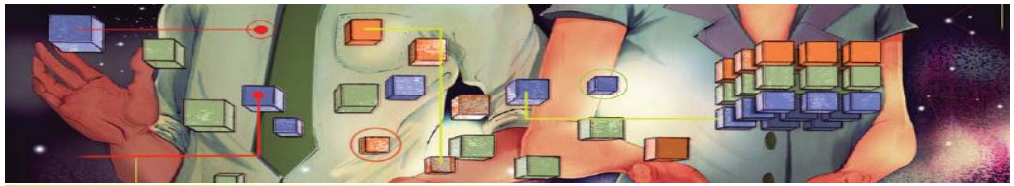
The Concept & Application of Compact Modules:

-From Oxetanes to Spiro-Oxetanes and Beyond

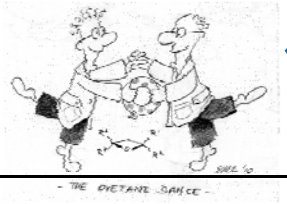
Mark Rogers-Evans

IASOC, Monday 24th September 2012



Quality Teamwork Unity Bench to bedside and back again Passion
Patient focus Pride Medical Need Focus Personalized treatment
Empowerment Excellence in execution Integrity Aim for Cure
Academic collaborations Courage Cutting edge science Quality

pRED *Small Molecule Research*
Pharma Research & Early Development



Compact Modules: Need & Diversity

Oxetanes & Spiro-Oxetanes

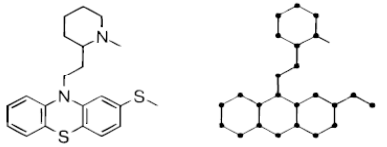
Spiro-Bisazetidines

Spiro-Cyclic Sulphonyl Modules

What Lies Ahead

Ischia, we have a diversity problem...

" … from 5120 (drug like: CMC) compounds analyzed, the shapes of half of the drugs in the database are described by the 32 most frequently occurring frameworks …"



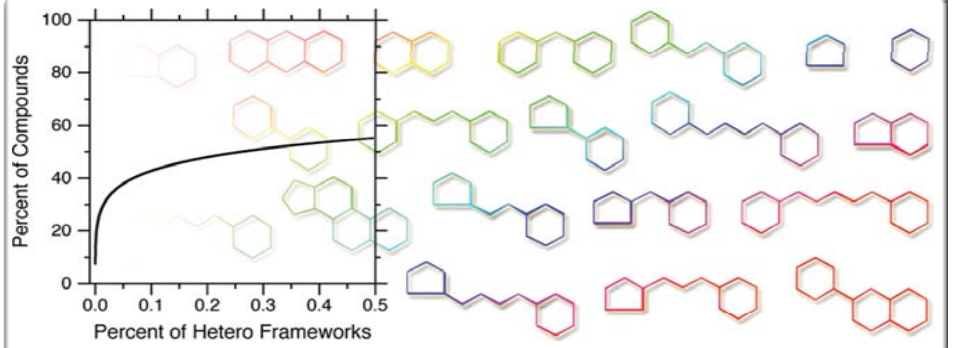
Thioridazine Graph Representation

Graph representation of a typical drug molecule.

"… this suggests that the diversity of shapes in the set of known drugs is extremely low …"

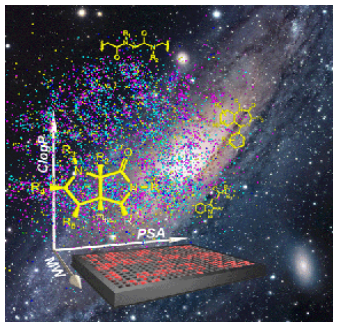
The Properties of Known Drugs. 1. Molecular Frameworks
Mark A. Murcko et al., *J. Med. Chem.* **1996,** *39,* 2887-2893

"50% of the **known universe of chemistry** can be described by only 143 framework shapes"



Structural Diversity of Organic Chemistry. A Scaffold Analysis of the CAS Registry
A. H. Lipkus et al., *J. Org. Chem.* **2008**, *73*, 4443–4451

What does "*the special one*" say about it...?



"...Lack of efficient access to collections of synthetic compounds that have skeletal diversity is a key bottleneck in the small-molecule discovery process..."

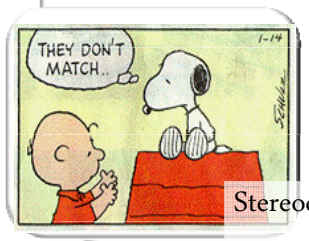
Generating Diverse Skeletons of Small Molecules Combinatorially
Stuart L. Schreiber et al., *Science* **2003**, *302*, 613-618

Interrogating *Biological Space* with *Shape Diversity*

Appendage

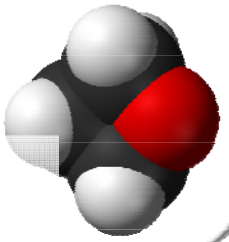
Functional Group

Diversity



Stereochemical

Scaffold



Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules
W. R. J. D. Galloway et al., *Nat. Comm.*, **2010**, *1*, 80

The Need:

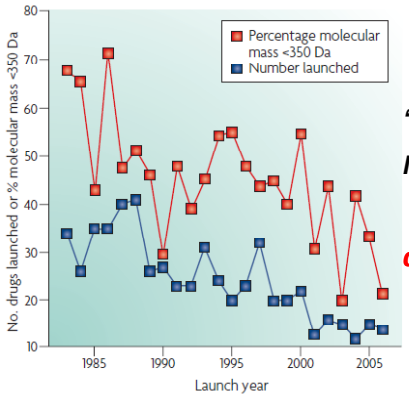
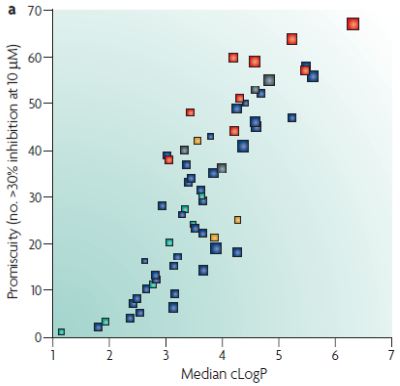


Figure 2 | **Trends in drug approvals and their molecular mass.** The number of oral drugs approved per annum worldwide from 1983 to 2006 and the percentage of these drugs that have molecular mass <350 Da are shown.

"...The reduction in the proportion of launched low molecular-mass oral drugs over time correlates with the established decline in new drug launches ..."

The influence of drug-like concepts on decision-making in medicinal chemistry
P. D. Leeson et al., *Rev. Drug Disc.* **2007**, *6*, 881

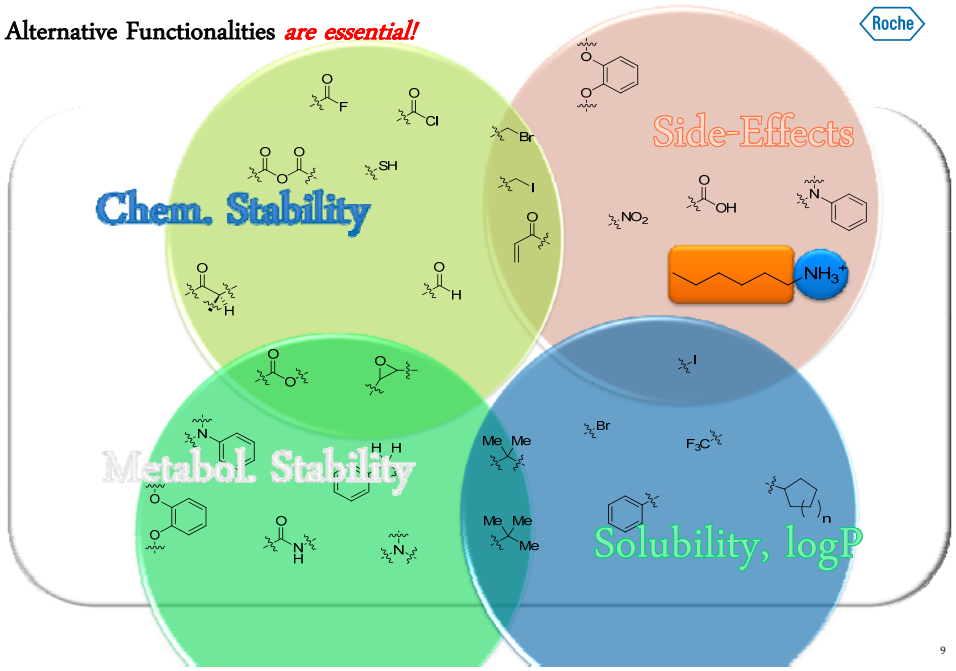
The Need:



"... If lipophilicity is too high, there is an increased likelihood of binding to multiple targets and resultant pharmacologically based toxicology, as well as poor solubility and metabolic clearance..."

The influence of drug-like concepts on decision-making in medicinal chemistry
P. D. Leeson et al., *Rev. Drug Disc.* **2007**, *6*, 881

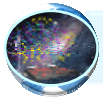
Alternative Functionalities *are essential!*



Modules: Requirements

1. Novelty: ip position
2. Vectorization: shape diversity
3. Compact
4. Tunable Polarity: sol, perm, safety
5. Chemical & Metabolic Stable
6. Easily available

Have Compact Modules Come of Age?


Concept: addressing novel, useful Chem/Biol Space


Roche Funded Research


Applications at Roche

CM: Need & Diversity ?

Oxetanes & Spiro-Oxetanes

Spiro-Bisazetidines

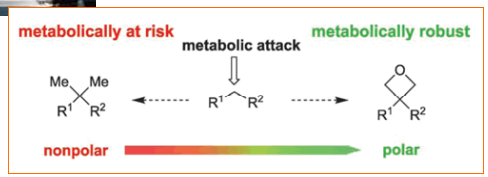
Spiro-Cyclic Sulphonyl Modules

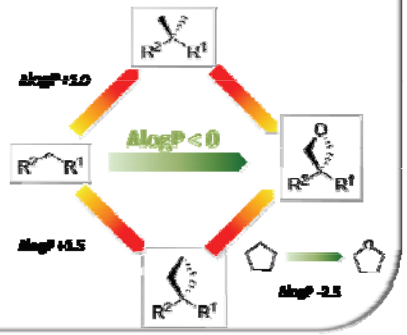
What Lies Ahead

Mark Rogers-Evans
Klaus Müller

Georg Wuitschik
Erick M Carreira

2005-2008

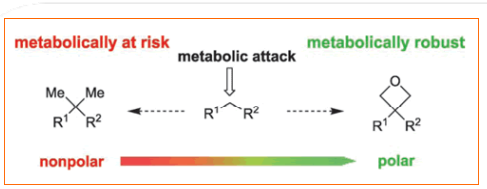


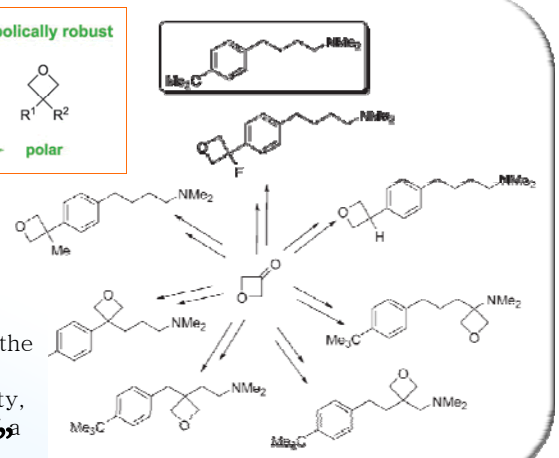


Concept 1:

Roche

Modifying the properties of the underlying scaffold





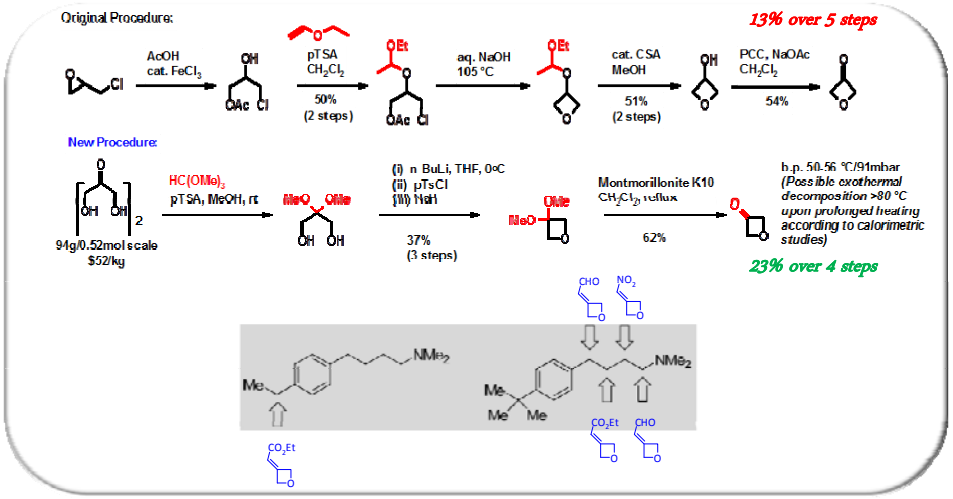
"… The oxetane ring confers enhanced solubility, reduces the metabolic degredation, lipophilicity, and amphiphilicity, and modulates the basicity of a nearby amine group…"

Oxetanes as Promising Modules in Drug Discovery
G. Wuitschik, M. Rogers-Evans*, K. Müller, E. M. Carreira* et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 7736

The essential BB: Oxetan-3-one

Roche

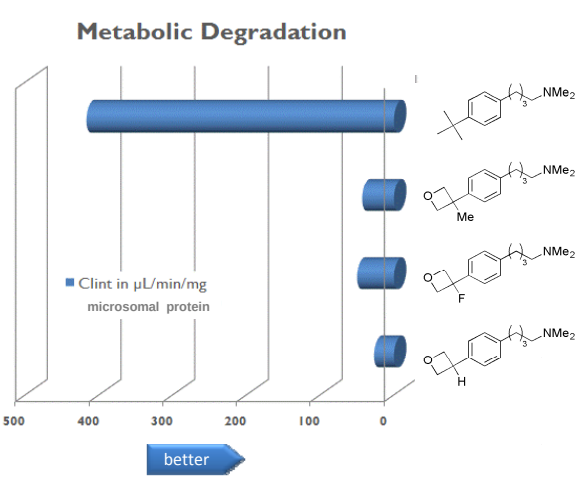
Modifying the properties of the underlying scaffold

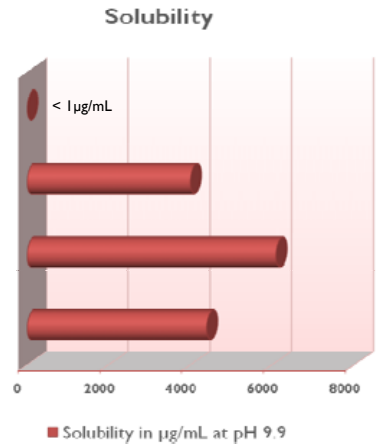


Oxetanes as Promising Modules in Drug Discovery
G. Wuitschik, M. Rogers-Evans*, K. Müller, E. M. Carreira* et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 7736

Some Data Points: Oxetane V's gem-Dimethyl

Modifying the properties of the underlying scaffold

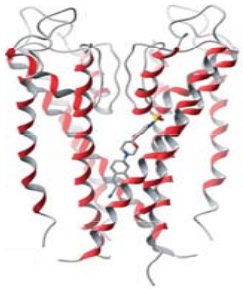




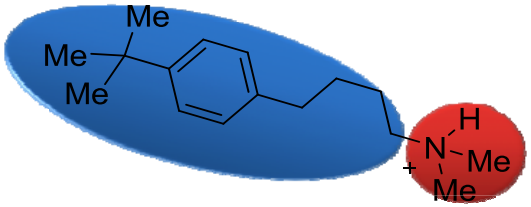
hERG binding: gem-dimethyl => Oxetane

Modifying the properties of the underlying scaffold

hERG IC_{50} = 7.5 µM



http://www.neurionpharma.com/hergmap.htm



"… compds that interact with the hERG channel share structural features such as a basic amine (pKa > 7.3), high lipophilicity (LogP > 3.7), the absence of negatively ionizable groups or absence of oxygen hydrogen bond acceptors…"

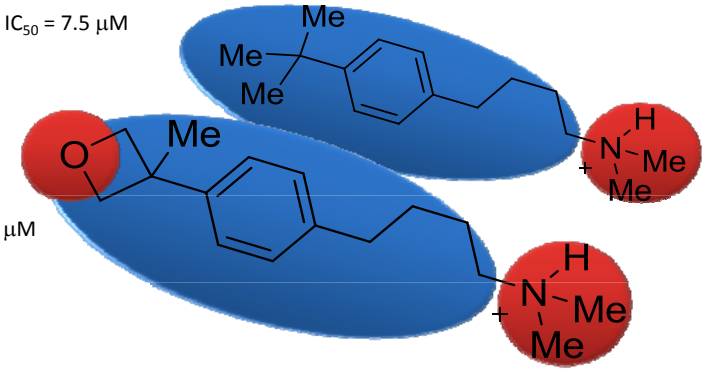
hERG-Interactions are common → **Important safety test!**

hERG binding: gem-dimethyl => Oxetane

Modifying the properties of the underlying scaffold

hERG IC_{50} = 7.5 µM

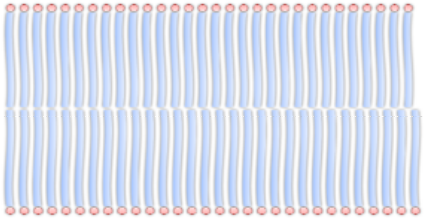
hERG IC_{50} = 35 µM



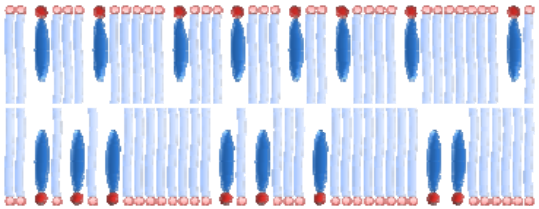
"… compds that interact with the hERG channel share structural features such as a basic amine (pKa > 7.3), high lipophilicity (LogP > 3.7), the absence of negatively ionizable groups or absence of oxygen hydrogen bond acceptors…"

Interaction with Cell Membranes

Modifying the properties of the underlying scaffold



Simplified Example of a Cell Membrane



Amphiphilic compounds integrate into membranes and disrupt the metabolism of phospholipids which leads to an intracellular accumulation of Phospholipids.

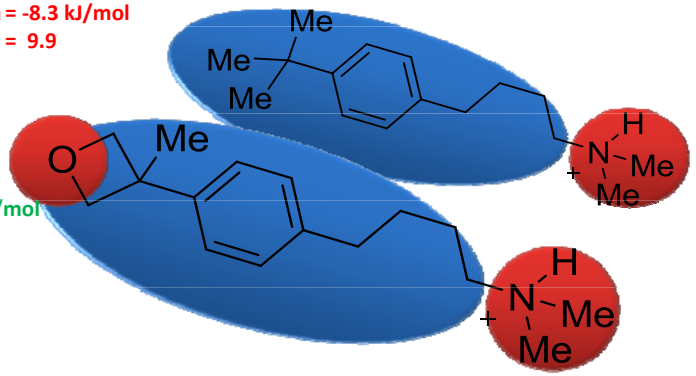
→ Phospholipidosis

PhosphoLipiDosis: gem-dimethyl => Oxetane

Modifying the properties of the underlying scaffold

$\Delta\Delta G_{AM}$ = -8.3 kJ/mol
pKa = 9.9

$\Delta\Delta G_{AM}$ = -3.2 kJ/mol
pKa = 9.9

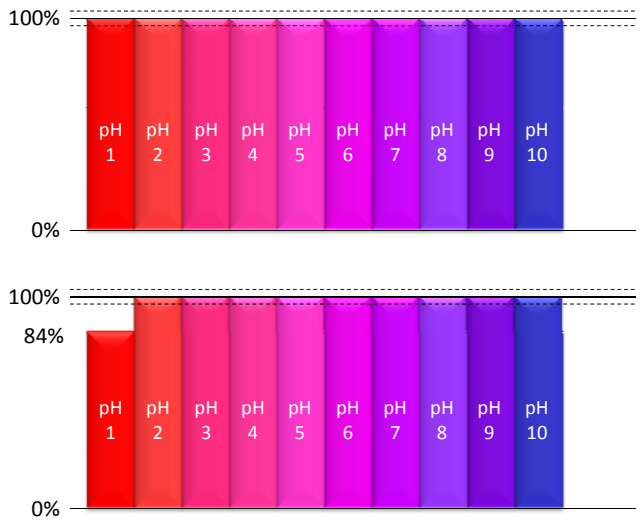


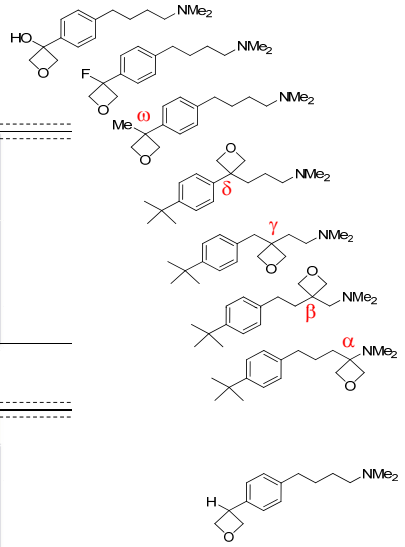
"… drug induced PLD is commonly induced by the repeated administration of cationic amphiphilic drugs (CADs)…defined as the spatial difference between a distinct hydrophilic and hydrophobic region in a molecule…"

In Silico Assay for Assessing Phospholipidosis Potential of Small Druglike Molecules:
H. Fischer et al., *J. Med. Chem.* **2011**, *55*, 126

Chemical Stability

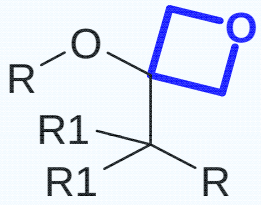
Exposure to aqueous buffer at given pH, 37°C, 2hrs recovery by calibrated HPLC





Reagent Compatibility of Oxetanes-2

Advanced Project Example: No Decomposition



R1=H; EWG

(i) $TiCl_4$, CH_2Cl_2, -78°, 2.5h

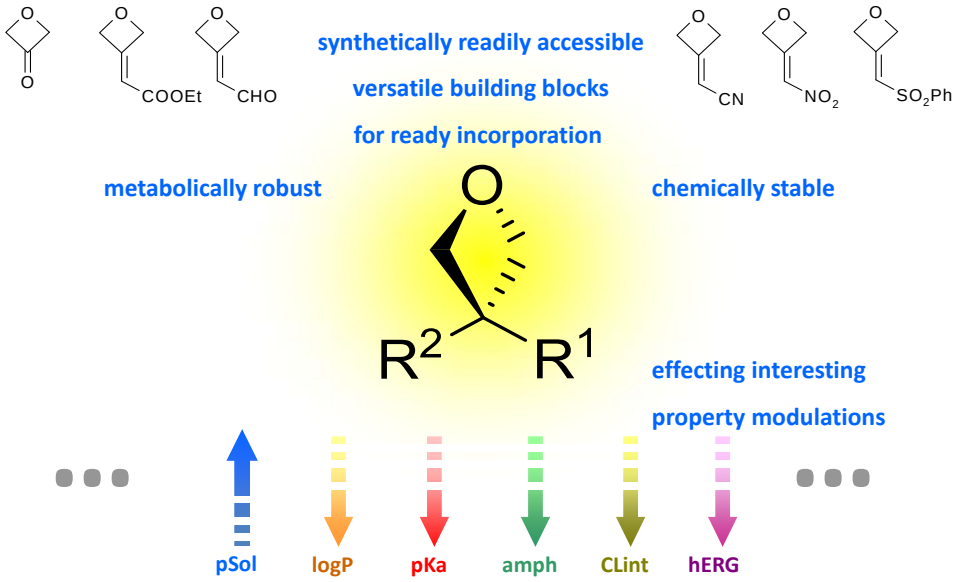
(ii) $Ti(OEt)_4$, THF, Reflux, 2h

(iii) MeLi/Me_3Al, Toluene, -78°, 1h

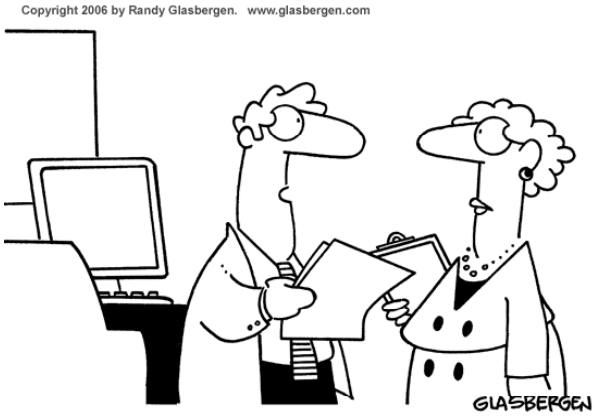
(iv) 4N HCl, 0°, Dioxane, 2h

(v) Fuming HNO_3/H_2SO_4, 0°, 30min

Oxetanes as *gem*-Dimethyl Surrogates

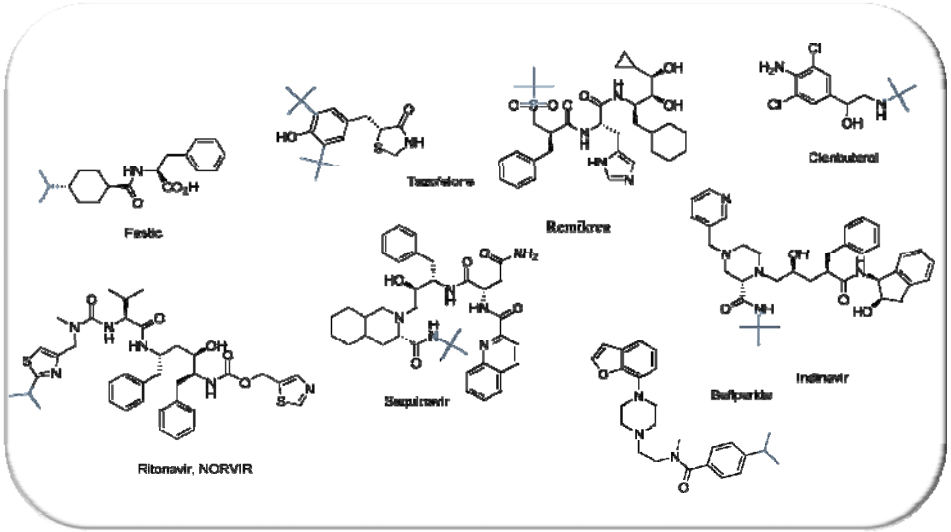


So What?



"My team has created a very innovative solution, but we're still looking for a problem to go with it."

Many Possibilities for Introduction:

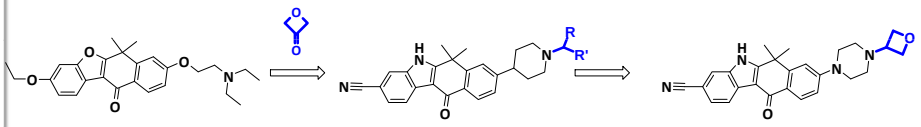


The influence of drug-like concepts on decision-making in medicinal chemistry
P. D. Leeson et al., *Rev. Drug Disc.* **2007**, *6*, 881

Selective, Orally Active, Stable & Potent!

Roche Chugai: Anaplastic Lymphoma Kinase Inhibitors for NSCLC

"… Inhibition of particular kinases is considered to have Risk of Adverse Events; KIT & KDR are associated with: Bone Marrow Suppression & Hypertension …"



HTS Hit
- ALK IC50 = 1336 nM

Optimized Hit 1
- ALK IC50 = < 10 nM
- High Clearance

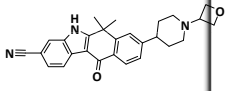
Optimized Hit 2
- ALK IC50 = < 10 nM
- Reduced Clearance

Discovery of novel tetracyclic compounds as anaplastic lymphoma kinase inhibitors
K. Kinoshita* et al., *J. Med. Chem.* **2011**, *54*, 6286 & Bioorg. Med. Chem. **2012**, *20*, 1271

Selective, Orally Active, Stable & Potent!

Anaplastic Lymphoma Kinase Inhibitors for NSCLC

Substitution	IC50 (nM) ALK	IC50 (nM) KARPAS-299	CL (µl/min/mg) Mouse (NADPH+)	CL (µl/min/mg) Human (NADPH+)
	33.4	331	58.9	39.5
	18.5	134	8.1	33.6
OH	114	115	24.6	7.1
	37.4	263	19.8	**19.2**
	1.8	33.6	23.1	**82.7**
	27	47.9	15.1	**9.6**
	1.5	21.4	10.4	**10.2**

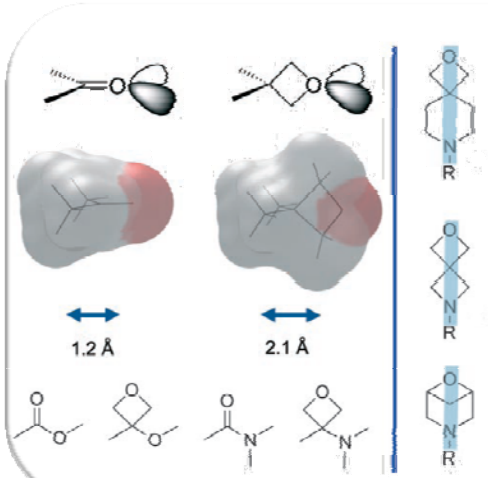


Optimized Hit 1
- ALK IC50 = 1.5 nM
- KDR IC50 = 100 nM
- KARPAS-299 IC50 = 21 nM

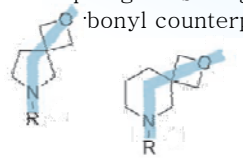
Discovery of novel tetracyclic compounds as anaplastic lymphoma kinase inhibitors
K. Kinoshita* et al., *J. Med. Chem.* **2011**, *54*, 6286 & Bioorg. Med. Chem. **2012**, *20*, 1271

Concept 2: Ether & Carbonyl Isosteres

Expanding Chemical Space

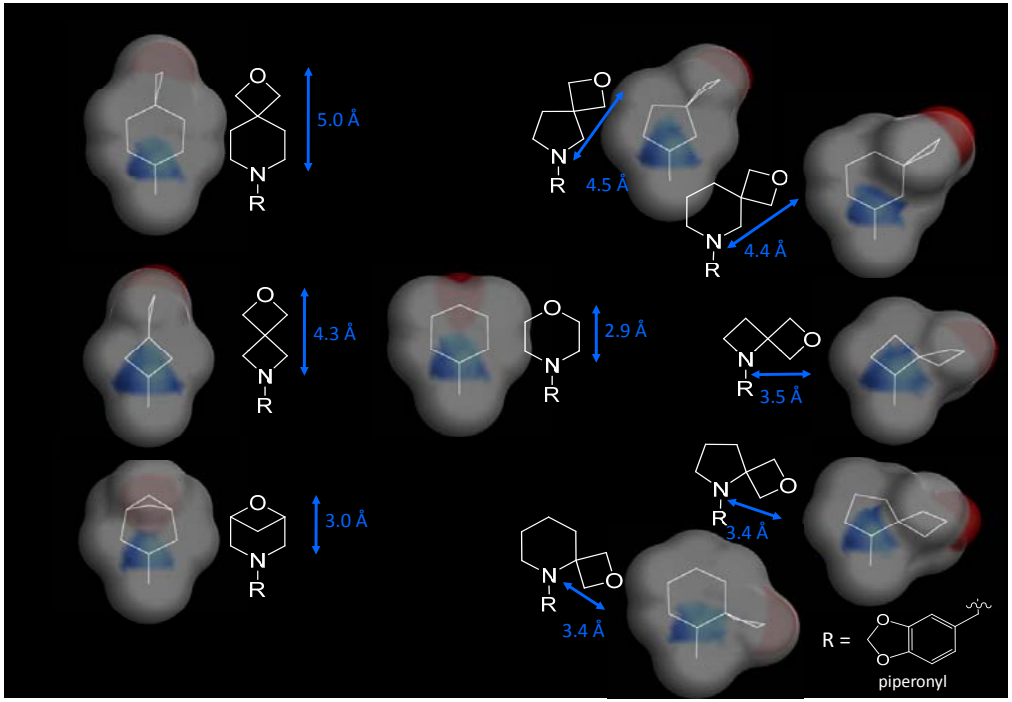


"… Spirocyclic oxetanes are described as analogues of morpholine and also as topological siblings of their carbonyl counterparts…"

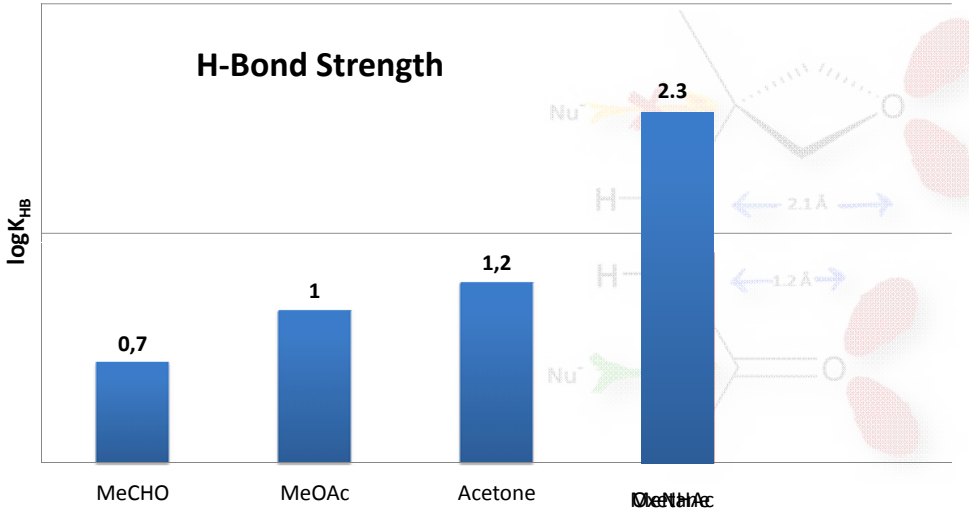


Effects on
Lipophilicity
Basicity
Solubility

G. Wuitschik, M. Rogers-Evans*, K. Müller*, E.M. Carreira* et al., *Angew. Chem. Int. Ed.* **2008**, *47*, 4512

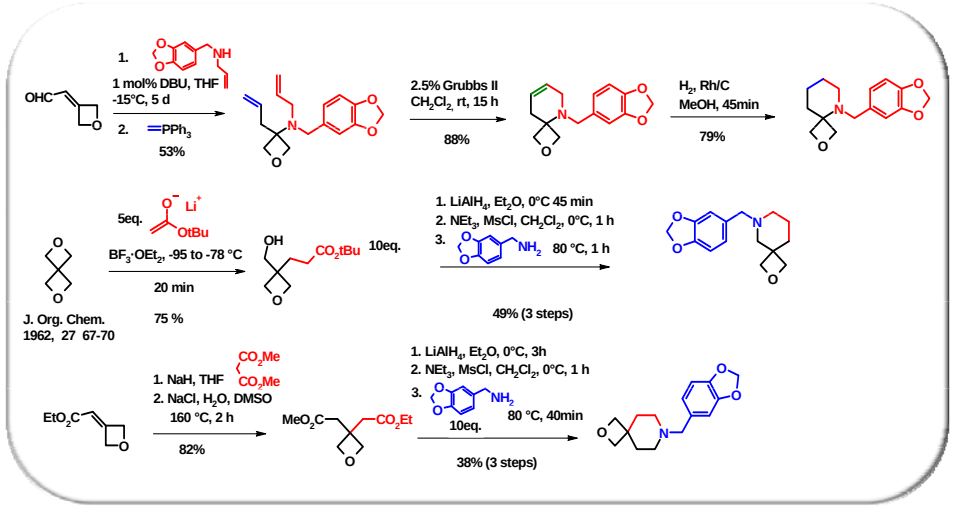


Oxetanes as Carbonyl Analogues



Construction of of 4.6-Spirocyclic Oxetanes

Roche



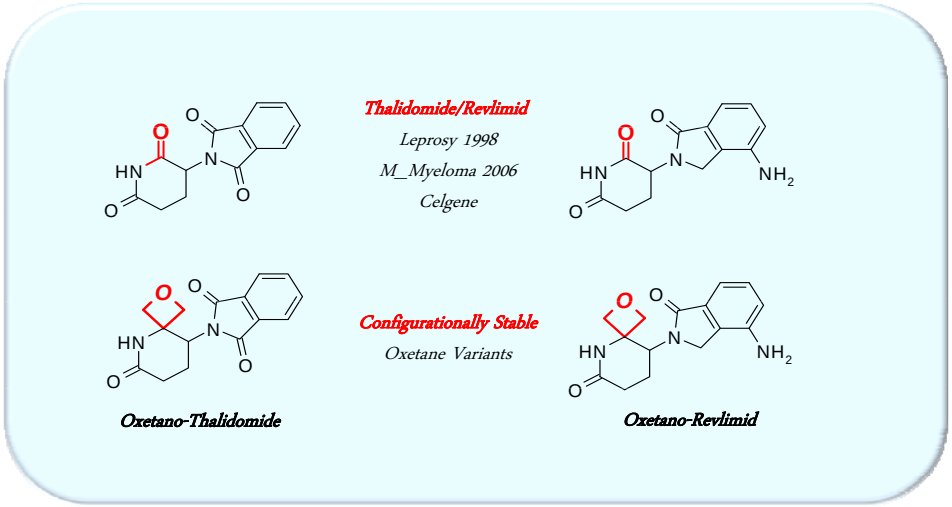
Spirocyclic Oxetanes: Synthesis and Properties

G. Wuitschik, M. Rogers-Evans*, K. Müller*, E.M. Carreira* et al., *Angew. Chem. Int. Ed.* **2008**, *47*, 4512

C=O to Oxetane

Roche

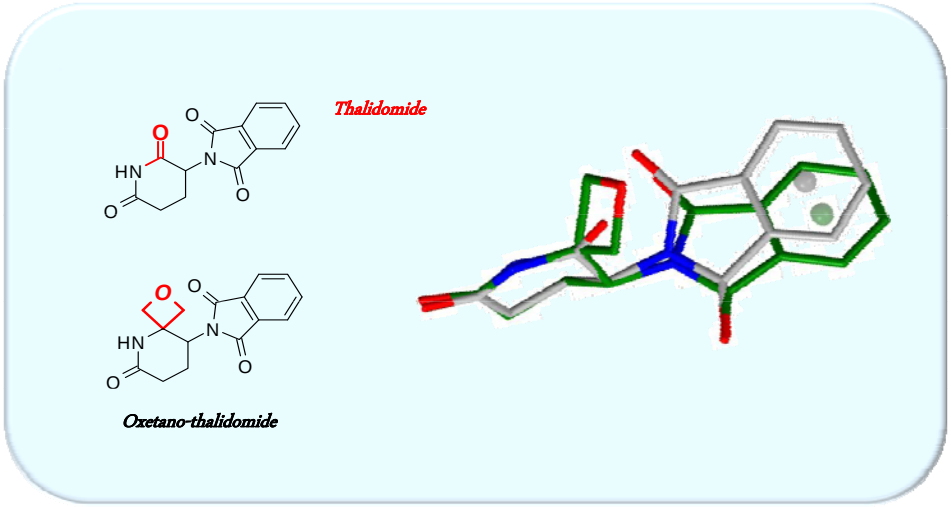
Application to Marketed Drugs



New Opportunities for Four-Membered Heterocycles
J. A. Burkhard, Ph. D. Dissertation, ETH Zurich. 2011

C=O to Oxetane

Predicted Retention of Potency



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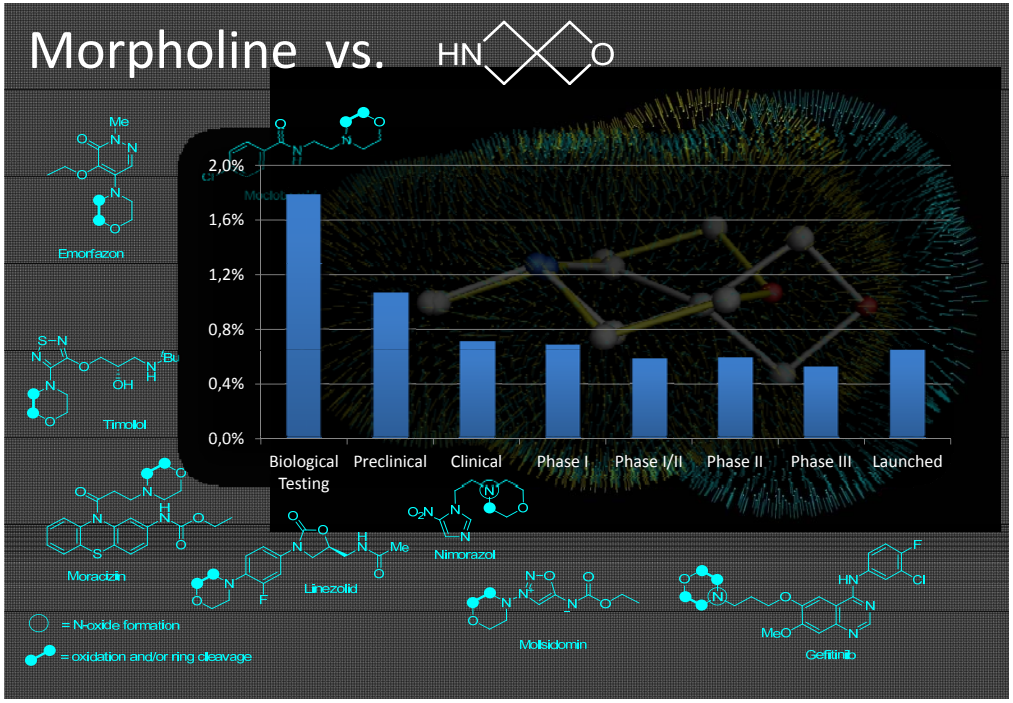
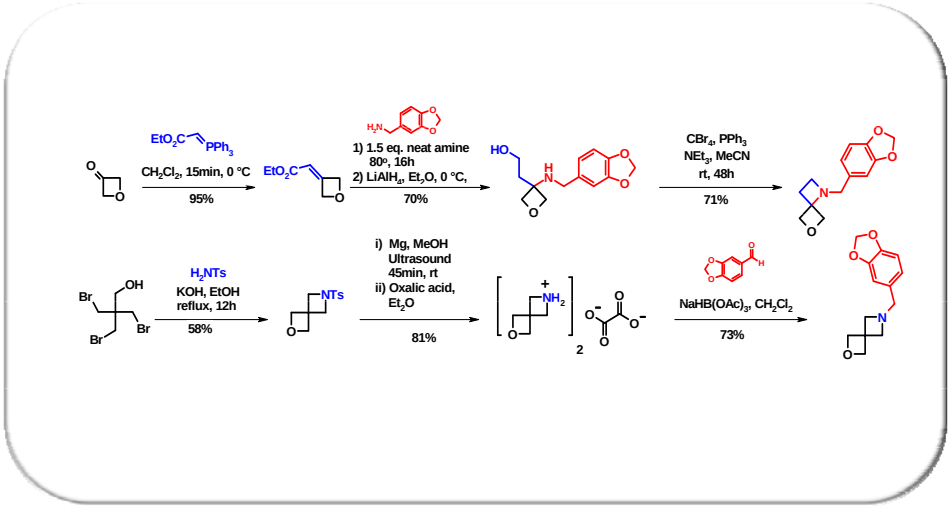


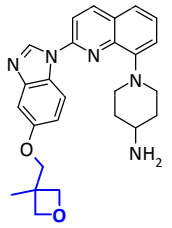
Construction of 4,4-Spirocyclic Oxetanes

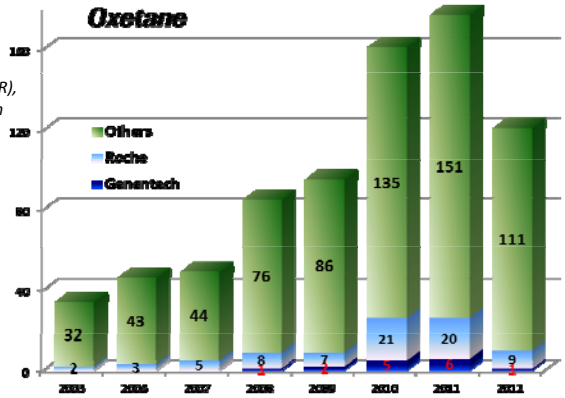


Spirocyclic Oxetanes: Synthesis and Properties
G. Wuitschik, M. Rogers-Evans*, K. Müller*, E.M. Carreira* et al., *Angew. Chem. Int. Ed.* **2008**, *47*, 4512

Uptake in the Pharma Industry

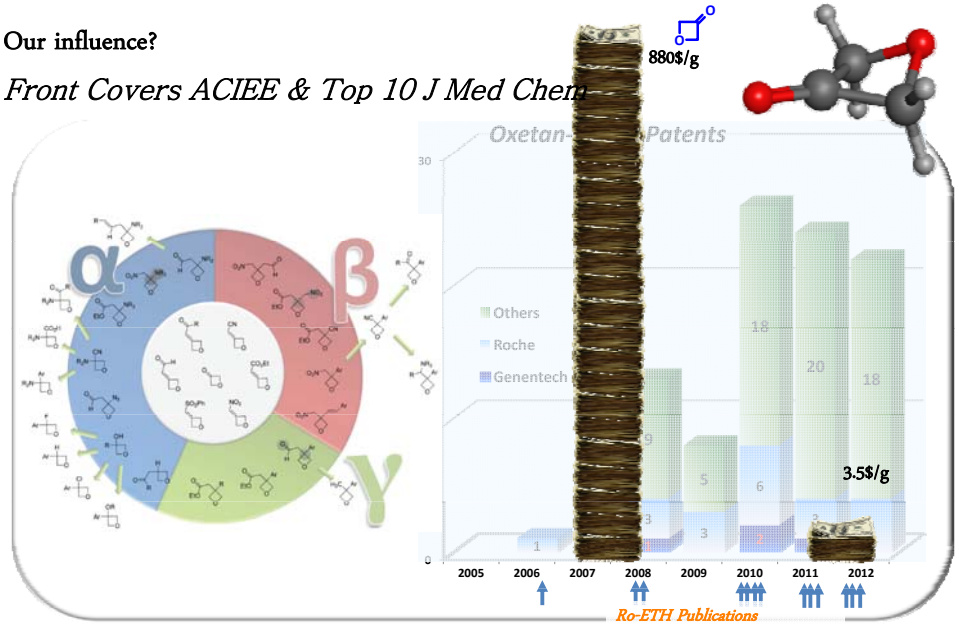
Creolanib (ex Pfizer) CP-868,596 is an orally bioavailable small molecule, targeting the platelet-derived growth factor receptor (PDGFR), for Gastrointestinal Stromal Tumors and Gliom (Currently in Two Phase II & one Phase I trials).





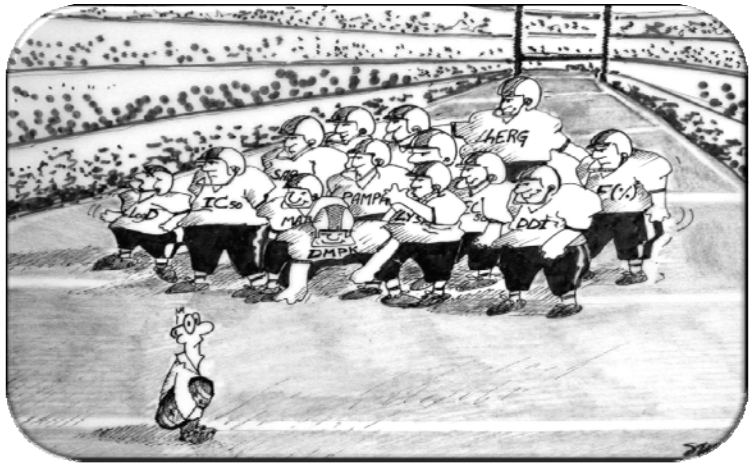
Our influence?

Front Covers ACIEE & Top 10 J Med Chem



The "Oxetane" Strategy

An Additional Tool for Lead Optimization



Gift to author from Dr. Simona Ceccarelli, Hoffmann-La Roche

Roche

CM: Need & Diversity ?

Oxtanes & Spiro-Oxetanes

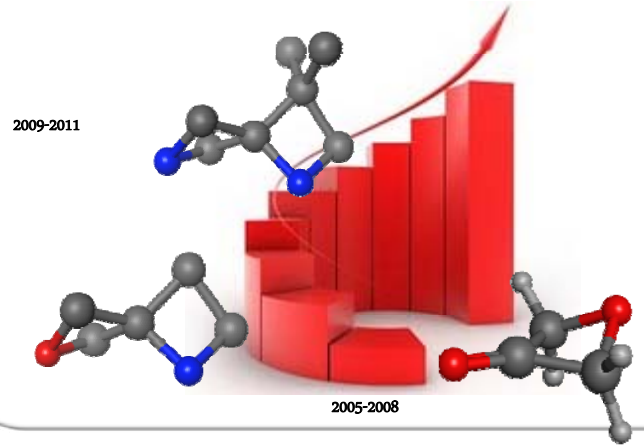
Spiro-Bisazetidines

Spiro-Cyclic Sulphonyl Modules

What Lies Ahead

Evolution of Roche-ETH Collab.

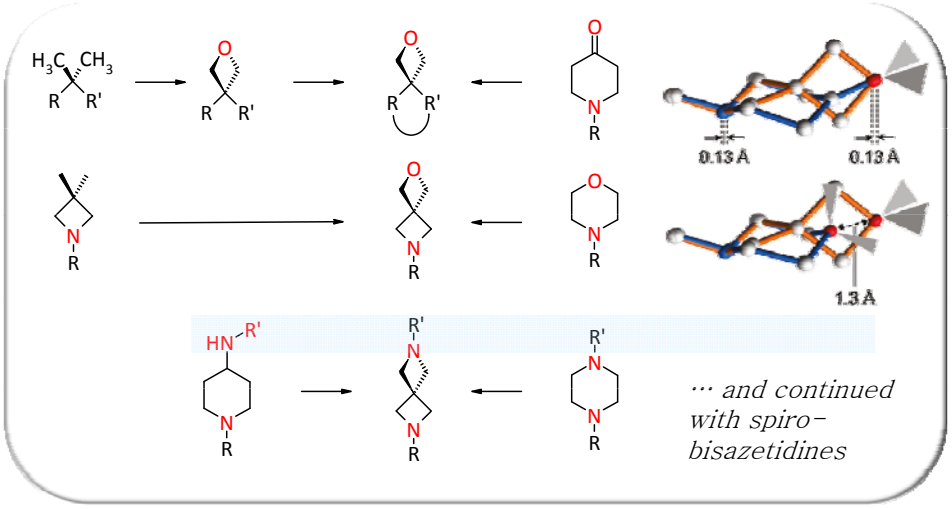
Drug Discovery Graduate Program => Roche Funded Postdoc



The Chemical Modules Story

Roche

Starts with Oxetanes …



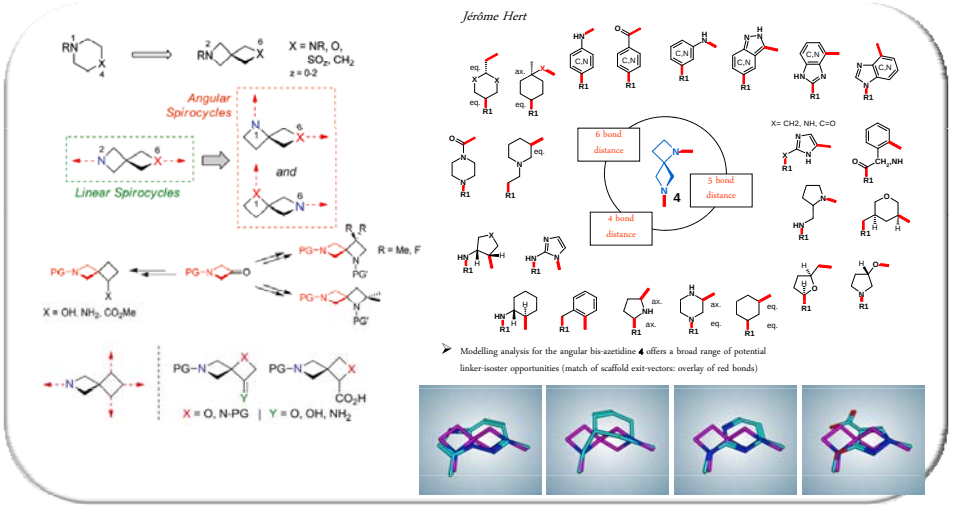
Synthesis of Azaspirocycles and their Evaluation in Drug Discovery

J. A. Burkhard, B. Wagner. H. Fischer, F. Schuler, K. Müller*, E. M. Carreira*, *Angew. Chem. Int. Ed.* **2010**, *49*, 3524

From linear to angular bis-azetidines

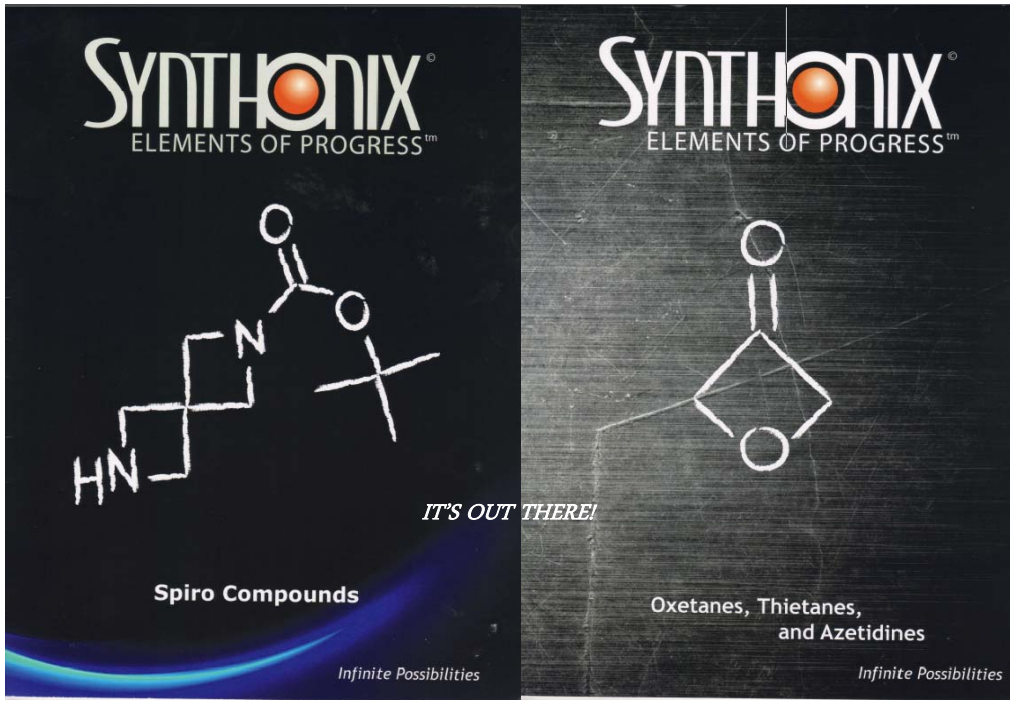
Roche

A variety of opportunities



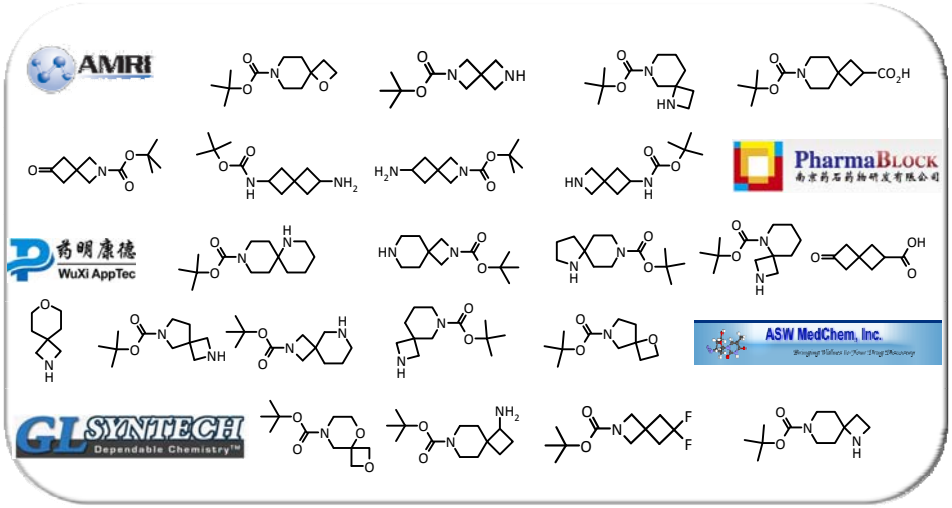
Expanding the Azaspiro[3.3]heptane Family: Synthesis of Novel Highly Functionalized Building Blocks

J. A. Burkhard, C. Guérot, H. Knust, E. M. Carreira*, *Org. Lett.* **2011**, *14*, 66



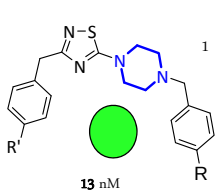
Commercial and Novel!

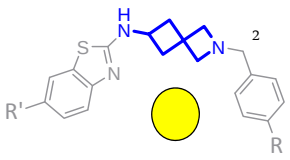
Roche

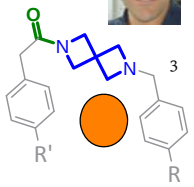


Top two novel compounds targeting (AD)

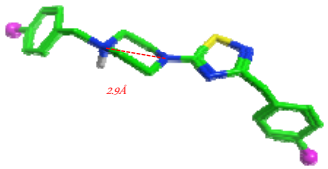
Roche

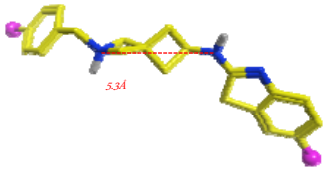


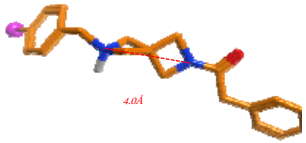




EC50:	**13** nM		

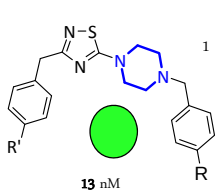


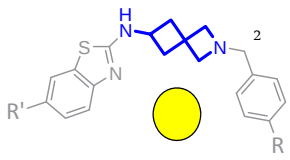


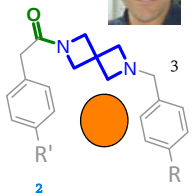


Top two novel compounds targeting (AD)

Roche







	EC50:	**13** nM	0.1	2
	MAB (h/m):	65 / 25 %	93 / 56	100 / 66
	PK mice			
DMPK	Clearance	105 ml/min/kg	5.8	22
DMPK	Bioavailability	**47** %	**47**	100
DMPK	Brain/Plasma:	3.3	2.4	1.2
Safety	**GSH:**	Flag	No Flag	No Flag
Safety	**MNT** & **Ames**:	–	Clean	Clean
Phys-chem	**Lysa / Thesa**	< 1 µg/ml	4/6	335/>2736
Phys-chem	**ASTA:**	–	Stable	Stable

Roche

CM: Need & Diversity ?

Oxtanes & Spiro-Oxetanes

Spiro-Bisazetidines

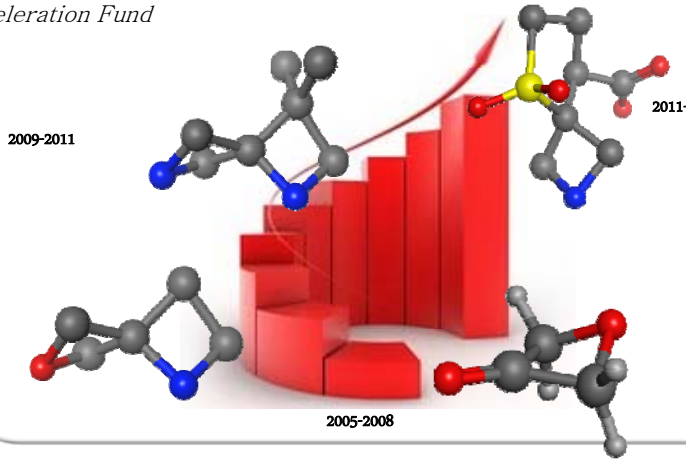
Spiro-Cyclic Sulphonyl Modules

What Lies Ahead

Evolution of Roche-ETH Collab.

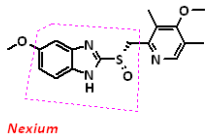
Roche

Drug Discovery Graduate Program => Roche Funded Postdoc => Roche Acceleration Fund

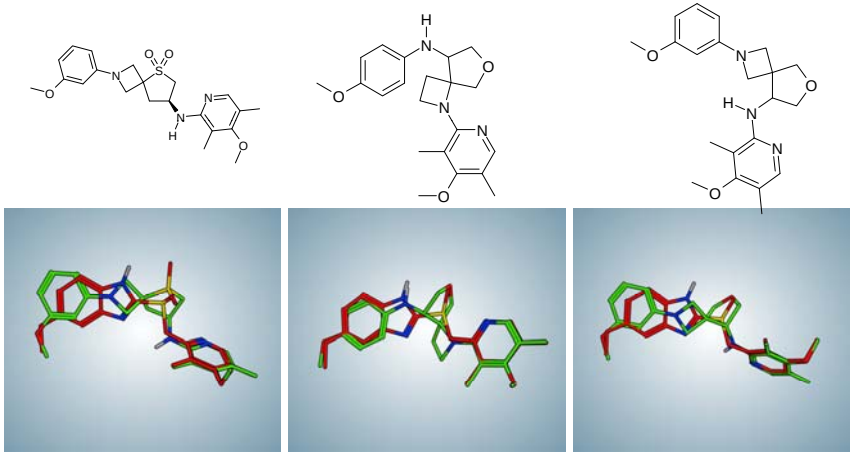


Future Spiro-Modules

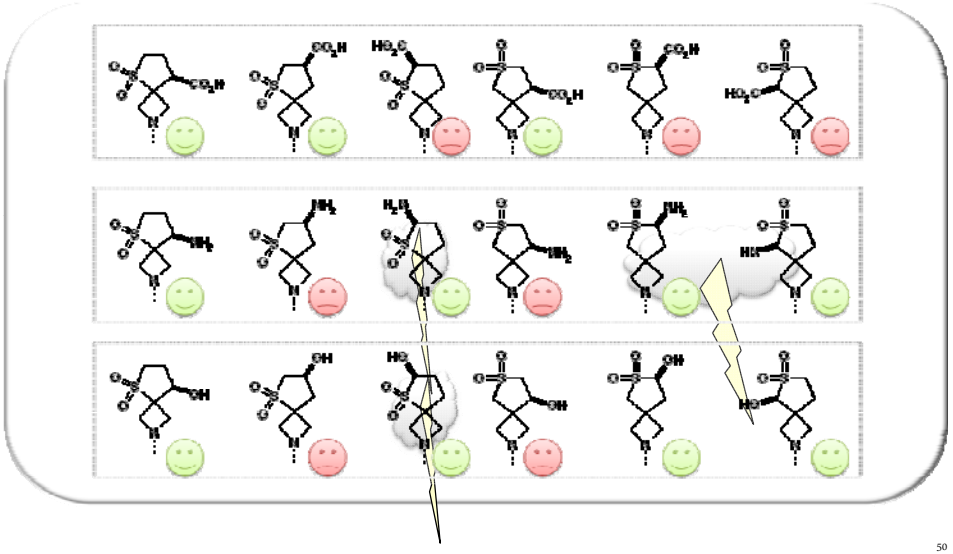
Proposed Drug Fragments



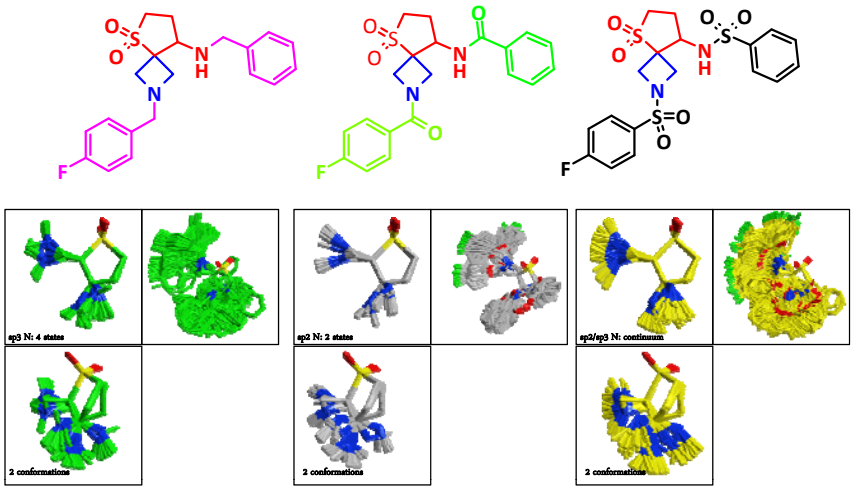
Nexium



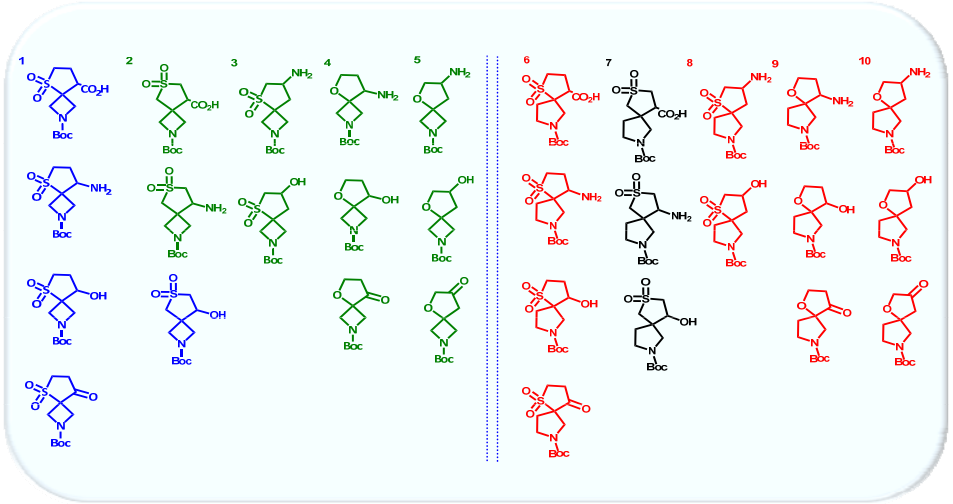
Idea=>Feedback=>Synthesis



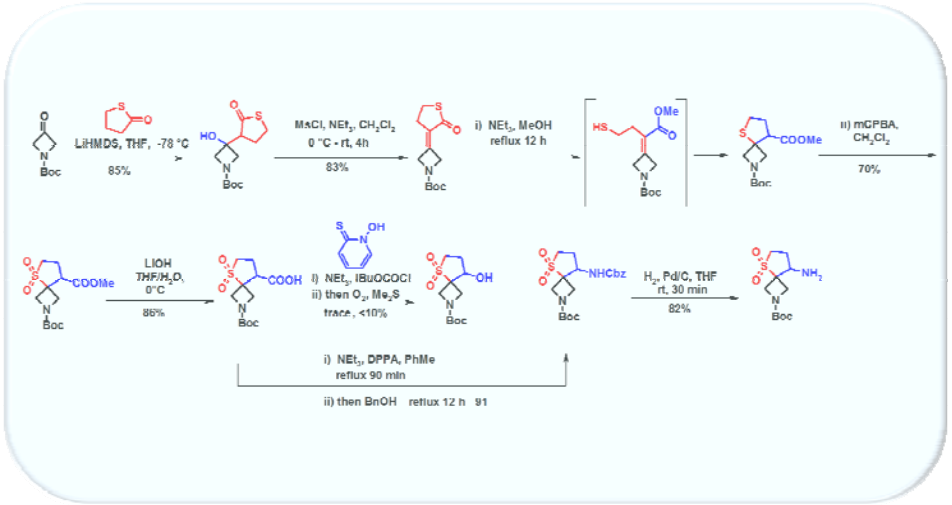
Multiple Conformations Dependent upon Substitution



30 Modules in 10 Columns



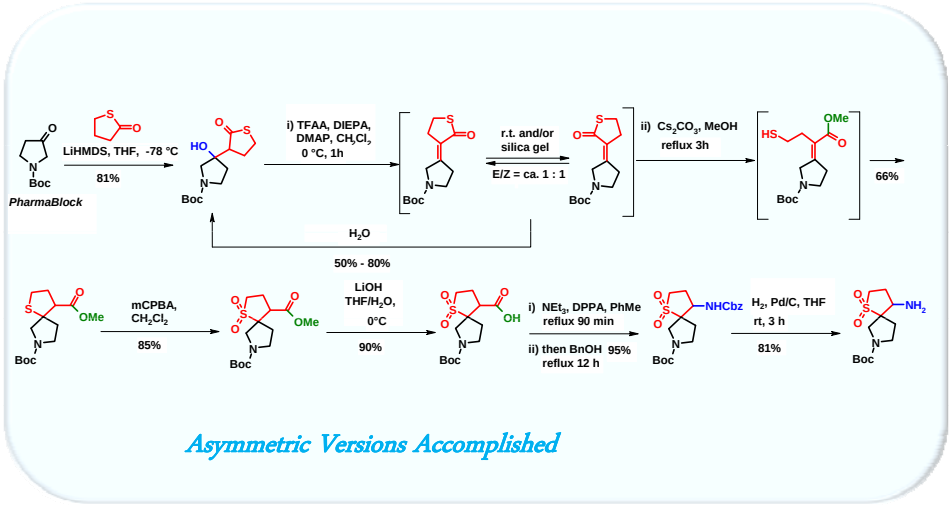
Example: Column 1



Synthesis of Novel Azaspiro[3.4]octanes as Multifunctional Modules in Drug Discovery

D.B. Li, M. Rogers-Evans*, E.M. Carreira*, *Org. Lett.* **2011**, *13*, 6134

Example: Column 6



Asymmetric Versions Accomplished

Manuscript in Preparation

D.B. Li, M. Rogers-Evans*, E.M. Carreira*, *2012*

CM: Need & Diversity ?

Oxetanes & Spiro-Oxetanes

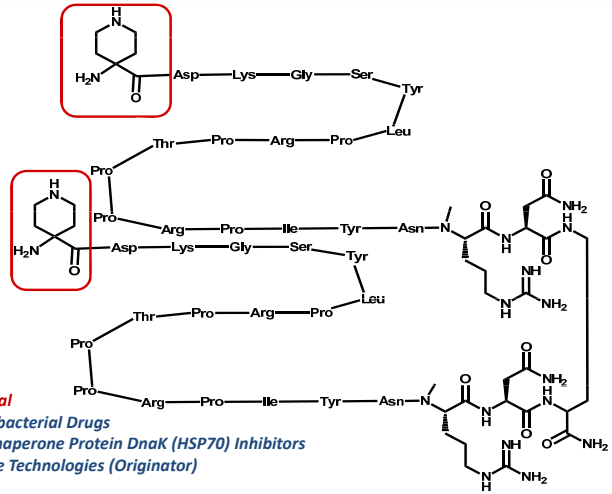
Spiro-Bisazetidines

Spiro-Cyclic Sulphonyl Modules

What Lies Ahead: Module Peptides & Phenotypic Screening

Modules in Peptides: A Plethora of Opportunities

CHP-105: a Pyrrhocoricin-Derived DnaK Inhibitor

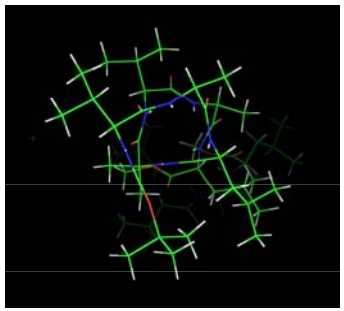


Drug Name: CHP-105
Highest Phase : Preclinical
Therapeutic Group: Antibacterial Drugs
Mechanism of Action: Chaperone Protein DnaK (HSP70) Inhibitors
Organization: Chaperone Technologies (Originator)

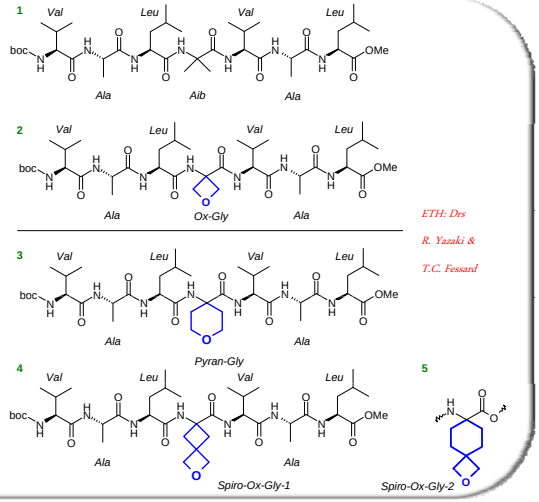
Activity of Levofloxacin Alone and in Combination with a DnaK Inhibitor against Gram-Negative Rods

P. C. Appelbaum *et al.*, *Antimicrob. Agents Chemother.* **2009**, *53*, 814

Module Analogues of the Balaram Peptide



Synthesis & Properties Complete; PK ongoing



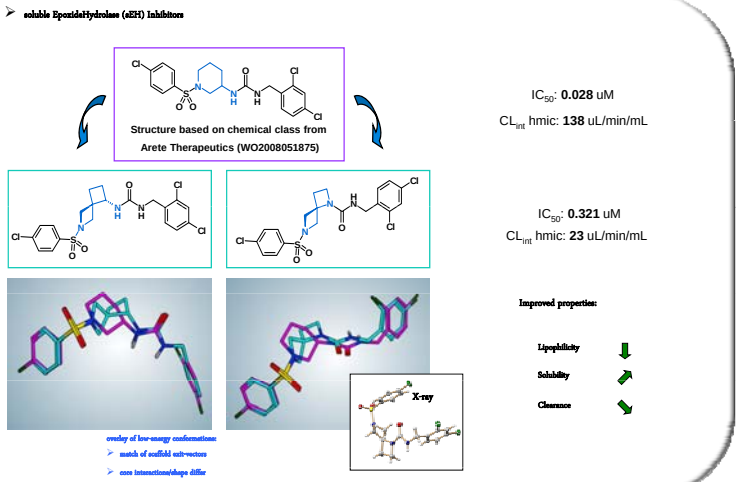
ETH: Drs R. Yazaki & T.C. Fessard

Unfolding of an alpha-helix in peptide crystals by solvation: conformational fragility in a heptapeptide

I. L. Karle, J. L. Flippen-Anderson, K. Uma, P. Balaram, *Biopolymers*,**1993**, *33*, 827

Concept: modules in biological relevant space

Objective: improving profiles of existing drugs



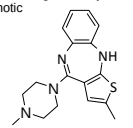
Application of Modules: the quest for sHE-inhibitors

H. Knust, S. Ceccarelli, T. Schulz-Gasch, C. Guérot: *patent application filed, manuscript in preparation*

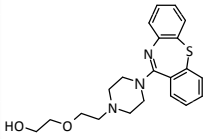
Concept: modules in biological relevant space

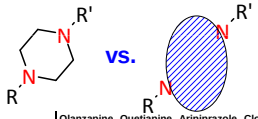
Objective: improve profiles & phenotypes of existing drugs

piperazine analog: **olanzapine** antipsychotic



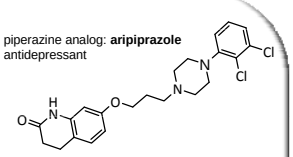
piperazine analog: **quetiapine** antipsychotic



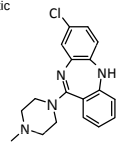


Data	Olanzapine	Quetiapine	Aripiprazole	Clozapine
5-HT1A_(h)	inactive	0.457	0.407	0.372
5-HT2A_(h)_(agonist_site)	0.005	0.062	0.389	0.011
5-HT2B_(h)_(agonist_site/DOI)	0.010	0.170	0.015	0.010
5-HT2C_(h)_(agonist_site)	0.020	inactive	inactive	0.076
5-HT3_(h)	0.398	inactive	inactive	0.871
5-HT6_(h)	0.035	inactive	0.331	0.014
5-HT7_(h)	0.229	0.603	0.955	0.083
5-HT_transporter_(h)	inactive	inactive	0.759	inactive
D1_(h)	0.058	inactive	inactive	0.095
D2S_(h)_(agonist_site)	0.014	0.380	0.309	0.151
D3_(h)	0.158	inactive	0.051	0.794
H1_(h)	0.046	0.039	0.257	0.004
H4_(h)	inactive	inactive	inactive	0.933
M1_(h)	0.037	inactive	inactive	0.016
M2_(h)	0.078	inactive	inactive	0.302
M3_(h)	0.151	inactive	inactive	0.251
M4_(h)	0.031	inactive	inactive	0.129
NE_transporter_(h)	inactive	inactive	inactive	inactive
sigma_(non-selective)	inactive	inactive	inactive	inactive
alpha_1B_(h)	0.026	0.009	0.065	0.003
alpha_2A_(h)	inactive	inactive	inactive	0.347
alpha_2B_(h)	0.708	0.141	inactive	0.042
alpha_2C_(h)	0.676	0.182	inactive	0.007
delta_2_(h)_(DOP)	inactive	inactive	inactive	inactive

piperazine analog: **aripiprazole** antidepressant



piperazine analog: **clozapine** antipsychotic



BIOPRINT-data from the respective drugs

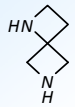
specific compounds not known in SCI-F; "kinked" bisazetidine derivatives also unknown, Jan 2011

CM at Roche: A Well Established Process

Proposed Evolution from Concept to Use

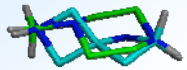
Stage 1:

CM Concept



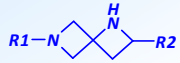
Stage 2:

Overlay

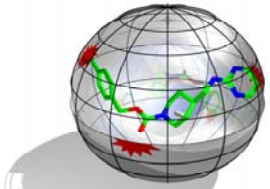


Stage 3:

Synthesis

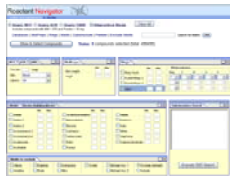


Stage 6:



Novel scaffolds allow access to non-traditional Chemistry space scanning pharmacological hot spots

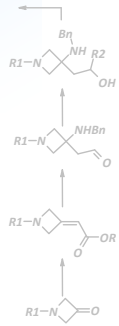
Stage 5:



RN allows Chem logic searching of modules & scaffolds filtered by calc. properties or top. similarity

Stage 4:

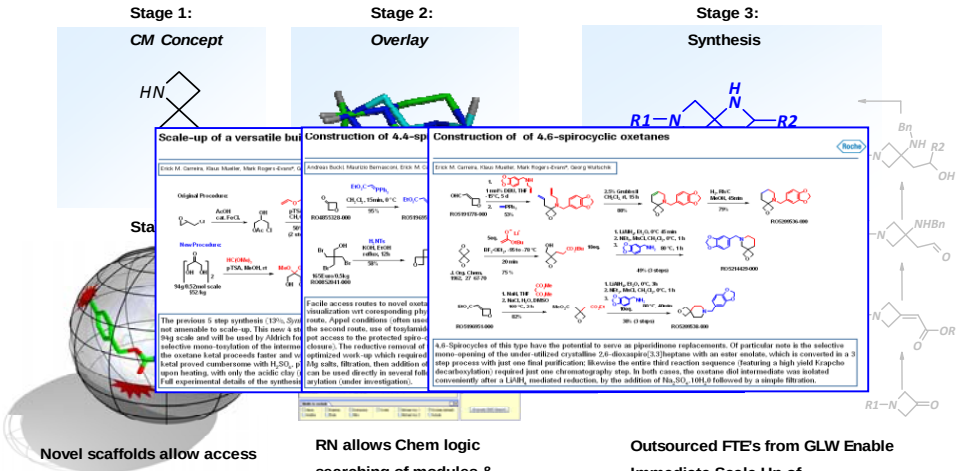
GLW



Outsourced FTE's from GLW Enable Immediate Scale Up of Research Syntheses for Project Use

CM at Roche: A Well Established Process

Proposed Evolution from Concept to Use

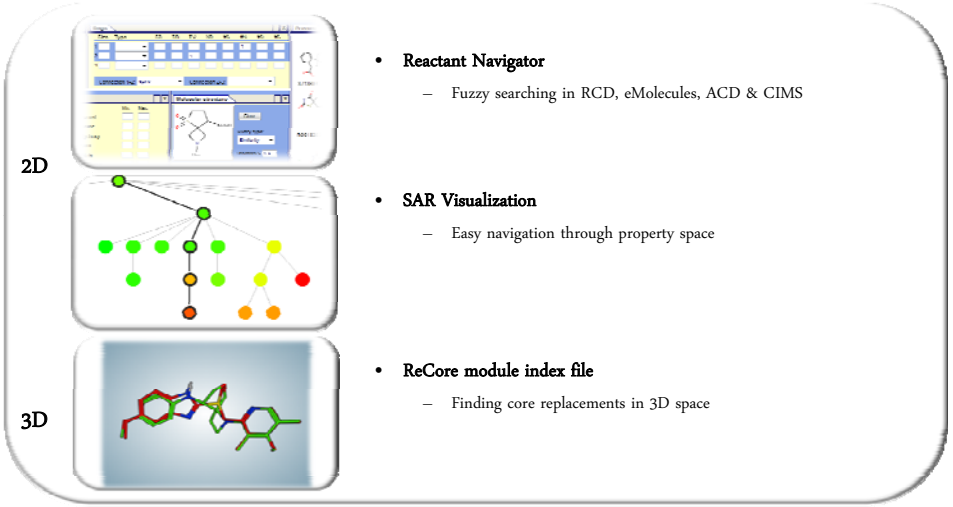


Novel scaffolds allow access to non-traditional Chemistry space scanning pharmacological hot spots

RN allows Chem logic searching of modules & scaffolds filtered by calc. properties or top. similarity

Outsourced FTE's from GLW Enable Immediate Scale Up of Research Syntheses for Project Use

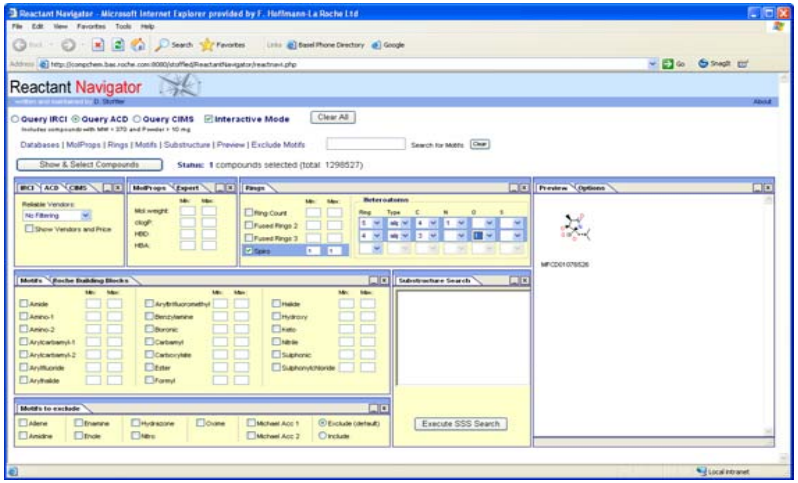
Searching & Navigating



- **Reactant Navigator**
  - Fuzzy searching in RCD, eMolecules, ACD & CIMS
- **SAR Visualization**
  - Easy navigation through property space
- **ReCore module index file**
  - Finding core replacements in 3D space

Compact Modules as Surrogates

Fuzzy Logic Non Structural Searching to ID Surrogates



Have Compact Modules Come of Age?