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A Research Study in the Synthesis and the Applications of Coumarin Derivatives

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Abstract: Many organic and medicinal chemists are interested in the coumarin compounds due to their potential for use in pharmaceuticals and other industries. Coumarin compounds are a significant class of biologically active chemicals. Here, we outline the steps for producing coumarin derivatives quickly and effectively from commercially accessible substrates via multicomponent condensation processes involving pyrone and benzene derivatives. These substances were examined for their potential anti-tumor effects, including their ability to block carbonic anhydrase, activate the cell apoptosis protein, and coumarin and its derivatives are the primary oral anticoagulants. Candida albicans, Aspergillus fumigatus, and Fusarium solani are three distinct fungus species that are resistant to the antifungal properties of synthetic coumarins. Long known are the coumarins' antibacterial due to its biological activities against some kinds of bacteria such as *Zeitschrift für Naturforschung C*, as well as their antifilarial, antiulcerogenic, anti-inflammatory, and antioxidant effects for its capacity to inhibit their growth activities. Coumarin has long been valued as a major raw element in the fragrance sector due to its distinct sweet aroma and stability. When mixed with organic essential oils like lavender, citrus, rosemary, and oak moss, it is used as an odour-enhancer to produce a long-lasting impact. It has been utilized as a bleaching or brightening agent in detergents when it revealed a remarkable brightening effect with excellent overall stability on fibers of synthetic origin. Materials such as liquid crystalline, organic/inorganic composites, as well as light harvesting, energy transferring compounds, and electro-optics materials are all employed as a dye in organic photo-redox catalysis and as potent photo-sensitizers reagent. These materials polymerize epoxy-silicones, under near-UV and visible light. Coumarin has also found useful as metal-free sensitizers for solar cells.

Keywords: Synthesis, applications, Coumarin derivatives, UV light, heterocyclic, aromatic ring

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1. Introduction

The broad and well-studied class of chemicals known as coumarins contains many compounds with the 1-benzopyran-2-one pattern. This structure is made up of a benzene ring fused to a pyrone ring which composed of a six-membered heterocyclic, non-aromatic ring, made up of five carbon atoms and one oxygen atom and containing two double bonds with the carbonyl group of the pyrone in position 2. This structure is also referred to as 2H-chromen-2-one according to the latest edition of the International Union of Pure and Applied Chemistry (IUPAC) Terminology. (Fig. 1).

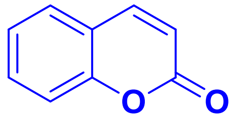
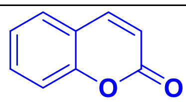
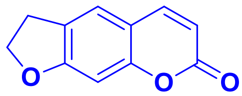
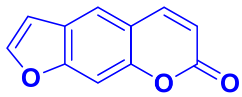
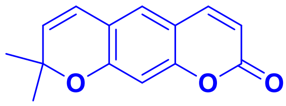
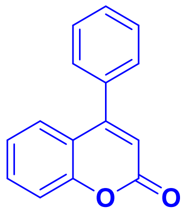
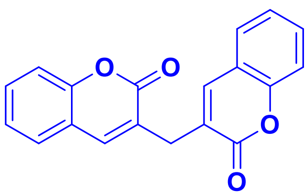


Fig. 1 - Structure of 2H-chromen-2-one

The development of coumarin's chemistry dates back over 200 years. Vogel and Guibourt [1] separately identified this interesting oxygen-containing heterocyclic chemical from tonka beans in 1820 and later from sweet clover, bison grass, and woodruff [2]. Coumarin is also present in fungi and bacteria [3], the latter of which is also credited with naming the substance after the tonka bean in French, coumarou. Several plants in the families Orchidaceae, Leguminoceae, Rutaceae, Umbelliferae, and Latbiatae naturally produce coumarins in large quantities [4].

Coumarin is a white, crystalline powder with a hay-like, sweet, fragrant, and creamy scent that has some nutty undertones. It is widely used in synthetic form as a fragrance component for perfumes as well as for soaps and detergents with fragrance. Simple coumarin derivatives, dihydrofurano coumarin derivatives, furano coumarine derivatives, pyrano coumarin derivatives (linear and angular), bis-coumarin derivatives, and phenyl coumarin derivatives are the six basic natural kinds of coumarin (Table 1).

Table 1 - Six basic natural kinds of coumarin

Class	Compound structure
Simple coumarins	
Dihydrofurano coumarins	
Furano coumarins	
Pyrano coumarins	
Phenyl coumarins	
Bi-coumarins	

The pharmacological actions of the roots of Ferulago campestris extracted from a Sicilian medicinal plant source were displayed as anti-biologically active. In the same purpose, coumarins were isolated from the same herb family and displayed further biological and pharmaceutical activities including antiproliferative, antidiabetic, antibacterial, neuroprotective, anti-inflammatory, and anticoagulant [5]. Food industry also considers their significance because of their fungicide and antioxidant activities [6,7]. Also, several naturally occurring benzo-coumarins exhibit anti-algal action [8].

Coumarins are classified based on their chemical composition such as, Furano-coumarins, which have a furan ring of five-membered heterocyclic compound attached to the coumarin and include linear furano-coumarins (for example, xanthotoxin), as well as simple coumarins, which have been hydroxylated, alkoxylated, or alkylated on the benzene ring (for example, umbelliferone), are some examples of simple coumarins (e.g. Angeligin) (Fig. 2).

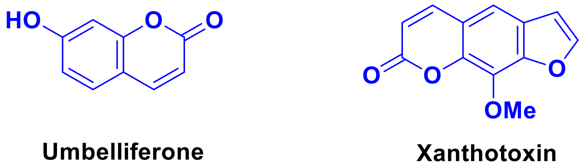


Fig. 2 - Structure of coumarin derivatives

Pyrano coumarins with a ring of six members connected to the coumarin moiety (e.g. Seselin and Xanthyletin). Coumarins that have pyrone ring substituents, such as Warfarin (Fig. 3) [9].

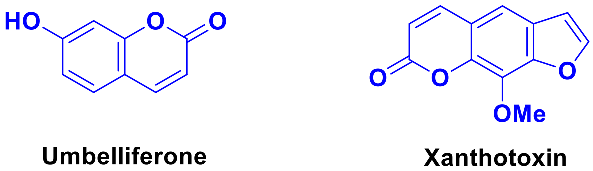


Fig. 3 - Pyrano coumarins structure

Coumarin is produced chemically for the first time by Perkin in 1868 through mixing sodium salt of salicylaldehyde with acetic acid under heating. This work also started the research that eventually led to the Perkin reaction [10]. Since 1872, everyone has agreed that the structure of coumarin, which is described as 1-benzopyran-2-one, as postulated via Strecker, Fittig, and Tiemann is true [11].

2. Methods for Synthesis of Coumarin Derivatives

There are various synthetic ways to make coumarin, all of which revolve around the potential for adding the pyrone ring to an appropriate benzene derivative. The Perkin reaction is done by mixing salicylaldehyde with acetic anhydride and anhydrous sodium acetate under heating (Fig. 4) [12]. Meanwhile, Pechmann [13] discovered that the coumarin derivative is produced by mixing phenol and malic acid under heating conditions and using concentrated sulfuric acid to catalyze the reaction (Fig. 5).

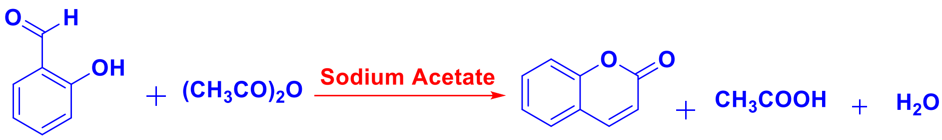


Fig. 4 - Perkin reaction

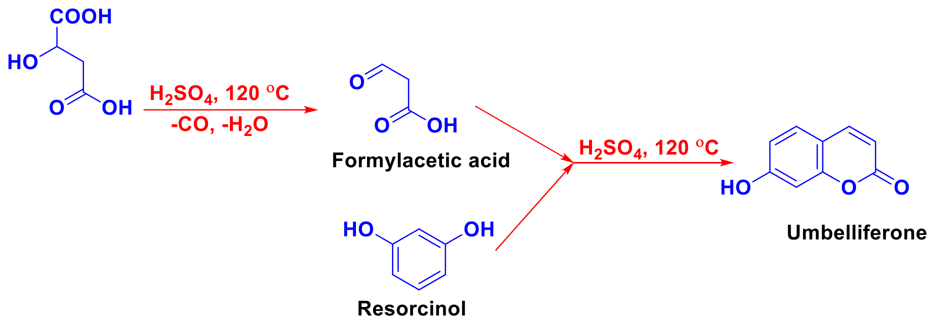


Fig. 5 - Pechmann reaction

Limited applications exist for this technique. Only coumarins that are substitution in the pyrone ring go through this reaction, which excludes many substituted phenols. According to Pechmann and Duisberg [14], coumarin derivative was produced via reacting condensed phenols with -ketonic esters in the presence of sulfuric acid (Fig. 6). Meanwhile, the Knoevenagel reaction is initiated by Knoevenagel [15] to yield coumarin derivatives from o-hydroxy aldehydes. This reaction involves condensing ethyl malonate with ethyl cyanoacetate and their derivatives with addition of piperidine, pyridine, and other organic bases in order as a catalyst (Fig. 7). Under the Hoesch reaction conditions, resorcinol was found to condense with cyanoacetate [16] to produce ketimines hydrochloride via hydrolysis reaction to finally yield 4,7-dihydroxycoumarin known as Sonn reaction.

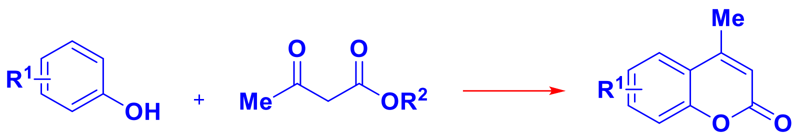


Fig. 6 - Pechmann-Duisberg reaction

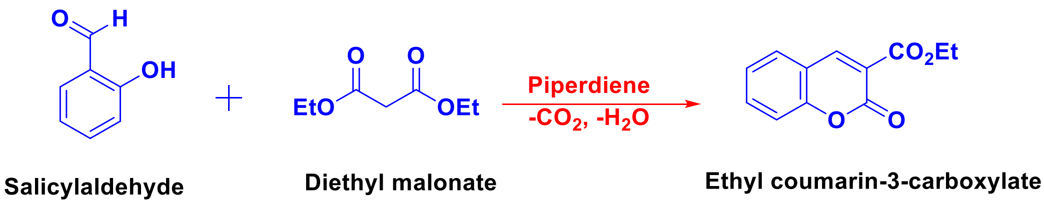


Fig. 7 - Knoevenagel reaction

3. Biological Applications of Coumarin

The main oral anticoagulants are coumarin and its derivatives. Although coumarin is hydrophobic, the 4-hydroxy substitution endows the molecule with weak acidic properties, which changes its hydrophobicity to become hydrophilic under slightly alkaline conditions (Fig. 8).

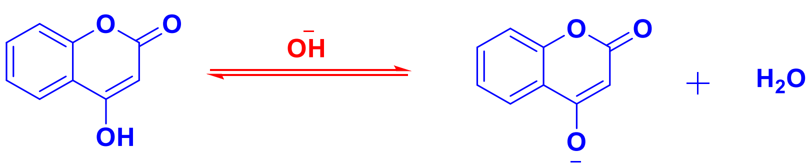


Fig. 8 - Coumarin soluble in water

As the sodium salt of coumarin derivatives, warfarin is commercialized (Fig. 9). There is only one chiral center signed with * which display the biological activity of the compound. Although commercial warfarin is a racemic mixture, the S (-) isomer of the drug is approximately 5 to 8 times more powerful than the R (+) isomer.

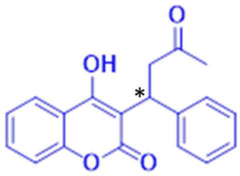


Fig. 9 - Structure of Warfarin

4. Industrial Applications of Coumarin

Liquid crystalline materials, organic-inorganic hybrid materials, light-harvesting/energy-transferring materials, electrooptical materials, and other application domains have all seen extensive use of coumarin-containing polymers. [17-21]. However, because of the technical developments in extensive domains such as photolithography [22], nonlinear optical materials [23], liquid crystalline materials [24], and holographic elements [25], the majority of reported coumarin-containing polymers were photopolymers, which represents an important topic of study in the science of polymers. Using polymers based on methylacrylate with coumarin side groups as a thermal stabilizer was discovered by Nursel Ayaz [26].

Keto-coumarin can also be scaffolded for use in 3D printing and photo-composites (Fig. 10) [27]. The compound is reacted using various techniques such as Fourier transform infrared spectroscopy, UV visible or fluorescent spectroscopy, etc. offering good reaction and excellent photopolymerization initiation capabilities for two specific and high value-added applications such as 3D printing Dimensions at 405 nm and preparation of thick fiberglass optical composites with excellent curing depth.

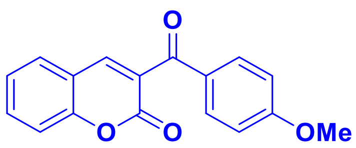
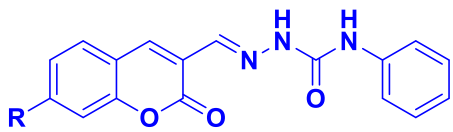


Fig. 10 - Chemical structures of the keto-coumarin

These compounds play a significant role in fluorescence sensors, switches, and probes (Fig. 11) [28]. Coumarin is used as a dye in organic photo redox catalysis (Fig. 12) [29]. The liquid crystallized coumarin derivatives were used in the manufacture of new metal-free sensitizers for the development of solar cells (Fig. 13) [30].



R= H, $N(Me)_2$, Me, OMe

Fig. 11 - Molecular structure of coumarin derivatives

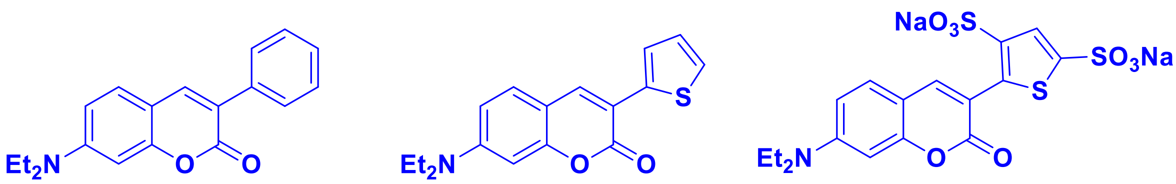


Fig. 12 - Molecular structure of coumarin derivatives as dyes

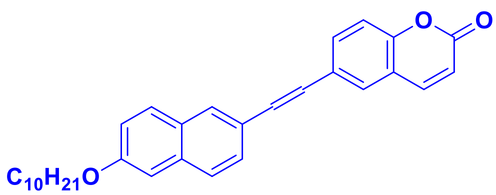


Fig. 13 - Structure of crystalline coumarin derivatives

Applications of 3D printing technology and Coumarins as effective photosensitizers for the cationic polymerization process of epoxy silicon by focusing near ultraviolet and visible light (Fig. 14) [31].

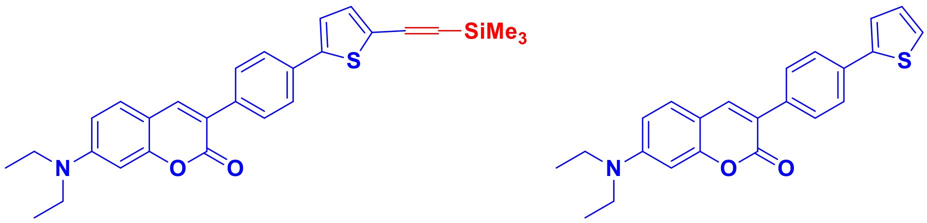


Fig. 14 - Chemical structures of coumarins derivatives

Fluorescent monomers based on coumarin are incorporated into co-oligomeric molecules (Fig. 15) [31]. 3-(1H-benzoimidazol-2-yl) coumarine-2-one is used as the starting material in a unique process for the manufacture of coumarin laser dyes (Fig. 16) [32].

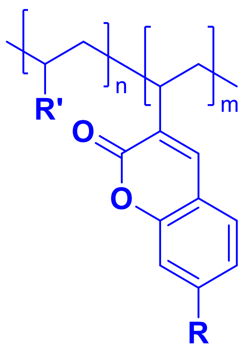


Fig. 15 - Fluorescent monomer based on coumarin

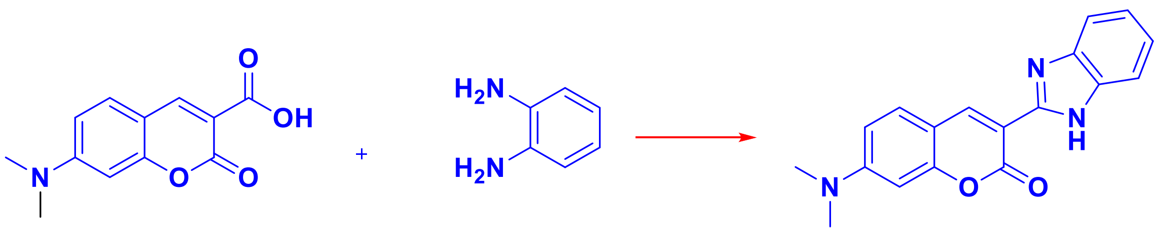


Fig. 16 - Reaction of synthesizing coumarin dye

Coumarins possess a wide range of anti-tumor actions, such as the inhibition of carbonic anhydrase, the activation of the cell apoptosis protein, as well as inhibiting the resistance of tumor multidrug [33-35]. It has been demonstrated that coumarin (a benzo-pyrone) which causes the rapid discharge of protein from healthy or burned tissue as well as from lymphedematous [36].

Three different fungus species, Candida albicans, Aspergillus fumigatus, and Fusarium solani, were resistant to the antifungal effects of synthetic coumarins [17]. The antioxidant [38], anti-inflammatory [39], antifilarial [40], antiulcerogenic [41], and antibacterial [42] properties of coumarins have also long been known.

5. Coumarins in Medicinal Herbs

The Coumarin family contains an increase of valuable species that are used widely as medicinal and aromatic plants. Coumarins are part of the active principles in many of these species, which have been biologically documented. It showed great pharmacological interest after it was chemically isolated from various plant families. It has also gained wide popularity among several communities and scientists as part of the herbal medicine repositories in Europe, Asia, and the Americas [43]. Among the plants listed are species with a great historical record of ethno-medicine uses, found in traditional medicine systems such as Ayurvedic medicine, traditional Chinese medicine, Greek medicine, or in other modern cultures [44]. Coumarins are distributed in the northeastern region of Brazil where several species belong to different botanical families [45]. Folk medicine describes some of them as traditional medicines to treat respiratory diseases. [46]. Coumarins have also been associated with anti-tumor, antimicrobial, anti-inflammatory, and anti-clotting activities [45]. Many studies and review manuscripts are focused on coumarin as a promising substance in biological activity [45-47]. Furthermore, several recent reviews summarize and highlight advances in the application of coumarins, especially concerning their antioxidant and anti- cancer properties [47] (Fig. 17).

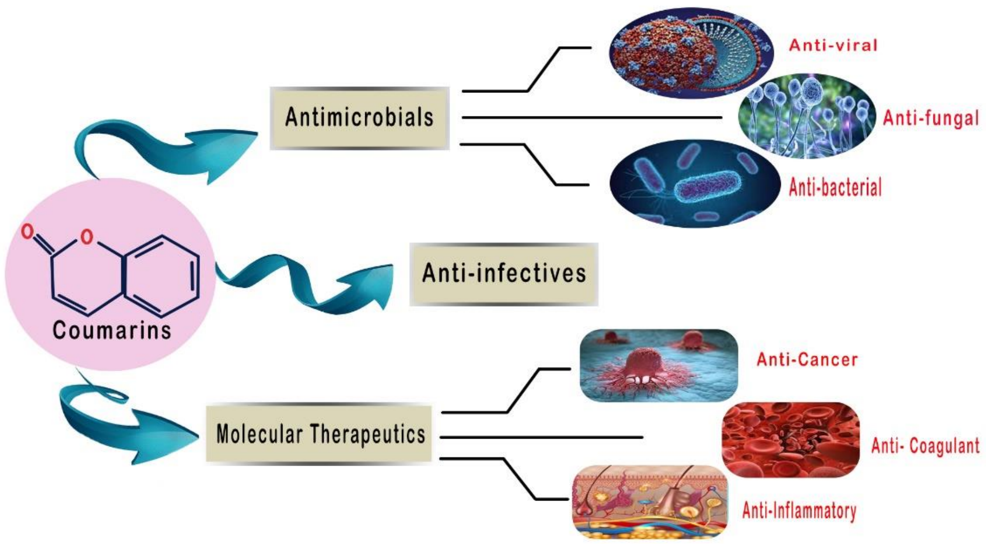


Fig. 17 - Schematic representation pathways of the most representative coumarins

6. Conclusion

Coumarins are categorized as one of the natural chemical compounds, which were initially extracted from the tonka bean. This compound is found in a plethora of medicinal herb types which belong to a distinct family used for wide applications in biomedicine. Their simplicity, chemical properties, and efficiency in synthetic approaches to obtain a wide range of substitution patterns make these compounds to acquire a significant interest and versatility among the researchers of medicine, pharmacy and cosmetics industry. The steps for synthesizing coumarin derivatives from commercially accessible substrates in a multicomponent condensation are reviewed. Moreover, with its ability to inhibit carbonic anhydrase and activate cellular apoptosis, coumarin and its derivatives have been considered one of the most crucial oral anticoagulants as well as, the potential anti-tumor effects, including their ability to block carbonic anhydrase, activate the cell apoptosis protein. Moreover, the uses of the compound in many other industrial fields were illustrated. For instance, coumarin is considered a vital raw ingredient in the preparation of perfumes. Furthermore, it was found that it can be used in the manufacture of detergents as a bleaching agent or lightening of clothes. It has also been utilized in the manufacture of liquid crystalline compounds and organic/inorganic compounds, in addition to its use in light harvesting, as energy transfer compounds, and as photoelectric materials as a dye in organic photo-oxidation catalysts and as a powerful photosensitizing agent. Finally, fiberglass photovoltaic composites were fabricated using 3D printing technique to keep pace with the development of usage of this material within the latest modern technologies.

Acknowledgement

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