Coumarin as a Potential Pharmacophore in Medicinal Chemistry

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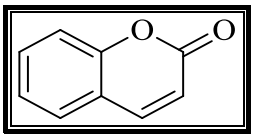
Abstract:
Coumarin is very useful pharmacophore in the medicinal chemistry provides broad range of therapeutic activity. In this article all the activities in different biological targets have been descried. Synthetic methods of coumarin developed by different group have been discussed thoroughly.

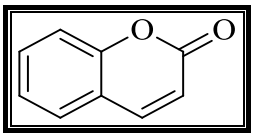


Keywords: *Anticancer, Antiviral, Coumarin, Heterocyclic chemistry, Medicinal chemistry*

1. Introduction

Coumarin is the best known aromatic lactones.[1] The isolation of coumarin was first reported by Vogel[2] in Munich in1820. He associated the pleasant odor of the tonka bean from Guiana with that of clover, Melilotous officinalis, which gives rise to the characteristic aroma of new -mown hay. Vogel then concluded that the long colorless crystals which he discovered on slicing open Tonka beans and which crystallized as glistening needles from aqueous alcohol were identical with similar crystals he obtained, albeit in much lower yield, by extracting fresh clover blossoms.[3] The name coumarin originated[4] from a Caribbean word 'coumarou' for the tonka tree, which was known botanically at one time as Coumarouna odorata aubl. Coumarin is now well, accepted trivial name. The IUPAC nomenclature of the coumarin ring system is 2H-1-benzopyran-2-one (I) (Figure-1).

Figure 1



The coumarin ring system has an easy acceptability in the biological system compared to its isomeric chromones and flavones nucleus[5] and is widely distributed in nature.[6-9] An excellent account of these naturally occurring coumarin is presented by Murray and Brown[10]

Coumarin comprises a group of natural compounds found in a variety of plant sources. The very long association of plant coumarin with various animal species and other organisms throughout evolution may account for the extraordinary range of biochemical and pharmacological activities of these chemicals in mammalian and other biological systems. The coumarins that were studied have diverse biological properties and various effects on the different cellular systems. A lot of biological parameters should be evaluated to increase our understanding of mechanisms by which

these coumarin act. Coumarin has important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection. The coumarins have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities. The hydroxycoumarins are typical phenolic compounds and, therefore, act as potent metal chelators and free radical scavengers. They are powerful chain-breaking antioxidants. The coumarin displays a remarkable array of biochemical and pharmacological actions, some of which suggest that certain members of this group of compounds may significantly affect the function of various mammalian cellular systems. The coumarins are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence their biological activity. Vast majority of coumarin, completely innocuous, may be beneficial in a variety of human disorders, in spite of some ongoing controversy. There has been, in recent years, a major rekindling of interest in pharmacognosy. Coumarin turns out to be present in many natural therapeutically utilized products. They hold a place apart in view of their cytotoxic activity. It was suggested that alterations in the chemical structure of coumarin could change their cytotoxic properties.[11]

Coumarin and its derivatives have been prominently accepted as natural pharmaceuticals[12] worldwide, has revealed new biological activities with interesting therapeutic applications, besides their traditional employment as anticoagulants (anti-vitamin K activity),[13] antibiotics (novobiocin and analogues)[14] and anti AIDS.[15] Apart from this, they also possess anti-cancerous,[11] antibacterial,[16] neurotropic,[17] immunosuppressive,[18] anti inflammatory,[19] antiulcerous,[20] anti PAF (anti platelet activating factor)[21] and antimutagenic[22] effects.

2. Pharmacology

Numerous biological activities have been associated with simple coumarin and its analogues. Among them, antimicrobial, antiviral, anticancer, enzyme inhibition, anti-inflammatory, antioxidant, anticoagulant and effect on central nervous system are most prominent. Coumarin nucleus possesses diversified biological activities that can be briefly summarized as under:

1. Antimicrobial and Molluscicidal [23-45]
2. Antiviral [46-50]
3. Anticancer [51-61]
4. As Enzyme Inhibition [62-67]
5. Antioxidant [68-71]
6. Anti-inflammatory [72-76]
7. Anticoagulant and Cardiovascular [77-80]
8. Effect on Central nervous system [81-82]

4-Hydroxycoumarin is a versatile scaffold and is being consistently used as a building block in organic chemistry as well as in heterocyclic chemistry for the synthesis of different heterocyclic compounds. The synthetic versatility of 4-hydroxy coumarin has led to the extensive use of this compound in organic synthesis. 4-hydroxy coumarin shows diversified chemical reactivity.

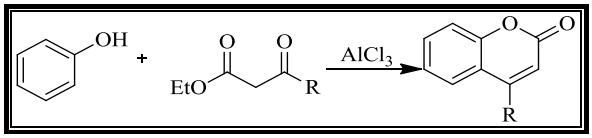
3. Synthetic methods

Coumarin and its derivatives were synthesized by many researchers using different methods. Perkin[84] synthesized coumarin and then several methods are reported for the synthesis of 4-hydroxy coumarins and their 4-hydroxy substituted derivatives namely:

1. Anschutz method [85]	5. Robertson synthesis [89]	9. Kaneyuki method [93]
2. Pauli Lockemann synthesis [86]	6. Ziegler and Junek method [90]	10. Resplandy's method [94]

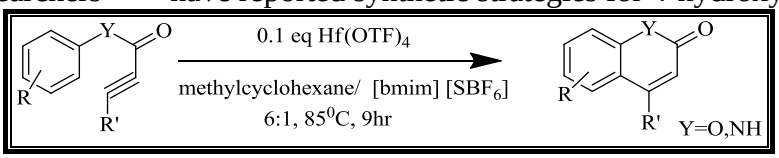
3. Sonn's synthesis [87]	7. Garden's method [91]	11. Jain, Rohatagi and Sheshadri's method [95]
4. Mentzer's synthesis [88]	8. Shah, Bose and Shah's method[96]	12. Shah, Bhatt and Thakor's method [96]

Shah et al.[92-96] have prepared 4-hydroxy coumarin derivatives in good yield by condensation of different phenols with malonic acid in the presence of zinc chloride and phosphorous oxychloride. The method is useful as single step preparation of 4-hydroxy coumarin derivatives substituted in benzenoid part.

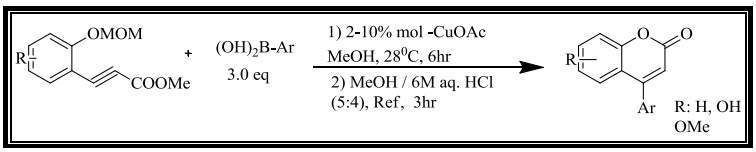


Pechmann Coumarin Synthesis

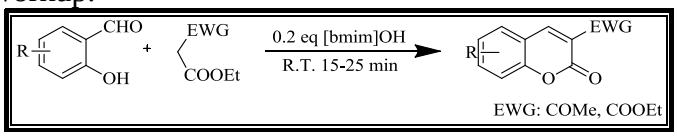
Recently many researchers[97-128] have reported synthetic strategies for 4-hydroxy coumarin.



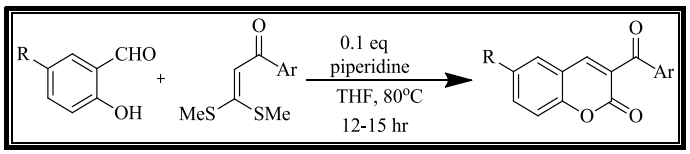
The employment of hydrophobic ionic liquids dramatically enhanced the activity of metal triflates in Friedel-Crafts alkenylations of aromatic compounds with various alkyl-and aryl-substitutedalkynes.[129]



Arylpropionic acid methyl esters having a MOM-protected hydroxy group at the ortho position underwent hydroarylation with various arylboronic acids in MeOH at ambient temperature in the presence of a catalytic amount of CuOAc, resulting in the formation of 4-arylcoumarins in high yields after the acidic workup.[130]

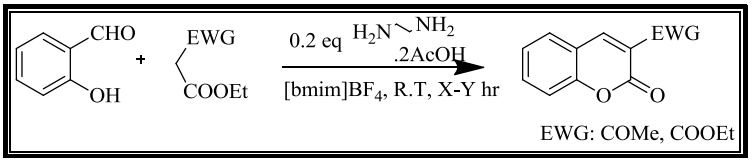


The basic ionic liquid 1-butyl-3-methylimidazolium hydroxide, [bmim]OH, efficiently catalyzes the Knoevenagel condensation of various aliphatic and aromatic aldehydes and ketones with active methylenes at room temperature without requirement of any organic solvent.[131]

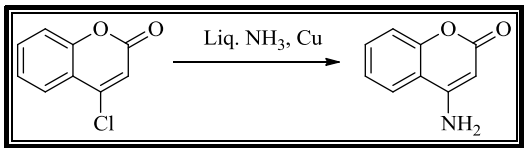


A facile, convenient, efficient and high yielding synthesis of a combinatorial library of 3-aroylcoumarins has been developed by the condensation of easily available aroylketene

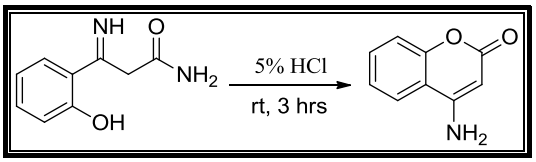
dithioacetals and 2-hydroxybenzaldehydes in the presence of catalytic amount of piperidine in THF reflux.[132]



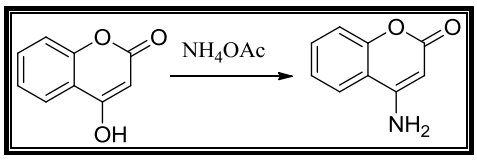
The ionic liquid 1-butyl-3-methylimidazonium tetrafluoroborate [bmim]BF_4 was used for ethylenediammonium diacetate (EDDA) catalyzed Knoevenagel condensation between aldehydes or ketones with active methylene compounds. Catalyst and solvent were recyclable.[133]



Zagorevskii, V. A. and Dudykina, N. V. was prepared 4-aminocoumarin from 4-chlorocooumarin using liq. Ammonia and copper.[134]



3-(2-Hydroxyphenyl)-3-iminopropanamide treated with 5% HCl at room temperature for 3 hours to yield 4-aminocoumarin.[135]



Ivanov, I. et al reports the amination of 4-hydroxycoumarin using ammonium acetate as a catalyst.[136,137]

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