Three-Dimensional Quantitative Structure-Activity Relationship Analysis of Human CYP51 Inhibitors

Sean Ekins,1 Dayna C. Mankowski,2 Dennis J. Hoover, Michael P. Lawton, Judith L. Treadway, and H. James Harwood, Jr.

Pfizer Global Research and Development, Groton Laboratories, Groton, Connecticut

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ABSTRACT:

CYP51 fulfills an essential requirement for all cells, by catalyzing three sequential mono-oxidations within the cholesterol biosynthesis cascade. Inhibition of fungal CYP51 is used as a therapy for treating fungal infections, whereas inhibition of human CYP51 has been considered as a pharmacological approach to treat dyslipidemia and some forms of cancer. To predict the interaction of inhibitors with the active site of human CYP51, a three-dimensional quantitative structure-activity relationship model was constructed. This pharmacophore model of the common structural features of CYP51 inhibitors was built using the program Catalyst from molecular modeling software. This study has demonstrated the potential for ligand-based computational pharmacophore modeling of human CYP51 and enables a high-throughput screening system for drug discovery and database mining.

Cytochrome P450 enzymes (P450s) are a widely studied, large superfamily of heme-thiolate proteins involved in the metabolism of endobiotics and xenobiotics across eukaryotes and prokaryotes (Nelson et al., 1996). The clinical relevance of P450s is their central role in drug metabolism, which can occur in all human tissues and may be inhibited by the coadministration of competing xenobiotics for the same enzyme (Waterman and Lepesheva, 2005). CYP51 is one of the most conserved P450s across phyla and is involved in sterol metabolism. It catalyzes the conversion of lanosterol to lanosterol 14α-demethylase, which is essential for all cells, by catalyzing three sequential mono-oxidations within the cholesterol biosynthesis cascade (Trzaskos et al., 1986; Waterman and Lepesheva, 2005). CYP51 is one of the most conserved P450s across phyla (Aoyama et al., 1996; Yoshida et al., 1997), with a 93% amino acid sequence identity between rat and human and 39 to 42% identity between mammalian and fungal enzymes (Aoyama et al., 1996; Yoshida et al., 1997). In humans there are three CYP51 genes, including two pseudogenes and a functional gene on chromosome 7 (Rozman et al., 1996). Substrates for CYP51 from mammals, plants, and fungi are lanosterol, obtusifoliol, and 24-methylene-dihydroxylanosterol, respectively (Lamb et al., 1998). Such substrate specificities can be explained by a limited number of amino acid substitutions in substrate recognition sites 1, 2, and 5 between mammalian and fungal CYP51, and it is likely that these locations are responsible for conferring selectivity for sterol metabolism (Yoshida et al., 1997). Before the sequences of fungal and human CYP51 were known, this enzyme was identified as an antifungal therapeutic target that could be inhibited by many imidazole, triazole (Vanden Bossche et al., 1987, 1995; Hartman and Sanglard, 1997), and nonazole compounds (Aoyama et al., 1983, 1987; Yoshida and Aoyama, 1985; Gebhardt et al., 1994; Hartman and Sanglard, 1997). Many of these marketed compounds are specific toward a single fungal species, whereas others have widespread application (Hartman and Sanglard, 1997). The selectivity of these antifungals is also variable, with some exhibiting no interaction with the mammalian enzyme. Many of these azole antifungals are also potent inhibitors of other mammalian P450s involved in drug metabolism and there is thus the potential for clinically significant drug-drug interactions when they are coadministered with substrates for the same enzymes (Strolin Benedetti and Bani, 1999).

ABBREVIATIONS: P450, cytochrome P450; QSAR, quantitative structure-activity relationship; 3D, three-dimensional.
There have been many studies usingazole, oxysterol, and mecha-
nism-based inactivator-type inhibitors of fungal or mammalian
CYP51 (Trzaskos et al., 1986, 1993, 1995; Frye et al., 1993, 1994). In
addition, the purification (Sonoda et al., 1993) and expression of
human CYP51 have allowed the determination of its regulation by
oxysterols (Stromstedt et al., 1996). However, because of the mem-
brane-bound nature of mammalian P450s, there is as yet no crystal
structure for human CYP51. Therefore, our understanding of the struc-
tural requirements of the human CYP51 active site are limited to homol-
gy models constructed using various bacterial P450s (Ishida et al., 1988;
Tuck et al., 1991, 1992; Tafi et al., 1996; Talele et al., 1997; Holte and
Fattorusso, 1998; Lewis et al., 1999), including Mycobacterium tubercu-
losis CYP51 (Matsuura et al., 2005; Rupp et al., 2005) and the crystal
structure of M. tuberculosis CYP51 (Podust et al., 2001).

There have also been few quantitative structure-activity relation-
ship (QSAR) models of CYP51 to date and they have dealt exclu-
sively with the fungal CYP51s (Tafi et al., 1996; Fujita, 1997). The
utility of more classic QSAR models has also been reviewed for the
production ofazole-type agricultural fungicides (Fujita, 1997). How-
ever, approaches to modeling the common features of inhibitors of
other human P450s have been widely shown using a Catalyst phar-
macophore approach (Ekins et al., 2001), comparative molecular field
analysis (Jones et al., 1996), and other QSAR methods (Ekins et al.,
2003). These techniques have also been used to predict a test set of
molecules excluded from the training set (Ekins et al., 1999).

Recently a series of dual-acting hypoglycemic and hypcholeste-
romelic agents were found to inhibit glycogen phosphorylase and
human CYP51 (Harwood et al., 2005). The prototype of this series,
CP-320626, inhibited glycogen phosphorylase and human CYP51
with ICso values of 155 nM and 4 μM, respectively, reduced glyco-
genolysis and cholesterologenesis in cultured cells, and lowered
plasma glucose and plasma cholesterol in experimental animals
(Harwood et al., 2005). To understand the characteristics of these CP-
320626-related CYP51 inhibitors and other inhibitors of this human
CYP51 enzyme, we have used a computational approach to produce a
predictive Catalyst pharmacophore. This model was constructed using
a training set of structurally diverse commercially available molecules and CP-320626-related CYP51 inhibitors with varying ICso values. The validity of the predictions made by this model was then evaluated using test sets of molecules not in the training set. These test sets contained both commercially available molecules and structurally diverse CP-320626-related CYP51 inhibitors for which in vitro data were subsequently generated.

Materials and Methods

Materials. Human cytochrome P450 reductase was obtained from Panvera
(now InVitrogen, Madison, WI). Rat microsomal lipid was prepared as de-
scribed by Sundin et al. (1987). Triarimol, CP-320626, and all other related
CYP51 inhibitors denoted as A-P and 1–48 (see supplemental Table for structures) in the tables were synthesized as described previously (Hoover et al.,
1998; Martin et al., 1998; Rath et al., 2000; Treadway et al., 2001;
Harwood et al., 2005; Yu et al., 2006) and in the patents cited in these
publications. Lovastatin was purchased from Calbiochem (La Jolla, CA).
Azaconazole, itraconazole, and teraconazole were obtained from Research
Diagnostics (Flanders, NJ). Sulfaphenazole was purchased from Gentest Corp.
(now BD Gentest, Woburn, MA). Dioleoyl phosphatidyl choline, lanosterol
(97% pure), ergosterol, and all other chemicals were obtained from Sigma-
Aldrich (St. Louis, MO) or Steraloids (Newport, RI).

CYP51 Lanosterol Demethylase Assay. Human CYP51 expressed in Topp
3 cells was partially purified using the method of Stromstedt et al. (1996).
Protein concentrations were measured using a BCA Protein Assay kit (Pierce
Chemical, Rockford, IL) with bovine serum albumin as a standard as described by the manufacturer. Cytochrome P450 content was measured by the method of Omura and Sato (1964). Initial rate conditions for the formation of 4,4-
dimethylcholesta-8,14,24-trien-3β-ol (trien) were determined in preliminary
studies with the CYP51 reconstitution system. In brief, 25 μl of lanosterol (1
mM, suspended in a mixture of 50:50 tyloxapol-acetone, dioleoyl phosphatidyl
choline micelles (5 mg/ml), methanol, and 100 mM potassium phosphate
buffer, pH 7.4) was added to tubes to provide a final lanosterol concentration
of 50 μM (approximate Km). Inhibitors (from 0.01 to 200 μM in methanol or
methanol (control) were then added to the tubes, and the lanos-
erol-inhibitor mixture was allowed to dry under nitrogen for 10 min. To dried
substrate and inhibitor tubes, 20 pmol of CYP51, 125 pmol of human reduct-
tase, and 50 μl of rat lipid were added and allowed to sit at room temperature
for 10 to 15 min for enzyme reconstitution. Buffer (100 mM potassium phosphat,
PH 7.4, with 20% glycerol, 0.1 mM dithiothreitol, 0.1 mM EDTA, and
0.5 mM potassium cyanide) was added to the tubes after the reconstitution
period for a final incubation volume of 0.5 ml. Tubes were preincubated for 2
min at 37°C, and the reaction was initiated by the addition of 50 μl of a
NADPH regenerating system (final incubation concentration: 10 mM MgCl2,
0.54 mM NADP, 6.2 mM tri-isocitric acid, and 0.5 U/ml tri-isocitric dehy-
drogenase). Reactions were terminated at 60 min with the addition of 25 μl of
ergosterol (1 mg/ml in ethyl acetate), followed by extraction with 5 ml of ethyl
acetate. Tubes were then vortexed before centrifugation followed by removal
of 3 to 4 ml of supernatant and transfer to fresh tubes and evaporation under
nitrogen at 50°C. The evaporated samples were reconstituted in a 150-μl
mobile phase, and 25 to 50 μl was injected onto the high-performance liquid
chromatography system (see below).

Triene formation was determined using a modification of the method
of Stromstedt et al. (1996). In brief, triene metabolite and ergosterol were sepa-
rated on a Waters NovaPak C18 column (4.0 μM; 150 mm × 3.9 mm; Waters;
Bedford, MA) with a mobile phase consisting of methanol-acetonitrile-high-
performance liquid chromatography grade water (45:45:10), at a flow rate of
1.5 ml/min. The triene and ergosterol were monitored by UV detection at 248
nm using a SpectrMonitor variable wavelength detector (LDC Analytical,
Riviera Beach, FL) and the Multichrom data acquisition system (version. 2.11;
Fisons Instruments, Beverly, MA) was used for data collection, analysis, and
reporting. Approximate retention times for triene metabolite and ergosterol
were 25 and 30 min, respectively.

Interpretation of CYP51 Lanosterol Demethylation Assay Results.
The percent inhibition of triene formation with methanol controls was determined
with each inhibitor at three to six concentrations in triplicate and the average
was used as described previously (Harwood et al., 2005). The ICso was
calculated from a graph of percent CYP51 activity remaining versus inhibitor
concentration using DeltaGraph (version 4.0; Monterey, CA).

Molecular Modeling. The computational molecular modeling studies were
carried out using a Silicon Graphics Octane workstation and based on a
pharmacophore methodology described previously for other P450s (Ekins et al.,
1999, 2001). The pharmacophore method described below represents the
features on the ligands used and cannot be related easily to features in the
protein binding site. This method has also been applied to other proteins of
relevance to absorption, distribution, metabolism, excretion, and toxicity
(Ekins and Swaan, 2004). The receptor surface modeling method also de-
scribed below attempts to provide information relating to the volume require-
ments of the enzyme active site for the heme and nonheme binding compounds
with highest affinity.

Modeling with Catalyst. The three-dimensional structures of CYP51 in-
hibitors from the present study or literature data sets were built interactively
using Catalyst (version 4.0; Accelrys Software, Inc., San Diego, CA). The
number of conformers generated for each inhibitor was limited to a maximum
of 255 with an energy range of 0 to 20 kcal/mol. A training set of 26 molecules
was selected and used to build the pharmacophore (Table 1). Ten hypotheses
were generated using these conformers for each of the molecules, and ICso
values were generated after selection of the following features for the inhibi-
tors: hydrogen bond donor, hydrogen bond acceptor, hydrophobic, positive
ionizable, and ring aromatic. After assessment of all 10 hypotheses generated,
the lowest energy cost hypothesis was considered the best.

The goodness of the structure activity correlation was estimated by means
of the correlation coefficient r value. Catalyst also calculates the total energy
cost of the generated pharmacophores from the deviation between the esti-
mated activity and the observed activity, combined with the complexity of the

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### TABLE 1

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Structure</th>
<th>Observed CYP51 IC₅₀</th>
<th>Estimated CYP51 IC₅₀</th>
</tr>
</thead>
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<tr>
<td>Clotrimazole</td>
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<td>0.13</td>
<td>1.3</td>
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<tr>
<td>Ketoconazole</td>
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<td>0.082</td>
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<tr>
<td>Miconazole</td>
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<td>0.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Analog A</td>
<td><img src="image" alt="Structure" /></td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Analog B</td>
<td><img src="image" alt="Structure" /></td>
<td>0.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Analog C</td>
<td><img src="image" alt="Structure" /></td>
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<td>2</td>
</tr>
<tr>
<td>Analog D</td>
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<td>6.9</td>
</tr>
<tr>
<td>Analog E</td>
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<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Analog F</td>
<td><img src="image" alt="Structure" /></td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>CP-320626</td>
<td><img src="image" alt="Structure" /></td>
<td>4.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Analog G</td>
<td><img src="image" alt="Structure" /></td>
<td>4.5</td>
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<td>Analog H</td>
<td><img src="image" alt="Structure" /></td>
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<td>Analog I</td>
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<td>Analog J</td>
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<tr>
<td>Analog K</td>
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<td>60</td>
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</table>

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Structure</th>
<th>Observed CYP51 IC₅₀</th>
<th>Estimated CYP51 IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
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<tr>
<td>Griseofulvin</td>
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<tr>
<td>Tonalftate</td>
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<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Testosterone</td>
<td><img src="image" alt="Structure" /></td>
<td>50</td>
<td>160</td>
</tr>
</tbody>
</table>

*Note: CYP51 IC₅₀ values are given in μM.*
Values. Two test sets of 19 commercially available molecules and 48 proprietary compounds, respectively, were subjected to the fast-fit algorithm for the Catalyst hypothesis to predict an IC50 value. None of these molecules was included in the initial training set for the CYP51 IC50 pharmacophore. The fast-fit algorithm refers to the method of finding the optimal fit of the substrate to the hypothesis among all the conformers of the molecule without performing an energy minimization on the conformers of the molecule (Catalyst tutorials release 3.0; Accelrys Software, Inc.). The computational predictions derived using the fit to the CYP51 Catalyst pharmacophore were compared with the observed in vitro values. We selected an acceptable arbitrary cutoff for potency of inhibition as accepted of ≤10 μM.

**Catalyst CYP51 Pharmacophore Model.** Catalyst uses a collection of molecules with inhibitory activity over multiple orders of magnitude for the enzyme of interest to construct a model of the structural features (pharmacophore) necessary for interaction of the molecules with the active site of the enzyme. The resultant pharmacophore hypotheses explain the variability of the potency of inhibition with respect to the geometric localization of these features of the molecules. The IC50 values for structurally diverse inhibitors of CYP51 generated in this study cover >3 orders of magnitude (0.13–93 μM) (Table 1) and related CYP51 inhibitors were screened in the IC50 assay (Tables 1–3).

**Results.**

**CYP51 in Vitro Inhibition Data.** Partially purified CYP51 was characterized for protein and carbon monoxide difference spectra (data not shown). Total P450 was determined as 0.22 nmol/mg of protein. The assay conditions were also developed to provide optimal lanosterol turnover using a final ratio of P450/reductase of 1:6. The Km determined for lanosterol with the reconstituted human CYP51 was ~30 μM (data not shown), in agreement with previously determined values (Lamb et al., 1998). Using a standard concentration of 50 μM lanosterol, 93 commercially available molecules including the competitive inhibitor CP-320626 (Harwood et al., 2005) and related CYP51 inhibitors were screened in the IC50 assay (Tables 1–3).

**Catalyst CYP51 Pharmacophore Validation Using Test Sets of IC50 Values.** Two test sets of 19 commercially available molecules and 48 proprietary compounds, respectively, were subjected to the fast-fit algorithm for the Catalyst hypothesis to predict an IC50 value. None of these molecules was included in the initial training set for the CYP51 IC50 pharmacophore. The fast-fit algorithm refers to the method of finding the optimal fit of the substrate to the hypothesis among all the conformers of the molecule without performing...
acceptor, and two ring aromatic features (additional hydrophobes). The Catalyst pharmacophore demonstrated a good correlation of observed versus estimated IC$_{50}$ values ($r = 0.92$) (Fig. 2).

The total energy cost of the hypothesis (117.3) and the null hypothesis (154.1) suggest that the model was significant as the difference was sizeable. Permuting the training set molecule structures with activities can suggest that the model was significant as the difference was 148.7, almost identical to the null hypothesis value. The total energy cost of the hypothesis (117.3) and the null hypothesis (154.1) suggest that the model was significant as the difference was sizeable. Permuting the training set molecule structures with activities can suggest that the model was significant as the difference was 148.7, almost identical to the null hypothesis value.

### Discussion
In humans, beyond its obvious role in cholesterol and steroid hormone biosynthesis (Trzaskos et al., 1986), the physiological roles...
of CYP51 in, for example, spermatogenesis and oogenesis (Stromstedt et al., 1988) are poorly defined. In addition, inhibition of cholesterol biosynthesis through inhibition of mammalian CYP51 results in an increase in cellular lanosterol concentrations (Miettinen, 1988), the consequences of which remain poorly defined. Furthermore, the poor specificity of most current mammalian CYP51 inhibitors for CYP51 versus steroidogenic or drug-metabolizing P450s (Hartman and Sando, 1997; Boscott and Grant, 1994), in agreement with earlier work (Yoshida et al., 1994), indicates that the human enzyme may have a larger and differently shaped active site cavity due to the replacement of Phe-255 with Leu-310 (Matsuura et al., 2005; Rupp et al., 2005).

Although there are data sets in the literature describing the fungal activity of CYP51 inhibitors (Steinmann and de Waard, 1995), there is little information relating to human disease. The present study has described, to our knowledge, the first 3D-QSAR relationship using in vitro data for inhibitors of human CYP51. By using 26 structurally diverse molecules with a range of inhibitory activity, we constructed a predictive pharmacophore model that was used to score the activity of test molecules and predict whether new chemical entities might interact with this enzyme. The model for the data set generated in this study suggested a pharmacophore with four features, indicating the predominance of hydrophobic features (Fig. 1) in agreement with previous reports (Matsuura et al., 2005; Rupp et al., 2005) and a high correlation ($r = 0.92$) (Fig. 2) between predicted and observed $IC_{50}$ values.

One of the best ways to test the validity of a 3D-QSAR is to predict the activity of molecules excluded from the training set and then compare these to observed values. In addition to prospectively assessing many proprietary compounds, several commercially available molecules were evaluated in vitro as they had either important endogenous roles (cholesterol, arachidonic acid, progesterone, pregnenolone, and anandamide), were known P450 substrates (erythromycin, tolbutamid, lovastatin, chlorpropamide, and propafenone), or were known P450 inhibitors (sulfaphenazole, flucloxacide, azacnazol, econazole, bifonazole, terconazole, itraconazole, triarimol, and sulfipyrazole). It was thought that these molecules would provide a structurally diverse test set to validate the pharmacophore constructed from a similarly structurally diverse training set including home-binding azoles and non-heme-binding CP-320626-related compounds (Harwood et al., 2005). In vitro $IC_{50}$ values were generated for CYP51 inhibition for 19 commercially available molecules. Sixteen of the 19 (84%) molecules fulfilled the criterion (Table 2). Non-heme-binding CP-320626-related CYP51 inhibitors were also successfully predicted using the same pharmacophore model with an ~80% prediction rate (Table 3). These results suggest that the CYP51 pharmacophore has utility for both classification of novel molecules that are either known heme binders or nonheme binders with an acceptable level of accuracy for early screening.

By aligning the most potent CYP51 inhibitors (azoles and CP-320626-related compounds) with the pharmacophore, it was possible...
to generate a receptor surface model of their volume. The receptor surface model of these active inhibitors forms an elongated shape (Fig. 3A), not too dissimilar from that of lanosterol and the volume generated by Rupp et al. (2005). This receptor surface model can also be used to explain the apparent lack of inhibitory activity toward human CYP51 by inactive molecules, by first mapping them to the pharmacophore and then placing them inside this receptor surface model. Features outside of the volume could suggest poor steric interactions within the active site of the enzyme that would be unfavorable for binding and therefore inhibition. As an example, we have fitted fluconazole to the pharmacophore and shown that a triazole ring is outside of the surface volume generated by the active compounds (Fig. 3B). This may explain the lack of potency of fluconazole toward the human CYP51 but subsequent activity toward the fungal P450. Indeed this is in agreement with a recent study that has also shown that fluconazole is considerably less active than ketoconazole with C. albicans. This is outside of the surface volume generated by the active compounds (Agarwal et al., 2003) and might also result in part because fluconazole possesses a hydrophilic triazole and hydroxy groups that would decrease affinity for the hydrophobic binding site relative to the more hydrophobic ketoconazole (Matsuura et al., 2005). The computational techniques described and applied in this article may allow elucidation of areas within the human CYP51 active site that can be targeted by directed synthesis to enable production of more selective anti fungal agents. Likewise, if human CYP51 is pursued as a therapeutic target, for example, in cancer (Downie et al., 2005; Kumarakulasingham et al., 2005), this pharmacophore model enables mining of compound data bases for inhibitors and may help in understanding the affinity of inhibitors for the human CYP51 active site. Specific inhibitors of human CYP51 (Harwood et al., 2005) might also be applicable, for example, as agents for lipid lowering, either alone or in combination with other agents (e.g., 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) currently marketed and/or in development (Harwood and Hamanaka, 1998) for use as therapeutic interventions in areas with substantial medical needs such as coronary heart disease, obesity, and diabetes.

Although the pharmacophore technique could represent an approach for identifying modulators of human CYP51, possibly by data base screening, we have taken the same approach with in vitro data for antifungal activity (Tafi et al., 1996), to create a second pharmacophore for fungal CYP51 (data not shown). Therefore, it is possible to differentiate between the human and fungal CYP51 enzymes in silico to develop selective modulators of this enzyme across phyla. The human CYP51 pharmacophores may allow this in combination with the protein models (de Groot and Ekins, 2002).

In conclusion, this study has described a large number of molecules tested as potential CYP51 inhibitors and has enabled the identification of nonoxazoles with low micromolar potency. These molecules have been used to build and test the first 3D-QSAR for human CYP51, which can be used to predict the inhibitory potential of other molecules toward this enzyme. We suggest that this CYP51 pharmacophore may be used to garner information regarding the interactions with the active site of this P450 and visually describe the selectivity of antifungal agents. This model could also enable rapid discovery of further modulators of this enzyme for therapeutic use.

Acknowledgments. We gratefully acknowledge Professor Michael R. Waterman (Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN) for supplying clones expressing recombinant CYP51, Joanne Jeffries-Grifor (Molecular Sciences, Pfizer Global Research and Development, Groton, CT) for partial purification of CYP51 from these clones, and Dr. Patrick Dorr (Pfizer, Sandwich, UK) for supplying several of the compounds evaluated in these studies.

References

Matsuura K, Yoshikura S, Tosa T, Hori H, Ishimori K, Kitagawa T, Morishima I, Kagawa N, and


CORRECTION TO “THREE-DIMENSIONAL QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP ANALYSIS OF HUMAN CYP51 INHIBITORS”

In Table 1 on page 496 of the article above [Ekins S, Mankowski DC, Hoover DJ, Lawton MP, Treadway JL, and Harwood HJ Jr (2007) Drug Metab Dispos 35:493–500], the chemical structure for analog L was inadvertently dropped and replaced with a duplicate of the structure for benzimidazole. The correct structure for analog L appears below.

The online version of this article will be corrected in departure from the print version.

The printer regrets this error and apologizes for any confusion or inconvenience it may have caused.

![Correct structure for analog L](image-url)