

Predictive Flip Regression: A Technique for QSAR of Derivatives of Symmetric Molecules

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Received May 11, 2005

We have for the first time used the flip regression technique to predict the activity of unknown drugs given a substantial series of derivatives of symmetrical molecules such as benzene, with known activity. As descriptors we have used quantum theoretic parameters such as orbital energies and the orientation of π -orbital nodes and Mulliken charges of atoms. Flip regression is a technique for dealing with multiply substituted derivatives of symmetric molecules, such as phenethylamine or benzenesulfonamide. The method has been tried on two large data sets: thrombin inhibitors and carbonic anhydrase (CA) inhibitors. Multiple validation tests were run, randomly splitting the data into training and test sets and successfully predicting the activity of the test sets, with predictive R^2 of around 0.9 for the thrombin inhibitors and 0.7 for the CA inhibitors.

INTRODUCTION

When carrying out QSAR on flat, symmetrical, usually aromatic molecules, symmetry considerations often dictate that alternative orientations be examined. For phenethylamines, for example, there are five substitution sites on the benzene nucleus. If substituents with property P_i were introduced to site i ($i = 2-6$), an equation may be developed: $\log A = \sum_i C_i P_i + C_0$, where A is activity and C_i are constants to be determined by regression techniques. It must be remembered, however, that, for example, 2-methoxyphenethylamine is identical with 6-methoxyphenethylamine, so the equation must predict the same activity for both molecules. At first sight it may appear that C_2 must equal C_6 and C_3 must equal C_5 , but that this is not the case becomes apparent when considering 2,3,4-trimethoxyamphetamine and 2,4,5-trimethoxyamphetamine. Simply equating the C values would predict the same activity for both these substances, but experimentally one of these is a potent hallucinogen and the other is inactive.¹

The problem of symmetry seems to have been first recognized by Kishida and Manabe² in the context of bifunctional benzenesulfonamides. They handled it using a computer program that swapped descriptor values, in a way very similar to one of our procedures. Other authors have handled the symmetry problem by ignoring it altogether,³ restricting the substitution pattern of the compounds studied⁴⁻⁷ introducing indicator variables for crowding, or by introducing classical statistical interaction variables.⁸ None of these options is entirely satisfactory. The first introduces ambiguity as to numbering the ring, the second severely restricts the compounds that can be studied, and the third and fourth can become complex in highly substituted cases. A similar

Table 1. Sulfonylguanidines ($\text{RSO}_2\text{N}=\text{C}(\text{NH}_2)_2$) **A1–A25** Prepared in the Present Study, with Their Inhibition Data against Human Thrombin

R	compound	K_i^a (nM)
p-F-C ₆ H ₄ –	A1	240
p-Cl-C ₆ H ₄ –	A2	225
p-Br-C ₆ H ₄ –	A3	220
p-I-C ₆ H ₄ –	A4	210
p-CH ₃ -C ₆ H ₄ –	A5	290
p-O ₂ N-C ₆ H ₄ –	A6	180
m-O ₂ N-C ₆ H ₄ –	A7	190
o-O ₂ N-C ₆ H ₄ –	A8	320
3-Cl-4-O ₂ N-C ₆ H ₃ –	A9	160
p-AcNH-C ₆ H ₄ –	A10	195
p-H ₂ N-C ₆ H ₄ –	A11	95
m-H ₂ N-C ₆ H ₄ –	A12	107
C ₆ F ₅ –	A13	146
o-HOOC-C ₆ H ₄ –	A14	240
m-HOOC-C ₆ H ₄ –	A15	121
p-HOOC-C ₆ H ₄ –	A16	104
o-HOOC-C ₆ Br ₄ –	A17	225
p-CH ₃ O-C ₆ H ₄ –	A18	240
2,4,6-(CH ₃) ₃ -C ₆ H ₂ –	A19	255
4-CH ₃ O-3-H ₂ N-C ₆ H ₃ –	A20	103
2-HO-3,5-Cl ₂ -C ₆ H ₂ –	A21	152
4-Me ₂ N-C ₆ H ₄ -N=N-C ₆ H ₄ –	A22	134
5-dimethylamino-1-naphthyl-	A23	120
1-naphthyl	A24	136
2-naphthyl	A25	132

^a K_i values were obtained from Dixon plots using a linear regression program, from at least three different assays. Errors (data not shown) were $\pm 5-10\%$ of the shown values.

problem arises when using the components of the dipole moment as a descriptor: how do we assign the sign. The same thing happens when we consider the orientation of the nodes in the π orbitals, a factor that we have found to be a very useful: which way around the ring do we consider positive. The problem has been solved using a procedure similar to that of Kishida and Manabe. We must realize that the physical counterpart of this mathematical problem is the

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Table 2. Derivatives (p -RNH-C₆H₄-SO₂N=C(NH₂)₂) **A26–A33** Obtained from Sulfaguanidine **A11** as Lead, with Their Inhibition Data against Human Thrombin^b

R ^c	compound	K _i ^a (nM)
Cbz-D-Phe	A26	54
ts-D-Phe	A27	43
ts-L-Pro	A28	48
ts-D-PhePro	A29	12
Cbz-D-PhePro	A30	13
ts-GlyHis	A31	18
ts-β-AlaHis	A32	15
ts-L-ProGly	A33	21

^a K_i values were obtained from Dixon plots using a linear regression program, from at least three different assays. Errors (data not shown) were ±5–10% of the shown values. ^b From ref 5a. ^c Cbz = PhCH₂OCO; ts = p-MeC₆H₄SO₂NHCO-; these groups acylate the amino-terminal H₂N moiety. When configuration is not specified, L-amino acid moieties were employed. The usual polypeptide formalism is used: the amino-terminal residue is written first (and it is always protected either by the Cbz or the ts moieties), whereas the carboxyterminal residue is acylating the sulfaguanidine N-4 amino group.

Table 3. Sulfonyl-O-Methyl-Isoureas (RSO₂N=C(NH₂)OMe) **B1–B25** Prepared in the Present Study, with Their Inhibition Data against Human Thrombin

R	compound	K _i ^a (nM)
p-F-C ₆ H ₄ -	B1	280
p-Cl-C ₆ H ₄ -	B2	266
p-Br-C ₆ H ₄ -	B3	265
p-I-C ₆ H ₄ -	B4	243
p-CH ₃ -C ₆ H ₄ -	B5	328
p-O ₂ N-C ₆ H ₄ -	B6	189
m-O ₂ N-C ₆ H ₄ -	B7	213
o-O ₂ N-C ₆ H ₄ -	B8	355
3-Cl-4-O ₂ N-C ₆ H ₃ -	B9	177
p-AcNH-C ₆ H ₄ -	B10	202
p-H ₂ N-C ₆ H ₄ -	B11	106
m-H ₂ N-C ₆ H ₄ -	B12	99
C ₆ F ₅ -	B13	153
o-HOOC-C ₆ H ₄ -	B14	325
m-HOOC-C ₆ H ₄ -	B15	197
p-HOOC-C ₆ H ₄ -	B16	133
o-HOOC-C ₆ Br ₄ -	B17	239
p-CH ₃ O-C ₆ H ₄ -	B18	276
2,4,6-(CH ₃) ₃ -C ₆ H ₂ -	B19	348
4-CH ₃ O-3-H ₂ N-C ₆ H ₃ -	B20	96
2-HO-3,5-Cl ₂ -C ₆ H ₂ -	B21	170
4-Me ₂ N-C ₆ H ₄ -N=N-C ₆ H ₄ -	B22	169
5-dimethylamino-1-naphthyl-	B23	138
1-naphthyl	B24	154
2-naphthyl	B25	147

^a K_i values were obtained from Dixon plots using a linear regression program, from at least three different assays. Errors (data not shown) were ±5–10% of the shown values.

Table 4. Derivatives (p -RNH-C₆H₄-SO₂N=C(NH₂)OMe) Obtained from Sulfonyl-O-Methyl-Isourea **B11** as Lead and Their Inhibition Data against Human Thrombin

R ^b	compound	K _i ^a (nM)
Cbz-D-Phe	B26	62
ts-D-Phe	B27	60
ts-L-Pro	B28	63
ts-D-PhePro	B29	18
Cbz-D-PhePro	B30	16
ts-GlyHis	B31	21
ts-β-AlaHis	B32	19
ts-L-ProGly	B33	27

^a K_i values were obtained from Dixon plots using a linear regression program, from at least three different assays. Errors (data not shown) were ±5–10% of the shown values. ^b Cbz = PhCH₂OCO; ts = p-MeC₆H₄SO₂NHCO-; these groups acylate the amino-terminal H₂N moiety. When configuration is not specified, it means that L-amino acid moieties were employed. The usual polypeptide formalism is used: the amino-terminal residue is written first (and it is always protected either by the Cbz or the ts moieties), whereas the carboxyterminal residue is acylating the sulfonyl-O-methyl-isourea N-4 amino group.

Table 5. Sulfonylaminoguanidines (RSO₂NHN=C(NH₂)₂) **C1–C25** Prepared in the Present Study, with Their Inhibition Data against Human Thrombin

R	compound	K _i ^a (nM)
p-F-C ₆ H ₄ -	C1	225
p-Cl-C ₆ H ₄ -	C2	212
p-Br-C ₆ H ₄ -	C3	203
p-I-C ₆ H ₄ -	C4	177
p-CH ₃ -C ₆ H ₄ -	C5	270
p-O ₂ N-C ₆ H ₄ -	C6	166
m-O ₂ N-C ₆ H ₄ -	C7	170
o-O ₂ N-C ₆ H ₄ -	C8	324
3-Cl-4-O ₂ N-C ₆ H ₃ -	C9	154
p-AcNH-C ₆ H ₄ -	C10	172
p-H ₂ N-C ₆ H ₄ -	C11	91
m-H ₂ N-C ₆ H ₄ -	C12	88
C ₆ F ₅ -	C13	123
o-HOOC-C ₆ H ₄ -	C14	205
m-HOOC-C ₆ H ₄ -	C15	112
p-HOOC-C ₆ H ₄ -	C16	97
o-HOOC-C ₆ Br ₄ -	C17	213
p-CH ₃ O-C ₆ H ₄ -	C18	227
2,4,6-(CH ₃) ₃ -C ₆ H ₂ -	C19	219
4-CH ₃ O-3-H ₂ N-C ₆ H ₃ -	C20	219
2-HO-3,5-Cl ₂ -C ₆ H ₂ -	C21	98
4-Me ₂ N-C ₆ H ₄ -N=N-C ₆ H ₄ -	C22	139
5-dimethylamino-1-naphthyl-	C23	130
1-naphthyl	C24	125
2-naphthyl	C25	129

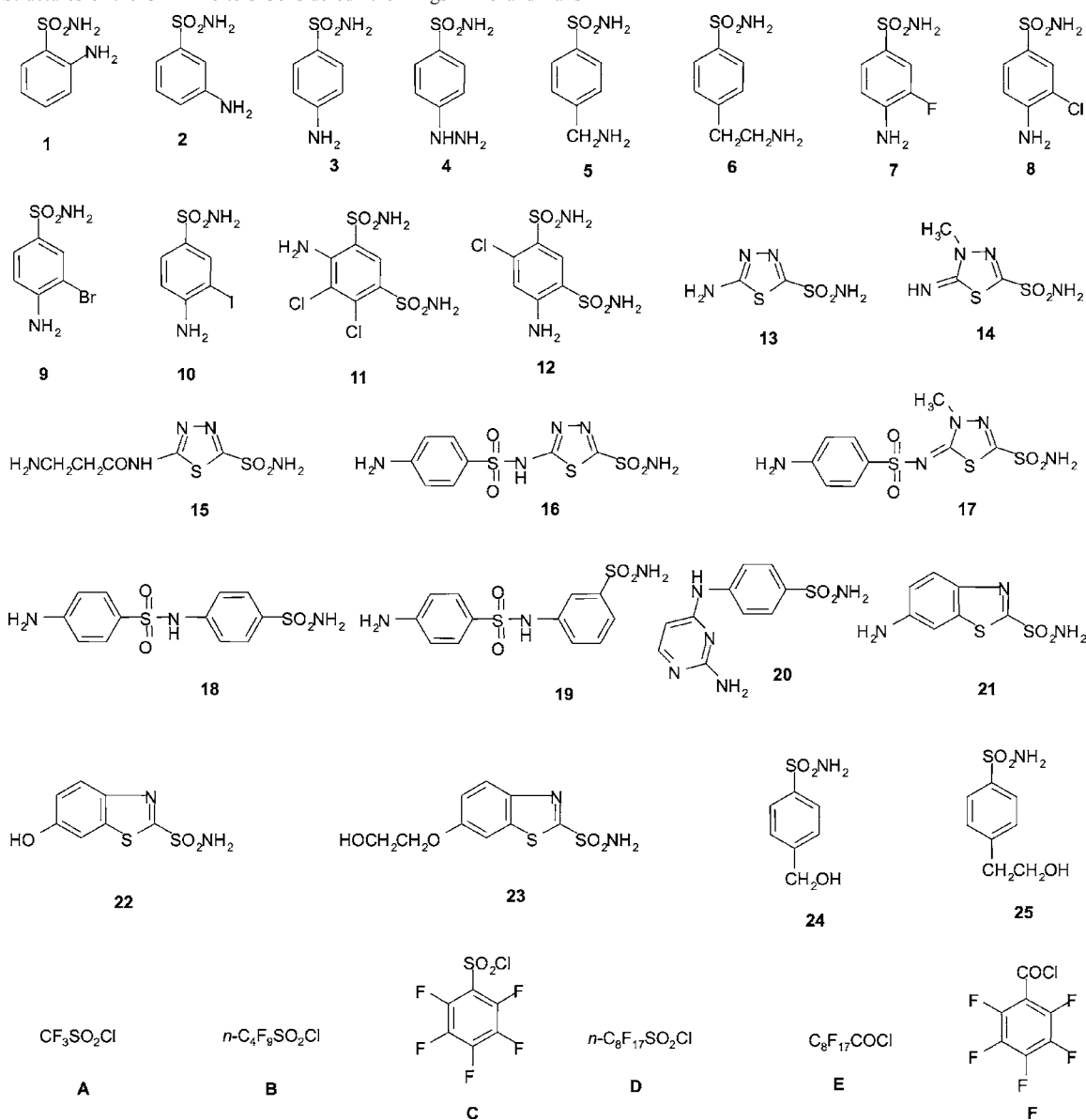
^a K_i values were obtained from Dixon plots using a linear regression program, from at least three different assays. Errors (data not shown) were ±5–10% of the shown values.

ability of the molecule to lay on the receptor surface, or in a pocket, in two ways, flipping about, in this case, the 1–4 axis.⁹ Which way it does lay will be determined by energetic considerations. So how do we find which way the drugs in a series actually bind?

In the absence of structural data the only way in which we can proceed is to carry out regressions with every combination of each drug in both orientations and find which regression fits best. For N drugs this requires 2^N regressions. With N at all large this rapidly becomes impossible if we proceed directly. Using the iterative technique of Kishida and Manabe is fast but will usually find a local rather than a global minimum. The problem is one of combinatorial

optimization, and the classic solution to such problems requires techniques such as genetic algorithms, evolutionary programming, or, in this case, simulated annealing. We refer to this procedure as flip regression, and we have discussed it in a previous publication.⁹ To date however we have not discussed the very important problem of using the technique to predict the activity of untested compounds. This is the subject of the present contribution.

When we have the regression coefficients for a series of drugs we can use them directly to predict the activity of an unknown substance. But there are two predicted activities: that for the formula as written and that for the “flipped” version, with the ring numbered in the opposite sense. Which

Chart 1. Structures of the CA Inhibitors Considered—the Rings 1–25 and Tails A–F**Table 6.** Derivatives C26–C33

(*p*-RNH–C₆H₄–SO₂NHN=C(NH₂)₂) Obtained from Sulfanilylamino-guanidine **C11** as Lead, with Their Inhibition Data against Human Thrombin^b

R ^c	compound	K _i ^a (nM)
Cbz-D-Phe	C26	50
ts-D-Phe	C27	44
ts-L-Pro	C28	43
ts-D-PhePro	C29	10
Cbz-D-PhePro	C30	11
ts-GlyHis	C31	15
ts-β-AlaHis	C32	10
ts-L-ProGly	C33	15

^a K_i values were obtained from Dixon plots using a linear regression program, from at least three different assays. Errors (data not shown) were ±5–10% of the shown values. ^b From ref 5a. ^c Cbz = PhCH₂OCO; ts = *p*-MeC₆H₄SO₂NHCO–; these groups acylate the amino-terminal H₂N moiety. When configuration is not specified, L-amino acid moieties were employed. The usual polypeptide formalism is used: the amino-terminal residue is written first (and it is always protected either by the Cbz or the ts moieties), whereas the carboxyterminal residue is acylating the sulfaguanidine N-4 amino group.

Table 7. Activities of the CA II Inhibitors of Chart 1

Cmp	K _i	Cmp	K _i	Cmp	K _i	Cmp	K _i	Cmp	K _i	Cmp	K _i
A01	20500	B01	250	C01	24	D01	96	E01	103	F01	35
A02	18700	B02	170	C02	10	D02	67	E02	69	F02	19
A03	10900	B03	160	C03	10	D03	62	E03	66	F03	17
A04	14800	B04	180	C04	16	D04	110	E04	107	F04	23
A05	5000	B05	150	C05	15	D05	60	E05	62	F05	20
A06	600	B06	150	C06	15	D06	54	E06	55	F06	17
A07	500	B07	98	C07	9	D07	125	E07	51	F07	15
A08	730	B08	425	C08	110	D08	550	E08	55	F08	125
A09	1040	B09	485	C09	125	D09	680	E09	69	F09	156
A11	430	B11	51	C11	15	D11	98	E11	72	F11	38
A12	90	B12	8	C12	5	D12	32	E12	35	F12	12
A13	100	B13	2	C13	0.3	D13	3	E13	5	F13	2
A14	24	B14	2	C14	0.3	D14	3	E14	6	F14	1.5
A15	13	B15	3	C15	0.4	D15	2	E15	2	F15	2
A16	3	B16	2	C16	1.0	D16	2	E16	1.5	F16	8
A17	5	B17	4	C17	1.5	D17	3	E17	2.0	F17	7
A18	21	B18	15	C18	8	D18	12	E18	11	F18	18
A19	23	B19	20	C19	8	D19	21	E19	16	F19	36
A20	25	B20	20	C20	11	D20	20	E20	22	F20	27
A21	0.9	B21	0.5	C21	0.2	D21	0.6	E21	1.0	F21	0.5
A22	0.9	B22	0.5	C22	0.3	D22	0.5	E22	3	F22	0.6
A23	1.0	B23	1.0	C23	0.5	D23	0.6	E23	2	F23	0.7
A24	5100	B24	460	C24	40	D24	540	E24	550	F24	54
A25	550	B25	385	C25	35	D25	440	E25	410	F25	50

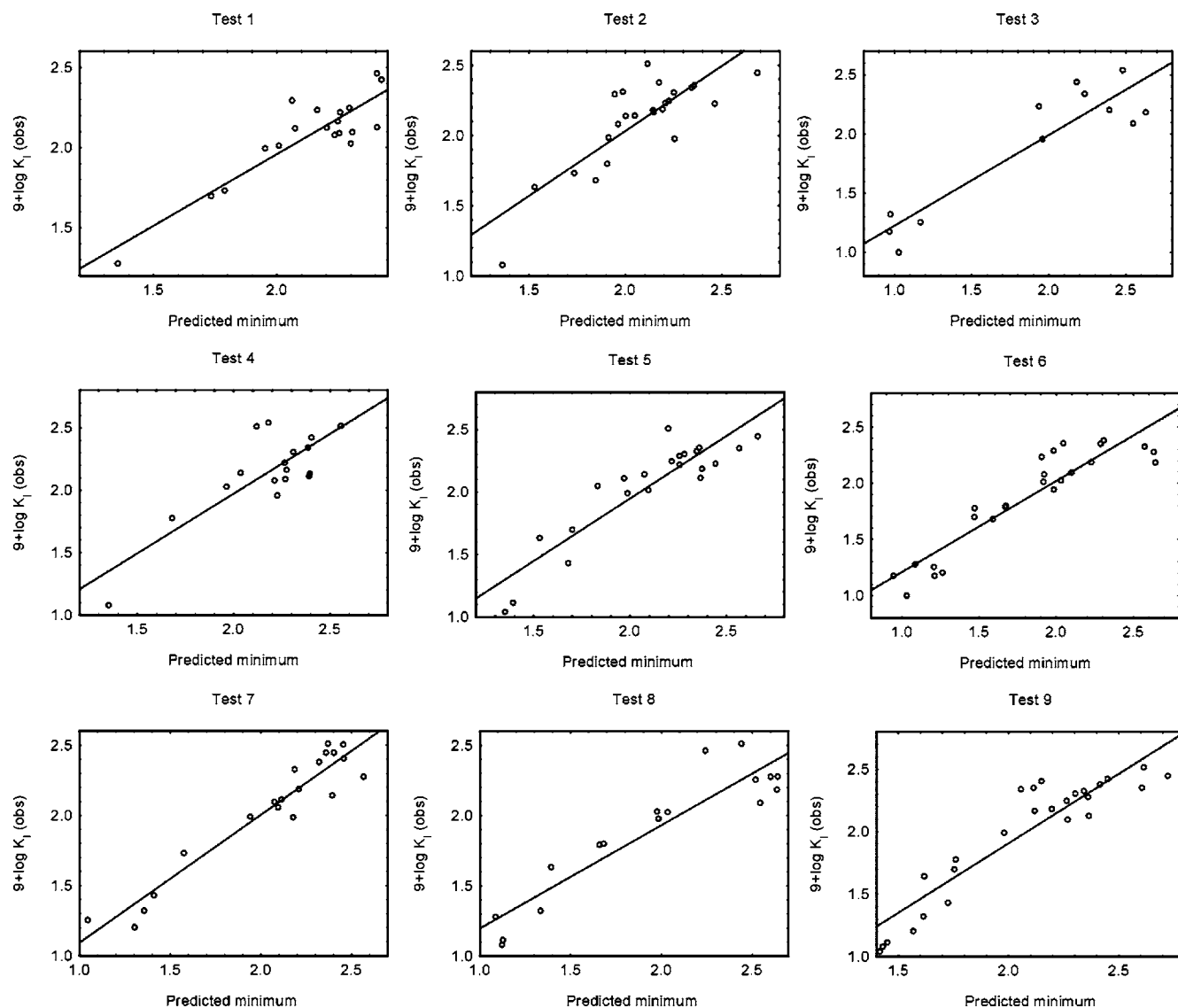


Figure 1. Plots of observed $\log K_I$ against the lower predicted $\log K_I$ for the thrombin inhibitor test sets.

Table 8. Descriptors Considered for Thrombin Inhibitors

symbol	<i>a</i>	descriptor
$\log P$	*	lipophilicity – ClogP
I_A		indicator – 1 for isoureas, 0 otherwise
I_S	*	indicator – 1 for sulfonylaminoguanidines, 0 otherwise
Π_{xx}	*	polarizability component – longest axis
Π_{yy}	*	polarizability component – intermediate axis
Π_{zz}	*	polarizability component – shortest axis
E_{SH}	*	energy of second highest occupied π -like orbital
E_H	*	energy of highest occupied π -like orbital
E_L	*	energy of lowest unoccupied π -like orbital
E_{SL}	*	energy of second lowest unoccupied π -like orbital
D_l	*	local dipole index
ΔH_S	*	solvation energy from AM1/COSMO calculation
Θ_H	*	orientation of node in highest occupied π -like orbital
Θ_L	*	orientation of node in lowest unoccupied π -like orbital
Q_{NA}	*	potential-based charge on guanidine N
Q_{NB}		potential-based charge on sulfonamide N
Q_H		potential-based charge on sulfonamide H
Q_S		potential-based charge on sulfonamide S
Q_O		potential-based charge on sulfonamide O
Q_C		potential-based charge on C bearing sulfonamide

^a *Variable retained after running FLIPSTEP.

Table 9. Descriptors Considered for the CA Inhibitors

symbol	<i>a</i>	descriptor
Φ_H	*	angle between node in highest occupied π orbital and SO_2NH_2 group, DFT (degrees)
Φ_L	*	angle between node in lowest unoccupied π orbital and SO_2NH_2 group, DFT (degrees)
E_H	*	energy of highest occupied π orbital, DFT (eV)
E_{SH}	*	energy of second highest occupied π orbital, DFT (eV)
E_L	*	energy of lowest unoccupied π orbital, DFT (eV)
E_{SL}	*	energy of second lowest unoccupied π orbital, DFT (eV)
Q_M	*	mean absolute Mulliken charge over all atoms, AM1
Q_N		Mulliken charge on sulfonamide N, DFT
Q_O	*	Mulliken charge on sulfonamide O, DFT
Q_S		Mulliken charge on sulfonamide S, DFT
Q_C	*	Mulliken charge on C attached to sulfonamide, DFT
Q_H		Mulliken charge on sulfonamide H, DFT
Π_{xx}		component of polarizability, longest axis, AM1 ($\text{\AA}^3$)
Π_{yy}		component of polarizability, intermediate axis, AM1 ($\text{\AA}^3$)
Π_{zz}		component of polarizability, shortest axis, AM1 ($\text{\AA}^3$)
ΔH_S	*	difference between heats of formation with and without COSMO, AM1 (kcal)
π_{tail}	*	ClogP value for tail

^a *Variable retained after running FLIPSTEP.

do we choose? That which gives the maximum value of the predicted activity, assuming that activity reflects the energy

of binding. So we have written FLIPPRED, an addition to the authors MARTHA package. The program accepts as data

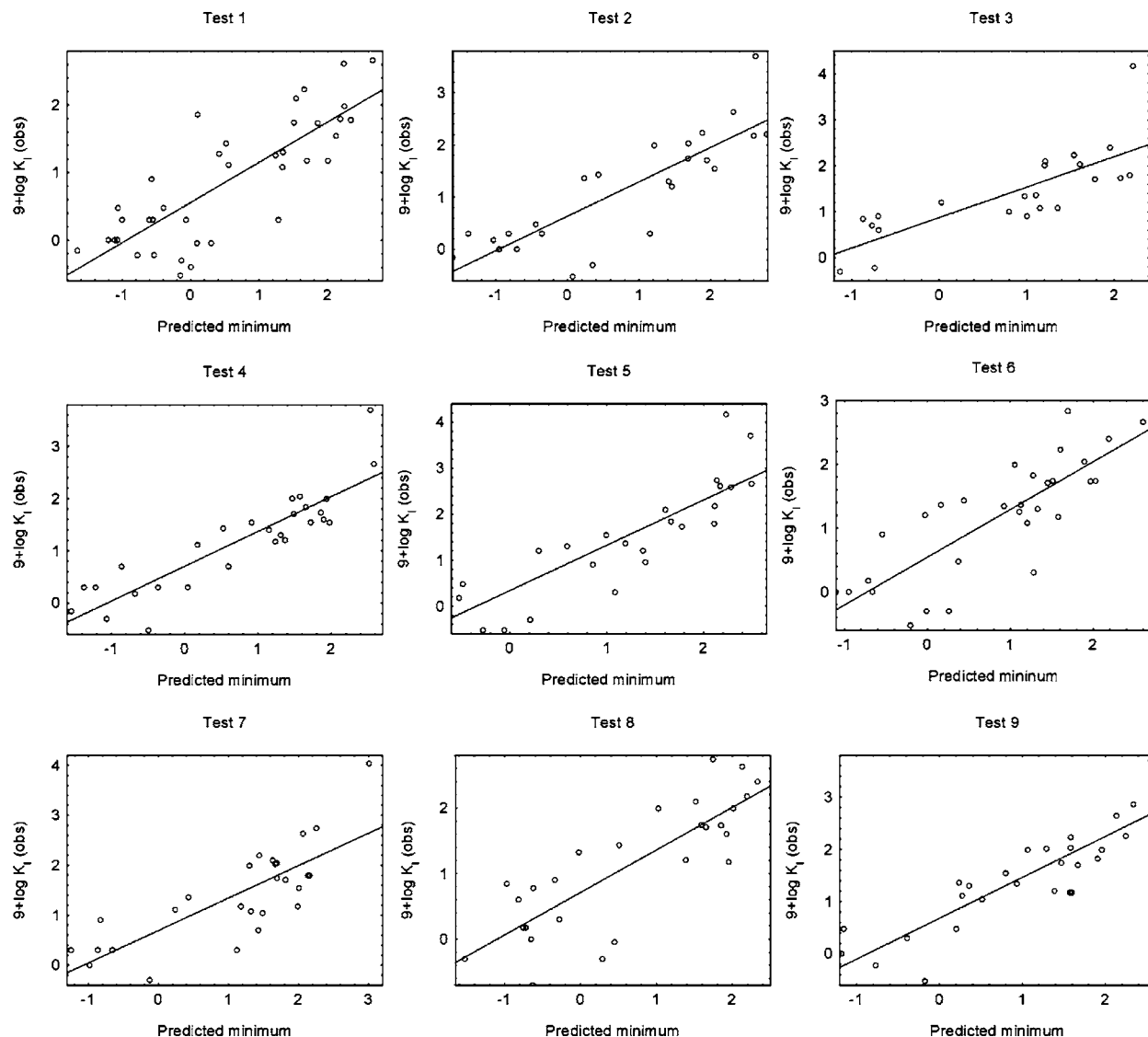


Figure 2. Plots of observed $\log K_1$ against the lower predicted $\log K_1$ for the CA inhibitor test sets.

a MARTHA file with activity as the last variable as a training set, carries out flip regression on it, then accepts another MARTHA file with identical variables as a test set and computes both a high and a low activity, and appends these to an output MARTHA file, along with a status variable that indicates whether the compound has or has not flipped in order to give the maximum activity. In practice the test and training sets are obtained from a preliminary regression using FLIPSTEP, a stepwise flip regression and backward stepwise variable elimination program.

We shall consider two series of drugs, both of which we have described previously. One is a series of inhibitors of human thrombin,¹⁰ the structures and inhibition constants of which are provided in Tables 1–6. The other is a series of inhibitors of carbonic anhydrase,¹¹ the structures and inhibition constants of which are provided in Chart 1 and Table 7.

EXPERIMENTAL AND CALCULATIONS

The preparation of the drugs and measurement of their inhibitory properties have been described previously.^{10,11} The calculation of the descriptors using MOPAC 93¹² and AM1¹³

for the thrombin inhibitors, Gaussian 2003¹⁴ for the CA inhibitors, and the authors program NODANGLE¹⁵ for the angles has also been described previously, and the numbers used here are taken directly from those publications.^{11,16} NODANGLE calculates the orientation of π -orbital nodes after a MOPAC or Gaussian calculation and is available free on the WWW. For thrombin the descriptors used were those listed in Table 8, and for CA II they are listed in Table 9. The calculated values are given in the Supporting Information.

The descriptors were reduced in number, and collinear variables and variables of poor significance were eliminated using the program FLIPSTEP,¹¹ which is part of the authors MARTHA package,¹⁷ using the default parameters SIGMAX = 0.05 and VIFMAX = 30, as described previously. MARTHA is available free of charge on the WWW. FLIPSTEP is a classical backward-stepwise variable selection program adapted to handle flipping and written so that a flippable pair of variables is eliminated only if both members of the pair are unacceptable through either collinearity or poor statistical significance.

The variables selected by FLIPSTEP were isolated from the full data set with the MARTHA routine EDIT. Asterisks

Table 10. Thrombin Inhibition: Regression of Observed $\log K_i$ on Low and High Predicted Values, Giving Slope, Intercept, R^2 , and Standard Error of Estimate

no.	low				high			
	R^2	s	slope	int	R^2	s	slope	int
1	0.83	0.11	0.75	0.57	0.79	0.13	0.71	0.46
2	0.83	0.13	0.89	0.33	0.85	0.13	0.85	0.17
3	0.87	0.21	0.91	0.28	0.87	0.21	0.91	0.07
4	0.78	0.16	0.89	0.29	0.76	0.17	0.85	0.17
5	0.89	0.14	0.98	0.12	0.87	0.15	0.96	-0.05
6	0.91	0.13	0.94	0.20	0.91	0.14	0.93	-0.02
7	0.90	0.14	0.97	0.21	0.85	0.17	0.95	0.02
8	0.90	0.13	0.93	0.25	0.89	0.14	0.83	0.02
9	0.92	0.15	1.02	0.04	0.91	0.15	1.01	-0.18

Table 11. CA II Inhibition: Regression of Observed $\log K_i$ on Low and High Predicted Values, Giving Slope, Intercept, R^2 , and Standard Error of Estimate

no.	low				high			
	R^2	s	slope	int	R^2	s	slope	int
1	0.65	0.54	0.59	0.09	0.56	0.61	0.62	0.02
2	0.71	0.60	0.66	0.63	0.55	0.74	0.65	0.11
3	0.61	0.69	0.66	0.87	0.50	0.68	0.62	0.40
4	0.78	0.44	0.67	0.70	0.68	0.54	0.75	0.10
5	0.70	0.68	0.98	0.34	0.53	0.84	1.15	-0.58
6	0.64	0.56	0.73	0.57	0.52	0.64	0.69	0.05
7	0.62	0.60	0.65	0.69	0.55	0.66	0.71	0.17
8	0.70	0.60	0.71	0.72	0.62	0.67	0.76	0.10
9	0.76	0.48	0.78	0.68	0.68	0.55	0.85	-0.02

in Tables 8 and 9 mark the subsets of variables selected for inclusion. Each of the two reduced sets of data was divided into a training set (80%) and a test set (20%) using the MARTHA routine SPLIT. For each of the two data sets nine training and test sets were created. SPLIT accepts a probability of inclusion in the training set and splits on that basis. The actual number in each set varies from run to run. Each of the training sets was tested with FLIPSTEP. In most cases no further variables were rejected. Those training sets for which FLIPSTEP did reject further variables were discarded. Thus the training sets that were used has no single variables or complete variable pairs with a statistical significance greater than 0.05. This step is important as it was found that training sets containing nonsignificant variables can give bizarre predictions.

The new program FLIPPRED was applied to each training-set test-set pair. FLIPPRED carries out a standard flip regression on the training set to generate regression coefficients and then applied these to the test set to give two predicted values for each drug in the test set, corresponding to the flipped and unflipped orientation of the drug. The program sorted these predictions into a low and high value and appended these, together with a flip status value, to an output file.

It is assumed that because a low value of the inhibition constant indicates tight bonding of inhibitor to enzyme, the low value will be the relevant prediction. The observed inhibition constant was then regressed on the high and low predicted value using the MARTHA routine MULTLR. The results of these regressions are tabulated in Tables 10 and 11 for thrombin and CA II, respectively, and a plot of observed activity against low predicted activity for the nine test runs on the two enzymes in Figures 1 and 2.

RESULTS

The results of stepwise flip regressions on the two original data sets are given in the following two equations:

For CA II inhibition

$$\begin{aligned} \log K_i = & 7.53(10.2) Q_M - 10.29(4.4) Q_C - \\ & 1.32(9.5) E_H - 0.709(4.8) E_{SL} + 0.8105(6.8) \pi_{\text{tail}} + \\ & 0.0354(8.6) \Delta H_S - 38.65(18.1) Q_O - \\ & 0.1660(2.1) \cos 2\Phi_H + 0.173(11.7) \sin 2\Phi_H - \\ & 0.8583(3.8) \cos 4\Phi_L - 0.1503(2.1) \sin 4\Phi_L + 53.41 \quad (1) \end{aligned}$$

$$N = 144, R^2 = 0.876, Q^2 = 0.854, F = 85.06, \\ s = 0.39, \alpha = 7 \times 10^{-61}$$

For thrombin inhibition:

$$\begin{aligned} \log K_i = & 0.108(13.0) \log P + 0.105(8.5) I_S - \\ & 0.0024(13.6) \Pi_{yy} - 0.0022(12.2) \Pi_{zz} + 0.497(6.5) D_1 + \\ & 0.0018(5.7) \Delta H_S + 0.159(5.2) E_{SH} - 0.115(5.2) E_H - \\ & 0.194(5.8) E_L + 0.099(3.9) E_{SL} + 0.904(5.5) Q_N - \\ & 0.030(2.1) \cos 2\Phi_H + 0.155(18.0) \sin 2\Phi_H + \\ & 0.044(2.6) \cos 4\Phi_L - 0.013(1.7) \sin 4\Phi_L + 3.46 \quad (2) \end{aligned}$$

$$N = 96, R^2 = 0.986, Q^2 = 0.979, F = 365.6, \\ s = 0.055, \alpha = 3 \times 10^{-152}$$

Here N is the number of compounds, R^2 is the square of the multiple correlation coefficient, Q^2 is the cross-validated value of the same, F is the Fisher variance ratio, s is the standard error of estimate, and α is the statistical significance based on a randomization test with 5000 randomizations. The numbers in parentheses are Students t values for the individual terms. A t greater than approximately 2 is indicative of statistical significance at the 0.05 confidence level, and higher values are indicative of more important terms.

CONCLUSIONS

It is apparent from eq 1 that by far the most important term for CA II inhibitors is Q_O , and from eq 2 that the most important term for the thrombin inhibitors is the angle Φ_H . Note also that one of the terms for thrombin inhibition is not significant at the 0.05 confidence level. Within a flippable pair of descriptors, when one term is significant, either both must be included, or both must be excluded.

Tables 10 and 11 list the results of nine splittings of the two reduced data sets into training and prediction sets and regressions of the observed prediction set activity on the low and high predicted activity. The observed activity in the prediction set has in no way been used in the prediction. Because a low value of K_i is indicative of strong binding it would be expected that the low value would correlate better, and that ideally R^2 would be near 1, s near zero, the slope close to unity, and the intercept close to zero. This indeed turns out to be the case. The correlation coefficient and slope are higher, and the standard error of estimate is lower for the low prediction than the high. Only the intercept goes against this trend. These results have in no way been imposed by the flip regression procedure. It follows directly from

thermodynamic considerations and is an independent confirmation of the assumptions of the procedure.

Figures 1 and 2 are plots of observed activity against the low predicted activity and illustrate the predictive ability of the procedure. It will be noted that the R^2 values in Tables 10 and 11 are not as good as those for eqs 1 and 2. In part this is because R^2 for a prediction set is always poorer than that for the training set, and in part because in the training process statistical significance becomes inflated by the swapping process. The very low α values for the randomization trials on the selection subsets of eqs 1 and 2 indicate that this inflation is not dominant, and the statistics of Tables 10 and 11 are entirely uncontaminated with any such inflation. The results confirm that quite good predictions can be obtained by the flip procedure, that the assumption that the lower of the two predicted values of $\log K_I$ is the relevant predictor, and that it corresponds to tightest binding is a valid one.

Supporting Information Available: Two tables containing values of all descriptors considered for the CA inhibitors and thrombin inhibitors. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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CI050191V

Supporting Information for
**Predictive Flip Regression: A Technique for QSAR of Derivatives
of Symmetric Molecules**

Brian W. Clare and Claudiu T. Supuran

Table SII
Values of calculated descriptors for thrombin inhibitors

Comp L	og P	I _A	I _S	Π _{xx}	Π _{yy}	Π _{zz}	E _{SH}
A1	0.12	0	0	129.3	65.9	105.1	-10.317
A2	0.69	0	0	145.4	67.7	105.6	-10.263
A3	0.84	0	0	153.1	68.9	106.1	-10.281
A4	0.23	0	0	139.8	74.3	111.1	-10.127
A5	0.01	0	0	142.7	73.7	127.0	-11.067
A6	0.01	0	0	145.9	128.1	63.8	-10.766
A7	-0.17	0	0	134.2	129.8	73.4	-10.662
A8	0.59	0	0	145.1	133.1	86.8	-11.159
A9	-1.02	0	0	189.9	90.2	120.1	-10.218
A10	-1.24	0	0	152.4	69.8	107.4	-10.237
A11	-1.24	0	0	130.3	103.0	89.6	-10.441
A12	0.80	0	0	132.0	132.3	60.0	-10.489
A13	-0.15	0	0	139.7	114.9	73.6	-10.494
A14	-0.15	0	0	143.7	129.3	62.0	-10.417
A15	-0.15	0	0	150.8	82.3	113.3	-10.553
A16	1.61	0	0	189.5	194.1	76.1	-10.399
A17	-0.07	0	0	158.8	75.0	111.9	-10.296
A18	1.23	0	0	157.5	134.8	88.5	-10.062
A19	-1.01	0	0	163.7	120.6	90.1	-10.101
A20	0.92	0	0	137.6	150.3	61.3	-10.466
A21	2.41	0	0	408.6	159.2	133.3	-10.254
A22	1.22	0	0	219.0	178.6	105.1	-9.845
A23	0.91	0	0	169.2	166.5	80.1	-9.789
A24	0.91	0	0	206.9	92.8	124.8	-10.013
A25	1.85	0	0	364.1	250.0	208.4	-10.249
A26	1.50	0	0	377.6	290.8	235.8	-10.259
A27	0.84	0	0	371.2	226.1	200.6	-10.269
A28	1.98	0	0	394.7	331.5	301.6	-10.192
A29	2.33	0	0	366.3	316.1	294.4	-10.267
A30	-1.36	0	0	394.0	293.6	247.4	-10.276
A31	-1.13	0	0	381.7	339.4	239.5	-10.199
A32	0.27	0	0	380.2	249.2	242.3	-10.273
C1	0.12	1	0	145.2	105.3	80.1	-10.371
C2	0.69	1	0	160.5	107.3	81.7	-10.367
C3	0.84	1	0	168.7	107.6	82.8	-10.381
C4	0.23	1	0	152.4	110.7	94.1	-10.249
C5	0.01	1	0	166.4	116.3	95.6	-11.160
C6	0.01	1	0	154.4	146.9	68.2	-10.962
C7	-0.17	1	0	155.2	129.7	83.4	-10.891
C8	0.59	1	0	168.5	149.0	82.4	-11.255
C9	-1.11	1	0	186.2	119.9	124.0	-10.321
C10	-1.24	1	0	163.1	112.6	85.3	-10.296
C11	-1.24	1	0	141.4	127.1	84.9	-10.548

C12	0.80	1	0	154.8	137.1	67.7	-10.671
C13	-0.15	1	0	156.5	123.9	83.3	-10.648
C14	-0.15	1	0	143.5	148.1	76.5	-10.708
C15	-0.15	1	0	145.2	109.8	118.0	-10.706
C16	1.61	1	0	198.7	188.1	117.7	-10.574
C17	-0.07	1	0	148.5	116.0	107.7	-10.355
C18	1.23	1	0	168.2	129.9	114.4	-10.920
C19	-1.01	1	0	177.5	131.9	96.7	-10.180
C20	0.92	1	0	161.5	155.4	67.3	-10.662
C21	2.41	1	0	421.0	142.5	171.6	-10.310
C22	1.22	1	0	221.0	185.3	125.8	-9.877
C23	0.91	1	0	164.1	176.6	105.6	-9.830
C24	0.91	1	0	204.2	140.1	109.6	-10.098
C25	1.85	1	0	380.7	236.7	240.9	-10.346
C26	1.50	1	0	396.1	302.1	239.0	-10.340
C27	0.84	1	0	317.8	284.4	231.6	-10.334
C28	1.98	1	0	387.5	348.0	335.9	-10.328
C29	2.33	1	0	379.0	306.8	323.6	-10.328
C30	-1.36	1	0	393.2	318.8	252.5	-10.348
C31	-1.13	1	0	471.6	325.8	205.8	-10.337
C32	0.27	1	0	350.3	287.6	265.6	-10.337
B1	0.12	0	1	124.8	79.9	110.5	-10.301
B2	0.69	0	1	141.3	80.3	111.9	-10.301
B3	0.84	0	1	150.2	79.6	113.2	-10.259
B4	0.23	0	1	135.2	88.4	116.3	-10.108
B5	0.01	0	1	148.4	87.4	125.2	-11.064
B6	0.01	0	1	142.1	134.5	79.4	-10.990
B7	-0.17	0	1	138.4	143.7	72.9	-10.698
B8	0.59	0	1	151.2	131.3	100.3	-11.155
B9	-1.02	0	1	183.4	117.1	112.6	-10.241
B10	-1.24	0	1	147.7	85.1	112.2	-10.221
B11	-1.24	0	1	129.2	108.4	100.6	-10.406
B12	0.80	0	1	137.5	130.8	76.1	-10.522
B13	-0.15	0	1	147.2	120.0	80.9	-10.515
B14	-0.15	0	1	156.0	134.1	65.6	-10.477
B15	-0.15	0	1	149.4	98.3	112.5	-10.513
B16	1.61	0	1	199.2	195.0	85.0	-10.419
B17	-0.07	0	1	151.9	92.0	116.1	-10.280
B18	1.23	0	1	152.0	142.7	100.3	-10.034
B19	-1.01	0	1	174.8	97.2	117.7	-10.043
B20	0.92	0	1	148.0	145.4	74.9	-10.513
B21	2.41	0	1	408.7	166.4	140.3	-10.234
B22	1.22	0	1	208.6	183.4	128.0	-9.954
B23	0.91	0	1	155.6	178.7	94.3	-9.776
B24	0.91	0	1	198.4	116.4	123.2	-9.998
B25	1.85	0	1	386.2	241.1	210.4	-10.249

B26	1.50	0	1	380.1	299.8	238.9	-10.253
B27	0.84	0	1	357.1	233.3	218.4	-10.243
B28	1.98	0	1	417.2	322.0	325.0	-10.253
B29	2.33	0	1	365.2	341.1	277.2	-10.219
B30	-1.36	0	1	355.6	267.4	324.3	-10.264
B31	-1.13	0	1	413.3	309.1	258.6	-10.235
B32	0.27	0	1	392.9	208.5	281.7	-10.242

Table SII (cont.)

Values of calculated descriptors for thrombin inhibitors

Comp	E _H	E _L	E _{SL}	D _I	ΔH _S	Φ _H	Φ _L
A1	-10.244	-0.721	0.003	1.2127	-41.97	59.7	120.3
A2	-10.260	-0.767	0.007	1.1688	-41.60	58.2	119.7
A3	-10.246	-0.827	0.005	1.1581	-42.18	150.0	119.8
A4	-10.118	-0.598	0.171	1.0785	-41.93	17.4	120.4
A5 -	10.347	-1.514	-0.109	1.1867	-51.63	150.1	120.0
A6 -	10.519	-1.265	-0.590	1.2222	-51.70	129.5	173.7
A7 -	10.488	-1.294	-0.379	1.1690	-46.80	168.8	79.9
A8 -	10.217	-1.464	-0.424	1.1756	-51.15	159.8	125.0
A9	-9.601	-0.670	0.116	1.0878	-53.98	59.7	120.6
A10	-9.146	-0.469	-0.201	1.1915	-47.43	60.0	120.2
A11	-9.040	-0.594	-0.324	1.1157	-46.74	175.1	118.0
A12	-9.905	-1.233	-0.937	1.2224	-43.03	150.9	117.5
A13	-10.087	-0.440	0.056	1.1613	-99.87	148.0	114.6
A14 -	10.071	-0.580	-0.085	1.2005	-109.89	149.4	118.3
A15	-10.178	-0.931	0.134	1.1525	-115.70	150.1	120.0
A16 -	10.054	-1.241	-0.945	1.1448	-94.14	158.6	135.0
A17	-9.856	-0.589	0.063	1.0661	-44.64	53.6	121.0
A18	-9.661	-0.583	0.085	0.9453	-37.32	150.8	120.5
A19	-8.968	-0.615	0.033	0.9998	-48.62	9.8	118.3
A20	-9.583	-0.705	-0.376	1.1955	-45.28	163.3	113.8
A21 -	10.075	-1.318	-0.270	0.7090	-49.95	44.1	120.1
A22	-8.905	-1.043	-0.256	0.7854	-43.05	41.8	118.0
A23	-9.323	-1.011	-0.236	0.9262	-41.32	56.0	117.9
A24	-9.186	-0.956	-0.481	0.9181	-43.17	165.5	143.1
A25	-9.582	-0.715	0.115	0.6177	-61.03	58.9	121.8
A26	-9.611	-0.751	-0.746	0.8780	-84.25	58.7	121.9
A27	-9.583	-0.763	0.110	0.9448	-78.93	61.4	118.8
A28	-9.478	-0.608	0.163	0.7716	-85.46	60.9	118.9
A29	-9.549	-0.728	0.114	0.5437	-65.86	58.9	121.9
A30	-9.549	-0.743	0.113	0.8717	-99.92	61.2	118.8
A31	-9.500	-0.632	0.158	0.8622	-101.36	59.1	121.8

A32	-9.557	-0.751	0.114	0.8972	-82.32	59.0	121.8
C1 -	10.360	-0.701	-0.030	1.0668	-39.21	60.4	119.9
C2 -	10.317	-0.747	-0.029	1.0251	-38.97	150.1	119.9
C3 -	10.298	-1.090	-0.796	1.0146	-39.60	150.1	119.7
C4	-10.183	-0.583	0.134	0.9595	-38.82	148.4	102.8
C5 -	10.426	-1.663	-0.184	1.0284	-47.56	149.9	119.9
C6 -	10.593	-1.306	-0.665	1.0619	-48.15	134.0	167.3
C7 -	10.585	-1.437	-0.534	1.0187	-43.53	158.2	87.8
C8 -	10.293	-1.623	-0.566	1.0178	-47.45	158.9	123.9
C9	-9.706	-1.008	-0.704	0.9639	-50.26	59.5	120.1
C10	-9.133	-0.358	0.215	1.0656	-44.89	59.9	119.9
C11	-9.057	-0.540	0.123	0.9839	-43.92	174.9	117.6
C12	-9.986	-1.492	-1.010	1.0523	-39.44	150.2	120.1
C13 -	10.168	-0.686	-0.029	1.0090	-96.45	149.5	113.2
C14 -	10.198	-0.641	-0.106	1.0477	-	172.03	148.9 127.6
C15 -	10.221	-1.161	-0.833	1.0284	-	110.74	149.9 119.7
C16 -	10.141	-1.579	-1.019	1.0043	-	108.57	156.6 129.5
C17	-9.962	-0.552	0.034	0.9520	-42.57	53.1	120.3
C18	-9.723	-0.579	0.040	0.8603	-35.89	150.5	119.4
C19	-8.996	-0.576	0.008	0.8965	-45.83	8.9	118.3
C20	-9.601	-1.059	-0.788	1.0375	-41.92	138.2	126.3
C21 -	10.122	-1.396	-0.375	0.6559	-47.23	43.3	120.2
C22	-8.914	-1.199	-0.277	0.7165	-40.63	80.6	122.3
C23	-9.410	-1.199	-0.898	0.8282	-38.42	67.8	123.0
C24	-9.226	-1.155	-0.876	0.8231	-40.07	134.7	101.1
C25	-9.702	-1.013	-0.728	0.5732	-56.66	59.1	121.1
C26	-9.660	-1.021	-0.719	0.8359	-83.41	58.6	121.2
C27	-9.639	-1.008	-0.707	0.8978	-74.45	59.0	121.1
C28	-9.629	-1.002	-0.695	0.7388	-83.84	61.3	118.3
C29	-9.637	-0.986	-0.691	0.5174	-63.00	59.0	120.9
C30	-9.648	-1.030	-0.714	0.8308	-97.04	61.1	118.7
C31	-9.723	-1.006	-0.723	0.8203	-96.89	59.2	120.9
C32	-9.641	-1.011	-0.703	0.8546	-79.78	61.2	118.6
B1	-10.212	-0.696	0.015	1.1066	-38.71	60.7	120.5
B2	-10.212	-0.696	0.015	1.0665	-38.31	60.7	120.5
B3	-10.235	-0.808	0.014	1.0561	-38.86	148.3	120.3
B4	-10.092	-0.557	0.183	0.9960	-38.51	61.6	120.3
B5 -	10.367	-1.541	-0.129	1.0649	-46.53	149.9	120.2
B6 -	10.534	-1.267	-0.661	1.0981	-46.81	170.1	67.1
B7 -	10.508	-1.321	-0.414	1.0540	-41.96	166.6	80.7
B8 -	10.237	-1.486	-0.456	1.0541	-46.21	140.3	115.3
B9	-9.481	-0.666	0.135	0.9982	-47.97	58.8	122.1
B10	-9.077	-0.439	-0.142	1.0996	-43.79	60.0	120.1
B11	-9.024	-0.573	-0.265	1.0264	-43.21	124.9	122.2
B12	-9.913	-1.277	-0.944	1.0898	-38.81	149.6	122.0
B13	-10.086	-0.465	0.057	1.0583	-96.04	152.1	124.5

B14 -	10.102	-0.638	-0.362	1.0830 -	103.05	149.6	117.7
B15	-10.153	-0.897	0.148	1.0711 -	112.94	150.0	120.6
B16 -	10.061	-1.265	-0.947	1.0380	-89.41	142.0	105.2
B17	-9.832	-0.570	0.073	0.9872	-41.13	54.0	121.0
B18	-9.650	-0.567	0.096	0.8848	-34.60	150.3	119.9
B19	-8.933	-0.555	0.078	0.9297	-43.99	10.0	118.0
B20	-9.490	-0.739	-0.305	1.0769	-40.65	163.6	112.0
B21 -	10.054	-1.303	-0.237	0.6746	-46.73	45.8	120.2
B22	-9.825	-1.022	-0.240	0.7430	-40.31	146.4	118.2
B23	-9.304	-0.996	-0.225	0.8627	-38.62	56.2	112.4
B24	-9.178	-0.943	-0.473	0.8569	-40.70	165.7	143.4
B25	-9.582	-0.734	0.116	0.5878	-54.94	60.9	118.2
B26	-9.584	-0.738	0.117	0.8521	-79.06	58.7	122.0
B27	-9.564	-0.723	0.126	0.9140	-75.77	61.4	118.3
B28	-9.525	-0.719	0.129	0.7496	-83.94	61.1	118.4
B29	-9.505	-0.676	0.154	0.5306	-62.51	60.7	118.5
B30	-9.576	-0.741	0.114	0.8480	-98.26	58.7	122.0
B31	-9.529	-0.700	0.135	0.8300	-93.99	61.0	118.3
B32	-9.523	-0.695	0.113	0.8677	-85.19	58.9	121.6

Table SI1 (cont.)

Values of calculated descriptors for thrombin inhibitors

Comp Q	NA	Q _{NB}	Q _H	Q _S	Q _O	Q _C
A1	-0.8823 -	1.2236	0.4279	2.6824 -	1.9564	0.9382
A2	-0.8781 -	1.2063	0.4276	2.6308 -	1.9344	0.9262
A3	-0.8795 -	1.2106	0.4281	2.6421 -	1.9403	0.9296
A4	-0.8776 -	1.2259	0.4249	2.7072 -	1.9736	0.9324
A5	-0.8650 -	1.1840	0.4243	2.7226 -	1.9717	0.9064
A6	-0.8593 -	1.1753	0.4248	2.6891 -	1.9624	0.8932
A7	-0.8382 -	1.1721	0.4190	2.6845 -	1.9251	0.8963
A8	-0.8663 -	1.1245	0.4288	2.6400 -	1.9286	0.8688
A9	-0.8546 -	1.1714	0.4157	2.7277 -	1.9899	0.8839
A10	-0.8703 -	1.2004	0.4212	2.6812 -	1.9694	0.9118
A11	-0.8724 -	1.2134	0.4241	2.6841 -	1.9629	0.9270
A12	-0.9040 -	1.2176	0.4444	2.7570 -	1.9537	0.9611
A13	-0.7469 -	1.1427	0.3723	2.6717 -	1.9755	0.8692
A14	-0.8624 -	1.1223	0.4296	2.5464 -	1.9116	0.8737
A15	-0.8496 -	1.1878	0.4098	2.6585 -	1.9412	0.8891
A16	-0.7660 -	1.1351	0.3861	2.7095 -	1.9996	0.8981
A17	-0.8777 -	1.2212	0.4256	2.6977 -	1.9691	0.9267
A18	-0.8697 -	1.2227	0.4205	2.7839 -	1.9813	0.9128
A19	-0.8760 -	1.2282	0.4248	2.7299 -	1.9840	0.9321
A20	-0.8697 -	1.1020	0.4318	2.5499 -	1.8711	0.8953
A21	-0.8884 -	1.2349	0.4287	2.7289 -	1.9770	0.9470
A22	-0.8808 -	1.2158	0.4237	2.7082 -	1.9602	0.9374

A23	-0.8743 -	1.2000	0.4223	2.7136 -	1.9608 0.9225
A24	-0.8826 -	1.2406	0.4276	2.7340 -	1.9837 0.9420
A25	-0.8418 -	1.1550	0.4108	2.6910 -	1.9711 0.8657
A26	-0.8411 -	1.1722	0.4139	2.6514 -	1.9557 0.8713
A27	-0.8535 -	1.2001	0.4180	2.6577 -	1.9563 0.8964
A28	-0.8417 -	1.1428	0.4217	2.6490 -	1.9539 0.8575
A29	-0.8476 -	1.2012	0.4165	2.6718 -	1.9571 0.8891
A30	-0.8537 -	1.2033	0.4175	2.6696 -	1.9565 0.8985
A31	-0.8680 -	1.1519	0.4205	2.6649 -	1.9647 0.8903
A32	-0.8475 -	1.1922	0.4162	2.6692 -	1.9617 0.8827
C1	-0.7847 -	0.6945	0.3698	2.3867 -	1.7665 0.5284
C2	-0.7867 -	0.6594	0.3708	2.3107 -	1.7342 0.5356
C3	-0.7866 -	0.6626	0.3708	2.3185 -	1.7388 0.5361
C4	-0.7553 -	0.6822	0.3507	2.4266 -	1.7862 0.4917
C5	-0.7561 -	0.6979	0.3603	2.4284 -	1.7677 0.4996
C6	-0.7960 -	0.7244	0.3759	2.4211 -	1.7702 0.5549
C7	-0.8379 -	0.7104	0.4008	2.3244 -	1.7220 0.6774
C8	-0.7491 -	0.6953	0.3604	2.3780 -	1.7321 0.4764
C9	-0.7659 -	0.7527	0.3613	2.5151 -	1.8179 0.4712
C10	-0.7755 -	0.6944	0.3642	2.4137 -	1.7947 0.4923
C11	-0.7771 -	0.7056	0.3669	2.4044 -	1.7774 0.5001
C12	-0.7911 -	0.7446	0.3754	2.4812 -	1.7593 0.5630
C13	-0.7405 -	0.7014	0.3514	2.4040 -	1.7841 0.5483
C14	-0.7722 -	0.6936	0.3551	2.3877 -	1.7759 0.4884
C15	-0.7524 -	0.6978	0.3485	2.4379 -	1.7856 0.4662
C16	-0.7628 -	0.6337	0.3512	2.1139 -	1.5960 0.4927
C17	-0.7644 -	0.7439	0.3602	2.4908 -	1.8112 0.4674
C18	-0.7812 -	0.8173	0.3632	2.6075 -	1.8372 0.5108
C19	-0.7763 -	0.7204	0.3654	2.4513 -	1.7998 0.4964
C20	-0.7850 -	0.6327	0.3675	2.2694 -	1.6785 0.5428
C21	-0.7846 -	0.7274	0.3686	2.4561 -	1.7965 0.5186
C22	-0.7775 -	0.7256	0.3647	2.4506 -	1.7856 0.4871
C23	-0.7579 -	0.7039	0.3475	2.4694 -	1.7838 0.4916
C24	-0.7546 -	0.6936	0.3509	2.4442 -	1.7927 0.4972
C25	-0.7786 -	0.6942	0.3654	2.4229 -	1.7866 0.5139
C26	-0.7829 -	0.6810	0.3650	2.4081 -	1.7890 0.5316
C27	-0.7793 -	0.7172	0.3650	2.4566 -	1.7009 0.5030
C28	-0.7800 -	0.7123	0.3648	2.4408 -	1.7999 0.5065
C29	-0.7793 -	0.7102	0.3654	2.4438 -	1.7966 0.5088
C30	-0.7799 -	0.6921	0.3642	2.4259 -	1.7948 0.5151
C31	-0.7854 -	0.7193	0.3686	2.4554 -	1.8060 0.5242
C32	-0.7796 -	0.7095	0.3647	2.4513 -	1.8048 0.5094
B1	-0.8243 -	1.0551	0.4414	2.6761 -	1.9591 0.7337
B2	-0.8243 -	1.0551	0.4414	2.5727 -	1.9164 0.6911
B3	-0.8294 -	1.0031	0.4471	2.5788 -	1.9200 0.6958
B4	-0.8283 -	1.0455	0.4414	2.6640 -	1.9576 0.7242

B5	-0.8221 -	1.0598	0.4463	2.6821 -	1.9459 0.7311
B6	-0.8260 -	1.0727	0.4460	2.6647 -	1.9395 0.7576
B7	-0.8001 -	1.0445	0.4469	2.6551 -	1.9089 0.7445
B8	-0.8190 -	1.0380	0.4486	2.6303 -	1.9108 0.7150
B9	-0.8192 -	1.0394	0.4390	2.6583 -	1.9536 0.7180
B10	-0.8418 -	1.0544	0.4410	2.6661 -	1.9617 0.7389
B11	-0.8092 -	1.0093	0.4384	2.6266 -	1.9454 0.6925
B12	-0.8124 -	1.0874	0.4457	2.7354 -	1.9382 0.7502
B13	-0.7010 -	0.9837	0.3850	2.5721 -	1.9293 0.6719
B14	-0.8812 -	1.0352	0.4724	2.5343 -	1.9003 0.7619
B15	-0.7729 -	1.0119	0.4151	2.6121 -	1.9271 0.6771
B16	-0.7363 -	1.0020	0.4137	2.6109 -	1.9436 0.7290
B17	-0.8372 -	1.0350	0.4442	2.6435 -	1.9477 0.7244
B18	-0.8192 -	1.0913	0.4335	2.7510 -	1.9647 0.7444
B19	-0.8329 -	1.0498	0.4475	2.5973 -	1.9243 0.7296
B20	-0.8361 -	1.0346	0.4461	2.5709 -	1.8690 0.7508
B21	-0.8327 -	1.0527	0.4436	2.6745 -	1.9600 0.7423
B22	-0.8067 -	0.9956	0.4352	2.6083 -	1.9253 0.6878
B23	-0.8107 -	1.0211	0.4375	2.6478 -	1.9379 0.6997
B24	-0.8372 -	1.0666	0.4435	2.6991 -	1.9743 0.7463
B25	-0.8238 -	1.0433	0.4428	2.5783 -	1.9135 0.7221
B26	-0.8316 -	1.0727	0.4421	2.6551 -	1.9568 0.7125
B27	-0.8157 -	1.0117	0.4379	2.6357 -	1.9510 0.6886
B28	-0.8530 -	1.0658	0.4445	2.6822 -	1.9620 0.7613
B29	-0.8326 -	1.0492	0.4453	2.5826 -	1.9163 0.7303
B30	-0.8338 -	1.0562	0.4425	2.6800 -	1.9632 0.7378
B31	-0.8286 -	1.0435	0.4436	2.5902 -	1.9222 0.7240
B32	-0.8304 -	1.0420	0.4410	2.6709 -	1.9608 0.7195

Table SI2
Descriptor values for CA inhibitors

<i>Comp</i>	Q_O (e)	Q_H (e)	Q_C (e)	Q_S (e)	Q_N (e)	Q_M (e)
A01	-1.0714	0.8059	-0.1684	1.1518	-0.8453	0.6149
A02	-1.0733	0.8256	-0.1318	1.1218	-0.8452	0.6054
A03	-1.0798	0.8196	-0.1167	1.1105	-0.8471	0.6152
A04	-1.0835	0.8176	-0.1198	1.1060	-0.8479	0.5789
A05	-1.0778	0.8211	-0.1151	1.1134	-0.8473	0.5572
A06	-1.0831	0.8182	-0.1175	1.1069	-0.8482	0.5169
A07	-1.0715	0.8240	-0.1104	1.1221	-0.8462	0.6065
A08	-1.0708	0.8260	-0.1045	1.1205	-0.8450	0.6080
A09	-1.0714	0.8256	-0.1046	1.1206	-0.8450	0.6199
A11	-1.0355	0.8419	-0.0988	1.1412	-0.8465	0.7477
A12	-1.0362	0.8360	-0.1002	1.1328	-0.8488	0.7576
A13	-1.0197	0.8490	-0.1716	1.1449	-0.8215	0.8012
A14	-1.0013	0.8543	-0.1520	1.1757	-0.8263	0.7113
A15	-1.0347	0.8392	-0.1890	1.1317	-0.8281	0.6108
A16	-1.0300	0.8416	-0.1767	1.1387	-0.8276	0.6941
A17	-1.0132	0.8470	-0.1534	1.1612	-0.8298	0.6412
A18	-1.0887	0.8136	-0.1188	1.0993	-0.8499	0.5992
A19	-1.0810	0.8206	-0.1230	1.1128	-0.8475	0.5904
A20	-1.0850	0.8159	-0.1167	1.1042	-0.8490	0.5082
A21	-1.0250	0.8442	-0.1473	1.1461	-0.8257	0.6157
A22	-1.0233	0.8450	-0.1456	1.1481	-0.8257	0.6171
A23	-1.0296	0.8404	-0.1488	1.1393	-0.8277	0.5169
A24	-1.0775	0.8215	-0.1131	1.1126	-0.8474	0.5577
A25	-1.0821	0.8178	-0.1168	1.1083	-0.8488	0.5154
B01 -	1.0705	0.8018	-0.1698	1.1529	-0.8433	0.4998
B02 -	1.0745	0.8248	-0.1264	1.1208	-0.8453	0.4915
B03 -	1.0793	0.8192	-0.1145	1.1107	-0.8478	0.5015
B04 -	1.0823	0.8173	-0.1186	1.1070	-0.8484	0.4785
B05 -	1.0775	0.8214	-0.1149	1.1138	-0.8472	0.4649
B06 -	1.0826	0.8179	-0.1179	1.1075	-0.8485	0.4407
B07 -	1.0713	0.8240	-0.1104	1.1223	-0.8462	0.4933
B08 -	1.0707	0.8247	-0.1050	1.1210	-0.8458	0.4960
B09 -	1.0710	0.8243	-0.1049	1.1211	-0.8460	0.5038
B11 -	1.0354	0.8419	-0.0989	1.1413	-0.8465	0.6163
B12 -	1.0363	0.8353	-0.1018	1.1297	-0.8486	0.6261
B13 -	1.0210	0.8480	-0.1760	1.1467	-0.8228	0.6087
B14 -	1.0011	0.8551	-0.1521	1.1771	-0.8256	0.5621
B15 -	1.0339	0.8393	-0.1882	1.1313	-0.8275	0.5110
B16 -	1.0294	0.8421	-0.1771	1.1365	-0.8265	0.5882
B17 -	1.0123	0.8464	-0.1536	1.1608	-0.8300	0.5522
B18 -	1.0887	0.8137	-0.1189	1.0995	-0.8498	0.5220
B19 -	1.0809	0.8207	-0.1232	1.1128	-0.8475	0.5147

B20 -	1.0850	0.8160	-0.1168	1.1043	-0.8490	0.4408
B21 -	1.0248	0.8442	-0.1474	1.1451	-0.8253	0.5076
B22 -	1.0235	0.8448	-0.1460	1.1477	-0.8253	0.5007
B23 -	1.0296	0.8402	-0.1492	1.1395	-0.8279	0.4453
B24 -	1.0774	0.8217	-0.1126	1.1130	-0.8472	0.4624
B25 -	1.0823	0.8178	-0.1170	1.1082	-0.8487	0.4373
C01 -	1.0812	0.8188	-0.1550	1.1581	-0.8633	0.5282
C02 -	1.0772	0.8212	-0.1231	1.1170	-0.8481	0.5214
C03 -	1.0853	0.8171	-0.1158	1.1034	-0.8484	0.5331
C04 -	1.0867	0.8163	-0.1203	1.1023	-0.8481	0.5026
C05 -	1.0808	0.8188	-0.1149	1.1098	-0.8479	0.4872
C06 -	1.0839	0.8171	-0.1174	1.1064	-0.8491	0.4587
C07 -	1.0771	0.8220	-0.1111	1.1152	-0.8467	0.5223
C08 -	1.0767	0.8221	-0.1063	1.1139	-0.8467	0.5261
C09 -	1.0769	0.8222	-0.1061	1.1142	-0.8466	0.5346
C11 -	1.0394	0.8384	-0.0964	1.1362	-0.8482	0.6516
C12 -	1.0474	0.8332	-0.1107	1.1263	-0.8497	0.6576
C13 -	1.0108	0.8454	-0.1774	1.1329	-0.8257	0.6462
C14 -	1.0091	0.8495	-0.1515	1.1667	-0.8289	0.5850
C15 -	1.0348	0.8384	-0.1883	1.1296	-0.8282	0.5340
C16 -	1.0270	0.8439	-0.1704	1.1364	-0.8255	0.6176
C17 -	1.0141	0.8466	-0.1528	1.1600	-0.8300	0.5767
C18 -	1.0895	0.8133	-0.1185	1.0985	-0.8500	0.5448
C19 -	1.0798	0.8202	-0.1234	1.1135	-0.8483	0.5363
C20 -	1.0875	0.8150	-0.1167	1.1013	-0.8493	0.4600
C21 -	1.0279	0.8423	-0.1483	1.1410	-0.8267	0.5350
C22 -	1.0267	0.8424	-0.1459	1.1427	-0.8270	0.5378
C23 -	1.0305	0.8398	-0.1487	1.1382	-0.8283	0.4663
C24 -	1.0809	0.8179	-0.1130	1.1100	-0.8480	0.4913
C25 -	1.0839	0.8174	-0.1165	1.1060	-0.8488	0.4598
D01	-1.0737	0.8290	-0.1712	1.1615	-0.8474	0.3903
D02	-1.0738	0.8239	-0.1281	1.1211	-0.8464	0.3850
D03	-1.0790	0.8192	-0.1144	1.1106	-0.8478	0.3909
D04	-1.0824	0.8174	-0.1186	1.1070	-0.8484	0.3791
D05	-1.0774	0.8215	-0.1149	1.1139	-0.8471	0.3713
D06	-1.0829	0.8182	-0.1177	1.1072	-0.8482	0.3588
D07	-1.0711	0.8241	-0.1103	1.1225	-0.8462	0.3851
D08	-1.0710	0.8243	-0.1054	1.1206	-0.8462	0.3869
D09	-1.0710	0.8243	-0.1049	1.1211	-0.8461	0.3924
D11	-1.0355	0.8420	-0.0989	1.1414	-0.8465	0.4841
D12	-1.0364	0.8353	-0.1016	1.1298	-0.8486	0.4911
D13	-1.0209	0.8481	-0.1758	1.1467	-0.8227	0.4493
D14	-1.0007	0.8545	-0.1522	1.1765	-0.8260	0.4276
D15	-1.0339	0.8395	-0.1883	1.1317	-0.8276	0.4088
D16	-1.0294	0.8421	-0.1771	1.1365	-0.8264	0.4743
D17	-1.0123	0.8464	-0.1536	1.1608	-0.8300	0.4526

D18	-1.0888	0.8137	-0.1189	1.0996	-0.8498	0.4326
D19	-1.0771	0.8236	-0.1283	1.1115	-0.8499	0.4267
D20	-1.0849	0.8159	-0.1169	1.1041	-0.8489	0.3647
D21	-1.0256	0.8433	-0.1484	1.1439	-0.8256	0.3999
D22	-1.0232	0.8448	-0.1460	1.1475	-0.8254	0.3927
D23	-1.0292	0.8403	-0.1498	1.1388	-0.8277	0.3651
D24	-1.0783	0.8208	-0.1151	1.1124	-0.8475	0.3682
D25	-1.0822	0.8182	-0.1171	1.1083	-0.8484	0.3546
E01	-1.0766	0.8269	-0.1880	1.1497	-0.8415	0.2991
E02	-1.0774	0.8218	-0.1215	1.1168	-0.8475	0.2944
E03	-1.0823	0.8183	-0.1128	1.1066	-0.8481	0.3003
E04	-1.0862	0.8159	-0.1203	1.1033	-0.8485	0.2909
E05	-1.0812	0.8191	-0.1158	1.1092	-0.8483	0.2850
E06	-1.0840	0.8173	-0.1177	1.1062	-0.8487	0.2761
E07	-1.0736	0.8236	-0.1078	1.1192	-0.8464	0.2927
E08	-1.0739	0.8235	-0.1033	1.1170	-0.8464	0.2959
E09	-1.0732	0.8239	-0.1018	1.1180	-0.8463	0.3000
E11	-1.0311	0.8391	-0.0872	1.1395	-0.8484	0.4034
E12	-1.0398	0.8336	-0.0996	1.1273	-0.8500	0.4100
E13	-1.0254	0.8443	-0.1818	1.1420	-0.8260	0.3469
E14	-1.0076	0.8496	-0.1706	1.1712	-0.8293	0.3149
E15	-1.0288	0.8415	-0.1678	1.1321	-0.8269	0.3220
E16	-1.0254	0.8436	-0.1679	1.1440	-0.8276	0.4020
E17	-1.0136	0.8465	-0.1527	1.1608	-0.8302	0.3825
E18	-1.0893	0.8140	-0.1183	1.0983	-0.8495	0.3643
E19	-1.0803	0.8191	-0.1197	1.1120	-0.8491	0.3579
E20	-1.0872	0.8151	-0.1169	1.1015	-0.8492	0.2879
E21	-1.0264	0.8449	-0.1461	1.1422	-0.8266	0.3112
E22	-1.0240	0.8444	-0.1449	1.1462	-0.8258	0.3083
E23	-1.0299	0.8408	-0.1490	1.1390	-0.8282	0.2895
E24	-1.0812	0.8190	-0.1143	1.1093	-0.8482	0.2819
E25	-1.0830	0.8179	-0.1171	1.1074	-0.8485	0.2735
F01	-1.0806	0.8036	-0.1929	1.1489	-0.8474	0.3704
F02	-1.0805	0.8203	-0.1200	1.1137	-0.8481	0.3606
F03	-1.0860	0.8159	-0.1137	1.1022	-0.8491	0.3708
F04	-1.0884	0.8139	-0.1206	1.1006	-0.8494	0.3545
F05	-1.0837	0.8180	-0.1168	1.1063	-0.8483	0.3401
F06	-1.0849	0.8165	-0.1174	1.1048	-0.8492	0.3226
F07	-1.0779	0.8210	-0.1095	1.1143	-0.8473	0.3602
F08	-1.0775	0.8212	-0.1044	1.1126	-0.8473	0.3640
F09	-1.0773	0.8213	-0.1037	1.1132	-0.8472	0.3724
F11	-1.0364	0.8356	-0.0947	1.1332	-0.8493	0.5148
F12	-1.0435	0.8316	-0.1012	1.1230	-0.8508	0.5243
F13	-1.0319	0.8401	-0.1870	1.1343	-0.8279	0.4608
F14	-1.0124	0.8460	-0.1747	1.1654	-0.8310	0.3921
F15	-1.0356	0.8378	-0.1883	1.1288	-0.8287	0.3956

F16	-1.0299	0.8397	-0.1793	1.1351	-0.8287	0.4936
F17	-1.0147	0.8455	-0.1534	1.1590	-0.8308	0.4637
F18	-1.0899	0.8132	-0.1184	1.0981	-0.8500	0.4358
F19	-1.0819	0.8200	-0.1214	1.1115	-0.8479	0.4278
F20	-1.0884	0.8147	-0.1168	1.1000	-0.8495	0.3354
F21	-1.0287	0.8414	-0.1469	1.1393	-0.8273	0.3835
F22	-1.0263	0.8425	-0.1457	1.1426	-0.8266	0.3824
F23	-1.0305	0.8396	-0.1489	1.1383	-0.8323	0.3392
F24	-1.0832	0.8177	-0.1142	1.1071	-0.8488	0.3385
F25	-1.0843	0.8173	-0.1172	1.1058	-0.8488	0.3208

Table SI2 (cont)
Descriptor values for CA inhibitors

<i>Comp</i>	E_{SH} (eV)	E_H (eV)	E_L (eV)	E_{SL} (eV)	π_{tail}	ΔH_s (kcal)
A01	-6.9440 -	7.2850 -	1.1700	-0.7190	0.885 -	47.37
A02	-7.1880 -	7.4500 -	1.1560	-0.8200	0.885 -	55.47
A03	-6.5410 -	7.4170 -	0.9230	-0.6120	0.885 -	46.68
A04	-6.3770 -	7.2480 -	0.7690	-0.4250	0.885 -	53.62
A05	-7.0030 -	7.2810 -	1.0570	-0.5040	0.885 -	58.41
A06	-6.7890 -	7.1660 -	0.8780	-0.3670	0.885 -	58.57
A07	-6.6990 -	7.3550 -	1.1650	-0.6300	0.885 -	54.23
A08	-6.7770 -	7.3160 -	1.2840	-0.8530	0.885 -	53.67
A09	-6.7420 -	7.2590 -	1.2690	-0.8820	0.885 -	54.09
A11	-7.1810 -	7.2700 -	1.9810	-1.5120	0.885 -	67.96
A12	-7.1920 -	7.4790 -	1.8540	-1.3150	0.885 -	75.23
A13	-6.9730 -	9.2470 -	2.0020	-0.3150	0.885 -	65.78
A14	-6.9470 -	9.2560 -	2.0160	-1.2320	0.885 -	61.93
A15	-6.5970 -	8.7160 -	1.8640	-0.5460	0.885 -	72.25
A16	-6.4870 -	8.7070 -	1.7440	0.0530	0.885 -	89.01
A17	-6.4130 -	8.4070 -	1.7540	-1.2450	0.885 -	82.84
A18	-6.1490 -	7.2380 -	0.5980	-0.3850	0.885 -	79.22
A19	-6.2820 -	7.0380 -	0.8930	-0.3510	0.885 -	79.23
A20	-6.0360 -	7.1550 -	1.3140	-0.3480	0.885 -	57.25
A21	-6.4880 -	6.9200 -	1.8120	-0.6130	0.885 -	58.37
A22	-6.7370 -	7.0130 -	1.9010	-0.7560	0.885 -	56.11
A23	-6.1470 -	6.8330 -	1.6540	-0.4340	0.885 -	60.61
A24	-7.0230 -	7.3100 -	1.0290	-0.5120	0.885 -	55.65
A25	-6.8380 -	7.1870 -	0.9310	-0.3840	0.885 -	55.62
B01	-6.9270 -	7.2860 -	1.2140	-0.7770	2.150 -	45.64
B02	-6.8030 -	7.2020 -	1.0670	-0.7760	2.150 -	52.26
B03	-6.6050 -	7.3820 -	1.0960	-0.5540	2.150 -	52.83
B04	-6.4060 -	7.2430 -	0.7930	-0.4200	2.150 -	51.35
B05	-7.0110 -	7.2870 -	1.0780	-0.5170	2.150 -	55.90
B06	-6.7970 -	7.1600 -	0.8670	-0.3720	2.150 -	56.63

B07	-6.6950 -	7.3530 -	1.2270	-0.6290	2.150 -	52.02
B08	-6.7520 -	7.2990 -	1.2520	-0.8290	2.150 -	52.27
B09	-6.7190 -	7.2500 -	1.2800	-0.8700	2.150 -	51.96
B11	-7.1670 -	7.2660 -	2.0000	-1.5220	2.150 -	65.59
B12	-7.1390 -	7.2420 -	1.7840	-1.3080	2.150 -	75.00
B13	-6.8400 -	9.2600 -	1.8880	-0.3000	2.150 -	54.98
B14	-6.9690 -	9.3690 -	2.0680	-1.2950	2.150 -	60.57
B15	-6.6160 -	9.1010 -	1.8940	-0.6150	2.150 -	70.45
B16	-6.4920 -	8.7240 -	1.7460	0.0540	2.150 -	-86.46
B17	-6.4240 -	8.8360 -	1.7560	-1.2690	2.150 -	79.87
B18	-6.1520 -	7.2400 -	0.7670	-0.3880	2.150 -	76.75
B19	-6.2920 -	7.0380 -	0.8960	-0.3620	2.150 -	76.92
B20	-6.0310 -	7.1510 -	1.3080	-0.3460	2.150 -	54.79
B21	-6.4910 -	6.9100 -	1.7900	-0.5960	2.150 -	57.54
B22	-6.7260 -	6.9920 -	1.8770	-0.6320	2.150 -	49.79
B23	-6.1210 -	6.8240 -	1.6440	-0.4170	2.150 -	57.24
B24	-7.0370 -	7.3030 -	1.2710	-0.5230	2.150 -	52.00
B25	-6.8330 -	7.1820 -	0.9370	-0.3790	2.150 -	52.40
C01	-6.7450 -	7.2010 -	1.0750	-0.5790	1.000 -	48.00
C02	-6.5540 -	7.1360 -	0.9560	-0.5470	1.000 -	56.14
C03	-6.3860 -	7.3140 -	0.8030	-0.4500	1.000 -	56.83
C04	-6.1410 -	7.2100 -	0.7370	-0.4280	1.000 -	59.04
C05	-6.9070 -	7.1950 -	0.9460	-0.4250	1.000 -	58.33
C06	-6.7490 -	7.1490 -	0.8670	-0.3500	1.000 -	59.06
C07	-6.4780 -	7.2720 -	0.9810	-0.5390	1.000 -	55.18
C08	-6.5250 -	7.2250 -	1.0340	-0.7420	1.000 -	54.93
C09	-6.5060 -	7.1780 -	1.0383	-0.7700	1.000 -	55.61
C11	-6.8470 -	7.2370 -	1.8980	-1.4730	1.000 -	73.67
C12	-6.7290 -	7.2490 -	1.6610	-1.3390	1.000 -	71.32
C13	-6.7360 -	9.2380 -	1.9330	-0.1710	1.000 -	65.12
C14	-6.6890 -	8.9310 -	1.9580	-1.4250	1.000 -	59.72
C15	-6.6000 -	8.7090 -	1.8790	-0.5990	1.000 -	72.80
C16	-6.4980 -	7.0320 -	2.0420	-0.1810	1.000 -	88.08
C17	-6.8550 -	8.3950 -	1.7750	-1.1670	1.000 -	84.28
C18	-6.1350 -	7.2390 -	0.7220	-0.3810	1.000 -	81.10
C19	-6.2310 -	7.0980 -	0.8600	-0.3200	1.000 -	81.79
C20	-5.9570 -	7.0790 -	1.2370	-0.3150	1.000 -	64.68
C21	-6.2390 -	6.8510 -	1.7560	-0.5020	1.000 -	59.32
C22	-6.5490 -	6.8990 -	1.7650	-0.5670	1.000 -	59.39
C23	-6.1080 -	6.8160 -	1.6460	-0.4130	1.000 -	62.82
C24	-6.9040 -	7.2180 -	0.9900	-0.4290	1.000 -	59.17
C25	-6.8110 -	7.1640 -	0.8800	-0.3590	1.000 -	58.98
D01	-6.9290 -	7.2680 -	1.1650	-0.6640	3.090 -	47.28
D02	-6.8970 -	7.2260 -	1.0480	-0.6780	3.090 -	54.09
D03	-6.6050 -	7.3810 -	1.1120	-0.5560	3.090 -	53.26
D04	-6.4040 -	7.2430 -	0.7920	-0.4200	3.090 -	51.70

D05	-7.0160 -	7.2920 -	1.0850	-0.5260	3.090 -	56.22
D06	-6.7900 -	7.1650 -	0.8760	-0.3670	3.090 -	56.77
D07	-6.6980 -	7.3530 -	1.2480	-0.6310	3.090 -	52.30
D08	-6.7300 -	7.3080 -	1.2960	-0.8390	3.090 -	51.62
D09	-6.7190 -	7.2520 -	1.3010	-0.8740	3.090 -	52.03
D11	-7.1640 -	7.2660 -	2.0000	-1.5230	3.090 -	65.80
D12	-7.1370 -	7.4220 -	1.7830	-1.3080	3.090 -	75.30
D13	-6.8480 -	8.8560 -	1.9020	-0.3030	3.090 -	55.68
D14	-6.9500 -	9.0360 -	2.0450	-1.2770	3.090 -	60.86
D15	-6.6200 -	8.7300 -	1.8990	-0.6250	3.090 -	72.04
D16	-6.4940 -	8.7110 -	1.7480	0.0510	3.090 -	86.32
D17	-6.4230 -	8.8350 -	1.7550	-1.2710	3.090 -	80.25
D18	-6.1510 -	7.2400 -	0.7660	-0.3880	3.090 -	77.10
D19	-6.2550 -	7.0690 -	0.9400	-0.2090	3.090 -	77.10
D20	-6.0260 -	7.1520 -	1.3120	-0.3460	3.090 -	55.27
D21	-6.3800 -	6.9000 -	1.7580	-0.6370	3.090 -	57.09
D22	-6.7220 -	6.9910 -	1.8780	-0.6440	3.090 -	50.44
D23	-6.1230 -	6.8260 -	1.6480	-0.4190	3.090 -	57.60
D24	-6.9700 -	7.2630 -	1.1190	-0.4710	3.090 -	50.60
D25	-6.8440 -	7.1850 -	0.9550	-0.3840	3.090 -	52.70
E01	-6.7260 -	7.1880 -	1.5800	-0.8470	3.430 -	32.29
E02	-6.5540 -	7.1350 -	1.4500	-0.8520	3.430 -	37.87
E03	-6.4980 -	7.3160 -	1.6110	-0.4600	3.430 -	38.58
E04	-6.2310 -	7.2370 -	0.6970	-0.4040	3.430 -	40.88
E05	-6.8730 -	7.2020 -	1.1010	-0.4050	3.430 -	39.87
E06	-6.7610 -	7.1440 -	0.9270	-0.3140	3.430 -	40.58
E07	-6.6410 -	7.3170 -	1.7320	-0.5660	3.430 -	36.51
E08	-6.6410 -	7.2550 -	1.8000	-0.7500	3.430 -	36.85
E09	-6.6740 -	7.2190 -	1.8070	-0.8020	3.430 -	36.22
E11	-7.2960 -	7.3840 -	2.1150	-1.4510	3.430 -	58.40
E12	-7.0500 -	7.3960 -	2.1080	-1.3300	3.430 -	59.30
E13	-6.8830 -	8.8690 -	2.3100	-1.1330	3.430 -	44.08
E14	-6.7610 -	8.9330 -	2.2660	-1.4210	3.430 -	39.98
E15	-6.6120 -	8.6790 -	1.9890	-0.5120	3.430 -	55.50
E16	-6.7290 -	8.9500 -	2.0970	-0.2270	3.430 -	69.18
E17	-6.3490 -	8.3910 -	1.5270	-0.8620	3.430 -	66.00
E18	-6.1530 -	7.2410 -	0.7490	-0.3900	3.430 -	62.32
E19	-6.1910 -	7.0710 -	0.8820	-0.2480	3.430 -	61.21
E20	-5.9950 -	7.2380 -	1.2360	-0.3140	3.430 -	48.94
E21	-6.3240 -	6.8730 -	1.9250	-0.4460	3.430 -	40.75
E22	-6.7320 -	6.9710 -	2.0030	-0.6080	3.430 -	39.05
E23	-6.1140 -	6.8220 -	1.6490	-0.4200	3.430 -	44.10
E24	-6.8900 -	7.2420 -	0.9590	-0.4270	3.430 -	37.30
E25	-6.8300 -	7.1770 -	0.8910	-0.3720	3.430 -	38.20
F01	-6.5460 -	7.1430 -	0.9540	-0.5080	2.020 -	35.98
F02	-6.4060 -	7.0750 -	0.8550	-0.4900	2.020 -	40.82

F03	-6.3460 -	7.2530 -	0.7480	-0.3820	2.020 -	41.69
F04	-6.1240 -	7.1740 -	0.6560	-0.3500	2.020 -	45.08
F05	-6.7310 -	7.1960 -	0.8680	-0.3980	2.020 -	43.01
F06	-6.6750 -	7.1400 -	0.8150	-0.3320	2.020 -	43.65
F07	-6.4390 -	7.2260 -	1.7510	-0.4690	2.020 -	40.35
F08	-6.4900 -	7.1900 -	1.8000	-0.6780	2.020 -	39.94
F09	-6.4680 -	7.1360 -	1.8000	-0.7120	2.020 -	40.33
F11	-7.0050 -	7.1350 -	2.0410	-1.4770	2.020 -	61.70
F12	-6.8770 -	7.3020 -	2.0220	-1.3690	2.020 -	62.83
F13	-6.6720 -	8.7650 -	2.2040	-1.4070	2.020 -	47.79
F14	-6.5850 -	8.8990 -	2.1150	-1.3870	2.020 -	41.86
F15	-6.5890 -	8.7000 -	1.8760	-0.5740	2.020 -	57.48
F16	-6.5250 -	8.9710 -	1.7850	-0.0320	2.020 -	70.13
F17	-6.6900 -	8.3580 -	1.8540	-1.0340	2.020 -	68.43
F18	-6.1400 -	7.2460 -	0.7260	-0.3750	2.020 -	66.23
F19	-6.2280 -	7.0580 -	0.8830	-0.3040	2.020 -	64.96
F20	-5.9600 -	7.1900 -	1.2000	-0.3060	2.020 -	52.33
F21	-6.1650 -	6.8050 -	1.8940	-0.4310	2.020 -	44.41
F22	-6.5850 -	6.8690 -	1.6990	-0.5070	2.020 -	42.74
F23	-6.0910 -	6.8120 -	1.6430	-0.4070	2.020 -	47.36
F24	-6.8250 -	7.1990 -	0.9120	-0.3850	2.020 -	41.06
F25	-6.7970 -	7.1550 -	0.8580	-0.3500	2.020 -	41.64

Table SI2 (cont)
Descriptor values for CA inhibitors

<i>Comp</i>	Π_{xx} (Å)	Π_{yy} (Å)	Π_{zz} (Å)	Φ_H (°)	Φ_L (°)
A01	138.75	125.90	75.42	149.6	34.8
A02	149.00	121.13	70.52	88.9	55.0
A03	166.61	120.78	63.73	88.7	44.1
A04	172.54	115.72	82.88	89.7	45.4
A05	164.67	111.88	90.87	92.2	42.4
A06	176.20	84.47	130.01	91.4	43.0
A07	166.52	119.02	74.27	76.0	39.7
A08	166.22	133.48	73.32	75.0	43.9
A09	166.92	140.82	73.66	74.7	44.5
A11	198.41	175.67	90.67	71.3	27.1
A12	185.74	159.85	91.36	117.7	31.6
A13	153.91	91.49	87.39	112.8	59.8
A14	178.70	120.35	71.44	119.4	58.0
A15	203.69	123.28	108.22	111.8	60.5
A16	232.34	185.55	161.07	114.1	57.5
A17	260.97	181.44	182.09	118.5	54.1
A18	304.75	158.58	149.42	88.9	46.5

A19	283.18	173.97	144.89	31.0	43.0
A20	259.46	201.60	93.60	89.0	44.3
A21	239.66	131.45	102.11	113.8	51.5
A22	247.78	133.78	98.60	123.2	52.3
A23	279.94	158.50	98.57	114.3	49.1
A24	165.71	126.26	73.56	93.0	42.5
A25	180.10	94.44	116.11	91.2	43.7
B01	169.14	152.22	128.94	150.3	33.1
B02	185.14	135.21	135.66	36.1	50.7
B03	208.01	113.12	144.08	90.4	46.2
B04	217.88	142.35	120.67	90.4	44.2
B05	219.47	138.58	121.12	91.8	42.6
B06	217.90	163.82	118.50	88.3	47.3
B07	207.91	127.41	136.62	76.2	39.8
B08	208.90	162.37	112.53	75.5	43.3
B09	207.15	173.27	113.29	75.6	43.8
B11	249.47	203.45	125.12	71.9	27.9
B12	229.09	200.97	122.40	114.9	28.6
B13	211.31	137.01	95.61	112.8	58.6
B14	229.74	143.23	111.96	119.3	59.6
B15	233.97	179.08	130.70	111.8	60.8
B16	285.89	226.65	178.37	114.1	57.6
B17	324.18	225.70	189.07	118.5	54.1
B18	359.35	192.12	175.81	88.8	45.8
B19	337.41	201.04	177.51	31.0	43.1
B20	286.69	257.88	122.42	88.9	44.3
B21	296.52	153.90	134.77	113.4	51.4
B22	314.25	185.34	104.23	123.4	52.2
B23	312.23	211.91	121.82	114.0	49.1
B24	211.15	161.26	105.70	94.6	42.3
B25	222.73	147.95	130.13	91.3	43.5
C01	221.80	193.41	72.73	148.0	36.0
C02	158.09	163.05	162.27	33.4	42.3
C03	177.11	143.22	171.21	88.7	47.4
C04	163.90	179.16	170.40	87.8	43.8
C05	136.48	169.04	186.36	86.6	48.0
C06	196.76	155.74	181.50	87.8	46.8
C07	180.21	154.96	164.18	77.8	44.2
C08	178.19	181.86	151.80	78.6	48.8
C09	177.22	205.10	137.38	78.2	51.4
C11	252.15	200.84	159.48	86.2	30.8
C12	236.85	192.69	160.76	93.6	29.3
C13	165.43	164.50	142.62	113.1	58.7
C14	206.22	175.03	137.41	118.7	59.3
C15	228.20	179.12	172.44	111.8	60.7
C16	277.30	227.27	212.90	114.6	60.8

C17	239.38	255.82	256.98	118.0	54.9
C18	335.15	210.18	210.22	88.9	45.7
C19	251.86	208.11	263.69	31.7	35.8
C20	264.97	287.59	151.97	88.7	44.7
C21	242.03	157.19	213.60	110.0	51.5
C22	324.35	223.38	88.29	117.4	50.9
C23	358.71	236.00	98.64	113.7	49.1
C24	140.66	174.23	176.90	85.6	47.4
C25	250.79	168.72	125.53	91.9	43.1
D01	279.79	209.93	150.01	150.9	37.7
D02	291.17	169.54	181.93	40.9	47.9
D03	277.84	177.78	196.17	89.6	43.9
D04	295.05	202.87	169.86	90.4	44.2
D05	305.87	191.58	169.01	91.7	42.6
D06	291.80	191.64	204.30	91.5	43.0
D07	278.36	181.99	198.66	76.2	39.9
D08	279.05	189.77	203.93	76.6	43.0
D09	279.88	215.64	185.29	75.7	43.8
D11	330.07	251.70	184.22	72.1	28.0
D12	308.45	256.01	174.96	114.7	28.6
D13	300.02	183.55	148.35	112.8	58.8
D14	290.51	181.68	196.53	119.3	59.1
D15	318.97	209.13	203.83	111.8	60.9
D16	371.79	270.24	236.86	114.1	57.6
D17	409.44	270.50	246.93	118.4	54.1
D18	433.75	251.83	229.42	89.1	46.5
D19	361.16	290.46	234.41	31.5	39.5
D20	358.61	327.14	169.53	89.1	44.3
D21	361.83	187.14	228.60	111.4	51.1
D22	406.51	235.56	153.04	123.1	52.3
D23	402.77	262.39	169.57	114.0	49.0
D24	301.72	198.40	162.26	93.4	43.0
D25	283.75	225.44	177.40	91.6	43.3
E01	258.21	189.05	172.80	151.2	25.4
E02	305.20	197.03	127.53	31.8	68.9
E03	316.67	196.95	123.71	87.8	45.1
E04	309.61	171.57	173.19	87.9	45.2
E05	270.96	197.05	166.55	94.5	42.5
E06	295.49	165.54	203.51	90.7	41.5
E07	287.61	176.25	175.87	74.7	42.9
E08	318.08	215.96	124.28	75.4	45.9
E09	290.75	193.58	176.02	74.0	46.0
E11	324.81	244.18	162.70	168.4	34.0
E12	319.08	233.08	166.83	107.0	35.3
E13	275.46	162.58	166.83	111.8	63.7
E14	293.26	182.96	173.86	117.0	66.6

E15	290.01	214.77	210.13	114.2	59.8
E16	449.56	248.55	183.38	114.3	61.2
E17	386.87	244.20	277.39	118.8	40.9
E18	446.04	228.64	226.60	88.7	45.9
E19	409.15	252.43	223.86	31.1	42.5
E20	371.91	313.32	153.86	88.7	44.5
E21	347.36	230.17	183.32	113.0	53.4
E22	359.64	162.38	216.96	126.0	54.0
E23	352.33	196.90	249.10	114.0	49.1
E24	251.80	203.84	174.15	86.2	47.1
E25	298.30	186.07	173.09	91.9	43.2
F01	238.10	183.22	65.17	152.5	43.2
F02	246.58	178.58	67.89	31.0	40.8
F03	266.46	154.82	82.54	87.9	47.1
F04	245.86	150.51	121.74	87.8	46.2
F05	243.72	186.50	75.15	87.2	47.4
F06	263.25	174.83	92.50	91.0	43.2
F07	268.75	159.60	83.16	76.8	43.7
F08	269.92	169.94	84.85	77.8	46.5
F09	269.41	175.22	87.61	77.4	46.8
F11	290.86	164.06	152.19	77.9	36.0
F12	289.09	212.71	87.70	100.7	35.1
F13	253.36	152.05	70.67	111.9	64.0
F14	270.25	158.91	91.99	117.3	65.8
F15	294.61	162.02	118.26	111.8	60.5
F16	409.03	188.91	156.09	112.9	57.3
F17	344.20	226.41	207.16	117.9	58.0
F18	418.73	201.43	151.21	88.8	45.5
F19	380.67	221.08	156.77	30.5	42.6
F20	300.07	291.31	106.99	88.8	44.4
F21	346.60	204.97	81.82	110.7	53.3
F22	329.98	215.67	61.42	120.7	49.8
F23	294.28	175.29	198.44	113.6	49.0
F24	244.07	198.14	57.03	93.7	42.4
F25	262.71	170.00	92.60	88.1	46.9