

TP-050: A Chemical Probe for GRIN2A

Version 1.0 (29th June 2022)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/TP-050>

Overview

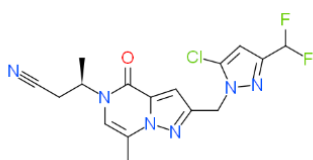
N-methyl-D-aspartate (NMDA) receptor channels are heteromers composed of the key subunit GRIN1 and one or more subunits of four different proteins namely [GRIN2A](#) (GluN2A), GRIN2B, GRIN2C and GRIN2D, and are involved in long-term potentiation. GRIN2A plays an important role in neuro protection and neuroplastic enhancement (synaptic plasticity). Selective GRIN2A activation is a promising therapeutic approach for cognitive impairment and psychiatric diseases such as schizophrenia, depression, and epilepsy.

Summary

Chemical Probe Name	TP-050
Negative control compound	TP-050n
Target(s) (synonyms)	GRIN2A (glutamate ionotropic receptor NMDA type subunit 2A), GluN2A
Recommended <i>in vitro</i> assay concentration	Use with control for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Tested in rats with po (10 mg/kg) and iv (1 mg/kg) administration. Shows good oral bioavailability, blood–brain barrier permeability and a significant neuroplastic enhancement in the rat hippocampus 24 h after oral administration.
Publications	PMID: 35051811 (Compound (R)-9, control (S)-9)
<i>In vitro</i> assay(s) used to characterise	N/A
Cellular assay(s) for target-engagement	Ca ²⁺ influx assay using CHO cells expressing GluN2A/ GluN1a in the presence of glutamate at an EC ₃₀ conc.

Chemical Probe & Negative Control Structures and Use

TP-050 Chemical Probe



SMILES: CC1=CN(C(c2cc(Cn3c(cc(C(F)F)n3)[Cl])nn12)=O)[C@H](C)CC#N

InChIKey: BEBDKSYNJJVZSO-SECBINFHSA-N

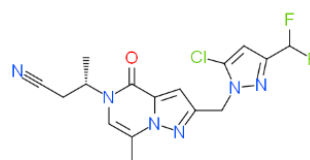
Molecular weight: 380.1 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.

DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

TP-050n Negative Control



SMILES: CC1=CN(C(c2cc(Cn3c(cc(C(F)F)n3)[Cl])nn12)=O)[C@@H](C)CC#N

InChIKey: BEBDKSYNJJVZSO-VIFPVBQESA-N

Molecular weight: 380.1 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.

DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

Selectivity:

TP-050 shows good NMDA-subtype selectivity (Ca²⁺ influx assay) (EC₅₀ [μM], max. potentiation): GRIN2B (> 30, < 150 %; > 59-fold), GRIN2C (> 30, < 200 %), GRIN2D (9.6, < 260 %, 19-fold). In the AMPA receptor scintillation proximity (SPA) binding assay the IC₅₀ was greater 30 μM. The DiscoverX SafetyScan (47 targets) was clean with the exception for PDE3A (7.9 μM).

Potency in Cells and Cellular Target Engagement:

TP-050 was active in the Ca²⁺ influx assay with EC₅₀ = 0.51 μM and a max. potentiation of 350 %.