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Andrew D. Westwell is currently Reader in Medicinal Chemistry at the School of Pharmacy and Pharmaceutical Sciences at Cardiff University (UK), having worked in Cardiff since 2006. He received his BSc (Hons) in Chemistry and PhD in organic chemistry at the University of Leeds (UK). Following a postdoctoral fellowship at Loughborough University (UK), he joined a Cancer Research UK Programme at the University of Nottingham (UK), initially as Senior Research Fellow, later as Lecturer. Following his move to Cardiff he has established a number of collaborative research projects focusing on breast cancer drug discovery, new synthetic chemistry methods, and cancer imaging by Positron Emission Tomography (PET). He has published more than 100 journal articles and reviews. Technology transfer activities have included a number of patent filings, and he was lead chemist in Nottingham on the development of a new molecule from discovery at the bench to early clinical evaluation. He is also scientific co-founder of the UK drug discovery and development company Tiziana Life Sciences. Other recent research related activities have included serving as Honorary Treasurer of the British Association for Cancer Research (2007-2012). He currently serves on the Editorial Board of the international journal *Future Medicinal Chemistry*.

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Foreword

Fluorinated pharmaceuticals: advances in medicinal chemistry: introductory remarks

Andrew D Westwell

Within the world of medicinal chemistry and drug discovery, fluorine is a truly remarkable element. Despite being almost entirely absent from natural products and naturally occurring biomolecules, fluorine is present in perhaps more than 20% of modern medicines and advanced drug candidates. The reasons for the prevalence of fluorine in drug molecules can be traced to a number of recurring factors that stem from the small size of the fluorine atom (with a covalent radius of around 60 picometres), and its status as the most electronegative atom in the periodic table. The following broad themes associated with fluorinated pharmaceuticals are developed throughout this book:

- Influence on drug lipophilicity ($\log P$), often associated with enhanced cellular penetration.
- Effects on acid/base (pK_a) properties of neighboring functional groups, for example, the lowering of amine function pK_a induced by the presence of fluorine atoms(s).
- Suppression of (undesired) oxidative metabolism.
- Bioisosteric effects on properties such as binding affinity and H-bonding interactions, for example, where fluorine replaces a hydrogen atom or hydroxyl group.

All of the above broad themes are developed throughout the book, with the emphasis firmly on the enhancement of therapeutic activity afforded by introduction of fluorine atom(s).

Chapter 1 begins with a broad overview of chemical methods for introduction of fluorine or the frequently encountered trifluoromethyl group. This area of synthetic chemistry has been, until quite recently, not especially well developed. With a wide range of commercially available fluorinated building blocks, specific introduction of the fluorine atom during multistep synthesis of drug candidates has often not been necessary. The poor inherent nucleophilicity of the fluoride ion and severe hazards associated with highly toxic fluorine gas necessitated the development of alternative fluorinating agents. However, the recent rapid development of ^{18}F -labeled noninvasive biomarkers for PET has provided fresh impetus to the fluorine chemistry field. With a ^{18}F radiochemical half-life of 110 min, efficient late-stage introduction of fluorine becomes imperative and new methods (such as transition-metal promoted procedures) compatible with ^{18}F -radiochemistry continue to emerge. The role of ^{18}F -labeled biomarkers provides a recurring theme throughout the book, particularly in the Chapter by Yousefi and Wester focusing on the role of PET biomarkers for diagnostic imaging in neurodegenerative disease.

Following discussion of the biomedical applications of fluorinated amino acids and peptides, the book is organized mainly according to major therapeutic areas where fluorinated pharmaceuticals play an important role. The major therapeutic areas of antiviral agents and other anti-infectives, oncology, CNS disorders and cardiovascular disease are all covered with respect to established and recent trends. It should be noted that the brief overview style of writing throughout this book means that coverage of fluorinated pharmaceuticals is not exhaustive and further examples of important fluorine-containing drug (candidate) molecules will fall outside the scope of this book.

Although the incorporation of fluorine into drug candidates is not, by any means, a new strategy in medicinal chemistry – the discovery of the anti-cancer drug 5-fluorouracil dates back more than 50 years for example – the impact of fluorine on drug discovery continues to flourish. The sustained global demand for new safe and efficacious small molecule drugs, and lack of inherent toxicity associated with fluorine substitution, will ensure that fluorinated pharmaceuticals will continue to occupy an important place in modern medicinal chemistry and drug discovery. The theme of current and emerging applications of fluorinated pharmaceuticals is a theme picked up in the final chapter of the book. I sincerely hope that this book inspires new research and progress in the further applications of fluorinated pharmaceuticals within the biomedical field.

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