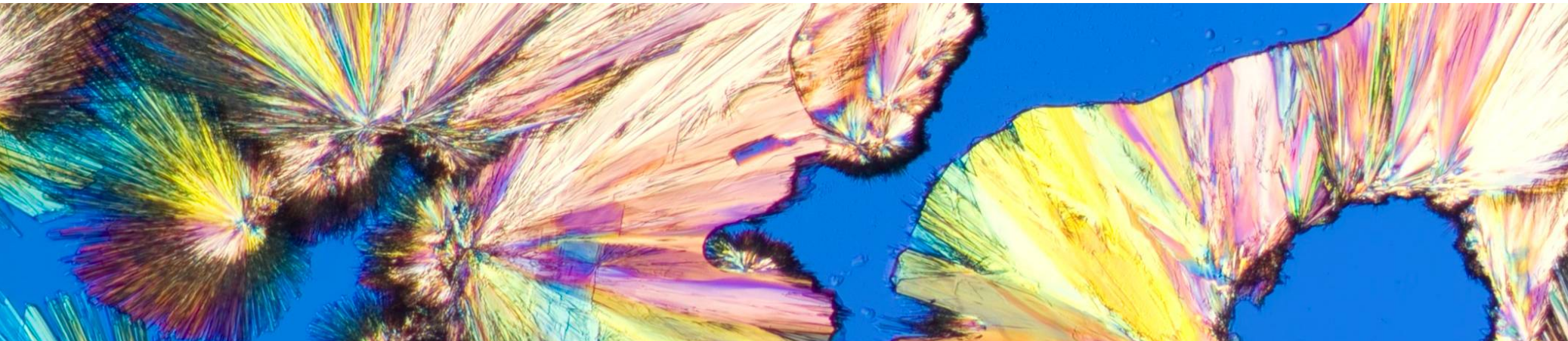
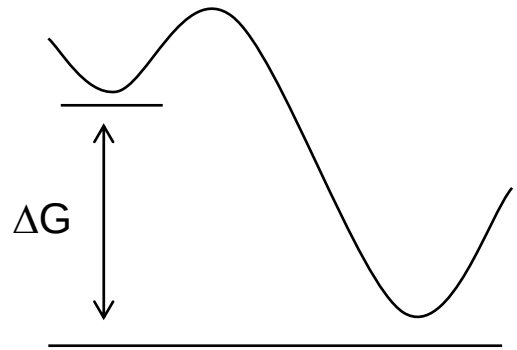
What Crystal Structure Databases Tell us about Conformations of Drug-like Molecules

Martin Stahl, Roche Basel, June 2008



Conformational Energies Matter

Strained Bioactive Conformations Affect Binding Energy



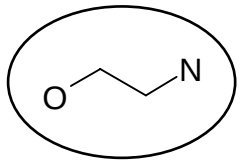
bioactive conformation

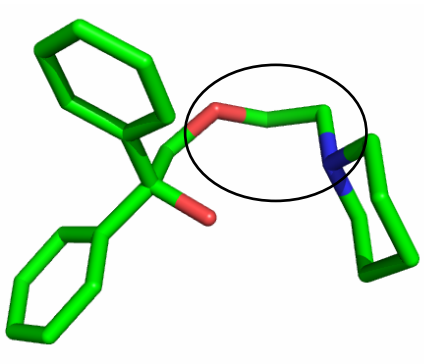
global minimum In solution

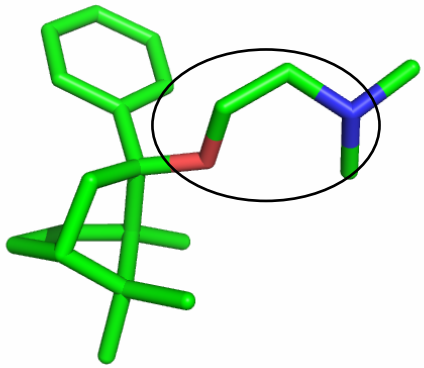
ΔG = 0.5 kcal/mol	→	factor 2.3 affinity reduction
ΔG = 1.0 kcal/mol	→	factor 5.4 affinity reduction
ΔG = 2.0 kcal/mol	→	factor 30 affinity reduction
ΔG = 3.0 kcal/mol	→	factor 160 affinity reduction

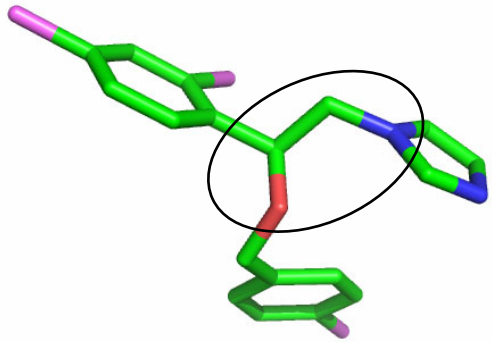
Required Generalizations

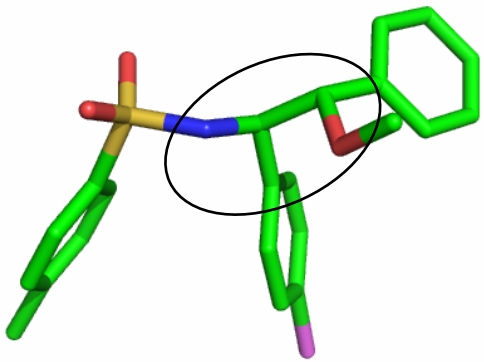
Statistics over Recurring Fragments

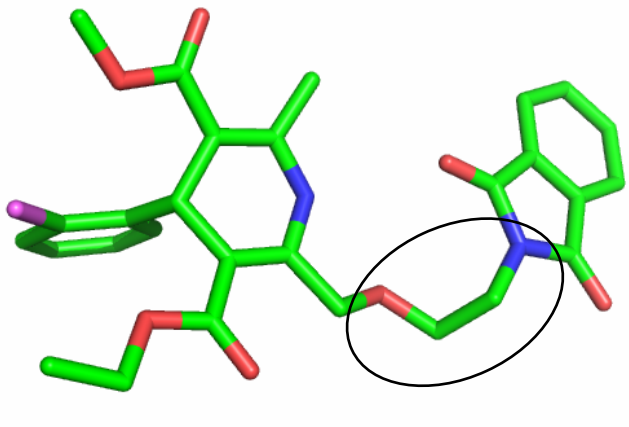


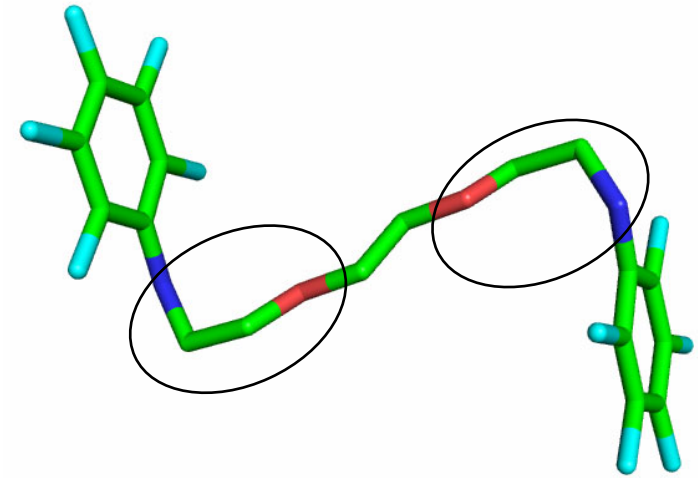


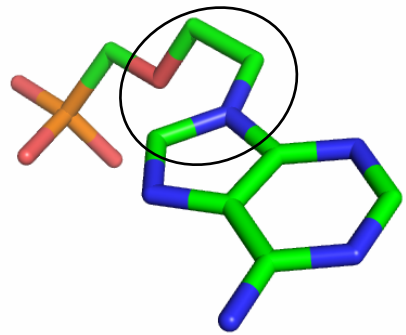




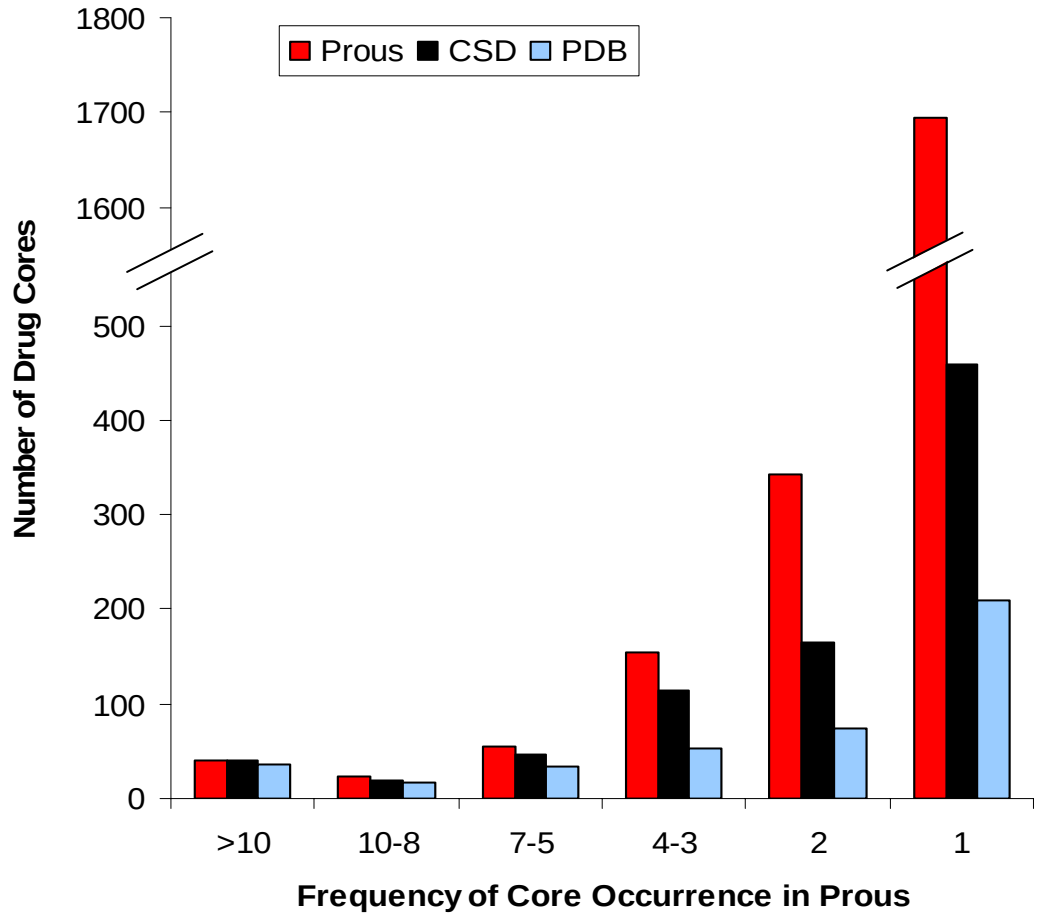








Coverage of Relevant Substructures In Crystal Structure Databases



Cis or Trans? From Amides to Electrostatic Repulsion

Generalized Allylic Strain

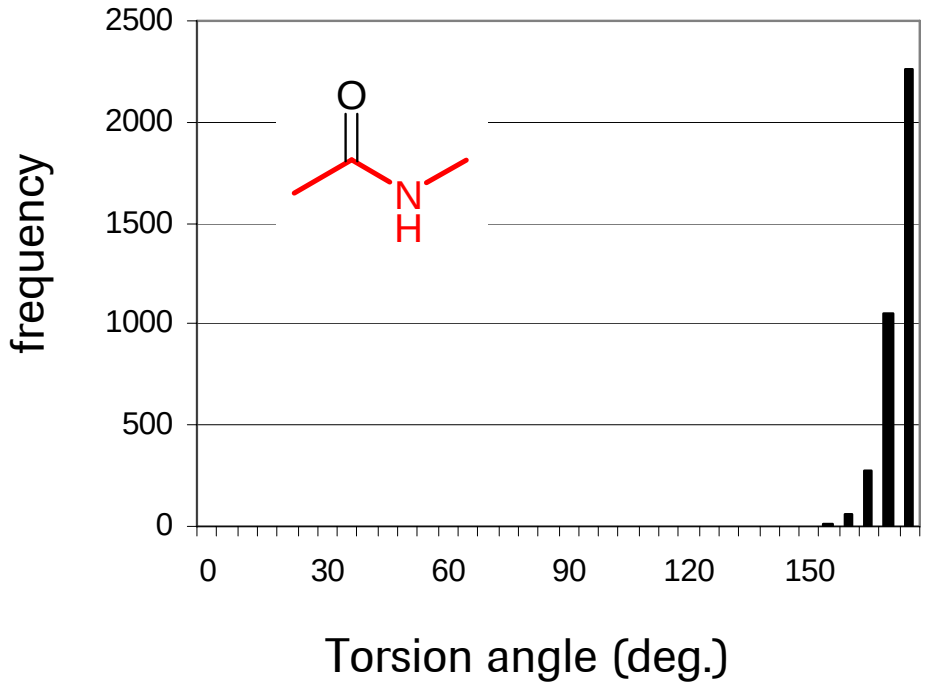
The Sulfonyl Group

Properties of Aniline Derivatives

Project Example: New F.VIIa Inhibitors

Amides

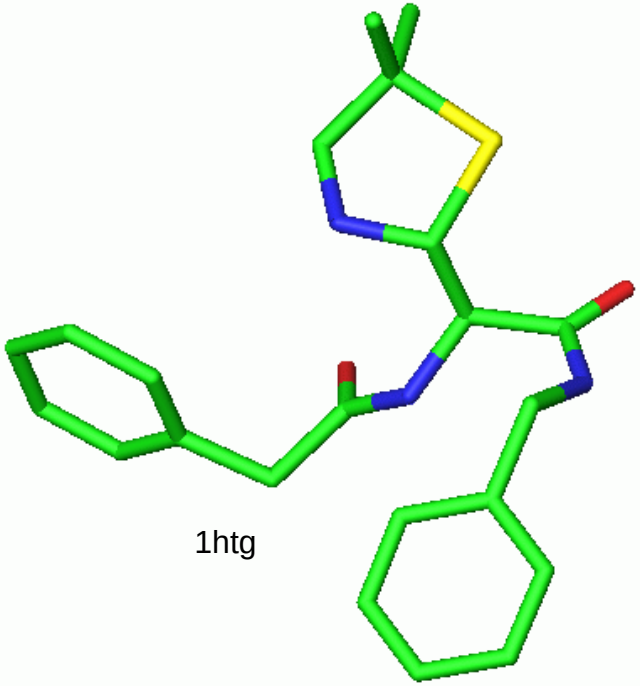
Planar Systems with trans *Configuration*



Examples of *Cis* Amide Bonds

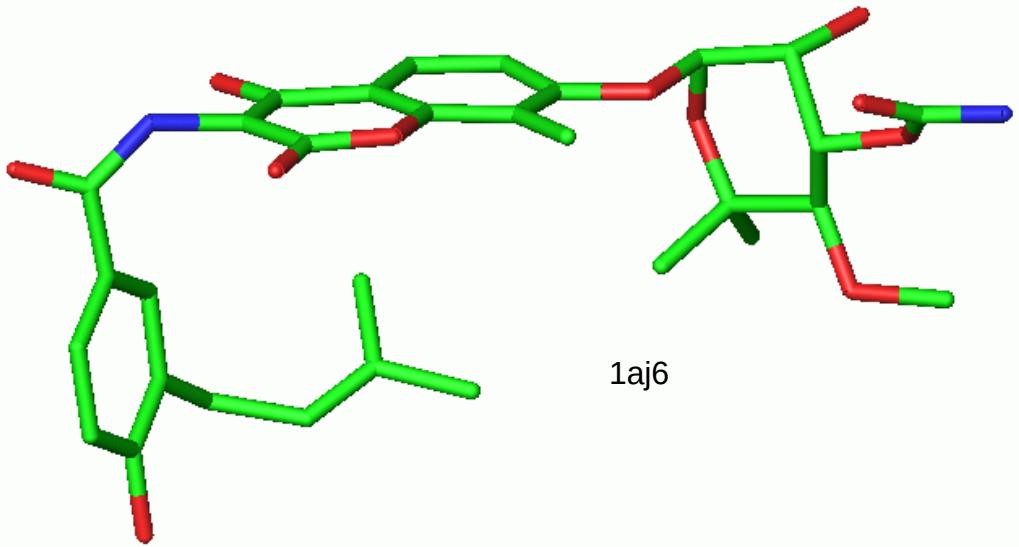
Protein-Ligand Complexes

A peptide inhibitor of HIV protease



1htg

Novobiocin – Gyrase complex



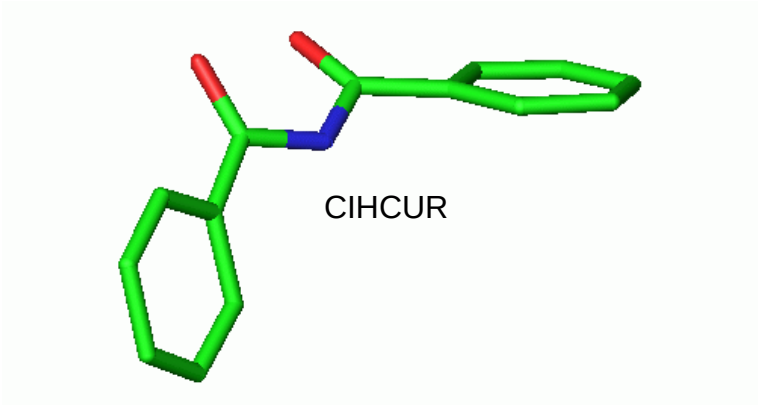
1aj6

In both cases the cis amide conformation allows the formation of significant lipophilic contacts.

Examples of *Cis* Amide Bonds

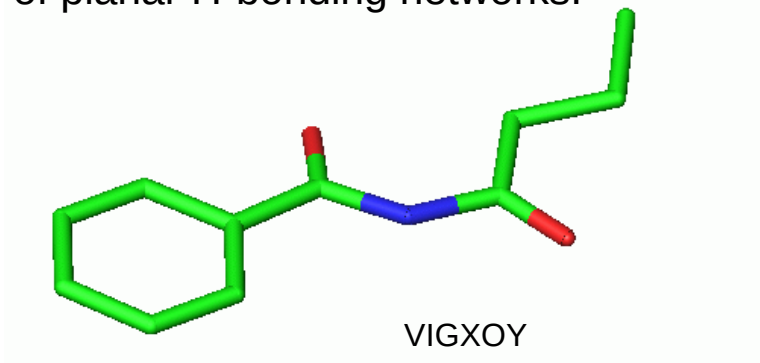
Imides

“normal” case:
Note deviation from planarity

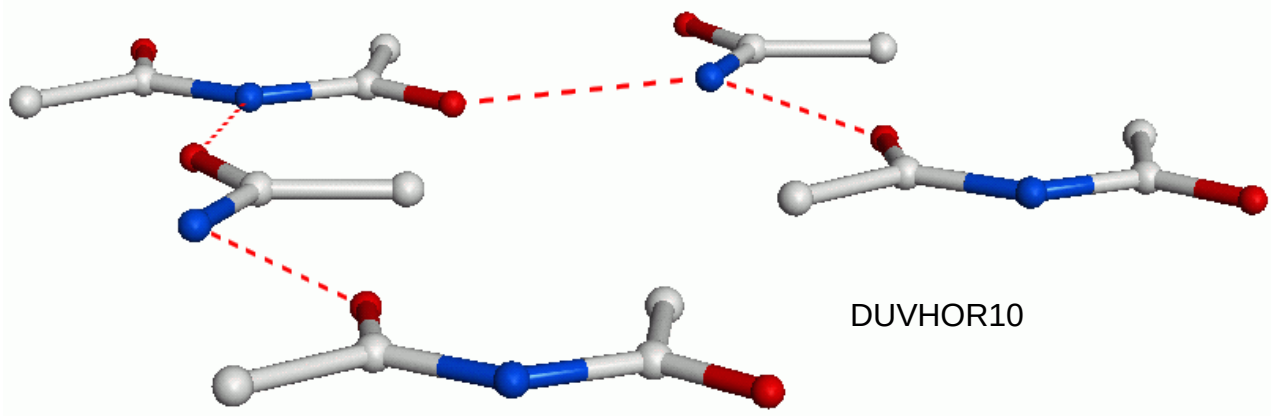


CIHCUR

The alternative *cis-trans* conformation is completely planar and allows the formation of planar H-bonding networks.



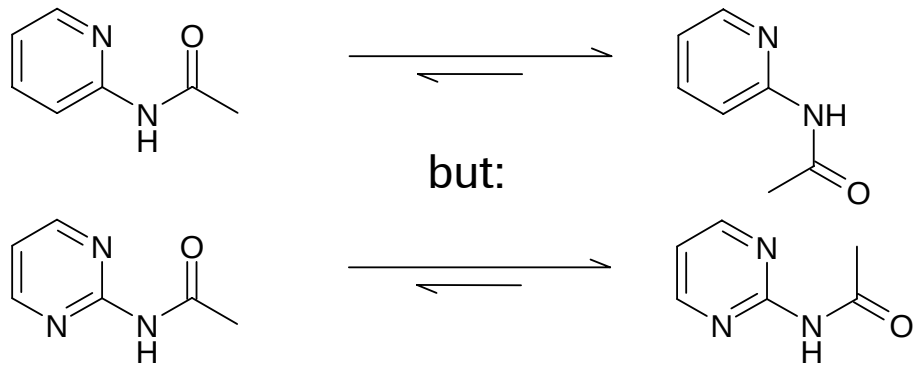
VIGXOY

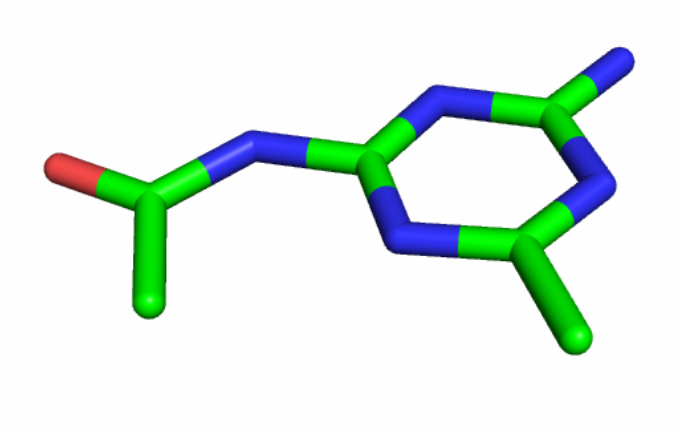


DUVHOR10

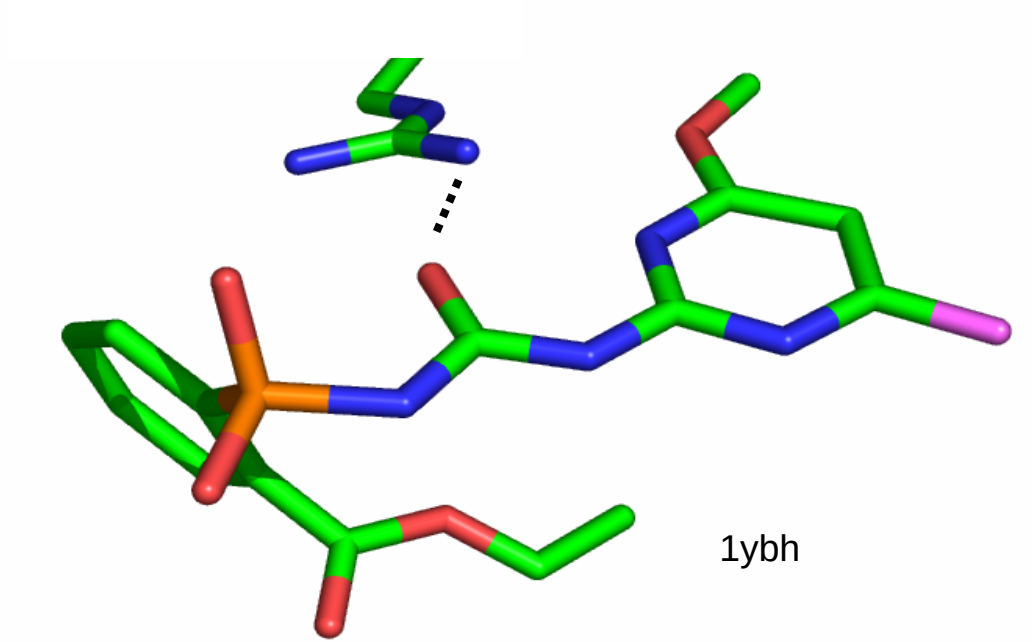
Acylated Aminopyrimidines

Cis Amide Conformations in the Absence of H-Bonds





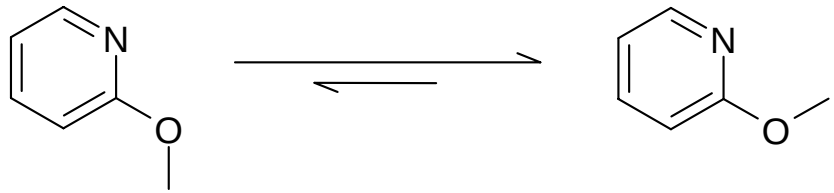
NICGAH

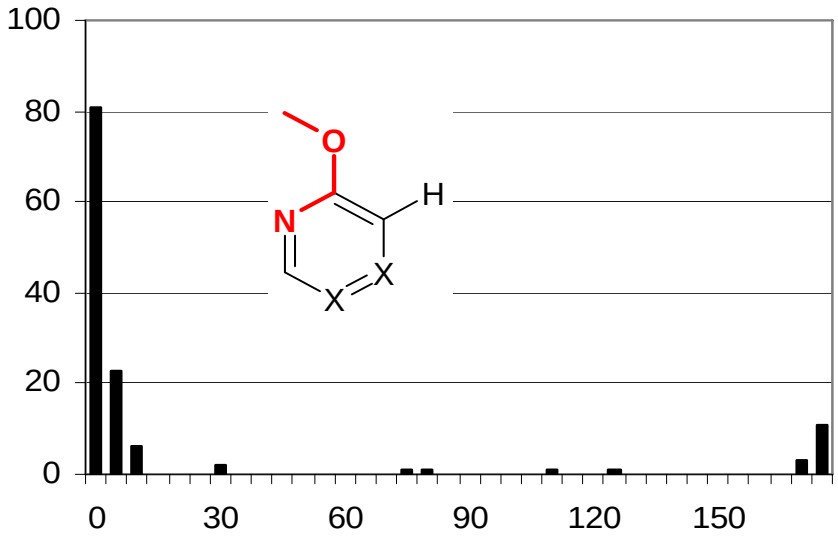


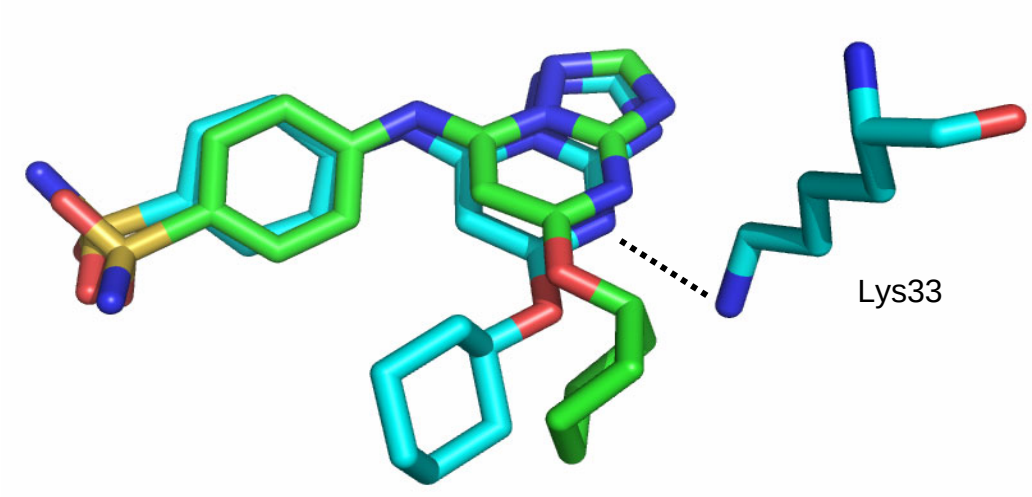
1ybh

Electrostatic Repulsion Determines Equilibria

Alkoxypyridines



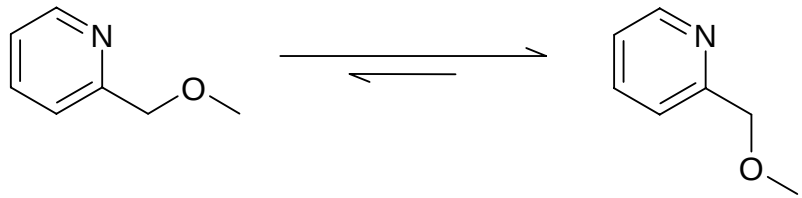


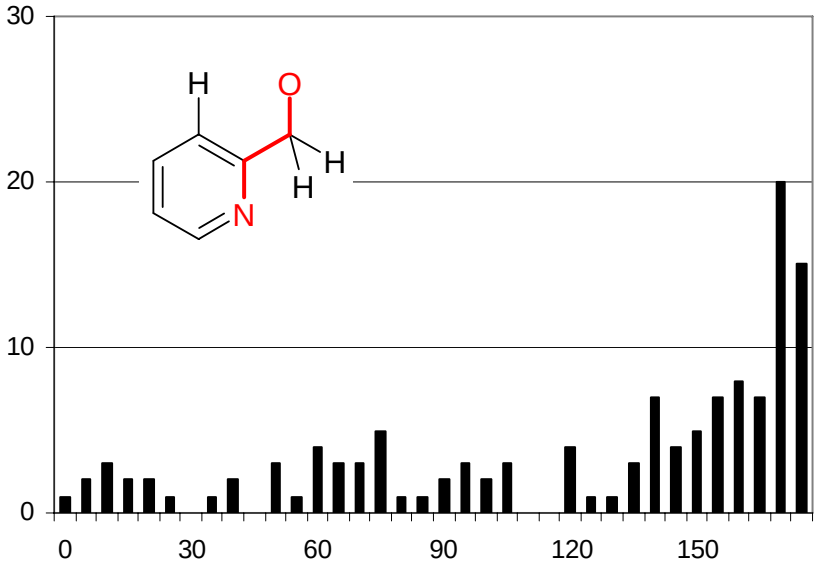


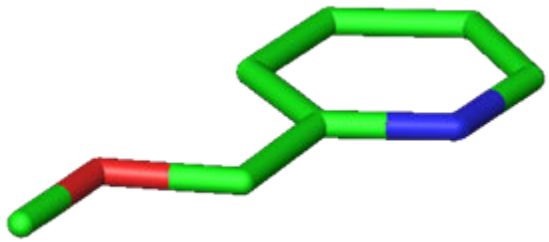
Inhibitor NU6102
with monomeric CDK2 (2c6t, green) and
in CDK2/cyclin A complex (2c6m, cyan).

Electrostatic Repulsion Determines Equilibria

Benzylic ortho Substituents at Pyridines







Roche

Cis or Trans? From Amides to Electrostatic Repulsion

Generalized Allylic Strain

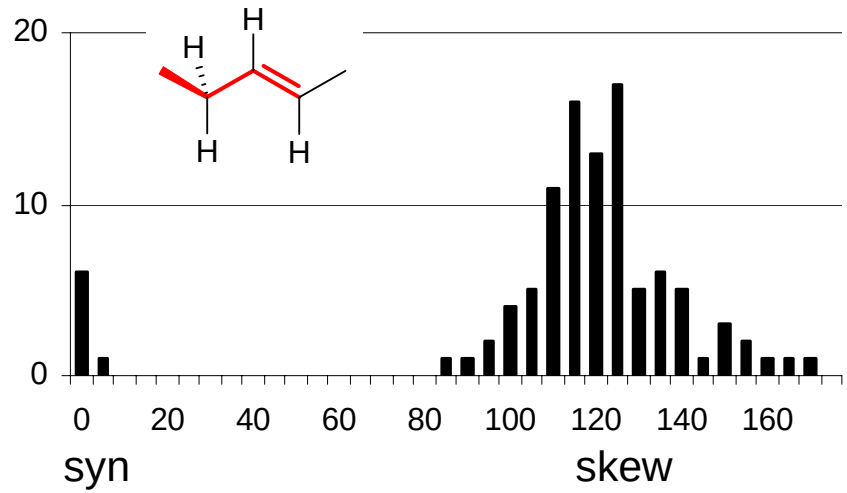
The Sulfonyl Group

Properties of Aniline Derivatives

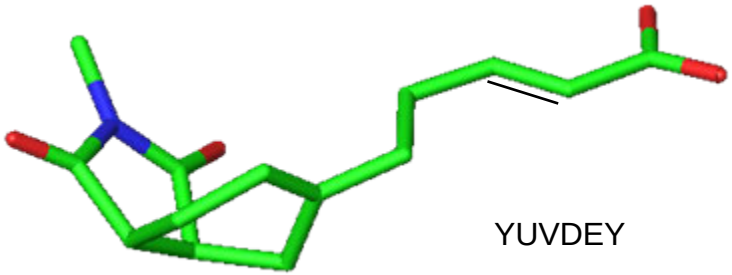
Project Example: New F.VIIa Inhibitors

Preferred Conformations of Allylic Systems

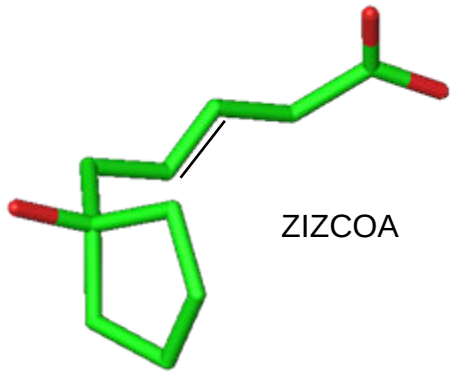
Energy Minima at 120° to Double Bond



For 1-butene, the *skew* conformation is favored by ~0.2 kcal/mol over *syn* (gas phase).



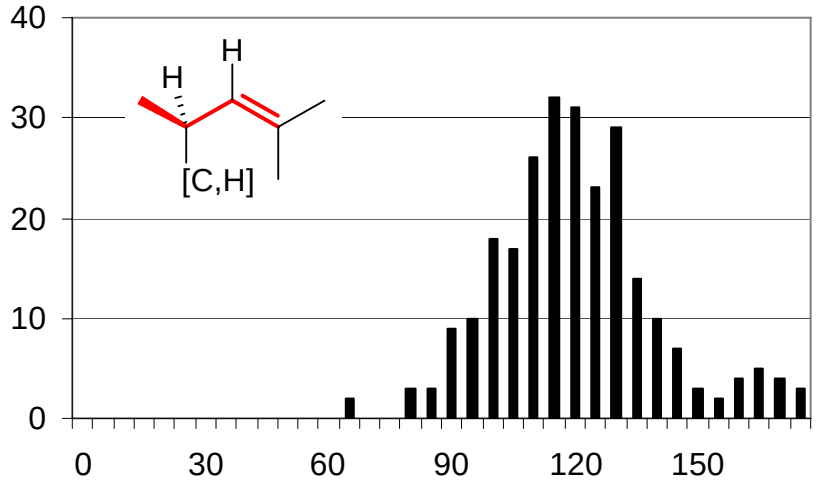
YUVDEY

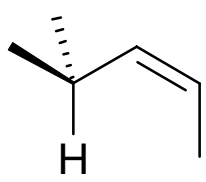


ZIZCOA

Preferred Conformations of Allylic Systems

Allylic 1,3-Strain: Syn-Rotamer Strongly Avoided





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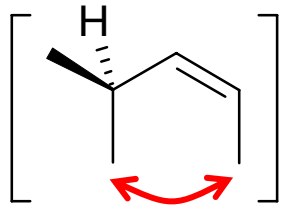
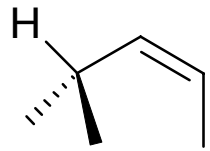


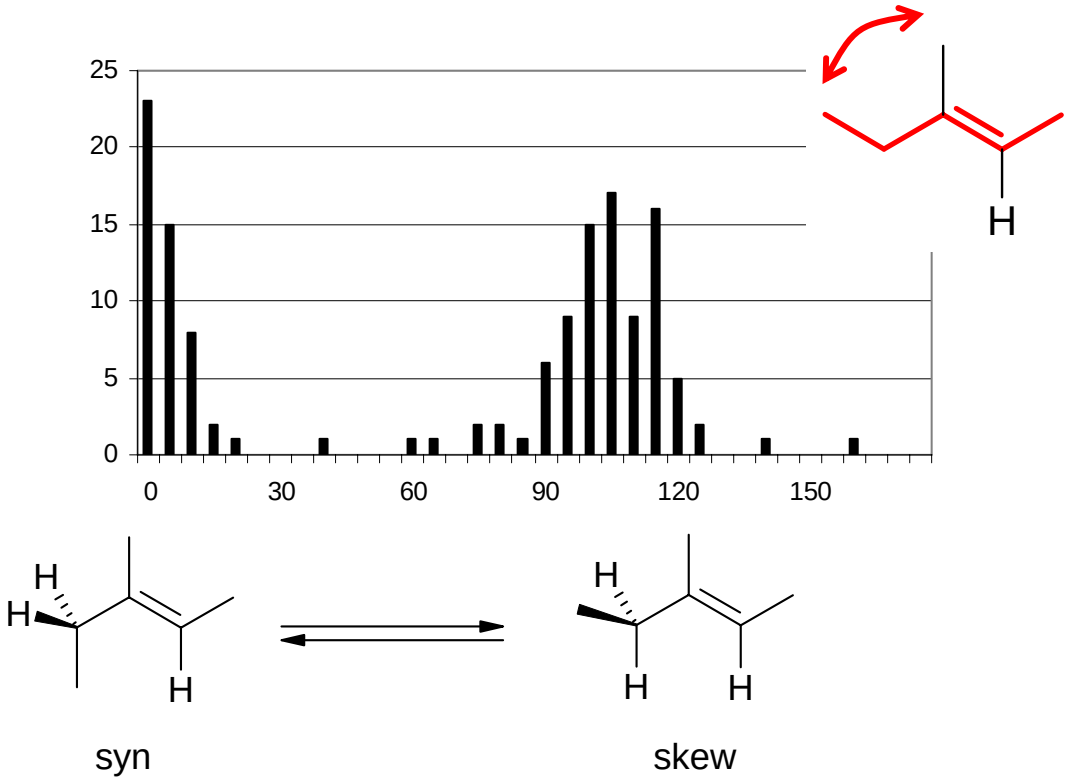
> 4 kcal/mol



~3.4 kcal/mol

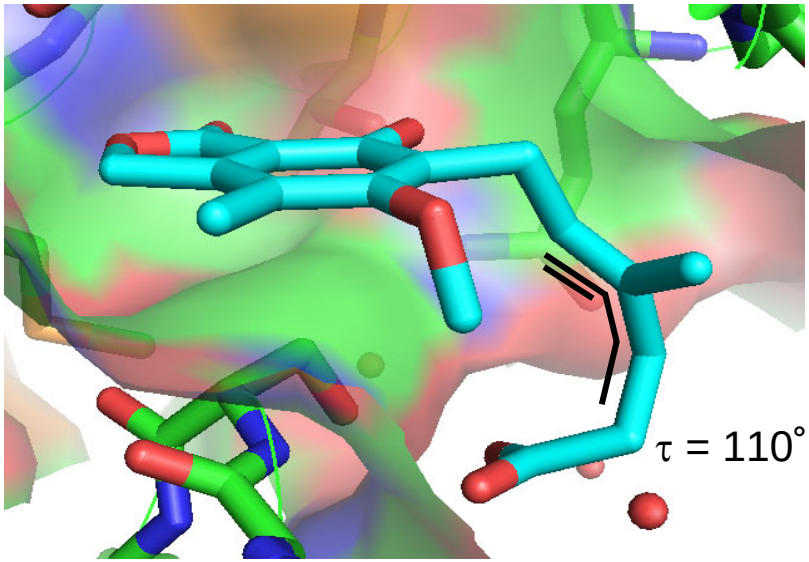
Preferred Conformations of Allylic Systems

Allylic 1,2-Strain: Syn-Rotamer Preferred

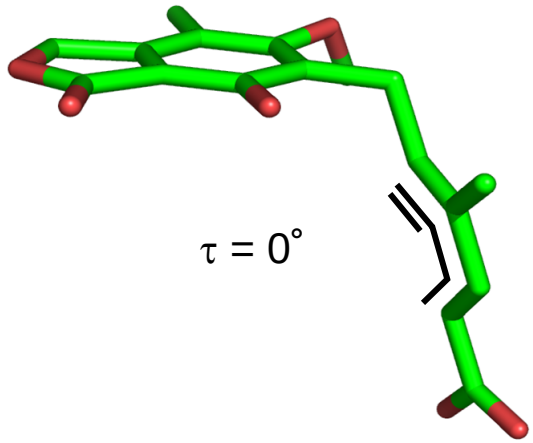


Allylic Strain in Action

The Example of Mycophenolic Acid



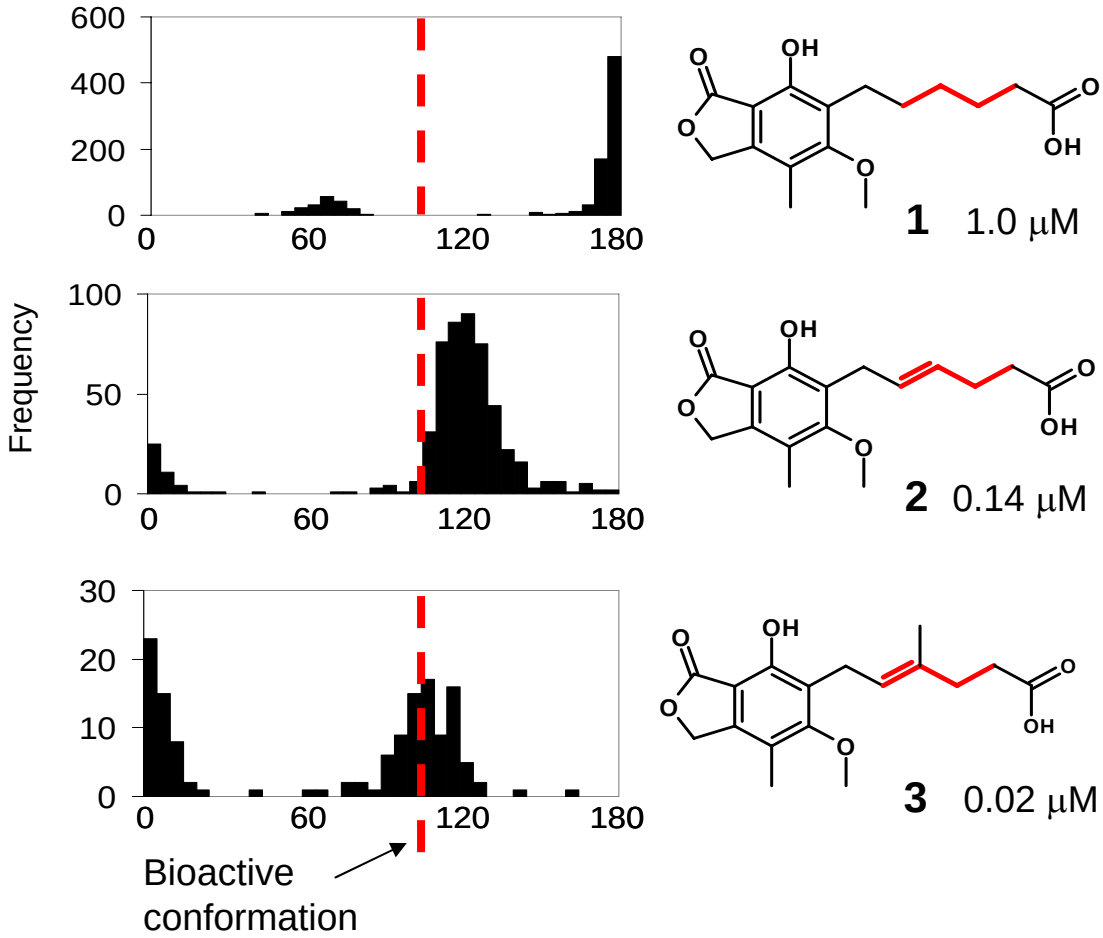
1jr1 (IMPDH Complex Structure)



MYCPHA

Mycophenolic Acid Analogs

Torsion Histograms of Alternative Linkers



Translating Allylic 1,3-Strain to Related Systems

Amide Analogies

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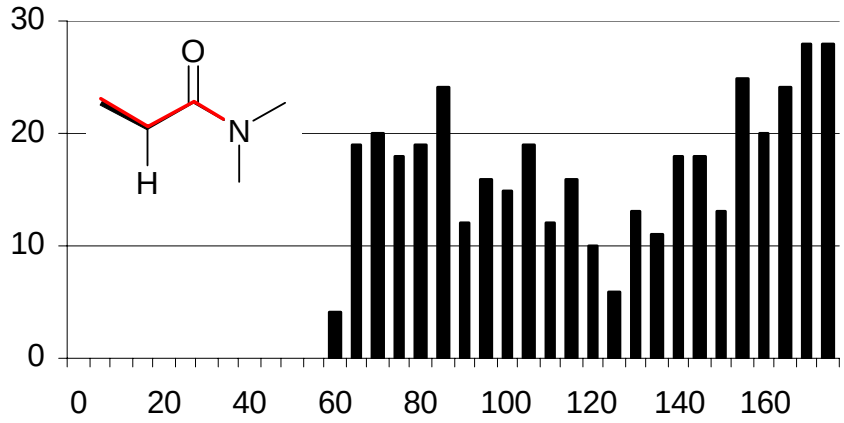

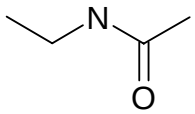

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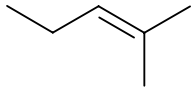
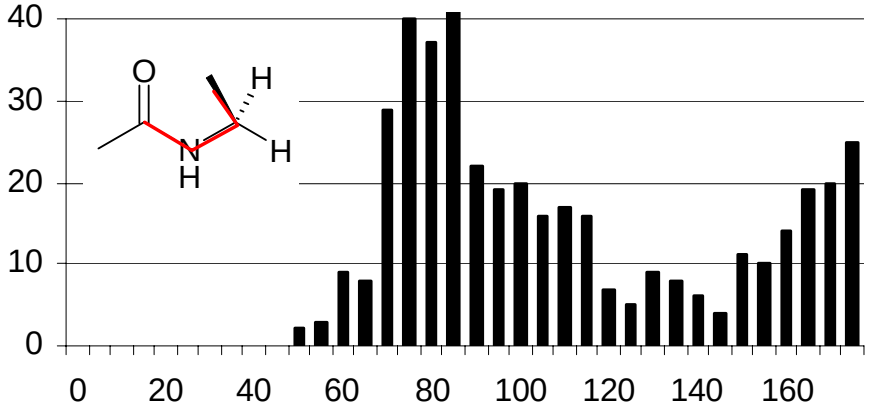
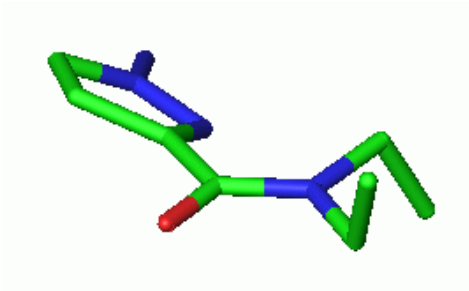


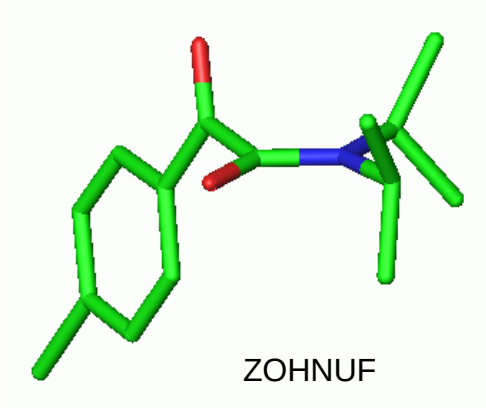


Tertiary Amides

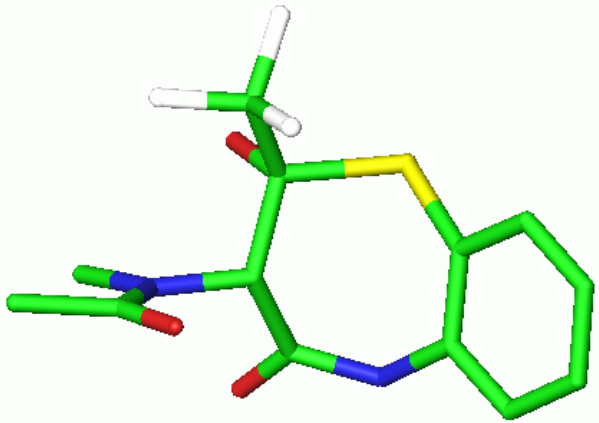
Substituents Point out of Plane



ZOWWEN



ZOHNUF

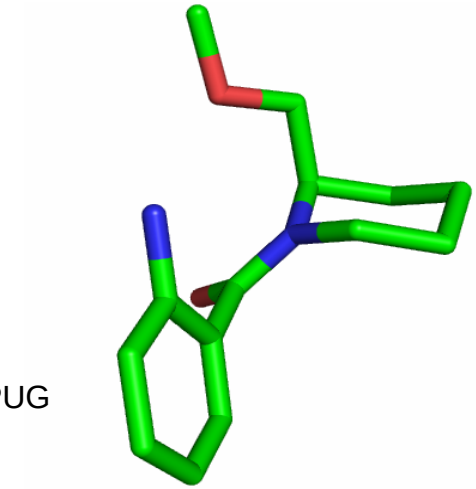


CAGDUK

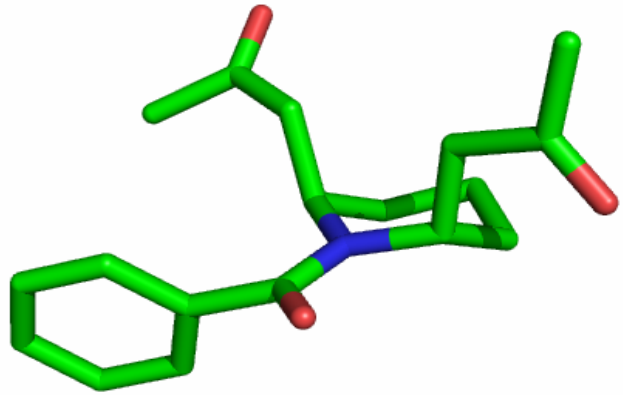
Acylated Piperidines

Enforcement of Axial Substituents

REYPUG

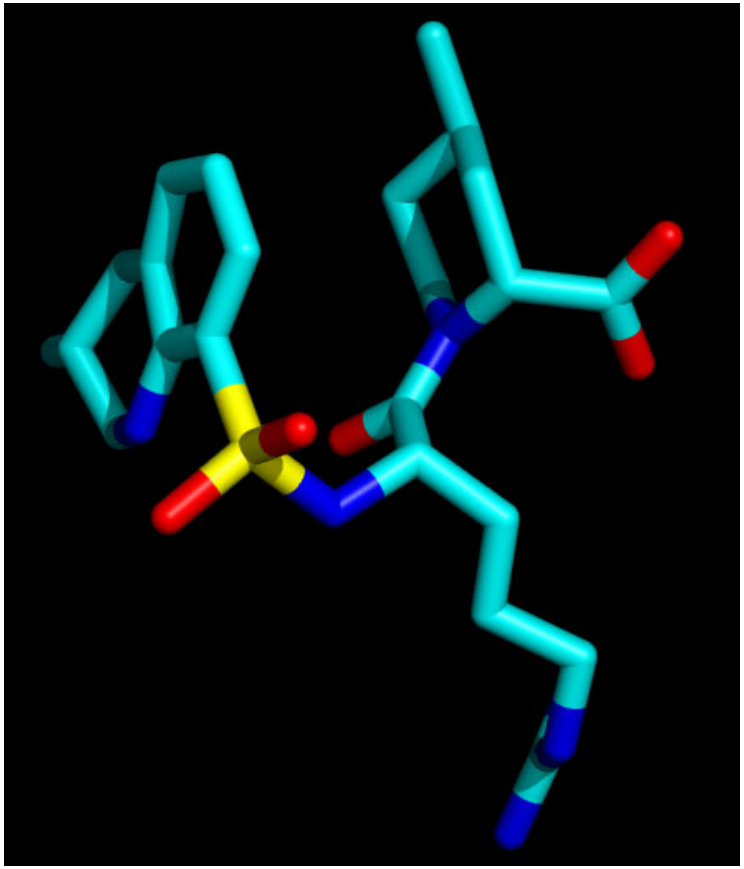


BOAYPI

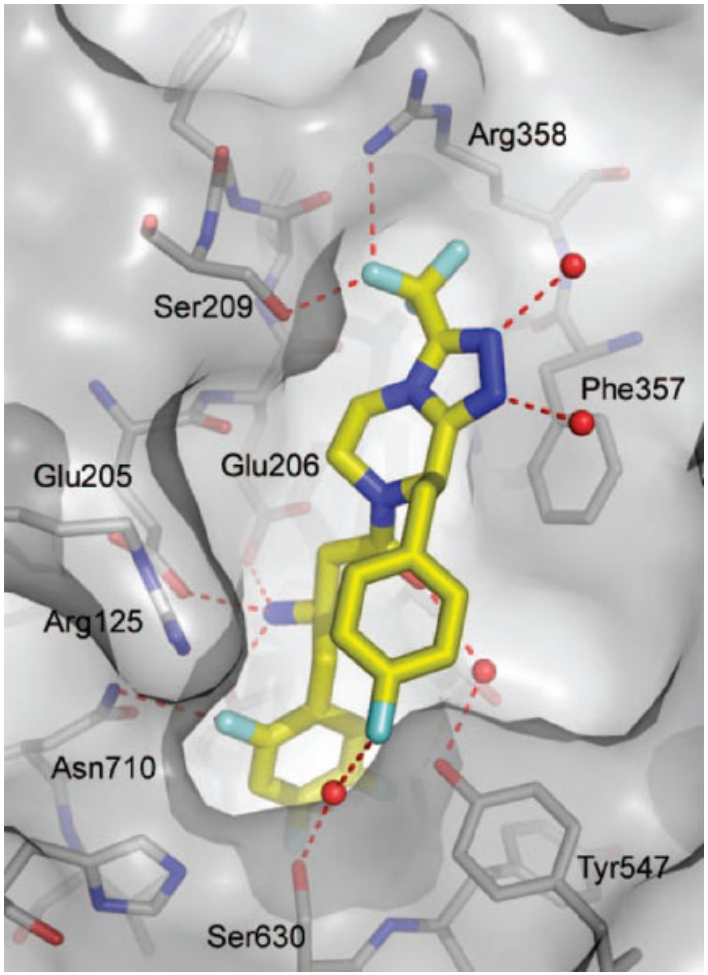


Acylated Piperidines and Related Structures

PDB Examples



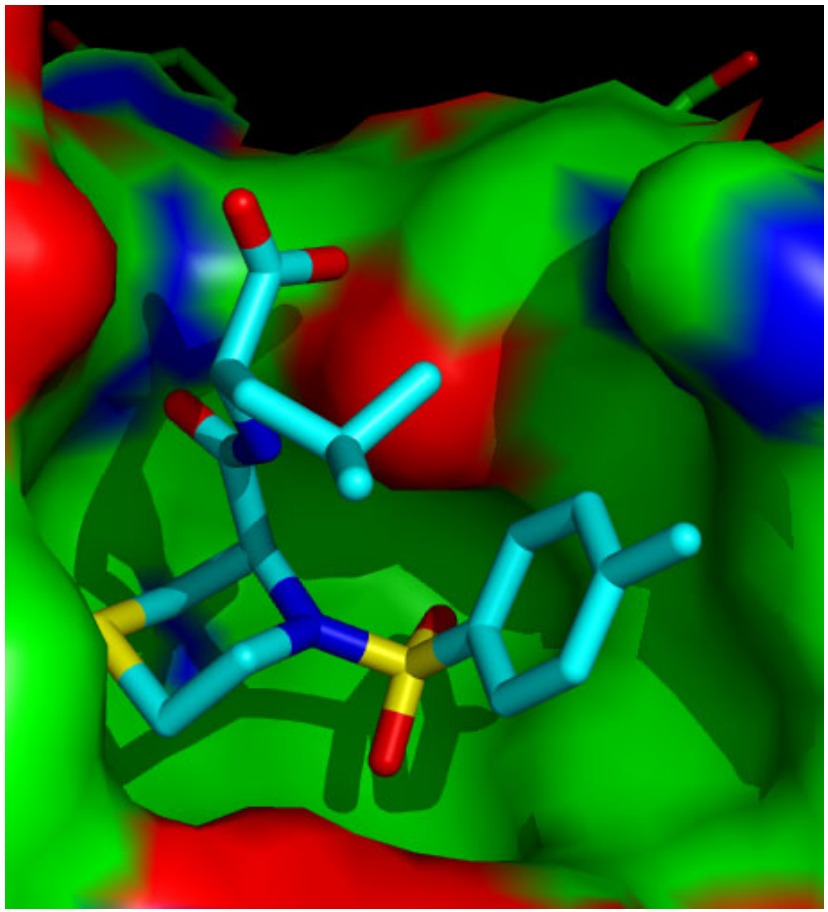
MQPA – thrombin complex (1etr)



DPPIV complex, J. Med. Chem. **2008,** 51, 589–602

Acylated Piperidines

Analogous Effects with Sulfonamides



FKBP12 complex structure (1j4i)

Cis or Trans? From Amides to Electrostatic Repulsion

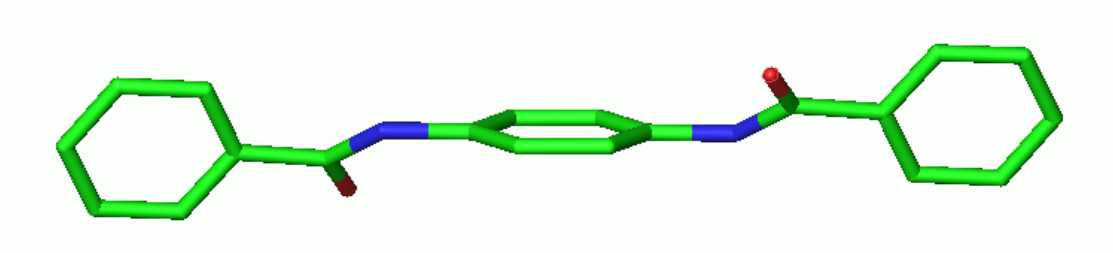
Generalized Allylic Strain

The Sulfonyl Compounds

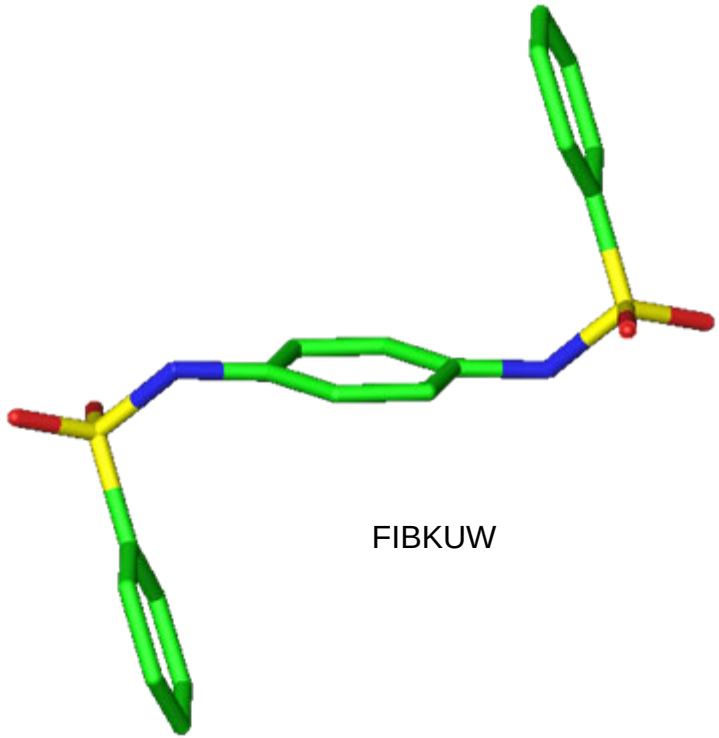
Properties of Aniline Derivatives

Project Example: New F.VIIa Inhibitors

Sulfonamides are not Amide Isosteres!



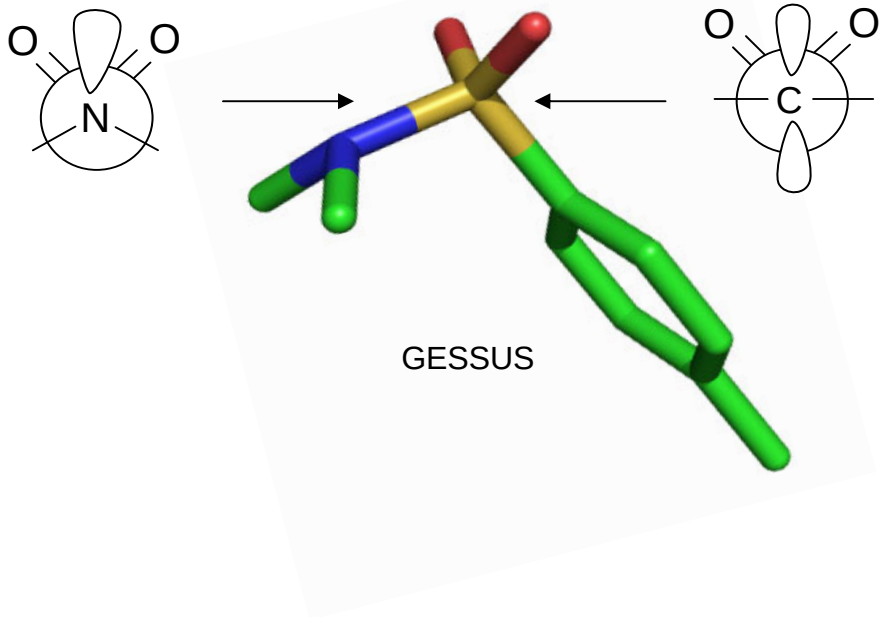
PABZAM

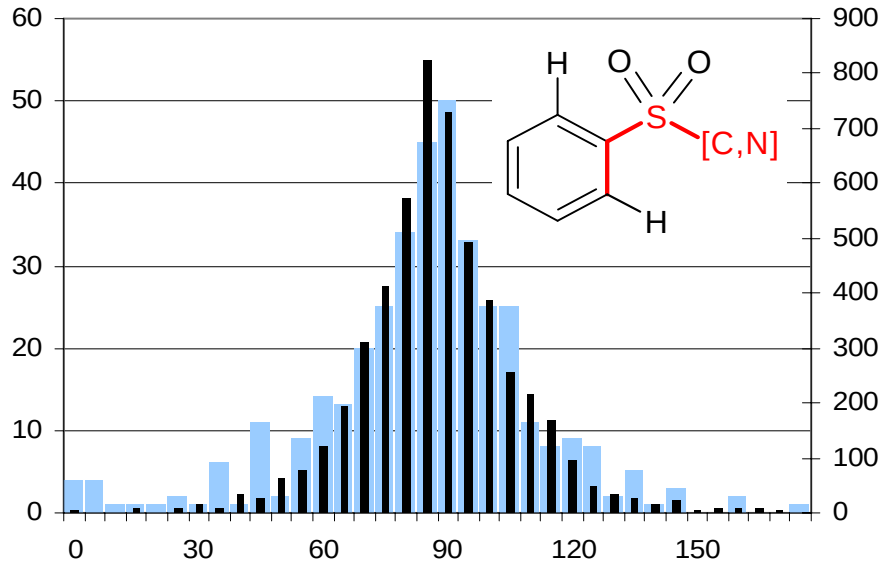


FIBKUW

Preferred Conformations of Sulfonamides

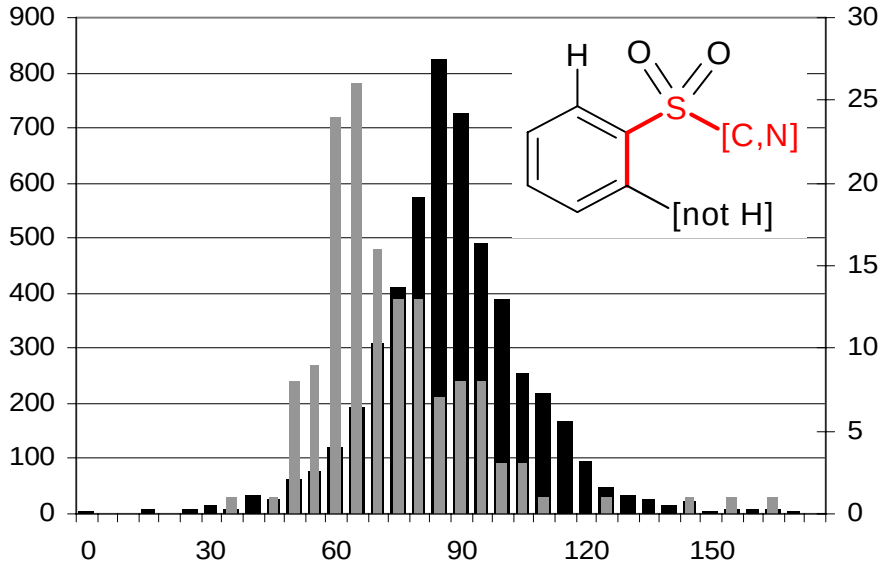
p Orbitals and Lone Pairs Bisect the O=S=O Angle

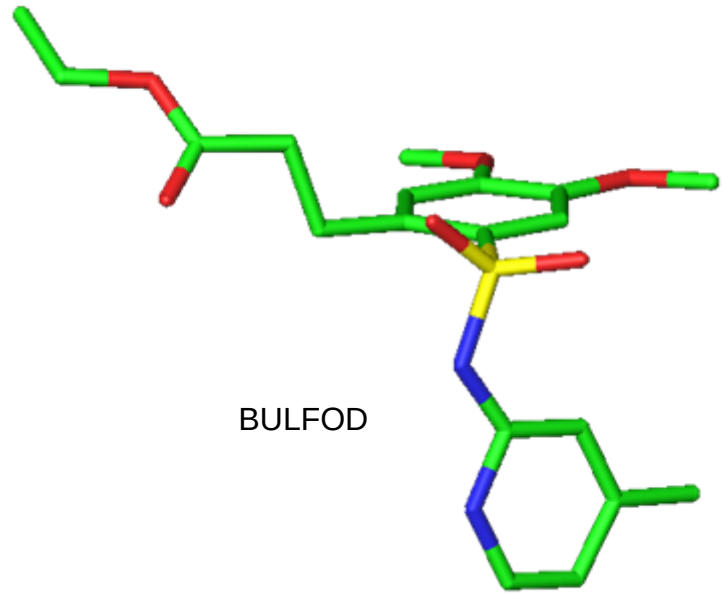




Aryl–Sulfonyl Compounds

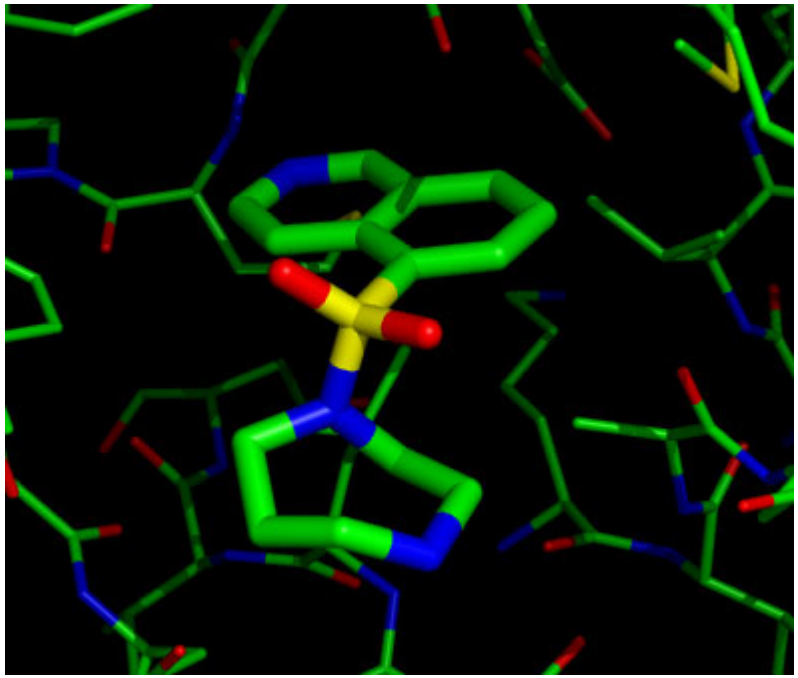
Ortho Substituents Shift the Torsion Angle Distribution

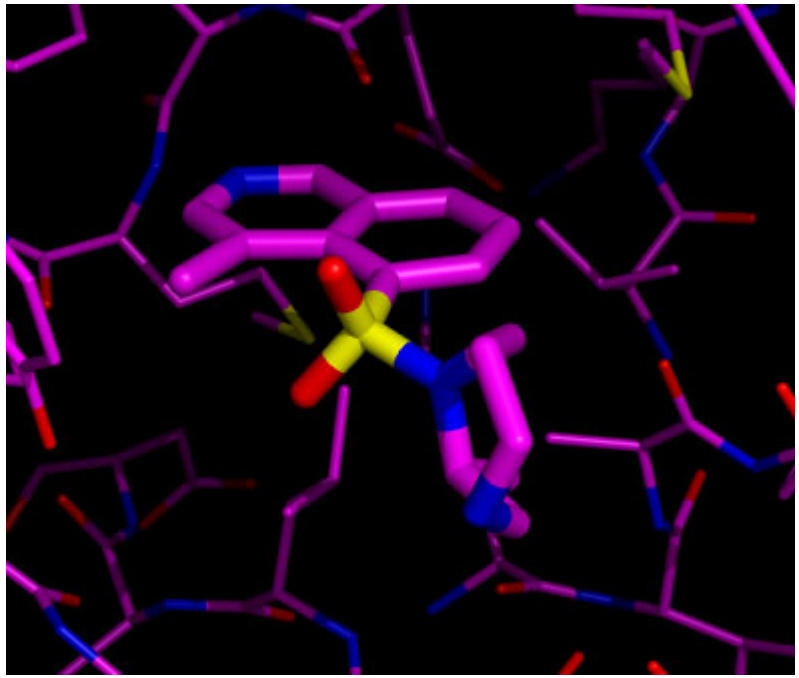




Aryl–Sulfonyl Compounds

Extreme Cases of ortho *Substitution*

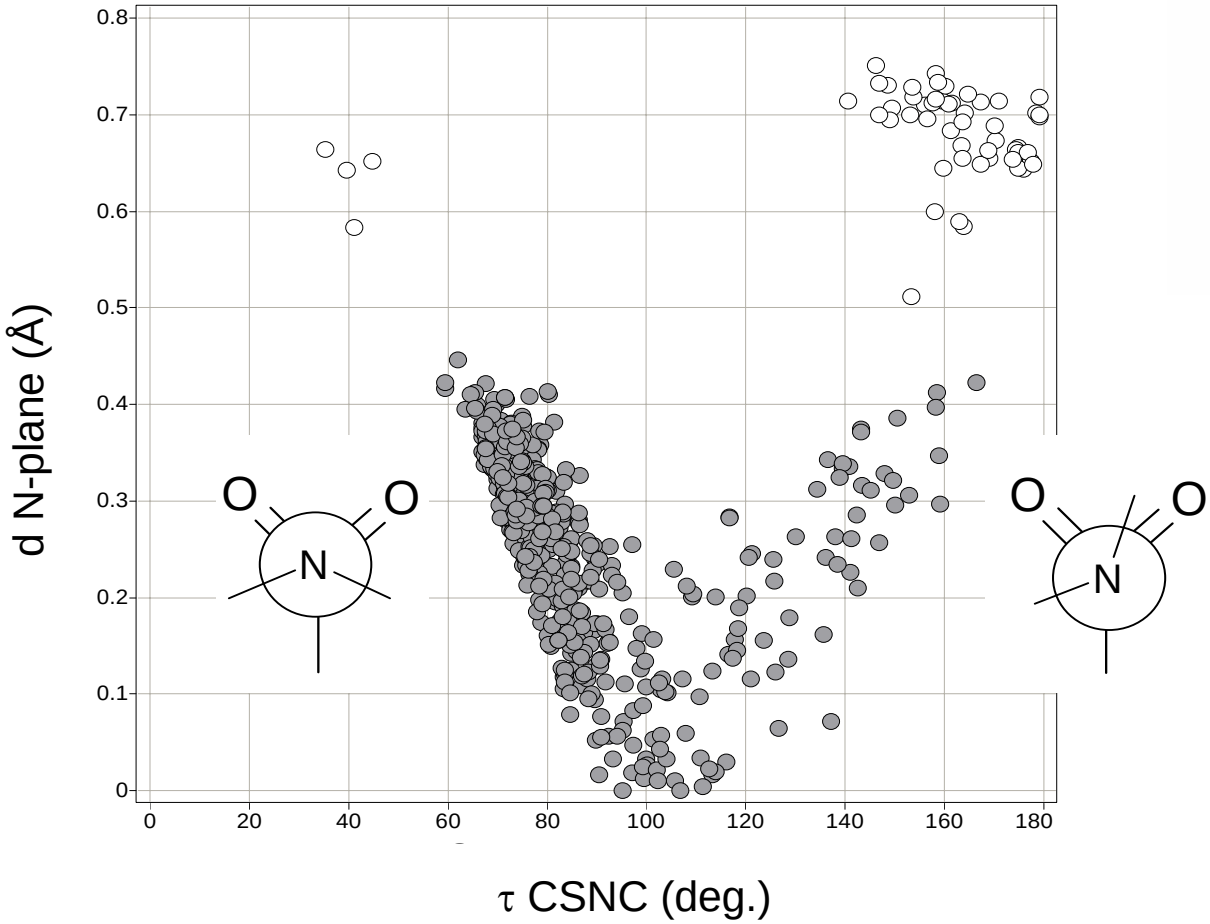


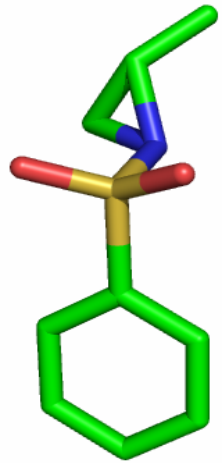


PKA fivefold mutant model of Rho-Kinase complexed with fasudil (2gni, left) and an analog (2gnh, right).

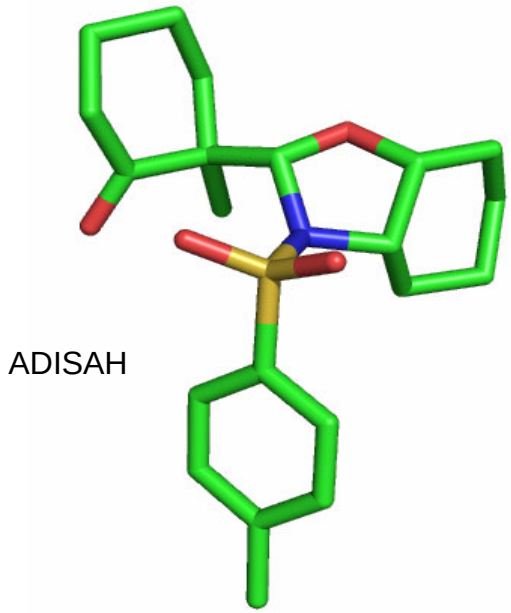
Alternate Sulfonamide Conformations

Nitrogen Hybridization and Inversion





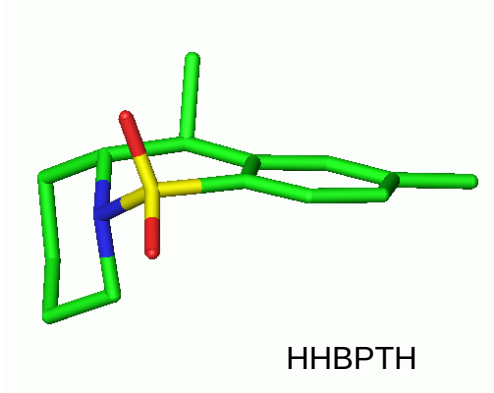
KATLEW



ADISAH

Aryl–Sulfonyl Compounds

Preferred S-N Torsion leads to Axial N Substituents



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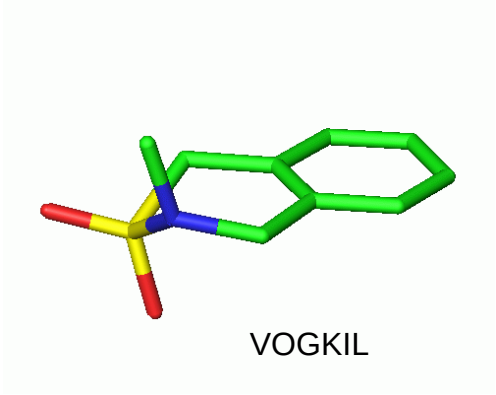
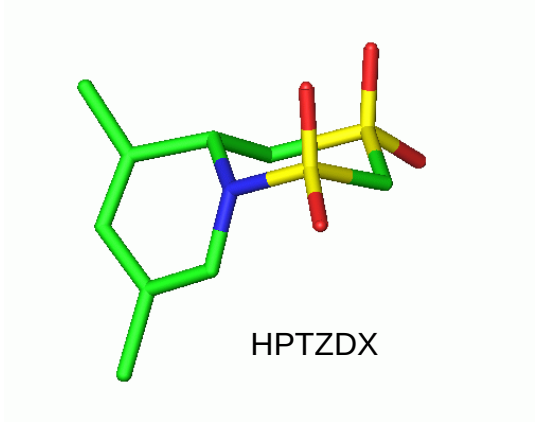


VOGKIL



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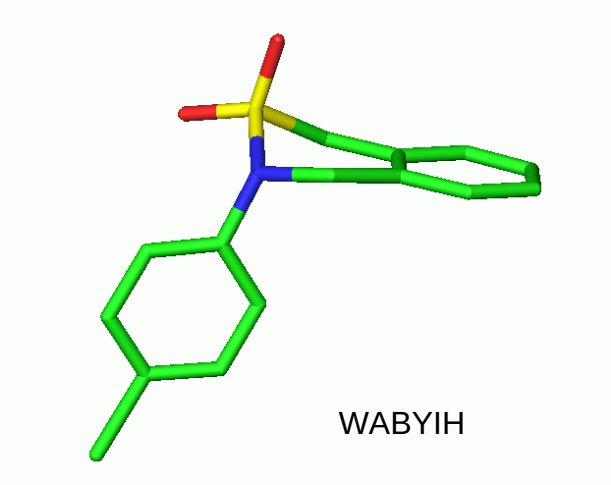
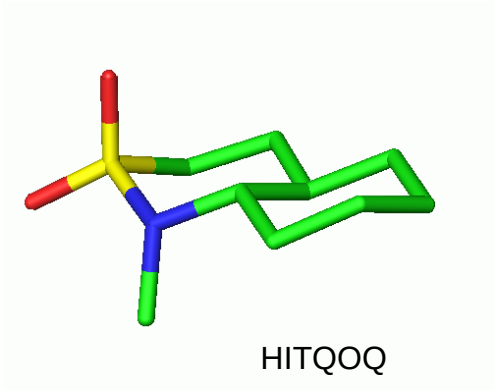
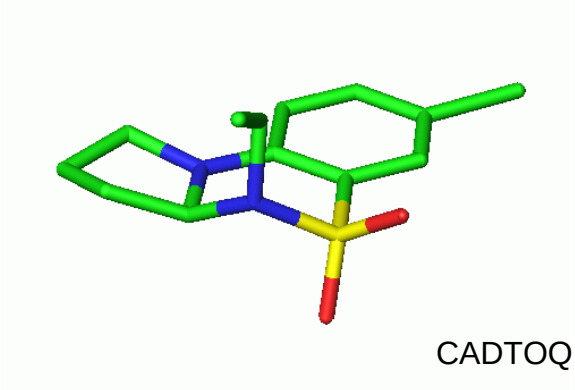


WABYIH



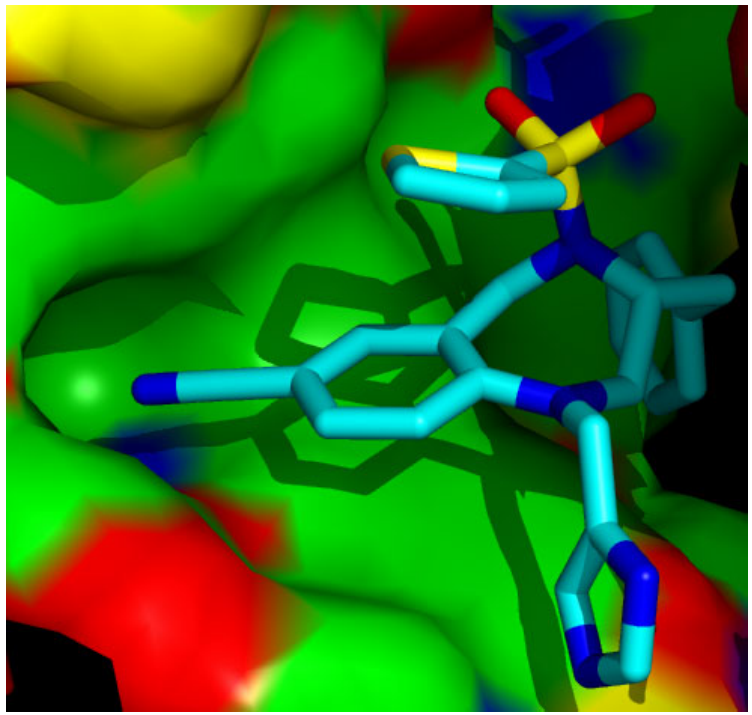
HITQOQ



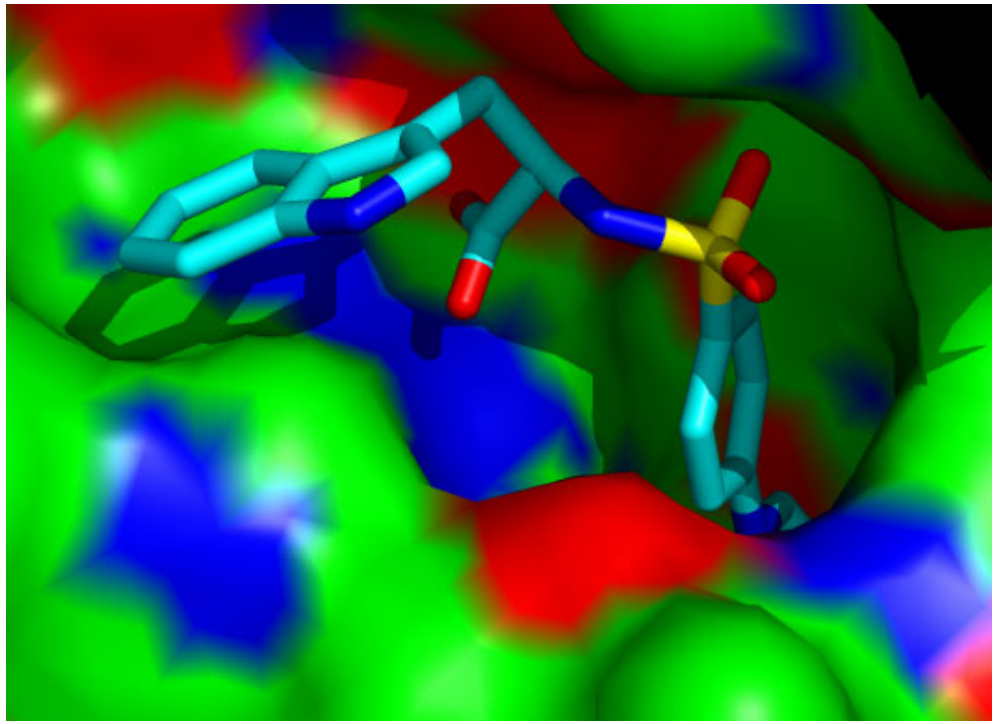
CADTOQ

Sulfonamide Special Effects

Longer Bond Distances Allow Folding Back



Farnelyltransferase complex (1sa5)



Stromelysin complex (1ciz)

Cis or Trans? From Amides to Electrostatic Repulsion

Generalized Allylic Strain

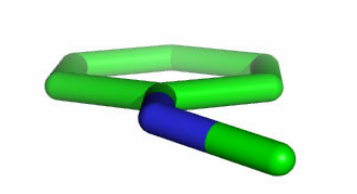
The Sulfonyl Compounds

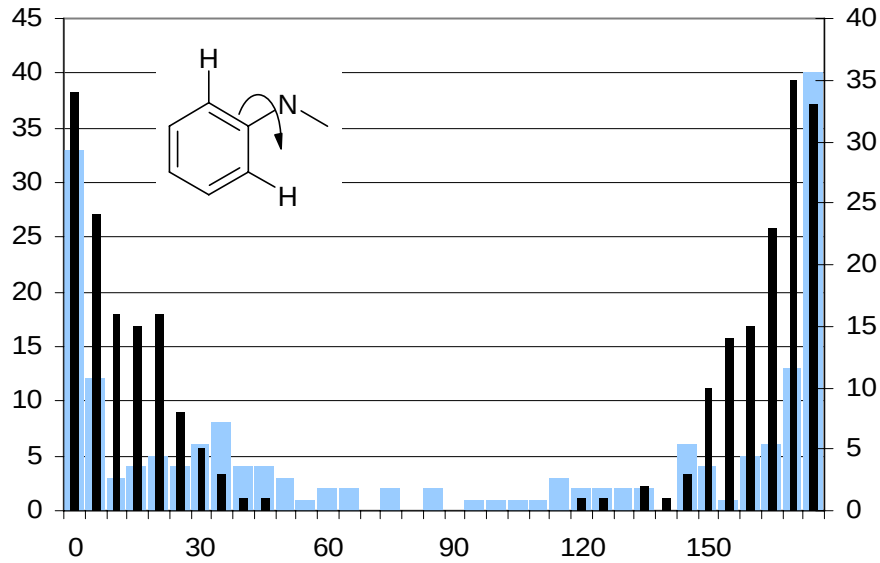
Properties of Aniline Derivatives

Project Example: New F.VIIa Inhibitors

Aryl Rings – Aniline Derivatives

Interplay between N Hybridization and Rotation

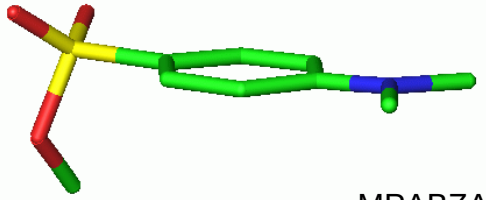




Aniline Derivatives

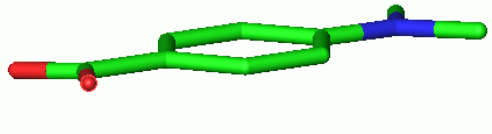
Varyin Degrees of Pyramidalization

electron withdrawing substituents decrease pyramidalization



MPABZA01

fully planar

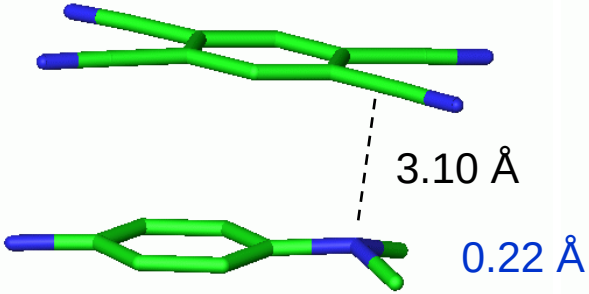


PDABZA01

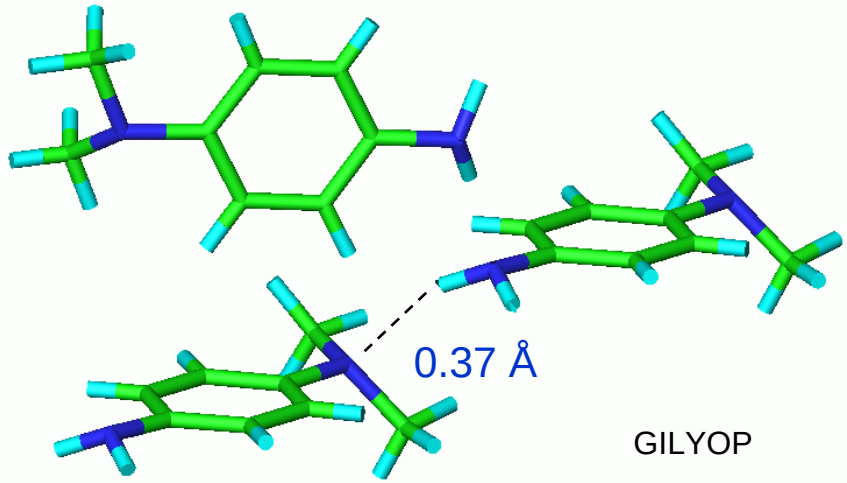
fully planar

electron pushing substituents increase pyramidalization.

environment plays an important role.



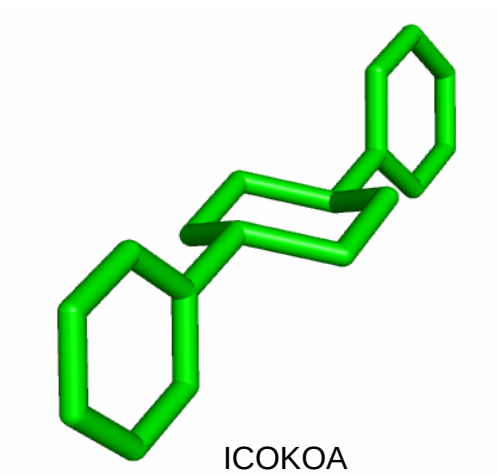
LIYSIV



GILYOP

Cyclic Aniline Derivatives

Pyramidalization Strongly Affects Molecular Shape



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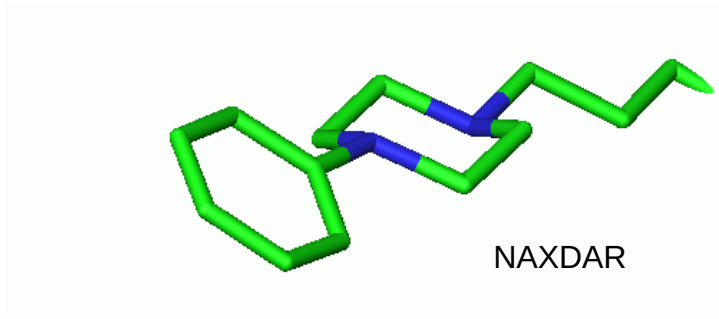

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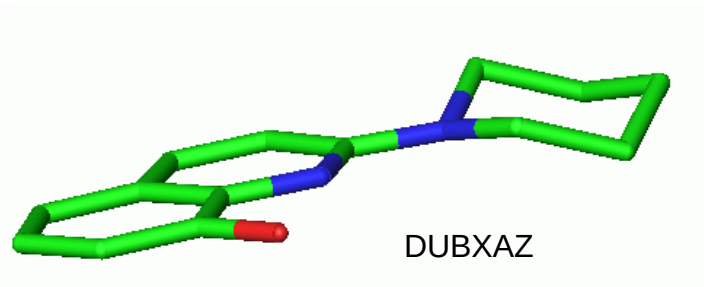

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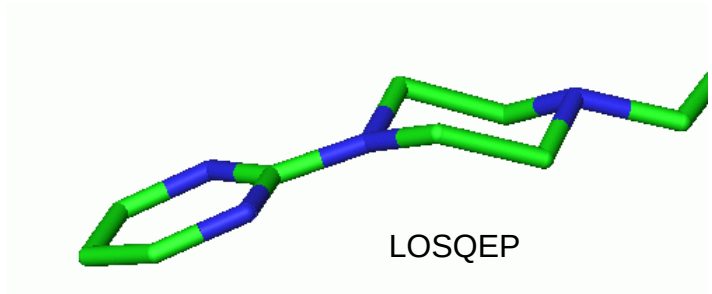

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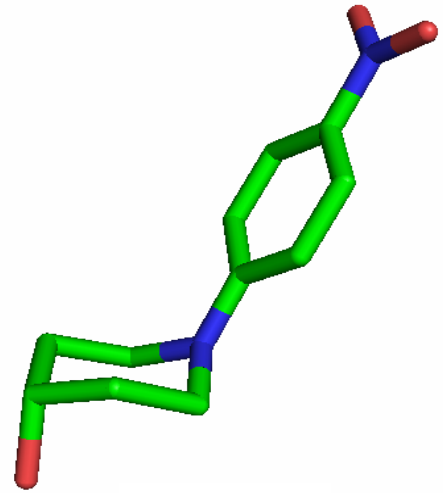

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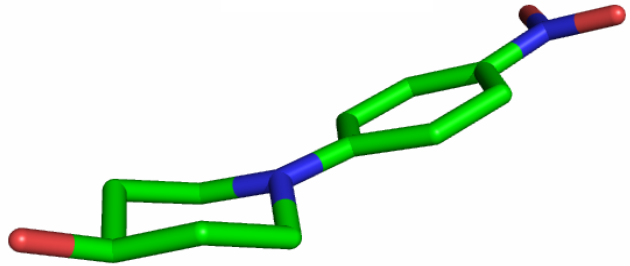
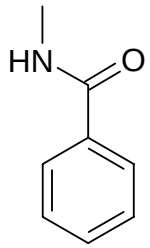
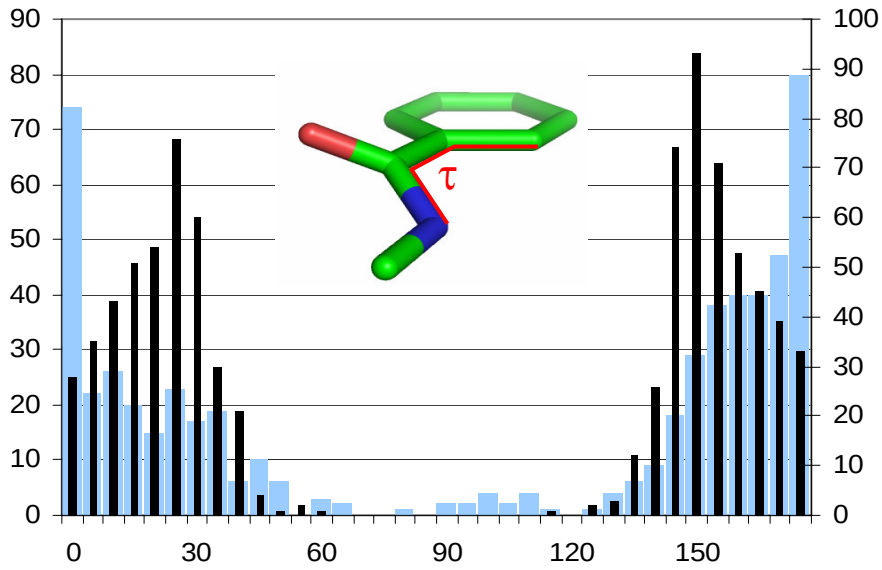


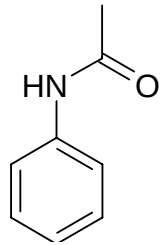
Benzamides and Acylated Anilines

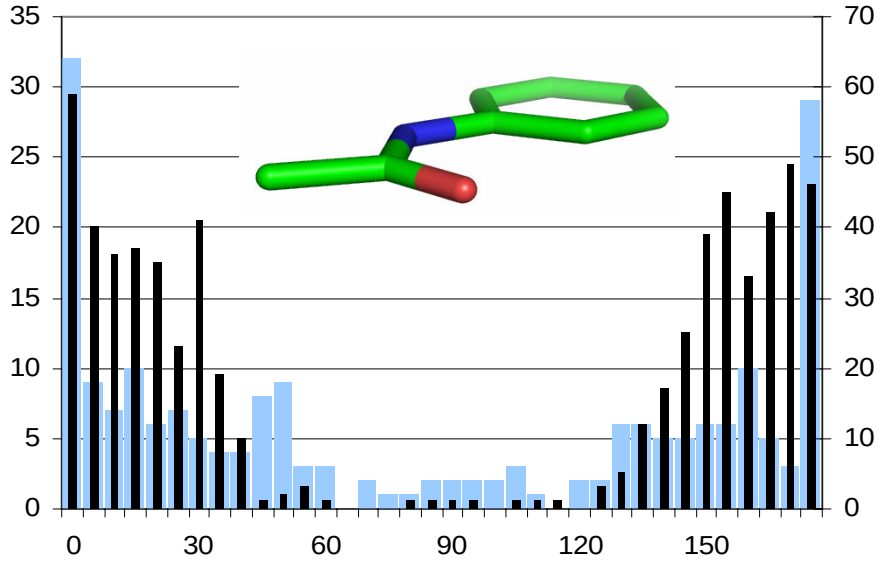
Planar or Nonplanar?





Local energy maximum at 0°,
but PDB structures mostly planar





Global energy minimum at 0°,
PDB structures mostly planar

Cis or Trans? From Amides to Electrostatic Repulsion

Generalized Allylic Strain

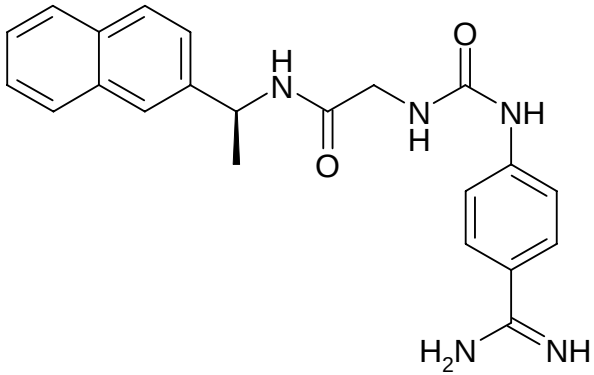
The Sulfonyl Group

Properties of Aniline Derivatives

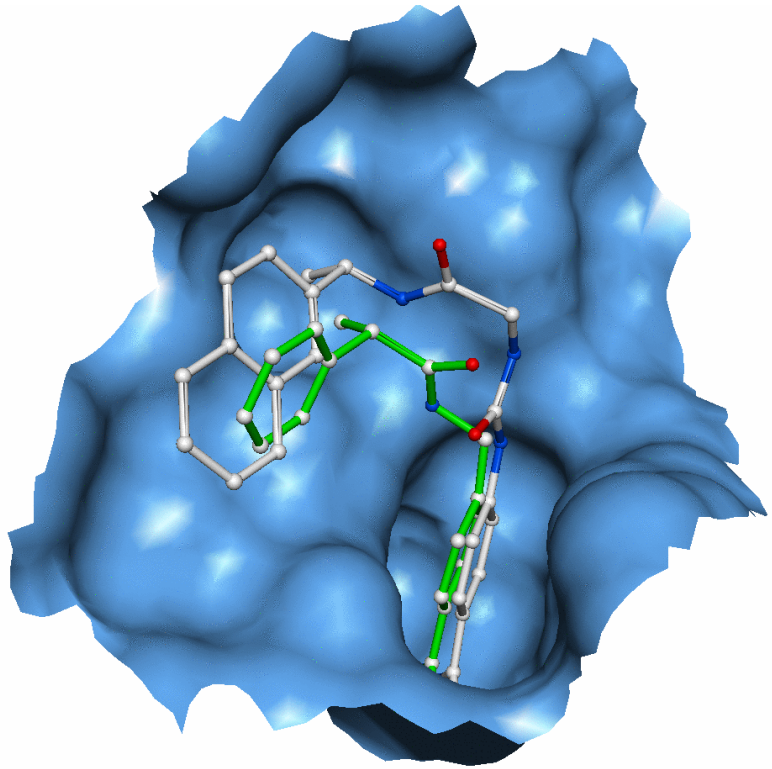
Project Example: New F.VIIa Inhibitors

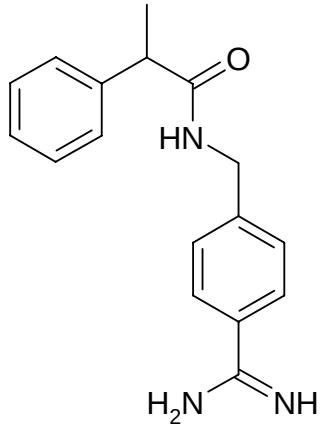
New F.VIIa Inhibitors

Design of a New Scaffold, First Iteration



0.12 μM

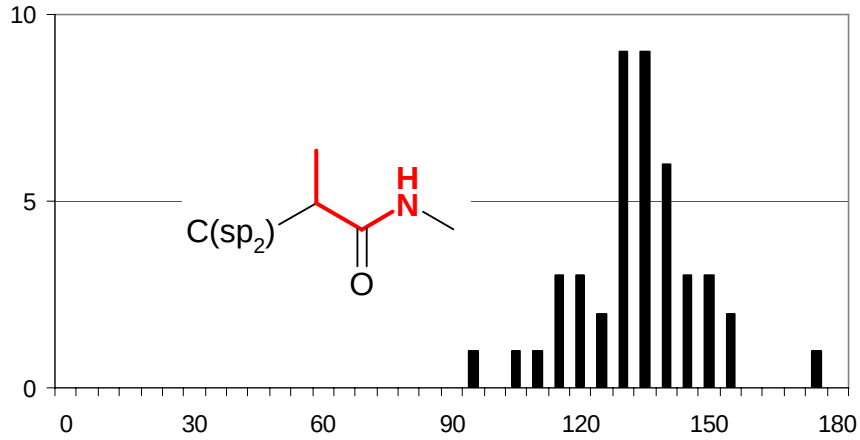


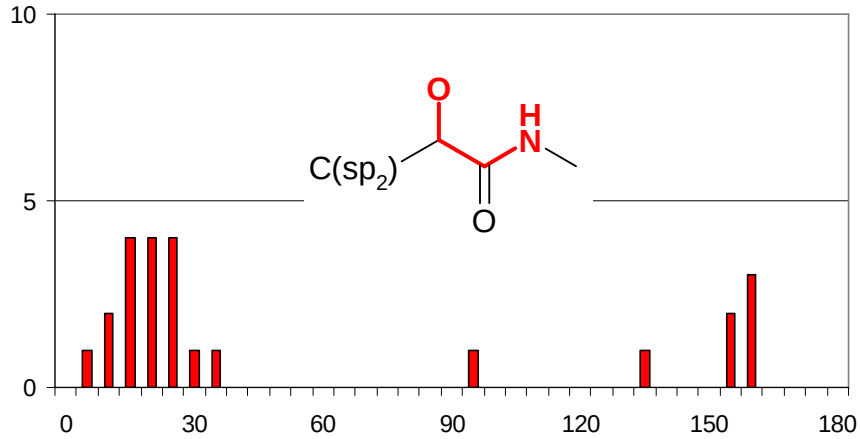


inactive!

New F.VIIa Inhibitors

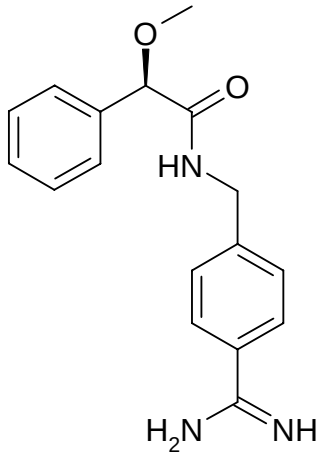
Conformations of Cabon and Oxygen Derivatives





New F.VIIa Inhibitors

Design of a New Scaffold, Second Iteration



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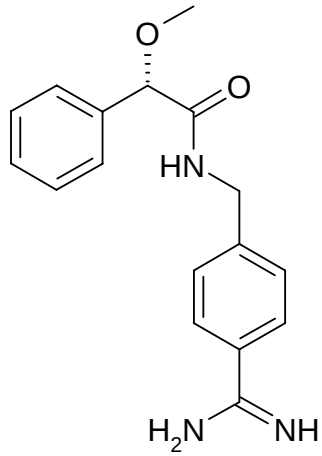
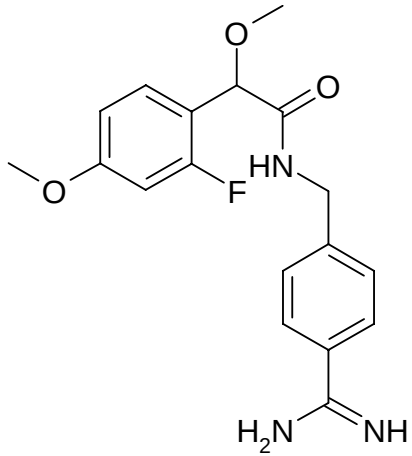


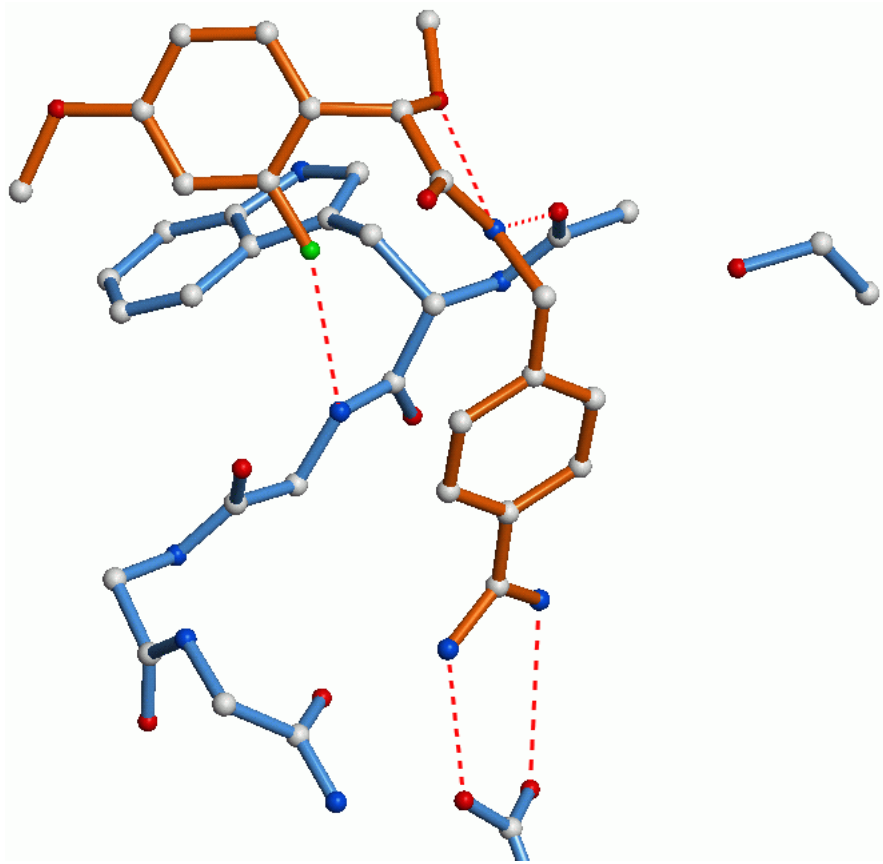
11 μM

New F.VIIa Inhibitors

Confirmed Binding Mode of Mandelic Acids

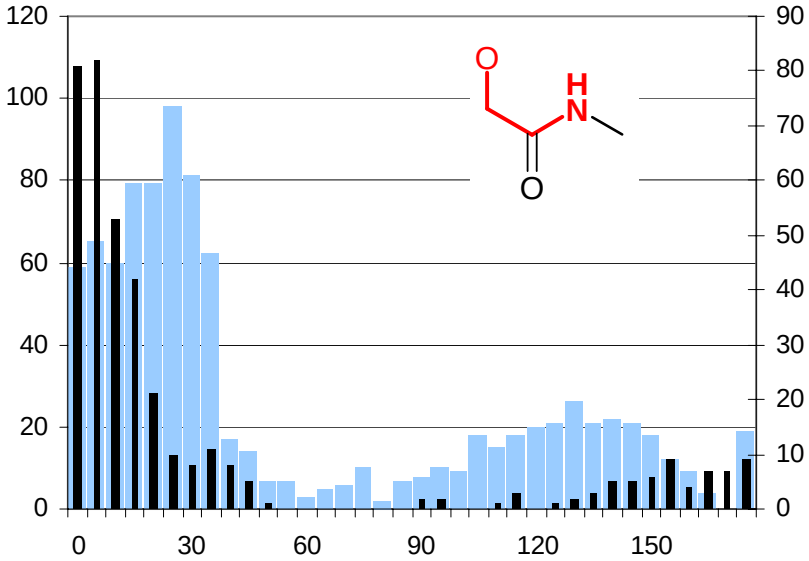


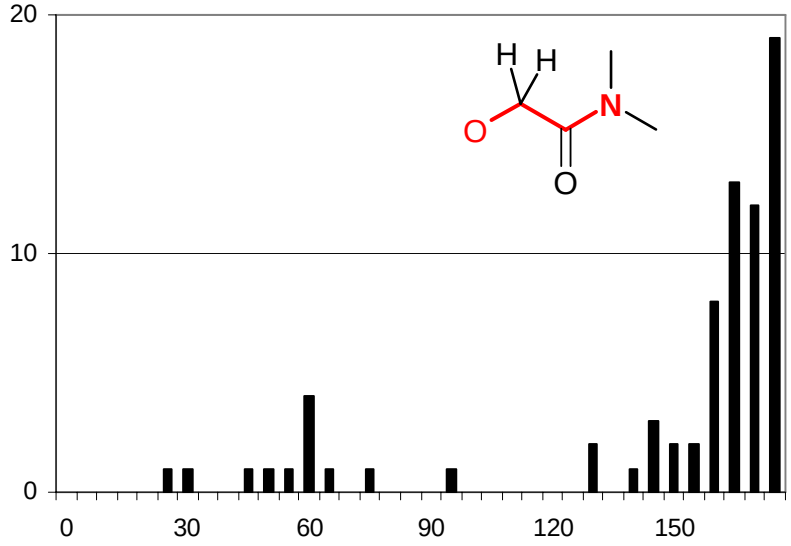
1.7 μM



Alkoxymethyl Amides – The General Case

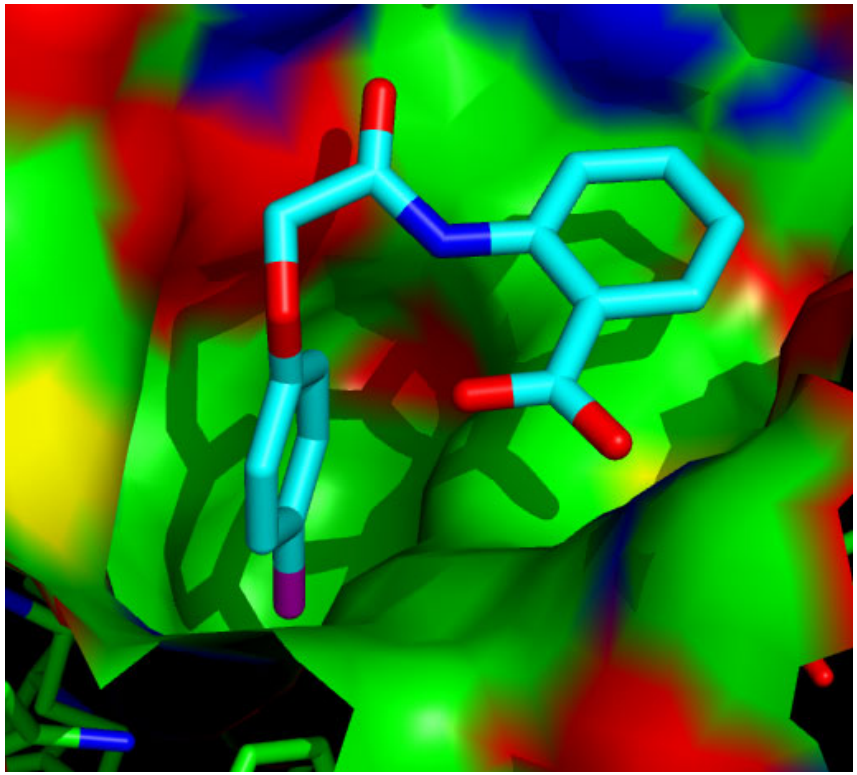
Secondary Amides: Syn - Tertiary Amides: Trans



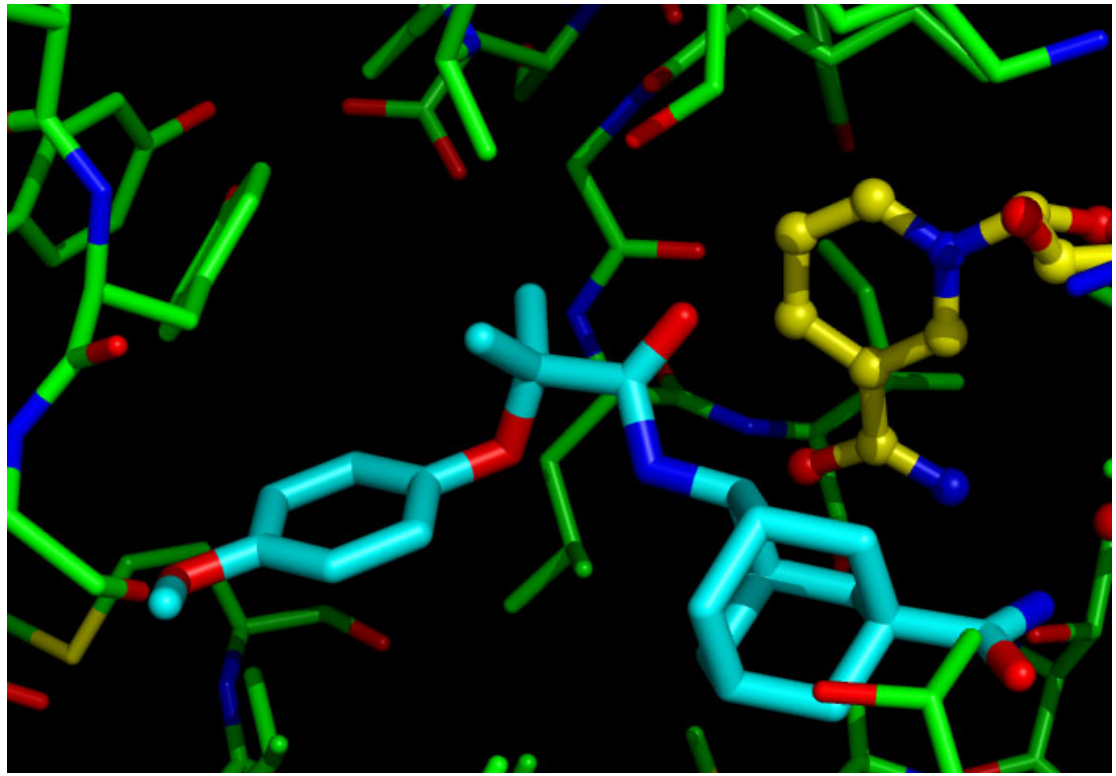


Alkoxymethyl Amides

PDB Examples



HCV polymerase palm site complex (2qe5)



locked: 11bHSD-1 complex (2irw)

Acknowledgments

- Scientists worldwide contributing to CSD and PDB
- Ken Brameld, Deborah Reuter, Roche Palo Alto
- Bernd Kuhn, Roche Basel
- Prof. Klaus Müller, Roche Basel
- Prof. François Diederich, ETH

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