Practical Medicinal Chemistry with Macrocycles
Practical Medicinal Chemistry with Macrocycles

Design, Synthesis, and Case Studies

Edited by

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Cyclic structures have always fascinated artists and scientists. In chemistry, the restriction of conformational space by cyclization has stimulated and inspired the understanding of three-dimensional molecular structure and the development of new shapes and entities. When our laboratory started research on conformational analysis of peptides about 40 years ago, we soon realized that the high flexibility of linear peptides results in a complex mixture of conformations. Cyclic peptides are conformationally more restricted and accordingly topologically more defined, and when their structures mimic receptor-interacting conformations, they become not only super-active but also selective for different receptor subtypes.

Nature has used these principles as well. Many biologically important peptides are macrocycles, which possess not only high affinity, but also relatively high stability against enzymatic degradation, and some are even orally available. The simultaneous optimization of synthetic ligands for both activity and bioavailability has become an exciting goal, which is often reached in a stepwise procedure where first activity is optimized; then chemical modifications are introduced to increase oral bioavailability. One successful example of this approach is the conversion of a cyclic hexapeptide with somatostatin activity into a derivative with oral availability \textit{in vivo} via multiple N-methylations while retaining its biological activity. To my knowledge, the reverse process—using an orally permeable scaffold and introducing functionalities required for biological function—has not been achieved yet. Many groups in the world are investigating cyclic scaffold models to understand their intestinal permeability, but their simultaneous functionalization to interact with a biological target remains to be realized.

Above and beyond peptides, many organic molecules form macrocycles with interesting biological properties. It is both surprising and limiting that scientists engaged in non-peptidic macrocycles and peptidic macromolecules live in different scientific worlds and do not exchange information more extensively. Recently, finally, the two communities are joining forces through the rising interest in therapeutic compounds that go beyond Lipinski’s rule of five (the so-called bRo5, or beyond Rule of five, compounds). This empirical rule, which segregates compounds with molecular weight above 500 out of the oral bioavailability zone, was derived from a comprehensive study of orally available drugs. An alternative rule by Veber \textit{et al.} added another important property, that is, the importance of rigidity in a molecule. Nevertheless, a “freely rotatable bond” is difficult to define, particularly in the context of macrocycles, where endocyclic bonds are not fully free to rotate but definitely more flexible than in smaller rings. We know that barriers to internal rotations or inversions vary strongly depending on the structural context. Both of the previous rules have been utilized as exclusive criteria in drug development and greatly reduced the interest of the pharmaceutical industry in macrocycles, at least for peptides, for a long period.

However, research in macrocyclic chemistry continued to advance in synthetic methods, conformational studies, and investigation of their role for controlling biological functions. Finally, very recently, the pharmaceutical industry rediscovered macrocycles. It was realized that such molecules not only open new areas for pharmacological treatment of diseases, but also raise hope that some of the problems in their stability and bioavailability might be overcome. Nature has shown us that molecules with sizes between proteins and small molecules can be orally available and, importantly, that this size range is a particularly good fit for targets requiring extended surface areas exemplified by protein–protein interactions. In addition, the criterion of oral availability is not an absolute requirement since more and more drug products are effectively administered by other routes. Indeed, pharmacists know very well that oral administration is not always the best choice since intestinal uptake can strongly vary as a function of patient and situation. As a result, accurate dosage control is more difficult.

Inspiration for new drug molecules often comes from natural compounds, such as secondary metabolites in living organisms that are bioavailable to be efficacious, as well as from regulatory proteins interacting with other
biomolecules. Peptide chemists realized long ago that loop regions in proteins, because of their exposed spatial arrangement (rigidity), are often critical determinants of interaction with other biomolecules and that these loops can be mimicked by cyclic peptides. Conformational control in cyclic peptides can be achieved by introduction of D-amino acids at distinct positions. Similarly, nature and medicinal chemists often modulate the conformation of non-peptides by controlling chirality at certain positions.

Increasing knowledge in biochemical pathways that control physiological conditions or disease states increases the demand for interference by medium-sized molecules like macrocycles. Compared to small molecules, medium-sized entities offer new ways to interact with protein–protein interaction surfaces. Hence, we are looking into an exciting future that will fill the gaps in medicinal applications, with macrocycles already positioned as privileged structures in this regard.

As a result, this book has collected a number of exciting contributions written by experts in the field of macrocycles. It is very timely in light of the aforementioned interest in macrocycles and covers a broad range of topics. These include chemical and biological synthesis, diversity generation, challenges specific to macrocycles, conformational analysis, design and realization of constraints for medium-sized molecules, and multiple examples of therapeutic applications of various classes of macrocycles.

The principles and the dimensions covered in this book on macrocycles, owing to their universal nature and to the practical way they are addressed, are also very relevant for medicinal chemistry applied to other classes of molecules. As a result, I feel this book should belong in the personal library of all medicinal chemists.

(NB: References to the concepts and works cited previously can be found all along the various chapters covered by this book.)

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Macrocycles are Great Cycles. This was the title of a review we wrote in 2011 to reflect the increasing attention being then given by medicinal chemists toward this unique compound class. Six years later, the interest has only grown, which strongly indicates that the macrocycle field is not just another trend that becomes hot, generates frenetic activity, then rapidly vanishes or dissipates into irrelevance—quite the contrary. Macrocycles of very diverse chemical classes continue to generate a high level of interest from the drug discovery community, with an impressive number already in or entering the clinic.

When we started working over 15 years ago at one of the pioneering companies in this area, NéoKimia (later Tranzyme Pharma), formed to realize the vision of Prof. Pierre Deslongchamps regarding libraries of conformationally defined and chemically diverse macrocyclic molecules, there was only one other company (Polyphor) primarily focused on using macrocycles for drug discovery purposes, and few academics had research focused on these structures. At the time, we met with considerable skepticism that such molecules could ever be effective synthetic drugs. Now, that situation has changed dramatically, with over 30 companies involved in pursuing macrocycles as a key aspect of their R&D, while the number of scientific papers on the topic has exploded.

As a result, we felt it would be very timely to assemble a reference book on the medicinal chemistry of macrocycles. From the onset, we wanted this to be a practical guide targeting both experts and their teams, as well as neophytes.

Accordingly, this book is directed to both scientists engaged in drug discovery with macrocycles and those contemplating the use of macrocycles yet have no previous experience with this chemical class. We did not cover allied topics in macrocyclic chemistry, even if they could have some pharmaceutical relevance, including molecular recognition, supramolecular architectures, host–guest molecules, metal chelators, or chromatographic stationary phases.

Macrocycles actually are, in several ways, a polarizing molecular class. On the one hand, they attract researchers for their extraordinary potential to tackle difficult targets, their versatility as scaffolds for diversity generation, and the multiple opportunities they provide to optimize lead compounds. On the other hand, macrocycles can elicit untoward feelings because of notions—often outdated—on the challenges of synthesis, scale-up, diversification, or optimization of drug-like properties. Granted, macrocycles are often more synthetically challenging than traditional small molecules yet have definitely proven their worth to tackle difficult pharmacological target classes. In that sense, macrocycles can be considered as “high hanging molecules for high hanging targets.”

In this volume, we have aimed to capture the important aspects of macrocycles as they pertain to medicinal chemistry. This ranges from critical challenges inherent to the class, to an analysis of the various subclasses of macrocycles and where they currently fit in drug discovery, through proven or exploratory methods to make and characterize them, and, finally, to further stimulate ideas of scientists interested in macrocycle drug discovery, several case studies from diverse compound classes and therapeutic indications. Throughout the preparation, we pressed individual authors to keep their contributions as hands-on and practical as possible—within the context of a reference book—to serve as a valuable information source or starting point depending on the reader's objectives. As a result, the book is separated into four main sections.

Part I focuses on challenges specific to macrocycles. The goal is to communicate what makes macrocycles special or distinctive in the context of drug discovery. In Chapter 1, Zaretsky and Yudin single out critical aspects related to the key transformation inherent in the synthesis of all macrocycles, that is, the cyclization process. The fact that this reaction is unimolecular brings significant challenges but also many opportunities. In Chapter 2, Craik, Kaas, and Wang give a detailed, hands-on description of the methods available to characterize and elucidate the structure of macrocycles, largely inspired from their extensive works on natural
Introduction

macrocyclic peptides, which have been structurally elucidated, synthesized, and diversified in all forms and sizes. Finally, in Chapter 3, Price, Mathiowetz, and Liras share their expertise, and that of their broad network of academic collaborators, on the current understanding of permeability and oral absorption of macrocycles and the ways to improve these important properties. This has been—and remains—an area of intense investigation in an effort to “crack the code,” assuming there is one, of structure–permeability relationships in macrocycles. These works relate mostly to macrocyclic peptides and have been the genesis of efforts to understand what is now commonly known as the beyond-Rule-of-5 (bRo5) class.

Part II is devoted to covering the main chemical classes of macrocycles and their potential in drug discovery, as these constitute the knowledge base for medicinal chemists and the starting points of their future efforts. In Chapter 4, this begins with naturally inspired macrocycles by Wessjohann, Bartelt, and Brandt. Chapter 5, from Bockus and Lokey, is devoted to macrocyclic peptides, which constitute one of the two main classes of macrocycles from natural and unnatural origins. Since diversity generation is an integral tool in drug discovery, with high-throughput screening of compound libraries providing the initiation point for most projects, we subsequently move to two chapters specifically aimed at exploring and expanding the chemical diversity of macrocycles. In Chapter 6, Qian, Dougherty, and Pei describe existing chemical approaches to macrocycle libraries. Vitali and Fasan in Chapter 7 then extensively review hybrid chemistry/biology strategies used for diversity generation. Indeed, these approaches, despite limitations inherent to the biological machinery employed, have exploded the numbers of compounds accessible and become a rapidly evolving mainstream method for massive diversity generation. Finally, in Chapter 8, Leitch and Tavassoli expand on the role of macrocycles specifically as modulators of protein–protein interactions (PPI), a target class for which small molecules have generally performed poorly and for which macrocycles have emerged as privileged scaffolds owing to their unique combination of large molecular surface area, conformational restriction, and spatial display of pharmacophores.

Part III, the synthetic toolbox, makes available to the reader the many and diverse synthetic methods useful to construct macrocycles. In Chapter 9, Biron, Vézina-Dawod, and Bédard describe the various methods for making macrocyclic peptides. Gaddam, Mallurwar, Konda, Khatravath, Aeluri, Mitra, and Arya exemplify in Chapter 10 the use of ring-closing metathesis (RCM), a method that nowadays needs no introduction since it became the subject of the Nobel Prize in Chemistry in 2005, to build specific pharmacologically relevant structural types of macrocycles investigated in their myriad synthetic efforts toward diversity generation. Owing to the numerous excellent reviews and books devoted to RCM, we decided not to provide yet another review on the topic here but rather to exemplify the actual use of RCM in diversity generation. In Chapter 11, Pehere and Abell describe Huisgen cycloadditions in the context of macrocyclization. Subsequently, Ronson, Unsworth, and Fairlamb describe the various and versatile Pd-catalyzed approaches employed for the synthesis of macrocycles in Chapter 12, whereas in Chapter 13, Santandrea, Bédard, de Léséleuc, Raymond, and Collins summarize the numerous other strategies used to make macrocycles. As a testimony to chemists’ creativity, this chapter presents a broad range of methods, leading to a wealth of macrocyclic structures. In Chapter 14, Wessjohann, Neves Filho, Puentes, and Morejón relate several multicomponent reactions (MCR) applied to the macrocyclization reaction. Finally, since efficient large-scale synthesis is one of the limiting steps to advance compounds into clinical development and macrocycles were perceived, at least 15 years ago as we recounted earlier, as molecules too difficult to prepare to be exploited as pharmaceutical agents, Kong presents in Chapter 15 several methods successfully applied to macrocycle synthesis at manufacturing scale. Although a number of these are proprietary and the subject of carefully guarded know-how, this chapter exemplifies how creative synthetic methods can deliver multi-kilogram quantities of macrocycles.

Finally, Part IV is dedicated to case studies of macrocycles in clinical development or approved as drugs. In Chapter 16, as an introduction to this section, Stotani and Giordanetto summarize the various classes of macrocycles and the individual compounds of each in clinical development. In Chapter 17, Terrett relates the discovery of XIAP antagonists stemming from DNA-encoded technologies. In Chapter 18, Yamazaki, Lam, and Johnson then share their experience in the discovery of lorlatinib, an inhibitor of the ALK kinase able to tackle resistant forms of the kinase, including those found in brain metastases. In Chapter 19, Hoveyda, Fraser, Marsault, Gagnon, and Peterson provide a detailed account of the efforts leading to TZP-102, a ghrelin receptor agonist for the treatment of hypomotility disorders. Finally, in Chapter 20, Pereira, Wu, Majuru, Schneider, and Pradeep describe the research that led to the identification of solithromycin, a very interesting example of a macrocyclic natural product derivative optimized through semisynthesis. The experienced reader will notice that no chapter is devoted to one of the targets that has benefited most from the particular attributes of macrocycles and provided the largest number of macrocyclic development candidates, that is, the hepatitis C virus NS3/4A protease. Similarly to RCM,
this has been covered extensively in previous reviews; thus, we made an editorial choice not to do so yet again. By no means does this indicate a lack of relevance of this particular inhibitor class, which has been one of the initial and most fertile playgrounds of macrocycle drug discovery. Readers are instead referred to the abundance of existing publications on the topic.

As editors, we gave individual authors considerable freedom to express their creativity within the themes that were entrusted to them, delve into their own experiences—good and bad—and provide the reader with hands-on examples and make choices for what was most relevant to their topic. As a result, some examples may be cited in more than one chapter, which is more a testimony to the broad impact of some works across various dimensions of macrocycle drug discovery, rather than simple editorial redundancy.

We sincerely hope that this book will prove useful and instructive for a broad variety of individuals, from novices looking to understand the ins and outs of macrocycle drug discovery to experienced practitioners willing to expand their knowledge on specific aspects of this exciting field.

Finally, we wish to sincerely thank all the coauthors who devoted numerous hours of their precious time and generously shared their knowledge and expertise on this stimulating topic. The book is the result of their collective hard work and dedication.
About the Contributors

Andrew D. Abell
Dr. Abell graduated from the University of Adelaide with B.Sc. (Hon) and Ph.D. degrees and then undertook a postdoctoral fellowship at the University of Cambridge. He held a professorship at the University of Canterbury before returning to the University of Adelaide in 2007, where he is currently a professor of chemistry and node director of the ARC Centre of Excellence for Nanoscale BioPhotonics. His research interests are concerned with understanding the fundamental link between the chemical structure and shape of key bioactive molecules and their biological function. While his work is very much driven by fundamental science, he has always had a keen interest in pursuing associated commercial opportunities. The seed for this was sown with a sabbatical leave working as a visiting scientist, consultant, and senior Fulbright fellow with SmithKline Beecham (now GSK) in Philadelphia. In Australia, he co-founded an Adelaide-based company (Calpain Therapeutics) to develop macrocyclic protease inhibitors as a potential treatment for cataract and other conditions. He served as the Head of School of Chemistry and Physics at the University of Adelaide and is a recent recipient of the Royal Australian Chemical Institute Adrien Albert Prize and the Alexander R. Matzuk Prize and Lecture in Drug Discovery (Baylor College of Medicine, Houston).

Madhu Aeluri
Madhu Aeluri was born in Telangana, India, in 1987. He completed his B.Sc. in 2007 and M.Sc. with specialization in organic chemistry in 2009 from Osmania University. He obtained his Ph.D. in chemistry in 2014 from the University of Hyderabad under the guidance of Professor Prabhat Arya at Dr. Reddy's Institute of Life Sciences (affiliated to University of Hyderabad). After the completion of his doctoral studies, he served as an associate scientific officer at GVK Biosciences Pvt Ltd., Hyderabad, for 2 years. Currently, he is working as a postdoctoral fellow in Professor Prabhat Arya's research group. His research interests are the synthesis of natural product-inspired and natural product-derived small molecules hunting for small molecule modulators of protein–protein interactions.

Prabhat Arya
Prabhat Arya was born in 1958 and grew up on the University of Delhi campus where he received his undergraduate and graduate training. Following postdoctoral tenures at Cambridge and McGill Universities, he joined the National Research Council of Canada in Ottawa and worked with this organization for nearly 20 years. Later, he also had a short stint at the Ontario Institute of Cancer Research helping build the Medicinal Chemistry Program. In July 2009, he decided to follow an adventurous path and moved back to India with the objectives of establishing an integrated chemical biology program and thoroughly connecting his academic program to society and the business world. For him, this has been an exciting journey and a good learning path so far. He enjoys spending time with students and teaching Stereoselective Organic Synthesis to a wider audience in India. Overall, his research is focused on developing synthesis methods that allow building a chemical toolbox with compounds that are closer to bioactive natural products. These compounds can be classified as natural product-inspired and hybrid natural products. The ultimate interest is in addressing challenging biological questions related to protein–protein interactions and pathways with an extensive use of small molecules emerging from his group. Prior to moving back to India (that he does not regret so far), he was also an adjunct professor at the...
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Richard Bartelt
Richard Bartelt was born in Wilhelm-Pieck-Stadt Guben, Germany, in 1987. He studied biochemistry at the Martin Luther University Halle-Wittenberg, received his bachelor’s degree in 2011 on the topic of “3D-QSAR of Substrates of the Human Amino Acid Transporter hPAT2,” and continued his studies until 2014. Under the supervision of Prof. Wessjohann and docent Dr. Brandt, he prepared his master’s thesis—“Homology Modelling of Prenylating Enzymes and Elucidation of Their Catalytic Mechanism”—at the Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry (IPB), Halle. Since then, he has focused on chemoinformatic analyses of macrocycles in the same research group.

Anne-Catherine Bédard
Anne-Catherine Bédard was born in Québec, Canada, in 1987. She received her B.Sc. in Biopharmaceutical Sciences from the University of Ottawa in 2010 and her Ph.D. from the Université de Montréal under the supervision of Prof. Shawn K. Collins in 2015. She is currently an NSERC postdoctoral fellow in the laboratories of Prof. Tim F. Jamison at MIT.

François Bédard
François Bédard has completed a B.Sc. in Biochemistry and an M.Sc. in Pharmaceutical Sciences at Université Laval. He then commenced his Ph.D. studies in pharmaceutical sciences under the guidance of Prof. Éric Biron and Prof. Ismail Fliss at the Institute of Nutraceuticals and Functional Foods at Université Laval in 2014. As a Fonds de recherche du Québec – Nature et technologies (FRQNT) scholar, he is currently working on the synthesis, characterization, and pharmacokinetic studies of antimicrobial peptides from the bacteriocin family. His research interests include the synthesis and applications of natural cyclic peptides with antimicrobial activities and the design and development of antimicrobial peptide mimetics.

Éric Biron
Éric Biron obtained his Ph.D. in Chemistry under the direction of Prof. Normand Voyer at Université Laval, Canada, on the design and synthesis of functional peptidic nanostructures as artificial ion channels and DNA intercalators. After his Ph.D. in 2003, he moved to the Technische Universität München in the laboratory of Prof. Horst Kessler as a postdoctoral Alexander von Humboldt fellow. During his stay, he worked on the synthesis of N-methylated peptide macrocycles and studied the effects of multiple N-methylations on the conformation and activity of bioactive cyclic peptides. Upon conclusion of his postdoctoral studies, he returned to Québec and joined the Faculty of Pharmacy at Université Laval as a junior research scholar from the Fonds de recherche du Québec en Santé (FRQS). His research program focuses on the design and synthesis of cyclic peptides and macrocyclic peptidomimetics with antimicrobial activities and the development of new strategies to prepare and screen combinatorial macrocycle libraries. Prof. Biron is currently an associate professor at the Faculty of Pharmacy of Université Laval and a researcher at the Laboratory of Medicinal Chemistry at the Centre de recherche du Centre hospitalier universitaire de Québec in Québec City, Canada.

Andrew T. Bockus
Andrew T. Bockus earned his B.A. in Chemistry from Skidmore College in 2008 where he engaged in enzymology research with Professor Michelle Frey. In the following year as an instructor of English at China University of Petroleum in Beijing, Andrew joined the lab of Professor Scott Lokey at the University of California, Santa Cruz, to study the structure–permeability relationships of cyclic peptides, completing
his Ph.D. in 2015. He continued his academic career postdoctoral work at Trinity University, where he taught undergraduate courses and studied the molecular recognition of peptides and proteins by synthetic hosts under the guidance of Professor Adam Urbach. Andrew currently works on the development of cyclic peptide therapeutics at Circle Pharma, Inc.

**Wolfgang Brandt**
Wolfgang Brandt studied chemistry at the Martin Luther University Halle-Wittenberg in Halle (Germany), where he received his degree in Chemistry in 1979 and his Ph.D. in 1982 for studies on “structure–activity relationships of auxins” under the supervision of Professor Alfred Barth. From 1985 to 1986, he was a scientific coworker at the Institute of Neurobiology and Brain Research Academy of Science of the GDR (then East Germany) in Magdeburg. In 1987, he became head of the research group “Molecular Modeling—Drug Design” at the Department of Biochemistry/Biotechnology of the University of Halle. In 1992, he was on sabbatical leave at the Clinical Research Institute of Montreal, Canada (Prof. Dr. P. W. Schiller). He received his “Habilitation” (Asst. Prof.) in 1997. In August 2001 he moved to the Department of Bioorganic Chemistry headed by Prof. Ludger Wessjohann at the Leibniz Institute of Plant Biochemistry in Halle as a group leader for computational chemistry. His research interests cover all fields of computational chemistry and molecular modeling. He has published over 170 scientific papers, books, and some licensed patents.

**Shawn K. Collins**
Shawn K. Collins obtained a B.Sc. degree from Concordia University in 1996 and his Ph.D. at the University of Ottawa (Prof. A. G. Fallis) in 2001. After an NSERC postdoctoral fellowship with Professor L. E. Overman (University of California, Irvine), he joined the faculty at Université de Montréal in September 2003 and was promoted to Full Professor in 2015. Professor Collins’ research group is interested in the development of novel synthetic methods, particularly involving catalysis, photochemistry, and continuous flow methods.

**David J. Craik**
David J. Craik obtained his Ph.D. in Organic Chemistry from La Trobe University in Melbourne, Australia, and undertook postdoctoral studies at Florida State and Syracuse Universities before taking up a lectureship at the Victorian College of Pharmacy in 1983. He was appointed Professor of Medicinal Chemistry and Head of School in 1988. He then moved to University of Queensland in 1995 to set up a new biomolecular NMR laboratory and is currently an NHMRC senior principal research fellow and group leader in IMB. His research focuses on applications of circular proteins, toxins, and NMR in drug design. He is also a fellow of the Australian Academy of Science and has received numerous awards for his research, including the Ralph F. Hirschmann Award from the American Chemical Society. He is an author of more than 600 scientific papers and has trained 60 Ph.D. students.

**Patrick G. Dougherty**
Patrick G. Dougherty completed his B.S. in Chemistry and Biochemistry at Florida State University in 2013. He joined the Pei group at the Ohio State University in 2014. His research currently focuses on integrating chemical biology and computational chemistry approaches for macrocyclic drug discovery and lead optimization against therapeutically relevant intracellular PPIs.

**Ian J. S. Fairlamb**
Ian J. S. Fairlamb was appointed as lecturer in York in 2001, following a Ph.D. with Dr. J. M. Dickinson in Manchester (1996/1999) and postdoctoral research with Prof. G. C. Lloyd-Jones in Bristol (2000/2001). He was a Royal Society URF (2004/2012) and promoted to Full Professor in 2010. He leads a talented research group interested in catalysis, mechanism, and synthesis. Recent work includes Pd and Mn catalyst and
ligand design, involvement of higher-order Pd species (e.g., nanoparticles), and exploitation of mechanistic understanding in purine and amino acid C–H functionalization. He has interests in the application of Pd and Au catalysis in macrocyclic ring synthesis, for example, phacelocarpus 2-pyrene A.

Rudi Fasan

Rudi Fasan was born in Italy and studied pharmaceutical chemistry at the University of Padua, where he received his undergraduate degree (B.S.) with the highest honors in 1999. In 2001, he joined the group of Prof. John A. Robinson at the University of Zurich (Switzerland) as a graduate student, working on the design and synthesis of beta-hairpin protein epitope mimetics. In 2005, he joined Prof. Frances H. Arnold’s group at the California Institute of Technology as a Swiss National Science Foundation postdoctoral fellow, working on the directed evolution of P450 enzymes for alkane oxidation. Dr. Fasan began his independent career as a member of the Department of Chemistry of the University of Rochester in 2008 and was promoted to the rank of Associate Professor in 2014. His research interests lie in the area of bioorganic chemistry, chemical biology, protein engineering, biocatalysis, and chemoenzymatic synthesis. His research group currently focuses on the synthesis, evolution, and application of macrocyclic peptides and organo-peptide hybrids for targeting and modulation of cancer-related protein–protein interactions and on the design and investigation of engineered and artificial metalloenzymes for selective late-stage C–H functionalization and for asymmetric synthesis of carbon–carbon and carbon–heteroatom bonds. His awards include a Swiss National Science Foundation Graduate Fellowship (2001–2005) and Postdoctoral Fellowship (2005–2007), the 2007 Friedrich-Weygand Outstanding Graduate Research Award, University of Rochester’s Multidisciplinary Research Award (2011) and University Award (2016), and the 2014 Tetrahedron Young Investigator Award for Bioorganic and Medicinal Chemistry.

Graeme L. Fraser

Graeme L. Fraser has more than 20 years of industry experience in both management and technical positions. Previously, Graeme was V.P. of Drug Discovery at Tranzyme Pharma (Sherbrooke, Canada) where he led the discovery and preclinical development activities for a pipeline of GPCR-small molecule programs. Earlier, he managed preclinical development activities at Viron Therapeutics Inc. (London, Canada) and led specific GPCR target validation activities at Astra Pain Control AB (Södertälje, Sweden, and Montreal, Canada). In total, he has directed research activities for three products currently in clinical development. Graeme received a Ph.D. from McGill University (Montreal, Canada) and is an author of over 50 publications and research abstracts, including 9 patents and 2 IND filings.

Jagan Gaddam

Jagan Gaddam was born in Telangana, India (1984). He was awarded a bachelor’s degree in life sciences from Osmania University, Hyderabad (2005) and a master’s degree in organic chemistry (2008) from Kakatiya University. He joined Professor Prabhat Arya’s research group in 2011 at Dr. Reddy’s Institute of Life Sciences of the University of Hyderabad for doctoral studies. His research interests are in the synthesis of natural product-inspired macrocycles and in building natural product-derived macrocyclic toolbox. His Ph.D. research is mainly focused on stereoselective synthesis of neopeltolide-inspired macrocycles.

René Gagnon

René Gagnon earned his Ph.D. in Organic Chemistry in 1993 from University Laval (Québec). He then joined the team of Stanley M. Roberts at University of Exeter (United Kingdom) as a postdoctoral fellow working on enzymatic catalyze in organic synthesis. In 1995, at the Armand-Frappier Institute, he was implicated in biosynthesis studies on taxol and related analogues. He moved in 1996 to Sherbrooke to be part of Prof. Pierre Deslongchamps team. In 1998, he was mandated to build the analytical division of a new promising drug discovery company named Neokimia (founded by Prof. Deslongchamps). He was appointed in 2003 as head manager of the analytical division of Tranzyme Pharma (resulting from the Tranzyme and Neokimia merger). Over the years, he was implicated in various fields related to drug
discovery, such as chemical library analysis, drug substance and drug product analysis, pharmacokinetic and stability studies, and purification and formulation of chemical entities. From 2007 to 2011, he was an associate professor at the genetic biomedical department of the CHUS working on pediatric diseases. From 2011 to 2015, he managed the mass spectrometry facility at the Chemistry Department of the University of Sherbrooke, where, since 2015, he joined its steering committee and also became the manager of the teaching laboratories.

**Fabrizio Giordanetto**

Fabrizio Giordanetto graduated with first-class honors in medicinal chemistry in 2000 from the University of Genova (Italy). He completed his Ph.D. in Computational Medicinal Chemistry in 2003 at the University of London (United Kingdom) while working for the chemistry unit of Pharmacia (Pfizer) in Nerviano (Italy). In 2004, he joined the Medicinal Chemistry Department of AstraZeneca in Mölndal (Sweden) where he grew professionally to the position of Principal Scientist and Preclinical Project Leader. Since 2013, he has been Director of Medicinal Chemistry for Taros GmbH, a research-based SME in Dortmund (Germany), where he leads proprietary and third-party medicinal chemistry activities. During his career, he worked on several drug discovery projects resulting in multiple clinical candidates spanning oncology and cardiovascular indications and has more than 80 peer-reviewed publications, book chapters, and international patents.

**Hamid R. Hoveyda**

Hamid R. Hoveyda obtained his Ph.D. from the University of British Columbia (Vancouver, Canada) followed by a stint at Harvard University as an NSERC postdoctoral fellow. He began his industrial career at the Affymax Research Institute (CA, USA) working on applications of diversity-oriented synthesis in drug discovery. In 2001, he joined Neokimia Inc. (Sherbrooke, Canada), which later became known as Tranzyme Pharma, where he contributed initially to the platform HTS library technology and was subsequently in charge of lead optimization efforts across several projects including the ghrelin project that culminated in two clinical candidates (ulimorelin, TZP-102) as potential GI therapeutics. Since September 2007, he has led medicinal chemistry efforts on various GPCR targets at Euroscreen (Belgium) that has resulted, inter alia, in the discovery of ESN364 clinical candidate, an NK3R antagonist currently in phase IIA for the treatment of sex-hormone disorders. His scientific contributions thus far have been captured in over 50 publications and patents.

**Ted W. Johnson**

During his undergraduate studies at the University of California, Irvine, as a Chemistry major, Ted performed research under the direction of Professor Harold Moore where he worked on the synthesis of quinone antitumor/antifungal agents, completing the synthesis of nanaomycin D and making progress toward the total synthesis of griseusin A. He received his B.S. degree in Chemistry in 1994. During his graduate studies at the University of California–Los Angeles with Professor Michael Jung, he completed the total synthesis of 7-deoxy-xestobergsterol A, xestobergsterol A, and several potent antihistamine unnatural analogues. He simultaneously carried out synthetic studies toward the synthesis of eleutherobin, a potent antitumor compound. He was awarded the Saul Weinstein Fellowship, the Gregory Research Fellowship, and the Distinguished First-Year Graduate Student Award. Ted received his Ph.D. in 1999. As an NIH postdoctoral fellow at Harvard University with Prof. E.J. Corey, Ted completed the total synthesis of putative pseudopteroxazole, a potent antituberculosis compound, showcasing an unprecedented diastereoselective intramolecular imidoquinone Diels–Alder reaction. During his studies and ongoing 15 years as a medicinal chemist at Pfizer in La Jolla, California, Ted published many high-profile patents and publications. He won the American Chemical Society Young Investigator Award in 2011 and the Pfizer Global Medicinal Chemistry Award in 2013. Most notably, he was the co-project leader of the ALK program and co-designed lorlatinib, which is currently a kinase inhibitor in phase 2 clinical trials for the treatment of ALK positive non-small cell lung cancer (NSCLC). Notably,
lorlatinib was designed to be potent against drug resistant mutants of ALK and also penetrate the central nervous system, a major challenge in kinase inhibitor space. Ted continues to work at Pfizer, La Jolla, in the Oncology Department.

Quentin Kaas
Quentin Kaas obtained his Chemical Engineering degree in 2001 from the École Nationale Supérieure de chimie de Montpellier (ENSCM) and his Ph.D. degree in chemical biology in 2005 from the University of Montpellier II. He conducted 1 year of postdoctoral research in the Laboratory of Immunoinformatics of Professor Marie‐Paule Lefranc in Montpellier, studying antigen/receptor interactions. He was then awarded an Australian postdoctoral fellowship by the Australian Research Council to undertake 3 years of postdoctoral research on plant cyclic peptide structure–activity relationships in the laboratory of Professor David J. Craik at the Institute for Molecular Bioscience of the University of Queensland, Australia. He is currently working in that laboratory where he focuses on structural bioinformatics and computational modeling studies of toxins extracted from plants and animals. He has developed and currently maintains the only database specialized on sequences and structures of cone snail toxins, ConoServer (http://www.conoserver.org/MacrocyclesDavidCraikManuscript_revised.doc).

Mahender Khatravath
Mahender Khatravath was born in Telangana, India (1988). He received his B.Sc. degree from Osmania University in 2008 and M.Sc. degree with specialization in organic chemistry from M.N.R. P.G. College (affiliated to Osmania University) in 2010. He joined as a doctoral student at the Dr. Reddy’s Institute of Life Sciences, University of Hyderabad, under the supervision of Professor Prabhat Arya and obtained his Ph.D. in Chemistry (2016). Currently, he is working as a national postdoctoral fellow under the supervision of Dr. Srinivasa Reddy at the National Chemical Laboratory, Pune. His research focuses on stereoselective synthesis of substructures of eribulin and related macrocyclic compounds.

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Saidulu Konda was born in Telangana, India (1985). He received his B.Sc. degree from Osmania University in 2007 and M.Sc. degree with specialization in organic chemistry from M.N.R. P.G. College (affiliated to Osmania University) in 2010. He received his Ph.D. degree from Hyderabad Central University in 2016. Presently, he is working as an associate scientist at GVK Biosciences Private Limited, Hyderabad.

Jongrock Kong
Jongrock Kong obtained his bachelor’s degree from Sungkyunkwan University and master’s degree from Pohang University of Science and Technology (POSTECH) in the Republic of Korea. In 2002, he started his graduate studies with Professor Michael J. Krische at the University of Texas at Austin, where he studied hydrogen-mediated reductive C–C bond formation. After the completion of his Ph.D. in 2007, he moved to Princeton University for a postdoctoral fellowship with Prof. David W. MacMillan and worked on enantioselective α-arylation of aldehyde via organo-SOMO catalysis. In 2009, he joined the Process Research Department at the Merck Research Laboratories in Rahway, NJ, where he has been focusing on the development of robust processes for drug candidates.

Justine L. Lam
Dr. Justine L. Lam is a senior principal scientist at Pfizer Worldwide Research and Development in the department of pharmacokinetics, dynamics and metabolism (San Diego, CA). She received her Ph.D. degree in pharmaceutical sciences and pharmacogenomics from the University of California in San Francisco, under the guidance of Professor Leslie Z. Benet. Since joining Pfizer in 2006, she provided DMPK strategies to projects in all stages of drug discovery and development.
As a member of AAPS and ISSX, Dr. Lam's expertise and research interests are in the area of drug transporters and their impact on drug disposition, metabolism, and drug–drug interaction. Her most recent research is focusing on the drug transporters in the blood–brain barrier and their impact on brain penetration.

Eilidh Leitch

Eilidh Leitch is currently a third-year Ph.D. student in the Tavassoli group at the University of Southampton, United Kingdom. Previously, Eilidh received her B.Sc. in Biochemistry and M.Sc. in Oncology, both at the University of Nottingham, United Kingdom. Eilidh then went on to work at Sygnature Discovery in Nottingham, within the bioscience department, providing assay development and routine screening as part of the integrated drug discovery model. Eilidh’s Ph.D. studies focus on the development, identification, and characterization of cyclic peptide inhibitors of a metabolic protein–protein interaction target through the utilization of SICLOPPS.

Mylène de Léséleuc

Mylène de Léséleuc was born in Hull, Québec, Canada, in 1989. In 2011, she received her B.Sc. in Chemistry from the University of Ottawa and pursued her graduate studies (Ph.D.) at the Université de Montréal under the supervision of Prof. Shawn K. Collins. She is currently a senior research scientist at OmegaChem in Laval, Québec.

Spiros Liras

Spiros Liras is the Vice President of Medicinal Chemistry and Head of the Cardiovascular, Metabolic, and Endocrine Diseases (CVMET) Medicinal Chemistry at Pfizer Worldwide Research and Development. Prior to joining CVMET, Spiros was Senior Director of Medicinal Chemistry in Neuroscience at Pfizer. In Neuroscience, Spiros was involved in research aiming to deliver treatments for addiction, depression, schizophrenia, cognition, and Alzheimer's disease. Spiros joined Pfizer medicinal chemistry in 1994 after completing postdoctoral research in organic synthesis at the University of Texas, Austin. Spiros obtained a Ph.D. in organic chemistry in 1990 from Iowa State University.

Shingai Majuru

Shingai Majuru is the Executive Director of Oral Drug Product Development at Cempra, Inc., Chapel Hill, North Carolina. He has 20 years of experience in the pharmaceutical industry. His areas of expertise include formulation development, clinical supplies manufacture, technology transfer, process scale-up, process validation, and drug delivery technology development. He earned a B. Pharm. (Hons) degree and a Master of Medicine from the College of Pharmacy of the University of Zimbabwe. He is also a holder of an M.Sc. and Ph.D. in Pharmaceutics from the College of Pharmacy of the University of Iowa. Shingai obtained an M.B.A. from Ancell School of Business of Western Connecticut State University.

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Naveen Kumar Mallurwar was born in Telangana, India (1985). He obtained his bachelor's degree in 2005 and master's degree with specialization in organic chemistry in 2007 from Kakatiya University. He received his Ph.D. degree from the University of Hyderabad in 2016 under the supervision of Professor Prabhat Arya at Dr. Reddy's Institute of Life Sciences of said university. His research interests are the synthesis of natural product-derived hybrid macrocycles and natural product-inspired macrocycles.

Eric Marsault

Eric Marsault obtained his Ph.D. at McGill University (Montreal, QC, Canada) in 1996 with the late Prof. George Just and then worked as a visiting scientist for Sanofi (Milan, Italy) prior to moving to Université de Sherbrooke (QC, Canada) as a postdoctoral fellow with Prof. Pierre Deslongchamps.
He joined Neokimia (which later became Tranzyme Pharma) in 2000, where he worked as a researcher, group leader, and then director of the medicinal chemistry department. During this time, he took an active role in maturing the first platform enabling high-throughput parallel synthesis of macrocycles that delivered up to 40,000 macrocyclic peptidomimetics and became the core of the company. Based on these, several drug discovery programs were established, aimed primarily at GPCR targets, leading to the identification of several preclinical candidates, including clinical candidates ulimorelin and TZP-102.

In 2009, he joined the Department of Pharmacology of Université de Sherbrooke as a professor, where he now focuses on the development of new molecules to validate emerging drug targets in the context of academic drug discovery, with a particular focus on peptidomimetics and macrocycles targeting GPCRs and transmembrane serine proteases for cardiovascular diseases, pain, and infectious diseases. He is coauthor of more than 50 publications and co-inventor of more than 30 patents. Since 2013, he is also the chairman of the Institut de pharmacologie de Sherbrooke.

Alan M. Mathiowetz

Alan M. Mathiowetz is currently the Director of Computational Chemistry in the Cardiovascular, Metabolic, and Endocrine Diseases (CVMET) Medicinal Chemistry Department within Pfizer Worldwide Research and Development. Alan obtained a B.A. in Chemistry at Rice University and a Ph.D. from the California Institute of Technology in Pasadena, California. Alan has worked in a number of technology and therapeutic areas within Pfizer, with an emphasis on structure-based design and virtual screening, in silico modeling and physical property analyses, and therapeutics targets for type II diabetes and obesity.

Prasenjit Mitra

Prasenjit Mitra researches on the regulation of cellular metabolism and energy homeostasis at the interface of diabetes and cancer. He has obtained his Ph.D. at the Indian Institute of Chemical Biology, Kolkata, India, and postdoctoral research at UMass Medical School, Worcester, MA, USA. Currently, he is working as a principal research scientist at the Dr. Reddy’s Institute of Life Sciences located in the University of Hyderabad campus.

Micjel Chávez Morejón

Micjel Chávez Morejón was born in Pinar del Río, Cuba, in 1985. He earned his Bachelor in Chemistry Science from the University of Havana in 2009, in the field of antimicrobial peptide mimetics. He received his Master of Science in Organic Chemistry in 2011 from the Faculty of Chemistry, University of Havana, on the topic of “Multicomponent synthesis of polycationic peptidomimetic peptide–peptoid hybrids.” In 2012, he joined the Ph.D. program of the Leibniz Institute of Plant Biochemistry, Halle (Saale), in collaboration with the Martin Luther University Halle-Wittenberg, Germany, and University of Havana, Cuba. Under the supervision of Prof. Wessjohann and Prof. Rivera, he focused on the development of new multicomponent reaction strategies for the synthesis of cyclic lipopeptides, inspired by natural products.

Ricardo A. W. Neves Filho

Ricardo Antonio Wanderley Neves Filho was born in Recife/PE, Brazil, in 1984. He received his B.Sc. and M.Sc. degrees from the Federal University of Pernambuco (UFPE) in 2006 and 2008, respectively. In 2010, he moved to Germany and enrolled in the Ph.D. program in the Division of Organic Chemistry of the Martin Luther University Halle-Wittenberg, while working at the Leibniz Institute of Plant Biochemistry under the supervision of Prof. Wessjohann. In 2015, he finished his Ph.D. research that focused on the development of reagents for multicomponent reactions and their applications in the synthesis of natural products.

Ashok D. Pehere

Ashok Pehere received his B.Sc. and M.Sc. (Organic Chemistry) at the University of Pune, India. He was a research chemist at Merck Pharmaceutical in Mumbai, India, in 2002–2008, then received his Ph.D. at the University of Adelaide, Australia, under the direction of Professor Andrew D. Abell. This was followed by postdoctoral research at the University of Minnesota, USA, under the
direction of Professor Thomas R. Hoye and Professor Marc A. Hillmyer, working on Diels–Alder reactions of furans and polymer synthesis. Currently working at UT MD Anderson Cancer Center, his research interest is related primarily to the design, synthesis, and characterization of cyclic peptide and new macromolecular materials.

Dehua Pei
Dr. Dehua Pei obtained his bachelor’s degree in chemistry from Wuhan University, China, and Ph.D. in Organic Chemistry in 1991 from the University of California in Berkeley. After a postdoctoral fellowship at Harvard Medical School, he joined the faculty of Ohio State University in 1995 and is currently a professor of chemistry and biochemistry. His current research interests include the development of new combinatorial chemistry methods for macrocycle synthesis and screening, discovery of novel cyclic cell-penetrating peptides, and integration of the aforementioned two areas to develop macrocyclic inhibitors against challenging drug targets, such as intracellular protein–protein interactions.

David Pereira
David Pereira received a B.S. in Biochemistry from Virginia Tech in 1981. He conducted research on pyrrolizidine and indole carbamates as potential antineoplastic agents at Virginia Commonwealth University and earned a Ph.D. in Medicinal Chemistry in 1985. From 1985 to 1988, he was a postdoctoral scientist in the laboratory of Professor Nelson Leonard at the University of Illinois. David has been a research scientist in the pharmaceutical industry for over 25 years and has held senior management positions at Cempra, Inc., since 2006.

Mark L. Peterson
Prior to co-founding Cyclenium in December 2013, Dr. Peterson was the Vice President of IP and Operations at Tranzyme Pharma where he led the chemistry R&D efforts during the technology development stage of the company and the initiation of its GPCR drug discovery programs. He later focused on building and maintaining an extensive portfolio of over 120 patents and applications protecting Tranzyme’s pioneering technology and pharmaceutical product candidates. Previously with Monsanto and Advanced ChemTech, he has productively worked in a wide variety of research areas, including structure-based design, solid phase organic chemistry, combinatorial libraries, synthesis automation, heterocycles, unnatural amino acids, peptides, and peptidomimetics. A native of Wisconsin, he received his Ph.D. in Organic Chemistry from Washington State University (asymmetric synthesis) and conducted postdoctoral research at the University of Minnesota (antiviral carbocyclic nucleosides) prior to starting his industrial career. He is author or coauthor of over 90 publications and abstracted presentations and three book chapters, as well as co-inventor on over 25 patents.

Lovy Pradeep
Lovy Pradeep obtained her Ph.D. in Biochemistry/Biophysics in the field of protein folding and stability in 2004. She continued her academic research in protein folding and misfolding diseases at Baker Labs in Cornell University and later addressed the binding of small molecules to nicotinic acetylcholine receptors (nAChRs) using electrophysiology techniques, directed toward understanding Alzheimer’s disease. Lovy joined Cempra in 2013 and is the holder of RAC and PMP globally recognized certifications. She is currently the Senior CMC Program Manager and continues to work on several aspects of the various solithromycin dosage forms.

David A. Price
David A. Price currently holds the position of Senior Director of Medicinal Chemistry in the Cardiovascular, Metabolic, and Endocrine Diseases (CVMET) department within Pfizer Worldwide Research and Development. David obtained a B.Sc. (First-Class Hons.) and Ph.D. from the University of Nottingham, United Kingdom, after which he carried out postdoctoral research at Colorado State University with Prof. Al Meyers. During his tenure with Pfizer, David has worked on projects to develop drugs for a wide variety of diseases including HIV/AIDS, hepatitis C, respiratory diseases, and, most recently, type II diabetes and obesity.
**Alfredo R. Puentes**

Alfredo R. Puentes was born in Pinar del Río, Cuba, in 1983. He obtained his B.Sc. (*summa cum laude*) from the Faculty of Chemistry, University of Havana, Cuba. He obtained his master’s degree under the guidance of Prof. Wessjohann (Halle) and Prof. Rivera (Havana) in 2014. Currently, he is a Ph.D. student at the Department of Bioorganic Chemistry of Leibniz Institute of Plant Biochemistry (IPB) in Halle (Saale), Germany, in a cooperative study between Halle and Havana, studying new beta-turn inducers with synthetic application in macrocyclization reactions.

**Ziqing Qian**

Dr. Ziqing “Leo” Qian obtained his Ph.D. in 2014 from the Ohio State University under the guidance of Dr. Dehua Pei. Currently, he is a postdoctoral researcher in the same group. His research interests include the development of cyclic cell-penetrating peptides for drug delivery and cell-permeable macrocycles as intracellular PPI inhibitors.

**Michaël Raymond**

Michaël Raymond was born in Rimouski, Québec, Canada, in 1989. In 2011, he received his B.Sc. in Chemistry from the University of Ottawa and is pursuing his graduate studies (Ph.D.) at the Université de Montréal under the supervision of Prof. Shawn K. Collins.

**Thomas O. Ronson**

Thomas O. Ronson was born and brought up in Bristol in the southwest of England. He completed his undergraduate studies at the University of Oxford in 2011, having carried out a Part II project in the group of Professor Jeremy Robertson. He then moved to the University of York to pursue a Ph.D. under the joint supervision of Professors Ian J. S. Fairlamb and Richard J. K. Taylor, working toward the total synthesis of unusual macrocyclic natural products using novel palladium catalysts. Following the completion of his Ph.D. studies in 2015, he moved to the University of Antwerp where he currently works as a postdoctoral researcher in the group of Professor Bert Maes.

**Jeffrey Santandrea**

Jeffrey Santandrea was born in Montréal, Québec, Canada, in 1990. In 2012, he received his B.Sc. in Chemistry from the Université de Montréal and is currently pursuing his graduate studies (Ph.D.) at the Université de Montréal under the supervision of Prof. Shawn K. Collins.

**Stephen E. Schneider**

Stephen E. Schneider was formally introduced to chemistry at the North Carolina School of Science and Math by Dr. Lawrence Knecht. He received his B.S. degree from the University of Texas in Austin in 1999 under the supervision of Professor Eric V. Anslyn. Stephen began his career as a process chemist at Trimeris, Inc., and is currently Executive Director, Chemistry at Cempra, Inc.

**R. Scott Lokey**

R. Scott Lokey did undergraduate research in organometallic chemistry with Professor Nancy Mills at Trinity University and received his Ph.D. at the University of Texas, Austin, working under Professor Brent Iverson, where his research centered on the synthesis of molecules that fold into protein-like shapes in water and bind to specific DNA sequences. He did postdoctoral research at Genentech, where he worked on the synthesis of bioactive cyclic peptides, and then at Harvard Medical School and the Institute of Chemistry and Cell Biology with Professors Timothy Mitchison and Marc Kirschner on chemical biology approaches to the study of the actin cytoskeleton. He joined the faculty of the Department of Chemistry and Biochemistry at UCSC in 2002, where his research group focuses on the relationship between molecular structure and drug-like