European Journal of Medicinal Chemistry 44 (2009) 3697–3702

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Regioselective reaction: Synthesis and pharmacological study of Mannich bases containing ibuprofen moiety

K.V. Sujith [a], Jyothi N. Rao [a], Prashanth Shetty [b], Balakrishna Kalluraya [a,*]

[a] Department of Studies in Chemistry, Mangalore University, Mangalagangothri 574199, Karnataka, India
[b] Department of Pharmacology, NGSM Institute of pharmaceutical Science, Deralakatte 574160, Karnataka, India

ARTICLE INFO

Article history:
Received 11 December 2008
Received in revised form
11 March 2009
Accepted 29 March 2009
Available online 14 April 2009

Keywords:
Ibuprofen
Schiff base
Mannich base
Anti-inflammatory agents
Analgesic agents

ABSTRACT

A series of 4-[(4-aryl)methylidene]amino-2-(substituted-4-ylmethyl)-5-{1-[4-(2-methylpropyl)phenyl]ethyl}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**6**) were synthesized from an arylpropionic acid namely, ibuprofen by a three-component Mannich reaction. Aminomethylation of 4-[(4-aryl)methylidene]amino-5-{1-[4-(2-methylpropyl)phenyl] ethyl}-4*H*-1,2,4-triazole-3-thiol (**5**) with formaldehyde and a secondary amine furnished this novel series of Mannich bases (**6**). Both Schiff bases (**5**) and Mannich bases (**6**) were well characterized on the basis of IR, NMR, mass spectra1 data and elemental analysis. They were screened for their anti-inflammatory, analgesic, antibacterial and antifungal activities. Some of the Mannich bases (**6**) carrying morpholino and N-methylpiperazino residues were found to be promising anti-inflammatory and analgesic agents.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are widely used in the treatment of pain and inflammation, including osteoarthritis and rheumatoid arthritis [1–3]. Prostaglandins (PGs) are well known to be the mediators of inflammation, pain and swelling. They are produced by the action of cyclooxygenase (COX) enzyme on arachidonic acid. Metabolites of the COX pathway are widely accepted as mediators of the inflammatory response. COX is known to be the principal target of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs, block the formation of PGs and have analgesic, antipyretic and anti-inflammatory activities [4]. In the early 1990s, it was discovered that the COX enzyme exists as two isoforms, one constitutive (COX-1) and the other inducible (COX-2) [5]. COX-1 is constitutively expressed and provides cytoprotection in the gastrointestinal (GI) tract while COX-2 is inducible and mediates inflammation [6–8]. The traditional NSAIDs show greater selectivity for COX-1 than COX-2 [9].

In fact, prolonged use of NSAIDs like ibuprofen has been associated with gastrointestinal complications ranging from stomach irritation to life-threatening GI ulceration bleeding and nephrotoxicity [10,11]. Therefore the development of new NSAIDs without these side effects has long been awaited. Selective COX-2 inhibitors with better safety profile have been marketed as a new generation of NSAIDs [12]. Thus there remains a compelling need for effective NSAIDs with an improved safety profile. Chronic use of NSAIDs, including ibuprofen, may elicit appreciable GI toxicity [13]; therefore, synthetic approaches based upon NSAIDs chemical modification have been undertaken with the aim of improving the NSAID safety profile. The GI damage from NSAIDs is generally attributed to two factors, local irritation by the carboxylic acid moiety, common to most NSAIDs (topical effect) and decreased tissue prostaglandin production, which undermines the physiological role of cytoprotective prostaglandins in maintaining the GI health and homeostasis [14]. It has been reported that the derivatization of the carboxyl function of representative NSAIDs, resulted in an increased anti-inflammatory activity with reduced ulcerogenic effect [15,16]. The search for novel analgesic and anti-inflammatory agents devoid of side effects continues to be an active area of research in medicinal chemistry. In fact 1,2,4-triazoles and their derivatives have been reported to possess various biological activities such as anti-inflammatory activity [17] and analgesic properties [18]. Similarly Mannich bases also possess comprehensive bioactivities like anticancer [19], analgesic [20], antibacterial and antifungal activities [21].

Multi-component reactions (MCRs) constitute a major part in the present day organic synthesis with advantages ranging from lower reaction times, increased reaction rates to higher yields and

* Corresponding author. Tel.: +91 824 2287262; fax: +91 824 2287367.
E-mail addresses: bkalluraya@gmail.com, kallurayab@yahoo.com (B. Kalluraya).

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doi:10.1016/j.ejmech.2009.03.044

reproducibility [22]. Mannich reaction is a three-component condensation reaction involving active hydrogen containing compound, formaldehyde and a secondary amine [23]. The aminoalkylation of aromatic substrates by Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds [24]. Similarly Schiff base derivatives of 1,2,4-triazole have displayed good biological activity [25]. So we herein synthesized some novel Schiff bases and Mannich bases carrying both the triazole nucleus as well as ibuprofen moiety and studied their biological properties.

2. Chemistry

The title compounds were synthesized in a one-pot multicomponent Mannich reaction involving ibuprofen triazole (**4**), formaldehyde and secondary amine in ethanol medium. The reaction proceeds via the formation of immonium salt which subsequently attacks the N-1 of triazole giving rise to regioselective Mannich base. It is interesting to note that the reaction is highly regioselective and furnishes only N-Mannich base and none of the S-Mannich derivatives, though the intermediate Schiff base can exist in the thiol–thione tautomeric equilibrium.

Ibuprofen triazole (**4**) was prepared according to the procedure outlined in Scheme 1. Ibuprofen hydrazide (**2**) was obtained by the hydrazinolysis of its corresponding ester. The required dithiocarbazinate (**3**) was synthesized by reacting acid hydrazide with carbon disulphide and potassium hydroxide in ethanol. This salt underwent ring closure on reacting with hydrazine hydrate to give the ibuprofen triazole [26]. Whereas ibuprofen triazole (**4**) was also synthesized in a one-pot reaction, involving the fusion of ibuprofen (**1**) and thiocarbohydrazide (TCH). This alternative one-pot synthesis has matured into a highly useful technique because of higher yield and shorter reaction time. In this one-pot synthesis several disadvantages like long reaction procedure and tedious work-up can be overcome. Due to these facts the one-pot procedure for ibuprofen triazole dominates over conventional Reid and Heindel method [27]. The triazole so synthesized was then condensed with suitable aldehydes in the presence of few drops of conc. Sulphuric acid as a catalyst to yield Schiff bases (**5**) in good yield. Mannich reaction of these Schiff bases was further obtained with formaldehyde and secondary amine in ethanol medium to give the N-Mannich bases (**6**) rather than the S-Mannich bases (Scheme 2). The structures of newly synthesized compounds were confirmed on the basis of spectral, elemental and crystal data. Characterization data of these compounds are given in Tables 1 and 2.

3. Pharmacology

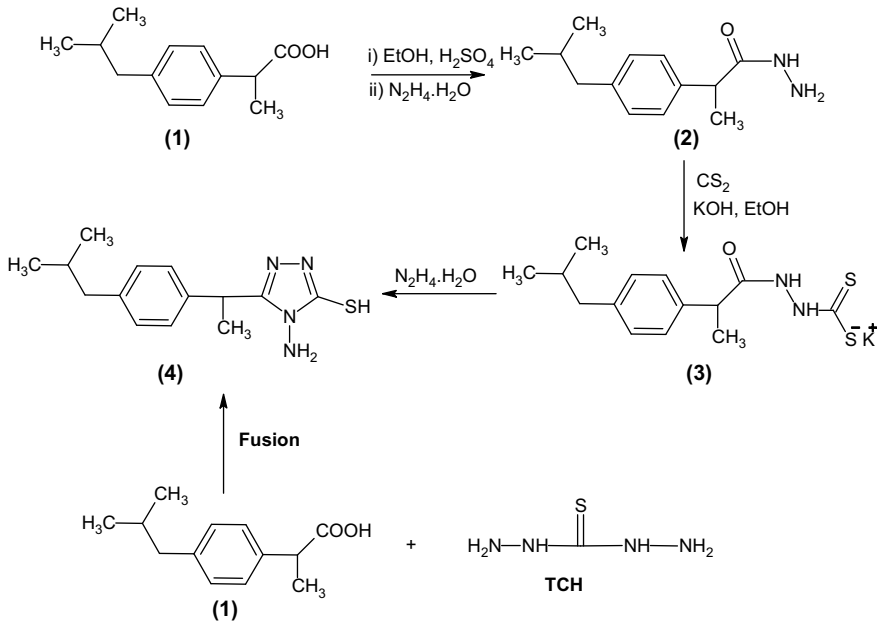
Some of the selected compounds were evaluated for analgesic and anti-inflammatory activities. The test compounds were administered in the form of a suspension (1% carboxy methyl cellulose as vehicle). Anti-inflammatory and analgesic activities of the test compounds were measured with respect to the control and compared with respect to the standard drug; diclofenac. All the pharmacological data are expressed as mean ± SEM; statistical analysis was applied to determine the significance of the difference between the control group and groups of animals treated with the test compounds. Ibuprofen is used as a second reference for comparison of anti-inflammatory activity. Similarly antibacterial and antifungal activity studies were carried out for selected compounds.

3.1. Anti-inflammatory activity

Anti-inflammatory activity was determined by the carrageenan-induced paw edema method in Wistar albino rats by using plethysmography following the method of Winter et al. [28]. Diclofenac at an oral dose of 20 mg/kg served as the standard drug for comparison. The test compounds (20 mg/kg) were administered orally 30 min prior to administration of carrageenan (0.1 mL of 1% w/v) in the plantar region of the paw. The paw volumes were measured at 30, 60, 90, 120, 150 and 180 min after carrageenan administration. The results are presented in Table 3.

3.2. Analgesic activity

Analgesic activities were evaluated on Swiss albino mice by hot plate method. In this method heat is used as a source of pain. Animals are grouped into 5, each containing 6 animals (n = 6).



Scheme 1.