Trop J Nat Prod Res, June 2024; 8(6):7547-7553 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Synthesis, Characterization and Biological Potentials of 1-phenylacetyl-pyrrolidine-2-Carboxyaldehyde and its Lanthanoid Complexes

Ocheni Adejoh[1]*, Ukoha O. Pius[2], Abraham O. Joseph[3]

[1]*Department of Pure and Industrial Chemistry, Kogi State University Anyigba, Nigeria*
[2]*Department of Chemistry,University of Nigeria Nsukka, Enugu State, Nigeria*
[3]*Department of Microbiology, Kogi State University Anyigba, Nigeria*

ARTICLE INFO

Article history:
Received 08 April 2024
Revised 14 May 2024
Accepted 17 May 2024
Published online 01 July 2024

ABSTRACT

Lanthanoid complexes have found potential application in diverse fields including biology and medicine. The present study aim to synthesize a new dione derivative of 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde and its Lanthanoid complexes and investigate their antimicrobial and antimalarial activities. The ligand 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde (L) and its Lanthanoid complexes; $Ce(L)_3](NO_3)_3.2H_2O$,$[Pr(L)_3](NO_3)_3.2H_2O$, and $[Nd(L)_3](NO_3)_3.2H_2O$were synthesized and their structures elucidated by spectroscopic techniques, including ultraviolet-visible (UV-Vis), Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR) spectroscopy, magnetic susceptibility and elemental analysis.The antimicrobial activity of the ligand and its complexes was evaluated by the agar-well diffusion method. The antimalarial activity of Nd(III) complex was assessed using the Peter's 4-day suppressive test in mice. Acute toxicity of Nd(III) complex was evaluated using the Lorke method. The synthesized compounds exhibited UV absorption between 282-380 nm. The FTIR spectra of the compounds showed absorption peaks for carbonyl (C=O) stretch at 1691-1703 cm^{-1}. The ^{1}H-NMR for the ligand and its complexes appeared as multiplets between 7.29-7.50 ppm and their ^{13}C-NMR spectra displayed signals between 127.07-135.40 ppm, and at 173 ppm attributed to the phenyl ring and the carbonyl carbons, respectively.The magnetic susceptibility results revealed the complexes were paramagnetic. Neodymium (III) complex ($[Nd(L)_3](NO_3)_3.2H_2O$) exhibited the most potent antimicrobial activity inhibiting more of the test organisms than its congeners.$[Nd(L)_3](NO_3)_3.2H_2O$exhibited a dose-dependent antimalarial activity with a mild to moderate reduction in percentage parasitaemia. Acute toxicity test showed an LD_{50}value of 2,154.07 mg/kg for $[Nd(L)_3](NO_3)_3.2H_2O$. The complex is relatively safe and has potential for use as antimicrobial and antimalarial agent

Keywords: Synthesis, Characterization, Biological Activity, Lanthanoid, Complexes.

Introduction

In the past few decades, the lanthanoids coordination chemistry has been an area of research focus due to their wide applications in luminescence studies, catalysis, magnetism and diagnostic tools in biology.[1]Selected lanthanoids such as cerium(III), praseodymium(III) and neodymium(III) complexes are mostly of interest due to their potential application in these areas.[2]Phenylacetyl chloride is a good starting material for synthesizing derivatives of multifunctional ligands and chelating agents with promising bioactivity. It is used as a key precursor in the synthesis of vialinin B which is a potent inhibitor of TNF alpha production and building blocks of carbonyl compounds.[3]

The choice of phenylacetylchloride as a starting material is attributed to its reactivity and potency in molecular design. The first and only reported dione bearing phenylacetyl moiety, homoserine lactone, was used for quorum sensing but little information are available on its metal complexes.

*Corresponding Authors: E-mail: Ochenades@yahoo.com
Tel: 08064664323

Citation: Adejoh O, Pius OU, Joseph OA. Synthesis, Characterization and Biological Potentials of 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde and its Lanthanoid Complexes. Trop J Nat Prod Res. 2024; 8(6): 7547-7553. https://doi.org/10.26538/tjnpr/v8i6.34

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Therefore capping this compound and its derivatives with lanthanides is expected to produce new compounds that could be exploited for their potent biological properties.[4]

Despite recent advances in malaria therapy, the infection remains a major public health problem affecting almost half a billion people worldwide and killing almost a million per annum.[5]Due to the few efficient antimalarial agents and the frequent development of resistance of malaria parasite to conventional drugs which consequently limit the effective treatment of the infection,[30] there is an urgent and continuous need to develop new compounds specifically the metal-based compounds with potent antimalarial activity.In the current study, effort has been made to synthesize, characterize novel 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde and its lanthanoid complexes and investigate their anti-microbialand anti-malarial activities. Evidence from existing literature suggest potential activities of related compounds against a wide range of microorganisms.

Materials and Methods

Chemicals/Reagents

All reagents used were of analytical grade, only few were of reagent grade and they were all used without further purification.Phenylacetylchloride (98%) and pyrrole-2-carboxyaldehyde (98%) were obtained from Sigma Aldrich. The metal salts, cerium(III) nitrate hexahydrate (99%), praseodymium(III) nitrate hexahydrate (99.9%), and neodymium(III) nitrate hexahydrate (99.9%) were equally obtained from Sigma Aldrich (Germany). Other reagents including chloroform (98%), ethanol (98%), and

tetrahydrofuran (THF) were of analytical grade and were obtained from Fluka.

Instruments/Equipment

All weighing were carried out using a PB303-N Mettler electronic balance. Corning PG-420D magnetic stirrer and thermostat hot plate were used for the heating and stirring of reaction mixtures. Conductivity meter of LF 90 WTW model was used for conductivity measurements.Thermogravimetric analysis (TGA) was done using a P erkin Elmer TGA 7 Series. Synergy Mx Biotex spectrometer was used for the UV-visible spectral analysis. The IR Spectra were determined using Perkin Elmer Universal ATR100 Fourier Transform ed infrared spectrophotometer. The nuclear magnetic resonance spectra were recorded using Bruker 300/400 MHz Spectrophotometer. The mass spectra were generated by Electrospray ionization on Bruker MicroOTOF Mass Spectrometer in positive ion mode using pneumatically assisted electrospray ionization: capillary voltage 2900V; sample cone voltage 15V; extracti on voltage 1V; source temperature 80°C; desolvation temperature 160 °C.[27] The microelemental analysis was carried out using Vario EL cub e superuser Elementar Analysansysteme GmbH serial number 191810 72. UKZN and the magnetic susceptibility were obtained on the Magnetic Susceptibility Balance of Sherwood Scientific model.

Preparation of ligand (L)

A dione derivative of 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde (L) was prepared following the method described by Bakr et al. (2012).[6]To a solution of 0.476 g of Pyrrol-2-carboxyaldehyde in 25 mL of chloroform, 0.66 mL of phenylacetylchloride was added and refluxed at room temperature for 20 min. The black crystals obtained were washed with cold water and recrystallized in ethanol (Figure1).

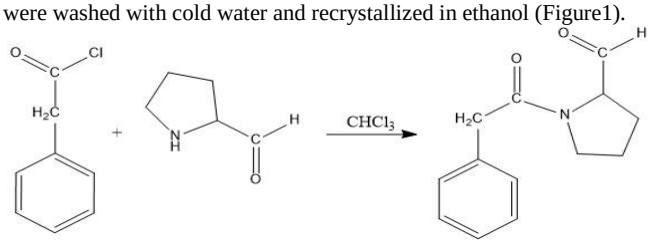

Figure 1: Synthesis of 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde (L)

Synthesis of the complexes

The Ce(III), Pr(III) and Nd(III) complexes of the ligand was prepared according to the method described by Heinosuke (1967).[7]Generally, the ligand(L) was reacted separately with the metal salts in a mole ratio of 2:1 under reflux for 2 h and the products formed were filtered and stored in the desiccators for further use (Equation 1).

$$Ln(NO_3)_3.6H_2O + L \xrightarrow{\text{Ethanol}} [Ln(L^1)_3](NO_3)_3.2H_2O \quad \text{…….. (Eqn. 1)}$$

Evaluation of antimicrobial activity

The antimicrobial activity of the ligand and complexes was done using agar well diffusion method as reported by Ocheniand Ukoha (2023)[8] and Ocheniet al. (2024).[28]

Evaluation of antimalarial activity

The Antimalarial activity of the ligand and complexes was carried out in vivousing Peter's 4-day suppressive test in mice.[9]

Acute toxicity test/LD_{50} determination

The acute toxicity of the ligand and complexes was evaluated according to the method of Lorke(1983).[10]Albino mice (20-25 g) of either sex were used. The median lethal dose (LD_{50}) was determined for each of the compounds using probit analysis.

Statistical analysis

Data were presented as means ± standard error of mean (SEM). Comparison between means was done using one-way analysis of variance (ANOVA). P-value less than 0.05 was regarded as significant. The statistical package for social science (SPSS) version 20 was used for the analysis.

Results and Discussion

Physical characteristics of the compounds

The percentage yield of L, $[Ce(L)_3](NO_3)_3.2H_2O$, $[Pr(L)_3](NO_3)_3.2H_2O$ and $[Nd(L)_3](NO_3)_3.2H_2O$ are 95%, 80%, 73% and 65%, respectively. Freshly prepared L was black and crystalline in nature but the Lanthanoid complexes were hygroscopic when exposed to air. This observation has been made for lanthanoidpyrrolidine complexes with increase in hygroscopic properties on moving along the Ln series.[11] The ligand L Fig 1 had melting point (m.p) of 150-153°C, and the correspondingcomplexes $[Ln(L)_3](NO_3)_3.2H_2O$ had m.p 102-103°C and appeared as a gray amorphous compound for Ce complex, while Pr complex had m.p 104 -106°C and appeared as a purple amorphous compound, and Nd complex had m.p103-105°C and appeared as apurple amorphous compound.The compounds were soluble in ethanol but insoluble in diethyl ether, acetone, THF, chloroform and water. The stoichiometry of M:Lwas 1:3 and the molar conductivity measurements (µS/cm) of 0.001moldm^{-3}solution of the compounds were 90.9 for L, 500.0, 390.0 and 315.0 for Ce, Pr and Nd complexes, respectively. Nitrate test showed the presence of NO_3^- as counter ions in the primary valences of the complexes. The second derivative thermogravimetric curve of $[Pr(L)_3](NO_3)_3.2H_2O$ (Figure 2) indicate the loss of coordinated water molecule at 100°C,whereas, at 94.95°C, a phenyl group was indicated by 2.38 mg (11.94%) reduction in the mass of the compound. Other decomposition at 250°C is aloss of 16 mg (80%) in mass due to complete degradation of the complex.Reportson praseodymium complex of pyrrolidine have show n similar trend.[12]The thermogravimetric curve of $[Nd(L)_3](NO_3)_3.2H_2O$ (Figure 3) showed similar pattern to that of $Pr(L)_3](NO_3)_3.2H_2O$ due to similarity in thephysicochemical properties of these complexes.Si milar reports have been made for Pr(III) and Nd(III) complexes of pyr rolidine derivatives.[12]

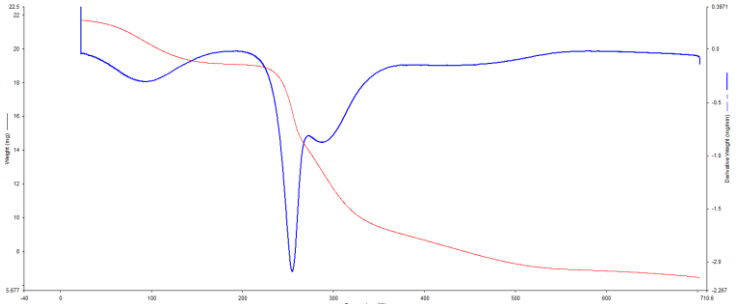

Figure 2: Thermo gravimetric analysis (TGA) Curve of $Pr(L)_3](NO_3)_3.2H_2O$

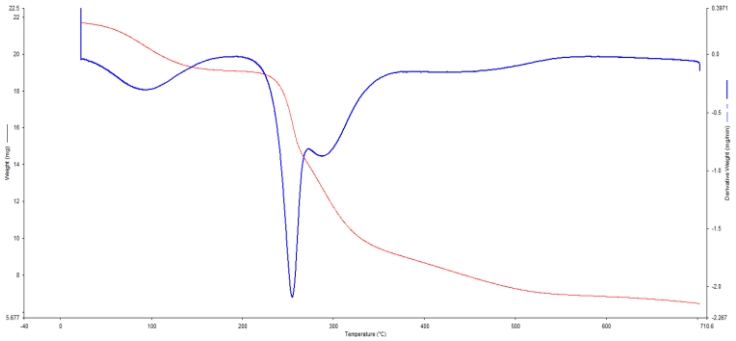

Figure 3: Thermo gravimetric analysis (TGA) Curve of $[Nd(L)_3](NO_3)_3.2H_2O$

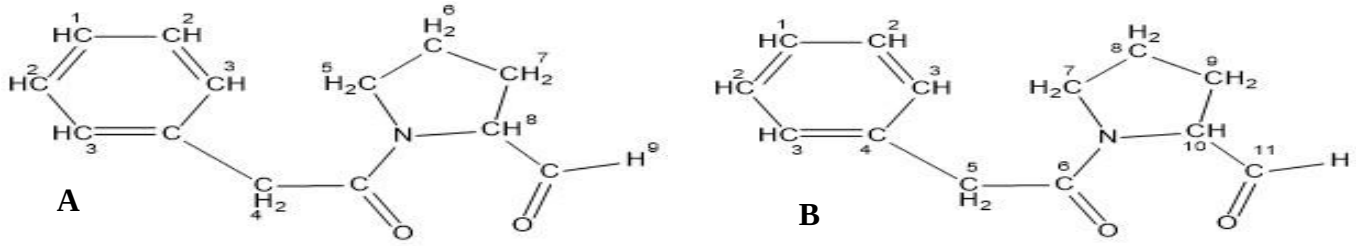

Figure 4: Structure of 1-phenylacetyl–pyrrolidine-2–carboxyaldehyde (L) showing;**(a):**proton numbering, **(b):** carbon numbering

Analytical data of the ligand (L)
m.p 150-153^{o}C, 95%, conductivity 0.001 moldm^{-3} 90.9 µs/cm. UV λ_{max}380 nm ε 253.0 dm^3 mol^{-1} cm^{-1}. IR (KBr) 3062, 3019, 2986, 1701, 1640, 1550 698 cm^{-1}. ^{1}H-NMR (400 MHZ, DMSO) δ 2.3 (s, 2H, H-4), 2.9 (s, 1H, H-9), 4.0 (m, 7H; s, 2H, H-4; t, 2H, H-5; m, 2H, H-6; m, 2H, H-7; t, 1H, H-8; s, 1H, H-9), 7.29 (m, *J* = 7.2Hz, 5H, ArH). ^{13}C-NMR (100 MHZ, DMSO) δ 31.12-41.14 (C-5, C-7, C-8, C-9, C-10), 127.07 (C-1), 128.72 (C-2), 129.75 (C-3), 135.40 (C-4), 173 (C-6, C-11). Elemental Anal calcd for $C_{13}H_{15}NO_2$, C 66.43%, H 6.7%, N 5.76%, Found C 66.53%, H 5.21%, N 4.82%.

Analytical data of [Ce(L)$_3$](NO$_3$)$_3$.2H$_2$O
m.p 102-103^{o}C, 80%, conductivity 0.001 moldm^{-3} 500 µs/cm. UV λ_{max}280 nm ε 283.8 dm^3 mol^{-1} cm^{-1}. IR (KBr) 3383, 3087, 3028, 2969, 1691, 1621, 1545, 1229, 751, 675, 392 cm^{-1}. ^{1}H-NMR (400 MHZ, DMSO) δ 2.0 (s, 2H, H-4), 2.5 (s, 1H, H-9), 3.5 (m, 7H; s, 2H, H-4; t, 2H, H-5; m, 2H, H-6; m, 2H, H-7; t, 1H, H-8; s, 1H, H-9) 7.5 (m, *J* = 6.55Hz, 5H, ArH). ^{13}C-NMR (100 MHZ DMSO) δ 31.12-41.14 (C-5, C-7, C-8, C-9, C-10), 127.07 (C-1), 128.72 (C-2), 129.75 (C-3), 135.40 (C-4), 173 (C-6, C-11).

Analytical data of [Pr(L)$_3$](NO$_3$)$_3$.2H$_2$O
m.p 104-106 ^{0}C, 73%, conductivity 0.001 moldm^{-3} 390 µs/cm. UV λ_{max}282 nm ε 283.1 dm^3 mol^{-1} cm^{-1}. IR (KBr) 3627, 3085, 3062, 2923, 1693, 1619, 1543, 1226, 751, 602, 395cm^{-1}. ^{1}H-NMR (400 MHZ, DMSO) δ 2.1 (s, 2H,H-4), 2.6 (s, 1H, H-9), 3.5 (m, 7H; s, 2H, H-4; t, 2H, H-5; m, 2H, H-6; m, 2H, H-7; t, 1H, H-8; s, 1H, H-9; 7.5 (m, *J* = 7.29Hz, 5H, ArH). ^{13}C-NMR (100 MHZ DMSO) δ 31.12-41.14 (C-5, C-7, C-8, C-9, C-10) 127.07 (C-1), 128.72 (C-2) 129.75 (C-3) 135.40 (C-4) 173 (C-6, C-11).

Analytical data of [Nd(L)$_3$](NO$_3$)$_3$.2H$_2$O
m.p 103-105 ^{0}C, 65% conductivity 0.001moldm^{-3}315.0µs/cm. UV λ_{max}300 nm ε 282.3 dm^3 mol^{-1} cm^{-1}. IR (KBr) 3187, 3063, 3033, 2970, 1692, 1579, 1496, 1231, 751, 674, 391cm^{-1}, ^{1}H-NMR (400 MHZ, DMSO) δ 2.1 (s, 2H, H-4), 2.6 (s, 1H, H-9), 3.5 (m, 7H; s, 2H, H-4; t, 2H, H-5, m, 2H, H-6; m, 2H, H-7; t, 1H, H-8; s, 1H, H-9; 7.5 (m, *J* = 6.36Hz, 5H, ArH). ^{13}C-NMR (100 MHZ DMSO) δ 31.12-41.14 (C-5, C-7, C-8, C-9, C-10), 127.07 (C-1), 128.72 (C-2), 129.75 (C-3), 135.40 (C-4), 173 (C-6, C-11).

Interpretation of UV spectra
The UV spectra of 1-phenylacetyl–pyrrolidine-2–carboxyaldehyde (L) and its complexes showed absorption bands between 280-380 nm. Comparison of the absorption bands of the complexes with that of the ligand indicate mainly intraligand electronic transitions of π^* - π and π^* - n from the conjugated aromatic ring and the oxygen hetero atom. This observation is in accordance with the structure of the ligand, and similar reports have been made previous study.[13]The shift in the absorption band in all the complexes is due to spin-orbit coupling enhanced by π-π^* and spin-forbidden ligand-metal charge transfer. These observations have been reported for oxygen ligand coordinated with lanthanoid ions.[13,14]The absorption spectra of Ce(III), Pr(III) and Nd(III) complexes of this ligand showed no significant difference because unlike the d-orbitals of the transition metal ions, the f orbital of the lanthanoidions are almost unaffected by the chemical environment and the energy levels are the same as in the free ion, due to very effective shielding by the overlying 5s^2 and 5p^6 shells, and the electronic spectra of lanthanoid ions resulting from f-f transitions are larporte-forbidden and weak in nature.[15,16]

Interpretation of FT-IR Spectra
The FTIR spectrum of l-phenylacetylpyrrolidine-2-carboxyaldehydeshows broad absorption in the region of 3627-3187 cm^{-1}assigned to stretching of O-H of hydrated complexes, this bands was absent in the ligand. The aromatic C-H stretch appeared between 3087 - 3019 cm^{-1} for the ligand and complexes, whereas, the aliphatic C-H stretch resulting from the phenyl ring and methylene protons appeared between 2986-2923cm^{-1}. This is in accordance with observed spectrum of octanal, illustrating typical aldehyde absorption characteristics.[17] The absorption of C=O stretch occurred at 1703 cm^{-1} for the ligand and for the complexes it occurred between 1691-1693 cm^{-1}. This isin agreement with the observed C=O band responsible for the coagulative capacity in water purification.[18] The Ce(III), Pr(III) and Nd(III) complexes showed significant shift in the infrared frequencies for the carbonyl group C=O with a strong absorption band at 1691, 1693, and 1692cm^{-1}, respectively. This is an evidence of ligation via the oxygen atom of the carbonyl group. Similar assertions have been made for complexes containing carbonyl group.[19,20] The absorptions between 1496-1640 cm^{-1} are due to C=C stretch of the aromatic ring. Characteristic aromatic compounds show absorption for C=C stretch in this region. The absorption due to the nitrate (NO_3) group of the complexes appeared between 1231-1226 cm^{-1}which is in agreement with values observed for coordinated nitrate group of cerium(III) complex of piperidin-4-one.[21]The Ln-O stretch appeared at 392, 395 and 391 cm^{-1},for the Ce(III), Pr(III) and Nd(III) complexes, respectively. These values are in agreement with those reported for Ln-O stretches in lanthanoid complexes of oxygen donors with average absorption band at 405cm^{-1}.[22]The water molecules in the cerium, praseodymium and neodymium complexes absorbed between 750-751 cm^{-1}. This was supported by therrmogravimetric analysis of the complexes which indicated a decomposition of water from the complexes at 100^{o}C.

Interpretation of magnetic data
The magnetic properties of the ligand complexes show the expected behaviors for isolated complexes of Ce(III),Pr(III), and Nd(III). Thus, the product of the magnetic susceptibility and temperature, X_mT (Table 3) and the $\mu_{B.M\ Cal.}$ (Table 1) agrees with the calculated values, $\mu_{B.M}$ calculated for ground term $^3H_4$, $^2f_{5/2}$, and $^4I_{9/2}$ of the complexes. The decrease observed in the complexes can be attributed to the progressive depopulation of the higher energy stark levels that arise from the splitting of the $^3H_4$, $^2F_{5/2}$, and $^4T_{9/2}$ ground levels due to the ligand field. Similar observation has been reported by Patricia *et al*. (2018).[23]Secondly, due to orbital coupling, the complexes show lower values than the calculated values. The observed behavior indicates that all the complexes are paramagnetic. The results of the elemental analysis for L, as presented in Table 2 revealed the percentage compositions of C, H, N and S in the ligand. The calculated and found percentages are in close agreement with each other.

*Nuclear Magnetic Resonance Spectra of 1-phenylacetyl–pyrrolidine-*2–carboxyaldehyde and the Metal Complexes
Figure 4a shows the proton numbering of the ligand and the spectral data presented in Table 10.

Table 1: Magnetic Properties of the Compounds Compared with Calculated Values

Compounds	G. state	Electrons	S	L	J	g	μ_{eff}	μ_B
L	N.D	N.D	N.D	N.D	N.D	N.D	-0.39	N.D
$[Ce(L)_3](NO_3)_3.2H_2O$	$^2f_{5/2}$	1	1/2	3	5/2	6/7	1.69	2.54
$[Pr(L)_3](NO_3)_3.2H_2O$	$^3H_4$	2	1	5	4	4/5	3.27	3.58
$[Nd(L)_3](NO_3)_3.2H_2O$	$^4I_{9/2}$	3	3/2	6	9/2	8/11	2.3	3.62

Table 2: Elemental composition of L

Element	Found % values	Calculated %values	Difference
C	66.53	66.43	0.10
H	5.21	6.17	0.96
N	4.82	5.76	0.94
S	0.00	0.00	0.00

The ^{1}H-NMR signals in the region of 7.29 ppm which appeared as multiplet accounted for the phenyl ring protons and separating the coupled protons by assigning different values was difficult. Similar assertion has been made in previous study.[13] The protons of the pyrrolidine moiety equally showed some level of multiplicity due to coupling of neighboring protons. These peaks appeared between 3.5 - 4.0 ppm. Characteristic aliphatic protons signals appeared in this region which was present in all the complexes. These values are in agreement with experimental reports on 4-(1-pyrrolidinyl) piperidine.[24] The methylene (CH_2) protons appeared as singlet (2H, s) at 2.3 ppm and the aldehyde proton also appeared as singlet (1H, s) at 2.9 ppm. The chemical shift for the aldehyde proton in the complexes shifted significantly which is an indication of ligation through the C=O group. The proton number 5, 6, 7 and 8 showed multiplet signals around 4.0 ppm with *J* = 92.71Hz. The integrated chemical shifts confirm to 7 aliphatic protons,The structure of the ligand showing the carbon numbering is presented in Figure 4band this shows significant signals that are in agreement with the structure of the ligand. The signal at 173 ppm is assigned to the carbonyl carbons at C-6 and C-11 which correspond to the carbonyl carbons of phenylacetyl moiety and the carbonyl carbon of the pyrrolidine-2–carboxyaldehyde. However, the shift which appeared in the ligand at 173 ppm were not present in the Ce(III) and Pr(III) complexes. This is an evidence of complex formation via the carbonyl group. The shift on the other hand in the case of Nd(III) complex could still be attributed to formation of complex. The result is in agreement with reports for ^{13}C-NMR spectrum of vinyl pyrrolidone Cu(II) complexes in which there was a shift to a higher frequency.[25]

Antimicrobial properties of the ligand and complexes

The antimicrobial properties of 1-phenylacetyl-pyrrolidine-2-carboxyaldehyde (L) ispresented in Table 3,and its neodymium complexes is shown in Table 4. The result shows that the ligand had activity only on *Bacillus subtilis* with minimum inhibitory concentration of 12.5 mg/mL and no activity was observed on other test organisms. The cerium and praseodymium complexes showed no activity against any of the test organism. However, the neodymium complex show significant activity against *Staphylococcus aureus, Bacillus substilis, Escherichia coli, Klebisella pneumonae, Salmonella typhi* and *Candida albicans*, with minimum inhibitory concentration of 25 mg/mL, 12.5 mg/mL, 12.5 mg/mL, 25 mg/mL, 50 mg/mL, and 12.5 mg/mL, respectively. The neodymium complex showed no activity against *Pseudomonas aeruginosa, Streptococcus pneumoniae* and *Aspergillus niger*. This result is in agreement with the activities demonstrated by transition metal complexes,[29] as well as lanthanide complexes of dione derivatives of p yrrole-2carboxyaldehyde.[26,28] The neodymium complex, $[Nd(L)_3](NO_3)_3.2H_2O$) which showed thehighestantimicrobial activity was evaluated for it s antimalarial activity and acute toxicity.

Antimalarial activity of $[Nd(L)_3](NO_3)_3.2H_2O$

The effects of the Nd(III) complex on pack cell volume (PCV) of *Plas modium berghie* infected mice is shown in Table 5. The result shows that $[Nd(L)_3](NO_3)_3.2H_2O$ has a dose-dependent effect on PCV with a percentage increase in PCV of 9.0% and 16.2% at doses of 250 mg/kg and 500 mg/kg bw, respectively. Similarly, the compound caused a significant and a dose-dependent increase in hemoglobin (Hb) concentration (Table 6). The Hb concentration increased by2.62% at 250 mg/kg, and by 7.24% at 500 mg/kg.For the red blood cell (RBC) count, treatment with Nd(III) complex led to a significant increase in RBC count, and this effect was higjer than that observed for the artesunate (positive control) treated group (Table 7). These observations suggest that the compound has antianemic effect, which is in agreement with findings from previous studies.[8,28]The effect of the complex$[Nd(L^1)_3](NO_3)_3.2H_2O$ on parasthemia of mice infected with *Plasmodium berghie* revealed that the complex resulted in a mild to moderate decrease in percentage parasitaemia of the infected mice,

Table 3: Antimicrobial activity of 1-phenylacetyl–pyrrolidine -2–carbonyaldehyde(L)

Concentration(mg/mL)	Minimum Inhibitory Concentration (mg/mL)								
	S.aureus	***B.subtilis***	***E.coli***	***P. aeruginosa***	***K. pneumonia***	***S. Typhii***	***S. pneumonia***	***C. albicans***	***A.niger***
100	-	14	-	-	-	-	-	-	-
50	-	11	-	-	-	-	-	-	-
25	-	9	-	-	-	-	-	-	-
12.5	-	8	-	-	-	-	-	-	-
6.25	-	-	-	-	-	-	-	-	-
Gent 30 µg/mL	16	24	21	15	19	16	20	-	-
Nystatin 30 µg/mL	-	-	-	-	-	-	-	17	13

Table 4: Antimicrobial Activity of Nd(III) Complex

Concentration mg/mL	Minimum Inhibitory Concentration (mg/mL)								
	S.aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***	***K. pneumonia***	***S. Typhii***	***S. pneumonia***	***C. albicans***	***A.niger***
100	13	16	14	-	11	12	-	14	-
50	11	13	11	-	10	9	-	12	-
25	9	10	9	-	8	-	-	9	-
12.5	-	8	7	-	-	-	-	7	-
6.25	-	-	-	-	-	-	-	-	-
Gent 30 µg/mL	16	24	21	15	19	16	20	-	-
Nystatin 30 µg/mL	-	-	-	-	-	-	-	17	13

Table 5: Effects of Nd(III) Complexon Park Cell Volume (PCV) of *Plasmodium berghei*Infected Mice

Compound	Dose (mg/kg)	Initial PCV (%)	After Ind. PCV (%)	Final PCV (%)	Change in PCV (%)
$[Nd(L)_3](NO_3)_3.2H_2O$	250	46.48 ± 0.28	44.40 ± 1.99	48.40 ±2.01	9.0
$[Nd(L)_3](NO_3)_3.2H_2O$	500	42.44 ± 0.242	39.40 ± 0.68	45.80 ± 0.80	16.2
Artesunate (Positive control)	5	43.18 ± 0.23	33.00 ± 1.05	44.00 ± 0.71	33.3
Distilled water (Negative control)		42.62 ± 0.35	38.00 ± 1.38	32.80 ± 0.86	-13.7

Table 6: Effects of Nd(III) Complexon Hemoglobin (Hb) of*Plasmodium berghei*Infected Mice

Compounds	Dose (mg/kg)	Initial Hb (g/dL)	After Ind. Hb (g/dL)	Final Hb (g/dL)	Change in Hb (%)
$[Nd(L)_3](NO_3)_3.2H_2O$	250	14.04 ± 0.16	13.76 ± 0.16	14.12 ± 0.30	2.62
$[Nd(L)_3](NO_3)_3.2H_2O$	500	14.12 ± 0.21	13.54 ± 0.18	14.52 ± 0.16	7.24
Artesunate (Positive control)	5	13.42 ± 0.22	13.65 ± 0.24	14.28 ± 0.14	4.61
Distilled water (Negative control)		14.00 ± 0.089	13.64 ± 0.12	13.46 ± 0.29	-1.32

Table 7: Effects of Nd(III) Complexon Red Blood Cell (RBC) countof*Plasmodium berghei*Infected Mice

Compounds	Dose (mg/kg)	Initial RBC (cells x 10^6)	After Ind. RBC (cells x 10^6)	Final RBC (cells x 10^6)	Change in RBC (%)
$[Nd(L)_3](NO_3)_3.2H_2O$	250	4.28 ± 0.06	3.64 ± 0.21	4.22 ± 0.07	16.7
$[Nd(L)_3](NO_3)_3.2H_2O$	500	4.12 ± 0.31	3.85 ± 0.05	4.44 ± 0.06	12.8
Artesunate (Positive control)	5	4.92 ± 0.19	3.82 ± 0.16	4.27 ± 0.09	13.2
Distilled water (Negative control)		4.46 ± 0.29	3.77 ± 0.09	3.50 ± 0.14	-7.8

Table 8: Effects of Nd(III) Complex on Parasthemia of *Plasmodium berghei*Infected Mice

Compound	Dose (mg/kg)	Initial parasthemia (%)	Final Parasthemia (%)	Change in Parasthemia (%)
$[Nd(L)_3](NO_3)_3.2H_2O$	250	33.80 ± 2.18	27.60 ±4.48	18.34
$[Nd(L)_3](NO_3)_3.2H_2O$	500	32.40 ± 2.23	17.80 ± 2.24	45.06
Artesunate (Positive control)	5	30.20 ± 1.93	3.40 ± 0.75	88.74
Distilled water (Negative control)		32.40 ± 2.23	37.20 ± 1.93	-14.81

Table 9: Acute Toxicity Effect of $Nd(L^1)_3](NO_3)_3$

Group	Mice	Dose of compound administered (mg/kg)	Weight of mice (g)	Amount of compound administered (mg/mL)	No. of Death	Time of Death (24h after admin.)
1	Head	10	25	0.25	-	-
	Trunk	10	27	0.27	-	-
	Tail	10	28	0.28	-	-
2	headtail	100	24	2.4	-	-

	Tail trunk	100	27	2.7	-	-
	Head Trunk	100	26	2.6	-	-
3	R. Hind	1000	25	25	-	-
	L. Hind	1000	23	23	-	-
	B. Hind	1000	21	21	-	-
One animal/group	RF	1000	20.5	20.5	-	-
(Day 2)	LF	1600	16.8	26.88	-	-
	BF	2900	15.2	44.08	1/1	20.50min
	R.S	5000	15.0	75.0	1/1	13.14min

Table 10 Proton (^{1}H) and ^{13}C-NMR Spectral Data of 1-phenylacetyl-pyrrolidine-2-carboxyldehyde (L^1) and its $[Ln(L)_3](NO_3)_3$ Complexes

Compounds	**(^{1}H) and ^{13}C-NMR Spectral Data**						
L	^{1}H	7.29m	4.0m	2.9(1H,s)	2.3(2H,s)		
	^{13}C	173	135	129	128	127	40(m)
$[Ce(L)_3](NO_3)_3$	^{1}H	7.5(m)	3.5(m)	2.5(1H,s)	2.0 (2H,s)		
	^{13}C	135	129	128	127	40(m)	30(s)
	^{13}CDEPT		129	128	127	39(m)	30(s)
$[Pr(L)_3](NO_3)_3$	^{1}H	7.5(m)	3.5(m)	2.6(1H,s)	2.1(2H,s)		
	^{13}C	135	129	128	127	40	39
$[Nd(L)_3](NO_3)_3$	^{1}H	7.3(m)	3.5(m)	2.5(1H,s)	2.1(2H,s)		
	^{13}C	172	135	129	128	127	40(m)

S = singlet, m = multiplet, Ln = Ce, Pr and Nd.

with a percentage decrease in parasitaemia of 18.34% and 45.06% at250 mg/kg and 500 mg/kg bw, respectively. However, these values were lower than that of the positive control (artesunate) which resulted in88.74% decrease in parasitaemia after treatment of the mice at a dose of 5 mg/kg (Table 8). The higher value recorded in this case by the positive control drug does not make it more efficacious than the synthesized compound $[Nd(L^1)_3](NO_3)_3.2H_2O$, since the compound recorded better in RBC and other haematological parameters determined in this study. Secondly, the use of artesunate over time could lead to the development of parasite resistance to the drug, hence, the need for new drugs, especially metal-basedligands to tackle the menace of malaria parasite, and that do not possess the side effects like dizziness, abdominal pain, diarrhea, injection site pain, fever with body pain and anemia that are associated with artesunate therapy.

Acute toxicity effect of $[Nd(L)_3](NO_3)_3.2H_2O$

The Acute Toxicity effect of neodymium complexes shown in Table 9. No mortality of mice was recorded up to a dose of 1600 mg/kg. Whereas, at doses of 2900 and 5000 mg/kg, the animal died. The LD_{50} which was calculated from the geometric mean of 1600 mg/kg and 2900 mg/kg was found to be 2,154.07 mg/kg.

Conclusion

The present study was undertaken to investigate the antimicrobial and antimalarial potentials of a novel dione derivative synthesized from the reactions of phenylacetylchloride and pyrrol-2-carboxyaldehyde and its lanthanoid complexes. The findings have shown that the ligand and its complexes possess interesting biological and magnetic properties. The LD_{50} of the neodymium complex indicate that it is safe for use even at high dose. Further investigation of these complexes on other disease targets and possible mechanism(s) of their activity is highly recommended.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

This research was supported by Kogi State University and TETFund, Ni geria. TETFUND/ES/AST&D/UNIV/ANYIGBA/VOL.1/ 2012/2013 MERGED. No. 9

References

1. Stephen F, Simon J, Pope A, Benjamin AP. Burton-pye Lanthanide Complexes for Luminescence Imaging Applications. Appl Spectrosc Rev. 2005; 40:1 – 31.
2. Oleksandra B, Irina S, Nadiya I, Olena T, Nataliya R, Sergiy S, Oleksandr R. Synthesis, Characterization, and Luminescent Properties of Polymer Complexes of Nd(III) with β-Dicarbonyl Ligands. Nanoscale Res Lett. 2017; 12:338.
3. Sigma-Aldrich. Phenylacetyl chloride. Available at: com/catalog/product/aldrich/P16753.Retrieved 5th January 2020.
4. GueyeMN, Dieng M, Thiam IE, Lo D, Barry AH, Gaye M, Retailleau P. Lanthanide(III) Complexes with Tridentate Schiff Base Ligand, Antioxidant Activity and X-Ray Crystal Structures of the Nd(III) and Sm(III) Complexes. S Afr J Chem. 2017; 70:8-15.
5. Christophe B, William C, Cyrille YB, Maribel N. The therapeutic potential of metal-based antimalarial agents:

Implications for the mechanism of action.Dalton Trans.2012; 41(21):6335-6349.

6. Bakr FA, Rizk EK, Abdel-basset AF, Abdel-Aziz S. 2-Chloroquioline–3– Carbaldehydes, Synthesis, Reactions and applications. Arkivoc. 2012; 1:211 – 276.
7. Heinosuke Y. Infrared Analysis of 2-pyrazolin-5-one derivatives. Appl Spectrosc.1967; 23(1):22-28.
8. Ocheni A and Ukoha PO. Synthesis, Characterization, Antimicrobial and Antimalarial Activities of 5-((2-phenylacetoxy) carbonyl)-1*H*-pyrazole-3-carboxylic Acid and its Ce(III), Pr(III) and Nd(III) Complexes. Trop J Nat Prod Res. 2023; 7(5):3028-3033.
9. Peter W, Portus H, Robinson L. The four-day suppressive *in vivo* anti-malarial test. Ann Trop Med Parasitol.1975; 69:155-171.
10. Lorke D. A new approach to practical acute toxicity testing. Arch Toxicol. 1983;54(4):275-287.
11. Larionov SV, Yu AB. Coordination Compounds of lanthanides with 1,1-dithiolate ligands.Russ J CoordChem.2016;42(5):293-310.
12. Moamen SR, Ibrahim, ME, Mohamed AZ, AbdelMajid AA, Mohamed IK. Spectroscopic, Structure and Electrical Conductivity Studies of Co(II), Ni(II) and Cu(II) Complexes Derived from 4-Acetylpyridine with Thiosemicarbazide.Int JElectrochem Sci.2013;8:9894–9917.
13. Qingrui Z, Xiuyun Y, Ruiping D, Liang Z, Yang Y,Yunhui L. Synthesis and near infrared luminescence properties of series of lanthanide complexes with POSS modified ligands. Mol. 2019; 24(7):1253.
14. Muliadi S, Suminar P, Alfian N, Indah R.The uv-visible, infrared spectra and luminescence analysis of lanthanum(III) and neodymium(III) (diphenyl amino)$_3$-(2,2-bipyridyl) complexes. Int J Appl Engr Res. 2018; 13(6):4049-4052.
15. Chempakam JA, Yesodharan S, Mathunni SS, Kochukittan M. Synthesis and spectroscopic characterization of some lanthanide(III) nitrate complexes of ethyl 2-[2-(1- acetyl-2- oxopropyl)azo]-4,5-dimethyl-3-thiophenecarboxyate. J Serb Chem Soc.2011; 76(2):249–261.
16. Obasi LN, Oruma US, Al-Swaidan IA, Ramasami P, EzeorahCJ,Ochonogor AE. Synthesis,characterization, and antibacterial studies of N-(benzothiazol-2-yl)-4-chlorobenzenesulphonamide and its neodymium(III) and thallium(III) complexes. Mol. 2017; 22(153):1-11.
17. Robert MS, Francis XW, David JK. Spectrometric identific ation of organic compounds.7th ed. John Wiley and sons.Inc. 2005; 86-101 p.
18. Afolabi AF, Oluyamo SS, Fuwape IA. Synthetic characterization of Cellulose from *Moringa oleifera*. J Nig Soc Phys Sci. 2021; 3:140-143.
19. Man S and Sushma A. Synthesis and Spectral Characterization of Praseodymium(III) Complex with New Amino Acid-Based Azo Dye.Int J Inorg Chem. 2012; 2012:Article ID 767080, 6 pages.
20. Guskos N, Paschalidis DG, Majszczyk J, Typek J, Maryniak M. Photoacoustic study of a new neodymium(III) hydrazone complex,Mater Sci-Poland.2005;23(4):1030-1034.
21. Kuppusamy S and Chinniagounder T. Studies of Cerium III Complexes of Piperidin-4-one.Indian J Chem. 2002; 41A:1417-1420.
22. Zhang N, Pan L, Liu M, Willian RR. Some Characteristics of infrared and Raman Spectra and Bonding of a series of Lanthanide complexes with L-Proline. Spectrosc Lett.2006; 30(1):61-70.
23. Patricia G, Samia B, Antonio H, Christian C, Carlos R, Joseph C, Andrés C, Carlos JG. Tuning the structure and properties of lanthanoid coordination polymers with an asymmetric anilato ligand. Magnetochem.2018; 4(6):1-21D.
24. OzgurA, CemalP,Metin B. Experimental and theoretical NMR study of 4-(1-pyrrolidinyl) Piperidine. Bull Chem Soc Ethiop.2011; 25(3):437-442.
25. Anasuya KV, Veeraiah MK, Hemalatha P. Synthesis and Characterization of Poly (Vinyl Pyrrolidone)-Copper (II) Complexes. Res J Chem Sci. 2015; 5(2):6469.
26. SubaraniR and Metilda P. Synthesis, characterization and antimicrobialactivity of transition metal complexes of pyrrole-2-carboxaldehyde with glycine. Int J Sci Engr Res. 2017; 8(9):2229-5518.
27. Patiny L and Borel A. Mass spectrometry of organoaluminium derivatives.J Chem Inf Model. 2013;53:1223.
28. Ocheni A, Pius OK, Eric CH, Nnaemeka N, Christopher OE, Chigozie JON, Chukwujindu MA I, Jayamoorthy K, Oguejiofo TU. Synthesis, Structure, Preliminary antimicrobial and antimalarial studies of 1,1-(piperazine-1,4-diyl)bis(2-phenylethan-1-one) and its lanthanide, Ce(III), Pr(III), and Nd(III) Complexes. J Mol Struct. 2024; 1300(2024):137287.
29. Ahmad W, Khan SA, Munawar KS, Khalid A, Kawanl S. Synthesis characterization and pharmacological evaluation of mixed ligand-metal complexes containing omeprazole and 8-hydroxyquinoline. Trop J Pharm Res. 2017; 16(5):1137-1146.
30. Oladapo JO, Esther OF, Olotomide AF, Adebomi AI.*Insilico* investigation of the Antimalarial Activity of some selected Alkaloids and Terpenoids Present in the Aerial Parts of *Andrographis paniculata*. Trop J Nat Prod Res. 2023; 7(8):3787–3799.