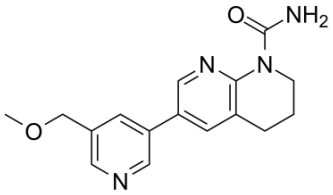
BI 689648

Cat. No.:	HY-101217
CAS No.:	1633009-87-6
Molecular Formula:	$C_{16}H_{18}N_4O_2$
Molecular Weight:	298.34
Target:	Cytochrome P450
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 30 mg/mL (100.56 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.3519 mL	16.7594 mL	33.5188 mL
	5 mM	0.6704 mL	3.3519 mL	6.7038 mL
	10 mM	0.3352 mL	1.6759 mL	3.3519 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 (8.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (8.38 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.38 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BI 689648 is a novel, highly selective aldosterone synthase inhibitor which can inhibit CYP11B1 and CYP11B2 with IC_{50}s of 310 and 2.1 nM, respectively.

IC_{50} & Target

IC50: 310 nM (CYP11B1), 2.1 nM (CYP11B2)[1]

In Vitro

Compare with the FADs and LCI699, BI 689648 is highly selective in vitro, providing an IC_{50} for CYP11B2 of 2.1 nM and a selectivity factor of 149 over CYP11B1. FAD286, by comparison, shows a similar IC_{50} for CYP11B2 (2.5 nM); however, its

	greater potency against CYP11B1 (94 nM) results in a comparatively modest selectivity factor of 38, approximately 4-fold less than BI 689648[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	After oral administration in cyno monkeys, BI 689648 (5 mg/kg) exhibits a peak plasma concentration of ~500 nM. For BI 689648 (aldosterone EC_{50}=2 nM), appreciable changes in 11-DOC are only noted at plasma concentrations >2000 nM or >1000-fold its aldosterone EC_{50} while FAD286 shows a window of ~100-fold. BI 689648 exhibits minimal impact on 11-DC and only at very high plasma concentrations (~10 μM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Homogenized adrenal glands are used to evaluate test compounds (including BI 689648) in a 96-well plate format. A mixture of concentrated homogenate and substrate is added to compound dilutions for analysis. Values for the concentration required to inhibit CS (CYP11B1) and AS (CYP11B2) enzyme activity by 50% (IC_{50}) are calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	For aldosterone synthase inhibitors (ASI) evaluation, the study cohort consists of 66 healthy animals. Each separate study day, 12 cyno monkeys are randomized to receive various doses of ASI or vehicle control (n=3/group); the animals are reused across studies, allowing a minimum of 2 weeks washout between studies. Aggregation of data across multiple studies is used to derive in vivo effective concentration (EC) values for aldosterone and cortisol by curve-fitting. Conscious, nonchaired monkeys receive vehicle (n=35), S-FAD (n=9), FAD286 (n=24), LCI699 (n=36), or BI 689648 (n=26) at doses ranging from 0.003 mg/kg to 10 mg/kg. Maximal adrenocorticotropin (ACTH)-induced aldosterone and cortisol production occurs quickly, within 15 minutes after challenge, at which time blood is collected for plasma aldosterone, cortisol, and test compound concentrations[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Weldon SM, et al. Selectivity of BI 689648, a Novel, Highly Selective Aldosterone Synthase Inhibitor: Comparison with FAD286 and LCI699 in Nonhuman Primates. J Pharmacol Exp Ther. 2016 Oct;359(1):142-50.

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