

Medicinal Chemistry in IUPAC

Accomplishments During the Last Decade

by Robin Ganellin

I previously reported on Medicinal Chemistry in IUPAC, its accomplishments during the previous decade from 1992 to 2002, and its relationships with industry, in an article in *Chemistry International* [1]. Medicinal Chemistry is a key topic for the Subcommittee on Drug Discovery and Development (SC-D3) of the IUPAC Chemistry and Human Health Division (Div VII).

In mid 2002, the Subcommittee was renamed the Subcommittee on Medicinal Chemistry and Drug Development because many medicinal chemists expressed concern about the loss of the subject name. Yet, to be more inclusive and recognizing that drug discovery involves the application of other scientific disciplines in addition to medicinal chemistry, the Subcommittee has recently reverted to its original name. Furthermore, the subject has broadened: drug discovery and development now has to include biological, as well as small-molecule drugs [2].

Members of the SC-D3 have been drawn mainly from the pharmaceutical industry and academia, and generally met twice a year, usually alternating between North America and Europe. The membership is truly international, in scope and diversity. The SC meetings provide the opportunity for invaluable discussions that generate and develop project ideas. The SC output has included publication of books, glossaries, and articles; establishment and operation of the IUPAC-Richter Prize in Medicinal Chemistry; and organization of educational schools in medicinal chemistry and international meetings.

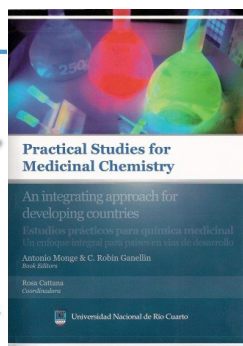
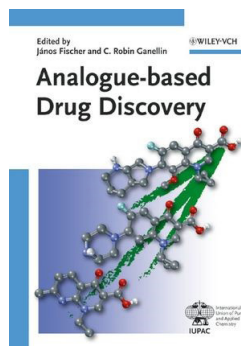
Books

Analogue-based Drug Discovery

A member of our Subcommittee, Dr. Janos Fischer, read in *SCRIP* that out of the 35 new substances marketed in Germany in 1998, 12 were classified as “novel”, 9 as “improvements on existing therapeutic principles”, and 14 as “me-toos” [3]. The description “me-too” is generally used pejoratively to denigrate pharmaceutical companies for not doing “real research”. The implication is that discovery of only novel (*i.e.* first in class) medicines

represent “real research”. The “me-toos” are considered copies made in order to share commercial success. This is not a reasonable view, however. Generally, these “me-toos” are analogues that improve upon properties of the “novel” (pioneer) medicines. The design and discovery of such analogues is actually the historical means by which a particular drug therapy becomes optimized for the benefit of the patients. This derogatory description of drug research inspired the SC-D3 to initiate a project documenting the valuable properties of analogue drugs. Articles on analogue drugs were compiled in a series of

books published by Wiley-VCH in 2006 [4], followed in 2010 and 2013 by two more books [5,6].



Practical Studies for Medicinal Chemistry

This textbook produced with Latin America and other less developed regions in mind, contains 41 practical experiments in medicinal chemistry that do not

require expensive starting materials or reagents and that only depend on low-cost instrumentation and techniques [7]. All experimental details are provided in English; most are also presented in Spanish or Portuguese. The book aims to assist in the post-graduate training of medicinal chemists and to better prepare them to conduct research into the discovery and development of new drugs to treat diseases indigenous to their own countries. The interdisciplinary laboratory exercises are representative of the field of medicinal chemistry and are easy to reproduce. The book is freely available online (see URL in ref. 7) and open to all interested teachers and students. A paper edition was published by the Universidad Nacional de Río Cuarto, Argentina.

Glossaries

Terms Related to Pharmaceutics

The terms used in pharmaceutics are rarely covered by existing glossaries, and when they are, their definitions are often inappropriate and require new or modified definitions to better fit the new context. In the **Glossary of Terms Related to Pharmaceutics** [8], pharmaceutics is defined as the science of preparation of drugs, dosage forms, and drug delivery systems, taking into account the pharmacokinetics and pharmacodynamics of the drug as well as its physical and chemical properties. Thus, many branches of chemistry, such as organic, inorganic,

physical, solid-state, colloid, and surface chemistry, as well as nanotechnology and others, play roles in pharmaceuticals. Even biopharmaceuticals, the more biologically oriented branch of pharmaceuticals, draws on chemical concepts such as (pharmaco)kinetics, absorption, dissolution, diffusion, and others.

Terms Used in Biomolecular Screening

Biomolecular screening has become a critical part of the drug discovery process. The **Glossary of Terms Used in Biomolecular Screening** [9] contains approximately 175 definitions related to various aspects of the screening process, such as assay types, data handling, and relevant technologies. The field of biomolecular screening is multidisciplinary in nature, and this glossary, which was compiled by a task force that included members of the Society for Biomolecular Screening and Professor Larry Walker, editor of *J. Biomolecular Screening*, contains authoritative definitions.

Terms Used in Medicinal Chemistry

A *Glossary of Terms Used in Medicinal Chemistry* was published by the Subcommittee in 1998 [10]. The web version clearly demonstrated the interest and value of such a tool, and between 1999 and 2007, the total usage based on a log of IP addresses was over 200 thousand. There were 25 countries that exceeded 500 uses, led by the USA, which had 73 700. It was appropriate, therefore, that we compiled a substantial list of 150 new entries to provide an update 10 years later. Part II of **A Glossary of Terms used in Medicinal Chemistry** was published in 2013 [11].

Terms Used in Computational Drug Design

A *Glossary of Terms Used in Computational Drug Design* was produced by the Subcommittee in 1997 [12]. Since then, the subject has undergone considerable change, particularly because new high-throughput technologies and the genomics revolution have fueled a need for novel computational methods to handle the resulting deluge of data. In addition, simple computational tools are now available for use by medicinal chemists. The update—or Part II—of this glossary will provide intellectual support for conversations between laboratory and computational chemists, and for the interpretation of calculations that a bench chemist or student might perform. Currently under preparation, it will add 210 new or revised terms that, inter alia, describe methods used in virtual screening, data mining, and cheminformatics (see IUPAC project 2010-057-3-700).

Other Glossaries under preparation

About 170 terms directly related to the **field of drug metabolism** have been compiled and defined under IUPAC project 2000-009-1-700. These represent just those terms that are considered to be most relevant for medicinal chemistry out of a list of some 600 that were originally compiled. The glossary has been reviewed publicly, revised, and is soon ready for submission as IUPAC recommendations. A project to revise the 1990 **Glossary of Terms Used in Combinatorial Chemistry** [13] was initiated in 2004. Since, however, the scope encompassed by the name “combinatorial chemistry” has evolved and so the project is still in progress (IUPAC project 2003-044-1-700).

Analysis of Glossary Terms to Establish Biological Context by Text Data Mining

This project sought to extend the usefulness and applicability of the glossaries in general, by exploring methods for identifying the various contexts in which the terms appear in the scientific literature. The study concentrated on Bioinformation in Drug Development. With the ongoing changes in the field, the glossary-based approach did not seem to adapt in concert with the evolution of terms and their use in the field. An alternative approach, using an ontology-based methodology, was adopted that was based, not on specific terms, but rather on concepts and relationships. This provided a computational platform that can be applied to a range of problems in pharmaceutical R&D. An example is summarized in a 2011 publication [14].

Articles

Stand-alone Drugs

The top 100 most frequently used drugs, which accounted for 56% of total sales based on their sales data in 2006, were analysed for their analogue basis. This led to the identification of nine “stand-alone drugs”, i.e. drugs which analogues that improve upon them have not yet been discovered. Examples of such “stand-alone drugs” are acetylsalicylic acid (aspirin), diltiazem (an L-type calcium antagonist), levodopa (dopamine pro-drug), acetaminophen (or paracetamol, antipyretic and analgesic), aripiprazole (dopamine partial agonist), metformin (oral hypoglycemic), and lamotrigine (anti-convulsant). Rather than publishing an article, a chapter in the book series *Analogue-based Drug Discovery* compiles these data [15].

Accomplishments During the Last Decade

New Drugs for Neglected Tropical Diseases

In Latin America and the Caribbean regions, at least 210 million people live below the poverty line. This is approximately 40% of the population. These impoverished and marginalized populations are heavily burdened with neglected tropical diseases (NTD's). Based on their prevalence and the healthy life years lost from disability, hookworm infection, other soil-transmitted helminth infections, and Chagas disease are the most important NTD's in Latin America and the Caribbean, followed by dengue, schistosomiasis, leishmaniasis, trachoma, leprosy, and lymphatic filariasis.

The solutions to this situation do not depend on simply having appropriate drugs, but are complex and involve public health, disease control, education, and political will. That said, having appropriate drugs would be very helpful. A project (IUPAC project 2009-033-1-700) aims to identify chemistry researchers and testing laboratories, and their equipment and facilities, in Latin America who are currently working to discover new drugs to treat NTD's. The survey data have been combined and published [16].

A networking workshop aimed at the currently identified researchers in Latin America is being planned. The next stage will be to stimulate other medicinal chemists in Latin America to also conduct research in this area, and to make contacts between them and the testing laboratories, promoting self-help.

Natural and Synthetic Substances Related to Human Health

There is a widespread belief on the part of the general public that natural substances are inherently superior to synthetic substances with regard to efficacy and safety in matters related to human health. This question was examined by reviewing the therapeutic use of drugs and herbal medicine preparations, the role of vitamins and nutrients, and the effects of toxic substances. A comparison of the characteristics of natural and synthetic substances within these categories shows a similar range of favourable and unfavourable effects. It is clear that molecular structure and dose determine the effect of substances on human health, not whether they are of natural or synthetic origin.

An IUPAC Technical Report has been published which purpose was to explore the subject by reviewing, in an illustrative manner, drug substances, herbal medicinal preparations, vitamins and nutrients, and toxic substances, with a view to providing an informed, rational perspective [17]. An abbreviated summary was released by EurekaAlert in April 2003 [18].

IUPAC-Richter Prize in Medicinal Chemistry

This Prize was arranged through Dr. Janos Fischer to improve the general awareness of IUPAC among medicinal chemists. It was established by a generous gift from the Hungarian Pharmaceutical Company Gedeon Richter, PLC (Budapest, Hungary) to acknowledge the key role that medicinal chemistry plays toward improving human health. The prize of \$10,000 is awarded every two years to a scientist whose activities or published accounts have made an outstanding contribution to the practice of medicinal chemistry, or to an outstanding example of new drug discovery. This prize has been presented five times between 2006 and 2014. The prize recipients have lectured at the ACS National Medicinal Chemistry Symposium in the USA and at the EFMC International Symposium on Medicinal Chemistry (ISMC) in Europe. Contact with the medicinal chemistry community has been outstanding. Past awardees: Prof. Malcolm F.G. Stevens, Nottingham Univ., UK (2006), Small molecule anticancer drugs, including temozolomide, lectured at Istanbul, Turkey, and Turin, Italy; Dr. Jan Heeres, Janssen Pharmaceutica, Belgium (2008), Ketoconazole and related heterocyclic antimycotics, lectured at Pittsburgh, PA, USA and Torquay, UK; Prof. Arun K. Ghosh, Purdue Univ., USA (2010), Use of backbone binding in discovery of HIV-1 protease inhibitor darunavir, lectured at Minneapolis, MN, USA and Brussels, Belgium; Prof. Stephen Hanessian, Montreal Univ., Canada (2012), For considerable synthesis contributions to medicinal chemistry, lectured at Tucson, AZ, USA and Berlin, Germany; and Dr. Helmut Buschman, ex Grünenthal, Aachen, Germany (2014), Novel analgesic, tapentadol, lectured at Charleston, SC, USA and Lisbon, Portugal.

The prize has been truly international in that seven different countries are represented overall, either for the place of work or for the original nationality of the recipient.

Training of Medicinal Chemists

SC-D3 published a series of papers on the formal training of medicinal chemists, aiming to circumvent the more haphazard learning that occurs when chemists are left to teach themselves "on the job". A summary was published in 2005 [19].

Research and Training in Latin America

This past decade, Prof. Antonio Monge has been very active in arranging for courses and symposia in various

countries in Latin America: short courses were established in Montevideo, Uruguay (September 1999); Rio de Janeiro, Brazil (August 2001); Peru (May 2003); Columbia (May 2003); Bolivia (June 2003); Lima, Peru (October 2004); Montevideo, Uruguay (December 2004); Havana, Cuba (November 2006); Reynosa and Monterrey, Mexico (March 2007); Istmo, Guatemala (August 2007); Huancayo, Peru (October 2007); Buenos Aires, Argentina (May 2010); and Lima, Peru (October 2010).

The Subcommittee also held meeting in Rio de Janeiro, Brazil (February 2005). The meeting also to coincide with the XI Summer School in Pharmaceutical and Medicinal Chemistry at the Laboratory of the Federal University of Rio de Janeiro and where seven SC-D3 members lectured at a short 4-day course entitled "Highlights in Medicinal Chemistry" [20].

Training in the Indian Subcontinent

Increased medicinal chemistry employment in Asian pharmaceutical companies and Contract Research Organizations collaborating with US and European companies have created a need for chemists with state of the art knowledge of medicinal chemistry. Dr. M. Chorghade has convinced the Indian Council of Scientific & Industrial Research (CSIR) to run courses in different cities. Two symposia were held in Rajkot and Nagpur (February 2011), at which five members of the Subcommittee gave lectures. An MCI course (Medicinal Chemistry in India) based on the successful Drew University Residential School on Medicinal Chemistry, was thought on 11-15 February 2013, at Sri Ramachandran University in Chennai. (The original course is taught annually since 1986 on the Drew University campus in Madison, New Jersey; www.drew.edu/resmed). The course was a resounding success: a total of 112 participants from industry (90) and academia attended this short course while industry and academic experts from USA participated in the interactive teaching sessions and discussions. 

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