MEETING REPORT

12th International Conference on the Chemistry of Antibiotics and other Bioactive Compounds (ICCA-12)

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The 12th International Conference on the Chemistry of Antibiotics and Other Bioactive Compounds (ICCA-12) was held at the Institute of Chemistry, Technische Universität Berlin, Germany, on September 11–14, 2011. A broad program was organized by Professors Roderich Süßmuth (TU Berlin) and Andreas Kirschning (Leibniz University of Hannover), which covered many important topics concerning antimicrobial agents and bioactive natural products. Approximately 70–80 participants attended the conference. The program schedule contained five plenary lectures, six invited lectures and sixteen normal lectures. Major topics that were covered at the conference ranged from new sources of antibiotic-producing microbes and isolation/structure elucidation of new secondary metabolites to total and semi-synthesis, biosynthesis (including metabolic and genetic modifications) and SAR studies. This report will briefly summarize some presentations that were given at the conference.

The conference opened with a plenary lecture by Prof. Peter Leadlay (University of Cambridge), who presented some research perspectives taken from his experiences with engineering polyketide biosynthesis. This field continues to advance in its capabilities to produce new molecules via mutasynthesis, modifications involving post-PKS enzymes, and combinatorial procedures. Other advances include elucidation of more biosynthetic pathways and better predictions of metabolite chemical structures from biosynthetic gene sequences. One current limitation is insufficient knowledge about the enzymology of these pathways, such as substrate- and precursor-specificity (or lack thereof), *in vitro* models, and detailed optimal organization of the multi-enzyme domains.¹ The goal is to integrate biosynthetic modifications with medicinal chemistry to create focused compound libraries that will serve as starting sources for new drug discoveries.

In other plenary lectures, Prof. Johann Mulzer (University of Vienna) described his syntheses of providencin, lycoflexine and branimycin.² Since an ideal multi-step synthesis should be short and efficient, he proposed that syntheses longer than 15–20 steps were too inefficient to be practical. Prof. Marcel Jaspars (University of Aberdeen) discussed his search for new secondary metabolites from marine microbes under nutrient-limited or high-pressure conditions and from terrestrial microbes collected from hyper-arid deserts.³ Newly isolated compounds included dermacozines, chaxamycins and chaxalactins. Dr Teresa Carlomagno (EMBL, Heidelberg) presented her

Group photograph in front of the chemistry building of TU Berlin.

studies of the INPHARMA NMR methodology to compare binding of low-affinity ligands at a common target.⁴ This method was very sensitive to inaccurate docking such that it could select the single most-favored docking mode for each ligand and accurately identify the correct docking mode. Prof. Wilfred van der Donk (University of Illinois) reported his work on the discovery and biosynthesis of lantibiotics. New lantibiotics have been isolated by using a structure-reprogramming strategy and from genome-mining studies.⁵ More recently, the first sulfur-linked glycopeptide has been discovered.⁶

The six invited lectures continued to explore these themes of discovery and utilization of antimicrobial natural products. Prof. Hans-Peter Fiedler (University of Tübingen) reported his analysis of culturable actinomycetes obtained from hyper-arid soils in the Atacama desert. From 16 diverse strains selected for further study, one streptomycete produced a 22-membered macrolide named atacamycin A, which showed some anti-tumor activity.⁷ Examination of other strains is still being pursued. Dr Karl Gademann (University of Basel) presented his work on the binding of various antimicrobial agents such as vancomycin or an iron chelator such as anachelin to

surfaces using a readily utilized process, thereby enabling immobilization of a variety of functional groups on the surfaces.⁸ Applications include ones such as antibiotic-immobilized surfaces to control pathogens. Prof. Toshiaki Sunazuka (Kitasato University) described his work on the total syntheses of unique alkaloids madindoline A and neoxaline and the new BASF/Meiji Seika insecticide ME5343 that is being developed for activity against piercing and sucking insects.

Dr Istvan Molnar (University of Arizona) reviewed polyketide biosynthesis in fungi that pertained to 12- and 14-membered macrolides in the resorcyate group (radicicol, zearalenone, curvularin). Future studies were planned to explore potential applications of combinatorial biosynthesis and enzymatic tailoring/decoration transformations (chlorination, epoxidation, O-methylation, oxidation and double-bond changes). Dr Ali Al-Mourabit (CNRS, Gif-sur-Yvette) reported studies on the marine invertebrate-derived group of pyrrole-2-imidazole alkaloids (clathrocin, palau'amine).⁹ Chemical analysis of sponges for new (related) active secondary metabolites yielded donnazole. Prof. Floris P.J. Rutjes (Radboud University, Nijmegen, Netherlands) reviewed the platensimycin/platencin class and the synthesis of analogs.¹⁰ In addition, inhibitors of human pantothenases were suggested as a novel target for finding new inhibitors of bacterial fatty acid biosynthesis and new antibiotics.

Several other lectures continued the topics of chemical synthesis of various complex natural products and accompanying SAR studies to improve bioactivity. Dr Akihiro Sugawara (Kitasato University) described the conversion of erythromycin A into 8R,9S-dihydro-6,9-spiroketal derivatives and further modification via *N*-demethylation and subsequent *N*-alkylation at the 3'-amino substituent of desosamine. Selected derivatives are being evaluated for potential treatment of certain gastrointestinal disorders.¹¹ Prof. Dirk Menche (University of Heidelberg) reported his synthetic studies of the anti-proliferative 38-membered macrolide rhizopodin. Prof. Sebastian Stecko (Polish Academy of Sciences) presented his synthetic approach to carbapenam-lactams using the Kinugasa reaction for copper(I)-catalyzed 1,3-dipolar additions of cyclic nitrones and terminal acetylenes, whereas Prof. Bartłomiej Furman (Polish Acad. Sciences) discussed the conversion of azetidinones to carbapenams and carbacephams. Dr Bernhard Westermann (Leibniz-Institute of Plant Biochemistry) reported his synthetic work on the antibacterial-antifungal hygrophorones obtained from *Hygrophorus* species. He also indicated that 4-oxocrotonate fatty acids exhibited good activity against *Phytophthora* potato blight. Prof. Manfred Braun (University of Düsseldorf) discussed the synthesis of certain aryl ketones as inhibitors of peptidyl-prolyl isomerases, which are of interest as potential anti-cancer agents.

Biosynthesis and combinatorial biosynthesis were frequently mentioned in many of the above presentations, as combinatorial strategies are being increasingly considered for producing new fermentation-derived natural products. Prof. Elke Dittmann (University of Potsdam) identified the biosynthetic gene cluster and elucidated the pathway for the cyclic thiopeptide, microviridin, from the cyanobacterium *Microcystis*.¹² This group has also developed methods to produce cryptic analogs. Prof. Russell Cox (University of Bristol) conducted several domain switches in *Aspergillus oryzae* between tenellin and desmethylbassianin that produced hybrid compounds, whose altered structures in length of side chain and type of methylation correlated with those predicted from the genetic changes.¹³

Additional lectures covered another important theme of the conference concerning investigations to find new sources of antibiotics. Prof. Helge Bode (Goethe University, Frankfurt), representing the GameXP Consortium, gave a progress report of their collaborative efforts with partners in Thailand, Vietnam and UK to examine

entomopathogenic bacteria as sources of new natural products. More than 250 strains of *Xenorhabdus* and *Photorhabdus* have been collected and analyzed for natural product production, and approximately 130 compounds have been isolated or synthesized thus far.¹⁴ Many additional unknown compounds have been found for future identification, whereas elucidation of biosynthetic pathways and genome sequencing are also being pursued. Dr Armin Bauer (Sanofi-Aventis, Frankfurt am Main) described a new series named armeniaspiroles, which was found by a chemical screening program as metabolites of *Streptomyces armeniacus*. The compounds showed good Gram-positive activity *in vitro* and represent a new scaffold for SAR studies. Prof. Jeroen Dickschat (Technische University, Braunschweig) presented chemical and biosynthetic studies on tropodithetic acid, a metabolite from *Phaeobacter gallaeciensis* that exhibited antibiotic activity against some fish pathogens. The final conference lecture was given by Prof. Karsten Krohn (University of Paderborn), who summarized the history for many of his discoveries of new bioactive fungal metabolites that demonstrated the structure and activity diversity and drug potential of this source for finding new bioactive natural products.^{15,16}

The evenings during the conference were pleasantly filled by a walking tour and dinner in Potsdam and a boat tour and on-board dinner on the Spree River.

The next conference in this series, ICCA-13, was announced for September 24-27, 2013, in Japan under the organization of Prof. Toshiaki Sunazuka (Kitasato University).

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