G protein-coupled receptors (GPCRs) are physiologically important integral membrane proteins that sense signaling molecules such as hormones and neurotransmitters, and are the pharmaceutical targets of over 30% of prescribed drugs. Recent high-resolution structures of several medically important GPCRs are charting the structural landscape of GPCRs and are defining the mechanisms of ligand binding and receptor activation. A systematic comparison of these structures has revealed conserved molecular features of the GPCR fold. Firstly, we have uncovered a conserved network of tertiary contacts present between the transmembrane (TM) helices in the structures of different GPCRs, in both inactive and active conformational states. Based on sequence analysis of Class A GPCRs, we show that the residues present in the inter-TM network are more conserved than the rest of the TM residues, suggesting that this network forms an evolutionary core of the GPCR fold. Importantly, this consensus set of inter-TM tertiary contacts should be valuable for GPCR engineering, de novo GPCR modeling and to increase the accuracy of GPCR homology models. Secondly, by systematically studying structures of all the different receptor-ligand complexes we have identified a conserved “ligand-binding cradle” of residues that forms the bottom of the ligand-binding pockets in GPCRs. This information of conserved ligand-receptor interactions can be exploited for fragment-based drug discovery and pharmacophore design for receptors that lack experimentally solved structures.