XIVth International Symposium on Medicinal Chemistry

This biennial meeting, held in Maastricht, The Netherlands, in September, attracted more than 800 delegates from 41 different countries. This article reviews some of the highlights.

CNS agents

Dr P.L. Ornstein (Lilly Research Laboratories, Indianapolis, IN, USA) described the preparation and pharmacological profiles of some novel antagonists for metabotropic glutamate receptors, based on the known antagonist (*S,S,S*)-M-CCG-1 (**1**; Figure 1). Replacing the α-methyl group with bulky lipophilic motifs has led to a series of compounds including (*S,S,S*)-LY 341,495 (**2**), which have nanomolar affinity for the group 2 metabotropic glutamate receptors.

Dr G.A.M. Giardina and coworkers (SmithKline Beecham, Milan, Italy) have identified a novel class of potent, selective, nonpeptide NK_3-receptor antagonists. A pharmacophore model was established from an overlay of known nonpeptide NK_1 antagonists. On using this as a search query for the company compound collection, the most promising lead, the 2-phenylquinoline SB 213,785 (**3**), transpired to be selective for the NK_3 receptor. SB 213,785 was optimized to give SB 223,414 (**4**), which is an orally bioavailable (63% in rat), selective NK_3 antagonist with 1 nM affinity for the NK_3 receptor.

Two speakers described their approaches to the design of ligands specific for the melatonin receptor. These compounds are not only important for studying the function, binding sites and mechanism of action of melatonin, but also have potential therapeutic applications in the treatment of biological rhythm disorders, such as seasonal depression and jet lag. Dr D. Lesieur and coworkers (Institut de Chimie Pharmaceutique, Lille, France) have developed some highly potent novel analogues of melatonin (**5**), replacing the indole ring with a variety of bioisosteres; the most active of which were naphthalene derivatives. S 20,098 (**6**; affinity of 0.07 nM at the melatonin receptor) is currently in Phase II clinical trials. Dr M. Mathe-Allainmat and coworkers (CNRS-BIOCIS, Chatenay-Malabry, France) have prepared conformationally restricted ligands such as the 2-amido-1,3-dihydro-1H-phenalene derivative **7**, which has subnanomolar affinity for the melatonin receptor.

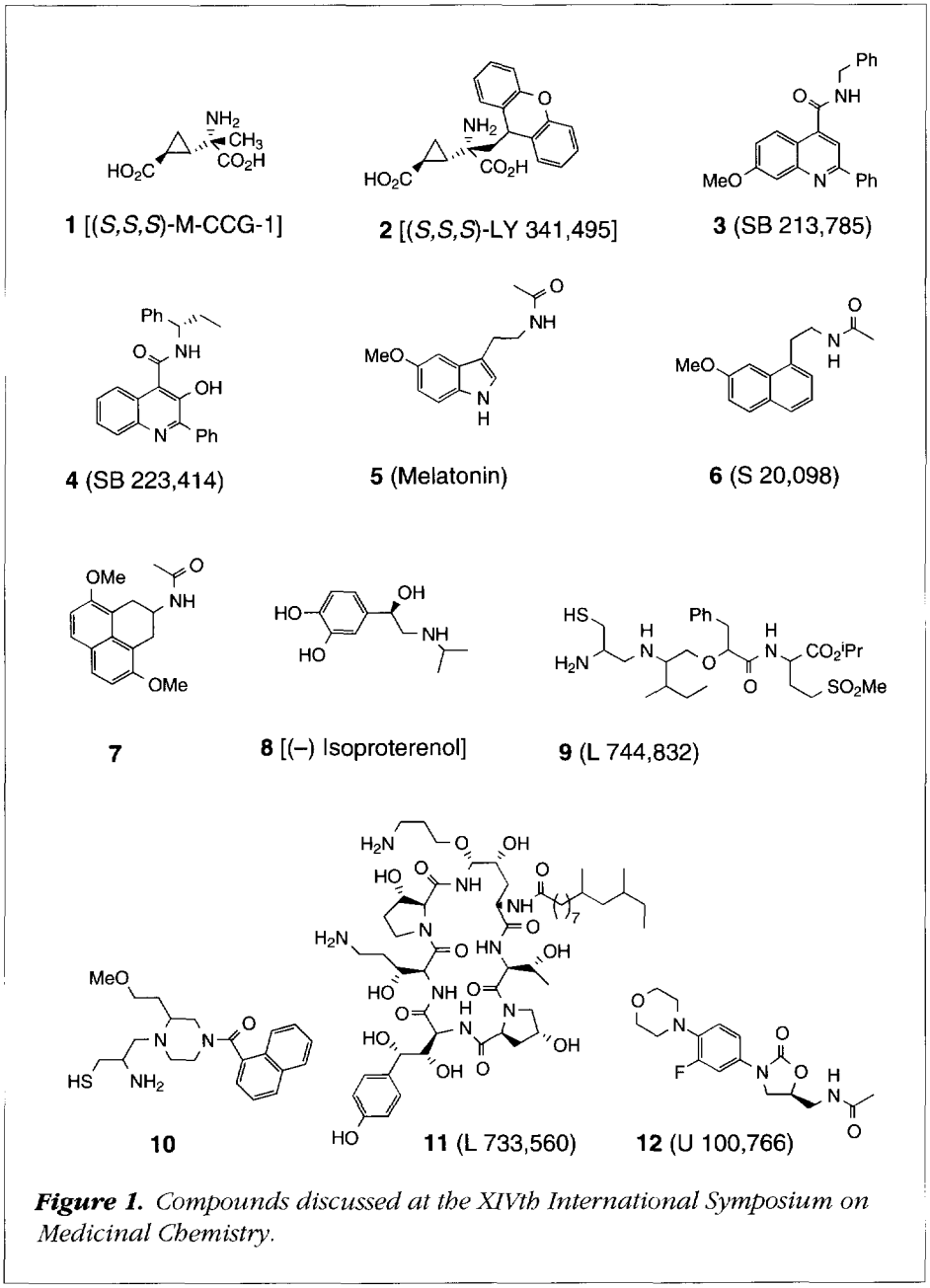


Figure 1. *Compounds discussed at the XIVth International Symposium on Medicinal Chemistry.*

Protein kinases and their signalling pathways

Dr M.J. Lohse (University of Würzburg, Germany) discussed some mechanisms of activation and deactivation of G-protein-coupled receptors with reference to the β-adrenergic receptor system. Activation of receptors is initiated by agonist binding (Figure 2a). (–) Isoproterenol (**8**; Figure 1) is a selective agonist at β-adrenergic receptors; it has been proposed that interaction of the β-hydroxyl group with the sixth transmembrane helix may be relevant for stereoselective agonist recognition and receptor activation. Agonist-induced movement of this helix may then be transmitted to the cytosolic loops of the receptor, which then interact with the G protein.

Inactivation of the receptor can be triggered by various processes including phosphorylation of the receptors by protein kinases. Phosphorylation is followed by binding to β-arrestin, which inactivates the receptor. The receptor is then internalized. Once inside the cell, β-arrestin can be detached, and the receptor dephosphorylated (Figure 2b). Only on returning to the cell membrane is it again available for activation by an agonist.

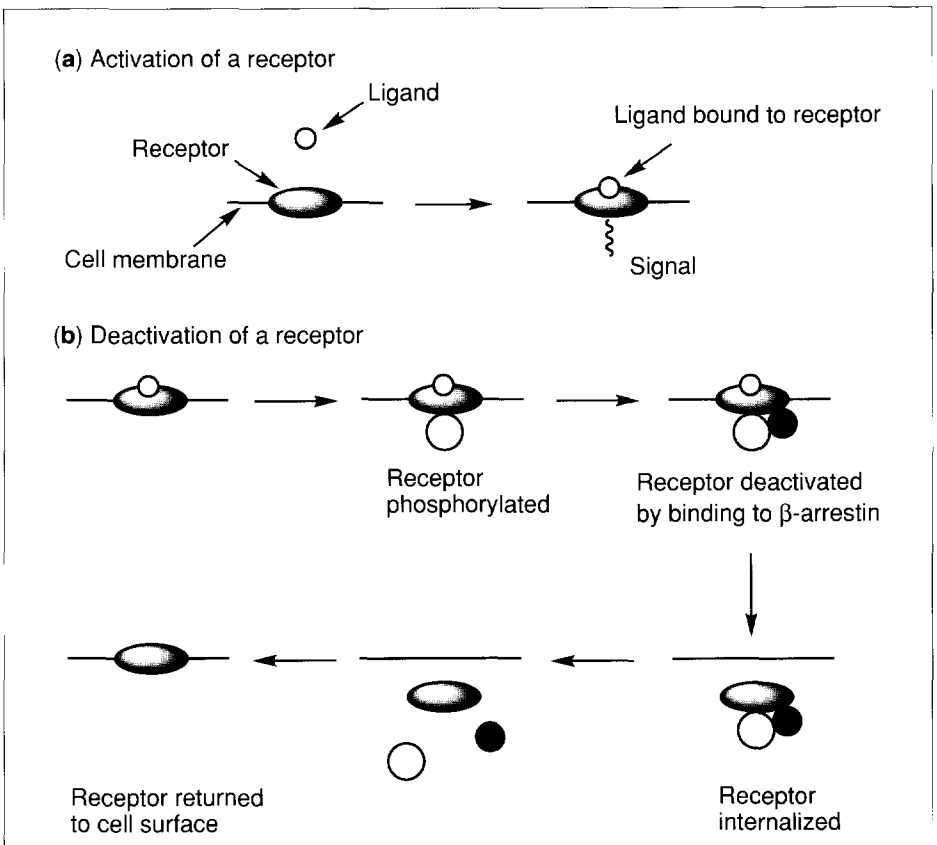


Figure 2. *(a) Activation and (b) deactivation mechanism of a G-protein-coupled receptor.*

Dr G.D. Hartman (Merck, West Point, PA, USA) discussed the design of nonpeptide inhibitors of ras farnesyltransferase. Ras proteins are of interest because they have a central role in cell growth. Inhibitors of this type have potential use in the treatment of malignant disease. The initial lead was an orally active peptidomimetic L 744,832 (**9**; affinity = 1.8 nM). This was truncated to give compounds based on a piperazine scaffold, of which the most active, **10**, has an affinity of 3 nM.

Antifungal and antibacterial agents

Some of the challenges encountered in the discovery of new antifungal and antibacterial agents were reviewed by Dr P.A. Lartey (Abbott, Abbott Park, IL, USA), who emphasized the need for new antibacterial agents with improved efficacy against resistant organisms, and for safe fungicidal agents. Dr J.M. Balkovic and coworkers (Merck, Rahway, NJ, USA) have modified the pneumocandins, a group of fungicidal cyclic hexapeptides that inhibit β-(1,3)-D-glucose synthesis, thereby affecting the structural integrity of fungal cell walls. The Merck compounds possess a lipophilic side chain and amine based cationic groups. An example is L 733,560 (**11**), which is a water-soluble, nanomolar inhibitor of β-(1,3)-D-glucose synthesis.

Dr M.R. Barbachyn (Pharmacia & Upjohn, Kalamazoo, MI, USA) focused on a class of orally active synthetic bacterial-protein-synthesis inhibitors, the oxazolidinones, of which U 100,766 (**12**) is currently undergoing Phase II clinical trials.

Combinatorial chemistry

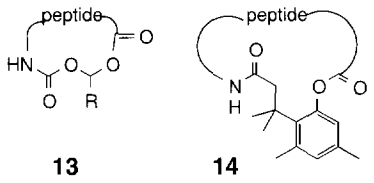
Dr J. Kiely (Houghten Pharmaceuticals, San Diego, CA, USA) described the preparation of a combinatorial library of 43,000 isoquinolones via a base-catalysed condensation of solid-support-bound imines with homophthalic anhydride. Fifty-two subsets, each containing over 800 compounds, were screened against μ- and κ-opioid and σ-receptors. Iterative deconvolution of the most active subset led to the identification of four useful lead compounds.

The automated molecular assembly plant available at ArQule was the subject of a presentation by Dr J. Hogan (ArQule, Medford, MA, USA). This highly automated system is capable of generating huge libraries of individual compounds on plates containing up to 2,500 wells using solution- and solid-phase chemistry. All of the speakers in this section emphasized that, at present, most of the time required to prepare combinatorial libraries is spent optimizing the chemical methodology.

Prodrugs

Professor D. Crommelin (University of Utrecht, The Netherlands) reported on the use of liposomes as versatile colloidal carrier systems for the delivery of peptides and proteins. Liposomes are advantageous in having low toxicity and in their ability to provide an internal aqueous medium for the encapsulated drug. His group has found evidence for the accumulation of such liposome carriers at diseased sites such as tumour cells and inflammation. Therefore these compounds have potential use as homing devices that can be used to deliver drugs to a target site.

Dr Gangwar and coworkers (University of Kansas, KS, USA) have improved the metabolic stability of peptides by synthesizing esterase-sensitive prodrugs **13** and **14** (Figure 3). Both prodrugs can mask a peptide against metabolic degradation by peptidases and increase permeation through biological membranes. Degradation of these prodrugs is catalysed by esterases.



13 **14**

Figure 3. *Esterase-sensitive prodrugs for peptides.*

Dr R. Cecchelli and coworkers (Serlia, Lille, France) have developed an *in vitro* system for studying the blood–brain barrier. A model of the endothelial–glial interface has been set up *in vitro* by coculturing brain capillary endothelial cells on one side of a porous filter and astrocytes on the other. Permeability of a variety of drugs through the *in vitro* system showed good correlation with results determined *in vivo*.

Over 300 posters were presented, and awards were given to the following: Professor R. Ganellin and coworkers (University College, London, UK) *Rational Design of Butabindide, The First Inhibitor of the Newly Identified Cholecystokinin-Inactivating Peptidase*; Dr C. Sahlberg and coworkers (Medivir AB, Huddinge, Sweden) *Synthesis and Anti HIV-1 Activities of Urea-PETT Analogues Belonging to a New Series of Potent Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors*; Dr W. Tögel and coworkers (Freie Universität Berlin, Germany) *Guanidines and Related Compounds With Direct G Protein Stimulatory Activity.*

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Book reviews

Computer Modelling in Molecular Biology edited by Julia M. Goodfellow, VCH, 1995. DM 178 (300 pages) ISBN 3 527 30062 7

The preface of this book states that it is intended to provide 'a series of snap-shots of the use of molecular simulation techniques to study a wide range of biological problems.' As such, it should not be viewed as a textbook or a systematic treatment of molecular modelling. Rather, the editor has assembled seven chapters, each covering a different topic, in addition to a brief general introduction. The topics include: modelling protein structures, molecular dynamics simulations on small peptides, molecular dynamics and free-energy perturbation calculations applied to barnase, molecular dynamics simulations applied to nucleic acids, molecular dynamics simulations applied to ion channels, modelling of major histocompatibility complex (MHC) protein–peptide interactions, and modelling of conformational transitions in large molecules. Obviously the particular choice of topics reflects the bias of the editor and the other contributors, but it is representative of the kind of computer modelling that is prevalent in molecular biology, and it does indeed provide a 'snapshot' of the field.

Each chapter is systematically laid out, covers its material thoroughly, and is well supported by figures, graphs and tables. All chapters are also well-referenced. Unfortunately, the references stop in 1993, suggesting that this book has taken too long in production. Most of the chapters describe one particular application of a computational method; other important applications of that method are not discussed. For example, the chapter on free-energy perturbation simulations only describes the application of those simulations to the enzyme barnase. The final chapter, which describes a new method for simulating conformational transitions in large molecules, such as proteins, seems slightly out of place. While interesting to those with a serious interest in the development of novel computational methods, this chapter is likely to be of less interest to the general reader.

The book has a continental flavor, with all but one of the contributors coming from Europe. Indeed, eight of the sixteen authors come from the UK. None of the contributors comes from the pharmaceutical industry, which along with the selection of contributors suggests that the perspective of the book may be somewhat narrow.

Overall, this is a useful book to gain a quick appreciation for a variety of ways in which modelling may be useful in molecular biology.

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