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Original Research Article

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

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ABSTRACT

In the past decade, the lanthanoid coordination chemistry was one of the most focused areas of research due to their wide applications as catalyst, magnetism, luminescence and diagnostic tools in biological studies. In this study, novel pyrazole; 5-((2-phenylacetoxy) carbonyl)-1*H*-pyrazole-3-carboxylic acid derivative and its lanthanoid complexes are designed and tested for potential antimicrobial and antimalarial activities. The binuclear ligand bridge complexes were obtained by the interaction of the ligand with the lanthanide salts. The compounds were characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, Ultraviolet-Visible spectroscopy, Fourier Transform infrared (FT-IR) spectroscopy, Mass spectrometry (MS), Elemental analysis and Magnetic susceptibility measurements. The *in vitro* antimicrobial assay was done by Agar well diffusion method and *in vivo* antimalarial studies were performed based on Peter's method. The results were analysed using one way analysis of variance (ANOVA). The antimicrobial and antiparasitic effects of these compounds were found to be dose-dependent and they showed greater effects at higher doses.

***Keywords*:**Pyrazole, Lanthanoid(III), *Plasmodium falciparum*, antimalarial.

Introduction

Pyrazoles are versatile chemical compounds widely used as core motifs for a good number of compounds due to their interesting chemistry and applications such astheir use in catalysis, as building blocks for other compounds, as agro-chemicals and in medicine.[1-8] Therefore, pyrazole-bearing phenylacetyl group will be a good compound expected to show a wide range of biological activity. The attractiveness of pyrazole and its derivatives is attributed to their versatility that allows for the synthesis of a series of analogues with different moieties in them, thus altering the properties of the resultant compounds. In medicine, pyrazole is found as a pharmacophore in some of the active biological molecules. While pyrazole derivatives have been extensively studied for many applications including their anticancer, antimicrobial, anti-inflammatory, antihyperglycaemic, anti-allergy and antiviral activities, much less have been reported on their metal complexes specifically the lanthanoids even though the metal-based compounds have been shown to impact more activity than the ligands.[9]

The development of new antimalarial drugs is an urgent priority as a result of the increasing prevalence of infections arising from *plasmodium falciparum* parasites.[10] Pyrazole derivatives are designed as part of efforts aimed at synthesizing potent antimalarial agents and the aryl derivatives have been reported to be potent antimalarial agents.[11]

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In the current study, we report new 3,5-disubtitutedpyrazole derivativeswhich are nitrogen and oxygen containing compounds with antiplasmodial activity. Evidence from existing literature shows potential antiplasmodial activity of new compounds containing nitrogen and sulphur.[10]The compounds were synthesized and evaluated for their antiplasmodial activity. They were also screened for their *in vitro* antimalarial activity against chloroquine-resistant strain of *P.falciparum.* The compounds shows more potentactivity thanpositivecontroland exhibited reasonable *in silico* drug- likeness and pharmacokinetic properties.[12]

Materials and Methods

Reagents

All reagents used were of analytical grade, only few were of reagent grade and they were all used without further purification.Phenylacetylchloride (98%), 3,5-pyrazoledicarboxylic acid mono hydrate (97%), and the metal salts were products of Sigma Aldrich.Other reagents like chloroform (98%), ethanol (98%), and tetrahydro furan (THF) were obtained from Fluka.

General Procedure for the Synthesis of 5-((2-phenylacetoxy) carbonyl)-1*H*-pyrazole-3-carboxylic acid

The ligand, 5-((2-phenylacetoxy) carbonyl)-1*H*-pyrazole-3-carboxylic acid was prepared by adopting methods reported in literature.[13,14] To equal mixture of chloroform and ethanol (50 mL), 2.612 g (5 mmol) of 3,5-Pyrazole dicarboxylic acid was added followed by 2.0 mL of phenylacetyl chloride under reflux for 2 h. The solution was left to stand for 2 weeks. A white crystal was obtained by filtration (Scheme 1).

Synthesis of the Complexes

The Ce(III), Pr(III) and Nd(III) complexes of the ligand were prepared according to the method described by Heinosuke (1967).[15] Generally, the ligand was reacted separately with the metal salts using mole ratio 2:1 under reflux for 2 h and the products formed were filtered and stored in the desiccator for further use.

Characterization of the synthesized compounds

The synthesized compounds and their metal complexes were characterized using various spectroscopic techniques including Ultraviolet-Visible spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, Fourier Transform infrared (FT-IR) spectroscopy, and Mass spectrometry (MS).

Antimicrobial activity

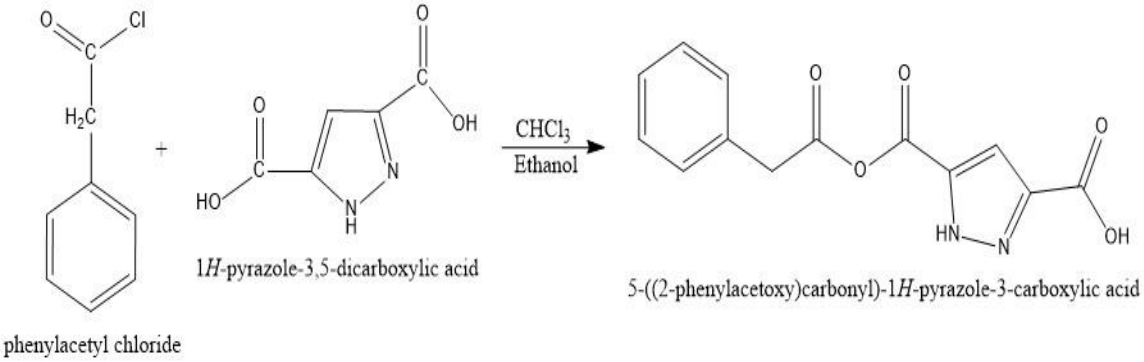
The antimicrobial activity was carried out following agar well diffusion method as reported by Balouiri*et al*., 2016.[16]

Antimalarial activity assay

The Antimalarial activity was carried out using Peter's 4-day suppressive test.[17]

Statistical analysis

Results were expressed 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 were regarded as significance. The statistical package for social science (SPSS) version 20 was used for the analysis.



Scheme 1: Synthesis of 5-((2-phenylacetoxy) carbonyl)-1*H*-pyrazole-3-carboxylic acid (L)

Results and Discussion

Analytical data of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid

Yield 60%, M.P. 205-206^{O}C, cond.(µS/cm) 0.001 moldm^{-3} 92.2; MS: m/z 274.2 [M+] for $C_{13}H_{10}N_2O_5$, Calcd: C 48.27, H 4.48, N 9.79. Found: C 47.40, H 3.65, N 10.20;UV-Vis (λ max (nm) 303; FT-IR (KBr) (cm^{-1}) 3524 (N-H), 3142 (O-H), 3062-3002 (C-H_{ar}), 2918 (C-H_{al}), 1691 (C=O), 1558 (C=N), 1490 (C=C), 1239 (N-N); ^{1}H-NMR (400 MHz, DMSO-*d*6) (Chemical Shift in ppm) δ 7.29 (5H, m, Ar-H), 4.5 (1H,s, C-H), 4.3 (1H, s, C-H), 3.5 (1H,s, N-H), 2.5 (2H, s, –CH_2-); ^{13}C-NMR (100 MHz, DMSO-*d*6) (Chemical Shift in ppm) δ 39.0 C_4Pyrazol, 40.0 C_2 Pyrazol, 60.0 C_3 & C_5 Pyrazol, 171 ß-carbonyl of pyrazol, 173 carbonyl of acetyl moiety, 111-129 Ar- carbons (C_4 111, C_3 127, C_2 128, C_1 129).

Analytical data of [$Ce_2(L)_2(NO_3)_4$]

Yield 70%, M.P. 100-102^{O}C, cond.(µS/cm) 0.001moldm^{-3} 120.0; m/z 952, μ_{eff}/μ_B 2.03/2.54; UV-Vis (λ max (nm) 260; FT-IR (KBr) (cm^{-1}) 3529, 3418 (N-H), 3155 (O-H), 3071 (C-H_{ar}), 2907 (C-H_{al}), 1703 (C=O), 1615 (C=N), 1581 (C=C), 1214 (N-N), 1183(-NO_3), 528 (Ln-O); ^{1}H-NMR (Chemical Shift in ppm) δ 7.30 (5H, m, Ar-H), 4.5 (1H,s, C-H), 4.3 (1H, s, C-H), 3.5 (1H,s, N-H), 2.5 (2H, s, –CH_2-); ^{13}C-NMR (Chemical Shift in ppm) δ 39.0 C_4Pyrazol, 40.0 C_2 Pyrazol, 60.0, 173 C=O, 111-129 Ar- carbons (C_4 111, C_3 127, C_2 128, C_1 129).

Analytical data of [$Pr_2(L)_2](NO_3)_4$]

Yield 65%, M.P. 109-110^{O}C, cond.(µS/cm) 0.001moldm^{-3} 105.0; m/z 953, μ_{eff}/μ_B 2.03/2.58; UV-Vis (λ max (nm) 270; FT-IR (KBr) (cm^{-1}) 3484, 3417 (N-H), 3143 (O-H), 3066 (C-H_{ar}), 2991 (C-H_{al}), 1704 (C=O), 1622 (C=N), 1579 (C=C), 1277 (N-N), 1185(-NO_3), 520 (Ln-O); ^{1}H-NMR (Chemical Shift in ppm) δ 7.30 (5H, m, Ar-H), 4.5 (1H,s, C-H), 4.3 (1H, s, C-H), 3.5 (1H,s, N-H), 2.5 (2H, s, –CH_2-); ^{13}C-NMR (Chemical Shift in ppm) δ 39.0 C_4Pyrazol, 41.0 C_2 Pyrazol, 62.0, 173 C=O, 111-129 Ar- carbons (C_4 111, C_3 127, C_2 128, C_1 129).

Analytical data of [$Nd_2(L)_2(NO_3)_4$]

Yield 63%, M.P. 115-116^{O}C, cond.(µS/cm) 0.001moldm^{-3} 115.2; m/z 956, μ_{eff}/μ_B 2.28/3.62; UV-Vis (λ max (nm) 275; FT-IR (KBr) (cm^{-1}) 3529, 3416 (N-H), 3143 (O-H), 3099 (C-H_{ar}), 2987 (C-H_{al}), 1698 (C=O), 1612 (C=N), 1589 (C=C), 1456 (N-N), 1184(-NO_3), 520 (Ln-O); ^{1}H-NMR (Chemical Shift in ppm) δ 7.30 (5H, m, Ar-H), 4.5 (1H,s, C-H), 4.3 (1H, s, C-H), 3.5 (1H,s, N-H), 2.5 (2H, s, –CH_2-); ^{13}C-NMR (Chemical Shift in ppm) δ39.0 C_4Pyrazol, 40.0 C_2 Pyrazol, 62.0, 173 C=O, 111-129 Ar- carbons (C_4 111, C_3 127, C_2 128, C_1 129).

Physical properties of the compounds

The percentage yield of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid (L) was 60%, M.P. 205-206^{O}C. More yields were obtained for its complexes. The conductance value of L was determined as 92.2 µS/cm whereas its complexes were within 105 – 120 µS/cm. In comparison with $Ce_2(SO_4)_3$ used as control, the ligand and its complexes are non-electrolyte. This is in agreement with the results obtained for qualitative nitrate test indicating the presence of nitrate (NO_3^-) group in the inner-sphere of the complexes. The suggested molecular formula of the complexes is in agreement with non-electrolytic nature of these complexes. The complexes were proposed as [$Ln_2(L)_2(NO_3)_4$] (Figure 1). Similar reports have been made for lanthanoid complexes with 3-substituted triazole Schiff base.[18]

Electronic Spectraldata of 5-((2-phenylacetoxy) carbonyl)-1*H*-pyrazole-3-carboxylic acid and the Metal Complexes

The absorption spectra of 5-((2-phenylacetoxy) carbonyl)-1*H*-Pyrazole-3-carboxylic acid (L) and its complexes show band between 260-303 nm due to π-π* and n-π* transition resulting from the lone pair of electrons on the oxygen and the nitrogen atoms of the pyrazole moiety. The shift towards a shorter wavelength in all the complexes is due to coordinated oxygen and nitrogen as well as electronic effect of the nitrate ions. Similar assertion has been made in nitrogenous ligand coordinate with lanthanoid ions.[19] The metal complexes show no significant difference in absorption band since the lanthanoid ions are almost unaffected by the chemical environment. This observation has been reported in literature.[20]

Infrared Spectral data of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid and the Metal Complexes

The FT-IR Spectra of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid and its complexes shows strong broad absorption within 3524 -3206 cm^{-1} assigned to the vibration of N-H of the pyrazole ring with its combination band at 2049-1811 cm^{-1} for the ligand and within 2180–1852 cm^{-1} for the complexes. There was no significant shift in N-H bands in the complexes indicating the N-H of the pyrazole was not involved in bonding with the metals. Similar assertions have been made for complexes containing N-H group.[21-23] The O-H stretching vibration for the ligand absorbed at 3142 cm^{-1} whereas that of the complexes were within 3143–3145 cm^{-1}. On comparing the ligand and the complexes, no significant shift was observed for the O-H stretching vibration indicating that O-H of the acid was not coordinated to the metals.The aromatic C-H stretch

appeared within 3099-3062 cm^{-1} and aliphatic C-H stretch appeared within 2907-2991 cm^{-1} for the ligand and its complexes. These observed bands are in accordance with typical aromatic and aliphatic C-H vibrations reported in literature.[24,25] The C=O stretching vibration occurred at 1691 cm^{-1} for the ligand whereas the complexes were within 1703-1698 cm^{-1}. The shift in absorption of C=O in the complexes to higher frequencies is an evidence of ligation via the carbonyl group. Emerging reports of complexes containing carbonyl group exist which are in agreement with this assertion.[22,25, 26] The C=C stretch appeared within 1589-1490 cm^{-1} for the compounds whereas C=N stretching bands appeared within 1622-1558 cm^{-1}. The C-N stretch appeared within 1589-1490 cm^{-1} for the ligand and its complexes. Characteristic C=N stretching vibration for typical pyrazole compounds have been reported to absorb within this range.[24, 27] Absorption of nitrate (NO_3) group in the complexes appeared within 1185-1183 cm^{-1} which is in agreement with values obtained for coordinated nitrate group in a typical lanthanoid(III) complex.[28]The band at 1239 $cm^{-1}$is attributed to N-N of the pyrazole moiety which appeared less than the value (1391 cm^{-1}) reported in literature.[24] The Ln-O bond absorbed at 528, 520 and 520 cm^{-1}, respectively for the complexes which are in agreement with values reportedfor cerium(III) complex of piperidin-4-one with M-O bond within 560-540.[28]Similar absorption range has been observed for N-(benzothiazol-2-yl)-4-chlorobenzenesulphonamide and its neodymium(III) and thallium(III) complexes.[21]

Nuclear Magnetic Resonance Spectra of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid and the Metal Complexes

Figure 2 shows the proton numbering of the ligand. The ^{1}H-NMR signals in the region of 7.3-7.5 ppm which appeared as multiplet accounted for the phenyl ring protons. These signals appeared in the complexes and the protons of the pyrazole moiety appeared within the range of 3.5- 4.5 ppm which is a little less than the observed signals for pyrazole-pyrazoline compounds reported as novel antimalarial agents.[29] The little difference could be as a result of solvent interaction. The pyrazole proton H_6 (1H,s) is assigned to signal at 4.3 whereas proton H_7 (1H,s) is assigned to signal at 4.5 ppm due to its chemical environment (pyrazole nitrogen). The O-H and N-H protons signals appeared at 3.5 ppm which are in agreement with values obtained for non-deuterated ^{1}H-NMR analysis of compounds containing the two groups. Protons on N and O typically have wide ranges of chemical shift and the actual value depends to certain extent on the solvent used, concentration and temperature, because these protons are acidic and therefore, exchangeable, and may be broad peaks and usually do not couple with neighbouring protons. Typically, they are broad singlet and if deuterated solvent is used, the signal will shrink or disappear entirely since Deuterium (^{2}H) does not show in ^{1}H-NMR. The methylene of the phenylacetyl ring, H_4 is assigned to the signal at 2.5 ppm while the peaks at 1.4-1.5 ppm are due to solvent interaction with water. The product (L) formed is hygroscopic and so may contain water of crystallization.

Figure 3 shows the carbon numbering of the compound (L). The ^{13}C-NMR signals at 171 ppm and 173 ppm were assigned to $C_8$and C_9 which correspond to the carbonyl carbons of phenylacetyl moiety and the ß-carbonyl carbon of the pyrazole moiety, respectively. The carbonyl carbon (C_{14}) of the acid group is assigned to 161 ppm. The phenyl carbons of the acetyl moiety appeared within 129 – 111 ppm. The signals at 129, 128, 127 and 111 ppm were attributed to carbons 1, 2, 3 and 4 of the phenyl ring, respectively. This is in agreement with the values obtained for phenyl ring of derivative of benzothiazole.[19] The shift at 40 ppm and 39 ppm are due to the carbon of the pyrazole moiety assigned to C_{13} and C_{11}, respectively. Similarly, the quaternary carbon of the pyrazole moiety (C_{12} and C_{10})appeared at 60 ppm. All the phenyl carbons appeared at 129, 128, 127 and 111 ppm. The ^{13}C-NMR of the Pr(III) complex show the disappearance of the peak assigned to carbonyl carbons in the ligand which is an indication of bonding through the carbonyl group. Although the Nd(III) complex seems to be paramagnetic, the evidence of coordination through the carbonyl group results in the disappearance of the peak assigned to the carbonyl carbons of the acetyl and acid moieties in the complex.

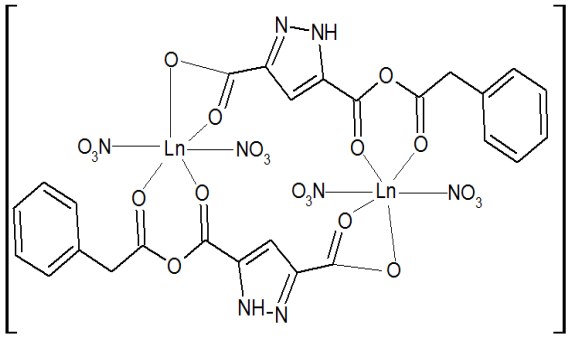


Figure 1: Proposed Structure of $[Ln_2(L)_2(NO_3)_4]$

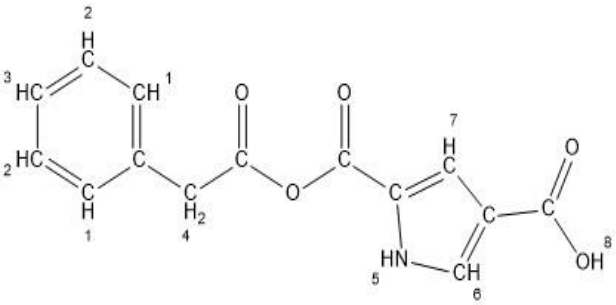


Figure 2: Structure of L showing proton numbering

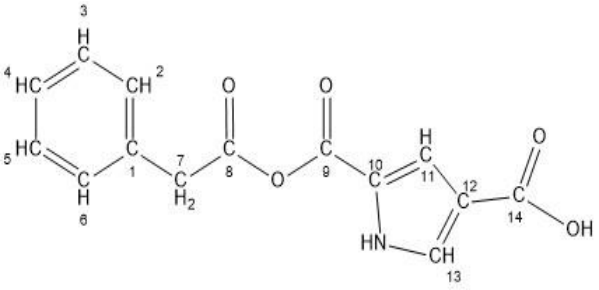


Figure 3: Structure of L showing carbon numbering

Magnetic Properties of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid and theMetal Complexes

The magnetic properties of the complexes(Table 1) show the expected behaviours for isolated Ce(III) Pr(III) and Nd(III) complexes. Thus, product of magnetic susceptibility and temperature, X_mT as well as the μ_{eff} agrees with calculated values, $\mu_{B.M}$ calculated for ground term $^3H_4$, $^2f_{5/2}$ and $^4I_{9/2}$ of the complexes. The observed decrease in the complexes was as a result of depopulation of the higher energy state levels due to the splitting of the $^3H_4$, $^2F_{5/2}$, and $^4T_{9/2}$ ground levels arising from the effects of the ligand field. Similar observation has been reported.[28]Secondly, due to orbital coupling, the complexes show less value than the calculated values. The observed behaviour indicates that all the complexes are paramagnetic. The decrease in the μeff compared to $\mu_{B.M}$ for $[Ln_2(L)_2(NO_3)_4]$ complexes could also be due to antiferromagnetic Ln-Ln coupling via the ligands bridge. Similar observation for lanthanoid coordination polymers with a symmetric anilato ligand has been reported.[30]

Antimicrobial Properties of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid and the Metal Complexes

The *in vitro* antimicrobial assay of 5-((2-phenylacetoxy)carbonyl)-1*H*-Pyrazole-3-carboxylic acid (L) show activity against *Basillus subtillis* with minimum inhibitory concentration of 12.5 mg/mL but not active against any other organisms tested. The Ce(III) complex was equally active against *Basillus subtillis* and S*taphylococcus aureus* at higher concentration of 100 mg/mL and 25 mg/mL but no activity was recorded against any other organism. The Pr(III) complex shows no activity against all the tested microbes, while the Nd(III) complex

show greater activity against *Staphylococcus aureus, Bacillus subtillus, Escherichia coli, Klebisella pneumoniae* and *Salmonella typhi* with minimum inhibitory concentrations of 25, 12.5, 25, 50 and 50 mg/mL, respectively. The enhanced activity could be attributed to the fact that metal base drugs have more activity than ordinary ligand as previously reported.[9]similarly, the broad antimicrobial activity of these compounds are in agreement with Nitrone compounds known to possess antioxidant, anticancer and antibacterial activities.[31]

Antimalarial Activity of 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid and the Metal Complexes

In the*in vivo* antimalarial study, the compounds exhibited adose-dependent effecton the packed cell volume (PCV) of the infected mice. From the result, the mice treated with the positive control drug, Artesunate had the highest PCVof 29.6%, followed by those treated with 500 mg/kg dose of $[Nd_2(L)_2(NO_3)_4]$ and 250 mg/kgdose of L with PCV of 27.8%. The compound L had better effect on PCV at 250 mg/kg dose than at higher dose of 500 mg/kg with PCV of 19.5%. A decrease in the PCV using higher dose could induce anemia as a result of drug reaction and immune mediated disorder. The effects of the ligand (L) and its complex on hemoglobin (Hb) concentration (Table 2) revealed that $[Ce_2(L)_2(NO_3)_4]$ treatment had the highest percentage change in Hb (7.85%). The Hb concentration decreases as the dose of L increases and increases as the dose of $[Ce_2(L)_2(NO_3)_4]$ increases.Theeffect of these compounds on hemoglobin level was found to be dose-dependent and they generally enhances the levels of hemoglobin in the treated animals.

The red blood cell counts (RBC) (Table 3) of the mice before and after treatment fell within the accepted range. These values ranges between 4.12 - 4.75 $x10^6$ cells/µL for the positive control group and the test groups indicating that the compounds may not cause anemia due to higher percentage increase in RBC count recorded for the test compounds compared to the positive control (Artesunate).

The effects of the compounds on parasthemiaof mice infected with *Plasmodium berghie*is presented in Table 4. The results revealed that the positive control, artesunate had the highest percentage parasitaemia suppression of 88.74%. The compounds L, $[Ce_2(L)_2(NO_3)_4]$ and $[Nd_2(L)_2(NO_3)_4]$ at 250 mg/kg dose each, exhibited percentage parasitaemia suppression of 63.48%, 26.19% and 63.51%, respectively, while higherpercentage parasitaemia suppression of 64.79%, 66.47%, and 85.06%, respectively were observed at 500 mg/kg dose of the compounds. Generally, the increase in parasitaemia suppression with increase in dose of the compounds isan indication of the antiplasmodial effect of these compounds at higher doses. However, the positive control (Artesunate) had the highest percentage parasitaemia suppression (88.74%) than all the compounds tested. The high value recorded in this case for the positive control drug does not make it more effective than the synthesized compounds since the compounds had better effect on the red blood cells and haemoglobin during treatment. On the other hand, theplasmodium parasite has been shown to develop resistance against the use of artesunate over time.Therefore, this has necessitated the need for newerdrugs specifically metal base drugs to tackle the menace of malaria parasiteresistance.The LD_{50} ofthe complex $[Nd_2(L)_2(NO_3)_4]$ has shown no mortality of mice even at a high dose of 5000 mg/kg.

Conclusion

The present study involved the synthesis of a pyrazole derivative and its lanthanoid complexes as potential antimalaria agents. The compounds were characterized by spectroscopic techniques and microanalysis. The ligand, 5-((2-phenylacetoxy) carbonyl)-1H-pyrazole-3-carboxylic acid (L) and its complexes show excellent antimalarial properties. The complexes could serve as template for further biological and magnetic studies due to their interesting properties.

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.

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Table 1: Experimental and Calculated Magnetic Properties of the Compounds

Compound	X_g	X_mT	G	e	S	L	J	g	μ_{eff}	μ_{BM}
$[Ce_2(L)_2(NO_3)_4]$	$1.73x10^{-6}$	$6.46x10^{-6}$	$^2f_{5/2}$	1	½	3	5/2	6/7	2.03	2.54
$[Pr_2(L)_2(NO_3)_4$	$1.73x10^{-6}$	$6.46x10^{-6}$	$^3H_4$	2	1	5	4	4/5	2.03	3.58
$[Nd_2(L)_2(NO_3)_4]$	$2.16x10^{-6}$	$8.09x10^{-6}$	$^4I_{9/2}$	3	3/2	6	9/2	8/11	2.28	3.62

Legend: X_g= magnetic susceptibility, X_mT = product of magnetic susceptibility in S.I.U with temperature, G = ground term, e = number of electrons, s = spin, L = orbital contribution, J = quantum number due to coupling of s and L, g = dimensionless magnetic moment, μ_{eff} = Experimental values, μ_{BM} = Calculated values.

Table 2: Effects of Compounds on the Hemoglobin of the Infected Mice

Compound	Dose (mg/kg)	Initial Hb Conc. (g/dL)	After Induction Hb Conc. (g/dL)	Final Hb Conc. (g/dL)	Change in HbConc. (%)
$[Nd_2(L)_2(NO_3)_4]$	250	14.34 ± 0.15	13.24 ± 0.23	14.12 ± 0.20	6.80
$[Nd_2(L)_2(NO_3)_4]$	500	14.40 ± 0.27	13.20 ± 0.11	14.12 ± 0.12	6.97
$[Ce_2(L)_2(NO_3)_4]$	250	14.33 ± 0.14	13.56 ± 0.11	14.24 ± 0.16	5.01
$[Ce_2(L)_2(NO_3)_4]$	500	14.48 ± 0.12	13.76 ± 0.07	14.84 ± 0.18	7.85
L	250	13.80 ± 0.18	13.86 ± 0.07	14.90 ± 0.14	7.50
L	500	14.52 ± 0.21	13.90 ± 0.18	14.84 ± 0.18	6.76
Artesunate	5	13.42 ± 0.22	13.65 ± 0.24	14.28 ± 0.14	4.61
Negative control		14.00 ± 0.09	13.64 ± 0.12	13.46 ± 0.29	-1.32

Legend: Hb = Hemoglobin

Table 3: Effects of Compounds on Red Blood Cell Count of the Infected Mice

Compound	Dose (mg/kg)	Initial RBC ($x10^6$ cells/µL)	After Ind. RBC ($x10^6$ cells/µL)	Final RBC ($x10^6$ cells/µL)	Change in RBC (%)
L	250	4.32 ± 0.11	3.64 ± 0.20	4.75 ± 0.06	33.3
L	500	4.90 ± 0.14	3.44 ± 0.10	4.59 ± 0.06	33.3
$[Ce_2(L)_2(NO_3)_4]$	250	4.68 ± 0.21	3.71 ± 0.13	4.34 ± 0.06	16.2
$[Ce_2(L)_2(NO_3)_4]$	500	4.32 ± 0.17	3.69 ± 0.13	4.55 ± 0.15	24.3
$[Nd_2(L)_2(NO_3)_4]$	250	4.26 ± 0.09	3.44 ± 0.09	3.92 ± 0.23	14.7
$[Nd_2(L)_2(NO_3)_4]$	500	4.30 ± 0.21	3.28 ± 0.05	4.12 ± 0.07	28.1
Arteunate	5	4.92 ± 0.19	3.82 ± 0.16	4.55 ± 0.15	13.2
Negative control		4.46 ± 0.29	3.77 ± 0.09	3.50 ± 0.14	-7.8

Legend: RBC = Red Blood Cell, Ind. = Induction

Table 4: Effects of Compounds on Parasitaemiain Mice

Compound	Dose (mg/kg)	Initial parasthemia (%)	Final Parasthemia (%)	Percentage Parasthemia Suppression (%)
L	250	35.60 ± 2.20	13.00 ± 2.66	63.48
L	500	28.40 ± 0.93	10.00 ± 2.00	64.79
$[Ce_2(L)_2(NO_3)_4]$	250	33.60 ± 3.19	24.80 ± 2.46	26.19
$[Ce_2(L)_2(NO_3)_4]$	500	34.00 ± 2.61	11.40 ± 1.40	66.47
$[Nd(L)_2(NO_3)_4]$	250	29.60 ± 0.93	10.80 ± 0.80	63.51
$[Nd_2(L)_2(NO_3)_4]$	500	30.80 ± 0.97	4.60 ± 1.33	85.06
Artesnate	5	30.20 ± 1.93	3.40 ± 0.75	88.74
Negative control		32.40 ± 2.23	37.20 ± 1.93	-14.81

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