



Recent Advances In Synthetic Developments Of Flavonoids: A Comprehensive Overview

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Article History	Abstract
Received: 20.01.2024 Revised: 02.02.2024 Accepted: 19.02.2024	Being ability to produce molecules with high enantiomeric purity and biological interest makes synthesis an increasingly useful technology. Flavonoids are organic substances having a variety of biological functions. Numerous methods of stereoselective synthesis have been used in order to produce enantiomerically pure forms and take use of their biological potential. These methods include the cycloaddition of 1,4-benzoquinone, Mitsunobu reaction, Sharpless asymmetric dihydroxylation, and chalcone epoxidation. In order to produce chiral bioactive flavonoids with a high enantiomeric ratio, chiral auxiliaries, organometallic, biocatalytic, and chiral auxiliaries were also used. There have also been reports of the Diels-Alder reaction being used to create pure enantiomers of flavonoids utilising catalyst complexes or a racemic mixing approach based on the stereodivergent reaction. As evidenced by the asymmetric coupling of 2-hydroxychalcones triggered by visible light, biomimetic routes also demonstrated a different strategy. The recent synthesis of (R,R)-cis-alcohols, which will serve as the building blocks for the stereoselective synthesis of flavonoids, also utilised an asymmetric transfer hydrogen-dynamic kinetic resolution.
CC License CC-BY-NC-SA 4.0	Keywords: Flavones, Synthesis, Chemistry, Derivatives, Strategies, Pharmacology

1. Introduction

A significant class of polyphenolic chemicals presents in plants, fruits, vegetables, and nuts are called flavonoids. They play a number of tasks in flora, including controlling cell development and protecting it from oxidative stress and harsh climatic circumstances. Additionally, they aid in fruit and blossom colour and fragrance, which encourages pollination [1,2]. Some bioactive flavonoids, in addition to those typically found in terrestrial plants, can also be found in marine sources [3]. A 15-carbon scaffold called a flavonoid is connected to two aromatic rings through a 3-carbon chain, which might be a heterocyclic ring known as a C ring. They can be divided into various groups based on the degree of unsaturation and oxidation of the C ring and the location of the B ring (**Figure 1**). Chalcones serve as the intermediates for the biosynthesis of the

other classes of flavonoids, and in nature, this vast variety of moieties is produced by combining the shikimate and acetate routes under enzymatic transformation.

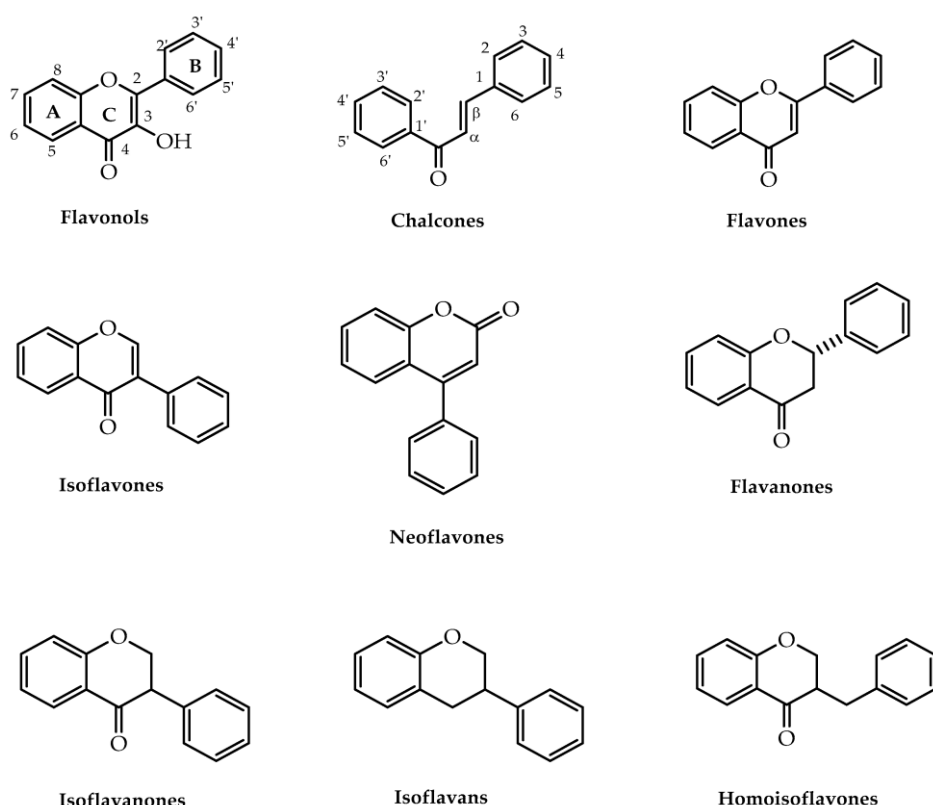


Figure 1. Categories of flavonoids.

It is widely recognised that flavonoids have a range of biological properties with therapeutic promise, including antioxidant [5], antimalarial [6], anti-inflammatory [7, 8], antiviral [9, 10], antibacterial [11], antidiabetic [8], antifungal [12], and anticancer [1, 13, 14, 15, 16]. As a result of their ability to scavenge ROS, it is also claimed that they protect the cardiovascular system from oxidative stress [17]. Additionally, flavonoids can be used in the cosmetic industry as preventative measures against skin degeneration and hyperpigmentation brought on by UV exposure [18]. Because of their inhibition of elastases, collagenases, and tyrosinases, they also help to increase skin firmness and elasticity and prevent the development of dark spots [18].

These polyphenolic chemicals can be exploited in the food sector as sweeteners and colouring agents in pastry items, in addition to their numerous medical benefits [19]. Due to their antioxidant activity, they can also serve as flavour enhancers and guard against lipid peroxidation in seed oils and biscuits [19]. Flavonoids can also be used in the textile industry to create fibres that are biocompatible and improve their quality [18]. Additionally, in order to achieve more ecologically friendly production, these natural substances can be used to the dyeing of fibres [18]. Additionally, flavonoids have been shown to have the ability to prevent metal corrosion, which is intriguing from a metallurgical industry standpoint [20].

Given the biological and industrial potential of natural flavonoids, a variety of chemical techniques have been developed to produce flavonoids that are inspired by nature (**Table 1**) [21-32].

Table 1. Synthetic methods for flavonoid classes.

FLAVONOID CLASSES	REACTION NAMES
Flavones	Oxidative cyclisation of 2'-hydroxychalcones, Baker–Venkataraman reaction, Allan–Robinson reaction, Mentzer pyrone synthesis, Kostanecki reaction, Suzuki–Miyaura reaction
Flavonols	Kostanecki methodology, Algar–Flynn–Oyamada reaction, Karl von Auwers reaction
Flavanones	Intramolecular cyclisation of 2'-hydroxychalcones
Isoflavones	Suzuki–Miyaura reaction, Allan–Robinson reaction, Reductive cleavage of isoxazoles, Deoxybenzoin route, Rearrangement and cyclisation of chalcone epoxides, Intramolecular ketene cycloaddition followed by decarboxylation, Cu(I)-mediated cyclisation of 3-(2-bromophenyl)-3-oxopropanol, Rearrangement of flavanones, Wacker–Cook tandem conversion of α -methylene deoxybenzoins
Neoflavones	Pechmann reaction, Suzuki–Miyaura reaction, Wittig reaction of benzophenones, Perkin reaction, Direct arylation by the palladium-catalysed oxidative Heck coupling of arylboronic acids to coumarins, Metal-catalysed cross-coupling reactions such as Stille type
Chalcones	Suzuki–Miyaura reaction, Claisen–Schmidt reaction, Heck coupling, Friedel–Crafts reaction

The synthesis of other groups of flavonoids, such as flavonols, flavones, and flavanones, can use 2'-hydroxychalcones as intermediates, just as it does in nature. They can be produced synthetically via the Claisen-Schmidt [21], Friedel-Crafts, and Heck coupling routes [21]. The Claisen-Schmidt reaction consists of the reaction of an aromatic aldehyde with a substituted acetophenone with basic catalysis (Scheme A, **Figure 2**). Microwave and ultrasonic technology can be used to speed up this process, increasing yields and decreasing reaction times [30,33]. According to the Friedel-Crafts process, phenols and (E)-3-phenylprop-2-enoyl chloride are condensed by the action of AlCl₃ [21] to produce 2'-hydroxychalcones (Scheme B, **Figure 2**). Additionally, the aryl, α,β -unsaturated ketone and iodobenzene mixture forms the foundation of the Heck coupling mechanism, which results in the synthesis of the appropriate chalcone [32] (Scheme C, **Figure 2**).

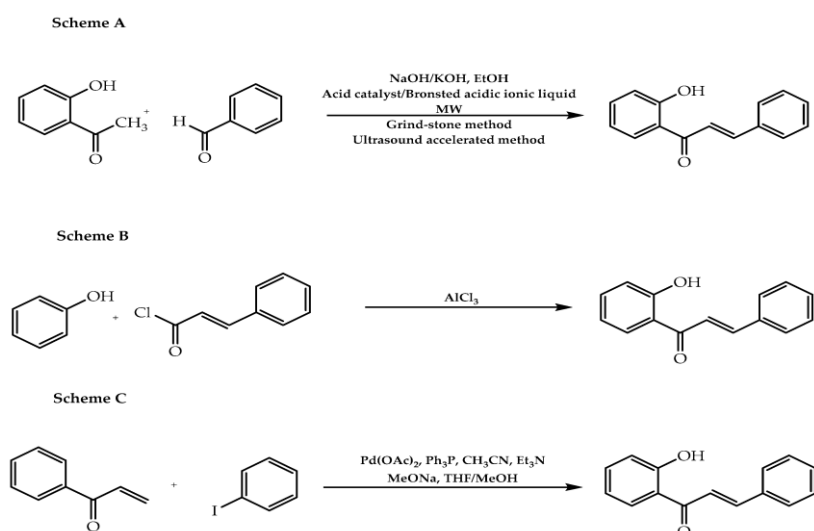


Figure 2. Methods for producing 2'-hydroxychalcones synthetically: **Scheme A:** Claisen–Schmidt reaction; **Scheme B:** Friedel–Crafts condensation; **Scheme C:** Heck coupling reaction.

The Algar-Flynn-Oyamada approach calls for the oxidative cyclization of 2'-hydroxychalcones into flavonols (way I, Figure 3) in an alkaline medium, mediated by hydrogen peroxide [21,34,35]. Additionally, flavanones and flavones may be produced using the 2'-hydroxychalcones as the building blocks (route II, Figure 3). If we take the previously described first class of flavonoids, we can find them using thermolysis [38], electrolysis [39], photolysis [40], microwave irradiation [41], a more environmentally friendly catalytic approach [42], and palladium(II) catalysis [43]. Flavones can be created by the process of oxidative cyclisation under a variety of circumstances, including the traditional I₂-DMSO technique [44] or the use of NH₄I in a solvent-free environment [45]. There has also been reported the use of phenyliodinium acetate (PIDA) [46], selenium (IV) reagents under microwave irradiation [47], indium (III) halides in a gel-silica support system [48], CuI-mediated catalysis in the ionic liquid [bmim] [NTf₂] as solvent [49], diphenyl disulfide at high temperatures [50], and oxalic acid-mediated catalysis [51] to obtain flavones via chalcones.

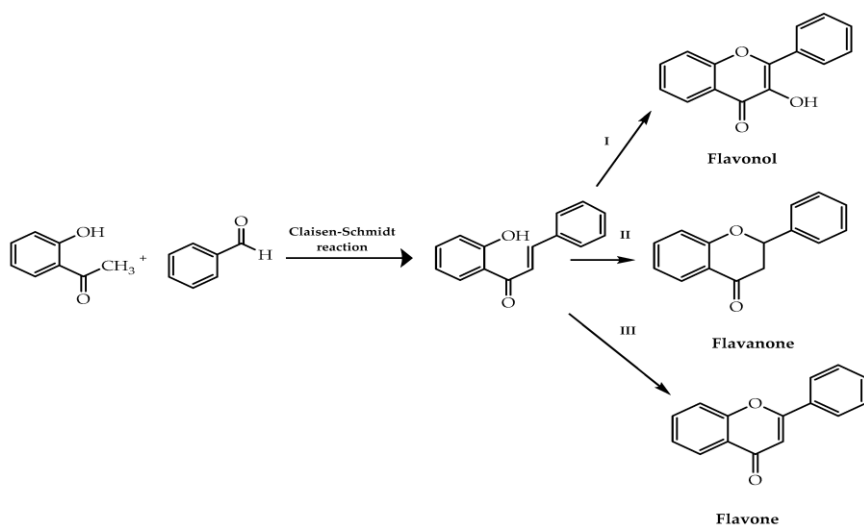
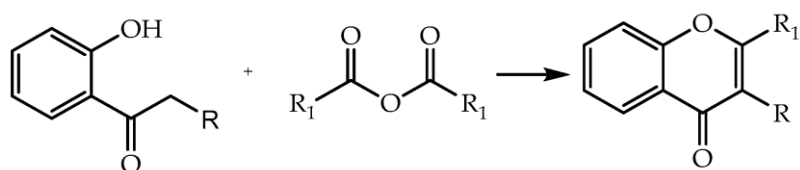


Figure 3. Use of 2'-hydroxychalcones as building blocks in the synthesis of flavonols, flavanones, and flavones.

The production of flavones may also be accomplished using other methods [21,52]. As a synthetic process to produce flavones and isoflavones, the condensation of o-hydroxyaryl ketones, aromatic acid anhydride, and the sodium salt of related aryl carboxylic acid anhydride is established as the Allan-Robinson technique (**Figure 4**) [53].



R₁ = Ph
R = any substituent

Figure 4. Allan–Robinson reaction.

Another technique used to create intermediates for the synthesis of flavones is called Baker-Venkataraman [21]. In this process, basic catalysis is used to change β-acyloxy ketone into β-diketones, and then cyclization takes place to make the final flavone [54] (**Figure 5**).

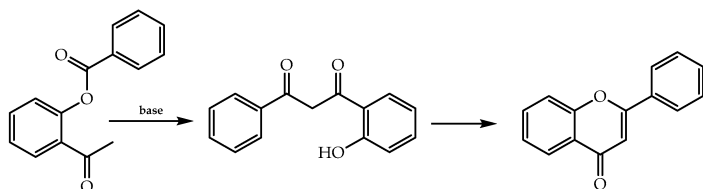
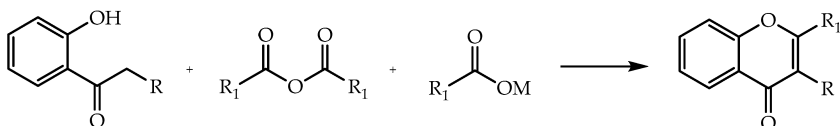


Figure 5. Baker–Venkataraman reaction.

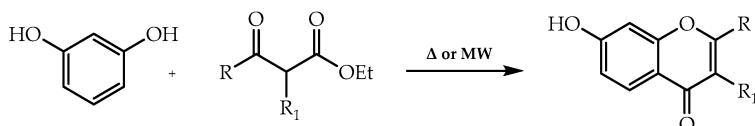
Another popular technique for producing flavonoids, namely flavones, is the Kostanecki method. It is made up of an o-hydroxyaryl ketone, aromatic acid anhydrides, and their associated salt [55] (**Figure 6**). There are several publications on the use of this method to create flavonoids with biological activity, particularly the work done by DeMeyer et al. [56].



R₁ = Ph
R = any substituent

Figure 6. Kostanecki reaction.

The Mentzer pyrone procedure involves synthesising flavone derivatives from phenol and β-ketoester without the use of a solvent, at high temperatures for an extended length of time, or by using microwave irradiation [57] (**Figure 7**). The synthesis of flavones with antifouling action [59] was a recent example of this technique being used by Pereira et al.



R = Ph
R₁ = any substituent

Figure 7. Mentzer reaction.

By means of a series of reactions, aurones are converted into flavonols using the Karl von Auwers technique [60] (**Figure 8**). Due to their chelating properties and capacity to scavenge free radicals, these molecules are

crucial for plants to provide protection against UV radiation and metallic ions. Therefore, using flavonols as a method of therapy for illnesses linked to oxidative stress is possible [61].

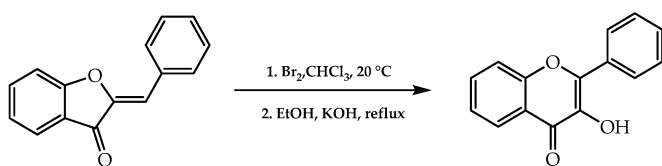


Figure 8. Karl von Auwers approach.

Recent developments in the synthesis of flavonoid moieties have used the Suzuki-Miyaura method [62]. An organohalide and boronic acid/esters are involved in a cross-coupling reaction when a palladium complex is present [63]. Because palladium input takes place in a sp²-hybridized carbon-halide bond, its utilisation is typically linked to the synthesis of chalcones, flavones, isoflavones, and neoflavones [62]. The flavonoid boronates, chrysin, luteolin, and quercetin derivatives were all synthesised by Hurtová et al. [64-104] using this approach.

CONCLUSION

Natural polyphenolic chemicals known as flavonoids are mostly found in plants and are linked to a variety of biological activities, such as antiviral, antibacterial, anticancer, and antioxidant properties. They can also work in the metallurgical, textile, food, cosmetic, and food industries. Due to the interest flavonoids have generated due to their biological importance, synthetic methods have been used to create these natural chemicals, including the following: Algar–Flynn–Oyamada, Baker–Venkataraman, Allan–Robinson, Karl von Auwers, Claisen–Schmidt, Mentzer Pyrone, Kostanecki, deoxybenzoin route, Suzuki–Miyaura, intramolecular ketene cycloaddition followed by decarboxylation, reductive cleavage of isoxazoles, rearrangement of flavanones, Wacker–Cook tandem conversion of α -methylene deoxybenzoin, rearrangement and cyclisation of chalcone epoxides, Pechmann reaction, Cu(I)-mediated cyclisation of 3-(2-bromophenyl)-3-oxopropanol, Wittig reaction of benzophenones, Perkin reaction, direct arylation of arylboronic acids to coumarins through palladium-catalysed oxidative, metal-catalysed cross-coupling reactions, Heck coupling, etc. From this point forward, it will be vital from a scientific standpoint to investigate the biological characteristics of the flavonoids produced using the methods indicated above, as well as to carry out enantioselectivity studies and further investigate their pharmaceutical potential.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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