EFFECT OF ANTIPSYCHOTIC DRUGS ON HUMAN LIVER CYTOCHROME P-450 (CYP) ISOFORMS IN VITRO: PREFERENTIAL INHIBITION OF CYP2D6

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ABSTRACT:
The ability of antipsychotic drugs to inhibit the catalytic activity of five cytochrome P-450 (CYP) isoforms was compared using in vitro human liver microsomal preparations to evaluate the relative potential of these drugs to inhibit drug metabolism. The apparent kinetic parameters for enzyme inhibition were determined by nonlinear regression analysis of the data. All antipsychotic drugs tested competitively inhibited dextromethorphan O-demethylation, a selective marker for CYP2D6, in a concentration-dependent manner. Thioridazine and perphenazine were the most potent, with IC50 values (2.7 and 1.5 μM) that were comparable to that of quinidine (0.52 μM). The estimated K_i values for CYP2D6-catalyzing dextorphan formation were ranked in the following order: perphenazine (0.8 μM), thioridazine (1.4 μM), chlorpromazine (6.4 μM), haloperidol (7.2 μM), fluphenazine (9.4 μM), risperidone (21.9 μM), clozapine (39.0 μM), and cis-thiothixene (65.0 μM). No remarkable inhibition of other CYP isoforms was observed except for moderate inhibition of CYP1A2-catalyzed phenacetin O-deethylation by fluphenazine (K_i = 40.2 μM) and perphenazine (K_i = 65.1 μM). The estimated K_i values for the inhibition of CYP2C9, 2C19, and 3A4 were >300 μM in almost all antipsychotics tested. These results suggest that antipsychotic drugs exhibit a striking selectivity for CYP2D6 compared with other CYP isoforms. This may reflect a remarkable commonality of structure between the therapeutic targets for these drugs, the transporters, and metabolic enzymes that distribute and eliminate them. Clinically, coadministration of these medicines with drugs that are primarily metabolized by CYP2D6 may result in significant drug interactions.
specific substrates of CYP1A2, CYP2D6, CYP2C9, CYP2C19, and CYP3A using human liver microsomes (HL) in vitro.

Materials and Methods

Chemicals. Chlorpromazine, pethidine, phenfenazine, thioridazine, cis-thiothixene, haloperidol, clozapine, phenacetin, acetaminophen, dextromethorphan hydrobromide, tolbutamide, quinidine sulfate, glucose 6-phosphate (G-6-P), glucose 6-phosphate dehydrogenase (G-6-PDH), β-nicotinamide adenine dinucleotide phosphate, and EDTA were purchased from Sigma Chemical Co. (St. Louis, MO). Risperidone was obtained from Research Diagnostics, Inc. (Flanders, NJ). 4-Methylhydroxytolbutamide was purchased from Ultrafine Chemicals (Manchester, England) and levalloipramine from U.S.P.C. (Rockville, MD). Dextrotoothmoran and 3-methoxymorphinan were obtained from Hoff- man-La Roche Inc. (Nutley, NJ). Omeprazole and 5-hydroxyomeprazole were generous gifts from Dr. Tommy Anderson (Clinical Pharmacology, Astra Hassle AB, Möndal, Sweden). N-(4-hydroxyphenyl)butanamide was kindly provided by Dr. John Strong (Division of Clinical Pharmacology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Rockville, MD). All other chemicals and reagents used were of the highest commercially available quality.

HL. Human liver tissues (n = 11), medically unsuitable for liver transplantation, were acquired under the auspices of the Washington Regional Transplant Consortium (Washington, DC) and frozen at –80°C within 3 h of the cross-clamp time. HL were prepared as described previously (Ko et al., 1997) and protein concentrations were determined by the Bradford method of Pollard et al. (1978). The microsomal pellets were resuspended to a protein concentration of 10 mg/ml in reaction buffer (0.1 M sodium and potassium phosphate, 1.0 mM EDTA, 5.0 mM MgCl2, pH 7.4) and some of the microsomal preparations were mixed together with others using equal volumes of each preparation used (mixed human liver, MHL). Microsomal suspensions were stored at –80°C and thawed before study.

Inhibition Studies. The effects of antipsychotic drugs on the metabolism of five different CYP isoform-specific substrates were studied: phenacetin O-deethylation for CYP1A2 (Tassaneeyakul et al., 1993), dextromethorphan O-demethylation for CYP2D6 (Broly et al., 1989), tolbutamide 4-methylhydroxylation for CYP2C9 (Relling et al., 1990), omeprazole 5-hydroxylation (Chiba et al., 1993; Balian et al., 1995; Ko et al., 1997), and dextrotoothmoran N-demethylation for CYP3A (Gorski et al., 1994).

In all experiments, pethidine, thioridazine, cis-thiothixene, haloperidol, clozapine, and piperidrone were dissolved and diluted serially in ethanol. For the incubation of these antipsychotic drugs, ethanol was removed by evaporation to dryness in the 1.5-ml microfuge tube using a Speedvac SC110 model RH40–12 (Savant Instruments Inc., Farmingdale, NY) and reconstituted in phosphate buffer. Chlorpromazine and phenfenazine were dissolved in ethanol and serial diluted with distilled water. The final concentration of antipsychotic drugs tested ranged from 1 to 100 μM and that of ethanol was less than 0.1% in 250 μl of reaction volume. The reaction mixtures were warmed at 37°C for 5 min before adding microsomes, then incubated for 30 or 60 min for the measurement of different CYP isoform activities. The incubation time and amount of microsomes were determined to be in the linear range for metabolite formation rate, which was expressed as the quantity of metabolite formed per unit of protein concentration and time.

The CYP1A2-catalyzed O-deethylation of phenacetin (Tassaneeyakul et al., 1993) was measured by a minor modification of the method described by Ko et al. (1997). The incubation mixtures (final volume, 250 μl) contained NADPH-regenerating system (1.3 mM β-nicotinamide adenine dinucleotide phosphate, 3.3 mM G-6-P, 3.3 mM MgCl2, and 1 U/ml G-6-PDH) and phenacetin (25–150 μM) with or without antipsychotic drug (concentration 1–100 μM) in 0.1 M phosphate buffer (pH 7.4). Reactions were started by adding microsomes (HL–7, -14, and -G, final concentration 0.25 mg/ml), incubated at 37°C for 30 min, and terminated by placing the samples on ice and adding 1.0 ml of acetonitrile with 2 μg of internal standard, N-(4-hydroxyphenyl)butanamide. The assay of acetaminophen and phenacetin in reaction mixtures were carried out as described previously (Ko et al., 1997). The enzyme activity was determined by acetaminophen formation rate from phenacetin and was expressed as the quantity of acetaminophen formed per unit of protein concentration and time.

The CYP2D6- and 3A-catalyzed dextromethorphan O- and N-demethyl-
where $\alpha$ is the factor by which $K_m$ changes when inhibitor occupies the enzyme and the values of $\alpha$ and $K_i$ entered into these formulae were generated from this study. For these calculations, the substrate concentration [S] was assumed as 1/10 of $K_m$ value because the therapeutic range of plasma drug concentration is usually much less than its $K_m$ value. The concentrations of antipsychotic drugs used in these calculations were the median values of the therapeutic range of plasma drug concentrations (Javaid, 1994; Hardman et al., 1995) and 100-fold concentrations of these median values with the assumption of high accumulation of all antipsychotics in liver tissue (Dinovo et al., 1978; Forsman et al., 1981).

## Results

The apparent metabolic constants ($K_m$, $V_{max}$) of HL used in these experiments were calculated from the nonlinear regression of the data on specific CYP isoform-catalyzed formation of metabolites (Table 1). Compared with $K_m$ values, $V_{max}$ values of the metabolic reactions tested showed large variations between different livers. All antipsychotic drugs preferentially inhibited CYP2D6-catalyzed dextromethorphan $O$-demethylation compared with other CYP isoform-catalyzed reactions (Fig. 1). Among the antipsychotic drugs tested, thioridazine and perphenazine were the most potent inhibitors and decreased the dextromethorphan formation rate to 26.5 and 19.7% of control activity at 10 $\mu$M, respectively. The inhibitory potency of these drugs on dextromethorphan $O$-demethylation was comparable to the inhibitory effect of 10 to 25 $\mu$M quinidine (Fig. 2). The estimated mean IC$_{50}$ values for thioridazine and perphenazine were 2.7 ± 0.5 and 1.5 ± 0.3 $\mu$M, respectively. The IC$_{50}$ of quinidine, a potent CYP2D6 inhibitor, was estimated to be 0.52 ± 0.2 $\mu$M under these conditions. The estimated IC$_{50}$S of chlorpromazine, fluphenazine, and haloperidol were 9.7, 16.3, and 14.4 $\mu$M, respectively (Fig. 2). Cis-thiothixene, clozapine, and risperidone exhibited weaker inhibition than the other drugs tested, with mean IC$_{50}$S estimated to be 136.6, 92.2, and 39.1 $\mu$M, respectively.

The double reciprocal plots, Dixon plots, and secondary plots of slope of double reciprocal plots versus inhibitor concentration of chlorpromazine, fluphenazine, cis-thiothixene, clozapine, and risperidone showed the same type of inhibition. Representative plots for chlorpromazine are presented in Fig. 3. All these plots indicated that chlorpromazine, fluphenazine, cis-thiothixene, clozapine, and risperidone competitively inhibited dextromethorphan $O$-demethylation. In addition, the inhibitory effects of these antipsychotic drugs were best fitted to a pure competitive inhibition model by nonlinear regression analysis using WinNonlin.

The double reciprocal plot, Dixon plot, and secondary plot versus antipsychotic concentration showed hyperbolic curves when thioridazine, perphenazine, and haloperidol were incubated as inhibitors of dextromethorphan $O$-demethylation. The plots for perphenazine are shown in Fig. 4. Partial competitive inhibition was the best model to describe these data.

### Table 1

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrate</th>
<th>Concentration $\mu$M</th>
<th>Microsomal Preparations</th>
<th>$K_m$ $\mu$M</th>
<th>$V_{max}$ mmol/min/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>dextromethorphan</td>
<td>10–75</td>
<td>HL-10</td>
<td>22.3 ± 4.0</td>
<td>0.20 ± 0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MHL-B$^e$</td>
<td>320.8 ± 75.4</td>
<td>0.84 ± 0.14</td>
</tr>
<tr>
<td>CYP3A</td>
<td>dextromethorphan</td>
<td>100–750</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Each value indicates the mean ± S.D. of three to eight different determinations.

$^b$ Mixed HL-5, -9, -10.


$^d$ Mixed HL-8, -11, -14.

$^e$ Mixed HL-8, -11, -14.
risperidone showed similar patterns with those of chlorpromazine. Each data point represents an average of duplicates. Double reciprocal plots versus chlorpromazine concentration. Double reciprocal plot, Dixon, and secondary plots of fluphenazine, cis-thiothixene, clozapine, and risperidone showed very weak inhibition of CYP2C9-catalyzed tolbutamide 4-methylhydroxylation, with estimated mean $K_i$ values of 174.6, 350, and 327.3 $\mu$M, respectively (Fig. 1C). The CYP2C19-catalyzed formation of 5-hydroxymeprazole and CYP3A-catalyzed formation of 3-methoxymorphinan from dextromethorphan were not inhibited by any of the antipsychotics tested (Fig. 1, D and E). The $K_i$ values were estimated to be >300 $\mu$M from the best-fitted competitive or noncompetitive inhibition models.

The $K_i$ values of antipsychotic drugs were obtained from nonlinear regression using the appropriate pure or partial competitive inhibition models (Table 2). Perphenazine and thioridazine showed the lowest $K_i$ values at around 1 $\mu$M. Mean $K_i$ values of chlorpromazine, haloperidol, and fluphenazine were 6.3, 7.2, and 9.4 $\mu$M, respectively. The drug with the highest $K_i$ was cis-thiothixene (65 $\mu$M). Of note, the atypical antipsychotics clozapine and risperidone, with estimated $K_i$ values of 39 and 21.9 $\mu$M, were weaker inhibitors than the conventional antipsychotic drugs tested.

A 20-min preincubation increased the inhibition by cis-thiothixene, haloperidol, and clozapine on CYP2D6-catalyzed dextromethorphan $O$-demethylation by 20% over control without preincubation (Fig. 5). No significant increase of inhibition was observed from the preincubation of thioridazine, perphenazine, fluphenazine, chlorpromazine, or risperidone.

The antipsychotic drugs had no remarkable inhibitory effect on CYP1A2-, CYP2C9-, CYP2C19-, or CYP3A-catalyzed reactions with the exception of moderate inhibition by fluphenazine and perphenazine of CYP1A2-catalyzed phenacetin $O$-deethylation (Fig. 1B). A competitive inhibition model was best-fitted to the data for inhibition by fluphenazine and perphenazine of CYP1A2-catalyzed phenacetin $O$-deethylation. The estimated mean $K_i$ values were 40.2 $\mu$M for fluphenazine and 65.1 $\mu$M for perphenazine.

Thioridazine, fluphenazine, and clozapine showed very weak inhibition of CYP2C9-catalyzed tolbutamide 4-methylhydroxylation, with estimated mean $K_i$ values of 174.6, 350, and 327.3 $\mu$M, respectively (Fig. 1C). The CYP2C19-catalyzed formation of 5-hydroxymeprazole and CYP3A-catalyzed formation of 3-methoxymorphinan from dextromethorphan were not inhibited by any of the antipsychotics tested (Fig. 1, D and E). The $K_i$ values were estimated to be >300 $\mu$M from the best-fitted competitive or noncompetitive inhibition models.

**Discussion**

In this study, all of the antipsychotic drugs tested strongly and competitively inhibited the CYP2D6-catalyzed $O$-demethylation of dextromethorphan, but they had no notable effect on the other CYP isoforms evaluated. It was interesting that clozapine, which is metabolized mainly by CYP1A2 and CYP3A4 (Eiermann et al., 1997), also showed competitive inhibition of CYP2D6-catalyzed dextromethorphan $O$-demethylation with a $K_i$ of 39.0 $\mu$M, but no remarkable inhibition of CYP1A2- and CYP3A-catalyzed enzyme reactions. There is a precedent for inhibition of CYP2D6 by drugs whose metabolism is not catalyzed by it. Quinidine and halofantrine compete for the substrate-binding site of CYP2D6 but are not metabolized by it (Otton et al., 1988; Halliday et al., 1995). Pimozide, an antipsychotic drug, is another example. Pimozide is metabolized by CYP3A and CYP1A2 and not by CYP2D6, but it does inhibit CYP2D6 (Desta et al., 1998). From the data obtained from this study, it seems clear that almost all antipsychotic drugs have the potential to inhibit CYP2D6. Many of these drugs (chlorpromazine, fluphenazine, perphenazine, haloperidol, thioridazine, risperidone, trifluperidol, and zuclopenthixol) are also metabolized by this CYP isoform (Taylor and Lader, 1996; Michaudes, 1998). It follows that antipsychotic drugs may develop pharmacokinetic drug interactions with concomitantly administered antipsychotics and antidepressants (amitriptyline, imipramine, nortriptyline, desipramine, clomipramine, maprotiline, trazodone, paroxetine, mirtazapine).

**Fig. 2. Comparison of the inhibitory effect of antipsychotic drugs on CYP2D6-catalyzed dextromethorphan $O$-demethylation with that of quinidine.**

HL-10 and -29, and MHL-D were incubated with 25 $\mu$M dextromethorphan and quinidine (1, 10, 25 $\mu$M) or antipsychotic drug (25 $\mu$M). All data represent mean ± S.E. of percent control activity. Abbreviations are Quin, quinidine; PPZ, perphenazine; TRD, thioridazine; CPZ, chlorpromazine; HAL, haloperidol; FPZ, fluphenazine; RIS, risperidone; CZP, clozapine; cTH, cis-thiothixene.

The antipsychotic drugs had no remarkable inhibitory effect on CYP1A2-, CYP2C9-, CYP2C19-, or CYP3A-catalyzed reactions with dextromethorphan (10 –25 $\mu$M) in the absence (○) or presence of 1 (■), 10 (▲), 25 (●), 50 (+), 75 (▪), or 100 (+) $\mu$M chlorpromazine. A, representative double reciprocal plot obtained from 30-min incubation of human liver microsomes (HL-29, 0.25 mg/ml) with an NADPH regenerating system and dextromethorphan (10 –25 $\mu$M) in the absence (○) or presence of 1 (■), 10 (▲), 25 (●), 50 (+), 75 (▪), or 100 (+) $\mu$M chlorpromazine. B, Dixon plot obtained from 30-min incubation with 10 (○), 25 (■), 50 (▲), or 75 (▪) $\mu$M of dextromethorphan in the absence or presence of chlorpromazine (1–100 $\mu$M). C, secondary plot of slopes taken from double reciprocal plots versus chlorpromazine concentration. Double reciprocal plot, Dixon, and secondary plots of fluphenazine, cis-thiothixene, clozapine, and risperidone showed similar patterns with those of chlorpromazine. Each data point represents an average of duplicates.

**Fig. 3. Inhibitory effect of chlorpromazine on CYP2D6-catalyzed dextromethorphan $O$-demethylation in HL.**

A, representative double reciprocal plot obtained from 30-min incubation of human liver microsomes (HL-29, 0.25 mg/ml) with an NADPH regenerating system and dextromethorphan (10 –25 $\mu$M) in the absence (○) or presence of 1 (■), 10 (▲), 25 (●), 50 (+), 75 (▪), or 100 (+) $\mu$M chlorpromazine. B, Dixon plot obtained from 30-min incubation with 10 (○), 25 (■), 50 (▲), or 75 (▪) $\mu$M of dextromethorphan in the absence or presence of chlorpromazine (1–100 $\mu$M). C, secondary plot of slopes taken from double reciprocal plots versus chlorpromazine concentration. Double reciprocal plot, Dixon, and secondary plots of fluphenazine, cis-thiothixene, clozapine, and risperidone showed similar patterns with those of chlorpromazine. Each data point represents an average of duplicates.
A, representative double reciprocal plot obtained from 30-min incubation of human liver microsomes (HL-29, 0.25 mg/ml) with an NADPH regenerating system and dextromethorphan (10–25 μM) in the absence (●) or presence of 1 (▲), 10 (▲), 25 (▲), 50 (+), 75 (●), or 100 (+) μM perphenazine. B, hyperbolic Dixon plot obtained from 30-min incubation with 10 (●), 25 (▲), 50 (▲), or 75 (●) μM of dextromethorphan in the absence or presence of perphenazine (1–100 μM). C, hyperbolic secondary plot of slopes taken from double reciprocal plots versus perphenazine concentration. Double reciprocal plot, Dixon, and secondary plots of thioridazine and haloperidol are similar to those of perphenazine. Each data point represents an average of duplicates.

**TABLE 2**

In vitro inhibition of CYP2D6-catalyzed dextromethorphan O-demethylation by antipsychotic drugs

<table>
<thead>
<tr>
<th>Antipsychotic Drug</th>
<th>Type of Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perphenazine</td>
<td>Partial Competitive</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Partial Competitive</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Competitive</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Partial Competitive</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Competitive</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Competitive</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Competitive</td>
</tr>
<tr>
<td>cis-Thiothixene</td>
<td>Competitive</td>
</tr>
</tbody>
</table>

*Each value indicates mean ± S.D. obtained from three different livers.

**FIG. 5.** Effect of preincubation on inhibition of CYP2D6-catalyzed dextromethorphan O-demethylation by antipsychotic drugs in human liver microsomal incubations.

Dextromethorphan O-demethylation was measured with or without 20-min preincubation of antipsychotics with preparation HL-10. Each value indicates average of duplicate determinations. Abbreviations: PPZ, perphenazine; TRD, thioridazine; CPZ, chlorpromazine; HAL, haloperidol; FPZ, fluphenazine; RIS, risperidone; CZP, clozapine; cTH, cis-thiothixene.

Differences in the \( K_i \) values may be caused partly by differences in the substrates used (Boobis, 1995).

To estimate the clinical relevance of CYP2D6 inhibition by antipsychotics, we compared the expected relative inhibitory potency in vivo to the known therapeutic plasma concentrations of antipsychotic drugs (Javaid, 1994; Hardman et al., 1995). For this purpose, we calculated the potency of inhibition relative to the therapeutic concentration \((II/K)\), a measure of specificity as well as potency of an inhibitor (Boobis, 1995) and the predicted percent inhibition as described (Table 3). Thioridazine showed the highest \( II/K_i \) with a value of 1.46. Those of chlorpromazine and clozapine were 0.06 and 0.04, respectively. The \( II/K_i \) of the remaining drugs were as follows: perphenazine (0.0069) > haloperidol (0.0039) > risperidone.
have a common structure that allows interaction with CYP2D6. Strobel et al. (1993) described a pharmacophore model for CYP2D6 in which at least one aromatic ring and a tertiary nitrogen atom that is protonated under physiologic condition are required. Most antipsychotic drugs tested do have an aromatic ring and tertiary nitrogen. Secondly, it is possible that antipsychotics inhibit CYP2D6 activity in the brain and that this may contribute to their therapeutic effects. CYP2D6 has been reported to be expressed in human brain and its pharmacological and immunological characteristics are similar to those of CYP2D6 from bovine and human liver tissues (Niznik et al., 1990; Gilham et al., 1997). Thirdly, the considerable evidence of structural and functional homogeneity between CYP2D6 and the dopamine transporter supports the concept that there may be a similarity between the therapeutic target of these drugs and substrates for CYP2D6 (Tyndale et al., 1991; Hiroi et al., 1997). This link appears analogous to the noted similarities between substrates of CYP3A4 and of P-glycoprotein (Zhang et al., 1998; Fischer et al., 1998).

In conclusion, we have conducted a comprehensive evaluation of the effects of eight antipsychotic drugs on five CYP isoforms across a wide range of substrate and antipsychotic concentrations using in vitro human liver microsomal preparations. All the antipsychotics we tested inhibited CYP2D6, but showed no notable inhibition of CYP1A2, CYP2C9, CYP2C19, or CYP3A. These findings suggest that all antipsychotic drugs have the potential to cause pharmacokinetic drug interactions with drugs that are metabolized by CYP2D6, but it is equally important to note that they are unlikely to cause significant pharmacokinetic interactions with drugs that are primarily metabolized by other CYP isoforms. Some antipsychotics are sufficiently selective that they may be able to serve as selective CYP2D6 inhibitors. Lastly, our data suggest that all antipsychotics have a common structure that allows binding to CYP2D6.

### References


<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Concentration [(\mu M)]</th>
<th>Inhibitory Potency</th>
<th>Predicted % Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>2.05</td>
<td>1.46±3</td>
<td>56.27</td>
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<td>Chlorpromazine</td>
<td>0.345</td>
<td>0.05±4</td>
<td>4.74</td>
</tr>
<tr>
<td>Clozapine</td>
<td>1.377</td>
<td>0.03±3</td>
<td>3.11</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>0.005</td>
<td>0.0069</td>
<td>0.58</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.028</td>
<td>0.0039</td>
<td>0.34</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.015</td>
<td>0.0007</td>
<td>0.06</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.0024</td>
<td>0.0003</td>
<td>0.02</td>
</tr>
<tr>
<td>cis-Thiothixene</td>
<td>0.019</td>
<td>0.0003</td>
<td>0.03</td>
</tr>
</tbody>
</table>

\(^{a}\) Median values of the reference plasma concentration range (Hardman et al., 1995; Javaid, 1994).

\(^{b}\) Intrinsic inhibitory potency = \(\frac{[I]}{K_{i}}\).

\(^{c}\) % Inhibition = \(\frac{\text{S}}{\text{S}}\) \(\times\) 100/\(\text{S}\) for competitive inhibition, \(\frac{\text{S}}{\text{S}}\) \(\times\) 100/\(\text{S}\) for partial competitive inhibition, which is calculated with the assumption of substrate concentration \(\frac{\text{S}}{\text{S}}\) \(\times\) 100/\(\text{S}\). Average \(K_{i}\) values in Table 2 were used for the calculation.


