Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 2178–2188
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Synthesis and biological activities of some new fluorinated coumarins and 1-aza coumarins

Rajesh G. Kalkhambkar [a], Geeta M. Kulkarni [a,*], Chandrappa M. Kamanavalli [a], N. Premkumar [b], S.M.B. Asdaq [b], Chung Ming Sun [c]

[a] *Department of Chemistry, Karnatak University's Karnatak Science College, College Road, Dharwad 580001, Karnataka, India*
[b] *Department of Pharmacology, Krupanidhi College of Pharmacy, Bangalore 560034, Karnataka, India*
[c] *Department of Applied Chemistry, National Chiao-Tung University, Hsinchu 300-50, Taiwan*

Received 5 May 2007; received in revised form 16 July 2007; accepted 9 August 2007
Available online 11 September 2007

Abstract

A series of new fluorinated coumarins and 1-aza coumarins have been synthesized and the presence of fluorine in these molecules and its effect on their anti-microbial, anti-inflammatory and analgesic activities are discussed. The results of bioassay showed that these newly synthesized compounds containing fluorine exhibit moderate analgesic and excellent anti-inflammatory and potential anti-bacterial and anti-fungal activities, compared to the other halogenated compounds. All the newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, EI-MS, and FAB-MS. The ORTEP diagram of one of the compounds is reported herein.

Keywords: Fluorinated coumarin; Fluorinated 1-aza coumarin; Anti-bacterial; Anti-fungal; Analgesic; Anti-inflammatory

1. Introduction

Coumarin and its nitrogen analogue 1-aza coumarin (also known as carbostyril) are a class of lactones and lactams, respectively, which are indispensable heterocyclic units to both the chemists and the biochemists. A comparative review of these two systems has been reported recently, for their natural occurrence, anti-microbial, anti-inflammatory, anti-cancer and other miscellaneous properties [1]. Many coumarin derivatives are known for their special property of scavenging Reactive Oxygen Species (ROS) and have been found to be inhibitors of cyclooxygenase and lipoxygenase in the arachidonic acid pathway of inflammation suppression [2]. Non steroidal anti-inflammatory drugs (NSAIDs) have a broad spectrum of effects in acute pain management and target the cyclooxygenase enzyme. Several coumarin derivatives have been reported for their significant anti-inflammatory activities and their ability to inhibit these enzymes in inhibiting inflammation [3–5]. The potential of coumarin derivatives as anti-inflammatory agents has been explored in our laboratory, by incorporating biocompatible pharmacophores like vanillyl, cyanoester and paracetamol, at the allylic position with respect to C3–C4 double bond of the coumarin moiety [6,7].

1-Aza coumarin derivatives, which ultimately metabolize as the corresponding 8-hydroxy coumarins in the biological system are therefore found to be very good anti-inflammatory and analgesic agents [8]. The triheterocyclic thiazoles synthesized from 4-aminomethyl carbostyrils and 3-bromoacetyl coumarins [9] in our laboratory were found to exhibit promising anti-inflammatory and analgesic activities even after 24 h.

Interest in coumarins and 1-aza coumarins as antibiotics is due to the recent observations that these are potent inhibitors of bacterial DNA gyrase, which is involved in cell growth [10,11]. Many coumarin and 1-aza coumarin derivatives, with variety of substituents at 4-position, with very good anti-bacterial activity have been reported from our laboratory [12–15].

* Corresponding author. Tel.: +91 836 2770476; fax: +91 836 2747884.
E-mail address: geeta_2562005@yahoo.com (G.M. Kulkarni).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.08.007

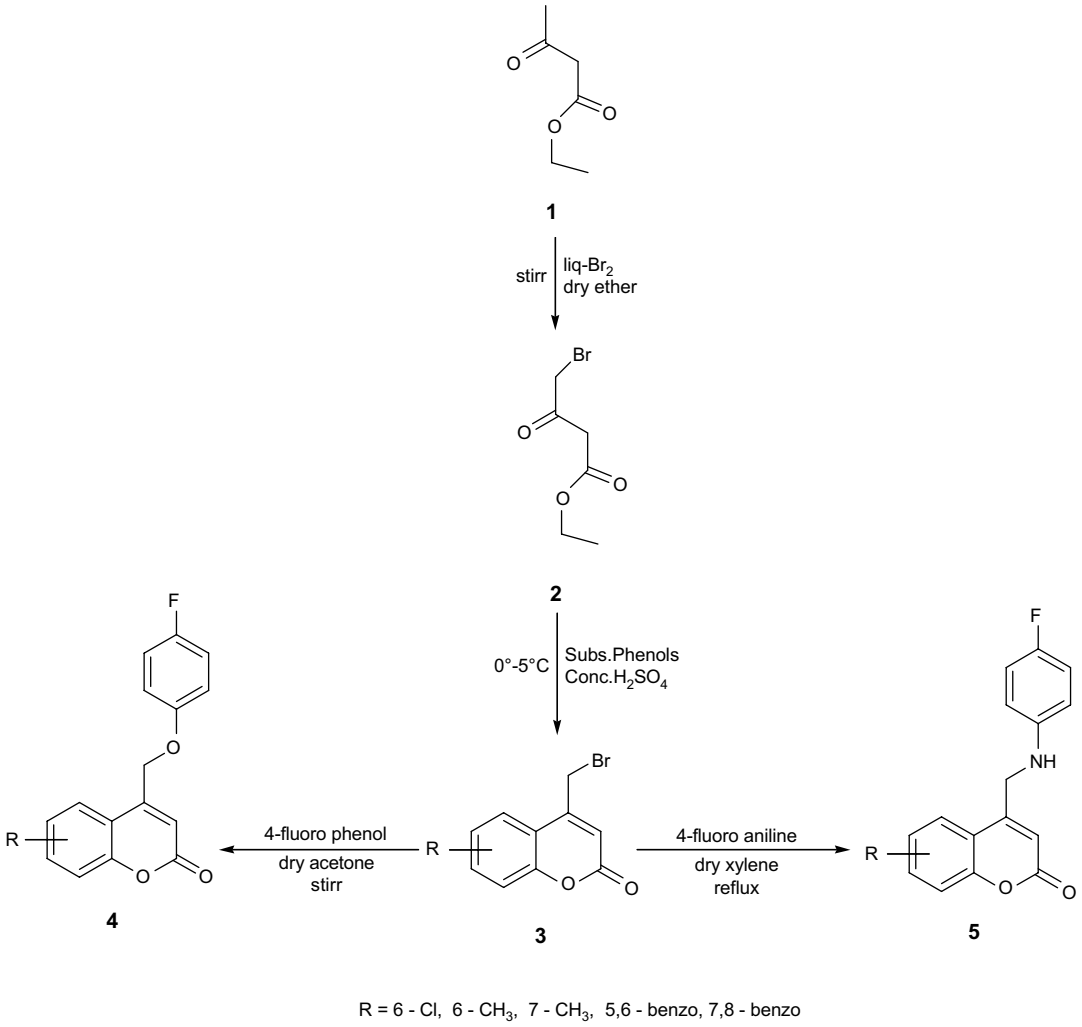
Incorporation of fluorine into organic molecules can lead to distinctive modification in their biological properties [16]. Fluorinated heterocycles have been found to exhibit enhanced enzyme inhibiting [17] and anti-microbial activities, as compared to their non-fluorinated analogues [18,19]. A series of 3-amino carbostyril derivatives containing fluorine have been reported as promising potassium (Maxi-K) channel openers, targeted for neuroprotection [20].

Hence the purpose of the present work was to explore and develop the new templates containing fluorine, coumarin and 1-aza coumarin, with three points of molecular diversity.

2. Chemistry

Synthesis of various 4-bromomethyl coumarins [21] was brought about by the Pechman cyclisation of phenols with 4-bromoethylacetoacetate (Scheme 1). The substituted 4-[(4′-fluoro) phenoxymethyl]-coumarins (**4a–e**) were synthesized at room temperature by stirring the reaction mixture of 4-fluorophenol and anhydrous K_2CO_3 with various 4-bromomethyl coumarins (**3a–e**) in dry acetone. On the other hand the substituted 4-[(4′-fluoro) anilinomethyl]-coumarins (**5a–e**) were synthesized by refluxing the reaction mixture of 4-fluoroaniline and various 4-bromomethyl coumarins in dry xylene at 135–148 °C. Similarly by a different sequence of reactions, 4-bromomethyl carbostyrils (**8a–d**) were synthesized by the bromination of acetoacetanilides and cyclising the intermediate ω-bromo acetoacetanilides in sulphuric acid [22] (Scheme 2). The substituted 4-[(4′-fluoro) phenoxymethyl]-carbostyrils (**9a–d**) were synthesized by refluxing the reaction mixture of 4-fluorophenol and anhydrous K_2CO_3 with various 4-bromomethyl carbostyrils in absolute alcohol at 100 °C. In an analogous manner the substituted 4-[(4′-fluoro)-anilinomethyl]-carbostyrils (**10a–d**) were synthesized by refluxing the reaction mixture of 4-fluoroaniline and various 4-bromomethyl carbostyrils in dry xylene at 135–148 °C.

All the products gave satisfactory analytical and spectroscopic data, which are in full accordance with their assigned structures. The ORTEP diagram of one of the compounds, 7-methyl-4-[(4′-fluoro)-anilinomethyl]-coumarin (**5c**), is reported (Fig. 1). The various new compounds synthesized during the present investigation are listed in Table 1.



Scheme 1. Synthesis of new 4-fluoro-aryloxymethyl and aminomethyl coumarins.