GluN2C/D-selective Antagonists for Treatment of Neurological Disorders

Published date: Dec. 22, 2015

Technology description

Market Summary

N-methyl-D-aspartate (NMDA) receptors are widely dispersed in the central nervous system (CNS) and are involved in important physiological processes such as synaptic plasticity and memory formation. NMDA receptors are also implicated in several pathophysiological conditions including Parkinson's disease, schizophrenia, depression and ischemia. Almost all drugs targeting NMDA receptors are in the discovery or preclinical phase. Additionally, most current drugs and drugs in development (dextromethorphan, esketamine) globally antagonize NMDA receptor function in the CNS, potentially resulting in adverse side-effects such as dissociative feelings and hallucinations.

Technical Summary

NMDA receptors are heterotetrameric ionic glutamate channels which comprise 2 GluN1 and 2 GluN2 subunits. While GluN2A and GluN2B subunits are broadly expressed in the CNS, the GluN2C and GluN2D subunits are more anatomically restricted, oftentimes in brain regions implicated in pathology. Therefore selective inhibition of the GluN2C/D subunits are attractive for treating certain neurological conditions. A class of GluN2C/D-specific antagonists of NMDA receptors has been discovered and characterized by the inventors. The dihydroquinolone-pyrazoline (DQP) class of NMDA receptor antagonists potently and selectively inhibit GluN2C/D-containing NMDA receptors. Moreover, some of the most potent analogs were further evaluated and possess good aqueous solubility, minimal degradation in human plasma, and potential for blood-brain barrier penetration.

Application area

A new series of compounds for selectively inhibiting N-methyl-D-aspartate (NMDA) receptor subunits for the treatment of Parkinson's disease, schizophrenia, treatment-resistant depression, and ischemia.

Advantages

Improved anatomical selectivity in NMDA receptor modulation may result in fewer adverse side effects. Targeted antagonism of the GluN2C/D subunits of the NMDA receptor may yield better pharmacological and pharmacokinetic properties than other NMDA receptor antagonists.

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