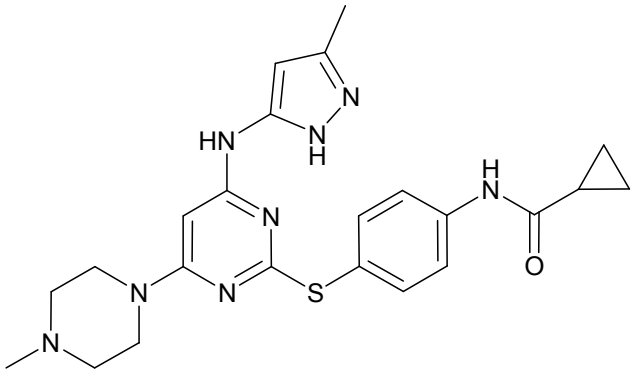
Tozasertib

SYN-1092



N-[4-[[4-(4-methyl-1-piperazinyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyrimidinyl]thio]phenyl]-cyclopropanecarboxamide

CAS Registry No.: 639089-54-6

Smiles String:
Cc1cc([nH]n1)Nc2cc(nc(n2)Sc3ccc(cc3)NC(=O)C4CC4)N5CCN(CC5)C

Molecular Weight: 464.59

Molecular Formula: C23H28N8OS

Lot Number: Refer to vial

1H-NMR: Available on request

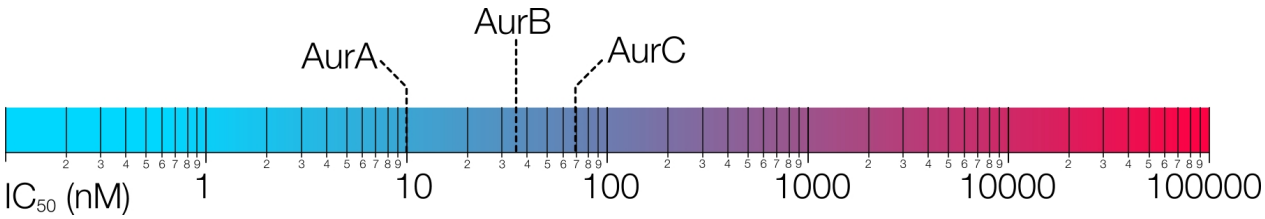
HPLC (Purity): > 95.0% @ 254 nm

ES-MS: Available on request

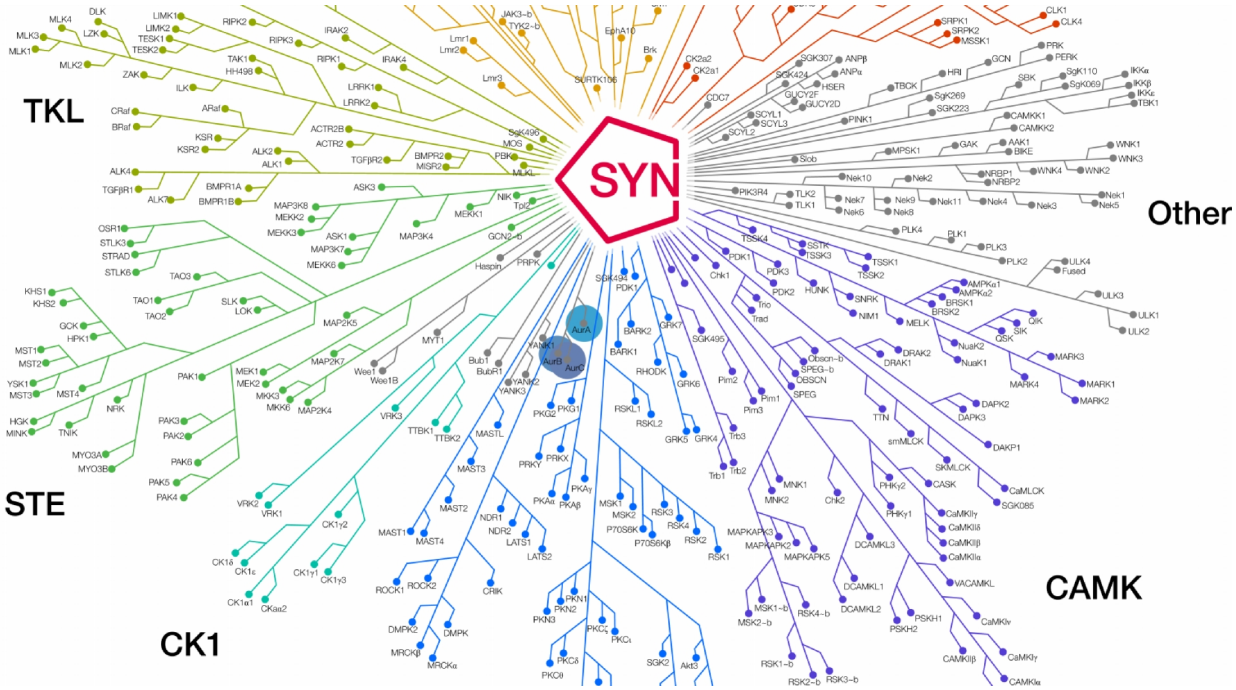
Description:

In mammals, three Aurora kinases, Aurora A, Aurora B, and Aurora C, are expressed. Aurora C expression is mainly restricted to testis, where it functions during meiosis, whereas Aurora A and B play key functions regulating mitosis. Aurora A is localized to the centrosome and spindle poles, where it drives centrosome maturation, separation, and bipolar spindle assembly. Aurora B is the central component of the chromosomal passenger complex (CPC) that also contains the inner centromere protein (INCENP), borealin, and survivin. These nonenzymatic components of the CPC play a key role in regulating kinase activity and localization. Over-expression of Aurora kinases can be oncogenic and they have thus long been targets for cancer therapy. Tozasertib, or VX-680, is a potent and selective inhibitor of Aurora kinases, particularly Aurora A and B. In vitro, VX-680 blocks cell cycle progression and induces apoptosis in a wide range of human tumor types at low IC50 values (i.e. 3.38 nM for human BE-13 cells, and 14.34 for NTERA cells). Moreover, VX680, also has very potent Ki values, with inhibition constants (Ki) of 0.6, 18, and 46 nM for Aurora A, B, and C, respectively [PMID:14981513]. VX-680 is also effective in vivo, being used in a Caki-1 xenograft model, VX-680 demonstrated a 75.7% ($P < 0.001$) decrease in Caki-1 xenograft tumor volume with no apparent alternation in animal body weight, peripheral blood counts, or other biological parameters [PMID: 20589168].

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

DMSO 93mg/mL, Ethanol 1mg/mL

Preparing Stock Solutions

Stock Solution (1ml DMSO)	1mM	10mM	20mM	50mM
Mass(mg)	0.4645	4.6459	9.2918	23.2295

References

1. Harrington EA, Bebbington D, Moore J, Rasmussen RK, Ajose-Adeogun AO, Nakayama T, Graham JA, Demur C, Hercend T, Diu-Hercend A, Su M, Golec JM, Miller KM. VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med. 2004 Mar;10(3):262-7. Epub 2004 Feb 22.

2. Lawrence HR, Martin MP, Luo Y, Pireddu R, Yang H, Gevariya H, Ozcan S, Zhu JY, Kendig R, Rodriguez M, Elias R, Cheng JQ, Sebti SM, Schonbrunn E, Lawrence NJ. Development of o-chlorophenyl substituted pyrimidines as exceptionally potent aurora kinase inhibitors. J Med Chem. 2012 Sep 13;55(17):7392-416. doi: 10.1021/jm300334d. Epub 2012 Aug 30.

3. Abraham S, Hadd MJ, Tran L, Vickers T, Sindac J, Milanov ZV, Holladay MW, Bhagwat SS, Hua H, Ford Pulido JM, Cramer MD, Gitnick D, James J, Dao A, Belli B, Armstrong RC, Treiber DK, Liu G. Novel series of pyrrolotriazine analogs as highly potent pan-Aurora kinase inhibitors. Bioorg Med Chem Lett. 2011 Sep 15;21(18):5296-300. doi: 10.1016/j.bmcl.2011.07.027. Epub 2011 Jul 14.

Ordering Information

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