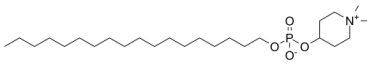
Data Sheet

Product Name:	Perifosine
Cat. No.:	CS-0209
CAS No.:	157716-52-4
Molecular Formula:	C25H52NO4P
Molecular Weight:	461.66
Target:	Akt; Apoptosis; Autophagy
Pathway:	Apoptosis; Autophagy; PI3K/Akt/mTOR
Solubility:	H2O : ≥ 153.33 mg/mL (332.13 mM); DMSO : < 1 mg/mL (insoluble or slightly soluble); DMF : < 1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

Perifosine is an oral **Akt** inhibitor. All cells are sensitive to the antiproliferative properties of Perifosine with an IC_{50} of ~0.6-8.9 μM. IC50 & Target: Akt[1] **In Vitro:** The IC_{50} for growth of Ntv-a/LacZ cell lines is determined by MTT assay. When the cells are cultured for 48 hours in 10% FCS-supplemented media, the IC_{50} for cells with constitutively active PDGF, Ras, or Akt signaling is similar and found to be ~45 μM[1].Perifosine, a oral-bioavailable alkylphospholipid (ALK), on the cell cycle kinetics of immortalized keratinocytes (HaCaT) as well as head and neck squamous carcinoma cells. Proliferation is assessed by the incorporation of [^{3}H]thymidine into cellular DNA. Exposure to Perifosine (0.1-30 μM) for 24 h results in a dose-dependent inhibition of [^{3}H]thymidine uptake in all cell lines tested. The IC_{50}s for growth are between 0.6 and 8.9 μM, reaching IC_{80}s of ~10 μM. Perifosine blocks cell cycle progression of head and neck squamous carcinoma cells at G_1-S and G_2-M by inducing $p21^{WAF1}$, irrespective of p53 function, and may be exploited clinically because the majority of human malignancies harbor p53 mutations. Perifosine (20 μM) induces both G_1-S and G_2-M cell cycle arrest, together with $p21^{WAF1}$ expression in both p53 wild-type and $p53^{-/-}$ clones[2]. **In Vivo:** Mice are identified with tumors by bioluminescence imaging and either treated them with 100 mg/kg Temozolomide, or 30 mg/kg Perifosine, or a combination with 100 mg/kg Temozolomide and 30 mg/kg Perifosine (Temozolomide+Perifosine) for 3 to 5 days. The mice are sacrificed and tumors analyzed histologically for cell proliferation by Ki-67 immunostaining. Ki-67 staining index is significantly reduced in mice treated with either Temozolomide (Ki-67 staining index=5.5±1.2%, n=4, P=0.0019) or Perifosine (Ki-67 staining index=3.2±1.1%, n=3, P=0.001) compared with Control, demonstrating the inhibitory effect on proliferation. Most importantly, the tumors treated with Temozolomide+Perifosine have the lowest Ki-67 staining index (1.7±1.2%, n=3, P=0.0005). The additional treatment with Perifosine results in a significantly lower proliferation rate than Temozolomide alone (P=0.0087)[1]. Perifosine markedly decreases p-Akt from 10 min to 24 hours and subsequently, moderately decreased p-S6 from 1h to 24 h after injection[3].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [2]Exponentially growing cells (HN12, HN30, and HaCaT) are lysed, and 500 μg of total cellular protein are used to immunoprecipitate active cdc2 and cdk2 complexes. After capturing with gammabind G Sepharose and subsequent washes, the active immune complexes are assessed for activity in the presence of increasing concentrations of Perifosine (0.1-30 μM) or flavopiridol (300 nM) in the kinase assay buffer containing [γ-^{32}P]ATP (3000 Ci/mmol) and 0.2 mg/mL histone H1, 25 μM ATP. Reactions are incubated at 37°C for 30 min and terminated by the addition of SDS-gel loading buffer, resolved in SDS-PAGE, and dried gels are subjected to autoradiography and phosphorimaging[2]. **Cell Assay:** Perifosine is reconstituted in PBS (100 mM) and further diluted in PBS to the working concentration (0.1-30 μM)[2].[2]Cell proliferation studies by measuring the uptake of [^{3}H]thymidine is performed. Briefly, HNSCC and HaCaT cells (1-2×10^4/well) are grown overnight in 24-well plates and exposed to either Perifosine (0.1-30 μM) or PBS (control). After treatment (24-48 h), cells are pulsed with [^{3}H]thymidine (1 μCi/well) for 4-6 h, fixed (5% trichloroacetic acid), and solubilized (0.5 M NaOH) before scintillation counting. Experiments are performed in triplicates[2]. **Animal Administration:** Perifosine

stock solutions are prepared in 0.9% NaCl solution (Mice)[1].
Perifosine is dissolved in DMSO and diluted in a vehicle solution containing Tween 80 (Rats)[3].[1][3]Mice[1]
Drug treatment of tumor-bearing mice. Image-positive Ef-luc Ntv-a mice are treated daily with i.p. administration of buffer alone as a control, or i.p. administration of 100 mg/kg Temozolomide, or oral administration of 30 mg/kg Perifosine, or a combination with Perifosine and Temozolomide for 3 to 5 days. The mean doses of the treatments are: Control, 5 (all five); Temozolomide, 3.75 (three to five); Perifosine, 3.75 (three to four); and Perifosine+Temozolomide, 3 (all three). Control buffer solution consisted of 5% DMSO and 1% Tween 80 in distilled water.
Rats[3]
To further determine whether the paradoxical effect of rapamycin on S6 phosphorylation is related to upstream signals of Akt-mTOR, rats are treated with Perifosine (20 mg/kg, ip, once), an Akt inhibitor, 30 min before rapamycin administration. Rats are sacrificed 1 h or 6 h after rapamycin injection.

References:

[1]. Momota H, et al. Perifosine inhibits multiple signaling pathways in glial progenitors and cooperates with temozolomide to arrest cell proliferation in gliomas in vivo. Cancer Res, 2005, 65(16), 7429-7435.

[2]. Vyomesh Patel, et al. Perifosine, a novel alkylphospholipid, induces p21(WAF1) expression in squamous carcinoma cells through a p53-independent pathway, leading to loss in cyclin-dependent kinase activity and cell cycle arrest. Cancer Res, 2002, 62(5), 14

[3]. Chen L, et al. Rapamycin has paradoxical effects on S6 phosphorylation in rats with and without seizures. Epilepsia. 2012 Nov;53(11):2026-33.

CAIndexNames:

Piperidinium, 4-[[hydroxy(octadecyloxy)phosphinyl]oxy]-1,1-dimethyl-, inner salt

SMILES:

[O-]P(OC1CC[N+](C)(CC1)C)(OCCCCCCCCCCCCCCCCCC)=O

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