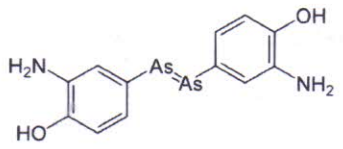
Examination "Drug Discovery" April 7th 2016 by Prof. Dr. C. van Boeckel and Dr. M. van der Stelt

Write your name and student number on every paper

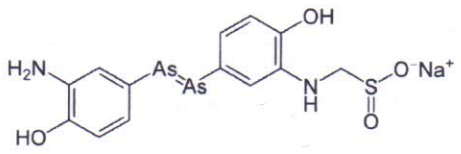
1 General (10p)

A) High throughput screening (HTS) gives a molecule (hit) that binds strongly to a disease-related target. (3p)
- *Mention **four** different properties of the molecule which have to be optimized also (in general terms) to make it a drug.*

B) The first important antibiotic against Syphilis was available in 1910 and called Salvarsan (left). Already at that time chemists wanted to improve certain bad properties of drugs and one year later Neo-Salvarsan (right) was launched. (3p)
-Which property was improved?

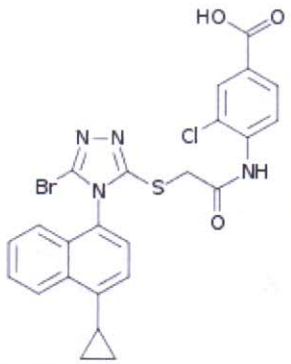


Salvarsan

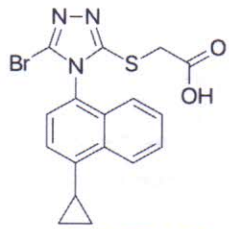


Neo-Salvarsan

C) RDEA806 is a reverse transcriptase inhibitor in clinical development for the treatment of AIDS. Unexpectedly, uric acid-lowering effect was also found in these clinical studies for which another compound: RDEA594 appears to be responsible. RDEA594 recently came on the market as a drug (Lesinurad: for lowering uric acid levels). (4p)
-What is (a short) explanation that they could study RDEA806 and RDEA594 in the same individuals?



RDEA806



RDEA594

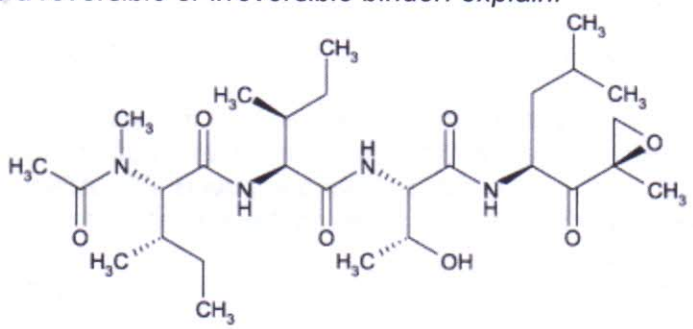
2 GPCRs (10p)

A) For high throughput screening on GPCR's one needs cellular assays in which the appropriate GPCR is (over) expressed. (5p)
- *Explain that is it important to know to which G-protein the GPCR is coupled in your assay?*
- *What sort of deselection assay can you use to ascertain that your hit acts on the GPCR and not on some other pathway protein?*

B) For GPCR's that interact with peptides many peptide analogues have been investigated as drugs. (5p)
- *Give two reasons why these peptides cannot be delivered orally.*
- *Some molecules found by HTS on this GPCR class are orally available and called allosteric agonists: what does that mean?*

3 Proteases (15p)

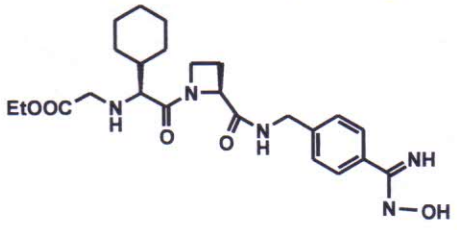
A) Epoxomicin is a natural compound that blocks the proteasome (4p)
- *What part is the warhead?*
- *Is this a reversible or irreversible binder: explain.*



Epoxomicin

B) Grazoprevir is a second generation HCV protease inhibitor active against many mutants of Hepatitis C virus. However, its Molecular Weight (MW) is very high for a drug in a tablet (MW~767). (5p)
-Mention two reasons why high MW drugs have poor bioavailability.
-Apparently, they could overcome the high MW problem for this type of disease and put the drug in a tablet: explain.

C) Ximelagatran, was the first orally active thrombin inhibitor on the market, but was withdrawn because of liver toxicity. It is a double prodrug of Melagatran, which also has been studied in the clinic. (6p)
-What is a prodrug?
-Why did they need a double prodrug (for which chemical moieties)?
-Probably, Astrazeneca did not make the best (double) prodrug of Melagatran: suggest a better prodrug for Melagatran.

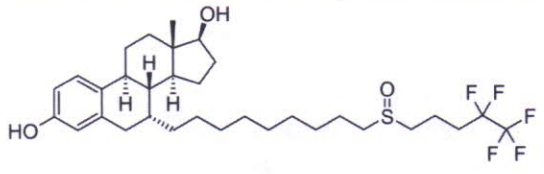


Ximelagatran

4 Nuclear Receptors (10p)

A) When steroids or synthetic analogues (agonists and antagonists) bind to the ligand binding site of their receptors you can expect at least 4 different types of biological responses. (4p)
- Explain this.

B) Faslodex is a full estrogen antagonist.(2p)
- what is the role of its long molecular chain?



Faslodex

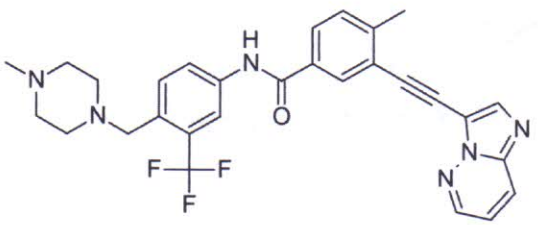
C) *-Mention an anti-breast cancer drug which interferes in the biosynthesis of steroids; which enzyme is inhibited?* (2p)

D) For Prostate cancer the enzyme inhibitor Abiraterone is used.(2p)
- explain and tell why they give it together with prednisone?

5 Kinases (10p)

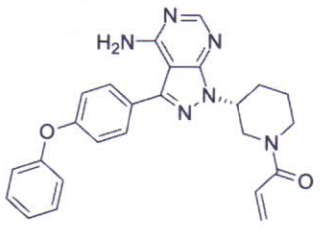
A) All kinase inhibitor drugs share one important property with ATP.
-which property? (2p)

B) -Explain what structural element in Ponatinib has been built (designed) in the molecule to make it active against the T315I mutation in BCR-ABL.(2p)



Ponatinib

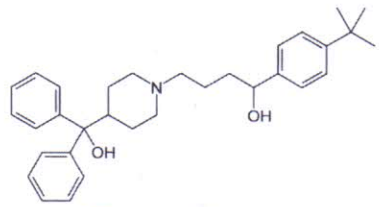
C) Ibrutinib is a covalent inhibitor of the kinase BTK.(6p)
- Mention a Pro and a Con for covalent inhibitors in general.
- Explain that the presence of the reactive group helps to make the molecule more selective for a small sub-set of kinases.
- How can you improve this drug further (mention two properties you can improve)?



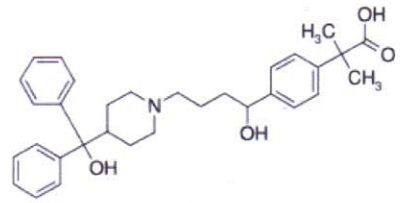
Ibrutinib

6 Ion Channels/Transporters (10p)

A) The antihistaminergic drug Terfenadine (see structures) was withdrawn from the market because of severe side effects. Its active metabolite Fexofenadin is still on the market and does not show these side effects. (5p)
- How is this metabolite formed?
- What sort of side effect do you expect and which Ion Channel is involved?
- Why is the active metabolite Fexofenadin not showing this side effect.

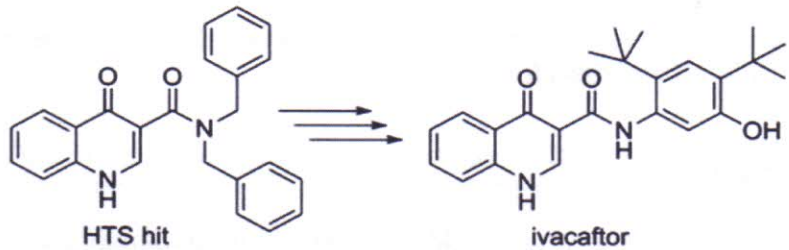


Terfenadine



Fexofenadin

B) Ivacaftor helps to cure Cystic Fibrosis.(5p)
- *Why does it show its best performance in only 5% of the patients?*



HTS hit ivacaftor

Ivacaftor was obtained after optimization of a hit from screening as illustrated. Two tert-butyl groups are introduced during optimization.
*-Mention a reason (but **not** increase in potency) why these groups were introduced during optimization.*

7 Nucleot(s)ides (10p)

A) The aminoglycoside antibiotic Neomycin is an aminoglycoside antibiotic showing, however, also side effects. (3p)
- *What is the target for this antibiotic?*
- *How can you reduce the side effects of this drug?*

B) Sofosbuvir is a new drug with impressive anti-hepatitis C activity; BCX4430 was originally developed as anti-hepatitis C drug, but is now tested against other viral diseases; both inhibit viral RNA-polymerases (4p)
- *Which derivatives are the real inhibitors of the viral RNA-polymerases?*
- *Why do we need a 5'-phosphate on Sofosbuvir but not on BCX4430?*
- *What is the role of the groups on the 5'-phosphate of Sofosbuvir?*