Most Cys-loop receptors form heteropentamers (e.g., the neuromuscular nicotinic acetylcholine receptor described above), but some can form homopentamers (e.g., the nicotinic α_7 receptor). Numerous subunits for both nicotinic acetylcholine receptors and $GABA_A$ receptors have been cloned which can theoretically heteromize to a staggering high number of subunit combinations. However, in reality, only certain subunit combinations are formed in vivo and even fewer combinations have therapeutic interest. The glycine and serotonin Cys-loop receptors have fewer subunits, but heteromerization still exists and leads to distinct receptor subtypes. Interestingly, some subunits are unable to form their part of the agonist binding pocket in either one or both sides of the two interfaces they participate in. Depending on their subunit composition, Cys-loop receptors can bind from two to five agonist molecules. For example, the neuromuscular nicotinic acetylcholine receptor binds two agonist molecules whereas the nicotinic α_7 receptor and AChBP can bind five agonist molecules (Figure 12.6). Whether all agonist binding sites need to be occupied in order to achieve receptor activation has yet to be demonstrated.

12.2.2.2 Ionotropic Glutamate Receptor Family

The ionotropic glutamate receptor family comprises the 16 NMDA, AMPA, and kainic acid receptors listed in Figure 12.1 and two orphan receptors (termed δ1–2) with unknown function. The name of the receptor family is a bit misleading as GluN1 and GluN3A-B actually have glycine as ligand (see Chapter 15). Nevertheless, all 18 receptor subunits have the same overall structure: two large extracellular domains referred to as the amino-terminal domain (ATD) and ligand-binding domain (LBD), a transmembrane domain (TMD) consisting of three transmembrane segments and a re-entry loop and a C-terminal domain (CTD) (Figure 12.7). It is quite interesting to note

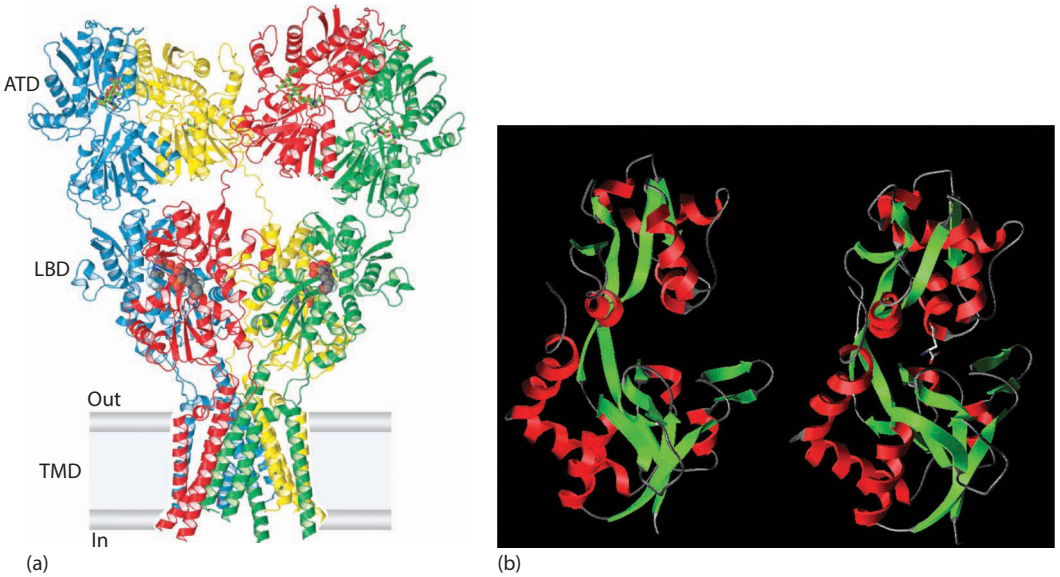

FIGURE 12.7 (a) 3D structure of the inactive conformation of full-length GluA2 ionotropic glutamate receptor with the antagonist ZK200775 (space filled) bound. Glycosylation moieties are shown as sticks. The location of the amino-terminal domain (ATD), ligand-binding domain (LBD), and transmembrane domain (TMD) is noted. The four subunits forming the receptor are shown in different colors. (Adapted with permission from Sobolevsky, A., Rosconi, M.P., and Gouaux, E., *Nature,* 462, 758, Copyright 2009, Macmillan Publishers Ltd.) (b) Structure of the LBD of GluA2 in the open inactive form (left) and the closed active form with glutamate bound in the cleft (right). The agonist-mediated closure of the LBD is thought to initiate the activation of the receptor via an outward pull of the M3 helices lining the ion channel. The structures were generated using the program "Swiss PDB viewer 3.5" with coordinates from Brookhaven Protein Data Base.