutoDock Tools graphical user interface provided by MGL Tools (Morris *et al.*, 2009). The binding site for the ligand was obtained using the Lamarckian genetic algorithm method. The ligand was optimized using Gaussian 09 (Frisch *et al.*, 2009), to obtain minimum structures.



3.0 Results and Discussion

The analytical data of H₃CT and its trinuclear complexes are in good agreement with the proposed molecular formula as shown in Table

1. Molar conductivity measurements in methanol at room temperature show that the trinuclear complexes are 1:1 electrolytes while the ligand is neutral (Ali *et al.*, 2013).

Table 1: Elemental and physical data of 2,4,6 - tris(4-carboxyphenylimino-4'-formylphenoxy) -1,3,5-triazine (H₃CT) and its Dy/Er(III) complexes

Compound	Colour	Λ_m ($\Omega^{-1}\text{cm}^2\text{mol}^{-1}$)	Yield (%)	g	M.p. (°C)	Elemental analysis % calcd. and found					
						C		H		N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
C ₄₅ H ₃₀ N ₆ O ₉ (H ₃ CT)	Yellow	-	0.47 (58.75)	282		67.67	67.50	3.76	3.60	10.53	10.70
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ · 3H ₂ O	Creamy	87	0.47 (53.41)	332 ^a		52.21	52.43	3.65	3.59	7.86	7.94
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ · 3H ₂ O	Milky	120	0.46 (51.69)	335 ^a		51.86	51.94	3.62	3.76	7.81	7.99

^a = decomposition temperature, Standard 1:1 electrolyte in Methanol = 80 – 122 ohm⁻¹cm²mol⁻¹

3.1 Computational Analysis

3.1.1 DFT Analysis

The fully optimized geometries of H₃CT is presented in Fig. 1. This was done to obtain a global minimum structure.

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) (Fig. 2) are presented in the form of frontier molecular orbitals (FMO) (Rauf *et al.*, 2015; Dumont, 2013). The electron donating ability of a complex is related to the E_{HOMO} and in general, the higher the E_{HOMO} energy (less negative), the more the ability to donate electrons (Ibeji *et al.*, 2015; Ekennia *et al.*, 2017). The ligand showed a low ΔE (band gap ($E_{\text{LUMO}} - E_{\text{HOMO}}$) of 2.11 eV suggesting high reactivity. The bandgap (or the $\pi-\pi^*$ electron transition) was estimated as the difference between the HOMO and LUMO orbital energies (Table S4). The negative value of HOMO energy is referred to as IP (Ibeji *et al.*, 2015; Salzner 2008; Ibeji *et al.*, 2018), whereas the negative values of LUMO is called the EA (Rauf *et al.*, 2015; Ekennia *et al.*, 2018). To further elucidate on the reactivity of ligand, the electronegativity (μ), chemical

hardness (η) and softness (S) was determined according to the equations:

$$\text{Chemical hardness, } \eta \quad (1)$$

$$\text{Global softness} \quad (2)$$

$$\text{Electronegativity } \mu \approx -\chi = - \quad (3)$$

where I and A are the ionization potential and electron affinity, $I = -E_{\text{HOMO}}$ and $A = -E_{\text{LUMO}}$, respectively.

As shown in Table S4, the compound studied is The simulated IR spectrum of H₃CT is in good agreement with the experimentally observed. H₃CT shows a very broad peak at 3241 cm⁻¹ assigned to the carboxylic OH group vibration. The IR spectrum of H₃CT showed two strong peaks for C=N(a) and C=N(b) at 1511 and 1525 cm⁻¹ respectively.

The predicted absorption UV spectra were also carried out on the ligand using TDDF based on the optimized geometry obtained by B3LYP/6-31+G(d,p). The results obtained indicated that the most intense peak is shown at 286 nm with an oscillator strength of 1.21 described as an allowed $\pi-\pi^*$ transition corresponding to HOMO—LUMO transition and a molecular contribution (Olanrewaju *et al.*, 2018) of 53.5%. This agrees with the obtained experimental data. Another peak was also



observed at 300 nm corresponding to HOMO—LUMO-1 transition with a molecular contribution of 61.8%. This is described as a forbidden transition since the oscillator strength is 0.1 (Olanrewaju *et al.*, 2018). As seen in Fig. 2, more electron density is delocalized in the HOMO orbital compared to the LUMO which is the lowest unoccupied orbital.

3.1.2 Molecular docking

Molecular docking studies were performed to gain further insight into the inhibition

potentials of the ligand, which will further help in projecting the binding abilities of the metal complexes. Docking result showed inhibition potentials with the ligand. This is evident in the hydrogen bond interactions around the active amino acid residues (Fig. 3). A similar protocol was performed by Bharatham *et al.* (Bharatham *et al.*, 2008).

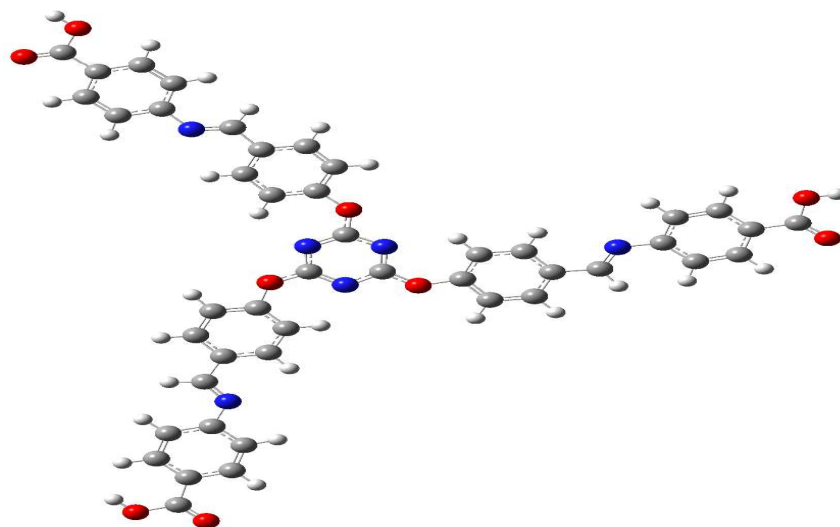


Fig.1: Optimized structure of H₃CT obtained at B3LYP/6-31+G(d,p) (red = oxygen atom; blue = nitrogen atom; white = hydrogen atom; and grey = carbon atom)

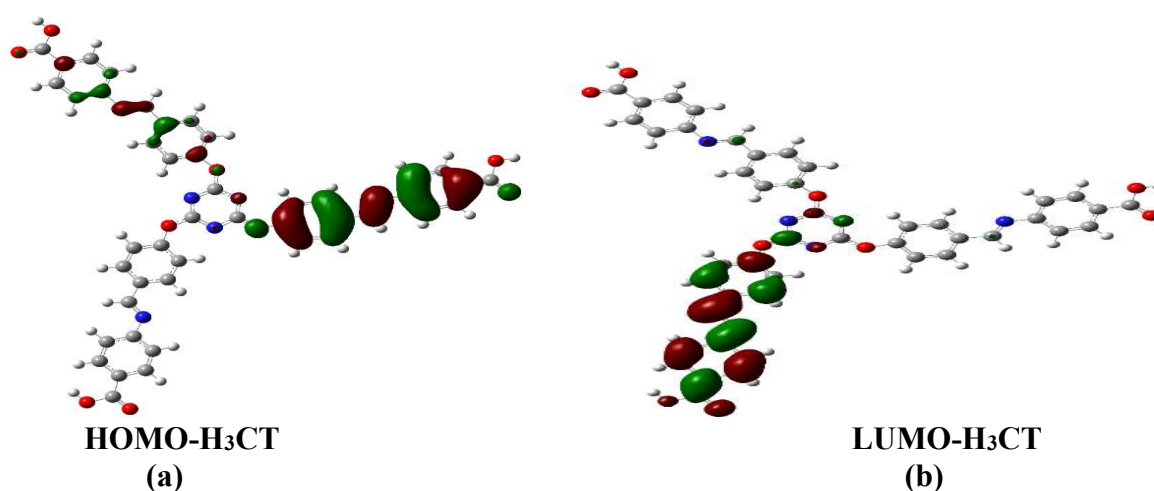


Fig.2: FMO orbital diagram showing the distribution of electron delocalization obtained by B3LYP/6-31+G(d,p)



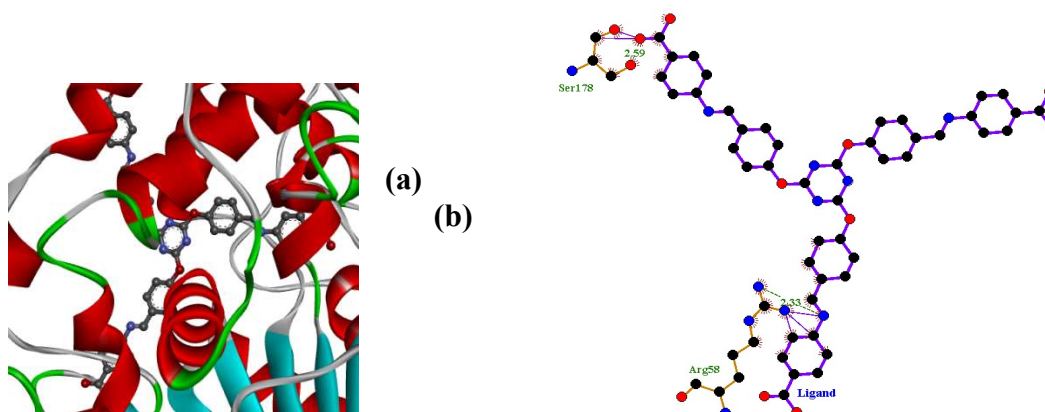


Fig. 3: 3D structure of (a) complex and (b) the interacting residues (with hydrogen bonding and hydrophobic) around the binding pocket of H₃CT complexed with *Staphylococcus aureus*

From the docking result (Table 2), the binding mode analysis of the ligand with some amino

acid residues provided important information for proposing the catalytic mechanism.

Table 2: Calculated binding energy, core amino acid residue and hydrogen bond distance between residues and H₃CT from molecular docking

Enzymes	Binding energy (kcal/mol)	Residues	Atoms of the residues	Distance (Å)
<i>Staphylococcus aureus</i>	-5.45	SER, ARG	O, N, C	2.59, 2.33

3.2 Electronic spectra

The UV/Vis absorption spectra of H₃CT and its complexes (10^{-5} M) were carried out in DMSO at room temperature in the range 200 – 800 nm. The spectral values of the absorption wavelength and the corresponding molar absorptivities (ϵ) are given in Table 3. The absorption spectra are displayed in supplementary materials. The absorption spectrum of H₃CT shows two peaks at 230 and 283 nm assigned to π – π^* transitions of the conjugated phenyl ring. The absorption spectra of the complexes show only one peak. This peak is assigned to charge transfer (LMCT) from the ligand, H₃CT, to the lanthanide ions. A similar observation has been made in the literature for Er(III) ions (Taha *et al.*, 2011; Fei *et al.*, 2016).

The changes in the values of ϵ indicate the formation of the Ln(III) complexes. There are no peaks due to f transition, since in lanthanides f–f transitions are Laporte-forbidden and very weak, they do not contribute much to the spectra of their complexes (Taha *et al.*, 2011; Cristóvão and Hnatejko, 2015; Görlner-Walrand and Binnemans, 1998).

3.3 IR Spectra

The IR spectrum of the tripodal ligand, H₃CT and its trinuclear complexes are displayed in Table 4. H₃CT displayed a very broad band centered at 3239 cm^{-1} . This band was assigned to the carboxylic OH group vibration (Kocand Ucan, 2007). However, in the complexes, this band did not disappear but shifted to a higher wavenumber in the range 3239 – 3260 cm^{-1} suggesting that the carboxylic



OH was not deprotonated before coordination to the Ln metal. The IR spectrum of H₃CT showed two strong bands for C=N(a) and C=N(b) at 1546 and 1594 cm⁻¹ respectively. However, in the complexes, three bands were observed: C=N(a) bands at 1593 – 1595 cm⁻¹, C=N(b) bands at 1623 – 1626 cm⁻¹ and C=N(c) bands at 1530 – 1539 cm⁻¹ respectively. Similar observation has been made in literature (Uysal and Koç, 2016; Uysal and Uçan, 2009 (a); Uysal *et al.*, 2012). 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 indicating delocalization of the double bond of the tripodal Schiff base on coordinating with the ligand complexes. While the C=N(c) band,

which was absent in the tripodal Schiff base ligand but present in the complexes confirms that the ligand complexes were capped to the tripod. Similar observation has been made in literature (Uysal and Uçan, 2009 (a); Uysal and Uçan, 2009 (b)). The vibration due to the COO⁻ group, was observed between 1332 – 1394 cm⁻¹ in the compounds. This band shifted to lower frequencies in the complexes suggesting the involvement of the COOH group in coordination with the Ln ions; (Uysal and Uçan, 2009 (a); Uysal *et al.*, 2012). Bands at 569 – 595 and 432 – 456 cm⁻¹ range are attributed to Ln –O and Ln –N stretch in the complexes and they confirm the binding mode (Taha *et al.*, 2011; Lekha *et al.*, 2014).

Table 3: Electronic absorption data of 2,4,6-tris(4-carboxyphenylimino-4¹-formyl phenoxy) -1,3,5-triazine (H₃CT) and its Dy/Er(III) complexes

Compound	λ_{\max}		$\epsilon \times 10^3$ (mol ⁻¹ dm ³ cm ⁻¹)	Band assignment
	Nm	cm ⁻¹		
H ₃ CT	230	43478	6.93	$\pi-\pi^*$
	283	35336	5.85	$\pi-\pi^*$
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ . 3H ₂ O	346	28901	4.38	LMCT
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ . 3H ₂ O	355	28169	10.30	LMCT

Table 4: IR band assignments (cm⁻¹) for 2,4,6 - tris(4-carboxyphenylimino-4¹-formyl phenoxy) -1,3,5-triazine (H₃CT) and its Dy/Er(III) complexes

Compound	ν (O – H)	ν (C = N)	ν C – C	ν COO-	ν C – N	ν Ln –O	ν Ln –N
H ₃ CT	3239(br)	1546(s)a 1594(s)b	1480	1394(s) 1384(s) 1367(s)	1111	-	-
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ . 3H ₂ O	3260(br)	1593(s)a 1625(s)b 1538(s)c	1467(s) 1448(s) 1432(m)	1390(s) 1340(m) 1332(s)	1144(m) 1121(m)	593(s) 569(m)	456(s) 432(m)
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ . 3H ₂ O	3250(br)	1595(s)a 1626(s)b 1539(s)c	1468(s) 1448(m) 1432(m)	1391(s) 1339(s)	1147	595(m) 572(m)	456(m) 438(m)



where ν (O – H) = from carboxylic acid. Where C = N(a) = from triazine ring, C = N(b) = from azomethine linkage, C = N(c) = from salen.

3.4 ^1H NMR Spectra

The ^1H NMR spectra of H_3CT and its Dy/Er(III) complexes were recorded in D_6 -DMSO (Table 5). The ^1H NMR spectra of H_3CT did not show the signal due to carboxylic OH. However, this peak was observed in $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ and $[\{\text{Er}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ suggesting that the trinuclear complexes were formed without deprotonation of the carboxylic proton (Koc and Ucan, 2007). The signal due to azomethine proton was observed downfield as

3.5 ^{13}C NMR Spectra

The ^{13}C NMR spectra of H_3CT and its Dy/Er(III) complexes are displayed in supplementary materials while the spectral data are presented in Table 6. The ^{13}C NMR spectrum of H_3CT shows only two signals due to phenyl carbons at 112.54 and 130.65 ppm. The spectra for the trinuclear complexes show only solvent peak probably due to the extent of paramagnetism of the Ln(III) ions (Karatas, and Ucan, 2014).

a singlet at 8.30 ppm in H_3CT (Mohan et al., 2014; Kadhum, 2011) and in the complexes, it suffers a downfield shift by about 0.05 – 0.53 ppm. This confirms the bonding mode as suggested by IR studies. The signal due to phenyl protons reflects the two different chemical environments of the protons. In H_3CT , protons on phenyl ring, position 1 and 2 were observed between 6.12 – 6.55 ppm while the protons occupying position 3 and 4 on the second phenyl ring (Fig. 4) were observed between 7.47 – 7.63 ppm (Tahmassebi and Sasaki, 1994). The spectra also reveal that the compounds contain water of hydration (Silverstein et al., 2014).

3.6 *In vitro* antimicrobial activity

The results of the *in vitro* antimicrobial screening carried out on the compounds are given in Table 7. Ciprofloxacin, tetracycline, gentamicin and fluconazole were used as

positive control while sterile DMSO served as a negative control. The structures of these drugs are shown in the supplementary material (Figure S23). Ciprofloxacin ($\text{C}_{17}\text{H}_{18}\text{FN}_3\text{O}_3$) belongs to fluoroquinolones and inhibits bacteria growth by preventing deoxyribonucleic acid (DNA) synthesis before mitosis. Tetracycline ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8$) 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 (Obasiet al., 2017; Wolters, 2009).

Gentamycin ($\text{C}_{21}\text{H}_{43}\text{N}_5\text{O}_7$) 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 the death of the bacterium. Fluconazole is an antifungal drug ($\text{C}_{13}\text{H}_{12}\text{F}_2\text{N}_6\text{O}$) and belongs to synthetic triazoles. Fluconazole inhibited fungal cytochrome P – 450, an enzyme responsible for fungal sterol synthesis, thereby causing fungal cell walls to weaken (Wolters 2009).

The results obtained (Table 7) 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, 2 – 11, 2 – 12, 4 – 5, 7 – 19, 5 – 10 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 *Pseudomonas aeruginosa* and had the same activity against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*). It was observed from the results (Table 7) that the activity of the trinuclear complex in most cases is higher than that of the tripodal ligands. The enhanced activity of the trinuclear complexes could be ascribed to the increased lipophilic nature of the complexes arising due to anion



coordination (Mohanani *et al.*, 2006). The Ln – salen complexes act as Lewis acids. Thus, are potential receptors for anions that can donate lone pair of electrons to the Ln metal (DallaCort *et al.*, 2010). The cell walls and cell membranes of the micro-organisms contain majorly lipids and polysaccharides. The interaction of the Ln ions with these cellular compounds are because all these structures contain a variety of functional groups that can donate lone pair of electrons to the metal (Chakrabarti 1995). This enables the compounds to penetrate the cell wall and cell membrane of the micro-organisms and interfere with the normal cell processes.

The inhibition zone diameter (IZD in mm) of the controls is displayed in 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 Table 8. From Table 8, the MIC of the compounds is found to be in the range 25 for *Bacillus cereus*, 25 – 50 for *Staphylococcus aureus*, 25 – 50 for *Pseudomonas aeruginosa*, 50 for *Escherichia coli*, 25 – >50 for *Candida albicans* and 25 – 50 for *Aspergillus niger*.

Table 5: ^1H NMR data of 2,4,6 - tris(4-carboxyphenylimino-4¹-formyl phenoxy) -1,3,5-triazine (H_3CT) and its Dy/Er(III) complexes (ppm)

Compound	OH carboxylic	CH = N	H _{aromatic}	CH ₂ =CH ₂	H ₂ O (hydration)	DMSO
H_3CT	-	8.30(1H,s)	6.12– 6.55(4H,d) 7.47 – 7.63(4H,d)	-	3.34	2.50
$[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$	12.98(1H,s)	8.83(1H,s)	6.32– 6.95(4H,d)	4.12(4H,s)	2.93	2.49
$[\{\text{Er}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$	11.35(1H,s)	8.35(1H,s)	-	-	3.4	2.50

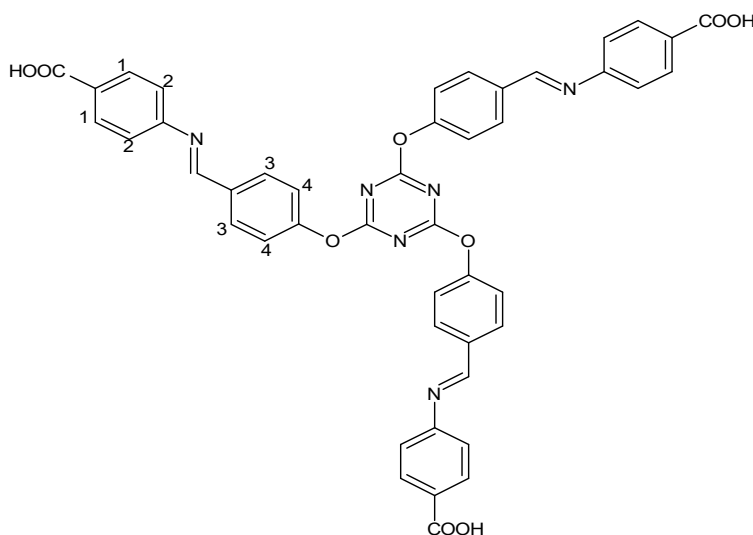


Fig. 4: Schematic drawing of H_3CT showing the positions of the protons



Table 6:¹³ C NMR Spectral data of 2,4,6 - tris(4-carboxyphenylimino-4¹-formyl phenoxy) - 1,3,5-triazine (H₃CT) and its Dy/Er(III) complexes (ppm)

Compound	Carboxylic carbon	Azomethine carbon	Carbons on triazine ring	Aromatic carbons	DMSO peak	Ethylene carbons
H ₃ CT	-	-	-	130.65, 112.54	39.91	-
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	-	-	-	-	39.88	-
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	-	-	-	-	39.91	-

Table 7: Inhibition zone diameter (IZD in mm) of the compounds against typed strains (ATCC CULTURES) microorganisms

50 µg/MI						
Compound	<i>B.c</i> (ATCC 14579)	<i>S.a</i> (ATCC 6538P)	<i>P.a</i> (ATCC 9027)	<i>E.c</i> (ATCC 6749)	<i>C.a</i>	<i>A.n</i>
H ₃ CT	11	2	3	4	-	9
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	10	11	12	5	13	10
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	5	5	3	4	19	10
25 µg/MI						
H ₃ CT	2	-	-	-	-	-
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	4	2	2	-	7	-
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	2	2	-	-	-	5
12.5 µg/mL						
H ₃ CT	-	-	-	-	-	-
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	-	-	-	-	-	-
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ .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.

Table 8: Minimum inhibitory concentration (MIC) of the compounds and controls against test bacteria and fungi

MIC (µg/mL)						
Compound	<i>B.c</i> (ATCC 14579)	<i>S.a</i> (ATCC 6538P)	<i>P.a</i> (ATCC 9027)	<i>E.c</i> (ATCC 6749)	<i>C.a</i>	<i>A.n</i>
H ₃ CT	25	50	50	50	>50	50
[{Dy(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	25	25	25	50	25	50
[{Er(salen)} ₃ (H ₃ CT)] ³⁺ .3H ₂ O	25	25	50	50	50	25
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 1.40 – 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*. From Table 7, it can also be seen that $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ is most active against the test microorganisms relative to the compounds.

3.7 Acute toxicity

The acute toxicity test was recorded for $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ as shown in Table S2. $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ was chosen because it shows higher sensitivity against the test micro-organisms. For mice

administered with $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$, no animal died within 24h after administration (Table S2). This implies that $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ is safe and have a wide range of effective dose (ED_{50}) (Alliet *al.*, 2011).

3.8 In vivo anti-malarial studies

The suppressive antiplasmodic effect of methanolic solutions of the test samples on albino mice is displayed in Table S3 while Table 9 gives the percentage parasitemia inhibition. Artesunate is an antimalarial drug with molecular formula of $\text{C}_{19}\text{H}_{28}\text{O}_8$. It was used as standard because of the presence of –COOH group in both Artesunate and H_3CT . The structure is shown in Figure S2

Table 9: Percentage parasitemia inhibition

Drugs/Dose (mg/kg)	% Parasitemia	%inhibition (PC)
$[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ 25	6.77 ± 1.76	78.59
$[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ 25	5.00 ± 0.58	84.02
Artesunate 5	4.00 ± 0.58	87.22
Dist. Water 5mL/kg	31.33 ± 3.38	00.00

The research work by Gopalakrishnana and Kumar has shown that artesunate induces DNA double-strand breaks in *P. falciparum* in a physiologically relevant dose- and time-dependent manner leading to parasite death (Gopalakrishnana and Kumar, 2015). It was observed from Table S3 that the effect of the samples on weight (Wt), PCV and Hb of the infected mice treated did not show an orderly pattern of dose dependent effect. However, the effect was significant comparing the negative control. $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ show a significant reduction with the effect of the sample on PCV dose dependently though in a negative manner. The effect of sample on Hb concentration shows the same effect as in PCV. Table 9 results show a general dose dependent significant parasitemia inhibition compared with the negative control with $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ having the highest inhibition of 84.02 % at 50 mg/kg close

to the value (87.22 %) of the standard drug Artesunate 5 mg/kg. This implies that $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ can be used as anti-malarial drugs after further tests.

4.0 Conclusion

A tripodal Schiff base ligand derived from 2,4,6-trichloro-1,3,5-triazine and its novel trinuclear Dy(III) and Er(III) Salen Capped Complexes were synthesized and characterized based on various physicochemical and spectral studies. The ligand was found to be tripodal and to coordinate to the ligand complexes via the carboxylic group. *In vitro* antimicrobial activity indicate that the trinuclear complexes are more active against the test micro-organisms relative to the ligand; with $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ having the highest antimicrobial activity. Acute toxicity studies reveal that $[\{\text{Dy}(\text{salen})\}_3(\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$ is safe and have



a wide range of effective dose (ED_{50}). *In vivo* antimalarial studies indicate that $[Dy(salen)_3(H_3CT)]^{3+} \cdot 3H_2O$ could serve as an effective anti-malarial agent since it has parasitemia inhibition of 84.02 % at 50 mg/kg close to the value (87.22 %) of the standard drug Artesunate 5 mg/kg. DFT calculations carried out enhanced more understanding of H_3CT at the molecular level. The molecular docking results revealed the binding mode of H_3CT complexed with *Staphylococcus aureus*.

5.0 Acknowledgments

The authors thank Dr. AnicetSiakamWendji, Technische Universität, Dortmund, Germany for recording the NMR and IR spectra. 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).

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Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper and are responsible for the contents and writing of the paper. The authors have filed a patent application for the synthesis of $[\{ \text{Dy/Er(salen)} \}_3 (\text{H}_3\text{CT})]^{3+} \cdot 3\text{H}_2\text{O}$.

