The Concept & Application of Compact Modules: From Oxetanes to Spiro-Oxetanes and Beyond

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IASOC, Monday 24th September 2012

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 ..."

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

The Properties of Known Drugs. 1. Molecular Frameworks

Structural Diversity of Organic Chemistry. A Scaffold Analysis of the CAS Registry
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...”

Interrogating Biological Space with Shape Diversity

Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules

The Need:

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

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...”
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?

CM: Need & Diversity ?

Ozetanes & Spiro-Ozetanes

Spiro-Bisazetidines

Spiro-Cyclic Sulphonyl Modules

What Lies Ahead
Concept 1:  
Modifying the properties of the underlying scaffold

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

Some Data Points: Oxetane V's gem-Dimethyl
Modifying the properties of the underlying scaffold

Oxetanes as Promising Modules in Drug Discovery
hERG binding: gem-dimethyl $\Rightarrow$ Oxetane

Modifying the properties of the underlying scaffold

hERG IC$_{50}$ = 7.5 $\mu$M

"...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 $\Rightarrow$ Important safety test!

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

Interaction with Cell Membranes

Modifying the properties of the underlying scaffold

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

Phospholipidosis: gem-dimethyl $\Rightarrow$ Oxetane

Modifying the properties of the underlying scaffold

$\Delta\Delta\text{GAM} = -8.3$ 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..."

Chemical Stability

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

Advanced Project Example: No Decomposition

(i) TiCl₄, CH₂Cl₂, -78°C, 2.5h
(ii) Ti(OEt)₄, THF, Reflux, 2h
(iii) MeLi/Me₃Al, Toluene, -78°C, 1h
(iv) 4N HCl, 0°C, Dioxane, 2h
(v) Fuming HNO₃/H₂SO₄, 0°C, 30min

R₁=H; EWG

Oxetanes as gem-Dimethyl Surrogates

Syntetically readily accessible versatile building blocks for ready incorporation

Metabolically robust chemically stable

effecting interesting property modulations

So What?

“...”
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 ..."

Discovery of novel tetracyclic compounds as anaplastic lymphoma kinase inhibitors


Discovery of novel tetracyclic compounds as anaplastic lymphoma kinase inhibitors


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

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

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..."

Oxetanes as Carbonyl Analuges

**H-Bond Strength**

<table>
<thead>
<tr>
<th></th>
<th>logK_H</th>
<th></th>
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<tbody>
<tr>
<td>MeCHO</td>
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<td>Acetone</td>
</tr>
<tr>
<td>MeOAc</td>
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**Construction of 4,6-Spirocyclic Oxetanes**

1. 1 mol% DBU, THF, -15°C, 5 d
2. 2.5% Grubbs II, CH2Cl2, rt, 15 h
3. H2, Rh/C, MeOH, 45 min

**C=O to Oxetane**

**Application to Marketed Drugs**

**Thalidomide/Revlimid**
- Lepra 1998
- Multiple Myeloma 2006
  - Celgene

**Oxetane-Thalidomide**
- Configurationally Stable
  - Oxetane Variants

**Oxetane-Revlimid**

**New Opportunities for Four-Membered Heterocycles**
- J. A. Burkhard, Ph. D. Dissertation, ETH Zurich, 2011
C=O to Oxetane

Predicted Retention of Potency

Morpholine vs. Oxetane

New Opportunities for Four-Membered Heterocycles

J. A. Burkhard, Ph. D. Dissertation, ETH Zurich. 2011

Construction of 4,4-Spirocyclic Oxetanes

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

CM: Need & Diversity?

Oxetanes & Spiro-Oxetanes

Spiro-Bisazetidines

Spiro-Cyclic Sulphonyl Modules

What Lies Ahead

Evolution of Roche-ETH Collab.

Drug Discovery Graduate Program => Roche Funded Postdoc

2005-2008

2009-2011
The Chemical Modules Story

Starts with Oxetanes …

From linear to angular bis-azetidines

A variety of opportunities

Synta and Novel!

Commercial and Novel!
Top two novel compounds targeting (AD)

EC50: 13 nM

Top two novel compounds targeting (AD)

EC50: 13 nM

IC50: 0.1

EC50: MAB (h/m): 65 / 25 %

PK mice

Clearance: 105 ml/min/kg

Brain/Plasma: 3.4

Safety

Bioavailability

GSH:

MNT & Ames:

Phy-chem

What Lies Ahead

Evolution of Roche-ETH Collab.

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

CM: Need & Diversity?

Oxanes & Spiro-Oxetanes

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What Lies Ahead
Future Spiro-Modules

Proposed Drug Fragments

Multiple Conformations Dependent upon Substitution

30 Modules in 10 Columns
Synthesis of Novel Azaspiro[3.4]octanes as Multifunctional Modules in Drug Discovery

Asymmetric Versions Accomplished
Manuscript in Preparation
D.B. Li, M. Rogers-Evans*, E.M. Carreira*, 2012

Modules in Peptides: A Plethora of Opportunities

CHP-105: a Pyrrhocoricin-Derived DnaK Inhibitor

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What Lies Ahead: Module Peptides & Phenotypic Screening

Activity of Levofloxacin Alone and in Combination with a DnaK Inhibitor against Gram-Negative Rods
Module Analogues of the Balaram Peptide

Objective: improving profiles of existing drugs

Application of Modules: the quest for sEH-inhibitors

H. Knust, S. Ceccarelli, T. Schulz-Gasch, C. Guedini; patent application filed, manuscript in preparation

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

BIOPRINT-data from the respective drugs
specific compounds not known in SCLP; "tested" bisazetidin 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 4:
Outsourced FTE’s from GLW Enable Immediate Scale Up of Novel scaffolds allow access to non-traditional Chemistry space scanning pharmacological hot spots

Stage 5:
Research Syntheses for Project Use

Stage 6:
RN allows Chem logic searching of modules & scaffolds filtered by calc. properties or top. similarity

Outsourced FTE’s from GLW Enable

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?

YES!