RESEARCH CONFERENCES

ESF-COST High-Level Research Conference

Natural Products Chemistry, Biology and Medicine IV

Hotel Villa del Mare, Acquafredda di Maratea • Italy
28 August – 2 September 2011

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Highlights & Scientific Report

Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

The conference on Natural Products: Chemistry, Biology and Medicine was held for a fourth time at acquafredda di Maratea. 17 invited lectures from leading academic and industrial scientists, as well as 11 short oral communications and 41 poster presentations in two sessions provided for a highly stimulating setting for discussion during the coffee breaks and afternoon breaks. Altogether 77 scientists participated in this meeting. Natural products have played an important and central role in the discovery and development of drugs, and the international pharmaceutical industry has well appreciated this fact. With increasing economical pressures, especially coming from new players from emerging economies, financial pressures have lead several companies to drop their natural product screening activities. However, in recent years it has become more and more evident that the innate chemical and structural diversity of natural products far exceeds that of even the widest synthetic libraries, and more importantly, better matches that of the natural targets of drugs. This has lead to renewed interest in natural product chemistry, and this was also reflected both in the lectures and especially in the discussions during the meeting.

From the two poster sessions, a scientific panel (consisting of chairmen of the sessions) selected the winners of the best poster prize for each session (Jennifer Beaudoin, Broad Institute of Harvard and MIT, USA, and Yahui Wang, Universitat Rovira i Virgili, Tarragona, Spain). The winners were presented with book prizes (Corey and Kurti, Enantioselective Chemical Synthesis).

The topics covered in the meeting ranged from industrial aspects of pharmaceutical production to identification of individual active compounds for specific functions. The broadest area covered, however, centered on exploring the possibilities how synthetic chemistry can meet the challenges posed today, and especially in the future for the construction of chemicals that are of practical value to the health and welfare of mankind.

New synthetic methods were highlighted in a number of high level lectures, and a few selected forward looking lectures gave good impressions of where to look next.

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Scientific Report

Executive Summary

(2 pages max)

Modern organic synthesis is concerned with the rational construction of complex organic compounds from readily available starting materials. Such an endeavor requires several reaction steps and thus careful planning emphasizing all aspects of efficiency, related to both individual steps (tactical level) as well as to complete reaction sequences (strategy level). Of equal significance is the growing awareness regarding the necessity of using enantiomerically pure chiral substances whenever they are expected to interact with a chiral environment.

Natural products have been the inspiration for new medicines since ancient times. The majority of these compounds intercept important biological signalling pathways ranging from embryonic differentiation, to the control of normal cellular growth and proliferation. Alternatively, other such molecules may participate in pathogenic processes resulting from regulation, malfunction or microbial infection. Natural products undoubtedly yield valuable leads for medicinal chemistry, but they give only limited access to the chemically diverse structural space of possible molecules.

Modern medicinal chemistry was conceived with the elucidation of the structure of morphine, but even before this natural products provided the first challenges upon which chemical synthesis was developed (urea, sugars, terpenes, peptides). The bewildering complexity of natural product structures continues to challenge chemists to invent new reactions, reagents and strategies to tackle the ever increasing complexity of the challenges nature provides. It can safely be said that the state-of-the-art of organic synthesis is defined by the complexity of the target structures that can be attacked and conquered.

The development of new pharmaceutical agents is critically dependent on our ability to efficiently synthesize the active molecular species. This efficiency is ever more demanding, since new requirements make the target structures increasingly more challenging; chiral compounds necessitate access to single enantiomeric products; environmental considerations require the production processes to be clean and economical in terms of atom efficiency and energy consumption; synthetic proficiency requires shorter synthesis routes; potentially hazardous reagents and solvents are not tolerated; excessive heating/cooling should be avoided as this leads to increased energy consumption, and reaction media should be renewable, recyclable and non-hazardous (the principles of Green chemistry).

The rapid development in the genomics and proteomics research has brought about an unprecedented number of potential new drug targets, which translates into an ever-increasing need to rapidly assemble highly pure small molecules (Mr < 850) with an increased structural complexity ‘to identify a small molecule partner for every gene product’. These developments have lead to the emergence of completely new subdisciplines of life sciences between chemistry and biology. Chemical biology of the mid-1990’s has been followed by chemical genomics, a field of systematic study of biology through carefully planned and synthesized organic molecules.

Scientific Content of the Conference

(1 page min.)

- *Summary of the conference sessions focusing on the scientific highlights*
- *Assessment of the results and their potential impact on future research or applications*

The conference consisted of seven sessions of lectures given by both invited eminent lecturers as well as lecturers elected from the pool of candidates who expressed their willingness to present their results in a lecture format. In addition, two sessions also contained a poster presentation session, reserved for preliminary communications. Altogether 17 longer invited lectures were delivered, as well as 11 short oral communications. The lectures covered both general topics such as natural products as leads for drug development, a very important aspect currently as the pharmaceutical business is undergoing changes in both strategy and tactics because of changing competition situation with many patent protected drugs entering the generic market period. Dr Hans-Jurgen Federsen from Astra-Zeneca, Sweden, highlighted the changing paradigms in the big pharma, and emphasised the green chemistry aspects of process development and scale-up. The biosynthesis of natural products and the relationship of the biosynthetic information and the functions of the natural products was discussed in an inspiring lecture by professor Hartmut Laatsch (University of Göttingen, Germany). Target identification based chemical proteomics was discussed by professor Raffaelle Riccio (University of Salerno, Italy), and professor Francesco Nicotra (University of Milano Bicocca, Italy) introduced a view on tool for biomedical applications with natural products. Specific classes of medicinal agents were discussed in most lectures; nicotinic agonists are an emerging class of compounds with potential for the treatment of cognitive diseases, and this topic was covered by professor Timothy Gallagher (University oif Bristol. U.K.). Beta-secretase and Myosin ATPase inhibitors were covered in a lecture by professor Hans-Joachim Knölker (University if Dreaden, Germany), and a related topic on activation of G-protein-coupled receptors by professor Peter Gmeiner (University of Erlangen-Nürnburg, Germny). Anthony Burgett (Harvard University, USA) discussed the oxysterol binding proteins as targets for antiproliferative natural products. Dr. Alba Silippo discussed the connection of glycoconjugates and eukaryotic innate immunity, and Dr Franz von Nussbaum (Bayer Schering Pharma, Germany) gave an industrial chemists view on chemical post evolution of natural antibiotics.

Synthesis, being of central value for the production of new potential chemicals for any use, let alone for medicinal purposes, was the most intensively presented and discussed topic. Professor Thomas Hudlicky (Brock University, Canada) gave a talk on biocatalytic synthesis of natural products and their analogues, and also gave important insights on the evaluations of different synthetic strategies. Individual reactions and target structure classes were discussed by: Dr. Nuni Maulide (Max Planck Institute fur Kohlenforschung, Germany) described his group's work on cyclobutene synthesis, Erik van der Eycken (Katholieke Universiteit Leeuven, Belgium) gave an account on microwave chemistry in the construction of medium sized ring systems in natural products. Professor Stephen Clark (University of Glasgow, UK) gave another angle to medium size ring construcion by discussing their work related to polyethers. Development of novel organometal reactions in the synthesis of complex targets was discussed by professors William Kerr (University of Strathclyde, UK) and Thomas NIelsen (Technical University of Denmark), Antonio Echavarran (Institute of Chemical Research of Catalonia, Spain), Gong Chen (Pennsylvania State University, USA), and Uttam Tambar (University of Texas Southwestern Medical Center, USA). Professor Hisashi Yamamoto (University of Chicago, USA) gave a very insightful account on the development of Lewis acid and base derived catalysts for highly efficient synthesis of several complex target compounds.

A number of lectures centered on specific target molecules or target molecule classes: Professor Jon Rainier (University of Utah, USA) discussed the synthesis of quaternary substituted indolines, and professor Jim Thomas (University of Manchester, UK) decribed their impressive recent achievements in bryostatin syntheses. Futher synthetic targets described covered norzoanthamine (Jiong Yang, Texas A&M, USA), pladienolide (Martin Maier, Tübingen University, Germany), myxobacterial chivosazoles (Markus Kalesse, University of Hannover, Germany), ripostatin analogues (Evgeny Prusov, Helmholz Center for Infection Research, Germany), and psammapin and chaeotcin (Matthew John Fuchter, Imperial College, UK).

Appropriately to conclude the theme and atmosphere of the conference, the final presentation by professor Paul Wender (Stanford University) focused on The Chemistry-Medicine Continuum. In this lecture he emphasised the need of not only being able to generate syntheses for defined natural products in a target oriented way. More importantly, the synthesis development should focus also on economical ways (including step economy, redox economy, atom economy) of producing compounds which retain, or even emphasize, the activity of natural products. Several cases were highlighted both from Wender's own laboratory as well as elsewhere. The structural simplifications gained through this function oriented synthesis is beautifully showcased by the bryostatin story, where the natural product synthesis requires over 70 chemical steps and is thus incapable of producing enough material for even extensive clinical studies. Isolation form nature (marine sponge) would require devastation of practically all the natural source. The function oriented desigh has made a number of bryologues available, which are presently under clinical evauation.

Forward Look

(1 page min.)

- *Assessment of the results*
- *Contribution to the future direction of the field – identification of issues in the 5-10 years & timeframe*
- *Identification of emerging topics*

The meeting clearly met the needs the participants and the organising committee had in mind in planning stages. A forum for a wide dissemination of results was well appreciated, and several important aspects of the development of natural product chemistry for the future were clearly identified.
Synthesis per se is of important value for the generation of new chemicals for use by other discplines of science and industry. One cannot create the future materials without access to new building blocks. With the requirement that the new materials must have new functions, it is not sufficient to rely on existing building blocks but ever more complex starting units will be required. This will naturally necessitates more and more sophisticated synthesis methods and tactics to meet the challenges. As the scientific content of (synthetic) chemistry deepens, there is also a fear that the interfaces with other neighboring sciences will face communication difficulties unless modern chemical thinking is also urgently taught on a wider basis.
Issues and topics that need to be covered in the near-to-midterm future include (but are not limited to):
- access to new sources on natural products needs to be further stregthened. These include the more conventional marine sources, but also myxobacteria, symbionts like bacterial symbionts of sponges and endophytic fungi.
- genetically driven natural product discovery is already a reality in many cases where the genetic machinery for the production and processing of secondary metabolites has been unveiled. Utilisation of this information to produce undiscovered natural products will broaden the chemical space available for new drug discovery. This has potential to uncover completely novel chemical structures as exemplified by a recent disclosure of a 51-member macrolide stambomycin.
- a related topic is genetic manipulation of the genes coding for existing natural products. Polyketides, nonribosomal peptides and many terpenes and alkaloids have revealed their genetic codes and are thus amenable to mutation studies to generate more focused libraries.
- development of synthetic methods that allow large scale production of advanced intermediates for the development of drugs and drug candidates for evaluation
- development of asymmetric synthesis methods that are capable of producing ultra pure materials without extensive purification by e.g. chromatographic methods; this will also have an impact on energy efficiency of the whole industry.
- development of ways to discover molecular structures optimised for function, not structure. This

will allow the generation of chemical libraries for screening, that are already predisposed for desired features (solubility, membrane penetration tissue targeting) and simultaneously not burdened with over-engineering the structural complexity.
- education of scientists of neighboring scientific disciplines in modern chemistry so that exchange of ideas will not be limited by the difference in vocabulary

- Is there a need for a foresight-type initiative?

Atmosphere and Infrastructure

- *The reaction of the participants to the location and the organization, including networking, and any other relevant comments*

The selection of speakers was considered excellent (several e-mails after the meeting have praised the meeting as e.g. 'the best meeting I have ever participated').
The location has been observed to be excellent already during the previous meetings. One aspect that has been emphasised is that the location is secluded and distractions are few. However, the venue allows for ample time for informal discussions by being flexible with the opening hours of the different areas in the venue.

Confidential Issues

▪ *Any other issues, not to be included in the published report.*

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Date & Author:

October 24, 2011 Ari Koskinen