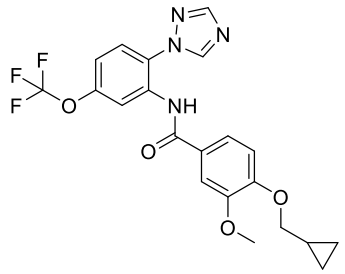
Product data sheet

MedKoo Cat#: 555413 Name: VU6012962 CAS#: 2313526-86-0 Chemical Formula: $C_{21}H_{19}F_3N_4O_4$ Exact Mass: 448.1358 Molecular Weight: 448.4022	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
VU6012962 is an orally bioavailable and CNS-penetrant metabotropic glutamate receptor 7 (mGlu7) negative allosteric modulator (NAM) that achieves exposure in cerebral spinal fluid (CSF) 2.5x above the in vitro IC50 at minimum effective doses (MEDs) of 3 mg/kg in preclinical anxiety models.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	125	278.77

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.23 mL	11.15 mL	22.30 mL
5 mM	0.45 mL	2.23 mL	4.46 mL
10 mM	0.22 mL	1.12 mL	2.23 mL
50 mM	0.04 mL	0.22 mL	0.45 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Reed CW, Yohn SE, Washecheck JP, Roenfanz HF, Quitalig MC, Luscombe VB, Jenkins MT, Rodriguez AL, Engers DW, Blobaum AL, Conn PJ, Niswender CM, Lindsley CW. Discovery of an Orally Bioavailable and Central Nervous System (CNS) Penetrant mGlu7 Negative Allosteric Modulator (NAM) in Vivo Tool Compound: N-(2-(1 H-1,2,4-triazol-1-yl)-5-(trifluoromethoxy)phenyl)-4-(cyclopropylmethoxy)-3-methoxybenzamide (VU6012962). J Med Chem. 2019 Feb 14;62(3):1690-1695. doi: 10.1021/acs.jmedchem.8b01810. Epub 2019 Jan 17. PMID: 30608678; PMCID: PMC6501583.

In vivo study

1. Reed CW, Yohn SE, Washecheck JP, Roenfanz HF, Quitalig MC, Luscombe VB, Jenkins MT, Rodriguez AL, Engers DW, Blobaum AL, Conn PJ, Niswender CM, Lindsley CW. Discovery of an Orally Bioavailable and Central Nervous System (CNS) Penetrant mGlu7 Negative Allosteric Modulator (NAM) in Vivo Tool Compound: N-(2-(1 H-1,2,4-triazol-1-yl)-5-(trifluoromethoxy)phenyl)-4-(cyclopropylmethoxy)-3-methoxybenzamide (VU6012962). J Med Chem. 2019 Feb 14;62(3):1690-1695. doi: 10.1021/acs.jmedchem.8b01810. Epub 2019 Jan 17. PMID: 30608678; PMCID: PMC6501583.

7. Bioactivity
Biological target:

Product data sheet

VU6012962 is an orally bioavailable and CNS-penetrant metabotropic glutamate receptor 7 negative allosteric modulator (mGlu7 NAM) with an IC50 of 347 nM.

In vitro activity

As many mGlu allosteric ligands engage induced-fit pockets, SAR can be challenging, and the “right” fit may only be “found” by exploring libraries of analogs via an exercise in strategic serendipity. VU6012962 (7d) proved optimal (IC50 = 350 nM, pIC50 = 6.46 ± 0.10, 12.6 ± 1.5% L-AP4 min) and the most potent within this chemotype to date. Beyond an enhancement in mGlu7 NAM potency, 7d also showed a significant improvement in predicted hepatic clearance (rat CLhep = 15.9 mL min–1 kg–1), generating enthusiasm for the further profiling of 7d. 7d was selective for mGlu7 versus the other seven mGlu receptors (>10 μM versus mGlu1–6,8) and largely devoid of ancillary pharmacology (compound activity at only one target, 5-HT2B receptor, that was greater than 50% at 10 μM) in a Eurofins lead profiling panel of 68 GPCRs, ion channels, and transporters. A 30 mg/kg (ip) tissue distribution study in rat was performed to assess levels of 7d in plasma, brain, and CSF. Here, it was noted that a brain:plasma Kp of 1.24 (([plasma]tot = 598 nM), [brain]tot = 745 nM) and a Kp,uu of 0.38 ([plasma]Unbound = 16.7 nM, [brain]unbound = 6.4 nM); however, the CSF:plasma Kp was 2.15, with levels of 7d in CSF of 1.3 μM, or ~3.8-fold above the in vitro IC50.

Reference: J Med Chem. 2019 Feb 14;62(3):1690-1695. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/30608678/

In vivo activity

Having established a 3 mg/kg MED in the EZM assay, 7d was evaluated in two other mouse anxiety models: the light/dark box and marble burying assay. The effects of 3 mg/kg 7d were compared to the selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX, Figure 4).22 Results from the light/dark box assay showed that administration of either 7d (3 mg/kg ip) or fluoxetine (15 mg/kg ip) increased total time spent in the light side of the chamber compare to vehicle (VEH) controls (Figure 4A). Similarly, both 7d and fluoxetine decreased the number of marbles buried in a mouse marble-burying assay, consistent with an anxiolytic effect, compared to vehicle-control conditions (Figure 4B). The observation of efficacy at the 3 mg/kg dose prompted us to perform a pharmacokinetic assessment at this dose and the 1 h time point used for treatment in mice. These studies revealed values of [plasma]tot = 303 nM and [CSF] = 883 nM; this CSF level is 2.5× higher than the in vitro IC50 of 350 nM. Taken together, mGlu7 NAM 7d decreases anxiety responses in three distinct preclinical models and displays a low of MED of 3 mg/kg, highlighting improvements of this tool compound in the realms of potency, physiochemical properties, disposition, and unbound CSF/brain levels.

Reference: J Med Chem. 2019 Feb 14;62(3):1690-1695. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/30608678/