The Preclinical Profile of DSR-141562: A Novel Phosphodiesterase 1 Inhibitor for the Treatment of Positive Symptoms, Negative Symptoms and Cognitive Impairments Associated with Schizophrenia.

Takeshi Enomoto, Ayaka Tatara, Masao Goda, Yohei Nishizato, Kantaro Nishigori, Atsushi Kitamura, Mami Kamada, Shiori Taga, Takashi Hashimoto, Kazuhito Ikeda, Yuki Fujii

Research Division, Sumitomo Dainippon Pharma Co., Ltd.

We discovered a novel orally-available and brain-penetrant phosphodiesterase 1 (PDE1) inhibitor, DSR-141562. This compound has high selectivity for the PDE1 family over other PDE families and 65 off-targets. Further, it has the preferential selectivity for predominantly brain-expressed PDE1B over other PDE1 family isoforms. Since PDE1B is believed to regulate dopaminergic and glutamatergic signal transduction, we evaluated the effects of this compound using schizophrenia-related behavioral assays. DSR-141562 at 3-30 mg/kg potently inhibited methamphetamine-induced locomotor hyperactivity in rats, while it had only minimal effects on the spontaneous locomotor activity. DSR-141562 at 0.3-3 mg/kg reversed social interaction and novel object recognition deficits induced by repeated treatment with an N-methyl-D-aspartate receptor antagonist phencyclidine, in mice and rats, respectively. In common marmosets, DSR-141562 at 3 and 30 mg/kg improved success rate in the object retrieval with detour task. DSR-141562 at 30 and 100 mg/kg potently elevated the cGMP concentration in monkey cerebrospinal fluid, which could be used as a translational biomarker. These results suggest that DSR-141562 would have the therapeutic potential for positive symptoms, negative symptoms and cognitive impairments in schizophrenia.