Title: Procognitive properties of a novel series of GABA-A receptor positive modulators with efficacy at alpha-a subunit: potential therapeutics for cognitive decline

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Abstract: A deficit in the main inhibitory neurotransmitter (GABA) has been reported across multiple diseases such as depression, Alzheimer's and in normal or pathological aging. Such conditions are often associated with cognitive impairments that are not alleviated by currently available drugs. Interestingly, the a5-containing GABA type A receptors (a5-GABAA-R) are highly expressed in the prefrontal cortex and the hippocampus, brain regions involved in cognitive processes. Recent work suggests that modulating inhibition through these receptors has pro-cognitive effect, reinforcing our hypothesis that augmenting inhibition through a5-GABAA-R is a novel avenue for therapeutic intervention. Our group has now developed a series of compounds that facilitate a5-GABAA-R function, display drug-like properties and therapeutic efficacy in preclinical models with cognitive deficits. Preliminary results in preclinical models identified three potential lead compounds with proven pro-cognitive efficacy in a working memory test. Our goals are now to confirm their pro-cognitive effects in adult preclinical models with stress-induced cognitive deficits, to extend these findings to other cognitive functions and to validate their pro-cognitive effects in a preclinical model of age-related cognitive deficits. To do so, we will assess the pro-cognitive efficacy of our three lead candidates in several cognitive tasks assessing different subtypes of cognitive functions in preclinical models. The tests will be performed at CAMH, in collaboration between the Sibille and Fletcher groups, to identify a potential lead, which will be validated in an aging model. The goal of this study is to identify a lead compound with robust pro-cognitive effects in adult and aged preclinical models, as a necessary component of new drug applications to the US FDA and Health Canada for moving these new compounds into clinical settings.

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