

Product Data Sheet

Product Name: Danusertib (PHA-739358)

Cat. No.: GC15217

Chemical Properties

Cas. No. 827318-97-8

Chemical Name N-[5-[(2R)-2-methoxy-2-phenylacetyl]-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

SMILES CN1CCN(CC1)C2=CC=C(C=C2)C(=O)NC3=NNC4=C3CN(C4)C(=O)C(C5=CC=CC=C5)OC

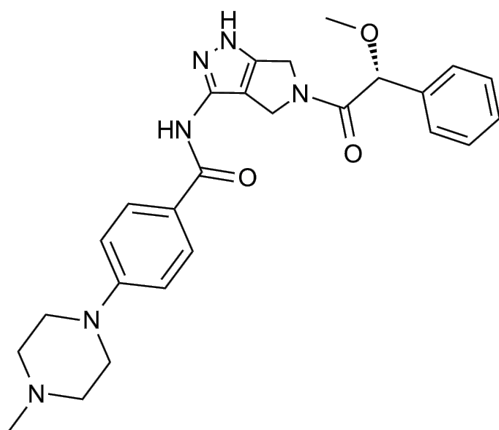
Formula $C_{26}H_{30}N_6O_3$ M.Wt 474.55

Solubility ≥ 23.75 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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Biochemical kinase assays The Km values for ATP and the specific substrate were initially determined, and each assay was then run at optimized ATP (2Km) and substrate (5Km) concentrations. This setting enabled direct comparison of IC50 values of Danusertib across the applied kinase selectivity screening panel for the evaluation of the selectivity profile.

Cell experiment [2]:

Cell lines CD34+ cells

Preparation method The solubility of this compound in DMSO is >10 mM. 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.

Reaction Conditions 5 µM; 5 days

Applications In CD34+ cells from an IM-resistant CML patient, Danusertib induced apoptosis and reduced phosphorylation of P-CrkL.

Animal experiment [2]:

Animal models Female SCID mice s.c. injected with K562 cells

Dosage form 15 mg/kg; i.p.; b.i.d., for 10 days

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Applications Danusertib significantly inhibited K562 cell proliferation and virtually suppressed tumor growth.

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]. Carpinelli P, Ceruti R, Giorgini ML, Cappella P, Gianellini L, Croci V, Degrassi A, Texido G, Rocchetti M, Vianello P, Rusconi L, Storici P, Zugnoni P, Arrigoni C, Soncini C, Alli C, Patton V, Marsiglio A, Ballinari D, Pesenti E, Fancelli D, Moll J. PHA-739358, a potent inhibitor of aurora kinases with a selective target inhibition profile relevant to cancer. *Mol Cancer Ther* 2007; 6(12 Pt 1): 3158-3168.

[2]. Gontarewicz A, Balabanov S, Keller G, Colombo R, Graziano A, Pesenti E, Benten D, Bokemeyer C, Fiedler W, Moll J, Brümmendorf TH. Simultaneous targeting of Aurora kinases and Bcr-Abl kinase by the small molecule inhibitor PHA-739358 is effective against imatinib-resistant BCR-ABL mutations including T315I. *Blood*. 2008 Apr 15;111(8):4355-64.

Background

Danusertib (previously known as PHA-739358), a 3-aminopyrazole derivative identified during the development of the pyrrolopyrazole sub-series, is a potent small-molecule inhibitor of aurora kinases family members with a dominant inhibition for aurora B kinase (ABK). This pan-aurora kinases inhibitor is also able to inhibit several tyrosine kinases, including T315I mutant, Ret, Trk-A and fibroblast growth factor receptor-1 (FGFR-1), which are involved in multiple malignancies, such as chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), thyroid prostate and breast carcinoma. Thus, in many previous studies, danusertib exhibits remarkable antitumor activity in a number of different xenografts, spontaneous, and transgenic animal tumor models with a favorable pharmacokinetic and safety profile.

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[1]. Carpinelli P, Ceruti R, Giorgini ML, Cappella P, Gianellini L, Croci V, Degrassi A, Texido G, Rocchetti M, Vianello P, Rusconi L, Storici P, Zugnoni P, Arrigoni C, Soncini C, Alli C, Patton V, Marsiglio A, Ballinari D, Pesenti E, Fancelli D, Moll J. PHA-739358, a potent inhibitor of aurora kinases with a selective target inhibition profile relevant to cancer. *Mol Cancer Ther* 2007; 6(12 Pt 1): 3158-3168

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