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A DIMINUTIVE REVIEW ON SYNTHESIS PATHWAY AND PHARMACOLOGICAL EVALUATION OF TRANSITION METAL ION COMPLEXES IN COUMARIN

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Abstract

A recurrent pattern in compounds (both natural and synthetic) with a wide range of biological activities including anti-inflammatory, antioxidant, antiviral, antibacterial, and anticancer medicines and enzyme inhibitors. However, in contrast to coumarin-based ligands, it has been suggested that the addition of a metal ion to coumarin derivatives can boost the activity of complexes. The current development of coumarin metal complexes with established biological characteristics is briefly summarized in this review. Agents that may have useful uses in the identification of biologically significant species are also given consideration. In conclusion, we compiled significant developments in coumarin-metal complexes from 2009 to 2023 as antioxidant, antifungal, pesticidal, anthelmintic, anticancer, and/or enzyme mimics or inhibitors. The cytotoxic effects of metal complexes containing coumarin-based ligands have been extensively studied in an effort to discover new therapeutic drugs to fight cancer. The development of new antimicrobial medications is a significant research topic that is looking at coumarin-based metal complexes in light of the increase in multi-drug resistance microbial illnesses. The compounds that contain coumarin-metal complexes are valuable and show promise as lead compounds in the development of anti-neurogenerative drugs.

Keywords: Coumarin, Transition metals, biological activities, metal complexes

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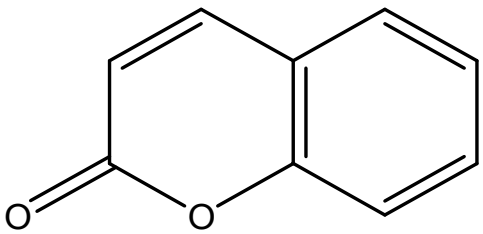
INTRODUCTION

In addition to occurring naturally in plants, coumarin is a white, crystalline molecule with a characteristic benzopyrone structure. There are various chemical processes that can be used to create coumarin [1,2]. The coumarins can be categorized into simple coumarins, furanocoumarins, pyrano coumarins, and other coumarins based on the various substituents in the overring [3-5]. The linear type and angular type of the furanocoumarins and pyrano coumarins can be distinguished from one another [6]. The biological action of coumarin derivatives, both natural and synthetic, is thought to span a wide range of activities including anti-inflammatory, antioxidant, antiviral, antibacterial, and anticancer medicines and enzyme inhibitors [7,8]. As a result of their numerous desirable properties, including Coumarins are important as lead compounds in therapeutic research due to their low toxicity [9], simple structure [10], high bioavailability [11], and solubility in most organic solvents. The hydroxy group is substituted in the simplest natural coumarins (e.g., umbelliferon's 7-hydroxycoumarin), while other simple hydroxy or methoxycoumarins (aesculetin's 6,7-DHC, daphnetin's 7,8-DHC, scopoletin's 7-hydroxy-6-methoxycoumarin, and scoparone's 6,7-DMC) and their glycosides. These uncomplicated substances have a wide range of potentially fascinating biological features, such as the capacity to chelate metals and restrain the activity of enzymes that generate reactive oxygen and nitrogen species (ROS and RNS) [12]. The ability of the transition metal ions to create coordination compounds with O, N donor ligands- which can donate an electron pair- is good. Some coumarins have distinctive physiological, photodynamic, and bacteriostatic actions and are used in a wide range of applications. Their chelating properties have long been noted, and chelation appears to be the cause of the bacteriostatic activity. The coumarins with chelating groups in the proper positions and their metal complexes have been studied physicochemically, and the results show that the ligands have potential as analytical reagents. Co(II), Ni(II), Pd(II), Zn(II), Cd(II), and Cu(II) complexes of these ligands with transition metal ions will be a preferable option for this research. Since the complexes created by these metal ions play a significant role in improving the metabolic and catalytic activities of the compounds [13,14]. Because of their many biological activities and drug-like qualities including high solubility, low molecular weight, high bioavailability, and low toxicity [15], coumarins have been regarded as the best small molecule candidates for the drug discovery and development process [16].



coumarin

CLASSIFICATION OF COUMARIN

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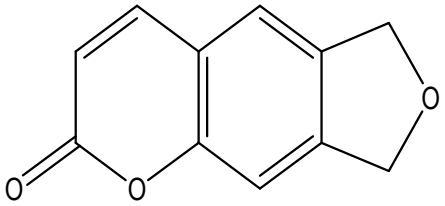
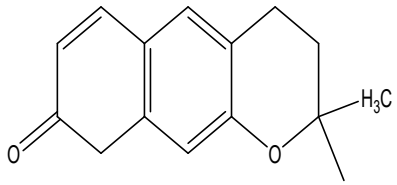
On the basis of the various substituents on the coumarin nucleus, coumarins can be categorised into four categories: Simple coumarin, Furano coumarin, pyrano coumarin and other coumarin like dicoumarol [17,18]. Coumarins are composed of fused benzene and -pyrone rings. Simple coumarins with antibacterial activity include Ammoresinol, Ostruthin, Novobiocin, Coumermysin, and Chartreusin, whereas Osthole exhibits biological activity against cancer [19].

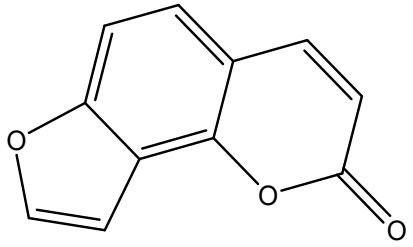
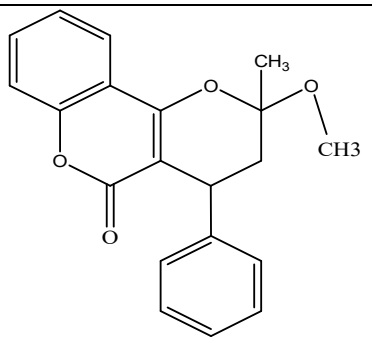
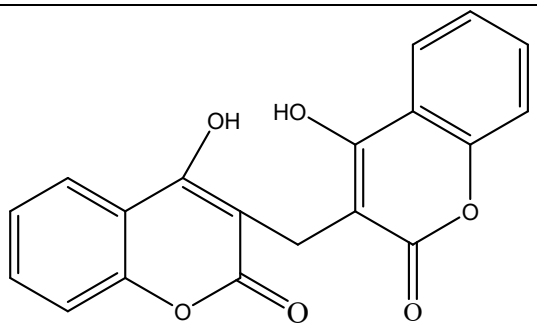


6*H*-furo[3,4-*g*]chromen-2(8*H*)-one



3,4-dihydro-2,2-dimethyl-2*H*-benzo[*g*]chromen-8(9*H*)-one

Table 1: Types of coumarins

FURANOCOUMARINS	
PYRANOCOUMARINS	
PYRONE-SUBSTITUTED COUMARIN	

Derivatives and glycosides of coumarin that lack any hydroxyl, alkoxy, or alkyl groups are referred to as "simple coumarins," and include compounds like umbelliferone, esculetin [20].

EXPERIMENTAL METHODS

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Detailed literature survey of different metallic complexed coumarin derivatives which are synthesized by different synthetic methods like heat-assisted synthesis, microwave-assisted synthesis, pH adjustment, and Chelation-assisted synthesis carried under different experimental conditions:

Halli et al. The complexes' geometry has been suggested by magnetic studies, 1H NMR, IR, UV-Vis, and ESR spectral data in addition to analytical data. The compounds are non-electrolytic in nature, as indicated by the ΓM values. These investigations have led to the assignment of tetrahedral geometry to Zn(II), Cd(II), and Hg(II) complexes and octahedral structure to Co(II), Ni(II), and Cu(II) complexes (Fig 1). The antibacterial properties of the Schiff base and its metal complexes have been investigated.

According to Shivashankar M. Kinnal et al., the addition of halogen atoms causes the ligands to become more lipophilic. The bioactivity of such ligands is further enhanced by the presence of halogen atoms. The presence of such electronegative atoms increases the bioactivity of the core moiety. The ligand in this instance exhibits partial cleavage with the Co(II) and Ni(II) complexes, while the Ni(II) complex cleaves entirely (Fig 2).

Muhammad Mujahid et al. revealed that spectroscopic techniques and microanalytical data were used to produce and characterize novel silver(I) complexes of coumarin oxyacetate ligands and their phenanthroline adducts. An Ag(I) complex's crystal structure was ascertained using X-ray diffraction research. Based on chemical structure modeling and subsequent spectra simulation using the density functional theory approach, the experimental spectroscopic data have been interpreted. The most likely ligand binding in the series of complexes examined has been determined by theoretically modeling and discussing the binding modalities of the coumarins and phenanthroline ligands. After the complexes' antimicrobial and antifungal activities were assessed, it was discovered that most of them had moderate antibacterial activity. However, some of the phenanthroline adducts showed antifungal activity against the clinically significant fungus C. albicans, which was on par with that of commercial agents like ketoconazole and amphotericin B. The silver complexes' capacity to function as a superoxide dismutase mimic may be connected to their antimicrobial activity, according to preliminary research into their potential mechanism of action, which revealed that they did not interact with DNA via nuclease activity or intercalation Fig (3)[7].Imen Ketata et al. reported that a new transition metal complex of Cobalt(III) of the ligand (E)-3-(1-(2-aminoethylimino)ethyl)-4-hydroxy2H-chromen-2-one was synthesized by reacting cobalt(III) salt with the ligand in amounts equivalent to the metal-ligand molar ratio of 1:2. The ligand was derived from condensation of ethylene diamine with 3-acetyl-4-hydroxy-chromene2-one. The Co (III) complex and the Schiff base were both studied using 1H NMR, 13C NMR, UV-vis, and IR spectroscopic methods. that the cobalt complex is triclinic P-1, with a = 10.426(5) Å, b = 11.3234(2) Å, c = 15. According to S. Radha et al., a number of methods have been used to synthesize and characterize three metal complexes of the 3-benzoyl-7-

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methoxycoumarin ligand. The existence of nitrate ions in the coordination sphere was confirmed by the infrared spectra of the ligand and its complexes, which demonstrated the ligand's bidentate behavior. The existence of nitrate ions in these complexes was confirmed by thermogravimetric and differential thermal analysis, which was used to investigate the thermal stability of the complexes. The geometry of each complex surrounded the metal center in an octahedral pattern. Cyclic voltametry was used to study the redox property of the metal complexes, and the results indicated that all of the complexes displayed a quasi-reversible nature. Studies on the antimicrobial properties of these metal complexes and the ligand were carried out against the following species: Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa, Aspergillus niger, and Escherichia coli. In comparison to the ligand, metal complexes exhibited stronger antibacterial activity. The zinc complex of coumarin derivative was optimized for structure using the 6-311G++G (d,p) basis set in the DFT/RB3LYP method. The zinc complex's shape, structure, and vibrational assignments were determined using density functional theory computations (Fig. 5). A new sensing approach based on CdN isomerization was disclosed by Jia-Sheng Wu et al.; it is proved to provide a very considerable fluorescence amplification to the metal cations in a straightforward and effective manner [21-23]. To serve as an example, a coumarin derivative (L) with a CdN group was created. As a result of the excited state CdN double bond isomerization, the free ligand L is nearly nonfluorescent. Nevertheless, the addition of Zn(ClO4)2 to the ligand solution results in a roughly 30% increase in fluorescence quantum yield (approximately 200 times). This is due to C=N isomerization, which effectively and simply exhibits a very strong fluorescence enhancement of the compounds that are coumarin derivatives to the metal cations. It can be expanded to include additional sensor devices for identifying various species [24].

Table 2: Structure Of Coumarin Metal Complexes

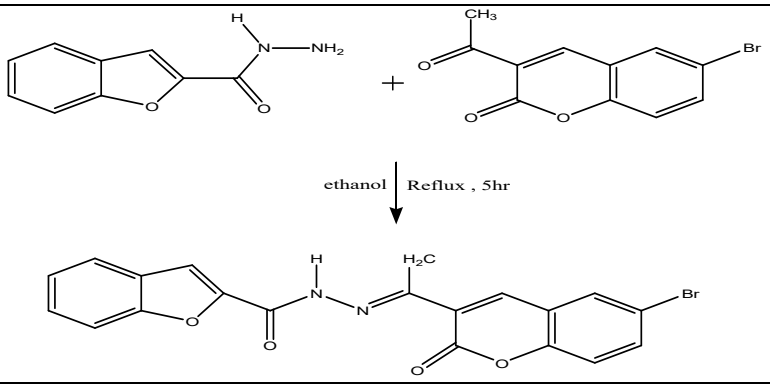
Fig 1	

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Fig 2

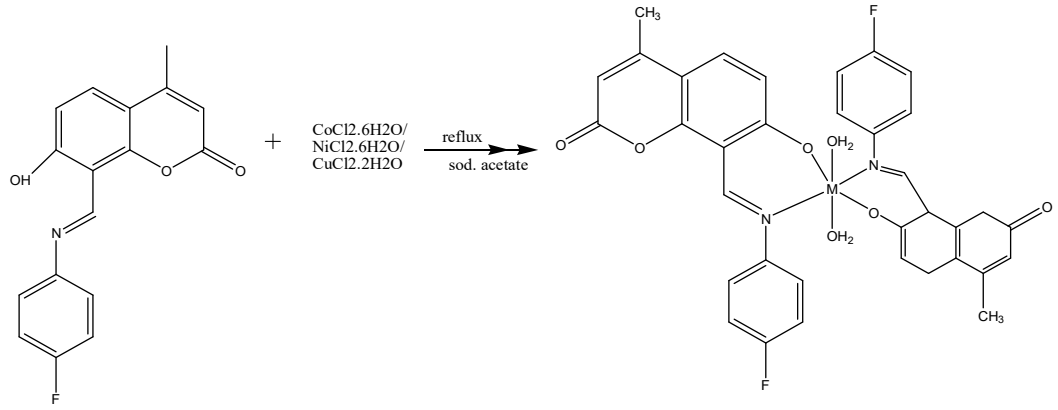
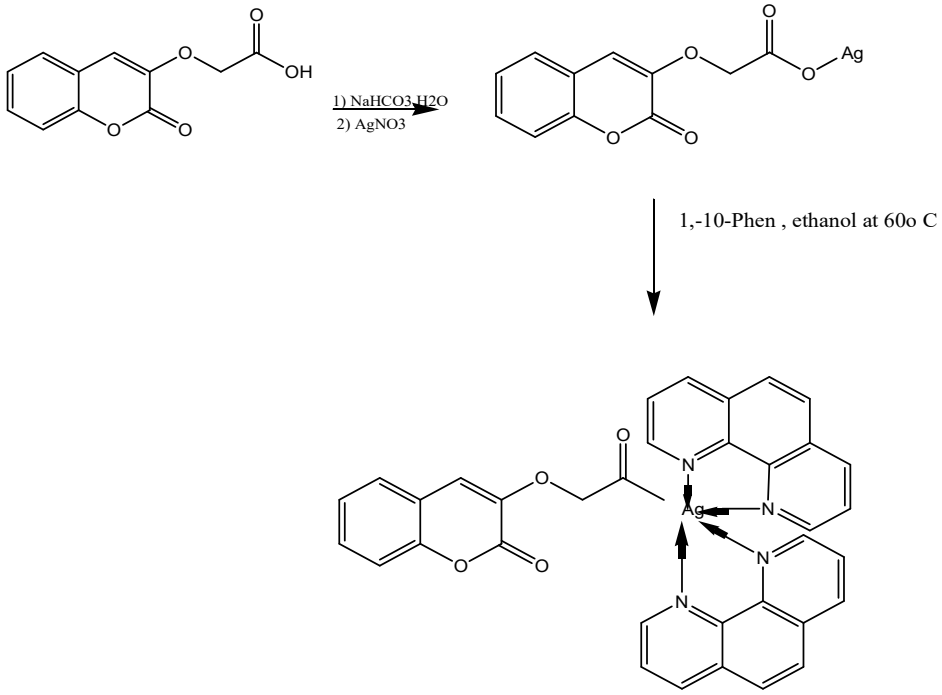
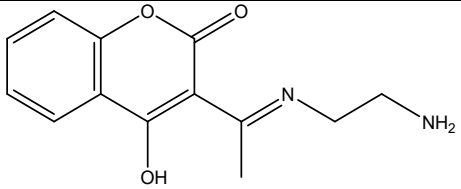


Fig 3



General reaction scheme for the synthesis of 2-[(2-oxo-2H-chromen-3-yl)oxy]acetic acid-based silver(I) complex and its phen adduct

Fig 4



(E)-3-(1-(2- aminoethylimino)ethyl)-4-hydroxy-2H-chromen-2-one

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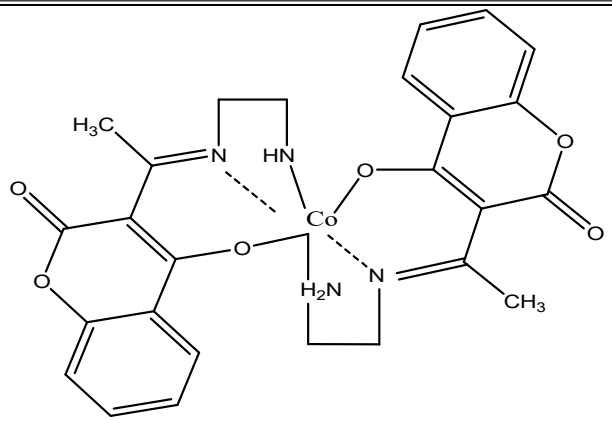
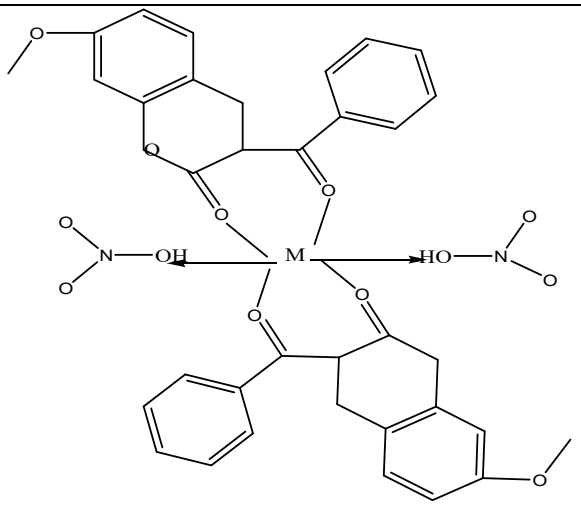


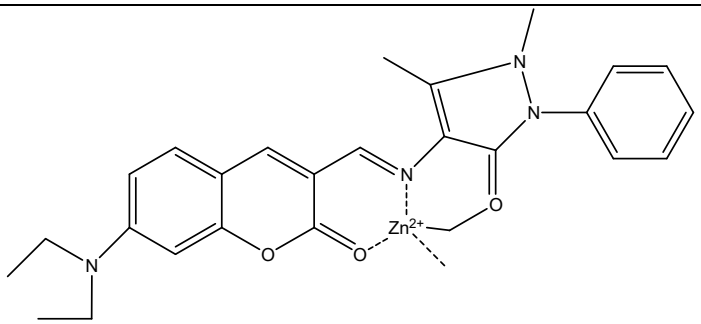
(E)-3-(1-(2-aminoethylimino)ethyl)-4-hydroxy-2H-chromen-2-one complexation reaction with cobalt

Fig 5



Structure of the metal complexes M=Ni, Cu, Zn (Fig 5)

Fig 6



Proposed interaction mode between L and Zn2+ (Fig 6)

VARIOUS COUMARIN METAL COMPLEXES WITH DIFFERENT PHARMACOLOGICAL ACTIVITIES

Anti-Microbial Complexes

➢ Novel therapeutic agents and medications are needed, as the resistance to routinely used antibiotics is increasing. Note that there are still few therapeutic alternatives available for many

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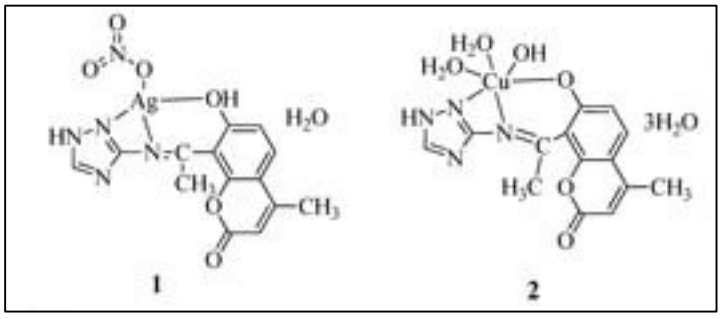
strains of bacteria, and research on the construction of metal complexes has been the main focus of efforts to find new antimicrobial medications. Recently published publications provide important insights into coumarin antibacterial metal compounds (Claude et al. 2020). The copper (II) and zinc (II) complexes of 3-(2-hydroxybenzoyl)-2H-chromen-2-one (12) and (13) were reported by Belkhir-Talbi et al. in 2019 as efficacious agents against the Gram-positive bacterial strain Staphylococcus aureus (ATCC 25923). When compared to cefoxitin, a reference second-generation cephamycin group antibiotic (diameter of inhibition zone: 20 mm), it was shown that both complexes showed modest antibacterial activity and their inhibition zone widths ranged from 14-17mm. Moreover, scavenging activity was greater in complexes 12 and 13 than in the free ligand. The non-toxic and non-carcinogenic characteristics of these compounds were validated by silico ADMET and drug likeness profile [25,26].

- Avdovic et al. (2019) synthesized metal complexes with 3-[1-(2-hydroxypropylamino) ethylidene]chroman-2,4-dione, 3-[1-(phenylamino) ethylidene] chroman2,4-dione, 3-[1-(o-toluidino)ethylidene]chroman-2,4-dione,3-[1-(m-toluidino)ethylidene]-chroman-2,4-dione and 3-[1-(2- mercaptoethylamino) ethylidene]chroman-2,4-dione in order to evaluate their antimicrobial activity. In general, the activity of the complexes was higher or similar to that of the corresponding ligands. Among them, Pd(II) complex 14 was found to be more active against Bifidobacterium animalis subsp. lactis, Pseudomonas aeruginosa, Escherichia coli than the reference ligand - 3-[1-(2-hydroxypropylamino) [27].
- Farghaly et al. (2021) synthesized a Schiff base (Sbat) using 3-amion-1,2,4-triazole and 8-acetyl-7-hydroxy-4-methyl coumarin. The Ag(Sbat)(NO3)]H2O (1) and [Cu(Sbat)(OH)(H2O)2 were formed by the Schiff base's reaction with Ag(I) and Cu(II) metal ions. Complexes of 3H2O (2). The standard agar diffusion test was used to assess the antimicrobial properties of Gram-positive bacteria, namely Staphylococcus aureus (S. aureus), Staphylococcus faecalis (S. faecalis), and Bacillus subtilis (B. subtilis). Gram-negative bacteria, on the other hand, included Escherichia coli (E. coli), Neisseria gonorrhoeae (N. gonorrhoeae), and Pseudomonas aeruginosa (P. aeruginosa). Using the produced complexes, antifungal efficacy against Aspergillus flavus (A. flavus) and Candida albicans (C. albicans) was further investigated. The Schiff base was shown to have no effect against the two fungal species based on the activity studies that were done [23].



Alzheimer Complexes

- Giriraj Kalaiarasi et al; stated that via spectroscopic and analytical methods, four copper (II) complexes 1-4 of 3-acetylchromene-2-one and substituted 3-acetylchromene-2-one derived Schiff bases were created and structurally described. Single crystal X-ray diffraction investigations have validated the molecular structure of complex 1, revealing that ligand 3-acetylchromene-2-one-4 N-semicarbazone is coupled to the metal as an ONO pincer type ligand. Initial biological investigations, such as DNA and protein binding examinations, demonstrated that the ligands and complexes bound to both bovine serum albumin and calf thymus DNA. The impact of complexes 1-4 on amyloid-β (Aβ) toxicity through the use of transgenic Caenorhabditis elegans strains that express human Aβ1-42 specific to muscles and neurons. The findings demonstrated that the strong antioxidant and antiaggregative qualities of complexes 2-4 significantly decreased the Aβ-induced paralysis phenotype, Aβ plaque formation, and other Alzheimer's disease-related functional impairments in C. elegans. Complexes 2-4 postponed the diseases associated with Alzheimer's disease, offering a foundation for additional research into these impacts on higher models.
- Namy George et al; said that spectrum analysis was used to analyze the chemical structures of the hybrid compounds, which were created by a Pechman reaction. The coumarin-oxadiazole hybrid compounds have been shown to operate on various targets in the pathogenesis of AD, including inhibition of cholinesterase, scavenging of free radicals, decreasing oxidative stress, and by reducing inflammation, according to PASS's in-silico biological property prediction. Many of the compounds are more powerful AChE and BuChE inhibitors than the conventional chemical, according to in vitro biological experiments performed for the proposed ligands. 4-methyl-7-((5-(3,4,5-trihydroxyphenyl)-1,3,4-oxadiazol-2-yl)methoxy)–2H-chromen-2-one) is one of the chemicals and 4e (7-((5-(3,4-dihydroxyphenyl)-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one) showed the most potent inhibitory activity against AChE with an IC50 value of 28.68 and 29.56 mM while compound 4m (7-((5-(benzo[d][1,3]dioxol-4-ylmethyl)-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one) showed higher activity against BuChE with IC50 value of 23.97mM. The compounds 4g and 4e also showed higher selectivity index (SI) of 1.652 and 1.552 as compared to standard galantamine (SI= 1.132). The results showed that the linker between coumarin and 1,3,4-oxadizole is important for the inhibitory effect against AChE. Also, there is remarkable decrease in the activity of the compounds having the linkers (vinyl) between the 1,3,4-oxadiazole ring and the di or trihydroxy containing phenyl ring. It was also noticed that there is considerable decrease in activity if any of the hydroxyl group of the phenol is replaced by other electron donating methoxy or methylenedioxy groups. The docking studies results showed these potent compounds act through the inhibition of both AChE and BuChE. Further investigations and modification of these proposed compounds can lead to the development of highly potent therapeutics for the treatment of AD [27,28].
- The sole appropriate target utilized in the therapy of Alzheimer's disease (AD) is cholinesterase inhibition. Thus, the creation and production of novel cholinesterase inhibitor compounds is perpetually required. Palladium and platinum complexes made by coupling coumarin and thiazole with 3-tertiary butyl salicylaldehyde, a novel Schiff base, were recently reported by Ozdemir and colleagues. Using a variety of spectroscopic methods, the structural characteristics of metal

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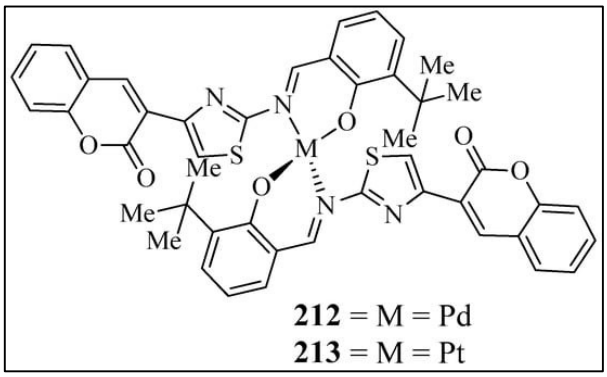
complexes 212 and 213 were determined. Furthermore, the authors examined the inhibitory strengths of metal complexes on three esterase enzymes: pancreatic cholesterol esterase activities (CEase), butyrylcholinesterase (BChE), and acetylcholinesterase (AChE). The results of the anti-esterase activity indicated that metal complexes effectively block the pancreatic cholesterol (CEase) and cholinesterase (AChE/BChE) enzymes. When compared to the reference medications, platinum complex 213 in particular showed a strong inhibitory action with lower IC50 values (12.0 μM for AChE, 23 μM for BChE, and 21.0 μM for CEase) [29].



212 = M = Pd
213 = M = Pt

Anti-Cancer Complexes

- Gramni et al. created and synthesized a novel octahedral paramagnetic ruthenium (III) complex 5 of 4-{[bis(pyridin-2-ylmethyl)amino]methyl}-7-methoxy-2H-chromen2-one (chrdpa) that same year. X-ray crystallography and TOF-mass spectrometry were used to confirm the structure of the compound. With an estimated IC50 of 137 μM, compound 5 demonstrated lethal effects against HeLa cervical cancer cells in vitro. (Gramni and others, 2019). DNA binding experiments using calf-thymus DNA titrated with complex 5 showed a characteristic hypochromic impact by 33% in the UV-Vis spectrum profile, suggesting that complex 5 is a groove binding agent [30].
- Despite the fact that anticancer drugs are widely used in medicine, their usage is accompanied by serious side effects and poor efficacy. As a result, one crucial aspect of antitumor medication design continues to be the creation of innovative chemotherapeutics. One intriguing approach to treating cancer is to block the activity of cyclooxygenase (COX). Given that COX plays a critical role in inflammation linked to cancer, which in turn causes the growth and spread of cancer, a number of COX-targeted inhibitors have the potential to be used as anticancer medications.In 2019, Wang and associates synthesized and assessed the anticancer activity of a series of bi-functional platinum (IV) complexes 1-4 with 7-hydroxycoumarin ligands in an axial position (Wang et al., 2019). Complex 3 showed promising effects, inhibiting rhCOX-2 activity in a dose-dependent manner from 20.1 to 65.8%. Complex 3 causes the release of the proper coumaric acid derivative, which lowers inflammation linked to tumors. Furthermore, it has been proposed that the platinum (IV) complexes 1-4 in cancerous tissues could be converted to a comparable quantity of platinum (II) compounds that cause damage to DNA, indicating a bi-functional mechanism of action.
- The synthesis of novel coumarin-metal complexes was revealed by Lu W. et al. in 2020; these compounds may find application in the treatment of cervical cancer. A single-crystal X-ray diffraction investigation unequivocally established the structure of the octahedral copper (II)

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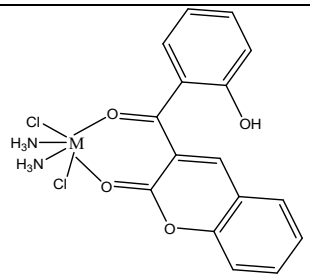
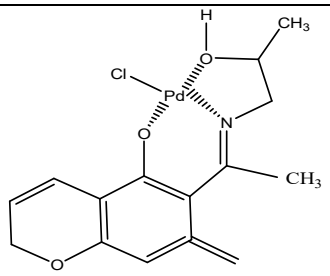
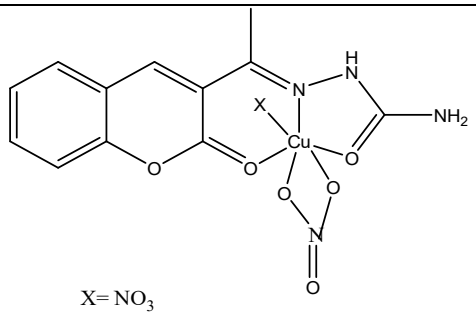
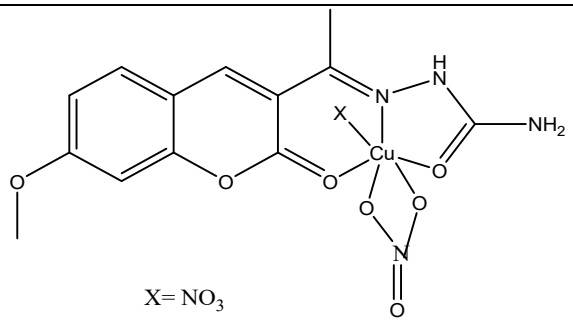
complex 6, which was produced under mild reaction conditions by the reaction of 8-(tert-butyl)-3-(pyridin-2-yl)-2H-chromen-2-one with copper (II) nitrate trihydrate. With an IC50 value of 18.05 μM, this chemical demonstrated strong antiproliferative action against the HeLa cell line, a model of cervical tumors. Furthermore, complex 6's solution exhibited a hypochromic impact upon the addition of DNA, indicating that this molecule may have an interactive mode of action. These findings are supported by DNA binding tests [31,32].

Table 3 | Coumarin-based metal complexes with diverse biological activities.

COMPLEX	**Chemical structure**	**Activity**
Complex 12, 13 12= Cu, 13= Zn		Anti-Microbial
Complex 14		Anti-Microbial
COMPLEX 1	 X= NO_3	Anti-Alzheimer's
COMPLEX 2	 X= NO_3	Anti-Alzheimer's

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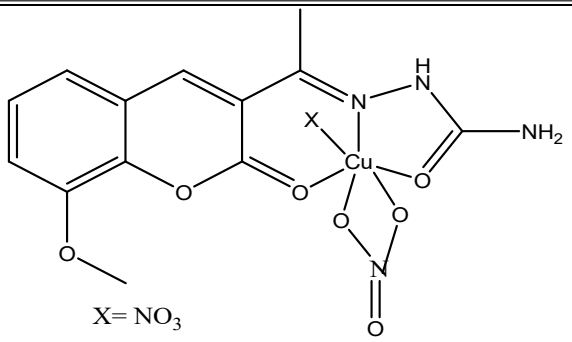
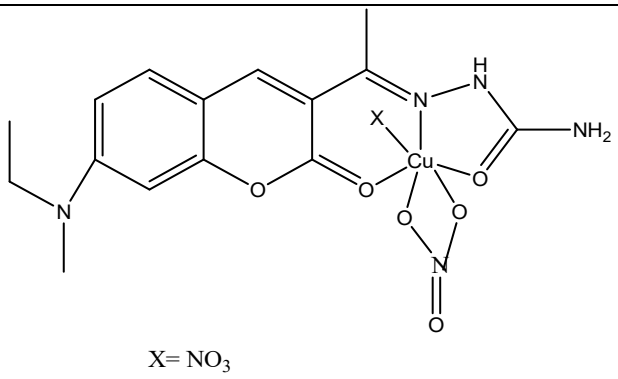
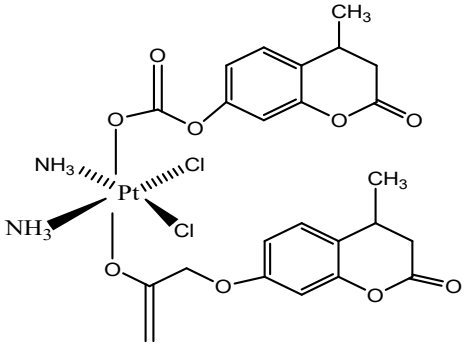
COMPLEX 3		Anti-Alzheimer's
COMPLEX 4		Anti-Alzheimer's
COMPLEX 1, 2		Anti-cancer

Antioxidant complex

Sinha et al. (2011) using pyridine-2-carboxaldehyde and 6-aminocoumarin condensation to create a ligand. Complexes (201–203) were produced by the ligand's reaction with Cr(CO)4, Mo(CO)4, and W(CO)4 (Figure 7). The antioxidant characteristics of the three complexes were evaluated, and their radical scavenging ability (antioxidant activity) was investigated in relation to superoxide (O2−), nitroxyl radical (NO), hydroxyl radical (OH·), and 1,1-diphenyl-2-picrylhydrazyl (DPPH). The results showed that for [Cr(CO)4(L)], [Mo(CO)4(L)], and [W(CO)4(L)], respectively, the complexes had a maximum percentage of inhibition at concentrations of 0.03 mg/mL, 0.3 mg/mL, and 0.01 mg/mL. As a result, complex 203 has the greatest scavenging ability due to its heaviest element (W) [24].

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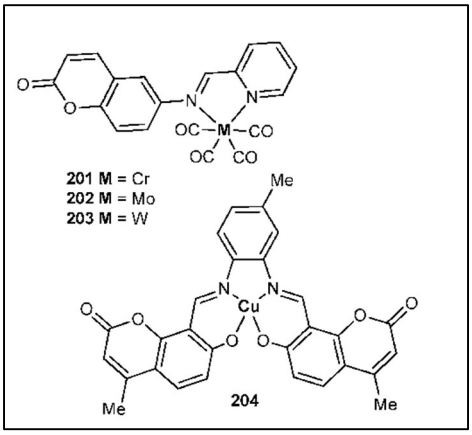
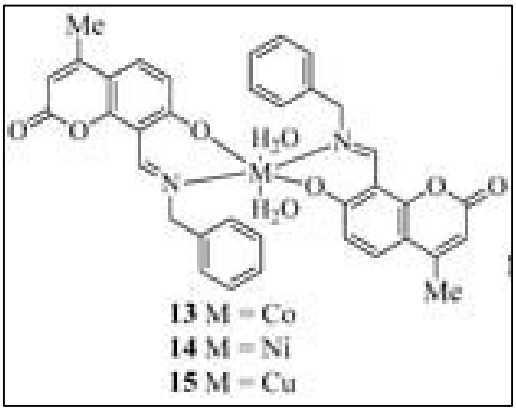


Anthelmintic complex

Anthelmintics are medications used to treat animal diseases caused by parasitic worms. The coumarin-derived imine complexes Co(II), Ni(II), and Cu(II) were reported by Badami et al. (2015) for an anthelmintic (Pheretima posthuma) activity research. It is possible to conclude that metal complexes are more active than their parent ligands based on the results obtained. At a dose of 10 μg/mL, Cu(II) complex 15 demonstrated superior action in comparison to albendazole, the usual medication [33].



Pesticidal

Together, nematodes and pests disrupt the entire ecological equilibrium by occupying many trophic levels. They proliferate for centuries, spreading a variety of diseases that are infamously fatal to people, animals, and plants. Finding long-lasting, potent pesticides and nematodes is essential because of this persistent problem. Kulkarni et al. (2009) of the pesticidal and nematocidal effects of lanthanide(III) complexes (129-131) (Figure 5) against Tribolium castaneum and Meloidogyne incognita using 3-formyl-4-chlorocoumarin hydrazinecarbothioamide and 3-formyl-4-chlorocoumarin hydrazinecarboxamide. Comparing the metal complexes to their respective ligands, all of them showed good pesticidal efficacy. Based on a comparison analysis of their percentage mortality statistics with other metal complexes (129 and 131), Sm(III) complex 130 was particularly effective. The nematocidal activity shows that

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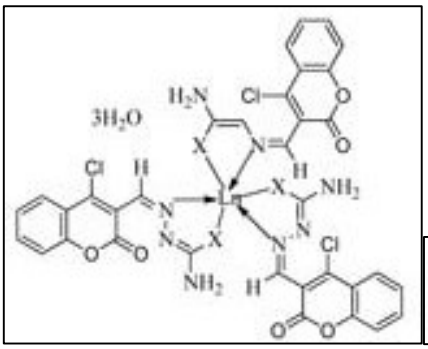
metal complexes 129–131 were more effective than the corresponding ligands in reducing the hatching of eggs [34].



129 M = Nd, X = O
130 M = Sm, X = O
131 M = Gd, X = O

CONCLUSION

In conclusion, significant developments in coumarin-metal complexes from 2009 to 2023 were reported as antioxidant, pesticidal, anthelmintic, antifungal, anticancer, and/or enzyme mimics or inhibitors. The cytotoxic effects of metal complexes containing coumarin-based ligands have been extensively studied in an effort to discover new therapeutic drugs to fight cancer.

The development of new antimicrobial medications is a significant research topic that is looking at coumarin-based metal complexes in light of the increase in multi-drug resistance microbial illnesses. The compounds that contain coumarin-metal complexes are valuable and show promise as lead compounds in the development of anti-neurogenerative drugs.

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Nil.

CONFLICT OF INTEREST

None' conflict of interest declared by the authors.

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