## Antagonists

In some cases, test compounds exhibit strong binding interactions with a macromolecular target, but do not elicit a functional response. In other words, the compound is capable of effectively competing with the natural ligand for the binding site, but binding of the test compound produces no measurable response. Compounds of this type have no impact in the absence of the natural ligand, but can effectively block the action of the natural ligand when both are present. In practice, screening for antagonist activity must be done in the presence of the natural ligand (or a ligand that elicits the same response), and signal reduction (such as lowering of cAMP production) is measured to determine antagonist activity.

## Basal Activity and Inverse Agonists

While biological systems such as GPCRs are often viewed as on/off switches, it is important to realize that they actually exists as an equilibrium mixture of conformations. Conformations that do not support functional activity predominate in the absence of an activating ligand, but the equilibrium is often not 100% in favor of the inactive conformation. The presence of low levels of conformations that support functional activity provides an intrinsic level of biological activity that occurs in the absence of a ligand or agonist. Such systems are described as constitutively active, and basal activity is the result of a macromolecule spontaneously adopting the active conformation in the absence of the ligand. Compounds that bind to the ligand binding site and stabilize the inactive conformation decrease the basal activity in systems that are constitutively active. Although they bind to the same site that would be occupied by an agonist, compounds of this type produce the opposite pharmacological response (decreased signaling activity), and are thus referred to as inverse agonists. Compounds of this type can also block the action of the endogenous ligand or other agonists, making them functional antagonists in certain circumstances.[10]

## Allosteric Modulation

The most direct route toward impacting the biological activity of a given macromolecule is interaction at the binding site for its natural substrate/ligand, often referred to as the orthosteric binding site. There are, however, other alternatives. As discussed in Chapter 3, it is often possible to alter the course of biochemical events by employing molecules that interact with binding site that are remote from the active site of the targeted macromolecule. Such compounds bind at an allosteric site and induce