

Characterization of Cytochrome P450 Mechanism-Based Inhibition

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1 INTRODUCTION

Oxidative metabolism mediated by the superfamily of hepatic enzymes known as the cytochrome P450s represents a significant clearance pathway for many drugs prescribed today (Wienkers and Heath, 2005). Of the possible hepatic cytochrome P450 enzymes identified to date, P450 1A2, P450 2C8, P450 2C9, P450 2C19, P450 2D6, and P450 3A4/5 are responsible for greater than 80% of the known oxidative drug metabolism reactions (Fig. 1). In light of the small number of P450 enzymes responsible for the metabolism of a large number of drugs, it is not surprising that a significant portion of drugs possess overlapping P450 enzyme specificities (Guengerich, 1997). A consequence of this disproportionate ratio between the numbers of enzymes and substrates is that for many multidrug therapies, it is common for a patient to receive two or more drugs that interact with the same P450 enzyme. Under these polytherapeutic conditions, a patient is significantly at risk for incurring a P450-based, drug–drug interaction (DDI) (Black *et al.*, 1996; Friedman *et al.*, 1999). There are many clinically important mechanism-based P450 inhibitors that span several therapeutic areas including *antiarrhythmics* [e.g. amiodarone (Polasek *et al.*, 2004)], *antibacterials* [e.g. clarithromycin (Ito *et al.*, 2003) and troleandomycin (Yamazaki and Shimada, 1998)], *antidepressants* [e.g. fluoxetine (Murray and Murray, 2003) and paroxetine (Hara *et al.*, 2005)], *anti-HIV agents* [e.g. ritonavir (von Moltke *et al.*, 2000) and delavirdine (Voorman *et al.*, 1998)], *antihypertensives* [e.g. diltiazem (Jones *et al.*, 1999), and verapamil (Wang, Jones and Hall, 2005)], *nonsteroidal anti-inflammatory drugs* (NSAIDs) [suprofen (O'Donnell *et al.*, 2003) and zileuton (Lu *et al.*, 2003)], *steroids/receptor modulators* [e.g. gestodene (Guengerich, 1990), raloxifene (Chen *et al.*, 2002; Baer, Wienkers and Rock, 2007)], and *methylenedioxymethamphetamine* (MDMA) (Van *et al.*, 2007), and *oncology drugs* [e.g. tamoxifen (Zhao *et al.*, 2002) and irinotecan (Hanioka *et al.*, 2002)]. In addition, P450 mechanism-based inhibitors (MBIs) can be found in environmental sources such as *illicit drugs* [e.g. phencyclidine (PCP) (Jushchyshyn *et al.*, 2005)] and *various dietary*