

DISCOVERY OF A SERIES OF MOLECULES ACTING AS POTENT ALPHA7 NACHR AGONISTS WITH PRO-COGNITIVE AND NEUROPROTECTIVE PROPERTIES

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Nicotinic acetylcholine receptors of the alpha7 type have emerged as promising therapeutic targets for treatment of Alzheimer disease and schizophrenia owing to their involvement in cognition, memory and neurodegeneration. Using a functional FLIPR-based calcium assay employing the rat alpha7 nAChR stably expressed in a GH4C1 cell line, a novel chemical series of potent small molecule agonists of the alpha7 nAChR was discovered. Examples of this series were selective over alpha1, alpha4 nAChRs and 5HT-3 receptors and showed micromolar antagonistic activity at the alpha3 nAChR. Two prototypic compounds, SEN-WAY-1 and SEN-WAY-3, identified as partial and full agonist with an EC₅₀ of 3.0 and 2.3 microM respectively are presented in greater detail. The neuroprotective potential of these compounds was investigated in an assay of NMDA-mediated neurotoxicity employing rat cortical neurons. Both SEN-WAY-1 and SEN-WAY-3 reduced significantly the NMDA induced toxicity. The pharmacological and neuroprotective properties of these small molecules were also investigated extensively *in vivo*. Following a single IP dose of 3 or 10 mg/kg, SEN-WAY-1 and SEN-WAY-3 were detected in the plasma and brain of rats resulting in brain-to-plasma ratios equal to or greater than 1 and C_{max} concentrations above their FLIPR EC₅₀ values. Effects on cognition were assessed in a model of short working memory (passive avoidance) and episodic memory (novel object recognition test). In both cognitive paradigms, SEN-WAY-1 and SEN-WAY-3 reversed the amnesic effects of scopolamine at a dose of 3 mg/kg when acutely administered (i.p.) after scopolamine injection. Neuroprotection was demonstrated in rats that had been lesioned by quisqualic acid injection in the nucleus basalis of Meynert (NBM). A sub-chronic treatment with 3 mg/kg SEN-WAY-1 or SEN-WAY-3 for 7 days significantly attenuated the decrease in the number of ChAT-positive neurons in this brain region. Therefore, like other known alpha 7 agonists, these new alpha7 nAChR agonists also demonstrate pro-cognitive and neuroprotective effects and may be useful for treating neurodegenerative diseases such as Alzheimer disease as well as neuropsychiatric disorders.