and barbiturates increases the activity of $GABA_AR$. When compounds such as phenobarbital[71] and lorazepam[72] (Figure 3.34) bind to their respective allosteric sites on $GABA_AR$, they cause a conformational change in its

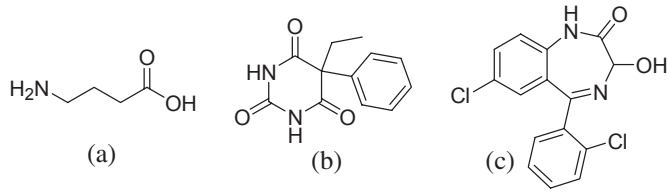


**FIGURE 3.34** (a) γ-aminobutyric acid (GABA). (b) Phenobarbital, a barbiturate. (c) Lorazepam, a benzodiazepine.

structure generating a configuration with significantly higher affinity for GABA. This, in turn, increases the frequency of the opening of the associated chloride channel, increasing chloride transfer across the membrane, hyperpolarizing the associated neuron.

## Voltage-Gated Channels

The voltage-gated channels represent another major class of ion channels. Unlike ligand-gated channels, voltage-gated channels have no natural ligand. They open and close as a result of changes in membrane potential produced as electrical currents move through biological systems. Voltage-sensing domains allow these channels to be exquisitely sensitive to changes in membrane potential, making them ideally suited for the propagation of nerve impulse through axons, muscle contraction, and cardiac function. The opening and subsequent closing of ion channels give rise to action potentials (Figures 3.35 and 3.36), the rapid rise and fall of the cellular membrane potential, which gives rise to the aforementioned functions. Mechanistically, voltage-gated channels are closed when the membrane electrical potential is at its resting potential. It is worth noting at this point that different types of voltage-gated channels will have different resting potentials, and thus will activate at different membrane potentials. If an electrical impulse (or other stimulus) causes the membrane potential to rise above the membrane threshold for activation, the channel will open via a series of conformational changes, causing a rapid change in membrane polarization via ion flow across the membrane. This leads to hyperpolarization of the cellular membrane, triggering inactivation of the voltage-gated channel through another series of conformational changes, stopping ion flow. Once the voltage-gated channel is inactivated by membrane hyperpolarization, it will not respond to another stimulus