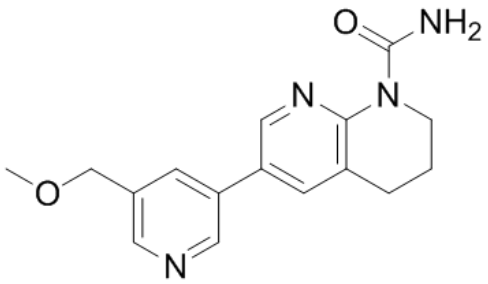
Product Data Sheet

Product Name: BI 689648
Cat. No.: GC32419

Chemical Properties

Cas. No.	1633009-87-6		
SMILES	O=C(N1CCCC2=C1N=CC(C3=CC(COC)=CN=C3)=C2)N		
Formula	$C_{16}H_{18}N_4O_2$	M.Wt	298.34
Solubility	DMSO : 30 mg/mL (100.56 mM)	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

Cell experiment: 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% (IC50) are calculated[1].

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Animal experiment: 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].

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.

Background

BI 689648 is a novel, highly selective aldosterone synthase inhibitor which can inhibit CYP11B1 and CYP11B2 with IC50s of 310 and 2.1 nM, respectively.

Compare with the FADs and LCI699, BI 689648 is highly selective in vitro, providing an IC50 for CYP11B2 of 2.1 nM and a selectivity factor of 149 over CYP11B1. FAD286, by comparison, shows a similar IC50 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].

After oral administration in cyno monkeys, BI 689648 (5 mg/kg) exhibits a peak plasma concentration of ~500 nM. For BI 689648 (aldosterone EC50=2 nM), appreciable changes in 11-DOC are only noted at plasma concentrations >2000 nM or >1000-fold its aldosterone EC50 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].

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[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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