Although the antiepileptic properties of α-substituted lactams, acetamides, and cyclic imides have been known for over 60 years, the mechanism by which they act remains unclear. I report here that these compounds bind to the nicotinic acetylcholine receptor (nAChR) and inhibit its function. Using transient kinetic measurements with functionally active, nondesensitized receptors, I have discovered that (i) α-substituted lactams and cyclic imides are noncompetitive inhibitors of heteromeric subtypes (such as α4β2 and α3β4) of neuronal nAChRs and (ii) the binding affinity of these compounds toward the nAChR correlates with their potency in preventing maximal electroshock (MES)-induced convulsions in mice. Based on the hypothesis that α-substituted amide group is the essential pharmacophore of these drugs, I found and tested a simple compound, 2-phenylbutyramide. This compound indeed inhibits nAChR and shows good anticonvulsant activity in mice. Molecular docking simulations suggest that α-substituted lactams, acetamides, and cyclic imides bind to the same sites on the extracellular domain of the receptor. These new findings indicate that inhibition of brain nAChRs may play an important role in the action of these antiepileptic drugs, a role that has not been previously recognized.