Contents

Short Biography xiii
Preface xv
Importance of this Book xvii

1. General Aspects of Organofluorine Compounds

1. **Introduction** 1
2. **C–F Bond Strengths** 4
3. **Effect of the Neighboring C–F Bonds on the C–H Bond Dissociation Energies** 6
4. **Effect of Fluorine on the Acidity and Basicity** 8
5. **Effect of Fluorine on the Metabolic Stability** 9
6. **Effect of Fluorine on the Bioavailability** 12
7. **Positron Emission Tomography Tracers** 15
8. **^{19}F NMR Spectroscopic Techniques for Probing Biochemical Mechanisms** 15
   - 8.1 ^{19}F NMR in Fragment-Based Drug Screening 18
   - 8.2 ^{19}F NMR in the Study of Protein Dynamics 19
   - 8.3 ^{19}F NMR in the Study of Enzyme Mechanisms 21
   - 8.4 ^{19}F Magnetic Resonance Imaging (MRI) 23
9. **Summary and Outlook** 23

References 24

2. Fluorinated Compounds in Enzyme-Catalyzed Reactions

1. **Introduction** 29
2. **Bacterial Metabolism of the Fluoroacetate** 32
3. **Biosynthesis of Fluoroacetate and Fluorothreonine** 33
4. **Enzymatic Defluorination** 35
5. **Mechanism-Based Enzyme Inhibitors** 35
   - 5.1 Irreversible Inhibitors (Suicide Inhibitors) 37
   - 5.2 Suicide Inactivation of Ornithine Decarboxylase 42
   - 5.3 Irreversible Inactivation of Thymidylate Synthase by 5-Fluoro-2′-Deoxyuridine 5′-Monophosphate (FdUMP) 45
   - 5.4 Block Effect on Enzyme Inhibition: Aconitase Inhibition in the Citric Acid Cycle 47

6. **Reversible Inhibitors** 48
6.1 Reversible Transition State Analog Inhibitors 48
6.2 Reversible Inhibitors for Human and Plasmodium Arginases 50
6.3 Serotonin Reuptake Inhibitors 52
7. **Summary and Outlook** 54
References 54

3. Synthetic Methods

1. **Introduction** 59
2. **Fluorination by Elemental Fluorine** 61
2.1 C–H Fluorination 61
2.2 Fluorination of Alkenes 63
3. **Hydrogen Fluoride and its Amine Complexes** 64
3.1 Hydrofluorination of Alkenes and Alkynes, and Deoxyfluorination of Alcohols 64
4. **Selective *ortho*-Fluorination of Pyridines By AgF_2** 67
5. **Deoxyfluorinations by DAST and Related Reagents** 69
6. **Dediazoniation–Fluorination of Amines** 73
7. ***gem*-Difluorinations** 74
8. **Trifluoromethylations** 77
8.1 Nucleophilic Trifluoromethylation 77
8.2 Electrophilic Trifluoromethylation 80
8.3 Trifluoromethylation by Photoredox Catalysis 82
8.4 Pd-Catalyzed Aryl and Vinyl Trifluoromethylations 83
9. **Pentafluorosulfanyl Compounds** 85
9.1 Click Reactions of Pentafluorosulfanyl Acetylene 88
9.2 Pentafluorosulfanyl Carbonyl Compounds 89
9.3 SF_5-Containing Pharmaceuticals 89
10. **Summary and Outlook** 92
References 93

4. Fluorinated Amino Acids, Peptides, and Proteins

1. **Introduction** 101
1.1 Fluorinated Amino Acids in Protein Engineering 103
1.2 Synthesis and Purification of Fluorinated Peptides and Proteins 103
2. **Fluorinated Leucine** 105
2.1 Fluorinated Glucagon-Like Peptide-1 106
2.2 Fluorinated Antimicrobial Peptides 107
2.3 Fluorinated Chloramphenicol Acetyltransferase 107
2.4 Fluorinated Coiled Coil Proteins 108
2.5 Synthesis of L-5,5,5,5′,5′,5′-Hexafluoroleucine (HfLeu) 109
3. **Fluorinated Proline and its Effect on Collagen** 110
3.1 Synthesis of 4-fluoroproline 113
3.2 Therapeutic Applications of Collagen Peptide Mimetics 114
4. **Fluorinated Methionines** 115
4.1 Synthesis of Fluorinated Methionines 116
5. **Fluorinated Tyrosines** 117
5.1 Synthesis of Fluorinated Tyrosines 120

6. **Fluorinated Phenylalanine** 120
6.1 Synthesis of Fluorinated Phenylalanines 123
7. **Peptide Mimetics in Drug Discovery** 125
8. **Summary and Outlook** 128
References 129

5. Organofluorine Pharmaceuticals

1. **Introduction** 133
1.1 Blockbuster Drugs 134
2. **Pharmaceuticals with *gem*-Difluoromethylene and Trifluoromethyl Moieties** 136
3. **Antibacterials** 137
3.1 Flurithromycin 137
3.2 Quinolone Antibiotics 138
4. **Antimalarials** 140
4.1 Synthesis of DSM190 144
4.2 Fluorinated Artemisinins 144
5. **Antidiabetics** 147
5.1 Sitagliptin 148
5.2 Synthesis of Sitagliptin 150
5.3 Aldose Reductase Inhibitors 150
6. **Nonsteroidal Antiinflammatory Drugs** 152
7. **Corticosteroids** 154
7.1 Synthesis of the Fluorinated Corticosteroids 156
8. **Antiviral Drugs** 158
8.1 Efavirenz 158
8.2 Tipranavir 160
8.3 Trifluridine 160
8.4 Fluorinated Nucleosides as Antibacterials and Antiviral Compounds 161
9. **Antidepressant Drugs** 163
10. **Antihypercholesterolemia Drugs** 165
10.1 Ezetimibe 166
10.2 Lomitapide 168
11. **Anticoagulating (Blood-Thinning) Agents** 168
11.1 Ticagrelor 168
11.2 Other Inhibitors of $P2Y_{12}$ Receptors 170
12. **Summary and Outlook** 171
References 172

6. Organofluorine Anesthetics

1. **Introduction** 179
2. **Mechanism of Action of Inhalation Anesthetics** 181
2.1 (G-Protein)-Coupled Receptor Binding Sites for Anesthetics 182
2.2 LGIC Receptors in the Binding of Anesthetics 184
3. **Chiral Anesthetics** 187
4. **Environmental Impact of Fluorinated Anesthetics** 187

5. **Synthesis and Toxicity of Fluorinated Anesthetics** 188
5.1 Halothane 188
5.2 Isoflurane 191
5.3 Enflurane 192
5.4 Sevoflurane 193
5.5 Desflurane 193
6. **Summary and Outlook** 196
References 197

7. Organofluorine Compounds as Positron Emission Tomography Tracers

1. **Introduction** 202
2. **^{18}F-Labeled Pharmaceuticals** 205
2.1 Antipsychotic Drugs 205
2.2 ^{18}F Tracers for Aβ Plaques 205
3. **Synthesis of ^{18}F-Labeled Compounds** 210
3.1 General Synthetic Methods 210
3.2 Aliphatic Nucleophilic Substitution Reactions 211
3.3 Fluorination via Aromatic Nucleophilic Substitution Reactions 215
3.4 Pd-Catalyzed ^{18}F Labeling of Proteins 216
3.5 [^{18}F]Trifluoromethylation 218
4. **^{18}F-Labeled Neurotransmitters** 220
4.1 [^{18}F]-L-DOPA 221
4.2 6-[^{18}F]Fluoronorepinephrine 222
5. **[^{18}F]Corticosteroids** 223
6. **^{18}F-Labeled Nucleosides** 224
7. **^{18}F-Radiolabeling of Peptides and Proteins** 225
7.1 3-[^{18}F]Fluorosilylbenzamide Derivatives 225
7.2 ^{18}F-Labeled 2-Cyanobenzothiazole for Radiofluorination of Peptides and Proteins 225
7.3 ^{18}F-Labeled Peptide Derivatives 226
8. **Enzymatic Synthesis of ^{18}F-PET Tracers** 230
9. **Summary and Outlook** 232
References 234

8. Organofluorine Compounds in Neurological Disorders

1. **Introduction** 241
2. **BACE-1 Inhibitors** 245
2.1 Synthesis of BACE-1 Inhibitor **7** 249
3. **GSMs and γ-secretase Inhibitors** 250
3.1 Synthesis of BMS-708163 252
3.2 Synthesis of the GS Inhibitor **16**, a BMS-708163 Analog 254
3.3 ELND006 and ELND007 254
4. **Cell Cycle Inhibitors** 255
5. **Antiinflammatory Compounds as Therapeutics of AD** 258
6. **Summary and Outlook** 258
References 259

9. Organofluorine Compounds as Anticancer Agents

1. **Introduction** 265
2. **Nucleoside-Based Therapeutics** 266
   2.1 Gemcitabine and Clofarabine 266
3. **Receptor Tyrosine Kinase Inhibitors** 270
   3.1 Afatinib 271
   3.2 Afatinib Analogs 272
   3.3 Sorafenib and Regorafenib 275
   3.4 Sunitinib 276
   3.5 *Cabozantinib* 278
4. **Capecitabine and Lapatinib** 279
   4.1 Synthesis of Capecitabine 281
5. **Trametinib and Dabrafenib** 281
   5.1 Synthesis of Trametinib and Dabrafenib 283
6. **Paclitaxel and Related Taxoids** 283
7. **Bicalutamide** 287
8. **Vemurafenib** 288
   8.1 *Synthesis of Vemurafenib* 290
9. **Sonidegib** 290
   9.1 Synthesis of Sonidegib 290
10. **Ponatinib** 291
    10.1 Synthesis of Ponatinib 291
11. **Faslodex** 292
    11.1 Synthesis of Faslodex 293
12. **Vinflunine** 293
    12.1 Synthesis of Vinflunine 294
13. **Summary and Outlook** 295

References 296

Index 301