Bioorganic & Medicinal Chemistry 22 (2014) 2080–2089

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and biological evaluation of new pyrazolone–pyridazine conjugates as anti-inflammatory and analgesic agents

Nadia Abdalla Khalil [a], Eman Mohamed Ahmed [a], Khaled Omar Mohamed [a], Yassin Mohammed Nissan [b,*], Sawsan Abo-Bakr Zaitone [c]

[a] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Kasr Elini st., Cairo 11562, Egypt
[b] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt
[c] Department of Pharmacology & Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt

ARTICLE INFO

Article history:
Received 17 December 2013
Revised 11 February 2014
Accepted 19 February 2014
Available online 3 March 2014

Keywords:
Pyrazolone
Pyridazine
Analgesic
Anti-inflammatory

ABSTRACT

A new series of pyrazolone–pyridazine conjugates **3** and **4a–l** were synthesized and characterized by spectroscopic means and elemental analyses. All compounds were tested in vivo for their anti-inflammatory and analgesic properties against diclofenac, as reference compound. The synthesized compounds were also evaluated for their ability to inhibit the production of certain inflammatory cytokines such as TNF-α and IL-6 in serum samples. The ulcerogenic potential of the synthesized compounds was also determined. IC_{50} values for inhibition of COX-1 and COX-2 enzymes were investigated in vitro for the most active candidates. Molecular docking was performed on the active site of COX-2 to predict their mode of binding to the amino acids. Among the synthesized derivatives, compounds **4c** and **4e** showed good analgesic and anti-inflammatory activities with lower ulcer index than the reference drug.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of compounds used for the treatment of pain, fever and inflammation, particularly arthritis.[1,2] The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting cyclooxygenases (COXs), which exist in three distinct isoforms: COX-1, COX-2 and COX-3.[3–5] The COX-1 is a constitutive enzyme and is responsible for the production of cytoprotective prostaglandins in the gastrointestinal (GI) tract, thrombogenesis and homeostasis, while COX-2 is an inducible enzyme, which is induced in response to the release of several pro-inflammatory mediators such as endotoxins, mitogens or cytokines including tumor necrosis factor α (TNFα) and interleukins (ILs) such as IL-6 and IL-1.[6,7] Further, COX-3 which is considered as a variant of COX-1, is present in central nervous system and has been proposed to be another target for anti-inflammatory agents.[8] However, the beneficial effects of NSAIDs are usually balanced by their side effects especially on the GI system due to inhibition of COX-1 isoform. Many NSAIDs interact with both COX-1 and COX-2 isoforms and non-selectively inhibit their enzymatic activity, leading to reduction of prostaglandins PGE2 and PGI2 production, which possess an adverse ulcerogenic effect.[9,10] Chronic use of NSAIDs may induce GI haemorrhage, ulceration, perforation as well as nephrotoxicity, which greatly limit their therapeutic usefulness.[11,12] Therefore, drugs that selectively inhibit COX-2 isoform (coxibs) have been marketed as a new generation NSAIDs.[13] However, prospective examination of coxibs has revealed unexpected cardiovascular adverse effects such as myocardial infarction.[14] COX-2 selective inhibition also will lead to depletion of PGI2 and further increase in thromboxane formation which may cause atherosclerosis.[15,16] Several clinical studies showed an increased cardiovascular risks in treated patients with coxibs compared to others treated with traditional NSAIDs by five folds.[17,18] On the other hand, coxibs showed similar renal side effects to that exhibited by traditional NSAIDs as they reduce acutely medullary blood flow, sodium excretion and urine volume.[19] Therefore, there exists an unmet medical need to develop novel gastrointestinal-sparing NSAIDs with an improved safety profile.

Since the development of antipyrine, the first pyrazoline derivative used in the management of pain, inflammation and fever, great attention has been focused on pyrazoline derivatives as a potent class of anti-inflammatory, analgesic and antipyretic agents,[20–23], (Fig. 1). However, some potent analgesic and anti-inflammatory pyrazoline derivatives including dipyrone and phenylbutazone possess GI side effects that limit the clinical use of these drugs.[24]

* Corresponding author. Tel.: +20 1000848844.
E-mail address: yassin.nissan@hotmail.com (Y.M. Nissan).

http://dx.doi.org/10.1016/j.bmc.2014.02.042
0968-0896/

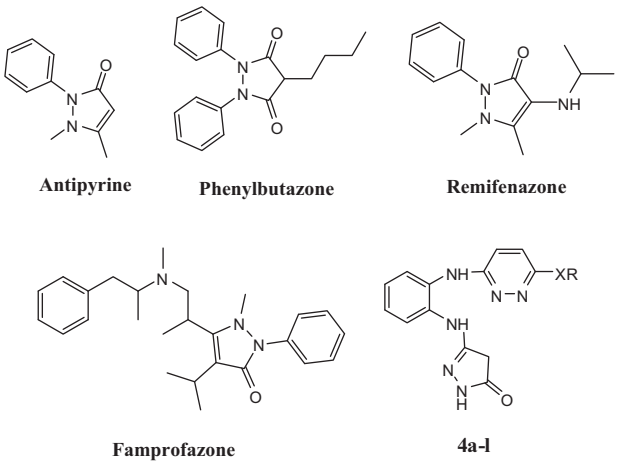


Figure 1. Some reported pyrazolone-containing anti-inflammatory agents and the newly synthesized compounds.

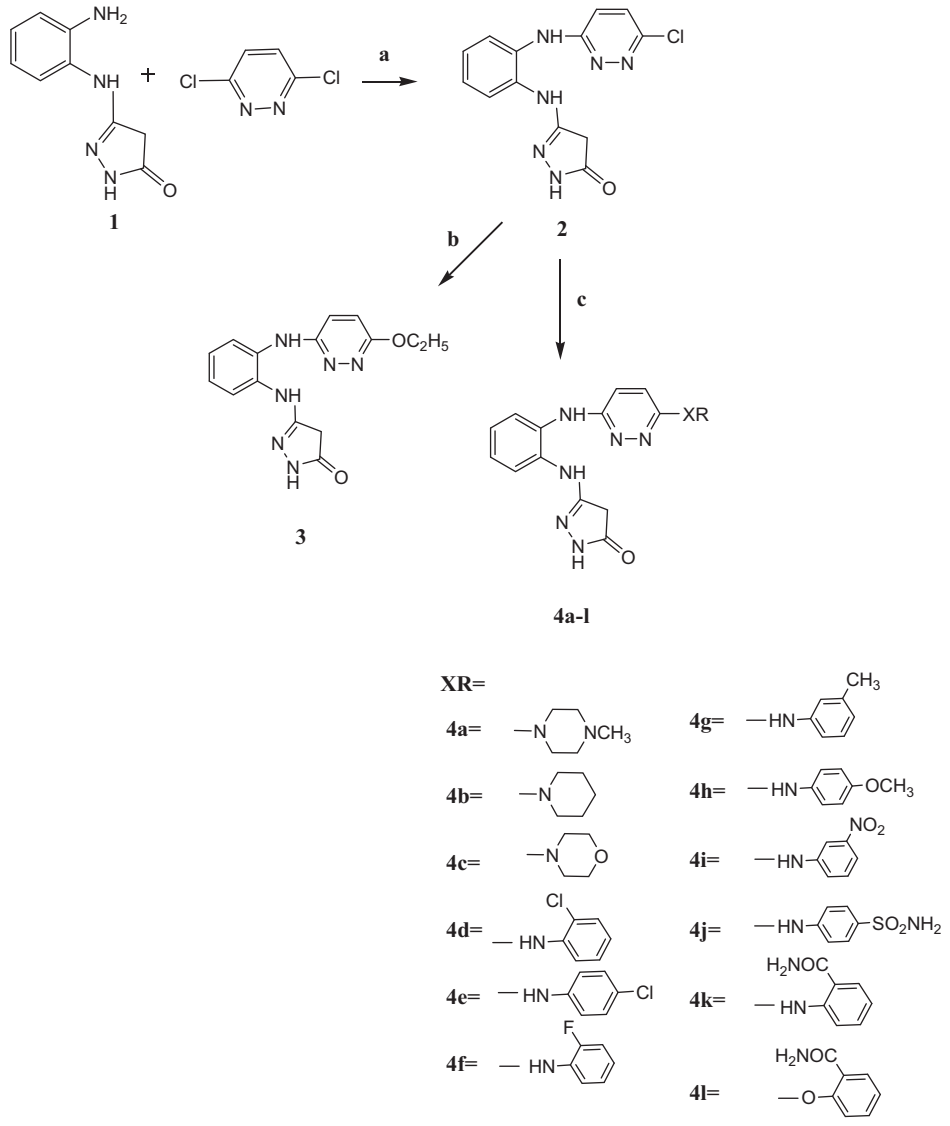
On the other hand, a large number of pyridazine and pyridazinone derivatives have been reported as analgesic and anti-inflammatory agents without gastrointestinal side effect.[25–27] Literature survey showed that pyridazine and pyrazole cores were often used as versatile scaffolds to develop new compounds endowed with interesting pharmacological properties against cyclooxygenase and lipoxygenase pathways.[28–30]

Encouraged with the well-documented anti-inflammatory properties associated with these heterocyclic cores, herein we report the synthesis of new pyrazolone derivatives in combination with pyridazine scaffold. The analgesic and anti-inflammatory activities were investigated for the title compounds utilizing the acetic acid-induced writhing test and the carrageenan-induced hind paw edema test, respectively. All the compounds were also evaluated for the irritative and ulcerogenic action on gastric mucosa.

2. Results and discussion

2.1. Chemistry

The synthetic route to the target compounds **3** and **4a–l** is outlined in Scheme 1. Briefly, 3-(2-aminophenylamino)-1*H*-pyrazol-5(4*H*)-one **1**, was prepared according to a procedure previously described.[31] Reaction of **1** with an equimolar amount of the commercially available 3,6-dichloropyridazine was achieved via



Scheme 1. Reagents and conditions: (a) isopropanol/K_2CO_3/reflux 4 h; (b) sodium ethoxide/ethanol, reflux 30 min; (c) amine/*n*-butanol/reflux 6 h.