A Prologue

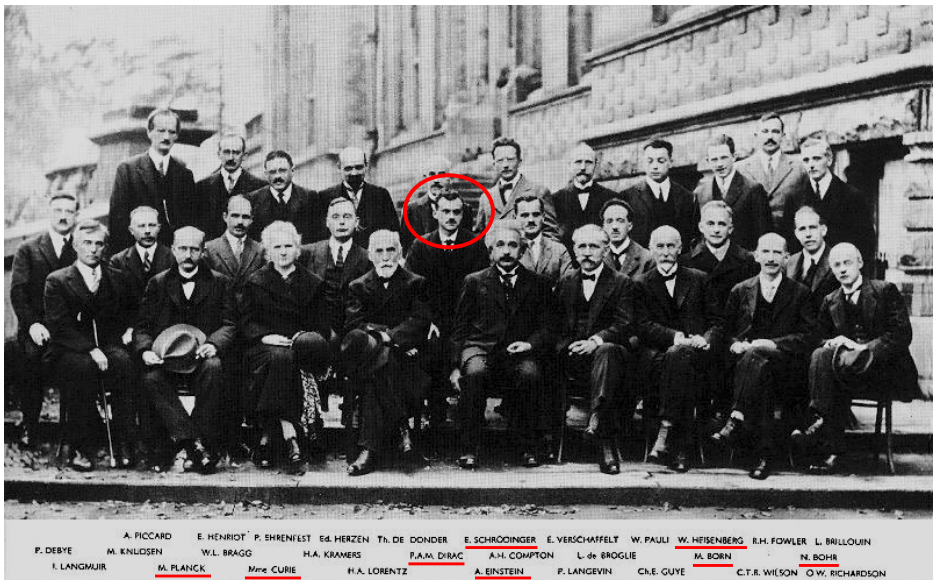
to Ant and his friends

or: the problem with physics

The Dilemma of Computer-Aided Drug Design

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.

P. A. M. Dirac, Proc. R. Soc. London 123, 714-733 (1929)



Fifth Solvay Congress, Brussels (1927)

Hugo Kubinyi, www.kubinyi.de

“Wolpertinger” (Bavaria, Germany)

Scaffold Hopping - A Successful Design Strategy

Hugo Kubinyi

Germany

E-Mail kubinyi@t-online.de
URL www.kubinyi.de

Overview

Medicinal chemists always used scaffold hops

Oldies but goodies: the program CAVEAT

Straightforward design of peptidomimetics

Scaffold hops by fragment similarity

Don't forget the pharmacophore

Surprises - scaffold hops may result in binding hops

Scaffold hops are a perfect modification strategy

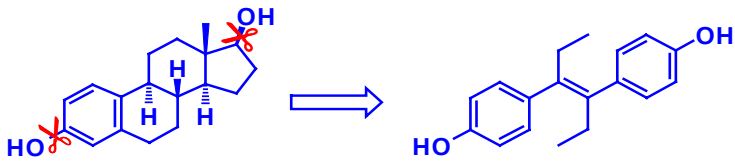
Many blockbuster drugs resulted from scaffold hops

BROOD - comparison of scaffold MEPs

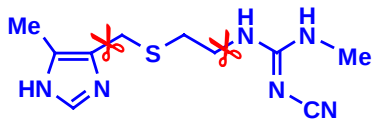
ReCore - a versatile scaffold hopping program

Conclusions

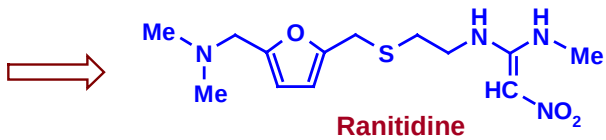
Classical Scaffold Hops: Receptor Ligands



Estradiol Diethylstilbestrol

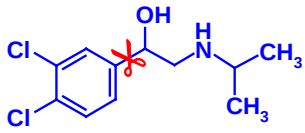


Cimetidine

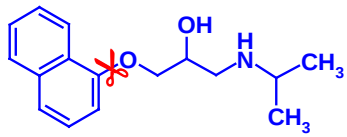


Ranitidine

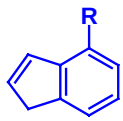
Classical Scaffold Hops: Receptor Ligands



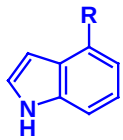
Dichloroisoprenaline



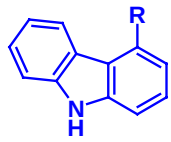
Propranolol



Indenolol



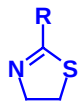
Pindolol



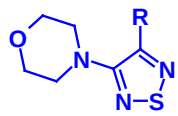
Carazolol

Carteolol

Nadolol



Tazolol

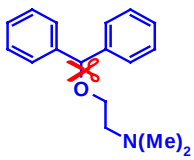


Timolol

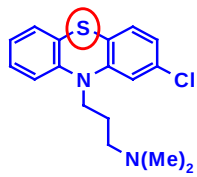
and many others ...

Hugo Kubinyi, www.kubinyi.de

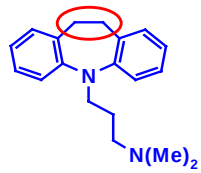
Classical Scaffold Hops: Receptor Ligands



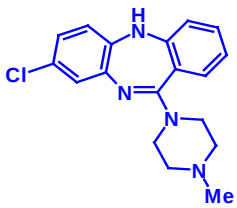
diphenhydramine
(H_1 antagonist)



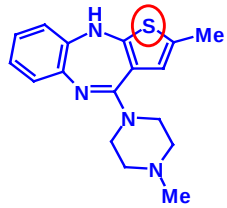
chlorpromazine
(neuroleptic)



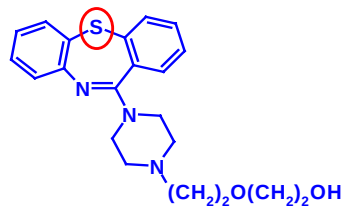
imipramine
(antidepressant)



clozapine
(atypical neuroleptic)

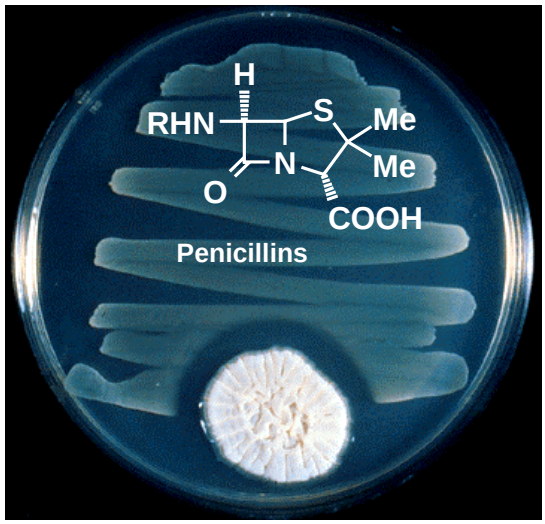


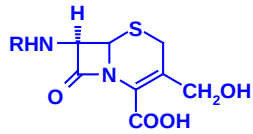
olanzapine
(atypical neuroleptic)



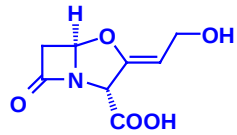
quetiapine
(atypical neuroleptic)

Even Nature Uses Scaffold Hops: Antibiotics

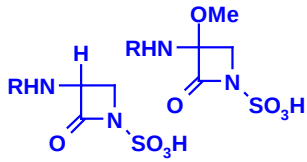




Cephalosporins

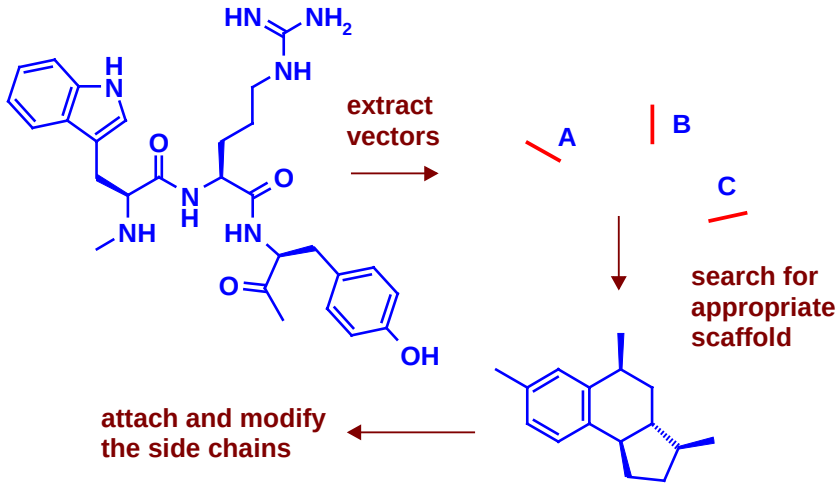


Clavulanic acid



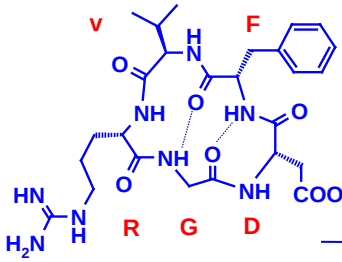
Monobactams

CAVEAT for the Design of Peptidomimetics



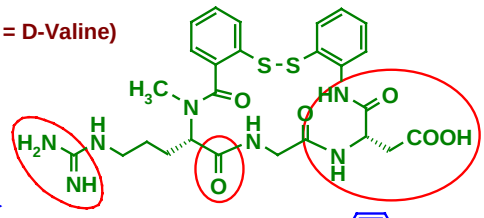
G. Lauri and P. A. Bartlett, J. Comput.-Aided Mol. Design 8, 51-66 (1994)

Rational Design of Integrin Ligands

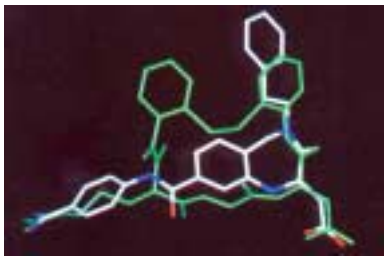


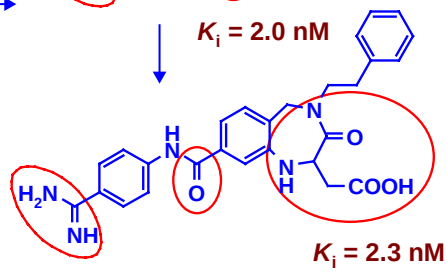
cyclo(RGDFv)

(v = D-Valine)



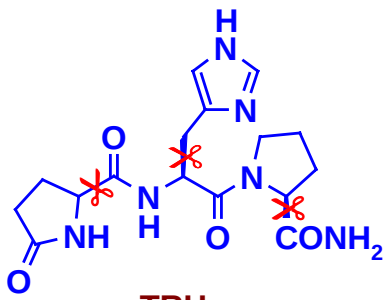
K_i = 2.0 nM



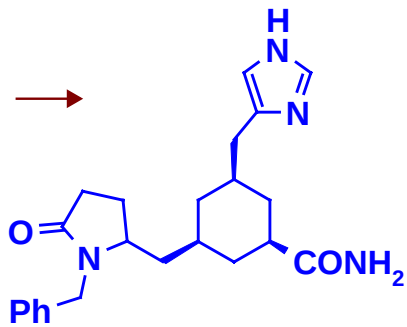


K_i = 2.3 nM

Design of an Orally Active TRH Mimetic



TRH

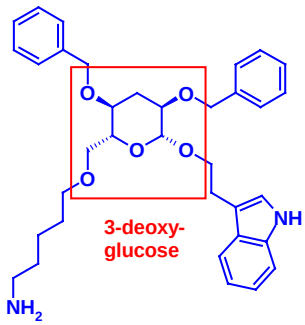


metabolically not stable, no oral bioavailability

peptidomimetic, orally bioavailable, sufficient half-life time

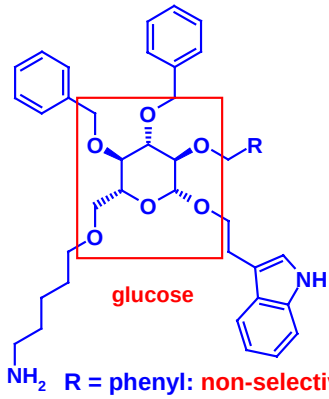
G. L. Olson et al., J. Med. Chem. 36, 3039-3049 (1993)

Scaffold Hops to Somatostatin Mimics



mimic of the receptor-recognizing ß-turn Phe7-Trp8-Lys9-Thr10 of somatostatin; agonist activity at 3 µM

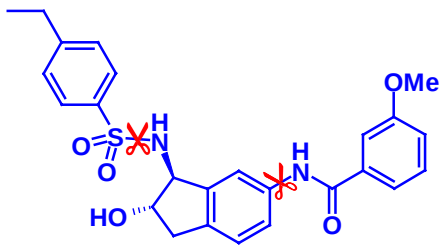
K. C. Nicolaou et al., Peptide Chem. Struct. Biol., Proceedings of the 11th Am. Peptide Symp., 1990, pp. 881-884



R = phenyl: non-selective, weak sst-receptor partial agonist
R = imidazol-4-yl: selective sst4-receptor agonist, 100 nM

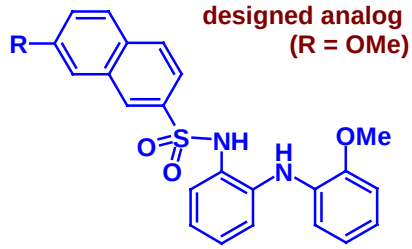
R. Hirschmann et al., J. Med. Chem. 41, 1382-1391 (1998)

TOPAS (TOPology-Assigning System)



template

K_i hK channel 1.5 = 0.11 µM

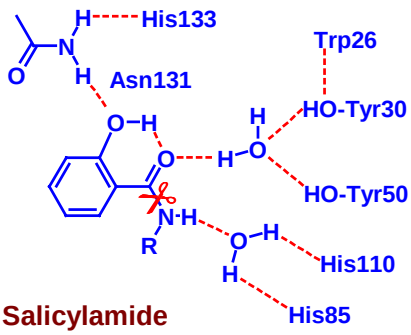


R = OMe: K_i hK channel 1.5 = 7.34 µM
R = H: K_i hK channel 1.5 = 0.47 µM

Scaffolds and building blocks from a RECAP process are re-assembled by their 3D similarity to the template („fragment-based evolutionary design“).

G. Schneider et al., Angew. Chem. Int. Ed. Engl. 39, 4130-4133 (2000)

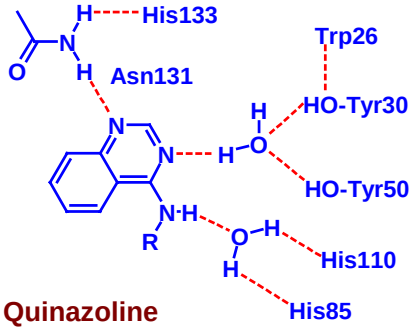
A Binding Site Recognizes Pharmacophores, not Atoms: Scytalone Dehydratase Inhibitors



Salicylamide

R = -CH(CH$_3$)C$_6$H$_4$-p-Br

***K*$_i$ = 0.14 nM**



Quinazoline

R = -CH$_2$CH$_2$CH(C$_6$H$_5$)$_2$

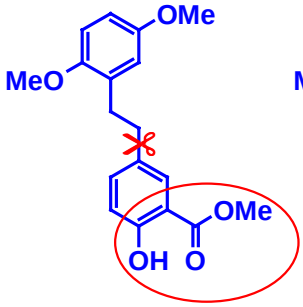
***K*$_i$ = 0.15 nM**

J. M. Chen et al., Biochemistry 37, 17735-17744 (1998)

Hugo Kubinyi, www.kubinyi.de

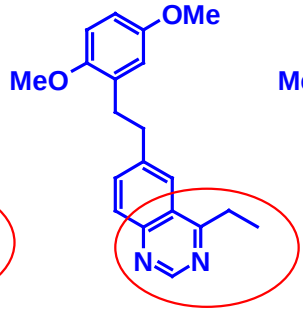
Bioisosterism of Salicylates and Quinazolines

SDZ LAP 977

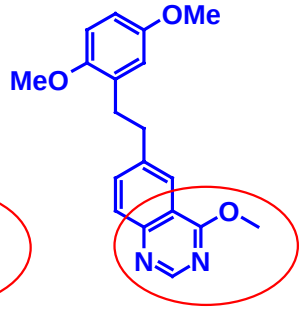


IC$_{50}$ = 47 nM

SDZ LAV 694



7 nM



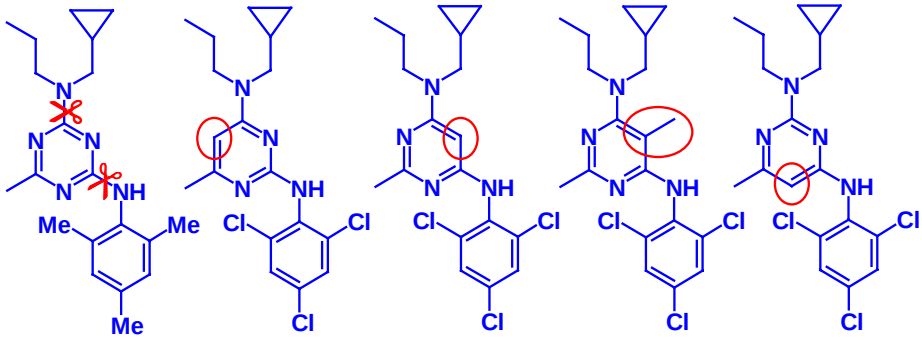
4 nM

(inhibition of tubulin polymerisation; antiproliferative activity in a keratinocyte cell line)

P. Nussbaumer, Novartis, 17th Int. Symp. Med. Chem., Sept. 2002

Scaffold Hops Should Consider Pharmacophores

(corticotropin-releasing factor-1 (CRF1) receptor antagonists)



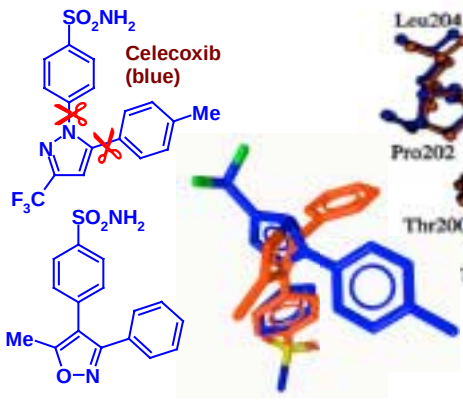
K_i CRF1 =				
57 nM	70 nM	30 nM	2 nM	>10,000 nM

C. Chen et al., J. Med. Chem. 39, 4358-4360 (1996)

Hugo Kubinyi, www.kubinyi.de

Scaffold Hops Should Consider Pharmacophores

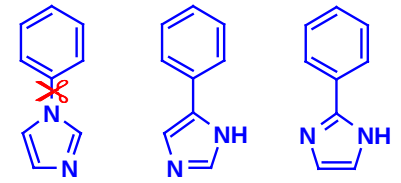
(binding modes of COX2 inhibitors to carbonic anhydrase)



Valdecoxib (red)

(1oq5, 2aw1)

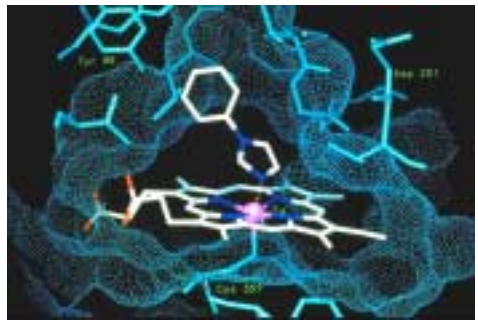
A. Di Fiore et al., Bioorg. Med. Chem. Lett. 16, 437-442 (2006)

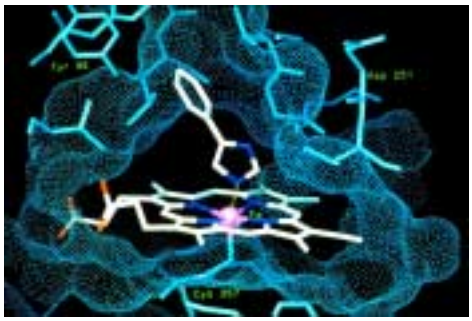


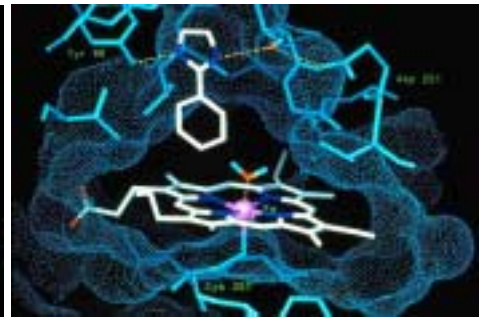
1-Phenyl-imidazole $1.0 \cdot 10^{-7}$ M

4-Phenyl-imidazole $4.0 \cdot 10^{-5}$ M

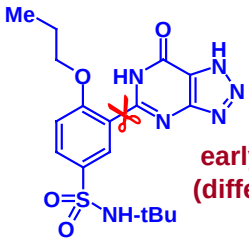
2-Phenyl-imidazole $7.0 \cdot 10^{-6}$ M



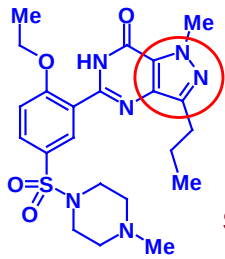




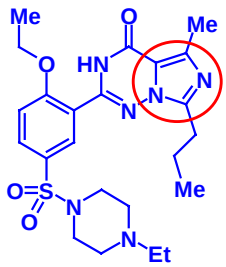
Scaffold Hops to „me too“ Analogs



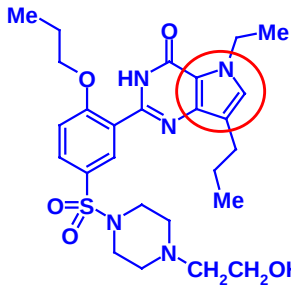
early lead structure (different indication)



Sildenafil

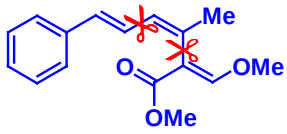


Vardenafil

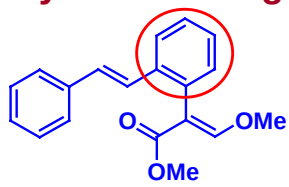


Mirodenafil

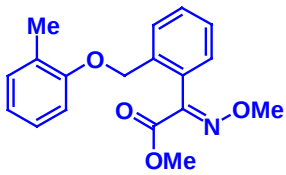
Scaffold Hops to Chemically Stable Fungicides



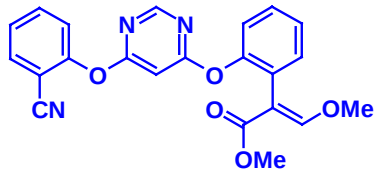
strobilurin A
(potent fungicide, unstable)



first lead structure
(chemically stable)



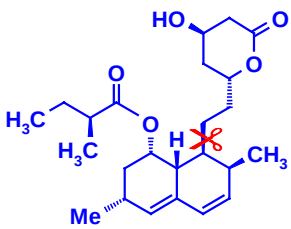
kresoxim methyl
(BASF)



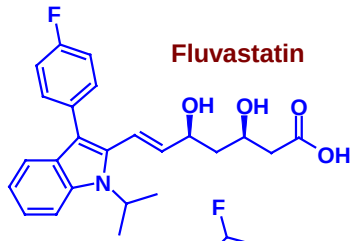
azoxystrobin
(ICI / Zeneca)

Hugo Kubinyi, www.kubinyi.de

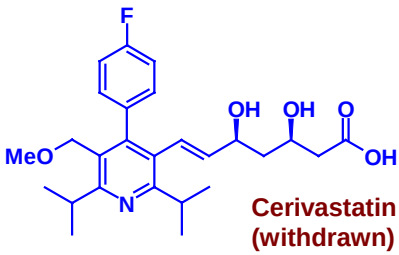
A Huge Hop to a Blockbuster



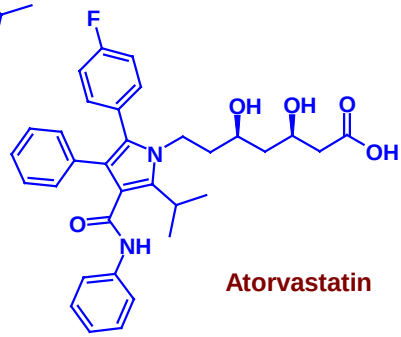
Lovastatin



Fluvastatin

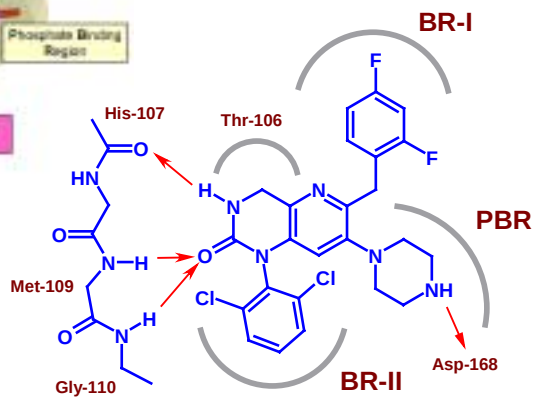


Cerivastatin
(withdrawn)



Atorvastatin

Kinase Inhibitors: Various Scaffold Hops to Mimic ATP



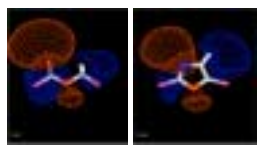
R. Buijsman, in H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

Hugo Kubinyi, www.kubinyi.de

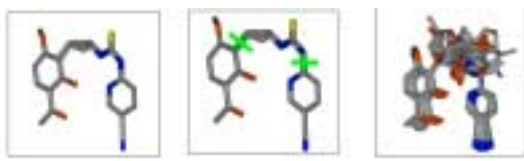
Software for Scaffold Hopping

CAVEAT (Paul Bartlett)
CATS and TOPAS (Gisbert Schneider, Roche)
Skelgen (Phil Dean, Roche)
Shop (Ismael Zamora)
FieldStere (Cresset)

BROOD (OpenEye)



ReCore (Matthias Rarey, BioSolveIT)



Conclusions

Scaffold hops are a well-established strategy in lead structure optimization

Scaffold hops offer new opportunities and chances
- **enhancement of biological activity**
- **modulation of selectivity**
- **modulation of physicochemical properties**
- **intellectual property of „me too“ analogs**

***Cave*: modification of the pharmacophore may change the binding mode**

Software should stimulate your creativity

“whenever people turn on the computer, they are tempted to switch off their brain at the same time, relying too much on some intelligence within the (commercial) programs”

quoted from Nature Rev. Drug. Discov. 2, 665-668 (2003)

Selected References

G. Lauri and P. A. Bartlett, CAVEAT: A program to facilitate the design of organic molecules, J. Comput.-Aided Mol. Design 8, 51-66 (1994).

G. Schneider, W. Neidhart, T. Giller and G. Schmid, "Scaffold-hopping" by topological pharmacophore search: a contribution to virtual screening, Angew. Chem. Int. Ed. Engl. 38, 2894-2896 (1999).

D. G. Lloyd, C. L. Buenemann, N. P. Todorov, D. T. Manallack and P. M. Dean, Scaffold hopping in *de novo* design. Ligand generation in the absence of receptor information, J. Med. Chem. 47, 493-496 (2004).

S. Renner and G. Schneider, Scaffold-hopping potential of ligand-based similarity concepts, ChemMedChem 1, 181-185 (2006).

P. Maass, T. Schulz-Gasch, M. Stahl and M. Rarey, Recore: a fast and versatile method for scaffold hopping based on small molecule crystal structure conformations, J. Chem. Inf. Model. 47, 390-399 (2007).