

Sector: Pharmaceuticals

Sub-sector: Oncology; chemosensitizer

Hippuristanol and derivatives as Adjuvants in Chemotherapy

Information Summary

Reference Code:	ROI 05082
Technology overview:	compounds to sensitize tumors to chemotherapy
Application:	chemosensitizing agents that restore antitumor activity of Doxorubicin.
Validation:	Rodent lymphoma model <i>in vivo</i> .
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Technology Description

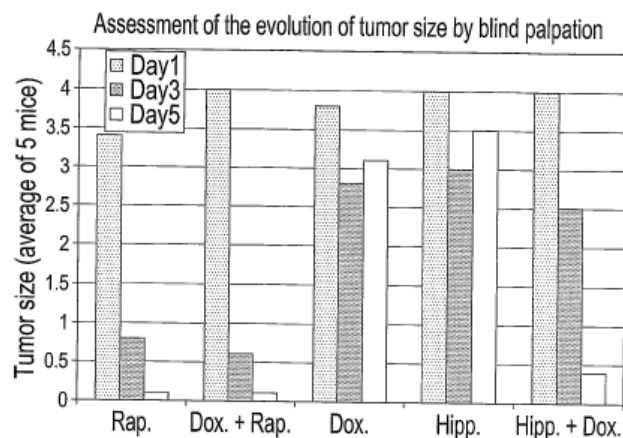
The present invention relates to Hippuristanol and its derivatives as inhibitors of eukaryotic ribosome recruitment phase of translation initiation and their use as antiproliferative, chemotherapeutic agents or as adjuvant in combination therapy with cytotoxic agents. Hippurins are polyoxygenated steroids isolated from marine organisms; they have been reported to be cytotoxic to cell growth. EIF4A is an RNA-dependent helicase involved in recruiting ribosomes to mRNA templates during initiation of protein synthesis. Hippuristanol and its derivatives interfere with EIF4A dependent translation initiation. The patent application governs the utility of the compounds as chemosensitizing agents.

Advantages

Disruption of one or more steps in the control of protein synthesis has been associated with alterations in the cell cycle and/or regulation of cell growth. The ribosome recruitment step of translation initiation is rate-limiting and an important regulatory point whereby cellular environmental cues are linked to the process of

translation. Thus, proteins involved in translation initiation pathways could act as key regulators of malignant progression. Several inhibitors of translation have been evaluated as anti-cancer agents; the majority of these compounds target the elongation phase of translation. Recent experiments suggest that targeting translation initiation may be a more effective approach.

Hippuristanol and its derivatives have been characterized *in vitro* and *in vivo* in mice bearing Akt-driven E μ -myc lymphomas. The evolution of tumor size was assessed and showed an enhancement of the effect of doxorubicin in inhibiting cellular proliferation. Hippuristanol had no effect on its own. Hippuristanol and its derivatives target eIF4A downstream of mTOR and thus are expected to be more specific than rapamycin.



Medical Need and Opportunity

Chemotherapy is still a key approach to cancer treatment. Chemosensitizers would contribute to improve the efficacy of current therapeutic drugs and potentially improve their side effect profile. The world cancer market was established at \$23 billion in 2004 and is expected to grow to \$61 billion by 2011 with a CAGR of 14.7%.

Additional Reference Material

International patent application WO 2007/009264.



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Research Focus: Cancer Genetics; Chemical Genomics; mRNA Translation; Protein Synthesis; Small Molecule Ligands

Research Interests

The use of small molecule ligands to perturb protein function is a powerful approach to understanding gene function that complements the genetic approach. The laboratory applies a chemical biology approach to three research areas:

- (I) To dissect and further elucidate the process of eukaryotic protein synthesis.
- (II) To target specific RNA motifs involved in disease with small molecule ligands to perturb gene expression.
- (III) Understanding changes in gene expression that occurs during the transformation process.