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# SECOND JOINT ITALIAN-SWISS MEETING ON MEDICINAL CHEMISTRY ITCHMC2005

**Eight years after the First Joint Italian-Swiss Meeting on Medicinal Chemistry in Torino, September 23-26, 1997 (1) the Divisions for Medicinal Chemistry of the Italian and Swiss Chemical** Societies organized a Second Joint Meeting in lovely Modena. We could welcome 260 scientists (215 Italian and Swiss and 45 colleagues from 11 other nations) in the elegant Forum Guido Monzani. Seven plenary lectures and 16 main lectures dealt with six main topics: "Carbohydrate Chemistry in Drug Design", "Nuclear Receptors", "Progress in Design and Development of Protease Inhibitors", "Progress in Oncology Research", "Pain" and "Neurodegenerative Diseases". In addition, 19 short communications and 134 posters were presented covering many other aspects of medicinal chemistry. The highlights of the plenary and main lectures are here reported.

Peter H. Seeberger (ETH, Zurich) presented his pioneering work on automated solid-phase synthesis of oligosaccharides, which allows syntheses of e.g. deca-saccharides in 16 hours. The technology has been further refined to continuous flow microreactors. As many as 40 reactions can be carried out with 100 mg glycosylating reagent in 4 hours. A promising anti-malaria vaccine candidate, 10 ng of which administered to mice two weeks prior to the infection achieved 75% survival, was prepared [2].

Beat Ernst (Univ. of Basel) showed examples of optimization of carbohydrate leads to drugs. The physicochemical properties of carbohydrate leads are not at all drug-like (logP=~-4; PSA>340 Å$^2$, mol. weight >800) resulting in extremely short half-lifes. The neuraminidase inhibitor Tamiflu is a beautiful example of optimization work starting from a sugar lead, i.e. 2,3-didehydro-2-deoxy-*N*-acetylneuraminic acid inhibiting influenza neuraminidase ($K_i$=4 mM). Tamiflu's properties: logP=+1.5; PSA=90 Å$^2$, mol. weight: 312; $IC_{50}$=1 nM (Fig. 1).

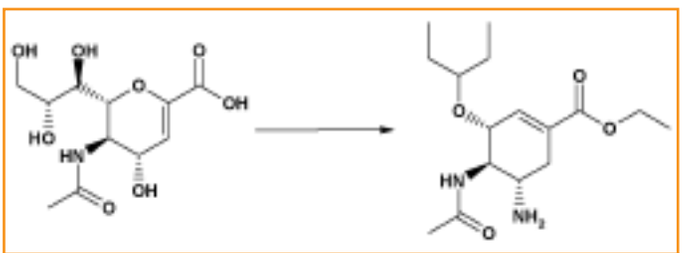

Fig. 1

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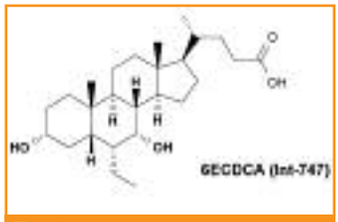
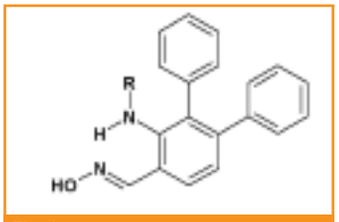


Fig. 2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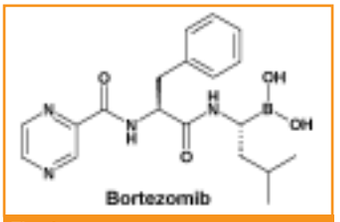

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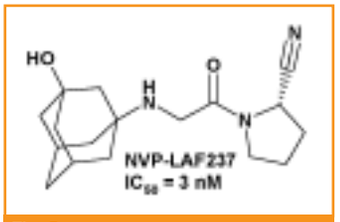

Fig. 5

Alessandro Dondoni (Univ. of Ferrara) presented syntheses of heterocycles decorated with carbohydrates using classical multicomponent reactions, such as the Biginelli, Hantsch and Staudinger reactions. Some examples: Monastrol is a cell permeable lead compound for the development of new anticancer drugs; a C6 ribofuranosyl containing nifedipine was prepared in order to improve the compound's bioavailability; syntheses of C-glycosyl-β-lactams via the Staudinger reaction allowed the preparation of chiral β-amino-α-hydroxy-aminoacids (isoserines) [3-5].

Maria Pappalardo (Univ. of Catania) presented glycopeptide- and carbohydrate-based synthetic vaccines for cancer immunotherapy. Membrane-bound glycoproteins such as mucins can be excellent targets for cancer immunotherapy. MUC-1 is expressed by a wide variety of carcinomas. The authors developed a series of glycolipopeptides by assembling via spacers the Tn antigen, the MUC-1 T-epitope sequence PDTRP and a lipopeptide immunoadjuvant [6].

## Nuclear Receptors

Roberto Pellicciari (Univ. of Perugia) gave an overview on nuclear receptors with emphasis on the race towards ligands for the farnesoid X receptor. Pellicciari group identified 6-α-ethylchenodeoxycholic acid (Fig. 2) ($ED_{50}$=90 nM), which is now in clinical trials for the treatment of liver fibrosis. For details on the molecular modeling based on the X-ray structure of the receptor-ligand complex and an in depth discussion on the system biology of nuclear receptors see the superb Perspectives Article [7].

Marco Macchia (Univ. of Pisa) presented salicylaldoximes and anthranyl-aldoximes as novel selective estrogen receptor modulators (SERMs). The "pseudoring" formed by the intramolecular H-bond between the phenolic OH - or the aniline - and the oxime nitrogen atom mimicks the phenolic A ring of estrogen. The anthranyl-aldoximes proved to be the superior compounds. (for R = Me: $K_i$ = 5 nM for ERa, 10 nM for ERb, respectively; Fig. 3).

## Progress in Design and Development of Protease Inhibitors

Sylvain Cottens (Novartis, Basel) gave a comprehensive overview of proteases and their inhibitors. At present 514 active human proteases have been found in the humane genome subdivided into 4 classes: 16 aspartic proteases, 143 cysteine proteases, 193 serine/threonine proteases, and 162 metalloproteases. A famous example of a serine protease inhibitor is Bortezomib (Fig. 4). of Millenium Pharmaceuticals, the first drug on the market containing a boronic acid for the treatment of multiple myeloma, which inhibits selectively the 26S proteasome with $K_i$=0.62 nM. Several other significative examples were presented.

Edwin B. Villhauer (Novartis, East Hanover, NJ) presented the discovery of NVP-LAF237 (Vildagliptin) (Fig. 5), a dipeptidylpeptidase IV (DPP-IV) inhibitor for the treatment of type-2 diabetes. The work started with a library of N-substituted 2-(S)-pyrrolidinecarbonitriles (such as PKF273-237, inhibiting human DPP-IV with an $IC_{50}$ of 8 nM). The follow-up compound is the 3-hydroxy-1-adamantyl derivative NVP-LAF237, whose advantage is the longer terminal half life (90 min. versus 35 min. for DPP728). Maximum inhibition of plasma DPP-IV activity was observed 2 hours postdose (30 min. for DPP728). Therefore, LAF237 provides a better profile for a once-a-day administration. Phase 3 clinical trials are nearly completed.

Katrin Groebke-Zbinden (Roche, Basel) works with a large team towards efficacious and orally bioavailable Tissue Factor/Factor VIIa inhibitors, which, due to their selective influence on the extrinsic pathway of the coagulation cascade, should be able to interfere with thrombotic events without prolonged bleeding time. Good oral bioavailability was achieved by preparation of a prodrug (Fig. 6).

Martin Missbach (Novartis, Basel) presented novel Cathepsin K inhibitors for the treatment of osteoporose. The interaction of the inhibitor with the cysteine protease is reversible. The front runner compound (Fig. 7) was tested in Cynomolgus monkeys rendered estrogen deficient by a depot GnRH agonist. After administration of 5 mg/kg b.i.d. po two serum markers of bone resorption,

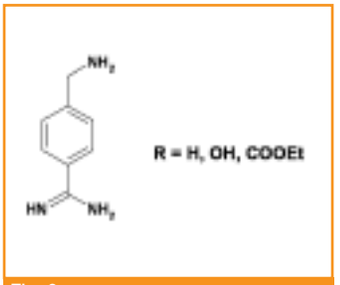

Fig. 6

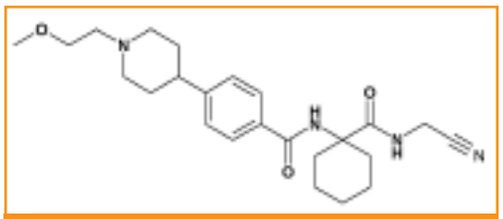
Fig. 7

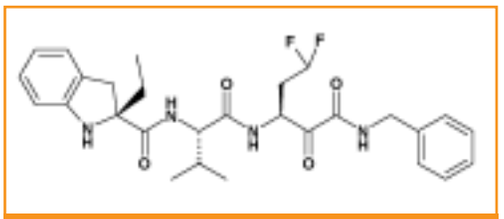
Fig. 8

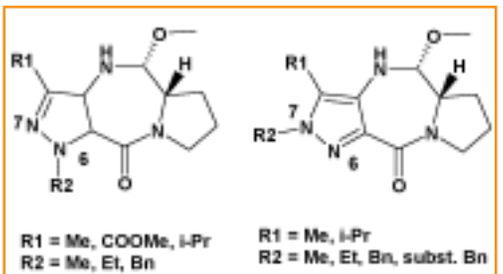

Fig. 9

CTx and NTx, were reduced far below levels of the non-GnRH treated group at day 1. In man a dose of 50 ng/patient caused a 70% inhibition of serum CTx.

Vincenzo Summa (Merck, Pomezia) presented progress in the search for Hepatitis C virus NS3/4c serine protease inhibitors. Starting from the end terminal hexapeptide AcDEMEEC-OH typical serine protease traps were incorporated in the S1 pocket Reducing the hexa- to a tripeptide and preparing the benzylamide of an $\alpha$-ketoacid a potent inhibitor (Fig. 8) ($IC_{50=}$4 nM) was generated. Advanced competitor compounds in this field are Ciluprevir (BILN 2061) of Boehringer Ingelheim, VX-950 of Vertex and SCH 503034 of Schering.

## Progress in Oncology Research

Dale L. Boger (Scripps Institute, La Jolla, CA) gave the Opening Lecture in the impressive Palazzo Ducale of Modena used now as Military Academy. He gave a fascinating overview on three approaches towards oncology drug discovery, structure based design of GAR Tfase inhibitors, on combinatorial chemistry to probe protein-protein interaction targets and on natural products chemistry for oncology application [8-10].

Pier Giovanni Baraldi (Univ. of Ferrara) is interested in agents that bind to the minor groove of double-helical B DNA. Baraldi's group prepared numerous heterocyclic analogues of the pyrrolo [2,1-c][1,4] benzodiazepine (PBDs) (Fig. 9). The five membered heterocyclic compounds were consistently more potent than the more basic six membered heterocycles (pyrido-, pyrimido and pyrazino-derivatives). CC-1065 of the class of cyclopropylindole (CPI) antitumor antibiotics binds to AT rich sequences in the minor groove of double stranded DNA. Also in this series different heterocyclic analogues were prepared in order to modulate the reactivity of the cyclopropane ring. A big effort was made to combine different natural antitumor agents in one molecule.

Ippolito Antonini (Univ. of Camerino) presented progress on the syntheses of bis intercalator derivatives as potent antitumor agents. Bis-acridone derivatives (Fig. 10) had high DNA affinity and potent cytotoxic activity against HT29 human colon adenocarcinoma ($IC_{50}$=<1 nM) and were selected for screening on 60 human tumor cell lines at the National Cancer Institute. Tetracyclic bis-pyrazolo[3,4,5-kl]acridinecarboxamides showed very potent antiproliferative activity and promising *in vivo* results in the hollow fiber assay.

Maurizio Botta (Univ. of Siena) works on the design of novel taxol derivatives as potential anticancer and MDR reversing agents. In an extensive study a common pharmacophore model for the microtubule-stabilizing antimitotic agents (MSAA) taxanes, epothilones, discodermolide and laulimalide was elaborated [11].

A novel approach for the synthesis of the taxol side chain was discussed [12].

Karl-Heinz Altmann (ETH, Zurich) showed recent developments in the chemistry and biology of epothilones. The elucidation of the conformation of epothilone in its tubulin bound state provided additional information for drug design. Antiproliferative activity superior to the natural epothilones was found in benzo-heterocyclic analogues (Fig. 11). Trans epothilones (olefine and epoxide) proved to be superior to the natural compounds, whereas the corresponding cyclopropyl derivative did not show enhanced antiproliferative activity. 3-deoxy epothilone B was 20 times less active than epo B. For a comprehensive review see [13].

## Pain Research

Romano di Fabio (GSK, Verona) and his team explore glycine and non-competitive metabotropic glutamate receptor antagonists for the treatment of neuropathic pain. In a high throughput screen novel mGluR1 antagonists were discovered, which were optimized

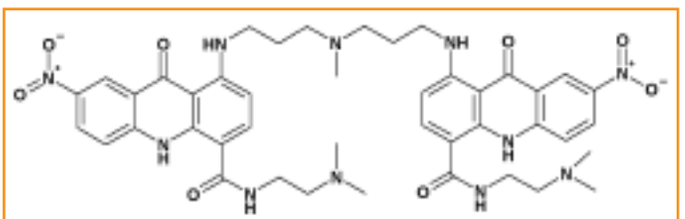
Fig. 10

by preparing a library of 1,600 compounds to identify a very potent ($IC_{50}$=16 nM) and very selective (> 100 fold versus mGluR 2, 4 and 5) mGluR1 antagonist. More drug-like compounds, such as the tetrahydro-β-carboline derivative were investigated to identify potent and orally active mGluR1 antagonists ($IC_{50}$=64 nM) with good bioavailability (F=36%) and good PK values (brain/plasma ratio=6:1) (Fig. 12).

Terry Hart (Peakdale Molecular Ltd., UK) gave an overview on new approaches for the treatment of neuropathic pain. Current targets are NMDA-NR2b, AMPA, Na channels 1.3, 1.4, 1.7, 1.8, TRPV1, nACh α4β2, KCNQ, P2X3, TRPM8, and VDCCα2δ subunit, the presumed target of Gabapentin as well as the GPCRs BK-1, NK-1, CCK-8, ORL-1, and galanin. The author has contributed significantly to the discovery of peripheralized cannabinoid receptor 1 agonists in order to avoid CNS effects [13]).

## Neurodegenerative Diseases

Carlo Melchiorre (Univ. of Bologna), the memorial lecturer in honor of Maria Di Bella (1933-1998), Professor of Medicinal Chemistry in Modena, presented multi-functional drugs for the treatment of Alzheimer's disease. He designs ligands binding to the catalytic and peripheral anionic site of acetyl cholinesterase, such as lipocrine, combining tacrine and lipoic acid, and memoquine, a polyamine, which may present a universal template for receptor recognition. Both compounds very potently inhibit human recombinant AChE ($IC_{50}$'s=0.25 and 1,55 nM, $K_i$=0.155 and 2.6 nM, respectively). Lipocrine and memoquin (Fig. 13) were able to inhibit Aα aggregation induced by AChE with $IC_{50}$ values of 45 and 28 μM, respectively approaching the value of propidium ($IC_{50}$=12.6 μM). Memoquin was also tested *in vivo* in an object recognition test in mice. Chronic treatment with a dose of 15 mg/kg/day p.o. for 15 days counteracted the memory impairing effects of scopolamine.

Vincenza Andrisano (Univ. of Bologna) is responsible for the analytical support of the laboratories of Professors Melchiorre and Recanatini in their efforts to identify compounds simultaneously blocking both the catalytic and β-amyloid pro-aggregatory activities of AChE. She developed a micro-immobilized enzyme reactor (micro-IMER) with human recombinant acetylcholinesterase, which was inserted in a HPLC system. The effects of the AChE inhibitors are evaluated by simultaneous injection of each inhibitor with the substrate. Analyses times are less than 2 minutes.

Alexander Alanine (Roche, Basel) reported on the optimization work on non-competitive group II metabotropic glutamate receptor antagonists. High throughput screening of the Roche compound library allowed the identification of a series of 1,5-benzodiazepine the optimization of which led to single digit nanomolar compounds. The best compounds showed $ED_{50}$'s of 3 mg/kg p.o. in the reversal of hypo-locomotor activity induced by a dose of 15 mg/kg i.p. of the mGluRs agonist LY 354740 (Fig. 14).

Roger Norcross (Roche, Basel) investigated 2-amino-pyrimidines as selective adenosine receptor 2a antagonists for the treatment of Parkinson's disease. The currently most advanced compound KW 6002 (istradefylline, Kyowa Hakko) showed in clinical Phase 3 trials that it can potentiate the effects of levodopa causing less dyskinesia. However, its disadvantage is its light sensitivity.

HTS allowed to identify a series of 2-aminopyrimidine from library of Roche compounds. The most advanced compound (Fig. 15) showed good *in vivo* activity to reverse a 0.01 mg/kg s.c. APEC induced hypo-locomotion with an $IC_{50}$ of 3 mg/kg p.o.

Maria Novella Romanelli (Univ. of Florence) looks for novel nicotinic receptor ligands via 3D searches of the Cambridge Structural database. Starting from the high affinity nicotinic acetylcholine receptor agonist pyrido [3,4-b] homotropane (PHT, $IC_{50}$=5 nM) the 3D search revealed a basic skeleton of 6-aminomethyl-quinolines. The most promising of the synthesized compounds, LG168 with $IC_{50}$=132 nM (central α4β2 nAChRs, displacement of [$^3$H]cytosine from rat cerebral cortex membranes).

Clelia Dallenoce (Univ. of Milano) investigates ligands for neuronal nicotinic acetylcholine receptors derived from the potent analgesic epibatidine ($K_i$=0.026 nM for α4β2 nAChRs). The Δ2 isoxazole derivatives synthesized via 1,3-cycloaddition showed high affinities to α7 nAChRs ($K_i$'s of 27 and 32 nM for the two most interested compounds).

Two researchers were honored with the Farmindustria Prize (Euro 3,000 each).

Paola Conti (Univ. of Milano) investigates NMDA receptor antagonists and inhibitors of the EAA transporters. The synthesis and biological characterization of the pure enantiomer (-)-5-(2-amino-2-

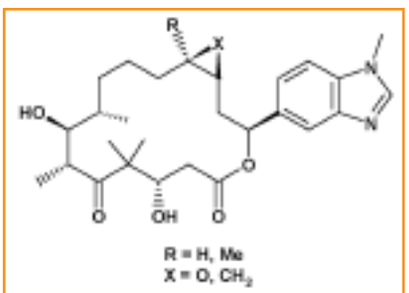

Fig. 11

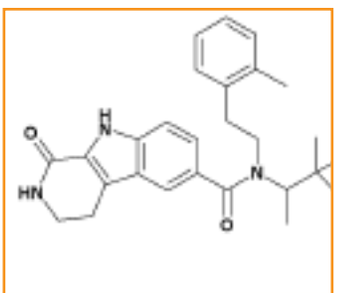

Fig. 12

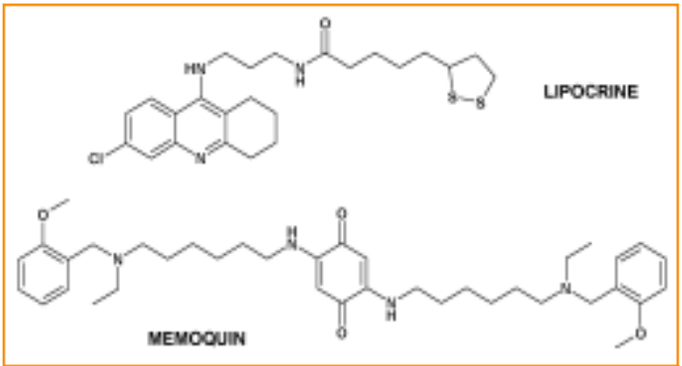

Fig. 13

carboxyethyl)-4,5-dihydroisoxazole-3-carboxlic acid ($K_i$=100 nM, displacement of [$^3$H]CGP 39653 from rat cortical membranes) is described in extensive detail in [14]. The compound showed significant neuroprotective effects in an oxygen glucose deprivation cell culture test. Racemic HIP-A is a potent and noncompetitive inhibitor of [$^3$H]-L-glutamate uptake ($IC_{50}$=18 μM).

The second Farmindustria Prize was awarded to Anna Vulpetti (Nerviano Medical Science Institute). She is investigating the interaction of specific inhibitors of protein kinases docked into the ATP pocket. One example was the optimization of CDK2 ligands of the class of benzo-di-pyrazoles up to $IC_{50}$ values of 7 nM.

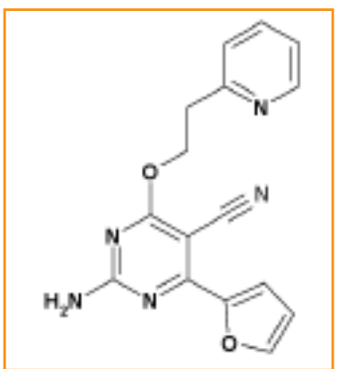
Fig. 15

The jury for the poster prize, A. Carotti, C. De Micheli and W. Froestl, had quite a hard time to select one single out of 134 posters of high quality. Finally,

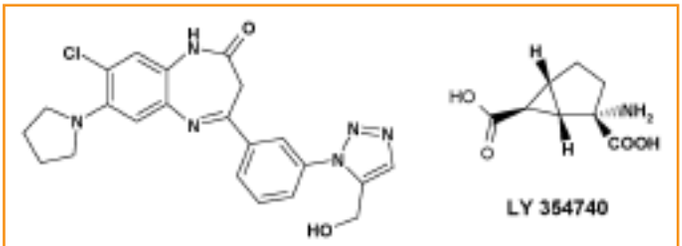

Fig. 14

the poster prize of euro 500 (CINSPAN-Modena) was awarded to poster no. 131 of Sabrina Castellano, H. Fiji and O. Kwon (Univ. of Salerno and UCLA, Los Angeles) for their presentation on diversity oriented synthesis (DOS, see [15]) of a library of multicyclic compounds via cycloadditions. The reaction route was validated on SynPhase Wang Lanterns. One particularly efficient cycloaddition is the [4+2] annulation of allene esters and imines to tetrahydropyridines. The compounds of the library were subjected to testing in Zebrafish according to Mark C. Fishman *et al.* [16].

## Concluding remarks

In summary, the Second Joint Italian-Swiss Meeting on Medicinal Chemistry in Modena 2005 was a scientifically very rewarding meeting fostering exchange of information and helping to establish personal contacts in a lovely surrounding. All participants are very grateful to Livio Brasili and his Organizing Committee as well as to the staff of Modenatur for the impeccable organization of the congress and the very attractive social program. Giuseppe Ronsisvalle, the president of the Division for Medicinal Chemistry of the Italian Chemical Society, and the author of this report hope that our successors will accept the challenge to organize a third meeting of this series in due time.

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