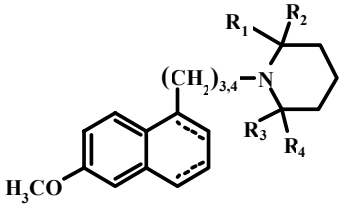
BINDING SELECTIVITY FOR SIGMA RECEPTOR SUBTYPES TRIED BY NOVEL DIMETHYLPIPERIDINE LIGANDS

Francesco Berardi, Savina Ferorelli, Maria Paola Pedone, Nicola Antonio Colabufo, Marialessandra Contino, Roberto Perrone and Vincenzo Tortorella

Dipartimento Farmacochimico, Università di Bari, via Orabona, 4, 70126 Bari, Italy

On the basis of present knowledge, σ (sigma) receptors are almost two subtypes of intracellular binding sites related to signal modulating function involving Ca^{++} release from endoplasmic reticulum. They are localized in high density in the brain, heart, spleen, kidney, liver and in endocrine, immune and reproductive tissues, suggesting their involvement in various modulating activities. Furthermore, they are overexpressed by several cancer cell lines. Cloning of human σ_1 receptor pointed out a moderate homology with a yeast Δ_8-Δ_7 sterol isomerase (SI) involved in ergosterol biosynthesis. Therefore, it has been hypothesized that σ_1 receptor may belong to the family of human SI.
Although no specific σ ligand has reached the market, the σ_1 agents are thought to be useful in the treatment of several central nervous system disorders and deficits, including schizophrenia, pain, memory and cognitive deficits, Alzheimer's disease, neurodamage and cocaine abuse. σ_2 Agents have been found to promote cell apoptosis and inhibit p-glycoprotein expression in some tumour cell lines. An important role can be played by σ ligands in tumour diagnosis through P.E.T. (Positron Emission Tomography) analysis.
Several high-affinity σ ligands are known, that are rather selective for σ_1 receptor subtype, while very few ligands display only a moderate selectivity for σ_2 receptor subtype. Since a decade we have been dealing with the synthesis and biological evaluation of a number of novel σ receptor ligands, with the aim to explore structure-affinity/activity relationships and prepare lead compounds selective for each σ subtype receptor.
A recently prepared series of *N*-[6-methoxytetralin(and -naphthyl)alkyl]methylpiperidines demonstrated high to very high affinity toward σ_1 receptor and only moderate affinity toward σ_2 receptor. Exploring the effect of methyl position on the piperidine ring, 3,3-dimethylpiperidine derivatives displayed the lowest σ_2 affinity, but yet considerable affinity toward SI. In a new effort to extend our investigation on σ receptor subtype selectivity, we prepared a series of piperidine analogues bearing more methyl substituents in α-position relative to N-atom, in order to cause some steric hindrance.



R_1, R_2, R_3, R_4 = CH_3, H

Binding assays on σ_1 and σ_2 receptors and SI site are in progress. Preliminary results showed dramatic changes in σ_1 and σ_2 receptors affinities, while less ones in SI affinities. These findings proved the importance of piperidine N-atom and its neighbourhood in binding selectively σ receptors.