ligand are referred to as partial agonists. In some cases, partial agonists can effectively compete with the natural ligand, effectively lowering the response of the GPCR to signal induction.

Antagonists, on the other hand, bind to the GPCR, but do not elicit a cellular response. In the absence of an agonist or the endogenous ligand, an antagonist has no effect on cellular activity. However, the presence of an antagonist can prevent GPCR-mediated cellular responses, as binding of the antagonist prevents binding of the natural ligand or agonist, preventing conformational changes necessary for the initiation signaling events. Antagonists can be binding site mimics that directly block the natural ligand, or they can bind to an allosteric site that causes conformational changes that prevent the formation of the GPCR/ligand complex that starts the signaling cascade.

Inverse agonists can also block the activity of an endogenous ligand or agonists, thereby presenting themselves as antagonists, but they are also capable of producing a pharmacological response opposite to that mediated by the endogenous ligand in some situations. This inversion of action is only possible, however, if the GPCR target is constitutively active which provides an intrinsic or basal level of signaling that is present in the absence of the endogenous ligand. Basal signaling is the result of a GPCR spontaneously adopting the active conformation in the absence of the ligand. While GPCRs are often viewed as on/off switches, it is important to realize that GPCRs exist as an equilibrium mixture of conformations. Conformations that do not support signaling predominate in the absence of an activating ligand, but the equilibrium is often not 100% in favor of the deactivated GPCR signaling mechanism. GPCRs that display basal activity exist at least in some small level in the active signaling conformation irrespective of the presence of the natural ligand. The natural ligand tips the equilibrium heavily in favor of the active signaling conformation, boosting the signal beyond its basal level. An inverse agonist, on the other hand, binds to the same site as the endogenous ligand, but stabilizes the inactive, non-signaling conformation of the GPCR in question. This suppresses basal activity of the GPCR, blocking the signal that is normally present even when the endogenous ligand is not present.

It is interesting to note that despite their complexity, GPCR activity is often modulated by surprisingly simple molecules (Figure 3.27). Compounds such as serotonin,[35] histamine,[47] and dopamine[36] play critical roles in GPCR signaling, and yet they are tiny by comparison to the GPCRs that they stimulate. Fentanyl, a μ-opioid agonist, acts at the same GPCR as β-endorphin, which has a molecular weight of over 3400, despite the fact that it is only one-tenth the size of β-endorphin. Size and complexity are not the driving forces mediating GPCR function. Just as the GPCRs must obtain a specific conformation in order to propagate a signal, compounds that modulate GPCR activity must be able to adopt the specific conformation required by the binding site that they are targeting. Those interested in more detailed information on particular GPCRs are encouraged to consult the modern literature for a more detailed analysis.