New Product Highlights

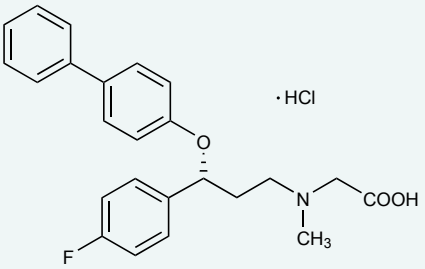
ALX 5407: A potent, selective, and non-transportable GlyT-1 glycine transporter inhibitor

In the central nervous system (CNS), the amino acid **glycine** (Prod. No. G 7403), acts as an inhibitory neurotransmitter at strychnine-sensitive glycine receptors and as an excitatory, co-agonist at strychnine-insensitive glycine sites on NMDA glutamate receptors [1]. Glycine levels are modulated by reuptake via glycine transporters. Two types of glycine transporters have been characterized and are referred to as GlyT-1 and GlyT-2 [2]. They are members of the sodium/chloride-dependent family of transporters and both have multiple subtypes. GlyT-1 is widely expressed in the CNS and its distribution is predominantly glial. GlyT-2 expression is predominantly neuronal and limited to the spinal cord, brainstem and cerebellum.

GlyT-1 performs a critical role in establishing and maintaining subsaturating extracellular glycine concentration. Modulation of glycine levels influences the activation of NMDA glutamate receptors [3]. and recent evidence suggest that the, blockade of glycine reuptake may be of therapeutic interest for the treatment of schizophrenia [4].

Sigma-RBI has recently introduced **ALX 5407** (Prod. No. A 8977), a potent and selective inhibitor of the GlyT-1 glycine transporter [5]. ALX 5407 consists of a sarcosine headgroup with a bulky hydrophobic tail. This compound blocked glycine uptake in QT6 cells expressing GlyT-1, displaying an IC_{50} value of 3 nM, while exhibiting no effect on glycine uptake in QT6 cells expressing GlyT-2. In addition, unlike glycine and **sarcosine** (Prod. No. S 7672), ALX 5407 is not a substrate for the glycine transporter.

ALX 5407 will be of interest to researchers seeking to understand the role of glycine transporters in the regulation of NMDA glutamate receptor activity. Such studies should facilitate the development of potential drug candidates that modulate glycine transport and may be of use in the treatment of schizophrenia.



ALX 5407 HCl
Prod. No. A 8977

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Angiostatin and endostatin: Endogenous inhibitors of angiogenesis

Angiogenesis, the sprouting of new capillary growth from pre-existing blood vessels, is a multi-step process [1] and is a rate-limiting step in tumor growth. Avascular tumors are limited in size by the diffusion distance of oxygen, nutrients, and cellular waste through the interstitium. Although tumors often initially co-opt the existing vasculature, an angiogenic switch, i.e., the production of factors that induce angiogenic sprouting of the vasculature, is a necessary part of the phenotype of a successful tumor. Under normal conditions, there is a balance between endogenous angiogenic inducers and endogenous angiogenic inhibitors that keeps the angiogenic process in check and prevents inappropriate vascularization of tissues. Angiogenesis inhibitors are often derived from circulating extracellular matrix proteins, e.g. fibronectin, prolactin, collagen XVIII (endostatin), hepatocyte growth factor fragment NK_1 and angiostatin. Virtually all endogenous angiogenesis inhibitors suppress tumor growth in animal models.

Angiostatin is an amino-terminal fragment of plasminogen that contains the first three or four kringle (K) domains [2]. Agents containing K1-3 [3], K1-4 [2], K1-5 [4] and K1-4 plus a fragment of K5 [5] show potent anti-angiogenic and/or anti-tumor growth activity. These fragments, as well as the individual kringle modules, are also inhibitory toward endothelial cell migration and/or proliferation *in vitro*. Endostatin is a cleaved product of the carboxyl-terminal domain of collagen XVIII [6,7]. Endostatin inhibits endothelial cell migration *in vivo* and *in vitro* and induces endothelial cell apoptosis [8]. Endostatin has an important role in endothelial cell adhesion and cytoskeletal organization [9].

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New Product Highlights

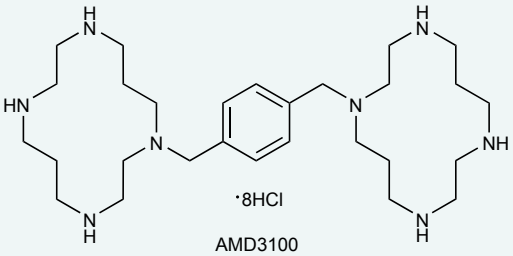
AMD3100: CXCR4 chemokine receptor antagonist

AMD3100 (Prod. No. **A 5602**) is the first non-peptide CXCR4 chemokine receptor antagonist. It has potential clinical applications in treating HIV/AIDS, inflammatory diseases and cancer and in enhancing stem cell mobilization for transplantation.

The CXCR4 chemokine receptor is a cellular virus co-receptor. Viral entry requires interaction of viral envelope protein Gp120 with the (cellular virus receptor) CD4 and the CXCR4 chemokine receptor. AMD3100, at 1-10 nM, blocks interaction between the Gp120 HIV envelope protein and the CXCR4 chemokine receptor. Currently, AMD3100 is the first co-receptor antagonist in phase II clinical trials against AIDS. The molecular target of AMD3100 confers selectivity against T-tropic (T-cell targeting) HIV, with no activity towards M-tropic (macrophage targeting) HIV variants. This is in agreement with HIV co-receptor usage; viral entry by T-tropic viruses uses the CXCR4 chemokine receptor while viral entry by M-tropic viruses uses the CCR5 chemokine receptor.

In mouse models of asthma, AMD3100 treatment significantly reduced airway hyperactivity, peribronchial eosinophilia and altered the cytokine profile. Specifically, pulmonary levels of **interleukin-4** (IL-4, Prod. No. **I 4269**) and **interleukin-5** (IL-5, Prod. No. **I 5273**) were reduced while levels of **interleukin-12** (IL-12, Prod. No. **I 2276**) and **interferon-γ** (IFN-γ, Prod. No. **I 1520**) were increased. Production of **CCL22** (MDC, macrophage-derived chemokine, Prod. No. **M-251**) and **CCL17** (TARC, thymus and activation regulated chemokine, Prod. No. **T 9694**), chemokines important in the response of T helper cells, Th2, to allergen, were also reduced.

AMD3100 is a useful tool for studying the myriad of physiological functions mediated by the CXCR4 chemokine receptor.



AMD3100
Prod. No. A 5602

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Angiostatin and endostatin *(continued)*

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Sigma has recently introduced **angiostatin** (Prod. No. **A 1477**) and **endostatin** (Prod. Nos. **E 8154**, **E 8279**) - the endogenous inhibitors of angiogenesis. The products are recombinantly expressed in *Pichia pastoris*. Inhibition activity is assessed by the ability to inhibit tumor metastases using an *in vivo* anti-tumor efficacy test using B16BL6 melanoma cells.

Proteins	
Angiostatin K1-3, Human, recombinant	A 1477
Endostatin, Human, recombinant	E 8154
Endostatin, Mouse, recombinant	E 8279
Antibodies	
Monoclonal Anti-Angiostatin, Human	A 0976
Anti-Angiostatin, Human	A 1101
Monoclonal Anti-Endostatin, Mouse	E 3904
Anti-Endostatin, Mouse	E 3779

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