Comparison of Methods of Synthesis of Coumarin Derivatives from Aldehydes.

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Abstract : : Coumarin was first extracted from tonka bean by Vogel. Compounds containing various coumarin backbone are a very important group of compounds due to their usage in pharmacy and medicine. Coumarins have different properties and biological activities and have a significant role in the development of new drugs. Therefore, many different methods and techniques have been reported in order to synthesize coumarin derivatives. Coumarin derivatives could be obtained from different starting materials with various methods but with big differences in yield. This review summarized various methods, techniques and reaction conditions for synthesis of coumarins from aldehydes.

Index Terms **- Coumarin Derivatives, Aldehydes, Green Synthesis.**

I. INTRODUCTION

Coumarins (2*H*-1-benzopyran-2-one) are a subclass of lactones chemically [1]. Coumarin is also known as o-hydroxycinnamic acid-8-lactone or 1,2-benzopyrone [2]. Simple coumarins, furanocoumarins, pyrano coumarins (linear and angular type), dihydrofurano coumarins, phenyl coumarins, and bicoumarins are the six basic categories of natural coumarins (Figure 1) [3]. Vogel [4,5] discovered the first parent coumarin from tonka bean (Dipteryx odorata) in 1820. The word "coumarin" comes from the French term "Coumarou," which means "tonka bean" [6,7]. Coumarins are extensively distributed in nature and may be found as secondary metabolites in many plant roots, flowers, leaves, peels, seeds, and fruits. From the roots of Angelica dahurica, which possesses therapeutic powers, Seo et al. and Bai et al. extracted more than 20 coumarins [8,9].

Three coumarins were obtained from the roots of Ferula flabelliloba by Iranshahi et al., while two novel coumarins were extracted from the roots of Clausena excavata by Peng et al. [10,11]. Ferulago suvelutina yielded six coumarins with modest antioxidant activity. Many coumarins may also be found in the roots of several Ferulago species [12]. Coumarins have been isolated from the flowers of Bombax ceiba [13], Peltophorum pterocarpum [14], and Trifolium repens [15] plants. Joselin et al. looked on the existence of phytochemical components in Apocynaceae flowers. Coumarins were found in all floral extracts from the four species studied (Allamanda cathartica, Allamanda violacea, Wrightia tinctoria, and Nerium oleander) [16]. Numerous investigations have shown that the plant leaves are an excellent source of coumarin derivatives. Wang et al. isolated 12 coumarin derivatives from the leaves of 11 bamboo species [17]. The leaves of Zanthoxylum schinifolium [18] and Zanthoxylum avicennae [19] were used to isolate anti-inflammatory coumarins. Sakunpak et al. [20] extracted monoterpene coumarins from Micromelum minutum leaves, which had significant cytotoxic action against Leishmania major. Coumarins have been extracted from the leaves of Matricaria chamomilla L. [21], Murraya paniculata [22], Bambusa pervariabilis [23], and Calophyllum Inophyllum [24]. Different coumarins can also be found in seeds. From Zosima absinthifolia seeds, Razavi and colleagues discovered furanocoumarin imperatorin and two additional coumarins [25]. Ferula sinkiangensis seeds were used to extract several sesquiterpene coumarins [26,27]. The coumarins osthole, xanthotoxin, and imperatorin were isolated from the extract of Cnidium monnieri L. seeds [28]. The majority of the coumarins detected in plant peels are obtained from citrus peels [29–31].

The plants indicated above are only a small portion of the coumarin-rich plant species. Since the majority of recovered coumarins exhibit biological activity, coumarin derivatives are increasingly being synthesised because coumarin extraction from plants is time-consuming and unprofitable (too many operation stages to the end product) [32]. Coumarins can be made via a variety of techniques, including the Perkin reaction, Knoevenagel condensation, Pechmann condensation, Wittig reaction, Baylis-Hillman reaction, Claisen rearrangement, Vilsmeier-Haack and Suzuki cross-coupling reactions [33,34]. Many studies on the therapeutic qualities of coumarins have been reported [4,6,12,35–37].

Coumarins have antimicrobial properties [38–44] and antifungal properties [40,45–48]. Several coumarin compounds have been shown to have considerable antioxidant properties [49–53]. Some coumarins have been synthesised as acetylcholinesterase (AchE) inhibitors, which might be used to treat Alzheimer's disease [54–56]. Anti-inflammatory [57,58], anti-HIV [6,59], anticancer [8,53,60], antituberculosis [61], anticoagulant [62], antiviral [63], and antihyperglycemic [64] are only a few of the biological actions linked with coumarins. Because coumarins have shown to be excellent pharmacophores, demand for their manufacture is increasing.

They have been synthesised using a variety of techniques, each of which uses distinct starting ingredients and reaction circumstances. The current article summarises recently published studies in which various components, techniques, and procedures were applied in the synthesis of coumarin derivatives.

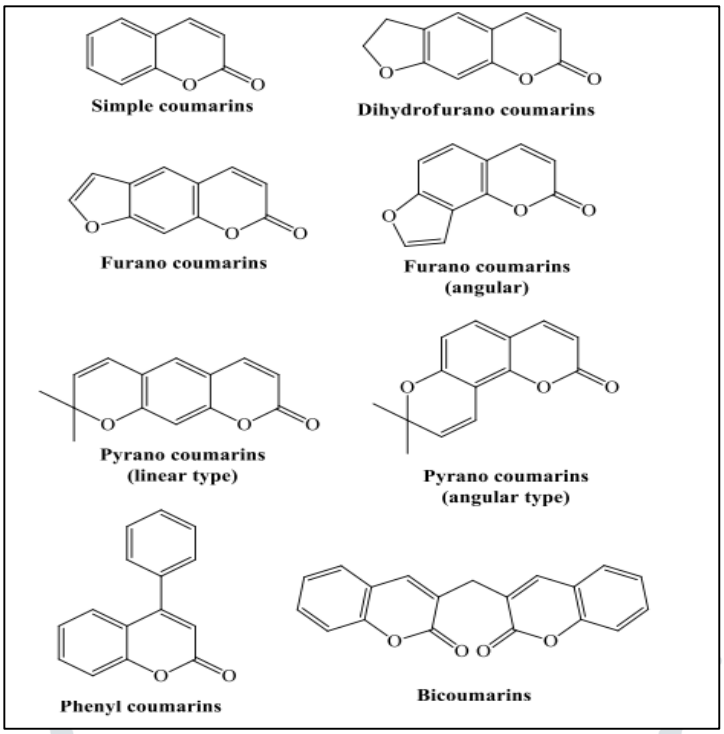
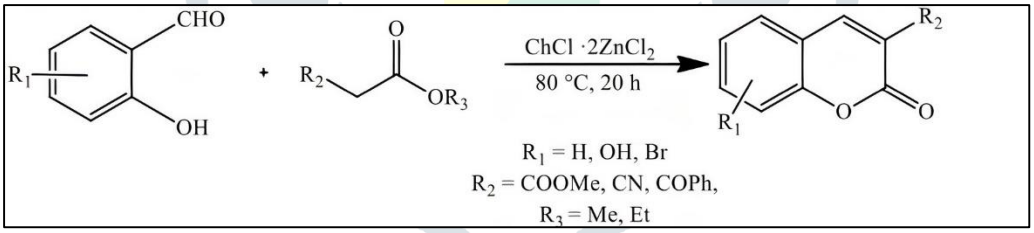


Figure 1. Six basic groups of natural coumarins

II. Coumarin Derivatives Synthesized from Aldehydes

2.1 Green synthesis of coumarin derivatives in deep eutectic solvent

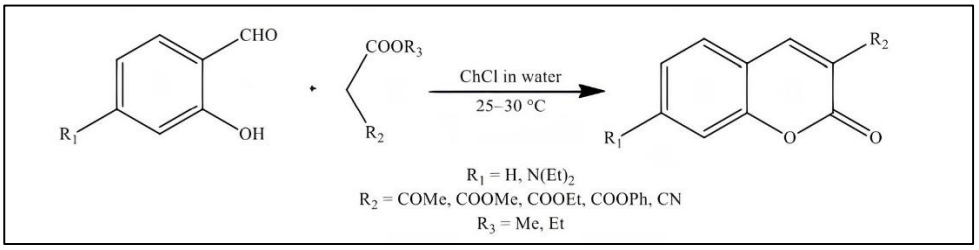
The green synthesis of coumarin derivatives in deep eutectic solvent (DES) via Knoevenagel condensation was reported by Keshavarzipour and Tavakol [65]. At 100 degrees Celsius, DES was made by combining choline chloride (ChCl) with zinc chloride. Simple or modified salicylaldehydes (4-hydroxy, 5-bromo) and methylene compounds (dimethyl malonate, ethyl cyanoacetate, ethyl 3-oxo-3-phenylpropanoate) were employed to make coumarin derivatives (Scheme 1). The yields were high (61–96%), and DES served as a solvent as well as a catalyst.



Scheme 1. Green synthesis of coumarin derivatives in deep eutectic solvent.

2.2 Coumarin derivatives obtained in aqueous media with ChCl as catalyst.

The reactions were carried out by Phadtare and Shankarling in order to get coumarin derivatives [66]. In aqueous medium, all mixes were agitated at 25–30°C. Knoevenagel condensation was used to synthesize substituted aldehydes and active methylene compounds in the presence of ChCl as a catalyst (Scheme 2). The yields of coumarin derivatives produced ranged from 79 to 98 percent.



Scheme 2. Coumarin derivatives obtained in aqueous media with ChCl as catalyst.

In a 3-acyl-4-aryl preparation, Mi and colleagues showed metal-free tandem oxidative acylation and cyclization between alkynoates and aldehydes [67]. To attain optimal reaction conditions, a reaction between phenyl 3-phenylpropionate and diethyl p-tolu aldehyde was carried out. The following parameters were adjusted during reaction optimization: additive (pivalic acid, n-Bu_4NF, n-Bu_4NCl, n-Bu_4NBr, n-Bu_4NI, and Et_4NBr), oxidant (tert-butyl hydroperoxide, $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)2S2O_8$), solvent (1,2-

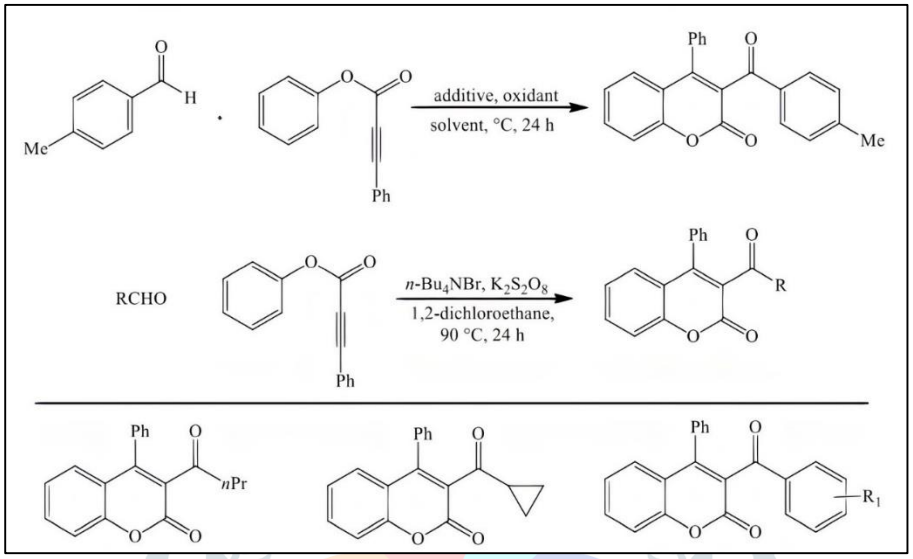
dichloroethane, MeCN, dioxane, toluene, chlorobenzene and H_2O) and temperature (80, 90 and 100 °C). For 24 hours, all reactions were carried out in sealed tubes in an oil bath with N2. The optimal reaction conditions were discovered to be $K_2S_2O_8$ as the oxidant, n-Bu_4NBr as the additive, 1,2-dichlorethane as the solvent, and a temperature of 90°C.

2.3 Cyclization reaction of phenyl 3-phenylpropiolate with various aldehydes and Alkynoates.

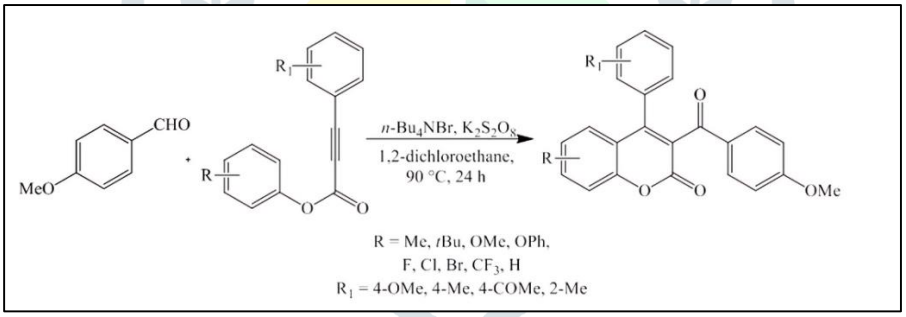
The phenyl 3-phenylpropiolate cyclization reaction with different aldehydes was carried out under optimal circumstances (Scheme 3). Cyclization reactions of 4-methoxybenzaldehyde and different alkynoates are shown in Scheme 4.

2.4 Synthesis of coumarin derivatives in the presence of piperidine and acetic acid as catalysts

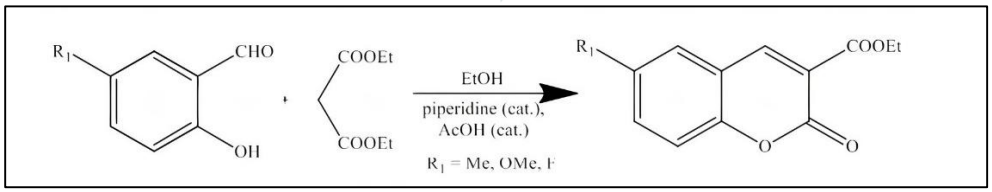
The synthesis of coumarins by Knoevenagel condensation of salicylaldehyde and diethyl malonate in EtOH (Scheme 5) was described by Suljic and Pietruszka [68]. As catalysts, piperidine and acetic acid were used. In a continuous flow hydrogenation procedure, chromanones were produced from the produced coumarins. A variety of catechol's were also reacted with chromanones in laccase-catalyzed arylation.



Scheme 3. Cyclization reaction of phenyl 3-phenylpropiolate with various aldehydes.



Scheme 4. Cyclization reactions of 4-methoxybenzaldehyde and various alkynoates.

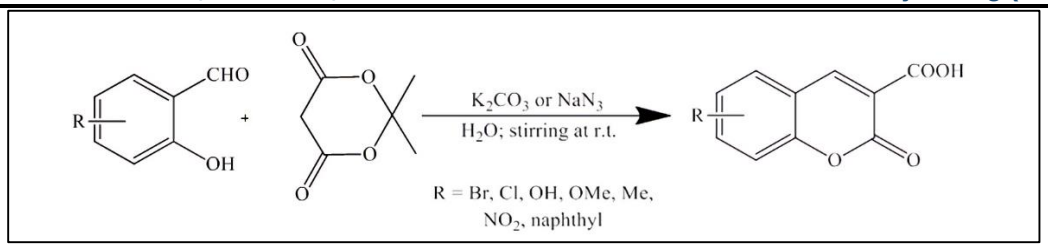


Scheme 5. Synthesis of coumarin derivatives in the presence of piperidine and acetic acid as catalysts.

Using Knoevenagel condensation, Brahma Chari reported one-pot synthesis of coumarin-3-carboxylic acids [69]. Syntheses were carried out in water at room temperature (RT). First, a model reaction between salicylaldehyde and Meldrum's acid was carried out in order to identify the catalyst that would allow for high product yields. Sodium azide and potassium carbonate were found to be the best catalysts, with product yields of 99 and 92 percent, respectively.

2.5 One-pot synthesis of coumarin-3-carboxylic acids in water

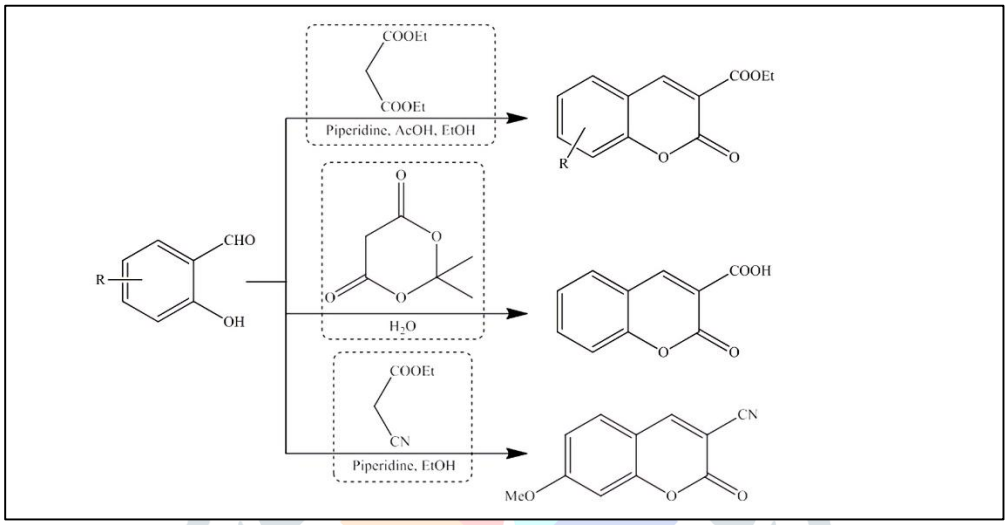
The reaction of various substituted salicylaldehyde and Meldrum's acid with both catalysts yielded a number of substituted coumarin-3-carboxylic acids (Scheme 6) in yields ranging from 73 to 99 percent. It should be emphasized that sodium azide is quite hazardous in the short term. It's worth noting that sodium azide is extremely poisonous, especially in the concentrations used in the processes (50 mol percent). As a result, a technique using potassium carbonate (20 mol%) as a catalyst is suggested.



Scheme 6. One-pot synthesis of coumarin-3-carboxylic acids in water.

2.6 Synthesis of different coumarins from active methylene compounds and salicylaldehydes.

By Knoevenagel condensation (Scheme 7) [70], Silveira Pinto and Souza synthesized several coumarins from active methylene compounds (diethylmalonate, Meldrum's acid, and ethyl cyanoacetate) and salicylaldehydes. Piperidine and glacial AcOH were added to the reaction, which was carried out in 100% EtOH or H_2O. A model reaction of salicylaldehyde and diethyl malonate was carried out utilizing a heating and ultrasonic technique. In the case of ultrasound irradiation, the yield is greater and the reaction time is shorter as compared to the reflux technique (40 min compared with 7 h). Variety coumarins were isolated using ultrasonic irradiation at a frequency of 20 kHz with a power output of 90% and no pulsing.



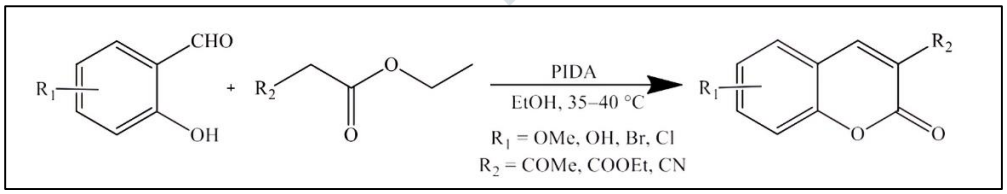
Scheme 7. Synthesis of different coumarins from active methylene compounds and salicylaldehydes.

2.7 Phenyliododiacetate mediated reaction of salicylaldehydes and α-substituted ethyl acetates

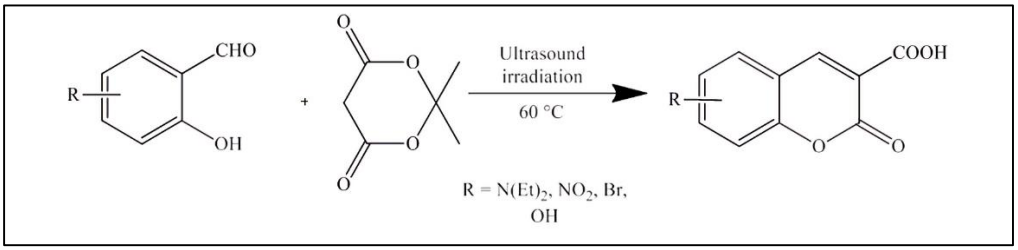
Khan et al. described an effective Knoevenagel condensation synthesis of coumarin derivatives [71]. In order to obtain the optimal reaction conditions in terms of yield, reaction parameters (solvent, catalyst) were adjusted. The reaction conditions that proved to be the optimum after optimization were: Phenyliododiacetate (PIDA) catalyzed reaction in EtOH at 35–40 degree C, yielding 90–92%. Salicylaldehydes and -substituted ethyl acetates processes (Scheme 8) yielded 80–92% product yields under ideal circumstances.

2.8 Green method for synthesis of coumarin-3-carboxylic acids under ultrasound irradiation.

By using Knoevenagel condensation, Fiorito et al. developed a green approach for the preparation of coumarin-3-carboxylic acids [72]. Solvents such as vegetable juices, the liqueur limoncello, and waste waters from the processing of olive and buttermilk were used in this innovative approach. Under ultrasonic irradiation at 60°C, reactions of substituted salicylaldehydes and Meldrum's acid were carried out (Scheme 9). Products were obtained in high yields (91–99 percent), with lemon juice having the greatest conversions.



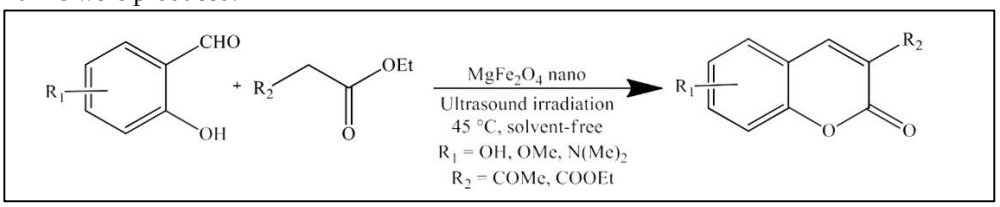
Scheme 8. Phenyliododiacetate mediated reaction of salicylaldehydes and α-substituted ethyl acetates.



Scheme 9. Green method for synthesis of coumarin-3-carboxylic acids under ultrasound irradiation.

2.9 Synthesis of 3-substituted coumarins between salicylaldehydes and 1,3-dicarbonyl compounds in presence of nano $MgFe_2O_4$.

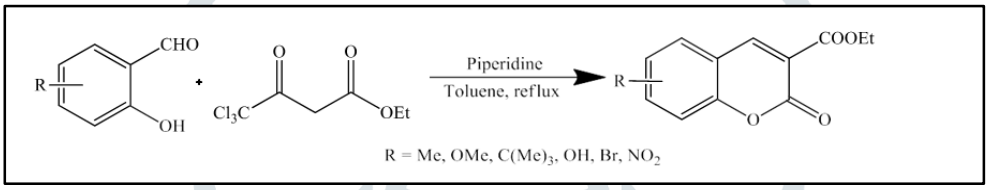
Ghomi and Akbarzadeh [73] used a solvent-free Knoevenagel condensation method to make 3-substituted coumarins. Different solvents (DMF, MeOH, MeCN, EtOH, and no solvent) and catalysts (nano CuO, nano MgO, nano ZnO, and nano $MgFe_2O_4$) were utilized to improve reaction conditions. At 45°C, ultrasonic irradiation was used to perform green synthesis in the presence of MgFe2O4 nanoparticles between different salicylaldehydes and 1,3-dicarbonyl compounds (Scheme 10). 63–73 percent yields of 3-substituted coumarins were produced.



Scheme 10. Synthesis of 3-substituted coumarins between salicylaldehydes and 1,3-dicarbonylcompounds in presence of nano $MgFe_2O_4$.

2.10 Synthesis of 2H-chromene-3-carboxylates in presence of piperidine in toluene.

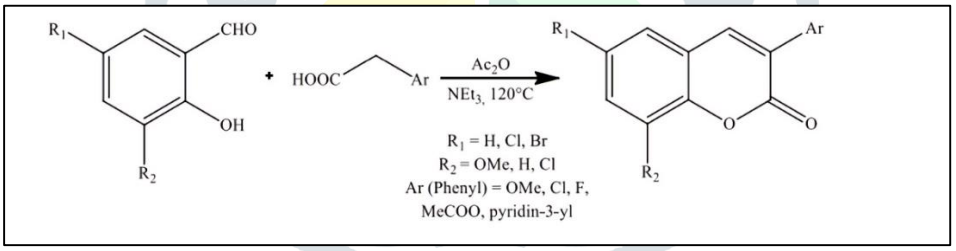
Sairam et al. [74] used the Knoevenagel method to synthesis 2H-chromene-3-carboxylates from salicylaldehydes and 4,4,4-trichloro-3-oxobutanoate. Various solvents (EtOH, DCM, DMF, MeCN, THF, ether, MeOH, and toluene) and catalysts (piperidine, PPh_3, DABCO, DMAP, $N(C_2H_5)3$, pyridine, imidazole, EtN(Pr)2, 2,6-lutidine, NaOMe, KOH, and K_2CO_3) were used to optimise reaction conditions. As stated in Scheme 11, a number of coumarin derivatives were synthesised under ideal circumstances (toluene and piperidine). The yields of the coumarins produced ranged from 25 to 82 percent.



Scheme 11. Synthesis of 2H-chromene-3-carboxylates in presence of piperidine in toluene.

2.11 Synthesis of 3-arylcoumarins via Perkin condensation in the presence of anhydride and trimethylamine.

3- Arylcoumarins were synthesised from salicylaldehydes and phenylacetic acids by Perkin condensation (Scheme 12). The reactions were carried out at 120°C with stirring in the presence of acetic anhydride and triethylamine. 3-arylcoumarins were produced in moderate to fair yields (46–74%) after purification [58].



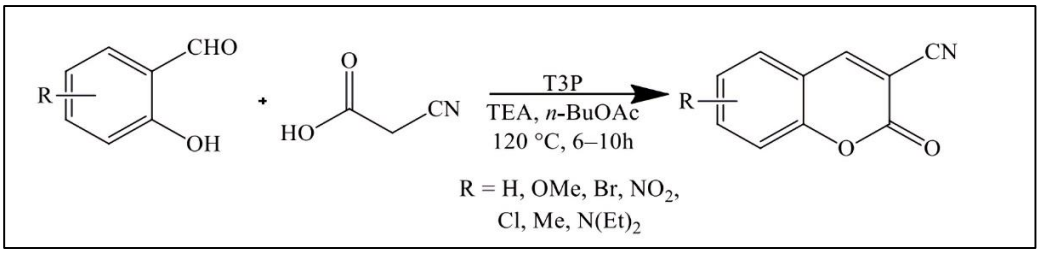
Scheme 12. Synthesis of 3-arylcoumarins via Perkin condensation in the presence of anhydrideand trimethylamine.

2.12 One-pot synthesis of cyanocoumarins in presence of T3P, trimethylamine and butyl acetate

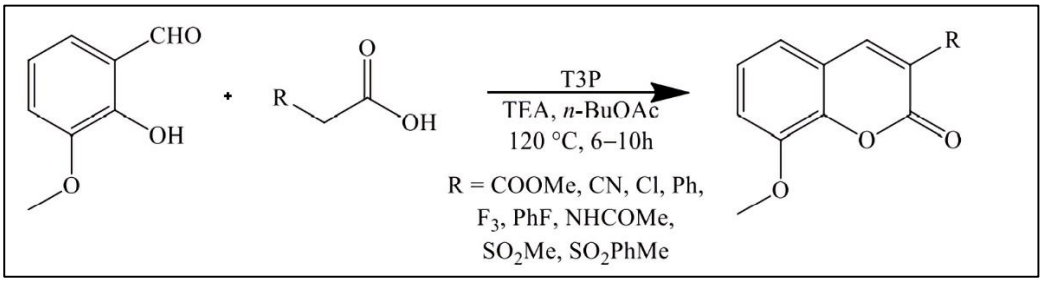
Augustine and coworkers adopted Perkin condensation to generate a one-pot synthesis of substituted coumarins [75]. As a model reaction, the reaction between salicylaldehyde and cyanoacetic acid was used. In order to find the optimal reaction conditions, eight reactions with varied parameters (time, temperature, and molarity of propyl phosphonic anhydride T3P) were undertaken. T3P, TEA (triethylamine), and n-BuOAc were used in all of the reactions (butyl acetate). Moreover, coumarin derivatives were obtained by reacting different substituted salicylaldehydes with cyanoacetic acid (Scheme 13).

2.13 Synthesis of coumarin derivatives trough reaction of carboxylic acids and 2-hydroxy-3- methoxybenzaldehyde

Furthermore, coumarin derivatives were created by reacting different carboxylic acids with 2-hydroxy-3-methoxybenzaldehyde under optimized conditions (Scheme 14).



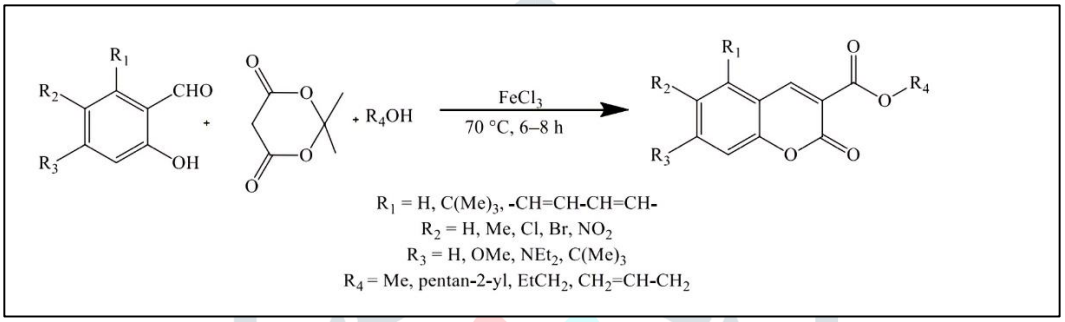
Scheme 13. One-pot synthesis of cyanocoumarins in presence of T3P, trimethylamine and butyl acetate



Scheme 14. Synthesis of coumarin derivatives trough reaction of carboxylic acids and 2-hydroxy-3-methoxybenzaldehyde.

2.14 Synthesis of coumarin-3-carboxylic esters in multicomponent reaction in the presence of FeCl3

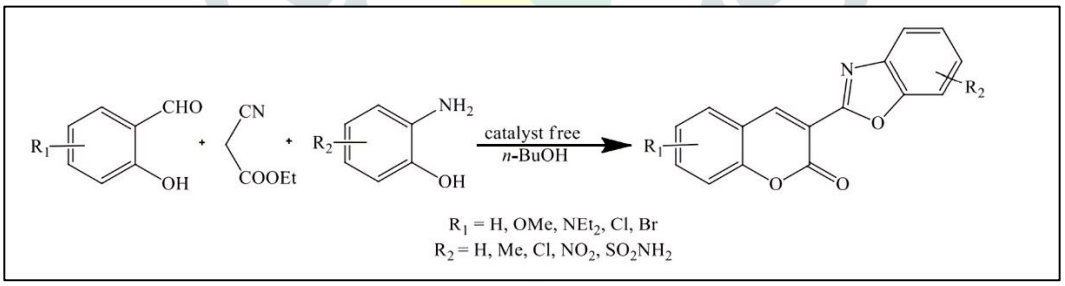
He et al. [76] used multicomponent processes to produce coumrin-3-carboxylic esters. The catalysts (Cu(OAc)2, CuBr, CuSO4, NiCl26H2O, AgNO3, K3Fe(CN)6, and FeCl3) were screened, and FeCl3 was shown to be the best. Different solvents (EtOH, DMF, THF, MeCN, toluene, DMSO, cyclohexane, and H2O) and temperatures (RT, 50, 70, and 100 C) were used to optimise the reaction conditions. In EtOH at 70°C, the greatest yield of 93 percent was produced. The reaction of substituted salicylaldehydes, Meldrum's acid, and different alcohols was carried out using these parameters (Scheme 15). The yields of coumarin-3-carboxylic acids were high to excellent (73–91%).



Scheme 15. Synthesis of coumarin-3-carboxylic esters in multicomponent reaction in the presence of $FeCl_3$

2.15 Three-component one-pot synthesis of 3-benzoxazole coumarins.

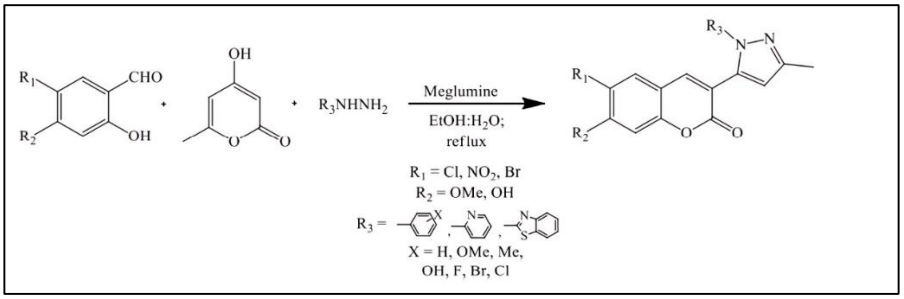
Jiang et al. [77] established a three-component one-pot coumarin derivative synthesis. To discover a suitable solvent, a trial reaction of salicylaldehyde, ethyl cyanoacetate, and o-aminophenol was carried out (MeOH, EtOH, BuOH and amyl alcohol). In n-BuOH, the greatest yield of 66 percent was achieved. 3-Benzoxazole coumarins were synthesised from substituted salicylaldehydes, ethyl cyanoacetate, and o-aminophenols (Scheme 16) with yields of 40–79%.



Scheme 16. Three-component one-pot synthesis of 3-benzoxazole coumarins.

2.16 Synthesis of pyrazolyl coumarins in a multicomponent reaction.

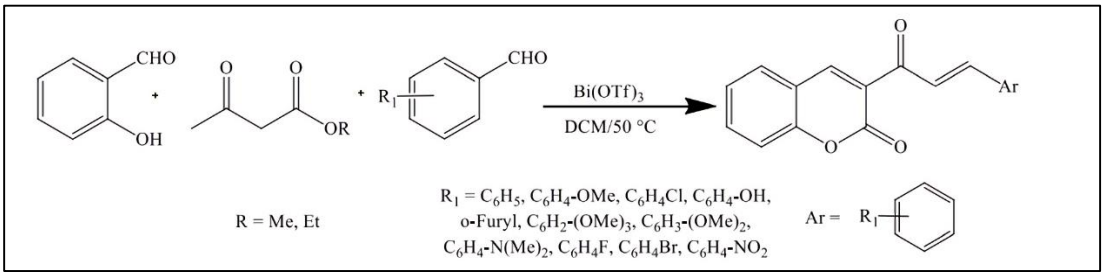
Li et al. [78] synthesized pyraolylcoumarins at conditions determined to be the best in prior reaction optimization. Various solvents (EtOH, EtOH: H2O (1:1), H2O, glycerin, MeCN, and deep eutectic solvents), catalysts (without catalyst, Fe2O3, L-proline, CaCO3, piperidine, 1,3-dimethylurea, chitosan, betaine HCl, mannitol, DABCO, and meglumine), and temperatures (reflux, 80°C) were used Under the following circumstances, the greatest yield of 80% was obtained: EtOH: H2O (1:1), meglumine, reflux. Various salicylaldehydes, 4-hydroxy-6-methyl-2H-pyran 2-one, and hydraines were used to make a range of pyraolylcoumarins in a one-pot three-component process (Scheme 17). Good to excellent yields (70–89%) were achieved when the products were synthesized.



Scheme 17. Synthesis of pyrazolylcoumarins in a multicomponent reaction.

2.17 Synthesis of coumarin-chalcone compounds in multicomponent reaction.

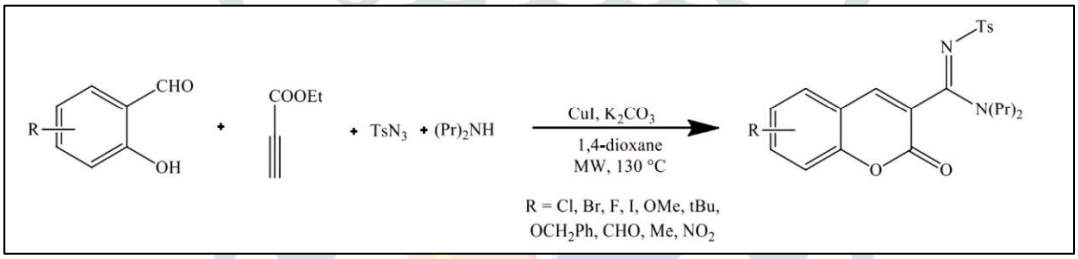
Salicylaldehyde, -ketoester, and different aromatic aldehydes were used in one-pot three-component processes (Scheme 18) [79]. Several reactions were carried out to improve reaction conditions by adjusting the catalyst ($FeCl_3$ 6H2O, Fe $(OTf)_3$, $ZnBr_2$, Zn $(OTf)_2$, $MgCl_2$, Mg (OTf), $CuCl_2$, Cu $(OTf)_2$, and Bi $(OTf)_3$) and solvent ($FeCl_3$ $6H_2O$, Fe $(OTf)_3$, $ZnBr_2$, Zn (OTf)2, MgCl2, Mg (OTf) (MeOH, N, N-dimethylformamide, toluene, MeCN and DCM). In the presence of Bi (OTf)3 in DCM at 50°C, the greatest yield of 96 percent was achieved. Excellent yields of coumarin-chalcone compounds (88–96%) were produced.



Scheme 18. Synthesis of coumarin-chalcone compounds in multicomponent reaction.

2.18 Microwave assisted four-component synthesis of 3-N-sulfonylamidine coumarins.

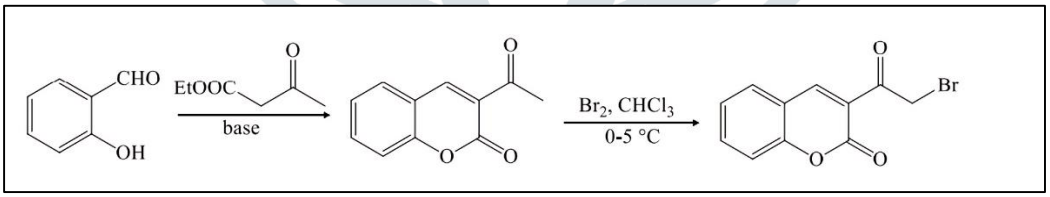
Microwave aided four-component synthesis of 3-N-sulfonylamidine coumarins was reported by Murugavel and Punniyamurthy [80]. In the presence of several copper salts (CuI, CuBr, CuCl, and $Cu(acac)_2$), bases (K_3PO_4, K_2CO_3, Cs_2CO_3, Na_2CO_3, and DBU), and solvents, a model reaction was carried out between salicylaldehyde, ethyl propiolate, tosyl azide, and diisopropylamine (1,4-dioxane, DMSO, toluene and DMF). CuI, K_2CO_3, and dioxane were found to be the optimal reaction conditions, and a range of coumarins were synthesized with moderate to high yields (Scheme 19).



Scheme 19. Microwave assisted four-component synthesis of 3-N-sulfonylamidine coumarins.

2.19 Two-step synthesis of bromoacetylcoumarin under microwave irradiation.

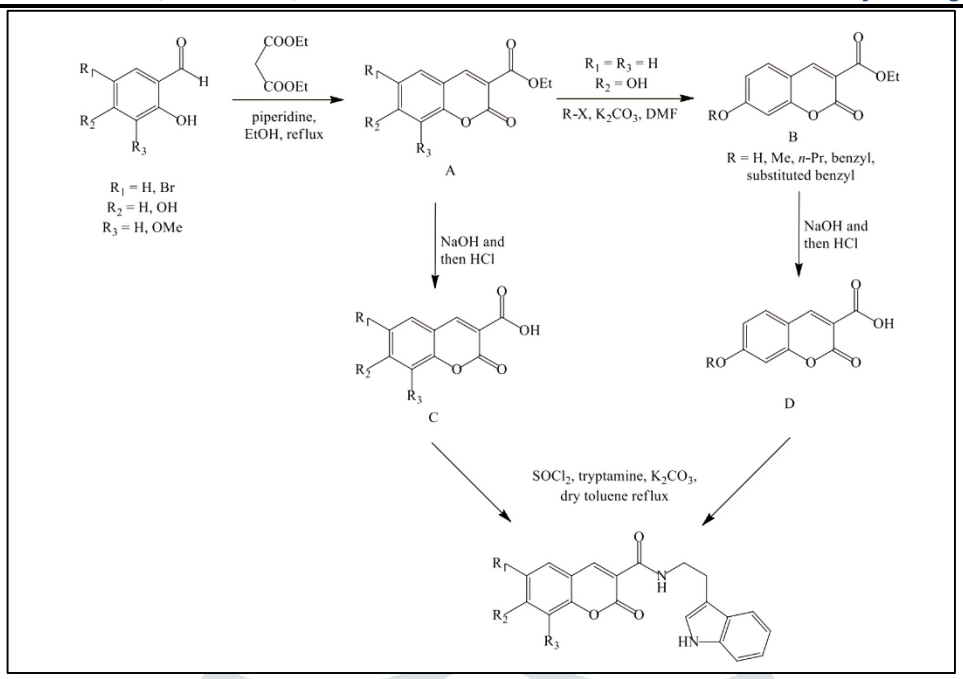
Microwave irradiation was used by Osman et al. to produce bromoacetylcoumarin in two steps [81]. At 50°C and 120°C, the model reaction was carried out in EtOH or solvent-free. As a base, piperidine and L-proline were employed. In EtOH with piperidine at 50°C, a yield of 99 percent was reported. The synthesis of 3-acetylcoumarin from salicylaldehyde and ethyl acetoacetate was the first step. The electrophilic bromination of 3-acetylcoumarin in $CHCl_3$ was the second reaction (Scheme 20).



Scheme 20. Two-step synthesis of bromoacetylcoumarin under microwave irradiation.

2.20 Three and four-step synthesis of N-(2-(1H-indol-3-yl) ethyl)-2-oxo-2H-chromene-3-carboxamides.

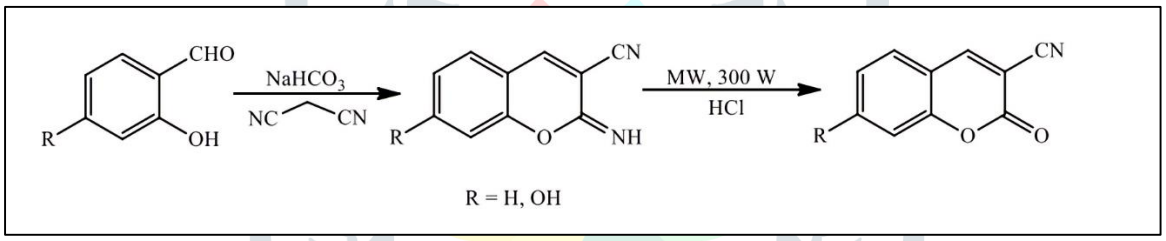
Ghanei-Nasab et al. created N-(2-(1H-indol-3-yl) ethyl)-2- oxo-2H-chromene-3-carboxamides in three and four steps, which were evaluated against AChE and BuChE (Scheme 21) [82]. Salicylaldehyde derivatives, diethyl malonate, and piperidine were refluxed in EtOH in the first stage, yielding ethyl coumarins-3-carboxylates (compounds A). Using potassium carbonate in DMF, 7-hydroxy derivatives were reacted with alkyl halides or benzyl derivatives to produce O-alkyl or O-benzyl derivatives (compounds B). In the presence of sodium hydroxide, all of the produced ethyl esters were hydrolyzed to yield coumarin-3-carboxylic acids (compounds C and D). Thionyl chloride was used to convert coumarin-3-carboxylic acids to acid chlorides. Acid chlorides and tryptamine were reacted with potassium carbonate in dry toluene to produce the final products. The last stage of the reaction was carried out under varied circumstances to reduce reaction time (microwave irradiation in different solvents; solvent-free conditions). In compared to traditional circumstances, the greatest results were obtained utilising MeCN as a solvent under microwave irradiation, where the reaction time was reduced from 15 hours to 5 minutes.



Scheme 21. Three and four-step synthesis of N-(2-(1H-indol-3-yl) ethyl)-2-oxo-2H-chromene-3-carboxamides.

2.21 Two-step synthesis of substituted 3-cyanocoumarins under microwave irradiation.

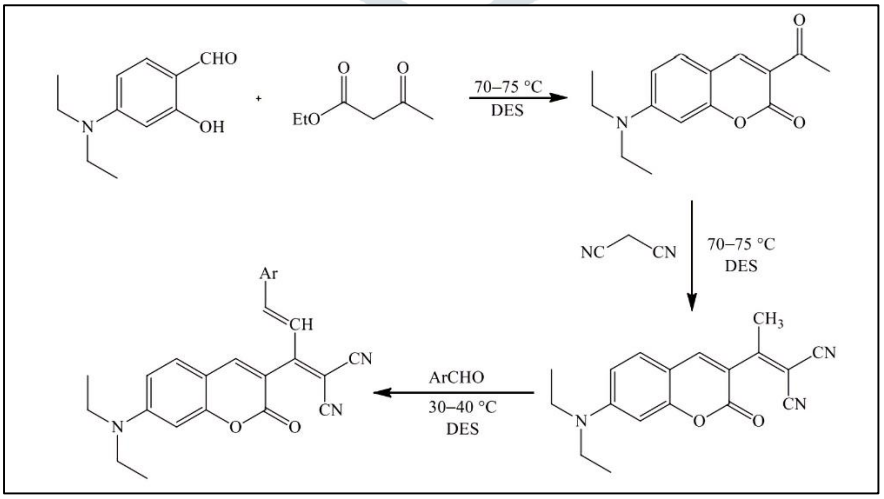
Rabahi et al. synthesised coumarins in a two-step reaction from salicylaldehydes and malononitrile [83]. In the first step, iminocoumarins were obtained from salicylaldehyde and malonitrile in the presence of $NaHCO_3$. Further, iminocoumarins were hydrolyzed in the presence of HCl under microwave irradiation. Both reaction steps are shown in Scheme 22.



Scheme 22 Two-step synthesis of substituted 3-cyanocoumarins under microwave irradiation.

2.22 One-pot synthesis of fluorescent colorant in deep eutectic solvents

Phadtare et al. created a cyanocoumarins-based fluorescent colourant. Deep eutectic solvent (DES) (ChCl: urea) [84] was used to do one-pot synthesis. In the first stage, DES was used to combine 4-(diethylamino)-2-hydroxybenzaldehyde and ethyl acetoacetate. Malononitrile was added after the reaction was completed to yield 3-acetyl-7-(diethylamino)-2H-chromen-2-one. To obtain fluorescent colourant, the last stage entailed the addition of several aromatic aldehydes. Scheme 23 shows all of the reaction stages.



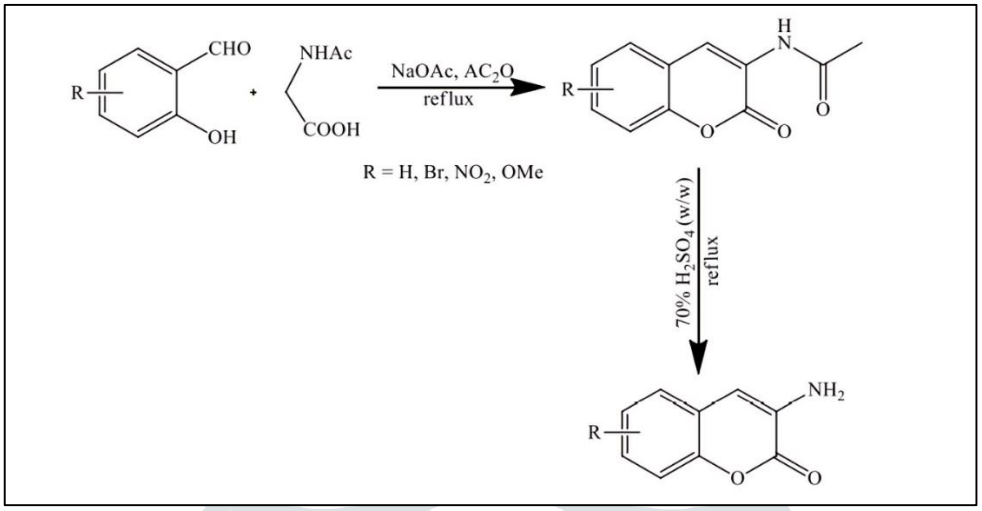
Scheme 23. One-pot synthesis of fluorescent colorant in deep eutectic solvents.

2.23 Synthesis of substituted 3-aminocoumarins in two-step reaction.

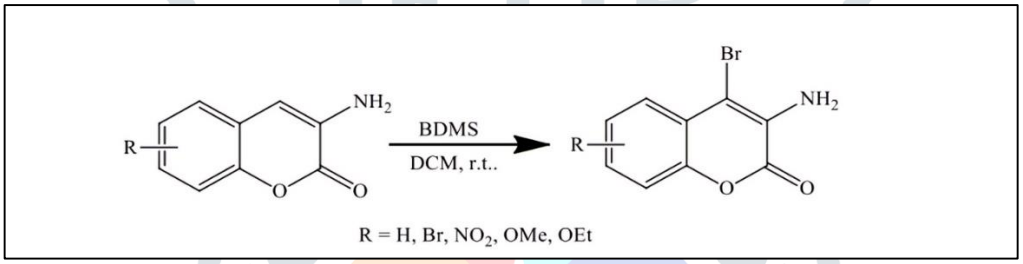
Das et al. [85] devised a method for synthesizing 3-amino-4-bromocoumarin. Initially, different salicylaldehydes and N-acetyl glycine were used to produce 3-acetamidocoumarins, which were then hydrolyzed to provide 3-aminocoumarins (Scheme 24).

2.24 Synthesis of substituted 3-amino-4-bromocoumarins in the presence of Bromodimethylsulfonium bromide.

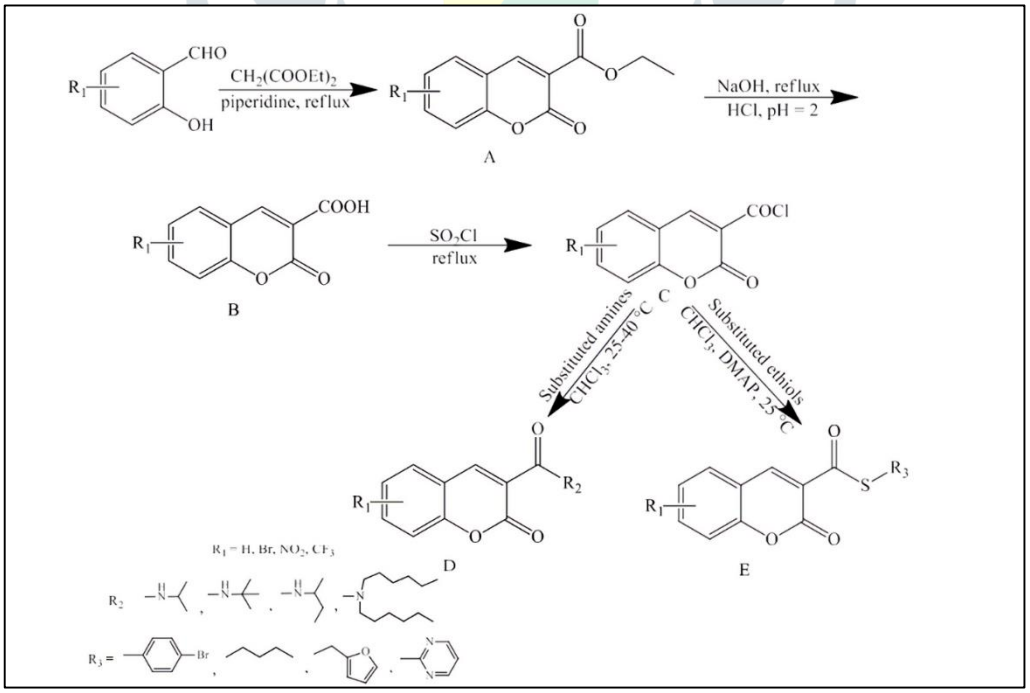
Bromodimethylsulfonium bromide (BDMS) was utilized as a brominating reagent. 3-aminocoumarin and BDMS reactions were carried out in DCM at room temperature (Scheme 25). Brominated compound yields ranged from 84 to 92 percent.



Scheme 24. Synthesis of substituted 3-aminocoumarins in two-step reaction.



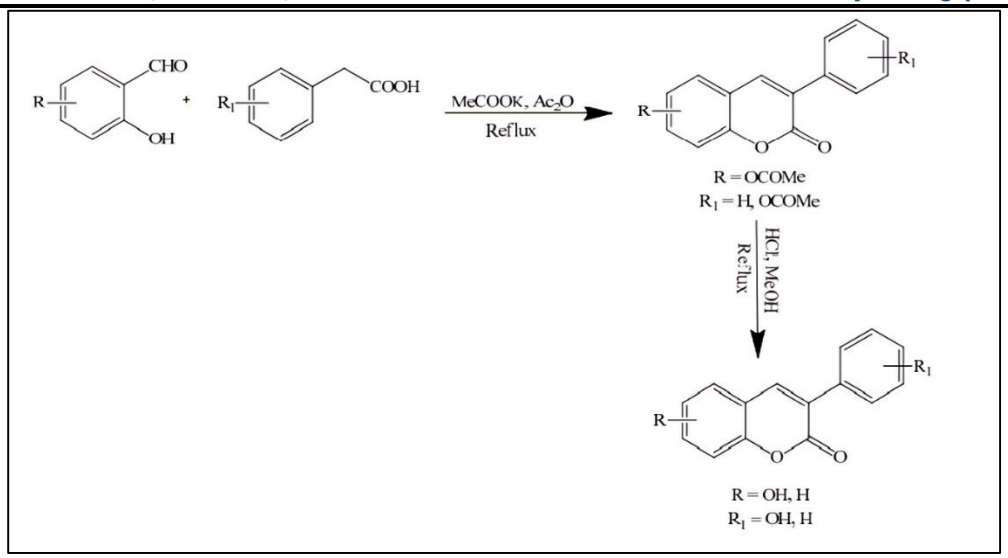
Scheme 25. Synthesis of substituted 3-amino-4-bromocoumarins in the presence of Bromodimethylsulfonium bromide.



Scheme 26. Four-step reaction in synthesis of coumarin derivatives.

2.25 Four-step reaction in synthesis of coumarin derivatives.

In the presence of piperidine, He et al. reported synthesis of many coumarin derivatives commencing with the condensation of substituted salicylaldehyde and malonate [86]. Coumarins A were obtained using sodium hydroxide and hydrochloric acid to synthesis component B. Component B reactions and compound C of thionyl chloride. In order to generate compounds D or E respectively, 2-Oxo - 2H - chromen-3 - carbonyl chlorides (C) have been reacted to 4-dimethylaminopyridine or substituted ethiols. The Scheme 26 shows all synthesis steps and reactions.



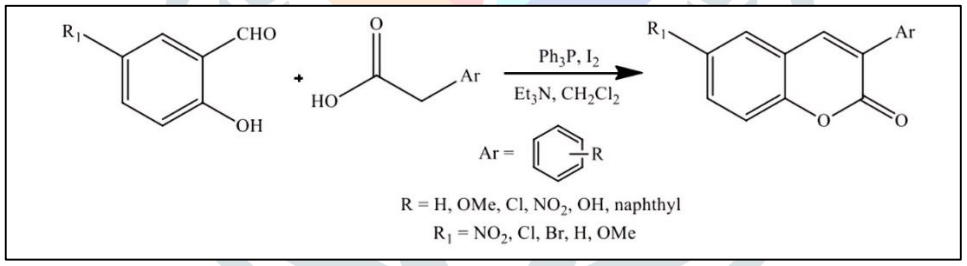
Scheme 27. Efficient two-step synthesis of hydroxylated 3-phenylcoumarins.

2.26 Efficient two-step synthesis of hydroxylated 3-phenylcoumarins.

Matos et al. developed efficient two-step synthesis of hydroxylated 3-phenylcoumarins [50]. Initially, acetoxy-3-phenylcoumarins were synthesized in the reaction of salicylaldehydes and phenylacetic acid in the presence of anhydrous potassium acetate (CH3CO2K) and acetic anhydride. Obtained products were hydroxylated under reflux in the presence of aqueous hydrochloric acid and MeOH (Scheme 27).

2.27 One-pot two-step synthesis of 3-aryl coumarins in the presence of Ph_3P/I_2-Et_3N.

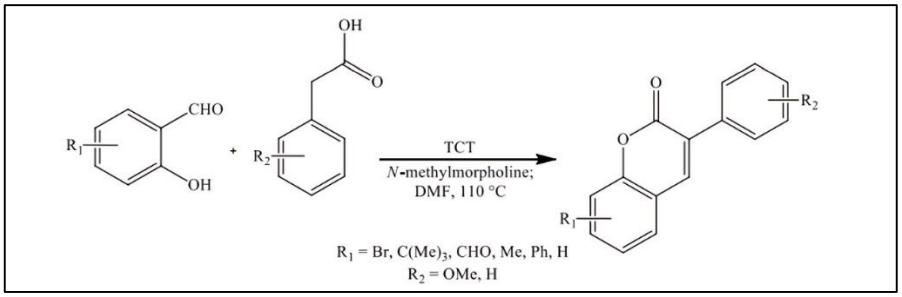
In the presence of Ph3P/I2-Et3N (Scheme 28), Phakhodee and colleagues reported a one-pot two-step synthesis of 3-aryl coumarins between aryl acetic acids and 2-hydroxybenzaladehydes [87]. The kind of base (Et3N, DMAP, imidazole, DABCO, and NNM) and solvent used in a model reaction of salicylaldehyde and 4-methoxyphenylacetic acid were varied (DCM, toluene, DMF and MeCN). When DCM was utilized as the solvent and triethylamine was utilized as the base, the best yield of 98 percent was obtained. The yields of the products produced under such reaction conditions ranged from 41 to 98 percent.



Scheme 28. One-pot two-step synthesis of 3-aryl coumarins in the presence of Ph_3P/I_2-Et_3N.

2.28Ultrasound assisted synthesis of 3-phenylcoumarin derivatives in presence of tetrahydrofuran and K_2CO_3.

Ultrasonic irradiation was used by Sripathi and Logeeswari to synthesise 3-aryl coumarin derivatives [88]. With the addition of tetrahydrofuran (THF) and K_2CO_3, 3-phenylcoumarins were produced from salicylaldehydes and phenyl acetyl chloride (Scheme 29). The yields of 3-phenylcoumarins produced varied between 7% and 98 percent.

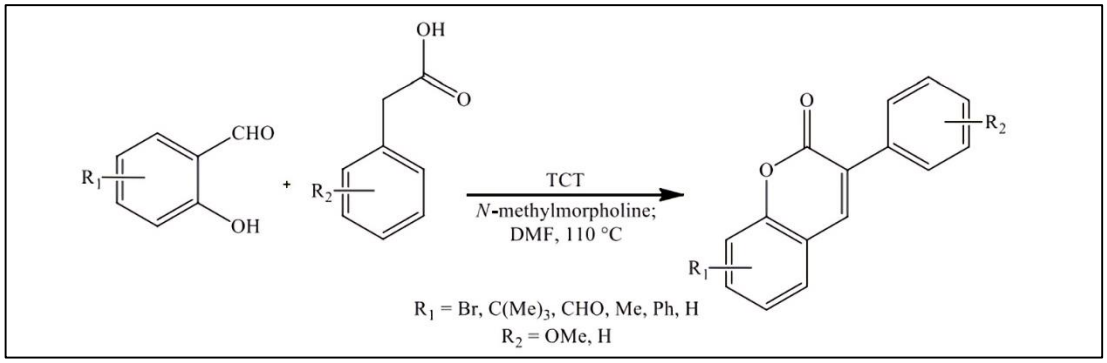


Scheme 29. Ultrasound assisted synthesis of 3-phenylcoumarin derivatives in presence oftetrahydrofuran and K_2CO_3.

2.29Efficient synthesis of 3-aryl coumarin derivatives in presence of N-methyl morpholine.

Through the interaction of 2-hydroxybenzaldehyde and phenylacetic acid derivatives (Scheme 30), Sashidhara et al. demonstrated an effective synthesis of 3-aryl coumarin derivatives [89]. In the presence of cyanuric chloride, this reaction was carried out (2,4,6-trichloro-1,3,5-triazine, TCT). Various factors were changed to optimise reaction conditions (base types and molar ratios, reaction times, temperatures and solvents). The optimum reaction conditions were determined to be N-methyl morpholine at

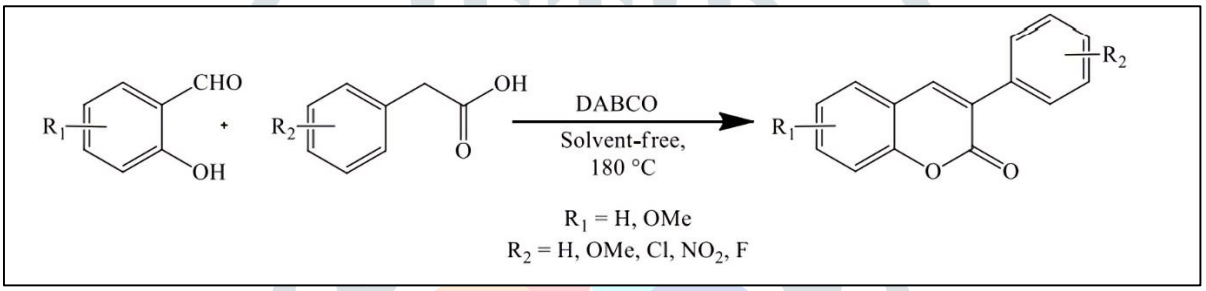
1.5 mmol in DMF at 110°C, yielding a 95% product yield. After optimization, reactions of substituted 2-hydroxybenzaldehydes with various phenylacetic acids were carried out to obtain the desired results corresponding 3-aryl coumarins.



Scheme 30. Efficient synthesis of 3-aryl coumarin derivatives in presence of N-methyl morpholine.

2.30 Solvent-free synthesis of 3-aryl coumarins in the presence of DABCO as the catalyst.

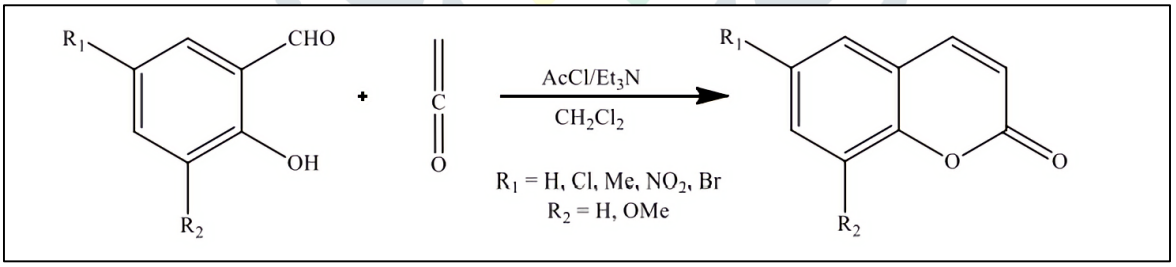
In the presence of 1,4-diazabicyclo [2.2.2] octane (DABCO), Rahmani-Nezhad et al. performed a solvent-free reaction between substituted salicylaldehydes and different phenylacetic acids to provide 3-aryl coumarins (Scheme 31) [90]. Changes in solvents (EtOH, MeOH, toluene, THF, DMF, and solvent-free), temperature, and DABCO quantity were used to optimize the reaction conditions. At 180°C, under solvent-free conditions, the highest yield of 90% was attained. Good to excellent yields (61–91%) were obtained when 3-aryl coumarins were synthesized.



Scheme 31. Solvent-free synthesis of 3-aryl coumarins in the presence of DABCO as the catalyst.

2.31Synthesis of substituted coumarin derivatives from salicylaldehydes and ketene.

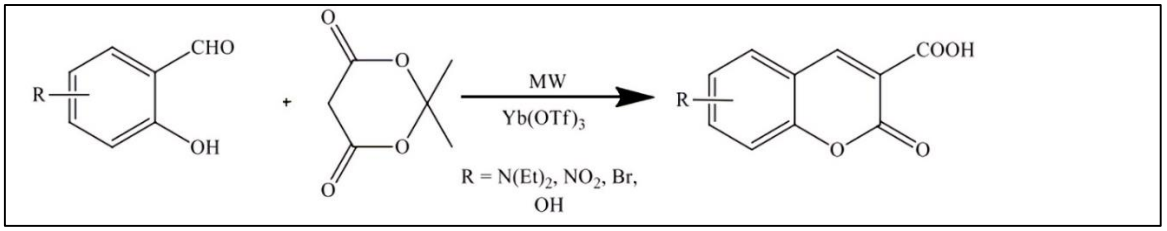
The synthesis of coumarin derivatives from various salicylaldehydes and ketene (Scheme 32) was described by Chandrasekhar and Kumar [91]. In the presence of trimethylamine, acetyl chloride, and DCM, all reactions were carried out. The yields of crude products ranged from 58 to 72 percent.



Scheme 32. Synthesis of substituted coumarin derivatives from salicylaldehydes and ketene.

2.32Solvent-free synthesis of coumarin-3-carboxylic acids under microwave irradiation.

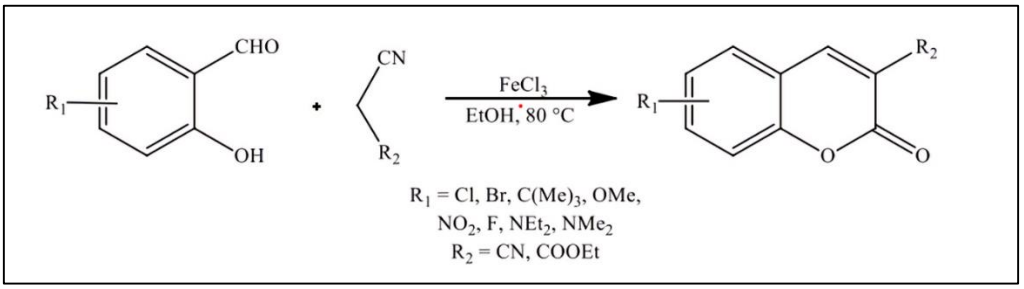
For the production of coumarin-3-carboxylic acids, Fiorito et al. established a technique [92]. Substituted salicylaldehydes and Meldrum's acid were used in this approach (Scheme 33). In the presence of ytterbium triflate (Yb (OTf)$_3$), reactions were carried out under microwave irradiation and in solvent-free conditions. Excellent yields (93–98%) are reported.



Scheme 33. Solvent-free synthesis of coumarin-3-carboxylic acids under microwave irradiation.

2.33 Synthesis of 3-substituted coumarins catalyzed by iron (III) chloride.

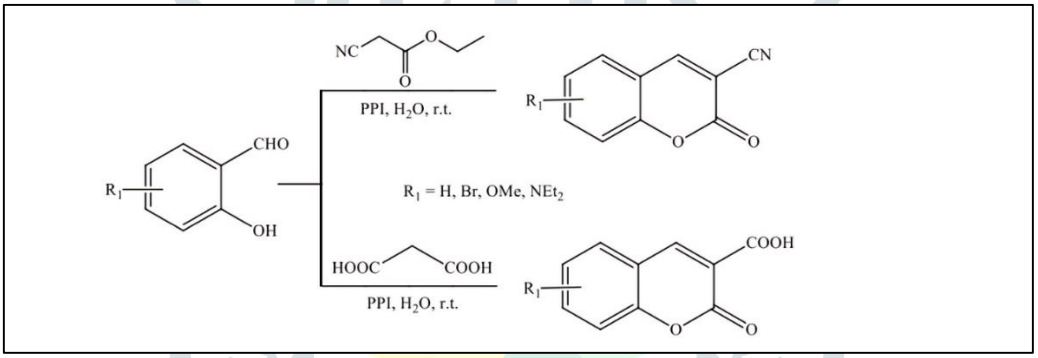
He et al. [34] described the synthesis of 3-substituted coumarins catalysed by iron (III) chloride. The optimal reaction conditions for salicylaldehydes and malononitrile were determined using a model reaction. Among the several solvents used in the reaction (MeOH, EtOH, MeCN, THF, DMF, H_2O, toluene, and DMSO), EtOH was chosen as the best because of the greatest yield (72 percent). Also investigated were reactions between substituted salicylaldehydes and malononitrile or ethyl 2-cyanoacetate (Scheme 34). The yields of ethyl 2-cyanoacetate were greater than those of malononitrile.



Scheme 34. Synthesis of 3-substituted coumarins catalyzed by iron (III) chloride.

2.34 Synthesis of 3-substituted coumarins in the presence of potassium phtalamide.

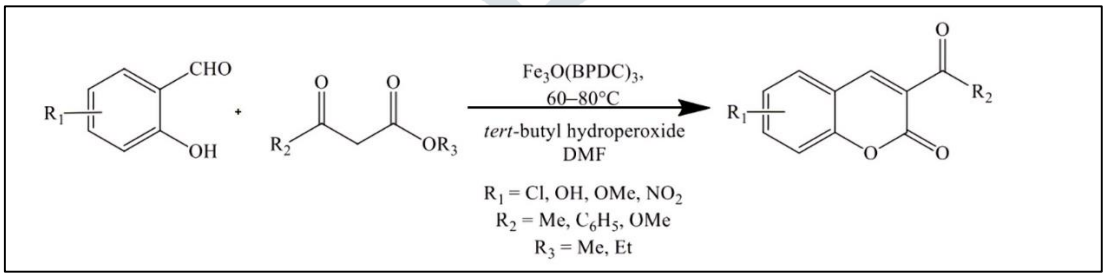
In the presence of potassium phtalamide (PPI), Kiyani and Daroonkala produced 3-substituted coumarins [93]. Initially, a model reaction was carried out to determine the best reaction conditions. Different catalysts (sodium ascorbate, sodium citrate, sodium tetraborate, K_2CO_3, Na_2CO_3, and PPI), solvents (EtOH, MeOH, MeCN, CH_2Cl_2, and water), and temperatures (room temperature, 50, 75, and reflux) were used in the reaction of salicylaldehydes and malononitrile. At room temperature, in the presence of PPI and water, the greatest yield of 92 percent was recorded. Substituted salicylaldehydes and malonic acid or ethyl 2-cyanoacetate reactions were carried out under optimum conditions (Scheme 35). The yields of the items produced ranged from 87 to 93 percent.



Scheme 35. Synthesis of 3-substituted coumarins in the presence of potassium phtalamide.

2.35 Synthesis of substituted coumarins catalysed by $Fe_3O(BPDC)_3$.

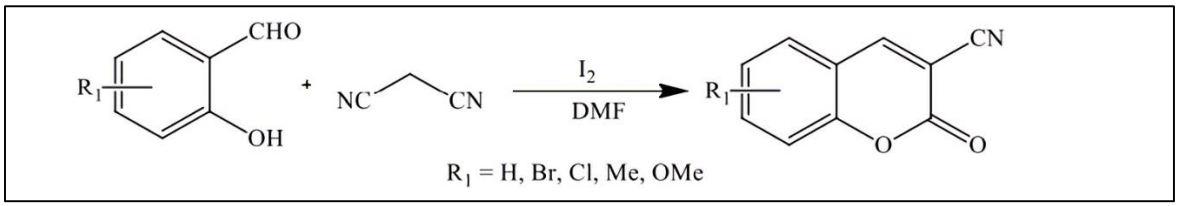
Lieu et al. [94] reported the synthesis of various coumarins catalysed by $Fe_3O(BPDC)_3$. The influence of temperature, solvent, catalyst concentration, reagent molar ratio, oxidant concentration and type, non-grinded and grinded $Fe_3O(BPDC)_3$ and other homogeneous catalysts were tested in order to determine the optimal reaction conditions. The synthesis of coumarins between different substituted salicylaldehydes and activated methylene compounds was carried out under optimal reaction conditions, as illustrated in Scheme 36.



Scheme 36. Synthesis of substituted coumarins catalyzed by $Fe_3O(BPDC)_3$.

2.36 Synthesis of 3-cyanocoumarins performed under heating and microwave conditions

Sharma and Makrandi synthesised 3-cyanocoumarins using microwave irradiation and heating conditions [95]. In DMF, 2-hydroxybenzaldehydes were reacted with malononitrile in the presence of iodine as a catalyst (Scheme 37). The yields of 3-cyanocoumarins synthesised under heating and microwave conditions were in the ranges of 80–92% and 85–95%, respectively.



Scheme 37. Synthesis of 3-cyanocoumarins performed under heating and microwave conditions.

The most widely documented coumarin derivative synthesis techniques are presented in Table 1,2,3,4,5. All described procedures produced substituted 2-oxo-2H-chromene-3-carboxylic acids in high to excellent yields (73–99%) (Table 1-5). Under microwave irradiation in the presence of Yb $(OTf)_3$, the greatest yields (93–98%) were produced using a solvent-free approach. Except for the technique done in the presence of sodium azide, which is poisonous, all of the techniques for the synthesis of 2-oxo-2H-chromene-3-carboxylic acids listed may be considered green. This approach can simply be substituted by the techniques indicated above due to the minor variations in acquired yields.

Table 1-5 lists ten techniques for the synthesis of substituted 2-oxo-2*H*-chromene-3-carbonitriles. The obtained products had a yield of 49–98 percent. Two environmentally friendly approaches should be mentioned: synthesis in a deep eutectic solvent and synthesis in water with choline chloride as a catalyst. Deep eutectic solvents, which serve as both a solvent and a catalyst, are called green solvents, and choline chloride is a biodegradable catalyst. The yields obtained using both approaches were good to exceptional.

Augustine and coworkers [75] stated that their process yielded high yields ranging from 85 to 98 percent. However, high temperatures and the use of hazardous propyl phosphonic anhydride and trimethylamine should be substituted with a technique that uses gentle reaction conditions. For the synthesis of substituted 3-acetyl-2H-chromen-2-ones, Table 1-5 lists four techniques. Under solvent-free conditions and ultrasonic irradiation, the best yields (92–96%) were produced in an ecologically friendly technique. In the synthesis of substituted ethyl 2-oxo-2*H*-chromene-3-carboxylates, piperidine, which possesses poisonous characteristics, was used in three different ways. These reactions yielded lesser yields than the procedures listed under moderate conditions.

Table 1. Comparison of methods for the synthesis of Substituted Substituted 2-oxo-2*H*-chromene-3-carbonitriles from aldehydes.

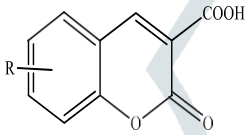
Coumarin Derivative	Reaction Conditions	Solvent	Catalyst	% Yield	Reference
 Substituted 2-oxo-2*H*-chromene-3-carboxylic acids	Microwave Irradiation	Solvent free	$Yb(OTf)_3$	93–98	[77]
	Stirring RT	Water	Potassium phtalamide (PPI)	87–90	[78]
	Stirring RT	Water	NaN3 K_2CO_3	73–93 78-99	[69]
	Ultrasound Irradiation	Water	NaN_3	80	[70]
	Reflux	Water	No-catalyst	95	[70]
	Stirring at Room Temperature	Lemon, pomegranate, grapefruit, carrot, tomato, kiwi and limoncello juice, vinegar, olive mil and buttermilk waste water	No-catalyst	91-99	[72]

Table 2. Comparison of methods for the synthesis of Substituted 2-oxo-2*H*-chromene-3-carbonitriles from aldehydes.

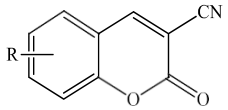
Coumarin Derivative	Reaction Conditions	Solvent	Catalyst	% Yield	Reference
 Substituted 2-oxo-2*H*-chromene-3-carbonitriles	Stirring, 25–30 ˚C	Water	Choline chloride	79–87	[66]
	Stirring, RT	Water	Potassium phtalamide (PPI)	89–93	[76]
	Ultrasound irradiation	Ethanol	Piperidine	49	[70]
	Reflux			50	[71]
	Stirring, 35–40 ˚C	Ethanol	$PhI(OAc)_2$	80–92	[34]
	Stirring, 80 ˚C	Ethanol	$FeCl_3$	72–93 *	[65]
	Stirring, 80 ˚C	Deep eutectic solvent	Deep eutectic solvent	73–92	[80]
	Reflux	Dimethylformamide	I_2	80–92	[80]
	Microwave Irradiation	Dimethylformamide	-	85-95	[75]
	Stirring at 120˚	Butyl acetate	Propyl phosphonic Anhydride T3P), trimethylamine (TEA)	85-95	[75]

Table 3. Comparison of methods for the synthesis of Substituted 3-acetyl-2H-chromen-2-ones from aldehydes.

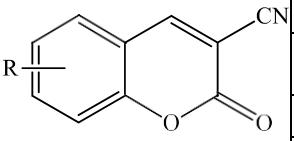
Coumarin Derivative	Reaction Conditions	Solvent	Catalyst	% Yield	Reference
 Substituted 3-acetyl-2H-chromen-2-ones	Ultrasound irradiation, 45 ˚C	Solvent-free	$MgFe_2O_4$ nanoparticles	92-96	[73]
	Stirring, 25–30 ˚C	Water	Choline chloride	90	[66]
	Stirring, 35–40 ˚C	Ethanol	$PhI(OAc)_2$	82-92	[71]
	Stirring, 60–80 ◦C, *tert*-butyl hydroperoxide	Dimethyl formamide	$Fe_3O(BPDC)_3$	65-96	[79]

Table 4. Comparison of methods for the synthesis of Substituted methyl Substituted methyl 2-oxo-2*H*-chromene-3-carboxylate from aldehydes.

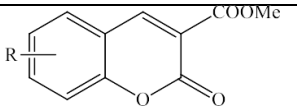
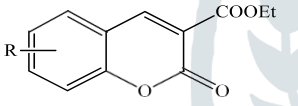
Coumarin Derivative	Reaction Conditions	Solvent	Catalyst	% Yield	Reference
 Substituted methyl 2-oxo-2H-chromene-3-carboxylate	Stirring, 2–30 ˚C	Water	Choline chloride	87–96	[66]
	Stirring, 120 ˚C	Butyl acetate	Polyphosphoric anhydride (T3P), trimethylamine (TEA)	94	[75]
	Stirring 60–80 ˚C, *tert*-butyl hydroperoxide	Dimethyl formamide	$Fe_3O(BPDC)_3$	28	[79]

Table 5. Comparison of methods for the synthesis of Substituted ethyl 2-oxo-2*H*-chromene-3-carboxylates from aldehydes

Coumarin Derivative	Reaction Conditions	Solvent	Catalyst	% Yield	Reference
 Substituted ethyl 2-oxo-2H-chromene-3-carboxylates	Ultrasound irradiation, 45 ˚C	Solvent-free	$MgFe_2O_4$ nanoparticles	88–93	[73]
	Stirring, 25–30 ˚C	Water	Choline chloride	91–92	[66]
	Stirring, RT	Ethanol	Piperidine, AcOH	67–83	[68]
	Stirring, 35–40 ˚C	Ethanol	$PhI(OAc)_2$	84–92	[71]
	Ultrasound irradiation	Ethanol	Piperidine, AcOH	60–88	[70]
	Reflux	Ethanol	Piperidine, AcOH	48–85	[34]
	Stirring, 80 ˚C	Ethanol	$FeCl_3$	70–95	[74]

III CONCLUSION

The medicinal properties of coumarin have been discovered due to their presence in different medicinal plants. Coumarin isolation process from those plants is time consuming and expensive and only small amounts of desired compounds can be obtained Therefore, the synthesis of these derivatives is a faster and, in some cases, "greener" way to obtain the desired compounds. Coumarins possess various biological activities and have a positive effect on human health. The purpose of this review was to present different methods of coumarin synthesis, both conventional and green ones. Syntheses from different starting compounds like aldehydes were described, in order to provide a deeper insight into the possibilities of their formation and offer the researchers dealing with this subject a range of different synthetic approaches. All of these syntheses have different reaction conditions. Different techniques such as heating, microwave and ultrasound irradiation were employed in coumarin synthesis. In addition, various solvents and catalysts were used in order to obtain coumarin derivatives in high yields. Some of catalysts and solvents are harmful and some have green character. In some cases, it has been shown that compounds obtained by green methods have higher yields than compound obtained with conventional methods. As it tends to reduce environmental pollution, there is an increasing interest in developing green methods and reducing the use of harmful compounds. During synthesis, it is important to reduce energy consumption, to avoid harmful substances and to obtain pure compounds in high yields. This comparison of reaction conditions and obtained yields of compounds will be useful to scientists in this field of work to develop new efficient methods.

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V. REFERANCES

[1] Nikhil, B.; Shikha, B.; Anil, P.; Prakash, N.B. Diverse pharmacological activities of 3-substituted coumarins:A review. *Int. Res. J. Pharm.* **2012**, *3*, 24–29.

[2] Kontogiorgis, C.; Detsi, A.; Hadjipavlou-Litina, D. Coumarin-based drugs: A patent review (2008–present). *Expert Opin. Ther. Pat.* **2012**, *22*, 437–454. [CrossRef]

[3] Venugopala, K.N.; Rashmi, V.; Odhav, B. Review on Natural Coumarin Lead Compounds for Their Pharmacological Activity. *BioMed Res. Int.* **2013**, *2013*, 1–14. [CrossRef] [PubMed]

[4] Prahadeesh, N.; Sithambaresan, M.; Mathiventhan, U. A Study on Hydrogen Peroxide Scavenging Activity and Ferric Reducing Ability of Simple Coumarins. *Emerg. Sci. J.* **2018**, *2*, 417–427. [CrossRef]

[5] Kulkarni, M.V.; Kulkarni, G.M.; Lin, C.-H.; Sun, C.-M. Recent advances in coumarins and 1-azacoumarins as versatile biodynamic agents. *Curr. Med. Chem.* **2006**, *13*, 2795–2818. [CrossRef] [PubMed]

[6] Bairagi, S.H.; Salaskar, P.P.; Loke, S.D.; Surve, N.N.; Tandel, D.V.; Dusara, M.D. Medicinal significance of coumarins: A review. *Int. J. Pharm. Res.* **2012**, *4*, 16–19.

[7] Thakur, A.; Singla, R.; Jaitak, V. Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. *Eur. J. Med. Chem.* **2015**, *101*, 476–495. [CrossRef]

[8] Seo, W.D.; Kim, J.Y.; Ryu, H.W.; Kim, J.H.; Han, S.-I.; Ra, J.-E.; Seo, K.H.; Jang, K.C.; Lee, J.H. Identification and characterisation of coumarins from the roots of *Angelica dahurica* and their inhibitory effects against cholinesterase. *J. Funct. Foods* **2013**, *5*, 1421–1431. [CrossRef]

[9] Bai, Y.; Li, D.; Zhou, T.; Qin, N.; Li, Z.; Yu, Z.; Hua, H. Coumarins from the roots of *Angelica dahurica* with antioxidant and antiproliferative activities. *J. Funct. Foods* **2016**, *20*, 453–462. [CrossRef]

[10] Iranshahi, M.; Kalategi, F.; Sahebkar, A.; Sardashti, A.; Schneider, B. New sesquiterpene coumarins from the roots of *Ferula flabelliloba*. *Pharm. Boil.* **2010**, *48*, 217–220. [CrossRef]

[11] Peng, W.-W.; Zheng, Y.-Q.; Chen, Y.-S.; Zhao, S.-M.; Ji, C.-J.; Tan, N.-H. Coumarins from roots of *Clausenaexcavata*. *J. Asian Nat. Prod. Res.* **2013**, *15*, 215–220. [CrossRef] [PubMed]

[12] Naseri, M.; Monsef-Esfehani, H.; Saeidnia, S.; Dastan, D.; Gohari, A. Antioxidative Coumarins from the Roots of *Ferulago subvelutina*. *Asian J. Chem.* **2013**, *25*, 1875–1878. [CrossRef]

[13] Joshi, K.R.; Devkota, H.P.; Yahara, S. Chemical Analysis of Flowers of *Bombax ceiba* from Nepal. *Nat. Prod. Commun.* **2013**, *8*, 583–584. [CrossRef]

[14] Sukumaran, S.; Kiruba, S.; Mahesh, M.; Nisha, S.; Miller, P.Z.; Ben, C.; Jeeva, S. Phytochemical constituents and antibacterial efficacy of the flowers of *Peltophorum pterocarpum* (DC.) Baker ex Heyne. *Asian Pac. J. Trop.Med.* **2011**, *4*, 735–738. [CrossRef]

[15] Kicel, A.; Wolbis, M. Coumarins from the flowers of *Trifolium repens*. *Chem. Nat. Compd.* **2012**, *48*, 130–132. [CrossRef]

[16] Joselin, J.; Brintha, T.S.S.; Florence, A.R.; Jeeva, S. Screening of select ornamental flowers of the family *Apocynaceae* for phytochemical constituents. *Asian Pac. J. Trop. Dis.* **2012**, *2*, S260–S264. [CrossRef]

[17] Wang, S.; Tang, F.; Yue, Y.; Yao, X.; Wei, Q.; Yu, J. Simultaneous Determination of 12 Coumarins in *Bamboo* Leaves by HPLC. *J. AOAC Int.* **2013**, *96*, 942–946. [CrossRef]

[18] Nguyen, P.-H.; Zhao, B.T.; Kim, O.; Lee, J.H.; Choi, J.S.; Min, B.S.; Woo, M.H. Anti-inflammatory terpenylated coumarins from the leaves of *Zanthoxylum schinifolium* with α-glucosidase inhibitory activity. *J. Nat. Med.* **2016**, *70*, 276–281. [CrossRef]

[19] Cho, J.-Y.; Hwang, T.-L.; Chang, T.-H.; Lim, Y.-P.; Sung, P.-J.; Lee, T.-H.; Chen, J.-J. New coumarins and anti-inflammatory constituents from *Zanthoxylum avicennae*. *Food Chem.* **2012**, *135*, 17–23. [CrossRef]

[20] Sakunpak, A.; Matsunami, K.; Otsuka, H.; Panichayupakaranant, P. Isolation of new monoterpene coumarins from *Micromelum minutum* leaves and their cytotoxic activity against *Leishmania major* and cancer cells. *FoodChem.* **2013**, *139*, 458–463. [CrossRef]

[21] Petrul'ová-Poracká, V.; Repcak, M.; Vilkova, M.; Imrich, J. Coumarins of *Matricaria chamomilla* L.: Aglycones and glycosides. *Food Chem.* **2013**, *141*, 54–59. [CrossRef] [PubMed]

[22] Aziz, S.S.S.A.; Sukari, M.A.; Rahmani, M.; Kitajima, M.; Aimi, N.; Ahpandi, N.J. Coumarins from *Murrayapaniculata* (Rutaceae). *Malays. J. Anal. Sci.* **2010**, *14*, 1–5.

[23] Sun, J.; Yue, Y.-D.; Tang, F.; Guo, X.-F. Coumarins from the leaves of *Bambusa pervariabilis* McClure. *J. AsianNat. Prod. Res.* **2010**, *12*, 248–251. [CrossRef] [PubMed]

[24] Li, Z.-L.; Li, Y.; Qin, N.-B.; Li, D.-H.; Liu, Z.-G.; Liu, Q.; Hua, H.-M. Four new coumarins from the leaves of *Calophyllum inophyllum*. *Phytochem. Lett.* **2016**, *16*, 203–206. [CrossRef]

[25] Razavi, S.M.; Imanzadeh, G.; Davari, M. Coumarins from *Zosima absinthifolia* seeds, with allelopatic effects. *Eur. Asian J. Biosci.* **2010**, *4*, 17–22. [CrossRef]

[26] Li, G.; Li, X.; Cao, L.; Zhang, L.; Shen, L.; Zhu, J.; Wang, J.; Si, J. Sesquiterpene coumarins from seeds of *Ferula sinkiangensis*. *Fitoterapia* **2015**, *103*, 222–226. [CrossRef] [PubMed]

[27] Li, G.; Wang, J.; Li, X.; Cao, L.; Lv, N.; Chen, G.; Zhu, J.; Si, J. Two new sesquiterpene coumarins from the seeds of *Ferula sinkiangensis*. *Phytochem. Lett.* **2015**, *13*, 123–126. [CrossRef]

[28] Dien, P.H.; Nhan, N.T.; Le Thuy, H.T.; Quang, D.N. Main constituents from the seeds of Vietnamese *Cnidium monnieri* and cytotoxic activity. *Nat. Prod. Res.* **2012**, *26*, 2107–2111.

[29] Dugrand, A.; Olry, A.; Duval, T.; Hehn, A.; Froelicher, Y.; Bourgaud, F.; Dugrand-Judek, A. Coumarin and Furanocoumarin Quantitation in Citrus Peel via Ultraperformance Liquid Chromatography Coupled with Mass Spectrometry (UPLC-MS). *J. Agric. Food Chem.* **2013**, *61*, 10677–10684. [CrossRef]

[30] Dhanavade, M.J.; Jalkute, C.B.; Ghosh, J.S.; Sonawane, K.D. Study antimicrobial activity of lemon (*Citrus lemon* L.) peel extract. *Br. J. Pharm. Toxicol.* **2011**, *2*, 119–122.

[31] Miyake, Y.; Hiramitsu, M. Isolation and extraction of antimicrobial substances against oral bacteria from lemon peel. *J. Food Sci. Technol.* **2011**, *48*, 635–639. [CrossRef]

[32] Sasidharan, S.; Chen, Y.; Saravanan, D.; Sundram, K.M.; Latha, L.Y. Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr. J. Tradit. Complement. Altern. Med.* **2011**, *8*, 1–10. [CrossRef] [PubMed]

[33] Vekariya, R.H.; Patel, H.D. Recent advances in the synthesis of coumarin derivatives via *Knoevenagel condensation*: A review. *Synth. Commun.* **2014**, *44*, 2756–2788. [CrossRef]

[34] He, X.; Yan, Z.; Hu, X.; Zuo, Y.; Jiang, C.; Jin, L.; Shang, Y. FeCl 3-Catalyzed Cascade Reaction: An EfficientApproach to Functionalized Coumarin Derivatives. *Synth. Commun.* **2014**, *44*, 1507–1514. [CrossRef]

[35] Asif, M. Pharmacologically potentials of different substituted coumarin derivatives. *Chem. Int.* **2015**, *1*, 1–11.

[36] Barot, K.P.; Jain, S.V.; Kremer, L.; Singh, S.; Ghate, M.D. Recent advances and therapeutic journey of coumarins: Current status and perspectives. *Med. Chem. Res.* **2015**, *24*, 2771–2798. [CrossRef]

[37] Dighe, N.S.; Pattan, S.R.; Dengale, S.S.; Musmade, D.S.; Shelar, M.; Tambe, V.; Hole, M.B. Synthetic and pharmacological profiles of coumarins: A review. *Sch. Res. Libr.* **2010**, *2*, 65–71.

[38] Abdou, M.M. 3-Acetyl-4-hydroxycoumarin: Synthesis, reactions and applications. *Arab. J. Chem.* **2017**, *10*, S3664–S3675. [CrossRef]

[39] Al-Ayed, A.S. Synthesis, Spectroscopy and Electrochemistry of New 3-(5-Aryl-4,5-Dihydro-1H-Pyrazol-3-yl)- 4-Hydroxy-2H-Chromene-2-One 4, 5 as a Novel Class of Potential Antibacterial and Antioxidant Derivatives. *Int. J. Org. Chem.* **2011**, *1*, 87–96. [CrossRef]

[40] Al-Majedy, Y.K.; Kadhum, A.A.H.; Al-Amiery, A.A.; Mohamad, A.B. Coumarins: The Antimicrobial agents. *Syst. Rev. Pharm.* **2017**, *8*, 62–70. [CrossRef]

[41] Aslam, K.K.; Khosa, M.K.; Jahan, N.; Nosheen, S. Short communication: Synthesis and applications of Coumarin. *Pak. J. Pharm. Sci.* **2010**, *23*, 449–454.

[42] Liu, H.; Ren, Z.-L.; Wang, W.; Gong, J.-X.; Chu, M.-J.; Ma, Q.-W.; Wang, J.-C.; Lv, X.-H. Novel coumarin- pyrazole carboxamide derivatives as potential topoisomerase II inhibitors: Design, synthesis and antibacterial activity. *Eur. J. Med. Chem.* **2018**, *157*, 81–87. [CrossRef] [PubMed]

[43] Sahoo, J.; Kumar, P.S.; Mekap, S.K. Synthesis, spectral characterization of some new 3-heteroaryl azo 4-hydroxy coumarin derivatives and their antimicrobial evaluation. *J. Taibah Univ. Sci.* **2015**, *9*, 187–195. [CrossRef]

[44] Vekariya, R.H.; Patel, K.D.; Rajani, D.P.; Rajani, S.D.; Patel, H.D. A one pot, three component synthesis of coumarin hybrid thiosemicarbazone derivatives and their antimicrobial evolution. *J. Assoc. Arab. Univ. Basic Appl. Sci.* **2017**, *23*, 10–19. [CrossRef]

[45] Basanagouda, M.; Shivashankar, K.; Kulkarni, M.V.; Rasal, V.P.; Patel, H.; Mutha, S.S.; Mohite, A.A. Synthesis and antimicrobial studies on novel sulfonamides containing 4-azidomethyl coumarin. *Eur. J. Med. Chem.* **2010**, *45*, 1151–1157. [CrossRef]

[46] Soni, J.N.; Soman, S.S. Reactions of coumarin-3-carboxylate, its crystallographic study and antimicrobial activity. *Pharma Chem.* **2014**, *6*, 396–403.

[47] Vyas, K.B.; Nimavat, K.S.; Jani, G.R.; Hathi, M.V. Synthesis and antimicrobial activity of coumarin derivatives metal complexes: An in vitro evaluation. *Orbital Electron. J. Chem.* **2009**, *1*, 183–192.

[48] Wei, Y.; Li, S.Q.; Hao, S.H. New angular oxazole-fused coumarin derivatives: Synthesis and biological activities. *Nat. Prod. Res.* **2018**, *32*, 1824–1831. [CrossRef]

[49] Al-Amiery, A.A.; Al-Majedy, Y.K.; Kadhum, A.A.H.; Mohamad, A.B. Novel macromolecules derived fromcoumarin: Synthesis and antioxidant activity. *Sci. Rep.* **2015**, *5*, 11825. [CrossRef]

[50] Matos, M.J.; Mura, F.; Vazquez-Rodriguez, S.; Borges, F.; Santana, L.; Uriarte, E.; Olea-Azar, C. Study of Coumarin-Resveratrol Hybrids as Potent Antioxidant Compounds. *Molecules* **2015**, *20*, 3290–3308. [CrossRef]

[51] Pérez-Cruz, K.; Moncada-Basualto, M.; Morales-Valenzuela, J.; Barriga-González, G.; Navarrete-Encina, P.; Núñez-Vergara, L.; Squella, J.; Olea-Azar, C.; Barriga, G. Synthesis and antioxidant study of new polyphenolic hybrid-coumarins. *Arab. J. Chem.* **2018**, *11*, 525–537. [CrossRef]

[52] Nagamallu, R.; Srinivasan, B.; Ningappa, M.B.; Kariyappa, A.K. Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 690–694. [CrossRef] [PubMed]

[53] Salem, M.A.I.; Marzouk, M.I.; El-Kazak, A.M. Synthesis and Characterization of Some New Coumarins within Vitro Antitumor and Antioxidant Activity and High Protective Effects against DNA Damage. *Molecules* **2016**, *21*, 249. [CrossRef] [PubMed]

[54] Anand, P.; Singh, B.; Singh, N. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. *Bioorg. Med. Chem.* **2012**, *20*, 1175–1180. [CrossRef] [PubMed]

[55] Bagheri, S.M.; Khoobi, M.; Nadri, H.; Moradi, A.; Emami, S.; Jalili-Baleh, L.; Jafarpour, F.; Moghadam, F.H.;Foroumadi, A.; Shafiee, A. Synthesis and Anticholinergic Activity of 4-hydroxycoumarin Derivatives Containing Substituted Benzyl-1,2,3-triazole Moiety. *Chem. Boil. Drug Des.* **2015**, *86*, 1215–1220. [CrossRef]

[56] Razavi, S.F.; Khoobi, M.; Nadri, H.; Sakhteman, A.; Moradi, A.; Emami, S.; Foroumadi, A.; Shafiee, A. Synthesis and evaluation of 4-substituted coumarins as novel acetylcholinesterase inhibitors. Eur. J. Med. Chem. 2013, 64, 252–259. [CrossRef]

[57] Chen, L.Z.; Sun, W.W.; Bo, L.; Wang, J.Q.; Xiu, C.; Tang, W.J.; Shi, J.B.; Zhou, H.P.; Liu, X.H. New arylpyrazoline-coumarins: Synthesis and anti-inflammatory activity. Eur. J. Med. Chem. 2017, 138, 170–181. [CrossRef]

[58] Pu, W.; Lin, Y.; Zhang, J.; Wang, F.; Wang, C.; Zhang, G. 3-Arylcoumarins: Synthesis and potent anti-inflammatory activity. Bioorg. Med. Chem. Lett. 2014, 24, 5432–5434. [CrossRef]

[59] Olmedo, D.; Sancho, R.; Bedoya, L.M.; López-Pérez, J.L.; Del Olmo, E.; Muñoz, E.; Alcami, J.; Gupta, M.P.; Feliciano, A.S. 3-Phenylcoumarins as Inhibitors of HIV-1 Replication. Molecules 2012, 17, 9245–9257. [CrossRef]

[60] Emami, S.; Dadashpour, S. Current developments of coumarin-based anti-cancer agents in medicinal chemistry. Eur. J. Med. Chem. 2015, 102, 611–630. [CrossRef]

[61] Keri, R.S.; Sasidhar, B.S.; Nagaraja, B.M.; Santos, M.A. Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents. Eur. J. Med. Chem. 2015, 100, 257–269. [CrossRef] [PubMed]

[62] Akoudad, S.; Darweesh, S.K.; Leening, M.J.; Koudstaal, P.J.; Hofman, A.; Van Der Lugt, A.; Stricker, B.H.; Ikram, M.A.; Vernooij, M.W. Use of Coumarin Anticoagulants and Cerebral Microbleeds in the General Population. Stroke 2014, 45, 3436–3439. [CrossRef] [PubMed]

[63] Hassan, M.Z.; Osman, H.; Ali, M.A.; Ahsan, M.J.; Ahsan, M.J. Therapeutic potential of coumarins as antiviral agents. Eur. J. Med. Chem. 2016, 123, 236–255. [CrossRef] [PubMed]

[64] Wijayabandara, M.D.J.; Choudhary, M.I.; Adhikari, A. Characterization of an anti-hyperglycemic coumarin from the fruits of Averrhoa. P. Ann. Sci. Sess. Fac. Med. Sci. 2015, 2.

[65] Keshavarzipour, F.; Tavakol, H. The synthesis of coumarin derivatives using choline chloride/zinc chloride as a deep eutectic solvent. J. Iran. Chem. Soc. 2016, 13, 149–153. [CrossRef]

[66] Phadtare, S.B.; Shankarling, G.S. Greener coumarin synthesis by Knoevenagel condensation using biodegradable choline chloride. Environ. Chem. Lett. 2012, 10, 363–368. [CrossRef]

[67] Mi, X.; Wang, C.; Huang, M.; Wu, Y.; Wu, Y. Preparation of 3-Acyl-4-arylcoumarins via Metal-Free Tandem Oxidative Acylation/Cyclization between Alkynoates with Aldehydes. J. Org. Chem. 2014, 80, 148–155. [CrossRef]

[68] Suljic´, S.; Pietruszka, J. Synthesis of 3-Arylated 3,4-Dihydrocoumarins: Combining Continuous Flow Hydrogenation with Laccase-Catalysed Oxidation. Adv. Synth. Catal. 2014, 356, 1007–1020. [CrossRef]

[69] Brahmachari, G. Room Temperature One-Pot Green Synthesis of Coumarin-3-carboxylic Acids in Water: A Practical Method for the Large-Scale Synthesis. ACS Sustain. Chem. Eng. 2015, 3, 2350–2358. [CrossRef]

[70] Pinto, L.D.S.; De Souza, M.V.N. Sonochemistry as a General Procedure for the Synthesis of Coumarins, Including Multigram Synthesis. Synthesis 2017, 49, 2677–2682.

[71] Khan, D.; Mukhtar, S.; Alsharif, M.A.; Alahmdi, M.I.; Ahmed, N. PhI(OAc) 2 mediated an efficient Knoevenagel reaction and their synthetic application for coumarin derivatives. Tetrahedron Lett. 2017, 58, 3183–3187. [CrossRef]

[72] Fiorito, S.; Taddeo, V.A.; Genovese, S.; Epifano, F. A green chemical synthesis of coumarin-3-carboxylic and cinnamic acids using crop-derived products and waste waters as solvents. Tetrahedron Lett. 2016, 57, 4795–4798. [CrossRef]

[73] Ghomi, J.S.; Akbarzadeh, Z. Ultrasonic accelerated Knoevenagel condensation by magnetically recoverable MgFe2O4 nanocatalyst: A rapid and green synthesis of coumarins under solvent-free conditions. Ultrason. Sonochem. 2018, 40, 78–83. [CrossRef] [PubMed]

[74] Sairam, M.; Saidachary, G.; Raju, B.C. Condensation of salicylaldehydes with ethyl 4, 4, 4-trichloro- 3-oxobutanoate: A facile approach for the synthesis of substituted 2H-chromene-3-carboxylates. Tetrahedron Lett. 2015, 56, 1338–1343. [CrossRef]

[75] Augustine, J.K.; Bombrun, A.; Ramappa, B.; Boodappa, C. An efficient one-pot synthesis of coumarins mediated by propylphosphonic anhydride (T3P) via the Perkin condensation. Tetrahedron Lett. 2012, 53, 4422–4425. [CrossRef]

[76] Chandrasekhar, S.; Kumar, H.V. ChemInform Abstract: An Expeditious Coumarin Synthesis via a “Pseudocycloaddition” Between Salicylaldehydes and Ketene. *Synth. Commun.* **2015**, *46*, 232–235. [CrossRef]

[77] Fiorito, S.; Genovese, S.; Taddeo, V.A.; Epifano, F. Microwave-assisted synthesis of coumarin-3-carboxylicacids under ytterbium triflate catalysis. *Tetrahedron Lett.* **2015**, *56*, 2434–2436. [CrossRef]

[78] Kiyani, H.; Daroonkala, M.D. A cost-effective and green aqueous synthesis of 3-substituted coumarins catalyzed by potassium phthalimide. *Bull. Chem. Soc. Ethiop.* **2015**, *29*, 449. [CrossRef]

[79] Lieu, T.N.; Nguyen, K.D.; Le, D.T.; Truong, T.; Phan, N.T.S. Application of iron-based metal–organic frameworks in catalysis: Oxidant-promoted formation of coumarins using Fe 3 O(BPDC) 3 as an efficient heterogeneous catalyst. *Catal. Sci. Technol.* **2016**, *6*, 5916–5926. [CrossRef].

[80] Sharma, D.; Makrandi, J.K. Iodine-mediated one-pot synthesis of 3-cyanocoumarins and 3-cyano-4-methylcoumarins. *J. Serb. Chem. Soc.* **2014**, *79*, 527–531. [CrossRef]