Supporting information

cΔlog \( k_w^{IAM} \): can we afford estimation of small molecules’ blood-brain barrier passage based upon \textit{in silico} phospholipophilicity?

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| Table S1. Definition of the physico-chemical descriptors reported in the manuscript |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Descriptor                     | Definition                                                                                                                                                                                                                                                                 |
| miLogP                         | octanol-water partition coefficient (log P) calculated by Molinspiration Cheminformatics (1)                                                                                                                                                                                                 |
| Heavy Atoms                    | Number of heavy atoms                                                                                                                                                                                                                                                                                                                   |
| HLB\(_M\)                      | Mean of HLB\(_{PSA}\) values, HLB values calculated according to Griffin’s method(2) and HLB values calculated according to Davies’s method(3)                                                                                                                                   |
| HLB\(_{PSA}\)                  | hydrophilic-lipophilic balance (HLB) calculated according to the following: \( HLB_{PSA} = 20 \times \frac{PSA}{Surface} \) in which PSA is the polar surface area and Surface is the total surface                                                                                                                                         |
| Rotatable bonds                | Number of rotatable bonds                                                                                                                                                                                                                                                                                                             |
| TPSA(NO)                       | topological polar surface area using N,O polar contributions                                                                                                                                                                                                                                                                         |
| ALOGPS\_logP                   | octanol-water partition coefficient (log P) calculated by the software ALOGPS 2.1(4)                                                                                                                                                                                                                                                   |
| nO                             | Number of oxygen atoms                                                                                                                                                                                                                                                                                                                  |
| TPSA(Tot)                      | topological polar surface area using N,O,S,P polar contributions                                                                                                                                                                                                                                                                      |
| nROH                           | number of hydroxyl groups                                                                                                                                                                                                                                                                                                              |
Table S2. Descriptors employed in the multiple linear regression.

| Molecule                          | nROH | TPSA(Tot) | ALOGPS_logP |
|-----------------------------------|------|-----------|-------------|
| 1,1,1-trichloroethane             | 0    | 0         | 2.45        |
| 1,2-dimethylbenzene               | 0    | 0         | 3.16        |
| 1,4-dimethylbenzene               | 0    | 0         | 3.15        |
| 1,7-dimethylxanthine              | 0    | 72.68     | -0.63       |
| 1-chloro-2,2,2-trifluoroethane    | 0    | 0         | 1.82        |
| 1-Hydroxymidazolam                | 1    | 50.41     | 3.09        |
| 2,2-dimethylbutane                | 0    | 0         | 3.74        |
| 2-methylpentane                   | 0    | 0         | 3.6         |
| 3-methylhexane                    | 0    | 0         | 4.18        |
| 3-methylpentane                   | 0    | 0         | 3.98        |
| 4-Hydroxymidazolam                | 1    | 50.41     | 3.05        |
| acetaminophen                     | 0    | 49.33     | 0.51        |
| acetone                           | 0    | 17.07     | -0.29       |
| aminopyrine                       | 0    | 30.17     | 0.94        |
| amobarbital                       | 0    | 75.27     | 1.87        |
| antipyrine                        | 0    | 26.93     | 1.18        |
| Bretazenil                        | 0    | 64.43     | 3.05        |
| cyclohexane                       | 0    | 0         | 3.46        |
| cyclopropane                      | 0    | 0         | 1.56        |
| desmonomethylpromazine            | 0    | 45.2      | 4.28        |
| didanosine                        | 1    | 93.03     | -1.26       |
| Diethylene glycol divinyl ether   | 0    | 27.69     | 1.26        |
| enflurane                         | 0    | 9.23      | 2.24        |
| ethanol                           | 1    | 20.23     | -0.4        |
| ethyl ether                       | 0    | 9.23      | 1.12        |
| ethylbenzene                      | 0    | 0         | 3.27        |
| flunitrazepam                     | 0    | 78.49     | 2.2         |
| Fluroxene                         | 0    | 9.23      | 1.7         |
| halothane                         | 0    | 0         | 2.5         |
| indinavir                         | 2    | 118.03    | 3.26        |
| isobutyl alcohol                  | 1    | 20.23     | 0.6         |
| isoflurane                        | 0    | 9.23      | 2.3         |
| Isopropyl alcohol                 | 1    | 20.23     | 0.04        |
| mesoridazine                      | 0    | 72.69     | 3.83        |
| methoxyfluorane                   | 0    | 9.23      | 2.01        |
| methyl cyclopentane               | 0    | 0         | 3.15        |
| methyl ethyl ketone               | 0    | 17.07     | 0.41        |
| mirtazapine                       | 0    | 19.37     | 2.9         |
| m-xylene                          | 0    | 0         | 3.15        |
| nevirapine                        | 0    | 63.57     | 1.75        |
| N-heptane                         | 0    | 0         | 4.33        |
| N-hexane                          | 0    | 0         | 4.02        |
| nordazepam                        | 0    | 41.46     | 2.79        |
| Substance            | Log P | octanol-water partition coefficient | Vdw partition coefficient |
|----------------------|-------|-------------------------------------|---------------------------|
| Northioridazine      | 0     | 70.5                                | 5.29                      |
| N-pentane            | 0     | 0                                   | 3.41                      |
| Quinidine            | 1     | 45.59                               | 2.82                      |
| Sulforidazine        | 0     | 78.93                               | 4.32                      |
| Teflurane            | 0     | 0                                   | 2.07                      |
| thioridazine         | 0     | 61.71                               | 5.93                      |
| thioxolone           | 0     | 78.68                               | 1.97                      |
| Tiotidine            | 0     | 191.04                              | 0.59                      |
| triazolam            | 0     | 43.07                               | 2.94                      |
| trichloroethylene    | 0     | 0                                   | 2.45                      |
| trifluoperazine      | 0     | 39.65                               | 4.87                      |
| Valproic acid        | 1     | 37.3                                | 2.54                      |
| zidovudine           | 0     | 133.08                              | -0.1                      |

REFERENCES

1. Molinspiration: log P n-octanol-water partition coefficient. [Available from: http://www.molinspiration.com/services/logp.html](http://www.molinspiration.com/services/logp.html).
2. Griffin WC. Calculation of HLB Values of Non-ionic Surfactants. J Soc Cosmet Chem. 1954;5:249-56.
3. Davies J, editor A QUANTITATIVE KINETIC THEORY OF EMULSION TYPE. I. PHYSICAL CHEMISTRY OF THE EMULSIFYING2003.
4. Tetko IV, Tanchuk VY. Application of Associative Neural Networks for Prediction of Lipophilicity in ALOGPS 2.1 Program. Journal of Chemical Information and Computer Sciences. 2002;42(5):1136-45.