GDC-0834

Cat. No.: HY-15427

CAS No.: 1133432-49-1

Molecular Formula: $C_{33}H_{36}N_6O_3S$

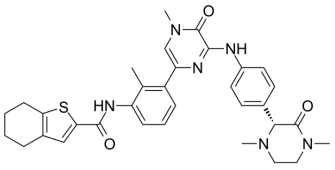
Molecular Weight: 596.74

Target: Btk

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 32 mg/mL (53.62 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.6758 mL	8.3789 mL	16.7577 mL
5 mM	0.3352 mL	1.6758 mL	3.3515 mL
10 mM	0.1676 mL	0.8379 mL	1.6758 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

GDC-0834 is a potent and selective BTK inhibitor. GDC-0834 inhibits BTK with an in vitro IC_{50} of 5.9 and 6.4 nM in biochemical and cellular assays, respectively, and in vivo IC_{50} of 1.1 and 5.6 μM in mouse and rat, respectively.

IC_{50} & Target

IC50: 5.9 nM (BTK)[1]

In Vitro

GDC-0834 suppresses BTK kinase activity with an IC_{50} value of 5.9±1.1 nM with Hill slope value of −0.84±0.07 (mean±S.E.)[1]. GDC-0834 is shown to be a potent reversible inhibitor of six known aldehyde oxidase (AO) substrates with IC_{50} values ranging from 0.86 to 1.87 μM[2].

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

In Vivo

The treatment of BALB/c mice with GDC-0834 results in dose-dependent inhibition of pBTK-Tyr223. Animals dosed with 150 or 100 mg/kg GDC-0834 for 2 h show complete inhibition of pBTK-Tyr223 levels in blood, with a mean inhibition of 97 and 96%, respectively. In the rat CIA study, GDC-0834 inhibits pBTK-Tyr223 in rat blood in a dose-dependent manner. The IC_{50} estimate of pBTK-Tyr223 inhibition in rats is determined to be 5.6±1.6 μM with m of 0.51±0.087 (mean±S.E.)[1].

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PROTOCOL

Kinase Assay [1]

Btk activity is quantified by determining phosphorylation of an exogenous peptide product in a Lanthascreen assay. The K_m values for ATP and peptide are also assessed before selecting the final reaction conditions. In a final reaction volume of 25 µL, Btk [human, full-length, C-terminal V5-6× His, expressed in Sf9 cells; 0.075 ng/25 µL reaction) is incubated with 50 mM HEPES, pH 7.5, 10 mM $MgCl_2$, 2 mM $MnCl_2$, 2 mM dithiothreitol, 0.2 mM $NaVO_4$, 0.01% casein, 0.01% Triton X-100, 2.5% glycerol, and 0.4 µM fluorescein poly-Glu/Ala/Tyr]. The reaction is initiated by the addition of ATP to 25 µM (K_m of ATP). After incubation for 60 min at room temperature, the reaction is stopped by the addition of a final concentration of 2 nM Tb-PY20 detection antibody in 60 mM EDTA for 30 min at room temperature. Detection is determined on a PerkinElmer Envision with 340 nM excitation and emission at 495 and 520 nm. The response versus BTK inhibitor concentration data are fitted with GraphPad Prism version 5.00[1].

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Animal Administration [1]

Mice[1]

To investigate the in vivo potency of GDC-0834 on inhibiting pBTK-Tyr223 in blood in mice, BALB/c mice are dosed orally with GDC-0834 at 25, 50, 100, and 150 mg/kg, and the terminal blood samples are collected from mice at 2, 4, or 6 h postdose. Three animals per each time point are sacrificed for the blood sampling. GDC-0834 plasma levels are quantitated using LC/MS/MS as described below. Levels of BTK-pTyr223 (pBTK) and total BTK are determined in blood by Western blot. A rabbit polyclonal pBTK and a mouse monoclonal total BTK are used. The bands are quantified with LI-COR Odyssey imager and software. The pBTK is normalized to total BTK in each sample. Normalized values for each sample are then compared with values from normalized vehicle-treated blood samples to determine the percentage of inhibition of BTK-Tyr223 phosphorylation in the sample. Specifically, the following equation is used: percentage of inhibition of pBTK=(1−(normalized pBTK of test sample/normalized pBTK of vehicle-treated sample))×100. A secondary objective of this study is to investigate any time delays in effect by examining the time course of pBTK inhibition relative to the GDC-0834 blood concentrations. No hysteresis is evident in plots of pBTK inhibition versus GDC-0834 concentration.

Rats[1]

Arthritis is induced in female Lewis rats at Bolder BioPATH. In brief, animals (10 rats per group) are anesthetized with isoflurane and injected with 300 µL of Freund's incomplete adjuvant containing 2 mg/mL bovine type II collagen at the base of the tail and two sites on the back on days 0 and 6. Oral dosing of GDC-0834 [vehicle, 1, 3, 10, 30, and 100 mg/kg b.i.d. (twice daily) at 12-h intervals, vehicle, 10, 30, 100 mg/kg once daily (QD) at 24-h intervals, and 100 mg/kg every other day (Q2D) at 48 intervals] is initiated on day 0 of the study and continued through day 16. The caliper measurements of ankles are taken every day starting from day 9 to day 17, and the area under the ankle diameter-time curves are calculated based on the trapezoidal rule. After final body weight measurement on day 17, animals are anesthetized for terminal serum collection and then euthanized for tissue collection. Ankle diameters are also measured in the normal rats treated with the vehicle (n=6).

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REFERENCES

[1]. Liu L, et al. Antiarthritis effect of a novel Bruton's tyrosine kinase (BTK) inhibitor in rat collagen-induced arthritis and mechanism-based pharmacokinetic/pharmacodynamic modeling: relationships between inhibition of BTK phosphorylation and efficacy. J

[2]. Sodhi JK, et al. A novel reaction mediated by human aldehyde oxidase: amide hydrolysis of GDC-0834. Drug Metab Dispos. 2015 Jun;43(6):908-15

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

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