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Second Joint French–Swiss Meeting on Medicinal Chemistry 39èmes Rencontres Internationales de Chimie Thérapeutique

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Ten years after the First Joint French–Swiss Meeting on Medicinal Chemistry in Dijon, September 26–28, 1993 [1] the Société Française de Chimie Thérapeutique and the Division for Medicinal Chemistry of the Swiss Chemical Society organized again a meeting in Burgundy, this time in the lovely town of Beaune. We could welcome 290 scientists (170 French, 40 Swiss, 15 Belgian, 10 British, and colleagues from twelve other nations), a substantial increase from 210 delegates in 1993, in the new and very well-equipped Palais de Congrès. 17 lectures dealt with four main topics: 'Ligands for Selected G-Protein Coupled Receptors', 'Highlights in Medicinal Chemistry', 'Protein Kinase Inhibitors' and 'Progress in Oncology Research'. 86 posters were on display during the whole congress. In addition, 14 companies presented their products in the commercial exhibition. The highlights of the plenary and main lectures were:

1. Ligands for Selected G-Protein Coupled Receptors

Catherine Llorens-Cortès (Collège de France, Paris) presented her work on orphan GPCRs. From the human genome 367 GPCRs (excluding the sensory receptors) have been reported, of which endogenous ligands are known for 224 receptors. The remaining 143 GPCRs constitute the pool of orphan GPCRs. A very powerful strategy to isolate ligands for orphan GPCRs is reverse pharmacology. The orphan receptor is stably transfected into mammalian cells, which are then exposed to purified reverse phase HPLC fractions from tissue extracts containing natural peptides. Activation of the orphan receptor by its ligand results in the activation of transduction pathways, such as mobilization of Ca^{2+}, or production of cAMP or arachidonic acid. A novel screening process is based on the property of GPCRs to internalize upon ligand exposure, which can be visualized by fluorescent tagging of the orphan GPCR. The cloned orphan rat APJ receptor was fused at its C-terminus to enhanced green fluorescent protein (EGFP) and exposed to 120 reversed HPLC fractions obtained from 2500 frog brains. The induced receptor internalization was monitored by confocal microscopy. This allowed the confirmation that apelin, a 36 amino acid peptide, previously identified by a Japanese group, is indeed the endogenous APJ receptor ligand. Apelin derives from a large precursor prepro-apelin. The apelin receptor is particularly abundant in the hypothalamus, the piriform and entorhinal cortex, and the dentate gyrus. Apelin receptors are expressed by vasopressinergic neurons. These data suggest that apelin locally synthesized in the supraoptic nucleus may exert a direct inhibitory action on vasopressin release, thus playing an important role in the central control of body fluid homeostasis and cardiovascular functions [2][3].

Marcel Hibert (Laboratoire de Pharmacochimie, Strasbourg) lectured on post-genomic medicinal chemistry. The main challenge after the elucidation of the human genome is the understanding of the relationship between genes, coded proteins and their biological functions. Medicinal chemists may play an important role in this process by providing selective ligands for a large number of new targets. The vasopressin (V_{1a}, V_{1b}, and V_2) receptors and the oxytocin receptor have been cloned and sequenced in the early 1990s. A 3D model was derived from bacterial rhodopsin using homology molecular modeling. AVP was docked into a central cleft defined by transmembrane domains 2 to 7 of the V_{1a} receptor. A non-peptide V_{1a} receptor antagonist SR 49059 (Fig. 1) was predicted to bind at the bottom of the binding cleft. Site directed mutagenesis of two TM7 residues confirmed these findings. A new procedure, which may replace the tedious photoaffinity labeling studies, may be site-directed covalent labeling. Starting from a model, a residue in close vicinity to the ligand interaction is mutated into a cysteine. Then an electrophilic group (*e.g.* N=C=S) is introduced as a contact point into the ligand. This has been applied to the V_{1a} receptor and SR 49059 (Fig. 1) (for details *vide infra*, lecture of C. Barberis).

A complementary approach is high-throughput screening of large libraries such as the Chimiothèque Nationale, started by a joint effort of Strasbourg, Institut Curie and Gif-sur-Yvette. Into this collection GPCR ligand pharmacophores, such as arylpiper-

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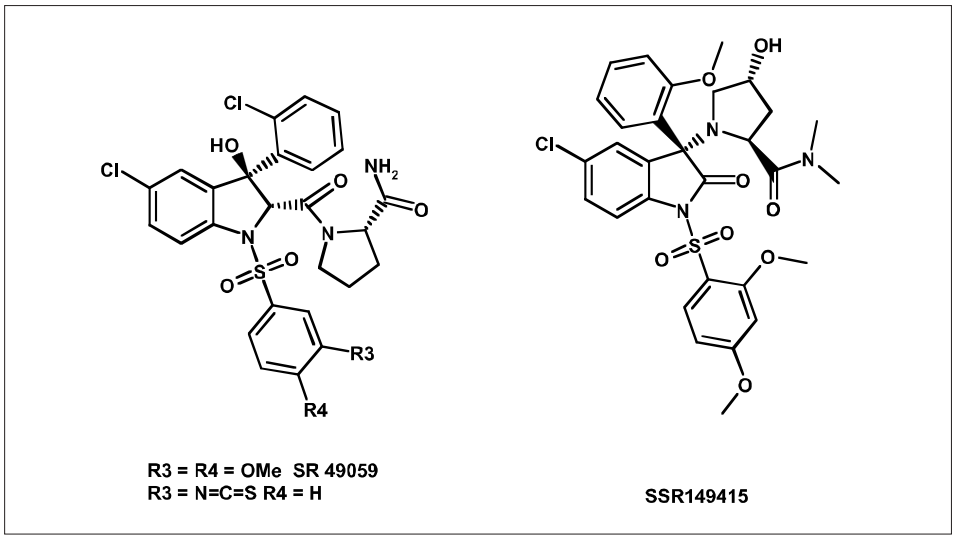


Fig. 1.

azines, aminopyridazines and disulfide-bridged hexapeptide libraries are continuously fed. A generic assay for most GPCRs uses FRET (Fluorescence Resonance Energy Transfer). Recombinant GPCRs are fused with Green Fluorescent Protein (GFP) at its N-terminal. If a ligand carrying a relevant fluorophore (F) binds to the chimeric receptor fluorescence energy will be transferred from GFP to F. This signal is very sensitive and 100% specific as only ligands in direct contact with the target receptor will quench GFP emission energy and emit at its own wavelength [4][5].

Claude Barberis (INSERM, Montpellier) is the expert on vasopressin and oxytocin receptors. Over the years his group has produced a whole repertoire of valuable ligands for extensive receptor characterization. First he designed an extremely potent peptide V_{1a} receptor antagonist (IC_{50} = 8 pM). The tyrosine residue was subsequently labeled with ^{125}I allowing detailed light microscopic autoradiographic studies of vasopressin receptors in rat brain and spinal cord. A radioactive and photosensitive ligand was prepared, which bound covalently to the transmembrane domain 7. Based on these results three-dimensional models of the antagonist bound receptors were constructed and then verified by site-directed mutagenesis. Fluorescent ligands were prepared by attaching tetraethyl-rhodaminyl derivatives to a lysine residue (IC_{50} = 70 pM) allowing cytofluorimetric experiments and fluorescence microscopy.

Finally, the binding site of the non-peptidic antagonist SR 49059 (Fig. 1) to the V_{1a} vasopressin receptor was identified by the irreversible reaction of the F225C mutant with isothiocyanate derivative of SR 49059 ('site-directed covalent labeling', see: M. Hibert *vide supra*). Treatment of the F225 mutant with the isothiocyanate derivative led to dose dependent inhibition of the residual binding of the radiolabeled antagonist. This inhibition is the consequence of a covalent irreversible chemical modification [4][6].

Guy Griebel (Sanofi-Synthélabo, Bagneux) gave a fascinating overview of the properties of the first selective, orally active, non-peptidic V_{1b} receptor antagonist SSR149415 (Fig. 1) for the treatment of stress-related disorders. K_i values are: 1.5 nM for human V_{1b}, 91 nM for human V_{1a}, 1412 nM for human V_2 receptors (all expressed in CHO cells) and 174 nM for human oxytocin receptors expressed in Ltk^- cells. There are no interactions with 90 other receptors or channels. SSR149415 is a competitive V_{1b} receptor antagonist. It was active in a variety of classical *in vivo* tests for anxiolytic-like compounds, such as the four-plate test, the light/dark test, social interaction, punished drinking, elevated plus maze. The anxiolytic activity of a dose of 10 mg/kg p.o. lasted for 4 h and was still present after repeated administration of the drug for 7 d indicating a long lasting effect and the absence of tolerance. These effects were not accompanied by undesirable side effects, such as sedation, decrease in spontaneous locomotor activity or motor coordination disturbances. No deterioration of spatial memory (Morris water maze) or change of sleep EEG were observed. Tests in the forced swim-test and in the chronic mild stress test for 39 d showed antidepressant-like effects. SSR149415 may represent a new therapeutic strategy for the treatment of depression and some forms of anxiety in stressful situations [7][8].

2. Highlights in Medicinal Chemistry

Christine Wurth (Roche, Basel) presented her studies carried out with Prof. Michael H. Hecht of Princeton University on the sequence determinants of aggregation of Alzheimer's Aβ peptide. It was found that fusions of the wild type Aβ(1-42) sequence with green fluorescent protein (GFP) forms insoluble aggregates, in which GFP is inactive, *i.e.* that bacterial cells expressing such fusions do not exhibit green fluorescence. Libraries of Aβ(1-42)–GFP fusions were constructed and screened in which the sequence of Aβ(1-42) was randomly mutated. Cells expressing GFP fusions to soluble (non-aggregating) variants of Aβ(1-42) exhibited green fluorescence. Implementation of this screen enabled the isolation of 36 variants of Aβ42 with reduced tendency to aggregate. Four segments appeared to be particularly important. The central hydrophobic cluster Leu17-Val18-Phe19-Phe20-Ala21 emerged as a key determinant of fibrillogenesis. In particular, position 19 is well known to affect folding and assembly of Aβ. Mutations of either Ile31 or Ile32 reduced aggregation. Met35 seems to be important. Mutation of Met35 to either Glu, Gln, Ser or Leu reduced aggregation. The fourth region of high importance is the C-terminal hydrophobic sequence Val39-Val40-Ile41-Ala42. The double mutation Leu34-Pro and Ala42-Ser has a higher fluorescence than the single mutant Leu34-Pro [9].

Peter L. Toogood (Pfizer, Ann Arbor, MI) dealt with the difficult, but increasingly important topic of inhibition of protein–protein association as a target for drug discovery. Interaction surfaces typically span at least 600 $Å^2$ per monomer. Approximately 17 residues per monomer participate in the P–P interaction, mostly nonpolar amino acids, such as Phe, Tyr, Met, and charged aa as Arg [10][11].

Early success emerged in the field of integrin inhibitors, the first target being the $\alpha_{IIB}\beta_3$ fibrinogen receptor. Merck chemists optimized a HTS hit (IC_{50} = 27 μM) to the drug tirofiban (Fig. 2) (Aggrastat^{TM}; IC_{50} = 9 nM).

The BH3 domain proteins include the Bcl-2 related proteins that promote or antagonize cell death (proapoptotic: BAD, Bak, BAX; antiapoptotic: Bcl-x_L, Bcl-2). The X-ray structure of Bcl-x_L has been very important [12]. A Bcl-2 homology model based on the structure of Bcl-x_L allowed virtual screening of 200,000 compounds to yield the compound HA14-1 (Fig. 3), which binds to Bcl-2 with IC_{50} of 9 μM and induces apoptosis in HL-60 cells [13].

Another example are inhibitors of SH-2 domain proteins, which recognize proteins phosphorylated on tyrosine, a common recognition event mediating a large number of signaling interactions. A potent inhibitor was published recently (Fig. 4); IC_{50} = 2 nM, inhibiting cell survival in MDA MB 453 breast carcinoma with EC_{50} = 0.8 μM [14].

Paolo Carloni (SISSA, Trieste) is professor of theoretical chemistry at the Inter-

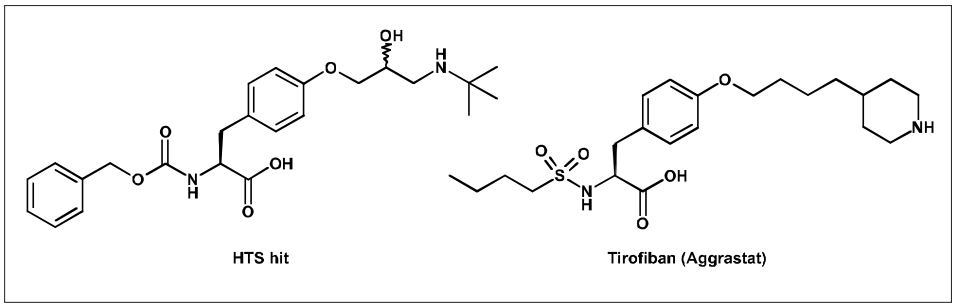


Fig. 2.

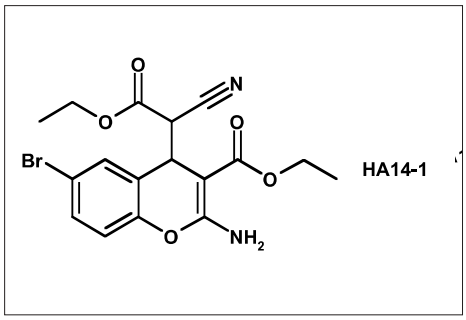


Fig. 3.

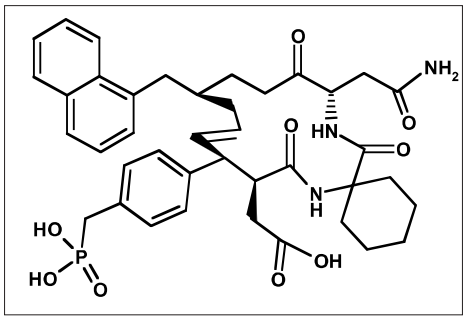


Fig. 4.

national School for Advanced Studies. *Ab initio* molecular dynamics using the Car & Parrinello equation can play an important role for modeling systems of pharmacological interest. One application deals with structural and electronic aspects of K^+ permeation through the binding sites of the KcsA channel's selectivity filter. The X-ray structure of the KcsA channel showed that the protein is a tetramer. Each monomer contains two transmembrane helices forming a pore across the cell membrane. The selectivity filter is constituted by highly conserved residues T75-V76-G77-Y78-G79. Four binding sites S1 to S4 were identified for K^+ and a water molecule. Carbonyls of the four subunits bind to the metal atoms. During the translocation process from one binding site to the other the K^+ ion polarizes significantly its ligands, backbone carbonyl groups and a water molecule [15].

Another example is the *ab initio* molecular dynamics simulation of a complex between the enzyme HIV-protease and a peptide substrate. Classical MD calculations reveal large-scale protein motions modulating the conformational properties of the substrate at the cleavage site. The *ab initio* calculations show that the substrate motion modulates the activation free energy barrier of the enzymatic reaction. The catalytic power of the enzyme arises from the protein mechanical fluctuation. These data provide a rationale for some of the observed drug-resistant mutations [16].

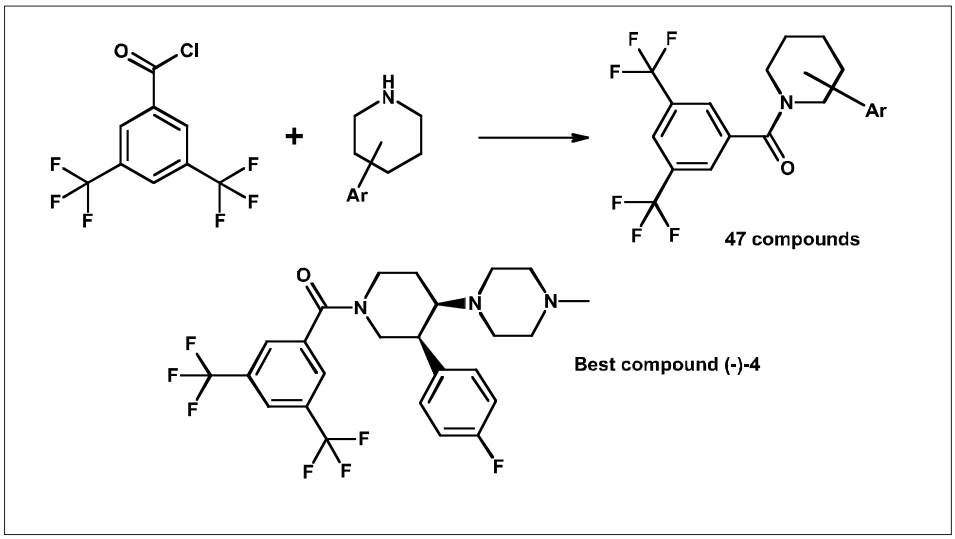
Didier Rognan (Laboratoire de Pharmacochimie, Strasbourg) is head of the bioinformatics group. He has made essential contributions to virtual screening techniques. Protein-based virtual screening has mostly been applied to high-resolution X-ray structures. However, there are still numerous limitations mainly due to the inaccuracy of docking/scoring tools to quantify protein–ligand interactions. The reverse approach, given a known ligand to find the most likely target was investigated starting from the Protein Data Bank using InvGOLD.

This leads to the next step, to proteome-based screening *via* a new computational tool (GPCRmod). First the seven transmembrane domains of 322 human GPCRs were accurately aligned, clustered into three different classes, rhodopsin-like, secretin-like, and metabotropic glutamate-like, and then converted into high quality 3D models [17–19].

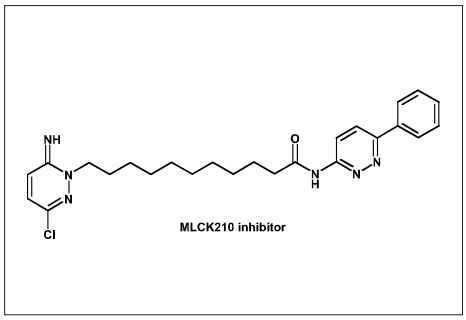
A beautiful example is the difference of selectivities of SR 49059 (Fig. 1), a V_{1a} antagonist (K_i = 2.8 nM) to SSR149415 (Fig. 1), a V_{1b} antagonist (K_i = 2.6 nM). Two positions in the binding cavity differ between the two receptor subtypes, *i.e.* Met220 & Ala334. Two single mutations are sufficient to confer to the corresponding V_{1a} mutants typical V_{1b} binding properties (for the formulae of the ligands *vide supra,* lecture of C. Barberis).

Virtual screening of the GPCR library based on bovine rhodopsin was quite successful for *antagonists*, as it is a good template for modeling ground state GPCRs. In order to screen for *agonists* the receptor 3D coordinates must be changed to accommodate for the motions occurring on specific helices (TMs 3, 5, 6, and 7). A lot of effort is currently devoted to these active state models [20].

Sabine Kolczewski (Roche, Basel) presented the design and syntheses of potent, selective and orally active NK1 receptor antagonists. A common structural feature of many potent NK1 antagonists is the 3,5-bis-(trifluoromethyl)-phenyl substructure, which was chosen as the core of a NK1 focused library. In two subsequent optimization steps a *cis*-3,4-di-phenyl-piperidine was modified first to a *cis*-3-phenyl-4-N-methylpiperazine derivative, which was additionally substituted by a fluorine in the phenyl ring to produce a very promising pure enantiomer (–)-**4** (Scheme 1). Properties: pK_i (NK1) = 8.61, ID_{50} = 0.6 mg/kg p.o. in the gerbil foot tapping model, half life of 5.6 h, F = 78%, logD = 2.6, solubility: 1 mg/ml at pH = 6.7). An X-ray structure of the antagonist bound to the receptor is available [21].



Scheme 1.



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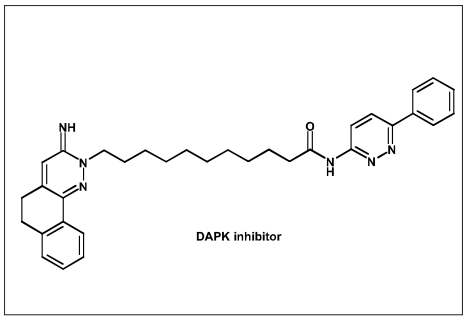

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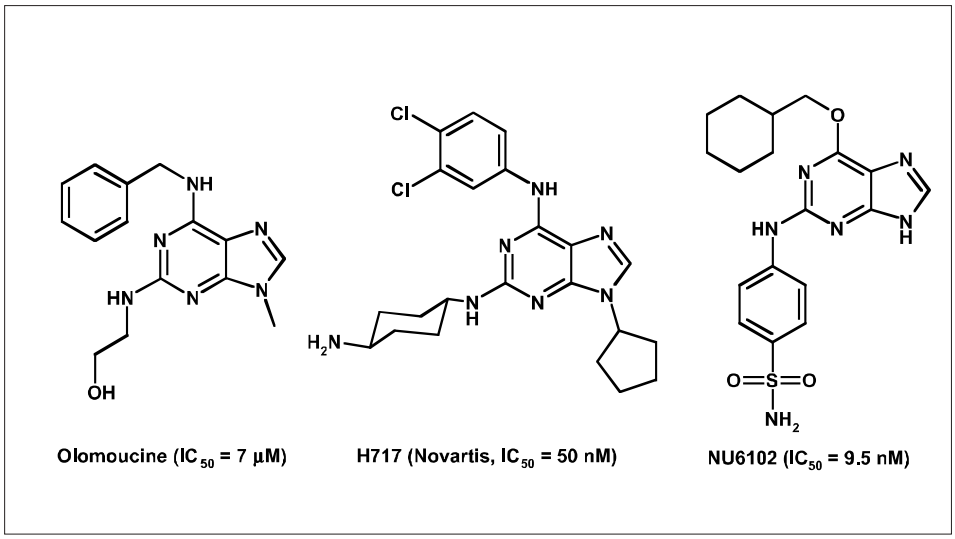
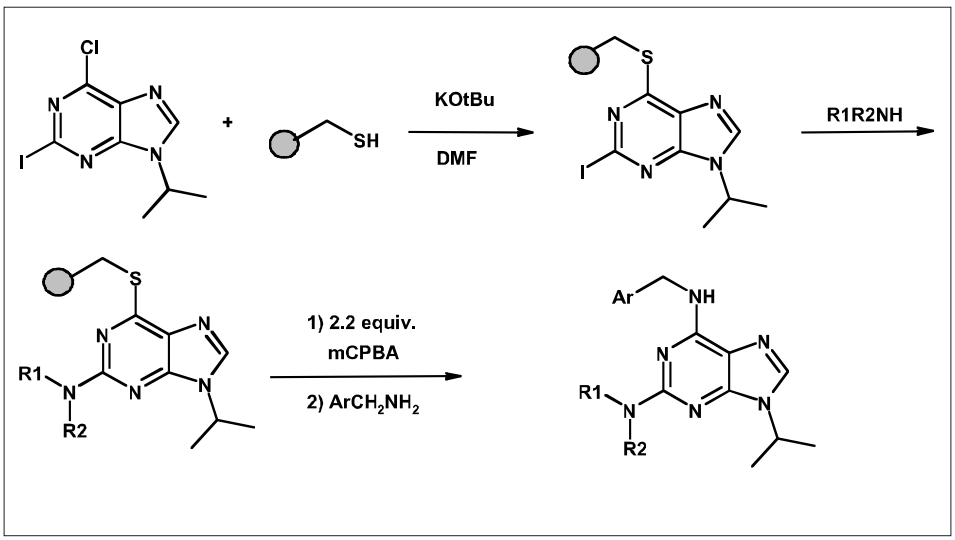


Fig. 7.

3. Protein Kinase Inhibitors

D. Martin Watterson (Northwestern University, Chicago) discovered new small molecule inhibitors of serine/threonine kinases *via* a chemical genomics approach by employing fragment-based, structure-assisted synthetic library design. One example is the discovery of inhibitors of the myosin light chain kinase (MLCK) 210 isoform (Fig. 5) to treat acute lung injury associated with sepsis. Starting from 3-amino-6-phenyl-pyridazines, Prof. Camille G. Wermuth's favorite structure [22] with very weak activity (about 50 μM) a large number of analogues was synthesized using commercially available fragments with "drugable" molecular properties. The best compounds appear to target the catalytic domain of the kinase (K_i = 5 μM) [23].



Scheme 2.

A second example is the inhibition of the death associated protein kinase (DAPK) as a target for acute brain injury. A quantitative enzyme assay for DAPK allowed the screening of a pharmacologically focused library, again on the basis of the 3-amino-pyridazine chemotype. Subsequently the parent structure was diversified through parallel synthesis to discover the DAPK inhibitor (Fig. 6) (IC_{50} = 13 μM) [24]. The crystal structure of the complex between the DAPK catalytic domain and the 3-amino-6-phenyl-pyridazine fragment of the DAPK inhibitor was determined at 1.9 Å resolution revealing unoccupied space, which can be used for further rational drug design. This approach of 'growing out' an inhibitor into other pockets of the protein is described by Carr and Jhoti [25].

David S. Grierson (CNRS-Institut Curie, Orsay) investigates cyclin dependent kinase (CDK) directed heterocycle libraries using solid phase parallel synthesis technology. Tri-substituted purine derivatives (Fig. 7) can compete with ATP for binding in the catalytic site of the kinase. X-ray structures revealed that these molecules bind in a different orientation than ATP to the ATP site showing that considerable room exists for the development of new CDK inhibitors.

A general and economical solid support synthesis of 2,6,9 trisubstituted purine libraries uses a sulfur linkage approach starting *e.g.* from 2-iodo-9-isopropyl-purine. After oxidation to the corresponding sulfone this was reacted with substituted benzylamines in THF. No competing N-oxidation occurred at the 2-amino-substituent (Scheme 2).

For 2-acetylenic purines palladium-catalyzed coupling reactions, in particular using $Pd(dppe)Cl_2$ was successful (Scheme 3).

Successful were also Suzuki reactions at C(2) or $Cu(OAc)_2$ promoted couplings of (heteroaromatic)-boronates at the N(9) nitrogen. For tetrasubstituted purine analogues S(8) benzyl substituted purines may be used (Scheme 4) [26-29].

Laurent Meijer (Cell Cycle Laboratory, Roscoff), ***the winner of this year's Aventis Prize,*** investigates inhibition of cyclin-dependent kinases (CDKs), which regulate the cell division cycle, apoptosis, transcription and differentiation, and of glycogen synthase kinase-3 (GSK-3), an essential element of the wnt signaling pathway. CDKs are serine/threonine kinases. Human genome sequences revealed 13 CDKs and 25 cyclin-box-containing proteins. More than 50 CDK inhibitors have been described, many of which have been co-crystallized with CDK2. There are two classes of selective inhibitors, for CDK1, 2, and 5 (and possibly CDK 9) and those selective for CDK4 and 6. So far, no inhibitor for a single CDK has been discovered. The first

application was for the treatment of cancer, where additional inhibition of ERK1 &2 is beneficial. Increasingly, the role of CDK5 in Alzheimer's disease is investigated. The abnormal phosphorylation of the microtubule-binding protein tau (>20 sites) is caused by several kinases including CDK5 and GSK-3. In addition, CDK inhibitors have been reported to prevent β-amyloid phosphorylation and β-amyloid induced cytotoxicity [30].

GSK-3 inhibitors include indirubin, paullones and the recently discovered aloisines (Fig. 8), *i.e.* 6-phenyl[5H]pyrrolo[2,3-b]pyrazines. Aloisin A (R5 = H, R7 = n-Bu, X = *p*-OH) was tested for selectivity on 26 highly purified kinases to show excellent selectivity for CDKs 1, 2, and 5 and for GSK-3: IC_{50}s: CDK1/cyclin B: 150 nM, CDK2/cyclin A: 120 nM, CDK2/cyclin E: 400 nM, CDK5/p35: 160 nM, GSK-3α: 500 nM [31].

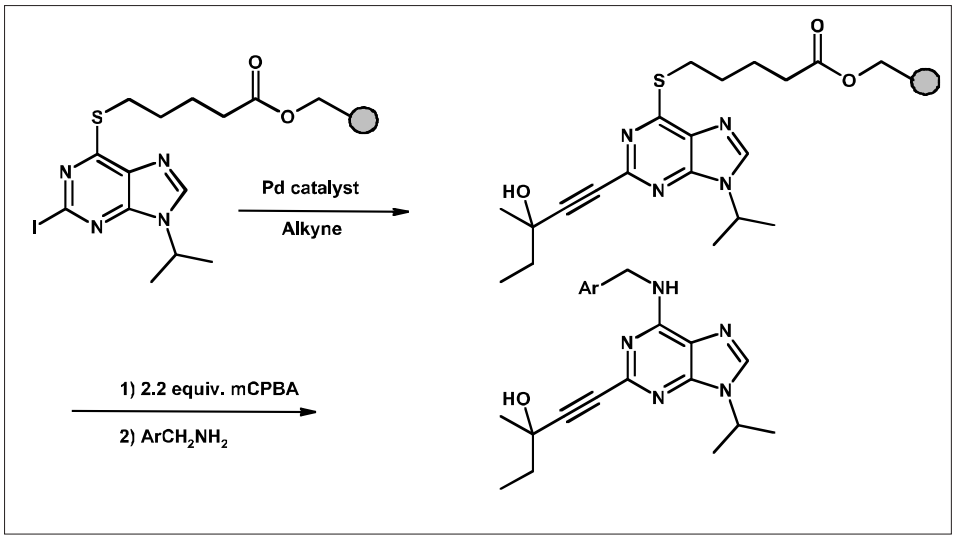
Peter Traxler (Novartis, Basel) presented a lecture on tyrosine kinase inhibitors already on the occasion of the First Joint French–Swiss Meeting on Medicinal Chemistry in Dijon in September 1993. In the last ten years substantial progress has been achieved. The human genome encodes for about 90–100 protein kinases, 50 of which are involved in human cancer. The first tyrosine kinase inhibitors have entered the market: the monoclonal HER-2 antibody Herceptin for breast cancer, the Bcr-Abl inhibitor Glivec for the therapy of patients with chronic myelogous leukemia (CML) and the epidermal growth factor receptor (EGFR) inhibitor Iressa. More than 20 ATP-competitive tyrosine kinase inhibitors are currently in clinical evaluation.

The pyrrolo[2,3-d]pyrimidine scaffold was found in a high-throughput screen at Novartis (IC_{50} = 5.9 μM) and was subsequently optimized to give the EGFR tyrosine kinase inhibitor NVP-AEE788 (Fig. 9) (EGFR: IC_{50} = 1 nM; ErbB2: IC_{50} = 8 nM; KDR: IC_{50} = 77 nM) currently in PL 1 clinical evaluation.

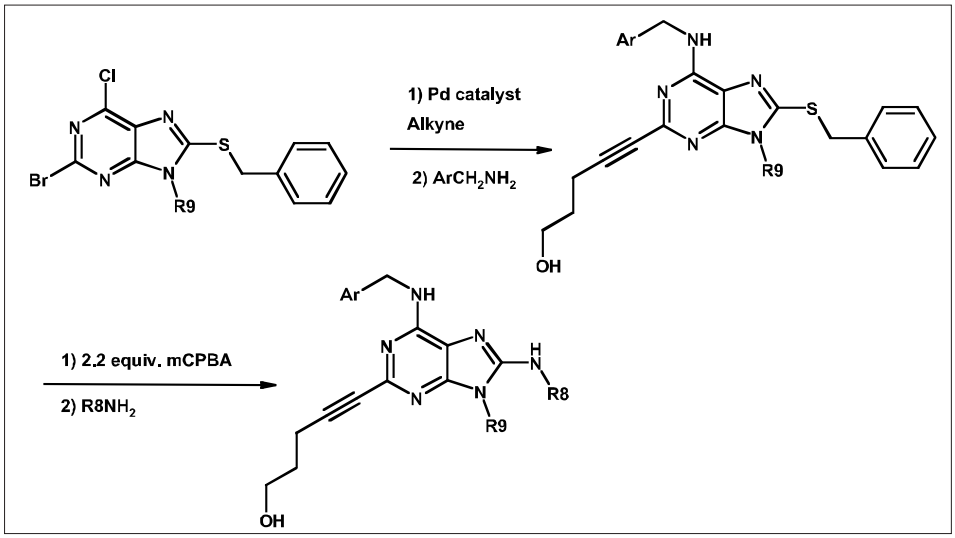
Glivec (Fig. 10) is an inhibitor of Bcr-Abl tyrosine kinase. This kinase is present in 95% of all patients suffering from chronic myelogous leukemia (CML). The drug resulted from an optimization process starting from a phenylamino-pyrimidine scaffold (cellular profile: inhibition of autophosphorylation: v-Abl: IC_{50} = 100–300 nM; of c-kit: IC_{50} = 100 nM, of PDGFR: IC_{50} = 100 nM). Its inhibition of c-kit and PDGFR tyrosine kinases led also to Glivec's clinical use in solid tumors, *e.g.* gastrointestinal stromal tumors, GIST [32].

4. Progress in Oncology Research

Herbert Waldmann (Max Planck Institut für Molekulare Physiologie, Dortmund)



Scheme 3.



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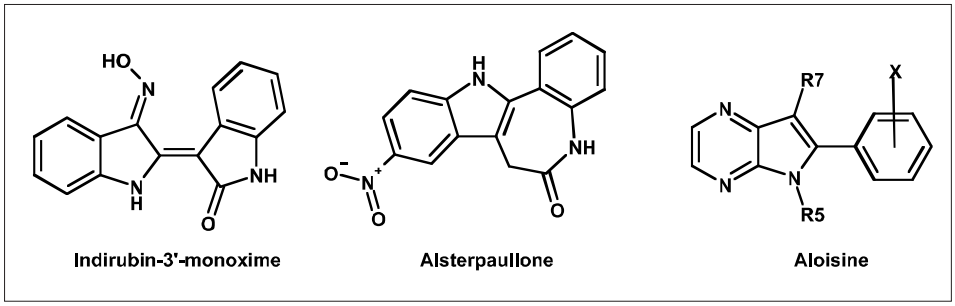

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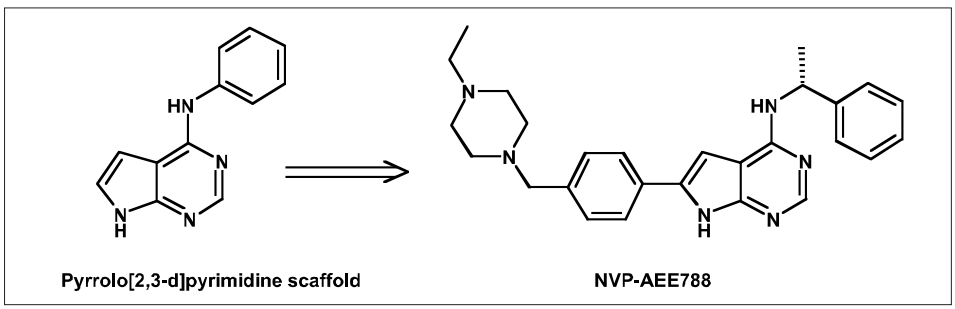


Fig. 9.

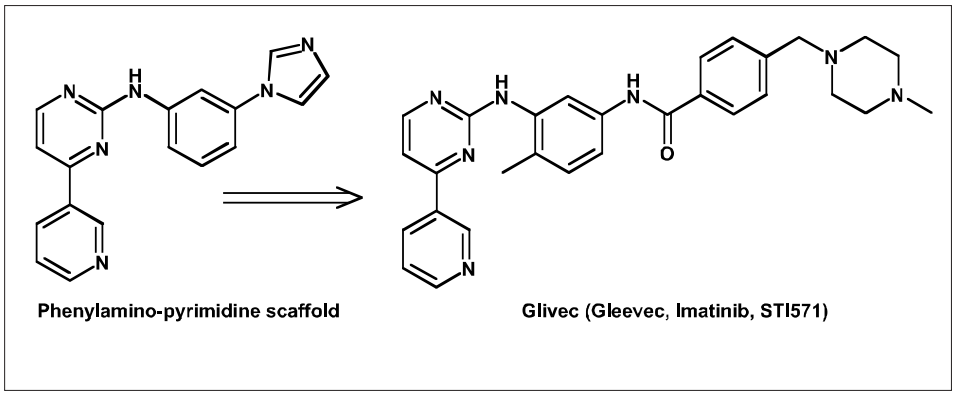
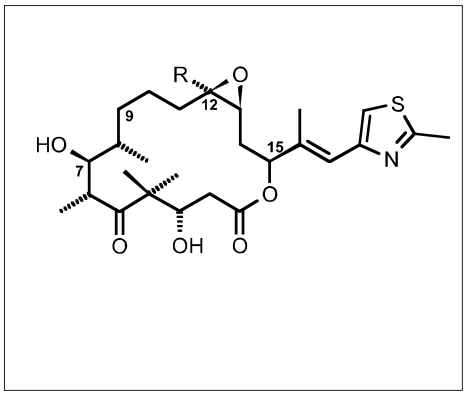


Fig. 10.



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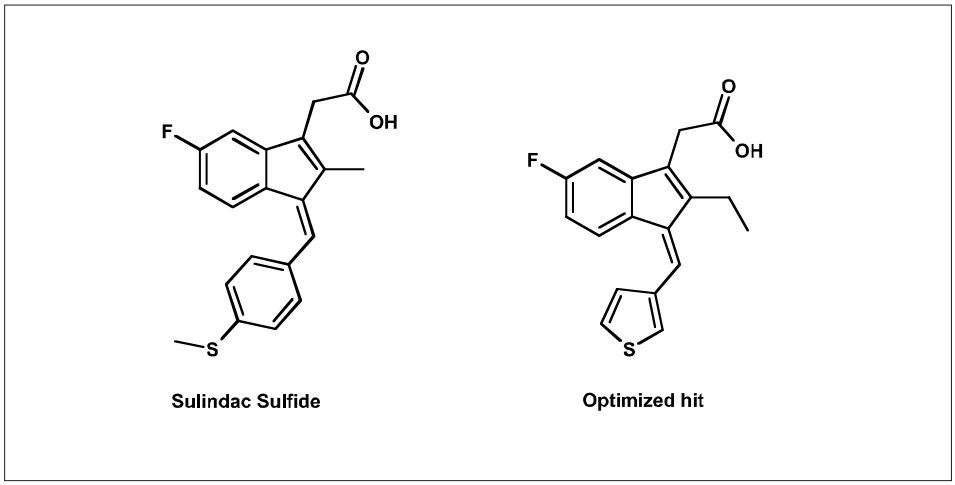

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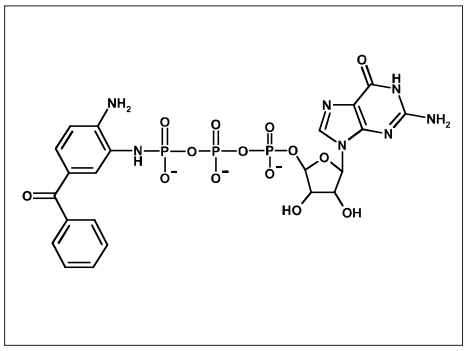

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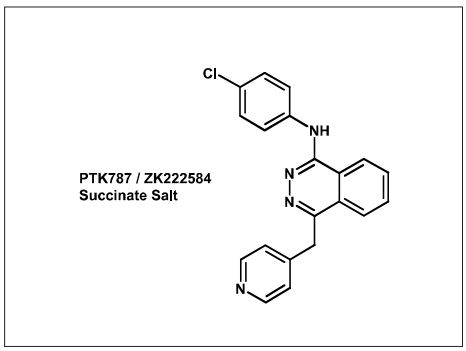


Fig. 13.

investigates the Ras-protein as a drug target [33].

Ras is the prototype of a superfamily of proteins, the Ras-related GTP-binding proteins with mol. wt. of 20–25 KDa, with the ability to bind guanine nucleotides. They function as molecular switches by cycling between a GTP-bound active state and a GDP-bound inactive state. They regulate a multitude of signaling proteins being involved in communication between cells and also of transport factors regulating the delivery of material between cellular compartments.

Three approaches of anti-Ras drugs were presented: The anchoring of the Ras proteins to the plasma membrane is mediated by lipid groups. Farnesylation is essential to Ras function. Farnesyltransferase inhibitors have been investigated extensively, some of which have progressed to PL 2 and 3 clinical trials. Recent investigations deal with palmitoyltransferase, in particular the acyl protein thioesterase 1 (APT1).

A second approach targets the Ras-Raf-1 interaction. It was found in a high-throughput screen that the non-steroidal anti-inflammatory drug Sulindac sulfide (Fig. 11) inhibits this protein–protein interaction. Libraries of >250 Sulindac-type structures were prepared, of which nine compounds turned out to be promising inhibitors.

To switch off GTP-binding proteins, bound GTP has to be hydrolyzed to GDP. If the GTP hydrolysis is impaired, these proteins are permanently switched on. Mutated forms of Ras act as oncogenes in human tumors. The 3,4-diamino-benzophenone-phosphoramidate of GTP (DABP-GTP) (Fig. 12) allows inactivation of oncogenic GTP-binding proteins with a rate acceleration of up to 1000-fold [34].

Jeanette M. Wood (Novartis, Basel) leads the Novartis angiogenesis platform. Angiogenesis is the formation of new blood vessels from existing blood vessels. Neovascularization contributes to the pathophysiology of inflammatory and proliferative diseases, such as cancer, rheumatoid arthritis, psoriasis and ocular neovascularization. One of the mediators of angiogenesis is the vascular endothelial growth factor (VEGF), whose signaling is transmitted by VEGF receptors expressed specifically on endothelial cells. The VEGF pathway can be modulated by low molecular weight synthetic molecules targeting the VEGF receptor tyrosine kinases.

The aniline-phtalazine PTK787/ZK222584 (Fig. 13) was discovered by high-throughput screening and inhibits VEGF receptor tyrosine kinases in submicromolar concentrations (VEGF-R1/Flt-1: IC_{50} = 77 nM; VEGF-R2/KDR: IC_{50} = 37 nM; VEGF-R3/Flt-4: IC_{50} = 664 nM; PDGF-R: IC_{50} = 580 nM; c-kit: IC_{50} = 730 nM). The compound is not active against kinases such as EGFR, FGFR-1 or c-src.

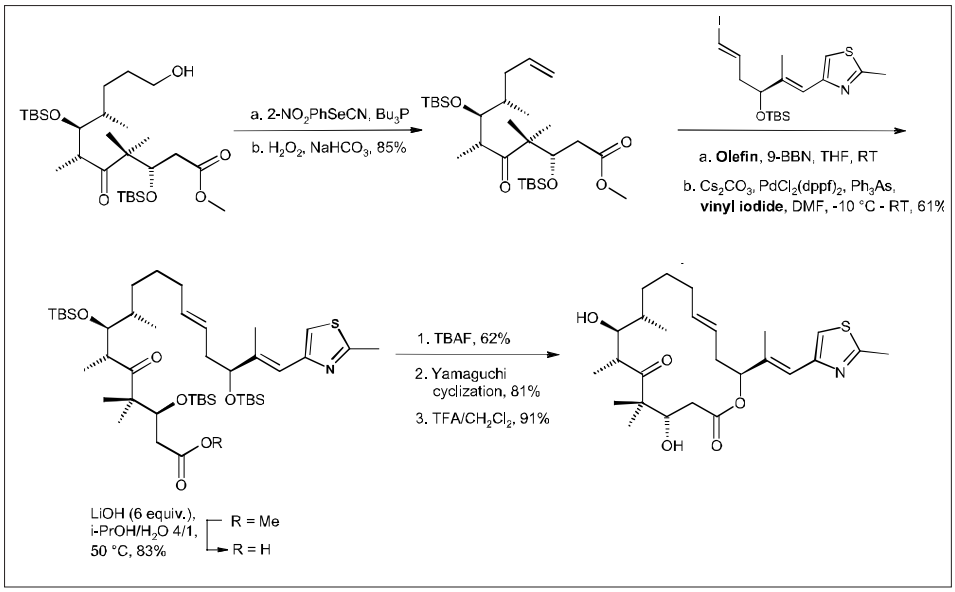
PTK787/ZK222584 is developed in a collaboration of Novartis AG and Schering AG and is currently in PL 3 clinical trials for the treatment of colorectal cancer.

Karl-Heinz Altmann (ETH Zürich) described the contributions of his former group at Novartis to the syntheses and biological characterization of analogues of Epothilone B (R = Me) (Fig. 14), a microtubule depolymerization inhibitor, which is 3–30 fold

more potent as inhibitor of human cancer cell growth than paclitaxel. Epothilone B is currently in PL 2 clinical trials.

In particular, derivatives with modifications of the C(9)-C(12) region (epoxide site) and the heterocyclic side chain were synthesized in a highly convergent general strategy (Scheme 5). This involved a stereoselective synthesis or the terminal olefin, which underwent smooth B-alkyl Suzuki coupling with the vinyliodide and subsequent Yamaguchi cyclization (for synthetic details see [35]).

Alex N. Eberle (University Hospital Basel) focuses on the synthesis of α-MSH peptides conjugated to DOTA, a universal metal chelator, which binds *e.g.* radioactive ^{111}In ($t_{1/2}$ = 67.9 h). These constructs are used for melanoma tumour diagnosis as well as for internal radiotherapy. It was shown that the radioactivity was concentrated exclusively in and localized throughout the tumour tissue. The ratios of radioactivity in melanoma tissue to that in non-target tissue 4 h after injection were as high as 100 except for liver and kidneys. This is the main objective to find modified DOTA structures such as Bz-DTPA, TETA or DOTATOC. The best ratio tumour/kidney was achieved by the complex of DOTA with a newly designed α-MSH octapeptide analogue [β-Ala^3-Nle^4-Asp^5-D-Phe^7-Lys^{10}] α-MSH$_{3-10}$ (MSH$_{oct}$) with ^{111}In [36].



Scheme 5.

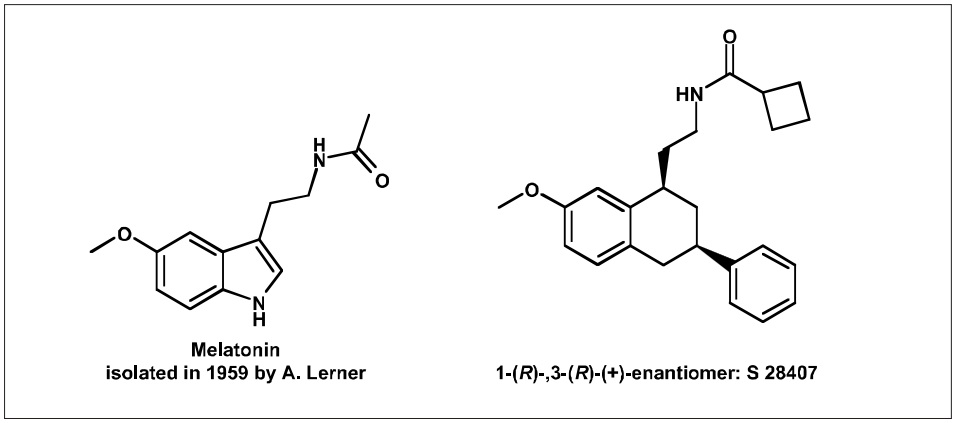


Fig. 15.

5. Prizes

Sophie Durieux-Poissonnier (University of Lille) received the "Prix de Vocation en Chimie Thérapeutique" donated by Servier. She presented new melatonin receptor 2 antagonists (Fig. 15) with subnanomolar affinities for MT_2 receptors and selectivities over MT_1 of up to a factor of 880 [37][38].

86 posters were on display during all three days of the conference. All eight members of the Scientific Committee participated actively in the selection of the two best posters.

Anne Décor (Institut de Chimie des Substances Naturelles, Gif-sur-Yvette) presented structure activity relationships of ring B modifications of (–)-Rhazinilam (R1 = R2 = H) (Fig. 16), a naturally occurring cytotoxic agent (Poster 8).

Samantha M. Benito (University of Basel) received the second poster prize. By self-assembling of block copolymers hollow nanocapsules or nanocontainers can be obtained. Active targeting is facilitated when specific receptors, such as the scavenger receptor A1 (SRA-1), are expressed by targeting cells. Biotinylated nanocontainers were coupled *via* streptavidin to the oligoribonucleotide polyG ligands to produce active targeting drug delivery complexes (Poster 78).

6. Final Remark

In summary the Second Joint French–Swiss Meeting on Medicinal Chemistry in Beaune 2003 was a scientifically very rewarding meeting in a lovely surrounding. We from the organizing committee (Jean-Jacques Bourguignon for the SCT and the author for DMC) hope that our successors will organize the third meeting of this series in due time.

Received: December 30, 2003

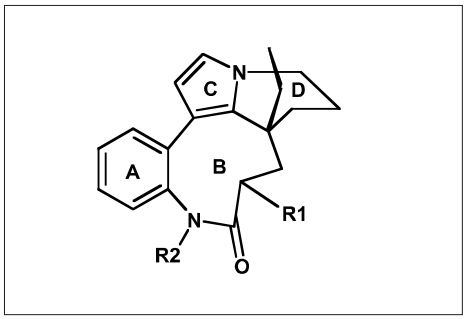


Fig. 16.

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