SOCIÉTÉ CHIMIQUE DE GENÈVE

# Polar lipocompatible units for property modulation in drug discovery


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Optimization of lead compounds in Drug Discovery requires structural variation not only to enhance target potency and selectivity, but also to improve pharmacologically relevant physico- and biochemical properties. Small structural modules that (i) can be easily incorporated into a lead compound, (ii) are compatible with a given target, and (iii) modulate compound properties in distinct and predictable ways are of considerable interest in these regards. Among such structural modules are the *gem*-difluoro, sulfone, and oxetane groups. They are all small units with molecular volumes equal to or less than that of a *gem*-dimethyl group, exert characteristic impacts on compound properties, such as lipophilicity, polarity, solubility, basicity, metabolic stability, and conformation, while not creating a new chiral center upon incorporation into a lead structure.

Much work has been done in the recent past to arrive at a structure-based understanding of their physicochemical property modulation, which is a prerequisite for successful compound property design. This work has relied heavily on a novel database mining tool, ComPair, which allows us to retrieve very efficiently all compound pairs that differ only in a distinct pre-specified structural modification and for which experimentally measured properties are available for comparison. This tool has enabled extensive data mining through an immense repository of experimental physico- and biochemical data.

In spite of these vast data resources, there is still a need for further specific exploratory studies to fully capture the property-modulating effects of small structural units in different structural and conformational contexts. Such studies are permanently ongoing.

3-substituted oxetane is a promising small structural unit that has only recently been introduced into Medicinal Chemistry. Its property modulating aspects have been investigated in a series of exploratory work and has already triggered many diverse applications as well as studies of related 4-membered heterocyclic modules.

This lecture will highlight our findings regarding the above mentioned small modules, discuss their impacts on compound properties in a comparative structure-based way, illustrating some striking similarities and differences.


**Conférence présentée le**

## LUNDI 13 DÉCEMBRE 2010 à 17h30

**Université de Genève – Bâtiment Sciences II**
**Auditoire A. Pictet – A100 (attention : nouvel auditoire)**
**30, quai Ernest-Ansermet, Genève**

**La conférence est publique**


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