Sila-haloperidol, a Silicon Analogue of the Dopamine (D$_2$) Receptor Antagonist Haloperidol: Synthesis, Pharmacological Properties, and Metabolic Fate


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Haloperidol, a dopamine (D$_2$) receptor antagonist, is in clinical use as an antipsychotic agent. Carbon/silicon exchange (sila-substitution) at the 4-position of the piperidine ring of 1a (R$_3$COH $\rightarrow$ R$_3$SiOH) leads to sila-haloperidol (1b). Sila-haloperidol was synthesized in a new multi-step synthesis starting from tetramethoxysilane, and taking advantage of the properties of the 2,4,6-trimethoxyphenyl unit as a unique protecting group for silicon (for an alternative synthesis of 1b, see ref [1]). The pharmacological profile of the C/Si analogues 1a/1b was studied in competitive receptor binding assays at D$_1$–D$_5$, σ$_1$, and σ$_2$ receptors. It was found that sila-haloperidol (1b) exhibits different receptor subtype selectivity than haloperidol (1a) at both receptor families. Additionally, studies on the metabolism of sila-haloperidol have been undertaken. The metabolic fate of the silicon compound 1b is totally different from that of its carbon analogue 1a. These studies were performed in context with our systematic investigations on silicon-based drugs (for recent publications, see ref [2]–[4]).