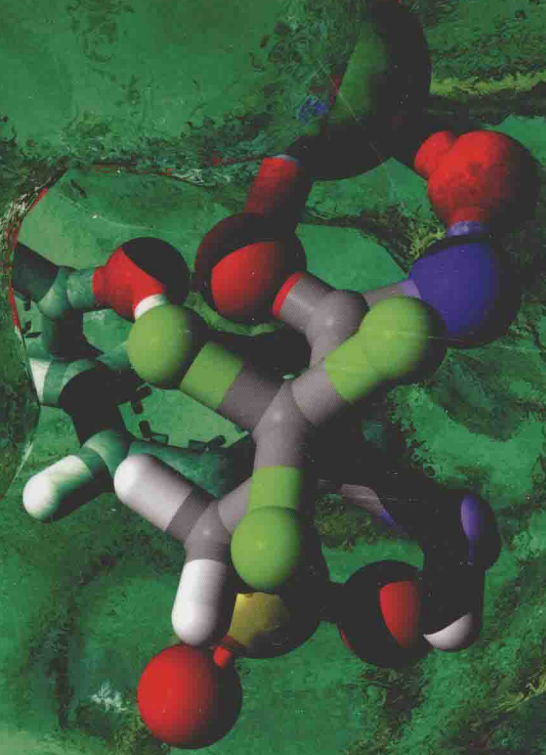
Volume 6

Molecular Medicine and Medicinal Chemistry

# Fluorine in Pharmaceutical and Medicinal Chemistry

## From Biophysical Aspects to Clinical Applications



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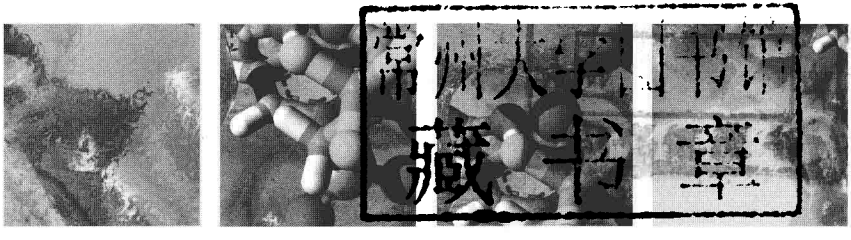


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# Fluorine in Pharmaceutical and Medicinal Chemistry

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## Molecular Medicine and Medicinal Chemistry



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**Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications**
*edited by Véronique Gouverneur (University of Oxford, UK) and Klaus Müller (F Hoffmann-La Roche AG, Switzerland)*

# Foreword

*François Diederich*

For almost a century after the first preparation of elemental $F_2$ by Moissan in 1886, synthetic fluorine chemistry was pursued and developed by a small community of experts capable of handling the aggressive gas using special laboratory equipment. Important technological developments resulted from this work, such as the bulk-scale preparation of fluorinated hydrocarbons for refrigerators and other cooling devices, which, however, later became banned due to their atmospheric greenhouse effects and the depletion of the ozone layer. Nonetheless, lasting successful applications resulted, for example, from the development of fluorinated polymers such as Teflon®, of volatile gases for anesthesia, and of the separation of uranium isotopes using $UF_6$ centrifuges, for the production of nuclear fuel for use in powerplants.

The development of fluorine-containing drugs started in 1957 and was in the following years strongly aided by the increasing availability of commercial fluorinating agents allowing the safe and selective introduction of organofluorine, i.e. C–F bonds, using common laboratory equipment. This has resulted in the introduction of over 150 fluorinated drugs to the market, and currently nearly 20% of all pharmaceuticals and 40% of all agrochemicals in development contain organofluorine.

The reasons for this explosive growth in interest in the introduction of organofluorine are multiple. While beneficial effects on ADME (absorption, distribution, metabolism, and excretion) and safety were recognized earlier on, the interest in organofluorine has lately focused on more atom-based properties, such as distinct conformational and stereoelectronic properties, modulation of the $pK_a$-value of neighboring

Brønstedt acid/base centers, polarity, and the influence on lipophilicity as expressed by the distribution coefficient log*D* and the partition coefficient log*P* (both for the octanol/water system). Additionally, attention has shifted on intermolecular interactions of organofluorine, such as H-bonding and dipolar interactions, and it has been shown that selective organofluorine interactions with protein residues can be used to substantially enhance protein–ligand binding affinity and selectivity. New fluorinated building blocks are emerging at an increasing speed and are introduced into innovative drugs and agrochemicals. Substituting C–H by C–F bonds clearly benefits from the fact that the size of organofluorine is only slightly larger than the size and volume of the hydrogen substituent and that consequently no particular steric hindrance is encountered in most H/F replacements. All of this is extensively documented in the various chapters of this timely monograph, which prepares the chemists in modern drug discovery research and in crop protection sciences in great depth for using organofluorine in an appropriate way to tune and improve the properties of their actives and leads.

Another contemporary area in pharmaceutical and biomedical research involving organofluorine is the development of new fluorinated probes for use in solid-state $^{19}F$ NMR investigations and in non-invasive clinical and molecular imaging. Furthermore, the introduction of $^{18}F$-radiolabels is increasingly competing with $^{11}C$-radiolabels for the preparation of probes for positron emission tomography (PET) imaging. These biomedical applications are also covered in great depth in this monograph.

The twelve chapters in the monograph are written by leaders in the field and are grouped into three sections. The first section describes the synthesis of fluorinated biomolecules and how the introduction of organofluorine alters and enhances physicochemical and molecular recognition properties. The first chapter *Synthesis and Properties of Fluorinated Nucleobases in DNA and RNA* by H. Gohlke, J. Bozilovic, and J. W. Engels starts with an overview on organofluorine in molecular recognition, which focuses on C–F···H–N interactions in the context of fluorinated nucleobase analogs. The incorporation of the corresponding nucleotides into oligonucleotides and their interactions with complementary native

nucleobases in RNA, ribozymes, and siRNA are subsequently reviewed. Analysis of these interactions is based on a multi-dimensional approach combining X-ray data, results from thermodynamic studies, and computer simulations. Additionally, the synthesis of selected fluorinated nucleoside analogs is covered. The nature and polarity of molecular environments is critical for organofluorine interactions in proteins, as described in the second chapter *Molecular Interactions of Fluorinated Amino Acids within the Hydrophobic Core of a Coiled Coil Peptide* by T. Vagt, M. Salwiczek, and B. Koksch. $\alpha$-Helical coiled coils are investigated as model systems to decipher the interactions of organofluorine within a native protein environment. This is achieved by introducing amino acids with hydrophobic fluorinated side chains of different volume and polarity into the folding peptides. The studies reveal that the effect of fluorinated amino acids strongly depends on the immediate microenvironment: the helical peptide model systems are selectively stabilized by interactions of organofluorine, in particular of $CF_3$ groups, with the lipophilic amino acids Leu, Ile, and Val. The $CF_3$ group is at the center of the chapter *Probing the Binding Affinity and Proteolytic Stability of Trifluoromethyl Peptide Mimics as Protease Inhibitors* by M. Zanda, A. Volonterio, M. Sani, and S. Dall'Angelo. $\alpha,\alpha$-Difluoro- and $\alpha,\alpha,\alpha$-trifluorocarbonyl residues are fully hydrated in aqueous solution and these hydrates, as part of peptidomimetic ligands, are good entities to bind to the catalytic Asp dyad in aspartic proteases. In the meanwhile, $\alpha,\alpha,\alpha$-trifluoroacetyl groups have been recognized as general binding elements for biological targets with polar active sites and their introduction into ligands for proteolytic enzymes, such as endopeptidases and matrix metalloproteases, as well as their specific intermolecular interactions with the proteins are described. The last chapter in Section 1, entitled *Trifluoromethyl-Substituted $\alpha$-Amino Acids as Solid-State $^{19}$F-NMR Labels for Structural Studies of Membrane-Bound Peptides*, written by V. S. Kubyshkin, I. V. Komarov, S. Afonin, P. K. Mykhailiuk, S. L. Grage, and A. S. Ulrich presents the synthesis of trifluoromethyl-substituted natural and unnatural $\alpha$-amino acids as $^{19}$F-NMR labels to study membrane-associated polypeptides in the solid state. The chapter starts by outlining biostructural applications of solid-state $^{19}$F NMR methods and subsequently focuses on the synthesis of

the probes and their incorporation into peptides. Challenges in the preparation of hitherto missing probes, such as $F_3C$–substituted proline, are identified.

Section 2 deals with the introduction of organofluorine into biomedical leads and drugs and their use against various biological targets. The chapter by S. Swallow on *Fluorine-Containing Pharmaceuticals* starts with a general survey of organofluorine in drug discovery and development. It subsequently presents several interesting case studies that highlight the effects of H/F substitutions on the development of commercial drugs. Beneficial organofluorine contributions are established and confirmed in revealing structure–activity relationships (SARs). The range of these benefits is indeed quite impressive and extends from improved potency to more favorable ADME, pharmacokinetic, and safety properties. A more focused chapter by J. T. Welch describes *Applications of Pentafluorosulfanyl Substitution in Life Sciences Research.* While popular for quite some time in agrochemicals, this "super-trifluoromethyl" group, with a size slightly smaller than a *t*-butyl group, has in recent years also found increasing application in pharmaceuticals development. As $SF_5$–substituted building blocks become rapidly commercially available, there is usually no need for direct fluorination. The chapter *Strategic Incorporation of Fluorine into Taxoid Anticancer Agents* by A. Pepe, L. Sun, and I. Ojima illustrates how the metabolic stability of taxoid anticancer drugs is improved and their general cytotoxicity reduced by introduction of organofluorine. It also describes the use of solid-state $^{19}F$ NMR spectroscopy to elucidate the bioactive conformations of taxoids. A comprehensive and useful coverage of *Synthesis and Antiviral, Antitumour Activities of Fluorinated Sugar Nucleosides* is provided by F. Zheng, X.-L. Qiu, and F.-L. Qing. They present the preparation of a large variety of nucleoside building blocks with fluorinated ribose moieties and discuss the conformational effects resulting from organofluorine introduction. M. Winkler and D. O'Hagan in their chapter on *Synthesis of Fluorinated Neurotransmitter Analogues* report on the development of non-peptidic fluorinated small molecules that find application in biomedical $^{19}F$ NMR and $^{18}F$ PET studies. Fluorinated adrenaline and dopamine analogs are covered as well as a diversity of

other compounds binding to central neuroreceptors such as the glutamine, histamine, acetylcholine, and serotonin receptors.

The third and final section deals with the use of $^{19}F$ probes in NMR and of $^{18}F$-radiolabeled probes in PET imaging applications. An authoritative survey of *$^{18}F$-Radionuclide Chemistry* is provided by R. Bejot and V. Gouverneur. The introduction of the radiolabels into probes for PET studies requires special protocols for synthesis and purification due to the limited half-life of the radionucleus, and these protocols are covered in an informative way. *$^{18}F$-Labelled Tracers for PET Oncology and Neurology Applications* by S. K. Luthra and E. G. Robins describes the protocols for the preparation of specific PET probes for *in vivo* imaging to elucidate disease-based mechanisms in oncology and neurology. The authors cover the synthesis of $^{18}F$-labeled nucleosides, RGD (Arg–Gly–Asp) sequences, peptides that bind to specific biological targets (and the application of these probes to *in vivo* imaging of tumor angiogenesis), apoptosis, and amyloid plaque formation. The final chapter by V. D. Kodibagkar, R. R. Hallac, D. Zhao, J.-X. Yu, and R. P. Mason on *$^{19}F$ NMR: Clinical and Molecular Imaging Applications* discusses the use of fluorinated probes in non-invasive clinical and molecular imaging to investigate enzyme activities and cell tracking in various diseases. It connects well to the earlier chapters reporting the synthesis of such probes.

All chapters are carefully selected and contribute to a unique, well-rounded monograph. Learning is fully ensured, as I can certify from the preparation of this foreword. I am not aware of any other monograph covering organofluorine applications in such depth and diversity. It will be of great practical use to scientists in industry — both pharmaceutical and agrochemical — and in academia. Both experts and novice practitioners will benefit from the reading. The monograph should also find use as a basis for advanced courses on organofluorine applications in biomedical research in masters and doctoral degree programs. The chosen format of individual chapters, namely comprehensive coverage of both modern synthetic methodology and *in vitro* and *in vivo* biological applications of the resulting building blocks and ligands, is highly attractive. It becomes quite clear that there is lots of room for further developments of innovative

fluorinated building blocks and investigations of their physicochemical and biological properties. There is no doubt that this monograph will stimulate much future research on organofluorine in pharmaceutical and biomedical chemistry.

François Diederich
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Zurich, November 1, 2011

# Preface

*Véronique Gouverneur and Klaus Müller*

Fluorine has a distinctive place in the periodic table and has absorbed the attention of numerous scientists over many decades. Fluorine chemistry today is a well-established branch of modern sciences, which has tremendously benefited various research areas from material to medical sciences. The synthesis of fluorinated compounds has been extensively explored. Today, this field of research still stretches to the limit the creativity of chemists eager to develop new concepts for both selective fluorination and clever design and manipulation of fluorinated building blocks. The increased availability of fluorinated compounds has led to insightful studies aimed at deciphering the effects of fluorine substitution on physicochemical properties. Aspects of fluorine chemistry have been competently discussed in numerous books and reviews. This monograph is intended for a broad readership of professionals and researchers particularly interested in life sciences and medicine. An effort has been made to integrate chemistry, biology, drug discovery and medicine in a way that gives the reader an appreciation of how fluorine has enriched the life sciences in many respects. Molecules substituted with fluorine have improved our understanding of the molecular mechanisms of disease states and are continuously contributing to the advancement of drug discovery and diagnostic imaging. These aspects are covered in this book, which is organised around three sections. The first part provides answers on the fundamental question of how the introduction of fluorine modulates the physicochemical and molecular recognition properties of biologically

relevant molecules. This is followed by an in-depth coverage of the impact that fluorine has made on drug discovery and development. The last section gives the reader informative accounts on the use of $^{19}$F-spinlabelled and $^{18}$F-radiolabelled probes for imaging by nuclear magnetic resonance and positron emission tomography, respectively.

In this multi-authored monograph, industrial and academic experts in the field bring the reader up to date with twelve chapters discussing all aspects of their respective research areas from essential background information to the most recent developments. In the process of editing this book, we have come to appreciate the enormous amount of talent of 'fluorine scientists' that has enabled spectacular advances in molecular medicine. We wish to express our most sincere gratitude and thanks to the authors of this monograph (Holger Gohlke, Jelena Bozilovic, Joachim W. Engels, Toni Vagt, Mario Salwiczek, Beate Koksch, Matteo Zanda, Alessandro Volonterio, Monica Sani, Sergio Dall'Angelo, Vladimir S. Kubyshkin, Igor V. Komarov, Sergii Afonin, Pavel K. Mykhailiuk, Stephan L. Grage, Anne S. Ulrich, Steve Swallow, John T. Welch, Antonella Pepe, Liang Sun, Iwao Ojima, Feng Zheng, Xiao-Long Qiu, Feng-Ling Qing, Margit Winkler, David O'Hagan, Romain Bejot, Véronique Gouverneur, Sajinder K. Luthra, Edward G. Robins, Vikram D. Kodibagkar, Rami R. Hallac, Dawen Zhao, Jian-Xin Yu and Ralph P. Mason), to François Diederich who has kindly agreed to comment on this monograph and to the countless chemists, biologists, physicists, physicians and clinicians around the world who have contributed to advancing life sciences and medicine over the years using fluorine as an enabling element. Heartfelt thanks to the members of the Gouverneur research group for helping with the proofreading (Matthew Tredwell, Matthew Hopkinson, Jamie Wolstenhulme, Charlotte Hollingworth, George Blessley, Ida Sofia Stenhagen and Guy Giuffredi).

We very much hope that this monograph will inspire many dedicated scientists and stimulate further developments relying on fluorine, with even more key discoveries in and for the future.

Véronique Gouverneur and Klaus Müller
Oxford, 9 November 2011

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