DOI: 10.1002/cmdc.200700268

Highlighting the New Advances in Drug Discovery and Development

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The 5th Joint Meeting on Medicinal Chemistry, organised by the Medicinal Chemistry section of the Slovenian Pharmaceutical Society under the auspices of the European Federation for Medicinal Chemistry (EFMC), was a continuation of the tradition of prior Joint Meetings, the first of which was held in Taormina, Italy in 1999. Subsequent meetings were held in Budapest, Hungary (2001), Kraków, Poland (2003), and Vienna, Austria (2005). The 5th congress was held in Portorož, Slovenia from the 17th to the 21st of June 2007, and was announced as an Austrian–German–Hungarian–Italian–Polish–Slovenian medicinal chemistry meeting, even though it proved to be a worldwide event, attended by over 300 registered participants, most of whom were from Europe, although there were also researchers from Turkey, India, Uruguay, and Japan. The location, with its rich landscape, Mediterranean vegetation, and favourable climate, provided the perfect atmosphere for a stimulating scientific meeting.

A lot of fascinating work was presented over the three and a half days of the meeting, covering diverse areas of medicinal chemistry research. These included anti-infectives, drugs for cardiovascular and metabolic disorders, enzymes and receptors as targets for new drugs, computer-aided drug design and discovery, emerging strategies in drug discovery, and medicinal chemistry case studies. The scientific programme was made up of six plenary lectures, 20 keynote lectures, 15 oral presentations, and two poster sessions with about 170 posters in all. The participation of medicinal chemists and other scientists involved in drug discovery and development processes from 26 countries gave this meeting a truly international character.

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The inaugural plenary lecture on Sunday the 17th was given by the Nobel Laureate, Professor Robert Huber (Max-Planck-Institüt für Biochemie, Martinsried, Germany), who discussed the fundamental role of protein structure information in the understanding of the chemical, physical, and biological properties of proteins, allowing the design and development of specific ligands as useful tools for therapeutic intervention and plant protection.

Sessions 1 and 2

Keynote lectures by P. Nussbaumer, B. Lesyng, and M. Sollner Dolenc dealt with the interesting field of inhibition of intracellular signal transduction for the development of new drugs.

On Monday morning, the proceedings started with "Drug Proteomics" by Giulio Superti-Furga (CeMM, Centre for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria), who illustrated integrated approaches using proteomics as a central "glue" to obtain physical, functional, and knowledge maps of entire human disease pathways, and to build active chemical compounds back on the pathways by identifying the protein that interact with the immobilised compounds. Novel therapeutic and diagnostic approaches could thus be implemented by determining the mode of action of novel and existing clinical drugs as well as natural products and metabolites, and then linking them to the biological processes. For example, two second-generation tyrosine kinase inhibitors, dasatinib and nilotinib, were analyzed and compared with imatinib to reveal dramatically different specificities and effects on molecular networks. The upshot of this talk was that this kind of "systems biology" approach might inaugurate a truly post-genomic era of molecular medicine.

Peter Nussbaumer (Novartis Institute for Biomedical Research, Vienna, Austria) provided insight into the field of research on sphingolipids, the medicinal chemistry aspects of which are still largely unexplored. The entry into phase III clinical trials of FTY720, for the therapeutic treatment of multiple sclerosis, significantly enhanced scientific interest in sphingolipid-like structures. Potential drug targets in the sphingolipid metabolism and signalling area were discussed extensively, particularly enzyme targets in sphingolipid catabolism. The fundamental role that medicinal chemistry plays in this field by enabling more insight and solving biological problems was demonstrated by selected examples, such as the design of an assay substrate for sphingosine kinases.

Professor Bogdan Lesyng (University of Warsaw, Poland) presented his research group's work on inhibitors of JAK2 and/or JAK3, janus kinases that activate the signal transducer and activator of transcription (STAT) proteins, one of the most recently recognised oncogenic signalling pathways. The constitutive activation of STAT has been detected at high frequency in various human cancers, including leukaemias, lymphomas, and breast, pancreatic, and prostate cancers. An overview of the modelling of these inhibitors was followed by a discussion of their synthesis and the evaluation of their effects on tumour cell lines, and preliminary work on the design of the JAK/STAT signalling system was discussed.

Marija Sollner Dolenc (University of Ljubljana, Slovenia) illustrated recent developments in the field of modulators of integrin receptors, which transmit bidirectional signals during many physiological processes, including remodelling, repair, angiogenesis, development, immune response, and homeostasis. Recent efforts to simultaneously block multiple integrins to achieve synergistic therapeutic effects, for example, to stop the invasion of malignant astrocytoma cells towards osteopontin, thus improving patient prognosis, have led to the design of new compounds featuring the 1,2,4-oxadiazole or triazine scaffold.

An intriguing example of the application of the inhibitors of signalling pathways as new drugs was given by Bernd Riedl (Bayer HealthCare AG, Elberfeld, Germany), who discussed the discovery of Nexavar (soranefib tosylate), which belongs to a novel class of kinase inhibitors that exhibit a dual mode of action. This compound, which is the result of collaboration between Bayer HealthCare and Onyx Pharmaceuticals, inhibits Raf kinase, a key mediator of the MAP kinase pathway, thereby blocking tumour cell proliferation; at the same time, it also inhibits a series of receptor tyrosine kinases involved in angiogenesis and stromal activation. Nexavar, approved in the US in late 2005 for the treatment of advanced renal cell carcinoma, was developed from a medicinal chemistry project starting from a lead structure identified by high-throughput screening; the hit, thienylphenylurea, was then optimised using classical medicinal chemistry and combinatorial chemistry techniques. At present, it is undergoing additional phase III clinical trials to evaluate its potential in the treatment of hepatocellular carcinoma and non-small-cell lung carcinoma.

The series of talks in the first two sessions, concerning the inhibition of various signalling pathways as tools for the development of new drugs, was completed by two short presentations, in which Uwe Rix (CeMM, Vienna, Austria) and György Dormàn (AMRI, Budapest, Hungary) discussed their research progress in the field of selective tyrosine kinase inhibitors.

Sessions 3 and 4

The third session of the meeting was opened by Gerhard Klebe (University of Marburg, Germany) with an interesting plenary lecture in which he discussed a new approach for ligand design using crystallography, data mining, and virtual screening, referring particularly to its application in the development of novel leads and to probe structure–activity relationships. This approach starts from a privileged ligand scaffold well suited to address the key interaction of the conserved recognition pattern of a given target protein family. Insertion of specific side chains to generate a library was easily achieved by means of standard synthetic chemistry guided by an iterative cycle of design, synthesis, testing, and crystal structure analysis. An example concerning the binding of two closely related ligands to thrombin showed that binding properties result from a complex interplay of structure and dynamics, and that structure–activity relationships, which at first glance appear trivial and obvious, do not necessarily display the anticipated straightforward correlation.

An extensive overview of the expanding research field of receptor modelling, computer-aided drug design, and virtual screening was offered by the lectures given by G. Wolber, A. J. Bojarski, and M. Recanatini.

Gerhard Wolber (Inte:Ligand, Vienna, Austria) discussed 3D pharmacophore screening as an alternative approach for pharmacophore modelling and efficient virtual screening. It has the advantages of being faster than docking and more eligible for virtual screening with respect to the screening algorithm. These advantages were demonstrated by the application of this novel rigid 3D pharmacophore super-positioning technique to several examples, such as three CDK2 inhibitors.

The available rhodopsin-based serotonin receptor homology models were reviewed by Andrzej J. Bojarski (Polish Academy of Sciences, Kraków, Poland), with particular reference to the different approaches used in their construction. The experimental site-directed mutagenesis data on serotonin receptors were briefly summarised, with particular emphasis on their application in the process of receptor modelling and prediction of ligand binding mode, highlighting the differences in amino acid composition of the different subtypes, and their possible influence on ligand selectivity. Arylpiperazine-type ligands were discussed as a key study to compare the binding modes proposed by different authors.

Analogously, Maurizio Recanatini (University of Bologna, Italy) gave a talk entitled "Modelling the hERG Potassium Channel and Its Interaction with Drugs", which provided insight into recent efforts devoted to understanding the determinants of hERG blockade by drugs. Different approaches were summarised, including site-directed mutagenesis combined with the voltage-clamp technique, ligand-based QSAR and target-based studies, and the recent drug–hERG docking simulations of increasing quality. All these findings promise to become useful tools for predicting the hERG binding affinity and rationalising hERG blockade by small molecules.

Two oral presentations completed these sessions: Janez Konc (National Institute of Chemistry, Ljubljana, Slovenia) described the development of a new method to predict protein–protein binding sites, while Michael Demel (University of Vienna, Austria) discussed a comparative analysis of two different classifiers for computer-assisted prediction of P-glycoprotein substrates.

Sessions 5 and 6

These sessions, which dealt mainly with anti-infective agents, were introduced with the plenary lecture by Ian Chopra (Antimicrobial Research Centre and Institute of Molecular and Cellular Biology, University of Leeds, UK)

An extensive review of antibacterial chemotherapy was presented, starting from the discovery of prontosil in 1935, through the widespread introduction of these drugs over the next three decades, the rise in resistance, the discovery of new therapeutic agents with different modes of action, and the declining com-

mitment to antibacterial drug discovery by major pharmaceutical companies that caused a decrease in their clinical use. This was followed by a discussion of the urgent need to select suitable molecular targets for the discovery of new drugs, for example by targeting biochemical pathways inhibited by drugs already in use. In this vein, a rational approach to discover novel antimicrobial RNA ligands was illustrated by Markus Weidlich (University of Frankfurt, Germany) during his short communication.

Connected with this topic, Stanislaw Gobec (University of Ljubljana, Slovenia) presented his research group's work on the design and synthesis of a series of phosphinate, sulfonamide, and diazenedicarboxamide derivatives as antibacterial agents directed at novel under-exploited targets such as Mur ligases and D-alanine–D-alanine ligase, two enzymes that catalyse the cytoplasmic steps of bacterial peptidoglycan biosynthesis.

In an effort to solve the problem of bacterial resistance, Tom Šolmajer (Lek Pharmaceuticals d.d., Ljubljana, Slovenia) discussed a series of novel 4-substituted trinems designed as broad-spectrum bacterial β-lactamase inhibitors, whereas Noel J. de Souza (Mumbai University, Matunga, India) interestingly showed the strategy adopted by his team to discover novel drug entities against multidrug-resistant Gram-positive pathogens. It allowed the successful identification and validation of an injectable form of the arginine salt of the orally active chiral isomer of nadifloxacin, and a prodrug of the same active isomer for use in a solid oral dosage form. The series of talks focussed on antibacterials was completed by Pál Herczegh (University of Debrecen, Hungary) who spoke about a new method for the synthesis of the "warhead" of multifunctional antibiotics, in particular the DNA-cleaving antibiotic leinamycin and several of its analogues.

Referring to the fight against AIDS, Maurizio Botta (University of Siena, Italy) delivered a lecture concerning the study of a new class of novel non-nucleoside HIV-1 reverse transcriptase inhibitors capable of overcoming the effects of drug resistance mutations. A series of compounds featuring a 6-vinylpyrimidine scaffold were illustrated, the peculiar behaviour of which is to inhibit HIV-1 reverse transcriptase by a competitive mechanism, unlike the inhibitors reported to date.

Finally, these sessions were completed with two oral presentations by Colin W. G. Fishwick (University of Leeds, UK) and Hugo Cerecetto (University of Montevideo, Uruguay) dealing with the rational design of inhibitors of dihydroorotate dehydrogenase (DHODH) from *Plasmodium falciparum* as new antimalarials, and the study of ethenylbenzofuroxanes active against *Trypanosoma cruzi* as new drugs for the treatment of Chagas' disease, respectively.

Sessions 7–9

Sessions 7, 8, and 9 gave a fine overview of several key studies in medicinal chemistry research, spanning from CNS disorders to cardiovascular diseases.

Session 7 was opened by an interesting plenary lecture by Giuseppe Ronsisvalle (University of Catania, Italy), who provided insight into the role of an improper activation of tissue transglutaminase-2 (tTG-2), a calcium-dependent enzyme involved in several neurodegenerative disorders such as Alzheimer's and Huntington's diseases. He also described in detail his research group's study on selective sigma ligands as important tools to modulate intracellular calcium levels and the consequent pathological up-regulation of tTG-2.

Within this context, Slawomir Filipek (International Institute of Molecular and Cell Biology, Warsaw, Poland) presented conceptual models of presenilin-1 (PS-1) based on patterns of familiar forms of Alzheimer's disease mutations to explain why some mutations of PS-1 are harmful and some neutral, and to predict which amino acid mutations may be potentially dangerous.

Two nice examples of small molecules targeting CNS diseases were given by Benoit Kenda (UCB, Braine-l'Alleud, Belgium) and Paola Conti (University of Milan, Italy): the former dealt with the study of new Levetiracetam Keppra pyrrolidone analogues, leading to the discovery of Brivaracetam as an interesting antiepileptic candidate drug; the latter described the investigation of two enantiomerically pure conformationally constrained aspartate and glutamate analogues, (−)-HIP-A and (+)-HIP-B, as potent inhibitors of synaptosomal excitatory amino acid transporters useful in the treatment of neurodegenerative and neurological disorders.

Impressive examples of indole synthesis were given by Czaba Szántay (University of Budapest, Hungary) and Balás Volk (Egis Pharmaceutical, Budapest, Hungary), who reported on new synthetic pathways to obtain the ergoline skeleton and a number of vindoline derivatives, and a series of oxoindole 5-HT7 antagonists, respectively.

Sessions 7 and 8 were completed by Géza Toth (Biologica Research Centre, HAS, Szeged, Hungary), who spoke about alicyclic β-amino acid endomorphin analogues, and Concettina La Motta (University of Pisa, Italy), who presented some novel acetic acid derived inhibitors of aldose reductase featuring a five-membered heterocyclic core endowed with anti-cataract activity in animal models.

The research field of cardiovascular diseases of session 9 was introduced by Botond Penke (University of Szeged, Hungary) with his key lecture, which illustrated the possible therapeutic applications of tocopherols. Thanks to their antioxidant activity, they have been recently considered a potential supplement to decrease the risk of atherosclerosis, to moderate oxidative neuronal damage in Alzheimer's disease patients, and to be beneficial in the treatment of vascular disorders. However, tocopherols themselves, which have limited penetration across the blood–brain barrier, gave negative results in clinical trials. To overcome this problem, tocopherol composites with suitable carrier molecules have been investigated.

Two representatives of industrial research spheres presented some interesting examples of medicinal chemistry strategies for the discovery of therapeutically active molecules. Henning Priepke (Boheringer–Ingelheim Pharma, Biberach, Germany) gave a historical description of the structure-based design of new anticoagulants, starting from dabigatran to a new selective factor Xa inhibitor. Thomas

Ullrich (Novartis Institutes for Biomedical Research, Vienna, Austria) captured the audience's interest by describing the withdrawal of several marketed drugs due to the lethal cardiac event linked to their inhibition of the hERG potassium channel. The usefulness of hERG computational models, such as those developed at Novartis, in the discovery of hERG-inactive drugs was reviewed.

Roberta Fruttero (University of Turin, Italy) gave an overview of NO-donor aspirin-like agents that have fewer gastrointestinal side effects, but that retain the anti-inflammatory and anti-thrombotic actions of the parent drug. As an application, she described a new class of these drugs in which the acetyl group of acetylsalicylic acid is substituted by an NO-donating acyl substructure.

This session was concluded with the short presentation by Krzysztof Jozwiak (Medical University of Lublin, Poland) who discussed the synthesis, biological evaluation, and molecular modelling studies of a series of stereoisomers of fenoterol as part of a research programme that aims to investigate their enantioselective interactions with the β2 adrenergic receptor, and to develop a pseudoreceptor model useful for guiding the design of new selective agents for the treatment of congestive heart failure and asthma.

The Final Sessions

Sessions 10 and 11 were principally devoted to anticancer agents.

Krzysztof Bielawski (Medical University of Bialystok, Poland) reviewed recent studies on nitrogen-mustard alkylating antitumour drugs aiming to improve the efficacy of this class of compounds by the use of DNA minor-groove-binding ligands. He further pointed out recent significant progress in the identification of cancer-specific cellular drug targets, that exploit the biochemical differences between normal and cancerous cells, such as the expression of the enzyme prolidase, which is involved in the metabolism of proline-containing products. Therefore, the synthesis of proline prodrugs of anti-neoplastic agents was discussed as an attractive strategy to obtain anticancer drugs with an improved therapeutic index.

The talk by Janez Košmirlj (University of Ljubljana, Slovenia) illustrated a combination cancer treatment, describing the design and biological evaluation of new diazene-coordinated cisplatin analogues. The diazene moiety imparts these compounds with the ability to decrease the intracellular concentration of glutathione (GSH), the elevated levels of which represent one cause of the acquired resistance to platinum drugs. Moreover, a synergistic antiproliferative effect was obtained when diazenes and cisplatin were applied together.

An interesting example of collaborative efforts of medicinal chemistry, structural biology, and computational chemistry was illustrated by Ulrich Lücking (Bayer Schering Pharma AG, Berlin, Germany), whose keynote lecture dealt with the identification and optimisation of a series of macrocyclic aminopyrimidines as potent cyclin-dependent kinase (CDK) and endothelial cell-specific vascular endothelial growth factor receptor (VEGF-R) inhibitors. This session devoted to anticancer drugs was completed by a short communication by Pawel Kafarski (University of Wroclaw, Poland), concerning the construction of diagnostic chips for evaluation of the cancerous state of thyroid cells.

The last session of the meeting included two lectures: Slavko Pečar (University of Ljubljana, Slovenia) reviewed the role of nitroxides in medicinal chemistry, including their use as imaging tools, SOD mimetics and potent antioxidants, labelled ligands to study receptors, and more examples. Jean Martinez (University of Montpellier, France) presented a programme to generate active peptides from protein and genomic sequence data, their automated synthesis on solid support, and their biological and pharmacological evaluation.

The Round Table

Another notable event of the meeting was the round table organised by the Education and Training Committee of EFMC, concerning "Education and Training in Medicinal Chemistry". The chairman of the discussion was Peter Mátyus (University of Budapest, Hungary), with the participation of Professors Gloria Cristalli (University of Camerino, Italy), Peter Mohr (F. Hoffmann–La Roche Ltd., Discovery Research Basel, Switzerland), Giuseppe Ronsisvalle (Università di Catania, Italia), Noel J. de Souza (Mumbai University, India) and Anna Tsantili (University of Athens, Greece); a report of the round table will appear in a forthcoming special issue of *ChemMedChem* that features several papers drawing on some of the research presented at this meeting.

Poster Sessions

Last but not least, during the two evening poster sessions, several young researchers presented their current research results, covering a wide range of topics in medicinal chemistry, from receptor ligands, enzyme inhibitors, anti-infective and antitumour agents, and computer-aided studies, to diagnostic and analytical methods. Importantly, great relevance was given to the synthetic aspect of medicinal chemistry, especially to heterocyclic, stereoselective, and non-conventional microwave-assisted synthesis.

In conclusion, the combination of a pleasant location, excellent organisation, fine speakers, and fruitful discussions by the participants made the 5th Joint Meeting on Medicinal Chemistry a great success, both for creative scientific interaction and for the spread of new ideas. For its 10th anniversary, this event will be held again in Taormina, Italy in 2009.

Received: September 26, 2007
Published online on November 19, 2007

