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LEADER IN ADME/PK-PREDICTIONS

www.prosilico.com

Delivering high quality *in silico* estimates of human ADME/PK

Strategy used to build confidence in PROSILICO's *in silico* methods for prediction of human clinical ADME/PK

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Early experiences (Years at AstraZeneca: ADME/PK-prediction methodology)

- At CD-selection and FTIM-dose setting:
  - Choice driven by tradition and subjectivism
  - Many opinions & No consensus

- Opinion - *In silico* less accurate than *in vitro*- and animal *in vivo*-data

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- Decent *in silico* methods available for some parameters
- Poor for other and secondary parameters
- Common with limited and non-representative test datasets and retrospective fits
  (rather than complete cross-validations and true forward-looking predictions)

→ Opportunity to improve

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1. Systematic review of prediction methods

- 11 research papers
- Pros and cons highlighted
- Common with cherry-picking and non-reported failures
- No consensus
- Needs and areas of improvement highlighted

→ Ideas & opportunities

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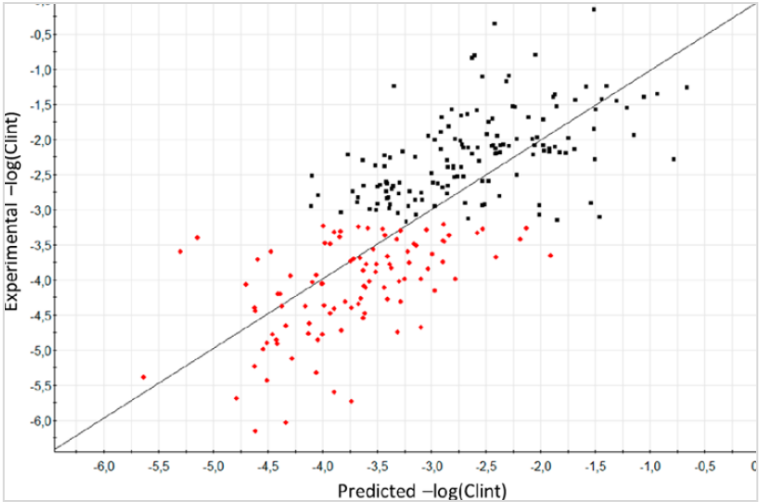
2. Data collection & pilot model building

- Collection/estimation of data for two parameters
- Model building and validation

→ Encouraging results

Better than microsomes and hepatocytes



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3. Extensive collection, quality-checking & stratification of data

Restrictions / challenges

- ~1500 marketed drugs
- Common with data gaps
- Many erratic/questionable data in reports
- Difficult to stratify data according to mechanisms

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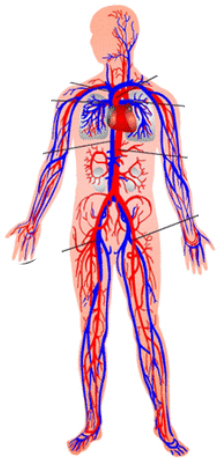
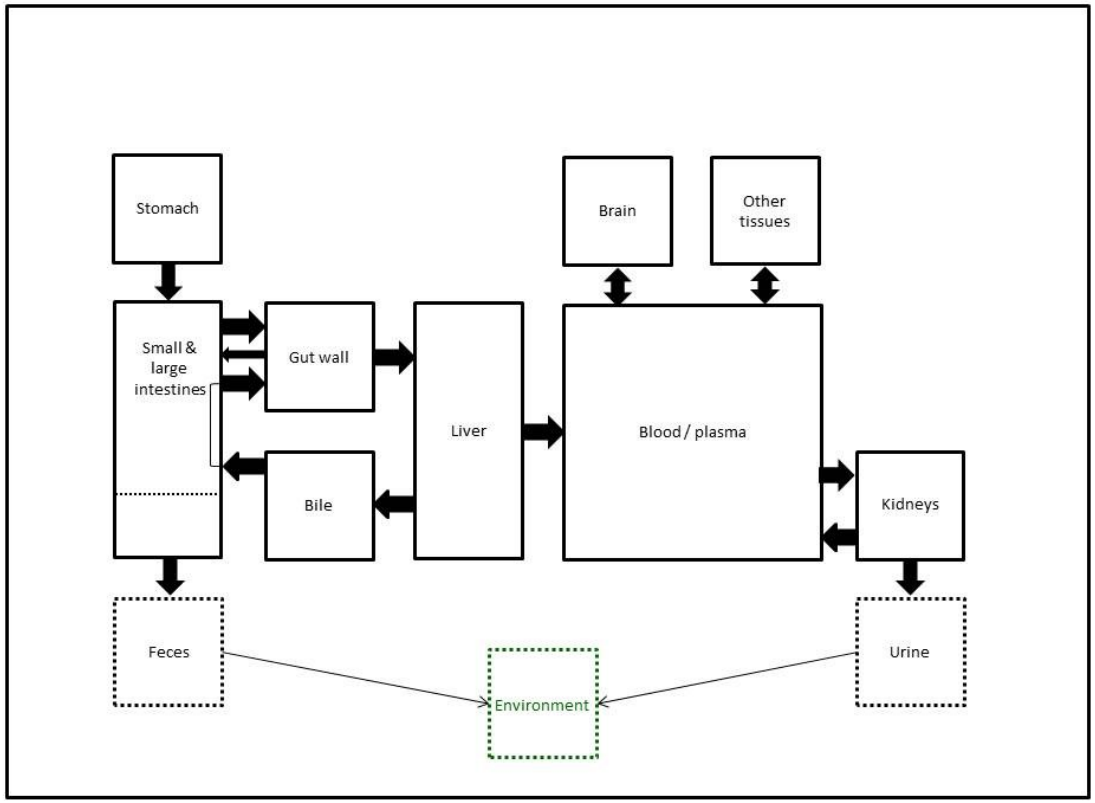
4. Creation of new algorithms and PBPK-model





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5. Model building, validation and selection

- Applied different *in silico* methods (incl. machine learning)
  Directly from molecular structure to human *in vivo*
  Cross-validation = True, forward-looking predictions

- Developed and validated models for >50 parameters

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The Prediction Platform

A collection of fully validated human ADME/PK-models

Oral F & $t_{½}$

F_{abs} & k_a
considering efflux & low solubility
colon uptake (ER-potental)
BCS-classing

DDIs & food interaction

CL_{int} & CL_H
Also for metabolically stable cmpds

Renal & biliary CL

Total CL & V_{ss}

F_{gut}

AUC, C_{max}, t_{max}

BBB uptake & CNS-exposure

Eye, skin & lung uptake

Metabolite PK & exp.

Prodrug PK

CYPID & -inhibition

f_u in plasma, blood & brain

Environmental excretion

6. Competitor evaluation

- Some good models
- Often lack of validation results
  - in particular for secondary parameters such as exposure, clearance & t½
  - often partial validation (with limited and favourable test sets)
- More common with simulations (rather than predictions)
- Poor prediction accuracy when testing software

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7. Confidence building I-III (internal & external)

I. Complete cross-validations
   =true, forward-looking predictions

II. Predictions for new drugs on the market (2012-18)

III. Early customer predictions & experiences
   Including 3 FTIM-studies

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8. Confidence building IV

IV. External blind validations by small to major international pharmaceutical companies

>150 non-marketed compounds with clinical PK-data

9. Confidence building V

V. Application of conformal prediction methodology

- Assigns confidence measurements in predictions that are both based on the training data and the test objects
- Takes into account strangeness of a new compound *vs* training data
- Smaller prediction intervals produced for “easier” compounds
- Each prediction comes with an estimate and confidence interval
  E.g. 31% (15%; 54%) and 31% (7%; 84%)

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10. Confidence building VI-IX

VI. Satisfied customers and positive reviews

VII. Visibility (marketing, publishing, conference attendance, social media)

VIII. Customers among major companies

IX. Benchmarking (successful)

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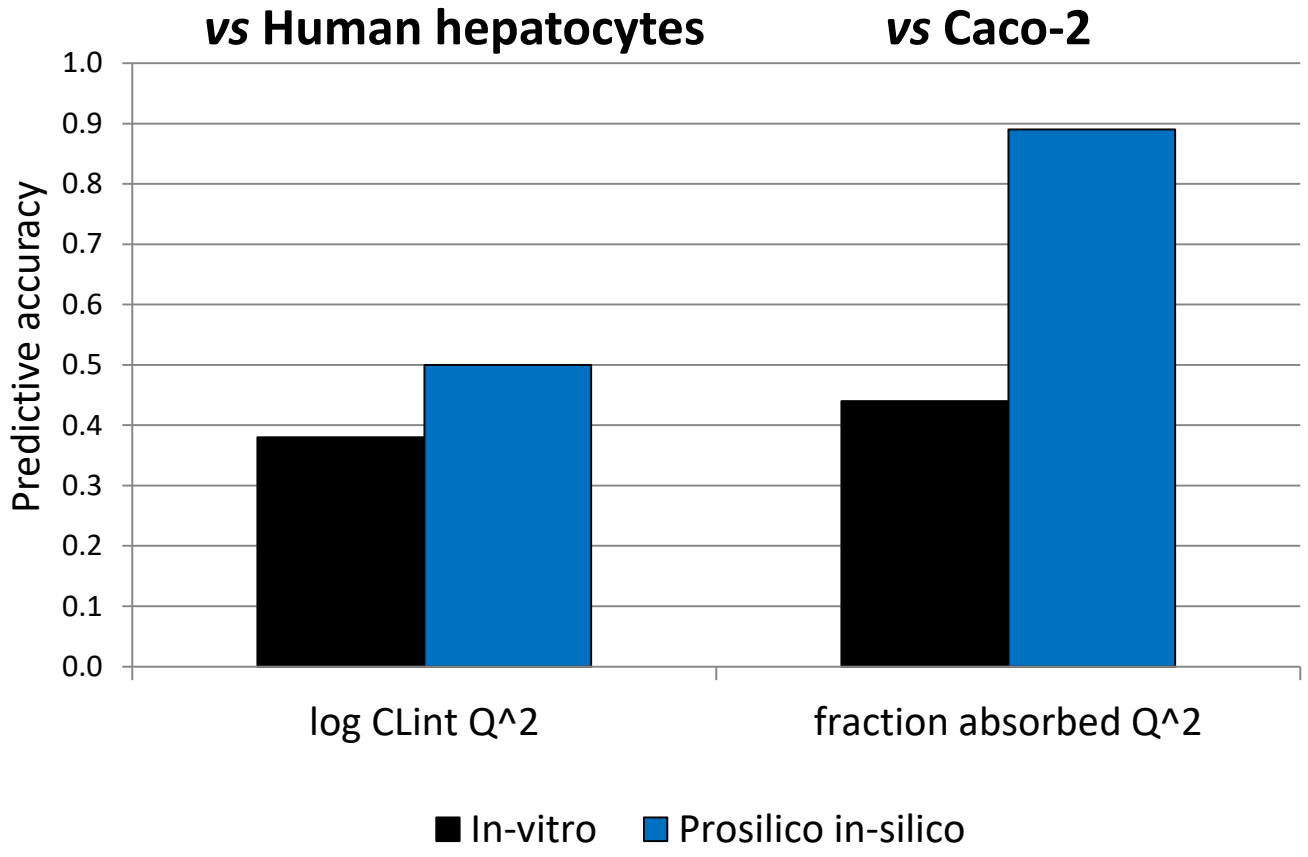
PERFORMANCE - BENCHMARKING



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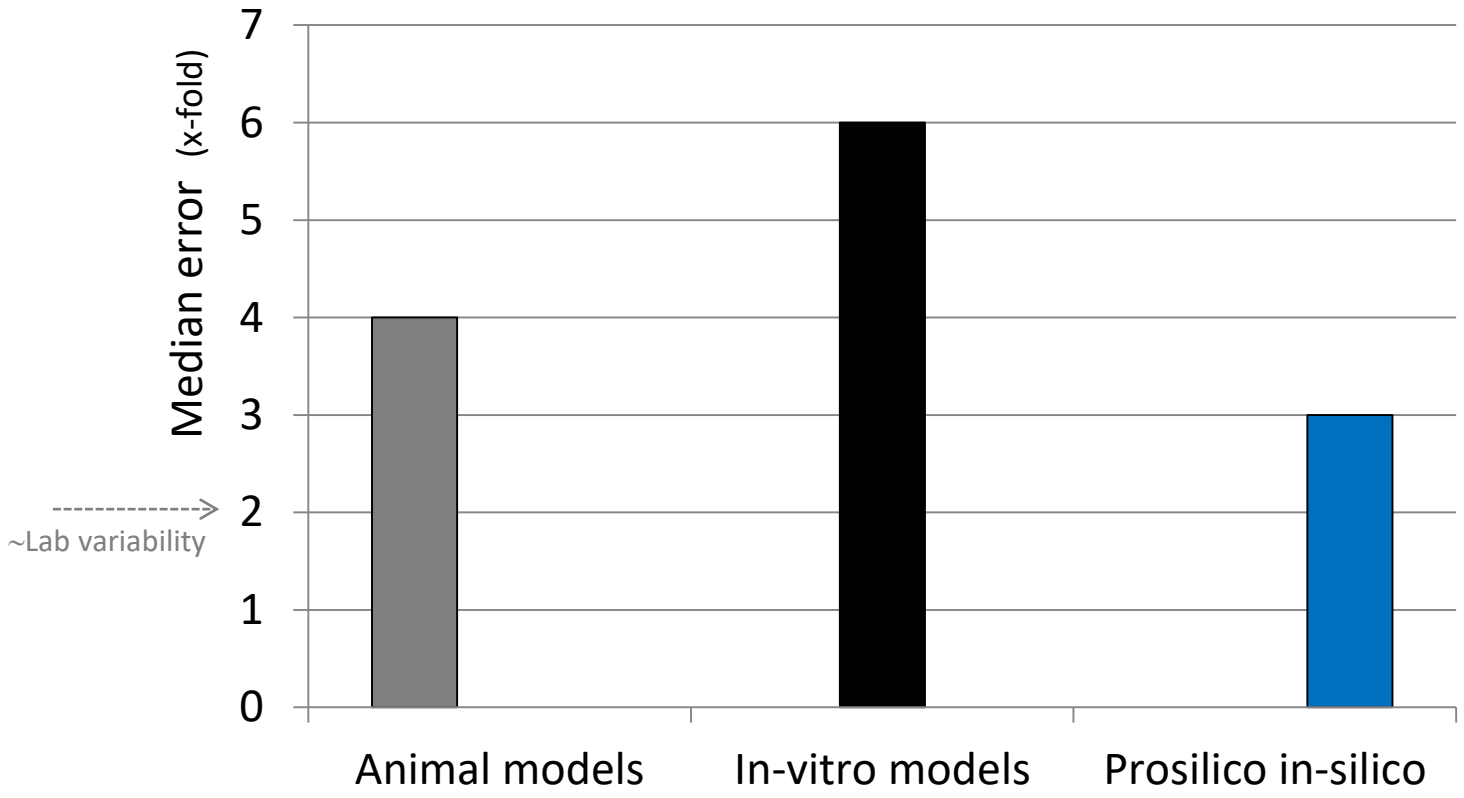
Prediction of exposure after oral dosing (AUC_{po})



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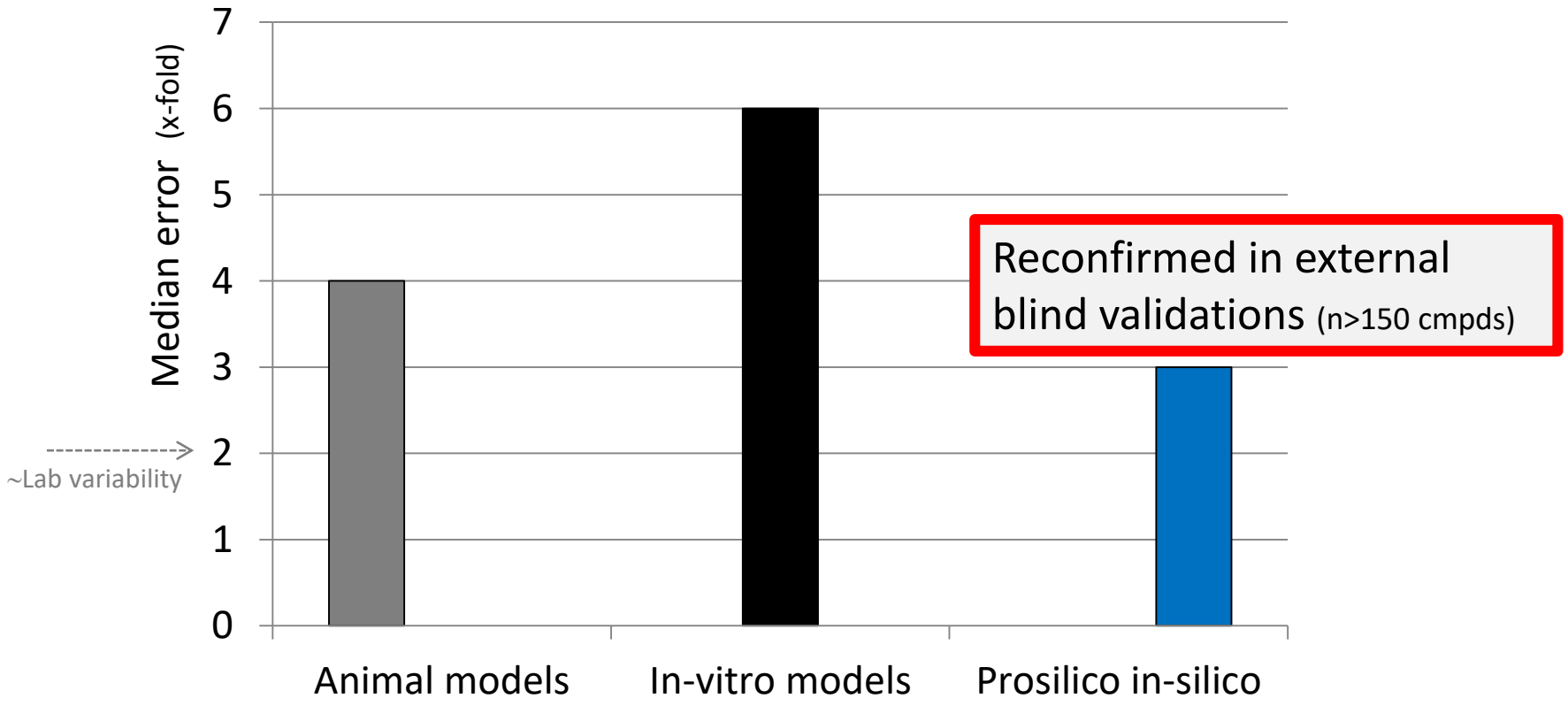

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11. Authority (MPA) views and guidelines

- **No quality standards/limits** for human clinical ADME/PK and dose predictions
  ”*Different from case to case*”!

- Apparantly, **accepts poor methods**
  With >1,000 to ~1,000,000-fold maximum prediction errors

- **Uncertain if accepts performance of our methods**

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12. Confidence building X-XI

X. Let customers make predictions and evaluations themselves – build software

XI. Transparency with results, limitations and strenghts

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Human Clinical ADME/PK-Studio

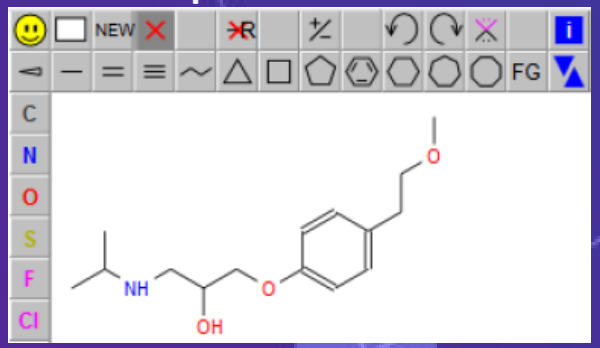
Web-based or intranet installation

Design, Predict & Optimize ADME/PK with Confidence

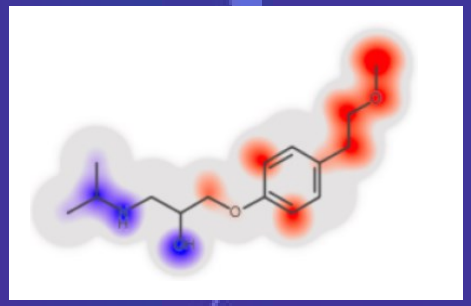
Higher accuracy and broader range than lab methods

Guaranteed confidence limits

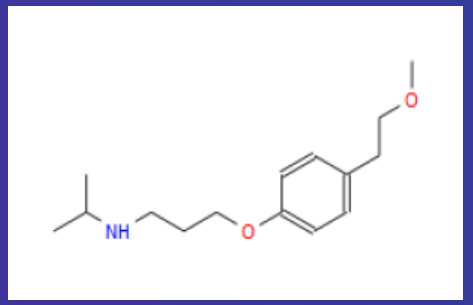
Sketch or paste structure



Guidance

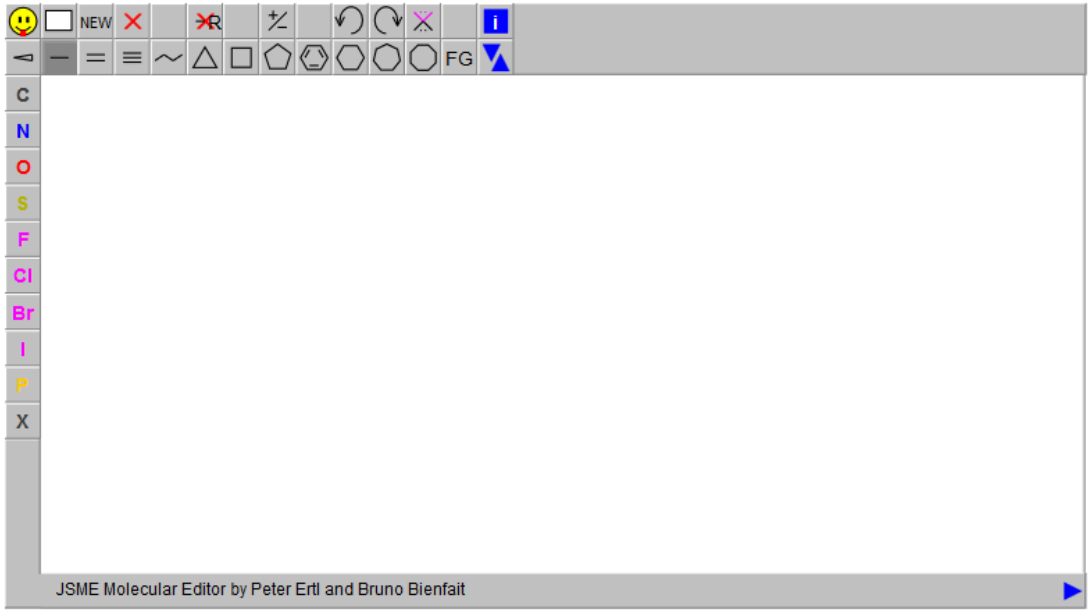


Optimize



Human Clinical ADME/PK-Studio

Prosilico



About

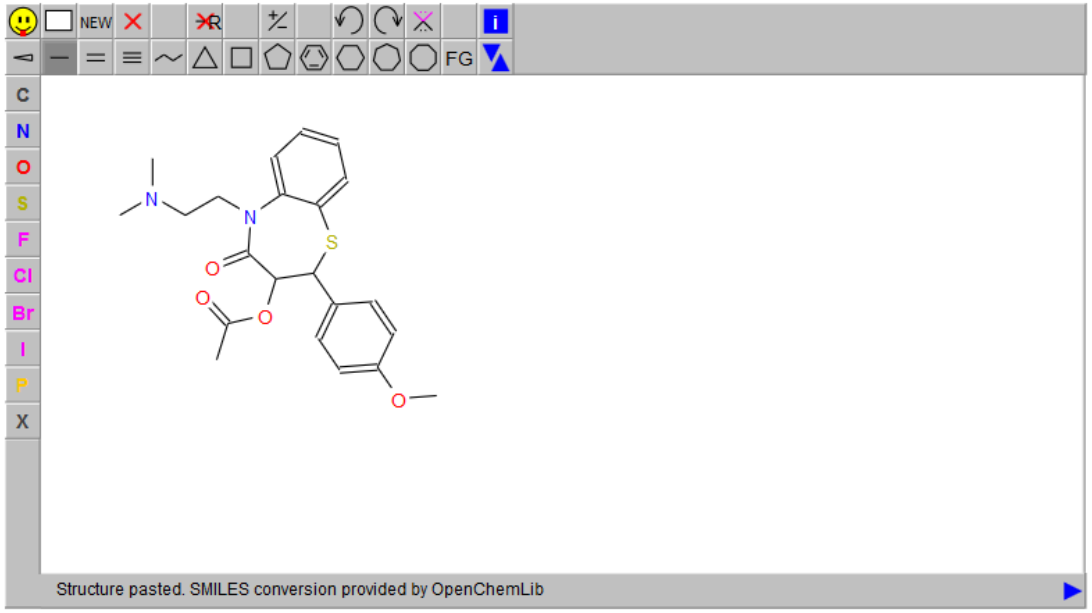
PROSILICO's studio for prediction and optimization of human *in-vivo* ADME/PK.

Read more...

Clear JSME editor

Human Clinical ADME/PK-Studio

Prosilico



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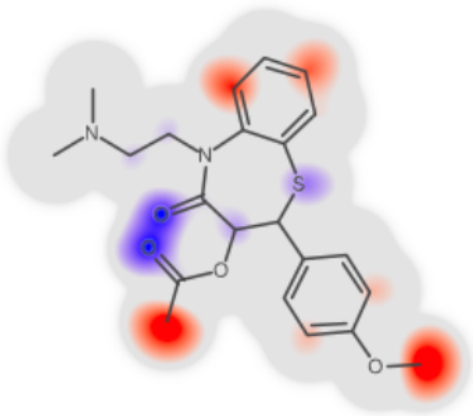
fabs



Absorption

fabs	100% (86%, 100%)
fdiss	100% (77%, 100%)

Distribution

fu	18.0% (4.29%, 51.7%)
Vss	4.1 (1.9, 8.9) L/kg

Metabolism

CLint	1778 (277, 11402) mL/min

Secondary Parameters

CLH	263 mL/min	
t½	13 h	Long Half-life
F	82 %	High Bioavailability

Indications

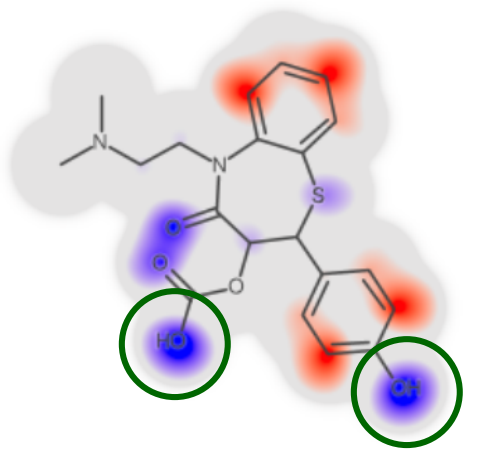
⚠ Renal and/or biliary clearance could contribute significantly to total clearance and produce a lower t½ than estimated based on hepatic clearance only.

⚠ Potential for significant influence of efflux on fabs and F (if efflux occurs)

Contact Prosilico for additional prediction of renal and biliary excretion.

Contact Prosilico for additional predictions of efflux (MDR1, BCRP, MRP2) and its role.

fabs



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Absorption

fabs	87% (73%, 100%)
fdiss	100% (76%, 100%)

Distribution

fu	26.8% (6.54%, 65.7%)
Vss	2.1 (0.84, 5.1) L/kg

Metabolism

CLint	1694 (257, 11143) mL/min

Secondary Parameters

CLH	349 mL/min	
t½	5 h	Medium Half-life
F	67 %	High Bioavailability

Indications

⚠ Renal and/or biliary clearance could contribute significantly to total clearance and produce a lower t½ than estimated based on hepatic clearance only.

⚠ Potential for significant influence of efflux on fabs and F (if efflux occurs)

Contact Prosilico for additional prediction of renal and biliary excretion.

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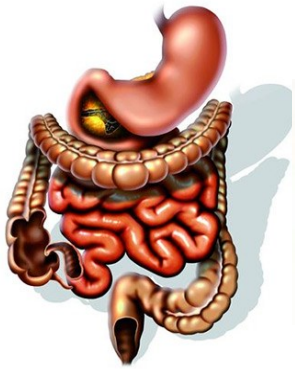
Barrier uptake models

- applicable for tox./risk-evaluations



Q^2 = 0.8

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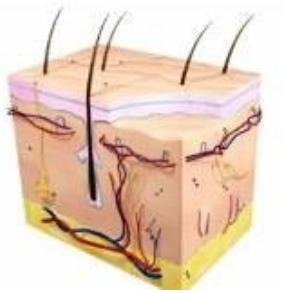
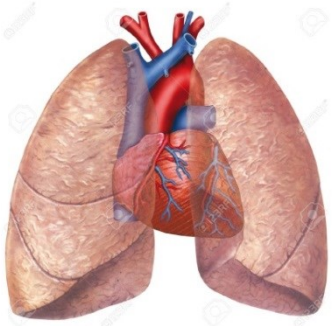
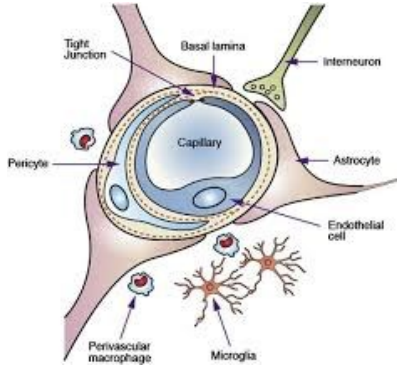


Q^2 = 0.5



Q^2 = 0.5



Q^2 = 0.5

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Summary - Confidence building

I. Cross-validations / only true forward predictions
II. Predictions for new drugs
III. Customer predictions & experiences
IV. External blind validations
V. Conformal prediction methodology
VI. Satisfied customers and positive reviews
VII. Visibility
VIII. Major pharma customers
IX. Successful benchmarking
X. Software (customers can make predictions and evaluations themselves)
XI. Transparency

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Integration of ProSilico into OpenRiskNet

- Publish models under ORN APIs
  - 5 primary endpoints (CPSign models)
  - 3 secondary endpoints
- Run ProSilico services on ORN production cluster
- Incorporate Authentication and Authorization using KeyCloak for ProSilico ORN services
  - Support custom license for ProSilico service
  - ProSilico allowed to authorize specific users with expiry date

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Demo: Accessing ProSilico as OpenRiskNet services via Jupyter Notebook

https://github.com/OpenRiskNet/notebooks/blob/master/prosilico/prosilico-orn.ipynb