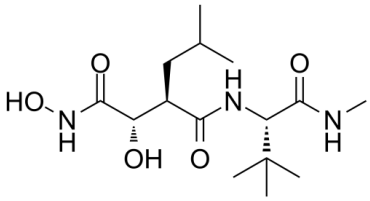
Data Sheet

Product Name:	Marimastat
Cat. No.:	CS-3456
CAS No.:	154039-60-8
Molecular Formula:	C15H29N3O5
Molecular Weight:	331.41
Target:	MMP
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : 100 mg/mL (301.74 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Marimastat (BB2516) is a broad spectrum and orally bioavailable inhibitor of **MMPs**, with potent activity against MMP-9 (**IC_{50}**=3 nM), MMP-1 (**IC_{50}**=5 nM), MMP-2 (**IC_{50}**=6 nM), MMP-14 (**IC_{50}**=9 nM) and MMP-7 (**IC_{50}**=13 nM), used in the treatment of cancer. Marimastat (BB2516) is an angiogenesis and metastasis inhibitor, which limits the growth and production of blood vessels. As an antimetatstatic agent it prevents malignant cells from breaching the basement membranes[1][2]. IC50 & Target: IC50: 3 nM (MMP-9), 5 nM (MMP-1), 6 nM (MMP-2), 9 nM (MMP-14), 13 nM (MMP-7) **In Vitro:** Marimastat (BB2516) (1 μM) shows inhibition of vascular outgrowth, and selectively affects angiogenesis[3]. **In Vivo:** Animals receiving chemoradiation + Marimastat (BB2516) (8.7 mg/kg) have statistically significant delayed growth, compared to animals receiving chemoradiation alone. Marimastat (BB2516) may work in combination with chemotherapy and radiation to inhibit tumor growth[4].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]Compounds 1, 2, 7-9 and 11-16 are pre-incubated with MMP-1 or MMP-3 (10 nM) at different concentrations (0-10 μM) in a mixture of Tris-HCl (50 mM, pH 7.5), NaCl (150 mM), $CaCl_2$ (10 mM), NaN_3 (0.02%) and Brij-35 (0.05%) for 1 hour at 37°C. Residual activity is measured using the fluorogenic MMP substrate (2 μM) by fluorescence increase (emission at 393 nm and excitation at 325 nm) on a fluorescence plate reader. The data are fitted to the tight binding inhibitor equation: v=[(E-I-k+[(E-I-k)2+4Ek]1/2)/(2E)], where v is the velocity of the reaction, E is the enzyme concentration, I is the initial inhibitor concentration, and k is the apparent inhibition constant, using the software Prism. **Animal Administration:** Marimastat is dissolved in DMSO.[3]Three-month-old female nude mice are inoculated using a trochar needle with 2 mm^2 established SCC-1 tissue subcutaneously in the flank. Treatment started once the tumors are 5-6 mm in diameter. Mice are randomLy divided into groups of 8 mice to receive different treatments: (1) control, (2) marimastat alone, (3) cisplatin + radiation in combination and (4) marimastat + cisplatin + radiation in combination. All animalsreceive a 14-day osmotic pump containing dimethylsulfoxide (DMSO) as a control for both the pump and vehicle. Animals treated with marimastatreceive the same osmotic pump containing 200 μL of marimastat with DMSO to result in a daily dose of 8.7 mg/kg 10 days after the initiation of treatment. Lead-shielded animalsreceive 8 Gy of 60Co radiation to the exposed tumor, divided into 4 fractions on days 8, 12, 16 and 20. A dose of 8 Gy is chosen because 7.5 Gy (7,500 rad) has been shown in previous experiments to inhibit tumor growth without being a curative dose. Animals receive 4 intraperitoneal doses of cisplatin (3 mg/kg) 1 h before each fraction of radiation. Tumors are measured biweekly for 32 days. Potential treatment toxicity is monitored using mouse weight. Tumor size (surface area equal to product of two largest diameters) and regression rates are determined in each treatment group. After 32 days, tumors are harvested for immunohistochemistry. Day 32 is chosen due to death of control group animals and euthanization of animals showing clinical signs of illness to allow for statistical analysis of data acquired from surviving animals.

References:

[1]. Rasmussen HS, et al. Matrix metalloproteinase inhibition as a novel anticancer strategy: a review with special focus on batimastat and marimastat. Pharmacol Ther. 1997;75(1):69-75.

[2]. Yu M, et al. Incorporation of Bulky and Cationic Cyclam-Triazole Moieties into Marimastat Can Generate Potent MMP Inhibitory Activity without Inducing Cytotoxicity. ChemistryOpen. 2013 Jun;2(3):99-105.

[3]. van Wijngaarden J, et al. An in vitro model that can distinguish between effects on angiogenesis and on established vasculature: actions of TNP-470, marimastat and the tubulin-binding agent Ang-510. Biochem Biophys Res Commun. 2010 Jan 8;391(2):1161-5.

[4]. Skipper JB, et al. In vivo efficacy of marimastat and chemoradiation in head and neck cancer xenografts. ORL J Otorhinolaryngol Relat Spec. 2009;71(1):1-5.

CAIndexNames:

Butanediamide, N4-[(1S)-2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, (2S,3R)-

SMILES:

O=C(NO)[C@@H](O)[C@@H](CC(C)C)C(N[C@H](C(NC)=O)C(C)(C)C)=O

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