Supporting Materials

Table S1. The PDB entries, the descriptions of the complexes and the experimental binding free energies

No.	PDB	$\Delta G_{exp.}$	Descriptions	References
a1	1D3D	-12.39	alpha-thrombin/benzo[B]thiophene inhibitor 4	[1]
a2	1D3P	-10.08	alpha-thrombin/benzo[B]thiophene inhibitor 3	[1]
a3	1D3Q	-8.92	alpha-thrombin/benzo[B]thiophene inhibitor 2	[1]
a4	1D3T	-7.68	alpha-thrombin/benzo[B]thiophene inhibitor 1	[1]
a5	1DWB	-3.98	alpha-thrombin/benzamidine	[2]
a6	1DWC	-10.6	alpha-thrombin/MD-805	[3]
a7	1DWD	-11.57	alpha-thrombin/napap	[4]
b1	1AVD	-20.40	avidin/biotin	[5]
b2	×	-14.30	avidin/2′-iminobiotin	[5]
b3	×	-14.00	avidin/desthiobiotin	[5]
b4	×	-8.80	avidin/1′-*N*methoxycarbonylbiotinmethyl ester	[5]
b5	×	-8.20	avidin/D-4-*n*-hexyl-2-iminoimidazolidine	[5]
b6	×	-5.00	avidin/D-4-*n*-hexyloxazolidone	[5]
b7	×	-4.50	avidin/imidazolidone	[5]
c1	1AC4	-3.85	cytochrome C peroxidase/2,3,4-trimethyl-1,3-thiazole	[6]
c2	1AC8	-4.78	cytochrome C peroxidase/3,4,5-trimethylthiazole	[6]
c3	1AEB	-4.81	cytochrome C peroxidase/3-methylthiazole	[6]
c4	1AED	-5.86	cytochrome C peroxidase/3,4-dimethylthiazole	[6]
c5	1AEE	-3.96	cytochrome C peroxidase/aniline	[6]
c6	1AEF	-6.00	cytochrome C peroxidase/3-aminopyridine	[6]
c7	1AEG	-5.99	cytochrome C peroxidase/4-aminopyridine	[6]
c8	1AEH	-4.96	cytochrome C peroxidase/2-amino-4-methylthiazole	[6]
c9	1AEJ	-5.21	cytochrome C peroxidase/1-vinylimidazole	[6]
c10	1AEK	-4.92	cytochrome C peroxidase/indoline	[6]
c11	1AEM	-4.92	cytochrome C peroxidase/imidazo[1,2-A]pyridine	[6]
c12	1AEN	-7.07	cytochrome C peroxidase/2-amino-5-methylthiazole	[6]
c13	1AEO	-5.02	cytochrome C peroxidase/2-aminopyridine	[6]
c14	1AEQ	-4.73	cytochrome C peroxidase/2-ethylimidazole	[6]
c15	1AES	-4.33	cytochrome C peroxidase/imidazole	[6]
c16	1AET	-5.82	cytochrome C peroxidase/1-methylimidazole	[6]
c17	1AEU	-5.94	cytochrome C peroxidase/2-methylimidazole	[6]
c18	1AEV	-6.06	cytochrome C peroxidase/2-aminothiazole	[6]
d1	1NSC	-4.09	neuraminidase/sialic acid	[7]
d2	1NSD	-7.23	neuraminidase/dana	[8]
d3	2QWB	-3.74	mutated neuraminidase/sialic acid	[9]
d4	2QWC	-4.84	mutated neuraminidase/neu5ac2en	[9]
d5	2QWD	-6.61	mutated neuraminidase/4-amino-neu5ac2en	[9]

d6	2QWE	-10.20	mutated neuraminidase/4-guanidino-neu5ac2en	[9]
d7	2QWF	-7.73	mutated neuraminidase/g20	[9]
d8	2QWG	-11.45	mutated neuraminidase/g28	[9]
e1	2CPP	-7.90	P450cam/Camphor	[10]
e2	6CPP	-5.91	P450cam/Camphane	[10]
e3	×	-6.54	P450cam/Camphoroquinone	[10]
e4	7CPP	-5.57	P450cam/Norcamphor	[10]
e5	×	-5.52	P450cam/ethylbenzene	[10]
e6	×	-5.93	P450cam/3,3,5,5-tetramethylcyclohexanone	[10]
e7	8CPP	-7.53	P450cam/thiocamphore	[10]
e8	4CPP	-5.90	P450cam/Adamantine	[10]
e9	5CPP	-7.40	P450cam/adamantanone	[10]
f1	1APT	-12.83	penicillopepsin/pepstatin analogue	[11]
f2	1APU	-10.51	penicillopepsin/pepstatin analogue	[11]
f3	1APV	-12.27	penicillopepsin/iva-val-val(H)Dfo-n-methylamide	[12]
f4	1APW	-10.91	penicillopepsin/iva-val-valDfo-n-methylamide	[9]
f5	2WEA	-8.37	penicillopepsin/pp6	[13]
f6	2WEB	-7.03	penicillopepsin/pp4	[13]
f7	2WEC	-6.80	penicillopepsin/pp5	[13]

Table S2. The binding free energies for the α-thrombin ligands based on two different solute dielectric constants (ε_{in}= 1 and ε_{in}= 2) calculated by MM/PBSA (kcal/mol)

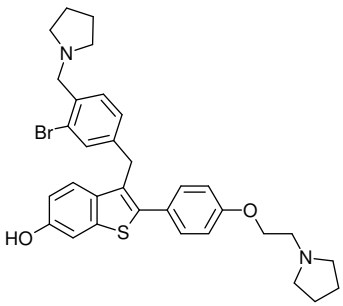
No.	ΔE_{vdw}	ΔE_{ele}	ΔG_{PB}	ΔG_{SA}	$\Delta E_{ele}+\Delta G_{PB}$	$\Delta E_{vdw}+\Delta G_{SA}$	$T\Delta S$	$\Delta G_{cal.}$	$\Delta G_{exp.}$
				ε_{in}= 1					
a1	-58.86±1.09[a]	-17.49±0.98	57.19±1.70	-7.61±0.17	39.71±0.73	-66.47±1.27	-22.81±1.57	-3.96±1.03	–12.39
a2	-62.42±1.69	-14.56±9.43	60.57±7.55	-7.65±0.03	46.01±1.88	-70.06±1.72	20.20±3.01	-3.85±2.85	–10.08
a3	-52.69±1.18	-8.61±1.06	49.43±1.78	-6.68±0.24	40.82±0.72	-59.37±1.42	-20.01±0.65	1.47±1.36	–8.92
a4	-50.58±2.58	-1.85±0.27	37.73±0.54	-6.42±0.13	35.88±0.27	57.00±2.71	-17.97±1.06	-3.16±1.38	–7.68
a5	-18.73±0.24	-133.38±1.13	193.46±0.23	-2.79±0.00	60.08±1.36	-21.51±0.24	-15.50±0.82	54.07±0.79	–3.98
a6	-57.79±0.46	-72.31±0.44	121.35±0.61	-7.11±0.01	49.04±0.17	-64.89±0.45	-24.99±1.73	9.14±2.01	–10.6
a7	-58.27±0.17	-162.49±0.25	249.30±0.92	-7.02±0.04	86.81±1.18	-65.29±0.13	-22.53±0.33	44.05±0.98	–11.57
				ε_{in}= 2					
a1	-58.86±1.09[a]	-8.74±0.49	28.29±0.70	-7.61±0.17	19.54±0.22	-66.47±1.27	-22.81±1.57	-24.12±0.52	–12.39
a2	-62.42±1.69	-7.28±4.71	29.74±3.64	-7.65±0.03	22.46±1.07	-70.06±1.72	20.20±3.01	-27.40±3.65	–10.08
a3	-52.69±1.18	-4.30±0.53	23.97±0.88	-6.68±0.24	19.66±0.35	-59.37±1.42	-20.01±0.65	-19.69±1.73	–8.92
a4	-50.58±2.58	-0.93±0.13	18.23±0.31	-6.42±0.13	17.31±0.17	57.00±2.71	-17.97±1.06	-21.73±1.47	–7.68
a5	-18.73±0.24	-66.69±0.56	93.87±0.16	-2.79±0.00	27.18±0.72	-21.51±0.24	-15.50±0.82	21.16±0.15	–3.98
a6	-57.79±0.46	-36.15±0.22	59.07±0.27	-7.11±0.01	22.92±0.05	-64.89±0.45	-24.99±1.73	-16.99±2.13	–10.6
a7	-58.27±0.17	-81.24±0.13	120.87±0.44	-7.02±0.04	39.63±0.57	-65.29±0.13	-22.53±0.33	-3.14±0.37	–11.57

Table S3. The experimental and the predicted binding free energies and the corresponding energy terms calculated by MM/GBSA (kcal/mol)

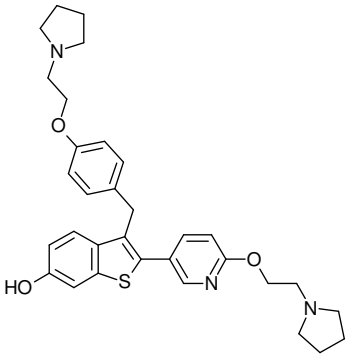
No.	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	$\Delta E_{ele}+\Delta G_{GB}$	$\Delta E_{vdw}+\Delta G_{SA}$	TΔS	$\Delta G_{cal.}$	$\Delta G_{exp.}$
				α-thrombin (ε_{in} = 4)					
a1	-58.86±1.09[a]	-8.75±0.49	17.62±0.25	-7.61±0.17	8.87±0.23	-66.47±1.27	-22.81±1.57	-34.79±0.07	-12.39
a2	-62.42±1.69	-7.28±4.71	18.84±2.34	-7.65±0.03	11.56±2.37	-70.06±1.72	20.20±3.01	-38.31±2.35	-10.08
a3	-52.69±1.18	-4.30±0.53	15.17±0.75	-6.68±0.24	10.86±0.22	-59.37±1.42	-20.01±0.65	-28.49±1.85	-8.92
a4	-50.58±2.58	-0.93±0.13	11.48±0.39	-6.42±0.13	10.56±0.25	57.00±2.71	-17.97±1.06	-28.48±1.39	-7.68
a5	-18.73±0.24	-66.69±0.56	61.51±0.59	-2.79±0.00	5.18±0.02	-21.51±0.24	-15.50±0.82	-11.20±0.60	-3.98
a6	-57.79±0.46	-36.15±0.22	44.74±0.21	-7.11±0.01	8.58±0.01	-64.89±0.45	-24.99±1.73	-31.32±2.19	-10.6
a7	-58.27±0.17	-81.24±0.13	82.18±0.10	-7.02±0.04	0.94±0.02	-65.29±0.13	-22.53±0.33	-41.83±0.17	-11.57
				avidin (ε_{in} = 1)					
b1	-30.31±0.30	-172.54±4.72	157.25±4.70	-4.21±0.01	-15.29±0.02	-34.52±0.31	-18.69±0.22	-31.12±0.50	-20.4
b2	-30.10±0.83	-156.76±4.74	145.28±4.07	-4.27±0.04	-11.48±0.67	-34.57±0.79	-20.44±0.65	-25.41±0.81	-14.3
b3	-28.80±0.19	-165.47±5.49	147.76±3.32	-4.21±0.01	-17.71±2.17	-33.01±0.17	-21.33±0.43	-29.39±1.92	-14.0
b4	-40.31±0.14	-28.99±0.50	37.95±0.22	-5.55±0.06	8.96±0.72	-45.86±0.19	-17.64±1.61	-19.44±2.14	-8.8
b5	-28.52±1.39	-21.67±7.19	23.89±3.15	-4.09±0.04	2.22±4.03	-32.61±1.43	-15.19±1.03	-15.21±3.63	-8.2
b6	-25.53±1.00	-21.97±0.20	22.87±0.01	-3.69±0.28	0.90±0.19	-29.22±1.28	-14.30±1.61	-14.01±0.14	-5.0
b7	-11.99±0.16	-25.11±0.30	19.93±0.11	-2.12±0.01	-5.18±0.14	-14.10±0.16	-13.57±1.08	-5.71±0.78	-4.5
				cytochrome C peroxidase (ε_{in} = 1)					
c1	-25.60±0.02	-352.29±0.21	354.69±0.20	-2.81±0.01	2.40±0.01	-28.41±0.03	-15.50±0.09	-10.51±0.06	-3.85
c2	-25.84±0.06	-354.14±0.11	354.21±0.08	-2.79±0.02	0.06±0.03	-28.63±0.04	-16.87±1.10	-11.69±1.10	-4.78
c3	-17.90±0.91	-361.70±3.03	361.23±2.79	-1.93±0.43	-0.47±0.24	-19.82±1.34	-14.53±0.06	-5.76±1.16	-4.81
c4	-22.28±0.15	-353.88±1.88	353.41±1.97	-2.62±0.00	-0.47±0.10	-24.90±0.16	-15.05±1.02	-10.31±0.96	-5.86
c5	-18.07±0.07	-365.62±6.40	362.08±4.85	-2.47±0.02	-3.54±1.55	-20.53±0.05	-13.19±1.28	-10.88±2.88	-3.96
c6	-17.74±0.48	-377.44±0.95	372.47±0.56	-2.86±0.44	-4.97±0.39	-20.60±0.05	-15.63±0.03	-9.94±0.41	-6.00
c7	-17.94±0.12	-372.64±3.54	369.19±3.19	-2.40±0.01	-3.45±0.35	-20.34±0.12	-15.73±0.04	-8.06±0.50	-5.99
c8	-21.33±0.03	-360.68±2.15	359.78±2.11	-2.49±0.00	-0.90±0.04	-23.83±0.03	-15.50±0.40	-9.23±0.47	-4.96
c9	-17.09±0.41	-372.32±1.53	367.54±1.25	-2.44±0.00	-4.77±0.28	-19.52±0.41	-15.44±0.14	-8.86±0.01	-5.21
c10	-20.72±0.31	-372.36±0.79	366.06±1.03	-3.29±0.43	-6.30±0.24	-24.01±0.74	-15.45±2.08	-14.86±1.11	-4.92
c11	-21.89±0.08	-363.77±3.15	358.94±3.22	-2.64±0.01	-4.84±0.08	-24.53±0.06	-14.50±0.33	-14.86±0.19	-4.92

c12	-18.40±0.08	-379.84±2.79	366.23±3.09	-2.48±0.00	-13.61±0.30	-20.88±0.08	-14.39±0.48	-20.10±0.69	-7.07
c13	-16.64±0.04	-381.35±2.81	367.75±2.68	-2.78±0.42	-13.61±0.13	-19.42±0.46	-13.81±0.31	-19.22±0.02	-5.02
c14	-19.34±0.12	-366.62±1.23	362.71±1.06	-2.62±0.00	-3.91±0.17	-21.96±0.12	-15.22±0.93	-10.64±0.88	-4.73
c15	-11.42±0.03	-372.89±0.16	366.57±0.51	-2.42±0.44	-6.32±0.35	-13.84±0.42	-12.09±0.29	-8.07±1.05	-4.33
c16	-15.83±0.06	-375.74±2.87	369.63±2.73	-2.26±0.00	-6.10±0.14	-18.09±0.06	-15.19±0.04	-9.00±0.16	-5.82
c17	-16.35±0.00	-370.52±1.42	365.21±1.33	-2.34±0.00	-5.31±0.09	-18.69±0.01	-14.95±0.68	-9.05±0.77	-5.94
c18	-15.64±0.13	-369.60±2.73	363.27±1.55	-2.35±0.01	-6.33±1.18	-17.980.14	-16.93±0.07	-7.38±0.96	-6.06
					neuraminidase (ε_{in} = 4)				
d1	-22.63±0.30	-29.30±0.41	23.53±0.13	-3.99±0.38	-5.77±0.54	-26.61±0.08	-21.97±1.02	-10.41±0.56	-4.09
d2	-22.95±0.57	-33.69±1.21	27.53±0.89	-4.65±0.03	-6.16±0.31	-27.60±0.59	-15.78±2.65	-17.97±2.93	-7.23
d3	-21.19±0.17	-26.07±0.54	22.73±0.49	-4.45±0.00	-3.34±1.02	-25.64±0.17	-21.54±0.07	-7.43±0.78	-3.74
d4	-21.84±0.52	-22.36±0.17	20.43±0.30	-4.64±0.01	-1.93±0.13	-26.49±0.53	-20.75±2.30	-7.67±2.96	-4.84
d5	-20.12±0.64	-23.62±0.04	21.98±1.10	-4.58±0.04	-1.64±1.06	-24.71±0.68	-19.03±0.08	-7.31±1.66	-6.61
d6	-28.40±0.03	-22.53±3.39	20.18±2.05	-4.99±0.03	-2.35±1.33	-33.39±0.05	-19.29±1.83	-16.45±3.11	-10.2
d7	-27.83±0.38	-3.53±0.35	7.02±0.37	-4.98±1.16	3.69±0.02	-32.81±1.55	-22.86±2.01	-6.26±0.48	-7.73
d8	-29.43±0.01	-13.36±0.42	14.97±0.53	-4.49±0.47	1.42±0.95	-33.92±0.46	-17.72±2.16	-14.77±2.65	-11.45
					P450cam (ε_{in} = 2)				
e1	-27.57±0.61	-4.55±0.13	5.37±0.06	-2.78±0.58	0.82±0.07	-30.35±0.03	-15.25±0.85	-14.29±0.75	-7.90
e2	-26.94±0.28	-0.07±0.02	1.16±0.05	-3.33±0.03	1.09±0.03	-30.27±0.25	-16.63±0.62	-12.55±0.34	-5.91
e3	-29.03±0.24	-4.30±0.06	6.86±0.19	-3.38±0.00	2.57±0.13	-31.41±0.24	-14.45±1.76	-15.39±1.39	-6.54
e4	-20.35±0.05	-0.93±0.05	3.61±0.12	-2.79±0.02	2.69±0.07	-23.14±0.03	-15.04±0.27	-5.41±0.31	-5.57
e5	-21.13±0.24	-0.12±0.04	3.89±0.03	-2.37±0.55	3.78±0.07	-23.50±0.78	-14.40±0.32	-5.32±0.39	-5.52
e6	-27.68±0.36	-4.51±1.17	5.00±0.57	-3.56±0.01	0.49±0.60	-31.25±0.35	-15.31±0.54	-15.44±0.30	-5.93
e7	-29.42±0.10	-2.61±0.08	4.21±0.04	-3.48±0.01	2.05±0.04	-32.89±0.10	-13.24±0.42	-17.61±0.28	-7.53
e8	-26.36±0.04	-0.01±0.00	1.95±0.01	-2.60±0.55	1.94±0.01	-28.96±0.51	-13.99±0.56	-13.03±0.04	-5.90
e9	-28.09±0.11	-1.44±0.04	4.54±0.03	-3.15±0.01	3.10±0.01	-31.23±0.10	-15.10±0.60	-13.03±0.71	-7.40
					penicillopepsin (ε_{in} = 2)				
f1	-50.93±1.01	-17.01±2.12	28.28±1.51	-8.59±0.00	11.27±0.61	-59.52±1.02	-22.43±1.30	-22.81±0.33	-12.83
f2	-41.34±1.58	-12.23±3.30	21.88±2.62	-6.78±0.18	9.65±0.68	-48.12±1.76	-22.01±0.44	-16.64±1.52	-10.51
f3	-48.82±1.24	-33.59±0.82	34.00±1.20	-6.34±0.13	0.42±0.42	-55.16±1.37	-24.89±0.64	-29.86±1.63	-12.27

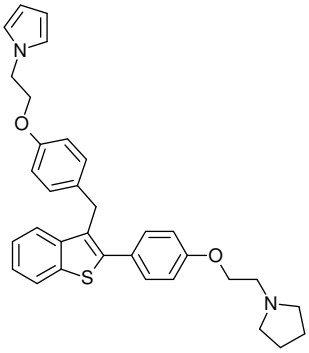
f4	-40.62±2.30	-13.06±3.58	19.72±1.92	-6.79±0.29	6.66±1.66	-47.41±2.59	-16.09±1.52	-24.65±5.77	-10.91
f5	-38.63±4.78	-7.32±0.62	16.34±1.55	-5.48±0.85	9.02±0.93	-44.10±5.63	-20.06±0.16	-15.02±4.86	-8.37
f6	-42.23±4.33	-8.75±0.99	20.74±1.21	-6.60±0.05	11.99±0.22	-48.83±4.28	-21.31±0.23	-15.53±3.83	-7.03
f7	-45.28±2.23	-15.07±2.75	25.78±3.23	-7.51±0.48	10.72±0.48	-52.79±2.72	-23.67±2.29	-18.41±0.06	-6.80



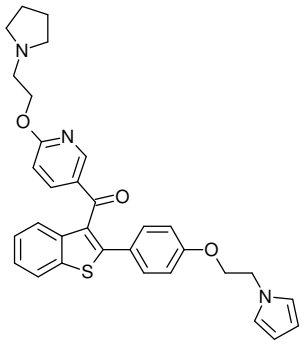
a1



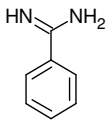
a2



a3



a4



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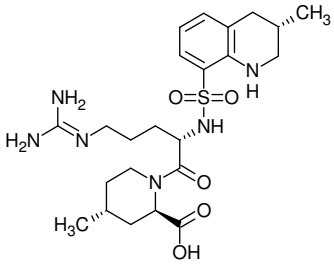

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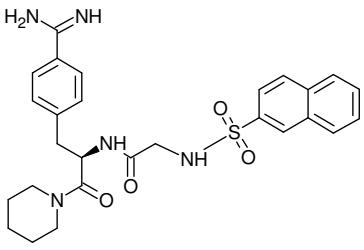
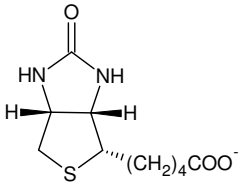


a7

α-thrombin inhibitors



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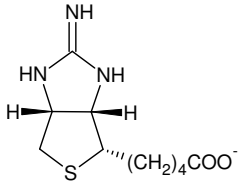

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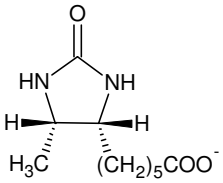

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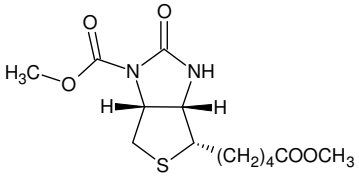

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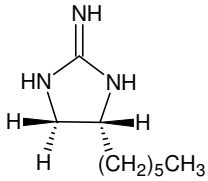

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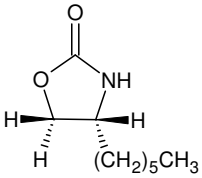

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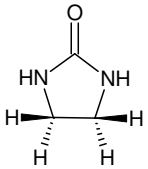

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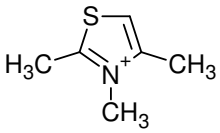
avidin inhibitors



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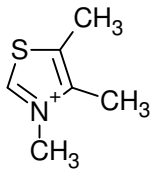

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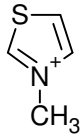

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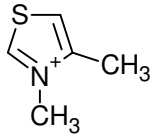

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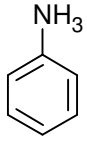

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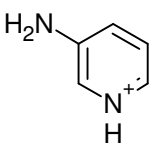

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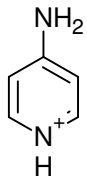

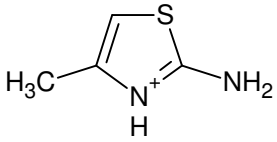

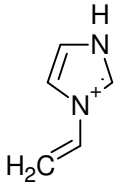

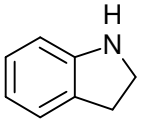

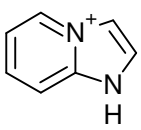

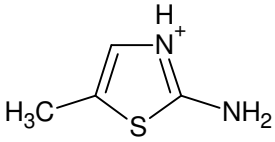

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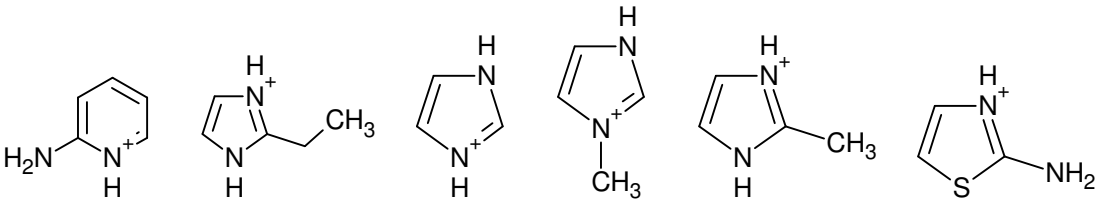
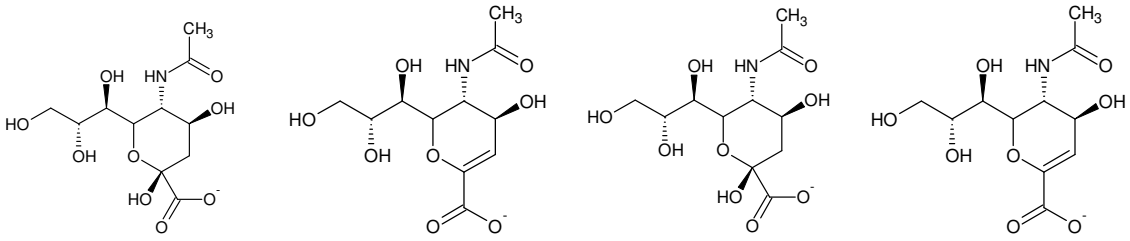


c13 c14 c15 c16 c17 c18

cytochrome C peroxidase inhibitors



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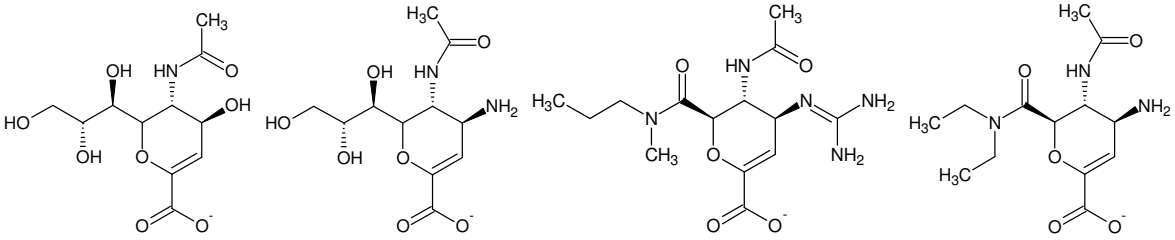
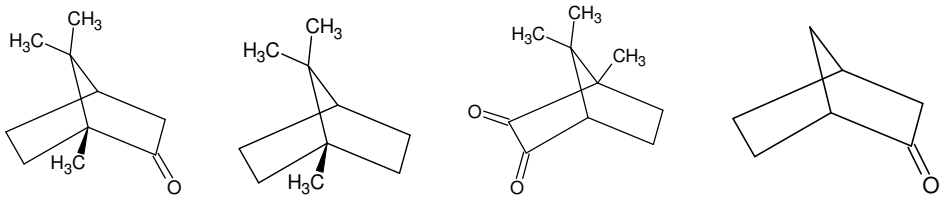


d5 d6 d7 d8

neuraminidase inhibitors



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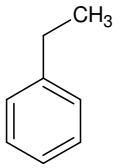

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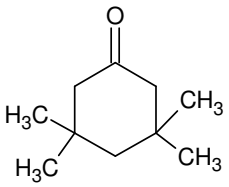

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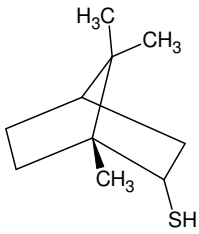

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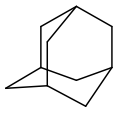

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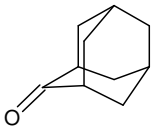

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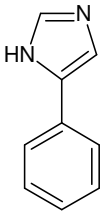

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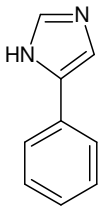

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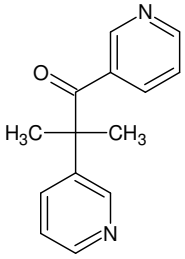
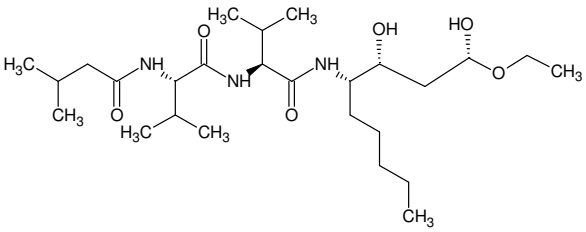


e12

P450cam inhibitors



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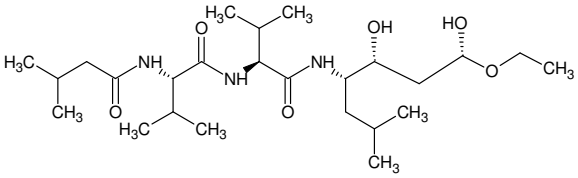

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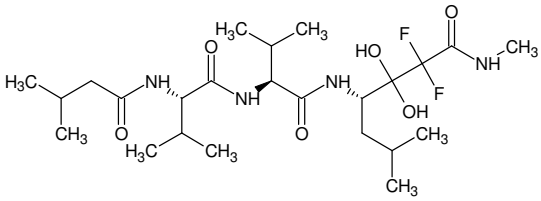

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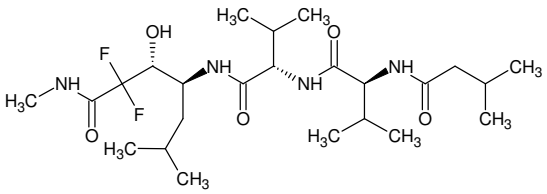

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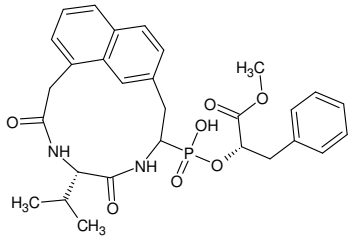

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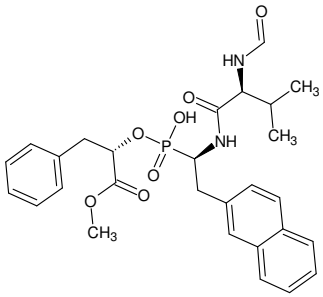

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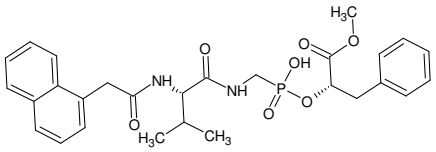

f7

penicillopepsin inhibitors

Figure S1. Structures of the inhibitors studied: (a1~a7) al-thrombin inhibitors, (b1~b7) avidin inhibitors, (c1~c18) cytochrome C peroxidase inhibitors, (d1~d8) neuraminidase inhibitors, (e1~e12) P450cam inhibitors, (f1~f7) penicillopepsin inhibitors. The name of the inhibitors can be found in Table S1 in the supplementary materials.

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