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Synthesis and evaluation of 2′-substituted cyclobutyl nucleosides and nucleotides as potential anti-HIV agents

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Abstract—A series of 2′-substituted cyclobutyl nucleoside analogs were efficiently prepared by constructing the core cyclobutyl ring using different [2+2] cycloaddition approaches. The triphosphate derivative of a cyclobutyl nucleoside was also synthesized and evaluated against wild-type and mutant HIV reverse transcriptases (RT). Whereas the nucleoside analogs were inactive against HIV-1 in culture, the nucleotide showed good activity not only against wild-type and recombinant HIV RT (IC_{50} = 4.7, 6.9 μM), but also against the M184I and M184V mutants (IC_{50} = 6.1, 6.9 μM) in cell-free assays.
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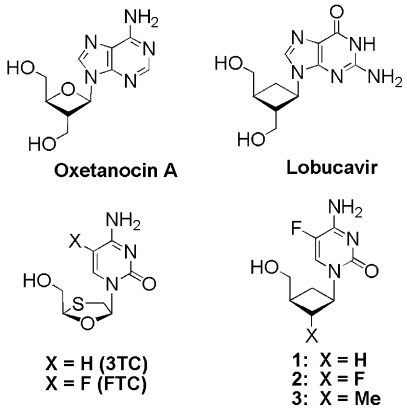
Acquired immune deficiency syndrome (AIDS) has rapidly become one of the major causes of death in the world. It is estimated that over 40 million people have developed human immunodeficiency virus (HIV) infections, which is the causative agent of AIDS.[1] In 1985, 3′-azido-3′-deoxythymidine (AZT) was approved as the first synthetic nucleoside to inhibit the replication of HIV. Since then, a number of other synthetic nucleoside analogs have been proven to be effective against HIV. After cellular phosphorylation to the triphosphate form by cellular kinases, the nucleotides are incorporated into a growing strand of viral DNA and cause chain termination due to the absence of the 3′-hydroxyl group.

Despite the enormous success of nucleoside based therapy of HIV infection, there is still no cure for AIDS. One reason is that the prolonged clinical use of nucleoside analogs gives rise to resistant viruses that contain mutations in the RT.[2] For example, the M184V/I mutation in HIV-1 RT is associated with high level resistance to lamivudine (3TC) and emtricitabine (FTC). Structural studies suggest that the mechanism of resistance of HIV-1 RT carrying the M184V/I mutation involves steric hindrance, which would prevent further incorporation of nucleoside analogs such as 3TC and FTC in the nucleotide forms.[3]



We postulated that the more rigid and smaller cyclobutyl ring would enable the nucleoside analog to fit into the more sterically hindered active site of RT containing the M184V/I mutants. Nucleoside analogs of this type received a great deal of attention several years ago with the discovery of naturally occurring Oxetanocin A, which shows activity against HIV and Lobucavir (Cyclobut-G) with activity against HBV. However, virtually all of the reported derivatives possess the

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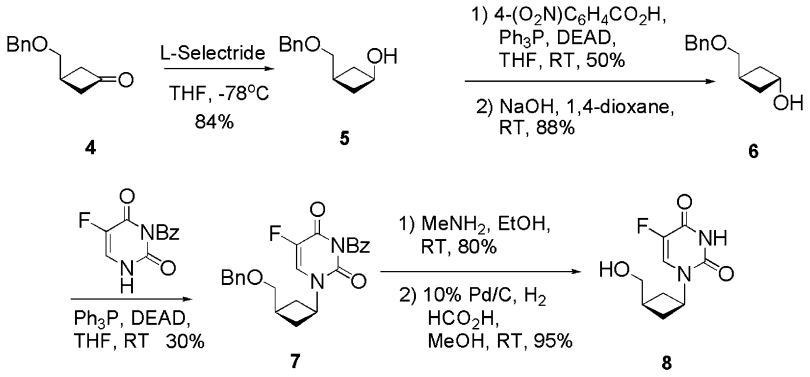
2′3′-bis-hydroxyl motif that enables them to be phosphorylated and incorporated into growing strands of DNA. We were interested in preparing a series of 2′-substituted cyclobutyl nucleosides that only have the 3′-hydroxymethyl for phosphorylation, but not the 2′-hydroxymethyl motif. We reasoned that these nucleoside analogs could fit into the more sterically hindered active site of M184I/V mutant forms of RT.

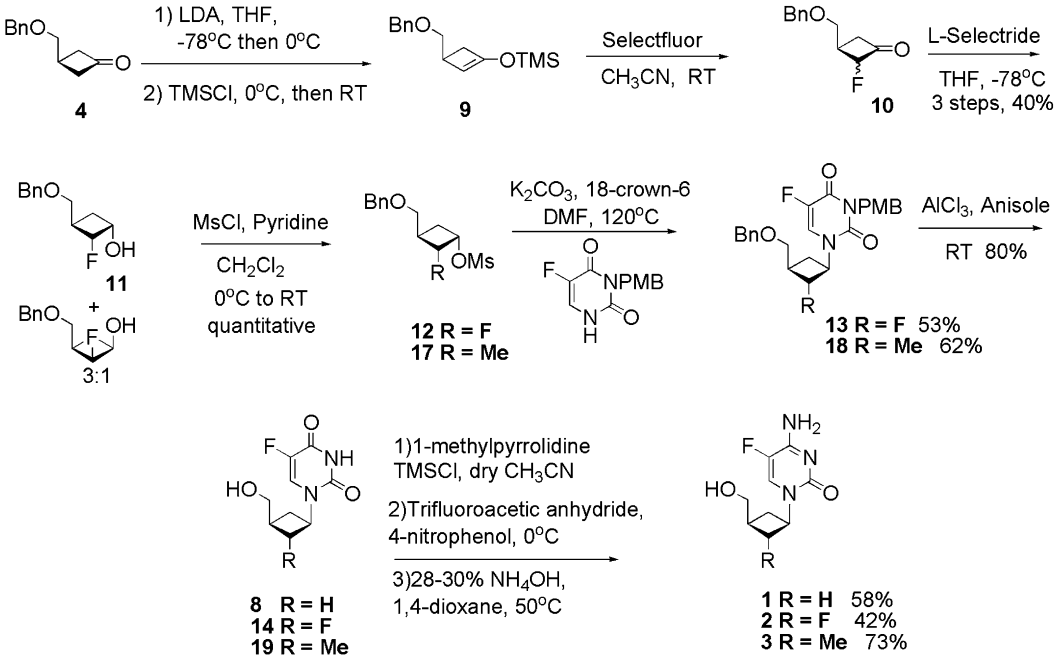
In this paper, we report the synthesis and biological evaluation of 2′-substituted cyclobutyl nucleosides as potential anti-HIV agents. To elucidate the mechanism of action of these novel cyclobutyl nucleosides, a triphosphate derivative **21** was also synthesized and evaluated against wild-type and mutant HIV-1 RT.

The 5-fluoro-1-[*cis*-3-(hydroxymethyl)-cyclobutyl]-cytosine **1** was synthesized using a reported procedure.[4] As shown in Scheme 1, reduction of the cyclobutanone **4** with L-Selectride in THF solution gave *cis*-compound **5**, which was converted to *trans*-(3-benzyloxymethyl)cyclobutanol **6** via Mitsunobu reaction followed by hydrolysis of the resulting ester. Cyclobutanol **6** reacted with N^3-benzoyl-5-fluorouracil under Mitsunobu conditions to give nucleoside **7** which was deprotected to give 5-fluorouracil nucleoside **8** in moderate yield. Finally, compound **8** was converted to the corresponding 5-fluorocytosine derivative **1** by the procedure shown in Scheme 2.

Fluorine as a substituent is isosteric with hydrogen; therefore, it should not affect the spatial disposition of atoms in the molecule. On the other hand, the physico-chemical properties of a fluorine atom can, due to its high electron negativity, profoundly affect the electrostatic properties of the bonds around it, thereby influencing both the conformation of the four-membered ring and the innate strength of the bonds.



Scheme 1. Synthesis of 5-fluoro-1-[*cis*-3-(hydroxymethyl)-cyclobutyl]-uracil.



Scheme 2. Synthesis of 2′-substituted cyclobutyl 5-fluorocytidine analogs.