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ORIGINAL ARTICLE

Microwave-assisted synthesis, characterization and biological activity of novel pyrazole derivatives

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Pyrazole;
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Abstract A series of 1-(4-substitutedphenyl)-3-phenyl-1*H*-pyrazole-4-carbaldehydes **4a–l** have been synthesized and tested for their biological activities. Formation of the pyrazole derivatives was achieved by treating with Vilsmeier-Haack reagent. The newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activities compared to Diclofenac sodium as standard drug. Compounds **4g**, **4i** and **4k** exhibited the maximum anti-inflammatory and analgesic activities. The detailed synthesis, spectroscopic and toxicity data are reported.

1. Introduction

Pain is an unpleasant sensation and it is widely accepted to be one of the most important determinants of quality of life. A study reported by the World Health Organization (WHO) demonstrated that individuals who live with persistent pain suffer fourfold more from depression (or) anxiety compared to healthy subjects (Gureje et al., 1998). The identification of compounds able to treat both acute and chronic pain with limited side effects is one of the prominent goals in biomedical research. Non-steroidal anti-inflammatory drugs (NSAIDs) exert their effects by inhibition of prostaglandin production. The pharmacological target of NSAIDs is cyclooxygenase (COX), which catalyzes the first committed step in arachidonic acid metabolism. Two isoforms of the membrane protein COX are known: COX-1, which is constitutively expressed in most tissues, is responsible for the physiological production of prostaglandins; and COX-2, which is induced by cytokines, mitogens and endotoxins in inflammatory cells, is responsible for the elevated production of prostaglandins during inflammation (Kurumbail et al., 1996). The widely prescribed anti-inflammatory pyrazole derivatives such as, Celecoxib, Deracoxib,

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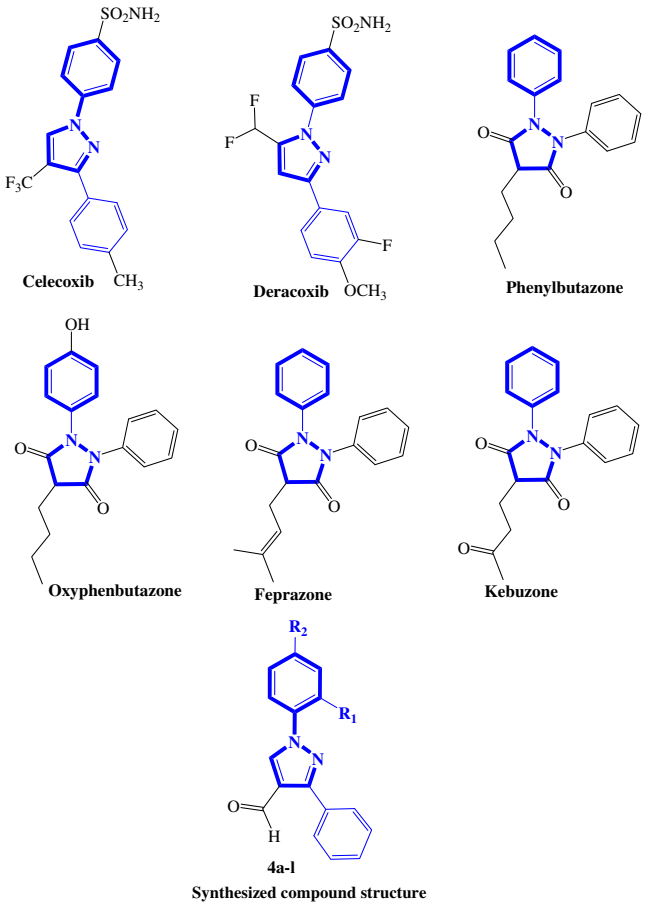


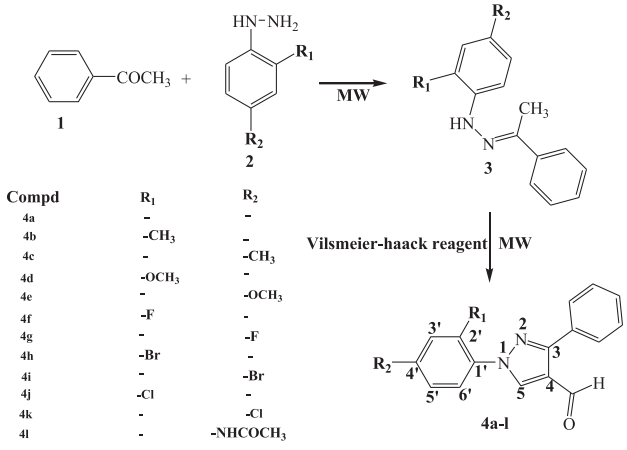
Figure 1 Structures of well established NSAIDs and title compounds with its common pharmacophore features.

Phenylbutazone, Oxyphenbutazone, Feprazone and Kebuzone Fig. 1 are COX inhibitors with reduced ulcerogenic side effects. Due to the importance of pyrazole derivatives considerable efforts have been made by several investigators, to prepare new compounds bearing a single substituent or more complicated systems, including the heterocyclic rings mainly at 1-, 3- and 4-positions. Also, the literature survey reveals excellent anti-inflammatory, analgesic (Farghaly et al., 2001; Balsamo et al., 2003; Youssef et al., 2007; Souza et al., 2001; Godoy et al., 2004; Souza et al., 2002; Prokopp et al., 2006), anti-microbial (Pimerova et al., 2001; Bekhit et al., 2008), anti-viral, anti-tumor (Park et al., 2005), anti-convulsant (Michon et al., 1995), anti-histaminic (Yildirim et al., 2005) and anti-depressant (Bailey et al., 1985) activities with some compounds containing the heterocyclic ring such as pyrazole. Based on the above mentioned research results, the objective of this study aimed to synthesize some novel derivatives of 1-(4-substitutedphenyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde **4a–l** in order to screen them for anti-inflammatory and analgesic activities.

2. Experimental

2.1. Materials

Synthetic starting material, reagents and solvents were of analytical grade or of the highest quality commercially available.



Compd	R_1	R_2
4a	-	-
4b	$-CH_3$	-
4c	-	$-CH_3$
4d	$-OCH_3$	-
4e	-	$-OCH_3$
4f	-F	-
4g	-	-F
4h	-Br	-
4i	-	-Br
4j	-Cl	-
4k	-	-Cl
4l	-	$-NHCOCH_3$

Scheme 1 Pyrazole-4-carbaldehyde derivatives.

The chemicals were purchased from Aldrich Chemical Co., and Merck Chemical Co., respectively, these solvents used were of analytical grade and purified before their use.

2.2. Instrumentation

The silica gel G used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. Solvent systems used were $CHCl_3$–MeOH (7:3). All the melting points were taken in an open glass capillary and are uncorrected. ^1H NMR spectra were taken on a Bruker ultra shield (300 MHz) NMR spectrometer in $CDCl_3$ using tetramethylsilane [$(CH_3)_4Si$] as an internal standard. Chemical shifts (δ) are expressed in ppm. Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. All the IR spectra were recorded in KBr pellets on a Jasco FT-IR 410 spectrometer. Elemental analyses were performed on a Perkin Elmer model 240c analyzer and were within $\pm 0.4\%$ of the theoretical values.

2.3. General procedure

The synthetic strategy of the target compounds is illustrated in Scheme 1. The acetophenone (0.01 mol), substituted phenyl hydrazine (0.01 mol) and DMF (0.5 mL) were exposed to microwave at 200 W intermittently at 10 s intervals. The specified reaction time of 3 min was observed of compound 1-substituted phenyl-2-(1-phenylethylidene)hydrazine **3**. The reaction mixture was cooled with cold water. The precipitate thus obtained was filtered, washed with water and purified by recrystallization from ethanol to furnish **3**. The compound **3** (0.01 mol) was added portion wise with Vilsmeier-Haack reagent ($POCl_3$–DMF/SiO_2) (0.03 mol). After the addition was complete, the reaction flask was kept at room temperature for 5 min and silica gel 3 g was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder is then irradiated in a microwave oven at 400 W intermittently at 30 s intervals. The specified reaction time of 5 min was observed of compound **4a–l**. The reaction mixture was cooled and treated with cold water. The solid obtained by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from methanol to afford **4a–l**. The completion of reaction is monitored by TLC method [eluent: $CHCl_3$–MeOH (7:3)].