Thieno[2,3-d]oxazin-4-ones as Alternate Substrate Inhibitors of Pancreatic Cholesterol Esterase

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Cholesterol esterase (EC 3.1.1.13) is involved in dietary lipid digestion and hepatic metabolism(1,2). Increased chylomicron levels might result from high plasma levels of the esterase leading to an enhanced concentration of LPL and cholesterol. Thus cholesteryl esterase is a target for the development of low molecular weight inhibitors(3-7). We have biochemically investigated a series of heterocyclic compounds as alternate substrate inhibitors of the pancreatic esterase. Reaction of thieno[2,3-d]oxazin-4-ones and thieno[2,3-d]thiazin-4-ones with bovine pancreatic cholesterol esterase (Sigma-Aldrich, Steinheim, Germany).

The piperazinyl-substituted 3,1-oxazin-4-ones and 3,1-thiazin-4-ones with bovine pancreatic cholesterol esterase (Sigma-Aldrich, Steinheim, Germany). The pK\textsubscript{a} values for the inhibition of the esterase, the rate law and the rate constant for the reaction of the esterase with the substrates (sustained concentration 10-25 µM) are shown.

A series of 42 heterocyclic compounds was investigated as inhibitors of bovine pancreatic cholesterol esterase. 2-Thienylmorpholin-3-yl-1,3-oxazin-4-ones were alternate substrate inhibitors of the enzyme. Analogous 2-Thienyl-1,3-oxazin-4-ones were slowly converted. Compound 8 inhibited the esterase with \(k = 3.00 \pm 0.10 \text{ nM}^{-1} \text{ s}^{-1}\) and 2-(5-(2-piperazinyl)thiophen-3-yl)acetyl-5,6-dihydro-tetrazolium (the 5,6-dihydro-4-thiazin-3-yl-carboxylic acid) \(S_\text{NH} = 0.085 \text{ min}^{-1}\) was shown to be formed. The reaction followed first order kinetics with rate constant \(k = 0.085 \text{ min}^{-1}\).

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References: