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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Ulcerogenicity devoid novel non-steroidal anti-inflammatory agents (NSAIDS): syntheses, computational studies, and activity of 5-aryliden-2-imino-4-thiazolidinones

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Abstract A series of new 5-aryliden-2-imino-4-thiazolidinones (**5a–e** and **6a–e**) were synthesized via a three-step reaction and characterized by physicochemical and spectral data. The uniqueness of the derivatives lies in the fact that none of them had an acidic group, like conventional NSAIDS, but exhibited significant in vivo activity in acute inflammation models. In particular, 5-(3-chlorobenzyliden)-2-(pyridin-2-yl-imino)-4-thiazolidinone(**5a**) and 5-(3-chlorobenzyliden)-2-(5-methylisoxazol-3-yl-imino)-4-thiazolidinone (**6a**) showed remarkable paw oedema inhibition (67.76 and 74.47 % oedema inhibition, respectively, after 3 h) comparable to that of Ibuprofen (74.56 % oedema inhibition, after 3 h) at half of the dose of the standard drug. Also, compounds **5a** (72.86 %) and **6a** (80.20 %) were found to possess significant inhibition of albumin denaturation when screened for in vitro anti-inflammatory activity. In addition, these compounds were docked into the known active site of COX-2 protein using Glide XP and QPLD algorithms, and the binding-free energy was calculated using Prime MM/GBSA simulation methods. The combined use of molecular docking and MM/GBSA methods gave a good correlation between the predicted binding-free energy and experimentally determined biological activities. It was also evident from the docking results that 2-methylisoxazolylimino or 2-(pyridin-2-yl-imino substitution and 3-chloro moiety on 5-benzylidin nucleus of these 4-thiazolidinone derivatives can easily occupy the COX-2 binding pocket, considered as the critical interaction for COX-2 inhibition. Moreover, pharmacokinetic properties of all the synthesized compounds were predicted, with good results. Further, the synthesized derivatives showed neither acute toxicity nor symptoms of gastric ulceration, at extended doses, owing to the absence of an acidic group.

Keywords NSAIDS · 4-Thiazolidinones · COX-2 inhibitors · Glide-XP docking · MM/GBSA · In silico ADME prediction

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Introduction

Inflammation is a multi-factorial process. It reflects the response of an organism to various stimuli and is related to many disorders such as arthritis, asthma, and psoriasis, which require prolonged or repeated treatment. Although several mediators support the inflammatory processes, the main target of nonsteroidal anti-inflammatory drugs (NSAIDs) is cyclooxygenase (COX) enzyme. Traditional NSAIDs act via the inhibition of the COX-1 isoenzyme or the combined inhibition of COX-1 and COX-2 isoenzymes (Geronikaki *et al.*, 2008; Leval *et al.*, 2002; Vane and Botting 1987). Because COX-2 isoenzyme was found to be over expressed during inflammation, drug investigation was focused on selective COX-2 inhibition, hoping to prevent inflammation by sidestepping the undesired side

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