

HCV-796: A Potent and Selective Non-Nucleoside Inhibitor of HCV NS5B

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Background: In order to address the need for improved therapy of hepatitis C virus (HCV), medicinal chemists have had a committed search for an inhibitor of HCV RNA-dependent RNA polymerase (NS5B). Such an inhibitor could potentially be a mainstay of HCV therapy as in the case of non-nucleoside inhibitors of HIV RT.

Methods: Evaluation of compounds for their ability to inhibit HCV genotype 1b NS5B polymerase resulted in the identification of benzofurans as a potent series of inhibitors. Chemists synthesized over 400 compounds in a Structure Activity Relationship (SAR) campaign aimed at optimizing potency. Compounds were tested in a biochemical assay at multiple concentrations to generate a standard inhibitory curve and corresponding IC₅₀s. Subsequent testing in an HCV subgenomic replicon assay provided potency information in the context of a cellular system. Potent compounds were assayed for selectivity against a panel of human and unrelated viral polymerases.

Ultimately, this screening paradigm led to the discovery of (5-cyclopropyl-2-(4-fluoro-phenyl)-6-[(2-hydroxy-ethyl)-methanesulfonyl-amino]-benzofuran-3-carboxylic acid methylamide, HCV-796. This potent inhibitor was efficiently synthesized from commercially available starting materials.

Results: Chemists developed SAR around an active series of benzofurans using a serial combination of biochemical and replicon assays. Clinical candidate HCV-796 was identified as a potent and selective inhibitor of HCV NS5B displaying an IC₅₀ of 0.04±0.02 μM (n=35), EC₅₀ of 8.6±4.0 nM (n=14) and no inhibitory activity against a panel of human and unrelated viral polymerases.

HCV-796 was synthesized from easily available starting materials in 12 steps. The average yield per reaction step is 74% and the total yield of the synthesis is 7%.

Conclusions: HCV-796 was efficiently synthesized from readily available commercial starting materials. HCV-796 is a novel small molecule of the benzofuran class directed against HCV NS5B. In vitro, HCV-796 shows potent selective inhibitory activity in the biochemical and replicon assays. Based on its biological activity, HCV-796 is a promising antiviral agent currently in Phase 1 clinical development.