Poster Flash Presentations

UK QSAR (Spring) 2015

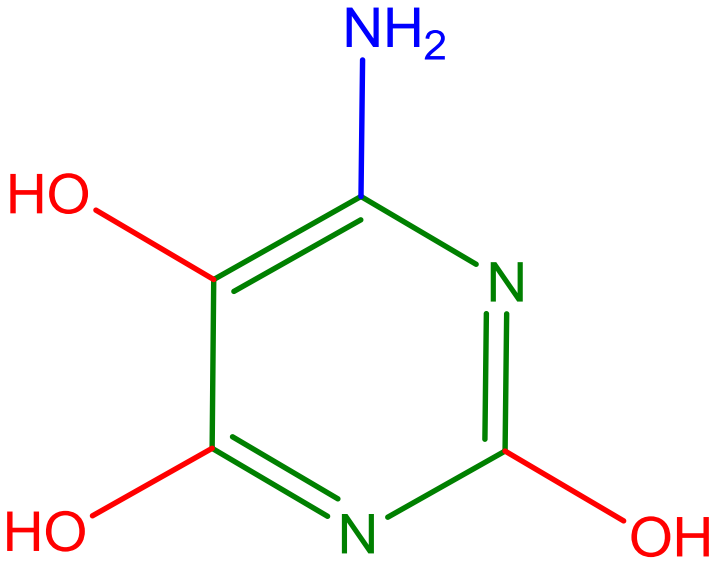
Chemistry Enabling Chinese, Japanese and Korean Patents

6-aminopyrimidine-2,4,5-triol

Chinese (Hanzi used for each morpheme)

6-氨基嘧啶-2,4,5-三醇

ammonia radical pyrimidine three alcohol



Japanese (Phonetic translation to Katakana)

6-アミノピリミジン-2,4,5-トリオール

amino pyrimidine tri ol

Korean (Phonetic translation to Hangul)

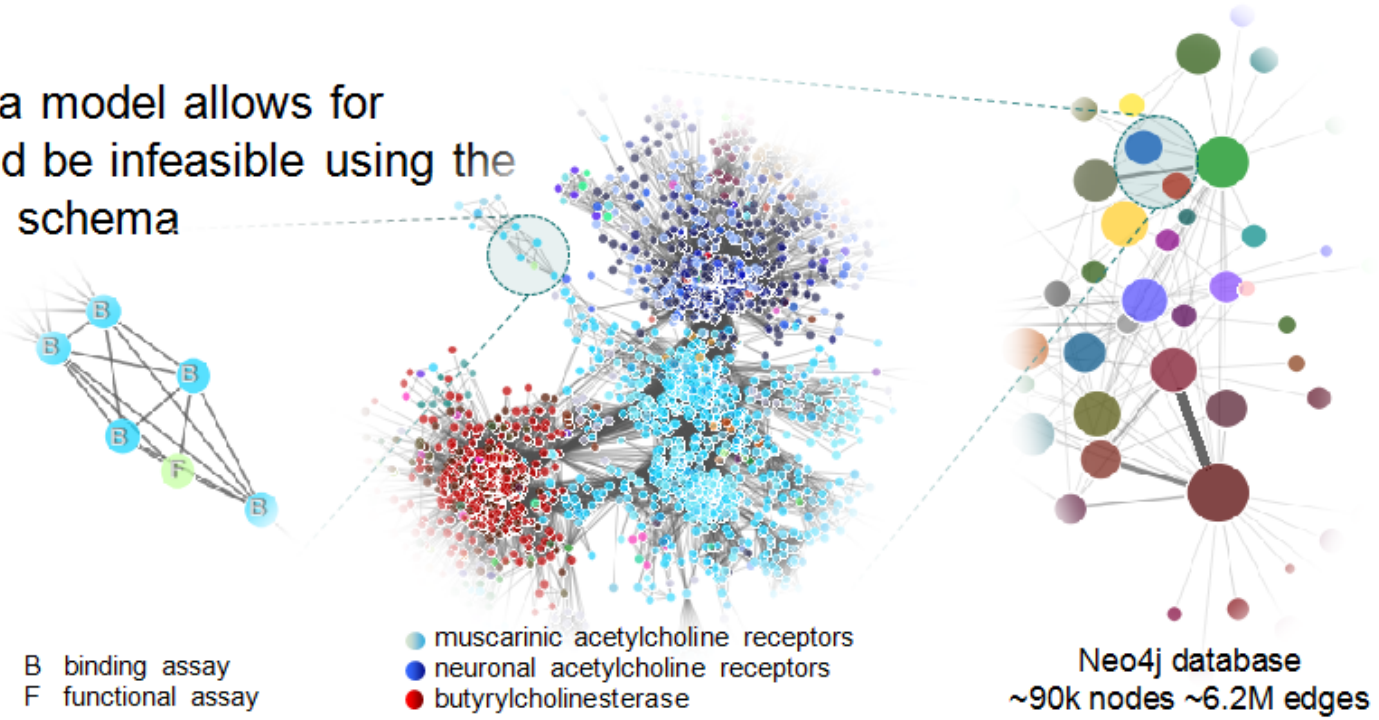
6-아미노피리미딘-2,4,5-트리올

amino pyrimidine tri ol

Graph technologies in chemogenomics

From relational to graph database

- ChEMBL is a freely available database containing literature data for a large number of bioactive compounds
- We have built a Neo4j database using the ChEMBL data
- Graph-based data model allows for queries that would be infeasible using the original relational schema



Magdalena Zwierzyna, Francis Atkinson & John P. Overington
(ChEMBL group)

EMBL-EBI

How not to develop a QSAR: an extreme example

Murcia-Soler et al., *J. Chem. Inf. Comput. Sci.* **41** (2001) 1345-1354

Anti-hyperglycæmic potency (RP) of sulphonylurea drugs

$\log RP = - 5.57(\pm 4.21)\ {}^{4}\chi_c^{v} + 1.20\ (\pm 0.79)\ {}^{3}\chi_c^{v} + 0.09(\pm 0.05)$

$- {}^{0}\chi^{v}\ 1.15(\pm 0.41)$

$n = 13 \quad R^2 = 0.799 \quad s = 0.345 \quad F = 12.0$

There are ELEVEN things wrong with that QSAR!

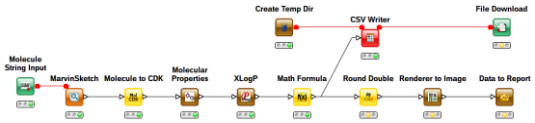
Some are obvious; some are less obvious; some are not at all obvious without detailed investigation. They are all identified on the poster.

Murcia-Soler et al. also modelled LD_{50} and plasma protein-binding of the same drugs. Those QSARs are also wrong. There was no room on the poster to mention them, but our paper based on the above is in press in *SAR & QSAR in Environmental Research.*

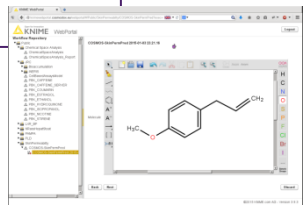
KNIME Workflows to Predict ADMET Properties to Support Chemical Safety Assessment

Series of computational models focussing on cosmetics-related substances, for which the dermal exposure route is important, implemented into KNIME workflows

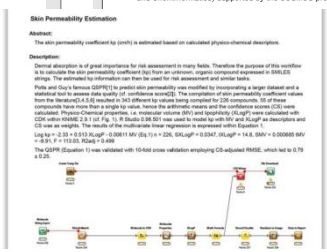
- **Biokinetics**
  (PBK models, Virtual Cell Based Assay, Human bioaccumulation factor)
- **Absorption** (skin permeability, gastrointestinal absorption)
- **Structural Alerts and Models for Toxicity** (structural alerts profilers, binding to nuclear receptors)
- **Chemical Space Analysis**

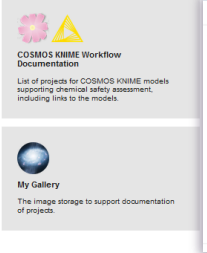


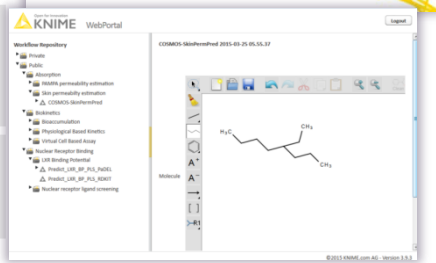
KNIME workflow



User-friendly version in KNIME WebPortal





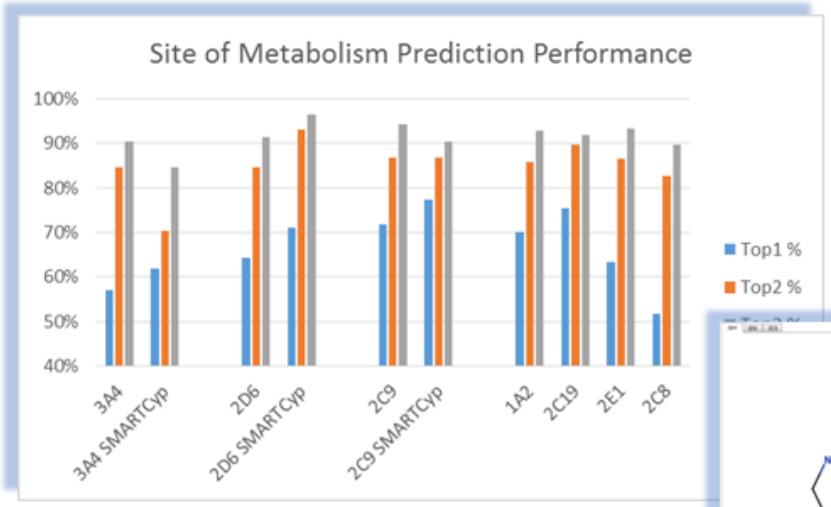


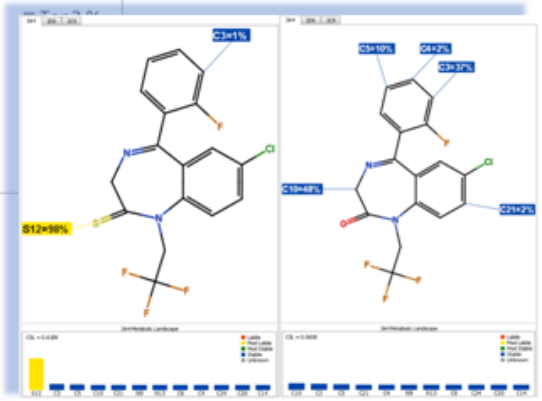
More information and links to WebPortal / COSMOS Space :

http://www.cosmostox.eu

Predicting Regioselectivity and Lability of Cytochrome P450 Metabolism using Quantum Mechanical Simulations

Jonathan Tyzack, Nicholas Foster, Peter Hunt, Matthew Segall
Optibrium Ltd, Cambridge, UK



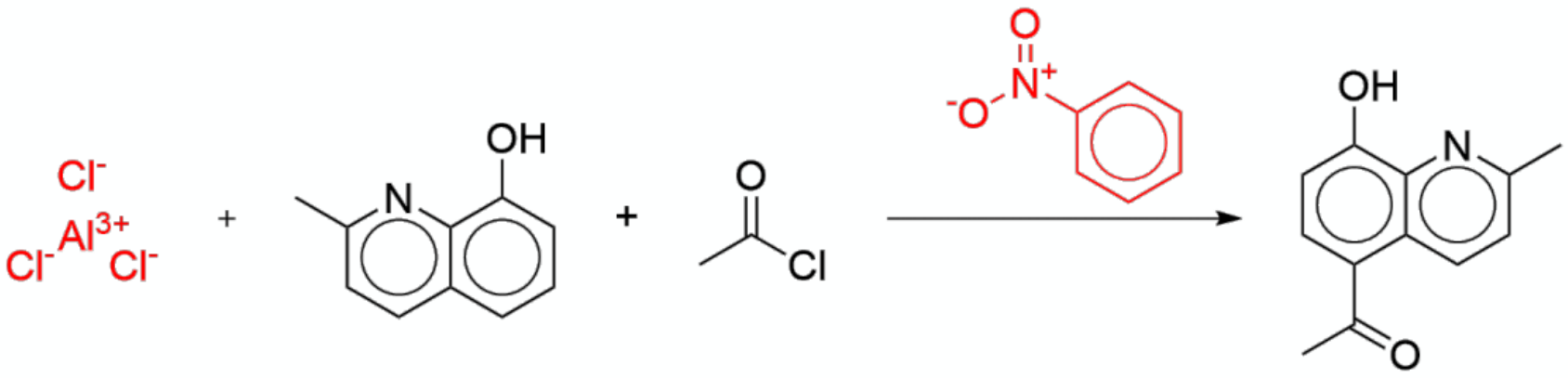


Optibrium™, as part of the European HeCaTos project, has developed metabolism models which now include the modelling of epoxidation pathways and the capability to model the xenobiotic metabolism of an additional 4 P450 isoforms: 1A2, 2C19, 2E1 and 2C8.

The predictive performance of the models on independent test sets is over 80% where a SOM is identified in the top 2 predictions.

The use of a QM approach provides a quantitative estimate of the reactivity of each SOM, to complement the regioselectivity predictions.

REACTIVE CHEMICAL HAZARD ALERTING

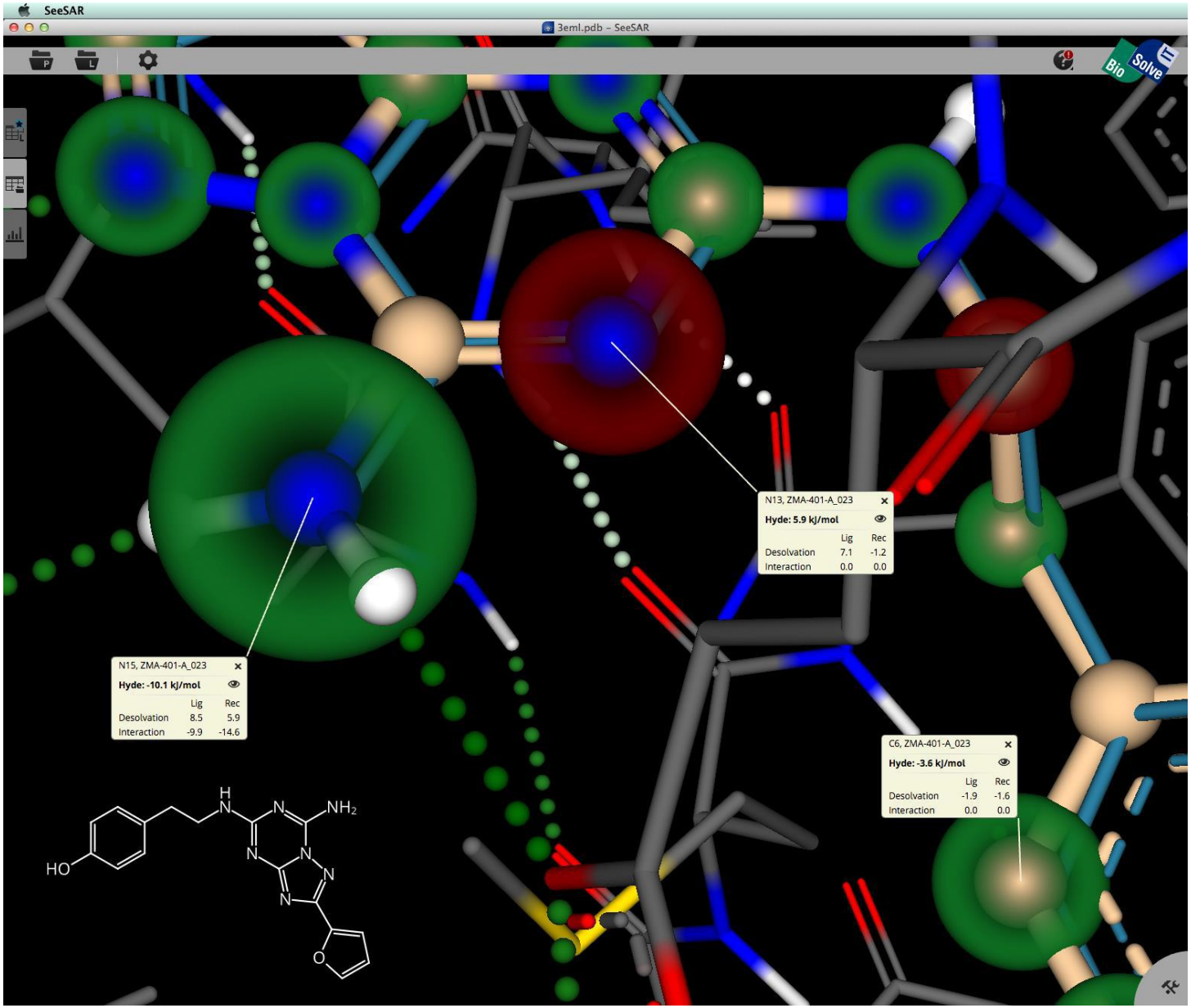


US20110224242A1 [0108]

[0108] To a solution of commercial 2-methylquinolin-8-ol (4.00 g, 25.13 mmol) in **nitrobenzene** (10 mL) were added acetyl chloride (1.96 mL, 27.64 mmol) and **aluminium chloride** (8.38 g, 62.82 mmol). The **reaction mixture was heated at 70° C. overnight**. … to give 1-(8-hydroxy-2-methylquinolin-5-yl)ethanone as a pale yellow powder (3.51 g, 70%).

Nitrobenzene forms explosive mixtures with **$AlCl_3$**.
Reithman, J. *et al.* 1974

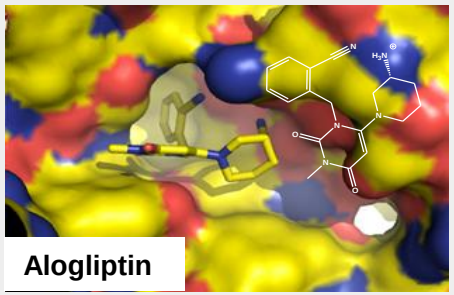
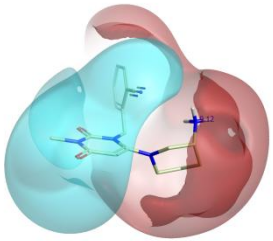
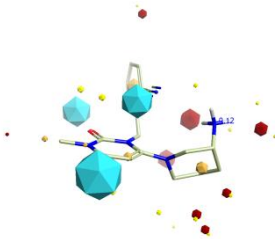
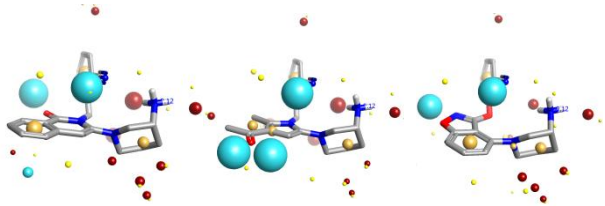
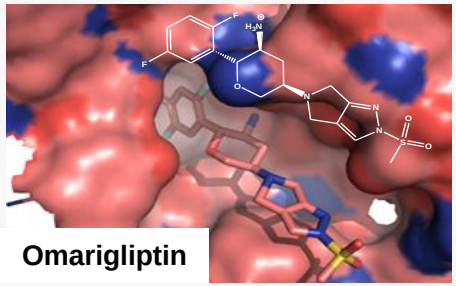
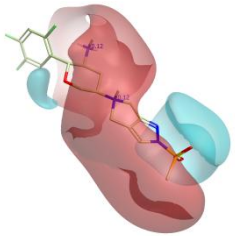
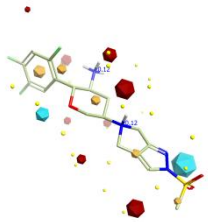
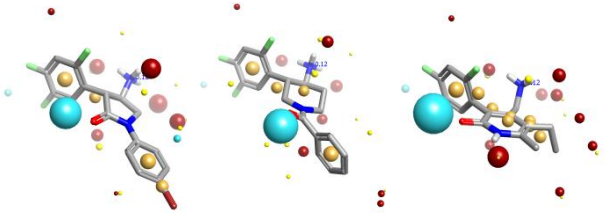
SeeSAR: Atom-based binding-mode analysis



Scaffold hopping into new DPP-IV protease inhibitors

Giovanna Tedesco, Cresset

- Two peptide hormones GLP-1 and GIP mediate lowering of blood glucose level; through stimulation of insulin release and inhibition of Glucagon release
- DPP-IV cleaves a dipeptide from the N-terminus of both GLP-1 and GIP hormones, to give their inactive forms, thus abolishing their glucose lowering action
- DPP-IV inhibitors have been shown to be important agents useful for treating type II diabetes
- Cresset has powerful scaffold hopping and fragment replacement software that can be used to leverage existing molecule electrostatic patterns to quickly and efficiently generate new molecular designs which are more biologically relevant

Input: 3D structure	Cresset electrostatics	Field points	Output: Rapid, feasible designs
 Alogliptin			
 Omarigliptin			

The Use of Matched Molecular Pair Analysis (MMPA) to Share Knowledge Between Multiple Companies

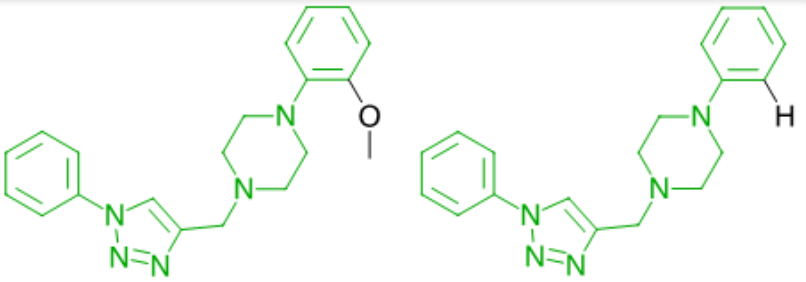
Lauren Reid

MedChemica

How can pharmaceutical companies speed up lead compound optimisation by sharing ADMET knowledge, without sharing confidential structures or data measurements?

- Find **MMP's** (matched molecular pairs) within **individual company databases**
- Share chemical **transformations** and **local environments** as SMIRKS code

Confidential



Non-confidential

4 atom environment:

[C:8]([H])([H])[N:7]([C:9]([H])([H]))[c:2]1[c:3]([H])[c:4]([H])[c:5]([H])[c:6]([H])[c:1]1[O][C]([H])([H])([H])>>[C:8]([H])([H])[N:7]([C:9]([H])([H]))[c:2]1[c:1]([H])[c:6]([H])[c:5]([H])[c:4]([H])[c:3]1([H])

To find out more about MMPA for knowledge sharing and how this has already been implemented, please visit my poster.

Poster details

Poster #	Poster
1	**Chemistry enabling Chinese, Japanese and Korean patents** *Daniel Lowe, NextMove Software*
2	**Graph technologies in chemogenomics** *Magdalena Zwierzyna, EMBL-EBI*
3	**How not to develop a QSAR: an extreme example** *John Dearden, Liverpool John Moores University*
4	**KNIME workflows to predict ADMET properties to support chemical safety assessment** *Andrea Richarz, Liverpool John Moores University*
5	**Predicting regioselectivity and liability of CYP450 metabolism using QM simulations** *Peter Hunt, Optibrium Ltd.*
6	**Reactive chemical hazard alerting in pharmaceutical electronic lab notebooks** *John May, NextMove Software*
7	**Real-time, entropy-aware, visual fragment growing with the computer** *Christian Lemmen, BioSolveIT GmbH*
8	**Scaffold hopping into new DPP-IV protease inhibitors** *Giovanna Tedesco, Cresset*
9	**The use of matched molecular pair analysis (MMPA) to share knowledge between multiple companies** *Lauren Reid, MedChemica*

Coffee & Posters

Lhasa Limited Registered Office
Granary Wharf House, 2 Canal Wharf, Leeds LS11 5PS
UK Registered Charity (290866)

+44 (0)113 394 6020
info@lhasalimited.org
www.lhasalimited.org