**Design and synthesis of new derivatives of 2-Thiocoumarin as 15-lipoxygenase inhibitors**

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**Introduction:**

15-Lipoxygenases are a family of iron-containing proteins that have the capability for unsaturated fatty acid peroxidation in animals and plants. Human lipoxygenase can be set in two Subgroup 15-LO-1 and 15-LO-2. In terms of tissue distribution or enzyme properties, 15-LO-1 is converted linoleic acid and arachidonic acid to related metabolites. Studies show that 15-LO-1 can be affect process of developing coronary artery disease. Therefore, strong efforts is taken seeking and synthesis of specific and appropriate inhibitors of enzymes that is involved in fatty acid oxidation of arachidonic. In this research, with design and synthesis thiocoumarin derivatives, we intend to find the chromophore groups in coumarin structure for example thio group. Also with synthesize prenyloxy thiocourin derivatives SAR study had been done.

**Methods / Experimentals:**

In the first step, by using malonic acid, aniline and suitable benzaldehyde in reflux condition, 3carboxylic coumarin (compound 1) was produced. In the second step, from hydrolysis of product that preparated in the previous reaction in reflux, in present of concentration sulfuric acid and H2O with accompanied by the emission of CO2. The next step involved adding Phosphorus pentasulfide and produced intended thiocoumarin which in continue with using prenyl bromide compound 4 has been synthesized [1].

**Results and Discussion:**

According to scheme 1, after hydrolysis of 3-carboxyliccoumarin and making 2-thiocoumarin, the intended derivatives obtained by reaction of prenyl bromids and base in DMF. The inhibitory activity of the synthetic compounds against soybean 15-LOX was determined utilizing modified catalytic oxidative coupling of 3-methyl-2-benzothiazolinone (MBTH) with 3-(dimethylamino) benzoic acid (DMAB) as reported in previous studies. In this method, the basis for the determination of lipoxygenase activity is the measurement of peroxide concentration. Among the synthetic O-prenylated compounds,5 –farnesyloxy had the best result on the soybean 15-LOX. Bonding affinity of the designed molecular structures toward soybean 15-LOX was studied. Docked conformers were generated in AutoDockTools (ADT) software. This convergence was significantly observed for farnesyl and geranyl derivatives. In the earlier mentioned cluster (LFC), most of the conformers have hydrogen bonds with Fe-OH core through their thio groups and their prenyl portion are covered by side chain of some of amino acids in active side. In addition, the ability of the prenyl portion of the compounds to fill the lipophilic pocket which is formed by Ile663, Ala404, Arg403 (butyl portion), Ile400, Ile173 and Phe167 side chains can explain the direct relationship between lipoxygenase inhibition potency and prenyl length chain. To find the effect of thio group on inhibitory potency, lipoxygenase inhibition of the synthetic compounds was also compared to the related analogs with no thio group substituent. For this purpose, lipoxygenase inhibitory of O-farnesyl derivatives of 5-, 6-, 7-, and 8-hydroxythiocoumarin, and their inhibitory activity against 15-LOX reported in previous study [3], were measured in comparison with the present compounds.

Scheme 1

**Conclusion :**

All of the favorite mono prenyloxythiocoumarins were synthesized and their inhibitory potency against SLO were evaluated. The SAR studies showed the importance of prenyl length in SLO inhibition. It was also found that for farnesyl derivatives the role of thiocoumarin substitution site in SLO inhibition is very predominant. The observed inhibition differences between the mentioned enzymes originated from chemical nature and hydrophobic property of their active side pocket residues [3].

**References:**

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