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Syntheses, characterization and evaluation of novel 2,6-diarylpiperidin-4-ones as potential analgesic-antipyretic agents

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ABSTRACT

A novel series of N-(N-methylpiperazinoacetyl)-2,6-diarylpiperidin-4-one derivatives (**1c**–**3c** and **5c**) were synthesized, via base catalyzed nucleophilic substitution of N-chloroacetyl-2,6-diarylpiperidin-4-ones (**1b**–**6b**) with N-methyl piperazine. The newly synthesized compounds were characterized by FTIR, Mass and NMR spectral studies. All the compounds were screened for their possible analgesic and antipyretic activities. The compound **2c** exhibited promising antipyretic activity, comparable to that of paracetamol at 60 mg/kg dose. The compounds **2b** and **2c** showed significant analgesic profile at a dose of 60 mg/kg and were also found to be more potent than the reference drug, diclofenac sodium. Thus, it can be concluded that the synthesized 2,6-diarylpiperidin-4-ones exhibit promising antipyretic and analgesic activities and could be potential drug candidates.

1. Introduction

Inflammation is a normal and essential response to any noxious stimulus that threatens the host and may vary from a localized response to a generalized response [1]. Generally, this response acts to protect the host but at times it may lead to a spectrum of inflammatory diseases, thus necessitating medication to dampen or abolish the inflammatory response [2].

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the signs and symptoms of inflammation and pain. NSAIDs exert their effect mainly through the inhibition of cyclooxygenase (COX), the key enzyme in prostaglandin (PG) biosynthesis from arachidonic acid (AA). The potentiality of NSAIDs to alleviate pain, inflammation and fever, coupled with a number of pathological conditions, makes them one of the most useful therapeutic agents [3].

NSAIDs are particularly effective when inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. Pain, that accompanies inflammation and tissue injury, probably results from local stimulation of pain fibers and enhanced pain sensitivity (hyperalgesia), in part a consequence of increased excitability of central neurons in the spinal cord. Bradykinin, released from plasma kininogen and cytokines, such as TNF-α, IL-1 and IL-8 appear to be particularly important in eliciting the pain related to inflammation. These agents liberate prostaglandins and probably other mediators that promote hyperalgesia. Neuropeptides, such as substance-P, calcitonin gene-related peptide (CGRP) may also be involved in eliciting pain. Non-opoid analgesics act by inhibition of cyclooxygenase (COX) enzyme, and specially COX-2 which plays a key role in the production of inflammatory mediators like prostaglandins and prostacyclins from cyclic endoperoxides. Prostaglandin PGE_2 and prostacyclin PGI_2 sensitize the pain receptors in various organs. Thus, stimuli which are normally painless are able to elicit pain. Some other mediators like bradykinin and cytokines, i.e. tissue necrosis factor (TNF-α), interleukins (IL-1, IL-8) stimulate the COX enzyme and thus produce prostaglandins which act in mediating hyperalgesia [4].

Fever is a complex physiologic response triggered by infectious or aseptic stimuli, due to increased concentrations of prostaglandin E(2) (PGE(2)) within certain areas of the brain. These elevations alter the firing rate of neurons that control thermoregulation in the hypothalamus. Antipyretics, such as aspirin, have been widely used since the late 19th century but the mechanisms by which they relieve fever have only been characterized in the last few decades. It is now clear that most antipyretics work by inhibiting the enzyme cyclooxygenase and reducing the levels of PGE(2) within the hypothalamus. Recently, other mechanisms of action for antipyretic

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