

Directing the Metabolism of Drugs Away from CYP450: The Use of Oxetane Rings

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Abstract

Treatment of health problems that accompany aging often includes pharmacotherapy. It is thus common for older adults—and, increasingly, younger adults—to be on multiple medications, either prescription or over-the-counter (OTC). With the consumption of multiple medications, drug-drug interactions (DDIs) are a concern. The site of drug-drug interactions is often at the level of drug metabolism. If a drug inhibits (or enhances) the metabolism of another, the blood level (therapeutic effect) can be decreased below the required level, or adverse effects can increase. Because most currently used drugs are metabolized *via* cytochrome P450-catalyzed pathways, drug discoverers seek drugs that are metabolized by alternate pathways. Medicinal chemists have come upon a strategy—the incorporation of oxetane rings in the drug structure—that increases the likelihood that a drug will not be metabolized *via* CYP450. The same modification gives other desirable physical properties to the molecule. Although there are no guarantees that there will be fewer DDIs or an absence of other unexpected problems, the strategy could pave the way for new drugs that are safer and easier to use with concomitant medications.

Keywords

Drug Metabolism, CYP450, Drug-Drug Interaction, Oxetane, Analgesic, Drug Discovery

1. Introduction

In the past century, populations in many parts of the world are aging [1]. And a significant rise in life expectancy in almost all regions of the world has contri-

buted to an increasingly older population. Since the aging process predisposes a person to increased vulnerability and susceptibility to external threats and internal physiological decline in organ function and defensive processes against disease, concurrent with the increasing population is an increase in the needs for healthcare and related services [2] [3] (Figure 1).

The physiological changes that occur with aging affect the functioning of the heart and blood vessels, gastrointestinal tract, liver, kidneys, central nervous system, and others [4] [5] [6] [7]. With the advances in basic research and translation to drug discovery, a large fraction of healthcare includes pharmacotherapy. Therefore, medication use increases substantially with aging in conjunction with the healthcare needs and, because there is often more than one health problem, polypharmacy is commonly the result [2] [3] [8] [9] [10]. While not inherently a contraindication, polypharmacy can inadvertently lead to serious adverse consequences [11] [12] [13]. The occurrence of such an event is termed a “drug-drug interaction” (DDI). One of the major physiological mechanisms leading to a DDI is an interaction at the level of drug metabolism. The CYP450 system is more affected by the aging process than are other drug metabolizing systems. Therefore, a strategy that could limit the occurrence of a DDI at the level of CYP450 drug metabolism could have a significant benefit.

2. Drug Metabolism via CYP450

The CYP450 monooxygenase system is a family of hemeprotein isozymes that catalyze the biotransformation (metabolism) of many current drugs (Figure 2)

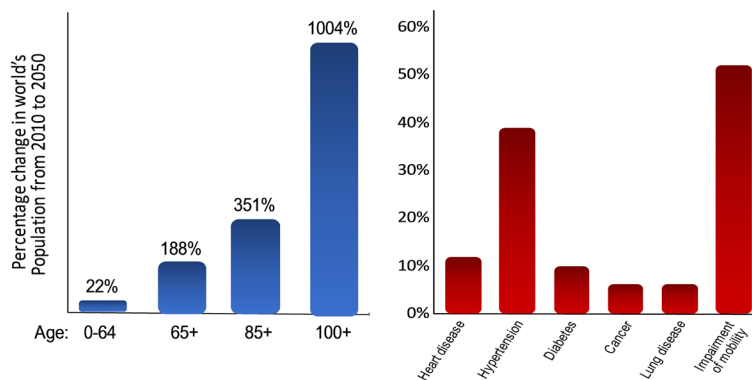


Figure 1. (Left) Increase in world population and (right) prevalence of chronic health problems. Source: United Nations, World Population Prospects: Available at: <http://esa.un.org/unpd/wpp>.

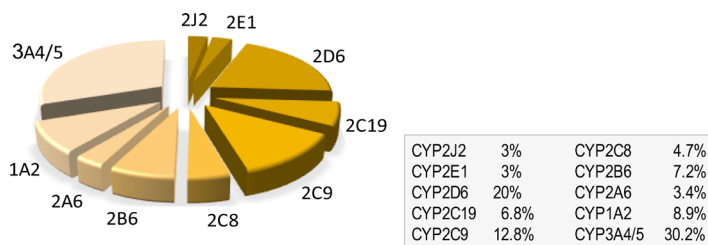


Figure 2. Approximate estimate of the percentage of current drugs that are metabolized via pathways of the CYP isozymes. Based on [15] with permission.

[14] [15] [16]. The liver is the major site of drug metabolism in humans, functioning both to detoxify (alter the chemical structure) and to facilitate excretion of foreign chemicals (xenobiotics) such as drugs by enzymatically converting lipophilic (lipid-soluble) compounds to less lipophilic (hydrophilic, water-soluble) compounds, which are more favorably excreted through the kidneys. Drug metabolism is achieved through phase I type reactions (chemical reactions such as oxidation, reduction, and hydrolysis), phase II reactions (mostly conjugations), or both (the most frequent situation for most drugs) [17]. Oxidation is the most common of the phase I reactions, and these are catalyzed by members of the CYP450 system. CYP450 was discovered in 1954 as a novel protein in hepatocytes during research on steroid hormone metabolism [18]. Its function and significance as a catalyst in steroid hormone synthesis and drug metabolism was determined almost a decade later (1963), and it was confirmed to be a key enzyme involved in drug and steroid hydroxylation reactions [19].

3. Oxetanes: The Basics

Oxetane is a four-member ring organic compound consisting of three carbon atoms and one oxygen atom with formula C_3H_6O and molecular weight 58.08 Dalton (Figure 3). A drug (or any organic compound) that contains this particular heterocycle is called an “oxetane”. The reason that the oxetane ring is of interest to drug discovery as a strategy to reduce DDIs is that compared to a molecule without the ring, the incorporation of an oxetane ring can impart significant differences in the structural and physiochemical properties of molecules, and thus the drug-favoring characteristics of a compound, for example its water or lipid solubility, pK_a , receptor or enzyme conformational preference, and of particular relevance to the present topic—metabolic stability [20] [21].

The oxetane ring can thus be thought of as a functional group, and it can be used as a substitute or as preferred surrogate for other functionalities that are commonly used in drug discovery (Figure 4). Some uses have included [22]

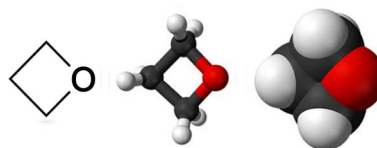


Figure 3. Representations of Oxetane (1,3-Propylene oxide, 1,3-Epoxypropane, Oxacyclobutane, Trimethylene oxide. Source: Wikipedia and Wikimedia Commons.

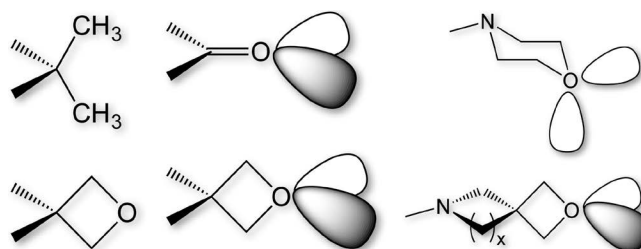


Figure 4. Oxetanes as surrogates for commonly encountered functional groups [22].

introduction of steric bulk to fill receptor pockets (for better complementary fit to increase intrinsic activity or block active sites, shield nearby functional groups from chemical or metabolic susceptibility without introducing an undesired increase in lipophilicity [23]-[29]. They have successfully been used to improve the physiochemical properties and provide more favorable pharmacokinetic profiles in several drug discovery programs [30]-[37]. The magnitude of the changes depends on the structural context of course. As an example, substitution with an oxetane can increase the aqueous solubility by only about 4-fold, or more than an astounding 4000-fold [22]. Substitution usually increases the metabolic stability.

4. Oxetanes: Designing Away from DDIs

Toselli *et al.* have recently reported on the use of oxetane rings as design elements to alter the metabolic pathways of drugs [30]. They “map” the enzymes that contribute to a drug’s metabolism to determine exaggerated dependence on one specific pathway (specifically a specific CYP450 pathway), since this increases the risk of DDIs with co-administered drugs. They previously reported that oxetane rings can be hydrolyzed (opened to yield diols) by the human microsomal enzyme epoxide hydrolase (mEH) (EC 3.2.2.9) [38]. This was quite surprising, since it represents an unusual non-oxidative metabolic route, and it was the first example of a non-epoxide substrate for this phase I type drug-metabolizing enzyme [39] [40]. Findings of additional examples of oxetane substrates of mEH prompted renaming of the enzyme to “microsomal oxirane/oxetane hydrolase” [41].

A critical finding was that the rate of hydrolysis of an oxetane by mEH is affected by structural elements in the vicinity of the oxetane [41]. This offers the potential that the rate of metabolism could be built-in or fine-tuned by using oxetane-containing building blocks as part of the drug design discovery process as tools to shuttle metabolism through non-CYP450 pathways, thus decreasing the likelihood of a DDI with co-administered other drugs (Figure 5). Indeed,

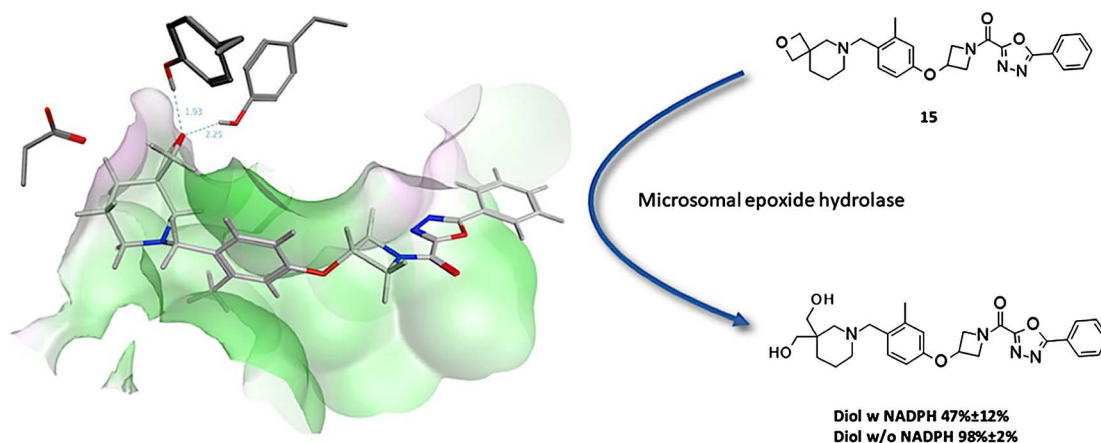


Figure 5. A representative example of a molecule containing an oxetane ring metabolized to a diol in a reaction catalyzed by mEH (microsomal epoxide hydrolase). Note the opening of the oxetane ring. Source: Ref [30], with permission.

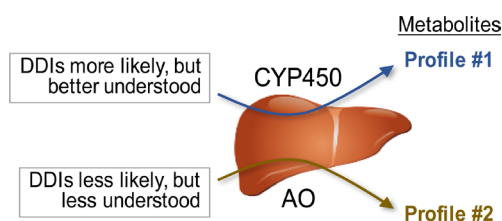


Figure 6. Shuttling of drug metabolism away from CYP450 and towards another enzymatic pathway such as AO (aldehyde oxidase) could be quite beneficial, is not devoid of potential problems.

Toselli *et al.* demonstrated for a set of structurally diverse oxetanes that oxetanes can be used as design elements for directing drug metabolism toward mEH, and thus away from CYP450 pathways [30].

Toselli *et al.* expressed a note of caution that the shuttling of drug metabolism down the mEH pathway 1) did not guarantee avoidance of a DDI, and 2) did not introduce its own set of potential problems [30]. Some problems might be anticipated, such as undesirable effects on pharmacokinetics [42] [43] [44] [45], but other problems might arise simply due to the less mature understanding of this metabolic pathway compared to those of the very well-known CYP450's (Figure 6).

5. Conclusion

The fact that the majority of currently prescribed drugs, and several OTC products, are metabolized through the same pathways involving CYP450 raises the concern of potential drug-drug interactions leading to adverse effects that would be avoided if the drugs were metabolized by non-overlapping mechanism. Oxetanes offer a strategy to design-in this capability early in drug discovery. Although not a guarantee, they are one example of a broader attempt to decrease DDIs early in the drug discovery process.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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