Proceedings of the Third Rhône-Poulenc Round Table Conference

Drug Design: Fact or Fantasy?

edited by
G. Jolles and
K. R. H. Wooldridge

Drug Design: Fact or Fantasy?

Edited by

G. JOLLES

Rhône-Poulenc Santé
Paris, France

K.R.H. WOOLDRIDGE

May and Baker Ltd
Dagenham, Essex
Great Britain

1984

ACADEMIC PRESS

A Subsidiary of Harcourt Brace Jovanovich, Publishers

London Orlando San Diego San Francisco New York
Toronto Montreal Sydney Tokyo São Paulo

ACADEMIC PRESS INC. (LONDON) LTD
24/28 Oval Road
London NW1

United States Edition published by
ACADEMIC PRESS INC.
(Harcourt Brace Jovanovich, Inc.)
Orlando, Florida 32887

British Library Cataloguing in Publication Data
Drug design.
1. Pharmacology—Congresses
I. Jolles, Georges II. Wooldridge, K.R.H.
615'.1 RM300

ISBN 0-12-388180-3
LCCCN 83-70976

Printed in Great Britain by
Galliard (Printers) Limited, Great Yarmouth

List of Participants

Andrews P.R. Professor, Dean, School of Pharmaceutical Chemistry, Victorian College of Pharmacy Ltd., 381 Royal Parade, Parkville, Victoria 3052, Australia.

Ashford A. Biological Research Manager, May and Baker Ltd., Dagenham, Essex, Great Britain.

Ashton M.J. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Barreau M. Département de Chimie Pharmaceutique, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Blanchard J.C. Département de Pharmacologie, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Blondel J.C. Direction Scientifique, Rhône-Poulenc Santé, Paris-La Défense, France.

Bost P.E. Directeur des Programmes et des Projets de Recherches, Rhône-Poulenc Santé, Paris-La Défense, France.

Bouchaudon J. Département de Chimie Pharmaceutique, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Bowden K. Department of Chemistry, University of Essex, Colchester, Great Britain.

Caillard C. Adjoint au Directeur du Département de Pharmacologie, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Caton M.P.L. Chemical Research Manager, May and Baker Ltd., Dagenham, Essex, Great Britain.

Cattier-Humblet C. Laboratoire de Pharmacochimie Moléculaire, Centre de Neurochimie du C.N.R.S., Strasbourg, France.

Chapman R.F. Assistant Chemical Research Manager, May and Baker Ltd., Dagenham, Essex, Great Britain.

Choplin F. Service de Documentation, Rhône-Poulenc Recherches, Centre de Recherches des Carrières, St. Fons, France.

Clementi S. Professor, Dipartimento di Chimica, Universita di Perugia, Via Elce di Sotto, 10-06100, Perugia, Italy.

Cotrel C. Département de Chimie Pharmaceutique, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Dearden J.C. School of Pharmacy, Liverpool, Great Britain.

Debarre F. Direction Scientifique, Rhône-Poulenc Santé, Paris-La Défense, France.

Depaire H. Service d'Analyse Structurale, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Dreux C. Professeur, Université René Descartes, (Paris V), Vice-Président de SPECIA, Paris, France.

Dubosc Y. Chef du Service Documentation, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Farge D. Adjoint au Directeur des Recherches Chimiques Pharmaceutiques, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Fenton G. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Fujita T. Professor, Department of Agricultural Chemistry, Kyoto University, Kyoto 606, Japan.

Guinot F. Directeur Général Adjoint, Rhône-Poulenc Santé, Paris-La Défense, France.

Hansch C. Professor, Seaver Chemistry Laboratory, Pomona College, Claremont, California 91711, USA.

Iddon B. Department of Chemistry and Applied Chemistry, University of Salford, Salford, Great Britain.

James C. Département de Chimie Pharmaceutique, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Jeambourquin R. Directeur du Centre de Recherches de Vitry, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Jollès G. Directeur Scientifique, Rhône-Poulenc Santé, Paris-La Défense, France.

Julou L. Directeur des Recherches Biologiques Pharmaceutiques, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Loveless A. Biological Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Lunt E. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

McFadzean J.A. Director of Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Marshall G.R. Professor, Department of Physiology and Biophysics, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110, USA.

Messer M. Directeur des Recherches Chimiques et Biochimiques Pharmaceutiques, Rhône-Poulenc Recherches, Centre Nicolas Grillet, B.P. 14 F 94400 Vitry-sur-Seine, France.

Moutonnier C. Département de Chimie Pharmaceutique, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Ollis D. Professor, Department of Chemistry, The University, Sheffield, Great Britain.

Palfreyman M.N. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Phillipson R.F. Resources Manager Pharmaceutical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Ponsinet G. Département de Chimie Pharmaceutique, Rhône-Poulenc Recherches, Centre Nicolas Grillet, Vitry-sur-Seine, France.

Rabin B.R. Professor, Department of Biochemistry, University College, London, Great Britain.

Ramsden C.A.R. Corporate Chemistry Unit, May and Baker Ltd., Dagenham, Essex, Great Britain.

Riche C. Institut de Chimie des Substances Naturelles du C.N.R.S., Gif-sur-Yvette, France.

Roques B.P. Professeur, Département de Chimie Organique, U.E.R. des Sciences Pharmaceutiques et Biologiques, Université René Descartes, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France.

Salmon J. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Smith C. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Stevens M. Professor, Department of Pharmacy, University of Aston in Birmingham, Birmingham, Great Britain.

Tomlinson E. Professor, Department of Pharmacy, University of Amsterdam, Amsterdam, The Netherlands.

Trouet A. Professeur, Faculté de Médecine, Université Catholique de Louvain, International Institute of Cellular and Molecular Pathology, 75 Avenue Hippocrate, B-1200 Brussels, Belgium.

Walsh R.J.A. Chemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Warburton D. Assistant Chemical Research Manager, May and Baker Ltd., Dagenham, Essex, Great Britain.

Wermuth, C.G. Professeur, Laboratoire de Chimie Organique, Faculté de Pharmacie, Université Louis Pasteur, 74 Route du Rhin, B.P.10, 67048 Strasbourg Cedex, France.

Whalley W.B. Professor, Pharmaceutical Chemistry, The School of Pharmacy, University of London, London, Great Britain.

Withnall M. Biochemical Research, May and Baker Ltd., Dagenham, Essex, Great Britain.

Wold S. Chemometrics Research Fellow, Research Group for Chemometrics, Umeå University, S-901 87 Umeå, Sweden.

Woolridge K.R.H. Pharmaceutical Research Manager, May and Baker Ltd., Dagenham, Essex, RM10 7XS Great Britain. Visiting Professor, City University and University of Essex.

Preface

"L'inconnaissable n'est
que de l'inconnu provisoire"

This volume contains the Proceedings of the Third Rhône-Poulenc Round Table, held at Eastbourne on the south coast of England in November 1982.

The aim of this meeting was to determine to what extent modern tools offered by computers, mathematics or new biological theories could now be effectively used to achieve the old dream fostered by chemotherapists, i.e. to design a new drug by logical thought and calculation and, as far as possible, not to rely on chance.

"What is unknowable is but temporarily unknown".

"If only man willingly collects and implements the appropriate means, then ignorance fades away, as a shadow from sunlight. Only material obstacles build a screen between the truth and ourselves. Human ignorance is not hopeless: with time and money, man may acquire and learn everything."

This credo assigned to scientists by Grassé in his essay on the natural history of man* is quite reassuring for the future of drug design which, undoubtedly, will be outstanding. But today, in 1983, what is the situation, Fact or fantasy?

The objective of the Eastbourne Round Table was to seek an answer from top specialists in various methodologies of drug design who met with scientists from the pharmaceutical industry who are faced every

* P.P. Grassé (1971) 'Toi, ce petit Dieu" p. 227, Albin Michel, Paris.

day with practical problems. The former successively reviewed their personal approaches and the latter explained the philosophy which they adopted after long and concrete experience. In this book, the reader will in no way discover recipes but an overall evaluation. He will confront his own convictions and, with a view to his own choices, will find the basic parameters of drug design and the evaluation obtained after many discussions. In fact, this book not only contains the presentations of the contributors but also the main discussions of the subgroups in which the participants expressed themselves more freely and reached sometimes differing conclusions which were finally discussed by the full conference.

It is our objective that this book should provide a better understanding of the knowledge acquired and of the shortcomings in the field of drug design and that it should give rise to positive cross-fertilization between optimists and pessimists for improved efficacy in research. It is our hope that by helping research scientists in their strategic considerations, it will contribute to the discovery of new and valuable drugs.

G. Jolles and K.R.H. Wooldridge

Acknowledgements

It is our real pleasure to thank warmly all the contributors and participants who agreed to attend the meeting and to work actively together, in a friendly atmosphere of free discussion. We are especially thankful to the four chairmen of the Round Table: Professors Rabin, Tomlinson, Whalley and Ollis.

We are particularly indebted to Drs Blondel and Phillipson who assisted us most efficiently in the organization of the meeting and to Drs Bowden, Julou, McFadzean, Messer and Professor Wermuth for their advice and help in preparing the programme of the conference.

We want further to express our gratitude to our colleagues of the Rhône-Poulenc Group of Companies who assisted us in the editorial task of reviewing, preparing and finalizing the text of the various contributions and discussions: M. Barreau, J.C. Blondel, M. Caton, R. Chapman, F. Choplin, E. Lunt, A. Loveless, R. Phillipson, C. Ramsden, C. Smith, R. Walsh and M. Withnall.

Finally we wish to acknowledge the efficiency of Dr Mary Firth in charge of the transcription of the discussions, of the translators of the French presentations Miss Eiglier and Mrs Tantet, and of Miss Cox who took care of our guests.

The expert assistance of the staff of Academic Press Inc. (London) Ltd. in producing this volume was greatly appreciated.

G. Jolles and K.R.H. Wooldridge

Opening Remarks

Dr G. JOLLES

It is my honour and privilege to open this morning the third Round Table Conference organized by the Rhône-Poulenc Group of Companies, a meeting for which we have chosen the deliberately provocative title: "Drug Design: Fact or Fantasy?"

For the past few years, it has been our objective to examine at regular intervals a scientific topic of current interest by organizing round tables with university specialists and research staff from the industry. The purpose of such meetings was to carry out a synthetic approach to the topics in order to prepare the way for new research strategies and to stimulate new activities in that particular field.

It was in this way that, in 1978, we achieved an overview of the Pharmacology of Immunoregulation and, in 1980, tried to determine the Future of Antibiotherapy and Antibiotic Research. Today, we wish to concentrate on a different issue, an issue which often gives rise to passionate arguments and directly concerns our everyday work.

"Drug Design: Fact or Fantasy?": this title actually requires two explanations: what do we mean by drug design and why the question mark?

A few weeks ago, I attended an International Symposium at which research executives of some large pharmaceutical companies were discussing many of their problems. At one point, we were trying to find the French or German equivalent to "drug design", but in the end it appeared that fairly long paraphrases were required to express this same concept. In order to avoid any problem of semantics during the present meeting for this unique and very concise expression, I should like to state that, in our opinion, it corresponds to rational methodologies which give access to a new drug either through the noblest pathway, namely total innovation, or through the more tangible pathway, optimization.

On the other hand, why in fact do we question the reality of drug design?

Is it a dispute between the ancients and moderns; between conservative and progressive tendencies? Definitely not. Yet everything has its share of reality and dream: in the best champagne, we must distinguish the foam, which we see, from the wine, which we drink, and what is expected of a good drug research scientist is that he acts intelligent not that he looks intelligent.

As a matter of fact, I am now close to the point where I may be blamed for trying to advocate a pre-established opinion, and this is exactly what I should like to avoid during this symposium. There is no pre-established opinion to back up in favour of fact or fantasy: drug design exists; otherwise what would be the point of such a programme, and how could we have managed to gather such a panel of personalities all of whom have accepted to talk about their methodologies and their techniques.

But what are the real possibilities of application today; what are the domains in which drug design may be most fruitful; what are the actual limitations which must be overcome to make it perform better tomorrow? These are the real questions to which we trust you will help provide the answers.

The review to which we shall proceed together consists of two distinct parts. In the first part, specialists of the major techniques proposed to design new drugs or to optimize them will explain the main features of their areas of activity and the results of their research. Furthermore, two of our experts will present, under two different aspects, the view of research scientists who have been faced for many years with the problem of discovering new drugs. In the second part, all the participants will meet in syndicates in order to facilitate discussions on a very broad basis of the various theories and methodologies, with special emphasis on their individual experiences.

During the final session, a general and constructive evaluation of the discussions and of the answers to our questions will be worked out with a view to conferring practical usefulness to this Round Table which, we hope, will be rewarding for all of us.

We have excluded, intentionally, from our programme all presentations of results which would be too restrictive, and of course, although the example of an original research work may be welcome to illustrate the recommended methods, we hope that the discussions will concentrate less on the technical aspects of each methodology than on its potential as a tool for the discovery of new drugs.

It is, in fact, on drug design potential, strategy and, may I say, philosophy, that we wish to lay stress and I am certain that our meeting will be successful if we can meet this goal.

I should like to thank now all our speakers, some of whom have come from far away, and all our university guests who accepted our invitation and give of their precious time to be with us. I know that everybody will be interested to see how the individual areas can be integrated into the very broad spectrum of possible approaches to drug design.

I want to thank, also, all those who participated in the organization of this Round Table, my colleague Dr Wooldridge with whom I have been working hand in hand and Drs Phillipson and Blondel who took care of the general technical arrangements. We really tried to make this meeting a symbol of the excellent cooperation between the centres of the Health Division in France and those of May and Baker.

The discovery of a new drug is indeed an extremely difficult task. Maybe it was imprudent of us to adopt this shining expression, "Drug Design", from people who are really designers, who design aeroplanes, cars, equipment: they know exactly what they are aiming for; they are aware of most of the parameters involved in their project; they can calculate.

The crucial difference in drug research is that we do not dominate all the parameters as far as we have even identified them and, therefore, work under a serious handicap. For this reason, many scientists nowadays still believe in the virtues of intelligent screening as a major tool for innovation, and among them are some of the most successful ones. Others have total faith in the available rational approaches; they cannot stand even to hear about screening and practice the most evident disdain for an alliance with serendipity.

What then is the truth about drug design at this time? Well, we have prepared the dossier; we have provided the experts; there will be prosecutors and defendants either for fact or for fantasy; but the judges will be you.

Please, let it be a fair trial.

Contents

List of Participants v
Preface ix
Acknowledgements xi
Opening Remarks xiii

Session I

1 Targeting of Drugs 3
A. Trouet, D. Deprez-de Campeneere, R. Baurain and Y.-J. Schneider

2 The Role of QSAR in Drug Design 19
T. Fujita

3 Computational Chemistry and Receptor Characterization 35
G.R. Marshall

4 Designing Prodrugs and Bioprecursors 47
C.G. Wermuth

5 Statistics and Drug Design 73
S. Clementi

6 Pattern Recognition as a Tool for Drug Design 95
S. Wold, W.J. Dunn III and S. Hellberg

7 Pharmacological Receptors and Drug Design 119
B.P. Roques

8 The Design and Medicinal Applications of Transition State Analogues 145
P.R. Andrews and D.A. Winkler

9 General Discussion of Session I 175

Session II

10 The New Look to QSAR 185
C. Hansch and J.M. Blaney

11 The Virtues of Present Strategies for Drug Discovery 209
K.R.H. Wooldridge

12 Traditional or Pragmatic Research 217
M. Messer

13 General Discussion of Session II 225

Session III

14 Syndicate Discussions 237
K.R.H. Wooldridge

15 General Discussion of Conference 247

16 Conclusions 261

Subject Index 263

Session I