Talarozole

Cat. No.: HY-14531

CAS No.: 201410-53-9

Molecular Formula: $C_{21}H_{23}N_5S$

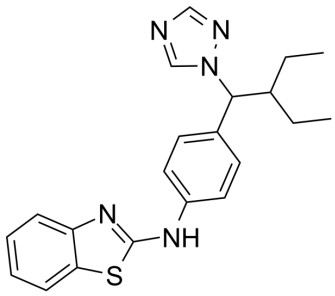
Molecular Weight: 377.51

Target: RAR/RXR; Cytochrome P450; Autophagy

Pathway: Metabolic Enzyme/Protease; Vitamin D Related/Nuclear Receptor; Autophagy

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 : 33.33 mg/mL (88.29 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6489 mL	13.2447 mL	26.4894 mL
	5 mM	0.5298 mL	2.6489 mL	5.2979 mL
	10 mM	0.2649 mL	1.3245 mL	2.6489 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 mg/mL (5.30 mM); Suspended solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2 mg/mL (5.30 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Talarozole (R115866) is an oral systemic all-trans retinoic acid metabolism blocking agent (RAMBA) which increases intracellular levels of endogenous all-trans retinoic acid (RA). Talarozole inhibits both CYP26A1 and CYP26B1 with IC_{50}s of 5.4 and 0.46 nM, respectively.

IC_{50} & Target

CYP26

In Vitro

When HepG2 cells are cotreated with atRA and Talarozole (1 μM), 4-OH-RA and 4-oxo-RA formation is significantly decreased [2].

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

In Vivo	A maximum 84% inhibition of CYP26 activity at 0.5 hours post-dose is predicted based on Talarozole (TLZ) C_{max} of 80 nM and a K_i of 1 nM following a single dose of Talarozole. Due to the short Talarozole half-life (2.2 hrs) CYP26 activity is predicted to return to 100% by 12 hours. In agreement with the predictions, atRA concentrations are increased by 82, 63 and 60% at 4 hours post-dose in the serum, liver and testes, respectively, and concentrations returned to baseline by 24 hours. Following multiple doses of Talarozole, liver CYP26 mRNA and activity are increased suggesting autoinduction of CYP26 due to increased atRA concentrations. In agreement, atRA concentrations are elevated in serum and liver at all timepoints measured. This increase in atRA concentrations is associated with increased mRNA of the mitochondrial biogenesis markers PGC-1β and NRF-1 in comparison to control mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Human liver microsomes (0.2 mg/mL) are incubated with 4-OH-atRA (500 nM) and NADPH, $NADP^+$ or NAD^+ (each at 2 mM) in 100 mM KPi buffer pH 7.4. In addition, 4-OH-atRA is incubated with human liver microsomes in the presence and absence of Talarozole (1 μM), a CYP26A1 specific inhibitor, and Ketoconazole (10 μM) a pan-P450 inhibitor and with NADPH as a cofactor. Following a 5 min pre-incubation, the reactions are initiated with the addition of cofactor and incubated for 30 minutes. At 30 min the reactions are quenched with equal volume of Acetonitrile and centrifuged at 3,000 g for 15 min. The supernatants are collected and 4-oxo-atRA formation is analyzed by LC-MS/MS. All incubations are normalized to a no cofactor control[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Mice[3] Talarozole is administered to mice as a single dose (2.5 mg/kg) or as multiple doses for three days. Serum Talarozole concentrations and serum, liver and testes atRA concentrations are measured by LC-MS/MS. Inhibition of CYP26 and changes inatRA concentrations in each tissue are predicted based on CYP26 activity in vitro and Talarozole disposition. Markers of fatty acid oxidation in the liver and spermatogonial differentiation in the testes are measured following Talarozole treatment. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Dev Cell. 2018 Dec 17;47(6):711-726.e5.
- Neurosci Bull. 2023 Aug 28.
- J Cell Physiol. 2018 Feb;233(2):1129-1145.
- J Enzyme Inhib Med Chem. 2016;31(sup2):148-161.
- Development. 2019 May 13;146(12). pii: dev173088.

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REFERENCES

[1]. Diaz P, et al. Development and Characterization of Novel and Selective Inhibitors of Cytochrome P450 CYP26A1, theHuman Liver Retinoic Acid Hydroxylase. J Med Chem. 2016 Mar 24;59(6):2579-95.

[2]. Topletz AR, et al. Induction of CYP26A1 by metabolites of retinoic acid: evidence that CYP26A1 is an important enzyme in theelimination of active retinoids. Mol Pharmacol. 2015;87(3):430-41.

[3]. Faith Stevison, et al. CYP26 Inhibition Increases Retinoic Acid Concentrations in Target Tissues and Alters Retinoid Signaling

[4]. Tripathy S, et al.All-Trans-Retinoic Acid Enhances Mitochondrial Function in Models of Human Liver. Mol Pharmacol. 2016 May;89(5):560-74.

[5]. Bovenschen HJ, et al. Oral retinoic acid metabolism blocking agent Rambazole for plaque psoriasis: an immunohistochemical study. Br J Dermatol. 2007 Feb;156(2):263-70.

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