Biochemistry Cumulative Examination
Chemical Biology
5 November 2015

Total: **100 points**

(1) List the major differences between fragment-based drug discovery (FBDD) and traditional high-throughput screening (HTS) to discover small molecule hits for lead optimization in the drug discovery process. What are the pros and cons of each strategy? (25 points)

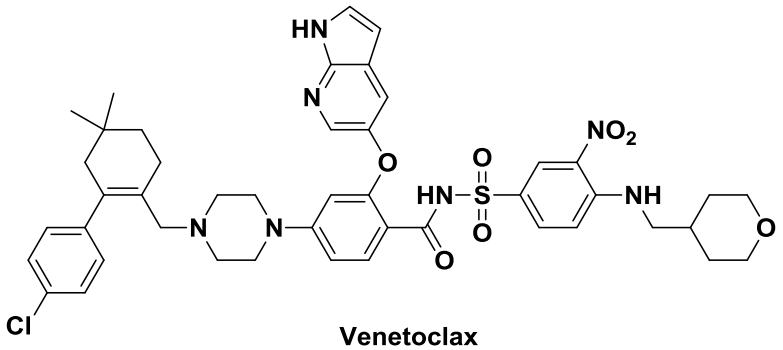
(2a) List four techniques that are commonly used to identify fragment hits in FBDD. (8 points)

(2b) Describe how **two of the four** techniques work and how they are specifically used to identify fragment hits in FBDD. (18 points)

(3) What are the three strategies for putting together fragment hits with micromolar potency to yield a small-molecule lead with nanomolar potency? Describe each of the strategies. (15 points)

(4) Once a fragment-derived lead has been optimized, propose two experiments you could perform to determine if the small-molecule lead is selective for its target and has the desired effect in cells and/or animals. Please use a theoretical example in your response. (18 points)

(4) Venetoclax is a small-molecule BH3 mimetic that is selective for BCL-2, was discovered through FBDD, and has recently (Aug 2015) met its primary endpoint in Phase II clinical trials for the treatment of chronic lymphocytic leukemia (CLL). Propose a reasonable retrosynthetic analysis of venetoclax. Indicate your disconnections on the structure below and draw all of the structures of your proposed starting materials, which may contain **no more than 9** carbon atoms each. (16 points)



Venetoclax