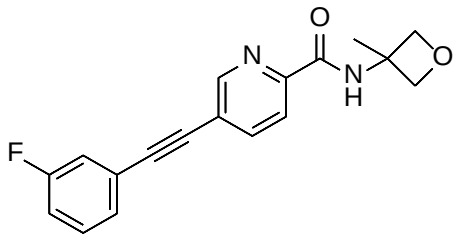
Product data sheet

MedKoo Cat#: 555938 Name: ML-254 CAS: 1428630-86-7 Chemical Formula: $C_{18}H_{15}FN_2O_2$ Exact Mass: 310.1118 Molecular Weight: 310.3284	
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:

ML-254, also known as VU0430644; is Positive Allosteric Modulators (PAMs) of mGlu5 with Competitive MPEP-Site Interaction. ML254 is highly selective for mGlu5 versus other mGlu receptors, has a clean ancillary Ricerca profile, and suitable dystrophia myotonica protein kinase (DMPK) properties for systemic dosing in rodents. Preliminary experiments at a single dose in an in vivo model of psychosis using ML254 demonstrates a robust reversal of amphetamine induced hyperlocomotion. ML254 will serve as a significant pure-PAM tool compound for the field with potential for studies within in vivo paradigms. Structure activity relationship (SAR) and characterization of ML254 are described.

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
TBD	TBD	TBD

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	3.22 mL	16.11 mL	32.22 mL
5 mM	0.64 mL	3.22 mL	6.44 mL
10 mM	0.32 mL	1.61 mL	3.22 mL
50 mM	0.06 mL	0.32 mL	0.64 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

Turlington M, Noetzel MJ, Chun A, Zhou Y, Gogliotti RD, Nguyen ED, Gregory KJ, Vinson PN, Rook JM, Gogi KK, Xiang Z, Bridges TM, Daniels JS, Jones C, Niswender CM, Meiler J, Conn PJ, Lindsley CW, Stauffer SR. Exploration of allosteric agonism structure-activity relationships within an acetylene series of metabotropic glutamate receptor 5 (mGlu5) positive allosteric modulators (PAMs): discovery of 5-((3-fluorophenyl)ethynyl)-N-(3-methyloxetan-3-yl)picolinamide (ML254). J Med Chem. 2013 Oct 24;56(20):7976-96. doi: 10.1021/jm401028t. Epub 2013 Oct 9. PMID: 24050755; PMCID: PMC3908770.

In vivo study

Turlington M, Noetzel MJ, Chun A, Zhou Y, Gogliotti RD, Nguyen ED, Gregory KJ, Vinson PN, Rook JM, Gogi KK, Xiang Z, Bridges TM, Daniels JS, Jones C, Niswender CM, Meiler J, Conn PJ, Lindsley CW, Stauffer SR. Exploration of allosteric agonism structure-activity relationships within an acetylene series of metabotropic glutamate receptor 5 (mGlu5) positive allosteric modulators (PAMs): discovery of 5-((3-fluorophenyl)ethynyl)-N-(3-methyloxetan-3-yl)picolinamide (ML254). J Med Chem. 2013 Oct 24;56(20):7976-96. doi: 10.1021/jm401028t. Epub 2013 Oct 9. PMID: 24050755; PMCID: PMC3908770.

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7. Bioactivity

Biological target:

ML-254, also known as VU0430644; is Positive Allosteric Modulators (PAMs) of mGlu5 with Competitive MPEP-Site Interaction.

In vitro activity

To validate that 38t (ML-254) interacts with mGlu5 at the MPEP binding site radioligand binding studies were performed with [3H]methoxyPEPy. Increasing concentrations of 38t resulted in complete inhibition of [3H]methoxyPEPy binding supporting a competitive interaction between the two ligands (Figure 9). 38t (ML-254) exhibited a Ki of 90 nM, representing a ~10-fold higher functional activity (EC50 = 9.3 nM) compared to binding. In addition, screening of 10 µM 38t against a panel of 68 GPCRs, ion channels and transporters revealed no significant off target activity (Eurofins Inc.).

Reference: J Med Chem. 2013 Oct 24;56(20):7976-96. https://pubmed.ncbi.nlm.nih.gov/24050755/

In vivo activity

Rat brain homogenate binding was used to determine fraction unbound in brain for 38t (ML-254); these studies revealed fu brain values of 1.6%. To assess drug-drug interactions, inhibition of the major human cytochrome P450 (CYP) enzymes (2C9, 2D6, 3A4, 1A2) was measured in human liver microsomes and 38t was found to display inhibitory activity at 1A2 (IC50 = 5.30 µM) while no activity was observed against the other CYPs tested (IC50 >30 µM). Solubility of 38t was found to be modest with a Fassif (fasted simulated intestinal fluid) solubility of 10–23 µg/mL.

Reference: J Med Chem. 2013 Oct 24;56(20):7976-96. https://pubmed.ncbi.nlm.nih.gov/24050755/

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.