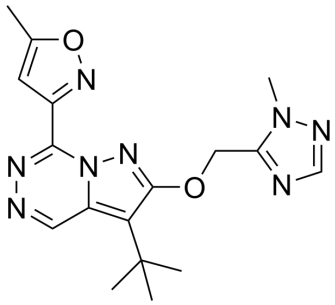
MRK-016

Cat. No.:	HY-100370
CAS No.:	342652-67-9
Molecular Formula:	$C_{17}H_{20}N_8O_2$
Molecular Weight:	368.39
Target:	GABA Receptor
Pathway:	Membrane Transporter/Ion Channel; Neuronal Signaling
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (135.73 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7145 mL	13.5726 mL	27.1451 mL
	5 mM	0.5429 mL	2.7145 mL	5.4290 mL
	10 mM	0.2715 mL	1.3573 mL	2.7145 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.75 mg/mL (7.46 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.75 mg/mL (7.46 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.75 mg/mL (7.46 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MRK-016 is a selective, orally bioavailable inverse agonist of $GABA_A$ α5 receptor, with an EC_{50} of 3 nM for $GABA_A$ α5, and K_is of 0.83, 0.85, 0.77 and 1.4 nM for human $GABA_A$ α1β3γ2, $GABA_A$ α2β3γ2, $GABA_A$ α3β3γ2, and $GABA_A$ α5β3γ2, respectively; MRK-016 also readily penetrates the CNS.

IC_{50} & Target

EC50: 3 nM ($GABA_A$ α5)[1]
Ki: 0.83 nM (Human $GABA_A$ α1β3γ2), 0.85 nM (Human $GABA_A$ α2β3γ2), 0.77 nM (Human $GABA_A$ α3β3γ2), 1.4 nM (Human $GABA_A$ α5β3γ2)[1]

In Vitro	MRK-016 is a selective, orally bioavailable inverse agonist of $GABA_A$ α5 receptor, with an EC_{50} of 3 nM for $GABA_A$ α5, and K_is of 0.83, 0.85, 0.77 and 1.4 nM for human $GABA_A$ α1β3γ2, $GABA_A$ α2β3γ2, $GABA_A$ α3β3γ2, and $GABA_A$ α5β3γ2, respectively[1][2]. MRK-016 is a full inverse agonist at the α5-subtype, shows very weak affinity at the $GABA_A$ α4β3γ2-subtype (K_i 395 ± 173 nM) and is essentially inactive at the $GABA_A$ α6β3γ2 receptor (K_i > 4000 nM)[1]. MRK-016 shows a weak effect on $GABA_A$ α4β3γ2 with a K_i of 400 nM. MRK-016 (100 nM) alao increases long-term potentiation in mouse hippocampal slices[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	MRK-016 does not enhance pentylenetetrazole-induced convulsions at 10 mg/kg via ip, or cause seizures at 30 mg/kg, via po for 20 days in mice. MRK-016 shows no obvious anxiogenic-like effects in rats at doses that occupy >95% of benzodiazepine (BZ) binding sites. MRK-016 (0.3, 1, and 3 mg/kg, p.o.) dose-dependently improves performance of rats hippocampal-dependent memory task[1]. MRK-016 (0.3-30 mg/kg, p.o.) causes good receptor occupancy in rats. MRK-016 (0.3, 1, or 3 mg/kg p.o.) shows cognition-enhancing activity in the delayed matching-to-position version of the Morris water maze. MRK-016 (1, 3, or 10 mg/kg i.p.) does not produce kindling in mice[2]. MRK-016 (3 mg/kg, i.p.) protects against LPS-induced learning/memory decrements in mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	L(tk$^-$) cells expressing human recombinant $GABA_A$ receptors containing β3- and γ2-subunits in combinatioon with various α-subunits are harvested and binding performed. The displacement of [^{3}H]Ro 15-1788 binding by the test compounds (MRK-016, etc.) is measured in $GABA_A$ receptors containing eigher an α1-, α2-, α3-, and α5-subunit and from the IC_{50} and the K_i is calculated assuming respective K_d values of [^{3}H]Ro 15-1788 binding of 0.92, 1.05, 0.58 and 0.45 nM at the α1-, α2-, α3-, and α5-subtypes. Nonspecific binding is defined by the inclusion of 10 μM flunitrazepam for the α1-, α2-, α3-, and α5-subtypes. The percentage inhibition of [^{3}H]Ro 15-1788, the IC_{50} and the K_i values are calculated using ActivityBase[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] The proconvulsant potential MRK-016 is determined in this assay. The convulsant is pentylenetetrazole which is dosed at 15 mg/mL with an infusion rate of 0.2 mL/min. This rate is chosen to ensure that drug-naive mince reach the terminal convulsion sign within 1 min. MRK-016 is dosed intraperitoneally (ip) at a concentration of 1, 3, and 10 mg/kg in 70% PEG 300[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Chambers MS, et al. An orally bioavailable, functionally selective inverse agonist at the benzodiazepine site of GABAA alpha5 receptors with cognition enhancing properties. J Med Chem. 2004 Nov 18;47(24):5829-32.

[2]. Atack JR, et al. In vitro and in vivo properties of 3-tert-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1H-1,2,4-triazol-5-ylmethoxy)-pyrazolo[1,5-d]-[1,2,4]triazine (MRK-016), a GABAA receptor alpha5 subtype-selective inverse agonist. J Pharmacol Exp Ther. 2009 Nov;331(2):470-84.

[3]. Eimerbrink MJ, et al. Administration of the inverse benzodiazepine agonist MRK-016 rescues acquisition and memory consolidation following peripheral administration of bacterial endotoxin. Behav Brain Res. 2015 Jul 15;288:50-3.

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