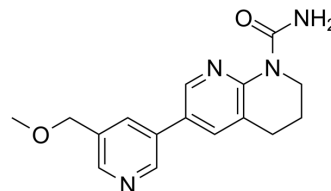


## BI 689648

Cat. No.:	HY-101217		
CAS No.:	1633009-87-6		
Molecular Formula:	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>		
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	2 years
		-20°C	1 year



### SOLVENT & SOLUBILITY

In Vitro	DMSO : 30 mg/mL (100.56 mM; Need ultrasonic and warming)					
		Solvent Concentration	Mass	1 mg	5 mg	10 mg
	Preparing Stock Solutions	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	<ol style="list-style-type: none"> <li>Add each solvent one by one: 10% DMSO &gt;&gt; 40% PEG300 &gt;&gt; 5% Tween-80 &gt;&gt; 45% saline Solubility: ≥ 2.5 mg/mL (8.38 mM); Clear solution</li> <li>Add each solvent one by one: 10% DMSO &gt;&gt; 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (8.38 mM); Clear solution</li> <li>Add each solvent one by one: 10% DMSO &gt;&gt; 90% corn oil Solubility: ≥ 2.5 mg/mL (8.38 mM); Clear solution</li> </ol>					

### BIOLOGICAL ACTIVITY

Description	BI 689648 is a novel, highly selective aldosterone synthase inhibitor which can inhibit CYP11B1 and CYP11B2 with IC <sub>50</sub> s of 310 and 2.1 nM, respectively.
IC <sub>50</sub> & Target	IC <sub>50</sub> : 310 nM (CYP11B1), 2.1 nM (CYP11B2) <sup>[1]</sup>
In Vitro	Compare with the FADs and LCI699, BI 689648 is highly selective in vitro, providing an IC <sub>50</sub> for CYP11B2 of 2.1 nM and a selectivity factor of 149 over CYP11B1. FAD286, by comparison, shows a similar IC <sub>50</sub> 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<sup>[1]</sup>.

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<sub>50</sub>=2 nM), appreciable changes in 11-DOC are only noted at plasma concentrations >2000 nM or >1000-fold its aldosterone EC<sub>50</sub> 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)<sup>[1]</sup>.

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## PROTOCOL

#### Cell Assay <sup>[1]</sup>

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<sub>50</sub>) are calculated<sup>[1]</sup>.

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

#### Animal Administration <sup>[1]</sup>

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<sup>[1]</sup>.

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.

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

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