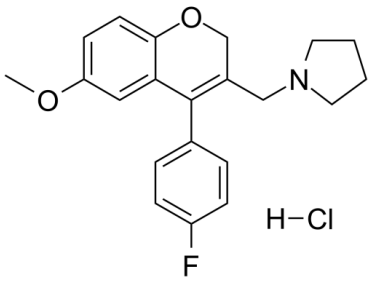
Data Sheet

Product Name:	AX-024 hydrochloride
Cat. No.:	CS-8002
CAS No.:	1704801-24-0
Molecular Formula:	C21H23ClFNO2
Molecular Weight:	375.86
Target:	IFNAR; Interleukin Related; TNF Receptor
Pathway:	Apoptosis; Immunology/Inflammation
Solubility:	H2O : 16.67 mg/mL (44.35 mM; Need ultrasonic); DMSO : 33 mg/mL (87.80 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

AX-024 hydrochloride is an orally available, first-in-class inhibitor of the **TCR-Nck** interaction that selectively inhibits TCR-triggered T cell activation with an **IC_{50}** ~1 nM. AX-024 hydrochloride modulates cell signaling by targeting **SH3** domains. AX-024 hydrochloride has low-acute toxicity and high potency and selectivity, and strongly inhibit the production of **IL-6**, **TNF-α**, **IFN-γ**, **IL-10** and **IL-17A**. IC50 & Target: IL-6, TNFα, IFN-γ, IL-10 and IL-17A[1] **In Vitro:** AX-024 hydrochloride is >10,000-fold more potent than the AX-000 hit in terms of inhibition of TCR-triggered T cell proliferation. The IC_{50} of AX-024 hydrochloride in this assay is 1 nM, although it shows inhibitory effects at a concentration of 1 pM or less. AX-024 hydrochloride is also a much more potent inhibitor of cytokine release by human peripheral blood mononuclear cells stimulated with anti-CD3 than AX-000, strongly hindering interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), interferon-γ (IFN-γ), IL-10, and IL-17A production at a concentration of 10 nM. In $CD8^+$ T cells of OT1 TCR transgenic ($OT1^{Tg}$) mice bearing wild-type (WT) AX-024 hydrochloride strongly inhibits T cell proliferation at a concentration of 0.1 nM when $OT1^{Tg}$ T cells are WT for the PRS mutation. Coimmunoprecipitation experiments in these cells show that Nck recruitment to the TCR is induced upon stimulation in the absence of drug but is inhibited in the presence of AX-024 hydrochloride in a dose-dependent manner at concentrations starting from 1 nM[1]. **In Vivo:** The AX-024 hydrochloride-treated group presents less scales and reduces skin thickening compare to the vehicle group. AX-024 hydrochloride significantly reduces thickening of both skin layers, but more effectively of the dermis, which rather resembles that of mice treated with a control cream lacking imiquimod (IMQ). AX-024 hydrochloride significantly diminishes the number of airway inflammatory cells in both assays. Mice receiving AX-024 hydrochloride rapidly recovers from neurological impairment and weight loss, becoming symptom-free by day 30, unlike mice that receives the vehicle, in which ataxia and loss of the righting reflex persist[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]Spleen B cells from C57BL/6 mice are labeled with Cell Trace Violet and incubated for 72 hours with either anti-IgM (10 mg/mL) or anti-CD40 (5 mg/mL), supplemented with IL-4 (5 ng/mL) or LPS (2.5 mg/mL) in the presence of different concentrations of AX-024 hydrochloride. Proliferation is calculated according to the total number of cell divisions[1]. **Animal Administration:** [1]Eight-week-old CD-1 mice are injected intraperitoneally with different amounts of the AX-024 hydrochloride dissolved in 0.5 mL of saline. All animals are observed clinically for the appearance of macroscopically visible adverse reactions twice daily over 14 days, as well as immediately after AX-024 hydrochloride administration. A necropsy is carried out on each animal on day 14, and the abdominal, thoracic, and cranial cavities are examined in situ, together with their associated organs[1].

References:

[1]. Borroto A, et al. First-in-class inhibitor of the T cell receptor for the treatment of autoimmune diseases. Sci Transl Med. 2016 Dec 21;8(370):370ra184.

CAIndexNames:

Pyrrolidine, 1-[[4-(4-fluorophenyl)-6-methoxy-2H-1-benzopyran-3-yl]methyl]-, hydrochloride (1:1)

SMILES:

COC1=CC=C(OC2)C(C(C3=CC=C(F)C=C3)=C2CN4CCCC4)=C1.[H]Cl

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