Class B GPCRs share heptahelical topology and G protein binding with other superfamily members, yet have unique structures and modes of activation. Natural ligands are moderate length peptides with carboxyl-terminal alpha helices. NMR and crystal structures of the peptide-bound disulfide-bonded receptor amino-terminal domains demonstrate that these helices occupy a conserved groove, however docking the biologically important peptide amino terminus is unclear. We previously utilized photoaffinity labeling to define spatial approximations between sixteen positions within secretin and its receptor, but insights have been inadequate to orient the receptor domains. Secretin alanine scanning, phenolic residue scanning, and lactam constraints provide insights adequate for rational modification of the peptide carboxyl terminus to increase its binding affinity. We have systematically explored cysteine-trapping between five amino-terminal residues within secretin and 61 residues in the extracellular loops of its receptor. Only Cys² and Cys⁵ peptides retained adequate binding affinity and biological activity to be used, with each yielding distinct patterns. Cys² predominantly labeled residues in the amino terminus of ECL2 and ECL3, while Cys⁵ predominantly labeled those in the carboxyl terminus of ECL2 and ECL3. These constraints were used in molecular modeling to extend understanding of the structure of the helical bundle and interconnecting loops, the orientation between receptor domains, and the molecular basis of ligand docking. Key spatial approximations predicted by this model were examined by mutagenesis and residue-residue complementation studies, further supporting this model.