Principles & Applications of Halogen Bonding:

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

547 citations, > 25,000 downloads
**Halogen Bonding:**
**Anisotropy of Electron Distribution**

\[ \delta^- \text{- hole concept:} \]

\[ \delta^- \text{- interactions} \]

\[ \delta^- \text{- interactions} \]


**Methods:**

- Chemical Biology & Medicinal/Peptide Chemistry
- Molecular Biology & Biochemistry/physics & Structural Biology
- Molecular Design & Chem/Bioinformatics & Computational Chemistry

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Understanding Molecular Recognition:

Dependence of interaction quality from geometry:

\[ X = \text{Cl, Br, I} \]
**Halogen Bonding Interaction Partners:**

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

- **Hydroxyl contacts**
  - 317 pm 174.2°
  - SER 247
  - 310 pm
  - ASP 220

- **Carboxylates/amides**

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

- **Sulfur contacts (Met)**

- **Nitrogen contacts (His)**

- **π - systems**
  - in preparation

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**Examples of Molecular Design:**

**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:

**EXAMPLES OF MOLECULAR DESIGN:**

Iodine … sulfur distance too small!

→ why is Met146 not more flexible???
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Iodine … sulfur distance too small!

→ why is Met146 not more flexible???

**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:

- Hole size and shape depend on the chemical context.
σ - HOLE SIZE AND SHAPE DEPENDS ON THE CHEMICAL CONTEXT

Substituent effects: a (e.g. fluorine)

→ cooperativity by tuning and enhancing the binding motifs

Almost optimal X-bond geometry + stabilization by interstitial water

Top-5% of all Halogen-Carbonyl contacts in the PDB
From Fragments to Amino Acids:

1) ABCN, NBS, CCl₄, 12h, reflux

13 → 1) ACN, KI, K₂CO₃, COOEt

EtOOC → NHAc

2) 37% HCl, reflux

3) Fmoc-ONs, KHCO₃

16 → 15

8.8% ¹⁹F
7.4% 254nm HPLC

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