Synthesis, Characterization, and Applications of Coumarin Derivatives: A Short Review

Norhanis Sakinah, Juliana Jumal
Faculty of Science and Technology, Universiti Sains Islam Malaysia, Bandar Baru Nilai, 71800 Nilai, Negeri Sembilan
Corresponding author: juliana.j@usim.edu.my

Abstract— Coumarin and its derivatives represent one of the most active curriculums of compound possessing a broad spectrum of biological activity along with other applications such as insecticide and fragrance. There are various methodologies developed for the synthesis of coumarins. Classical routes to coumarins include Pechmann condensation, Knoevenagel condensation, Perkin reaction, and Wittig condensation reactions. Researchers have carried out adjustments and improvements to increase the efficacy and overcome the limitations from the classical route. In this review outline, coumarin derivatives were characterized by using FTIR and $^1$H NMR spectroscopy. This review paper focuses on various synthesis and characterization techniques to analyze coumarin derivatives and their potential application in various fields.

Keywords— coumarin, biological activity, synthesis, characterization, application

I. INTRODUCTION

Many organic compounds with coumarin moiety (2H-1chromen-2-one) are present in plants. Coumarins' chemical structure composes of α-pyrone rings and fused benzene, with six available sites for substitution. Due to this reason, more than 1300 coumarins have been identified from natural sources [1]. Since they are easily found, many studies were conducted regarding their characteristics. Coumarins are significantly well known as they exhibit valuable biological properties such as anticancer [2], anti-inflammation, antimicrobial [3], antioxidant [4], and enzymatic inhibitory activities [5]. Besides various biological activities, most compounds show many valuable applications in pharmaceutical, fragrance, insecticides, and dyes [6].

Coumarin derivatives can be synthesized using various methodologies. The synthetic methods include Perkin reaction, Pechmann condensation, Knoevenagel reaction, and Wittig reaction. The Perkin reaction is commonly performed using salicylaldehyde with a carboxylic acid anhydride in the presence of a base catalyst. This method used to be the best method to synthesize coumarin during the years after its discovery [7]. However, due to limited access to various anhydrides, this method is difficult to be carried out. Among these methods, Pechmann condensation is proven to be the most superior method [8]. In this method, three factors affect the reaction's progress: the β-ketonic esters, the phenols' nature, and the catalyst [9]. Knoevenagel condensation is also one of the most widely used methods to synthesize coumarin derivatives [10]. It is conducted by treating carbonyl compound (aldehyde or ketone) with an active hydrogen compound in the presence of a basic catalyst (α,β-unsaturated compound) acting as a solvent [11].

Numerous methods can be used to characterize coumarin derivatives. Fourier-transform infrared (FTIR) spectroscopy is used to determine functional groups present in the coumarin derivatives compounds. It works by detecting chemical bond vibrations, either through bending or stretching in various ways upon irradiation with specific wavelengths of light. FTIR is one of the characterization methods that is non-destructive [12]. Proton Nuclear Magnetic Resonance ($^1$H NMR) spectroscopy gives information about the molecular structure of coumarin derivatives. The hydrogen atom absorbs the energy of different wavelengths depending on the bonding environment [13]. When an external magnetic field is applied, the nuclei sample excites and produces nuclear magnetic resonance. Sensitive radio receivers then detect this signal. The use of $^1$H NMR is much-preferred compared to the carbon-13 NMR (13C NMR) analysis, which might be due to proton spectra being much easier to obtain than carbon spectra [14].

This paper reviews several methodologies on synthesis and characterization of coumarin derivatives. Apart from that, several coumarin derivatives applications were reviewed, including their biological activities, toxicology activity, and coumarin derivatives in fragrance. The results obtained were then compared and evaluated.
II. SYNTHESIS METHODS OF COUMARIN DERIVATIVES

There are various methods used to synthesize coumarin derivatives. These methods include Perkin reaction, Pechmann condensation, Wittig reaction, and Knoevenagel reaction. These methods have their advantages and limitations. Variations of these methods have been developed to improve the reaction conditions and yield [15].

A. Perkin reaction

Perkin reaction is commonly performed using salicylaldehyde with carboxylic acid anhydride as a base catalyst. The classical Perkin condensation might be the simplest and most direct method to synthesize coumarin derivatives [17]. However, it is difficult to be carried out due to the limitations, such as limited range for substrate and strong acids. Scheme 1 shows coumarin synthesis by Perkin reaction with salicylaldehyde as the starting material [18].

Further optimization is carried out to improve the method's practicality and broaden the substrate and functional group tolerance. A study by Augustine et al. [17] used propyl phosphonic anhydride (T3P) to mediate coumarin derivatives' one-pot synthesis. T3P is a prevailing peptide coupling reagent having a low toxicity. The experiment was performed using various commercially accessible salicylaldehydes with T3P mediated coumarin synthesis under optimum conditions. The result showed that the conditions were suitable with different substituents on the aromatic ring and resulted in good yields of respective coumarins. The scope of a substrate in the reaction was expanded further to diverse substituted acetic acids. Salicylaldehyde was reacted with various carboxylic acids with the presence of T3P. The observation obtained was that all acetic acids' reaction proceeded well with good yields of respective coumarins. The usage of T3P as a mediator resulted in milder reaction conditions able to endure sensitive functional groups and form a more effective and practical synthesis method of coumarin.

B. Pechmann condensation

Pechmann condensation is one of the common methods used to synthesize 4-methyl coumarin derivatives. The reaction is a synthesis of coumarins, using phenol as the starting material with either carboxylic acid or ester containing $\beta$-carbonyl group. This reaction is conducted under acidic conditions. Scheme 2 shows the mechanism of synthesis of coumarin by Pechmann condensation [19]. Esterification or transesterification between phenol (1) and $\beta$-keto ester (2) is the mechanism used in the presence of protonic acid or Lewis acid. Compound 4 is produced, followed by an attack of the activated carbonyl ortho to the oxygen to generate the new ring at compound 5. Dehydration is the final step, which obeys an aldol condensation to produce coumarin derivative. Pechmann reaction is commonly used to synthesize coumarin due to mild reaction conditions, simple starting materials, and outstanding yields of the products in short reaction times [20]. In the past few years, Lewis acids, such as GaI$_3$, ZrCl$_4$, InCl$_3$, and Sm(NO$_3$)$_3$, have been utilized as catalysts in Pechmann condensation.

Zirconium salts are used as homogenous catalysts in various organic transformations [21]. Zirconyl salt, ZrOCl$_2$.8H$_2$O crystallizes from dilute hydrochloric acid solutions. Karami and his co-researchers [19] used ZrOCl$_2$.8H$_2$O/SiO$_2$ as a catalyst in the reaction between $\beta$-keto ester and phenol. The expected coumarins were obtained with a high yield of pure products under solvent-free conditions. Comparisons were made with other catalysts to ensure the effectiveness of ZrOCl$_2$.8H$_2$O/SiO$_2$. The results are shown in Table I. The data shows that the ZrOCl$_2$.8H$_2$O/SiO$_2$ catalyzed coumarin synthesis gives more practical and better qualification of Pechmann condensation [21].

TABLE I. COMPARISON OF THE RESULTS FOR THE PREPARATION OF 7-HYDROXY-4-METHYL-2H-CHROMEN-2-ONE WITH OTHER CATALYSTS [21]

| Catalyst         | mol % | Time (min) | Temperature (℃) | Yield (%) |
|------------------|-------|------------|-----------------|-----------|
| Sn(OTf)$_2$      | 10    | 60         | 80              | 99        |
| Ca(NO$_3$)$_2$   | 10    | 10         | 110             | 94        |
| ZrCl$_4$         | 2     | 8          | 70              | 95        |
| GaI$_3$          | 10    | 42         | Reflux (under CH$_2$Cl$_2$) | 96 |
| Sm(NO$_3$)$_3$, 6H$_2$O | 10  | 20         | 80              | 98        |
| InCl$_3$         | 10    | 30         | 65              | 98        |
| Bi(NO$_3$)$_3$, 5H$_2$O | 5   | 15         | 80              | 94        |
| ZrOCl$_2$.8H$_2$O/SiO$_2$ | 10 | 10         | 80              | 98        |

C. Knoevenagel condensation

Knoevenagel condensation reaction is a classical organic synthesis. It is a modified aldol condensation of aldehyde or ketone with active hydrogen compound in the presence of a basic catalyst such as piperidine, pyridine, ammonia, or
sodium ethoxide in organic solvents [22], resulting in carbon-carbon formation. The active hydrogen compound contains a carbon-hydrogen bond which the basic catalyst can deprotonate. Scheme 3 shows the synthesis of ethyl coumarin-3-carboxylate by Knoevenagel condensation [22]. However, it has some drawbacks, such as low yield [23] as well as dangerous and toxic solvents like pyridine [24].

\[
\text{O} \quad \text{OH} \quad + \quad \text{EtO} \quad \text{OEt} \quad \text{Piperidine} \quad \text{O} \quad \text{COEt} \\
\text{salicylaldehyde} \quad \text{diethyl malonate} \quad \text{ethyl coumarin-3-carboxylate}
\]

Scheme 3. Synthesis of ethyl coumarin-3-carboxylate by Knoevenagel condensation

Recently, magnetic nanoparticles such as magnesium ferrite, MgFe₂O₄ are widely used as catalysts, as they are easily separated from reactants using an external magnet [25]. These nanomaterials are also easy to recover, can be reused several times, and environmentally safe [26]. Generally, nanoparticles are considered reactive because they offer a high surface area, which resulted in higher catalytic activity on the surface. Using ultrasonic irradiation, MgFe₂O₄ nanoparticles are successfully dispersed, thus providing more sites for cavity construction on the surface. Fig. 1 shows the morphology of MgFe₂O₄ nanoparticles using scanning electron microscopy (SEM) [26]. The use of MgFe₂O₄ nanoparticles in Knoevenagel condensation provides excellent yields of coumarin derivatives with a green process.

![Fig. 1. Scanning electron microscopy (SEM) image of MgFe₂O₄ nanoparticle][26]

### III. CHARACTERIZATION TECHNIQUES

A. Fourier-transform infrared (FTIR) spectroscopy

Fourier-transform infrared spectroscopy (FTIR) is a technique used to detect a range of functional groups by absorbing infrared radiation from the sample's material, including solid, liquid, or gas. FTIR gives qualitative information such as functional groups and characterizes covalent bonding information. Wahy and his co-researchers [27] characterized four novel coumarin derivatives using FTIR. The first compound, 7,7-(propane-1,3-diylbis(oxy))bis(4-methyl-2H-chromen-2-one) (A1) possess wider band at 1722 cm⁻¹ due to C=O stretching of α,β-unsaturated ester. Compound B1, 7,7-(1,3-phenylene bis(methylene))bis(oxy)bis(4-methyl-2H-chromen-2-one), exhibits strong peak at 1716 cm⁻¹. This is caused by C=O stretching of α,β-unsaturated ester. The next compound, 7,7-(1,4-phenylenebis(methylene))bis(oxy)bis(4-methyl-2H-chromen-2-one) (C1) produced spectrum with wider band at 1736 cm⁻¹. This is also due to the C=O stretching of α,β-unsaturated ester. Meanwhile, compound 7,7-(naphthalene-2,6-diylbis(methylene))bis(oxy)bis(4-methyl-2H-chromen-2-one) (D1) exhibits strong peak at 1722 cm⁻¹, also caused by C=O stretching of α,β-unsaturated ester.

B. Proton Nuclear Magnetic Resonance (¹H NMR) spectroscopy

¹H NMR spectroscopy is a method used to determine the type and number of hydrogen atoms in a molecule. ¹H NMR uses radio waves as the source of energy. The number of signals indicates how many types of hydrogen are in the molecule. The position of signals along the x-axis determines the magnetic environment. In addition, the area under the signal gives information about the number of hydrogen atoms.

Moghanian and his co-researchers [28] conducted a study on the characterization of 8-formyl-7-hydroxy-4-methyl coumarin (A2) using ¹H NMR spectroscopy. Fig. 2 is the molecular structure of the compound A2. The chemical shift was observed at 2.363-12.118 ppm. Downfield signal of H1 is observed at δ=10.528 ppm, which is due to the proton in the formyl group. The downfield signals appeared at δ value of 6.129 ppm, 6.837 ppm, and 7.675 ppm for protons H2, H5 and H4, respectively, corresponding to the aromatic and olefinic protons of the heterocyclic ring. The downfield signal of H6, the signal appeared at δ=12.118 ppm. The oxygen atom bonded to H6 is electronegative. The presence of this electronreceptive oxygen in the carbon atom causes proton H6 to be deshielded. Strong intramolecular hydrogen bonding of oxygen atom and H6 causes reduction of electron density of proton H6. This affected the appearance of the chemical downfield signal. On the other hand, the up-field signal is detected at δ=2.363 ppm for H3 attributed to the methyl group's protons.

![Fig. 2. Molecular structure of 8-formyl-7-hydroxy-4-methyl coumarin (A2)]](image)

In another previous literature, Al-Majedy and his co-workers [29] used ¹H NMR spectroscopy to characterize some new 4-hydroxycoumarin derivatives. The first compound, methyl 2-(coumarin-4-ylxoy)acetate (A3), displays a singlet of the upfield signal at δ=3.63 ppm attributed to the three protons of the methyl group. The proton is α to the oxygen atom that is attached to the carbon atom. The second upfield signal was exhibited at a singlet of δ=4.45 ppm for compound 2-(coumarin-4-ylxoy) acetohydrazide (B3). This is due to the two CH₃ protons, where the protons are α to the neighboring oxygen atom. In addition, a singlet downfield signal is exhibited at δ=8.21 ppm due to the single proton of NH corresponding to the proton of amide.
Both of the compounds A3 and B3 consist of protons from the methyl group. Signal for A3 is detected at δ=2.363 ppm, which is still in the range of methyl group protons (2.2 ppm – 2.4 ppm). However, the signal for B3 is discovered out of the range. This might be caused by the use of a different solvent that created a slightly different environment. Compound B3 comprises amide, which does not exist in A3, leading to different signals from both compounds.

IV. APPLICATIONS

Previous studies prove that coumarins can be used in several applications. Apart from antioxidants, coumarins have been identified to exhibit multiple biological and pharmaceutical benefits. Among these benefits are anticancer, anti-inflammatory, anticoagulant, antimicrobial, and antiviral [30]. Table II lists some of the coumarin derivatives and their application in biological activities.

**TABLE II. COUMARIN DERIVATIVES AND THEIR APPLICATION IN BIOLOGICAL ACTIVITIES**

| Coumarin derivatives                        | Applications                  | Researchers                     |
|---------------------------------------------|-------------------------------|--------------------------------|
| 7,8-dihydroxy-4-methyl coumarin             | Antioxidant                   | Natella and co-workers, 2010 [1]|
| 6-(3-(4-chloro phenyl)-acyrloyl)-5-hydroxy-4-methyl coumarin | Anti-HIV (Reverse transcriptase inhibitors) | Srivastav and co-workers, 2017 [51]|
| 7-hydroxy coumarin                          | Anticoagulant                 | Lei and co-workers, 2015 [45]   |
| 4-chloro-3-formyl coumarin and 4-chloro-3-cyano coumarin | Anticancer                   | Ashwin Barasara, 2018 [52]     |
| 7-hydroxy coumarin                          | Antibacterial                 | Kostova, 2011 [38]              |
| 3-acetyl-6-bromo-coumarin                   | Antimicrobial                 | Kasumbwe, 2014 [53]             |

A. Biological activity

1) Antioxidant

An antioxidant can be described as any material that slows down, inhibits, or eliminates oxidative damage to a target molecule [31]. This interpretation includes small molecules such as vitamin C and large molecules such as for sacrificial proteins (albumin). Antioxidants blocked oxidative stress by nullifying the damaging effects of reactive oxygen species (ROS). Therefore, it is logical to conclude that they are beneficial for diseases related to oxidative stress [32]. Antioxidants can be assorted into multiple categories based on their activity, solubility, and size [33]. Coumarin derivatives are known as potent antioxidants. They exhibit tissue-protective antioxidant properties that can disturb the formation and scavenging of ROS [34]. Coumarins help to minimize oxidative damage caused by ROS and delay or prevent pathological changes. In a study of scavenging capacity by Paya and his co-researchers [35] in 1994, they found that only 7,8-dihydroxycoumarins were active. The phenolic compounds in hydroxycoumarins act as free radical scavengers and potent metal chelators.

The free radical scavenging assay method is one of the global tests for screening antioxidative activities of distinct compounds [36]. DPPH radical, a very stable nitrogen-centered radical, may be utilized to discover the potential of free radical scavenging, which is correlated to their antioxidative activities. The method depends on the concentration changes of DPPH that will be measured by spectrophotometric. The changes are the results of DPPH interaction with an antioxidant. When the extract is added, the violet color in the DPPH assay is reduced to yellow colored. This indicated that DPPH turns to the product diphenyl picryl hydrazine [37]. This process has been widely utilized as it takes a relatively short time for analysis.

2) Anti-HIV

Acquired immunodeficiency syndrome (AIDS) is a pandemic caused by the human immunodeficiency virus (HIV). Since its presence, many researchers conducted studies to search for antiviral chemotherapeutic agents or antiviral compounds. Studies were carried out to develop chemotherapy to fight the causative agent, HIV [38]. HIV invades the central nervous system and infects important cells in the human immune system. These would cause failure in the immune system, which leads to a high possibility of getting dangerous infections and developing cancer. There are two types of HIV, HIV-1 and HIV-2. It is found that HIV-1 is more lethal and infective than HIV-2 [39]. HIV-2 has lower infectivity, indicating fewer people are infected per exposure to HIV-2 and is largely confined to West Africa [40].

Numerous coumarins with different structures have been recognized, in vitro, to convert the viral RNA genome, also known as reverse-transcribed of certain retroviruses, including HIV. Currently, the inhibition of HIV reverse transcriptase is viewed as a practical approach in AIDS treatment. Therefore, natural products that exhibit inhibitory properties have also been explored widely.

A study by Hamdy and his co-researchers [40] reported that two derivatives from 4-methyl-6,7-dihydroxy coumarin, which are aryalted coumarins, show considerable anti-HIV activity due to the implantation of methyl groups on phenyl groups of the coumarin ring. The methyl group increases anti-HIV activity; however, the selectivity and activity are insufficient to carry out mode-of-action studies. Meanwhile, Kostova and his co-researchers [41] reported that they removed the methyl group completely from the coumarin derivative. The result obtained was that the anti-HIV activity decreases. Upon substituting methyl group with isopropyl moiety, the anti-HIV activity was eliminated completely.

In 2008, 25 various compounds had been approved as anti-HIV drugs for clinical use [42]. The drugs were classified into six categories: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, protease inhibitors, called entry inhibitors and co-receptor inhibitors, and integrase inhibitors. To achieve the highest possible efficiency and benefit, these compounds should be employed in drug combination regimens. This also can increase compliance and tolerability while reducing the risk of resistance.

3) Anticoagulant
Thromboembolism can cause cardio-cerebrovascular disease, which threatens human health. Coumarins are used broadly for antithrombotic therapy at the clinical level. Warfarin is one of the coumarin derivatives that is commonly used as a rodenticide. However, further studies reported that the compound is currently used as an anticoagulant [43]. Coumarin anticoagulants are considered antivitamin K. Vitamin K is a cofactor of the microsomal enzyme 2,3-epoxide reductase, which has a vital function in the active synthesis process of prothrombin, factors VII, IX, and X, proteins C, and S [44]. Vitamin K 2,3-epoxide reductase was attacked in liver microsomes by coumarins. Vitamin K 2,3-epoxide reductase is an enzyme hindered by anticoagulants in therapeutic doses by decreasing the production of anticoagulant factors.

The anticoagulant activity was analyzed by monitoring the activated partial thromboplastin time (APTT), thrombin time (TT), and prothrombin time (PT). 7-Hydroxycoumarin derivatives demonstrate a moderate coagulant activity in vitro by raising the PT significantly until they exceed the instrument's full scale [45]. This result was obtained due to the presence of 3-hydroxy moiety. In vivo coagulation study of the derivatives was performed in Wistar rats. The observation showed that PT and TT in the rats were prolonged on the fifth day. Moreover, no death of rat was found, proving that 7-hydroxycoumarin derivatives are non-toxic to the liver.

B. Insecticides

Nowadays, the widespread use of synthetic chemical insecticides resulted in environmental pollution, leading to worldwide ecological challenges [46]. Synthetic insecticides based on natural products have been used for a long time. A few studies on them revealed that they have significant impacts and contributions in the agricultural insecticide market. Solvent extracts and essential oils from plants that contain coumarin exhibit remarkable performance in controlling pests and insects. However, further studies are needed on the impact on biological activities.

C. Fragrance

Coumarin displays an odor of freshly-mown hay and sweet almonds, with a vanilla undertone. It is an iconic chemical that potentially present in approximately 90% of all perfumes. In 2000, coumarin was primarily used as a fragrance ingredient in products, including detergents and cosmetics, including lotions, cream, and toothpaste [50]. However, serious concerns on the safety of coumarin have been raised way before in the mid-1950s. This started when rats and dogs supplied with coumarin in their diets were found to develop liver lesions.

On the other hand, the results of studies on human skin are conflicting. According to studies sponsored by the Research Institute of Fragrance Materials (RIFM), coumarin was found not to be a sensitizer [50]. Despite that, a clinical study by Malten and his co-researchers in 1984 concluded that coumarin was a sensitizer [50]. The risk of using coumarin in fragrance has been dubious throughout the years.

V. CONCLUSION

Numerous research processes are carried out towards the synthesis of coumarin derivatives, as they have many excellent biological properties and various applications in multiple fields. Therefore, several methods for the synthesis have been employed to utilize new variations, such as the use of catalysts to improve the production and yield. FTIR can be used in the characterization of coumarin derivatives. It detects a range of functional groups by absorbing infrared radiation from the material of the sample. 1H NMR is utilized to determine information of structure, reaction state, and chemical environment of coumarin derivatives. Other methods such as ultraviolet-visible spectroscopy (UV-Vis) and micro elemental analysis (CHNO) can also be used to characterize coumarin derivatives. Various functional groups in coumarin derivatives lead to useful biological activities, toxicology, and fragrance applications. Due to numerous biological activities, researchers' studies on coumarin derivatives are still ongoing to determine more potential industrial applications.

ACKNOWLEDGEMENT

The authors would like to thank Universiti Sains Islam Malaysia (USIM) for the research grant PPPI/FST/0207/051000/12518 and Faculty of Science and Technology (FST), USIM, for all the facilities provided.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received 23rd February 2021; Revised 14th March 2021; Accepted 15th March 2021; Published 1st April 2021

Academic Editor: Azira Khalil
USIM Press
Malaysian Journal of Science, Health & Technology Vol. 7, No. 1 (2021), 7 pages
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