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SYNTHESIS AND DNA PHOTOCLEAVAGE ACTIVITY OF LANTHANUM AND NICKEL COMPLEXES OF PYRAZOLYL BISCOUMARIN DERIVATIVES

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ABSTRACT: Hybrid molecules, furnished by combining coumarin and pyrazoles, have been synthesized in the present study. In addition, the binding ability of these coumarin-based molecules has been investigated for Nickel and less studied lanthanum. Lanthanum and nickel complexes with 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methyl)-2H-chromen-2-one (4a) and 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methyl)-2H-chromen-2-one (4b) were synthesized using lanthanum nitrate hexahydrate ($La(NO_3).6H_2O$) and nickel dichloride hexahydrate ($NiCl_2.6H_2O$). The synthesized complexes 5a-d were isolated and characterized by IR, Mass, and ^{1}HNMR spectroscopy. The spectra of complexes 5a-d were interpreted on the basis of comparison with the spectrum of the free ligand. These complexes were screened for DNA photocleavage activity. Two complexes, 5a, and 5b, gave significantly good results found to degrade both forms of DNA (SC and NC). Our data give the reason to conclude that these compounds can act as lead compounds and should be submitted to further more detailed biological evaluation.

INTRODUCTION: Coumarin is an intense family of natural and synthetic origin that has attracted the attention of researchers because of its wide pharmaceutical and biological profile. A number of biological properties are assigned to coumarin and its derivatives, such as central nervous system stimulants [1], antibacterial agents, [2, 3] anti-inflammatory agents, [4] anti-cancer [5] and, also works as dyes [6].

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Naturally occurring coumarins, such as 4-hydroxy coumarin, is reported to show inhibition action against cell proliferation in a gastric carcinoma cell line [7]. Furthermore, coumarin derivatives, such as biscoumarins also exhibit several biological and pharmaceutical properties. Biscoumarins are reported to act as anticoagulants, rodenticides, anti-inflammatory agents, urease inhibitors, and HIV-1 integrase inhibitors [8-14]. In addition, many researchers have amplified their role not only as of the target point but also as intermediates and nucleus of many organic motifs [15-17].

In the past decades, transition metals and their complexes seek the attention of researchers due to their enriched biological and pharmaceutical

activity. Complexes of transition metals either amplify the existing properties of ligand or introduced some new properties. The complexation of transition metals with the ligand is reported with biological activities such as, antitumor, anti-inflammatory, anti-parasitic properties, as well as uses against other diseases [18-19]. The complexes of rare-earth ions have aroused much interest. Lanthanide ions are the subject of increasing interest in bioinorganic and coordination chemistry [20, 21]. Literature studies showed that complexes of lanthanides are associated with several biological properties such as cytotoxic effect and anticancer effect [19, 22-26]. Kostova group reported the antineoplastic activity of lanthanide complex compounds with 3,3'-benzylidenebis[4-hydroxy-coumarin] [27].

In the present study, we investigated the coordination ability of 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methyl)-2H-chromen-2-one (4a) and 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methyl)-2H-chromen-2-one (4b) with Lanthanum and Nickel metal ions. The synthesized complex compounds 5 were screened for their DNA photocleavage activity.

EXPERIMENTAL:

Chemistry:

Synthesis of 1-phenyl-3-aryl-4-formylpyrazoles 3: [28-29] 1-Phenyl-3-aryl-4-formylpyrazoles 3, required for the present study were synthesized by the Vilsmeier-Haack reaction of hydrazones 2.

Synthesis of Ligands 4: [30-31] To an ethanolic solution of 1-Phenyl-3-aryl-4-formylpyrazole (3, 10mmol), was added 4-hydroxy coumarin (20mmol) and catalytic amount (2-3 drops) of conc. HCl. This ethanolic solution was refluxed for 25-30 mins, which on cooling afforded yellow colored solid. The solid, thus obtained, was collected by filtration and washed with water followed by hot ethanol to afford pure compound 4.

General Procedure for the Synthesis of Complex Compounds 5: [32-34] To the methanolic solution of ligand 4 (10mmol), was added aq. solution of metal salt (lanthanum nitrate ($La(NO_3).6H_2O$) or nickel chloride ($NiCl_2.6H_2O$). The pH of the solution was maintained at 5.5 by the addition of NaOH solution. After overnight stirring, a solid separated out. The solid, thus obtained, was filtered and washed thrice with water to get the complex compound 5.

Pharmacology:

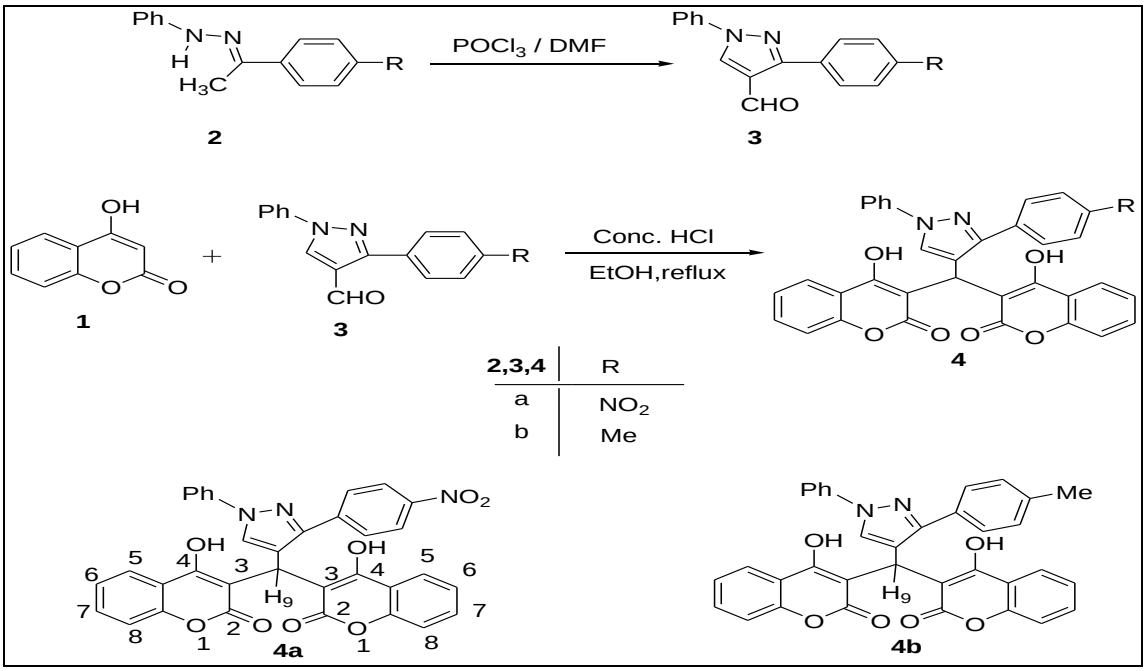
General Procedure for DNA Photocleavge Activity: [35] DNA photocleavage experiment was performed by taking 10 µl solution containing plasmid DNA in TE (Tris 10mM, EDTA 0.01mM, pH 8.0) buffer in the presence of 10 µg & 25 µg of synthesized complexes 5a-d. The sample solution held in caps of polyethylene microcentrifuge tubes was placed directly on the surface of a trans-illuminator (8000 mW/cm) at 360 nm and was irradiated for 30 min at room temperature. After irradiation, samples were further incubated at 37°C for 1 h. Irradiated samples were mixed with 6X loading dye containing 0.25% bromophenol blue and 30% glycerol. The samples were then analyzed by electrophoresis on a 0.8% agarose horizontal slab gel in Tris-acetate EDTA buffer (40 mM Tris, 20 mM acetic acid, 1 mM EDTA, pH: 8.0). Untreated plasmid DNA was maintained as a control in each run of gel electrophoresis, which was carried out at 5V/cm for 2.0 hr. The gel was stained with ethidium bromide (1 µg/mL) and photographed under UV light. To account the effect of synthesized complexes 5a-d on DNA, the band intensities were analyzed using the GelQuant. NET software was provided by biochemlabsolutions.com.

RESULTS AND DISCUSSION:

Chemistry: Ligands 4a-b were prepared by the condensation of 1-Phenyl-3-aryl-4-formylpyrazoles 3 with 4-hydroxycoumarin **Scheme 1**. The biscoumarin compounds 4a-b were characterized by comparing its spectral and physical data with the reported data [31]. The 1-Phenyl-3-aryl-4-formylpyrazoles 3, required for the present study, were synthesized by the Vilsmeier-Haack reaction of hydrazones 2 as shown in **Scheme 1**.

The fragmentation of the complex 5a showed molecular ion peak at 770, which confirmed the complex formation with formula $La(C_{34}H_{21}N_3O_8)(OH)(H_2O)$ when taken in ratio of 2:1. Similarly, another lanthanum complex 5b using ligand 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methyl)-2H-

chromen-2-one (4b) was synthesized. Encouraged by these results, Nickel complexes 5c-d were also prepared by stirring the ligands 4a-b and $NiCl_2.6H_2O$ in 2:1 ratio using a similar synthetic approach. The characteristic peaks observed in the mass spectra of the ligands 4a-b and its metal complexes 5 are discussed in **Table 1**.



SCHEME 1

Lanthanum complex **5a** was synthesized by treating 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methyl)-2H-chromen-2-one (**4a**) with lanthanum nitrate hexahydrate by selecting ligand : metal molar ratio of 2:1 (**Scheme 2**).

4 + $La(NO_3)_2.6H_2O$ $\xrightarrow{pH= 5.5}$ $La(\mathbf{4})(OH).H_2O$

5a-b

SCHEME 2

TABLE 1: MASS-SPECTRAL DATA OF BISCOUMARINS WITH THEIR La (III) AND Ni(II) COMPLEXES

Ligand	m/z	%	Complex	m/z	%
$C_{34}H_{21}N_3O_8$ (4a)	601	100	$La(C_{34}H_{21}N_3O_8)(OH).H_2O$ (5a)	770	20
	569	30		573	100
				446	10
				265	50
				229	05
			$Ni(C_{34}H_{21}N_2O_6)(OH).H_2O$ (5c)	660	10
				515	10
				483	100
				470	10
$C_{35}H_{24}N_2O_6$ (4b)	569	100	$La(C_{35}H_{24}N_2O_6)(OH).H_2O$ (5b)	766	20
	568	30		569	100
				442	05
				407	30
				263	40
			$Ni(C_{35}H_{24}N_2O_6)(OH).H_2O$ (5d)	694	05
				569	100
				338	05
				261	05

Furthermore, a comparison of the ^{1}HNMR spectra of complexes 5 and of the ligand 4 revealed that the resonances of the protons of the ligand were considerably broadened and also shifted, indicating complexation [36]. These shifts are considered as a valuable indication to confirm the coordination of metal with the ligand. Similar observations have often been made for coordination compounds and metal complexes [37-45]. As reported in the literature, these values indicate the coordination mode of the coumarin-system [46] **Table 2**.

TABLE 2: COMPARISON OF ^{1}HNMR SHIFTS OF COMPLEXES

Entry	Δ (ppm) H_9
4a	6.82
Complex 5a	6.49
Complex 5c	5.59
4b	6.09
Complex 5b	5.76
Complex 5d	5.59

On the basis of a detailed IR study of the spectral behavior of lanthanum complexes and their ligands, it was suggested that ligand bound to La(III) ions through both oxygen atoms of the carbonyl group from the ligands **Table 3**. The (C=O) bands in the ligand spectrum exhibited a redshift in the spectra of the complexes. This finding may be taken as evidence for participation of the C=O group in coordination with the metal ion. Further, a comparison between the ligand and complex IR spectra revealed that the absorption bands associated with the stretching (O–H) of the phenolic groups disappeared in La (III) complex spectra, indicating a loss of phenolic protons on complexation and thus forming a metal-oxygen bond [47].

TABLE 3: SELECTED EXPERIMENTAL IR FREQUENCIES

Compound	ν C=O (cm^{-1})
4a	1657
Complex 5a	1633
Complex 5c	1633
Ligand 4b	1660
Complex 5b	1648
Complex 5d	1645

Pharmacology: Photo cleavage efficiency of the drug is basically related to the tendency of relaxation of the supercoiled (SC) DNA into nonlinear circular (NC) DNA or, more specifically, degradation of both the SC and OC form of DNA [48]. To test the potential of complexes 5a-d, agarose gel electrophoresis was used for the analysis of DNA photocleavage activity. The cleavage potential of the complexes was assessed by comparing the bands that appeared in control and test compounds in the absence and presence of UV-irradiation [49]. The compounds were evaluated at two conc. 10µg and 25 µg as shown in **Table 4.**

It has been observed that in the absence of UV-irradiation, the test compounds 5c, 5d showed no appreciable DNA degradation because the intensity of both forms was found to be the same in comparison to control. Complex 5a showed the degradation of both forms of DNA when taken at 25 µg. In addition, complex 5b also degraded the SC form of DNA when evaluated at both conc. of 10µg and 25 µg.

TABLE 4: DNA PHOTOCLEAVAGE STUDY OF THE COMPLEX COMPOUNDS 5A-D

Entry	At conc. 10µg		Entry	At conc. 25µg	
	% NC	% SC		% NC	% SC
5a	18.5	16.6	5a	-	-
5b	20.1	-	5b	22.4	-
5c	39.2	32.1	5c	37.6	31.6
5d	13.7	17.6	5d	18.2	19.4
C	40.0	60.0	C*	-	100.0

From overall results, it is evident that complexes 5a and 5b can be recognized as biologically potent complexes and can be explored further.

CONCLUSION: The coordination of the pyrazolylbiscoumarins 4a-b with lanthanum and nickel-metal ions has been studied. The interpretation of the complex formation was concluded on the basis of comparison of IR, 1HNMR, and mass spectral data of the free ligand and the complexes. The DNA photocleavage screening studies of the synthesized complex compounds 5a-d revealed that these complexes possessed good biological profile and further study in this direction would be beneficial in developing medicinally important targets.

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