Public Abstract
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Title: The Effect of Structural Modifications on Sigma Receptor Binding

The sigma receptor is a unique receptor family that has two subtypes: sigma1 and sigma2. Sigma1 receptors are involved in several physiological functions such as psychosis and depression. Sigma2 receptors are expressed in a variety of human tumors. Thus the selective sigma1 ligands have potential usage in central nervous system diseases, while sigma2 selective ligands can play an important role as biomarkers and therapeutic agents of tumor proliferation.

Two well characterized compounds, **SA4503** and conformationally flexible benzamide were chosen as our leads. Structural modifications were conducted in order to study the effect of structural elements on sigma binding properties; the possibility of new ligands as potential SPECT imaging agents was also explored.

The result showed most of the **SA4503** analogs had moderate affinity and no selectivity between sigma1 and sigma2 receptor subtype. All of these analogs had increased binding affinity for sigma2 subtype than their lead compound **SA4503**. The modifications made by replacing the left phenylpropyl group of **SA4503** with an N-iodoallyl group yielded a sigma1 selective ligand (**1h-7,** ***E*****-IA-DM-PE-PIPZ**) that had appropriate lipophilicity for penetrating the blood brain barrier in the CNS. The *in vivo* studies using radioiodinated **1h-7** showed that it had high specific binding to the sigma1 receptor in the mouse brain and thus it had great potential as SPECT agent for brain imaging.

The modifications on the benzamide series of compounds by rigid dioxy rings showed similar trend in binding affinities as observed in the similar modification made on the **SA4503** phenolic side chain, the most rigid methylenedioxy analog had the highest affinity and the least rigid propylenedioxy had the lowest affinity for sigma1 subtype. Sigma2 affinity was not affected significantly by the size of the dioxy ring. The modification of the strained tetrahydroisoquinoline ring with a freely rotating amine chain maintained the sigma1 affinity unchanged, while decreasing the sigma2 binding affinity dramatically. Thus a rigid tetrahydroisoquinoline is an important structural element for selective sigma2 binding in the benzamides series compounds.