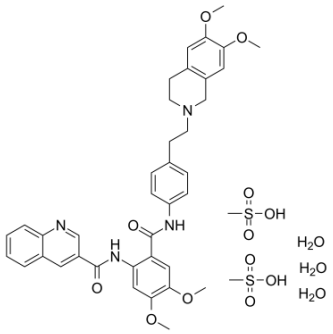
Tariquidar methanesulfonate, hydrate

Cat. No.:	HY-10550A
CAS No.:	625375-83-9
Molecular Formula:	$C_{40}H_{52}N_4O_{15}S_2$
Molecular Weight:	892.99
Target:	P-glycoprotein
Pathway:	Membrane Transporter/Ion Channel
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 296 mg/mL (331.47 mM)

H_2O : 5 mg/mL (5.60 mM; Need ultrasonic)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.1198 mL	5.5992 mL	11.1983 mL
	5 mM	0.2240 mL	1.1198 mL	2.2397 mL
	10 mM	0.1120 mL	0.5599 mL	1.1198 mL

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

In Vivo

1. Tariquidar methanesulfonate, hydrate is prepared in vehicle (2.5 % glucose solution)[3].

BIOLOGICAL ACTIVITY

Description

Tariquidar methanesulfonate, hydrate (XR9576 methanesulfonate, hydrate) is a potent and specific inhibitor of P-glycoprotein (P-gp) with a K_d of 5.1 nM.

IC_{50} & Target

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

In Vitro

Tariquidar methanesulfonate, hydrate (XR9576 methanesulfonate, hydrate) 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 XR9576 (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 Tariquidar. 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 methanesulfonate, hydrate (XR9576 methanesulfonate, hydrate) 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 methanesulfonate 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. Rat[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 methanesulfonate (10 mg/kg). Tariquidar methanesulfonate 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

- Small. 2020 Oct 8;e2004172.
- Sci Bull. 2016 Apr;61(7):552-560.
- J Cereb Blood Flow Metab. 2020 Oct 20;271678X20965500.
- J Cereb Blood Flow Metab. 2020 Jan;40(1):150-162.
- J Cereb Blood Flow Metab. 2016 Aug;36(8):1412-23.

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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]. Vraka C, et al. A new method measuring the interaction of radiotracers with the human P-glycoprotein (P-gp) transporter. Nucl Med Biol. 2018 Feb 14;60:29-36.

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