ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

A REVIEW ON HETEROCYCLIC AND THEIR APPLICATION IN CHEMISTRY OF COUMARIN MOIETY

Dr. Amal Hussein Anatheil
Department of Pharmaceutical Chemistry,
College of Pharmacy, University of Thi-Qar, Thi-Qar, Iraq.
amalhussein21@utq.edu.iq

Dr. Muntaha Yassen Hayal
Department of Pharmaceutical Chemistry,
College of Pharmacy, University of Thi-Qar, Thi-Qar, Iraq.
Muntaha84chem@ sci.utq.edu.iq

Dr.Azhar Hameed
Department of Pharmaceutical Chemistry,
College of Pharmacy, University of Thi-Qar, Thi-Qar, Iraq.
azharhameed@utq.edu.iq

Dr.Wafa S. Abdulredhad
Department of Pharmaceutical Chemistry,
College of Pharmacy, University of Thi-Qar, Thi-Qar, Iraq.
wafaabdulredha81@utq.edu.iq

ABSTRACT

In organic chemistry, the largest families of organic compounds have related to the heterocyclic compounds. Familiarly, the importance of heterocyclic compounds is very essential and has a broad range of applications in medicinal chemistry and agrochemical products. Heterocyclic compounds applications are also found in developers, as corrosion inhibitors, sanitizers, copolymers, antioxidants, dyestuff. Now in literature survey reveals that more than 85-95% of new drugs containing heterocycles, which has rich scientific insight into the biological system. Coumarin-based heterocyclic compounds, for instance, have a good role in medicinal chemistry with broad applications in diagnostics and pathology. The aims of this review work to the reported Coumarin derivatives with pharmaceuticals activity during the previous years.

Keywords: Coumarin, Coumarin-based heterocyclic compounds**.**

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

Introduction

Heterocyclic compounds are of main interest in medicinal chemistry. The most complex branches of chemistry are normally heterocyclic chemistry. It is equally contributed in interesting for the industrial and physiological significances. and for its diversity of its synthetic procedure as well as its theoretical implication[1]. Synthetic heterocyclic chemistry has not only played an important role in every place of human life and also found its application in diverse fields like agriculture, medicine, polymer, and various industries. Most of the synthetic heterocyclic compounds act as a drug is used as anticonvulsants, hypnotics, antineoplastic, antiseptics, antihistaminic, antiviral, anti-tumor, etc. Every year a large number of heterocyclic drugs are being introduced in pharmacopeias. The size and type of ring structures, together with the effective substituent groups of the mother scaffold, showed strongly their physicochemical properties[2][3][4]. Among the various medical applications, heterocyclic compounds have a significant active role as anti-viral[5], anti-bacterial[6], anti-inflammatory[7], anti-fungal[8], and anti-tumor drugs[9].

1. Coumarins

Coumarins are aromatic compounds was used as perfumes since 1882. Their name is derived from coumarou, the vernacular name of the tonka bean. It was isolated in 1820[10]. Coumarins are a family of compounds that belong to benzopyrons[11], figure (1).

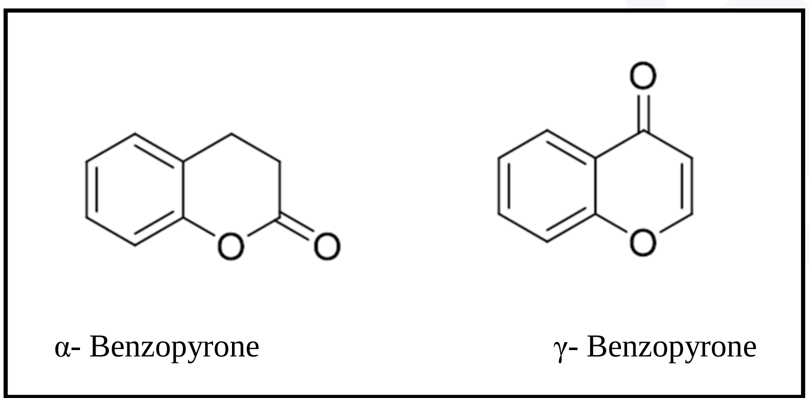


Figure (1) Structural formulas of the benzopyrone subclasses.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

Besides Coumarins functional groups, other functional groups were observed, as depicted in figure (2)[12][13][14][15][16][17].

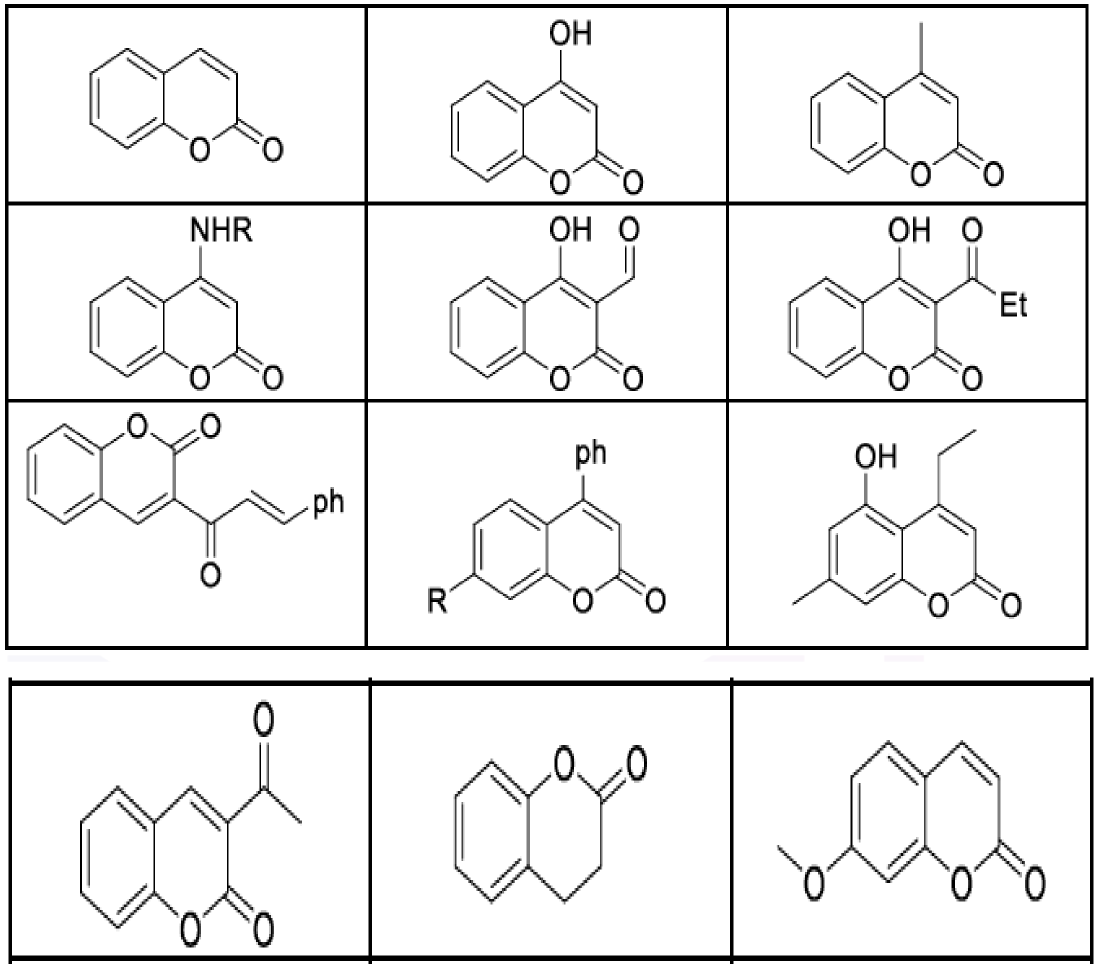
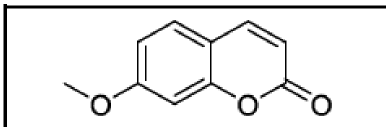
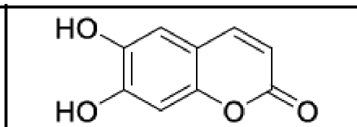
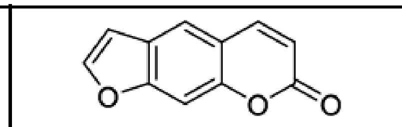
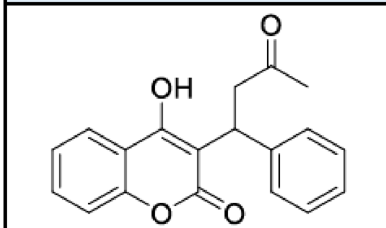
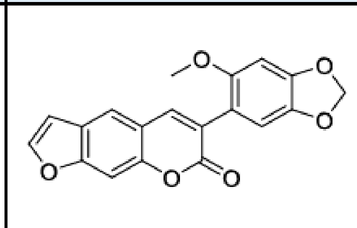
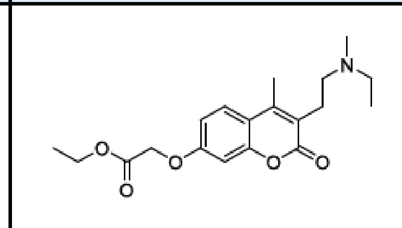
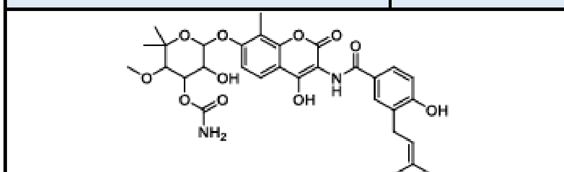
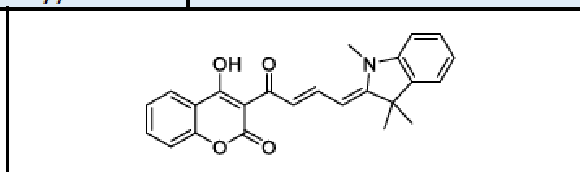


Figure (2) Examples of few heterocyclic containing Coumarin moieties, which shoes most active drugs in pharmaceutical, industries etc.

The presence of heterocycles merely not only essential for some drugs ,figure (**3**)[18][19][20][21][11][22] but it is found equally important in various fields such as fertilizer, optics, electronics, agrochemical research, and material sciences. The synthesis of Coumarin and its derivatives as therapeutic agents for the curing and prevention of diseases has played a critical role in the practice of organic synthesis for many years. The use of natural extracts for medicinal purposes goes back thousands of years; however, it has been only since the last half-century efforts are being taken to search for new drugs by synthetic chemistry.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

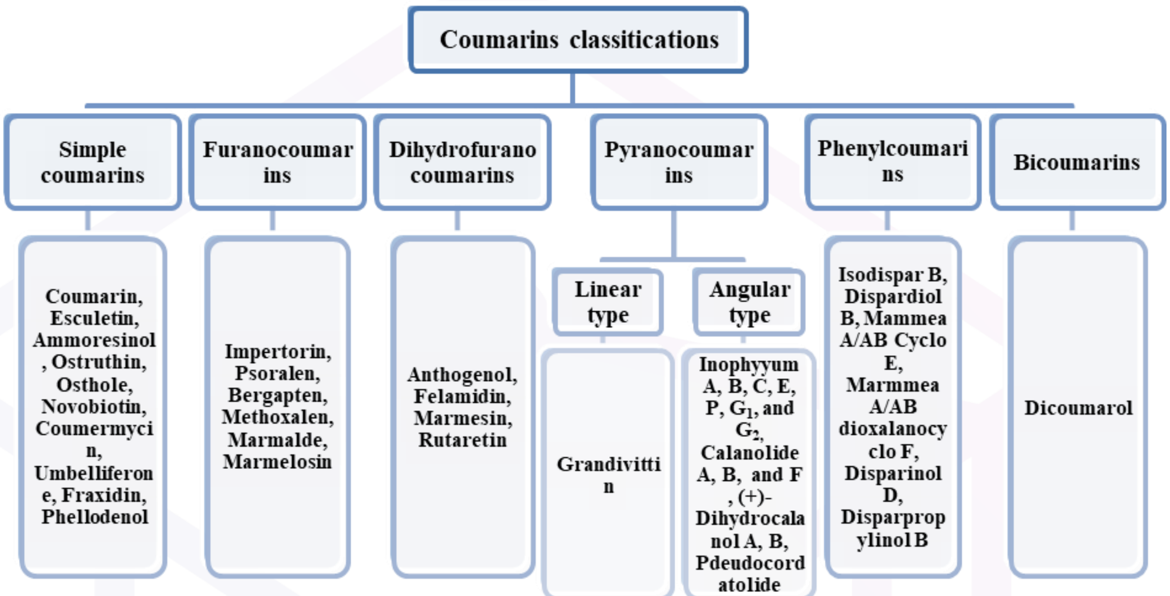
<table>
<tr><td></td><td></td><td colspan="2"></td></tr>
<tr><td>Herniarin (anti-oxidant)</td><td>Aesculetin (anti-coagulant)</td><td colspan="2">Psoralen (anti-psoriasis)</td></tr>
<tr><td></td><td></td><td colspan="2"></td></tr>
<tr><td>Watfarin (anti-coagulant)</td><td>Pachyrrhizine (mosquitocidal activity)</td><td colspan="2">Carbocromen (coronary heart disease treatment)</td></tr>
<tr><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td colspan="2">Novobiocine (anti-biotic)</td><td colspan="2">Fluorescent chemosensors for DNA, RNA</td></tr>
</table>

Although distributed throughout all parts of the plant, the coumarins occur at the highest levels in the fruits, followed by the roots, stems and leaves. Environmental conditions and seasonal changes can influence the occurrence in diverse parts of the plant.The simple Coumarins (e.g. Coumarin, 7-hydroxycoumarin, and 6,7-dihydroxy coumarin), are the hydroxylated, alkoxylated, and alkylated derivatives of the parent compound Coumarin, along with their glycosides. Coumarins comprise a very large class of compounds found throughout the plant kingdom. They are found at high levels in some essential oils, particularly *cinnamon bark oil* (7,000 ppm), *cassia leaf oil* (up to 87,300 ppm), and *lavender oil*. Coumarin is also found in fruits (e.g. *bilberry, cloudberry*), *green tea,* and other foods such as *chicory*. Most Coumarins occur in higher plants, with the richest sources being the *Rutaceae* and *Umbelliferon*[23].

Major coumarin parts isolated from plants. There are six different classifications for coumarin derivatives. Commonly, they can be classified according to the most common compounds: simple coumarins, complex coumarins, and multiple coumarins. Also, they can be classified as simple coumarins, furocoumarins,

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

dihydrofurocoumarins, pyranocoumarins (it can be classified as linear and angular pyranocoumarins), phenylcoumarins, and biscoumarins **,scheme (1)**[22].

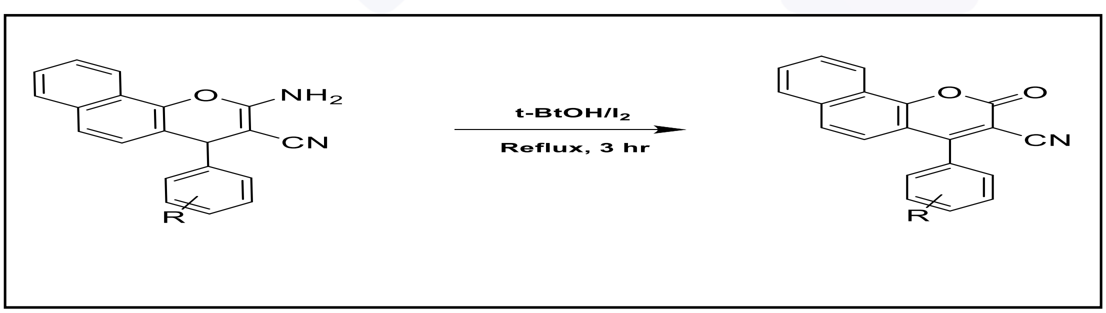


Scheme (1) Classifications of Naturals Coumarins

2. Synthesis of Coumarin

A) Synthesis of Coumarin derivatives by Microwave Irradiation Method

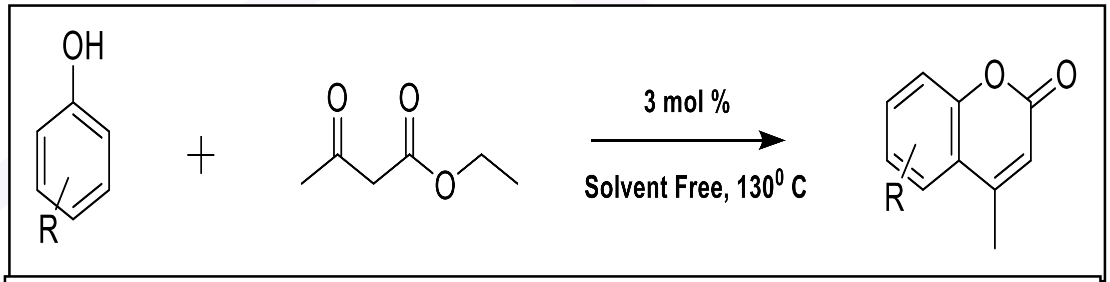
Microwave chemistry is based on the efficiency of the interaction of molecules in the reaction mixture and on the polarity of the molecule. Where, the larger the dielectric constant, the greater is the interaction with microwaves. Thus, solvents such as water, methanol, DMF, ethyl acetate, acetic acid, acetone, etc. They are all heated rapidly when irradiated with microwaves[24].

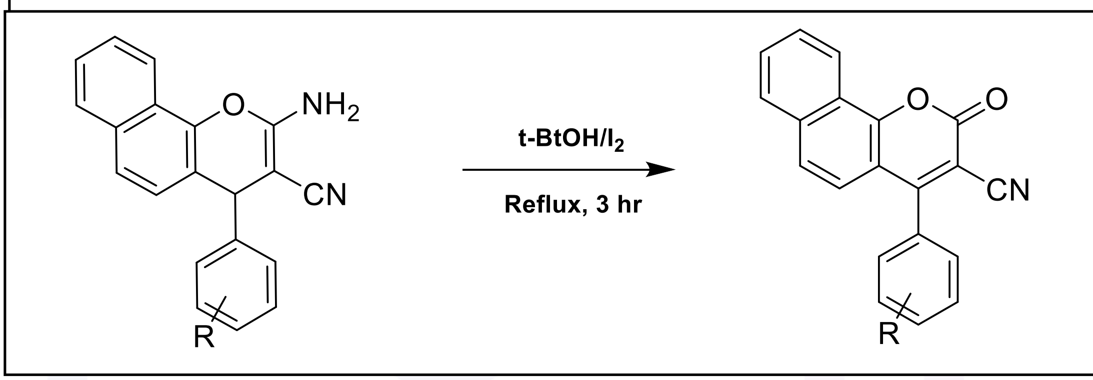


ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

B) Synthesis of Coumarin derivatives by Conventional Method:

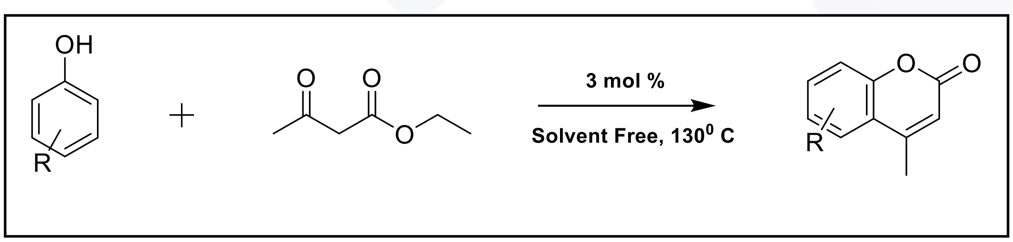
Synthesis of product is made by providing refluxing the reaction mixture with or without catalyst and solvent. Often in the conventional method solvent performs an important role in chemical reactions, it presents one or more liquid phases for reaction, control temperatures, controlled exothermic reactions, isolate and purify compounds by extractions or recrystallization, generates azeotropes for separation, assists characterization and structural of chemicals, etc[25].





C) Synthesis of Coumarin derivatives by using Solvent:

In organic synthesis, the reaction yields can moderately in the absence of solvent or in a water suspension which directs to minimize pollution and develop environment-friendly synthetic procedure, this has led to the dynamic research activity of known reactions to achieve organic synthesis under solvent-free condition[26].

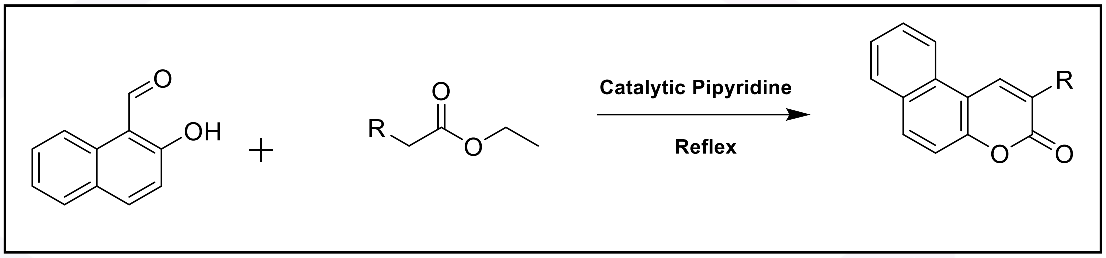


ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

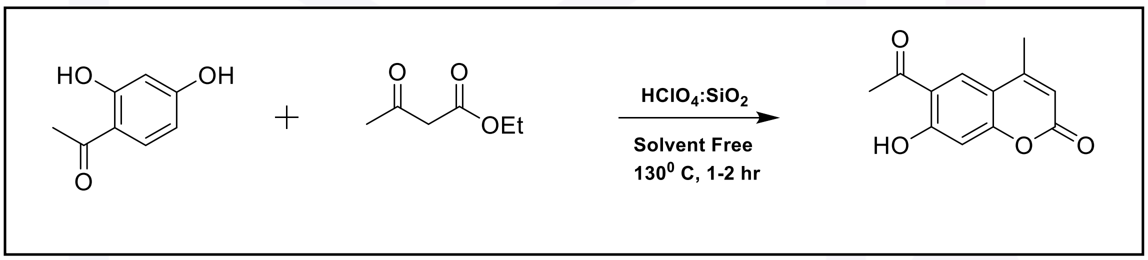
D) Synthesis of Coumarin derivatives by using catalyst:

The catalyst plays an important role in the synthesis of Coumarin derivatives, which stimulate the rate of reaction. It proved their value to minimize the adverse environmental impact and decrease the costs of the processes. Catalysts used for the synthesis of Coumarin are as follows.

1) **Homogeneous catalyst:** A catalytic system in which the substrates and the catalyst are brought in one phase together, regularly the liquid phase, or if the reactants are present in the same phase as the catalyst, is called a homogeneous catalyst.



2) **Heterogeneous catalyst:** If the catalyst compounds are present in a different phase as compared to the substrates, it is described as a heterogeneous catalyst, and this type of reaction is called heterogeneous catalysis[27][28].



The heterogeneously catalyzed reaction has a certain advantage over its counterpart like,

a) Low toxicity and safety in handling and more stability.

b) Better selectivity.

c) Reusability.

d) Separation from the product is easier.

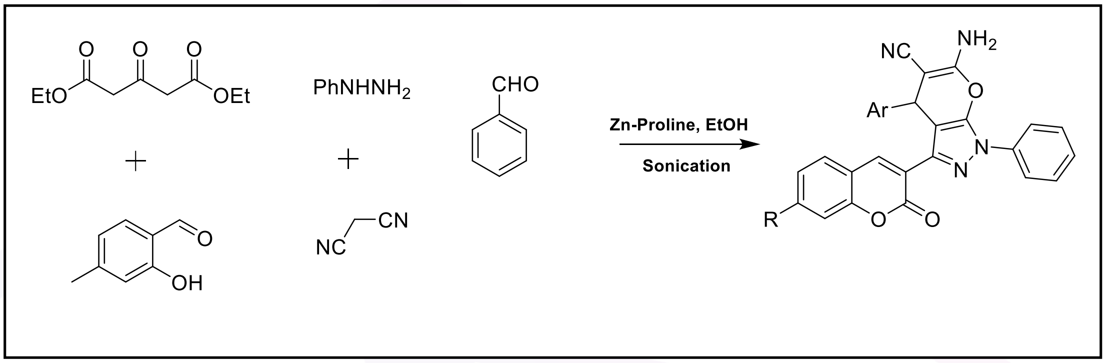
e) Faster rate of reaction

f) high cost.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

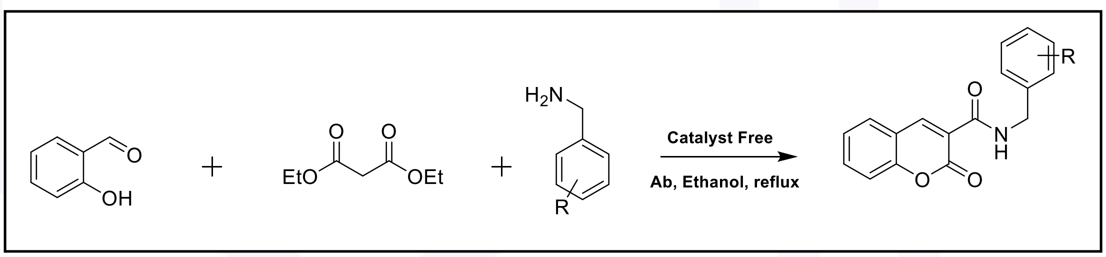
E) Synthesis of Coumarin derivatives by Ultrasound assisted techniques:

The use of ultrasonication in the field of heterocyclic organic chemistry has got considerable attention in the previous few decades, increase the safety and yields of reactions, significantly.



The technique stimulates the rate of reaction, increases the yields, and generally includes simple work procedures than the conventional methods. The physical effects outside the bubble-like shear forces, jets, and shock waves, which produce the physical, chemical, and biological changes more efficiently at a faster rate. These factors have attracted researchers to investigate their applications in chemistry[29][30].

F) Synthesis of Coumarin derivatives without catalyst compound:

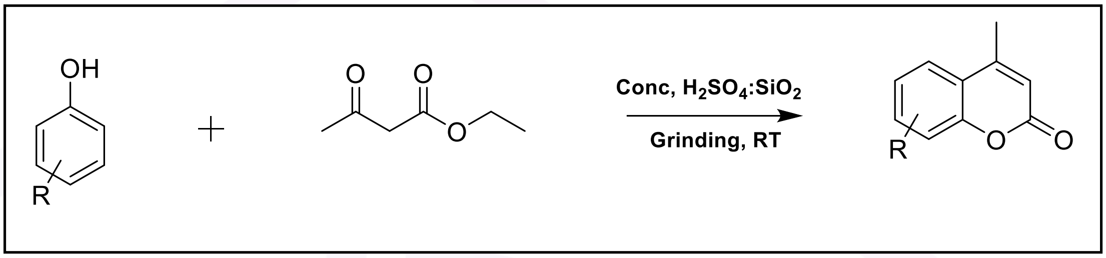


A vetisyan and *et al* reported the conventional method for synthesis coumarin by condensation of more than three components in absolute ethanol land using the catalyst. This is one of the great methods for the formation of Coumarin derivatives[31].

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

G) Synthesis of Coumarin derivatives by Simple Technique:

The grinding technique is a simple process, it involves applying pressure on reactant to obtain the product. This product is known as 'Grindstone Chemistry' which is one important of the 'Green Chemistry'. The grindstone chemistry has advantages to avoid pollution by saving. Thermal and electrical energy and economical and ecologically favorable procedure in chemistry[32][33].



Conclusion:

Coumarin ring-containing compounds play a significant role in medicinal chemistry as drugs, pathologic, and diagnostic agents. In particular, a large number of coumarin-based compounds as clinical antibacterial, anticancer, antifungal, antihypertensive, antineuropathic, antiparasitic, antihistaminic agents, and used widely in the clinic in preventing and treating different types of diseases with low toxicity, bioavailability, biocompatibility, and curative effects.

References

1. A. H. Anatheil, M. E. Al-dokheily, and I. A. Flifel, "Synthesis, Characterization and Electrical Study of Ligand 5, 5'-(4H-1, 2, 4- triazole - 3, 5- diyl) bis (azaneylylidene)) bis (methaneylylidene)) bis (4,1-phenylene)) bis (methaneylylidene)) bis (azaneylylidene)) bis (4H-1, 2, 4- triazol- 3- amine with S," *J. Glob. Pharma Technol.*, vol. 11, no. 9, pp. 447–461, 2019.
2. M. Y. Haya and M. S. Magtoof, "Syntheses, Characterization and Biological Activity of some 4-Thiazolldinones," *Int. J. Pharm. Res.*, vol. 12, no. 3, pp. 818–821, 2020.
3. A. H. Gatea, "Synthesis , Characterization , Antimicrobial of Studies New 2,2'-{(1Z,2Z) ethane-1,2 Diylidenebis[(2Z)Hydrazin-1-yl-2-ylidene-1,3,4 oxadiazole-5,2-diyl]}Diphenol and their Transition Metal Complexes," *J. Glob. Pharma Technol.*, vol. 10, no. 3, pp. 102–11, 2018.

4. R. N.aljabery, Azharhameedgatea, and I. M. A. Flifel, "Synthesis, characterization, antimicrobial studies of New5-[(2E)-2-{(2Z)-2-[2-(5-sulfanyl-1,3,4-thiadiazol-2-yl)hydrazinylidene]ethylidene}hydrazinyl]-1,3,4-thiadiazole-2-thioland their transition metal complexes," *Int. J. Pharm. Res.*, vol. 10, no. 4, pp. 557–566, 2018.
5. V. A. Shiryaev and Y. N. Klimochkin, "Heterocyclic Inhibitors of Viroporins in the Design of Antiviral Compounds," *Chem. Heterocycl. Compd.*, vol. 56, no. 6, pp. 626–635, 2020.
6. "Synthesis of Bioactive Imidazoles: A Review," *Chem. Sci. J.*, vol. 6, no. 2, pp. 1–13, 2015.
7. J. Jumal and Norhanis Sakinah, "Synthesis, Characterization, and Applications of Coumarin Derivatives: A Short Review," *Malaysian J. Sci. Heal. Technol.*, vol. 7, no. 1, pp. 62–68, 2021.
8. C. Wu, P. Tao, J. Li, Y. Gao, S. Shang, and Z. Song, "Antifungal application of pine derived products for sustainable forest resource exploitation," *Ind. Crops Prod.*, pp. 1–9, 2020.
9. J. T. Gupton, "Pyrrole Natural Products with Antitumor Properties," *Heterocycl. Antitumor Antibiot.*, vol. 2, no. March, pp. 53–92, 2006.
10. A. Lacy, "Studies on Coumarins and Coumarin-Related Compounds to Determine their Therapeutic Role in the Treatment of Cancer," *Curr. Pharm. Des.*, vol. 10, no. 30, pp. 3797–3811, 2005.
11. E. K. Akkol, Y. Genç, B. Karpuz, E. Sobarzo-Sánchez, and R. Capasso, "Coumarins and coumarin-related compounds in pharmacotherapy of cancer," *Cancers (Basel).*, vol. 12, no. 7, pp. 1–25, 2020.
12. E. Eudragit, D. M. Aragón, N. E. Vergel, L. F. Ospina, and J. E. Rosas, "Enhanced anticonvulsant activity of coumarin in mice after its Enhanced Anticonvulsant Activity of Coumarin in Mice after its Microencapsulation in Eudragit ® E100 Microparticles," no. February 2016, 2015.
13. A. Stefanachi *et al.*, *Coumarin : A Natural , Privileged and Versatile Scaffold for Bioactive Compounds*. 2018.
14. O. S. C. and M. A. Baseer, "Comparative study of various synthetic methods of 7-hydroxy-4-methyl coumarins via Pechmann reaction," vol. 5, no. 5, pp. 67–70, 2014.
15. A. Behrami, "Characterization , Biological activity and synthesis of new

derivatives of Chromen-2-one," *J. Adv. Chem.*, vol. 15, no. March, pp. 6130–6135, 2018.

16. O. S. Chavan, S. B. Chavan, and M. A. Baseer, "An efficient synthesis of formyl coumarins by microwave irradiation method- duff formylation," *Sch. Res. Libr.*, vol. 7, no. 1, pp. 197–200, 2015.
17. M. A. El-fattah, H. A. El-wahab, M. S. Bashandy, R. A. El-eisawy, and F. A. El-hai, "Progress in Organic Coatings Potential application of some coumarin derivatives incorporated thiazole ring as ecofriendly antimicrobial , fl ame retardant and corrosion inhibitor additives for polyurethane coating," *Prog. Org. Coatings*, vol. 111, no. March, pp. 57–66, 2017, doi: 10.1016/j.porgcoat.2017.05.005.
18. A. Manuscript, "A Review of Coumarin Derivatives in Pharmacotherapy of Breast Cancer," *NIH Public Access*, vol. 15, no. 26, pp. 2664–2679, 2013.
19. K. N. Venugopala, V. Rashmi, and B. Odhav, "Review on Natural Coumarin Lead Compounds for Their Pharmacological Activity," *Hindawi Publ. Corp.*, vol. 2013, no. Table 1, 2013.
20. M. Baran, P. Miziak, and K. Bonio, "Characteristic of warfarin," *Licens. Open J. Syst. Nicolaus Copernicus Univ. Torun*, vol. 10, no. 8, pp. 78–80, 2020.
21. I. Najmanová, M. Dosed, R. Hrdina, and P. Anzenbacher, "Cardiovascular Effects Of Coumarins Besides Their Antioxidant Activity," *Tomáš Filipský*, vol. 15, no. August, pp. 1–20, 2015.
22. H. Li, L. Cai, and Z. Chen, "Coumarin-Derived Fluorescent Chemosensors," *Adv. Chem. Sensors*, 1945.
23. Y. F. Ting Tan, a, Yun Luo, b, Chen-Cong Zhonga, Xu Xua, "Comprehensive profiling and characterization of coumarins from roots, stems, leaves, branches, and seeds of Chimonanthus nitens Oliv. using ultra-performance liquid chromatography/quadrupole-time-of-flight mass spectrometry combined with modified mass def," *Phytochem. - Isol. Characterisation Role Hum. Heal.*, pp. 113–139, 2017.
24. F. Yılmaz and Ö. Faiz, "Microwave-assisted synthesis and biological evaluation of some coumarin hydrazides," *J. Turkish Chem. Soc. Sect. A Chem.*, vol. 5, no. 2, pp. 551–568, 2018.
25. R. M. Okasha *et al.*, "Design of new Benzo[h] chromene derivatives: Antitumor activities and structure-activity relationships of the 2,3-Positions and fused

rings at the 2,3-positions," *Molecules*, vol. 22, no. 3, 2017.

26. D. Zareyee and M. Serehneh, "Recyclable CMK-5 supported sulfonic acid as an environmentally benign catalyst for solvent-free one-pot construction of coumarin through Pechmann condensation," *J. Mol. Catal. A Chem.*, vol. 391, no. 1, pp. 88–91, 2014.
27. F. F. Ye, J. R. Gao, W. J. Sheng, and J. H. Jia, "One-pot synthesis of coumarin derivatives," *Dye. Pigment.*, vol. 77, no. 3, pp. 556–558, 2008.
28. M. Lončarić, D. G. Sokač, S. Jokić, and M. Molnar, "Recent advances in the synthesis of coumarin derivatives from different starting materials," *Biomolecules*, vol. 10, no. 1, pp. 1–36, 2020.
29. G. Mohammadi Ziarani, Z. Kheilkordi, and P. Gholamzadeh, *Ultrasound-assisted synthesis of heterocyclic compounds*, vol. 24, no. 3. Springer International Publishing, 2020.
30. M. Lucas, A. Gachagan, and A. Cardoni, "Research applications and opportunities in power ultrasonics," *Proc. Inst. Mech. Eng. Part C J. Mech. Eng. Sci.*, vol. 223, no. 12, pp. 2949–2965, 2009.
31. B. F. Abdel-Wahab, H. A. Mohamed, and A. A. Farhat, "Ethyl coumarin-3-carboxylate: Synthesis and chemical properties," *Org. Commun.*, vol. 7, no. 1, pp. 1–27, 2014.
32. P. T. Kaye and M. A. Musa, "Application of Baylis-Hillman methodology in the synthesis of coumarin derivatives," *Synth. Commun.*, vol. 33, no. 10, pp. 1755–1770, 2003.
33. L. Rong, X. Li, H. Wang, D. Shi, S. Tu, and Q. Zhuang, "Efficient green procedure for the synthesis of coumarin derivatives by a one-pot, three-component reaction under solvent-free conditions," *Synth. Commun.*, vol. 37, no. 2, pp. 183–189, 2007.