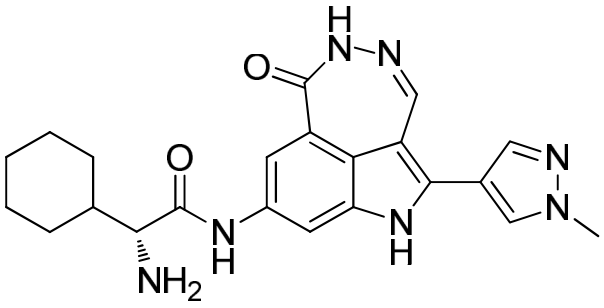
PF0477736

SYN-1174



(R)-2-amino-2-cyclohexyl-N-(2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indol-8-yl)acetamide

CAS Registry No.: 952021-60-2

Smiles String:
O=C1C2=C3C(NC(C4=CN(C)N=C4)=C3C=NN1)=CC(NC([C@H](N)C5CCCCC5)=O)=C2

Molecular Weight: 419.48

Molecular Formula: C22H25N7O2

Lot Number: Refer to vial

1H-NMR: Available on request

HPLC (Purity): > 95.0% @ 254 nm

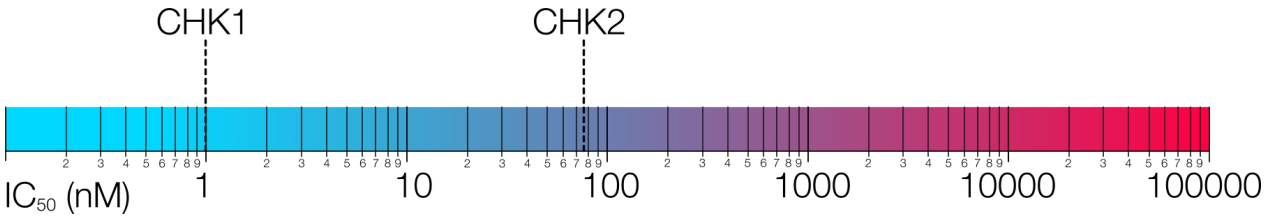
ES-MS: Available on request

Description:

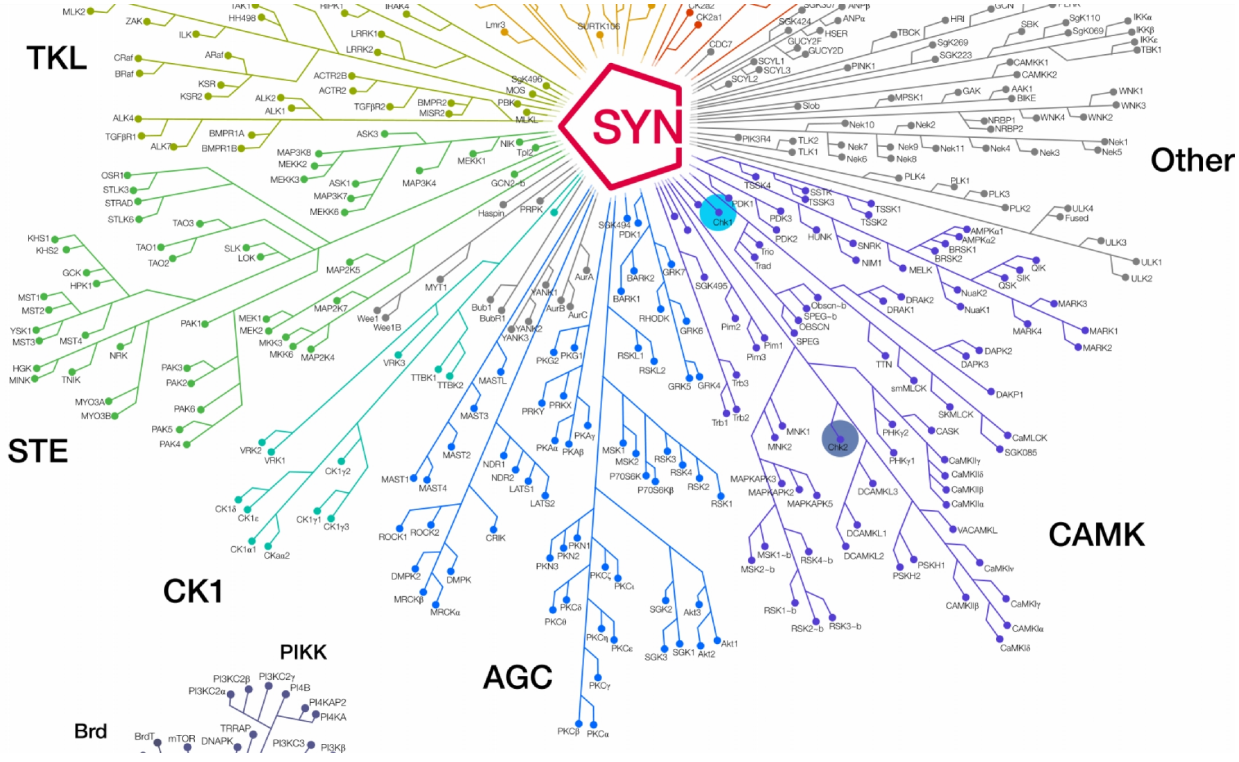
Eukaryotic cell cycle transitions are closely regulated by checkpoint signaling pathways. There are at least three DNA damage checkpoints, at the G1-S, S, and G2-M transitions, as well as one mitotic spindle checkpoint. Checkpoint kinase 1 (Chk1) is a key regulator of S, G2-M, and mitotic spindle checkpoints. In normal cells, DNA damage activates the p53-dependent G1 checkpoint and triggers DNA repair. In p53-deficient tumors, which account for over half of human cancers, the Chk1-mediated cell cycle arrest becomes the dominant defense mechanism. In response to DNA damage, Chk1 is phosphorylated by ATR at Ser346 and Ser317 sites and becomes activated. Chk1 then inactivates the Cdc25C protein phosphatase by phospohorylating Cdc25C at Ser216, which promotes its sequestration into the cytoplasm and in turn prevents activation of the cyclin B/Cdc2 mitotic kinase complex, finally resulting in G2 cell cycle arrest and suppression of mitotic entry. Chk1 also triggers the mitotic spindle checkpoint by activating Aurora B, which signals through the Bub and Mad proteins to inhibit APC/Cdc20 to result in mitotic arrest. Thus, antagonizing the Chk1-mediated cell cycle checkpoints have emerged as an attractive target for anticancer therapy. If Chk1 activity is blocked, DNA-damaged or spindle-disrupted cells would exit cell cycle arrest before full repair and subsequently undergo mitotic catastrophe or cell death. Chk1 inhibitors consequently increase the therapeutic index of DNA-damaging or antimitotic agents as well. PF-00477736 is a

selective, potent ATP-competitive Chk1 inhibitor, derived from PF-00394691, inhibits Chk1 (Ki, 0.49nM) and Chk2 (Ki, 47nM) in vitro. In tests, PF-00477736 was identified as a potent, selective ATP-competitive small-molecule inhibitor that inhibits Chk1 with a Ki of 0.49 nM. PF-00477736 abrogates cell cycle arrest induced by DNA damage and enhances cytotoxicity of clinically important chemotherapeutic agents, including gemcitabine and carboplatin. In xenografts, PF-00477736 enhanced the antitumor activity of gemcitabine in a dose-dependent manner. PF-00477736 combinations were well tolerated with no exacerbation of side effects commonly associated with cytotoxic agents. [Mol Cancer Ther 2008;7(8):2394-404].

Biological Activity



Kinome Mapping



Shipping and Storage Temperature

Shipping:
Ambient

Storage:
2 years -20C, Powder 1 month, -4C in DMSO, More than one month -80C in DMSO

Solubility

20 mM in DMSO

Preparing Stock Solutions

Stock Solution (1ml DMSO)	1mM	10mM	20mM	50mM
Mass(mg)	0.4194	4.1948	8.3896	20.9740

References

1. Blasina A, Hallin J, Chen E, Arango ME, Kraynov E, Register J, Grant S, Ninkovic S, Chen P, Nichols T, O'Connor P, Anderes K. Breaching the DNA damage checkpoint via PF-00477736, a novel small-molecule inhibitor of checkpoint kinase 1. Mol Cancer Ther. 2008 Aug;7(8):2394-404. doi: 10.1158/1535-7163.MCT-07-2391.

2. Ashwell S, Zabludoff S. DNA damage detection and repair pathways--recent advances with inhibitors of checkpoint kinases in cancer therapy. Clin Cancer Res. 2008 Jul 1;14(13):4032-7. doi: 10.1158/1078-0432.CCR-07-5138.

3. Zhang C, Yan Z, Painter CL, Zhang Q, Chen E, Arango ME, Kuszpit K, Zasadny K, Hallin M, Hallin J, Wong A, Buckman D, Sun G, Qiu M, Anderes K, Christensen JG. PF-00477736 mediates checkpoint kinase 1 signaling pathway and potentiates docetaxel-induced efficacy in xenografts. Clin Cancer Res. 2009 Jul 15;15(14):4630-40. doi: 10.1158/1078-0432.CCR-08-3272. Epub 2009 Jul 7.

Ordering Information

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