Identification of a novel multifunctional ligand for simultaneous inhibition of Amyloid-Beta ($A\beta_{42}$) and chelation of zinc metal ion

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Supporting information

Tables:

Table S1 Secondary structure composition of the initial configuration and the average configurations of Aβ during 200 ns simulation of trilateral interactions. The percentage content of the secondary structures is provided for all simulations.

% Secondary Structure		Coil	B-Bridge	Bend	Turn	A-Helix	5-Helix	3-Helix	B-Sheet
1Z0Q	Initial	9.523	0	21.428	33.333	26.190	0	7.142	0
C1	mode I	34.062	0.569	10.883	10.559	40.189	0.010	1.346	0.002
	mode II	41.328	0.005	15.455	5.190	35.070	0.001	0.571	0
C2	mode I	34.049	0.010	10.201	11.996	40.181	0.006	1.177	0
	mode II	31.329	0.008	10.140	9.386	45.416	0.093	1.249	0
C3	mode I	34.335	0.189	16.499	8.426	36.427	0.019	1.714	0.011
	mode II	35.390	0.370	13.531	6.965	41.183	0.014	0.168	0

Table S2 Secondary structure composition of the initial configuration and the average configurations during 200 ns simulation of Aβ relaxation. The percentage content of the secondary structures is provided for all simulations.

%Secondary Structure	Coil	B-Bridge	Bend	Turn	A-Helix	5-Helix	3-Helix	B-Sheet
1Z0Q	9.523	0	21.428	33.333	26.190	0	7.142	0
R1	44.540	2.476	15.055	8.002	20.129	0.001	1.269	6.149
R2	42.045	4.590	16.619	15.651	16.700	0.0029	1.935	0.077
R3	53.412	1.447	19.935	7.315	13.562	0	0.376	1.575
R4	37.235	0.883	18.323	9.972	27.145	0	0.770	3.294

Table S3 Top 25 receptor-ligand hydrophobic interactions by propensity(%), for the Aβ-ligand-Zn^{2+} complex simulations. subtables of (a), (b) and (c) refer to hydrophobic interactions of C1, C2, and C3, respectively

(a) Complex Dock 1						(b) Complex Dock 2					
mode I			mode II			mode I			mode II		
Ligand	Receptor	%	Ligand	Receptor	%	Ligand	Receptor	%	Ligand	Receptor	%
Met13	Phe19	92.1	Met4	Phe20	76	Met13	Phe4	71	Met4	Ala21	64.2
Met13	Val40	74.4	Val5	Phe20	74.8	Met4	Val39	64.1	Leu3	Val40	58
Met13	Ile41	72.3	Leu3	Met35	74.2	Met4	Leu17	61.4	Met4	Leu17	57.5
Met13	Ala42	59.8	Val5	Leu17	71.3	Met13	Val40	60.5	Met4	Val18	52.5
Val5	Leu34	54.1	Leu3	Leu17	70.4	Met4	Val24	57.1	Ile1	Val40	48.1
Met4	Leu34	44.8	Met13	Phe19	69.8	Met4	Ile41	55.9	Leu3	Val39	46.5
Met13	Val39	43.3	Met4	Leu17	62.8	Met13	Ala2	54.4	Leu3	Ile41	45.7
Met4	Ile31	38.7	Leu3	Phe20	58.7	Met4	Ile32	47.4	Ile1	Ile41	39.7
Met4	Ile32	34.6	Leu3	Leu34	54.9	Leu3	Ile41	46.7	Met4	Ile41	36.6
Met4	Ala30	33.5	Leu3	Val24	47.1	Met13	Ala42	44.4	Met4	Val36	35.9
Leu3	Ile31	33.4	Met4	Met35	46.5	Met4	Ala21	41.7	Met4	Met35	35.6
Met13	Phe20	30.9	Leu3	Val40	38.2	Met4	Phe20	39.9	Ile1	Ala42	35.3
Leu3	Leu34	28.8	Ile1	Leu34	37	Met4	Val36	38.5	Met4	Val39	34.2
Met13	Val12	28.7	Met4	Phe4	33.7	Leu3	Leu17	37.7	Met4	Leu34	33.6
Val5	Ile31	28.6	Met4	Ala2	33.6	Leu3	Ala21	34.5	Leu3	Val36	33.1
Val5	Met35	28.4	Val5	Phe4	32.6	Ile1	Leu17	34	Ile1	Leu17	32.5
Met13	Leu34	27.3	Met4	Val24	32.2	Ile1	Ala21	33.7	Val5	Val18	32.2
Val5	Ile32	25.8	Leu3	Ala21	32.1	Val5	Val24	32.5	Val5	Met35	32.2
Val5	Phe19	25.7	Met4	Val40	31.7	Val5	Ile32	32.3	Ile1	Val39	32.1
Val5	Val39	24.7	Leu3	Val39	31	Met13	Ile41	30.6	Leu3	Met35	30
Met4	Met35	21.9	Leu3	Ile32	30.9	Leu3	Val24	28.8	Leu3	Leu17	29
Met13	Val36	21.6	Val5	Met35	30.8	Ile1	Val18	27.3	Val5	Ala21	28.3
Val5	Ala30	21.1	Leu3	Ile31	28.2	Ile1	Ile41	25.8	Leu3	Ala21	28.3
Leu3	Val39	19.6	Met4	Ala21	27.3	Leu3	Val18	24.9	Ile1	Val36	26.6
Val5	Val40	19.5	Met13	Phe20	27.1	Ile1	Val24	24.3	Val5	Ile41	25.1

(C) Complex Dock 3					
mode I			mode II		
Ligand	Receptor	%	Ligand	Receptor	%
Val5	Leu17	76.2	Leu3	Val39	89.3
Val5	Ala30	74.7	Met4	Val39	88.9
Val5	Ala21	65.1	Val5	Ile41	80.9
Val5	Val18	60.2	Val5	Val40	79.6
Val5	Ile31	46	Met4	Met35	79.4
Met13	Leu17	45	Met13	Ala42	73.3
Met13	Ile31	35.3	Val5	Phe20	72.5
Met4	Val18	35	Leu3	Ile41	70.4
Leu3	Val18	32.5	Met4	Ile41	67.9
Leu3	Leu17	26.7	Met4	Val40	67.4
Met4	Val24	24.6	Leu3	Phe19	66.9
Val5	Val24	20.3	Leu3	Phe20	66.3
Met13	Met35	17.2	Leu3	Val40	63.8
Met13	Phe4	17	Leu3	Val12	59
Met13	Val36	15.1	Met13	Ile41	52.5
Met13	Leu34	14.6	Val5	Met35	49.3
Met4	Ala30	14.4	Val5	Ala42	49.2
Met13	Ala30	12.8	Met13	Leu17	46.8
Leu3	Ala21	12.2	Ile1	Val39	46.4
Met4	Ala21	11.6	Val5	Ile31	45.4
Met13	Val18	9.1	Met4	Phe20	43.2
Leu3	Val24	9	Met4	Val36	40.9
Leu3	Ala30	8.8	Met4	Leu34	38.8
Ile1	Val18	8.6	Leu3	Phe4	37.9
Met13	Ala2	7.6	Ile1	Met35	36.2

Table S4 The details of top 25 H-bonds by propensity (%) between the receptor and the ligand for the Aβ-ligand-Zn^{2+} complex simulations. subtables of (a), (b) and (c) refer to C1, C2, and C3, respectively

(a) Complex Dock 1						(b) Complex Dock 2					
mode I			mode II			mode I			mode II		
Donor	Acceptor	%	Donor	Acceptor	%	Donor	Acceptor	%	Donor	Acceptor	%
Ile1	Glu11	53.41	Lys16	Gly7	110.98	Gly10	Val39	64.13	Gly7	His14	38.89
Met13	Phe19	28.33	Lys16	Gly9	98.63	Asn11	Val39	29.87	Gly9	Gly9	35.5
Gly10	Leu34	26.58	Lys16	Gly6	82.35	Ile41	Asn11	25.35	Gly6	His14	34.47
Phe19	Met13	24.06	Lys16	Gly8	75.82	Gly38	Gly9	25.11	Tyr10	Gly10	33.82
Gly2	Val39	23.18	Lys16	Gly10	41.21	Gly6	Ala30	23.9	Tyr10	Asn11	26.59
Gly38	Leu3	21.23	His13	Gly8	38.77	Ser12	Ala42	23.47	Gly9	Ser8	25.12
Asn11	Gly37	20.79	Arg5	Val5	32.24	Gly37	Gly8	22.05	Ser12	Gln15	24.09
Gly10	Val36	20.46	Leu17	Leu3	31.93	Ile32	Gly7	20.48	Gly2	Gly38	22.83
Gly38	Gly7	19.63	Gly2	Leu34	29.42	Val24	Val5	18.53	Met4	Met35	22.73
Ala42	Asn11	19.44	Ile1	Asp1	29.12	Val40	Asn11	18.4	Gly37	Gly2	22.69
Leu3	Val39	18.57	Val5	His13	27	Asn11	Gly38	15.83	Gly10	Tyr10	22.16
Val39	Leu3	18.53	His13	Gly6	25.1	Gly7	Ala30	15.12	Gly7	Glu11	22.06
Ser12	Val40	18.5	Met4	Glu3	24.52	Gly38	Gly8	14.83	Ile1	Ala42	20.81
Asn11	Gly38	17.56	Lys16	Ser12	24.38	Val40	Asn11	14.52	Gln15	Ser12	17.95
Leu34	Gly10	16.53	Val5	Phe20	21.83	Ile32	Gly7	14.43	Gly8	Glu11	17.52
Met13	Val40	16.45	Phe20	Gly6	21.02	Gly9	Val39	13.61	Gly8	His14	17.32
Met13	Val40	16.29	Phe20	Met4	20.99	Gly37	Gly9	13.37	Met4	Met35	17.26
Asn11	Val36	15.5	Leu17	Met4	20.33	Met13	Ile41	13.13	Ile1	Glu22	16.28
Asn11	Val39	15.04	Ile1	Glu22	18.93	Val40	Met13	13.11	Gly8	Gly9	14.64
Val39	Gly8	14.31	Gly6	Phe20	18.39	Gly6	Gly29	13.02	Met4	Leu34	14.62
Ser12	Val40	14.3	Gly7	Phe20	17.75	Ser12	Ile41	12.22	Gly38	Val5	14.57
Gly10	Val39	13.94	Val5	Val40	16.23	Val39	Gly9	12.13	His6	Gly9	14.56
Ala42	Asn11	13.86	Leu3	Leu34	15.66	Gly10	Gly37	11.54	Ile1	Val40	13.66
Val39	Gly10	13.57	Ala42	Val5-	15.58	Val24	Gly2	11.21	His14	Gly6	13.33
Gly9	Leu34	13.34	Phe19	Ser12	15	Met13	Phe4	11.13	Gly2	Gly37	13.28

(C) Complex Dock 3					
mode I			mode II		
Donor	Acceptor	%	Donor	Acceptor	%
Gly29	Gly8	35.59	Lys16	Met13	113.95
His14	Met4	34.55	Lys16	Ser12	85.66
Leu3	His14	33.62	Gly6	Ile41	71.12
Ala21	Gly6	30.61	Ile41	Met4	64.14
Gly8	Gly25	28.55	Ile1	Asp1	61.12
Ile31	Gly6	27.43	Ile1	Asp23	53.06
Gly8	Val24	25.38	Gly38	Gly2	51.16
Gly8	Asp23	23.71	Met4	Val39	50.76
Ala30	Gly6	22.68	Gly2	Asp23	40.39
Gly7	Asp23	20.31	Met4	Gly37	39.68
Leu3	Tyr10	19.11	Val39	Gly2	39.55
Ile31	Gly6	18.42	Lys28	Gly9	38.48
Gly10	Val36	18.36	Val40	Gly6	36.74
Ile31	Gly9	17.03	Lys28	Gly8	35.36
Val39	Gly8	17.01	Ile1	Glu3	34.73
Gly10	Gly37	16.75	Lys28	Gly6	33.79
Gly8	Val39	16.3	Val40	Met4	33.67
Ile31	Gly7	15.65	Lys28	Gly7	33.13
Ile31	Gly8	15.46	Asn27	Leu3	31.98
Gly8	Lys28	14.24	Leu3	Lys16	30.71
Gly6	Val24	14.08	Ile1	Glu3	26.98
Gly29	Gly6	14.07	Ile1	Glu3	25.92
His14	Leu3	13.31	Gly29	Gly6	24.93
Gly38	Gly8	13.3	His13	Met13	23.14
Gly7	Ala21	12.79	Gly6	Val40	23.01

Figures:

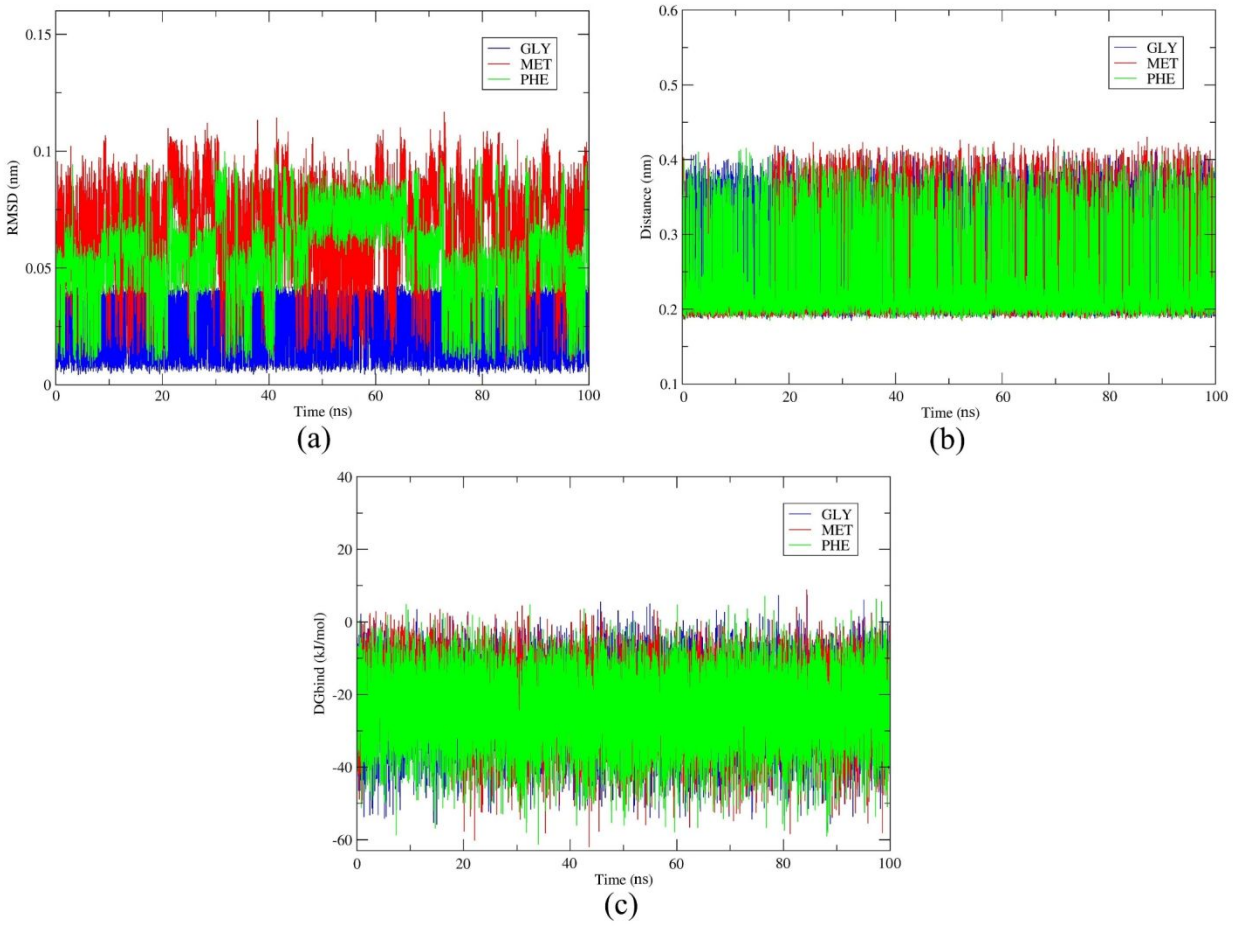

Figure S1 Analysis of the Zn^{2+} interactions with Glycine, Methionine, and Phenylalanine. The three results of Gly, Met, and Phe interaction are specified by blue, red and green colors respectively. (a) RMSD plotted against time (b) Distance between the OT2 of the carboxyl group and the zinc metal ion (c) LIE free energy estimate of the amino acids-Zn^{2+} interactions

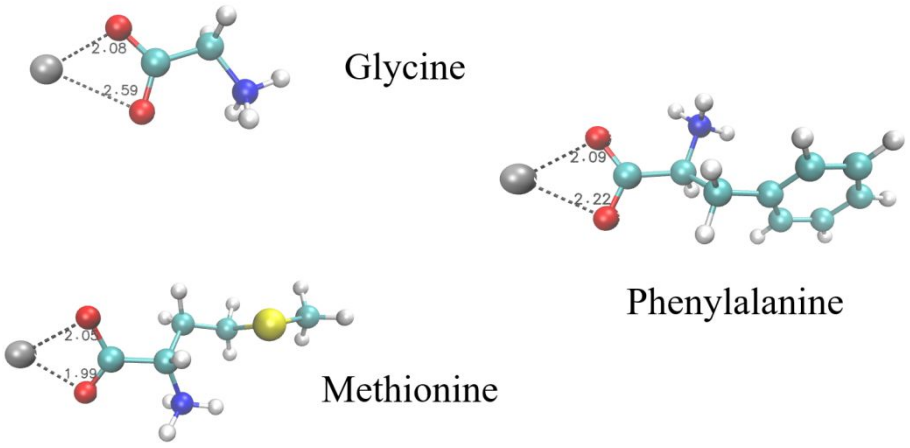

Figure S2 final snapshots of 100 ns interaction between amino acids including Glycine, Methionine, and Phenylalanine with zinc metal ion at 298 K. The atoms of oxygen, carbon, nitrogen, hydrogen, and sulfur are colored by red, cyan, blue, white and yellow respectively. The distances between the oxygen atoms of the carboxyl group (OT1 and OT2) and the zinc metal ion are specified in the final snapshot for all three simulations.

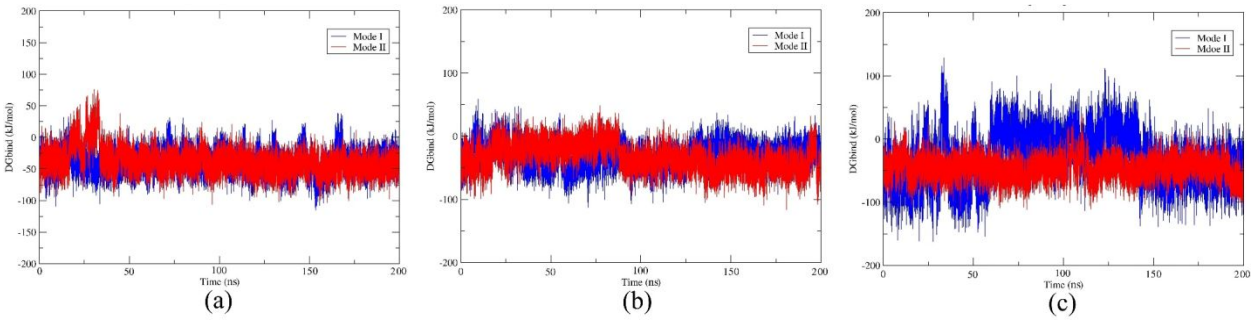

Figure S3 LIE free energy estimate of Aβ-ligand interactions. Subfigures of (a), (b), and (c), refer to the binding free energy for C1, C2, and C3, respectively. In every subfigure, the first and the second modes are colored as blue and red respectively.

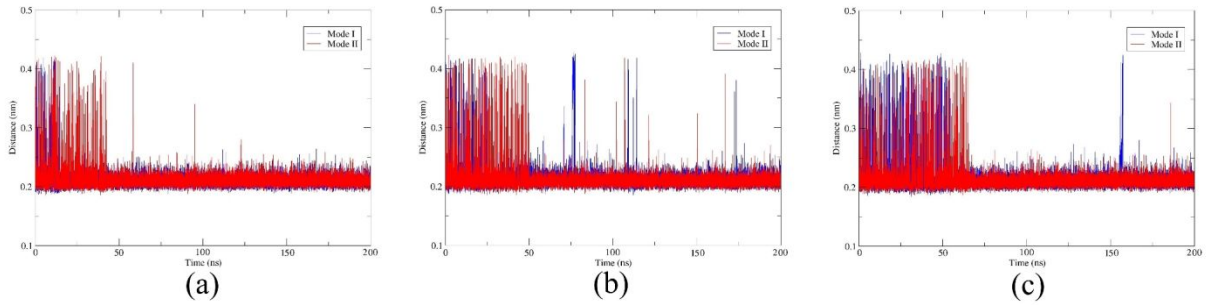

Figure S4 Time development of distances between MET13:OT2 and Zinc metal ion for the six simulations of Aβ-ligand-Zn^{2+} trilateral interactions. (a), (b) and (c) refer to modes of C1, C2, and C3, respectively. In every subfigure, the first and the second modes are colored as blue and red respectively.