Geldanamycin Analogs

Geldanamycin NSC 333507

17-AAG (NSC 333507)

Background
- The parent compound, geldanamycin (NSC 127750), was first isolated as a fermentation product of Streptomyces hygroscopicus.
- The geldanamycin structure resembles that of actinomycin D with a primary difference in the presence of a 17-membered ring that is not present in actinomycin D.

17-AAG is selective for heat shock protein (HSP) 90 chaperon function.

Potential Studies
- High exposure to geldanamycin prevents heat shock protein induction in vitro.
- Inhibition of heat shock protein chaperone is required for geldanamycin activity.

Clinical Trials Experience
- Phase I and II Trials have been conducted.
- Maximum tolerated dose (MTD) was 25 mg/kg/day given i.v.
- Phase I and II Trials are underway.
- Isolation of pure geldanamycin has produced approximately 1.2 kg of product.
- Geldanamycin is produced using a 3,000-gallon fermentor at the SAIC facility in Frederick, Maryland.
- Use of the Microfluidics patented processing technology (a large manufacturing unit is depicted at the right) has been a challenge.

In Vivo Studies
- Administration of geldanamycin to tumor-bearing mice produced antitumor activity in lung, breast, and colon tumor xenografts.
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Toxicology Studies
- 900 mg/m² administered as a single i.v. infusion was lethal.
- 600 mg/m² administered as a single i.v. infusion was lethal.
- Two-course repeat at 100 mg/m² twice each 3 weeks (total 150 mg/m²) was well tolerated.

Pharmacokinetic (PK) Studies
- Microfluidizer® technology (a large manufacturing unit is depicted at the right) has been a challenge.
- If purchased commercially, 1.2 kg parent would cost more than $383 million.

In Vitro Advantages over 17-AAG
- Although both agents are active in the assay when dosed i.p., only 17-AAG is active when dosed orally.
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Clinical Advantages
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Phase I and II Trials
- In vitro activity was 600 nM (HC-110, HT-29, H460, and MDA-MB-231) at drug concentrations of less than 1 µM were sufficient to cause growth inhibition.
- Inhibition is through heat shock protein (HSP) 90 chaperon function.

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