NOVEL NUCLEOS(T)IDE ANALOGS OF POTENTIAL THERAPEUTIC INTEREST

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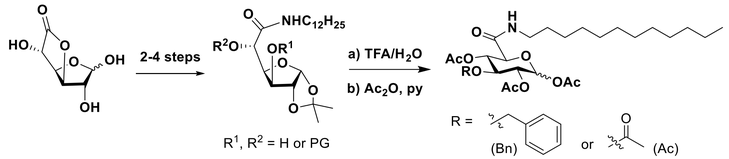
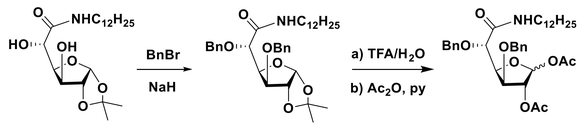
Abstract: Synthetic nucleosides, nucleotides and analogs have attracted considerable interest in medicinal chemistry, due to their ability to display a variety biological activities.
Their relevance in anticancer and in antiviral drug research is well demonstrated by the variety of compounds which are effective drugs [1].
In this communication, the synthesis and anticancer evaluation of novel nucleosides and nucleotide analogs constructed on glucuronamide or on 5'/6'-azido glycosyl units is presented.

• *N-Dodecyl Glucuronamide-based Nucleosides*





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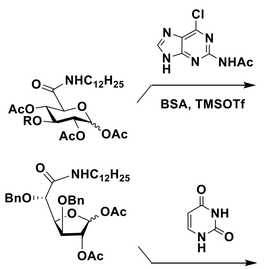
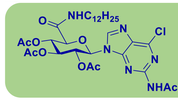
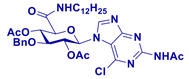
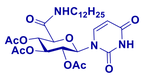
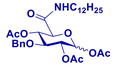
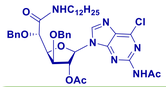
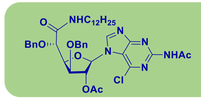
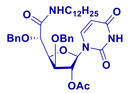
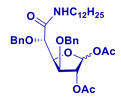
Org. Biomol. Chem. **2017**, *15*, 4667.

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

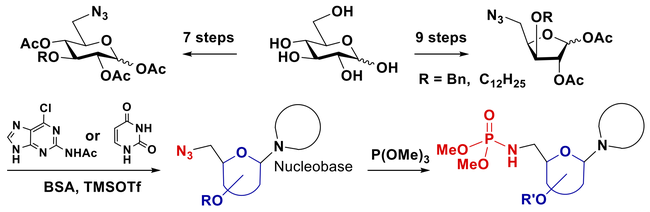
K562
chronic myeloid leukemia

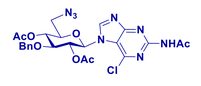
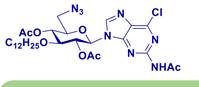
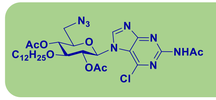
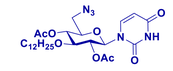
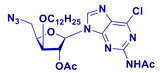
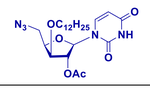
MCF-7
breast adenocarcinoma

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

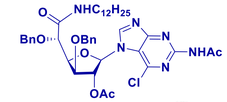
• *Azido Nucleosides and Phosphoramidates*

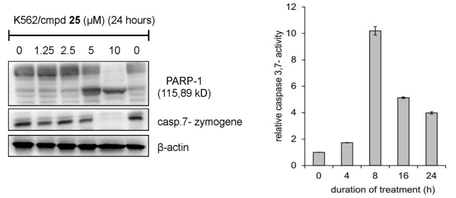


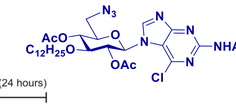
Compounds	GI_{50} (μM) K562	GI_{50} (μM) MCF-7
	8.8	12.8
	13.7	17.1
	3.2	3.2
	12.5	24.1
	10.2	18.5
	13.7	21.7

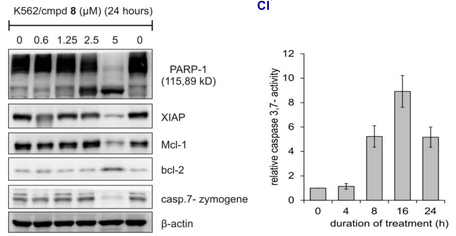
Mechanism of Action

- *Induction of apoptosis*









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

[1] L. P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nat. Rev. Drug. Discov.*, **2013**, *12*, 447-464.

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