

## Supporting information

### Supplementary Material 3: Tables S1–S3, Figures S5–S7

**Table S1.** Molecular docking results from three different experiments for open-ring (OR) form of midazolam formulated with TRIMEB.

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
1	OR	1	-5.590	1	-5.550	1	-5.570
2	OR	2	-5.540	2	-5.140	2	-5.110
3	OR	3	-5.360	3	-4.990	3	-4.960
4	OR	4	-5.000	4	-4.950	4	-4.710
5	OR	5	-4.940	5	-4.870	5	-4.600
6	OR	6	-4.910	6	-4.780	6	-4.510
7	OR	7	-4.810	7	-4.730	7	-4.390
8	OR	8	-4.800	8	-4.620	8	-4.320
9	OR	9	-4.590	9	-4.560	9	-4.310
10	OR	10	-4.590	10	-4.460	10	-4.290
11	OR	11	-4.510	11	-4.340	11	-4.250
12	OR	12	-4.470	12	-4.260	12	-4.240
13	OR	13	-4.470	13	-4.240	13	-4.220
14	OR	14	-4.380	14	-4.230	14	-4.210
15	OR	15	-4.310	15	-4.180	15	-4.160
16	OR	16	-4.270	16	-4.170	16	-4.060
17	OR	18	-4.250	17	-4.160	17	-4.010
18	OR	17	-4.250	18	-4.120	18	-3.910
19	OR	19	-4.240	19	-3.940	19	-3.890
20	OR	20	-4.210	20	-3.920	20	-3.880
21	OR	21	-4.180	22	-3.880	21	-3.820
22	OR	23	-4.140	21	-3.880	22	-3.810
23	OR	22	-4.140	23	-3.830	23	-3.770
24	OR	24	-4.140	24	-3.620	24	-3.760
25	OR	25	-4.130	25	-3.560	25	-3.700
26	OR	26	-4.070	26	-3.530	26	-3.690
27	OR	27	-4.040	27	-3.420	27	-3.680
28	OR	28	-3.900	28	-3.340	28	-3.630
29	OR	29	-3.880	29	-3.320	29	-3.620
30	OR	30	-3.820	30	-3.310	30	-3.590
31	OR	31	-3.790	31	-3.290	31	-3.550
32	OR	32	-3.710	32	-3.290	32	-3.550
33	OR	33	-3.680	33	-3.250	33	-3.540
34	OR	34	-3.610	34	-3.240	34	-3.480
35	OR	35	-3.570	35	-3.240	35	-3.470
36	OR	36	-3.540	36	-3.240	36	-3.450
37	OR	37	-3.450	37	-3.200	37	-3.440
38	OR	38	-3.380	38	-3.180	38	-3.440
39	OR	39	-3.380	39	-3.140	39	-3.430
40	OR	40	-3.360	40	-3.130	40	-3.380
41	OR	41	-3.250	41	-3.120	41	-3.330
42	OR	43	-3.250	42	-3.080	42	-3.300

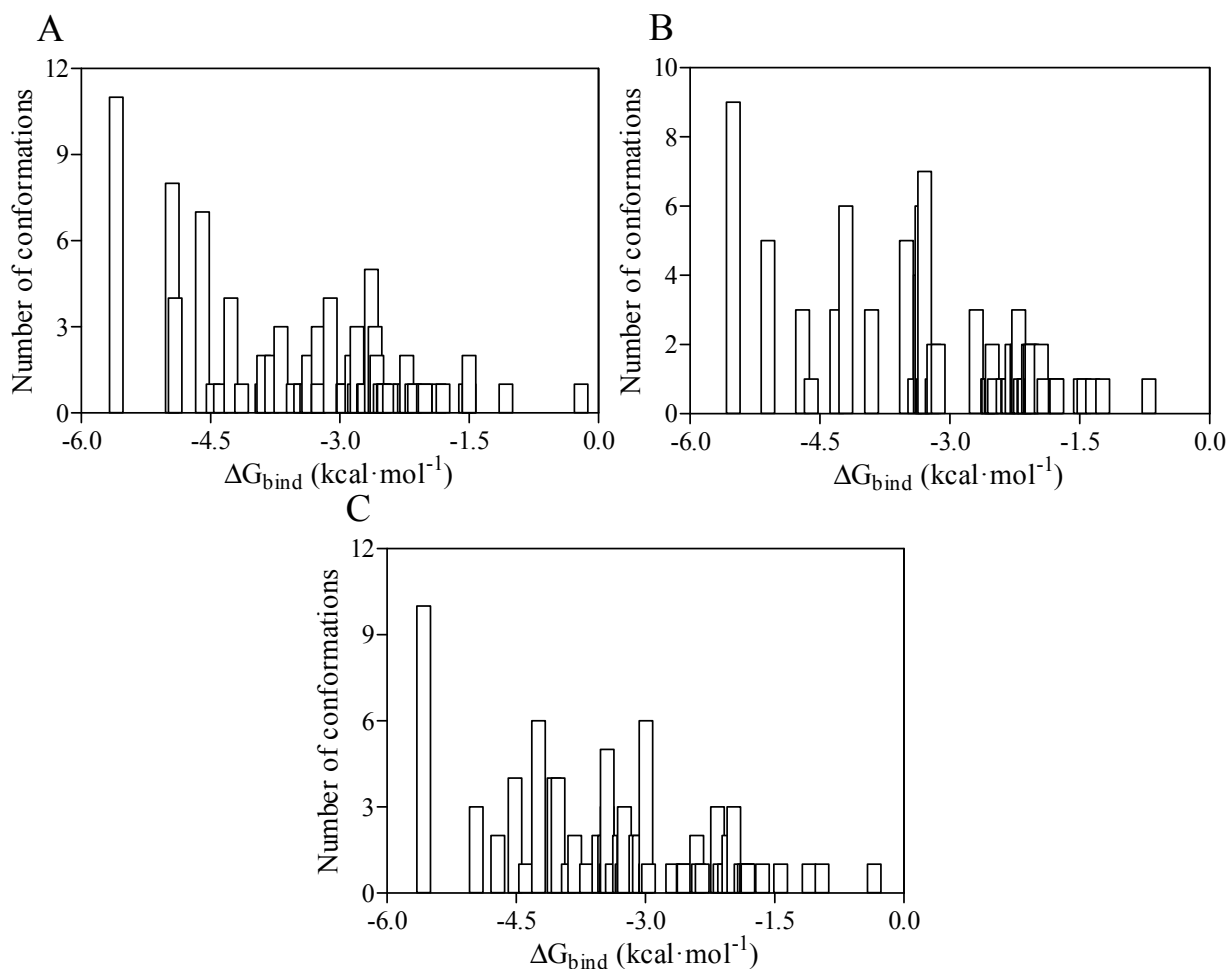
Table S1. *Cont.*

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
43	OR	42	-3.250	44	-3.070	43	-3.270
44	OR	44	-3.240	43	-3.070	44	-3.260
45	OR	45	-3.200	45	-3.060	45	-3.250
46	OR	46	-3.150	46	-3.040	46	-3.240
47	OR	47	-3.130	47	-3.020	47	-3.110
48	OR	48	-3.110	49	-2.950	48	-3.110
49	OR	49	-3.090	48	-2.950	49	-3.100
50	OR	50	-3.050	50	-2.770	50	-3.080
51	OR	51	-3.030	51	-2.690	51	-3.080
52	OR	52	-3.010	52	-2.680	52	-3.070
53	OR	53	-2.990	53	-2.630	53	-3.020
54	OR	54	-2.960	54	-2.620	56	-2.990
55	OR	55	-2.960	56	-2.560	54	-2.990
56	OR	56	-2.950	55	-2.560	55	-2.990
57	OR	57	-2.860	57	-2.550	58	-2.960
58	OR	58	-2.830	58	-2.520	57	-2.960
59	OR	59	-2.820	61	-2.510	60	-2.910
60	OR	60	-2.800	60	-2.510	59	-2.910
61	OR	61	-2.720	59	-2.510	61	-2.890
62	OR	62	-2.710	62	-2.480	62	-2.850
63	OR	63	-2.630	64	-2.380	63	-2.820
64	OR	66	-2.590	63	-2.380	64	-2.780
65	OR	65	-2.590	65	-2.330	65	-2.680
66	OR	64	-2.590	66	-2.320	66	-2.670
67	OR	67	-2.580	67	-2.310	67	-2.560
68	OR	69	-2.570	68	-2.280	68	-2.550
69	OR	68	-2.570	69	-2.240	69	-2.460
70	OR	70	-2.550	70	-2.220	70	-2.400
71	OR	71	-2.530	71	-2.210	71	-2.400
72	OR	72	-2.510	72	-2.200	72	-2.380
73	OR	73	-2.490	73	-2.200	73	-2.340
74	OR	74	-2.480	74	-2.180	74	-2.260
75	OR	75	-2.460	75	-2.140	75	-2.250
76	OR	76	-2.450	76	-2.130	76	-2.220
77	OR	78	-2.420	77	-2.130	77	-2.160
78	OR	77	-2.420	78	-2.090	78	-2.130
79	OR	79	-2.410	79	-2.070	79	-2.130
80	OR	80	-2.370	80	-2.060	80	-2.080
81	OR	81	-2.360	81	-2.050	81	-2.050
82	OR	82	-2.330	82	-2.010	82	-2.030
83	OR	83	-2.300	83	-2.000	83	-1.970
84	OR	84	-2.250	84	-2.000	85	-1.950
85	OR	85	-2.220	85	-1.940	84	-1.950
86	OR	86	-2.160	86	-1.940	86	-1.920
87	OR	87	-2.130	87	-1.910	87	-1.860

Table S1. *Cont.*

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
88	OR	88	-2.040	89	-1.880	88	-1.850
89	OR	89	-2.030	88	-1.880	90	-1.820
90	OR	90	-2.010	90	-1.790	89	-1.820
91	OR	92	-1.850	91	-1.780	91	-1.810
92	OR	91	-1.850	92	-1.770	92	-1.790
93	OR	93	-1.800	93	-1.760	93	-1.780
94	OR	94	-1.540	94	-1.610	94	-1.660
95	OR	95	-1.500	95	-1.490	95	-1.640
96	OR	96	-1.500	96	-1.450	96	-1.430
97	OR	97	-1.370	97	-1.420	97	-1.350
98	OR	98	-1.340	98	-1.350	98	-1.100
99	OR	99	-1.070	99	-1.230	99	-0.95
100	OR	100	-0.2	100	-0.7	100	-0.34

**Figure S5.** Histograms of clustered binding conformations for open-ring (OR) form of midazolam formulated with TRIMEB. The conformational clustering was performed for three different molecular docking experiments (A–C) using a root-mean-square-deviation cut-off value of 2.0 Å.



**Table S2.** Molecular docking results from three different experiments for transition state (TS) form of midazolam formulated with TRIMEB.

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
1	TS	12	-5.150	12	-5.150	12	-5.150
2	TS	13	-5.150	13	-5.150	13	-5.150
3	TS	10	-5.150	10	-5.150	10	-5.150
4	TS	11	-5.150	11	-5.150	11	-5.150
5	TS	16	-5.150	16	-5.150	16	-5.150
6	TS	17	-5.150	17	-5.150	17	-5.150
7	TS	14	-5.150	14	-5.150	14	-5.150
8	TS	15	-5.150	15	-5.150	15	-5.150
9	TS	18	-5.150	18	-5.150	18	-5.150
10	TS	19	-5.150	19	-5.150	19	-5.150
11	TS	8	-5.150	24	-5.150	8	-5.150
12	TS	9	-5.150	25	-5.150	9	-5.150
13	TS	1	-5.150	8	-5.150	1	-5.150
14	TS	2	-5.150	9	-5.150	2	-5.150
15	TS	3	-5.150	1	-5.150	3	-5.150
16	TS	4	-5.150	2	-5.150	4	-5.150
17	TS	5	-5.150	3	-5.150	5	-5.150
18	TS	6	-5.150	4	-5.150	6	-5.150
19	TS	7	-5.150	5	-5.150	7	-5.150
20	TS	21	-5.150	6	-5.150	22	-5.150
21	TS	20	-5.150	7	-5.150	21	-5.150
22	TS	24	-5.140	23	-5.150	20	-5.150
23	TS	25	-5.140	22	-5.150	24	-5.140
24	TS	23	-5.140	21	-5.150	25	-5.140
25	TS	22	-5.140	20	-5.150	28	-5.140
26	TS	26	-5.140	28	-5.140	30	-5.140
27	TS	28	-5.130	30	-5.140	31	-5.140
28	TS	27	-5.130	31	-5.140	32	-5.140
29	TS	29	-5.100	29	-5.140	29	-5.140
30	TS	30	-4.980	27	-5.140	23	-5.140
31	TS	31	-4.140	26	-5.140	27	-5.140
32	TS	32	-4.120	32	-5.130	26	-5.140
33	TS	33	-4.100	34	-5.120	34	-5.130
34	TS	38	-4.090	33	-5.120	35	-5.130
35	TS	39	-4.090	35	-5.110	33	-5.130
36	TS	34	-4.090	36	-5.090	36	-5.110
37	TS	35	-4.090	37	-4.950	37	-4.890
38	TS	36	-4.090	38	-4.910	38	-4.860
39	TS	37	-4.090	39	-4.330	39	-4.190
40	TS	49	-4.080	40	-4.320	41	-4.100
41	TS	48	-4.080	41	-4.280	40	-4.100
42	TS	45	-4.080	42	-4.230	45	-4.090
43	TS	44	-4.080	43	-4.140	44	-4.090

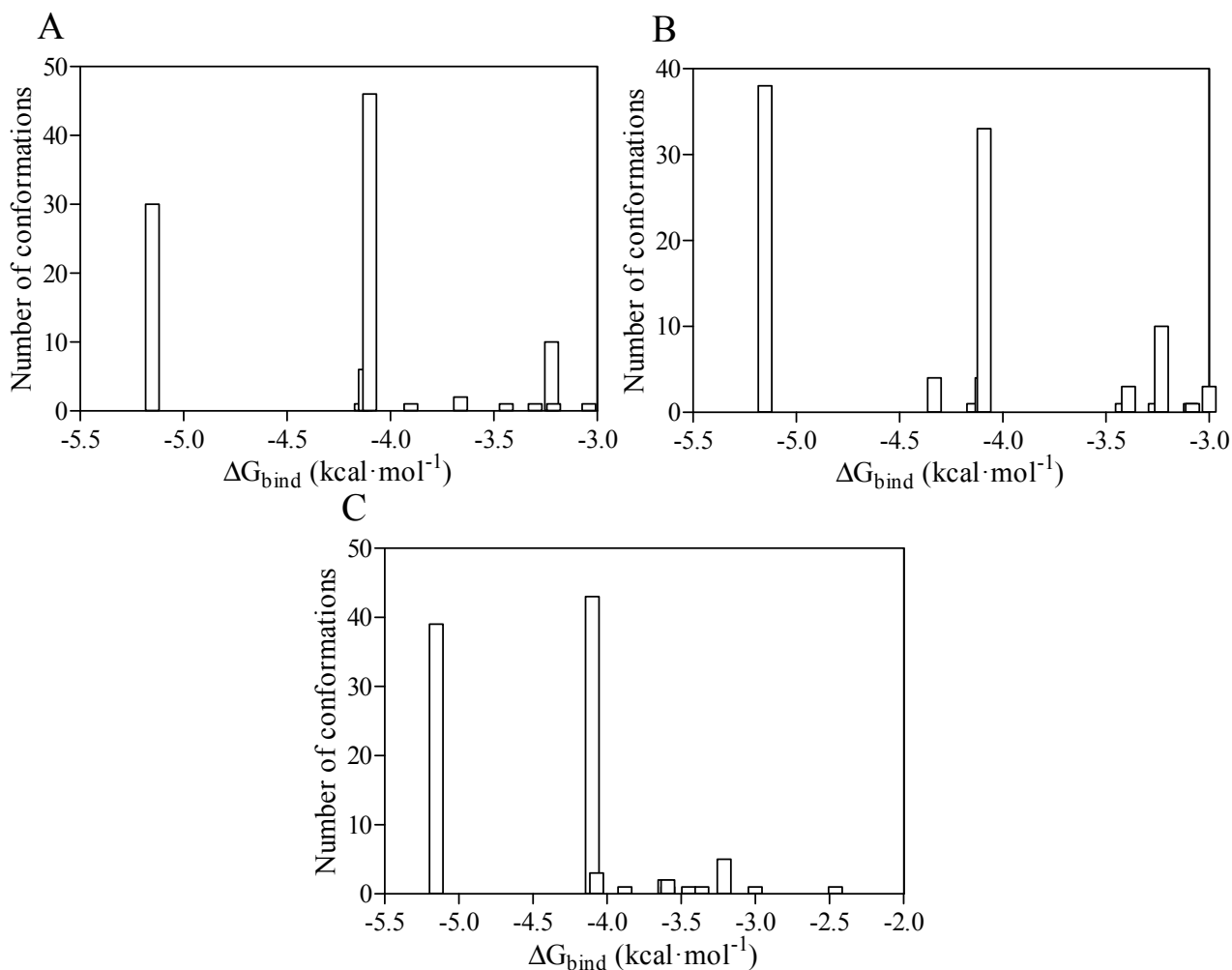
Table S2. *Cont.*

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
44	TS	47	-4.080	44	-4.100	47	-4.090
45	TS	46	-4.080	49	-4.090	46	-4.090
46	TS	41	-4.080	48	-4.090	43	-4.090
47	TS	40	-4.080	45	-4.090	42	-4.090
48	TS	43	-4.080	47	-4.090	49	-4.080
49	TS	42	-4.080	46	-4.090	48	-4.080
50	TS	52	-4.080	50	-4.090	54	-4.080
51	TS	53	-4.080	56	-4.080	52	-4.080
52	TS	50	-4.080	57	-4.080	53	-4.080
53	TS	51	-4.080	54	-4.080	50	-4.080
54	TS	70	-4.070	55	-4.080	51	-4.080
55	TS	71	-4.070	52	-4.080	78	-4.070
56	TS	58	-4.070	53	-4.080	70	-4.070
57	TS	59	-4.070	51	-4.080	71	-4.070
58	TS	56	-4.070	70	-4.070	72	-4.070
59	TS	57	-4.070	71	-4.070	73	-4.070
60	TS	54	-4.070	72	-4.070	74	-4.070
61	TS	55	-4.070	73	-4.070	75	-4.070
62	TS	67	-4.070	58	-4.070	76	-4.070
63	TS	66	-4.070	59	-4.070	77	-4.070
64	TS	65	-4.070	67	-4.070	58	-4.070
65	TS	64	-4.070	66	-4.070	59	-4.070
66	TS	63	-4.070	65	-4.070	56	-4.070
67	TS	62	-4.070	64	-4.070	57	-4.070
68	TS	61	-4.070	63	-4.070	55	-4.070
69	TS	60	-4.070	62	-4.070	67	-4.070
70	TS	69	-4.070	61	-4.070	66	-4.070
71	TS	68	-4.070	60	-4.070	65	-4.070
72	TS	72	-4.060	69	-4.070	64	-4.070
73	TS	73	-4.060	68	-4.070	63	-4.070
74	TS	74	-4.060	74	-4.060	62	-4.070
75	TS	75	-4.040	75	-4.060	61	-4.070
76	TS	76	-4.030	76	-3.830	60	-4.070
77	TS	77	-4.010	77	-3.720	69	-4.070
78	TS	78	-3.990	78	-3.610	68	-4.070
79	TS	79	-3.980	79	-3.600	81	-4.060
80	TS	80	-3.900	80	-3.580	80	-4.060
81	TS	81	-3.870	81	-3.420	79	-4.060
82	TS	82	-3.740	82	-3.390	83	-4.040
83	TS	83	-3.680	83	-3.370	82	-4.040
84	TS	84	-3.670	84	-3.370	84	-3.880
85	TS	85	-3.660	85	-3.260	85	-3.640
86	TS	86	-3.630	87	-3.230	86	-3.610
87	TS	87	-3.440	86	-3.230	88	-3.590
88	TS	88	-3.300	88	-3.220	87	-3.590

Table S2. *Cont.*

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
89	TS	89	-3.220	89	-3.210	89	-3.450
90	TS	92	-3.210	90	-3.210	90	-3.390
91	TS	90	-3.210	92	-3.200	91	-3.360
92	TS	91	-3.210	91	-3.200	92	-3.250
93	TS	93	-3.200	93	-3.190	93	-3.210
94	TS	94	-3.190	94	-3.190	94	-3.200
95	TS	95	-3.180	95	-3.190	95	-3.190
96	TS	96	-3.170	96	-3.090	96	-3.180
97	TS	97	-3.170	97	-3.080	97	-3.170
98	TS	98	-3.160	98	-3.000	98	-3.080
99	TS	99	-3.120	99	-3.000	99	-3.000
100	TS	100	-3.040	100	-2.990	100	-2.460

**Figure S6.** Histograms of clustered binding conformations for transition state (TS) form of midazolam formulated with TRIMEB. The conformational clustering was performed for three different molecular docking experiments (A–C) using a root-mean-square-deviation cut-off value of 2.0 Å.



**Table S3.** Molecular docking results from three different experiments for closed-ring (CR) form of midazolam formulated with TRIMEB.

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
1	CR	3	-5.150	3	-4.410	12	-4.410
2	CR	2	-5.150	2	-4.410	11	-4.410
3	CR	1	-5.150	1	-4.410	10	-4.410
4	CR	13	-5.140	7	-4.410	3	-4.410
5	CR	12	-5.140	6	-4.410	2	-4.410
6	CR	11	-5.140	5	-4.410	1	-4.410
7	CR	10	-5.140	4	-4.410	7	-4.410
8	CR	7	-5.140	9	-4.410	6	-4.410
9	CR	6	-5.140	8	-4.410	5	-4.410
10	CR	5	-5.140	17	-4.400	4	-4.410
11	CR	4	-5.140	16	-4.400	9	-4.410
12	CR	9	-5.140	15	-4.400	8	-4.410
13	CR	8	-5.140	14	-4.400	17	-4.400
14	CR	17	-5.130	13	-4.400	16	-4.400
15	CR	16	-5.130	12	-4.400	15	-4.400
16	CR	15	-5.130	11	-4.400	14	-4.400
17	CR	14	-5.130	10	-4.400	13	-4.400
18	CR	19	-5.130	19	-4.400	19	-4.400
19	CR	18	-5.130	18	-4.400	18	-4.400
20	CR	20	-5.130	20	-4.400	20	-4.400
21	CR	24	-5.120	24	-4.390	21	-4.400
22	CR	25	-5.120	25	-4.390	24	-4.390
23	CR	22	-5.120	22	-4.390	25	-4.390
24	CR	23	-5.120	23	-4.390	28	-4.390
25	CR	21	-5.120	21	-4.390	22	-4.390
26	CR	26	-5.120	26	-4.380	23	-4.390
27	CR	28	-5.110	27	-4.380	26	-4.390
28	CR	27	-5.110	28	-4.370	27	-4.390
29	CR	29	-5.110	30	-4.370	31	-4.380
30	CR	31	-5.100	29	-4.370	30	-4.380
31	CR	30	-5.100	35	-4.360	32	-4.380
32	CR	32	-5.070	31	-4.360	29	-4.380
33	CR	33	-5.050	33	-4.360	33	-4.370
34	CR	34	-5.040	32	-4.360	35	-4.360
35	CR	36	-4.990	34	-4.360	34	-4.360
36	CR	35	-4.990	36	-4.340	36	-4.350
37	CR	37	-4.990	37	-4.340	37	-4.350
38	CR	38	-4.990	38	-4.340	38	-4.350
39	CR	39	-4.950	39	-4.330	39	-4.350
40	CR	53	-4.930	40	-4.330	40	-4.350
41	CR	52	-4.930	41	-4.330	44	-4.340
42	CR	51	-4.930	42	-4.330	45	-4.340
43	CR	50	-4.930	43	-4.330	46	-4.340

Table S3. *Cont.*

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
44	CR	55	-4.930	44	-4.320	41	-4.340
45	CR	54	-4.930	45	-4.320	42	-4.340
46	CR	44	-4.930	46	-4.320	43	-4.340
47	CR	45	-4.930	47	-4.320	52	-4.330
48	CR	46	-4.930	48	-4.320	51	-4.330
49	CR	47	-4.930	51	-4.310	50	-4.330
50	CR	40	-4.930	50	-4.310	47	-4.330
51	CR	41	-4.930	49	-4.310	48	-4.330
52	CR	42	-4.930	53	-4.300	49	-4.330
53	CR	43	-4.930	52	-4.300	53	-4.320
54	CR	48	-4.930	57	-4.300	56	-4.320
55	CR	49	-4.930	56	-4.300	55	-4.320
56	CR	65	-4.920	55	-4.300	54	-4.320
57	CR	57	-4.920	54	-4.300	57	-4.310
58	CR	56	-4.920	58	-4.300	59	-4.310
59	CR	59	-4.920	65	-4.290	58	-4.310
60	CR	58	-4.920	59	-4.290	60	-4.310
61	CR	92	-4.920	71	-4.290	65	-4.300
62	CR	91	-4.920	70	-4.290	68	-4.300
63	CR	90	-4.920	68	-4.290	66	-4.300
64	CR	78	-4.920	69	-4.290	67	-4.300
65	CR	79	-4.920	66	-4.290	64	-4.300
66	CR	74	-4.920	67	-4.290	62	-4.300
67	CR	77	-4.920	64	-4.290	63	-4.300
68	CR	76	-4.920	62	-4.290	61	-4.300
69	CR	71	-4.920	63	-4.290	74	-4.290
70	CR	70	-4.920	60	-4.290	76	-4.290
71	CR	73	-4.920	61	-4.290	71	-4.290
72	CR	72	-4.920	78	-4.280	70	-4.290
73	CR	80	-4.920	74	-4.280	73	-4.290
74	CR	81	-4.920	77	-4.280	72	-4.290
75	CR	82	-4.920	76	-4.280	69	-4.290
76	CR	83	-4.920	73	-4.280	75	-4.290
77	CR	84	-4.920	72	-4.280	78	-4.280
78	CR	85	-4.920	75	-4.280	79	-4.280
79	CR	86	-4.920	79	-4.270	77	-4.280
80	CR	87	-4.920	80	-4.270	80	-4.280
81	CR	88	-4.920	81	-4.250	81	-4.280
82	CR	89	-4.920	82	-4.240	82	-4.280
83	CR	68	-4.920	83	-4.230	83	-4.280
84	CR	69	-4.920	84	-4.230	84	-4.280
85	CR	66	-4.920	85	-4.220	85	-4.280
86	CR	67	-4.920	86	-4.220	86	-4.280
87	CR	64	-4.920	87	-4.200	87	-4.270
88	CR	62	-4.920	88	-3.940	92	-4.260



Table S3. *Cont.*

Rank	Form	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$	Pose	$\Delta G_{\text{bind}}$
89	CR	63	-4.920	89	-3.630	91	-4.260
90	CR	60	-4.920	90	-3.620	90	-4.260
91	CR	61	-4.920	91	-3.590	88	-4.260
92	CR	75	-4.920	92	-3.570	89	-4.260
93	CR	96	-4.910	93	-3.460	93	-4.250
94	CR	93	-4.910	94	-3.460	94	-4.250
95	CR	95	-4.910	95	-3.450	95	-4.240
96	CR	94	-4.910	97	-3.440	96	-4.090
97	CR	97	-4.840	96	-3.440	97	-3.620
98	CR	98	-4.770	98	-3.430	98	-3.450
99	CR	99	-4.760	99	-3.390	99	-3.310
100	CR	100	-4.720	100	-3.340	100	-2.980

**Figure S7.** Histograms of clustered binding conformations for closed-ring (CR) form of midazolam formulated with TRIMEB. The conformational clustering was performed for three different molecular docking experiments (A–C) using a root-mean-square-deviation cut-off value of 2.0 Å.

