RESULTS

1. Inhibition of CYP2C8 by Clopidogrel Glucuronide

Clopidogrel glucuronide inhibited CYP2C8 activity toward paclitaxel and amodiaquine with IC50 values of 190 µM and 400 µM, respectively. As shown in Figure 3 and Table 1, preincubation with NADPH-fortified human liver microsomes did not significantly increase its inhibitory effect of CYP2C8.

The results of the experiments shown in Figure 2 are summarized in Table 1.

![Clopidogrel Glucuronide](image)

**Table 1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (µM)</th>
<th>NADPH Preincubation</th>
<th>No Preincubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel Glucuronide</td>
<td>190 µM</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clopidogrel Acid</td>
<td>400 µM</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>19 µM</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

![Clopidogrel Glucuronide](image)

**Figure 1** Chemical structures of clopidogrel, clopidogrel carboxylic acid and clopidogrel acyl glucuronide.

![Clopidogrel Glucuronide](image)

**Figure 2** Evaluation of clopidogrel, clopidogrel acid and clopidogrel acyl glucuronide as direct and metabolism-dependent inhibitor of CYP2C8 activity toward paclitaxel hydroxylation and amodiaquine N-demethylation.

![Clopidogrel Glucuronide](image)

**Figure 3** Direct and metabolism-dependent inhibition of CYP2C8 activity toward paclitaxel hydroxylation and amodiaquine N-demethylation by clopidogrel, clopidogrel acid and clopidogrel glucuronide.

**MATERIALS AND METHODS**

**Chemicals and Reagents**

Clopidogrel, clopidogrel carboxylic acid and clopidogrel glucuronide were purchased from Toronto Research Chemicals (Toronto, Canada). Clopidogrel glucuronide was enzymatically synthesized at XenoTech (Lenexa, KS) as described previously. The molar concentrations of chemicals are indicated in the figures and text of this study.

**Biosynthesis of Clopidogrel Glucuronide**

Given the implication of a pharmacokinetic interaction between clopidogrel and cerivastatin men-

**Figure 1** shows the results obtained with gemfibrozil glucuronide. In this case, a 30% inhibition with NADPH was observed and comparable to those obtained with clopidogrel, whereas no inhibition was observed with gemfibrozil.

**REFERENCES**


**CONCLUSION**

Unlike gemfibrozil glucuronide, which is a potent, mechanism-based inhibitor of CYP2C8, the aglycone of clopidogrel is a weak non-competitive inhibitor toward CYP2C8 that is thus expected to have a slightly more inhibitory effect on CYP2C8 activity toward paclitaxel and amodiaquine in the absence of NADPH. Consistent with this expectation, neither compound significantly inhibited the activity of CYP2C8 toward paclitaxel or amodiaquine in the absence of NADPH.

The results of the experiments shown in Figures 1 and 2 are summarized in Table 1.