

How to improve the accuracy of drug-drug interaction risk prediction for mechanism based inhibitors

Benjamin Kably¹, [Ludwig Vincent](#)², Laurence Proust², Julie Trasbot², Laurence Launay², Maud Beneton², Yannick Parmentier², Marylore Chenel²

¹Pharmacology, Hôpital Européen Georges Pompidou, AP-HP, ²Centre of Excellence in Pharmacokinetics, Servier, France



PURPOSE

- Mechanism-based inhibition (MBI) is a subtype of enzymatic inhibition in which the enzyme is permanently inactivated by an intermediate reactive metabolite that irreversibly binds to the active site.
- It has been shown that for this type of inhibitors, the recommended methods to predict the risk of drug-drug interactions (DDI) used in early development stages tend to over-estimate the real interaction observed in clinical studies.
- Several factors may impact these predictions and could explain this over-prediction: inhibitor concentration ($[I]$), inhibition parameters (K_i/k_{inact}) or enzyme degradation constants (k_{deg}) used in the calculations.
- The aim of this work was to evaluate the different DDI risk assessment methods for MBI and the impact of each parameter in order to identify the optimal conditions for a more accurate prediction.

METHODS

Literature review

We first identified 14 MBI drugs and collected the parameters needed to predict DDI (f_l , C_{max} , k_{deg} or $t_{1/2}$ (CYP), K_i , k_{inact} , F_g , f_m (CYP)) : casopitant, cimetidine, clopidogrel, dalcetrapib, dasatinib, diltiazem, erythromycin, gemfibrozil, nelfinavir, paroxetin, ritonavir, rofecoxib, saquinavir and tienilic acid

Prediction models comparison

We compared the different calculation methods for inhibition ratio R :

- **the basic model** : $R = \frac{AUC_i}{AUC} = \frac{k_{obs} + K_{deg}}{K_{deg}}$ with $k_{obs} = \frac{k_{inact} \times K_{deg}}{K_i + [I]}$

For the MBI concentration $[I]$, different values were compared : C_{max} , $C_{max,u}$, C_{in} , $C_{in,u}$
Two experimental methods used for determining K_i/k_{inact} were also tested (see below)

- **the mechanistic static model** :

As described by Fahmi et al. (1), this model was applied to 4 drugs for which the static model mispredicted the risk, whatever the parameters used : Ritonavir, Saquinavir, Dasatinib and Rofecoxib

$$R = \frac{AUC_i}{AUC} = \left(\frac{1}{[A_g \times Bg \times Cg] \times (1 - Fg) + Fg} \right) \times \left(\frac{1}{[A_h \times Bh \times Ch] \times fm + (1 - fm)} \right)$$

- **the dynamic PBPK model**

The PBPK models were developed and qualified with SimCYP® version 16 for Dasatinib and Rofecoxib (implemented parameters are shown here).

The Ritonavir and Saquinavir models used are from the software compound libraby.



TABLE 1: Input parameter values used to simulate the kinetics of Rofecoxib and Dasatinib

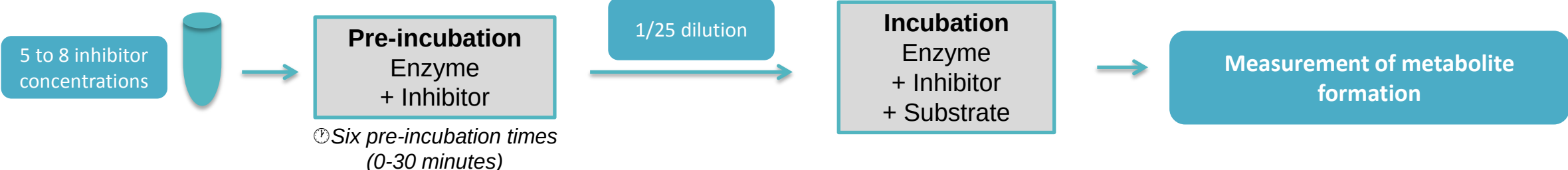
	Rofecoxib	Reference / PMID	Dasatinib	Reference / PMID
Molecule Type	Small Molecule	-	Small Molecule	-
Mol Weight (g/mol)	314,360	www.drugbank.ca	488,01	www.drugbank.ca
log P	3,200	-	1,8	-
Compound Type	Monoprotic Base	-	Diprotic Base	-
pKa 1 – pKa 2	14,0	www.drugbank.ca	3,1 – 6,8	Guidlink product information
B/P	1,0	Fixed	1,8	FDA Review NDA021986-022072
fu	0,130	Rofecoxib SmPC	0,04	Dasatinib SmPC
Absorption Model	1st order	-	1st order	-
fa	1,000	Fixed	0,775	SimCYP® prediction tool
ka (1/h)	2,100	16985100	6,0	Fixed
fu(Gut)	0,015	SimCYP® prediction tool	0,178	SimCYP® prediction tool
Q(Gut) (L/h)	0,824	-	12,049	tool
Distribution Model	Minimal PBPK Model	-	Minimal PBPK Model	-
Vss (L/kg)	1,350	Rofecoxib SmPC	4,2	17429625
LiverKp	1,000	Fixed	1,0	Fixed
Clearance Type	In Vivo Clearance	-	In Vivo Clearance	-
CL (po) (L/h)	5,130	Rofecoxib SmPC	90,3	17429625
Enzyme	CYP1A2	-	CYP3A4	-
MBI Kapp (µM)	4,800	16985100	6,3	22685217
MBI Kinact (1/h)	4,200	16985100	2,04	22685217

K_i/k_{inact} determination methods comparison

Two experimental methods used for determining these parameters were compared to evaluate the impact of the values on the R calculations

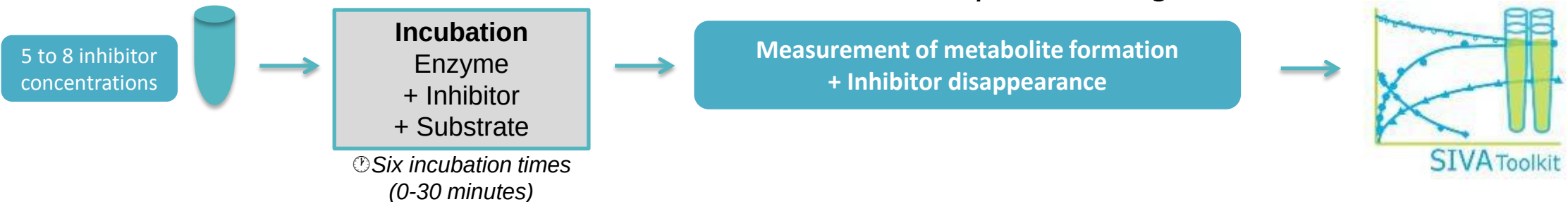
① a conventional method

- includes a pre-incubation step with the MBI before the substrate co-incubation



② an alternative one-step substrate disappearance kinetic method

- allows to take the inhibitor depletion and the competitive inhibition into account
- results obtained from this method were computed using the SIVA® software



RESULTS (1)

Static model calculations

The comparison of the DDI risk predictions obtained for 14 MBI drugs with the static method showed that the $C_{max,u}$ gave the largest number of acceptable predictions among the 4 possible inhibitor concentration values

$[I]$	% of $R_{predicted}/R_{observed}$ ratios contained within [0.5; 2]
C_{max}	12,2
$C_{max,u}$	39,3
C_{in}	0
$C_{in,u}$	8,2

TABLE 2 : Accuracy of predictions calculated with the static model depending of the $[I]$ value

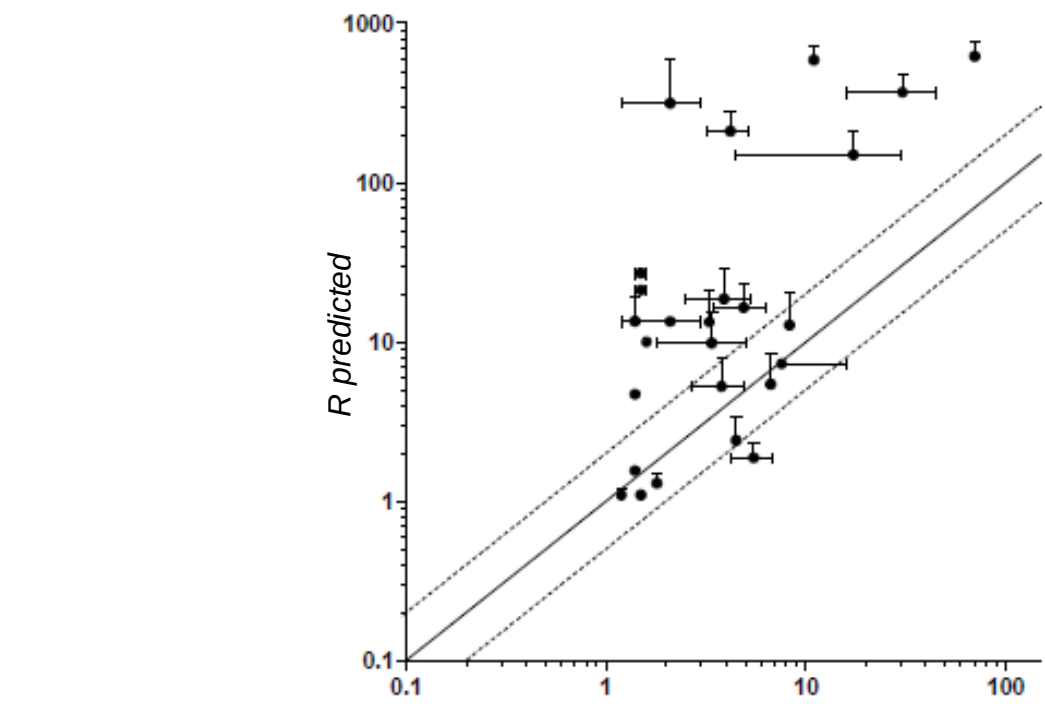


FIGURE 1: Predicted and observed R values (means and standard deviation) for 14 MBI drugs when using the static model and $[I] = C_{max,u}$

REFERENCES

- (1) Fahmi et al., Drug Metab. Dispos. Biol. Fate Chem., vol. 37, no. 8, pp. 1658–1666, Aug. 2009
- (2) Bachmann et al., J. Clin. Pharmacol., vol. 43, no. 10, pp. 1082–1090, Oct. 2003
- (3) Greenblatt et al., Br. J. Clin. Pharmacol., vol. 68, no. 6, pp. 920–927, Dec. 2009
- (4) Dasatinib FDA Review (Clinical Pharmacology and Biopharmaceutics review)
- (5) Abel et al., Br. J. Clin. Pharmacol., vol. 65 Suppl 1, pp. 27–37, Apr. 2008

The parameters implemented within the PBPK models obtained from the literature were found in the DDB database

CONCLUSION & DISCUSSION

Our results showed that the basic model more accurately predicts the risk of DDI with MBIs using $C_{max,u}$ as the inhibitor concentration. The alternative method for K_i/k_{inact} determination, that can potentially overcome several hypotheses made by the two-step conventional method, was evaluated but did not show a clear benefit in the case of the Ritonavir, although a largest evaluation is needed. Nevertheless, the simultaneous estimation of other parameters (K_{cat} , K_d , K_m) on top of the MBI's parameters (K_i/k_{inact}) may explain the shortcoming of this model. All the more since these parameters are often unknown in early stages of the development.

Despite the need of many parameters to be qualified and used as a tool for clinical studies simulations, the use of PBPK modeling showed a real improvement regarding the accuracy of DDI risk prediction for MBIs.

RESULTS (2)

Mechanistic static model simulations

When applied to the 4 selected MBI drugs, the mechanistic static model showed better results in the accuracy of DDI predictions : 61,8 % of the clinical studies simulated resulted in acceptable $R_{predicted}/R_{observed}$ ratios

Inhibitor	Clinical study		Prediction			Ratio (basic model)
	Dose (mg)	Substrate	$R_{observed}$	$R_{predicted}$	Ratio	
Rofecoxib	50	Theophyllin	1,6 (2)	2.3	1.4	6.3
Ritonavir	100	Midazolam	25,6 (3)	27.4	1.1	3.5
Dasatinib	100	Simvastatin	1,2 (4)	6.1	5.1	1.0
Saquinavir	1200	Maraviroc	4.25 (5)	6.4	1.5	19.1

TABLE 3 : DDI interaction ratios calculated using the mechanistic static model (one example per drug)

RESULTS (3)

PBPK model qualification

Pharmacokinetic studies of the selected MBI drugs administered alone were simulated using the built models. The PBPK models correctly described Dasatinib, Rofecoxib and Ritonavir concentration-time profiles and showed AUC and C_{max} predicted/observed ratios within the [0,5 ; 2] interval and were therefore qualified. The Saquinavir model could not be qualified.

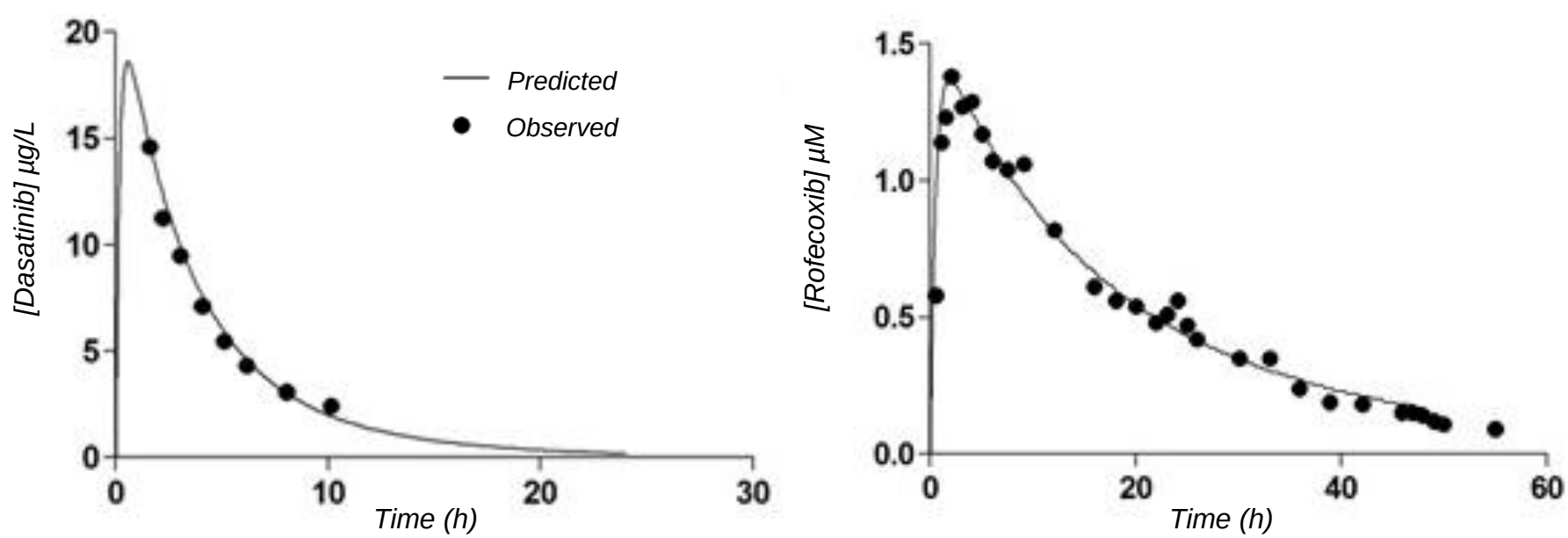


FIGURE 2: Observed and simulated pharmacokinetic of Dasatinib and Rofecoxib following a single PO administration in healthy volunteers.

PBPK model simulations

The DDI risk assessment performed using PBPK modeling for the selected molecules showed acceptable $R_{predicted}/R_{observed}$ ratios for all the interaction studies simulated and therefore greatly improved the predictions.

Inhibitor	Clinical study				$R_{predicted}$	Ratio	Ratio (basic model)	Ratio (mechanistic model)
	Dose (mg)	Substrate	$R_{observed}$	PMID				
Rofecoxib	12,5	Theophyllin	1,38	14517190	1.79	1.30	3.4	1.3
	25	Theophyllin	1,5		2.08	1.39	4.9	1.4
	50	Theophyllin	1,6		2.33	1.46	6.3	1.4
Ritonavir	500	Sildenafil	11	10930961	10.8	0.98	62.4	0.9
	200	Triazolam	20,4	10935688	25.83	1.27	14.9	1.7
	200	Triazolam	40,7	16513448	25.83	0.63	7.5	0.9
	100	Midazolam	25,6	20002087	14.15	0.55	3.5	1.1
Dasatinib	100	Simvastatine	1,2	FDA Review	1.1	1.30	1.0	5.1
Saquinavir	1200	Midazolam	5.18	10430107	ND		15.6	6.7
	1200	Sildenafil	3.1	10930961	ND		26.1	3.2
	1200	Maraviroc	4.25	18333863	ND		19.1	1.5

TABLE 4 : DDI interaction ratios calculated using PBPK simulations (all studies simulated are shown and ratios are compared with those obtained with the basic and mechanistic models)

RESULTS (4)

K_i/k_{inact} determination methods comparison

Using the conventional method, all the inhibition parameters K_i and k_{inact} were determined. The values found were similar to the previously published values (less similar for Saquinavir with no obvious reason).

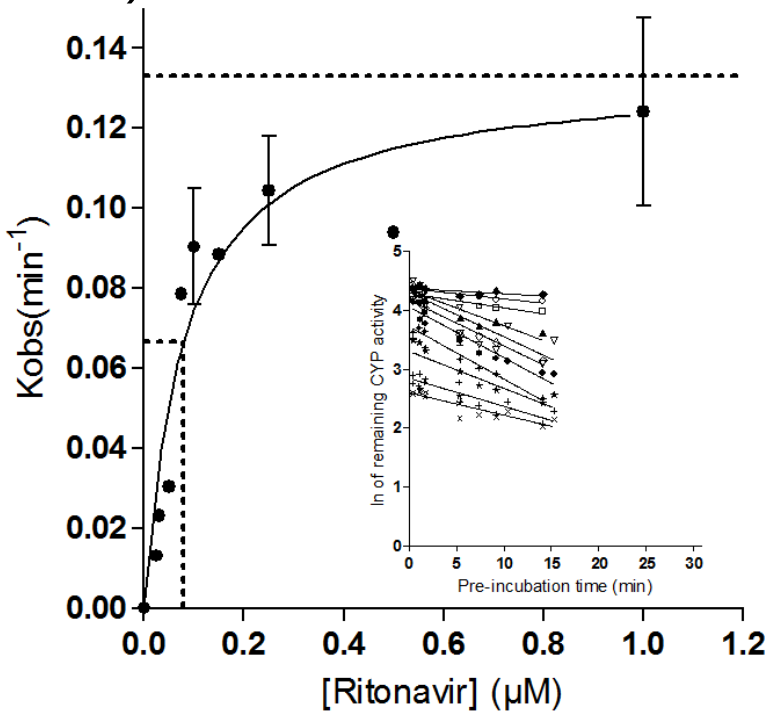


FIGURE 3 : Inhibition parameters determination for Ritonavir with the conventional two-step method

Rofecoxib		Ritonavir		Saquinavir		Dasatinib	
Conventional 2-step method							
K_I	k_{inact}	K_I	k_{inact}	K_I	k_{inact}	K_I	k_{inact}
4.63	0.031	0.08	0.1332	4.88	0.041	9.33	0.025
Published values							
K_I	k_{inact}	K_I	k_{inact}	K_I	k_{inact}	K_I	k_{inact}
4.87	0.07	0.38	0.45	0.65	0.25	6.3	0.034
Alternative 1-step method							
K_I	k_{inact}	K_I	k_{inact}	K_I	k_{inact}	K_I	k_{inact}
ND	ND	0.524	0.328	ND	ND	ND	ND

TABLE 5 : In vitro inhibition parameters obtained with the conventional and alternative method

Using the alternative method, the inhibition parameters K_i and k_{inact} could only be determined for one drug (Ritonavir) and the values were similar to the previously published values.

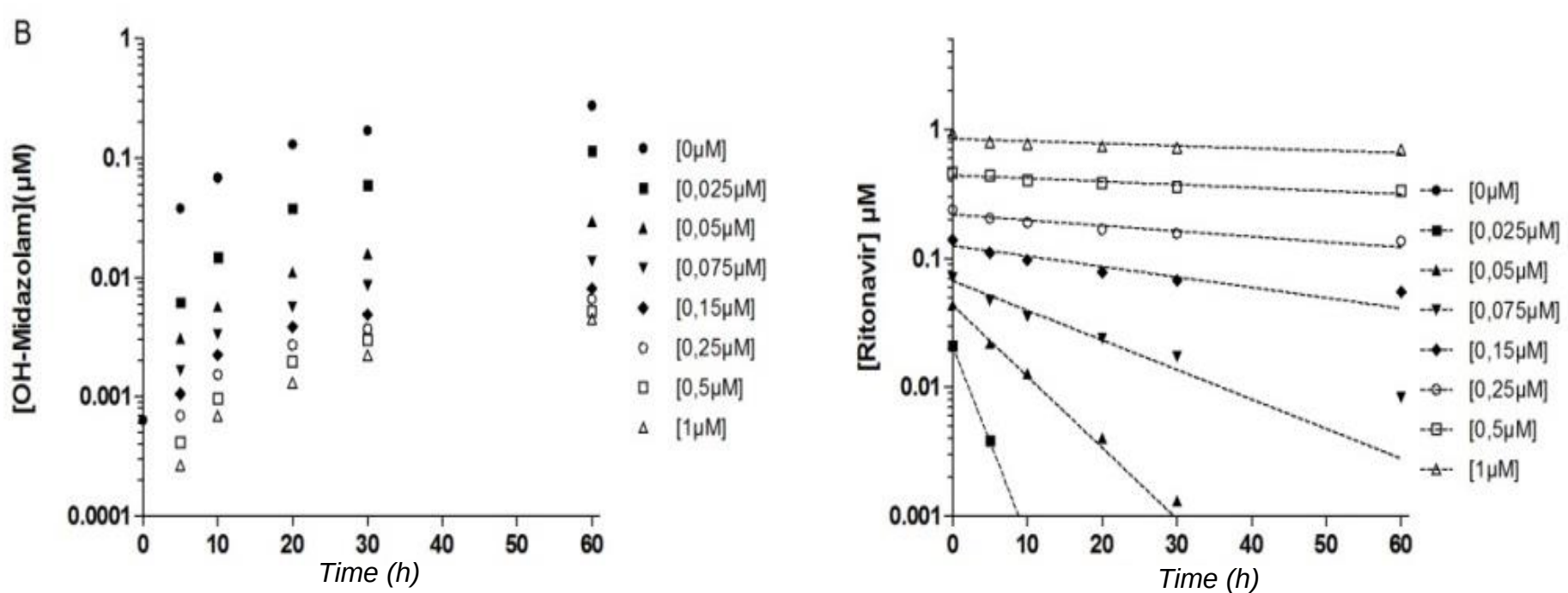


FIGURE 4 : Inhibition parameters determination for Ritonavir with the alternative one-step method