Testa B & Jenner P. Inhibitors of cytochrome P-450s and their mechanism of action. *Drug Metab. Rev.* 12:1-117, 1981.
[School of Pharmacy, University of Lausanne, Switzerland and Department of Neurology, Institute of Psychiatry, London, England]

This paper reviews the many compounds acting to inhibit cytochrome P-450 enzymes. The presentation is a systematic one, being based on functional groups and chemical mechanisms of action; in other words, it relates chemical properties and biological reactivity. [The *SCI*® indicates that this paper has been cited in more than 155 publications.]

The Multifaceted Inhibition of Cytochrome P-450

Bernard Testa
Institut de Chimie Thérapeutique
Ecolé de Pharmacié
Université de Lausanne
CH-1005 Lausanne
Switzerland
and
Peter Jenner
King's College
University of London
London SW3 6LX
England*

The story surrounding the inception and publication of our first review and our book on drug metabolism has been told in a previous essay[1] to which the interested reader is kindly referred. By the time this book was published, we were both fortunate to have reached an echelon in the academic ladder that offered healthy breathing and a back row stool in the establishment's colosseum. Of greater relevance, our fields of interest were progressively diverging for reasons of nature and nurture (in other words, predisposition and grants). While one of us had become a medicinal chemist engrossed in structural chemistry, molecular mechanisms, and drug design, the other, as a molecular pharmacologist, had made receptors and enzymes his favorite objects of study.

Paradoxically, divergence led to complementarity rather than severance, a felicitous but not fortuitous state of affairs. When one partner is called "structure" and the other "activity," the name of the game can only be "relationships." This is how our collaboration continued to thrive on various aspects of structure/activity relationships; for example, thermodynamic approaches of drug-receptor interactions.[2,3] The inhibition of enzymes, be they involved in the metabolism of xenobiotics or endogenous compounds, also was a topic of common interest. Noteworthy among these enzymes were the cytochrome P-450 monooxygenases, which occupy a pivotal position in the metabolism of many xenobiotics, such as drugs, and of endobiotics, such as steroidal hormones.

We both had accumulated innumerable references on the topic and shared a sense of confusion when trying to grasp the chemical and mechanistic diversity of cytochrome P-450 inhibitors. Indeed, many compounds inhibit cytochrome P-450, a fast growing list that could be reduced to manageable size when one no longer considered active molecules but the functional groups that account for this activity. An even greater bonus of this approach was that the various mechanisms of inhibition now appeared as counterpart to functional groups.

By classifying the mechanisms into direct reversible inhibition, indirect reversible inhibition, and irreversible inhibition, three clusters of functional groups became apparent. This in turn made it relatively straightforward to order logically the many inhibitors worthy of consideration. At this point, the idea of making the most of our ratiocinations in the form of a review article had become irresistible. In compliance with our inclination, it was smooth but long lasting sailing to write a text of more than 100 printed pages.

A few reviews had appeared already on various aspects of cytochrome P-450 inhibition; none, however, offered a comprehensive attempt at rationally covering so wide a subject. Now, 10 years after its publication, the text retains its full validity as far as the classification criteria are concerned, and a short review has just been published to update some of its factual content.[4]

Bringing a semblance of order and clarity into a complex and large amount of data should account for part of the success of the review. Another reason is presumably the expedience of citing a single background review in lieu of a number of original papers.

1. **Testa B & Jenner P.** The coming of age of drug metabolism. Citation Classic. Commentary on *Drug metabolism: chemical and biochemical aspects.* New York: Dekker, 1976. 500 p. *Current Contents/Clinical Medicine* and *Current Contents/Life Sciences* 13 August 1990. p. 17.
2. **Kilpatrick G J, El Tayar N, van de Waterbeemd H, Jenner P, Testa B & Marsden C D.** The thermodynamics of agonist and antagonist binding to dopamine D-2 receptors. *Mol. Pharmacol.* 30:226-43, 1986. (Cited 15 times.)
3. **Testa B, Jenner P, Kilpatrick G J, El Tayar N, van de Waterbeemd H & Marsden C D.** Do thermodynamic studies provide information on both the binding to and the activation of dopaminergic and other receptors? *Biochem. Pharmacol.* 36:4041-6, 1987. (Cited 5 times.)
4. **Testa B.** Mechanisms of inhibition of xenobiotic-metabolising enzymes. *Xenobiotica* 20:1129-37, 1990.

*Received September 13, 1990