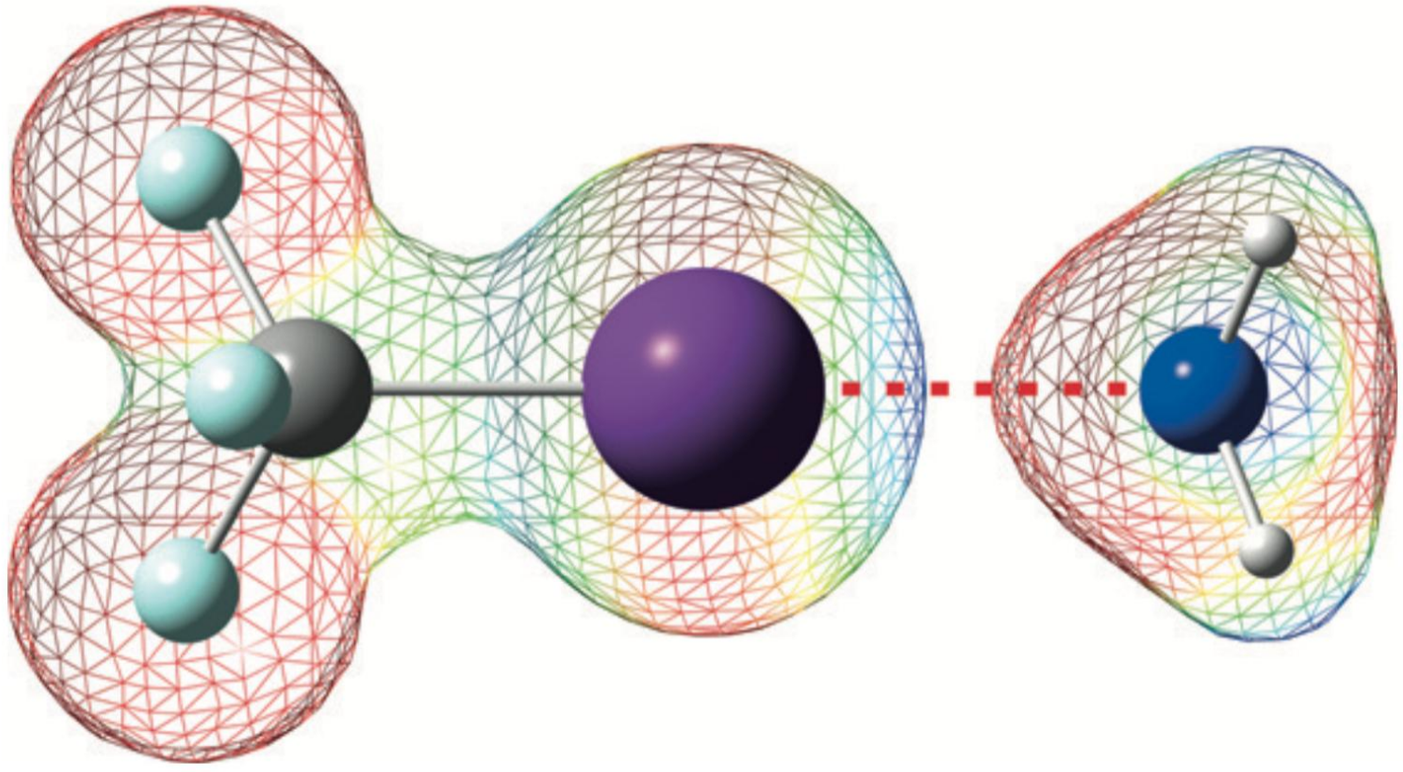
Halogen Bonding



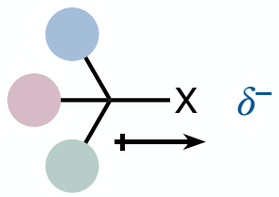
Gabrielle Lovett

MacMillan Group Meeting

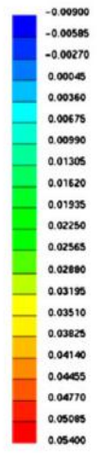
June 6, 2019

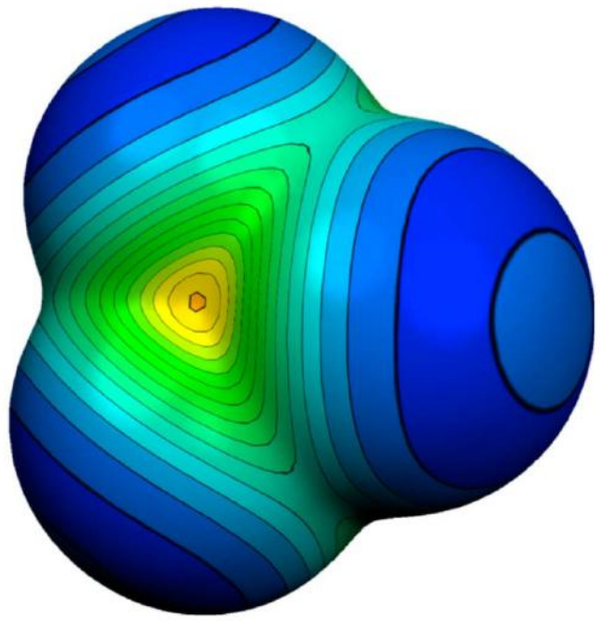
Introduction to the Halogen Bond

traditional view



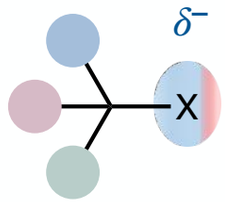
e.g.; CF_4



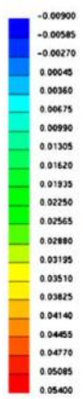


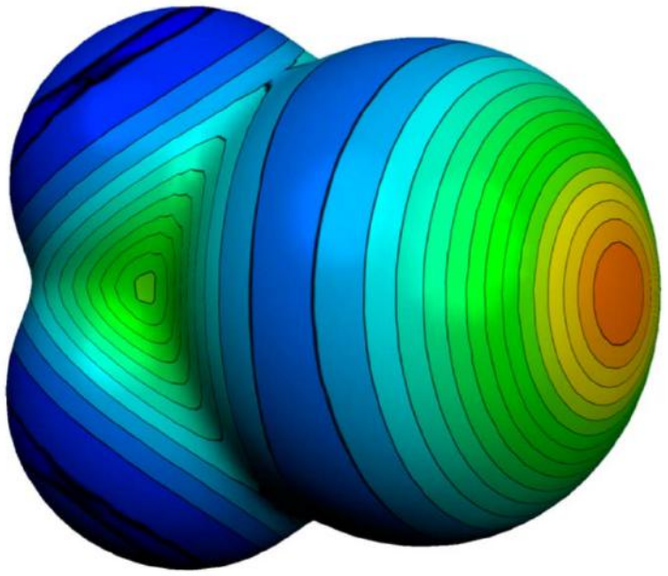
electronegative halogens possess higher e⁻ density

σ-hole view



e.g.; CF_3Br



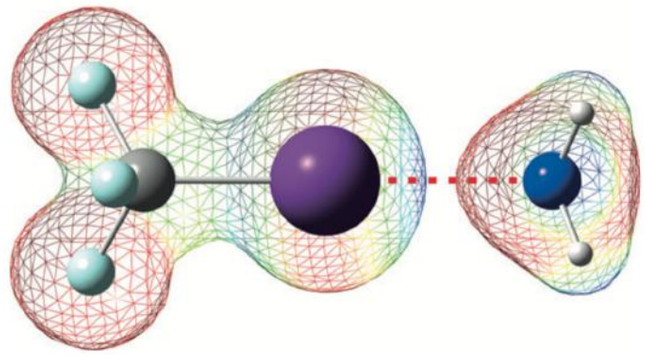


region of lower e⁻ density along the R–X axis

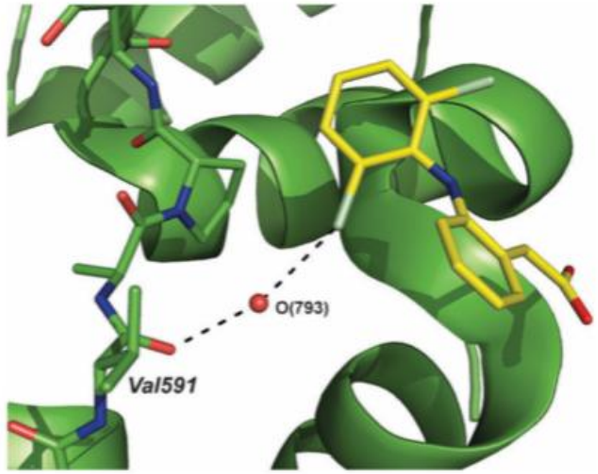
Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P. *J. Mol. Model* **2007**, *13*, 291.

Outline

- Introduction to Halogen Bonding
  - definition
  - origin of halogen bonding
    - electrostatics
    - charge transfer
    - dispersion and polarization



- Applications
  - crystal engineering and supramolecular chemistry
  - halogen bonds in biological settings
  - medicinal chemistry and rational drug design
  - catalysis



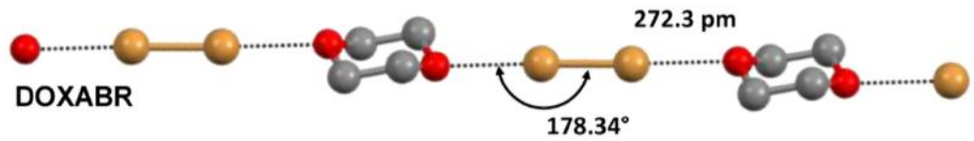
Halogen Bonding Before "The Halogen Bond"

- Reports of I_2 complexed with Lewis bases as early as 1814: I—I ··· :NH_3

- Early 20th century: I_2 in many organic solvents turns different colors forming DA complexes

- X-ray crystallographic studies in the 1950's identifying "halogen-atom bridges"

Br—Br ··· $O(CH_2CH_2)_2O$



  - intermolecular distances shorter than sum of van der Waals radii

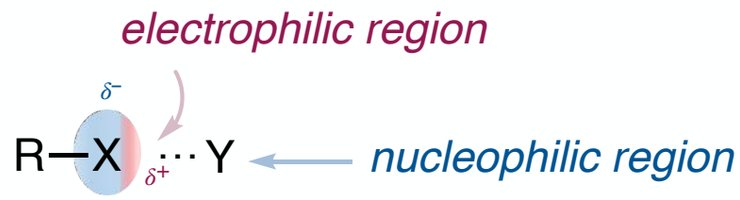
  - highly directional interaction: bond angle close to 180°

- Early 2000's: development of concept of "σ-holes" to explain observed phenomena

Hassel, O.; Hvoslef, J. *Acta Chem. Scand.* **1954**, *8*, 873.
Colin, M.M.; Gaultier de Claubry. H. *Ann. Chim.* **1814**, *90*, 87.
Kleinberg, J.; Davidson, A. W.; *Chem. Rev.* **1948**, *42*, 601.

Definition of Halogen Bonding

"A halogen bond occurs when there is evidence of a net attracive interaction between an ***electrophilic region associated with a halogen atom*** *in a molecular entity and a* ***nucleophilic region*** *in another, or the same, molecular entity"* - IUPAC, 2013



X: halogen

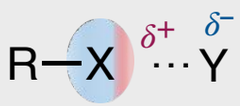
Y*:* lone pair or π-system

R–X: "halogen-bond donor"

Y: "halogen-bond acceptor"

what is the origin of this seemingly counterintuitive interaction?

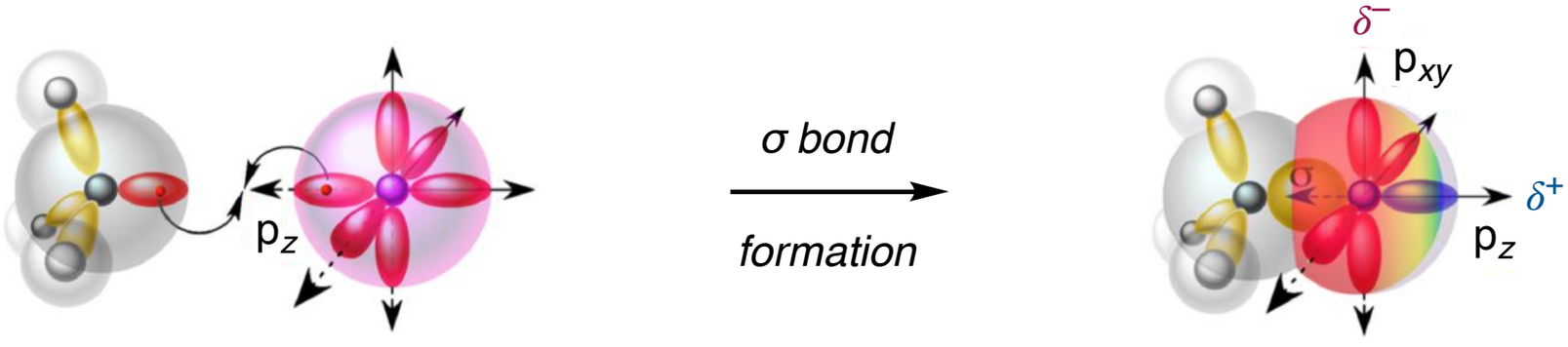
electrostatic component: σ-hole



charge-transfer component

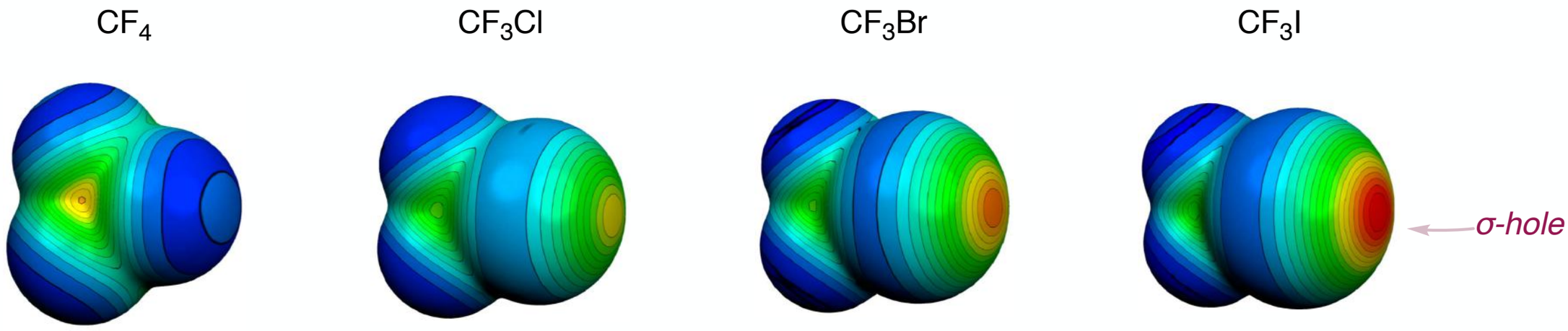
$R^{-}\,[XY]^{+}$

Electrostatic Component: the σ-Hole



σ-hole

the lobe of p_z orbital opposite the C–X σ bond becomes depopulated, leading to electron deficient hole



σ-hole increases with increasing X-atom polarizability (F < Cl < Br < I)

the size and magnitude of the σ-hole (generally) correlate with the strength of the halogen bond

Ford, M. C.; Ho, P. S. *J. Med. Chem.* **2016**, *59*, 1655.

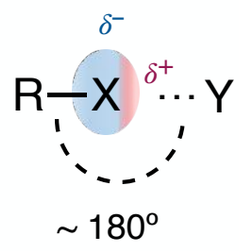
Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P. *J. Mol. Model*, **2007**, *13*, 291.

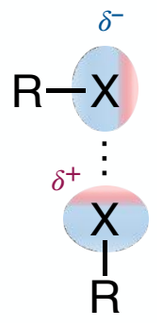
Halogen Bonding and the σ-Hole

tunability: varying strength of XB donor and acceptor

XB donor ability of X atom	**hybridization of C of the C–X bond**	**EWG on atom the XB donor is bound to**
I > Br > Cl > F	C(sp) > C(sp^2) > C(sp^3)	e.g., –CN, –NO_2, protonated heretoarene

highly directional: Y enters along the σ-bond axis (σ-hole)





when Y = π-system, the symmetry axis of the π-system lies along σ-bond axis

Chem. Rev. **2016**, *116*, 2478.

The Charge Transfer Component

- XB has long been attributed to charge-transfer, motivated by UV-Vis studies

- XB directionality attributed to donation into σ^* of the R–X bond: n $\longrightarrow$ σ^*

Dr. Robert S. Mulliken

Mulliken "outer complex"

RX ··· B

little charge transfer
weaker

Mulliken "inner complex"

$[BX]^+ R^-$

significant charge
redistribution

- Experimental and computational data suggest the important role of CT in XB

  - lengthening of C–X bond
  - HOMO/LUMO overlap (not always site of σ-hole)

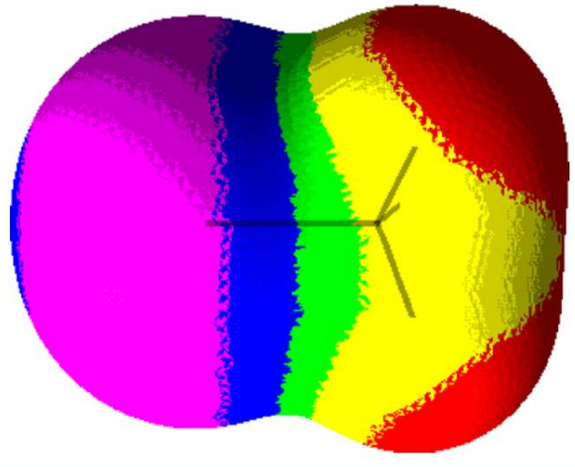
Mulliken, R. S. *J. Am. Chem. Soc.* **1950**, *72*, 600.
Chem. Rev. **2016**, *116*, 2478.

Dispersion and Polarization

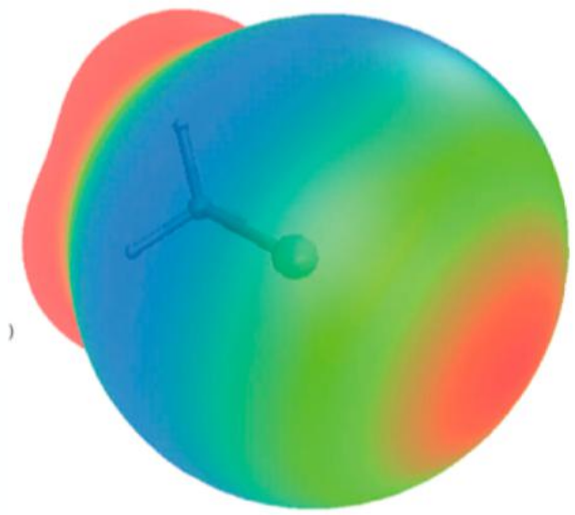
calculated electrostatic potential: CH_3Cl

purple indicates ***negative*** potential

no σ-hole for CH_3Cl!



but halogen bonded complexes with CH_3Cl with folmaldehyde have been predicted…



as CH_3Cl interacts with formaldehyde

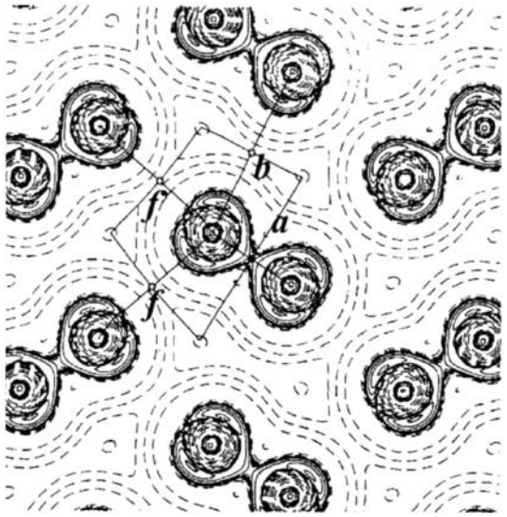
electron densities of each are polarized

now σ-hole for CH_3Cl is predicted

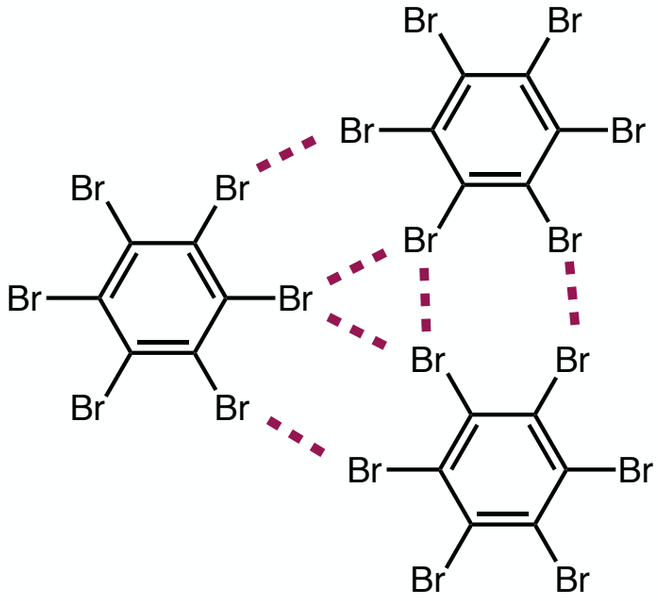
important to recognize dispersion and polarization for an accurate interpretation

Wiley Interdiscip. Rev. Comput. Mol. Sci. **2015**, *5*, 169.
Hennemann, M.; Murray, J. S.; Politzer, P.; Riley, K. E.; Clark, T. *J. Mol. Model,* **2012**, *18*, 2461.

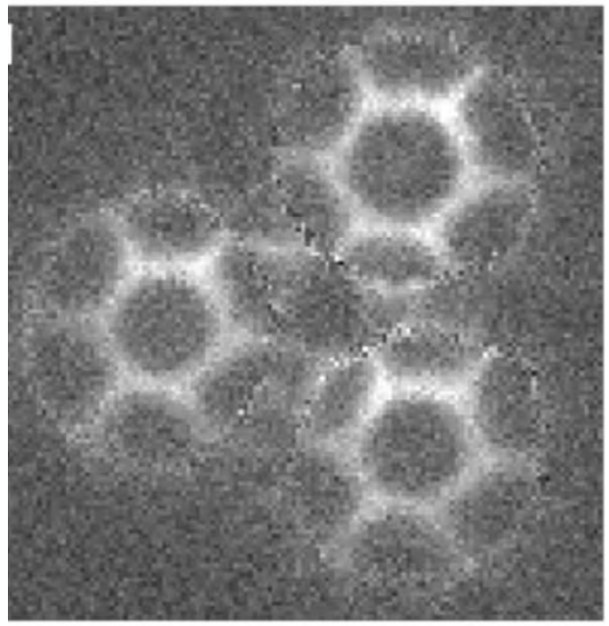
XB in Crystal Engineering and Supramolecular Chemistry



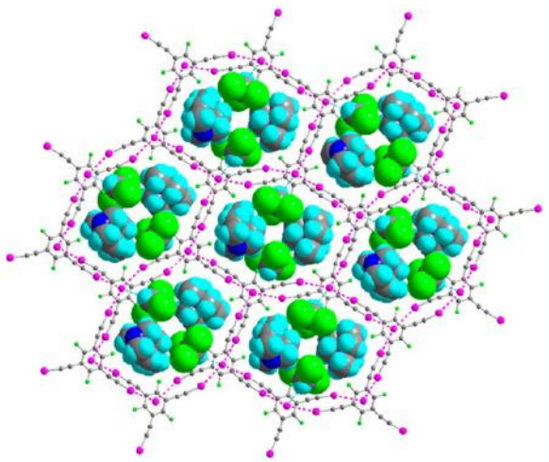
layered crystal structure of solid Cl_2

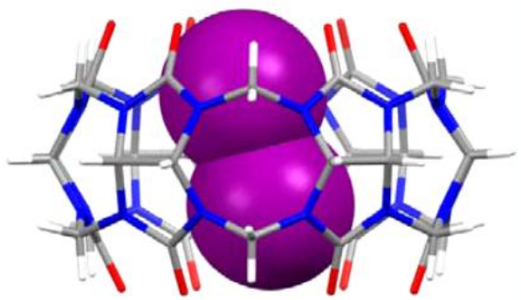


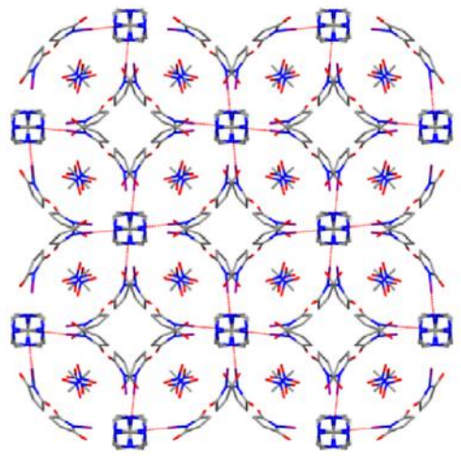
≡



"windmill" self-assembled C_6Br_6







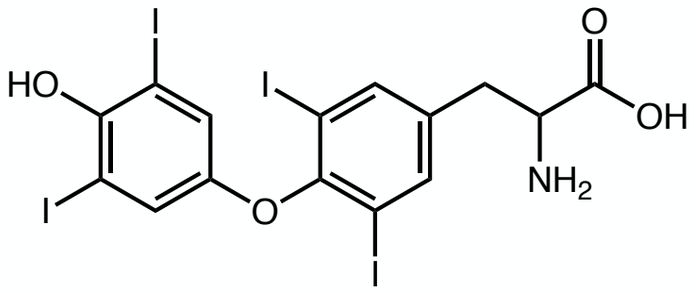
- anion organic networks
- molecular recognition
- materials science
- chiral resolution

For review on this area: *Chem. Rev.* **2015**, *115*, 7118.

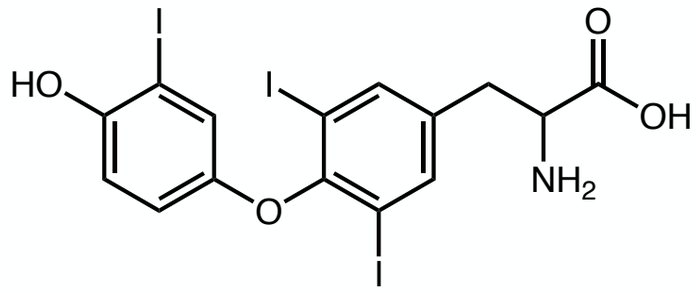
Han, *et. al.*, *Science*, **2017**i, *358*, 206.

Naturally Occuring Bioactive XB Systems

Naturally Occuring XB Donors



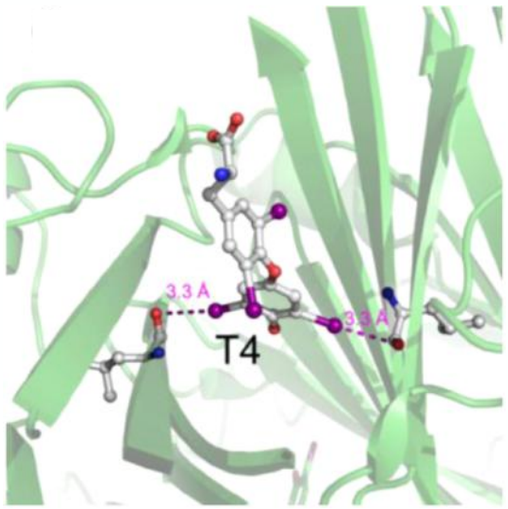
Thyroid Hormone T3

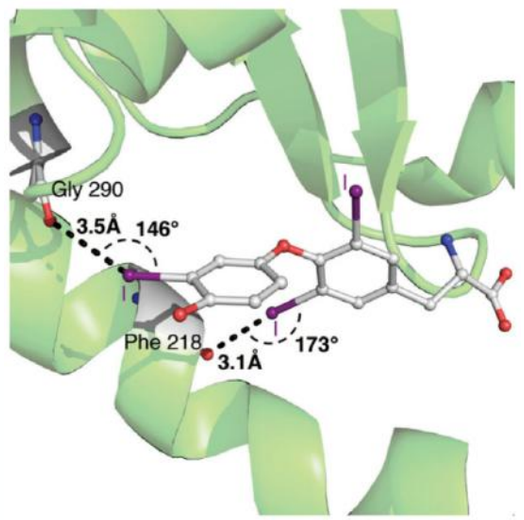


Thyroid Hormone T4

numerous I ··· O contacts play important role in thyroid hormone recognition

XB formed between T4 and transporter protein transthyretin (TTR)



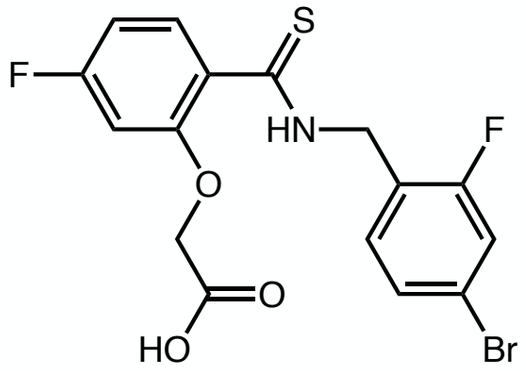


Recognition of T3 by human thyroid hormone receptor

Wojtczak, A. et. al. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2001**, *57*, 1061.

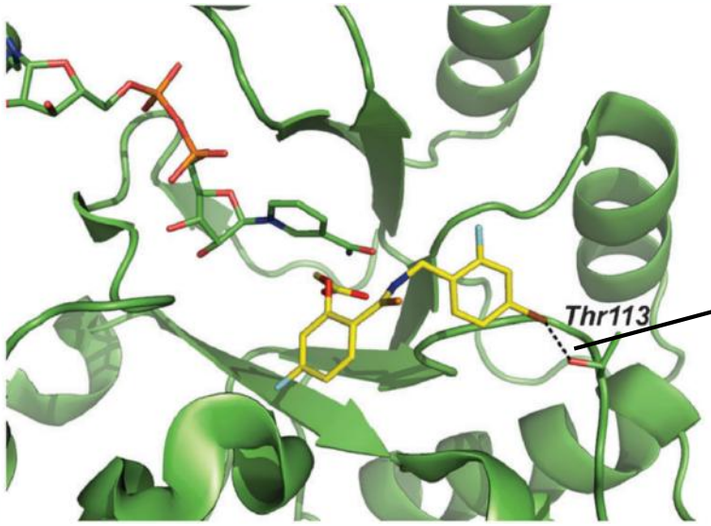
Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci.* **2004**, *101*, 16789.

Early Examples of XB in Biological Systems



IDD594

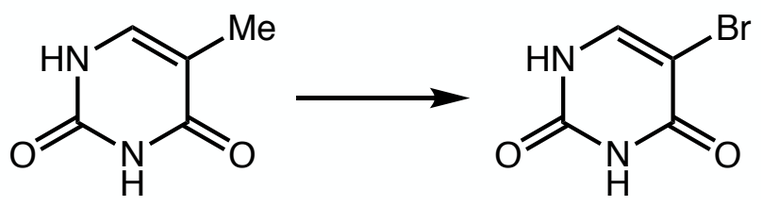
human aldose reductase (AR) inhibitor



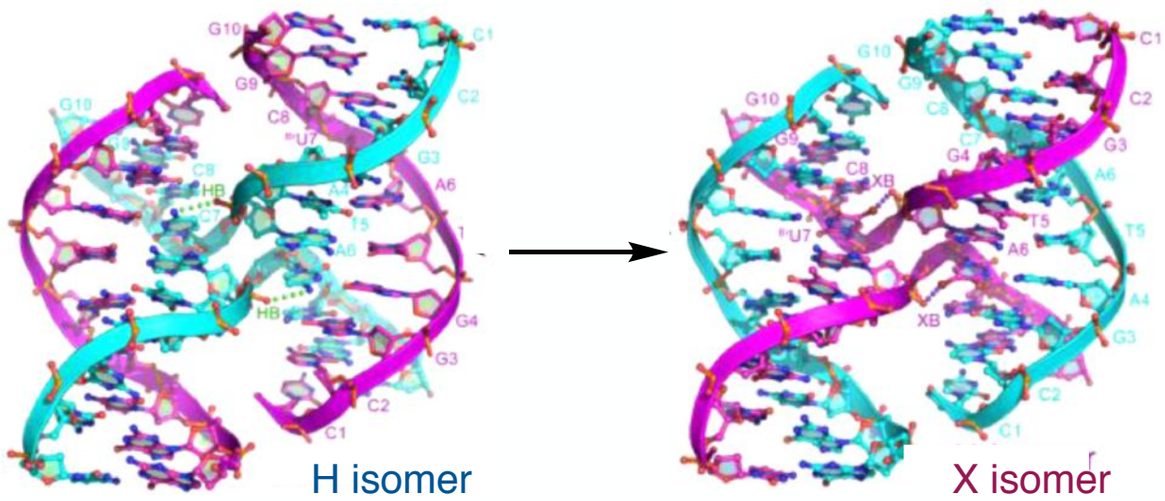
short Br ··· O contact between IDD594 and AR

- *replacing Br with Cl led to decrease in IC_{50} from 500 to 1300 nM*
- *XB promoted specifity over aldehyde reductase (where Thr113 is a bulkier Tyr)*

DNA Holliday Junction: HB vs. XB



XB is 5 kcal/mol stronger!



Howard, E. I., et. al. *Proteins: Struct., Funct., Genet.* **2004**, *55*, 792.

Hays, F. A.; Vargason, J. M.; Ho, P. S. *Biochemistry*, **2003**, *42*, 9586.

Halogen and Hydrogen Bonds in Biological Settings

H–Bond and X–Bond Acceptors

Proteins	Nucleic Acids	Ligands
peptide bond (O/N/π)	base (O)	(O/N/S)
side chains (O/O^-,N/S/π)	phosphoribose (O/O^-)	X (F, Cl, Br, I)
solvent (O)	solvent (O)	

H– and X– bond donors include biomolecules as well as synthetic molecules (e.g., pharmaceuticals)

chemical complexity of biological systems leads to diverse set of interactions (less geometrically/structurally defined)

Identifying XB in biological settings → **Protein Data Bank (PDB)**

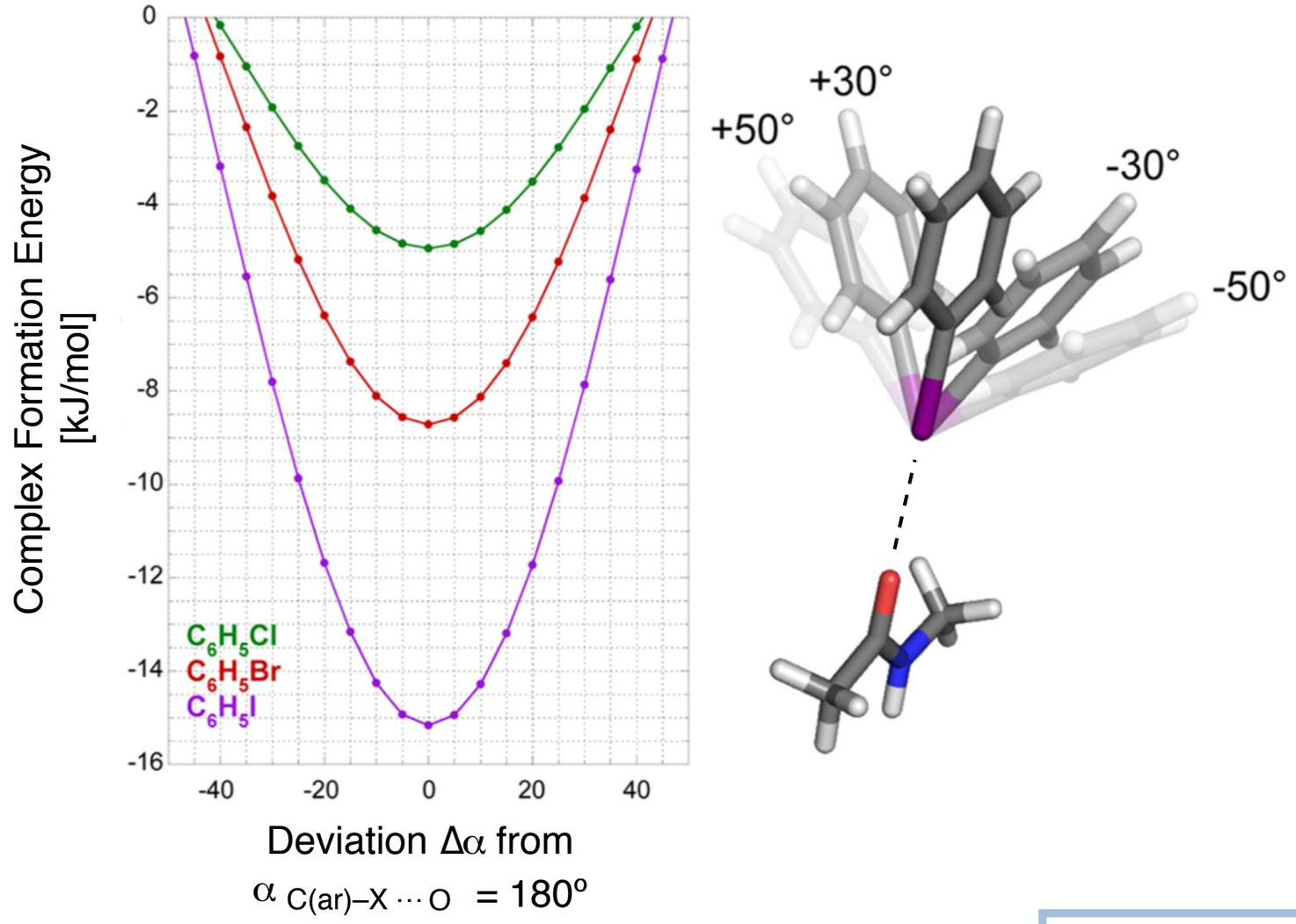
- X–LB distance ≤ sum of van der Waal radii
- angle of approach > 120°

> 700 halogen–protein interactions found

Scholfield, M. R., et. al. *Protein Science*, **2013**, *22*, 139.

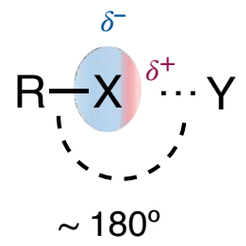
Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci.* **2004**, *101*, 16789.

Halogen Bonding in the Protein Data Bank



no significant attractive forces beyond 40° deviation

larger deviations negatively impact I more than Br or Cl

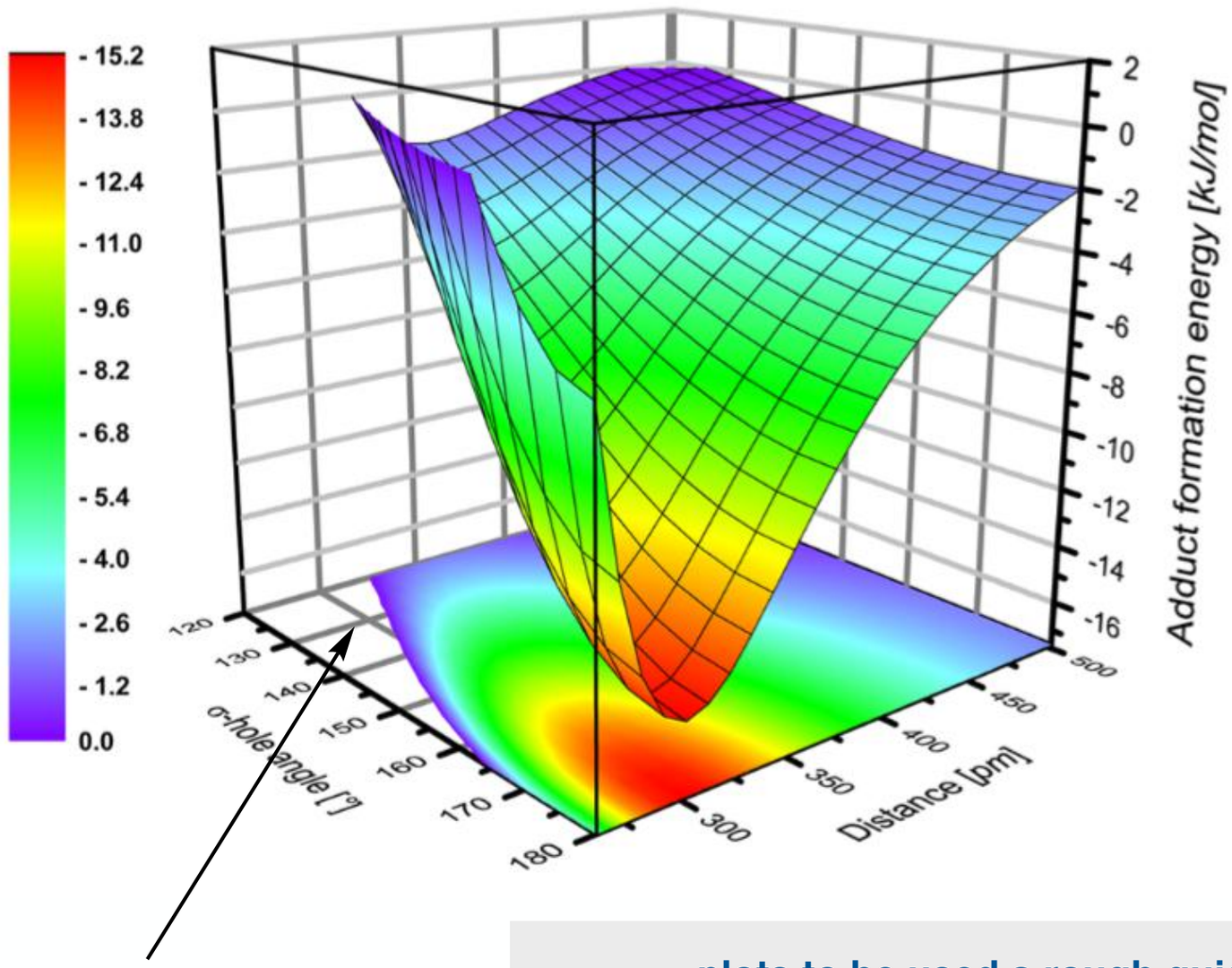


strongest XB at 180°

Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

Effects of Angle and Distance on the XB Strength

trends for I·· O contacts between Ar–I and backbone C=O

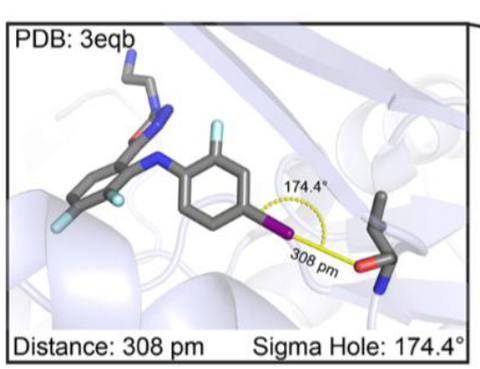


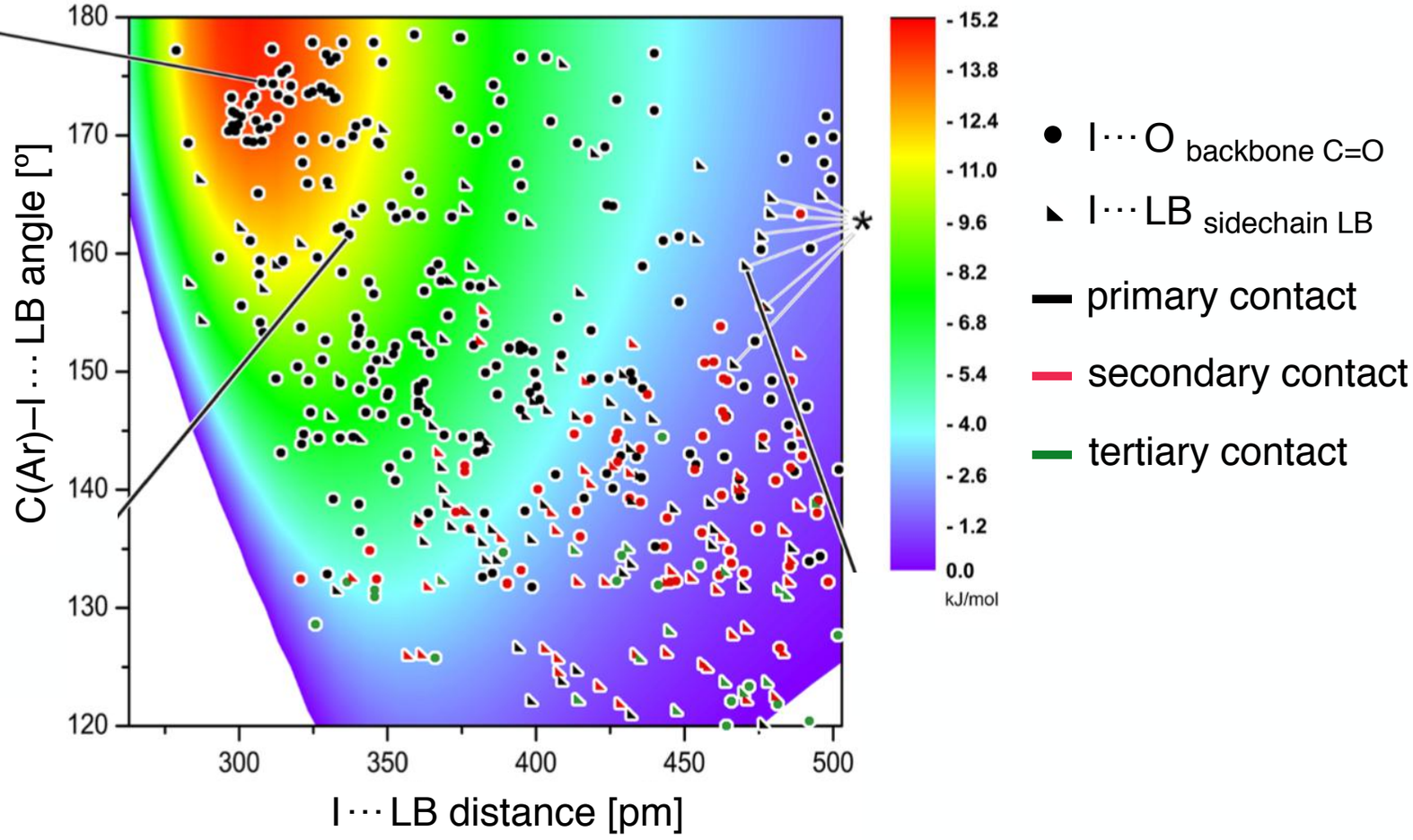
white space indicates
areas of repulsive interactions

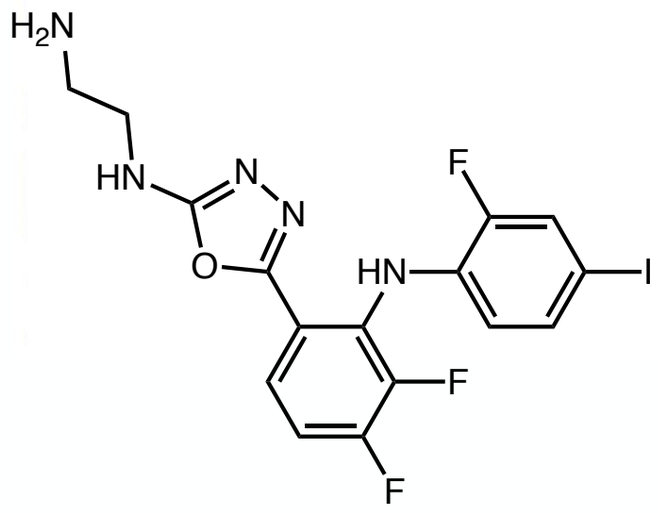
plots to be used a rough guidelines
scaffold, substitution pattern, polarization effects
all may effect binding in the protein

Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

A Closer Look at I–O Interactions in the PDB







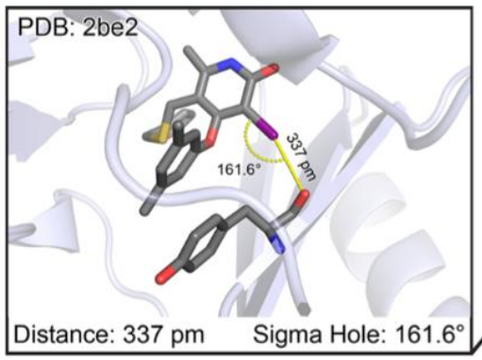
MAP ERK kinase inhibitor complex with MEK1

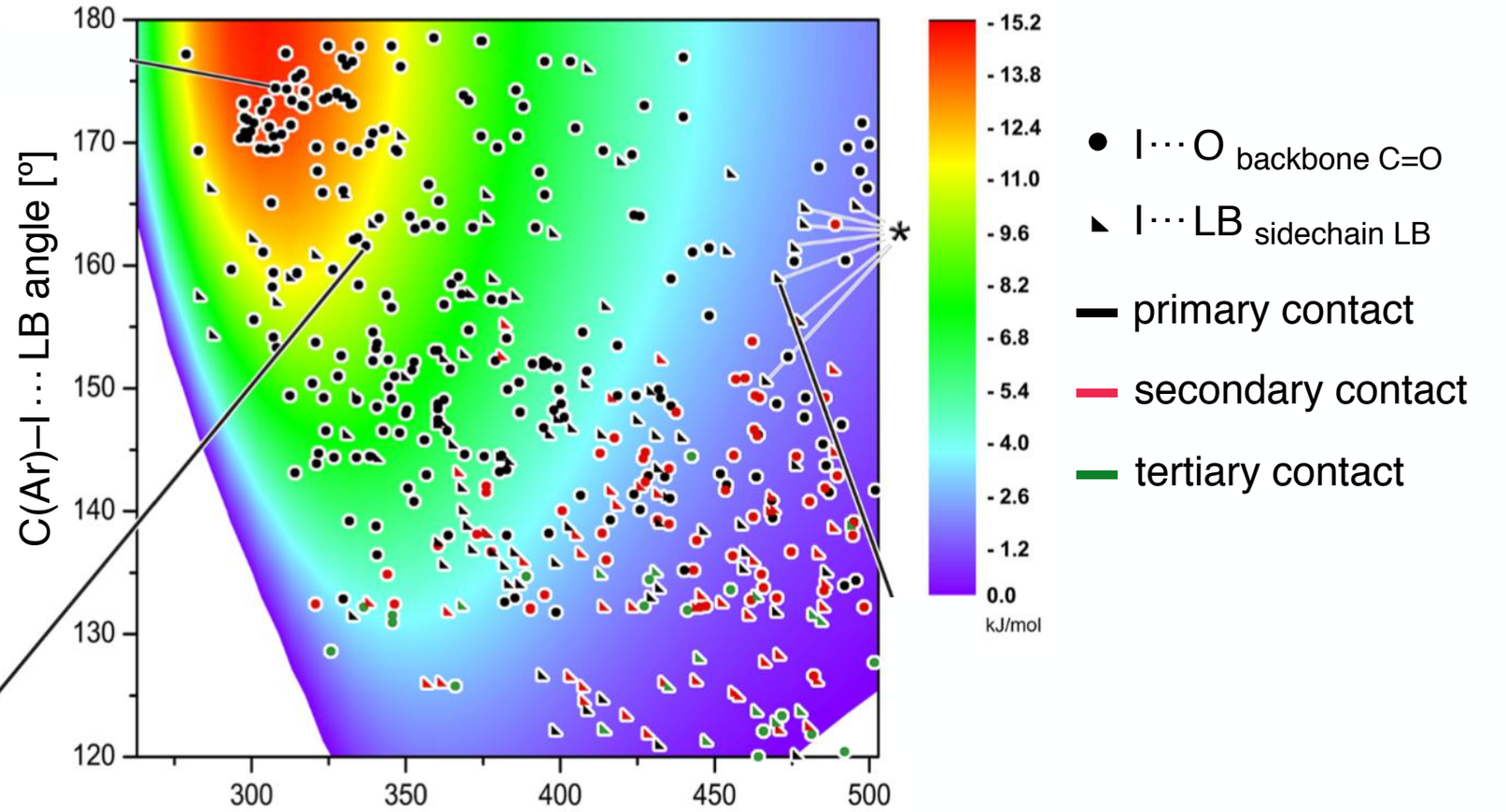
IC_{50} = 15 nM in C26 colon carcinoma cells

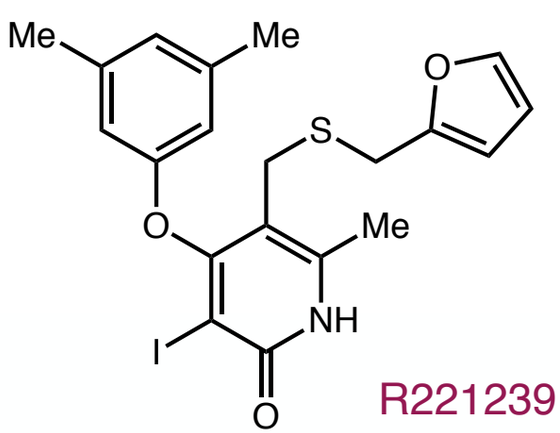
intramolecular H-bond stabilizes bioactive conformation

Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

A Closer Look at I–O Interactions in the PDB







R221239

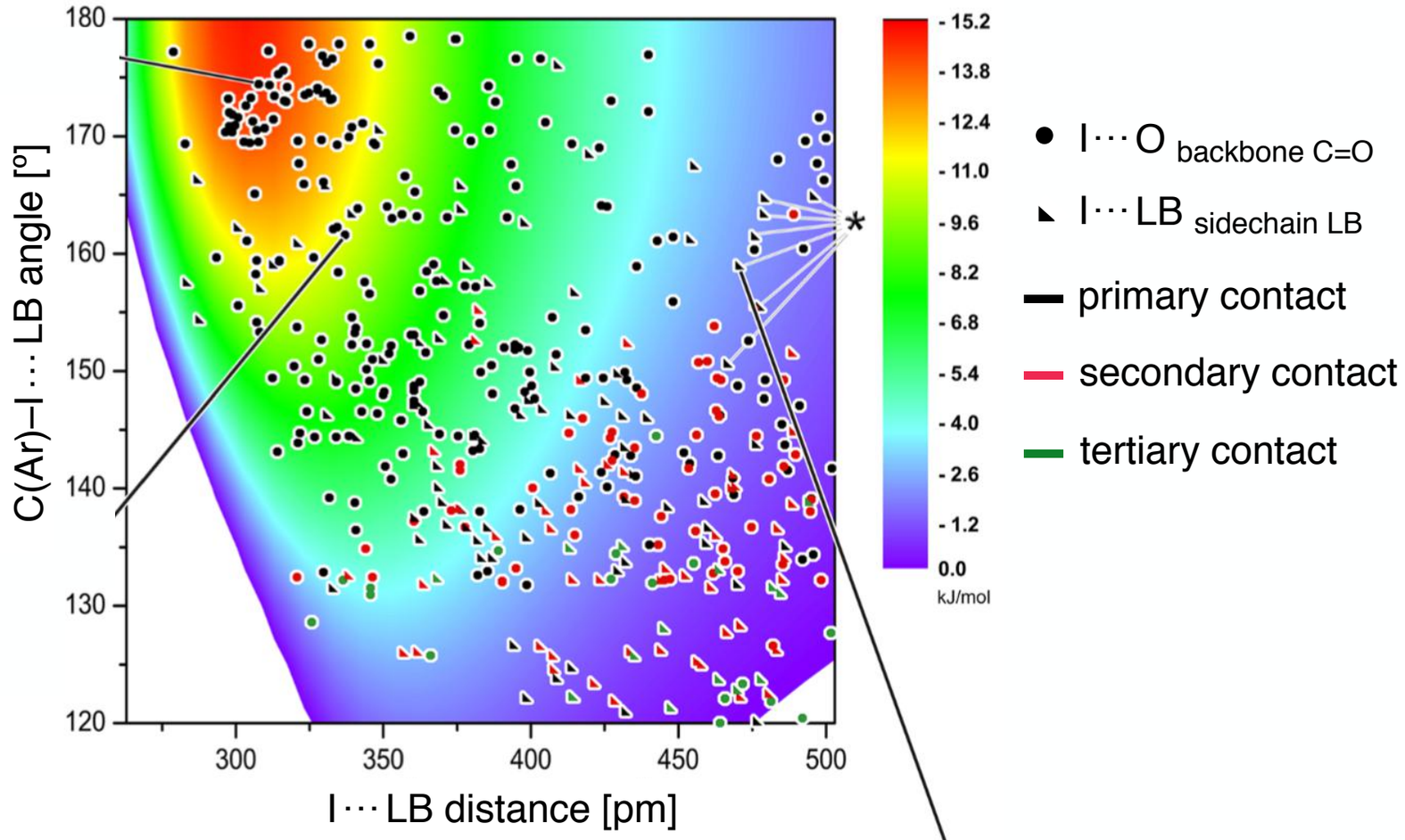
HIV1-reverse transciptase inhibitor

highly potent inhibitor: IC_{50} = 2 nM

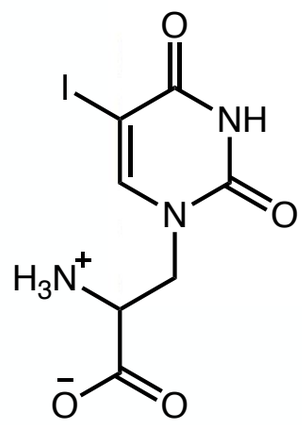
network of H-bond, π-π, and halogen bond

Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

A Closer Look at Interactions with Iodine in the PDB



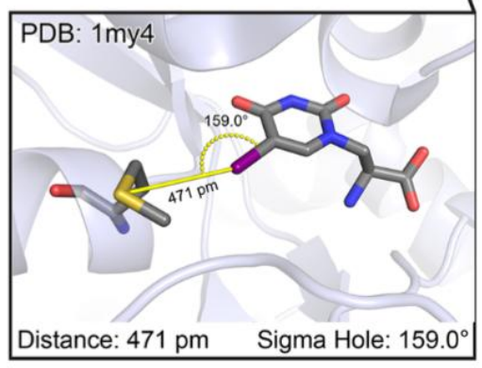
finding false positive and redundancies



ligand facing the shielded region of S

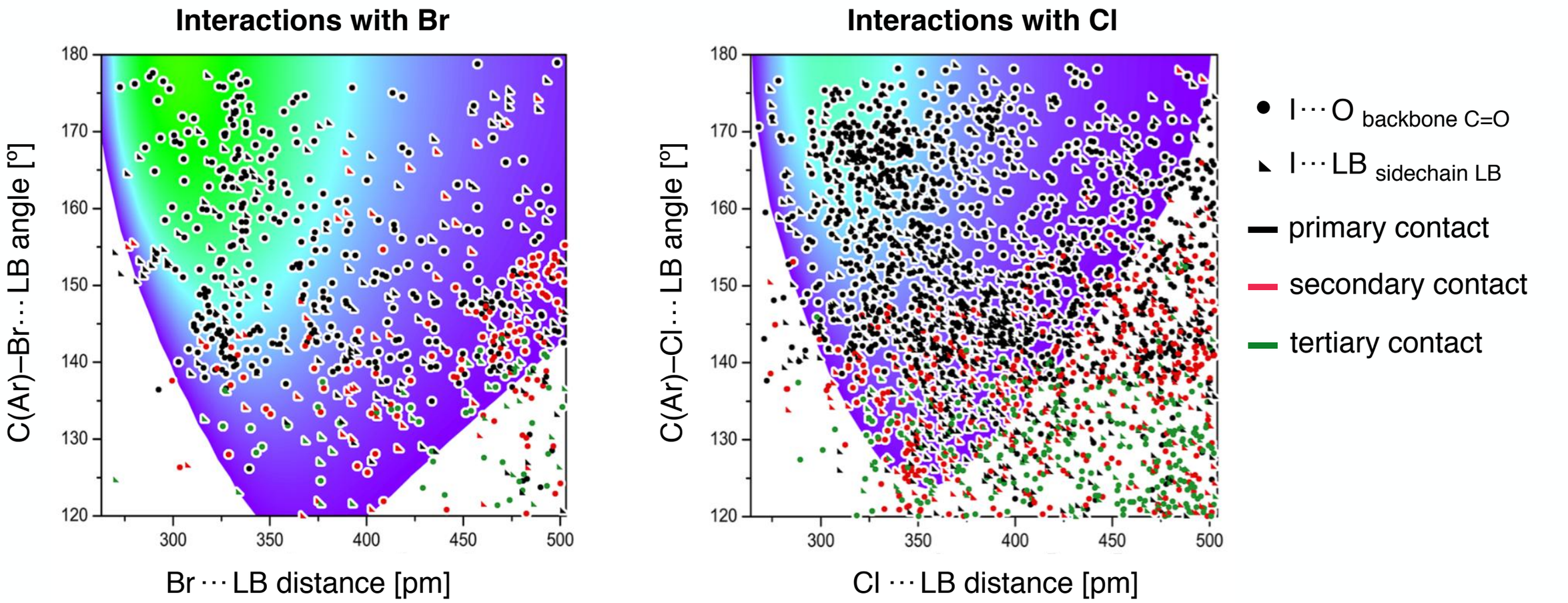
not consistent with a true XB

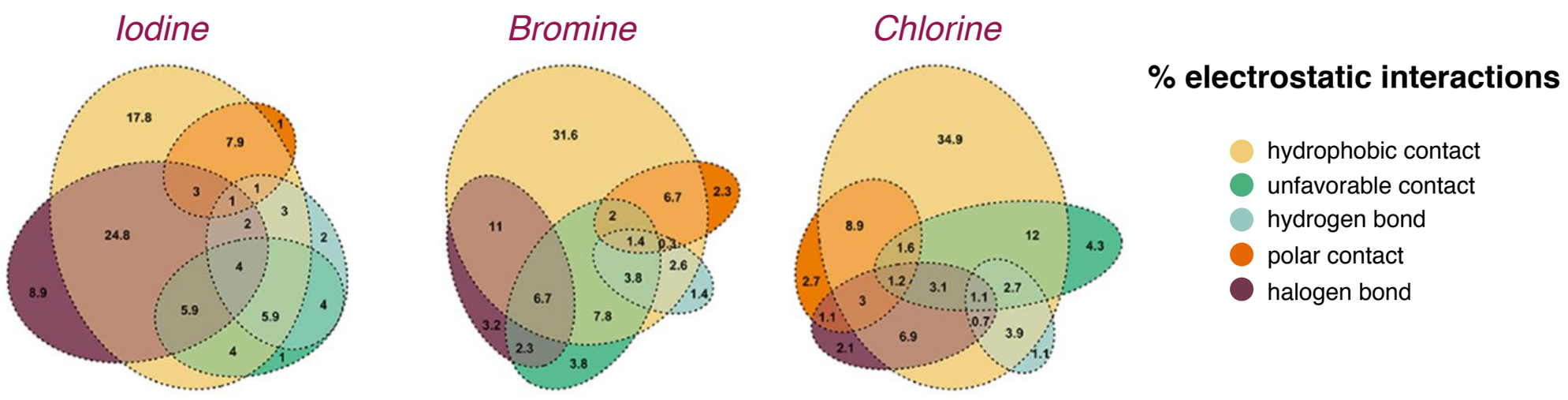
*indicates multiple signals where methionine bound to identical ligand



Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

Interactions with Br and Cl in the PDB



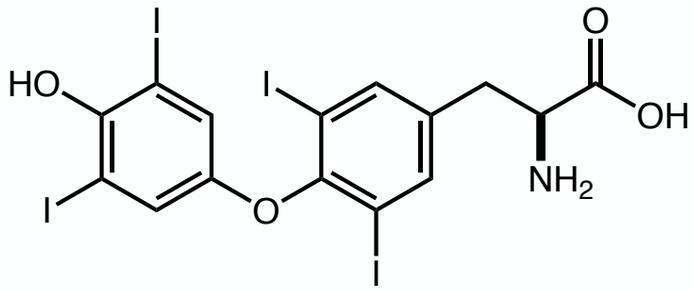


Shinada, N. K.; de Brevern, A. G.; Schmidtke, P. *J. Med. Chem.* **2019**, *Just Accepted*

Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

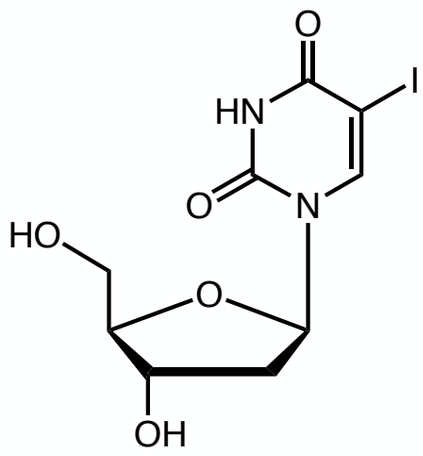
Approved Drugs Containing Iodine and Bromine

launched drugs containing iodine: ~ 1%



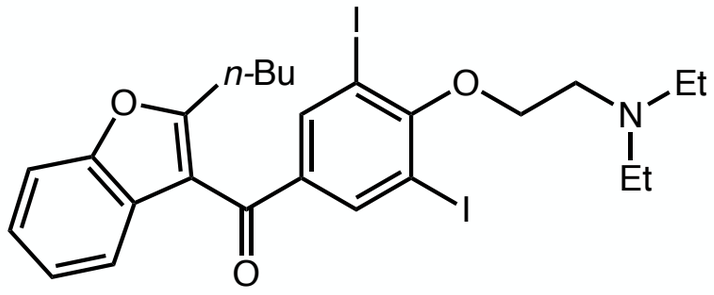
Levothyroxine

thyroid hormone deficiency



Idoxuridine

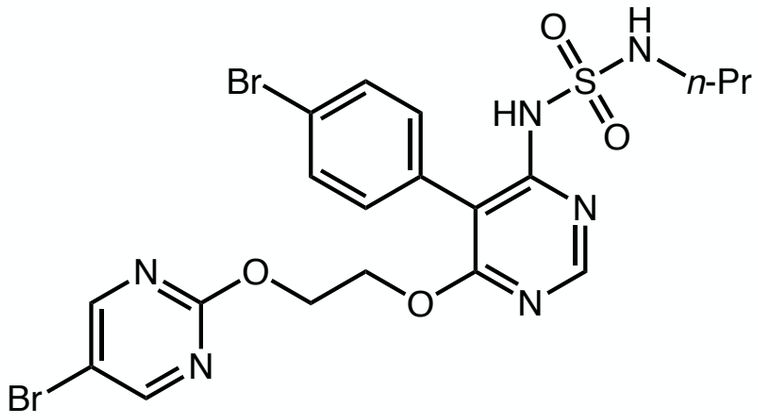
anti-herpesvirus antiviral



Amiodarone

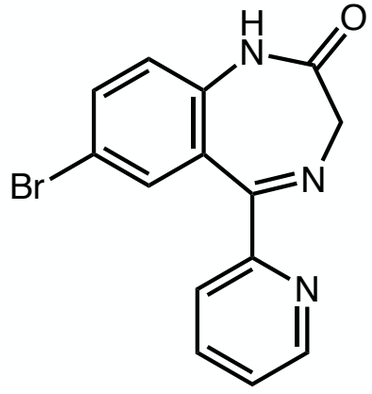
antiarrhythmic medication

launched drugs containing bromine: ~ 1.5%



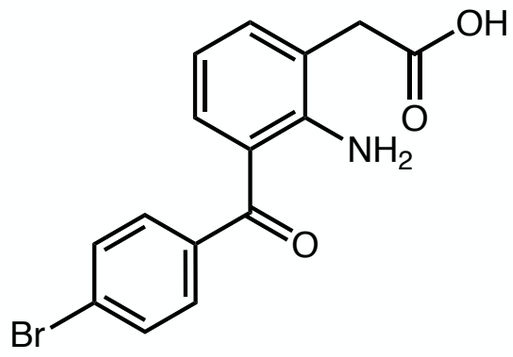
Macitentan

pulmonary arterial hypertension



Bromazepam

anti-anxiety agent



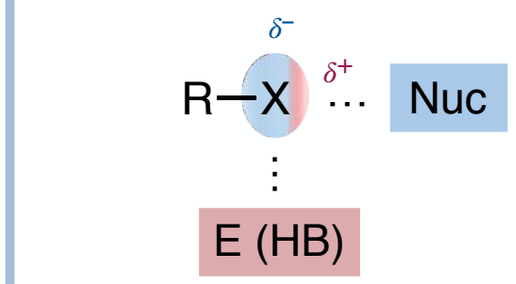
Bromfenac

NSAID

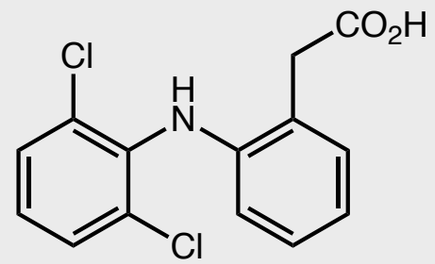
~15% of drugs contain at least one chlorine atom

Wilcken, R.; Zimmerman, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

Halogen-Water-Hydrogen Bridges

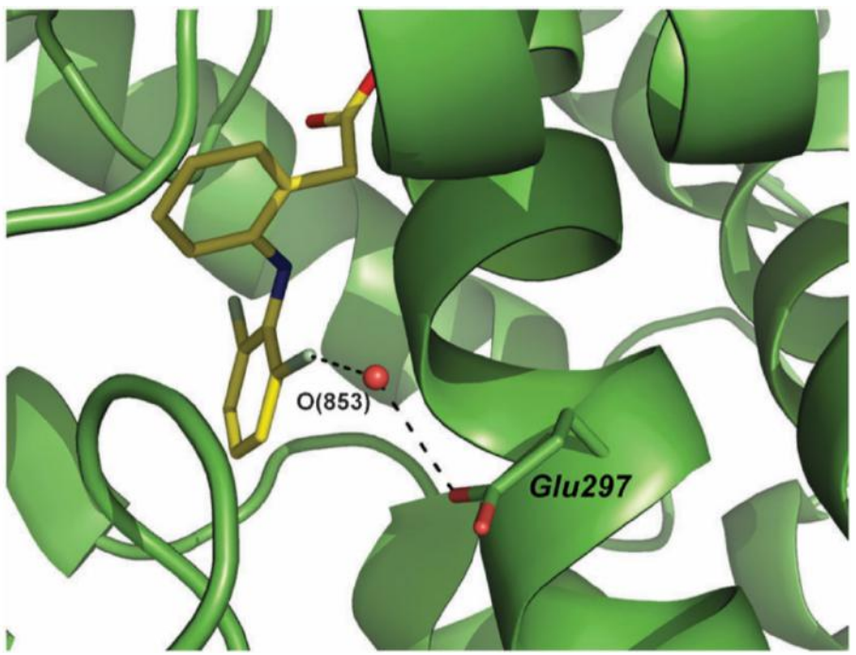


X atom can interact with both e⁻ rich and poor sites

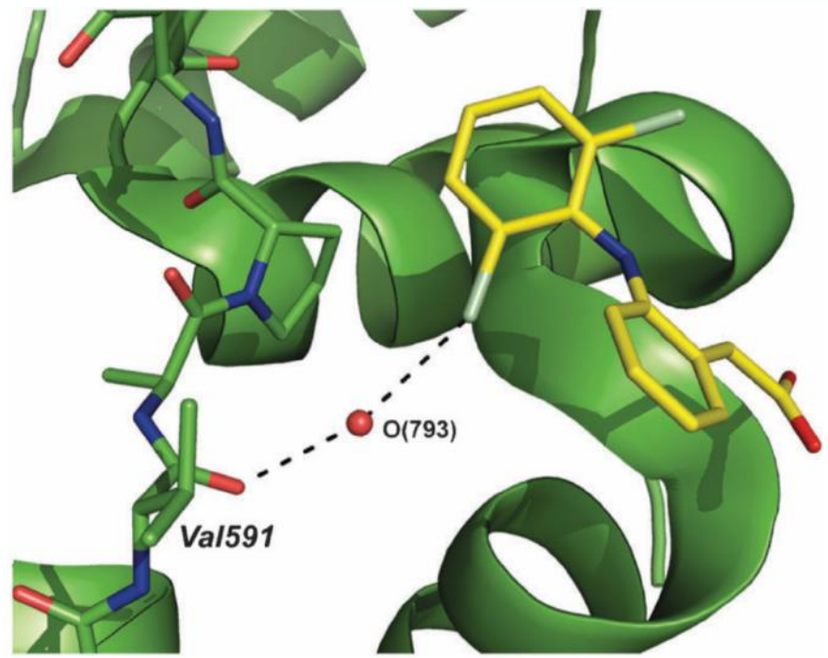


diclofenac

pain reliever (NSAID)



H_2O for simultaneous XB with diclofenac and HB with cytochrome P_{450} complex

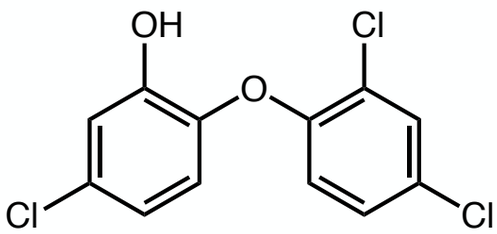


H_2O for simultaneous XB with diclofenac and HB with lactoferrin

XWH bridges difficult to exploit in rational design, but importance of XB in stabilizing conformations

Parisini, E.; Metrangolo, P.; Pilati, T.; Resnati, G..; Terraneo, G. *Chem. Soc. Rev.* **2011**, *40*, 2267.

Halogen Bonding and Triclosan



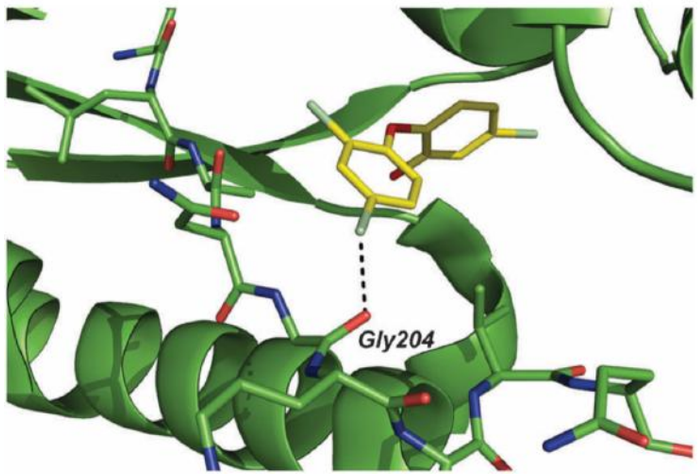
triclosan

anti-microbial

FDA in 2017 banned triclosan from “consumer antiseptic washes”

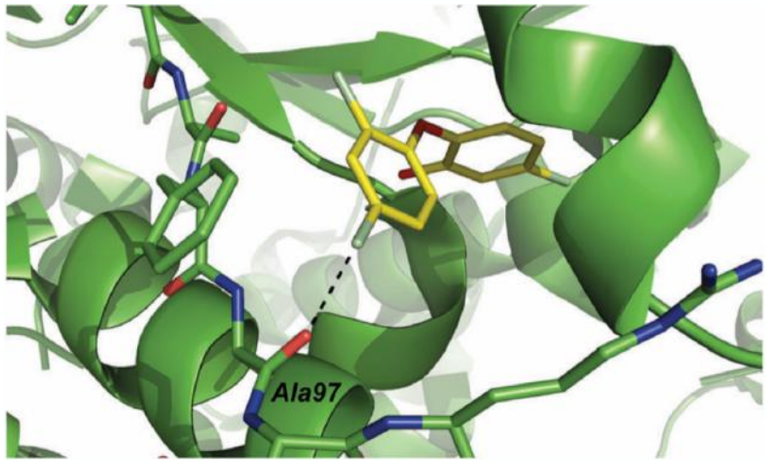
triclosan interactions with enoyl-acyl protein reductase (ENR)

XB with C=O of Glyc204
of ENR from *Plasmodium berghei*



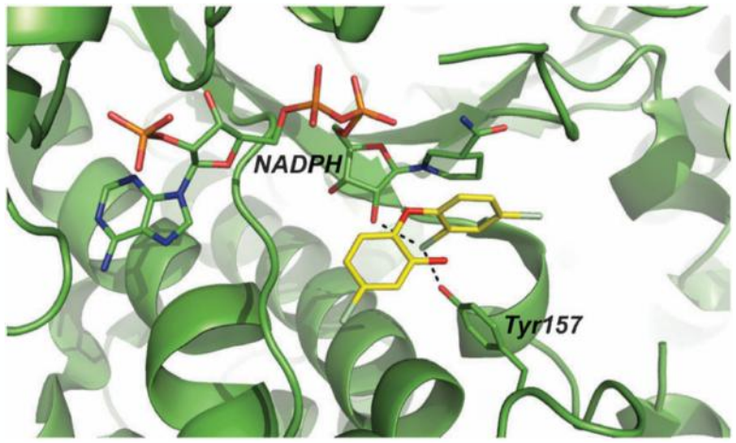
XB is 3.25 Å and 162.4º

XB with C=O of Ala97
of ENR from *Bacillus anthracis*



XB is 3.08 Å and 166.2º

with ENR from *Staphylococcus aureus*
with NADPH and triclosan



2 simultaneous H-bond at 90º

Wilcken, R.; Zimmerman, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

Can exploitation of halogen bonds be used in rational drug design?

Curent Challenges for Rational Design of XB

Halogens in Pharmaceuticals

Many halogens have been installed in drugs through trial and error, rather than by design

- increase membrane permeability
- fill spaces in binding pockets

computational modelling
to exploit XB?

Goal: high-throughput virtual screening

density functional theory (DFT)

inadequate description of dispersion forces

force field approach (e.g., docking)

fail to capture anisotropic nature of XB

semi-empirical methods:

often fail to accurately predict XB

high-level QM calculations

accurate, but computationally costly

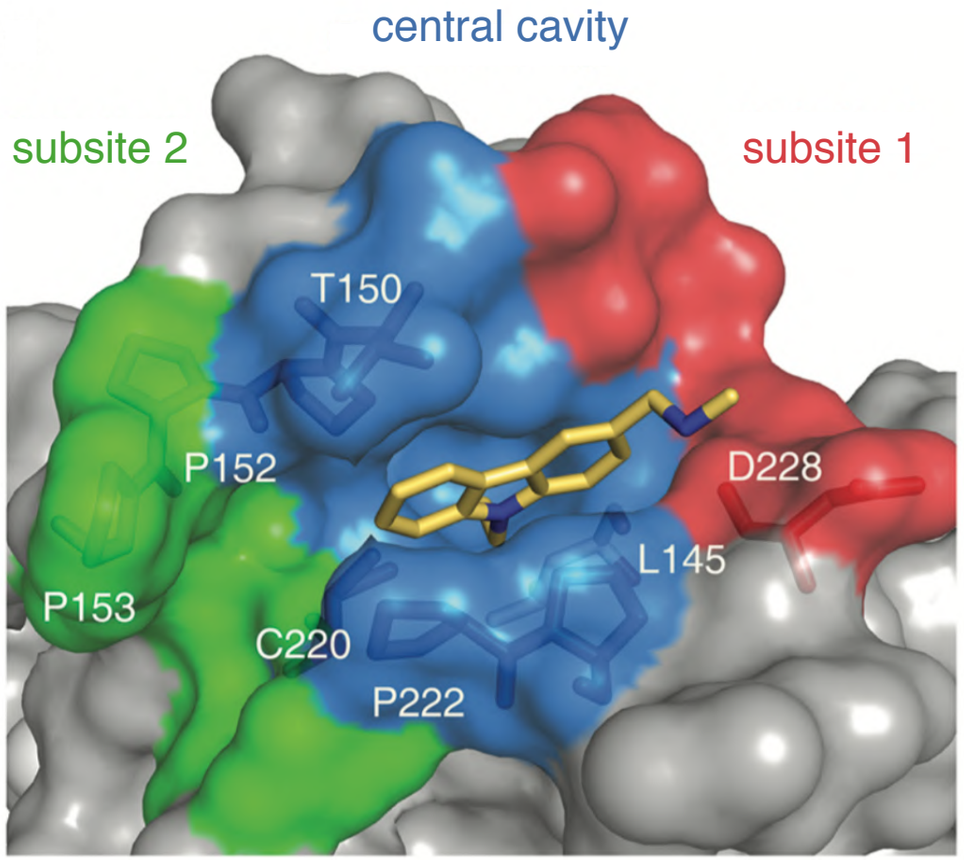
Ford, M. C.; Ho, P. S.; *J. Med. Chem.* **2015**, *59*, 1655
Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A.C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

Rational Design in Drug Discovery

p53 is inactivated in many cancers (mutation or pathway perturbation)

~1/3 of mutations slightly lower melting temp. ⟶ protein unfolds at body temp.

Goal: bind molecules to protein to stabilize the folded state



mutant Y220C

"cancer hotspot" (75,000 cases/yr)

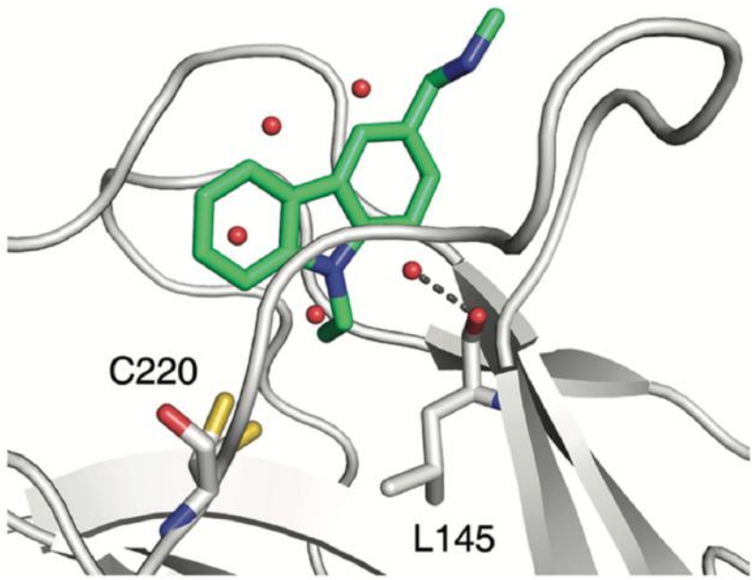
halogen enriched fragment library (HEFLibs)

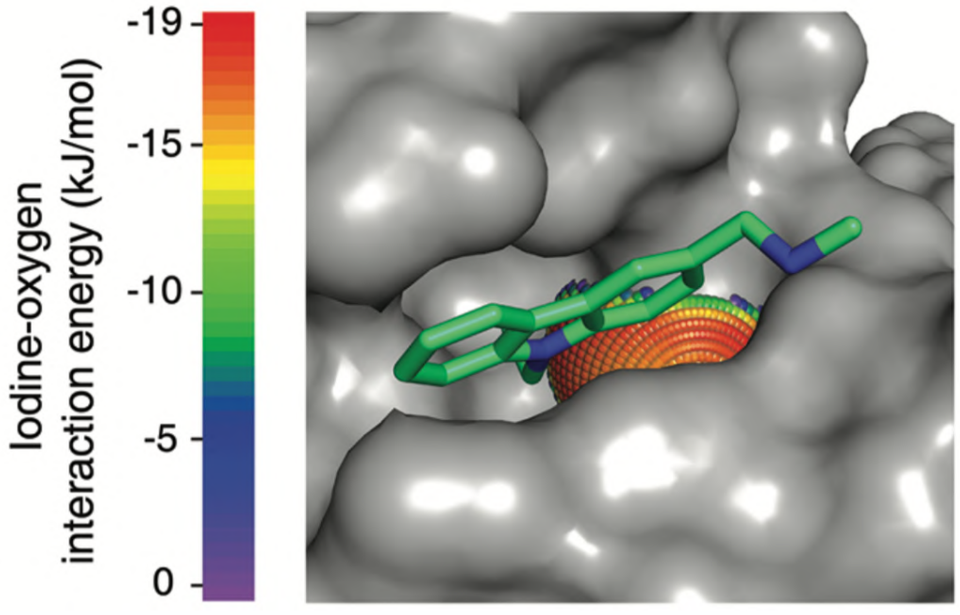
quantum chemical calculations

exploit XB for lead discovery

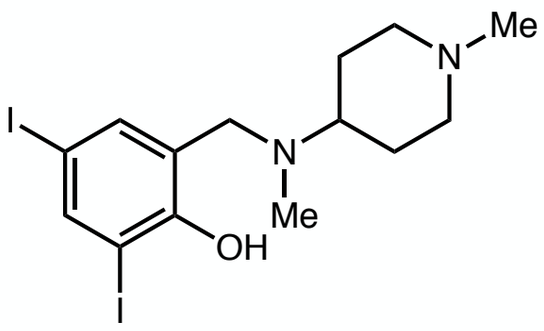
Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Rational Design in Drug Discovery





calculations suggest potential for strong I-O contact with L145



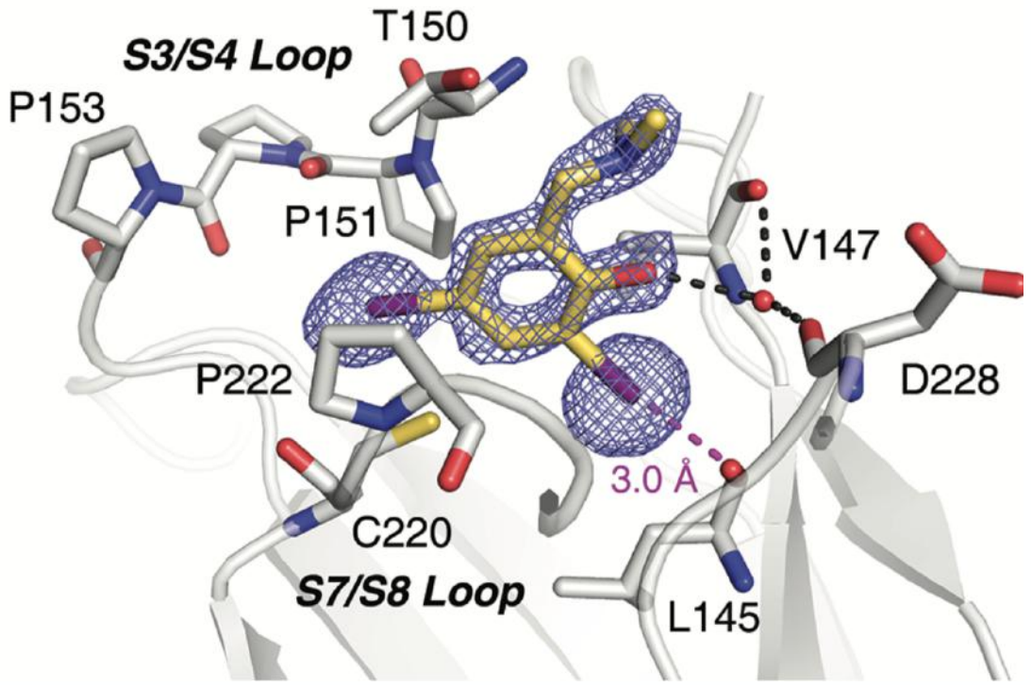
promising lead

via thermal shift assay and NMR

K_D = 184 μM

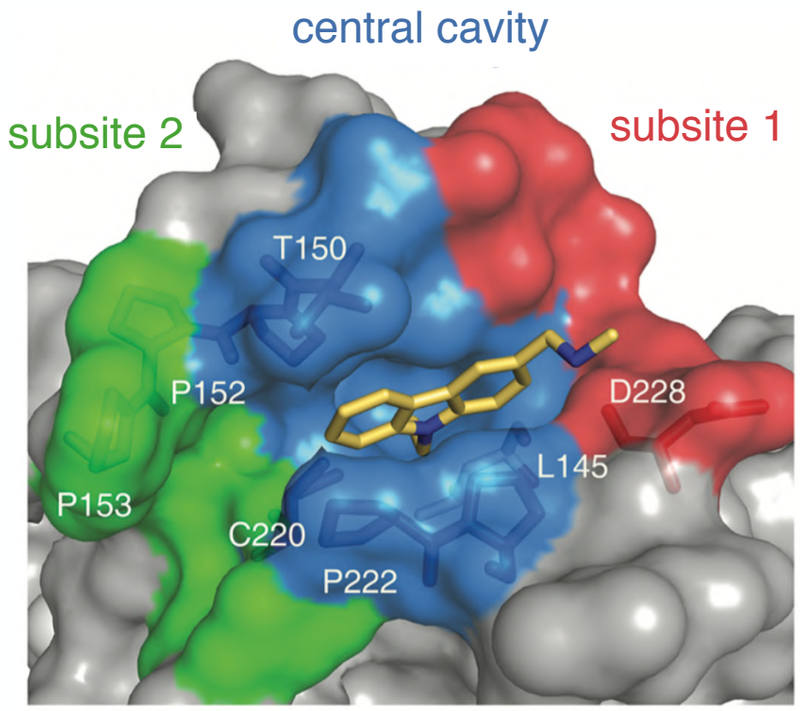
solve crystal structure

of Y220C mutant bound complex



Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Rational Design in Drug Discovery

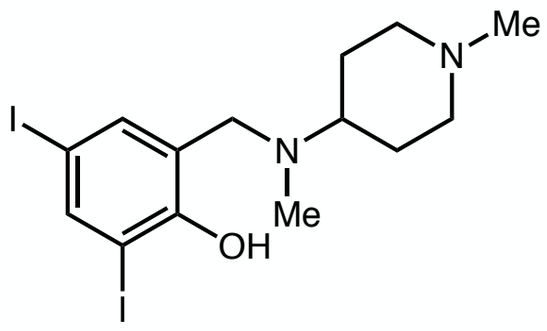


Goals:

extend ligand into subsite 1 and 2

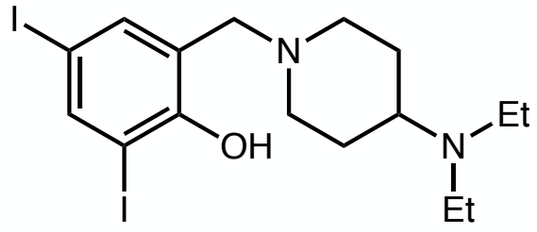
increase melting temperature

decrease K_D



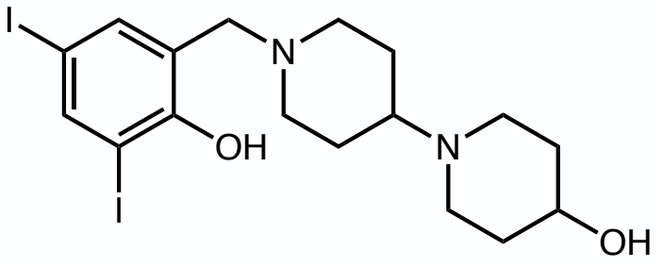
K_D = 184 μM

ΔT_m (K) = 0.55



K_D = 104 μM

ΔT_m (K) = 0.97

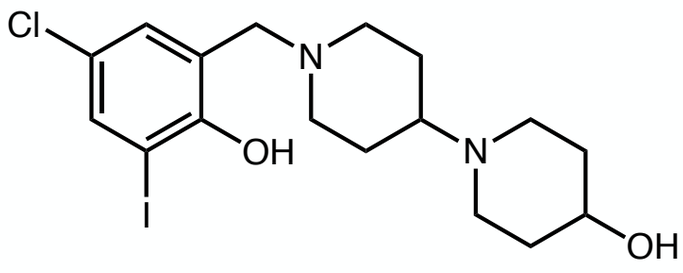


K_D = 87 μM

ΔT_m (K) = 1.10

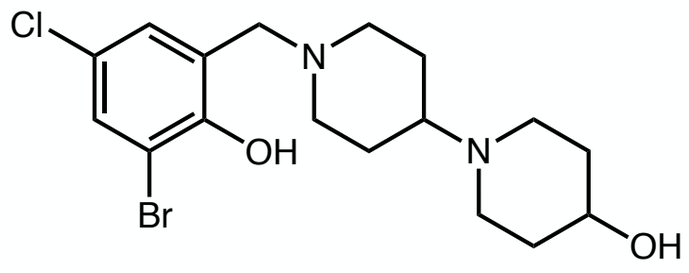
Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Rational Design in Drug Discovery



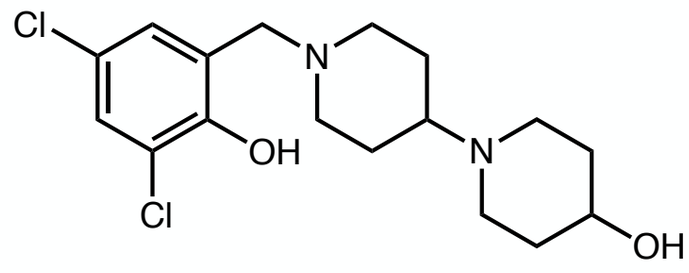
K_D = 247 μM

ΔT_m (K) = 0.31



K_D = 1040 μM

ΔT_m (K) = 0.03

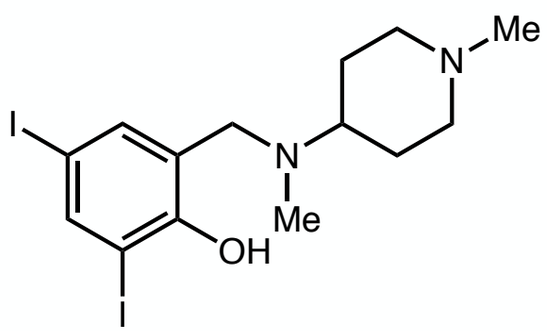


K_D = 4900 μM

ΔT_m (K) = –0.05

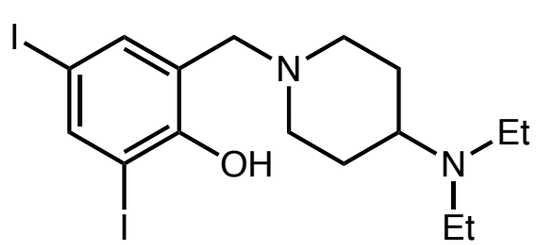
decreasing strength of halogen bond

up to 20-fold loss in binding affinity



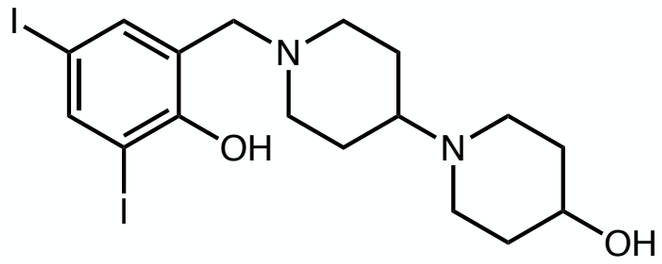
K_D = 184 μM

ΔT_m (K) = 0.55



K_D = 104 μM

ΔT_m (K) = 0.97



K_D = 87 μM

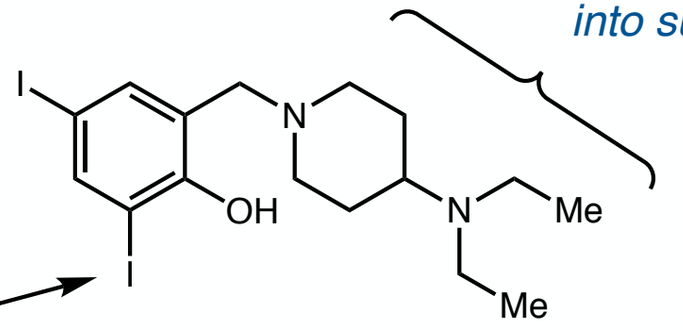
ΔT_m (K) = 1.10

Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Rational Design in Drug Discovery

unit allows extention into subsite 1

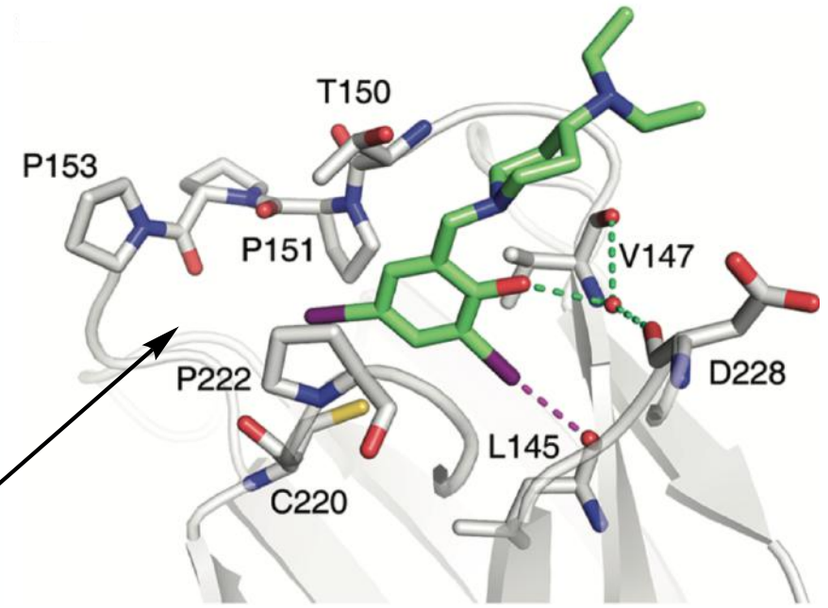
no XB contact →



involved in XB →

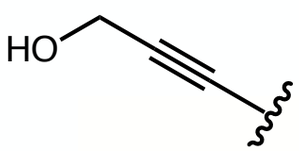
K_D = 104 μM

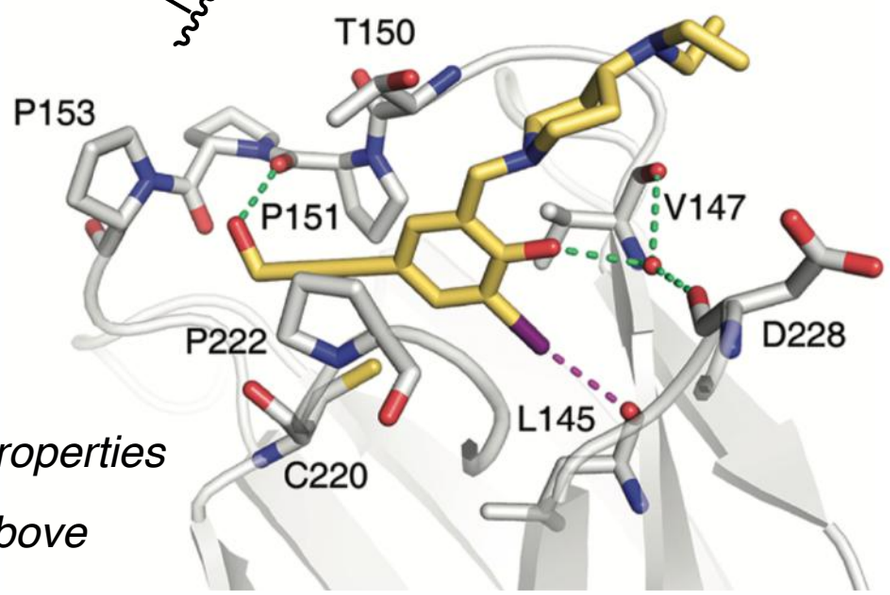
ΔT_m (K) = 0.97



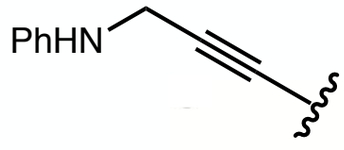
extend into subsite 2 using I not involved in XB

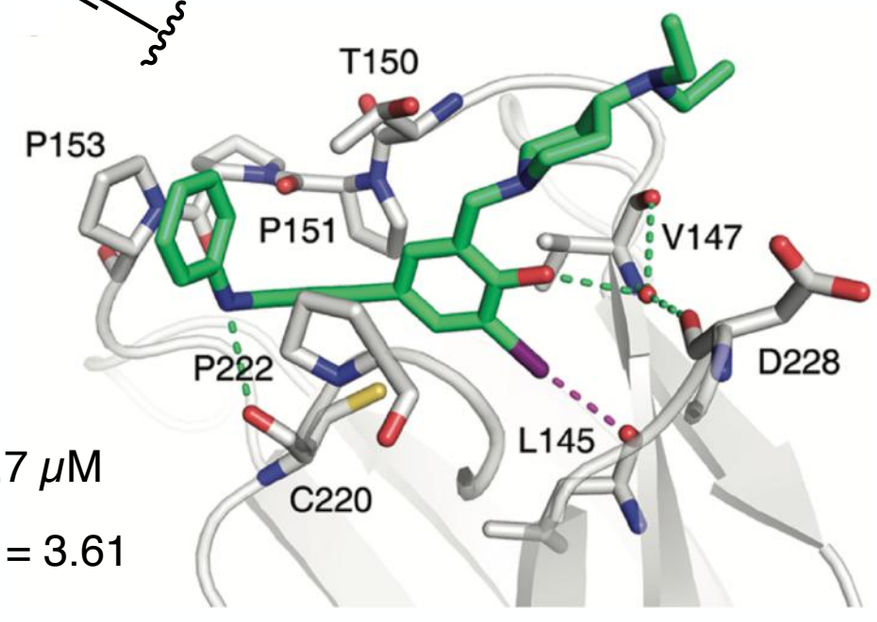
replace non-XB I with:





similar properties as above





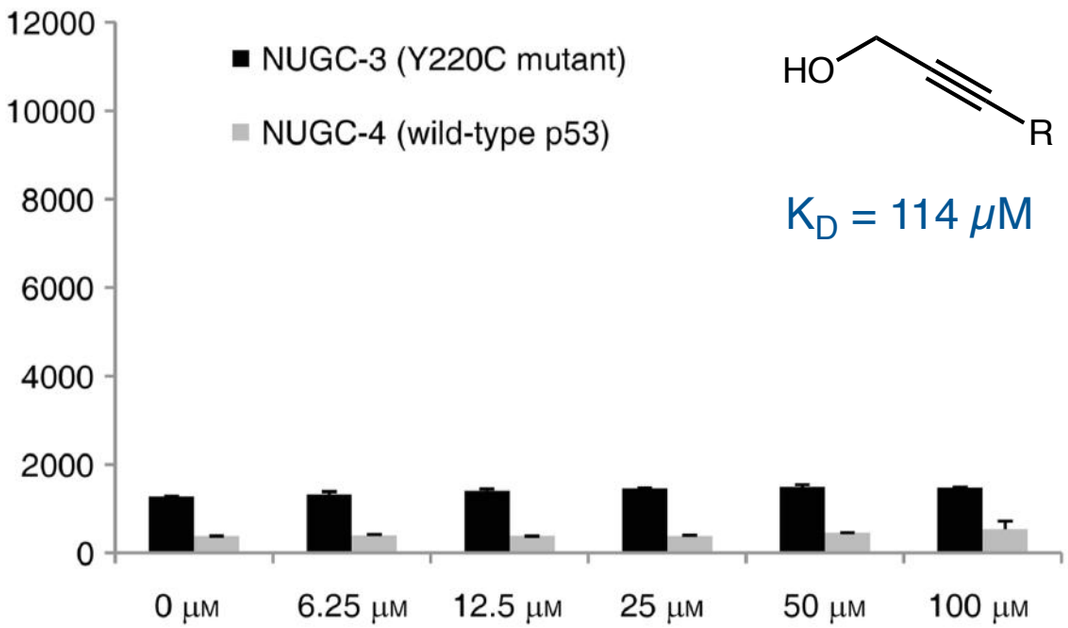
K_D = 9.7 μM

ΔT_m (K) = 3.61

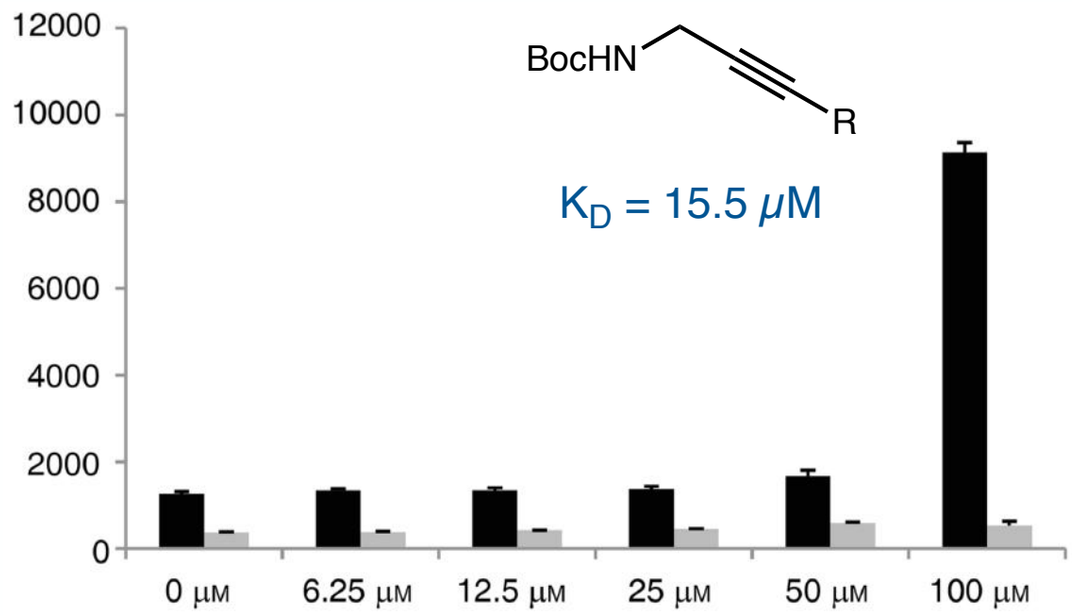
Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Rational Design in Drug Discovery

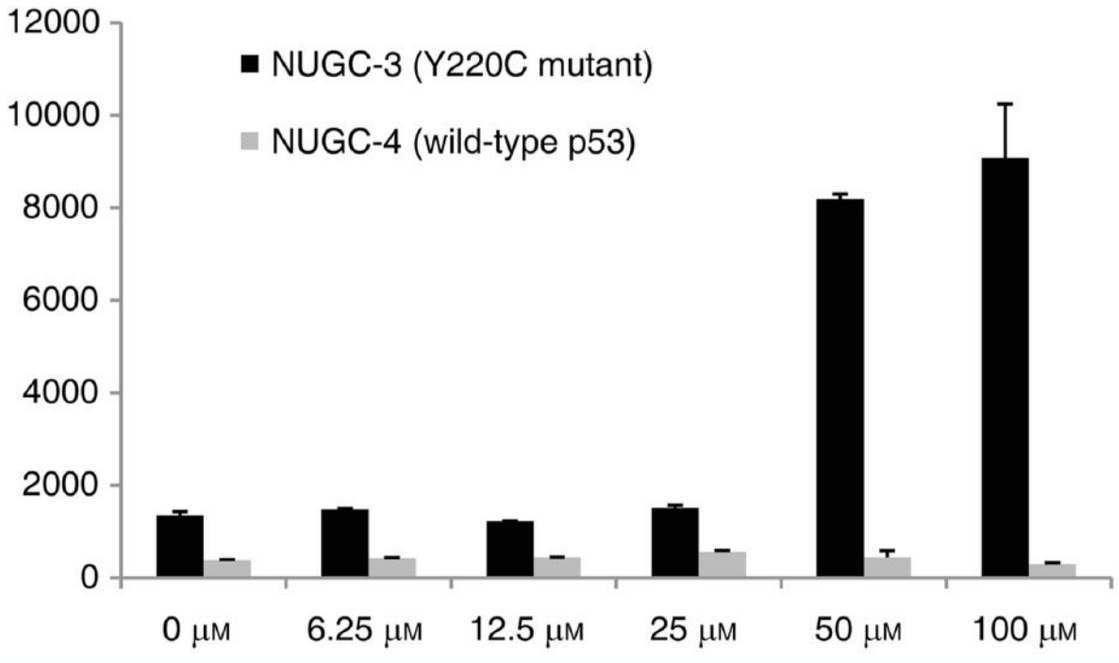
testing the apoptotic effects in human gastric cancer cell lines NUGC-3

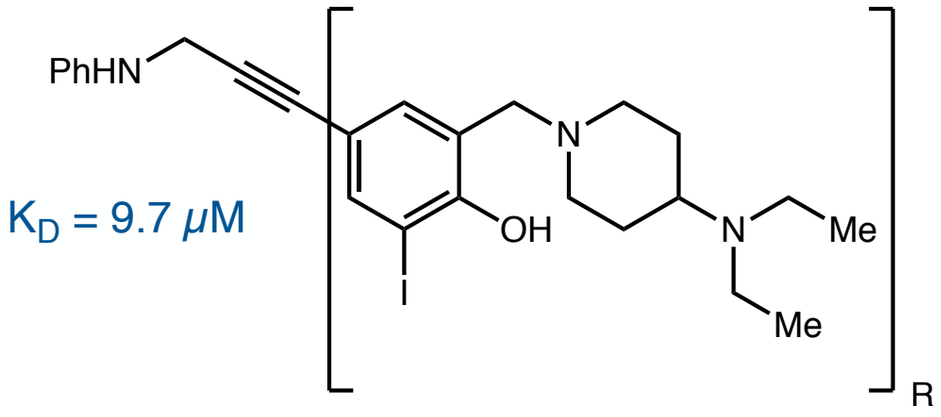


K_D = 114 μM



K_D = 15.5 μM





K_D = 9.7 μM

Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Rational Design in Drug Discovery

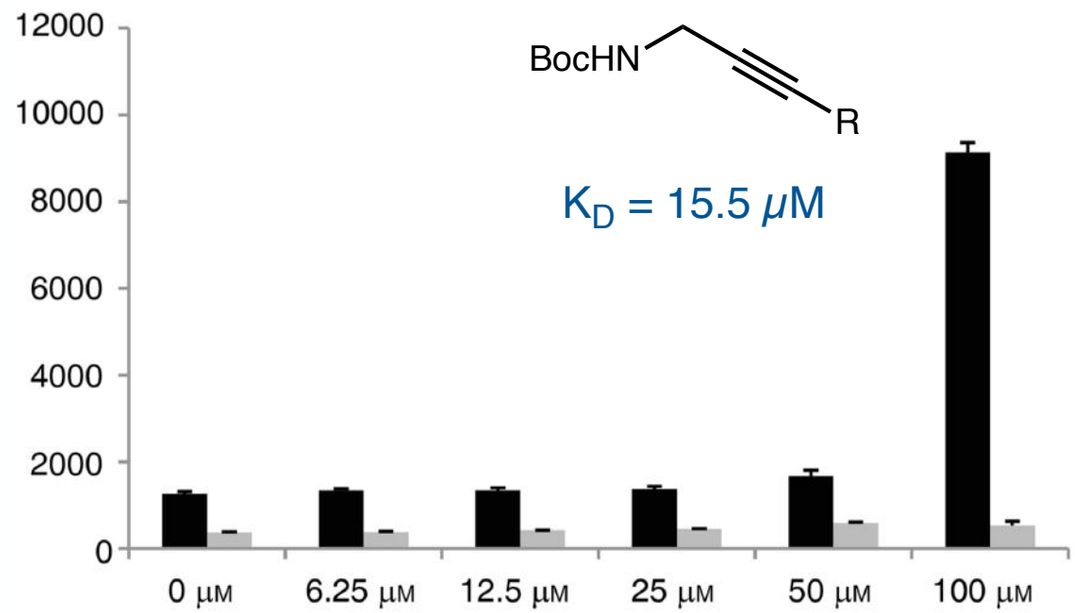
testing the apoptotic effects in human gastric cancer cell lines NUGC-3

dose-dependent onset of apoptosis

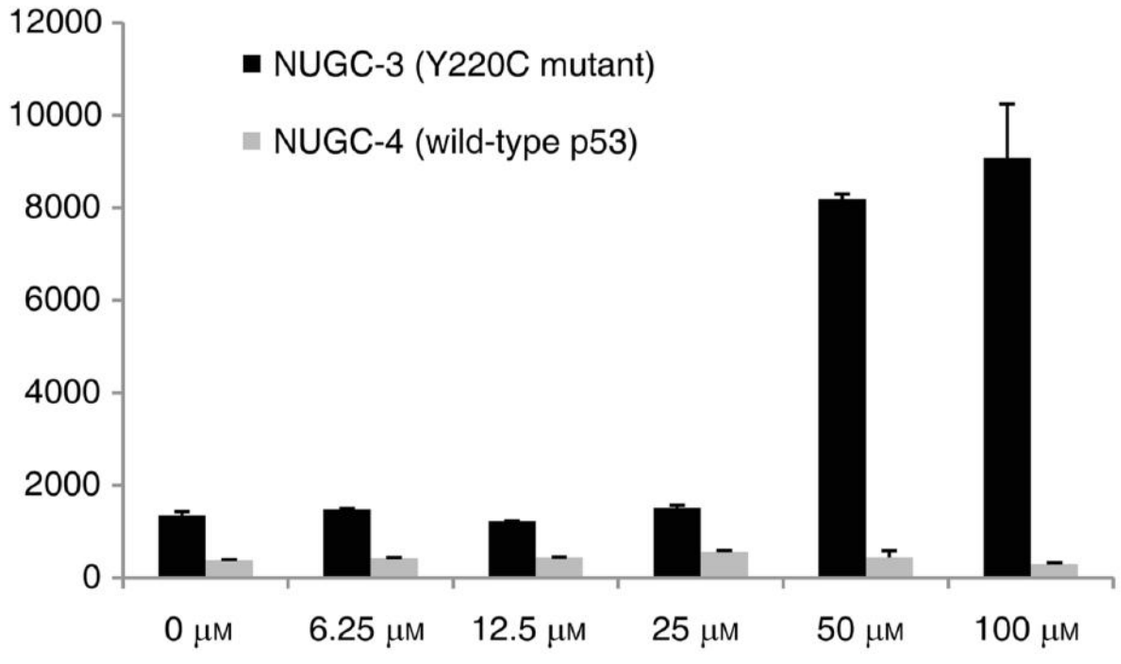
in more strongly bound cases

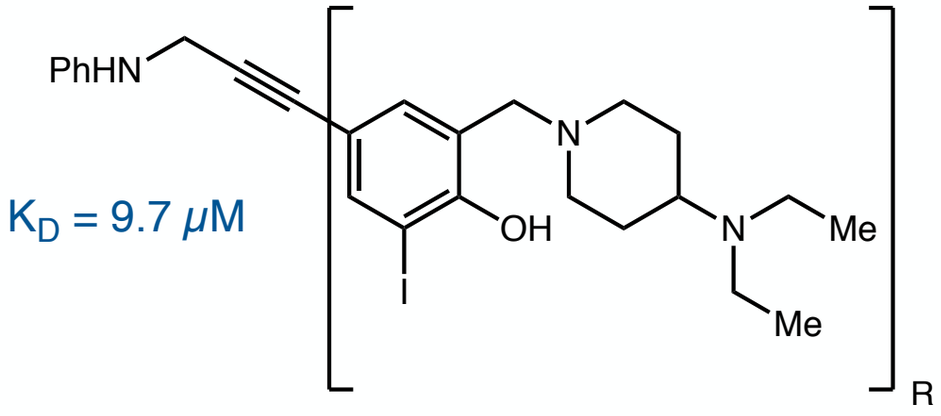
both molecules showed cytotoxic

effects at 50 and 100 μM



K_D = 15.5 μM



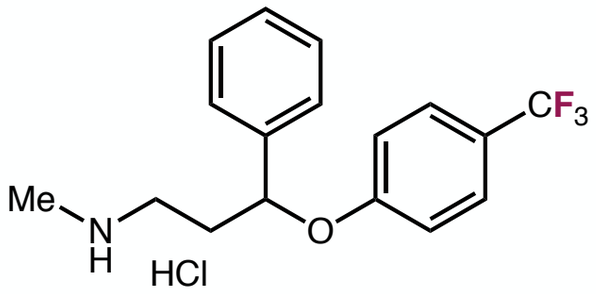


K_D = 9.7 μM

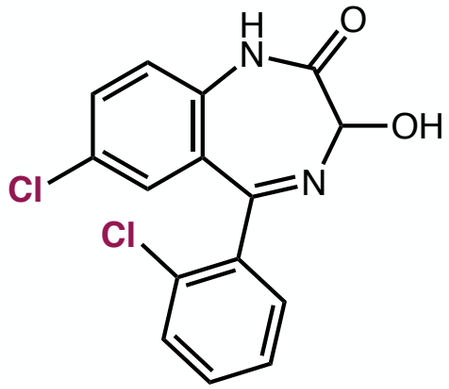
Wilcken et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6810.

Halogenation of Drugs: Pros and Cons

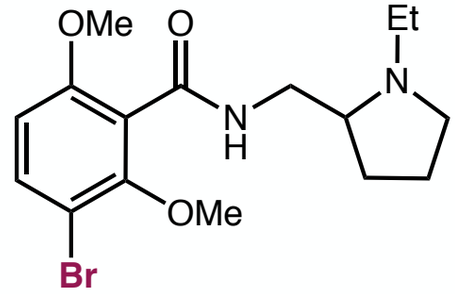
prevalence of halogens in pharmaceuticals



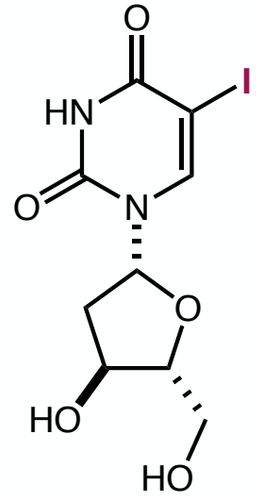
Prozac



Lorazepam



Remoxipride



Iodoxuridine

fewer drugs containing the heavier halogens →

Pros for halogen installation:

- improve selectivity and affinity (XB)
- increase ADME properties (F/Cl)
- increase metabolic stability (F/Cl)

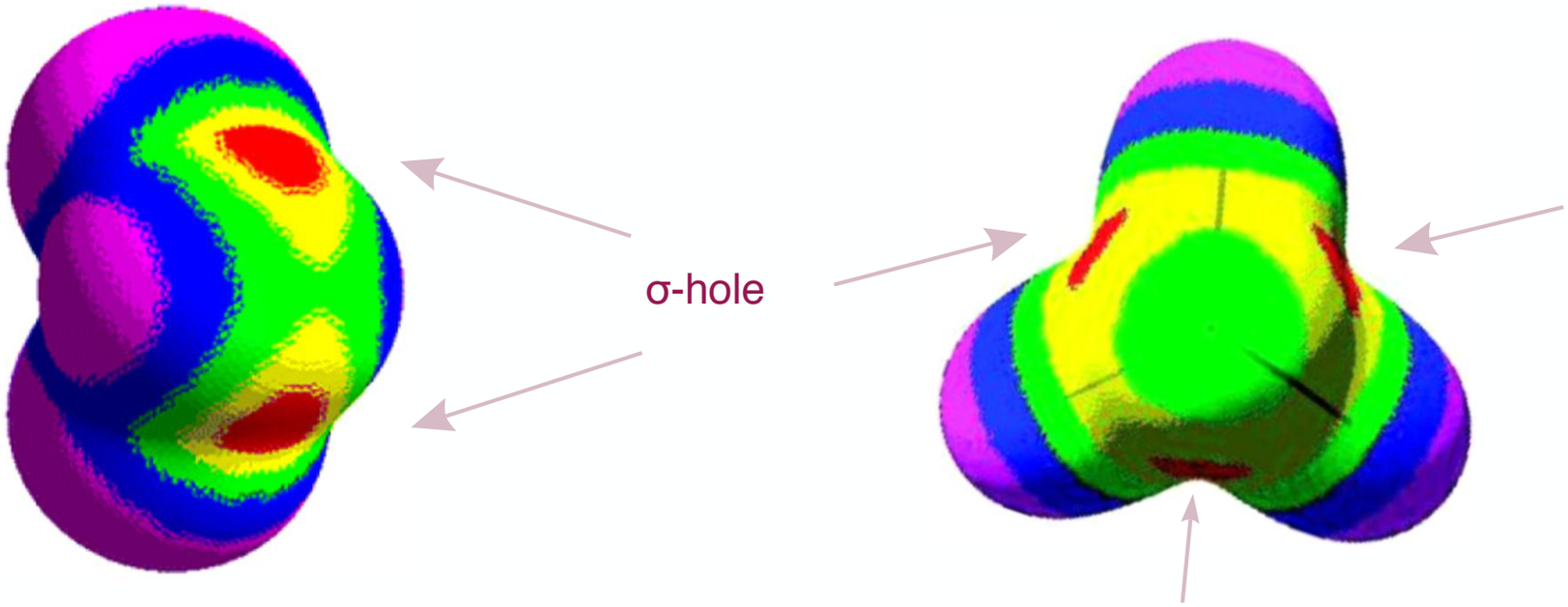
Cons for halogen installation:

- synthesis of drugs with Ar–Br/I
- addition of MW, lipophilicity with “heavy” atoms
- metabolic and toxicity issues (Ar-I)

Wilcken, R.; Zimmerman, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

σ-Hole Interactions Beyond the Halogens

σ-hole interactions similarly found in chalcogen and pnicogen series



calculated electrostatic potential of SCl_2 (2 σ-holes)

calculated electrostatic potential of $As(CN)_3$ (3 σ-holes)

similar trends for magnitude of the σ-hole as XB:

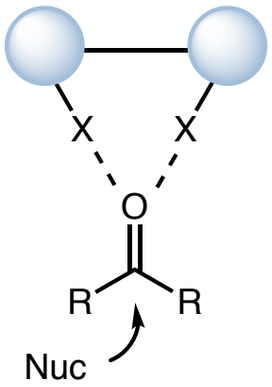
● less electronegative ● more polarizable ⟶ larger σ-holes

as with F, unlikely to see σ-holes on C, N, or O

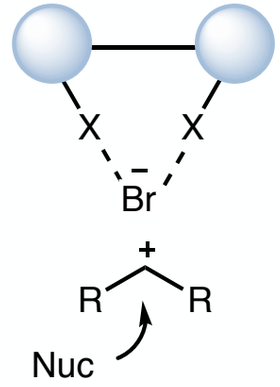
Cavallo, G. et. al., *Chem. Rev*. **2016**, *116*, 2478.

Halogen Bonding and Catalysis

"the lipophilic hydrogen bond"

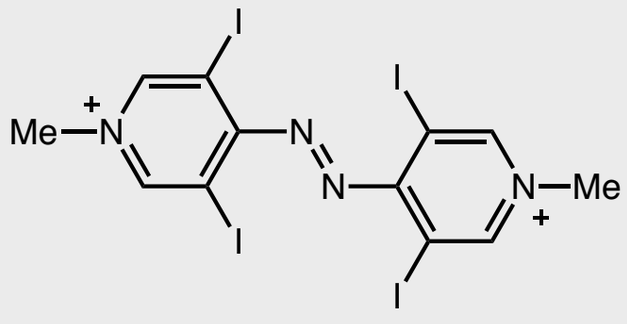


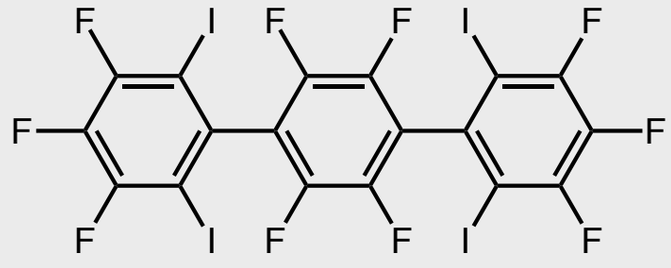
substrate activation

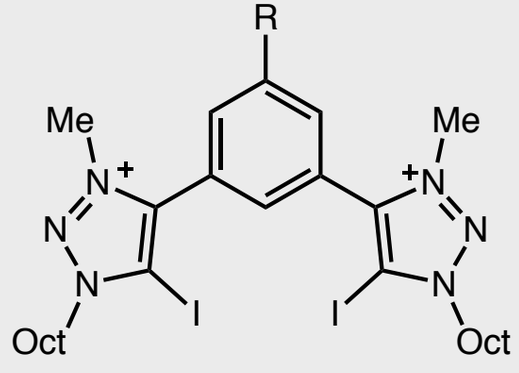


halide binding

examples of bidentate XB donor catalysts



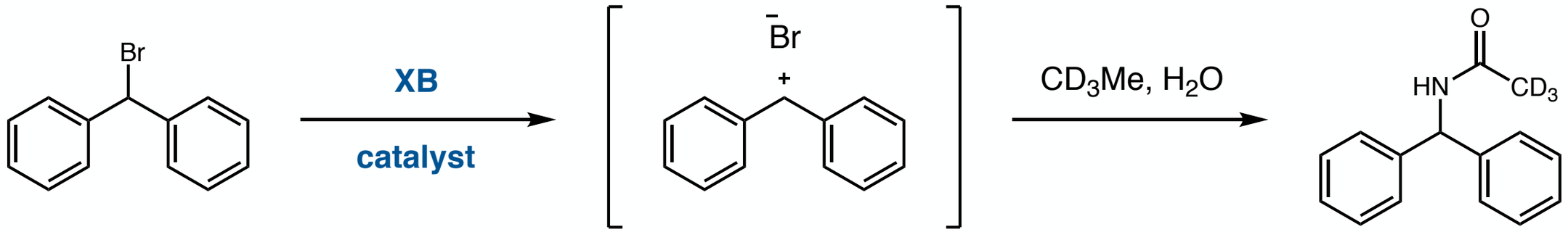


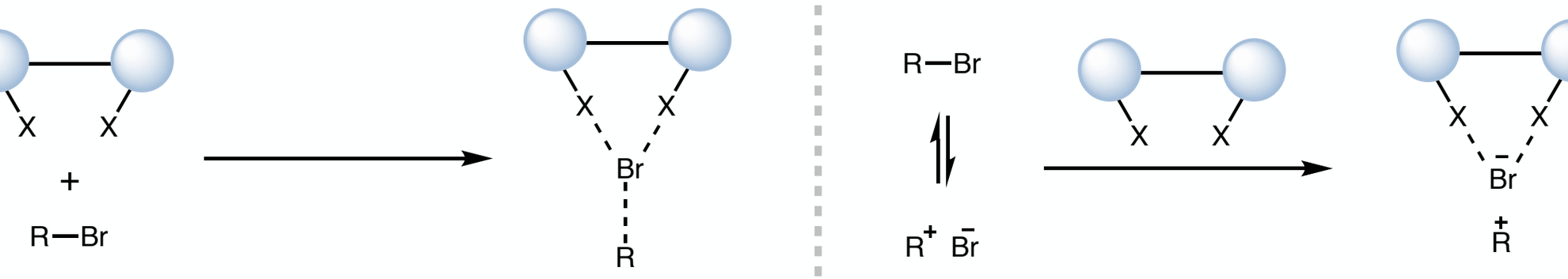


Chem. Eur. J. **2016**, *22*, 14434.

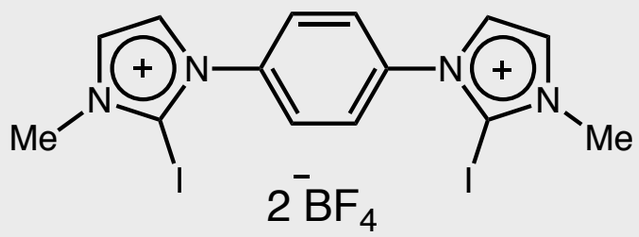
Chem. Rev. **2016**, *116*, 2478.

Halogen Bonding and Catalysis





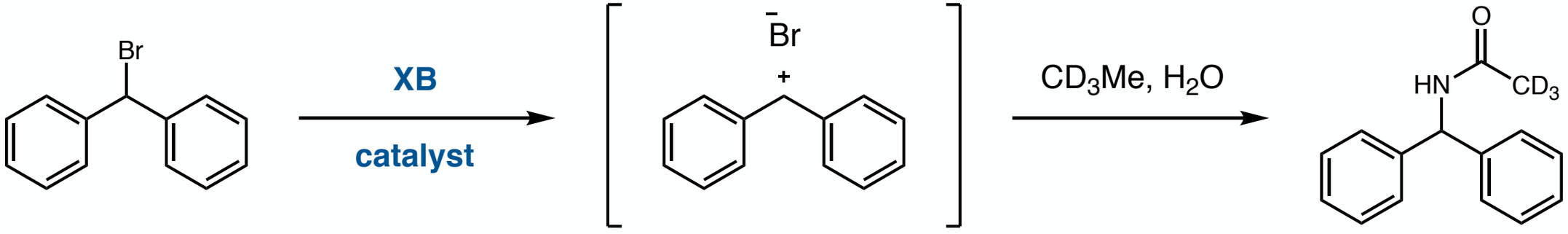
XB catalyst

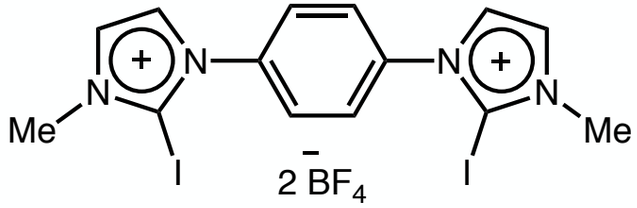


catalyst	yield
XB cat	97%
none	< 5%

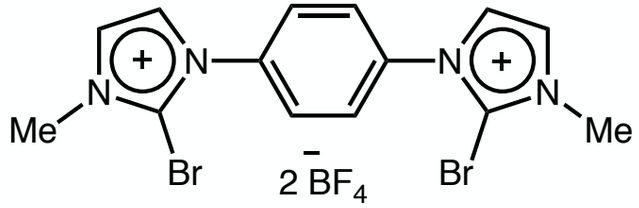
Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2011**,*50*, 7187.

Halogen Bonding and Catalysis

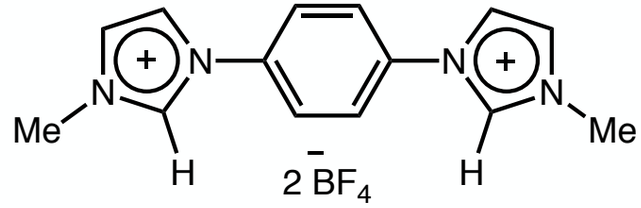




97% yield



54% yield



7% yield

decreasing XB donor strength

decreased yield

when no XB donor present

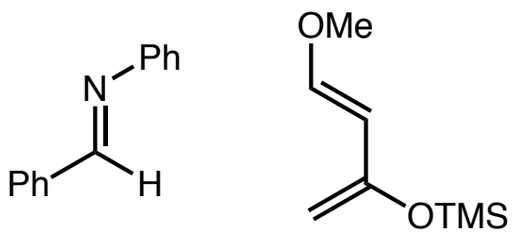
poor yields obtained

substrate activation via halogen bond donor catalyst

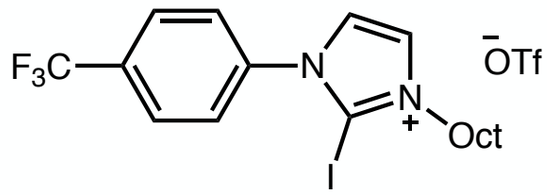
Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2011**,*50*, 7187.

XB Catalysts for Lewis Acid Activation

Aza-Diels-Alder

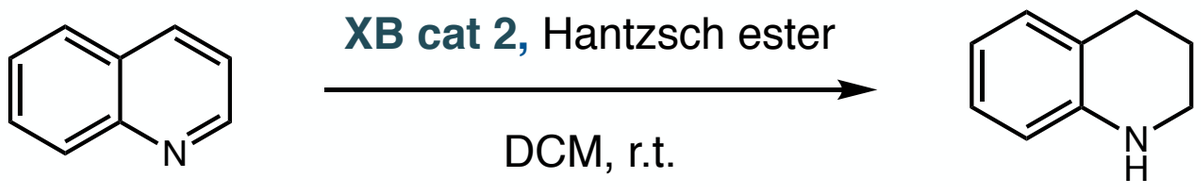


Org. Lett. **2015**, *17*, 318.

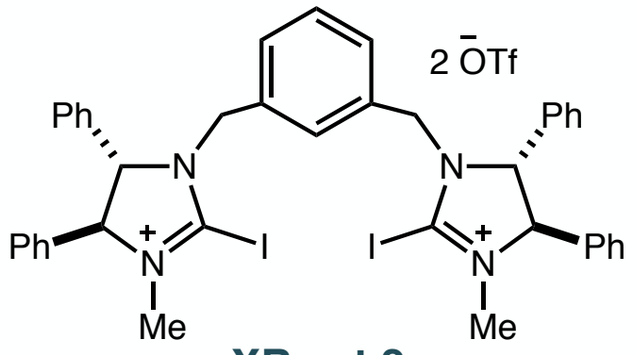


XB cat 1

Quinoline and Imine Reduction



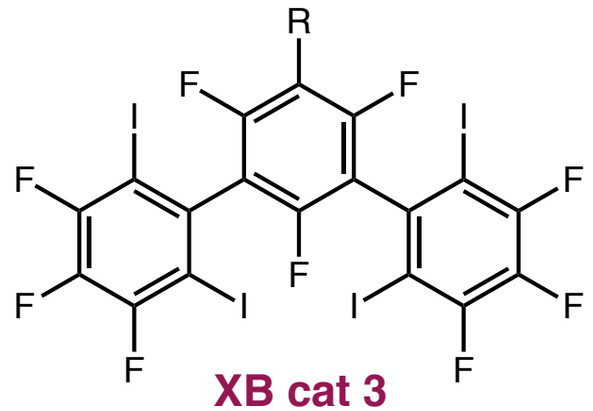
Org. Lett. **2014**, *16*, 3244.



XB cat 2

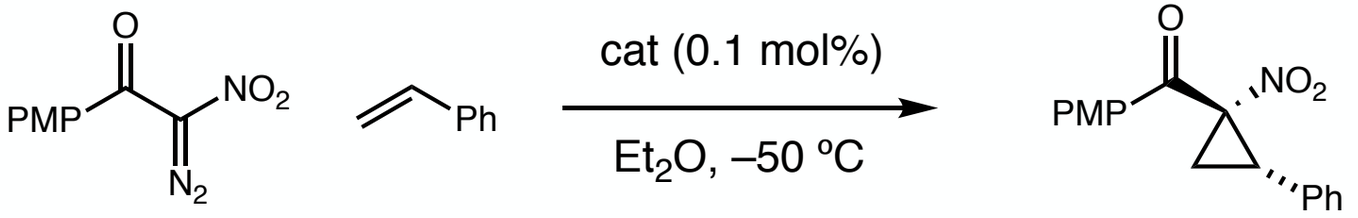
C–C bond formation with neutral XB cat

J. Am. Chem. Soc. **2015**, *137*, 12110.



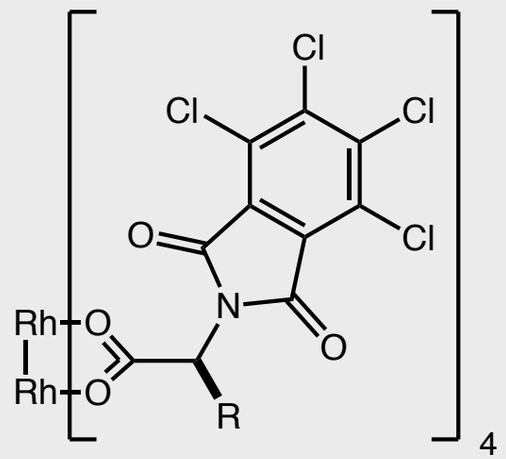
XB cat 3

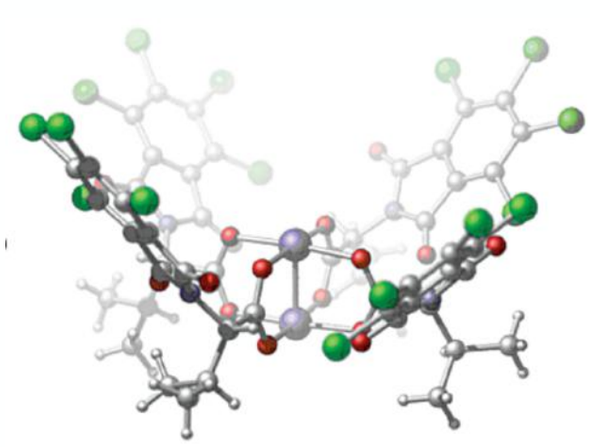
Intramolecular Hydrogen Bonding and Asymmetric Catalysis

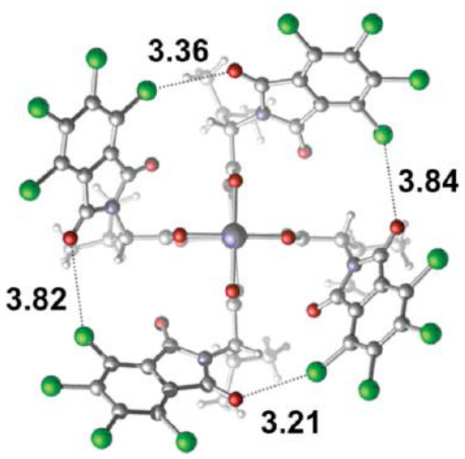


80% yield

93% e.e., >20:1 d.r.

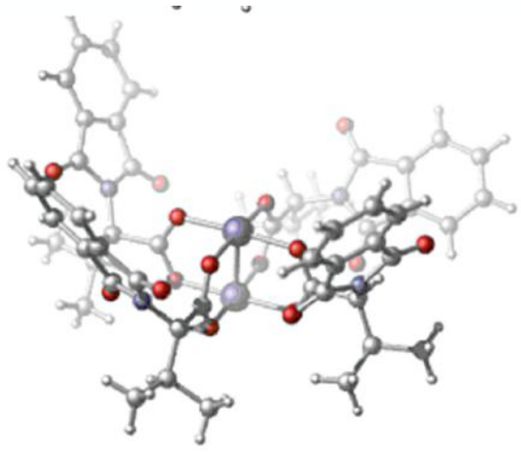


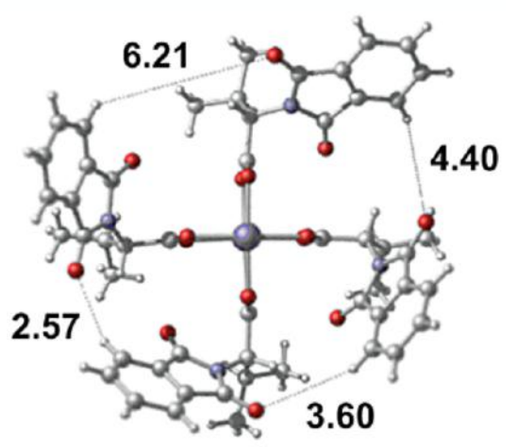




XB leads to rigid "all-up" structure

high e.e.'s





H in place of Cl on catalyst

low e.e.'s (< 5%)

Cl ··· O XB induces the catalyst conformation assumed to be responsible for asymmetric induction

Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383.