Supporting Information

Computational Prediction and Biochemical Analyses of New Inverse Agonists for the CB1 Receptor

Caitlin E. Scott[1,†], Kwang H. Ahn[2], Steven T. Graf[2], William A. Goddard III[1,], Debra A. Kendall[2,*], Ravinder Abrol[1,‡,*]*

[1]Materials and Process Simulation Center, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA

[2]Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT 06269, USA

*Corresponding authors (WAG: wag@wag.caltech.edu; DAK: debra.kendall@uconn.edu; RA: abrolr@csmc.edu)

[†]Current address: Department of Chemistry, University of Kentucky, Lexington, KY 40506

[‡]Current address: Departments of BioMedical Sciences and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048

Table S1. Calculated binding energy for the rimonabant and 16 **MSC** compounds.

Compound	Binding Energy (kcal/mol)
Rimonabant[a]	**-67.37**
MSC1	**-70.95**
MSC2	-68.35
MSC3	**-70.49**
MSC4	-68.52
MSC5	**-67.84**
MSC6	-66.04
MSC7	-64.48
MSC8	**-64.67**
MSC9	**-69.47**
MSC10	-65.30
MSC11	-68.42
MSC12	-73.10
MSC13	-67.25
MSC14	-57.65
MSC15	-52.43
MSC16	-59.98

[a] The compounds tested experimentally are in shaded cells.

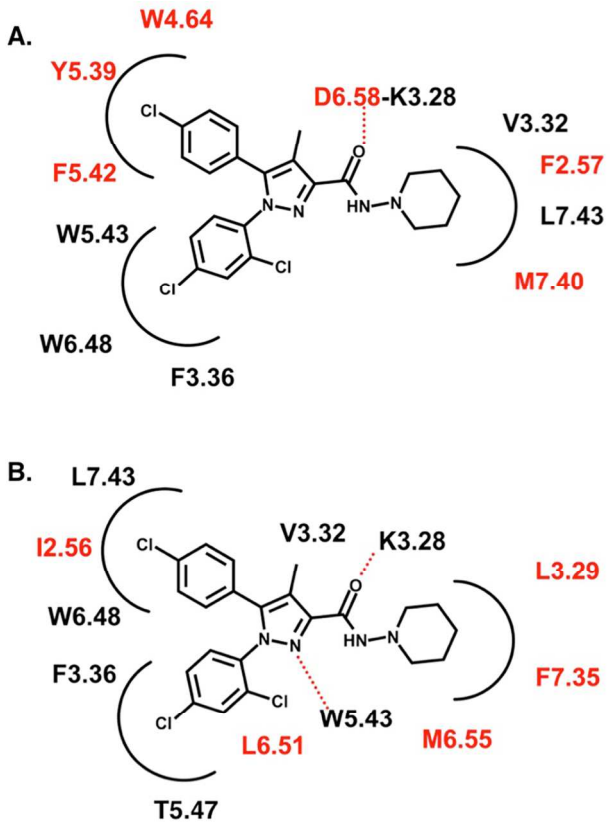

Figure S1. CB1-rimonabant pharmacophores with side chains important for receptor-ligand interactions labeled. **(A)** Lange and Kruse published a pharmacophore [1] based on prior docking studies [2-5] involving the human CB1 receptor predicted using homology modeling with ~~bRho~~. These studies find that rimonabant forms one hydrogen bond with K3.28 and sandwiches W5.43. **(B)** Our predicted pharmacophore shows that rimonabant has a different binding site in our GEnSeMBLE-derived CB1 structure that allows it to form two hydrogen bonds, including one with W5.43, and have strong aromatic interactions with the receptor. Residues in the binding site are labeled in both **Figures S1A** and **S1B**. Residues labeled in red in **Figure S1B** are unique to that particular pharmacophore and are not found in the binding site shown in **Figure S1A**.

REFERENCES

1. Lange, J. H. M.; Kruse, C. G., Medicinal Chemistry Strategies to CB1 Cannabinoid Receptor Antagonists. *Drug Discov. Today* **2005**, 10, 693-702.
2. McAllister, S. D.; Rizvi, G.; Anavi-Goffer, S.; Hurst, D. P.; Barnett-Norris, J.; Lynch, D. L.; Reggio, P. H.; Abood, M. E., An Aromatic Microdomain at the Cannabinoid CB_1 Receptor Constitutes an Agonist/Inverse Agonist Binding Region. *J. Med. Chem.* **2003**, 46, 5139-5152.
3. Salo, O. M. H.; Lahtela-Kakkonen, M.; Gynther, J.; Jarvinen, T.; Poso, A., Development of a 3D Model for the Human Cannabinoid CB1 Receptor. *J. Med. Chem.* **2004**, 47, 3048-3057.
4. Silvestri, R.; Cascio, M. G.; La Regina, G.; Piscitelli, F.; Lavecchia, A.; Brizzi, A.; Pasquini, S.; Botta, M.; Novellino, E.; Di Marzo, V.; Corelli, F., Synthesis, Cannabinoid Receptor Affinity, and Molecular Modeling Studies of Substituted 1-Aryl-5-(1H-Pyrrol-1-yl)-1H-Pyrazole-3-Carboxamides. *J. Med. Chem.* **2008**, 51, 1560-1576.
5. Hurst, D. P.; Lynch, D. L.; Barnett-Norris, J.; Hyatt, S. M.; Seltzman, H. H.; Zhong, M.; Song, Z. H.; Nie, J. J.; Lewis, D.; Reggio, P. H., N-(Piperidin-1-yl)-5-(4-Chlorophenyl)-1-(2,4-Dichlorophenyl)-4-Methyl-1H-Pyrazole-3-Carboxamide (SR141716A) Interaction with Lys 3.28(192) Is Crucial for Its Inverse Agonism at the Cannabinoid CB1 Receptor. *Mol. Pharmacol.* **2002**, 62, 1274-1287.