FLUORINATED TRIHYDROXYPIPERIDINES AS POTENTIAL PHARMACOLOGICAL CHAPERONES FOR GLUCOCEREBROSIDASE

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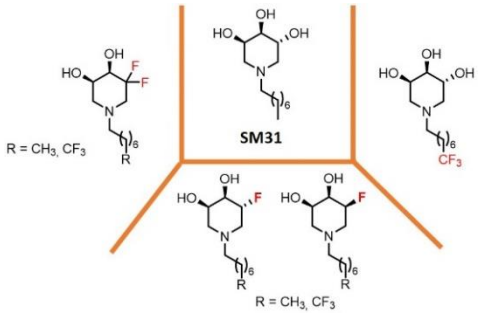
Glucocerebrosidase (Glucosylceramidase Beta or GCase) is a lysosomal enzyme that hydrolyses glucocerebroside to glucose and ceramide. *GBA1* mutations impair GCase function, leading to substrate accumulation in macrophages. This underlies Gaucher disease, one of the most common lysosomal storage disorders (LSDs) [1], and is a major genetic risk factor for α-synucleinopathies, including Parkinson's Disease [2]. Pharmacological chaperones (PCs) have emerged as a promising therapeutic strategy to restore GCase function. These small molecules bind and stabilize misfolded enzymes, enhancing residual activity at sub-inhibitory concentrations. Glycomimetics, particularly iminosugar derivatives, are the most widely studied PC class for LSDs [3]. Various substitutions and modifications in heterocyclic carbon configurations have been explored. Of these, the incorporation of fluorine has garnered significant interest due to its ability to influence conformation, pKa, potency, membrane permeability, metabolic pathways and pharmacokinetic characteristics [4].
Our current research explores substituted trihydroxypiperidines for GCase function restoration [5]. In this communication, I will outline our synthetic efforts to integrate fluorine into the iminosugar core of one of our best-in-class PC (SM31) [6], aiming to explore the fluorine contribution on the physicochemical properties and the efficacy of the system.



Scheme 1. Fluorine integration on our best-in-class PC (SM31)

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