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Lecture Abstracts

Plenary Sessions

September 7, 2018
École Polytechnique Fédérale de Lausanne (EPFL)
http://scg.ch/fallmeeting/2018

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Sandmeyer Award Lecture 2018: A new generation of agrochemicals: design, synthesis and biological evaluation of stigolactone- and strigolactam derivatives for potential crop enhancement applications in modern agriculture

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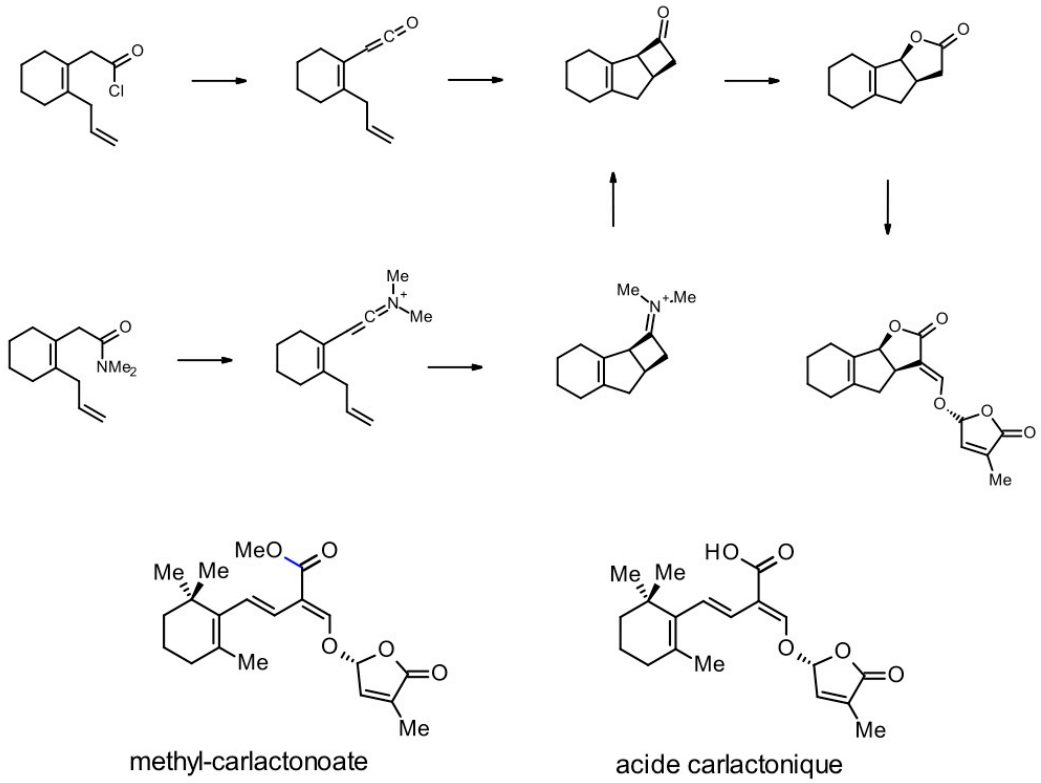
Strigolactones are the last discovered phytohormones. Among the numerous roles that strigolactones play in plant growth and development, they have been shown to control the root and shoot architecture, having significant consequences on plant adaptation to environmental conditions and abiotic stress. In addition, strigolactones signaling might influence the harvest yield of field crops.

We describe the stereoselective synthesis of natural strigolactones, as well as of their strigolactams derivatives displaying improved biological performance, using ketene-iminium salts as key intermediates. We disclose also the synthesis of non-canonical strigolactones as methyl carlactonoate and carlactonic acid. The improved properties of strigolactams compared to strigolactones derivatives will be exemplified for the induction of seed germination of corn seeds under cold stress conditions.

Scheme:



SISF-SCS Distinguished Investigator Award Lecture 2018: Synthesis and Characterisation of Some Metabolites of Anti-Leukemia Drugs

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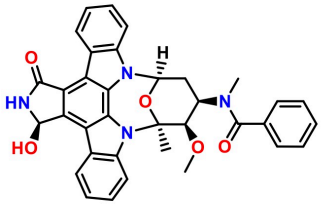
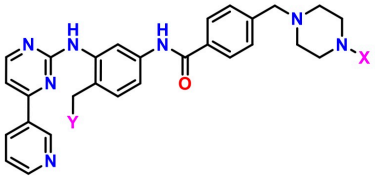
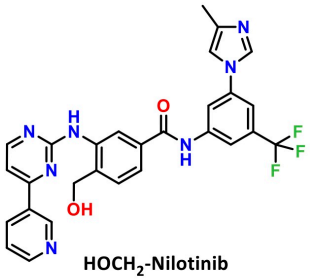
The efficacy and side-effects of drugs do not just reflect the biochemical and pharmacodynamic properties of the parent compound, but often comprise of cooperative effects between the properties of the parent and active metabolites. This can be explified in the cases of midostaurin, imatinib and nilotinib, by their circulating metabolites: 3-(*R*)-HO-midostaurin,*N*-desmethyl-imatinib, hydroxymethyl-imatinib and hydroxymethyl-nilotinib.



3-(*R*)-HO-Midostaurin



N-DesMe-Imatinib (R=H; Y=H)
$HOCH_2$-Imatinib (R=CH_3; Y=OH)



$HOCH_2$-Nilotinib

As will be presented, these metabolites have been synthesised and evaluated in assays to compare their properties as protein kinase inhibitors with the parent drugs:
3-(*R*)-HO-midostaurin shows appreciable accumulation following chronic drug administration and, in addition to inhibiting mutant forms of FLT3, it potently inhibits the PDPK1 and VEGFR2 kinases (IC_{50}values <100 nM), suggesting that it might play a role in the efficacy of midostaurin in acute myeloid leukemia patients.
N-Desmethyl-imatinib is substantially less active than imatinib as a BCR-ABL1 kinase inhibitor, thus providing an explanation as to why patients producing high levels of this metabolite show a relatively low response rate in chronic myeloid leukemia (CML) patients.
The hydroxymethyl-metabolites of imatinib and nilotinib are only weakly active as BCR-ABL1 kinase inhibitors and are unlikely to play a role in the efficacy of imatinib or nilotinib in CML.

[1] Paul W. Manley, Giorgio Caravatti, Pascal Furet, *et al*. *Blood*, **2017**:*130(suppl 1)*, Abst#1383.
[2] Paul W. Manley, Francesca Blasco, Jürgen Mestan, *et al*. *Bioorg. Med. Chem*.,**2013**, *21*, 3231-3239.

SISF-SCS Senior Industrial Science Award Lecture 2018: Episodes from the Continuous Search for Solutions against Downy Mildew Diseases

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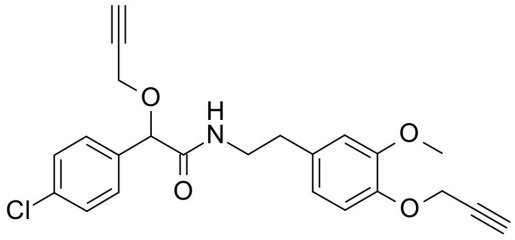
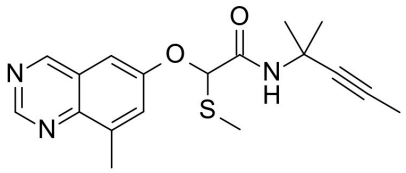
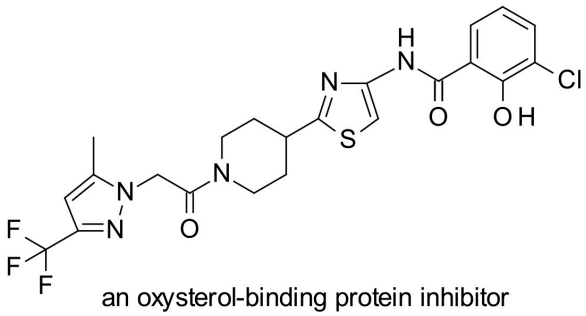
Downy mildew diseases have always been a threat to mankind; for instance, *Phytophthora infestans*, belonging to the fungi class of Oomycetes and being the causal agent of potato late blight, was responsible for the Irish potato famine in the 19thcentury. Because of resistance issues and the desire to replace older, less environmentally friendly active ingredients, there is still a huge effort across the agrochemical industry to find new solutions against these devastating plant diseases. In this regard, we have made significant contributions over the past 25 years by working on inhibitors of cellulose synthase,[1]tubulin polymerization[2]and oxysterol-binding protein.[3]Discovery, synthesis and structure-activity relationships of these novel Oomycetes-selective mode of action classes will be presented.



Mandipropamid,
a cellulose synthase inhibitor



a tubulin polymerization inhibitor



an oxysterol-binding protein inhibitor

[1] C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf, R. Zeun *Bioorg. Med. Chem*. **2008**, *16*, 1531-1545.
[2] R. Beaudegnies, L. Quaranta, F. Murphy Kessabi, C. Lamberth, G. Knauf-Beiter, T. Fraser *Bioorg. Med. Chem.***2016**, *24*, 444-452.
[3] S. Sulzer-Mosse, F. Cederbaum, C. Lamberth, G. Berthon, J. Umarye, V. Grasso, A. Schlereth, M. Blum, R. Waldmeier *Bioorg. Med. Chem.***2015**, *23*, 2129-2138.

Paracelsus Award Lecture 2018: «Mass spectrometric exploration of the biochemical basis of living systems»

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What differentiates living systems from non-living systems is one of the fundamental scientific questions. Research throughout much of the 20thcentury has established that living systems are characterized by a multitude of chemical reactions that are catalysed, controlled and coordinated by proteins and by the precise organization of molecules into functional modules, pathways and organelles. Decades of biochemical research have resulted in deep insights into the structure and function of specific molecules, but the relation of the specific functions to the living system as whole have remained elusive. More recently, genomic and other “omics” technologies have created the age of data driven science, where large scale datasets collected from suitably selected sample cohorts are used to establish statistical associations, e.g. between genomic variability and a specific (disease) phenotype. Whereas data driven approaches have provided a broad characterization of the molecular makeup of living systems, it remains challenging to convert statistical associations into mechanistic understanding.

In this presentation we will discuss the development and the application concepts and mass spectrometry based proteomic techniques that aim at providing a bridge between data driven and classical biochemical approaches. We define the term *Proteotype* as the acute state of the proteome of a living cell in terms of its composition of proteins and their organization into functional modules. We will discuss a range of mass spectrometric and computational techniques to quantify the state of hundreds of functional modules in parallel and to thus quantify the proteotype and define the biochemical state of a cell. This approach extends to the “OMICS” level the seminal insights from Pauling et al [1] and Hartwell et al [2] that suggest that cell biology is essentially modular and that a change in the abundance, subunit composition, subunit topology and structure of the functional modules determines the biochemical state and phenotype of a living system. We will discuss the current state of proteotype quantification and show with selected examples how genomic variation affects the proteotype and thus the biochemical state of a living system.

[1] L. Paulingand H.A. Itano, *Science*. 110, 543–548 (1949)
[2] L. H. Hartwell, etal *Nature*. 402, C47–52 (1999)