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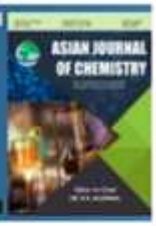

Cu(II) and Fe(III) Catalyzed Synthesis of Novel Thiophene Hybridized Thiadiazolyl Schiff Bases (TTS) as COX-2 Selective Inhibitor

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A novel series of thiophene hybridized thiadiazolyl Schiff bases (TTS) were designed and synthesized using copper nitrate (Cu^{II}) catalyzed synthesis of Schiff bases and their subsequent ferric chloride (Fe^{III}) catalyzed cyclization into thiadiazoles. The design of molecules was inspired by the well-documented anti-inflammatory properties of thiadiazoles, Schiff bases and thiophene. Based on information from mass spectroscopy, IR, ^1H and ^{13}C NMR measurements, the structures of the recently synthesized compounds were determined. The purpose of molecular docking was to better understand the interactions between drug candidates and COX-1 (PDB ID: 3KK6) and COX-2 (PDB ID: 3Q7D) inflammation-related targets. Compounds **3a-f** showed a more stable binding complex with COX-2 (-8.09 to -9.13 kcal/mol) when compared to COX-1 (-4.86 to -5.94 kcal/mol). Additionally, the carrageenan-induced rat paw oedema model was used for the *in vivo* analysis and compound **3a** demonstrated excellent anti-inflammatory activity when compared to the reference drug, diclofenac. Interestingly, the mRNA expression analysis using qRT-PCR demonstrates a specific suppression of COX-2 as compared to COX-1, further supporting the earlier findings. Altogether, the findings could provide an opportunity for these compounds to be developed as novel lead molecules for rational alternatives of NSAIDS.

Keywords: Thiophene-thiadiazolyl Schiff base, Catalysis Anti-inflammatory activity, NSAIDs, COX-1, COX-2.

INTRODUCTION

Inflammation is a complex defense mechanism against any adverse stimuli that is characterized by the buildup of fluids and leukocytes causing edema and pain [1]. There are different physiological and immunological factors involved in both acute and chronic inflammation that often mediate this inflammatory response [2]. Non-steroidal anti-inflammatory medicines, in particular rheumatoid arthritis, are frequently used to treat pain and inflammation associated with these conditions. However, long-term use of these drugs has been linked to kidney damage, bleeding and GIT ulceration [3]. Therefore, even if there are many anti-inflammatory medications on the market, it is necessary to discover new medications with improved safety profiles.

Cyclooxygenases (COXs) are enzymes producing prostanoids, which can cause inflammation and thrombosis [4]. The majority of anti-inflammatory medications block COX-1 and COX-2 enzymes that are responsible for producing the inflammatory mediators, prostaglandins and thromboxane [5]. There are several steroidal and non-steroidal anti-inflammatory drugs currently used to treat diseases associated with inflammation [6,7]. Nonsteroidal anti-inflammatory medications (NSAIDS), mostly used for arthritis, pain and inflammation, include indomethacin and diclofenac. The therapeutic effect of NSAIDs is mainly due to the inhibition of cyclooxygenase (COX) enzyme, leading to prevention of prostaglandins synthesis.

A significant group of heterocyclic compounds known as 1,3,4-thiadiazoles has a wide range of biological actions including anticancer [8], antiviral [9], antibacterial [10], antioxidant [11], antitubercular [12], anticonvulsant [13] and anti-inflammatory [14,15] properties. Cruz *et al.* [16] reviewed the importance of thiophene-based compounds as privileged structures for the design and discovery of novel anti-inflammatory agents. The