Examination "Modern Drug Discovery" 17-4-2013 by Prof. Dr. C. van Boeckel and Dr. M. van der Stelt

Write your name and student number on every paper.

1. GPCRs

A) Several peptides (e.g. angiotensin; substance P) or proteins (e.g. FSH, LH) activate GPCRs; the same agonistic activity can also be induced by small molecules (allosteric agonists); 1 Explain this allosteric agonistic activity; 2. How can we find such small molecules?; 3. What is the advantage of these small molecules as a drug?

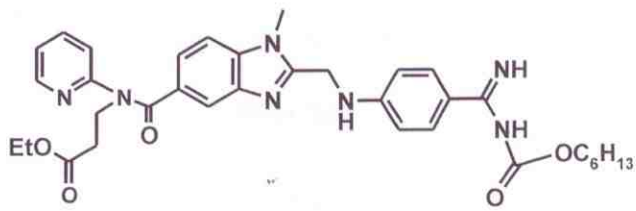
B) Many ligands for GPCRs have structural elements in common (privileged structures); How can we profit from that in drug discovery to find novel ligands for GPCRs?

C) The noble prize chemistry 2012 was given to the pioneers on GPCR research; What sort of arguments (mention two) do you think the committee considered very important?

2. Proteases

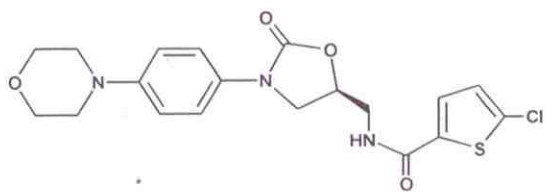
A) What class of proteases (serine, cysteine, metallo or aspartic) is inhibited by this molecule?; Highlight the warhead and explain.

B) The only orally active thrombin inhibitor on the market today is Dabigatran. It is a so called double prodrug; 1.Explain what this means and 2. Why in this case it is of importance to get oral bioavailability?



Dabigatran

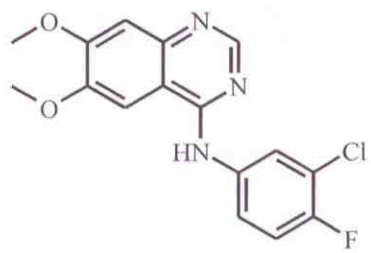
C) The specificity (S1) pocket of factor Xa mainly recognizes basic side chains such as amine, amidine or guanine groups; Explain why the lipophilic chlorothiophene unit of Rivaroxaban also gives a favourable interaction.



3. Kinases

A) Mention at least three reasons why one thought initially that it would be extremely difficult to make drugs acting on kinases (kinase inhibitors).

B) This compound is the precursor of the Kinase Inhibitor Drug Iressa. The compound is potent and selective, but why is it not a drug and what improvement is required?; How?

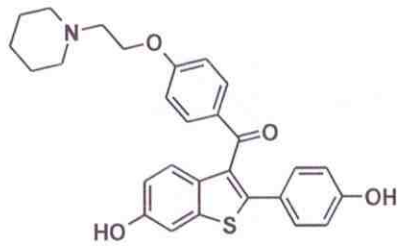


C) What is the importance of the next generation drug Tasigna as follow up of Gleevec?

D) How is it possible that so many different chemotypes (chemicals with different structures) can compete (with ATP) in the ATP binding pocket of a kinase?; Mention also one aspect that is crucial for interaction of the inhibitor in this pocket.

4. Nuclear Receptors

A) Raloxifene is a so called Selective Estrogen Receptor Modulator (SERM). Explain that this estrogen analogue has a different binding mode with the ER receptor. Hint: the crystal structures provide the clue.



Raloxifene

B) Explain the four different biological activities that can be brought about when small molecules bind to the ligand binding domains of steroid receptors (or other Nuclear Receptors).

5. Ion-Channels

A) Explain how three ion channels are involved in the process of insulin secretion in beta-cells; also explain the mode of action of sulphonylurea drugs, which are used for diabetes control.

B) Mention three molecular properties of the cyclodextrin antidote Suggamadex that play a role to neutralize the neuromuscular blocking agent Rocuronium

C) Mention two properties of drug candidates, which you should take care of, which may cause interaction with hERG, a potassium channel on heart cells.

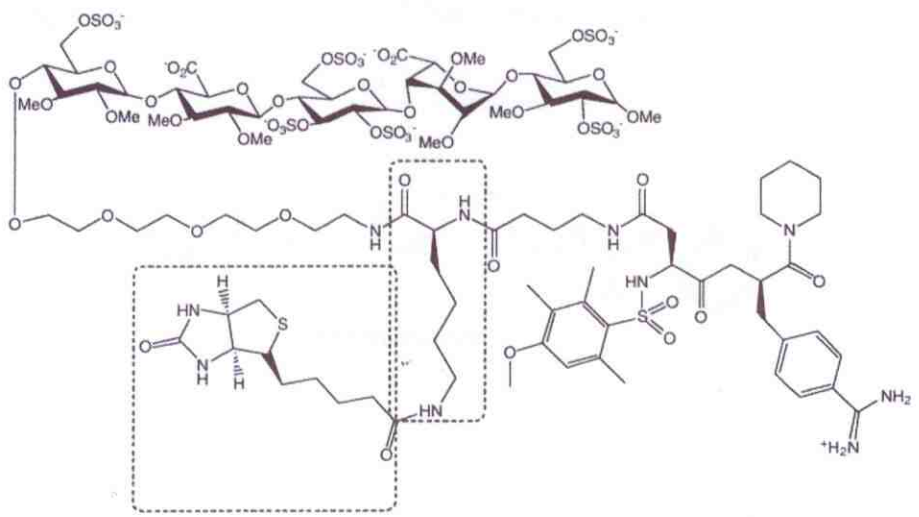
6. Heparin

Org/EP 217609 is a new complex antithrombotic drug under investigation in Phase 2 clinical trials.

A) Explain that this drug has both factor Xa and thrombin inhibitory activity (dual mode).

B) Explain that the thrombin inhibitory part of this multivalent drug has a much longer half life in circulation in comparison to the non conjugated thrombin inhibitor.

C) In the window a conjugate with biotin is highlighted; Explain the role of this entity in the complex drug.

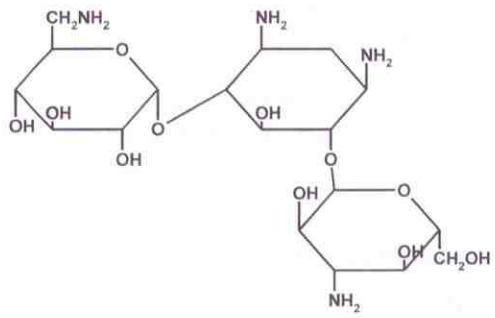


Org/EP 217609

7. Nucleotides

A) What is the major hurdle (biggest problem) to turn oligonucleotides (e.g. antisense DNA; RNAi) into effective drugs?

B) 1.What is the biological target of Kanamycine A?; 2. How can you make this antibiotic more potent? 3. What do you expect for its selectivity after that modification?

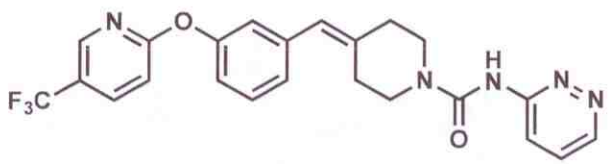


Kanamycin A

8. Marijuana and Medicine

A) Mention 2 reasons why not to use THC, the main psychoactive principle in marijuana, as a drug to alleviate chronic pain.

B) FAAH inhibitors, such as PF-04457845, have been developed as an alternative for CB1 receptor agonists. Explain how PF-04457845 inhibits FAAH.



PF-04457845