The family of G protein coupled receptors (GPCRs) have for long been recognized as one the most important class of drug targets and is still subject of huge medicinal chemistry efforts. While recently fragment-based approaches have entered the toolbox of medicinal chemists, its use in the field of GPCR ligands has so far been quite limited, most likely due to the lack of biophysical approaches that has long been hampering its application. In view of the success of High Concentration Screening (HCS) in some of our non-GPCR FBDD projects, we recently started an HCS FBDD-approach to discover new ligands for two of the histamine receptors, the H1 and the H4 receptors. Moreover, with the recent progress in the area of GPCR structural biology, also computational approaches have become efficient tools to discover fragments as new starting points for GPCR medicinal chemistry programs. In this presentation, the results of both HCS and computational approaches (IFP-PLANTS) for the discovery of new ligands, targeting GPCRs will be presented.