Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib and nilotinib

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Summary
Several cancer treatments are shifting from traditional, time-limited, non-specific cytotoxic chemotherapy cycles to continuous oral treatment with specific protein targeted therapies. In this line, imatinib mesylate, a selective tyrosine kinases inhibitor (TKI), has excellent efficacy in the treatment of chronic myeloid leukemia (CML). It has opened the way to the development of additional anti-CML TKIs, including nilotinib and dasatinib. TKIs are prescribed for prolonged periods, often in patients with comorbidities. Therefore they are regularly co-administered along with treatments at risk of drug-drug interactions. This aspect has been partially addressed so far, calling for a comprehensive review of the published data. We review here the available evidence and pharmacological mechanisms of interactions between imatinib, dasatinib and nilotinib, and widely prescribed co-medications, including known inhibitors or inducers of cytochromes P450 or drug transporters. Information is mostly available for imatinib, well introduced in clinical practice. Several pharmacokinetic aspects yet remain insufficiently investigated for these drugs. Regular updates will be mandatory, and so is the prospective reporting of unexpected clinical observations.

Keywords
Tyrosine kinase inhibitor; drug interactions; targeted cancer therapy; cytochrome P-450 enzyme system; P-glycoprotein; chronic myeloid leukemia; ABCG2 protein, organic cation transporter 1
Introduction

Targeted cancer therapies have been designed to interact with particular proteins associated with tumor development or progression. Many of these agents are tyrosine kinases inhibitors (TKIs), targeting enzymes whose disregulated expression and activity are associated with various cancers. The pioneer small-molecule TKI imatinib has revolutionized the treatment and prognosis of chronic myeloid leukemia (CML). Imatinib inhibits the tyrosine kinase Bcr-Abl, a fusion oncoprotein resulting from the translocation t(9;22)(q34;q11), which is associated with the characteristic Philadelphia chromosome, a hallmark of CML and of some acute lymphoblastic leukemias (ALL).

However, some patients, especially those in the advanced phase of the disease, develop resistance to imatinib therapy, due to various mechanisms such as BCR-ABL gene amplification, low imatinib absorption, or more frequently point mutations into the oncprotein sequence. Several new inhibitors have been developed with increased potency and a broader range of activity against imatinib-resistant mutants. In vitro studies have shown that nilotinib, an imatinib derivative, and dasatinib, structurally unrelated to imatinib, are respectively 20 and 300-fold more potent than imatinib against unmutated Abl, and are active against many imatinib–resistant Bcr-Abl mutants.

TKIs are extensively metabolized by cytochrome P450 enzymes (CYP), whose activities are characterized by a large degree of inter-individual variability. Some TKIs are also substrates or inhibitors of the drug transporters P-glycoprotein (Pgp; coded by ABCB1) Breast Cancer Resistance Protein (BCRP; ABCG2) and the organic cation carrier 1 (hOCT1; SLC22A1). A standard regimen can therefore produce very different circulating and cell concentration profiles from one patient to another, thus favoring the selection of resistant cellular clones by sub-therapeutic drug exposure, or the occurrence of toxicity in case of overexposure. Identifying the best active and safe dosing schedule for individual patients to maximize therapeutic benefit has turned to be a scientific and clinical challenge. Combination therapies have been investigated in various conditions, which certainly add a level of treatment complexity, as overlapping toxicities and pharmacokinetic interactions have to be taken into consideration.

We review here systematically and present under an easy-consulting form (Tables) the information available on pharmacological interactions between imatinib, dasatinib and nilotinib, and drugs concomitantly prescribed to patients receiving TKIs. The drugs were selected based on the information extracted from our database, used within the framework of Therapeutic Drug Monitoring (TDM) of TKIs. Moreover, classical inhibitors or inducers of cytochromes P450 or drug transporters were also included in this review. We do not intend here to replace individualized medical evaluation and the data presented here should be used in addition to thorough clinical judgment. Indeed, it may be that our searches still missed some interactions, and actually most interactions do not represent true contra-indications, but rather call for appropriate dosage adjustments and treatment monitoring measures.
Review of the literature

In addition to official monographies of the drugs, literature from Medline and Evidence-Based Medicine Reviews was systematically searched, using the following MeSH terms: ‘Drug interactions’, ‘Cytochrome P-450 Enzyme System’, ‘P-Glycoprotein’, ‘ABCG2 protein’, ‘organic cation transporter 1’, ‘Protein binding’, the respective TKI and concomitant drugs names. Additionally, two drug information databases (UpToDate online and Cancer Care Ontario) were screened, and abstracts of international and national conferences, review articles and references given in identified articles were also scanned. All relevant cited literature on pharmacokinetic or pharmacodynamic interactions was considered for inclusion in the Table.

Drug interactions were either clinically documented or derived from mechanistic considerations on proven or putative metabolic pathways, protein binding and transmembrane transport. When data on a particular combination were unavailable, potential interactions were extrapolated from the reported disposition mechanisms of the agents and of similar substrates.

Interaction with imatinib

Imatinib is metabolized mainly by CYP isoenzyme 3A4, while CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 are reported to play a minor role in its metabolism. This TKI has also been demonstrated to be a substrate of hOCT-1, Pgp and BCRP. However, a controversial report suggests that imatinib is an inhibitor rather than a substrate of BCRP, thus leaving uncertainty about the role of this pathway. The metabolites of imatinib are eliminated predominantly through biliary excretion. One metabolite, an N-demethylated piperizine derivative (CGP 74588) shows pharmacological activity comparable to the parent drug, but the systemic exposure represents approximately 10% to 15% of that for imatinib. The fecal to urinary excretion ratio is approximately 5:1. Moreover, imatinib can competitively inhibit the metabolism of drugs that are CYP2C9, CYP2C19, CYP2D6 and CYP3A4 substrates. Imatinib is approximately 95% bound to human plasma proteins, mainly albumin and α1-acid glycoprotein.

Interactions should therefore be considered when administering inhibitors of the CYP3A family in combination with imatinib. Strong inhibition, such as achieved with ketoconazole, caused a 40% increase of imatinib exposure in healthy volunteers. Interactions are likely to occur with other inhibitors of CYP3A4, such as levotyroxine, voriconazole, or amiodarone, leading to increase in plasma concentrations of imatinib. Nevertheless, a study suggests that inhibition of CYP3A4 by the potent irreversible inhibitor ritonavir does not result in increased steady-state plasma concentrations of imatinib, possibly due to the induction of compensatory metabolism or transport mechanisms by ritonavir.

Concomitant administration of imatinib with inhibitors of both CYP3A4 and Pgp, increase not only plasma but also intracellular imatinib concentrations. Dual CYP3A4 and Pgp inhibitors such as verapamil, erythromycin, clarithromycin, ciclosporin, ketoconazole, fluconazole,
itraconazole increase intracellular concentrations of imatinib by inhibiting both its metabolism and its efflux via Pgp and might therefore increase its cellular toxicity. Moreover, inhibition of Pgp by proton pump inhibitors such as pantoprazole was shown to increase brain penetration of imatinib. Concomitant administration of a Mg^2+-Al^3+-based antacid is not associated with meaningful alterations in imatinib absorption.

Concomitant administration of CYP3A4 inducers such as rifampicin or certain antiepileptics may lead to a reduction of as much as 74% in imatinib exposure. Moreover, the pharmacokinetic profile of imatinib was significantly altered by St. John's wort, with reductions of 30% in the median area under the concentration-time curve. Concomitant use of enzyme inducers, including St John's wort, may thus necessitate an increase in imatinib dosages to maintain clinical effectiveness.

Interactions with quinidine, ranitidine or midazolam, known inhibitors of hOCT-1, may paradoxically increase the circulating concentrations of imatinib but decrease the intracellular exposure of target cancer cells, known to express this carrier.

With regard to all these mechanisms, it is worth recalling that plasma concentrations of imatinib appear correlated with efficacy and toxicity. A change in imatinib exposure because of a drug interaction might therefore definitely influence its therapeutic efficacy.

TKIs can also inhibit drug transporters and enzymes, leading to changes in the exposure of co-administered drugs. Imatinib enhances the intestinal absorption of ciclosporin, a CYP3A4 and Pgp substrate, and may increase the pharmacological effects and possibly toxicity of ciclosporin. Moreover, the clearance of simvastatin (a CYP3A4 substrate) was reduced by 70% when associated with imatinib. Administration of imatinib together with metoprolol, a CYP2D6 substrate, resulted in an increase in metoprolol exposure by 23%.

Data concerning interactions involving protein binding are poorly documented for imatinib. A study showed that St. John's wort does not alter the protein binding of imatinib over a wide range of concentrations in vivo.

Interactions of potential clinical relevance can occur with calcium channel blockers such as verapamil and diltiazem, substrates of CYP3A4, which circulating levels are increased when associated with imatinib. Interactions with simvastatin, amiodarone and quinidine, involving the same P450 isoenzyme, may also be of clinical relevance. In patients taking imatinib, such drugs should be either tapered or avoided and replaced by safer alternatives (e.g. pravastatin or sotalol).

Imatinib is also known to inhibit the O-glucuronidation of acetaminophen, possibly inducing hepatotoxicity and liver failure. The use of acetaminophen should be limited in patients taking imatinib. A limit has been suggested to 1300 mg acetaminophen per day. Liver function tests might be useful to monitor during prolonged treatment. Acenocoumarol and phenprocoumon, substrates of CYP2C9, show also increased concentrations, however this interaction can be compensated by the monitoring of PT/INR.

Finally, physicians should be aware that hypothyroid patients receiving imatinib need increased levothyroxine (T4) doses. The suspected mechanism responsible for this phenomenon is an
induction of nondeiodination clearance.\textsuperscript{32,33} The fraction of T4 that is deiodinated into biologically active triiodothyronine (T3) is mainly subject to conjugation with glucuronates and sulfates.\textsuperscript{32,33} Although the liver primarily mediates glucuronidation and sulfation, these conjugations occur in extrahepatic sites such as the kidney and intestine as well.\textsuperscript{32,33} Therefore induction of UDP-glucuronyl transferases (UGTs) seems to be involved.\textsuperscript{32,33} A 2-fold increase in levothyroxine substitution therapy at initiation of imatinib treatment is recommended, along with close monitoring of thyroid function.\textsuperscript{32,33}

**Interaction with dasatinib**

Dasatinib is metabolized in an active derivative and other inactive metabolites by the CYP3A4 isoenzyme, and was also reported to be a substrate of BCRP and Pgp.\textsuperscript{9,18,53} The active metabolite appears to play a negligible role in therapeutic activity. Dasatinib has an inhibitory activity against CYP2C8 and CYP3A4. Plasma protein binding is approximately 96% for dasatinib, mainly to albumin.\textsuperscript{54,55}

In healthy subjects receiving ketoconazole, systemic exposure (AUC) to dasatinib was increased by 5-fold.\textsuperscript{40} Interactions may then occur between dasatinib and other inhibitors of CYP3A4, such as levothyroxine\textsuperscript{32,33} and voriconazole,\textsuperscript{34} leading to marked increase in plasma concentrations of this TKI. Drugs that inhibit both BCRP and CYP3A4, such as verapamil,\textsuperscript{56} may lead to even larger increase in dasatinib exposure.

Inhibitors of both CYP3A4 and Pgp, will increase not only plasma but also intracellular concentrations of dasatinib: this is expected for verapamil,\textsuperscript{9} erythromycin,\textsuperscript{9,18} clarithromycin,\textsuperscript{9,18} ciclosporin,\textsuperscript{39} ketoconazole,\textsuperscript{40} fluconazole,\textsuperscript{9,18} and itraconazole.\textsuperscript{9,18}

Concomitant administration of the CYP3A4 inducer rifampicin leads to a reduction of 80% in dasatinib exposure.\textsuperscript{12,13,43} St. John’s wort, a CYP3A4 inducer, may also decrease dasatinib plasma concentrations and should be discouraged in patients receiving dasatinib.\textsuperscript{57} Antiepileptics (phenobarbital, phenytoin, carbamazepin) are expected to decrease dasatinib concentrations as well. Moreover, the solubility of dasatinib appears to be pH dependent. Dasatinib exposure is reduced by 61% when famotidine is administered before dasatinib dosing.\textsuperscript{58} As a result, concomitant administration of agents that provide prolonged gastric acid suppression, such as H2 antagonists and proton pump inhibitors, is not recommended.\textsuperscript{43} In contrast, dasatinib exposure is unchanged when Mg\textsuperscript{2+}-Al\textsuperscript{3+}-based antacids are administered at least 2 hours before dasatinib; but coadministration reduced dasatinib exposure by 55% to 58%.\textsuperscript{58}

Dasatinib can also slightly inhibit drug transporters and enzymes, leading to changes in the exposure of co-administered drugs.\textsuperscript{9,18} The co-ingestion of dasatinib with simvastatin resulted in a 20% increased exposure to simvastatin.\textsuperscript{13} Concurrent use with calcium channel blockers such as verapamil and diltiazem, substrates of CYP3A4, should be avoided.\textsuperscript{18,52} Studies regarding interactions involving protein binding were unavailable for dasatinib.
In clinical trials, dasatinib treatment has been associated with prolongation of the QTc interval on electrocardiograms, and sudden cardiac deaths have occurred, which are likely related to ventricular repolarization abnormalities. Association of QT prolonging drugs such as digoxin, quinolones, methadone or seval psychotropic medications, may increase the risk of such events by additive effect. Regular ECG controls are strongly recommended in such situations.

**Interactions with nilotinib**

Nilotinib undergoes metabolism by CYP3A4. It is also a substrate of the efflux transporter BCRP. Nilotinib is known to inhibit CYP2C8, CYP2C9, CYP2D6, CYP3A4, UGT1A1 and Pgp. In vitro studies suggest that nilotinib induces CYP2B6 enzymes. It is also worth noting that UGT1A1 inhibition has been associated with increase in bilirubin levels (especially in patients homozygous for the UGT1A1*28 reduced-function variant). The determination of UGT1A1*28 is approved by the FDA as a valid pharmacogenetic test for patients treated by nilotinib.

Nilotinib exposure is expected to increase under CYP3A4 inhibitors. For example, AUC of nilotinib was increased by a 3-fold factor in healthy subjects receiving ketoconazole. Moreover, a study showed that concurrent intake of 240 mL grapefruit juice increased by 60% nilotinib AUC. Concomitant administration of nilotinib with grapefruit juice is therefore not recommended. Conversely, concomitant administration of CYP3A4 inducers such as rifampicin leads to a reduction by a 4.8 factor in nilotinib exposure.

Literature concerning interactions involving protein binding were lacking for nilotinib.

The same potential clinically significant interactions with imatinib and dasatinib can occur with nilotinib. For example, acenocoumarol and phenprocoumon, substrates of CYP2C9, show increased concentrations, imposing careful monitoring of PT/INR. Moreover, as dasatinib, nilotinib has been associated with prolongation of the QTc interval, and cases of sudden cardiac deaths have been reported. Accordingly, nilotinib prescribing information includes a black box warning regarding the risk of QTc prolongation and sudden death, and warns that nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome, either congenital or drug-induced.

**Conclusion**

Pharmacokinetic, drug interactions and safety recommendations are best characterized for imatinib, which was the first TKI on the market. The other TKIs, just recently marketed, have so far only a limited documentation about clinically relevant interactions. Their concentration profile might be affected to a more dramatic degree by interactions than imatinib exposure.

The three TKIs reviewed are indeed substrates of several drug transporters and metabolizing enzymes. They are also capable of inhibiting drug transporters and enzymes making their disposition and metabolism rather complex and difficult to predict.
Most of the available pharmacokinetic information is based on information obtained from in vitro experiments, animal studies, drug–drug interaction studies and studies in healthy volunteers with a single dose of the aimed TKI. These results must be translated into treatment adjustment recommendation for the clinical oncology practice, where these drugs are administered on a daily basis in patients receiving various comedications. The actual relevance of predicted drug interactions is still uncertain. Most of the interactions outlined in the table (excepted those in boldface) are theoretical and have not been confirmed in clinical studies; therefore they should only be considered indicative. Further interaction mechanisms may still be unknown at present.

We advise the reader to regularly monitor for updates regarding this topic. Therapeutic Drug Monitoring of TKIs should be considered if a drug interaction is suspected, or in case of toxicity, or lack of satisfactory clinical response. Finally, documenting unexpected observations and reporting them to the Pharmacovigilance network is of definite importance.

**Authorships**

A. Haouala, N. Widmer, M. Ducholal, M. Montemurro, T. Buclin and L. Decosterd are the sole authors of this review article. A. Haouala and N. Widmer wrote the manuscript which was corrected and edited by M. Duchosal and M. Montemurro (for hematology and oncology aspects), and T. Buclin and L.Decosterd (for clinical pharmacology aspects).

**Conflict of interest disclosure**

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References


Table legend
The Table (in 17 parts) summarizes observed or potential drug interactions between TKIs and commonly concomitantly prescribed drugs or classical interacting agents (lines) sorted according to the ATC classification. The arrows ↑ and ↓ indicate an increase or decrease of drug concentration respectively. **Boldface text** outlines interactions reported in the literature (reference number), whereas standard characters represent potential interactions predicted from theoretical considerations (but not yet reported in the literature). Absence of interaction means that a clinical study concluded to the absence of interaction (reference number), and a box shaded in grey means that no interaction is either reported or theoretically expected.
Alimentary tract and metabolism

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### Cardiovascular system

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<td><strong>Amlodipine</strong></td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ amlodipine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ amlodipine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ amlodipine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<tr>
<td><strong>Molsidomine</strong></td>
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<tr>
<td><strong>Isosorbid</strong></td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ ISMN exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ ISMN exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ ISMN exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<tr>
<td>mononitrate</td>
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<tr>
<td>(ISMN)</td>
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<tr>
<td><strong>Isosorbid</strong></td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ ISDN exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ ISDN exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ ISDN exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>dinitrate</td>
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<td><strong>Nitroglycerine</strong></td>
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<td><strong>Simvastatin</strong></td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ simvastatin exposure&lt;sup&gt;9;18;19;49&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ simvastatin exposure&lt;sup&gt;9;18;19;49&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ simvastatin exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>• Inhibition of Pgp by simvastatin: ↑ imatinib exposure&lt;sup&gt;9;24;25;70-74&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by simvastatin: ↑ dasatinib exposure&lt;sup&gt;9;10;53;68;69&lt;/sup&gt;</td>
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<td><strong>Pravastatin</strong></td>
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<td><strong>Atorvastatin</strong></td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ atorvastatin exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ atorvastatin exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ atorvastatin exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>• Inhibition of Pgp by atorvastatin: ↑ imatinib exposure&lt;sup&gt;9;24;25;70-74&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by atorvastatin: ↑ dasatinib exposure&lt;sup&gt;9;10;53;68;69&lt;/sup&gt;</td>
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<td><strong>Rosuvastatin</strong></td>
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<td><strong>Amiodarone</strong></td>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ amiodarone exposure&lt;sup&gt;9;24;25;70;71;73;77&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ amiodarone exposure&lt;sup&gt;9;24;25;70;71;73;77&lt;/sup&gt;</td>
<td>• Inhibition of Pgp and CYP 3A4 by nilotinib: ↑ amiodarone exposure&lt;sup&gt;9;18;19;26;75&lt;/sup&gt;</td>
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<td>• Inhibition of CYP3A4 and Pgp by amiodarone: ↑ imatinib exposure&lt;sup&gt;9;24;25;70;71;73;77&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ amiodarone exposure&lt;sup&gt;9;24;25;70;71;73;77&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by amiodarone: ↑ nilotinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>Inhibition of hOCT1 by amiodarone: ↓ imatinib intracellular exposure&lt;sup&gt;9;18;65&lt;/sup&gt;</td>
<td>Inhibition of hOCT1 by amiodarone: ↓ dasatinib intracellular exposure&lt;sup&gt;9;10;68;69;77&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ QT interval&lt;sup&gt;19&lt;/sup&gt; (additive effect) =&gt; monitor ECG</td>
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<tr>
<td><strong>Quinidine</strong></td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ quinidine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ quinidine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ quinidine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>• Inhibition of Pgp by quinidine: ↑ imatinib exposure&lt;sup&gt;9;24;25;70-74&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by quinidine: ↑ dasatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>• Inhibition of hOCT1 by quinidine: ↓ imatinib intracellular exposure&lt;sup&gt;9;18;65&lt;/sup&gt;</td>
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<td>Drug Class</td>
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<td>Dasatinib</td>
<td>Nilotinib</td>
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<td><strong>Diuretics</strong></td>
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<tr>
<td>Furosemide</td>
<td>• Absence of interaction&lt;sup&gt;78&lt;/sup&gt;</td>
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<td>Torasemide</td>
<td>• Inhibition of CYP 2C9 by imatinib: ↑ torasemide exposure&lt;sup&gt;6;18&lt;/sup&gt;</td>
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<td>• Inhibition of CYP 2C9 by nilotinib: ↑ torasemide exposure&lt;sup&gt;11;18&lt;/sup&gt;</td>
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<td>Hydrochlorothiazide</td>
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<td>Spironolactone</td>
<td>• Inhibition of Pgp by spironolactone: ↑ imatinib exposure&lt;sup&gt;9,65&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by spironolactone: ↑ dasatinib exposure&lt;sup&gt;9,10,53,68&lt;/sup&gt;</td>
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<td><strong>Beta blockers</strong></td>
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<tr>
<td>Metoprolol</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ metoprolol exposure&lt;sup&gt;18&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by metoprolol: ↑ dasatinib exposure&lt;sup&gt;9,10,53,68&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2D6 by nilotinib: ↑ metoprolol exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ bisoprolol exposure&lt;sup&gt;18&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ bisoprolol exposure&lt;sup&gt;9,18&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2D6 by nilotinib: ↑ bisoprolol exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<tr>
<td>Carvedilol</td>
<td>• Inhibition of CYP 2C9 and 2D6 by imatinib: ↑ carvedilol exposure&lt;sup&gt;18&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by carvedilol: ↑ dasatinib exposure&lt;sup&gt;9,10,53,68,69,79&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C9 and 2D6 by nilotinib: ↑ carvedilol exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<tr>
<td>Atenolol</td>
<td>• Absence of interaction&lt;sup&gt;9&lt;/sup&gt;</td>
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<td><strong>ACE inhibitors</strong></td>
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<tr>
<td>Captopril</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ captopril exposure&lt;sup&gt;18&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by captopril: ↑ dasatinib exposure&lt;sup&gt;9,10,53,68&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2D6 by nilotinib: ↑ captopril exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<tr>
<td>Enalapril</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ enalapril exposure&lt;sup&gt;18&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by enalapril: ↑ dasatinib exposure&lt;sup&gt;9,10,53,68&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ enalapril exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<td>Ramipril</td>
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<tr>
<td>Lisinopril</td>
<td>• Inhibition of Pgp by imatinib: ↑ lisinopril exposure&lt;sup&gt;9,18,24,45,71,73&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by lisinopril: ↑ dasatinib exposure&lt;sup&gt;9,10,53,68&lt;/sup&gt;</td>
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<tr>
<td><strong>AT II receptor blockers</strong></td>
<td>• Inhibition of CYP 2C9 and 3A4 by imatinib: ↑ losartan exposure and ↓ losartan bioactivation&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ losartan exposure&lt;sup&gt;9,18&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C9 and 3A4 by nilotinib: ↑ losartan exposure and ↓ losartan bioactivation&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<tr>
<td>Losartan</td>
<td>• Inhibition of Pgp by losartan: ↑ dasatinib exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<td>Candesartan</td>
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<tr>
<td><strong>Cardiac glycosides</strong></td>
<td>• ↓ digoxin absorption&lt;sup&gt;5,18,19&lt;/sup&gt; (unknown mechanism)</td>
<td>• ↑ QT interval&lt;sup&gt;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
<td>• ↑ QT interval&lt;sup&gt;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
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<tr>
<td>Digoxin</td>
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<td>• Inhibition of Pgp by nilotinib: ↑ digoxin exposure&lt;sup&gt;5,18,19&lt;/sup&gt;</td>
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### Hormonal preparations

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<thead>
<tr>
<th>Corticosteroids</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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<tbody>
<tr>
<td>Prednisone</td>
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<tr>
<td>Dexamethasone</td>
<td>• Induction of CYP 3A4 by dexamethasone: ↓ imatinib exposure¹⁹</td>
<td>• Induction of CYP 3A4 by dexamethasone: ↓ dasatinib exposure¹⁹</td>
<td>• Induction of CYP 3A4 by dexamethasone: ↓ nilotinib exposure⁹;¹⁸;¹⁹</td>
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<td>Betamethasone</td>
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<tr>
<th>Thyroid therapy</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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<tbody>
<tr>
<td>Levothyroxine</td>
<td>• Induction of UGTs by imatinib: ↓ levothyroxine³²;³³</td>
<td>• Inhibition of CYP 3A4 by levothyroxine: ↑ dasatinib exposure⁹;¹⁹</td>
<td>• Inhibition of CYP 3A4 by levothyroxine: ↑ nilotinib exposure⁹;¹⁹</td>
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<td>Carbimazole</td>
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<tr>
<th>Antineoplastic agents</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>• Inhibition of CYP 2D6 and 3A4 by imatinib: ↑ cyclophosphamide exposure ↓ cyclophosphamide bioactivation⁹;¹⁹</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ cyclophosphamide exposure ↓ cyclophosphamide bioactivation⁹;¹⁹</td>
<td>• Induction of CYP 2B6 by nilotinib: ↓ cyclophosphamide exposure ↑ cyclophosphamide bioactivation¹⁹</td>
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<tr>
<th>Antiestrogen agent</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>• Inhibition of CYP 2D6 and 3A4 by imatinib: ↑ tamoxifen exposure ↓ tamoxifen bioactivation¹⁸;⁸⁰</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ tamoxifen exposure ↓ tamoxifen bioactivation¹⁸;⁸⁰</td>
<td>• Inhibition of CYP 2D6 and 3A4 by nilotinib: ↑ tamoxifen exposure ↓ tamoxifen bioactivation¹⁸;⁸⁰</td>
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# Anti-infectives

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<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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<tr>
<td>Penicillins</td>
<td>Amoxicillin</td>
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<td>Flucloxacillin</td>
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<td>Cephalosporins</td>
<td>Cefuroxime</td>
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<td>Cefpodoxime</td>
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<td>Ceftriaxone</td>
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<td>Macrolides</td>
<td>Clarithromycin</td>
<td>• Inhibition of CYP 3A4 and Pgp by clarithromycin: ↑ imatinib exposure 9,18,19,37</td>
<td>• Inhibition of CYP 3A4 and Pgp by clarithromycin: ↑ dasatinib exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by clarithromycin: ↑ nilotinib exposure 9,18,19</td>
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<td>Azithromycin</td>
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<td></td>
<td>Erythromycin</td>
<td>• Inhibition of CYP 3A4 and Pgp by erythromycin: ↑ imatinib exposure 9,18,19,37</td>
<td>• Inhibition of CYP 3A4 and Pgp by erythromycin: ↑ dasatinib exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by erythromycin: ↑ nilotinib exposure 1,2,5</td>
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<td>Tetacyclines</td>
<td>Doxycyclin</td>
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<td>Ciprofl oxacin</td>
<td>• Inhibition of Pgp by ciprofloxacin: ↑ imatinib exposure 9,18,24,65,71,73</td>
<td>• ↑ QT interval 18,19 (additive effect) → monitor ECG</td>
<td>• ↑ QT interval 18,19 (additive effect) → monitor ECG</td>
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<tr>
<td>Quinolones</td>
<td>Levofloxacin</td>
<td>• Inhibition of Pgp by levofloxacin: ↑ imatinib exposure 9,18,24,65,71,73</td>
<td>• ↑ QT interval 18,19 (additive effect) → monitor ECG</td>
<td>• ↑ QT interval 18,19 (additive effect) → monitor ECG</td>
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<td>• Inhibition of hOCT1 by levofloxacin: ↓ imatinib intracellular exposure 9,18,66</td>
<td>• Inhibition of Pgp by levofloxacin: ↑ dasatinib exposure 9,10,53,68,69</td>
<td>• Inhibition of Pgp by levofloxacin: ↑ dasatinib exposure 9,10,53,68,69</td>
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<td></td>
<td>Norfloxacin</td>
<td></td>
<td>• ↑ QT interval 18,19 (additive effect) → monitor ECG</td>
<td>• ↑ QT interval 18,19 (additive effect) → monitor ECG</td>
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<tr>
<td>Sulfonamides</td>
<td>Co-trimoxazole</td>
<td>• Inhibition of CYP 2C9 by imatinib: ↑ co-trimoxazole 9,18,19</td>
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<td>• Inhibition of CYP 2C9 by nilotinib: ↑ co-trimoxazole 9,18,19</td>
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<tr>
<td>Drug Interactions with Tyrosine Kinase Inhibitors</td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
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<td><strong>Azoles</strong></td>
<td><strong>Imatinib</strong></td>
<td><strong>Dasatinib</strong></td>
<td><strong>Nilotinib</strong></td>
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<td>Itraconazole</td>
<td>Inhibition of CYP 3A4 and Pgp by itraconazole: ↑ imatinib exposure</td>
<td>↑ dasatinib exposure</td>
<td>Inhibition of CYP 3A4 by itraconazole: ↑ nilotinib exposure</td>
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<tr>
<td>Fluconazole</td>
<td>Inhibition of CYP 3A4 and Pgp by fluconazole: ↑ imatinib exposure</td>
<td>↑ dasatinib exposure</td>
<td>Inhibition of CYP 3A4 by fluconazole: ↑ nilotinib exposure</td>
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<td>Voriconazole</td>
<td>Inhibition of CYP 3A4 by voriconazole: ↑ imatinib exposure</td>
<td>↑ dasatinib exposure</td>
<td>Inhibition of CYP 3A4 by voriconazole: ↑ nilotinib exposure</td>
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<td>Ketoconazole</td>
<td>Inhibition of CYP 3A4 and Pgp by ketoconazole: ↑ imatinib exposure</td>
<td>↑ dasatinib exposure</td>
<td>Inhibition of CYP 3A4 by ketoconazole: ↑ nilotinib exposure</td>
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<td><strong>Allylamine</strong></td>
<td><strong>Terbinafine</strong></td>
<td><strong>Dasatinib</strong></td>
<td><strong>Nilotinib</strong></td>
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<td><strong>Nitromidazole</strong></td>
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<td><strong>Terbinafine</strong></td>
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<td><strong>Antiviral/Nucleoside analog</strong></td>
<td><strong>Aciclovir</strong></td>
<td><strong>Valaciclovir</strong></td>
<td><strong>Ganciclovir</strong></td>
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<td><strong>Rifampicine</strong></td>
<td><strong>Rifampicine</strong></td>
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<td>Protease inhibitors</td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
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<tr>
<td>Ritonavir</td>
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<td>• Inhibition of CYP 3A4 by ritonavir: ↑ nilotinib exposure 9;18;19;83 • ↑ QT interval (additive effect) 18;19 → monitor ECG</td>
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<tr>
<td>Saquinavir</td>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ saquinavir exposure 9;18;19;83 • Inhibition of hOCT1 by saquinavir: ↓ imatinib intracellular exposure 6;18,65</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ saquinavir exposure 9;18;19;83 • ↑ QT interval (additive effect) 18;19 → monitor ECG</td>
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<tr>
<td>• Inhibition of CYP 3A4 by ritonavir: ↑ dasatinib exposure 9;18;19;83 • ↑ QT interval (additive effect) 18;19 → monitor ECG</td>
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<tr>
<td>Darunavir</td>
<td>• Inhibition of CYP 3A4 by darunavir: ↑ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ nilotinib exposure 9;18;19;83</td>
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<tr>
<td>Atazanavir</td>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ atazanavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ atazanavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ atazanavir exposure 9;18;19;83</td>
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<tr>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ saquinavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by saquinavir: ↑ saquinavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by saquinavir: ↑ saquinavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by saquinavir: ↑ saquinavir exposure 9;18;19;83</td>
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</tr>
<tr>
<td>Tipranavir</td>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ tipranavir exposure 9;18;19;83 • Inhibition of CYP 3A4 by tipranavir: ↑ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ tipranavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ tipranavir exposure 9;18;19;83</td>
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<tr>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ indinavir exposure 9;18;19;83 • Inhibition of hOCT1 by indinavir: ↓ imatinib intracellular exposure 6;18,65</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ indinavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ indinavir exposure 9;18;19;83</td>
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<tr>
<td>Indinavir</td>
<td>• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ indinavir exposure 9;18;19;83 • Inhibition of hOCT1 by indinavir: ↓ imatinib intracellular exposure 6;18,65</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ indinavir exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ indinavir exposure 9;18;19;83</td>
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<tr>
<td>Lamivudine</td>
<td>• Inhibition of hOCT1 by lamivudine: ↓ imatinib intracellular exposure 6;18,65</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ lamivudine exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ lamivudine exposure 9;18;19;83</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ efavirenz exposure 9;18;19;83 • Induction of CYP 3A4 by efavirenz: ↓ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ efavirenz exposure 9;18;19;83 • Induction of CYP 3A4 by efavirenz: ↓ dasatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ efavirenz exposure 9;18;19;83 • Induction of CYP 3A4 by efavirenz: ↓ nilotinib exposure 9;18;19;83</td>
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</tr>
<tr>
<td>Zidovudine</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ efavirenz exposure 9;18;19;83 • Induction of CYP 3A4 by efavirenz: ↓ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ efavirenz exposure 9;18;19;83 • Induction of CYP 3A4 by efavirenz: ↓ dasatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ efavirenz exposure 9;18;19;83 • Induction of CYP 3A4 by efavirenz: ↓ nilotinib exposure 9;18;19;83</td>
<td></td>
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<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ nevirapine exposure 9;18;19;83 • Induction of CYP 3A4 by nevirapine: ↓ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ nevirapine exposure 9;18;19;83 • Induction of CYP 3A4 by dasatinib: ↓ nevirapine exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ nevirapine exposure 9;18;19;83 • Induction of CYP 3A4 by nevirapine: ↓ nilotinib exposure 9;18;19;83</td>
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<tr>
<td>Nevirapine</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ nevirapine exposure 9;18;19;83 • Induction of CYP 3A4 by nevirapine: ↓ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ nevirapine exposure 9;18;19;83 • Induction of CYP 3A4 by dasatinib: ↓ nevirapine exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ nevirapine exposure 9;18;19;83 • Induction of CYP 3A4 by nevirapine: ↓ nilotinib exposure 9;18;19;83</td>
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<tr>
<td>Etravirine</td>
<td>• Inhibition of CYP 2C9 and 3A4 by imatinib: ↑ etravirine exposure 9;18;19;83 • Induction of CYP 3A4 by etravirine: ↓ imatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ etravirine exposure 9;18;19;83 • Induction of CYP 3A4 by etravirine: ↓ dasatinib exposure 9;18;19;83</td>
<td>• Inhibition of CYP 2C9 and 3A4 by nilotinib: ↑ etravirine exposure 9;18;19;83 • Induction of CYP 3A4 by etravirine: ↓ nilotinib exposure 9;18;19;83</td>
<td></td>
</tr>
<tr>
<td>Antimalarial drugs</td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
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</tbody>
</table>
| Quinine            | • Inhibition of CYP 3A4 by imatinib: ↑ quinidine exposure\(^{9,18,19}\)  
                     • Inhibition of CYP 2D6 and Pgp by quinidine: ↑ imatinib exposure\(^{9,18,19}\)  
                     • Inhibition of hOCT1 by quinine: ↓ imatinib intracellular exposure\(^{9,18,65}\) | • Inhibition of CYP 3A4 by dasatinib: ↑ quinidine exposure\(^{9,18,19}\)  
                     • Inhibition of CYP 3A4 by nilotinib: ↑ quinidine exposure\(^{9,18,19}\) | | |
| Chloroquine        | • Inhibition of Pgp by chloroquine: ↑ imatinib exposure\(^{9,18,19}\)  
                     • Inhibition of hOCT1 by chloroquine: ↓ imatinib intracellular exposure\(^{9,18,65}\) | • Inhibition of Pgp by chloroquine: ↑ dasatinib exposure\(^{9,18,19}\)  
                     • ↑ QT interval\(^{18,19}\) (additive effect)  
                     → monitor ECG | • ↑ QT interval\(^{18,19}\) (additive effect)  
                     → monitor ECG |
| Mefloquine          | • Inhibition of CYP 3A4 and Pgp by imatinib: ↑ mefloquine exposure\(^{9,18,19}\)  
                     • Inhibition of Pgp by mefloquine: ↑ imatinib exposure\(^{9,18,19}\) | • Inhibition of CYP 3A4 by dasatinib: ↑ mefloquine exposure\(^{9,18,19}\)  
                     • Inhibition of Pgp by mefloquine: ↑ dasatinib exposure\(^{9,18,19}\)  
                     • ↑ QT interval\(^{18,19}\) (additive effect)  
                     → monitor ECG | • Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ mefloquine exposure\(^{9,18,19}\)  
                     • ↑ QT interval\(^{18,19}\) (additive effect)  
                     → monitor ECG |
| Proguanil           | • Inhibition of CYP 2C19 and Pgp by imatinib: ↑ proguanil exposure  
                     ↓ proguanil bioactivation\(^{9,18,19}\) | | | |
| Atovaquone          | | | | |
| Doxycycline         | | | |
### Immunomodulating agents

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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</thead>
<tbody>
<tr>
<td>Ciclosporin</td>
<td>- Inhibition of CYP 3A4 and Pgp by imatinib:</td>
<td>- Inhibition of CYP 3A4 by dasatinib:</td>
<td>- Inhibition of CYP 3A4 and Pgp by nilotinib:</td>
</tr>
<tr>
<td></td>
<td>↑ ciclosporin exposure&lt;sup&gt;38,39&lt;/sup&gt;</td>
<td>↑ ciclosporin exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ nilotinib exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
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<tr>
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<td>- Inhibition of Pgp and CYP 3A4 by ciclosporin:</td>
<td>- Inhibition of CYP3A4 and Pgp by ciclosporin:</td>
<td>- Inhibition of CYP3A4 by ciclosporin:</td>
</tr>
<tr>
<td></td>
<td>↑ imatinib exposure&lt;sup&gt;38,39&lt;/sup&gt;</td>
<td>↑ dasatinib exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ nilotinib exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>- Inhibition of CYP 3A4 by imatinib:</td>
<td>- Inhibition of CYP 3A4 by dasatinib:</td>
<td>- Inhibition of CYP 3A4 and Pgp by nilotinib:</td>
</tr>
<tr>
<td></td>
<td>↑ tacrolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ tacrolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ tacrolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Inhibition of Pgp by tacrolimus:</td>
<td>- Inhibition of Pgp by tacrolimus:</td>
<td>- Inhibition of CYP 3A4 and Pgp by nilotinib:</td>
</tr>
<tr>
<td></td>
<td>↑ imatinib exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ dasatinib exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ nilotinib exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>- Inhibition of CYP 3A4 and Pgp by imatinib:</td>
<td>- Inhibition of CYP 3A4 by dasatinib:</td>
<td>- Inhibition of CYP 3A4 and Pgp by nilotinib:</td>
</tr>
<tr>
<td></td>
<td>↑ sirolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ sirolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ sirolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
</tr>
<tr>
<td>Everolimus</td>
<td>- Inhibition of CYP 3A4 and Pgp by imatinib:</td>
<td>- Inhibition of CYP 3A4 by dasatinib:</td>
<td>- Inhibition of CYP 3A4 and Pgp by nilotinib:</td>
</tr>
<tr>
<td></td>
<td>↑ everolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ everolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
<td>↑ everolimus exposure&lt;sup&gt;9,18,19,84&lt;/sup&gt;</td>
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</tbody>
</table>

### Immunosuppressants

- Mycophenolate mofetil
- Methotrexate
- Azathioprine

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<sup>*For personal use only.*</sup>
### Musculo-skeletal system

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>• Thrombocytopenic effect of dasatinib: ↑ risk of bleeding&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 by dasatinib: ↑ ibuprofen exposure&lt;sup&gt;9;18;85;96&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 and 2C9 by nilotinib: ↑ ibuprofen exposure&lt;sup&gt;9;18;85;96&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>• Inhibition of CYP 2C9 by imatinib: ↑ ibuprofen exposure&lt;sup&gt;9;18;85;96&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 by dasatinib: ↑ ibuprofen exposure&lt;sup&gt;9;18;85;96&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 and 2C9 by nilotinib: ↑ ibuprofen exposure&lt;sup&gt;9;18;85;96&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mefenacid</td>
<td>• Inhibition of CYP 2C9 by imatinib: ↑ mefenacid exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 by dasatinib: ↑ mefenacid exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 and 2C9 by nilotinib: ↑ mefenacid exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metamizole</td>
<td>• Induction of CYP 3A4 by metamizole: ↓ imatinib exposure&lt;sup&gt;9;18;87&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by dasatinib: ↓ metamizole: ↓ dasatinib exposure&lt;sup&gt;9;18;87&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by metamizole: ↓ nilotinib exposure&lt;sup&gt;9;18;87&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>• Inhibition of CYP 2C9 by imatinib: ↑ diclofenac exposure&lt;sup&gt;9;18;88&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 by dasatinib: ↑ diclofenac exposure&lt;sup&gt;9;18;88&lt;/sup&gt;</td>
<td>• Inhibition of CYP 2C8 and 2C9 and by nilotinib: ↑ diclofenac exposure&lt;sup&gt;9;18;98&lt;/sup&gt;</td>
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</table>

**Antigout preparations**
- Allopurinol
  - For personal use only.
### Nervous system

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ fluoxetine exposure 9,18,19,99,56</td>
<td>• ↑ QT interval 9,18,19,99: (additive effect) → monitor ECG</td>
<td>• ↑ QT interval 9,18,19,99: (additive effect) → monitor ECG</td>
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<tr>
<td>Fluoxetine</td>
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<tr>
<td></td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ fluvoxamine exposure 9,18,19</td>
<td></td>
<td>• Inhibition of CYP 2D6 by nilotinib: ↑ fluvoxamine exposure 9,18,19</td>
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<tr>
<td>Fluvoxamine</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ fluoxetine exposure 9,18,19,19</td>
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<td></td>
<td>• Inhibition of CYP 2D6 by nilotinib: ↑ fluoxetine exposure 9,18,19</td>
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<tr>
<td>Paroxetine</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ paroxetine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ paroxetine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ paroxetine exposure 9,18,19</td>
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<td>• ↑ QT interval 9,18,19: (additive effect) → monitor ECG</td>
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<tr>
<td>Citalopram</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ citalopram exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ citalopram exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ citalopram exposure 9,18,19</td>
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<tr>
<td>Sertraline</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ sertraline exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ sertraline exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ sertraline exposure 9,18,19</td>
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<td>• ↑ QT interval 9,18,19: (additive effect) → monitor ECG</td>
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<tr>
<td>Venlafaxine</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ venlafaxine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ venlafaxine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ venlafaxine exposure 9,18,19</td>
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<td>• ↑ QT interval 9,18,19: (additive effect) → monitor ECG</td>
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<tr>
<td>Duloxetine</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ duloxetine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ duloxetine exposure 9,18,19</td>
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<tr>
<td>Mirtazapine</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ mirtazapine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ mirtazapine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ mirtazapine exposure 9,18,19</td>
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<tr>
<td>Trimipramine</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ trimipramine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ trimipramine exposure 9,18,19</td>
<td>• Inhibition of CYP 2D6 by nilotinib: ↑ trimipramine exposure 9,18,19</td>
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<tr>
<td>Amitriptyline</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ amitriptyline exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ amitriptyline exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ amitriptyline exposure 9,18,19</td>
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<td>Levomepromazine</td>
<td>• Inhibition of CYP 2D6 by imatinib: ↑ levomepromazine exposure 9,18,19</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ levomepromazine exposure 9,18,19</td>
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<tr>
<td></td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
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<tr>
<td><strong>Z-drugs</strong></td>
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</table>
| Zolpidem | - Inhibition of CYP 3A4 by imatinib:  
  ↑ zolpidem exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ zolpidem exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ zolpidem exposure<sup>9;18;19</sup> |
| Zaleplon  | - Inhibition of CYP 3A4 by imatinib:  
  ↑ zaleplon exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ zaleplon exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ zaleplon exposure<sup>9;18;19</sup> |
| Zopiclon  | - Inhibition of CYP 3A4 by imatinib:  
  ↑ zopiclon exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ zopiclon exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ zopiclon exposure<sup>9;18;19</sup> |
| **Benzodiazepines** |                                                                            |                                                                                           |                                                                                           |
| Alprazolam | - Inhibition of CYP 3A4 by imatinib:  
  ↑ alprazolam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ alprazolam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ alprazolam exposure<sup>9;18;19</sup> |
| Bromazepam | - Inhibition of CYP 3A4 by imatinib:  
  ↑ bromazepam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ bromazepam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ bromazepam exposure<sup>9;18;19</sup> |
| Clonazepam | - Inhibition of CYP 3A4 by imatinib:  
  ↑ clonazepam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ clonazepam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ clonazepam exposure<sup>9;18;19</sup> |
| Oxazepam |                                                                            |                                                                                           |                                                                                           |
| Lorazepam |                                                                            |                                                                                           |                                                                                           |
| Diazepam  | - Inhibition of CYP 3A4 by imatinib:  
  ↑ diazepam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ diazepam exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ diazepam exposure<sup>9;18;19</sup> |
| Midazolam | - Inhibition of CYP 3A4 by imatinib:  
  ↑ midazolam exposure<sup>9;18;19</sup>  
  • Inhibition of Pgp by midazolam:  
  ↑ imatinib exposure<sup>9;18;19</sup>  
  • Inhibition of hOCT1 by midazolam:  
  ↓ imatinib intracellular exposure<sup>9;18;65</sup> | - Inhibition of CYP 3A4 by dasatinib:  
  ↑ midazolam exposure<sup>9;18;19</sup>  
  • Inhibition of Pgp by midazolam:  
  ↑ dasatinib exposure<sup>9;18;19</sup> | - Inhibition of CYP 3A4 by nilotinib:  
  ↑ midazolam exposure<sup>9;18;19</sup>  
  • Inhibition of Pgp by midazolam:  
  ↑ nilotinib exposure<sup>9;18;19</sup> |
| **Barbiturates** |                                                                            |                                                                                           |                                                                                           |
| Phenobarbital | - Inhibition of CYP 2C9 and 2C19 by imatinib:  
  ↑ phenobarbital exposure<sup>9;18;19</sup>  
  • Induction of CYP 3A4 by phenobarbital:  
  ↓ imatinib exposure<sup>9;18;19</sup> | - Induction of CYP 3A4 by dasatinib:  
  ↓ dasatinib exposure<sup>9;18;19</sup> | - Induction of CYP 3A4 by nilotinib:  
  ↓ nilotinib exposure<sup>9;18;19</sup> |

*Note: The table above outlines drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib.*
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Interaction with Imatinib</th>
<th>Interaction with Dasatinib</th>
<th>Interaction with Nilotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic agents</td>
<td>Haloperidol</td>
<td>- Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ haloperidol exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>- Inhibition of CYP 3A4 by dasatinib: ↑ haloperidol exposure&lt;sup&gt;9;18;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
<td>• ↑ QT interval&lt;sup&gt;18;19&lt;/sup&gt; (additive effect)</td>
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<td></td>
<td>Clozapine</td>
<td>- Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ clozapine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>- Inhibition of CYP 3A4 by dasatinib: ↑ clozapine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• ↑ QT interval&lt;sup&gt;18;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>- Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ clozapine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>- Inhibition of CYP 3A4 by dasatinib: ↑ clozapine exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• ↑ QT interval&lt;sup&gt;18;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
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<tr>
<td></td>
<td>Risperidone</td>
<td>- Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ risperidone exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>- Inhibition of CYP 3A4 by dasatinib: ↑ risperidone exposure&lt;sup&gt;9;18;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
<td>• ↑ QT interval&lt;sup&gt;18;19&lt;/sup&gt; (additive effect) → monitor ECG</td>
</tr>
<tr>
<td>Antiseizure drugs</td>
<td>Phenytoin</td>
<td>• Induction of CYP 3A4 by phenytoin: ↓ imatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by phenytoin: ↓ dasatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by phenytoin: ↓ nilotinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>Valproic acid</td>
<td>• Induction of CYP 2C9 and 2C19 by imatinib: ↑ valproic acid exposure</td>
<td>• Induction of CYP 3A4 by valproic acid: ↑ dasatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 2C9 by valproic acid: ↑ nilotinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td>Carbamazepine</td>
<td>• Induction of CYP 3A4 and Pgp by carbamazepine: ↓ imatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 and Pgp by carbamazepine: ↓ dasatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by carbamazepine: ↓ nilotinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td></td>
<td>Lamotrigine</td>
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<td>Gabapentin</td>
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<td>Topiramate</td>
<td>• Induction of CYP 3A4 by topiramate: ↓ imatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by topiramate: ↓ dasatinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
<td>• Induction of CYP 3A4 by topiramate: ↓ nilotinib exposure&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
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<td></td>
<td>Levetiracetam</td>
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<td>Antimanic drug</td>
<td>Lithium</td>
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<tr>
<td>Aminoketone</td>
<td>Bupropion</td>
<td>-</td>
<td>-</td>
<td>• Induction of CYP 2B6 by nilotinib: ↓ bupropion exposure ↑ bupropion bioactivation&lt;sup&gt;9;18;19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Opioids</td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
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<tr>
<td>Morphine</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ tramadol exposure(^9;18;19) \n↓ tramadol bioactivation(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ tramadol exposure(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ tramadol exposure(^9;18;19) \n↓ tramadol bioactivation(^9;18;19)</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>• Inhibition of CYP 3A4 by imatinib : ↑ tramadol exposure(^9;18;19) \n↓ tramadol bioactivation(^9;18;19)</td>
<td>• ↑ QT interval(^b) 18;19 (additive effect)</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ methadone exposure(^9;18;19) \n• Induction of CYP 2B6 by nilotinib: ↓ methadone exposure(^19) \n• ↑ QT interval(^b) 18;19 (additive effect)</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ methadone exposure(^9;18;19) \n• Inhibition of Pgp by methadone: ↑ methadone exposure(^9;18;19) \n• Inhibition of Pgp by methadone: ↑ dasatinib exposure(^9;18;19)</td>
<td>• ↑ QT interval(^b) 18;19 (additive effect)</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ methadone exposure(^9;18;19) \n• Induction of CYP 2B6 by nilotinib: ↓ methadone exposure(^19) \n• ↑ QT interval(^b) 18;19 (additive effect)</td>
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<td>Hydromorphone</td>
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<tr>
<td>Oxycodone</td>
<td>• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ oxycodone exposure(^9;18;19) \n↓ oxycodone bioactivation(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ oxycodone exposure(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ oxycodone exposure(^9;18;19) \n↓ oxycodone bioactivation(^9;18;19)</td>
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<tr>
<td>Buprenorphine</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ buprenorphine exposure(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ buprenorphine exposure(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ buprenorphine exposure(^9;18;19)</td>
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<tr>
<td>Acetaminophen</td>
<td>• Inhibition of o-glucuronidation by imatinib: ↑ acetaminophen exposure(^9;18;19;31)</td>
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<tr>
<td>Dihydroergotamine</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ dihydroergotamine exposure(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ dihydroergotamine exposure(^9;18;19)</td>
<td>• Inhibition of CYP 3A4 by nilotinib: ↑ dihydroergotamine exposure(^9;18;19)</td>
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<tr>
<td>Sumatriptan</td>
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## Respiratory system

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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<tbody>
<tr>
<td><strong>H1-antagonists</strong></td>
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<tr>
<td>Cetirizin</td>
<td></td>
<td></td>
<td>• Inhibition of Pgp by nilotinib: ↑ cetirizin exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<tr>
<td>Levocetirizin</td>
<td></td>
<td></td>
<td>• Inhibition of Pgp by nilotinib: ↑ cetirizin exposure&lt;sup&gt;9,17,18&lt;/sup&gt;</td>
</tr>
<tr>
<td>Loratadin</td>
<td>• Inhibition of CYP 3A4 by imatinib: ↑ loratadin exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
<td>• Inhibition of CYP 3A4 by dasatinib: ↑ loratadin exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
<td>• Inhibition of Pgp by nilotinib: ↑ loratadin exposure&lt;sup&gt;9,18,19&lt;/sup&gt;</td>
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<tr>
<td>Fexofenadin</td>
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<tr>
<td><strong>Anti asthma drugs</strong></td>
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<td>Salbutamol</td>
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<td>Theophylline</td>
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### Miscellaneous

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
</tr>
</thead>
</table>
| **St John’s wort** | • **Induction of CYP 3A4 by St John’s wort:**  
↓ imatinib exposure  
44,45 | • **Induction of CYP 3A4 by St John’s wort:**  
↓ dasatinib exposure  
67 | • **Induction of CYP 3A4 by St John’s wort:**  
↓ nilotinib exposure  
9,18 |
| **Grapefruit**    | • **Inhibition of CYP 3A4 and Pgp by grapefruit:**  
↑ imatinib exposure  
9,18 | • **Inhibition of CYP 3A4 and Pgp by grapefruit:**  
↑ dasatinib exposure  
9,18 | • **Inhibition of CYP 3A4 by grapefruit:**  
↑ nilotinib exposure  
63 |
| **Licorice**      | • **Inhibition of CYP 3A4 by licorice:**  
↑ imatinib exposure  
9,18,91 | • **Inhibition of CYP 3A4 by licorice:**  
↑ dasatinib exposure  
9,18,91 | • **Inhibition of CYP 3A4 by licorice:**  
↑ nilotinib exposure  
9,18,91 |

* TKIs in general can cause thrombocytopenia, which is usually of no clinical relevance, please take that into consideration when coadministrating with anticoagulant medication.
Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib

Amina Haouala, Nicolas Widmer, Michel A. Duchosal, Michael Montemurro, Thierry Buclin and Laurent A. Decosterd