Novel Bioactive Nucleoside and Isonucleotide Analogs of Therapeutic Interest

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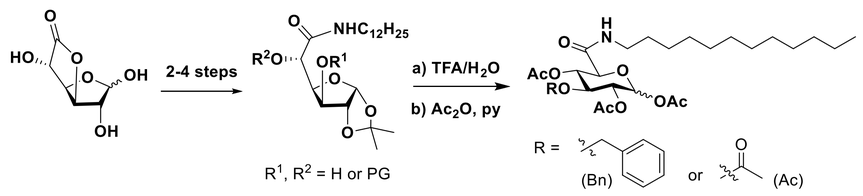
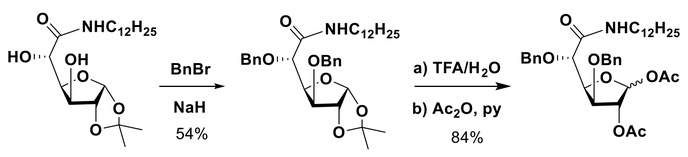
Abstract: Synthetic nucleosides, nucleotides and analogs have attracted much interest in medicinal chemistry, due to their ability to display a variety of biological activities. A number of nucleos(t)ide analogs became effective anticancer or antiviral drugs [1], while some reports showed the ability of these types of molecules to display antimicrobial effects [2] or to inhibit cholinesterases [3]. In this work, the synthesis of novel D-glucuronamide-based nucleosides and purine isonucleos(t)ides, and the evaluation of their antiproliferative or anticholinesterasic profiles, respectively, is presented. Some compounds emerged as promising lead molecules for cancer or for Alzheimer's disease.

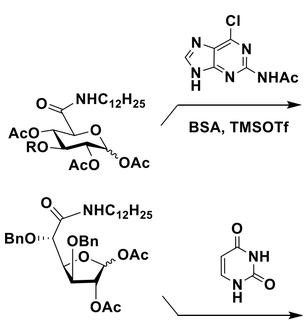
● *N-Dodecyl Glucuronamide-based Nucleosides with Anticancer Potential*

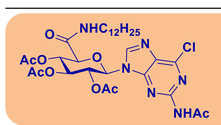
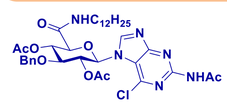
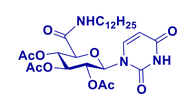
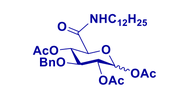


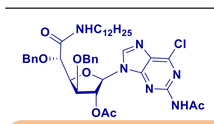
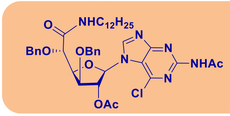
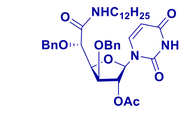
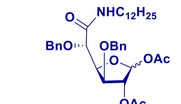


N. M. Xavier *et al.*,
Pure Appl. Chem. **2019**, *91*, 1085.
Org. Biomol. Chem. **2017**, *15*, 4667.

Antiproliferative Evaluation



Compounds	GI_{50} (μM) K562	GI_{50} (μM) MCF-7
	11.2	7.2
	30.3	15.9
	> 50	> 50
	14.8	13.3

Compounds	GI_{50} (μM) K562	GI_{50} (μM) MCF-7
	7.4	10.4
	3.3	3.3
	6.7	8.6
	23.9	17.1

K562
chronic myeloid leukemia

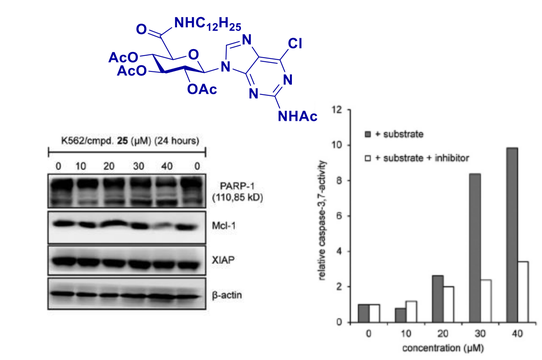
MCF-7
breast adenocarcinoma

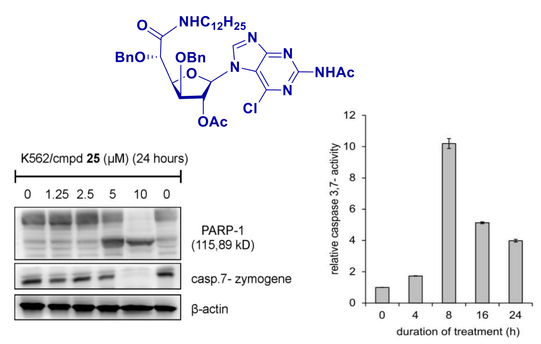
Imatinib GI_{50} (**K562**) = 0.5 μM ; GI_{50} (**MCF-7**) = 26.8

5-Fluorouracil GI_{50} (**K562**) > 100 ; GI_{50} (**MCF-7**) = 9.7 μM

Mechanism of Action

Induction of apoptosis

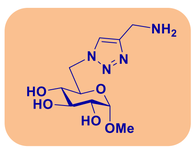




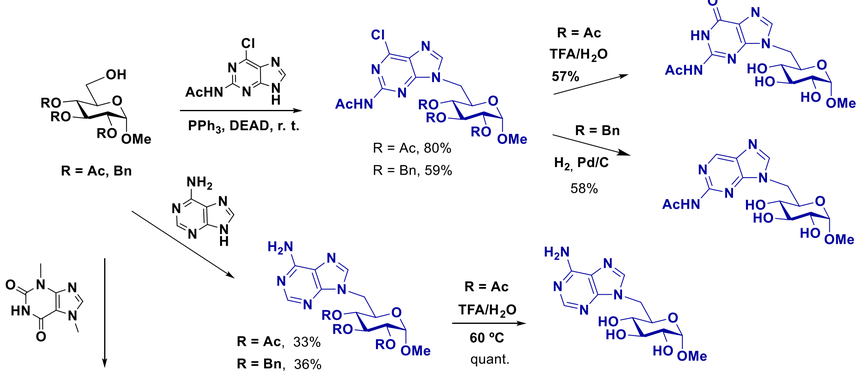
- activation of caspases
- cleavage of PARP-1
- downregulation of anti-apoptotic proteins

● *Terminal Isonucleosides as Cholinesterase (ChE) Inhibitors*

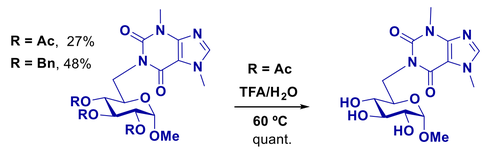
Triazole 6'-isonucleoside



AChE: K_i = 11.9 ± 1.6 μM
Nontoxic to healthy cells



Purine 6'-isonucleosides



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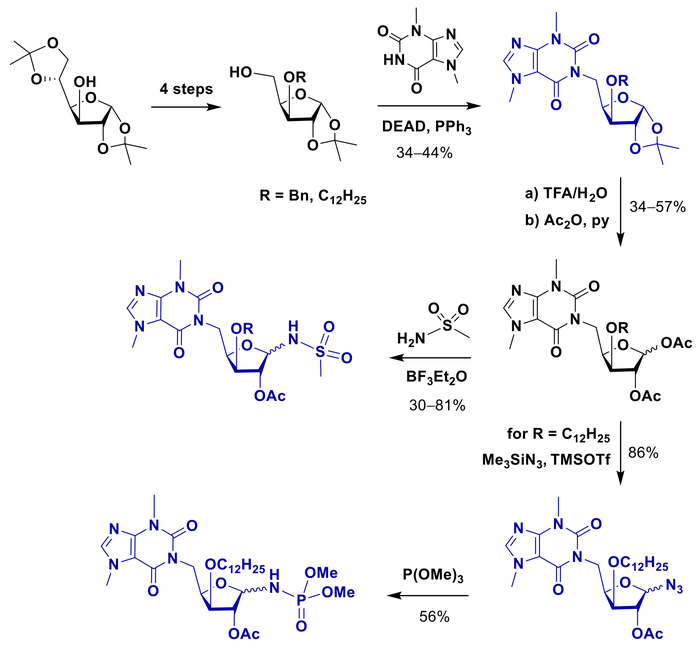
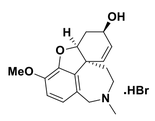
Pharmaceuticals **2019**, *12*, 103.
Eur. J. Org Chem. **2018**, *2018, 2667*.

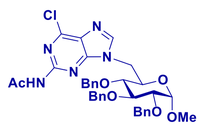
Theobromine 5'/6'-Isonucleosides



Cholinesterase Inhibitory Profiles



Galantamine.HBr
K_i (**AChE**) = 0.5 ± 0.0 μM
*K*i (**BChE**) = 9.4 ± 0.7 μM
(competitive)

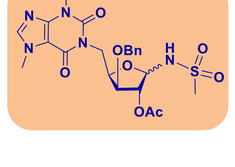


AChE:
K_i > 20
[K_i' = **7.1 ± 0.3 μM**]
(mixed-type)

AChE:
K_i = **4.3 ± 0.8 μM**
[K_i' = 66.3 ± 12.2 μM]
(mixed-type)

Cholinesterase Inhibitory Profiles

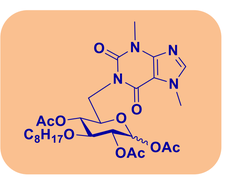
N-Isonucleosidyl Sulfonamide



AChE:K_i = **6.6 ± 0.2** μM
[K_i' > 200 μM
(mixed-type)
IC_{50} N27 = 44.22 μM
IC_{50} NHDF > 50 μM

Galantamine.HBr
K_i (**AChE**) = 0.5 ± 0.0 μM
*K*i (**BChE**) = 9.4 ± 0.7 μM

Glucopyranos-6'-yl Theobromine

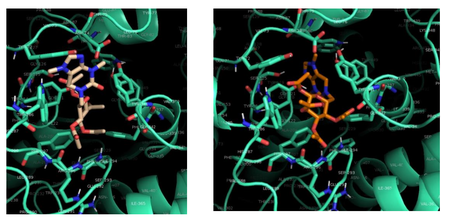


AChE: K_i = **3.1 ± 0.2** μM
[K_i' > 100 μM]
BChE: K_i = **5.4 ± 0.3** μM
[K_i' > 60 μM]
(mixed-type)

IC_{50} NIH 3T3 > 30 μM

Galantamine.HBr
K_i (**AChE**) = 0.2 ± 0.1 μM
*K*i (**BChE**) = 2.4 ± 0.0 μM

Docking into AChE



References:
[1] J. Shelton *et al.*, *Chem. Rev.* **2016**, *116*, 14379.
[2] M. Serpi *et al.*, *J. Med. Chem.* **2016**, *59*, 10343.
[3] a) C. Meier *et al.*, *J. Med. Chem.* **2004**, *47*, 2839.; b) S. Schwarz *et al., Org. Biomol. Chem.* **2014**, *12*, 2446.; c) N. M. Xavier *et al.*, *Synlett* **2015**, *26*, 2663.

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