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产品名称：Talarozole
产品别名：他拉罗唑；R115866

生物活性：

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	IC50: 0.46/5.1 nM (CYP26B1/A1)[1]
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].
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, *at*RA 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 *at*RA concentrations. In agreement, *at*RA concentrations are elevated in serum and liver at all timepoints measured. This increase in *at*RA concentrations is associated with increased mRNA of the mitochondrial biogenesis markers PGC-1β and NRF-1 in comparison to control mice[3].

Solvent&Solubility

In Vitro:

DMSO： ≥ 36 mg/mL (95.36 mM)

* "≥" means soluble, but saturation unknown.

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (6.62 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.62 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；

	向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (6.62 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.62 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.62 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.62 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	Human liver microsomes (0.2 mg/mL) are incubated with 4-OH-*at*RA (500 nM) and NADPH, $NADP^+$ or NAD^+ (each at 2 mM) in 100 mM KPi buffer pH 7.4. In addition, 4-OH-*at*RA 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-*at*RA formation is analyzed by LC-MS/MS. All incubations are normalized to a no cofactor control[2].
Animal Administration	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 *at*RA concentrations are measured by LC-MS/MS. Inhibition of CYP26 and changes in*at*RA 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.
	[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

References	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.