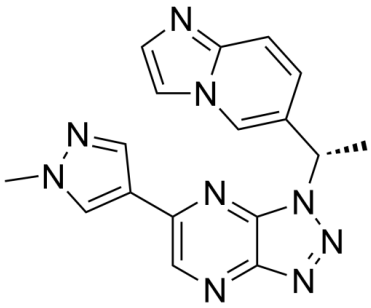
Data Sheet

Product Name:	Savolitinib
Cat. No.:	CS-4062
CAS No.:	1313725-88-0
Molecular Formula:	$C_{17}H_{15}N_9$
Molecular Weight:	345.36
Target:	c-Met/HGFR
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 20.83 mg/mL



BIOLOGICAL ACTIVITY:

Savolitinib (AZD-6094) is a potent, highly selective, and orally bioavailable **c-Met** inhibitor with **IC_{50}** s of 5 nM and 3 nM for c-Met and p-Met, respectively. Savolitinib (AZD-6094) selectively binds to and inhibits the activation of c-Met in an ATP-competitive manner, and disrupts c-Met signal transduction pathways. Antineoplastic activity[1][2]. IC50 & Target: IC50: 5 nM (c-Met) and 3 nM (p-Met)[1] ***In Vivo:*** Savolitinib (Compound 28; 1-10.0 mg/kg; oral administration; daily; for 21 days; athymic nude mice) demonstrates dose-dependent tumor growth inhibition in a U87MG subcutaneous xenograft model. In addition, none of the mice in the dosing groups exhibits body weight loss during the experiment[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase assay [1] Inhibition of test compound on c-Met kinase activity was measured by using of Transcreener FP ADP Assay (Bellbrook Lab) that was developed to detect ADP generated in the enzyme reaction. The kinase reaction buffer was composed of 67 mM of HEPES/pH = 7.4, 0.013% of Triton X-100, 27 mM of MgCl2, 0.67 mM of MnCl2, 1.25 mM of DTT. Test compound was tested in a 8- point series dilution. The enzymatic reaction contains 0.2 μg/mL of recombinant c-Met catalytic domain (Invitrogen Co.), 25 μg/mL of Poly E4Y substrate (Sigma-Aldrich), 5 μL of tested compound diluted in 20% DMSO, and 10 μM of ATP. All components were diluted in assay buffer. The final concentration of DMSO in the reaction was 4%. ATP was the last component to be added, for initiating the reaction. The reaction mixture was incubated at 25 °C for 45 min. Then ADP detection mixture was added and incubated at 25 °C for additional 1 h. Florescence polarization is measured on TECAN F500 at excitation of 610 nm and emission of 670 nm. Produced ADP concentration was calculated using standard curve obtained in the same study based on the recommendation of manufacturer. Cell assay [1] Briefly, NCI-H441 cells were plated at a density of 15,000 cells/well in RPMI-1640 medium with 10% FBS in 96-well plates. After incubation overnight, cells were then treated with serially diluted test compounds at 37 °C for 1 h. Then the medium was removed, and cells were lysed in 100 μL/well lysis buffer (1% NP-40, 20 mM Tris/pH = 8.0, 137 mM NaCl, 10% glycerol, 2 mM EDTA, 1 mM activated sodium orthovanadate, 10 mg/mL Aprotinin, 10 mg/mL Leupeptin). The plates containing cell lysate were kept at -80 °C overnight. The next day, the plates were thawed on ice, mixed gently. Twenty-five μL/well of lysates were added into the assay plates precoated with anti-p-Met antibody to detect p-c-Met signal. p-c-Met level was determined at 450 and 570 nm using Labsystems Multiskan K3. The inhibition rate was calculated according to the following equation, and IC50 was determined using XLFit2.0 software. Animal administration [1] U87MG tumor cells were inoculated into the flanks of athymic nude mice (3 × 106 cells/mouse). When tumor volume reached 200 mm3, the mice were randomized into vehicle treated and compound 28 treated groups. The animals were orally administered with compound 28 once a day at 1.0, 2.5, and 10.0 mg/kg or treated with vehicle 0.5% CMC-Na at pH = 2.1. Tumor size was measured 2-3 times per week. Tumor volumes were calculated using the formula: TV = (Length × Width2)/2. The percentage of tumor growth inhibition (%TGI = [1 (Vt V0)drug treated/(Vt V0)vehicle control] × 100%) was used for

evaluation of the antitumor efficacy. V0 represents mean tumor volume at the first day of treatment; and Vt represents mean tumor volume at the last day of treatment. Animal body weight and behavior were observed during the experiment. Statistical analysis for tumor volume was performed by the student t test for a mean comparison.

References:

[1]. Jia H, et al. Discovery of (S)-1-(1-(Imidazo[1,2-a]pyridin-6-yl)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine (volitinib) as a highly potent and selective mesenchymal-epithelial transition factor (c-Met) inhibitor in clinical development for treatment of cancer. J Med Chem. 2014 Sep 25;57(18):7577-89.

[2]. Gavine PR, et al. Volitinib, a potent and highly selective c-Met inhibitor, effectively blocks c-Met signaling and growth in c-MET amplified gastric cancer patient-derived tumor xenograft models. Mol Oncol. 2015 Jan;9(1):323-33.

CAIndexNames:

1H-1,2,3-Triazolo[4,5-b]pyrazine, 1-[(1S)-1-imidazo[1,2-a]pyridin-6-ylethyl]-6-(1-methyl-1H-pyrazol-4-yl)-

SMILES:

CN1N=CC(C2=CN=C3C(N([C@H](C4=CN5C(C=C4)=NC=C5)C)N=N3)=N2)=C1

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