TABLE 5-3 DRUGS WITH A HIGH RISK OF GENERATING PHARMACOKINETIC INTERACTIONS

Drug	Mechanism	Examples
Antacids	Reduced absorption	Antacids/tetracyclines
Bile acid sequestrants		Cholestyramine/digoxin
Proton pump inhibitors	Altered gastric pH	Ketoconazole absorption decreased
H_2-receptor blockers		
Rifampin	Induction of CYPs and/or P-glycoprotein	Decreased concentration and effects of
Carbamazepine		warfarin
Barbiturates		quinidine
Phenytoin		cyclosporine
St. John's wort		losartan
Glutethimide		oral contraceptives
Nevirapine (CYP3A; CYP2B6)		methadone, dabigatran
Tricyclic antidepressants	Inhibitors of CYP2D6	Increased effect of many β blockers
Fluoxetine		Decreased codeine effect; possible decreased tamoxifen effect
Quinidine		
Cimetidine	Inhibitor of multiple CYPs	Increased concentration and effects of
		warfarin
		theophylline
		phenytoin
Ketoconazole, itraconazole	Inhibitor of CYP3A	Increased concentration and toxicity of some HMG-CoA reductase inhibitors
Erythromycin, clarithromycin		cyclosporine, cisapride, terfenadine (now withdrawn)
Calcium channel blockers		Increased concentration and effects of indinavir (with ritonavir)
Ritonavir		Decreased clearance and dose requirement for cyclosporine (with calcium channel blockers)
Allopurinol	Xanthine oxidase inhibitor	Azathioprine and 6-mercaptopurine toxicity
Amiodarone	Inhibitor of many CYPs and of P-glycoprotein	Decreased clearance (risk of toxicity) for
		warfarin
		digoxin
		quinidine
Gemfibrozil (and other fibrates)	CYP3A inhibition	Rhabdomyolysis when co-prescribed with some HMG-CoA reductase inhibitors
Quinidine	P-glycoprotein inhibition	Risk of toxicity with P-glycoprotein substrates (e.g., digoxin, dabigatran)
Amiodarone		
Verapamil		
Cyclosporine		
Itraconazole		
Erythromycin		
Phenylbutazone	Inhibition of renal tubular transport	Increased risk of methotrexate toxicity with salicylates
Probenecid		
Salicylates		

erythromycin and some other macrolide antibiotics (clarithromycin but not azithromycin), ketoconazole and other azole antifungals, the antiretroviral agent ritonavir, and high concentrations of grapefruit juice (Table 5-3). The consequences of such interactions will depend on the drug whose elimination is being inhibited (see "The Concept of High-Risk Pharmacokinetics," above). Examples include CYP3A inhibitors increasing the risk of cyclosporine toxicity or of rhabdomyolysis with some HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin, but not pravastatin), and P-glycoprotein inhibitors increasing the risk of toxicity with digoxin therapy or of bleeding with the thrombin inhibitor dabigatran.

These interactions can occasionally be exploited to therapeutic benefit. The antiviral ritonavir is a very potent CYP3A4 inhibitor that is sometimes added to anti-HIV regimens, not because of its antiviral effects but because it decreases clearance, and hence increases efficacy, of other anti-HIV agents. Similarly, calcium channel blockers have been deliberately coadministered with cyclosporine to reduce its clearance and thus its maintenance dosage and cost.

Phenytoin, an inducer of many systems, including CYP3A, inhibits CYP2C9. CYP2C9 metabolism of losartan to its active metabolite is inhibited by phenytoin, with potential loss of antihypertensive effect.

Grapefruit (but not orange) juice inhibits CYP3A, especially at high doses; patients receiving drugs where even modest CYP3A inhibition may increase the risk of adverse effects (e.g., cyclosporine, some HMG-CoA reductase inhibitors) should therefore avoid grapefruit juice.

CYP2D6 is markedly inhibited by quinidine, a number of neuroleptic drugs (chlorpromazine and haloperidol), and the SSRIs fluoxetine and paroxetine. The clinical consequences of fluoxetine's interaction with CYP2D6 substrates may not be apparent for weeks after the drug is started, because of its very long half-life and slow generation of a CYP2D6-inhibiting metabolite.

6-Mercaptopurine is metabolized not only by TPMT but also by xanthine oxidase. When allopurinol, an inhibitor of xanthine oxidase, is administered with standard doses of azathioprine or 6-mercaptopurine, life-threatening toxicity (bone marrow suppression) can result.

A number of drugs are secreted by the renal tubular transport systems for organic anions. Inhibition of these systems can cause excessive drug accumulation. Salicylate, for example, reduces the renal clearance of methotrexate, an interaction that may lead to methotrexate toxicity. Renal tubular secretion contributes substantially to the elimination of penicillin, which can be inhibited (to increase its therapeutic effect) by