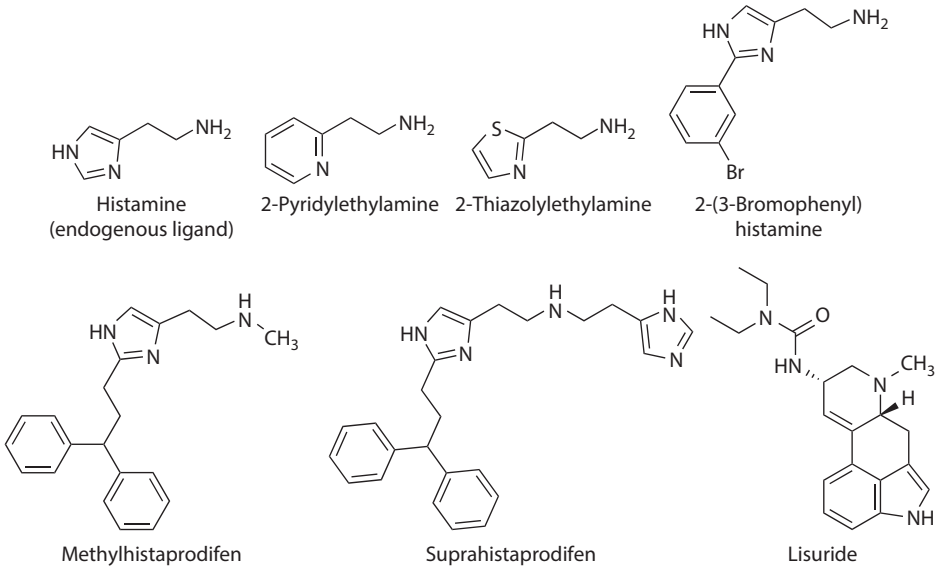

FIGURE 17.1 Histamine H_1 receptor agonists.

colleagues subsequently developed a series of the so-called histaprodifens on the basis of the hypothesis that the introduction of a diphenylalkyl substituent on the 2-position of the imidazole ring yields high-affinity agonists. This hypothesis was based on the realization that a diphenylmethyl group is a common feature of high-affinity H_1 antagonists (see Section 17.2.3). The introduction of the diphenylpropyl substituent at the 2-position of the imidazole ring and N-methylation of the ethylamine side chain results in the high potency agonist *N*-methyl-histaprodifen. Further modifications of the diphenylmethyl moiety were unsuccessful and indicated a considerable difference in SAR (and most likely receptor binding site) of the diphenyl moieties of the histaprodifens and the structurally related H_1 antagonists. A further increase in H_1 receptor agonist potency was obtained by a bivalent ligand approach. Suprahistaprodifen, a dimer of histaprodifen and histamine, is currently one of the most potent H_1 receptor agonists available. Surprisingly, recent high-throughput screening (HTS) of CNS-active drugs at the histamine H_1 receptor has identified the nonimidazole ergot derivative lisuride as another high-affinity H_1 receptor agonist.

17.2.3 H_1 Receptor Antagonists

The first antihistamines were identified and optimized by exclusively studying in vivo activities. This might be the explanation why several compounds originally reported as antihistamines were later on developed for other applications; e.g., the first so-called tricyclic antidepressants (e.g., doxepin, Figure 17.2) are often also very potent H_1 antagonists. More modern approaches, using genetically modified cells expressing the human H_1 receptor, currently provides more in-depth information on the molecular mechanism of actions. All therapeutically used H_1 antagonists in fact act as inverse agonists and favor an inactive conformation of the GPCR protein. In view of the detectable level of spontaneous activity of the H_1 receptor (i.e., receptor signaling without agonist, also known as constitutive GPCR activity), the H_1 antagonists tested so far all inhibit the constitutive activation of, e.g., nuclear factor-κB (NF-κB). Moreover, following the recent elucidation of the X-ray structure (resolution of 3.1 angstrom) of a T4-lysozyme stabilized human H_1 receptor, we now also have a clear idea on the binding interactions of the H_1 antagonists. In the X-ray structure, earlier predictions of the binding pocket of H_1 antagonists have proven reality (Figure 17.3); the tricyclic doxepin binds relatively deep in the binding pocket of the H_1 receptor via an ionic interaction of its