

Product Data Sheet

Product Name: PP58
Cat. No.: GC32835

Chemical Properties

Cas. No. 212391-58-7

SMILES NCCOC1=CC=C(NC(N=C2N3C)=NC=C2C=C(C4=C(Cl)C=CC=C4Cl)C3=O)C=C1

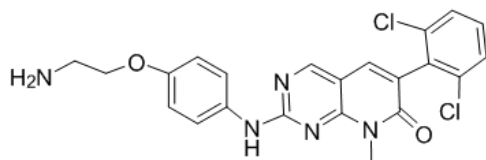
Formula $C_{22}H_{19}Cl_2N_5O_2$ M.Wt 456.32

Solubility Soluble 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

Caution: Product has not been fully validated for medical applications. For research use only.

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Kinase experiment: MEK1 and Aurora A activities are tested at 37 °C in a total volume of 30 µL. The kinases are assayed using 50 µM ATP and 1 µCi [γ -³²P]ATP in the presence of different PP58 concentrations. Kinase substrate proteins included are 0.25 mg/mL inactive GST-ERK2 for MEK1 and 0.025 mg/mL kemptide for Aurora A, respectively. Reactions are stopped by addition of SDS sample buffer. Determination of IC₅₀ [0–100%] values is performed using GraFit software[1].

References:

- [1]. Wissing J, et al. Chemical Proteomic Analysis Reveals Alternative Modes of Action for Pyrido[2,3-d]pyrimidine Kinase Inhibitors. Mol Cell Proteomics. 2004 Dec;3(12):1181-93.
[2]. Blencke S, et al. Characterization of a conserved structural determinant controlling protein kinase sensitivity to selective inhibitors. Chem Biol. 2004 May;11(5):691-701.

Background

PP58 is a pyrido[2,3-d]pyrimidine-based compound that inhibits PDGFR, FGFR and Src family activities with nanomolar IC₅₀ values.

PP58 inhibits Src with a subnanomolar IC₅₀ value in the assays. PP58 behaves as a titration reagent at higher Src protein concentrations. As analyzed by immunoblotting with specific antiserum, the PP58 matrix specifically depletes Src from total lysate, whereas binding to the PP58 beads is prevented when free inhibitor is included. The ectopically expressed FGFR1 receptor tyrosine kinase is specifically retained on PP58 beads. PP58 matrix could be a novel affinity reagent for the purification of cellular pyrido[2,3-d]pyrimidine inhibitor targets. PP58 affinity chromatography leads to the identification of protein kinases belonging to various different groups and families, indicating that the pyrido[2,3-d]pyrimidine inhibitor is not selective for a set of phylogenetically related members of the human kinome. The K_i values of PP58 for p38 α and JNK2 are 3.8 $\pm$ 1.9 nM and 0.32 $\pm$ 0.04 µM, respectively. PP58 affinity matrix also serves as an efficient purification reagent for a variety of protein kinases, which lack this structural feature and have much lower affinities for the pyrido[2,3-d]pyrimidine inhibitor PP58. PP58 inhibits anisomycin activated p38 in a dose-dependent manner with an IC₅₀ below 10 nM. LPS-stimulated TNF- α production is potently inhibited by PP58 with a cellular IC₅₀ value of around 3 nM[1]. The T341M mutation abrogates the sensitivity to PP58

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inhibition by increasing the cellular IC₅₀ value of about 10 nM by more than 1000-fold. The cellular wild-type FGFR1 activity is potently inhibited by low nanomolar concentrations of PP58, whereas dramatic resistance formation is detected for the FGFR1-V561M mutant. PP58 inhibits CSK activity with an IC₅₀ value of around 100 nM[2].

PP58 can exhibit some degree of selectivity at low nanomolar concentrations in vivo[1].

[1]. Wissing J, et al. Chemical Proteomic Analysis Reveals Alternative Modes of Action for Pyrido[2,3-d]pyrimidine Kinase Inhibitors. Mol Cell Proteomics. 2004 Dec;3(12):1181-93. [2]. Blencke S, et al. Characterization of a conserved structural determinant controlling protein kinase sensitivity to selective inhibitors. Chem Biol. 2004 May;11(5):691-701.

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