**Design and synthesis of new derivatives of 3-acetylthiocoumarinas 15-lipoxygenase inhibitors**

Sara Zerang Nasrabad a, Seyed Mohamad Seyedi b\*, Hamid Sadeghian c ,Atena Jabari e

a Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

b Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

c Department of Biology, Faculty of Sciences, Ferdowsi University of Mashhad, Iran

d Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

 **Email address** : smseyedi@um.ac.ir

**Introduction:**

Lipoxygenases (LOs) are a main group of the non-heme iron containing proteins in lipid metabolism unsaturated fatty acids include arachidonic acid and linoleic acid convert to related metabolits by lipoxygenases and they are classified based on the position of the oxygenation of arachidonic acid (carbon number). Hydroproxydation at 5 or 15 carbon position of the arachidonic acid respectively were converted to leukotrienes and lipoxines and eoxines in the next section,leukotrienes are released by white blood cells and play a major role in the development of inflemmatory disease of the respiratory system. Research indicate these enzyme play a significat role in human disease such as cancer. In this research, with design and synthesize coumarin derivatives, we intend to revealed the chromophor groups in coumarin structure also study effect of increasing the length of prenyloxy chains in different position of coumarin ring on inhibitory activity of 15-lipoxygenase [1].

**Methods / Experimentals:**

In the first step the appropriate ketone 1 was added to dimethyl trithiocarbonate compound 2 the mixture stirred for 30 min at room tempreture and then refluxed for 2 hours for preparation of intended $β$-Oxodithioesters 3. In the second step salicyldehyde/ substituted salicyldehyde 4 and $β$-Oxodithioesters that preparated in previous step,were heated and stirred for 1-2 hour. then the progress of the reactions was monitored by thin layer chromatography after completion of the raction, water was added and the product was extracted with ethyl acetate [2]. The next step with using prenyl bromide compounds the corresponding derivatives 6 were synthesized.

**Results and Discussion:**

Based on scheme 1 O-Prenyled drivatives 6 were obtained from prenyl bromid in DMF in present of base ,after synthesis 3-acetyl-2-thiocoumarin compound 5 that was prepared from reaction of $β$-Oxodithioesters with intended benzaldehyde. 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. In docking process, flexible side chain of the active site pocket residues of soybean 15-LOX were allowed to be To perform better analysis on docking results, the average Ki (estimated inhibitory constant) of the most populated cluster (KiMPC), average of all the lowest Ki from each cluster (KiLEC), average Ki of all the conformers (KiAC) and average Ki of a cluster in which lactone portion of thiocoumarin directed towards Fe-OH core (KiLFC), were calculated for each compound. Among the four clusters, there was only an acceptable convergence between KiLFC and IC50 results. 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 acetyl 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 [3,4].



Scheme 1

**Conclusion:**

In this research, compound of 3-acetylthiocoumarin was synthesized and derivated by combination of prenyl bromide. These derivatives are reviewed by using the molecular docking techniques and their tension of inhibition are surveyed on 15-lipoxygenase enzyme. In the following, these mentioned compound were compered with prenyled coumarin deravitives in terms of inhibitory activity against on 15-lipoxygenase enzyme , There was a direct relationship between lipoxygenase inhibitory potency and prenyl length chain. generally, 5-O-prenyled compounds [1] were shown to have a better effect on 15-LOX.

**References:**

[1] M. Iranshahi et al. / European Journal of Medicinal Chemistry 57 (2012) 134-142

[2] O.M. Singh et al. / European Journal of Medicinal Chemistry 45 (2010) 2250–2257

[3] L. Toledo, L. Masgrau, J.D. Mare´chal, J.M.. Lluch, A. Gonza´lez-Lafont, Insights into the Mechanism of Binding of Arachidonic Acid to Mammalian 15-Lipoxygenases, J. Phys. Chem. B.114 (2010) 7037–7046.

[4] J. Choi, J.K. Chon, S. Kim, W. Shin, Conformational flexibility in mammalian 15S-lipoxygenase: Reinterpretation of the crystallographic data, Proteins. 70 (2008) 1023–1032.