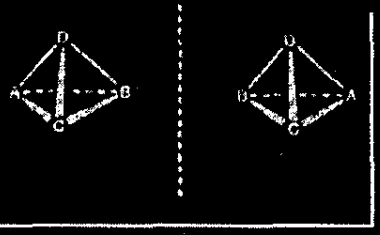
CHIRALITY and the BIOLOGICAL ACTIVITY of DRUGS



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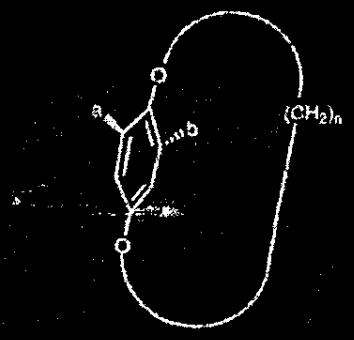

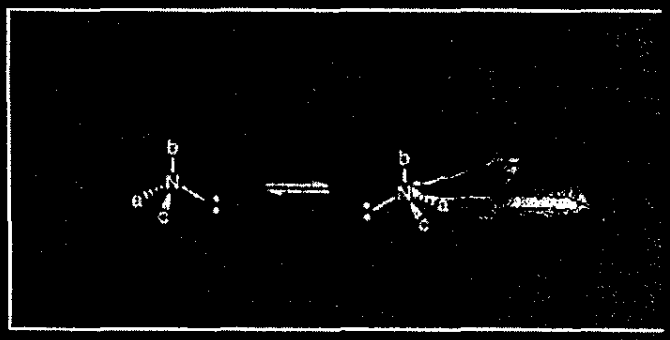

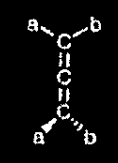

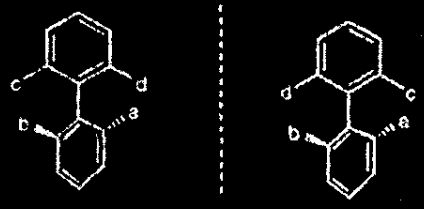

CHIRALITY and the BIOLOGICAL ACTIVITY of DRUGS

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optimization of a series of enantiomer pairs by the comparison of the eutomers and distomers in a series of analogs. The ratio of the affinities or potencies of two enantiomers is called the **eudismic ratio** (ER) and the logarithm of this is termed the **eudismic index** (EI). These terms are analogous to **stereospecific ratio** and **stereospecific index** which are used in a similar way. Because the free energy of binding is related to the logarithm of the concentration required to produce a half-maximal effect, so the EI can be a direct measure of the difference in free energy of binding between enantiomers. Pfeiffer's Rule indicates that the EI should increase as the affinity for the eutomer increases and indeed, this is found to be the case in many series of enantiomeric pairs (but not all) which have been studied.[12,13,21-29]

If, in a series of homologous compounds, a plot is made of the EI against the logarithm of the potency of the eutomer, a straight line is obtained, the slope of which is the rate of change in the EI with affinity and is called the **eudismic activity quotient** (EAQ); (Figure 2.6). A positive slope (positive EAQ) provides a validation of Pfeiffer's Rule and is found in most of the cases where there is a correlation. Such a correlation was obtained in about 60% of datasets examined in a study of over a hundred series and accounted for 69% of the data points.[13] Lack of a correlation probably indicates a lack of involvement of the element of chirality in the binding process, but it could also be due to other competing factors in a complex system or to contamination with small amounts of opposite enantiomers. In general, an EAQ of 0.5 is predicted on theoretical grounds[12] to represent an optimal involvement of the element of chirality and this is close to the mean (0.4) found in the large dataset above.

On occasions, a slope of zero (EAQ = 0) is observed and this can be used to make deductions as to the mode of binding. For example, the EAQ of a series of isopropylphosphothionates was found to be 0.62 for acetylcholinesterase inhibition but 0 for butyrylcholinesterase inhibition.[13] The interpretation[12] being that at least a three-point interaction (cf. Easson-Steadman hypothesis) is involved in the first case and only a two-point interaction in the second case. It is, however, probably more correct to discuss the relative involvement of the element of chirality in the binding

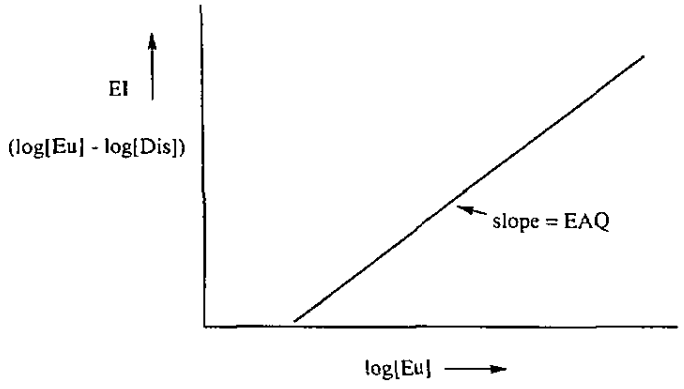

FIGURE 2.6 Eudismic analysis.

process and to consider whether a modification to the structure could provide a greater level of involvement.

On rare occasions, a negative EAQ is obtained which, although a violation of the Pfeiffer Rule, can also be instructive. One particularly interesting example[13] is found with 32 pairs of auxin analogs comprising sets of aryloxycarboxylic acids, β-naphthyloxycarboxylic acids and arylpropionic acids. The arylpropionic acids were found to have an EAQ of –0.37, which implies that the stereospecificity decreases with an increase in affinity and notably the intercept of the line with the abscissa occurs exactly at the point corresponding to the natural plant hormone indoleacetic acid.[13] Presumably the system has developed to maximize interactions with this achiral ligand, and this may therefore implicate a symmetry in its interactions which are disrupted by chiral ligands. These series also provide exemplification of another use in drug design of eudismic analysis. The EAQ of the aryloxypropionic acids and the β-naphthyloxypropionic acids taken together as a single series is 0.86 ($r^2 = 0.77$), but a better correlation is obtained for the subset of β-naphthyloxypropionic acids on their own (EAQ = 1.07, $r^2 = 0.98$). This may or may not be relevant in this case as there is a large substituent variation across the whole series and such differences can be an indication of a change in mode of binding. It is unlikely that different modes of binding to a particular receptor would produce the same EAQ so such correlations can be used to divide apparently homologous series into more optimal groupings for SAR studies.

It is also possible, by comparing the eudismic correlations for the same series of compounds with different receptor types, to discern the relative involvement of the element of chirality with each receptor-binding process. For example, the antihistaminic and anticholinergic activities of a series of diphenhydramine derivatives have significantly different EAQs (0.52 and 0.76, respectively) and there is also a different rank order to the relationships.[13] This indicates that the mode of interaction with each receptor is different and further analysis using standard molecular modeling techniques could, therefore, be used to advantage. If the correlations were identical there arguably would be little point in trying to optimize this particular series.

Eudismic-activity correlations can be used to determine the criticality of various chiral centers in a binding process and thus lead on to a greater appreciation of the mode of binding in a particular series. In other words, the more an element of chirality can be seen to influence the activity, the more it is central to that activity and implicated in the pharmacophore. One example is the muscarinic agonist potential of a series of pyrrolidinones (Figure 2.7, where R′ = methyl, propyl and R″ = methyl) which display a reasonable correlation when a traditional EA is carried out on enantiomeric pairs.[26] With two chiral centers it is also possible to study the effect of epimerization of R′ or R″ separately for this series of compounds. When the mydriatic activity was measured there was a good correlation with epimers of R′ with EAQ = 3.8 showing a strong effect of the chirality at this center. For the epimers of R″ there was also a good correlation but here the EAQ = 0 showed that there was no dependence at this site. The obvious conclusion, therefore, is that the principal interactions with the receptor are on the right-hand half of the molecule, around the basic nitrogen, and that the pyrrolidone is less important as the primary determinant

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