Abstract

A general and modular synthetic approach to 4-substituted phenyl, 2-substituted pyridin-5-yl and 5-substituted pyridin-2-yl 2′-*C*-methyl-*C*-ribonucleosides as potential anti-HCV agents was developed. Addition of halo(het)aryllithium reagents to benzylated 2-*C*-methyl-D-ribonolactone gave the corresponding hemiketals, which were subsequently converted to the β-anomeric benzyl-protected bromo(het)aryl-*C*-nucleosides via either direct reduction (in the case of phenyl derivative) or acetylation followed by reduction of the resulting hemiketal acetates (in the case of pyridyl derivatives). The key halogenated (het)aryl-*C*-nucleoside intermediates were further transformed by Pd-catalyzed cross-coupling, hydroxylation and amination reactions affording series of protected *C*-nucleosides with small hydrophilic and hydrophobic substituents. The final protecting group removal was rather problematic, and different debenzylation methods, such as hydrogenation on Pd/C or treatment with BCl_3, had to be optimized for each derivative to minimize the formation of side-products. The final *C*-nucleosides were also converted into their 5′-*O*-triphosphates, and biological activity screenings revealed that none of the free *C*-nucleosides possesses any antiviral activity in the HCV replicon assay, and none of their NTPs significantly inhibits the HCV RNA polymerase.

Two series of isomeric pyrrolo-fused 7-deazapurine ribonucleosides were prepared in order to extend the promising class of biologically active modified nucleosides featuring 7-deazapurine nucleobase with annulated five-membered heteroaromatic ring. The synthetic strategy was based on thermal heterocyclizations of 4-azido-6-chloro-5-pyrrolylpyrymidines to construct the tricyclic nucleobases, followed by glycosylation and further derivatization via various cross-coupling and nucleophilic substitution reactions. The final nucleosides bearing hetaryl, amino, dimethylamino, methyl, methoxy and methylsulfanyl groups were then screened for antiviral and cytotoxic activities. While pyrrolo[3',2':4,5]pyrrolo[2,3-*d*]pyrimidine nucleosides were devoid of any cytotoxic activity, their isomeric pyrrolo[2',3':4,5]pyrrolo[2,3-*d*]pyrimidine analogues exerted submicromolar cytotoxicity, and within this series, methyl, methoxy and methylsulfanyl derivatives showed the highest activity with good selectivity toward cancer cells. It was also shown that the nucleosides are intracellularly phosphorylated and then get incorporated into RNA and DNA where they cause DNA damage. Some pyrrolo-fused 7-deazapurine ribonucleosides also showed submicromolar anti-HCV activities, but there is still a need for further deeper studies to prove the mechanism and biological targets.