Angiogenesis

PRODUCT GUIDE

www.biomol.com/angiogenesis

Featuring:

VEGF

Angiogenesis inhibitors

Akt and PI 3-kinase

HIF-1α

Sphingosine-1-phosphate

MMPs and cathepsins

Cytoskeleton

Nitric oxide

BIOMOL®

INTERNATIONAL, LP

Lifetime Achievement Award presented to Judah Folkman (right) at the Miami Nature Winter Symposium, 2006.

BIOMOL Honors Judah Folkman with Lifetime Achievement Award

In 1971, a promising young surgeon and researcher hypothesized that all tumor growth is dependent on the formation of new blood vessels – a process termed angiogenesis – and that inhibition of angiogenesis would be an effective strategy to treat cancer[1]. With that paper, the field of angiogenesis research was born and to date $4 billion dollars has been spent on research and development of medicines that promote or reduce angiogenesis[2]. The pioneering idea to treat cancer with angiogenesis inhibitors put forth by this young scientist is becoming a reality with the recent FDA approval of angiogenesis inhibitors for cancer and other pathological diseases. This may only be the beginning, for it is predicted that in the coming decades, over 500 million people are expected to benefit from pro- or anti-angiogenic treatments worldwide[3].

BIOMOL is the proud sponsor of a Lifetime Achievement Award given to the researcher who originally proposed these ideas and founded the field of angiogenesis, Dr. Judah Folkman, Professor of Cell Biology at Harvard Medical School and Director of the Vascular Biology Program at Children's Hospital Boston. Dr. Folkman continues to be a leader in the field of angiogenesis research with 389 original peer-reviewed papers and 106 book chapters and monographs, including the discovery of the first angiogenic protein identified from a tumor.

Since the publication of Folkman's seminal paper in 1971, the understanding of angiogenesis has matured with the characterization of many pathways that regulate new blood vessel formation. One of the most important is the VEGF pathway, which when inhibited, blocks tumor growth[4]. VEGF is a major target of anti-angiogenesis drug discovery with FDA approvel of several drugs which interfere with VEGF signaling. VEGF expression is regulated by the hypoxia inducible factor, HIF-1α[5]. At normoxic conditions, HIF-1α is ubiquitinylated and degraded by the proteasome, but under the hypoxic conditions of a growing tumor, HIF-1α is stabilized and leads to upregulation of VEGF and other proangiogenic factors.

Sphingosine-1-phosphate (S1P) is another important regulator of vascular growth and development[6,7]. S1P regulates endothelial migration and survival[8], induces morphogenesis of endothelial cells into capillary-like structures[9-11], and synergizes with FGF2 and VEGF to induce angiogenesis in vivo[9]. S1P1, a S1P receptor is induced during angiogenesis in vivo and S1P signaling has recently been demonstrated to be required for tumor angiogenesis[12]. Given S1P signals through GPCRs, which have historically been highly druggable targets, the S1P pathway is an important target for anti-angiogenesis drugs.

Many stimulators of angiogenesis induce the release of nitric oxide (NO), which mediates endothelial survival, proliferation, migration and interaction with the extracellular matrix[13]. Inhibition of NO production impairs angiogenesis and agents which increase NO synthesis stimulate angiogenesis.

Upon stimulation, endothelial cells induce proteases belonging to the matrix metalloproteinase (MMP), serine and cysteine protease families to degrade the extracellular matrix (ECM), and migrate as new vascular 'sprouts'[14]. In addition, protease activity contributes to the release of positive and negative angiogenic factors from the ECM and cell surface.

Angiogenesis is a tightly regulated process influenced by not only the positive factors mentioned above, but negative regulatory factors as well. Angiostatin[15] and endostatin[16] are proteolytic fragments of larger proteins that act as negative regulators of angiogenesis. These factors act through binding specific integrins and stimulating many kinases including PKC, ERK1/2, Akt and FAK[17]. Many exogenous substances have been demonstrated to inhibit angiogenesis including the natural products fumagillin[18], borreledin[19], and withaferin[20] suggesting that natural products may be a rich source of new angiogenesis inhibitors.

With the increased understanding of the molecular pathways that regulate angiogenesis, there are now more opportunities to dissect angiogenic mechanisms and to develop new angiogenesis inhibitors for cancer, ocular diseases and inflammatory disorders. In addition, emerging ideas like therapeutic angiogenesis to treat ischemic disorders are creating new exciting areas of research. BIOMOL intends to continue its tradition of supplying cutting-edge reagents for angiogenesis research and helping you make the next seminal discovery.

Terms in YELLOW indicate important targets for which BIOMOL offers products.

1. J. Folkman N. Engl. *J. Med.* 1971 **285** 1182
2. N. DeWitt *Nature* 2005 **438** 931
3. P. Carmeliet *Nature* 2005 **438** 932
4. L. Coultas *et al. Nature* 2005 **438** 937
5. M. Safran and W.J. Kaelin Jr. *J. Clin. Invest.* 2003 **111** 779
6. T. Hla *Prostaglandins Other Lipid Mediat.* 2001 **64** 135
7. V.M. Sarder *et al. Biochim. Biophys. Acta* 1582 **309** 3
8. J.H. Paik *et al. J. Biol. Chem.* 2001 **276** 1183
9. M.J. Lee *et al. Cell* 1999 **99** 301
10. T. Sanchez *et al. J. Biol. Chem.* 2003 **278** 47281
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12. S-S. Chae *et al. J. Clin. Invest.* 2004 **114** 1082
13. J.P. Cook *Atheroscler Suppl.* 2003 **4** 53
14. R. Roy *et al. Exp Cell Res.* 2006 **312** 608
15. Y.H. Cao *et al. J. Biol. Chem.* 1996 **271** 29461
16. M.S. O'Reilly *et al. Cell* 1997 **88** 277
17. P. Nyberg *et al. Cancer Res.* 2005 **65** 3967
18. D. Ingber *et al. Nature* 1990 **348** 555
19. T. Wakabayashi *et al. J. Antibiot.(Tokyo)* 1997 **50** 671
20. R. Mohan *et al. Angiogenesis* 2004 **7** 115

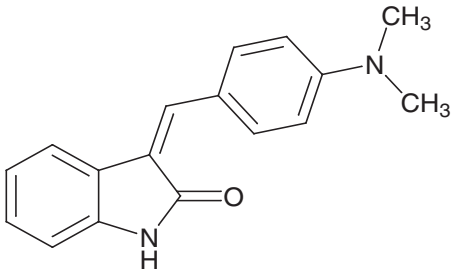
ANGIOGENESIS

TABLE OF CONTENTS

VEGF

SU 4312 EI-306

A potent and selective inhibitor of VEGFR2. It displays a 100-fold greater potency for the unactivated form of the kinase (K_i=0.04 μM) compared to the activated form (K_i=4 μM).



VEGFR2 SE-404

Human, recombinant cytoplasmic domain (a.a. 805-1356) with N-terminal GST tag, expressed in insect cells.

Receptor Tyrosine Kinases

Each is active cytoplasmic domain expressed in insect cells.

EphA2 . . . . . SE-432
EphB2 . . . . . SE-433
EphB4 . . . . . SE-405
FGFR1 . . . . . SE-291
FGFR3 . . . . . SE-292
Tie2 . . . . . SE-437

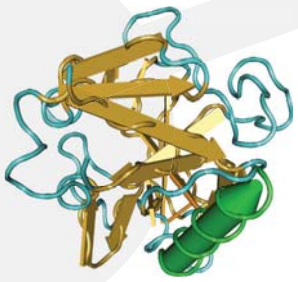
Angiostatin/Endostatin

Angiostatin (K1-3) (human, recombinant) SE-299

Recombinant angiostatin comprising Kringles 1-3 of human plasminogen. An endogenous inhibitor of tumor growth and angiogenesis.

Endostatin (human, recombinant) SE-300

Recombinant glycosylated endostatin comprising the C-terminal fragment (noncollagenous 1 domain) of collagen XVIII. An endogenous inhibitor of tumor growth and angiogenesis.



Tumor Necrosis Factor

Important Inducers of Angiogenesis

TNF-α SE-303

Recombinant human TNF-α produced in E. coli as a single, non-glycosylated polypeptide.

TNF-β SE-304

Recombinant, human TNF-β produced in E. coli as a single, non-glycosylated polypeptide.

MAP Kinase Pathway

The MAP kinase pathway functions both upstream and downstream of the VEGF signaling pathway regulating VEGF expression and mediating downstream VEGF and other receptor tyrosine kinase signaling.

Enzymes

H-Ras, wild-type	Human, recombinant	**SE-131**
H-Ras, CVLL-type	Human, recombinant with a C-terminal mutation to CVLL	**SE-132**
Raf1	Human, containing a GST tag, expressed in insect cells	**SE-414**
Erk1	Active, full-length Erk1 with an N-terminal GST tag	**SE-343**
Erk2, Activated	Rat Erk2 expressed in E. coli and activated by MEK1	**SE-137**
Erk2, Nonactivated	Same as above, but not activated by MEK1	**SE-139**
p38α	Full-length human; produced in a cell-free expression system	**SE-309**
p38γ	Full-length human; expressed in insect cells	**SE-426**
p38δ	Full-length human; expressed in insect cells	**SE-427**
JNK2α1	Full-length human; expressed in E. coli	**SE-265**
JNK2α2	Full-length human; expressed in E. coli	**SE-266**
JNK3	Full-length human; expressed in a cell-free expression system	**SE-320**

MAPK Pathway Inhibitors

ZM 336372	Potent and specific inhibitor of c-Raf (IC_{50}=70 nM)	**EI-298**
GW-5074	Potent c-Raf (IC_{50}=9 nM) inhibitor	**EI-307**
PD-98059	A potent and selective inhibitor of MEK	**EI-360**
U0126	MEK inhibitor (IC_{50}=72 nM) 100-fold more potent than PD-98059	**EI-282**
Olomoucine	Inhibits ERK1 (IC_{50}=25 μM)	**CC-200**
5-Iodotubercidin	Inhibits ERK2 (K_i=525 nM)	**EI-293**
SB-203580	A potent and selective inhibitor of p38 MAP kinase (K_i=21 nM)	**EI-286**
SB-202190	Inhibits p38 α and β (K_i=30 nM) but not γ and δ isoforms	**EI-294**

Antibodies

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
Shc (pY317)	rabbit pAb	H, M	WB	**SA-349**
Ras (amino-terminus)	rabbit pAb	H	WB	**SA-431**
Ras (a.a. 31-43)	rabbit pAb	H, M, R, C	IHC	**SA-435**
c-Raf-1 (pY340,pY341)	rabbit pAb	H, M, R	WB, IHC	**SA-366**
MEK1/2 (pS218, PS222)	rabbit pAb	H	WB	**SA-383**
MEK7	mAb (3F5)	H	WB	**SA-347**
ERK1&2 (MAPK)	rabbit pAb	H, M, R, C	WB	**SA-278**
ERK1&2 (pT185, pY187)	mAb (AMK1)	H	WB	**MA1366**
ERK 1&2 (pT185, pY187)	rabbit pAb	H, M, R, Ch	WB, IHC	**SA-275**
p38 (pT180, pY182)	rabbit pAb	H, M, R, D	WB	**SA-266**

C - cow, Ch - chicken, D - dog, H - human, M - mouse, R - rat; IHC - immunohistochemistry, WB - western blot

HIF-1α

An important transcriptional regulator of VEGF and other proangiogenic factors.

Modulators

DMOG (Dimethyloxaloylglycine) EI-347

A prolyl-4-hydroxylase inhibitor which upregulates HIF activity.

R59949 EI-202

R59949 is a prolyl-4-hydroxylase activator which inhibits the accumulation of HIF-1/2α.

YC-1 (3-(5'-Hydroxymethyl-2'-furyl)-1-benzylindazole) CN-223

Suppresses the DNA-binding activity and expression of HIF-1α. Inhibits tumor growth in several mouse models.

Dimethyl-Bisphenol A GR-339

Promotes HIF-1α degradation by dissociating HSP90 from HIF-1α.

Oligomycin A CM-111

Oligomycin inhibits HIF-1α expression in hypoxic tumor cells.

2-Methoxyestradiol S-540

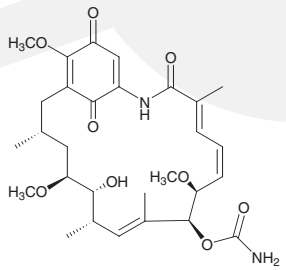
Posttranscriptionally downregulates HIF-1α expression. Potent inhibitor of endothelial cell proliferation and migration.

Antibodies

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
HIF-1α	mAb (H1α67)	H, M, R	WB, IP	**SA-287**
HIF-1α	mAb (OZ12)	H	GS	**SA-289**

H - human, M - mouse, R - rat; GS - gel supershift, IP - immunoprecipitation, WB - western blot

Geldanamycin



Geldanamycin EI-280

Geldanamycin is a benzoquinoid ansamycin produced by Streptomyces hygroscopicus. It binds specifically to heat shock protein HSP90 and downregulates target proteins including tyrosine kinases, steroid receptors, transcription factors and cell cycle regulatory kinases. It induces the inactivation, destabilization and eventual degradation of HIF-1α.

17-AAG (17-Allylamino-demethoxygeldanamycin) EI-308

A less toxic and more stable geldanamycin analog.

17-DMAG (17-Dimethyaminoethylamino-demethoxygeldanamycin) EI-337

A less toxic and more stable analog of geldanamcyin with superior pharmacological properties.

17-GMB-APA-GA (17-(3-(4-Maleimidobutyrcarboxamido)propylamino)-demethoxygeldanamycin) EI-338

An analog suitable for preparation of geldanamycin immunoconjugates.

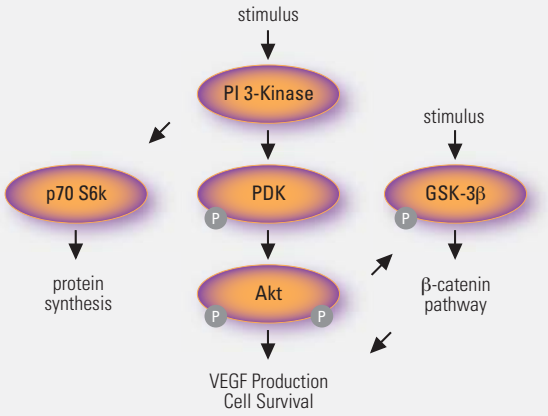
Biotin-Geldanamycin EI-341

A useful analog for affinity purification of HSP90 and related proteins containing ATP-binding domains.

Please inquire about the following geldanamycin analogs:

Aminopropylaminogeldanamycin - contains a linker arm that can accommodate various coupling chemistries.
17-DMAPG - A new analog with moderate potency at inhibition of SKBr3 tumor cell growth.

PI 3-Kinase/Akt



Enzymes

PI 3-Kinase SE-436

Full-length p110α and p85α

PDK1 SE-351

Human, recombinant (full length)

Akt1 (PKBα) SE-416

Human, recombinant (a.a. 2-480)

Akt2 (PKBβ) SE-247

Human, recombinant (a.a. 119-481)

Akt2 (PKBβ), Activated SE-248

Human, recombinant (a.a. 119-481)
Contains S473D and T308E activating mutations

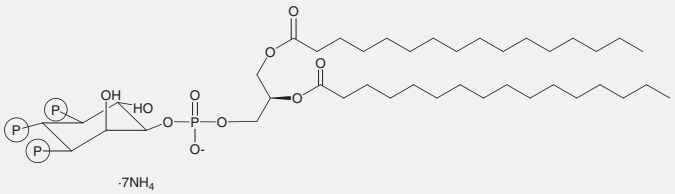
p70 S6 Kinase SE-345

Human, recombinant (full length)

GSK-3β SE-355

Human, recombinant (full length)

Phosphatidylinositols



PtdIns-3-P PH-105

Lipid product of PI 3-Kinase

PtdIns-3,4-P_2 PH-106

Lipid product of PI 3-Kinase; stimulates Akt

PtdIns-3,4,5-P_3 PH-107

Lipid product of PI 3-Kinase

PtdIns-4-P PH-101

Substrate for PI 3-Kinase

PtdIns-4,5-P_2 PH-102

Substrate for PI 3-Kinase

Akt and GSK3 Substrates

Akt (PKB) Peptide Substrate P-129

A variation of the GSK-3 phosphorylation site

Crosstide P-149

Derived from the GSK-3 phosphorylation site

PRAS40 SE-308

Proline-rich Akt Substrate (a. a. 2-256)

GSK-3 Peptide Substrate P-151

Sequence surrounding S540 of eIF2B

Antibodies

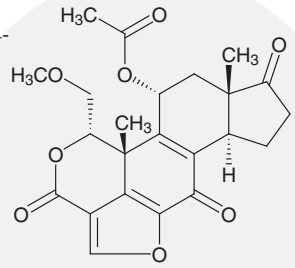
Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
PI 3-Kinase	mouse mAb (8-2D-4D)	H, M, R	WB, IF, IP	SA-269
Akt	mouse mAb (8F4)	H, M, A	WB	SA-312
Akt (pS473)	rabbit pAb	H, M, R, D	WB	SA-450
Dephospho-Akt (S473)	mouse mAb (11A11)	H, M, A	WB	SA-313
Akt (pT308)	rabbit pAb	H, M	WB	SA-290
PRAS40 (pT246)	rabbit pAb	H	WB	SA-360
GSK-3β	mouse mAb (6D3)	H, M	WB	SA-309
GSK-3β (pS9)	mouse mAb (2D3)	H, M	WB	SA-310
GSK-3α/β	mouse mAb (1HB)	H, M, R, F	WB, IP	SA-364
GSK-3β	mouse mAb (11B9)	H, M, R, D	WB	SA-414

A - Arabidopsis, D - dog, F - frog, H - human, M - mouse, R - rat; IF - immunofluorescence, IP - immunoprecipitation, WB - western blot

PI 3-Kinase Inhibitors

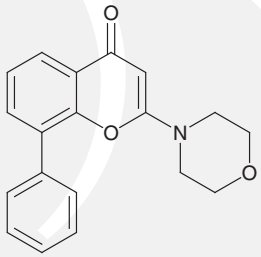
Wortmannin — ST-415

A potent and selective inhibitor of PI 3-kinase (IC_{50}=5 nM). Inhibits PI 4-kinase and MLCK at concentrations 100 fold higher than that required for inhibition of PI 3-kinase.



LY 294002 — ST-420

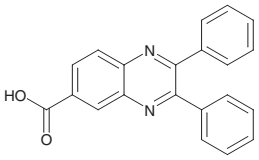
A potent and specific cell-permeable inhibitor of PI 3-kinase (1.4 µM). Inhibits all isoforms equally. PKC, PKA, MAP kinase, S6 kinase, EGFR, Src, PI 4-kinase, DAG kinase are not inhibited at 50 µM.



Akt Inhibitors

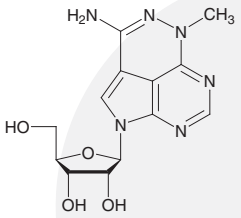
BML-257 — EI-336

[2,3-Diphenylquinoxaline-6-carboxylic acid] - Inhibits the translocation of Akt.



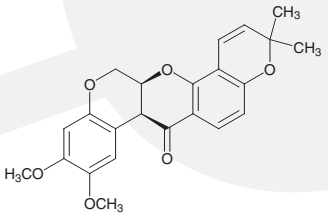
Triciribine — EI-332

Inhibits the phosphorylation of Akt-2 at Thr-309 and Ser-474, sites required for full activation of the enzyme. Triciribine inhibits an as yet unknown upstream activator of Akt but does not inhibit PI 3-kinase or PDK1. It inhibits cell growth and induces apoptosis preferentially in cells expressing aberrant Akt. Triciribine is phosphorylated by adenosine kinase and this may be required for its activity.



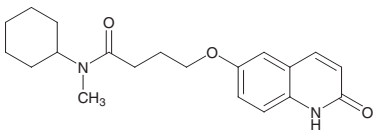
Deguelin — EI-329

Deguelin is a natural plant product isolated from Mundulea sericea that displays profound antiproliferative activity mediated via inhibition of the PI 3-K/Akt signaling pathway. Malignant human bronchial epithelial cells are highly sensitive to deguelin compared to normal cells.



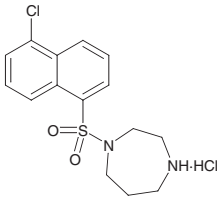
Cilostamide — PD-125

A selective inhibitor of phosphodiesterase PDE-3B. Blocks Akt signaling by inhibiting Akt-activated PDE-3B.



ML-9 — EI-153

Cell-permeable non-selective Akt inhibitor (IC_{50}=10-50 µM).



Geldanamycin

Akt forms a complex with HSP90. Geldanamycin inhibition of Akt-HSP90 binding leads to the dephosphorylation and inactivation of Akt, increasing sensitivity of cells to apoptosis-inducing stimuli.

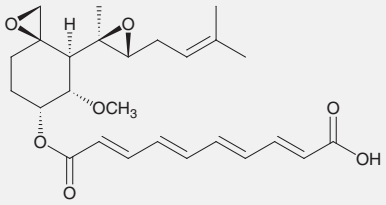
See page 3 for more information on geldanamycin and geldanamycin analogs.

Angiogenesis Inhibitors

Natural products - a rich source of angiogenesis inhibitors

Fumagillin **CT-100**

A structurally novel natural product isolated from the fermentation broth of Aspergillus fumigatus and member of a small family of related compounds which includes ovalicin. It is a potent inhibitor of angiogenesis which directly inhibits endothelial cell proliferation. Fumagillin inhibits the aminopeptidase activity of methionine aminopeptidase 2 (MetAP2) without interfering with its association with eIF-2α.

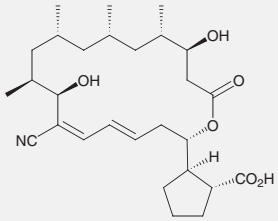


Fumagillin analogs and bulk supply – Selected analogs of fumagillin such as biotinylated fumagillin and other analogs with interesting chemical modifications are available. Please inquire with BIOMOL Technical Service (techserv@biomol.com).

Fumagillin is now available from BIOMOL in bulk quantities at economical prices. Please inquire.

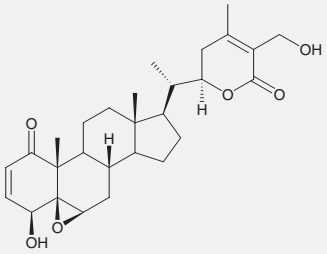
Borrelidin **CT-103**

Displays pronounced anti-angiogenic activity (IC_{50}=0.8 nM) and also induces the collapse of formed capillary tubes in a dose-dependent fashion. In HUVECs, the capillary tube collapsing activity is mediated by the induction of apoptosis.



Withaferin A **CT-104**

A potent inhibitor of endothelial cell (HUVEC) sprouting (IC_{50}=12 nM) and is active in vivo. It alters cytoskeletal architecture by covalently binding annexin II and stimulating its basal F-actin cross-linking activity, which inhibits the migratory and invasive capability of endothelial cells.



Taxol **T-104**

Antitumor agent isolated from the bark of the Pacific Yew tree (Taxus brevifolia). Stabilizes microtubules and lowers the critical concentration for tubulin polymerization.

Shikonin **CT-115**

Inhibits TNFα- and B6 melanoma-induced angiogenesis in mice. Blocks expression of integrin $\alpha_v\beta_3$ and inhibits endothelial cell proliferation and migration in vitro.

Cytochalasin E **CT-120**

An actin microfilament disrupting agent that inhibits the proliferation of bovine capillary endothelial cells. Inhibits angiogenesis and tumor growth in vivo.

Ursolic Acid **CT-105**

Inhibits endothelial cell proliferation and migration (IC_{50}=5 μM) and angiogenesis.

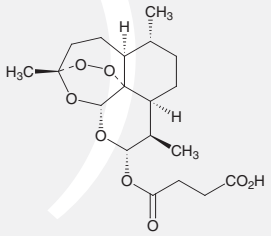
Natural Products Library – The Natural Products Library (**Cat. # 2865**) is a rich source of chemically and mechanistically diverse compounds for screening. Historically, natural products have been the most successful source of new drugs. The Natural Products Library offers over 500 highly purified natural products of known structure. Individual compounds or subsets can be resupplied in gram quantities.

For more details and complete structure files contact BIOMOL Technical Services at techserv@biomol.com

Structurally and mechanistically diverse inhibitors

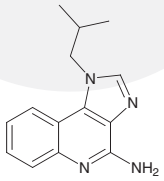
Artesunate PR-117

Artesunate is a semisynthetic derivative of artemisinin, an antimalarial drug extracted from the plant Artemisia annua. Artesunate has been shown to inhibit angiogenesis in vivo and in vitro. Artesunate remarkably lowers VEGF expression in tumor cells and VEGF receptor expression on endothelial cells.



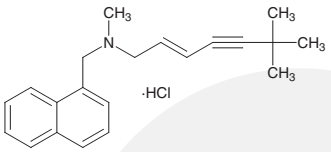
Imiquimod CT-106

A topical immune response modifier that inhibits angiogenesis. The mechanisms involved in its antiangiogenic activity include upregulation of antiangiogenic cytokines such as IL-18 and downregulation of MMP-9.



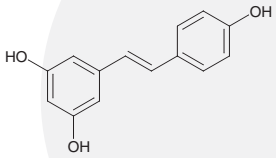
Terbinafine EI-318

A CDK inhibitor that blocks HUVEC proliferation and capillary-like tube formation in chorioallantoic membrane assays.



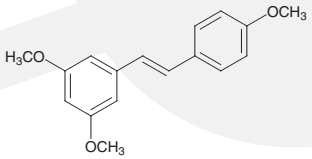
Resveratrol FR-104

Resveratrol is a natural polyphenolic stilbene found in red wine. It stimulates the histone deacetylase SIRT1, activates estrogen receptors, quenches free radicals and is considered a natural cancer chemopreventive agent. It has been shown to induce apoptosis and inhibit angiogenesis in human breast cancer xenografts in vivo.



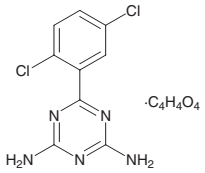
3,5,4'-Trimethoxystilbene T-128

A resveratrol analog that is 30- to 100-fold more potent than resveratrol in inhibiting endothelial cell proliferation, sprouting, collagen gel invasion, and morphogenesis (ID_{50} = 0.3-3.0 mM). Acts via microtubule disassembly and tubulin depolymerization.



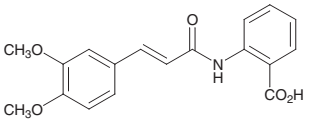
Irsogladine PD-141

Irsogladine is a selective PDE4 inhibitor which also upregulates gap junction intercellular communication. It inhibits angiogenesis in wild-type and plasminogen activator-deficient mice.



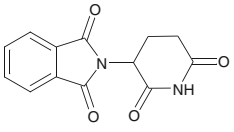
Tranilast CT-110

An anti-allergic drug that inhibits VEGF-induced angiogenesis in vivo. It inhibits proliferation, chemotaxis and tube formation of human endothelial cells in vitro.



Thalidomide T-115

Inhibits TNFα production and angiogenesis. Thalidomide is finding applications in various angiogenesis-dependent diseases.



Matrix Metalloproteinases (MMPs)

Drug Discovery Kits

For screening MMP inhibitors, these kits contain human recombinant MMP catalytic domain, chromogenic or fluorogenic substrate, control inhibitor, assay buffer, detailed instruction booklet, and a 96-well microplate.

BIOMOL offers fluorimetric and colorimetric drug discovery kits and recombinant catalytic domains for the following MMPs:

MMP-1 **MMP-2** **MMP-3** **MMP-7** **MMP-8** **MMP-9** **MMP-10**
MMP-11 (enzyme only) **MMP-12** **MMP-13** **MMP-14**

Visit www.biomol.com/MMPs for more information.

Antibodies

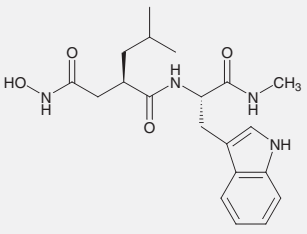
Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
MMP-1 Hinge Region	rabbit pAb	most mammalian species	WB, IP, IHC	**SA-102**
MMP-1 Catalytic Domain	rabbit pAb	most mammalian species	WB, IP, IHC	**SA-353**
MMP-2 Hinge Region	rabbit pAb	most mammalian species	WB, IP, IHC	**SA-103**
MMP-2 Catalytic Domain	rabbit pAb	most mammalian species	WB, IP, IHC	**SA-351**
MMP-3 Hinge Region	rabbit pAb	H, P	WB, IP, IHC	**SA-104**
MMP-7 Hinge Region	rabbit pAb	H, M	WB, IP, IHC	**SA-105**
MMP-8 Hinge Region	rabbit pAb	H, M, R	WB, IP, IHC	**SA-370**
MMP-9 Hinge Region	rabbit pAb	most mammalian species	WB, IP, IHC	**SA-106**
MMP-9 Catalytic Domain	rabbit pAb	most mammalian species	WB, IP, IHC	**SA-352**
MMP-10 Hinge Region	rabbit pAb	H	WB	**SA-434**
MMP-11 Hinge Region	rabbit pAb	H, M, R	WB, IP, IHC	**SA-371**
MMP-12 Hinge Region	rabbit pAb	H, M	WB, IP, IHC	**SA-107**
MMP-12 Catalytic Domain	rabbit pAb	H, M, R	WB	**SA-453**
MMP-12, C-terminus	rabbit pAb	M, R	WB	**SA-467**
MMP-13 Hinge Region	rabbit pAb	H, M, R, P	WB, IP, IHC	**SA-372**
MMP-14 Hinge Region	rabbit pAb	H	WB, IP, IHC	**SA-108**
TIMP-1	rabbit pAb	H	WB, IP, IHC	**SA-373**
TIMP-2	rabbit pAb	most mammalian species	WB	**SA-374**
TIMP-3	rabbit pAb	H	WB, IP, IHC	**SA-375**
TIMP-4	rabbit pAb	H, R, Rb	WB	**SA-380**
MMP Antibody Set	10 µgs of each hinge region antibody			**SA-384**

H - human, M - mouse, P - pig, R - rat, Rb - rabbit; IHC - immunohistochemistry, IP - immunoprecipitation, WB - western blot

Inhibitors

GM6001 **EI-300**

Potent, broad-spectrum hydroxamate inhibitor of matrix metalloproteinases (MMPs) and ADAMs (including TACE) with K_i's in the nanomolar range.



Visit www.biomol.com/MMPs for more MMP inhibitors, fluorogenic and chromogenic substrates, and immunoblotting standards

Cathepsin B

Cathepsin B is a lysosomal cysteine protease involved in degradation, apoptosis, and inflammation. An increasing body of evidence has implicated cathepsin B as a key protease involved in angiogenesis. Several different systems, including matrigel invasion and endothelial tube formation, demonstrated that inhibition of cathepsin B activity by small molecule inhibitors and RNAi suppresses angiogenesis both *in vitro* and *in vivo*. The key roles of cathepsin B in angiogenesis strongly suggest that it may be an important new target for the development of anti-angiogenic drugs.

CV-Cathepsin B Detection Kit — **AK-125**

Detects cathepsin B activity in living cells using cresyl violet and fluorescence microscopy.
Once cells are grown, staining is completed in just a few minutes.

ENZYME

Cathepsin B (human)	Active cathepsin B from human liver	**SE-198**

ANTIBODY

Cathepsin B rabbit pAb	Recognizes human; applications: WB and ELISA	**SA-361**

INHIBITORS

CA-074	Potent and selective cathepsin B inhibitor	**PI-131**
CA-074 Me	Cell-permeable methyl ester of CA-074	**PI-126**

SUBSTRATES

Z-RR-AMC	Fluorogenic substrate specific for cathepsin B	**P-137**
Z-RR-pNA	Chromogenic substrate specific for cathepsin B	**P-138**

Additional Cathepsin Products

ENZYMES

Cathepsin D	Active cathepsin D from human liver	**SE-199**
Cathepsin G	Active cathepsin G from human neutrophils	**SE-283**
Cathepsin H	Active cathepsin H from human liver	**SE-200**
Cathepsin L	Active cathepsin L from human liver	**SE-201**

DETECTION KITS

CV-Cathepsin K	Allows fluorescent detection of cathepsin K in living cells	**AK-126**
CV-Cathepsin L	Allows fluorescent detection of cathepsin L in living cells	**AK-127**

INHIBITORS

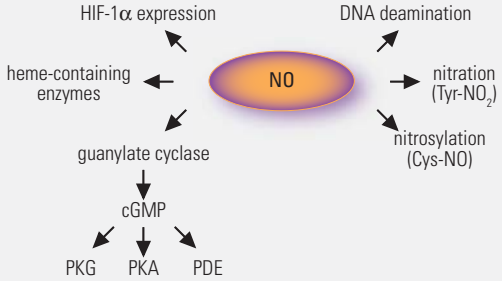
BML-244	A potent, cell-permeable inhibitor of cathepsin K (IC_{50}=51 nM)	**PI-140**
ALLM	Inhibits cathepsin L (K_i=0.6 nM) and cathepsin B (K_i=100 nM)	**PI-100**
E-64-d	Cell-permeable inhibitor of cathepsins B, H and L	**PI-107**
Z-FA-FMK	Irreversible inhibitor of cathepins B, L, S and likely H	**PI-138**
NapSul-Ile-Trp-CHO	Potent and selective inhibitor of cathepsin L	**PI-125**
Mu-Phe-hPhe-FMK	Irreversible, cell-permeable inhibitor of cathepsins B and L	**EI-323**

CATHEPSIN ANTIBODIES

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
Cathepsin B	rabbit pAb	human	western blot, ELISA	**SA-361**
Cathepsin D	rabbit pAb	human	western blot, ELISA	**SA-398**
Cathepsin G	rabbit pAb	human	western blot, ELISA	**SA-354**
Cathepsin H	rabbit pAb	human	western blot, ELISA	**SA-355**
Cathepsin L	rabbit pAb	human	western blot, ELISA	**SA-362**

Nitric Oxide

Many stimulators of angiogenesis induce the release of nitric oxide (NO), which mediates endothelial survival, proliferation, migration and interaction with the extracellular matrix. Inhibition of NO production impairs angiogenesis and agents which increase NO synthesis stimulate angiogenesis.



Nitric Oxide Colorimetric Assay Kit **AK-136**

Allows quantitative determination of total nitric oxide in biological fluids. The assay is based on the enzymatic conversion of nitrate to nitrite by the enzyme nitrate reductase, followed by the Griess reaction to form a colored product.

ANTIBODIES

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
eNOS	mouse mAb (H32)	most mammalian species	WB, IHC, IP	**SA-258**
eNOS	rabbit pAb	H, M, R	WB, IHC	**SA-201**
eNOS (pS1177)	mouse mAb (15E2)	H, M	WB	**SA-308**
iNOS	rabbit pAb	H, M, R	WB, IHC	**SA-200**
bNOS	rabbit pAb	H, M, R	WB, IF	**SA-227**
uNOS	rabbit pAb	most mammalian species	WB, IHC	**SA-277**
Nitrotyrosine	mouse mAb (HM11)	independent	WB, IHC	**SA-468**
Nitrotyrosine	rabbit pAb	independent	WB	**SA-297**

H - human, M - mouse, R - rat; IHC - immunohistochemistry, IF - immunofluorescence, IP - immunoprecipitation, WB - western blot

NO DONORS

Hydroxyguanidine sulfate	Forms an adduct with NO that is a potent and stable vasodilator	**CN-247**
Molsidomine	Orally active, long acting, NO releasing vasodilator	**CN-244**
SIN-1	Releases NO under physiological conditions	**CN-245**
SNAP	Spontaneously releases NO under physiological conditions	**CN-210**
S-Nitrosoglutathione (GSNO)	A useful NO donor which inhibits endothelial cell proliferation	**CN-253**
NOR-1	Non-thiol-based NO donor with a half-life of 1.7 minutes	**CN-263**
NOR-3	Non-thiol-based NO donor with a half-life of 30 minutes	**CN-264**
NOR-4	Non-thiol-based NO donor with a half-life of 60 minutes	**CN-265**
Furoxan	Releases NO in the presence of thiols	**CN-255**
Streptozotocin	N-nitroso containing glucose derivative; reported NO donor	**EI-138**
Tetrahydrobiopterin (THB)	THB is a cofactor for NO synthase	**CN-250**

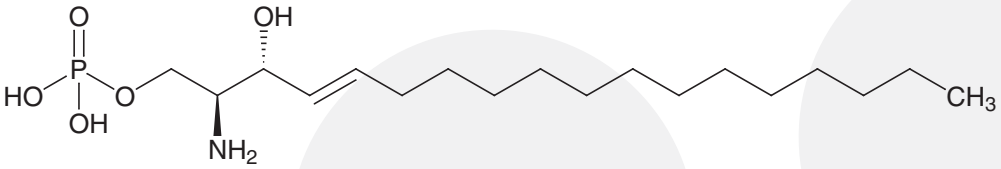
NOS INHIBITORS

4-Amino-(6R)-tetrahydro-L-biopterin	Inhibits tetrahydrobiopterin stimulation of NOS activity	**CN-267**
Dexamethasone	Inhibits the induction of NOS in the macrophage cell line J774	**EI-126**
Diphenyleneiodonium chloride (DPI)	Irreversible inhibitor of NO synthase (NOS)	**CN-240**
S-Ethylisothiourea·HBr	Cell-permeable inhibitor of all NOS isoforms	**CN-260**
L-NIO	5 times more potent inhibitor of eNOS than L-NAME and L-NMMA	**CN-248**
L-NMMA	Competitively inhibits the generation of NO from arginine	**EI-182**
L-NAME	Competitive inhibitor of NO synthase	**CN-242**

NO INHIBITORS

Carboxy-PTIO	Reacts stoichiometrically with NO and inhibits NO-mediated processes	**CN-262**
LY 83583	Inhibits nitric oxide-induced activation of soluble guanylate cyclase	**CN-200**

Sphingosine-1-Phosphate



Sphingosine -1-phosphate (S1P) is an important regulator of vascular growth and development. S1P regulates endothelial migration and survival, induces morphogenesis of endothelial cells into capillary-like structures, and synergizes with FGF2 and VEGF to induce angiogenesis *in vivo*. S1P1, a S1P receptor is induced during angiogenesis *in vivo* and S1P signaling has recently been demonstrated to be required for tumor angiogenesis. Given S1P signals through GPCRs, which have historically been highly druggable targets, the S1P pathway is an important target for anti-angiogenesis drugs.

Sphingosine Kinase

ENZYMES

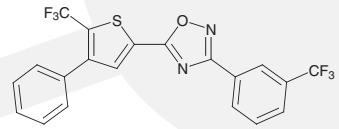
Sphingosine Kinase 1	Full-length human SPHK1 expressed in insect cells with an N-terminal His tag	SE-424
Sphingosine Kinase 2	Full-length human SPHK2 expressed in insect cells with an N-terminal His tag	SE-425

INHIBITORS

N,N-Dimethylsphingosine	Inhibits S1P formation by inhibiting sphingosine kinase	SL-105
DL-threo-Dihydrosphingosine	Potent, cell-permeable, competitive inhibitor of sphingosine kinases	SL-205

Synthetic S1P Receptor Agonists and Antagonists

SEW-2871 LP-106



A novel, potent S1P receptor agonist structurally unrelated to S1P and is highly selective for the human S1P1 receptor. It produces immunosuppression without associated bradycardia which is induced by other less selective S1P agonists. In mice, SEW-2871 blocked TNFα induced monocyte adhesion to endothelium.

BML-241	Novel S1P receptor antagonist acting at S1P3 receptors	SL-227

Endogenous Ligands

Sphingosine-1-phosphate	Endogenous agonist for S1P1 receptors	SL-140
Dihydrosphingosine-1-phosphate	Endogenous agonist for S1P1 receptors	SL-143

Receptor Antibodies

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
S1P1	rabbit pAb	human, rat	western blotting	SA-292
S1P2	rabbit pAb	human	western blotting	SA-299
S1P3	mouse mAb	human, rat	western blotting	SA-295

Cytoskeleton

FAK ANTIBODIES

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
FAK	rabbit pAb	H, M, R, D, F	WB, IF, IP	**SA-430**
FAK (pY397)	rabbit pAb	H, M, Ch, F	WB, IHC, ICC	**SA-433**
FAK (pY407)	rabbit pAb	H, M, Ch, F	WB	**SA-342**
FAK (pY576)	rabbit pAb	H, M, Ch, F	WB	**SA-343**

Ch - chicken, D - dog, F - frog, H - human, M - mouse, R - rat
ICC - immunocytochemistry, IF - immunofluorescence, IHC - immunohistochemistry, IP - immunoprecipitation, WB - western blot

INTEGRIN ANTAGONISTS AND ANTIBODIES

Cyclo [Arg-Gly-Asp-D-Phe-Val] . . Integrin a_vb_3 antagonist. Inhibits angiogenesis and induces rapid regression of human tumors. **AM-100**

RGD peptide (GRGDNP) . . . . . Integrin a_vb_3 antagonist. Inhibits cell adhesion to fibronectin. **P-700**

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
αIIb Integrin	mouse mAb (BB10)	H	WB, ICC, IHC	**IG6065**
β-1 Integrin	mouse mAb (DF5)	H	WB, ICC, IHC	**IG6060**
β-1 Integrin	mouse mAb (DF7)	H	WB, ICC, IHC	**IG6061**

H - human; ICC - immunocytochemistry, IHC - immunohistochemistry, WB - western blot

OTHER CYTOSKELETON AND ECM ANTIBODIES

Target	Antibody type (clone)	Species reactivity	Applications	Cat. #
Actinin	mouse mAb (CB11)	Ma, Ch	WB, ICC, IHC	**AG6070**
Caldesmon	mouse mAb (TD107)	H	WB, ICC, IHC, IF	**CA1120**
Vinculin	mouse mAb (FB11)	H	WB, ICC, IHC	**VG6110**
Fibronectin	mouse mAb (DH1)	H	WB, ICC, IHC	**FG6010**
Vitronectin	mouse mAb (BE10)	H	WB, ICC, IHC	**VG6050**
Desmin	mouse mAb (37EH)	Ma	WB, ICC, IHC	**DG6080**
Laminin	mouse mAb (DG10)	H	WB, ICC, IHC	**LG6030**
Vimentin	mouse mAb (65E)	H	WB, ICC, IHC	**VG6100**

Ch - Chicken, H - human, Ma - Mammalian; ICC - immunocytochemistry, IF - immunofluorescence, IHC - immunohistochemistry, WB - western blot

SRC-family Kinases

ENZYMES

CSK . . . . . Human CSK expressed in insect cells **SE-380**

Hck . . . . . Human Hck expressed in insect cells **SE-384**

FynT . . . . . Human FynT expressed in insect cells **SE-287**

Lck . . . . . Human Lck expressed in insect cells **SE-356**

Src . . . . . Human Src expressed in E. coli **SE-357**

INHIBITORS

PP1 . . . . . IC_{50}s for Lck, Fyn and Src: 5 nM, 6 nM, and 170 nM **EI-275**

PP2 . . . . . IC_{50}s for Lck, Fyn and Hck: 4 nM, 5 nM, and 4 nM **EI-297**

ANTIBODIES

Anti-Src . . . . . Species reactivity: human, chicken; application: WB **SA-300**

Anti-Scr (pY416) . . . . . Species reactivity: human, mouse, rat; application: WB **SA-314**

Anti-Src (pY529) . . . . . Species reactivity: human, mouse, rat, chicken; application: WB **SA-413**

PLCγ

ENZYME

Phospholipase C	Phosphatidylinositol-specific from B. cereus	**SE-242**

INHIBITORS

D609	Selective inhibitor or phosphatidylcholine-specific PLC (PC-PLC) Inhibits HIF-1α expression via blocking phosphatidic acid synthesis	**ST-330**
ET-18-OCH$_3$	Inhibits phosphatidylinositol-specific PLC (IC_{50}=0.4-9.6 μM)	**L-108**
U-73122	Inhibits agonist induced PLC activation in platelets and neutrophils	**ST-391**

ANTIBODY

Anti-PLC γ-1 (pY783)	Species reactivity: human, rat, and Xenopus; applications: WB	**SA-365**

Proteasome Inhibitors

Proteasome inhibition blocks angiogenesis and induces apoptosis in cancer cells with limited toxicity in normal cells. Over 30 proteasome inhibitors are available.
Visit www.biomol.com/proteasome for a complete listing.

Epoxomicin	Highly specific, irreversible epoxyketone inhibitor of the chymotrypsin-like activity	**PI-127**
YU102	Highly specific, irreversible epoxyketone inhibitor of the caspase-like activity	**YW9180**
Ac-Ala-Pro-Nle-Asp-CHO	Highly specific aldehyde inhibitor of the caspase-like activity	**AW9485**
Lactacystin	Potent, selective inhibitor of chymotrypsin-like and trypsin-like activities	**PI-104**
clasto-Lactacystin β-lactone	20-fold more potent than lactacystin	**PI-108**
MG132 (Z-Leu-Leu-Leu-CHO)	Peptide aldehyde that inhibits chymotrypsin- and caspase-like activities	**PI-102**
PR39	Non-competitive peptide inhibitor of all three activities	**PW8850**

Histone Deacetylases

HDAC inhibitors block tumor angiogenesis *in vitro* and *in vivo*.

INHIBITORS

Depudecin	A potent HDAC inhibitor (IC_{50}=4.7 μM); Inhibits angiogenesis	**EI-319**
Trichostatin A (TSA)	A potent and reversible HDAC inhibitor; Inhibits angiogenesis	**GR-309**
HC Toxin	A cell-permeable, cyclopeptide HDAC inhibitor (IC_{50}=30 nM)	**GR-320**

More HDAC inhibitors are available. **Visit www.biomol.com/HDAC for a complete listing.**

ANTIBODIES

Anti-Acetyl-Lysine	Species reactivity: wide; applications: WB, IP, IF, ELISA	**SA-440**
Anti-HDAC1	Species reactivity: human, mouse, rat; applications: WB, IP	**SA-401**
Anti-HDAC2	Species reactivity: human, mouse, rat; applications: WB, IP	**SA-402**
Anti-HDAC3	Species reactivity: human, rat, dog; applications: WB, IP	**SA-403**
Anti-HDAC4	Species reactivity: human; applications: WB	**SA-404**

HDAC Fluorescent Activity Assay/Drug Discovery Kit **AK-500**

BIOMOL has developed the ***Fluor de Lys***™ Substrate/Developer System for nonradioactive assay of HDAC activity.

Deacetylation of the ***Fluor de Lys*** substrate sensitizes it so that, in a second step, treatment with the ***Fluor de Lys*** Developer produces a fluorophore. The assay is compatible with class I and II HDACs and sirtuins, and the original ***Fluor de Lys*** substrate is cell-permeable allowing cell-based determination of HDAC activity. Includes: HeLa Nuclear Extract for use as source of HDAC activity or positive control, ***Fluor de Lys*** Substrate and Developer, Assay Buffer, the HDAC inhbitor, Trichostatin A, 2 x ½-volume 96-well plates, detailed instructions.

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