Assessment of quantum optimized $mGlu_1R$ in virtual screening

Paweł Śliwa[1], *Rafał Kurczab*[2], *Andrzej Bojarski*[2]
email: psliwa@chemia.pk.edu.pl

[1] *Faculty of Chemical Engineering and Technology, Cracow University of Technology, 24 Warszawska Street, 31-155 Kraków, Poland*
[2] *Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, 31-343 Kraków, Poland*

Background

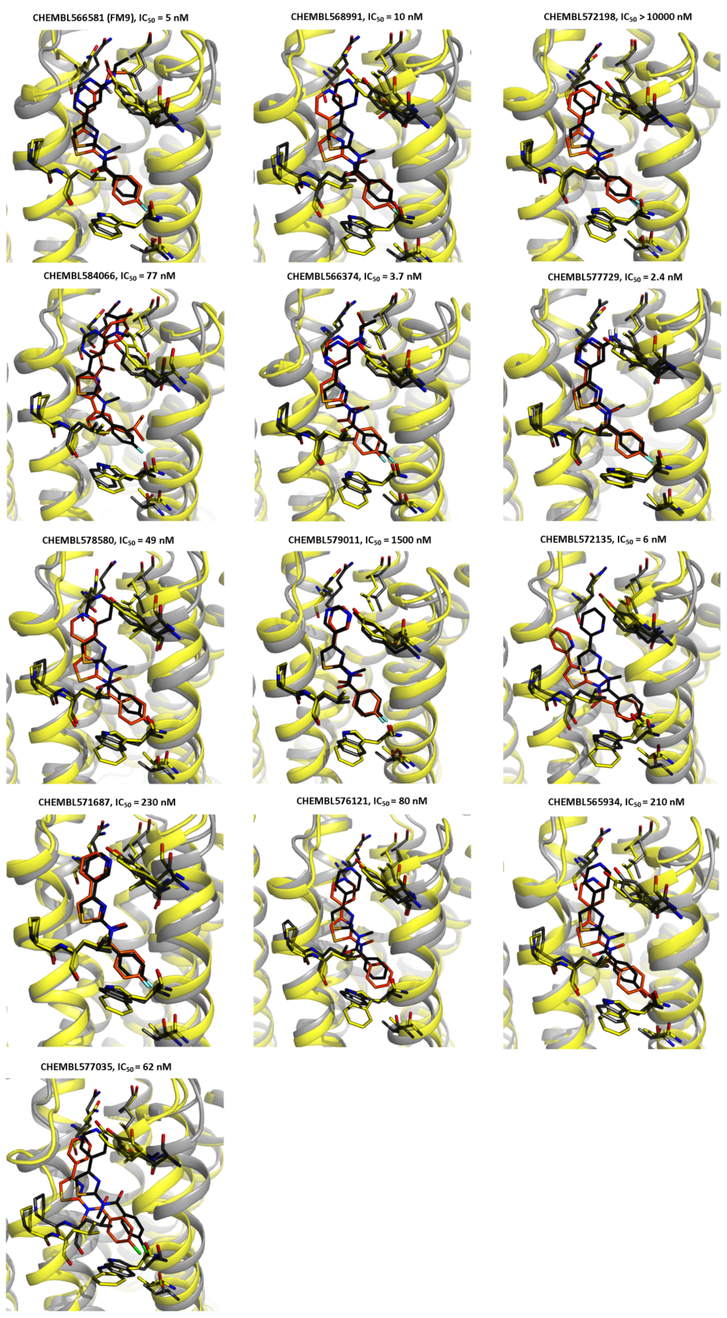
The mGlu1 and mGlu5 receptors (metabotropic glutamate receptor 1 and 5) are considered promising therapeutic targets to treat diseases including chronic pain, schizophrenia, Alzheimer's disease, anxiety, and autism [1-3]. However, the development of selective small-molecule ligands that might serve as drug candidates for these receptors has been hampered by the conservation of the orthosteric (glutamate) binding site. This can be overcome by using allosteric modulators that act at alternative binding sites; i.e., within the 7TM domain of the receptors [1].

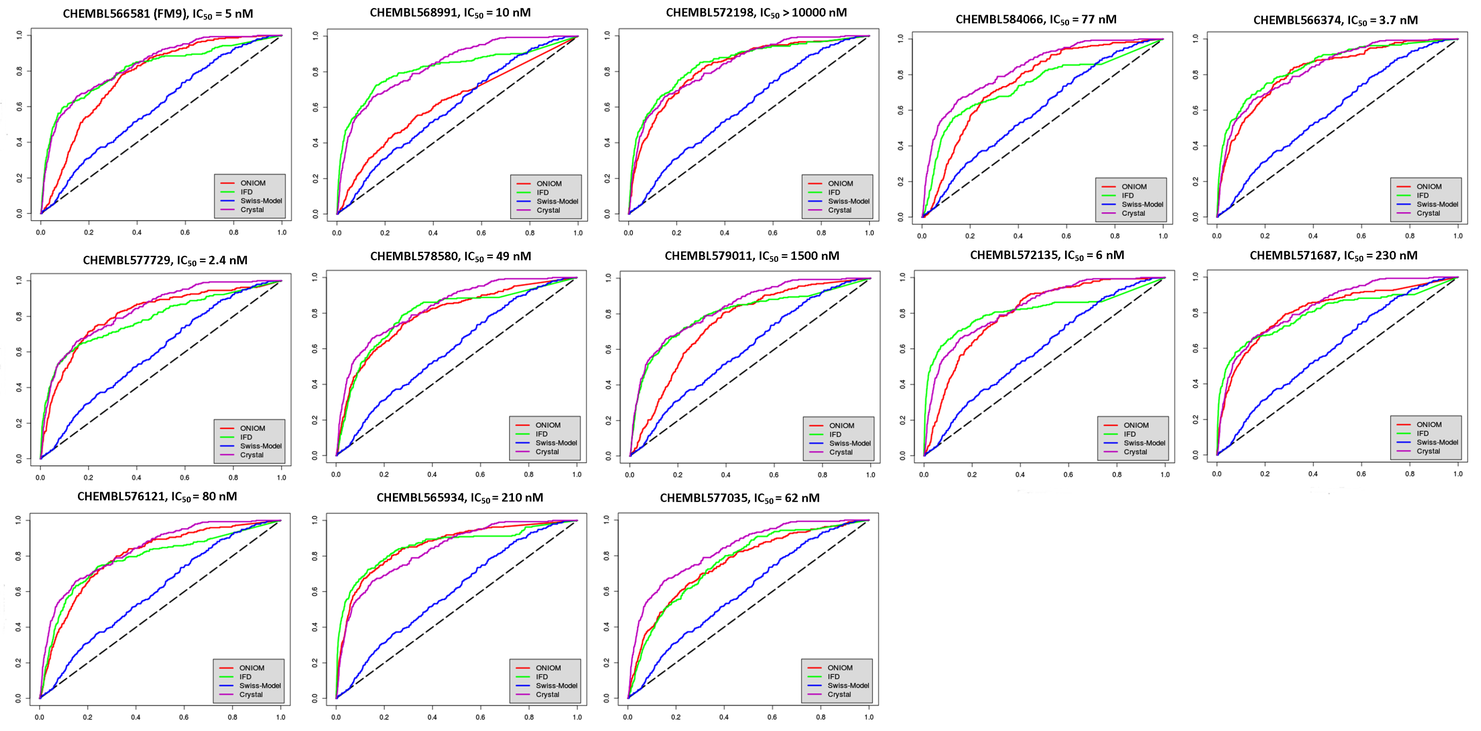
[1] Wu H. et al, *Science* 344 (2014) 58-64,
[2] Niswender C. M. and Conn P. J., *Annu. Rev. Pharmacol. Toxicol.* 50 (2010) 295–322,
[3] Dölen G. et al., *Pharmacol. Ther.* 127 (2010) 78–93,

Methodology

In this study the potential of 23 quantum optimized (ONIOM method) conformations of $mGlu_1R$ in virtual screening was tested. The active site was tuned on structures of thirteen known allosteric modulators (2.4 nM < IC50 > 10000 nM) as well as modeled using 10 different calculation methods (7 different DFT methods, 3 different basis sets). Each resulting conformation was evaluated by docking the test set (195 active and 14465 non-active molecules) and several performance metrics were calculated: ROC AUC, BEDROC.

Tunning by ligand



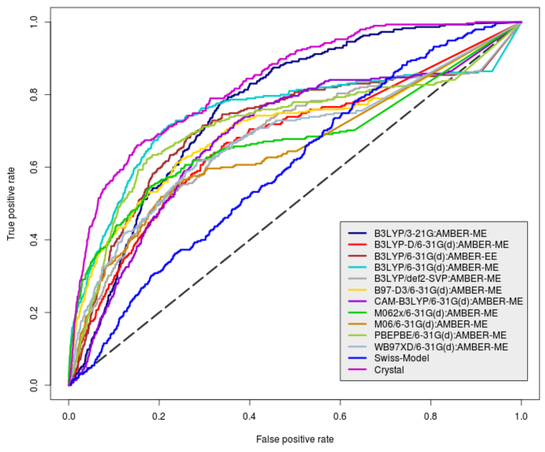


Conformation	IC_{50} [nM]	ONIOM		IFD	
		AUC	BEDROC	AUC	BEDROC
FM9	5.1	0.77	0.14	0.81	0.42
CHEMBL568991	10	0.8	0.29	0.82	0.47
CHEMBL572198	> 10000	0.82	0.34	0.85	0.44
CHEMBL584066	77	0.75	0.13	0.74	0.25
CHEMBL566374	3.7	0.82	0.35	0.85	0.47
CHEMBL577729	2.4	0.81	0.31	0.79	0.42
CHEMBL578580	49	0.79	0.30	0.79	0.28
CHEMBL579011	1500	0.74	0.14	0.80	0.37
CHEMBL572135	6	0.76	0.15	0.81	0.54
CHEMBL571687	230	0.79	0.26	0.80	0.49
CHEMBL576121	80	0.8	0.25	0.78	0.29
CHEMBL565934	210	0.86	0.43	0.86	0.53
Crystal 4OR2	-	0.83	0.38	0.83	0.38

Tunning by method

Model	RMSD*
B3LYP/3-21G:AMBER-ME	**0.976**
B3LYP-D/6-31G(d):AMBER-ME	1.025
B3LYP/6-31G(d):AMBER-EE	0.992
B3LYP/6-31G(d):AMBER-ME	1.274
B3LYP/def2-SVP:AMBER-ME	1.050
B97-D3/6-31G(d):AMBER-ME	**0.940**
CAM-B3LYP/6-31G(d):AMBER-ME	0.987
M062x/6-31G(d):AMBER-ME	0.997
M06/6-31G(d):AMBER-ME	1.173
PBEPBE/6-31G(d):AMBER-ME	1.040
WB97XD/6-31G(d):AMBER-ME	0.982

* Based on C_{alfa}-alignment to the crystal structure



Model	BEDROC	AUC
B3LYP/3-21G:AMBER-ME	0.14	0.77
B3LYP-D/6-31G(d):AMBER-ME	0.18	0.67
B3LYP/6-31G(d):AMBER-EE	0.20	0.71
B3LYP/6-31G(d):AMBER-ME	0.33	0.75
B3LYP/def2-SVP:AMBER-ME	0.20	0.68
B97-D3/6-31G(d):AMBER-ME	0.29	0.70
CAM-B3LYP/6-31G(d):AMBER-ME	0.13	0.69
M062x/6-31G(d):AMBER-ME	0.32	0.68
M06/6-31G(d):AMBER-ME	0.21	0.65
PBEPBE/6-31G(d):AMBER-ME	0.23	0.72
WB97XD/6-31G(d):AMBER-ME	0.23	0.68

Conclusion

Interestingly, the best discriminative model was obtained by optimizing the complex of receptor with CHEMBL565934, for which the experimentally determined affinity was 210 nM.

Acknowledgements

.Authors acknowledge the computing resources from PL-Grid Infrastructure.