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ORIGINAL RESEARCH

Recent Advances in Synthesis of Coumarins: Coumarin Derivatives and Their Biological Application

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Abstract

Coumarin was first extracted from Tonka bean by Vogel in 1820. Coumarin and its derivatives are important groups of compounds due to their medicinal and pharmacological properties. These compounds have a significant role in the development of new drugs. Many different conventional methods and non-conventional methods have been developed to synthesize coumarin derivatives. The objective of this review paper is to present the various methods of coumarin synthesis, both conventional and green synthesis. Techniques such as heating, microwave, and ultrasound irradiation were employed. Moreover, various solvents and catalysts were employed in order to obtain better yields. The present review revealed that the conventional methods are time-consuming, environmentally polluting, and lower in yield whereas the green synthesis of coumarin derivatives is better in yield, environmentally eco-friendly and rapid. This review summarized several conventional methods, non-conventional methods and reaction conditions for the synthesis of coumarin derivatives from various precursors such as aldehydes, carboxylic acids, ketones and phenols. Literature collection was conducted using various search engines.

Keywords: Coumarin, synthesis; coumarin derivatives; conventional method, nonconventional method

Introduction

Coumarins (IUPAC name: 2H-chromen-2-one) are well-known naturally occurring oxygen containing heterocyclic compounds isolated from various plants with pleasant flavour. They belong to the family of lactones having 1-benzopyran-2-one system that can be isolated from plants as well as synthesized (Blahova and Svobodova, 2012). Coumarins (benzo-α-pyrone) are a very large and important family of compounds consisting of fused pyrone and benzene rings, with the pyrone carbonyl group at position 2; this structure is illustrated in Fig.1 for the coumarin parent molecule (Jain and Joshi, 2016).

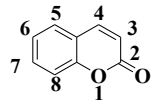

Fig 1: structure of simple coumarin

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REVIEW ARTICLE

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Coumarin was first extracted from Tonka bean by Vogel in 1820. Coumarin and its derivatives are important groups of compounds due to their medicinal and pharmacological properties. These compounds have a significant role in the development of new drugs. Many different conventional methods and non-conventional methods have been developed to synthesize coumarin derivatives. The objective of this review paper is to present the various methods of coumarin synthesis, both conventional and green synthesis. Techniques such as heating, microwave, and ultrasound irradiation were employed. Moreover, various solvents and catalysts were employed in order to obtain better yields. The present review revealed that the conventional methods are time-consuming, environmentally polluting, and lower in yield whereas the green synthesis of coumarin derivatives is better in yield, environmentally eco-friendly and rapid. This review summarized several conventional methods, non-conventional methods and reaction conditions for the synthesis of coumarin derivatives from various precursors such as aldehydes, carboxylic acids, ketones and phenols. Literature collection was conducted using various search engines.

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1. Introduction

Coumarins (IUPAC name: 2H-chromen-2-one) are well-known naturally occurring oxygen containing heterocyclic compounds isolated from various plants with pleasant flavour. They belong to the family of lactones having 1-benzopyran-2-one system that can be isolated from plants as well as synthesized (Blahova and Svobodova, 2012). Coumarins (benzo-*α*-pyrone) are a very large and important family of compounds consisting of fused pyrone and benzene rings, with the pyrone carbonyl group at position 2; this structure is illustrated in Fig.1 for the coumarin parent molecule (Jain and Joshi, 2016).

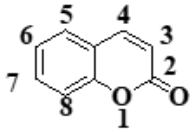


Fig 1: structure of simple coumarin

Many coumarins and their derivatives have been isolated from the plant parts (Tonk bean, woodruff, vanilla, etc.) and reported to possess broad range of pharmacological activities namely, anti-inflammatory & antipyretics, antioxidant, brochodialator, vasodialator, antiamoebic, anticoagulation, anti–tumor, antiasthmatic, anti-HIV, cytotoxic, antibacterial and antifungal activities (Bhatnagar *et al*, 2010). Especially, 7-hydroxycoumarin has antioxidant properties and cytostatic, antibacterial, antiviral, xanthine oxidase inhibitor, vasorelaxant, antitubercular (Klenker and Molner, 2015). They are also used as enhancing agent in cosmetic products like perfumes, soap, detergents, toothpaste and alcoholic beverages. The biochemical, pharmacological and therapeutic applications of simple coumarins could be influenced by the substitution pattern (Rohini and Srikumar, 2014). It was first isolated by Vogel in 1820 by extraction from Tonka beans (*Dipteryx odorata*) species previously known as *Coumarona odorata*, hence the term coumarin emerged (Melita *et al*., 2020).

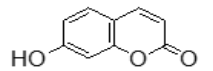
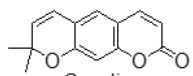
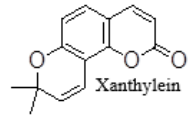
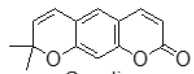
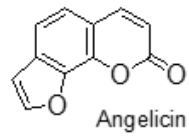
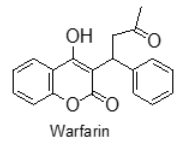
1.1. Occurrence

Coumarins occur as secondary metabolites in seeds, roots and leaves of many plant species, notably in high concentration in the Tonka bean and thus the name comes from a French word, coumarou, for the Tonka bean (Akkol *et al*., 2020). Coumarins cover a very wide range of compounds throughout the plant kingdom and are rich in fruits (e.g. bilberry, cloudberry) and stems. They are also rich in cassia leaf oil (up to 87,300 ppm), lavender oil and cinnamon bark oil (7,000 ppm). Most coumarins occur in higher plants, with the richest sources being the *Rutaceae* and *Umbelliferae*. Coumarins are also found in selective microorganisms. Members of coumarins isolated from microbial sources are novobiocin from *Streptomycin* and aflatoxin from *Aspergillus species*. Although distributed throughout all parts of the plant, the coumarins occur at the highest levels in fruits, followed by roots, stems and leaves. Environmental conditions and seasonal changes can influence the occurrence in diverse parts of the plant (Jain and Joshi, 2021).

1.2. Classification of Coumarins

Coumarins are classified based on their chemical composition as shown in Table 1 (Chaudhary *et al.*, 2021):

Table 1: Types and Examples of Coumarins

Classification	Structural features	Examples
Simple coumarins	Hydroxylated, Alkylated, Alkoxylated on benzene ring	 7-hydroxycoumarin
Furanocoumarins	5 membered furan ring Attached on benzene ring	 Seselin  Xanthylein
Pyranocoumarins	6 membered pyrone ring attached on benzene ring	 Seselin  Angelicin
Pyrone substituted coumarins	Substitution on pyrone ring	 Warfarin

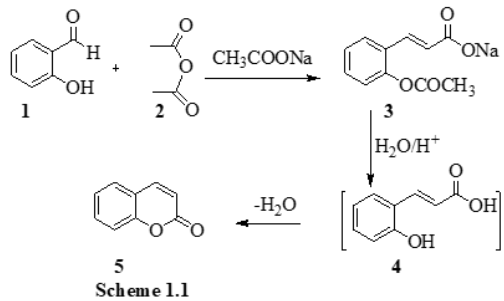
1.3. Synthesis of Coumarins and Its Derivatives Through Conventional Methods

Because of their varied biological applications, synthesis of coumarins and their derivatives has attracted considerable attention of organic and medicinal chemists from many years as the large number of natural products contain this heterocyclic nucleus (Asif, 2015).

Numerous methods have been developed for the synthesis of coumarins that include via Pechmann condensation, Perkin reaction, Knoevenagel condensation, Wittig reaction, Reformatsky reaction etc (Kumar *et al*., 2015). Coumarin derivatives are readily synthesized by the above - mentioned reactions; however, they usually require harsh reaction conditions and non-environmentally friendly solvents. Recently, some methods for the synthesis of coumarin have been reported (Saour *et al*., 2012). For instance, ionic liquids have attracted extensive interest as environmentally benign reagents to their favorable properties, and a variety of catalytic reactions have been successfully conducted using ionic liquids as solvents.

1.3.1. Perkin Reaction

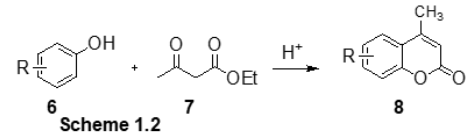
Coumarins were first synthesized *via* the Perkin reaction in 1868 from salicylaldehyde **1** by heating it with acetic anhydride **2** in the presence of anhydrous sodium acetate. This reaction occurs with the formation of an intermediate o-hydroxycinnamic acid derivative **4** which on elimination of a molecule of water forms the lactone ring **5** *(Scheme 1.1*). Many simple coumarins are still synthesized through this method (Sangh and Pathak, 2016).



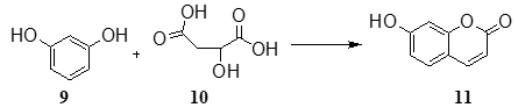
Scheme 1.1

1.3.2. Von Pechmann Reaction

Pechmann condensation reaction was first reported in 1883. It has been widely employed for the synthesis of coumarins because of its preparative simplicity and inexpensive starting material. Pechmann reported his alternative method of coumarin synthesis **8** which involves the reaction of β-ketoester **7** and phenols **6** in the presence of strong acid as catalyst (*Scheme 1.2*). Pechmann also found that a coumarin derivative **11** is formed when a mixture of a phenol **9** and malic acid **10** is heated in the presence of concentrated sulfuric acid *(Scheme 1.3).*



Scheme 1.2



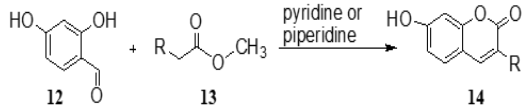
Scheme 1.3

Von Pechmann Reaction Procedures

This method has limited applicability. Many substituted phenols do not undergo this reaction; only coumarins unsubstituted in the pyrone ring are obtained (Onar and Vandar, 2018).

1.3.3. Knoevenagel Reaction

In the early nineties (1900s), the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxylic acid at the C-3 position. Knoevenagel developed a method for the synthesis of coumarin derivatives **14** from o-hydroxyaldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate **13**, etc., in the presence of piperidine, pyridine, and other organic bases *(Scheme 1.4)* (Abdel-Wahab *et al*., 2014).

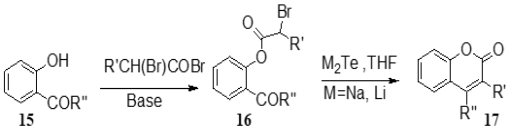


Scheme 1.4

Knoevenagel Reaction Procedures

1.3.4. Reformatsky Reaction

Bhinder and Kaur (2014) reported the sodium telluride-triggered cyclization of the bromoacetate of salicylaldehyde **15** to coumarin **17** *via* modified Reformatsky reaction. The cyclization proceeds by formation of the phenolate ester enolate **16**, elemental tellurium and bromide ion. The enolate anion either attacks the *ortho* carbonyl group leading to cyclization or eliminates a phenolate ion to give a ketene *(Scheme 1.5).*

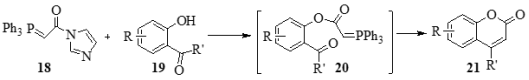


Scheme 1.5

Reformatsky Reaction Procedures

1.3.5. Wittig Reaction

Sangh and Pathak (2016) reported a novel one-pot synthesis of coumarins *via* intramolecular Wittig cyclization from the reaction of phenolic compounds containing *ortho*-carbonyl group **19** and triphenyl(α-carboxymethylene) phosphorane imidazolide **18** which resulted in intermediate **20**. Subsequent cyclization of the resulting intermediate **20** affords coumarin **21** *(Scheme 1.6*).



Scheme 1.6

Wittig Reaction Procedures

2. *Synthesis of Coumarins and Their Derivatives Through Conventional, Microwave Assisted and Solvent Free Synthesis*

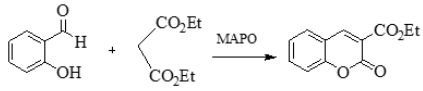
The traditional approach to most reactions is to use a solvent and heat under reflux for a long period of time. But, solvents create lots of problem in the reaction as they are generally toxic, difficult to remove, increases the cost of the product and most importantly they are environment polluting agents. Development of potent and effective antimicrobial drugs is one of the most pressing goals of current research in chemistry. A green protocol has been used to synthesize a novel series of coumarin derivatives in a shorter reaction time, higher yields and simple operations when compared with the conventional heating method (Melita *et al*., 2020).

Even though several methods for coumarin synthesis have been reported, the majority of their earlier syntheses require reactant material which is expensive, in some methods high amount of energy is required to complete the reaction, some methods produce by products which are hazarded to environment, other methods are not possible in large industrial scale, while some are having low practical yield (Kodape *et al*., 2012).

Hence the solvent free reaction is an approach towards green synthesis. Several experiments showed that Pechmann Reaction is an exothermic reaction when conducted in the solvent-free mode and it continued to completion spontaneously after initiation by small burst of energy, which can be supplied by Grinding or by Microwave "Jump Start" method. The current investigation is an effort towards "green chemistry" in the eco-friendly synthesis of biologically important coumarins. The noteworthy feature of many researchers' investigation is the development of more eco-friendly synthetic methods (Melita *et al*., 2020).

2.1. Substituted 3-Carboxycoumarin Derivatives

The Knoevenagel condensation of 2-hydroxybenzaldehyde **1** with diethyl malonate **22** was catalyzed with different catalysts to give ethyl coumarin-3-carboxylate **23** *(Scheme 2.1).* Various catalysts were used in this reaction, such as piperidine, molecular sieves/piperidine catalyst, magnesium aluminophosphate (MAPO) (Abdel-Wahab *et al.*, 2014).

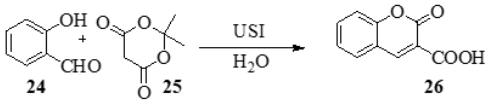


Scheme 2.1

Substituted 3-Carboxycoumarin Derivatives Synthesis

Loncaric *et al* (2010) reported that ultrasound irradiation has been increasingly used in organic synthesis in last three decades. Compared 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 reaction conditions under ultrasound irradiation. Recently organic reactions in water without the use of harmful organic solvents have drawn much more attention because water is a cheap, safe, and environmentally benign solvent.

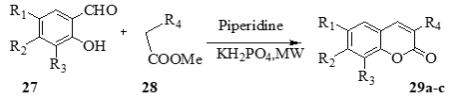
2-hydroxybenzaldehyde **24** is treated with Meldrum's acid **25** under ultrasound irradiation in the presence of water to give 3-carboxycoumarin **26**.



Scheme 2.2

Ultrasound Irradiation in the Presence of Water

Anthony and Ghag (*2015*) described that the Knoevenagel condensation can be successfully applied to the synthesis of a number of coumarins under the microwave irradiation. Here they reported a very simple, fast and general procedure for the condensation of 2-hydroxy benzaldehyde **27** with derivative of ethyl acetate **28** using potassium dihydrogen phosphate catalyst to produce coumarin derivatives **29a-c** (*Scheme 2.3*). Therefore, owing to the importance of potassium dihydrogen phosphate as facile catalyst it can be used for the green synthesis of new derivatives of coumarin and studied their anti-inflammatory properties.

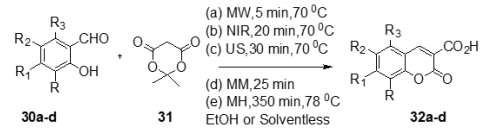


Compound	R1	R2	R3	R4
29a	NO_2	H	H	COMe
29b	NO_2	H	H	COOMe
29c	NO_2	H	H	CN

Scheme 2.3

Ultrasound Irradiation in the Presence of Water

Martínez *et al.* (2016) carried out various attempts to make the energy input as efficient as possible for the production of the 3-carboxycoumarins **32a–d**. Four salicylaldehydes **30a–d** were treated with Meldrum's acid **31** under four nonconventional activating methods (MW, NIR, US, and MM) compared with mantle heating (MH) under solvent-free conditions or in ethanol, a green solvent without a catalyst (*Scheme 2.4*). In general, these one - pot processes occur via a typical Knoevenagel condensation. A green contribution in short reaction times with moderate yields to produce coumarin-3-carboxylic acid **32** is offered. Near-infrared and microwave irradiations deliver the best yields in contrast to ultrasound and mechanical milling; moreover, these four processes offered shorter reaction times in comparison with the conventional mantle heating method.



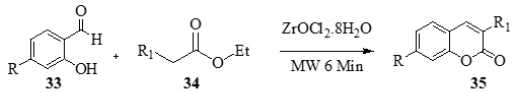
Cmpd	R	R1	R2	R3
32a	H	H	H	H
32b	H	H	Me	H
32c	Me	H	H	H
32d	H	OMe	H	H

Scheme 2.4

Non-conventional Method of Coumarin Synthesis

2.1.1. 3-Substituted Coumarin Derivatives

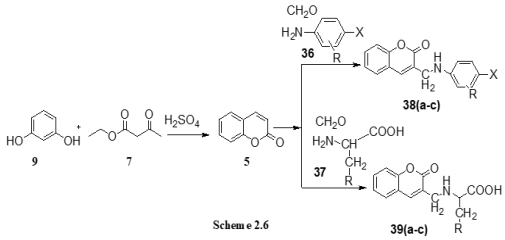
Paramjeet *et al.* (2012) reported that $ZrOCl_2.8H_2O$ shows high catalytic activities for the synthesis of 3-subsituted coumarins **35** from salicylaldehydes **33** and ethyl acetoacetate **34** via knoevenagel condensation under solvent free conditions by microwave heating. The procedure offers several advantages including the low loading of catalyst, high yields, clean reaction and the use of a variety of substrate which makes it a useful and attractive strategy for the synthesis of 3-substituted coumarins.



Scheme 2.5

Synthesis of 3-subsituted Coumarins

Selvam *et al* (2010) synthesized a new series of coumarin derivatives **38a-c** and **39a-c** by treating coumarin **5** with aniline derivatives **36** and amino acids **37** respectively. These compounds were screened (evaluated) for their antioxidant, analgesic and anti-inflammatory activities. Electron donating groups exhibit better activity than electron withdrawing groups.

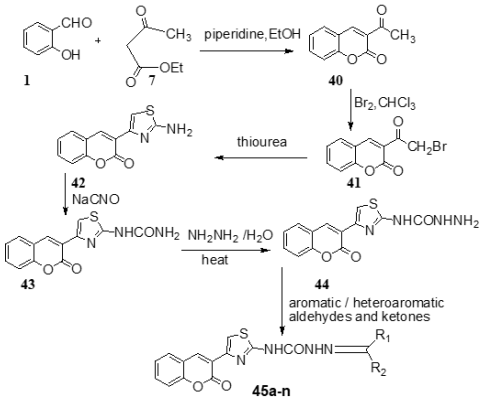


Scheme 2.6

Synthesis of Various Coumarin Derivatives

Siddiqui *et al* (2009) synthesized the compounds **45a-n** according to the procedure indicated in (*Scheme 2.7*). The synthesis of 3-acetyl- 2*H*-chromen-2-one **40** involved a reaction between salicylaldehyde **1** and ethyl acetoacetate **7** in the presence of piperidine. In the second step, bromination of compound **40** yielded 3-(bromoacetyl)-2*H*chromen- 2-one **41** which on cyclization in the presence of thiourea formed 3-(2-amino-1,3-thiazol-4- yl)-2*H*-chromen-2-one **42 .** In the presence of sodium cyanate and a small amount of glacial acetic acid, compound **42** produced *N*-[4-(2-oxo-2*H*chromen- 3-yl)-1,3-thiazol-2-yl]urea **43**. Compound **43** heated with hydrazine hydrate produced *N*-[4-(2-oxo-2*H*-chromen-3-yl)-1,3 -thiazol- 2-yl] hydrazinecarboxamide **44.** In the last step compound **44** was condensed with different aromatic/ heteroaromatic aldehydes and ketones to form the final products (*1E*)-1-arylalkane-1-one-*N*-[4-(2-oxo-2*H*-chromen-2-yl)-1,3-thiazol-2 yl] semicarbazones **(45a-n)**.

Mados *et al* (2010) synthesized a series of 3-phenylcoumarin derivatives with different number of substituents in both coumarinic and 3-phenyl rings. The coumarin derivatives **50a-k** were efficiently synthesized according to the synthetic protocol outlined in Scheme 2.8. The preparation of 3-phenylcoumarins **50a-g** was performed via

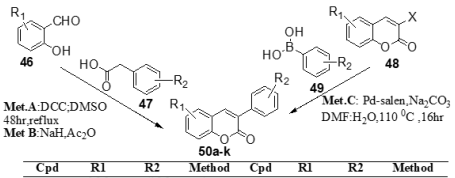


	R1	R2		R1	R2
a	phenyl	CH_3	**h**	2,4-dihydroxyphenyl	CH_3
b	4-chlorophenyl	CH_3	**i**	2-methoxyphenyl	CH_3
c	2,4-dichlorophenyl	CH_3	**j**	3-methoxyphenyl	CH_3
d	3,4-dichlorophenyl	CH_3	**k**	4-methoxyphenyl	CH_3
e	2-hydroxyphenyl	CH_3	**l**	2,4-dimethoxyphenyl	CH_3
f	3-hydroxyphenyl	CH_3	**m**	3,4-dimethoxyphenyl	CH_3
g	4-hydroxyphenyl	CH_3	**n**	4-bromophenyl	CH_3

Scheme 2.7

Synthesis of Various Substituted Coumarin Derivatives

the classical Perkin reaction (method A). This reaction occurs by condensation of the substituted salicylaldehyde **46** and the conveniently substituted phenylacetic acids **47**, with *N,N'*-dicyclohexylcarbodiimide (DCC) as dehydrating agent, in reflux of DMSO, during 24 hours. The reaction to obtain **50a-g** is very clean and the yields are between 57-73 %. The synthesis of 3-phenylcoumarin **50h** was performed via method B, using sodium hydride and acetic anhydride, at room temperature. Compounds **50i-k** were synthesized via palladium-catalyzed synthesis, starting from the 3-chlorocoumarin **48** and the conveniently substituted phenyl boronic acid **49**, with Na_2CO_3 and a Pd-salen complex method C. The reaction was carried out in DMF: H_2O (1:1).

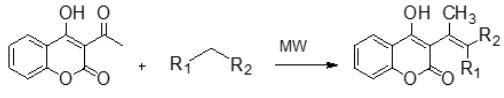


Cpd	R1	R2	Method	Cpd	R1	R2	Method
a	6-Me	4'-Me	**A**	**g**	8-Me	4'-OMe	**A**
b	6-OMe	4'-Me	**A**	**h**	6-Me	3'-NO_2	**B**
c	8-Me	H	**A**	**i**	H	3'-NH_2	**C**
d	8-OEt	H	**A**	**j**	H	3'-NO_2	**C**
e	6-Me	4'-OMe	**A**	**k**	H	3'-OH	**C**
f	6-OMe	4'-Br	**A**				

Scheme 2.8

Synthesis of Various Substituted Coumarin Derivatives Using Different Methods

Abdou (2014) reported the solvent-free conditions for the fast synthesis of novel coumarin derivatives by the Knoevenagel condensation under microwave irradiation. Different carbonyl, ester and cyano-derivatives **52** were used in the condensations with 3-acetyl coumarin **51** to achieve structural variety in the produced coumarins **53** (*Scheme 2.9*).



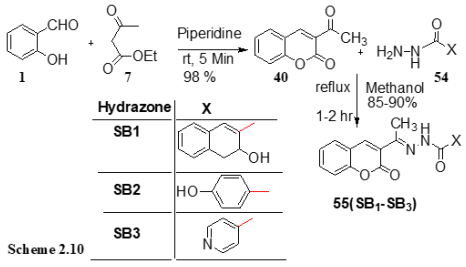
51 **52** **53a-g**

Cpd	R1	R2	Cpd	R1	R2
a	COOEt	COOEt	e	COMe	COMe
b	COMe	COOMe	f	CN	COOH
c	H	COOMe	g	COMe	COOH
d	CN	COOMe			

Scheme 2.9

Synthesis of Various Substituted Coumarin Derivatives via Microwave Irradiation

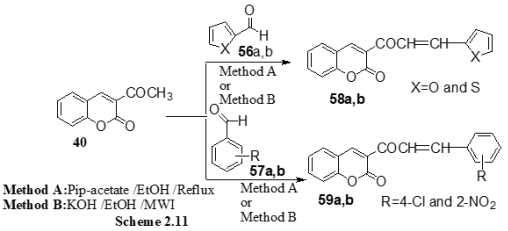
Pangal *et al* (*2013*) reported a new synthesis of schiff's bases **55** SB1, SB2 and SB3 from 3-acetylcoumarin and different acid hydrazides **54**. The 3-acetylcoumarin **40** was synthesized starting from salicylaldehyde **1** and ethylacetoacetate **7** (*Scheme 2.10*). As coumarin and hydrazones are biologically active independently, they conclude that their conjugate will be moreHelmy *et al* (*2014)*



Scheme 2.10

Synthesis of Schiff's Bases Using Coumarin Derivatives

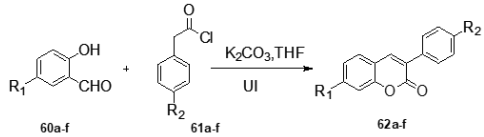
described new, simple, and efficient procedures for the synthesis of the target coumarinylchalcones (**58a, b** and **59a, b**). Microwave irradiation (method B) was used to obtain the desired products (**58a, b** and **59a, b**) in short time (4-6 min) under solvent-free conditions. Piperidine was used as a catalyst to facilitate the reaction between 3-acetyl coumarin **40** and various substituted aromatic aldehydes (**56a, b** and **57a, b**)in an excellent yield (83- 90%) (*Scheme 2.11*). The synthesized compounds were screened for the antimicrobial activity against gram positive and gram negative bacteria.



Scheme 2.11

Simple, and Efficient Procedures for the Synthesis Coumarin Derivatives

Sripathi and Logees (2013) reported that coumarins occupy an important place in the realm of natural products and synthetic organic chemistry. A fast and highly efficient green method for synthesizing 3-aryl coumarin derivatives **62** from salicylaldehyde **60** and phenyl acetyl chloride **61** in the presence of tetrahydrofuran and K_2CO_3 by a one-pot method using ultrasound irradiation was reported. Ultrasound assisted reactions have resulted in better yields and faster reaction time of the desired products than when prepared under conventional conditions. The presence of nitro substituents either at C-6 or C-6 and C-4' together or C-2' and C-4' together in the aromatic rings of the coumarin skeleton favour coumarin formation. However, substitution of a lone nitro group at C-4' position does not give a good yield of the 3-aryl coumarin ally Sripathi



60a-f **61a-f** **62a-f**

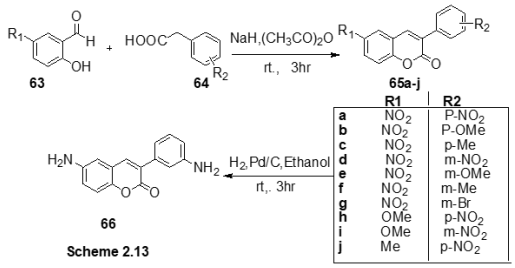
	R1	R2
a	H	H
b	NO_2	H
c	Br	H
d	H	NO_2
e	NO_2	NO_2
f	Br	NO_2

Scheme 2.12

Ultrasound Irradiation Methods for the Synthesis of Coumarin Derivatives

and Logees (2013) synthesized a new series of amino/nitro substituted 3-arylcoumarins **66** starting from substituted salicylaldehyde **63** and benzyl carboxylic acid **64** in the presence of NaH, $(CH_3CO)_2O$ to produce the intermediate

6-substituted 3-arylcoumarins **65**. Compound **65a-j** went palladium catalyzed reduction reaction to afford amino substituted 3-arylcoumarins **66** (*Scheme 2.13*) and evaluated for their antibacterial activity against Gram-positive and Gram-negative. With the aim of finding out structural features for the antibacterial activity and selectivity, they decided to explore the importance of the nature and position of small groups (methoxy, bromo, nitro, amino and methyl substituents) into both coumarin nucleus and 3-aryl ring (Scheme 2.13). The best derivative of the studied series is compound **65f**, active and selective against Gram-positive bacteria.



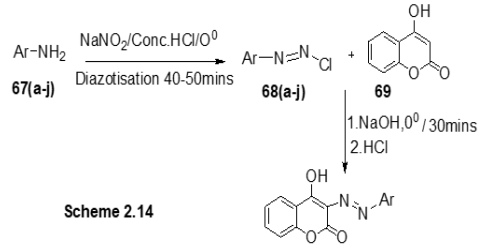
	R1	R2
a	NO_2	P-NO_2
b	NO_2	P-OMe
c	NO_2	p-Me
d	NO_2	m-NO_2
e	NO_2	m-OMe
f	NO_2	m-Me
g	NO_2	m-Br
h	OMe	p-NO_2
i	OMe	m-NO_2
j	Me	p-NO_2

Scheme 2.13

Synthesis of Biologically Active Amino/Nitro Substituted Coumarin Derivatives

Kumar *et al* (2013) synthesized a series of 4-hydroxy-3-(substituted phenyldiazenyl)-2H-chromen-2-one **70a-j** by coupling of diazonium salt of aniline derivatives **68a-j** with 4-hydroxycoumarin **69** in the presence of NaOH (*Scheme 2.15)*. 4-hydroxycoumarin **74** nucleus containing active hydrogen group at C -3 position which on attack by strong N_2^+ electrophiles to produce 3-azosubstitutedcoumarin **70**. The enolic - OH group of all the compounds were chemically detected by the treatment with $FeCl_3$ solution, which gives characteristic colour. Then, **70a-j** newly synthesized compounds were screened for their antibacterial activity against Gram-positive and Gram-negative bacterial strains by using zone of inhibition method. The activity of each compound was compared with ciprofloxacin as the standard.

Chavan *et al* (*2015*) carried out a convenient facile regioselective, quantitative synthesis of ortho derivatives of 4-hydroxy coumarins **72a-i** by treating 4-hydroxy coumarins **69** with different reagents **71a-i** in the presence of

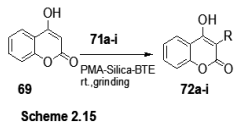


Scheme 2.14

Compound	Aryl Substituent	Compound	Aryl Substituent
a	phenyl	f	4-carboxyphenyl
b	4-methoxyphenyl	g	4-nitrophenyl
c	4-chlorophenyl	h	4-sulphamidophenyl
d	4-bromophenyl	i	4-bromo-3-methylphenyl
e	4-hydroxyphenyl	j	Napthyl

Synthesis of Coumarin Derivatives in the Presence of Substituted Aromatic Groups

Phosphomolybdic acid (PMA) and Silica supported BF_3: Etharate as a catalyst, at room temperature with excellent yield. This method was proven to be efficient protocol for obtaining 3-substituted 4-hydroxy coumarins.



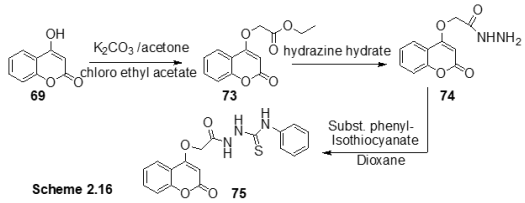
Scheme 2.15

Reagents (71a-i)		compd	R
71a	NBS	72a	-Br
71b	NCS	72b	-Cl
71c	Iodic acid	72c	-I
71d	$NaNO_3$	72d	-NO_2
71e	$FeSO_4$/cat.H_2SO_4	72e	-SO_3H
71f	DMFA	72f	-CHO
71g	AcCl	72g	-Ac
71h	HCHO/DMA	72h	-$CH_2N(CH_3)_2$
71i	Allyl bromide	72i	-$CH_2CH{=}CH_2$

Synthesis of 3-substituted 4-hydroxy Coumarins

2.1.2. 4-Substituted Coumarin Derivatives

Chowdhary *et al* (2015) synthesized a series of coumarin derivatives by treating 4-hydroxycoumarin **69** with chloroethylacetate in the presence of K_2CO_3 to form an intermediate **73** which was further treated with hydrazine hydrate to form hydrazino derivative of coumarin **74** and finally the intermediate **74** was condensed by substituted isothiocynate derivatives to form final compound **75**. All the compounds were screened for their anti-microbial activity. It was found that the derivatives showed moderate activity as compared to standard.

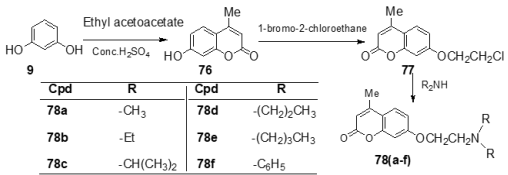


Scheme 2.16

Synthesis of 4-Substituted Coumarin Derivatives

2.1.3. 7-Substituted Coumarin Derivatives

Pankaj *et al* (2010) synthesized coumarin derivatives starting from resorcinol **9** and EAA in the presence of conc. H_2SO_4 to afford the resulting intermediate **7**-Hydroxy-4-methyl coumarin **76**. Combination of 7-Hydroxy-4-Methyl coumarin **76** with 1-bromo-2-chloroethane affords 7-Hydroxy-4-methyl coumarin derivatives **77.** Compound **77** nucleus was treated with different secondary amines through two carbons spacing to obtain compounds **78.** All synthesized compounds were evaluated for antipsychotic activity and have shown dopaminergic and 5-HT receptor blocking action.

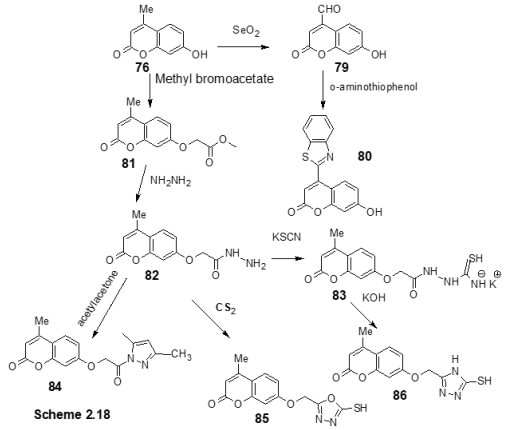


Cpd	R	Cpd	R
78a	-CH_3	78d	-$(CH_2)_2CH_3$
78b	-Et	78e	-$(CH_2)_3CH_3$
78c	-$CH(CH_3)_2$	78f	-C_6H_5

Scheme 2.17

Synthesis of 7-Substituted Coumarin Derivatives

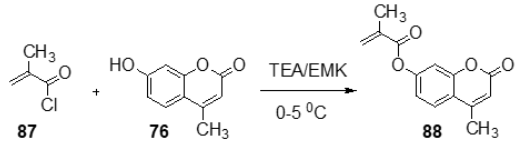
Al-Amiery *et al* (2015) described the synthesis of the coumarin derivatives **79-86** under microwave irradiation and normal reflux conditions as shown in (*Scheme 2.18*) starting from 7-hydroxy-4-methylcoumarin **76**. Compound **81**, namely, methyl 2- ((4-methyl-2-oxo-2H-chromen-7-yl) oxy) acetate, was synthesized by the reflux of methyl bromoacetate, 7-hydroxy-4-methylcoumarin **76**, anhydrous potassium carbonate and anhydrous acetone. Compound **81** was reacted with hydrazine hydrate to afford hydrazide **82** in good yield. Compound **82** was refluxed with KSCN in ethanol as the solvent containing catalytic amounts of HCl to yield salt **83**, which was converted directly to **86** in good yield by heating in aqueous KOH followed by acidification with HCl. Compound **85** was prepared accordingly by heating **82** with CS_2 in the presence of ethanolic potassium hydroxide. By condensation of **82** with acetyl acetone in ethanol with a few drops of acetic acid, the corresponding derivative **84** was obtained in 54% yield. Compound **76** also treated with SeO_2 to produce compound **79** and this compound **79** was reacted with *o*-aminotiophenol in the presence of AcOH to afford compound **80**. New derivatives of 7-hydroxy-4-methylcoumarin were synthesized using a chemical method and a microwave-assisted method. The synthesized compounds exhibited excellent radical scavenging activities.



Scheme 2.18

Synthesis of Coumarin Derivatives Using Chemical and Microwave-Assisted Methods

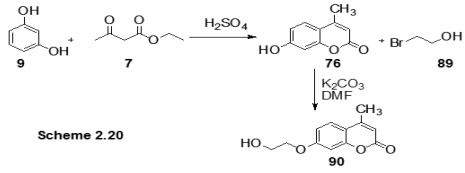
Venkatesan *et al* (2016) synthesized 7-Methacryloyloxy-4-methylcoumarin (MAOMC) **88** by reacting 7-hydroxy-4-methyl coumarin **76** with Methacryloyl chloride **87** in the presence of trimethylamine and ethylmethylketone (*Scheme 2.19*). This shows that coumarin moiety plays very important role as antimicrobial agent.



Scheme 2.19

Synthesis of 7-Methacryloyloxy-4-methylcoumarin

Rivero *et al* (2016) synthesized 7-hydroxyethoxy-4-methylcoumarin (HEOMC) **90** as described in literature in two steps by treating 7-hydroxy-4-methyl coumarin **76** with 2- bromoethanol **89** as shown in (*Scheme 2.20*).

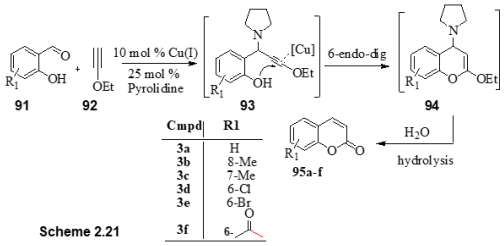


Scheme 2.20

Synthesis of 7-hydroxyethoxy-4-methylcoumarin

2.1.4. Benzene Ring Substituted 4-Methyl Coumarin Derivatives

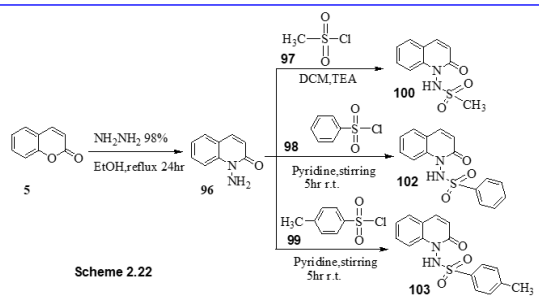
Reddy *et al* (2013) reported synthesis of coumarins from salicylaldehydes **91** by a Cu-catalyzed A3 coupling of ethoxyacetylene **92**, pyrrolidine led to a concurrent cycloisomerization **93** followed by hydrolysis of the resultant vinyl ether **94** to afford coumarins **95** in a cascade process. The reaction proceeded through exclusive 6-*endo-dig* electrophilic cyclization of the intermediate hydroxyphenylpropargylamine **93** as shown in (*Scheme 2.21*) and is compatible with halo and keto groups giving coumarins in good to moderate yields.



Scheme 2.21

Synthesis of 4-Methyl Coumarin Derivatives

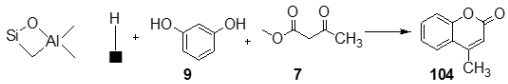
Saour *et al* (2012) synthesized a series of new coumarin and N-amino-2-quinolone derivatives. The reaction of coumarin **5** with excess of Hydrazine hydrate 98% yielded 1-amino-2-quinolone **96**. Compound **96** was reacted with different sulfonyl chloride (methane sulfonyl chloride **97**, benzene sulfonyl chloride **98** and *p*-toluene sulfonyl chloride **99**) respectively, to yield sulfonamides N-(2-oxoquinolin-1(2H)-yl) methane sulfonamide (**100**), N-(2-oxoquinolin-1(2H)-yl) benzene sulfonamide (**102**) and 4-methyl-N-(2-oxoquinolin-1(2H)-yl) benzene sulfonamide **(103**), in dichloromethane and triethylamine as a base in case of compound (**100**), and in pyridine in case of compounds (**102**) and (**103**). The reaction proceeds via nucleophilic attack of the amine on sulfur atom of the sulfonylchloride with liberation of HCl, as shown in the (*Scheme 2.22*). The synthesized compounds were evaluated for their anti-bacterial and antifungal activity.



Scheme 2.22

Synthesis of Coumarin Derivatives via Nucleophilic Attack

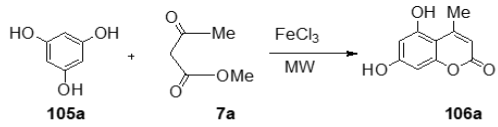
Prouris *et al* (2014) reported an ecofriendly route for the Pechmann synthesis of coumarin derivatives **104** by reaction of resorcinol **9** and β-keto ester **7** over Al-MCM-41 and it was supported as a catalyst under solvent-free condition (*Scheme 2.23*).



Scheme 2.23

Synthesis of Coumarin Derivatives Under Solvent-Free Condition

Chaudhary and Datta (2013) performed the Pechmann reaction between phloroglucinol **105** and methyl acetoacetate **7a** in the presence of 10% mol anhydrous $FeCl_3$ with heating at 100^0C and the desired product **106a** was formed in 3 h in 98% yield under solvent-free conditions and microwave irradiation (*Scheme 2.24*). In the absence of $FeCl_3$ no product formation was observed with heating either at 70 ^{0}Cor 100 ^{0}C.

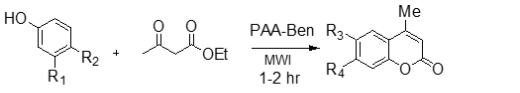


Scheme 2.24

Synthesis of Coumarin Derivatives Using Anhydrous $FeCl_3$

Chavan & Baseer **(**2014**)** synthesized the coumarin derivatives **108a-c** using phosphotungstic acid intercalated Bentonite via pechmann condensation from substituted phenols **107a-c** and ethyl acetoacetate **7** (*Scheme 2.25*) using microwave irradiation under solvent free conditions in the presence of catalysts in excellent yield and high purity.

A catalyst (Pillared Acid activated Bentonite (PAA-Ben)) based on clay has been found to be a potential catalyst for synthesis of coumarin derivatives.



107a-c **7** **108a-c**

107a: R_1=H,R_2=OH **108a**: R_3=OH,R_4=H

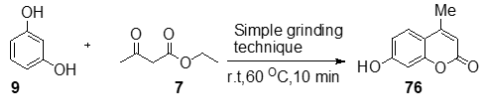
107b: R_1=OH,R_2=H **108b**: R_3=H,R_4=OH

107c: R_1=H,R_2=NH_2 **108c**: R_3=NH_2,R_4=H

Scheme 2.25

Synthesis of Coumarin Derivatives Using Phosphotungstic Acid Intercalated Bentonite

Chavan *et al* (2015) carried out synthesis of 7 -hydroxy-4 –Methyl Coumarin **76** by Pechmann condensation from resorcinol **9** condensed with ethyl acetoacetate **7** by green synthetic method via simple grinding technique (*Scheme 2.26*). The product was



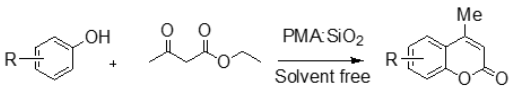
9 **7** **76**

Scheme 2.26

Synthesis of 7-hydroxy-4 –Methyl Coumarin

obtained within few minutes.

Bhatnagar *et al* (2010) reported synthesis of substituted coumarins **110** from phenol **109** and β-ketoester **7** via Pechmann condensation using heterogeneous catalyst phosphomolybdic acid (PMA): Silica supported BF_3:OEt_2 under solvent free condition (*Scheme 2.27*). Among various methods of synthesis of coumarin, Pechmann is preferred due to its easy mode of operation and availability of starting materials.



109a-e **7** **110a-e**

R		R	
109a	-H	**110a**	-H
109b	3-OH	**110b**	7-OH
109c	3,5-OH	**110c**	5,7-OH
109d	3-OMe	**110d**	7-OMe
109e	2-Me-3-OH	**110e**	6-OH,7-Me

Scheme 2.27

Synthesis of Substituted Coumarins

3. Biological Applications of Coumarins and Their Derivatives

The pharmacological properties as well as therapeutic applications of coumarins depend upon the pattern of substitution and recently they are reported to possess many pharmacological activities (Fig. 2). Substituted coumarins exhibit high potency as antimicrobial activities. Introduction of fluoro and sulfonamide moieties into coumarin side chain improve the biological activity of the compound (Asif, 2015). When coumarin ring fused with other rings, a synergistic effect of both the rings in their biological activities are obtained, such compounds are exploited in development of various important molecule which provides scaffolds for drug development (Bhatnagar *et al*., 2010).

The coumarins containing a Schiff base are expected to have enhanced antitumor and other biological activity. It is well established that the biological activity associated with the hydrazone compounds attributed to the presence of the active pharmacophore (-CONH-N=C-). Hence many hydrazone compounds containing this active moiety showed good anticancer bioactivities. Modifications on the 3-position of coumarin nucleus and a series of 7-diethylaminocoumarin compounds have resulted in a large number of compounds having anticancer activity. Among the series, compound with bromo group in the benzophenone moiety was endowed with excellent anti-cancer activity. Various analogues of 4-substituted coumarin such as 4-chlorocoumarins exhibit antimicrobial activity; furocoumarins have cytotoxic activity devoid of serious side effects (Paramjeet *et al*., 2012).

It has been identified that phenolic compounds present antioxidant activity. The presence of electron-withdrawing groups on the phenyl ring of position 3 favours anti-oxidant activity. The presence of the phenolic hydroxyl group (6-, 7- or 8-) seems to support the antioxidant activity but the effect on activity is independent of the position of hydroxyl group (Asif, 2015). 4-hydroxcoumarin derivatives like Warfarin type compounds revealed anticoagulant activities (Mados *et al.,* 2010).

Anti-inflammatory activity is considered for coumarin-based carbamates which have inhibitory activity of (pro inflammatory agent) and angularly fused polycyclic heterocycles with coumarin derivatives, in which presence of electron withdrawing or accepting substitutions at different positions shows an important role. For anti-hepatitis and hepatoprotective activity substituted benzimidazole - coumarin conjugated compounds are studied (Chawla *et al.,* 2012)

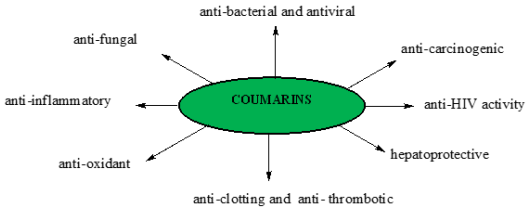


Fig 2 : Applications of Coumarins

4. Conclusion

Coumarins (2*H*-chromen-2-one) are synthetically versatile substrate, which can be used for the synthesis of a large variety of heterocyclic compounds. The advances in the use of coumarin for organic synthesis as well as a survey of its biological and pharmacological properties were reported. 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. Several studies have shown that the structural changes in the basic structure of coumarin concerning the substituents at different positions (1, 3, 4, 6 and 7) of the bicyclic system, allowed the emergence of new derivatives with a broad spectrum of biological activity. Similarly, structural changes on the different positions of the base molecule improves its pharmacological profile conferring anti-oxidant, anticonvulsant, anti-coagulant, anti-fungal, anti-inflammatory, anti-microbial, anti-HIV and anti-cancer and, etc.

New coumarin derivatives have been synthesized using conventional, ionic liquid and microwave heating methodologies. The advantages in the use of ionic liquids that act as alternative solvents, catalysts and microwave methodology are that coumarin products were obtained in high purity, shorter reaction times and in higher yields, compared to the corresponding yields produced by heating in conventional solvents. The combination of solvent free reaction condition and microwave irradiation leads to significantly reduced reaction times, enhanced conversions and sometime higher selectivity with several advantages for the ecofriendly approach, termed as "Green Chemistry". In conclusion, the importance of coumarin derivatives is undeniable. Therefore, the development of mild, efficient, and environmentally benign synthetic approaches is crucial.

5. References

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