

Product Data Sheet

Product Name: GDC-0623

Cat. No.: GC14247

Chemical Properties

Cas. No. 1168091-68-6

Chemical Name 5-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)imidazo[1,5-a]pyridine-6-carboxamide

SMILES C1=CC(=C(C=C1I)F)NC2=C(C=CC3=CN=CN32)C(=O)NOCCO

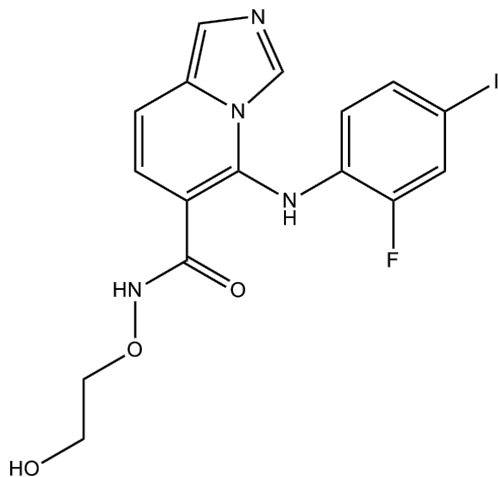
Formula $C_{16}H_{14}FIN_4O_3$ M.Wt 456.21

Solubility $\geq 16.85\text{mg/mL}$ 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

Kinase experiment [1]:

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In vitro Kinase assays

0.14 μ M of purified inactive recombinant MEK-1 protein is preincubated with inhibitors in 15 μ L of kinase buffer including (20 mM MOPS pH7.2, 25 mM beta glycerol phosphate, 5 mM EGTA, 1 mM sodium orthovanadate, 1 mM DTT, 100 μ M ATP, 15 mM MgCl₂). After incubating 10 minutes at 30°C, 1 ng of BRAF, CRAF or BRAF V600E combined with 0.5 μ g of inactive recombinant ERK2 is added to the reaction in total volume of 20 μ L. After incubating 30 minutes at 30°C the reaction is stopped by adding Laemmle sample buffer. Enzyme activity is measured by determining level of phosphor-MEK by SDS-PAGE. Immunoreactive proteins are visualized with SuperSignal West Pico Chemiluminescent Substrate.

Cell experiment [1, 2]:

Cell lines KRAS mutant HCT116 or SW620 cells

Preparation method Soluble in DMSO. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition 0.01-0.15 μ mol/L; 3h-48 h;

Applications

GDC-0623 dose- and time-dependently up-regulated the pro-apoptotic BH3-only protein BIM in HCT116 cells or KRAS mutant HCT116 or SW620 cells. GDC-0623 inhibited cellular proliferation with EC₅₀ values of 4 nM, 53 nM, 11 nM, 18 nM and 94 nM for A375 (BRAFFV600E), HCT116 (KRASG13D), COLO 205, HT-29, and HCT116 cells, respectively.

Animal experiment [1]:

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Animal models	Mice bearing A375, MiaPaCa-2, and HCT116 xenografts
Dosage form	40 mg/kg, oral gavage (PO), by mouth once a day, for 20 days
Applications	GDC-0623 showed tumour growth inhibition of 120% and 115% in MiaPaCa-2 and HCT116 xenografts tumour models, respectively.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

1. Hatzivassiliou, G., Haling, J. R., Chen, H., Song, K., Price, S., Heald, R., Hewitt, J. F., Zak, M., Peck, A., Orr, C., Merchant, M., Hoeflich, K. P., Chan, J., Luoh, S. M., Anderson, D. J., Ludlam, M. J., Wiesmann, C., Ultsch, M., Friedman, L. S., Malek, S. and Belvin, M. (2013) Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. *Nature*. 501, 232-236
2. Zaanani, A., Okamoto, K., Kawakami, H., Khazaie, K., Huang, S. and Sinicrope, F. A. (2015) The Mutant KRAS Gene Up-regulates BCL-XL Protein via STAT3 to Confer Apoptosis Resistance That Is Reversed by BIM Protein Induction and BCL-XL Antagonism. *J Biol Chem*. 290, 23838-23849

Background

GDC-0623 is a potent and ATP-uncompetitive inhibitor of MEK1 with K_i value of 0.13nM [1].

GDC-0623 is an allosteric MEK inhibitor and has efficacy against both mutant BRAF and mutant KRAS. In the cell viability assays, GDC-0623 inhibits BRAF (V600E) and KRAS (G13D) with EC_{50} values of 7nM and 42nM, respectively in A375 cells and HCT116 cells. Besides that, GDC-0623 shows similar efficacy in the two genotypes in a panel of BRAF and KRAS-mutant cancer cell lines. GDC-0623 is found to prevent MEK phosphorylation in cells, resulting in more effective inhibition of

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pERK. Furthermore, it is found that GDC-0623 blocks RAF activation through the effect on MEK. It induces dimerization of MEK with both BRAF and CRAF and stabilizes the RAF–MEK complex. In addition, GDC-0623 also suppresses RAF activation via inhibiting the formation of BRAF–CRAF heterodimer and the translocation of RAF in plasma membrane [1].

References:

[1] Hatzivassiliou G, Haling J R, Chen H, et al. Mechanism of MEK inhibition determines efficacy in mutant KRAS-versus BRAF-driven cancers. *Nature*, 2013, 501(7466): 232-236.

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