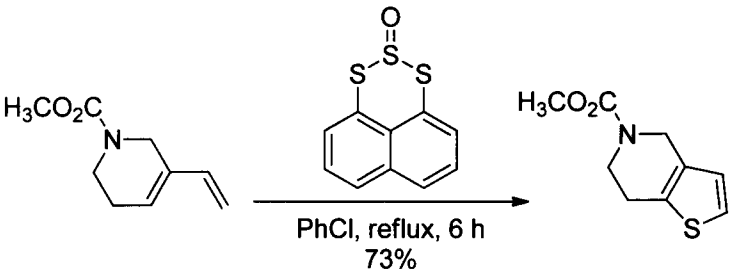
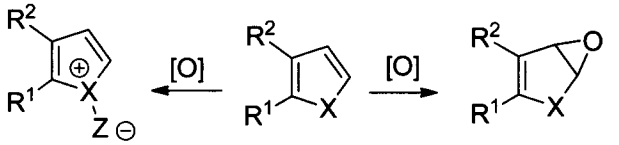


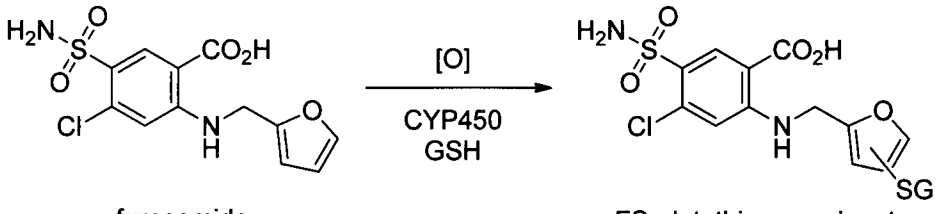
4.4 Possible Liabilities of Furan- and Thiophene-Containing Drugs

Electron-rich furan and thiophene ring systems are susceptible to oxidation by cytochrome P-450 (CYP450) enzymes. The oxidized products are then capable of reacting with various biological nucleophiles; the resulting metabolites can lead to toxicity, typically hepatotoxicity.[124–128]



In general, the furan ring system appears to far less reactive than the thiophene system, and it is therefore much less toxic. This is most likely due to the higher electronegativity of the oxygen atom, which reduces the reactivity of the ring toward oxidation.

Of the furan-containing drugs on the market, furosemide, a diuretic, has been shown to cause hepatic necrosis in mice.[128] The mechanism involves metabolic activation of furosemide by oxidation of the furan ring by CYP450 followed by conjugation to glutathione to produce a furosemide-glutathione conjugate. Despite these results, furosemide has not been shown to present significant toxicity to humans.



furosemide FS-glutathione conjugate

Tienilic acid, a thiophene-based diuretic used to treat hypertension, has been shown to cause hepatotoxicity. Oxidation of the thiophene and subsequent reactions of the activated product with nucleophilic proteins is