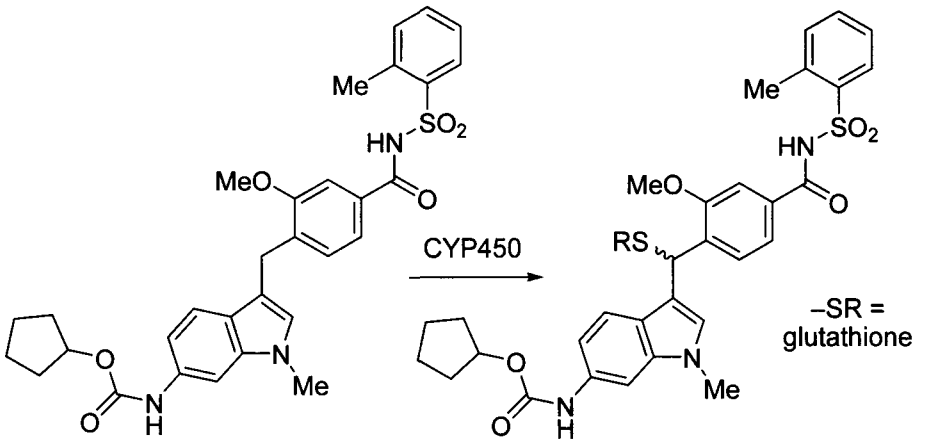
Oxidation of the 3-methyl group occurs either directly via deoxygenation or via epoxidation of the 2,3-double bond leading to 2,3-epoxy-3-methylindole, the reactive intermediate that can be trapped by endogenous nucleophiles, such as glutathione.

The presence of a leaving group on the C3-methyl increases the likelihood of formation of electrophilic reactive intermediates.

Zafirlukast (Accolate) is a leukotriene antagonist indicated for the treatment of mild-to-moderate asthma, but the drug has been associated with occasional idiosyncratic hepatotoxicity. Structurally, zafirlukast is similar to 3-methylindole because it contains an *N*-methylindole moiety that has a 3-alkyl substituent on the indole ring. The results presented here describe the metabolic activation of zafirlukast via a similar mechanism to that described for 3-methylindole. NADP(H)-dependent biotransformation of zafirlukast by hepatic microsomes from rats and humans afforded a reactive metabolite, which was detected as its GSH adduct.[93] The formation of this reactive metabolite in human liver microsomes was shown to be exclusively catalyzed by CYP3A enzymes. Evidence for *in vivo* metabolic activation of zafirlukast was obtained when the same GSH adduct was detected in bile of rats given an *i.v.* or oral dose of the drug.

The observation of *in vitro* metabolic activation of the 3-benzylindole moiety in zafirlukast, an anti-asthma drug, to give the glutathione adduct is an indication that the 3-methyl-indole activation pathway applies to other activated 3-alkyl indoles as well.[94]



zafirlukast (Accolate)