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Synthesis of new chromeno-carbamodithioate derivatives and preliminary evaluation of their antioxidant activity and molecular docking studies

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ABSTRACT

New chromeno carbamodithioates (**7a-i**), have been synthesised from 2, 3-dimethyl-7-(oxiran-2-ylmethoxy)-4H-chromen-4-one (**5**), carbondisulphide and commercially available acyclic and cyclic secondary amines in acetonitrile with good to excellent yields. The free radical scavenging activity of novel chromone-carbamodithioate analogues was quantitatively estimated by spectrophotometric method. Whereas, molecular docking studies were performed with the active site of cyclooxygenase-2 to identify hydrogen bonding, hydrophobic and ionic interactions between protein and ligands. The compounds **7g** and **7h** demonstrated potent antioxidant activity with IC_{50} of 1.405 ± 0.019mM and 1.382 ± 0.35mM respectively compared to Ascorbic acid.

1. Introduction

Reactive Oxygen Species (ROS) and free radicals play an important role in a number of biological processes, some of which are necessary for life such as the intra cellular killing of bacteria by phagocytic cells.[1] However, excessive production of Reactive Oxygen Species and free radicals can cause damage to bio-molecules such as lipids, proteins, enzymes, and DNA in cells and tissues.[2] This triggers to various diseases such as atherosclerosis, heart failure, neuro degenerative disorders, aging, cancer, diabetes mellitus, hypertension. Furthermore, the free radicals can also be generated from environmental pollutants, radiation, chemicals, toxins, deep fried and spicy food, oxidative stress, physical stress, which cause depletion of immune system[3]. Thus, the utility of antioxidants in diet would combat the attacks caused by the free radicals and ROS and reduce the risk of various diseases[4,5]. Apparently, the antioxidants have been currently fabricated as drug candidate to counter these diseases.

It is known that chromone system is present in many compounds widely found in plants and particularly in flavones and isoflavones.[6] In recent years chromone heterocyclic synthesis had attracted tremendous interest among researchers due to their potential applications in medicinal chemistry. Scientific studies on chromones make public hundreds of structures with laxative effect,[7] anti-inflammation,[8] tyrosinase inhibition,[9] skin protection,[10] anti-ulcer[11] and other biological activities. In this context, in continuous of our study on the synthesis of different chromeno analogues and their biological activity,[12,13] here we have synthesized some promising chromone-carbamodithioate analogues with good to excellent yields and inspected their antioxidant activity by Charge Transfer Complex (CTC), a simple spectrophotometric method. Molecular docking studies were also performed on these analogues to suggest the binding site interactions between protein and ligands. To the best of our knowledge, this is the first aspect of study of antioxidant activity on chromeno-carbamodithiates.

2. Results & Discussion

Epoxy chromone **5** is an ideal source for diversity of reactions, as they can be opened with various nucleophiles. The epoxide opening took place in highly regioselective manner preferentially from less hindered site in appropriate reaction times by terminal attack of the nucleophiles[14-17]. In most of the epoxide ring opening reactions nucleophiles were amines (primary or secondary) [15-21] in which, β-amino alcohols were formed by C-N bond linkage with designed core moiety. The scrutiny of the earlier reports on ring opening of 1,2-epoxide with thiol-derived nucleophiles revealed that there are practically seldom reports on only the synthesis of hydroxy dithiocarbamates[22-25] but not on their biological activity studies. Hydroxy dithiocarbamates are very important biologically active compounds and have diverse applications in medicinal chemistry[26], agriculture[27], intermediates in organic synthesis[28] and multifunctional lubricant additives[29].