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# Activation of prodrugs affected by CYP induction/inhibition

## Definition

Prodrugs are inactive precursors designed to be converted to an active form after administration. This is to overcome poor physio-chemical or pharmacokinetic properties of the active drug.

## Prodrugs – methods of activation

Prodrugs are activated by a variety of mechanisms including:

- Conversion by cytochrome CYP450 enzymes, e.g. codeine is converted to morphine
- Esterases in the plasma or liver e.g. enalapril is converted to enalaprilat (active), and dabigatran etexilate to dabigatran (active).
- Specific enzymes in the target site e.g. aromatic amino acid decarboxylase in the brain converts levodopa to dopamine (active).
- Bacterial activation e.g. sulfasalazine is converted in gastrointestinal tract to sulfapyridine and 5-aminosalicylic acid (both active).

Most prodrugs are unaffected by concomitant administration with other medicines, however significant interactions may occur for prodrugs activated by cytochrome CYP450 enzymes.

Activation by cytochrome P450 enzymes may be affected by other medicines taken concomitantly or by genetic differences. The significance of the interaction will depend on:

- Inactive prodrugs requiring activation cytochrome P450 enzymes e.g. tamoxifen, codeine, tramadol, clopidogrel, and losartan. Inhibitors of these enzymes will decrease the activity of these drugs (and may increase toxicity of the parent compound). Inducers increase the activation of the prodrug and potentially its toxicity although effects are not usually clinically significant.
- The number of pathways by which a prodrug is activated. If activated by multiple pathways the inhibition of a single pathway is unlikely to significantly alter the extent of activation of the prodrug or its clinical efficacy, e.g. prasugrel is activated by both CYP3A and CYP2B6
- If the parent compound has similar or greater activity than the metabolite, then alterations in the conversion of the parent medicine are unlikely to affect the efficacy of the medicine, e.g. venlafaxine is converted to desvenlafaxine by CYP2D6, with both venlafaxine and desvenlafaxine being pharmacologically active.

| **Enzyme Responsible** | **Prodrugs effected** | **Inhibitors[1]** *(Reduce activity)* | **Inducers[1]** *(Increase activity, usually not clinically significant)* | **Incidence of genetic polymorphisms[1]** |
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| CYP2D6 | **Tamoxifen** converted to endoxifen which is 30-100x more potent as an antagonist of estrogen receptors.<br><br>**Codeine** has minimal analgesic efficacy until converted to morphine.<br><br>**Tramadol** is converted to O-desmethyl-tramadol (M1) active metabolite by CYP2D6 (inhibition may decrease analgesia and produce symptoms of opiate withdrawal). | Strong<br>Fluoxetine<br>Paroxetine<br><br>Moderate<br>Cocaine<br>Flecainide<br>Haloperidol<br>Moclobemide<br>Terbinafine | Not applicable,<br>CYP2D6 is not subject to induction | Decreased activation:<br>Caucasians 5-10%<br>Maori 5%<br>Polynesians 1-2%<br>Asians 1-2% |
| CYP2C19 | **Clopidogrel** is converted to active thiol metabolite. | Strong<br>Fluconazole<br><br>Moderate<br>Clarithromycin<br>Fluoxetine<br>Ketoconazole<br>Omeprazole | Carbamazepine<br>Phenytoin<br>Rifampicin | Decreased activation:<br>Maori 25%<br>Asians 20%<br>Polynesians 13%<br>Caucasians <5%<br><br>Increased activation<br>Caucasians 10% |
| CYP2C9 | **Losartan**, 14% converted by CYP2C9 to active metabolite E3174, remainder converted by CYP3A to inactive metabolites | Strong<br>Fluconazole<br><br>Moderate<br>Amiodarone<br>Ketoconazole<br>Ritonavir<br>Voriconazole | Phenobarbital<br>Phenytoin<br>Rifampicin | Decreased activation:<br>Caucasians 2-10% |

[1] See Pink Book, Cytochrome P450 Enzymes pinkbook.org.nz/index.htm?toc.htm?102194.htm