

## Supplementary Information for

### Prediction models for brain distribution of drugs based on biomimetic chromatographic data

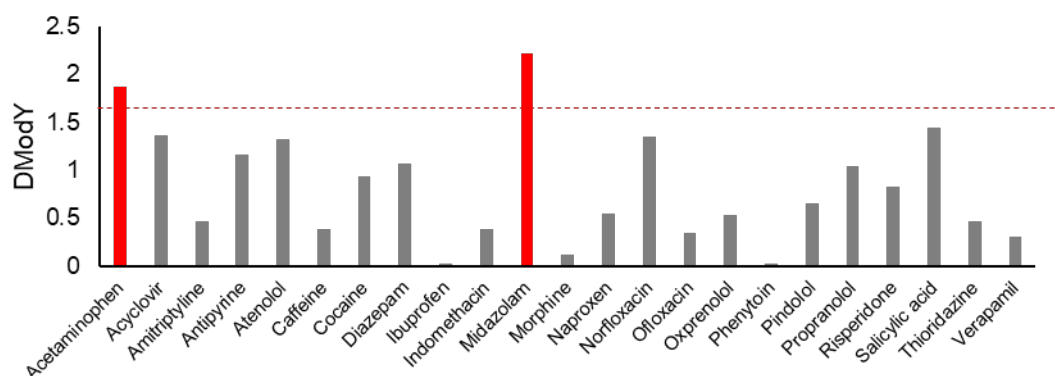
Theodosia Vallianatou, Fotios Tsopelas and Anna Tsantili –Kakoulidou

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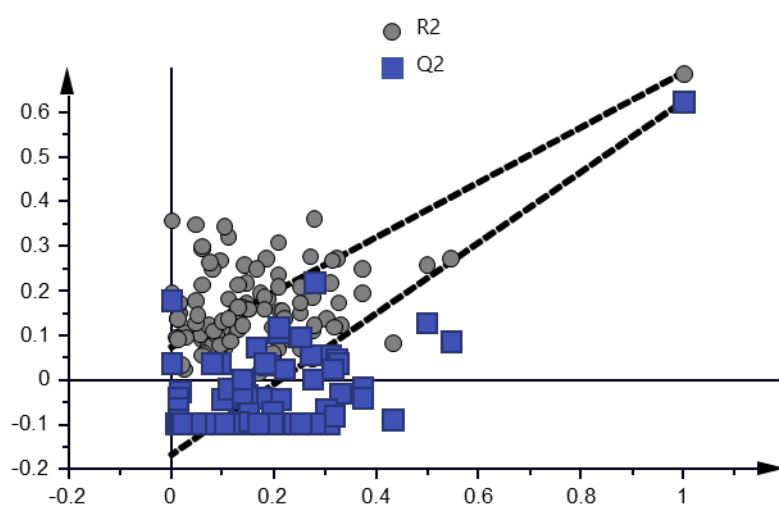
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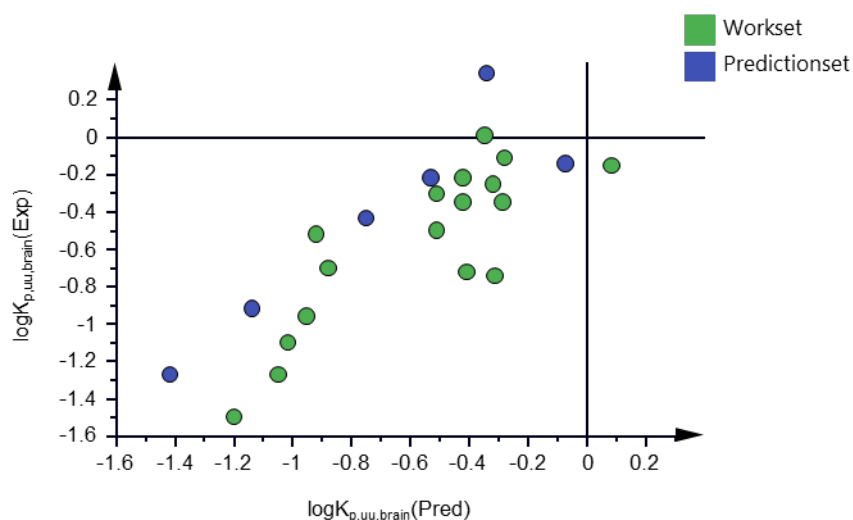
## Supplementary Figures



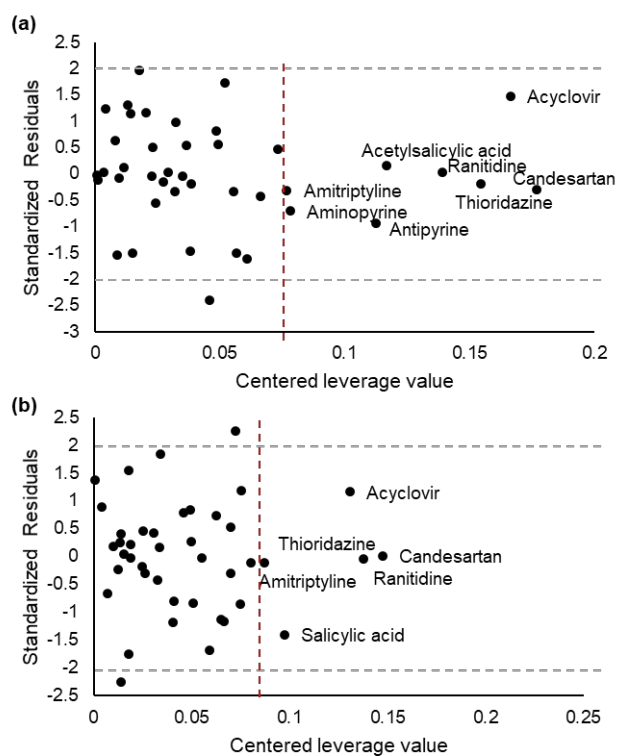
**Figure S1. DmodY bar plot for PLS model 4 of  $\log K_{p,uu,brain}$  including computational descriptors.** The red dashed line indicates the critical limit (1.65). Acetaminophen (1) and midazolam (11) extending it are highlighted with red bars.



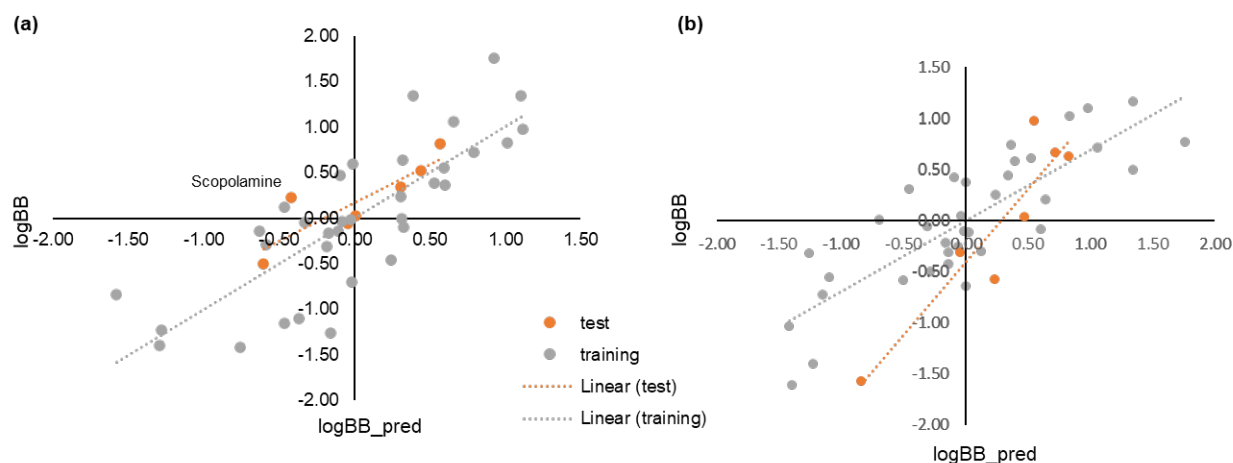
**Figure S2. Permutation test (based on 100 permutations) for the PLS model 4 of  $\log K_{p,uu,brain}$ .**



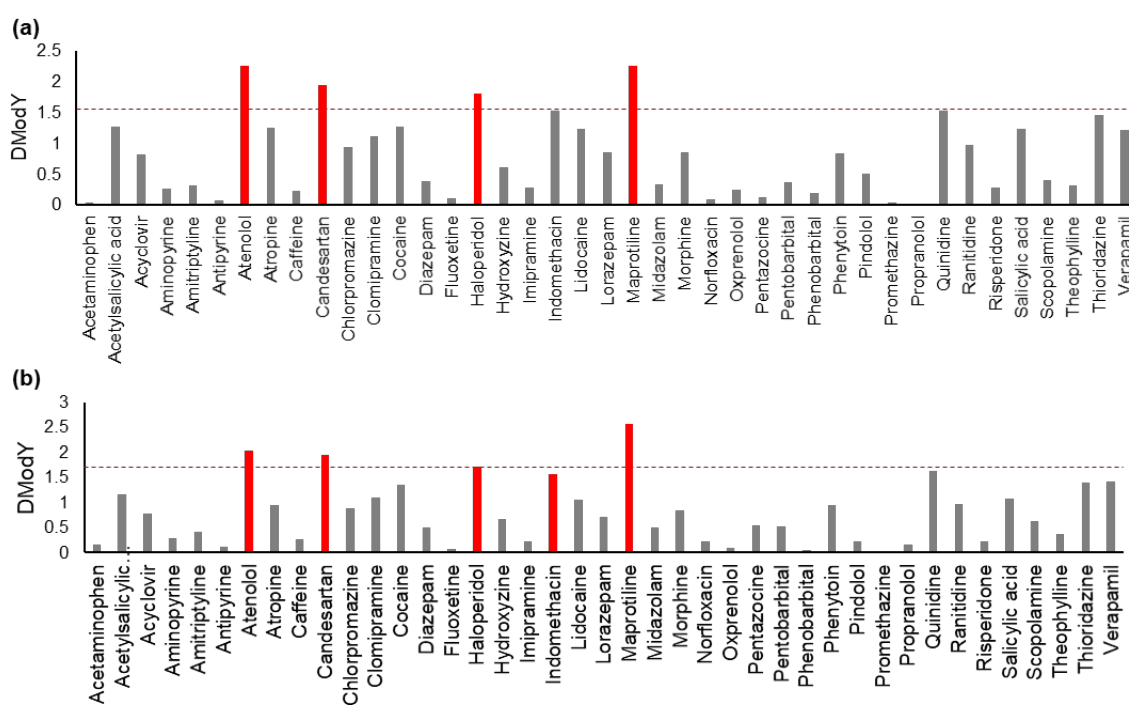
**Figure S3.** Representative plot of observed vs predicted  $\log K_{p,uu,brain}$  values from external validation of PLS model 4.



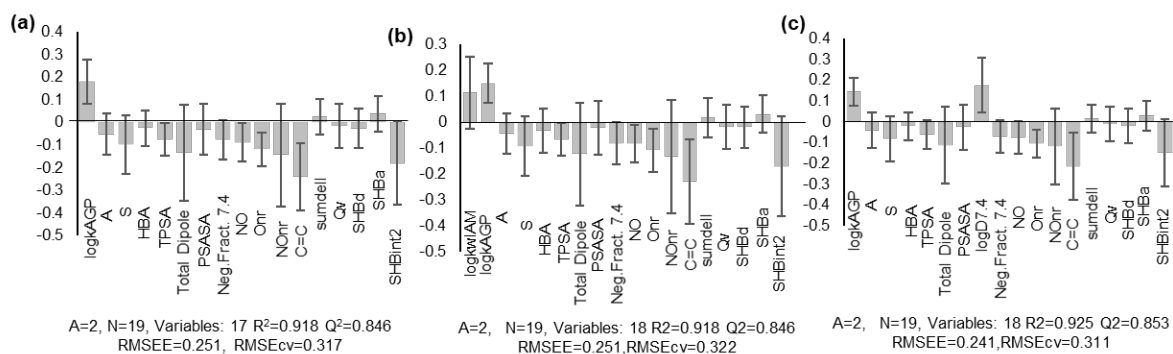
**Figure S4.** Williams plots of standardized residuals versus the leverage; (a) calculated from Eq.1; (b) calculated from Eq.2. Dashed grey lines indicate the  $\pm 2$ \*standard deviation space of the standardized residuals. Dashed red line indicates the  $h^*$  value of each data set.



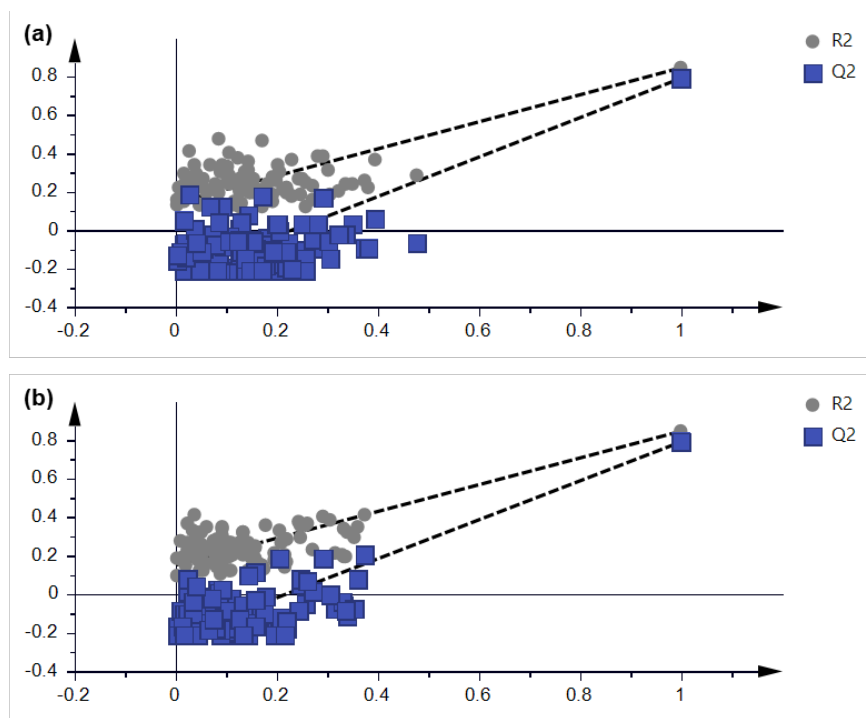
**Figure S5. Representative plot of observed vs predicted logBB values from external validation of (a) Eq. (1); (b) Eq.2.**



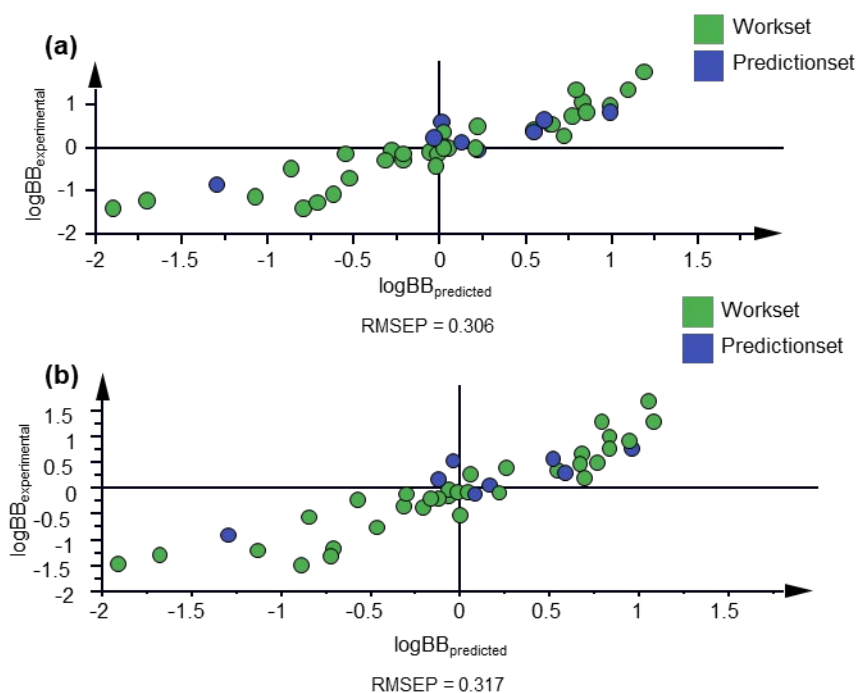
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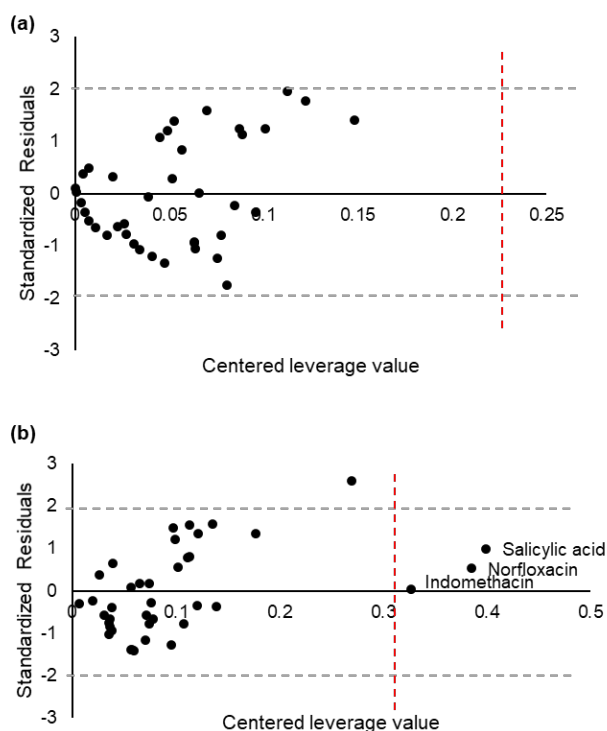
**Figure S7. PLS models of logBB prediction including only the compounds with experimental logK<sub>WAGP</sub> values. (a)** PLS model based only on logK<sub>WAGP</sub> and computational descriptors; **(b)** PLS model based on logK<sub>WAGP</sub>, logK<sub>WIAM</sub> and computational descriptors; **(c)** PLS model based on logK<sub>WAGP</sub>, logD<sub>7.4</sub> and computational descriptors.



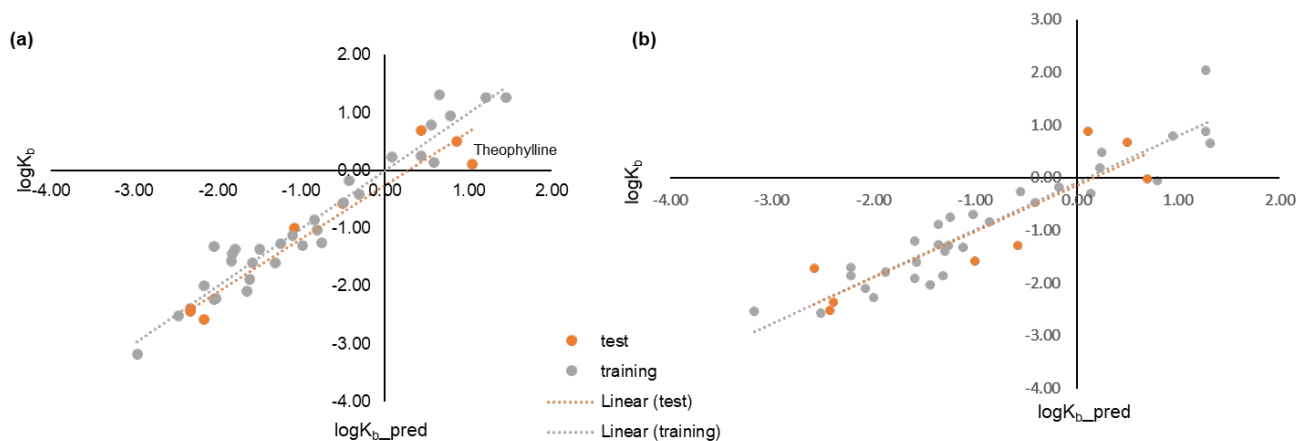
**Figure S8. Permutation tests for the PLS models of logBB prediction. (a)** Permutation test (100 permutations) for the PLS model 5 including IAM retention factors; **(b)** Permutation test (100 permutations) for the PLS model 6 including logD<sub>7.4</sub>.



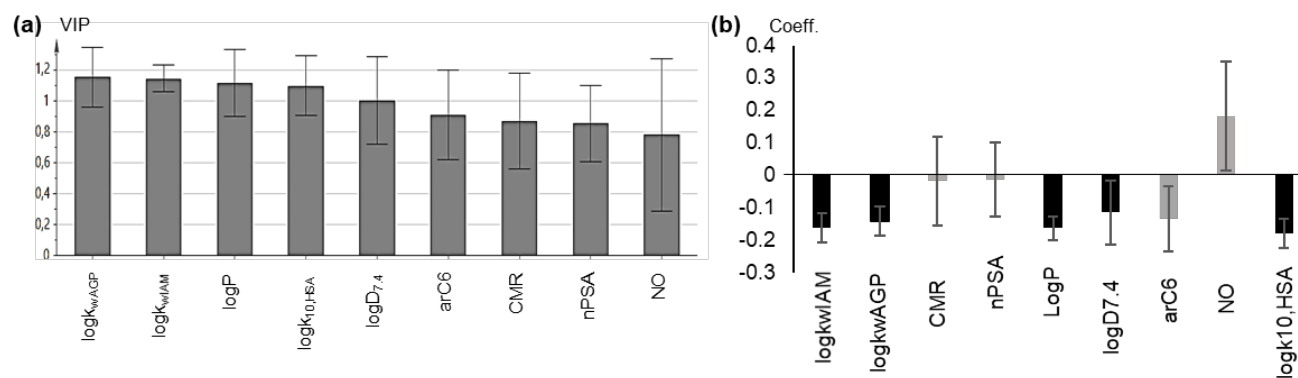
**Figure S9. Representative plot of observed vs predicted logBB values from external validation of PLS model including (a) IAM retention factors/PLS model 5; (b) lipophilicity parameters/PLS model 6.**



**Figure S10. Williams plots of standardized residuals versus the leverage; (a) calculated from Eq.7; (b) calculated from Eq.11. Dashed grey lines indicate the  $\pm 2$ \*standard deviation space of the standardized residuals. Dashed red line indicates the  $h^*$  value of each data set.**

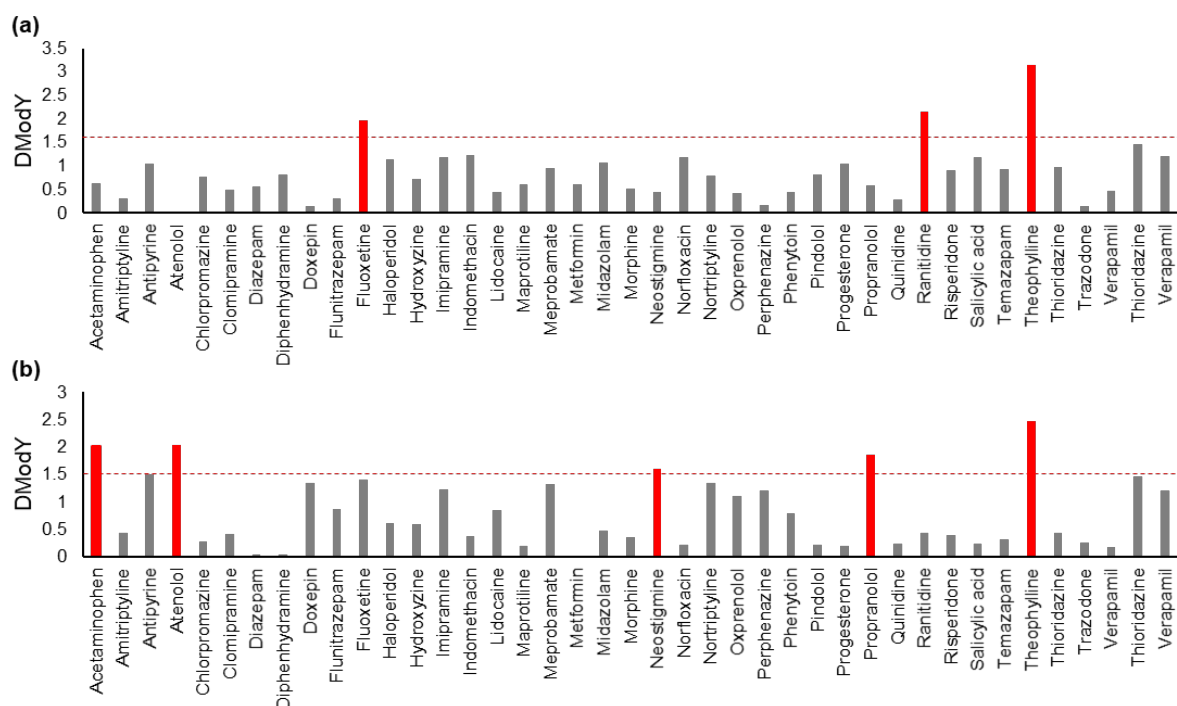


**Figure S11. Representative plot of observed vs predicted  $\log K_b$  values from external validation of (a) Eq. (7); (b) Eq. 11.**

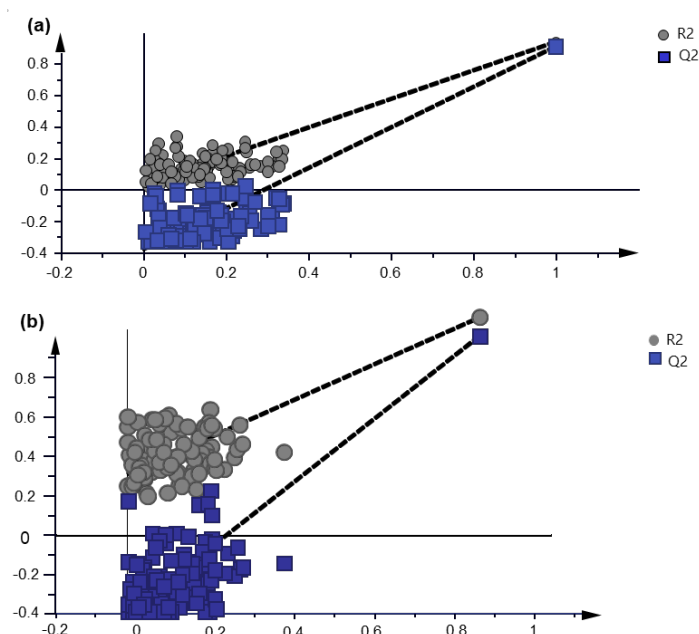


**Figure S12. (a) Variable Importance ranking (b) Coefficient plot of the original variables in the PLS model 7. Original variables with  $\text{VIP} > 1$  are highlighted in black.**

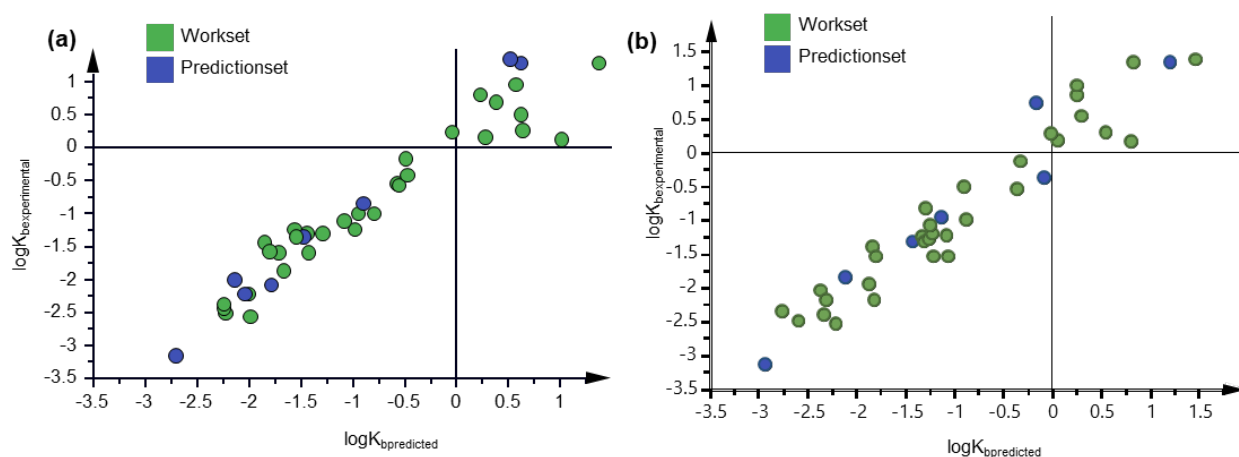




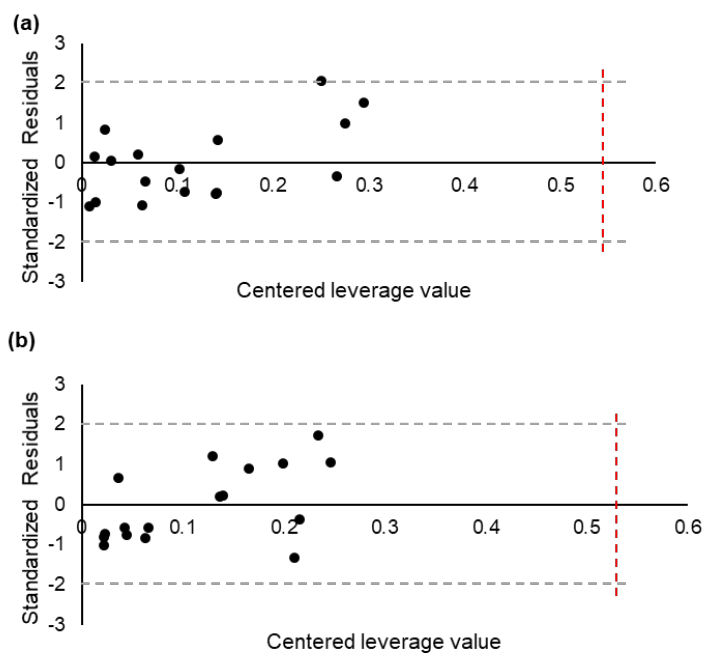
**Figure S13. (a) DmodY bar plot for the PLS model 8 of logK<sub>b</sub> prediction including IAM retention factors. (b) DmodY bar plot for the PLS model 9 of logK<sub>b</sub> prediction including logP and logD<sub>7.4</sub>. The red dashed line indicates the critical limit and the compounds extending it are highlighted with red bars.**



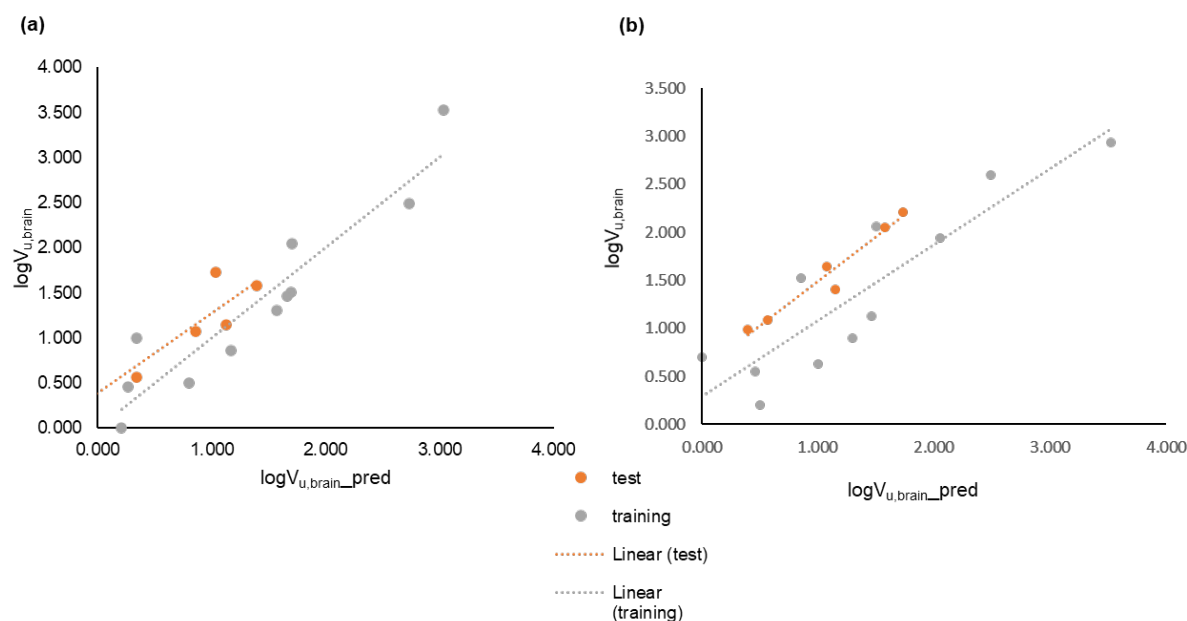
**Figure S14. Permutation tests for the PLS models of logK<sub>b</sub> prediction. (a) Permutation test (100 permutations) for the PLS model including IAM retention factors; (b) Permutation test (100 permutations) for the PLS model including logP and logD<sub>7.4</sub>.**



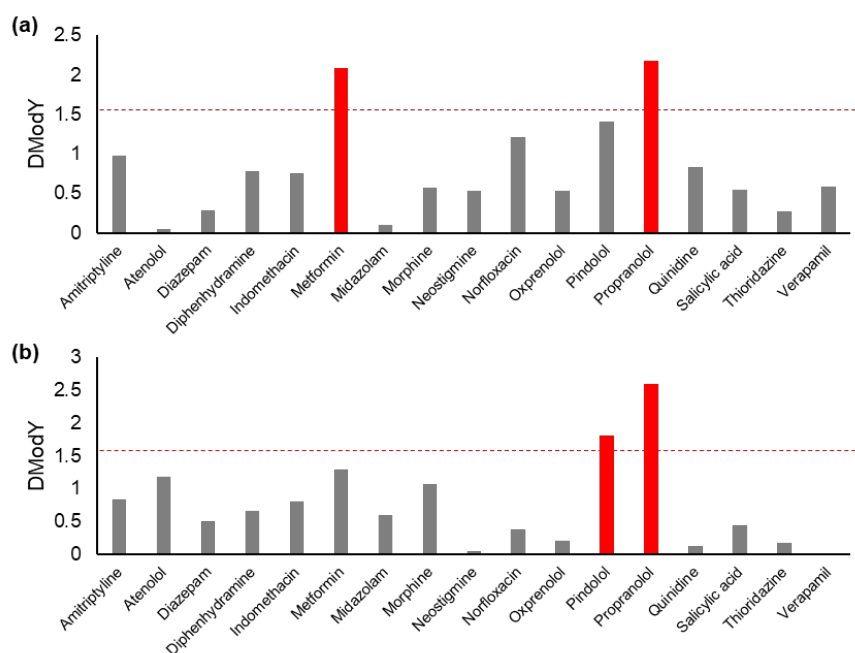
**Figure S15. Representative plot of observed vs predicted  $\log K_b$  values from external validation of PLS model including (a) IAM retention factor- PLS model 8; (b) lipophilicity parameters- PLS model 9.**



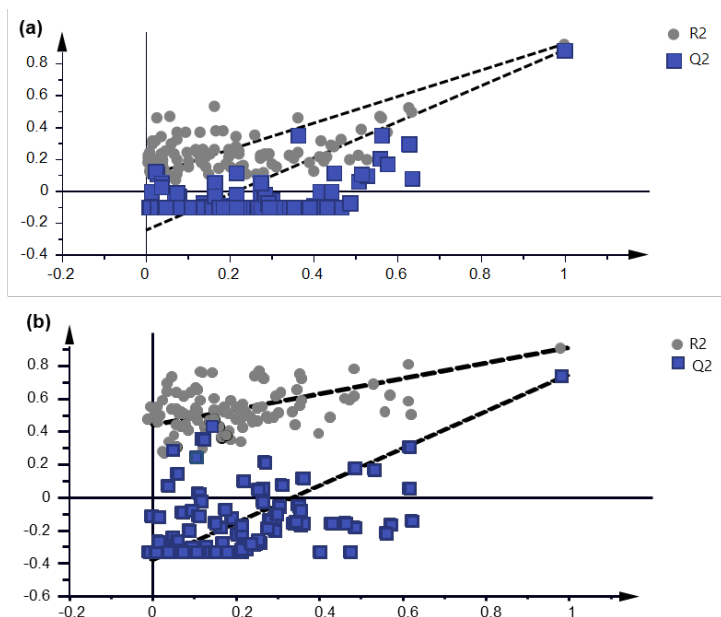
**Figure S16. Williams plots of standardized residuals versus the leverage; (a) calculated from Eq.15; (b) calculated from Eq.17. Dashed grey lines indicate the  $\pm 2$  standard deviation space of the standardized residuals. Dashed red line indicates the  $h^*$  value of each data set.**



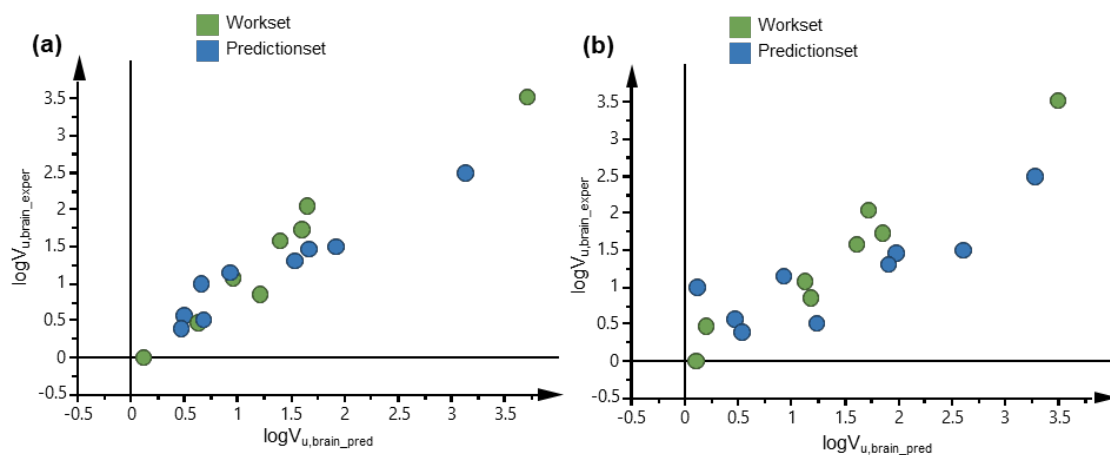
**Figure S17.** Representative plot of observed vs predicted  $\log V_{u,brain}$  values from external validation of (a) Eq. (15); (b) Eq.17.



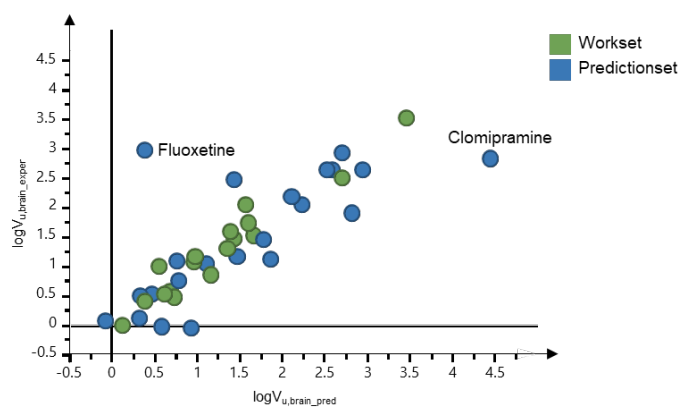
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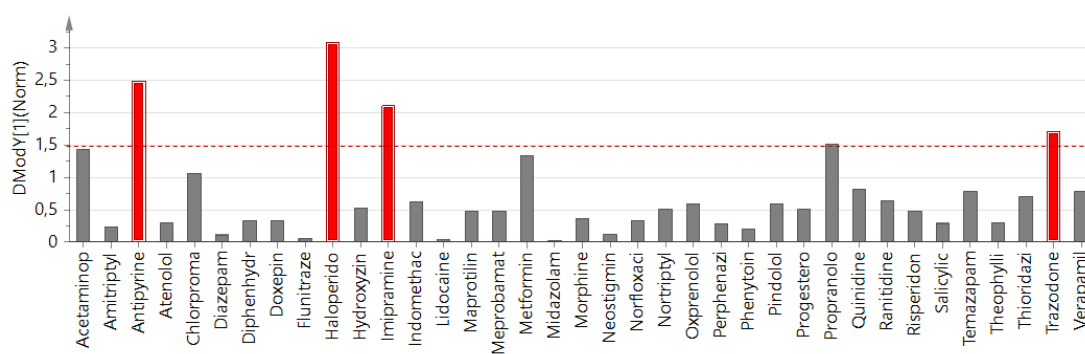
**Figure S19. Permutation tests for the PLS models of  $\log V_{u, \text{brain}}$  prediction. (a)** Permutation test (100 permutations) for the PLS model including IAM retention factors; **(b)** Permutation test (100 permutations) for the PLS model including logP.



**Figure S20. Representative plot of observed vs predicted  $\log V_{u, \text{brain}}$  values from external validation of PLS model including (a)** IAM retention factors- PLS model 10; **(b)** lipophilicity parameters- PLS model 11.



**Figure S21. Plot of observed vs predicted  $\log V_{u,brain}$  values from PLS model 12.** Experimental  $\log V_{u,brain}$  values were used as the training set and  $\log V_{u,brain}$  values predicted from Eq. (13) were used as the test set.



**Figure S22. DmodY bar plot for the PLS model 12 of  $\log V_{u,brain}$ .**

## Supplementary Tables

**Table S1. Compounds included in the data set; pharmaceutical classification, chromatographic data and lipophilicity parameters.**

| Compound             | Pharmaceutical class  | logP  | pH=7.4                           |                                    |                                  |       | pH=5.0                           |       |
|----------------------|---|-------|----------------------------------|------------------------------------|----------------------------------|-------|----------------------------------|-------|
|                      |   |       | log <sub>k</sub> <sub>WIAM</sub> | log <sub>k</sub> <sub>10,HSA</sub> | log <sub>k</sub> <sub>WAGP</sub> | logD  | log <sub>k</sub> <sub>WIAM</sub> | logD  |
| Acetaminophen        | Analgesic, antipyretic  | 0.51  | 0.18                             | -0.56                              | 0.10                             | 0.51  | -0.06                            | 0.51  |
| Acetylsalicylic acid | Analgesic   | 0.90  | -0.81                            | 0.38                               |                                  | -1.20 | -0.48                            | -0.29 |
| Acyclovir            | Guanosine analogue, antiviral   | -1.56 | -1.15                            | -1.33                              |                                  | -1.56 | -1.37                            | -1.56 |
| Aminopyrine          | Analgesic   | 0.85  | 0.71                             | -0.30                              |                                  | 0.63  |                                  | 0.86  |
| Amitriptyline        | Tricyclic antidepressant  | 4.92  | 2.99                             | 0.89                               | 2.40                             | 2.50  | 2.06                             | 1.13  |
| Antipyrine           | Antipyretic   | 0.56  | 0.45                             | -1.04                              | 0.88                             | 0.56  |                                  | 0.54  |
| Atenolol             | beta-1 selective blocker, treatment of hypertension                             | 0.16  | 0.51                             | -1.04                              | 0.10                             | -1.61 | -0.20                            | -2.55 |
| Atropine             | Muscarinic antagonist   | 1.89  | 1.05                             | -0.36                              |                                  | -0.66 |                                  | -1.76 |
| Caffeine             | Purine based stimulant  | -0.07 | 0.26                             | -0.74                              |                                  | -0.07 |                                  | -0.45 |
| Candesartan          | Angiotensin-receptor blocker, treatment of hypertension                         | 3.36  | 1.00                             | 0.42                               | 0.09                             | -1.35 | 1.57                             | 1.00  |
| Chlorpromazine       | Phenothiazine antipsychotic   | 5.41  | 3.33                             | 1.34                               | 2.30                             | 3.38  | 2.58                             | 1.84  |
| Clomipramine         | Tricyclic antidepressant  | 5.46  | 3.29                             | 1.12                               | 2.70                             | 3.30  | 2.49                             | 2.19  |
| Cocaine              | Ester local anesthetic  | 3.01  | 1.90                             | 0.33                               |                                  | 1.07  |                                  | -0.96 |
| Diazepam             | Long-acting benzodiazepine with rapid onset                                     | 2.79  | 2.12                             | 1.02                               | 1.80                             | 2.79  | 2.12                             | 2.79  |
| Diphenhydramine      | H1 receptor antihistamine, treatment of seasonal allergies                      | 3.4   | 1.82                             | 0.14                               | 1.87                             | 1.29  |                                  | -0.19 |
| Doxepin              | Tricyclic antidepressant and serotonin–norepinephrine reuptake inhibitor (SNRI) | 3.96  | 2.50                             | 0.56                               | 2.30                             | 2.22  | 1.98                             | 0.86  |
| Flunitrazepam        | Benzodiazepine, anxiolytic  | 2.06  | 1.79                             | 0.26                               | 1.44                             | 2.06  |                                  | 2.06  |
| Fluoxetine           | Selective serotonin reuptake inhibitor (SSRI) antidepressant                    | 4.26  | 2.98                             | 1.13                               | 2.10                             | 1.83  | 2.46                             | 0.94  |

|               |   |       |       |       |      |       |       |       |
|---------------|---|-------|-------|-------|------|-------|-------|-------|
| Haloperidol   | Antipsychotic   | 4.28  | 2.65  | 0.77  |      | 2.98  | 1.86  | 1.15  |
| Hydroxyzine   | Antihistamine, anxiolytic   | 3.5   | 3.01  | 0.60  |      | 3.01  | 2.23  | 0.73  |
| Ibuprofen     | Nonsteroidal anti-inflammatory (NSAID) and non-selective COX inhibitor, analgesic             | 3.5   | 0.87  | 1.33  |      | 1.07  | 1.55  | 2.15  |
| Imipramine    | Tricyclic antidepressant  | 4.44  | 2.73  | 0.77  | 2.25 | 2.40  | 2.05  | 1.29  |
| Indomethacin  | Nonsteroidal anti-inflammatory (NSAID), symptomatic treatment of chronic musculoskeletal pain | 4.27  | 2.41  | 1.76  | 1.59 | 1.03  | 2.93  | 2.95  |
| Lidocaine     | Local anesthetic  | 2.26  | 1.27  | 0.07  | 1.25 | 1.71  | 0.38  | 0.37  |
| Lorazepam     | Short-acting benzodiazepine, anxiolytic   | 2.51  | 2.03  | 0.67  | 1.33 | 2.51  | 2.01  | 2.51  |
| Maprotiline   | Tetracyclic antidepressant  | 4.14  | 2.81  | 0.80  |      | 1.44  | 2.25  | 1.19  |
| Meprobamate   | Anxiolytic  | 0.70  | 0.72  | -0.36 |      | 0.70  | 0.54  | 1.07  |
| Metformin     | Biguanide antihyperglycemic (type 2 diabetes mellitus)  | -0.91 | -0.37 | -1.37 |      | -3.91 |       | -3.91 |
| Midazolam     | Short-acting benzodiazepine, anxiolytic   | 3.27  | 2.77  | 0.99  |      | 3.27  | 1.93  | 1.95  |
| Morphine      | Opioid agonist, analgesic   | 0.89  | 0.63  | -0.55 |      | -0.06 | 0.10  | -2.03 |
| Naproxen      | Nonsteroidal anti-inflammatory (NSAID)  | 3.18  | 0.98  | 1.55  | 0.20 | 0.33  | 1.71  | 2.24  |
| Neostigmine   | Cholinesterase inhibitor used in the symptomatic treatment of myasthenia gravis               | -2.16 | 0.37  | -1.91 |      | -2.16 | -0.08 | -2.16 |
| Norfloxacin   | Broad-spectrum fluoroquinolone antibiotic   | -1.03 | 1.01  | -0.92 |      | -1.03 | 1.31  | -1.17 |
| Nortriptyline | Tricyclic antidepressant  | 4.04  | 2.83  | 0.82  | 2.30 | 1.70  | 2.12  | 1.16  |
| Ofloxacin     | Antibacterial agent   | -0.39 | 1.30  | -0.65 |      | -0.44 | 1.35  | -1.31 |
| Oxprenolol    | Non-selective beta-adrenergic antagonist, treatment of hypertension, angina pectoris,         | 2.1   | 1.47  | -0.25 |      | 0.32  | 0.87  | -0.61 |

|                |  |       |       |       |      |       |       |       |
|----------------|--|-------|-------|-------|------|-------|-------|-------|
|                | arrhythmias, and anxiety   |       |       |       |      |       |       |       |
| Pentazocine    | Analgesic  | 4.64  | 2.06  | 1.09  |      | 4.02  | 1.70  | 1.24  |
| Pentobarbital  | Barbiturate drug, sedative, antiepileptic  | 2.07  | 1.29  | -0.04 | 1.35 | 1.95  | 1.40  | 1.88  |
| Perphenazine   | Phenothiazine antipsychotic  | 4.20  | 3.67  | 1.24  | 3.19 | 3.65  |       | 1.61  |
| Phenobarbital  | Long-lasting barbiturate and anticonvulsant  | 1.47  | 0.28  | -0.22 | 1.10 | 1.14  | 0.71  | 1.47  |
| Phenytoin      | Anticonvulsant   | 2.24  | 1.75  | 0.44  | 1.60 | 2.17  | 1.94  | 1.95  |
| Pindolol       | Beta adrenoceptor antagonist, treatment of hypertension, edema, ventricular tachycardias, and atrial fibrillation. | 1.75  | 1.47  | -0.03 |      | -0.21 | 0.73  | -1.15 |
| Piracetam      | Nootropic cyclic GABA derivative   | -1.54 |       | -1.32 |      | -1.54 |       | -1.54 |
| Progesterone   | Endogenous steroid sex hormone   | 3.48  | 3.06  | 0.84  |      | 3.48  |       | 3.89  |
| Promethazine   | First-generation antihistamine   | 4.81  | 2.78  | 1.05  | 2.50 | 2.79  | 2.18  | 1.59  |
| Propranolol    | Non-selective beta-adrenergic antagonist   | 2.98  | 2.33  | 0.48  | 2.20 | 1.26  | 1.63  | 0.32  |
| Quinidine      | Class I antiarrhythmic agent   | 3.44  | 2.34  | 0.29  | 1.71 | 2.41  |       | -1.30 |
| Ranitidine     | Histamine H2 antagonist  | 1.28  | 0.61  | -0.41 |      | -0.53 |       | -3.37 |
| Risperidone    | Second-generation antipsychotic  | 2.50  | 2.49  | 0.13  |      | 1.63  |       | -1.24 |
| Salicylic acid | Salicylate, treatment of acne, psoriasis, calluses, corns, keratosis pilaris, and warts.                           | 2.19  | -0.08 | 0.34  |      | -1.68 | 0.46  | 0.04  |
| Scopolamine    | Belladonna alkaloid with anticholinergic effect  | 0.55  | 1.15  | -0.64 |      | -0.23 | 0.73  | -2.31 |
| Temazepam      | Short-acting benzodiazepine, anxiolytic  | 2.19  | 1.76  | 0.28  |      | 2.19  | 1.76  | 2.32  |
| Theophylline   | Xanthine analogue phosphodiesterase inhibiting drug used in therapy for respiratory diseases                       | -0.02 | -0.08 | -0.67 |      | -0.02 | -0.26 | -0.02 |



|              |   |      |      |      |      |      |      |      |
|--------------|---|------|------|------|------|------|------|------|
| Thioridazine | Phenothiazine antipsychotic   | 5.90 | 3.98 | 1.59 |      | 3.34 |      | 3.06 |
| Trazodone    | Serotonin uptake inhibitor, antidepressant  | 3.80 | 2.34 | 0.82 | 2.36 | 3.70 |      | 2.89 |
| Verapamil    | Non-dihydropyridine calcium channel blocker, treatment of angina, arrhythmia, and hypertension. | 3.79 | 2.76 | 0.66 | 0.10 | 2.57 | 1.86 | 1.20 |

**Table S2. Brain disposition data, i.e.,  $K_{p,brain}$ ,  $K_{p,uu,brain}$ ,  $f_{u,brain}$ ,  $V_{u,brain}$  for the investigated compounds.**

| Compound             | $K_{p,brain}$ | $K_{p,uu,brain}$ | $f_{u,brain}$ | $V_{u,brain}$ |
|----------------------|---------------|------------------|---------------|---------------|
| Acetaminophen        | 0.49          | 0.18             | 0.832         |               |
| Acetylsalicylic acid | 0.32          |                  |               |               |
| Acyclovir            | 0.14          | 0.3              |               |               |
| Aminopyrine          | 1.00          |                  |               |               |
| Amitriptyline        | 9.55          | 0.73             | 0.010         | 310.00        |
| Antipyrine           | 0.80          | 0.71             | 0.862         |               |
| Atenolol             | 0.04          | 0.03             | 0.900         | 2.50          |
| Atropine             | 0.87          |                  |               |               |
| Caffeine             | 0.89          | 0.77             |               |               |
| Candesartan          | 0.04          |                  |               |               |
| Chlorpromazine       | 11.48         |                  | 0.003         |               |
| Clomipramine         | 21.88         |                  | 0.004         |               |
| Cocaine              | 3.98          | 0.37             |               |               |
| Diazepam             | 3.31          | 1.02             | 0.042         | 20.00         |
| Diphenhydramine      |               |                  | 0.048         | 32.00         |
| Doxepin              |               |                  | 0.025         |               |
| Flunitrazepam        |               |                  | 0.219         |               |
| Fluoxetine           | 5.25          |                  | 0.003         |               |
| Haloperidol          | 21.88         |                  | 0.008         |               |
| Hydroxyzine          | 2.45          |                  | 0.013         |               |
| Ibuprofen            |               | 0.56             |               |               |
| Imipramine           | 6.76          |                  | 0.035         |               |
| Indomethacin         | 0.05          | 0.11             | 0.042         | 14.00         |
| Lidocaine            | 2.19          |                  | 0.209         |               |
| Lorazepam            | 2.95          |                  |               |               |
| Maprotiline          | 57.54         |                  | 0.006         |               |
| Meprobamate          |               |                  | 0.638         |               |
| Metformin            |               |                  | 0.950         | 10.00         |
| Midazolam            | 2.29          | 2.19             | 0.026         | 29.00         |
| Morphine             | 0.69          | 0.32             | 0.760         | 3.70          |
| Naproxen             |               | 0.60             |               |               |
| Neostigmine          |               |                  | 0.950         | 3.20          |
| Norfloxacin          | 0.07          | 0.05             | 0.580         | 2.90          |
| Nortriptyline        |               |                  | 0.006         |               |
| Ofloxacin            |               | 0.12             |               |               |
| Oxprenolol           | 1.06          | 0.2              | 0.280         | 11.80         |
| Pentazocine          | 3.51          |                  |               |               |
| Pentobarbital        | 1.32          |                  |               |               |
| Perphenazine         |               |                  | 0.004         |               |
| Phenobarbital        | 0.72          |                  |               |               |
| Phenytoin            | 0.91          | 0.45             | 0.121         |               |
| Pindolol             | 0.72          | 0.5              | 0.400         | 7.20          |
| Piracetam            | 1.00          |                  |               |               |
| Progesterone         |               |                  | 0.046         |               |
| Promethazine         | 6.67          |                  |               |               |

|                |      |      |       |         |
|----------------|------|------|-------|---------|
| Propranolol    | 4.37 | 0.61 | 0.025 | 112.00  |
| Quinidine      | 0.35 | 0.03 | 0.090 | 38.00   |
| Ranitidine     | 0.06 |      | 0.955 |         |
| Risperidone    | 0.95 | 0.08 | 0.087 |         |
| Salicylic acid | 0.08 | 0.19 | 0.630 | 1.00    |
| Scopolamine    | 1.70 |      |       |         |
| Temazepam      |      |      | 0.054 |         |
| Theophylline   | 0.51 | 0.05 | 0.562 |         |
| Thioridazine   | 1.74 | 0.45 | 0.001 | 3333.00 |
| Trazodone      |      |      | 0.071 |         |
| Verapamil      | 0.20 | 0.05 | 0.052 | 54.00   |

**Table S3. Variable Importance to Projection (VIP) values in the PLS model 4 for  $\log K_{p,uu,brain}$  on the basis of biomimetic properties, lipophilicity and computational descriptors.**

| Variable         | VIP    | Variable                | VIP   |
|------------------|--------|-------------------------|-------|
| TPSA             | 1.398  | WASA                    | 1.29  |
| SHBa             | 1.365  | SHBint2                 | 1.38  |
| NO <sub>nr</sub> | 1.35   | Pos.Fract. 7.4          | 0.814 |
| sumdell          | 1.287  | SASA                    | 1.37  |
| ka3              | 1.248  | N <sub>nr</sub>         | 1.41  |
| suml             | 1.227  | gmin                    | 0.967 |
| phia             | 1.223  | SAVol                   | 1.33  |
| Rotlbonds        | 1.161  | A                       | 1.29  |
| DipoleY          | 1.16   | SssO                    | 1.6   |
| O                | 1.158  | PSASA                   | 0.756 |
| ka2              | 1.157  | WAVol                   | 1.32  |
| ka1              | 1.134  | hmax                    | 1.26  |
| SHCsats          | 1.133  | Total Dipole            | 0.831 |
| S                | 1.125  | nvx                     | 1.31  |
| Onr              | 1.121  | V                       | 1.37  |
| NO               | 1.121  | molweight               | 1.29  |
| SdssC            | 1.106  | Ioniz Gr                | 1.44  |
| logkAGP          | 1.1    | SHother                 | 0.961 |
| DipoleX          | 1.079  | SHBd                    | 0.992 |
| B                | 1.068  | SHaaCH                  | 0.95  |
| logD5.0          | 1.043  | logkHSA10ACN            | 0.886 |
| HBA              | 1.036  | HBD                     | 1.03  |
| logD7.4          | 1.01   | Pos.Fract. 5            | 0.947 |
| SwHBa            | 0.9934 | SssCH2                  | 1.3   |
| SaaCH            | 0.9813 | LogP                    | 1.04  |
| SHBint4          | 0.9762 | logk <sub>WIAM5.0</sub> | 0.954 |
| pKa              | 0.969  | logk <sub>WIAM</sub>    | 1.2   |

**Table S4. Observed and predicted  $\log K_{p,uu,brain}$  values by the PLS model 4, based on computational descriptors.**

| Compound       | $\log K_{p,uu,brain}(obs)$ | $\log K_{p,uu,brain}(pred)$ |
|----------------|----------------------------|-----------------------------|
| Acetaminophen  | -0.745                     | -0,269                      |
| Acyclovir      | -0.523                     | -0,868                      |
| Amitriptyline  | -0.137                     | -0,0203                     |
| Antipyrine     | -0.149                     | 0,146                       |
| Atenolol       | -1.495                     | -1,16                       |
| Caffeine       | -0.113                     | -0,211                      |
| Cocaine        | -0.432                     | -0,67                       |
| Diazepam       | 0.011                      | -0,261                      |
| Indomethacin   | -0.959                     | -0,256                      |
| Midazolam      | 0.340                      | -0,863                      |
| Morphine       | -0.495                     | -0,224                      |
| Naproxen       | -0.222                     | -0,465                      |
| Norfloxacin    | -1.27                      | -0,361                      |
| Ofloxacin      | -0.921                     | -0,933                      |
| Oxprenolol     | -0.699                     | -1,01                       |
| Phenytoin      | -0.347                     | -0,835                      |
| Pindolol       | -0.301                     | -0,343                      |
| Propranolol    | -0.215                     | -0,467                      |
| Qunidine*      | -1.523                     | -0.483                      |
| Risperidone    | -1.097                     | -0,886                      |
| Salicylic acid | -0.721                     | -0,354                      |
| Theophylline*  | -1.301                     | -0,185                      |
| Thioridazine   | -0.347                     | -0,229                      |
| Verapamil      | -1.276                     | -1,35                       |

\*Not included in the model

**Table S5. Experimental and predicted logBB values by MLR and PLS models.**

| Compound             | logBB exper. | logBB pred.<br>Eq. (1) | logBB pred.<br>Eq. (2) | logBB pred. PLS<br>model 5 | logBB pred.<br>PLS model 6 |
|----------------------|--------------|------------------------|------------------------|----------------------------|----------------------------|
| Acetaminophen        | -0.31        | -0.15                  | 0.00                   | -0.30                      | -0.27                      |
| Acetylsalicylic acid | -0.5         | -0.57                  | -0.49                  | -0.88                      | -0.85                      |
| Acyclovir            | -0.84        | -1.53                  | -1.37                  | -1.09                      | -1.07                      |
| Aminopyrine          | 0.00         | 0.34                   | 0.38                   | 0.08                       | 0.09                       |
| Amitriptyline        | 0.98         | 1.13                   | 1.04                   | 0.88                       | 0.86                       |
| Antipyrine           | -0.097       | 0.35                   | 0.42                   | -0.07                      | -0.06                      |
| Atenolol             | -1.42        | -0.73                  | -0.89                  | -0.74                      | -0.81                      |
| Atropine             | -0.06        | -0.02                  | -0.18                  | 0.32                       | 0.22                       |
| Caffeine             | -0.05        | -0.30                  | -0.24                  | -0.12                      | -0.13                      |
| Candesartan          | -1.4         | -1.25                  | -1.40                  | -1.99                      | -1.99                      |
| Chlorpromazine       | 1.06         | 0.68                   | 0.70                   | 0.78                       | 0.79                       |
| Clomipramine         | 1.34         | 1.12                   | 1.10                   | 1.00                       | 1.01                       |
| Cocaine              | 0.6          | 0.02                   | -0.03                  | 0.22                       | 0.19                       |
| Diazepam             | 0.52         | 0.46                   | 0.60                   | 0.63                       | 0.67                       |
| Fluoxetine           | 0.72         | 0.81                   | 0.65                   | 0.75                       | 0.70                       |
| Haloperidol          | 1.34         | 0.41                   | 0.50                   | 0.79                       | 0.82                       |
| Hydroxyzine          | 0.39         | 0.55                   | 0.58                   | 0.57                       | 0.59                       |
| Imipramine           | 0.83         | 1.03                   | 0.97                   | 0.92                       | 0.90                       |
| Indomethacin         | -1.26        | -0.13                  | -0.24                  | -0.80                      | -0.79                      |
| Lidocaine            | 0.34         | 0.33                   | 0.45                   | -0.03                      | 0.02                       |
| Lorazepam            | 0.47         | -0.07                  | 0.09                   | 0.21                       | 0.26                       |
| Maprotiline          | 1.76         | 0.94                   | 0.74                   | 1.08                       | 0.99                       |
| Midazolam            | 0.36         | 0.62                   | 0.72                   | 0.46                       | 0.51                       |
| Morphine             | -0.16        | -0.14                  | -0.15                  | -0.41                      | -0.41                      |
| Norfloxacin          | -1.15        | -0.44                  | -0.61                  | -1.18                      | -1.22                      |
| Oxprenolol           | 0.025        | 0.04                   | -0.05                  | 0.10                       | 0.05                       |
| Pentazocine          | 0.545        | 0.62                   | 0.93                   | 0.58                       | 0.71                       |
| Pentobarbital        | 0.12         | -0.43                  | -0.21                  | 0.23                       | 0.28                       |
| Phenobarbital        | -0.14        | -0.60                  | -0.33                  | -0.20                      | -0.13                      |
| Phenytoin            | -0.04        | -0.05                  | 0.10                   | 0.21                       | 0.25                       |
| Pindolol             | -0.14        | -0.08                  | -0.24                  | 0.01                       | -0.07                      |
| Promethazine         | 0.824        | 0.59                   | -0.54                  | 0.81                       | 0.82                       |
| Propranolol          | 0.64         | 0.34                   | 0.62                   | 0.65                       | 0.59                       |
| Quinidine            | -0.46        | 0.27                   | 0.23                   | 0.00                       | 0.03                       |
| Ranitidine           | -1.23        | -1.24                  | 0.34                   | -1.52                      | -1.52                      |
| Risperidone          | -0.02        | 0.00                   | -1.21                  | 0.07                       | 0.05                       |
| Salicylic acid       | -1.1         | -0.34                  | -0.04                  | -0.73                      | -0.78                      |
| Scopolamine          | 0.23         | -0.39                  | -0.46                  | 0.11                       | 0.04                       |
| Theophylline         | -0.29        | -0.55                  | -0.47                  | -0.19                      | -0.18                      |
| Thioridazine         | 0.24         | 0.34                   | -0.41                  | 0.68                       | 0.66                       |
| Verapamil            | -0.7         | 0.01                   | 0.29                   | -0.33                      | -0.28                      |

**Table S6. Experimental and predicted logK<sub>b</sub> values by MLR and PLS models.**

| Compound        | logK <sub>b</sub> exper. | logK <sub>b</sub> pred.<br>Eq. (7) | logK <sub>b</sub> pred.<br>Eq. (11) | logK <sub>b</sub> pred. PLS<br>model 8 | logK <sub>b</sub> pred. PLS<br>model 9 |
|-----------------|--------------------------|------------------------------------|-------------------------------------|--|--|
| Acetaminophen   | 0.692                    | 0.407                              | -0.006                              | 0.505                                  | 0.218                                  |
| Amitriptyline   | -1.996                   | -2.148                             | -2.226                              | -2.089                                 | -2.182                                 |
| Antipyrine      | 0.792                    | 0.522                              | -0.033                              | 0.479                                  | 0.065                                  |
| Atenolol        | 0.950                    | 0.713                              | 0.758                               | 0.959                                  | 0.579                                  |
| Chlorpromazine  | -2.522                   | -2.468                             | -2.522                              | -2.292                                 | -2.160                                 |
| Clomipramine    | -2.431                   | -2.326                             | -2.479                              | -2.284                                 | -2.192                                 |
| Diazepam        | -1.359                   | -1.519                             | -1.247                              | -1.527                                 | -1.334                                 |
| Diphenhydramine | -1.298                   | -0.985                             | -1.365                              | -1.055                                 | -1.491                                 |
| Doxepin         | -1.592                   | -1.587                             | -1.884                              | -1.636                                 | -1.927                                 |
| Flunitrazepam   | -0.553                   | -0.586                             | -0.282                              | -0.645                                 | -0.967                                 |
| Fluoxetine      | -2.584                   | -2.162                             | -1.684                              | -1.996                                 | -2.108                                 |
| Haloperidol     | -2.083                   | -1.672                             | -2.071                              | -1.744                                 | -2.034                                 |
| Hydroxyzine     | -1.881                   | -1.664                             | -1.779                              | -1.665                                 | -1.886                                 |
| Imipramine      | -1.441                   | -1.828                             | -1.989                              | -1.792                                 | -1.826                                 |
| Indomethacin    | -1.359                   | -1.858                             | -0.885                              | -1.727                                 | -1.628                                 |
| Lidocaine       | -0.579                   | -0.534                             | -1.269                              | -0.447                                 | -0.034                                 |
| Maprotiline     | -2.220                   | -2.000                             | -1.662                              | -2.035                                 | -2.118                                 |
| Meprobamate     | 0.245                    | 0.338                              | 0.458                               | 0.528                                  | 1.098                                  |
| Metformin       | 1.270                    | 1.375                              | 2.005                               | 1.453                                  | 1.862                                  |
| Midazolam       | -1.574                   | -1.858                             | -1.559                              | -1.895                                 | -1.822                                 |
| Morphine        | 0.499                    | 0.716                              | 0.598                               | 0.653                                  | 0.464                                  |
| Neostigmine     | 1.270                    | 1.154                              | 0.864                               | 1.138                                  | 0.992                                  |
| Norfloxacin     | 0.139                    | 0.486                              | -0.322                              | 0.490                                  | 0.302                                  |
| Nortriptyline   | -2.227                   | -2.022                             | -1.803                              | -1.989                                 | -2.085                                 |
| Oxprenolol      | -0.411                   | -0.356                             | -0.481                              | -0.283                                 | -0.366                                 |
| Perphenazine    | -2.397                   | -2.375                             | -2.352                              | -2.448                                 | -2.061                                 |
| Phenytoin       | -0.862                   | -0.887                             | -0.82                               | -0.997                                 | -1.195                                 |
| Pindolol        | -0.177                   | -0.477                             | -0.193                              | -0.421                                 | -0.340                                 |
| Progesterone    | -1.317                   | -2.047                             | -1.811                              | -1.630                                 | -1.034                                 |
| Propranolol     | -1.592                   | -1.338                             | -1.182                              | -1.421                                 | -0.966                                 |
| Quinidine       | -1.005                   | -1.128                             | -1.581                              | -0.917                                 | -1.151                                 |
| Ranitidine      | 1.317                    | 0.538                              | 0.596                               | 0.672                                  | 0.640                                  |
| Risperidone     | -1.021                   | -0.898                             | -0.724                              | -0.751                                 | -1.288                                 |
| Salicylic acid  | 0.230                    | 0.057                              | 0.209                               | -0.122                                 | -0.201                                 |
| Temazepam       | -1.244                   | -0.805                             | -0.731                              | -0.964                                 | -1.037                                 |
| Theophylline    | 0.107                    | 0.946                              | 0.85                                | 1.043                                  | 0.710                                  |
| Thioridazine    | -3.174                   | -2.960                             | -2.501                              | -2.880                                 | -2.615                                 |
| Trazodone       | -1.121                   | -1.193                             | -1.343                              | -1.164                                 | -1.491                                 |
| Verapamil       | -1.261                   | -1.336                             | -1.318                              | -1.400                                 | -1.157                                 |

**Table S7. Observed vs predicted  $f_{u,brain}$  correlation:  $f_{u,brain} = a \cdot f_{u,brain,pred} + b$ .**

|                         | a             | b             | n  | R <sup>2</sup> | s     |
|-------------------------|---------------|---------------|----|----------------|-------|
| Eq. (7)- IAM retention  | 0.974(±0.039) | 0.007(±0.017) | 39 | 0.944          | 0.083 |
| Eq. (11)- Lipophilicity | 1.004(±0.060) | 0.016(±0.024) | 39 | 0.983          | 0.119 |
| PLS- IAM retention      | 0.951(±0.040) | 0.007(±0.018) | 39 | 0.939          | 0.087 |
| PLS- Lipophilicity      | 0.966(±0.057) | 0.018(±0.024) | 39 | 0.886          | 0.118 |

**Table S8. Experimental and predicted  $\log V_{u,brain}$  values by MLR and PLS models.**

| Compound        | $\log V_{u,brain}$<br>exper. | $\log V_{u,brain}$<br>pred. Eq. (15) | $\log V_{u,brain}$<br>pred. Eq. (17) | $\log V_{u,brain}$ pred. PLS<br>model 10 | $\log V_{u,brain}$ pred. PLS<br>model 11 |
|-----------------|------------------------------|--------------------------------------|--------------------------------------|--|--|
| Amitriptyline   | 2.491                        | 2.607                                | 2.383                                | 2.745                                    | 2.701                                    |
| Atenolol        | 0.398                        | 0.206                                | 0.792                                | 0.443                                    | 0.695                                    |
| Diazepam        | 1.301                        | 1.637                                | 0.822                                | 1.415                                    | 1.173                                    |
| Diphenhydramine | 1.505                        | 1.663                                | 1.857                                | 1.616                                    | 1.671                                    |
| Indomethacin    | 1.146                        | 1.391                                | 1.32                                 | 1.152                                    | 0.946                                    |
| Metformin       | 1.000                        | 0.298                                | 0.437                                | 0.541                                    | 0.678                                    |
| Midazolam       | 1.462                        | 1.829                                | 1.04                                 | 1.499                                    | 1.311                                    |
| Morphine        | 0.568                        | 0.494                                | 0.908                                | 0.689                                    | 0.838                                    |
| Neostigmine     | 0.505                        | 0.759                                | 0.017                                | 0.619                                    | 0.491                                    |
| Norfloxacin     | 0.462                        | 0.518                                | 0.367                                | 0.724                                    | 0.557                                    |
| Oxprenolol      | 1.072                        | 1.018                                | 1.445                                | 0.865                                    | 1.019                                    |
| Pindolol        | 0.857                        | 1.232                                | 1.327                                | 1.090                                    | 1.310                                    |
| Propranolol     | 2.049                        | 1.768                                | 1.741                                | 1.472                                    | 1.400                                    |
| Quinidine       | 1.580                        | 1.561                                | 1.854                                | 1.368                                    | 1.546                                    |
| Salicylic acid  | 0.000                        | 0.265                                | 0.62                                 | 0.175                                    | 0.110                                    |
| Thioridazine    | 3.523                        | 3.011                                | 2.72                                 | 3.470                                    | 3.481                                    |
| Verapamil       | 1.732                        | 1.396                                | 2.003                                | 1.608                                    | 1.727                                    |