**1. Structure of PBPK-DDI Model**

During the development of the PBPK (Physiologically Based Pharmacokinetic) model, we encountered challenges in obtaining comprehensive human tissue distribution data. The inclusion of these data, whether through computational simulations or estimations based on preclinical data, introduces an inherent variable that cannot be controlled in the PBPK model. Mechanistically, drug absorption predominantly occurs in the intestines and liver, where drug-drug interactions (DDIs) occur. The concentrations in these organs play a pivotal role in influencing the occurrence of DDIs. Additionally, renal excretion has a significant impact on the contribution of liver metabolism to overall drug clearance, making it a crucial parameter. To address these complexities, we have simplified the PBPK model by retaining the key organs involved in absorption and metabolism, namely the intestines, liver, kidneys, and plasma, while integrating the remaining organs. The resulting simplified model is visually represented in the diagram below:

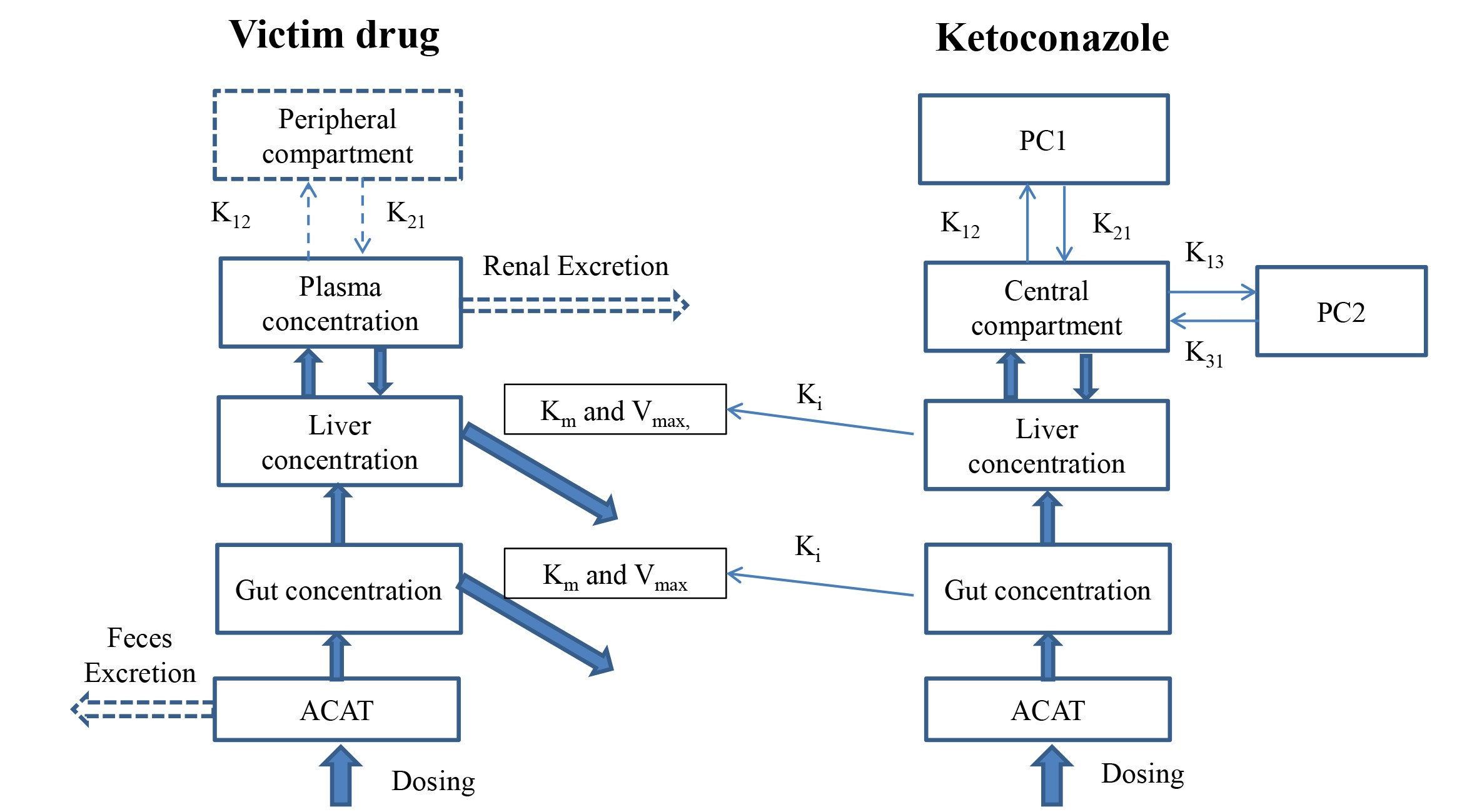


Figure S1. Model of PBPK-DDI model.

Compartments and arrows with dash lines represent the options in the model. PC1, peripheral compartment 1; PC2, peripheral compartment 2; K12, transfer rate constant from central compartment to peripheral compartment; K21, transfer rate constant from peripheral compartment to peripheral central compartment; K13, transfer rate constant from central compartment to peripheral compartment 2; K31, transfer rate constant from peripheral compartment 2 to peripheral central compartment; Vmax and Km, the constants of Michaelis-Menten reaction kinetics mediated by CYP3A4, which was assumed to be the unique metabolism rout; Ki is the inhibition rate constant of ketoconazole on the Kmax and Vmax of victim; ACAT, Advanced Compartmental Absorption & Transit model, which was utilized to simulate and predict oral drug absorption. The absorption and dissolution related parameters, including permeability, solubility, mean precipitation time, and solubility factor were optimized by matching simulated excretion of unchanged drug in feces with actual data. The renal clearance can get the optimized values by matching the simulated excretion of unchanged drug in urine with actual data. The Km, Vmax, K12, K21, and Vc were calculated by matching the plasma pharmacokinetic profiles with the actual data.

The details of ketoconazole PBPK model have been reported in our previous paper [9]. The model parameters were attached in Table S2.

Table S2. The PBPK parameters of ketoconazole.

|  |  |
| --- | --- |
| Parameters | Value |
| ***Physicochemical Parameters*** |  |
| Molecular Weight (g/mol) | 531.44 |
| LogP (LogD) | 2.67 (@ pH 7.4) |
| pKa (Base) | 6.51, 2.94 |
| Aqueous Solubility (mg/mL) | 0.0069 (@ pH 6.5) |
| Biorelevant Solubility (mg/mL) | 0.02158 (FaSSIF) |
| Solubilization Ratio (SR) | 87800 |
| Particle Radius (μm) | 5 |
| Mean Precipitation Time (s) | 8000 |
| Peff (cm/s·104) | 1.235 |
| ***Distribution Parameters*** |  |
| BP | 0.6 |
| *fu* (%) | 1.5 |
| Vc (L/Kg) | 0.07617 |
| K12 (1/h) | 0.29888 |
| K21 (1/h) | 0.19759 |
| K13 (1/h) | 13.257 |
| K31 (1/h) | 4.0672 |
| ***Metabolism Parameters*** |  |
| Km (Gut, mg/L) | 0.008 |
| Km (Liver, mg/L) | 0.008 |
| Vmax (Gut, mg/s) | 0.01 |
| Vmax (Liver, mg/s) | 0.01 |
| Inhibition Parameters |  |
| Ki (μM) | 0.015 |

1. **Validation of the victims PBPK Model**
   1. Absorption

To simulate oral drug absorption, we primarily utilized the ACAT (Advanced Compartmental Absorption & Transit) model. The ACAT model is a comprehensive compartmental modeling approach that considers the complex dynamics of drug absorption and transit through the gastrointestinal (GI) tract. This model integrates the dissolution model, permeability calculations, and physiological parameters within the GastroPlus software to simulate the intricate processes involved in oral drug absorption. The dissolution model was employed to simulate the drug's dissolution in GI fluids. This model takes into account factors such as drug solubility and pH, providing insight into the dissolution rate and availability of the drug for absorption. The permeability of the drug following dissolution in the GI tract considers various permeability mechanisms, including transcellular transport and paracellular diffusion. In vitro apparent permeability data from Caco-2 cell experiments were combined with the permeability model to estimate the drug's permeability across the GI tract. Essential physiological parameters were factored into the ACAT model to better predict oral drug absorption. These parameters include: ⅰ) Gastrointestinal transit time. ⅱ) Surface area: The available surface area within the GI tract for drug absorption. ⅲ) Blood flow rate.

The primary factors affecting absorption are solubility and permeability. To assess solubility and permeability, we gathered both qualitative (such as low, median, and high solubility or permeability） and quantitative data (solubility at different pH value and PappA-B value in Caco-2). Considering the discrepancies between *in vitro* and *in vivo* environments, we didn’t use the quantitative *in vitro* data directed, but restricted the parameter settings related to solubility and permeability in the PBPK model to a qualitative perspective only. For the validation of the absorption model, we employed *in vivo* Fa (fraction absorbed): Firstly, we obtained data from mass balance studies using radiolabeled substances, specifically determining the proportion of drug excreted in feces. Using this data, we evaluated the Fa value, defined as Fa = 1 minus the proportion of unchanged drug excreted in feces. Finally, we compared the simulated Fa values with the measured Fa values, as illustrated in the Figure below.

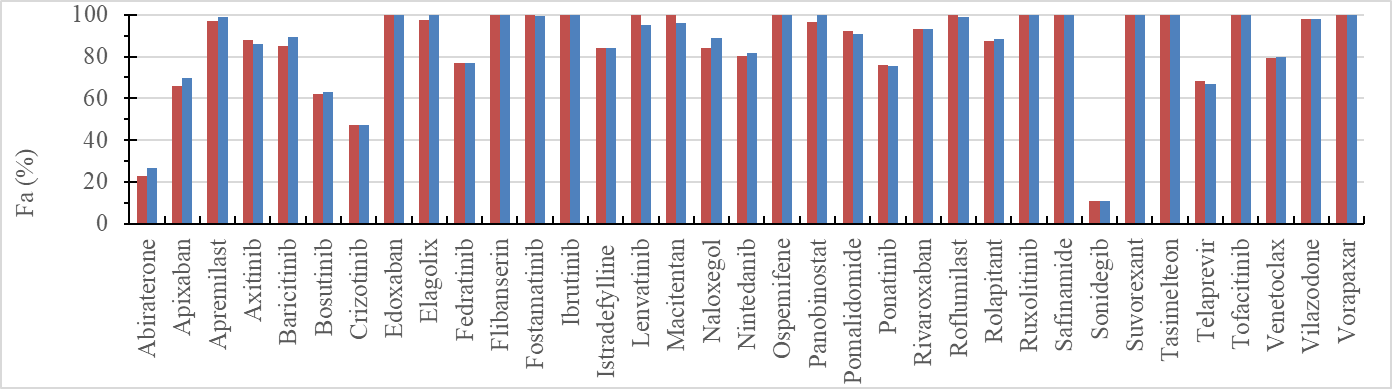


Figure S2. The comparison of Fa values between the simulated (blue column) and observed (red column).

* 1. Elimination (Metabolism and excretion)

Firstly, since fecal excretion has already been validated through Fa determination for the unchanged drug, we will not elaborate on it further at this point.

Secondly, for renal excretion, we can obtain the cumulative excretion proportion of the unchanged drug through the kidneys and use it to compare and validate the simulated renal excretion in the model. Please find the comparison of simulated renal excretion and actual renal excretion in the following table:

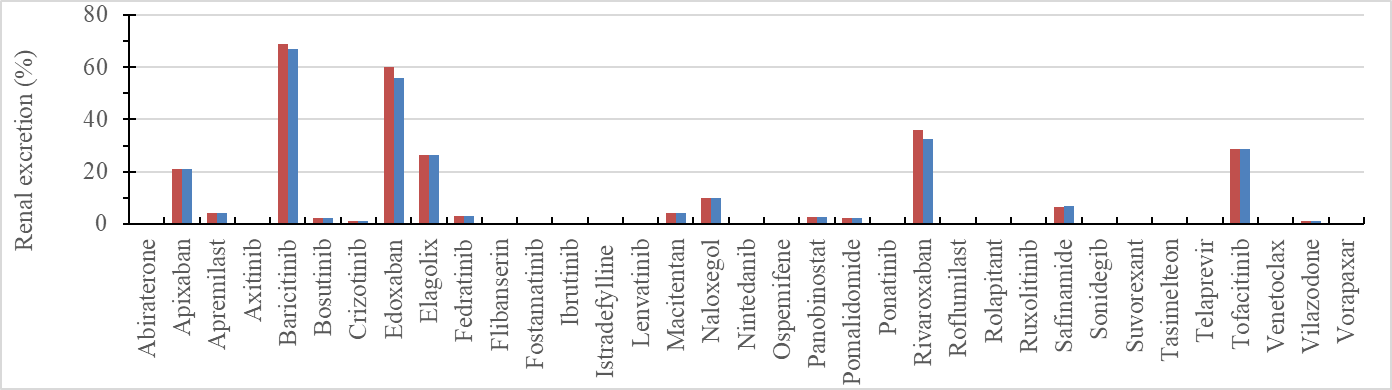
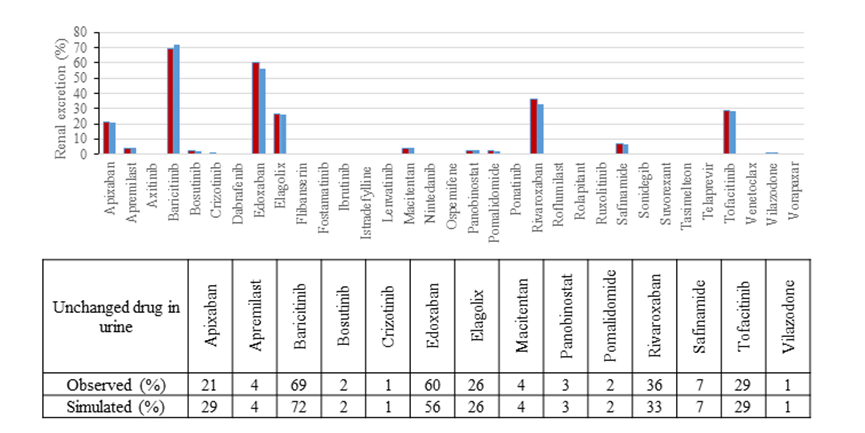


Figure S3. The comparison of renal excretion values between the simulated (blue column) and observed (red column). The table presented below the figure summarizes the renal excretion data for drugs exhibiting renal elimination characteristics. For drugs not featured in the table, both observed and simulated renal excretion values for the parent compound are reported as 0.

Finally, we assume the absence of extrahepatic metabolism, with all metabolism occurring within the liver and intestines. The distribution of the drug in tissues is reversible, ultimately returning to the plasma. Thus, assuming fixed excretion parameters, there should be a strong relationship between the metabolism of the drug in the liver and the level of the unchanged drug present in the plasma. Please find the comparison of the simulated AUC with actual AUC in the following Figure:

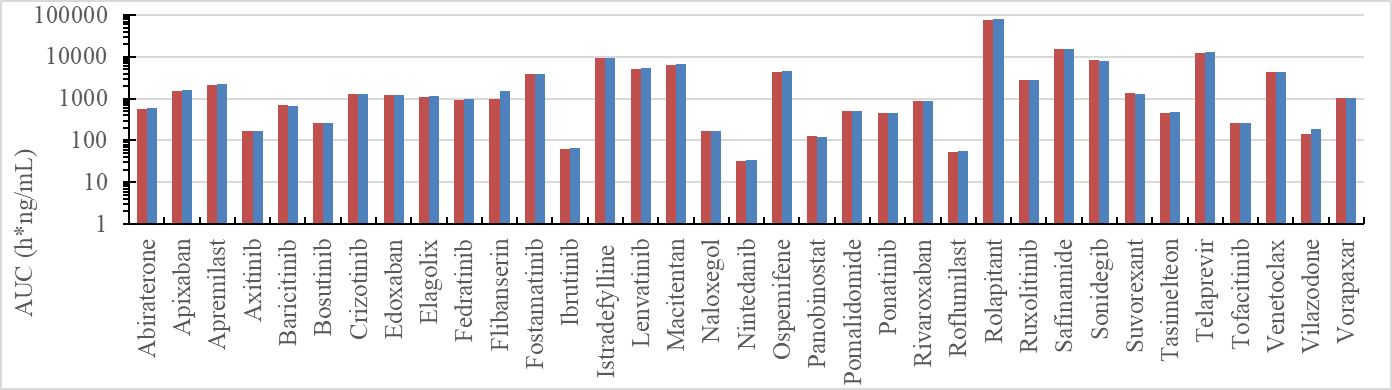


Figure S4. The comparison of renal excretion values between the simulated (blue column) and observed (red column).

* 1. Distribution:

In our predictions, we utilized a compartmental modeling approach, specifically the two-compartment model. This model includes distinct compartments representing key physiological sites such as the intestine, liver, central compartment, and peripheral compartment. The two-compartment model provides a simplified yet comprehensive representation of drug distribution dynamics within the body.

Given the utilization of the two-compartment model, the concepts of perfusion-limited and permeability-limited distribution mechanisms are not directly applicable. Instead, the model inherently accounts for the complexities of drug distribution by characterizing the movement of drugs between the central and peripheral compartments, which represent highly perfused and less perfused tissues, respectively.

In this model, we have implemented two approaches to ensure a distribution profile that closely resembles real-world conditions.

Firstly, we have incorporated measured values for distribution-related parameters such as plasma protein binding and blood-to-plasma ratio (BP ratio). This enables us to align these parameters in the model with empirically observed values.

Secondly, we consider distribution to be a reversible process. Therefore, the primary factor determining distribution is the drug's ability to return to the plasma after entering other compartments assuming fixed absorption, metabolism, and excretion. Consequently, the shape and distribution of the drug within the plasma exhibit greater relevance. The simulated PK profiles of victims are compared with the actual PK profiles in the following figure:

图表

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图形用户界面

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Figure S5. Model-simulated pharmacokinetic plasma profiles, following p.o. alone, overlaid with the observed data. Blue solid lines and circles represent the fitted pharmacokinetic profiles and the observed mean data after p.o. alone, respectively.

By above validations, we strived to achieve a more accurate representation of drug absorption, distribution, metabolism, and excretion within the model, closely resembling its behavior in real-world scenarios.

**3. The comparison between the predicted PK profiles of the victim drug and the observed PK profiles after co-administration with ketoconazole**

We utilized a PBPK-DDI model to predict the PK profiles of the victim drugs following co-administration with ketoconazole. The specific co-administration scheme can be found in Table S3.

Table S3. The dosing method in the clinical DDI studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| General name | Dosing of ketoconazole | Dosing of test article | AUCR (90% confidence interval) | Reference |
|  |
| Apixaban | 400 mg, QD | 10 mg, day4 | 1.99(1.81, 2.18) | S1 |  |
| Apremilast | 400 mg, QD | 20 mg, day5 | 1.36(1.26, 1.47) | S2 |  |
| Axitinib | 400 mg, QD | 5 mg, on day4 | 2.06(1.84, 2.30) | S3 |  |
| Baricitinib | 400 mg, QD | 10 mg, day4 | 1.21(1.17, 1.24) | S4 |  |
| Bosutinib | 400 mg, QD after 12h of the first dose | 100 mg after 12 h the first dosing | 7.55(6.42, 8.88) | S5 |  |
| Crizotinib | 200 mg, BID | 150 mg on day4 | 3.16(2.86, 3.50) | S6 |  |
| Edoxaban | 400mg, QD | 60 mg, on day4 | 1.87(1.76, 1.98) | S7 |  |
| Elagolix | 400mg, QD | 150 mg on day4 | 2.20(1.98, 2.44) | S8 |  |
| Fedratinib | 200, BID | 50 mg, on day6 | 3.85(2.89, 5.12) | S9 |  |
| Flibanserin | 400 mg, QD, day1~day5 | 50 mg, on day5 | 4.5 | S10 |  |
| Fostamatinib | 200mg, BID | 80 mg, on day 2 | 2.02(1.77, 2.30) | S11 |  |
| Ibrutinib | 400 mg, QD | 40 mg on day4, 1h post dose. | 26.2(20.0, 34.4) | S12 |  |
| Istradefylline | 200, BID | 40 mg on day4 | 2.47(1.92, 3.18) | S13 |  |
| Lenvatinib | 400mg, QD | 5 mg, on day5 | 1.15(1.08, 1.21) | S14 |  |
| Macitentan | 400 mg, QD | 10 mg on day5 | 2.30(2.10, 2.50) | S15 |  |
| Nintedanib | 400 mg, QD, day-2~day1 | 50 mg, 1h after last dosing on day1 | 1.61(1.48, 1.74) | S16 |  |
| Ospemifene | 400 mg, QD | 60 mg, on day 6 | 1.42(1.27, 1.60) | S17 |  |
| Panobinostat | 400 mg, QD | 20 mg, 1 h after dosing on day 4 | 1.78(1.45, 2.20) | S18 |  |
| Pomalidomide | 200, BID | 4 mg, on day5 | 1.19(1.10, 1.28) | S19 |  |
| Ponatinib | 400 mg, QD | 15 mg, on day5 | 1.78(1.66, 1.91) | S20 |  |
| Rivaroxaban | 400 mg, QD | 10 mg, on day5 | 2.58(2.36, 2.82) | S21 |  |
| Roflumilast | 200 mg, on day 11 | 0.5 mg, QD, day1~day11 | 1.34(1.29, 1.39) | S22 |  |
| Rolapitant | 400 mg, QD | 90 mg, 2h after dosing on day2 | 1.21(1.04, 1.41) | S23 |  |
| Ruxolitinib | 200 mg, BID | 10 mg, on day4 | 1.91(1.72, 2.21) | S24 |  |
| Safinamide | 200 mg, BID | 100 mg, on day 3 | 1.13(1.10, 1.16) | S25 |  |
| Sonidegib | 200 mg, BID | 800 mg, on day5 | 2.25(1.78, 2.86) | S26 |  |
| Suvorexant | 400 mg, QD | 4 mg on day2 | 2.79(2.35, 3.31) | S27 |  |
| Tasimelteon | 400 mg, QD | 20 mg on day5 | 1.54(1.38, 1.72) | S28 |  |
| Telaprevir | 400 mg, SD | 750 mg, SD | 1.62(1.45, 1.81) | S29 |  |
| Tofacitinib | 400 mg on day1~3 | 10 mg on day3 | 2.03(1.91, 2.16) | S30 |  |
| Venetoclax | 400 mg, QD | 50 mg on day4 | 6.40(4.47, 9.17) | S31 |  |
| Vilazodone | 200 mg, QD | 5 mg on day4 | 1.42(1.31, 1.55) | S32 |  |
| Vorapaxar | 400 mg, QD | 20 mg, on day7 | 1.23(1.05, 1.46) | S33 |  |

A comparison was made between the predicted PK profiles and the observed data, and the results are depicted in Figure S6. The comparison shows a close resemblance between the predicted PK profiles and the observed data, both in terms of the overall shape and trend. This indicates a good predictive performance of our model, demonstrating its accuracy in predicting the PK outcomes.



图表, 折线图

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Figure S6. Model-predicted pharmacokinetic plasma profiles of victims after co-administering with ketoconazole, overlaid with the observed data. Red solid lines and circles represent the fitted pharmacokinetic profiles and the observed mean data, respectively.

**4. The comparison of DDI predictions between PBPK model and MSMs**

The predictive performance of PBPK-DDI model was much better than mechanistic static models (MSMs).

Table S4. The comparison between the predicted AUCR using MSMs and PBPK models with the observed data.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound | AUCR | | | |
| Static mechanistic models | | PBPK model | Observed |
| Liver | Liver+Gut | Liver+Gut |
| Apixaban | 2.17 | 429 | 1 | 1.99(1.81, 2.18) |
| Apremilast | 5.94 | 1165 | 1.844 | 1.36(1.26, 1.47) |
| Axitinib | 8.15 | 1603 | 5.96 | 2.06(1.84, 2.30) |
| Baricitinib | 1.21 | 238 | 1 | 1.21(1.17, 1.24) |
| Bosutinib | 2.58 | 255 | 8.35 | 7.55(6.42, 8.88) |
| Crizotinib | 3.36 | 336 | 2.552 | 3.16(2.86, 3.50) |
| Edoxaban | 1.38 | 270 | 1 | 1.87(1.76, 1.98) |
| Elagolix | 1.64 | 323 | 1.17 | 2.20(1.98, 2.44) |
| Fedratinib | 3.73 | 375 | 3.468 | 3.85(2.89, 5.12) |
| Flibanserin | 8.15 | 1604 | 6.581 | 4.5 |
| Fostamatinib | 4.01 | 405 | 1.443 | 2.02(1.77, 2.30) |
| Ibrutinib | 8.15 | 237 | 26.09 | 26.2(20.0, 34.4) |
| Istradefylline | 4.01 | 404 | 2.136 | 2.47(1.92, 3.18) |
| Lenvatinib | 8.15 | 1591 | 1 | 1.15(1.08, 1.21) |
| Macitentan | 8.15 | 1591 | 2.904 | 2.30(2.10, 2.50) |
| Nintedanib | 3.76 | 111 | 1.817 | 1.61(1.48, 1.74) |
| Ospemifene | 8.15 | 1608 | 1.991 | 1.42(1.27, 1.60) |
| Panobinostat | 5.82 | 166 | 2.8 | 1.78(1.45, 2.20) |
| Pomalidomide | 3.7 | 374 | 1.029 | 1.19(1.10, 1.28) |
| Ponatinib | 8.15 | 1602 | 2.607 | 1.78(1.66, 1.91) |
| Rivaroxaban | 2.16 | 425 | 1.574 | 2.58(2.36, 2.82) |
| Roflumilast | 1.74 | 1.74 | 1.027 | 1.34(1.29, 1.39) |
| Rolapitant | 4.39 | 8.97 | 1.58 | 1.21(1.04, 1.41) |
| Ruxolitinib | 4.01 | 405 | 1.432 | 1.91(1.72, 2.21) |
| Safinamide | 3.27 | 330 | 1 | 1.13(1.10, 1.16) |
| Sonidegib | 4.01 | 391 | 1.526 | 2.25(1.78, 2.86) |
| Suvorexant | 3.76 | 740 | 3.418 | 2.79(2.35, 3.31) |
| Tasimelteon | 8.15 | 1604 | 1 | 1.54(1.38, 1.72) |
| Telaprevir | 3.76 | 742 | 2.579 | 1.62(1.45, 1.81) |
| Tofacitinib | 2.17 | 430 | 2.075 | 2.03(1.91, 2.16) |
| Venetoclax | 8.15 | 1599 | 2.64 | 6.40(4.47, 9.17) |
| Vilazodone | 3.43 | 346 | 4.333 | 1.42(1.31, 1.55) |
| Vorapaxar | 8.15 | 1590 | 1.082 | 1.23(1.05, 1.46) |

**5. Predictive performance of the PBPK-DDI model using Tmax and Cmax**

The comparison of TmaxR and CmaxR predictions made using three different *fm*s with the measured TmaxR values were showed in Figure S7 and Figure S8. Notably, the predicted TmaxR was found to be accurate within 2 times the observed TmaxR when using in silico or *in vitro fm* methods, but not with 100% *fm*. The *in vitro fm* was the most precise method, as it accurately predicted the CmaxR of 31 drugs within 2 times of the measured results. In contrast, the use of 100% *fm* and in silico *fm* led to lower prediction accuracy. Only 24 drugs had their CmaxR predicted within 2 times of the measured results when using 100% *fm* or in silico *fm*, and 26 drugs for CmaxR when using in silico *fm*. The findings demonstrate that incorporating *in vitro fm* data into PBPK models significantly enhances the accuracy of predicting the extent of DDIs for the parameters studied. While in silico *fm* shows some promise, its impact on prediction is limited.

图示, 工程绘图

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Figure S7. Comparison of TmaxR predictions made using three different *fm*s with the measured TmaxR values. The left panel assumes a fixed *fm* value of 100%, the middle panel uses an *in silico* *fm*, and the right panel uses an *in vitro fm*

图示

描述已自动生成Figure S8. Comparison of CmaxR predictions made using three different *fm*s with the measured CmaxR values. The left panel assumes a fixed *fm* value of 100%, the middle panel uses an *in silico* *fm*, and the right panel uses an *in vitro fm*

Reference

S1. Apixaban (Eliquis) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. < https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2012/202155Orig1s000ClinPharmR.pdf> (2012). Accessed July 2023.

S2. Apremilast (Otezla) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/205437Orig1s000ClinPharmR.pdf> (2014). Accessed July 2023.

S3. Axitinib (Inlyta) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2012/202324Orig1s000ClinPharmR.pdf> (2012). Accessed July 2023.

S4. Baricitinib (Olumiant) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2018/207924Orig1s000ClinPharmR.pdf> (2018). Accessed July 2023.

S5. Bosutinib (Bosulif) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2012/203341Orig1s000ClinPharmR.pdf> (2012). Accessed July 2023.

S6. Crizotinib (Xalkori) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/202570Orig1s000ClinPharmR.pdf> (2011). Accessed July 2023.

S7. Edoxaban (Savaysa)[U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2015/206316Orig1Orig2s000ClinPharmR.pdf.> (2015). Accessed July 2023.

S8. Elagolix (Orilissa)[U.S. new drug application, Multi-Discipline Review/Summary, Clinical, Non-Clinical]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2018/210450Orig1s000MultiD.pdf> (2018). Accessed July 2023.

S9. Fedratinib (Inrebic) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2019/212327Orig1s000MultidisciplineR.pdf> (2019). Accessed July 2023.

S10. Flibanserin(Addyi) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2015/022526Orig1s000ClinPharmR.pdf> (2015). Accessed July 2023.

S11. Fostamatinib (Tavalisse)[U.S. new drug application, Multi-Discipline Review/Summary, Clinical, Non-Clinical]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2018/209299Orig1s000MultidisciplineR.pdf> (2018). Accessed July 2023.

S12. Ibrutinib (Imbruvica) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/205552Orig2s000ClinPharmR.pdf> (2014). Accessed July 2023.

S13. Istradefylline (Nourianz) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2019/022075Orig1s000ClinPharmR.pdf> (2019). Accessed July 2023.

S14. Lenvatinib (Lenvima) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2015/206947Orig1s000ClinPharmR.pdf> (2015). Accessed July 2023.

S15. Macitentan (Opsumit) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2013/204410Orig1s000ClinPharmR.pdf> (2013). Accessed July 2023.

S16. Nintedanib (Ofev) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/205832Orig1s000ClinPharmR.pdf> (2014). Accessed July 2023.

S17. Ospemifene (Osphena) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2013/203505Orig1s000ClinPharmR.pdf> (2013). Accessed July 2023.

S18. Panobinostat (Farydak) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2015/205353Orig1s000ClinPharmR.pdf> (2015). Accessed July 2023.

S19. Pomalidomide (Pomalyst) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2013/204026Orig1s000ClinPharmR.pdf> (2012). Accessed July 2023.

S20. Ponatinib (Iclusig) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2012/203469Orig1s000ClinPharmR.pdf> (2012). Accessed July 2023.

S21. Rivaroxaban (Xarelto) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/022406Orig1s000ClinPharmR.pdf> (2011). Accessed July 2023.

S22. Roflumilast (Daliresp) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/022522Orig1s000ClinPharmR.pdf> (2011). Accessed July 2023.

S23. Rolapitant (Varubi) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2015/206500Orig1s000ClinPharmR.pdf > (2015). Accessed July 2023.

S24. Ruxolitinib (Jakafi) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/202192Orig1s000ClinPharmR.pdf> (2011). Accessed July 2023.

S25. Safinamide (Xadago) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2017/207145Orig1s000ClinPharmR.pdf> (2017). Accessed July 2023.

S26. Sonidegib (Odomzo) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2015/205266Orig1s000ClinPharmR.pdf> (2015). Accessed July 2023.

S27. Suvorexant (Belsomra) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. < https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/204569Orig1s000ClinPharmR.pdf> (2014). Accessed July 2023.

S28. Tasimelteon (Hetlioz) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/205677Orig1s000ClinPharmR.pdf > (2014). Accessed July 2023.

S29. Telaprevir (Incivek) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. < https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/201917Orig1s000ClinPharmR.pdf> (2011). Accessed July 2023.

S30. Tofacitinib (Xeljanz) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2012/203214Orig1s000ClinPharmR.pdf> (2012). Accessed July 2023.

S31. Venetoclax (Venclexta) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. < https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2016/208573Orig1s000ClinPharmR.pdf> (2016). Accessed July 2023.

S32. Vilazodone (Viibryd) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/022567Orig1s000ClinPharmR.pdf> (2011). Accessed July 2023.

S33. Vorapaxar (Zontivity) [U.S. new drug application, clinical pharmacology and biopharmaceutics reviews]. <https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/204886Orig1s000ClinPharmR.pdf> (2014). Accessed July 2023.