

Preface

Volume 27 of our series “Methods and Principles in Medicinal Chemistry” is dedicated to “Molecular Interaction Fields” and their impact on current drug research.

In the early 1980s Peter Goodford developed the GRID force field for determining energetically favorable binding sites on molecules of known structure. The GRID force field has always been calibrated as far as possible by studying experimental measurements, and the calibration is then checked by studying how well GRID predicts observed crystal structures. Crystal packing is determined by free energy considerations rather than by enthalpy alone. The force field includes entropic terms; GRID can detect the hydrophobic binding regions which are so important when high-affinity ligands are being designed, and it can also detect sites for the polar groups which determine ligand selectivity. GRID may be used to study individual molecules such as drugs, molecular arrays such as membranes or crystals, and macromolecules such as proteins, nucleic acids, glycoproteins or polysaccharides.

Moreover GRID can be used to understand the structural differences related to enzyme selectivity, a fundamental field in the rational design of drugs. GRID maps can also be used as descriptor input in statistical procedures like CoMFA, GOLPE or SIMCA for QSAR or 3D-QSAR analyses.

The GRID force field represents the basis for several software packages specifically developed for application to pharmacodynamic aspects of drug research, including the programs ALMOND, Pathfinder, and FLAP or, in the ADME field, the programs VolSurf and MetaSite.

Correspondingly, the present volume is quite logically divided into three sections. An introductory section contains two chapters dealing with the theoretical background. The chapter of Peter Goodford, who originally developed the GRID software, focuses in detail on the basic principles of GRID, whereas the chapter by Rebecca Wade is dedicated to “Calculation and Application of Molecular Interaction Fields”.

The second section refers to pharmacodynamic aspects and contains chapters on “Protein selectivity studies using GRID-MIF” by Thomas Fox, “The Complexity of Molecular Interaction: Molecular Shape Fingerprint by PathFinder Approach” by McLay, Hann, Carosati, Cruciani, and Baroni, “Alignment-Independent Descriptors from Molecular Interaction Fields” by Manuel Pastor, “FLAP: 4-point pharma-

cophore fingerprints from GRID” by Perruccio, Mason, Sciabola, and Baroni as well as a chapter on “3D QSAR using the GRID/GOLPE approach” by Wolfgang Sippl.

The third and last section is dedicated to pharmacokinetics including chapters on “Molecular Interaction Fields in ADME and Safety” by Cianchetta, Li, Singleton, Zhang, Wildgoose, Rampe, Kang, and Vaz, “MIF-based VolSurf descriptors in Physicochemical and Pharmacokinetic studies” by Mannhold, Berellini, Carosati, and Benedetti, “Progress in ADME prediction using GRID-Molecular Interaction Fields” by Zamora, Ridderström, Ungell, Andersson, and Afzelius, “Rapid ADME filters for Lead Discovery” by Oprea, Benedetti, Berellini, Olah, Fejgin, and Boyer and finally a chapter on “GRID-Derived Molecular Interaction Fields for Predicting the Site of Metabolism in Human Cytochromes” by Cruciani, Aristei, Vianello, and Baroni.

A remarkable peculiarity of this volume is the inclusion of a CD-ROM containing some software packages used in the three sections of the book.

The series editors believe that this book is unique in its topic and presentation and adds a fascinating facet to the series. We are indebted to all authors for their well-elaborated contributions and we would like to thank Gabriele Cruciani for his enthusiasm in organizing this volume. We also want to express our gratitude to Renate Doetzer and Frank Weinreich from Wiley-VCH for their valuable contributions to this project.

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