Sys Rev Pharm 2020; 11(6): 598 – 612
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

# Original and Innovative Advances in the Synthetic Schemes of Coumarin-Based Derivatives: A Review

Yasser Fakri Mustafa[1*], Moath Kahtan Bashir[2], Mahmood Khudhayer Oglah[3]
[1,2,3]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.
***Corresponding Author:** Yasser Fakri Mustafa
E-mail: Dr.yassermustafa@uomosul.edu.iq

*Article History:* *Submitted: 05.04.2020* *Revised: 11.05.2020* *Accepted: 21.06.2020*

ABSTRACT
Coumarin, a chemical nucleus, is award gifted from nature. This description is due to the versatile of its derivatives and the wide variety of their biological activities. Although many coumarins have been originally isolated from natural origins, there is a mounting interest in the past decades to synthesize the coumarins in the laboratory. Many synthetic routes have been documented named Perkin, Wittig, Pechmann, Claisen, Reformatsky, and Knoevenagel pathways. To maximize the yield, reduce the reaction period, minimize the side products, and make these reactions environmentally friend, several innovative approaches have been developed. These include the use of ultrasound, microwave, and solvent-free conditions to satisfy these goals. This review was focused on the traditional synthetic routes of coumarins and their innovative improvements as well as the benefits arising from the use of each of them.

**Keywords:** Coumarins, Synthesis, Traditional methods, Innovative advances, Comparison.

**Correspondence:**
Yasser Fakri Mustafa
Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq
E-mail: Dr.yassermustafa@uomosul.edu.iq

**DOI:** 10.31838/srp.2020.6.90



## INTRODUCTION

Coumarins reign their class term to 'Coumarou', which is the vulgarity name of the plant belongs to the *Fabaceae* family named tonka bean. The parent compound, coumarin itself, was novally isolated by Vogel at 1820 (1).

This class of natural products is highly publicized throughout the plant, animal, and microorganisms kingdoms (2). However, most natural coumarins are isolated from the higher plants especially those belong to *Rutaceae* and *Umbelliferae* families (3). In these families, coumarin-based derivatives can achieve towering levels in many plant parts including the roots, fruits, leaves, and stems. The ecological and seasonal variables can exert a considerable impact on the foundation of coumarins in these parts (4).

Some pharmacologically important coumarins as those shown in Figure 1 have been isolated from several microorganisms. For instance, aflatoxins and novobiocin were isolated from *Aspergillus* and *Streptomyces* species respectively (5,6).

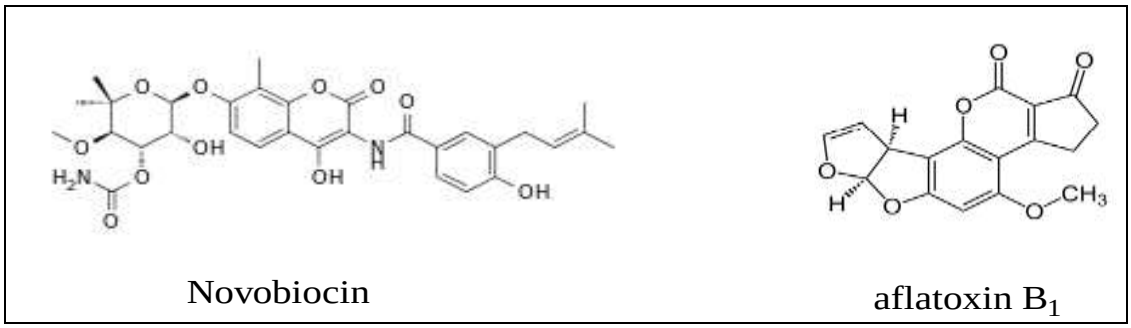



Figure 1: Natural coumarins isolated from microorganisms.

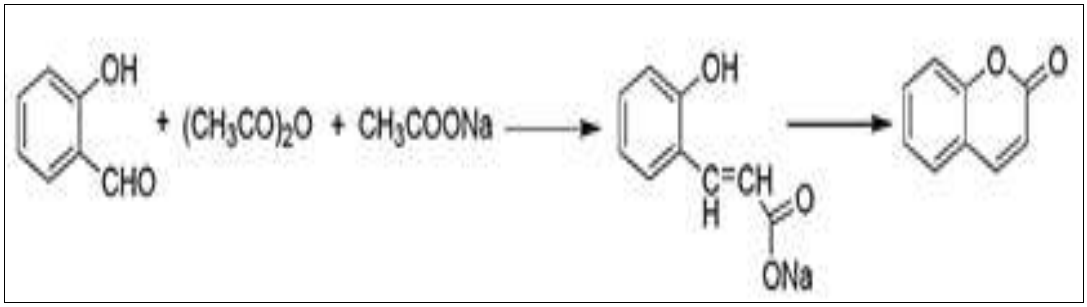
Coumarins with different structural characteristics may be useful in the management of various clinical conditions such as high protein edema (7), chronic infections (8,9), cancer (10–12), blood coagulation (13), oxidative stress (14), Alzheimer (15), and inflammation (16).

### Chemical synthesis of coumarin-based derivatives

Many routes for the synthesis of coumarins have been developed since now. These include the Perkin, Wittig, Pechmann, Claisen, Reformatsky, and Knoevenagel pathways (17).

### Perkin reaction

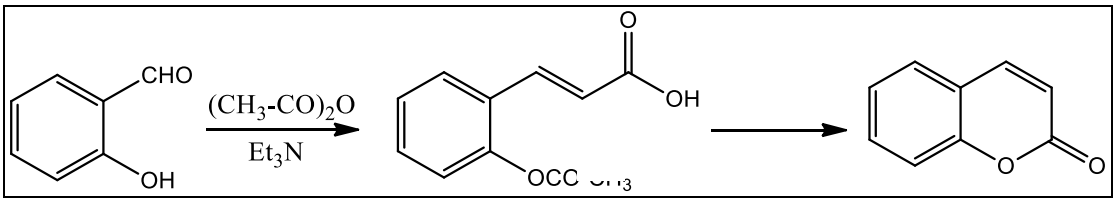
The chemical synthesis of coumarin was originally achieved by Perkin. In this reaction as displayed in Scheme 1, the coumarin-based derivative was generated from the heat-dependent reaction of acetic anhydride with salicylaldehyde utilizing a basic dry salt like sodium acetate. The reaction intermediate termed *orth*-hydroxycinnamic acid is afforded and spontaneously lactonized forming the target product (18).




Scheme 1: The synthetic pathway of coumarin developed by Perkin.

As for many chemical reactions, Perkin synthetic route has several advantages and disadvantages. The most important reported benefit is the improbability for the generation of structural isomer named chromane-based derivative as a side-product. The most significant failure of this reaction is the fakir yield that results from the generation of many side-products as a consequence of the applied temperature. However, this failure can be optimized by doubling the molar concentration of the employed anhydride at the expense of the aldehyde (19).

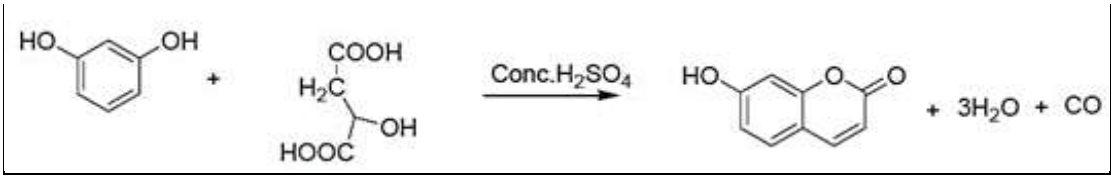
One of the most influential modifications of the Perkin reaction is showed in Scheme 2 and involved the utilization of tertiary amine instead of basic salt as a catalyst for the reaction involves acetic anhydride and salicylaldehyde (20).




Scheme 2: The influential modification of Perkin synthetic reaction.

Pechmann reaction

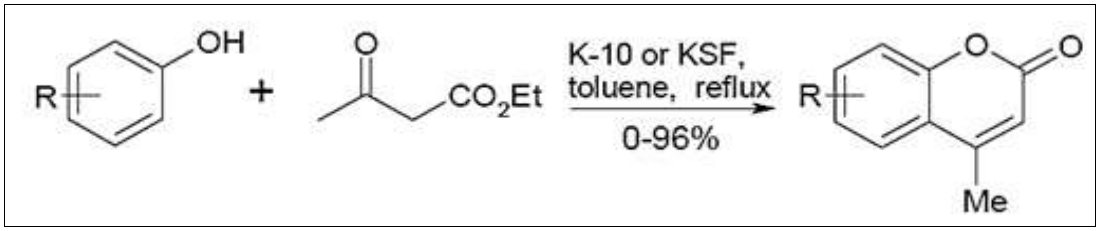
This reaction as shown in Scheme 3 implies the synthesis of coumarin-based derivative via the utilization of concentrated inorganic acid to catalyze the condensation of dicarboxylic acid-containing compound with phenolic derivative (21).




Scheme 3: The synthetic pathway of coumarin-based derivative developed by Pechmann.

It is reported that the Pechmann reaction is the most applicable synthetic route for the synthesis of coumarin-based derivatives that affords the target product in an encouraging yield. Pechmann reaction can be carried out by utilizing either homogeneous or heterogeneous acid catalyst. The first type may include inorganic acids such as trifluoroacetic, phosphoric, hydrochloric, and sulphuric acids, and Lewis acids such as aluminum, zinc, iron (III), titanium, and tin (IV) chlorides (22). The heterogeneous acid catalysts may include zeolite-HBEA, Nafion-H, cation-exchange resins, and other solid acids (23).

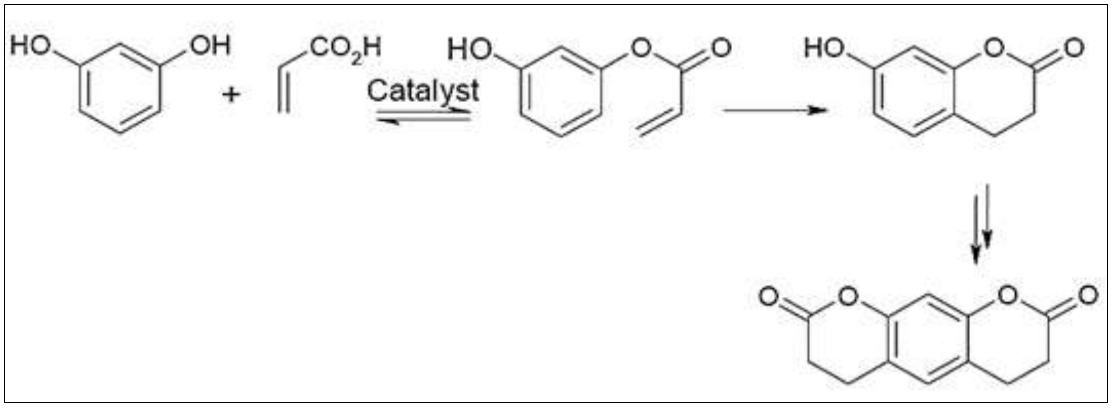
It is reported that the highest yield of the synthesized coumarin-based derivative as shown in Scheme 4 can be achieved via the Pechmann reaction facilitated by a solid catalyst like KSF or montmorillonite K-10. This procedure is cheaper and ecologically friendly than that involves the utilization of a homogenous acid catalyst (24). Concerning that issue, Zhan-Hui Zhang et al have reported three concerns; the first is the Pechmann reaction proceeds better with a heterogeneous acid catalyst than that belongs to the homogenous catalysts corresponding to the reaction yield and time. The second is that the KSF as a catalyst is less effective than montmorillonite K-10. The final one is that the heterogeneous catalysts have advanced characteristics such as the minimum ecological risk, facilitated separation of both the catalyst and product, and the possibility of reuse this catalyst for several times (25).




Scheme 4: The synthetic pathway of coumarins developed by Pechmann using a heterogeneous acid catalyst.

Concerning the utilization of the cation exchange resins as heterogeneous solid catalysts for Pechmann reaction, these catalysts such as Amberlite ir-120 and Zeokarb 225 offer several advantages. Among them are the cheapness, recycling, and facile separation of both the catalyst and product (26). Additionally, the reaction yield can be optimized by employing such resin in the w/w ratio of 30% to the aggregated weight of the reactants (27).

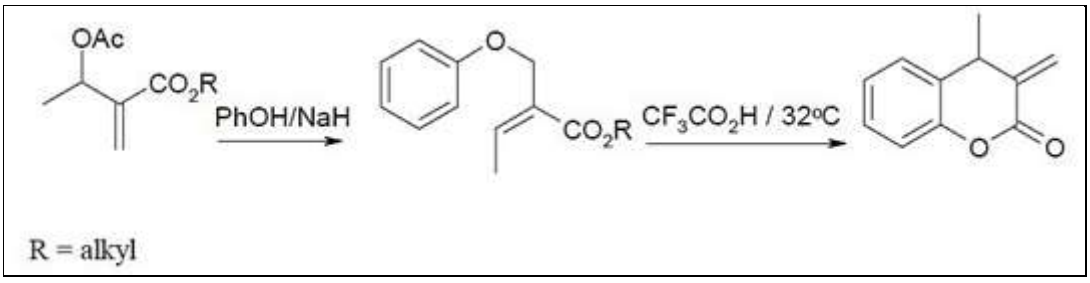
It has been reported that the synthesis of 7-hydroxycoumarin can be carried out by reacting the resorcinol with acrylic acid or its ester. The highest yield can be achieved by the employment of equimolar amounts of these reactants in the existence of Amberlyst-15 or zeolite H-beta [Si/Al=14] as a heterogeneous solid catalyst. The hypothesized mechanism as shown in Scheme 5 involves the esterification of the phenolic derivative to succeed with the lactonization affording the side-product termed chemically as 3,4,6,7-tetrahydrobenzo[1,2-b:5,4-b′] dipyran-2,8-dione in addition to the target dihydrocoumarin product (28).




Scheme 5: The hypothesized mechanism for the synthesis of dihydrocoumarin using a heterogeneous solid factor.

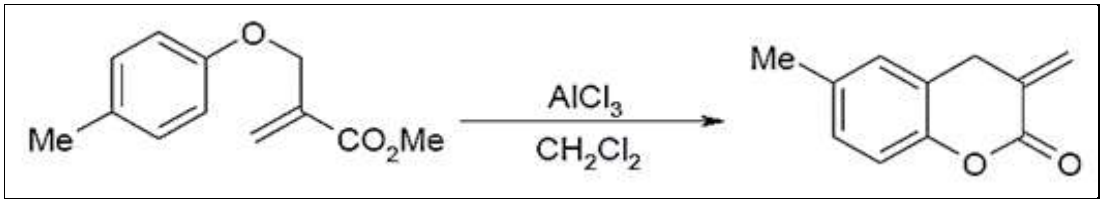
Claisen rearrangement

It has been reported that the synthesis of 3,4-dihydro-4-methyl-3-methylenecoumarin as shown in Scheme 6 can be performed via the Claisen rearrangement by reacting the aryl ether intramolecularly using a trifluoroacetic acid as a homogenous catalyst (29). Although this compound has been priorly prepared by others, Drewes and his co-workers have developed a novel synthetic method. This involved the *in situ* preparation of the intermediate termed chemically as 2-methylene-3-acetoxy alkylbutanoate by acetylating of what is called Baylis-Hillman product. The cyclization of this intermediate was facilitated by trifluoroacetic acid to give 86% yield of the target product in a one-pot technique (30).



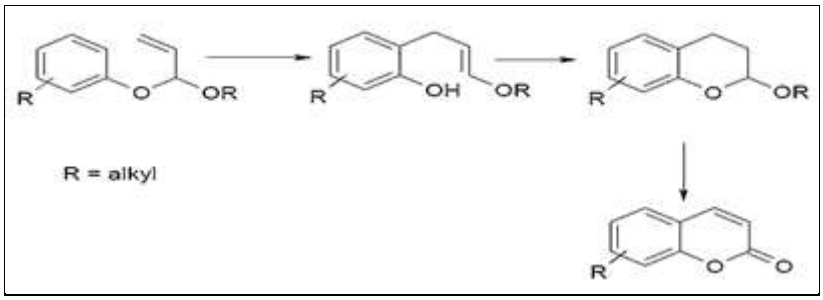

Scheme 6: The preparation of 3,4-dihydro-4-methyl-3-methylenecoumarin via Claisen reaction.

Previously, a comparable advancement for the synthesis of 3-methylenecoumarin has been documented. This synthesis involved the Claisen rearrangement of the reaction intermediate chemically termed as α-aryloxymethylacrylate ester in the presence of Lewis acid as shown in Scheme 7. The dimer may be afforded in a tiny amount in this reaction as a by-product and usually results from the high reactivity of the double bond of the aforementioned intermediate (31).




Scheme 7: The Lewis acid-catalyzed synthesis of 3-methylenecoumarin using a Claisen rearrangement.

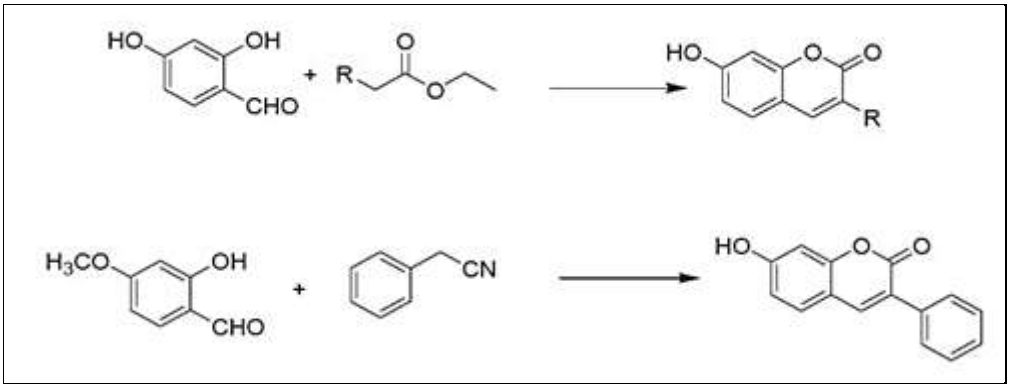
In an attempt to clobber the obstacles linked to the synthesis of coumarin-based derivatives via Pechmann reaction, a novel modification of the Claisen rearrangement has been reported. This modification as shown in Scheme 8 involved the utilization of aryl ethers conjugated via their oxygen with the double or triple bond (32). This modification was applied in case of failure of the formation of a coumarin-based derivative by ordinary Pechmann reaction. Considering its reaction mechanism, this modification proceeded through the transformation of the reactant to form an intermediate chemically termed as alkoxychroman, which is subsequently oxidized to coumarin-based derivative (33).




Scheme 8: The synthesis of coumarin derivative using oxygenated allyl or propargyl aryl ethers in a Claisen rearrangement reaction.

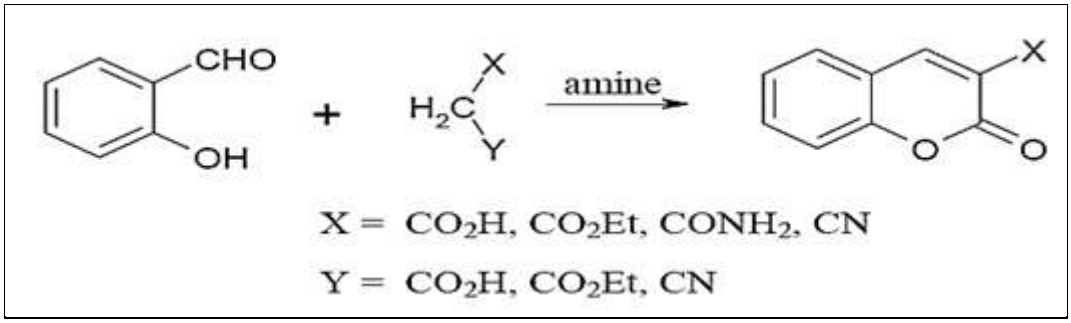
Knoevenagel reaction

It involved the synthesis of coumarin-based derivatives as shown in Scheme 9 by condensing orth-hydroxy aryl aldehydes with β-ketoester such as ethyl cyanoacetate, ethyl acetoacetate, and ethyl malonate utilizing an organic base like piperidine or pyridine as a catalyst (34).



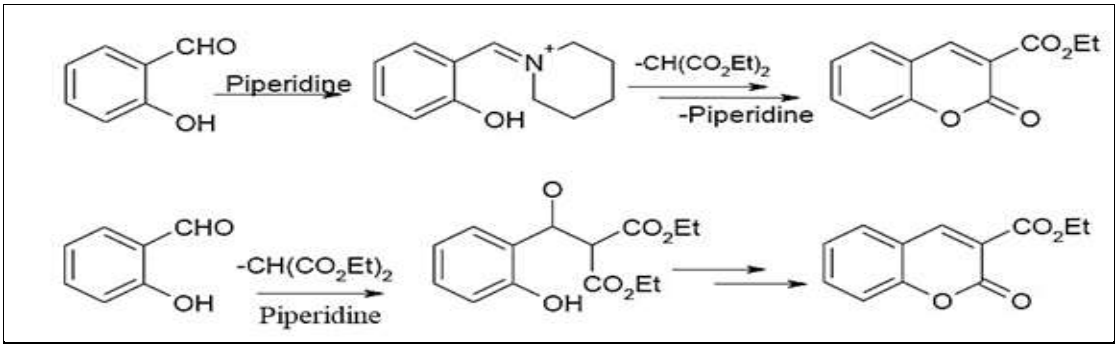

Scheme 9: Coumarin-based derivatives synthesized by Knoevenagel reaction.

The Knoevenagel reaction as represented in Scheme 10 is usually utilized to vanquish the collateral obstacles associated with the generation of coumarin-based derivatives by the employment of Perkin reaction. This is because the requirements of the Knoevenagel reaction are milder than those recommended in the Perkin reaction. Although a high number of coumarin-based derivatives have been synthesized by this preparative route, the same essential structural feature should be present in the reacting aryl aldehyde. This is the presence of the phenolic hydroxyl group ortho to the aldehyde. This electron-donating group directs the reaction toward the formation of a coumarin-based derivative rather than its corresponding cinnamic acid derivative (35).




Scheme 10: The general presentation of the Knoevenagel reaction.

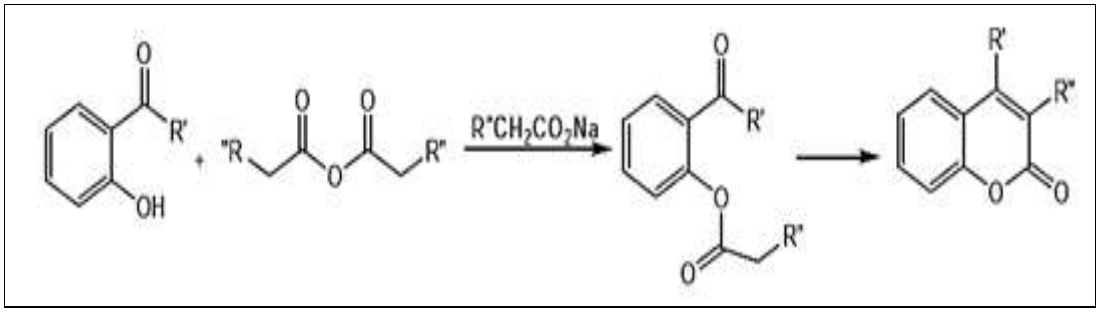
For Knoevenagel reaction, two different mechanisms as shown in Scheme 11 have been hypothesized (36). In the first hypothesized mechanism, the aryl aldehyde condenses with an organic base affording an imine or its iminium salt. At the same time, the enolate intermediate generates from the deprotonation of the active methylene-containing compound by the same organic base. Then, the last intermediate nucleophilically attacks the primary generated one eliminating the amine and cyclizing into a coumarin-based derivative. The second hypothesized mechanism initiates via the deprotonation achieved by organic base on the active methylene-containing compound and the subsequently formed a carbanion that attacks the carbonyl carbon of the aryl aldehyde. This attack is followed by the oncoming processes: the proton migration, the cycling of the ring, and the dehydration (37).




Scheme 11: The two hypothesized mechanisms of Knoevenagel coupling.

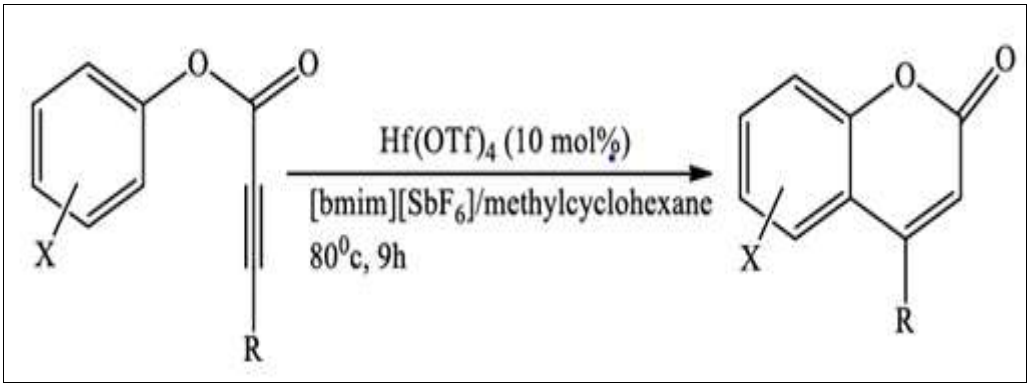
Kostanecki-Robinson coupling reaction

In this reaction as depicted in Scheme 12, the condensation of aliphatic anhydride with aryl ketone substituted at position 2 by hydroxyl group results in the generation of coumarin-based derivative functionalized at carbon number 3 or 4 (38,39).



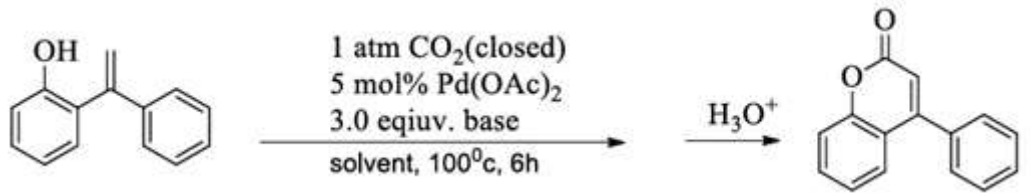

Scheme 12: The general synthetic route of coumarins by the Kostanecki-Robinson reaction.

Besides, several transition metals can be employed to mediate the synthesis of different coumarin-based derivatives. Song and his co-workers, for instance, have reported a two-phase reaction related to that of Kostanecki-Robinson. In which, 4-butyl-3-methylimidazolium bromide and $Hf(OTf)_4$ were utilized as phase transfer and metallic catalysts respectively. This reaction as shown in Scheme 13 resulted in a good yield of the target product named 4-phenylcoumarins (40).



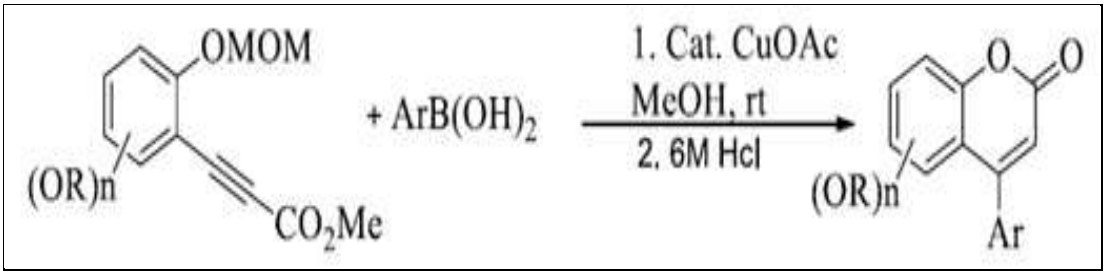

Scheme 13: The utilization of transition metal to mediate the synthesis of different coumarin-based derivatives via the Kostanecki-Robinson reaction.

Sasano and his co-workers have investigated a commensurate reaction as shown in Scheme 14 catalyzed by palladium metal. In this reaction, the isolable alkenylpalladium intermediate can be nucleophilically added to the environmental $CO_2$ affording the target coumarin-based derivative. Also, this reaction requires an enclosed atmosphere and heat-stable solvent (41).



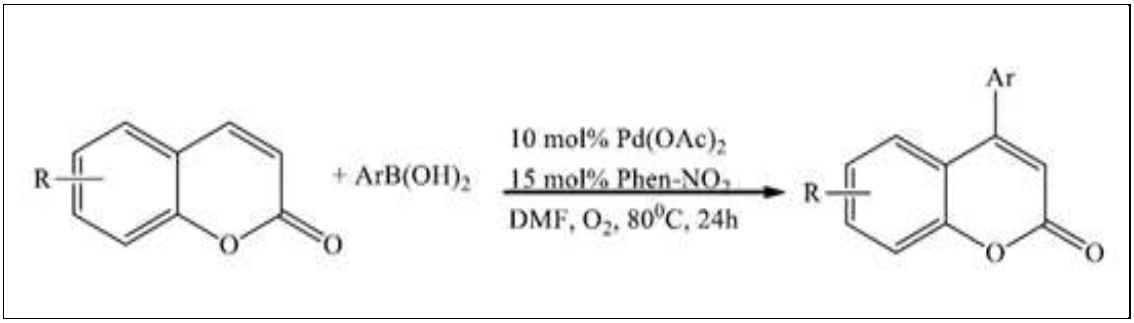

Scheme 14: The Pd-catalyzed synthetic pathway proposed by Sasano et al.

Also, it has been reported the possibility of the synthesis of coumarin-based derivative functionalized at position 4 with an aryl group as shown in Scheme 15. This reaction is catalyzed by copper (I) acetate and involved the condensation of boronic acid with an oxygen-protected methyl phenylpropiolate derivative (42).



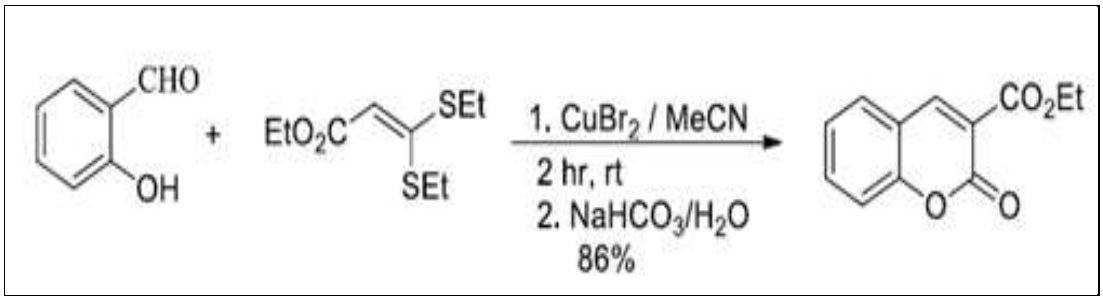

Scheme 15: The synthetic route of 4-arylcoumarins developed by Yamamoto and Kirai.

Recently, an efficient protocol was investigated by Wang et al and involved the preparation of coumarin-based derivatives functionalized at position 4 with aryl group as shown in Scheme 16. This protocol involved the reaction of coumarin-based derivative in the presence of metallic palladium with arylboronic acid. This protocol was successful when the aromatic ring of the coumarin nucleus functionalized by different electron-donating or -withdrawing groups (43).




Scheme 16: The synthetic route of 4-arylcoumarins developed by Wang et al.

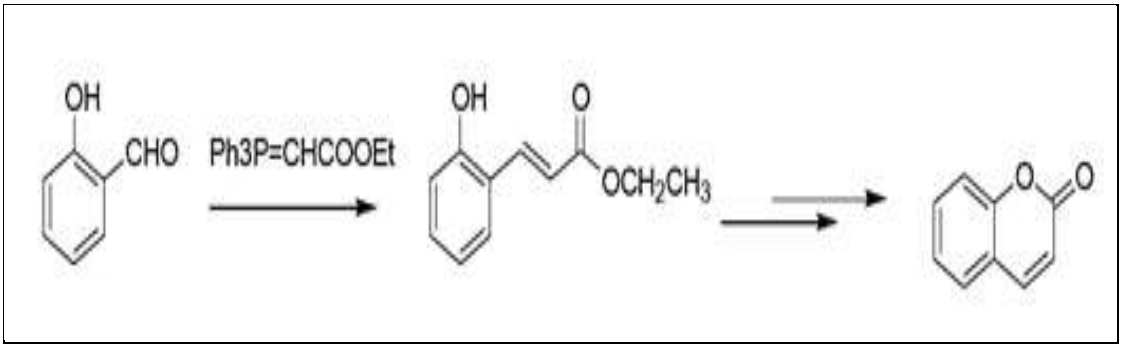
Analogue to this, Yuan et al have reported the preparation of coumarin-based derivative functionalized at position 3 by the substituent of different types as shown in Scheme 17 (44).




Scheme 17: The synthetic route of 3-substituted coumarin developed by Yuan et al.

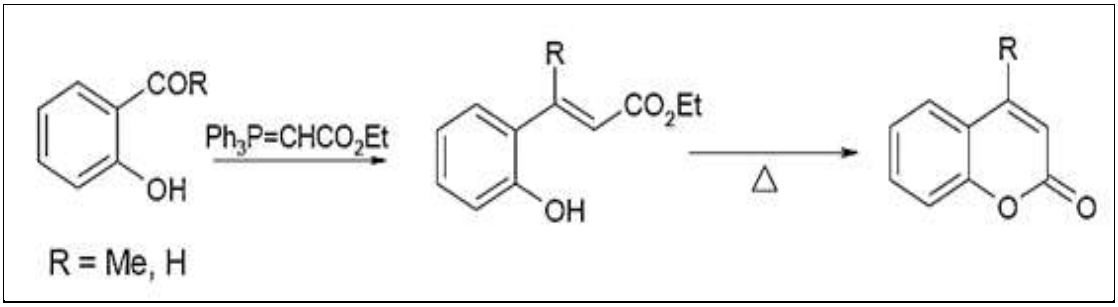
Wittig reaction

In this reaction, phosphonium ylide reacts with aryl aldehyde or aryl ketone as shown in Scheme 18 resulting in the generation of conjugated alkene, which is transformed into coumarin-based derivative by one of the oncoming reaction intermediates: oxaphosphetane or betaine (45). On the basis of Witting reaction, many synthetic coumarin-based derivatives were prepared (46). Also, some natural coumarin-based derivatives were naturally synthesized depending on the basis of this reaction especially those belonged to the prenylated and allylated classes of coumarins (47).



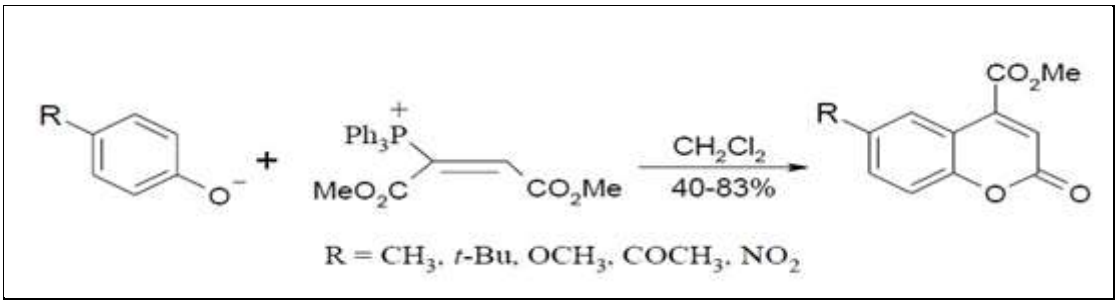

Scheme 18: The general synthetic route of coumarins by Wittig reaction.

It is documented that the coumarin-based derivatives functionalized at position 4 can be prepared via Witting reaction as shown in Scheme 19. This was carried out by coupling aryl aldehyde or aryl ketone substituted at ortho position with a phenolic hydroxyl group and the stable phosphorene like (carboxymethyl)triphenylphosphonium bromide ethyl ester (48).




Scheme 19: The synthetic route of coumarins as reported by Hepwarh et al.

A novel advancement in the synthesis of coumarin-based derivatives functionalized at position 4 with carboxymethyl group was dependent on the aromatic electrophilic substitution reaction. This advancement as shown in Scheme 20 involved the formation of betaine intermediate by condensing the dimethyl acetylenedicarboxylate and stable triphenylphospine (49). This intermediate was then reacted with phenoxide-containing compound to afford the target product (50). Comparing with the other methods for the synthesis of coumarin-based derivatives, this advancement offers a very efficient technique for the synthesis of coumarins substituted by acid- or base-susceptible groups (51).



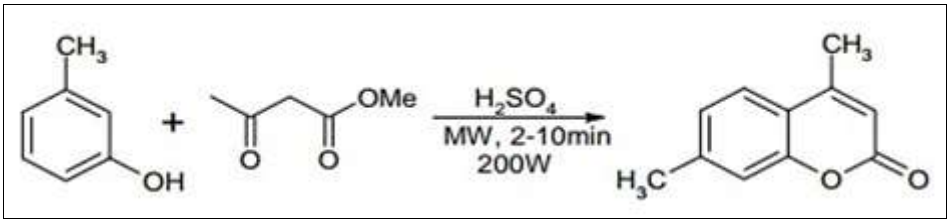

Scheme 20: The synthetic route of coumarins as reported by Yavari et al.

Innovative advancements for the synthesis of coumarins

Microwave-helped synthesis

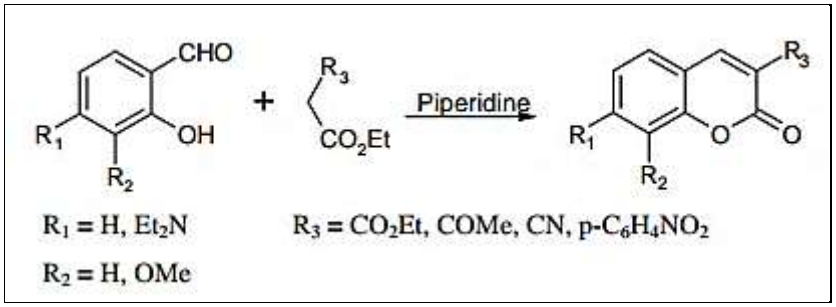
In comparison with the conventional methods of heating, microwave irradiation has revealed many benefits such as the potential inner heating that results in a marked reduction in the time required for the reaction to be finished, in addition to being an ecologically benign source of energy (52). Also, the use of microwaves to evoke the chemical reactions may reveal a high % yield due to the dropping in the possibilities of the unwanted side reactions. Accordingly, this type of heating can be considered as a part of the global trend toward the application of green chemistry (53).

It has been reported the utilization of a microwave-helped Pechmann reaction can offer an efficient technique to synthesize coumarin-based derivatives in a fast, simple, economically working method. For instance, the synthesis of 4,7-dimethylcoumarin as shown in Scheme 21 from the condensation of *m*-cresol and ethyl acetoacetate utilizing $H_2SO_4$ as a homogenous acid catalyst (54).



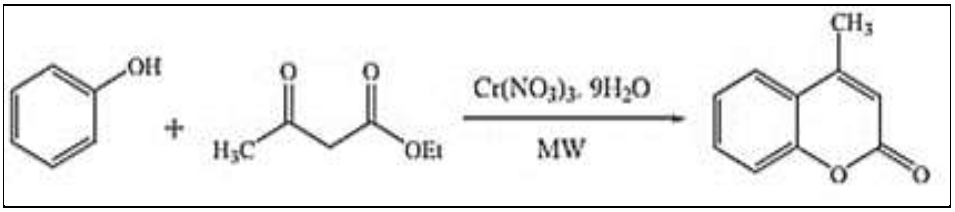

Scheme 21: The synthesis of 4,7-dimethylcoumarin via microwave-helped Pechmann reaction.

It has been shown that the utilization of microwave irradiation as a source of energy may rise the possibility of getting up the ideal %yield. For instance, the microwave-helped synthesis of trisubstituted coumarin-based derivatives as shown in Scheme 22 by reacting different carboxylic ester- and salicylaldehyde-based derivatives. This condensation is usually performed in a solvent-free environment and catalyzed by an organic base (55).



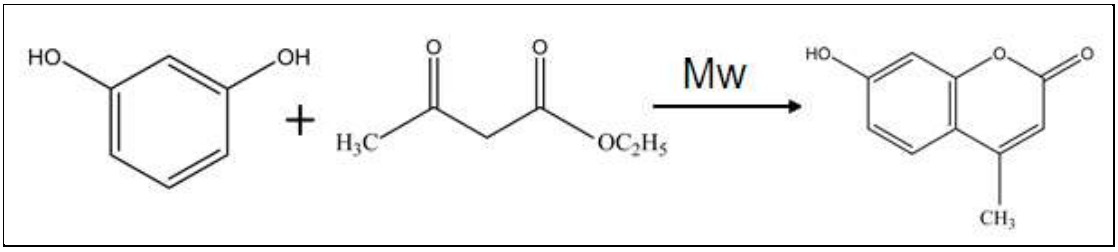

Scheme 22: The microwave-helped synthesis of coumarins as reported by Bogdal.

To investigate the ability of $Cr(NO_3)_3.9H_2O$ to act as an efficient catalyst in the microwave-helped Pechmann condensation, the reaction as shown in Scheme 23 of the ethyl acetoacetate and phenol was chosen as a model. It is indicated that, under microwave irradiation, the use of a very small amount of this catalyst (10 mmol) can dynamically promote the finishing of the reaction in several minutes. Unfortunately, this type of reaction used the aforementioned conditions was failed to prepare coumarin-based derivatives functionalized with electron-withdrawing group(s) at the benzene component of the coumarin frame (56).




Scheme 23: The microwave-helped Pechmann condensation catalyzed by $Cr(NO_3)_3.9H_2O$.

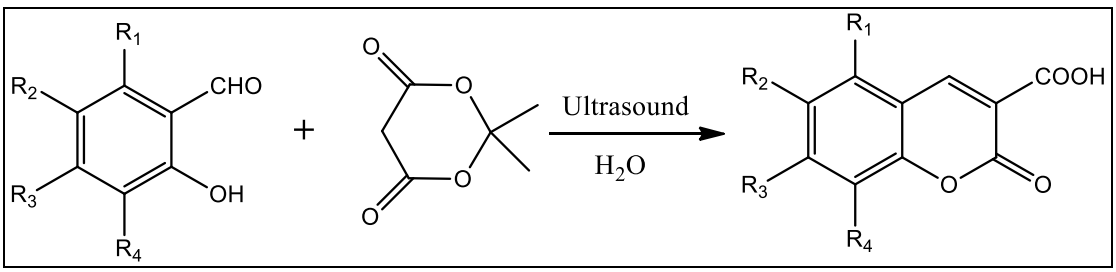
Latterly, the microwave-helped Pechmann condensation reaction catalyzed by $Cr(NO_3)_3.9H_2O$ was investigated by using the reaction of the ethyl acetoacetate and resorcinol as a reaction model as shown in Scheme 24 (52).




Scheme 24: Pechmann condensation catalyzed by a microwave irritation.

Ultrasound-helped synthesis

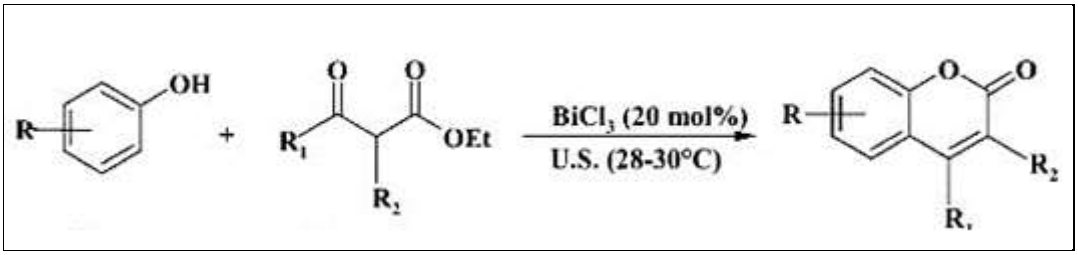
The utilization of ultrasound radiation has been grown for organic chemistry in the last three decades. This may be attributed to the efficiency and ease of monitoring this type of energy. In the literature, it seems to find a huge number of scientific papers utilized this type of energy to facilitate many synthetic pathways (57,58). Although most of these reactions were carried out by utilizing organic solvents, there are many attempts to replace these organic solvents with water. These attempts were evoked by the desirable properties of water such as the availability, cheapness, safety, and ecologically friended compound. For instance, the ultrasound-helped synthesis of tetrasubstituted coumarin-3-carboxylic acid derivatives performed in an aqueous medium as shown in Scheme 25 (59,60).




Scheme 25: The ultrasound-helped synthesis of tetrasubstituted coumarin-3-carboxylic acid derivatives.

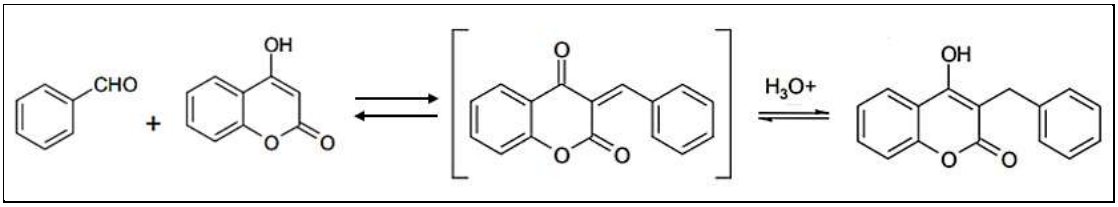
As Lewis acid catalysts, the bismuth-related products have been characterized by their reasonable safety, cost, and stability (61). Recently, they have regarded as potential catalysts for various organic transformations including those that contributed to the synthesis of coumarin-based derivatives (62). In this context, it is documented that the utilization of this type of catalyst for the reactions operated and performed under ultrasound radiation has been reported in many types of reactions including brominating reaction (63) and Heck reaction (64).

For instance, the condensation shown in Scheme 26 between the β-ketoester derivatives and phenol-based products utilizing $BiC1_3$ and ultrasound as a catalyst and source of energy, respectively (38,62).



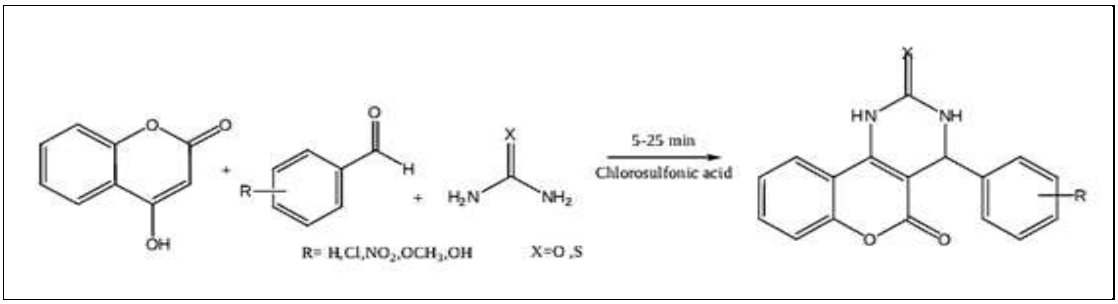

Scheme 26: The sonication reaction catalyzed by $BiC1_3$.

Another example is the reaction shown in Scheme 27 between the coumarin substituted at position 4 with a hydroxyl group and benzaldehyde. This ultrasound-helped reaction performed in an aqueous environment at 40°C for 90 minutes to afford the target product in a very high percent (88%) (65).



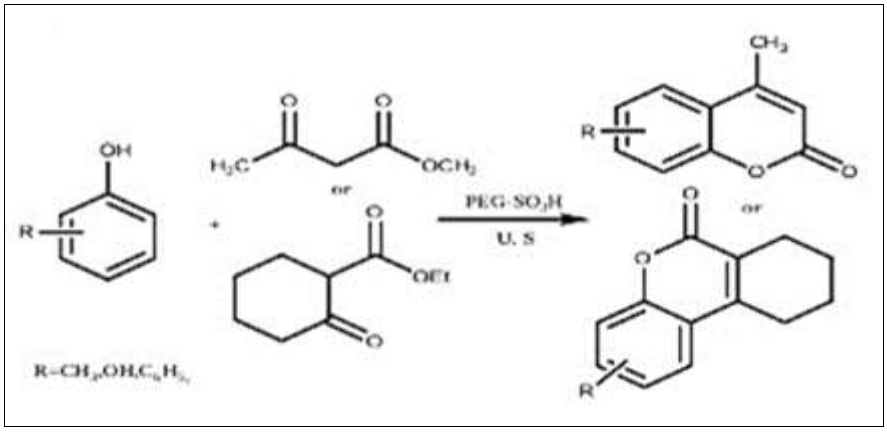

Scheme 27: The reaction between benzaldehyde and hydroxycoumarin as investigated by Palmisano et al.

The efficient and simple synthesis of pyranopyrimidine derivatives as shown in Scheme 28 using chlorosulfonic acid as a catalyst under ultrasound radiation was developed to further functionalize these nitrogen-heterocycles with another moiety that is recognized for its numerous useful properties (66).



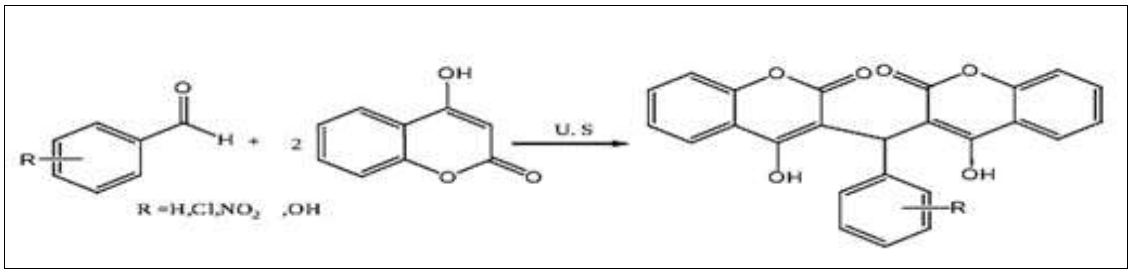

Scheme 28: The ultrasound-helped one-pot synthesis of pyranopyrimidine derivatives.

The synthesis of coumarin-based derivatives can also be performed by utilizing PEG-$SO_3H$ as a catalyst. For instance, the ultrasound-helped reaction shown in Scheme 29 between the active methylene compounds and phenol-related products (67).




Scheme 29: The ultrasound-helped synthesis of coumarins utilizing PEG-$SO_3H$ as a catalyst.

The ultrasound-helped synthesis of biscoumarin derivatives performed in an aqueous medium was investigated efficiently in many scientific papers (68). To further functionalize these derivatives, many attempts have been initiated to achieve this goal by reacting two moles of hydroxycoumarins with one mole of aldehydes in an aqueous environment. One of the most successful trials involved the utilization of ultrasound radiation in a catalyst-free methodology as shown in Scheme 30 (69).

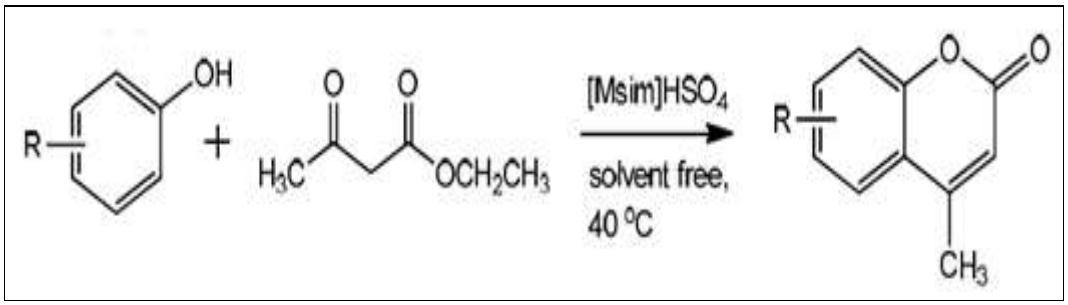



Scheme 30: The ultrasound-helped reaction for the functionalization of biscoumarin derivatives.

Solvent-free synthesis

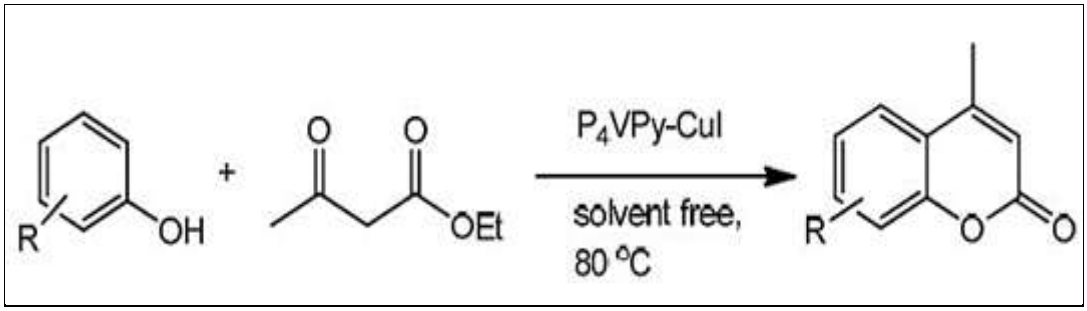
The traditional way of carrying out the organic reactions requires the use of toxic organic solvents. Owing to their volatile and toxic features, nowadays many efforts are being made by the scientific community to make these reactions solvent-free (70).

It is reported the possibility of synthesizing coumarin-based derivatives via a green methodology from the reaction of the phenol-based product and β-keto esters. This solvent-free reaction as shown in Scheme 31 was facilitated by [Msim] $HSO_4$ and carried out at 40°C. Also, this methodology offered the recycling of the employed catalyst for several times without any potential influence on its catalytic activity (71).



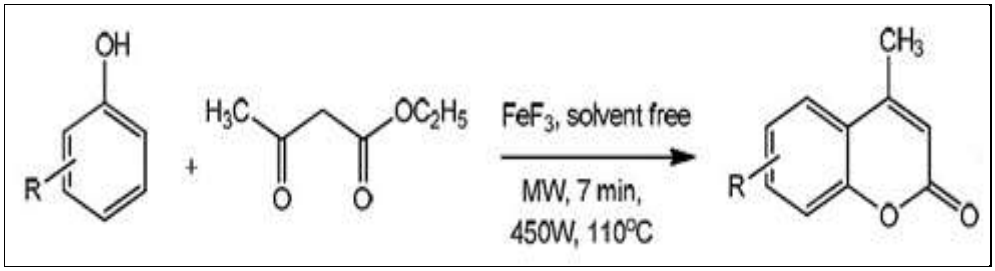

Scheme 31: The synthesis of disubstituted coumarin-based derivatives in solvent-free conditions.

In a scientific paper reported by Jalal et al, the synthesis of disubstituted coumarin-based derivatives was investigated under a solvent-free environment utilizing a specific catalyst chemically named poly (4-vinylpyridine)-CuI. This reaction as shown in Scheme 32 was designed to involve this catalyst as well as the phenol-related products and ethyl acetoacetate (72).




Scheme 32: The use of poly (4-vinylpyridine)-CuI as a catalyst for the Pechmann reaction.

Alternatively, it is reported the use of $FeF_3$ instead of poly (4-vinylpyridine)-CuI to facilitate the solvent-free synthesis of coumarin-based derivatives. This microwave-helped reaction as shown in Scheme 33 was performed at a high temperature but afforded a high yield (73).




Scheme 33: The use of $FeF_3$ as a catalyst for the Pechmann reaction.

## CONCLUSION

There are many synthetic routes for the preparation of coumarin-based derivatives such as Perkin, Wittig, Pechmann, Claisen, Reformatsky, and Knoevenagel pathways. Although these aforementioned reactions have been utilized for several decades, new advancements such as microwave-, ultrasound-helped, and solvent-free were applied in an attempt to maximize the percentage of yield, short the reaction time, and reduce the side reactions as well as making these reactions more ecologically benign. This review concluded that these advancements can play a mounting role in the synthesis of coumarin-based derivatives by modifying the undesirable conditions associated with the traditional synthetic routes.

## ACKNOWLEDGEMENTS

The authors are grateful to the College of Pharmacy/University of Mosul for the assistance provided by its colleagues to ameliorate the quality of this report.

## CONFLICT OF INTEREST

The authors reported that there are no conflicts of interest.

## REFERENCES

1. Mohammed ET, Mustafa YF. Coumarins from Red Delicious Apple Seeds : Extraction , Phytochemical Analysis , and Evaluation as Antimicrobial Agents. Syst Rev Pharm. 2020;11(2):64–70.
2. Khalil RR, Mustafa YF. Phytochemical , Antioxidant and Antitumor Studies of Coumarins Extracted from Granny Smith Apple Seeds by Different Methods. Syst Rev Pharm. 2020;11(2):57–63.
3. Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity. Biomed Res Int. 2013;2013.
4. Mustafa YF, Najem MA, Tawffiq ZS. Coumarins from Creston apple seeds: Isolation, chemical modification, and cytotoxicity study. J Appl Pharm Sci. 2018;8(8):049–56.
5. Barot KP, Jain S V., Kremer L, Singh S, Ghate MD. Recent advances and therapeutic journey of coumarins: Current status and perspectives. Vol. 24, Medicinal Chemistry Research. 2015. p. 2771–98.
6. Bashir MK, Mustafa YF, Oglah MK. Antitumor, antioxidant, and antibacterial activities of glycosyl-conjugated compounds: A review. Syst Rev Pharm. 2020;11(4):175–87.
7. Nejres AM, Mustafa YF, Aldewachi HS. Evaluation of natural asphalt properties treated with egg shell waste and low density polyethylene. Int J Pavement Eng [Internet]. 2020;0(0):1–7. Available from: https://doi.org/10.1080/10298436.2020.1728534
8. Mustafa YF, Khalil RR, Mohammed ET. Antimicrobial Activity of Aqueous Extracts Acquired from the Seeds of Two Apples ' Cultivars. Syst Rev Pharm. 2020;11(2):382–7.
9. Mustafa YF. Synthesis, characterization and antibacterial activity of novel heterocycle, coumacine, and two of its derivatives. Saudi Pharm J [Internet]. 2018;26(6):870–5. Available from: https://doi.org/10.1016/j.jsps.2018.03.010
10. Mustafa YF. Synthesis, characterization and preliminary cytotoxic study of sinapic acid and its analogues. J Glob Pharma Technol. 2019;11(9):1–10.
11. Oglah MK, Mustafa YF. Synthesis , Antioxidant , and Preliminary Antitumor Activities of New curcumin Analogues. J Glob Pharma Technol. 2020;12(2):854–

62.
12. Mustafa YF, Mohammed ET, Khalil RR. Antioxidant and Antitumor Activities of Methanolic Extracts Obtained from Red Delicious and Granny Smith Apples ' Seeds. Syst Rev Pharm. 2020;11(4):570–6.
13. Yasser Fakri Mustafa. Synthesis of new coumarin derivatives with suspected anticoagulant activity. Iraqi J Pharm. 2011;12(1):20–32.
14. Oglah MK, Mustafa YF, Bashir MK, Jasim MH. Curcumin and its derivatives: A review of their biological activities. Syst Rev Pharm. 2020;11(3):472–81.
15. Mahmood AAJ, Mustafa YF, Abdulstaar M. New coumarinic azo-derivatives of metoclopramide and diphenhydramine: Synthesis and in vitro testing for cholinesterase inhibitory effect and protection ability against chlorpyrifos. Int Med J Malaysia. 2014;13(1):3–12.
16. Mustafa YF, Oglah MK, Bashir MK. Conjugation of sinapic acid analogues with 5- Fluorouracil: Synthesis, preliminary cytotoxicity, and release study. Syst Rev Pharm. 2020;11(3):482–9.
17. Detsi A, Kontogiorgis C, Hadjipavlou-Litina D. Coumarin derivatives: an updated patent review (2015-2016). Expert Opin Ther Pat [Internet]. 2017;27(11):1201–26. Available from: http://dx.doi.org/10.1080/13543776.2017.1360284
18. Kumar KA, Nagamallu R, Govindappa VK. Comprehensive review on coumarins : Molecules of potential chemical and pharmacological interest Comprehensive review on coumarins : Molecules of potential chemical and pharmacological interest. J Chem Pharm Res. 2015;7(9):67–81.
19. Melita Lonˇcari´c, Dajana Gašo-Sokaˇc SJ and MM. Recent Advances in the Synthesis of Coumarin Derivatives from Di erent Starting Materials. Biomolecules. 2020;10(151).
20. Jadhav NH, Sakate SS, Rasal NK, Shinde DR, Pawar RA. Heterogeneously Catalyzed Pechmann Condensation Employing the Tailored Zn 0.925 Ti 0.075 O NPs: Synthesis of Coumarin. ACS Omega. 2019;4(5):8522–7.
21. Oglah MK, Mustafa YF. Curcumin analogs: synthesis and biological activities. Med Chem Res. 2020;29(3):479–86.
22. Weng KG, Yuan YL. Synthesis and evaluation of coumarin derivatives against human lung cancer cell lines. Brazilian J Med Biol Res. 2017;50(11):2–7.
23. Opanasenko M, Shamzhy M, Čejka J. Solid Acid Catalysts for Coumarin Synthesis by the Pechmann Reaction: MOFs versus Zeolites. ChemCatChem. 2013;5(4):1024–31.
24. Rahmatpour A, Mohammadian S. An environmentally friendly, chemoselective, and efficient protocol for the preparation of coumarin derivatives by Pechman condensation reaction using new and reusable heterogeneous Lewis acid catalyst polystyrene-supported GaCl 3. Comptes Rendus Chim [Internet]. 2013;16(3):271–8. Available from: http://dx.doi.org/10.1016/j.crci.2013.01.006
25. Li TS, Zhang ZH, Yang F, Fu CG. Montmorillonite Clay Catalysis. Part 7.1 An Environmentally Friendly Procedure for the Synthesis of Coumarins via Pechmann Condensation of Phenols with Ethyl Acetoacetate. J Chem Res - Part S. 1998;(1):38–9.
26. Manesh AA, Nazari T. Silica supported Thallium (III) Nitrate: An effective oxidant for oxidation of alcohols to the carbonyl compounds. J Chil Chem Soc. 2015;60(3):3001–4.
27. Jr LFS, Sousa RMF, Ferraz HMC, Aguilar AM. Thallium Trinitrate-Mediated Ring Contraction of 1,2-Dihydronaphthalenes: The Effect of Electron-donating and Electron-withdrawing Groups. J Braz Chem Soc. 2005;16(6):1160–73.
28. Chen K, Liu S, Wang D, Hao WJ, Zhou P, Tu SJ, et al. Silver/Scandium-Cocatalyzed Bicyclization of β-Alkynyl Ketones Leading to Benzo[c]xanthenes and Naphtho[1,2-b]benzofurans. J Org Chem. 2017;82(21):11524–30.
29. Drewes SE, Emslie ND, Karodia N, Loizou G. Synthesis of useful intermediates from the claisen-rearrangement of α-hydroxy alkyl acrylate precursors. Synth Commun. 1990;20(10):1437–43.
30. Howard BE, Woerpel KA. Synthesis of tertiary α-hydroxy acids by silylene transfer to α-keto esters. Org Lett. 2007;9(22):4651–3.
31. Balaaubramanian KK. A new route to the synthesis of 3-methylenecoumarins via Lewis acid catalyzed rearrangement of methyl alpha-aryloxymethylcrylates. Tetrahedron Lett. 1984;25(29):3125–6.
32. Dalpozzo R, Bartoli G, Sambri L, Melchiorre P. Perchloric acid and its salts: Very powerful catalysts in organic chemistry. Chem Rev. 2010;110(6):3501–51.
33. Jung JW, Kim NJ, Yun H, Han YT. Recent advances in synthesis of 4-arylcoumarins. Vol. 23, Molecules. 2018.
34. Venkatanarayana M, Dubey PK. Simple and efficient Knoevenagel synthesis of (E)-2-((1H-indol-3-yl) methylene)-3-oxoindolylnitrile catalysed by PPh3. J Chem Sci. 2011;123(5):609–14.
35. Vekariya RH, Patel HD. Recent advances in the synthesis of coumarin derivatives via Knoevenagel condensation: A review. Synth Commun. 2014;44(19):2756–88.
36. Vitório F, Pereira TM, Castro RN, Guedes GP, Graebin CS, Kümmerle AE. Synthesis and mechanism of novel fluorescent coumarin-dihydropyrimidinone dyads obtained by the Biginelli multicomponent reaction. New J Chem. 2015;39(3):2323–32.
37. van Schijndel J, Molendijk D, Spakman H, Knaven E, Canalle LA, Meuldijk J. Mechanistic considerations and characterization of ammonia-based catalytic active intermediates of the green Knoevenagel reaction of various benzaldehydes*. Green Chem Lett Rev. 2019;12(3):323–31.
38. Hwang IT, Lee SA, Hwang JS, Lee KI. A facile synthesis of highly functionalized 4-arylcoumarins via kostanecki reactions mediated by DBU. Molecules. 2011;16(8):6313–21.
39. Calcio Gaudino E, Tagliapietra S, Martina K,

Palmisano G, Cravotto G. Recent advances and perspectives in the synthesis of bioactive coumarins. RSC Adv. 2016;6(52):46394–405.

40. Song CE, Jung DU, Choung SY, Roh EJ, Lee SG. Dramatic enhancement of catalytic activity in an ionic liquid: Highly practical Friedel-Crafts alkenylation of arenes with alkynes catalyzed by metal triflates. Angew Chemie - Int Ed. 2004;43(45):6183–5.
41. Sasano K, Takaya J, Iwasawa N. Palladium(II)-catalyzed direct carboxylation of alkenyl C-H bonds with CO2. J Am Chem Soc. 2013;135(30):10954–7.
42. Yamamoto Y, Kirai N. Synthesis of 4-arylcoumarins via Cu-catalyzed hydroarylation with arylboronic acids. Org Lett. 2008;10(24):5513–6.
43. Kim S, Kang D, Lee CH, Lee PH. Synthesis of substituted coumarins via Brønsted acid mediated condensation of allenes with substituted phenols or anisoles. J Org Chem. 2012;77(15):6530–7.
44. Yuan HJ, Wang M, Liu YJ, Liu Q. Copper(II)-catalyzed C-C bond-forming reactions of α-electron-withdrawing group-substituted ketene S,S-acetals with carbonyl compounds and a facile synthesis of coumarins. Adv Synth Catal. 2009;351(1–2):112–6.
45. Cerqueira NMFSA, Oliveira-Campos AMF, Coelho PJ, Melo De Carvalho LH, Samat A, Guglielmetti R. Synthesis of photochromic dyes based on annulated coumarin systems. Helv Chim Acta. 2002;85(2):442–50.
46. Takeuchi Y, Ueda N, Uesugi K, Abe H, Nishioka H, Harayama T. Convenient synthesis of a simple coumarin from salicylaldehyde and wittig reagent. IV: Improved synthetic method of substituted coumarins. Heterocycles. 2003;59(1):217–24.
47. Borges F, Roleira F, Milhazes N, Santana L, Uriarte E. Simple Coumarins and Analogues in Medicinal Chemistry: Occurrence, Synthesis and Biological Activity. Curr Med Chem. 2005;12(8):887–916.
48. Krachko T, Lyaskovskyy V, Lutz M, Lammertsma K, Slootweg JC. Brønsted Acid Promoted Reduction of Tertiary Phosphine Oxides. Zeitschrift fur Anorg und Allg Chemie. 2017;643(14):916–21.
49. Yavari I, Hekmat-Shoar R, Zonouzi A. A new and efficient route to 4-carboxymethylcoumarins mediated by vinyltriphenylphosphonium salt. Tetrahedron Lett. 1998;39(16):2391–2.
50. Medina FG, Marrero JG, Macías-Alonso M, González MC, Córdova-Guerrero I, Teissier García AG, et al. Coumarin heterocyclic derivatives: Chemical synthesis and biological activity. Natural Product Reports. 2015;32:1472–507.
51. Gilchrist TL. Synthesis of aromatic heterocycles. J Chem Soc - Perkin Trans 1. 1998;(3):615–28.
52. Bouasla S, Amaro-Gahete J, Esquivel D, López MI, Jiménez-Sanchidrián C, Teguiche M, et al. Coumarin derivatives solvent-free synthesis under microwave irradiation over heterogeneous solid catalysts. Molecules. 2017;22(12).
53. Elavarasan S, Bhakiaraj D, Elavarasan T, Gopalakrishnan M. An efficient green procedure for synthesis of some fluorinated curcumin analogues catalyzed by calcium oxide under microwave irradiation and its antibacterial evaluation. J Chem. 2013;2013.
54. Shilpa C, Dipak S, Vimukta S, Arti D. Comparative study of microwave and conventional synthesis and pharmacological activity of pyrimidines: A review. Int J Pharm Sci Rev Res. 2012;15(1):15–22.
55. Bogdal D. Coumarins: Fast Synthesis by Knoevenagel Condensation under Microwave Irradiation. J Chem Res - Part S. 1998;(8):468–9.
56. Hari Krishna M, Thriveni P. Synthesis of coumarins via Pechmann reaction using $Cr(NO_3)_3.9H_2O$ as a Catalyst under microwave irradiation. Der Pharma Chem. 2016;8(9):94–8.
57. Jin H, Xiang L, Wen F, Tao K, Liu Q, Hou T. Improved synthesis of chalconoid-like compounds under ultrasound irradiation. Ultrason Sonochem. 2008;15(5):681–3.
58. Li JT, Han JF, Yang JH, Li TS. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH2SO3H under ultrasound irradiation. Ultrason Sonochem. 2003;10(3):119–22.
59. Bigi F, Maggi R, Sartori G. Selected syntheses of ureas through phosgene substitutes. Green Chem. 2000;2(4):140–8.
60. Du J-L, Li L-J, Zhang D-H. Ultrasound Promoted Synthesis of 3-Carboxycoumarins in Aqueous Media. E-Journal Chem. 2006;3(1):1–4.
61. Shahbazi MA, Faghfouri L, Ferreira MPA, Figueiredo P, Maleki H, Sefat F, et al. The versatile biomedical applications of bismuth-based nanoparticles and composites: Therapeutic, diagnostic, biosensing, and regenerative properties. Chem Soc Rev. 2020;49(4):1253–321.
62. Taylor P, Patil SB, Bhat RP, Raje VP, Shriniwas D. Synthetic Communications : An International Journal for Rapid Communication of Synthetic Organic Chemistry Ultrasound - Assisted Pechmann Condensation of Phenols With β - Ketoesters to Form Coumarins , in the Presence of Bismuth ( III ) Chloride Catalyst. J Synth Commun. 2006;36(4):37–41.
63. Sana S, Rajanna KC, Reddy KR, Bhooshan M, Venkateswarlu M, Kumar MS, et al. Ultrasonically Assisted Regioselective Nitration of Aromatic Compounds in Presence of Certain Group V and VI Metal Salts. Green Sustain Chem. 2012;02(03):97–111.
64. Ambulgekar G V., Bhanage BM, Samant SD. Low temperature recyclable catalyst for Heck reactions using ultrasound. Tetrahedron Lett. 2005;46(14):2483–5.
65. Palmisano G, Tibiletti F, Penoni A, Colombo F, Tollari S, Garella D, et al. Ultrasound-enhanced one-pot synthesis of 3-(Het)arylmethyl-4-hydroxycoumarins in water. Ultrason Sonochem [Internet]. 2011;18(2):652–60. Available from: http://dx.doi.org/10.1016/j.ultsonch.2010.08.009
66. Al-Kadasi AMA, Nazeruddin GM. A facile and efficient ultrasound-assisted chlorosulfonic acid catalyzed onepot synthesis of

benzopyranopyrimidines under solvent-free conditions. J Chem Pharm Res. 2013;5(7):204–10.
67. Nazeruddin GM, Pandharpatte MS, Mulani KB. PEG-SO 3H: A mild and efficient recyclable catalyst for the synthesis of coumarin derivatives. Comptes Rendus Chim [Internet]. 2012;15(1):91–5. Available from: http://dx.doi.org/10.1016/j.crci.2011.10.005
68. Aldewachi H, Mustafa YF, Najm R, Ammar F. Adulteration of Slimming Products and its Detection Methods. Syst Rev Pharm. 2020;11(3):289–96.
69. Draye M, Chatel G, Duwald R. Ultrasound for drug synthesis: A green approach. Pharmaceuticals. 2020;13(2).
70. Montero-Calderon A, Cortes C, Zulueta A, Frigola A, Esteve MJ. Green solvents and Ultrasound-Assisted Extraction of bioactive orange (Citrus sinensis) peel compounds. Sci Rep [Internet]. 2019;9(1):1–8. Available from: http://dx.doi.org/10.1038/s41598-019-52717-1
71. Khaligh NG. Synthesis of coumarins via Pechmann reaction catalyzed by 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate as an efficient, halogen-free and reusable acidic ionic liquid. Catal Sci Technol. 2012;2(8):1633–6.
72. Ćiraković J, Driver TG, Woerpel KA. Metal-catalyzed di-tert-butylsilylene transfer: Synthesis and reactivity of silacyclopropanes. J Org Chem. 2004;69(12):4007–12.
73. Vahabi V, Hatamjafari F. Microwave assisted convenient one-pot synthesis of coumarin derivatives via Pechmann condensation catalyzed by FeF3 under solvent-free conditions and antimicrobial activities of the products. Molecules. 2014;19(9):13093–103.