Enhanced Ligand Sampling for Relative Protein-Ligand Binding Free Energy Calculations

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Supporting Information

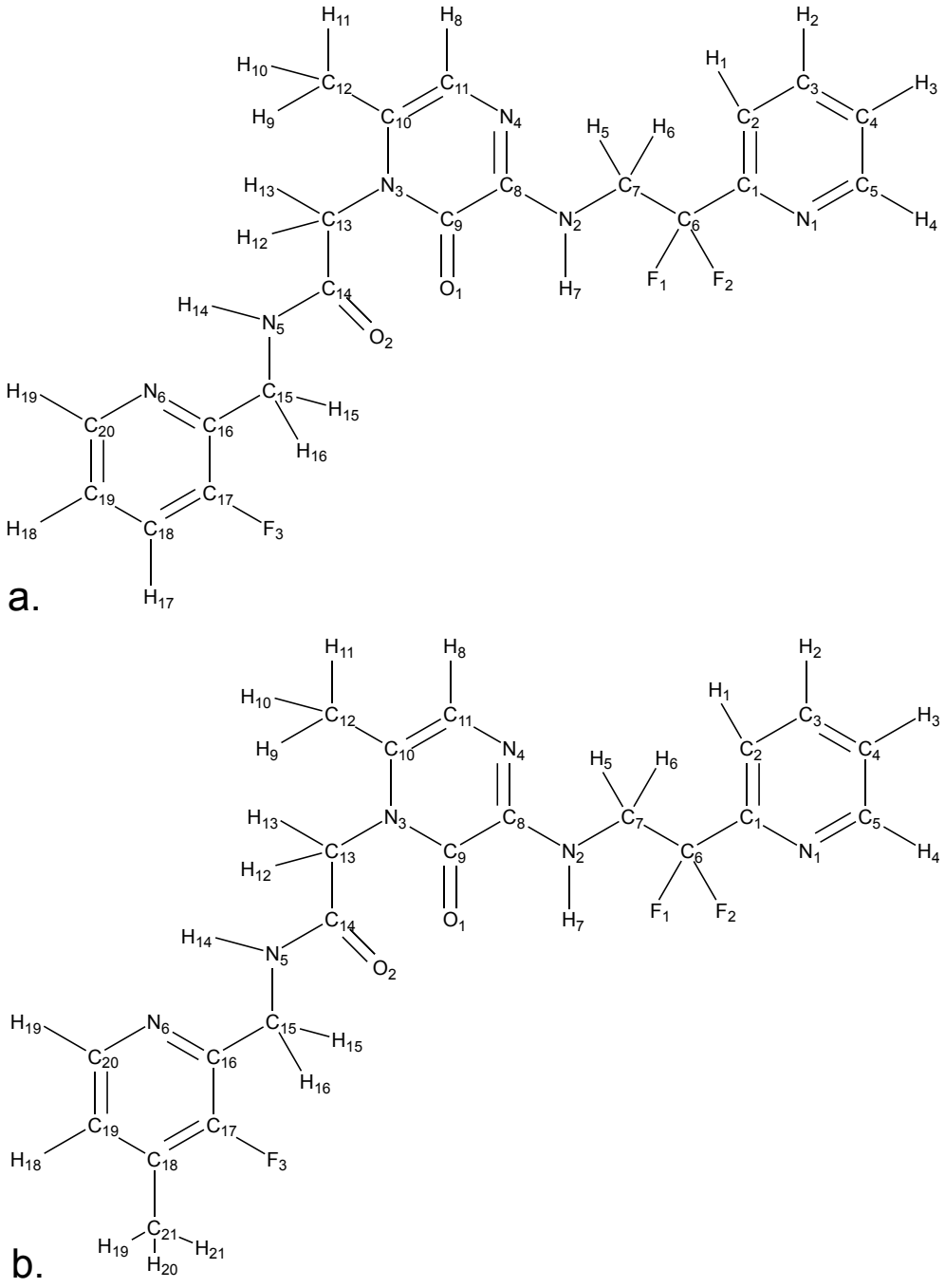

Figure S 1: The structures and atom names for the Thrombin ligands a) CDA and b) CDB.

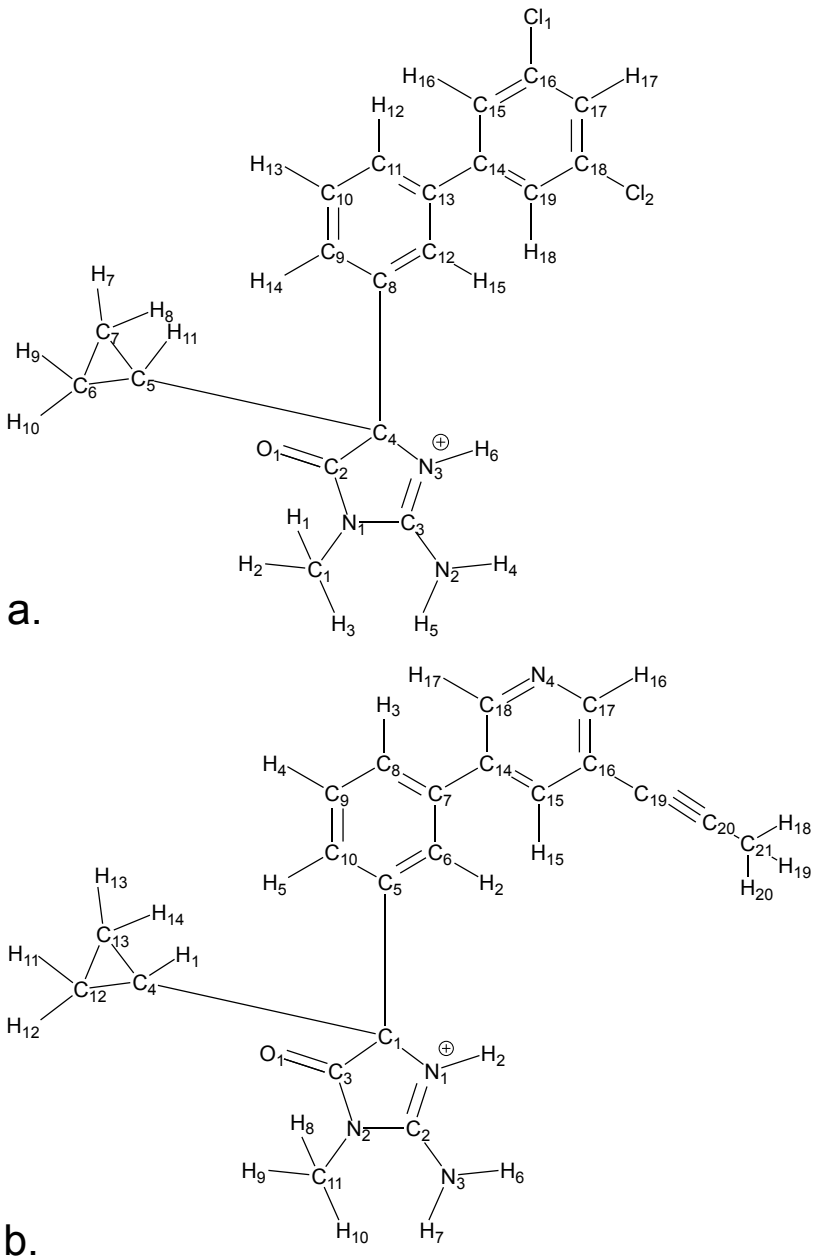

Figure S 2: The structures and atom names for the BACE1 ligands a) 17a and b) 24 of BACE1.

Table S 1: GAFF Atom types and partial charges for CDA (see Figure S1a).

Atom Name	Atom Type	Partial Charge	Atom Name	Atom Type	Partial Charge
C20	ca	0.096703	C12	c3	-0.4586
N6	nb	-0.377379	H9	hc	0.152835
H19	h4	0.124529	H10	hc	0.152835
C19	ca	-0.287306	H11	hc	0.152835
H18	ha	0.179329	C9	c	0.356933
C18	ca	-0.099078	O1	o	-0.572387
H17	ha	0.177581	C8	cc	0.533186
C17	ca	0.116652	N2	nh	-0.659232
F3	f	-0.197162	H7	hn	0.353717
C16	ca	0.348115	C7	c3	0.12318
C15	c3	-0.097875	H5	h1	0.052032
H15	h1	0.102647	H6	h1	0.052032
H16	h1	0.102647	C6	c3	0.308871
N5	n	-0.431195	F1	f	-0.228623
H14	hn	0.219453	F2	f	-0.228623
C14	c	0.731423	C1	ca	0.49594
O2	o	-0.615796	N1	nb	-0.541785
C13	c3	-0.250141	C5	ca	0.298925
H12	h1	0.12114	H4	h4	0.078074
H13	h1	0.12114	C4	ca	-0.384422
N3	n	0.056757	H3	ha	0.176746
C10	cc	0.052845	C3	ca	0.102239
C11	cd	-0.17781	H2	ha	0.12547
N4	nd	-0.407801	C2	ca	-0.434052
H8	h4	0.185363	H1	ha	0.197092

Table S 2: GAFF Atom types and partial charges for CDB (see Figure S1b).

Atom Name	Atom Type	Partial Charge	Atom Name	Atom Type	Partial Charge
C20	ca	0.319031	H8	h4	0.186333
N6	nb	-0.625632	C12	c3	-0.464758
H18	h4	0.090746	H9	hc	0.155338
C19	ca	-0.559542	H10	hc	0.155338
H17	ha	0.219323	H11	hc	0.155338
C18	ca	0.415675	C9	c	0.317715
C21	c3	-0.460437	O1	o	-0.568285
H19	hc	0.143587	C8	cc	0.515622
H20	hc	0.143587	N2	nh	-0.619241
H21	hc	0.143587	H7	hn	0.334388
C17	ca	-0.128979	C7	c3	0.113064
F3	f	-0.136524	H5	h1	0.053337
C16	ca	0.464366	H6	h1	0.053337
C15	c3	0.029658	C6	c3	0.299592
H15	h1	0.068821	F1	f	-0.228867
H16	h1	0.068821	F2	f	-0.228867
N5	n	-0.56162	C1	ca	0.52
H14	hn	0.317318	N1	nb	-0.556409
C14	c	0.74971	C5	ca	0.307317
O2	o	-0.5963	H4	h4	0.076862
C13	c3	-0.23602	C4	ca	-0.388736
H12	h1	0.105076	H3	ha	0.176994
H13	h1	0.105076	C3	ca	0.108417
N3	n	0.103744	H2	ha	0.125203
C10	cc	0.05075	C2	ca	-0.446748
C11	cd	-0.175702	H1	ha	0.198848
N4	nd	-0.409251			

Table S 3: GAFF atom types and partial charges for BACE1 ligand 17a (see Figure S2a).

Atom Name	Atom Type	Partial Charge	Atom Name	Atom Type	Partial Charge
O1	o	-0.420996	C8	ca	0.035066
C2	c	0.431864	C12	ca	-0.113999
N1	n	-0.010074	H15	ha	0.045473
C1	c3	-0.445537	C9	ca	-0.153281
H1	h1	0.200946	H14	ha	0.168731
H2	h1	0.200946	C10	ca	-0.183727
H3	h1	0.200946	H13	ha	0.180644
C3	cz	0.522994	C11	ca	-0.086165
N2	nh	-0.871394	H12	ha	0.162396
H4	hn	0.45887	C13	cp	0.000903
H5	hn	0.45887	C14	cp	-0.004201
N3	nh	-0.352492	C19	ca	-0.037461
H6	hn	0.408688	H18	ha	0.124191
C4	c3	0.016373	C15	ca	-0.037461
C5	cx	-0.100077	H16	ha	0.124191
C6	cx	-0.189835	C16	ca	-0.108417
C7	cx	-0.189835	Cl1	cl	-0.066924
H7	hc	0.107251	C17	ca	0.081031
H8	hc	0.107251	H17	ha	0.129663
H9	hc	0.107251	C18	ca	-0.108417
H10	hc	0.107251	Cl2	cl	-0.066924
H11	hc	0.165423			

Table S 4: GAFF atom types and partial charges for BACE1 ligand 24 (see Figure S2b).

Atom Name	Atom Type	Partial Charge	Atom Name	Atom Type	Partial Charge
C21	c3	-0.326405	C5	ca	0.03703
H18	hc	0.13282	C1	c3	-0.051868
H19	hc	0.13282	C4	cx	-0.084258
H20	hc	0.13282	C12	cx	-0.186601
C20	c1	0.157053	C13	cx	-0.186601
C19	cg	-0.430907	H13	hc	0.105009
C16	ca	0.096974	H14	hc	0.105009
C17	ca	0.285575	H11	hc	0.105009
N4	nb	-0.603502	H12	hc	0.105009
C18	ca	0.341428	H1	hc	0.165481
H17	h4	0.072048	N1	nh	-0.359905
H16	h4	0.108777	H21	hn	0.404658
C15	ca	-0.005904	C2	cz	0.559392
H15	ha	0.15041	N3	nh	-0.882896
C14	cp	-0.222984	H6	hn	0.461914
C7	cp	0.035282	H7	hn	0.461914
C8	ca	-0.095128	N2	n	-0.034431
C9	ca	-0.177191	C11	c3	-0.438673
C10	ca	-0.151483	H8	h1	0.198684
H5	ha	0.167775	H9	h1	0.198684
H4	ha	0.178333	H10	h1	0.198684
H3	ha	0.152977	C3	c	0.482504
C6	ca	-0.126197	O1	o	-0.431915
H2	ha	0.062777			

Table S 5: The number of λ values used for each simulation.

		Complex		Free	
Thrombin	State	In	Out	In	Out
	AIM	11	11	11	11
	AcclAIM	13	12	12	12
	AIM/MC	11	11	11	11
BACE1	AIM	11	11	11	11
	AcclAIM	12	13	14	13
	AIM/MC	11	11	11	11

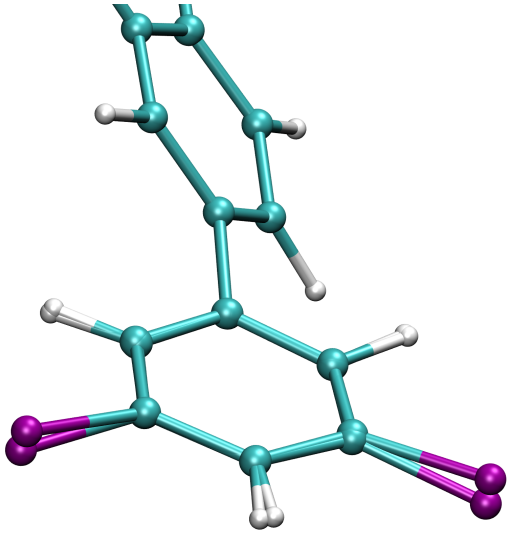

Figure S 3: Structure of the BACE1 ligand 17a before and after an attempted rotation. The Chlorine atoms (purple) have small differences in their location before and after the rotation, causing an unfavorable increase in the potential energy. These small differences in the coordinates are responsible for reducing the acceptance probability given by eq 3 in the manuscript. Tachyon[1] in visual molecular dynamics[2] was used for rendering.

References

(1) Stone, J. An Efficient Library for Parallel Ray Tracing and Animation. M.Sc. thesis, Computer Science Department, University of Missouri-Rolla, 1998.

(2) Humphrey, W.; Dalke, A.; Schulten, K. VMD – Visual Molecular Dynamics. *J. Molec. Graphics* **1996**, *14*, 33–38.