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Synthetic and pharmacological profiles of coumarins: A review

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Abstract

The Benzopyrones are a group of compounds whose members include Coumarins and flavonoides. Dietary exposure to benzopyrones is quite significant, as these compounds are found in vegetables, fruit, seeds, nuts, coffee, tea and wine. It is estimated that the average western diet contains approximately 1g/day of mixed benzopyrones. It is, therefore, not difficult to see why extensive research into their pharmacological and therapeutic properties is underway over many years. Coumarin is a natural substance that has shown anti-tumour activity in vivo, with the effect believed to be due to its metabolites (e.g. 7-hydroxycoumarin). This review is based on recent studies of Coumarins and Coumarin related compounds. Therefore, the focus will be on these relevant compounds and their therapeutic importance along with the various methods of synthesis.

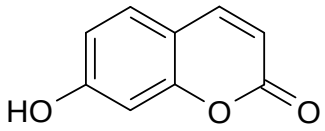
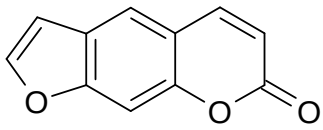
Key words: Benzopyrone, Coumarin, Pharmacological activities, SAR, Total synthesis.

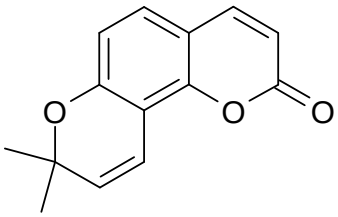
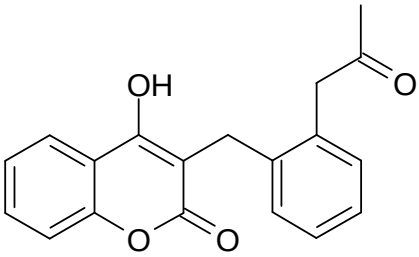
INTRODUCTION

Coumarins owe their class name to ‘Coumarou’, the vernacular name of the Tonka bean (*Dipteryx odorata Willd*, Fabaceae), from which Coumarin itself was isolated in 1820[1]. Coumarin is classified as a member of the Benzopyrone family of compounds, all of which consist of a benzene ring joined to a pyrone ring [2]. The benzopyrones can be subdivided into the benzo-a-pyrones to which the Coumarins belong and the benzo-g-pyrones, of which the flavonoids are principal members. Some important compounds isolated from Coumarins Novobiocin, Clorobiocin etc. Coumarin and its derivatives can be synthesized by various methods, which include Pechmann reaction, Perkin reaction, Reformatsky reaction and Knovenegal reaction. The plant extracts containing coumarin-related heterocycles, which were employed as herbal remedies in early days, have now been extensively studied for their biological activities. These investigations have revealed their potentials as versatile biodynamic

agents. For example, coumarins with phenolic hydroxyl groups have the ability to scavenge reactive oxygen species and thus prevent the formation of 5-HETE and HHT in the arachidonic pathway of inflammation suppression. Recent in vivo studies have revealed the role of coumarins in hepatotoxicity and also in depletion of cytochrome P450. Similarly 1-azacoumarins which is part of quinoline alkaloids are known for their diverse biological activity and recently, a 6-functionalized 1-aza coumarins are undergoing human clinical trials as an orally active anti-tumor drug in view of its farnesyl protein-inhibiting activity in the nanomolar range. Furthermore, several synthetic coumarins with a variety of pharmacophoric groups at C-3, C-4 and C-7 positions have been intensively screened for anti-microbial, anti-HIV, anti-cancer, lipid-lowering, anti-oxidant, and anti-coagulation activities. Specifically, coumarin-3-sulfonamides and carboxamides were reported to exhibit selective cytotoxicity against mammalian cancer cell lines. The C4-substituted aryloxymethyl, arylaminomethyl, and dichloroacetamidomethyl coumarins, along with the corresponding 1-azacoumarins, have been demonstrated to be potential anti-microbial and anti-inflammatory agents. To expand the structural diversity of synthetic courmarins for biological functions, attempts have also been made to attach a chloramphenicol side chain at C-3 position of courmarin. In addition, the bi- and tri-heterocyclic coumarins and 1-azacoumarins with benzofuran, furan and thiazole ring systems along with biocompatible fragments like vanillin have shown remarkable potency as anti-inflammatory agents in animal models. Photobiological studies on pyridine-fused polycyclic coumarins have highlighted their potential as thymine dimer photosensitisers and the structurally related compounds of both coumarin and carbostyrils have also been found to act via the DNA gyrase pathway in their anti-bacterial activity. Apart from the above works, the present review also addresses the potential roles of coumarins and carbostyrils as protease inhibitors, or fluorescent probes in mechanistic investigation of biochemical pathways, and their application for QSAR in theoretical studies. Though 1-Azacoumarins have received less attention as compared to coumarins in the literature, an attempt has been made to compare both the systems at various stages, so that it can spark new thoughts on synthetic methodologies, reactivity pattern and biological activities. [3]

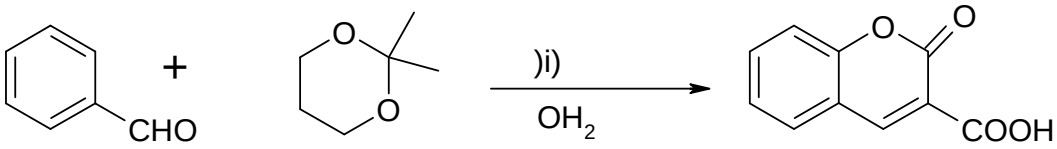
Table no: 1: Types and examples of Coumarins

Classification	Features	Examples
Simple Coumarins	Hydroxylated, Alkylated, Alkoxylated on benzene ring	 4-Hydroxycoumarin
Furano Coumarins	5 membered furan ring attached on benzene ring.	 Psoralene

Pyranocoumarins	Six membered pyrone ring attached on benzene ring.	 Seselin
Pyrone substituted Coumarins	Substitution on pyrone ring.	 Warfarin

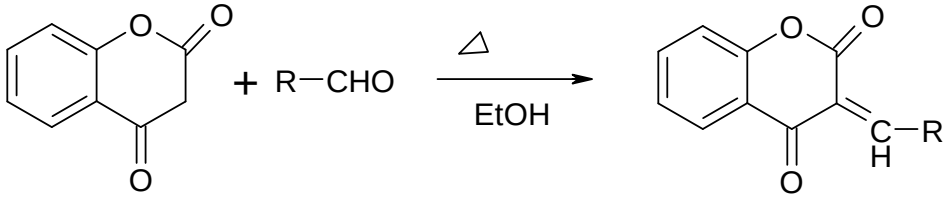
Ultrasound Promoted Synthesis of 3-Carboxycoumarins in Aqueous Media

Ultrasound irradiation has been increasingly used in organic synthesis in last three decades. Comparing with traditional methods, this method is more conveniently and easily controlled. A large number of organic reactions have been carried out in higher yield, shorter reaction time and milder condition under ultrasound irradiation. In all reactions, organic solvents are always being used. Recently organic reactions in water without use of harmful organic solvents have drawn much more attention, because water is a cheap, safe and environmentally benign solvent. [4]



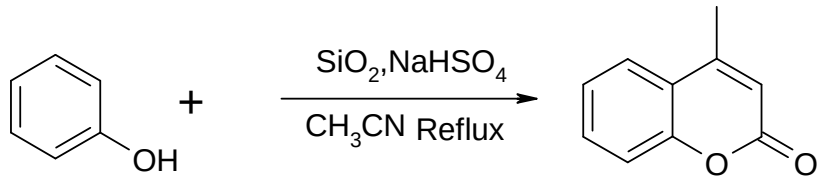
MW assisted synthesis of New Bis(benzopyrano) Fused Dihydropyridines Using Dry Media

A new and efficient synthesis of the novel bioactive bis(benzopyrano) fused dihydropyridines is described. The conventionally developed route is a two step multicomponent condensation reaction. This is latter modified by a one pot microwave (MW) assisted reaction using inorganic solid support *via* the arylidene derivative intermediate. With this environmentally benign approach, the reaction time is brought down from hours to minutes along with a yield enhancement. Furthermore, the role of different solid supports is studied and it is concluded that the acidic alumina is the best solid support for the present investigation. [5]



Silica gel Supported NaHSO4 Catalyzed synthesis of Coumarins

Heterogeneous solid acid–catalyzed organic reactions the use of silica gel supported NaHSO4 as a heterogeneous catalyst in a convenient synthesis of Coumarins by the Pechmann reaction. [6]



Solvent free synthesis of Coumarins

Pechmann reaction has been extensively used for the preparation of coumarin and its derivatives from simple starting materials. The present investigation describes an ecofriendly route for the Pechmann synthesis of coumarin derivatives over Al-MCM-41 and its supported catalysts under solvent-free condition. [7]

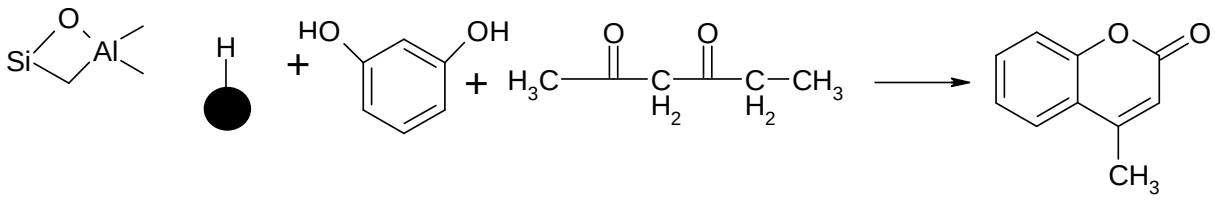
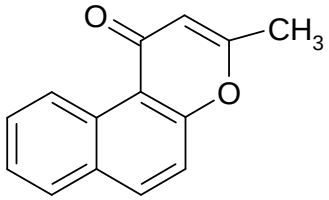
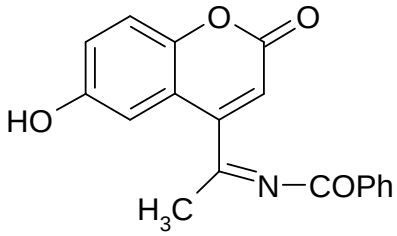
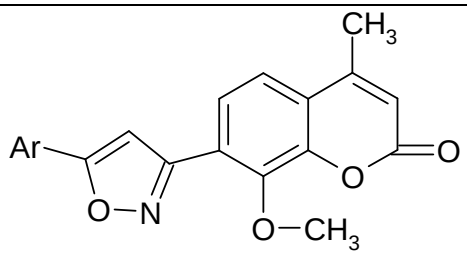
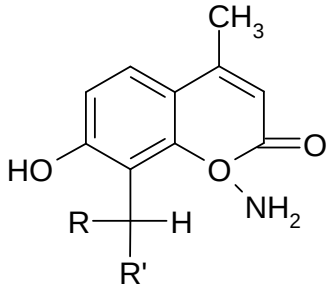
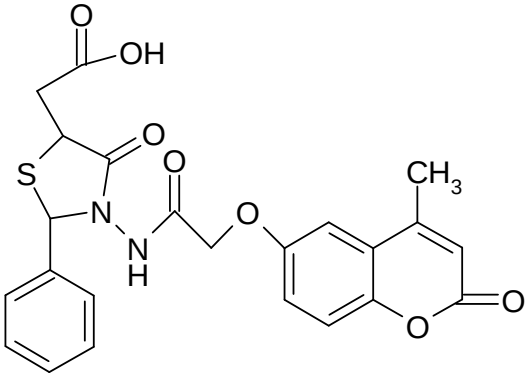
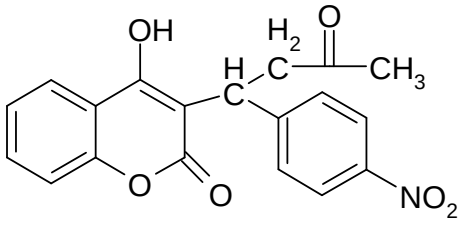
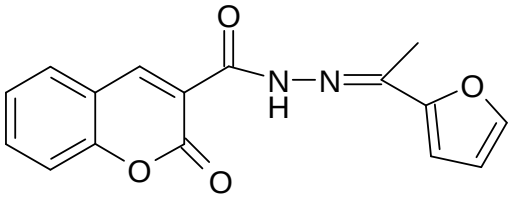
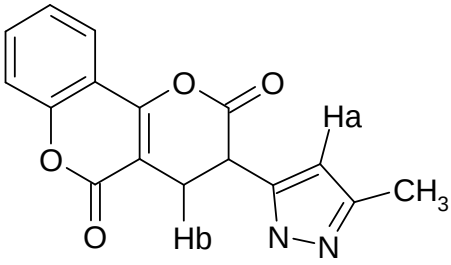
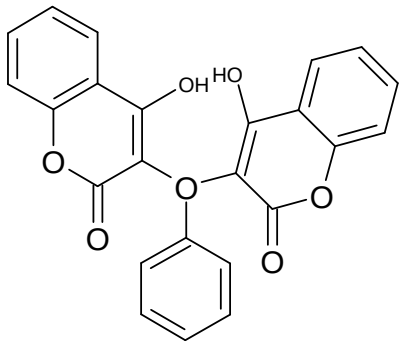


Table no:2: Pharmacological activities of Coumarins

Sr.no	Authors	Structure	Pharmacological activity
1	Hakan Kolancilar *et al*;2008		Antimicrobial Activity [8]
2	Antigoni Kotali *et al*;2008		Antileucemic Activity [9]

3	Gummudavelly Sandeep *et al* ;2009		Anti inflammatory Activity[10]
4	Vinod Kumar Pandey *et al*;2004		antiviral activity and antihypertensive activity [11]
5	Parameswaran Manojkumar *et al;*2009		Anti cancer activity [12]
6	Irena Kostova *et al*;2006		Anticoagulant Activity [13]
7	Rafat M. Mohareb *et al;*2009		Antimicrobial Activity [14]
8	Mohammad Asad *et al;*2009		Anti-Inflammatory Activity [15]

9	Irena Kostova et al;2006		Cytotoxic Activity [16]

Natural coumarins possessing anti-HIV activity
Dipyranocoumarins-Calanolides
(+)-Calanolide A, (+)-[10R, 11S, 12S]- 10,11-trans-dihydro-12-hydroxy-6,6,10,11-tetramethyl-4-propyl-2H,6H-benzo[1,2-b:3,4-b':5,6 b"]tripyran-2-one, is a novel nonnucleoside RT inhibitor (NNRTI) with potent activity against HIV-1 .

Costatolides
Two isomers of calanolide A, (-)-calanolide B (costatolide) and (-)-dihydrocalanolide B (dihydrocostatolide), possess antiviral properties similar to those of calanolide A. Each of these three compounds has properties of NNRTIs. The calanolide analogues, however, exhibit enhanced antiviral activity against drug-resistant viruses after NNRTI treatment. Costatolide and dihydrocostatolide are highly effective inhibitors of clinical strains, including those representing various HIV-1 clades, SIs, NSIs, T- and M-tropic isolates.

Inophyllums
The seeds of Calophyllum cerasiferum Vesque (Family-Clusiaceae) and Calophyllum inophyllum Linn. (Family-Clusiaceae) contain several known coumarins, among them the potent HIV-1 RT inhibitors costatolide and inophyllum P. Calophyllum cerasiferum contained (-)-calanolide B. [17]

CONCLUSION

Coumarin and Coumarin-related compounds have proved for many years to have significant therapeutic potential. They come from a wide variety of natural sources and new Coumarin derivatives are being discovered or synthesized on a regular basis. Coumarin is a simple molecule and many of its derivatives have been known for more than a century. However, their vital role in plant and animal biology has not been fully exploited. It is evident from the research described that Coumarin and Coumarin-related compounds are a plentiful source of potential drugs candidate in relation to its safety and efficacy.

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