Imagine that a drug discovery program generated the two lead compounds shown below. The compounds bind to the same target receptor protein. The compounds have different $K_B$ values for binding to the target (please recall that $\Delta G = -RT\ln K_B$). The compounds have very different structures. The question: which is the best lead to advance into further lead modification studies? For help, let’s go to the Molinspiration website:

http://www.molinspiration.com/cgi-bin/properties

Molinspiration is a company that sells software designed to facilitate drug discovery. We’ll be using a free, web-based application that calculates drug-like properties for organic molecules. Draw compound “A” into the structure-editing window of this website. Then click on the blue, “calculate properties” button. This will generate a set of interesting information including MW, cLogP (calculated LogP), and total polar surface area (TPSA). Write down the information or print it and attach a copy of the output to your assignment.) Repeat for “B”. Then answer the questions below.

Which compound (A or B) would you advance to the next stage of the discovery process: lead modification?
(a) …based on “Ligand Efficiency” (LE) (show the equation and explain your choice)

(b) …based on “Ligand Lipophilicity Efficiency” (LLE) (show the equation and explain your choice)

(c) Do either of the compounds violate Lipinski’s rule of fives? List the rules and tabulate the results for each compound.

(d) In class, we discussed a variant of Lipinski’s rules that considers only two criteria. Show the short version of Lipinski’s rules and indicates whether compounds A or B are acceptable under the short version of Lipinski’s rules?