Subunit-Selective Modulator for Treatment of Neurological Disorders

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Technology description

NMDARs have the potential to treat central nervous system (CNS) disorders that involve NMDAR dysfunction, including Alzheimer’s disease, Parkinson’s disease, depression, stroke, schizophrenia, and psychosis. All isoforms of NMDAR subunits are expressed at varying levels throughout the CNS and have unique functional and pharmacological properties implicating different CNS disorders. Current market offers several non-specific NMDAR modulators, as well as GluN2B-selective inhibitors like ifenprodil, and a GluN2C/D selective positive allosteric modulator CIQ. CIQ is useful as a tool compound for assessing GluN2C/D involvement in CNS processes, but its utility is limited by modest potency and poor solubility. In addition, this scaffold lacks druggable properties. Therefore, a more efficacious subunit-selective molecule is needed to modulate NMDAR activity for treatment of neurological disorders.
Emory University researchers have developed a novel series of quinolines in which the dimethoxy phenyl substituent of CIQ is replaced with various heterocycles. Analogs based around the structure have been synthesized resulting in compounds with improved potency, efficacy, and drug-like properties compared to CIQ, while also maintaining subunit-selectivity for GluN2C and GluN2D. These compounds may be effective in treating a wide range of neurological disorders involving memory, learning and synaptic plasticity such as Alzheimer’s disease, Parkinson’s disease, depression, stroke, schizophrenia, and psychosis.

Application area

Subunit-selective GluN2C and GluN2D positive allosteric modulators of N-methyl-D-aspartic acid receptors (NMDAR) for treatment of neurological disorders.

Advantages

Specifically targets GluN2C/D subunits for positive modulation of NMDAR activity.
Higher potency compared to non-selective modulators.
Improved drug-like properties compared to CIQ.

Institution

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