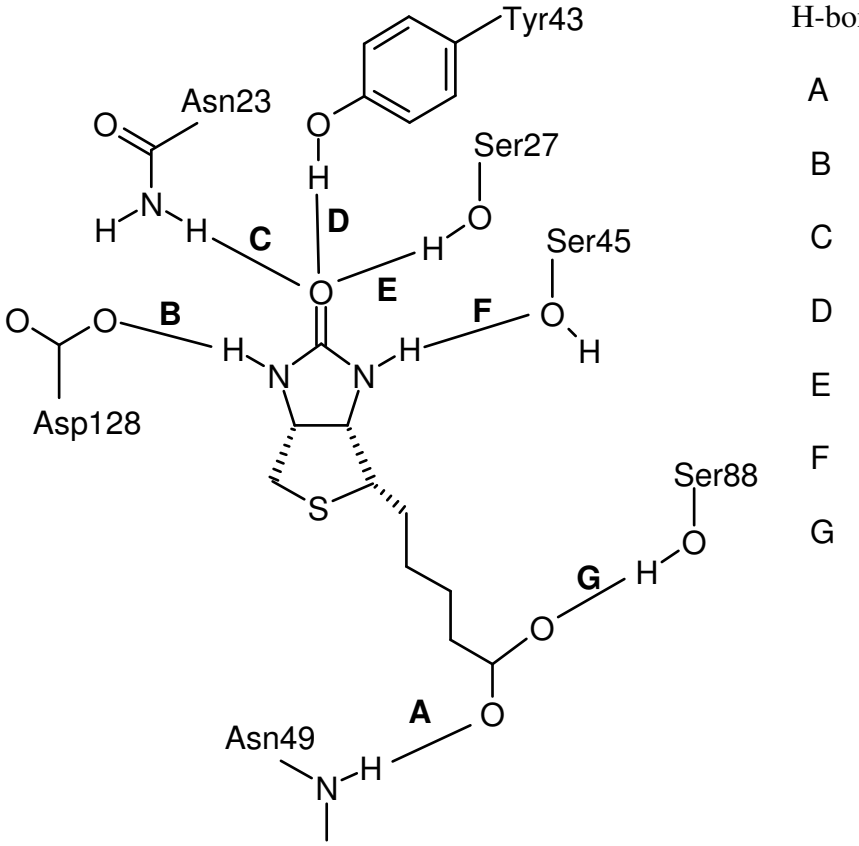
Exercises to the lecture „Modern Methods in Drug Discovery“ WS13/14

2nd Assignment to be handed in until 11.11.2013

your name:

1. Biotin is a highly affine ligand of streptavidin (K_i = 2.5 ·10^{-13} M) that shows a total of 7 hydrogen bonds in the binding pocket (see scheme below).

a) Determine the length of these hydrogen bonds (A to G) from the X-ray structure with the pdb entry code 2RTF. Report the distance between the respective non-hydrogen atoms. (It does not matter which one of the two biotin molecules in the X-ray structure you chose).
(35 points)



H-bond	length
A	
B	
C	
D	
E	
F	
G	

b) Explain (briefly) the physical reason why X-ray structures do not show hydrogen atoms.
(5 points)

c) Assume that the free energy of binding $\Delta G = -RT \ln(K_i)$ at 298 K (R = 8.314 J K^{-1} mol^{-1}) stems from the hydrogen bonds, only. Calculate the average contributing energy of one hydrogen bond. (10 points)

d) For the S45A mutant (Ser45 replaced by alanine) of streptavidin a ΔG value of 57266 J mol^{-1} was measured at 37° Celsius. Calculate the corresponding K_i value using the formula given in c). (10 points)

e) How many hydrogen bonds between biotin and streptavidin are left in this mutant?
(by visual inspection of the figure shown in part 1a)
Compute the corresponding energy of binding using the average energy from one hydrogen bond in part a). Compare that to the experimental value given in part d). (5 points)

2. Compare the X-ray structures of tACE with the bound inhibitors lisinopril (1O86.pdb) and captopril (1UZF.pdb).
a) Which amino acids form interactions with the zinc ion? (list these with amino acid type and their residue number) (15 points)

b) What is the difference in binding the zinc between captopril and lisinopril ?
(polar, ionic,..) hint: the SH-group of captopril is assumed to be protonated. (5 points)

c) Which other, specific interactions (hydrogen bonds, salt bridges) are possible inside the binding pocket for other inhibitors? List three of them including the according residues numbers that could form such contacts. (15 points)