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Mini-review

Recent advances of chroman-4-one derivatives: Synthetic approaches and bioactivities

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ABSTRACT

Chroman-4-one scaffold is a privileged structure in heterocyclic chemistry and drug discovery. Also, chroman-4-ones are important intermediates and interesting building blocks in organic synthesis and drug design. The structural diversity found in the chroman-4-one family led to their division into several categories including benzylidene-4-chromanones, flavanones (2-phenyl-4-chromanones), isoflavanones (3-phenyl-4-chromanones), spirochromanones, and C-4 modified chroman-4-ones such as hydrazones and oxime derivatives. This review addresses the most significant synthetic methods reported on 4-chromanone-derived compounds and consequently emphasizes on the biological relevance of such compounds.

1. Introduction

Chroman-4-one (2,3-dihydro-1-benzopyran-4-one) belongs to the six-membered heterocyclic compounds and is composed a benzene nucleus fused to 2,3-dihydro-γ-pyranone ring [1]. The structure of chroman-4-one is distinct from chromone by reduction of C_2–C_3 double bond (Fig. 1). This small difference in the structure of chroman-4-ones and chromones resulted in big differences in their chemistry and bioactivity.

The 2-phenyl chroman-4-one derivatives are known as flavanones which are naturally occurring compounds with diverse biological activities. For example, sakuranetin is a flavanone acts as a phytoalexin against spore germination of *Pyriculariaoryzae* [2]. Naringin, a flavanone glycoside acts as inhibitor of vascular endothelial growth factor (VEGF) release [3], reduces diabetes-induced neuropathy in rats [4] and also displays protective effects on cognition and oxidative damage in rats [5]. Naringenin is a polyhydroxylated flavanone and acts as antioxidant, free radical scavenger, anti-inflammatory and immune system modulator [6]. Eriodictyol and sterubin are cathecholic flavanones which used as taste-modifying agents [7] (Fig. 2).

Chroman-4-one scaffold is a privileged structure in drug discovery and development. Chroman-4-one derivatives such as (2*S*)-5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-2,3-dihydro-4*H*-chromen-4-one, 4′-hydroxyflavanone, 5-deoxyflavanone, 5,4′-dideoxyflavanone, and (2*S*,3*S*)-*trans*-dihydroquercetin are under experimental or clinical development, and hesperetin has been approved as a cholesterol-lowering agent [8] (Fig. 3).

The synthesis of chroman-4-one derivatives and their chemistry are of great interest in the field of organic and medicinal chemistry. The chroman-4-one scaffold is an important intermediate and interesting building block in organic synthesis and design of new lead compounds in drug design and discovery. We discussed in our review about importance of chroman-4-one scaffold in drug design and discovery and their synthetic approaches.

2. Convenient methods for the synthesis of chroman-4-ones

2.1. Synthesis of chroman-4-ones via Michael addition

A two-step, efficient and practical synthesis of a variety of 4-chromanones **3** was described by Zhong et al. (Fig. 4). The synthetic route is initiated from the Michael addition of phenols **1** to acrylonitrile in *tert*-butanol and in the presence of potassium

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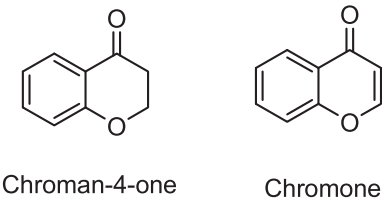

Fig. 1. Structures of chroman-4-one and chromone.

carbonate as catalyst. Intermolecular Houben–Hoesch reaction of 3-aryloxypropanenitriles **2** by using trifluoromethane sulfonic acid (1.5 equiv) and trifluoroacetic acid (5 equiv) affords desired 4-chromanones **3** in excellent yields [9].

2.2. Synthesis of chroman-4-ones from o-(trimethylsilyl) phenyltriflate and acrylic acids

As illustrated in Fig. 5, the heating of acrylic acids **4** with *o*-(trimethylsilyl)phenyltriflate **5** in THF in the presence of CsF (5.0 equiv) gives the desired 4-chromanones **6** [10].

2.3. Synthesis of chroman-4-ones via aldol condensation of 2′-hydroxyacetophenones with aldehydes

For instance, Fridén-Saxin and co-workers synthesized 2-substituted 4-chromanone **9** by using microwave irradiation. Aldol condensation of 2′-hydroxyacetophenones **7** with appropriate aldehydes **8** by heating the ethanolic mixture of them to 160–170 °C using microwave (MW) irradiation in the presence of

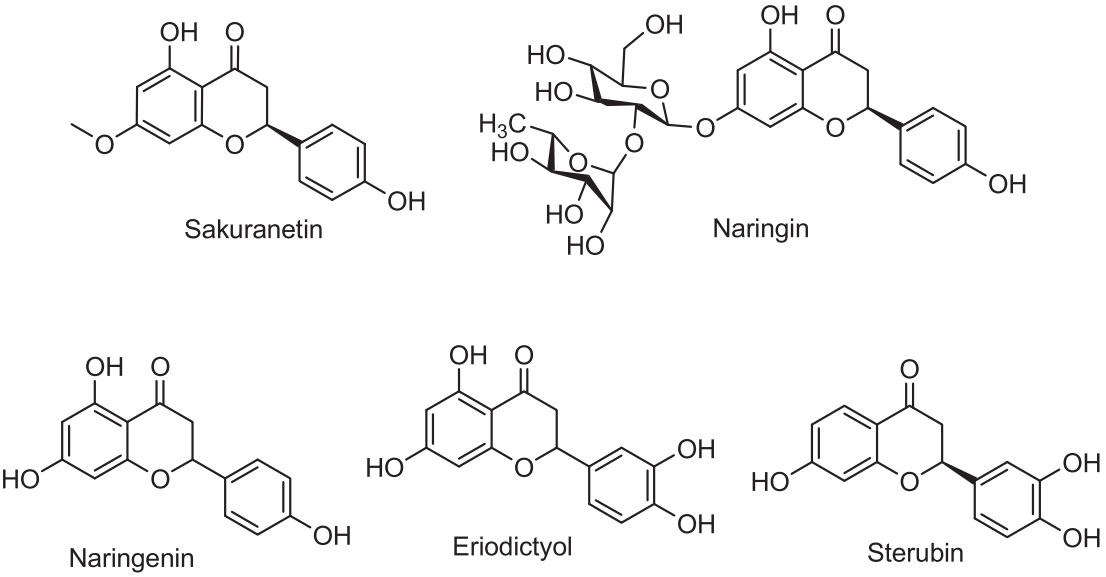

Fig. 2. Structures of some naturally occurring 2-phenyl chroman-4-ones (flavanones).

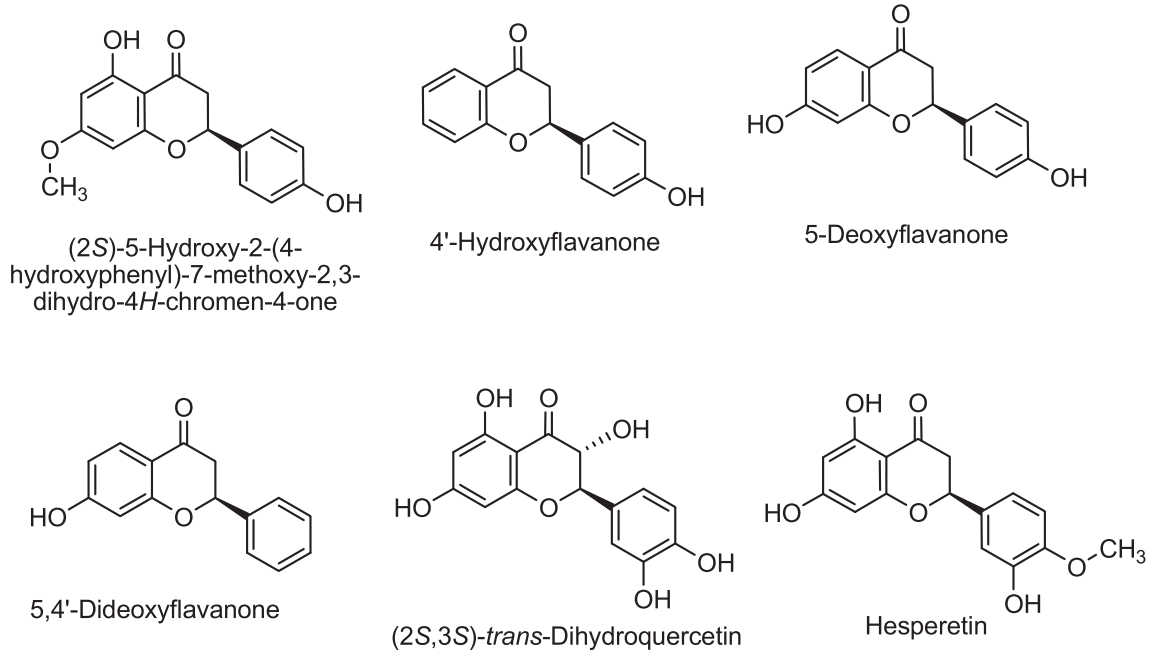

Fig. 3. Structures of some 4-chromanone-drived drugs under development.