ATP-dependent system, thus propagating the signal induced at the cell surface by the ligand.

Signal termination is just as important in the IP_3 signaling pathway as it is in the cAMP pathway, and there are several ways in which the cascade events can be interrupted. The G_α protein's GTPase activity that slowly converts GTP to GDP causes G_α to be released from phospholipase C, deactivating it. This halts the production of IP_3 and DAG, terminating the signal. Also, removal of calcium from the cytosol by calcium ATPase pumps will dampen the signal (PKC requires calcium for enzymatic activity), while conversion of IP_3 to inositol by a series of phosphatase removes its influence from the signaling cascade. DAG, on the other hand, can be either converted to glycerol or phosphorylated by the appropriate enzymatic systems, but in either case, once it is removed from the signaling pathway, PKC reconfigures itself such that the regulatory domain suppresses its catalytic activity, halting signal propagation.

Modulating GPCR Activity

As complex as these systems are, it is important to understand that GPCRs do not exist in isolation, and the flow of information across a cell membrane is often not a linear event. In general, cells express multiple GPCRs that respond to the environment in different manners, have overlapping effects, can impact each other's activity, and form an integrated mosaic of information flow. Proteins such as β-arrestin[45] and G-protein-coupled receptor kinases[46] can also alter the signal pathways, giving rise to differential activities for ligand and GPCRs depending on their cellular context. The recent introduction of the concept of biased ligand, which suggests that there are multiple active conformations of a single GPCR that can create different downstream events depending on the chemical structure of the ligand, further complicates the picture (Figure 3.25). It should be clear that targeting a GPCR for new drug development is a complex endeavor.

Despite these complexities, the majority of drugs that interact with GPCRs can be described as falling into one of three categories, agonist, antagonists (also referred to as neutral antagonists), and inverse agonists (Figure 3.26). In simple terms, an agonist mimics the natural ligand of a given GPCR and produces the same cellular response as the natural ligand. The activity of an agonist is generally measured as a function of its binding affinity for the GPCR in question and its efficacy relative to the natural ligand. The cellular response prompted by saturation levels of the endogenous ligand is considered 100% efficacy, and potential drug candidates that provide this level of response are considered full agonists. Compounds that elicit a cellular response that is below that of the endogenous