上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：Banoxantrone (dihydrochloride)
产品别名：AQ4N dihydrochloride

生物活性：

Description	Banoxantrone dihydrochloride is a novel bioreductive agent that can be reduced to a stable, DNA-affinic compound AQ4, which is a potent topoisomerase II inhibitor.
IC_{50} & Target	Topoisomerase II
In Vitro	Banoxantrone (AQ4N) can be reduced in a hypoxic environment to a stable DNA-affinic agent AQ4. AQ4, a potent topoisomerase II inhibitor, would be capable of damaging cells recruited into the cell cycle following radiation damage to the well-oxygenated cells of the tumor[1]. Banoxantrone shows more than 8-fold higher cytotoxicity under hypoxia than normoxia in cultures of 9L rat gliosarcoma and H460 human non-small-cell lung carcinoma cells but not for 11 other human cancer cell lines. DT-diaphorase protein levels and banoxantrone chemosensitivity are poorly correlated across the cancer cell line panel, and banoxantrone chemosensitivity is not affected by DT-diaphorase inhibitors[2]. Banoxantrone is a bis-N-oxide that is reduced via two sequential two-electron reductions to the tertiary amine, AQ4, which is a potent cytotoxic agent toward both aerobic and hypoxic cells. AQ4, but not AQ4N, intercalates in DNA with high affinity to generate a stable persistent complex that can inhibit topoisomerase II and cause DNA damage and cell death[3].
In Vivo	Banoxantrone (200 mg/kg) significantly enhances the tumor growth delay caused by radiation. This occurred when radiation is administered both as a single dose (12 Gy) and in a multifraction regimen (5x3 Gy). A study of the scheduling of Banoxantrone (AQ4N) administration shows that there is a very long time period over which a maximal effect can be elicited (drug given 4 days before to 6 h after radiation). These results suggest that Banoxantrone has significant potential as a bioreductive drug[1]. The activation of banoxantrone cytotoxicity in vivo requires tumor hypoxia that is more extensive or prolonged than can readily be achieved by vasodilation or by antiangiogenic drug treatment[2]. Incorporation of banoxantrone into conventional chemoradiation protocols therefore targets both oxygenated and hypoxic regions of tumors, and potentially will increase the effectiveness of therapy. A single dose of 60 mg/kg banoxantrone enhances the response of RT112 (bladder) and Calu-6 (lung) xenografts to treatment with cisplatin and radiation therapy. Banoxantrone will increase the efficacy of chemoradiotherapy in preclinical models[3].

In Vitro:

DMSO : ≥ 300 mg/mL (579.82 mM)

H_2O : 25 mg/mL (48.32 mM; Need ultrasonic and warming)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	1.9327 mL	9.6637 mL	19.3274 mL
	5 mM	0.3865 mL	1.9327 mL	3.8655 mL
	10 mM	0.1933 mL	0.9664 mL	1.9327 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。

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

Solvent&Solubility	储存时，请在 1 个月内使用。 ***In Vivo:*** 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 7.5 mg/mL (14.50 mM); Clear solution 此方案可获得 ≥ 7.5 mg/mL (14.50 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 75.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 7.5 mg/mL (14.50 mM); Clear solution 此方案可获得 ≥ 7.5 mg/mL (14.50 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 75.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。
References	[1]. Hejmadi MV, et al. DNA damage following combination of radiation with the bioreductive drug AQ4N: possible selective toxicity to oxic and hypoxic tumour cells. Br J Cancer. 1996 Feb;73(4):499-505. [2]. Manley E Jr, et al. Impact of tumor blood flow modulation on tumor sensitivity to the bioreductive drug banoxantrone. J Pharmacol Exp Ther. 2013 Feb;344(2):368-77. [3]. Williams KJ, et al. In vivo activation of the hypoxia-targeted cytotoxin AQ4N in human tumor xenografts. Mol Cancer Ther. 2009 Dec;8(12):3266-75.

实验参考：

Animal Administration	Mice[1] T50/80 tumor-bearing mice are used. These experiments are carried out when tumors reach a geometric diameter (GMD) of 6.5-9.0 mm. Banoxantrone (AQ4N) is administered as a single i.p. injection at a dose of 200 mg/kg. The drug is given 30 min before a single dose of X-irradiation of 12 Gy (300 kVp Siemens Stabilipan with a dose rate of 2.56 Gy min^{-1}). Tumors are excised at a range of times following treatment and placed on ice. Single cell suspensions are prepared in ice-cold PBS as outlined above. Following centrifugation the cells are diluted in cold EMEM containing 10% FCS ($1x10^6$ cells/mL). An aliquot of 100 μL of this suspension is used in the comet assay. This procedure is carried out on tumors excised at various time intervals ranging from 0 to 120 h following irradiation. The results are pooled from three individual experiments.
	Untreated T50/80 tumors (6.5-9.0 mm geometric diameter (GMD) are excised and gently disaggregated by mechanical disruption in ice-cold phosphate-buffered saline (PBS). Single cell suspensions are prepared by filtration through a 40μm mesh. These are then centrifuged and resuspended in Eagle's minimal essential medium (EMEM) containing 10% fetal calf serum (FCS) at a concentration of 10^6 cells/mL. Cells (20 mL) are placed in 125 mL rubber sealed glass bottles.

Kinase Assay	These are gassed for 2 h at 37°C to provide welloxygenated conditions, i.e. 95% air/5% carbon dioxide or hypoxic conditions 95% N_2/5% CO_2. Banoxantrone (AQ4N) (20μM) is added for the last 90 min of this period by injection through the sealed lid. Drug is washed off and cells resuspended in fresh medium. For analysis of DNA damage, aliquots (10^5 cells) are processed at various times ranging from 0 to 96 h after this procedure. To evaluate the effect of maintaining the excised tumor cells in culture, samples are also maintained in the culture medium above at 37°C, 95% air/5% CO_2 for 24 h. The cells, which grow in suspension, are then harvested and placed in glass bottles and the experiment outlined above is carried out. Each experiment is carried out twice and the results pooled[1].
References	[1]. Hejmadi MV, et al. DNA damage following combination of radiation with the bioreductive drug AQ4N: possible selective toxicity to oxic and hypoxic tumour cells. Br J Cancer. 1996 Feb;73(4):499-505. [2]. Manley E Jr, et al. Impact of tumor blood flow modulation on tumor sensitivity to the bioreductive drug banoxantrone. J Pharmacol Exp Ther. 2013 Feb;344(2):368-77. [3]. Williams KJ, et al. In vivo activation of the hypoxia-targeted cytotoxin AQ4N in human tumor xenografts. Mol Cancer Ther. 2009 Dec;8(12):3266-75.