

Preface

Why do we address G protein coupled receptors (GPCRs) as drug targets and emphasize their constitutive activity in our series on „Methods and Principles in Medicinal Chemistry“? Taking into account that a large variety of currently used drugs are either agonists or antagonists at GPCRs, the broad interest of medicinal chemists in GPCRs is obvious. But why do we highlight the constitutive activity of GPCRs? When this phenomenon was described first in the 1980's it was regarded with high scepticism and often attributed to experimental artefacts. Nevertheless, during the last two decades the phenomenon has gained more and more scientific attention and thus constitutive GPCR activity has been included in the theoretical and molecular models of GPCR activation. Consequently, GPCR ligands are today subgrouped into full agonists, partial agonists, neutral antagonist and inverse agonists. Interestingly, many of the clinically used „GPCR-blockers“ turned out to be not neutral antagonists but inverse agonists at their respective receptors.

Therefore, the present book comprehensively discusses an important biological process that has not yet been covered in such depth in any other existing books on GPCRs. In the first part the international team of authors addresses in detail current models and concepts to introduce medicinal chemists, physiologists, pharmacologists and medical researchers into the advances in the understanding of GPCR activation and constitutive activity. In addition, the book provides a chapter with an overview on methods of investigating constitutive GPCR activity on a cellular and subcellular level. In the second part of the book, the knowledge on constitutive activity of selected important GPCR systems is described in more detail. This includes consequences of constitutive activity for drug action and side effects. Most important, one chapter of the book is attributed to the major unresolved issue of constitutive GPCR activity, i.e. its physiological, pathophysiological and therapeutic relevance.

The series editors believe that this book adds a fascinating facet to the series which is unique in its topic and presentation. We are indebted to the international consortium of highly distinguished authors for their contributions which reflect today's situation in biosciences, i.e., that scientists from many disciplines have to work together closely to advance our knowledge on such important but complex issues. We would like to thank Roland Seifert and Thomas Wieland for their enthusiasm to organize this volume. We also want to express our gratitude to Frank Weinreich from Wiley-VCH for his valuable contributions to this project.

May 2005

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zürich