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Synthesis and structure-activity relationship for a novel class of potent and selective carbamoyl-triazole based inhibitors of hormone sensitive lipase.

AU

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Article

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English

ED

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AB

The central role of the intracellular enzyme hormone-sensitive lipase (HSL) in regulating fatty acid metabolism makes it an interesting pharmacological target for the treatment of insulin resistant and dyslipidemic disorders where a decrease in delivery of fatty acids to the circulation is desirable, e.g., in individuals with type 2 diabetes, metabolic syndrome, or impaired glucose tolerance. On the basis of a lead structure from high throughput screening, we have identified a very potent type of carbamoyl-triazole inhibitors of HSL. As part of the lead optimization program, four new classes of carbamoyl-triazoles were synthesized and tested with respect to potency, efficacy and selectivity. Methyl-phenyl-carbamoyl-triazoles were identified as potent and efficacious HSL inhibitors. These compounds do not inhibit other hydrolases such as hepatic lipase, lipoprotein lipase, pancreatic lipase, and butyrylcholine esterase. However, the inhibitors 4b and 4g with IC50 values for HSL of 0.17 and 0.25 muM, respectively, were the only inhibitors selective against acetylcholine esterase. A reversible pseudosubstrate inhibition mechanism is proposed for this class of inhibitors.

CC

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Endocrine - Pancreas 17008
Pharmacology - General 22002

IT

Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Pharmaceuticals (Pharmacology)

IT

Diseases
type 2 diabetes: endocrine disease/pancreas, metabolic disease
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)

IT

Chemicals & Biochemicals
carbamoyl-triazole based inhibitors: enzyme inhibitor-drug; hormone sensitive lipase

IT

Methods & Equipment
drug synthesis: laboratory techniques; structure-activity relationships
analysis: laboratory techniques

RN

9001-62-1 (hormone sensitive lipase)