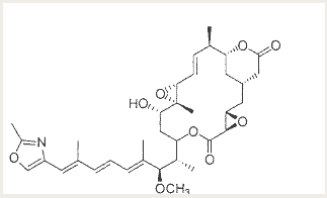
Novel cytotoxic and cytostatic substances for the treatment of cancer

A Company of the Life-Science Fondation for the Promotion of Science and Research

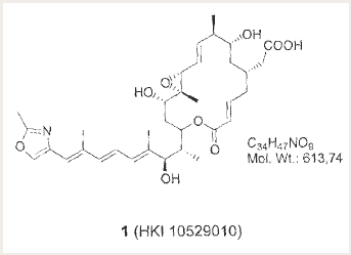
The Challenge

Cancer diseases are the second frequent causes of death in Europe and the USA. From a total of 58 million deaths worldwide in 2005, cancer accounts for 7.6 million (or 13%) of all deaths according to the World Health Organisation (WHO). Due to the significant adverse effects of the common used anti-cancer drugs there is an ongoing demand for new efficient substances with minor adverse effects.

A



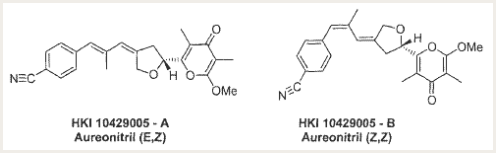
B



1 (HKI 10529010)

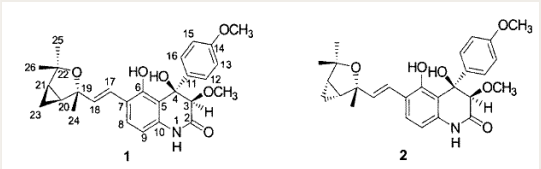
Structures of Rhizoxin (A), a Rhizoxin derivative (B),

C



two new Aureothin derivatives (C)

D



and the new Aspoquinolones

The Technology

All of the following substances are showing cytotoxic or cytostatic effects, respectively, and might be used as basis for new therapeutic agents against cancer diseases.

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TO 10-00017: *Burkholderia rhizoxina*, new endosymbiont from *Rhizopus ssp*. and methods to produce Rhizoxins
This invention discloses the newly discovered bacterial species *Burkholderia rhizoxina* as well as the usage of these microorganisms for the fermentative production of the toxin Rhizoxin and its derivatives. Besides of its antifungal activity Rhizoxin shows also cytotoxic effects. The polyketide Rhizoxin binds very efficiently to ß-tubulin and inhibits the polymerisation of the tubulin molecules, which is a prerequisite for the forming of the mitotic apparatus and the cell division. Due to its mitostatic effects Rhizoxin was already used in clinical studies as therapeutic agent against cancer. Rhizoxin itself is not efficient enough as treatment against cancer but some of the new isolated derivatives are quite promising.

Patent situation: German patent is granted (DE 10 2005 026 417), EP, US, JP, CA, AU applications pending.

TO 10-00021: New antimitotic Rhizoxin derivatives
This invention discloses four new Rhizoxin derivatives isolated from the newly discovered bacteria species *Burkholderia rhizoxina*. These substances, which are belonging to the class of macrocyclic polyketides are characterized by strong antiproliferative, cytotoxic and antifungal effects and can be produced by fermentation using the above mentioned endosymbiotic microorganisms. As explained for the invention before, Rhizoxin itself is not efficient enough for the treatment of cancer but these new isolated derivatives are showing distinct higher effects.

Patent situation: German patent is pending (DE 10 2005 048 556.1). EP, US, JP, CA, AU applications pending.

TO 10-00031: HKI 10429005, new cytostatic drugs

This invention discloses new Aureothin derivatives, Aureonitril A and B, which are showing high cytostatic effects. Aureothins are already described since over 50 years ago as biological acive polyketides from *Streptomyces thioluteus*. Also its cytostatic, antifungal and pesticide effects are well-known. In the meantime the gene cluster, which is responsible for the biosynthesis from *S. luteus* could be isolated. In addition the complete synthesis of some of the Aureothin derivatives succeeded. The application of Aureothines and derivatives thereof as anti-cancer drugs is a completely new approach to our knowledge. Besides a weak antibiotic activity the Aureonitrils A and B are showing a good antifungal effect, especially against *Candida albicans* and distinct strong cytostatic effects compared to the Aureonitrils which are already known. These cytostatic effects could be shown successfully by *in vitro* data. Even more, experiments using different concentrations of this Aureonitrils showed that these substances have a broad spectrum from cytostatic to cytotoxic effects. These effects are provoked by the inhibition of the cell's energy metabolism, which is due to their higher dividing activity much higher in tumor cells. In detail, the Aureonitriles are acting as non-competitive inhibitors of the NADH:Ubiquinon oxidoreductase.

Patent situation: German patent is pending (DE 10 2004 040 014).

Further Reading: Ziehl, M. *et al*. 2005. Mutasynthesis of Aureonitrile: An Aureothin Derivative with Significantly Improved Cytostatic Effect. Angew. Chem. Int. Ed. 44: 1202-1205.

TO 10-00061: Aspoquinolones
This invention discloses 2 new Aspoquinolones isolated from the filamentous fungus *Aspergillus nidulans*. These prenylated quinoline-2-one alkaloids are

characterized by strong antiproliferative, that could be shown successfully amongst others in a human leukemia cell line. These promising compounds can be new lead structures for the development of new anti-cancer therapeutics.

Patent situation: German patent granted (DE 2006 006 893).

Further Reading: Scherlach and Hertweck 2006. Discovery of aspoquinolones A-D, prenylated quinoline-2-one alkaloids from Aspergillus nidulans, motivated by genome mining. Org. Biomol. Chem. 4: 3517-3520.

Commercial Opportunity

Due to the significant adverse effects of the common used anti-cancer drugs there is an ongoing demand for new efficient substances with minor adverse effects. Advantages of the offered novel substances are

- easy and cost effective biotechnological production by fermentation
- strong cytotoxic effects on tumor cells
- the Aureonitriles are showing a broad therapeutic spectrum from cytostatic to cytotoxic effects

A cooperation agreement with option for an exclusive or non-exclusive license or a license agreement (exclusive or non-exclusive) are possible deals.