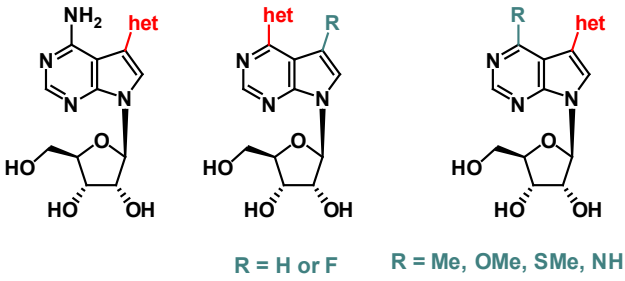
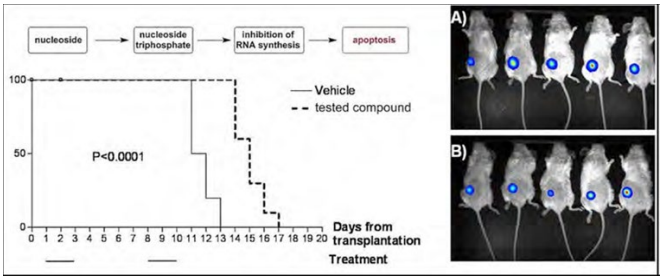
Substituted 7-dezapurine ribonucleosides for cancer treatment

Introduction:
Several purine nucleosides are clinically used in cancer therapy, but their use is limited to the treatment of hematological malignancies. The mechanism of action of these nucleosides is based in their incorporation into cellular DNA and subsequent inhibition of DNA synthesis. However, purine nucleosides and nucleotides are participating on many other cellular processes including e.g. de novo synthesis of nucleic acid components, RNA synthesis, protein synthesis, cell signaling, and regulation. Targeting of these processes by purine nucleoside analogs can provide cytotoxic nucleosides with new mechanisms of action in the treatment of solid tumors and drug-resistant malignancies.

Technology description:
A library of novel hetaryl 7-deazapurine nucleosides was prepared and tested for cytotoxic activity against cancer cell lines and normal fibroblasts. The compounds showed strong cytotoxic activities (low nanomolar range) against cancer cell lines derived both from solid tumors and leukemia, including p53-mutated cell lines and cell lines resistant to taxol and daunorubicin. On the other hand, the compounds possessed low cytotoxicities (> 10 μM) towards normal fibroblasts. Selected compounds have been tested in a P388D1 leukemic syngeneic mouse model and in ovarian (SK-OV-3), colorectal (HT-29) and breast (BT-549) tumor xenografts. Tests of acute toxicity were successfully completed and chronical toxicity tests are ongoing. The tested compounds significantly prolonged survival of treated animals and reduced tumor volumes. Further studies showed that hetaryl 7-deazapurine nucleosides are effectively phosphorylated in cells to the corresponding nucleoside triphosphates. Fast inhibition of cellular RNA synthesis and apoptosis induction were observed *in vitro*, whereas DNA synthesis was barely affected. Furthermore, rapid inhibition of protein expression after treatment with hetaryl 7-deazapurine nucleoside was shown in mice bearing 4T1-luc2 tumors. These indicate that hetaryl 7-deazapurine nucleosides possess a different mechanism of action than conventional purine nucleoside cytostatics and therefore they could provide broader application range in cancer therapy. Hetaryl 7-deazapurine nucleosides are phosphorylated in cells to nucleoside triphosphates and inhibit cellular RNA synthesis which leads to induction of apoptosis. *In vivo* antitumor activity of selected hetaryl 7-deazapurine nucleoside in P388D1 syngeneic tumor model is demonstrated by prolonged mean survival time and a significant increase of overall survival in mice. Lines indicate administration of active molecule or vehicle in control animals. The selected compound showed inhibition of luciferase activity (i.e. protein expression) in mice bearing T1-luc2 tumors after 4h treatment with tested compound (B) which was not observed in mice treated by vehicle (A).





Development status:
Early preclinical stage, *in vitro* and *in vivo* testing, xenografts, toxicology, pharmacokinetics.

Publications:
Perlikova, P., G. Rylova, P. Naus, T. Elbert, E. Tloustova, A. Bourderioux, L. P. Slavetinska, K. Motyka, D. Dolezal, P. Znojek, A. Nova, M. Harvanova, P. Dzubak, M. Siller, J. Hlavac, M. Hajduch, M. Hocek. 17-(2-Thienyl)-7-Deazaadenosine (AB61), a New Potent Nucleoside Cytostatic with a Complex Mode of Action. Molecular cancer therapeutics. 2016, 15(5), 922-37. ISSN: 1535-7163. IF: 5.365. PMID: 26819331

IP protection:
CZ 305466
US 9,586,986
AU 20142777740

Commercial offer:
The project is offered for co-development and licensing

Ownership:
Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague;
Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University, Olomouc

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM´s director (director@imtm.upol.cz) or the technology transfer office (tto@imtm.upol.cz)