Saudi Pharmaceutical Journal (2011) **19**, 233–243

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Microwave assisted synthesis of novel pyrazolone derivatives attached to a pyrimidine moiety and evaluation of their anti-inflammatory, analgesic and antipyretic activities

Rishikesh V. Antre [a,*], A. Cendilkumar [a], Divakar Goli [a], Ganesh S. Andhale [a], Rajesh J. Oswal [b]

[a] *Medicinal Chemistry Research Laboratory, Acharya & B.M. Reddy College of Pharmacy, Bangalore 560 090, Karnataka, India*
[b] *Medicinal Chemistry Research Laboratory, JSPM's Charak College of Pharmacy & Research, Pune 412 207, Maharashtra, India*

Received 24 May 2011; accepted 25 May 2011
Available online 25 June 2011

KEYWORDS

Pyrazolone;
Amino pyrimidine;
Schiff bases;
Anti-inflammatory;
Analgesic;
Antipyretic

Abstract In the present research work, the motto was to develop new chemical entities as potential anti-inflammatory, analgesic and antipyretic agents. Various 4-(2-amino-6-(substituted)pyrimidin-4-yl)-3-methyl-1-(substituted)-1*H*-pyrazol-5(4*H*)-one derivatives (**5a**–**5j**) and their Schiff bases (**6a**–**6j**) were synthesized. The newly synthesized compounds were characterized by TLC and spectral data. The compounds containing pyrazolone and amino pyrimidine as basic moieties (**5a**–**5j**), were screened for their anti-inflammatory, analgesic and antipyretic activities, compounds **5a**, **5c**–**5f**, **5h** exhibited activities nearly similar to the standard. The pharmacological studies reveal that the presence of 4-hydroxy, 4-methoxy, 4-(N,N-dimethylamino) or 2-hydroxy groups on phenyl ring at C_6 of amino pyrimidine exhibits anti-inflammatory, analgesic and antipyretic activities nearly

* Corresponding author. Address: Medicinal Chemistry Research Laboratory, Acharya & B.M. Reddy College of Pharmacy, 89/90, Soldevanahalli, Chikkabanavara Post, Heseraghatta Main Road, Bangalore 560 090, Karnataka, India. Mobile: +91 9970517333; fax: +91 80 2839 3541.
E-mail address: rishiantre@gmail.com (R.V. Antre).

Peer review under responsibility of King Saud University.
doi:10.1016/j.jsps.2011.05.006

Production and hosting by Elsevier

similar to the standard and substitutions like 4-chloro, 2-nitro, 3-nitro or 4-nitro on same phenyl ring lead to a decrease in activities.

1. Introduction

In the past decade, numerous advances have taken place in the understanding of pathogenesis and as a result, significant progress has been made and is still being made in the development of novel anti-inflammatory drugs (Bhandari et al., 2009). Inflammation is a fundamental physiological process that is essential for survival but at the same time is one of the major causes of human morbidity and mortality (O'Neill, 2006; Cheeseright et al., 2009). Therefore, investigation of new anti-inflammatory agents is still a major challenge (Chao et al., 2008; Stefan et al., 2008; Hynes et al., 2008). A few COX-2 inhibitors have also been studied for the treatment of cancer (Kalgutkar and Zhao, 2001) and Alzheimer's disease (Pasinetti, 1998).

Pyrazolone is an important pharmacophore which exhibits widespread pharmacological properties, such as anticancer (Brana et al., 2006), analgesic (Filho et al., 1998; Gokce et al., 2009), anti-inflammatory (Ismail et al., 2007; El-Hawash et al., 2006), antipyretic (El-Hawash et al., 2006; Souza et al., 2002), antioxidant (Manojkumar et al., 2009), antiproliferative (Kim et al., 2005), antimicrobial (Ragavan et al., 2009; Raman et al., 2002, 2005; Bondock et al., 2008), activities. Edaravone (Pal et al., 2008; Chegaev et al., 2009), (3-methyl-1-phenyl-2-pyrazolin-5-one) is found as a promising drug for brain ischemia (Watanabe et al., 1994), myocardial ischemia (Kawai et al., 1997), treatment of fatal neurodegenerative diseases (Kimata et al., 2007) and cardiovascular diseases (Higashi et al., 2006).

In the present study, we have demonstrated the ability of an unusual class of synthetic molecules containing a pair of basic moieties like pyrazolone and amino pyrimidine (**5a**–**5j**) as anti-inflammatory, analgesic and antipyretic agents. Microwave assisted synthesis for (**5a**–**5j**) and (**6a**–**6j**) were employed in solvent-free conditions, the reaction time required was limited to an average of less than 10 min. Pharmacological evaluation of the molecules reveals that compounds **5a**, **5c**–**5f**, **5h** exhibited anti-inflammatory, analgesic and antipyretic efficacy nearly similar to the standard.

2. Materials and methods

2.1. Chemistry

The title compounds were synthesized as per Scheme 1.

The starting materials, 3-methyl-1-substituted-*1H*-pyrazol-5(*4H*)-ones (**2a**–**2b**), were obtained in high yields as per the method reported (Pal et al., 2008; Kimata et al., 2007) by the treatment of ethyl acetoacetate with 1-phenylhydrazine (**1a**) or 1-(2,4-dinitrophenyl)hydrazine (**1b**) using a microwave oven. The 4-acetyl-3-methyl-1-substituted-*1H*-pyrazol-5(*4H*)-ones (**3a**–**3b**) were prepared by the acylation of (**2a**–**2b**) with the corresponding acid chloride following Jensen's procedure (Jensen, 1959). The chalcone derivatives, 4-(3-(substituted)acryloyl)-3-methyl-1-(substituted)-1*H*-pyrazol-5(4*H*)-ones, (**4a**–**4j**), were prepared by reacting (**3a**–**3b**) with different substituted aromatic aldehydes by using 60% sodium hydroxide in ethanol. 4-(2-amino-6-(substituted)pyrimidin-4-yl)-3-methyl-1-(substituted)-*1H*-pyrazol-5(*4H*)-one (**5a**–**5j**) were prepared by reacting (**4a**–**4j**) with guanidine hydrochloride. Finally (**5a**–**5j**) were reacted with substituted aromatic aldehydes to give corresponding Schiff bases (**6a**–**6j**) in very good yields.

The synthesized compounds were assigned on the basis of chromatographic, FT-IR, ^{1}H NMR, Mass spectral data and CHN analysis.

The FTIR spectra of the Schiff bases exhibited very similar features and showed the expected bands for the characteristic groups which are present in the compounds, such as C—H and the C=N stretching vibrations and another specific band for Ar—C—N vibrations. Compounds (**6a**–**6j**) have C=O stretching bands in the range 1680–1655. The presence of only one C=O stretching band at 1640–1660 cm^{-1} in (**5a**–**5j**) derivatives as compared with (**4a**–**4j**) is an evidence of ring closure.

In the proton NMR spectral data, all protons were seen according to the expected chemical shift and integral values. The aromatic protons appeared as multiplet peaks within the range 7.0–7.80 δ ppm. Singlet signals derived from (—NH_2) and ArH of pyrimidine (**5a**–**5j**) structure appeared at 3.50–3.70 and 8.10–8.15 δ ppm, respectively. In case of (**4a**–**4j**), two doublets in the range of 6.50–6.60 and 6.80–6.90 δ ppm are derived from —CH=CH.

2.2. General

All the reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Microwave irradiation was carried out using microwave oven (KENSTAR Model No. OM-9928c, microwave 1200 W, input range 230V-ac 50 Hz, microwave frequency 250 MHz). All the products obtained were purified by column chromatography using silica gel (100–200 mesh). Melting points were determined by open capillary on Thermonik precision apparatus (Model-C-PMP-2, Mumbai, India) and are uncorrected. FT-IR spectra of the powdered compounds were recorded on a Tensor 27 spectrophotometer, Bruker optik (Germany) using ATR method. ^{1}H NMR spectra were recorded on a Bruker spectrophotometer using TMS as an internal reference (chemical shift represented in δ ppm). Mass spectra were recorded on GC–MS QP5050A System (benchtop quadrupole mass spectrophotometer). Elemental analysis was carried out in CHN analyzer EA-1112, Thermo Finnigan. Purity of the compounds was checked on TLC plates using silica gel G as the stationary phase and was visualized using iodine chamber or under UV chambers.

2.2.1. General procedure for preparation of 3-methyl-1-(substituted)-1H-pyrazol-5(4H)-one (*2a*–*2b*)

The 3-methyl-1-(substituted)-1*H*-pyrazol-5(4*H*)-one derivatives were prepared as per the reported method and purified by recrystallization from ethanol (Pal et al., 2008; Kimata et al., 2007).