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Syntheses of nucleosides with 2′-spirolactam and 2′-spiropyrrolidine moieties as potential inhibitors of hepatitis C virus NS5B polymerase

Qun Dang [a,*], Zhibo Zhang [b], Bingyu Tang [b], Yang Song [b], Ling Wu [b], Tongqian Chen [b], Stephane Bogen [a], Vinay Girijavallabhan [a], David B. Olsen [c], Peter T. Meinke [a]

[a] Discovery Chemistry, Merck Research Laboratories, 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA
[b] Pharmaron Beijing Co. Ltd, 6 Tai-He Road, BDA, Beijing 100176, China
[c] Discovery Biology, Merck Research Laboratories, 770 Sumneytown Pike, West Point, PA 19486, USA

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ABSTRACT

To discover novel nucleosides as potential antiviral agents, 2′-spirolactam and 2′-spiropyrrolidine-containing nucleoside analogs were envisioned. Efficient synthetic routes were developed with an epoxide opening as the key step to establish the quaternary center at the 2′ position, leading to the design and synthesis of uridine analogs **8** and **21**, prodrugs **13**–**16**, and cytidine analog **11**.

Nucleoside analogs have a rich and vibrant history in the treatment of human viral infections with many reaching the market to produce profound impacts. For example, zidovudine (AZT) was approved in 1987 to treat HIV infections,[1] entecavir was approved in 2005 to treat hepatitis B infections,[2] and the recently approved sofosbuvir to treat hepatitis C virus (HCV) infections[3] (Fig. 1).

Discovery of novel nucleosides as HCV NS5B inhibitors proved to be extremely challenging due to the daunting synthetic challenges they pose and the observations that many seemingly minor structural modifications ablate useful biological activity.[4,5] After decades of efforts, while many nucleosides advanced into clinical trials, including MK-608,[6] NM-107,[7] PSI-6130,[8] and compound **1**[9] (Fig. 2); only sofosbuvir reached the market recently. The 2′-modifications have been the focus of most HCV nucleoside drug discovery programs since it is one area that tolerates some variations without significant loss of activity against HCV.[10,6,11–17]

One interesting 2′-modification is the introduction of a spirocyclic group, which has led to the discovery of the 2′-spirocyclopropane analog **1**, as well as the 2′-spirooxetane analog **2**[18,19] both showing anti-HCV activity. However, to date nucleosides functionalized with 2′-spirolactams and 2′-spiropyrrolidines have not been reported. It was envisioned that a 2′-spirolactam or 2′-spiropyrrolidine could mimic the 2′-hydroxy group of MK-608 while the β-face methylene could function the same way as the key β-methyl group of many known nucleoside HCV NS5B inhibitors; the 2′-spirooxetane analog (**2**) inhibited HCV replication in a cellular assay,

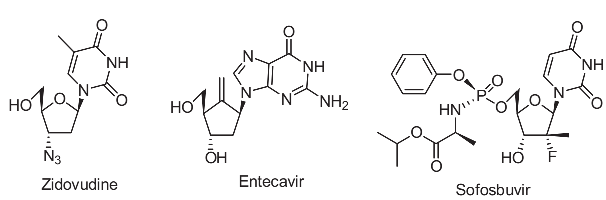

Figure 1. Nucleoside analogs as antiviral drugs.

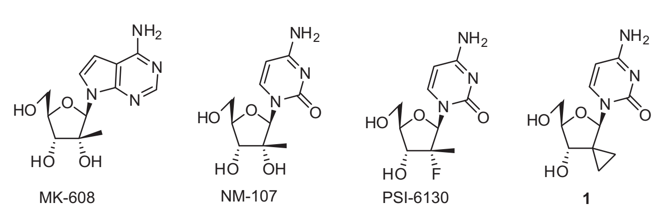

Figure 2. Clinically evaluated nucleoside HCV NS5B inhibitors.

* Corresponding author. Tel.: +1 908 740 3789.
E-mail address: qun_dang@merck.com (Q. Dang).

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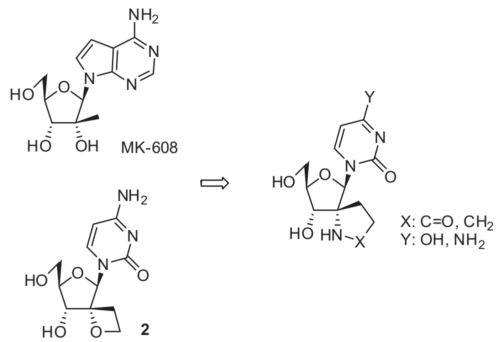


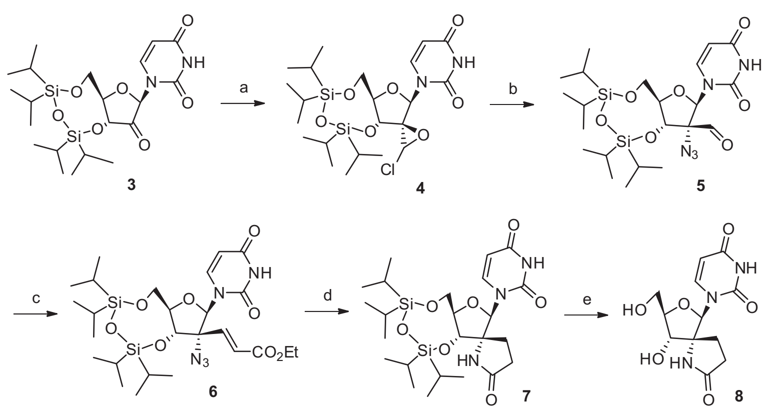
Figure 3. Novel 2′-spirocyclic amide and amine-containing nucleosides.

suggesting that some steric bulk is tolerated at the 2′-position (Fig. 3). Herein, our syntheses of these novel nucleosides are reported.

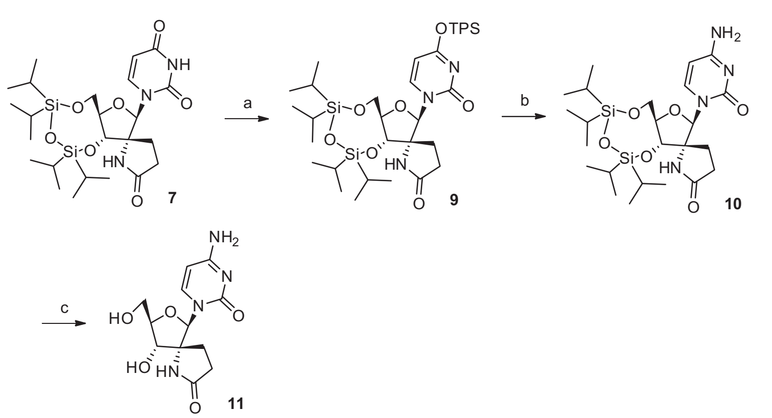
To access the 2′-spirolactam nucleoside scaffold, the Lukacs azide-epoxide opening chemistry[20] was selected as the key step of our synthesis in order to install the quaternary center at the 2′-position (Scheme 1). The synthesis started with the 3′,5′-TIPS protected 2′-ketone of uridine (**3**), which was prepared using the Jonckers' protocol.[9] Under Lukacs' conditions, addition of dichloromethyl lithium to ketone **3** gave epoxide **4** in 27% yield (structural assignment of compound **4** was carried out by an NOESY experiment, see Supplementary material section), and subsequent epoxide opening with sodium azide gave the key 2′-azido-2′-aldehyde **5** in 70% yield, establishing the key quaternary center. Wittig reaction of aldehyde **5** with $Ph_3P{=}CHCO_2Et$ gave compound **6** in 81% yield. Reduction of both the azido group and the olefin under hydrogenation conditions and subsequent cyclization gave lactam **7** in 70% yield, over the two steps. Removal of the TIPS protecting group produced the desired uridine analog **8** with a 2′-spirocyclic lactam in 66% yield.

Conversion of uridine analog **8** to its corresponding cytidine analog was achieved using the Sekine procedure[21] (Scheme 2). Treatment of lactam **8** with 2,4,6-tris(isopropyl)benzenesulfonyl chloride (TPSCl) in the presence of DMAP and triethylamine led to regio-selective *O*-sulfonate formation at the 4-position of uridine, producing compound **9** in 67% yield. Aminolysis of compound **9** using an ammonia-saturated anhydrous THF solution gave cytidine analog **10** in 90% yield, and a final removal of the TIPS protecting group using TBAF gave the desired cytidine 2′-spirolactam **11** in 61% yield.

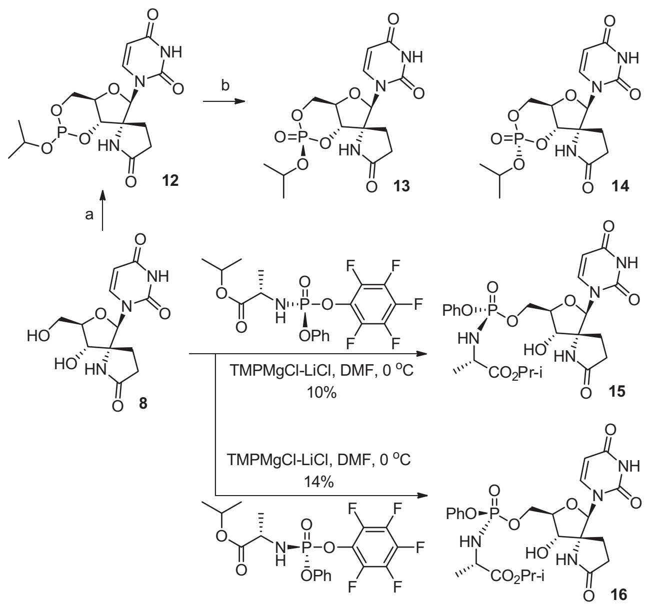
Nucleoside prodrugs are frequently utilized to improve efficacy in the HCV replicon cellular assay, therefore it is important to demonstrate that these 2′-spirolactam and 2′-spiropyrrolidine analogs are amenable to common prodrug chemistry as well. Thus, the classical McGuigan[22] and the 3′,5′-cyclic phosphate[23] prodrugs of the uridine lactam **8** were prepared as illustrated in Scheme 3. Treatment of lactam **8** with $(i\mathrm{Pr}_2\mathrm{N})_2(i\mathrm{PrO})\mathrm{P}$ in the presence of 4,5-dicyanoimidazole gave the cyclic phosphite **12** and subsequent



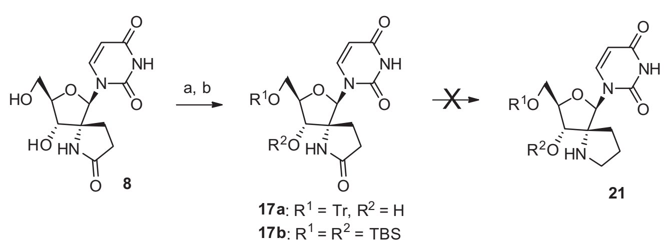
Scheme 1. Synthesis of compound **8**. Reagents and conditions: (a) dichloromethane (4.0 equiv), LDA (3.5 equiv), THF, −70 °C to 25 °C, 12 h, 27%; (b) 15-crown-5 ether (0.5 equiv), NaN_3 (5 equiv), DMF, 30 °C, 2 h, 70%; (c) $Ph_3P{=}CHCO_2Et$ (1.3 equiv), CH_2Cl_2, 35 °C, 2 h, 81%; (d) i. Pd—C (10%), H_2, EtOAc, 25 °C, 3 h; ii. HOAc–EtOAc (1:15, v/v), 25 °C, 2 h, 70%; (e) TREAT-HF (3.0 equiv), TEA (1.75 equiv), THF, 25 °C, 3 h, 66%.



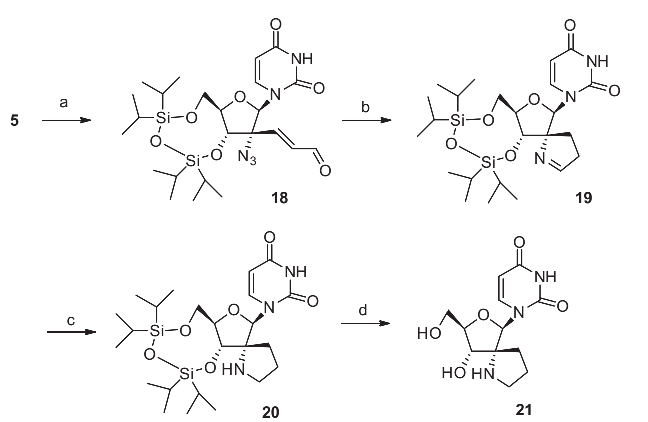
Scheme 2. Synthesis of compound **11**. Reagents and conditions: (a) TPSCl (3.0 equiv), DMAP (0.2 equiv), TEA (4.0 equiv), DCM, 15 °C, 1 h, 67%; (b) NH_3 (saturated), THF, 15 °C, 12 h, 90%; (c) TBAF (2.0 equiv), THF, 15 °C, 1 h, 61%.



Scheme 3. Synthesis of prodrugs **13–16**. Reagents and conditions: (a) $(iPr_2N)_2(iPrO)P$ (1.3 equiv), 1H-imidazole-4,5-dicarbonitrile (2.5 equiv), MeCN–NMP (2:1, v/v), 0 °C, 12 h; (b) I_2 (1.0 equiv), THF–pyridine–water (39:10:1), 0 °C, 1 h, **13**, 8%; **14**, 19%.



Scheme 4. Attempted preparation of compound **21**. Reagents and conditions: (a) TrCl (1.43 equiv), pyridine, 25 °C, quantitative; (b) TBSCl (2.1 equiv), imidazole (3.0 equiv), DMF, 25 °C, 90%.



Scheme 5. Preparation of compounds **21**. Reagents and conditions: (a) $Ph_3P{=}CHCHO$ (1.0 equiv), DCM, 25 °C, 6 h, 76%; (b) Pd—C (10%), H_2, EtOAc, 25 °C, 3 h; (c) $NaBH(OAc)_3$ (2.0 equiv), 1,2-dichloroethane, 25 °C, 12 h, 34% over the two-steps; (d) TBAF (1.5 equiv), THF, 0 °C, then 25 °C, 1.5 h, 65%.

iodine oxidation gave the desired 3′,5′-cyclicphosphate prodrugs as a pair of isomers (**13** and **14**, in 8% and 19% yields, respectively). The stereochemistry assignment for compounds **13** and **14** was carried out based on Reddy's work by comparing chemical shifts of ^{31}P NMR.[15] Alternatively, stereo-controlled synthesis of McGuigan prodrugs **15** and **16** was carried out using the method developed by Ross et al.[24] Treatment of lactam **8** with the two chiral phosphoramidites of phenol, pentafluorophenol and L-alanine isopropyl ester in the presence of tetramethylpiperidinyl magnesium chloride-lithium chloride (TMPMgCl–LiCl)[25] gave the McGuigan prodrugs **15** and **16**, in 10% and 14% yields, respectively.

The preparation of the 2′-spirocyclic amine analog (**21**) proved to be much more challenging. Direct reduction of the lactam **8** under various conditions (e.g. $LiAlH_4$ 2.0 equiv, THF, 25 °C or 40–75 °C; no reaction occurred) failed to produce requisite compound **21**, thus several protecting groups were introduced to enhance the possibility of success. However, as evident from Scheme 4, protecting the 5′-hydroxy with a trityl group or protecting the 3′ and 5′-hydroxy groups as TBS ethers did not enable the successful reduction of the lactam (e.g. $LiAlH_4$, THF, 0 °C to reflux: no reaction or messy; BH_3SMe_2, THF, 0 °C to reflux, 6 h: no reaction). Therefore, a new synthetic route was designed to accomplish the synthesis of the 2′-spirocyclic amine analog **21**.

Wittig reaction of aldehyde **5** with $Ph_3P{=}CHCHO$ gave the desired compound **18** in 76% yield (Scheme 5). Reduction of the 2′-azide group under hydrogenation conditions gave the 2′-spirocyclic imine **19**, which was subjected to sodium triacetoxyborohydride reduction to give the TIPS-protected 2′-spirocyclic amine **20**, 34% yield over the two steps. Final TIPS removal using TBAF gave the desired 2′-spirocyclic amine **21** in 65% yield.

In summary, 2′-spirolactam- and spiropyrrolidine-containing nucleosides were designed as potential inhibitors of HCV NS5B. New synthetic routes have been developed to access these novel nucleoside analogs and their prodrugs. The 2′-spirolactam scaffold was demonstrated on the uridine and cytidine nucleoside series, while the 2′-spiropyrrolidine scaffold was exemplified on the uridine series. Testing of these novel nucleosides against HCV should provide important SAR information to help us to expand the understanding of the field; results will be reported in due course.

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.051.

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