PK-Map™: A Powerful Tool for Early ADME Prediction and Visualization

Stefan Willmann [1], Walter Schmitt [1], Jörg Lippert [2], Michael Sevestre [2], Juri Solodenko [2] and Jörg Keldenich [3]

[1] Bayer Technology Services GmbH, Process Technology, Competence Center Biophysics, D-51368 Leverkusen, Germany

[2] Bayer Technology Services GmbH, Process Technology, Competence Center Computational Solutions, D-51368 Leverkusen, Germany

[3] BayerHealthcare AG, Division Pharma, Chemical Research, D-42096 Wuppertal, Germany

INTRODUCTION

ADME properties (Absorption, Distribution, Metabolism, and Excretion) are a key factor for a compound's potential to become a drug. It is, therefore, decisive for an effective compound selection and optimization to determine the most relevent ADME parameters as early as possible during the drug R&D process. PK-Map™ is a new software tool for the assessment of ADME properties of large sets of substances [1]. It combines validated physiologically-based prediction models with powerful visualization and selection features.

PHYSIOLOGICAL PREDICTION MODELS

The built-in models of PK-Map™ relate important ADME properties such as **intestinal permeability**, **fraction dose absorbed**, **volume of distribution**, and **organ/plasma partition coefficients** for most organs to basic physico-chemical properties such as **lipophilicity**, **plasma protein binding**, **solubility**, and **molecular weight.**

A) Absorption Model

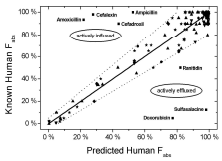
The physiological details of the absorption model are described in detail in [2,3]. The Fraction Dose Absorbed is calculated based on a passive intestinal permeability coefficient, that is derived from the compounds membrane affinity (LogMA as e.g. determined by the NIMBUS Transil® assay [4,5]) and effective molecular weight [3], and an intestinal solubility, if absorption is solubility-limited.

B) Distribution Model

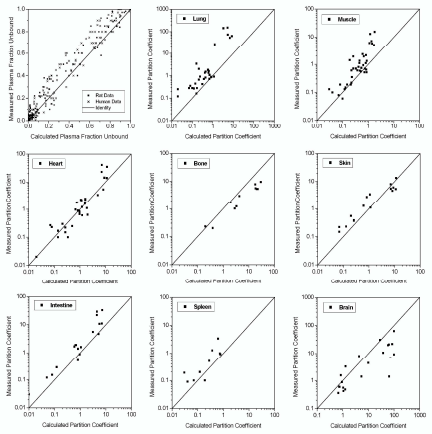
The fraction unbound in plasma is calculated from the binding constant to human serum albumine ($LogK_{d,HSA}$ determined from the NIMBUS Transil®-HSA assay [4]). The distribution into the organs is further determined by the physiological water, protein, and lipid contents of the respective organ and the membrane affinity [6,7].

MODEL VALIDATION

In the right figure, the correlation between measured and predicted human fraction dose absorbed is shown for a chemically diverse data set of 126 marketed drugs with non-solubility-limited absorption [3]. Since only passively transported compounds are regarded, actively transported compounds must fall off the correlation



The following figure shows the correlation between measured and calculated fraction unbound and organ/plasma partition coefficients for a chemically diverse data set (marketed drugs and Bayer *in house* compounds):



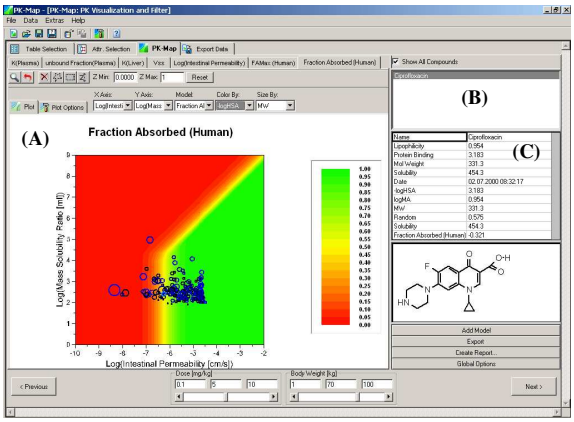
PK-MAP™ User-Interface

The PK-Map™ window is organized in three main parts: the **ADME Plot** (**A**), the **Selected Compound List** (**B**), and the **Compound Information Table** (**C**).

In the **ADME Plot**, the chosen ADME model is displayed as a color coded, two dimensional graphic with compound related physicochemical properties representing the x- and y-axis (the so called "ADME map"). The compounds that are selected are listed in the **Selected Compound List**. Physico-chemical as well as calculated ADME related information about the highlighted compound are available in the **Compound Information Table**.

Due to its intuitive graphical user interface, PK-Map™ is easy to use by medicinal chemist and ADME/PK experts.

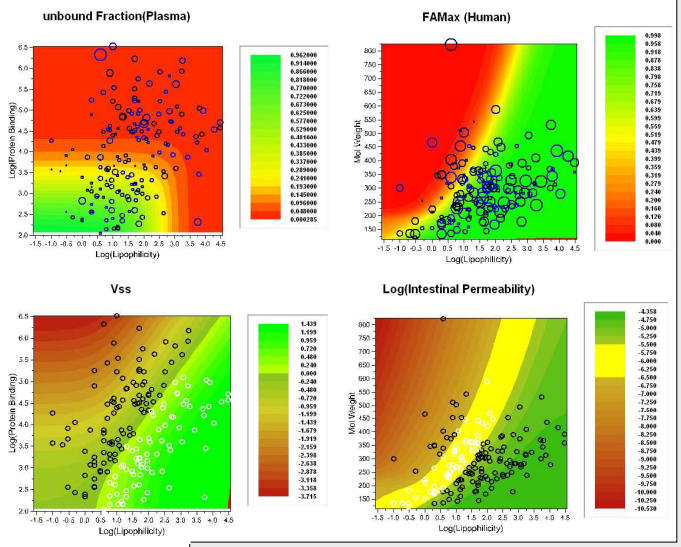
Integration into an existing IT environment is also easily possible due to a flexible handling of the data input format. Additionally, PK-Map™ offers the flexibility to integrate customized models.



A) Visualization Features

Each compound is represented by a single data point within an ADME map. The "position" within the ADME space is determined by its physico-chemical properties. In addition, other substance specific information (e. g. biological activity) can be displayed as a modulation of the color and/or size of the data point.

The ADME maps allow to easily identify compounds with favorable or unfavorable ADME properties. They furthermore contain information, in which chemical direction a compound has to be varied in order to obtain a more suitable ADME profile.



B) Selection Features

Besides standard tools for graphical selection, PK-Map™ provides the possibility to select compounds according to their value in the ADME space (e.g. all compounds with an intestinal permeability coefficient between $10^{-6.5}$ and $10^{-5.5}$ cm/s or all compounds with a volume of distribution greater than 1 L/kg):

C) Classification Features

After the definition of the preferred ADME space and the selection of compounds, PK-Map™ creates an output table. The compounds are ranked in order of their conformity to the predefined requirements. This classification feature is especially useful to prioritize the most promising drug candidates from a large chemical data set.

SUMMARY

PK-Map™ is a valuable tool for early ADME calculations combining reliable physiological ADME models with powerful visualization. PK-Map™ supports graphical as well as model dependent selection. ADME maps allow to easily identify the most promising drug candidates and to specify the demands for chemical optimization with respect to a better ADME behavior. The sum of these features makes PK-Map™ an unique tool that is ideally suited for early drug discovery and lead optimization.

REFERENCES

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