SYNTHESIS OF FLEXIBLE NUCLEOSIDES FOR THE DISCOVERY OF VIRUS CURES

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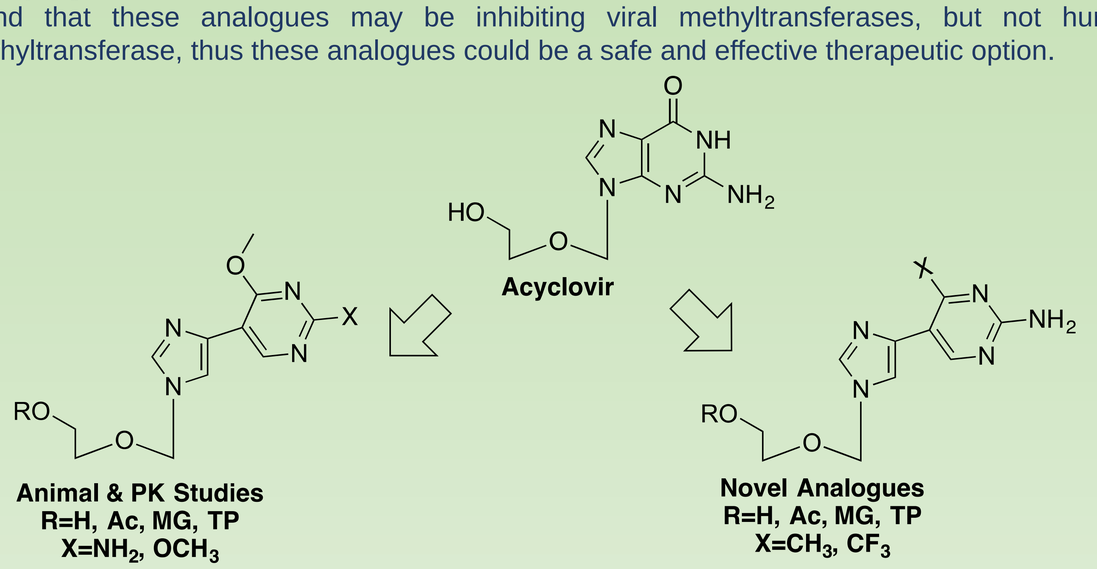
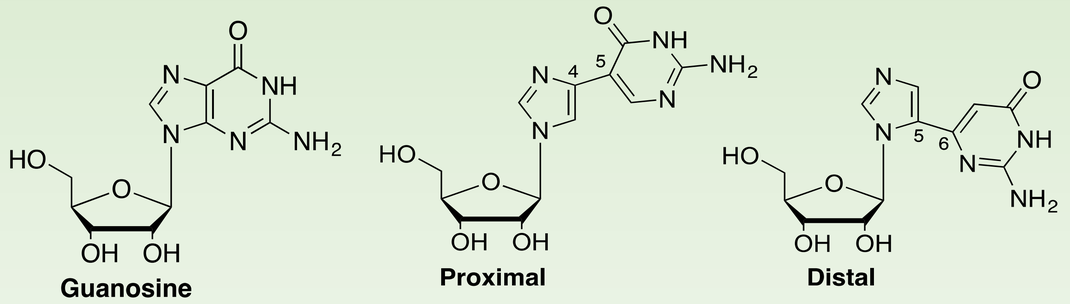
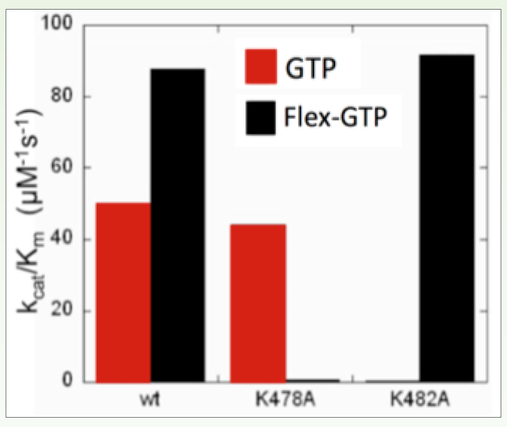
Abstract

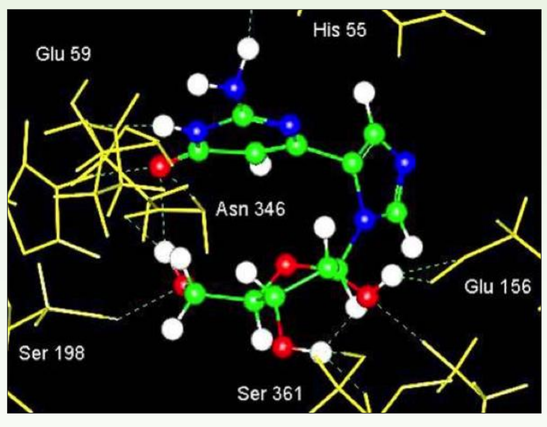
Filoviruses, coronaviruses, and flaviviruses are the cause of highly contagious, lethal diseases, leading to epidemics with the potential of re-emergence. Currently there are no FDA approved drugs for treatment of these viruses, which include the Ebola, Sudan, Dengue, and Zika viruses. One potential treatment option is nucleoside analogues, a promising therapy known to disrupt viral replication; however, mutating, drug resistant viruses rapidly outmode new medicines. To combat these viruses, the Seley-Radtke lab has pioneered the development of nucleoside fleximers - molecules capable of overcoming viral point mutations. These fleximers retain the minimal basic scaffold required for enzyme recognition – while maximizing favorable interactions with the target enzyme. Previously, this lab discovered nucleoside fleximers based on the structure of the FDA-approved analogue Acyclovir that demonstrate broad spectrum *in vitro* activity against filoviruses, coronaviruses, and flaviviruses. Mechanism of action studies have found that these analogues may be inhibiting viral methyltransferases, but not human methyltransferase, thus these analogues could be a safe and effective therapeutic option.



Fleximer Nucleoside Analogues as Antiviral Therapeutics



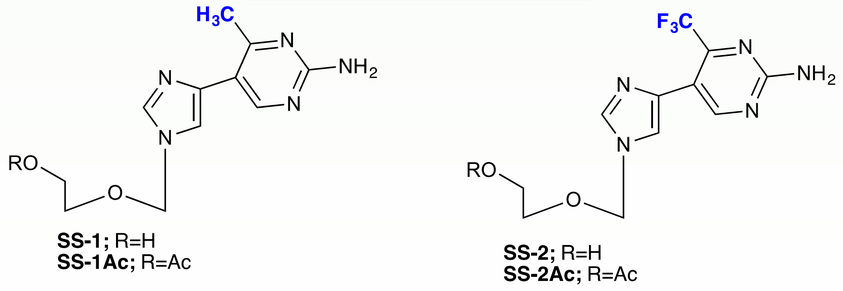




Flex GTP is a substrate in the human GTP Fucose Pyrophosphorylase enzyme interacting with different residues than the parent compound.

The guanosine-fleximer was a weak inhibitor for SAHase in modeling studies by forming adenosine-like *syn* conformation.

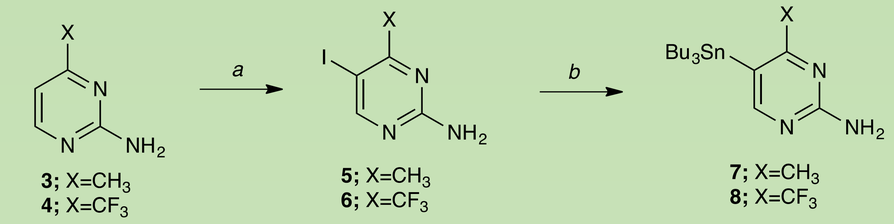
Target Compounds



SS-1; R=H
SS-1Ac; R=Ac

SS-2; R=H
SS-2Ac; R=Ac

Synthesis

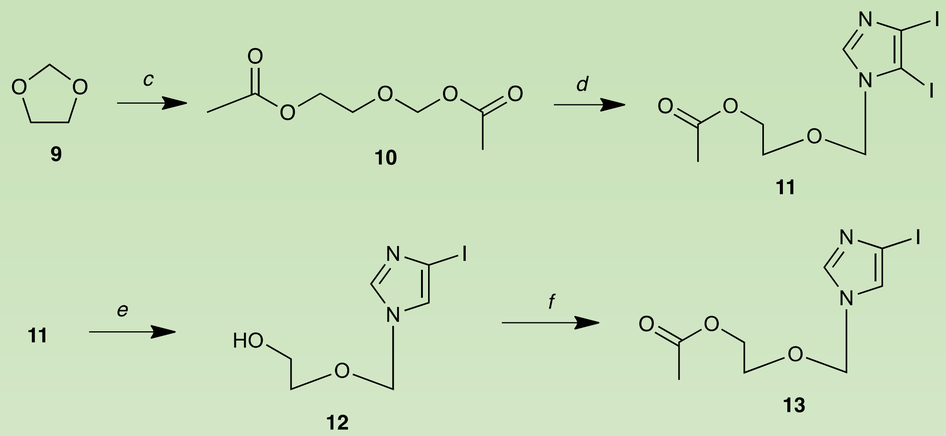


3; X=CH_3
4; X=CF_3

5; X=CH_3
6; X=CF_3

7; X=CH_3
8; X=CF_3

Scheme 1*:* Reagents and conditions: *a.* NIS, AcOH, 80°C, 2h; *b.* $(SnBu_3)_2$, $Pd_2dba_3{\cdot}CHCl_3$, 65°C, 3h.



9

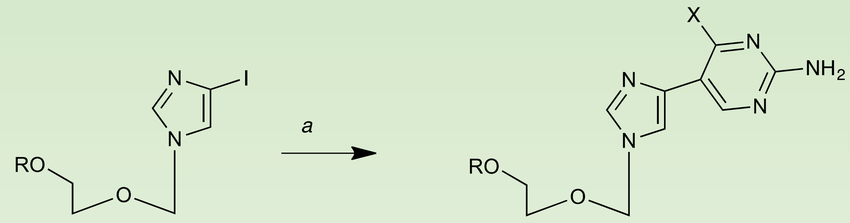
10

11

12

13

Scheme 2: Reagents and conditions: *c.* Ac_2O, H_2SO_4, -15°C to rt, 18h; *d.* diiodoimidazole, BSA, TMSOTf, ACN, rt to 80°C, 18h; *e.* Na_2SO_3, 30% EtOH/H_2O, 120°C, 18h; *f.* Ac_2O, TEA, DMAP, DCM, rt, 2h.

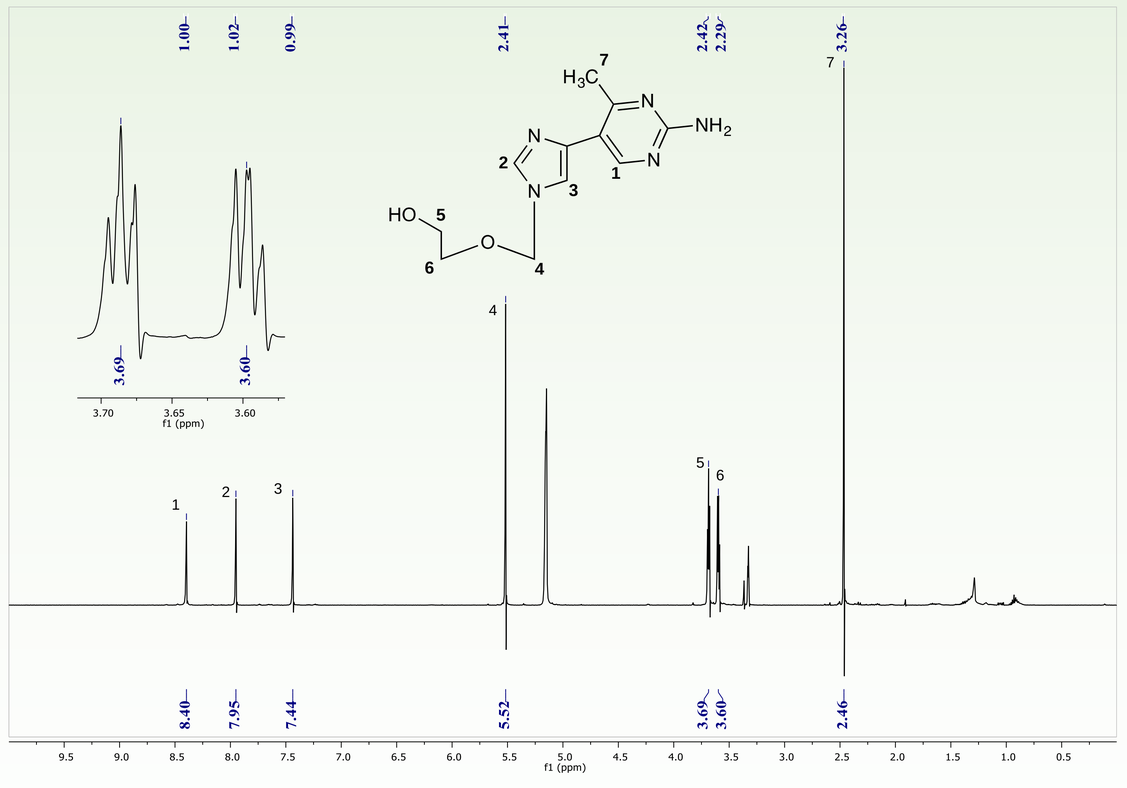


12; R=H
13; R=Ac

SS-1; R=H, X=CH_3 28%
SS-1Ac; R=Ac, X=CH_3
SS-2; R=H, X=CF_3 16%
SS-2Ac; R=Ac, X=CF_3

Scheme 3: Reagents and conditions: *a.* stannyl pyrimidine **7** or **8**, $Pd(PPh_3)_4$ CuI, CsF, DMF, 65°C.

NMR Data



References

Peters, H.L. et al. *Curr. Med. Chem.,* **2015,** *22,* 3910-3921.; Seley-Radtke, K.L. et al. *Antiviral Res.,* **2018,** *154,* 66-86.; Seley, K.L. et al. *J. Org. Chem.* **2005,** *70,* 1612-1619.; Yates, M.K. et al. *Bioorg. Med. Chem. Lett.,* **2017,** *27,* 2800-2802.; Seley, K.L. et al. *Bioorg. Med. Chem. Lett.,* **2003,** *13,* 1985-1988.; Quirk, S. et al. *Biochemistry*, **2005,** *44,* 10854-10863.

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