



Laboratoire PPSM – UMR CNRS 8531

Photochimie et Photophysique Supramoléculaires et Macromoléculaires

Séminaire PPSM

Mercredi 29 novembre 2017 - 9h30

Auditorium D. Chemla - Bâtiment IDA

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Invité par : Joanne Xie

«sp² Iminosugars: opportunities for new glycotherapies»

The unmet potential of carbohydrates to engender molecular diversity and control the function of other biomolecules through conjugation or molecular recognition makes sugars essential players in cell life and clear-cut sensors of cell state alterations. A straight consequence is that any deregulation in carbohydrate metabolism generally translates into severe disease conditions, ranging from metabolic disorders such as diabetes or lysosomal storage disorders to neurodegeneration or cancer development. Sugar mimetics capable to interfere with and modulate enzymatic routes and binding events involving oligosaccharides and glycoconjugates bear thus a high therapeutic promise. Since their discovery in the 1960's, sugar-like polyhydroxylated alkaloids of the iminosugar family have largely dominated research in this field, inspiring much synthetic work and becoming essential utensils in glycobiology. Disappointingly, the efforts to apply the fundamental knowledge accumulated over the years on the biological activities of iminosugars to drug design and therapies have met little success after several clinical trials failures. The inability of iminosugars to properly mimic the acetal-type bond characteristic of glycosides, therefore missing essential structural information for enzyme or receptor recognition, and their strong hydrophilic nature often result in poor selectivity and pharmacokinetics, which seriously handicap their translation into the clinics. We found that replacing the amine-type endocyclic nitrogen of iminosugars into a pseudoamide-type nitrogen (sp²-iminosugars) significantly enhances the stability and drugability of the prototypes, further enabling tuning of their affinity towards complementary receptor/enzyme partners. Interestingly, sp²-iminosugars can be subjected to the typical transformations of monosaccharides, including glycosylation reactions; in other words, they are true carbohydrate chemical mimics from which glycoside functional mimetics with unprecedented selectivity profiles can be accessed. The concept has been applied to the development of drug candidates against several lysosomal storage disorders with strong neurological implications such as Gaucher, GM1-gangliosidosis or Fabry diseases.[1,2] Further developments include anti-inflammatory,[3] anticancer[4] and antileishmanial derivatives.[5] The biochemical mechanisms underlining their therapeutic potential will be discussed.

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