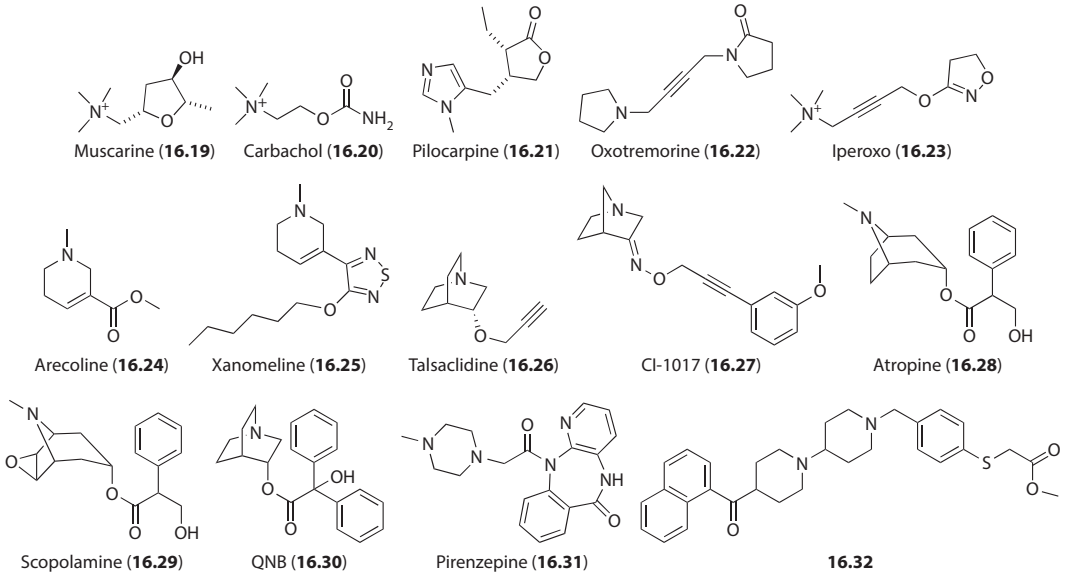

FIGURE 16.7 Chemical structures of orthosteric mAChR ligands.

Analogous to the lack of subtype-selective orthosteric agonists, it has also been difficult to develop truly subtype-selective competitive antagonists. The alkaloids atropine (**16.28**) and scopolamine (**16.29**) found in the berries of deadly nightshade (*Atropa belladonna*) and the close structural analog quinuclidinyl benzilate (QNB, **16.30**) are potent but nonselective mAChR antagonists that have been important pharmacological tools for the delineations of physiological functions of mAChRs over the years (Figure 16.7). Pirenzepine (**16.31**) is a M_1-preferring antagonist displaying significantly higher binding affinities for brain mAChRs (mainly M_1) over mAChRs in heart tissue (mainly M_2), although this M_1-over-M_2 selectivity has been less impressive when pirenzepine has been tested at recombinant mAChR subtypes. Conversely, truly selective M_2 receptor antagonists such as **16.32** have been developed and entered into clinical trials for cognitive enhancement but these have all been discontinued.

16.4.2 Allosteric and Bitopic Ligands of mAChRs

The renewed interest in mAChRs as CNS drug targets has been driven by the recently developed potent and subtype-selective allosteric ligands, but the concept of allosteric modulation (Chapter 12) is by no means new in the mAChR field. In fact, mAChRs have been the prototypic GPCRs in this respect since a wide range of diverse compounds capable of modulating their signaling have been known for decades. The first generation of these positive or negative allosteric modulators (PAMs and NAMs, respectively) had quite complex structures, as exemplified by **16.33**–**16.35**. Furthermore, the compounds were all characterized by having poor pharmacokinetic properties, low modulatory potencies at the mAChRs and activities at several other targets. Thus, it has been the emergence of high throughput (HTP) screening approaches enabling the search for novel structures from large compound libraries that has facilitated the identification of more potent and subtype-selective allosteric ligands suitable for in vivo studies.

The discovery of AC-42 (**16.36**) in a HTP screening represents the first example of a completely subtype-selective mAChR agonist (Figure 16.8). The compound is a fairly potent partial M_1 agonist exhibiting no activity at the other four mAChRs, and AC-42 analogs have been in clinical trials for the treatment of glaucoma. While AC-42 is not an orthosteric agonist, it does not have a completely allosteric mode of action either, and thus it is believed to be a bitopic ligand