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产品名称: **A 419259 (trihydrochloride)**

产品别名: **RK 20449 trihydrochloride**

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| 生物活性:                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                     |           |           |            |
| Description               | A 419259 trihydrochloride is a Src family kinases inhibitor with IC <sub>50</sub> s of 9 nM, 3 nM and 3 nM for Src, Lck and Lyn, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |           |           |            |
| IC <sub>50</sub> & Target | IC50: 9 nM (Src), <3 nM (Lck), <3 nM (Lyn), 3 μM (Abl) <sup>[1]</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |           |           |            |
| In Vitro                  | A 419259 Trihydrochloride is a second-generation pyrrolo-pyrimidine designed to enhance selectivity towards the Src family relative to other cytoplasmic tyrosine kinases. A-419259 inhibits K-562 cells with an IC <sub>50</sub> between 0.1 and 0.3 μM, and Meg-01 proliferation with an IC <sub>50</sub> of approximately 0.1 μM. A-419259 also potently induces apoptosis in K-562 cells beginning at 0.1 μM and increasing in a dose-dependent manner. PP2 inhibits Src kinase autophosphorylation in both Ph <sup>+</sup> cell lines (K-562 and Meg-01) with an IC <sub>50</sub> between 3 and 10 μM, while A-419259 blocks kinase activation between 0.1 and 0.3 μM. A-419259 strongly inhibits DAGM/Bcr-Abl cell proliferation in the absence of IL-3 with an IC <sub>50</sub> between 0.1 and 0.3 μM <sup>[1]</sup> . A-419259 is a broad-spectrum pyrrolo-pyrimidine inhibitor, and blocks proliferation and induces apoptosis in CML cell lines. A-419259 inhibits overall SFK activity in K562 and other CML cell lines with an IC <sub>50</sub> value of 0.1-0.3 μM <sup>[2]</sup> . |                                     |           |           |            |
| Solvent&Solubility        | <b><i>In Vitro:</i></b><br><b>H<sub>2</sub>O : ≥ 55 mg/mL (92.91 mM)</b><br><b>DMSO : 1 mg/mL (1.69 mM; Need ultrasonic)</b><br><br>* "≥" means soluble, but saturation unknown.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                     |           |           |            |
|                           | Preparing Stock Solutions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <div>SolventMassConcentration</div> | 1 mg      | 5 mg      | 10 mg      |
|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1 mM                                | 1.6892 mL | 8.4459 mL | 16.8919 mL |
|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 5 mM                                | 0.3378 mL | 1.6892 mL | 3.3784 mL  |
|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 10 mM                               | 0.1689 mL | 0.8446 mL | 1.6892 mL  |
|                           | *请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液; 一旦配成溶液, 请分装保存, 避免反复冻融造成的产品失效。<br><br>储备液的保存方式和期限: -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |           |           |            |
| References                | [1]. Wilson MB, et al. Selective pyrrolo-pyrimidine inhibitors reveal a necessary role for Src family kinases in Bcr-Abl signal transduction and oncogenesis. Oncogene. 2002 Nov 21;21(53):8075-88.<br><br>[2]. Pene-Dumitrescu T, et al. An inhibitor-resistant mutant of Hck protects CML cells against the antiproliferative and apoptotic effects of the broad-spectrum Src family kinase inhibitor A-419259.Oncogene (2008) 27, 7055-7069                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |           |           |            |
| 实验参考:                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                     |           |           |            |
|                           | K-562 cells are grown in RPMI 1640 supplemented with 10% fetal calf serum (FCS), and 50 g/mL Gentamycin. Meg-01 cells are cultured in Vitacell modified RPMI 1640 (ATCC), supplemented with 10% FCS and 50 μg/mL Gentamycin. The human GM-CSF-dependent myeloid leukemia cell line TF-1 is grown in RPMI 1640 supplemented with 10% FCS, 50 μg/mL Gentamycin, and 1 ng/mL of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                     |           |           |            |



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| <b>Cell Assay</b>   | <p>recombinant human GM-CSF. DAGM murine myeloid leukemia cells are cultured in RPMI 1640 supplemented with 10% FCS, 50 µg/mL Gentamycin, and 0.5 ng/mL recombinant IL-3. Concentrated stock solutions of PP2 (5 mM) and A-419259 (2 mM) are prepared in DMSO and stored at -20°C. Cellular proliferation is measured using the Live/Dead growth assay. This assay employs calcein-AM, a fluorogenic esterase substrate that is taken up by viable cells and hydrolyzed intracellularly, releasing a green fluorescent product. Briefly, 10<sup>4</sup> cells are plated per well in 96-well plates for each day of a 4-day time course. Various concentrations of PP2, A-419259 or vehicle control are added to the wells (five wells per concentration per day) and the plates are incubated at 37°C. At each time point, one plate is centrifuged at 1500 g for 10 min to pellet the cells. Cells are washed with phosphate buffered saline (PBS), and calcein-AM is added to each well to a final concentration of 1 µM. Plates are incubated in the dark at room temperature for 1 h. The plates are then read at 485/530 nm (excitation/emission) using a SpectraMax Gemini XS fluorescent plate reader and data are analysed with SoftMax Pro software<sup>[1]</sup>.</p> |
| <b>Kinase Assay</b> | <p>In vitro kinase assays are performed on His<sub>6</sub>-tagged Lck (residues 62-509) and full-length c-Abl purified from Sf-9 cells, and commercial sources of Lyn, Src and PKC. Lck, Lyn, Src and Abl activities are measured with an ELISA-based assay. Flat bottom 96-well ELISA plates are incubated with a 200 µg/mL solution of Poly(Glu,Tyr) 4 : 1 substrate in phosphate buffered saline (PBS) for 1 h at 37°C and then washed with PBS containing 0.1% Tween-20 (PBS-T). Inhibitor dilutions are added to the washed plates already containing the appropriate enzyme in kinase assay buffer (250 mM Mopso, pH 6.75, 10 mM MgCl<sub>2</sub>, 2 mM MnCl<sub>2</sub>, 2.5 mM DTT, 0.02% BSA, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 5% DMSO, 5 µM ATP). After incubation at room temperature for 20 min, plates are washed three times with PBS-T and plate-bound phosphotyrosine is detected with an anti-phosphotyrosine-HRP antibody conjugate and subsequent color development with K-Blue reagents. All assays are optimized to use the least amount of enzyme necessary for a reproducible signal-to-noise ratio<sup>[1]</sup>.</p>                                                                                                                                  |
| <b>References</b>   | <p>[1]. Wilson MB, et al. Selective pyrrolo-pyrimidine inhibitors reveal a necessary role for Src family kinases in Bcr-Abl signal transduction and oncogenesis. <i>Oncogene</i>. 2002 Nov 21;21(53):8075-88.</p> <p>[2]. Pene-Dumitrescu T, et al. An inhibitor-resistant mutant of Hck protects CML cells against the antiproliferative and apoptotic effects of the broad-spectrum Src family kinase inhibitor A-419259. <i>Oncogene</i> (2008) 27, 7055-7069</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |