P-glycoprotein) and organic anion transporting polypeptides (OATPs, SLCOs), were inducible by various drugs and supplements.[19] If a substrate drug is extensively eliminated by inducible metabolizing enzymes or transporters other than CYP3A4, the present method would misestimate the magnitude of DDI. Furthermore, the interactions with protease inhibitors for treatment of HIV were excluded, because those drugs exhibited a marked potential to induce and inhibit CYP3A4 simultaneously *in vivo*.[20-22] In spite of these limitations, the present study is the first method which can predict the magnitude of inductive DDIs between multiple drugs in a systematic manner.

[Methods]

Data source

Information on clinical DDI studies of seven drugs and supplements which are known to induce CYP3A4 (bosentan, carbamazepine, efavirenz, phenytoin, pioglitazone, rifampicin, and St. John's Wort) were collected from the literature. We used information on inducers of CYP3A4 as much as possible, but did not incorporated drugs which exhibit potent induction and inhibition at the same time, such as protease inhibitors for treatment of HIV. On the other hand, efavirenz, a nucleoside reverse transcriptase inhibitor for treatment of HIV, was included as an inducer, although it exhibits both inductive and inhibitory activities *in vitro*.[17, 23] This was because blood concentrations of drugs were reduced following coadministration of efavirenz for all the cases reported in the literature.[24] Concerning the data of St. John's Wort (SJW), studies using high-dose hyperforin extracts (>10 mg day^{-1}) were used.[25] Reductions in the AUC of drug plasma or serum concentrations produced by enzyme induction were quantitatively evaluated. Values of the apparent contribution of CYP3A4 to oral clearance (CR_{CYP3A4}) were extracted for 13 substrate drugs from a previous study.[18] In addition to these 13 substrates, information on inhibitory clinical DDI studies was collected for 9 substrates of CYP3A4 (amitriptyline, etizolam, gefitinib, imatinib, mefloquine, prednisolone, quetiapine, ziprasidone, and zopiclone) to calculate CR_{CYP3A4} in the present study.

Theory

The oral clearance, CL_{oral}, of drugs can be described with Eq. 1.[18]

$$F_a \cdot CL_{oral} = fu \cdot CL_{int(H)} \qquad \text{Eq. 1}$$

where F_a, fu and $CL_{int(H)}$ are the fraction absorbed, unbound fraction in the blood, and hepatic intrinsic clearance of substrates, respectively. Two simplifications were used in the development of Eq. 1. The first one is that the urinary excretion of the unchanged substrate drug is minimal as often the case for lipophilic CYP3A4 substrates. Another simplification is that the contribution of intestinal metabolism was combined with that of hepatic metabolism. The appropriateness of the latter hypothesis will be examined in the Discussion section. We assume two intrinsic metabolic clearances, $CL_{int(CYP3A4)}$ and $CL_{int(others)}$, which represent the metabolism of substrates mediated by CYP3A4 and the sum of other metabolic pathways, respectively.

$$CL_{int(H)} = CL_{int(CYP3A4)} + CL_{int(others)} \qquad \text{Eq. 2}$$

In the following equations, asterisks denote parameters altered by induction of CYP3A4. When the amount of CYP3A4 is increased by inducers with an induction ratio of $R_{induction}$, the $CL_{int(H)}$ of substrates is increased as follows.

$$CL^{*}_{int(H)} = R_{induction} \cdot CL_{int(CYP3A4)} + CL_{int(others)} \qquad \text{Eq. 3}$$

It should be noted that $CL_{int(others)}$ is assumed not to be altered by induction of CYP3A4 under the assumption of Eq. 3. This is one of the basic assumptions of the present method. The apparent ratio of the contribution of CYP3A4 to the oral clearance of a substrate (CR_{CYP3A4}) is defined by Eq.4 where $CL_{oral(-CYP3A4)}$ is an altered *in vivo* oral clearance when $CL_{int(CYP3A4)}$ is blocked completely.[18]

$$CR_{CYP3A4} = \frac{CL_{oral} - CL_{oral(-CYP3A4)}}{CL_{oral}} \qquad \text{Eq. 4}$$

The definition of CR is similar to that of Fm, the fraction metabolized by the enzyme, which has been frequently used in the literature,[26, 27] but a distinct nomenclature has been used to make it clear that the CR values are an apparent estimation from *in vivo* outcomes. Considering that CR_{CYP3A4} is expressed by $CL_{int(CYP3A4)}$ / $CL_{int(H)}$ when the extra-hepatic clearance is minimal, Eq.3 is transformed to Eq. 5.

$$\begin{aligned} CL^{*}_{int(H)} &= (1 + (R_{induction} - 1) \cdot CR_{CYP3A4}) \cdot CL_{int(H)} \\ &= (1 + IC_{CYP3A4} \cdot CR_{CYP3A4}) \cdot CL_{int(H)} \end{aligned} \qquad \text{Eq. 5}$$

where IC_{CYP3A4} is the apparent increase in clearance for substrates produced by induction of CYP3A4, which is calculated by $R_{induction} - 1$. The alternations in the AUC of substrates produced by induction of CYP3A4 are given by Eq. 6.

$$\frac{AUC^{*}_{oral}}{AUC_{oral}} = \frac{CL_{oral}}{CL^{*}_{oral}} = \frac{CL_{int(H)}}{CL^{*}_{int(H)}} = \frac{1}{1 + CR_{CYP3A4} \cdot IC_{CYP3A4}} \qquad \text{Eq. 6}$$

There is a clear similarity between Eq. 6 and Eq. 7, the latter involves the alternations in the AUC of substrates produced by inhibitory DDIs with CYP3A4.[18]

$$\frac{AUC^{*}_{oral}}{AUC_{oral}} = \frac{1}{1 - CR_{CYP3A4} \cdot IR_{CYP3A4}} \qquad \text{Eq. 7}$$

where IR_{CYP3A4} is a time-averaged apparent inhibition ratio of CYP3A4.

When the nonlinear dose-response of enzyme induction needs to be considered, the following theory would be helpful. In order to estimate *in vivo* enzyme induction from *in vitro* experimental data, Eq. 8 has been used.[11, 12]

$$R_{induction} = 1 + \frac{E_{max} \cdot I}{EC_{50} + I} \qquad \text{Eq. 8}$$

where E_{max} and EC_{50} are the maximum induction effect and the half maximal effective concentration, respectively, which are determined *in vitro*, and I is the drug concentration at the target site. Under an assumption of linear pharmacokinetics of an inducer drug, Eq. 9 is obtained from Eq. 8.

$$IC_{CYP3A4} = \frac{IC_{CYP3A4(max)} \cdot D}{ED_{50} + D} \qquad \text{Eq. 9}$$

where $IC_{CYP3A4(max)}$, D and ED_{50} are the maximum IC_{CYP3A4}, dose, and half maximal effective dose of induction, respectively. In the present study, however, we could not evaluate $IC_{CYP3A4(max)}$ and ED_{50} values because the dose-response of CYP3A4 induction has not been fully characterized in clinical studies.

Calculation of CR_{CYP3A4} and IC_{CYP3A4} values

The CR_{CYP3A4} values were obtained from the previous report[18] for thirteen substrate drugs, while CR_{CYP3A4} of nine substrate drugs were newly calculated from Eq. 7 based on alternations in AUCs reported in the literature for inhibitory DDIs where itraconazole or ketoconazole was coadministered.[18] The detailed information was listed in Table II. On the other hand, the IC_{CYP3A4} values of CYP3A4 inducers were calculated from Eq. 6 from alternations in the AUC of a standard substrate produced by inductive DDIs. In our analysis, we chose a substrate having as high a level of CR_{CYP3A4} as possible for the standard to minimize the estimation error. From this standpoint, simvastatin was chosen as the standard drug for the calculation of IC_{CYP3A4} of rifampicin, carbamazepine, efavirenz, and bosentan. For pioglitazone and SJW, we used midazolam since the *in vivo* effects of these drug and supplement on simvastatin have not been reported yet. For phenytoin, quetinapine was chosen as the standard drug. We did not use any regression analysis or fitting calculations to estimate CR_{CYP3A4} and IC_{CYP3A4} values. Although overall estimation errors would be minimized by using fitting calculations, we regarded the present standard drug approach is sufficiently precise and more practical. It should be noted that, strictly speaking, all parameters need to be recalculated when new information is added for the fitting approach, because the CR and IR (or IC) values are interdependent.

Statistics

Predicted AUC increases were assessed by the observed values. The average-fold error (AFE) and mean prediction error (MPE) were calculated to indicate relative and absolute precisions, respectively, and root mean square prediction error (RMSE) was calculated to investigate deviations as follows.

$$AFE = 10^{\left|\frac{1}{n}\sum \log\frac{Predicted}{Observed}\right|} \quad \text{Eq. 10}$$

$$MPE = \frac{1}{n}\sum(Predicted - Observed) \quad \text{Eq. 11}$$

$$RMSE = \sqrt{\frac{1}{n}\sum(Predicted - Observed)^2} \quad \text{Eq. 12}$$

where n is the number of studies. χ^2-test was performed using the mean square prediction errors.

[Results]

In the present study, we surveyed 42 *in vivo* inductive DDI studies published in 37 articles (table I). In typical induction studies, the inducers were administered consecutively for several days. The IC_{CYP3A4} values were estimated for seven inducers of CYP3A4 from Eq. 6 using known CR_{CYP3A4} values of substrates and alterations in AUCs observed in 10 clinical DDI studies of CYP3A4 induction. These 10 clinical DDI studies to determine IC_{CYP3A4} values are referred to as the estimation set and are shown in Table I. In the calculation of IC_{CYP3A4}, the algebraic mean of the reduction in the AUCs was used when more than one article was available for the same interaction set. In these cases, however, a significant deviation was sometimes observed in the AUC reductions between or among reports even if the doses were the same, as shown in Fig. 1.

In order to validate the suitability of this method, the extent of reduction in AUCs was predicted for additional clinical studies which are independent of the estimation set. These 32 clinical DDI studies to validate the method are referred to as the validation set in Table I. This prediction was performed by substituting the values of CR_{CYP3A4} and IC_{CYP3A4} in Eq. 6. For this purpose, we extended the survey conducted in our previous report[18] to determine the CR_{CYP3A4} values. Table II lists the CR_{CYP3A4} values for 22 substrate drugs.

The predicted alternations in AUC were plotted against the observed values (Fig. 2). It was demonstrated that we can successfully predict the inductive DDIs in a quantitative manner; indeed, the magnitude of the deviation between the mean values of the observed and predicted AUCs of all substrate drugs were less than 20% of the AUCs of the respective substrate drugs before administration of inducers. The AFE values were from 0.76 to 1.17 for each inducer, and 1.07 for the validation set (Table III). The MPE values were within -0.1~0.1 for all inducers. These data suggested overall small average deviations between the predictions and the observations even although we did not conducted any fitting calculations. The individual deviation for each substrate drug was also small as represented by an acceptable RMSE value of 0.09 for the validation set. No significant difference was detected for any of the inducers between the prediction and the observation by χ^2-test ($p > 0.1$).

The relationships between the CR_{CYP3A4} values and the reductions in the AUCs of several substrates were plotted for each inducer (Fig. 3). The lines represent the calculated AUC changes by Eq. 6 from IC_{CYP3A4} and CR_{CYP3A4}. The open and closed symbols represent the dataset shown in Figs. 1 and 2, respectively. As indicated in Eq. 9, IC_{CYP3A4} values are theoretically dose-dependent. However, higher doses of an inducer were not always associated with a more marked reduction in the AUC of substrates as shown in Fig. 3. For example, although 900 mg of SJW reduced the AUC of ciclosporin to 68% of the control, 600 mg of SJW also reduced the AUC of ciclosporin to 55% of the control. Such deviation may be due to fluctuation in the *in vivo* experiments. The present analysis indicated that the deviation in the inducer dose may not markedly affect the results, as long as the dose selected is within the therapeutic range. The reductions in AUCs for 154 matches of DDIs between 22 substrate drugs and 7 inducers were systemically predicted (Fig. 4). It was found that a marked reduction in AUCs is anticipated when substrate drugs with a high CR_{CYP3A4} were administered with a potent inducer with a high IC_{CYP3A4} (Fig. 4).

Among the compounds analyzed in the present study, rifampicin was found to be the most potent inducer and the AUCs of coadministered drugs have often reduced to less than 1/10. As shown in table III, The IC_{CYP3A4} of rifampicin was calculated to be 7.7, followed by phenytoin and carbamazepine with values of approximately 4.7 and 3.0, respectively. Rifampicin may reduce AUCs of coadministered CYP3A4 substrate drugs to less than half if the CR_{CYP3A4} of the substrate drugs is greater than 0.13 (Fig. 3a). Phenytoin and carbamazepine may also reduce the AUCs of substrate drugs to less than half if the CR_{CYP3A4} of the substrate drugs is greater than 0.21 and 0.33, respectively (Fig. 3b,c). The IC_{CYP3A4} of all the other CYP3A4 inducers analyzed in the present study were approximately 1 or less, which suggests that the AUCs of coadministered drugs will not be decreased to less than approximately 1/2 even in the case of a substrate drug metabolized solely by CYP3A4 (Fig. 3d-g).

[Discussion]

In the present study, we have successfully demonstrated that the alternations in AUCs produced by enzyme induction of CYP3A4 for any drug-drug combination can be predicted by evaluating the CR_{CYP3A4} values for substrate drugs and the IC_{CYP3A4} values for inducer drugs. Nevertheless, it needs to be kept in mind that the accuracy is for the average values and that marked inter- and intra-subject differences are observed routinely in drug blood concentrations. Cares should be taken when this method is applied to predictions of individual pharmacokinetics.

It has been reported that the role of the intestinal CYP3A4 in drug metabolism was comparable to hepatic CYP3A4 for some substrate drugs even although the expression level of the former is only 1/100 of the latter.[71, 72] For an example of inductive DDI, bioavailability of ciclosporin with concomitant rifampicin administration was reported to be markedly less than that predicted by hepatic enzyme induction.[42] Theoretically, intestinal CYP3A4 plays an important role in the first-pass effect but does not alter total drug clearance after a drug reaches the systemic circulation.[73] In contrast, alterations in the expression levels of hepatic CYP3A4 regulate the oral clearance by affecting the first-pass effect as well as affecting

the total clearance. Furthermore, it has been well-established that MDR1 acts as an efficient absorption barrier in conjunction with CYP3A4 in the intestine.[73-75] Strictly speaking, the contributions to drug clearance in the liver and the intestine, and also by CYP3A4 and MDR1, need to be accounted separately for the accurate prediction of DDIs. However, it is practically impossible to apply the precise theory to the very wide range of drugs available commercially, since these factors have been evaluated separately only for a few drugs.[73] Therefore, we adopted the simplified theory in the present study assuming that these factors may closely correlate with each other and can be combined. Indeed, similarities have been reported in the substrate specificities of CYP3A4 and MDR1.[73] In addition, CYP3A4 and MDR1 are co-induced via the PXR/FXR mechanism.[76] The present simplified method successfully predicted alternations in AUCs by CYP3A4 induction without exceptions, suggesting the appropriateness of our hypothesis.

The IC_{CYP3A4} values should be compared with the degree of *in vivo* induction of CYP3A4 and MDR1. The measurement of human hepatic CYP3A4 content by biopsy revealed that the induction ratio was approximately 3- to 5-fold after administration of rifampicin.[77, 78] In the same manner, rifampicin also induced CYP3A4 and MDR1 in the intestine by approximately 3.3- to 4.4-fold[79, 80] and 3.5- to 4.2- fold,[79, 81, 82] resepectively, under *in vivo* experimental conditions. The synergistic effect of the induction of both CYP3A4 and MDR1 in both the intestine and liver may be responsible for the induction ratio of 7.7 (Table III) estimated in the present study from the IC_{CYP3A4} of rifampicin.

Inductions are also frequently observed for metabolizing enzymes and transporters other than CYP3A4. It has been established that PXR/RXR are involved in the inductions of CYP2C8, 2C9, and 2C19[19] along with CYP3A4 and MDR1. Consequently, if these enzymes are also involved in the elimination of the standard substrates which were used in the present study for the calculation of the IC_{CYP3A4} of an inducer, the value of IC_{CYP3A4} could possibly be overestimated. In contrast, if the substrate drug undergoes metabolism by inducible CYPs other than CYP3A4, the alternations in AUC would be underestimated even if the IC_{CYP3A4} was evaluated accurately. In some cases, these over- and under-estimations can be canceled out. One of such examples may be amitriptyline which has a low CR_{CYP3A4} value of 0.25 and undergoes extensive metabolism by CYP2C19.[68] Although the present prediction for alternations in the AUC of amitriptyline by coadministration of SJW agreed with the observed ratio of 0.78, a contribution of CYP2C19 may be significant to some degree because CYP2C19 is also inducible *via* PXR-mediated process.

Some very important clinical DDIs like those with oral contraceptives do not result exclusively from alternations in CYP activities.[83] Cumulative pieces of evidences suggest that ethinyl estradiol is metabolized by CYP3A4, but it was not included in the present study because a clinical DDI study capable to estimate CR_{CYP3A4} have not been reported. For the determination of CR_{CYP3A4}, coadministration of a selective CYP3A4 inhibitor, such as ketoconazole or itraconazole, is required. Nevertheless, its AUC was reported to be increased by 25 to 30% by coadministration with fluconazole,[84, 85] a potent inhibitor of both CYP3A4 and CYP2C9.[86] Accordingly, the CR value of ethinyl estradiol for CYP3A4 and CYP2C9 in total was

assumed to be approximately 0.2 which was roughly in accordance with an observation that its AUC decreased approximately by half by coadministration with rifampicin (Fig. 3a).[87] However, we should refrain from predicting pharmacokinetics of ethinyl estradiol only from a viewpoint of CYP activities since it has been well established that other inducible metabolizing pathways, particularly sulfation and glucuronidation contribute greatly to its clearance.[88, 89]

Furthermore, it should be noted that rifampicin, a representative CYP3A4 inducer, also inhibits OATPs which are transporters responsible for the uptake of a broad range of organic anions, such as atorvastatin and fexofenadine.[90-92] Accordingly, the involvements of inhibition of OATPs would need to be considered carefully for DDIs involving rifampicin. Attentions should be paid to consider actions of any alternations in drug clearance triggered by enzyme induction. In the future, it would be advantageous to separate each contribution by metabolizing enzyme/transporter for substrate drugs, and also to separate each alternation of clearance pathways for inducer drugs.

For prediction of any pharmacokinetic alterations, particular care needs to be taken when multiple factors are simultaneously involved. Some of CYP3A4 inducers may also inhibit CYP3A4, as is frequently found in the case of drugs used for the treatment of HIV infection, such as ritonavir, atazanavir, indinavir, and saquinavir.[93-96] In some cases, the inhibition is accounted for by mechanism-based inhibition,[93, 96] which may lead to the nonlinear and/or time-dependent pharmacokinetics of these kinds of inducers. Based on these considerations, the analysis of the effect of these inducers was not included in the present study. For such analysis, construction of much precise *in vivo* / *in vitro* pharmacokinetic model is required in which the time profiles of the disposition of these inducers can be taken into account.

Although *in vitro* experiments using primary cultured hepatocytes or several cultured cell lines have been used to examine the induction of compounds,[11, 97-99] the current method for the prediction of inductive DDIs based on *in vivo* information will be more accurate and broadly applicable to a variety of drugs. Indeed, the present method may also be used during the clinical drug development. For drug candidates which may induce CYP3A4, the following procedure may be used for the quantitative prediction of their ability to induce the enzyme.

- A clinical study will be conducted for an evaluation of inductive DDIs where inductive potential of CYP3A4 has been suggested by *in vitro* experiments and/or in experimental animals. The pharmacokinetics of a standard CYP3A4 substrate with a known CR_{CYP3A4} (such as midazolam and simvastatin) will be investigated before and after consecutive dosing of a drug candidate typically for 1 to 2 weeks.
- From such *in vivo* studies, the IC_{CYP3A4} value for this compound will be calculated. If clinically important DDIs are anticipated with other any CYP3A4 substrates with the known CR_{CYP3A4} values, clinical studies will also be performed, and the results should be compared with the predicted values.

For drug candidates which are metabolized by CYP3A4 in *in vitro* experiments, the following procedure may be used for the quantitative prediction of alterations in the AUCs produced by coadministered inducers.

- CR_{CYP3A4} value of such a drug candidate can be determined *in vivo* by performing inhibitory and/or inductive DDI studies. In the case of the inhibitory DDI studies, a standard inhibitor of CYP3A4, typically itraconazole or ketoconazole, will be coadministered to examine the increase in AUC. For the inductive DDI studies, a standard inducer of CYP3A4, typically rifampicin, will be coadministered to examine the decrease in AUC.
- From these results, CR_{CYP3A4} values can be calculated. If clinically important DDIs are anticipated with any other inducers with known IC_{CYP3A4} values, clinical studies will be performed, and the results should be compared with the predicted values.

By applying and extending these methods, it will be possible to predict almost all clinical significant pharmacokinetic DDIs *via* metabolism by CYP3A4 in a quantitative manner in the future.

[Conclusion]

We have constructed general framework for the prediction of oral drug interactions caused by CYP3A4 induction from *in vivo* information. The accuracy and robustness of the method have been demonstrated satisfactorily. By using this method, the susceptibilities of a CYP3A4 substrate to both inhibitory and inductive DDIs can be estimated by conducting a single inhibitory DDI study during the early stages of clinical development.

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Table I. List of publications of inductive drug-drug-interactions involving CYP3A4 used to evaluate the propriety of the present method.

a) The results of these reports (the estimation set) were used to calculate the apparent increase in clearance by induction of CYP3A4 (IC_{CYP3A4}). The other studies contributed towards the validation set.

Inducers	Substrates																					
	ALP	AMI	ATO	BUS	CIC	ETI	FEL	GEF	IMA	LOV	MEF	MID	NIF	NIS	PRE	QUE	SIM	TEL	TRI	ZIP	ZOL	ZOP
BOS					[28]												[29][a]					
CAR	[30]				[31]	[32]										[33]	[34][a]			[35]		
EFA			[24]														[24][a]					
PHE					[36]											[37][a]						
PIO			[38]									[38][a]	[38]									
RIF	[39]		[40]	[41]	[42]		[43]	[44]		[45]	[46] [47]		[48]		[49] [50]		[51][a] [47][a]	[52]	[53]		[54]	[55]
SJW	[56]	[57]			[58] [59] [60]			[61]				[59][a] [62][a] [63][a]										

ALP = alprazolam; AMI = amitriptyline; ATO = atorvastatin; BOS = bosentan; BUS = buspirone, CAR = carbamazepine; CIC = ciclosporin; EFA = efavirenz; ETI = etizolam; FEL = felodipine; GEF = gefitinib; IMA = imatinib; LOV = lovastatin; MEF = mefloquine; MID = midazolam; NIF = nifedipine; NIS = nisoldipine; PHE = phenytoin; PIO = pioglitazone; PRE = prednisolone; QUE = quetiapine; RIF = rifampicin; SIM = simvastatin; SJW = St. John's Wort; TEL = telithromycin; TRI = triazolam; ZIP = ziprasidone; ZOL = zolpidem; ZOP = zopiclone.

Table II. Calculated ratios of the contribution of CYP3A4 to the oral clearance (CR_{CYP3A4}) for substrates

Substrates	CR_{CYP3A4}	Inhibitors to calculate CR_{CYP3A4}	Observed AUC increase (fold)	reference
Simvastatin	1.00	Itraconazole	18.6	[18]
Lovastatin	1.00	Itraconazole	15.4-22.1	[18]
Buspirone	0.99	Itraconazole	14.5-19.2	[18]
Nisoldipine	0.96	Ketoconazole	24.4	[18]
Triazolam	0.93	Ketoconazole	9.16-22.4	[18]
Midazolam	0.92	Itraconazole	5.75-10.8	[18]
Felodipine	0.89	Itraconazole	6.34	[18]
Quetiapine	0.85	Ketoconazole	6.49	[33]
Ciclosporin	0.80	Ketoconazole	4.39-5.31	[18]
Nifedipine	0.78	Diltiazem	2.22-3.11	[18]
Alprazolam	0.75	Ketoconazole	3.98	[18]
Atorvastatin	0.68	Itraconazole	2.50-3.20	[18]
Telithromycin	0.49	Ketoconazole	1.95	[18]
Mefloquine	0.44	Ketoconazole	1.79	[64]
Zopiclone	0.44	Itraconazole	1.73	[65]
Zolpidem	0.40	Ketoconazole	1.67	[18]
Gefitinib	0.39	Itraconazole	1.58	[43]
Etizolam	0.36	Itraconazole	1.53	[66]
Imatinib	0.28	Ketoconazole	1.38	[67]
Amitriptyline	0.25	Ketoconazole	1.35	[68]
Ziprasidone	0.25	Ketoconazole	1.33	[35]
Prednisolone	0.18	Itraconazole	1.18-1.24	[69, 70]

Table III.

Inducers	Daily dose	IC_{CYP3A4}	AFE[1]	MPE[2]	RMSE[3]
Rifampicin	450-600mg	7.7	1.17	0.008	0.06
Phenytoin	300-400mg	4.7	0.76	-0.075	0.11
Carbamazepine	200-600mg	3.0	0.99	-0.031	0.09
Efavirenz	600mg	1.4	1.01	0.001	0.08
St.John's Wort	600-900mg	1.2	0.95	-0.029	0.04
Bosentan	500mg	0.49	1.16	0.093	0.13
Pioglitazone	45mg	0.38	0.91	-0.079	0.10
validation set[4]	-	-	1.07	-0.009	0.09
All	-	-	1.05	-0.007	0.08

Calculated apparent increase in clearance by induction of CYP3A4 (IC_{CYP3A4}) for inducers

1) average-fold error
2) mean prediction error
3) root mean square prediction error
4) see Table I
See Eqs. 10~12 for calculations of AFE, MPE, and RMSE, respectively.
No significant difference was detected for any of the inducers between the prediction and the observation by χ^2-test ($p > 0.1$).

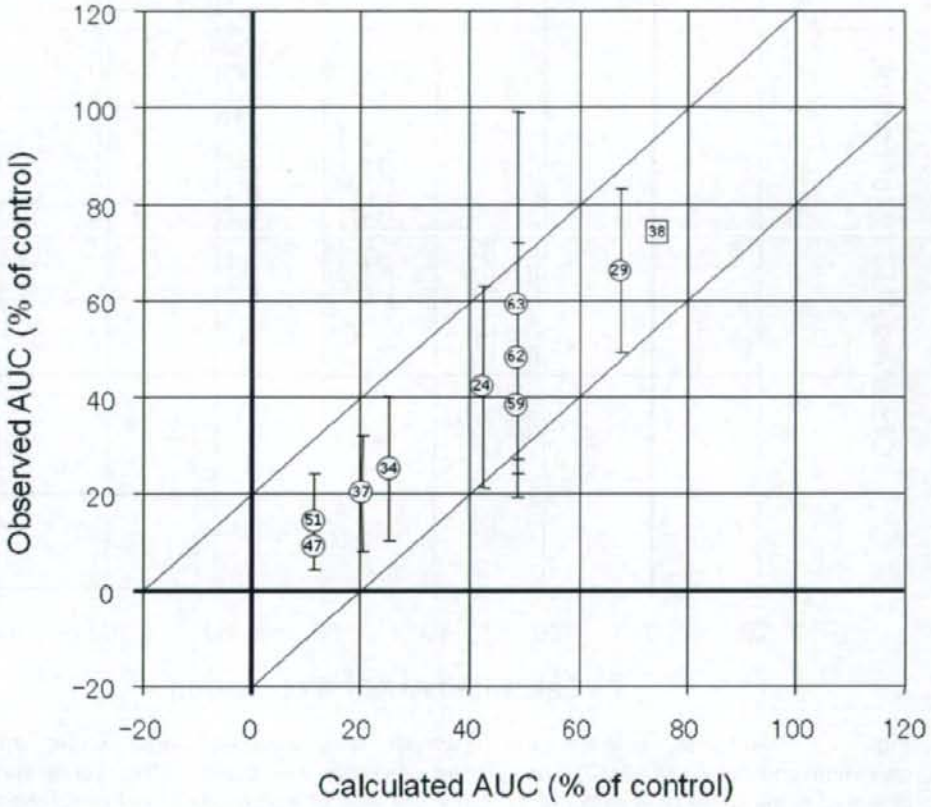

Fig. 1. Relationship between the observed and calculated area under the concentration-time curve (AUC) changes by drug-drug-interactions. This figure was prepared for the purpose of demonstrating the deviation of AUC values among 10 clinical studies (the estimation set; table I), the mean values of which were used to determine the IC_{CYP3A4} values. Each circle and vertical bar represents the mean ± SD values of subjects reported in each article. Where the SD values or the ranges were not reported in the article, the reported mean value is shown by a square. The solid lines represent ± 20% of the calculated AUC changes. Numbers in symbols represent the corresponding reference number.

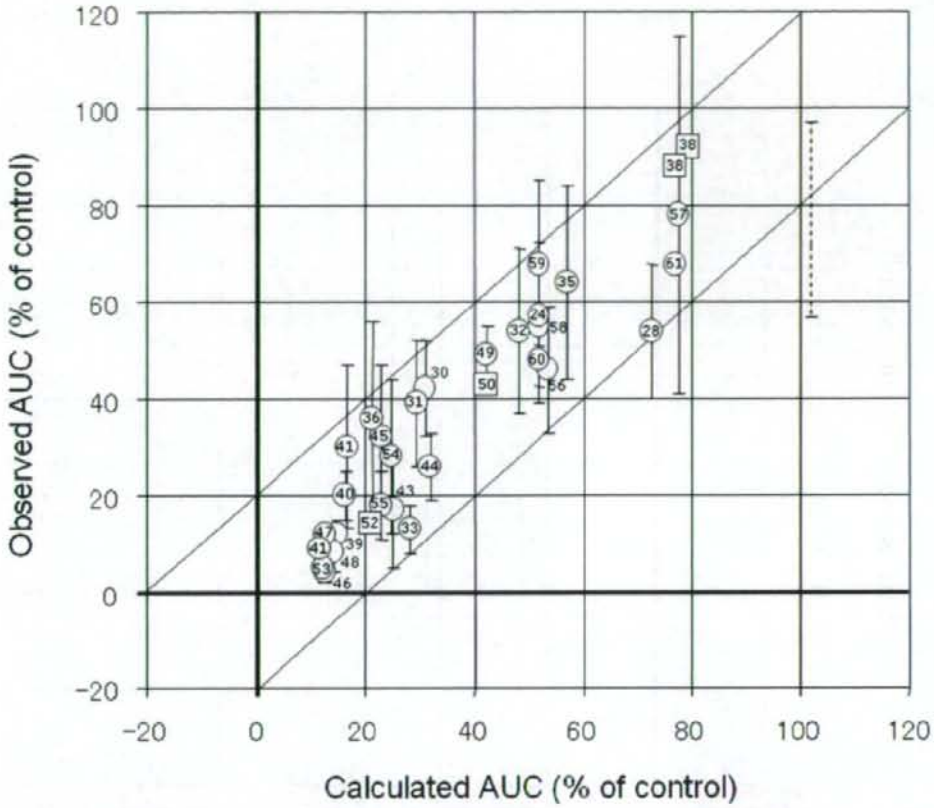

Fig. 2. Relationship between the observed and calculated area under the concentration-time curve (AUC) changes by drug-drug-interactions. This figure was prepared in the same style as figure 1. Using the ratio of the contribution of cytochrome P450 (CYP) 3A4 to oral clearance (CR_{CYP3A4}) and the apparent increase in clearance by induction of CYP3A4 (IC_{CYP3A4}) values shown in tables II and III, respectively, the alternations in AUC of substrate drugs by drug interactions reported in 32 clinical studies (the validation set; table I) were predicted with Eq. 6. Each circle and vertical bar represents the mean ± SD values of subjects reported in each article. A dashed bar represents the range. Where the SD values or the ranges were not reported in the article, the reported mean value is shown by a square. The solid lines represent ±20% of the calculated AUC changes. Numbers in symbols represent the corresponding reference number.

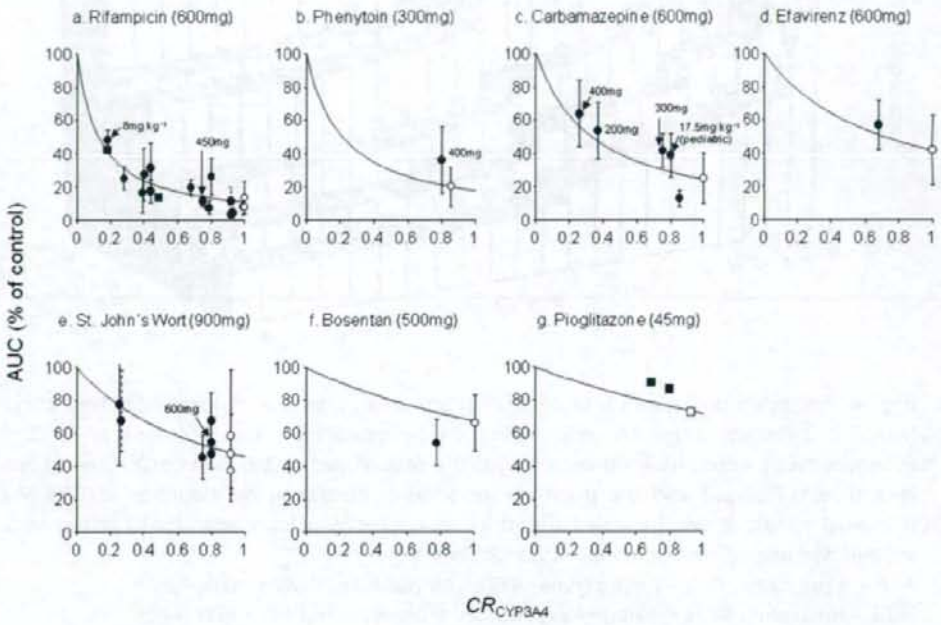

Fig. 3. Area under the concentration-time curve (AUC) changes of the substrate drugs by drug-drug-interactions for each inducer. The data shown in Figs. 1 and 2 were reorganised for each inducer to show the AUC changes of each substrate drug as a function of the contribution ratio of CYP3A4 to the oral clearance (CR_{CYP3A4}) values of the substrate drugs. The lines represent the calculated AUC changes by Eq. 6 from the IC_{CYP3A4} and the CR_{CYP3A4}. The open and closed symbols represent the dataset shown in Figs. 1 and 2, respectively. See legends to Figs. 1 and 2 for details.