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ORIGINAL RESEARCH

Novel 2-(substituted phenyl Imino)-5-benzylidene-4-thiazolidinones as possible non-ulcerogenic tri-action drug candidates: synthesis, characterization, biological evaluation And docking studies

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Abstract
The present research was aimed at the synthesis and screening of 35 novel 2-(substituted phenyl imino)-5-benzylidene-4-thiazolidinones having different substitutions at imino phenyl and arylidene groups. The title compounds were synthesized by Knoevenagel condensation at the 5th position of the 4-thiazolidinone ring, in the presence of sodium acetate. The structures were assigned on the basis of spectral data. The compounds were screened for in vivo anti-inflammatory, antinociceptive and in vitro free-radical scavenging activities. The compounds exhibited significant activities when compared with standard drugs. The distinctive property of the derivatives was that none of them had an acidic group, like conventional NSAIDs, but exhibited significant in vivo activity in acute inflammation models. Further, the active compounds of each series were docked against cyclooxygeanase (COX)-2 enzyme using Glide module of Maestro 11.1 program. It was evident from the docking results that 3-chlorophenylimino and 2-chloro moiety on 5-benzylidene nucleus of the 4-thiazolidinone derivative (**30**) could easily fit into the COX-2-binding pocket, considered as critical interaction for COX-2 inhibition. Interestingly, some of the compounds exhibited the potential of becoming dual action or even triple action drug candidates, which could target degenerative disorders associated with excessive free-radical generation.

Keywords 4-thiazolidinones · Anti-inflammatory · Antinociceptive · Free-radical scavenging · Docking · Knoevenagel condensation

Introduction

An imbalance between cellular production of reactive oxygen species (ROS) and body's antioxidant defence mechanism always leads to oxidative stress. ROS such as superoxide radical, peroxynitryl, hydroxyl radical, and hydrogen peroxide are constantly produced as a result of the metabolic reactions in living systems. Pathogenesis of a number of diseases has been reported to involve oxygen-derived free-radicals or ROS (Halliwell and Gutteridge 2015). In addition to playing a role in direct tissue damage, their generation may also amplify body's general inflammatory response and promote further cell injury (Clarkson and Tremblay 1988). The role of free radicals in inflammatory process is well known (Flohe et al. 1985). A number of non-steroidal anti-inflammatory drugs have been reported to act either as inhibitors of free-radical production or as radical scavengers (Saldanha et al. 1990). Thus, compounds with antioxidant properties may offer protection in rheumatoid arthritis and inflammation and lead to potentially

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