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Synthesis, enzyme inhibition and molecular docking studies of pyrazolo [1,5-*a*][1,3,5] triazine derivatives as potential antioxidant agents

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ABSTRACT

We developed and produced a series of pyrazolo[1,5-*a*][1,3,5]triazine derivatives (5a-l) in three stages using condensation, intramolecular ring annulation, and acylation processes under moderate conditions. Various spectroscopic techniques and elemental analyses were used to characterize all newly synthesized molecules. By using FRAP and DPPH radical scavenging assays, the antioxidant activity of these compounds was assessed. These conjugates were shown to have moderate to substantial antioxidant activity in both assays. In DPPH and FRAP experiments, compounds 5c, 5d, 5f, and 5 g had the highest levels of antioxidants, with IC_{50} values of 80.33–99.04 μM and 85.69–102.81 μM, respectively. The SAR study's findings indicate that compounds with electron-donating groups (5b-g) are more potent than those with electron-withdrawing groups (5h-l) and unsubstituted compound (5a). Additionally, the lipoxygenase (LOX) and xanthine oxidase (XO) enzymes were used to assess the potent compounds (5b-g) for their ability to suppress enzyme activity. With an IC_{50} value of 16.85–49.02 μM and 23.01–57.38 μM, respectively, these compounds significantly inhibited the activity of the LOX and XO enzymes. Particularly, a number of the designed compounds bearing hydroxyl substituted on phenyl ring linked to pyrazolo[1,5-*a*][1,3,5]triazine system showed excellent not only in antioxidant activity but also in LOX and XO enzyme inhibition. Among these compound 5f was proved to be the top one with an antioxidant and enzyme inhibition ability that was even comparable to that of the standards used. Finally, molecular docking studies of the most effective compounds have been carried out, and the results have shown that the docking scores obtained for compounds 5c, 5f, and 5 g have a significant correlation with the values of antioxidant and enzyme inhibition activity that were found through experimentation.

1. Introduction

In numerous biological processes, reactive oxygen species (ROS), which are a by-product of cellular aerobic metabolism, are crucial. Numerous external factors, including smoking, pollution, xenobiotics, or ionizing radiations, can also cause ROS [1]. Under oxidative stress, ROS in the form of free radicals and neutral molecules cause damage to biological macromolecules. Oxidative stress is brought on by an imbalance between the production and elimination of free radical species. Due to its significant contribution to the etiology of several health issues, including cancer, inflammation, atherosclerosis, cardiovascular, and neurological illnesses [2,3], oxidative stress is a major contributor to these issues. The human body does contain vital defensive mechanisms against oxidative stress, either internally through the production of antioxidant enzymes or externally through dietary supplements [4]. However, our native antioxidant defense mechanisms are insufficient without exogenous antioxidant chemicals [5]. It is well known that the action that promoted antioxidant activity battled against several illnesses. Additionally, they are employed as additives in the cosmetic, pharmaceutical, and food industries [6]. The hunt for novel antioxidants that can serve as free radical scavengers must continue even though the discovery of antioxidant compounds has been the subject of extensive

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