as 12.6 ± 2.2 μM for the inhibition hydroxylation of midazolam and as 55.9 ± 4.2 μM for the inhibition of testosterone 6ß-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
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285
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 μM) in the absence or presence of R-138727 or R-106583 (0.7 to 267 μM) or R-95913 (10 to 200 μM) bufuralol: 5.0 to 100 μM.
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 μM) in the absence or presence of R-138727 or R-106583 (0.5 to 200 μM) or R-95913 (10 to 200 μM) Diclofenac bufuralol: 2.5 to 50 μM.
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 μM) in the absence or presence of R-138727 or R-106583 (0.5 to 200 μM) or R-95913 (0.5 to 20 μM) S-Mephenytoin: 0.5 to 100 μM.
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 μM) in the absence or presence of R-106583, R-138727 or R-95913 (0.5 to 200 μM)
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 ± 0.8 μM and Vmax of 99.9 ± 3.2 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 ± 4.4 μM. 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 (pmol/min/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 Km 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 Km and Vmax values of 5.2 ± 0.4 μM and 1361 ± 27 pmol/min/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 Ki value of 82.3 ± 10.3 μM. 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 (pmol/min/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 Km and Vmax values of 23.4 ± 2.6 μM and 23.7 ± 1.4 pmol/min/mg protein, respectively. The inhibition of S-mephenytoin metabolism by R-95913 was found to model best to competitive inhibition, yielding an apparent Ki value of 7.2 ± 0.9 μM (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 (pmol/min/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 μM
CYP2C9: Diclofenac 4'-Hydroxylation	competitive	82.3 ± 10.3 μM
CYP2C19: *S*-Mephenytoin 4'-Hydroxylation	competitive	7.2 ± 0.9 μM

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 μM 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 (μM)	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 Ki value of 40.8 μM. The maximum peak plasma concentration (Cmax) achieved in Study H7T-EW-TAAE was 616 ng/mL (1.9 μM) 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 μM) might result in a 4% inhibition of CYP2D6 mediated metabolism in vivo. At concentrations up to 267 μM, 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 Ki value of 82.3 μM. When this Ki value was entered into the formula for percent inhibition, it was predicted that the maximumconcentration of R-95913 estimated to be present at the enzyme site (1.9 μM) might result in a 2% inhibition of CYP2C9 mediated metabolism in vivo. At concentrations up to 200 μM, 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 Ki value of 7.2 μM. When this Ki 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 R95913, 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
Conducted by: James A. Eckstein, Jessica L. Fayer, John B. Heim, Steve C. Kasper, Barbara J. Ring, and Steven A. Wrighton
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285
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 μM), 2C19 (omeprazole, 10 μM), or 3A (ketoconazole, 2.0 μM)
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 μM R-95913 in 100 mM Na2HPO3, 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.

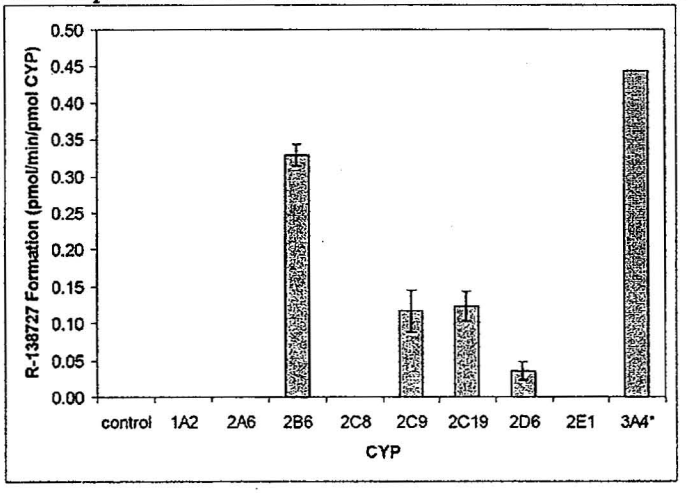


Figure 25. Formation of R-138727 by expressed CYPs following incubation with 20 μM R-95913.

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} (pmol/min/pmol)	CL_{int} (V_{max}/K_m) (μL/min/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 ± 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.

Table 18. Percent Inhibition of R-138727 Formation in the Presence of Sulfaphenazole, Omeprazole, or Ketoconazole

Microsomal Sample	Sulfaphenazole (CYP2C9)	Omeprazole (CYP2C19)	Ketoconazole (CYP3A)
		2.0 µM R-95913	
HLC	-24 %	21 %[a]	29 %[a]
HLD[b]	5.6 %	40 %	50 %[a]
HLG	-30 %	31 %	55 %[a]
HLL[b]	-40 %	8.6 %[a]	8.6 %[a]
		20 µM R-95913	
HLC	13 %	8.3 %	33 %
HLD[b]	32 %	-37 %	47 %
HLG	12 %	11 %	83 %
HLL[b]	24 %	29 %	86 %[a]

[a] The LLOQ level was reached. Minimum inhibition percentages are indicated. Inhibition percentages are likely actually greater than the values indicated.

[b] HLD and HLL are deficient in CYP2C19.

Minor and more variable inhibition was observed with sulfaphenazole and omeprazole. To evaluate the effect of expression of CYP3A subfamily members CYP3A4 and CYP3A5 on R-138727 formation, enzyme kinetic parameters for the formation of R-138727 were determined in microsomes prepared from insect cells and engineered to express CYP3A4 + CYP reductase or CYP3A5 + CYP reductase.

Table 19. Enzyme Kinetic Profiles for the Formation of R-138727 by Expressed CYP3A4 and CYP3A5 Supersomes□

Expressed CYP	K_m (µM)	V_{max} (pmol/min/pmol CYP)	CL_{int} (V_{max}/K_m) (µL/min/pmol CYP)
CYP3A4	18 ± 2	0.50 ± 0.04	0.03
CYP3A5	48 ± 11	1.1 ± 0.2	0.02

In vitro, these two enzymes exhibited similar efficiency of converting R-95913 to R-138727, so the presence or absence of the polymorphically expressed CYP3A5 in patients would be expected to be of little consequence for this biotransformation.

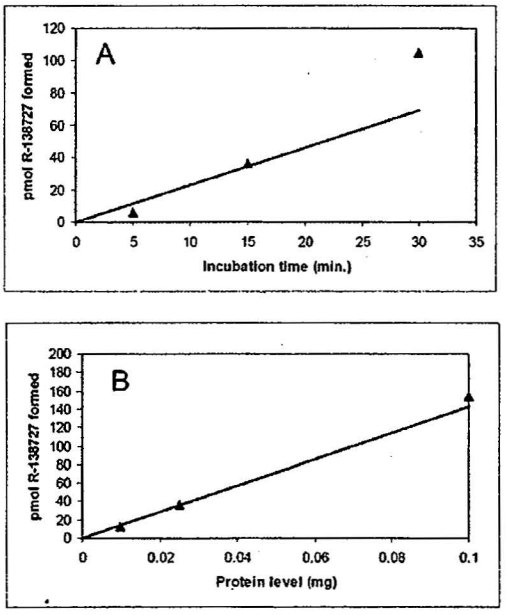


Figure 26. Formation of R-138727 from R-95913 (10 μM) with respect to time (A) and with respect to protein (B).

Reviewer's Comments

1. The sponsor' conclusion that CYP3A is the major enzyme responsible for the formation of R-138727 from R-95913 is reasonable.
2. The raw data of this study were not submitted for review.

4.1.7 Characterization of the Human Cytochromes P450 Responsible for the Formation of the Isomer Sets (RS/RR and SR/SS) of R-138727, the Active Metabolites of LY640315, from R-95913

Reported by: Jessica A. Baker, Olukayode A. Oluyedun and Yingying Guo
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285
September 2007

Objective	To further determine the contribution of each enzyme in the production of different stereo-isomers of R-138727.
Incubation Conditions	Metabolism of R-95913 to the two sets of isomers (RS/RR and SR/SS) of R-138727 was accomplished in vitro with 100 µL incubations containing the indicated concentrations of R-95913 with human liver microsomes, GSH, and NADPH. Incubation mixtures containing 0.0125 mg (0.125 mg/mL) human liver microsomal protein in 100 mM sodium phosphate buffer, pH 7.4, 5 mM GSH (an additive which maintains monothiols, reduces disulfides, and provides an environment necessary for the detection of R-138727 [Fayer 2003]), and R-95913 were preincubated for approximately three minutes at 37°C. Reactions were initiated with the addition of 2 mM NADPH and stopped after 10 min with acetonitrile containing 20 ng/mL internal standard (D4-R-138727).
Enzyme kinetics	Estimation of the apparent parameters for the formation of the sets of isomers of R-138727 by human liver microsomal sample BHMQ was determined in three separate experiments with each sample in triplicate. The concentrations of R-95913 ranged from 0.625 µM to 80 µM in one experiment and 1.25 µM to 160 µM in the other two experiments.
Expressed CYPs	Microsomes prepared from insect cells engineered to over-express cDNA for human CYPs and CYP reductase were examined for their abilities to form the two isomer sets of R-138727. Incubations (100 µL) were performed under linear rate conditions with microsomes (0.0125 mg; 0.125 mg/mL) specific for CYP2B6, CYP2C9, CYP2C19, CYP3A4 or CYP3A5, 5 mM GSH, 2 mM NADPH, and R-95913 in 100 mM sodium phosphate buffer, pH 7.4 for 10 minutes at approximately 37°C.
Assay validation	Internal standard: D4-R-138727 Validation range: 0.5 nM to 512 nM of R-138727 in 200 µL final concentration. For CYP3A5 expressed enzyme studies a validation was performed over a range of 0.70 nM to 714 nM.
Data analysis	WinNonlin Professional, version 5.0.1 was used to estimate parameters: Km, Vmax, and Ki and the standard errors

Results:

The rate of formation of the two isomer sets of R-138727 by BHMQ microsomes over a range of R-95913 concentrations was determined. The human liver microsomal sample BHMQ exhibited apparent Km values of 25.4 µM, and 28.2 µM for isomer sets RS/RR and SR/SS respectively, for R-138727 formation. The corresponding CLint values in these microsomal samples were 6.95 and 4.23 µL/minute/mg protein (Table below).

Table 20. Enzyme Kinetic Profiles for the Formation of RS/RR and SR/SS R-138727 from R-95913 in Human Liver Microsomes

Microsomal Sample	R-138727 Isomer set	K_m (μM)	V_{max} (pmol/min/mg)	Cl_{int} (V_{max}/K_m) (μL/min/mg)
BHMQ	RS/RR	25.4 ± 1.0	176 ± 8	6.95
BHMQ	SR/SS	28.2 ± 0.7	119 ± 6	4.23

The enzymes capable of forming RS/RR of R-138727, in rank order, were CYP2B6 > CYP3A4 ~ CYP2C19 > CYP3A5 > CYP2C9 and SR/SS of R-138727, in rank order, were CYP2B6 > CYP2C19 > CYP3A4 > CYP3A5>CYP2C9 (Figure below). The ratios of the RS/RR to SR/SS isomer sets after incubation with 20 μM R-95913 for CYP2B6, CYP2C19, CYP2C9, CYP3A4, and CYP3A5 were 0.64, 0.85, 0.49, 1.6, and 1.6, respectively, indicating that only CYP3A4 and CYP3A5 generate more RS/RR over SR/SS isomers.

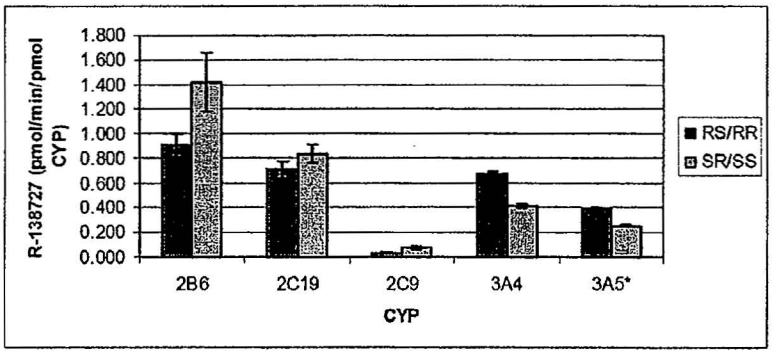


Figure 27 Formation of isomer sets of R-138727 by expressed CYPs following incubation with 20 μM R-95913.

Enzyme kinetic parameters for the formation of the two isomer sets of R-138727 by expressed CYP2B6, CYP2C19, CYP2C9, CYP3A4, and CYP3A5 are shown in the table below.

Table 21. Enzyme Kinetic Profiles for the Formation of RS/RR and SR/SS R-138727 from R-95913 in Expressed Supersomes™

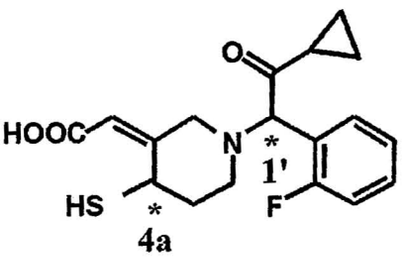
Microsomal Sample	R-138727 Isomer set	K_m (μM)	V_{max} (pmol/min/pmol)	Cl_{int} (V_{max}/K_m) (μL/min/pmol)
CYP2B6	RS/RR	4.52 ± 0.82	1.15 ± 0.04	0.255
CYP2B6	SR/SS	4.62 ± 0.67	1.75 ± 0.13	0.379
CYP2C19	RS/RR	4.98 ± 0.39	0.873 ± 0.096	0.175
CYP2C19	SR/SS	4.56 ± 0.33	0.978 ± 0.102	0.215
CYP2C9	RS/RR	26.8 ± 2.3	0.087 ± 0.007	0.003
CYP2C9	SR/SS	19.8 ± 1.0	0.147 ± 0.011	0.007
CYP3A4	RS/RR	15.2 ± 1.3	1.13 ± 0.07	0.074
CYP3A4	SR/SS	8.12 ± 0.62	0.569 ± 0.033	0.070
CYP3A5*	RS/RR	128 ± 8	2.94 ± 0.23	0.023
CYP3A5*	SR/SS	21.8 ± 1.2	0.563 ± 0.035	0.026

Michaelis-Menten kinetic parameters for the formation of isomers of R-138727 were determined in pooled human liver microsomes from four different donors. The kinetic analyses were consistent with a single enzyme being responsible for the conversion of R-95913 to either isomer set, with the apparent Km values of 25.4 and 28.2 μM, and intrinsic clearances of 6.95 and 4.23 μl/min/mg, respectively, for the isomer sets RS/RR and SR/SS.
The specific CYPs were assessed for their abilities to produce both isomer sets of R-138727. Following incubations with 20 μM R-95913, all five CYPs formed the RS/RR isomer set of R-138727. The ratios of RS/RR to SR/SS isomer sets generated at this concentration were approximately 0.6:1, 0.8:1, 0.5:1, 1.6:1 and 1.6:1, respectively, for CYP2B6, 2C19, 2C9, 3A4 and 3A5, suggesting CYP3A4 and 3A5 preferentially form RS/RR while 2B6, 2C19 and 2C9 prefer SR/SS formation.
Considering the relative abundance of each CYP enzyme in human liver and proximal small intestine, the CYP3A subfamily would be suggested as the enzymes predominantly responsible for the formation of both isomer sets of R-138727. The role of CYP3A in R-138727 formation in vivo is further supported by the higher RS/RR intrinsic clearance value than that of SR/SS in human liver microsomes and the observation that only CYP3A is capable of forming more RS/RR than SR/SS among all CYPs examined. Relative to CYP3A5, CYP3A4 appears to be a relative high affinity but low capacity enzyme in formation of both isomer sets of R-138727.

Sponsor's Conclusions

1. The members of the CYP3A subfamily are primarily responsible for the conversion of R-95913 to both isomer sets of R-138727, with RS/RR being preferentially formed over SR/SS isomers at the ratio of 1.6.
2. CYP2B6, CYP2C9, and CYP2C19 are also capable of forming either isomer set of R-138727. These results imply that the effects of altered activity of any of the CYPs involved in R-138727 isomer formation in vivo would be compensated for by the abilities of multiple CYPs to form the active metabolites.
3. At the same time, factors other than the stereoselective formation of R-138727 enantiomers by CYPs may contribute to their stereoselective disposition.

From study TAAD:
The ratios of the distereomers found in the plasma samples are also listed in the bioanalytical data summary section of this report. The RS-and RR-diastereomers of R-138727 comprised about 84%, while the SR and SS diastereomers accounted for about 16%, of the R-138727 present in plasma. The RS- and RR-diastereomers of R-138727 (R-125690 and R-125689, respectively) are the most potent of the 4 isomers with IC50 values of 0.19 μM and 3.1 μM. The IC50 values of the other two diastereomers are 28 μM (R-125687) and 36 μM (R-125688). The ratios of the R-138727 stereoisomers were consistent among subjects, regardless of the dose, time of sample collection, or whether the blood was sampled after the first CS-747 dose or after a few weeks of therapy.



Compd No.	4a	1'
R-125690	R	S
R-125689	R	R
R-125687	S	S
R-125688	S	R

R-99224 (SR+RS)

R-138727 (SR+RS+RR+SS)

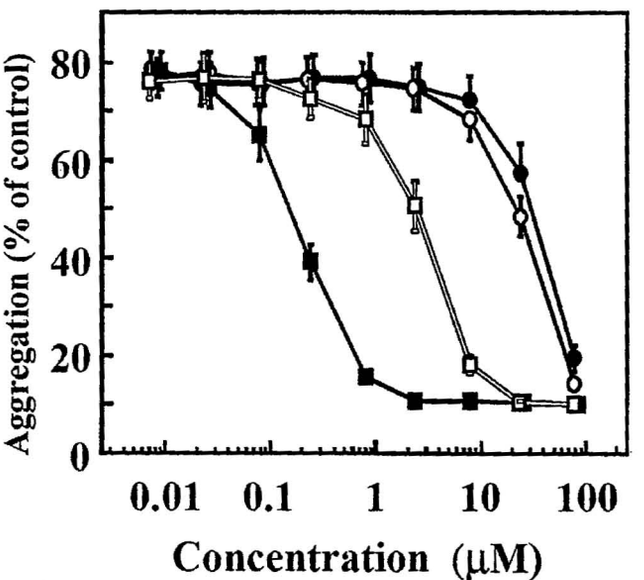


Figure 28. The structures of R-138727 stereoisomers and their relative activity towards inhibition of platelet aggregation.