The secretin receptor is prototypic of Family B GPCRs, based on its structural and functional characteristics and those of its natural agonist ligand. Secretin represents a linear 27-residue peptide with diffuse pharmacophoric domain. The secretin receptor includes the typical signature sequences for Family B within its predicted transmembrane segments and the highly conserved six cysteine residues contributing to three intradomain disulfide bonds within its long amino-terminal tail. The receptor tail is critical for secretin binding based on receptor mutagenesis and photoaffinity labeling studies. Full agonist analogues of secretin incorporating a photolabile moiety at various positions throughout the pharmacophore covalently label residues within this region, while only amino-terminal probes have labeled the core helical bundle domain. Combining insights coming from receptor structural studies, peptide SAR considerations, photoaffinity labeling, and application of fluorescence techniques has resulted in the development of a working model of the secretin-receptor complex. This supports the initial docking of the peptide agonist within a cleft in the amino terminus, providing the opportunity for an endogenous sequence within that domain to interact with the core of the receptor. This interaction is believed to be key in the molecular basis of conformational change associated with activation of this receptor. This could provide a possible target for small molecule agonists to act.