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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1004361>Available online at: <http://www.iajps.com>*Review Article***A REVIEW ON BIOLOGICAL ACTIVITY AND SYNTHETIS OF
COUMARINS****G.Nagaraju^{1*}, Dr.Vijaya Kuchana²**

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Abstract:

Coumarin (1,2-Benzopyrone or 2H-1-benzopyran-2-one, or phenylpropanoids, 1) and its derivatives (coumarins) are widely distributed throughout nature and many exhibit useful and diverse biological activities^{1,2}. Coumarins occur as secondary metabolites in the 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. Their function is far from clear, although suggestions include plant growth regulations, fungistasis, bacteriostasis and, even, waste products³. Some naturally occurring coumarin derivatives include warfarin (2), umbelliferone (7-hydroxycoumarin, 3), aesculetin (6,7-dihydroxycoumarin, 4), herniarin (7-methoxycoumarin, 5), psoralen (6) and imperatorin (7). Now the diversity of coumarin derivatives, both natural and synthetic, has grown and are thus divided into several subclasses. Most reviews classify coumarins according to whether particular compounds are simple coumarins (e.g. coumarin, 1 and limettin, 8), linear furanocoumarins (e.g. imperatorin, 7 and isopimpinellin, 9), angular furanocoumarins (e.g. angelicin, 10), linear pyranocoumarins (e.g. xanthyletin, 11) or angular pyranocoumarins (e.g. seselin, 12)⁴. Murray et al. ⁵ however, used a biogenetic approach based upon the number of nuclear oxygen atoms in classifying coumarin-containing compounds. Because of their varied biological activities, the preparation of coumarin and its derivatives has attracted the attention of organic chemists. Various synthetic methods have been developed for the synthesis of coumarin. These include use of the Knoevenagel condensation, Wittig reactions, Perkin reaction and Pechmann reaction.

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INTRODUCTION:

Coumarins are an important class of benzopyrones being the core unit of different natural products and exhibit a spectrum of biological activity [1-6]. Naturally occurring coumarins are found in many plants, notably in high concentration in tonka bean, woodruff, lavender, licorice, strawberries, apricots, cherries, cinnamon, sweet clover and bison grass having vanilla like flavour. Coumarins be bound their class name to 'coumarou' the vernacular name of the Tonka bean (*Dipteryx odorata willd, Fabaceae*), from which coumarin itself was isolated in 1820 by Vogel [7]. Due to the potential application in fragrance, pharmaceutical and agrochemical industries it occupies an important position in natural and synthetic organic chemistry. Coumarins comprise a vast array of biologically active compounds with several types pharmaceutical agents possessing anticancer, anti-HIV, anticoagulant, spasmolytic and antibacterial activity, cytotoxic activity in vitro and in vivo [8]. Natural coumarins, such as calanolides, isolated from *Calophyllum* genus have shown potent anti-HIV activity [9]. Wedelolactone 1 is another naturally occurring product that is used as a venomous snake-bite antidote; and Novobiocin 2 (Fig 1) is an antibiotic, which acts as a competitive inhibitor of the bacterial ATP binding gyrase B subunit [10]. Many synthetic compounds, which contain the coumarin moiety, are well known for their odour, stability to alkali, and availability. They are widely used in perfume, soaps and detergents [11] and in the preparation of insecticides, optical brightening agents [12]. Coumarin was once used as food flavourant, but

was banned by the FDA

due to carcinogenicity [13]. Some 3-substituted and 7-hydroxycoumarin have been shown to act as photostable laser dyes that emit in the blue-green region of the visible spectrum. The emission range increases when the 3-substituent is a heterocyclic moiety [14]. Coumarin also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones and 2-acylresorcinols [15].

DIFFERENT BIOLOGICAL ACTIVITIES OF COUMARINS

ACOUMARINS AND BREAST CANCER

Breast cancer is a major cause of mortality in western countries and it has been reported that about one-third of postmenopausal breast cancer patients have hormone-dependent tumors involving the stimulation of estrogen receptor [16,17]. Treatment as well as prevention has been the focus of much laboratory work and clinical trials over the past 30 years. Clinical studies focusing on the use of therapeutic agents that prevent the synthesis and action of estrogens (ER antagonists) are known to be very successful in the treatment of breast cancer [18]. The current strategy thus involves the development of ER antagonists as a new approach for the treatment of postmenopausal women with hormone-dependent breast tumors. The high levels of estrogen as a result of its *in situ* synthesis are associated with the growth of tumors in endocrine-dependent tissues. Estrogens are formed exclusively in peripheral tissues, and there are two pathways associated with their synthesis in such tissues, the aromatase and sulfatase pathways (Fig. 1).

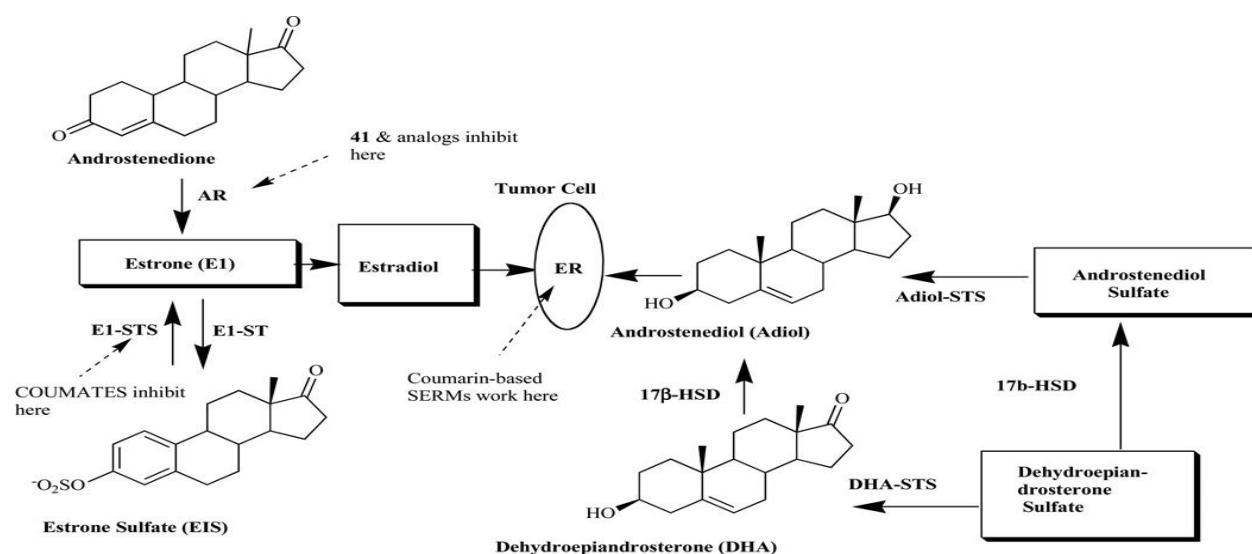
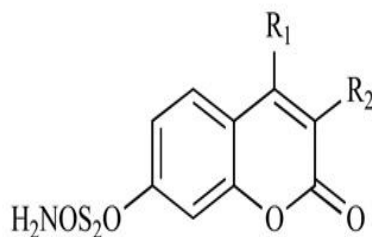


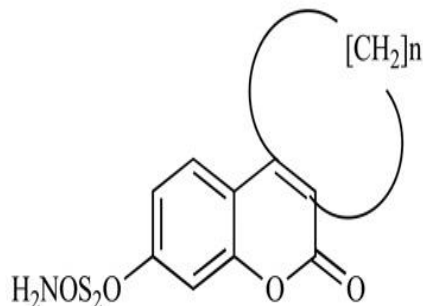
Fig-1

SULFATASE INHIBITOR

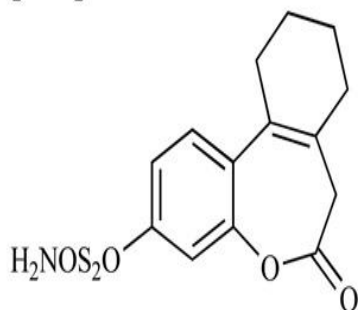
As illustrated in Fig. (1), the cleavage of sulfated steroid hormone precursors, e.g. estrone sulfate, to the active hormones by STS represents the first step in the local production of estrogen and androgens. Therefore, the inhibition of this enzyme (STS), which should decrease the biosynthesis of active hormones, has been a new therapeutic option in the treatment for hormone-dependent diseases [18-21] such as breast, endometrial and prostate cancers, acne and

Bicyclic Coumarin Sulfamates

- 23, $R_1 = H$, $R_2 = H$
 24, $R_1 = H$, $R_2 = CH_3$ (COUMATE)
 25, $R_1 = CH_3$, $R_2 = CH_3$
 26, $R_1 = CH_3CH_2$, $R_2 = CH_3$
 27, $R_1 = CH_3CH_2CH_2$, $R_2 = CH_3$

Tricyclic Coumarin Sulfamates

- | | |
|------------------------|--------------------------|
| 28, n = 3, 665 COUMATE | 33, n = 8, 6610 COUMATE |
| 29, n = 4, 666 COUMATE | 34, n = 9, 6611 COUMATE |
| 30, n = 5, 667 COUMATE | 35, n = 10, 6612 COUMATE |
| 31, n = 6, 668 COUMATE | 36, n = 11, 6613 COUMATE |
| 32, n = 7, 669 COUMATE | 37, n = 12, 6615 COUMATE |



- 38, 676 OXEPIN

Fig 2: Structures of coumarin sulfamates and tricyclic coumarin sulfamates.

Chemically, bicyclic and tricyclic COUMATES (23–37) and their close relatives the 676 OXEPINs (e.g. 38) are aryl sulfamates (Ar-SO₂NH₂), which are irreversible inhibitors of STS. The crystal structures of the soluble enzymes arylsulfatase A (ASA) and arylsulfatase B (ASB) [34,35] have provided an insight in the mechanism through which sulfamate group irreversibly inactivates steroid STS. The mechanisms for irreversibly inhibiting STS activity by COUMATES and its congeners i) the L-C α -formylglycine (FGly), ii) the aldehyde hydrate (gem-diol residue), and iii) random specific or nonspecific sulfamoylation of amino acid residues in the active site [36-40]. Random specific or nonspecific sulfamoylation is proposed to occur *via* two mechanisms – a direct nucleophilic attack by the amino acid residue at the sulfur atom of, for example, compound 30 and elimination of sulfamic acid by an E1cB mechanism, assisted by the extended conjugation present in the coumarin ring [41].

SAR studies involving bicyclic COUMATES revealed that compound 25 (Fig. 2) displays stronger binding affinity for the enzyme active site *via* a hydrophobic interaction provided by the methyl groups at the 3- and 4- positions, thereby mimicking the A/B ring of EMATE [42,43]. Bilban *et al* [44] demonstrated that the oxygen functionality substitution at position 7 of the coumarin core structure also mimics the A/B ring of EMATE. Previous computer-modelling study has shown that the seven-membered ring (third ring) of COUMATE (30) could not be described as closely mimicking the C/D ring regions of EMATE, attributed to its chair conformation form which is similar to the cycloheptene ring structure (Fig. 3) [45]. However, recent finding indicated that the third ring appears to be predominately in the boat conformation rather than previously proposed chair conformation based on temperature factors (B-factors) and electron density map results. With the advent of this new finding regarding the conformation of the 7-membered ring on compound 30 it can now be explained that its higher potency (IC₅₀ value of 8 nM and K_i value of 40 nM) than EMATE (IC₅₀ = 25 nM and K_i = 670 nM) is attributed to the tendency to mimic the steroidal CD-ring; perhaps, better hydrophobic interactions due to favorable binding to the active site of the enzyme are in play [46,47].

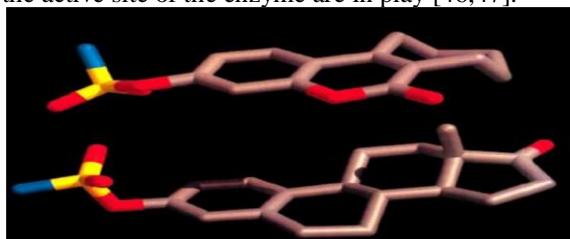


Fig. (3)

Molecular modelling of 667 COUMATE (top) and EMATE (bottom) (adapted from with permission).

Benzocoumarin sulfamates, another group of aryl sulfamates closely related to compound 30, mimics the ABC-ring of the steroidal skeleton. Although less active than EMATE, these sulfamates show high inhibitory potency due to strong binding of the benzocoumarin core structure to the enzyme. Removal or disruption of the coumarin ring conjugation results in lower potency due to the resulting higher pK_a value for the parent phenol. The extended conjugation present in the coumarin ring structure assists in the S-O-Ar bond breakage during E1-STC catalyzed sulfamoylation by improving the leaving ability of the coumarin compound as a result of lower pK_a value of the phenol. On the contrary, an extension of the coumarin conjugation core structure and the relocation of the sulfamate group to the 6-position of the ring resulted in lower potency exhibited by the COUMATE analogs.

AROMATASE INHIBITOR

Aromatase inhibitors (AIs) include drugs that are currently used for the treatment of hormone-dependent breast cancer, which involves blocking the estrogen action on tumor cells by preventing the biosynthesis of estrogen [48]. AI prevents breast cancer *via* reduction of cell proliferation, which involves reduction of estrogen level and thus prevention of the formation of genotoxic metabolites of estrogen. The genotoxic estrogen metabolites include i) catechol estrogens, which bind covalently to DNA and induce mutations that initiate cancer; ii) 2-hydroxyl-estradiol, which forms stable DNA adduct; and iii) 4-hydroxy-estradiol, which is a potential carcinogenic metabolite forming depurinating estrogen-DNA adducts with guanine base that are unstable and are rapidly lost from the DNA⁴⁹⁻⁵¹. Clinical trial results have shown AIs to be of superior efficacy to tamoxifen as anti-estrogenic compounds with more favorable toxicity profiles [52-54]. In postmenopausal women, AIs have the potential to suppress circulating estrogen levels by approximately >96.7–98.9% and also abrogate autocrine and paracrine estrogen production by peritumoral stromal cells located in both primary and metastatic sites of the tumor [55-61]. The FDA has approved a number of AIs, e.g., anastrozole (Arimidex), exemestana (Femara) and letrozole (Aromasin), as first-line agents for the treatment of postmenopausal women with hormone receptor positive breast cancer [62-66]. In postmenopausal women, clinical results have shown that AIs used only as monotherapy are very effective in treating estrogen-dependent and aromatase-mediated diseases including breast cancer [67]. However, in

premenopausal women there is an incomplete blockade of estrogen synthesis resulting in a reflex rise in gonadotrophin level, which in turn can stimulate ovarian aromatase and overcome the estrogen suppression [68].

COUMARIN-BASED SERMS

Selective estrogen receptor modulators (SERMs) are a new category of therapeutic agents that are used for the prevention and in the treatment of diseases such as osteoporosis and uterus and breast cancers [69,70]. They are known to have high affinity for ER, but no specific affinity for any other steroid hormone receptors. In addition, SERMs are known to stimulate estrogenic actions (ER agonist) in tissues, such as the bone, liver, and cardiovascular system but block estrogen action at other sites (ER antagonist) where stimulation is considered undesirable, such as the breast and uterus [71-75]. This agonistic or antagonistic activity causes different conformational changes of the receptors particularly at the helix 12 [75-77], resulting in activation (transactivation) or repression (transrepression) of the estrogen target genes⁷⁶. Examples of drugs classified as SERMs are: estrogen metabolites, clomiphene, tamoxifen, toremifene, idoxifene and droloxifene [77-79]. Tamoxifen is the most widely used hormonal therapy for breast cancer today.

COUMARIN-ESTROGEN CONJUGATES

There is an over-expressed ER in breast tumor cell in the earlier stage and during hormonal treatment [89-70]. The non-selectivity and acute toxicity of many antitumor agents have been the major deterrent in their usage for treating human cancer [71]. Among the current cancer therapy focusing on the improvement of drug selectivity, conjugation of cytotoxic drug components to a carrier with selectivity toward the tumor tissues has proven to be an effective strategy in the development of efficient antitumor drugs with high therapeutic indices⁷²⁻⁷⁷. Studies have shown that coupling of cytotoxic agent with steroid hormones results in improvement of antitumor activity and in the target selectivity of the conjugate as the result of sufficient binding to the ER, allowing selective accumulation of the conjugates in ER-rich cells [78-82]. During the past decades, the application of bioconjugates (i.e. biomolecules bearing unnatural organic structures) in molecular and cell biology has significantly increased [83].

We have recently extended this novel concept of bioconjugation involving 3-substituted coumarins and estradiol (**50-51**) (Fig. 4) to show antiproliferative activity in NCI-7 human breast

cancer cell lines. Comparisons of the GI₅₀ values among the conjugates showed that conjugate **50** has the highest antiproliferation activity against MDA-MB-435 breast cancer cell lines while conjugates (**50-51**) displayed the highest antiproliferative activities against MDA-MB-231/ATCC. As far as the distinction between noninvasive and invasive breast cancer cell lines, overall conjugate **50** appears to be active against both types while conjugate **50** has the least inhibitory activities against noninvasive MDA-MB-231/ATCC and NCI/ADR-RES cell lines among the conjugates. Moreover, conjugate **50** was surprisingly inactive against the estrogen receptor enriched MCF-7. In general, it was shown that cytotoxicity occurred at around 100 μM for all of the conjugates. It was also observed that conjugate **50** displayed the most cytostatic properties based upon TGI values being less than LC₅₀ values. The detailed results will be published elsewhere and is available on request from the author [84-89].

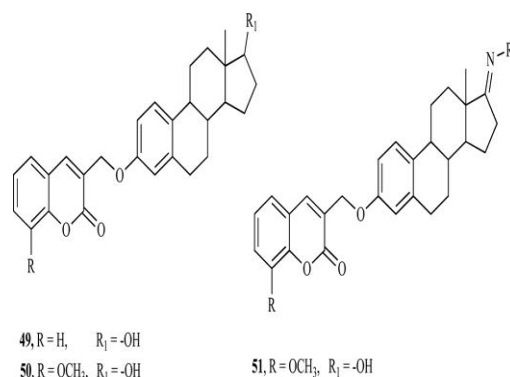
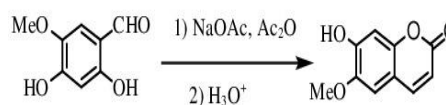


Fig. 4: Structures of coumarin-estradiol conjugates.

SYNTHETIC PROCEDURES FOR COUMARINS

Perkin Reaction:

Perkin reaction⁹⁰ involves heating an *o*-hydroxybenzaldehyde with acetic anhydride in presence of sodium acetate to afford a *trans*-cinnamic acid at 200 °C. Isomerization of the *trans*-cinnamic acid by irradiation or treatment with iodine followed by cyclization affords the coumarin. When a 1:2 molar ratio of aldehyde to anhydride is used, optimum yields of Coumarins are obtained (**scheme 1**).

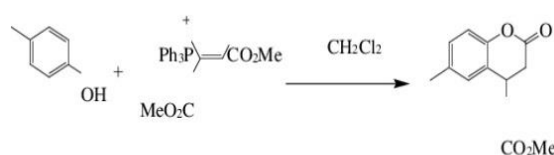


Scheme 1

Generally poor yield of the coumarins are obtained, due to the production of tarry materials under the severe reaction conditions which is the main disadvantage of Perkin reaction.

Wittig Reaction:

Wittig reaction bears significant impact for the synthesis of coumarin derivatives. There are several reported methods for the synthesis of coumarin derivatives by using Wittig reaction such as I. Yavari *et al*⁹¹ developed a new and efficient route to the synthesis of 4-carboxymethylcoumarins based on an aromatic electrophilic substitution reaction between the conjugate base of a substituted phenol and the betaine formed by the addition of triphenylphosphine to dimethyl acetylenedicarboxylate (DMAD) (scheme 2).

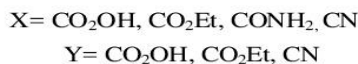
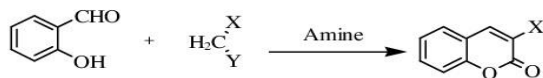


Scheme 2

Scheme 2

Knoevenagel condensation:

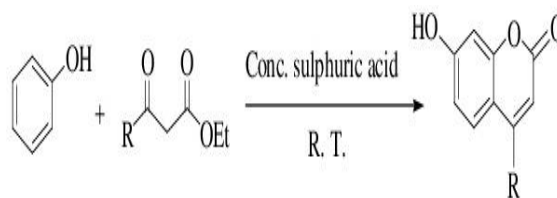
The Knoevenagel reaction [92] involves the condensation of benzaldehydes with activated methylene compounds in the presence of an amine. When a 2-hydroxy substituent is present in the aromatic aldehyde, there is formation of coumarin derivatives instead of normal product cinnamic acid. Various coumarins have been prepared via Knoevenagel condensation of salicylaldehyde with activated methylene compounds as illustrated in scheme 3.



Scheme 3

Pechmann Reaction:

The Pechmann reaction [93] is a widely used method for preparing coumarins in good yield. In 1884, V.H. Pechmann and C. Duisberg synthesized coumarin by the reaction of a phenol with a B-ketoester in the presence of conc. H₂SO₄ (scheme 4).



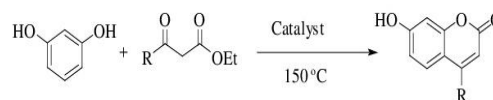
Scheme 4

Among the above classical methods, Pechmann reaction is one of the simplest and direct methods for the synthesis of coumarins since it proceeds from very simple starting materials, namely, phenols and B-ketoesters in presence of concentrated sulfuric acid and gives good yield of variously substituted coumarins. But, due to the direct use of concentrated sulfuric acid, this process causes formation of by products and encompasses corrosion problems.

SYNTHESIS OF COUMARINS VIA PECHMANN REACTION: A REVIEW

Over the years, numerous methods have been developed for the modifications of Pechmann reaction's conditions using a variety of reagents for the synthesis of coumarin derivatives. A short review of these work are summarized here before going to our attempt.

In 1961, E. V. O. John and S. S. Israelstam [94] modified the Pechmann condensation by using cation exchange resins, Zeokarb 225 and Amberlite IR.120, as condensing agents in the synthesis of hydroxycoumarins (scheme 5).

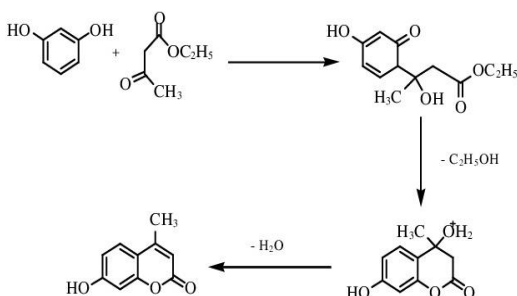


Catalyst: cation exchange resin Zeokarb 225 and Amberlite IR.120

Scheme 5

The main advantages of cation exchange resins are that they simplify the isolation of the product and tend to be relatively inexpensive. In order to obtain a maximum yield of the coumarin, between 20 and 40% of the resin by weight of the total reactants is used. They showed that when a non-polar compound, such as n-hexane, is used as a solvent, the rate of reaction is increased due to the fact that there is an increased percentage of enol form of the B-keto ester in n-hexane.

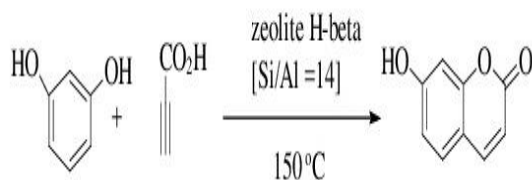
The reaction is considered to involve the following steps:- (i) addition across the double bond of the enolic form of the B-keto ester; (ii) ring closure; and (iii) dehydration.



Scheme 6

In 1962, L. L. Woods and John Sapp [95] reported a method for the synthesis of coumarin derivatives from the reaction of phenols and β -keto esters in the presence of trifluoroacetic acid under reflux conditions. According to them, phenol, catechol, 4, 6-dichlororesorcinol, cresols and hydroquinone all are failed to give the coumarin under present reaction conditions (**scheme 6**).

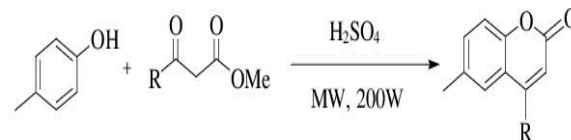
The use of zeolite H-beta catalyst in the synthesis of coumarin derivatives from the reaction of resorcinol and propynoic acid at high temperature (150 °C) has been reported by Bekkum *et al*⁹⁶ (**scheme 7**).



Scheme 7

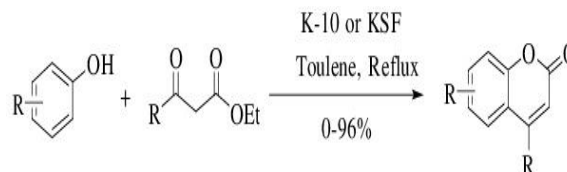
They explained that equimolar amounts of resorcinol and propynoic acid in the presence of zeolite H-beta catalyst undergo esterification followed by ring closure to give the desired coumarin.

1996, Kad *et al* [96] have reported the use of a microwave-assisted Pechmann reaction in the rapid and simple preparation of substituted coumarins, in yields of 72-82%, from substituted phenols and methyl acetoacetate in the presence of H_2SO_4 (**scheme 8**).



Scheme 8

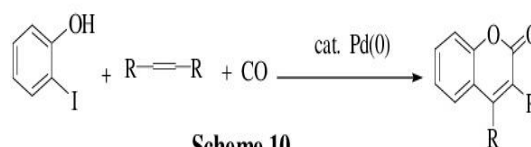
Zhan-Hui Zhang *et al* [97] used montmorillonite K-10 or KSF as heterogeneous catalysts for the synthesis of coumarins in yields of up to 96% *via* the Pechmann reaction (**scheme 9**).



Scheme 9

They reported that K-10 worked better than KSF in terms of reaction time and yield. This method has the advantages of easy separation of the product, minimal environmental effect and recyclability of the catalyst. One of the vital drawbacks of this method is that the reaction involves toxic solvent under drastic conditions.

In 2000, Dmitry V. Kadnikov and Richard C. Laroc [98] developed a facile method for the synthesis of substituted coumarins in good yields by palladium-catalyzed coupling of *o*-iodophenols with internal alkynes and 1 atm of carbon monoxide (**scheme 10**).

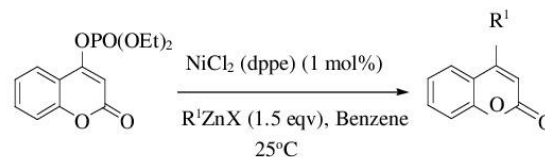


Scheme 10

They showed that 1 equiv of *o*-iodophenol, 5 equiv of alkyne, 1 atm of CO, 5 mol % of Pd (OAc)₂, 2 equiv of pyridine, and 1 equiv of *n*-Bu₄NCl in

DMF at 120 °C is the optimal conditions of the reaction. The use of pyridine as a base is crucial for the success of the reaction. Inorganic bases or tertiary alkylamines as the base decreases the yield of the product. One atmosphere of carbon monoxide is sufficient for the reaction.

In 2001, Jie Wu and Zhen [99] Yang introduced an efficient new methodology for the synthesis of 4-substituted coumarins by nickel-catalyzed cross-couplings of 4-diethylphosphonoxy coumarins with organozinc reagents (**scheme 11**)



Scheme 11

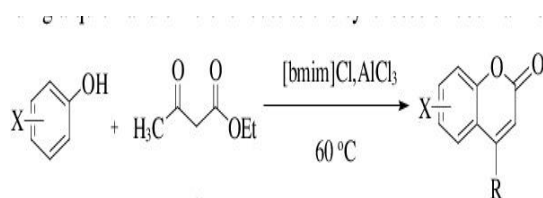
They found that among the catalysts tested [Pd(Ph₃P)₄, PdCl₂(Ph₃P)₂, NiCl₂(dppe)], NiCl₂(dppe) is the most efficient and among the solvents tested (THF, dioxane, and benzene), benzene is the best choice.

A variety of structurally diverse organozincs were subjected for the synthesis of 4-substituted coumarins which are summarized in **Table 1**.

Table 1. Nickel-catalyzed cross-coupling reactions

Entry	Substrate	Time (min)	Yield (%) ^a
1		0.5	82
2		1	78
3		1	86
4		1	75
5		1	84
6		4	56
7		8	32
8		30 min	90
9		8	58

Later on, M. M. Salunkhe and his group¹⁰⁰ used 1-Butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·2AlCl₃ ionic liquid as an alternative to conventional acid catalysts in the Pechmann condensation of phenols with ethyl acetoacetate leading to the formation of coumarin derivatives. They showed that the ionic liquid plays the dual role of solvent and Lewis acid catalyst providing a quick and efficient route to the syntheses of coumarins (scheme 12).

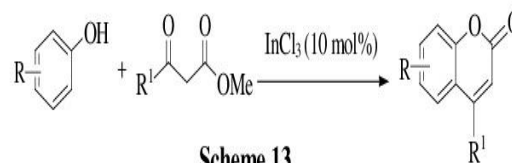


Scheme 12

Disadvantages of this method is that Chloroaluminate ionic liquids that are used in the reaction are moisture sensitive and cannot be recycled after the reaction and use of HCl for quenching the reaction mixture, that makes the process costly and environmentally hazardous. In 2002, D. S. Bose *et al*¹⁰¹ provided an efficient and much improved modification of the von

Pechmann reaction for the synthesis of coumarins by the indium (III) chloride catalyzed condensation of phenol and β -ketoesters under reflux conditions. They found that use of just 10

Mol% of InCl₃ is sufficient to push the reaction forward. Higher amounts of InCl₃ did not improve the result to any extent (scheme 13).



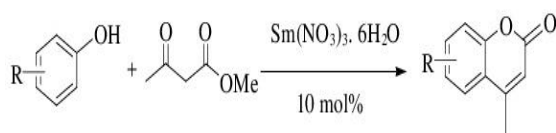
Scheme 13

They showed that phenols with electron donating groups in the para position to the site of electrophilic substitution give maximum yields under mild reaction conditions in a short period of time and phenols having no electron donating group require a higher reaction temperature and longer reaction duration. Different phenols were subjected to afford the coumarins in good to excellent yield as shown in the Table 2.

Table 2. Synthesis of coumarins via von Pechmann condensation of phenols with β -ketoesters induced by In(III)Cl₃

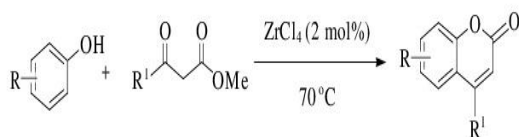
Entry	Phenol	β -ketoester	Temperature	Time (min)	Yield (%) ^a
1			65	30	98
2			65	30	96
3			65	30	95
4			65	30	92
5			65	30	90
6			95	90	88
7			65	120	55
8			130	240	65

In 2004, B. Shinde and his co-worker¹⁰² introduced a simple and mild method for the von Pechmann condensation of phenols with ethyl acetoacetate leading to the formation of coumarinderivatives in presence of Samarium (III) nitrate hexahydrate as a catalyst under solvent free conditions. A wide range of structurally varied phenols reacted smoothly and very quickly to give the corresponding coumarins in high yield and purity (scheme 14).



Scheme 14

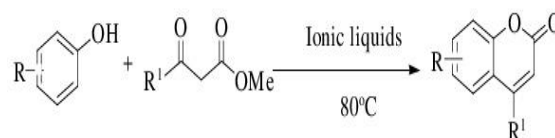
In the same year, G. Smitha and Ch. Sanjeeva Reddy¹⁰³ reported a mild and convenient method for the synthesis of coumarins under the Pechmann reaction conditions using $ZrCl_4$ as an efficient catalyst. They made the interesting observation that the electron donating group in phenol promotes the reaction while the electron withdrawing group inhibits the reaction under the present reaction conditions (scheme 15).



Scheme 15

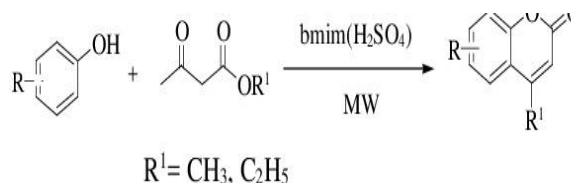
In 2005, Youquan Deng and his group [104] presented an environmentally benign process for the synthesis of coumarin derivatives using non-chloroaluminate acidic ionic liquids as catalyst under solvent-free conditions. They observed that ionic liquid loads as low as 5 mol% can be used leading to high yields with activated phenols at an

oil bath temperature of 80 °C (scheme 16).



Scheme 16

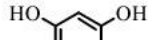
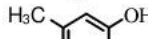
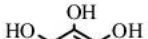
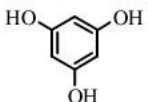

Later on, Vasundhara Singh *et al* [105] have developed a simplified and benign procedure for the synthesis of coumarins using [bmim][HSO₄] ionic liquid as an acid catalyst under microwave irradiation and solventless conditions in short duration of time with quantitative yields (scheme 17).



Scheme 17

They showed that catalytic quantity of the [bmim][HSO₄], a bronsted acid with acidic counterion gives clean products by the condensation of phenols and *B*-ketoesters in high yields (65–96%) and purity. They also carried out the reaction by thermal heating. The yields of the products obtained by microwave irradiation verses thermal heating are higher with remarkable reduction in reaction time due to homogeneous heating (as a result of strong agitation of reactant molecules) throughout the reaction media by microwave irradiation as compared to convection currents in thermal heating. A variety of structurally diverse phenols were subjected for the synthesis of coumarin derivatives which are summarized in **Table 3**.

Table 3. Results of [bmim][HSO₄] catalyzed synthesis of coumarins

Entry	Phenols	Microwave heating		Thermal heating	
		Time (min)	Yield (%)	Time (h)	Yield (%)
1		2	81	12	62
2		3	65	5	45
3		10	79	15	58
4		9	85	20	65
5		6	96	6	75

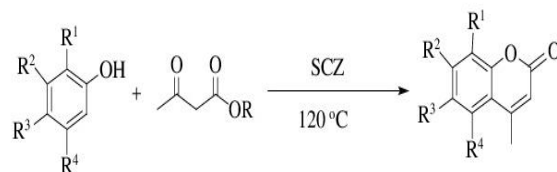
Manikrao M. Salunkhe and his coworkers [106] have demonstrated the use of neutral ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim] BF₄) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) for Pechmann condensation as a recyclable media. [Bmim]PF₆ ionic liquid, in particular has been employed at high temperature without any acid catalyst providing cleaner and economically viable protocol for Pechmann condensation. They observed that the ionic liquid [bmim]BF₄ is unable to catalyze the reaction without any acid catalyst (**scheme 18**).

**Scheme 18**

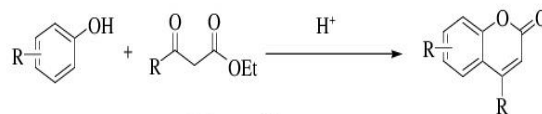
They examined several acid catalysts for the reaction such as phosphorus pentoxide, phosphorus oxychloride, trifluoroacetic acid and 4-toluene sulphonic acid. The reaction proceeded smoothly at room temperature by using phosphorus oxychloride (POCl₃) giving high yield of coumarins.

In 2006, Benjaram M. Reddy and his group¹⁰⁷ reported an efficient method for the preparation of coumarins using a novel SO₄²⁻/Ce_xZr_{1-x}O₂ composite solid acid catalyst in the Pechmann reaction of a neat mixture of a phenol and a B-keto ester. They used 10 wt. % (to that of phenols)

catalyst without any solvent at 120 °C (**scheme 19**).

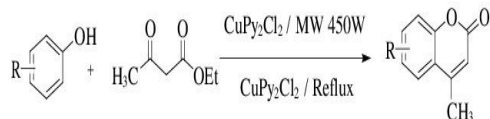
**Scheme 19**

Presented a new energy-saving procedure for the efficient preparation of coumarins by the reaction of phenols and B-keto esters under microwave irradiations. A wide variety of coumarins are obtained by this method in about 20 min, under this solvent-free, green reaction conditions (**scheme 20**)

**Scheme 20**

2- B. Rajitha and his group [109] used dipyridine copper chloride as an efficient catalyst in the Pechmann condensation reaction of phenols with ethyl acetoacetate, in solvent-free media leading to the formation of coumarin derivatives using both

conventional heating and microwave irradiation in excellent yields with good purity. Because of the presence of two pyridine rings, the electron deficiency increases on the nitrogen so it efficiently acts as a lewis acid (**scheme 21**).



Scheme 21

phenols and ethyl acetoacetate were heated under reflux in the presence of dipyrindine copper chloride to afford the products in 30-135 min. In method B, different phenols were heated under solvent free conditions with ethyl acetoacetate in the presence of dipyrindine copper chloride in a microwave oven for the appropriate time to yield the desired products. The brief results are shown in **Table 4**.

In the conventional method (Method A) different

Table 4. Dipyrindine copper catalyzed synthesis of coumarins

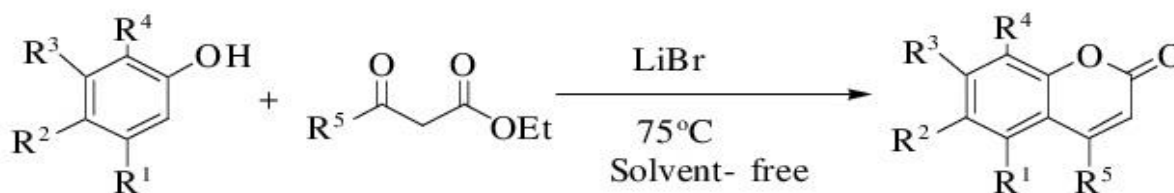
Entry	Substrate	Method A		Method B	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1		135	55	12	65
2		30	96	10	93
3		30	93	10	86
4		30	89	10	85
5		30	90	10	89
6		30	85	10	80
7		30	80	10	75

They reported that Substrates (**entries 2-6**) having electron-donating groups in the para position to the site of electrophilic substitution gave maximum yields under mild reaction conditions in a short period of time. Phenol required a higher reaction temperature and a longer reaction time, as

Various phenols and B-keto esters were successfully employed to furnish the corresponding coumarin derivatives in high yields in shorter reaction times. They also mentioned that there is no formation of side products of the chromanone type under the present reaction

no electron-donating group is present. Jagir S. Sandhu *et al*¹¹⁰ employed LiBr as lewis acid catalyst in the synthesis of coumarins via von Pechmann reaction of phenols and B-keto esters under solvent free conditions at 75 °C (**scheme 22**).

conditions. They compared the activity of catalysts in the synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one and showed that LiBr without solvent at 75 °C is the superior catalyst in respect of yields and reaction times as shown in **Table 5**

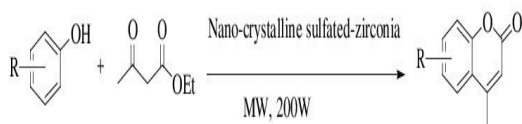


Scheme 22

Table 5. Activity of catalysts in the synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one

Entry	Catalyst	Amount of catalyst used	Time	Yield (%)
1	TFA	excess	20 h	91
2	Amberlite IR 120	25% w/w of total reactants	40 min	79
3	Sulfated zircona	0.01 eq	24 h	91
4	Sulfated Ce _x Zr _{1-x} O ₂	0.1 eq	143 min	87
5	[bmim]PF ₆	excess	45 min	91
6	LiBr	0.1 eq	15 min	92

In 2008, Raksh V. Jasra [111] and his group introduced nano-crystalline sulfated-zirconia solid acid as catalyst for microwave-assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarin by Pechmann reaction. The catalyst showed good activity for activated *m*-hydroxy phenol substrates, viz., phloroglucinol and pyrogallol with ethyl acetoacetate for the synthesis of 5, 7-dihydroxy 4-methyl coumarin and 7,8-dihydroxy 4-methyl coumarin, respectively, showing significant yields ranging from 78 to 85% within 5–20 min at 13°C (scheme 23).

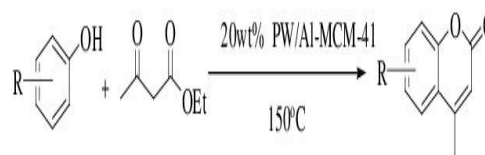


Scheme 23

However, the less activated phenol and *m*-methyl phenol was observed to be inactive for the synthesis of 4-methyl coumarin and 4, 7-dimethyl coumarin, respectively, under the studied experimental conditions.

Later on, V. Murugesan *et al*¹¹² synthesized Al-MCM-41 (Mobil Composition Mater) (Si/Al = 25) molecular sieve hydrothermally and 20 and 40 wt% phosphotungstic acid (PW) was supported on it. Then they examined catalytic performance of the materials in the liquid phase condensation of resorcinol and ethyl acetoacetate. They

observed that 7-Hydroxy- 4-methylcoumarin is the only product in this reaction. The reaction parameters were optimized to obtain high selectivity of the desired product at maximum resorcinol conversion. They revealed that 20 wt% PW/Al-MCM-41 is more active than other catalysts (scheme 24).



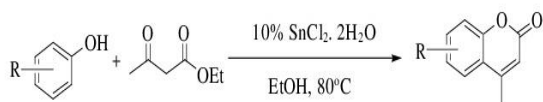
Scheme 24

In order to understand the substituent effect, they performed the reaction with several substituted phenolic derivatives with ethyl acetoacetate over 20 wt% PW/Al-MCM-41 and the results are summarized in Table 5. The reaction appeared to be feasible with resorcinol, phenol, *m*-cresol and *p*-cresol but 2-amino, 2-chloro and 2nitrophenols did not undergo this reaction. Thus electron donating group in phenol promote the reaction while electron withdrawing group inhibit the reaction. The absence of condensation reaction with these substrates may be attributed to the formation of intermolecular hydrogen bonding, which decrease the nucleophilicity of phenolic oxygen could be discerned. A brief result has been displayed in Table 6.

Table 6. Synthesis of coumarin derivatives from various substituted phenols with ethyl acetoacetate over 20 wt% PW/Al-MCM-41

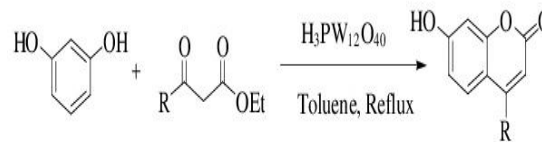
Entry	Substrate	Solvent/ Temperature (°C)	Time (h)	Yield (%)
1	Resorcinol	None/150	6	79.3
2	phenol	None/150	2	55.2
3	<i>m</i> -Cresol	None/150	8	64.7
4	<i>p</i> -Cresol	None/150	8	60.5
5	2-Aminophenol	None/150	12	–
6	2-Nitrophenol	None/150	12	–
7	2-Chlorophenol	None/150	12	–

K. K. Upadhyay and his co-workers [113] developed a simple and environmentally benign methodology for the synthesis of substituted coumarins by von-Pechmann condensation using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (10 mol%) as catalyst in ethanolic medium (scheme 25).



Scheme 25

commercially available, easy to handle, environmentally benign and non-corrosive catalyst. The advantages of the present protocol are the shorter reaction times, milder reaction conditions and high yields (scheme 26).



Scheme 26

Very recently, B China Raju *et al* reported an efficient method for the synthesis of coumarins using $\text{H}_3\text{PW}_{12}\text{O}_{40}$ as an inexpensive,

Brief results of the present protocol are summarized in Table 7.

Table 7. $\text{H}_3\text{PW}_{12}\text{O}_{40}$ -catalyzed synthesis of coumarins

Entry	Phenol	beta-ketoester	Coumarin	Time (min)	Yield (%) ^a
1				20	96
2				20	78
4				25	94
5				30	94
6				40	88
7				60	82
8				60	80

CONCLUSION:

The Pechmann reaction for the synthesis of coumarins has come a long way since its discovery by Von Pechmann in 1884 through the acid catalysed condensation of phenols and B-keto ester. A series of improvements in the process using different types of Lewis acid and other catalysts towards milder reaction conditions, variations of substituent in phenol and B-keto ester and better yield has been reported from time to time. Although these reported methods are suitable for certain synthetic conditions, many of these procedures suffered from one or more disadvantages such as harsh reaction conditions, long reaction times, tedious work-up procedure, low selectivity, large amount of catalysts and also problem of reusability of the catalyst. As coumarin derivatives are extremely important in pharmaceuticals and industry, the development of mild, efficient and environmentally benign methodology is still desirable.

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