عنوان مقاله:

New Insight into the SAR of Pyrimido [۴,۵-b][۱,۴] Benzothiazines as ۱۵-lipoxygenase Inhibitors

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خلاصه مقاله:

Objective(s): Recently we reported that the soybean ۱۵-lipoxygenase (SLO) inhibitory activity of pyrimido[۴,۵-b][۱,۴]benzothiazines largely depends on the orientation of sulfur atom of thiazine core towards FeIII-OH in the active site pocket of the enzyme with subsequent oxidation of sulfur to sulfoxide. In this paper the results of a comparative study on the SLO inhibitory activities of the mentioned compounds using ab initio calculations and docking analyses has been reported. Materials and Methods: Structure optimization and docking analyses were performed using HyperChem ۷.۵ and AutoDock Tools ۴.۰ respectively. Enzyme assessment was reduced using spectrophotometric MBTH-DMAB method. Results : The inhibitory activity of synthetic ۲-substituted pyrimido[۴,۵-b][۱,۴]benzothiazines against soybean ۱۵-lipoxygenase (SLO) was evaluated and structure activity relationships and binding modes of their ۴-H and ۴-methyl analogs were studied using docking analysis and ab initio calculations. Discussion: The results of these studies showed that the lack of ۴-methyl substituent in the pyrimido[۴,۵-b][۱,۴]benzothiazine molecules greatly reduces their lipoxygenase inhibitory activities and it was also found that the HOMO energy difference between the ۴-H and ۴-Methyl analogs can be responsible for the observed inhibitory activity reduction. Conclusion: Our molecular modeling studies shows that by using more flexible amino acids during the docking process, more rational results can be obtained. The method of measuring the lipoxygenase activity is also of prime importance for the study of structure activity relationship.

کلمات کلیدی:

DMAB Docking MBTH Peroxide formation SLO