Supporting Material

Computational Determination of Binding Structures and Free Energies of Phosphodiesterase-2 with Benzo[1,4]diazepin-2-one Derivatives

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Supporting Information Available: Figures and Table for the more detailed information about the simulated PDE2A-inhibitor binding structures and the results from the binding energy decomposition. This material is available free of charge via the Internet at http://pubs.acs.org.

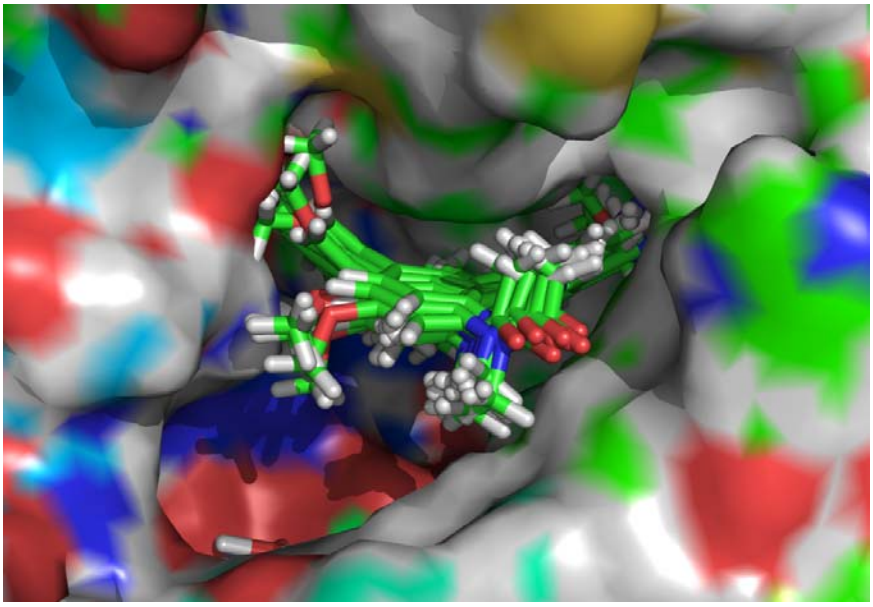

Figure S1. Superposition of the docked binding structures for the 11 ligands in the PDE2A activity site.

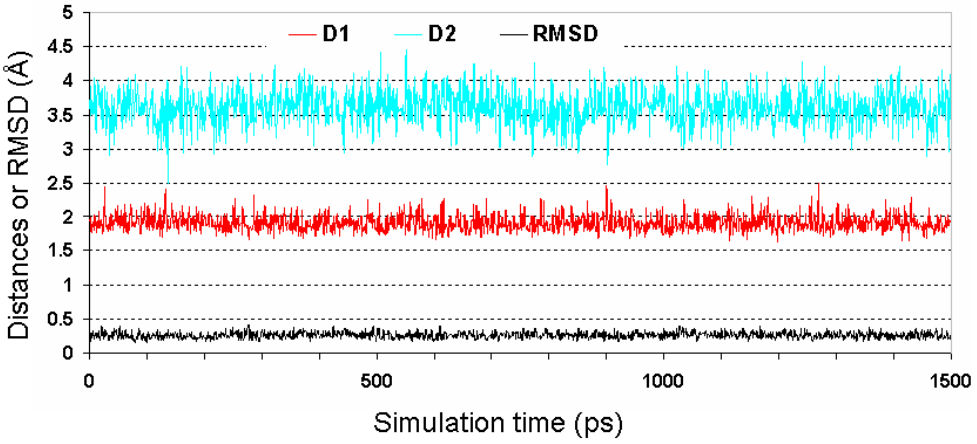

Figure S2. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **2**. Trace D1 represents the internuclear distance between the oxygen of the methoxy group (R^4) and a hydrogen atom of the amine group in Gln859 side chain. Trace D2 refers to the internuclear distance between the oxygen atom of a methoxy group in R^3 and a hydrogen atom of the amine group in Asn704 side chain.

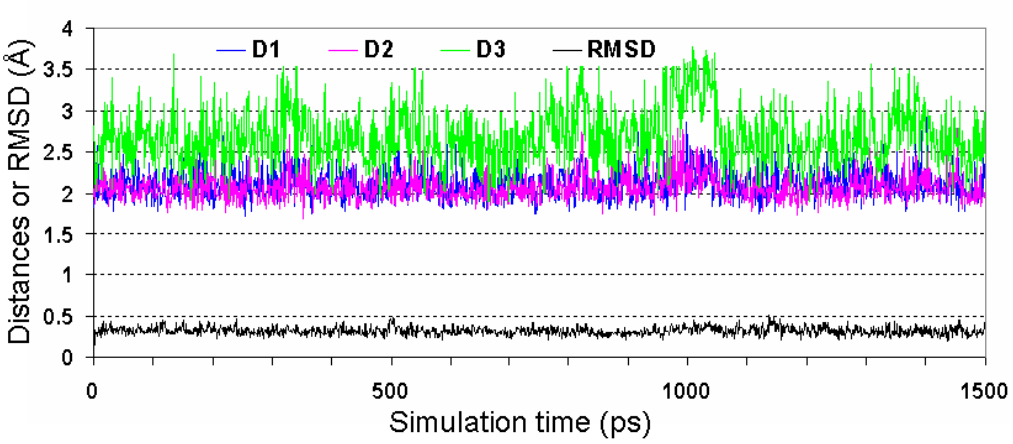

Figure S3. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **4**. Traces D1 and D2 represent the H···O distances associated with a pair of hydrogen bonds (N-H···O) between the amide group in R^4 and the amide group of Gln859 side chain. Trace D3 refers to the internuclear distance between the oxygen of a methoxy group in R^3 and a hydrogen atom of the amine group in Asn704 side chain.

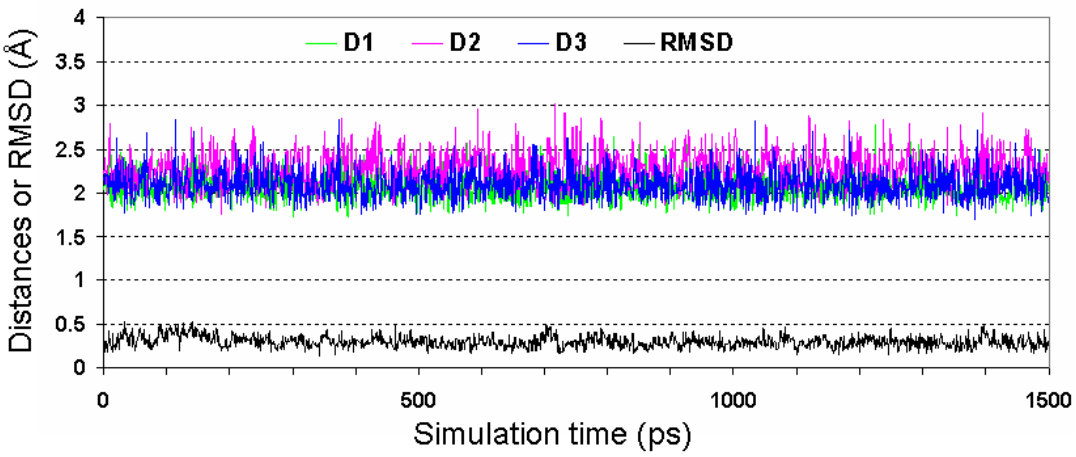

Figure S4. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **5**. Traces D1 and D2 represent the H···O distances associated with a pair of hydrogen bonds (N-H···O) between the amide group in R^4 and the amide group of Gln859 side chain. Trace D3 refers to the internuclear distance between the oxygen of the methoxy group (R^2) and a hydrogen atom of the amine group in Asn704 side chain.

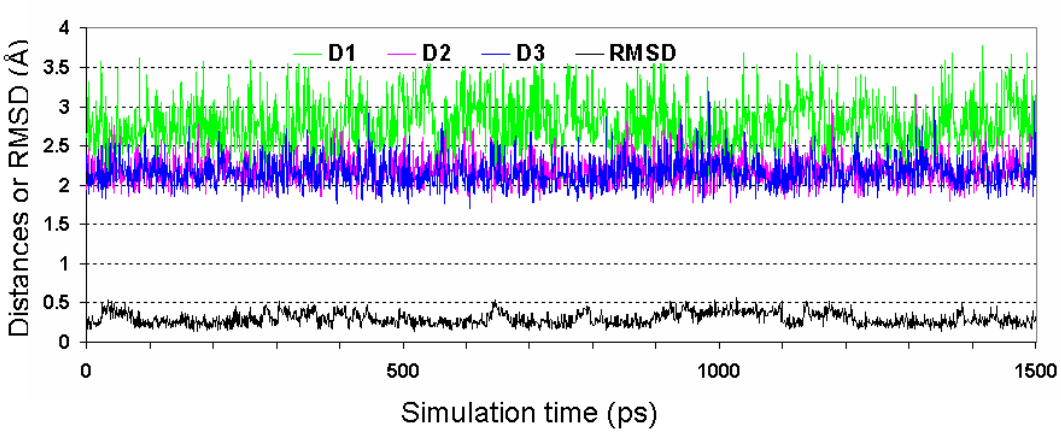

Figure S5. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **6**. Traces D1 and D2 represent the H···O distances associated with a pair of hydrogen bonds (N-H···O) between the amide group in R^4 and the amide group of Gln859 side chain. Trace D3 refers to the distance between the oxygen of the ligand methoxy group in R^2 and a hydrogen atom of the amine group in Asn704 side chain.

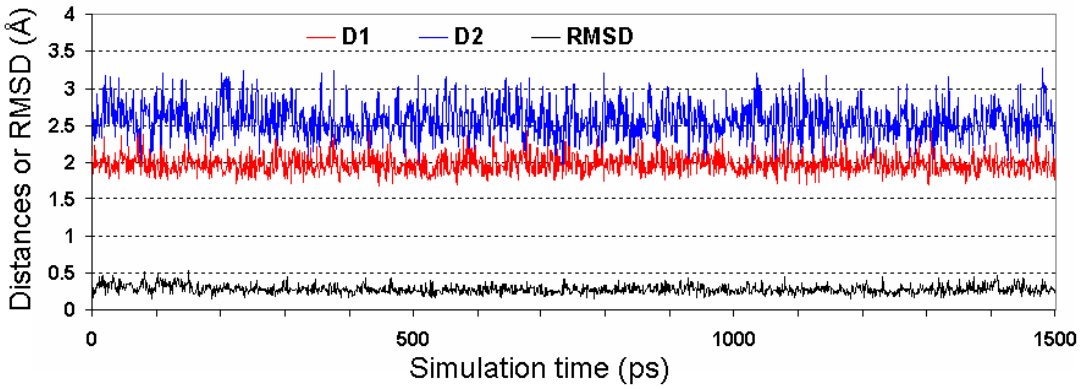

Figure S6. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **7**. Trace D1 represents the hydrogen bond distances between the oxygen atom of the ligand CH_2OCH_3 group at the R^4 position and the hydrogen in amide side chain of Gln859 residue. Trace D2 refers to the distance between the oxygen of the methoxy group (R^2) position and a hydrogen atom of the amine group in Asn704 side chain.

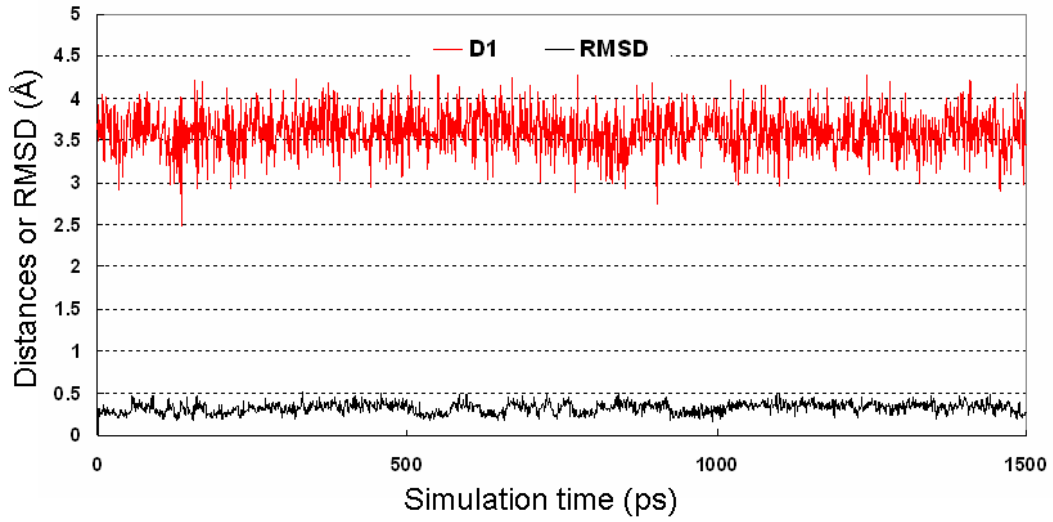

Figure S7. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **8**. Trace D1 represents the internuclear distance between the oxygen of a methoxy group in R^3 and a hydrogen atom of the amine group in Asn704 side chain.

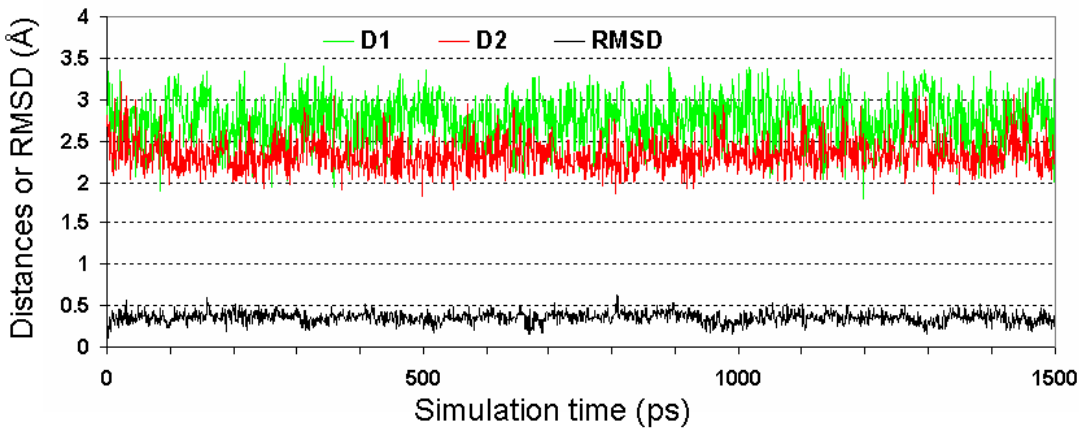

Figure S8. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **9**. Trace D1 represents the hydrogen bond distances between the nitrogen of the ligand cyano group (R^4) and the hydrogen of amide group in Gln859 side chain. Trace D2 refers to the internuclear distance between the oxygen of a methoxy group in R^3 and a hydrogen atom of the amine group in Asn704 side chain.

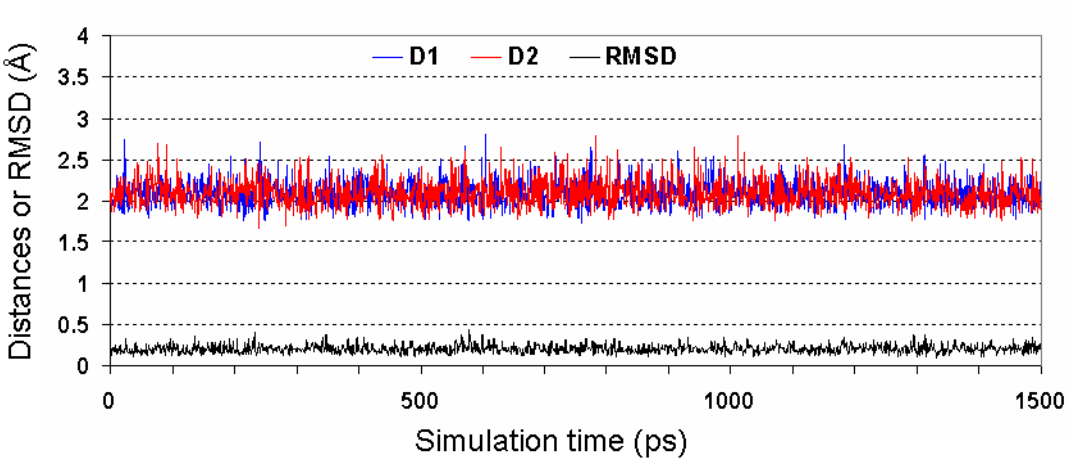

Figure S9. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **10**. Traces D1 and D2 represent the H···O distances associated with a pair of hydrogen bonds (N-H···O) between the amide group in R^4 and the amide group of Gln859 side chain.

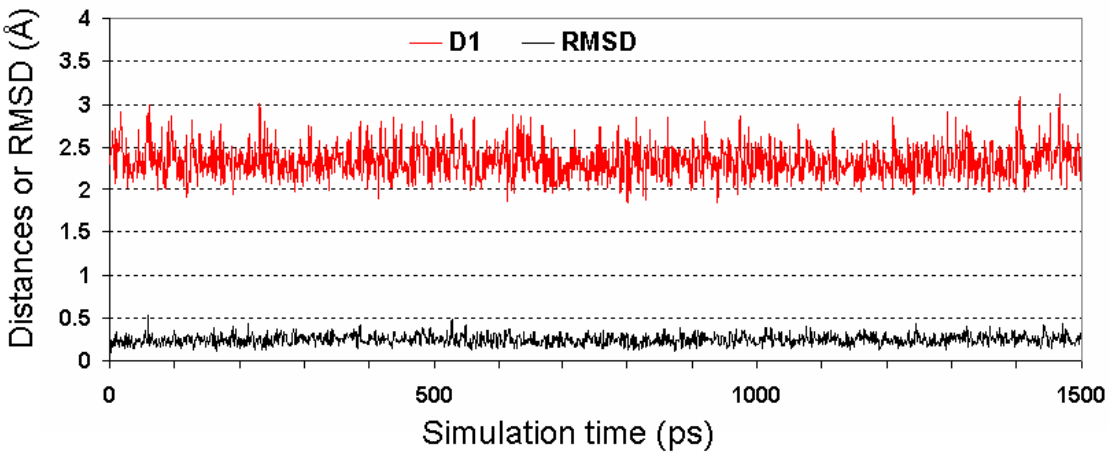

Figure S10. Plots of MD-simulated internuclear distances and RMSD for atomic positions of the ligand *versus* the simulation time for PDE2A binding with compound **11**. Trace D1 represents the hydrogen bond distances between the nitrogen of the ligand cyano group (R^4) and a hydrogen atom of the amine group in Gln859 side chain.

Table S1. Binding free energy contributions of key binding-site residues calculated from the binding energy decomposition for five representative compounds. All energy values are in kcal/mol.

	Compound **1**					Compound **2**				
	vdW	ele	MM	GB	ΔG_{bind}^{GBSA}	vdW	ele	MM	GB	ΔG_{bind}^{GBSA}
Tyr655	-0.96	-0.13	-1.09	0.18	-0.91	-1.08	-0.06	-1.14	0.07	-1.07
Hid656	-1.27	-0.31	-1.57	0.28	-1.29	-0.99	0.40	-0.58	-0.35	-0.93
Asn704	-1.28	-3.49	-4.78	2.86	-1.91	-1.15	-0.73	-1.88	1.67	-0.22
Leu770	-0.51	0.24	-0.27	-0.26	-0.53	-0.52	0.07	-0.45	-0.10	-0.55
Leu809	-0.80	0.15	-0.65	-0.23	-0.89	-0.77	0.13	-0.64	-0.22	-0.85
Ile826	-2.54	-0.02	-2.56	-0.12	-2.68	-2.56	-0.09	-2.65	-0.02	-2.67
Glu829	-1.27	-2.66	-3.93	3.48	-0.45	-1.30	-3.68	-4.98	4.44	-0.54
Phe830	-4.74	0.02	-4.72	0.56	-4.16	-4.74	0.14	-4.60	0.56	-4.04
Leu858	-0.72	0.09	-0.63	-0.15	-0.78	-0.72	0.14	-0.58	-0.18	-0.77
Gln859	-0.62	-2.76	-3.38	1.24	-2.14	-0.65	-3.03	-3.68	1.38	-2.30
Phe862	-2.54	0.15	-2.39	0.11	-2.28	-2.60	0.15	-2.44	0.09	-2.36
Ile866	-1.50	-0.21	-1.70	-0.07	-1.78	-1.53	-0.24	-1.77	-0.06	-1.83
	Compound **3**					Compound **4**				
	vdW	ele	MM	GB	ΔG_{bind}^{GBSA}	vdW	ele	MM	GB	ΔG_{bind}^{GBSA}
Tyr655	-0.61	0.03	-0.58	-0.02	-0.6	-0.73	0.14	-0.59	-0.06	-0.65
Hid656	-0.92	0.12	-0.8	0.06	-0.74	-0.92	0.13	-0.79	-0.13	-0.91
Asn704	-1.52	-2.96	-4.49	2.27	-2.22	-0.65	-1.7	-2.36	1.44	-0.91
Leu770	-0.64	0.25	-0.38	-0.24	-0.62	-0.58	0.1	-0.48	-0.1	-0.58
Leu809	-0.75	0.07	-0.69	-0.13	-0.81	-0.94	0.07	-0.87	-0.15	-1.02
Ile826	-1.16	-0.16	-1.32	-0.14	-1.45	-1.49	-0.42	-1.91	0.05	-1.85
Glu829	-0.9	-1.55	-2.45	2.39	-0.06	-0.98	-2.27	-3.24	3.17	-0.07
Phe830	-4.33	0.07	-4.27	0.18	-4.09	-4.32	0.14	-4.18	0.48	-3.7
Leu858	-0.7	0.03	-0.68	0.04	-0.64	-0.65	0.06	-0.58	-0.01	-0.6

Gln859	-0.62	-2.24	-2.85	1.95	-0.91	-0.25	-2.57	-2.82	2.06	-0.76
Phe862	-2.76	0.03	-2.73	-0.15	-2.87	-2.79	0	-2.79	-0.17	-2.96
Ile866	-1.66	-0.1	-1.76	-0.12	-1.88	-1.77	-0.13	-1.9	-0.12	-2.01

Compound **10**

	vdW	ele	MM	GB	ΔG_{bind}^{GBSA}
Tyr655	-0.35	0.00	-0.35	0.02	-0.32
Hid656	-0.53	-0.01	-0.53	-0.02	-0.55
Asn704	-0.54	-0.32	-0.87	1.14	0.27
Leu770	-0.33	0.10	-0.23	-0.16	-0.39
Leu809	-0.73	0.07	-0.66	-0.16	-0.82
Ile826	-1.25	-0.17	-1.42	-0.11	-1.52
Glu829	-1.09	-1.00	-2.10	1.70	-0.40
Phe830	-4.67	-0.11	-4.78	0.58	-4.20
Leu858	-0.74	0.06	-0.68	0.06	-0.62
Gln859	-0.67	-2.07	-2.75	2.08	-0.67
Phe862	-2.98	-0.06	-3.04	-0.11	-3.15
Ile866	-1.53	-0.14	-1.67	-0.11	-1.77