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Probing the Antioxidant and Cytotoxic Properties of Neodymium (III) Complexes Incorporating Coumarin Derivatives and Clioquinol

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ABSTRACT

This study investigates the antioxidant and cytotoxic properties of neodymium (III) complexes featuring coumarin and clioquinol ligands, known for their cure potential. The complexes are synthesized using coordination chemistry techniques, resulting in unique molecular structures. Antioxidant activities were assessed through various assays, revealing their ability to combat oxidative stress. Cytotoxicity studies demonstrate their potential as anticancer agents. Structural and spectroscopic analyses provide insights into their coordination geometries and electronic properties, the pathways behind their impacts. Overall, this study notifies the development of therapeutic agents targeting oxidative stress-related disorders and cancer with enhanced efficacy and fewer side effects.

Keywords: Coumarin**,** Clioquinol, Neodymium, Cytotoxic, Antioxidant.

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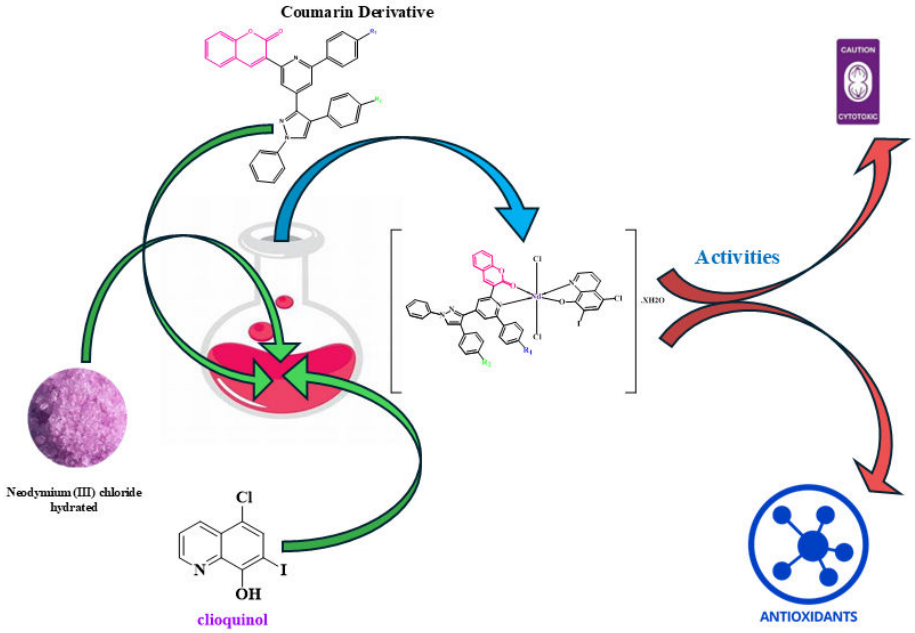
Graphical Abstract:



1. INTRODUCTION

Coumarin derivatives have emerged as a significant class of compounds characterized by a wide range of pharmacological properties, including antioxidant and cytotoxic activities. These attributes render them promising candidates for drug development and therapeutic applications. Structurally related to coumarin, these derivatives exhibit enhanced or modified biological activities that are particularly valuable in addressing various diseases, notably those associated with oxidative stress and cancer. This review seeks to examine the antioxidant and cytotoxic properties of coumarin derivatives, emphasizing their potential as effective agents within the realm of medicinal chemistry [1-10]. Clioquinol, a hydroxyquinoline compound, has been the subject of investigation due to its potential antioxidant and cytotoxic properties, positioning it as a promising candidate for therapeutic applications across a range of diseases. Its distinctive chemical structure and pharmacological characteristics have demonstrated considerable efficacy in mitigating conditions related to oxidative stress and in exerting cytotoxic effects on cancer cells. This review aims to elucidate the antioxidant and cytotoxic activities of clioquinol, focusing on its mechanisms of action and prospective clinical applications [11-15]. Neodymium, a rare earth metal, has recently attracted attention for its potential applications in various domains, including medicine. A particularly intriguing area of research involves the utilization of neodymium complexes as antioxidants and cytotoxic agents in cancer therapy. These complexes have demonstrated antioxidant properties, which may protect cells from oxidative stress and damage a critical factor given the association of oxidative stress with the onset of numerous diseases, including cancer. By scavenging free radicals and mitigating oxidative damage, neodymium complexes may contribute to the prevention or retardation of disease progression. In addition to their antioxidant capabilities, neodymium complexes have also exhibited cytotoxic activities, indicating their potential to induce cell death in cancerous cells.

This property positions them as viable candidates for cancer treatment, as they may facilitate tumor reduction and enhance patient outcomes. Numerous studies have been conducted to assess the antioxidant and cytotoxic properties of neodymium complexes. For instance, research published in the Journal of Inorganic Biochemistry reported strong antioxidant activity in a neodymium complex, while another study in the Journal of Medicinal Chemistry highlighted the cytotoxic effects of neodymium complexes on cancer cells.

Overall, the investigation into neodymium complexes as antioxidants and cytotoxic agents is promising, warranting further research to fully elucidate their potential in medical applications. Given their unique properties and prospective benefits, neodymium complexes may play a pivotal role in the development of novel and improved treatments for diseases such as cancer [16-17]. Additionally, neodymium complexes have been extensively studied for their catalytic properties, while coumarin derivatives have garnered interest for their diverse applications, including antioxidant functions. Clioquinol has also been explored for its potential as an autophagy-targeted antimetastatic agent. The antioxidant and cytotoxic activities of various natural and synthetic compounds have been the focus of extensive research [18-23].

2. EXPERIMENTAL

2.1. Materials

The reagents salicylaldehyde, p-bromoacetophenone, p-chloroacetophenone, p-methylacetophenone, p-methoxyacetophenone, ethyl acetoacetate, and piperidine were procured from Chemdyes Corporation (Rajkot, India) and utilized without additional purification. Clioquinol was generously provided by Atul Limited (Valsad, India). Neodymium trichloride hydrate was obtained from Loba Chemie PVT. LTD. (India).

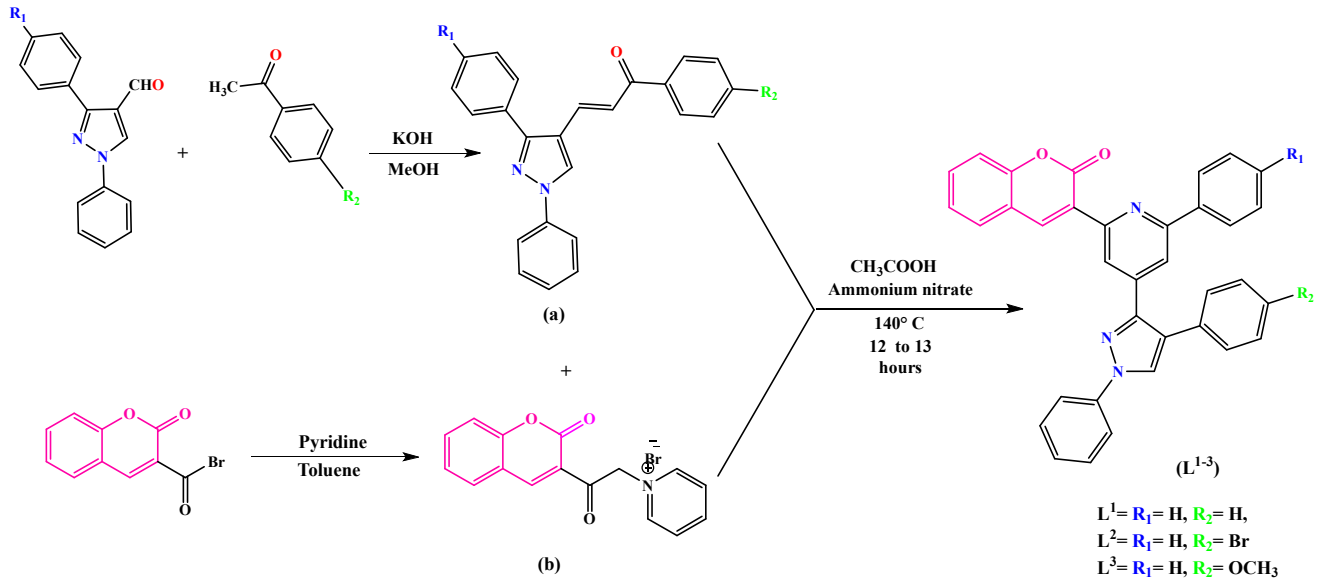
2.2. Instrumentation

Microanalyses for carbon, hydrogen, and nitrogen content were conducted using a Perkin Elmer 240 elemental analyzer. The metal content of the complexes was assessed through EDTA titration following the decomposition of organic matter with a mixture of $HClO_4$, H_2SO_4, and HNO_3 in a ratio of 1:1.5:2.5. Magnetic susceptibility measurements at room temperature were performed using a Gouy magnetic balance, calibrated with mercury (II) tetrathiocyanatocobaltate(II) ($Xg = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Electronic spectra were recorded on a UVISEL 2 UV-Visible spectrophotometer (Horiba Scientific, Delhi, India) while infrared spectra were obtained using an FT-IR Shimadzu spectrophotometer in KBr pellet form, covering the range of 4000-400 cm^{-1}. The fast atom bombardment (FAB) mass spectrum of the complex was recorded at the Central University of Gujarat using a mass spectrometer.

2.3. Synthesis of Ligands (L^{1-3})

All bidentate ligands were synthesized according to well-established procedures documented in the literature. The synthesis of these ligands involves several intricate steps, which are outlined below:
The process begins with the treatment of salicylaldehyde with ethyl acetoacetate, leading to the formation of 3-acetyl-2H-chromen-2-one. This compound undergoes bromination, resulting in the production of 3-(2-bromoacetyl)–2H-chromen-2-one. Subsequently, 3-(2-bromoacetyl)–2H-chromen-2-one is treated with toluene and pyridine, yielding the coumarin pyridinium salt (a). In parallel, we synthesized the chalcone of pyrazole (b) and performed a condensation reaction with (a), resulting in the formation of the coumarin ligand (L^{1-3}). (Scheme-1)

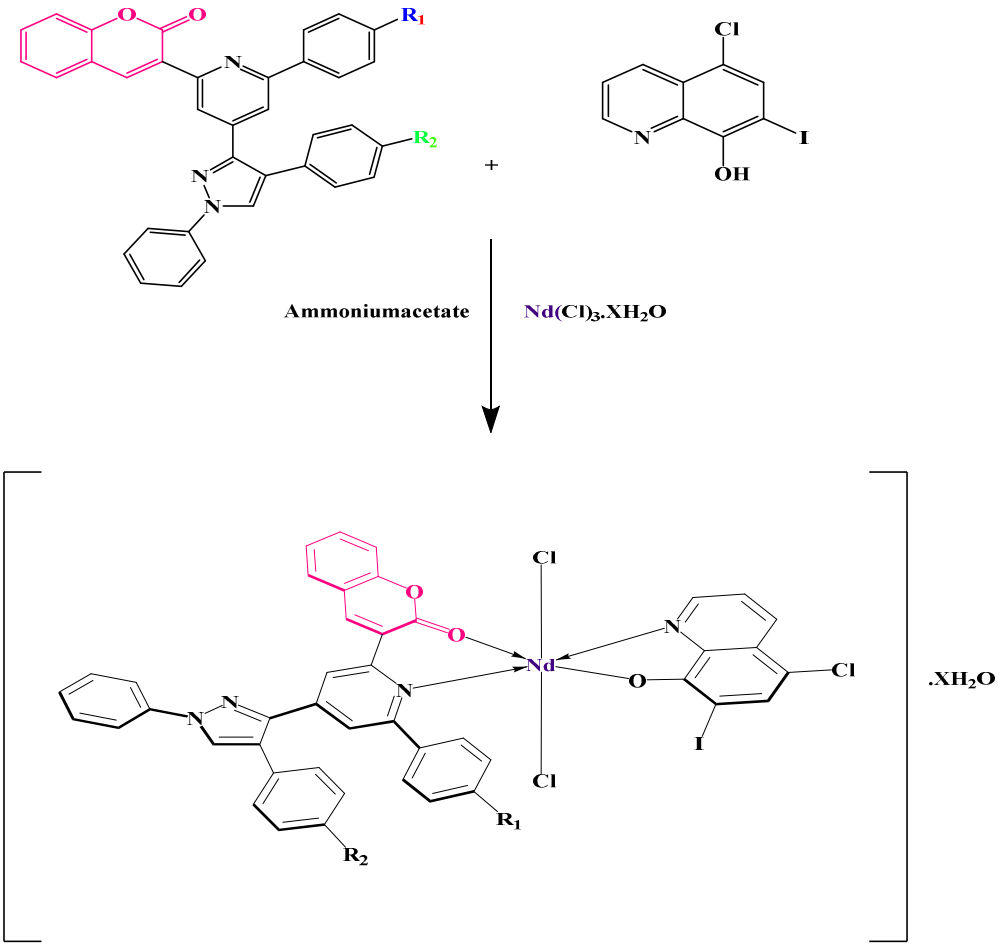
This multi-step synthetic pathway highlights the complexity and precision required in ligand synthesis, showcasing the careful manipulation of chemical reactions to achieve desired outcomes. The bidentate nature of the ligands synthesized ensures their efficacy in coordination chemistry applications. Overall, the synthesis of these bidentate ligands not only adheres to established protocols but also exemplifies the analytical rigor necessary for producing compounds with defined structural properties. [22-23]



Scheme 1. Ligands synthesis (L^{1-3})

2.4. General Procedure for the Synthesis of Complexes

The neodymium (III) complexes were synthesized through the reaction of neodymium (III) salt with the ligands 3-(6-phenyl-4-(1-phenyl-4-(p-tolyl)-1H-pyrazol-3-yl)pyridin-2-yl)-2H-chromen-2-one, 3-(4-(4-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-6-phenylpyridin-2-yl)-2H-chromen-2-one, and 3-(4-(4-(4-bromophenyl)-1-phenyl-1H-pyrazol-3-yl)-6-phenylpyridin-2-yl)-2H-chromen-2-one, maintaining a metal to ligand molar ratio of 1:2. The synthesis involved the gradual addition of an aqueous solution of neodymium (III) salt to an aqueous solution of the ligand, followed by a gradual increase in the pH of the mixture to approximately 5.0 through the addition of a dilute sodium hydroxide solution. The reaction mixtures were stirred using an electromagnetic stirrer at 25 °C for one hour, during which precipitates formed. These precipitates were subsequently filtered, washed multiple times with water, and dried in a desiccator until a constant weight was achieved. (Scheme 2)



Scheme 2. Complexes Synthesis (C^{1-3}).

2.5. Antioxidant Studies

The ferric-reducing antioxidant power (FRAP) was assessed using a modified methodology. The antioxidant capacity of the compounds was evaluated based on their ability to reduce the TPTZ–Fe(III) complex to the TPTZ–Fe(II) complex. This method is characterized by its simplicity, rapid execution, and reproducibility. The total antioxidant capacity of biological samples is expressed in terms of ascorbic acid equivalents (mmol 100 g^{-1} of the dried compound).

Preparation of Solutions:

a) Acetate buffer, 300 mM, pH 3.6, was prepared by dissolving 3.1 g of sodium acetate trihydrate and 16 mL of concentrated acetic acid per liter of buffer solution.
b) 10 mM solution of 2,4,6-tripyridyl-s-triazine (TPTZ) (M.W. 312.34) was prepared in 40 mM HCl.
c) 20 mM solution of $FeCl_3 \cdot 6H_2O$ (M.W. 270.30) was prepared in distilled water.
d) 1 mM solution of ascorbic acid (M.W. 176.13 g mol^{-1}) was prepared in 100 mL of distilled water.

The FRAP working solution was created by mixing the aforementioned solutions (a), (b), and (c) in a ratio of 10:1:1, respectively. A mixture consisting of 40.0 µL of a 0.5 mM sample solution and 1.2 mL of the FRAP reagent was incubated at 37 °C for 15 minutes. It is essential that working solutions are prepared fresh. Ascorbic acid served as the standard antioxidant compound.

2.6. Cytotoxic Studie

The coordination capability of the ligands was demonstrated through their complexation with the neodymium(III)ion. Spectroscopic analyses, including ^{1}H-NMR, ^{13}C-NMR, and IR, of the ligands and their Nd(III) complexes confirmed the proposed coordination through both hydroxyl and carbonyl oxygen atoms. Preliminary screening results indicated that all novel Nd complexes achieved 50% inhibition of malignant cell proliferation, thereby suggesting their potential biological activity based on the IC50 values obtained. The compounds Nd(L^1)(OH).H_2O and Nd(L^3)(OH).$2H_2O$ demonstrated superior activity relative to the other complexes. These results, along with the apparent absence of cross-resistance to these agents in HL-60/Dox, provide a compelling rationale for further comprehensive pharmacological and toxicological studies of Nd(L^1)(OH). H_2O and Nd(L^3)(OH).$2H_2O$. It is anticipated that neodymium(III) complexes exhibit cytotoxic activity, which is distinctly evident in their in vitro effects. These findings corroborate our prior observations regarding their cytotoxic potential. The structural characterization of all synthesized ligands (L^{1-3}) was conducted through elemental analysis (Table-1).

3. RESULT AND DISCUSSION

3.1. Elemental Analysis

Table 1. Elemental analysis of coumarin ligand and their neodymium complex.

Compound	Colour	Molecular Weight Found (Cal.)	% Analysis found				μ_{eff} (B.M.)
			C	H	N	Nd (III)	
L^1/$C_{35}H_{23}N_3O_2$	Yellow	517.588 (517.574)	81.22	4.48	8.12	-	-
L^2/$C_{35}H_{22}ClN_3O_2$	Yellow	551.140 (551.122)	76.15	4.02	7.61	-	-
L^3/$C_{35}H_{22}BrN_3O_2$	Yellow	596.484 (596.484)	70.48	3.72	7.04	-	-
[Nd(L^1)(CQ)Cl_2].$3H_2O$/ $C_{44}H_{33}Cl_3IN_4NdO_9$	Reddis	1091.266 (1091.260)	48.43	3.05	5.13	13.22	4.24
[Nd(L^1)(CQ) Cl_2]. H_2O/ $C_{44}H_{28}Cl_4IN_4NdO_4$	Reddis	1089.674 (1089.660)	48.50	2.59	5.14	13.24	4.20
[Nd(L^1)(CQ)Cl_2].$2H_2O$/ $C_{44}H_{30}BrCl_3IN_4NdO_5$	Reddis	1152.139 (1152.120)	45.87	2.62	4.86	12.52	4.22

3.2. Infrared Spectroscopy

Infrared spectroscopy and proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. The following chemical reaction illustrates the formation of the complexes: The significant infrared spectral bands and their provisional assignments for clioquinol and its complexes were recorded using KBr disks and are detailed in the accompanying table. The 8-hydroxyquinoline base ligands examined in this study exhibit a broad band centred at 3400 cm^{-1}, indicative of a strongly hydrogen-bonded hydroxyl (-OH) group.

In the complexes of 8-hydroxyquinoline with divalent metals, the stretching frequency of the carbon-oxygen (υ(C-O)) bond appears in the region of 1120cm^{-1}, with slight variations in position depending on the specific metal involved.

The complexes under investigation display bands in the ranges of 3418−3437 cm^{-1},1278−1295cm^{-1}, 865−875cm^{-1}, and 705−710cm^{-1}, which are attributed to the stretching, bending, rocking, and wagging vibrations of the -OH group, respectively, due to the presence of coordinated water molecules. The observation of a rocking band further supports the coordinated nature of the water molecule. The υ (C-O) frequency, which is observed at 1090 cm^{-1} in the free oxene molecule, shifts to a higher frequency of 1110 cm^{-1} in all mixed ligand complexes, indicating the coordination of 8-hydroxyquinoline within these complexes. Additionally, the clioquinol band at 1600 cm^{-1}, corresponding to the υ(C=N) mode, shifts to a lower frequency of 1580 cm–1 upon complexation, while the band at 1500 cm^{-1}, associated with υ(C=C), shifts to a higher frequency of 1518 cm^{-1}. In the far-infrared region, two new bands at 508-511 cm^{-1} and 537–540 cm^{-1} in the complexes are assigned to the υ(Cu–O) and υ(Cu–N) modes of clioquinol, respectively. Collectively, these findings confirm that clioquinol acts as a mono-negative bidentate ligand, forming a conjugated chelate ring. (Table-2)

Table 2 The characteristic IR bands of the metal complexes.

Complexes	**υ (O-H) cm^{-1}**	**υ (C=N) cm^{-1}**	**υ (C=C) cm^{-1} (aromatic)**	**υ (Nd-O) cm^{-1}**	**υ (Nd-N) cm^{-1}**
CQ	3401(br)	1620(w)	1500(s)	-	-
C_1	3411(br)	1601(w)	1523(s)	510	540
C_2	3406(br)	1615(w)	1530(s)	508	537
C_3	3404(br)	1611(w)	1525(s)	511	538

s= strong, w = weak, br = broad

3.3. Antioxidant Activity

The in *vitro* antioxidant activity of complexes C^1–C^3 was assessed using the Ferric Reducing Antioxidant Power (FRAP) assay, with results expressed in millimoles of ascorbic acid per 100 grams of sample. The findings, presented in the accompanying table, indicate moderate to good antioxidant activity. Among the tested compounds, derivatives substituted with a chloro group exhibited greater ferric reducing power compared to those with bromo or methoxy substitutions. Consequently, the potency order based on the various substituents attached to the phenyl ring is established as –Cl > –Br. Notably, all complexes demonstrated significant antioxidant activity in comparison to the standard ascorbic acid. (Table-3)

Table 3. Antioxidant activity assay with standard ascorbic acid.

Compound/M.F.	Untreated control	31.25 (µM)	62.5 (µM)	125 (µM)	250 (µM)	500 (µM)
$[Nd(L^1)(CQ)Cl_2].3H_2O$/ $C_{44}H_{33}Cl_3IN_4NdO_9$	0.2772 ± 0.0114	0.2973 ± 0.0220	0.1785 ± 0.2014	0.1450 ± 0.0068	0.1070 ± 0.0118	0.08200 ± 0.00099
$[Nd(L^2)(CQ)Cl_2].H_2O$/ $C_{44}H_{28}Cl_4IN_4NdO_4$	0.2772 ± 0.0114	0.3173 ± 0.008	0.2990 ± 0.0240	0.1300 ± 0.0240	0.1210 ± 0.0010	0.1100 ± 0.0078
$[Nd(L^3)(CQ)Cl_2].2H_2O$/ $C_{44}H_{30}BrCl_3IN_4NdO_5$	0.2772 ± 0.0114	0.2607 ± 0.0102	0.2625 ± 0.0439	0.1389 ± 0.0100	0.1158 ± 0.0102	0.0790 ± 0.0115

3.2. Cytotoxicity Assessment

The cytotoxicity of the neodymium complexes under investigation was evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) dye reduction assay, as outlined by Mosmann [27-33], with certain modifications. This assay is predicated on the capacity of viable cells to reduce the yellow tetrazolium dye MTT to violet, water-insoluble formazan. Following the dissolution of the formazan crystals through acidification and the addition of an organic solvent, the concentration of formazan, which correlates with the number of viable cells, is quantified spectrophotometrically. In brief, logarithmically growing cells were plated in 96-well microplates (100 µl/well at a density of 1×10^5 cells/ml) and subjected to various concentrations of the tested compounds for a duration of 72 hours. Post-incubation with the test compound, MTT solution (10 mg/ml in PBS) was introduced (10 µl/well). The plates were subsequently incubated for 4 hours at 37 °C, after which the formed formazan crystals were dissolved by the addition of 100 µl/well of 5% formic acid in 2-propanol. Absorbance was measured using an ELISA reader (Uniscan–Titertek) at 540 nm, with a reference filter set at 690 nm. A minimum of eight wells were utilized for each concentration. The blank solution comprised 100 µl of RPMI 1640 medium, 10 µl of MTT stock, and 100 µl of 5% formic acid in 2-propanol. (Table-4 & 5)

Table 4. IC50 values of the investigated Nd complexes on HL-60, HL-60/Dox, and SKW-3 cells after 74h incubation.

Compound	IC50 value		
	HL-60	HL-60/ Dox	SKW-3
$[Nd(L^1)(CQ)Cl_2].3H_2O/C_{44}H_{33}Cl_3IN_4NdO_9$	90.010	90.010	131.59
$[Nd(L^2)(CQ)Cl_2].H_2O/C_{44}H_{28}Cl_4IN_4NdO_4$	161.64	161.64	123.1
$[Nd(L^3)(CQ)Cl_2].2H_2O/C_{44}H_{30}BrCl_3IN_4NdO_5$	209.40	209.40	192.4

Table 5. Spectrophotometric data from MTT assay concerning the cytotoxic activity of the investigated Nd complexes on HL60cells after 74 incubations.

Compounds	MTT-formazan absorption at 580nm					
	Untreated control	**31.25(M)**	**62.5(M)**	**125(M)**	**250(M)**	**500(M)**
$[Nd(L^1)(CQ)Cl_2].3H_2O$/ $C_{44}H_{33}Cl_3IN_4NdO_9$	0.6037 ± 0.0351	0.479 ± 0.0570	0.330 ± 0.0130	0.2650 ± 0.0330	0.230 ± 0.0100	0.1540 ± 0.0070
$[Nd(L^2)(CQ)Cl_2].H_2O$/ $C_{44}H_{28}Cl_4IN_4NdO_4$	0.6037 ± 0.0351	0.582± 0.0169	0.503± 03030	03222 ± 0.0180	0.248 ± 0.00180	0.2133± 0.0040
$[Nd(L^3)(CQ)Cl_2].2H_2O$/ $C_{44}H_{30}BrCl_3IN_4NdO_5$	0.6037 ± 0.0351	0.5930± 0.0180	0.5990± 0.0550	0.469 ± 0.0422	0.3020 ± 0.0168	0.2211± 0.0177

4. CONCLUSION

In conclusion, the investigation into the cytotoxic and antioxidant properties of a clioquinol complex and a coumarin derivative containing neodymium has yielded promising results. The conjugated system of the coumarin scaffold facilitates excellent charge and electron transport capabilities, which are critical for its biological activity. Although the complex retains significant antioxidant properties, it has been observed that the introduction of a diethylamino substituent at position 7 of the coumarin structure, along with the substitution of the 4-OH group on the benzene ring with a 3-Me group, diminishes its antioxidant efficacy. Furthermore, the synthesized coumarin derivatives exhibit a broad spectrum of physiological effects, including antioxidant properties that are vital for the prevention of diseases associated with oxidative stress. These attributes appear to be enhanced through complexation with neodymium, potentially offering a novel approach for the development of pharmaceutical agents.

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Abbreviation

CQ= Clioquinol

L= L^1, L^2, L^3

L^1= 3-(6-phenyl-4-(1-phenyl-4-(p-tolyl)-1H-pyrazole-3-yl) pyridine-2-yl)-2H-chromene-2-one

L^2= 3-(4-(4-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-6-phenylpyridin-2-yl)-2H-chromen-2-one

L^3= 3-(4-(4-(4-bromophenyl)-1-phenyl-1H-pyrazol-3-yl)-6-phenylpyridin-2-yl)-2H-chromen-2-one

C_1= $[Nd(L^1)(CQ)Cl_2].3H_2O$ / $C_{44}H_{33}Cl_3IN_4NdO_9$
C_2= $[Nd(L^2)(CQ)Cl_2].H_2O$ / $C_{44}H_{28}Cl_4IN_4NdO_4$
C_3= $[Nd(L^3)(CQ)Cl_2].2H_2O$ / $C_{44}H_{30}BrCl_3IN_4NdO_5$
B.M.= Bohr Magneton

TGA= Thermogravimetric Analysis

LB = Luria Broth

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