Second Joint Italian-Swiss Meeting on Medicinal Chemistry (ITCHMC2005)

Modena, Italy, 12-16 September 2005.

The **Second Joint Italian-Swiss Meeting on Medicinal Chemistry (ITCHMC2005)** was held in Modena, (Italy) from September 12 to 16, 2005, under the auspices of the European Federation of Medicinal Chemistry (EFMC).

This year, the annual meeting of the Division of Medicinal Chemistry of the Italian Chemical Society was co-organized with the Division for Medicinal Chemistry of the Swiss Chemical Society and it followed the first, successful one held in Torino in September 1997. This important event in the field of medicinal chemistry brought together scientists from both academia and industry to discuss different aspects of modern medicinal chemistry. Top-ranking scientists from medicinal chemistry and clinical development had the opportunity to meet and discuss the following topics: Carbohydrate Chemistry in Drug Design, Nuclear Receptors, Progress in Design and Development of Protease Inhibitors, Progress in Oncology Research and finally, Pain and Neurodegenerative Diseases.

Introduction

The conference was attended by 300 scientists from 13 countries, with most of the participants from Italy and Switzerland. The meeting allowed an extensive exchange of information and widespread networking. Of the 134 posters on display, 19 were selected for short oral presentations and two were selected for the Farminidustria awards. The meeeting was organized in six sessions with 6 Plenary (PL), 16 Main Lectures (ML) and 19 short communications (SC).

The scientific sessions were held at the *Forum Guido Monzani*, a modern complex with multifunctional facilities; the opening ceremony took place at *Accadenia Militare di Modena,* housed in the seventeenth century Palazzo Ducale.

Modena, city of art, culture and prosperous economy, offered an exciting background for stimulating scientific interactions. Participants were mainly from academia and other research centers together with 46 pharmaceutical companies; among them, six presented their work, namely **Novartis Basel** , **Roche Basel**, **Novartis East Hannover USA**, **IRBM Pomezia Italy**, **Santhera Pharmaceutical AG**, **Heidelberg, GlaxoSmithKline (GSK) Verona, S-IN Soluzioni Informatiche, Vicenza**. The areas covered by the meeting were advanced medicinal chemistry including computational chemistry, established drug targets, libraries and screens, inhibitor

design and clinical advances. There were two poster sessions, with presentations given mainly by young scientists.

Carbohydrate Chemistry in Drug Design

The first topic focused on **Carbohydrate Chemistry in Drug Design.** Investigations over the past 10 years have revealed carbohydrates to possess an enormous potential as lead structures for drug discovery, e.g. in cancer, inflammatory diseases, viral or bacterial infections and genetic diseases. Whereas the inhibition of carbohydrate-processing enzymes has yielded a number of approved drugs (e.g. Acarbose, Zanamivir, Oseltamivir), only limited progress has been made in antagonizing the interaction of physiological carbohydrate-ligands with their receptor proteins.

The reasons for this disappointingly slow progress are many. Firstly, physiological carbohydrate-lectin interactions are notoriously weak – in the μM to mM range – in accordance with their biological roles. Secondly, the dynamics of the binding process of carbohydrates to lectins is still poorly understood. Thirdly, the development of drugs from carbohydrate leads requires complex syntheses, which hampers lead optimization and scale-up of potential drug candidates. In addition to these drawbacks, the pharmacokinetic properties of carbohydrate leads have been investigated and optimized in only a limited number of cases. Thus, data for absorption, distribution, metabolism, elimination and toxicity are rarely available.

The plenary lecture on the topic was by Peter H. Seeberger (ETH, Zurich), who presented a lecture on "Automated synthesis of oligosaccharides as basis for drug discovery: from carbohydrate arrays to a malaria vaccine".

Three main lectures followed by (i) B.Ernst (Basel University) who discussed three examples covering three areas: the selectins, the myelin-associated glycoprotein (MAG) and the asialoglycoprotein receptor (ASGP-R); (ii) by A.Dondoni (Ferrara University) introduced the synthetic organic chemistry of glycoside decoration; and (iii) by M.Pappalardo, Catania University,who dicussed glycopeptides and carbohydrate-based synthetic vaccines for cancer immunotherapy.

The SCs presented by M.Pregnolato (Pavia University) and A.Guaragna (Napoli University) focused mainly on synthetic aspects of carbohydrate chemistry and in particular, an efficient process for obtaining deprotected derivatives of intermediates bearing only one free hydroxyl group in the C-4 position, valuable synthons for the preparation of *N*-acetyl-D-lactosamine octa-acetate, a building-block on the synthetic pathway of oligosaccharides like Sialyl Lewis.

Drugs Targeting of Nuclear Receptors

The second session focused on **Nuclear Receptors.** The nuclear receptor super-family provides a diversity of function that affords profound insights into the fundamental basis of the differences

between species. An understanding of the role of nuclear receptors in health and disease will provide key strategies in the development of novel therapeutics. The plenary lecture presented by F.Gualtieri (Perugia Uinversity) was entitled "The Farnesoid X receptor in drug discovery: from functions to therapeutic exploitation". During recent years great progress has been made in the elucidation of properties, functions and therapeutic applications of nuclear receptors with particular attention reserved to a group referred to as 'adopted orphans' since natural ligands have recently been identified for them. Included in this group are receptors for fatty acids, cholesterol metabolites and xenobiotics and three of them LXRα, β and FXR, in particular, are known to be activated by cholesterol metabolites and to play important roles in cholesterol biosynthesis and catabolism. Whereas LXRs are oxysterols sensors, FXR is a bile acid receptor highly expressed in liver, intestine, kidney and the adrenal gland with chenodeoxycholic acid (CDCA) as the most potent natural ligand.

Recently, it has been discovered that FXR activation also modifies the transcriptional activity of a variety of transcription factors controlling gluconeogenesis and lipogenesis thus affecting in concert bile acid, lipid and carbohydrate metabolism. Thus, molecular mechanisms underlying lipid homeostasis and energy balance can be unraveled and intriguing possibilities for the use of FXR modulators in the metabolic syndrome revealed.

The ML was presented by M.Macchia, Pisa University, on the topic of "Salicylaldoximes and anthranylaldoximes as alternatives to phenol-based estrogen receptor ligands" Estrogens regulate the development and function of reproductive tissues. They also have significant effects on a wide variety of other tissues, such as bone, cardiovascular and the central nervous systems and liver. The actions of estrogens are mediated by specific receptors (ERs), which function as ligand-inducible nuclear transcription factors. ERs are also involved in several diseases, such as breast and uterine cancer, prostate hypertrophy and osteoporosis. Selective estrogen receptor modulators (SERMs) are considered useful therapeutic agents, as they may stimulate the desired estrogen action in bone and liver, and, at the same time, they may inhibit the undesirable estrogenic effect on breast and uterus. In a search for new molecular entities that might bind to the ER and thereby increase the chemical diversity of estrogen ligands, the possibility of replacing the phenolic ring of estrogen ligands with new chemical units which might act as bioisosters, has been considered.

The SCs of this session focused on Histone deacetylase as a drug target and were presented by K.Vanommeslaeghe (Vrije Universiteit Brussel) and R.Ragno (Rome, La Sapienza University). Two free SCs on structural biology of peripheral anionic site of human AchE (A.Cavalli, Bologna University) and PET studies (E.Lacivita, Bari University) were also presented.

Progress in Design and Development of Protease Inhibitors

The third session was dedicated to "**Progress in design and development of protease inhibitors**." Proteases, a group of proteins, which have the ability to catalyse the cleavage of peptide bonds, play an essential role in the control of many biological processes. The selective, limited and efficient cleavage of protein substrates represents an important post-translational modification, which regulates processes as diverse as the activation or inactivation of cytokines, hormones or growth factors, the cellular localization of proteins or ectodomain shedding from the cell surface. Alterations in the regulation of proteases underlie pathological processes such as arthritis, cardiovascular or neurodegenerative diseases. Moreover, the survival of many infectious organisms is dependent on their ability to generate essential proteins through effective proteolysis.

Many proteases have been selected as drug target by the pharmaceutical industry. Orally available inhibitors of the angiotensin converting enzyme (ACE) or of the HIV protease are well established drugs in the treatment of hypertension or of AIDS. More recently a proteasome inhibitor was introduced to treat multiple myeloma patients. In addition a number of proteases inhibitors are in late clinical trials for diabetes (DPPIV inhibitors), hypertension (renin inhibitors) or osteoarthritis (cathepsin K inhibitors). Despite these successes, protease-directed drug discovery has not resulted in as many drugs as could have been expected with respect to the significant effort and investments made in this field. Key hurdles have been a lack of target validation (e.g MMP inhibitors in cancer), difficulties in obtaining and appropriately assessing inhibitor selectivity (e.g MMP inhibitors in arthritis) and the difficulty of turning peptidic inhibitors into orally active drugs (e.g. renin). Scientists who presented this topic basically come from pharmaceutical companies, highlighting the central role of this important enzyme class as drug targets.

S. Cottens (Novartis, Basel) presented the introductory PL entitled "From proteases to protease inhibitors to drugs". The lecture described the project in development at Novartis addressing these hurdles in a more systematic way. Novartis recently established an Expertise Platform Proteases to study the activities of the Protease Platform from identification of suitable drug targets to the delivery of high-quality development candidates. E. Villhauer (Novartis East Hannover, USA) described the Story of Vildagliptin (LAF237): a dipeptidyl peptidase IV (DPP4) inhibitor for the treatment of type 2 diabetes. The results of the study suggest that Vildagliptin is a potent, stable, selective DPP4 inhibitor possessing excellent oral bioavailability and potent antihyperglycemic activity with potential for once-a-day administration.

K. Groebke Zbinden (Roche Basel) introduced the topic of the development of efficacious and orally bioavailable tissue Factor/Factor VIIa inhibitors. Mandelic acid amide lead structures, which inhibit TF/F.VIIa with submicromolar activity, were generated by a combination of molecular modeling interaction studies (*in silico* screening) of a virtual library and rational design. Extensive lead optimization led to improvement of *in vitro* as well as functional activity. Interaction of a sub-series of inhibitors with a novel binding pocket in the active site of F.VIIa

was explored by x-ray analysis and the topic was discussed in detail. M.Missbach (Novartis, Basel) presented a talk on the development of selective and orally active inhibitors of Cathepsin K as novel treatment for osteoporosis. V.Summa (IRBM, Pomezia) presented a talk on serine proteases inhibitors in Hepatitis C Virus NS3/4a; N.Micale (Messina University) and S.Bulat (Santhera Pharmaceutical) presented their work on cysteine protease inhibitors and thrombin inhibitors respectively.

Progress in Oncology Research

The fourth session was dedicated to **Progress in Oncology Research.** The PL was by PG Baraldi (Ferrara University). Minor groove binders are one of the most widely studied classes of agents characterized by a high level of sequence specificity and they are an interesting class of DNA ligands which possess several biological activities. These agents, most of which bind thymine-adenine (TA) rich sequences of the minor groove include, mitomycin C, anthramycin, CC-1065 and its synthetic analogues plus a second class mainly represented by Distamacyn A. Derivatives of the above mentioned compounds were presented. The second speaker, I. Antonini (Camerino University) discussed another class of DNA interacting agents, bis-intercalator derivatives. M.Botta (Siena Uinversity) presented a topic entitled "A pharmacophore modeling approach to design new Taxol mimics: towards the synthesis of potential anticancer and MDR reversing agents". Novel bicyclic 3,8-secotaxane diterpenoids, such as Taxuspine X and U, whose bicyclic skeleton has been proposed as biogenetic precursors for taxanes not previously explored, were synthesized adopting the SAMP/RAMP-hydrazones methodology. K. Altmann (ETH, Zurich) described recent developments in the chemistry and biology of Epothilones. A.Mai (La Sapienza, Roma) presented a novel Gcn5p inhibitor that represses cell growth, gene transcription and histone acetylation in budding yeast. Other anticancer compounds series were proposed as potential new inhibitors such as 3'-*C*-Methyl-ribosyl nucleosides (L.Cappellacci, Camerino University) and isoindolo[1,2-*a*]quinoxaline derivatives (A.Martorana, Palermo Uiversity). A systematic computational approach to the data analysis of tyrosine kinases X-ray crystal structures was proposed by L.Moretti (Geneva University).

New approaches to the treatment of Pain

The fifth topic centered on **Pain.** Pain is an unpleasant sensory experience and is often associated with tissue damage. Current therapies have side effects, which affect the patient's quality of life. They are only effective in a relatively low percentage of the patients population. In an aging population, the treatment of chronic pain is, therefore, a high unmet need. However, during the last decade our knowledge of the pain pathways has increased dramatically and new drugable targets are currently being investigated for the treatment of chronic neuropathic pain.

The PL was introduced by R.Di Fabio (GSK, Verona). This presentation provided a review of the results achieved in GSK on the appropriate modulation of the NMDA receptor at the non-competitive glycine binding site, emphasizing both the medicinal chemistry and the SAR associated with these targets. In addition, the pharmacological profile of the best compounds identified in different animal models of acute and chronic pain was discussed in detail. This might represent an efficacious strategy for the treatment of chronic pain. Terry Hart (Novartis, London) presented a ML on "New approaches to the treatment of neuropathic pain". The four SC presented the following topics: [^{11}C]PB167 as a probe to recognize sigma receptors by in vivo PET using EMT-6 tumor cells implanted in mice model" (N.A.Colabufo); "MT2 selective melatonin receptor antagonists: design and structure-activity relationships (S.Rivara); "Fullerene derivatives in medicinal chemistry" (T. DaRos); "1-Deazaadenine nucleoside analogs: synthesis, characterization and antiviral properties (S.Vittori).

Recent Achievements in the Treatment of Neurodegenerative Diseases

The final session covered **neurodegenerative diseases.** This session was dedicated to the memory of Prof. Maria Di Bella (Modena and Reggio Emilia University) and was chaired by V.Tortorella (Bari University); the session centered on Alzheimer's disease (AD). AD is a complex neurological affection, characterized by loss of memory and progressive deficiency in different cognitive domains and by massive deposits of aggregated proteins to form the intracellular tangles and the extra-cellular senile plaques. AD still represents a challenge to medicinal chemists because, despite the large amount of basic research carried out into the causes of the disease, progress toward effective pharmacological treatments has been remarkably slow.

C.Melchiorre presented the memorial lecture dedicated to Prof.M.Di Bella on the topic of "Multi-functional drugs and Alzheimer's disease" addressing the discovery of anti-Alzheimer drugs designed to hit different selected targets. A.Alanine (Roche, Basel) presented the ML on the Identification of potent, non-competitive group-II metabotropic glutamate antagonists. He introduced the non-competitive allosteric antagonists of human group-II metabotropic glutamate receptors as therapeutic agents in symptomatic treatment of cognitive CNS disorders such as Alzheimers disease. High throughput screening of the Roche compound library led to the identification of a number of hits including several 1,5-benzodiazepines, which possessed moderate binding affinity toward mGluR2/3 receptors. Systematic investigation of the structure-activity relationships (SAR) guided the optimization of this class to provide compounds with significant binding affinity. R.Norcross (Roche, Basel) presented a ML on the topic "Development of 2-Amino-Pyrimidines as selective adenosine hA_{2a} receptor antagonists". N.Romanelli (Florence University) gave a ML on "Design, synthesis and binding affinity of new nicotinic ligands." V.Andrisano, M. (Bologna University) discussed a topic on Alzheimer's

disease: “In vitro affinity studies of potential drugs to biopolymeric targets by fluorometric, circular dichroism and HPLC methods.”

The last two SC were given by M.Parenti (SIN, Vicenza) on “Induced fit and pharmacophore generation approach applied to A_{2A} adenosine receptor antagonists” and C.Dellanoce (Milan University) who discussed the “Synthesis and binding affinity at neuronal ncotinic acetylcholine receptors of novel Epibatidine-related Δ^2-isoxazoline derivatives”.

Finally the best poster prize was given to two young investigators.

Prizes and Awards

1. Farmindustria Prize Winners (3000 euros each). Paola Conti (University of Milano) for investigations on “NMDA receptor antagonists and inhibitors of EAA transporters” Anna Vulpetti (Nerviano Medical Science Institute) for investigations on “The binding modes of ATP-competitive CDK2 inhibitors as antitumor agents.”
2. Best poster Prize (500 euro, sponsored by CISPAN) Sabrina Castellano (Univ. of Salerno and UCLA, Los Angeles) “Diversity-oriented synthesis of a library of multicyclic compounds via cycloadditions.”
3. Giacomello Medal Roberto Pellicciari (University of Perugia) “The farnesoid X receptor and drug discovery. From functions unraveling to therapeutic exploitation.”

The following congress proceedings represent a collection of PL, ML and SC by authors who accepted the invitation to participate to the compilation of this Volume 6 Part (viii) of ARKIVOC.

M.P.Costi, University of Modena & Reggio Emilia, 27 Dec. 2005.