Supplementary Information

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Abstract: MGluR2 is G protein-coupled receptor that is targeted for diseases like anxiety, depression, Parkinson's disease and schizophrenia. Herein, we report the three-dimensional quantitative structure–activity relationship (3D-QSAR) studies of a series of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives as mGluR2 antagonists. Two series of models using two different activities of the antagonists against rat mGluR2, which has been shown to be very similar to the human mGluR2, (activity I: inhibition of [^{3}H]-LY354740; activity II: mGluR2 (1S,3R)-ACPD inhibition of forskolin stimulated cAMP.) were derived from datasets composed of 137 and 69 molecules respectively. For activity I study, the best predictive model obtained from CoMFA analysis yielded a Q^2 of 0.513, R^2_{ncv} of 0.868, $R^2_{pred} = 0.876$, while the CoMSIA model yielded a Q^2 of 0.450, $R^2_{ncv} = 0.899$, $R^2_{pred} = 0.735$. For activity II study, CoMFA model yielded statistics of $Q^2 = 0.5$, $R^2_{ncv} = 0.715$, $R^2_{pred} = 0.723$. These results prove the high predictability of the models. Furthermore, a combined analysis between the CoMFA, CoMSIA contour maps shows that: (1) Bulky substituents in R_7, R_3 and position A benefit activity I of the antagonists, but decrease it when projected in R_8 and position B; (2) Hydrophilic groups at position A and B increase both antagonistic activity I and II; (3) Electrostatic field plays an essential rule in the variance of activity II. In search for more potent mGluR2 antagonists, two pharmacophore models were developed separately for the two activities. The first model reveals six pharmacophoric features, namely an aromatic center, two hydrophobic centers, an H-donor atom, an H-acceptor atom and an H-donor site. The second model shares all features of the first one

and has an additional acceptor site, a positive N and an aromatic center. These models can be used as guidance for the development of new mGluR2 antagonists of high activity and selectivity. This work is the first report on 3D-QSAR modeling of these mGluR2 antagonists. All the conclusions may lead to a better understanding of the mechanism of antagonism and be helpful in the design of new potent mGluR2 antagonists.

Keywords: 3D-QSAR; mGluR2 antagonist; CoMFA; CoMSIA; pharmacophore modeling

Table S1. Structure–activity relationship data related to the series of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives described in this study (group 14).
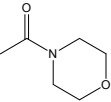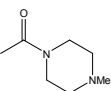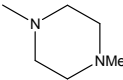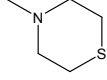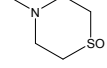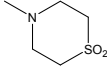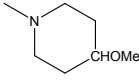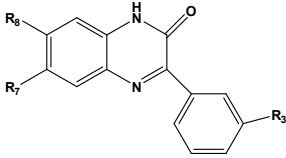

NO	R_3	R_8	R_7	Activity I (pIC_{50})	Activity II (pIC_{50})
1[#]	H	Me	H	5.1938	
2[§]	CN	Ph-C≡C-	H	7.4685	7.7696
14a	MeO	Me	H	5.1818	
14b	Cl	Me	H	5.5498	
14c[#]	CF_3	Me	H	5.8153	
14d	CN	Me	H	5.5376	
14e[#]	H	Ph-C≡C-	H	7.5850	
14f	MeO	Ph-C≡C-	H	6.0168	
14g	Cl	Ph-C≡C-	H	7.0969	
14h	CF_3	Ph-C≡C-	H	6.5719	
14i	I	Ph-C≡C-	H	6.8125	
14j	$CONH_2$	Ph-C≡C-	H	6.4461	
14k	(acetyl morpholine)	Ph-C≡C-	H	6.4437	
14l	(acetyl N-methylpiperazine)	Ph-C≡C-	H	5.9830	
14m	CN	Ph-C≡C-	H	7.4685	
14n[#]	CN	2-Cl-C_6H_4-C≡C-	H	7.1192	
14o	CN	4-Me-C_6H_4-C≡C-	H	7.1938	
14p[#]	CN	4-MeO-C_6H_4-C≡C-	H	7.1675	
14q	CN	4-F-C_6H_4-C≡C-	H	7.4685	
14r	CN	2-F-C_6H_4-C≡C-	H	7.5229	

Table 1S. *Cont.*

14s	CN	2,4-di-F-C$_6$H$_4$-C≡C-	H	6.3188
14t	CN	2-Thiophenyl-C≡C-	H	7.4949
14u	CN	2-Thiazolyl-C≡C-	H	6.5229
14v	CN	2-Pyridyl-C≡C-	H	6.0605
14w	CN	HO(Me)$_2$C-C≡C-	H	4.5850
14x	CN	H$_2$C=C(Me)-C≡C-	H	6.3979
14y	CN	Ph-C≡C-	-NMe$_2$	7.2218
14z	CN	Ph-C≡C-	*N-methylmorpholin-yl (O)*	6.4225
14aa[#]	CN	Ph-C≡C-	*N-methylpiperazinyl (NMe)*	6.5560
14ab	CN	Ph-C≡C-	*N-methylthiomorpholinyl (S)*	7.3979
14ac[#]	CN	Ph-C≡C-	*N-methylthiomorpholinyl S-oxide (SO)*	6.3507
14ad[#]	CN	Ph-C≡C-	*N-methylthiomorpholinyl S,S-dioxide (SO$_2$)*	6.7959
14ae	CN	Ph-C≡C-	*N-methylpiperidinyl (CHOMe)*	7.0862
14af	CN	Ph-C≡C-	-OMe	7.0362
14ag[#]	CN	Ph-C≡C-	-OCH$_2$CH$_2$OMe	7.5528
14ah	CN	Ph-C≡C-	-OCH$_2$CO$_2$H	6.2218
14ai	CN	Ph-C≡C-	-OCH$_2$CONH$_2$	5.6198
14aj	CN	Ph-C≡C-	-OCH$_2$CONHBu^t	7.5850
14ak	CN	Ph-C≡C-	-OCH$_2$CN	7.7447

Test set for activity I; § Test set for activity II.

Table S2 Structure–activity relationship data related to the series of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives described in this study (group 15).

NO	R_3	R_8	R_7	Activity I (pIC$_{50}$)	Activity II (pIC$_{50}$)
15a[#]	(1-methylimidazolyl)	Ph-C≡C-	H	7.8861	8.0000
15b	(1-methylimidazolyl)	4-F-C$_6$H$_4$-C≡C-	H	8.0458	8.0458
15c	(1-methylimidazolyl)	2-F-C$_6$H$_4$-C≡C-	H	7.6990	7.7959
15d	(4-Me-1-methylimidazolyl)	4-F-C$_6$H$_4$-C≡C-	H	7.0088	
15e	(2,5-dimethyl-1-methylimidazolyl)	Ph-C≡C-	H	6.7696	
15f	(Me-1-methyltriazolyl)	Ph-C≡C-	H	6.1367	
15g	(1-methyl-1,2,4-triazolyl)	4-F-C$_6$H$_4$-C≡C-	H	7.0088	
15h	(1-methyl-1,2,3-triazolyl)	4-F-C$_6$H$_4$-C≡C-	H	8.2218	7.9208
15i	(1-methyltetrazolyl)	4-F-C$_6$H$_4$-C≡C-	H	7.1427	
15j	(1-methylimidazolyl)	Ph-C≡C-	-OCH$_2$CH$_2$OMe	7.6383	7.8239
15k	(1-methylimidazolyl)	Ph-C≡C-	-OCH$_2$CH$_2$OH	7.1938	
15l	(1-methylimidazolyl)	4-F-C$_6$H$_4$-C≡C-	-OCH$_2$CH$_2$OH	7.3372	
15m	(1-methylimidazolyl)	Ph-C≡C-	-OCH$_2$CN	7.7447	7.8861
15n	(1-methylimidazolyl)	4-F-C$_6$H$_4$-C≡C-	-N(Me)CH$_2$CH$_2$OH	6.8539	
15o	(1-methylimidazolyl)	4-F-C$_6$H$_4$-C≡C-	-OH	7.5850	7.9586
15p	(1-methylpyrazolyl)	Ph-C≡C-	-NMe$_2$	7.4437	
15q	(1-methylpyrazolyl)	4-F-C$_6$H$_4$-C≡C-	-OH	7.6990	7.7696
15r[#]	(1-methyl-CH$_2$OH-triazolyl)	4-F-C$_6$H$_4$-C≡C-	OH	6.4225	

\# Test set for activity I; § Test set for activity II.

Table S3 Structure–activity relationship data related to the series of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives described in this study (group 7).
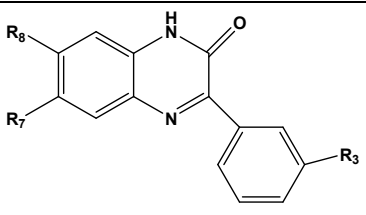

NO	R$_3$	R$_8$	R$_7$	Activity I (pIC$_{50}$)	Activity II (pIC$_{50}$)
7a[§]	(imidazolyl)	Ph	H	7.4089	7.3279
7b	(imidazolyl)	4-F-C$_6$H$_4$-	H	7.7696	7.6198
7c	(imidazolyl)	2-F-C$_6$H$_4$-	H	7.9208	7.5686
7d	(imidazolyl)	3-F-C$_6$H$_4$-	H	7.6021	
7e	(imidazolyl)	2,5-Di-F-C$_6$H$_3$-	H	8.1549	7.7696
7f	(imidazolyl)	2-F-C$_6$H$_4$-	HO-	7.6576	
7g	(imidazolyl)	*Cyclo*-propyl	H	6.6778	
7h	(imidazolyl)	Br	H	7.1427	
7i[#]	(imidazolyl)	F$_3$C-	H	7.3665	
7j[#]	(imidazolyl)	F$_3$C-	-NMe$_2$	8.0458	7.2840
7k	(imidazolyl)	F$_3$C-	*Iso*-butylNH	7.7212	7.1367
7l	(imidazolyl)	F$_3$C-	Cl	7.7696	7.8239
7m	(imidazolyl)	F$_3$C-	Me	7.9208	7.7212
7n	(imidazolyl)	F$_3$C-	Et	8.3979	8.0000
7o	(triazolyl)	4-F-C$_6$H$_4$-	H	7.5086	7.4437
7p[#]	(triazolyl)	2-F-C$_6$H$_4$-	H	7.7959	7.4318
7q[#]	(triazolyl)	2,5-Di-F-C$_6$H$_3$-	H	7.7696	7.7447

Table S3. *Cont.*

7r		*Iso*-propyl	H	6.3316	
7s		Br	H	6.8861	
7t[#]		Cl	H	7.2218	
7u[#]		F_3C-	H	7.0362	
7v[#]		F_2CH-	H	6.2161	
7w		F_3CCH_2O-	H	7.1549	
7x[§]		F_3C-	Me_2N	7.4202	6.7352
7y		F_3C-	*Iso*-butylNH	7.3768	6.5719
7z		F_3C-	*Iso*-butylN(Me)	7.9586	7.8539
7aa		F_3C-	Cl	7.5686	6.9355
7ab		F_3C-	Me	8.0458	7.4089
7ac		F_3C-	MeO	7.5376	7.1308
7ad[#]		F_3C-	EtO	8.1549	7.4685

Test set for activity I; § Test set for activity II.

Table S4 Structure–activity relationship data related to the series of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives described in this study (group 8).

NO	R₃	R₈	R₇	Activity I (pIC₅₀)	Activity II (pIC₅₀)
8a		F$_3$C-	Me	7.9208	7.7212
8b		F$_3$C-	Me	8.0458	7.4089
8c		F$_3$C-	Me	8.3010	8.0458
8d		F$_3$C-	Me	8.0969	7.1249
8e		F$_3$C-	H	6.4559	
8f[#]		F$_3$C-	H	7.4089	7.7212
8g		F$_3$C-	Me	6.9208	
8h[§]		F$_3$C-	Me	8.3979	7.9586
8i[#]		F$_3$C-	Me	8.3979	8.3979
8j		F$_3$C-	Me	8.0969	8.3010
8k[#][§]		F$_3$C-	Me	7.9208	7.7447
8l		F$_3$C-	Me	7.1805	
8m[§]		F$_3$C-	Me	8.0000	8.2218
8n		F$_3$C-	Me	8.3979	8.0000

Table S4. *Cont.*
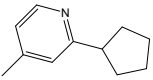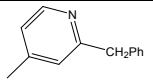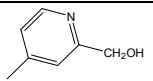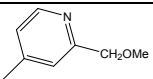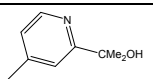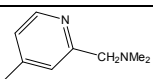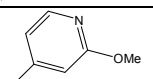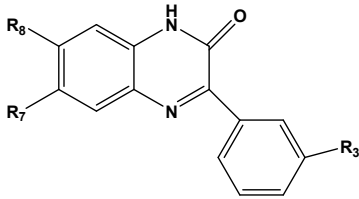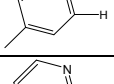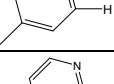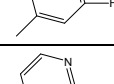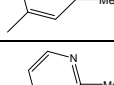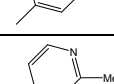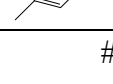
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8q		F$_3$C-	Me	7.7959	8.3010
8r		F$_3$C-	Me	7.8861	7.7447
8s		F$_3$C-	Me	7.8861	8.2218
8t		F$_3$C-	Me	7.3979	7.8539
8u		F$_3$C-	Me	6.5622	
8v		F$_3$C-	Me	7.8861	7.7959
8w		F$_3$C-	Me	7.2291	
8x		F$_3$C-	Me	7.5376	
8y		F$_3$C-	Me	7.5850	7.5229
8z		F$_3$C-	Me	8.6990	7.5229
8aa		F$_3$C-	Me	7.8861	8.3010
8ab		F$_3$C-	Me	8.0458	7.7447
8ac[§]		F$_3$C-	Me	8.2218	7.6990
8ad		F$_3$C-	Me	8.0000	8.0000
8ae[#]		F$_3$C-	Me	8.3010	8.0000
8af		F$_3$C-	Me	7.8539	6.7959
8ag		F$_3$C-	Me	7.0655	
8ah[#] [§]		F$_3$C-	Me	7.7447	7.1427
8ai		F$_3$C-	Me	6.8928	
8aj		F$_3$C-	Me	8.2218	7.3010

Table S4. *Cont.*

8ak[#]	(5-methylpyrimidinyl)	F₃C-	Me	7.6383	7.3188
8al	(3-methylpyrazinyl)	F₃C-	Me	7.6990	7.7959

NO	R₃	R₈	R₇	Activity I (pIC$_{50}$)	Activity II (pIC$_{50}$)
8am	(2,6-diMe-pyridinyl)	F₃C-	Me	8.6990	8.5229
8an	(2-Me-6-Et-pyridinyl)	F₃C-	Me	8.6990	8.3979
8ao[# §]	(2-Me-6-cyclopropyl-pyridinyl)	F₃C-	Me	8.6990	8.3979
8ap[§]	(Me, CH₂OH-pyridinyl)	F₃C-	Me	7.8539	7.8239
8aq	(Me, CH₂OMe-pyridinyl)	F₃C-	Me	8.0969	8.3010
8ar	(Me, Me-pyridinyl)	F₃C-	F₃C-	8.1549	8.1549
8as[#]	(pyridinyl, H)	F₃C-	H	8.0000	7.5850
8at	(pyridinyl, H)	F₃C-	OEt	8.3979	8.0000
8au	(pyridinyl, H)	Cl	H	8.0969	8.5229
8av	(2-Me-pyridinyl)	Cl	Cl	8.3979	8.6990
8aw[§]	(2-Me-pyridinyl)	F₃C	H	7.7447	7.4437
8ax	(2-Me-pyridinyl)	F₃C	OEt	8.2218	8.0969

Test set for activity I; § Test set for activity II.

Table S5. Observed and CoMFA/CoMSIA predicted mGluR2 inhibitory activity I (pIC$_{50}$ value).

NO	Observed activity	CoMFA		CoMSIA	
		Predicted	Residual	Predicted	Residual
1	5.19	5.799	-0.609	6.125	-0.935
2	7.47	7.441	0.029	7.621	-0.151
14a	5.18	5.233	-0.053	5.567	-0.387
14b	5.55	5.541	0.009	5.846	-0.296
14c	5.82	6.182	-0.362	6.391	-0.571
14d	5.54	5.404	0.136	5.802	-0.262
14e	7.59	7.026	0.564	6.677	0.913
14f	6.02	6.440	-0.420	6.450	-0.430
14g	7.10	6.932	0.168	6.719	0.381
14h	6.57	6.956	-0.386	6.800	-0.230
14i	6.81	7.117	-0.307	6.714	0.096
14j	6.45	6.784	-0.334	6.304	0.146
14k	6.44	6.987	-0.547	6.493	-0.053
14l	5.98	6.036	-0.056	6.026	-0.046
14m	7.47	7.063	0.407	7.073	0.397
14n	7.12	6.904	0.216	6.982	0.138
14o	7.19	7.206	-0.016	7.417	-0.227
14p	7.17	6.869	0.301	7.144	0.026
14q	7.47	7.285	0.185	7.408	0.062
14r	7.52	7.295	0.225	7.433	0.087
14s	6.32	6.262	0.058	6.381	-0.061
14t	7.49	7.485	0.005	7.668	-0.178
14u	6.52	6.626	-0.106	6.753	-0.233
14v	6.06	6.127	-0.067	6.081	-0.021
14w	4.59	5.086	-0.496	4.204	0.386
14x	6.40	5.847	0.553	6.090	0.310
14y	7.22	6.883	0.337	7.207	0.013
14z	6.42	6.474	-0.054	6.814	-0.394
14aa	6.56	6.529	0.031	6.866	-0.306
14ab	7.40	7.088	0.312	7.626	-0.226
14ac	6.35	6.587	-0.237	7.064	-0.714
14ad	6.80	6.592	0.208	7.136	-0.336
14ae	7.09	6.640	0.450	7.119	-0.029
14af	7.04	7.035	0.005	7.229	-0.189
14ag	7.55	7.395	0.155	7.738	-0.188
14ah	6.22	6.233	-0.013	6.020	0.200
14ai	5.62	5.843	-0.223	5.660	-0.040
14aj	7.59	7.515	0.075	7.620	-0.030
14ak	7.74	8.063	-0.323	7.918	-0.178
15a	7.89	7.484	0.406	7.758	0.132
15b	8.05	7.959	0.091	7.858	0.192
15c	7.70	7.359	0.341	7.577	0.123
15d	7.01	7.032	-0.022	7.009	0.001
15e	6.77	7.105	-0.335	6.672	0.098
15f	6.14	6.158	-0.018	6.069	0.071

Table S5. *Cont.*

15g	7.01	7.640	-0.630	7.370	-0.360
15h	8.22	8.130	0.090	7.524	0.696
15i	7.14	7.322	-0.182	7.046	0.094
15j	7.64	7.710	-0.070	7.728	-0.088
15k	7.19	6.941	0.249	7.336	-0.146
15l	7.34	7.547	-0.207	7.294	0.046
15m	7.74	7.719	0.021	7.754	-0.014
15n	6.85	6.704	0.146	6.616	0.234
15o	7.59	7.470	0.120	7.421	0.169
15p	7.44	7.591	-0.151	7.469	-0.029
15q	7.70	7.379	0.321	7.857	-0.157
15r	6.42	6.258	0.162	6.453	-0.033
7a	7.41	7.466	-0.056	7.665	-0.255
7b	7.77	7.651	0.119	7.737	0.033
7c	7.92	7.793	0.127	7.777	0.143
7d	7.60	7.582	0.018	7.660	-0.060
7e	8.15	7.850	0.300	7.745	0.405
7f	7.66	7.427	0.233	7.727	-0.067
7g	6.68	6.832	-0.152	6.998	-0.318
7h	7.14	7.270	-0.130	6.959	0.181
7i	7.37	7.462	-0.092	7.877	-0.507
7j	8.05	7.830	0.220	7.989	0.061
7k	7.72	7.226	0.494	7.632	0.088
7l	7.77	7.829	-0.059	8.049	-0.279
7m	7.92	8.101	-0.181	8.118	-0.198
7n	8.40	8.148	0.252	8.181	0.219
7o	7.51	7.241	0.269	7.293	0.217
7p	7.80	7.364	0.436	7.311	0.489
7q	7.77	7.410	0.360	7.280	0.490
7r	6.33	6.752	-0.422	6.804	-0.474
7s	6.89	6.373	0.517	6.288	0.602
7t	7.22	6.739	0.481	7.188	0.032
7u	7.04	6.978	0.062	7.397	-0.357
7v	6.22	6.283	-0.063	6.613	-0.393
7w	7.15	7.266	-0.116	7.319	-0.169
7x	7.42	7.560	-0.140	7.642	-0.222
7y	7.38	7.583	-0.203	7.502	-0.122
7z	7.96	8.008	-0.048	7.931	0.029
7aa	7.57	7.683	-0.113	7.707	-0.137
7ab	8.05	7.953	0.097	8.024	0.026
7ac	7.54	7.744	-0.204	7.650	-0.110
7ad	8.15	8.256	-0.106	8.086	0.064
8a	7.92	8.144	-0.224	7.982	-0.062
8b	8.05	7.953	0.097	8.024	0.026
8c	8.30	8.113	0.187	7.980	0.320
8d	8.10	7.414	0.686	7.720	0.380
8e	6.46	6.872	-0.412	6.729	-0.269
8f	7.41	7.346	0.064	7.463	-0.053

Table S5. *Cont.*

8g	6.92	6.626	0.294	6.618	0.302
8h	8.40	8.517	-0.117	8.277	0.123
8i	8.40	8.374	0.026	8.190	0.210
8j	8.10	8.404	-0.304	8.167	-0.067
8k	7.92	7.670	0.250	7.106	0.814
8l	7.18	7.583	-0.403	7.240	-0.060
8m	8.00	7.341	0.659	7.723	0.277
8n	8.40	7.994	0.406	7.983	0.417
8o	8.00	7.629	0.371	7.578	0.422
8p	6.93	7.297	-0.367	7.222	-0.292
8q	7.80	7.881	-0.081	7.934	-0.134
8r	7.89	8.193	-0.303	7.881	0.009
8s	7.89	8.249	-0.359	7.675	0.215
8t	7.40	7.436	-0.036	7.137	0.263
8u	6.56	7.181	-0.621	7.223	-0.663
8v	7.89	7.929	-0.039	7.827	0.063
8w	7.23	7.121	0.109	7.320	-0.090
8x	7.54	7.404	0.136	7.443	0.097
8y	7.59	7.926	-0.336	7.600	-0.010
8z	8.70	8.065	0.635	8.099	0.601
8aa	7.89	7.728	0.162	7.896	-0.006
8ab	8.05	8.063	-0.013	8.068	-0.018
8ac	8.22	7.913	0.307	8.115	0.105
8ad	8.00	7.912	0.088	7.971	0.029
8ae	8.30	7.992	0.308	7.997	0.303
8af	7.85	7.972	-0.122	7.856	-0.006
8ag	7.07	7.606	-0.536	7.901	-0.831
8ah	7.74	7.843	-0.103	7.850	-0.110
8ai	6.89	7.389	-0.499	7.445	-0.555
8aj	8.22	7.808	0.412	7.836	0.384
8ak	7.64	7.618	0.022	7.788	-0.148
8al	7.70	7.592	0.108	7.363	0.337
8am	8.70	8.666	0.034	8.527	0.173
8an	8.70	8.706	-0.006	8.466	0.234
8ao	8.70	8.313	0.387	8.416	0.284
8ap	7.85	8.133	-0.283	7.957	-0.107
8aq	8.10	7.756	0.344	7.875	0.225
8ar	8.15	8.429	-0.279	8.595	-0.445
8as	8.00	7.901	0.099	7.929	0.071
8at	8.40	8.448	-0.048	8.496	-0.096
8au	8.10	7.686	0.414	7.808	0.292
8av	8.40	8.190	0.210	8.298	0.102
8aw	7.74	7.763	-0.270	8.007	-0.267
8ax	8.22	8.338	0.420	8.462	-0.242

Table S6. Observed and CoMFA/CoMSIA predicted mGluR2 inhibitory activity II (pIC_{50} value).

NO	Observed activity	CoMFA		CoMSIA	
		Predicted	Residual	Predicted	Residual
2	7.77	7.935	-0.165	6.970	-0.400
15a	8.00	7.939	0.061	7.581	-0.861
15b	8.05	7.900	0.150	7.712	-0.912
15c	7.80	8.037	-0.237	7.248	-0.308
15h	7.92	8.000	-0.080	7.118	0.002
15j	7.82	8.006	-0.186	7.080	0.050
15m	7.89	7.905	-0.015	7.338	-0.198
15o	7.96	7.945	0.015	7.496	-0.216
15q	7.77	7.564	0.206	7.660	-0.360
7a	7.33	7.606	-0.276	7.564	-0.244
7b	7.62	7.669	-0.049	7.129	0.341
7c	7.57	7.640	-0.070	8.018	-0.498
7e	7.77	7.695	0.075	7.777	-0.207
7j	7.28	7.410	-0.130	7.707	-0.117
7k	7.14	7.004	0.136	7.797	-0.177
7l	7.82	7.543	0.277	7.644	0.076
7m	7.72	7.562	0.158	7.656	0.064
7n	8.00	7.676	0.324	7.404	0.336
7o	7.44	7.604	-0.164	7.976	-0.236
7p	7.43	7.552	-0.122	7.919	-0.179
7q	7.74	7.630	0.110	7.806	-0.036
7x	6.74	7.312	-0.572	7.398	0.372
7y	6.57	6.446	0.124	8.175	-0.375
7z	7.85	7.822	0.028	7.599	0.201
7aa	6.94	7.157	-0.217	7.230	0.180
7ab	7.41	7.423	-0.013	7.225	0.185
7ac	7.13	7.221	-0.091	7.376	0.054
7ad	7.47	7.369	0.101	7.392	0.048
8a	7.72	7.576	0.144	8.001	-0.201
8aa	8.30	7.746	0.554	7.716	0.104
8ab	7.74	7.866	-0.126	7.971	-0.151
8ac	7.70	7.842	-0.142	8.007	-0.157
8ad	8.00	7.976	0.024	7.417	0.433
8ae	8.00	7.893	0.107	7.792	0.098
8af	6.80	7.507	-0.707	7.768	0.152
8ah	7.14	7.430	-0.290	8.026	-0.066
8aj	7.30	7.535	-0.235	8.334	-0.334
8ak	7.32	7.366	-0.046	7.752	0.248
8al	7.80	7.453	0.347	7.890	0.110
8am	8.52	8.353	0.167	7.989	0.011
8an	8.40	8.067	0.333	7.909	0.091
8ao	8.40	8.442	-0.042	8.007	-0.007
8ap	7.82	8.056	-0.236	8.089	-0.039
8aq	8.30	8.121	0.179	7.879	0.171
8ar	8.15	7.978	0.172	8.051	0.099
8as	7.59	7.582	0.008	8.440	-0.290

Table S6. *Cont.*

8at	8.00	7.962	0.038	8.057	0.163
8au	8.52	8.184	0.336	8.174	0.126
8av	8.70	8.549	0.151	8.227	0.073
8aw	7.44	7.679	-0.239	7.853	0.447
8ax	8.10	8.107	-0.007	8.431	-0.131
8b	7.41	7.418	-0.008	8.121	0.279
8c	8.05	8.207	-0.157	8.082	0.318
8d	7.12	7.210	-0.090	7.906	0.614
8f	6.72	7.446	-0.726	8.034	0.486
8h	7.96	7.969	-0.009	8.262	0.258
8i	8.40	8.123	0.277	8.215	0.485
8j	8.30	8.269	0.031	7.089	-0.349
8k	7.74	7.962	-0.222	7.578	-0.438
8m	8.22	8.240	-0.020	7.734	-0.404
8n	8.00	8.371	-0.371	7.807	-0.367
8o	8.15	8.504	-0.354	7.945	-0.245
8q	8.30	8.547	-0.247	7.920	-0.180
8r	7.74	7.902	-0.162	7.891	-0.121
8s	8.22	8.021	0.199	8.117	-0.297
8t	7.85	7.938	-0.088	8.009	-0.049
8v	7.80	8.143	-0.343	8.023	0.077
8y	7.52	7.886	-0.366	8.271	-0.051
8z	8.52	7.974	0.546	8.364	0.036

Figure S1. CoMSIA StDev*Coeff contour maps for activityII.(**A**) Electrostatic contour map (red/blue) in combination with compound **8av**. Red contours indicate regions where negative charges increase activity; blue contours indicate regions where positive charges increase activity; (**b**) Hydrophobic contour map (yellow/white) in combination with compound **8av**. Yellow contours indicate regions where hydrophobic substituents enhance activity; white contours indicate regions where hydrophilic substituents enhance activity II.
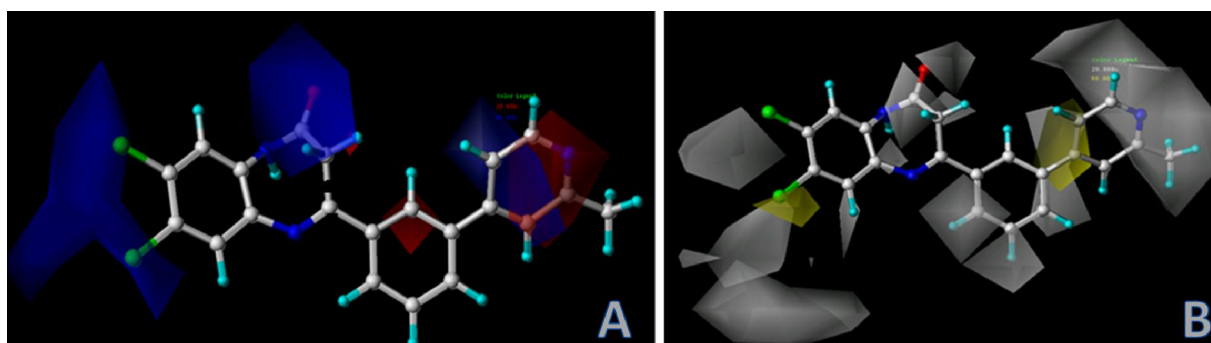
Figure S2. The ligand-based correlation plots of the CoMSIA predicted versus the actual pIC_{50} values using the training (filled black square) and the test (filled blue circle) sets for activity II.
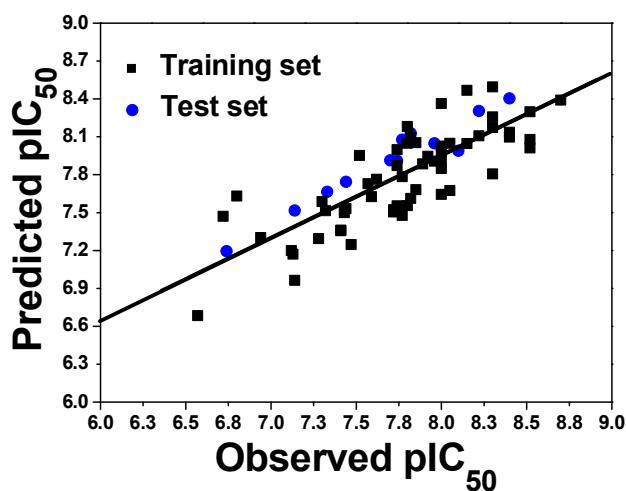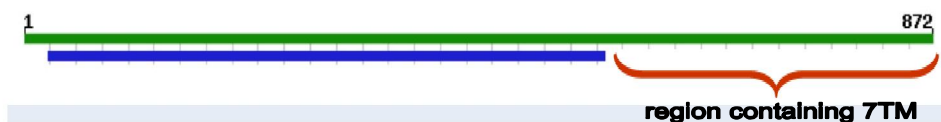

Figure S3. Homology modeling result sheet for mGluR2.

Workunit: P000002
Title:123

1   872

region containing 7TM

Model Details: Batch.1

model pic

Target:	
modelled residue range:	23 to 558
based on template	2e4uB (2.35 A)
Sequence Identity [%]:	65.428
Evalue:	0