Tariquidar

Cat. No.: HY-10550

CAS No.: 206873-63-4

Molecular Formula: $C_{38}H_{38}N_4O_6$

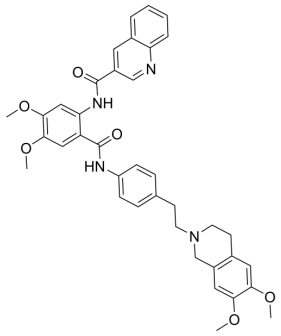
Molecular Weight: 646.73

Target: P-glycoprotein

Pathway: Membrane Transporter/Ion Channel

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 16 mg/mL (24.74 mM; ultrasonic and warming and adjust pH to 3 with HCl and heat to 60°C)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.5462 mL	7.7312 mL	15.4624 mL
5 mM	0.3092 mL	1.5462 mL	3.0925 mL
10 mM	0.1546 mL	0.7731 mL	1.5462 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (3.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tariquidar (XR9576) is a potent and specific inhibitor of P-glycoprotein (P-gp) with the high affinity (K_d=5.1 nM)[1].

IC_{50} & Target

Kd: 5.1 nM (P-gp)[1]

In Vitro

Tariquidar (XR9576) is a potent modulator of P-gp mediated [^{3}H]-Vinblastine and [^{3}H]-Paclitaxel transport as it increases the steady-state accumulation of these cytotoxics in CH^{r}B30 cells to levels observed in non-P-gp-expressing AuxB1 cells (EC_{50} =487±50 nM). [^{3}H]-Tariquidar binds to CH^{r}B30 membranes with the highest affinity (K_d=5.1±0.9 nM, n=7) and a binding capacity (B_{max}) of 275±15 pmol/mg membrane protein. In contrast to the parental cell line, the accumulation of [^{3}H]-Vinblastine is increased in a dose-dependent fashion by the modulators Tariquidar (EC_{50}=487±50 nM). The MDR modulator Tariquidar is able to inhibit 60-70% of the vanadate-sensitive ATPase activity, with potent IC_{50} value of 43±9 nM[1]. Tariquidar (XR9576) potentiates the cytotoxicity of several drugs including Doxorubicin, Paclitaxel, Etoposide, and

	Vincristine; complete reversal of resistance is achieved in the presence of 25-80 nM XR9576. Tariquidar is a potent inhibitor of photoaffinity labeling of P-gp by [^{3}H]Azidopine implying a direct interaction with the protein[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In mice bearing the intrinsically resistant MC26 colon tumors, coadministration of Tariquidar (XR9576) potentiates the antitumor activity of Doxorubicin without a significant increase in toxicity; maximum potentiation is observed at 2.5-4.0 mg/kg dosed either i.v. or p.o. In addition, coadministration of Tariquidar (6-12 mg/kg p.o.) fully restores the antitumor activity of Paclitaxel, Etoposide, and Vincristine against two highly resistant MDR human tumor xenografts (2780AD, H69/LX4) in nude mice. Tariquidar is found to also significantly potentiate the antitumor activity of doxorubicin against s.c. MC26 tumors in vivo[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Cells (EMT6 AR1.0 8×10^2/well; A2780 5×10^3/well; 2780AD 6×10^3/well) are seeded into 96-well plates. After ~4 h, varying concentrations of Tariquidar are added, and cells are incubated for an additional 4 days (EMT6 AR1.0) or 6 days (2780AD) before quantification of cell growth and calculation of IC_{10} values (concentration resulting in 10% inhibition of cell growth) [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] MC26 tumor slurry is implanted s.c. in BALB/c mice (day 0). The animals are then randomized, 24 h later, into groups of 15-18 and treated once with various regimens. Tariquidar or vehicle is administered either i.v. via a lateral tail vein or p.o. with Doxorubicin (5 mg/kg) or vehicle i.v. The modulator is administered either i.v. at 2-4 mg/kg (10 mL/kg) at the same time as Doxorubicin or p.o. at 2-8 mg/kg (10 mL/kg) 1 h before the Cytotoxic drug. GG918 is administered p.o. 1 h before doxorubicin. All of the animals are weighed twice weekly. The animals are killed by cervical dislocation on day 14, and the tumors are excised and weighed. The data are analyzed by Student's t test. Rats[2] Male CD rats (3 animals per time point) are dosed i.v. with paclitaxel alone [15 min infusion at 10 mg/kg in Tween 80:ethanol:5% dextrose (5:10:85% v/v/v)] or in combination with Tariquidar (10 mg/kg). Tariquidar is administered as a bolus (i.v.) dose 15 min before infusion of Paclitaxel. Blood samples are collected by cardiac puncture using heparinized syringes at various times between 0.083 and 48 h and are centrifuged to prepare plasma, which is stored at −20°C until analysis. Paclitaxel concentration in plasma samples is measured by a LC-MS/MS assay. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2023 Dec 7;186(25):5500-5516.e21.
- Sci Bull. 2016 Apr;61(7):552-560.
- Small. 2020 Nov;16(44):e2004172.
- J Control Release. 2022 Jul 8;349:109-117.
- J Control Release. 2021 Dec 28;342:44-52.

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REFERENCES

[1]. Martin C, et al. The molecular interaction of the high affinity reversal agent XR9576 with P-glycoprotein. Br J Pharmacol, 1999, 128(2), 403-411.

[2]. Mistry P, et al. In vitro and in vivo reversal of P-glycoprotein-mediated multidrug resistance by a novel potent modulator, XR9576. Cancer Res, 2001, 61(2), 749-758.

[3]. Zimmermann ES, et al. Simultaneous Semimechanistic Population Analyses of Levofloxacin in Plasma, Lung, and Prostate To Describe the Influence of Efflux Transporters on Drug Distribution following Intravenous and Intratracheal Administration. Antimicrob Agents Chemother. 2015 Nov 30;60(2):946-54.

[4]. Kao YH, et al. Regulation of P-glycoprotein expression in brain capillaries in Huntington's disease and its impact on brain availability of antipsychotic agents risperidone and paliperidone. J Cereb Blood Flow Metab. 2016 Aug;36(8):1412-23.

[5]. Matzneller P, et al. Pharmacokinetics of the P-gp Inhibitor Tariquidar in Rats After Intravenous, Oral, and Intraperitoneal Administration. Eur J Drug Metab Pharmacokinet. 2018 Apr 3.

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