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Chiral Drug Potency: Pfeiffer's Rule and Computed Chirality Coefficients

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Abstract: Since the thalidomide tragedy there has been an increased awareness of the potential dangers in using racemic drugs. Pharmaceutical companies are required to justify each decision to manufacture a racemic drug in preference to its homochiral version. This process of justification is both time-consuming and costly. Any method for its simplification would be most valuable. The computer-aided molecular design method suggested here produces a sensitive quantitative structure activity relation between the eudismic ratios of drug enantiomers and a computed 'chirality coefficient' defined as (1 - molecular similarity). The advantage of this correlation is that it permits the explanation of previous experimental results and also the potency prediction of new drugs within a series.

Physically handicapped thalidomide children are chilling evidence of the hidden dangers in the use of racemic drugs[1]. Together with the desired tranquillising effect of its left-handed enantiomer, racemic thalidomide contains an equal amount of a right-handed enantiomer which in retrospect was found to be possibly responsible for these tragic deformities[2]. Whether the use of homochiral thalidomide, containing only left-handed enantiomer, would have prevented this catastrophe, is open to speculation since the possibility of racemisation *in vivo* has never been investigated[3]. Since the thalidomide case, there is an enhanced tendency for drug regulatory authorities to treat racemic drugs as containing 50% impurities and to encourage the development of homochiral drugs. The current policy is not to draw definitive guidelines forbidding racemic drugs, but to leave the decision whether to develop homochiral or racemic drugs in the hands of the pharmaceutical companies, with the onus on them to justify their preference for a racemic drug over one of its homochiral versions[4]. Key questions in this decision-making process are what are the relative potencies of the two enantiomers for the principal therapeutic activity, for unwanted effects, and for secondary desired effects?[5]

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The aim of this report is to show that by using computer-aided molecular design (CAMD) methods, a quantitative structure activity relation (QSAR) can be drawn between the potency ratio of two enantiomers (eudismic ratio, ER) and the chiral coefficient[6] of the enantiomer pair. The ER itself is the quotient of the potencies *in vivo* of the more potent enantiomer (eutomer) and the less potent one (distomer). The chiral coefficient is a quantitative index of the dissimilarity between enantiomers (or 1 - similarity). Such a correlation, either for therapeutic activity or for other effects, permits the prediction, within a homologous series, of the ERs of new enantiomer pairs. Previous similar correlations, obtained by experimental methods[7-9], can be explained in terms of the dissimilarity in shape[10] and in electrostatic potential (ESP)[11] of the enantiomer pairs. The ability to predict ERs as well as the ability to explain existing correlations, can aid medicinal chemists in making informed decisions.

A correlation of this type was first described by Pfeiffer in a paper published 37 years ago[7]. According to Pfeiffer, there is a correlation between the degree of drug geometric conformity to the locus of action, and drug potency. The better the drug-receptor match, the greater the drug potency. Taking average human dosage as a measure of drug activity, he postulated that "The lower the effective dose of a drug, the greater the difference in the pharmacological effect between the optical isomers". This postulate was supported by tracing a linear correlation between the logarithm of the ER (eudismic index, EI) of 14 randomly chosen enantiomeric pairs and the logarithm of the average human dose (Fig. 1).

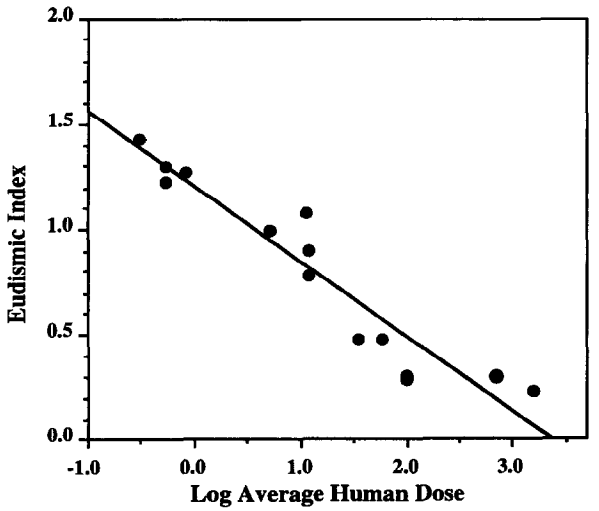

Fig. 1: Pfeiffer's original observation for 14 randomly chosen drugs (redrawn from Ref. 7). There is a linear correlation between the ER and the logarithm of the average human dose. $\log y = 1.19 - 0.454 (\log x)$, $r > 0.9$.

Pfeiffer's rule has been subject to criticism[12-14] for various reasons, such as that it involves drugs with a variety of therapeutic activities; it ignores optical impurities; and that although it was presented as a general rule some of those drugs investigated did not obey the correlation. Much of the criticism can be eliminated by limiting the correlation to related series, as indeed was done by Lehmann *et al.* for 101 different series of three

or more enantiomeric pairs[9], and by others[8,12]. Of the 101 Lehmann sets, over half showed a significant correlation between the EI and the logarithm of the eutomer potency, with 27 of these showing an increase in the EI with an increase of the eutomer potency, i.e. obeying Pfeiffer's rule; a further 29 pairs showing independence of the EI from the eutomer potency; and only three pairs showing an anti-Pfeiffer's rule correlation[15]. The main conclusion that can be drawn from Lehmann's work is that stereoselectivity does not occur randomly.

If this conclusion is valid, our postulate is that the ERs of potent drugs can be correlated with the differences in the intermolecular interaction energy between the drug enantiomers and the receptor (Fig. 2.). These differences can be analysed in terms of the degree of chirality of the enantiomer pair. Notice that chirality is not treated as an existing/non-existing property, but as a continuous one[6,10,16]. The chirality coefficient is defined as 1 if the enantiomers do not overlap at all (zero similarity or total dissimilarity), and continuously decreases as the degree of overlap between the enantiomers increases, until full similarity (zero chirality or identity) is reached. Among the different properties that can be overlapped, such as electron density[17], electric field[18], elements of symmetry[16], ESP[11] and shape[10], the latter two are of interest to us; the ESP surrounding the molecule because it governs the attractive part of the intermolecular energy curve; and the shape (drug-receptor structural fit) since it largely determines the repulsive part. Hence, for potent drugs, a combination of the chirality coefficients from both the shape and the ESP properties should give the desired quantitative measurement of the dissimilarity between the potential curves.

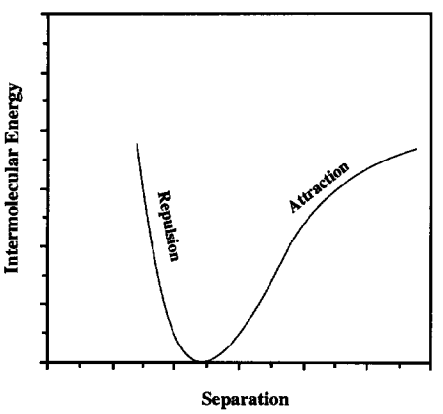

Fig. 2: The general form of the intermolecular interaction between a drug and its receptor.

The first set of drug enantiomers to be examined in this study was also the first homologous set of this kind to be presented in the literature[8], where a log-log correlation was found between the ERs and inhibition potencies of five different derivatives of S-alkyl *p*-nitrophenyl methylphosphonothiolates (Fig. 3), for the receptors acetylcholinesterase (AcChE) and butylcholinesterase (BuChE). The calculations of the chirality coefficients of each chiral drug were performed as follows: each pair of enantiomers was built in Chem-X®[19] using standard bond lengths and angles. The resulting structures were optimised in MOPAC[20] using the semi-empirical AM1 Hamiltonian[21]. Notice that this study utilises drugs in their most stable conformation only. Point charges were calculated using RATTLER®[22,23]. The enantiomers in their most stable conformation

were then superimposed, so as to ensure maximal overlap of the stereogenic centres and two of the four branches emanating from them (the phosphorus stereogenic centres and the two oxygen branches in this case).

For ESP, the degree of chirality was calculated by a method originally introduced by Carbo *et al.*.[17] within the ASP® program[24]. Following Carbo's method, if the two enantiomers to be compared, *A* and *B*, are computationally superimposed, their similarity index, R_{AB}, can be calculated from

$$R_{AB} = \frac{\int P_A P_B \, dv}{\left(\int P_A{}^2 dv\right)^{1/2}\left(\int P_B{}^2 dv\right)^{1/2}} \tag{1}$$

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 normalises the similarity result obtained such that the range of similarity is between zero and unity (identity). Since R_{AB} measures the similarity between enantiomers, the complementary term, $1\text{-}R_{AB}$, is the chirality coefficient. R_{AB} can be calculated either numerically using a gridded box, or analytically using a Gaussian function approximation[25] as utilised in this work for three Gaussians.

An analogous index for evaluating molecular shape similarity, suggested by Meyer[10], was adopted here. According to Meyer's method, the superimposed enantiomers are defined by their van der Waals volume and placed in a three-dimensional gridded box. The number of grid points included within the volume of each molecule, T_A and T_B, and the number of grid points falling inside both enantiomers, *C*, are counted. The similarity index, S_{AB}, is given by

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

and the chirality coefficient for the shape property is calculated from $1\text{-}S_{AB}$. In this work using ASP® grid spacing was chosen to be 0.2Å.

Having obtained the two chirality coefficients, it was observed that both coefficients of the first four derivatives can be correlated independently with the ERs obtained from the interaction with AcChE and BuChE, to form a simple linear correlation, as opposed to the experimental log-log correlation. High sensitivity of the shape coefficient to an increase in chirality was also observed. However, the ER is not a function of a single coefficient but reflects a combination of the two, such that averaging them yields a single coefficient that describes the difference between the drug-receptor interaction curves. Plotting the ERs for both AcChE and BuChE against this single chirality coefficient yields the linear correlations shown in Fig. 3. The two different slopes indicate that for this homologous set, the interaction with AcChE is more stereoselective then that with BuChE. The linear correlations confirm that the drug-receptor interaction involves the drug's most stable conformation.

The fifth member of this set (n-pentyl), which appears in an exceptional location on the experimental curve, could not be correlated to any extent with the other derivatives presented in Fig. 3. This reveals the enhanced sensitivity of the approach suggested here, where the ERs are plotted against an independent factor, as compared to the experimental analyses where the ERs are plotted against eutomer potencies apart from Pfeiffer's set.

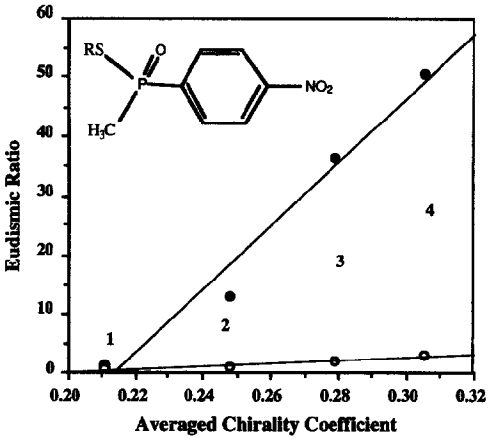

Fig. 3: A linear correlation between the ERs and the averaged chirality coefficients of S-alkyl *p*-nitrophenyl methylphosphonothiolates (R = (1) methyl, (2) ethyl, (3) n-propyl, (4) n-butyl). ● AcChE: y = -115 + 540x, r = 0.987. ○ BuChE: y = -4.8 + 24.5x, r = 0.952.

The experimental log-log plot of a second set is presented in an extended form in Lehmann's seminal work[9]. Shape and ESP coefficients of four derivatives of 1,3-dioxolane (molecule in Fig. 4), which mimic AcCh at the muscarinic receptor of the guinea-pig ileum smooth muscle, were calculated as above, by overlapping the stereogenic centres and the oxolane rings. Here again, the sensitivity to the chirality coefficient was greater for the shape chirality than for the ESP chirality and the averaged chirality coefficients were linearly correlated with the ERs as shown in Fig. 4. The higher sensitivity of the last three stereoselective reactions to changes in the shape chirality coefficient, compared to their sensitivity to changes in the ESP chirality coefficient, can be explained by noting that in Fig. 2 the repulsion and not the attraction is the more discriminating factor.

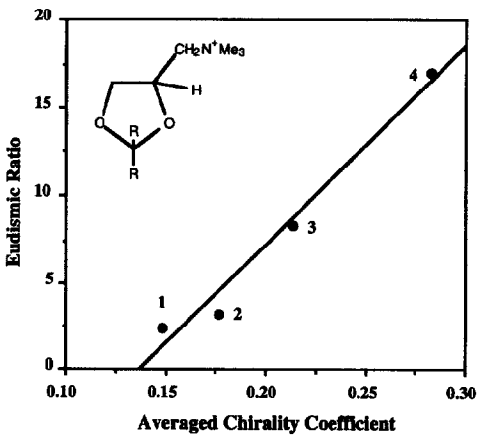

Fig. 4: A linear correlation between the ERs and the averaged chirality coefficients of muscarinic 1,3-dioxolanes (R = (1) isopropyl, (2) ethyl, (3) methyl, (4) hydrogen). y = 16 + 114x, r = 0.986.

Returning to Pfeiffer's set, it was found here that neither the shape coefficient nor the ESP coefficient can be independently correlated with the ER. The fluctuations in both correlations are not surprising since the drugs in Pfeiffer's study do not constitute a homologous set. Interestingly, averaging the two coefficients yields a simple linear correlation for the first eight most potent drugs as shown in Fig. 5. These correlated drugs can therefore be treated as a pseudo-homologous set with the two chirality properties complementing one another. For the first and third molecules in the set, norepinephrine and epinephrine, the ESP chirality is the main source of their high ERs; for the second molecule, atropine, both chirality properties contribute to the resultant high ER but with more influence of the shape property; for the eighth molecule, methadone, the low chirality in both properties indicates high similarity between the enantiomers and hence a low ER. The inability to correlate the last six drugs in Pfeiffer's set can be explained by their relatively low potency, where drug-receptor interactions become less important to the ER and factors such as kinetic differences become more influential upon enantiomer potency. It appears that the combination of a log-log plot, which tends to be less sensitive to aberrant points than a simple linear plot, and a pseudo-homologous set of drugs, is the source of Pfeiffer's linear correlation.

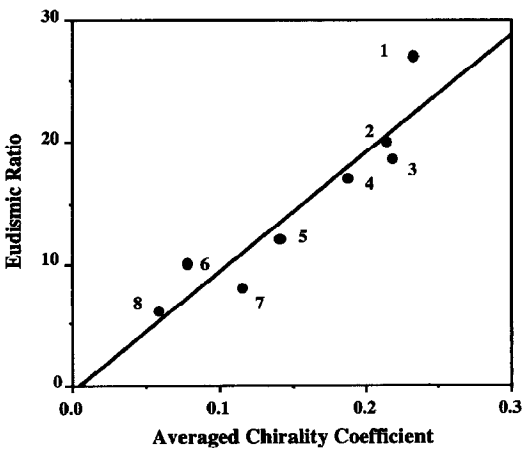

Fig. 5: A linear correlation between the ERs and the averaged chirality coefficients of the first eight most potent drugs in Pfeiffer's set. y = -0.4 + 97x, r = 0.930. (1) norepinephrine, (2) atropine, (3) epinephrine, (4) scopolamine, (5) amphetamine, (6) dromoran, (7) metamphetamine, (8) methadone.

The main conclusion to be drawn from the above analyses is that eudismic ratios of potent drugs belonging to homologous sets can be correlated with their chirality coefficients. Such a correlation can assist the prediction of eudismic ratios prior to experiments.

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