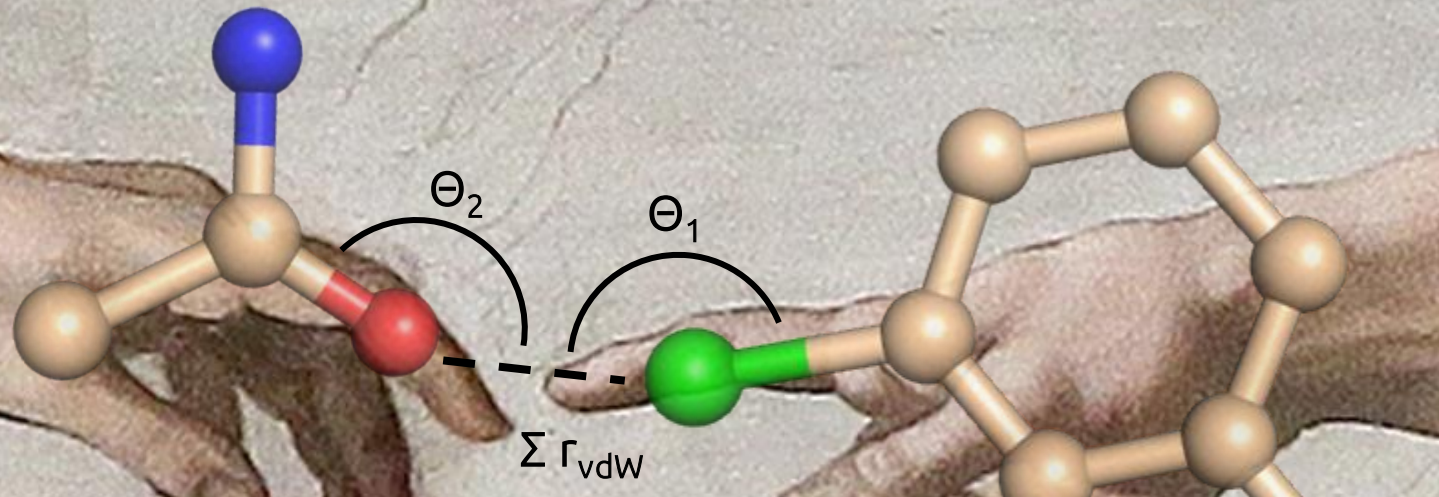
Unravelling the Impact of Halogen Interactions in Medicinal Chemistry

Christoph P. Sager

SCS Spring School on Digital Chemistry – 19 April 2023

Agenda

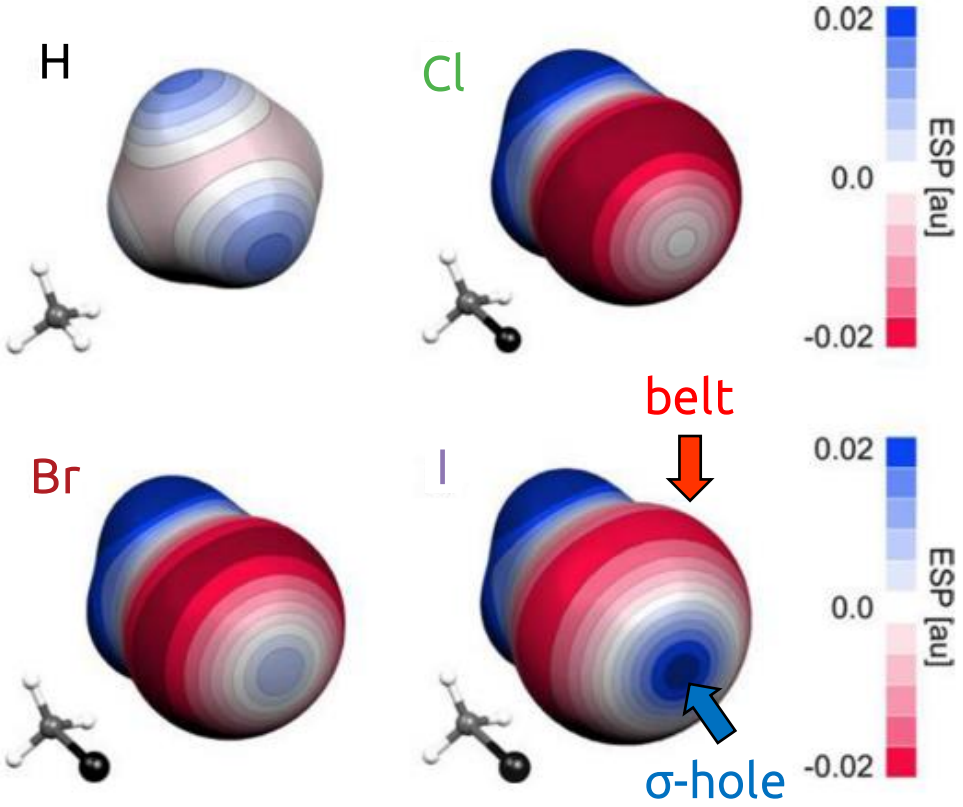


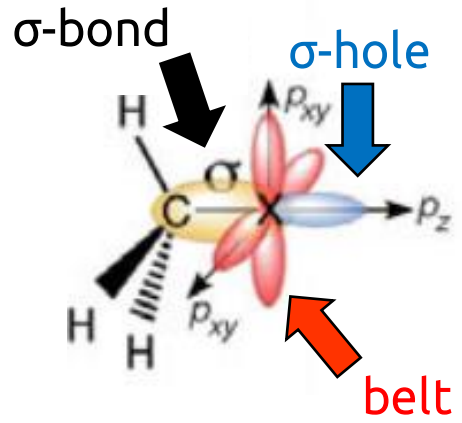
- Halogen bonds and their interactions
- Exercise #2.1
- Application of halogen bonds in our projects
- Sulfur-oxygen interactions
- Fluorine multipolar interactions
- Exercise #2.2
- Summary

Halogen bonds

Halogen bonding – the σ-hole

Scholfield et al. / Shinada et al. / Cramer et al.





- Group VII has **5 electrons** in the *p*-atomic orbitals
  - Single valence electron (p_z orbital) forms the covalent **σ-bond**
  - The opposite side of the p_z orbital is depopulated -> σ-hole
  - Remaining 4 electrons (p_{xy} orbitals) form the negative belt

VII

9 F Fluorine Halogen

17 Cl Chlorine Halogen

35 Br Bromine Halogen

53 I Iodine Halogen

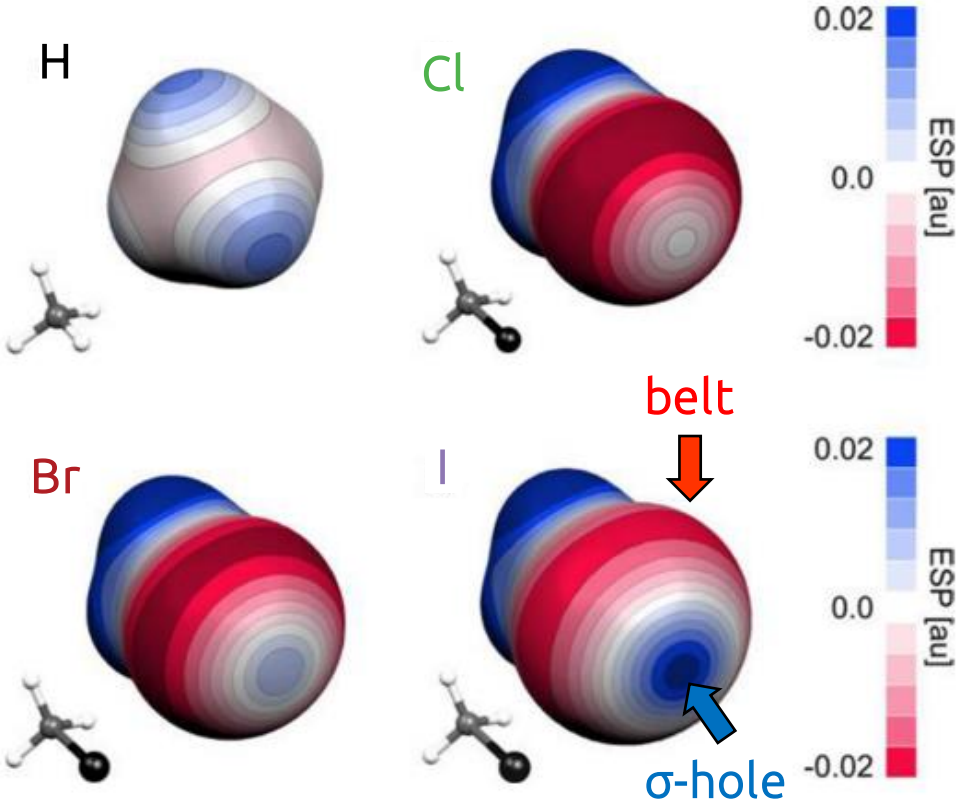
85 At Astatine Halogen

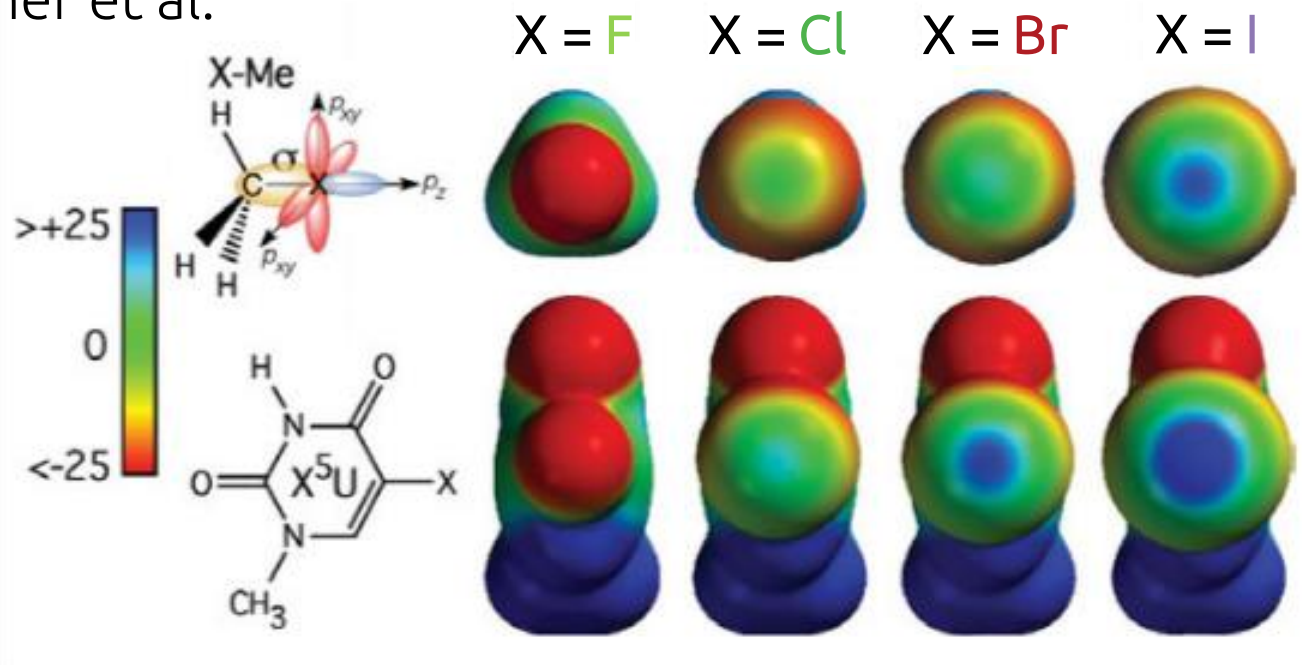
117 Ts Tennessine Halogen

Protein Science. 2013, 22:139-152; *J. Med. Chem.* 2019, 62, 21, 9341-9356; *J. Med. Chem.* 2019, 62, 20, 8915–8930

Halogen bonding – the σ-hole

Scholfield et al. / Shinada et al. / Cramer et al.





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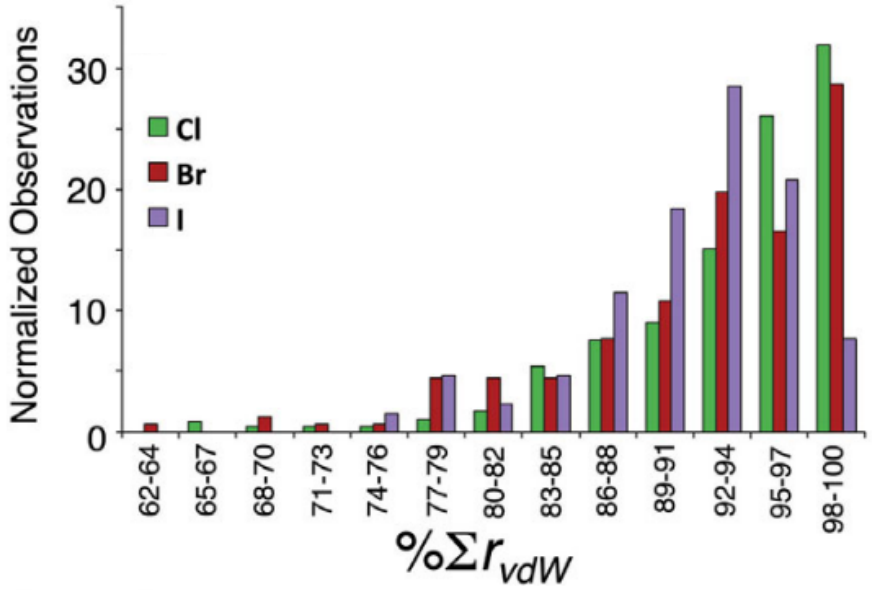
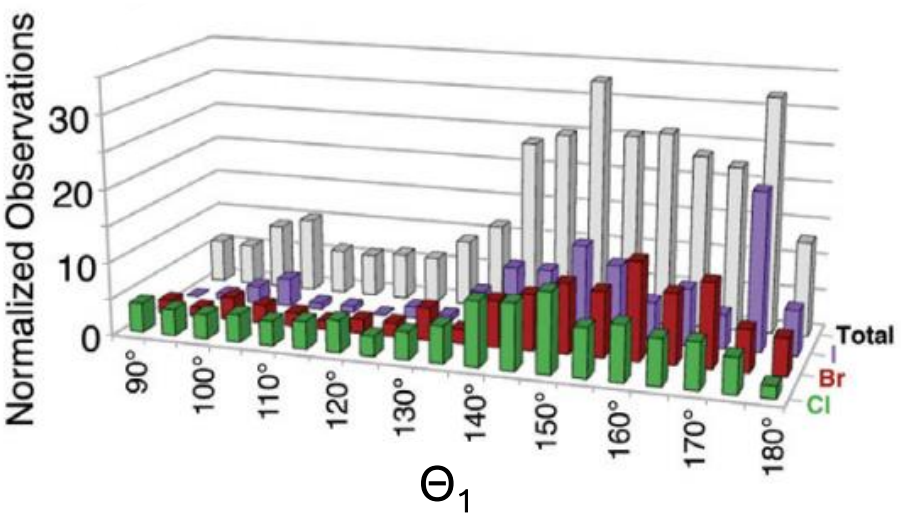
- Group VII has **5 electrons** in the *p*-atomic orbitals
  - Single valence electron (p_z orbital) forms the covalent **σ-bond**
  - The opposite side of the p_z orbital is depopulated -> σ-hole
  - Remaining 4 electrons (p_{xy} orbitals) form the negative belt
- Polarizability/Size: F < Cl < Br < I ~ 4–8 kJ mol^{-1}
  - Electron withdrawing partner: 16 kJ mol^{-1}
- Classical hydrogen bonds: 18 – 21 kJ mol-1
- Desolvation cost of a hydroxyl group: 11 – 24 kJ mol-1

Protein Science. 2013, 22:139-152; *J. Med. Chem.* 2019, 62, 21, 9341-9356; *J. Med. Chem.* 2019, 62, 20, 8915–8930

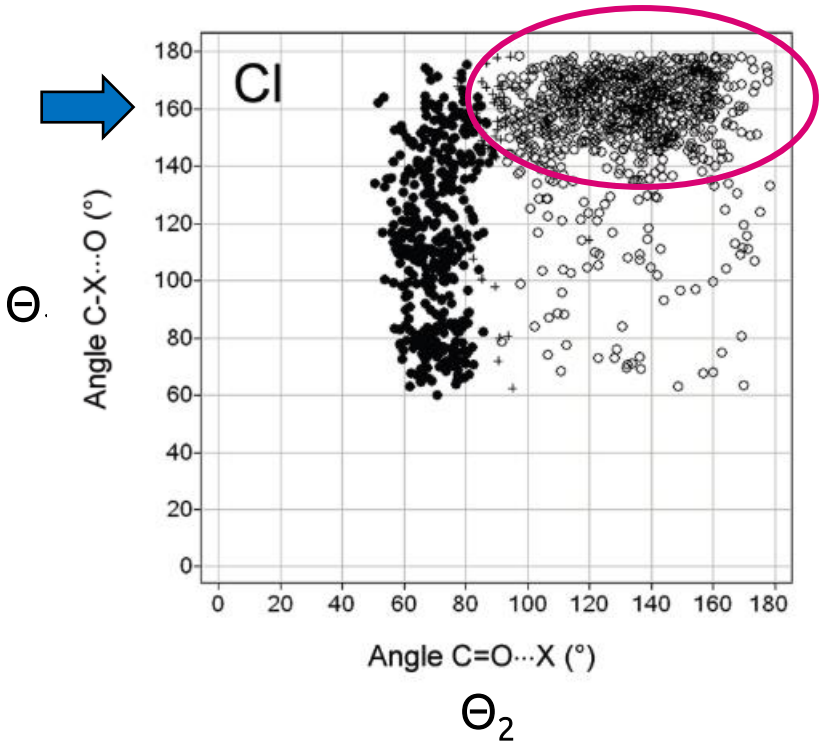
Halogen bonding - geometries

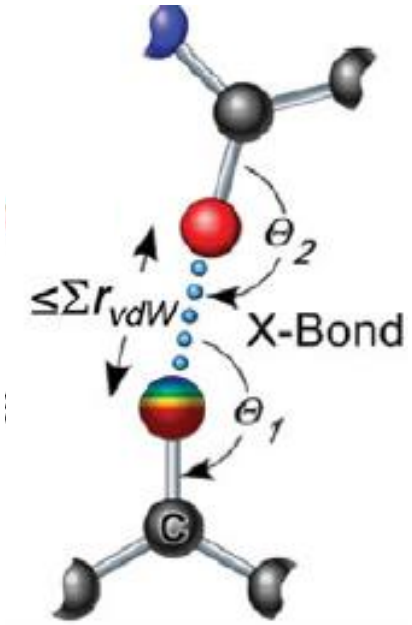
Scholfield et al. / Bissantz et al.





- Distance: ≤ $\sum r_{vdW}$ Å,
  - ≤ 3.24 Å, ≤ 3.37 Å, ≤ 3.5 Å
- Linearity (Θ_1) = 160°–165°
- Planarity (Θ_2) = 120°

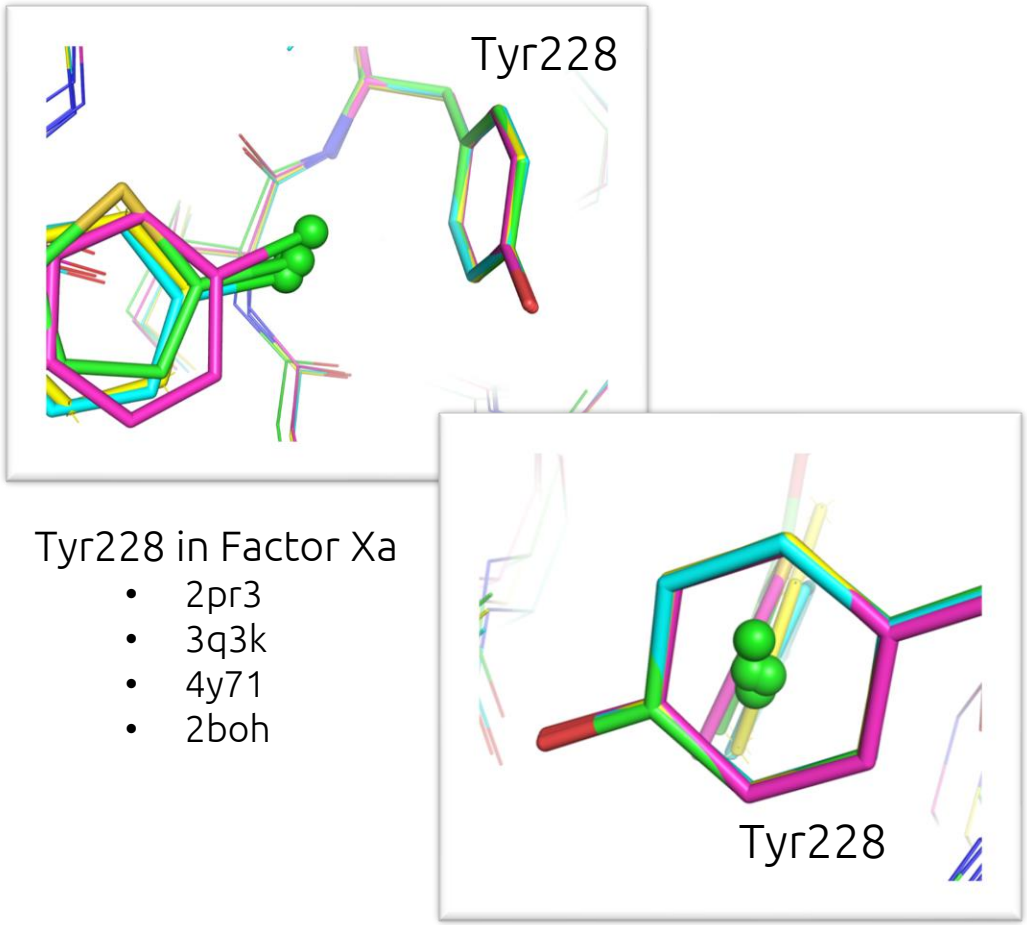




Protein Science. 2013, 22:139-152, *J. Med. Chem. 2010, 53, 5061–5084*

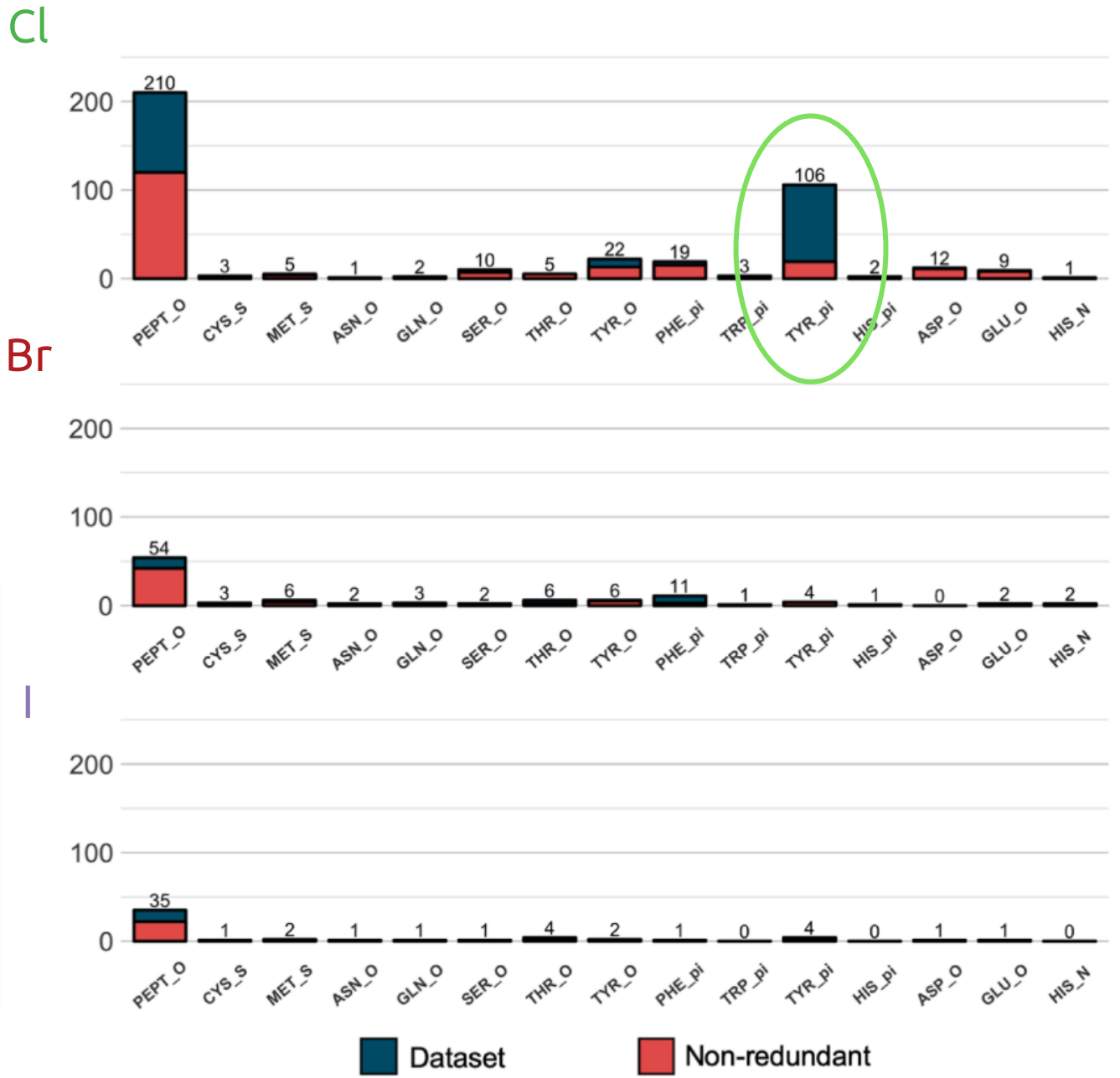
X-bond interactions

Shinada et al.



Tyr228 in Factor Xa

- 2pr3
- 3q3k
- 4y71
- 2boh



J. Med. Chem. 2019, 62, 21, 9341-9356

Exercise #2.1
Cathepsin L & MAP ERK kinase

Odd-Groups (1, 3, 5, …)
Open: Cathepsin_L_example.pdb

Even-Groups (2, 4, 6, …)
Open: MAP_ERK_kinase_example.pdb

Goal: Add/Change only 1 atom to improve affinity

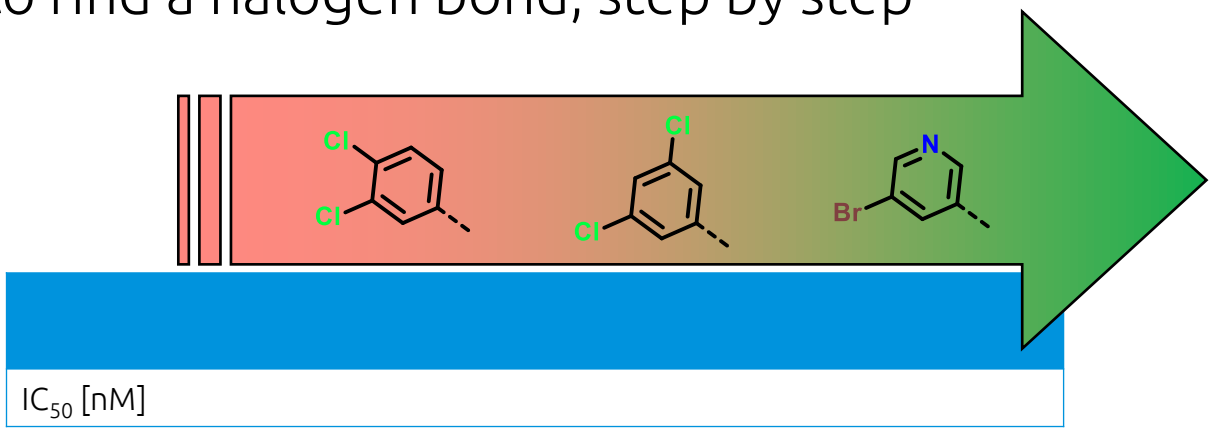
Time: 10 min

Presentation: Two groups (1 odd & 1 even group), 2 min each

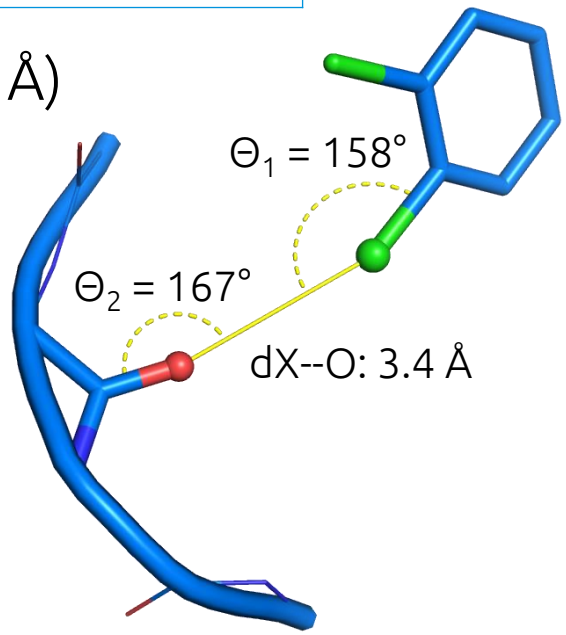
Application of halogen bonds in our projects

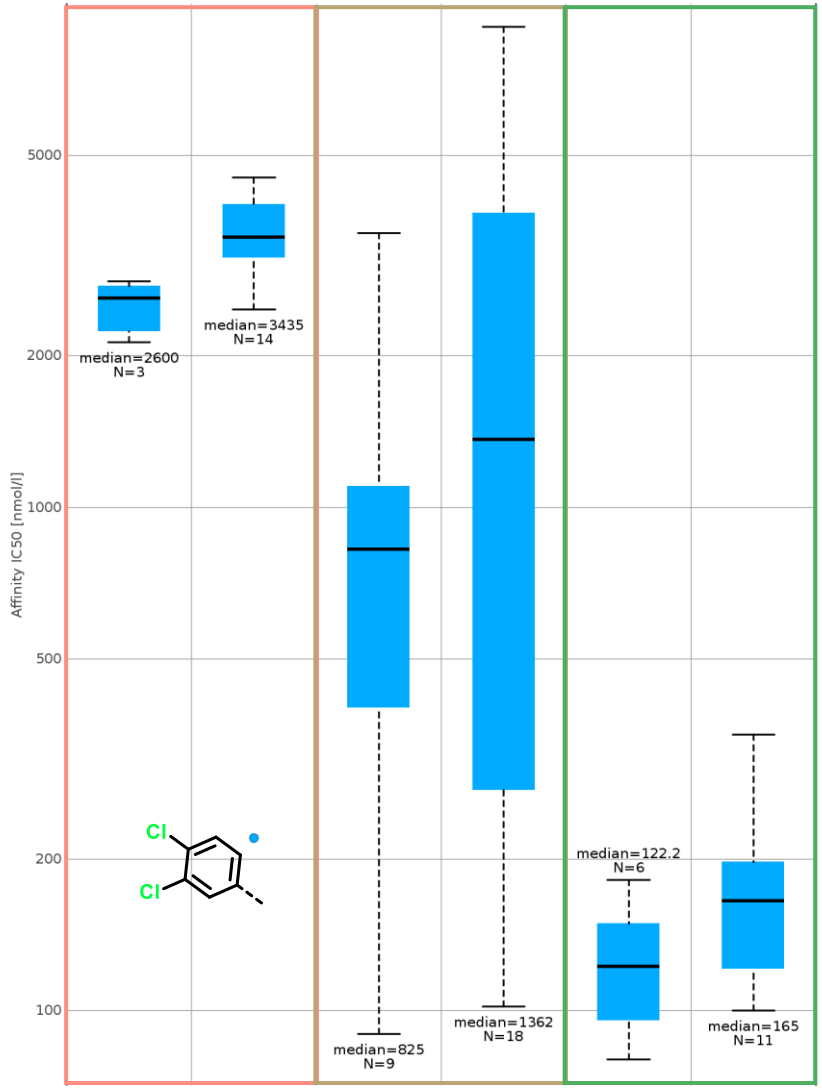
Crystallography enables virtual screening

How to find a halogen bond, step by step



- Crystal Structures: 120+ (avg. 1.4 Å)
- Starting point: 4500 nM
- Docking: 14’000
- Synthesized: 17 (220 – 4000 nM)
- Follow-up: 27 (90 – 9000 nM)
- 2nd follow-up: 17 (80 – 350 nM)

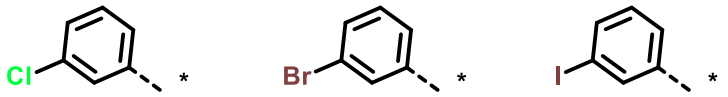




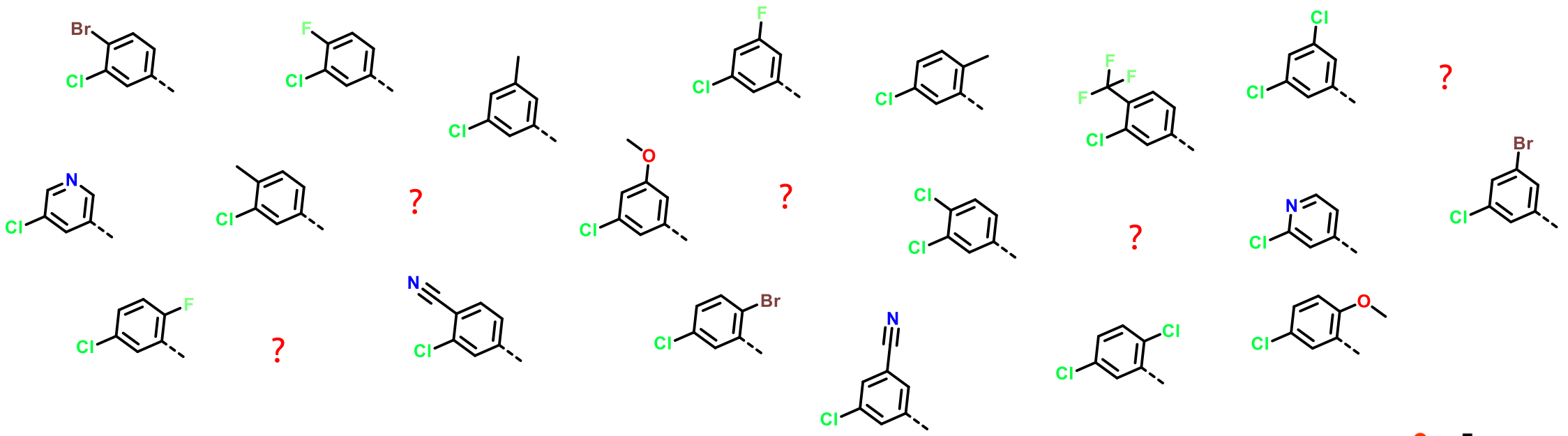
Probing halogen bonding

Knowledge transfer to other series

	Phenyl	Meta-F	Meta-Cl	Meta-Br
IC_{50} [nM]	67 (n = 4)	49 (n = 1)	16 (n = 6)	22 (n = 3)

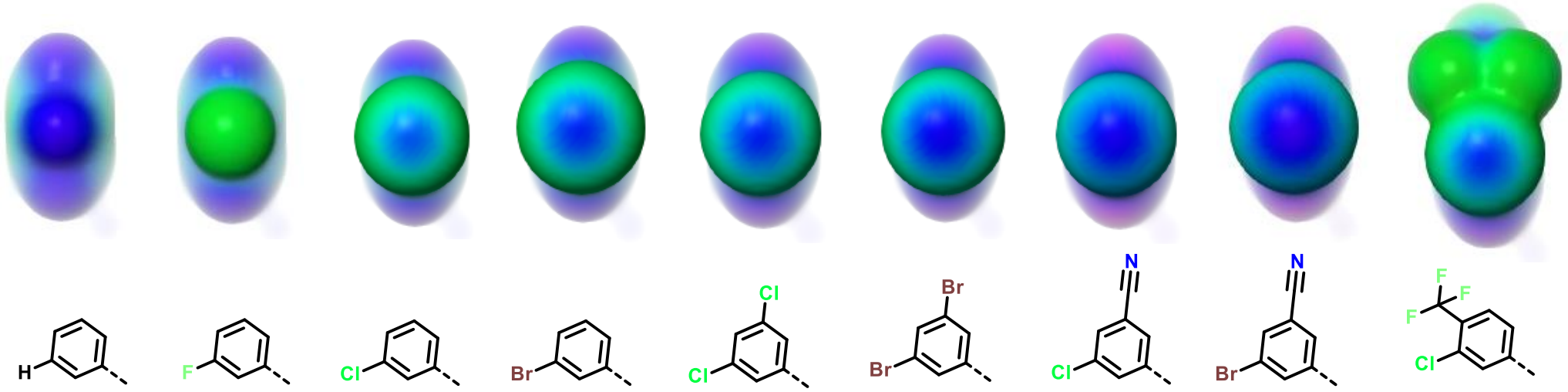


Meta-Cl*	Meta-Br*	Meta-I*
37 (n = 2)	79 (n = 1)	42 (n = 2)



Increasing the σ-hole effect

Electrostatic surface potentials



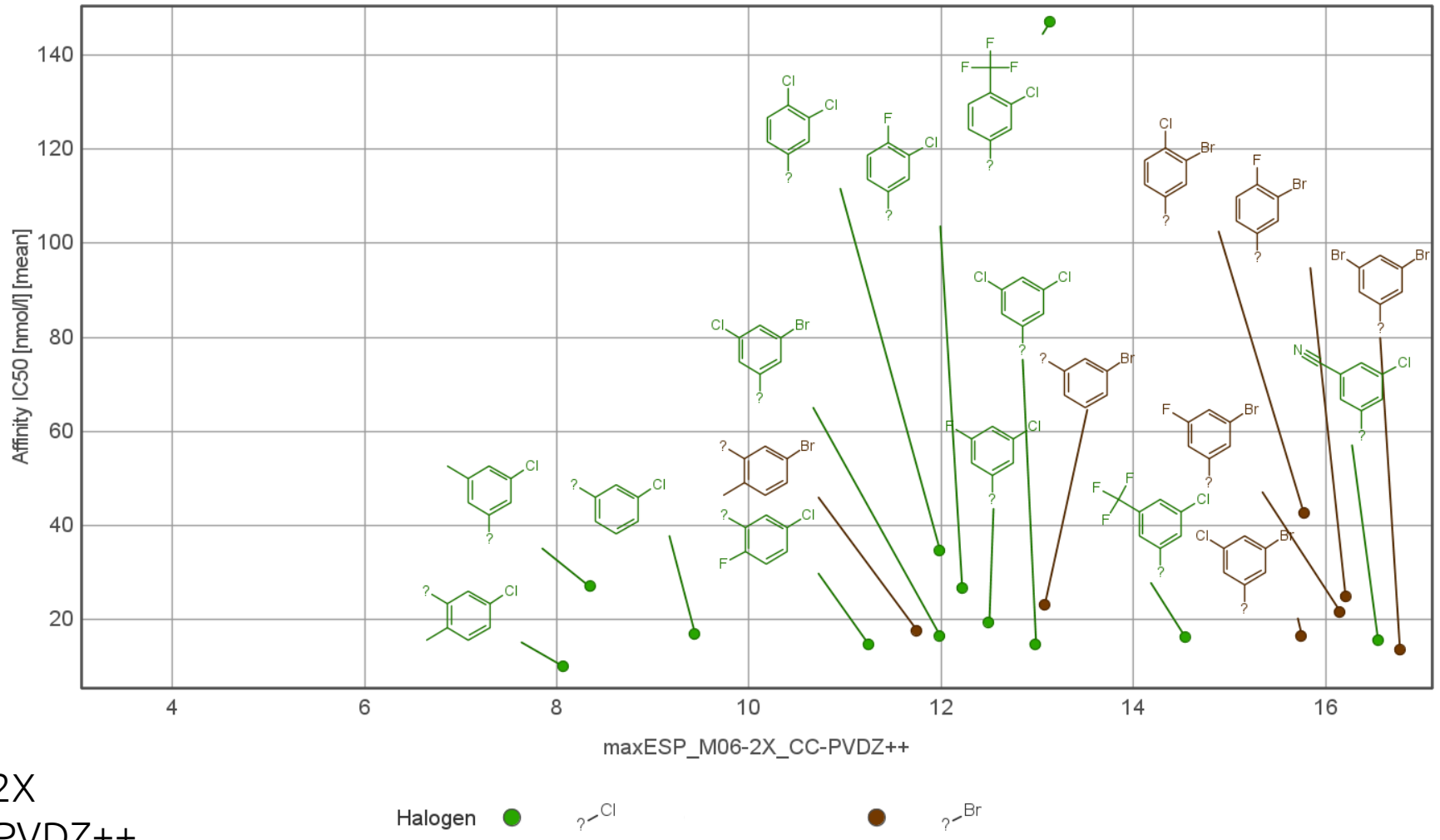
	Phenyl	Meta-F	Meta-Cl	Meta-Br	Meta-meta-Cl	Meta-meta-Br	Meta-Cl meta-cyano	Meta-Br meta-cyano	Meta-Cl para-CF_3
ESP [kcal/mol]	20.3	5.6	9.7	12.9	13.2	16.5	17.3	20.6	12.4
IC_{50} [nM]	67 (n = 4)	49 (n = 1)	16 (n = 6)	22 (n = 3)	13 (n = 16)	12 (n = 4)	15 (n = 7)	11 (n = 4)	147 (n = 1)

Jaguar
Theory: M06-2X
Basis-Set: CC-PVDZ++

J. Chem. Theory Comput. 2013, 9, 1918-1931

Increasing the σ-hole effect

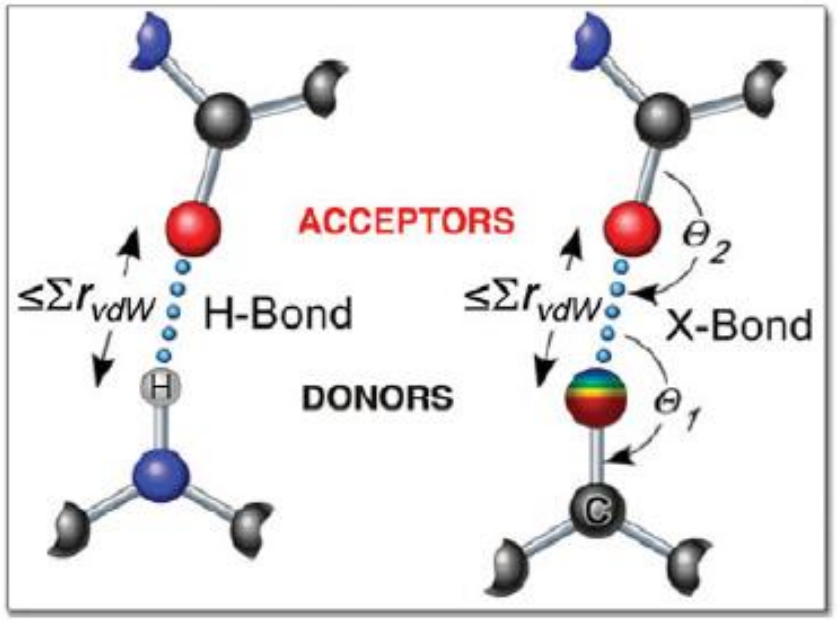
Affinity vs. ESP



Jaguar
Theory: M06-2X
Basis-Set: CC-PVDZ++

Crystal structure analysis

Gabriele Conti



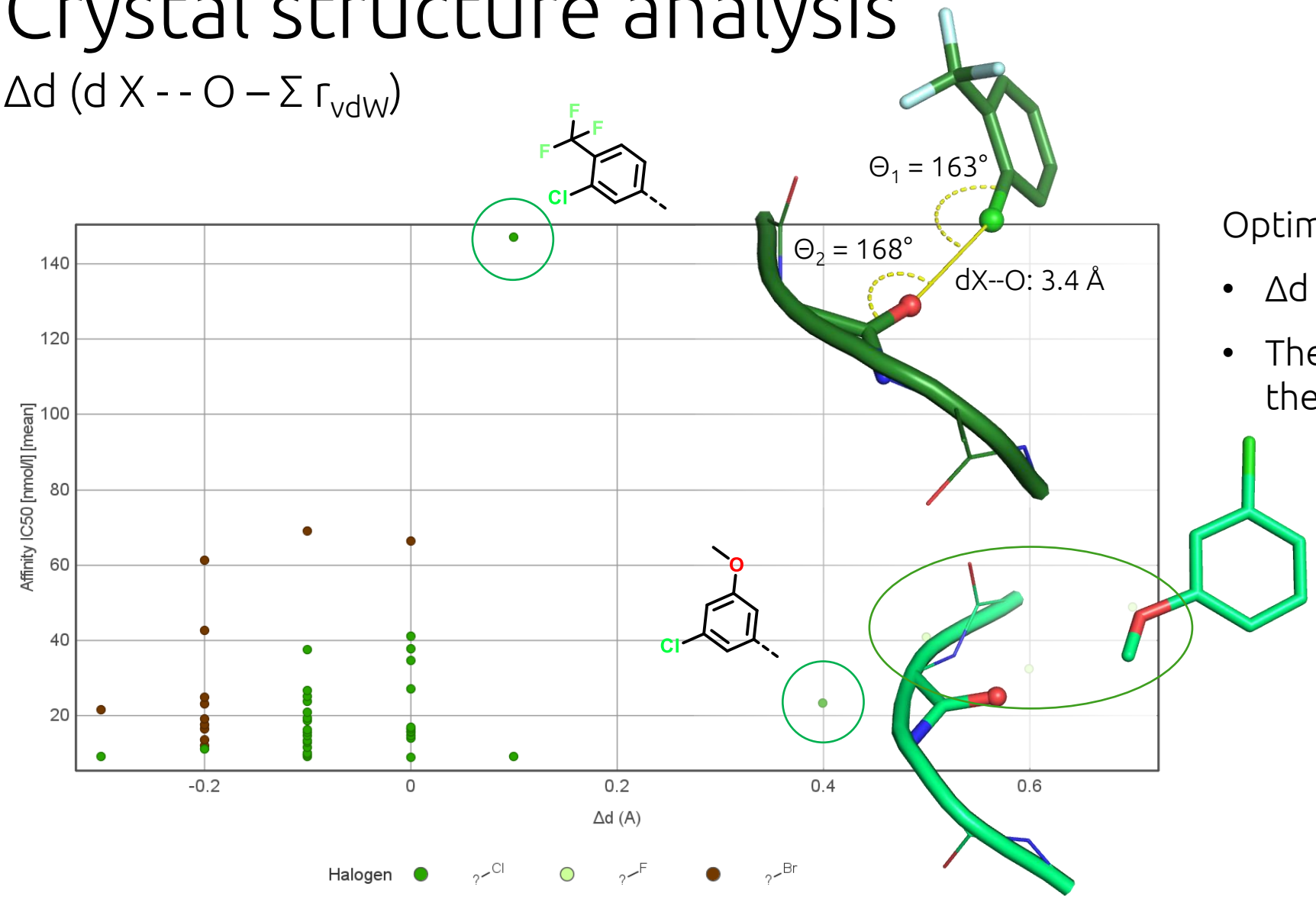
72 crystal structures analyzed in term of:

- d X - - O
- Θ_1
- Θ_2

- Σr_{vdW}
- ≤ 3.24 Å, ≤ 3.37 Å, ≤ 3.5 Å
- Δd (d X - - O – Σr_{vdW})

Crystal structure analysis

Δd (d X - - O – Σr_{vdW})

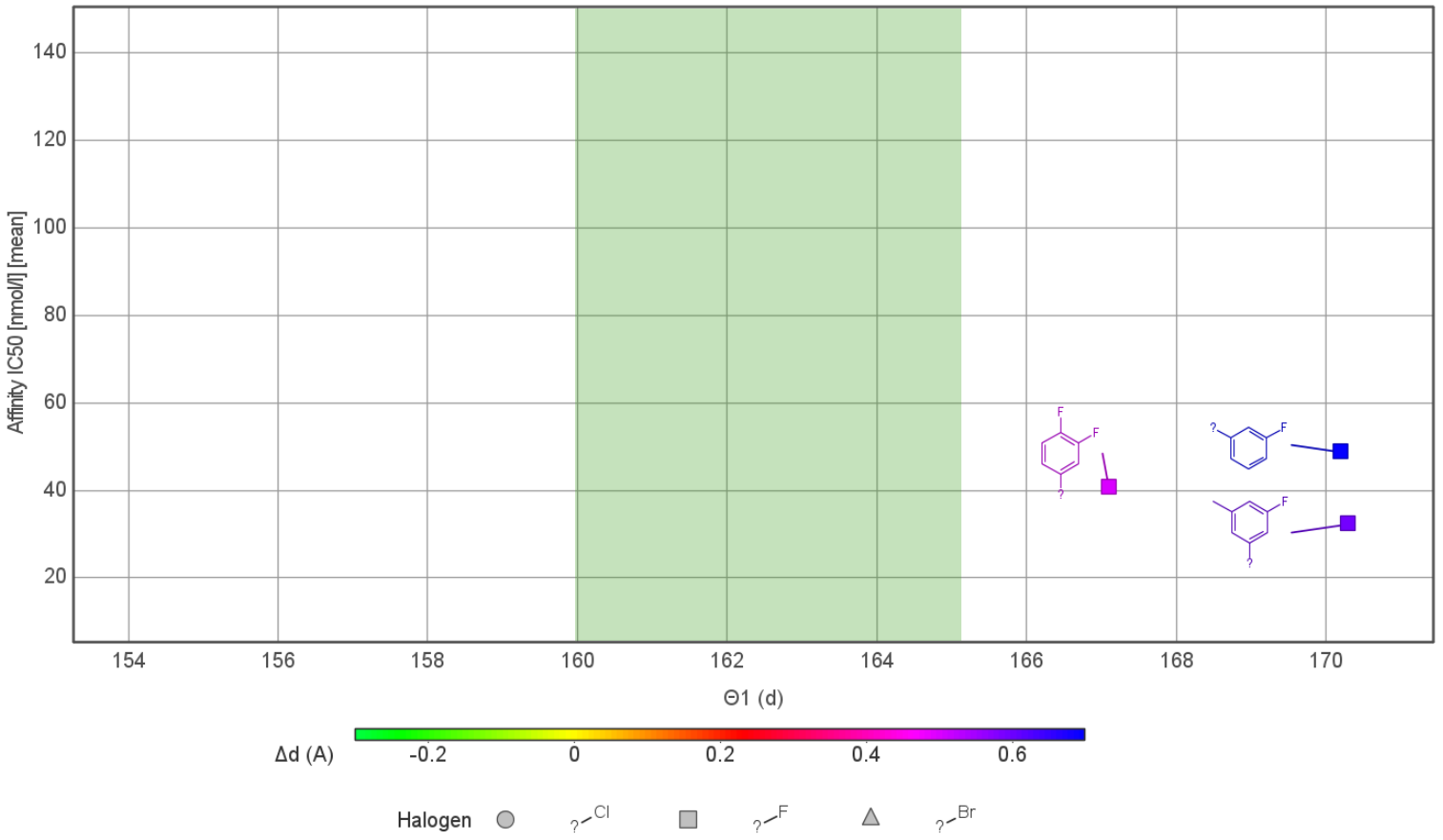


Optimal values:

- Δd (d X - - O – Σr_{vdW}) < O
- The shorter the X – O distances, the higher the affinities

Crystal structure analysis

Fluorine Θ_1



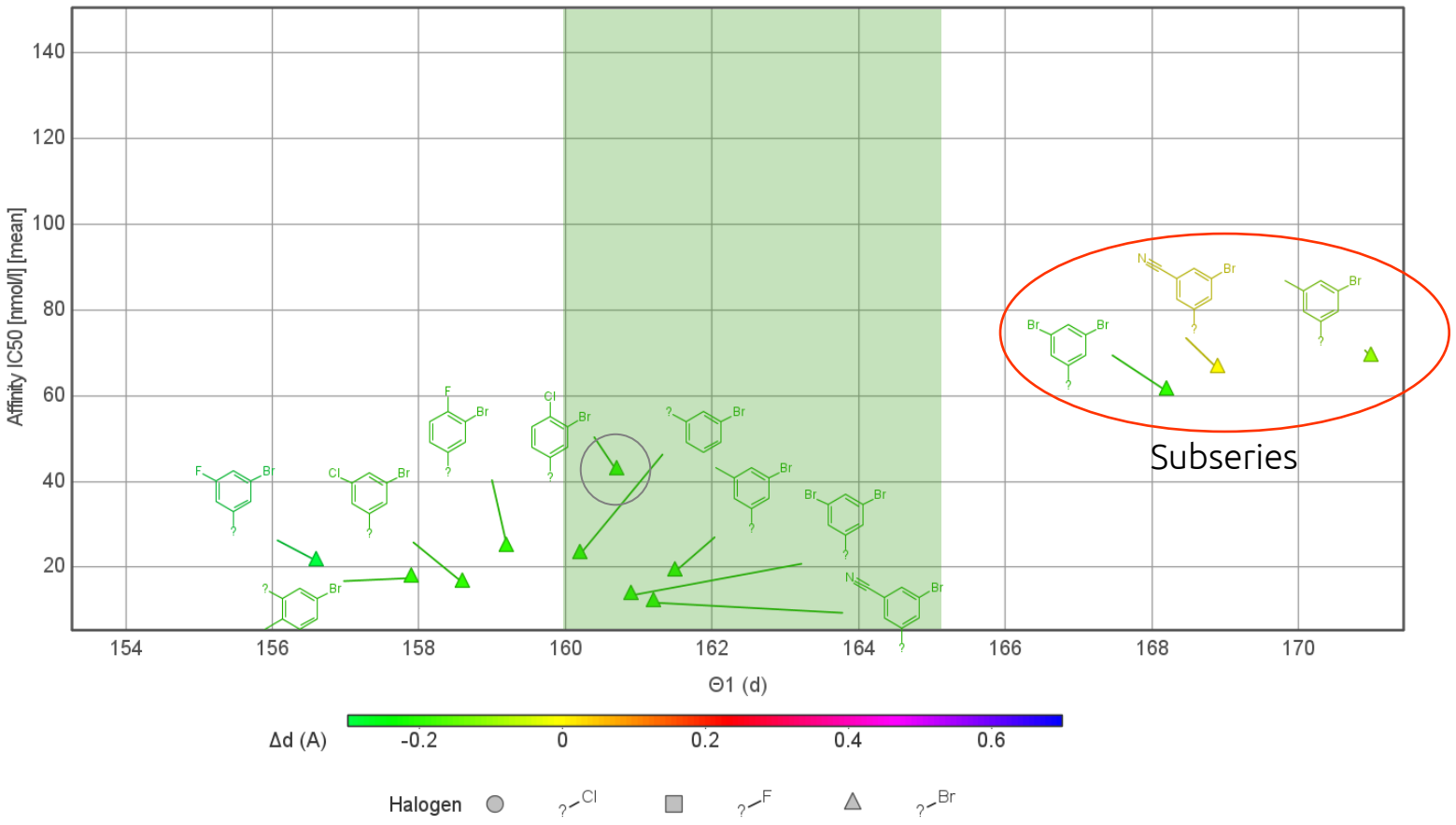
Optimal values:

- Δd (d X - - O – Σr_{vdW}) < O
- The shorter the X – O distances, the higher the affinities
- Literature: $\Theta_1 \approx$ 160 – 165°
- No fluorine halogen bond

J. Chem. Thermodynamics 156 (2021) 106382

Crystal structure analysis

Bromine Θ_1

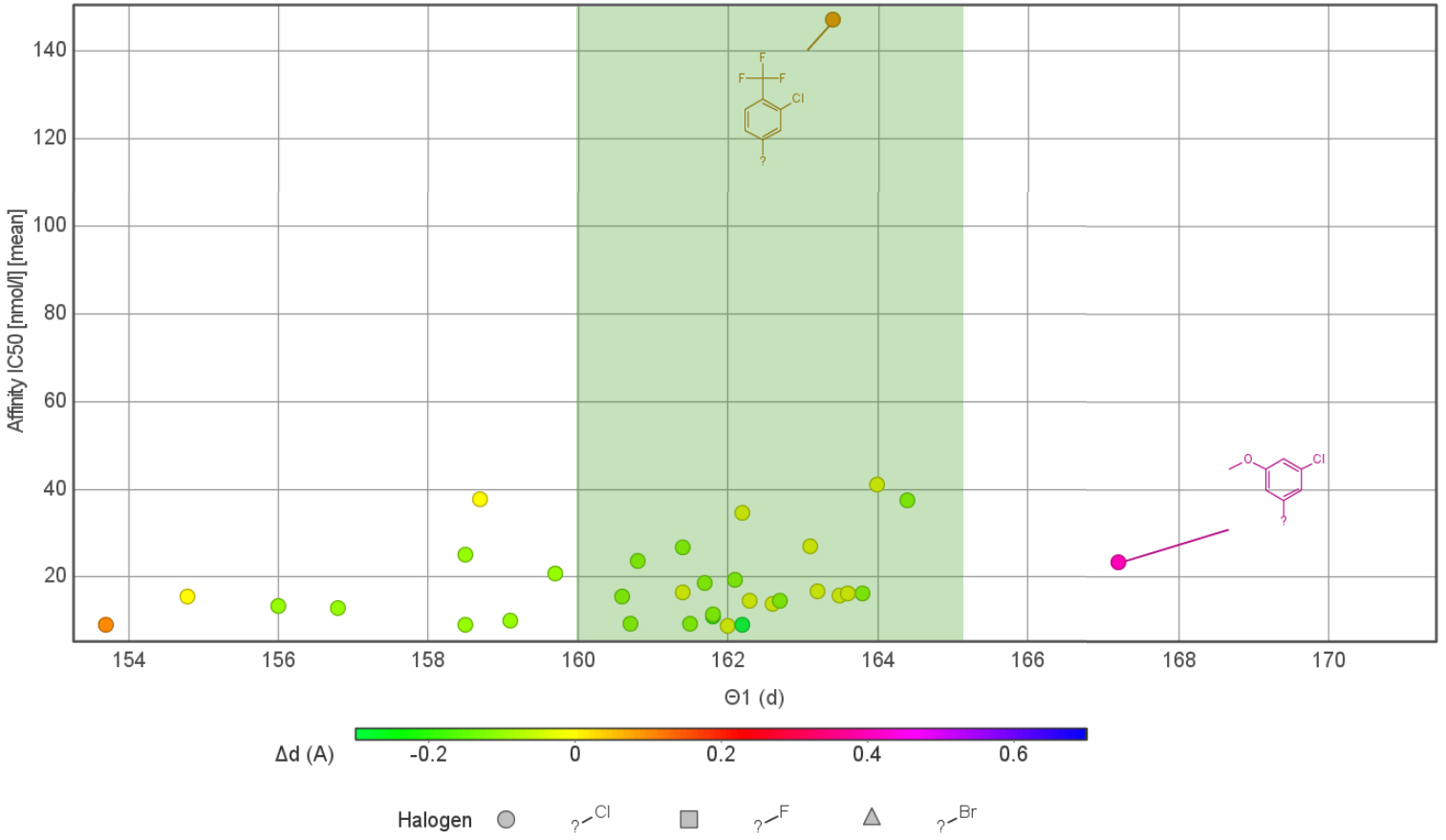


Optimal values:

- Δd (d X - - O – Σr_{vdW}) < O
- The shorter the X – O distances, the higher the affinities
- Literature: $\Theta_1 \approx 160 – 165°$
- Para substituent lower affinity

Crystal structure analysis

Chlorine Θ_1

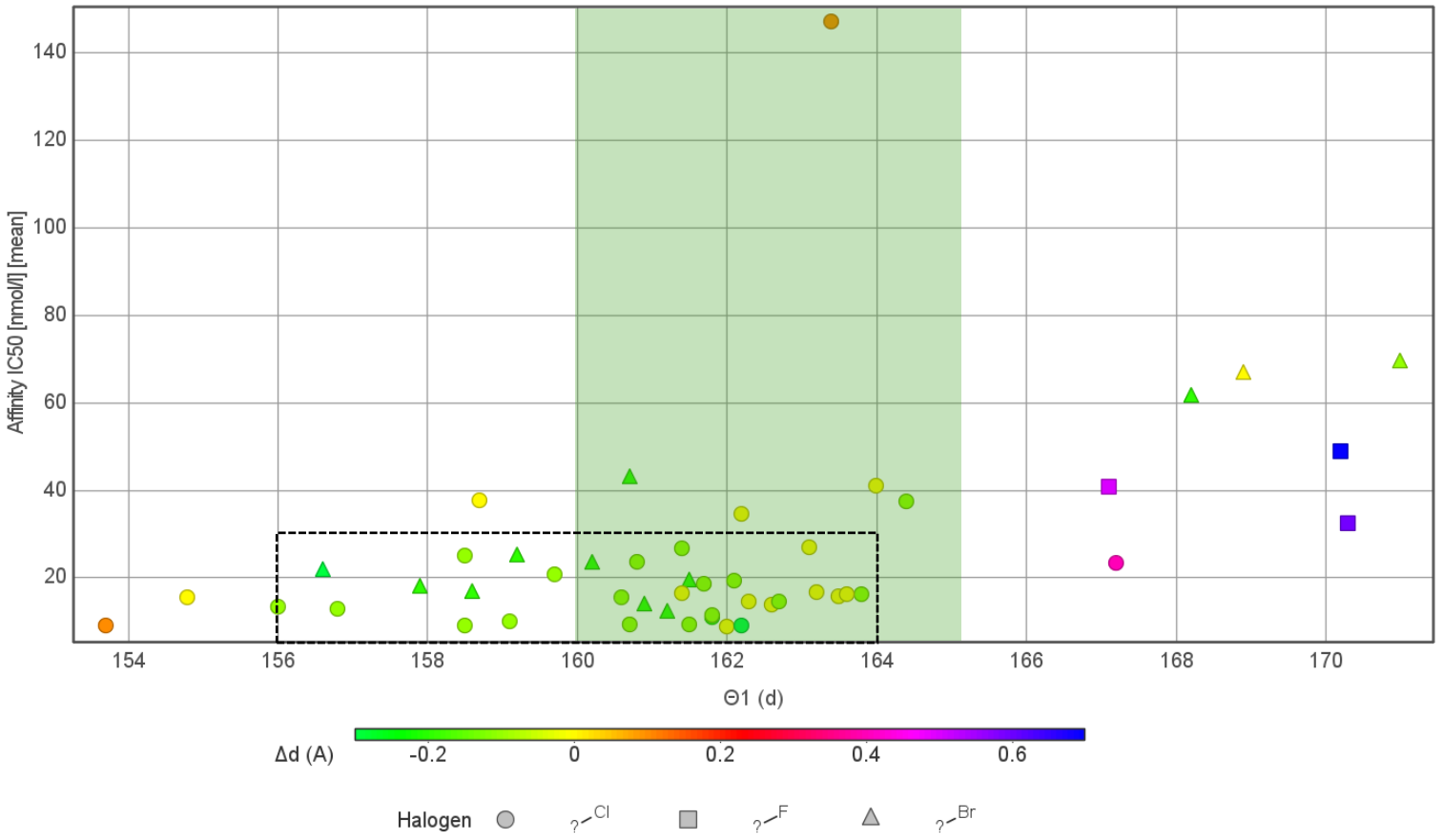


Optimal values:

- Δd (d X - - O – Σ r_{vdW}) < O
- The shorter the X – O distances, the higher the affinities
- Literature: $\Theta_1 \approx 160 – 165°$
- Para substituent lower affinity

Crystal structure analysis

Summary Θ_1

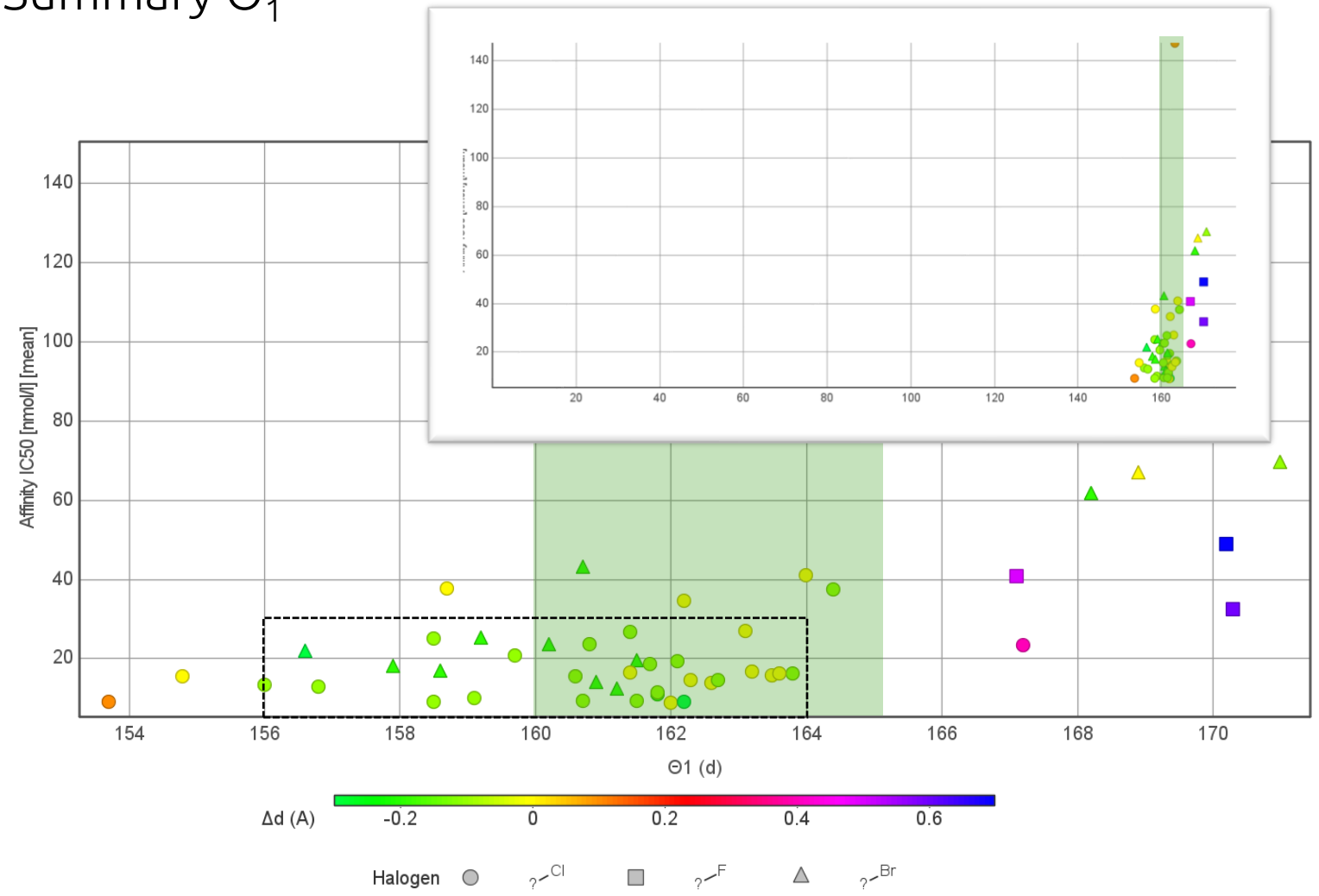


Optimal values:

- Δd (d X - - O – Σr_{vdW}) < O
- The shorter the X – O distances, the higher the affinities
- Literature: $\Theta_1 \approx 160 – 165°$
- Compounds with Θ_1 values close to 156 – 164 ° show the highest activity
- Para substituent influences affinity: $CF_3 < CH_3 < Cl < F < H$
- Lipophilic groups allowed

Crystal structure analysis

Summary Θ_1

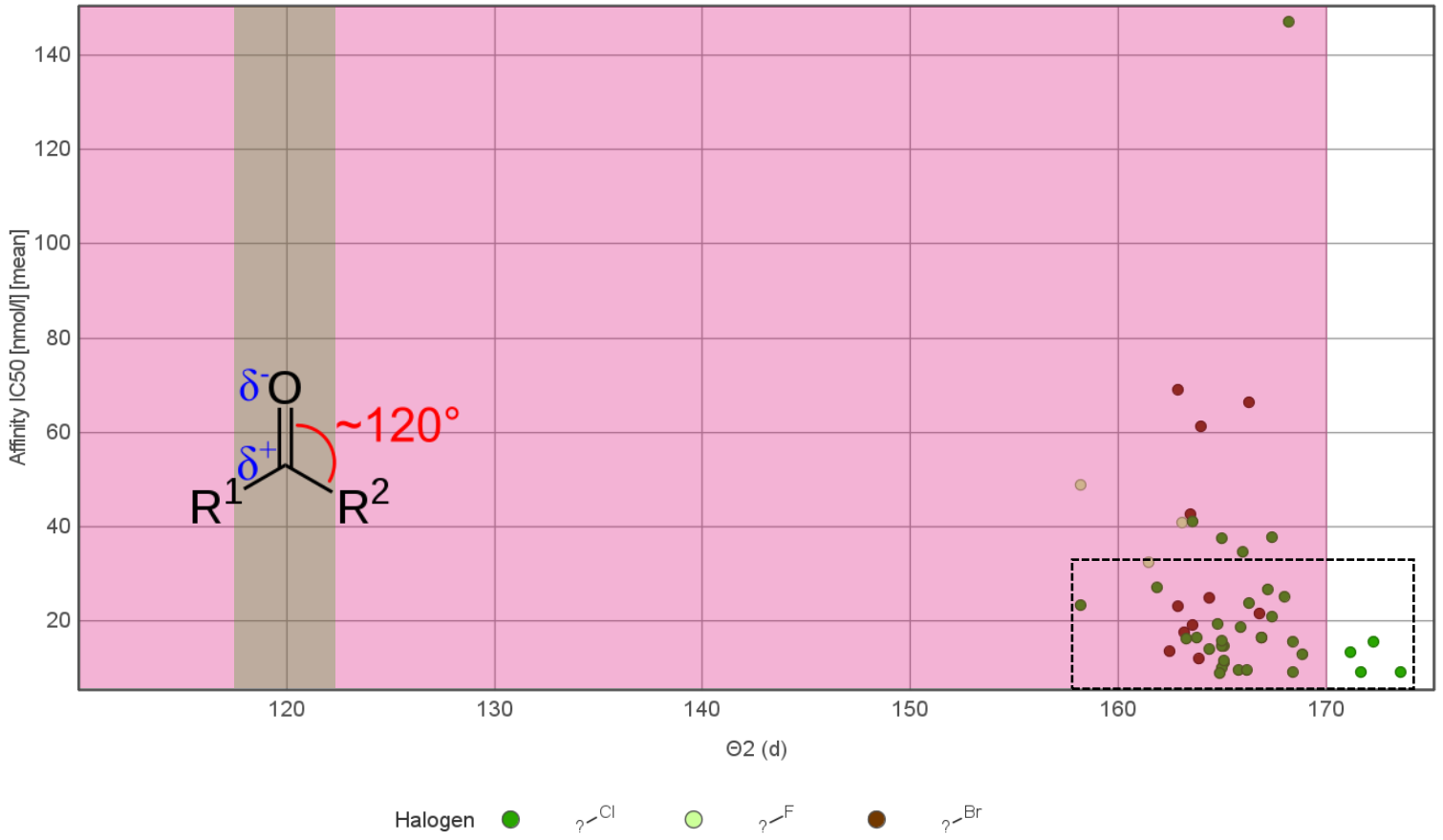


Optimal values:

- Δd (d X - - O – Σr_{vdW}) < O
- The shorter the X – O distances, the higher the affinities
- Literature: $\Theta_1 \approx 160 – 165°$
- Compounds with Θ_1 values close to 156 – 164 ° show the highest activity
- Para substituent influences affinity: $CF_3 < CH_3 < Cl < F < H$
- Lipophilic groups allowed

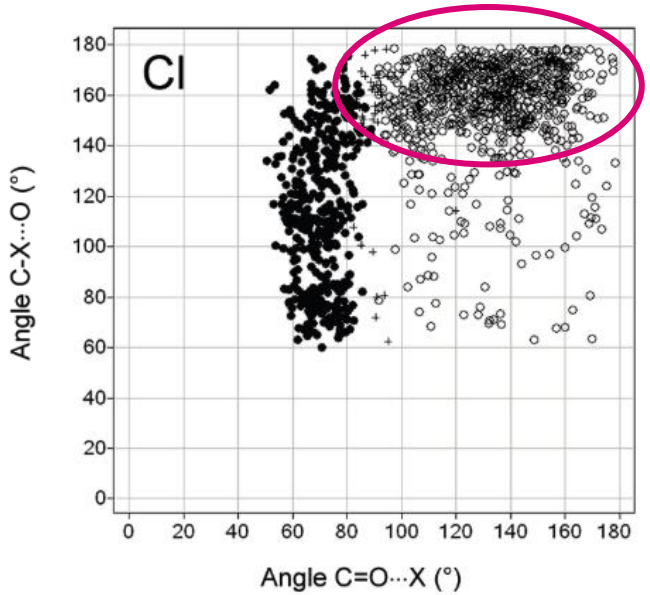
Crystal structure analysis

Summary Θ_2



Optimal values:

- Literature: $\Theta_2 \approx 120°$
- Our observed range: 160 – 175°
- Θ_2 less impact on affinity



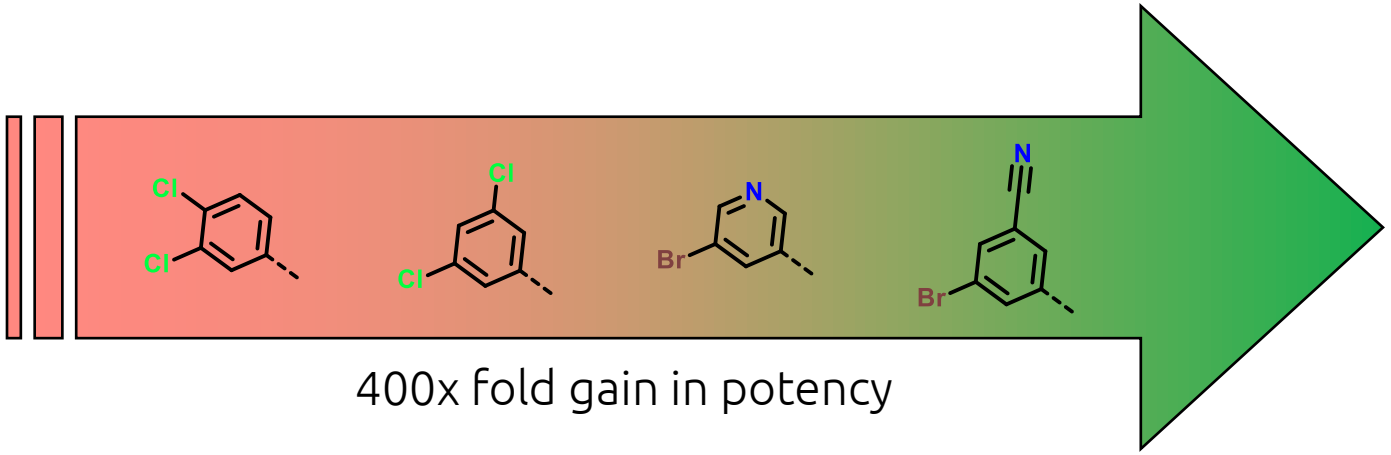
Θ_2

J. Med. Chem. 2010, 53, 5061–5084

Summary

Halogen Bonds in Medicinal Chemistry

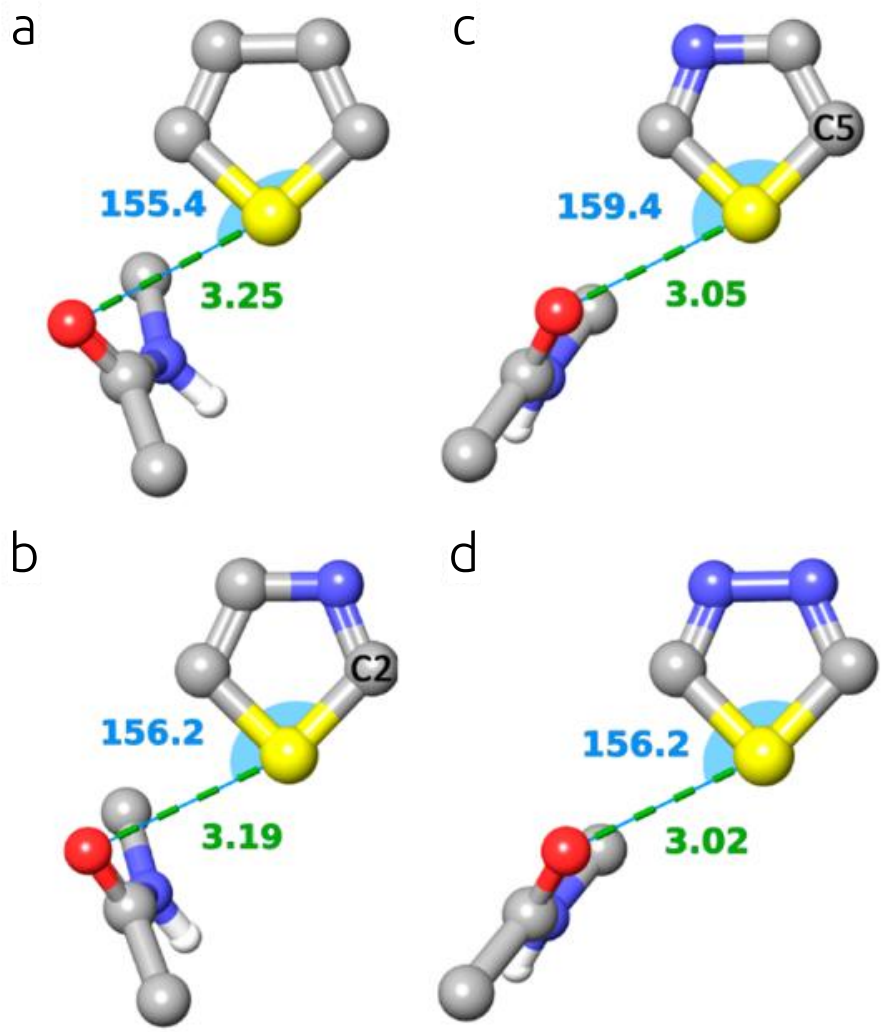
- Crystal structure support is a great asset for challenging projects
- In depths (geometric) analysis of high-resolution structures combined with QM calculations lead to more specific SAR understanding
- Proper understanding of the interactions involved in a system is essential for making informed decisions and optimizing outcomes.



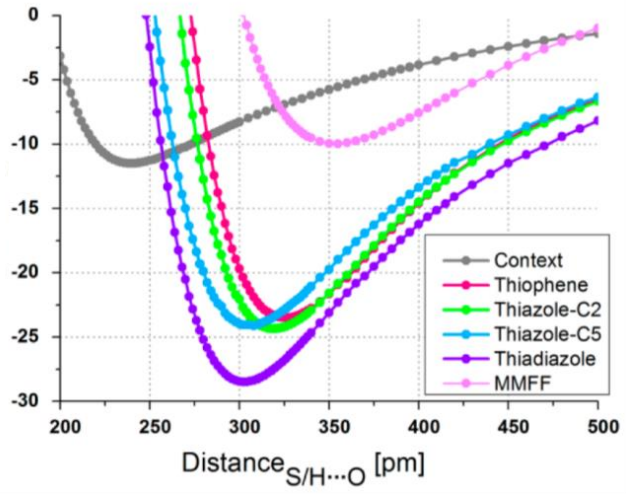
Sulfur-oxygen interactions

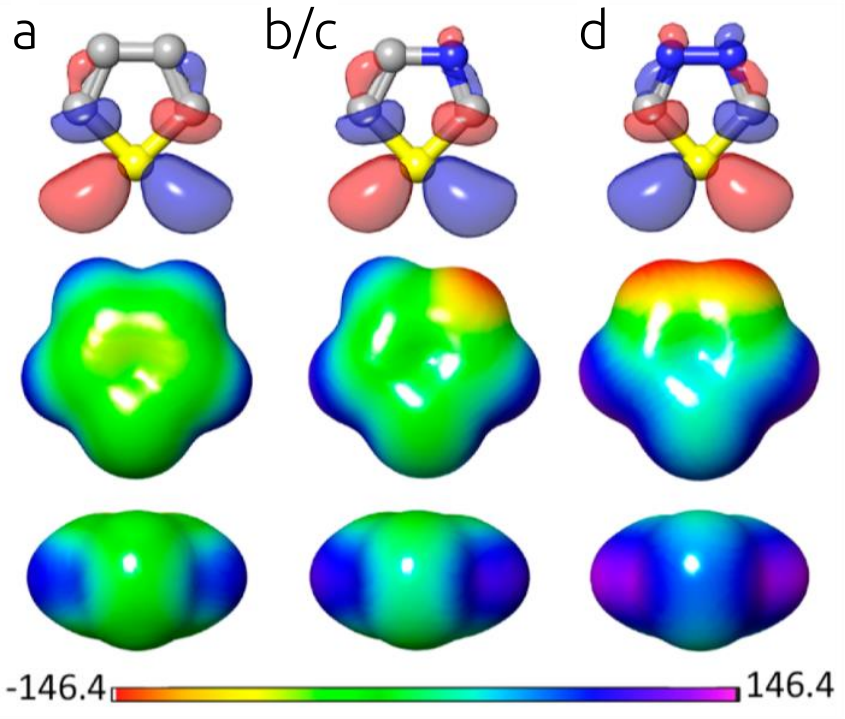
Sulfur-oxygen interaction – σ-hole part II

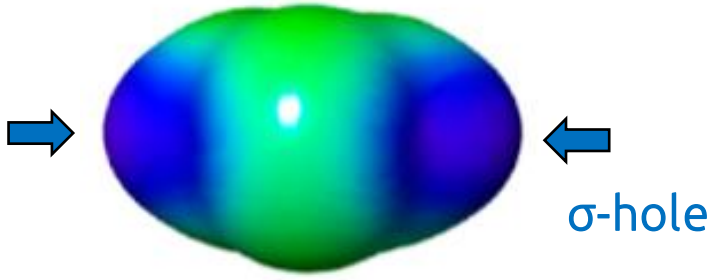
Zhang et al.



	E [kJ mol^{-1}]
Thiophene (a)	21.8
Thiazole (b)	22.9
Thiazole (c)	22.6
Thiadiazole (d)	26.9!
Oxazole	11.1
Hydrogen Bond (exp)	18-21



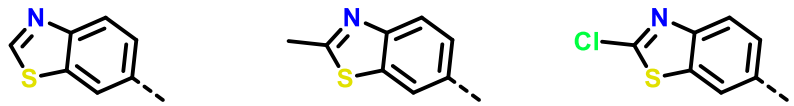




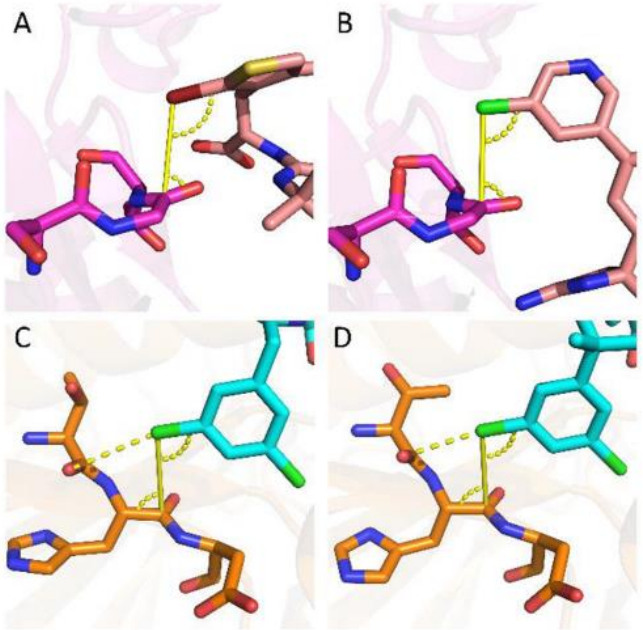
J. Chem. Inf. Model. 2015, 55, 10, 2138–2153

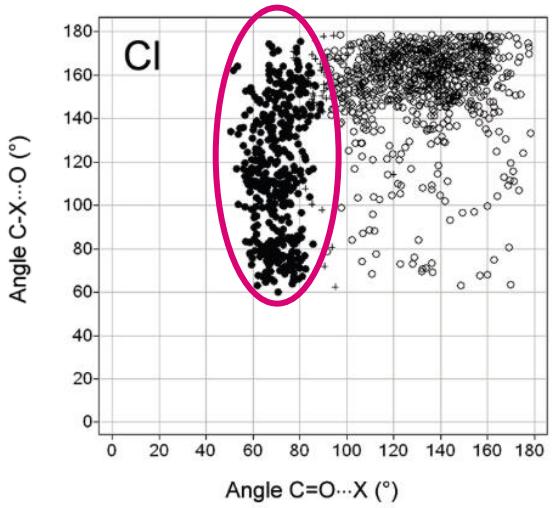
Sulfur-oxygen interaction at Idorsia

Benzothiazoles with a σ-hole

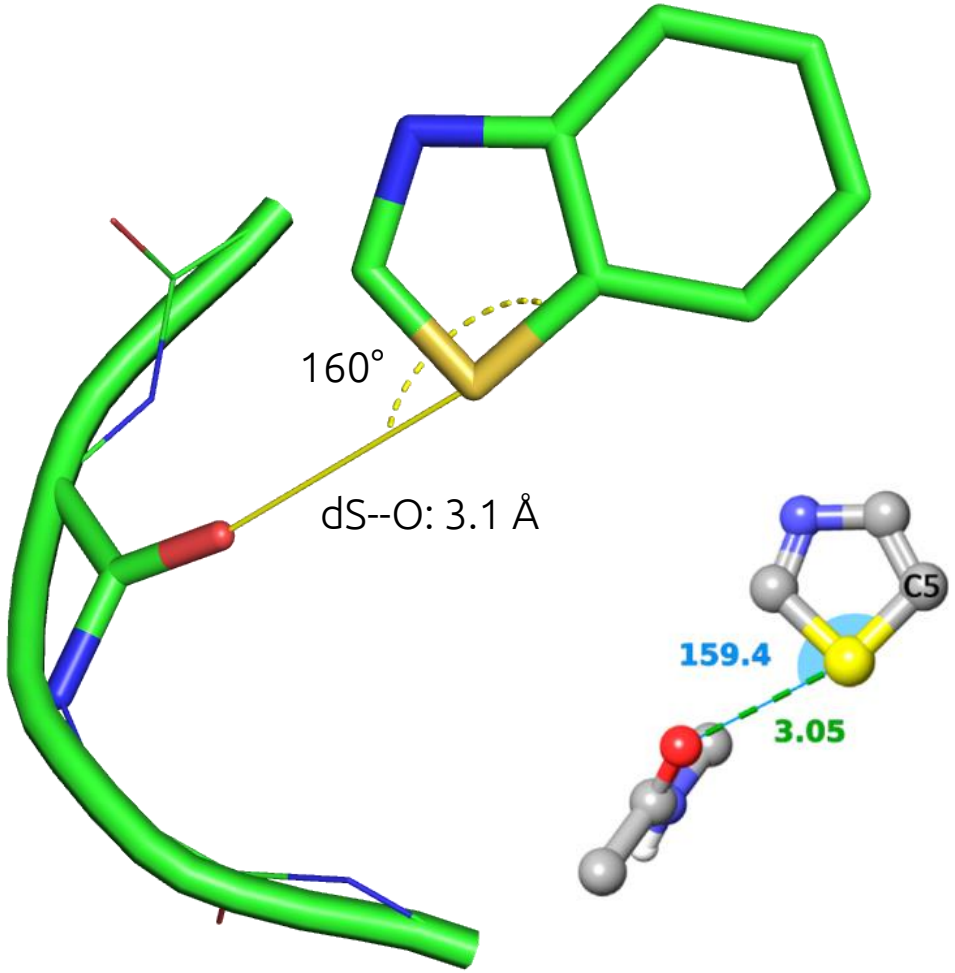


	Benzothiazole	Benzothiazole-Me
IC_{50} [nM]	20 (n = 5)	31 (n = 3)





Θ_2

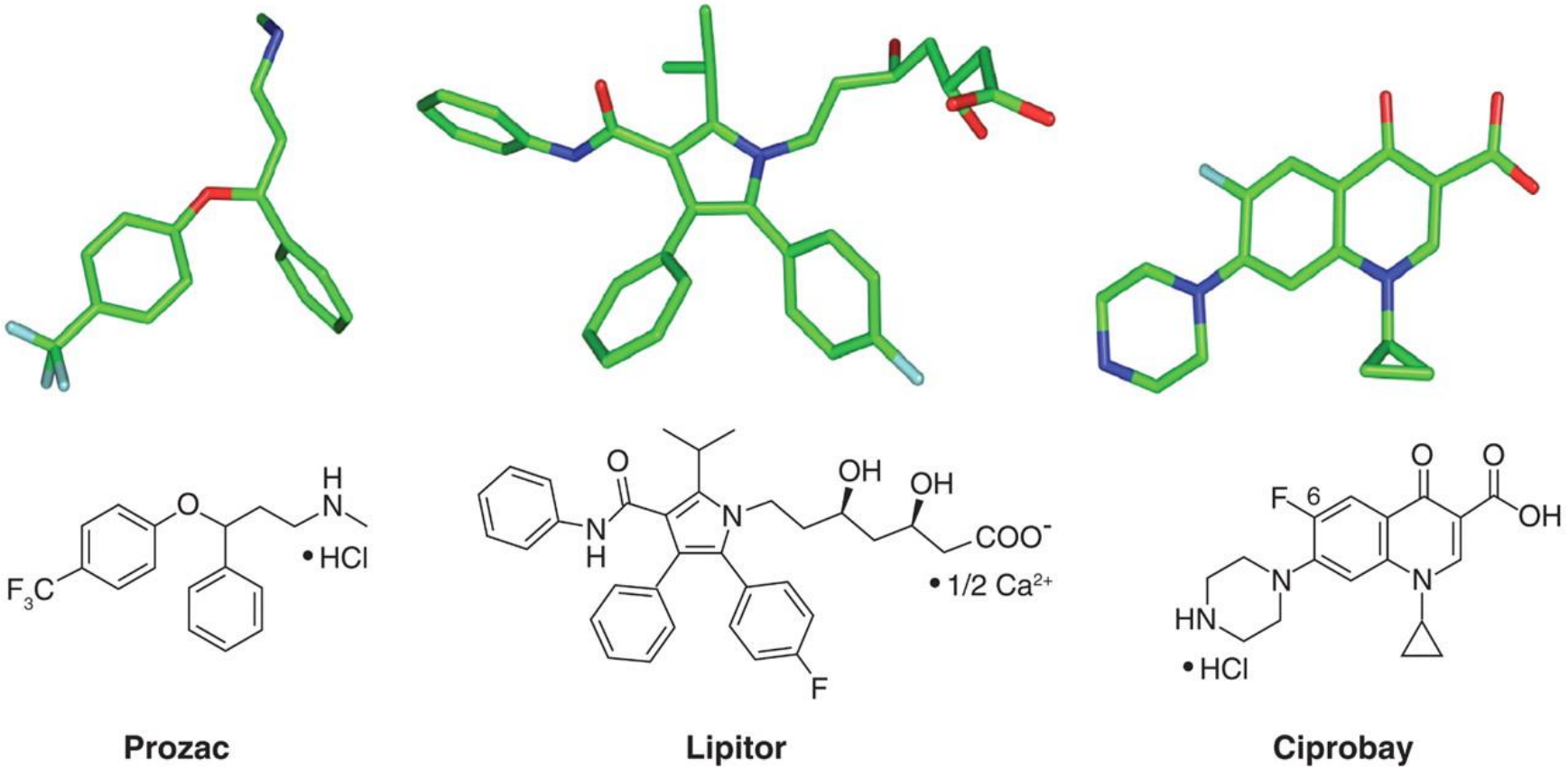


J. Med. Chem. 2019, 62, 21, 9341-9356;
J. Med. Chem. 2010, 53, 5061–5084

Fluorine multipolar interactions

Fluorine in Pharmaceuticals: Looking Beyond Intuition

Diederich group

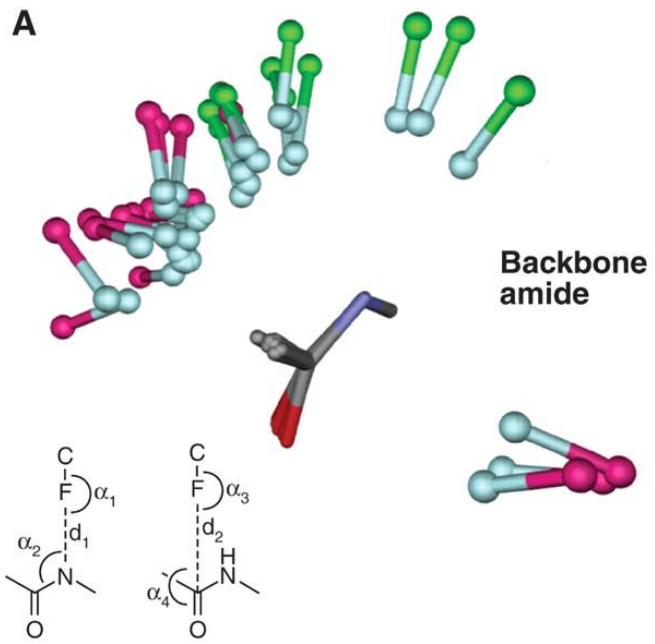


- Fluorine substituents are widely used in drugs due to the development of safe and selective fluorinating agents.
- Fluorine has significant effects on the physical and pharmacokinetic properties of a drug compound (ADME).
- The inductive effects of fluorine are relatively well understood and can enhance bioavailability by reducing the basicity of neighboring amines.

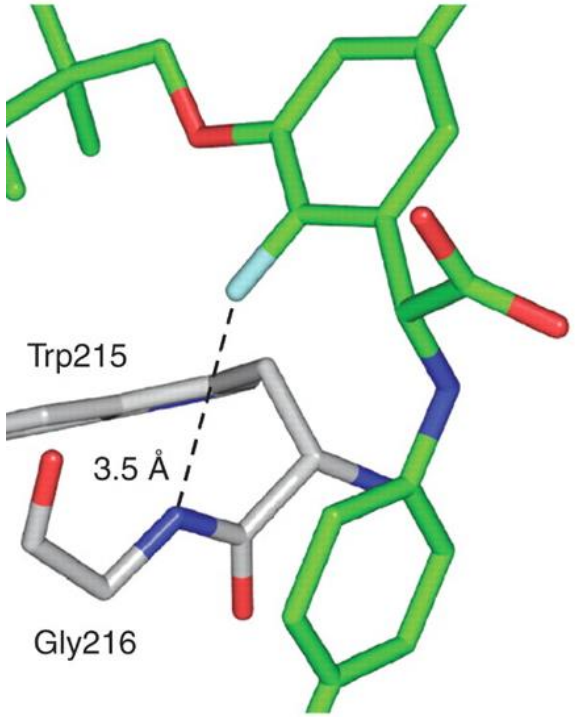
Science Vol 317, Issue 5846 pp. 1881-1886

C–F···H–N interactions

Diederich group



- The C-F unit is **not a good** acceptor for hydrogen bonds because it has a low proton affinity and is weakly polarizable.
- A study of **788** C-F containing structures found that in only **11** of them, the C-F part of the molecule points towards the H-N bond when the **F···N distance is below 3.1 Å** and the angles α1 and α2 meet certain criteria (α1 ≥ 150° and 90° ≤ α2 ≤ 150°)
- Thrombin inhibitor comparison: The F-containing inhibitor is shown to be **5 times more potent than the H-containing inhibitor**.



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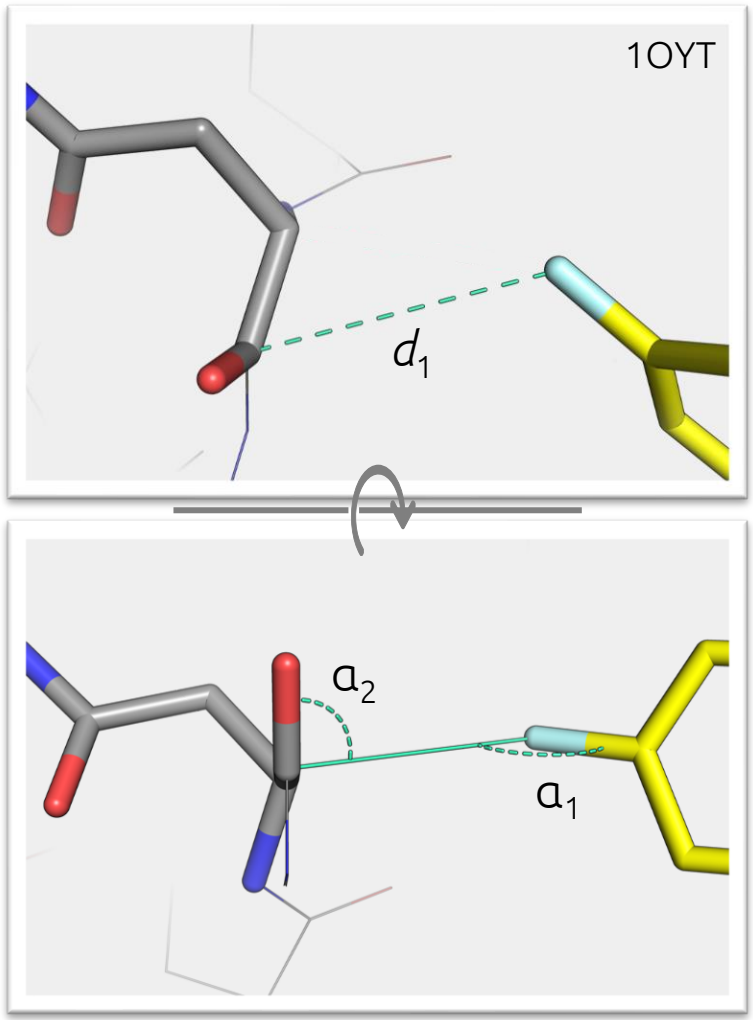
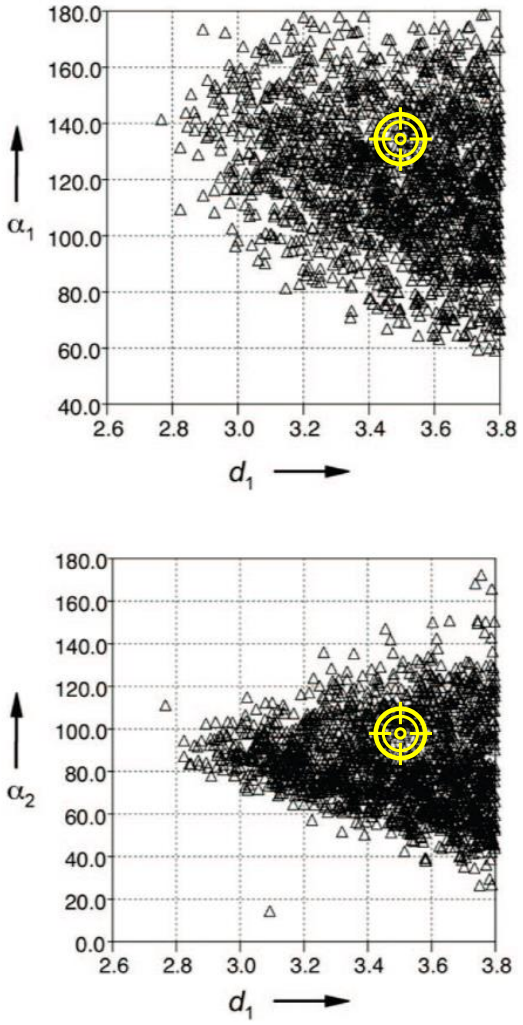
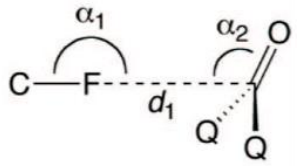
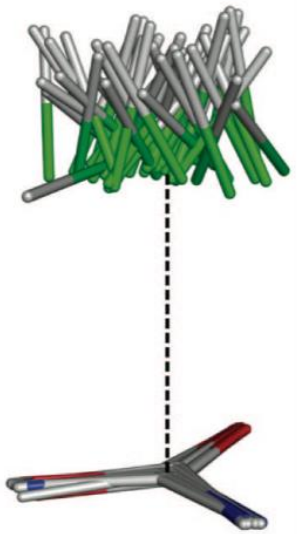
C–F···C=O interactions

Diederich group









- Distance: 2.8 Å < d_1 < 3.8 Å
  - C_{VdW}: 1.7 Å
  - F_{VdW}: 1.47 Å

  } 3.17 Å
- Linearity (α_1) = 180°
  - Weaker dependence at longer distance
- Planarity (α_2) = 90° ± 10-40°
  - Distance dependent
- $\Delta\Delta G$ from C_{sp2}-H to C_{sp2}-F
  - -1.0 ± 0.2 kJ mol^{-1}

J. Org. Chem. 2008, 73, 12, 4345-4361

Exercise #2.2
Galectin-3

All Groups

Open: Galectin-3_example.pdb

Goal: Implement what you have learned

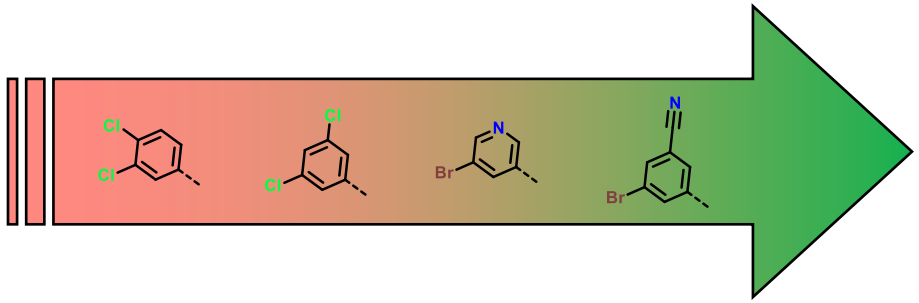
- Halogen bonds
- Sulfur-oxygen interaction
- Fluorine multipolar interactions

Time: 15 min

Presentation: Min. two groups

Summary

Interactions in Medicinal Chemistry



- Proper understanding of the interactions involved in a system is essential for making informed decisions and optimizing outcomes.
  - Perfectly placed halogens and thiazoles enhance protein-ligand affinity and may serve as core interactions for lead discovery projects.
  - Fluorine residues can enhance physicochemical properties to improve ADME properties and strengthen protein-ligand binding interactions.
- Academic research plays a critical role in advancing our understanding of complex systems and developing new solutions.
- Continuous learning and improvement is essential for staying up-to-date and making meaningful contributions to scientific research and innovation.

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Curious to learn more?

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Constantly expanding our knowledge

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