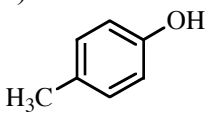
Answers to end-of-chapter questions

1)

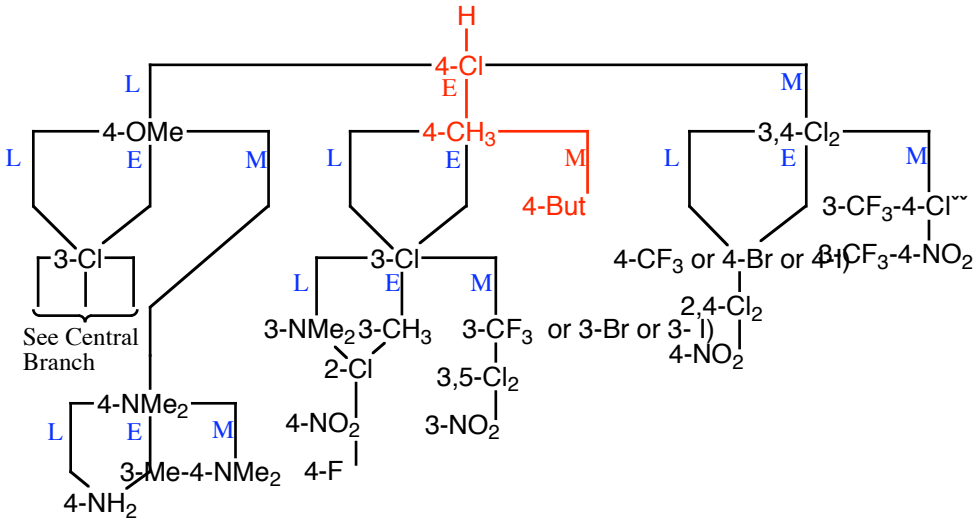


(I)

$$\text{Log}P = \log P(\text{benzene}) + \pi(CH_3) + \pi(OH)$$
$$= 2.13 + 0.52 + (-0.67)$$
$$= 1.98$$

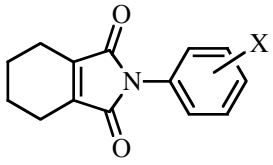
2) It is worth looking at the Craig plot (Fig. 18.12) in order to judge the suitability of these substituents. The plot reveals that the substituents have a wide range of hydophobicity constants and so they would be suitable for a study concentrating on that property. However, the substituents are all electron withdrawing and so they would not be suitable for a study comparing the electronic effects of substituents on activity.

3) The Topliss scheme in figure 18.13 can be used to answer this question. The analogues described so far follow the suggestions of the scheme with a *para*-chloro substituent being suggested first. Activity is little changed and so the next subtituent to be tried is *para*-methyl. This shows increased activity. According to the table, the next substituent should be a tertiary butyl group at the *para* position.



The rationale for the progression is as follows.
The chloro substituent is more hydrophobic and electron withdrawing than the original hydrogen. Since there is little effect on activity, the effect of the two properties on activity might be cancelling each other out. In general, increasing hydrophobicity is good for activity, so it is likely that electron-withdrawing substituents might be bad for activity.
Therefore, a methyl group is tried instead. It is comparable in size to a chloro substituent, has a similar hydrophobicity, but is electron donating.
Since activity increases, it is assumed that hydrophobic, electron-donating substituents are good for activity and a larger alkyl group is tried. This should have both increased hydrophobcity and a stronger electron-donating effect.

4)

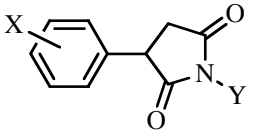


$\log 1/C = 1.08\pi_X + 2.41F_X + 1.40\ R_X - 0.072\ MR_X + 5.25$ ($n = 16$, $r^2 = 0.840$, $s = 0.59$)

log 1/C
This is a measure of the drug's biological activity. C is the concentration of drug required to produce a defined effect.
π_X
This is the hydrophobicity constant for the substituent X.
F_X
This is a measure of the electronic effect of the substituent X, in particular its inductive effect.
R_X
This is a measure of the electronic effect of the substituent X, in particular its resonance effect.
MR_X
This stands for molar refractivity and it is a steric measure for the substituent X.
n
The number of compounds tested in the study.
r
The correlation coefficient is a measure of how well the equation explains the variance in activity observed in terms of the physicochemical parameters present in the equation. Values of r^2 that are greater than 0.8 are considered good. In this case, the value is above 0.8 and so the equation is valid.
s
This is the standard deviation. It is a statistical measure for the goodness of fit for the equation.

Positive values of π, *F* and *R* are good for activity. This corresponds to substituents which are hydrophobic and which are electron withdrawing. The equation indicates that activity drops slightly as the size of the substituent increases.

5)



$\log 1/C = 0.92\ \pi_X - 0.34\ \pi_X^2 + 3.18$ (n=15, r^2=0.902, s=0.09, π_O=1.35)

The equation is parabolic and indicates that activity increases with the hydrophobicity of the substituent X until an optimum value is reached when π_X=1.35. Beyond that, activity drops with increasing hydrophobicity.

The π_X values for H, CH_3 and CF_3 are 0, 0.52 and 1.16 respectively. Activity should be greatest for the analogue with X=CF_3.

6) $\log 1/C = 0.92\,\pi + 2.08\,\sigma - 3.26$ (n=12, r^2=0.794, s=0.314).

High mutagenic activity would be expected for a substituent that is hydrophobic (a positive π value) and electron withdrawing (a positive σ value).