

Product Data Sheet

Product Name: MRK 016

Cat. No.: GC16528

Chemical Properties

Cas. No. 783331-24-8,342652-67-9

Chemical Name 3-(9-(tert-butyl)-8-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)pyrazolo[1,5-d][1,2,4]triazin-2-yl)-5-methylisoxazole

SMILES CC(C)(C)C1=C2N(C(C3=NOC(C)=C3)=NN=C2)N=C1OCC4=NC=NN4C

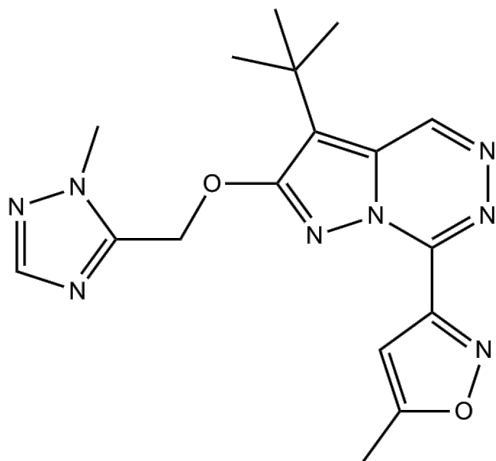
Formula $C_{17}H_{20}N_8O_2$ M.Wt 368.39

Solubility <36.84mg/ml in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Caution: Product has not been fully validated for medical applications. For research use only.

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Kinase experiment: L(tk-) cells expressing human recombinant GABAA receptors containing $\beta 3$ - and $\gamma 2$ -subunits in combination with various α -subunits are harvested and binding performed. The displacement of [3H]Ro 15-1788 binding by the test compounds (MRK-016, etc.) is measured in GABAA receptors containing either an $\alpha 1$ -, $\alpha 2$ -, $\alpha 3$ -, and $\alpha 5$ -subunit and from the IC₅₀ and the K_i is calculated assuming respective K_d values of [3H]Ro 15-1788 binding of 0.92, 1.05, 0.58 and 0.45 nM at the $\alpha 1$ -, $\alpha 2$ -, $\alpha 3$ -, and $\alpha 5$ -subtypes. Nonspecific binding is defined by the inclusion of 10 μ M flunitrazepam for the $\alpha 1$ -, $\alpha 2$ -, $\alpha 3$ -, and $\alpha 5$ -subtypes. The percentage inhibition of [3H]Ro 15-1788, the IC₅₀ and the K_i values are calculated using ActivityBase[1].

Animal experiment: 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-naïve mice 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].

References:

- [1]. Chambers MS, et al. An orally bioavailable, functionally selective inverse agonist at the benzodiazepine site of GABAA $\alpha 5$ receptors with cognition enhancing properties. J Med Chem. 2004 Nov 18;47(24):5829-32.
- [2]. Attack 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 $\alpha 5$ 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.

Background

MRK-016 is a selective, orally bioavailable inverse agonist of GABAA $\alpha 5$ receptor, with an EC₅₀ of 3

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nM for GABAA α 5, and Kis of 0.83, 0.85, 0.77 and 1.4 nM for human GABAA α 1 β 3 γ 2, GABAA α 2 β 3 γ 2, GABAA α 3 β 3 γ 2, and GABAA α 5 β 3 γ 2, respectively; MRK-016 also readily penetrates the CNS.

MRK-016 is a selective, orally bioavailable inverse agonist of GABAA α 5 receptor, with an EC50 of 3 nM for GABAA α 5, and Kis of 0.83, 0.85, 0.77 and 1.4 nM for human GABAA α 1 β 3 γ 2, GABAA α 2 β 3 γ 2, GABAA α 3 β 3 γ 2, and GABAA α 5 β 3 γ 2, respectively[1][2]. MRK-016 is a full inverse agonist at the α 5-subtype, shows very weak affinity at the GABAA α 4 β 3 γ 2-subtype (K_i 395 $\pm$ 173 nM) and is essentially inactive at the GABAA α 6 β 3 γ 2 receptor (K_i > 4000 nM)[1]. MRK-016 shows a weak effect on GABAA α 4 β 3 γ 2 with a K_i of 400 nM. MRK-016 (100 nM) also increases long-term potentiation in mouse hippocampal slices[2].

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].

References:

- [1]. Chambers MS, et al. An orally bioavailable, functionally selective inverse agonist at the benzodiazepine site of GABAA α 5 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 α 5 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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