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Hydroxymethyl bioisosteres of phenolic GluN2B-selective NMDA receptor antagonists: Design, synthesis and pharmacological evaluation

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Abstract

Antagonists addressing selectively NMDA receptors containing the GluN2B subunit are of particular interest for the treatment of various neurological disorders including neurodegenerative diseases. With the aim to bioisosterically replace the metabolically labile phenol of 7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-ols, several analogs were docked into the ifenprodil binding site leading to the hydroxymethyl derivatives **4** as promising candidates. They display the same binding pose as Ro 25-6981 and the same H-bond interactions with Gln110 and Glu236 within the GluN2B subunit. The phenylalkyl moieties occupy the hydrophobic pocket formed predominantly by Pro78 (GluN2B), Phe114 (GluN2B), and Tyr109 (GluN1b).