CHIMIA 51 (1997) Nr. 11 (November)

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CONFERENCE REPORTS

Chimia 51 (1997) 841–845

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Section for Medicinal Chemistry (SMC)
of the New Swiss Chemical Society (NSCS)

First Italian-Swiss Meeting on Medicinal Chemistry

Torino, September 23–26, 1997

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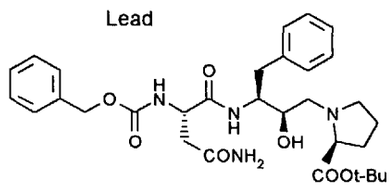

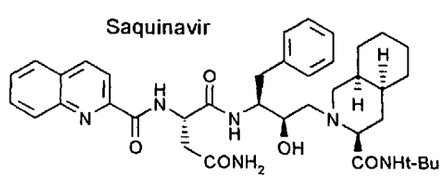

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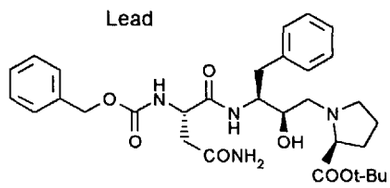
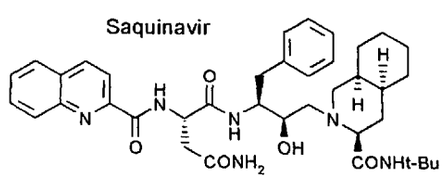
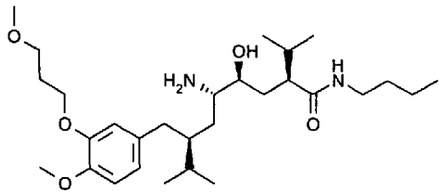


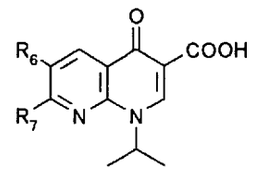


Jürgen Maibaum (*Novartis*, Basel) outlined the design of orally bioavailable peptidomimetic renin inhibitors. Peptide-like transition-state mimetics, as CGP 38560A, provided valuable information on the bioactive conformation of the active site of human renin suggesting that the S(3) and S(1) binding sites constitute a large hydrophobic pocket. A lipophilic P(3) heterocycle (tetrahydroquinoline) was linked *via* an appropriate spacer to a δ-amino-hydroxyethylene dipeptide isoster. An X-ray analysis of recombinant human renin complexed with this inhibitor revealed a hitherto unknown distinct non-substrate binding site. A novel benzyl spacer template additionally substituted with a methoxy-propoxy side chain led to a potent (IC_{50} = 0.7 nM) and *in vivo* effective renin inhibitor (3 mg/kg po: reduction of MAP of 18–20 mm Hg after 0.5 to 1 h lasting for 12 h).

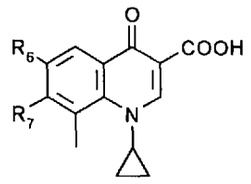


Markus Boehringer (*Roche*, Basel) described efforts to discover β-lactamase-stable antibiotics. The crystal structure of a class C (chromosomally encoded) β-lactamase gave new insight into the architecture of the active site. The β-lactamase attacks the β-lactam to form an acyl-enzyme intermediate. Access of deacylating water molecules is possible only after a rotation around the axis of this bond. By bridging monobactams, carbacephems, and isocephems with an additional ring (annelated pyrrolidine) this rotation can be prevented leading to both class C and A (plasmid-encoded) β-lactamase-stable antibiotics as Ro 48-8391 and Ro 48-5545.

Violetta Cecchetti (Univ. Perugia) investigated the SAR of quinolone antibiotics interacting with the DNA gyrase-DNA cleavage complex. A major improvement over nalidixic acid was the introduction of a fluorine substituent in position 6 with appropriate heterocyclic amines as substituents in position 7. Compounds with increased potency and a broader spectrum were discovered by replacing the nitrogen of the 8-azaquinolones series by a CH or C–CH_3 and replacing the fluorine in position 6 by H or NH_2. 6-Desfluoro-quinolones (*e.g.*, MF 5137) are an independent family of antibacterial agents, which may overcome resistance to current drugs (*J. Med. Chem.* **1996**, *39*, 4952).



R_6 = H R_7 = Me: Nalidixic Acid
R_6 = F R_7 = het. amine

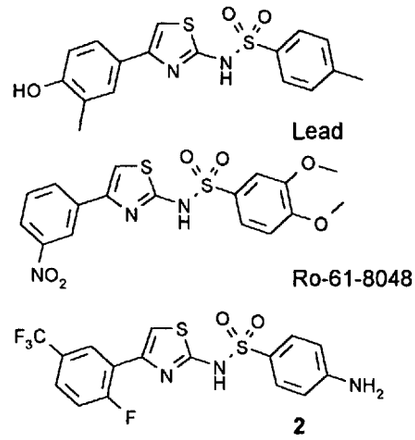


R_6 = H or NH_2
R_7 = het. amine

Gloria Cristalli (Univ. Modena) informed about the SAR's of different classes of adenosine deaminase (ADA) inhibitors. ADA is a key enzyme in purine metabolism converting adenosine and deoxy-adenosine into inosine and deoxy-inosine. Increased ADA activity was found in patients suffering from rheumatoid arthritis, viral hepatitis, and HIV. Adenosine acts as an endogenous antihypoxic and anticonvulsant agent. 1-Deaza-adenosine and its 2'-deoxy derivative were identified as first ADA inhibitors (K_i's = 660; 190 nM). By replacing the sugar moiety of adenosine EHNA (*erythro*-9-(2-hydroxy-3-nonyl)-adenine, K_i = 7 nM) was discovered.

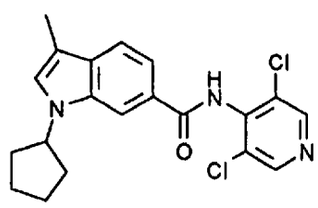
Mario Varasi (*Pharmacia & Upjohn*, Milano) presented novel kynurenate-3-hydroxylase inhibitors as potential neuroprotective agents. Both the neuroprotective endogenous EAA antagonist kynurenic acid and the excitotoxic NMDA agonist quinolinic acid are metabolites of the degradation of L-tryptophan. Blockade of the enzyme 3-hydroxy-kynurenase prevents the formation of quinolinic acid, thus producing larger amounts of kynurenic acid provided that the enzyme kynurenine aminotransferase (KAT) is not blocked as well. Structurally to kynurenine related benzoylalanine was the starting point of a medicinal chemistry program, which led to the discovery of PNU 156561A, *i.e.* (*S*)-3,4-dichlorobenzoylalanine (IC_{50} = 250 nM), which does not block KAT, NMDA receptors, or the MK-801 binding site. The compound showed neuroprotective affects in an ischemia model in gerbils.

Stephan Röver (*Roche*, Basel) showed the first synthesis of tritiated kynurenine and high affinity inhibitors of rat kynurenine-3-hydroxylase. Using high throughput screening a sulfonamide from the *Roche* compound pool was identified (IC_{50} = 110 nM). Variation of the substituents on both aromatic rings led to Ro 61-8048 (IC_{50} = 37 nM) and **2** (IC_{50} = 19 nM) showing good anti-ischemia properties in a gerbil model.



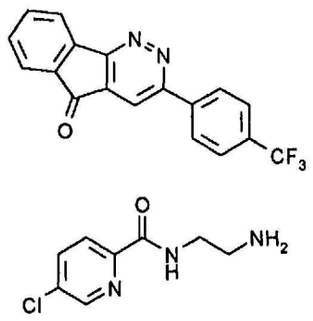
Vittorio Dal Piaz (Univ. Florence) showed selective phosphodiesterase IV inhibitors as potential antiasthmatics and anti-inflammatory agents. A pyrrolopyridazinone derivative showed comparable potency (IC_{50} = 0.6 μM) as rolipram (IC_{50} = 0.3 μM), but was less active at the [^{3}H]rolipram binding site (IC_{50}'s 2 μM *vs.* 6 nM, for rolipram) responsible for CNS side effects as emesis and nausea (*J. Med. Chem.* **1997**, *40*, 1417).

Paul J. Cox (*Rhône Poulenc Rorer*, Dagenham, UK) embarked on a different class of selective phosphodiesterase IV inhibitors as potential antiasthmatics, *i.e.* indole-6-carboxamides. Using ComFA for the optimization *N*-(4-amino-3,5-dichloropyridyl)-1-cyclopentyl-3-methylindole-6-carboxamide was discovered (IC_{50} = 10 nM; [^{3}H]rolipram binding: IC_{50} = 374 nM).



Cosimo Altomare (Univ. Bari) analyzed X-ray structures and 2D and 3D QSAR studies of condensed pyridazines and pyrimidines to obtain information for the design of reversible MAO-B inhibitors as potential antidepressants. This work led to the discovery of 3-phenyl-substituted indeno[1,2-*c*]pyridazine-5-ones. A 4-tri-

fluoromethyl derivative with IC_{50} of 90 nM was comparable to lazabemide (IC_{50} = 30 nM; *J. Med. Chem.* **1995**, *38*, 3874).



Lazabemide

Drugs Acting *via* Receptors

Susanna Cotecchia (Univ. Lausanne) gave a fascinating lecture on the molecular mechanisms of activation of G-protein-coupled receptors. Site-directed mutagenesis studies revealed that the important interaction sites for cationic neurotransmitters (catecholamines), in particular in the α_{1B} adrenoceptor, are an aspartate (D142) on the cytosolic end of TM III for the amino group and serine residues on TM V for the catechol moiety. Systematic point mutations of A293 to all natural aa's conferred a high spontaneous activity to the α_{1B} adrenoceptor, particularly pronounced for E, K, or L mutants. This means that the equilibrium between receptor resting state R and active state R* has been changed towards the active (unconstrained) conformation *via* the constitutively active mutations. Computational simulations of molecular dynamics for the inactive and the active state revealed that R143 in the resting state is buried within TM III. In the constitutively active mutants, R143 rotates out of the polar pocket thus interrupting a network of H-bonds with D91 and N63. A similar activating effect is obtained on protonation of the conserved negatively charged amino acids, as D142. The point mutation D142A changes the receptor back to R (*Proc. Natl. Acad. Scil. U.S.A.* **1997**, *94*, 808).

Carlo Melchiorre (Univ. Bologna), the recipient of this year's *Giacomello* Prize, explained the concept of neutral and negative receptor antagonists. Receptors are in an equilibrium between the inactive state R and the active state R*. Receptor agonists bind preferentially to R*. Receptor antagonists, however, either bind preferentially to R (agonist-independent response: inverse agonists; $pK_i \neq pK_b$) or display the same affinity to R and R* (neutral antagonists; $pK_i = pK_b$). Only the latter are useful for receptor classification. Propranolol (β adrenoceptor), atropin (muscarinic AChR), pirenzepine (M_1 AChR), or prazosin (α_1 adrenoceptor) are negative antagonists, therefore not useful for receptor classification. This may be the reason, why functional results do not agree with binding data obtained with antagonists, *i.e.*, potency and affinity are not necessarily comparable.

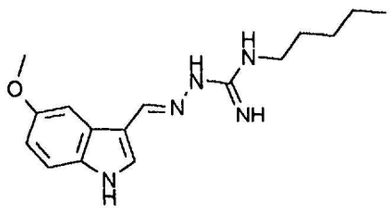
Pier Andrea Borea (Univ. Ferrara) studies receptor-binding thermodynamics as a tool for linking drug efficacy and affinity. Determination of drug-receptor binding constants by radiochemical specific binding assays provide association constants K_a, which allow to calculate the standard free energy, but not the standard enthalpy and entropy, respectively.

$$\Delta G° = -RT \ln K_a$$
$$\Delta G° = \Delta H° - T\Delta S°$$

Several receptors were investigated for their thermodynamic discrimination, whether agonist binding is enthalpy- or entropy-driven. Enthalpy and entropy measurements were carried out using Scatchard plot analyses over a temperature range (*e.g.*, 0 to 35°). Although the phenomenon of thermodynamic discrimination is not yet fully understood, it is most probably due to changes in solvent reorganization in the receptor cavities (See also: E. Grunwald, C. Steel, *J. Am. Chem. Soc.* **1995**, *117*, 5689).

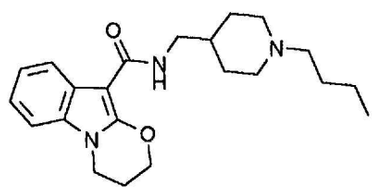
Didier Rognan (ETH-Zürich) works on the structure-based design of nonnatural ligands for class-1 MHC proteins (major histocompatibility complex encoded class-1 proteins), which play a role in the immune surveillance of intracellular pathogens. Starting from the X-ray of human leukocyte antigen protein HLA-B27, the nonapeptide QRLKEAAEK, nonpeptidic ligands were designed: the first aa was exchanged by a β-aa, the third by an unnatural aa, aa's 4–8 by spacers like 4-aminobutyric acid, $(Aba)_3$, 6-aminohexanoic acid, $(Aha)_2$, (*R*)-3-hydroxybutyric acid (HB) tri- or tetramer, and 11-aminoundecanoic acid (Aua). The protein-ligand complexes were analyzed by CD spectroscopy for thermal stability: m.p. for natural MHC protein: 62.8°, for QRL-$(HB)_3$-K: 63.2°.

Hans-Jürgen Pfannkuche (*Novartis*, Basel) gave a comprehensive overview on 5-HT_4 receptors and on 5-HT_4 receptor agonists and antagonists. 5-HT_4 receptors were first characterized pharmacologically by *Joël Bockaert* (Montpellier) in rat collicoli neurons in 1980. Cloned recently, two splice variants were identified: 5-HT_{4S} (387 aa's) and 5-HT_{4L} (406 aa's), G-protein-coupled receptors, positively coupled to adenylylcyclase. (*EMBO J.* **1995**, *14*, 2806). The peripherally active 5-HT_4 receptor agonist, the amino-guanidino-indole SDZ HTF 919 (ZELMAC®) is currently tested in clinical trials for functional motility disorders of the gut (5-HT_4: IC_{50} = 12 nM; 5-HT_3: IC_{50} = 6.3 µM). The potent 5-HT_4 receptor antagonist SB 207266 (IC_{50} = 0.03 nM) is in clinical development for the treatment of irritable bowel syndrom.



SDZ HTF 919

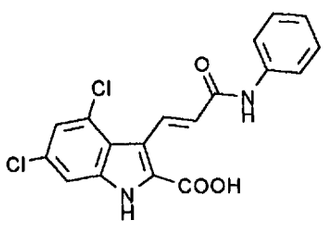
Receptor	Agonist Binding	Antagonist Binding
β-adrenoceptor	H-driven	S&H-driven
adenosine A_1	S-driven	H&S-driven
adenosine A_2	S-driven	H&S-driven
glycine	S-driven	H&S-driven
$GABA_A$	S-driven	H&S-driven
5-HT_3	S-driven	H&S-driven
n-ACh	H&S-driven	S-driven



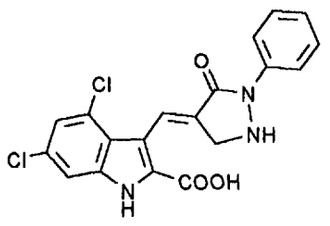
SB 207266

Daniele Donati (*Glaxo*, Verona) showed new results on glycine receptor antagonists as potential anti-ischemia agents. Medicinal chemistry started from 3-car-

boxyethyl-4,6-dichloroindole-2-carboxylic acid (IC_{50} = 140 nM) and led to unsaturated indole-3-carboxylic acid anilide GV 150156A: K_i = 3 nM for recombinant rat GR, K_i = 4 nM for r-human-GR; protects against NMDA induced convulsions: ED_{50} = 0.06 mg/kg iv; 6 mg/kg po. Anti-ischemic effects: MCAO, rat: pre-ischemic admin. ED_{50} = 0.9 mg/kg iv; post-ischemic: ED_{50} = 3 mg/kg iv, reaching the potency of MK-801 without its prohibitive side effects. GV 150156A is in clinical trials. GV 213237A is the follow-up compound (*J. Med. Chem.* **1997**, *40*, 841).

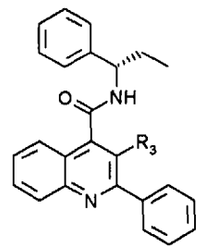


GV 150156A

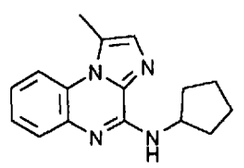


GV 213237A

Luca F. Raveglia (*SK&B*, Milano) showed an interesting approach in the search for non-brain-penetrating NK-3 receptor antagonists. Starting from centrally active 2-phenylquinoline-4-carboxamide SB 223412 (K_i = 1 nM), chemists attached hydrophilic substituents to position 3 to obtain derivatives with $\Delta \log P > 4.5$ ($\log P$ *n*-octanol/water minus $\log P$ cyclohexane/water).



R_3 = OH SB 223412
R_3 = $OCH_2CH_2CH_2COOH$



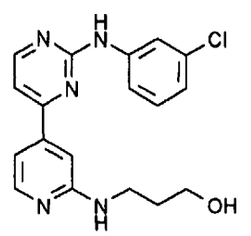
IRFI 165

Stefano Ceccarelli (*Biomedica Foscama*, Ferentino) described antidepressant activities of the non-xanthine adenosine A_1 receptor antagonist IRFI 165, a 4-aminoimidazo[1,2-*a*]quinoxaline (IC_{50} = 8 nM, formula *vide supra*).

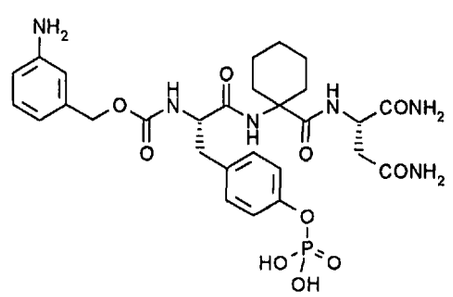
Drugs Interfering with the Signal Transduction Pathway

Paul Burn (*Roche*, Nutley), head of the department for metabolic diseases, presented an outstanding lecture on genomic and molecular biology-based approaches to drug target indentification within signal transduction pathways. Obesity is a disease, which is partially genetically determined. Five mice and one rat mutations served as experimental models for obesity, *ob*/*ob*, *db*/*db*, *fat*/*fat*, *tub*/*tub* and *agouti* mice and *falfa* (or Zucker) rats. *J.M. Friedman* of the Rockefeller University was the first to clone the *ob* protein expressed by the *ob*/*ob* gene (*Science* **1995**, 475, 540, 543, 546). Administration of recombinant *ob* protein to obese animals reduces food intake. ^{125}I-radiolabelled recombinant *ob* protein can enter the brain and binds to *ob* receptors in the choroid plexus and the hypothalamus (*Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 5668). Choroid plexus tissue of 100 mice was used to construct a cDNA library for expression cloning of two splice variants of the *ob* receptor, a single membrane receptor of the cytokine superfamily: *ob*R_L, located in the choroid plexus and *ob*R_S in the arc nucleus. *db*/*db* Mice have a defect on the *ob*R_S splice variant, which does not allow signal transduction in the hypothalamus. It is the *ob*R_L splice variant that provides the 'stop eating' signal. Icv injection of *ob* protein into *ob*/*ob* mice leads to decreased levels of mRNA for NPY in the arcuate nucleus and to increased levels of mRNA for CRH in the PV nucleus. These results suggest that antagonists for NPY and agonists for CRH may reduce energy intake. The *agouti* protein cloned in 1992 is a potent α-MSH antagonist with high affinity to MC-1 and MC-4 receptors. MC-4 R knock-out mice are obese. MC-4 R agonists may reduce body fat.

Jürgen Zimmermann (*Novartis*, Basel) informed about a new class of potent and selective protein kinase inhibitors as antitumor agents. In 1993, an X-ray of a protein kinase was published. By modelling the ATP binding pocket in combination with random screening, a lead of the class of phenyl-amino-pyrimidines was identified. A set of SAR's was combined with the knowledge of SAR's of staurosporine derivatives. Additional spacer groups were attached to mimic the sugar moiety of staurosporine leading to the identification of CGP 60474. (*In vitro* effects: blockade of cell cycle: CDK1, IC_{50} = 17 nM; CDK2, IC_{50} = 50 nM; PKCα, IC_{50} = 310 nM; Erk-1, IC_{50} = 600 nM; *in vivo* effects: arrests tumor growth of human bladder carcinoma grafts on nude mice after ip and po administration.) A combination therapy with adriamycin allows to overcome the Pgp-1 mediated multidrug resistance.



CGP 60474



Carlos Garcia-Echeverria (*Novartis*, Basel) presented new potent inhibitors of the Src homology 2 (SH2) domain of the growth factor receptor-bound protein 2 (Grb2). The Grb2-SH2 domain docks onto the phosphotyrosine site of the dimerized epidermal growth factor (EGF). Agents, which specifically disrupt this protein-protein interaction, may shut down the *Ras* pathway, which triggers the MAP kinase cascade essential for cell growth and differentiation. For the SH2 domain of Grb2 the consensus sequence is Tyr(PO_3H_2)-Xxx-Asn-Yyy (Xxx = Val, Gln, Tyr, Ile; Yyy = Gln, Tyr, Phe). Synthetic peptides (*e.g.*, H-Glu-Tyr(PO_3H_2)-Ile-Asn-NH_2) had low μM affinities (IC_{50} = 7.9 μM). Incorporation of anthranilic acid to the N-terminal part caused an unexpected increase of binding affinity: Abz-Glu-Tyr(PO_3H_2)-Ile-Asn-NH_2: IC_{50} = 22 nM. The known X-ray of the Lck-SH2 domain, similar to the Grb2-SH2 domain, of which no X-ray is known, served as a model for energy minimization calculations to understand the binding mode of

the anthranilic-acid residue: a π-π stacking interaction with an arginine residue and additional H-bonding of the 2-amino group with one of the phosphotyrosine phosphate oxygens. This knowledge led to the synthesis of the potent 1-amino-1-carboxycyclohexyl derivative (IC_{50} = 1 nM; formula *vide supra*).

Special Plenary Lectures

Bernard Testa (Univ. Lausanne) explained in great detail the manifold ramifications of xenobiotic metabolism. Drugs are metabolized *via* redox processes (oxidoreductases), *via* hydration (hydrolases or lyases), or by conjugation (transferases). Metabolism usually increases water solublity to facilitate urinary excretion. However, there are exceptions. The hydrophilicity of morphine-3- and -6-glucuronides is only 5–10-fold higher than that of morphine. Both metabolites enter the brain *via* active and passive transport. Morphine-6-glucuronide can adopt two low-energy conformations, the folded being more hydrophilic than the extended conformation. Lipophilicity parameters should be studied within the physiological pH range: the H_1 receptor antagonist cetirizine does not acculumulate in the brain (no sedation), nor in lean tissue as heart (no cardiotoxicity), as it is present as a zwitterion over the whole physiological pH range. Prodrugs are often required to overcome poor oral absorption or short duration of action. Prodrugs, which are cleaved by enzymes, should be avoided, due to species differences.

Roberto Pellicciari (Univ. Perugia) ventured into new avenues in the search for new neuroprotective agents, *e.g.*, by suppressing reactive oxygen species by free-radical scavengers. Following an observation by *D.W. Choi* (*Proc. Natl. Acad. Scil. U.S.A.* **1997**, *94*, 9434) that fullerenes exert neuroprotective effects, he prepared hexacarboxy-fullerenes, which reversed apoptotic cell death in serum-deprived PC12 cells at 10 µM. A second avenue is his continued search for metabotropic glutamate receptor modulators, as (+)-(*S*)-(2-carboxybicyclo[1.1.1]pentyl)glycine, a mGluR group-I antagonist (UPF 596: IC_{50} = 25 µM; *J. Med. Chem.* **1996**, *39*, 2874) and 1-aminoindan-1,5-dicarboxylic acid (AIDA, UPF 523, IC_{50} = 7 µM; *J. Med. Chem.* **1995**, *38*, 3717). Both drugs fully protected gerbils in a model of global ischemia.

In summary, the organizing committee of the First Italian-Swiss Meeting on Medicinal Chemistry (co-presided by *A. Gasco* for the Divisione di Chimica Farmaceutica and *E. Kyburz* for the SMC) offered a well-balanced program covering many hot topics of modern medicinal chemistry. The pleasant ambiance provided good opportunities for personal contacts, which, hopefully, will be reinforced at the occasion of the XVIth International Symposium on Medicinal Chemistry in Bologna in September 2000.

Basel, October 6, 1997
Dr. Wolfgang Fröstl
Novartis