CLAIMS

1. A water-soluble variant of a G-protein coupled receptor (GPCR), wherein in said variant, all 7-transmembrane α-helical hydrophobic residues Leucine (L), isoleucine (I), valine (V), and phenylalanine (F) in hydrophilic surface α-helical positions *b*, *c*, and *f* but not positions *a*, *d*, *e*, and *g* of the GPCR have been substituted by glutamine (Q), threonine (T), threonine (T), and tyrosine (Y), respectively.

2. The variant of claim 1, wherein the variant retains ligand-binding activity of the GPCR.

3. The variant of claim 1 or 2, wherein the pI of the variant is substantially the same as the pI of the GPCR.

4. The variant of any one of claims 1-3, wherein the GPCR is a mammalian receptor.

5. The variant of any one of claims 1-4, wherein the GPCR is selected from the group consisting of: purinergic receptors (P2Y1, P2Y2, P2Y4, P2Y6), M1 and M3 muscarinic acetylcholine receptors, receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2], thromboxane (TXA2), sphingosine 1-phosphate (S1P2, S1P3, S1P4 and SIP5), lysophosphatidic acid (LPA1, LPA2, LPA3), angiotensin II (AT1), serotonin (5- HT2c and 5-HT4), somatostatin (sst5), endothelin (ETA and ETB), cholecystokinin (CCK1), V1a vasopressin receptors, D5 dopamine receptors, fMLP formyl peptide receptors, GAL2 galanin receptors, EP3 prostanoid receptors, A1 adenosine receptors, α1 adrenergic receptors, BB2 bombesin receptors, B2 bradykinin receptors, calcium- sensing receptors, chemokine receptors, KSHV-ORF74 chemokine receptors, NK1 tachykinin receptors, thyroid-stimulating hormone (TSH) receptors, protease-activated receptors, neuropeptide receptors, adenosine A2B receptors, P2Y purinoceptors, metabolic glutamate receptors, GRK5, GPCR-30, and CXCR4.

6. The variant of any one of claims 1-5, wherein the GPCR is a CXCR4.

7. The variant of claim 1, wherein at least one transmembrane domain has a sequence of SEQ ID NO: 3, 4, 5, 6, or 8.

8. A method of preparing a water-soluble variant of a G-protein coupled receptor (GPCR), the method comprising replacing all 7-transmembrane α-helical hydrophobic residues Leucine (L), isoleucine (I), valine (V), and phenylalanine (F) in hydrophilic surface α helical positions *b*, *c*, and *f* but not positions *a*, *d*, *e*, and *g* of the GPCR, with glutamine (Q), threonine (T), threonine (T), and tyrosine (Y), respectively.

9. The method of claim 8, further comprising measuring ligand binding.

10. The method of claim 8 or 9, wherein the GPCR is prepared using a cell- free system.

11. A cell comprising the variant of any one of claims 1-7.