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Nuno Manuel Xavier

Universidade de Lisboa, Portugal

Synthesis and therapeutic potential of innovative nucleoside and nucleotide analogs

The development of nucleoside and nucleotide analogs or mimetics is a relevant approach in medicinal chemistry, aiming at accessing molecules that may interfere with biological processes in which natural nucleos(t)ides act and are over-activated in diseases such as cancer or viral infections. Among these events are nucleic acid replication, the inhibition or the blocking of which conduces to anticancer or to antiviral effects. In this context, some synthetic nucleos(t)ides have reached clinical application. Acquisition of resistance of cancer cells and some virus towards nucleos(t)ides analogs is a major limitation of their use as drugs. The ability of these types of molecules to show antimicrobial effects and to inhibit cholinesterases has also been described. Therefore, the development of novel nucleos(t)ide-based structures that may exhibit new mechanisms of action as well as the exploitation on rather less studied potential therapeutic uses for these types of compounds is highly encouraging. In this context, in this communication the synthesis and the biological evaluation of novel nucleosides constructed on 5/6-azido glycosyl units and on D-glucuronamide templates, 5'/6'-isonucleosides and nucleotide analogs comprising potential neutral and relatively stable bioisostere moieties for a phosphate system, namely phosphoramidate, sulfonamide or phosphonate groups, is presented. The synthetic strategies for their access included N-glycosylation, sugar azidation, azide-alkyne 1,3-dipolar cycloaddition, Mitsunobu coupling, Arbuzov or Staudinger-type reactions as key steps. Some molecules revealed potent antiproliferative effects in cancer cells or showed their ability to inhibit cholinesterases. Their GI50 or Ki values were similar or close to those of standard drugs, turning them promising lead molecules for cancer or for Alzheimer's disease. Preliminary assays also indicated the potential interest of some nucleosides as anti-flavivirus agents, due to their propensity to inhibit or to destabilize an essential ATP-dependent non-structural enzyme for Zika-virus replication.

Speaker Biography

Nuno M Xavier (b. Nov. 1982, Vila Real, Portugal) received a dual Ph.D. degree in Organic Chemistry from the University of Lisbon and from the National Institute of Applied Sciences of Lyon in 2011, where he devised new synthetic methodologies for novel highly functionalized monosaccharide derivatives of antimicrobial potential. He worked afterwards as Postdoctoral Researcher in the University of Natural Resources and Life Sciences of Vienna in the synthesis of new potentially antibacterial heptose-based compounds. He carried out another postdoctoral research period at the Faculty of Sciences, University of Lisbon and in 2014 he became Researcher (FCT Investigator) at this Institution. His research activities, reported in more than 30 publications and frequently presented in international conferences, are within the context of organic and medicinal chemistry and focus on the development of new bioactive carbohydrate derivatives and nucleos(t)ide analogs as inhibitors of relevant therapeutic targets or disease-associated biological events.

e: nmxavier@fc.ul.pt

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