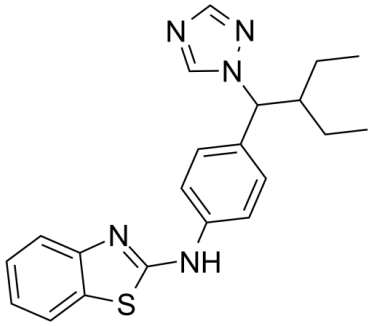
Data Sheet

Product Name:	Talarozole
Cat. No.:	CS-1343
CAS No.:	201410-53-9
Molecular Formula:	C21H23N5S
Molecular Weight:	377.51
Target:	Autophagy; Cytochrome P450; RAR/RXR
Pathway:	Autophagy; Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 36 mg/mL (95.36 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 0.46/5.1 nM (CYP26B1/A1)[1] **In Vitro:** When HepG2 cells are cotreated with atRA and Talarozole (1 μ M), 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, 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Talarozole is dissolved in DMSO and stored, and then diluted with appropriate medium before use[2].[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]. **Animal Administration:** Talarozole is dissolved in DMSO and then diluted with PBS or saline[3].[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.

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.

CAIndexNames:

2-Benzothiazolamine, N-[4-[2-ethyl-1-(1H-1,2,4-triazol-1-yl)butyl]phenyl]-

SMILES:

CCC(CC)C(C1=CC=C(NC2=NC3=CC=CC=C3S2)C=C1)N4N=CN=C4

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA