ADRENERGIC PROBLEM SET 6 KEY

1. For the compounds shown below circle the appropriate response or responses. There may be more than one correct answer, or no correct answer ("None"):

   ![Chemical Structures](image)

   a. Which compounds would form a reactive aziridinium ion? **Answer:** A and B. Only compounds that contain the "β-haloethylamine" structural fragment can cyclize to form an aziridinium ion. For this reaction to occur the compound must contain a nucleophilic (basic) nitrogen atom positioned two carbon atoms from a good leaving group (like Cl\(^-\)). This allows for the intramolecular nucleophilic displacement reaction to occur to yield the aziridinum as shown below. When the aziridinum ion forms and the overall structure is sufficient for receptor binding (see part b below), then it can alkylate that receptor if a nucleophile is positioned properly for reaction:

   ![Aziridinium Formation](image)

   **Aziridinium ion formation**

   ![Receptor Alkylation](image)

   **Receptor Alkylation (covalent)**

   b. Which compounds are chiral bases? **Answer:** None. All three compounds above have a basic amino group ("free pair of electrons on nitrogen, not "tied up" in resonance delocalization) and thus are bases. But none of the compounds have a chiral center in their structure.

   ![Chiral Centers](image)

   c. Which compounds could antagonize NE at alpha-1-receptors? **Answer:** A and C. The basic structural requirements for binding to and functioning as an antagonist at alpha-1 receptors includes two aromatic rings linked by one or several atoms to a tertiary amine group, as shown below. Both compounds A and C have these minimal structural features and thus can bind. Compound B has the tertiary amine, but only three small alkyl groups are linked to it, so its affinity for alpha-1 receptors is quite low!

   ![Pharmacophore](image)

   **Pharmacophore for alpha-1 receptor antagonism ("reversible")**

   **Pharmacophore for alpha-1 receptor antagonism ("irreversible")**
d. Which compound produces longest acting alpha blockade? **Answer:** A. Only compound A possesses the beta-haloethylamine moiety necessary for aziridinium ion formation, AND the two aromatic ring system to facilitate binding to alpha receptors (SEE FIGURES ABOVE!). Thus only this compound can both bind to the receptor and "react with" a nucleophile on the receptor, resulting in prolonged blockade. Compound B does not have the basic minimum "pharmacophore" (structure) for alpha receptor binding, so it will not be effective. Compound C has the basic pharmacophore to function as an antagonists, but cannot form an aziridinium ion to alkylate the receptor and produce long-lasting blockade.

e. Which compounds are predominantly ionized in plasma? **Answer:** All. As mentioned in b. above, all three compounds are organic bases. As tertiary amines they would have pKas of approximately 9. Thus at physiologic pH (about 7), they would all be predominantly ionized (protonated).

**Additional Questions:**

1. All three compounds below can form aziridinium ions, but will do so at different rates based on their differing structures. Rank these compounds as "fast", "intermediate" or "slow" in terms ability to form aziridinium ions:

   ![Chemical Structures A, B, C]

2. Which compounds below are chiral AND basic? Which could form an aziridinium ion?

   ![Chemical Structures A, B, C]

3. Would the compound shown below be capable of alkylating alpha receptors and producing long-lasting blockade?

   ![Chemical Structure]

4. Why do many alpha-1 receptor blockers produce anti-muscarinic and antihistaminic side effects?

5. What is the predominant form (ionized or non-ionized) of all alpha-receptor blockers currently marketed (see notes for list and structures)?
2. Why is dibenamine a potent, long-lasting alpha-antagonist? It has the appropriate "pharmacophore to interact with alpha-receptors, and a reactive beta-chloro-ethylamine and alkylate receptors like POB above:

3. Based on structural differences and chemical properties, explain why terazosin has higher oral bioavailability and a longer duration of action than prazosin?

Answer: the only difference in the structures of prazosin and terazosin is the furan or tetrahydrofuran ring attached to the piperazine nitrogen. In terazosin the "reduced" ring (tetrahydrofuran) imparts additional polarity to the molecule because its oxygen electrons are "free" to hydrogen bond with water (and other polar functional groups). In prazosin the "aromatic furan ring allows for resonance delocalization of oxygens electrons. Thus they are not as free to hydrogen bond as the corresponding oxygen in terazosin. This results in terazosin being more polar than prazosin, and less likely to diffuse in the tissues of metabolism and to be metabolized. Put another way, both of these compounds may be metabolized by the same enzymatic processes (cytochrome-mediated O-demethylation), but the extent of terazosin metabolism is lower due to its polarity!