SIXTH FRAMEWORK PROGRAMME PRIORITY 1
Life sciences, genomics and biotechnology for health
(LifeSciHealth)

No. 503466

Project acronym: **CombiGyrase**

Development of New Gyrase Inhibitors by Combinatorial Biosynthesis

Specific Targeted Research Project

Thematic Priority: LSH-2002-1.2.5-3: Combinatorial biosynthesis as a tool for generating new drug candidates

Publishable Final Activity Report

Period covered: **from 1.1.04 to 31.12.06**

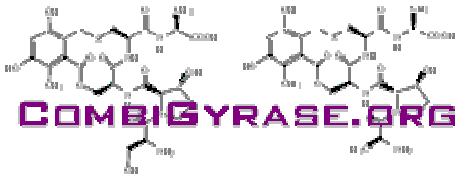
Date of preparation: **12.2.07**

Start date of project: **1.1.2004**

Duration: **3 years**

Project coordinator:
Prof. Dr. Lutz Heide
University Tübingen, Germany

Version 3, 12.2.07



Objectives of the CombiGyrase project:

A constant threat to the population of the European Community is the ever-increasing problem of antibiotic resistance. Widespread use of antibiotics has led to the emergence of antibiotic-resistant strains. The increase and spread of resistance are a matter of serious public health concern worldwide. For example, vancomycin has long been considered as the solution to methicillin-resistant *Staphylococcus aureus* (MRSA) infections, but vancomycin-resistant strains of *S. aureus* have already begun to emerge. Nowadays, the risk of infection increases with a prolonged hospital stay, and so does failure of antibiotic therapy because of multidrug resistance.

In the last decade, many pharmaceutical companies have reduced their efforts to discover new anti-infectives, particularly new antibiotics, and redirected their R&D efforts to other fields perceived as more profitable. However, infectious diseases represent a large market with high unmet medical needs, as shown by the strong interest of many large pharmaceutical companies to acquire novel antibiotics once they have reached late development/registration stages.

The EU, including the most recent member states, possesses a long tradition in basic and applied research on antibiotic-producing microorganisms in both academic and industrial institutions. European scientists have made seminal contributions in several disciplines, ranging from bacterial taxonomy to natural product chemistry, from molecular genetics to bacterial physiology. These disciplines have now been complemented by combinatorial chemistry, genomics and combinatorial biosynthesis. This provides a step change in our ability to produce new bioactive compounds capable of addressing serious medical needs.

The bacterial enzyme DNA gyrase is well validated as a target for a number of antibacterial compounds. The CombiGyrase consortium took advantage of the expertise that existed across Europe to research and develop new drugs that are urgently needed. It represented an ideal platform to expand the diversity of potent gyrase inhibitors found in nature by methods of combinatorial biosynthesis. Combinatorial biosynthesis is a novel technology that uses genetic manipulation to improve the chemical properties and pharmacological activity of naturally occurring compounds.

The **principal objectives** of the CombiGyrase project were:

- the development of new antiinfectives, that target gyrase and/or bacterial topoisomerase IV, by combinatorial biosynthesis in Streptomycetes;
- the evaluation of the activity of these compounds as inhibitors of gyrase and of topoisomerase IV, and of the resulting antibacterial activity against bacterial pathogens;
- the evaluation of the suitability of these compounds as drug candidates, especially for the treatment of infections with multi-drug-resistant bacteria.

The focus was on the development of derivatives of the following antibiotics, which are produced by different Streptomyces strains and represent highly potent inhibitors of gyrase:

- the aminocoumarin antibiotics novobiocin, clorobiocin and coumermycin A1;
- the mixed aminocoumarin/angucycline antibiotic simocyclinone D8;
- the mixed peptide/polyketide antibiotics cyclothialidine and GR122222X.

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Contractors involved in the project:

01: Prof. Lutz Heide (Coordinator), Eberhard Karls-Universität Tübingen, **Germany**
www.uni-tuebingen.de/pharmazie/abteilungen/biologie/en/forschung.html
02: Prof. Jose A. Salas, Universidad de Oviedo, **Spain**
www12.uniovi.es/investigacion/jasalas/
03: Prof. A. Bechthold, Albert-Ludwigs-Universität Freiburg, **Germany**
www.chemie.uni-freiburg.de/pharma/pharmbiol/bechthold/index_b.htm
04: Prof. Anthony Maxwell, John Innes Centre, Norwich, **UK**
www.jic.bbsrc.ac.uk/staff/tony-maxwell/index.htm
05: Prof. Manlio Palumbo, University of Padova, **Italy**
www.dsfarm.unipd.it/
06: Dr. Andreas Vente, Combinature Biopharm AG, Berlin, **Germany**
www.combinature.com
07: Prof. Malcolm Page, Basilea Pharmaceutica Ltd, Basel, **Switzerland**
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Co-ordinator contact details

Prof. Dr. Lutz Heide, Pharmazeutisches Institut, Universität Tübingen,
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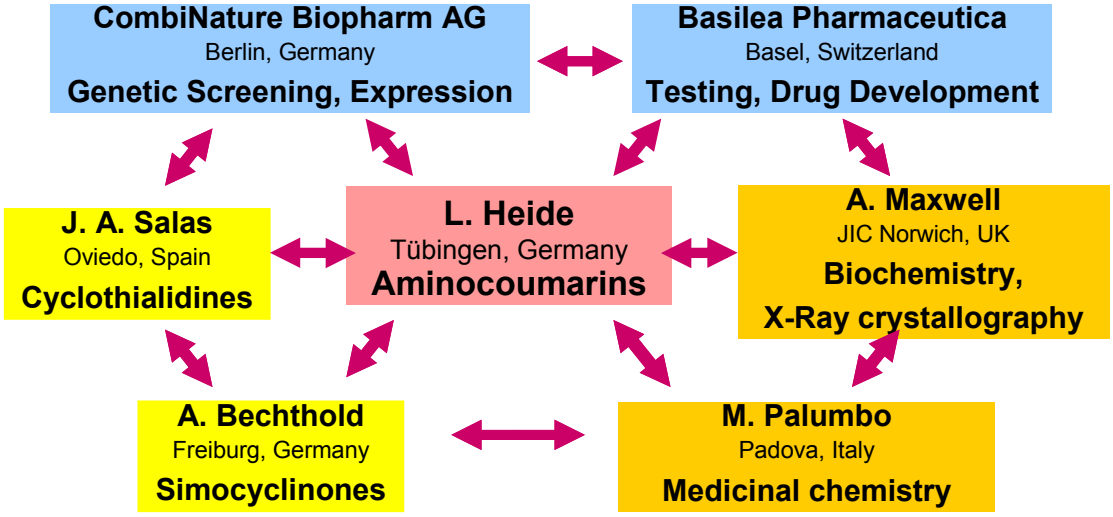
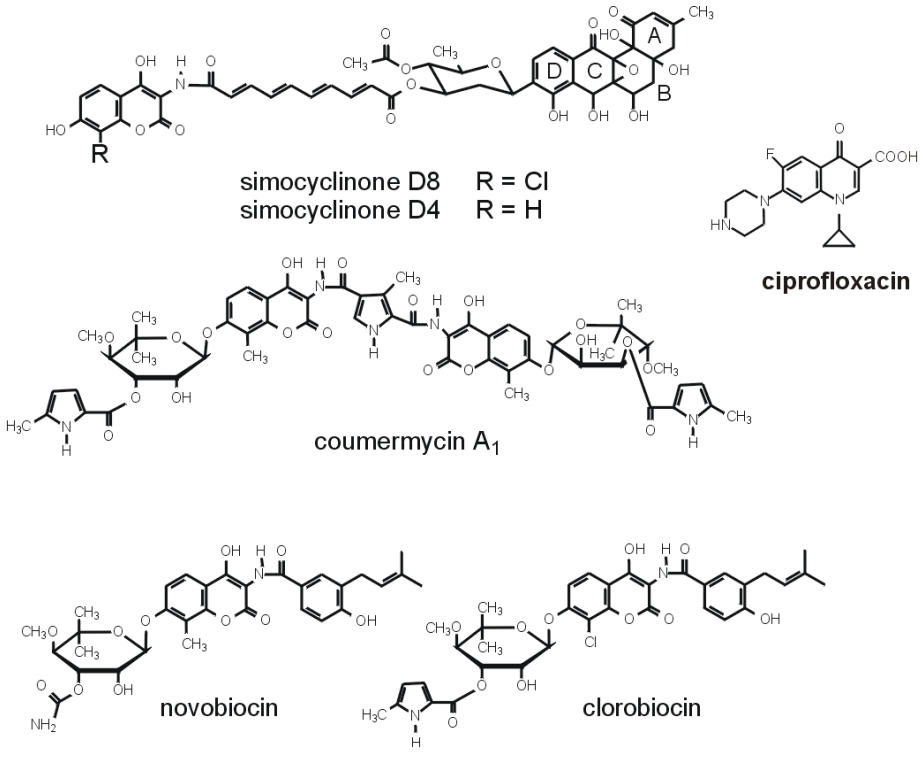
Project website:

www.combigyrase.org

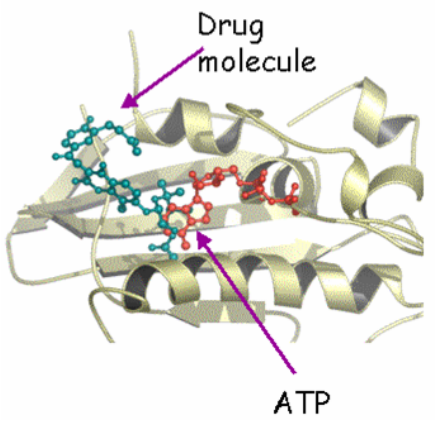
Participants of the CombiGyrase consortium at a project workshop in Basel, Switzerland, Feb 2005



Major achievements of the CombiGyrase Consortium:



Gyrase inhibitors like the synthetic compound ciprofloxacin are clinically very important antiinfective drugs. Using microorganisms which produce natural gyrase-inhibiting antibiotics, the CombiGyrase consortium successfully demonstrated that novel 'designer' antibiotics can be developed by combinatorial genetic methods.



A model how the antibiotic novobiocin (in blue) is bound to its target DNA gyrase (yellow ribbon) and how it prevents binding of the substrate molecule (ATP, in red).

Novobiocin and clorobiocin are aminocoumarin antibiotics and potent inhibitors of bacterial gyrase. Structurally, the two compounds differ by the substitution pattern at two positions. Using genetic engineering of the antibiotic-producing microorganisms, **we generated a series of structural analogs** of these antibiotics. In a subsequent cooperative study by two partners of the CombiGyrase consortium, comparison of the inhibitory activity of these compounds on gyrase and on topoisomerase IV provided the first systematic evaluation of aminocoumarins against both drug targets, and provided new, detailed insight into the **structure-activity relationships of these antibiotics.** This creates the basis to design more potent agents of antiinfective drugs from this class.

Publication: Flatman, R.H., Eustaquio, A., Li, S.M., **Heide, L.** and **Maxwell, A.** (2006) Structure-activity relationships of aminocoumarin-type gyrase and topoisomerase IV inhibitors obtained by combinatorial biosynthesis. Antimicrob Agents Chemother, 50, 1136-1142.

Two **key enzymes of novobiocin and clorobiocin biosynthesis could be crystallized and structurally elucidated** in cooperation between two partners of the consortium. These results provide the basis for a rational redesign of these antibiotics through the manipulation of the individual enzymes in the pathways.

Publication: Keller S, Pojer F, **Heide L**, **Lawson DM** (2006) Crystallization and preliminary X-ray analysis of the aromatic prenyltransferase CloQ from the clorobiocin biosynthetic cluster of Streptomyces roseochromogenes. Acta Cryst. F 62, 1153–1155

Publication: Keller S, Pojer F, **Heide L**, **Lawson DM** (2006) Molecular replacement in the "twilight zone": crystal structure determination of the non-heme iron oxygenase NovR from Streptomyces spheroides through repeated density modification of a poor molecular replacement solution. Acta Cryst D 62:1564-1570

A **key regulator of novobiocin biosynthesis** was identified and successfully used to **increase the production of the antibiotic** in the producer strain.

Publication: Eustáquio AS, Li S-M, **Heide L** (2005) NovG, a DNA-binding protein acting as a positive regulator of novobiocin biosynthesis. Microbiology 151: 1949-1961

The aminocoumarin antibiotic clorobiocin contains an **unusual branched deoxysugar** with a 5,5-*gem*-dimethyl structure. We **identified the gene which is responsible for the generation of this unusual structure**. Genetic modification of the producing micro-organism allowed the **generation of two new structural analogs of clorobiocin**. Both compounds were isolated, their structures were elucidated, and their antibacterial activity was assayed. However, only low amounts of the desired glycosides were formed in this experiment. In a subsequent cooperative study by two partners of the consortium (01 and 02), we **clarified the limiting steps for the formation of the desired antibiotics in the genetically engineered micro-organism**. Introduction of appropriate genes from another antibiotic-producing organism then **allowed a 26-fold increase of the production** of the desired antibiotic.

Publication: Freitag, A., Méndez, C., **Salas, J.A.**, Kammerer, B., Li, S.-M., **Heide, L** (2006). Metabolic engineering of the heterologous production of clorobiocin derivatives and elloramycin in Streptomyces coelicolor M512. Metabolic Engineering 8: 653-661

Mutant strains producing **new novobiocin and clorobiocin derivatives** with altered substituents at the aminocoumarin ring were generated by genetic methods.

Publication: Eustáquio AS, Gust B, Li S-M, **Pelzer S**, Wohlleben W, Chater KF, **Heide L** (2004) Production of 8´-halogenated and 8´-unsubstituted novobiocin derivatives in genetically engineered Streptomyces coelicolor strains. Chem & Biol 11: 1561-1572

In a further study, the **methyltransferase gene *cloP* was inactivated in the biosynthetic gene cluster of clorobiocin**. Expression of the modified gene cluster in the heterologous host *Streptomyces coelicolor* M512 led to the formation of three new aminocoumarin antibiotics.

Publication: Anja Freitag, Heike Rapp, **Lutz Heide**, Shu-Ming Li (2005) Metabolic engineering of aminocoumarins: Inactivation of the methyltransferase gene cloP and generation of new clorobiocin derivatives in a heterologous host. ChemBiochem 6, 1411 – 1418

In a further **study**, **new aminocoumarin antibiotics were isolated from a *cloQ*-defective mutant of the clorobiocin producer**.

Publication: Freitag A, Galm U, Li S.-M, **Heide L** (2004). New aminocoumarin antibiotics from a cloQ-defective mutant of the clorobiocin producer Streptomyces roseochromogenes DS12.976. J Antibiotics 57: 205-210

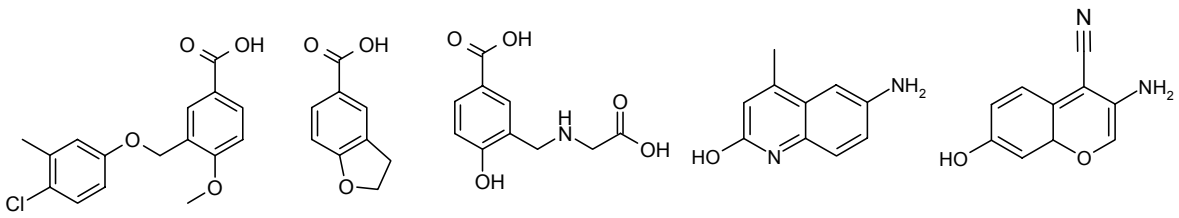
Furthermore, **five new aminocoumarin antibiotics were produced by a combined mutational and chemoenzymatic approach**.

Publication: Xu H, **Heide L**, Li S-M (2004) New aminocoumarin antibiotics formed by a combined mutational and chemoenzymatic approach utilizing the carbamoyltransferase NovN. Chem & Biol 11: 655-662

In order to develop a **general analytical method for pathway monitoring of aminocoumarin antibiotics from culture extracts** of Streptomyces strains we developed superior mass spectrometric methods.

Publication: Kammerer B, Kahlich R, Laufer S, Li SM, **Heide L**, Gleiter CH (2004) Mass spectrometric pathway monitoring of secondary metabolites - Systematic analysis of culture extracts of Streptomyces species. Anal Biochem 335, 17-29

Computer-aided structural modeling was performed **to predict structures of improved aminocoumarin amino antibiotics**, both by individual inspection of target structures and automatically using algorithms to search through larger selections of potential ligands. Sources of the corresponding substrates for feeding experiments were identified in commercial chemical libraries. Several analogs of structural moieties of these antibiotics (ring A & ring B) were selected by these approaches:



Structural moieties for new aminocoumarin antibiotics

Utilizing the genetic, biotechnological, bioinformatic and pharmacological knowledge generated in the CombiGyrase consortium, **33 new aminocoumarins were generated by mutasynthesis experiments** using genetically optimized microorganisms. The structures of these compounds were elucidated, and in cooperation between three partners of the

consortium, the new antibiotics were **tested for gyrase inhibition in vitro and in a cell-based reporter gene expression assay, and for their activity against bacterial pathogens**. A high-throughput assay for the ATPase activity of gyrase B was established and validated with known inhibitors. This assay was used to screen >30 novel novobiocin analogues. Several compounds with anti-microbial activity in the same range as the most potent known antibiotic, clorobiocin, were identified. A secondary assay for detecting the mode of action of novel anti-microbial compounds, based on the induction of target promoters at sub-inhibitory concentrations of antibiotics, was validated for gyrase B inhibitors. The mode of action of the novobiocin analogues on gyrase B was confirmed. Routine cytotoxicity testing was used to further characterize the new derivatives. Cytotoxicity testing using several cell lines was also used to profile a series on modified coumarins that had **potential to be topoisomerase II inhibitors**.

Heide L et al. **European patent** 02 794 562.5-2405: Nucleic acids for aminocoumarin biosynthesis.

Heide L et al. **US patent application** 10/485,710: Nucleic acids for aminocoumarin biosynthesis.

Heide L et al. **German patent application**: New aminocoumarins, methods for their preparation, and their applications. Patent application of Tübingen University, No. AFK-E-0701.

From micro-organisms producing **highly potent antibiotics of the cyclothialidine class**, several cosmids containing cyclothialidine genes were identified. Partial sequence of the cloned DNA region allowed to identify several NRPS genes. Several mutants in NRPS genes have been generated, which were unable to produce cyclothialidine and biosynthetic intermediates. Interestingly, a gene was identified coding for a protein with high similarity to phthalate dioxygenases. This protein could play a role in the modification of the resorcinol ring in cyclothialidine biosynthesis.

For the generation of new glycosylated anti-infectives by combinatorial biosynthesis, a **glycosyltransferase gene tool box** was set up in a cooperation of two partners of the consortium. 30 new genes encoding glycosyl transferases were subcloned from proprietary and published gene clusters. The tool box now contains more than 80 glycosyltransferase genes. This was **successfully used for the generation of novel "unnatural natural products".**

Publication: Luzhetskyy, A., Taguchi, T., Fedoryshyn, M., Dürr, C., Wohlert, S., Novikov, V., **Bechthold, A.** 2005. LanGT2 catalyzes the first glycosylation step during landomycin A biosynthesis. ChemBioChem. 6(8):1406-1410.

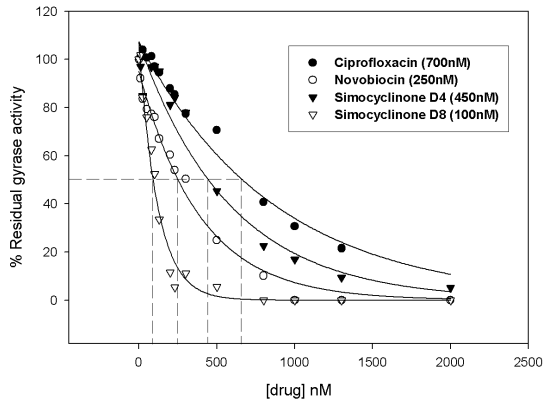
Publication: Berner, M., Krug, D., Bihlmaier, C., Vente, A., Müller, R., **Bechthold, A.** 2006. Genes and Enzymes Involved in Caffeic Acid Biosynthesis in the Actinomycete Saccharothrix espanaensis. J. Bacteriol., 188(7): 2666-73.

In a cooperation of two partners of the consortium, the role of metal ions in the structure and stability of the DNA gyrase B protein was examined, providing further valuable **insights into the mechanism of action of DNA-gyrase at a molecular level**. The results suggest a double role played by metal ions in the catalytic steps involving DNA gyrase B. The observed structural changes paralleled the changes in biological response.

Publication: Sissi, C., Marangon, E., Chemello, A., Noble, C.G., **Maxwell, A.** and **Palumbo, M.** (2005) The effects of metal ions on the structure and stability of the DNA gyrase B protein. J Mol Biol, 353, 1152-1160.

Publication: C. Sissi, A. Chemello, E. Vazquez, C.G. Noble, **A. Maxwell** and **M. Palumbo**: Divalent metal ion replacement for Mg2+: further insight into the mechanism of action of DNA-Gyrase. J. Mol. Biol., submitted

We discovered the mode of action of a completely novel class of DNA gyrase inhibitors (the simocyclinones):

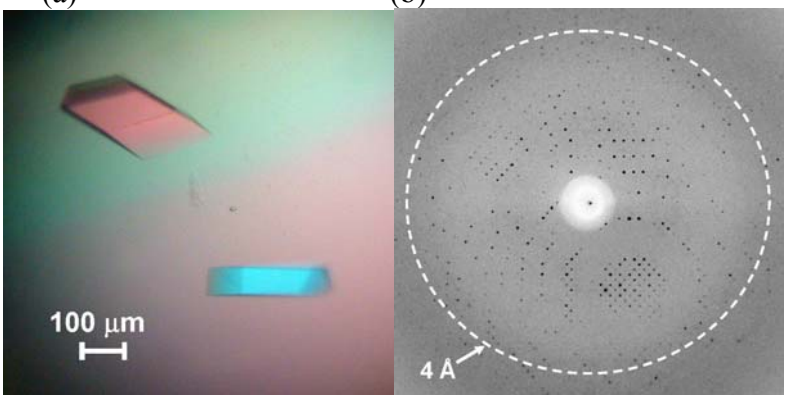


Estimation of IC50s (in parentheses) of simocyclinones D4 and D8 compared with those of novobiocin and ciprofloxacin

Publication: Flatman RH, Howells AJ, **Heide L**, Fiedler H-P, **Maxwell A** (2005) Simocyclinone D8: an inhibitor of DNA gyrase with a novel mode of action. Antimicrob Agents Chemother 49: 1093-100

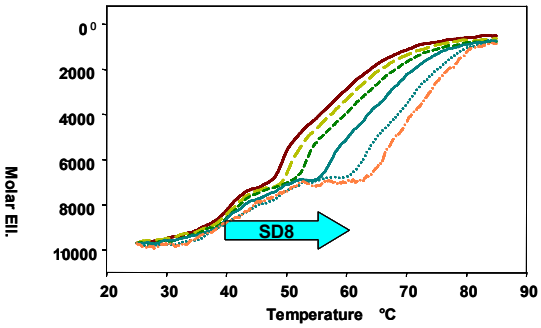
Simocyclinones share some structural similarities with aminocoumarins but a number of differences. We have found that these compounds target gyrase and that **simocyclinone D8 is a more potent inhibitor than novobiocin**. Surprisingly simocyclinones inhibit gyrase by a mechanism that is distinct from that of the aminocoumarins; rather than binding at the ATPase site of GyrB they bind to GyrA and prevent DNA binding. This is a completely novel mechanism of gyrase inhibition and is of great interest in terms of the development of new anti-bacterials. To obtain information on the drug-protein contacts we now **crystallized the N-terminal fragment of GyrA (GyrA59) in the presence of simocyclinone D8**. This has yielded crystals that diffract to ~2.6 Å and we have now solved the structure. **The mode of binding of the drug is completely novel** and is consistent with binding measurements using the Biacore T100.

(a) (b)



Crystallography of the GyrA59-simocyclinone D8 complex. (a) Large single crystals grown by hanging drop vapour diffusion; (b) preliminary diffraction analysis at room temperature using in-house X-ray equipment of Partner 04 (John Innes Centre, Norwihc, UK.

Further work on simocyclinones has included analysis of GyrA59-simocyclinone binding using the Biacore T100, which has yielded a preliminary binding constant (K_D) of 12 µM. Simocyclinone D8 also induced a clear shift in the melting profile of GyrB to higher temperature. This effect was drug concentration dependent and reached saturation at higher drug contents if compared to novobiocin in all tested experimental conditions. However, in analogy to aminocoumarins, the protein-drug complex formation was not largely affected by the presence of Mg2+.



Simocyclinone D8 binding to DNA-gyrase

A protocol was developed by a further partner of the consortium allowing the **reliable genetic manipulation of the simocyclinone producer strain**. Mutants of *S. antibioticus* Tü6040 were generated producing novel simocyclinone derivatives.

Manuscript in preparation: Peintner, I., Luzhetskyy, A., Bihlmaier, C., Welle, E., **Bechthold, A.** 2007. Generation of novel simocyclinone derivatives by genetic engineering. Journal of Biotechnology.

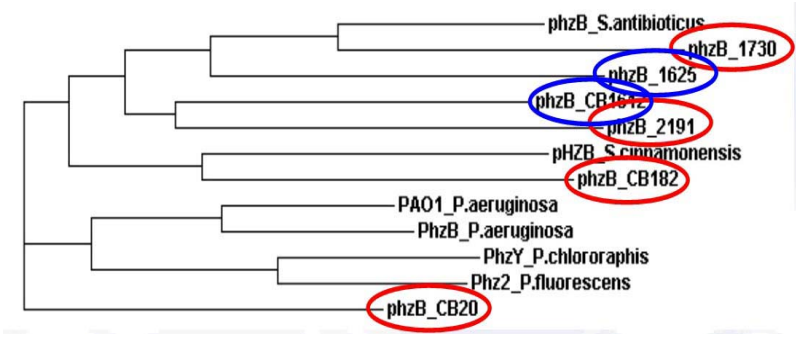
Novobiocin and the other aminocoumarin antibiotics are of interest not only as antibacterial drug but also as **anticancer agents**. Recent studies have shown that novobiocin binds to a previously unrecognized ATP-binding site at the C-terminus of heat-shock protein 90 (Hsp90) and induces degradation of Hsp90-dependent client proteins at approximately 700 microM. In an effort **to develop more efficacious inhibitors** of the C-terminal binding site, a **library of novobiocin analogues was prepared** and initial structure-activity relationships revealed. Thus, the first set of compounds was developed that clearly differentiate between the C-terminus of Hsp90 and DNA gyrase, converted a well-established gyrase inhibitor into a selective Hsp90 inhibitor, and confirmed **essential structure-activity relationships for the coumermycin family of antibiotics**.

Publication: Burlison, J.A., Neckers, L., Smith, A.B., **Maxwell, A.** and Blagg, B.S. (2006) Novobiocin: Redesigning a DNA Gyrase Inhibitor for Selective Inhibition of Hsp90. J Am Chem Soc, 128, 15529-15536.

The **phytotoxin albicidin** was identified as an inhibitor of gyrase with a potentially novel mode of action. *Xanthomonas albilineans* produces a family of polyketide-peptide compounds called. We have shown that **albicidin is a potent inhibitor of the supercoiling activity of bacterial and plant DNA gyrases**, with 50% inhibitory concentrations (40 to 50 nM) less than those of most coumarins and quinolones. The novel features of the gyrase-albicidin interaction indicate the **potential for the development of new antibacterial drugs.**

Publication: Hashimi, S.M., Wall, M.K., Smith, A.B., **Maxwell, A.** and Birch, R.G. (2007) The Phytotoxin Albicidin is a Novel Inhibitor of DNA Gyrase. Antimicrob Agents Chemother. 51:181-7

Phenazines are known **inhibitors of topoisomerases I and II** and display antibacterial, antiparasitic and antitumor activity. A **genetic screening for new actinomycetes phenazine producer** strains was set up in cooperation between two partners of the consortium, and 190 actinomycetes genomes have been screened. Genomes which were tested positive with a primer set for a first phenazine biosynthesis gene (approx. 13%) were verified using a set of primers for another phenazine biosynthesis gene. Six genomic libraries were identified that contained the first gene, and four of those also contained the other gene. A total of 57 cosmids containing phenazine biosynthesis genes were isolated. Further analysis of the strains and cosmids identified by this screening will determine their biosynthetic potential.



Phylogenetic analysis of six PCR products amplified with phzB-specific primers. Red circle: genes for which a phzD sequence could be identified in close vicinity. Blue circle: genes for which no phzD sequence could be identified in close vicinity.

Exploitable Knowledge
Identification of DNA gyrase as the target of the antibiotic simocyclinone; demonstration that it has a novel mode of action, and solving of the structure of the GyrA-simocyclinone complex.
Functional identification of genes for the development of novel aminocoumarin antibiotics
Production method for new aminocoumarin antibiotics
Rational design of new antibiotics and anticancer agents related to aminocoumarin antibiotics
Generation of approximately 50 novel antibiotics and determination of their structure-activity relationships.
Plasmids containing different combinations of deoxysugar biosynthesis genes for drug development by genetic and chemoenzymatic methods
A tool box of glycosyltransferase genes for drug development by genetic and chemoenzymatic methods
Genes and gene clusters for phenazine biosynthesis
Mutants of *Streptomyces antibioticus* Tü6040 producing novel simocyclinone derivatives
High-throughput topoisomerase assay.
Optimisation of existing antibiotics through structure-activity relationship studies

Publishable results

Scientific Publications:

Berner, M., Krug, D., Bihlmaier, C**., Vente, A**., Müller, R., **Bechthold, A.** 2006. Genes and Enzymes Involved in Caffeic Acid Biosynthesis in the Actinomycete *Saccharothrix espanaensis*. J. Bacteriol., 188(7): 2666-73.

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C. Sissi, A. Chemello, E. Vazquez, C.G. Noble, **A. Maxwell** and **M. Palumbo**: Divalent metal ion replacement for Mg2+: further insight into the mechanism of action of DNA-Gyrase. J. Mol. Biol., submitted

Eustáquio AS, Gust B, Li S-M, **Pelzer S**, Wohlleben W, Chater KF, **Heide L** (2004) Production of 8´-halogenated and 8´-unsubstituted novobiocin derivatives in genetically engineered Streptomyces coelicolor strains. Chem & Biol 11: 1561-1572

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Flatman RH, Howells AJ, **Heide L,** Fiedler H-P, **Maxwell A** (2005) Simocyclinone D8: an inhibitor of DNA gyrase with a novel mode of action. Antimicrob Agents Chemother 49:1093-100

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Freitag A, Rapp H, **Heide L**, Li S-M (2005) Metabolic engineering of aminocoumarins: Inactivation of the methyltransferase gene cloP and generation of new clorobiocin derivatives in a heterologous host. ChemBiochem 6, 1411 – 1418

Freitag, A., Méndez, C., **Salas, J.A.**, Kammerer, B., Li, S.-M., **Heide, L** (2006). Metabolic engineering of the heterologous production of clorobiocin derivatives and elloramycin in Streptomyces coelicolor M512. Metabolic Engineering 8: 653-661

Hashimi, S.M., Wall, M.K., Smith, A.B., **Maxwell, A.** and Birch, R.G. (2007) The Phytotoxin Albicidin is a Novel Inhibitor of DNA Gyrase. Antimicrob Agents Chemother. 51:181-7

Kammerer B, Kahlich R, Laufer S, Li SM, **Heide L**, Gleiter CH (2004) Mass spectrometric pathway monitoring of secondary metabolites - Systematic analysis of culture extracts of Streptomyces species. Anal Biochem 335, 17-29

Keller S, Pojer F, **Heide L**, **Lawson DM** (2006) Crystallization and preliminary X-ray analysis of the aromatic prenyltransferase CloQ from the clorobiocin biosynthetic cluster of Streptomyces roseochromogenes. Acta Cryst. F 62, 1153–1155

Keller S, Pojer F, **Heide L**, **Lawson DM** (2006) Molecular replacement in the "twilight zone": crystal structure determination of the non-heme iron oxygenase NovR from Streptomyces spheroides through repeated density modification of a poor molecular replacement solution. Acta Cryst D 62:1564-1570

Li S-M, **Heide L** (2005) New aminocoumarin antibiotics from genetically engineered Streptomyces strains. Curr Med Chem 12, 763-771

Luzhetskyy, A., Taguchi, T., Fedoryshyn, M., Dürr, C., Wohlert, S., Novikov, V., **Bechthold, A.** 2005. LanGT2 catalyzes the first glycosylation step during landomycin A biosynthesis. ChemBioChem. 6(8):1406-1410.

Sissi, C., Marangon, E., Chemello, A., Noble, C.G., **Maxwell, A.** and **Palumbo, M.** (2005) The effects of metal ions on the structure and stability of the DNA gyrase B protein. J Mol Biol, 353, 1152-1160.

Xu H, **Heide L**, Li S-M (2004) New aminocoumarin antibiotics formed by a combined mutational and chemoenzymatic approach utilizing the carbamoyltransferase NovN. Chem & Biol 11: 655-662

Manuscripts in preparation:

Anderle C, Hennig S, Kammerer B, Li S-M, Wessjohann L, Gust B, **Heide L**: Mutasynthesis experiments: New approaches in the production of modified aminocoumarin antibiotics

Anderle C, Li S-M, Kammerer B, Gust B, **Heide L**: New aminocoumarin antibiotics based on the biosynthesis of 4-hydroxycinnamic acid generated by the clorobiocin producer

Anderle C, Stieger M, Burrell M, Reinelt S, **Maxwell A**, **Page M**, **Heide L**: Biological activities of novel aminocoumarin derivatives produced by mutasynthesis

C. Sissi, A. Chemello, E. Vazquez, C.G. Noble, **A. Maxwell** and **M. Palumbo**: On the binding mode of new antibacterial drugs targeted at DNA-Gyrase.

Linnenbrink, A., Luzhetskyy, A.,Welle, **Heide, L.**, **Bechthold, A.** 2007. Novel glycosylated derivatives by biotransfiormation.

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