Supplementary Note

Detailed derivation of the new model (Eq. 6)

The dynamics of the enzyme reaction between a single enzyme and single substrate (Eq. 1) can be fully captured by the following ordinary differential equations based on mass action kinetics, which is referred to as the *full model* in this study:

$$\begin{aligned} \frac{dS}{dt} &= -k_f SE + k_b C, \\ \frac{dC}{dt} &= k_f SE - k_b C - V_{max} C, \\ \frac{dP}{dt} &= k_{cat} C. \end{aligned} \tag{8}$$

As $E_T = E + C$ is conserved, $\frac{dE}{dt} = -\frac{dC}{dt}$. $E(0) = E_T, \, ,S(0) = S_T, C(0) = 0,$ and $P(0) = 0$ are used as initial conditions following the typical in vitro enzyme kinetics protocol[1]. The full model can be simplified under the assumption that C rapidly equilibrates to its quasi-steady-state[2]:

$$C(S) = \frac{E_T S}{S + K_M},$$

where $K_M = \frac{k_b + k_{cat}}{k_f}$ (µM) is the Michaelis constant. By substituting this equation into the full model, the simplified MM model (Eq. 2) can be derived. The MM model is shown to be accurate only when the enzyme concentration is low (*i.e.* $E_T \ll K_M + S$) so that an insignificant fraction of substrate is bound to the enzyme and the metabolism rate increases proportionally to the enzyme concentration[1–3].

Another way to simplify the full model (Eq. 8) is based on the total quasi-steady-state approximation, where the quasi-steady-state of C is derived in terms of $\bar{S} = S + C$ rather than S[1,3–8]:

$$C(\bar{S}) = \frac{E_T + K_M + \bar{S} - \sqrt{(E_T + K_M + \bar{S})^2 - 4E_T\bar{S}}}{2}. \tag{9}$$

Using this and replacing the notation of k_{cat} with the nomralized V_{max} (pmol·min^{-1}·pmol^{-1} CYP), the full model can be simplified as

$$\frac{dP}{dt} = V_{max}C(\bar{S}),$$

which has been shown to be accurate regardless of enzyme concentration, in contrast to the MM model[1,3–8]. This model can be further simplified when $S_T \ll E_T + K_M$, leading to the new model (Eq. 6):

$$\frac{dP}{dt} = V_{max}C(\bar{S}) \approx \frac{V_{max}E_T\bar{S}}{K_M + E_T} = CL_{int}^{vitro}E_T\frac{K_M}{K_M + E_T}\bar{S},$$

where the approximation comes from the Taylor expansion of $C(\bar{S})$ in terms of $\frac{4E_T\bar{S}}{(E_T+K_M+\bar{S})^2} \ll 1$[5–7].

Prediction of *CL_h*

CL_{int}^{liver} values estimated from canonical and new approaches were converted to CL_h based on the following three hepatic distribution models: the well-stirred model, the parallel tube model and the dispersion model[9]:

1. Well-stirred model:

$$CL_h = \frac{Q_h \cdot f_{u-blood} \cdot \frac{CL_{int}^{liver}}{f_{u-mic}}}{Q_h + f_{u-blood} \cdot \frac{CL_{int}^{liver}}{f_{u-mic}}}$$

2. Parallel tube model:

$$CL_h = Q_h \cdot [1 - e^{(-\frac{f_{u-blood} \cdot CL_{int}^{liver}}{Q_h \cdot f_{u-mic}})}]$$

3. Dispersion model:

$$CL_h = Q_h \cdot [1 - \frac{4a}{(1+a)^2 \cdot e^{[(a-1)/2 \cdot D_n]} - (1-a)^2 \cdot e^{[-(a+1)/2 \cdot D_n]}}],$$

where $D_n = 0.17,\ a = \sqrt{1 + 4 \cdot R_n \cdot D_n}$ and $R_n = \frac{f_{u-blood} \cdot CL_{int}^{liver}}{Q_h \cdot f_{u-mic}}$.

1,450 ml·min^{-1} was used for the human hepatic blood flow (Q_h)[10]. See Table 2 for the values of blood unbound fraction ($f_{\text{u-blood}}$) and microsomes ($f_{\text{u-mic}}$) for each drug.

Accuracy and precision of predicted CL_h

To calculate the accuracy of predicted CL_h, the average-fold-error (AFE) and absolute-average-fold-error (AAFE) were used, and for precision, the root-mean-squared-error (RMSE) and relative-root-mean-squared-error (R-RMSE) were used[11,12]:

$$AFE = 10^{\frac{1}{N}\sum log\frac{Predicted}{Observed}},$$

$$AAFE = 10^{\frac{1}{N}\sum\left|log\frac{Predicted}{Observed}\right|},$$

$$RMSE = \sqrt{\frac{1}{N}\sum(Predicted - Observed)^2},$$

$$R - RMSE = \sqrt{\frac{1}{N}\sum(Predicted / Observed - 1)^2}.$$

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