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Sigma1 and Sigma2 binding studies of novel receptor ligands

Sigma receptors are studied due to their presence both in the central nervous system and also in human tumors of neural origin. There are two types of sigma receptors: sigma1 and sigma2. Sigma1 receptors may be involved with diseases such as schizophrenia, dementia, ischemia, and some peripheral nervous system diseases. Sigma2 receptor expression may be indicative of the proliferative status of certain cancers. We are studying structural analogs of a sigma1 selective agonist, 1-(3',4'-dimethoxyphenethyl)-4-(3''-phenylpropyl)piperazine, developed by Santen Pharmaceutical Co. This compound is commonly referred to as SA 4503. We tested 7 novel compounds in order to see how their structural differences affect their affinity for sigma1 and sigma2 receptors. The technique used is referred to as a radioreceptor binding assay. Experiments were conducted using 10 inhibitor concentrations of test ligands in membranes (0.25 mg/ml protein) prepared from guinea pig brains in TRIS-HCl buffers (50 mM; pH 7.4, 25 degrees, sigma1; pH 8.0, 25 degrees, sigma2). Sigma1 assays used [3H]-pentazocine ([3H]-PTZ; 1.0 nM) at 37 degrees for 150 min with haloperidol (1.0 uM) to define non-specific binding. The sigma2 assays used [3H]-ditolylguanidine ([3H]-DTG; 3.0 nM) at 25 degrees for 120 min with DTG (100 uM) to define non-specific binding. The sigma2 assays were run in the presence of cold (+)-PTZ (200 nM) to mask sigma1 sites. Inhibition data and statistics for model fits were analyzed by non-linear, least-squares regression using the KELL (Biosoft) and Prism (GraphPad) suite of programs. Apparent affinity (Ki) values ranged from 1.75 +/- 0.17 nM to 30.13 +/- 1.24 nM for sigma1 sites, and from 6.75 +/- 0.20 nM to 113.2 +/- 11.7 nM for sigma2 sites. The findings may aid in the development of structure activity relationships allowing the design of ligands selective for one or the other of the sigma receptor types.