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Presentation of the Four Sections of the New Swiss Chemical Society (NSCS)

As a feature each section of the New Swiss Chemical Society (NSCS) is taking turns to introduce itself. This process was initiated by the Section for Analytical Chemistry (SACh), *Chimia* **1996**, *50* (10), 487–488.

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The Section for Medicinal Chemistry (SMC) of the New Swiss Chemical Society (NSCS)

Wolfgang Fröstl, **Rudolf Giger***, and **Emilio Kyburz**

The Section for Medicinal Chemistry (SMC) of the NSCS intends to provide a forum for scientists interested in medicinal chemistry and related fields. The SMC organizes or supports symposia, seminars, presentations, and courses in order to give medicinal chemists and other scientists opportunities to meet, exchange ideas, discuss specific problems, and to get to know each other. The activities of the SMC are coordinated with the NSCS and the European Federation for Medicinal Chemistry (EFMC) and their meetings. The SMC represents its members within the EFMC, is in contact with the IUPAC section of Human Health *via* the NSCS, and is represented in the IUPAC Medicinal Chemistry Section. At present the SMC membership stands at 418 members.

History

Considering the importance of the Swiss pharmaceutical industry the SMC was established relatively late, *e.g.* in comparison to the Medicinal Chemistry Division of the American Chemical Society, which was founded in 1946. The SMC was started by an initiative of chemists of the pharmaceutical industry (*A. Kaiser*†, *J. Kalvoda*, *F. Kunz*, *E. Kyburz*, *M. Montavon*, and *U. Renner*), who met in January 1984 at *Hoffmann-La Roche* and discussed the foundation of a Medicinal Chemistry Section within the former Swiss Chemical Society (SCS). This initiative was endorsed by *K. Heusler*, a former president of the SCS. As a first step the SCS Executive Committee (SCS-EC) nominated a working group composed of *F. Kunz* (chairman), *E. Kyburz* (secretary), *J. Kalvoda*, and *A. Vasella*. In April 1986 a 'Declaration of Intent' was drawn up, and in autumn of 1987 modification of the regulations of the SCS finally paved the way for official establishment of the SMC. As first task a joint meeting with the GDCh in Freiburg im Breisgau was organized in October 1987. In the same year the SMC obtained the membership of the European Federation for Medicinal Chemistry (EFMC) and was invited to organize the 'XIIth International Symposium on Medicinal Chemistry' 1992 in Basel. In 1988 a committee consisting of *E. Kyburz* (chairman), *J. Kalvoda* (treasurer), *R. Giger* (secretary), *J.-L. Fauchère*, *D. Hauser*, *B. Testa*, and *W.-D. Woggon* started to enrol members for the SMC. At the Autumn Meeting of the SCS 1988 the first session on Medicinal Chemistry was organized by the SMC. Plenary lectures were presented by *J.-L. Fauchère* ('Design and Synthesis of Peptide Mimetics') and *R.H. Abeles* ('Inhibition of Serine-Proteases and Esterases by Fluoroketones'). The attendance at these meetings and the rapidly rising membership of the SMC clearly confirmed the expectations of the promoters. At the SCS Autumn Meeting 1989 lectures were given by *C.R. Ganellin* ('Designing Drugs for Histamine Receptors') and *B. Testa* ('Mechanism of Chiral Recognition in Pharmacokinetic and Pharmacodynamic Processes'). Provisional regulations were prepared for the SMC. The official foundation took place on May 16, 1990, on the occasion of the First Annual Meeting of the SMC. The attendance of more than 1200 scientists at the XIIth International Symposium on Medicinal Chemistry in September 1992 in Basel can be considered as a well deserved success.

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Chronicle of the SMC Activities

1st Annual Meeting, May 16, 1990, at *Hoffmann-La Roche*, Basel. Panel discussion: 'Medicinal Chemistry in the Present and in the Future'. Moderator was *A. Pletscher* (Swiss Academy of Medical Sciences, former Head of Research at *Hoffmann-La Roche*), and the panel members were: *A. Eschenmoser* (Laboratory for Organic Chemistry of the ETH-Zürich and former chairman of the SCS), *Bernard Testa* (Head of the Institute of Medicinal Chemistry, School of Pharmacy, Lausanne and member of the Executive Committee of the SMC), *Stephan Guttmann* (Head of Research and Development at *Sandoz Pharma*), *Dieter Hinzen* (Head of Pharma Research at *Hoffmann-La Roche*, Basel), *Jakob Nüesch* (Head of Pharma Research of *Ciba-Geigy*, Basel), and *E. Kyburz* (Chairman of the SMC). The lively discussion shed light on topics such as the importance and significance of medicinal chemistry in pharmaceutical research and its relationship to modern biology and gene technology. Whilst some participants believed that a crisis faced chemists involved in drug research, because the role of chemistry was obscured by the great advances made in the biological sciences, the majority found this could be more an opportunity than a crisis. These advances make it all the more evident, that the chemist involved in drug research, who by training is a pure organic chemist, cannot simply remain a specialist who knows 'how' to synthesize molecules, but should also be able to decide 'what' to synthesize, *i.e.* he must learn to be a true medicinal chemist. Medicinal chemists and biologists should be equal partners, engaged in a constant dialogue and working together in a multidisciplinary environment to provide creative, innovative solutions to human health problems.

Debate focused on the question of how far a rational approach to drug design can replace the previous, widely employed, empirical approach. It was emphasized that also in the past rational techniques, according to the experience and knowledge of the time, have been applied in drug research (*e.g.* isosteric replacement, structure-activity relationships, *etc.*). However, in spite of the great advances in the biological sciences, it remains impossible to grasp the full complexity of nature. Therefore, it was concluded, that in the search for new drugs, empirical approaches will remain valid, a prediction that has been corroborated by the recent use of high-throughput screening techniques for a large range of biomolecular targets, using radioligand binding or enzymatic assays in addition to the classical screens against microorganisms.

The panel concluded that the training of future medicinal chemists should start with a sound basis in organic chemistry. However, the need for those involved in drug research to acquire further knowledge in medicinal chemistry and related disciplines, as well as the development of personal skills was clearly identified. A successful drug researcher needs to be not only a first-rate synthetic organic chemist with a good understanding of biochemistry, pharmacology, physiology, molecular biology, enzymology, quantitative structure-activity relationships, computational modelling, pharmacokinetics, drug metabolism, toxicology, *etc.*, but should also be able to communicate and work effectively within teams, and be ready to learn and keep up with a rapidly expanding field of knowledge. Since it is nearly impossible to find all these qualities in a single person, chemists involved in drug discovery in the large research teams of the pharmaceutical industry, usually specialize in particular areas. Some scientists are interested primarily in medicinal chemistry and develop knowledge and intuition in this discipline, whilst others cultivate their synthetic skills, a differentiation that is also valid in the different stages of drug discovery and drug development.

The question of how to teach medicinal chemistry was addressed authoritatively by *A. Eschenmoser*, who sketched a very broad definition of chemistry, which in his view encompasses all biologically relevant molecules, small and large. Therefore, when structure, recognition, and kinetics are involved, chemistry is part of biological chemistry and molecular biology. Therefore, in his opinion it should be sufficient to teach organic chemistry in a broad sense. Nevertheless he advocated finally the establishment of Chairs on Medicinal Chemistry at Organic Chemistry Departments which would be involved in both research and teaching activities. The audience felt, that indeed an opportunity for chemists to learn in time the essentials of medicinal chemistry and to develop the ability to communicate effectively with future team colleagues from other disciplines would be a step in the right direction.

At the end of the roundtable discussion *H.-P. Schreiber*, theologist and philosopher highlighted the manifold and complex ethical questions connected with man's scientific, technical, and economic activities, in the frame of a pluralistic culture. In our society there is no authority entitled and able to give an ultimate answer to these questions. The widespread consensus of the past century towards the scientific and technical progress, then considered synonymous of social progress, has left place to a diffuse uncertainty, scepticism, and even fear. Although often unjustified the latter has to be taken seriously by the scientific and technical communities.

Obviously mankind has problems in developing and using some new scientific and technical discoveries. These problems should be solved in patient, democratic discussions and brought into common politics which, while observing man's dignity, should safeguard the freedom of research.

2nd Annual Meeting 1991: Auditorium *Sandoz, P. Krogsgaard-Larsen*: 'Drug design strategies in *Alzheimer* disease. Focus on glutamic acid, GABA and acetylcholine' and *H. Timmermann*: 'Searching for selective ligands of histamine receptors'.

3rd Annual Meeting 1992: Auditorium Royal, *Ciba-Geigy, A. Kessler*: 'Problems relating to the Basel region as a location for industry and future prospects'.

4th Annual Meeting 1993: Auditorium *Sandoz, Sydney Brenner*: 'New Genetic Approaches to Human Biology and Medicine' and *Hans Lehrach*: 'Molecular Genetic Analysis of Mammalian Chromosomes'.

5th Annual Meeting 1994: Org. Chem. Institute of the University of Basel, *J.A. Ellman*: 'Combinatorial Synthesis and Evaluation of Compound Libraries Based upon Pharmacophore Structures'.

6th Annual Meeting 1995: Org. Chem. Institute of the University of Basel, *Peter North, Glaxo*, UK: 'The Case of Sumatriptan'.

7th Annual Meeting 1996: Mini-Symposium at the University of Basel (organized together with the Basel Chemical Society and supported by the Pharmaceutical Industries of Basel). 'Synthesis of Small Molecules on Solid Phase'; contributions by *J.A. Ellman* ('The Solid-Phase Synthesis of Complex Small Molecules'), *R. Armstrong* ('Microchip-Encoded Combinatorial Libraries: Generation of a Spatially Encoded Library from a Pool Synthesis'), *M.J. Kurth* ('The Solid-Phase Part of Supported Small-Molecule Synthesis'), and *R. Ramage* ('Consideration of Solid-Phase Synthesis with Reference to Quinolone Antibiotics').

8th Annual Meeting 1997: Mini-Symposium at the University of Basel (organized together with the Basel Chemical Society and supported by the Pharmaceutical Industries of Basel). 'Application of

Combinatorial Libraries to Lead Finding'; contributions by *M. Geysen* ('Combinatorial Chemistry: A New Paradigm for Drug Discovery'), *E.M. Gordon* ('Combinatorial Organic Synthesis: Application to Drug Discovery'), *M. Pavia* ('Identifying Novel Leads Using Combinatorial Libraries: Issues and Successes'), and *R. Storer* ('Solution-Phase Combinatorial Chemistry in Lead Generation').

Spring Meeting of the NSCS Organized by SMC

March 31, 1995, Lausanne: 'Perspectives in Carbohydrate Research: New Opportunities for Drug Discovery'; contributions by *James C. Paulson* ('Glyco-Information: Sialosides, Sialytransferases and Selectins'), *Serge Pérez* ('Carbohydrate-Protein Interactions: The Molecular Aspects'), *Peter M. Colman* ('Influenza Virus Neuraminidase Inhibitors – Design and Antiviral Properties'), and *Beat Ernst* ('Chemical and Enzymatic Synthesis of Complex Carbohydrates').

Swiss Courses on Medicinal Chemistry, Leysin

These courses are held biennially. They offer young scientists with a few years experience in the pharmaceutical industry and interested Ph.D. students a broad overview of disciplines involved in modern preclinical drug research. The development of integrative abilities is a prerequisite to function in today's multidisciplinary drug discovery teams. The course is set up for synthetic organic chemists, as well as biologists and pharmacologists and those involved in drug design and the physicochemical characterization of biologically active compounds. Active participation in tutorials and the presentation of three case histories are important parts of the course.

1st, October 9–14, 1994, organized by *H. van de Waterbeemd* and *B. Testa* (17 speakers, 45 participants from industry and 19 students).

2nd, October 6–11, 1996, organized by *G. Folkers* and *H. van de Waterbeemd* (20 speakers, 40 participants from industry and 22 students).

International Meetings Organized by SMC

- October 6–10, 1987, Freiburg im Breisgau, Joint Meeting with Fachgruppe Medizinische Chemie GDCh, 'New Developments in Medicinal Chemistry: Agonists and Antagonists at Ion-Channels, Receptor Differentiation, Ficts and Facts'.
- September 13–17, 1992, Basel, XIIth EFMC International Symposium on Medicinal Chemistry. Proceedings: 'Perspectives in Medicinal Chemistry', VC/HCA, 1993.
- September 26–28, 1993, Dijon, First Joint French-Swiss Meeting on Medicinal Chemistry.
- September 23–26, Torino, 1997, First Italian-Swiss Meeting on Medicinal Chemistry.

Meetings Supported by SMC

- June 8–11, 1993, Interlaken, '12th Annual Conference of the Molecular Graphics Society'.
- March 21–24, 1995, Lausanne, 'Symposium on Lipophilicity in Drug Research and Toxicology'.
- July 23–27, 1995, Zürich, 'The 9th International Conference on Cytochrome P-450'.
- September 1–6, 1996, Lausanne, 'XIth European Symposium on Quantitative Structure-Activity Relationships'.

Participation in the Autumn Meetings of SCS and Later NSCS

- October 21, 1988, Bern (together with the Section for Organic Chemistry): *J.-L. Fauchère* ('Design and Synthesis of Peptide Mimetics') and *R.H. Abeles* ('Inhibition of Serine Proteases and Esterases by Fluoroketones').
- October 20, 1989, Bern: *C.R. Ganellin* ('Designing Drugs for Histamine Receptors'), *B. Testa*: ('Mechanism of Chiral Recognition in Pharmacokinetic and Pharmacodynamic Processes'), and 12 short communications.
- October 19, 1990, Bern: 13 short communications.
- October 18, 1991, Bern: 6 short communications.
- 1992: no participation due to 'XIIth International Symposium on Medicinal Chemistry', Basel.
- October 22, 1993: no participation due to 'First Joint French-Swiss Meeting on Medicinal Chemistry', Dijon.
- October 21, 1994, Bern: 6 short communications.
- October 20, 1995, Bern, 9 short communications and posters.
- November 21, 1996, Basel, 8 short communications and posters.
- October 15, 1997, Lausanne, 10 short communications and posters.

Executive Committees of the SMC 1990–1997

In September 1990 the members of SMC elected the Executive Committee for the period 1991–1992, 178 of the 314 members voting *via* mail. *E. Kyburz* (chairman), *R. Giger* (vice-chairman), *A. Storni* (treasurer), *W.-D. Woggon* (secretary), *W. Froestl*, *D. Hauser*, *J. Kalvoda*, *B. Testa*, and *P. Wyss* were elected.

Executive Committee elected in 1992 for the period 1993–95: *E. Kyburz* (chairman), *R. Giger* (vice-chairman), *A. Storni* (treasurer), *P. Wyss* (secretary), *W. Froestl*, *D. Hauser*, *J. Kalvoda*, *B. Testa*, and *W.-D. Woggon*.

Executive Committee elected in 1995 for the period 1996–1998: *R. Giger* (chairman), *E. Kyburz* (vice-chairman), *W. Froestl* (treasurer), *P. Wyss* (secretary), *P. Acklin*, *K. Burri*, *G. Folkers*, *H. van de Waterbeemd*, *W.-D. Woggon*, and *R. Ziegler*.

Current Executive Committee: *Rudolf Giger* (chairman), *Emilio Kyburz* (vice-chairman), *Wolfgang Froestl* (treasurer), *Peter Mohr* (secretary), *Pierre Acklin*, *Michael Boes*, *Kaspar Burri*, *Alex Eberle*, *Gerd Folkers*, and *Rainer Metternich*.

Information on the SMC Published in CHIMIA

- *Chimia* **1992**, *46* (7/8), 295–344: XIIth International Symposium on Medicinal Chemistry, Basel, September 13–17, 1992.
- *Chimia* **1993**, *47* (11), 438–439: First Joint French-Swiss Meeting on Medicinal Chemistry, Dijon.
- *Chimia* **1994**, *48* (7/8), 322: Report on 5th Annual Meeting.
- *Chimia* **1994**, *48* (12), 576–577: First Swiss Course on Medicinal Chemistry, Leysin, October 9–14, 1994.
- *Chimia* **1995**, *49* (10), 359–395: Editorial 'The Interdisciplinary Task of Medicinal Chemists' and articles on various aspects of medicinal chemistry.
- *Chimia* **1996**, *50* (1/2), 37: Annual Report 1995.
- *Chimia* **1996**, *50* (6), 257–270: Introduction and articles on the Mini-Symposium 1996.
- *Chimia* **1997**, *50* (11), 819–837: Editorial and articles on the Mini-Symposium 1997.

Future Activities of the SMC

The SMC will continue its efforts to offer to the Swiss community of scientists dedicated to drug research high-quality professional meetings and courses. It considers frequent exposure to international standards of research and the establishment of personal contacts during these events as essential for the advancement of own research projects. We therefore encourage our members to profit from the

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opportunities offered by the SMC for their own professional development, and to participate actively in our events. Suggestions and help are highly welcome and will contribute to improve our work! Finally we like to thank all those who have supported directly or indirectly our endeavors with advice, work, and financial means.

The Following Events are Planned:

- May 7, 1998: 3rd Mini-Symposium at the University of Basel, on 'Bioavailability Aspects in Drug Discovery and Development' organized together with the Basel Chemical Society and the Pharmaceutical Industries of Basel.
- October 11–16, 1998: 3rd Swiss Course on Medicinal Chemistry, Leysin, organized by *B. Testa* and *G. Folkers* (Homepage: http://www.pharma.ethz.ch/leysin).
- October 15, 1998: Session on Medicinal Chemistry at the Autumn Meeting of the NSCS, Zürich.
- March 22–23, 1999: Joint Meeting of the NSCS-SMC and GDCh-Fachgruppe Medizinische Chemie (with the support of the Chemical Society Basel and the Pharmaceutical Industries of Basel), Basel, Zentrum für Lehre und Forschung.

Homepage of the SMC

The Homepage of the SMC was established in spring 1996. It can be accessed directly (http://sgich1.unifr.ch/smc.html) or *via* Homepage of the NSCS (http://sgich1.unifr.ch/nscg.html). Links to the Homepage of the EFMC (http://sgich1.unifr.ch/efmc.html), IUPAC, and other medicinal chemistry Homepages have been implemented.

How to Become a Member of the SMC-NSCS

You wish to become a member of the SMC-NSCS? Click 'Become a member' on the Homepage of the NSCS. You may print out the 'Registration form' or click on 'interactive www' and register *via* the internet using 'Application for Membership'.

For all inquiries, suggestions, and comments, please do not hesitate to contact the members of the Executive Committee, their addresses are on the Homepage or contact the NSCS-Secretariat: Frau *L. Etter*, c/o *Ciba SC*, K-25.1.45, CH-4002 Basel. Tel. (061) 696 66 26, Internet: Lilly.Etter@chbs.mhs.ciba.com.

CONFERENCE REPORTS

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Section for Medicinal Chemistry (SMC)
of the New Swiss Chemical Society (NSCS)

First Italian-Swiss Meeting on Medicinal Chemistry

Torino, September 23–26, 1997

For the fourth time, the Section for Medicinal Chemistry was actively involved in the organization of an international symposium. After a first joint meeting with the 'Gesellschaft Deutscher Chemiker' on New Developments in Medicinal Chemistry (Oct. 6–9, 1987) in Freiburg, the XIIth International Symposium on Medicinal Chemistry (Sept. 13–17, 1992) in Basel, and the First Joint French-Swiss Meeting on Medicinal Chemistry with the Société Française de Chimie Thérapeutique in Dijon (Sept. 26–28, 1993) it organized this year the First Italian-Swiss Meeting on Medicinal Chemistry in Torino with the Division of Medicinal Chemistry of the Italian Chemical Society. 330 Scientists from 16 countries met at the Torino Incontra Congress Center nearly filling its maximum capacity of 350. Three full day symposia on drugs acting on enzymes, drugs acting *via* receptors, and drugs interfering with the signal transduction pathway were complemented by two special plenary lectures and 195 posters. The highlights of the plenary and main lectures were:

Drugs Acting on Enzymes

Joseph A. Martin (*Roche*, Welwyn, UK) gave an outstanding lecture on the discovery of the HIV protease inhibitor saquinavir. HIV protease, a member of the aspartic proteases, cleaves amide bonds between Phe-Pro or Tyr-Pro. Investigating several classes of transition-state mimics, it was found that particularly hydroxyethylamine analogues were quite potent HIV protease inhibitors. First lead was Cbz-Asn-Phe-HE-Pro*O*t-Bu (IC_{50} = 300 nM). Optimization was carried out by modifying each residue in turn, keeping all other elements of the structure constant. N-terminal benzyloxycarbonyl was replaced by β-naphthoyl and quinoline-2-carbonyl. The C-terminal *tert*-butyl ester was replaced by the more stable *tert*-butyl amide. Replacement of asparagine at P(2) resulted in a loss of potency. No improvement was found by the modification of the benzyl side chain of Phe. Modification of the Pro residue at P(1), led to potent compounds, the (*S*,*S*,*S*)-decahydroisoquinoline derivative being the best, *i.e.* Ro 31-8959, saquinavir, an extremely potent proteinase inhibitor (K_i = 0.12 nM) with potent antiviral activity (ED_{50} = 2 nM) devoid of cytotoxicity (TC_{50} >100 μM). The drug was well tolerated in man. Clinical studies showed efficient HIV inhibition leading to a drastic reduction of deaths. Double or triple combination therapy with reverse transcriptase inhibitors (AZT, ddC) was particularly effective.