A REVIEW ON SYNTHESIS AND BIOLOGICAL SIGNIFICANCE OF COUMARIN DERIVATIVES

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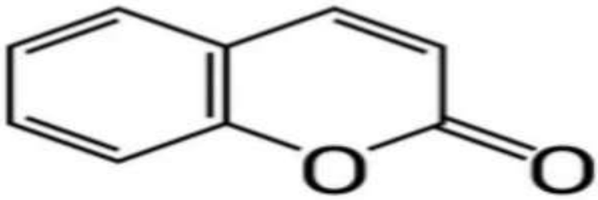
Abstract: Coumarin and its derivatives are an important class of heterocyclic compounds widely distributed in plants and known for their diverse pharmacological activities. The present study focuses on the synthesis of coumarin derivatives using three different approaches: natural extraction, conventional synthetic methods, and green synthesis techniques. Natural coumarin was obtained from plant sources through suitable extraction and purification processes. Synthetic derivatives were prepared using classical reactions such as Pechmann and Knoevenagel condensation, while green synthesis methods were employed using eco-friendly solvents and catalysts to reduce environmental impact. The synthesized compounds were purified and characterized using standard analytical techniques including melting point determination, thin layer chromatography (TLC), and spectroscopic methods. The biological activities of the synthesized coumarin derivatives were evaluated through in-vitro assays to assess their antimicrobial, antioxidant, and other potential pharmacological properties against selected microbial strains.

Keywords: Coumarin, synthetic synthesis, green synthesis, Microwave irradiation, Pechmann condensation, Benzo pyrone, anti-coagulant drug.

INTRODUCTION:

Coumarin | $C_9H_6O_2$



Coumarins (figure1) are a wide family of secondary metabolites found in various species of plants (more than 1300 coumarins have been identified from natural sources, especially green plants) but also fungi and microorganisms [1,2]. The main pathway of coumarin biosynthesis occurs by shikimic acid route, via cinnamic acid, through phenylalanine metabolism [3]. The history of these natural products began 200 years ago—the name of the class derived from the plant Coumarouna odorata (Dipteryx odorata) from which the simplest member of this family, coumarin itself was isolated by Vogel in 1820 [3,4]. Chemically speaking, coumarins are organic heterocycles and their nucleus is represented by benzo-α-pyrone (2H-1-benzopiran-2-one), whose systematic nomenclature was established by International Union of Pure and Applied Chemistry (IUPAC) [5].
Natural coumarins are subdivided in different classes based on their chemical diversity and complexity—simple coumarins, iso coumarins, furanocoumarins and pyranocoumarins (both angular and linear), bis coumarins and other coumarins such as phenyl coumarins [6].

PROPERTIES OF COUMARINS-

Coumarin is found in high concentrations in certain types of cinnamon. The Cassia cinnamon contains high amounts of coumarins, also found in sweet clover, lavender oil, and Tonka beans.

- It is slightly soluble in water and very soluble in ether, chloroform
- Its melting point is 71^0 C.
- It has vanilla caramel taste.
- It has aromatic Oduor.
- It is weakly acidic in nature.
- Molecular Formula: C9H6O2
- Molecular Weight: 146.145 g/mol

NEED OF STUDY

The study of natural, synthetic, and green synthesis of coumarin is important in pharmaceutical and chemical research for understanding production methods, improving drug development, and promoting environmentally safe processes. Coumarin occurs naturally in plants like Tonka beans, sweet clover, and cinnamon grass. Studying these sources helps identify medicinal plants containing coumarin. Natural coumarins show anticoagulant, anti-inflammatory, antimicrobial, and anticancer activities. Natural extraction gives low yield; chemical synthesis allows industrial production of coumarin[7]. Synthetic methods help create coumarin derivatives with improved therapeutic activity[8]. Green synthesis reduces toxic solvents and hazardous chemicals. Eco-friendly approach like water, ionic liquids, or solvent-free conditions[9].

SYNTHESIS OF COUMARIN

Synthesis of coumarin is done by three ways they are:

- Natural method
- Synthetic method
- Green synthesis

NATURAL SYNTHESIS OF COUMARIN

Coumarins are widely distributed in the plant kingdom, often acting as a chemical defence against predators.

- **Tonka Beans:** The primary source, from which they were first isolated.
- **Cinnamon:** Particularly *Cinnamomum cassia*, which contains high concentrations (up to 7,000 mg/kg).
- **Plants & Herbs:** Found in sweet woodruff, lavender, liquorice, cherry blossoms, and various citrus fruits.

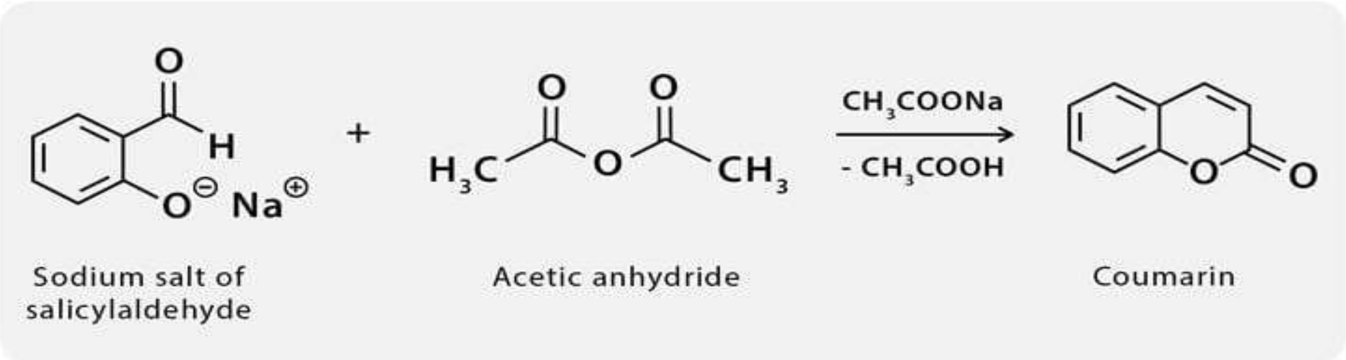
Roots & Seeds: High concentrations are found in the roots and seed coats of many species.

Naturally it is Prepared by taking 25-gram powdered cinnamon & mixed with 50 ml ethanol vigorously stirred for 10- 15 minutes followed by small amount anhydrous magnesium sulphate powder to remove any fine or traces or water. Filtered the solution, collected the filtrate and evaporated the content on hot plate to get dry powdered as residue.[10]
As the extraction was performed the color of the extract was found to be wine red. This coloration is may be due to pigment of cinnamon containing coumarin.

SYNTHETIC METHOD

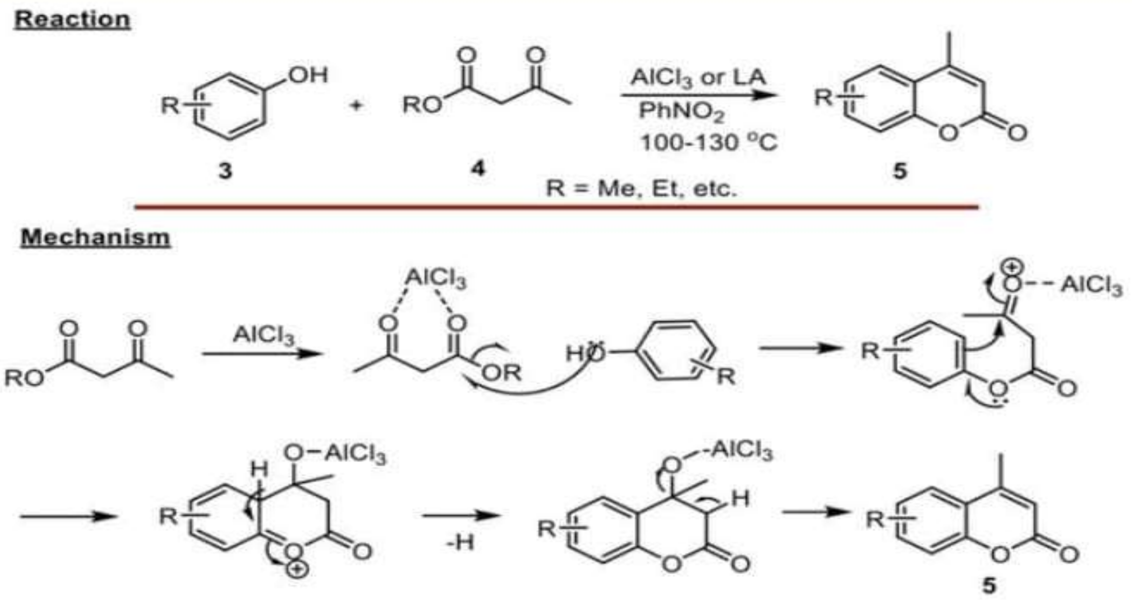
Perkin reaction

In 1968, the first time Pekin demonstrated the method for the construction of coumarin by the condensation reaction of simple salicylaldehyde in the presence of acetic anhydride [11]
The Perkin reaction of salicylaldehyde 1 and an acetic anhydride are mixed together in the basic reaction condition, a chemical process that furnished, α, β-unsaturated aromatic acid in the presence of sodium acetate followed by intramolecular cyclization produced the expected substituted coumarin 2. [12,13,14](figure 2)



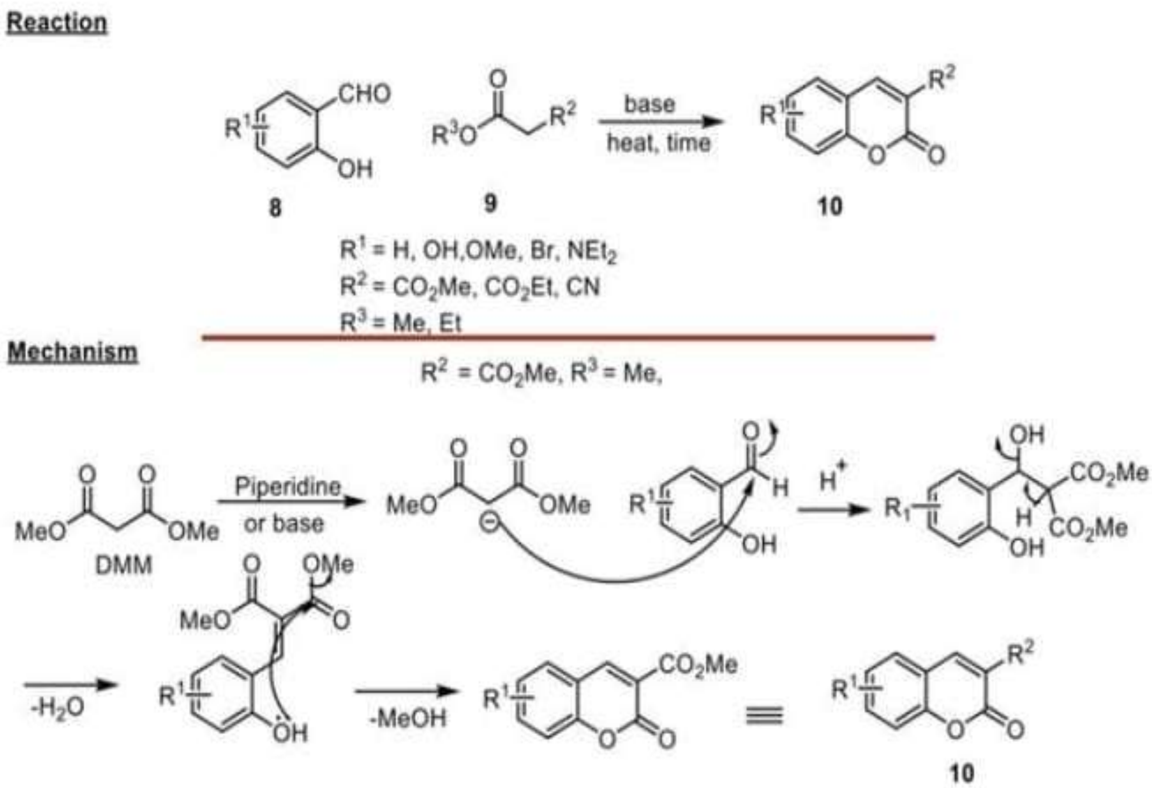
Pechmann reaction

The Pechmann achieved the initial discovery of the Pechmann condensation in 1883 [15]. Typically, carbolic acid 3 reacts with a carboxylic ester having α-carbonyl group 4 in an acidic environment to produce the desire coumarins 5 [16]. The most widely reported process for producing coumarins through Pechmann condensation, which scheme starts with two basic building blocks, phenol and β-keto ester, and produces good coumarin yields most of the cases. Several catalysts were tested for this reaction, including sulfuric acid, trifluoroacetic acid, phosphorous pentoxide, ZrCl4, TiCl4, and ionic liquids, etc. enabled by Pechmann condensation [17]. Various groups have reported for the preparation of coumarin scaffolds via Pechmann methods. In the mechanism of the reaction involved following paths initial step is esterification followed by the attack of activated carbonyl group, allows to forms the ring system. The last step of the reaction involves dehydration. By reacting substituted phenols and ethyl acetoacetate in the presence of a zinc-iodine mixture in refluxing toluene, a number of substituted coumarins have been produced in yields ranging from 25 to 77%.(figure 3)



Knoevenagel reaction

Many coumarin derivatives have been derived from suitable starting materials via a Knoevenagel reaction. 3-substituted coumarin derivatives can be synthesized via base mediated process. The reaction needs to be carried out in the presence of 2-hydroxy benzaldehydes 8 and coupling partner 9 containing an active methylene group in the presence of the base under heating conditions. The yield obtained from coumarin product 10 is acceptable range [18]. There are various reports present in the literature regarding the synthesis of scaffolds of coumarin via Knoevenagel reaction in the presence of ultrasound solvent-free conditions [19,20] (figure4).

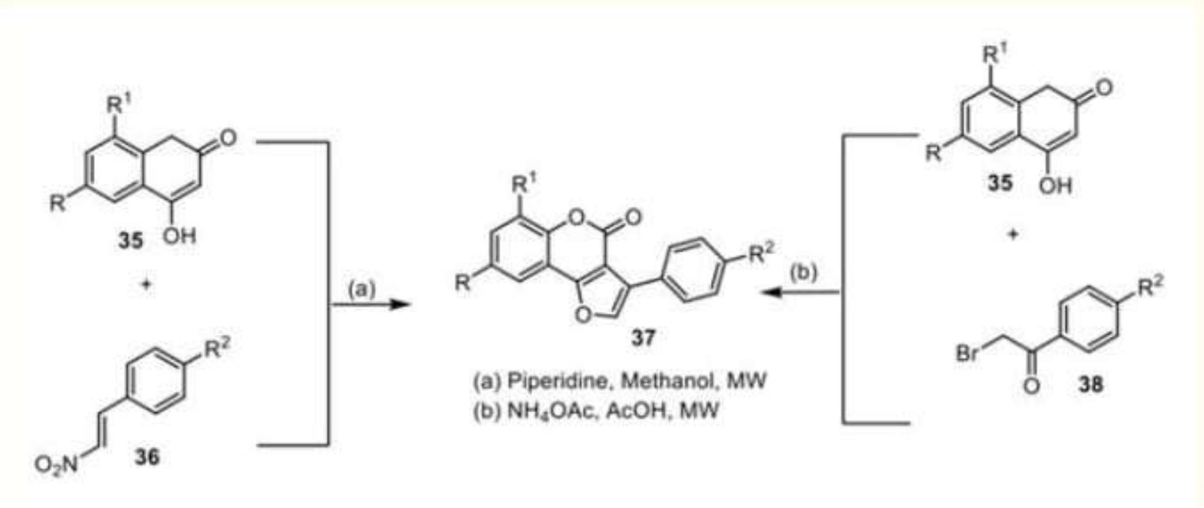


GREEN SYNTHESIS OF COUMARIN

Microwave mediated innovative synthesis

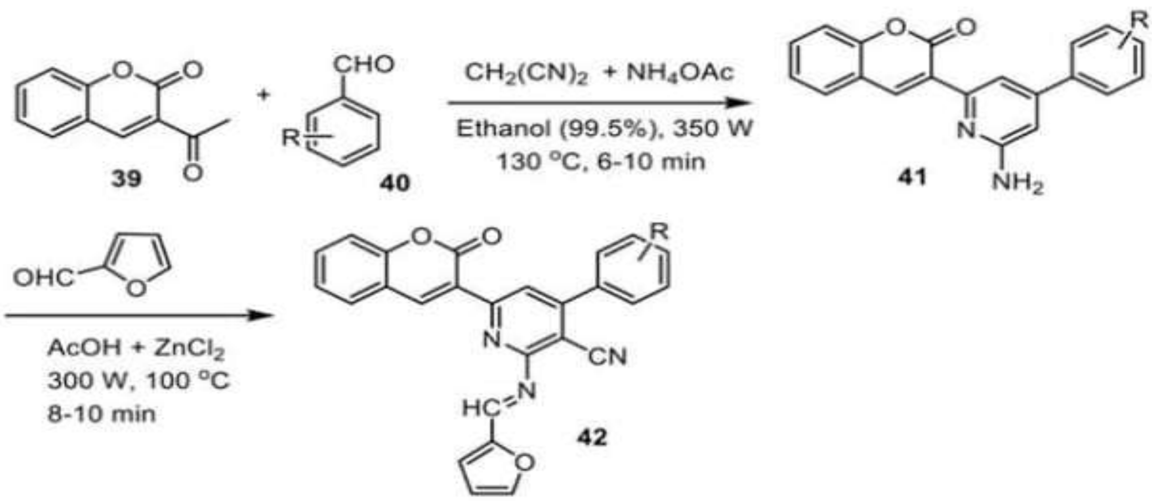
Recently, microwave-mediated organic synthesis has replaced conventional heating methods. In recent years, the synthesis of organic molecules has increasingly relied on the use of microwave energy to heat chemical reactions. In contrast to dramatically accelerating chemical reactions, direct microwave heating is known to reduce the formation of side products, increases yield, and improves the reproducibility. Various academic research institutions have already embraced microwave irradiation as a method for fast reaction in order to efficiently synthesize and discover new chemical substances [21].

In the year 2017, Brahmbatt and co-workers demonstrated the microwave- assisted preparation of 3-aryl-furo[3,2-c] coumarins 37. The time required for the synthesis was just 2–4 minutes and the yield was also good (72–82%) [22].(Figure 5)



Microwave assisted synthesis of 3-aryl-furo[3,2-c] coumarins.(figure 5)

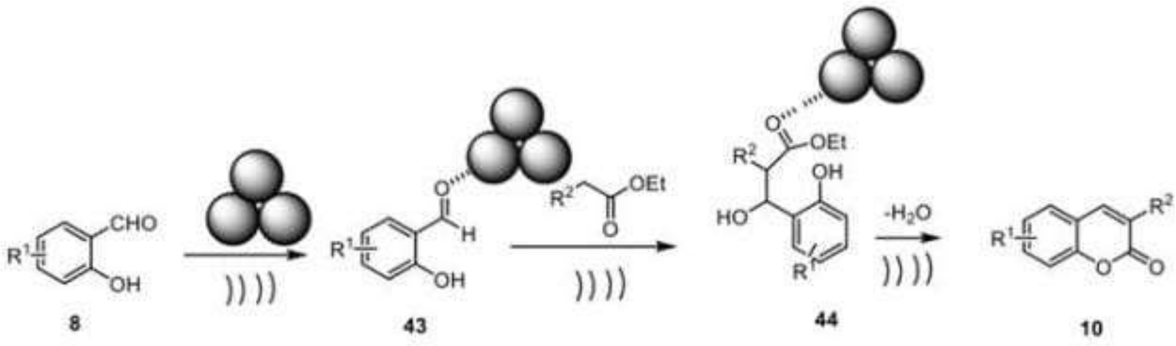
Desai et al. reported the preparation of 4-(substitutedphenyl)-2-(furan-2-ylmethyleneamino)-6-(2-oxo-2H-chromen-3-yl) nicotinonitrile derivatives 42. The reaction was carried out in a solvent-free condition, the reaction was performed with 2-amino-4-(substitutedphenyl)-6-(2-oxo-2H-chromen-3-yl)nicotinenitriles 41 and 2-furfuealdehyde and the microwaves (300 W) were irradiated for 8–10 min. in the presence of acetic acid and a catalytic amount of ZnCl2 [23].(Figure 6)



Synthesis of coumarin-based nicotinonitrile (Figure 6)

Ultrasound helped synthesis

The 3-substituted coumarins 10 can be synthesized in the presence of MgFe2O4 nanoparticle, and the reaction can be carried out between salicylaldehyde 8 and 1,3-dicarbonyl compound 9 in the existence of the Ultrasound radiation. The mechanism for the syntheis of 3-substituted coumarin 10 was reported by Ghomi and co workers in 2018 and has been shown in the Figure 18 [24].(Figure 7)



Mechanism of the synthesis of 3-substituted coumarins.(Figure 7)

COMPARISON OF NATURAL, SYNTHETIC AND GREEN SYNTHESIS OF COUMARIN

Coumarin obtained from natural plant sources and they are environmentally safe but limited availability[25] Coumarin prepared using chemical reactions in laboratories and often produces chemical waste and uses hazardous reagents[26], Coumarin produced using sustainable and eco-friendly methods it reduces waste and toxic chemicals [27].

BIOLOGICAL ACTIVITIES

1. Anticoagulant Activity

Coumarin derivatives show strong anticoagulant activity by inhibiting vitamin K–dependent clotting factors. The most famous derivative is Warfarin, which is widely used for preventing thrombosis and embolism. These compounds act by inhibiting the enzyme vitamin K epoxide reductase, thereby reducing the synthesis of clotting factors II, VII, IX, and X.[28].

2. Antimicrobial Activity

Several coumarin derivatives exhibit antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as fungi. Their mechanism generally involves inhibition of microbial enzymes, interference with DNA synthesis, or disruption of cell membranes.[29]

3. Anti-inflammatory Activity

Coumarins possess anti-inflammatory properties by inhibiting inflammatory mediators such as prostaglandins, cytokines, and nitric oxide. They can also suppress cyclooxygenase and lipoxygenase pathways.[30]

4. Antioxidant Activity

Coumarins act as antioxidants by scavenging free radicals and preventing oxidative stress. This activity helps protect cells from damage caused by reactive oxygen species (ROS).[31]

5. Anticancer Activity

Several coumarin derivatives exhibit anticancer activity through mechanisms such as induction of apoptosis, inhibition of tumor cell proliferation, and suppression of angiogenesis. Some derivatives have been studied for treatment of breast, lung, and prostate cancers.[32]

6. Antiviral Activity

Certain coumarin compounds have shown antiviral activity against viruses such as HIV and influenza by inhibiting viral replication and viral enzymes.[33]

7. Antidiabetic Activity

Coumarin derivatives may help regulate blood glucose levels by enhancing insulin secretion, improving glucose uptake, and inhibiting enzymes involved in carbohydrate metabolism.[34]

8. Alzheimer's disease Inhibition

Alzheimer's disease (AD) is the degenerative disease of the central nervous system characterized by memory impairment, cognitive dysfunction, personality change language barrier.

Recent researches showed that coumarin derivatives can inhibit the Alzheimer's disease. Marria Joao matos group designed and synthesized a series of three substituted coumarin derivatives for which the results of biology evaluation demonstrate that this compounds can both inhibit the MAO-A,MAO-B iso forms and Ache in the micromolar range.[35]

CONCLUSION

Coumarins can be obtained through natural biosynthesis, conventional chemical synthesis, or green chemistry approaches. Natural synthesis provides environmentally friendly compounds but has low yield, while synthetic methods offer higher production efficiency. Green synthesis combines the advantages of synthetic chemistry with environmentally sustainable techniques, making it a promising approach for future coumarin production.

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