A COMPARISON OF THE EFFECTS OF 3-HYDROXY-3-METHYLGLUTARYL-COENZYME A (HMG-CoA) REDUCTASE INHIBITORS ON THE CYP3A4-DEPENDENT OXIDATION OF MEXAZOLAM IN VITRO

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ABSTRACT:

HMG-CoA reductase inhibitors can be divided into two groups: those administered as the prodrug, i.e., the lactone form (e.g., simvastatin and lovastatin), and those administered in the active form, i.e., the acid form (e.g., pravastatin, fluvastatin, atorvastatin, and cerivastatin). In this study, the influence of the lactone and acid forms of various HMG-CoA reductase inhibitors on metabolism by CYP3A4, a major cytochrome P450 isoenzyme in human liver, was investigated by determining the in vitro inhibition constant ($K_i$) using an antianxiety agent, mexazolam, as a probe substrate. In human liver microsomes, all the lactone forms tested inhibited the oxidative metabolism of mexazolam more strongly than did the acid forms, which have lower partition coefficient ($\log D_{7.0}$) values. In addition, the degree of inhibition of mexazolam metabolism tended to increase with an increasing $\log D_{7.0}$ value of the HMG-CoA reductase inhibitors among the lactone and acid forms. In particular, pravastatin (acid form), which has the lowest $\log D_{7.0}$ value, failed to inhibit CYP3A4 activity. Taking account of the lipophilicity of the inhibitors, in conjunction with the CYP3A4-inhibitory activity, could be very useful in predicting drug interactions between substrates of CYP3A4 and HMG-CoA reductase inhibitors.

Drug interactions can be classified roughly into two types. In one case, the pharmacological effects or side effects of particular drugs are altered by concomitant administration of other drugs. In the other case, the effects of concomitant drugs are altered by the first drugs. In either case, the drug interactions have often been evaluated by the changes in plasma levels of drugs in clinical situations. In the case of HMG-CoA reductase inhibitors, plasma levels of lactone-form prodrugs simvastatin and lovastatin are reported to be increased 10 times or more by the concomitant administration of an antifungal agent, itraconazole, a potent inhibitor of CYP3A4 (Varhe et al., 1994), one of the isoforms of cytochrome P450 (Neuvonen and Jalava, 1996; Neuvonen et al., 1998). The possibility has also been discussed of predicting the drug interaction with HMG-CoA reductase inhibitors.

It was considered that the increase in the plasma levels of the prodrug type, i.e., the lactone forms of HMG-CoA reductase inhibitors, caused by the concomitant administration of itraconazole may be due to inhibition of the CYP3A4-mediated metabolism of simvastatin and lovastatin (Vickers et al., 1990; Wang et al., 1991; Prueksaritanont et al., 1997) by itraconazole. We have determined the in vitro $K_i$ values of itraconazole using human liver microsomes and applied them to a pharmacokinetic model (Ito et al., 1998), together with pharmacokinetic parameters for itraconazole. As a result, we have found that the predicted increase in plasma levels of simvastatin by concomitant administration of itraconazole agreed fairly well with the observed increase in clinical situations (Ishigami et al., 2001). However, as far as the water-soluble pravastatin was concerned, when administered in the active acid form, there was no evidence suggesting any drug interaction with itraconazole either in clinical situations (Neuvonen and Jalava, 1996; Neuvonen et al., 1998) or in vitro (Ishigami et al., submitted). These results strongly suggest that pravastatin does not exhibit a drug interaction with itraconazole because its metabolism is not mediated by CYP3A4.

As described above, most of the studies that investigated the cause of drug interactions have focused on the identification of the enzymes responsible for the metabolism of the tested drugs, and only a few studies have examined the relationship between drug interactions and the physicochemical properties of drugs. One of the most important physicochemical properties of a drug is its partition coefficient ($\log D_{7.0}$), but few studies have examined the relationship between $\log D_{7.0}$ values and the inhibition of drug-metabolizing enzymes. Therefore, in the present study, we investigated the correlation between the $\log D_{7.0}$ values of various HMG-CoA reductase inhibitors and the potential inhibition of P450. We selected CYP3A4 as the CYP isoform to be examined, since this isoform has been reported to be involved in the drug interaction with simvastatin. In the present study, we selected mexazolam, an anxiolytic benzodiazepine, as a substrate.
for CYP3A4. Previous studies with various P450 isoforms expressed in HepG2 cells demonstrated that mexazolam to M-1 via postulated intermediates (Fig. 1) is metabolized mainly by the CYP3A family (Ono et al., 1993).

In the present study, we investigated the inhibitory effects of the lactone and acid forms of various HMG-CoA reductase inhibitors (Fig. 2) on CYP3A4 using mexazolam as a probe to monitor CYP3A4 activity, and we evaluated the correlation between the potential inhibition of CYP3A4 and the logD7.0 values of the inhibitors. In addition, we compared and evaluated the HMG-CoA reductase inhibitors in terms of potential drug interactions.

**Materials and Methods**

**Chemicals and Reagents.** Pravastatin (acid form), pravastatin lactone, simvastatin (lactone form), simvastatin acid (Na⁺ salt), lovastatin (lactone form), lovastatin acid (Na⁺ salt), fluvastatin (acid form), fluvastatin lactone, atorvastatin (acid form), atorvastatin lactone, cerivastatin (acid form), cerivastatin lactone, mexazolam, and a metabolite of mexazolam (M-1) were synthesized at Sankyo Co., Ltd. (Tokyo, Japan). Human liver microsomes were obtained from the International Institute for the Advancement of Medicine (Exton, PA). Polyclonal antibodies for human P450 (anti-CYP2C antiserum from goat, and anti-CYP1A, -CYP2D6, and -CYP3A4 antisera from rabbit) were purchased from Daiichi Pure Chemicals Co., Ltd. (Tokyo, Japan). All other chemicals and reagents used were of analytical grade and were obtained commercially.

**In Vitro Metabolism of Mexazolam.** A final volume (0.2 ml) of a typical enzyme source mixture consisted of 0.04 mg of liver microsomal protein, 2 μmol of potassium phosphate buffer (pH 7.4), 2 μmol of MgCl₂, 0.5 μmol of NADP, 5 μmol of glucose 6-phosphate, and 0.4 units of glucose-6-phosphate dehydrogenase. To the enzyme source preincubated at 37°C for 3 min, mexazolam was added, and the mixture was incubated at 37°C for 15 min. The reaction was terminated by immersing the tubes in boiling water for 1 min, followed by extraction with ethyl acetate, and the extract was concentrated to dryness. Metabolites in brackets are the postulated intermediates that have not yet been isolated.
Mexazolam was incubated for 2 min at 37°C with pooled human liver microsomes (10 male subjects or 10 female subjects, 0.2 mg of protein/ml). Each value represents the mean ± S.E. of triplicate determinations.

Kinetic Analysis of Mexazolam Metabolism. Mexazolam was tested at a final concentration range of 2 to 100 μM in human liver microsomes to determine the kinetic parameters. The production of the mexazolam metabolite determined was fitted to the Hill equation (eq. 1) using a nonlinear regression program (WinNonlin, Scientific Consulting, Inc., Apex, NC) to estimate \( \text{K}_m \), \( \text{V}_{\text{max}} \), and \( n \):

\[
V_0 = V_{\text{max}} \times S^n / (K_m^n + S^n)
\]

where \( V_0 \) is the initial formation rate, \( V_{\text{max}} \) is the maximum metabolic rate, \( S \) is the substrate concentration, \( K_m \) is the substrate concentration showing a half-maximal velocity, and \( n \) is the Hill coefficient. The intrinsic metabolic clearance \( (\text{CL}_{\text{int}}) \) was evaluated using the following equation:

\[
\text{CL}_{\text{int}} = \frac{V_{\text{max}}}{K_m}
\]

For immunoinhibition studies, human liver microsomes (pooled from 10 male or 10 female subjects, 10 mg of protein/ml, 10 μl) were first incubated with antiserum or corresponding control serum (total, 25 μl) at room temperature for 30 min. The mixture was added with the cofactor solution and mexazolam solution (final concentration, 20 μM), and then a final volume of 0.5 ml was incubated in a similar manner as described under In Vitro Metabolism of Mexazolam. Finally, 1 ml of methanol was added to terminate the reaction, and after centrifugation the supernatant was subjected to HPLC.

Inhibition of Mexazolam Metabolism by HMG-CoA Reductase Inhibitors. To define the type of inhibition by HMG-CoA reductase inhibitors on mexazolam metabolism, mexazolam (5–50 μM) was coincubated with various HMG-CoA reductase inhibitors [50 to 400 μM pravastatin (acid form); 20 to 200 μM simvastatin acid, fluvastatin (acid form), atorvastatin (acid form), and cerivastatin (acid form); and 2 to 20 μM simvastatin (lactone form)] in the enzyme source mixture.

The \( 1/V_{\text{int}} \) values obtained for each concentration of HMG-CoA reductase inhibitor were applied to Dixon plots, and the \( K_i \) values were obtained by simultaneous fitting using WinNonlin (eq. 3):

\[
\frac{1}{V_{\text{int}}} = \frac{1}{V_{\text{int}}} + \frac{1}{V_{\text{int}}} \cdot \frac{K_m}{V_{\text{int}}} + \frac{S}{V_{\text{int}}}
\]

where \( "(+I)" \) represents the value after alteration by the drug-drug interaction, and \( S \) and \( I \) represent the concentration of substrate (mexazolam) and inhibitor (HMG-CoA reductase inhibitor), respectively.

In addition, to compare the \( K_i \) values for lactone and acid forms of HMG-CoA reductase inhibitors, HMG-CoA reductase inhibitors (0.1–200 μM) and mexazolam (20 μM) were incubated with human liver microsomes (pooled from 10 female subjects) for 2 min at 37°C, and the amount of the mexazolam metabolite M-1 formed was determined. The \( K_i \) value was calculated by fitting the data to the following equation using WinNonlin:

\[
\frac{V_0}{V_0} = \frac{K_m + S}{K_m + (1 + I/K_i) + S}
\]

Measurement of the logD<sub>7.0</sub> Value of HMG-CoA Reductase Inhibitors. Partition coefficients between phosphate buffer (pH 7.0, Britton Robinson Buffer) and 1-octanol were determined for each drug. Each drug was dissolved in 1-octanol-saturated buffer, and the solution was mixed with buffer-saturated 1-octanol solution. After shaking for 30 min at 25°C, the 1-octanol and buffer layers were separated by
centrifugation, and the drug concentrations in each layer were determined by HPLC as described in Table 1.

The distribution coefficients and logD 7.0 values were calculated from the following equation:

\[
\text{Distribution coefficients} = D_{ow} = \frac{C_o}{C_w} = \log_{10} \frac{D_{ow}}{5}
\]

in which \(C_o\) and \(C_w\) represent the concentration (mol/liter) of test drug in octanol and buffer layer, respectively.

### Results

The Characteristics of Mexazolam Metabolism by Human Liver Microsomes.

The formation of the mexazolam metabolite (M-1) in male and female human liver microsomes was inhibited by addition of anti-CYP3A4 serum to the reaction mixture in a concentration-dependent manner, but was not affected by the addition of anti-CYP1A, -CYP2C or -CYP2D6 sera (Fig. 3, a and b). When 0.25 mg of IgG of anti-CYP3A4 serum was added, the M-1 formation in human liver microsomes was inhibited by about 80% in both males and females.

The formation of M-1 at various concentrations of mexazolam in human liver microsomes was investigated to calculate the kinetic parameters for mexazolam metabolism. As shown in Fig. 4, an Eadie-Hofstee plot showed a convex curve, and kinetic parameters such as \(K_m\), \(V_{max}\), and the Hill coefficient (\(n\)) are shown in Table 2. The \(K_m\) and \(n\) values were similar for males and females, but the \(V_{max}\) value in females was about 2.4 times higher than that in males. In addition, the mean intrinsic clearance (\(V_{max}/K_m\)) in females was about 2.6 times higher than that in males.

Influence of HMG-CoA Reductase Inhibitors on Mexazolam Metabolism in Human Liver Microsomes.

The \(K_i\) values for the

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**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>(K_m) (μM)</th>
<th>(V_{max}) (nmol/min/mg)</th>
<th>(n)</th>
<th>(CL_{int}) (ml/min/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>29.2 ± 10.6</td>
<td>0.68 ± 0.12</td>
<td>1.34 ± 0.26</td>
<td>0.023</td>
</tr>
<tr>
<td>Female</td>
<td>26.5 ± 3.8</td>
<td>1.64 ± 0.11</td>
<td>1.30 ± 0.10</td>
<td>0.062</td>
</tr>
</tbody>
</table>

\(CL_{int}\) intrinsic clearance.
inhibition of mexazolam metabolism in male and female human liver microsomes by HMG-CoA reductase inhibitors were determined by a Dixon plot (Fig. 5, a and b; Table 3). The formation of M-1 from mexazolam in human liver microsomes was not inhibited by pravastatin (acid form), but it was inhibited competitively by other HMG-CoA reductase inhibitors. Also, there were no significant differences in the \( K_i \) values of various inhibitors between males and females. The extent of inhibition was in the following order: simvastatin (lactone form), cerivastatin (acid form), simvastatin acid, atorvastatin (acid form) and fluvastatin (acid form).

The effects of HMG-CoA reductase inhibitors (lactone and acid forms) on the formation of M-1 in human liver microsomes (female) are shown in Fig. 6. In this figure, the extent of inhibition of the formation of M-1 from mexazolam in female human liver microsomes was not inhibited by pravastatin (acid form), but it was inhibited competitively by other HMG-CoA reductase inhibitors. Also, there were no significant differences in the \( K_i \) values of various inhibitors between males and females. The extent of inhibition was in the following order: simvastatin (lactone form), cerivastatin (acid form), simvastatin acid, atorvastatin (acid form) and fluvastatin (acid form).

The effects of HMG-CoA reductase inhibitors (lactone and acid forms) on the formation of M-1 in human liver microsomes (female) are shown in Fig. 6. In this figure, the extent of inhibition of the formation of M-1 from mexazolam in female human liver microsomes was not inhibited by pravastatin (acid form), but it was inhibited competitively by other HMG-CoA reductase inhibitors. Also, there were no significant differences in the \( K_i \) values of various inhibitors between males and females. The extent of inhibition was in the following order: simvastatin (lactone form), cerivastatin (acid form), simvastatin acid, atorvastatin (acid form) and fluvastatin (acid form).

In Fig. 6, Effects of HMG-CoA reductase inhibitors on the formation of M-1 from mexazolam in female human liver microsomes.

Mexazolam (20 \( \mu \)M) was incubated for 2 min at 37°C with pooled human liver microsomes (10 female subjects, 0.2 mg of protein/ml) in the absence or presence of HMG-CoA reductase inhibitors (0.1–200 \( \mu \)M). Control activities were obtained in the absence of HMG-CoA reductase inhibitors. Results (mean ± S.E.) were based on triplicate determinations. □, acid form; ●, lactone form. Solid lines, theoretical curves calculated using the obtained values of \( K_m \), \( n \), and \( K_i \).

Table 3

<table>
<thead>
<tr>
<th>HMG-CoA Reductase Inhibitor</th>
<th>( K_i )</th>
<th>( K_m )</th>
<th>( n )</th>
<th>( K_i )</th>
<th>( K_m )</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin (acid)</td>
<td>No inhibition</td>
<td>No inhibition</td>
<td>No inhibition</td>
<td>No inhibition</td>
<td>No inhibition</td>
<td>No inhibition</td>
</tr>
<tr>
<td>Pravastatin lactone</td>
<td>91.9 ± 8.8</td>
<td>90.8 ± 26.4</td>
<td>10.7 ± 0.6</td>
<td>10.8 ± 1.3</td>
<td>10.0 ± 2.1</td>
<td>12.1 ± 0.6</td>
</tr>
<tr>
<td>Simvastatin (lactone)</td>
<td>3.57 ± 0.48</td>
<td>3.25 ± 0.70</td>
<td>8.57 ± 1.27</td>
<td>14.2 ± 0.7</td>
<td>10.3 ± 1.0</td>
<td>15.0 ± 0.8</td>
</tr>
<tr>
<td>Simvastatin acid</td>
<td>31.9 ± 4.8</td>
<td>23.0 ± 4.4</td>
<td>9.78 ± 1.05</td>
<td>10.7 ± 0.5</td>
<td>6.53 ± 1.04</td>
<td>13.8 ± 0.43</td>
</tr>
<tr>
<td>Fluvastatin (acid)</td>
<td>112 ± 14</td>
<td>90.9 ± 15.0</td>
<td>112 ± 5.6</td>
<td>90.9 ± 15.0</td>
<td>112 ± 5.6</td>
<td>90.9 ± 15.0</td>
</tr>
<tr>
<td>Atorvastatin (acid)</td>
<td>56.8 ± 5.6</td>
<td>63.3 ± 11.8</td>
<td>90.9 ± 15.0</td>
<td>112 ± 14</td>
<td>90.9 ± 15.0</td>
<td>112 ± 14</td>
</tr>
<tr>
<td>Cerivastatin (acid)</td>
<td>18.7 ± 3.6</td>
<td>25.1 ± 3.3</td>
<td>90.9 ± 15.0</td>
<td>112 ± 14</td>
<td>90.9 ± 15.0</td>
<td>112 ± 14</td>
</tr>
</tbody>
</table>

Correlation between logD7.0 and \( K_i \) for CYP3A4 Inhibition of HMG-CoA Reductase Inhibitors. Table 4 summarizes the logD7.0 values of HMG-CoA reductase inhibitors, including the values measured in this study (pravastatin (acid form), atorvastatin (acid form), atorvastatin lactone, fluvastatin (acid form), fluvastatin lactone, and cerivastatin lactone) and previously reported logD7.0 values for other HMG-CoA reductase inhibitors (Watanabe, 1990). The logD7.0 values of all HMG-CoA reductase inhibitors examined were positive, except for the negative value of pravastatin (acid form). All the lactone forms examined showed higher logD7.0 values compared with their corresponding acid forms. The difference in logD7.0 values between the lactone form and the corresponding acid form ranged from 2.9 to 1.9 units, and the mean difference was 2.54 units.

The logD7.0 values of HMG-CoA reductase inhibitors and \( K_i \) values for CYP3A4 inhibition by HMG-CoA reductase inhibitors are shown in Table 4, and the correlation between logD7.0 and \( K_i \) values are plotted in Fig. 7. The extent of inhibition of mexazolam metabolism increased with the inhibitor’s lipophilicity among the acid forms, except for fluvastatin, and water-soluble pravastatin produced no inhibition at all. The same tendency of stronger inhibition with higher lipophilicity was observed among the lactone forms, and the \( K_i \) value of 110 \( \mu \)M for pravastatin lactone was much higher than that of 10 \( \mu \)M or less for atorvastatin lactone, cerivastatin lactone, lovastatin (lactone), simvastatin (lactone), and fluvastatin lactone.
CYP3A4 INHIBITION BY HMG-CoA REDUCTASE INHIBITORS

form; lactone form (simvastatin, lovastatin, etc.) and those administered in the following two groups: those administered as a prodrug, i.e., the active form, i.e., the acid form (pravastatin, fluvastatin, atorvastatin, cerivastatin, etc.). The inhibition of CYP3A4 activity by the lactone forms is much higher than that by the acid forms. This correlated with the higher lipophilicity of the lactone form (logD7.0 value of the lactone forms was 2.54 units higher on average). Among the acid forms, only pravastatin (acid) showed a negative logD7.0 value, while all the other HMG-CoA reductase inhibitors, such as fluvastatin (acid), atorvastatin (acid), and cerivastatin (acid), had positive logD7.0 values, indicating the high lipophilicity of these compounds. This may explain the finding that only pravastatin (acid) did not inhibit CYP3A4 activity (Table 4). The Ki values for the inhibition of CYP3A4 activity were plotted against the logD7.0 values of HMG-CoA reductase inhibitors for every lactone and acid form to determine the correlation between logD7.0 and Ki values (Fig. 7). Consequently, with the exception of fluvastatin (acid) and pravastatin lactone, the extent of inhibition of CYP3A4 activity increased with the inhibitor’s lipophilicity (Fig. 7). Although pravastatin lactone and cerivastatin (acid) have a similar lipophilicity, the inhibition by pravastatin was lower than that by cerivastatin (acid), possibly because the pyridine in cerivastatin (acid) may play a key role in increasing the ability to inhibit CYP3A4 activity, or because the decalin ring structure and 6′-hydroxy group in pravastatin lactone may be responsible for reducing the inhibition activity.

Simvastatin (lactone), lovastatin (lactone), atorvastatin (acid), and cerivastatin (acid), which were reported to be the substrates for CYP3A4 (Vickers et al., 1990; Wang et al., 1991; Boberg et al., 1997; Pruksaritanont et al., 1997; Boyd et al., 2000), inhibit mexazolam metabolism. Simvastatin (lactone), lovastatin (lactone), and atorvastatin (acid) have been reported to exhibit a significant drug interaction with itraconazole, a well known inhibitor of CYP3A4, when both drugs are coadministered (Neuvonen and Jalava, 1996; Kantola et al., 1998; Neuvonen et al., 1998). Therefore, the potential for drug interactions between HMG-CoA reductase inhibitors and other drugs may be related to the metabolism of HMG-CoA reductase inhibitors by CYP3A4. Fluvastatin (acid) has been reported to be an inhibitor of CYP2C9 (Transon et al., 1995, 1996), and in the present study it was shown that fluvastatin (acid) also inhibited microsomal CYP3A4 activity.

Among the HMG-CoA reductase inhibitors examined in the present study, inhibitors with a higher lipophilicity generally tended to be stronger inhibitors of CYP3A4. P450s are involved in the conversion of a lipophilic drug to a more hydrophilic metabolite and excrete it from the body. Taking this into consideration, the present finding may reasonably be explained by the fact that lipophilic drugs have a high affinity for P450s and, as a result, produce inhibition of P450. Therefore, pravastatin is free from a drug interaction due to its high water solubility and its absence of metabolism by P450.

### TABLE 4

LogD7.0 and Ki values of various HMG-CoA reductase inhibitors for the inhibition of mexazolam metabolism by female human liver microsomes

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>LogD7.0</th>
<th>Ki value (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>2.42</td>
<td>115 ± 9</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>4.40</td>
<td>2.13 ± 0.14</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>3.91</td>
<td>2.98 ± 0.18</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>4.2</td>
<td>7.10 ± 0.39</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>3.65</td>
<td>2.54 ± 0.12</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>5.2</td>
<td>2.18 ± 0.10</td>
</tr>
</tbody>
</table>

Discussion

It has been reported from a study with cDNA-expressed human P450 isoforms (CYP1A2, -2A6, -2B6, -2C8, -2C9, -2D6, -2E1, -3A3, -3A4, and -3A5) in HepG2 cells that mexazolam is mainly metabolized by the CYP3A family (Ono et al., 1993). In the present study, the inhibitory activity by anti-CYP1A, -2C, -2D6, and -3A4 antisera on mexazolam metabolism in human liver microsomes was investigated, and it was shown that CYP3A4 was the main CYP isofrom responsible for mexazolam metabolism (Fig. 3). Furthermore, an Eadie- Hofstee plot for the formation of mexazolam metabolite, M-1, showed a convex curve (Fig. 4), which is characteristic of metabolism by the CYP3A family (Ueng et al., 1997). The metabolic activities (testosterone 6β-hydroxylation) of pooled human liver microsomes used in the present study were 3.7 nmol/min/mg of protein and 2.1 nmol/min/mg of protein for female and male human liver microsomes, respectively, i.e., about 1.8 times higher in females than in males (data from International Institute for the Advancement of Medicine). These data are consistent with our finding that the intrinsic metabolic clearance of mexazolam was about 2.3 times higher in females than in males (Table 2). These results indicate that mexazolam is a suitable probe for monitoring CYP3A4 activity.

HMG-CoA reductase inhibitors (Fig. 1) are classified into the following two groups: those administered as a prodrug, i.e., the lactone form (simvastatin, lovastatin, etc.) and those administered in

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Fig. 7. LogD7.0 of HMG-CoA reductase inhibitor and Ki for mexazolam metabolism in human liver microsomes.

Ki values were calculated from data shown in Fig. 6 according to eq. 4. ☀, lactone form. Solid line, linear regression line.

*K* values (mean ± calculated S.D.) were calculated from data shown in Fig. 6 according to eq. 4.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>LogD7.0</th>
<th>Acid</th>
<th>Lactone</th>
<th>Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>2.42</td>
<td>−0.47</td>
<td>115 ± 9</td>
<td>No inhibition</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>4.40</td>
<td>1.88</td>
<td>2.13 ± 0.14</td>
<td>69.6 ± 5.2</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>3.91</td>
<td>1.51</td>
<td>2.98 ± 0.18</td>
<td>179 ± 18</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>3.65</td>
<td>1.75</td>
<td>7.10 ± 0.39</td>
<td>289 ± 44</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>4.2</td>
<td>1.53</td>
<td>2.54 ± 0.12</td>
<td>189 ± 30</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>5.2</td>
<td>2.32</td>
<td>2.18 ± 0.10</td>
<td>46.3 ± 2.1</td>
</tr>
</tbody>
</table>

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Table 4: LogD7.0 and Ki values of various HMG-CoA reductase inhibitors for the inhibition of mexazolam metabolism by female human liver microsomes

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>LogD7.0</th>
<th>Ki value (μM)</th>
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<tr>
<td>Pravastatin</td>
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</tr>
<tr>
<td>Fluvastatin</td>
<td>3.65</td>
<td>2.54 ± 0.12</td>
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<tr>
<td>Cerivastatin</td>
<td>5.2</td>
<td>2.18 ± 0.10</td>
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References


