Thiazole-based Inhibitors and Bisamide Heterocycle Inhibitors of Scavenger Receptor BI

Technology #15787-15788

Applications

Scavenger receptor class B, type I (SR-BI) inhibitors act as molecular tools to probe for the function of SR-BI in greater detail. Additionally, because of the known role of SR-BI in the transfer of cholesterol between cells and high-density lipoproteins (HDL), SR-BI inhibitors can be used to increase plasma HDL-cholesterol (HDL-C) concentration, which epidemiologic studies have shown is inversely related to atherosclerosis severity. SR-BI inhibitors could also potentially block cellular entry of HCV and malaria parasites that use SR-BI as co-receptors, thus, acting as potential therapy against HCV infection and malaria.

Problem Addressed

SR-BI is a member of CD36 superfamily, and is the primary receptor responsible for mediating selective transport of cholesterol between high-density lipoprotein (HDL) and cells. The mechanism of this transport is poorly understood but it is known to be dramatically different from classic endocytic uptake. In addition to cholesterol, SR-BI can also interact and transport a wide variety of other lipids and ligands. Thus, there is a need for molecular tools to probe the biology of SR-BI further.

There are multiple potential therapeutic applications of SR-BI inhibitors. In addition to its significant influence on lipoprotein metabolism, SR-BI has been shown to influence a wide variety of physiologic and pathophysiologic systems, including hypercholesterolemia and coronary artery disease, female infertility, adrenal insufficiency, anemia, thrombocytopenia, endothelial dysfunction, immune/inflammatory defects, susceptibility to deep vein thrombosis and association with some cancers. In addition, SR-BI acts as a co-receptor for cellular entry of HCV and malaria parasites. In some of these cases (e.g., HCV and malarial infection, cancer), targeting SR-BI presents an attractive approach to therapy.

Technology

ML278 and ML279 are two of the inhibitors of SR-BI that were discovered in a high throughput screen. These molecules work by increasing the binding of HDL to SR-BI while reversibly inhibiting the transfer of cholesterol. ML278 and ML279 were shown to inhibit SR-B1 both selectively and potently in the screen assay with IC50s of 6 and 17 nM, respectively. It is important to note that these lead compounds showed superior potency in the screen assays compared to the clinical SR-B1 inhibitor ITX-5061.

Advantages

- ML278 and ML279 are selective, reversible, and potent inhibitors of SR-BI

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- The lead compounds have superior potency compared to the clinical compound ITX-5061
- Inhibitors of SR-BI could be potential therapeutic agents to treat atherosclerosis and HCV and malarial infections.

Categories For This Invention:

Chemicals
Life Sciences
Chemicals
Other (Chemicals)
Clinical Applications
Cardiovascular
Infectious Disease
Research Tools
Other (Research Tools)
Therapeutics
Small Molecule

Intellectual Property:

Bisamide heterocycle inhibitors of Scavenger Receptor BI
US Patent Pending
2015-0284371
Thiazole-based inhibitors of Scavenger Receptor BI
US Patent Pending
2016-0060254

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Publications:

Indolinyl-Thiazole Based Inhibitors of Scavenger Receptor-BI (SR-BI)-Mediated Lipid Transport
ACS Medicinal Chemistry Letters
2015 Apr 9; 6(4): 375–380. Published online 2015 Feb 2. doi: 10.1021/ml500154q
Discovery of Bisamide-Heterocycles as Inhibitors of Scavenger Receptor BI (SR-BI)-Mediated Lipid Uptake.
Bioorganic & Medicinal Chemistry Letters
2015 Jun 15;25(12):2594-8. doi: 10.1016/j.bmcl.2015.03.074. Epub 2015 Apr 11.

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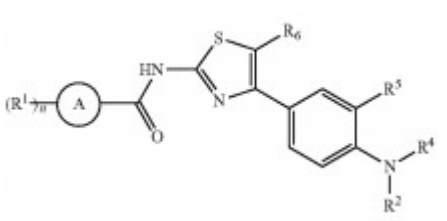

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