



Benzimidazole Thumb Pocket I finger-loop inhibitors of HCV NS5B polymerase: Improved drug-like properties through C-2 SAR in three sub-series

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ABSTRACT

SAR at the C-2 position of benzimidazole-based Thumb Pocket I inhibitors of HCV NS5B polymerase revealed parallel activity for distinct sub-series that harbor 5-hydroxytryptophan amides, neutral thiazole isosteres or recently disclosed cinnamic acid diamides. The consistent SAR among the three sub-series suggest a common binding mode to the Thumb Pocket I allosteric site. New inhibitors with sub-micromolar cell-based replicon potency and improved 'drug-like' features are disclosed along with preliminary characterization of their ADME-PK profile.

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Hepatitis C virus (HCV) infections, which are believed to afflict 1–3% of the world population, may lead to serious and often fatal liver diseases such as cirrhosis and hepatocellular carcinomas (HCC).¹ HCV is the leading cause of liver transplantation in the world and represents a major concern to public health in both industrialized and developing countries. The discovery of the virus 20 years ago and the development of diagnostic tools have greatly contributed to arresting the spread of new viral infections. Nevertheless, it is estimated that the number of newly diagnosed patients will continue to rise in the next 10 years before reaching a plateau and eventually decreasing as more effective and better tolerated antiviral therapies become available. The current standard of care, based on combinations of pegylated-interferon and ribavirin, is poorly tolerated and shows sub-optimal efficacy, particularly against genotype 1 (most abundant in the western world).²

NS5B, the RNA-dependent RNA polymerase of HCV is the enzyme that catalyzes replication of the virus's genome and has been the focus of extensive research efforts by academia and the pharmaceutical industry for the development of novel anti-HCV agents. NS5B polymerase is sensitive to inhibition by both substrate-based nucleoside analogs as well as non-nucleoside allosteric inhibitors. Several small molecule candidates from both classes of drugs have

progressed through early stages of clinical development and provided proof of concept of antiviral efficacy in man.^{3,4} Allosteric inhibitors of NS5B are divided into at least four different classes according to the location of their respective binding sites (referred to as Thumb Pocket I and II and Palm Sites I and II).⁴

Our group reported the discovery and subsequent optimization of benzimidazole-based allosteric inhibitors of HCV NS5B that bind to Thumb Pocket I of the enzyme (Fig. 1) and were shown by us and others to restrict conformational changes in the enzyme that are thought to be required at the initiation stage of RNA synthesis. We refer to this class of compounds as 'finger-loop inhibitors' since they prevent a key intra-molecular interaction of the $\lambda 1$ loop that extends from the finger domain with the thumb domain of the enzyme. This interference with a protein conformational change prevents the formation of a productive enzyme complex for RNA synthesis.⁵

In a recent Letter, we reported optimization of the right-hand side of benzimidazole-based inhibitors and the discovery of novel diamide derivatives (e.g., compound **C1**) that displayed excellent inhibition in biochemical assays with micromolar potency in a cell-based 1b HCV sub-genomic replicon assay (Fig. 1).⁶ We now describe C-2 SAR in this class of inhibitors and some comparison to previous series of compounds (5-hydroxytryptophans **A1** and thiazoles **B1**) that, despite significant structural changes on the right-hand side, provides evidence for parallel SAR and a common

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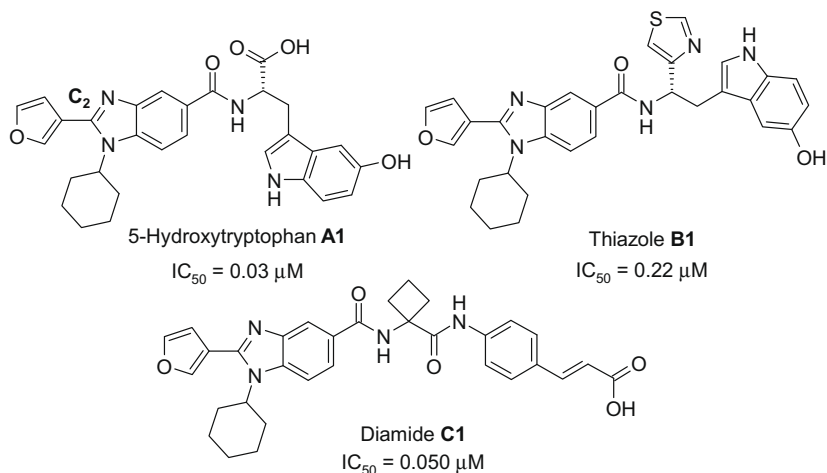


Figure 1. Representative members from three benzimidazole sub-series of finger-loop (Thumb Pocket I) inhibitors.

binding mode for the three sub-series. In addition, the furyl structural alert in lead inhibitors **A1**, **B1**, and **C1** was replaced and cellular potency improved to provide inhibitors with promising in vitro ADME and rat PK characteristics.

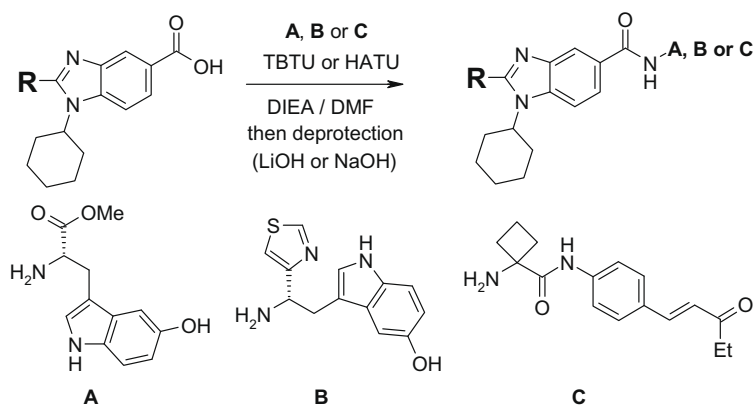
The three benzimidazole sub-series of NS5B inhibitors previously disclosed contain a 5-carboxybenzimidazole scaffold that features an optimal N¹-cyclohexyl moiety and a small heterocyclic C-2 substituent. While the N¹-position is very sensitive to small structural modifications, the C-2 position was shown in early work to tolerate a variety of substituents ranging from small heterocycles⁷ to large poly-aromatic systems.⁸ Recent disclosures from our group revealed how the electron-rich 5-hydroxytryptophan system may be replaced by a cinnamic acid moiety linked to the benzimidazole scaffold through an α,α -disubstituted cyclic α -amino acid linker.⁶ We wished to re-investigate SAR at the C-2 position of the benzimidazole left-hand side to verify that SAR remained parallel in the three sub-series and identify a more drug-like replacement for the furyl heterocycle at C-2.⁹

The synthesis of inhibitors was performed in solution as described in Scheme 1. Benzimidazole carboxylic acids with variations at C-2 or N¹ were prepared according to previously published procedures^{7,10} and coupled to amines **A**,¹¹ **B**,¹² or **C**⁶ using standard reagents for amide bond formation (TBTU or HATU) followed by removal of protecting groups by saponification if necessary.¹³

C-2 SAR was established early in truncated benzimidazole 5-carboxylic acid derivatives⁷ where a relatively 'flat' SAR was ob-

served at this position. Nonetheless, 2- and 3-furyl, 2-*N*-Me-pyrrole, 2- and 3-thiophenyl, and 2-pyridyl were identified as providing the best intrinsic potencies in a full-length NS5B biochemical assay.¹⁴

As the series progressed from the short benzimidazole carboxylic acid derivatives to more potent tryptophan-based amides (sub-series **A** and **B**), we had assumed similar inhibitor binding modes¹⁵ and SAR at this position. In order to validate this hypothesis, a series of analogs that contained these privileged C-2 substituents was prepared and tested in both the full-length NS5B and the C-terminally deleted Δ 21-NS5B format of the biochemical assays.¹⁴ Both assays gave similar IC₅₀ values and only data for the latter are reported in Table 1. As reported previously for the 3-furyl derivatives **A1** and **B1**, tryptophan analogs that contained a thiazole replacement for the α -carboxylic acid group were all less potent (3–12-fold), independent of the C-2 substituent. This observation may be rationalized by a key role for the carboxylic acid. It is believed to be solvent exposed and serves as a conformation orienting group,^{12,15} and is favorably hydrated in sub-series **A** compared to the more hydrophobic thiazole group present in sub-series **B**. However, the charge and high polarity of carboxylic acids **A1–8** were incompatible with cellular permeability and all compounds in this sub-series were inactive in an HCV genotype 1b cellular replicon assay.¹⁶ The more lipophilic and neutral thiazole analogs **B1–8**, on the other hand provided low-micromolar inhibition (EC₅₀ = 2–4 μ M) in the cell-based assay, regardless of the C-2 substituent present on the benzimidazole scaffold. As previously



Scheme 1. Synthesis of inhibitors.

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