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Frontiers in Medicinal Chemistry – Joint German-Swiss Meeting on Medicinal Chemistry

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Abstract: The 2007 congress Frontiers in Medicinal Chemistry was organized as a joint German–Swiss meeting on medicinal chemistry and was held at the Freie Universität Berlin. It focused on the areas of antiinfectives and tropical diseases, CNS disorders and neurodegeneration, and on oncology. Two additional sessions on new technologies and metabolism and on 'highlights' completed the program. The lectures covered a broad range of interdisciplinary topics, defining disease state, applying technologies to screen for pathological targets, molecular design and lead optimization programs, and challenges and aspects of industrial syntheses and process research.

Keywords: Antiinfectives · CNS disorders · Highlights in medicinal chemistry · Metabolism · Neurodegeneration · Oncology · Technologies · Tropical diseases

The Event

This congress was the third joint German–Swiss Chemistry Meeting following the ones in Freiburg i. Br. (1987) and Basel (1999). It was jointly organized by the Medicinal Chemistry Division of the Gesellschaft Deutscher Chemiker (GDCh), chaired by Dr. *H. U. Stilz*, the Division of Pharmaceutical/Medicinal Chemistry of the Deutsche Pharmazeutische Gesellschaft (DPhG), chaired by Prof. *B. Clement*, and the Division for Medicinal Chemistry of the Swiss Chemical Society, chaired by Dr. *H. P. Märki*. The congress took place in Berlin at the Freie Universität and was hosted by Prof. *H.-U. Reissig* (FU Berlin) and Prof. *E. Ottow* (Bayer Schering Pharma). About 300 participants came to Berlin. The welcome addresses were given by Prof. *R. Tauber* (Vice President of the FU Berlin), Prof. *H.-U. Reissig* and Dr. *H. P. Märki*.

Opening Lecture

The opening lecture was given by Prof. ***J. Clardy*** (Harvard Univ., Medical School, Boston) entitled 'New compounds from nature' and was chaired by Dr. Stilz.

Prof. Clardy presented an overview on the process of the discovery of natural products as potential new medicines. He outlined the traditional methods (organism, extraction, assay, molecule, biosynthesis) *vs.* the new approaches (organism, DNA, heterologous expression of genomic libraries, assay, molecule, biosynthetic genes). The new paradigm makes use of bacterial artificial chromosome vectors to construct libraries of genomic DNA of microorganisms.[1] DNA can also be directly isolated from soil samples as 'environmental' DNA.[2] The advantages of the new method include the fact that the full scope of microsomal diversity can be explored, and that there is no need to develop fermentation methods to produce the molecules later on as this approach gives straight excess to DNA conferring production.

The discovery of the two antibiotics pantoicyn A and B, derived from heterologous expression of a genomic DNA library from *Pantoea agglomerans* in *Escherichia coli*, served as an example to illustrate the method (Fig. 1). *P. agglomerans* is a non-pathogenic bacterium closely related to *Erwinia amylovora* which causes the devastating disease fire blight of rosaceous plants such as apple or pear trees.

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Dr. H. P. Märki

Dr. H. U. Stilz (left) with Prof. J. Clardy

As a second example Prof. Clardy presented bacillaene, a bacterial metabolite that was discovered through a combined phenotypic/genetic screen by coupling a differential NMR spectroscopic technique with genetically manipulated strains of *Bacillus subtilis*.[3]

Antiinfectives and Tropical Diseases

This session focused on the discovery of new therapeutics against tropical diseases and covered a broad area of interdisciplinary research with lectures on 'Structure-based Design Approaches' (Prof ***F. Diederich***, ETH Zürich), 'Structural Biology in the Search of New Therapeutics' (Prof. ***W. Hol***, Univ. of Washington), 'New Approaches in the Fight Against Tropical Diseases' (Prof. ***A. Matter***, Novartis Institute of Tropical Diseases, Singapore). Furthermore, medicinal chemistry optimization programs were presented in the area of malaria; 'Synthetic Peroxides and Novel Diamidines for Malaria and African Sleeping Sickness' (Prof. ***R. Brun***, Swiss Tropical Institute, Basel), antibacterials; 'Chemical Postevoluation of Antibacterial Natural Products' (Dr. ***D. Häbisch***, Bayer, Wuppertal) and antiprotozoic agents; 'Development of Benzophenone Derivatives as Anti-protozoic Agents' (Prof. ***M. Schlitzer***, Univ. of Marburg).

The session was opened by the lecture of Prof. Diederich on 'Structure-based Design Approaches in the Development of New Leads Against Infectious Diseases'. The main focus was on design and synthesis of new antimalarial drugs with a novel mode of action to overcome multi-drug resistance. Prof. Diederich outlined several approaches; one targets the non-mevalonate (MEP) pathway of isoprenoid synthesis which assembles C_5 precursors to terpenes, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) (Fig. 2). The non-mevalonate pathway is the sole source for IPP and DMAPP in higher plants and many bacteria including *Mycobacterium tubercolosis* and the protozoan *Plasmodium* parasites. Since mammals exclusively utilize the mevalonate pathway, the development of small-molecule compounds that inhibit specifically the enzymes of the non-mevalonate pathway may be a key step towards new antimalarial drugs, as pointed out by Prof. Diederich. Two design programs were discussed: inhibition of the enzymes IspE and IspF.

IspE, the fourth enzyme in the pathway, is a kinase which catalyses the phosphorylation of the 2-OH group of 4-diphosphocytidyl-2C-methyl-D-erythritol to give 4-diphosphocytidyl-2-C-methyl-D-erythri-

Prof. F. Diederich, Dr. Gölitz

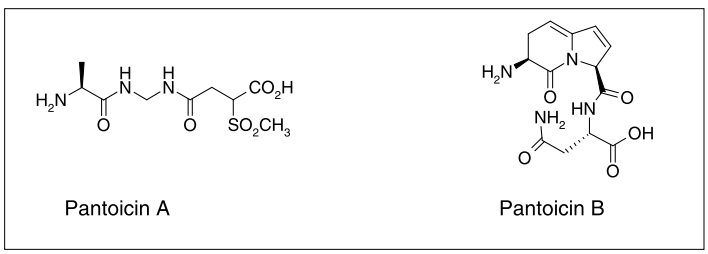

Fig. 1.

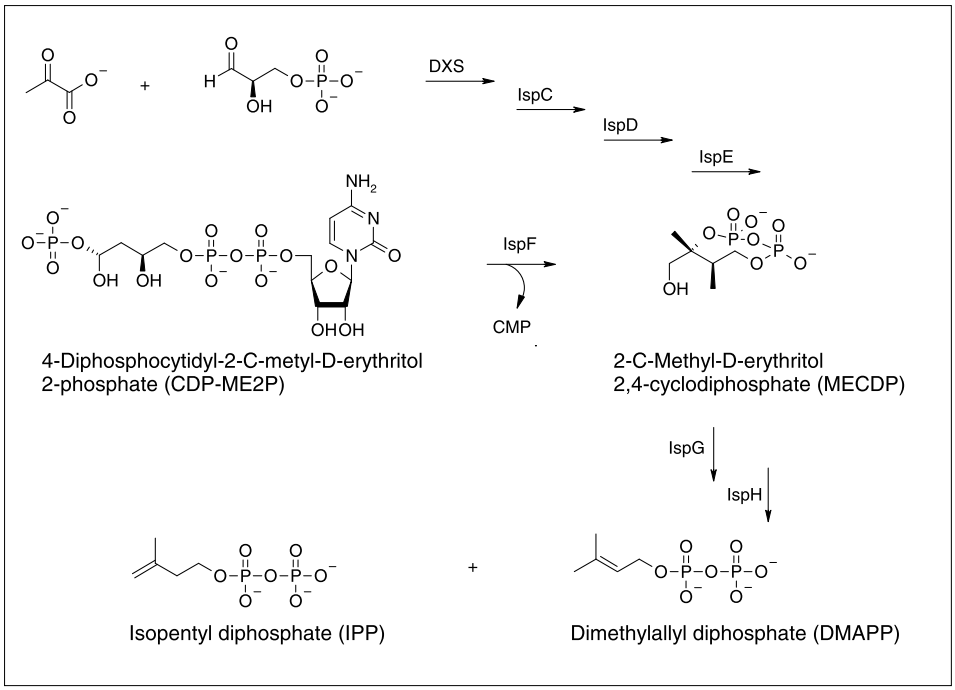

Fig. 2.

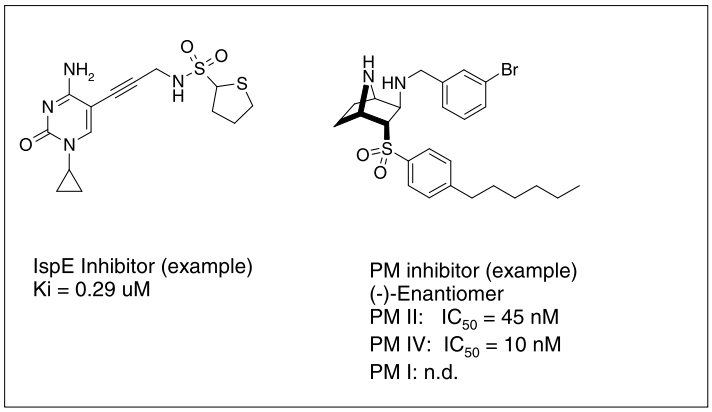

Fig. 3.

tol 2-phosphate (CDP-ME2P). Molecular design led to the identification of the first non-phosphate based competitive inhibitors in the nanomolar range which bind to the substrate site and a small newly detected hydrophobic sub-pocket at the active site, and not to the ATP site as most known kinase inhibitors (Fig. 3).[4]

IspF was presented as further target to interrupt the MEP pathway. It is the fifth enzyme in the cascade and catalyses the cylisation of 4-diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate (CDP-ME2P) to produce the key diphosphate intermediate 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (MECDP). Molecular design based on the crystal structure of IspF and targeting the substrate binding pocket (for the cytidine and erythritol moieties) led to compounds with binding affinities in the low micromolar range.[5]

In the search for new antimarials Prof. Diederich also outlined a program to inhibit the plasmepsins (PMs: PM I–IV), a family of *Plasmodium* aspartic proteases that digest human hemoglobin and deliver amino acids that are required for growth of the parasite. The PM II structure has been characterized and was used as starting point to design inhibitors targeting the active site of the enzyme, the catalytic site and the 'flap' pocket. Although designed for PM II the compounds are also active against PM I and PM IV (Fig. 3).[6]

Prof. Brun (Swiss Tropical Institute, Basel) gave on overview on the major tropical diseases and their epidemiological aspects: 11% of the world population is affected, but only 1% of novel drugs are developed to treat these diseases.

He outlined the list of 'neglected' and 'most neglected' tropical diseases, according to the WHO definition, where little or no industrial research is being pursued, like cholera, dengue fever, African sleeping sickness, leishmaniasis, Buruli ulcer and Chagas disease. He summarized recent initiatives to overcome this situation with the set-up of public–private partnerships (PPPs): the Medicines for Malaria Venture (MMV) and Drugs for Neglected Diseases Initiative (DNDi), with the Bill and Melinda Gates Foundation as key funder.

From the MMV initiative he outlined a program aimed towards novel synthetic peroxides as antimalarials. The goal is to develop cheap synthetic peroxides derived from artemisin that is a very efficient but an expensive natural antimalarial. Since the mode of action of artemisin has been elucidated (decomposition of the endoperoxide pharmacophore to radicals by hemoglobin erythrocytes, thus damaging the parasite that lives within), a discovery program on synthetic trioxolanes and trioxanes (>300 compounds tested) led to the experimental drug OZ 277 that has passed Phase I, II clinical studies in combination with piperaquine (Fig. 4). However, development is currently on hold due to lower than expected exposure in patients. Further studies might be funded by Ranbaxy.

Prof. Brun also outlined programs for treatment of the African sleeping sickness. This disease has two characteristic stages, the haemolymphatic stage and the chronic one during which the CNS is affected. This second stage is especially difficult to treat, because known drugs such as the arsenic melarsoprol do not cross the blood-brain barrier. New compounds that originate from a series of diamidines are currently being developed and have to be given in the form of pro-drugs (oral bioavailability is important because of the low standard of medical care) (Fig. 5). DB 289 is currently in Phase III clinical studies, but proved to be not very efficacious in the late stage of the disease. DB 844 is a preclinical compound under evaluation and is active in mouse CNS models of the late stage of sleeping sickness. In regard to mode of action, the compounds bind to the minor groove of the DNA, but this seems not to be the only target.

The talk of Prof. Matter (Novartis Institute for Tropical Diseases, NITD, Singapore) focused also on the health problems in the developing world, with the three major killer diseases HIV/AIDS (42 million infected, approx. 4 million dying/year), malaria (350–500 million infected annually, approx. 2 million dying/year) and tuber-

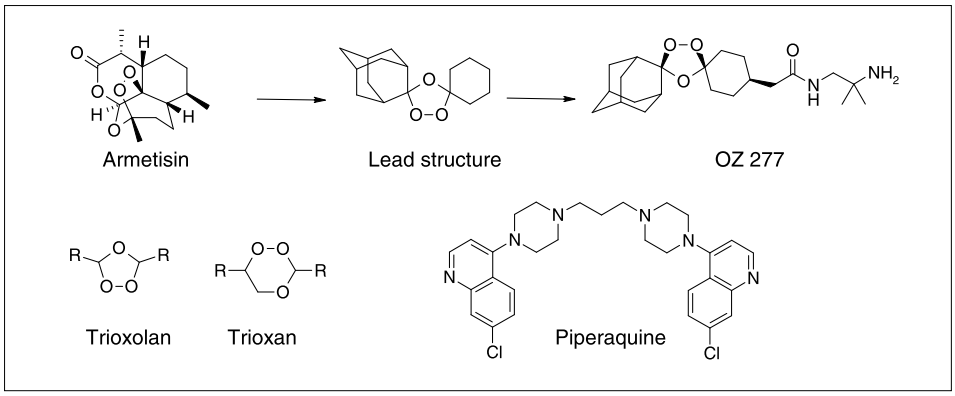

Fig. 4.

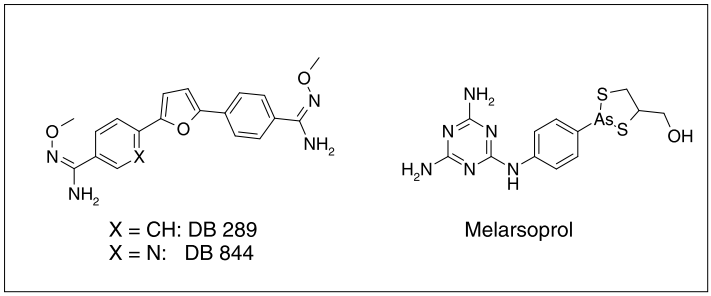

Fig. 5.

culosis (2 billion latently infected, 9 million new cases/year, 1.75 million dying/year). As he pointed out, these diseases are neglected by the established pharma industry, and new forms of collaboration had to be created, like the private partnership of Novartis with the Singapore government whose business model he outlined in some detail.

Prof. A. Matter

As examples of current research focus of the Institute, he presented a program towards novel treatment of dengue fever, a mosquito-borne viral disease for which no specific treatment is available (dengue vaccines are in clinical development but of unproven efficacy and safety). From analysis of translation of genes of the virus the N2B/NS3 protease has been selected as target for a rational design program that is ongoing at the Institute, based on the known structure of the enzyme (published in 2006).

Another topic that he discussed was the peptide deformylase (PDF) as a new antibacterial target. This originates from research performed at the Novartis Institutes for BioMedical Research (NIBR) and has been taken up by the NITD. PDF is preserved across bacterial species; the gene is essential in bacteria and some parasites, but not required in eukaryotes, and the target is distinct from that of current antimicrobials in clinical use. It is a metallo-enzyme with the opportunity for rational design and combinatorial chemistry approach, as pointed out by Prof. Matter. PDF inhibitors have been optimized and selected for MDR tuberculosis and *Mycobacterium tuberculosis* (Mtb) activity, *e.g.* NVS-KAA562, NVP-LCD320 (Fig. 6).

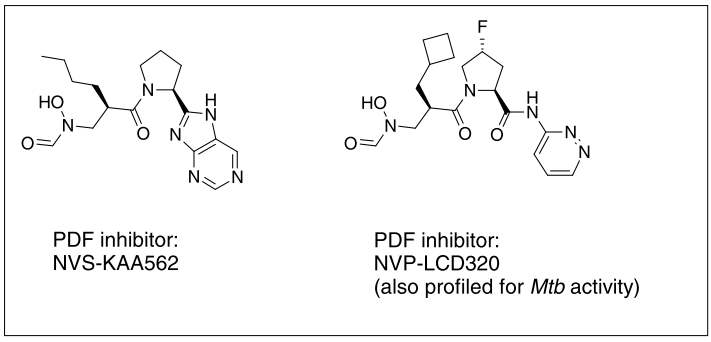

Fig. 6.

CNS Disorders and Neurodegeneration

The main focus was on Alzheimer's disease with the presentations of Dr. ***H. Jacobsen*** (Roche, Basel) on 'Pathologies of Alzheimer's Disease and Perspectives for Causal Treatment' and Dr. **J. E. Audia** (Lilly Research Laboratories, Indianapolis) entitled 'Testing the Amyloid Hypothesis: Optimization and Characterization of Novel Small Molecule Functional γ–Secretase Inhibitors'.

Dr. Jacobsen outlined the epidemiology of neurodegenerative diseases (prevalence for AD: 5.8 Mio in 2005, annual increase rate 2.4%) and discussed the different therapeutic approaches: symptomatic (cholinergic, glutamineric), disease modifying (amyloid, tau) and neuroprotective (neuronal cell death pathways, neurotrophic factors, inflammation/oxidative stress and axonal transport systems).

He referred to the genetics of Alzheimer's disease (AD): The majority of AD cases are sporadic and 5% are genetic, but all mutations of disease genes (APP, PS1, PS2 and others) lead to increase in Abeta 42. He introduced the amyloid cascade hypothesis which comprises that AD is triggered by an imbalance in Abeta production and clearance and discussed the possible points of intervention.

Current focus is to find inhibitors of the two aspartyl proteases involved in the production of Abeta, BACE1 (β-secretase) of which an X-ray structure is known, and γ-secretase. Both are essential for the production of Abeta from membrane bound APP (amyloid precursor protein).

Advanced compounds as potent β-secretase inhibitors have been identified and are active in cell assays (Fig. 7). However, so far no robust *in vivo* activity has been demonstrated, as pointed out by Dr. Jacobsen.

With respect to selective γ-secretase inhibitors, there are advanced compounds in Phase II clinical trials (LY450139) (Fig. 8). For potential challenges and pitfalls in view of the development of γ-secretase inhibitors, Dr. Jacobsen outlined the Notch issue: γ-secretase cleaves the substrate within the transmembrane domain and has low cleavage site specificity. Notch is also a substrate for the enzyme, and Notch cleavage products are signaling peptides, essential for cell division in adult organism.

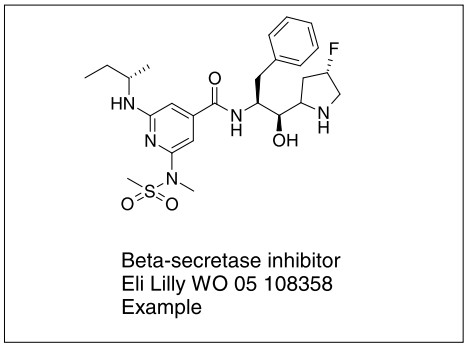

Fig. 7.

He also gave an overview on the available animal models, with transgenic mice having become the model of choice for AD. These mice expressing the human disease genes show extensive amyloidosis, have impairments in behavioral tests for cognition and memory, but lack some important aspects of AD pathology: they show no or little neuronal loss, only minor neuroinflammation. It was pointed out that current goal is to have disease modifying drugs, and that a clinical proof of the amyloid hypothesis is still missing. He also referred to biologicals, the anti-Abeta monoclonal antibodies (mAbs) that might play an important role in the future. Several anti-Abeta mAbs are currently in Phase I clinical trials.

In the subsequent lecture, Dr. Audia gave an account of the medicinal chemistry program that has been pursued at Eli Lilly to develop selective inhibitors of γ-secretase.

Starting from a screening hit, this was then optimized for potency in cell-based assays and pharmacokinetic properties (oral bioavailability and brain/plasma ratios >10). Acute and sub-chronic activity was tested in transgenic PDAPP mice. Regarding the issue of Notch processing, functional assays were set-up as well as an *in vivo* rat model (% decrease of GI tract weight and body weight). From this program LY450139 was finally selected for clinical development and is currently in Phase II. The compound

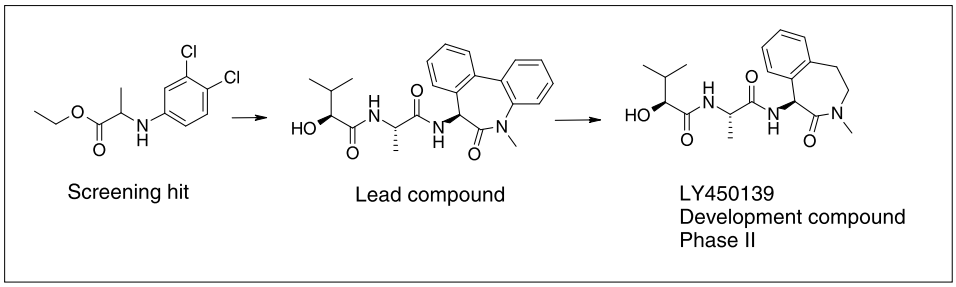

Fig. 8.

Dr. J. E. Audia

shows robust i*n vivo* efficacy, with dose-dependent reduction of plasma Abeta as biomarker.

Oncology

The oncology session covered key areas of current therapy with the talks of Prof. ***M. Trikha*** (Genentech, San Francisco) on monoclonal antibodies (mAbs) for treatment of cancer, Dr. ***P. W. Manley*** (Novartis, Basel) on the discovery and development of new small molecule tyrosine kinase inhibitors of the BCR-ABL onocprotein (nilotinib), Prof. ***M. Kalesse*** (Univ. of Hannover) on the use of natural products as leads in oncology research, and Dr. ***K. Schiemann*** (Merck KgaA, Darmstadt) on the development of selective inhibitors of the mitotic kinesin-5.

Prof. Trikha gave an overview of the key differences between biologicals (mAbs) and small molecules in regard to development. He further referred to the different pathways involved in tumor progression, described the different types of antibodies either approved or in development, and the preclinical tumor models. He discussed the points to be considered for antibodies during early drug development and outlined new developments in the field, the design of antibody drug conjugates.

As Prof. Trikha pointed out, there is need for tissue cross-reactivity studies and immunogenicity studies for biologicals (mAbs), but there is no necessity for toxicological studies in relevant species as antibodies are tailored for human and are not active in animals.

Regarding preclinical tumor models, their value is limited due to the high species specificity of antibodies. Mouse models are mainly used for identifying the optimal application schedule and for chemo-combination studies. In general, no major non-clinical safety related 'show stoppers' are identified with mAbs; however, in contrast to small molecules they are expensive to manufacture.

New developments that are currently in clinical trials (at Genentech) comprise antibody drug conjugates, conjugating small molecule anticancer drugs with mAbs as targeted chemotherapy, exploiting synergistic effects from antibody and drug through selective delivery to tumor cells. The small molecule drug needs to be highly active because of the low mAb concentration applied.

Dr. Manley (Novartis, Basel) outlined a program towards second-generation BCR ABL kinase inhibitors currently in development for the treatment of imatinib-resistant chronic myelogenous leukemia (CML). Imatinib (Glivec), a small-molecule ABL kinase inhibitor which has established a new paradigm of targeted anticancer therapy, is a highly effective drug for the treatment of early-phase chronic myeloid leukaemia (CML), a disease characterized by constitutively active ABL kinase activity owing to the expression of the BCR-ABL fusion protein. However, there is a considerable relapse rate among late-stage patients owing to the development of mutations in the ABL kinase domain that cause drug resistance.

The development of the phenylaminopyrimidine derivative nilotinib (AMN107, Novartis) was based on rational drug design, analyzing the crystal structures of inhibitors in complexes with ABL. It is about 30-fold more potent than imatinib as an ABL inhibitor and much more selective (Fig. 9). Nilotinib has completed Phase II clinical trials in imatinib-resistent CML patients and has been submitted for regulatory approval, as pointed out by Dr. Manley.

Technologies and Metabolism

The technology session focusing mainly on drug metabolism was chaired by Dr *M. Böhringer* (Roche, Basel). Lectures were given on 'Prediction of Human Metabolism' (Prof. ***G. Cruciano***, Univ. of Perugia), 'Minimizing the Potential of Metabolic Activation in Drug Discovery' (Dr ***A. S. Kalgutkar***, Pfizer, Groton, USA), 'Detection of Reactive Metabolite Formation in Early Drug Discovery' (Dr. ***T. A. Baillie***, MSD, West Point, USA) and on the 'Role of Pharmacologically Active Metabolites in Drug Discovery and Development' (Dr. *A. Fura*, Pfizer, Princeton, USA).

Dr. Baillie outlined the concept and showed evidence that small organic molecules can undergo bioactivation *in vivo* and that the resulting electrophiles (highly reactive intermediates) can adduct to biological macromolecules and elicit organ toxicity. He mentioned early studies providing strong evidence for the 'covalent binding theory' of xenobiotic-induced liver and lung toxicity. Dr. Baillie summarized the strategy at MSD to identify reactive metabolites early during lead optimization

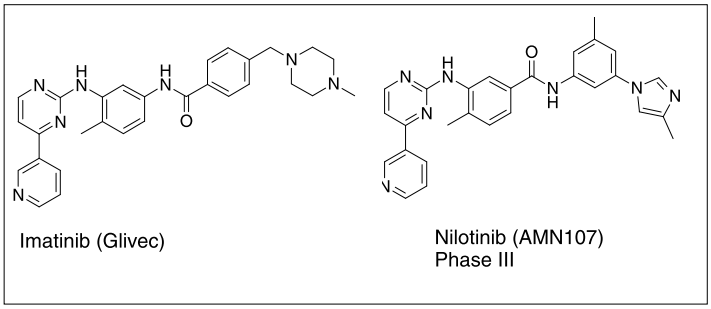

Fig. 9.

by the use of trapping agents like reduced gluthathione and cyanide, to form stable adducts that are amenable to characterization by LC-MS/MS. The trapping experiments are conducted in liver microsomal preparations. Based on this knowledge on biotransformation, a case study was presented where reactive intermediate formation that occurred *via* arene oxide formation on biological activation was avoided by small structural changes (*via* halogen aryl substitution and exchange of heterocylic cores (Fig. 10).

Dr. Kalkutgar covered the same topic of reactive metabolite formation and how to prevent it by introducing specific structural changes. He outlined a case study at Pfizer where selective hetero-aromatic fluorination eliminated the liability. The structural modifications were also based on the knowledge obtained from bioactivation studies in microsomes with trapping reagents (GSH).

Another topic, the development of fluorescence probes as tools to study cell function, was covered by the lecture of Prof. ***Y. Urano*** (Univ. of Tokyo) entitled 'Development of Novel Functional Fluorescence Probes Based on Rational and Flexible Design Strategies'. Prof. Urano summarized his work on the synthesis of fluorescence probes for continuous observation of dynamic intracellular processes in living cells. The design of the new probes was based on the fluoresceine molecule using the concept of intramolecular photoinduced electron transfer (PeT) and by changing the electron donor-acceptor system. Selective probes for singlet oxygen,[7] nitric oxide,[8] highly reactive oxygen species[9] and peroxynitrite[10] are now available.

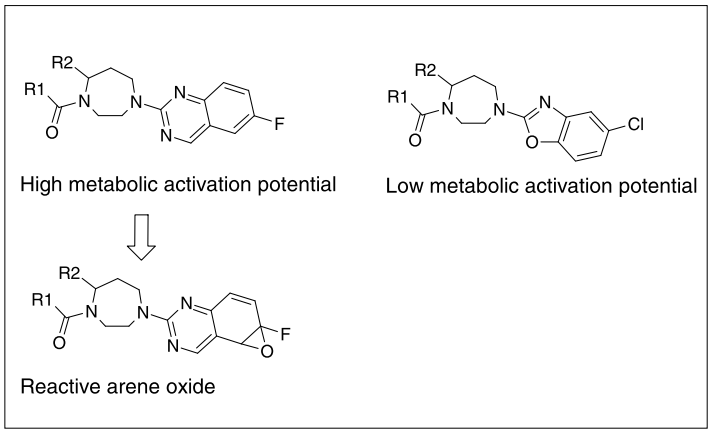

Fig. 10.

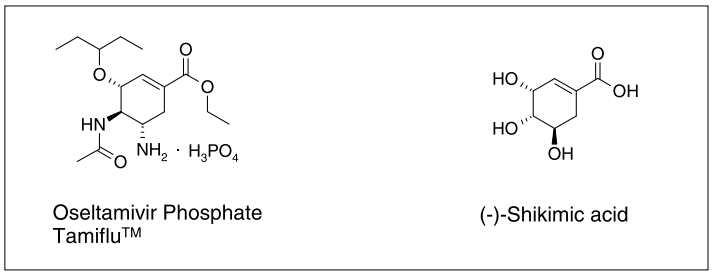

Fig. 11.

Highlight Sessions

There were two highlight sessions scheduled, the first one comprising lectures from Dr. ***M. Karpf*** (Roche, Basel) on 'The Synthetic Development of the Anti-influenza Neuramidinase Inhibitor Oseltamivir', and from Prof. ***C. A.A. van Boeckel*** (Organon, Oss, Netherlands) on synthetic heparins and novel carbocarrier technology in this field.

Dr M. Karpf outlined the role of neuraminidase in influenza virus replication, cleavage of terminal sialic acids from the infected cell surface, a prerequisite for the release of newly formed virus particles.

He gave then an overview on the syntheses that have been developed for the neuramidinase inhibitor drug oseltamivir (Tamiflu™). Dr. Karpf compared the original drug discovery synthesis from GILEAD that comprised 16 steps from (−)-quinic acid with an overall yield of ~10% with the current industrial synthesis developed at Roche, reduced to ten steps from (−)-shikimic acid with an overall yield of ~35% (Fig. 11). The source of shikimic acid is chinese star anis of which 13 g give about 1.3 g of shikimic acid after extraction. He summarized the results of Synthesis & Process Research work done at Roche to evaluate synthetic routes independent of shikimic acid, including Diels-Alder strategies, the 'furan Diels-Alder/nitrene-addition' concept, and an 'aromatic ring transformation and desymmetrization' strategy starting from pyrogallol.[11]

The second highlight session comprised lectures from Dr. ***L. Yang*** (MSD, Rahway, USA) on 'Small Molecule CCR2 Antagonists for Treatment of Inflammatory and Autoimmune Diseases' and Prof. ***E. M. Carreira*** (ETH Zürich) entitled 'Surprises and Discoveries with Natural Products'.

Prof. Carreira gave an overview on some recent research work covering different topics: synthesis and application of oxetanes as promising modules in drug discovery,[12] investigation into mode of action of the antimycotic agent amphotericin B, the synthesis of amphotericin derivatives as probes to obtain new insights into membrane biology, fluoresceine conjugates as probes to address location,[13] and the synthesis of new derivatives with improved properties, like lower hematotoxicity.[14]

Prof. E. M. Carreira with Dr. H. U. Stilz

He further discussed the total synthesis of deoxy-amphotericin B and new synthetic methodologies his group has recently developed ('Copper-BINAP' aldol reaction, asymmetric Zn-acetylide addition to aldehydes, nitrile oxide cycloaddition to alkenes).

Short Lectures

The meeting also offered a forum for young scientists to present their work; the following presentations were selected: 'Functionalized Pyrrolidines: A New Class of HIV-Protease Inhibitors' by Dr. *W. E. Diederich* (Univ. of Marburg), 'Pharmacological and Theoretical Characterization of Histamine H1 Receptor Species Isoforms'

by Dr. *A. Strasser* (Univ. of Regensburg), and 'Chemoselective Synthesis of Cyclic Peptides *via* Traceless Staudinger Ligation' by Dr. *C. P. R. Hackenberger* (FU Berlin).

Posters and Prizes

About 100 posters were presented of which three were recognized by the scientific committee with a prize. *S. Kuettel* (University of Geneva) received an award for her work on identification of new targets in *Trypanosoma brucei rhodesiense*, the causative agent of the acute form of African sleeping sickness through a chemical proteomics approach. The other two awards went to *A. Blum* and *J. Boettcher* (University of Marburg) for design and synthesis of new HIV inhibitors designed to overcome drug resistance and *U. Wefelscheid* (FU Berlin) for the synthesis of new pentacylic steroid analogues.

The innovation prize dedicated to young scientists for postdoctoral work in medicinal chemistry was given to Prof. *C. Sotriffer* (Univ. of Würzburg) for his contributions in the field of protein–ligand complexes, protein flexibility and virtual screening.

Conclusions

The meeting was highly successful, with an excellent scientific program, an international platform that allowed many stimulating discussions and exchange of ideas. It brought together scientists with diverse backgrounds from biology, medicinal chemistry, molecular design and molecular medicine, which was highly rewarding. It is planned to organize a 4th Joint German-Swiss Medicinal Chemistry meeting in 2009.

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