Nemtabrutinib

Cat. No.: HY-112215

CAS No.: 2095393-15-8

Molecular Formula: $C_{25}H_{23}ClN_4O_4$

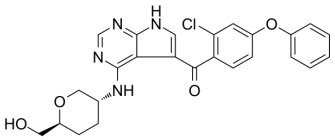
Molecular Weight: 478.93

Target: Btk

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 50 mg/mL (104.40 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0880 mL	10.4399 mL	20.8799 mL
5 mM	0.4176 mL	2.0880 mL	4.1760 mL
10 mM	0.2088 mL	1.0440 mL	2.0880 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.34 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.34 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.34 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

ARQ 531 (MK-1026) is a reversible non-covalent and orally active inhibitor of Bruton's Tyrosine Kinase (BTK), with IC_{50}s of 0.85 nM and 0.39 nM for WT-BTK and C481S-BTK, respectively.

IC_{50} & Target

IC50: 0.85 nM (WT-BTK), 0.39 nM (C481S-BTK)[1].

In Vitro

ARQ 531 shows strong target inhibition in TMD8 cell line. The IC_{50} values are 0.85 nM and 0.39 nM for WT-BTK and C481S-

	BTK, respectively, in biochemical assay. Additionally, ARQ 531 also shows strong inhibition of TEK kinases with IC_{50}s of 5.23 nM (BMX), 5.80 nM (TEC), 36.4 nM (TXK). The IC_{50}s of ARQ 531 for SRC kinases are 3.86 nM (LCK), 4.22 nM (YES), 9.71 nM (BLK), 18.3 nM (HCK), 18.8 nM (LYNa), 25.9 nM (FGR), 32.2 nM (FYN), 48.0 nM (FRK) and for TRK kinases are 11.7 nM (TrkB), 13.1 nM (TrkA), 19.1 nM (TrkC). ARQ 531 inhibits proliferation of diverse types of cell lines (TMD8: GI_{50}=0.13 μM, REC1: GI_{50}=0.18 nM) and shows potency in cell lines that are addict to BCR, Src-family kinase and PI3K/AKT pathways. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	ARQ 531 is efficacious in TMD-8 tumor xenograft model. ARQ 531 causes complete tumor regression after 14 days of treatment. ARQ 531 is also efficacious in collagen induced arthritis model. ARQ 531 demonstrates potent efficacy against arthritis in mouse model. In the BTK driven TMD8 xenograft mouse model, ARQ 531 demonstrates excellent anti-tumor activity with durable response. ARQ 531 demonstrates in vivo efficacy in a mouse collagen-induced arthritis (CIA) model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Biochemical inhibition assay is measured using full length BTK constructs of wild type or C481S mutant. Profiling on 236 kinases identifies 45 kinases with >50% inhibition at 200 nM concentration of ARQ 531. Subsequently, the potency of this ATP competitive inhibitor is determined on such kinases at the physiological 1 mM ATP concentration cells are treated with increasing concentrations of inhibitors in SUDHL-4 for 2 hours, following stimulation with either anti-IgM or growth factors cells are lysed for Western blot analysis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Six week old female CB-17 SCID mice (1-2 weeks) are used. Mice are housed in sterile micro isolator cages, five mice per cage and receive food and water ad libitum. Female SCID mice are implanted subcutaneously with $8x10^6$ TMD8 cells in 0.2 mL HBSS with 50% standard concentration BD matrigel in the upper right flank area. Mice are monitored and staged on day 14 (post injection of tumor cells) when size reaches approximately 400 mg. Oral daily dosing with ARQ 531 at 100 mg/kg or vehicle began on stage day. Tumor measurements and body weights are collected three times a week. In vivo Target and pathway inhibition is studied in mouse TMD8 xenograft model. Percent inhibition relative to the vehicle control is determined using densitometry analysis and the intensity of actin band is used as a loading control and the percentage of vehicle group is designated as 100%. DBA1/J mice are immunized with collagen to develop the arthritis, following the onset of arthritis, mice are randomized into treatment groups. Treatment is initiated by oral dosing of ARQ 531 at 25, 50 and 75 mg/kg and continued daily through arthritis day 14. Clinical scores are assessed for each of the paws on study arthritis days 1-15[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Biomed Chromatogr. 2020 Nov;34(11):e4937.

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REFERENCES

[1]. S Eathiraj, et al. Targeting PCI-32765-Resistant BTK-C481S Mutation with ARQ 531, a Reversible Non-Covalent Inhibitor of BTK. Clinical Lymphoma Myeloma & Leukemia, 2016, 16: S47-S48.

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

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