

## ANTI-CANCER AGENTS

### Terpenoids



Terpenoids are a large and diverse class of naturally-occurring organic chemicals found in all classes of living organisms. They are currently under investigation by numerous groups for anti-tumor, anti-inflammatory and other therapeutic properties.

### Geldanamycin & Analogues



Geldanamycin (GA), a benzoquinone ansamycin antibiotic inhibits the proliferation of cancer cells and shows anticancer activity in experimental animals. Numerous GA analogues have been synthesized which differ only in their 17-substituent that have completed phase I and are currently entering phase II clinical trials. InvivoGen provides Geldanamycin and its more promising analogues as well as other derivatives.

### Anticancer Agents - Epigenetic Inhibitors



InvivoGen provides two such inhibitors: 5Aza-dCyd, inhibitor of DNA methyltransferases (DNMTs) and Trichostatin A, inhibitor of histone deacetylases (HDACs). Both inhibitors have been demonstrated to be promising anticancer agents used either separately or in combination.

***For easy search of any product in the above categories, go to [www.lifetechindia.com](http://www.lifetechindia.com) and use the search catalogue facility on top right.***

## Terpenoids

Terpenoids are a large and diverse class of **naturally-occurring organic chemicals** found in all classes of living organisms. Plant terpenoids are used extensively for their aromatic qualities and play a role in traditional herbal remedies.

They are currently under investigation by numerous groups for **antitumor, anti-inflammatory** and other **therapeutic properties**.

### Celastrol

#### Description

Celastrol, a triterpenoid compound isolated from the root bark of the Chinese medicinal plant *Tripterygium wilfordii*, is known for its antitumor and anti-inflammatory properties but its mode of action and spectrum of cellular targets are poorly understood.

Celastrol was recently found to be a potent inhibitor of the heat-shock protein Hsp90 inducing the disruption of protein-protein interactions of Hsp90 and its co-chaperones [1, 2].

Furthermore, it was shown to act as an effective inhibitor of the transcription factor NF- $\kappa$ B potentiating the apoptosis induced by TNF- $\alpha$  and chemotherapeutic agents and inhibiting invasion [3].

1. Zhang T. et al., 2008. A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells. Mol. Cancer Ther.; 7: 162-170.

2. Hieronymus H. et al., 2006. Gene expression signature-based chemical genomic prediction identifies a novel class of HSP90 pathway modulators. Cancer Cell. ;10(4):321-30.

3. Sethi G. et al., 2007. Celastrol, a novel triterpene, potentiates TNF-induced apoptosis and suppresses invasion of tumor cells by inhibiting NF- $\kappa$ B-regulated gene products and TAK1-mediated NF- $\kappa$ B activation. Blood, 109: 2727 - 2735.

#### Formula

**Formula:** C<sub>29</sub>H<sub>38</sub>O<sub>4</sub>

**Molecular weight:** 450.61

#### Contents and Storage

Celastrol is provided as red cubic crystals. Product is shipped at room temperature. Store at -20°C. Celastrol is stable for 2 years.

## Triptolide

### Description

Triptolide, a diterpenoid isolated from the Chinese herb *Tripterygium wilfordii* hook F, has been used for centuries in traditional Chinese medicine to treat immune-related disorders.

In addition to its anti-inflammatory and immunosuppressive activities, triptolide possesses potent anti-tumor properties. It was shown to suppress the growth and induce apoptosis of a broad range of human tumor cells.

However, despite the recognized potent antitumor activity of triptolide, current knowledge regarding its mechanism of action is still limited. So far, triptolide is known to inhibit the heat shock response [1], block the activation of NF- $\kappa$ B [2] and induce caspase activation [3].

1. Westerheide SD. et al., 2006. Triptolide, an Inhibitor of the Human Heat Shock Response That Enhances Stress-induced Cell Death. J. Biol. Chem., 281: 9616 - 9622.

2. Lee KY. et al., 1999. PG490 (triptolide) cooperates with tumor necrosis factor $\alpha$  to induce apoptosis in tumor cells. J Biol Chem. 274: 13451-13455.

3. Bing ZC. et al., 2006. Triptolide induces caspase-dependent cell death mediated via the mitochondrial pathway in leukemic cells. Blood 108: 630 - 637.

### Formula

**Formula:**  $C_{20}H_{24}O_6$

**Molecular weight:** 360.40

### Contents and Storage

Triptolide is provided as a white solid. Product is shipped at room temperature.  
Keep away from light at -20°C for long term storage.

## Geldanamycin & Analogues

Geldanamycin (GA), a benzoquinone ansamycin antibiotic, interferes with the action of the heat shock protein 90 (Hsp90) leading to the degradation of Hsp90 client proteins. Since many of these client proteins are oncogenic proteins, **GA inhibits the proliferation of cancer cells** and shows **anticancer activity** in experimental animals.

However due to poor aqueous solubility and liver toxicity, GA has not moved forward in clinical trials. To overcome these undesirable properties, **numerous GA analogues** have been synthesized which differ only in their 17-substituent. These include 17-allylamino-demethoxygeldamycin (17-AAG) and 17-dimethylamino-geldanamycin (17-DMAG) that have completed phase I and are currently entering phase II clinical trials.

InvivoGen provides Geldanamycin and four of its more promising analogues as well as other derivatives.

**Bulk quantity readily available** – [customerservice@lifetechindia.com](mailto:customerservice@lifetechindia.com)

### **Geldanamycin**

#### Description

Geldanamycin (GA) is a natural product produced by *Streptomyces hygroscopicus*. InvivoGen produces GA from a mutant strain of *S. hygroscopicus*, inactivated for the synthesis of nigericin, a common contaminant of GA. GA binds with high affinity into the ATP binding pocket of Hsp90. Hsp90 is a ubiquitous molecular chaperone critical for the folding, assembly and activity of multiple mutated and overexpressed signaling proteins that promote the growth and/or survival of tumor cells.

Hsp90 client proteins include mutated p53, Raf-1, Akt, ErbB2 and hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ )[1].

Binding of GA to Hsp90 causes the destabilization and degradation of its client proteins[2].

1. Neckers L., 2002. Hsp90 inhibitors as novel cancer chemotherapeutic agents. Trends Mol Med 8(4 Suppl):S55-61
2. Whitesell L. et al., 1994. Inhibition of heat shock protein HSP90-pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation. Proc Natl Acad Sci U S A 91(18):8324-8

#### Formula

**Formula:** C<sub>29</sub>H<sub>40</sub>N<sub>2</sub>O<sub>9</sub>

**Molecular weight:** 560.64

**CAS Number :** 30562-34-6

#### Contents and Storage

Geldanamycin is provided as a yellow powder. Geldanamycin is shipped at room temperature.

Store at -20°C in the dark.

Geldanamycin is stable for 6 months when stored properly.

## **17-AAG**

Less Toxic and More Stable GA Analogue

### Description

17-Allylamino-17-demethoxygeldanamycin (17-AAG) is an analogue chemically derived from GA. 17-AAG is a less toxic and more stable analogue of geldanamycin (GA)[1]. Even though 17-AAG binding to Hsp90 is weaker than GA, 17-AAG displays similar antitumor effects as GA and a better toxicity profile.

17-AAG is currently in phase I clinical trial in several centers worldwide. Preliminary data obtained from these trials demonstrate that antitumor activity is achieved at concentrations below the maximum tolerated dose[2].

1. Schulte TW. & Neckers LM., 1998. The benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin binds to HSP90 and shares important biologic activities with geldanamycin. *Cancer Chemother Pharmacol* 42(4):273-9
2. Agnew EB. et al. 2001. Measurement of the novel antitumor agent 17-(allylamino)-17-demethoxygeldanamycin in human plasma by high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl* 755:237-43

### Formula

**Formula:**  $C_{31}H_{43}N_3O_8$   
**Molecular weight:** 585.69  
**CAS Number :** 75747-14-7

### Contents and Storage

17-AAG is provided as a purple powder. 17AAG is shipped at room temperature.

Store at -20°C in the dark.

17-AAG is stable for 6 months when stored properly.

## **17-DMAG**

Water-Soluble GA Analogue

### Description

#### Description

17-(Dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG, NSC 707545) is the first water-soluble analogue of 17-AAG. This Hsp90 inhibitor shows promise in preclinical models[1]. 17-DMAG has excellent bioavailability, is widely distributed to tissues, and is quantitatively metabolized much less than is 17-AAG[2].

1. Workman P., 2003. Overview: translating Hsp90 biology into Hsp90 drugs. *Curr Cancer Drug Targets* 3(5):297-300
2. Egorin MJ, et al., 2002. Pharmacokinetics, tissue distribution, and metabolism of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (NSC 707545) in CD2F1 mice and Fischer 344 rats. *Cancer Chemother Pharmacol* 49(1):7-19

### Formula

**Formula:**  $C_{32}H_{48}N_4O_8$ , HCl

**Molecular weight:** 652

### Contents and Storage

17-DMAG is provided as a purple powder. 17-DMAG is shipped at room temperature.

Store at -20°C in the dark.

17-DMAG is stable for 6 months when stored properly.

The use of 17-DMAG is covered under US Patent 6,890,917 owned and licensed by the NIH to InvivoGen.

## **17-AEP-GA**

Water-Soluble GA Analogue

### Description

17-[2-(Pyrrolidin-1-yl)ethyl]aminno-17-demethoxygeldanamycin (17-AEP-GA) is a new geldanamycin (GA) analogue with an alkylamino group in place of the methoxy moiety at C17. 17-AEP-GA is less cytotoxic than GA and remains biologically active. 17-AEP-GA was shown to induce similar tumor cell growth inhibition than 17-AAG and, unlike 17-AAG which is soluble in DMSO, to be water soluble.

1. Tian ZQ. *et al.*, 2004. Synthesis and biological activities of novel 17-aminogeldanamycin derivatives. *Bioorg Med Chem.* 12(20):5317-29.

### Formula

**Formula:**  $C_{34}H_{50}N_4O_8$

**Molecular weight:** 648.78

### Contents and Storage

17-AEP-GA is provided as a purple powder. 17-AEP-GA is shipped at room temperature.

Store at -20°C in the dark.

17-AEP-GA is stable for 6 months when stored properly.

## **17-DMAP-GA**

Water-Soluble GA Analogue

### Description

17-(Dimethylaminopropylamino)-17-demethoxygeldanamycin (17-DMAP-GA) belongs to a new set of geldanamycin analogues that have been synthesized based on binding affinity to Hsp90 and water solubility. 17-DMAP-GA was shown to greatly inhibit the growth of cancer cells (IC<sub>50</sub> below 100 nM) [1]. Its binding affinity to Hsp90 was not significantly affected while its water solubility was highly improved compared to 17-AAG.

1. Tian ZQ. *et al.*, 2004. Synthesis and biological activities of novel 17-aminogeldanamycin derivatives. *Bioorg Med Chem.* 12(20):5317-29.

### Formula

**Formula:** C<sub>33</sub>H<sub>50</sub>N<sub>4</sub>O<sub>8</sub>, HCl

**Molecular weight:** 667.23

### Contents and Storage

17-DMAP-GA is provided as a purple powder. 17-DMAP-GA is shipped at room temperature.  
Store at -20°C in the dark.

17-DMAP-GA is stable for 6 months when stored properly.

## Epigenetic Inhibitors

Epigenetic events, such as DNA methylation and covalent modification of histones, have been demonstrated to silence the expression of many genes that suppress malignancy. Since the event is reversible, it is an interesting target for intervention with specific inhibitors of DNA methylation and histone deacetylation.

InvivoGen provides two such inhibitors:

- [5-AzadCyd](#), inhibitor of DNA methyltransferases (DNMTs)
- [Trichostatin A](#), inhibitor of histone deacetylases (HDACs)

Both inhibitors have been demonstrated to be **promising anticancer agents** used either separately or in combination.

### 5-AzadCyd

#### Description

5-Aza-2'-deoxycytidine (5-AzadCyd, decitabine) is a specific inhibitor of DNA methylation. 5-AzaCyD is a prodrug that requires activation via phosphorylation by deoxycytidine kinase. The nucleotide analog is incorporated into DNA, where it produces an irreversible inactivation of DNA methyltransferase. 5-AZA-CdR is an S-phase-specific agent. The demethylation of DNA by this analog in neoplastic cells can lead to the reactivation of silent tumor-suppressor genes, induction of differentiation or senescence, growth inhibition, and loss of clonogenicity. 5-AZA-CdR was demonstrated to be a potent antineoplastic agent against leukemia and tumors in animal models. Preliminary clinical trials of 5-AZA-CdR using different dose-schedules have shown interesting antineoplastic activity in patients with leukemia, myelodysplastic syndrome (MDS), and non-small cell lung cancer (NSCLC).

#### Formula

**Working Concentration:** 0.1-10  $\mu$ M

**Molecular weight:** 228.21

**CAS number :** 2353-33-5

#### Contents and Storage

5-AzadCyd is supplied as an off white powder. Product is shipped at room temperature. Store at -20°C. 5-AzadCyd is stable for at least 1 year.

## **Trichostatin A**

### Description

Trichostatin A (TSA) is a potent and specific inhibitor of histone deacetylase (HDAC). HDAC is overexpressed in a variety of cancers and is closely correlated with oncogenic factors. TSA suppresses the activity of HDAC leading to an increase in histone acetylation. This histone acetylation induces an enhancement of the expression of specific genes that elicit extensive cellular morphologic and metabolic changes, such as growth arrest, differentiation and apoptosis. TSA has been shown to induce apoptosis in many cancer cells at submicromolar concentrations with very low toxicity toward normal cells.

### Formula

**Working Concentration:** 100 ng/ml

**Molecular weight:** 302,37

**CAS number :** 58880-19-6

### Contents and Storage

Trichostatin A is supplied as a white powder. Product is shipped at room temperature. Store at -20°C. Trichostatin A is stable for at least 1 year.