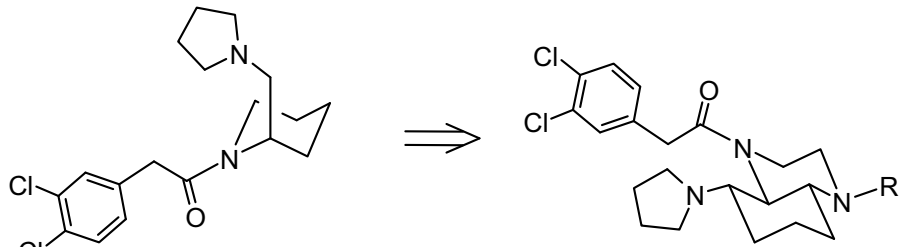
CL03 Quioxaline Based Peripheral κ-Opiod Receptor Agonists

Bernhard WÜNSCH
Institute of Pharmaceutical and Medicinal Chemistry, Westfalian Wilhelms-University of Münster

Activation of the three classical opioid receptors (μ-, δ-, and κ-opioid receptors) leads to strong analgesia. The clinically used strong analgesics are more of less selective μ receptor agonists and therefore associated with severe side effects like respiratory depression, euphoria, constipation and development of tolerance and dependency. κ Receptor agonists do not cause the dangerous μ agonist side effects (respiratory depression, addiction). However, κ agonists are not devoid of side effects, since they lead to centrally mediated dysphoria, sedation and strong diuresis. Therefore, our interest has been focused on κ agonists, which are restricted to the periphery by inhibition of the passage of the blood brain barrier. Peripherally restricted κ agonists can be used for the treatment of pain as well as inflammatory and itching skin diseases.

The starting point of our project is the piperidine derivative **1** belonging to the ethylenediamine class of κ agonists (K_i = 0.53 nM). The conformational flexibility of the side chain will be restricted by incorporation into a bicyclic framework. This framework should contain an additional atom (e.g. a N-atom) for the attachment of further substituents R influencing the physicochemical and thus controlling the pharmacokinetic properties (e.g. passage of the blood brain barrier) of the novel κ agonists **2**.



1 **2**