Taranabant

Cat. No.: HY-10013

CAS No.: 701977-09-5

Molecular Formula: $C_{27}H_{25}ClF_3N_3O_2$

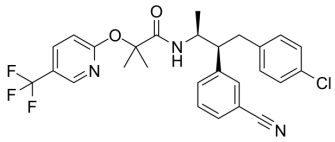
Molecular Weight: 515.95

Target: Cannabinoid Receptor

Pathway: GPCR/G Protein; 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 : ≥ 42 mg/mL (81.40 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9382 mL	9.6909 mL	19.3817 mL
	5 mM	0.3876 mL	1.9382 mL	3.8763 mL
	10 mM	0.1938 mL	0.9691 mL	1.9382 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: ≥ 2.5 mg/mL (4.85 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Taranabant is a highly potent and selective cannabinoid 1 (CB1) receptor inverse agonist that inhibits the binding and functional activity of various agonists, with a binding K_i of 0.13 nM for the human CB1R in vitro.

IC_{50} & Target

IC50: 0.3 nM (hCB1R), 0.4 nM (rCB1R)[1]
Ki: 0.13 nM (hCB1R), 0.27 nM (rCB1R)[1]

In Vitro

Taranabant (MK-0364) binds to human or rat CB1R with an IC_{50} of 0.3 and 0.4 nM, respectively, corresponding to a K_i value of 0.13 and 0.27 nM, respectively. Taranabant binds to the human or rat CB2R with an IC_{50} value of 290 and 470 nM, respectively, corresponding to a K_i value of 170 and 310 nM, respectively. The selectivity ratio of CB1R over CB2R is

approximately 1000-fold[1]. Taranabant (MK-0364) is a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity. IC_{50}s of Taranabant for CB1R and CB2R by substituted amides is 0.3±0.1 nM, and 290±60 nM, respectively. Taranabant is a CB1R inverse agonist with minimal potential for covalent protein binding. Taranabant is an exceptionally potent and selective (900-fold over CB2) CB1R inverse agonist with >500-fold improvement in affinity over the original lead. In a functional assay of cyclic-AMP production, Taranabant is determined to be an inverse agonist (EC_{50} =2.4±1.4 nM)[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Taranabant (MK-0364) dose-dependently inhibits 2 h and overnight food intake as well as overnight gains in body weight in C57BL/6N mice. At the 1- and 3-mg/kg doses (p.o.), Taranabant significantly inhibits 2-h food intake (36 and 69% reductions, respectively; P<0.05 and P<0.00001, respectively) and overnight food intake (13 and 40% reductions, respectively; P<0.05 and P<0.00001, respectively) as well as overnight gains in body weight (48 and 165% reductions, respectively; P<0.01 and P<0.00001, respectively). Taranabant dose-dependently inhibits food intake and weight gain, with an acute minimum effective dose of 1 mg/kg in diet-induced obese (DIO) rats[1]. Taranabant (MK-0364) has a good pharmacokinetic profile in three species (rat, 1 mg/kg iv, 2 mg/kg po, F=74%, $t_{1/2}$=2.7 h; dog, 0.2 mg/kg iv, 0.4 mg/kg po, F=31%; $t_{1/2}$=14 h; rhesus monkey, 0.2 mg/kg iv, 0.4 mg/kg po, F=31%, $t_{1/2}$=3.6 h) and good brain exposure (1 mg/kg iv, brain and plasma concentrations of 0.11 and 0.18 μM at 1 h, respectively)[2].

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PROTOCOL

Kinase Assay [1]

The binding assay is performed by incubating various concentrations of Taranabant (MK-0364) with 0.5 nM [^{3}H]CP 55,940, 1.5 μg of recombinant human CB1R-CHO membranes (or 0.1 μg of human CB2R-CHO membranes) in 50 mM Tris-HCl, pH 7.4, 5 mM $MgCl_2$, 2.5 mM EDTA, 0.5 mg/mL fatty acid-free bovine serum albumin (BSA), 1× proteinase inhibitor mix, and 1% DMSO. After 1-h incubation at 37°C, the reaction is stopped by filtration, and bound radioligand is separated from free radioligand by washing the filter plate. Total specifically bound radiolabel is approximately 10% of the total added radiolabel. Inhibitory IC_{50} values are calculated through nonlinear curve fitting, from which K_i values are then calculated. The CB1R density (B_{max}=5 pmol/mg based on [^{3}H]CP 55,940 binding) in the recombinant human CB1R-CHO membranes is close to that from rat brain membranes (3-5 pmol/mg)[1].

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Animal Administration [1]

Mice[1]

Male C57BL/6N wild-type mice are used. MK-0364 is dissolved or dispersed (with sonication) as a fine homogeneous suspension in 0.225% methylcellulose/10% Tween 80 in water for subsequent oral dosing of mice. All mice are weighed, and vehicle (0.225% methylcellulose/10% Tween 80 in water) or Taranabant (1 or 3 mg/kg) is administered by oral gavage to male mice approximately 30 min before the onset of the dark phase of the light cycle (n=12 per group, age 23 weeks, mean body weight 34.14±0.53 g). Mice are fed ad libitum in the dark phase after dosing. A preweighed aliquot of a highly palatable medium-high fat diet (25% kcal from sucrose, 32% kcal from fat, 4.41 kcal/g) is provided in the food hopper of the cage 5 min before the onset of the dark phase of the light cycle and weighed 2 and 18 h after the onset of the dark phase of the light cycle. In addition, all mice are weighed 18 h after the onset of the dark phase of the light cycle. The study is of crossover design, i.e., vehicle and 1-mk/kg groups are dosed first. After a 4-day washout, the previous vehicle group is dosed with 3 mg/kg Taranabant, and the previous 1-mg/kg group is dosed with vehicle.

Rats[1]

For acute experiments, male Sprague-Dawley DIO rats are randomized into groups (n=6 rats/group) for compound and vehicle dosing. Rats are weighed 17 h after dosing to determine effects on overnight body weight gain. Taranabant is administered orally to DIO rats 1 h before the start of the dark cycle (3:00 PM) at 0.3, 1, and 3 mg/kg p.o. Vehicle is 10% Tween 80 in water, and dosing volume is 2 mL/kg. Powdered food is provided in food cups that are weighed continuously at 5-min intervals over 18 h, and the data are recorded using a computerized system.

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CUSTOMER VALIDATION

- J Biomol NMR. 2018 Aug;71(4):203-211.

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REFERENCES

[1]. Fong TM, et al. Antiobesity Efficacy of a Novel Cannabinoid-1 Receptor Inverse Agonist, N-[(1S,2S)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2 -methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (MK-0364), in Rodents. J Pharmacol Exp T

[2]. Lin LS, et al. Discovery of N-[(1S,2S)-3-(4-Chlorophenyl)-2- (3-cyanophenyl)-1-methylpropyl]-2-methyl-2- {[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (MK-0364), a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity. J M

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