Novel Non-Peptidomimetic Prenyltransferase Inhibitors

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SUMMARY

UCLA Researchers in the Department of Chemistry & Biochemistry and School of Medicine have synthesized a series of small molecule therapeutics against GGTase-I and GGTase-II, both of which are critical oncology drug targets.

BACKGROUND

The Ras protein is typically abnormally active in cancer cells. Farnesyltransferase inhibitors (FTIs) are a class of cancer drugs that inhibits farnesylation of Ras proteins, thereby preventing the proper functioning of Ras. However, a key escape pathway for these oncogenic cells treated with FTIs is geranylgeranylation, a form of prenylation that serves as a functional substitute for farnesylation. This process can be catalyzed by either geranylgeranyltransferase (GGTase-I) or Rab geranylgeranyltransferase (RabGGTase or GGTase-II). *In vivo* studies on GGTase-I knockout mice have shown that inhibiting GGTase-I leads to tumor growth inhibition and induces apoptosis in cell lines. Small molecule antagonists of GGTase-I and GGTase-II are therefore promising candidates for fully blocking activation of Ras.

INNOVATION

A novel series of small molecule oncology therapeutics have been developed by UCLA Professors Ohyun Kwon and Fuyu Tamanoi. Structure-activity relationship (SAR) studies have elucidated important structural features of these compounds that can be modified for specific targeting of either GGTase-I, GGTase-II, or both.

The inventors have demonstrated the ability of the lead compounds to inhibit GGTAse-I geranylgeranylation of RhoA and KRas4B with *in vivo* studies of pancreatic and lung cancer models. *In vivo* studies on SCID mice with PANC-1 xenografts show a three-fold reduction in tumor volume at half the maximum-tolerated dose of one of the lead compounds with no effect on body weight. They show activity in a number of human cell lines including PANC-1 and MiaPaCa2. The inventors have also demonstrated that one of the lead compounds inhibits proliferation of NSCLC cell lines H358, H23 and H1507 by inhibiting geranylgeranylation, membrane association of RhoA and causing G1 accumulation associated with decreased cyclin D1/2. Control studies with an RhoA-F mutant suggests that the inhibition of proliferation occurs through the inhibition of RhoA. The compounds have been shown to be substrate-specific inhibitors and do not inhibit other prenyltransferases.

APPLICATIONS

Treatment of cancer

- Pancreatic
- Non-small cell lung
- Breast

ADVANTAGES

- Specificity
- Activity in several cell lines
- Molecular target is known
- First non-peptidomimetic leads against these targets

STATE OF DEVELOPMENT

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OTHER INFORMATION

KEYWORDS

small molecule drugs, oncology, tumor growth inhibition, geranylgeranylation, Ras inhibition, GGTase-I, GGTase-II, geranylgeranyltransferase, RabGGTase

CATEGORIZED AS

- **Materials & Chemicals**
  - Biological
  - Chemicals
- **Medical**
  - Disease: Cancer
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2008-541-0

The efficacy of the lead compounds have been demonstrated in *in vivo* studies, and SARs have been established.The molecular target is known and a crystal structure has been obtained. Further dose-response studies will be conducted.

RELATED MATERIALS

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PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	8,815,935	08/26/2014	2008-541

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Hydrodealkenylative C(Sp3)–C(Sp2) Bond Scission
- Small Molecule Agonists of VDAC2 to Treat Cardiac Arrhythmias and Heart Failure
- Compound Library Made Through Phosphine-Catalyzed Annulation/Tebbe/Diels-Alder Reaction

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