Dabrafenib

Cat. No.: HY-14660

CAS No.: 1195765-45-7

Molecular Formula: $C_{23}H_{20}F_3N_5O_2S_2$

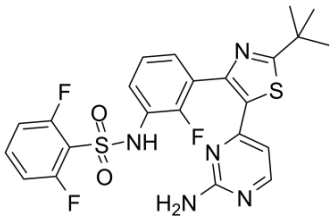
Molecular Weight: 519.56

Target: Raf

Pathway: MAPK/ERK Pathway

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 : ≥ 33 mg/mL (63.52 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9247 mL	9.6235 mL	19.2471 mL
5 mM	0.3849 mL	1.9247 mL	3.8494 mL
10 mM	0.1925 mL	0.9624 mL	1.9247 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: ≥ 2.5 mg/mL (4.81 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.81 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.81 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Dabrafenib (GSK2118436A) is an ATP-competitive inhibitor of Raf with IC_{50}s of 5 nM and 0.6 nM for C-Raf and B-Raf^{V600E}, respectively[4].

IC_{50} & Target

$BRaf^{V600E}$	CRAF
0.6 nM (IC_{50})	5 nM (IC_{50})

In Vitro	Dabrafenib (GSK2118436, 1 μM) with 0.01 μM GSK1120212 inhibits more than 90% of cell growth in the NRAS mutant clones. GSK2118436 is sufficient to reduce S6P phosphorylation in A375[1]. Dabrafenib suppresses the PolyP-mediated vascular barrier permeability, upregulation of inflammatory biomarkers, adhesion/migration of leukocytes, and activation and/or production of nuclear factor-κB, tumor necrosis factor-α, and interleukin-6[2]. Dabrafenib inhibits the release of HMGB1 and downregulates HMGB1-dependent inflammatory responses by enhancing the expressions of cell adhesion molecules (CAMs) in human endothelial cells[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Dabrafenib-treated females have mostly immature reproductive tracts with no evidence of ovulation, similar to age-matched controls; however, DAB-treated females have keratinized and histologically open vaginas[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	For longer term proliferation assays, cells are plated and treated with compound or combination of compounds in RMPI-1640 containing 10% FBS for 12 days. Compound treatments are replaced at least once during the assay. After 12 days, cells are stained with 0.5% methylene blue in 50% ethanol. Images are captured using flatbed scanner. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [5]	The rat pups selected as the test system are derived from 26 10-week-old, time-mated, virus-antibody-free SD (Crl:CD[SD]) female rats. Mated females are observed for natural deliveries from Day 20 to 23 pc (day parturition completed is designated PND 0). Litter examinations are conducted when parturition is complete, on PNDs 3 and 6, and included gender identification, individual pup weights, and external morphologic examinations. Parturient dams and their litters are selected for study based on clinical signs and body weights, and selected dams and their litters are randomized into study groups based on clinical observations and PND 3 litter mean body weights. On PND 3 or 4, litters are culled to four males and five females, with minimal fostering only when necessary to obtain the desired sex ratio, such that natural litters are maintained as much as possible. Records are kept of fostered pups of original and foster dams. All pups are identified by paw tattoo. To the extent possible, nonlittermates are assigned to subsets. DAB is formulated as a suspension in vehicle, 0.5% hydroxypropylmethylcellulose K15M, and 0.1% (v/v) Tween80 in purified water, and is given to juvenile male and female rats orally by gavage at a dose volume of 5 ml/kg, based on daily body weight. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367). pii: eaan4368.
- Cell. 2018 Aug 9;174(4):843-855.e19.
- Cancer Cell. 2020 Mar 16;37(3):387-402.e7.
- Nat Biomed Eng. 2018;2:578-588.
- Sci Transl Med. 2018 Jul 18;10(450). pii: eaaq1093.

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REFERENCES

[1]. Greger JG, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Mol Cancer Ther, 2012, 11(4), 909-920.

[2]. Lee S, et al. Anti-inflammatory effects of dabrafenib on polyphosphate-mediated vascular disruption. Chem Biol Interact. 2016 Jul 22.

[3]. Jung B, et al. Anti-septic effects of dabrafenib on HMGB1-mediated inflammatory responses. BMB Rep. 2016 Apr;49(4):214-9.

[4]. Alexander M Menzies, et al. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther. 2012; 6: 391–405.

[5]. Posobiec LM, et al. Early Vaginal Opening in Juvenile Female Rats Given BRAF-Inhibitor Dabrafenib Is Not Associated with Early Physiologic Sexual Maturation. Birth Defects Res B Dev Reprod Toxicol. 2015 Dec;104(6):244-52.

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