

# Geldanamania!

Heat Shock Proteins play important roles in the regulation of cell growth, cell survival, and oncogenesis. Inhibition of Hsp90 by geldanamycin leads to preferential degradation of a variety of tumor-specific mutated proteins as compared to their non-mutated counterparts in normal cells, which halts tumor genesis. Unfortunately geldanamycin is hepatotoxic, and has a variety of undesirable side-effects at effective concentrations *in vivo*. Therefore, a variety of geldanamycin analogues have been developed in the hopes of eliminating the undesirable effects and creating a viable drug candidate.

# Geldanamycin

Inhibits HSP90 by binding to its ATP-binding domain ( $K_d$ =1.2  $\mu$ M) and subsequently inhibits HSP90 client proteins. Induces apoptosis in various cell types<sup>1,2</sup>. Cell permeable.

#### 17-AAG

Semi-synthetic analog of geldanamycin which is less toxic and more stable. Selectively binds to and inhibits HSP90 from tumor cells. Anti-angiogenic activity. Cell permeable. <sup>3-5</sup>

## 17-DMAG

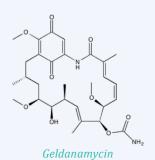
Geldanamycin analog that displays superior pharmacological properties. Inhibits HSP90 and induces apoptosis in a variety of tumor cell lines. Inhibits angiogenesis. Cell Permeable.<sup>6,7</sup>

## 17-GMP-APA-GA

Geldanamycin analog equipped with linker for coupling to proteins or antibodies for the preparation of immunoconjugates, for example. 8-10

#### Geldanamycin-biotin

Geldanamycin linked to biotin to allow for the affinity purification of HSP-90 and HSP-90 client proteins from a variety of samples. <sup>11</sup>



#### References

- 1. Neckers *et al.* (1999) Invest. New Drugs **17**
- 2. Zang *et al.* (2006) Mol. Cell. Biochem. **281**
- 3. Schulte *et al.* (1998) Cancer Chemother. Pharmacol. **42** 273
- 4. Kamal et al. (2003) Nature **425** 407
- Kaur *et al.* (2004) Clinical Cancer Res. **10** 4813
- 6. Glaze *et al.* (2005) Cancer Chemother. Pharmacol., **56** 637
- 7. Kaur et al. (2004) Clin. Cancer Res., **10** 4813
- 8. Mandler *et al.* (2004) Cancer Res., **64** 1460
- Mandler et al. (2002) Bioconj. Chem., 13 786
- 10. Mandler *et al.* (2000) J. Natl. Cancer Inst., **92** 1573
- 11. Clevenger et al. (2004) J. Org. Chem., **69** 437

