

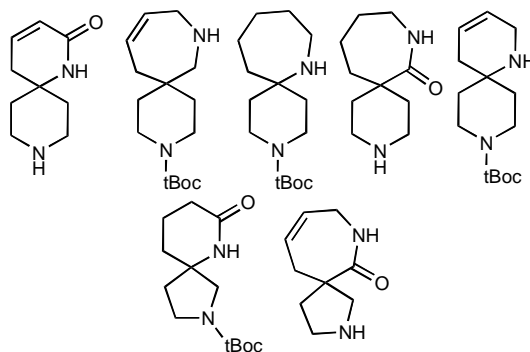
## Alkene Metathesis, a Peakdale Perspective.

### Ray Fisher

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A brief history of Peakdale's introduction to Olefin Metathesis was given, leading up to the decision to undertake a collaboration with Materia. The purpose of the collaboration is to introduce a series of pharmaceutically relevant intermediates designed to increase the awareness of the small molecule drug discovery industry in olefin metathesis.

A series of spirodiamines was unveiled as the first series in this collaboration which includes:



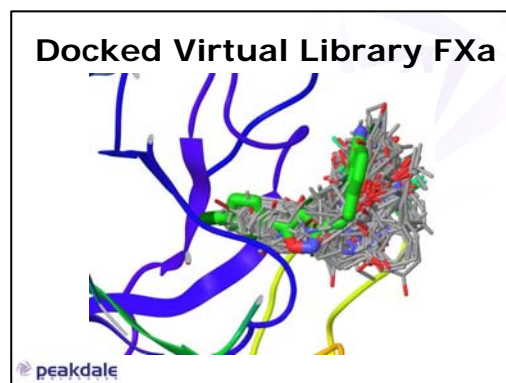
**Figure 1**

This first series has been introduced after consideration of the access to new drug space which Olefin Metathesis makes available. These, and the other examples are now, or soon will be, commercially available in research quantities

Parallels were shown between the types of molecules which had been traditionally generated through high throughput chemistry using, for examples, Suzuki and Buchwald chemistry, but which tended towards flat, two dimensional molecules where the OM molecules have a much more 3 dimensional feel to them.

A demonstration of fragment docking methodology was then given showing the exciting potential of these spirodiamines in a number of protein targets and concluded with the construction of a small virtual library of potential molecules which gave a high affinity profile to a specific protein target shown clustered around a known drug. (Figure 2).

Peakdale and Materia are looking forward to the impact this new class of intermediate molecule will have on the drug discovery industry and to introducing other series in the relatively near future.



**Figure 2**



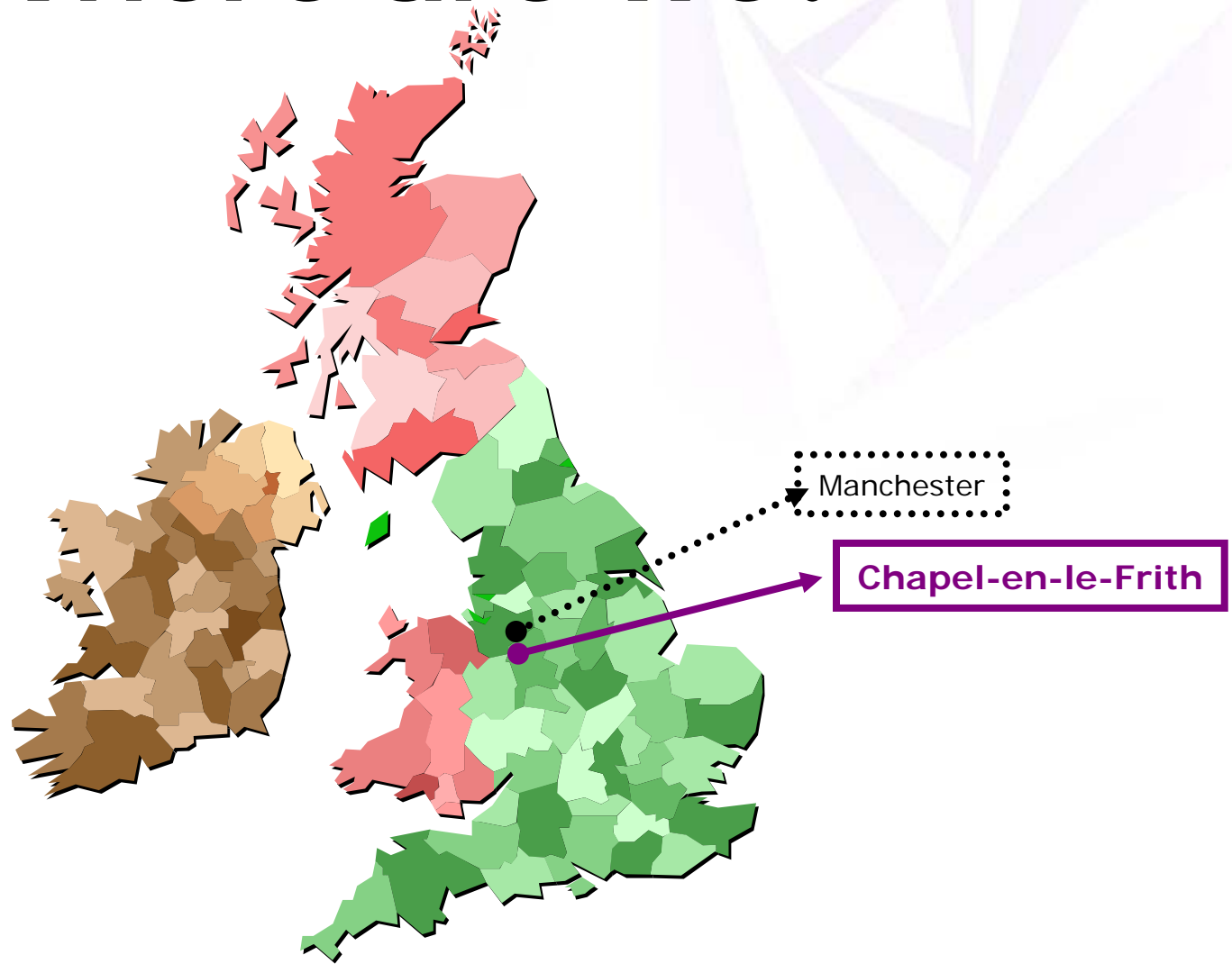
# **Alkene Metathesis A Peakdale Perspective**

**ISOM XVII 31 July 2007**

# Peakdale Site



# Where are we?



# Peakdale Site

- Purpose built 2001
- Phased roll out
- 12 staff → 45  
(Phase I)
- Currently 80 staff,  
60 chemists  
(Phase II)
- Double number of  
chemists in next  
18 months.



# Peakdale Products

- **Chemical contract research**
- **Primarily service provider**
  - Capable of generating own IP
- **Present customers**
  - Mainly large pharma (18 of top 20)
  - Expanding customer base into Biotechs
- **Offering MedChem & CADD services**
- **Expect to add ADME services soon**
- **Main area → small molecule drug discovery arena**

www.peakdale.co.uk

The screenshot shows a Windows Internet Explorer browser window displaying the Peakdale Molecular website. The browser's address bar shows the URL <http://www.peakdale.co.uk/>. The website features a dark blue navigation bar with the following menu items: Home, About Us, Products, Services, Collaborations, Contact Us, and Enquiries. The main content area is divided into several sections:

- Header:** The Peakdale Molecular logo is prominently displayed.
- Text:** A paragraph states: "Peakdale Molecular offers a range of products and services to its pharmaceutical and biotechnology customers to accelerate their drug discovery initiatives. The Company's approach is based upon its strength in synthetic organic chemistry and the desire to further research through novel compounds and methodologies."
- Image:** A photograph shows three scientists in a laboratory setting, working at a workstation.
- Section: Products and services include:**
  - **Exclusive custom synthesis** carried out either on a project basis or under a fixed term contract.
  - **Peakexplorer™ screening libraries** - highly diverse drug-like compounds for screening against GPCR targets.
  - **Intermediates catalogue** of over 550 non-exclusive compounds spanning drug discovery, synthetic, organic, analytical and medicinal chemistry.
  - **Medicinal chemistry services** providing external resources to complement customers' research either on an FTE arrangement or project basis.
  - **Peakfinder™ kinase chemogenetic arrays** focused yet novel compounds designed to accelerate the development of robust lead molecules.
- Section: PRODUCTS**
  - Intermediates Catalogue
  - Screening Compounds
  - peakexplorer™ - GPCRs
  - peakfinder™ Kinase Arrays
- Section: SERVICES**
  - Medicinal Chemistry
  - Custom Synthesis
  - Computational Chemistry
  - Analytical Services
- Section: LATEST NEWS**
  - 01/05/07** Peakdale Molecular and EnBioTec enter an agreement to develop nuclear receptor based lead compounds.
  - 01/03/07** Peakdale Molecular announces collaboration to commercialize Metathesis-Based privileged scaffolds with Materia Inc.

At the bottom of the main content area, there is a link for [New Opportunities](#). The browser's status bar at the bottom indicates the page is viewed in Internet mode at 100% zoom.

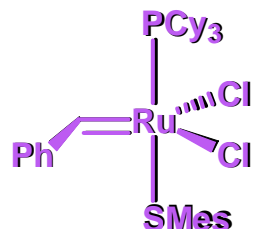


# **LINK ACCP Initiative**

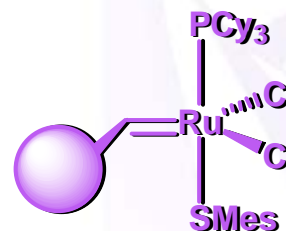
**(Applied Catalysis and Catalytical Processes)**

**In collaboration with GSK  
and Imperial College**

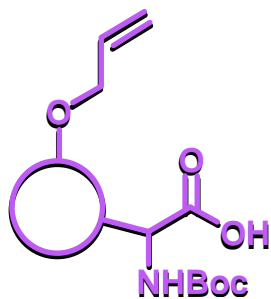
# Link Initiative



Grubbs' 2<sup>nd</sup>  
generation catalyst



Polymer available  
catalyst.  
'Boomerang catalyst'



alpha-Amino acid  
scaffold

Library of  
macrocyclic peptidic  
compounds for  
screening

ACCP News, 2001, No.4, pp4-5

A G M Barrett et al Synlett, 2000, pp 1007-1009

# Incidentally ....

- **Phenyldiazomethane**
  - ➔ Needed to produce the Grubbs' 1st generation catalyst
  - ➔ which was needed to produce the 2nd generation catalyst.
  - ➔ unpurified phenyldiazomethane solutions giving poor results
  - ➔ Decided to distil the phenyldiazomethane
  - ➔ Hazard!
  - ➔ Great care was taken and the pure, cold, bright red liquid was used immediately
- **The results were impressive and the stability of the catalyst so produced was markedly improved**

**Could alkene metathesis be used  
by Peakdale in its everyday work?**

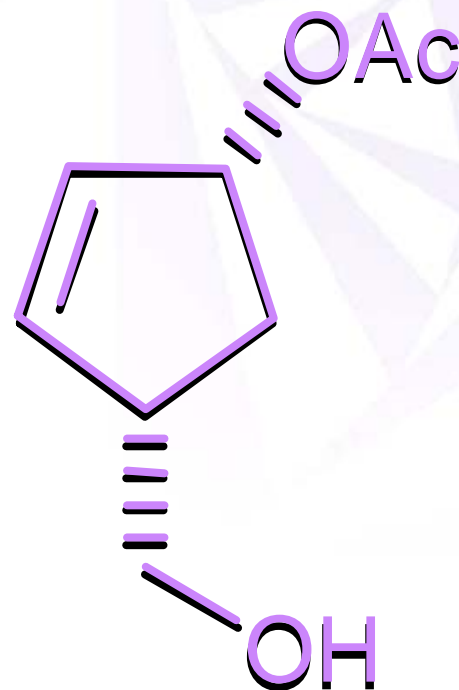
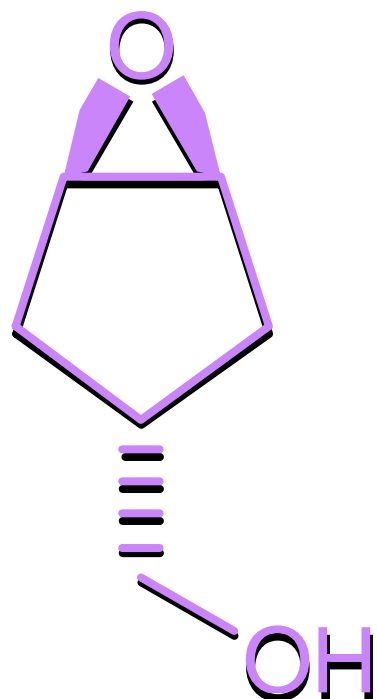
**Used to prepare polymers, macrocycles  
/ large molecules**



**of little interest to Peakdale**

# Other concerns

- **Metathesis – potential for great complexity**
- **Catalysts not easy to make and if bought could become expensive**
- **Potential for low levels of ruthenium contamination**
- **We did note down a number of attractive small molecules that could be useful**
- **Shelved this area ... until 4 years later ....**



**Identified as prospective useful intermediates for preparing carbocyclic sugar mimetics in a investigative nucleoside programme. A common intermediate was identified ....**



# Investigative work for Custom Synthesis

- Found other uses for OM in our work
- Ran out of stocked catalyst
- Visited Materia
- Started purchasing 1<sup>st</sup> & 2<sup>nd</sup> generation catalyst from Aldrich
- As catalyst use ↑ Materia contacted us to discuss collaboration further

# What form should the collaboration take?

- **Strengths of two companies**
  - Peakdale has a good
    - Understanding of small molecule drug design
    - Level of expertise in synthetic organic chemistry
  - Materia has a good
    - Understanding of all aspects of OM through both its unparalleled academic support and in-house expertise
    - Access to the various catalysts
- **After consideration of above, decided to make series of novel pharmaceutical intermediates to promote use of OM in small molecule drug discovery industry**

# How do we make collaboration successful?

- **Needed to analyse what makes a good Pharmaceutical Intermediate**
- **Small molecule drugs usually built up in sequence from**
  - Cores (aka scaffolds)
  - and
  - Caps (aka decoration)

# Cores

## ➤ Usually ...

- possess 2 or more functional groups/attachment points
- **Not** too large (MW < 200)
- **Not** long or straight chains containing many rotatable single bonds
- **Should** contain a few heteroatoms  
→ some polar surface area
- **Should not** contain any substructure with ADMET problems

# Caps

- Usually ...
  - smaller than cores, add on via cores functional groups/attachment points
  - **Not** too large (MW < 150)
  - **Not** long or straight chains containing many rotatable single bonds
  - **May** contain a few heteroatoms → some polar surface area but can be lipophilic groups
  - **Should not** contain any substructure with ADMET problems



# Features of modern drugs

- Previous examples are flat, mainly two dimensional structures with limited use of the 3<sup>rd</sup> dimension
- Combinatorial chemistry → impacting on numbers of small molecules which could be screened against drug targets
- Powerful new synthesis technique, Suzuki coupling emerging
- Gave access to carbon-carbon bond formation between aromatic compounds (otherwise hard to achieve)
- Buchwald methodology adds heteroatom-aromatic carbon atom bond formation
- You have the tools which can generate 10<sup>x</sup> new molecules in short order
- Needless to say a good few of these have been made.
- The attraction of the type of structure that usually emerges from these techniques is that the molecules produced are fairly flat, describing two dimensions well but the third can be quite restricted
- As it happens this type of molecule can fit fairly well into most of the known drug target structures

# Question

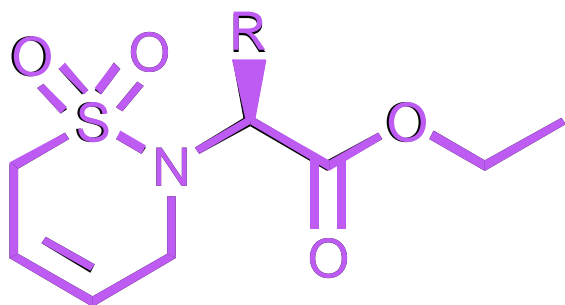
- **Are modern drugs the shape they are because of the techniques available for their construction**

**OR**

- **Are those shapes inherently suitable to be effective against the various known drug targets?**

**Is there a particular  
shape of small molecule  
favoured by alkene  
metathesis?**

# Examples of Core Structures

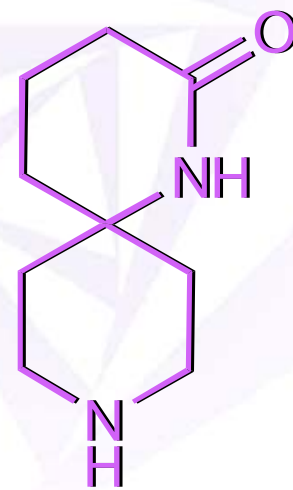
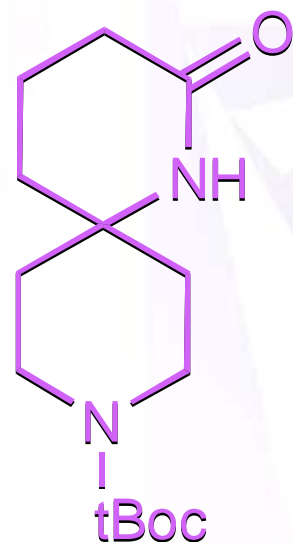
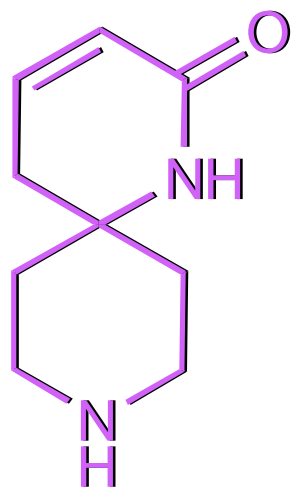
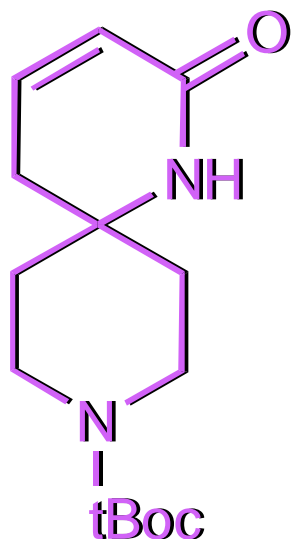


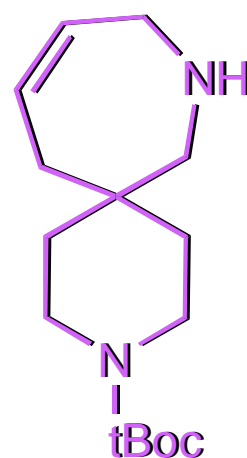
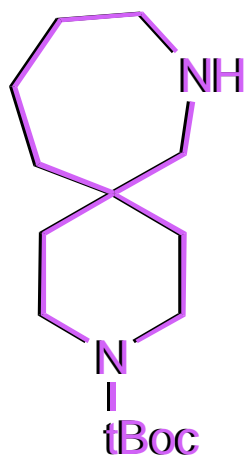
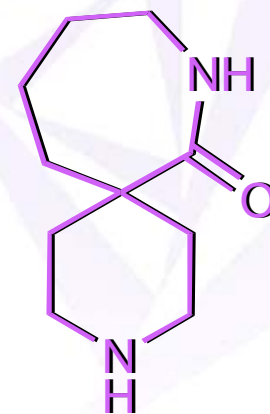
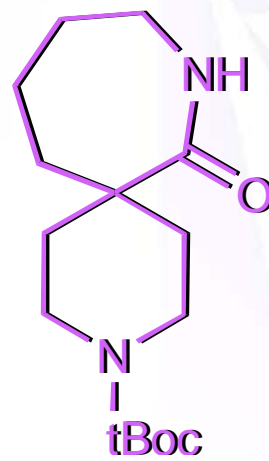
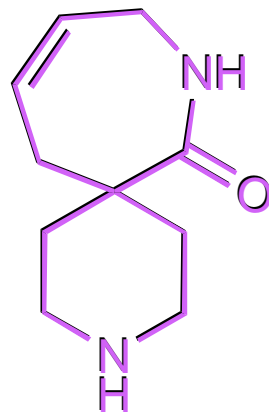
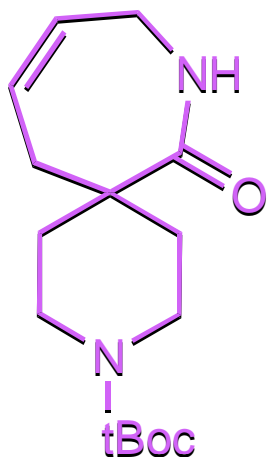
Tet. Lett., 1999, 40, 4761



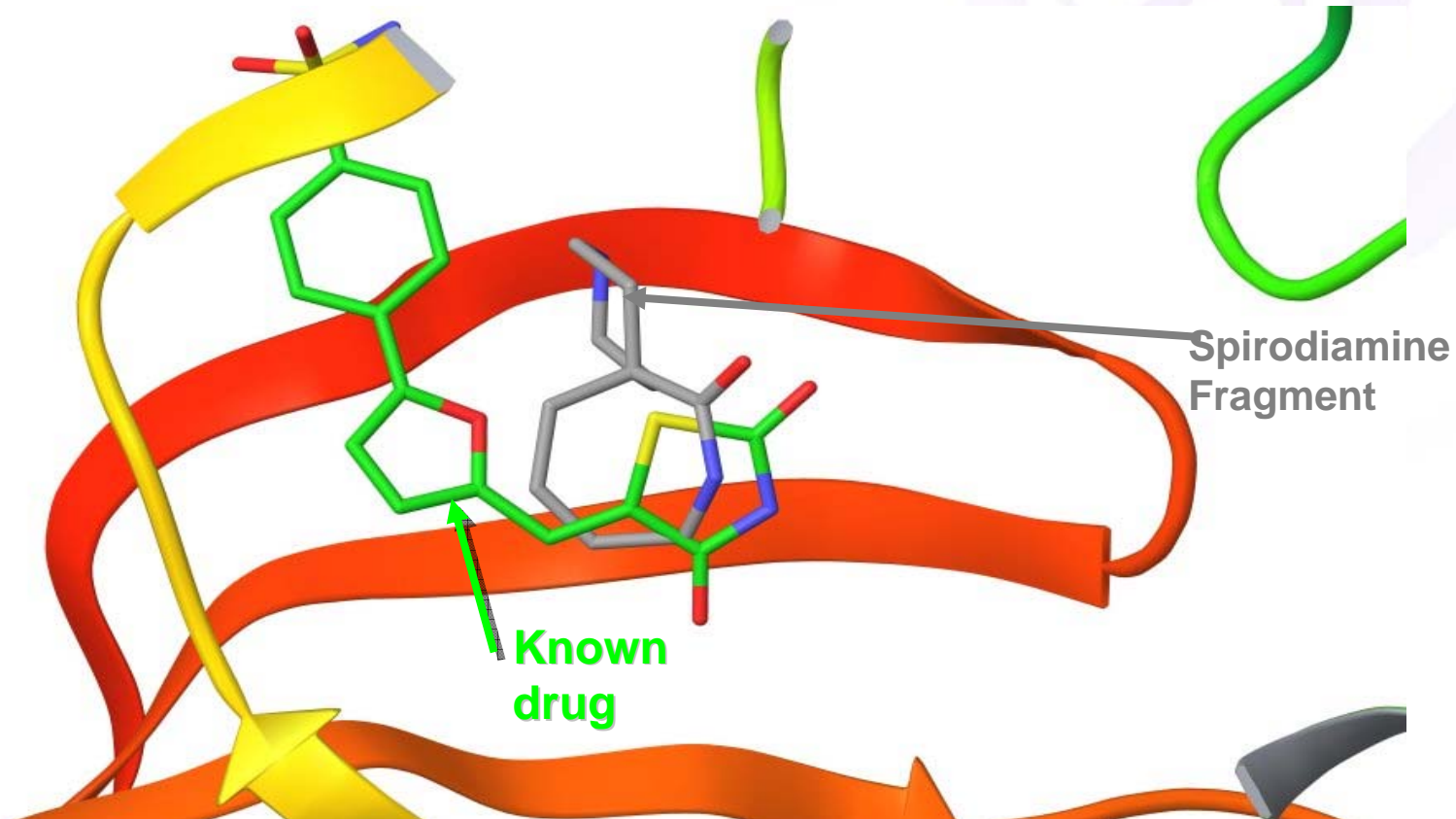
Walters JCC 2002, 4, 125

# Peakdale/Materia Collaboration First Series



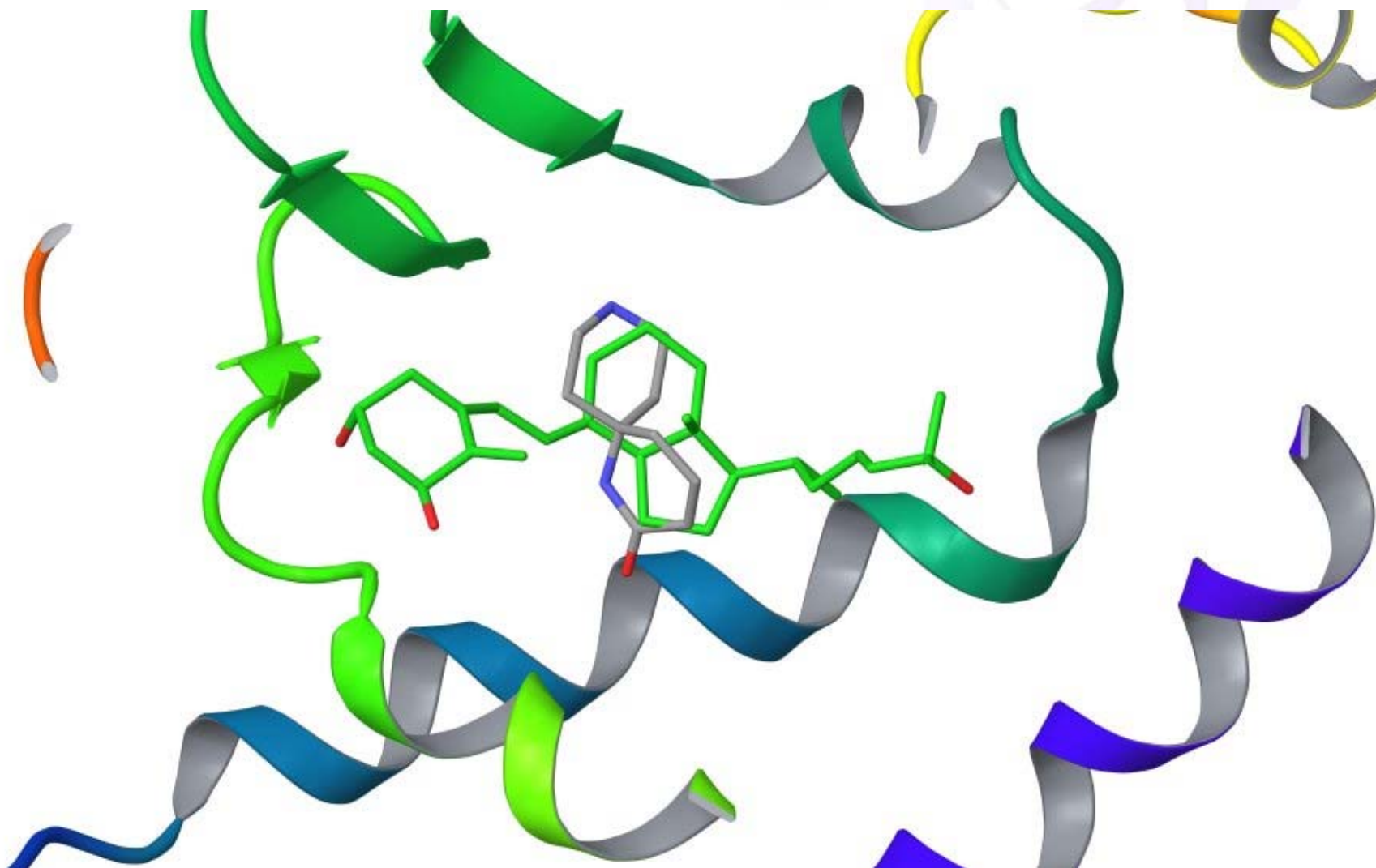


# Fragment Docking into Cyclin-Dependent K2 (Kinase)

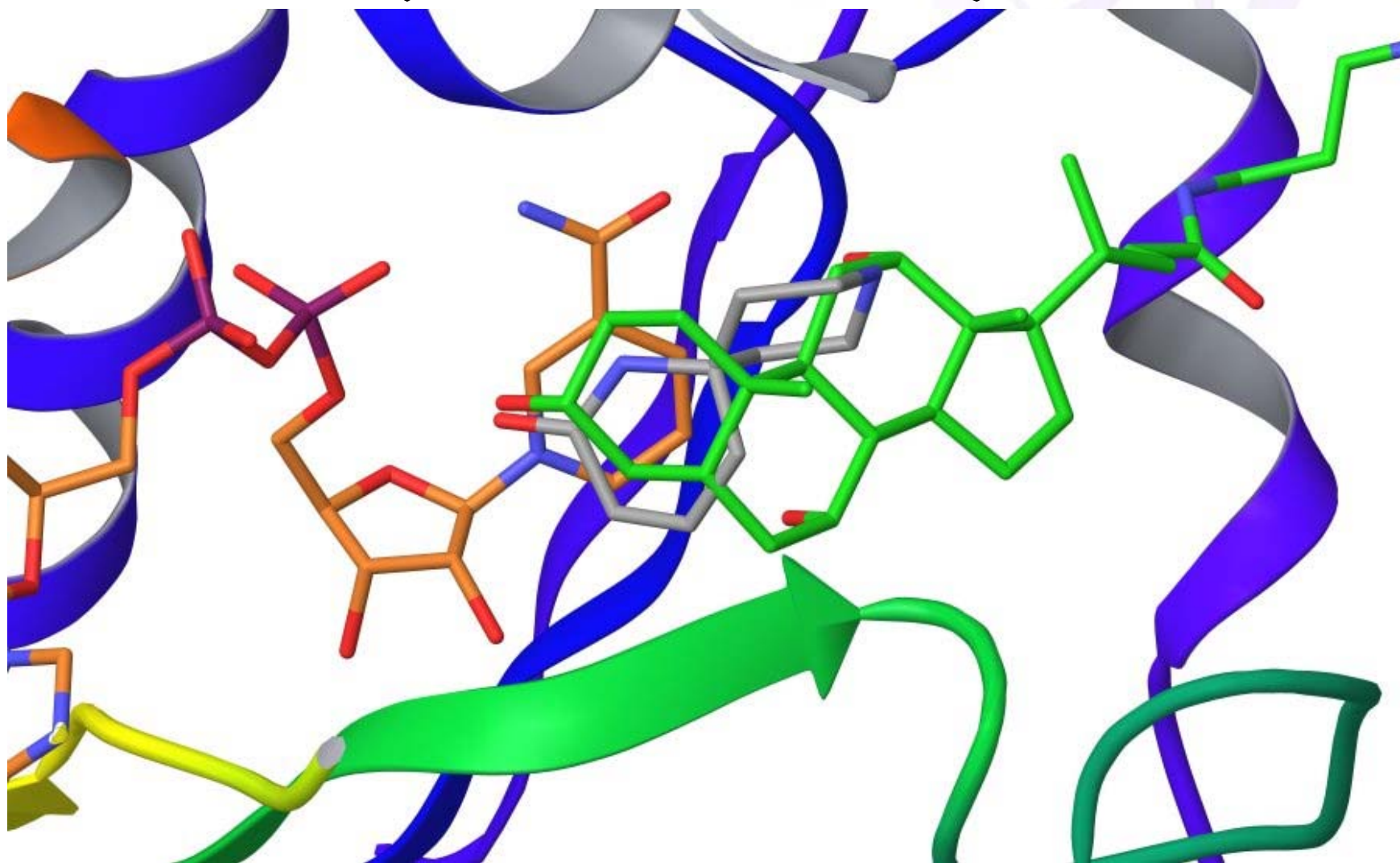


X-Ray Crystallography allows us to visualise the docking pose of a known drug at the binding site of the protein target. Here is an example of one of the first series of “cores” allowed to settle into lowest energy mode by computational analysis.

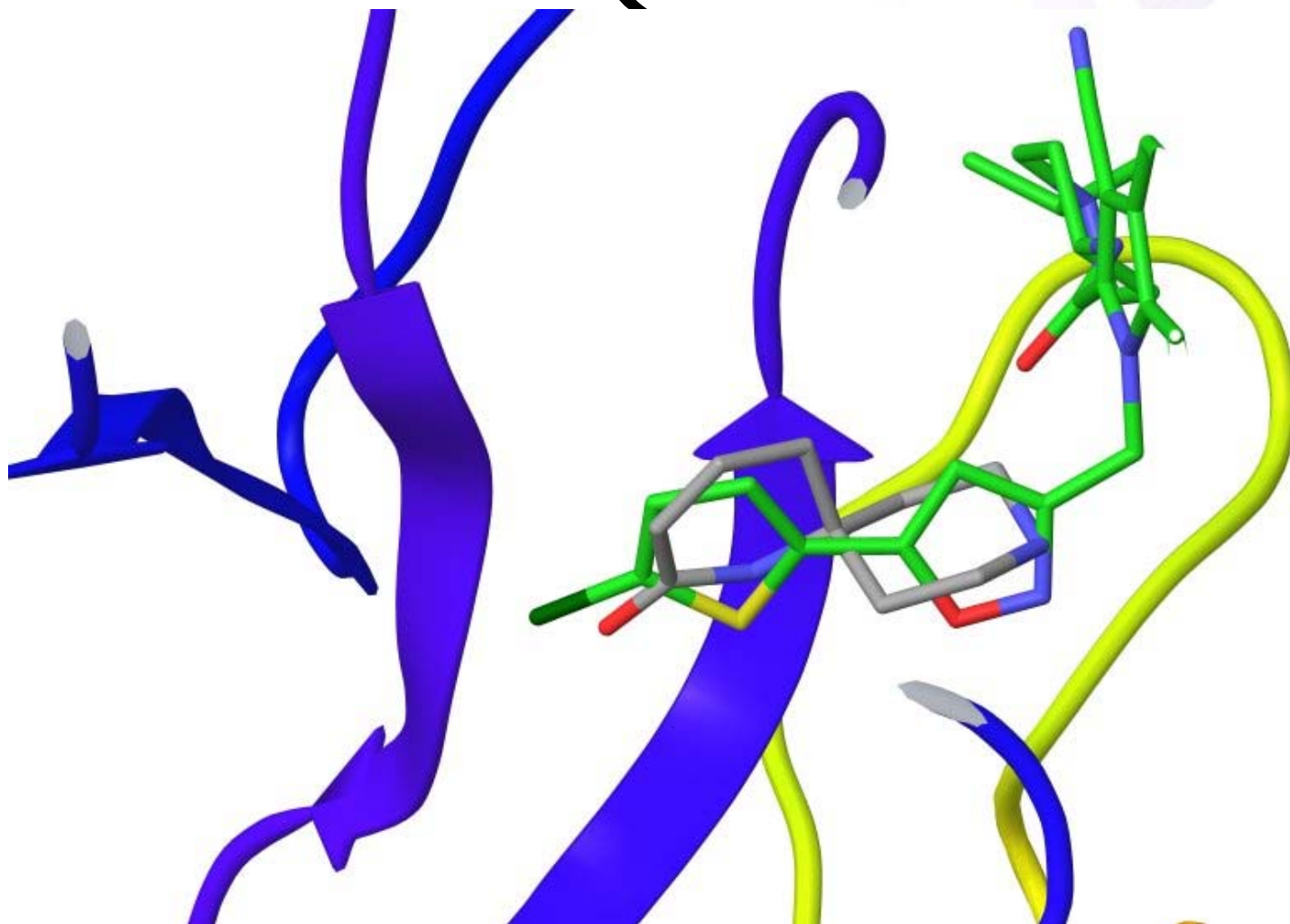
# Fragment Docked into the Nuclear Receptor for Vitamin D



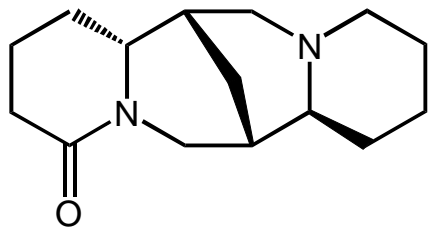
# Fragment Docked into the 11 Beta Hydroxysteroid Dehydrogenase Type 1 (Steriodal Mimics)



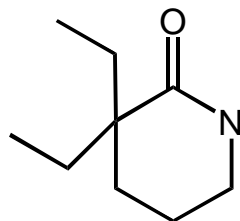
# Fragment Docking Into Factor 10a (Serine Protease)



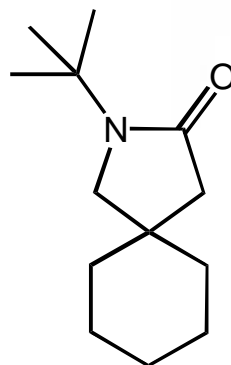
# Similarity Based Screening



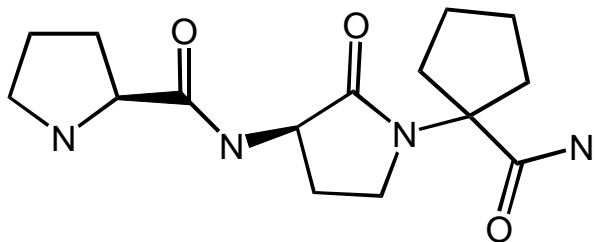
Lupanine  
Type 2 Diabetes



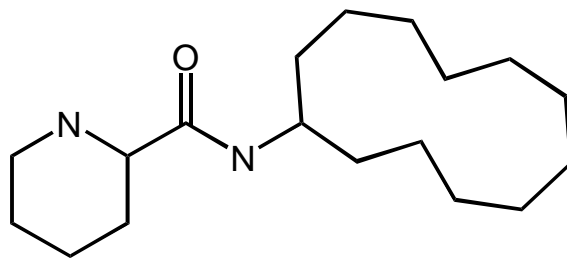
8-tert-butyl-Gabapentin-lactam  
Antiepileptic



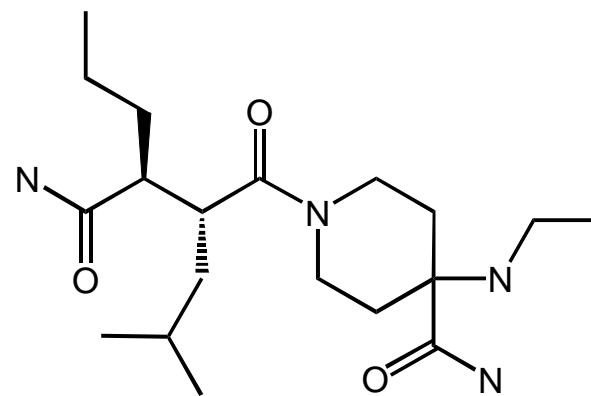
AF-134  
Cognition Disorders



Antiparkinsonian



Antiallergy / Antiasthmatic

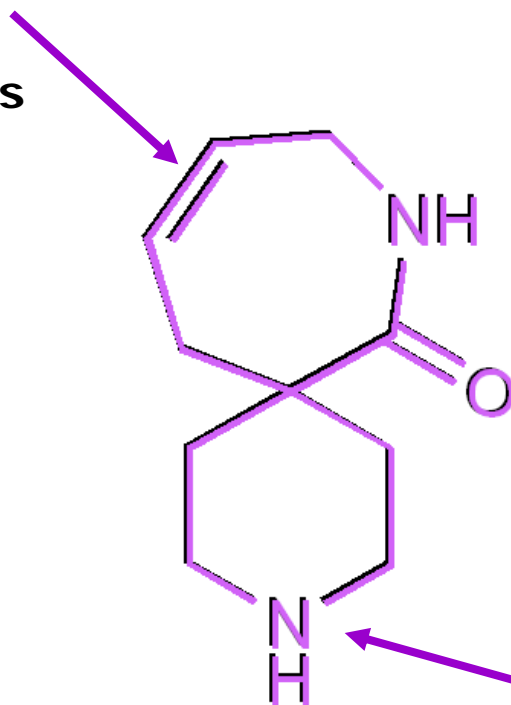


Alzheimer's

# Example of Virtual Library Creation

~500 Cmpds

Epoxidation  
Grignard Reagents  
RMgBr



~500 Cmpds

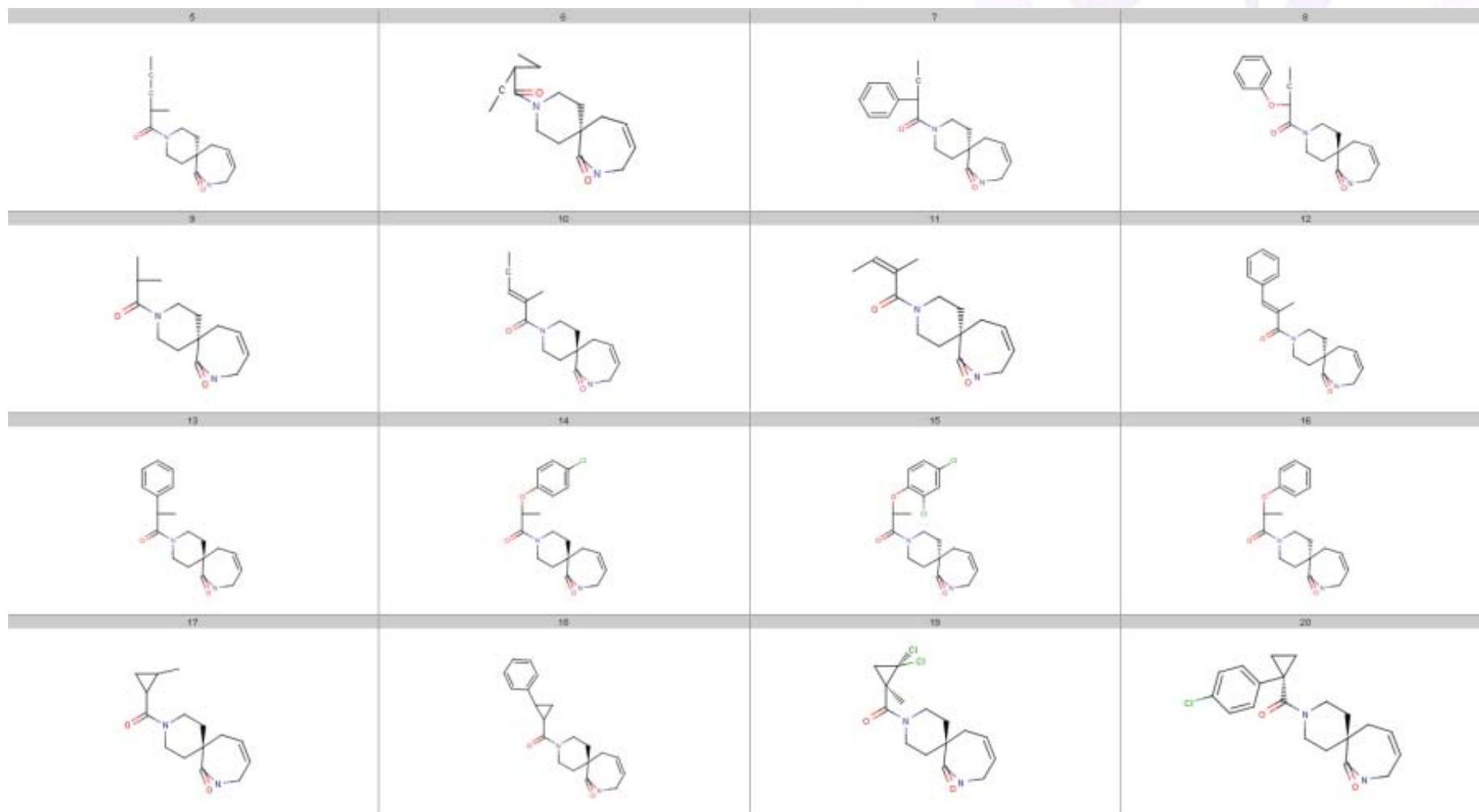
N-Alkylation R-Cl

~4000 Cmpds

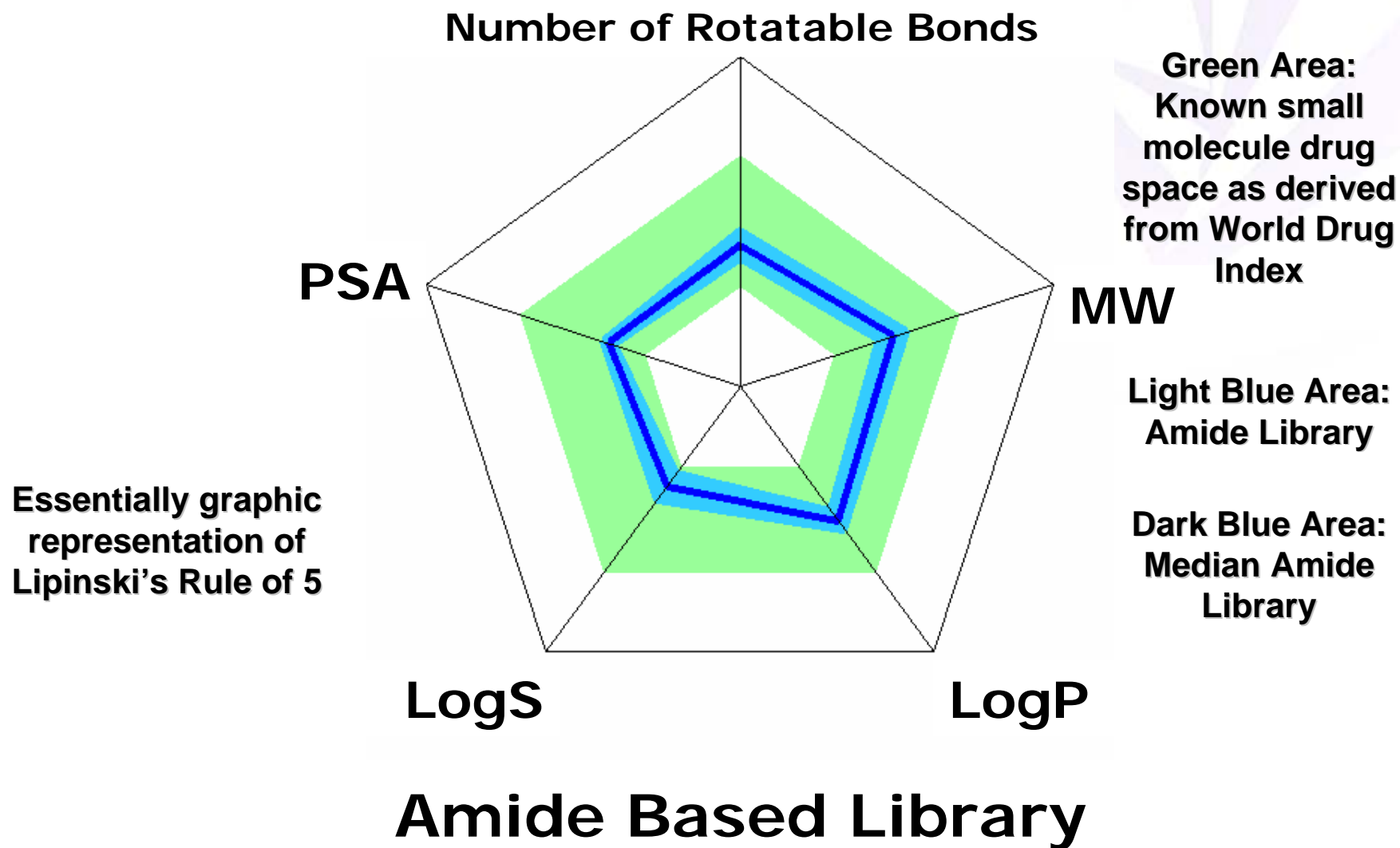
Amide Formation  $\text{RCO}_2\text{H}$

Approximately  $1 * 10^9$  Compounds

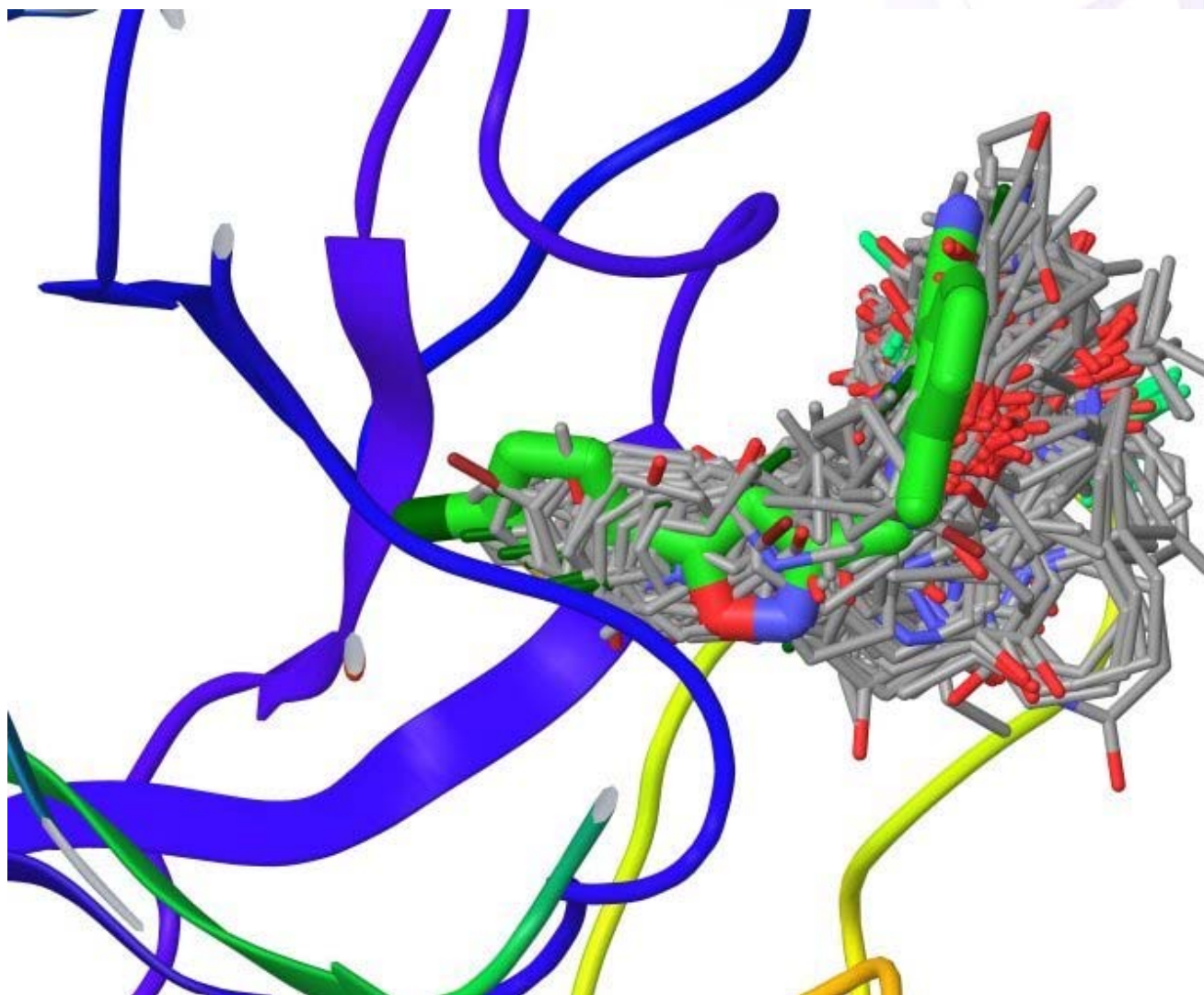
# Virtual Amide Library



# PeakRadar Plot of Library



# Docked Virtual Library FXa



# Conclusion

- **Have designed a useful new platform for development of future drugs**
- **Requiring alkene metathesis**
- **Looking forward to future series**

# Thanks to

- **Materia for the invitation, especially Dick Pedersen and John Kibler**
- **Colleagues at Peakdale, David Dawkins, Paul Beagley, Richard Fox and, our CADD team, particularly Andy Smith**
- **Caltech as hosts of the conference**
- **And thanks for your attention**