EBERHARD KARLS
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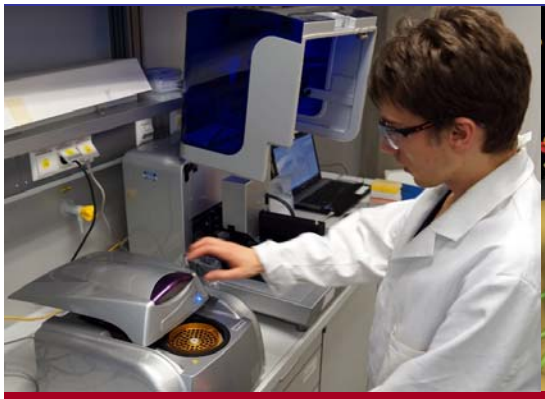

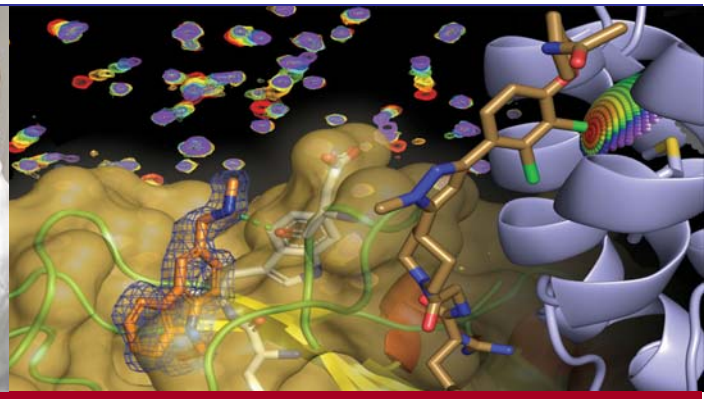

Wahlpflichtfach
Molekulares Design und Pharm. Biophysik

Prof. Dr. F. Böckler **24. April 2019**

PRINCIPLES & APPLICATIONS OF HALOGEN BONDING:

ACS Journalstars: Most cited papers in J. Med. Chem. 2013-15:

Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

Principles and Applications of Halogen Bonding in Medicinal Chemistry and Chemical Biology

Rainer Wilcken,[†,‡,§] Markus O. Zimmermann,[†,§] Andreas Lange,[†,§] Andreas C. Joerger,[‡] and Frank M. Boeckler*[,†]

[†]Laboratory for Molecular Design and Pharmaceutical Biophysics, Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard Karls University, Tuebingen, Auf der Morgenstelle 8, 72076 Tuebingen, Germany

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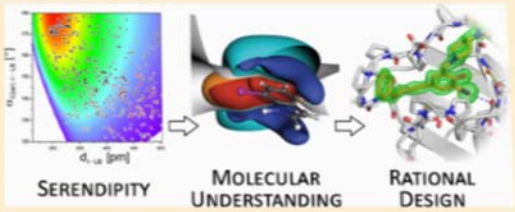
ABSTRACT: Halogen bonding has been known in material science for decades, but until recently, halogen bonds in protein−ligand interactions were largely the result of serendipitous discovery rather than rational design. In this Perspective, we provide insights into the phenomenon of halogen bonding, with special focus on its role in drug discovery. We summarize the theoretical background defining its strength and directionality, provide a systematic analysis of its occurrence and interaction geometries in protein−ligand complexes, and give recent examples where halogen bonding has been successfully harnessed for lead identification and optimization. In light of these data, we discuss the potential and limitations of exploiting halogen bonds for molecular recognition and rational drug design.

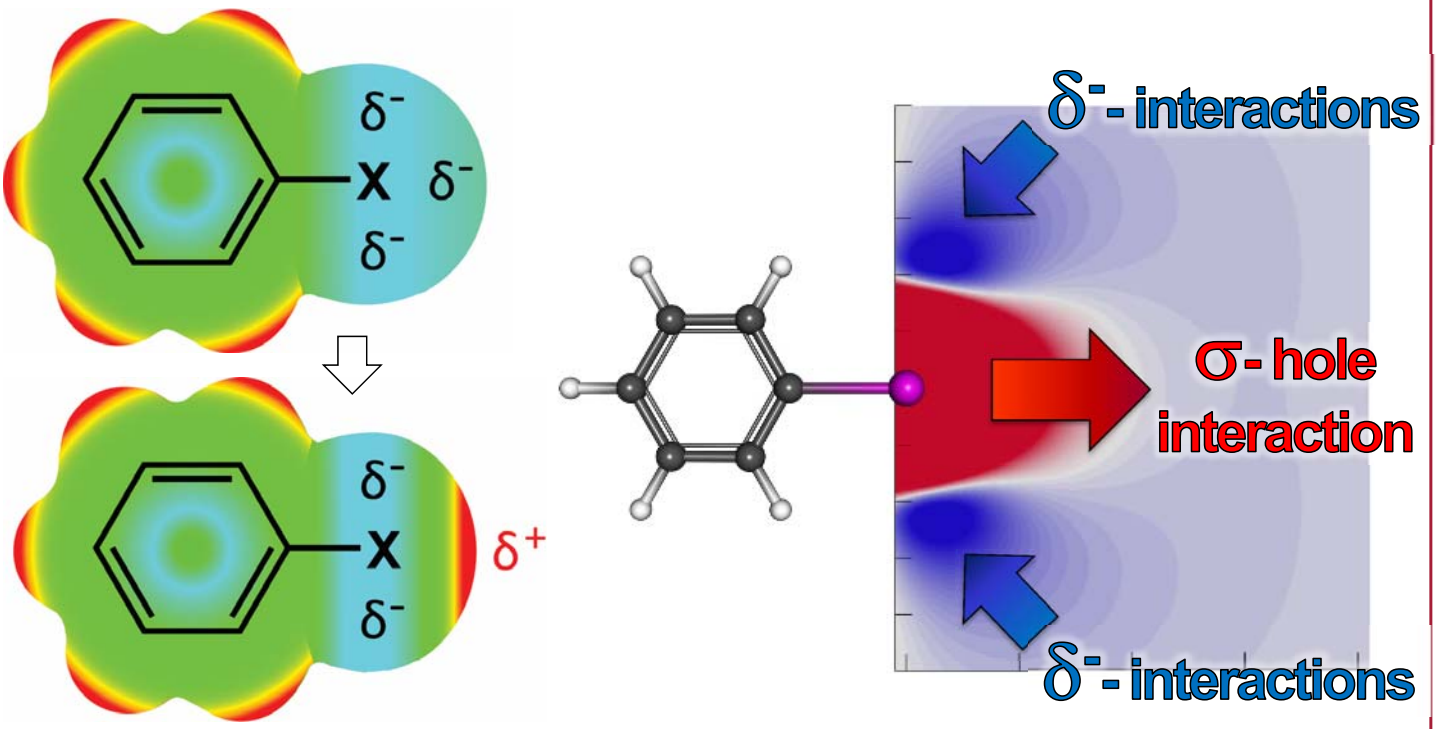


547 citations, > 25,000 downloads

Selected Most Cited Articles

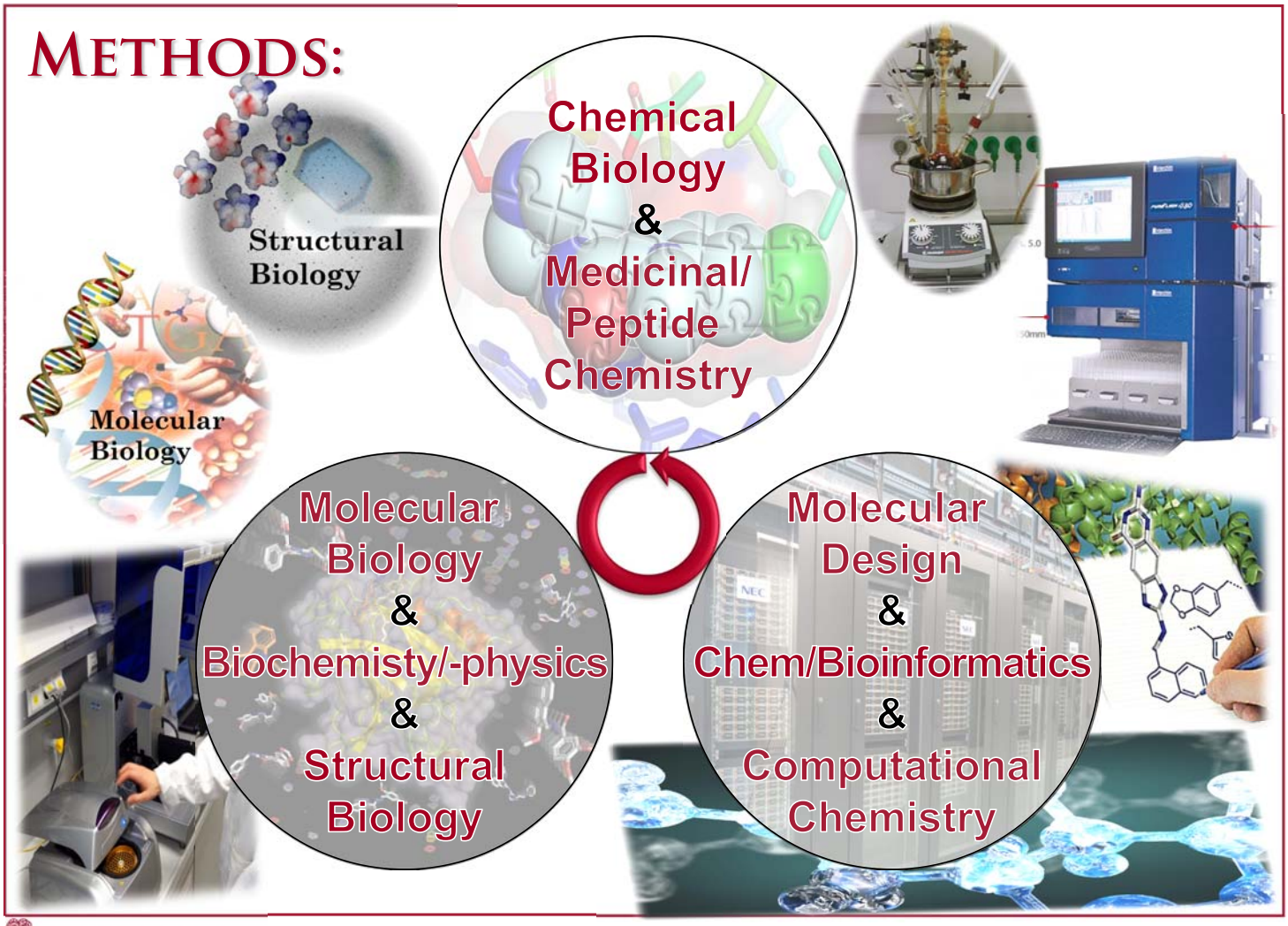
Halogen Bonding: Anisotropy of Electron Distribution

σ - hole concept:
T. Clark, M. Hennemann, J. Murray, P. Politzer, *J. Mol. Model.* 2007, 13, 291

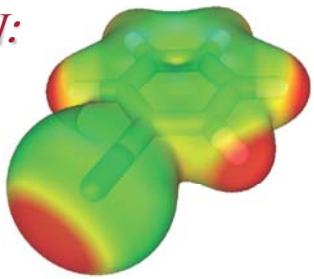


***J. Med. Chem.*, 2013, 56(4): 1363-88.**

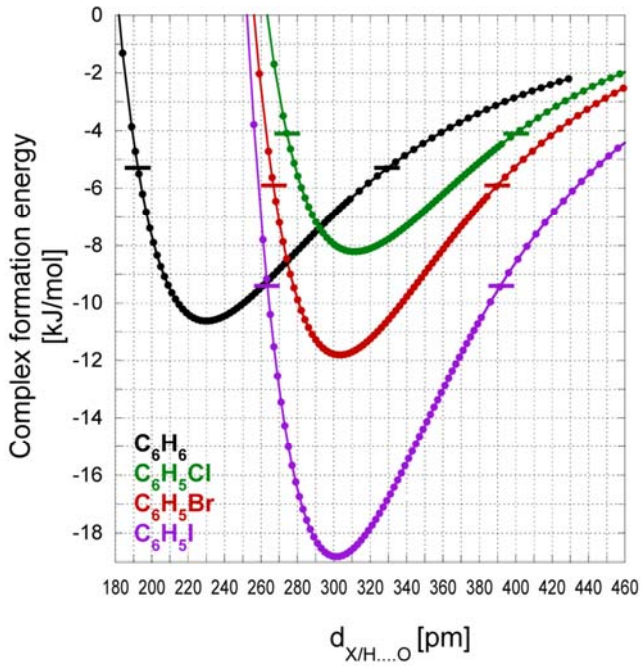
Methods:

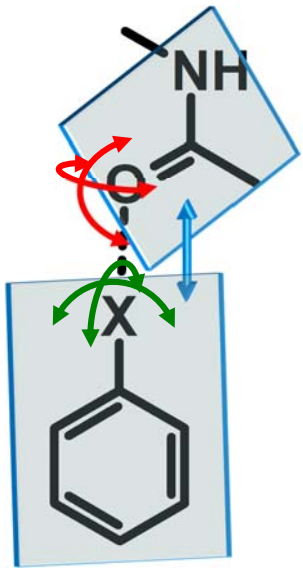


Understanding Molecular Recognition:



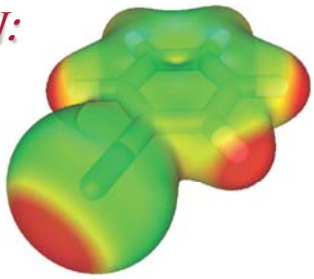
Dependence of interaction quality from geometry:





X = Cl, Br, I

Understanding Molecular Recognition:



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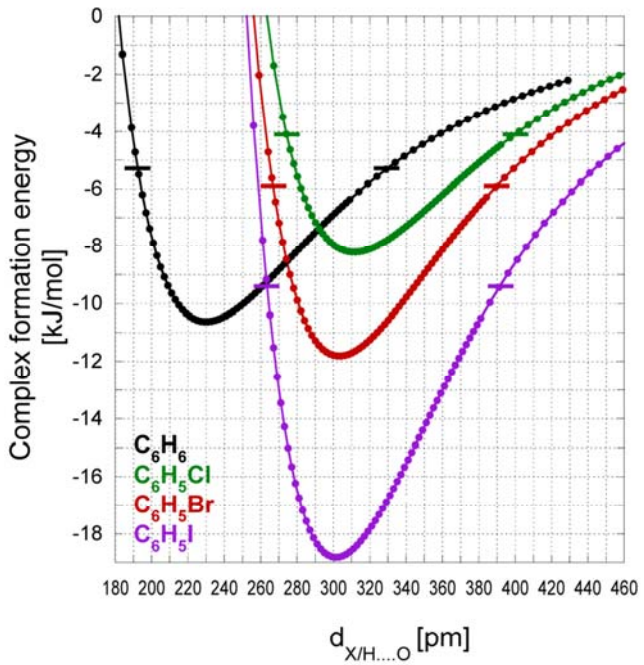
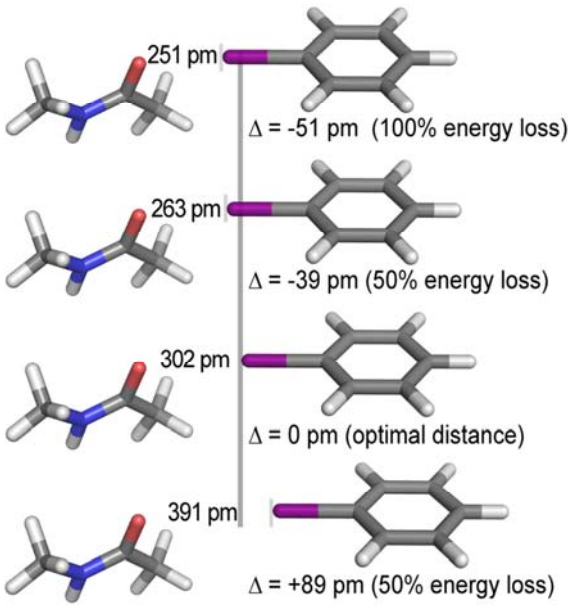
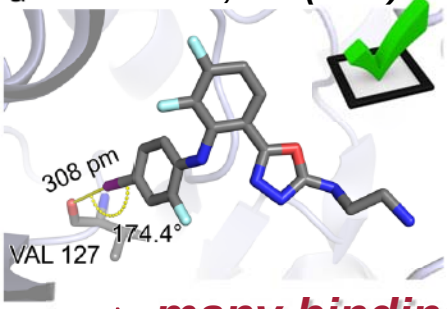




Halogen Bonding Interaction Partners:

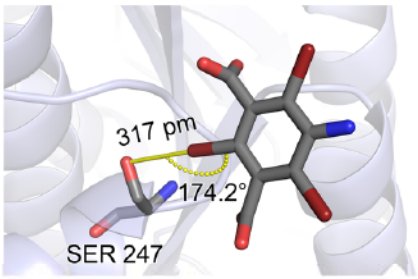
Backbone carbonyl
MedChemComm 7, 500 (2016)
JCAMD 26, 935 (2012)

a



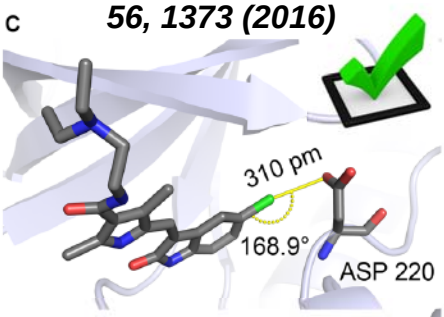
Hydroxyl contacts

b



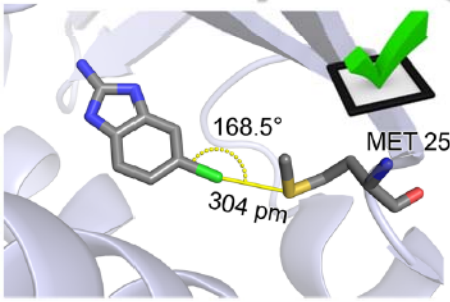
Carboxylates/amides
J. Chem. Inf. Model.
56, 1373 (2016)

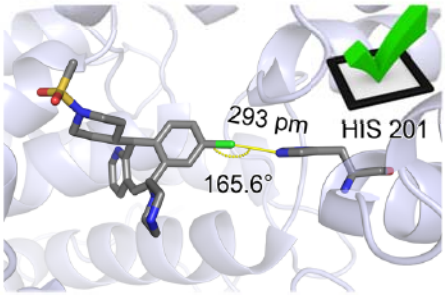
c

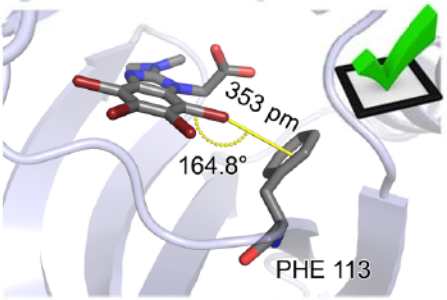


→ ***many binding opportunities, but only few hotspots!***

d







Sulfur contacts (Met)
J. Chem. Theory Comput.
7, 2307 (2011)

Nitrogen contacts (His)
J. Chem. Inf. Model.
53, 3178 (2013)

π - systems
in preparation

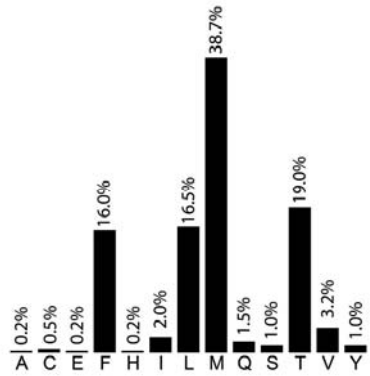
Examples of Molecular Design:

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

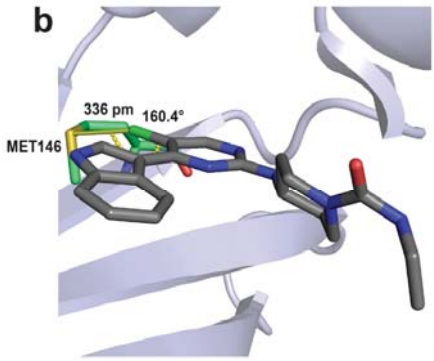
Targeting the Gatekeeper MET146 of C-Jun N-Terminal Kinase 3 Induces a Bivalent Halogen/Chalcogen Bond

Andreas Lange,[†,‡,§] Marcel B. Günther,[∥,§] Felix Michael Büttner,[#] Markus O. Zimmermann,[†,‡] Johannes Heidrich,[†,‡] Susanne Hennig,[†] Stefan Zahn,[¶] Christoph Schall,[#] Adrian Sievers-Engler,[⊥] Francesco Ansideri,[∥] Pierre Koch,[∥] Michael Laemmerhofer,[⊥] Thilo Stehle,[#,▽] Stefan A. Laufer,[∥] and Frank M. Boeckler[*,†,‡]

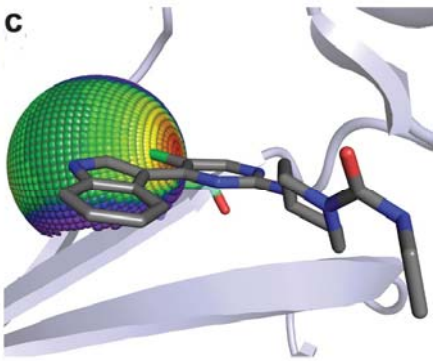
a



b

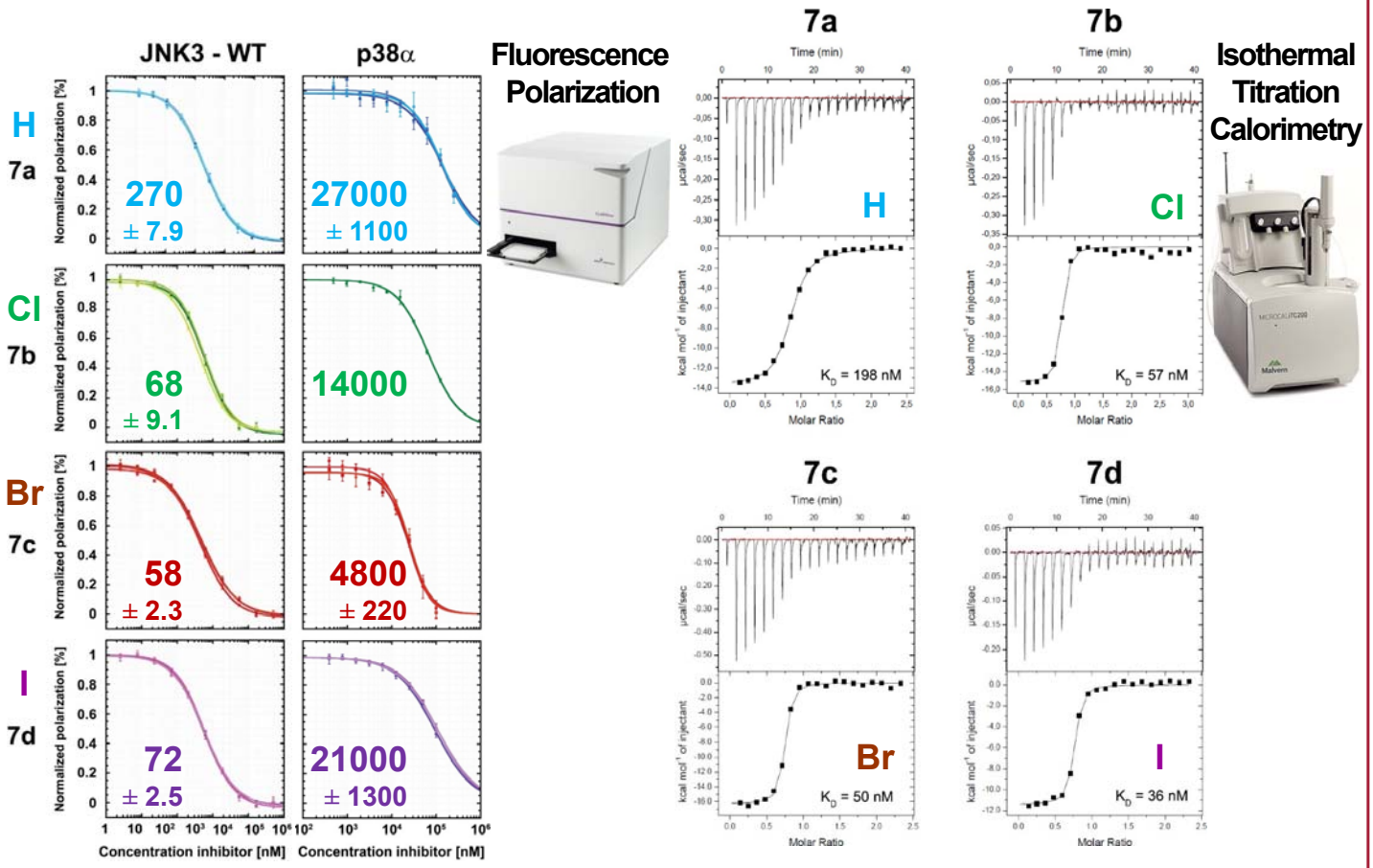


c



Based on: 2P33, Alam *et al.* Bioorg. Med. Chem. Lett. 17, 3463 (2007)

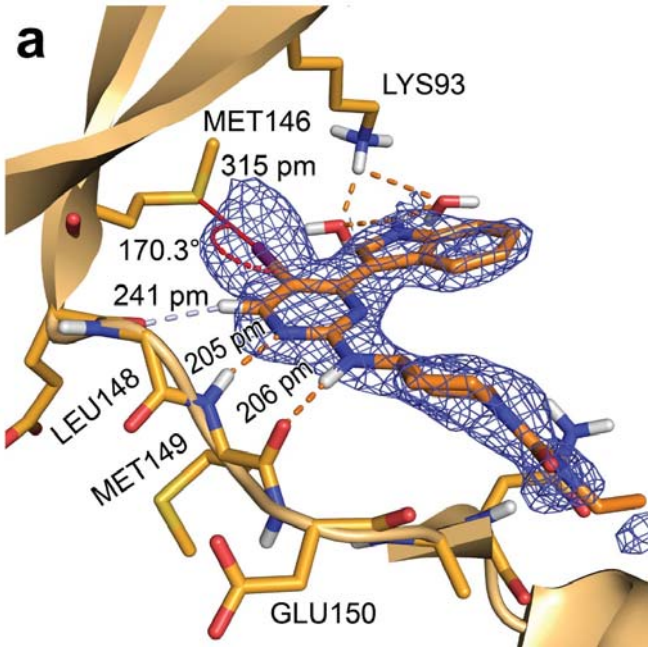
Examples of Molecular Design:



Examples of Molecular Design:

Iodine ··· sulfur distance too small!

➜ why is Met146 not more flexible???



Examples of Molecular Design:

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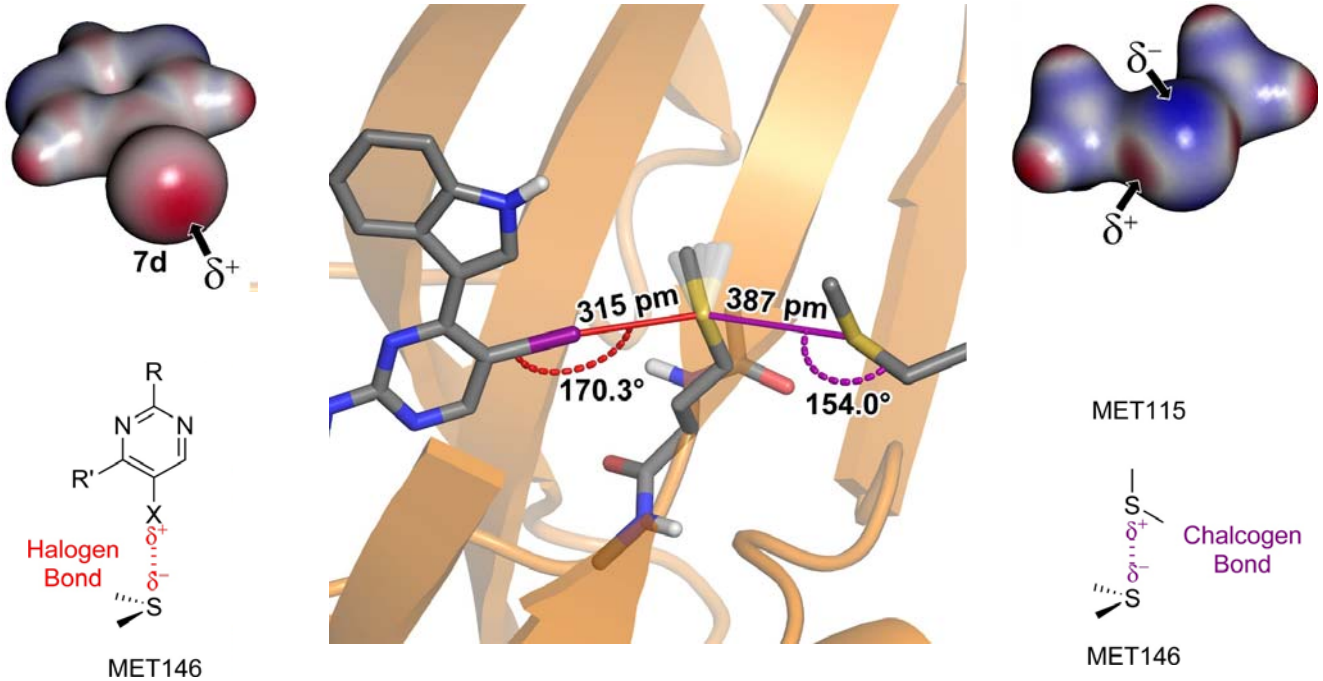
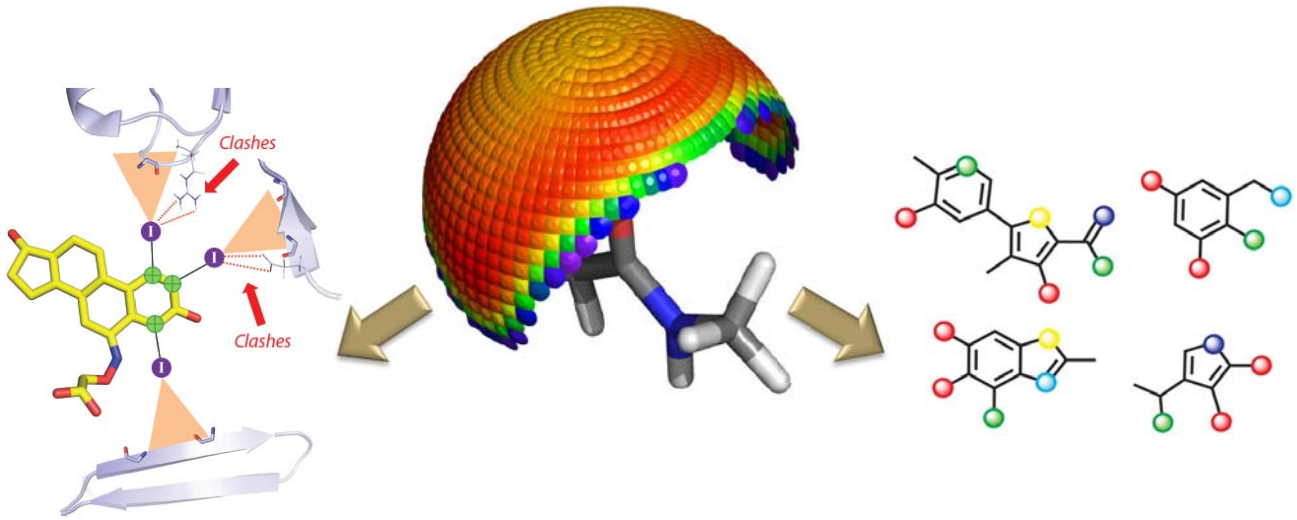


Shift from Molecular Design to HEFLibs:



In Molecular Design:

- **Geometric requirements for good XBs are difficult to meet (other interactions dominate the binding mode)**
- **Full potential of XBs is difficult to harness**

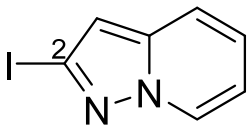
HEFLibs as Chemical Tools:

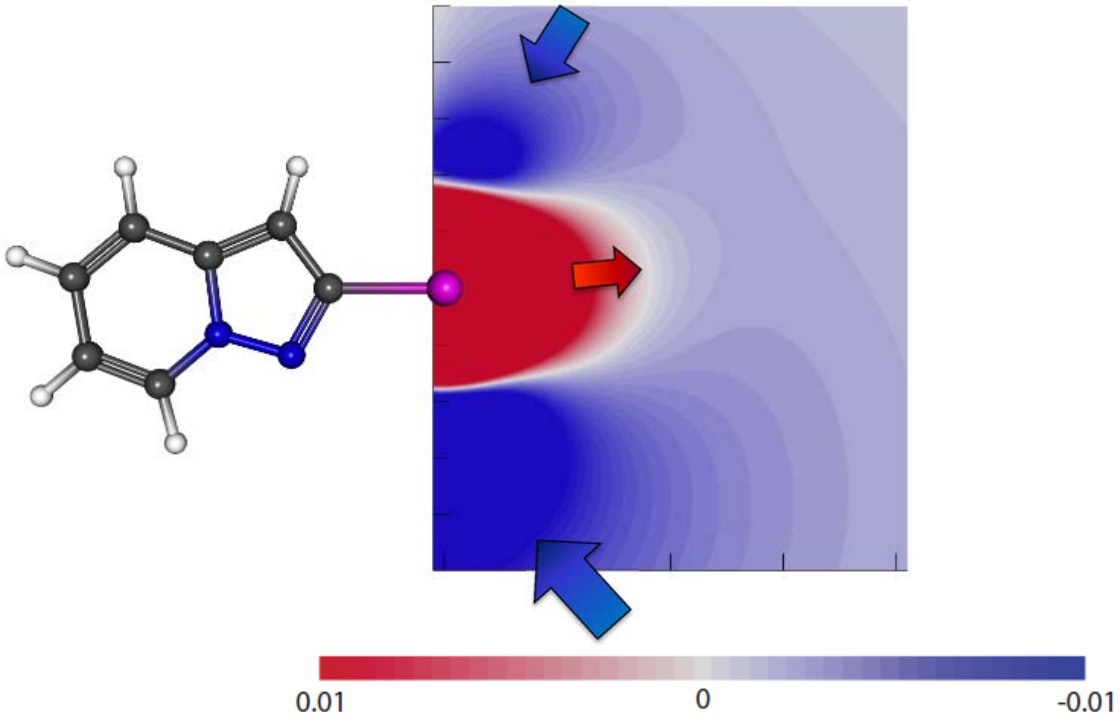
- **Integration of XBs in binding motifs / networks**
- **Tuning and cooperativity**

→ Diversity optimization for generalization of HEFLibs

σ - HOLE SIZE AND SHAPE DEPENDS ON THE CHEMICAL CONTEXT

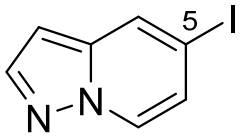
Pyrazolo[1,5-a]pyridines:

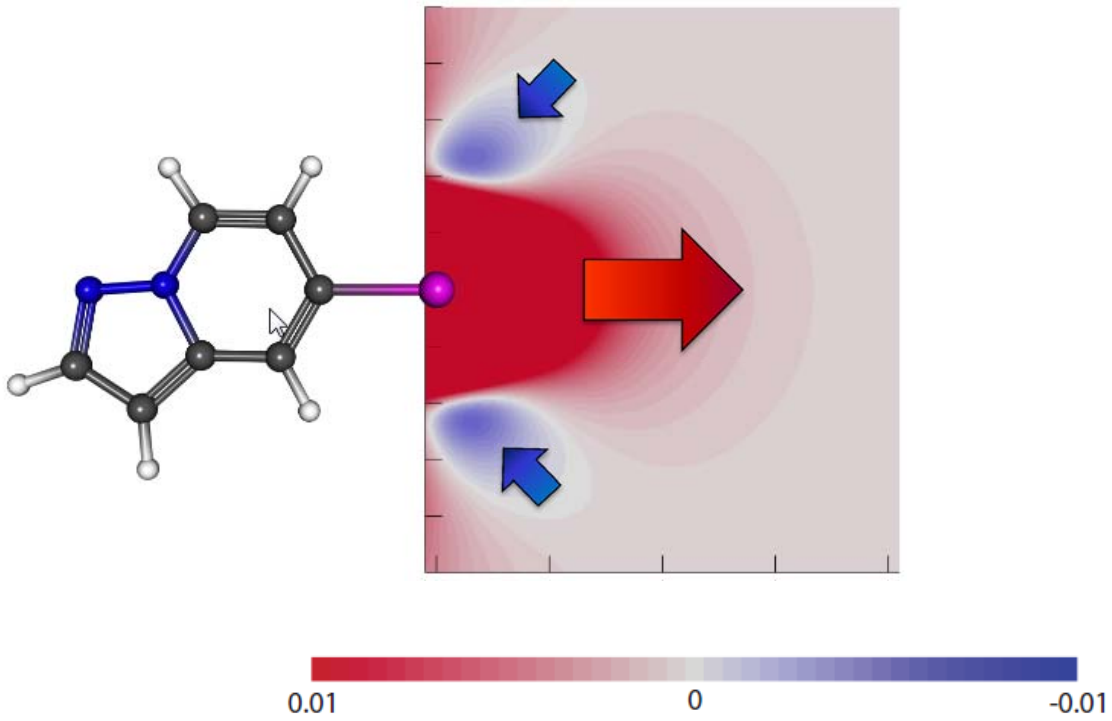




σ - HOLE SIZE AND SHAPE DEPENDS ON THE CHEMICAL CONTEXT

Pyrazolo[1,5-a]pyridines:

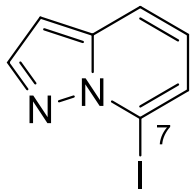


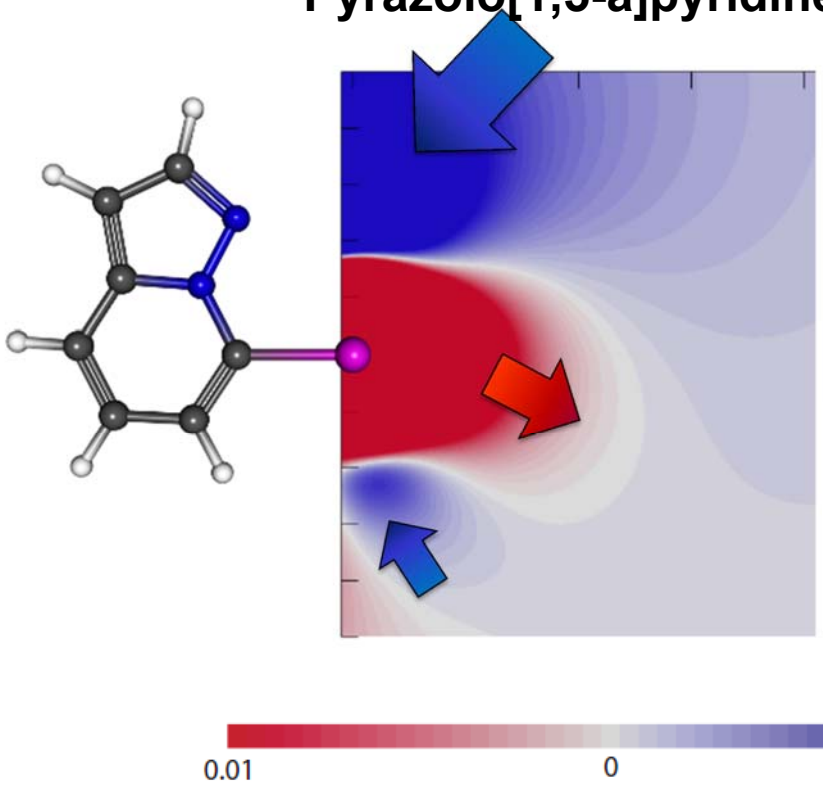


Frank M. Böckler *Wahlpflichtfach Molekulares Design & Pharmazeutische Biophysik* 26.04.2019

σ - HOLE SIZE AND SHAPE DEPENDS ON THE CHEMICAL CONTEXT

Pyrazolo[1,5-a]pyridines:



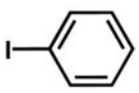


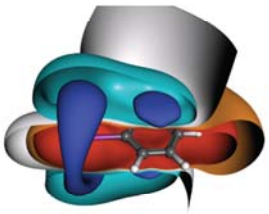
→ *vast number of binding motifs are possible*

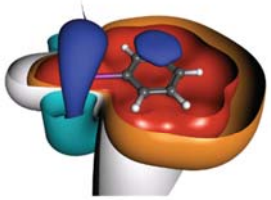
σ - HOLE SIZE AND SHAPE DEPENDS ON THE CHEMICAL CONTEXT

Substituent effects:
(e.g. fluorine)

a







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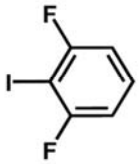

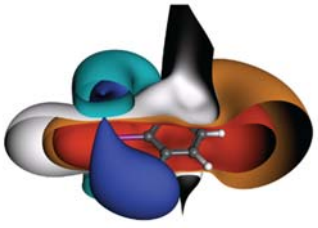

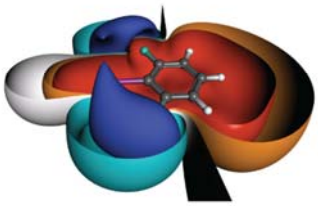

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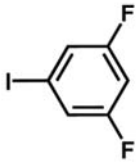
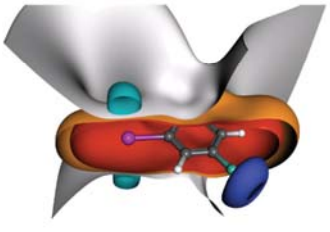
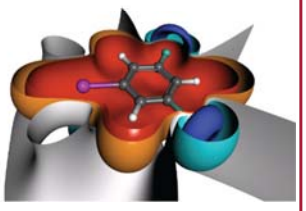




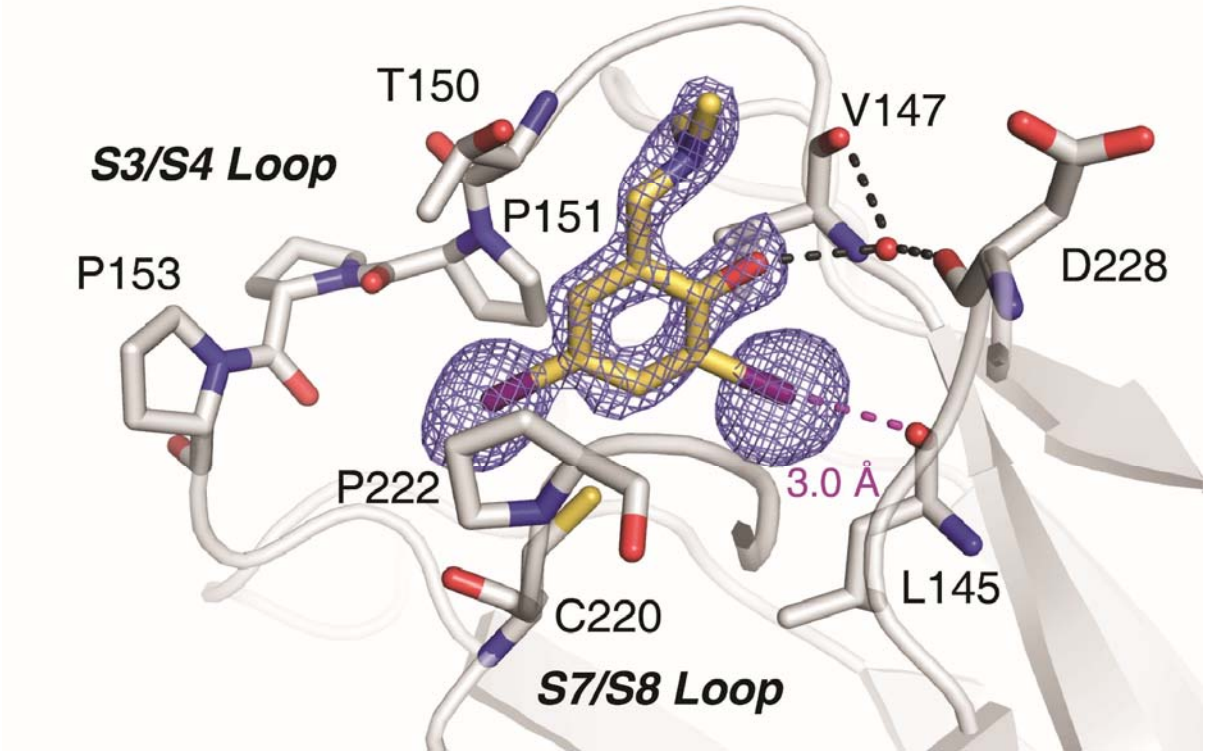


→ *cooperativity by tuning and enhancing the binding motifs*

J. Med. Chem., 2013, 56(4): 1363-88.

Frank M. Böckler *Wahlpflichtfach Molekulares Design & Pharmazeutische Biophysik* 26.04.2019

Showcase Example for HEFLibs Strategy :

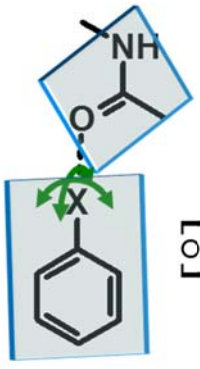


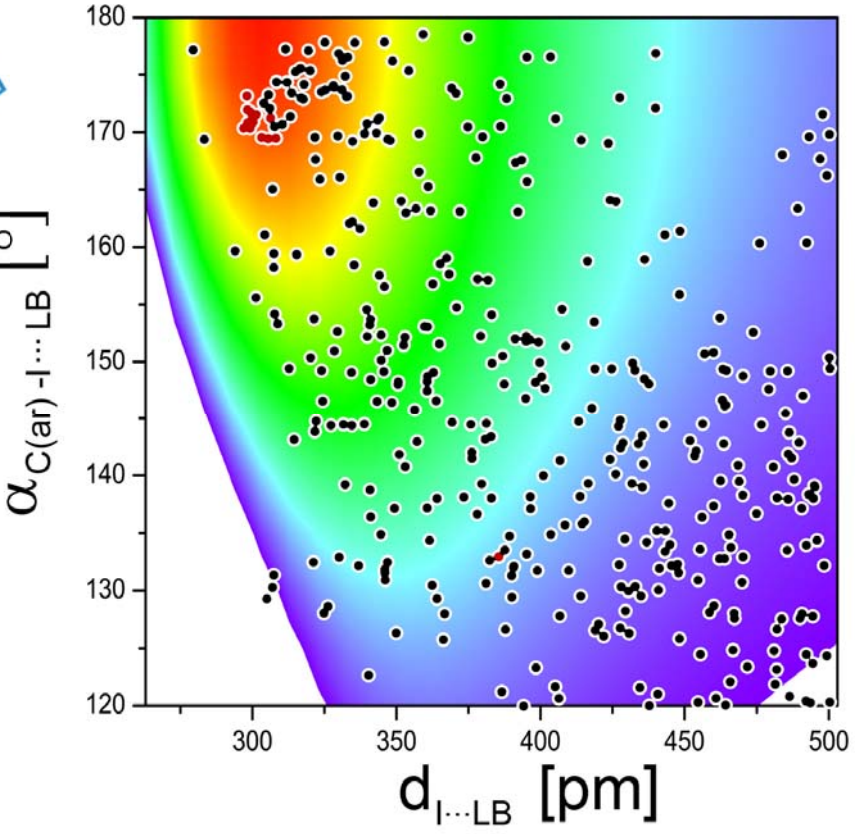
Almost optimal X-bond geometry + stabilization by interstitial water

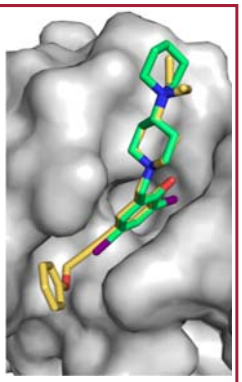
Wilcken R., ..., Boeckler F. M., *J. Am. Chem. Soc.* **2012**, 134, 6810−6818

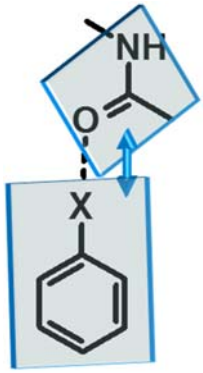
JACS-Spotlight: *J. Am. Chem. Soc.* **2012**, 134, 7195

Top-5% of all Halogen-Carbonyl contacts in the PDB

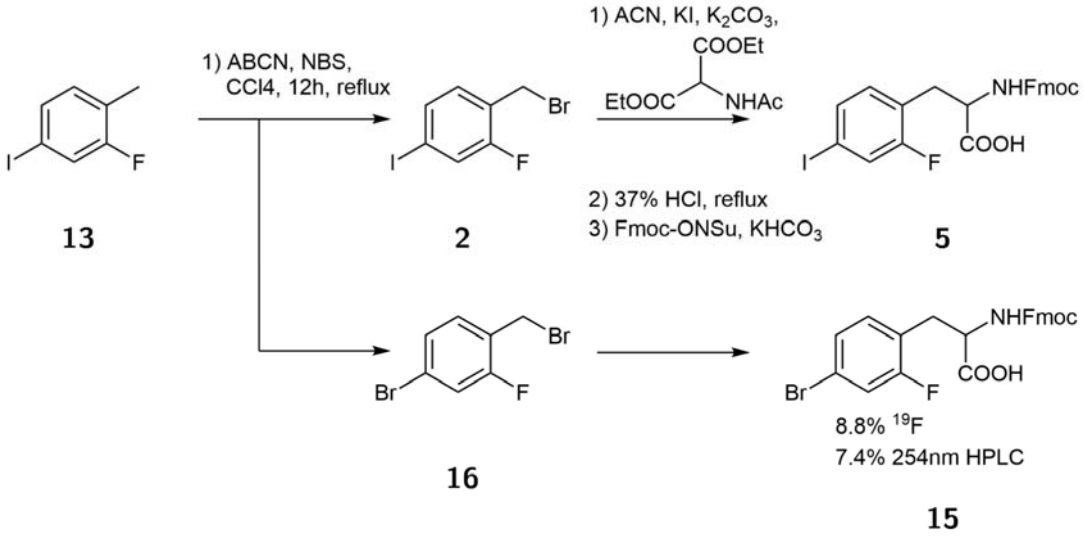


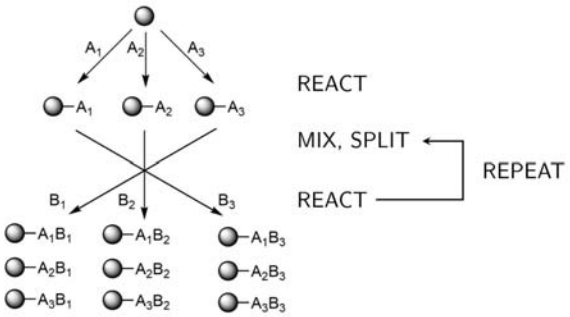


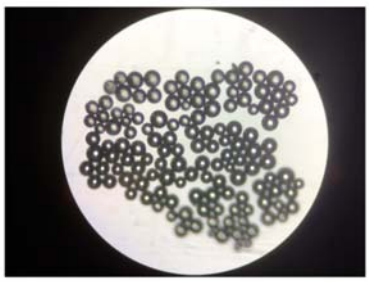




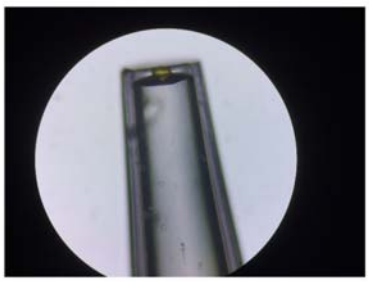
From Fragments to Amino Acids:



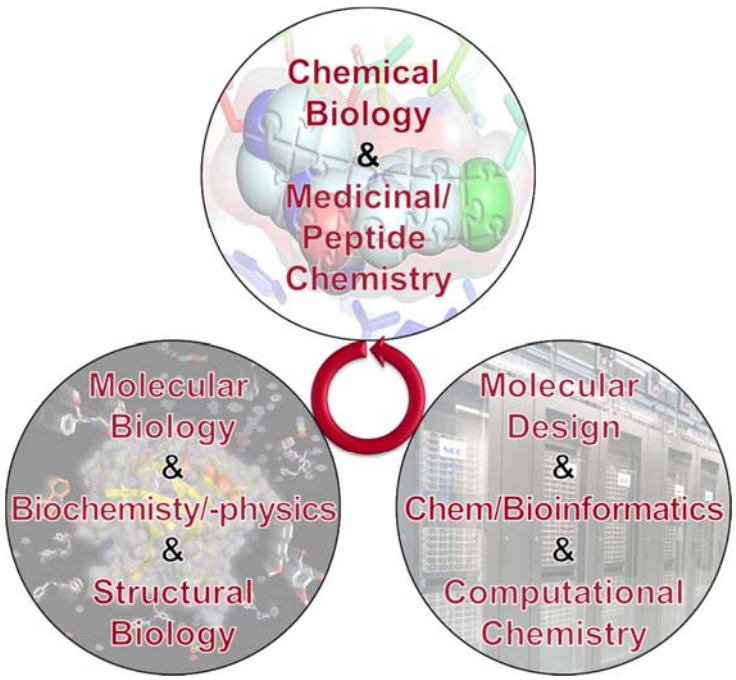




(a) *Multiple beads on a watch glass.*



(b) *Single bead picked by a 10 µL pipette tip.*



We Want You!