enzyme of the liver, for example, are likely to undergo a drug–drug interaction with compounds that are substantially metabolized by this enzyme. Compounds can be screened for their ability to block metabolic enzymes using *in vitro* assays designed to detect changes in the rate of metabolism of a known substrate. Changes in the rate of conversion of 7-benzyloxy-4-trifluoromethylcoumarin to 7-hydroxy-4-trifluoromethylcoumarin by CYP3A4 in the presence of a varying concentrations of a candidate compound, for example, provides an IC_{50} for the candidate compound's interaction with CYP3A4 (Figure 8.15).[31] In theory, it would be possible to generate IC_{50}s for a candidate compound's ability to block all of the metabolic CYP enzymes (Table 8.1), and this information could be used to predict which compounds

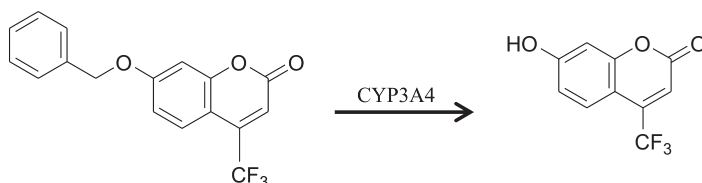

FIGURE 8.15 Monitoring the rate of conversion of 7-benzyloxy-4-trifluoromethylcoumarin into 7-hydroxy-4-trifluoromethyl coumarin by CYP3A4 is an effective means of identifying compounds that block CYP3A4 metabolism and represent a risk of drug–drug interactions.

TABLE 8.1 CYP Enzymes, Drug Substrates, and Metabolites that can be Used to Detect Possible Drug–Drug Interactions

CYP isozyme	Drug substrate	Drug metabolite
3A4	Midazolam	1′-Hydroxymidazolam
2D6	Bufuralol	1′-Hydroxybufuralol
2C9	Diclofenac	4′-Hydroxydiclofenac
1A2	Ethoxyresorufin	Resorfin
2C19	S-Mephenytoin	4′-Hydroxymephenytoin
2A6	Coumarin	7′-Hydroxycoumarin
2C8	Paclitaxel	6α-Hydroxypaclitaxel

would be at risk for drug–drug interactions. In practice, however, it is not cost-effective to screen compounds against all known metabolic enzymes. Instead, typical drug discovery programs often screen compounds of interest against the major CYP enzymes CYP3A4, CYP2D6, and CYP2C9 in order to obtain a preliminary sense of associated risks. As a candidate compound advances toward human trials, its ability to inhibit additional metabolic