SFU SIMON FRASER UNIVERSITY

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Intermediates and Process for Synthesizing Nucleosides and Nucleoside Analogues

A rapid and flexible synthesis of nucleosides and nucleoside analogues (NAs) has been discovered that will enable and inspire drug design.

Request an introduction

Reference: 2020-002

Header image is purely illustrative. Source: fizkes, stock.adobe.com/uk/303304617, stock.adobe.com

IP Status

Patent application submitted, Patented

Seeking

Development partner, Commercial partner

Background

Nucleoside analogues are a major class of drugs used most commonly in the treatment of cancer and viral infections. The processes for synthesis of NAs, however, are often protracted, not amenable to diversification and rely on a limited pool of chiral carbohydrate starting materials.

Tech Overview

SFU researchers have reported a new platform for NA synthesis, a straightforward process that involves a one-pot, proline-catalyzed a-fluorination-aldol reaction of heteroaryl-substituted acetaldehydes followed by reduction or organometallic addition and annulative fluoride displacement (AFD). This concise (2-3 step) process addresses several major and longstanding challenges in NA synthesis by enabling direct access to C3'/C5' protected NAs (and hence C2' modified NAs), providing flexibility in nucleobase substitution, and offering a direct route to C4' modified NAs (illustrated in Figure 1). Researchers expect this strategy will become a powerful tool that enables and inspires drug design.

Further Details

Publication

Benefits

- Unique, inexpensive, convenient and scalable synthesis of NAs that addresses several existing limitations
- Enables direct incorporation of a wide range of nucleobases and the selective functionalization of the C2' position of the furanose core (exemplified in the synthesis of a range of natural nucleosides and NAs), including *C*-linked or L-configured NAs
- Provides direct access to an array of C4'-modified NAs including LNAs
- Creates new opportunities for preparing diversity libraries that should influence the construction of diversity libraries and support future efforts in both drug discovery and development

Applications

Nucleoside analogues have been in use for over half a century for the treatment of cancer and represent the largest class of small molecule antivirals.

Patents

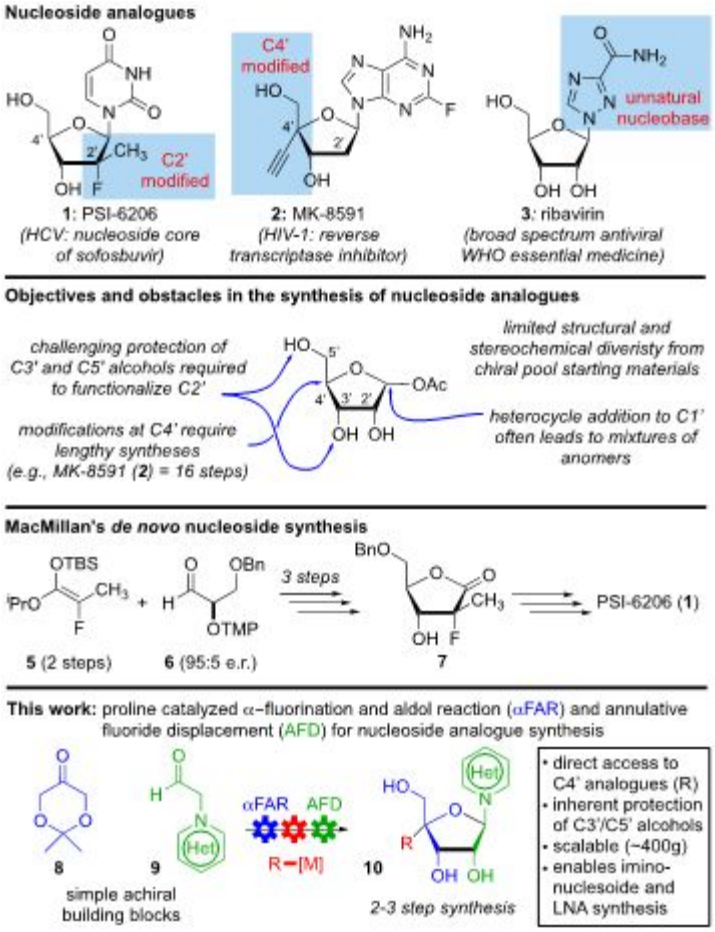
- PCT Application Filed- PCT/IB2021/052464, patented

Appendix 1

Figure 1

Nucleoside analogues: objectives and obstacles. Nucleoside analogues (NAs) play a critical role in treating viral infections and cancer. Modifications to the carbohydrate core are often key to NA activity (e.g., **1** - **3**) but present significant challenges for medicinal and process research chemists despite advances in *de novo* NA synthesis (e.g., **7**). Here, we demonstrate that NAs can be accessed through a short sequence of reactions involving an asymmetric a-fluorination aldol reaction (aFAR) followed by an unprecedented cyclization (annulation) reaction involving fluoride displacement (AFD reaction).

Meanwell et al., Science, Vol. 369 (6504), 725–730 (2020)



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