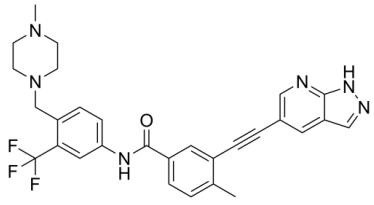
Data Sheet

Product Name:	Olverembatinib
Cat. No.:	CS-1444
CAS No.:	1257628-77-5
Molecular Formula:	$C_{29}H_{27}F_3N_6O$
Molecular Weight:	532.56
Target:	Bcr-Abl
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 41.67 mg/mL (ultrasonic;warming;heat to 60°C)



BIOLOGICAL ACTIVITY:

Olverembatinib (GZD824) is a potent and orally active pan-**Bcr-Abl** inhibitor. Olverembatinib potently inhibits a broad spectrum of Bcr-Abl mutants. Olverembatinib strongly inhibits native Bcr-Abl and Bcr-Abl^{T315I} with **IC_{50}**s of 0.34 nM and 0.68 nM, respectively. Olverembatinib has antitumor activity[1]. Olverembatinib is a click chemistry reagent, itcontains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups. IC50 & Target: IC50: 0.68 nM (Bcr-Abl ^{T315I}), 0.27 nM (Bcr-Abl^{E255K}) , 0.71 nM (Bcr-Abl^{G250E}) , 0.15 nM (Bcr-Abl^{Q252H}), 0.35 nM (Bcr-Abl ^{H396P}), 0.29 nM (Bcr-Abl ^{M351T}), 0.35 nM (Bcr-Abl^{Y253F}), Bcr-Abl^{F317L}[1] ***In Vitro:*** Olverembatinib shows antiproliferative activity in stably transformed Ba/F3 cells whose growth was driven by native Bcr-Abl or Bcr-Abl mutants[1].

Olverembatinib selectively and potently inhibits the proliferation of Bcr-Abl-positive leukemia cells[1].

Olverembatinib inhibits Bcr-Abl signaling in K562 (1-20 nM; 4.0 hours) and Ba/F3 stable cell lines expressing native Bcr-Abl (0.1-100 nM; 4.0 hours) or Bcr-Abl^{T315I}(0.1-100 nM; 4.0 hours)[1].

In Vivo: Olverembatinib suppresses tumor growth in mice bearing allografted Ba/F3 cells expressing Bcr-Abl ^{WT}[1].

Olverembatinib (1-20 mg/kg; i.g.; daily; for 10 days) significantly increases the median survival of the mice bearing allografted Ba/F3 cells expressing Bcr-Abl^{T315I}[1].

Olverembatinib exhibits a good oral bioavailability (rat 48.7%) and C_{max} (rat 390.5 μg/L) following oral administration (rat; 25 mg/kg)[1] .

Olverembatinib exhibits terminal elimination half-lives (rat 5.6 h) due to high plasma clearance (rat 1.7 L/h/kg) following intravenous administration (rat 5 mg/kg)[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase assay [1] The binding activities of GZD824 with native Abl or Abl mutants were analyzed by KINOMEscan system conducted by Ambit Bioscience. Briefly, kinases were tagged with DNA. The ligands were biotinylated and immobilized to streptavidincoated beads. The binding reactions were assembled by incubating DNA-tagged kinases, immobilized ligands, and GZD824 in binding reactions (20% SeaBlock, 0.17 × PBS, 0.05% tween-20, 6 mM DTT) for 1.0 h at room temperature. The affinity beads were washed with washing buffer (1 × PBS, 0.05% Tween-20) first and then elution buffer (1 × PBS, 0.05% Tween 20, 0.5 μM nonbiotinylated affinity ligands). The kinase concentration in the eluate was determined by quantitative PCR of the DNA tagged to the kinase. The ability of GZD824 to bind to the kinase was evaluated with percent control (%) as (test compound signal-positive control signal)/ negative control signal-positive control signal) × 100%. Negative control is DMSO control (100% ctrl) and positive control is control compound (0% ctrl). Animal administration [1] K562 cells or Ba/F3 cells expressing native Bcr-Abl or Bcr- Abl mutants were resuspended in normal saline (NS) solution (2.5 ×107 cell/mL). A 0.2 mL amount of cell suspension was injected subcutaneously into

the right flank of each mouse. Mice were randomly grouped based on the tumor volume when the mean tumor volume reached 100-200 mm3. GZD824 and imatinib were dissolved in a vehicle containing 1% DMSO, 22.5% Cremophor, 7.5% ethanol, and 69% normal saline (NS). Mice were treated for the 14 consecutive days once daily by oral gavage with GZD824 (at the indicated doses), imatinib (50 mg/kg), and vehicle, respectively. Tumor volume and body weight were monitored once every 2 days. Tumor volume was calculated as the L × W2/2 (L and W are the length and width of the tumor, respectively).

References:

[1]. Ren X, Pan X, Zhang Z, Identification of GZD824 as an orally bioavailable inhibitor that targets phosphorylated and nonphosphorylated breakpoint cluster region-Abelson (Bcr-Abl) kinase and overcomes clinically acquired mutation-induced resistance against imatinib. J Med Chem. 2013 Feb 14;56(3):879-94.

CAIndexNames:

Benzamide, 4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-3-[2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl]-

SMILES:

O=C(NC1=CC=C(CN2CCN(C)CC2)C(C(F)(F)F)=C1)C3=CC=C(C)C(C#CC4=CN=C(NN=C5)C5=C4)=C3

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