Synthesis of novel types of nucleosides and nucleotide mimetics as potential anticancer agents

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Synthetic nucleosides, nucleotides and their analogs or mimetics constitute relevant groups of molecules in medicinal chemistry, due to their propensity to exhibit biological activities. A number of compounds of these types are in clinical use against cancer and viral infections, acting through incorporation into nucleic acids and/or by inhibition of enzymes involved in their biosynthesis. However, some drawbacks limit their use, such as low oral bioavailability and the acquisition of resistance by cancer cells or virus towards their action. The development of novel bioactive nucleoside/nucleotide-like structures that may overcome these issues and act by innovative mechanisms of action remains of interest. Within this context, in this communication the synthesis of novel azido nucleosides, their phosphoramidates and of structurally diverse N-glycosyl derivatives containing D-glucuronamide moieties will be presented. Azido furanosyl and pyranosyl nucleosides were synthesized by N-glycosylation of purine or pyrimidine derivatives with azido 1-O-acetyl glycosyl donors and were subsequently converted into nucleoside phosphoramidates as potential mimetics of nucleoside monophosphates. 1-O-Acetyl glucuronamides were prepared and employed as precursors for the access to N-glycosylsulfonamides and N-glycosylphosphoramidates, in which the sulfonamide and the phosphoramidate moieties were planned as phosphate bioisosteres. N-Substituents of different polar character were introduced at C-6. Among the motifs installed was the benzyltriazole system, leading to novel types of potential nucleotide mimetics. Glucuronamide-based nucleosides as well as related N-glycosyl triazole analogs were also accessed. The evaluation of the compounds' antiproliferative effects on cancer cells revealed some active molecules at micromolar concentration range. Studies aiming at giving insight into the mode of action of the most potent compounds were performed. The synthetic methods and the results of the biological assays will be disclosed herein.

Recent Publications

1. L P Jordheim, D Durantel, F Zoulim and C Dumontet (2013) Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. Nature Reviews. Drug Discovery 12(6):447-464.

2. N M Xavier (2017) Recent advances on nucleotide analogs and mimetics: synthesis and biological properties in Elsevier Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, DOI: 10.1016/B978-0-12-409547-2.12655-1.

3. M Serpi, V Ferrari and F Pertusati (2016) Nucleoside derived antibiotics to fight microbial drug resistance: new utilities for an established class of drugs? Journal of Medicinal Chemistry 59(23):10343–10382.

4. N M Xavier, R Gonçalves-Pereira, R Jorda, E Řezníčková, V Kryštof and M C Oliveira (2017) Synthesis and antiproliferative evaluation of novel azido nucleosides and their phosphoramidate derivatives. Pure Appl. Chem. 89(9):1267–1281.

5. N M Xavier, A Porcheron, D Batista, R Jorda, E Řezníčková, V Kryštof and M C Oliveira (2017) Exploitation of new structurally diverse d-glucuronamide-containing N-glycosyl compounds: synthesis and anticancer potential. Organic and Biomolecular Chemistry 15(21):4667-4680.

Biography

Nuno M. Xavier (b. Nov. 1982, Vila Real, Portugal) graduated in Chemistry from the University of Lisbon in 2005. He received a dual Ph.D. degree in Organic Chemistry from the University of Lisbon and from the National Institute of Applied Sciences of Lyon (INSA Lyon) in 2011, where he worked in the development of new carbohydrate-based antimicrobial agents. He was afterwards a Postdoctoral Researcher at the University of Natural Resources and Life Sciences of Vienna (BOKU), where he focused on the synthesis of new heptose derivatives of antibacterial potential. After another post-doctoral period at the Faculty of Sciences, University of Lisbon, he became in 2014, Researcher (FCT Investigator) at this Institution. His scientific interests are within Organic and Medicinal Chemistry and are devoted to the development, using efficient synthetic methodologies, of new bioactive carbohydrate-containing molecules of potential therapeutic application. He has been particularly dedicated to the design and synthesis of structurally new nucleosides and nucleotide analogues as potential anticancer agents. His research activities have been reported in ca. 30 publications and are frequently presented and discussed in international scientific symposia.

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