PP59. QUANTUM MECHANICAL STUDY OF METABOTROPIC GLUTAMATE RECEPTOR 1

Paweł Śliwa[1], Rafał Kurczab[2], Andrzej Bojarski[2]

[1] Faculty of Chemical Engineering and Technology, Cracow University of Technology, ul. Warszawska 24, 31-155 Kraków, Poland; Tel.: (+48) 12 6282754; Fax: (+48) 12 6282037
[2] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, ul. Smetna 12, 31-343 Kraków, Poland
E-mail: psliwa@chemia.pk.edu.pl

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 problem can be overcome by using allosteric modulators that act at alternative binding sites; these compounds bind predominantly within the 7TM domain of the class C receptors. Allosteric modulators can alter the affinity or efficacy of native ligands in positive, negative, and neutral ways, demonstrating a spectrum of activity that cannot be achieved by orthosteric ligands alone [1].

In this work, the structure of mGlur1R complexed with 4-fluoro-N-(4-(6-(isopropylamino)pyrimidin-4-yl)thiazol-2-yl)-Nmethylbenzamide (FITM) and its twelve analogs of broad spectrum of affinity (2.4 nM < IC50 > 10000 nM) has been investigated by means of quantum mechanical methods. ONIOM (Our own N-layered Integrated molecular Orbital and molecular Mechanics) computation procedures were carried out to optimize molecular geometries of binding sites with complexed ligands. Calculations were performed with the use of B3LYP(DFT):AMBER(MM) approach. The optimized structure of ligands complexed with 21 residues was used for the ab initio FMO (Fragment Molecular Orbitals Method) calculations at the MP2/3-21G level of theory.

The performed calculations are helpful in the interpretation of the experimental results concerning the activation of protein receptors, as well as they provide the reasonable binding energies and binding patterns of ligand-protein interactions.

References:

1. H. Wu, C. Wang, K. J. Gregory, G. Won Han, H. P. Cho, Y. Xia, C. M. Niswender, V. Katritch, J. Meiler, V. Cherezov, P. J. Conn, R. C. Stevens, Science 344, 58-64 (2014).
2. C. M. Niswender, P. J. Conn, Annu. Rev. Pharmacol. Toxicol. 50, 295–322 (2010).
3. G. Dölen, R. L. Carpenter, T. D. Ocain, M. F. Bear, Pharmacol. Ther. 127, 78–93 (2010).