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European Medicinal Chemistry—Strategies, Targets, and Drugs under the Spotlight

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The Joint Meeting on Medicinal Chemistry in Vienna, Austria (June 20–23, 2005) was the fourth meeting in this vein organized by the medicinal section of the Austrian Chemical Society and the Austrian Pharmaceutical Society. Under the auspices of the European Federation for Medicinal Chemistry and announced as an Austrian-German-Hungarian-Italian-Polish-Spanish medicinal chemistry meeting, it was a European event attended by 480 registered participants mainly from Europe, yet there were also visitors from the USA, Japan, and Canada. For three and a half days, this scientific concourse included 80 lectures, 15 short oral presentations, and—last but not least—two poster sessions with about 200 posters in all. Thanks to the organizers, the conference talks covered a broad scientific spectrum of medicinal chemistry in which modern synthetic aspects of drugs, target-specific chemical approaches, and in silico methods for the analysis and management of chemical and related biological data were addressed.

Lectures by H. Waldmann, H. Kubinyi, T. Oprea, C. Melchiorre, and F. Gago covered the expanding research field of computer-aided molecular design and virtual screening.

H. Waldmann (Max-Planck-Institut für Molekulare Physiologie, Dortmund, Germany) discussed protein structure similarity clustering,[1] in which a defined protein structure is combined with the key interactions that are relevant for ligand binding in 3D space. Such coded frameworks are used for the clustering of protein–ligand complexes according to the similarity of their interactions instead of by comparison with defined protein sequences or fold similarities. In this way, more accessible alternatives to known natural ligands can be readily identified. This approach is reminiscent of the Relibase database or the general protein-based pharmacophore derived from protein–ligand complexes, in which structurally similar active sites are identified through common pharmacophores, that is, similarly interacting amino acids in the binding site.[2] It will be interesting to see if this clustering methodology can be developed further for the detection of biological transformations of molecules from the ligand-sensing or catalytic cores of the observed active sites.

H. Kubinyi (Universität Heidelberg, Germany) took the audience on a journey from leads to drugs in which he critically reviewed different aspects of drug research approaches.[3] Bioisosteric searches and the use of nature as a compound source for the initiation of lead-finding programs was mentioned. Additionally, synthetic approaches such as the formation of rings, rigidification of moieties, "me too" and "me better" approaches, the use of "privileged" structural elements, and—last but not least—selective optimization of side activities (SOSA) were elucidated with many examples.[4] Of course, the latest aspects of in silico-supported rational drug design such as fragment design and combination were also discussed. Finally, the issues of metabolism and prodrugs were related to illustrate the caveats and possibilities for drug development in this area that takes advantage of biotransformation.

The talk entitled "Pursuing of Lead Likeness in Pharmaceutical Research" by T. Oprea (University of New Mexico, Albuquerque, USA) illustrated different aspects of drug- and lead-likeness compound profiling, which is used to navigate chemical space toward the most promising drug candidates. The key in working with lead-likeness or drug-likeness compound profiles lies in the quality of the data used, which must be carefully prepared. The chemical profiles for drug-likeness in particular should be extracted from marketed or tested molecules in clinical phase I to phase III trials. For this purpose, Oprea's group developed the WOMBAT database to collect correct drug data.[5] In the course of his talk, Oprea presented a scheme for library design and generation that can provide unique lead-like structures.[6] He concluded with the recommendation that compound profiling rules should not be taken literally in the separation of leads and drugs.[7,8]

F. Gago (Universidad de Alcalá, Madrid, Spain) gave an overview of molecular modeling applied to the exploration of natural compounds that target proteins. Examples included human elongation factor EF1 A, phospholipase A2, and DNA intercalating agents that prevent cells from apoptosis defects. He illustrated the need for exhaustive conformational sampling for his techniques of pharmacophore detection. These involve the derivation of defined pharmacophores or "hot spots" from low-energy conformations of potential natural ligands by using field analysis tools such as the program GRID.[9–11]

This series of talks was complemented by J. Mestres (Universitat Pompeu Fabra, Barcelona, Spain), who introduced an identifier solution developed by his research group. It combines structural keys of ligands with the classification (EC nomenclature) of the related enzyme to provide unique identifiers for ligands. Use of this nomenclature for a com-

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pound label in place of the IUPAC standard permits a canonical view of structural datasets plus the possibility to identify privileged structures among protein classes or biological pathways.

J. Tallarico (Novartis, Cambridge, USA) presented an approach for pathway analysis which includes a cellular assay screening cascade and appears to be able to uncover the connections between phenotypes, target protein, and the related chemicals. Information on the observed genes, introduced protein mutations, cellular assay results, and all active compounds is stored with data management software developed in house. Pathway studies can be performed in a chemogenetic manner by using the gained knowledge of the database tool linked with that of target druggability.

An interesting talk given by C. Melchiorre (Università di Bologna, Italy) provided insight into multipotent drugs against Alzheimer's disease and disorders of the central nervous system. He explained that neurodegeneration with Alzheimer's disease involves a cascade of casually linked processes such as neuronal loss, cholinergic deficit, and the inflammatory response. With the variety of targets in mind, the project goal was to deliver a compound for multi-agent therapy. In this respect, his research group synthesized a series of polyamide derivatives that block the active site and peripheral anionic site of acetylcholinesterase (AChE) and which also contain a quinone group as an antioxidant. Furthermore, the ligands prevented AChE-induced α/β-amyloid protein aggregation. These impressive properties will be challenged by questions of pharmaceutical administration and potential allergic reactions, which are hurdles for this compound class. However, the ligands open the door to an appealing synthetic approach and provide convincing aspects of multiple properties and synthetic feasibility for further studies.[12]

Referring to the long-known natural compound cannabis, M. L. López-Rodríguez (Universidad Complutense, Madrid, Spain) presented her research group's work on inhibitors of endocannabinoid uptake which are thought to be potential drugs for several therapeutic fields such as those of neural disorders, cancer, and inflammation. Her talk highlighted a nice example of ligand-based lead optimization, which relies on traditional but not sufficiently explored natural molecules. Although the compounds are quite old, only did the discovery of the target receptors allow systematic research to take place in the early 1990s. The targets show potency for several diseases (control of movement, cardiovascular and immune regulation, and cellular proliferation), and the initial ligand activities were sufficiently appealing to warrant further ligand-based optimizations.[13]

Several representatives from industrial research spheres also provided interesting insight into medicinal chemistry. U. Stilz, P. Nussbaumer, A. Schoop, M. Bös, and M. Graupe presented case studies that highlighted the use of combined approaches such as automated synthesis, crystallization, X-ray structure analysis, rational design, and classical QSAR. Clearly, industrial research faces different bottlenecks than those encountered in academia.

U. Stilz (Sanofi-Aventis, Frankfurt, Germany) showed impressive examples of lead-finding campaigns, exemplified by that of inhibitors of the potassium channel Kv1.5. Hits resulting from a low-throughput patch-clamp screen were extended by a 2D similarity search followed by re-scaffolding, that is, the fast synthetic exploration of new scaffolds by using automated synthesis with scavenger resins. The development of a ligand-based pharmacophore model and in silico screening on a homology model were undertaken in parallel. These different approaches resulted in the identification of six lead-compound classes, two of which are currently in clinical trials. High-throughput screening (HTS) was established at a later point and identified leads in addition to those mentioned—which were not identified by HTS—underscoring the complementary nature of HTS and virtual screening approaches. Besides the scientific hurdles, the management of these parallel approaches presents a considerable challenge. Natural products as a complementary source for lead and drug molecules which is still attractive today was exemplified by the taxoid compound class.

The extensive use of crystal structures to drive synthesis in the kinase field was demonstrated by A. Schoop (Boehringer-Ingelheim, Vienna, Austria) with the example of 2,4-diaminopyrimidines as inhibitors of CDK1. The observation of binding modes by X-ray crystallography was essential in the lead-optimization program. In the same vein, structural information from protein crystallography and modeling was essential to guide the fast combinatorial solid-phase synthesis of 3-aminopyrazoles as inhibitors of CDK2 and Aurora, which was illustrated by M. Varasi (Nerviano, Milan, Italy).

A further example of the efforts undertaken to obtain structural information on inhibitors was given by M. Bös (Boehringer-Ingelheim, Laval, Canada). NS5B polymerase was identified as a promising target in the hepatitis C virus, and benzimidazoles were identified as promising inhibitors by HTS. As crystallization efforts were initially unsuccessful, photoaffinity labeling studies were performed to obtain information on inhibitor binding, which was later confirmed by X-ray crystallographic analyses.

A nice example of the use of microwave chemistry in medicinal chemistry was given by G.A.M. Giardina (NiKem, Milan, Italy), who used solvent-free microwave heating along with solid catalysts like silica, alumina, and clay for N-alkylation, N-arylation, and the formation of heterocycles. Clay, in particular, works remarkably well as a catalyst in these cases.

The tenacity needed to pursue an attractive target was illustrated by P. Nussbaumer (Novartis, Vienna, Austria) with the example of steroid sulfatase, inhibitors of which have the potential to address estrogen-dependant cancers and other androgen-dependant diseases. Arylsulfamates are irreversible inhibitors and suffer from estrogenicity and low chemical stability, features that are prohibitive for formulation development. Sulfonyl ureas were identified as a new lead class by HTS but suffered low cellular activity. Activity could be enhanced by a switch to acyl sulfonamides.

Synthesis in it finest art was highlighted by J. Mulzer (Universität Wien, Aus-

tria). The retrosynthetic discourse about the total syntheses of polycyclic natural products epothilone B, laulimalide, and isocarbacyclins carried out by his coworkers gave a good overview of state-of-the-art methods for chiral synthesis and protecting-group chemistry.[14]

B. Malawska, F. Hudecz, J. Polanski and K. Hideg outlined the high academic know-how and interesting results in synthetic chemistry and QSAR analyses despite the tight financial situation of some eastern European institutes. They presented arylpiperazine derivatives, which are affine towards α1 adrenoceptors, synthesis of oligopeptide–drug conjugates for targeting cancer cells, strategies toward robust QSAR results, and poly-ADP-ribose polymerase inhibitors.[15,16]

Importantly, several students gave short oral presentations about their current scientific work covering all aspects of medicinal chemistry; this concept is worthy of support for upcoming meetings. In conclusion, the talks and posters, open discussions by the participants during the meeting, and the excellent organization made this a very fruitful scientific meeting. The wonderful location of the conference itself was also quite inspiring.

[1] M. A. Koch, H. Waldmann, *Drug Discovery Today* **2005**, *10*, 471 – 483.
[2] M. Hendlich, *Acta Crystallogr. Sect. D* **1998**, *54*, 1178 – 1182.
[3] H. Kubinyi, *Chemogenomics in Drug Discovery: A Medicinal Chemistry Perspective* (Eds.: H. Kubinyi, G. Müller), Wiley-VCH, Weinheim, **2004**, pp. 43 – 68.
[4] C. G. Wermuth, *Med. Chem. Res.* **2001**, *10*, 431 – 439.
[5] M. Olah, M. Mracec, L. Ostopovici, R. Rad, A. Bora, N. Hadaruga, I. Olah, M. Banda, Z. Simon, M. Mracec, T. I. Oprea, *Chemoinformatics in Drug Discovery* (Ed.: T. I. Oprea), Wiley-VCH, New York, **2004**, pp. 223 – 239.
[6] M. A. Kappler, T. K. Allu , T. I. Oprea, *J. Chem. Inf. Model.* **2005**, in preparation.
[7] T. I. Oprea, J. Gottfries, *J. Comb. Chem.* **2001**, *3*, 157 – 166.
[8] T. I. Oprea, *Chemoinformatics in Drug Discovery* (Ed.: T. I. Oprea), Wiley-VCH, New York, **2004**, pp. 24 – 41.
[9] E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, F. C. Bailly, *J. Med. Chem.* **2005**; *48*, 3796 – 3807.
[10] F. Rodriguez-Barrios, J. Balzarini, F. Gago, *J. Am. Chem. Soc.* **2005**, *127*, 7570 – 7578.
[11] F. Gago, *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 401 – 403.
[12] C. Melchiorre, A. Antonello, R. Banzi, M. L. Bolognesi, A. Minarini, M. Rosini, V. Tumiatti, *Med. Res. Rev.* **2003**, *23*, 200 – 233.
[13] M. L. López-Rodríguez, *Mini. Rev. Med. Chem.* **2005**, *5*, 607.
[14] T. Gaich, J. Mulzer, *Org. Lett.* **2005**, *7*, 1311 – 1313.
[15] B. Malawska, K. Kulig, M. Ciechanowicz-Rutkowska, *Arch. Pharm.* **1997**, *330*, 91 – 99.
[16] J. Polanski, R. Gieleciak, A. Bak, *Comb. Chem. High Throughput Screening* **2004**, *7*, 793 – 807.

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