**Advanced Medicinal Chemistry**

**Exam: June 22nd 2015: 14:00- 17:00**

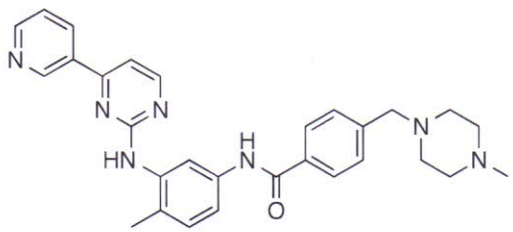
- Write your name and student number on every page.
- Book and slides are not allowed during the exam.
- You can use a self-made summary of max. 10 pages.
- Hand-in a copy of your self-made summary to earn 10 pt.
- There are 6 questions. Read carefully.

1. **(10 pt) Define the following concepts / abbreviations**
   a. Protean agonist (2 pt)
   b. Enthalpy-Entropy compensation (2 pt)
   c. Lipinski's Rule-of-Five (2 pt)
   d. ADME (2 pt)
   e. Therapeutic window (2 pt)

2. **(15 pt) Hit finding**

   A HTS with 300.000 compounds was performed using a Homogenous Time Resolved Fluorescence assay for BRAF, which a kinase mutated in metastatic melanomas. The mean activity was 15% with a standard deviation of 5%.

   a. Which cut-off percentage of inhibitory effect would you employ to obtain a list of primary actives using a 99,7% confidence limit ? (5 pt)
   b. A hit list with 300 actives was obtained. Which actions do you need to take to weed out the false positive hits? Explain. (5 pt)
   c. Which biological, physico-chemical properties or composite parameters (LipE, LE), would you use to prioritize your compounds? Explain. (5 pt)



**Compound 1**

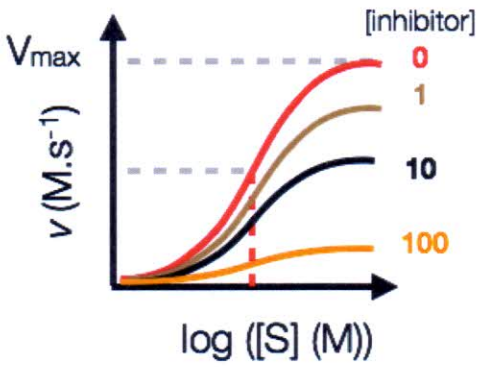
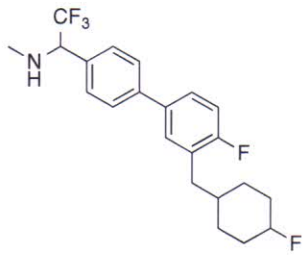


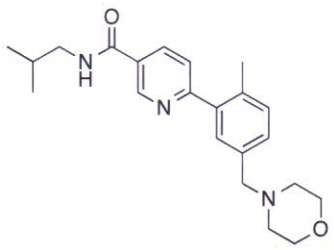

**Figure 1**

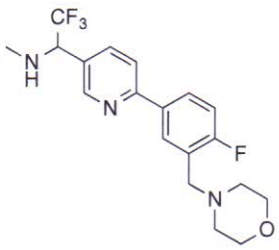
### 3. (25pt) Hit Optimization

You have discovered a new enzyme that is involved in the proliferation of cancer cells. You have developed a biochemical assay and identified compound (**1**) that is able to inhibit the enzyme in a concentration-dependent manner (See Figure 1). T = 310,15 K, R = 1,985 $10^{-3}$ kcal/mol/K. The substrate concentration is 10 μM and the $K_M$ = 10 μM. The $IC_{50}$ value is 1000 nM.

a. What type of inhibitor is compound (**1**)? (2 pt)
b. At what site does the inhibitor bind? (2 pt)
c. Calculate the free binding energy of the interaction. (3pt)
d. Indicate which type of interactions the inhibitor could have with the enzyme? (5pt)
e. Which two strategies would you employ to verify your binding mode? Draw three molecules that can be used to test your binding hypothesis. (5 pt)
f. The compound is rapidly metabolized. Indicate the metabolic soft spots in the molecule. (3 pt)
g. Which two strategies would you employ to stabilize the molecule? Draw three molecules with potentially improved metabolic stability to illustrate your strategies. (5 pt)




Compound **2** Compound **3** Compound **4**

| **Experiment** | **A** | **B** | **C** |
|---|---|---|---|
| Dose i.v. (mg/kg) | 1 | 1 | 1 |
| Dose oral (mg/kg) | 10 | 10 | 10 |
| AUCoral (μg min/ml) | 300 | 25 | 30 |
| AUCi.v. (μg min/ml) | 60 | 15 | 30 |
| Cmax i.v. (μg/ml) | 0,9 | 0,7 | 1,4 |

**4. (25 pt) Lead optimization: Pharmacokinetics**

The following three compounds (**2-4**) were tested in a rat PK study. Rat blood flow is 80 ml/min/kg. For each experiment **A, B and C**

a. Calculate $F_{po}$ (%) (2 pt)

   Calculate Cl (ml/min/kg) (2 pt)

   Calculate Vd (L/kg) (2 pt)

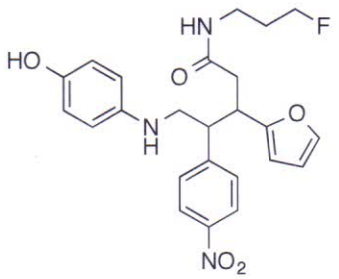
   Calculate $t_{1/2}$ (h) (2 pt)

   Calculate $f_{abs}$ (2 pt)

b. Which molecule belongs to which experiment? Explain. (5 pt)

c. Which property would you optimize to increase the half life for each molecule? Explain. (5 pt)

d. Which molecule (**2, 3, or 4**) would you select to perform an oral efficacy study? Explain (5 pt).




**Compound 5**

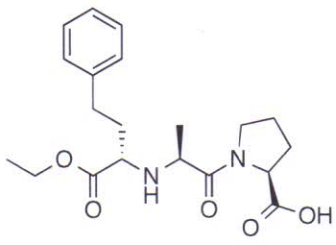
**5. (15 pt) Toxicity**

a. Explain why metabolism of your drug candidate by only CYP2D6 poses a problem. (2 pt)

b. What is cytotoxicity? List two methods to detect cytotoxicity. (3 pt)

c. What are the potential toxiphores of compound **5**. Explain. (4 pt)

d. Draw three new molecules in which one or more toxicophores are replaced with a bio-isostere. (6 pt)




Compound **6**

**6. (10 pt) Lead optimization**

Compound **6** is a drug (Enalapril) which is used for the treatment of hypertension.

a. Working backwards. List three lead optimization strategies that were employed to develop this drug. Explain. (6 pt)

b. List 4 different biological properties that may be affected if you increase the lipophilicity of a drug molecule. (4 pt)