CONFERENCE REPORT

Chimia 59 (2005) 851–861

ISSN 0009–4293

Second Joint Italian – Swiss Meeting on Medicinal Chemistry (ITCHMC 2005)

Modena, September 12-16, 2005

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Keywords: Carbohydrate chemistry · Conference Report, Italian-Swiss Meeting · Neurodegenerative diseases · Nuclear receptors · Oncology research · Pain research · Protease inhibitors

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 welcomed 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 were:

1. Carbohydrate Chemistry in Drug Design

Peter H. Seeberger (ETH Zürich) presented his pioneering work on automated solid-phase synthesis of oligosaccharides, which allows syntheses of *e.g.* deca-saccharides in 16 h [2]. The technology has been further refined to continuous flow microreactors [3]. As many as 40 reactions can be carried out with 100 mg glycosylating reagent in 4 h. Microreactor-HPLC analyses allow optimal reaction conditions to be determined over a temperature range from –78 °C to 20 °C with different glycosyl-donor stream flow rates. A beautiful example is the convergent synthesis of the fully lipidated glycosylphosphatidylinositol anchor of *Plasmodium falciparum*, which is responsible for mortality by malaria [4]. A promising anti-malaria vaccine candidate, 10 ng of which administered to mice two weeks prior to the infection achieved 75% survival, was prepared [5].

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-lives. 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 μM). Tamiflu's properties: logP = +1.5; PSA = 90 Å^2, mol. weight: 312; IC_{50} = 1 nM (Fig. 1) [6].

The pre-organization of the bioactive conformation is very important for the affinity of analogues. The tetrasaccharide sialyl Lewis^X is the carbohydrate epitope

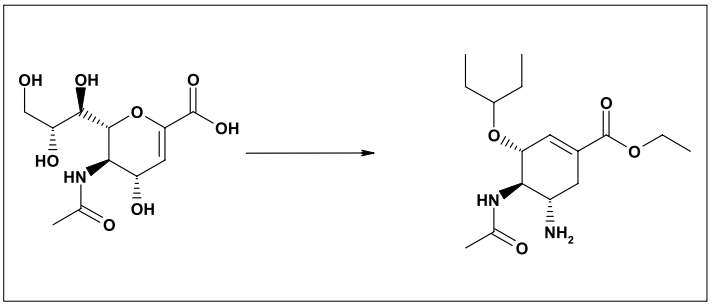

Fig. 1.

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recognized by E-selectin and became the lead structure for the design of selectin antagonists. The pharmacophores required for E-selectin recognition are the carboxylic acid function, the hydroxyls of fucose and the 4- and 6-OH of galactose. N-acetylglucosamine was replaced by glucal-derived derivatives. NMR spectroscopy revealed that the cause for the improved E-selectin blocking activities is the improved pre-organization of the bioactive conformation due to beneficial steric constraints imposed by equatorial substituents as simple as CH_2R [7].

Myelin-associated glycoprotein (MAG) binds to the nerve cell surface and inhibits nerve regeneration. Specific functional ligands are the nerve cell surface gangliosides GD1a and GT1b. Inhibitors of these ligands may provide novel approaches to enhance nerve regeneration after injury [8]. In SAR studies it was established that the α-(2,3) and α-(2,6) linked sialic acid moieties of the gangliosides are important elements for binding. Drug-like small molecules with very high inhibiting properties were prepared (clogP = +1.47; PSA = 175 Å^2, mol. weight: 537; IC_{50} = 0.8 nM; Fig. 2).

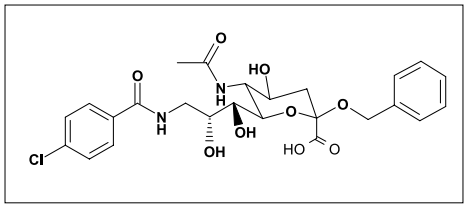


Fig. 2.

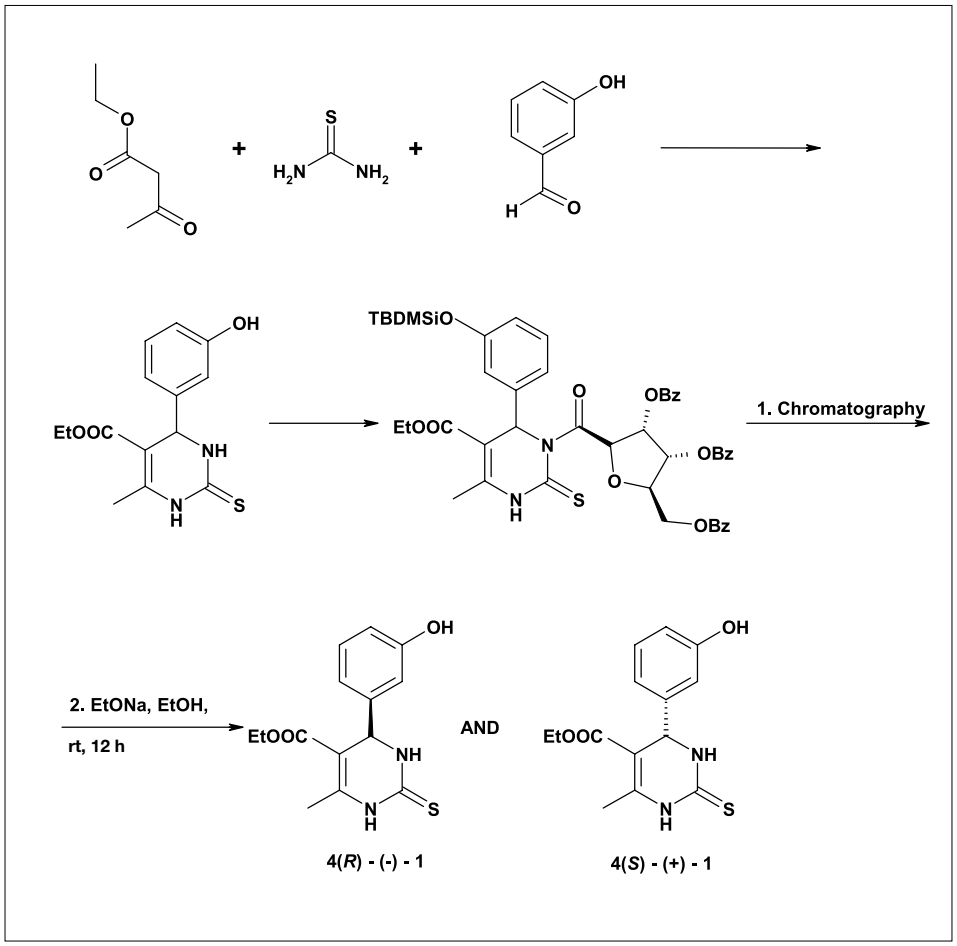
Alessandro Dondoni (Univ. of Ferrara) presented syntheses of heterocycles decorated with carbohydrates using classical multi-component reactions, such as the Biginelli, Hantsch, and Staudinger reactions. Some examples:

Monastrol is a cell permeable lead compound for the development of new anticancer drugs as it inhibits specifically and reversibly the motility of mitotic kinesin Eg5. The diastereoisomeric amides of the silyl protected monastrol were separated *via* flash chromatography to provide useful quantities of both enantiomers of monastrol after basic hydrolysis (Scheme 1) [9].

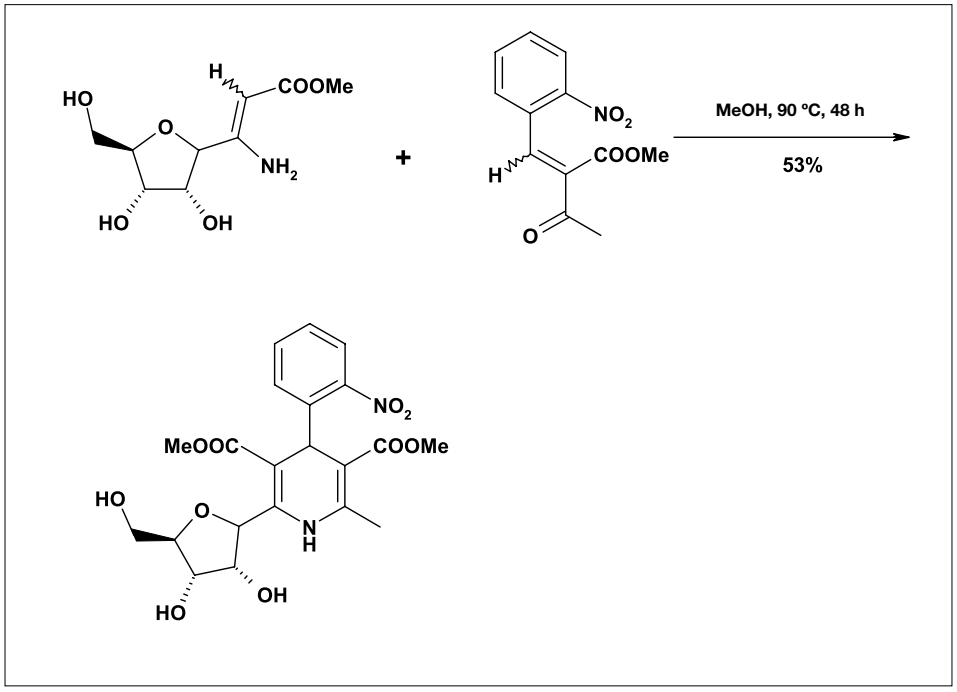
A C6 ribofuranosyl containing nifedipine was prepared in order to improve the compound's bioavailability (Scheme 2) [10]:

Syntheses of C-glycosyl-β-lactams *via* the Staudinger reaction allowed the preparation of chiral β-amino-α-hydroxy-amino acids (isoserines) [11].

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 extracellular domain of MUC-1 contains tandem repeating 20 amino acid sequences containing five sites of Ser and Thr, which are glycosylated with N-acetylgalactosamine (Tn antigen). The PDTRP core sequence of the MUC-1 tandem repeat



Scheme 1.



Scheme 2.

could be an immunodominant epitope for both B-cells and T-cells. In carcinomas the mucins are underglycosylated. 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 [12].

2. 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. The deorphanization of FXR took place in 1999, when three groups independently reported that bile acids are the endogenous ligands for FXR, the most potent being chenodeoxycholic acid. The group of Timothy Wilson at GSK, Research Triangle Park, NC found the highly potent agonist GW4064 (EC_{50} = 70 nM), K.C. Nicolaou and colleagues identified Fexerine (EC_{50} = 222 nM) and the related compounds Fexeramine and Fexarene, and the Pellicciari group identified 6-α-ethyl-chenodeoxycholic acid (ED_{50} = 90 nM), which is now in clinical trials for the treatment of liver fibrosis (Fig. 3). 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 [13].

Marco Macchia (Univ. of Pisa) presented salicylalooximes 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 mimics the phenolic A ring of estrogen. The anthranyl-aldoximes proved to be the superior compounds (for R = Me: K_i = 5 nM for ERα, 10 nM for ERβ, respectively; Fig. 4) [14][15].

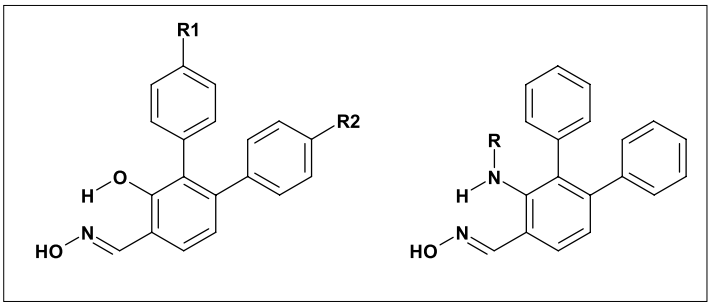


Fig. 4.

A new class of quinoline-based SERMs was discovered very recently by chemists of GSK at Research Triangle Park, NC using the technique of peptide interaction profiling (Fig. 5) [16].

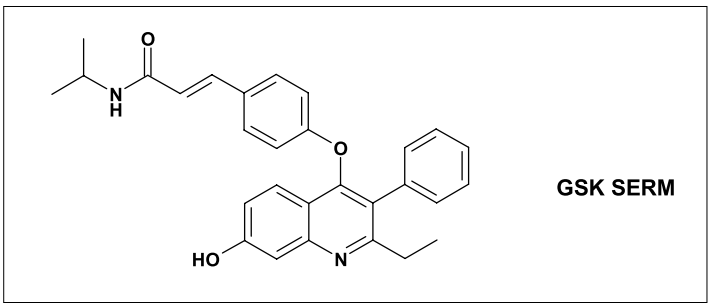


Fig. 5.

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 four classes: 16 aspartic proteases, 143 cysteine proteases, 193 serine/threonine protease, and 162 metalloproteases. A famous example of a serine protease inhibitor is Bortezomib 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 (Fig. 6) [17]. Other examples are Vertex' VX-950, a potent inhibitor of the enzyme HCV NS3/4A for viral load reduction, the thrombin inhibitors Ximelagatran and its ethyl ester-amidoxime prodrug Megagatran of Astra Zeneca and the Factor Xa inhibitor BAY 59-7939. For an excellent overview of protease inhibitors in the clinic see [18].

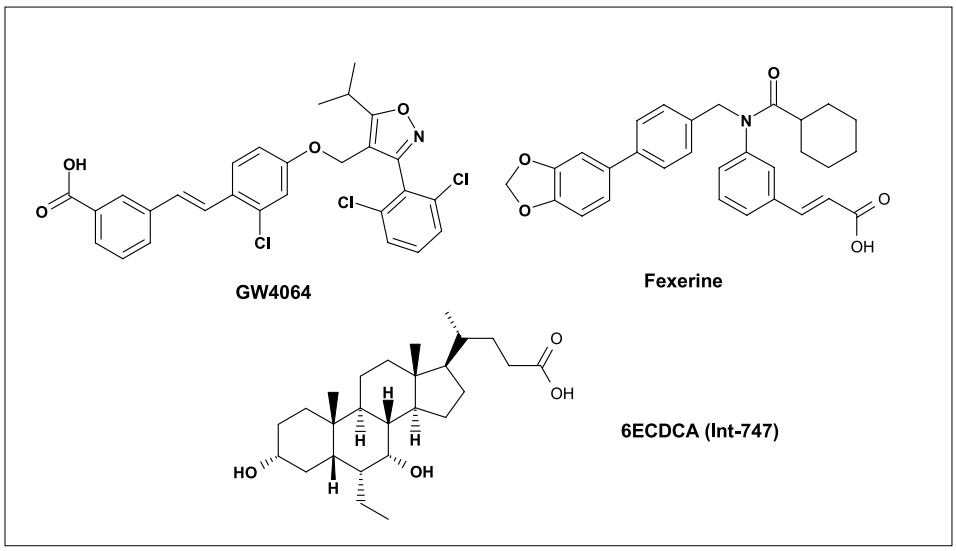


Fig. 3.

Well known cysteine protease inhibitors are the caspase-1 inhibitor Pralnacasan of Vertex, the cathepsin K inhibitors of GSK and Novartis (*vide infra* M. Missbach) and the rhinovirus 3C protease inhibitor Rupintrivir of Pfizer.

Metalloprotease inhibitors were investigated extensively and provided the famous ACE inhibitors, such as captopril, enelapril, benazepril, zofenopril, ramipril, cilazapril, lisinopril, fosinopril, and many others [18]. An advanced matrix metalloprotease inhibitor for the enzyme TACE (tumor necrosis factor-α containing enzyme) is BMS-561392 for the treatment of rheumatoid arthritis [18].

The family of aspartic proteases contains renin, β-secretase, cathepsin E and D, pepsin A and C, and the HIV proteases.

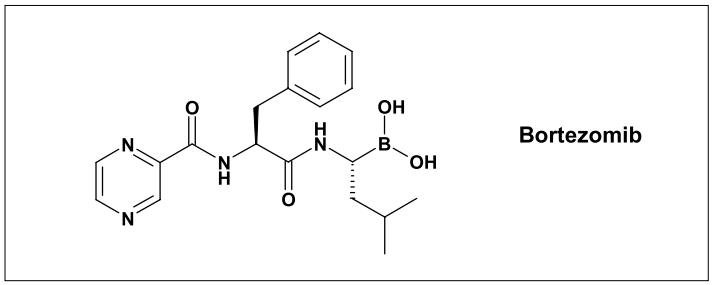


Fig. 6.

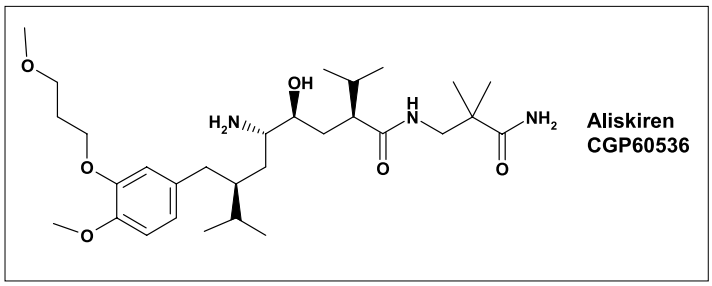


Fig. 7.

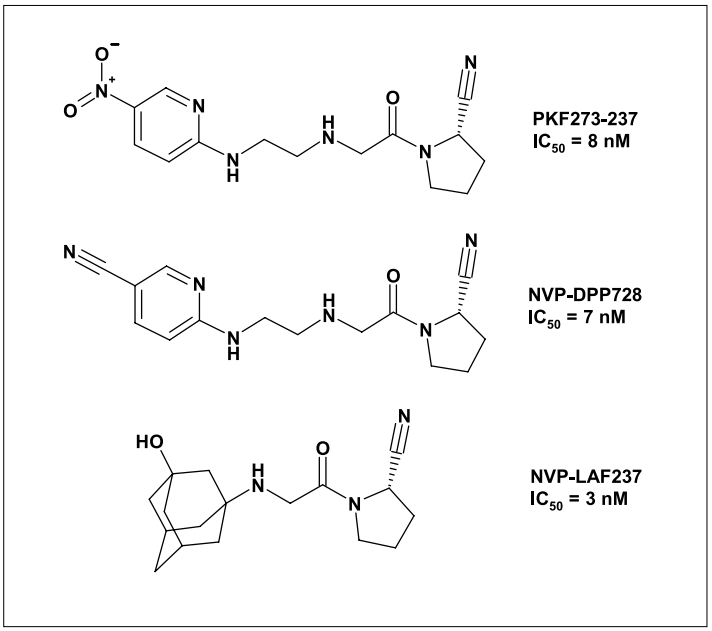


Fig. 8.

The discovery of pepstatin in 1970 started the chemistry of peptide bond mimics. Renin inhibitors were explored extensively in the 1990's (*e.g.* Remikiren (Roche), Terlakiren (Pfizer), CI-952 (Parke Davies), Zankiren (Abbott), FK-906 (Fujisawa), and CGP38560A (Ciba-Geigy). The latter was further optimized to Aliskiren, which is currently in Phase 3 clinical trials (Fig. 7).

Work on HIV protease inhibitors is continuing despite very substantial progress demonstrated by the discovery of Saquinavir (Roche), Ritonavir (Abbott), Indinavir (Merck), and Atazanavir (BMS licensed from Novartis).

Edwin B. Villhauer (Novartis, East Hanover, NJ) presented the discovery of NVP-LAF237 (Vildagliptin), 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, Fig. 8, inhibiting human DPP-IV with an IC_{50} of 8 nM) accessible in a five-step solid-phase and a three-step solution phase sequence. Optimization led to the potent, selective, and short-acting DPP-IV inhibitor NVP-DPP728, which after oral administration significantly reduced plasma glucose levels (38% reduction in the 0-90 min glucose AUC in Cynomolgus monkeys; absolute bioavailability in rat and monkeys is >74%). A 100 mg oral dose in humans provided a half life of 0.85 h and >80% inhibition of plasma DPP-IV for 4 h [19].

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 h postdose (30 min for DPP728). Therefore, LAF237 provides a better profile for a once-a-day administration. Phase 3 clinical trials are nearly completed [20].

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. In an *in silico* screen of a virtual library a S1 'needle' was identified (Fig. 9, left formula). Optimization work led to the aminopyridine derivative with an IC_{50} value of 0.39 μM (Fig. 9, middle formula), which was introduced in order to lower clogP. The fluoro substituents were added to provide a powerful dipole interaction with the carbonyl of Gly216 of the enzyme. Replacement of the difluoroaromate by triazoles was detrimental, however 2-pyridones were advantageous. Additional substituents on the aromatic ring of the benzamidine allowed an additional interaction with a Q pocket. The primary glycineamide provided a potent compound (IC_{50} = 13 nM). Good oral bioavailability was achieved by preparation of prodrugs on the amidine moiety (Fig. 9, right formula, R = OH or COOEt).

Martin Missbach (Novartis, Basel) presented novel Cathepsin K inhibitors for the treatment of osteoporosis. The interaction of the inhibitor with the cysteine protease is reversible (Scheme 3):

The already quite potent core structure (IC_{50} = 40 nM, top formula in Fig. 10) was optimized rapidly to obtain very potent (IC_{50} = <1nM) and highly selective (over Cathepsins L and S) Cathepsin K inhibitors with good bioavailability (F = 94%). However, the cyanomethyl-amide part of the compound (second formula in Fig. 10) was rapidly cleaved to the corresponding car-

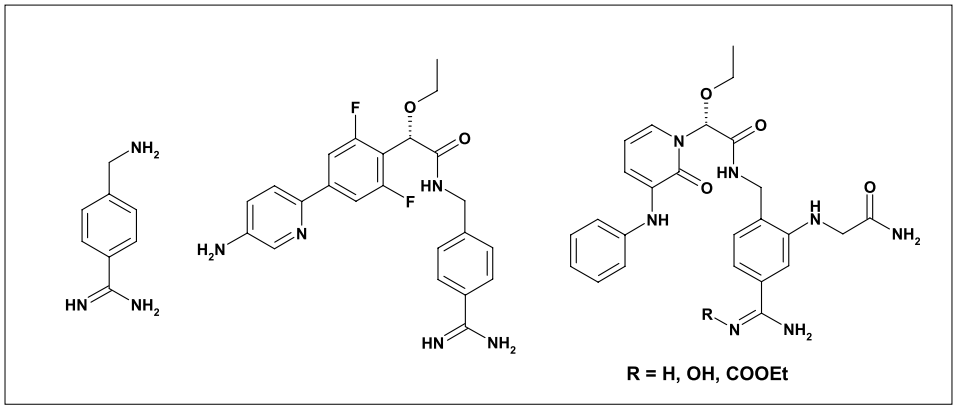
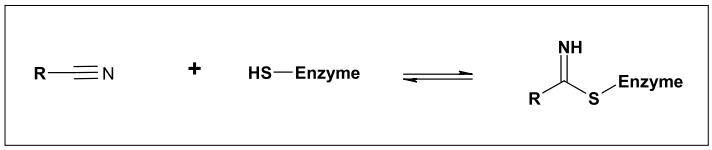


Fig. 9.



Scheme 3.

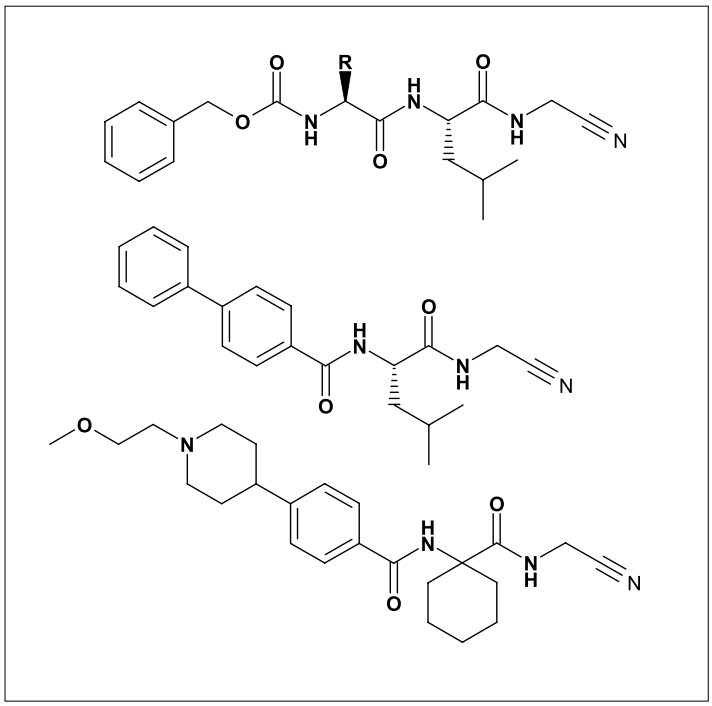


Fig. 10.

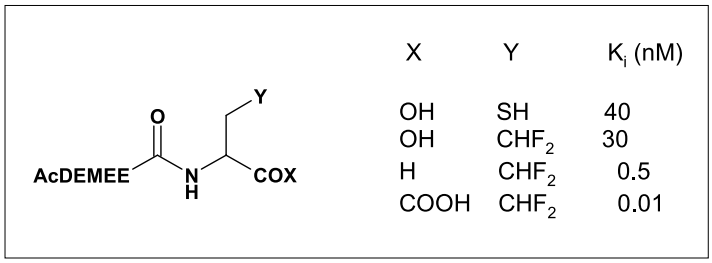


Fig. 11.

boxylic acid in rat liver. This problem could be solved by the preparation of α,α-disubstituted derivatives such as NVP-AAR494 (last formula in Fig. 10).

In vivo tests must be carried out in rabbits or in monkeys, because the mouse and rat enzyme has a single mutation in S2 (Ser instead of Ala). The front runner compound 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, 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 (Fig. 11).

Reducing the hexa- to a tripeptide and preparing the benzylamide of an α-ketoacid (Fig. 12) a potent inhibitor (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.

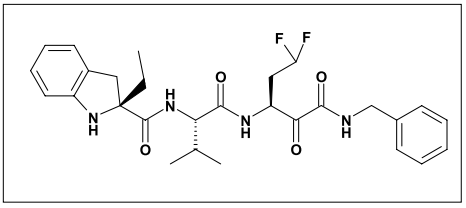


Fig. 12.

4. 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 the Military Academy. He gave a fascinating overview on three approaches towards oncology drug discovery: structure-based design of GAR Tfase inhibitors, combinatorial chemistry to probe protein–protein interaction targets, and natural products chemistry for oncology application.

Glycinamide ribonucleotide transformylase (GAR Tfase) catalyzes the first of two formyl transfer reactions in the biosynthetic pathway of purines. The conversion of glycinamide ribonucleotide to formyl glycinamide ribonucleotide uses 10-formyl-tetrahydrofolate as the cofactor in the pathway, which leads to inosine monophosphate and to other purines.

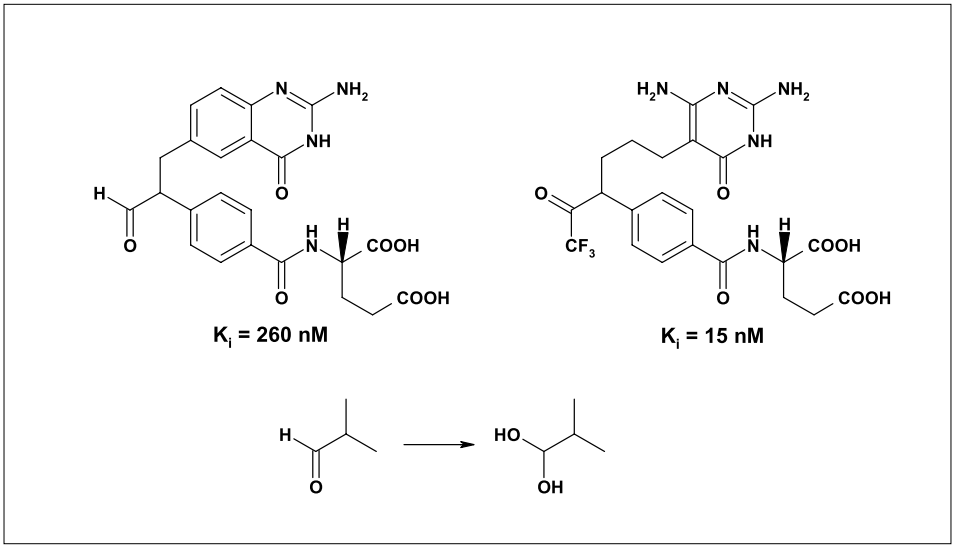


Fig. 13.

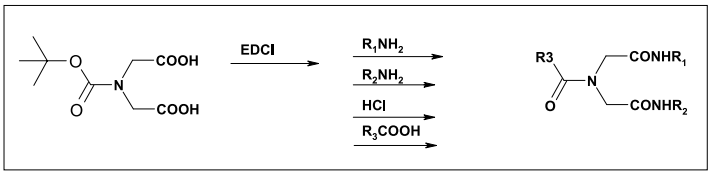
The first potent and selective GAR Tfase inhibitor was *Lilly's Lometrexol*, which demonstrated anti-tumor activity against a wide range of solid tumors in clinical trials. A potent inhibitor of GAR Tfase, 10-formyl-5,8,18-tri-deaza folic acid was identified by the Boger group in 1997 (Fig. 13, left formula) [21–24]. As it does not have a transferable formyl group, it binds to the enzyme as hydrated aldehyde (gem-diol) mimicking the tetrahedral intermediate (Fig. 13 below). A crystal structure of human GAR Tfase at low and high pH with its natural substrate β-glycinamide ribonucleotide was obtained [25] and provided the basis for extensive molecular modeling leading to a potent (K_i = 15 nM), stable and highly selective compound shown in Fig. 13 on the right. The compound is a potent inhibitor of tumor cell proliferation with IC_{50} of 16 nM, a ten-fold improvement over Lometrexol. It is effectively transported into the cell by the reduced folate carrier. An X-ray at 1.98 Å resolution was obtained [26].

The second topic targets protein–protein or protein–DNA interactions using *solution phase combinatorial chemistry*, of which Boger was one of the pioneers (for an extensive review see [27]). A classical example is the preparation of triamides from iminodiacetic acid (Scheme 4) [28].

Using six R1 amines (A1–A6), ten R2 amines (B1–B10) and ten diacids (C1–C10) a library of 600 compounds was prepared and tested for inhibition of the interaction of the integrin αvβ3 with the matrix metalloproteinase MMP2 to find novel anti-angiogenic agents. The B10 sublibrary was deconvoluted showing that it contained Cbz-lysine methylester subunits (Fig. 14, top). A second library of 77 analogues provided an improved lead structure, and further optimization led to TSRI265 (Fig. 14, bottom). It was shown that TSRI265 binds to the integrin αvβ3 and not to MMP2. The anti-angiogenesis effect was tested *in vivo* in a chick model causing a nearly complete reduction of the growth of solid tumors [29][30].

Many *natural products* have been identified to interact *via* sequence selective recognition of duplex DNA, the most famous being distamycin A, bleomycin A2, isochrysohermidin, luzopeptin A, and (+)-CC-1065 [31]. (+)-CC-1065 is an exceptionally potent antitumor agent alkylating the sequence 5′-WWWWA (W = A or T) [32][33]. The mechanism of DNA alkylation is demonstrated in Scheme 5 on the simpler structure of (+)-Duocarmycin SA.

Extensive studies have established the fundamental SAR of numerous derivatives and analogues of the Duocarmycin and CC-1065 alkylation subunits demonstrating a parabolic relationship between chemical stability and biological potency, *i.e.* cytotoxic activity. Electron-withdrawing substituents enhance, and electron-donating substituents decrease the solvolysis rate [34]. The most recent member of this family is (+)-Yatakemycin, whose revised structure and total synthesis was published in late 2004 [35].



Scheme 4.

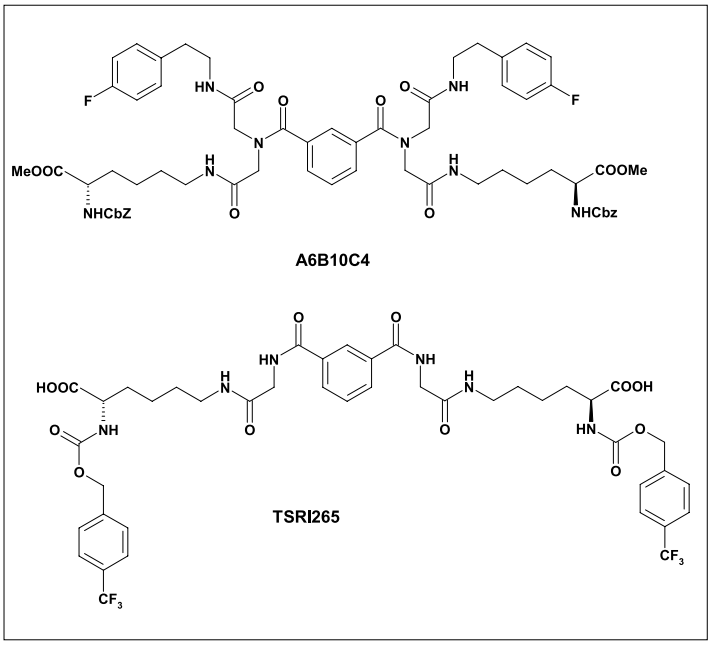
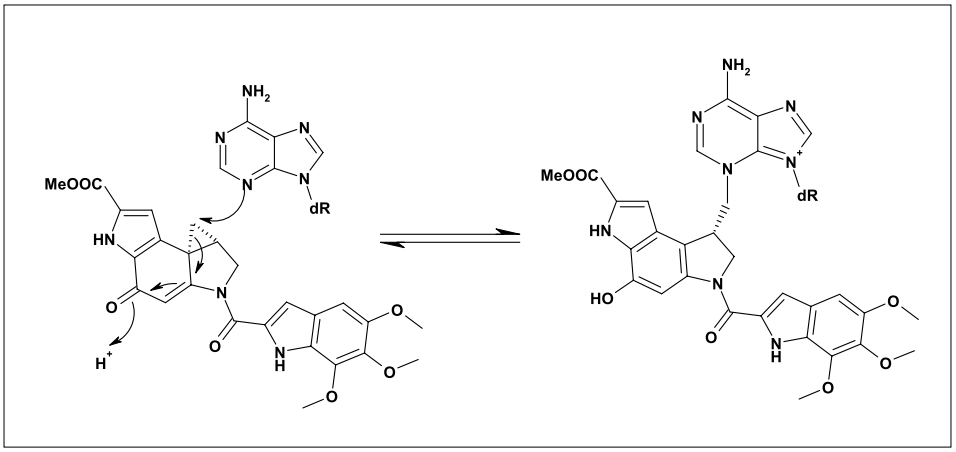


Fig. 14.



Scheme 5.

Pier Giovanni Baraldi (Univ. of Ferrara) is interested in agents that bind to the minor groove of double-helical B DNA.

The pyrrolo [2,1-c][1,4] benzodiazepine (PBDs) antitumor antibiotics, such as anthramycin bind to guanine-cytosine rich sequences. Baraldi's group prepared numerous heterocyclic analogues of the PBDs (Fig. 15). The five membered heterocyclic compounds were consistently more potent than the more basic six-membered heterocycles (pyrido-, pyrimido and pyrazino-derivatives, see top right formula in Fig. 15 [36][37]. In the pyrazole series N7 substituted benzyl derivatives (Fig. 15, bottom right formula) showed superior activity towards leukemic cell lines.

CC-1065 of the class of cyclopropylindole (CPI) antitumor antibiotics binds to AT rich sequences in the minor groove of

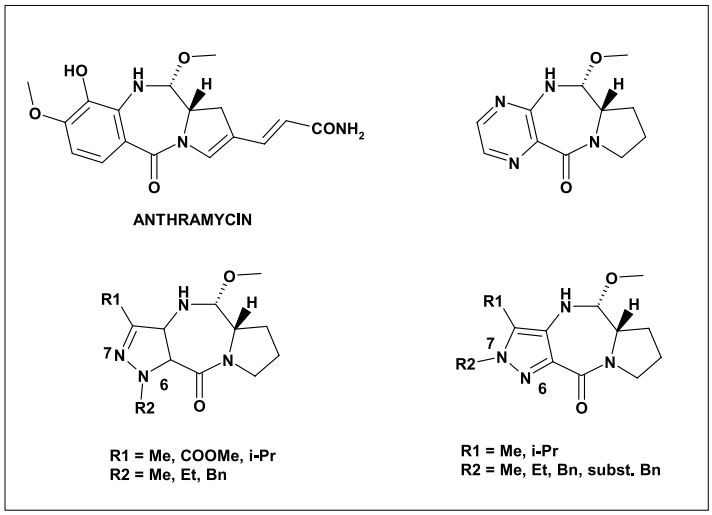


Fig. 15.

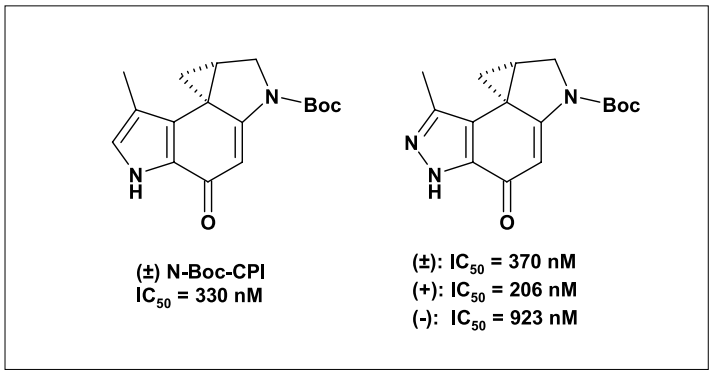


Fig. 16.

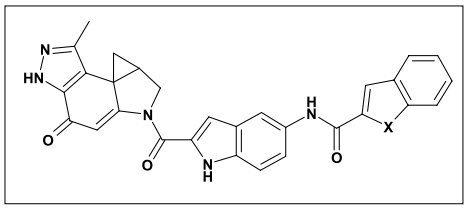


Fig. 17.

The tripyrrol peptide Distamycin A, and tallimustine, in which the formyl group has been replaced by a benzoyl nitrogen mustard, show a broad spectrum of antitumor activity. Replacing one or two pyrrols by pyrazol analogues superior antileukemic activities *in vivo* could be achieved (Fig. 18: same optimal dose of 6.25 mg/kg achieving higher % T/C values = median survival time of treated *versus* untreated mice: 125% for tallimustine and 213% for the pyrazole X = N derivative) [39].

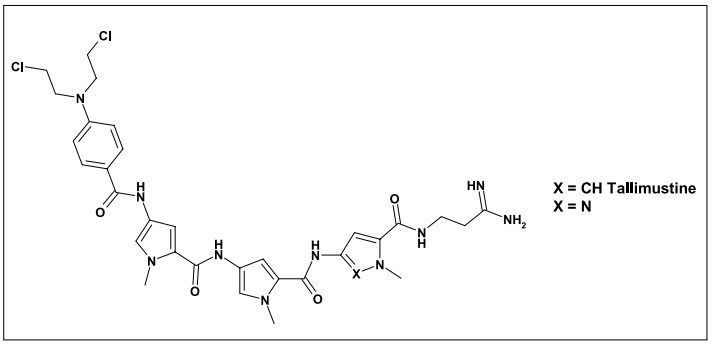


Fig. 18.

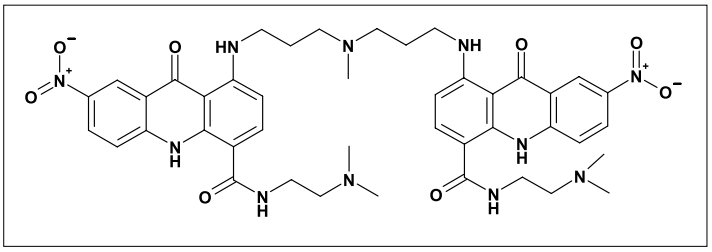
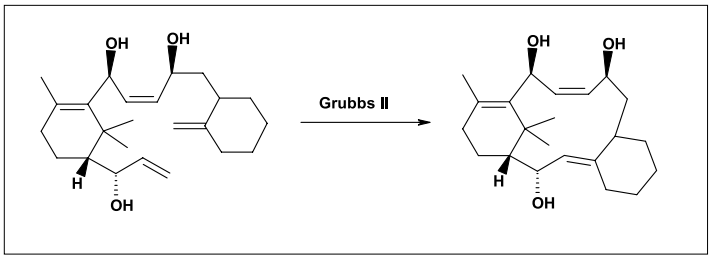


Fig. 19.



Scheme 6.

A big effort was made to combine different natural antitumor agents in one molecule: for combinations of anthramycin and distamycine A see [40], for combinations of CPI and distamycin A see [41] and of α-methylene-γ-butyrolactones and distamycine A see [42].

Ippolito Antonini (Univ. of Camerino) presented progress on the syntheses of bis intercalator derivatives as potent antitumor agents. Connecting two planar intercalating moieties generally increases DNA binding affinity and the drug's residence time in the DNA bound form. Bis-acridone derivatives, of which one compound is shown in Fig. 19, 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 [43]. Tetracyclic bis-pyrazolo[3,4,5-kl]acridinecarboxamides showed very potent antiproliferative activity and promising *in vivo* results in the hollow fiber assay [44].

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 [45].

Taxuspine X and U have been proposed as biogentic precursors for taxane. In particular, taxuspine X exhibits a remarkable multidrug resistance (MDR)- reversing activity. An elegant approach to simplified 12-membered macroyclic compounds *via* ring closure metathesis was presented (Scheme 6) [46].

A novel approach for the synthesis of the taxol side chain was discussed [47].

Karl-Heinz Altmann (ETH Zürich) 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 [48]. Antiproliferative activity superior to the natural epothilones was found in benzo-heterocyclic analogues (Fig. 20) [49]. Trans epothilones (olefin and epoxide) proved to be superior to the natural compounds, whereas the cor-

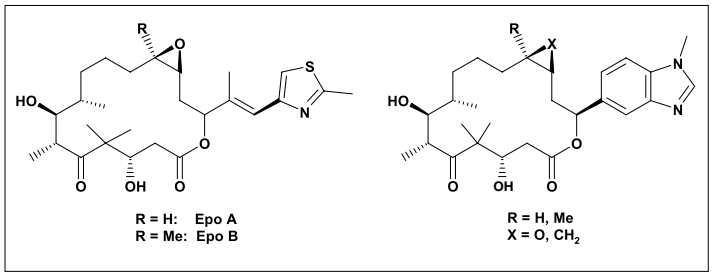


Fig. 20.

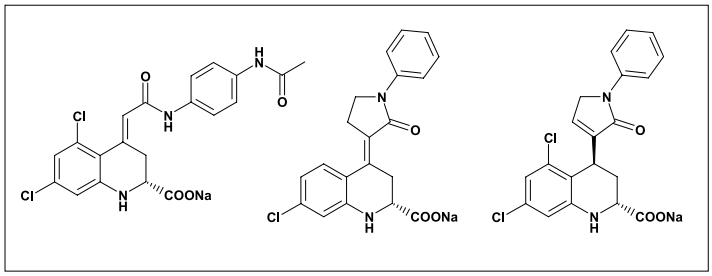


Fig. 21.

responding cyclopropyl derivative did not show enhanced anti-proliferative activity. 3-deoxy epothilone B was 20 times less active than epo B. For a comprehensive review see [50].

5. 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. The tetrahydroquinoline derivative in Fig. 21 (left molecule) is a very potent glycine receptor antagonist (pK_i = 8.52). The racemic compound was resolved *via* preparative HPLC of the diastereomeric lactate esters. The (+)-enantiomer showed pK_i = 8.79, the (–)-enantiomer pK_i = 7.30). However, the latter was more effective *in vivo* in the late phase of the formalin test in mice (ED_{50} = 0.14 mg/kg, compare to morphine ED_{50} = 0.73 mg/kg) as well as in the chronic constriction injury (CCI) model (EC_{50} = 0.14 mg/kg *versus* the previous frontrunner compound GV196771A with EC_{50} = 2.9 mg/kg) [51]. For an elegant stereocontrolled synthesis of the glycine antagonists with di- and tetrahydropyrrol structures (middle and right formulae in Fig. 21 see [52].

In a high-throughput screen novel mGluR1 antagonists were discovered, which were optimized by preparing a library of 1600 compounds to identify a very potent (IC_{50} = 16 nM) and very selective (>100 fold *versus* mGluR 2, 4 and 5) mGluR1 antagonist. The compound (Fig. 22, third molecule) was active in both the early and late phases of the formaline test with ED_{50} = 0.3 mg/kg, in the carageenan test in rats (ED_{50} = 3 mg/kg) and in the chronic constriction injury model in rats showing long-lasting analgesic effects of >4 h at a dose of 10 mg/kg i.p. In an isolated preparation of baby rat spinal cord the compound blocked the central sensitization process after 1 h perfusion with a concentration of 1 μM to reduce the amplitude of the ventral root potential [53]. More drug-like compounds, such as the tetrahydro-β-carboline derivative (Fig. 22 on the right) 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).

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 [54].

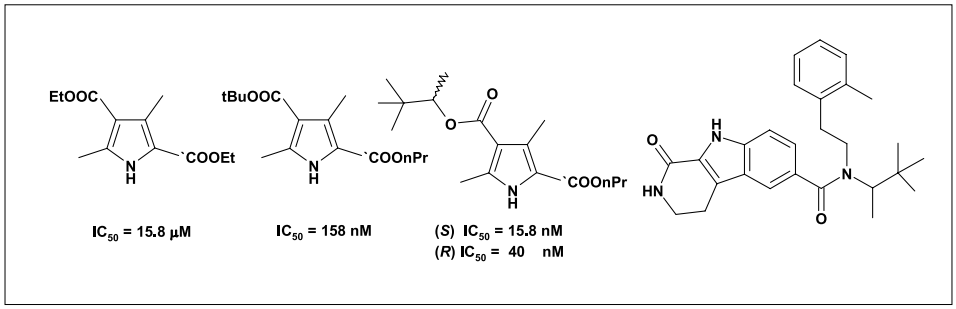


Fig. 22.

6. 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 (Fig. 23) [55]. 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 were able to inhibit Aβ aggregation induced by AChE with IC_{50} values of 45 and 28 μM, respectively, approaching the value of propidium (IC_{50} = 12.6 μM) [56]. 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 d 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 has developed a micro-immobilized enzyme reactor (micro-IMER) with human recombinant acetylcholinesterase covalently bound on an ethylendiamine monolithic convective interaction media (CIM) disk previously derivatized with glutaraldehyde. The micro-IMER was inserted in a HPLC system. The effects of the AChE inhibitors are evaluated by simultaneous injection of each inhibitor with the substrate. Analysis times are less than 2 min. The increased enzyme stability and the system automation allows large numbers of compounds to be analyzed in a continuous flow mode [57][58].

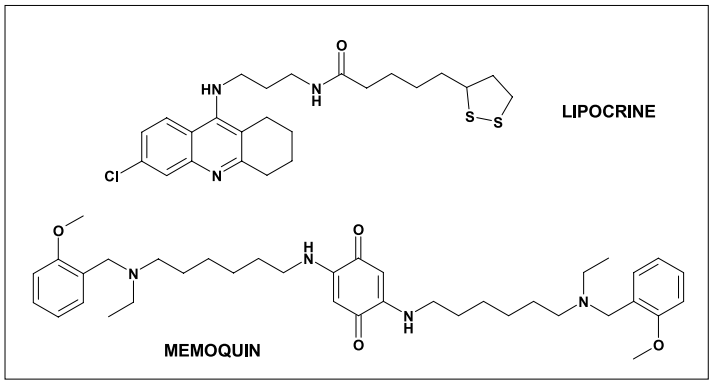


Fig. 23.

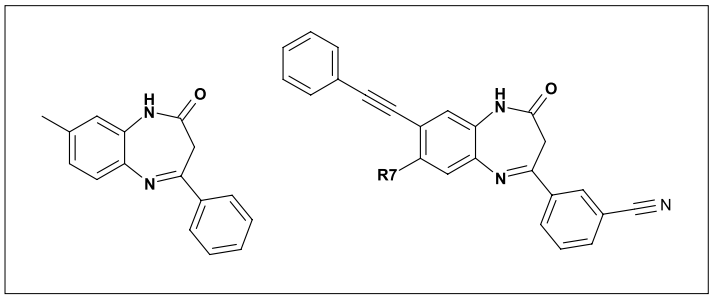


Fig. 24.

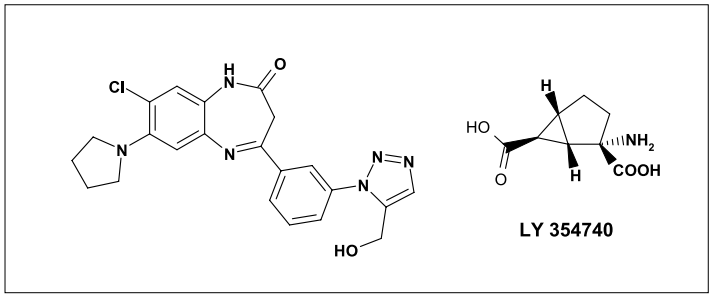


Fig. 25.

AChE may play a role in the development of senile plaques by acceleration of Aβ deposition presumably through its peripheral anionic site located close to the rim of the active gorge of the enzyme. Analytics were performed *via* circular dichroism (CD) studies for Aβ and Aβ plus AChE. The CD signal intensity at the negative band of 215 nm increases in the presence of h r AChE indicating the increasing formation of Aβ in the β-conformation preliminary to Aβ fibril formation. Also the fluorescence intensity of the thioflavin T emission of fluorescence at 490 nm increased [59–61].

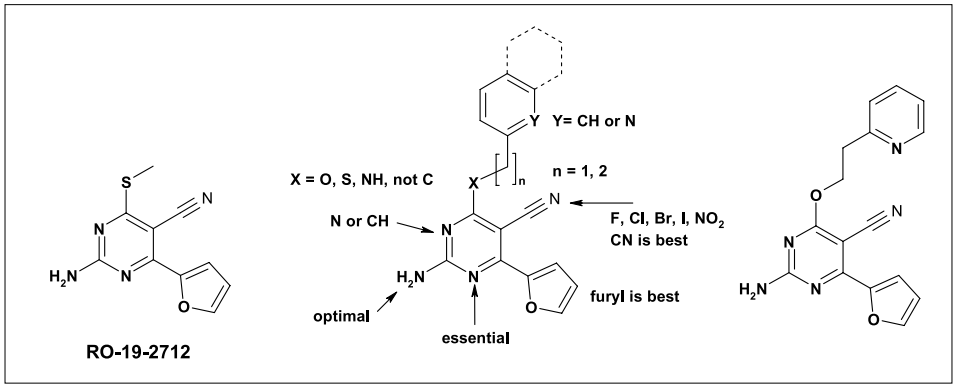


Fig. 26.

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 the 1,5-benzodiazepine with K_i = 3.2 μM (Fig. 24, left molecule). Acetylenic compounds, optionally substituted in position 7 led to very active compounds, *e.g.* $R_7 = CH_2OH$: IC_{50} = 18 nM, $R_7 = OCH_2CH_2OMe$: IC_{50} = 14 nM (Fig. 24, right molecule). However, the oral bioavailability was too low for *in vivo* evaluation. Replacing the substituted phenyl ring in position 4 by heterocycles, such as imidazole, 1,2,3- and 1,2,4-triazoles, led to single digit nanomolar compounds. But some interacted very strongly with CYP3A4 raising fears of drug–drug interactions.

In order to decrease lipophilicity the acetylene side chain was abandoned and polar and basic substituents introduced achieving a 500 times better water solubility (Fig. 25). 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. 25).

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 enabled the identification of the 2-aminopyrimidine RO-19-2712 from the library of Roche compounds, which has moderate affinity to A2aR, but insufficient selectivity. Extensive SAR work led to the following picture (Fig. 26):

The most advanced compound (Fig. 26, right molecule) 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. However, the furyl ring is metabolized rapidly, first to epoxyfurane, which is hydrolyzed to maleic dialdehyde interacting irreversibly with glutathione. Other advanced competitor compounds all contain furyl substituents, as ZM 241385 of Astra Zeneca and SCH 58261 of Schering.

Maria Novella Romanelli (Univ. of Florence) looks for novel nicotinic receptor ligands *via* 3D searches of the Cambridge Structural database [62]. 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), is shown in Fig. 27.

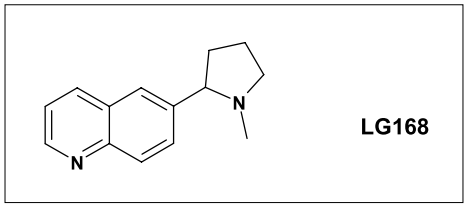


Fig. 27.

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_is of 27 and 32 nM for the two compounds in Fig. 28, respectively).

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-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 [63]. The compound showed significant neuroprotective effects in an oxygen glucose deprivation cell culture test (Fig. 29, left molecule). Racemic HIP-A is a potent and noncompetitive inhibitor of [^{3}H]-L-glutamate uptake (IC_{50} = 18 μM) [64].

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 [65]. One example was the optimization of CDK2 ligands of the class of benzo-di-pyrazoles (Fig. 30) up to IC_{50} values of 7 nM.

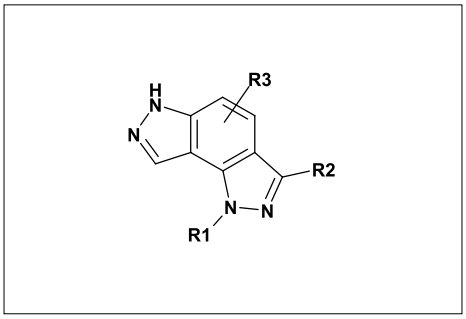


Fig. 30.

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 consistent high quality. Finally, the poster prize of Euro 500.– was awarded to poster #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 [66]) 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 (Scheme 7) [67]. The compounds of the library were subjected to testing in Zebrafish according to Mark C. Fishman and coworkers [68].

7. 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 Modinatur 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.

Received: October 4, 2005

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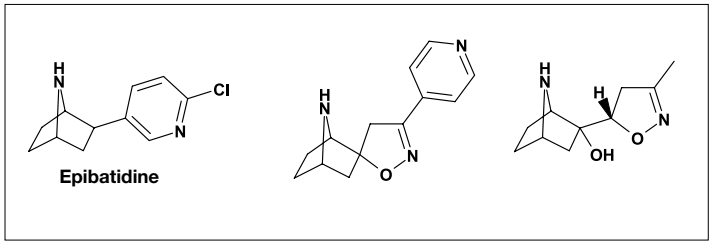


Fig. 28.

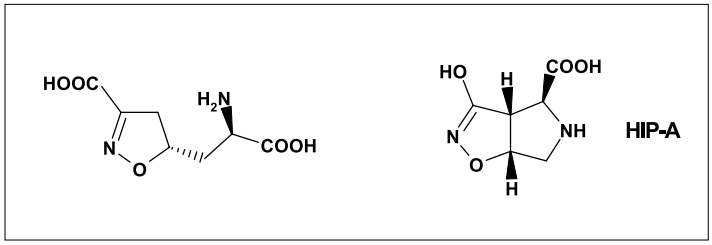
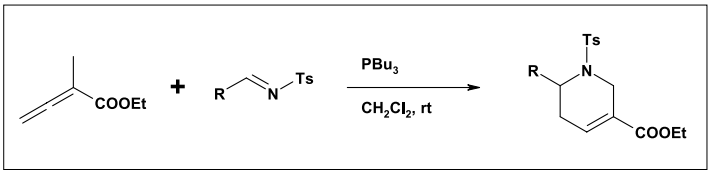


Fig. 29.



Scheme 7.

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