

Results

The human carboxylesterases hCE1 and hCE2 hydrolyzed prasugrel to R-95913. Figure 24(A) depicts the fit of standard Michaelis-Menten kinetics to the data for hCE1, with an apparent K_m of $9.25 \pm 0.78 \mu\text{M}$ and an apparent V_{max} of $0.725 \pm 0.035 \text{ nmol of R-95913/min}/\mu\text{g of protein}$. The results obtained using hCE2 were not fit to any standard kinetic model, as seen in (B). The sponsor described the data using 2 models. The first data set (prasugrel concentrations of 0.855 and 40.5 μM) was described with the Hill equation, K_s of $11.1 \pm 2.8 \mu\text{M}$, and V_{max} of $19.0 \pm 2.8 \text{ nmol of R-95913/min}/\mu\text{g of protein}$, and $N = 1.42 \pm 0.12$. The second portion of the curve resembles an inhibition plot and as such the data between 27.4 and 109 μM was modeled for inhibition to yield an apparent IC_{50} of $76.5 \pm 2.7 \mu\text{M}$.

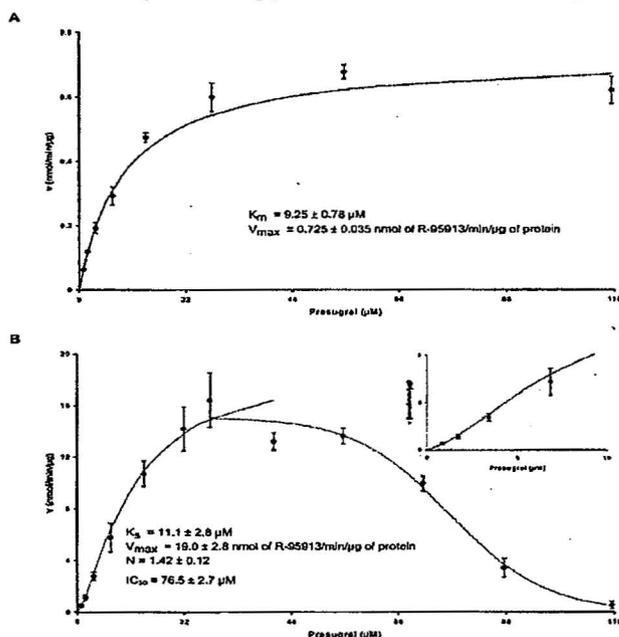


Figure 24. Formation of R-95913 by hCE1 (A) and hCE2 (B). The points with the error bars represent the average and standard error, while the lines represent the best model fit of their respective kinetic models. Inset shows the sigmoidicity of the Hill kinetics.

The hydrolysis of prasugrel with both hCE1 and hCE2 have similar K_m and K_s values. The hydrolysis activity (V_{max}) of hCE2 was about 26-times higher than that of hCE1. This is consistent with the published data regarding carboxylesterase substrate preferences (Sato et al. 2002).

Comment:

1. The raw data of this study were not available for the review.
2. This study determined the ability of expressed and purified human carboxylesterases 1 (hCE1) and 2 (hCE2), the dominant forms in the liver and intestine, respectively, to hydrolyze prasugrel to R-95913 in vitro. The study showed that these human carboxylesterases efficiently catalyze the conversion of prasugrel to R-95913, with 26 times the rate of turnover by hCE2 compared to hCE1.

4.1.3 Examination of Effects of LY640315 on CYP1A2 and CYP3A in Primary Cultures of Human Hepatocytes

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Date: August 2005

Objectives	To examine the ability of R-95913 to induce the catalytic activities associated with CYP1A2 and CYP3A in primary cultures of human hepatocytes from four separate donors.
Method of incubation	Primary cultures of human hepatocytes were treated for 72 hours with R-95913 at concentrations ranging from 0.1 to 100 μ M, and the effects of treatment on catalytic activities associated with CYP1A2 and CYP3A were compared to those activities in vehicle control cultures (0.1% DMSO). Omeprazole and rifampicin were used to demonstrate induction responses for CYP1A2 and CYP3A activity. The cells were incubated with 100 mcM testosterone or 2mcM 7-ethoxy-resorufin (with 3mM salicylamide) in HMM for 30 minutes. Cells were harvested by scraping in 1.0 mL 100 mM potassium phosphate buffer (pH 7.4), and were stored at approximately -80°C prior to determination of protein content.
Assay	HPLC with UV detection: the Lilly Global Chromatography Data System (GCDS), version 2, Eli Lilly and Company.

Results

At 0.1, 1.0, 10, and 100 μ M concentrations of R-95913, preparations in 3 human hepatocytes (HH) showed some changes in CYP1A2-mediated EROD activity, examples in 2 HH are shown below:

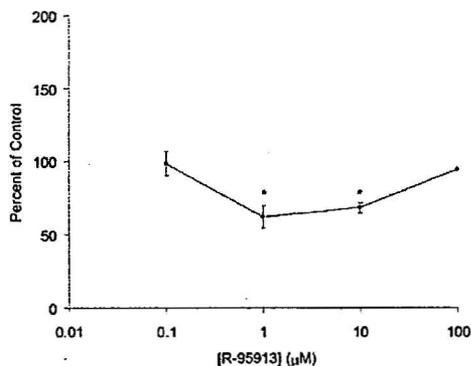


Figure 1: The effect of R-95913 on ethoxyresorufin O-deethylase activity in human hepatocyte preparation HH994.

Activities are expressed as percent of control \pm standard error of the mean. Mean control activity (n = 3) was 0.212 pmol/min/mg, and omeprazole-treated cells had 226-fold greater activity than controls.

*P-value less than 0.05.

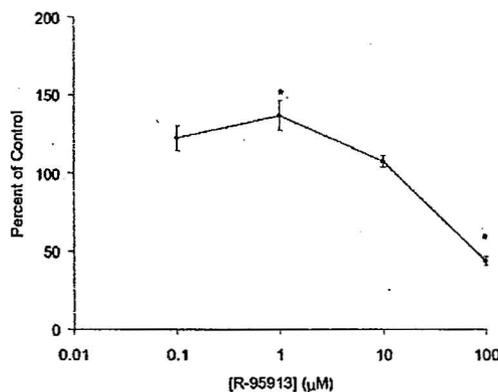


Figure 2: The effect of R-95913 on ethoxyresorufin O-deethylase activity in human hepatocyte preparation HH997.

Activities are expressed as percent of control \pm standard error of the mean. Mean control activity (n = 3) was 0.787 pmol/min/mg, and omeprazole-treated cells had 4-fold greater activity than controls.

In the last HH (not shown), the differences were not statistically different from control activity at any of the concentrations examined.

All three preparations showed statistically significant increases in CYP3A-mediated activity. Donor preparation HH993 showed approximately 8-fold induction at 10 μM R-95913 relative to controls, but activities returned toward controls at 100 μM . Concentration-dependent induction of up to about 6-fold was observed at all concentrations of R-95913 in preparation HH994. Concentration-related induction of up to about 3-fold was evident in preparation HH998 (not shown) at concentrations of 10 and 100 μM .

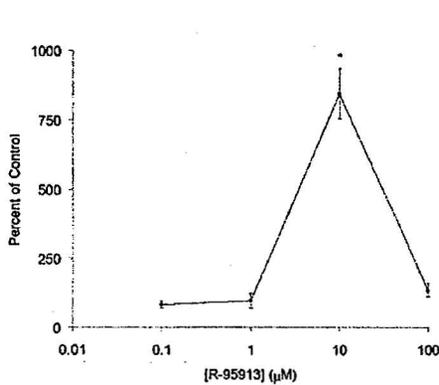


Figure 4: The effect of R-95913 on testosterone 6 β -hydroxylase activity in human hepatocyte preparation HH993.

Activities are expressed as percent of control \pm standard error of the mean. Mean control activity ($n = 3$) was 78.3 pmol/min/mg, and rifampicin-treated cells had 25-fold greater activity than that of control.

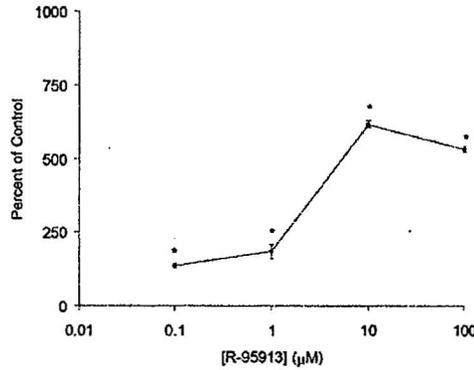


Figure 5: The effect of R-95913 on testosterone 6 β -hydroxylase activity in human hepatocyte preparation HH994.

Activities are expressed as percent of control \pm standard error of the mean. Mean control activity ($n = 3$) was 209 pmol/min/mg, and rifampicin-treated cells had 14-fold greater activity than that of control.

Comment:

This was a pilot study of the effects of catalytical activities for CYP1A2 and CYP3A in cultures of human hepatocytes. The results give some indication that the parent drug, prasugrel, may have a potential to induce hepatic CYP3A.

4.1.4 In Vitro Interaction of LY640315 (CS-747) Metabolites R-95913, R-138727, and R-106583 with Human Cytochrome P450 CYP3A

Study 2002IV-DI002

Conducted by: James A. Eckstein, Jessica L. Fayer, John B. Heim, Steve C. Kasper, Barbara J. Ring, and Steven A. Wrighton

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December 2002

Objective	To evaluate the abilities of the prasugrel active metabolite R-138727 and two inactive metabolites, R-95913 and R-106583, to inhibit metabolism mediated by CYP3A
Incubation Conditions Midazolam:	Time: 1-minute Assay of 1'-hydroxy midazolam by LC/MS/MS. Human liver microsomes (0.1 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and midazolam (2.5 μ M) in the absence or presence of R-138727 or R-106583 (0.5, 2.5, 10, 50, or 200 μ M) or R-95913 (10, 20, 40, or 60 μ M) midazolam: 2.5, 5.0, 10, 25, or 50 μ M. Formation of 1'-hydroxy midazolam under these conditions was linear with respect to time.
Incubation Conditions Testosterone:	Time: 10 min Assay of 6 β -hydroxy testosterone by HPLC. R-138727 was not examined (co-elution of substances related to R-138727 with the 6 β -hydroxy testosterone). Human liver microsomes (0.075 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and testosterone (5.0 μ M) in the absence or presence of R-106583 (0.5, 2.5, 10, 50, or 200 μ M) or R-95913 (25, 100, 150, or 200 μ M), and testosterone (5.0, 25, 50, 150, or 250 μ M). Formation of 6 β -hydroxy testosterone under these conditions was linear with respect to time.
Data analysis	WinNonlin Professional, version 3.1 was used to estimate parameters: Km, Vmax, and Ki and the standard errors

Results

The formation of 1'-hydroxy midazolam by R-95913 was described with a competitive inhibition model with

Km 4.5 ± 0.7 μ M

Vmax 921 ± 48 pmol/min/mg protein and

Ki 12.6 ± 2.2 μ M.

There was $\leq 11\%$ inhibition of CYP3A-mediated midazolam 1'-hydroxylation by R-138727 (see below)

Table 12. Effect of R-138727 In Vitro on the CYP3A Mediated Metabolism of Midazolam to 1'-Hydroxy Midazolam

Concentration of R-138727 (μM)	1'-Hydroxy Midazolam Formation (pmol/min/mg)	Percent of Control
0	348	100
0.5	343	99
2.5	338	97
10	368	106
50	334	96
200	311	89

and $\leq 18\%$ inhibition of CYP3A-mediated midazolam 1'-hydroxylation by R-106583 (see below).

Table 13. Effect of R-106583 In Vitro on the CYP3A Mediated Metabolism of Midazolam to 1'-Hydroxy Midazolam

Concentration of R-106583 (μM)	1'-Hydroxy Midazolam Formation (pmol/min/mg)	Percent of Control
0	348	100
0.5	355	102
2.5	328	94
10	346	100
50	286	82
200	312	90

The formation of 6 β -hydroxy testosterone was described with a simple Michaelis-Menten kinetics by the human microsomal mixture in the inhibition study with R-95913, yielding an apparent K_m value of $42.5 \pm 5.0 \mu\text{M}$ and V_{max} of $2259 \pm 88 \text{ pmol/min/mg protein}$.

The inhibition of testosterone metabolism by R-95913 was found to model best to noncompetitive inhibition yielding an apparent K_i value of $55.9 \pm 4.2 \mu\text{M}$. There was $\leq 24\%$ inhibition of CYP3A-mediated testosterone 6 β -hydroxylase activity by R-106583 (see below).

Table 14. Effect of R-106583 In Vitro on the CYP3A Mediated Metabolism of Testosterone to 6 β -Hydroxy Testosterone

Concentration of R-106583 (μM)	6 β -Hydroxy Testosterone Formation (pmol/min/mg)	Percent of Control
0	88.3	100
0.5	70.7	80
2.5	80.8	92
10	87.8	100
50	84.6	96
200	67.1	76

Comments:

1. The predicted in vivo inhibition by R-95913 of the CYP3A was calculated based on the highest reported mean C_{max} value for R-95913 as 616 ng/mL ($1.9 \mu\text{M}$) following a 60 mg loading dose of prasugrel. An apparent K_i value for R-95913 was estimated

as $12.6 \pm 2.2 \mu\text{M}$ for the inhibition hydroxylation of midazolam and as $55.9 \pm 4.2 \mu\text{M}$ for the inhibition of testosterone 6β -hydroxylation. The prediction of inhibition of CYP3A metabolism by R-95913 was about 13%. Although the assumptions from the in vitro situation cannot be extrapolated to the in vivo processes, the inhibition is weak and may not be of clinical significance.

2. The raw data of the experiments and model fittings are not available for review.

4.1.5 In Vitro Interaction of LY640315 (CS-747) Metabolites R-95913, R-138727, and R-106583 with Human Cytochromes P450 CYP2D6, CYP2C9, CYP2C19, and CYP1A2

Study 2002IV-DI003

Conducted by: James A. Eckstein, Jessica L. Fayer, John B. Heim, Steve C. Kasper, Barbara J. Ring, and Steven A. Wrighton

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February 2003

Objective	To evaluate the abilities of the prasugrel active metabolite R-138727 and two inactive metabolites, R-95913 and R-106583, to inhibit metabolism mediated by CYP2D6, CYP2C9, CYP2C19, CYP1A2.
Incubation Conditions Bufuralol (2D6)	Human liver microsomes (15mcg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and bufuralol (5 μ M) in the absence or presence of R-138727 or R-106583 (0.7 to 267 μ M) or R-95913 (10 to 200 μ M) bufuralol: 5.0 to 100 μ M.
Incubation Conditions Diclofenac (2C9)	Human liver microsomes (50mcg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and Diclofenac (2.5 μ M) in the absence or presence of R-138727 or R-106583 (0.5 to 200 μ M) or R-95913 (10 to 200 μ M) Diclofenac bufuralol: 2.5 to 50 μ M.
Incubation Conditions S-Mephenytoin (2C19)	Human liver microsomes (0.1mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and S-Mephenytoin (5 μ M) in the absence or presence of R-138727 or R-106583 (0.5 to 200 μ M) or R-95913 (0.5 to 20 μ M) S-Mephenytoin: 0.5 to 100 μ M.
Incubation Conditions (1A2)	Human liver microsomes (0.1 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and Phenacetin (12.5 μ M) in the absence or presence of R-106583, R-138727 or R-95913 (0.5 to 200 μ M)
Data analysis	WinNonlin Professional, version 3.1 was used to estimate parameters: Km, Vmax, and Ki and the standard errors

Results

The 1'-hydroxylation of bufuralol has been shown to be catalyzed by polymorphically expressed CYP2D6 and has been used as a form-selective catalytic activity for CYP2D6. The formation of 1'-hydroxy bufuralol was found to follow simple Michaelis-Menten kinetics by the human microsomal mixture in the inhibition study with R-95913, yielding an apparent Km value of $9.8 \pm 0.8 \mu\text{M}$ and Vmax of $99.9 \pm 3.2 \text{ pmol/min/mg protein}$. Table 15 shows that the inhibition of bufuralol metabolism by R-95913 was found to model best to mixed competitive/non-competitive inhibition, yielding an apparent Ki value of $40.8 \pm 4.4 \mu\text{M}$. The formation of 1'-hydroxy bufuralol was not significantly inhibited by R-138727 or R-106583, yielding = 10% (sponsor's Table 2) and = 4% (not shown) inhibition, over the range of concentrations studied, 0.7 to 267 μM .

Table 2: Effect of R-138727 In Vitro on the CYP2D6 Mediated Metabolism of Bufuralol to 1'-Hydroxy Bufuralol

Concentration of R-138727 (μM)	1'-Hydroxy Bufuralol Formation ($\text{pmol}/\text{min}/\text{mg}$)	Percent of Control
0	42.8	100
0.7	43.4	102
3.3	43.6	102
13	42.7	100
67	41.8	98
267	38.5	90

The low K_m human cytochrome P450 responsible for the biotransformation of diclofenac to 4'-hydroxy diclofenac has been shown to be CYP2C9. The kinetics of formation of 4'-hydroxy diclofenac by the human microsomal mixture in the inhibition study with R-95913 yielded apparent K_m and V_{max} values of $5.2 \pm 0.4 \mu\text{M}$ and $1361 \pm 27 \text{ pmol}/\text{min}/\text{mg}$ protein, respectively. The best fit model describing the inhibition of the formation of 4'-hydroxy diclofenac was found to be competitive for R-95913, yielding an apparent K_i value of $82.3 \pm 10.3 \mu\text{M}$. The formation of 4'-hydroxy diclofenac was not significantly inhibited by R-138727 or R-106583, yielding = 47% (sponsor's Table 4) and = 29% (not shown) inhibition, respectively, over the range of concentrations studied, 0.5 to 200 μM .

Table 4: Effect of R-138727 In Vitro on the CYP2C9 Mediated Metabolism of Diclofenac to 4'-Hydroxy Diclofenac

Concentration of R-138727 (μM)	4'-Hydroxy Diclofenac Formation ($\text{pmol}/\text{min}/\text{mg}$)	Percent of Control
0	361	100
0.5	360	100
2.5	343	95
10	358	99
50	252	70
200	190	53

S-mephenytoin metabolism to 4'-hydroxy S-mephenytoin has been demonstrated to be a form-selective catalytic activity for human CYP2C19. The kinetics of formation of 4'-hydroxy S-mephenytoin by the human microsomal mixture in the inhibition study with R-95913 yielded apparent K_m and V_{max} values of $23.4 \pm 2.6 \mu\text{M}$ and $23.7 \pm 1.4 \text{ pmol}/\text{min}/\text{mg}$ protein, respectively. The inhibition of S-mephenytoin metabolism by R-95913 was found to model best to competitive inhibition, yielding an apparent K_i value of $7.2 \pm 0.9 \mu\text{M}$ (Table 15). The formation of 4'-hydroxy S-mephenytoin was not significantly inhibited by R-138727 or R-106583, yielding = 40% (sponsor's Table 6) and = 13% (not shown) inhibition, over the range of concentrations studied, 0.5 to 200 μM .

Table 6: Effect of R-138727 In Vitro on the CYP2C19 Mediated Metabolism of S-Mephenytoin to 4'-Hydroxy S-Mephenytoin

Concentration of R-138727 (μM)	4'-Hydroxy S-Mephenytoin Formation ($\text{pmol}/\text{min}/\text{mg}$)	Percent of Control
0	4.7	100
0.5	4.7	101
2.5	4.4	94
10	4.6	98
50	4.1	89
200	2.8	60

Table 15. Inhibition of CYP2D6, CYP2C9, and CYP2C19 Form- Selective Catalytic Activities In Vitro by R-95913

Form-Selective Catalytic Activity	Type of Inhibition	Apparent K_i
CYP2D6: Bufuralol 1'-Hydroxylation	mixed competitive/noncompetitive	40.8 ± 4.4 μ M
CYP2C9: Diclofenac 4'-Hydroxylation	competitive	82.3 ± 10.3 μ M
CYP2C19: S-Mephenytoin 4'-Hydroxylation	competitive	7.2 ± 0.9 μ M

Phenacetin metabolism to acetaminophen has been shown to be catalyzed by CYP1A2 and was used as a form-selective catalytic activity for human CYP1A2 in this study. The sponsor's Table 9 presents the reductions in phenacetin O-deethylase activity by 19% that was observed over the 0.5 to 200 μ M range of concentrations studied for R-138727.

Table 9: Effect of R-138727 In Vitro on the CYP1A2 Mediated Metabolism of Phenacetin to Acetaminophen

Concentration of R-138727 (μ M)	Acetaminophen Formation (pmol/min/mg)	Percent of Control
0	139	100
0.5	139	100
2.5	150	108
10	125	90
50	131	95
200	112	81

The results for the inactive metabolites are not shown here.

R-95913 exhibited competitive inhibition of CYP2D6 catalyzed 1'-hydroxy bufuralol formation, yielding an apparent K_i value of 40.8 μ M. The maximum peak plasma concentration (C_{max}) achieved in Study H7T-EW-TAAE was 616 ng/mL (1.9 μ M) after a loading dose of 60 mg prasugrel. Therefore, for in vitro to in vivo extrapolation of potential CYP2D6 inhibition, the maximum plasma concentration of R-95913 estimated to be present at the enzyme site (1.9 μ M) might result in a 4% inhibition of CYP2D6 mediated metabolism in vivo. At concentrations up to 267 μ M, neither R-138727 nor R-106583 were found to be significant inhibitors of bufuralol.

Substrates for CYP2C9 include tolbutamide, phenytoin, non-steroidal anti-inflammatory agents such as diclofenac, and S-warfarin (Rettie et al. 2000). R-95913 exhibited competitive type inhibition with an apparent K_i value of 82.3 μ M. When this K_i value was entered into the formula for percent inhibition, it was predicted that the maximum concentration of R-95913 estimated to be present at the enzyme site (1.9 μ M) might result in a 2% inhibition of CYP2C9 mediated metabolism in vivo. At concentrations up to 200 μ M, neither R-138727 nor R-106583 were found to be significant inhibitors of diclofenac metabolism. These results suggest that R-95913, R-138727, and R-106583 would be unlikely to significantly inhibit the metabolism of co-administered CYP2C9 substrates.

R-95913 is a competitive inhibitor of CYP2C19 mediated S-mephenytoin 4'-hydroxylation, yielding an apparent K_i value of 7.2 μM . When this K_i value was entered into the formula for percent inhibition with the maximum estimated plasma concentration of R-95913, 21% inhibition of CYP2C19 mediated metabolism was predicted. At concentrations up to 200 μM , neither R-138727 nor R-106583 were found to be significant inhibitors of S-mephenytoin metabolism. These results suggest that R-95913, R-138727, and R-106583 would be unlikely to significantly inhibit the metabolism of co-administered CYP2C19 substrates.

Phenacetin metabolism to acetaminophen, a marker catalytic activity for CYP1A2, was used to study the interaction of R-95913, R-138727, and R-106583 and this enzyme. At concentrations up to 200 μM , these compounds were not significant inhibitors of acetaminophen formation. These results suggest that R-95913, R-138727, and R-106583 would be unlikely to significantly inhibit the metabolism of co-administered CYP1A2 substrates.

The sponsor concluded that none of the prasugrel metabolites tested (R-95913, R-138727, or R-106583) is expected to cause significant inhibition of the metabolism of co-administered drug whose primary route of metabolism is through CYP2D6, CYP2C9, CYP2C19, or CYP1A2. However, a prediction concerning the extent of inhibition expected in vivo from these in vitro data cannot be definitively modeled without information about the concentrations of R-95913, R-138727, and R-106583 at the active sites of these enzymes.

4.1.6 Identification of the Human Cytochromes P450 Responsible for the Formation of R-138727, the Active Metabolite of LY640315, from R-95913

Study 2003IV-EI001

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December 2003

Objective	To determine the human CYPs responsible for the formation of R-138727 from R-95913.
Incubation Conditions: Human Liver Microsomes	Human liver microsomes (25mcg protein) in 100 mM sodium phosphate buffer (pH 7.4), 5 mM GSH, 1nM NADPH and R-95913, with or without the addition of selective inhibitors of reactions mediated by 2C9 (sulfaphenazole, 10 μ M), 2C19 (omeprazole, 10 μ M), or 3A (ketoconazole, 2.0 μ M)
Incubation Conditions Expressed CYPs	Microsomes (0.025 mg) expressing CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4, 5 mM GSH, 2 mM NADPH, and 20 μ M R-95913 in 100 mM Na ₂ HPO ₃ , pH 7.4 for 15 min.
Data Analyses	WinNonlin, Version 3.1. Goodness of fit: randomness of the residuals, RSS, the 95% confidence limits, and SE with different weighting of the data. Univariate correlation analyses: JMP, Version 4.0.2, SAS Institute, Inc., Cary, NC)

Results:

Nine expressed CYPs were examined for their abilities to form R-138727.

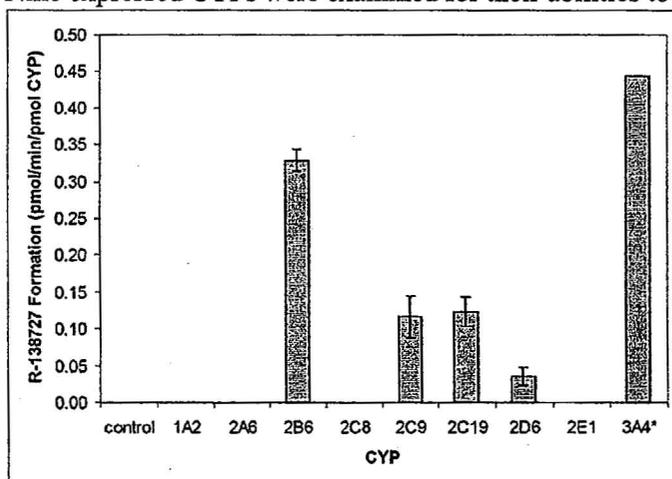


Figure 25. Formation of R-138727 by expressed CYPs following incubation with 20 μ M R-95913.

Five CYPs were capable of forming R-138727, with the following rank order of catalytic activities: CYP3A4 > CYP2B6 > CYP2C9 ~ CYP2C19 > CYP2D6. Kinetic parameters were determined for the four most active of these CYPs (Table below).

Table 16. Enzyme Kinetic Profiles for the Formation of R-138727 from R-95913 in Expressed CYPs

Expressed CYP	K_m (μM)	V_{max} ($\text{pmol}/\text{min}/\text{pmol}$)	CL_{int} (V_{max}/K_m) ($\mu\text{L}/\text{min}/\text{pmol}$)
2B6	2.3 ± 0.4	0.39 ± 0.02	0.17
2C9	11 ± 2	0.37 ± 0.02	0.03
2C19	3.8 ± 0.7	0.35 ± 0.01	0.09
3A4	21 ± 3	1.4 ± 0.1	0.07

The conversion rates of R-95913 to R-138727 were determined as indicated in Methods in triplicate incubations. Values for K_m and V_{max} are reported as parameter estimate \pm the standard error of the parameter estimate.

The addition of 2 μL of antibody had little effect on R-138727 formation. The addition of 4 μL of antibody inhibited the formation of R-138727 by 44% to 47% in HLD, HLG, and HLP. The maximum inhibition observed was following the addition of 8 μL of antibody, where the formation of R-138727 was inhibited by 48% to 52% in each of the four livers tested.

Table 17. Percent Inhibition of R-138727 Formation in the Presence of 2, 4, or 8 μL of Ascites Fluid Containing Monoclonal Antibodies to CYP2B6

Microsomal Sample	2 μL	4 μL	8 μL
HLC	-5.0 %	-1.4 %	51 %
HLD	-16 %	46 %	48 %
HLG	-24 %	44 %	50 %
HLP	-4.9 %	47 %	52 %

Inhibition percentages were determined by comparing the R-138727 formation rates of samples containing ascites fluid with the CYP2B6 antibody to samples containing control ascites fluid. Formation rates were determined as indicated in Methods and were the means of triplicate determinations. Negative values indicate that the mean formation rates of R-138727 in the samples containing the CYP2B6 antibody were greater than for the samples containing only control ascites fluid.

A monoclonal antibody that inhibits CYP2B6 and chemical inhibitors selective for CYP2C9 (sulfaphenazole), CYP2C19 (omeprazole), and CYP3A (ketoconazole) were examined for their effects on the formation of R-138727 in human liver microsome preparations. The inhibitory antibody for CYP2B6 and ketoconazole were found to substantially inhibit R-138727 formation.