

Product Data Sheet

Product Name: AZ 628
Cat. No.: GC15055

Chemical Properties

Cas. No. 878739-06-1

Chemical Name 3-(2-cyanopropan-2-yl)-N-[4-methyl-3-[(3-methyl-4-oxoquinazolin-6-yl)amino]phenyl]benzamide

SMILES CC1=C(C=C(C=C1)NC(=O)C2=CC(=CC=C2)C(C)(C)C#N)NC3=CC4=C(C=C3)N=CN(C4=O)C

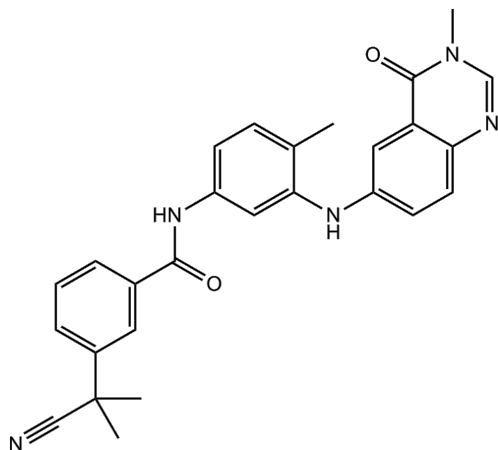
Formula $C_{27}H_{25}N_5O_2$ M.Wt 451.53

Solubility $\geq 22.6\text{mg/mL}$ in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

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

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Cell experiment: Cell viability quantified by Syto60 after 72 hours of AZ 628 (0.5, 1.0, and 1.5 μ M), CI-1040 or BAY61-3606 treatment in HCT-116 (K-RASG13D/+) or HKe-3 (K-RAS-/+) cell lines. Relative cell viability is normalized to DMSO vehicle treated control for each cell line[2].

References:

- [1]. Khazak V, et al. Selective Raf inhibition in cancer therapy. Expert Opin Ther Targets. 2007 Dec;11(12):1587-609.
- [2]. Lau KS, et al. BAY61-3606 affects the viability of colon cancer cells in a genotype-directed manner. PLoS One. 2012;7(7):e41343.

Background

AZ628 is a potent and newly discovered inhibitor of BRAF, c-Raf-1 and BRAFV600E with IC₅₀ values of 105 nM, 29 nM and 34 nM, respectively. This compound prevents CRAF activation through persistently occupying the ATP-binding site of Raf kinase. Specificity profile suggests that AZ628 also inhibits activation of other tyrosine protein kinases such as DDR2, VEGFR2, Lyn, Flt1, FMS and others.

Raf kinases a family of three serine/threonine-specific protein kinases and participate in the RAS-RAF-MEK-ERK signal transduction cascade, also known as the mitogen-activated protein kinase (MAPK) cascade. The activation of MAPK signaling leads to different cellular response such as cell proliferation, apoptosis and inflammation.

AZ628 has the potent anti-tumor activity. In human colon and melanoma-derived cell line that carries the recurrent V600E activating BRAF mutation, AZ628 was shown to inhibit anchorage-dependent and -independent growth, induce cell cycle arrest, and cause apoptosis [1]. AZ628 may be antiangiogenic due to inhibition of VEGFR2 [2].

Generation of melanoma cell line clones is obtained resistance to the RAF kinase inhibitor AZ628. Resistance to AZ628 is connected with raised levels of the RAF downstream effector p-ERK1/2. ERK1/2 initiation in AZ628-resistant clones is interceded by MEK. Supported multiplication of AZ628-resistant clones is to a great extent autonomous of BRAF kinase action. AZ628-resistant clones

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express elevated CRAF. Survival of AZ628-safe cells is subject to CRAF [1].

References:

1. Montagut C, Sharma SV, Shioda T, McDermott U, Ulman M, Ulkus LE, et al. Elevated CRAF as a potential mechanism of acquired resistance to BRAF inhibition in melanoma. *Cancer Res* 2008,68:4853-4861.
2. Khazak V, Astsaturov I, Serebriiskii IG, Golemis EA. Selective Raf inhibition in cancer therapy. *Expert Opin Ther Targets* 2007,11:1587-1609.

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