SYNTHESIS AND EVALUATION OF SIGMA RECEPTOR LIGANDS

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ABSTRACT

Sigma receptors are unique binding sites located in the central nervous system (CNS) and peripheral organs. Two sigma receptor subtypes (σ_1 and σ_2) have been described so far. It is known that the σ_1 receptor is involved in a number of CNS disorders and the σ_2 receptor is involved in tumor proliferation among others. Because of the important biological functions of the σ receptor, development of structure activity relationships (SAR) can aid in the identification of potential medications and imaging agents. Three series of analogs based on three lead compounds have been synthesized and evaluated for their *in vitro* affinity and selectivity for the σ_1 and σ_2 subtypes.

Lead I is a selective σ_1 receptor ligand with anti-cocaine activity, but its *in vivo* distribution is unknown. Our *in vitro* binding results showed that all the Lead I analogs are potent σ_1 receptor ligands. Furthermore, one of the Lead I analogs was radioiodinated and evaluated for its *in vivo* distribution. *In vivo* evaluation of the radioiodinated Lead I analog has shown high brain uptake and specific binding to σ_1 receptor of the radioligand. Lead II is also a selective σ_1 receptor ligand and

radioiodinated Lead II has been shown to be a potential imaging agent for the σ_1 receptor. Two of the Lead II analogs were shown to be potent σ_1 receptor ligands. The radioiodinated Lead II analogs were demonstrated to be potential imaging agents for σ_1 receptor *in vivo*. Lead III is one of the most selective σ_2 receptor ligands known to date. Only one of the newly synthesized Lead III analogs was found to be a selective σ_2 receptor ligand. The SAR study of Lead III analogs successfully indentified the important structural features in Lead III for σ_2 receptor binding. To summarize, the SAR studies based on the lead compounds have generated useful information and three potential σ_1 imaging agents were prepared in the studies.