

Product Data Sheet

Product Name: Elacridar
Cat. No.: GC17215

Chemical Properties

Cas. No. 143664-11-3

Chemical Name N-[4-[2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]phenyl]-5-methoxy-9-oxo-10H-acridine-4-carboxamide

SMILES COC1=CC=CC2=C1NC3=C(C2=O)C=CC=C3C(=O)NC4=CC=C(C=C4)CCN5CCC6=CC(=C(C=C6C5)OC)OC

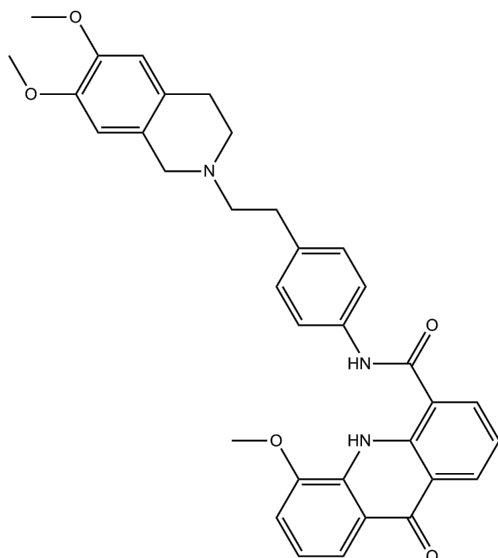
Formula $C_{34}H_{33}N_3O_5$ M.Wt 563.64

Solubility ≥ 56.4 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

Cell experiment [1]:

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Cell lines Human renal carcinoma cell lines 786-O and human breast cancer cell line MCF-7

Preparation method The solubility of this compound in DMSO is > 56.4mg/mL. 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.

Reacting condition 5 µM, 24 h

Applications Elacridar is a P-glycoprotein inhibitor that also block ABC Sub-family B Member 2 (ABCG2). Elacridar significantly enhanced sunitinib-induced cytotoxicity in 786-O cells. Confirmed by P-glycoprotein function assay, P-glycoprotein activity was inhibited by elacridar.

Animal experiment [2]:

Animal models 10-14-week wild-type, Abcb1a/1b^{-/-}, 32Abcg2^{-/-} and Abcb1a/1b/Abcg2^{-/-} mice, all of a >99% FVB genetic background

Dosage form Oral administration, 100 mg/kg

Application Elacridar significantly increased sunitinib brain accumulation in wild-type mice (12-fold), to levels equal to those in Abcb1a/1b/Abcg2^{-/-} mice. The sunitinib brain concentrations were not significantly affected by elacridar treatment in Abcb1a/1b/Abcg2^{-/-} mice.

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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]. Sato H, Siddig S, Uzu M, et al. Elacridar enhances the cytotoxic effects of sunitinib and prevents multidrug resistance in renal carcinoma cells[J]. European journal of pharmacology, 2015, 746: 258-266.

[2]. Tang S C, Lagas J S, Lankheet N A G, et al. Brain accumulation of sunitinib is restricted by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) and can be enhanced by oral elacridar and sunitinib coadministration[J]. International journal of cancer, 2012, 130(1): 223-233.

Background

Elacridar is a potent inhibitor of P-glycoprotein with IC₅₀ values of 193 nM. [1]

P-glycoprotein (permeability glycoprotein) is an important membrane protein. It pumps many foreign substances out of cells. P-glycoprotein belongs to the MDR/TAP subfamily. P-glycoprotein is transmembrane glycoprotein which is about 170 kDa. It is expressed in certain cell types primarily in the pancreas, liver, colon and kidney. It contains 6 transmembrane domains in the N-terminal half of the molecule. It also contains an ATP-binding site in the large cytoplasmic domain. P-glycoprotein binds to the substrate at the cytoplasmic side of the protein. When ATP binds to the cytoplasmic side, the substrate was excreted from the cell. P-glycoprotein can pump toxins or drugs back into the intestinal lumen, pumps them into bile ducts in liver cells. In some cancer cells, P-glycoprotein is overexpressed. It is involved in multidrug resistance of cancer cells.[2]

Elacridar can significantly inhibit the activity of P-glycoprotein at 1 μ M in MDCKII cells which overexpress P-glycoprotein.[3] In the parental MDCK-II cells, elacridar at 5 μ M completely inhibit the polarized sunitinib transport.[4] Elacridar did not inhibit the activity of several human cytochrome P450 enzymes in vitro. The absolute bioavailability was about 0.47 and 1.3 respectively, when elacridar was given in the orally and microemulsion, intraperitoneally at 10 mg/kg in mice.[3] Elacridar also can significantly increase sunitinib brain accumulation levels in mice at 10 mg/kg.[4]

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References:

- [1]. Bankstahl JP, Bankstahl M, Romermann K, Wanek T, Stanek J, Windhorst AD, Fedrowitz M, Erker T, Muller M, Loscher W et al: Tariquidar and elacridar are dose-dependently transported by P-glycoprotein and Bcrp at the blood-brain barrier: a small-animal positron emission tomography and in vitro study. *Drug Metab Dispos*, 41(4):754-762.
- [2]. Aller SG, Yu J, Ward A, Weng Y, Chittaboina S, Zhuo R, Harrell PM, Trinh YT, Zhang Q, Urbatsch IL et al: Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. *Science* 2009, 323(5922):1718-1722.
- [3]. Sane R, Mittapalli RK, Elmquist WF: Development and evaluation of a novel microemulsion formulation of elacridar to improve its bioavailability. *J Pharm Sci*, 102(4):1343-1354.
- [4]. Tang SC, Lagas JS, Lankheet NA, Poller B, Hillebrand MJ, Rosing H, Beijnen JH, Schinkel AH: Brain accumulation of sunitinib is restricted by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) and can be enhanced by oral elacridar and sunitinib coadministration. *Int J Cancer*, 130(1):223-233.

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