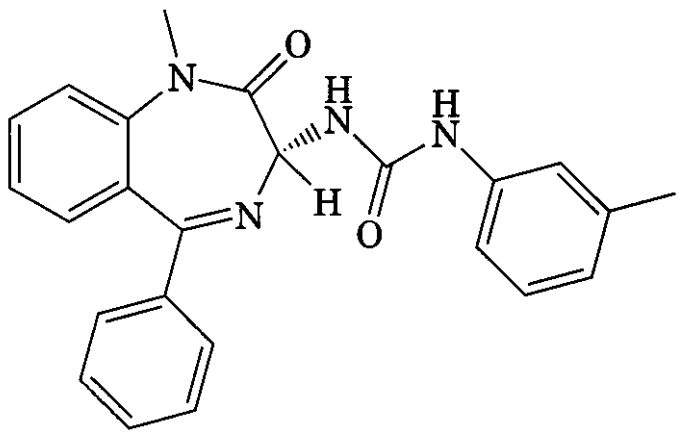
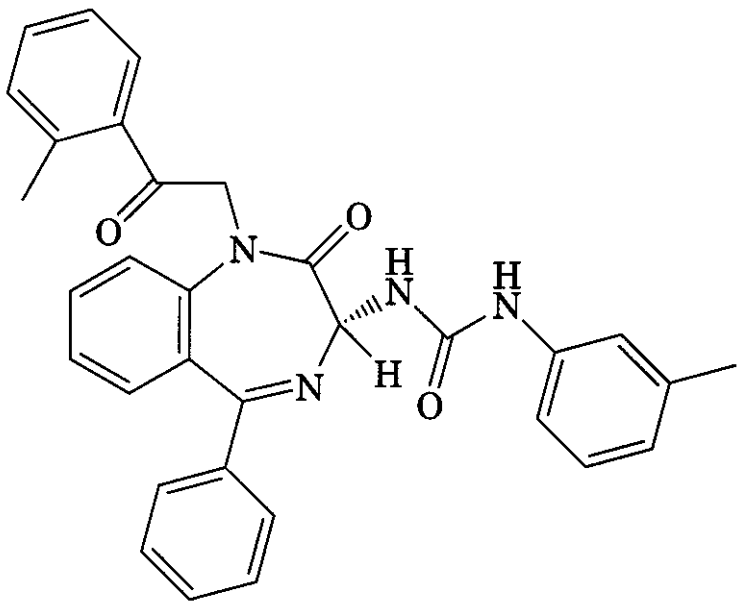
is governed by the stereochemistry at C3, the (*S*)-enantiomer showing greater affinity for CCK-A receptors. The (*R*)-enantiomer, known as L-365,260, prefers CCK-B receptors, antagonizes gastrin-stimulated acid secretion in animal models, and, among other CNS effects, induces analgesia in primates and displays anxiolytic properties (32).



(27)

Further development in this series has very substantially improved receptor affinity: YM-022 (28) has IC_{50} 0.05 nM/kg (38). Clinical trials of compounds in this series have been disappointing because of poor bioavailability, but the general concept of finding a therapeutic agent through antagonism of CCK_2 receptors is still viable and it is reported that the number of patents in this area has increased in the last 5 years (43).

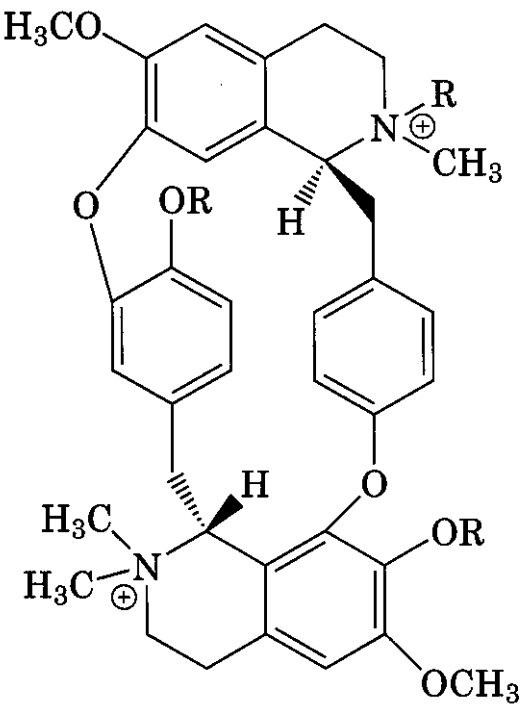


(28) YM-022

3 NEUROMUSCULAR BLOCKING DRUGS

3.1 Curare, Decamethonium, and Atracurium

The development and use of muscle relaxants, to allow a reduction in the level of anesthesia during surgery, follows entirely from studies of South American arrow poisons (44) and particularly from the isolation by King (45) of pure D-tubocurarine (29) in the 1930s, from tube curare. Another of the South American blowpipe poisons, calabash curare, was used for similar purposes and developed (46, 47), to give alcuronium (30) from the alkaloid C-toxiferine 1 (31). Both types of curare paralyze skeletal muscle by a similar mechanism, antagonizing the effect of acetylcholine at the neuromuscular junction (48).



(29) tubocurarine R = H
(32) metocurine R = CH_3

The muscle-paralyzing curare alkaloids are quaternary salts that are not absorbed when taken orally. For surgical procedures they must be administered by intravenous injection, which results in onset of paralysis in at most a few minutes: anesthesia is normally induced before administration of the muscle relaxant (44), which is followed by artificial respiration. Although the neuromuscular blocking agents are potentially lethal when administered alone, in the environment of an operating theater they are truly life-saving