N-benzylimidazole carboxamides as potent, orally active stearoyl CoA desaturase-1 inhibitors.

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Abstract

A potent, small molecule inhibitor with a favorable pharmacokinetic profile to allow for sustained SCD inhibition in vivo was identified. Starting from a low MW acyl guanidine (5a), identified with a RapidFire High-Throughput Mass Spectrometry (RF-MS) assay, iterative library design was used to rapidly probe the amide and tail regions of the molecule. Singleton synthesis was used to probe core changes. Biological evaluation of a SCD inhibitor (5b) included in vitro potency at SCD-1 and in vivo modulation of the plasma desaturation index (DI) in rats on a low essential fatty acid (LEFA) diet. In addition to dose-dependent decrease in DI, effects on rodent ocular tissue were noted. Therefore, in rat, these SCD inhibitors only recapitulate a portion of phenotype exhibited by the SCD-1 knockout mouse.