Analyzing molecular polar surface descriptors to predict blood-brain barrier permeation

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Introduction

Permeation of active drugs across the vascular brain endothelium into the central nervous system (CNS) is controlled by the blood-brain barrier (BBB). The BBB separates the bloodstream from the brain. Characteristics of the BBB are the restriction of paracellular substance permeation across the endothelium by intercellular tight junctions, the lack of cellular fenestrae and reduced pinocytosis (van Bree *et al*., 1992). In contrast to several endogenous hydrophilic nutrients (glucose, amino acids, etc...), which are transported by carrier-mediated mechanisms across the brain endothelium, the BBB prevents the entry into the CNS of the majority of polar drugs (Geldenhuys *et al*., 2010).

Some molecular quantities like polar surface (PS) descriptors are of key interest to medicinal chemists to predict the BBB permeation fate for different drug-like chemical compounds. The descriptors commonly used to account for polarity are the so-called polar surface descriptors, such as two-dimensional polar surface area (2D-PSA), topological polar surface area (TPSA) and three-dimensional polar surface area or polar area (3D-PSA, PA) (Kelder *et al*., 1999). The last has to be calculated with time consuming quantum-mechanical methods usually providing better results.

We report the prediction of the BBB permeation by analyzing polar surface descriptors of various CNS-active/inactive compounds to find a strong correlation of these descriptors with logBB values using the linear partial least squares (PLS) fitting technique. In the case of effective CNS- acting drugs, the understanding of permeation mechanism through the BBB is pivotal to filter potential leads and to estimate and diminish the various neurotoxic side-effects.

Materials and Methods

A good *in silico* model is based on good data sets; therefore, all necessary information regarding the chemical structures and experimental logBB values for 19 diverse drugs was taken from the literature (Kelder *et al*., 1999). All data sets contained the blood/brain concentration ratios taken as steady-state distribution values of rat model measurements.

The logBB ranged from -2.0 to 1.0 were either brain-penetrating (logBB ≥ 0.5), have moderate permeation (logBB from 0.0 to 0.5), possess little ability to cross the blood-brain barrier (logBB > -0.3) or demonstrate very little permeation (logBB < -0.3).

The three-dimensional structure of the corresponding molecules was built and minimized using the Spartan'10 general purpose molecular modeling tool. 2D-PSA (Spartan'10 calculated descriptor) was mainly defined as the area associated with oxygen, nitrogen and hydrogens attached to these polarizing atoms.

Finally, the root mean square difference (RMSD), an indication of the average error in the analysis; the square of the correlation coefficient (R^2), an indication of the quality of fit of all the data to a straight line were also calculated and compared for all the descriptors.
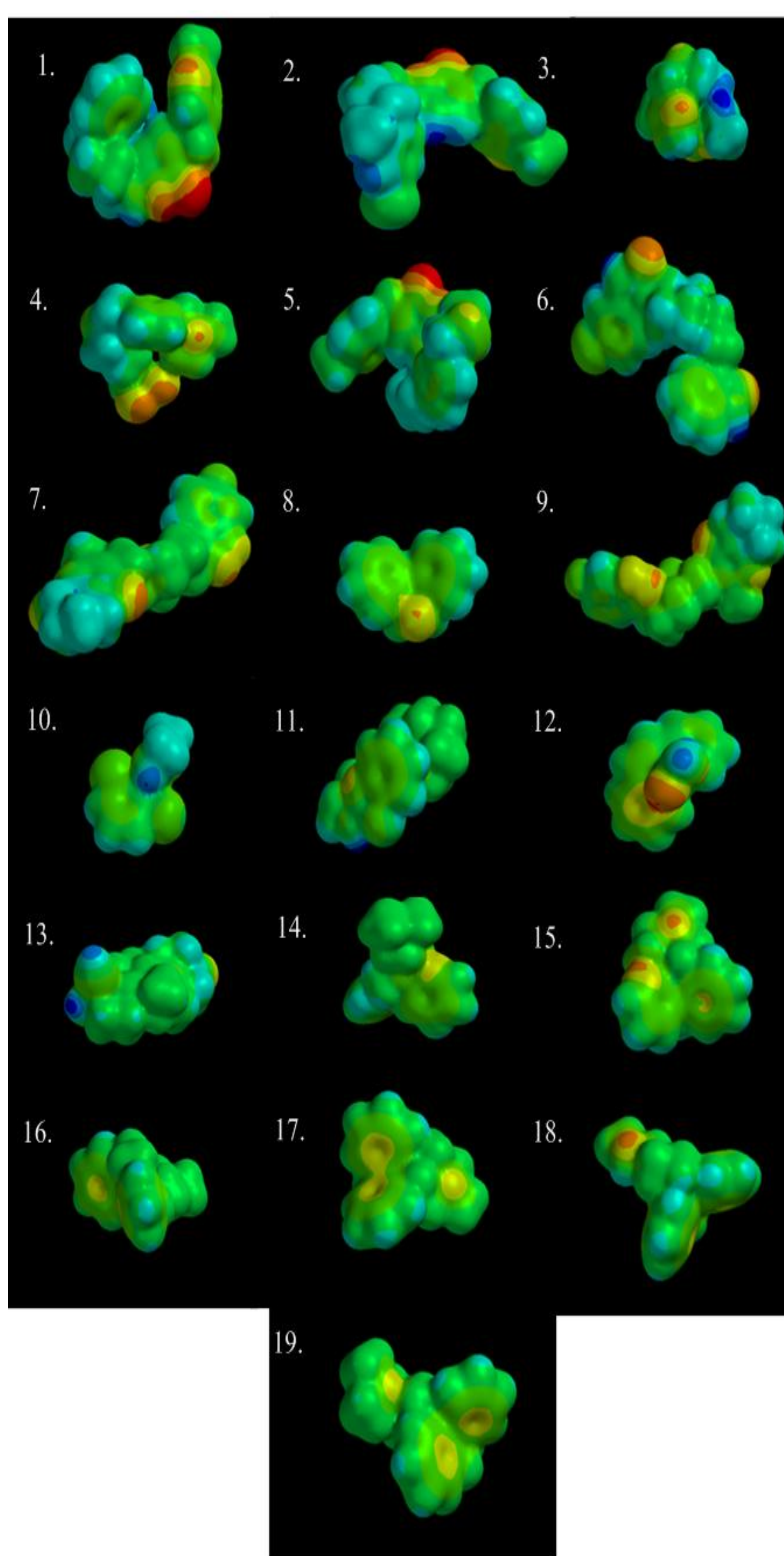

Figure 1 Electrostatic potential maps (3D-PSA) for 19 CNS-active/inactive diverse chemical compounds. Electrostatic potential maps correspond roughly to conventional space-filling models and overall sizes, and shapes were that of the electron densities. The colors indicate the value of the electrostatic potential. Red colors designate areas of negative potential (where a positive charge is most likely to be attracted), while blue colors depicted the areas of positive potential.
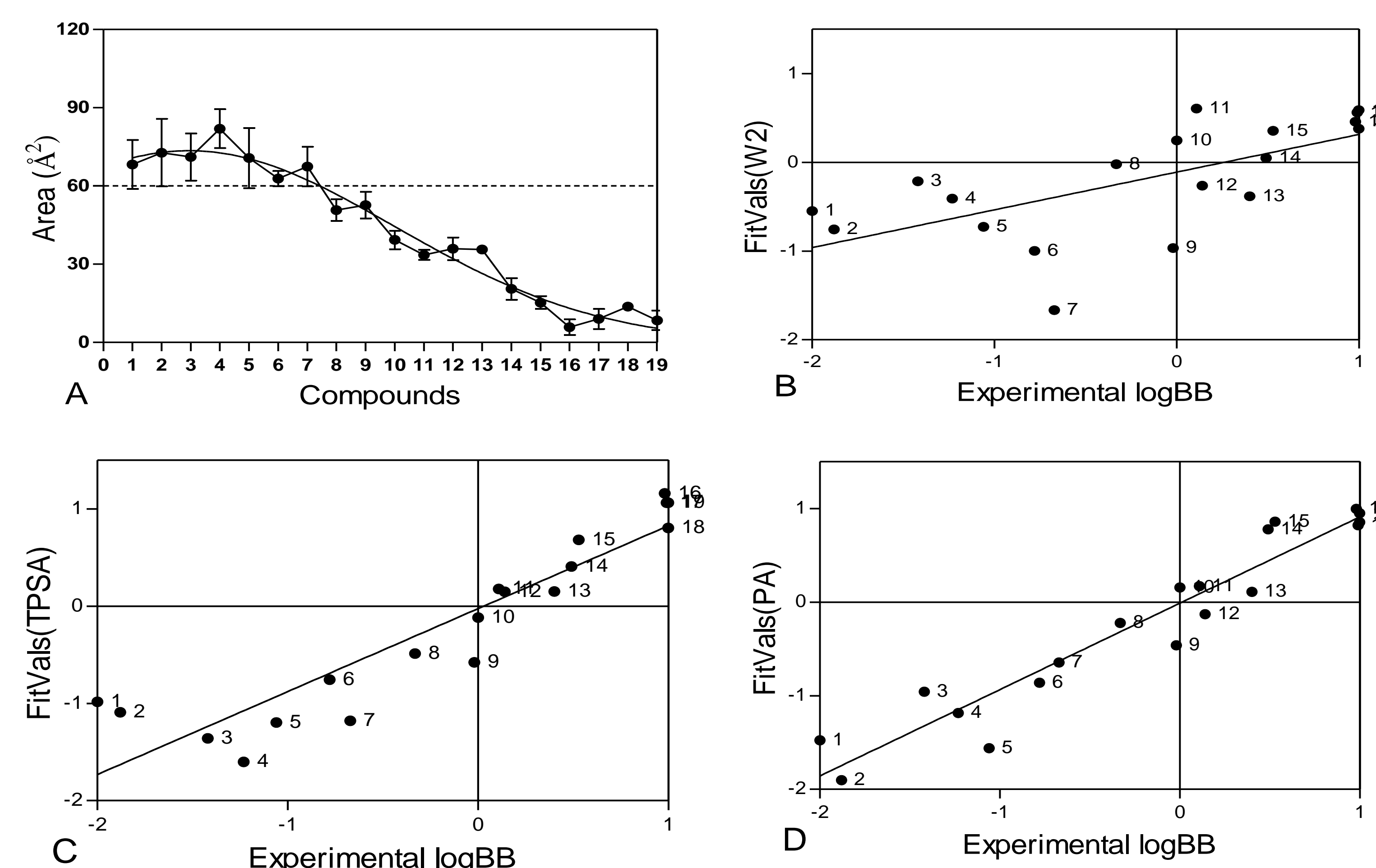
Results

Figure 2 (A) Comparing the overall polar surface descriptors against each others. The descriptors are highly correlated. There are BBB- and BBB+ clusters defined by the area threshold (60 Å). Plots of experimental logBB values versus calculated fit variables of polar surface descriptors are shown (**B-D**).
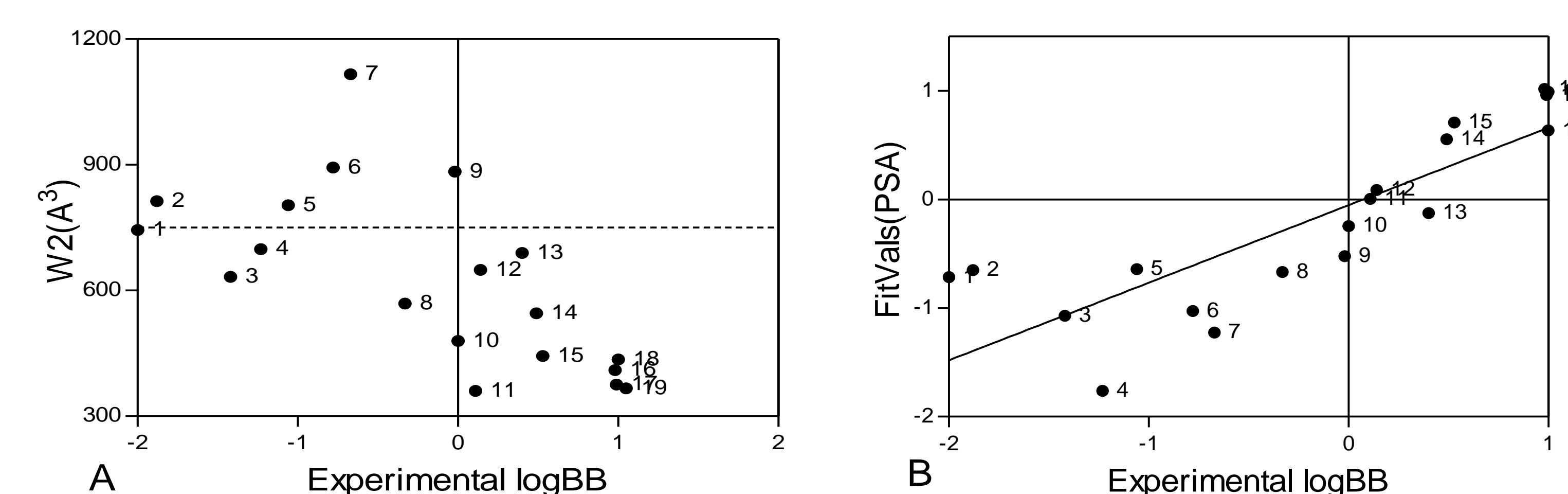

Figure 3 Relationships between experimental logBB and calculated hydrophilic volume (W2) descriptor **(A)** and its fit values **(B)**. The correlation clearly shows that W2 increases when the brain penetration decreases.

Conclusions

To function as a successful CNS-active molecular compound, a pivotal requirement for a molecule is the transport across the BBB. Our study shows that after accurate calculation of the electrostatic potential maps, the theoretically calculated PS descriptors, which were used to examine the transportation mechanisms that enable molecules to penetrate the BBB, are important descriptors. We also report the strong correlation of these descriptors with logBB values for the BBB permeation prediction using the linear partial least squares fitting technique. These findings are in accordance with recently published results and favorably compared with previous experimental studies. Some discrepancies, however, in the present analysis were due to the fact that some chemical substances are substrates of CYP3A4 and efflux transporters (mainly P-gp), which additionally restricts the access of various pharmacologic agents and xenobiotics to the CNS. Finally, we believe that the obtained results demonstrate that all introduced descriptors possess a valuable predictive potential; and a more robust prediction of the BBB permeation could be obtained from BBB data measured (as logBB or logPS) for compounds permeating by a purely passive mechanism.

Bibliography

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