Second Examination "Drug Discovery" 10-6-2016 by Prof. Dr. C. van Boeckel and Dr. M. van der Stelt

Short answers are appreciated.
All the best!!

1 Introduction 10p

A) Give two reasons as to why antibodies can be good leads for novel drugs on new biological targets and two reasons why not.

B) Give two reasons as to why small molecules can be good leads for novel drugs on new biological targets and two reasons why not.

C) Mention three physicochemical properties which we have to take into account if we optimize small molecules in drug discovery; explain.

2 GPCR 10p

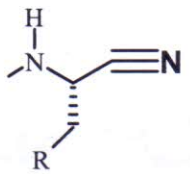
A) In Graves' disease autoimmune antibodies activate the TSH receptor, a GPCR of the same family as FSH and LH receptor.
Explain, taking into account your knowledge of GPCRs, how this is possible.

B) How can you find small molecules as a drug for this disease?

C) What is the mode of action of such a small molecule and where do you expect it to interact with the TSH receptor?

3 Protease Inhibitors 15p

A) What type of proteases are inhibited by the warheads 1 and 2 respectively?



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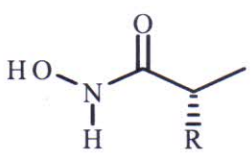

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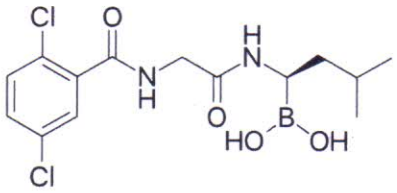
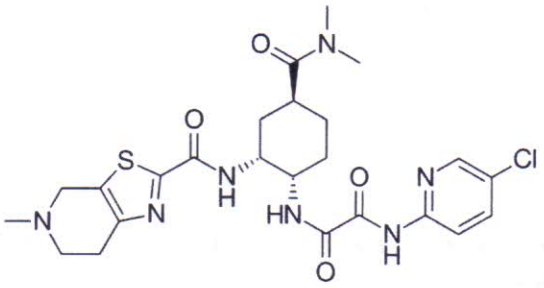
B) Explain why the compound below is a potent protease inhibitor; which protease is inhibited?



C) Factor Xa cleaves amide bonds and recognizes the basic group of arginine, in its specificity pocket. The orally active factor Xa inhibitor **Edoxaban** (see structure) has no positively charged group in the specificity pocket; explain why it is still a good Xa binder.

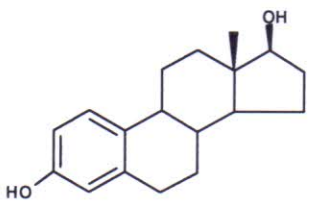


Edoxaban

4 Nuclear receptors 10p

A) Nuclear Receptors can bind co-activators and co-repressors; explain how you can find compounds that attract co-activators but not co-repressors.

B) What chemical modification is required to make an orally active analogue of **Estrogen**; explain.

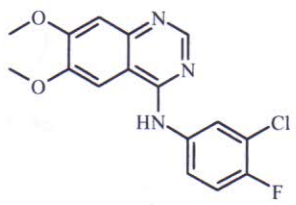


Estrogen

C) Describe which modification of **Estrogen** is required to get a full antagonistic analogue.

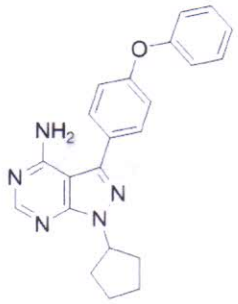
5 Kinases 15p

A) The compound below is a precursor of a Kinase inhibitor drug. The compound is potent and selective, but why is it still not a good drug and what improvement is required; how?



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

C) **PCI 29732** is a reversible Btk inhibitor. How can you modify this kinase inhibitor to make it an irreversible Btk inhibitor? The irreversible binder turns out to be a more selective kinase inhibitor; explain.

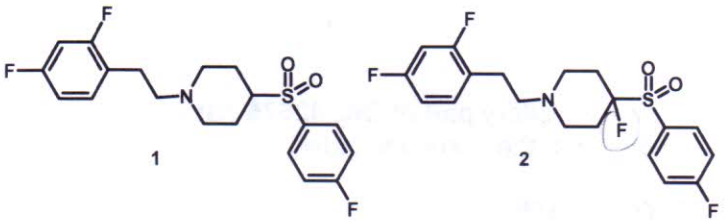


PCI 29732

6 Ion Channels 10p

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

B) Which compound interacts stronger with hERG: **1** or **2** ; explain?

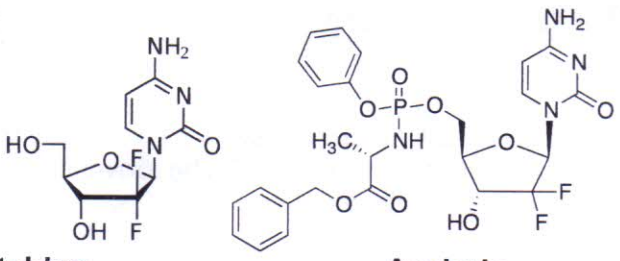


C) Mention four molecules from nature that block ion-channels and that may be used as 'pain-killer'.

7 Nucleot(s)ides 10p

A) The aminoglycoside antibiotic Gentamycin is an aminoglycoside antibiotic showing, however, also side effects.
What is the target for this antibiotic? Why is this drug used for treatment of Ménière's disease, which is not caused by a bacterial infection?

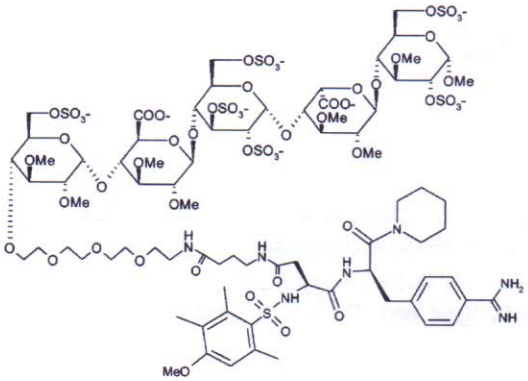
B) **Gemcitabine** is a known anti-cancer drug and **Acelarin** an anticancer drug in clinical trials. Both drugs generate in the cell the same active molecule; explain.
What is the role of the ester and amide group on the phosphate of Acelarin?



Gemcitabine **Acelarin**

8 Heparin 10p

A) Explain that the strong anticoagulant **Org 42675** has both factor Xa and thrombin inhibitory activity (dual mode).

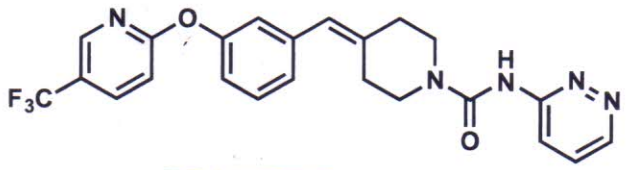


Org 42675

B) Explain that the thrombin inhibitory part of **Org 42675** has a much longer half life in circulation in comparison to the non-conjugated thrombin inhibitor.

C) How can you modify **Org 42675** in order to allow an antidote to remove it quickly from circulation e.g. when bleeding occurs; which antidote do you need?

9 Endocannabinoid 10p



PF-04457845

FAAH inhibitors, such as PF-04457845, have been developed as an alternative for CB1 receptor agonists. Unfortunately, PF-04457845 did not show efficacy in phase 2 clinical trials.

A) Explain how PF-04457845 inhibits FAAH. (5 pt)

B) Explain why inhibition of FAAH was considered to be an alternative for CB1 receptor agonists? (3pt)

C) In January 2016, another FAAH inhibitor (BIA 10-2474) was tested in phase 1 clinical trials and resulted in the dead of one healthy volunteer. Is the observed toxicity an on-target effect? Explain (2 pt).