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Synthesis and anti-HCV activity of 3′,4′-oxetane nucleosides

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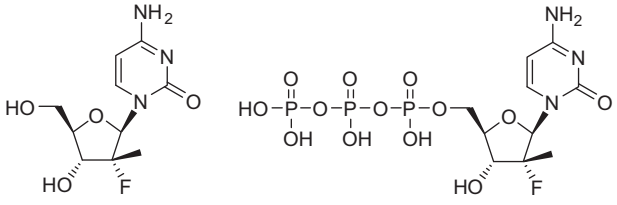
ABSTRACT

Hepatitis C virus afflicts approximately 180 million people worldwide and currently there are no direct acting antiviral agents available to treat this disease. Our first generation nucleoside HCV inhibitor, RG7128 has already established proof-of-concept in the clinic and is currently in phase IIb clinical trials. As part of our continuing efforts to discover novel anti-HCV agents, 3′,4′-oxetane cytidine and adenosine nucleosides were prepared as inhibitors of HCV RNA replication. These nucleosides were shown not to be inhibitors of HCV as determined in a whole cell subgenomic replicon assay. However, 2′-mono/difluoro analogs, **4**, **5**, and **6** were readily phosphorylated to their monophosphate metabolites by deoxycytidine kinase and their triphosphate derivatives were shown to be inhibitors of HCV NS5B polymerase in vitro. Lack of anti-HCV activity in the replicon assay may be due to the inability of the monophosphates to be converted to their corresponding diphosphates.

Hepatitis C virus (HCV) is a leading cause of chronic liver disease.[1] Nearly 1.6% of the U.S. population and an estimated 180 million people worldwide are infected with HCV.[2] Approximately 80% of infected individuals become chronically infected; this chronic infection can lead to liver cirrhosis and hepatocellular carcinoma in a significant number of patients.[3] The current standard of care (SOC) for those infected with HCV includes administration of pegylated interferon alpha and ribavirin. However, only 50% of patients infected with genotype 1 virus respond to treatment with SOC therapy. In addition, the SOC regimens are associated with various intolerable adverse side effects.[4] To date no vaccine has been developed to treat HCV due to the multiple genotypes of HCV and to the relatively high mutation rate associated with this virus.[5] Consequently, there is an urgent need for the identification of new small molecule direct acting antiviral agents to effectively treat chronic HCV infection.

RG7128 is a nucleoside prodrug of β-D-2′-deoxy-2′-α-fluoro-2′-*C*-methylcytidine **1** (PSI-6130, Fig. 1) and is a specific inhibitor of the HCV NS5B RNA dependent RNA polymerase (RdRp). Recently, we reported exceptional clinical efficacy of RG7128 as an anti-HCV direct acting antiviral agent.[6] Since **1** is a nucleoside, in order to inhibit the HCV RdRp, it must be phosphorylated by cellular kinases to its 5′-triphosphate form. The 5′-triphosphate of PSI-6130 (**2**) is an alternative substrate of the HCV RdRp and acts as a non-obligate chain terminator.[7,8]

Other than the 2′-α-fluoro-2′-*C*-methyl class of nucleosides represented by PSI-6130 (**1**), several other nucleoside classes have been reported to exhibit in vitro anti-HCV activity. These other nucleosides include 2′-deoxy-2′-α-fluorocytidine,[9] 2′-α-*O*-methyl substituted nucleosides, 2′-C-methyl ribonucleosides,[10,11] and 4′-substituted nucleoside derivatives where 2′-substitution can be either α-OH, β-OH, β-F or diF.[12,13] What is also known about these nucleosides is that the 4′-substituted nucleosides possess a different conformational preference (2′-endo) relative to the other classes which prefer a 3′-endo conformation (Fig. 2), yet they still demonstrate good in vitro potency as inhibitors of HCV.[7,12] Therefore, we were interested in taking key features of each of these



1, PSI-6130

EC_{90} = 4.6 μM

2

K_i = 0.059 μM for HCV NS5B

Figure 1.

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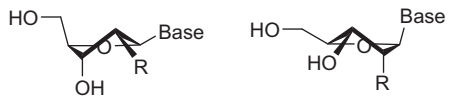


Figure 2. C2′- and C3′-endo conformations of nucleosides.

3, Base = cytosine, R^1 = F; R^2 = Me
4, Base = cytosine, R^1 = F; R^2 = H
5, Base = cytosine, R^1 = H; R^2 = F
6, Base = cytosine, R^1 = F; R^2 = F
7, Base = cytosine, R^1 = OMe; R^2 = H
8, Base = adenine, R^1 = F; R^2 = H

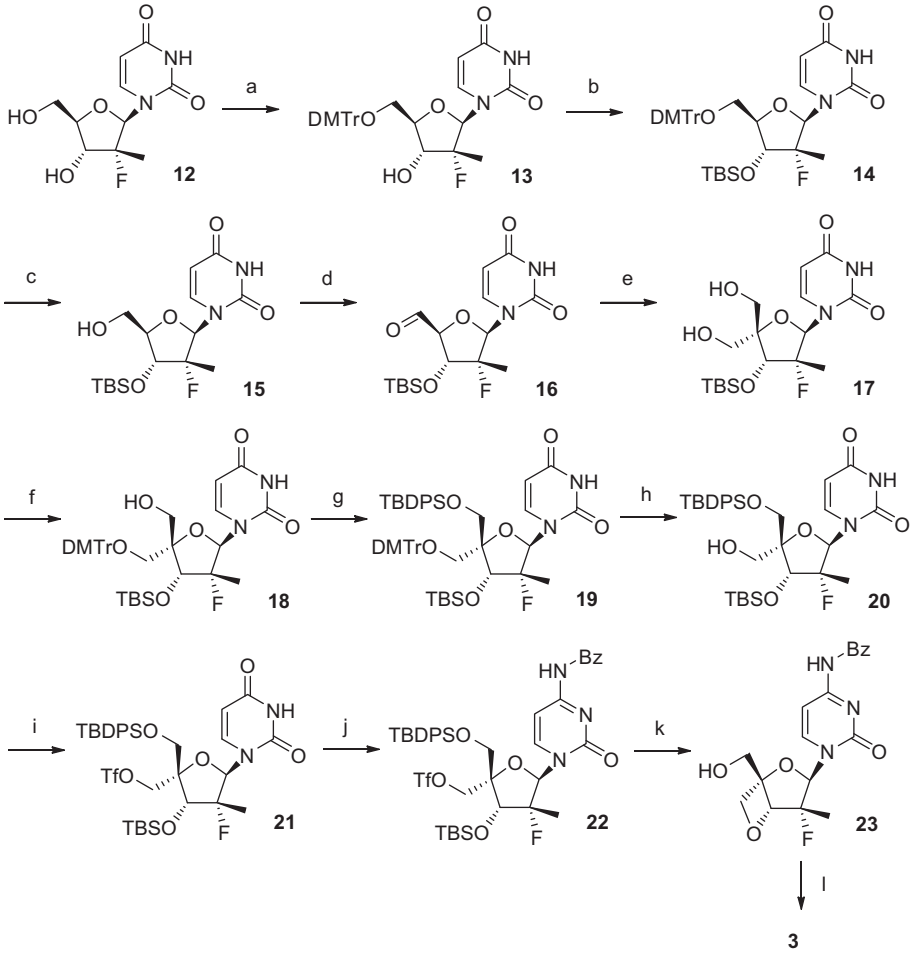
9, R^1 = F; R^2 = H
10, R^1 = H; R^2 = F
11, R^1 = F; R^2 = F

Figure 3.

nucleosides and developing a novel series of compounds as potential inhibitors of HCV replication.

In exploring the potential of novel nucleosides as anti-HCV agents, we were interested in investigating conformationally restricted nucleoside derivatives. Introducing a conformational restriction by the use of fused ring system is a well-established approach to enhance a specific biological activity of a nucleoside.[14] This modification has been extensively pursued not only for antisense oligonucleotides,[15,16] but also for direct-acting therapeutic agents such as antituberculosis,[17] antitumor,[18] and antivirals.[19] In pursuing this concept of conformationally restricted nucleosides we chose to investigate the 3′-*O*,4′-*C* methylene (3′,4′-oxetane) nucleoside template. The ribofuranose ring of a 3′,4′-oxetane nucleoside is known to prefer the C2′-endo (Southern-type) conformation similar to the 2′-deoxy-4′-azido substituted anti-HCV nucleosides.[12,16] However, the biological activity of this class of molecules against HCV remains unexplored. Therefore, we proceeded to investigate the anti-HCV activity of the 3′,4′-oxetane nucleosides introducing substitution at the 2′-position known to be compatible with anti-HCV activity (Fig. 3).

Oxetane nucleoside **3** was prepared from 2′-deoxy-2′-fluoro-2′-*C*-methyluridine **12** (Scheme 1). The 5′- and 3′-hydroxyl groups were sequentially protected with a dimethoxytrityl group and a *tert*-butyldimethylsilyl group. After deprotection under acidic conditions, the primary alcohol at C5′ was oxidized via the Pfitzner–Moffatt reaction[20] to give aldehyde **16**. Subsequent aldol reaction with formaldehyde followed by reduction of the aldehyde provided diol **17**. Then, the less hindered C5′-primary alcohol on the α-face of diol **17** was selectively protected with a dimethoxytrityl group. The other primary alcohol was then protected with TBDPS. Subse-



Scheme 1. Reagents and conditions: (a) DMTrCl, pyridine, 0 °C to rt, 8 h, 93%; (b) TBSCl, imidazole, rt, 16 h, 92%; (c) 3% TFA in DCM, rt, 3 h, 66%; (d) EDC, DMSO, pyridine, TFA, rt, 30 min, 50%; (e) CH_2O, NaOH, aq dioxane, rt, 30 min; $NaBH_4$, 0 °C to rt, 1 h, 45%; (f) DMTrCl, pyridine, 0–10 °C, 8 h, 67%; (g) TBDPSCl, imidazole, rt, 18 h, 46%; (h) CAN, MeCN, rt, 16 h, 83%; (i) Tf_2O, 2,6-lutidine, DCM, 16 h, 91%; (j) TIPBSCl, Hűnig's base, DMAP, CH_3CN, rt, 1 h; NH_4OH, rt, 0.5 h; BzCl, Hűnig's base, DMAP, rt, 1 h, 65%; (k) TBAF, THF, reflux, 3 h, 58%; (l) 7 N NH_3 in MeOH, rt, 6 h, 62%.

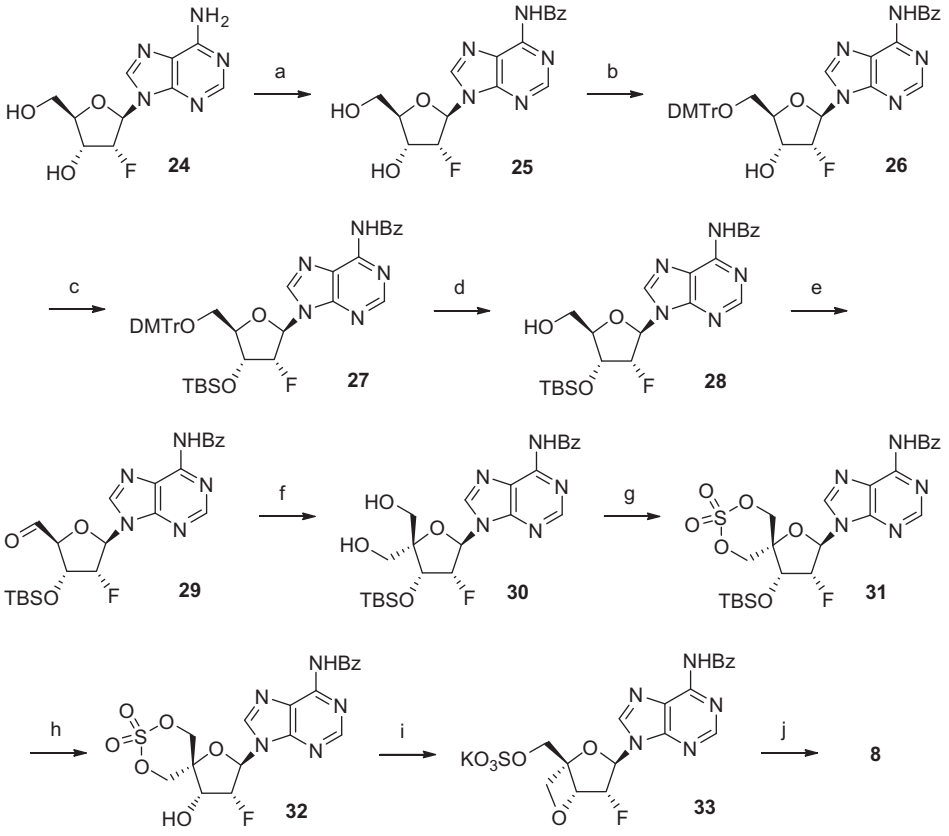
quent removal of the DMTr protection and derivatization as the triflate gave intermediate **21**. Conversion to the cytidine analog **22** was accomplished by mild ammonolysis of the 2,4,6-triisopropylbenzenesulfonyl ester. Deprotection of 3′-silyl group triggered the key ring closure to afford oxetane **23**. Finally, removal of the 6-*N*-benzoyl group gave the desired 3′,4′-oxetane cytidine modified nucleoside **3**. Cytidine nucleosides **4** to **7** were prepared via similar synthetic sequences starting from corresponding uridine nucleosides.

The 2′-deoxy-2′-*C*-methyl adenosine analog was shown to be a potent inhibitor in a HCV replicon assay.[10] Therefore, we wished to prepare a purine analog of a 3′,4′-oxetane nucleoside in addition to the pyrimidines. The synthesis began with N-6 protection of 2′-deoxy-2′-β-fluoro-adenosine (Scheme 2). After a series of protection and deprotection steps to give the nucleoside **28** containing a protected 3′-hydroxyl group, the free 5′-hydroxyl group was oxidized to give aldehyde **29**, which upon aldol condensation and reduction provided diol **30**. Unlike the case of the uridine analog **17**, selective derivatization of the hydroxyl group on the α-4′-hydroxymethylene moiety was not observed in diol **30**.[21] Instead, cyclicsulfate **31** was prepared as an intermediate for oxetane ring closure. After removal of the silyl protecting group on the 3′-oxygen, intermediate **32** was treated under basic conditions to effect oxetane ring formation. Hydrolysis of the sulfonic acid salt and removal of *N*-benzoyl protection group completed the sequence and afforded the desired 3′,4′-oxetane adenine nucleoside **8** in 67% from cyclic sulfate **31**.

Anti-HCV activity of the 2′-substituted-3′,4′-oxetane nucleosides was determined using the subgenomic replicon assay (Table 1).[22] The 2′-β-methyl-2′-α-fluoride derivative **3** which shares the same substitution pattern at C2′ as the potent HCV inhibitor, **1** did not show significant anti-HCV activity. As previously reported, 2′-α-fluorocytidine **9** showed effective inhibition of HCV; however, its corresponding oxetane derivative **4** did not significantly inhibit HCV.[9] The 4′-azido-2′-deoxy-2′-β-fluorocytidine was previously shown to be a potent inhibitor of HCV but, again, the 2′-deoxy-2′-β-fluoro-3′,4′-oxetane nucleoside **5** was inactive as an HCV inhibitor.[13] An attempt to gain activity by combining both an α- and β-fluoro group at 2′ gave oxetane **6**. However no HCV inhibitory activity was observed for this compound when assayed at 50 μM. The 2′-α-methoxy derivative **7** also did not show activity at 50 μM. To assess if a base modification could induce anti-HCV activity when combined with an oxetane template, the adenosine derivate **8** was evaluated, and again no significant activity was observed. It is also noteworthy that none of these oxetane nucleosides was shown to be cytotoxic when evaluated at

Table 1
HCV clone A replicon data

Compound	EC_{90} (μM)	CC_{50} (μM)
1	4.6	>50
3	>50	>50
4	>50	>50
5	>50	>50
6	>50	>50
7	>50	>50
8	>50	>50
9	5.21	>50
10	>50	>50
11	<1	<0.1



Scheme 2. Reagents and conditions: (a) TMSCl, pyridine, rt, 1 h, then, BzCl, 0 °C to rt, 3 h, 85%; (b) DMTrCl, pyridine, 0 °C to rt, 3 h, 94%; (c) TBSCl, imidazole, DMF, rt, 16 h; (d) TsOH, DCM/MeOH, 0 °C, 3 h, 70% in two steps; (e) Dess–Martin periodinane, DCM, 0 °C to rt, 4 h, 71%; (f) CH_2O, NaOH, aq dioxane, rt, 10 h; $NaBH_4$, EtOH, 0 °C to rt, 1 h, 47%; (g) $SOCl_2$, pyridine, DCM, −10 °C to 0 °C; $RuCl_3$–xH_2O, $NaIO_4$, DCM/MeCN/H_2O, rt, 1 h, 81%; (h) TBAF, THF, rt, 1 h, 76%; (i) KOtBu, THF, 0–10 °C, 30 min; (j) H_2SO_4, rt, 48 h; NH_3, MeOH, rt, 16 h, 67% in three steps.

concentrations up to 50 μM. Even in the case of the 2′-difluoro derivative **6** which is an analog of the highly cytotoxic nucleoside Gemcitabine (**11**) no cytotoxicity was observed.[23]

Since nucleosides must be anabolized to their triphosphate derivative in order to inhibit the HCV RdRp, it is possible that the lack of activity exhibited by these oxetane nucleosides may be as a result of their inability to be phosphorylated by cellular kinases in the phosphorylation cascade. To investigate this possibility, we prepared the triphosphates of three 3′,4′-oxetane nucleosides (**4-TP**, **5-TP**, and **6-TP**).[24] These triphosphates were shown to inhibit the HCV NS5B polymerase in vitro with IC_{50}s from 30 to 80 μM (Table 2). Since these triphosphates inhibited the HCV RdRp, lack of anti-HCV activity may be due to a problem with the phosphorylation of the nucleosides to their corresponding triphosphates. Therefore, the phosphorylation of the 3′,4′-oxetane nucleosides to their monophosphates by deoxycytidine kinase (dCK) was evaluated.[25] As shown in Table 3, several 3′,4′-oxetane nucleosides (**4**, **5**, and **6**) were determined to be substrates for dCK and showed similar or better substrate efficiency compared to the known HCV inhibitor **1**.

There are several known human nucleoside monophosphate kinases including UMP-CMP kinase, thymidylate kinase, adenylate kinase, and guaniylate kinase. Typically, UMP-CMP kinase is responsible for phosphorylation of deoxycytidine monophosphate and its analogs.[26] Therefore, the second phosphorylation step was studied by treating the 3′,4′-oxetane nucleosides (**4**, **5**, and **6**) with both dCK and UMP-CMP kinase and the phosphorylated products were detected by thin layer chromatography. Significant amounts of the monophosphate products were formed due to phosphorylation of the nucleosides by dCK but very little or no 3′,4′-oxetane nucleoside diphosphate products were detected, indicating that 3′,4′-oxetane nucleoside monophosphates are not substrates for UMP-CMP kinase (data not shown). Therefore, we can conclude that the lack of anti-HCV activity of the 3′,4′-oxetane nucleosides studied can most likely be attributed to the fact that their monophosphates are not substrates for the monophosphate kinases which are required for the biosynthesis of the active triphosphate in the cell.

In summary, we prepared several novel 3′,4′-oxetane nucleosides and studied their anti-HCV activities. Although these oxetane containing nucleosides did not show significant anti-HCV activity in the whole cell replicon assay, representative triphosphate derivatives (**4-TP**, **5-TP**, and **6-TP**) were shown to be inhibitors of the HCV NS5B RdRp with the triphosphate of **4** being the most potent (IC_{50} = 31 μM), Even though representative oxetane derivatives are substrates for the first kinase in the phosphorylation cascade (dCK), their lack of whole cell replicon activity can be attributed to the inability of the monophosphate kinases to phosphorylate the monophosphates of **4**, **5**, and **6**.

Table 2
Inhibition of HCV polymerase (NS5B) activity in vitro

Compound	IC_{50} (μM)
4-TP	30.96 ± 4.75
5-TP	78.91 ± 5.68
6-TP	32.76 ± 5.36
2, **PSI-6130-TP**	5.37 ± 0.50

Table 3
Steady-state parameters for dCK reactions

Compound	k_{cat} (s^{-1})	K_m (μM)	k_{cat}/K_m ($\mu M^{-1}\ s^{-1}$)
4	0.0214	60.95	3.5×10^{-4}
5	0.1221	81.1	1.5×10^{-3}
6	0.0599	27.6	2.2×10^{-3}
1, **PSI-6130**	0.016	81.2	1.9×10^{-4}

Supplementary data

Spectral data for all new 3',4'-oxetane nucleosides are provided. Details on NS5B RNA polymerase assays are given. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.025.

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