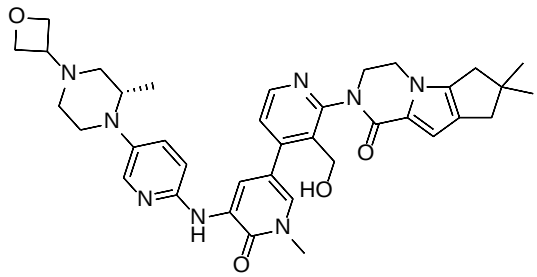
Product data sheet

MedKoo Cat#: 206475 Name: Fenebrutinib free base CAS#: 1434048-34-6 (free base) Chemical Formula: $C_{37}H_{44}N_8O_4$ Exact Mass: 664.3486 Molecular Weight: 664.81	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Fenebrutinib, also known as GDC-0853, is orally available inhibitor of Bruton's tyrosine kinase (BTK) with potential antineoplastic activity. Upon administration, GDC-0853 inhibits the activity of BTK and prevents the activation of the B-cell antigen receptor (BCR) signaling pathway. This prevents both B-cell activation and BTK-mediated activation of downstream survival pathways, which leads to the inhibition of the growth of malignant B-cells that overexpress BTK. BTK, a member of the Src-related BTK/Tec family of cytoplasmic tyrosine kinases, is overexpressed in B-cell malignancies; it plays an important role in B-lymphocyte development, activation, signaling, proliferation and survival.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under “QC And Documents” section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMF	20.0	30.08
DMSO	17.0	25.57
DMSO:PBS (pH 7.2) (1:2)	0.33	0.50
Ethanol	5.0	7.52

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	1.50 mL	7.52 mL	15.04 mL
5 mM	0.30 mL	1.50 mL	3.01 mL
10 mM	0.15 mL	0.75 mL	1.50 mL
50 mM	0.03 mL	0.15 mL	0.30 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of “Calculator”

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Jones NS, Yoshida K, Salphati L, Kenny JR, Durk MR, Chinn LW. Complex DDI by Fenebrutinib and the Use of Transporter Endogenous Biomarkers to Elucidate the Mechanism of DDI. Clin Pharmacol Ther. 2020 Jan;107(1):269-277. doi: 10.1002/cpt.1599. Epub 2019 Sep 16. PMID: 31376152; PMCID: PMC6977399.
2. Crawford JJ, Johnson AR, Misner DL, Belmont LD, Castanedo G, Choy R, Coraggio M, Dong L, Eigenbrot C, Erickson R, Ghilardi N, Hau J, Katewa A, Kohli PB, Lee W, Lubach JW, McKenzie BS, Ortwine DF, Schutt L, Tay S, Wei B, Reif K, Liu L, Wong H, Young WB. Discovery of GDC-0853: A Potent, Selective, and Noncovalent Bruton's Tyrosine Kinase Inhibitor in Early Clinical Development. J Med Chem. 2018 Mar 22;61(6):2227-2245. doi: 10.1021/acs.jmedchem.7b01712. Epub 2018 Feb 23. PMID: 29457982.

In vivo study

Product data sheet

1. Crawford JJ, Johnson AR, Misner DL, Belmont LD, Castanedo G, Choy R, Coraggio M, Dong L, Eigenbrot C, Erickson R, Ghilardi N, Hau J, Katewa A, Kohli PB, Lee W, Lubach JW, McKenzie BS, Ortwine DF, Schutt L, Tay S, Wei B, Reif K, Liu L, Wong H, Young WB. Discovery of GDC-0853: A Potent, Selective, and Noncovalent Bruton's Tyrosine Kinase Inhibitor in Early Clinical Development. J Med Chem. 2018 Mar 22;61(6):2227-2245. doi: 10.1021/acs.jmedchem.7b01712. Epub 2018 Feb 23. PMID: 29457982.

7. Bioactivity

Biological target: Fenebrutinib (GDC-0853) is a bruton's tyrosine kinase (Btk) inhibitor with Kis of 0.91 nM, 1.6, 1.3, 12.6, and 3.4 nM for WT Btk, and the C481S, C481R, T474I, T474M mutants.

In vitro activity

In isolated primary human B cells, GDC-0853 potently inhibited anti-IgM-induced Btk Y223 tyrosine phosphorylation (IC50 = 3.1 nM) and anti-IgM and CD40L-induced B-cell proliferation (IC50 = 1.2 nM and 1.4 nM, respectively) (Table 8). Btk inhibition by GDC-0853 prevented FcγRIII-triggered TNFα production in human monocytes (IC50 = 1.3 nM). In human blood, GDC-0853 potently inhibited up-regulation of the early activation marker CD69 on B cells after overnight anti-IgM stimulation (IC50 = 8 nM). Furthermore, GDC-0853 also suppressed anti-IgM induced Btk Y223 autophosphorylation in human whole blood (IC50 = 11 nM). Taken together, these data demonstrate that GDC-0853 is a highly selective Btk inhibitor that blocks both B-cell BCR and monocyte FcγR signaling.

Reference: J Med Chem. 2018 Mar 22;61(6):2227-2245. https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b01712

In vivo activity

To evaluate the in vivo efficacy of GDC-0853, it was tested in a B and myeloid cell-dependent inflammatory arthritis model. Female Lewis rats with developing collagen-induced arthritis were dosed orally for 16 days with GDC-0853 at a range of doses once (0.06, 0.25, 1, 4, and 16 mg/kg QD) (Figure 8A) or twice (0.125, 0.5, and 2 mg/kg BID) daily (Figure 8B). GDC-0853 dose-dependently reduced ankle thickness following QD (Figure 8A) and BID (Figure 8B) dosing regimens. Furthermore, GDC-0853 showed a dose responsive beneficial effect on a panel of ankle histopathology parameters (inflammation, pannus, cartilage damage, bone resorption; data not shown).

Reference: J Med Chem. 2018 Mar 22;61(6):2227-2245. https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b01712