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Preparation of 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives and their activity against DOT1L

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ABSTRACT

From a readily available 5-*C*-Me ribofuranoside, we have realized a reliable route to valuable 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives at gram scale with confirmed stereochemistry. These adenosine derivatives are useful starting materials for the preparation of 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives with higher complexity. From one of the new adenosine derivatives, some 5′-deoxy-5′-amino-5′-*C*-methyl adenosine DOT1L inhibitors were prepared in several steps. Data from DOT1L assay indicated that additional 5′-*C*-Me group improved the enzyme inhibitory activity.

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5′-Deoxy-5′-amino adenosine derivatives have been widely studied in terms of their preparation and biological activities.[1] In contrast, to our best knowledge, there was only one case[2] that 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives have been reported. And only another case[3] dealt with more complex 5′-*C*-substitution on 5′-deoxy-5′-amino adenosine. Although 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives could be potentially useful for medicinal chemistry research, extensive study using these molecules was still not likely because of the availability issue. According to very limited cases for the synthesis of 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives, nucleophilic addition to 5′-deoxy-5′-oxo adenosine derivatives seemed to be the only method.[2] Nevertheless, 5′-deoxy-5′-oxo adenosine derivative were difficult to access,[2,4] and the following addition reactions were of low yield and stereoselectivity.[2]

Meanwhile, our investigation of new nucleoside DOT1L (disruptor of telomeric silencing 1-like) inhibitors also demanded 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives. DOT1L is a validated therapeutic target against mixed lineage leukemia gene rearranged (MLL-*r*) subtypes of acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL).[5] The structure-activity[6] and structure-metabolic relationships[7] of nucleoside DOT1L inhibitors have been studied: Using the structure of pinometostat (EPZ5676, Fig. 1),[5] a typical DOT1L inhibitor as an example, 1) both side chains on *N*-5′ were found important for the activity and selectivity, and have been extensively optimized; 2) the modification on the sugar moiety of adenosine scaffold was rare,[8] presumably due to synthetic difficulties; 3) the high metabolic liability of pinometostat has several reasons including 5′-*N*-deisopropylation as a major metabolic pathway across different species.[7a] Since *C*-5′ is quite close to *N*-5′, one of the important elements bringing activity, selectivity, and metabolic liability to DOT1L inhibitors, introduction of methyl substitution on *C*-5′ could be interesting: The methyl substitution will contribute to the limited repertoire of ribose-modified DOT1L inhibitors. Furthermore, intriguing methylation effect[9] remains to be explored with this modification.

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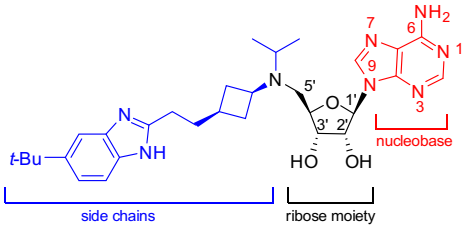


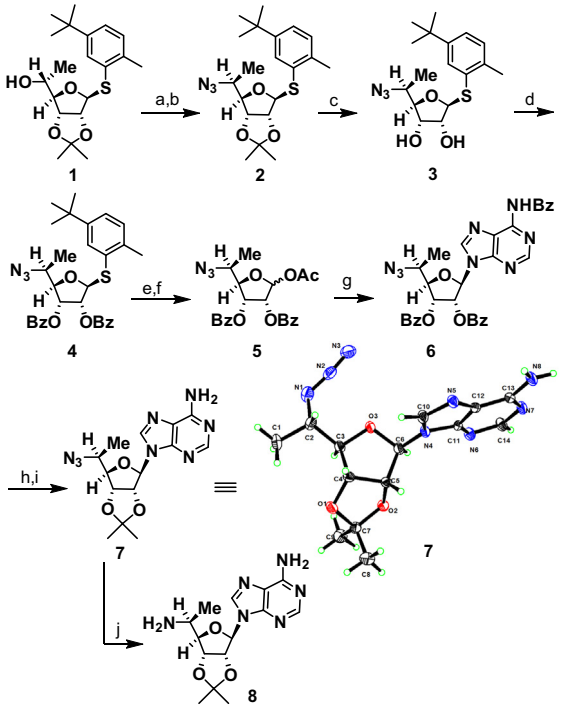
Fig. 1. Structure of pinometostat (EPZ-5676), a DOT1L inhibitor under clinical trial.

Recently, we have discovered a highly stereoselective route to 5-*C*-substituted ribose derivatives.[10] Among different possibilities to utilize these valuable products, one privilege we had was the stereoselective access of 5′-*C*-methyl nucleosides. From compound **1** as one of the products in last report, we have surmounted some significant synthetic problems and obtained a series of 5′-deoxy-5′-amino-5′-*C*-substituted adenosine derivatives. Some new compounds were then subjected to biological evaluation targeting DOT1L. The details of the work will be reported herein.

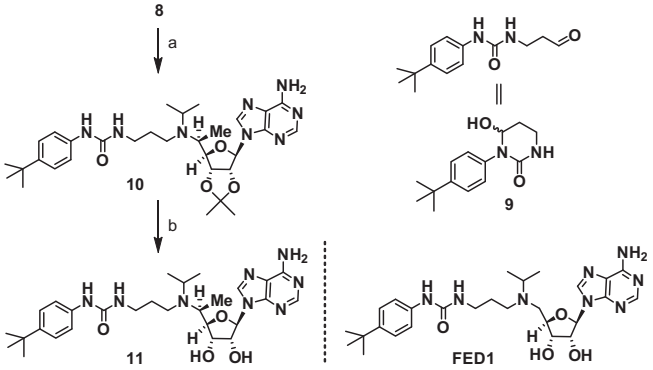
Starting from compound **1**, mesylation of 5-OH and the azide displacement of the mesylate provided oily product **2** with 69% yield (Scheme 1). The diastereomeric outcome was about 20:1 according to proton NMR. But at that time it was not clear whether this was because of highly stereoselective S_N1 reaction or due to highly stereospecific S_N2 mechanism, since the absolute stereochemistry of compound **2** could not be determined. Next, the acetonide was removed from compound **2** to give oily compound **3** with 80% yield, which was followed by benzoyl protection on 2,3-hydroxyls of compound **3** to give compound **4** as an oil with 80% yield. 1-Sulfide on compound **3** was oxidatively removed using NBS, and the resulting 1-hydroxyl was acetylated to produce oily compound **5** as an anomeric mixture with 69% yield for 2 steps. Traditional *N*-glycosylation method was applied on compound **5** with the aid of $SnCl_4$ to give 50% yield of nucleoside **6** as an oil. Both anomeric selectivity and regioselectivity of this glycosylation were perfect according to proton NMR study. The benzoyl protection on compound **6** was again switched back to acetonide to give compound **7** with 65% yield. Compound **7** was the first solid product in the whole reaction sequence described in Scheme 1. Thus, it was carefully crystallized from a mixture of chloroform and methanol. The crystal of compound **7** was subjected to X-ray analysis and the result[11] unambiguously showed that the absolute stereochemistry of 5′-*C* was *S*. Therefore the absolute stereochemistry of compounds **2**, **3**, **4**, **5**, **6**, and the following **8** could all be determined accordingly. Also, it was deduced that the formation of compound **2** followed an S_N2 mechanism with high stereospecificity. For the final step in Scheme 1, due to the steric hindrance posed by 5′-*C*-Me, the Staudinger reduction of azide on compound **7** was very slow with PPh_3. Therefore, PMe_3 was used instead to give 90% yield of 5′-deoxy-5′-NH_2 derivative **8** as a white solid.

Prepared at gram scale, compounds **6**, **7**, and **8** are useful synthetic intermediates for 5′-deoxy-5′-amino-5′-*C*-methyl adenosine derivatives of higher complexity. In our case, we used intermediate **8** to prepare some new 5′-deoxy-5′-amino-5′-*C*-methyl nucleoside DOT1L inhibitors.

From the key intermediate **8**, consecutive reductive amination, first with acetone and then with aldehyde **9** (a side chain used for known DOT1L inhibitors FED1[6c] and EPZ004777[5a]), furnished compound **10** (Scheme 2) with 63% yield. The temperature for the reaction with aldehyde **9** should not exceed 60 °C to prevent the decomposition of **9**. The acetonide protection was then removed from compound **10** with trifluoroacetic acid to yield a target molecule **11** with 92% yield. Compound **11** can be regarded as the 5′-*C*-Me analogue of a known DOT1L inhibitor FED1, which could be prepared with our new method.[12]



Scheme 1. Preparation of key 5′-deoxy-5′-amino-5′-*C*-Me adenosine derivative **8**. Reaction conditions: a) MsCl, pyridine, DCM, rt, 2 h; b) NaN_3, DMF, 80 °C, overnight, 69% for 2 steps; c) *p*-TSA, MeOH, 45 °C, overnight, 80%; d) BzCl, pyridine, rt, 12 h, 80%; e) NBS, acetone/H_2O = 9:1, −40 °C, 4 h; f) Ac_2O, pyridine, rt, overnight, 69% for 2 steps; g) *N*,*O*-bis(trimethylsilyl)acetamide, *N*-6-benzoyladenine, $SnCl_4$, anhydrous MeCN, rt −80 °C, 8 h, 50%; h) MeONa, MeOH, rt, 2 h; i) 2, 2-dimethoxypropane, *p*-TSA, acetone, rt, overnight, 65% for 2 steps; j) $P(CH_3)_3$, 1 M aq. NaOH, THF, rt, 6 h, 90%.



Scheme 2. Preparation of DOT1L inhibitor **11** bearing the side chain of FED1 as a known DOT1L inhibitor. Reaction conditions: a) acetone, AcOH, MeOH, rt, 20 min; then sodium triacetoxyborohydride (STAB), rt, 3 h; then MeCN, **9**, AcOH, rt, 10 min; then STAB, 50 °C, 48 h, 63 %; b) TFA/H_2O = 9:1, rt, 2 h, 92%.

Due to the steric hindrance of 5′-*C*-Me, similar consecutive reductive amination of intermediate **8** with acetone and ketone **12**[13] (a side chain used for pinometostat) could not proceed after isopropyl group being installed at 5′-NH_2. Therefore, intermediate **8** was directly treated with ketone **12** for prolonged reaction time. The desired product **13** was isolated with 36% yield after preparative HPLC. Interestingly, compound **14** bearing two side chains was also separated and characterized[14] with 42% yield after preparative HPLC. Compounds **13** and **14** were subjected to deprotection and gave 88% yield of product **15** and 90% yield of product **16**, respectively. During the reductive amination step, *cis*- and *trans*-isomers will be formed around the cyclobutane rings of compounds **13** and

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