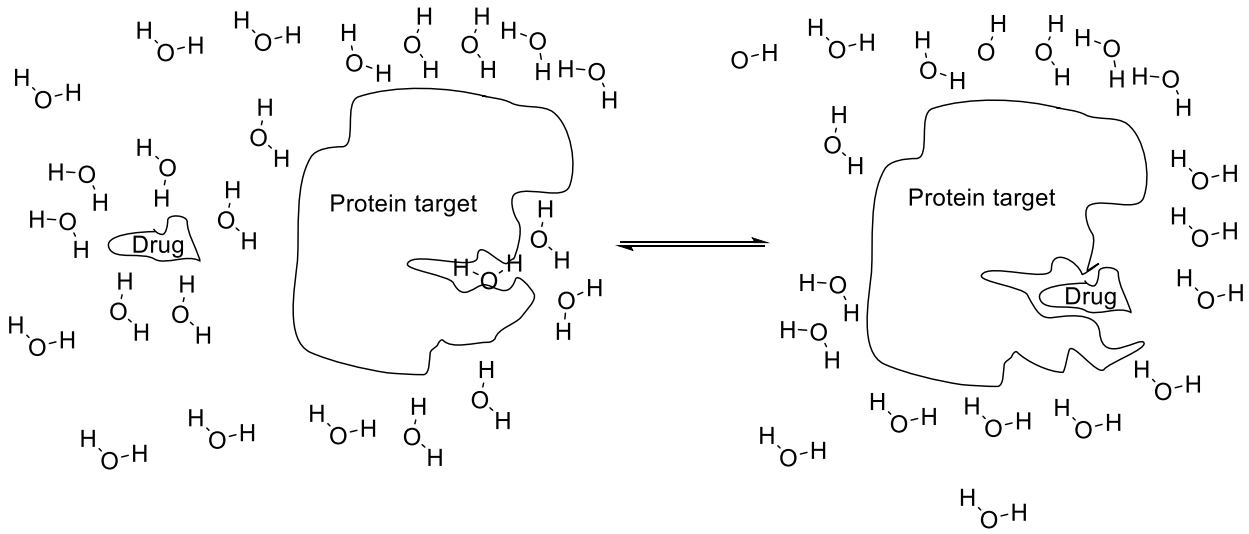
Lecture Handout for *J. Med. Chem*. **2010**, *53*, 5061-5084

Sept. 13, 2018

Overview: Molecular interactions with drugs

Pictorial representation of drug-target interaction



A. Issues to consider in protein-ligand binding

1. $\Delta G=\Delta H-T\Delta S= -RT \ln K_{eq}$

b) Thermodynamic analysis of substrate (or inhibitor) binding:

-for substrate…

-for inhibitor…

c) Detailed analysis:

E + S = E-S or D + R = D-R (drug-receptor)

if $\Delta G=-RTlnK_D$ and $R=8.314x10^{-3}$ kJ/mol*K, T=300 K

then $\Delta G=$

-**this approximates….

**Caution with this interpretation:

(1) $\Delta G=-RTlnK_a$ is for standard state conditions with [S]=1 M, that will probably not be the case.

(2)

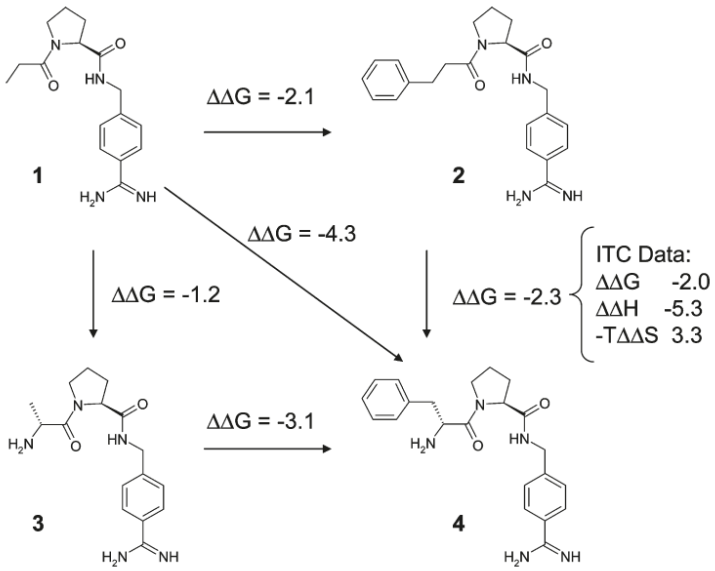


Figure 1. Cooperativity of hydrogen bond formation and hydrophobic contacts in a set of thrombin inhibitors. Extension of the lipophilic side chain alone increases affinity by 2.1 kcal/mol. Addition of the amino group increases affinity by 1.2 kcal/mol. Cooperativity therefore amounts to 4.3 − 2.1 − 1.2 = 1.0 kcal/mol. Data from refs 30 and 31 were converted to kcal/mol and rounded to 1 decimal place.

2. Entropic (ΔS) and enthalpic (ΔH) components of binding, but difficult to separate and optimize

Considerations…

ΔH events	**impact**	**ΔS events**	**impact**
a) H bonds with solvent lost by ligand (desolvation)		a) flexibility of ligand in solution lost	
b) H bonds with protein gained		b) hydrophobic effect—H_2O less organized with less hydrophobic surface area	
c) cooperativity of H-bonds: leading to even stronger bonding than the sum of each individual H-bond		c) flexibility of protein less with ligand bound?	
d) H bonds with water or other amino acids in active site are lost on ligand binding		d) H_2O and amino acid H-bonds in active site can lead to rigidification (less flexibility)	
		e) expel H_2O from active site leading to greater H_2O flexibility	

3. Conclusion: optimize for _____ and focus on:

a)

b)

B. Intermolecular Forces

1. Hydrogen bonds

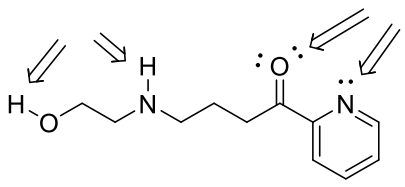
a) strong and weak

Additional facts:

-when ligand is the donor in –O-H / –C-H---O=C-protein,

-when ligand is the acceptor,

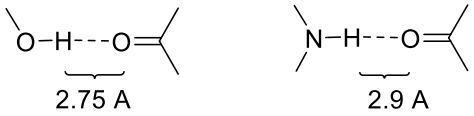
**-generally ligands have…



**-H bonds convey specificity to recognition process but do NOT always add much binding free energy (due to desolvation energy loss)

b) distances

-typically …



-charged H-bonds have shorter distances than uncharged:

-charged residues in active site: 20%; overall protein is 24%, so only slightly lower.

c) angles

-N-H---O and –O-H---O “tend toward _____”

d) multifurcated H-bonds are quite common:

e) Drug design principles involving H-bonding groups

Lipinski's rule of five:

1.

2.

3.

4.

2. Halogen bonds

a) description:

-Molecular orbital interpretation:

-strength:

b) example:

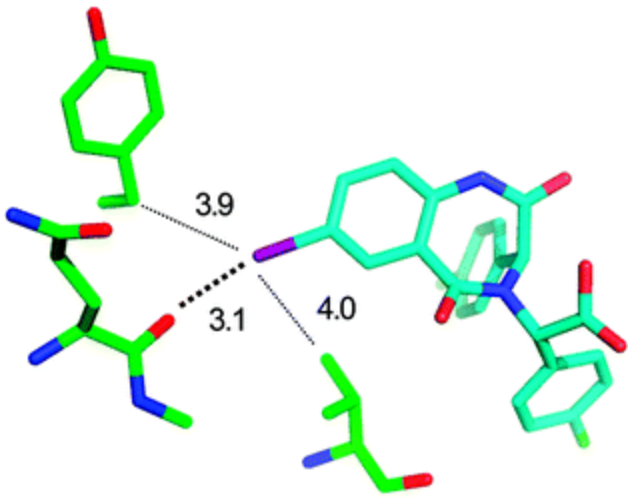
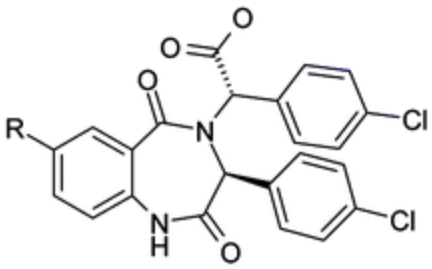


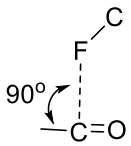
Figure 10. Iodine bond to a backbone carbonyl group in a HDM2 p53 domain crystal structure(145) (PDB code 1t4e, distances in Å).



R	Kd (μM)
-H	7.69
-I	0.067
-Br	0.83
-CCH	0.25

3. Orthogonal Multipolar Interactions

a) description



b) example

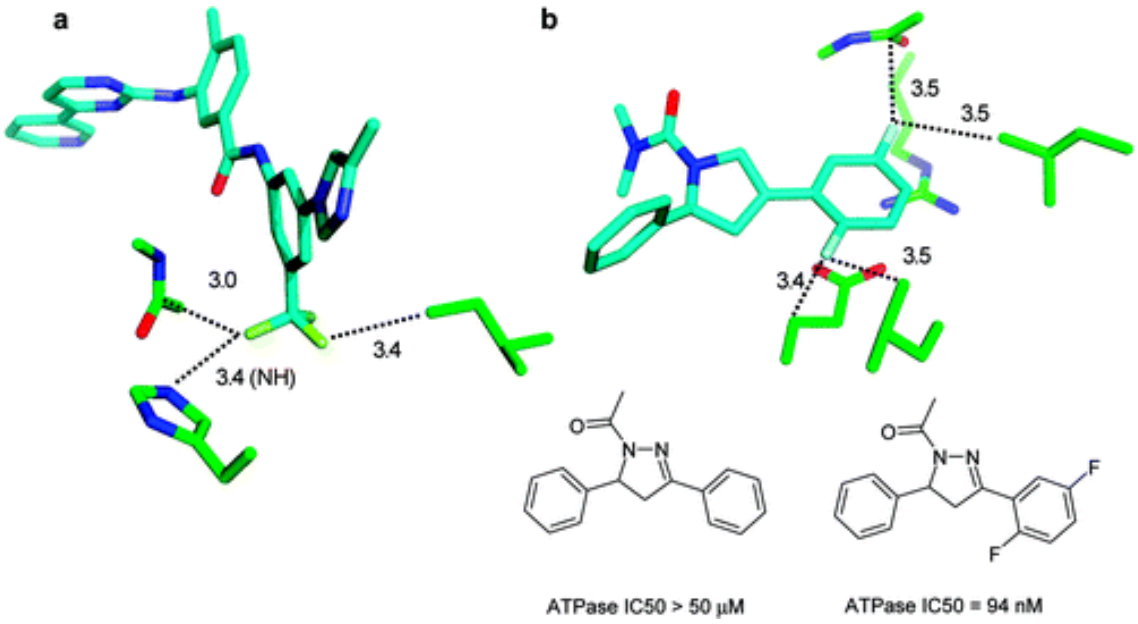
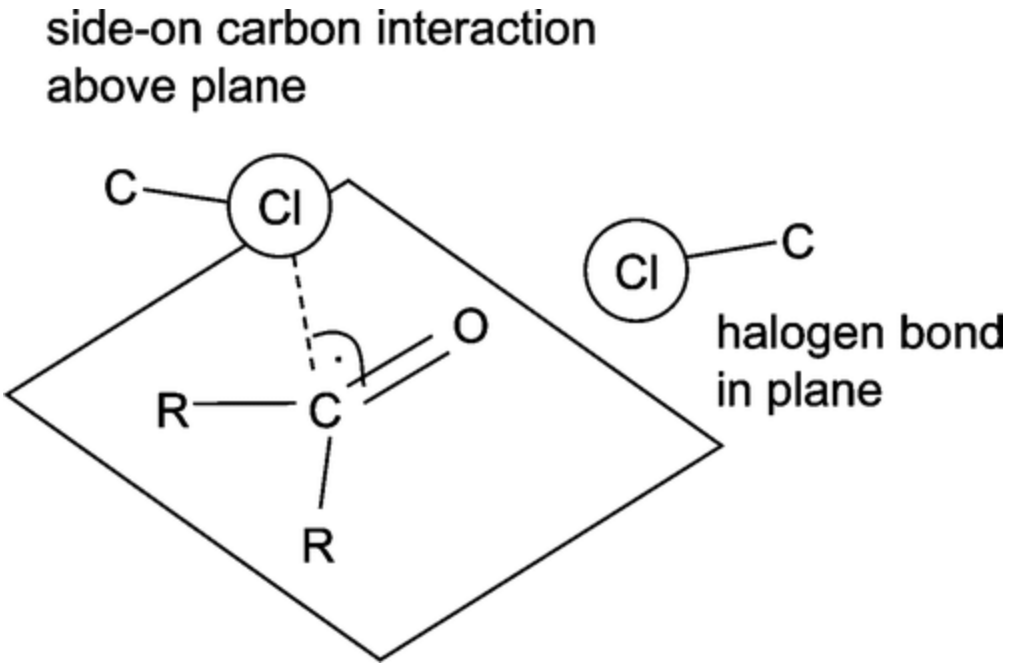


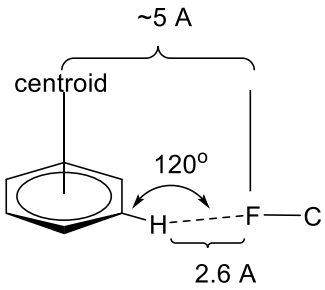
Figure 11. (a) Fluorine interactions in the complex between nilotinib and abl kinase (PDB code 3cs9).(159) (b) Kinesin spindle protein structure (2fl6) and activity data of two closely related inhibitor structures.(160)Distances are in Å.

c) Chlorine



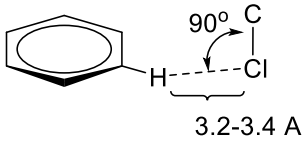
4. Halogen-Aromatic Rings

a) F:

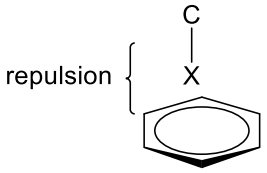


-very weak “H-bonds”

b) Cl:



c) repulsion of pi aromatic-halogens also seen:

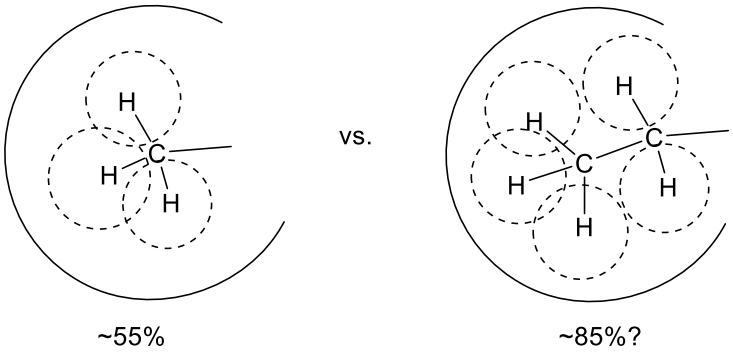


X=Br, Cl and F

5. Hydrophobic Interactions

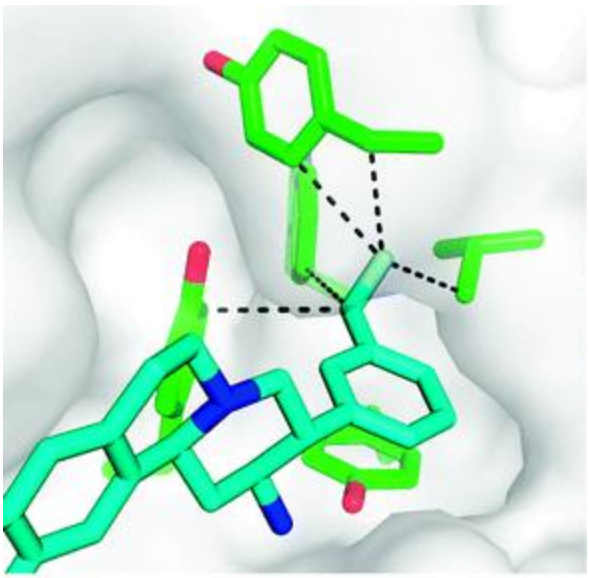
a) description: greasy, hydrophobic groups _____

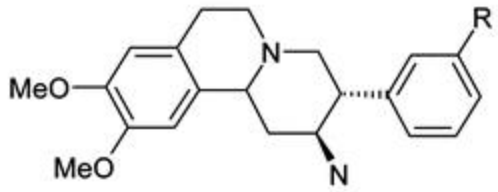
-55% fill of active/receptor site pocket is optimal



~55% ~85%?

b) example





R	K_d (nM)
H	200
CH_3	4.6
CH_2F	0.5

from ref. 180: BMCL 2010, 20, 1106.

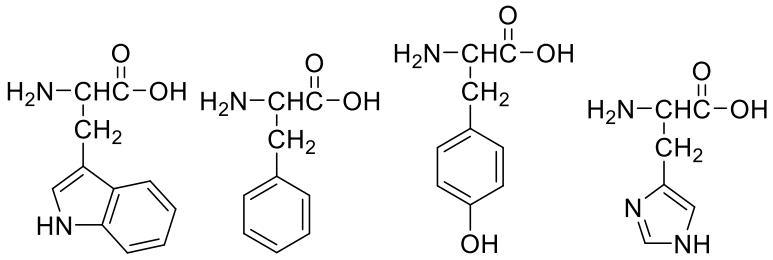
Figure 15. X-ray complex crystal structure of human DPP-IV with an aminobenzoquinolizine inhibitor (R = CH_2F) and affinity data for three derivatives.(180) The closest hydrophobic protein contacts of the CH_2F moiety (distances are less than the sum of van der Waals radius + 0.5 Å) are displayed (PDB code 3kwj).

6. Aryl-Aryl and Alkyl-Aryl Interactions

a) description: aromatic-aromatic and alkyl-aromatic interactions

b) background:

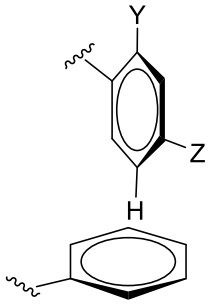
-evaluate protein aromatics:



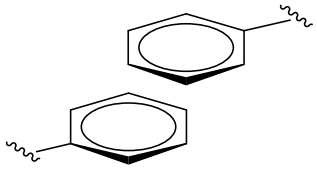
Analysis of electronic nature:

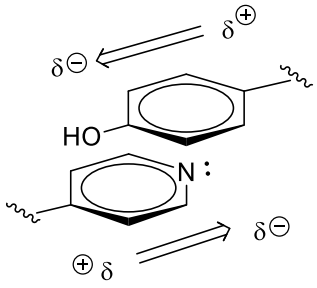
c) types of aryl-aryl interactions

(1) T-shaped/edge-to –face



(2) parallel-displaced stacking arrangement





c) example of alkyl-alkyl/alkyl-aryl interaction: (how is this different from hydrophobic?!)

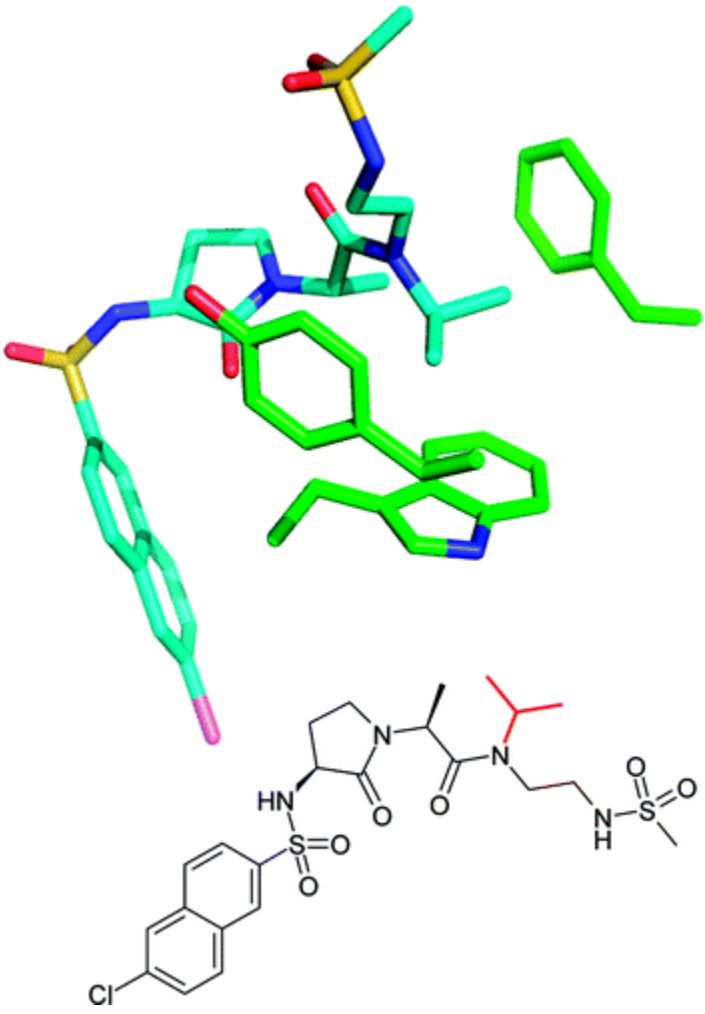


Figure 2. Binding mode of a factor Xa inhibitor from GSK.(40) The depicted compound (PDB code 2j4i) has a K_i of 1 nM. Replacing the isopropyl group (marked in red) by hydrogen reduces the affinity to 39 µM.

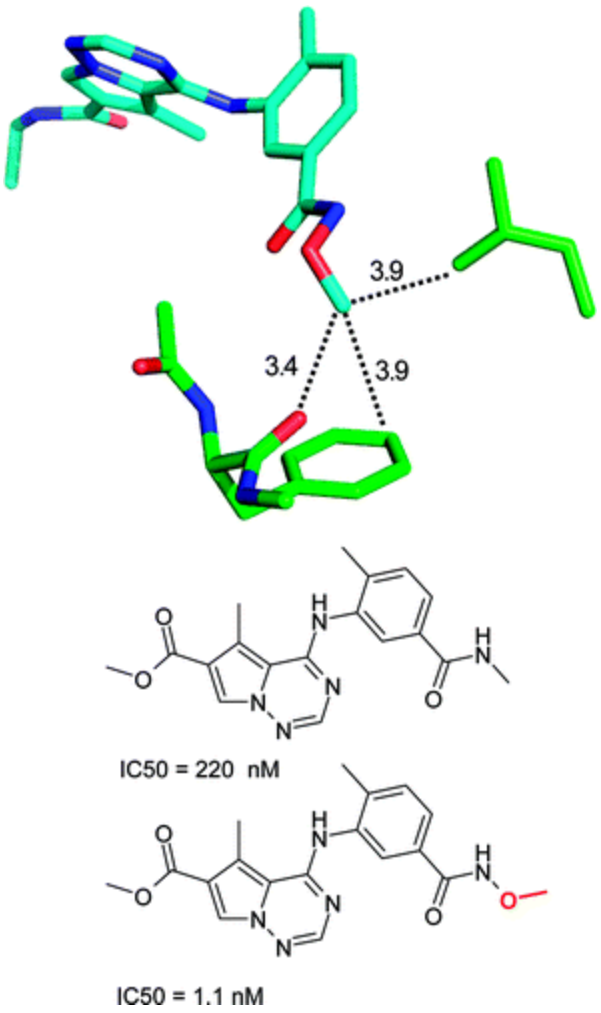
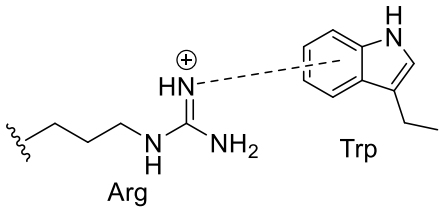
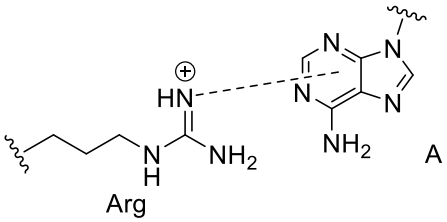


Figure 18. Effect of a methyl group on the IC_{50} of a p38 MAP kinase inhibitor(198) (PDB code 2rg5).

7. Cation-pi Interactions

a) description:





b) example:

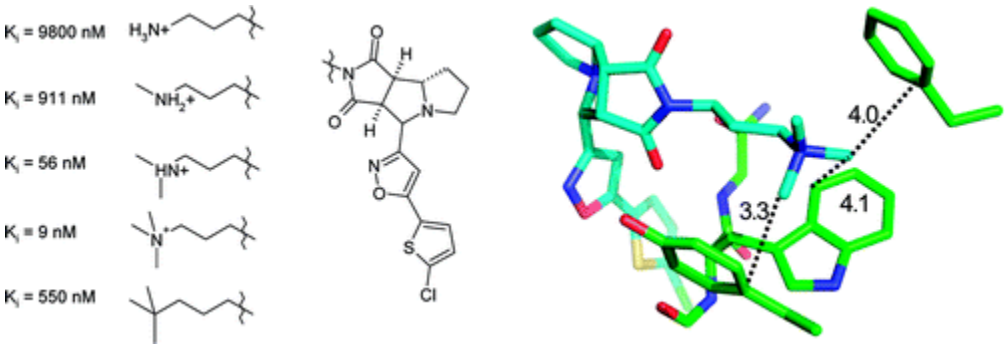


Figure 19. Example of cation−π interactions: a factor Xa inhibitor scaffold with systematically varied S4 pocket side chains (PDB code 2bok, distances in Å).(209)

8. Sulfur Interactions

a) description: