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Isfahan University of Medical Sciences

Inhibition of the P300 histone acetyl transferase by 3-(2H) isothiazolones and analogous oxazolidinone derivatives

N. Adibpour[1], B. Eshaghi[1,*], M. Salimi[2], M. Aberoomand[3], S. Rezaee[4], A. Khalaj[5],

[1]Department of Medicinal Chemistry,School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Pasteur Institute, Tehran, Iran
[3]Department of Biochemistry, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Department of Medicinal Chemistry, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Background and Aims: Acetylation of histone and non-histone proteins of chromatin which is influenced by the action of histone acetyltransferases (HATs) and histone deacetylases(HDACs) controls modifications of chromatin structure, gene expression and hence activity of the resulting proteins. Imbalance between histone acetylation and deacetylation can result in a variety of disease states, including several types of cancers. In the current study a number of 2-(4-substituted phenyl)-3(2H)-isothiazolone derivatives and isothiazolyl oxazolidinones were tested for their inhibitory effect on P300 HAT.
Methods: Phenyl isothiazolones were prepared through the reaction of sulfuryl chloride with appropriate dithiodipropionamides which in turn were obtained by the reaction of dithiodipropionyl chloride with the corresponding amines. 5-((3-Oxoisothiazol-2(3H)-yl)methyl)-3-phenyloxazolidin-2-ones were synthesized by nucleophilic displacement of the mesylate esters of 1,3-oxazolidin-2-ones with 3(2H)-isothiazolones. All mesylates were prepared through the reaction of methanesulfonyl chloride with 5-hydroxymethyl-2-oxazolidinones which were prepared by alkylation-cyclization of carbamates(made by the reaction of arylamines and ethyl chloroformate) with glycidyl butyrate in the presence of tetrahydrofuran solution of n-butyllithium at -78 °C. Histone acetyl transferase inhibition was assessed using a commercially available fluorescent HAT assay kit.
Results: Phenyl substituted chloroisothiazolne derivatives showed the highest P300 HAT inhibition activity with the IC50 values in the range of 1.2-4.7 µM. 5-Chloro-2-(4-fluorophenyl)isothiazol-3(2H)-one was the most potent inhibitor of P300 (IC50 = 1.2±0.1 µM). The lowest activity among phenyl isothiazolones was observed by the compound without any substitution at para position of phenyl ring. Phenyl oxazolidinone derivatives of isothiazolones showed weak inhibitory effect (IC50>10 µM).
Conclusions: Results of this study indicated that the presence of p-substituted (e.g fluoro) phenyl moiety on the nitrogen atom of isothiazolone lead to better inhibition of HAT in comparison to bulkier oxazolidinone group.The observed anticancer effect of these isothiazolyl oxazolidinones might be attributed to their interaction with a different target.

Keywords: P300 HAT; Isothiazolones; Oxazolidinones