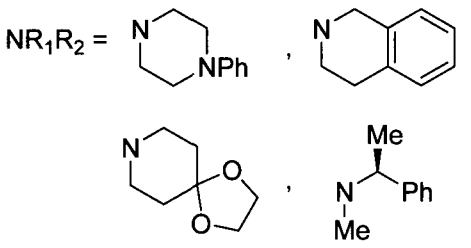
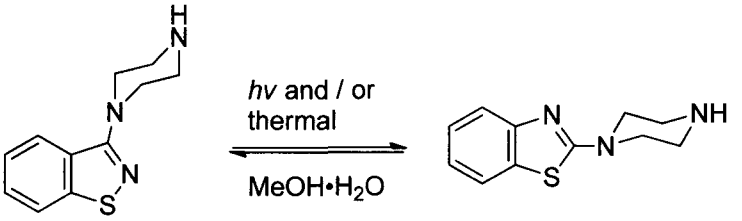


Photoisomerization of benzisothiazole to benzothiazole has been reported by Sharp et al. at Pfizer during their efforts to study photo-stability of ziprasidone, an anti-psychotic drug.[109] The transformation was proposed to proceed through an azirine intermediate followed by a nucleophilic displacement by sulphur either at nitrogen or carbon of the azirine ring, presumably assisted by an orthogonal aromatic π-bonding system in relation to the azirine nitrogen.



7.6 *Possible Liabilities of Drugs Containing Thiazoles and Benzothiazoles*

Commercially outsourced libraries as well as pharmaceuticals often have 1,3-thiazoles or benzothiazoles.[110] Yet thiazoles especially 2-aminothiazoles are considered as structural alerts and often excluded when considering the design of new drug candidates. The risk associated with structural alerts like these can be reduced by inducing an alternative metabolic pathway or simply low clinical exposure, but such an approach cannot accurately predict the human clinical response. An understanding of the "metabolic purpose" and the tendency to from reactive metabolites is therefore necessary. This is especially relevant from a position concerning hit triage and follow-up tactic strategies. The function of most cytochrome P450 (or CYP) enzymes, the major enzymes involved in drug metabolism, is to catalyze the oxidation of organic substances. 1,3-Thiazoles are prone to oxidative metabolism and typically undergo epoxidation. This happens at the 4,5-double bond and causes the formation of α-dicarbonyl metabolites and thioamide derivatives, such as thioamides, thioureas, or acylated thioureas. Both types of metabolites are capable of undergoing further metabolism to form reactive