CHAPTER I

INTRODUCTION

INTRODUCTION

Coumarins or benzo-α-pyrones are widely distributed in nature[1], either in the free state or in the combined state. Their principal sources have been classified into four major families from which most of the coumarins are isolated. These are-

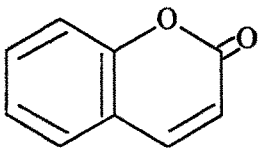
- Umbelliferae (e.g. Parsley, Parsnip, Celery, Ammi majus, Angelica archangelic)
- Rutaceae (e.g. Bergamot fruit, Lime gas plant, Cloves, Common rue)
- Leguminosae (e.g. Psoralea Corylifolia, Xanthoxylum flavum) and
- Moraceae (e.g. Ficus Carica)[2]

Some of these naturally occuring coumarins are pharmacologically active as anticoagulants, rodenticides and insecticides. The following are examples of some important naturally occuring coumarins:

Coumarin (1), Umbelliferone (2), Aesculetin (3), Daphnetin (4), Scopoletin (5), Fraxetin (6) and Ayapin (7).

These naturally occuring coumarins are classified into seven major groups.

- Coumarins substituted with one or more hydroxyl or methoxyl groups in the benzene ring e.g. Umbelliferone (2), Aesculetin (3).
- Coumarins substituted with isoprenoid residues e.g. Auraptene (8), Suberosin (9), Xanthyletin (10), Samidin (11).
- Coumarins with substituents at one or both of the remaining benzenoid positions e.g. Psoralen (12), Angelicin (13), Xanthotoxin (14).
- 3-Phenylcoumarins e.g. Pachyrrhizin (15).
- 4-Substituted coumarins such as 4-alkylcoumarins, 4-hydroxycoumarins, 4-phenylcoumarins e.g. Mammein (16), Dicoumarol (17), Dalbergin (18).
- 3-Phenyl-4-hydroxycoumarins e.g. Scandinin (19).
- 3,4-Benzocoumarins e.g. Ellagic acid (20).



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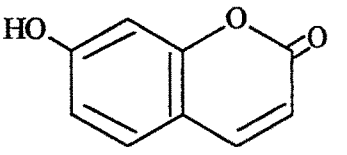

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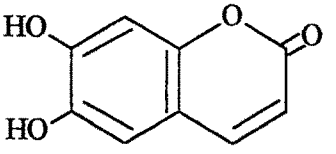

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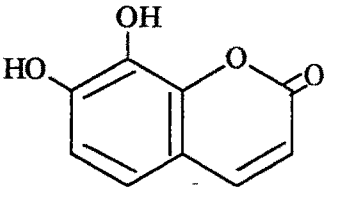

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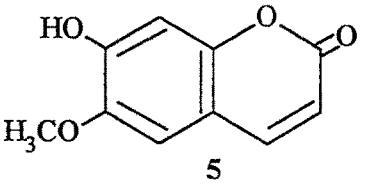

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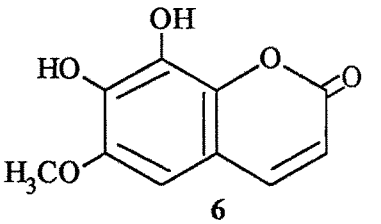

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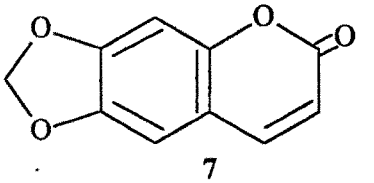

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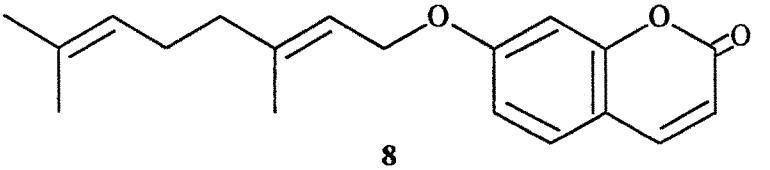

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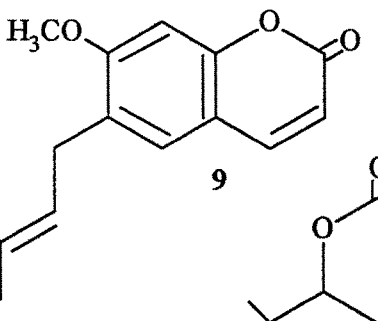

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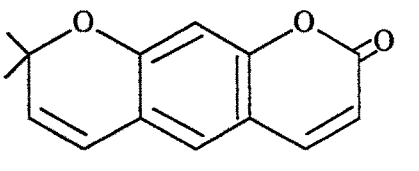

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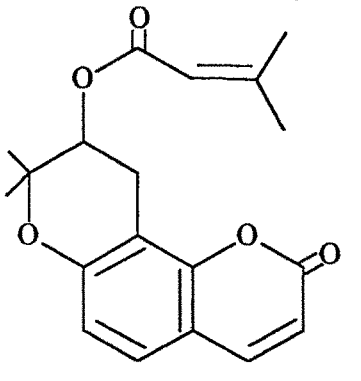

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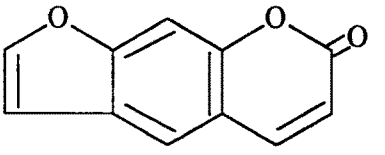

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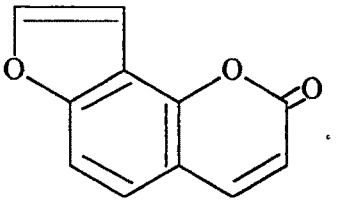

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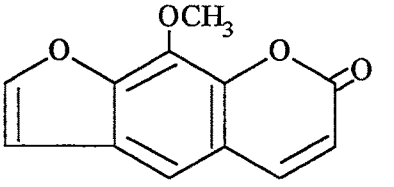

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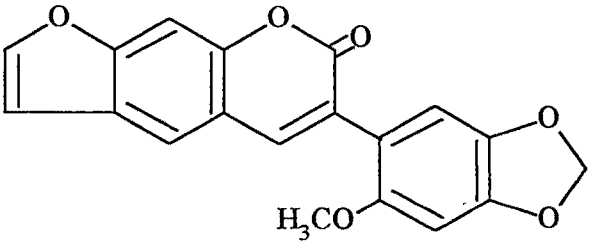

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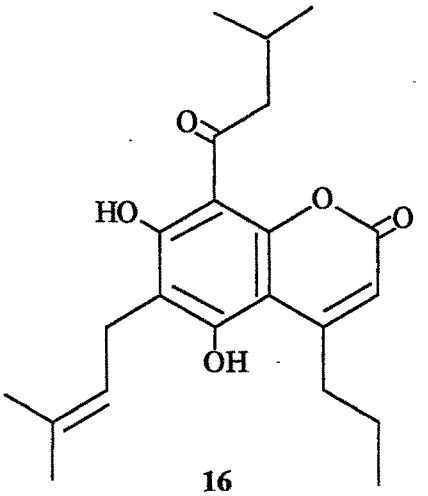

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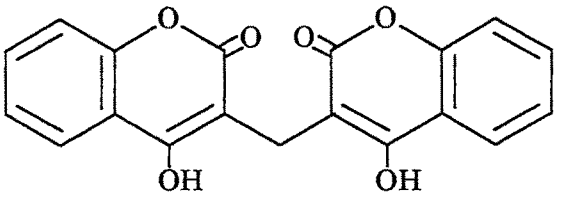

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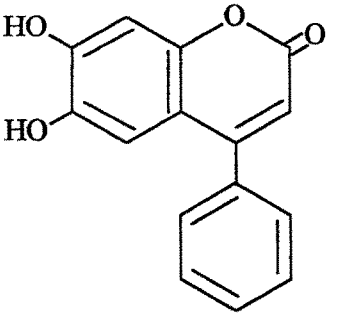

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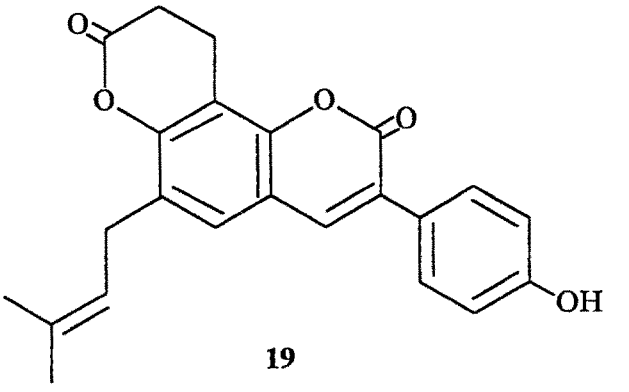

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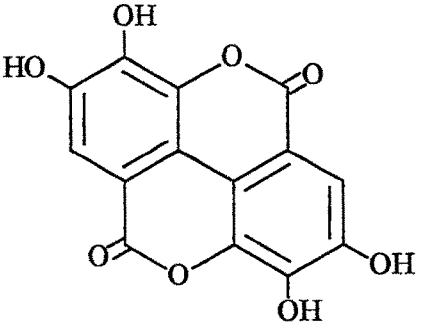

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PHYSIOLOGICAL PROPERTIES

Among so many heterocycles, coumarin and its derivatives have attracted considerable interest because of their various physiological and biochemical properties.

Many natural coumarins affect the living cells of plants and animals in various ways. Bose[3] has reviewed the biochemical properties of natural coumarins, whereas Sigmund[4] observed the effects of both aesculetin (3) and daphnetin (4) on seed germination and noted coumarin itself inhibits the germination and subsequent root growth of plants. Kelbs[5] noticed its toxic effect on algae. There is also a good probability that coumarins act as growth regulators in a number of plants[6].

Coumarin acts as a narcotic for some animals and as a sedative and hypnotic for mice[7]. Fraxin causes paralysis of the central nervous system of frogs and mice on intravenous injections[8] and it has been found to be superior to atophan in the treatment of gout[9]. It is interesting to note that some simple coumarins have the opposite effect. Herniarin (21) and ayapin (7) have been found to possess remarkable haemostatic properties and are active both in vitro and vivo[10]. Novobiocin[11] (22), an antibiotic isolated from streptomyces sp., has been found to be a coumarin derivative. The antibacterial spectrum of this antibiotic corresponds generally with that of penicillin and erythromycin, but in vitro is less potent.

Coumarins are also known for anticoagulant[12] and rodenticidal properties. A naturally occuring toxin present in spoiled sweet clover hay is 4-hydroxycoumarin derivative (e.g. dicoumarol (17)). This property has been well exploited in pharmaceuticals and is used in treatment of cardiovascular disease e.g. Warfarin (23) developed, as rodenticide is a useful anticoagulant drug.

3,4-Diaminocoumarins and 4-aminocoumarins have neutropic activity, while substituents on 4-amino group increase CNS activity[13]. Besides, the derivatives of coumarins found to have blood cholesterol lowering activity[14] and antispermatogenic activity[15].

Laurin *et al.*[16] synthesized amino substituted coumarins which are discovered as gyrase B inhibitors with promising antibacterial activity in vitro. Ferround *et al.*[17] introduced alkyl side chains at C-5 of coumarins which improved in vitro antibacterial properties, whereas Kayser *et al.*[18] synthesized coumarins with antibacterial broad spectrum activity.

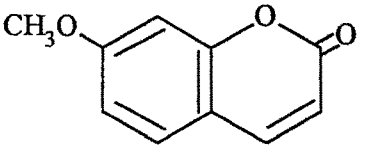
Okamoto and coworkers[19] synthesized coumarins, which were claimed for the treatment of liver diseases, whereas Trkovnik *et al.*[20] used coumarin derivatives for the treatment of digestive tract disorders and for reducing concentration or activity of transaminases.

Vijayakumar *et al.*[21] synthesized coumarin and its derivatives, which were antifungal on pathogenic fungi. Sardari *et al.*[22] synthesized non toxic coumarins and angular furobenzopyrones which showed antifungal activity. These furobenzo-α-pyrones are also widely used in the treatment of skin liaisons such as psoriasis[23], vitiligo[24] etc. in combination with UV-A light.

There is another class of naturally occuring coumarin derivative known as coumestan or benzofurobenzo-α-pyrones (24). These compounds possess estrogenic and phytoalexin properties[25-28].

Simple coumarins have antitumor activity. Coumarin itself has been reported to be a moderately potent inhibitor of chemical carcinogen induced neoplasia[29] and micromelin (25), mammein (16) and several related coumarins have antitumor activities[30,31]. Jimenez-Orozco *et al.*[32] found that coumarin has antitumor effects in vivo and cytostatic effects in vitro. Its half-life in human is short (1-1.5h) and the monohydroxylated biotransformation products have significantly longer half-lives. One or several of these products may thus be responsible for the antitumoral activity.

Lymphedema[33] of arms can be a serious consequence of local and regional therapy in women with breast cancer. Coumarin has been reported to be effective to the treatment of women with lymphedema, but not effective for women who have lymphedema of arm after the treatment for breast cancer.



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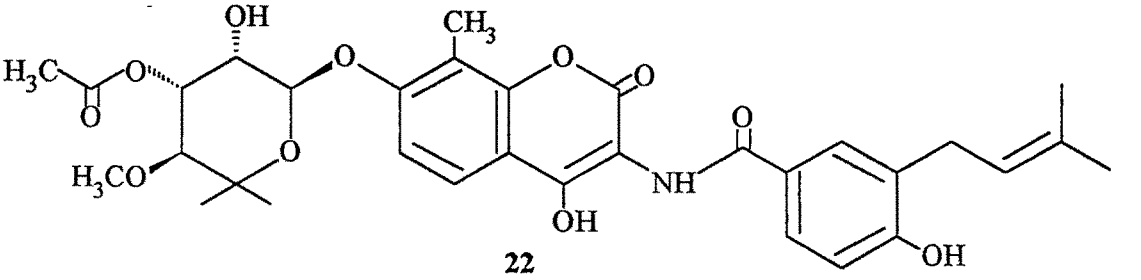

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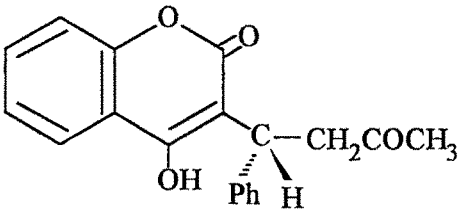

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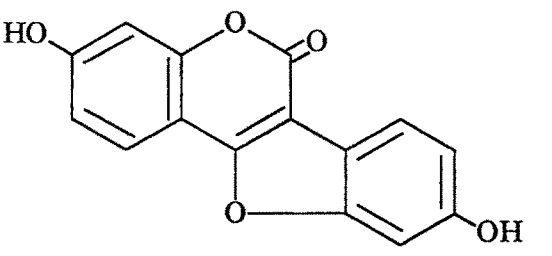

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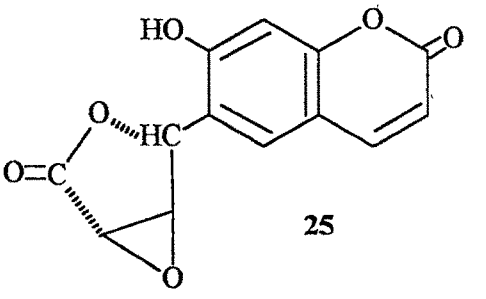

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IDENTIFICATION

UV Spectroscopy

UV absorption spectra are useful for distinguishing coumarins from chromones. Chromones (benzo-γ-pyrones) normally have a strong absorption at 240-250nm, where as coumarins have a minimum at this wavelength. Alkyl coumarin shows absorption bands at 274 and 311nm, which are due to the benzene and pyrone rings respectively[34]. Substitution of methyl group at C-3 leads to a small hypsochromic shift in the 311nm maxima. Methyl substitution at C-5, C-7 or C-8 leads to a bathochromic shift of 274nm maxima but leaves the 311nm maxima practically unchanged.

The introduction of hydroxyl group into coumarin nucleus causes a bathochromic shift of principal absorption band. The position of new maxima depends on the ability of hydroxyl group to conjugate with chromophoric system.

IR Spectroscopy

Apart from identifying the functional groups, IR spectra is useful in revealing the conjugated lactone function. Coumarins are isomeric with chromones, but these two differ considerably in their IR patterns. The carbonyl stretching frequency in coumarins[35,36] (α-pyrones) is observed in the region 1700-1750cm^{-1}, whereas in chromones (γ-pyrones) appears at 1650 cm^{-1}.

^{1}H-NMR Spectroscopy

A wide range of ^{1}H-NMR techniques have been applied to the structural elucidation of naturally occuring coumarins. The most important publication is of Steck and Mazurek[37], who drew up spectra-structure correlation rules.

Observation of a pair of doublets, J = 9.5Hz centered at δ 6.10-6.40 and 7.50-8.30 in the ^{1}H-NMR spectrum reveals unsubstituted coumarin in the pyrone ring system. These are the characteristic signals for C-3 and C-4 protons respectively.

Many 7-oxygenated coumarins are known with alkyl or alkoxy groups at C-8. The signal for C-5 proton is found at δ 7.30, downfield from C-6 proton, which resonates at δ 6.80. The presence of these ortho coupled protons can be recognized instantly as they give another pair of doublets with 9Hz coupling constant value.

Sometimes measurement of Nuclear Overhouser Effect (NOE) provides considerable assistance in assigning the geometry of the coumarins, especially when all the four positions on the benzenoid ring are substituted.

In poncitrin (26) the methoxy substituent is at C-5. On saturation of the methoxy signal at δ 3.82, the integrated intensities of the doublets produced from H-4 and H-4′, were increased by 9% and 13% respectively. From this it was concluded that the methoxy group must be close to H-4 and hence must be located at C-5 and also proximate to the pyran ring which therefore had to be linearly fused[38,39].

Aromatic methoxy groups normally resonate in the range of δ 3.80-4.40 and aromatic methyl groups at δ 2.45-2.75[40-42].

^{13}C-NMR Spectroscopy

With the availability of Fourier-Transform methods and computer development, ^{13}C-NMR has now become a sensitive and powerful tool in the structural elucidation of natural products. A number of publications have appeared in which complete assignment of ^{13}C chemical shifts and extensive assignments of carbon-proton coupling have been presented for hydroxy and methoxy coumarins[43-45] and also for furanocoumarins[46]. The chemical shift of carbonyl carbon atom has been found approximately the same at δ 160.0 for most of the coumarins. The chemical shifts for simple coumarin are:

C-2	160.4	C-4a	118.8	C-7	131.8
C-3	116.4	C-5	128.1	C-8	116.4
C-4	143.6	C-6	124.4	C-8a	153.9

Mass Spectroscopy

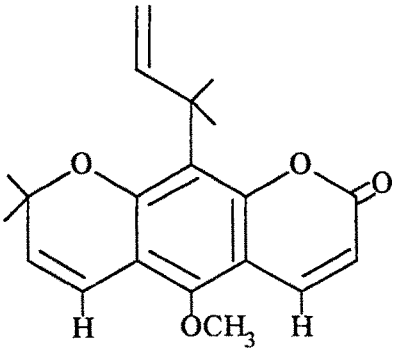
The mass spectra of simple coumarins are characterized by intense molecular ion peak indicating stable heterocyclic ring system. Coumarin gives a strong molecular ion (M^+ m/z 146, 76%) on electron impact and a base peak (m/z 118, 100%) 28 mass unit lower. The later ion formed directly from the molecular ion by the loss of carbon monoxide from the pyrone ring[47,48] resulting in the formation of molecular ion benzofuran, which further looses consecutively CO and hydrogen atom. **[Scheme I.1]**

The presence of furan ring in furocoumarins (benzopyrones) normally does not alter the fragmentation. However in methoxybenzopyrone such as in xanthotoxin, loss of methyl radical give rise to conjugated oxonium ion[48]. **[Scheme I.2]**

METHODS OF SYNTHESIS

Interest in naturally occuring coumarins and their derivatives has been revived for the past 30 years mainly due to the wide range of physiological properties that they have been shown to possess. Total synthesis of various natural coumarins have been achieved by many workers and the key step in most of the cases has been the formation of pyrone ring in which, the phenol containing requisite substituents of the natural coumarin is prepared first and then modified by steps such as nuclear oxygenation, O- or C- alkylation and finally building up of additional rings.

Some of the approaches of recent past for the synthesis are depicted here. **[Scheme I.3]**



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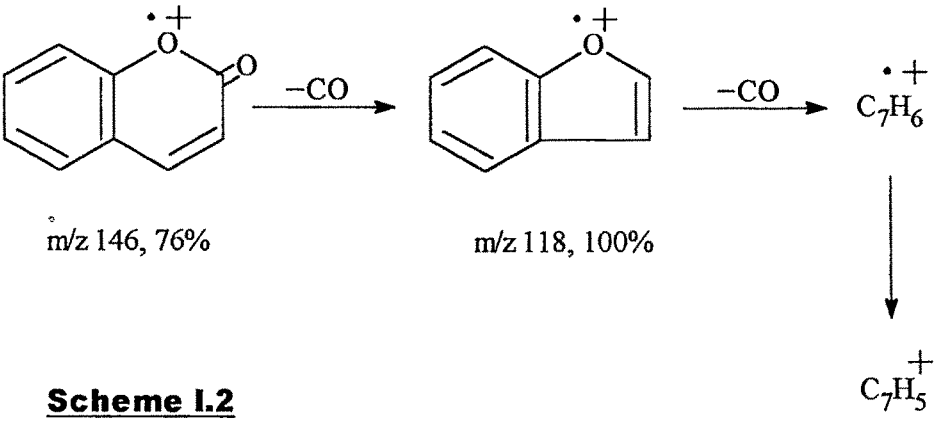
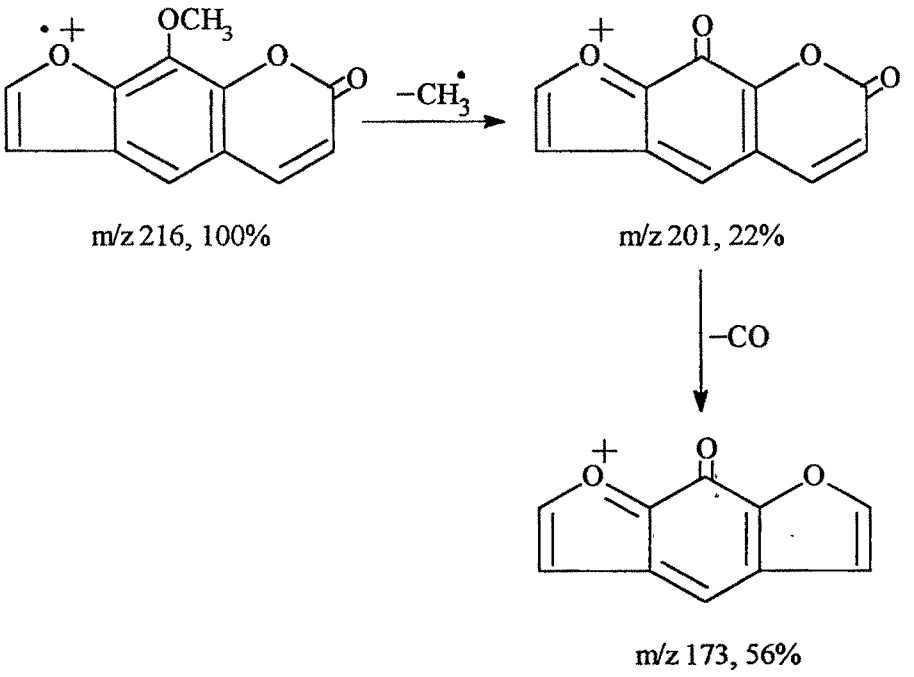
Scheme I.1

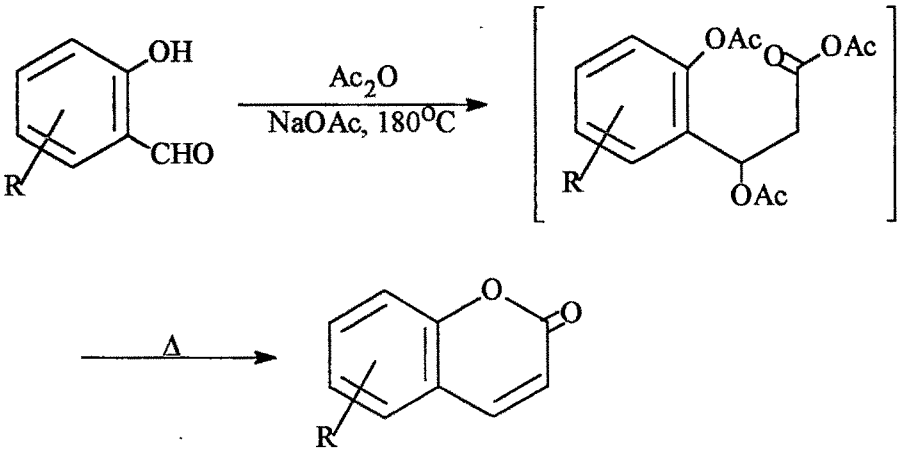


Scheme I.2

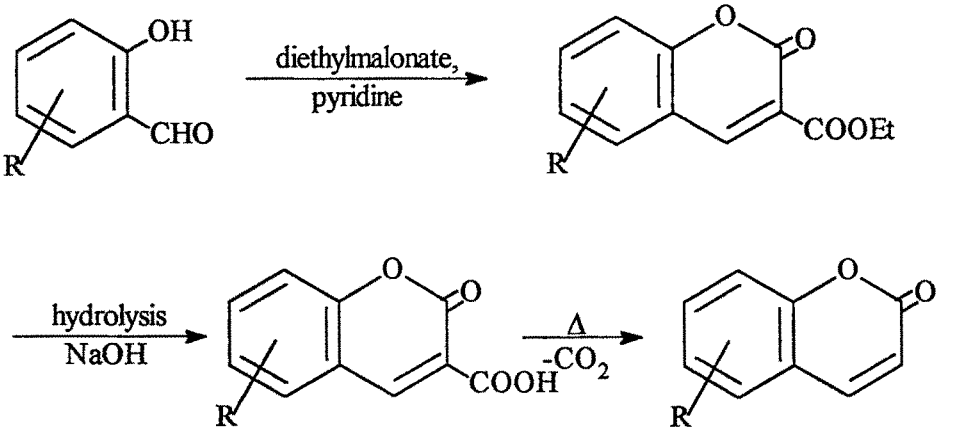


Scheme I.3

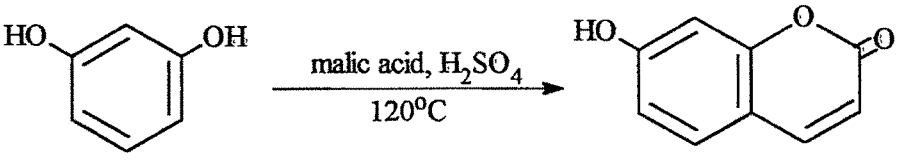
Perkin Synthesis



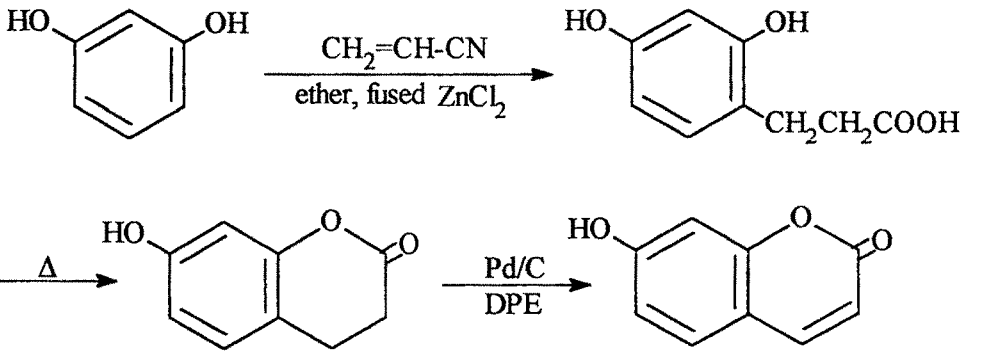
Knoevenagel Condensation



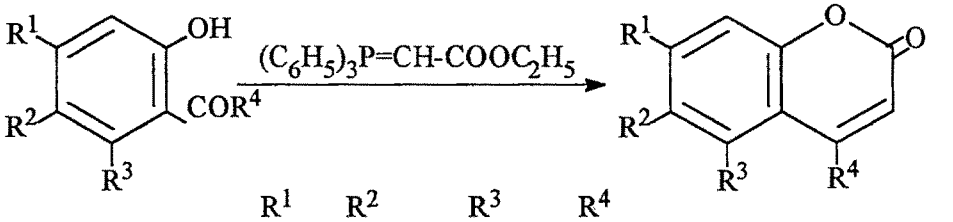
Pechmann Synthesis



Chatterjee *et al.*[49]

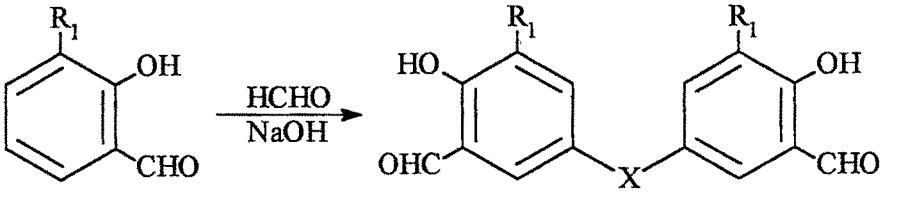


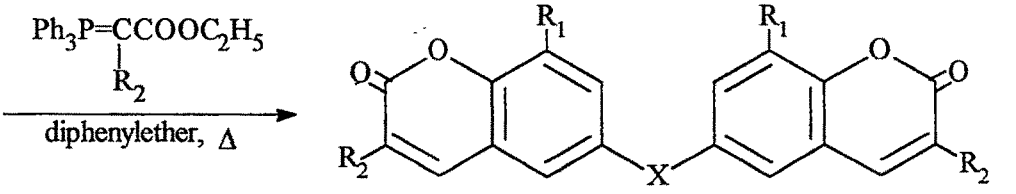
Mali *et al.*[50]



R^1	R^2	R^3	R^4
H	H	H	H
H	H	H	CH_3
OH	OCH_3	OCH_3	H

Brahmbhatt *et al.*[51]





R_1	R_2	X
H	H	CH_2
OCH_3	CH_3	CH_2
H	CH_2Ph	SO_2

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