Ligand-based drug design

1. By 2032, drug design has become one of the favorite pastimes of intellectuals in San Angeles because the local government has changed the old and obscure drug patent law to a new one that reads: "Any molecule that shows beneficial health effects without being significantly bad for you can be approved for marketing as long as no-one else has received an approval for exactly the same molecular structure."

It is Valentine's Day and you are receiving greetings e-mail with a small present from your friend. It comes with an attachment in the SDF format, and a note that (after being processed by the *Morality Filter*®) reads:

```
"Hi, ***y
I saw that the ***ets of a small pharmaceutical company formerly known as
SteriLife, Inc. were on sale at the bankruptcy auction, and I bought for you
the exclusive license to manufacture and sell the compounds described in
this SDF file.  The company was focused on the development of novel
antibacterial agents that target leucine transporters in bacterial cell
walls; however they went bankrupt because many of the ****s they developed
were not potent enough against bacteria, and others that were potent enough
were not liked by the patients because of the unpleasant side effects such
as the dry mouth. I know you are smart enough and can find a good use for
some of these molecules.

***s and ****es"
```

Take a look and see if this gift is worth something (*each subtask is worth 2 pts*)

a) Examine the file structure of the SDF file with a text editor. Notice that for each of the molecules, two data entries —the IC_{50} value (in μM units) for inhibiting the bacterial leucine transporter, and the percentage of adverse effects—are given. After you are sure that you understand how the SDF files are written, create a new SDF file that contains approximate two-dimensional structures and boiling point values for methane and tetrachloromethane. Submit this new SDF file with your homework after you verify (see the list of programs below that can be used for verification) that the file you created is indeed a valid SDF file.

b) Examine the molecules and associated data with a program that can parse SDF files. There are a number of programs that can visualize the structures in the SDF file. You can use any program (or create your own, e.g. using SDF Toolkit) to examine the structures. See the appendix about brief suggestions about programs that I am familiar with. Paste in the image of the compound that is the strongest inhibitor for the bacterial leucine transporter. Briefly discuss which program you found most useful for your analysis.

c) Perform structure-activity analysis considering only the binding affinity to the bacterial leucine transporter. Summarize the main conclusions from your analysis in a few concise statements. Describe the main features of the pharmacophore. Using a chemical drawing program, sketch structures of three novel (i.e. not present in the SDF file) molecules that are expected to show high affinity toward the bacterial leucine transporter.

d) Perform structure-activity analysis considering only the ability of drugs to induce the adverse side effect (dry mouth). Identify the main features of the toxicophore. Using a chemical drawing program, sketch structures of two novel (i.e. not present in the SDF file) molecules that are expected to show low (less than 12%) rate of dry mouth adverse effect while maintaining better than millimolar IC_{50} towards leucine transporter.

e) The now-bankrupt company already had figured out that these drugs are no good for human antibiotics: they either do not kill bacteria because of poor binding (IC_{50} > 500 μM is not a characteristic of a good drug), or kill bacteria but also cause a dry mouth. Search the publicly available chemical databases (PubChem, eMolecules, DrugBank[1]) to see if the molecules that you have rights for might be useful for something else than anti-bacterial compounds. Search by substructure or by similar molecules might be a vise choice at this stage. If you come up with an alternative use for some of your molecules, give a justification that includes a structure and name of at least one known drug that is similar to your structures and does not have a significant adverse effect of dry mouth (12% or less). What possible side effects should the patients of your drug be warned of?

Appendix: SDF Parsers

PowerMV (available for MS Windows at http://www.niss.org/PowerMV/) is probably the best choice as it displays all structures and associated properties together in one screen. After launching the program, click on the SDF icon on the toolbar and select the SDF file to be loaded. A new compound field is created; double click on it to view the structures. Check **Show Attributes** to see the associated data, such as antibacterial activity and the incidence of adverse reactions.

ACD/ChemSketch (available for MS Windows at http://www.acdlabs.com/products/chem_dsn_lab/chemsketch) is a nice structure editor that accepts SDF files as one of its many input formats. However, you need to load the SDF-To-Sketch converter via Options … ChemBasic Organizer into the toolbar before you can load SDF files. It is best to display one molecule per page from the SDF file; you can use PgUp and PgDown keys to scroll trough the structures. I am not sure how to display the properties. An interesting feature is the ability to search PubChem and eMolecules databases using molecular structures as inputs; you can try to see if any of the 20 molecules are known drugs. The program also performs 2D to 3D coordinate conversions and generates SMILES strings.

MarvinView (trial version available upon request from http://www.chemaxon.com/product/mview.html) is Java based and thus should work for people who do not have access to MS Windows platform. Please see their comprehensive documentation on how to visualize SDF files.

PyMOL (available at http://delsci.com/rel) is a visualization and modeling program for MS Windows, MacOS, and Linux. It places each structure in the SDF into own state/frame; you can use the player functions to browse individual structures. I am not aware of an easy way to display properties within PyMOL.

UCSF Chimera (available at http://www.cgl.ucsf.edu/chimera) is another multi-platform visualization and modeling program. It places each structure in the SDF file into own model; you can use the ModelPanel to select and move individual structures. You can move active structures freely around; for example you can group similar structures into one are of the screen and rotate them to emphasize the similarity.

---

[1] You can download an SDF file with all small molecule drugs from http://www.drugbank.ca/ and possibly compare (either visually or with the help of software) the content of your SDF file against about 4600 drugs in the DrugBank file. For some parsers, you may need to add an empty header line (there should be three) for each molecule. Substitute $$$$ with $$$$+newline (this is a 16 MB file, so be patient w/ MS Office).