

Abstract

Investigation of thiophene-2-carboxylic acid HCV NS5B site II inhibitors, guided by measurement of cell culture medium binding, revealed the structure-activity relationships for intrinsic cellular potency. The pharmacokinetic profile was enhanced through incorporation of heterocyclic ethers on the N-alkyl substituent. Hydroxyl groups were incorporated to modulate protein binding. Intrinsic potency was further improved through enantiospecific introduction of an olefin in the N-acyl motif, resulting in the discovery of the phase 2 clinical candidate GS-9669. The unexpected activity of this compound against the clinically relevant NS5B M423T mutant, relative to the wild type, was shown to arise from both the N-alkyl substituent and the N-acyl group.