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SHORT COMMUNICATION

# Synthesis, molecular properties, toxicity and biological evaluation of some new substituted imidazolidine derivatives in search of potent anti-inflammatory agents

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**Abstract** The aim of this study was to design and synthesize pharmaceutical agents containing imidazolidine heterocyclic ring in the hope of developing potent, safe and orally active anti-inflammatory agents. A number of substituted-imidazolidine derivatives (**3a–k**) were synthesized starting from ethylene diamine and aromatic aldehydes. The imidazolidine derivatives (**3a–k**) were investigated for their anticipated anti-inflammatory, and analgesic activity in Wistar albino rats and Swiss albino mice, respectively. Bioactivity score, molecular and pharmacokinetic properties of the imidazolidine derivatives were calculated by online computer software programs viz. Molinspiration and Osiris property explorer. The results of biological testing indicated that among the synthesized compounds only three imidazolidine derivatives namely 4-[1,3-Bis(2,6-

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dichlorobenzyl)-2-imidazolidinyl]phenyl-diethylamine (**3g**), 4-[1,3-Bis(3-hydroxy-4-methoxybenzyl)-2-imidazolidinyl]phenyl-diethylamine (**3i**) and 4-(1,3-Bis(4-methoxybenzyl)-4-methylimidazolidin-2-yl)-phenyl-diethylamine (**3j**) possess promising anti-inflammatory and analgesic actions. Additionally these derivatives displayed superior GI safety profile (low severity index) with respect to the positive control, Indomethacin. All synthesized compounds showed promising bioactivity score for drug targets by Molinspiration software. Almost all the compounds were predicted to have very low toxicity risk by Osiris online software. Compound number (**3i**) emerged as a potential candidate for further research as it obeyed Lipinski's rule of five for drug likeness, exhibited promising biological activity *in-vivo* and showed no risk of toxicity in computer aided screening.



## 1. Introduction

Inflammation is a normal, natural protective and defense mechanism of the organism to tissue injury caused by various factors which include physical trauma, injurious stimuli, chemical action or microbial infections (Ashley et al., 2012). It is a very common symptom of many chronic diseases such as arthritis, osteoarthritis, inflammatory bowel disease, and chronic asthma which put enormous burden on the economy of the countries. The prevalence of inflammatory diseases is on rise across the world, mostly affecting elderly population (Gautam and Jachak, 2009). Few epidemiological studies conducted elsewhere have also linked inflammation to pathogenesis of stroke, cardiovascular diseases, various types of cancer and to some extent neurodegenerative diseases. Mantovani and Pierotti in 2008 reported that inflammatory reactions and underlying infections are involved in 15–20% of all cancer deaths (Mantovani and Pierotti, 2008).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medicines for the management and treatment of various inflammatory conditions. These drugs interfere with the production of lipid autacoids known as prostaglandins (PGs), which play an important role in eliciting inflammatory reactions and its sign and symptoms (Ricciotti and Fitzgerald, 2011). NSAIDs block the biosynthesis of PGs primarily by inhibiting the arachidonic acid metabolism via inhibition of several enzymes involved in their synthesis including cyclooxygenase enzyme (COX-1 and COX-2) (Tan et al., 1992). Commonly used NSAIDs exhibit higher selectivity toward COX-1, an enzyme that is involved in the cytoprotection of the gastrointestinal tract (GIT), than COX-2 which is principally responsible to cause inflammation. A majority of the commonly used NSAIDs are non selective inhibitors of both the isozyme forms of cyclooxygenase and thus are associated with undesirable GI effects such as gastric irritation, ulceration, bleeding and renal disorders (Allison et al., 1992; Agnihotri et al., 2010). In order to overcome GI problems, highly selective COX-2 inhibitors (celecoxib, rofecoxib, etc.) were developed and marketed as gastro-protective NSAIDs (Lanza, 1998). However, long term use of some selective COX-2 inhibitors has shown potential limitations including cardiovascular complications, aggravation of ulcers among high-risk patients, delay in healing process of gastroduodenal ulcers, prostacyclin deficiency leading to thrombosis and kidney toxicity (Verrico et al., 2003; Buttgereit et al., 2001). Hence, selective COX-2 inhibitors because of their high cost and undesirable side effects are not the ideal candidates for the treatment/management of various chronic inflammatory disorders and therefore, efforts should be made for the development of new orally active, potent, improved and safer NSAIDs with low or no GI side effects.

Imidazolidines (saturated imidazoles), also known as tetrahydroimidazoles are biologically active nitrogen containing heterocyclic moiety which have been reported to shown wide array of significant bioactivities such as anti-inflammatory, analgesic, α-adrenergic receptor agonist, antimicrobial, antiparasitic, oral hypoglycemic and anticonvulsant activities (Marki et al., 1984; Sharma and Khan, 2001; Caterina et al., 2008; Saczewski et al., 2009; Neves et al., 2010; Robert et al., 2010). They have also been considered as important scaffolds and intermediates for designing and synthesis of medicinal compounds with potential cyclooxygenase-2 (COX-2) inhibition activity (Patel et al., 2004). Several substituted-imidazolidine derivatives have been shown to be potential anti-edema agents in animal models of inflammation. Khan and Chawla, reported them to be promising group of NSAIDs with potential anti-inflammatory activities (Khan and Chawla, 2002).

Literature survey revealed that imidazolidine, a versatile moiety, could be a possible pharmacophore in designing safer anti-inflammatory medicinal agents (Khan and Chawla, 2002; Sharma and Khan, 2001; Khan and Gupta, 2003). In continuation of our work on this moiety (Khan et al., 2012; Husain et al., 2013), it was thought-out to study some new 4-[1,3-bis(substituted-benzyl)-2-imidazolidinyl]phenyl-dialkylamines for their possible *in-vivo* anti-inflammatory plus analgesic actions including gastrointestinal safety (acute ulcerogenicity). Structure–activity relationships of imidazolidine derivatives were also studied to study the effect of various substituents on the biological activity. Oral bioavailability, toxicity potential and pharmacokinetic profile of synthesized compounds were also predicted with the aid of computer programs to select the best candidate(s) among the synthesized compounds for the drug development.

## 2. Experimental

### 2.1. Chemistry

Melting points of the synthesized compounds were determined using open capillary tubes on a liquid paraffin bath and are uncorrected. The chemical reactions progress was monitored on silica gel G coated TLC plates in the benzene-ethanol (8:2) solvent system. Compounds on TLC were spotted by exposing to iodine vapors or under UV light. The IR spectra