

Blood-Brain Barrier Permeability Predictor

Blood-brain barrier permeability is a measure of the partitioning of a compound across the blood-brain barrier. The property is measured experimentally as the ratio of the concentration in the brain, [brain], to that in the blood, [blood]:

$$BB = [\text{brain}] / [\text{blood}]$$

CSBBB™, the blood-brain permeability predictor from ChemSilico LLC, is a useful model for the prediction of blood-brain barrier partitioning to assess whether or not a compound is likely or not to permeate this barrier and measures the log of the blood-brain barrier coefficient for neutral molecules.

The only input required from the user to generate a prediction is a structure for each compound to be predicted. Structures may be imported as either MOL files or SD files or they can be drawn using the KnowItAll® Informatics System's built-in drawing application.

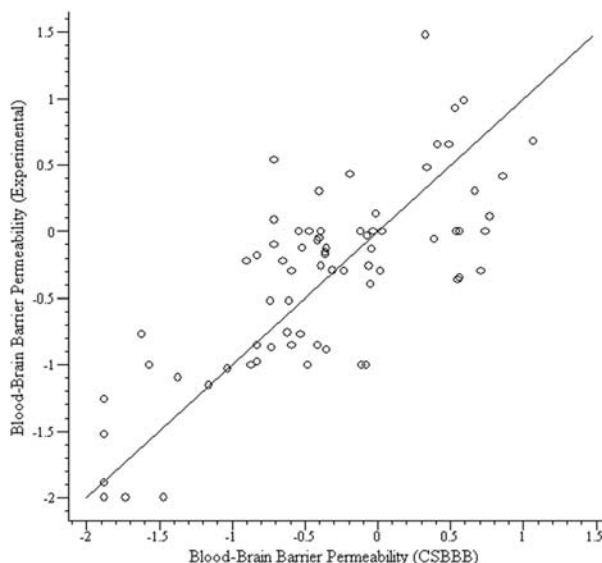
The CSBBB predictor is integrated into Bio-Rad's KnowItAll Informatics System with ADME/Tox prediction, cheminformatics, & data management tools for seamless import and transfer of data to improve workflow. All the tools needed for ADME/Tox evaluation, structure drawing, data mining, and reporting are provided in one consistent interface for quick access from the researcher's desktop. The system also offers additional ADME/Tox predictors to generate a complete *in silico* ADME/Tox profile for potential drug candidates.

This predictor can be used effectively with KnowItAll's Validatelt™ application for statistical validation of the prediction model by comparing actual experimental results to predicted results. The statistical analysis includes error binning, scatter plotting, mean average error, root mean square error, N-fold cross validation, and other tools for validation analysis.

External Validation of CSBBB

| | |
|----------------|-------|
| N | 74 |
| MAE | 0.387 |
| RMS | 0.486 |
| q ² | 0.618 |
| Error < 0.5 | 67.6% |
| Error < 1.0 | 95.9% |

MAE = Mean Absolute Error
RMS = Root Mean Square Error



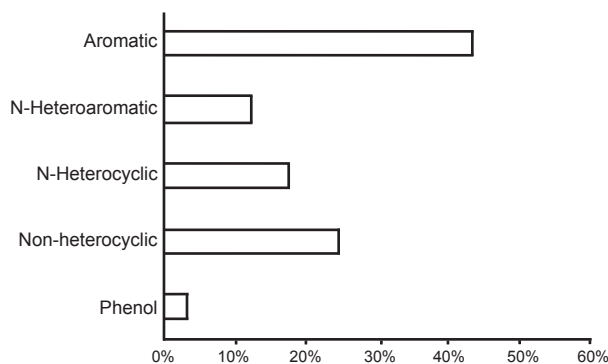
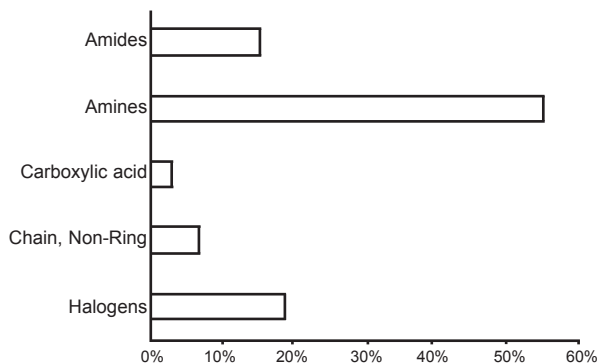
Profile of Training Set for CSBBB

Blood-brain barrier partitioning data came mainly from 11 sources (1) where protocols used an iv mode to administer compounds to rats. one hundred and seventy seven neutral compounds were selected of which 99% of the entities were either drugs or drug-like in terms of Lipinski's Rule of Five, with an average formula weight of 259.

(1). K. Rose, L. H. Hall, and L. B. Kier, J. Chem. Inf. Comput. Sci. (2002) 42, 651

Training Dataset for CSBBB: 177 Compounds

| Structure Group Present | Number of Groups |
|--------------------------|------------------|
| Ring(s) | 378 |
| Chain (non-ring) | 31 |
| Aromatic ring(s) | 159 |
| Non-heterocyclic ring(s) | 44 |
| N-Heteroaromatic ring(s) | 90 |
| N-Heterocyclic ring(s) | 63 |
| Amides | 70 |
| Amines | 252 |
| Phenol | 11 |
| H-Bond acceptors | 822 |
| H-Bond donors | 247 |
| Carboxylic acid | 15 |



- Average number of H-bond donors per compound = 4.8
- Average number of H-bond acceptors per compound = 1.4
- Average formula weight = 258.7
- Percent of drug-like compounds = 99%



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