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Progress in the synthesis of a Technetium-labeled complex as a potential Sigma receptor binding ligand

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The sigma receptors have been known to affect several physiological functions such as psychosis, depression and uncontrolled cell proliferation. But what makes the sigma receptors so great is the fact that they bind a variety of ligands. The phenylpiperazine and phenylpiperidine chemical classes of ligands have been identified to bind at sigma1 receptor sites and a pharmacological model has been proposed. On the other hand, due to the scarcity of sigma2 selective ligands, less is understood about this subtype. Non-invasive imaging of the sigma receptor in vivo would lead to a better understanding of the role that sigma receptors play in health and disease. Technetium-99m (Tc-99m) is the most commonly employed imaging radionuclide. This research project is focused on the preparation of a Tc-99m labeled complex designed to retain high affinity to the sigma1 receptor subtype. The design of the ligand is based upon 1-(3', 4'-dimethoxyphenethyl)-4-(3''-phenylpropyl) piperazine (1), a sigma1 agonist developed by Santen Pharmaceutical Co. Through a three-step synthesis, we have replaced one of the methyl groups with a diaminedithiol (DADT) chelating moiety attached through an alkyl chain (2). The first step, alkylation with dibromoethane, has been optimized to an excellent yield (82.5%). Steps two and three have not been optimized but have been shown to be feasible. Details of these reactions and progress toward complexation will be described.