

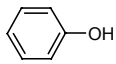
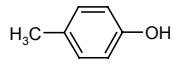
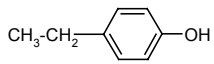
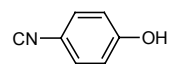
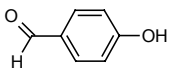
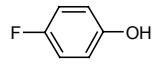
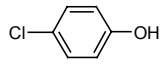
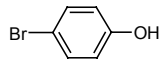
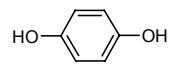
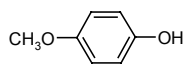
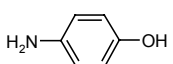
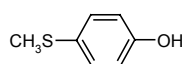
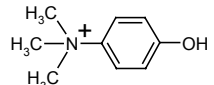
## QSAR

Table 1 lists Hammett sigma constants for substituents determined by measuring dissociation constants of meta- and para-substituted benzoic acids in water. Table 2 lists  $pK_a$  values of several para-substituted phenols in water.

Table 1.

| Substituent                                   | $\sigma_{\text{meta}}$ | $\sigma_{\text{para}}$ |
|-----------------------------------------------|------------------------|------------------------|
| H                                             | 0.00                   | 0.00                   |
| CH <sub>3</sub>                               | -0.07                  | -0.17                  |
| CH <sub>2</sub> CH <sub>3</sub>               | -0.07                  | -0.15                  |
| CN                                            | 0.56                   | 0.66                   |
| CHO                                           | 0.35                   | 0.42                   |
| COCH <sub>3</sub>                             | 0.38                   | 0.50                   |
| F                                             | 0.34                   | 0.06                   |
| Cl                                            | 0.37                   | 0.23                   |
| Br                                            | 0.39                   | 0.23                   |
| OH                                            | 0.12                   | -0.37                  |
| OCH <sub>3</sub>                              | 0.12                   | -0.27                  |
| NH <sub>2</sub>                               | -0.16                  | -0.66                  |
| S-CH <sub>3</sub>                             | 0.15                   | 0.00                   |
| N(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup> | 0.88                   | 0.82                   |

Table 2

|                                                                                      |       |
|--------------------------------------------------------------------------------------|-------|
|    | 9.95  |
|    | 10.19 |
|    | 10.00 |
|    | 7.59  |
|    | 7.66  |
|   | 9.95  |
|  | 9.38  |
|  | 9.34  |
|  | 9.96  |
|  | 10.20 |
|  | 10.30 |
|  | 9.53  |
|  | 8.00  |

- Which benzoic acid derivative in Table 1 has the lowest  $pK_a$ ? Briefly explain your reasoning.
- Based only on the data provided, estimate the  $pK_a$  value for 4-acetophenol. Show details of your work.
- Using molecular modeling programs (such as SYBYL in the SGI lab or PyMol on your PC) create 3D structures of phenol, *p*-methylphenol, *p*-ethylphenol, *p*-fluorophenol, *p*-chlorophenol, and *p*-bromophenol. Save the structure as MOL file. Provide images of each structure you created. See hints below for how to accomplish this with PyMol.
- Using any software capable of predicting molecular properties based on molecular structure, calculate the following molecular descriptors for each molecule for which you created 3D structure.

- Octanol –water partition coefficient (Moriguchi logP)
- Molar refractivity (Ghose-Crippen MR)
- Sum of atomic polarizabilities
- Radius of gyration

Organize your data in the following table:

|                              | Log P | Molar refractivity | Sum of polarizabilities | Radius of gyration |
|------------------------------|-------|--------------------|-------------------------|--------------------|
| <b>phenol</b>                |       |                    |                         |                    |
| <b><i>p</i>-methylphenol</b> |       |                    |                         |                    |
| <b><i>p</i>-ethylphenol</b>  |       |                    |                         |                    |
| <b><i>p</i>-fluorophenol</b> |       |                    |                         |                    |
| <b><i>p</i>-chlorophenol</b> |       |                    |                         |                    |
| <b><i>p</i>-bromophenol</b>  |       |                    |                         |                    |

- Which molecule is most lipophilic? Would you have predicted this based on your chemical intuition?

### PyMol editing hints

The current version of PyMol (0.95) has rudimentary molecular editing capabilities accessible via the **Build** menu. The program allows adding atoms and functional groups to a selected atom, remove selected atoms, or change torsional angles (rotation around bonds). Basic editing is best done while the mouse is in the **(3-Button) Universal Cycle** mode while rotations around bonds need mouse in the **(3-Button) Editing Mode**.

To create a new molecule, it is best to use one of the templates provided in the **Fragment** or **Residue** submenu of the **Build** menu. For example, you can use tyrosine (select Build -> Residue -> Tyrosine) as a template for all the substituted phenols. The atom marked with banded sphere is ready for editing.

To create *p*-ethylphenol from tyrosine, you need to delete atoms that are not present in *p*-ethylphenol. You want to delete four atoms: the amide hydrogen and amide nitrogen, the carbonyl oxygen and the carbonyl carbon. To delete atoms you need to select them first. To select atoms while in the universal cycle mode, select one atom at a time by doing *Ctrl-Right click* on the desired atom. To delete this atom, select **Remove** from the **Build** menu, or press *Ctrl-D*. Last, you need to fix the methyl group; PyMol can do it automatically when you select this carbon atom and then select **Cycle Bond Valence** from the **Build** menu.

To save the molecular structure as MOL file, select **Save Molecule** from the **File** menu, and make sure that the molecule name (e.g. tyr is highlighted). Select MOL as file format and give a unique MOL file name for each molecule saved. PyMol saves molecules as MDL molfiles (not to be confused with SYBYL molfile)

### Project Development.

In this part of the project development, propose a general synthetic route to prepare compounds that you anticipate will show desired pharmacological properties against disease you are working on. For example, if you are doing structure based drug design and want to synthesize transition state analogs, identify candidate structures and show what reactants are needed to prepare the analog. You need to identify the mechanisms/names of reaction steps that constitute your synthesis (e.g. nucleophilic addition, Grignard reaction, Birch reduction) but there is no need to specify reaction conditions (such as concentrations, times, pH, temperature etc). If you are planning to perform screening of libraries, show the chemistry needed for preparing your combinatorial library.