Spiroepoxide, Tetrahydrobenzo-triazoles and -Imidazoles as MetAP-II Inhibitors (P-1068)

Keywords
- Small molecule irreversible MetAP-II inhibitors
- Fumagillin-like inhibition mode
- Drug-like substances in novel chemical space
- Indications: Cancer, malaria, rheumatoid arthritis, pulmonary hypertension and obesity

Abstract
Methionine aminopeptidases (MetAPs) are metallo-proteinases responsible for the co-translational cleavage of initiator methionines from ribosomally synthesized proteins. Numerous studies have shown that selective inhibition of the MetAP-II subtype halts the growth of endothelial cells in culture, inhibits angiogenesis in animal models, and is a validated strategy for anti-angiogenic cancer therapy. More recently, MetAP-II has also emerged as a promising target for other indications, including malaria, rheumatoid arthritis, pulmonary hypertension and obesity.

The Technology
The design of the small molecules described in the invention was guided by the chemical structure of fumagillin. The substances have drug-like substructures, exist in novel chemical space, and the active enantiomeric series has been identified.

- They are potent MetAP-II inhibitors (low nM) and highly selective over MetAP-I and E. coli MetAP.
- They inhibit the growth of HUVEC cells (mid nM GI50), but are not cytotoxic.

Development Stage
Compounds in vitro successfully tested. In addition data on solubility and in vitro plasma stability are available.

Applications and Commercial Opportunity
These compounds represent promising lead structures for MetAP-II target-based approaches to anti-cancer, arthritis, hypertension, and obesity drug projects.

Inventors
The DKFZ inventors are: Christian Klein, Christian Jöst, Aubry Miller.

Scientific Reference
“Understanding the selectivity of fumagillin for the methionine aminopeptidase type II” in Oncol Res. 2003;13(12):513-20 by Klein C.D., Folkers G.

Intellectual Property
An European patent application “New spiroepoxide tetrahydrobenzo-triazoles and -imidazoles and their use as MetAP-II Inhibitors” EP 12 006 666.7 has been filed September 22, 2012.

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