European Journal of Medicinal Chemistry 65 (2013) 51–59

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis of some novel chalcones, flavanones and flavones and evaluation of their anti-inflammatory activity

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ARTICLE INFO

Article history:
Received 29 January 2013
Received in revised form
23 April 2013
Accepted 25 April 2013
Available online 3 May 2013

Keywords:
Chalcone
Flavanone
Flavone
Anti-inflammatory
Indomethacin
TNF-α

ABSTRACT

A novel series of synthetic 2′-hydroxychalcones (**1a**–**h**), 2′-methoxychalcones (**2a**–**l**), flavanones (**3a**–**k**) and flavones (**4a**–**f**) have been synthesized and evaluated for their anti-inflammatory activity in carrageenan induced rat paw oedema model. Compounds **1a**, **1e**–**g**, **2e**–**g**, **3j**, and **4f** showed potent anti-inflammatory activity comparable to the reference drug indomethacin with insignificant ulceration. Compound **1f** showed mild inhibition against the enzymatic activity of ovine COX-1 and COX-2 (in-vitro). Compound **1f** also exhibited inhibitory activity in LPS induced TNF-α production.

1. Introduction

Inflammation is clinically defined as a pathophysiological process characterized by redness, oedema, rise in temperature, pain, and loss of function. Although steroidal anti-inflammatory drugs (SAID) and nonsteroidal anti-inflammatory drugs (NSAID) are currently used to treat acute inflammation, these drugs have not been entirely successful in curing chronic inflammatory disorders as these compounds are accompanied with unexpected side effects. Since the critical aetiology and exacerbating mechanisms are not completely understood, it is difficult to develop a magic bullet for chronic inflammatory disorders. Therefore, there is a need for new and safe anti-inflammatory agents.

Flavonoids are a group of chemical entities of the compounds whose structure is based on C_6–C_3–C_6 (two phenyl rings are attached through a propane bridge). They are mainly classified as chalcones, flavanones, flavones, flavonols and isoflavones [1]. Natural and synthetic flavonoids have been dragging continuous attention due to their ample range of biological activities. They have shown to possess anxiolytic [2], anti-inflammatory [3,4], antiviral [5], antiprotozoal [6], anti-tuberculosis [7], antitumour [8], antioxidant [9] and antimicrobial [10] activity. Many have gastro-protective action and some of them act in healing of gastric ulcers [11]. Previous studies have also shown that certain flavonoids, especially flavone derivatives, express their anti-inflammatory activity at least in part by modulation of proinflammatory gene expression such as cyclooxygenase-2, inducible nitric oxide synthase, and several pivotal cytokines [3].

As part of our continuous search for potential anti-inflammatory drug candidates [12,13] and based on the diverse biological activities of flavonoids, in the present study we have synthesized some novel flavonoids [twenty chalcones (**1a**–**h** and **2a**–**l**), eleven flavanones (**3a**–**k**), and six flavones (**4a**–**f**)] and examined their *in vivo* anti-inflammatory activity. The compound which showed maximum anti-inflammatory activity (**1f**) was evaluated for its ulcerogenic effect and also tested for its ability to inhibit the enzymes COX-1 and COX-2. We also examined the effect of compound **1f** on the level of TNF-α in LPS-treated mouse macrophages.

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http://dx.doi.org/10.1016/j.ejmech.2013.04.056

2. Results and discussion

2.1. Chemistry

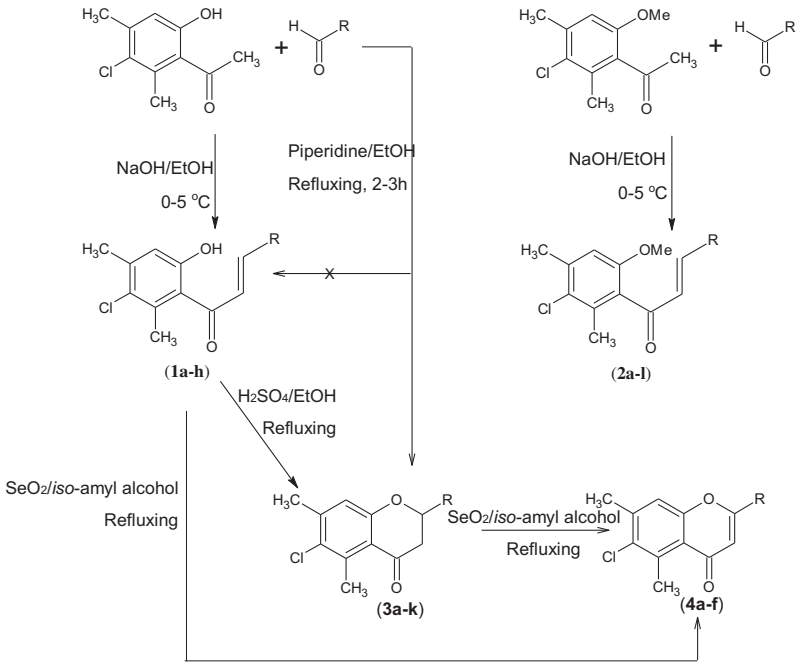
All the compounds were synthesized according to the steps outlined in Scheme 1. The chalcones (**1a**–**h** and **2a**–**l**) were prepared by condensing aromatic aldehydes and acetophenones in presence of sodium hydroxide in ethanol at 0–5 °C for 12 h. Eleven new flavanones (**3a**–**k**) were prepared either by refluxing 2′-hydroxychalcones in ethanol in presence of Conc. H_2SO_4 or by condensation of 2-hydroxyacetophenone with different aromatic aldehydes in the presence of piperidine. Flavones (**4a**–**f**) were synthesized by using traditional methodology from corresponding 2′-hydroxychalcones/flavanones. All the newly synthesized compounds were confirmed by the various analytical techniques (UV, IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis). In the ^{1}H NMR spectra of chalcones olefinic protons H-α and H-β appeared as doublets or multiplets in the range of δ 6.77–7.52 and δ 7.17–8.12 respectively. *trans*-Stereochemistry of propenone moiety of chalcones was confirmed by coupling constant of vinyl hydrogen (15–16 Hz). In flavones and flavanones hydrogen atoms attached to the C-3 appeared as a singlet in the range of δ 5.69–6.90. Hydrogen atoms attached to the C-8 in flavones appeared as a singlet in the range of δ 7.32–7.38. In the ^{13}C NMR spectra of 2′-hydroxychalcones (**1a**–**h**) the chemical shift values of olefinic C-α and C-β carbon atoms appear in the range of (118.70–123.56 ppm) and (135.74–144.60 ppm) respectively. The IR spectra of chalcones showed carbonyl absorption in the range of 1612–1702 cm^{-1} and an olefinic C=C in the range 1504–1602 cm^{-1}. Flavanones and flavones showed carbonyl absorption in the range of 1662–1683 cm^{-1} and 1626–1675 cm^{-1} respectively. In the mass spectra of all compounds M + 2 peaks correspond to M+ for 37Cl isotopes.

2.2. Pharmacology

2.2.1. Anti-inflammatory activity

The *in vivo* anti-inflammatory effect of the synthesized compounds was evaluated at the dose of 20 mg/kg body weight using carrageenan-induced hind paw oedema model (Table 1).

Compounds (**1a**–**h**), 2′-hydroxychalcones showed mild to strong anti-inflammatory activity (26–91% at 3 h, 14–90% at 5 h). It is interesting to note that introduction of atom or group (Cl, NO_2, OCH_3) at *ortho* or *para* positions (C-2 or C-4) leads to significant reduction in the activity (**1a** vs. **1d**, **1a** vs. **1h**, **1a** vs. **1b** and **1a** vs. **1e**). On the other hand introduction of oxy group at *meta* position (C-3 or C-5) leads to significant increase in the activity (**1a** vs. **1g**, **1a** vs. **1e**, and **1a** vs. **1f**). Among these chalcones (**1a**–**h**) compound **1f** showed most potent activity, about 90% inhibition of oedema. Two other compounds, **1a** and **1e** exhibited comparable activity with that of the reference drug at 5 h (82% inhibition in both cases), whereas compounds **1g**, **2e** and **2g** showed significant inhibition comparable to standard drug at 3 h.



1a, 2a, 3a, 4a, R= phenyl

1b, 2b, 3b, 4b, R= 4-methoxypheny

1c, 2c, 3c, 4c, R= 4-chloro phenyl

1d, 2d, 3d, 4d, R=2-chloro phenyl

1e, 2e, 3e, 4e, R= 3,4-dimethoxyphenyl

1f, 2f, 3f, 4f, R= 3,4,5-trimethoxyphenyl

1g, 2g, 3g, R= 3-hydroxyphenyl

2h,3h, R=2-hydroxyphenyl

2i,3i, R=3-nitrophenyl

2j,3j, R=4-N,N-dimethylaminophenyl

2k,3k, R=4-hydroxy-3-methoxyphenyl

1h,2l, R=2-nitrophenyl

Scheme 1. General procedures used to prepare 2′-hydroxychalcones, 2′-methoxychalcones, flavanones and flavones.