ACD/Labs

Data sheet

Blood-Brain Barrier Permeation Prediction Module

ACD/Percepta

Overview

The ACD/Labs Blood Brain Barrier (BBB) Penetration module predicts if a given compound is permeable enough to exhibit activity in the CNS. This module provides reliable and easily interpretable predictions of both rate and extent of BBB permeation by passive diffusion (expressed as Log*PS* and Log*BB* constants respectively). Predictions performed by this module allow ranking of compounds according to their passive transport across blood-brain barrier.

Features

- Calculates Log*PS* values as indicators of passive permeability across the blood brain barrier using physicochemical property values such as lipophilicity (Log*P*) and ionization (pK_a) as inputs.
- Calculates Log*BB* values – the steady-state distribution ratio between brain tissue and plasma.
- Calculates fraction of a drug that is unbound (i.e. pharmacologically active) in brain tissue.
- Provides a qualitative estimate as to whether brain uptake is sufficient for CNS activity
- Improve the accuracy of Log*PS* and Log*BB* predictions by entering experimentally measured physicochemical properties.
- Displays special alerts for compounds that are likely to undergo transport across blood-brain barrier by mechanisms different from passive diffusion.
- Lists experimental Log*PS* or Log*BB* values and literature references for up to 3 most similar structures from the respective training set.
- Visualizes the position of your compound on a plot of BBB transport parameters, in comparison to a number of CNS and peripheral drugs
- Fast batch calculations provide predictions for hundreds of molecules per minute. The calculations are performed automatically without user intervention.

Technical Information

Only a short summary of the main technical aspects of BBB penetration predictors is given here. For a more detailed description of the modeling approach and underlying theory please refer to the following articles:

- Lanevskij K et al. *Chem Biodivers*. **2009** Nov;6 (11):2050-4. [1]
- Lanevskij K et al. *J Pharm Sci.* **2009**;98 (1):122-34. [2]
- Lanevskij K et al. *J Pharm Sci*. **2011**;100 (6):2147-60. [3]

Calculated quantitative parameters

Main parameters:

- Rate of brain penetration (log *PS*). *PS* stands for Permeability-Surface area product and is defined from the kinetic equation of capillary transport ($PS = -F * (1 - e^{-K_{in}/F})$). By its physical meaning, *PS* is equal to influx rate constant K_{in} corrected for blood flow rate in cerebral micro capillaries denoted as *F*.
- Extent of brain penetration (log *BB*) determined by ratio of total drug concentrations in tissue and plasma at steady-state conditions ($\log BB = \log(c_{brain}^{SS}/c_{blood}^{SS})$).

Additional parameters:

- Fraction unbound in brain tissue ($f_{u,\,brain}$)
- Brain/plasma equilibration rate log ($PS * f_{u,\,brain}$) - *combination of permeation rate and fraction unbound in brain* (according to Liu X. et al. *J. Pharmacol. Exp. Ther.* **2005**; 313(3):1254-62. [4]).

Experimental data

The data sets used for modeling was compiled from original literature publications of BBB permeation studies in rodents. Quantitative log *PS* data were collected for more than 250 compounds. These were determined by one of the following experimental methods:

- Intravenous administration (IV)
- Brain uptake index (BUI)
- *In situ* brain perfusion.

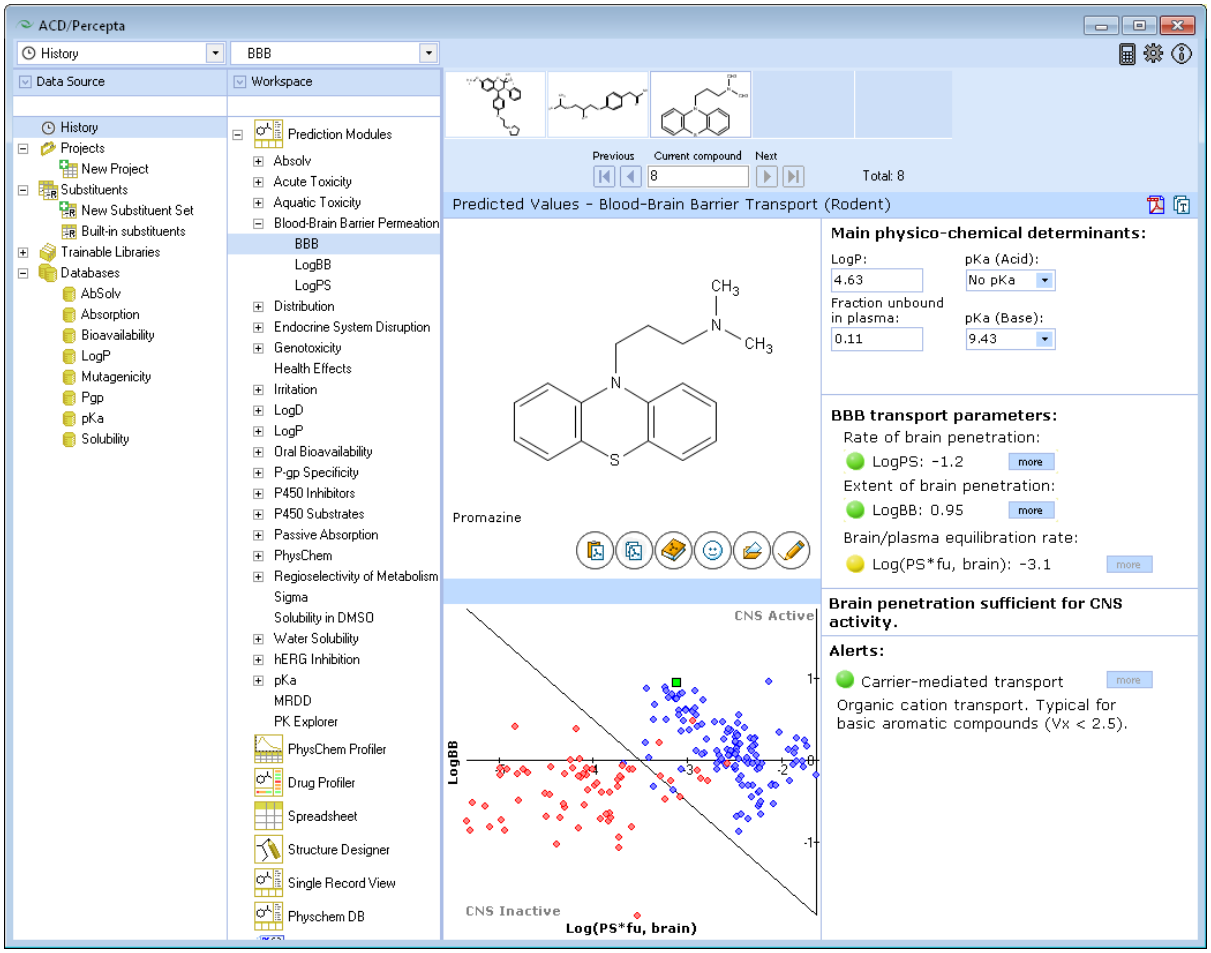

Figure 1. *Screenshot of ACD/Percepta Blood-Brain Barrier Permeation module*

Analysis of published brain/plasma distribution studies of drugs after intravenous (in some cases – intraperitoneal or oral) administration to rats and mice yielded a data set of log *BB* values for ~600 compounds. The collected data was thoroughly evaluated to ensure the results represented BBB transport by passive diffusion. The resulting data sets contained 178 log *PS* constants and 470 log *BB* ratios.

Modeling method & used descriptors

The predictive models of log *PS* and log *BB* constants were built using non-linear least squares regression. Non-linear fitting was necessary to account for the following aspects of the analyzed processes:

- Differentiation between diffusion-limited and cerebral blood flow-limited permeability (Log*PS*).
- Bilinear permeability - Log*P* dependence: rise of permeability with Log*P* up to a certain optimum point followed by subsequent decrease due to hydrophobic retention in the membrane (Log*PS*).
- Ionization-specific partitioning of electrolytes between phospolipid bilayer and plasma (Log*PS*) or brain tissue lipids and interstitial fluid (Log*BB*).

In both cases fitting was performed in a multi-step approach: the first stage involved determination of parameters describing membrane/plasma partitioning of neutral molecules while in the second stage these values were fixed and electrolyte-specific passive transport parameters were obtained.

Descriptors used for modeling included key physicochemical properties calculated with the ACD/Labs Algorithm Builder 1.8 development platform:

- Octanol/water Log*P* of neutral species as a determinant of lipophilicity
- Ion form fractions at pH 6.5 calculated from the respective pK_a values
- Number of hydrogen bond donors and acceptors in the molecule
- McGowan characteristic volume reflecting molecular size.

Prediction accuracy

Prior to development of the log *PS* and log *BB* predictive models, a part of each data set was reserved for validation purposes and not used in modeling (internal validation set). Additionally, two independent data sets representing another type of experimental data (directly measured $f_{u,\,brain}$ values) were extracted from recent publications (Kalvass J. C. et al. *Drug Metab. Dispos.* **2007**; 35(4):660-6 [5], and Summerfield S. G. et al. *Xenobiotica.* **2008**; 38(12):1518-35. [6]). These were used as external validation sets to confirm intrinsic correctness of the obtained model. Model performance on various validation sets is summarized in the Table below:

Table 1. Performance of the obtained BBB penetration models on various validation sets.

Data set	No. of compounds	R^2	RMSE
log *PS* internal validation set	53	0.82	0.49
log $f_{u,brain}$ internal validation set	137	0.74	0.41
log $f_{u,brain}$ external validation set ([5])	31	0.73	0.42
log $f_{u,brain}$ external validation set ([6])	20	0.70	0.36

Statistical parameters obtained for all test sets demonstrate good predictive power of the models with RMSE being close to error of experimental determination in the case of both log *PS* and log *BB*.

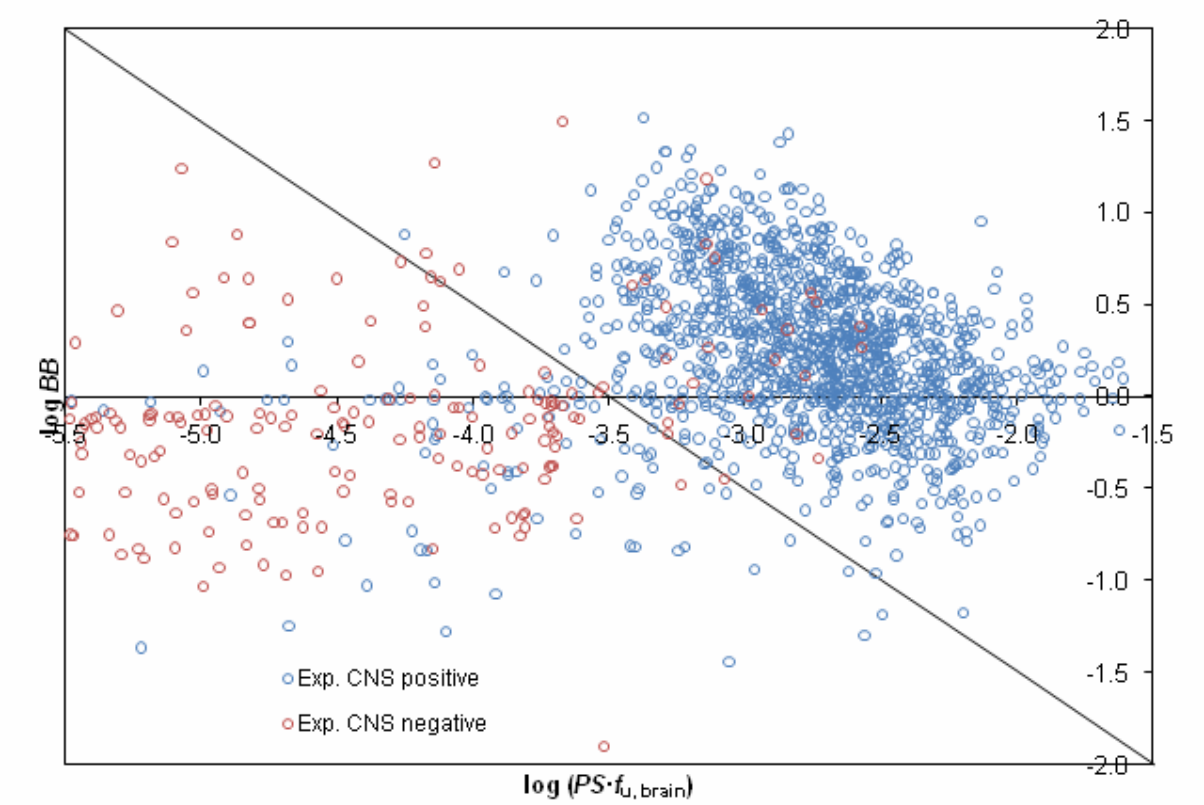

Figure 2. Classification of drugs by CNS access based on predicted values of log *BB* and brain/plasma equilibration rate.

Classification by Access to CNS

ACD/Percepta classifies compounds as CNS positive (sufficiently permeable to be active in CNS) or CNS negative (inactive due to low penetration) on the basis of the combination of two quantitative parameters – brain/plasma equilibration rate (log (*PS* * $f_{u, brain}$)), and extent of partitioning at equilibrium (log *BB*).

The proposed classification scheme was validated using experimentally assigned CNS activity categories for more than 1500 compounds presented in the study by Adenot M & Lahana R *J Chem Inf Comput Sci.* **2004**; 44(1):239-48. [7] After removing compounds, disposition of which is affected by P-gp efflux 92% of the remaining molecules were correctly classified by our model as shown in Fig. 2.

Transport mechanisms

The predictive models comprising the BBB module only account for **passive** transport of analyzed compounds across the blood-brain barrier. In order to propose a clear physicochemical explanation of passive diffusion process, the data used for development of both log *PS* and log *BB* models was thoroughly evaluated to exclude values affected by enzymatic efflux or influx. For such compounds special alerts are displayed in all sub modules related to the prediction of BBB transport parameters indicating that the observed parameters for these molecules may be higher or lower than predicted values due to presence of carrier-mediated processes, such as facilitated diffusion or P-gp efflux. Considered influx transporters include:

- Amino-acid transport systems (System A, L, y^+, x^-)
- Glucose carrier GLUT1
- Organic cation/carnitine transporters (OCTN)
- Organic anion transporting polypeptide (OATP)
- Various other carriers specific for nucleotides and other endogenous substances.