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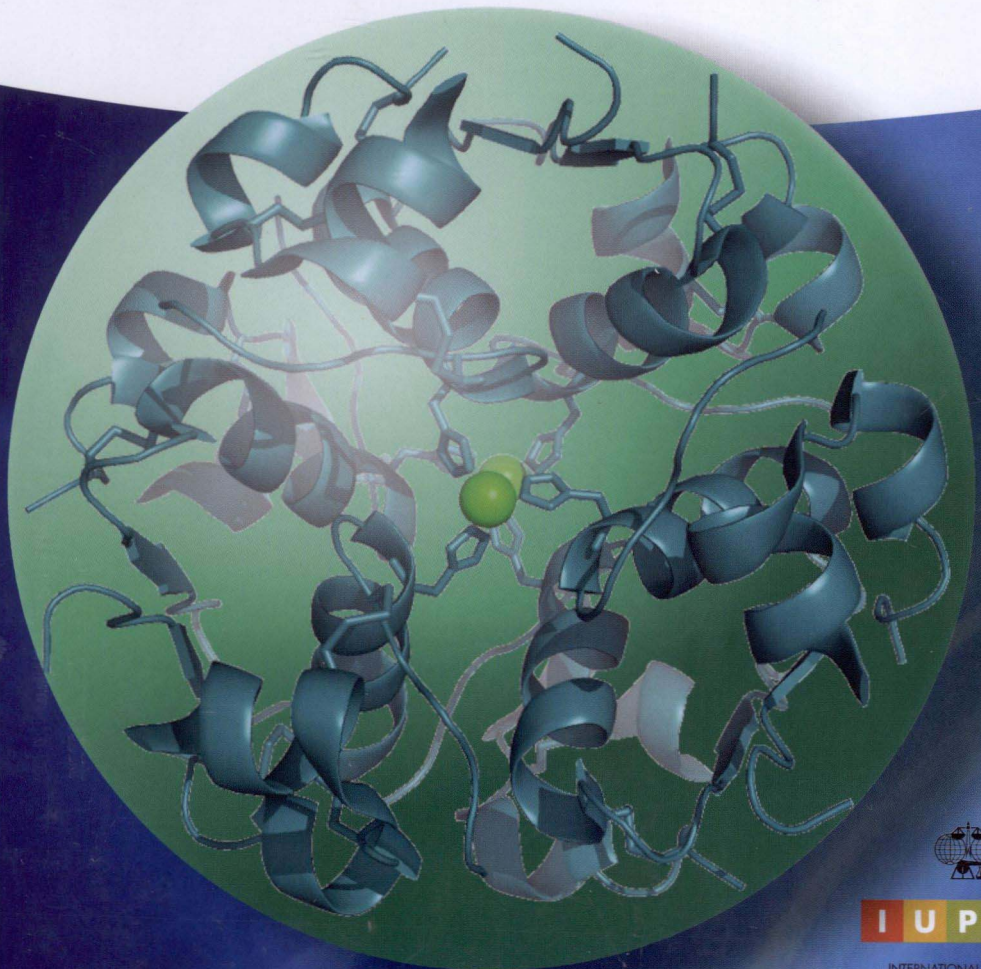
Edited by János Fischer and David P. Rotella

# Successful Drug Discovery



IUPAC
INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

*Edited by János Fischer and David P. Rotella*

# Successful Drug Discovery



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**Successful Drug Discovery**

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# Preface

The International Union of Pure and Applied Chemistry (IUPAC) has supported this new book project; the book has key inventors describe their new drug discoveries and aims to study the general aspects of successful drug discoveries and the optimization in a drug class.

The book *Successful Drug Discovery* is a continuation of the three volumes of *Analogue-based Drug Discovery* where analogs of existing drugs were the focus. The new book has a broader scope because it includes both pioneer drugs and their analogs and spans all the important types of small-molecule-, peptide-, and protein-based drugs.

The editors thank the advisory board members: Klaus P. Bøgesø (Lundbeck, Denmark), Kazumi Kondo (Otsuka, Japan), John A. Lowe III (JL3Pharma LLC, USA), and Barry VL Potter (University of Bath, UK). Special thanks are due to the following reviewers who helped both the authors and the editors: Klaus Bøgesø, Derek Buckle, Matthias Eckhardt, Arun Ganesan, William Greenlee, Katalin Hornok, Roy Jefferis, Béla Kiss, Patrizio Mattei, Eckhard Ottow, John Proudfoot, Joerg Senn-Bilfinger, István Tarnawa.

The first volume of *Successful Drug Discovery* consists of three parts.

### Part I: (General Aspects)

Serendipity is an important part of drug discovery that can be present at each step. The first chapter – written by the editors of this book – reveals special serendipitous cases of some important drug discoveries where the key lead molecule and the drug have been discovered on different targets.

David C. Swinney analyzed the molecular mechanism of action in drug discovery. Phenotypic and target-based drug discovery approaches are discussed from the viewpoint of pioneer drugs and analogs.

### Part II: (Drug Class)

John M. Beals gives an overview of insulin analogs, which optimize PK/PD profiles but also provide sufficient stability for the treatment of type 1 and type 2 diabetes mellitus. Rapid-acting and long-acting analogs are summarized.

**Part III: (Case Histories)**

1) *Avanafil*
Kiichiro Yamada, Tosiaki Sakamoto, Kenji Omori, and Kohei Kikkawa described the discovery of the new and highly selective PDE5 inhibitor with rapid onset of action. The researchers succeeded in a remarkably short period to create a structurally new drug.
2) *Dapagliflozin*
William N. Washburn reports on the discovery of dapagliflozin which was the first SGLT2 inhibitor approved for the treatment of type 2 of diabetes. A C-glucoside side product that was characterized during early SAR studies serendipitiously became the lead structure that ultimately produced the drug.
3) *Elvitegravir*
Hisashi Shinkai described the discovery of elvitegravir, a new HIV-1 integrase inhibitor by using a 4-quinolone-3-carboxylic acid scaffold. The once-daily single tablet of a combination of elvitegravir with a CYP3A4 inhibitor and a nucleoside reverse transcriptase inhibitor afforded potent and durable antiretroviral efficacy.
4) *Linagliptin*
Matthias Eckhardt, Thomas Klein, Herbert Nar, and Sandra Thiemann have written about the discovery of linagliptin a highly potent and long-acting DPP-4 inhibitor. Linagliptin has a non-linear pharmacokinetic and nonrenal elimination profile, unique within the class of approved DPP-4 inhibitors.
5) *Pemetrexed*
Edward C. Taylor gives an overview on the discovery of pemetrexed representing an excellent long term collaboration between academia and industry. The individual interest of the author in pterine chemistry provided a starting point for the discovery of pemetrexed, which is used for the treatment of pleural mesothelioma and non-small cell lung cancer.
6) *Perampanel*
Shigeki Hibi described the discovery of perampanel, a novel, noncompetitive AMPA receptor antagonist for the treatment of epilepsy. Starting from HTS, optimization of a promising triaryl-1*H*-pyridin-2-one scaffold afforded perampanel, which is the first AMPA antagonist approved as an antiepileptic drug.
7) *Telaprevir*
B. Govinda Rao, Mark A. Murcko, Mark J. Tebbe, and Ann D. Kwong have written the chapter on the discovery of telaprevir, a protease inhibitor to treat hepatitis C infection. Telaprevir, a NS3/NS4A serine protease inhibitor, was successfully used between 2011 and 2013 in triple combination with ribavirin and interferon.
8) *Trastuzumab emtansine*
Sandhya Girish, Gail D. Lewis Phillips, Fredric S. Jacobson, Jagath R. Junutula, and Ellie Guardino described the discovery and development

of trastuzumab emtansine. The antibody drug conjugate represents a novel approach in treating patients with HER-2-positive cancer. The drug conjugate enables selective delivery of DM-1, a potent cytotoxic agent, into HER-2-positive target cells.

Last but not least the editors and authors thank the coworkers of Wiley-VCH, especially Dr. Frank Weinreich for the excellent cooperation.

June 2014
Budapest, Hungary
Montclair, NJ, USA

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