

Public Abstract

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Title:Ligands for the Sigma Receptor and the mu-Opioid Receptor

The sigma receptor is a unique receptor family with two subtypes: sigma-1 and sigma-2. Both of the two subtype receptors are widely distributed in the central nervous system (CNS). Sigma-1 receptors are found to be related to several central nervous system diseases, while sigma-2 receptors are believed to be affiliated with the regulation of cell proliferation.

To date, a large number of ligands for both sigma subtypes have been explored. Pharmacophore models have also been defined to provide the guidance for ligand synthesis and binding studies. In order to conduct structure-activity relationship studies (SAR), a series of specific 1-phenylpropyl-4-benzylpiperidine and 1-phenylpropyl-4-benzylpiperazine analogues were synthesized. Sigma receptors binding assays were also conducted for the piperidine analogues.

The last chapter is concerned with a different receptor family, the opioid receptors. The opioid receptors belong to the family of G-protein coupled receptors and have three subtypes: mu, delta, and kappa. mu-opioid receptor is believed to mediate the analgesia and drug addiction by morphine and other opioids. Many synthetic peptides, such as Tyr-D-Arg-Phe-Lys-NH₂, Tyr-D-Arg-Phe-Ala-NH₂ and Dmt-D-Ala-Phe-Phe-NH₂ have been investigated as selective mu-opioid ligands. In order to obtain mu-opioid tetrapeptide ligand I-Dmt-D-Ala-Phe-Orn-NH₂ with high affinity and proper lipophilicity, mono-iodination reaction was studied on the 2,6-dimethyl-L-tyrosine residue.