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Current Topics in Medicinal Chemistry, **XXXX,** *XX,* **1-16**

REVIEW ARTICLE

Facile Synthesis and Applications of Flavonoid-heterocyclic Derivatives

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ARTICLE HISTORY

Received: January 15, 2024
Revised: April 04, 2024
Accepted: April 16, 2024

DOI:
10.2174/0115680266303704240524080333

Abstract: Flavonoids belong to the polyphenol group that naturally exists in fruits, vegetables, tea, and grains. Flavonoids, as secondary metabolites, show indispensable contributions to biological processes and the responses of plants to numerous environmental factors. The bioactivity of flavonoids depends on C6-C3-C6 ring substitution patterns that exhibit bioactive antioxidant, antimicrobial, antifungal, antitumor, and anti-inflammatory properties. The synthesis of flavonoids has been reported by various methodologies. Therefore, the present review systematically summarizes the synthesis of recent heterocyclic flavonoid derivatives *via* facile synthetic approaches since the research in flavonoids is useful for therapeutic and biotechnology fields.

Keywords: Activities, bioavailability, disease, flavonoids, flavone, synthesis.

1. INTRODUCTION

Flavonoids are secondary metabolites that have polyphenolic compounds [1, 2] and are produced in plants, fruits, vegetables, and crops [3, 4]. Flavonoids are mostly stored as glycosides form in plant cells [5]. The structure of flavonoids consists of three rings, **A**, **B**, and **C**, as the basic skeleton (Fig. **1**) [6]. Flavonoids have seven subclasses, such as flavones, flavonols, isoflavones, flavanones, flavanols, anthocyanidins, and chalcones, based on structural differences [3]. Flavonoid is one of the heterocyclic molecules similar to pyrazoline [7], pyrimidine [8], pyrazole [9], epoxide [10], benzodiazepine [11], that are easily synthesized from a well-known stable starting material of chalcone [12]. These heterocyclic flavonoid compounds are useful as insecticides [13] and also used to cure numerous diseases such as Alzheimer's [14] and Parkinson's disease [15], due to bioactivities, such as antioxidant [16-18], anti-inflammatory [19], anti-hepatitis [20], antimicrobial [21, 22], anti-diabetic [23], antifungal [24], antifouling [25], anticancer activities [26].

Flavonoids can be prepared *via* two common methodologies namely biosynthesis and chemical synthesis. In biosynthesis, flavonoids commonly exist in plant sources, such as rice [27], peanuts [28], citrus [29], fenugreek seeds [30], soy [31], tomato [32], apple [33], wheat, corn, tartary buckwheat, ginkgo biloba [34], and *Flos sophorae* flowers [16]. Plants have secondary metabolites [35a, b] containing flavonoids in many biological processes that are not frequently a part of diet due to bioactivities [34]. Furthermore, their bioactivities depend on the C6-C3-C6 substitutional pattern in their rings. Flavonoids epitomize the numerous plant metabolites that display various structures, ubiquitous supply, and contribute to plant growth and adaption, *i.e.*, signalling, coloration, and response to biotic/abiotic stresses [35a, b]. Flavonoids of all types of classes are synthesized from biosynthetic pathways *via* separate regulation through two steps such as step 1: Shikimate pathway and step 2: flavonoid biosynthesis [36, 37]. The shikimate pathway (step 1) starts from the modifications of shikimic acids into L-phenyl alanine [38], further modified into hydroxycinnamic acids under enzymatic actions that lead to the formation of hydroxyl cinnamoyl CoA. The flavonoid pathway (step 2) begins from the hydroxyl cinnamoyl CoA and malonyl CoA condensation that leads to the production of naringenin chalcones through the catalyst chalcone synthase (CHS) [39]. Then, naringenin chalcone is converted into naringenin under the catalysis of chalcone isomerase (CHI) *via* stereospecific and intramolecular cyclization [40]. CHI ensures the biologically active (S)-isomer formation and the contribution of CHS to the rate-limiting step catalyzes. Furthermore, naringenin is converted into dihydroflavonol and lastly into apigenin-targeted flavonol with the aid of flavanone 3-hydroxylase (F3H) and flavonol synthase (FLS), respectively [40, 41]. Luteolin and cheysin are also formed from slightly modified reagents and by following the same procedure reported for apigenin. The main drawback of biosynthetic methodology is the regulatory mechanisms of the genes, which depend upon diverse, complex, species-

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1568-0266/XX $65.00+.00

dependent flavonoids of interest (Fig. **2**) [36]. Zhao *et al.* (2021) investigated the AP2/ERF three transcription factors as positive regulators for flavonoid synthesis *via* CitCHIL1 expression [35a, b]. In enzyme-based methods, *Dianthus caryophyllus* generated enzymes, such as chalcone synthase and isomerase for the formation of chalcone and its derivatives [42].

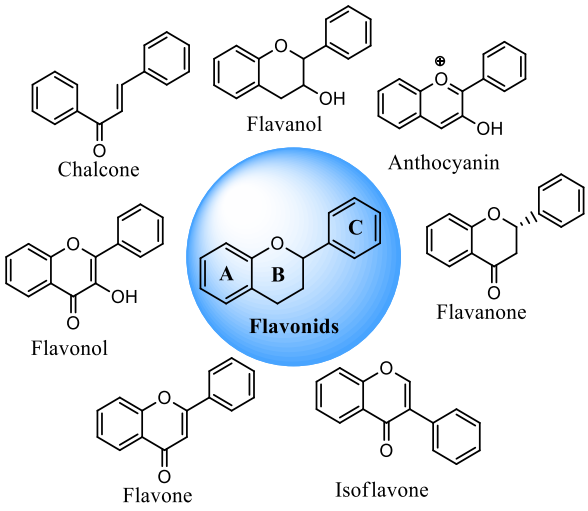

Fig. (1). Classification of flavonoids. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In Chemical Synthesis, numerous methods have been reported for flavonoid synthesis, such as Suzuki Miyaura reaction [43], oxidative cross-coupling of diazochromone and phenylboronic acid [43], acid chloride and hydroxy acetophenone (Baker-Venkataraman rearrangement) [44, 45], epoxy chalcone, hydroxy chalcone derivatives [46], and aldehyde and ketones [47, 48], along with Auwers synthesis (3-cyclooxapentanone and benzaldehyde) [49], Allan-Robinson reaction (aromatic anhydrides with hydroxyaryl ketones) [50], and Kostanecki synthesis (aliphatic acid anhydrides with hydroxyaryl ketones in the presence of salt) also known as Kostanecki- Robinson reaction [1, 51]. Among these all-synthesis routes, only chalcone-based synthesis is most frequently preferred due to easy, simple cyclization reaction [52], reaction conditions, easy purification, and commercial availability of reagents (Fig. **3**) [12].

In literature, numerous reviews have been reported regarding the potential of flavonoids [53, 54], their roles against human diseases [55, 56], and the advance of glycoside-flavonoids [57] and flavonoid compounds [58]. Panche *et al.* illustrated the contribution of flavonoids as natural products effective in curing Alzheimer's disease and its mechanisms [59] with some elaboration on the current trends of flavonoids in research and development, along with their dietary applications [60]. This review elaborated on the latest research about the synthesis of flavonoid-heterocyclic derivatives having five-membered and six-membered moieties, along with their specific applications and future research directions.

1.1. Synthesis of Flavonoid-heterocyclic Derivatives

Flavonoid-heterocyclic derivatives were synthesized with the different varieties of heterocyclic rings, such as five or six-membered rings, *i.e.*, imidazole, isoxazole, triazole, thiazole, dioxolane pyrrolidone, coumarins, pyridine, piperine, pyrazine, and pyran.

Five-membered rings of flavonoid-heterocyclic compounds have been commonly reported in literature. The flavonoid-incorporated imidazole derivatives are an example of five-membered rings flavonoids and were synthesized by using compound **(1)** treated with HOBt and DIC at room temperature. It was later treated with different amino acids or amines with the aid of DIEPA/DMF and further treated with $SnCl_2$/DMF to produce amide derivatives (**2** & **3**) with 96-99 % yield. Compounds (**2** & **3**) reacted with the isothiocyanates and aldehydes to achieve target compounds (**4-7**) with 96-99 % yield. These series of flavones exhibited antiproliferation activities for MDA-MB-231 and MCF-7 breast cancer cells. The 5 μM IC_{50} of compounds **4a** and **5c** exhibited good potential against cancer cell lines due to imidazole moiety (Scheme **1**) [61].

Benzimidazoles is known as imidazole, iminazole, 1H-benzimidazole, 1,3-benzodiazole, and benzoglyoxaline. It is an aromatic compound that has gained attention in the medicinal field as an anticancer drug [62]. The structure of benzimidazole was first synthesized by Hoebrecker, and its properties have made it an excellent scaffold for drug development [63]. Moreover, compound **8** was treated with *o*-phenylenediamine (OPDA) in acetic acid media for 4 h with stirring to get compound **9** and further treated with alkyl or aryl azides and $CuSO_4.5H_2O$ and sodium ascorbate to produce 65-80 % yield of imidazole-triazole substituted flavonoid (**10**). Isoxazole has oxygen and nitrogen moieties in its five-membered ring, which leads to excellent activities [64]. Pyrano-isoxazole incorporated flavonoids derivatives (**12**) were synthesized from the reaction of compound (**8**) with 3-bromoprop-1-yne in potassium carbonate, which was further treated with sodium acetate and hydroxylamine hydrochloride under 1 h reflux to produce compound **(11)**. The sample was further stirred for 30 min with ceric ammonium nitrate in acetonitrile to achieve product (**12**) with 62-70% yield (Scheme **2**). Among these, compound **10** (*p*-Cl-C_6H_4, *p*-NO_2-C_6H_4 and *p*-F-benzyl) showed IC_{50} values ranging from 14.2-19.1 μM for antiproliferative activities against MCF-7 breast cancer cell line. Furthermore, methyl substituted compound (**12**) showed 41.7% inhibition with 30 μM drug for the antimycobacterial activities against *M. bovisstrain* [65].

Flavonoids can be further incorporated into imidazole and triazole groups to form compound (**14** and **15**). Imidazole is an active compound with antifungal properties used to cure vulvovaginal candidiasis, seborrheic dermatitis, fungal skin infections, tinea pedis, and cutaneous candidiasis [66]. Nitrogenous compound, triazole also has medicinal applications, such as itraconazole, voriconazole, and posaconazole, which are used for *Aspergillus* disease treatment [67].