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Screening for Non-hallucinogenic Neuroplastogens as Drug Candidates for the Treatment of Anxiety, Depression, and Posttraumatic Stress Disorder

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Abstract : With the aim of establishing a holistic approach for the treatment of central nervous system (CNS) disorders, we are pursuing a drug development program rapidly progressing through discovery and characterization phases. The drug candidates identified in this program are referred to as neuroplastogens owing to their ability to mediate neuroplasticity, which can be beneficial to patients suffering from anxiety, depression, or posttraumatic stress disorder. These and other related neuropsychiatric conditions are associated with the onset of neuronal atrophy, which is defined as a reduction in the number and/or productivity of neurons. The stimulation of neuroplasticity results in an increase in the connectivity between neurons and promotes the restoration of healthy brain function. We have synthesized a substantial catalogue of proprietary indolethylamine derivatives based on the general structures of serotonin (5-hydroxytryptamine) and psychedelic molecules such as N,N-dimethyltryptamine (DMT) and psilocin (4-hydroxy-DMT) that function as neuroplastogens. A primary objective in our screening protocol is the identification of derivatives associated with a significant reduction in hallucination, which will allow administration of the drug at a dose that induces neuroplasticity and triggers other efficacious outcomes in the treatment of targeted CNS disorders but which does not cause a psychedelic response in the patient. Both neuroplasticity and hallucination are associated with engagement of the 5HT2A receptor, requiring drug candidates differentially coupled to these two outcomes at a molecular level. We use novel and proprietary artificial intelligence algorithms to predict the mode of binding to the 5HT2A receptor, which has been shown to correlate with the hallucinogenic response. Hallucination is tested using the mouse head-twitch response model, whereas mouse marble-burying and sucrose preference assays are used to evaluate anxiolytic and anti-depressive potential. Neuroplasticity is assays using dendritic outgrowth assays and cell-based ELISA analysis. Pharmacokinetics and additional receptor-binding analyses also contribute the selection of lead candidates. A summary of the program is presented.

Keywords : neuroplastogen, non-hallucinogenic, drug development, anxiety, depression, PTSD, indolethylamine derivatives, psychedelic-inspired, 5-HT2A receptor, computational chemistry, head-twitch response behavioural model, neurite outgrowth assay
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