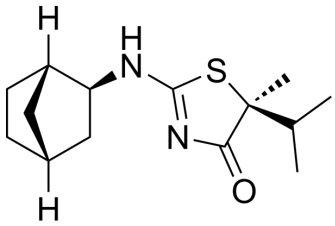
AMG-221

Cat. No.:	HY-10555
CAS No.:	1095565-81-3
Molecular Formula:	$C_{14}H_{22}N_2OS$
Molecular Weight:	266.4
Target:	11β-HSD
Pathway:	Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

AMG-221 is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) with a K_i of 12.8 nM in vitro biochemical scintillation proximity assay (SPA) and an IC_{50} of 10.1 nM in cell-based assays[1][2]. AMG-221 can be used for the research of type 2 diabetes[3].

In Vitro

AMG-221 shows selectivity over 11β-HSD2, 17β-HSD1, and glucocorticoid receptor (GR) (IC_{50} values for all assays are >10 μM)[2].

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

In Vivo

AMG-221 (25 or 50 mg/kg; b.i.d.; orally gavaged) inhibits 11β-HSD1 activity in DIO mice. At the end of the study, fed blood glucose shows statistically significant reduction in comparison to the vehicle group. On day 14 and after a 12 h fast, glucose tolerance is slightly improved in the AMG-221 treatment groups compared with the vehicle group[2].

11β-HSD1 activity is inhibited by 33%, 55%, and 47% in the inguinal fat at 4 h after AMG-221 is orally gavaged at 5, 15, and 50 mg/kg, respectively. At 8 h, the 11β-HSD1 activity in the inguinal fat of the 5 mg/kg group has returned to a level (-10% inhibition) close to that in the control animals treated with vehicle, but there is still significant inhibition in the 15 and 50 mg/kg groups (36% and 39% inhibition, respectively)[2].

AMG-221 has a good bioavailability in mouse, rat, and dog. However, the bioavailability in monkey is low[2].

AMG-221 exhibits moderate oral bioavailability (male CD1 mouse 31%) following oral administration (10 mg/kg)[3].

AMG-221 exhibits terminal elimination half-life (male CD1 mouse 3.32 h) due to high plasma clearance (3.31 L/h/kg) combined with large volumes of distribution (0.9 L/kg) following intravenous administration (2 mg/kg)[3].

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Animal Model:	Diet-Induced Obesity (DIO) Mice[2]
Dosage:	25 or 50 mg/kg (prepare in 0.1% Tween-80 and 0.5% CMC in water)
Administration:	Orally gavaged; twice a day for 13 or 14 days
Result:	There were statistically significant decreases in insulin levels in all treated groups when compared with the vehicle control group on day 13.

REFERENCES

[1]. Seb Caille, et al. Two asymmetric syntheses of AMG 221, an inhibitor of 11beta-hydroxysteroid dehydrogenase type 1.J Org Chem. 2009 May 15;74(10):3833-42.

[2]. Murielle M Véniant, et al. Discovery of a potent, orally active 11beta-hydroxysteroid dehydrogenase type 1 inhibitor for clinical study: identification of (S)-2-((1S,2S,4R)-bicyclo[2.2.1]heptan-2-ylamino)-5-isopropyl-5-methylthiazol-4(5H)-one (AMG 221). J Med Chem. 2010 Jun 10;53(11):4481-7.

[3]. Aiwen Li, et al. Synthesis and Evaluation of the Metabolites of AMG 221, a Clinical Candidate for the Treatment of Type 2 Diabetes. ACS Med Chem Lett. 2011 Sep 13;2(11):824-7.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

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