Biophysical Models for Prediction of Activity and ADME Parameters: Application to Quinolone Antibiotics

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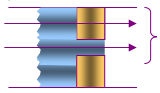
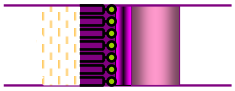
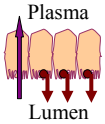
Outline

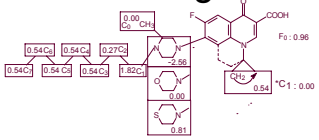
- Biophysical absorption models



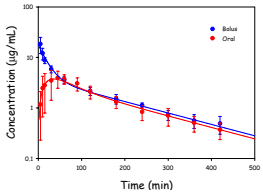




- QSAR methods in drug absorption and activity



- Oral absorption prediction in drug development



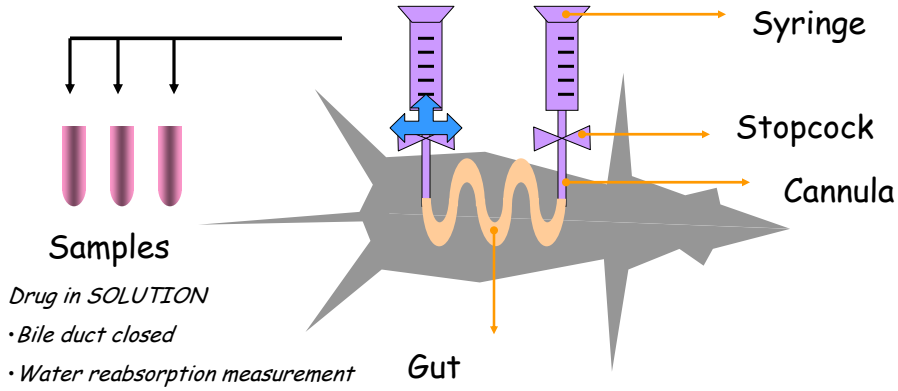
Closed Loop Perfusion Technique: Doluisio's method

Absorption rate coefficient:

$$A_c = A_0 \cdot e^{-ka \cdot t}$$

Permeability values

$$P_{eff} = \frac{k_a \cdot R}{2}$$



Drug in SOLUTION

- *Bile duct closed*
- *Water reabsorption measurement*

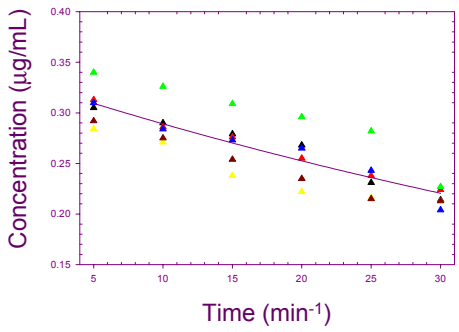
Closed Loop Perfusion Technique: Doluisio's method

Absorption rate constant:

$$A_c = A_0 \cdot e^{-ka \cdot t}$$

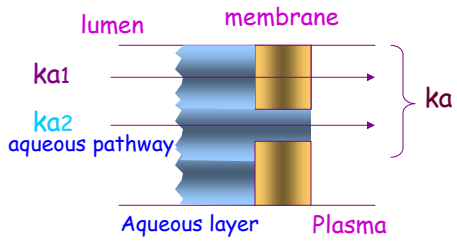
Permeability values

$$P_{eff} = \frac{k_a \cdot R}{2}$$

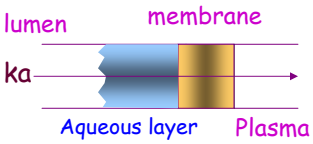


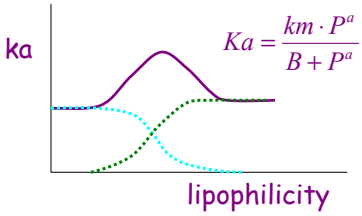
Biophysical Absorption Models: Plá-Delfina and Moreno

Small Intestine

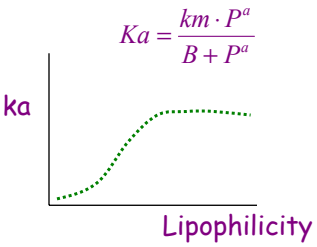


Colon





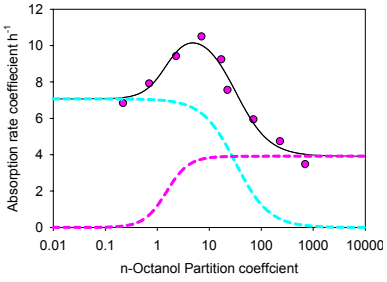
$$Ka = \frac{km \cdot P^a}{B + P^a} + \frac{kp \cdot C}{C + P^d}$$



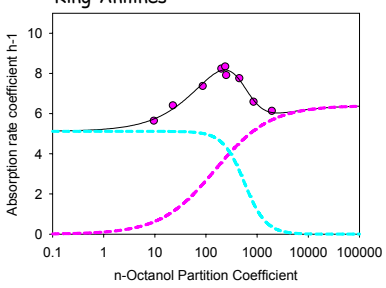
$$Ka = \frac{km \cdot P^a}{B + P^a}$$

Small intestine

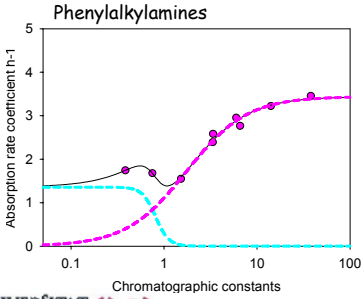
Carbamates



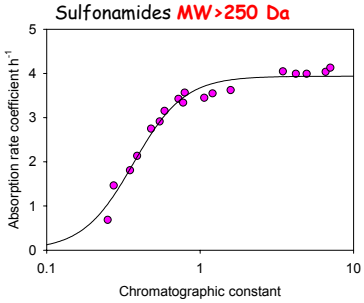
Ring-Anilines



Phenylalkylamines



Sulfonamides MW>250 Da



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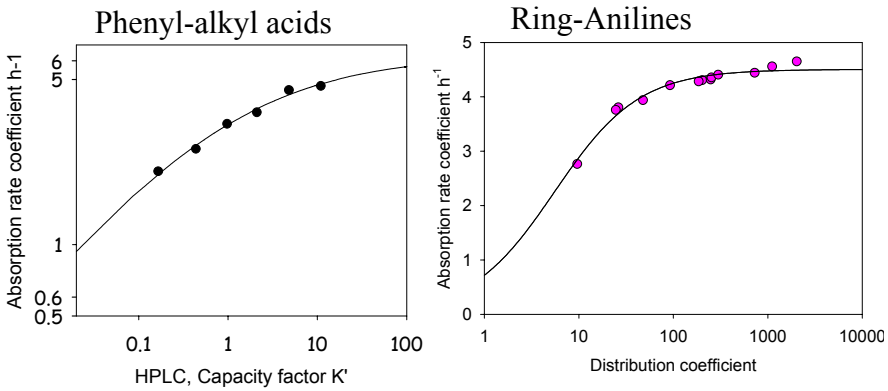
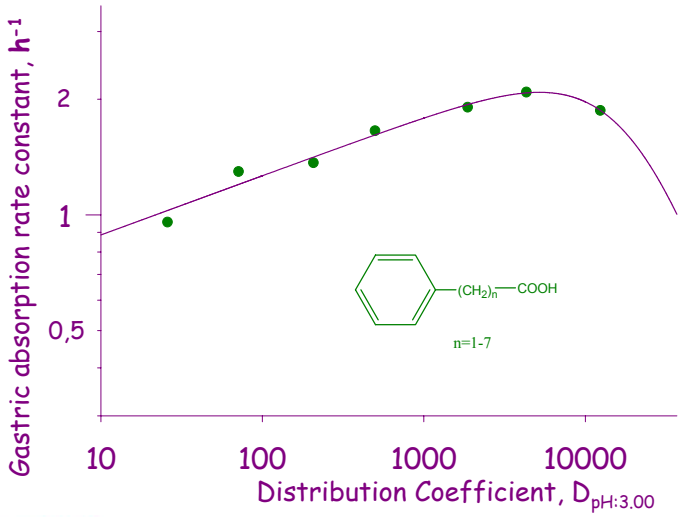


Biophysical Absorption Models: Plá-Delfina and Moreno



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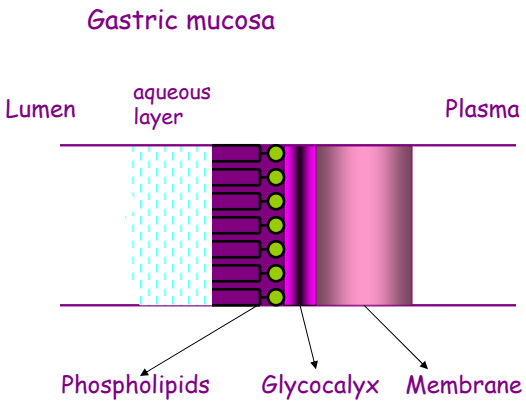
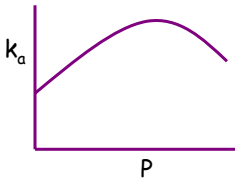
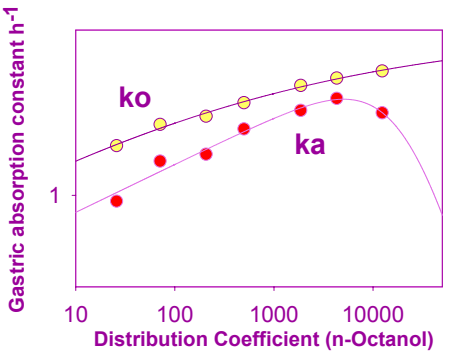
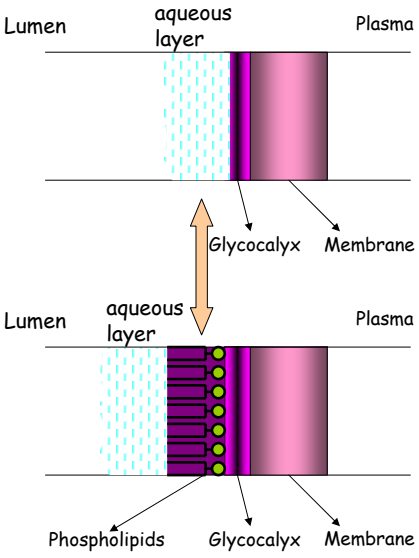




$$k_a = \frac{C \cdot P^d}{1 + E \cdot P^f}$$

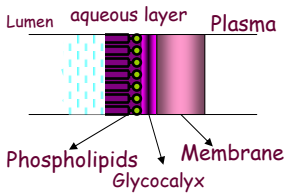
Na TAUROCHOLATE: INTERPRETATION OF ITS ULCEROGENIC EFFECT.

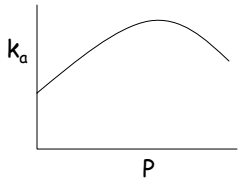




Biophysical Absorption Models: Summary

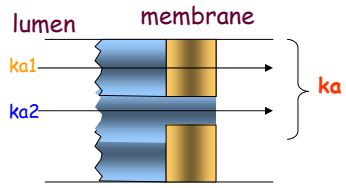
Stomach

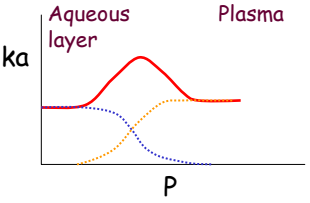




$$k_a = \frac{C \cdot P^d}{1 + E \cdot P^f}$$

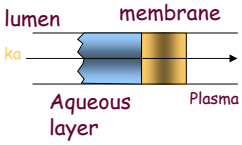
Small Intestine

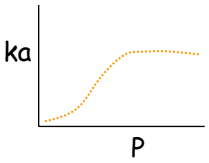




$$Ka = \frac{km \cdot P^a}{B + P^a} + \frac{kp \cdot C}{C + P^d}$$

Colon





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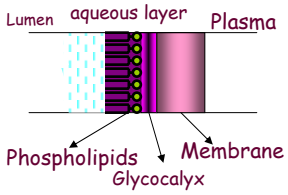
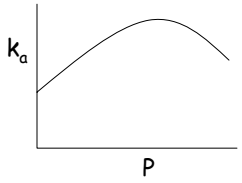
Biophysical Absorption Models: Summary

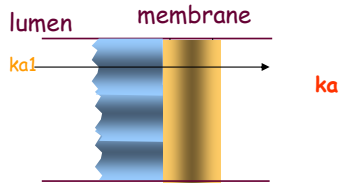
Stomach

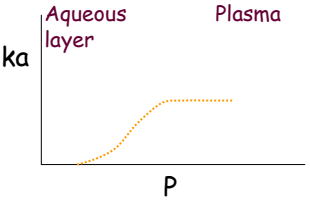




$$k_a = \frac{C \cdot P^d}{1 + E \cdot P^f}$$

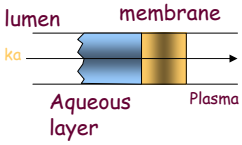
Small Intestine: MW> 250 Da

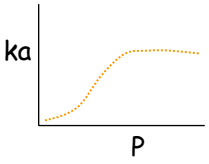




$$Ka = \frac{km \cdot P^a}{B + P^a}$$

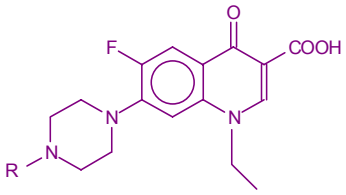
Colon

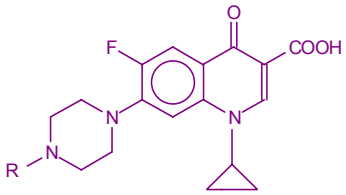




$$Ka = \frac{km \cdot P^a}{B + P^a}$$

Biophysical Absorption Models: Plá-Delfina and Moreno





R= H, Norfloxacin

R= H, Ciprofloxacin

R= CH_3 , CH_3-$(CH_2)_n$ -

n=1-5

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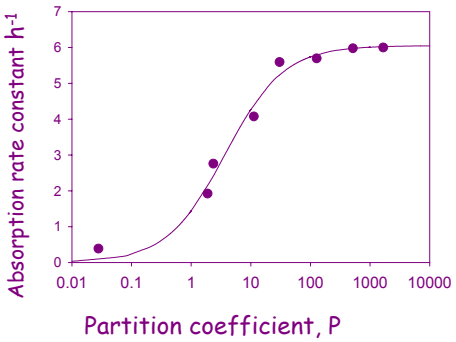
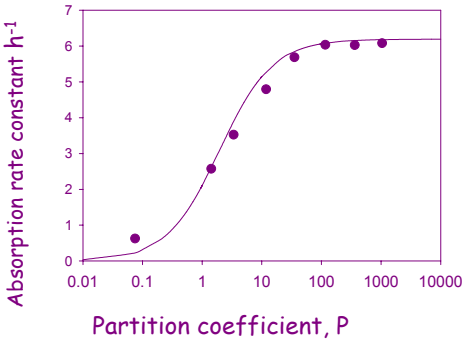
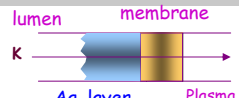
Biophysical Absorption Models: Plá-Delfina and Moreno

Norfloxacin



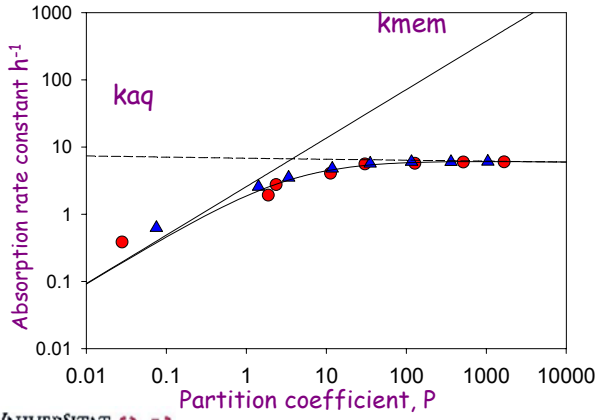
Ciprofloxacin





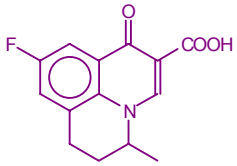
$$\frac{1}{ka} = \frac{1}{kaq} + \frac{1}{kmem}$$

$$k_a = \frac{C \cdot P^d}{1 + E \cdot \sqrt{MW} \cdot P^d}$$

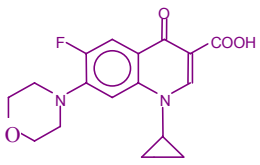


Kaq (h^{-1})	Kmem (h^{-1})
7.073	0.195
6.944	0.397
6.923	3.322
6.801	4.070
6.782	4.795
6.667	6.210
6.649	14.813
6.541	15.359
6.524	30.267
6.422	33.761
6.405	79.701
6.309	85.387
6.293	181.075
6.201	233.991
6.186	389.164
6.099	545.016

QSAR methodologies in drug absorption



Flumequine



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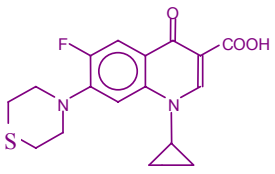

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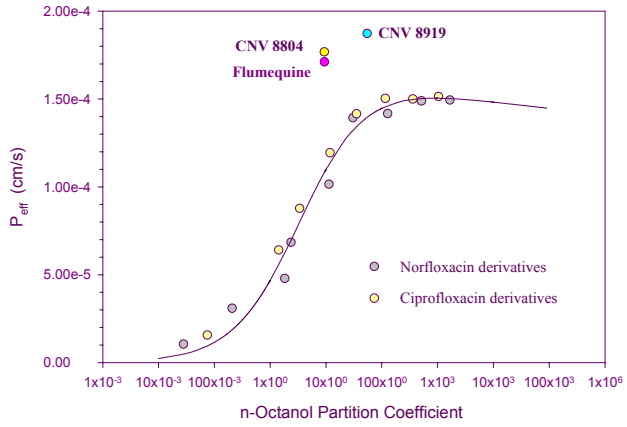
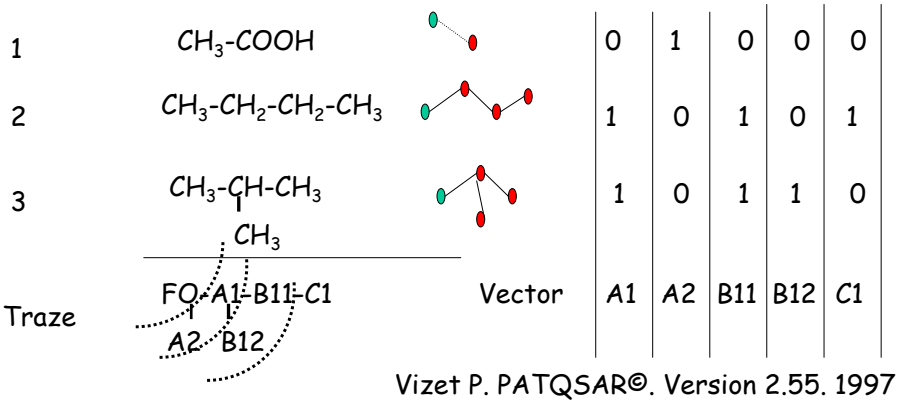
QSAR methodologies in drug absorption

ITODYS. Université Paris VII. France. Prof. Christiane Mercier



QSAR methodologies in drug absorption

ITODYS. Université Paris VII: Vizet P. PATQSAR©. Version 2.55. 1997



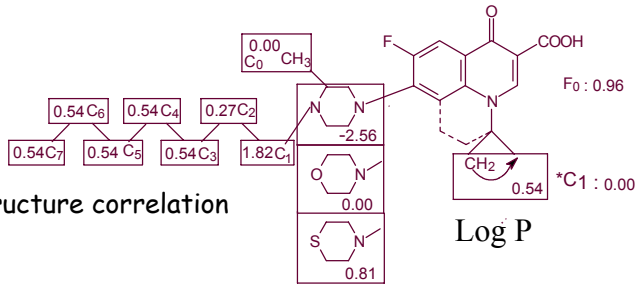
Vizet P. PATQSAR©. Version 2.55. 1997

Compounds	Log Ka exp	Log Ka calc	Log Ka diff	V2	V3	V4	V5	EQ(V6;V7; V8)
BER001	-0.377	-0.319179	-0.0578214	1	0	0	0	0
BER002	0.284	0.321088	-0.0370876	1	0	0	1	0
BER003	0.439	0.461563	-0.0225634	1	0	0	1	1
BER004	0.61	0.602039	0.00796083	1	0	0	1	2
BER005	0.748	0.742515	0.00548502	1	0	0	1	3
BER006	0.755	0.742515	0.012485	1	0	0	1	3
BER007	0.777	0.742515	0.034485	1	0	0	1	3
BER008	0.778	0.742515	0.035485	1	0	0	1	3
BER009	-0.202	-0.259821	0.0578214	1	1	0	0	0
BER010	0.406	0.380445	0.0255553	1	1	0	1	0
BER011	0.547	0.520921	0.0260795	1	1	0	1	1
BER012	0.681	0.661396	0.0196037	1	1	0	1	2
BER013	0.755	0.801872	-0.0468721	1	1	0	1	3
BER014	0.781	0.801872	-0.0208721	1	1	0	1	3
BER015	0.78	0.801872	-0.0218721	1	1	0	1	3
BER016	0.784	0.801872	-0.0178721	1	1	0	1	3
NEW002	0.092	0.092	1.39E-16	1	1	1	0	0
NEW003	0.876	0.874786	0.00121429	0	1	0	0	0
NEW004	0.852	0.874786	-0.0227857	0	1	0	0	0
NEW001	0.837	0.815429	0.0215714	0	0	0	0	0

Dependent variable

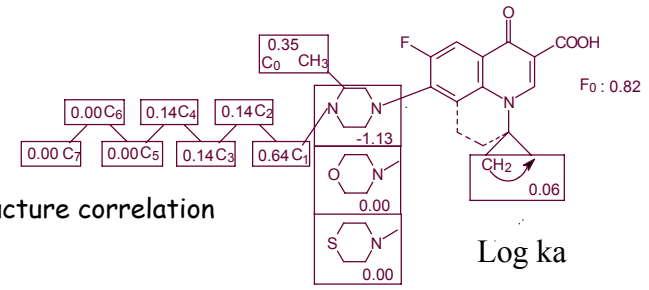
Topological matrix

QSAR methodologies in drug absorption



Lipophilicity-structure correlation

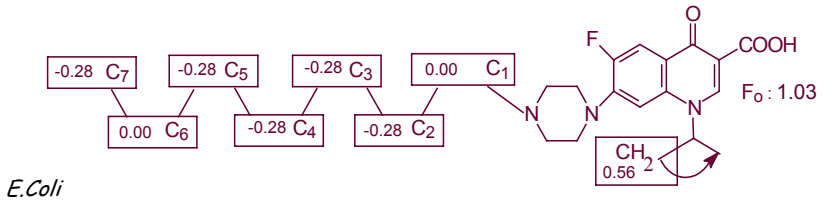
Log P



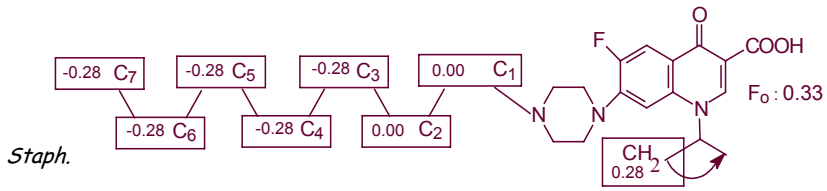
Absorption-structure correlation

Log ka

QSAR methodologies in drug absorption

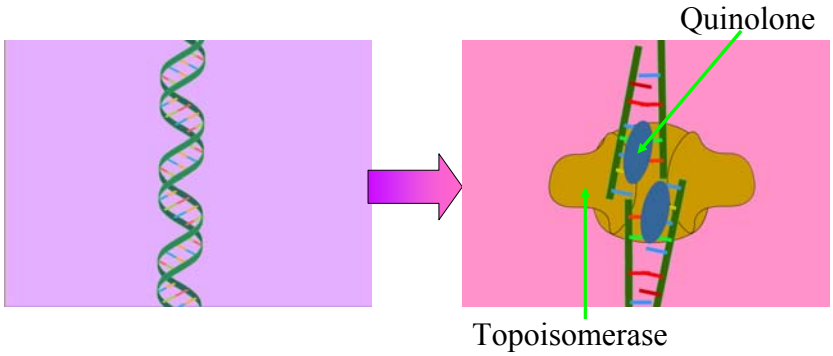


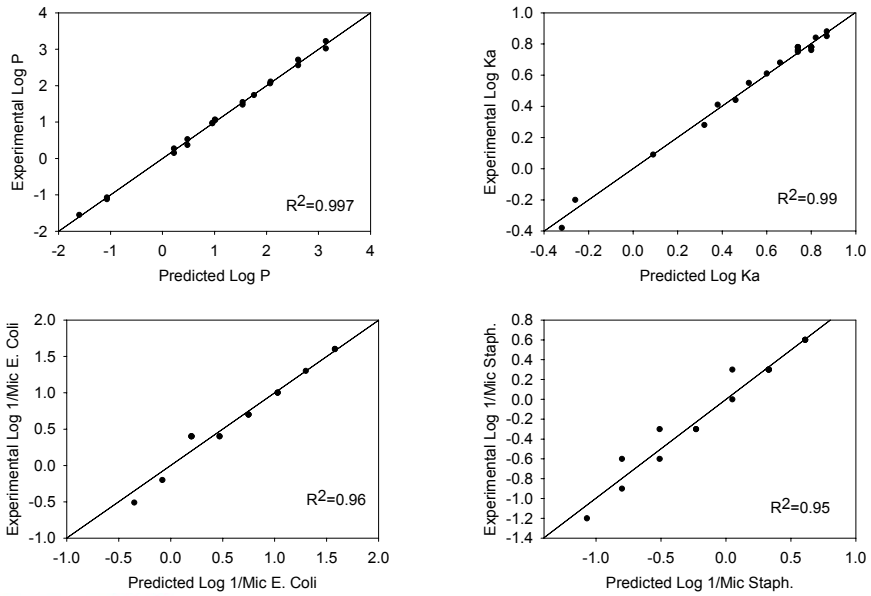
E.Coli



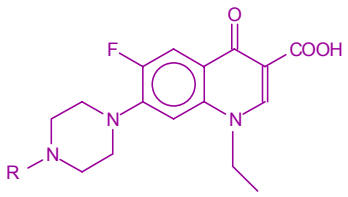
Staph.

Structure- antibacterial activity correlation Log 1/CMI

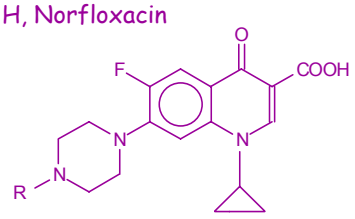




- Lipophilicity is the main factor governing quinolone absorption.
- The absorption-partition relationship has a good predictive performance of intestinal permeability.
- The antibacterial activity is decreased by the N' alkyl chain which hinders the access to the bacterial topoisomerase or drug binding to DNA.



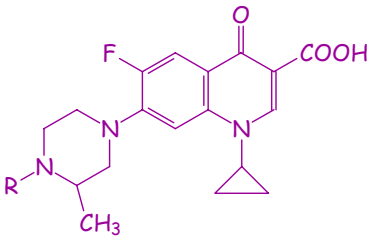
R= H, Norfloxacin



R= H, Ciprofloxacin

R= CH_3 , CH_3-$(CH_2)_n$ - n=1-5

Homologous Compounds



R	Name
H	CNV 97100
$-CH_3$	CNV 97101
$-CH_2-CH_3$	CNV 97102
$-(CH_2)_2-CH_3$	CNV 97103
$-(CH_2)_3-CH_3$	CNV 97104

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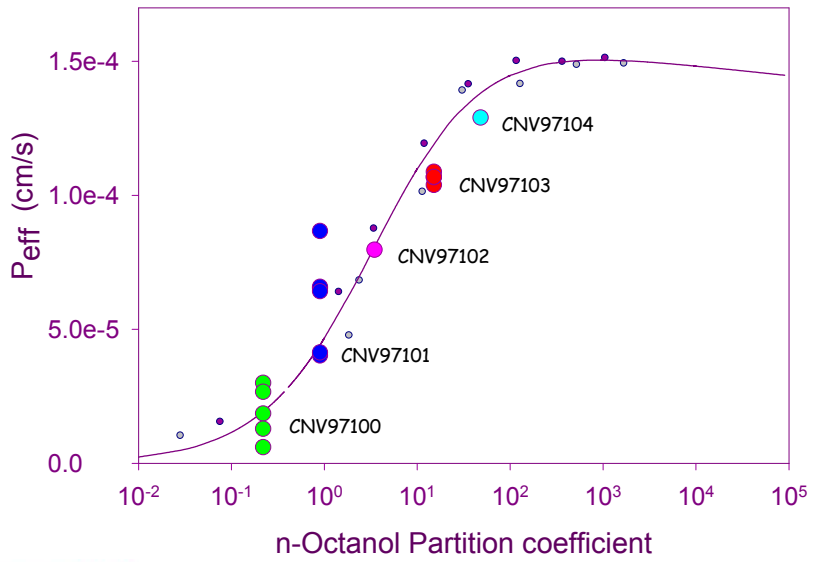
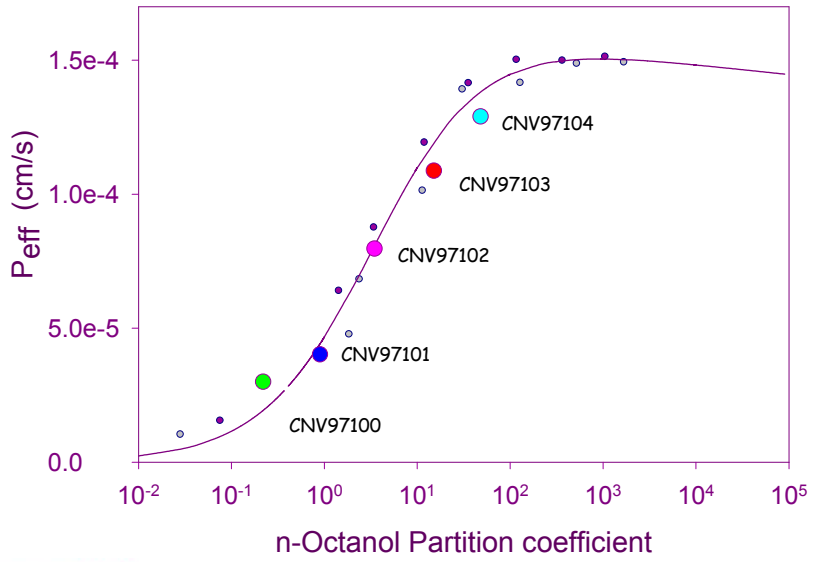
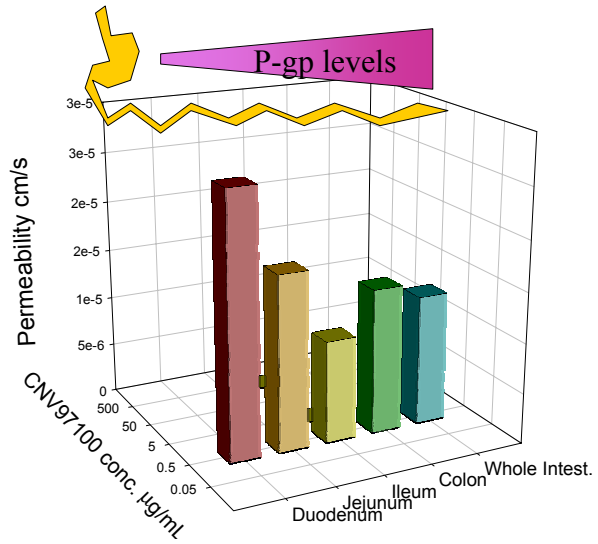
- **CNV9710X derivatives**

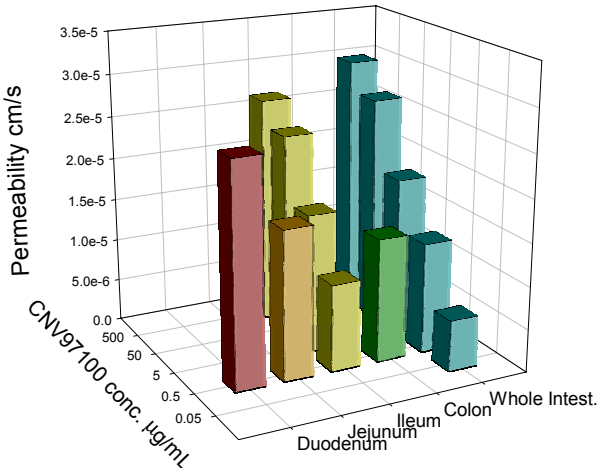


- **CNV9710X derivatives**

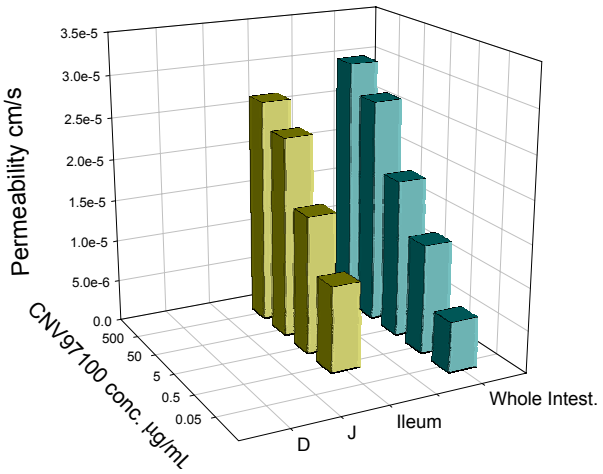


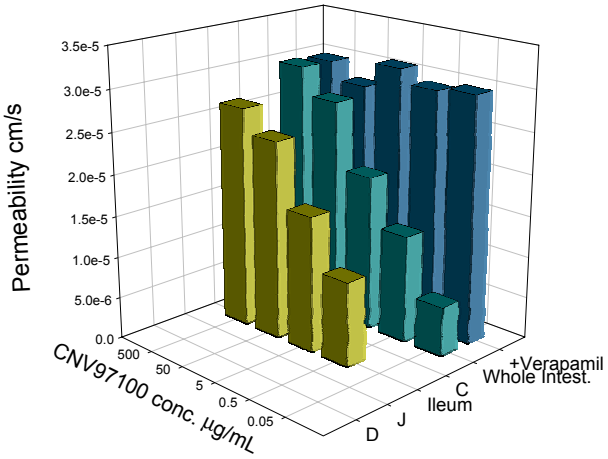


Biophysical models-ADME predictions



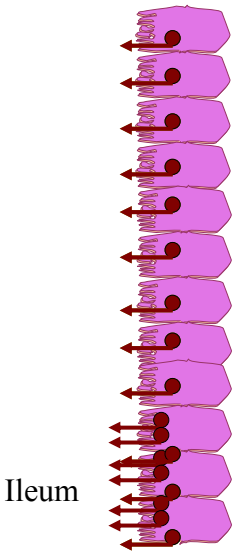
Biophysical models-ADME predictions

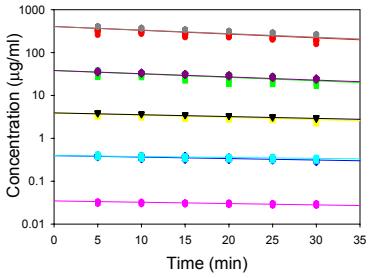




Model assumptions

- Pdiff unchanged along GI tract.
- Efflux system
- Km value (affinity) is unchanged along GI tract.
- Vm= f(expression level).





Parameter	*In situ study Value (SD)*
Pdiff(cm·s-1)	$3.07 \cdot 10^{-5}$ $(0.20 \cdot 10^{-5})$
Vm (nmol·s-1·cm-2) Whole intestine	$3.06 \cdot 10^{-4}$ $(1.76 \cdot 10^{-4})$
Vm (nmol·s-1·cm-2) ileum	$3.94 \cdot 10^{-4}$ $(2.06 \cdot 10^{-4})$
Km (µM)	15.94 (8.25)

Whole intestine

$$\frac{dC}{dt} = -\left(\frac{2}{R_a} \cdot P_{diff}\right) \cdot C + \frac{2}{R_a} \cdot \frac{V_{\max -a} \cdot C}{K_m + C}$$

Ileum

$$\frac{dC}{dt} = -\left(\frac{2}{R_b} \cdot P_{diff}\right) \cdot C + \frac{2}{R_b} \cdot \frac{V_{\max -b} \cdot C}{K_m + C}$$

CNV97100 shows a saturable efflux process verapamil sensitive.

The quinolone effective permeability is lower in rat ileum due to the higher P-glycoprotein expression level.

Oral absorption prediction in drug development

"Bioavailability prediction in drug development: fluoroquinolones. CICYT (SAF 96-1710)" Director. Prof. Plá-Delfina

$$F = Fa \cdot (1 - E_g) \cdot (1 - E_h)$$

E_g= gut first-pass effects

E_h= liver first-pass effects

Oral absorption prediction in drug development

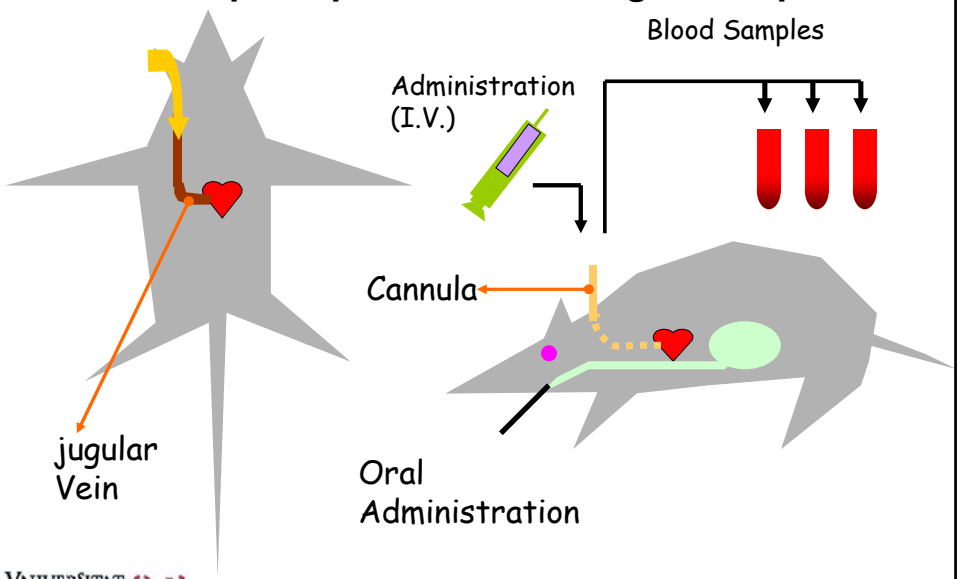
$$F = Fa \cdot$$

$$F_a = 1 - e^{-ka \cdot T}$$

$$F_a = 1 - e^{-(\frac{2}{R} P_{eff} \cdot T_{res})} \qquad F_a = 1 - e^{-(\frac{2}{T_{abs}} \cdot T_{res})}$$

$$F_a = 1 - e^{-(2 \cdot A_n)}$$

Oral absorption prediction in drug development



Oral absorption prediction in drug development

Oral administration
Group A (8-12 rats)

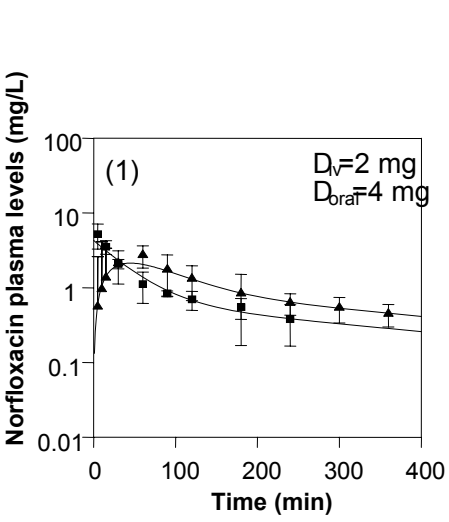
I.V administration
(bolus or perfusion)
Group B (8-12 rats)

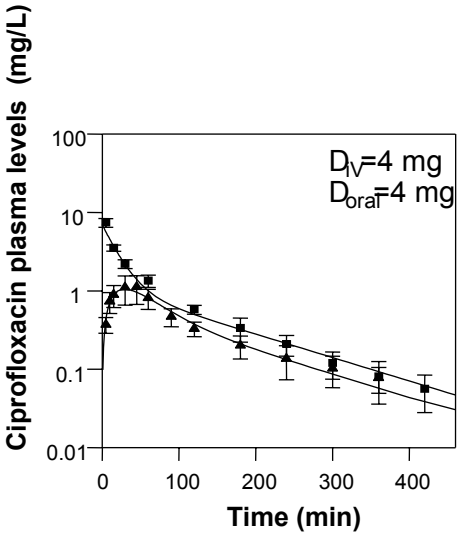
Plasma
sampling and
Analysis

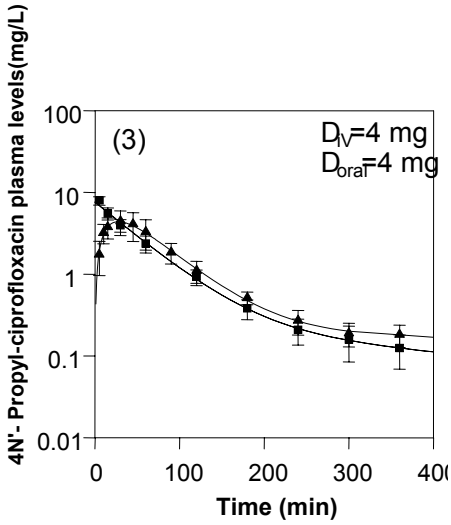
AUC_0^{∞}
calculation

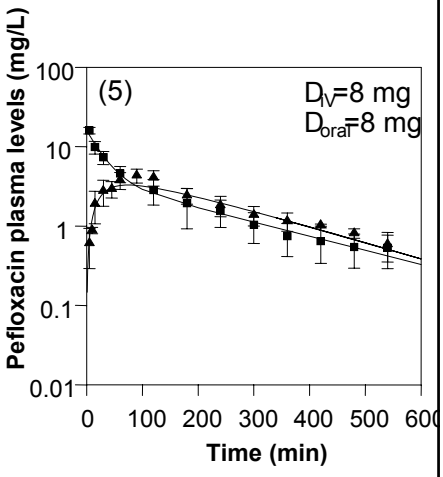
AUC_0^{t} + AUC_t^{∞}
(Trapezoidal rule) (C_t/k)

PK Population analysis: Nonmem v.5.0
Post-hoc Bayesian ind. parameter estimation

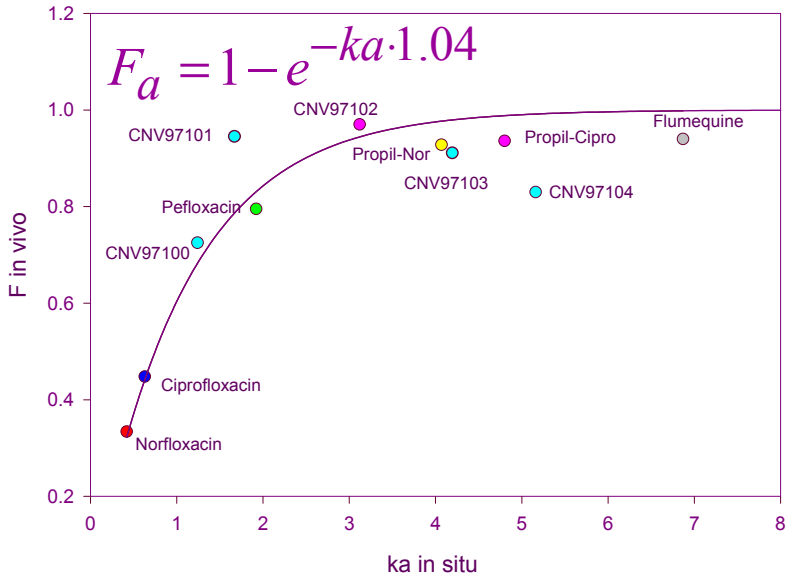




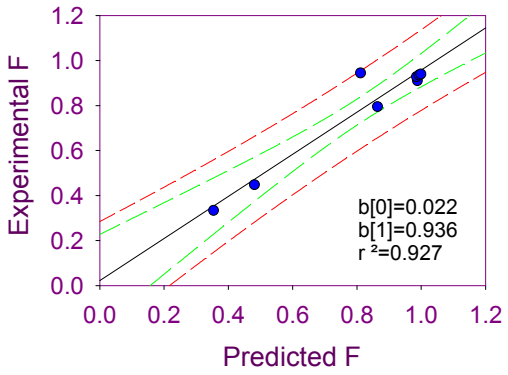


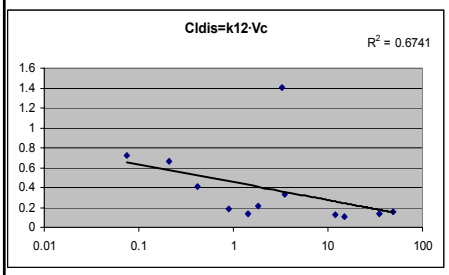


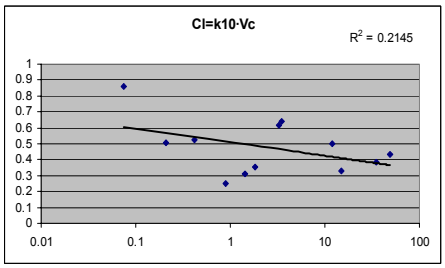
$$F_a = 1 - e^{-ka \cdot 1.04}$$

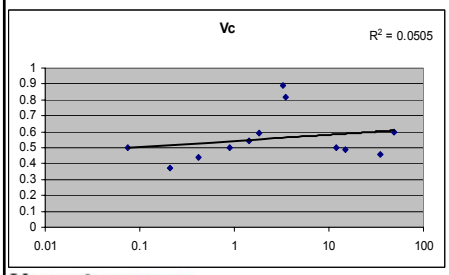


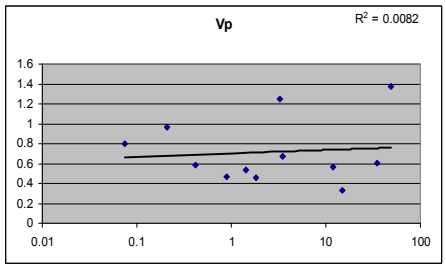
$$F_a = 1 - e^{-ka \cdot 1.04}$$



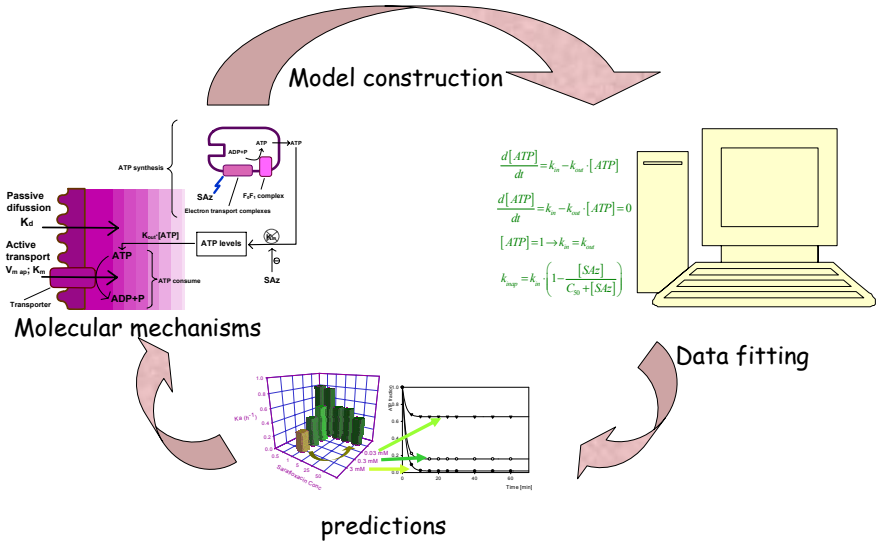




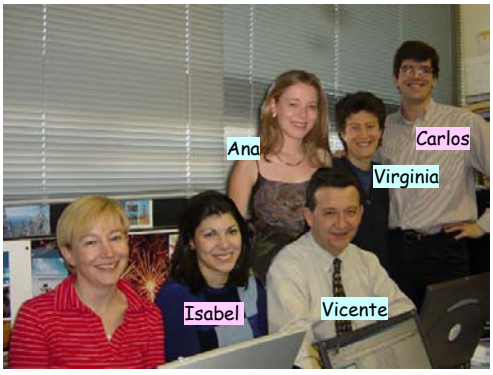




- The *in situ* intestinal permeability is a good predictive parameter of *in vivo* Fa.
- The saturable (efflux and absorption) processes observed *in situ* (and *in vitro*) had not a significant influence *in vivo* in rats at the oral doses used.
- Disposition parameters……..still under modelling



Acknowledgments



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