Notes

Molecular Similarity, Quantitative Chirality, and QSAR for Chiral Drugs

Alon Seri-Levy,† Susan West, and W. Graham Richards*

Physical Chemistry Laboratory, South Parks Road, Oxford OX1 3QZ, United Kingdom

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The current policy of drug regulatory authorities demanding that pharmaceutical companies justify their reasons for preferring drugs containing a mixture of enantiomers over one stereoisomer increases the importance of quantitative structure–activity relations (QSARs) for chiral drugs. The QSAR proposed by Pfeiffer for chiral drug enantiomer potencies was brought into question by the existence of sets obeying an anti-Pfeiffer rule. Using computer-aided molecular design methods and treating chirality not as an existing/nonexisting property but as a continuous one improve the QSAR proposed by Pfeiffer, yielding higher correlation coefficients and an independent ordinate. Calculated shape similarities reveal the details of the Pfeiffer behavior and the source of the anti-Pfeiffer behavior. Consequently revised models for the D2 and σ receptor are suggested.

Introduction

In recent years there is an enhanced tendency for drug regulatory authorities to treat racemic drugs as containing 50% impurities[1,2] and accordingly to encourage the development of chiral drugs containing only one enantiomer.[3] However, in some cases a drug containing a mixture of enantiomers is preferable to a pure chiral drug,[4] and hence the current policy is not to draw definitive guidelines forbidding racemic drugs but to demand that the pharmaceutical companies justify their reasons for preferring a mixture of enantiomers over one stereoisomer.[3] Any decision whether to develop an optically active chiral drug or a racemic drug should take into account the relative potency of the two drug enantiomers, both in the principal therapeutic activity and in side effects.[5] The relative potency is defined by the term eudismic ratio (ER), which is the quotient of the potencies of the more and less potent enantiomers (eutomer and distomer, respectively). A quantitative structure–activity relation (QSAR) for the ER can therefore be of great help to the medicinal chemist in making an informed decision whether to develop a single enantiomer drug or a racemate.

A rule governing the potency of chiral drugs was first suggested by Pfeiffer,[6] who claimed that the better the drug–receptor match, the greater the drug potency and the higher the ER. This rule, which was demonstrated for 14 randomly chosen drugs by drawing a linear correlation between the logarithm of the ER (eudismic index, EI) and the logarithm of the average human dose, was not restricted by Pfeiffer to a specific therapeutic activity and was presented as a general one, this generality being the main reason for much of the criticism of the rule.[7–9]

It should be emphasized that the basic assumptions behind Pfeiffer's rule were never criticized and that much of the antipathy can be eliminated by limiting the correlation to a homologous series of drugs acting on a specific receptor. This was done by Lehmann *et al.*[10] and by others,[11,12] who found correlations between the EI and the logarithm of the eutomer potency. The vast majority of the series of drugs which were tested and showed a significant correlation either obeyed Pfeiffer's rule, i.e. showed an increase in the EI with an increase in the eutomer potency, or showed non-Pfeiffer behavior, i.e. independence of the EI from the eutomer potency, which indicates that the chirality plays no role in this particular drug–receptor interaction. However, the presence of a few exceptional series which showed anti-Pfeiffer behavior, i.e. a decrease in the EI with an increase in the eutomer potency, cannot be explained by Pfeiffer's rule and cast doubt on the reliability of the QSAR which was derived from the rule, giving reason to be cautious in its use.

Eudismic analyses were also carried out by Van de Waterbeemd *et al.*[12] on the affinity of *N*-substituted 3-(3-hydroxyphenyl)piperidines (3HPP) for the dopamine D2 receptor and to the σ receptor (Figure 1a,b). It can be seen that while the affinity to the D2 receptor obeys Pfeiffer's rule (Figure 1a), the affinity to the σ receptor is more complicated (Figure 1b). 3HPP and the *N*-Me and *N*-Et derivatives produce the positive slope predicted by Pfeiffer; *N*-Et, *N*-*n*Pr, *N*-*n*Bu, and *N*-EtPh derivatives yield a negative slope and an anti-Pfeiffer behavior. The seventh derivative, *N*-*i*Pr, is an exception for both cases.

An indirect measurement of the EI can also be obtained for a homologous series in which only one out of the four ligands connected to a chiral center is modified along the series. In such cases the enantiomers can be divided into two separate sets, each set containing the enantiomers having the same absolute configuration for the three untouched ligands (the ligands can be overlapped within the group). An independent QSAR can be drawn for the two sets and the EIs can be predicted from the difference between the two correlations. Note that for the seven 3HPP derivatives the ligands priorities do not change along the series and hence the sets can be identified according to the *R* and *S* methodology.

Recently we have shown[13] that differences in the intermolecular interaction energy between homologous potent drugs and a given receptor can be analyzed in terms of similarity indices[14] and chirality coefficients[15–18] and that EIs can be correlated with chirality coefficients. In

† Postdoctoral researcher from the Hebrew University of Jerusalem, Jerusalem, Israel.

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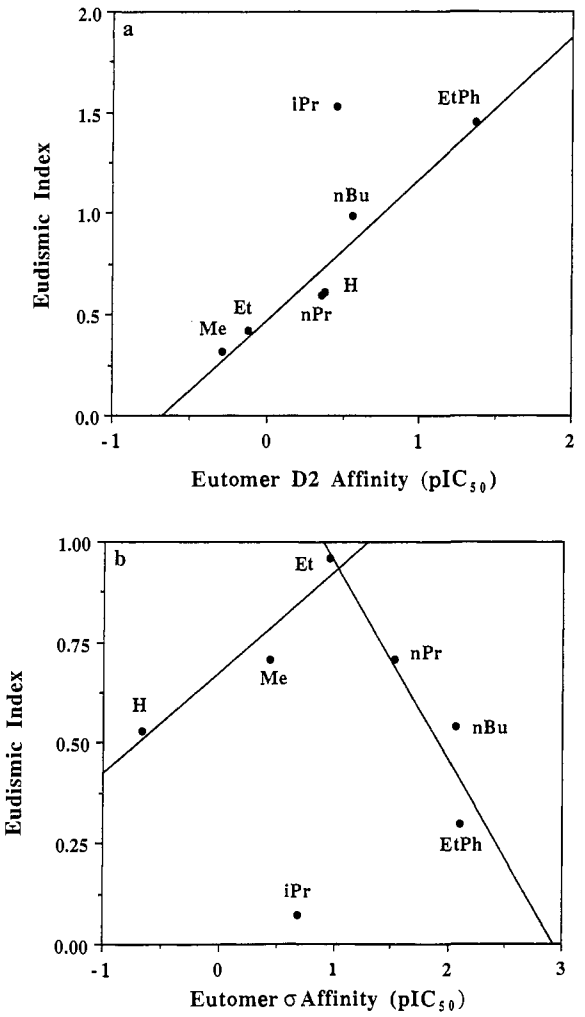


Figure 1. The EI is plotted against the eutomer affinity. Redrawn from Van de Waterbeemd *et al.* (ref 12). (a) D2 receptor. EI = 0.70 pIC_{50} + 0.47 (r^2 = 0.941). (b) σ receptor. Pfeiffer behavior: EI = 0.25 pIC_{50} + 0.67 (r^2 = 0.915). Anti-Pfeiffer behavior: EI = −0.49 pIC_{50} + 1.44 (r^2 = 0.898).

the current work we use both similarity indices and chirality coefficients to examine the details of the eudismic analysis suggested by Pfeiffer and the source of anti-Pfeiffer behavior. This provides a new paradigm for thinking about Pfeiffer, non-Pfeiffer, and anti-Pfeiffer behavior, permitting suggestions to be made for revised models of the dopamine D2 and σ receptors, although there are uncertainties in the data.

Molecular Similarity and Chirality Coefficients

In order for similarity indices to be useful, closely related molecules must have approximately the same similarity indices.[14] This can be achieved by superimposing the molecules according to the property under examination and then measuring their similarity in this property. Of the different properties that can be used, such as electron density,[19,20] electric field,[21] elements of symmetry,[22] electrostatic potential (ESP),[23,24] and shape,[17] the latter two are of interest to us: the ESP surrounding the molecule because it governs the attractive part of the drug–receptor intermolecular interaction and the shape (drug–receptor structural fit) since it largely determines hydrophobic attraction and the steep repulsive part of the interaction. It must be stressed that the shape cannot be replaced by volume since it is shape that is the basis of stereochemistry.

The ESP similarity index of two superimposed molecules, R_{AB}, is defined in a similar manner to Carbo's equation[19,20] but normalized to give values between 0 and 1.

$$R_{AB} = \left(1 + \frac{\int P_A P_B \, d\nu}{(\int P_A^2 \, d\nu)^{1/2} (\int P_B^2 \, d\nu)^{1/2}}\right)/2 \qquad (1)$$

where P_A and P_B are the ESPs at a point in space. The numerator measures the overlap in the ESP and the denominator normalizes the result.

The shape similarity index, S_{AB}, is measured by an analogous equation suggested by Meyer[17]

$$S_{AB} = \frac{C}{(T_A T_B)^{1/2}} \qquad (2)$$

Here the superimposed molecules are defined by their van der Waals volumes and (computationally) enclosed in a three-dimensional gridded box (illustrated in ref 17). The similarity index, which varies between 0 and 1, is calculated by counting the number of grid points, T_A and T_B, included within the volume of each molecule and the number of grid points, C, falling inside both enantiomers. The relative positions of the two structures being superimposed can be adjusted to yield a maximum value of similarity using optimization routines in the software. The achieved superposition used in one example discussed later appears in Figure 2 (bottom).

In case where A and B are enantiomers, it seems only natural to measure the enantiomers chirality coefficients instead of their similarity indices. Quantifying chirality is a new concept which not only determines whether a molecule is chiral or not but also measures its degree of chirality. According to the classical qualitative definition of chirality, a molecule is chiral if it cannot be overlapped with its mirror image. Hence one of the ways to quantify chirality[17] is by defining chirality as [1 − similarity], i.e. by superimposing the enantiomers and measuring the dissimilarity of the two. The chirality coefficient of a molecule is defined as 0 (similarity index = 1) if the molecule can be exactly superimposed on its mirror image (the molecule is achiral and the two forms are identical), and it continuously increases toward 1 with the decrease in the extent of the enantiomers' overlap (decrease in similarity). The shape chirality coefficient, S_{AB}', is therefore defined as 1 − S_{AB} and the ESP chirality coefficient, R_{AB}', is defined as 1 − R_{AB}.

The calculations of the similarity indices and chirality coefficients were performed as follows. Each pair of enantiomers was built in its agonist conformation as was proposed by Liljefors and Wikström,[25,26] using Chem-X[27] and based on the X-ray crystal structure[28] of *trans*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline, which has the same rigid agonist conformation[25] as the *S* enantiomer. The substituents were placed in the most extended conformation and in order to calculate the ESP similarity, atomic point charges were determined using RATTLER[29,30] and the AM1 Hamiltonian[31] in MOPAC.[32]

In order to investigate the influence of the alkyl derivatives in a homologous series on the drug affinity, all the *R* derivatives were superimposed onto *R*-3HPP and all the S derivatives onto *S*-3HPP, such that the common part (the aromatic and pyrimidine rings) overlapped exactly. For the investigation of the influence of chirality

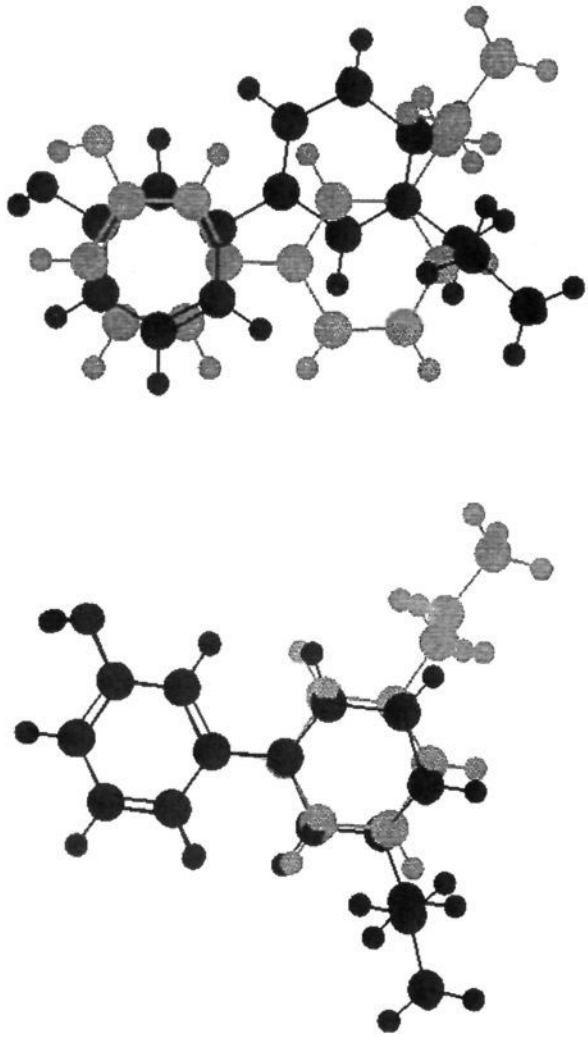


Figure 2. (top) The center of the aromatic rings and the nitrogens of the two enantiomers of 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine are superimposed. This is according to the model of Liljefors and Wikström (ref 25 and 26), *S* configuration, black circles; *R* configuration, gray circles. (bottom) The hydroxyphenyl groups are superimposed to obtain maximum overlap. Note that the two *N*-alkyl groups are facing in opposite directions.

on the drug affinity, each pair of enantiomers was superimposed in two different ways. In the first one the two enantiomers were overlapped according to the model of Liljefors and Wikström, i.e. the center of the aromatic rings and the nitrogens were superimposed (Figure 2, top). This model defines the overlap in this case and optimization of the similarity was not appropriate. In the second case, the hydroxyphenyl groups were superimposed to obtain maximum overlap (Figure 2, bottom) since this was found not only to give the highest shape similarity coefficients but also a plot of EI versus chirality (Figure 5a) similar to that obtained by Van de Waterbeemd *et al.*[12] (Figure 1a). (Whichever way the structures were superimposed a single straight line could not be obtained for Figure 5a.) It also leaves the two *N*-alkyl groups facing in opposite directions as in the model of Liljefors and Wikström in which the eutomer (*S* configuration) points "upwards" and the distomer (*R* configuration) points "downwards", but in contrast to their model, the nitrogens do not overlap. Notice that for the calculation of shape similarity indices and σ chirality coefficients both rings are superimposed; hence, replacing the agonist conformation by the most stable one (for the two superimposed molecules) would not significantly alter their values. Finally the shape similarities to 3HPP were calculated by the ASP program,[33] using a three-Gaussian approximation[34] for Carbo's equation and 0.02-nm grid spacing for eq 2.

Results and Discussion

The similarity indices and chirality coefficients of the seven 3HPP derivatives are summarized in Table 1. For all the correlations described below it was found from bivariate linear regressions that shape similarity is the discriminative property and that the ESP property does not contribute, indicating that the binding affinities increase with hydrophobic surface area in contact with the receptor. The similarity indices and chirality coefficients were therefore calculated from the shape only.

As in the original eudismic analysis (Figure 1a,b) the *N*-*i*Pr derivative is an exception and was not included in the correlations. It can be seen from Table 1 that the activity of the *R* isomer of *N*-*i*Pr is significantly lower at both the σ and D2 receptors than might be expected. It is evident from the superpositions described earlier that one of the methyl groups of both isomers of *N*-*i*Pr occupies space not occupied by any of the other derivatives. Also, Pfeiffer's analysis should be restricted to a homologous series and the *N*-*i*Pr derivative is the only one with a tertiary alkyl group. The other derivatives have primary alkyls.

D2 Receptor. The first correlation which was drawn from this table is between the EIs and the chirality coefficients (Figure 3a). The eudismic analysis in Figure 3a is in general agreement with Figure 1a but has the advantage of the ordinate being independent of the abscissa and a higher correlation coefficient ($r^2 = 0.965$ instead of $r^2 = 0.941$). Moreover, the high correlation coefficient indicates that the difference in activity of an enantiomeric pair can be explained in terms of the degree of shape chirality (dissimilarity) of the two enantiomers. This quantitative result is in agreement with the qualitative binding model proposed by Liljefors and Wikström[25,26] (Figure 2, top).

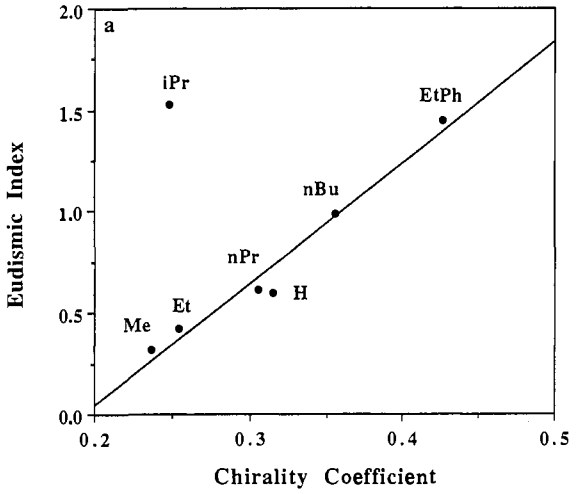
Note that in this QSAR the shape chirality coefficient for 3HPP is higher than might be expected from the trend observed for the other alkyl derivatives (increasing chirality coefficient with substituent size). This high chirality is a result of the superposition of the *R* and *S* isomers in which one of the α carbons in the piperidine ring overlaps the first carbon of the alkyl substituent, thus increasing the similarity between the isomers. There is therefore a greater dissimilarity between the *S*-3HPP and *R*-3HPP and a correspondingly higher EI coefficient than might be expected from the trend observed for the other alkyl derivatives.

The second correlation (Figure 3b) reveals the details of the eudismic analysis. Here the potencies of the *R* and *S* enantiomers were correlated separately with their similarity to *R*- and *S*-3HPP, respectively. Excluding 3HPP (to be explained below), two independent linear correlations ($EI(S) = -10.21S_{AB} + 9.30$ and $EI(R) = -3.04S_{AB} + 2.29$) were obtained. The accuracy of these two correlations can be exposed by calculating the EIs from the difference between the two correlations and then correlating these calculated EIs with the observed EIs (Figure 4). In the case of a perfect correlation, all the dots

Table 1

3HPP derivative		D2 affinity[a] (pIC_{50}, μM)		D2 chirality coefficient[b] ·		σ affinity[a] (pIC_{50}, μM)		σ chirality coefficient[c]		similarity index to 3HPP[d]	
derivative	config	pIC_{50}	EI	shape	ESP	pIC_{50}	EI	shape	ESP	shape	ESP
H	R	0.36	0.60	0.315	0.188	−0.66	0.53	0.070	0.100	1.000	1.000
H	S	−0.24				−1.19				1.000	1.000
Me	R	−0.61	0.32	0.237	0.115	0.43	0.71	0.134	0.143	0.952	0.970
Me	S	−0.29				−0.28				0.950	0.959
Et	R	−0.54	0.42	0.254	0.110	0.95	0.96	0.195	0.150	0.917	0.972
Et	S	−0.12				−0.01				0.912	0.962
*n*Pr	R	−0.23	0.61	0.306	0.123	1.52	0.71	0.256	0.166	0.881	0.964
*n*Pr	S	0.38				0.81				0.877	0.955
*i*Pr	R	−1.08	1.53	0.248	0.107	0.61	0.07	0.251	0.181	0.884	0.957
*i*Pr	S	0.45				0.68				0.877	0.941
*n*Bu	R	−0.43	0.99	0.356	0.120	2.05	0.54	0.310	0.178	0.849	0.959
*n*Bu	S	0.56				1.51				0.845	0.947
EtPh	R	−0.09	1.45	0.426	0.193	2.10	0.30	0.413	0.216	0.792	0.933
EtPh	S	1.36				1.80				0.786	0.925

[a] Data from Van de Waterbeemd *et al.* (ref 12). [b] Calculated by superimposing the center of aromatic rings and the nitrogens (Figure 2, top). [c] Calculated by superimposing the hydroxyphenyl groups (Figure 2, bottom). [d] Calculated by superimposing both aromatic and pyrimidine rings.



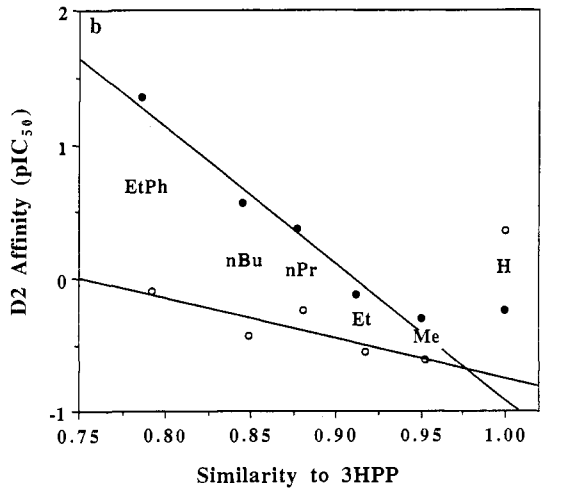


Figure 3. QSARs for D2 receptor. (a) The EI is plotted against the chirality coefficient. EI = 5.97 S_{AB}' − 1.15 (r^2 = 0.965). (b) The affinities of the *R* (m) and S (l) enantiomers are plotted against the similarity to *R*- and *S*-3HPP, respectively. The anomalous behavior of 3HPP (*N*-H) is discussed in the text. pIC_{50} (*R*) = −3.04 S_{AB} + 2.29 (r^2 = 0.750). pIC_{50} (*S*) = −10.21 S_{AB} + 9.30 (r^2 = 0.974).

should lie on the diagonal and indeed it can be noticed from Figure 4 that the five alkyl derivative dots lie fairly close to it (r^2 = 0.957).

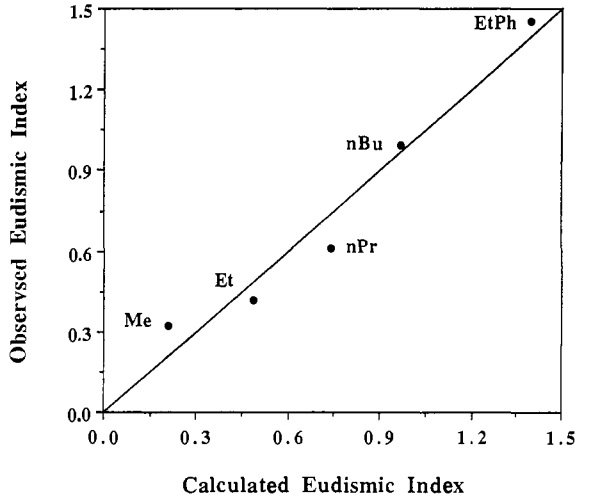


Figure 4. The observed EI is plotted against the EI calculated from the separation between the two linear correlations in Figure 3b. The proximity of the dots to the diagonal indicates the accuracy of the calculation (r^2 = 0.957).

Although 3HPP was included in the eudismic analysis in Figure 3a, neither of its enantiomers could be included in the linear correlations in Figure 3b. The high affinities of both 3HPP enantiomers may be attributed to the nitrogen being a hydrogen-bond donor. This effect is common to both enantiomers and hence the magnitude of the EI remained almost unchanged. Moreover, removing 3HPP from the eudismic analysis in Figure 3a would increase the correlation coefficient to r^2 = 0.987.

σ Receptor. As with the D2 receptor, a plot of EI versus chirality coefficient (Figure 5a) gave a similar graph to that of EI versus eutomer affinity (Figure 1b). Here again the correlation coefficients are higher (for the Pfeiffer behavior r^2 = 0.988 instead of r^2 = 0.915 and for the anti-Pfeiffer behavior r^2 = 0.980 instead of r^2 = 0.898) and the details of this eudismic analysis are revealed by correlating the eutomer and distomer potencies separately with similarity to 3HPP (Figure 5b). It can be seen that both the *N*-EtPh enantiomers have lower affinities than expected, presumably due to an additional repulsion from either the π electrons or their bulk and hence were excluded from the correlations. The remaining derivatives yield very high correlation coefficients both for the *R* (r^2 = 0.992)

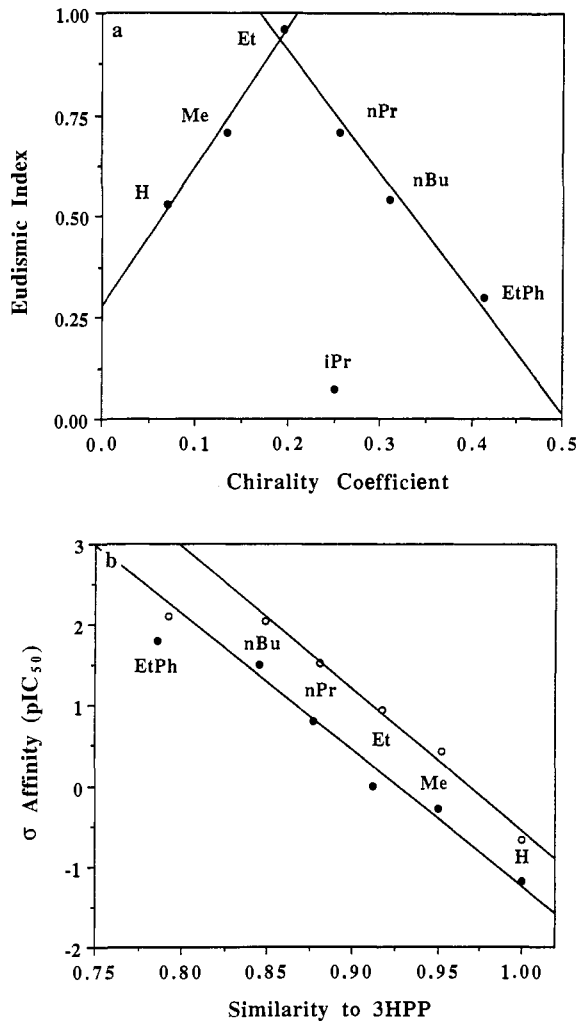


Figure 5. QSARs for σ receptor. (a) The EI is plotted against the chirality coefficient. Pfeiffer behavior: EI = 3.43 S_{AB}' + 0.28 (r^2 = 0.988). Anti-Pfeiffer behavior: EI = −2.98 S_{AB}' +1.50 (r^2 = 0.980). (b) The affinities of the R (m) and S (l) enantiomers are plotted against the similarity to R- and S-3HPP, respectively. The anomalous behavior of N-EtPh is discussed in the text. pIC_{50} (R) = −17.57 S_{AB} + 17.02 (r^2 = 0.992). pIC_{50} (S) = −16.83 S_{AB} + 15.60 (r^2 = 0.977).

and S (r^2 = 0.977) configurations. It should be noted that, in contrast to the D2 receptor, 3HPP was not anomalous presumably because there is no hydrogen-bond acceptor in the σ receptor. This type of correlation, which was found to be very reliable for the D2 receptor (Figure 4), indicates (Figure 5b) that in this case the two lines have similar slopes, which is a non-Pfeiffer behavior in contrast to the apparent anti-Pfeiffer behavior which was observed in the eudismic analyses (Figures 1b, 5a). One apparent difficulty in this type of analysis comes from the possible inaccuracies in the original experimental data (when error bars are not published[12]). If the IC_{50} values were only good to a factor of 2, then the ratio could be in error by a factor of 4 implying errors in the eudismic index of ±0.6. However, the fact that in Figure 5b the data lie on virtually parallel lines suggests that the trends in the data are reliable in a way which absolute values may not be.

Conclusions

We have shown that for a homologous series of drugs EI can be correlated with computed chirality coefficient and that this chirality coefficient has the advantage of not only being independent of the EI but also yielding a higher correlation coefficient.

Anomalous behavior which is masked in the eudismic analysis is exposed by separately correlating molecular potency with shape similarity for the two sets of enantiomers. Moreover, using these separate correlations reveals that the anti-Pfeiffer behavior is actually non-Pfeiffer behavior. According to this analysis it is suggested that there is a possibility of a hydrogen-bond acceptor in the D2 but not in the σ receptor and that there is the possibility of an additional repulsion between the σ receptor and the N-EtPh derivative, although it is impossible to eliminate other explanations due to the sparseness of the data.

This attempt to incorporate stereochemistry into QSAR is obviously a first step, but nonetheless does provide some satisfactory statistical correlations and the chance to postulate binding models.

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