Polar Molecular Surface as a Dominating Determinant for Oral Absorption and Brain Penetration of Drugs

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Purpose. To study oral absorption and brain penetration as a function of polar molecular surface area.

Methods. Measured brain penetration data of 45 drug molecules were investigated. The dynamic polar surface areas were calculated and correlated with the brain penetration data. Also the static polar surface areas of 776 orally administered CNS drugs that have reached at least Phase II efficacy studies were calculated. The same was done for a series of 1590 orally administered non-CNS drugs that have reached at least Phase II efficacy studies.

Results. A linear relationship between brain penetration and dynamic polar surface area (Å^2) was found ($n = 45$, $R = 0.917$, $F_{1,43} = 229$). Brain penetration decreases with increasing polar surface area. A clear difference between the distribution of the polar surface area of the 776 CNS and 1590 non-CNS drugs was found. It was deduced that orally active drugs that are transported passively by the transcellular route should not exceed a polar surface area of about 120 Å^2. They can be tailored to brain penetration by decreasing the polar surface to <60–70 Å^2. This conclusion is supported by the inverse linear relationship between experimental brain penetration data and the dynamic polar surface area of 45 drug molecules.

Conclusions. The polar molecular surface area is a dominating determinant for oral absorption and brain penetration of drugs that are transported by the transcellular route. This property should be considered in the early phase of drug screening.

KEY WORDS: polar molecular surface area; oral absorption; brain penetration.

INTRODUCTION

Oral absorption of compounds is a crucial issue in drug discovery research. Although our current understanding of the factors and mechanisms that determine absorption and bioavailability is still far from complete, it is generally realised that already in the early phases of drug discovery these matters should be taken into consideration. Molecular properties thought to be related to the oral absorption and bioavailability are molecular weight, number of hydrogen bond acceptors, lipophilicity, etc. (1).

Recently, a paper was published (2) on the prediction of passive transcellular intestinal absorption of drugs in humans as a function of their calculated polar molecular surface area. A satisfactory sigmoidal relationship between the absorbed fraction after oral administration and the dynamic polar molecular surface area was found for twenty structurally diverse drugs. The polar molecular surface area is defined as the surface area (Å^2) occupied by nitrogen and oxygen atoms, and polar hydrogens bonded to these heteroatoms. The dynamic polar surface is the Boltzmann averaged polar surface over a representative conformational sampling of the drug molecule.

We have validated this relationship by extending the series with yet another twenty compounds and found a similar sigmoidal relationship (results not shown). Our results concur the conclusions by Palm *et al.* (2) that orally administered drugs with large polar molecular surface areas (>120 Å^2) are hardly absorbed by the passive transcellular route, while drugs with a small polar molecular surface area (<60 Å^2) are almost completely absorbed. In both studies, drugs were excluded that suffer from poor water solubility, extensive metabolism in the intestine, or compounds that are absorbed paracellularly or transported by intestinal carriers.

Prediction of passage across the blood-brain barrier is of importance for centrally acting drugs or for peripherally acting drugs that should be devoid of CNS side-effects. In the current study we examined the relationship between the logarithm of brain/blood concentration ratios at steady-state conditions with the polar molecular surface area. It was already demonstrated (3) for a limited series of 20 compounds, that brain penetration at equilibrium decreases on increasing the hydrophilic part of the van der Waals surface (SP). In this study the molar volume was added as an extra descriptor to improve the correlation.

The objective of the current study is to explore the role of the polar molecular surface as a determinant for transport of drugs over the blood-brain barrier. Two strategies were followed. In the first one the polar molecular surfaces were calculated for 45 compounds for which the log (C_{brain}/C_{blood}) steady-state distribution values have been determined quantitatively. As independent validation we selected a set of 776 orally administered CNS active drugs, analysed their polar surfaces and made a comparison with a set of 1590 orally administered non-CNS active drugs. We will show that the polar molecular surface is an important and easy to calculate descriptor for transport over the blood-brain barrier.

METHODS

Selection of Drugs

Table 1 lists the log (C_{brain}/C_{blood}) steady-state distribution values in rats for a series of radiolabelled reference and Organon compounds (compounds 2–12 and 22) combined with similar data from the literature (4,5,6,7,8,9). All 45 compounds from Table 1 are assumed to enter the brain by passive transcellular diffusion.

Animal Management and Sample Treatment

Male Wistar rats, weighing 180–220 g were used. The animals were housed at room temperature (22 ± 2°C), and fed on standard rat food. Water was supplied ad libitum.

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Table 1. Brain Penetration Data and Calculated Polar Surface Areas for 45 Drug Molecules.

Compound	log (C_{brain}/C_{blood})	Dynamic polar surface (Å^2)	Static polar surface (Å^2)
1. desipramine	1.00	13.02	15.57
2. imipramine	1.05	5.21	5.19
3. mianserin	0.99	6.55	5.19
4. amitriptyline	0.98	4.19	5.13
5. Org 4428	0.82	24.19	21.15
6. Org 5222	1.03	11.02	10.41
7. Org 12962	1.64	23.45	27.51
8. Org 13011	0.16	36.68	30.93
9. Org 32104	0.52	32.67	32.73
10. Org 30526	0.39	19.97	22.89
11. mirtazapine	0.53	17.01	12.63
12. tibolone	0.40	31.75	36.57
13. clonidine	0.11	41.52	35.37
14. carbamazepine	0.00	39.96	42.63
15. epoxide of 14	−0.33	52.79	52.29
16. cimetidine	−1.42	67.83	78.21
17. ranitidine	−1.23	72.16	65.91
18. mepyramine	0.49	24.77	20.43
19. icotidine	−2.00	83.56	72.21
20. lupitidine	−1.06	75.75	69.99
21. domperidone	−0.78	68.57	68.55
22. Org 34167	0.00	40.14	45.03
23. risperidone	−0.02	57.32	45.63
24. 9-OH-risperidone	−0.67	74.28	62.61
25. L-663581	−0.30	60.70	55.05
26. M1L-663581	−1.34	77.62	74.79
27. M2L-663581	−1.82	94.62	92.55
28. temelastine	−1.88	75.70	67.53
29. SKF-93619	−1.30	64.09	59.85
30. compound 30	−1.17	74.49	80.61
31. compound 31	−0.67	66.19	69.87
32. compound 32	−0.66	66.97	70.47
33. compound 33	−1.15	90.11	102.81
34. compound 34	−1.57	97.42	98.01
35. compound 35	−1.12	67.23	71.79
36. compound 36	−0.73	63.79	67.05
37. compound 37	−0.27	68.73	71.37
38. compound 38	−0.28	70.71	71.61
39. compound 39	−0.46	40.49	34.83
40. compound 40	−0.24	36.57	29.37
41. compound 41	−0.02	29.86	31.83
42. compound 42	0.69	31.10	31.11
43. compound 43	0.44	30.10	34.59
44. zolantidine	0.14	30.16	33.45
45. compound 45	0.22	38.32	41.55

Radiolabelled drugs were given orally, as suspension, through gastric probes. At fixed time points after the dose heparinized blood samples were taken from the carotid artery. Samples were stored at approximately −20°C until used for analysis. Brains were perfused via the aorta with cold saline until they were free of blood within one minute, thereafter the brains were removed from the skulls. Brain samples were cut up and homogenized in methanol. The brain homogenates were centrifuged at approximately 15 000 N · Kg^{-1} for 5 minutes. Supernatants were stored at approximately −20°C until used for analysis.

Chromatography by HPLC analysis was performed after pretreatment of the collected blood and brain samples. The eluting radioactivity was determined off-line or on-line through liquid scintillation counting. Peak area of the parent compound in the chromatograms were used for calculation of the C_{brain}/C_{blood} ratio.

Molecular Surface Area Calculations

The 3D structures of the selected compounds were energy minimised starting from the Corina-built structures (10). All molecules were built in their neutral forms. Minimisation and molecular dynamics simulations were performed using the CHARMm program as implemented in Quanta 97 (11). Point charges were assigned to all atoms by using the charge template method in Quanta. A distance dependent dielectric $\varepsilon = R$ was used for all electrostatic interactions. The adopted-basis Newton-Raphson minimiser was continued until the root-mean-square energy gradient was lower than 0.001 kcal/(mole · Å). Subsequently, the system was heated to 1000 K. After a short equilibration of 1 psec a trajectory of 100 psec was calculated applying a time step of 1 fsec. The conformations at 1, 2, 3, etc. psec were stored and energy minimised, after which the polar surface area was calculated using the built-in CHARMm routines. The van der Waals surface area was calculated and split into polar and nonpolar areas. The parts of the surface area associated with nitrogen and oxygen atoms, and hydrogens bonded to these heteroatoms are considered to be polar. The surface area has been calculated as a Boltzmann average in which the polar surface area of each of the 100 low energy conformations is weighted by its probability of existence.

For the large series of compounds of orally administered CNS and non-CNS active drugs the static polar surface is calculated from the Corina-built structures with the in-house developed program Monika (12).

Statistical Analysis of CNS Drugs

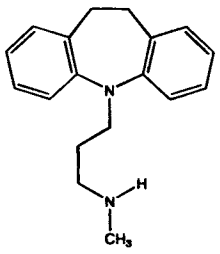
A subset of 776 orally administered CNS active drugs was extracted from our in-house database drugsfile which contains 14000 drugs from the literature. Selection criteria were that the CNS compounds are transported passively through the blood-brain barrier and that they have entered at least Phase II clinical efficacy studies. The static polar surface area was calculated from the Corina-built structures. The frequency distribution was generated as a histogram with the Unistat program (13).

RESULTS AND DISCUSSION

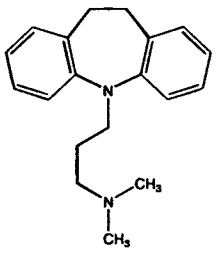
Figure 1 shows the correlation between the log (C_{brain}/C_{blood}) values and the dynamic polar surface as calculated with the CHARMm script described in the methods section. The correlation clearly shows that brain penetration decreases when the polar surface area increases. The isosteric replacement of a methine group in mianserin by nitrogen in mirtazapine increases the polar surface and decreases the observed log (C_{brain}/C_{blood}) value (compare compounds 3 and 11 in Fig. 1). The desmethyl derivative of Org 5222, Org 30526 is more polar according to the rules which explains the lower brain penetration (compare compounds 6 and 10 in Fig. 1). The same is true when the desmethyl compound of Org 4428, Org 32104, is compared with its parent compound (compounds 5 and 9 in

Table 2. Molecular Structures of the 45 Compounds used in Table 1 and Figures 1 and 2

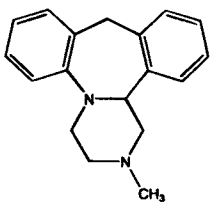
1. desipramine



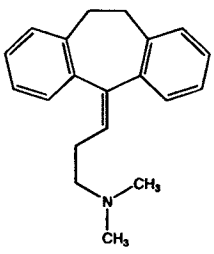
2. imipramine



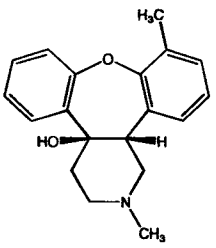
3. mianserin



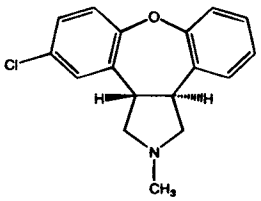
4. amitriptyline



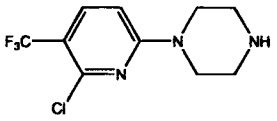
5. Org 4428



6. Org 5222



7. Org 12962



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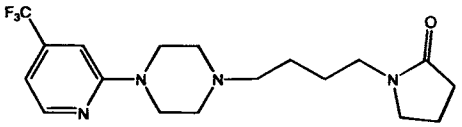
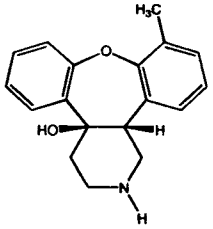
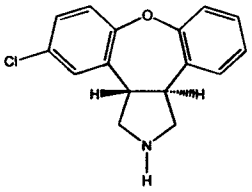


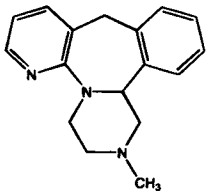
9. Org 32104



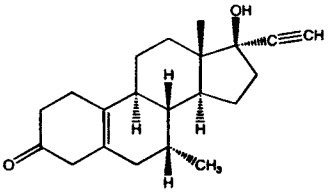
10. Org 30526



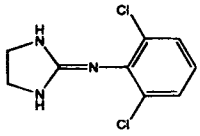
11. mirtazapine



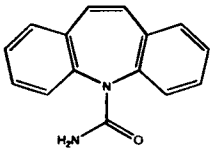
12. tibolone



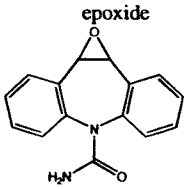
13. clonidine



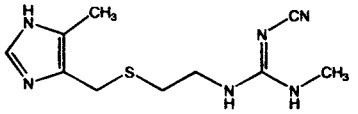
14. carbamazepine



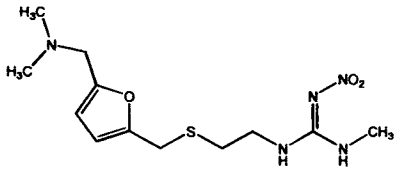
15. carbamazepine epoxide



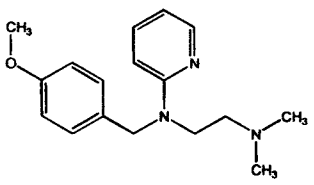
16. cimetidine



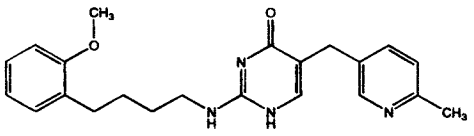
17. ranitidine



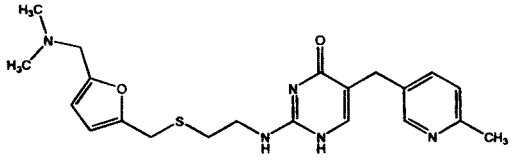
18. mepyramine



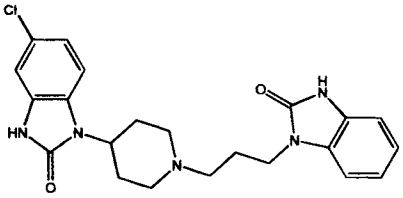
19. icotidine



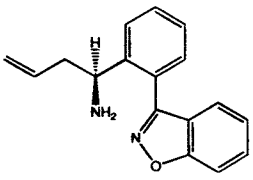
20. lupitidine



21. domperidone



22. Org 34167



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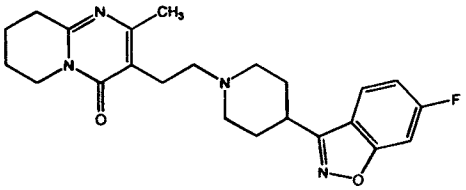

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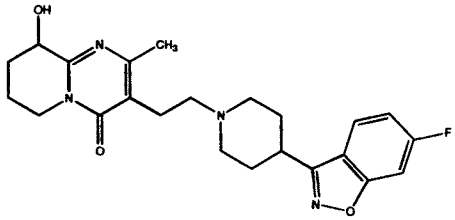
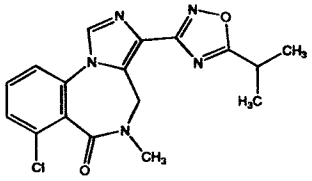


25. L-663581



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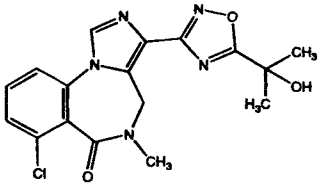

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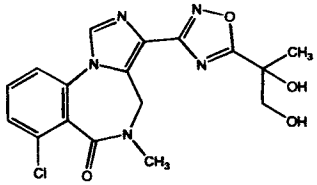

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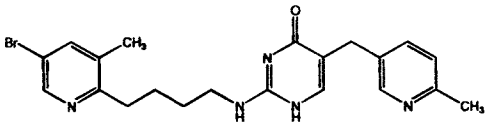

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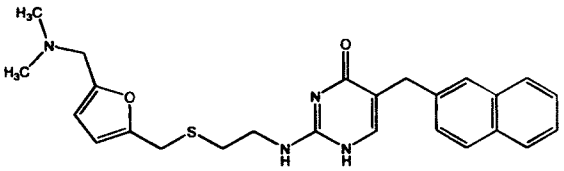

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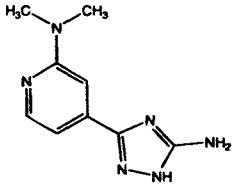

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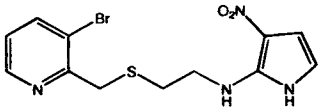

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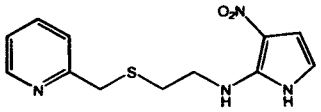

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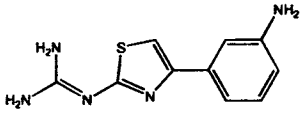

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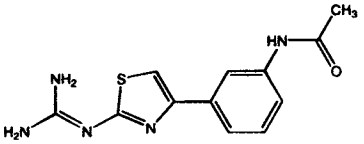

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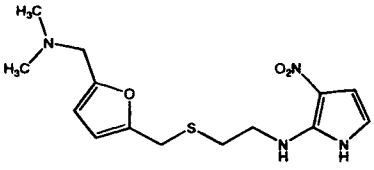

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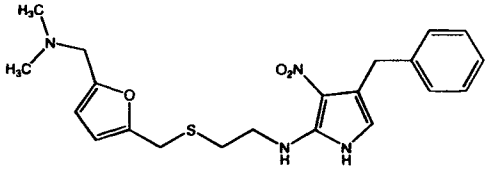
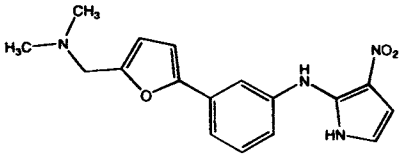
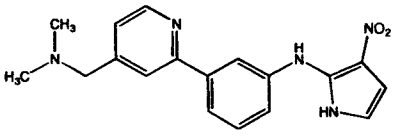


37. compound 37



38. compound 38



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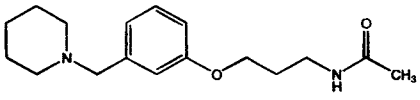
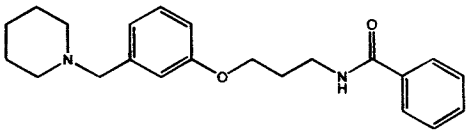


40. compound 40



41. compound 41

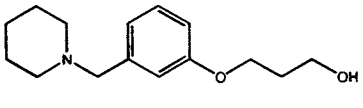


Table 2. Continued

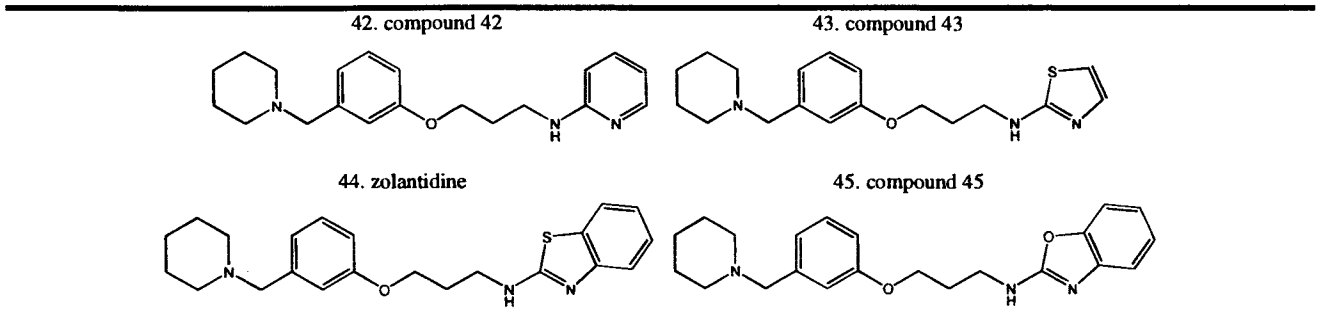


Fig. 1). The difference in brain penetration between imipramine (compound 2) and desipramine (compound 1) is much less, but in this region of Fig. 1 one might expect a more sigmoidal flattening of the curve. The epoxide of carbamazepine (compound 15) is more polar than carbamazepine (compound 14) and behaves as expected. The difference in distribution between risperidone (compound 23) and its 9-hydroxy metabolite (compound 24) is explained by the higher polar surface of the metabolite. The same holds for L-663581 (compound 25) and the two hydroxy metabolites M1L-663581 (compound 26) and M2L-663581 (compound 27). Org 12962 (compound 7 in Fig. 1) distributes much more to the brain than expected from its polar surface and is the only serious outlier in the range of compounds with high brain penetration. Other deviations from the calculated regression line typically distribute poorly to the brain. The possibility exists that the measured log (C_{brain}/C_{blood}) values are influenced by experimental difficulties, especially when the concentration in the rat brain is low. The correlation between the steady-state log (C_{brain}/C_{blood}) values and the static polar surface area calculated with the Monika program basically gives the same result, although the correlation is somewhat poorer ($R = 0.883$). Figure 2 shows the correlation between the dynamic polar surface area and the static polar surface area calculated for the 45 drug molecules. A variety of additional calculated properties such as molar weight, molecular volume, logP (14), dipole moment, apolar surface, etc., were examined by multiple regression analysis but none of these descriptors contributed significantly after the polar surface area entered the stepwise regression analysis.

From Fig. 1 it can be concluded that orally administered CNS active drugs should have a polar surface area <60 Å^2. This conclusion is confirmed by Fig. 3 where the polar surface of 776 orally administered CNS drugs is analysed. The frequency distribution in Fig. 3 shows that by far the most CNS active drugs that penetrate the brain by passive absorption have polar surface areas below 70 Å^2. Figure 4 shows that for most orally administered non-CNS active drugs the polar surface may display much larger values up to 120 Å^2. Apparently the blood-brain barrier forms an extra constraint for orally administered compounds reaching the brain, diminishing the maximal polar surface area of CNS-active compounds by approx. 50%.

Although the authors of reference 2 strongly suggest that the surface area should be calculated as a Boltzmann average in which the polar surface area is weighted by its probability of existence, our experience is that in most cases one reasonably

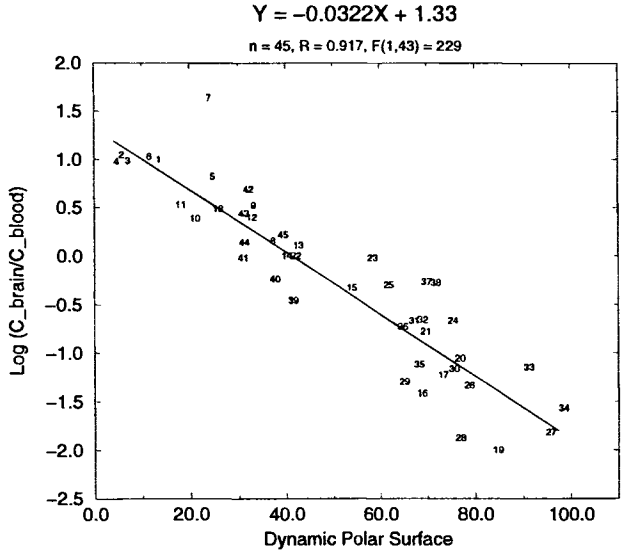


Fig. 1. Linear relationship between brain penetration and dynamic polar surface area (Å^2) of 45 drugs.

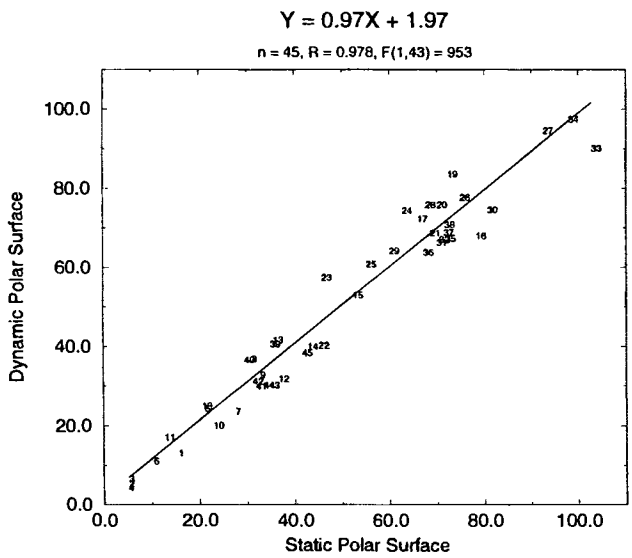


Fig. 2. Comparative plot between dynamic polar surface area (Å^2) and static polar surface area (Å^2) of 45 drugs.

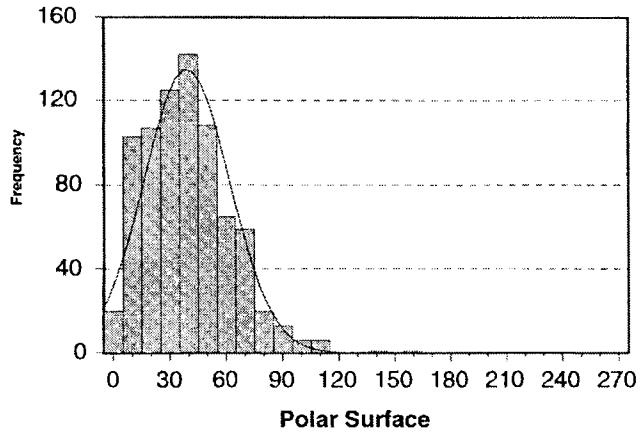


Fig. 3. Distribution of the polar surface area (Å^2) for 776 orally administered CNS drugs that have reached at least Phase II efficacy studies.

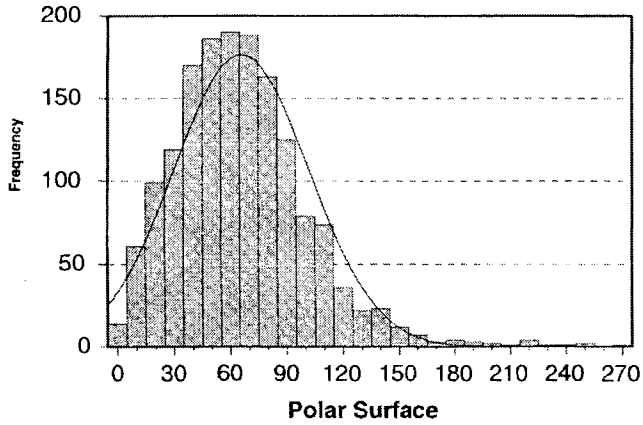


Fig. 4. Distribution of the polar surface area (Å^2) for 1590 orally administered non-CNS drugs that have reached at least Phase II efficacy studies.

well built three-dimensional structure gives a "static" polar molecular surface area which is close to the value of the dynamic polar surface area (Fig. 2). The polar surface is not very dependent on the conformation; only in the case of a hydrophobic collapse or strong intramolecular interactions, some differences may be observed.

CONCLUSIONS

Incorporation of relevant physicochemical compound properties in the early phases of drug discovery and lead optimisation is an important issue. Intestinal absorption of orally administered drugs is a critical issue in obtaining therapeutic levels. Passage through the blood-brain barrier is another key issue for CNS active drugs. We have shown and confirmed that the polar molecular surface area is an important descriptor for both passive transport routes. It is found that orally active drugs that are transported passively by the transcellular route should not exceed a polar surface of about 120 Å^2. They can be tailored to brain penetration by decreasing the polar surface (<60–70 Å^2). The ease of computation of the polar surface for any type of drug makes this important descriptor highly suited to be considered in the early phase of drug screening.

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