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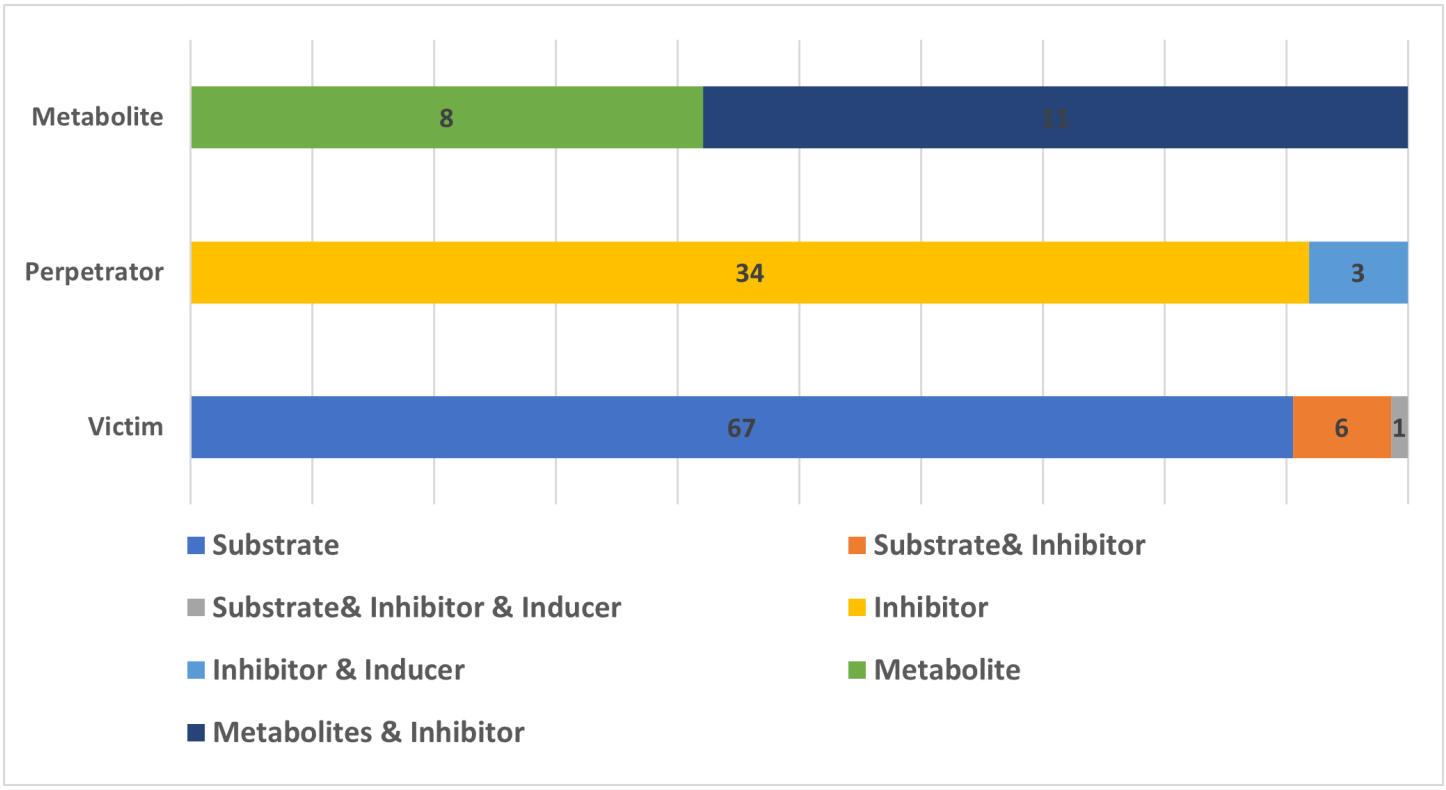
Introduction to compound summaries and overview of the Simcyp™ compound library

Compound files represent a library of input data required for the selected structural models that are specific for the compound and the purpose of the physiology-based pharmacokinetic/dynamic (PBPK/PD) model. For instance, CYP3A4 assigned drug-parameter are required, if the user would like to investigate that specific pathway as part of the structural model. As of Version 22, the Simcyp Simulator contains a library of 130 small molecule and 6 large molecule compound files, including substrates, inhibitors, inducers, and metabolites (Figure 1). In addition to the compound files within the Simcyp Simulator, a repository of over 100 published compound files developed by consortium members (n = 30), academic groups (n = 17), regulatory agencies (n = 23) and Simcyp research files (n = 14) is available on the Simcyp members area (https://members.certara.co.uk/Simcyp). The compound files within the compound library are prefixed with either Sim-, SV- and SB-. Sim- referring to files that have been developed using a "bottom-up" approach, SV- refers to files that have been optimised using in vivo data to give better predictions and SB- referring to therapeutic proteins.

Figure 1



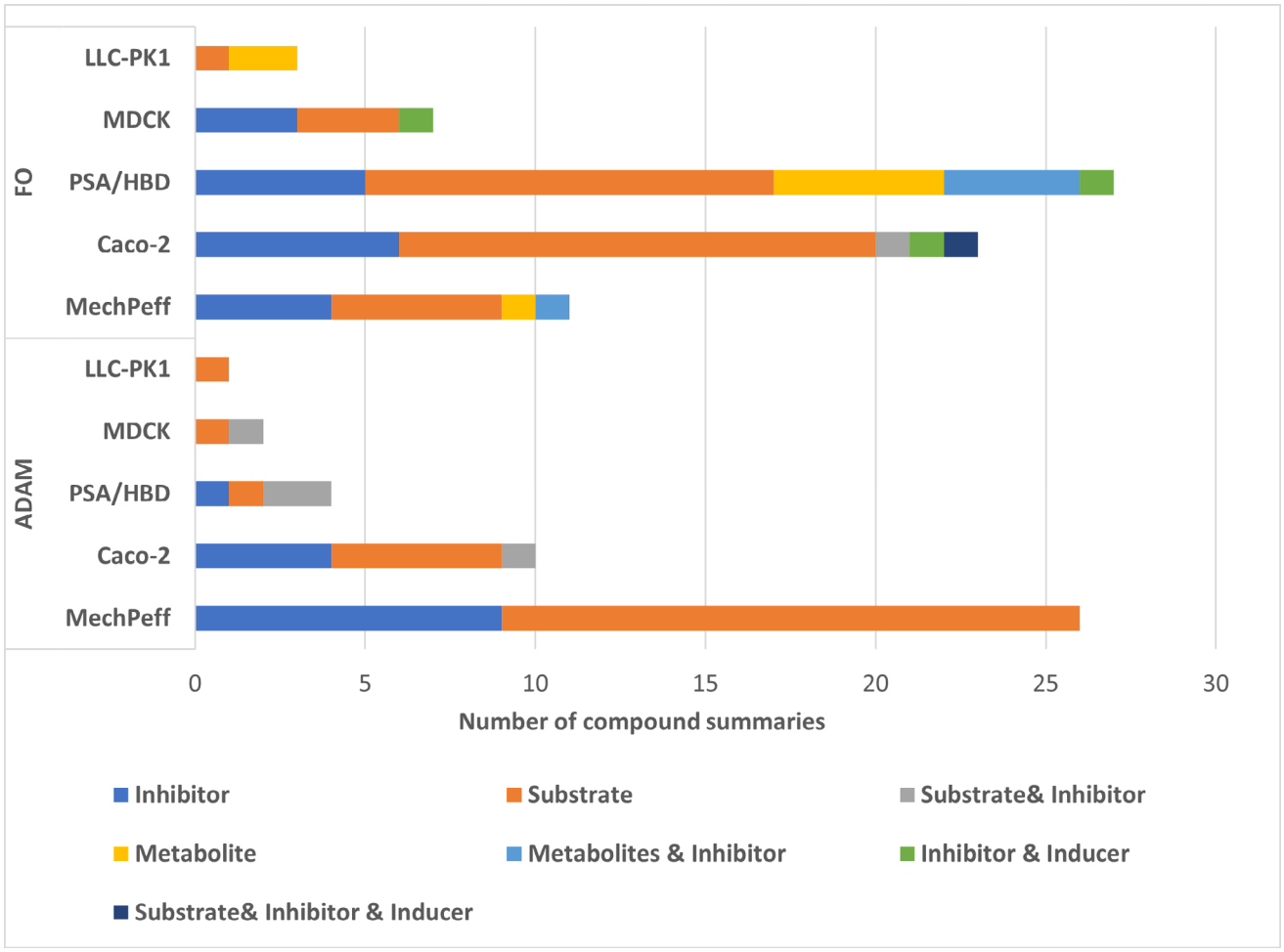
Composition of Simcyp compound library.

The development of compound files requires a thorough analysis of the literature and extensive verification before they are added to the Simcyp Simulator. Details of the development and verification of Simcyp compound files are provided on the members area in the form of compound summaries for each compound. Within these compound summaries, various structural models used within the overall PBPK/PD model that were used for the compound file development are provided.

In addition, the performance of the compound file in comparison to observed data is also highlighted, including concentration-time profiles, trial statistics of key parameters (such as Tmax, Cmax, AUC and clearance) and simulations of reported clinical DDIs and PD effects. Also, a table of the input parameters for each compound file and details of the derivation of the values are supplied. Currently, the compound summaries contain references to over 500 clinical PK profiles and over 500 DDIs that were compared to matched simulations accounting for population characteristics such as proportion of females in the population, age range, and ethnicity.

The table of inputs contain in addition to the physicochemical information like molecular weight, compound type, pKa and logP, required absorption, elimination, and interaction parameter inputs. Also, information on the structural model setting is included. Three options for the absorption model are provided within the Simcyp Simulator: (1) First order (FO) absorption, (2) advanced dissolution, absorption, and metabolism (ADAM) (Jamei et al., 2009) and (3) multi-layer gut wall within the ADAM (M-ADAM) model (REF). The regional permeability can be predicted through the mechanistic effective permeability model (MechPeff) (Pade et al., 2017), alternatively in vitro experiments, or physicochemical input data such as Polar Surface Area and Hydrogen Bond Donor (PSA/HBD) can be used to scale to the human jejunum effective permeability (Winiwarter et al., 1998). Over one-third of the compounds within the library have been developed employing the ADAM model, whilst the remainder use the FO absorption model. The former is predominantly used for substrate files, while the latter is often used for inhibitor files. Out of the 7 options available for predicting the permeability of the compounds, 5 have been used in the library compounds. The MechPeff model is the most predominantly used option within the ADAM model. For FO absorption model compounds, Caco-2 and PSA/HBD scaling to Peff,man are generally used (Figure 2).

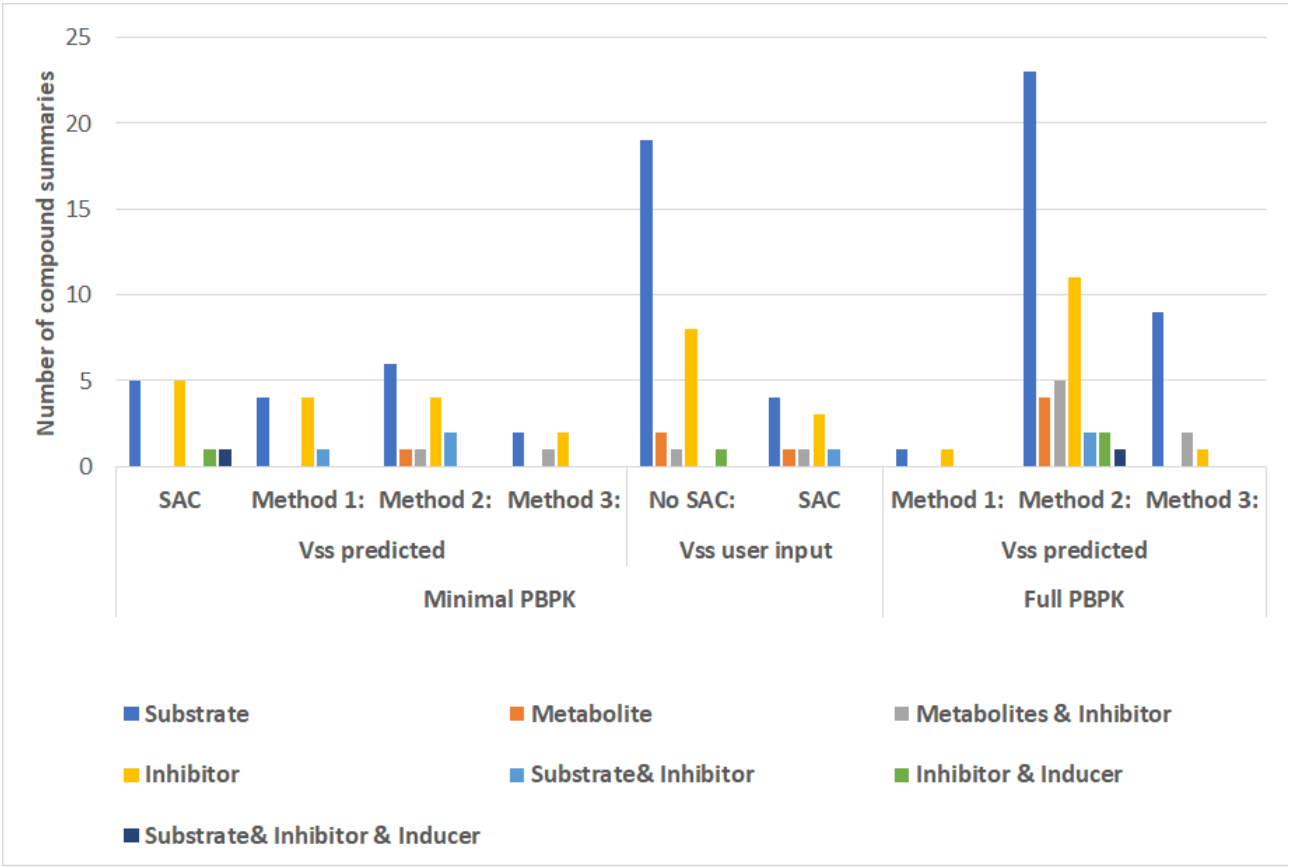
Figure 2



Overview of absorption models used within the compound library. FO: first order; ADAM: Advanced Dissolution, Absorption, and Metabolism

Two options are available for distribution modelling: minimal PBPK or full PBPK. The minimal PBPK accounts for the systemic, portal vein and liver compartments. A single adjusting compartment (SAC) can be combined with minimal PBPK which allows users to capture biphasic profiles from their observed clinical data. Several permeability-limited multi-compartment organ models (e.g., brain, kidneys, lungs, skin etc.) can be activated together with the full PBPK model. In the current compound library, the use of minimal PBPK and full PBPK is split relatively evenly, 53% and 47% respectively. Of the compounds which use minimal PBPK, 30% use a SAC. Three methods (Method 1: Poulin and Theil, Method 2: Rodgers and Rowland and Method 3: Fick-Nernst-Planck method) are available to predict Vss for the compounds. Where the volume of distribution is predicted, method 1 is used in 12 compounds, method 2 in 62 and method 3 in 17. In total 52% of minimal PBPK and 74% of full PBPK compounds use the Method 2 option (Figure 3).

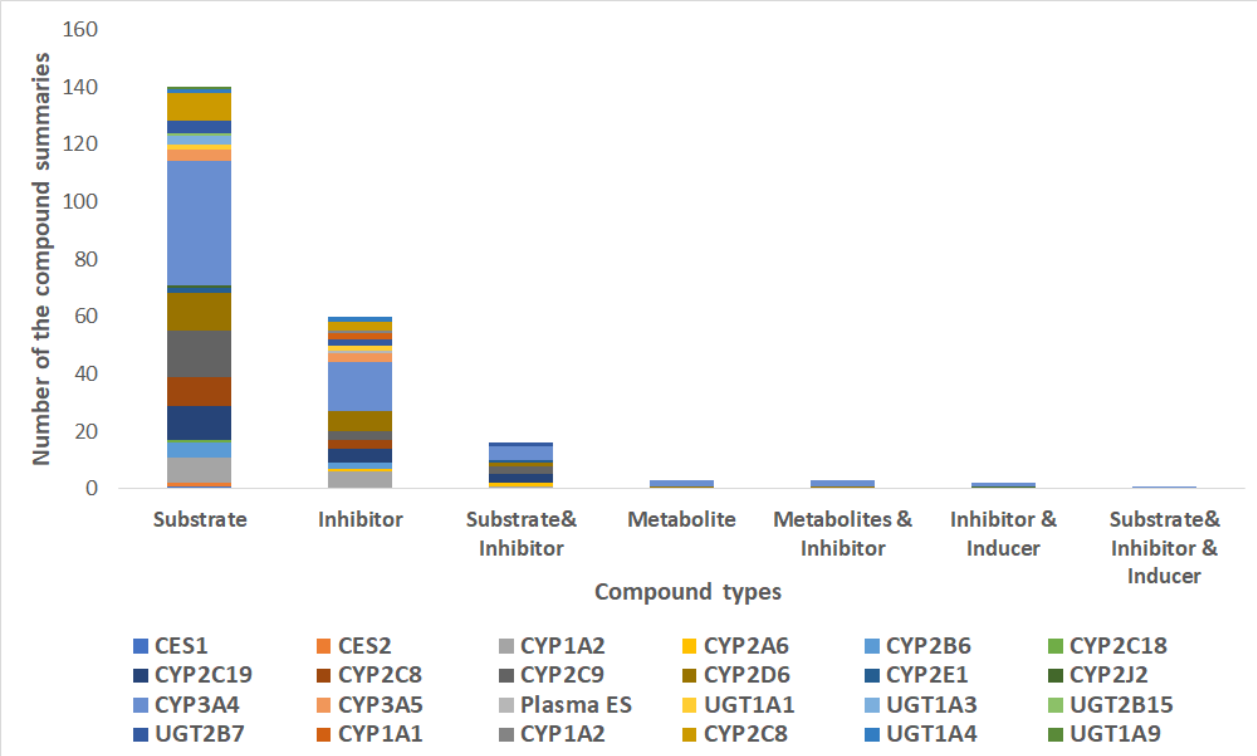
Figure 3



Overview of the distribution models used in the Simcyp compound library .

Enzyme and transporter information is important to describe the elimination of the drug mechanistically and define drug-drug interactions via a specified pathway. Although transporter are not always included in PBPK models, 17% of the compounds within the current library include kinetics for transporters expressed in different organs (gut, kidney, and/or liver), and 73% include input parameters of metabolism enzymes including CYP, UGT, and/or other pathways (i.e., CES, plasma ES). This information is either derived from in vitro or in vivo studies. Details of the most frequently used in vitro-in vivo extrapolation (IVIVE) scaling approaches in the simulator have been recently published by Ezuruike et al., 2022 and previous work by Howgate et al., 2006 and Jamei et al., 2014. Reflecting the fact that ¾ of the top 200 marketed drugs are metabolised by CYP3A4 (Wienkers and Heath, 2005) and that the Simulator platform is frequently used for CYP inhibition DDI evaluation in a regulatory context (Kilford et al., 2022, Shebley et al., 2018). Figure 4 indicates that CYP3A4 forms the most important interacting pathway among the different moieties.

Figure 4



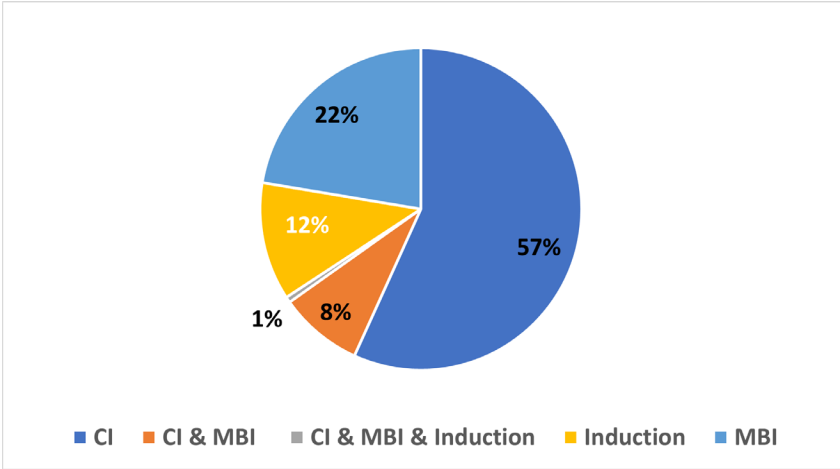
Overview of the enzyme metabolism pathways in the Simcyp compound library.

For transporter interactions, permeability-limited models are available for use in several organs (liver, kidneys, brain, and lungs). Of the compound files which use the transporter models, 11 use the mechanistic kidney model (MechKiM, Neuhoff et al., 2013), 13 use the permeability-limited liver model (PerL, Jamei et al., 2014) and 8 use the ADAM model with intestinal transporters.

The verification and some applications of the models are described in the compound summaries too. To ensure the model well-describes the exposure of the drug, the simulated performance of the compound file is compared against observed concentration-time profiles, if possible, over a wide dose range and for intravenous and oral applications. Within all compound summaries, observed profiles have been obtained from 547 clinical studies .

In addition to the Caucasian healthy volunteer population, where appropriate data is available, special populations, where the physiology and enzyme abundances of the subjects in

Figure 5



Overview of the Drug-Drug Interaction (DDI) mechanisms in the compound summaries. CI: competitive inhibition; MBI: Mechanism-based inactivation

the simulation are adjusted to reflect the population of interest, have also been used to verify the exposure of compounds. Special populations used to verify the performance of library compounds include those with different disease states including cancer and rheumatoid arthritis, different ethnicities including Japanese and Chinese subjects and populations with variations associated with age such as paediatric.

In total, 523 clinical drug-drug interactions (DDIs) from 319 publications have been used to further verify whether the kinetic inputs accurately define the drug-metabolizing enzymes and transporter-mediated activities. Four options are available in the Simcyp Simulator: Competitive inhibition (CI), mechanism-based inhibition (MBI), induction, and suppression. The majority, 57%, of the DDIs in the compound summaries are modelled as competitive inhibition (Figure 5).

Overall, the compound summaries are a useful resource for users of the Simcyp Simulator, giving detailed information on the development of compound files and the various models included within. These documents also highlight the performance of Simcyp compounds in comparison to clinically observed data and provide references to a large amount of relevant clinical studies.

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