
Product Data Sheet

Product Name: Istaroxime

Cat. No.: GC11448

Chemical Properties

Cas. No. 203737-93-3

Chemical Name (E)-3-((2-aminoethoxy)imino)-10,13-dimethyldodecahydro-1H-cyclopenta[a]phenanthrene-6,17(10H,14H)-dione

SMILES CC12CC/C(CC1C(CC3C2CCC4(C)C3CCC4=O)=O)=N\OCCNFormula $C_{21}H_{32}N_2O_3$ M.Wt 360.49

Solubility Soluble in Water Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.

Structure **Protocol**

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

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Kinase experiment:

Dog or guinea pig kidney outer medulla is homogenized with a Polytron in 250 mM sucrose and 30 mM histidine, at pH 7.2. The homogenate is centrifuged at 6,000g for 15 min at 4°C and the supernatant at 48,000g for 30 min at 20°C with SDS and then layered onto a discontinuous sucrose density gradient (10, 15, and 29%) and centrifuged at 60,000 rpm for 115 min at 4°C. The pellet is resuspended in 25 mM imidazole and 1 mM EDTA, pH 7.5. Protein content is measured. Na⁺/K⁺-ATPase activity is measured after the release of ³²P from [³²P]ATP. Increasing concentrations of compounds are preincubated with purified enzyme for 10 min at 37°C in 120 μL of final volume of medium containing 140 mM NaCl, 3 mM MgCl₂, 50 mM HEPES-Tris, and 3 mM ATP, pH 7.5. After preincubation, 10 μL of incubation solution containing 10 mM KCl and 20 nCi of [³²P]ATP (0.5-3 Ci/mmol) is added, and the reaction is carried out for 15 min at 37°C before being stopped by acidification with 30% (v/v) perchloric acid. ³²P is separated by centrifugation with activated charcoal and radioactivity measured by liquid scintillation counting. Inhibitory activity is expressed as percentage of control sample, carried out in the absence of standard compound. IC₅₀ is calculated by weighed nonlinear regression curve fitting to the mass-action equilibrium[3].

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Animal experiment:

Pigs[3] Male guinea Pigs (350-450 g) are used. Istaroxime (300 µg/kg) or Digoxin (75 µg/kg) are given by i.v. bolus 10 and 20 min before starting the exercise, respectively, and compared with vehicle. The following variables, HR, ECG, LVP, and aortic pressures, are recorded through a computerized acquisition system, which calculated the left ventricular rates of pressure changes. Data are analyzed from the real-time digitized recordings. Control values are obtained before compound administration.

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References:

[1]. Gobbini M, et al. Novel analogues of istaroxime, a potent inhibitor of Na⁺,K⁺-ATPase: synthesis and structure-activity relationship. J Med Chem. 2008 Aug 14;51(15):4601-8.

[2]. Gobbini M, et al. Novel analogues of Istaroxime, a potent inhibitor of Na(+),K(+)-ATPase: Synthesis, structure-activity relationship and 3D-quantitative structure-activity relationship of derivatives at position 6 on the androstane scaffold. Bioorg Med Ch

[3]. Micheletti R, et al. Pharmacological profile of the novel inotropic agent (E,Z)-3-((2-aminoethoxy)imino)androstane-6,17-dione hydrochloride (PST2744). J Pharmacol Exp Ther. 2002 Nov;303(2):592-600.

Background

Description: IC₅₀ Value: 0.43 ± 0.15 μM (Na⁺/K⁺-ATPase activity from dog kidney) [1] Istaroxime is a positive inotropic agent that mediates its action through inhibition of sodium/potassium adenosine triphosphatase (Na⁺/K⁺ ATPase). Istaroxime is an investigational drug originally patented and developed by the Italian pharmaceutical

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company Sigma-Tau. Istaroxime is now under development for treatment of acute decompensated heart failure by CVie Therapeutics. *in vitro*: PST2744 inhibited the Na⁺/K⁺-ATPase activity from dog kidney with an IC₅₀ value of 0.43 ± 0.15 μM [1]. The transient inward current (I(TI)) induced by a Ca(2⁺) transient in the presence of complete Na(+)/K(+) pump blockade was inhibited (-43%) by PST2744 but not by digoxin [2]. *in vivo*: Intravenous infusion of 0.2 mg/kg/min PST2744 in anesthetized guinea pigs exerted an immediate and long-lasting inotropic effect (ED(80) of 1.89 +/- 0.37 mg/kg) without causing lethal arrhythmias up to a cumulative dose of 18 mg/kg [1]. Istaroxime intravenous infusion (0.11 mg/kg per min) significantly increased both indices of contraction and relaxation (fractional shortening, +18+/-3.7%; aortic flow rate, +19+/-2.9%; peak myocardial systolic velocity, +36+/-7%; circumferential fiber shortening, +24+/-4.1%; peak atrial flow velocity, +69+/-8.6%; isovolumic relaxation time, +19+/-6.9%; and peak myocardial early diastolic velocity, +42+/-12%) [3]. In 5 animals, PST-2744 effects were compared with dobutamine. Heart rates, PR intervals and QT intervals were unchanged following PST-2744 administration. PST-2744 increased contractility (+dP/dt) by 56% from 1881 +/- 282 mm Hg/s to 2939 +/- 734 mm Hg/s (P < 0.01) [4]. Clinical trial: HORIZON-HF: A Phase II Trial to Assess Hemodynamic Effects of Istaroxime in Patients With Worsening HF and Reduced LV Systolic Function. Phase 2

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