Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Electronic Supplementary Information

Rational design of small modified peptides as ACE inhibitors

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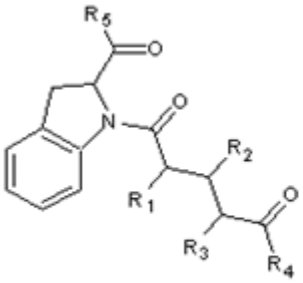
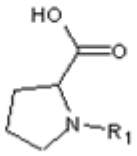
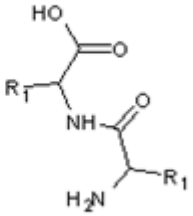
Table S1. Series of compounds used in the QSAR analyses.



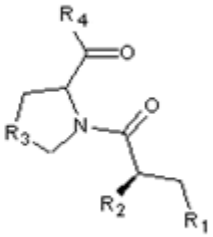
1-17



18-29

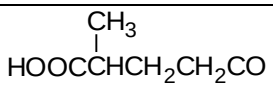
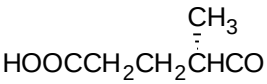


30-87



88-102

Cpd	R_1	R_2	R_3	R_4	R_5	pIC_{50} exp.
1[a]	H	H	H	OH	OH	6.585
2	Me	H	H	OH	OH	7.193
3	Me	H	H	OMe	OH	5.161
4	Me	H	H	NH_2	OH	4.795
5	(R)-Me	H	H	OH	OH	7.356
6[a]	(R)-Me	H	H	OEt	OH	4.958
7	*i*-Pr	H	H	OH	OH	7.301
8	H	Me	H	OH	OH	4.431
9	H	Me_2	H	OH	OH	3.537
10	H	H	Me	OH	OH	6.036
11[a]	H	H	Me	OH	OEt	3.769
12	Me	H	Me	OH	OEt	5.055
13	Me	H	Me	OH	OH	6.721
14	Me	H	Me	OH	OH	7.267
15[b]	(R)-Me	H	(R)-Me	OH	OH	7.552
16[a]	(R)-Me	H	(R)-Me	OEt	OH	5.259
17	(R)-Me	H	(R)-Me	OH	OEt	4.552
18	$HOOCCH_2\overset{\blacktriangledown}{C}H(CH_3)CO$	-	-	-	-	4.657
19	$HOOC\dot{C}HCH_2CO$ (CH3)	-	-	-	-	3.214
20	$HOOCCH_2\dot{C}HCO$ (CH3)	-	-	-	-	2.829
21[a]	$HOOC\overset{\blacktriangledown}{C}HCH_2CO$ (CH3)	-	-	-	-	2.585
22	$HOOCCH_2CH_2\overset{\blacktriangledown}{C}HCO$ (CH3)	-	-	-	-	5.309
23	$HOOCCH_2CH(CH_3)CH_2CO$	-	-	-	-	2.92

24		-	-	-	-	3.585
25		-	-	-	-	3.022
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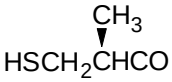
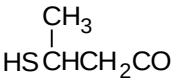
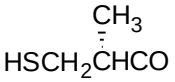
27[b]		-	-	-	-	7.638
28		-	-	-	-	5.958
29		-	-	-	-	5.619
30	YG	-	-	-	-	2.7
31[a]	YA	-	-	-	-	3.34
32	WG	-	-	-	-	2.23
33	VY	-	-	-	-	4.66
34[b]	VW	-	-	-	-	5.8
35	VP	-	-	-	-	3.38
36[a]	VG	-	-	-	-	2.96
37	VF	-	-	-	-	4.28
38	TG	-	-	-	-	2
39	SG	-	-	-	-	2.07
40	RW	-	-	-	-	4.8
41[a]	RP	-	-	-	-	3.74
42	RF	-	-	-	-	3.64
43	RA	-	-	-	-	3.34
44	QG	-	-	-	-	2.13
45	PG	-	-	-	-	1.77
46[a]	MG	-	-	-	-	2.32
47	LG	-	-	-	-	2.06
48	LA	-	-	-	-	3.51
49	KG	-	-	-	-	2.49
50	KA	-	-	-	-	3.42
51[a]	IY	-	-	-	-	5.43
52	IW	-	-	-	-	5.7
53	IP	-	-	-	-	3.89
54	IG	-	-	-	-	2.92
55	IF	-	-	-	-	3.03
56[a]	HL	-	-	-	-	2.49
57	HG	-	-	-	-	2.2
58	GY	-	-	-	-	3.68
59	GW	-	-	-	-	4.52
60	GV	-	-	-	-	2.34
61[a]	GT	-	-	-	-	2.24

62	GS	-	-	-	-	2.42
63	GR	-	-	-	-	2.49
64	GQ	-	-	-	-	2.15
65	GP	-	-	-	-	3.35
66[a]	GM	-	-	-	-	2.85
67	GL	-	-	-	-	2.6
68	GK	-	-	-	-	2.27
69	GI	-	-	-	-	2.92
70	GH	-	-	-	-	2.51
71[a]	GG	-	-	-	-	2.14
72	GF	-	-	-	-	3.2
73	GE	-	-	-	-	2.27
74	GD	-	-	-	-	2.04
75	GA	-	-	-	-	2.7
76[a]	FR	-	-	-	-	3.04
77	FG	-	-	-	-	2.43
78	EG	-	-	-	-	2
79	EA	-	-	-	-	2
80	DG	-	-	-	-	1.85
81[a]	DA	-	-	-	-	2.42
82	AY	-	-	-	-	4.06
83	AW	-	-	-	-	5
84	AP	-	-	-	-	3.64
85	AG	-	-	-	-	2.6
86[a]	AF	-	-	-	-	3.72
87	AA	-	-	-	-	3.21
88[b]	SeH	Me	-	OH	-	7.44
89	SeH	NH_2	-	OMe	-	6.47
90	SH	NH_2	-	OMe	-	5.19
91[a]	SeH	Me	-	F[c]	-	5.39
92	SeH	NH_2	-	F[c]	-	6.74
93	SH	NH_2	-	F[c]	-	5.46
94	SeH	NH_2	-	V[c]	-	5.06
95	SeH	NH_2	-	A[c]	-	4.90
96[a]	SeH	NH_2	CH_2	OMe	-	5.16
97	SH	Me	-	F	-	6.16
98[b]	SeH	Me	-	F	-	7.12
99	SeH	Me	-	Y	-	5.27
100	SeH	Me	-	V	-	5.29
101[a]	SeH	NH_2	-	OH	-	6.68
102	SH	NH_2	-	OH	-	5.640

[a] Test set compounds. [b] The most active compound of each series used to combined substructures to give the proposed compounds **A**-**I**. [c] The carboxylic hydrogen of the peptides were replaced by a methyl group.

Table S2. Statistical parameters of the QSAR analyses based on physicochemical descriptors (MIA-QSAR included for comparison).

QSAR model[a]		Calibration	LOOCV	Test set	Y-rand[b]
MIA-QSAR	r^2	0.909	0.604	0.779	0.600
	RMSE	0.492	1.044	0.687	1.028
Complete model	r^2	0.607	0.573	0.536	0.014
	RMSE	1.041	1.093	0.999	1.879
Variable selection with PCA	r^2	0.602	0.559	0.518	0.014
	RMSE	1.034	1.094	1.000	1.784
Variable selection with PCA/GA	r^2	0.537	0.463	0.390	0.033
	RMSE	1.113	1.217	1.148	1.650
Variable selection with GA	r^2	0.873	0.729	0.674	0.377
	RMSE	0.582	0.862	0.832	1.286
Variable selection with GA/PCA	r^2	0.622	0.562	0.552	0.061
	RMSE	1.003	1.082	0.938	1.580
Variable selection with GA/6×	r^2	0.787	0.742	0.650	0.068
	RMSE	0.753	0.831	0.884	1.574

[a] Complete model with 1459 physicochemical descriptors obtained from the Dragon software; models obtained from descriptors selected using: Principal Component Analysis (PCA, 11 descriptors with higher scores and loadings), PCA/GA (9 descriptors selected using PCA followed by genetic algorithm), GA (407 descriptors selected using genetic algorithm, in a single run), GA/PCA (4 descriptors selected using genetic algorithm followed by PCA), and GA/6× (5 descriptors selected using six algorithm genetic runs). Descriptors of the complete model and GA model were regressed against the corresponding pIC_{50} values using PLS, while MLR was used as regression method for the remaining physicochemical-based models. [b] Mean of 10 repetitions for the Y-randomization test.