ISSN 1070-3632, Russian Journal of General Chemistry, 2023, Vol. 93, No. 11, pp. 2889–2899. © Pleiades Publishing, Ltd., 2023.

Synthesis *In Silico* and ADMET Profile of Triazinethione Derivatives for Their Potential as Anti-Inflammatory Agents

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Received July 24, 2023; revised September 28, 2023; accepted October 3, 2023

Abstract—A series of triazinethiones was successfully synthesized through cycloaddition reaction between guanidine hydrochloride with isothiocyanate intermediates and further analyzed through *in silico* analysis employing molecular docking simulations and ADMET prediction to investigate their potential anti-inflammatory activity. The ADMET profile of the synthesized triazinethione derivatives were found to possess favorable drug-like properties with good solubility (0.58–1.89 mg/mL) and oral bioavailability (0.55). The molecular docking analysis showed that among the synthesized triazinethione, 6-amino-4-(4-nitrophenyl)-1,3,5-triazine-2(1*H*)-thione exhibited a higher binding affinity with anti-inflammatory related enzymes, COX-2 (–7.8 kcal/mol) and iNOS (–6.1 kcal/mol) in comparison to standard drugs of salicylic acid (–6.2 kcal/mol) and Imidazopyridines (–5.9 kcal/mol), respectively owing to the hydrogen bond and hydrophobic interaction. The findings imply that triazinethione derivatives could make excellent possibilities for the development of new anti-inflammatory drugs.

Keywords: triazinethione, COX-2, docking, guanidine hydrochloride, iNOS, isothiocyanate

DOI: 10.1134/S1070363223110208

INTRODUCTION

Inflammation is a complex biological response to harmful stimuli and a crucial immune system component [1]. However, chronic inflammation can lead to various diseases like diabetes, cardiovascular diseases, and cancer [2]. It is crucial to create new anti-inflammatory medications that effectively treat chronic inflammation in order to boost its efficacy and selectivity.

COX-2 and iNOS are two key enzymes involved in the inflammatory process, responsible for producing inflammatory mediators such as prostaglandins and nitric oxide, respectively [3]. Inflammation causes an increase in COX-2, an inducible enzyme that triggers the inflammatory cascade by converting arachidonic acid to prostaglandins. By selectively inhibiting COX-2 activity, it is possible to suppress the production of pro-inflammatory prostaglandins while preserving the beneficial effects of constitutive COX-1, which maintains normal physiological functions [4]. iNOS, conversely, is an enzyme induced in response to pro-inflammatory signals, leading to nitric oxide (NO) production. Nitric oxide is a critical mediator in the inflammatory response, vasodilation, immune cell activation, and oxidative stress. Due to iNOS overexpression, excessive nitric oxide production can contribute to tissue damage and chronic inflammation [5]. Therefore, inhibiting iNOS activity can help regulate nitric oxide levels and mitigate the inflammatory response. COX-2 and iNOS activity inhibition has emerged as a promising strategy for developing anti-inflammatory drugs [6].

Among the diverse range of chemical compounds, a six-member conjugated carbon-nitrogen atom cyclic ring known as triazine has garnered significant attention due to its versatile chemical reactivity and potential applications in pharmaceuticals, agrochemicals, and materials science [7]. Triazine units contain three sp^2 hybridized nitrogen atoms, which give them a larger electron affinity compared to other electron-deficient heteroaromatic rings [8]. Furthermore, the triazine ring's electron-deficient nature enables it to engage in