Product Data Sheet

Product Name: AGI-6780
Cat. No.: GC14757

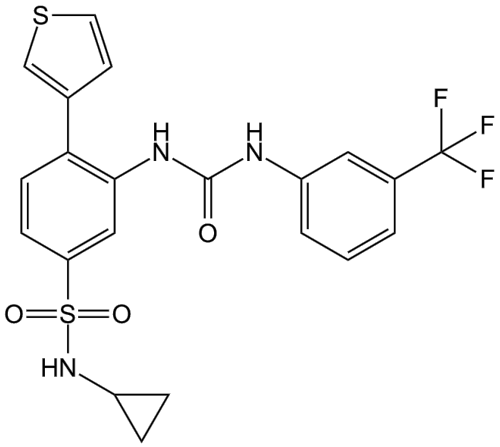
Chemical Properties

Cas. No.	1432660-47-3
Chemical Name	1-[5-(cyclopropylsulfamoyl)-2-thiophen-3-ylphenyl]-3-[3-(trifluoromethyl)phenyl]urea
SMILES	C1CC1NS(=O)(=O)C2=CC(=C(C=C2)C3=CSC=C3)NC(=O)NC4=CC=CC(=C4)C(F)(F)F

Formula	$C_{21}H_{18}F_3N_3O_3S_2$	M.Wt	481.51
Solubility	≥ 22.25 mg/mL in DMSO, ≥ 100.8 mg/mL in EtOH	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

Cell experiment [1]:

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Cell lines	K562 cells (human chronic myeloid leukemia cell line) and derivative K562 cells with acquired resistance to imatinib (IMA) or adriamycin (ADR)
Preparation Method	Cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin at 37°C with 5% CO_2. Cells were treated with AGI-6780 at 2 or 4μM alone or in combination with IMA or ADR for 48 hours.
Reaction Conditions	2 or 4μM; 48h
Applications	AGI-6780 did not affect the survival of parental K562 cells but significantly increased the sensitivity of resistant K562 cells to IMA and ADR, as evidenced by reduced IC_{50} values and synergistic effects observed in Bliss independence model.

Animal experiment [2]:

Animal models	Healthy young male C57BL/6J mice
Preparation Method	Mice were intraperitoneally injected with the IDH2 inhibitor AGI-6780 at 60mg/kg, and plasma AGI-6780 levels were measured by LC–MS/MS at multiple time points over 90min to define exposure; in the functional experiment, AGI-6780 was administered i.p. 30min before an intraperitoneal glucose bolus (1.5g glucose/kg), with blood sampled before AGI-6780 injection (–30min), just before glucose (0min), and post-bolus for plasma glucose, insulin, and glucagon measurements.

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Dosage form	60mg/kg; i.p.; single injection
Applications	At exposures achieving plasma AGI-6780 concentrations peaking at ~15μM (30–90min post-injection), AGI-6780 abolished the normal glucose-stimulated insulin secretion (GSIS) rise seen in vehicle (DMSO)-treated mice, and significantly lowered circulating glucagon after the glucose bolus, such that overall blood glucose excursions remained comparable to vehicle controls despite the blunted insulin secretory response.

References:
[1] Liu W, Sun Y, Ge W, et al. DIA-Based Proteomics Identifies IDH2 as a Targetable Regulator of Acquired Drug Resistance in Chronic Myeloid Leukemia. Mol Cell Proteomics. 2022 Feb;21(2):100187.
[2] Zhang GF, Jensen MV, Gray SM, et al. Reductive TCA cycle metabolism fuels glutamine- and glucose-stimulated insulin secretion. Cell Metab. 2021 Apr 6;33(4):804-817.e5.

Background

AGI-6780 is an orally active, potent and selective mutant isocitrate dehydrogenase 2 (IDH2 ^{R140Q}) inhibitor (IC_{50}=23±1.7nM). AGI-6780 allosterically binds at the IDH2 dimer interface to noncompetitively inhibit the substrate and uncompetitively inhibit the NADPH cofactor, thereby blocking the gain-of-function activity of mutant IDH2 (especially R140Q). AGI-6780 can be used in research related to acute myeloid leukemia (AML) and other IDH2 mutation-associated tumors (e.g., low-grade gliomas)[1-4].

In vitro, AGI-6780 (2-4μM) had been applied to treat K562 cells and imatinib/adriamycin-resistant K562 cells for 48h. AGI-6780 had shown little effect on the basal survival of K562 cells. AGI-6780 had reduced the IC_{50} of resistant K562 cells to imatinib or adriamycin[5]. AGI-6780 (5μM) had been used to treat multiple myeloma cell lines, mantle cell lymphoma and Burkitt lymphoma cell lines for 96h. AGI-6780 had impaired tricarboxylic acid cycle activity and mitochondrial ATP production in these cells, promoted cell cycle arrest at G0/G1 phase accompanied by cyclin downregulation, PARP-1

cleavage, and caspase-3/7/9 activation, thereby enhancing tumor cell death[6].

In vivo, AGI-6780 (60mg/kg; single injection) had been intraperitoneally administered to C57BL/6J mice, followed 30min later by an intraperitoneal glucose load (1.5g/kg) for an intraperitoneal glucose tolerance test. AGI-6780 had achieved a plasma drug concentration of approximately 15μM maintained between 30 and 90min, had abolished the normal insulin secretory response to glucose stimulation, and had significantly reduced circulating glucagon levels[7]. AGI-6780 (25mg/kg/day and 50mg/kg/day) had been intraperitoneally injected into BALB/c nude mice bearing orthotopic xenografts of MDA-MB-231 triple-negative breast cancer (starting when tumor diameter reached approximately 5-6mm) for 6 consecutive weeks. AGI-6780 had inhibited tumor growth in a dose-dependent manner[8].

References:
[1] Chen Y, Feng X, Yin X, et al. Prognostic and immunological role of RHEBL1 in pan-cancer: a target for survival and immunotherapy. Discov Oncol. 2025 May 14;16(1):766.
[2] Kim J, DeBerardinis RJ. Cancer. Silencing a metabolic oncogene. Science. 2013 May 3;340(6132):558-9.
[3] Chen J, Yang J, Sun X, et al. Allosteric inhibitor remotely modulates the conformation of the orthestric pockets in mutant IDH2/R140Q. Sci Rep. 2017 Nov 28;7(1):16458.
[4] Li J, He Y, Tan Z, et al. Wild-type IDH2 promotes the Warburg effect and tumor growth through HIF1α in lung cancer. Theranostics. 2018 Jul 16;8(15):4050-4061.
[5] Liu W, Sun Y, Ge W, et al. DIA-Based Proteomics Identifies IDH2 as a Targetable Regulator of Acquired Drug Resistance in Chronic Myeloid Leukemia. Mol Cell Proteomics. 2022 Feb;21(2):100187.
[6] Bergaggio E, Riganti C, Garaffo G, et al. IDH2 inhibition enhances proteasome inhibitor responsiveness in hematological malignancies. Blood. 2019 Jan 10;133(2):156-167.
[7] Zhang GF, Jensen MV, Gray SM, et al. Reductive TCA cycle metabolism fuels glutamine- and glucose-stimulated insulin secretion. Cell Metab. 2021 Apr 6;33(4):804-817.e5.
[8] Li JJ, Yu T, Zeng P, et al. Wild-type IDH2 is a therapeutic target for triple-negative breast cancer. Nat Commun. 2024 Apr 24;15(1):3445.