

Product Data Sheet

Product Name: JANEX-1

Cat. No.: GC14671

Chemical Properties

Cas. No. 202475-60-3

Chemical Name 4-[(6,7-dimethoxyquinazolin-4-yl)amino]phenol

SMILES COC1=C(C=C2C(=C1)C(=NC=N2)NC3=CC=C(C=C3)O)OC

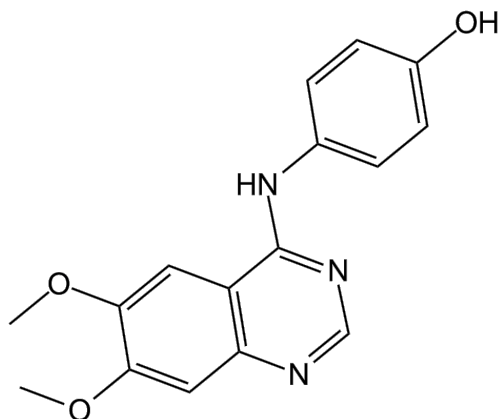
Formula $C_{16}H_{15}N_3O_3$ M.Wt 297.31

Solubility ≥ 11.65 mg/mL in DMSO, ≥ 2.53 mg/mL in Water with ultrasonic and warming
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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Cell experiment: The following cell lines are used in various biological assays: NALM-6 (pre-B-ALL), LC1;19 (pre-B-ALL), DAUDI (B-ALL), RAMOS (B-ALL), MOLT-3 (T-cell ALL), HL60 (acute myelogenous leukemia), BT-20 (breast cancer), M24-MET (melanoma), SQ20B (squamous cell carcinoma), and PC3 (prostate cancer). These cell lines are maintained in culture. Cells are seeded in six-well tissue culture plates at a density of 50×10^4 cells/well in a treatment medium containing various concentrations of JANEX-1 (0.1, 0.2, 0.3, 0.4 and 0.5 nM) and incubated for 24-48 h at 37°C in a humidified 5% CO₂ atmosphere. Cells are examined for apoptotic changes after treatment with JANEX-1 by the in situ TdT-mediated dUTP end-labeling assay using the ApopTag apoptosis detection kit[1].

Animal experiment: Mice[2] Pathogen-free 8-week-old male JAK3^{-/-} (129S4-Jak3^{tm1Ljb}) and C57BL/6 J mice are used. Mice are treated with JANEX-1 at a dose of 20 mg/kg (intraperitoneally) at 1 h before ischemia. Rats[3] Male Lewis rats are divided into two experimental groups of five and are injected either i.v. via the dorsal vein of the penis or i.p. with a single 3.3 mg/kg bolus dose of JANEX-1. The rats are anesthetized by the methoxyfluran, and blood samples (0.2 mL) are collected from rat tail vein before and at 5, 10, and 30 min and 1, 1.5, 2, 3, 4, and 6 h after i.v. injections or at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, and 7 h after i.p. injections.

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References:

- [1]. Sudbeck EA, et al. Structure-based design of specific inhibitors of Janus kinase 3 as apoptosis-inducing antileukemic agents. Clin Cancer Res. 1999 Jun;5(6):1569-82.
- [2]. Oh YB, et al. Inhibition of Janus activated kinase-3 protects against myocardial ischemia and reperfusion injury in mice. Exp Mol Med. 2013 May 17;45:e23
- [3]. Uckun FM, et al. In vivo toxicity and pharmacokinetic features of the janus kinase 3 inhibitor WHI-P131 [4-(4'hydroxyphenyl)-amino-6,7- dimethoxyquinazoline. Clin Cancer Res. 1999 Oct;5(10):2954-62.
- [4]. Xia F, et al. IL4 (interleukin 4) induces autophagy in B cells leading to exacerbated asthma. Autophagy. 2018;14(3):450-464.

Background

Janex-1 is an ATP-competitive and specific inhibitor of JAK3 with IC50 value of 78 μ M [1].

Janus kinase 3 (JAK3) is a tyrosine kinase which belongs to the Janus kinase family. It is associated with the type I cytokine receptors that use common gamma chain, and provides enzymatic activity to the receptor. When ligands bind to the receptor, the conformational change of the receptor will activate the JAK3 and thus initiate downstream signaling. JAK3 interacts with actin-binding protein villin, and subsequently promote cytoskeletal remodeling and mucosal wound repair.

When tested with human lymphoblastoid B-cell line, Janex-1 showed significant inhibitory effect on JAK3 activity, but do not affect other types of tyrosine kinases, including Janus family tyrosine kinase JAK1 and JAK2, the ZAP/SYK family tyrosine kinase SYK, the TEC family tyrosine kinase BTK, the SRC family tyrosine kinase LYN. It suggested Janex-1 was highly specific to JAK3 inhibition [1]. Pretreated mouse islet with Janex-1 showed resistance to cytokine toxicity, i.e. the decreased NO synthase (iNOS) expression and thereby the nitric oxide (NO) production and subsequent islet damage. The molecular mechanism was considered that Janex-1 inhibit iNOS expression via inhibit JAK3 and other signaling transduction [2].

In NOD mouse model of type 1 diabetes, 60% of control mice became diabetic after 25 weeks. However, injection of Janex-1 (100 mg/kg/day) from week 10 to week 25 resulted in only 9% mice became diabetic. Because type 1 diabetes was caused by JAK3 and downstream signaling, the

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suppression of diabetes onset suggested the inhibition of JAK3 by Janex-1 [3].

References:

- [1] Sudbeck E A et al. , Structure-based Design of Specific Inhibitors of Janus Kinase 3 as Apoptosis-inducing Antileukemic Agents. Clinical cancer research. 2007, 5: 1569-1582.
- [2] Lv N et al. , JANEX-1, a JAK3 inhibitor, protects pancreatic islets from cytokine toxicity through downregulation of NF- κ B activation and the JAK/STAT pathway. Experimental cell research. 2009, 315 (12): 2064-2071.
- [3] Cetkovic-Cvrlje M et al. , Targeting JAK3 with JANEX-1 for prevention of autoimmune type 1 diabetes in NOD mice. Clinical immunology. 2003, 106: 213-225.

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