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Coumarin Hydrazide: Chemistry, Synthesis and Pharmacological Activities - A Review

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ABSTRACT

Coumarins are heterocyclic compound with a benzopyrone structure. Coumarins are a large group of organic compounds found in several plants even in bacteria and fungi. The biological activities of coumarins and its derivatives includes anticoagulant, anticancer, antiulcer, antifungal, anti-HIV, antimicrobial, antiosteoporosis, antioxidant and anti-inflammatory activity. Hydrazide-hydrazone derivatives act as structural sub units in many pharmacologically active compounds including coumarins to give biological activities like antimicrobial, anticancer, antifungal, anti-inflammatory, antiviral, anti-tubercular, and antiprotozoal activity. The interest in the synthesis of coumarin derivatives has been gaining importance over the last decades, reflecting the importance of such compounds in both medical and chemical research. In this review hydrazide-hydrazone derivatives of coumarins are taken into consideration and emphasised on the anticancer, antitubercular, antimicrobial, antioxidant and antidiabetic activity of these derivatives.

Keywords: Coumarin, hydrazide, heterocyclic, benzopyran, antitumor, antimicrobial, antioxidant

INTRODUCTION

Coumarins are a large group of organic compounds found in several plants even in bacteria and fungi. Coumarins are heterocyclic compound with a benzopyrone structure. It was first discovered when it was isolated from plant Coumarouna odorata Aube (Dipteryx odorata) in 1820.[1] Coumarins and its derivative have a wide variety of medicinal property and several features like minimum toxicity and excellent stability to light. [2]

The biological activities of coumarins and its derivatives includes anticoagulant, anticancer, antiulcer, antifungal, anti-HIV, antimicrobial, antiosteoporosis, antioxidant and anti- inflammatory activity.[3]In this review hydrazide-hydrazone derivatives of coumarins are taken into consideration. Hydrazide-hydrazone derivatives act as structural sub units in many pharmacologically active compounds including coumarins to give biological activities like antimicrobial, anticancer, antifungal, anti-inflammatory, antiviral, anti-tubercular, and antiprotozoal activity.[4]

Chemistry

Coumarin

2H-chromen-2-one is an aromatic compound with molecular formula $C_9H_6O_2$ This molecule consist of a benzene ring with two adjacent hydrogen atoms are replaced by a lactone chain -(CH)=(CH)-(C=O)-O- which forms a second six membered hetero cycle that shares two carbon with the benzene ring.[5] The fused benzene and lactone ring contains a π-π

conjugated system which is rich in electrons and good charge carrier properties. These compounds form hydrophobic, π-π interactions, electrostatic interactions, metal co-ordinations, Van der Waals interactions, hydrogen bonding etc. with various active sites in organisms producing an action against them thus providing activity against various pathogens in humans.[6]

Hydrazide

Hydrazides are the class of pharmaceutically important compounds represented by $NHNH_2$ and NHN=CH- groups. A wide range of aldehydes and ketones contents with hydrazides giving hydrazones. Due to the less toxicity of the condensed hydrazones than the parent hydrazide they are more medicinally important. The less toxicity nature accounts due to the absence of availability of free NH_2.[4]

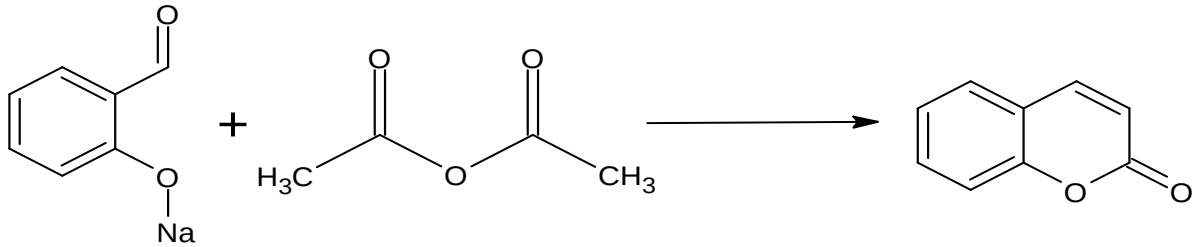
Natural occurrence

Since coumarin belong to the class of benzopyrone molecules, it is found in plants among the phenolic substances. It occurs naturally in a wide range of plant families over nearly 30 families and 150 species. Some of the families include Rutaceae, Umbelliferae, Clusiaceae, Caprifoliaceae, Oleaceae, Apiaceae etc. Plants like Sweet woodruff (Galium odoratum), Sweet-clover (genus Melilotus), Vanilla grass (Anthoxanthum odoratum), Ceylon cinnamon or true cinnamon (Cinnamomum verum), Deertongue (Carphephorus odoratissimus), Tilo (Justicia pectoralis), Mullein (genus Verbascum) are rich in coumarins.[7,8]

Synthesis

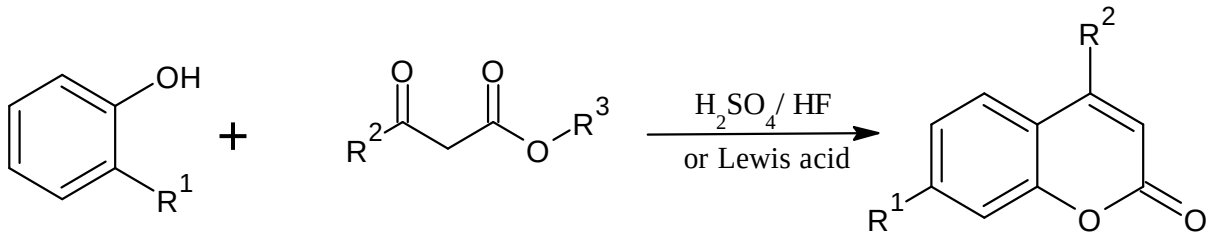
Synthesis of coumarin

Coumarins can be synthesized by Perkin, Pechmann or Knoevenagel reaction, as well as Wittig, Kostanecki-Robinson and Reformatsky reaction. Perkin reaction includes condensation of aromatic aldehydes and carboxylic acid anhydrides or carboxylic derivatives, in a base catalysed reaction, where cinnamic acid derivatives are formed. Coumarin synthesis by Perkin reaction proceeds by heating salicylaldehyde sodium salt with acetic anhydride (Scheme 1).



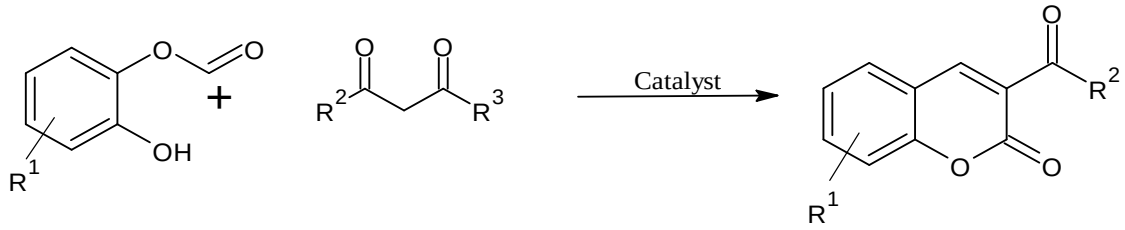
Scheme 1: Coumarin synthesis by Perkin reaction with sodium salt of salicylaldehyde with acetic anhydride

Pechmann condensation (Scheme 2), which is frequently acid catalysed, develops from phenols and -keto esters or -unsaturated carboxylic acids into coumarins.



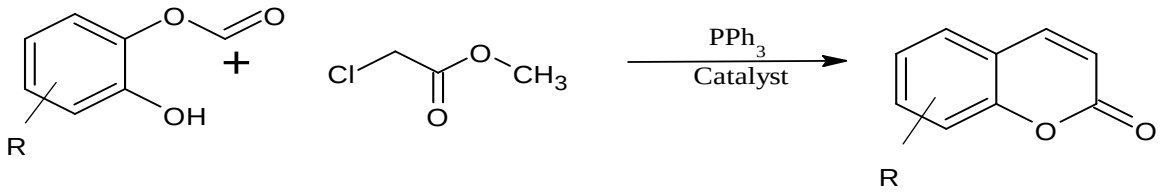
Scheme 2: Condensation of phenols and -keto esters

In a weak base-catalyzed process known as a knoevenagel condensation, an active methylene molecule is nucleophilically added to aldehydes or ketones. Water is often eliminated after this step. The reaction between salicylic aldehydes and malonic acid or esters leads to knoevenagel condensation into coumarins, which is typically accelerated by weak bases or Lewis acids (Scheme 3).



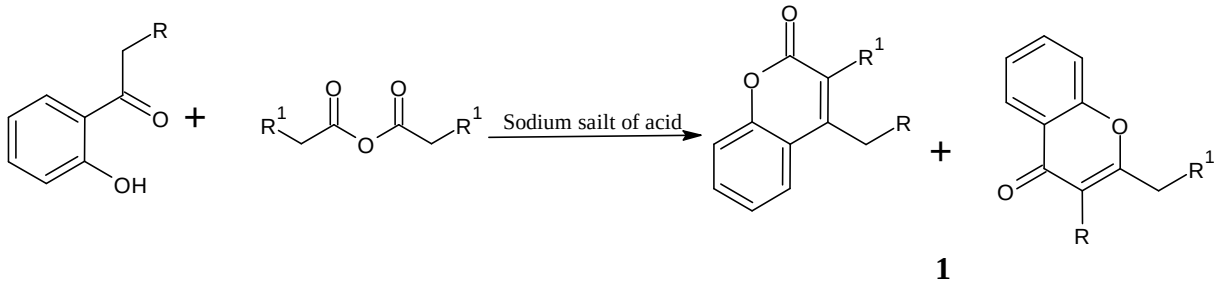
Scheme 3: Knoevenagel condensation of salicylic aldehydes and esters to into coumarins

Synthesis of substituted coumarins via Wittig reaction proceeds from the substituted salicylaldehydes, methyl or ethyl chloroacetate and triphenylphosphine (Scheme 4), using different catalysts.



Scheme 4: Wittig reaction of salicylaldehyde and ethyl chloroacetate

Kostanecki-Robinson synthesis of coumarins proceeds from hydroxy arylalkyl ketones, acid anhydride and the sodium salt of an acid, by the formation of the 3,4 carbon-carbon bond via the ester enolate (Scheme 5). When the reaction proceeds via keton enloate, chromones (4H-1-benzopyran-4-ones) **1** can be the major products. [9,10]



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Scheme 5: Kostanecki-Robinson synthesis of coumarins

In recent years, environmentally friendly synthetic techniques for making coumarins, like those involving microwaves or ultrasounds, solvent-free mechanosynthesis, or so-called designer solvents like ionic liquids or deep eutectic solvents, have modified or even replaced more traditional techniques.[11,12]

Synthesis of coumarin derivatives

M Shivaprasad Shetty et. al synthesised of coumarin derivatives by following method (scheme 6)

Ethyl 4-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)butanoate

In a round-bottom flask, dry DMF was added to a combination containing 7-hydroxy-4-methylcoumarin, anhydrous potassium carbonate, and ethyl-4-chlorobutyrate. After adding sodium iodide,

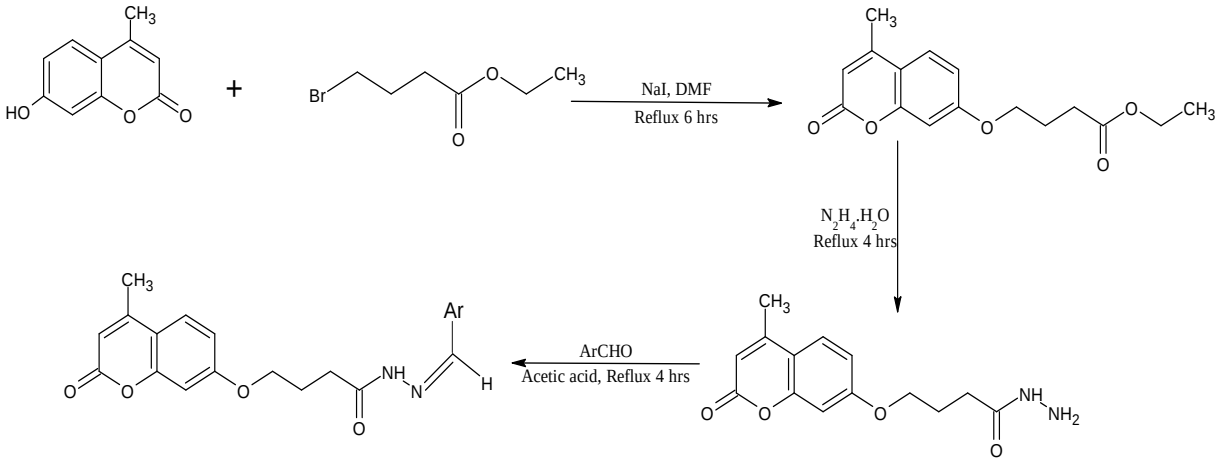
the liquid was refluxed for 6 hours while being constantly stirred. Following filtering, the mixture was decreased pressure-concentrated, vacuum-dried, and the solid was re-crystallized from ethanol.

4-((4-Methyl-2-oxo-2H-chromen-7-yl) oxy) butane hydrazide

To a solution of ethanol and hydrazine hydrate, ethyl 2-(4-methyl-2-oxo-2H-chromen- 7-yloxy) acetate was added, and the mixture was refluxed for 4 h. The product was precipitated, collected by suction filtration, washed with methanol, and recrystallized from diluted acetic acid.

Coumarin hydrazones

In the presence of a catalytic amount of glacial acetic, a combination of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide and the suitable aromatic aldehyde was refluxed in absolute ethanol for 4 hours. The reaction mixture was cooled, and the solid that had precipitated from methanol was filtered and recrystallized to produce compounds. [2]



Scheme 6: Synthesis of coumarin hydrazone

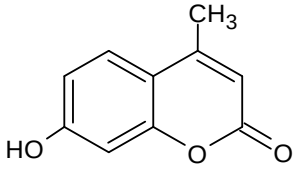
Pharmacological actions

Coumarin and its hydrazine derivatives possess numerous biological activities including, anticancer, anti-HIV, antimicrobial, antioxidant anti-inflammatory activities etc

Anti tumor activity

In every part of the world, cancer is one of the main causes of morbidity and mortality. In 2018, there were 9.6 million cancer deaths and an estimated 18.1 million new cancer diagnoses worldwide. 1 The structural hybridization strategy can be used to generate safe and selective anticancer medications with few side effects, which is still very desirable in order to lower the death rate from cancer.

Nongnaphat et. al combined 7-Hydroxy-4-methylcoumarin **2** with different aryl hydrazide–hydrazones and investigated their cytotoxic activity against human hepatic carcinoma (HepG2), breast carcinoma (SKBR-3), and colorectal adenocarcinoma (Caco-2) cell lines in vitro.



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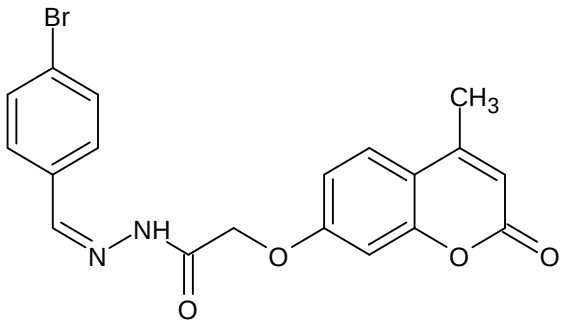
Coumarin hydrazide–hydrazones derivatives were screened their effects on cell viability in the HepG2 cell line. Furthermore, selected compounds were evaluated for in vitro antiproliferative activity against HepG2, SKBR-3, and Caco-2 cell lines. Among the test compounds, **3, 4** and **5** showed potent activities against both Hep-G2 and SKBR-3 cell lines. More significantly, compound 6d, having a 4-bromophenyl moiety, exhibited best

cytotoxic activity against Hep-G2 cell line with IC50 value of 2.84 ± 0.48 lg/mL which is comparable to the standard doxorubicin (IC50 = 2.11 ± 0.13 lg/mL). Comparing the evaluated coumarin hydrazide-hydrazone derivatives to compound 6f, which contains a 4-methoxyphenyl moiety, the latter showed the most powerful activity (IC50 = 2.34 0.68 lg/mL) against the SKBR-3 cell line. Unfortunately, doxorubicin and every synthetic substance were ineffective against the Caco-2 cell line. When tested against the Hep-G2 cell line, compound 6d had the strongest anti-proliferative activity (IC50- = 2.84 0.48 lg/mL) and an IC50 value comparable to that of doxorubicin (IC50- = 2.11 0.13 lg/mL). The two chemicals, 6d and 6f, were discovered to be promising for additional research to create fresh anti-cancer medications. [3,13]



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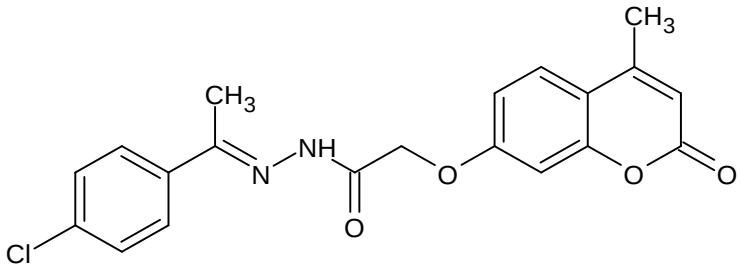

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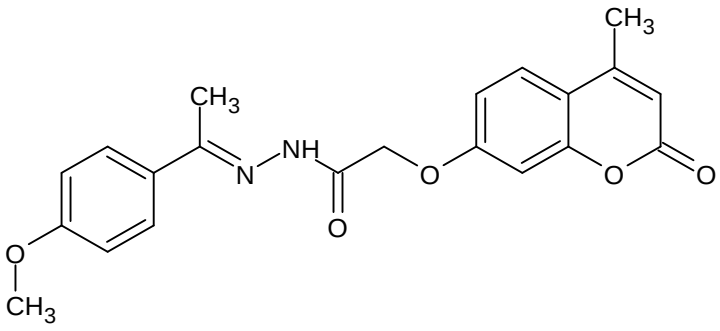

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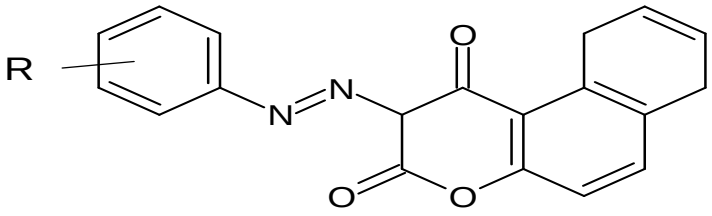
Anti-tubercular activity

Mycobacterium tuberculosis, which causes tuberculosis, an infectious disease that primarily affects the human respiratory system. The World Health Organization (WHO) estimates that ten million new cases of TB are recorded each year, and that two million people die from the disease. *Mycobacterium tuberculosis* strains that are multi-drug resistant, negative side effects of first- and second-line medications (e.g., isoniazid (INH), ethambutol (EMB), rifampicin (RIF), pyrazinamide, first-line drugs, and ethionamide (ETH), thiolactomycin (TLM), second-line medications), the increased incidence of tuberculosis associated with HIV and the emergence of new cases have led to the

revival of research in the field of natural products like coumarins. [14,15]

New coumarin hydrazide series **6** and **7** have been created and tested for their ability to combat M. TB. All the analogues showed moderate to good activity at MIC 6.25 g/mL. For both series, the SAR investigations showed that compounds with electron withdrawing groups were more active than those with electron donating groups. Additionally, the derivatives with nitro groups were discovered to be the most active in this class.[16]



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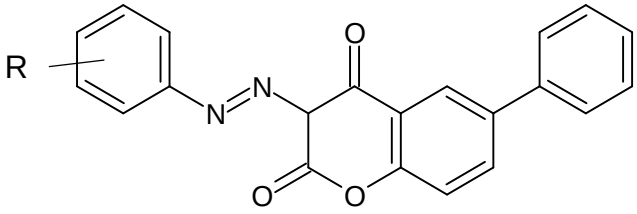

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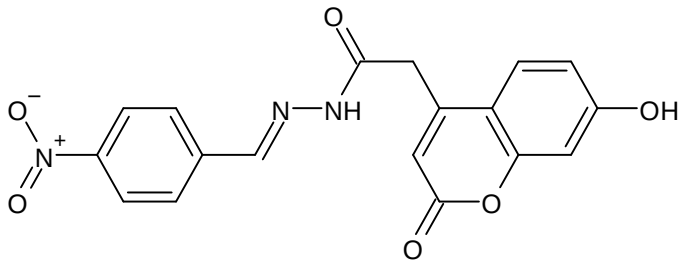
A set of coumarin-4-acetic acid benzylidene hydrazides were synthesized and evaluated for their antitubercular activity against M.TB H37Rv strain, using the BACTEC 460 system taking RIF as standard. 7-hydroxycoumarin containing nitro group at 3' position **8** showed the highest antimycobacterial activity with 93% inhibition at an MIC value 6.25 µg/mL.[16]



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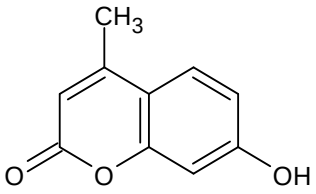
Antimicrobial activity

One of the most important tools for combating bacterial illnesses are antibiotics. The development of germ resistance to traditional antibiotics over the past few decades has made the search for novel antimicrobials a focus of intense research in the field of medicinal chemistry. Humans and the numerous microbes that cause infection and disease have engaged in a constant war throughout history. Wide-ranging structural alterations can be found in coumarin derivatives, which can act as molecular models for novel medications. Derivatives of coumarin are also taken into consideration as possible antimicrobials. Medimagh-Saidana et al. reported synthesis and antimicrobial activity of some coumarin esters and hydrazides . [17]

The antimicrobial activity was studied using Gram-positive bacteria (Staphylococcus aureus ATCC 25923, Sarcina lutea ATCC

9341, Bacillus cereus ATCC 14579), Gram-negative bacteria (Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853).

According to the results of the antibacterial studies, the efficacy of the tested compounds against Gram-positive bacteria was higher than that exhibited for Gram-negative bacteria. All the synthesized compounds were very active against S. aureus ATCC 25923, the most active compounds being **10, 12, 14,** and **16**. The replacement of the methyl radical in the fourth position with the propyl group was correlated with an increased activity against S. aureus ATCC 25923. The tested compounds exhibited excellent antibacterial activity against S. lutea, the most active derivatives being **10, 12, 14,** and **16**. They found a moderate action against B. cereus ATCC 14579, the most active being the umbelliferone derivatives with a methyl group attached to C4:**9**,11 and **15**. Against Escherichia coli ATCC 25922, the investigated compounds had a weaker action than the controls ampicillin and chloramphenicol. [18,19]



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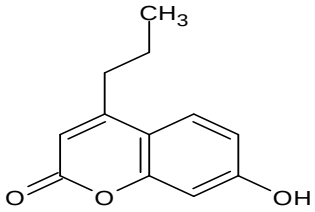

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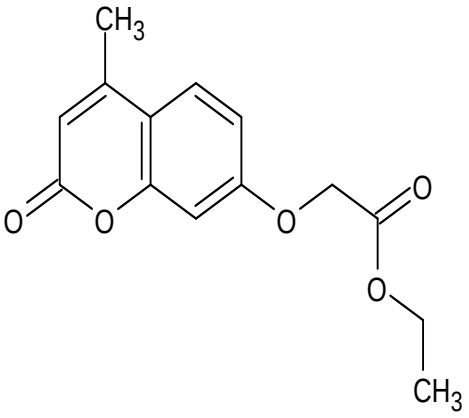

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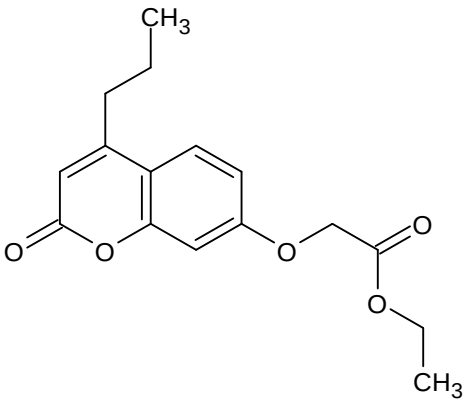

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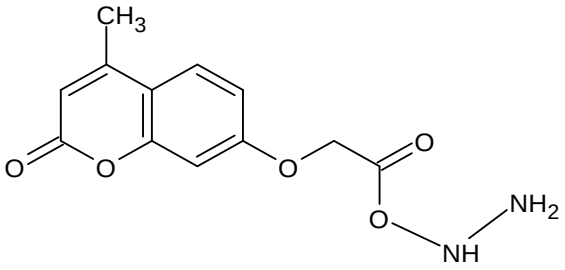

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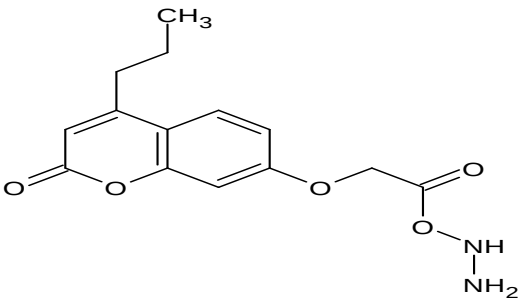

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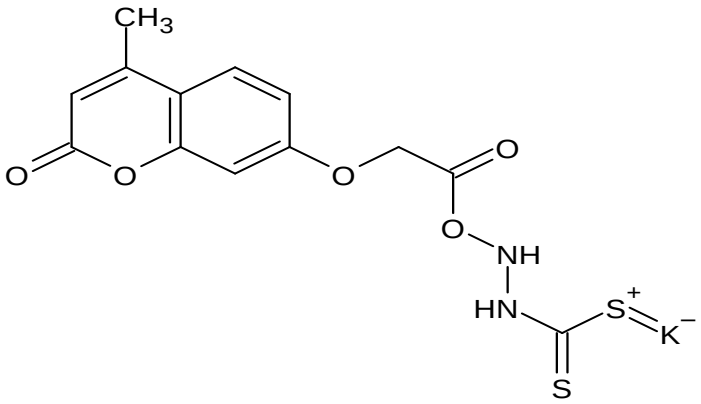

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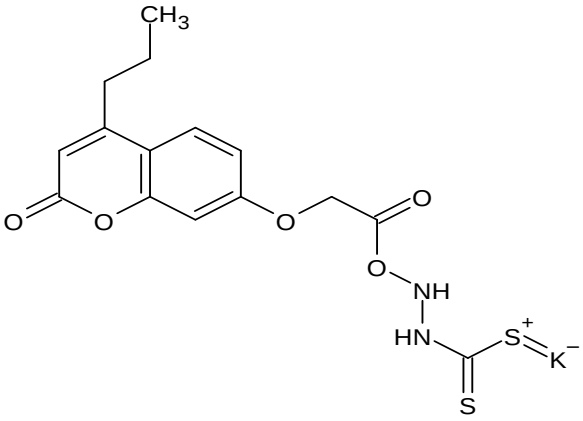

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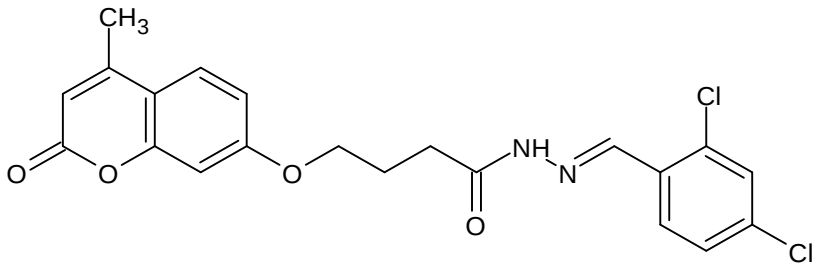
Antioxidant activity

Free radicals are molecular entities with an unpaired electron in an atomic orbital that are capable of independent existence; they are typically unstable and highly reactive. These species are typically created by vital metabolic processes in the human body, but they can also be brought on by environmental factors such exposure to X-rays, ozone, smoking, air pollution, and industrial toxins. Antioxidants are becoming more popular, especially those meant to guard against the alleged harmful effects of free radicals on the body as well as the deterioration of lipids and other food-related components. Antioxidants from natural sources are preferred over those derived from synthetic sources in both situations. Many coumarin derivatives have a special ability to scavenge reactive oxygen species and to influence processes involving free radical injury.[20,21]

Medimagh-Saidana et al. reported synthesis and antioxidant activity of some coumarin esters and hydrazides. In order to evaluate the antioxidant activity of synthesized compounds, we use three antioxidant assays: DPPH radical inhibition, total reducing power, and nitric oxide (NO) inhibition. The studied coumarin hydrazide derivatives were the most potent DPPH free radical scavengers (**13,14,15,16**) with an inhibitory percentage of over 90%, **15**'s activities were comparable to those of the standard, and the addition of sulphur atoms to the molecule had a favourable impact on its scavenging potential. Compared to their analogues with propyl radical, compounds IIIa and IVa with a methyl group were a little bit more active. The only compounds with a considerable amount of overall reducing power were the hydrazide derivatives **13** and **15**, although even then, their activity lagged behind that of the reference compound (ascorbic acid). Most of the substances that were studied were mild NO inhibitors.[18]

Antidiabetic activity

Diabetes mellitus is a never-ending metabolic disturbance described as hyperglycemia with variation in lipid, carbohydrate, and protein metabolism because of deficiency in insulin secretion, insulin action or both. The a-amylase enzyme inhibitors specifically block or slow down the absorption of starch to our body by inhibiting the hydrolysis of 1,4-glycosidic linkages and also oligosaccharides into maltose, maltriose, etc M Shivaprasad Shetty et. al synthesised series of nine molecules of coumarin hydrazone derivatives have been synthesized and investigated the anti-diabetic activity of synthesized coumarin derivatives by inhibition of a-amylase enzyme isolated from Aspergillus niger microbial strain. These studies revealed that the coumarin derivatives showed moderate inhibition of a-amylase. All samples tested at 5, 10, 50, and 100 g/mL were comparable with the reference drug acarbose at similar concentrations. The tests showed that compounds 17 (IC50 = 49.70 g/mL), **18** (IC50 = 79.20 g/mL), and **19** (IC50 = 48.80 g/mL) exhibited inhibition activity against the enzyme.[2]



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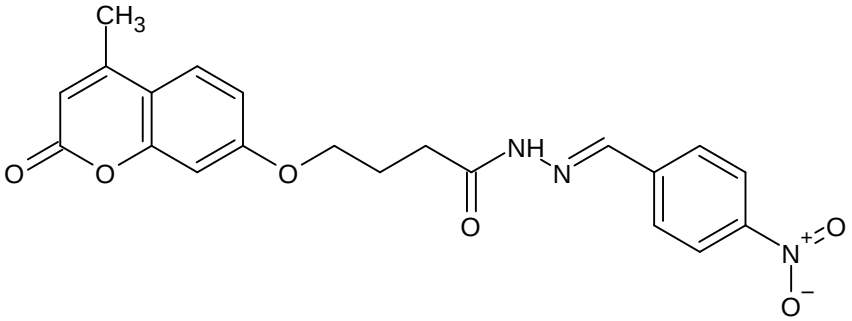

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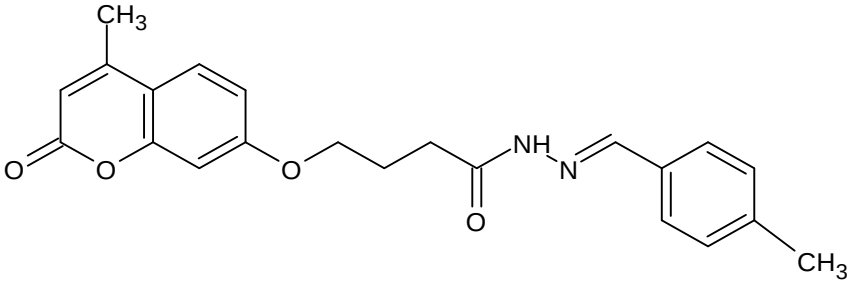

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CONCLUSION

The interest in the synthesis of coumarin derivatives has been gaining importance over the last decades, reflecting the importance of such compounds in both medical and chemical research. Some of the coumarin derivatives, which are already booming in the market, to quote a few,

brodifacoum (anticoagulant), warfarin (anticoagulant), difenacoum (anticoagulant), auraptene (chemopreventative agent), acenocoumarol (anticoagulant), ensaculin (NMDA antagonist and a 5HT1A agonist), armillarisin A (antibiotic), hymecromone (choleretic and antispasmodic), carbochromen, coronary disease), scopoletin, phenprocoumon (anticoagulant) and novobiocin. This review has emphasised on the anticancer, antitubercular, antimicrobial, antioxidant and antidiabetic activity of coumarin hydrazide. Future objectives in this area of study include the discovery, synthesis, and development of compounds with increased potency as well as supporting studies of structure-activity relationships aimed at figuring out the mechanisms of action of the most biologically active members of these product classes. Even though coumarin is a simple chemical moiety and many of its derivatives have been well-known for more than a century, their tremendous therapeutic potential keeps researchers interested in this abundant source of prospective drug candidates.[22]

Declaration by Authors

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Conflict of Interest: The authors declare no conflict of interest.

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