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Synthesis and binding studies of novel sigma receptor ligands

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Sigma receptors are binding sites that are found in the brain, in the endocrine and immune systems, and also in the lungs, kidneys, intestines, muscles and especially the liver. They are classified into two subtypes, sigma1 and sigma2, both of which have unique characteristics. Sigma receptors in the central nervous system are thought to be involved in disorders such as psychoses, Alzheimer's disease, and schizophrenia. A number of human tumors also show high densities of sigma receptors. In this study, three novel compounds were synthesized with the intent of characterizing how their structural differences affect affinity for the sigma1 and sigma2 receptors. We investigated derivatives of a potent sigma1 selective agonist, 1-(3',4'-dimethoxyphenethyl)-4-(3''-phenyl propyl)piperazine, developed by Santen Pharmaceutical Co. Specifically, the 4'-methoxy moiety was replaced by benzyloxy, phenethyloxy and 3-phenylpropyloxy substituents. These were prepared by reaction of the corresponding 4'-phenol with base and treatment with phenethyl bromide, 3-phenylpropyl bromide or benzyl bromide. For the phenethyl and 3-phenylpropyl derivatives, a mixture of 40% KOH and tetrabutylammonium hydroxide (1M in MeOH) was used as the base. Column chromatography provided these target compounds in 81 - 94% purified yields. The benzyl derivative proved difficult to obtain using this procedure, and different conditions were used to synthesize this compound. The 4'-phenol was reacted with benzyl bromide and potassium carbonate in ethanol to give the benzyl ether in 35% yield after purification by column chromatography. All three compounds were characterized by 1H NMR, and were analyzed by elemental analysis and HPLC. Currently, competition receptor binding studies are being run on the synthesized compounds to measure their affinities for sigma1 and sigma2 receptors.