European Journal of Medicinal Chemistry 78 (2014) 340–374

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Mini-review

Chromones as a privileged scaffold in drug discovery: A review

Rangappa S. Keri*, Srinivasa Budagumpi, Ranjith Krishna Pai, R. Geetha Balakrishna

Organic and Medicinal Chemistry Laboratory, Center for Nano and Material Sciences, Jain University, Jain Global Campus, Jakkasandra Post, Kanakapura Road, Ramanagara District, Karnataka 562112, India

ARTICLE INFO

Article history:
Received 26 October 2013
Received in revised form
14 March 2014
Accepted 15 March 2014
Available online 18 March 2014

Keywoards:
Heterocycles
Chromone
Synthesis
Pharmacological activities

ABSTRACT

The chromone and its derivatives are the most important heterocyclic compounds, which is a common and integral feature of a variety of natural products and medicinal agents. These heterocycles show a variety of pharmacological properties, and change of their structure offers a high degree of diversity that has proven useful for the search of new therapeutic agents. A large volume of research has been carried out on chromone and their derivatives, which has proved the pharmacological importance of this heterocyclic nucleus. The present review focuses on the pharmacological profile of chromone derivatives in the current literature with an update of recent research findings on this nucleus and the perspectives that they hold for future research.

1. Introduction

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [1]. Chromone (**1**) (4H-chromen-4-one, 4H-1-benzopyran-4-one) is an important class of oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring and they are part of the flavonoid family (Fig. 1). The chromone and related compounds are widespread in the plant kingdom from algae to conifers. Chromones have found to be active in a number of plant cycles, including growth regulation, indole acetic acid oxidation and dormancy inhibition as well as exhibiting cytokinin-type behavior and stimulating oxygen uptake in plant tissue [2].

Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activity like anti-bacterial, anti-fungal [3,4], anti-cancer [5], anti-oxidant [6], anti-HIV [7], anti-ulcers [8], immunostimulators [9], biocidal [10], wound healing [11], anti-inflammatory [12], and immune-stimulatory [13]. Many chromone derivatives are also photoactive and can be used easily in various photoinduced reactions affording diverse heterocyclic compounds [14]. Chromone derivatives are also active at benzodiazepine receptors [15] and on lipoxygenase and cyclooxygenase [16]. In addition to this, they have been shown to be possessing antimutagenic properties [17] as well as the ability to inhibit electron transport through inhibition at NADH:ubiquinone oxidoreductase and phorbol ester-inducedornithinedecarboxylase [18,19]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator [19b]. These compounds also possess low mammalian toxicity and are present in large amounts in the diet of humans due to their origin in plants [16]. To list a few chromone derivatives, which are actively used in pharmacological field are given below (Fig. 2). Although there are a large number of chromone derivatives known for their pharmacological properties there are only a few examples that have been or that are used as therapeutic agents today. Cromolyn or cromoglicate (Cromoglicic acid) is used as a mast cell stabilizer in allergic rhinitis, asthma and allergic conjunctivitis. Nedocromil (Alocril) is used to prevent wheezing, shortness of breath, and other breathing problems caused by asthma. Apigenin (4′,5,7-trihydroxyflavone) and used as a potent inhibitor of Cytochrome P450 2C9 (CYP2C9). Diosmin used in the treatment of venous disease, i.e., chronic venous insufficiency (CVI) and hemorrhoidal disease (HD), in acute or chronic haemorrhoids. Flavoxate (2-(1-piperidyl)ethyl 3-methyl-4-oxo-2-phenylchromene-8-carboxylate) is an anticholinergic with antimuscarinic effects [20]. Furthermore, around the 1950s, khellin was used as a smooth muscle relaxant in the treatment of angina pectoris and asthma. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure [21a]. The main objectives of chromones syntheses are not only for the development of more diverse and complex bioactive compounds for biological activity and structure–activity relationship (SAR) studies but also for

* Corresponding author.
E-mail addresses: keriphd@gmail.com, sk.rangappa@jainuniversity.ac.in (R.S. Keri).

http://dx.doi.org/10.1016/j.ejmech.2014.03.047
0223-5234/

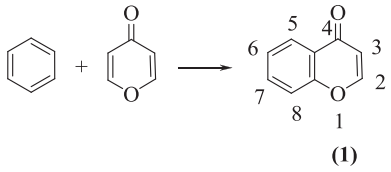

Fig. 1. Chemical structure of chromone.

other applications in medicinal chemistry, such as preparation of fluorescence probes, due to photochemical properties of chromones [21b]. Some reviews on involvement of chromone nucleus in anti-cancer activity [22a] and synthesis part are available in literature [22b]. Some compilations of reports on all activities associated with chromone nucleus are also reported. Sharma et al., have reviewed on the natural occurrence and biological activity of chromones [22c]. Khadem and Marles have reviewed on occurrence and bioactivity of chromone [22d]. Cazarolli et al., have published review on therapeutic potential of chromone nucleus for some activities [22e] but no comprehensive report on varied activities of chromone based compounds is available in literature till date (upto 2013). Hence, the present review gives a comprehensive insight into the current applications of chromone nucleus in varied therapeutic fields. In addition to various therapeutic uses chromone have been found as important intermediates in many organic reactions.

2. Chemistry

The synthesis of chromone derivatives is a research field of great interest and long history [23]. A number of methods have been developed for the synthesis of chromone derivatives: for example, the Allan-Robinson strategy, from chalcones and *via* an intramolecular Wittig strategy [24,25]. One of the most common methods involves acylation of an *o*-hydroxyacetophenone with an aromatic acid chloride yielding an aryl ester. The ester is then rearranged by a base (Baker–Venkataraman rearrangement) to a 1,3-diaryl 1,3-diketone, later compound gives a 2-arylchromone on cyclocondensation [26]. This is usually a catalyzed reaction and it has been carried out in different media. Some reaction conditions employed were the use of excess of sulfuric acid in glacial acetic acid [27], cationic exchange resins in isopropanol [28], glacial acetic acid-anhydrous sodium acetate or aqueous potassium carbonate [29] (Fig. 3). Greener procedures have been recently described, using $CuCl_2$ in ethanol [30], ionic liquid under microwave irradiation, heteropolyacids [31], and *ortho*-fluorobenzoyl chloride in condensation with a 1,3- keto – ester the fluoride is displaced in an intramolecular sense by enolate oxygen, and the chromone obtained directly. *ortho*-Hydroxyaryl alkynyl ketones are intermediates in palladium catalyzed coupling of *ortho*-hydroxyaryl iodides with terminal alkynes in the presence of carbon monoxide, ring closing to chromones *in situ* [32] (Fig. 4).

3. Pharmacological activities of the chromone analogs

Chromone and its analogs are important pharmacophores and privileged structures in medicinal chemistry and have featured in a number of clinically used drugs.

The most relevant and recent studies have revealed that chromones derivatives have a broad spectrum of pharmacological activities which can be classified into the following categories:

1. Anti-cancer agents
2. Anti-HIV agents
3. Anti-oxidant agents
4. Anti-tubercular agents
5. Anti-inflammatory and Analgesic agents

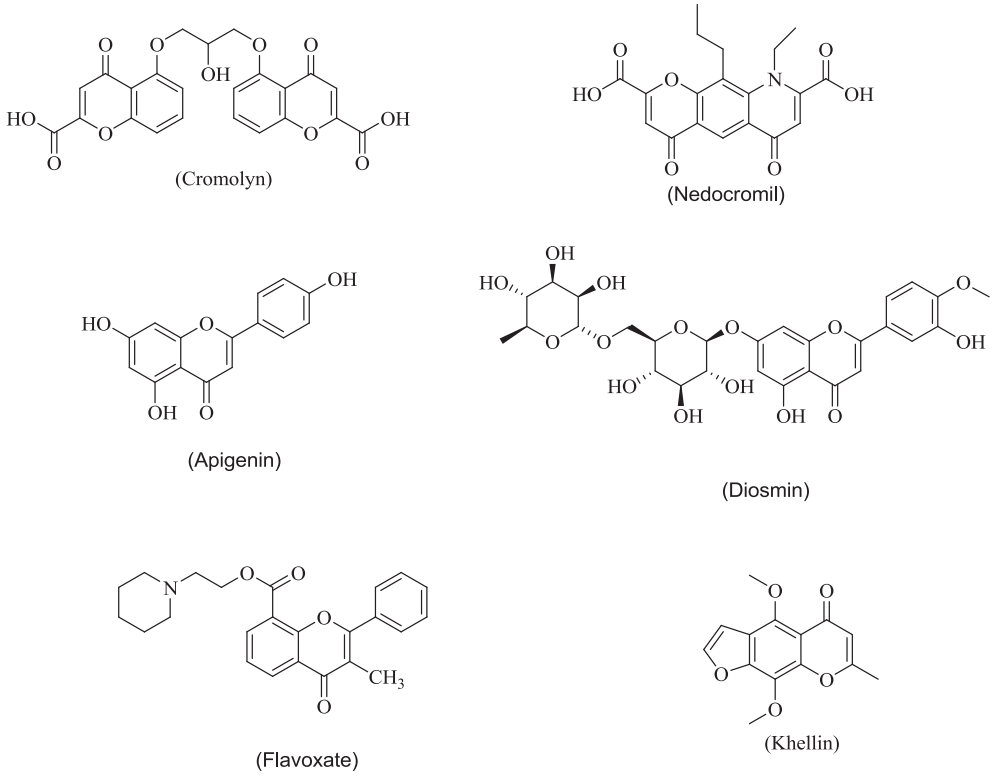

Fig. 2. Examples of chromone-based compounds that have been or that are used as pharmaceutical agents.