

# Contents

|   |    |
|---|----|
| <b>Introduction</b> .....   | 1  |
| <b>1 Studies on <math>\alpha</math>-Aminophosphonates with Antiviral Activity</b> .....                   | 7  |
| 1.1 Organocatalytic Synthesis and Antiviral Activity of Asymmetric $\alpha$ -<br>Aminophosphonates.....   | 7  |
| 1.1.1 Introduction.....   | 7  |
| 1.1.2 Materials and Methods.....  | 8  |
| 1.1.3 Results and Discussion.....   | 12 |
| 1.1.4 Conclusions.....  | 18 |
| 1.2 Synthesis & Bioactivity of $\alpha$ -Aminophosphonates Containing Amide<br>Moiety.....                | 19 |
| 1.2.1 Introduction.....   | 19 |
| 1.2.2 Materials and Methods.....  | 20 |
| 1.2.3 Results and Discussion.....   | 22 |
| 1.2.4 Conclusions.....  | 24 |
| 1.3 Green Synthesis & Bioactivity of $\alpha$ -Aminophosphonates Containing<br>an Alkoxyethyl Moiety..... | 25 |
| 1.3.1 Introduction.....   | 25 |
| 1.3.2 Materials and Methods.....  | 26 |
| 1.3.3 Results and Discussion.....   | 27 |
| 1.3.4 Conclusions.....  | 30 |
| 1.4 Green Synthesis & Bioactivity of Brominated $\alpha$ -<br>Aminophosphonates.....                      | 31 |
| 1.4.1 Introduction.....   | 31 |
| 1.4.2 Materials and Methods.....  | 32 |

|       |   |    |
|-------|---|----|
| 1.4.3 | Results and Discussion  | 33 |
| 1.4.4 | Conclusions   | 36 |
| 1.5   | Synthesis & Bioactivity of $\alpha$ -Aminophosphonates Containing Trifluorinated Methyl Moiety              | 36 |
| 1.5.1 | Introduction  | 36 |
| 1.5.2 | Materials and Methods   | 37 |
| 1.5.3 | Results and Discussion  | 39 |
| 1.5.4 | Conclusions   | 44 |
| 1.6   | Synthesis & Bioactivity of Chiral $\alpha$ -Aminophosphonates Containing Fluorine Moiety                    | 44 |
| 1.6.1 | Introduction  | 44 |
| 1.6.2 | Materials and Methods   | 45 |
| 1.6.3 | Results and Discussion  | 47 |
| 1.6.4 | Conclusions   | 53 |
| 1.7   | Green Synthesis of $\alpha$ -Aminophosphonates Containing Bromine and Fluorine under Ultrasonic Irradiation | 54 |
| 1.7.1 | Introduction  | 54 |
| 1.7.2 | Materials and Methods   | 55 |
| 1.7.3 | Results and Discussion  | 55 |
| 1.7.4 | Conclusions   | 57 |
| 1.8   | Synthesis & Bioactivity of $\alpha$ -Aminophosphonates Containing Isoxazole Moiety                          | 58 |
| 1.8.1 | Introduction  | 58 |
| 1.8.2 | Materials and Methods   | 59 |
| 1.8.3 | Results and Discussion  | 60 |
| 1.8.4 | Conclusions   | 64 |
| 1.9   | Synthesis & Bioactivity of $\alpha$ -Aminophosphonates Containing Benzothiazole Moiety                      | 64 |
| 1.9.1 | Introduction  | 64 |
| 1.9.2 | Materials and Methods   | 65 |
| 1.9.3 | Results and Discussion  | 66 |
| 1.9.4 | Conclusions   | 71 |
| 1.10  | Chiral Separation & Bioactivity of $\alpha$ -Aminophosphonates Containing Benzothiazole Moiety              | 71 |

|          |  |           |
|----------|--|-----------|
| 1.10.1   | Introduction .....   | 71        |
| 1.10.2   | Materials and Methods .....  | 72        |
| 1.10.3   | Results and Discussion .....   | 74        |
| 1.10.4   | Conclusions .....  | 84        |
| 1.11     | Crystal Structure of <i>O,O</i> -Dipropyl- $\alpha$ -aminophosphate<br>Containing Benzothiazole Moiety ..... | 84        |
| 1.11.1   | Introduction .....   | 84        |
| 1.11.2   | Materials and Methods .....  | 84        |
| 1.11.3   | Results and Discussion .....   | 85        |
|          | References .....   | 86        |
| <b>2</b> | <b>Synthesis, Characterization and Antiviral Activity of Cyanoacrylates<br/>and Derivatives .....</b>        | <b>95</b> |
| 2.1      | Synthesis and Antiviral Activity of Cyanoacrylates Containing<br>Phosphonyl Moiety .....                     | 95        |
| 2.1.1    | Introduction .....   | 95        |
| 2.1.2    | Materials and Methods .....  | 96        |
| 2.1.3    | Results and Discussion .....   | 97        |
| 2.1.4    | Conclusions .....  | 102       |
| 2.2      | Synthesis and Bioactivity of Cyanoacrylate Derivatives<br>Containing Pyridine Moiety .....                   | 102       |
| 2.2.1    | Introduction .....   | 102       |
| 2.2.2    | Materials and Methods .....  | 103       |
| 2.2.3    | Results and Discussion .....   | 104       |
| 2.2.4    | Conclusions .....  | 107       |
| 2.3      | Preparation of Chiral Cyanoarylate Derivatives under<br>Microwave Irradiation .....                          | 107       |
| 2.3.1    | Introduction .....   | 107       |
| 2.3.2    | Materials and Methods .....  | 108       |
| 2.3.3    | Results and Discussion .....   | 109       |
| 2.3.4    | Conclusions .....  | 112       |
| 2.4      | Preparation of Chiral Cyanoacrylate Derivatives from<br>Phenylethylamine .....                               | 112       |

|          |  |     |
|----------|--|-----|
| 2.4.1    | Introduction   | 112 |
| 2.4.2    | Materials and Methods  | 114 |
| 2.4.3    | Results and Discussion   | 115 |
| 2.4.4    | Conclusions  | 120 |
| 2.5      | Preparation and Antiviral Activity of Chiral Cyanoacrylate   |     |
|          | Derivatives from Aryl (Heterocyclic) Amine   | 120 |
| 2.5.1    | Introduction   | 120 |
| 2.5.2    | Materials and Methods  | 121 |
| 2.5.3    | Chemistry  | 124 |
| 2.5.4    | Antiviral Activity   | 126 |
| 2.5.5    | Discussion   | 129 |
| 2.5.6    | Conclusions  | 130 |
| 2.6      | Preparation and Antiviral Activity of Chiral Cyanoacrylate   |     |
|          | Derivatives Containing $\alpha$ -Aminophosphonate Moiety   | 130 |
| 2.6.1    | Introduction   | 130 |
| 2.6.2    | Materials and Methods  | 131 |
| 2.6.3    | Results and Discussion   | 132 |
| 2.6.4    | Conclusions  | 136 |
| 2.7      | Crystal Structure elucidation of Cyanoacrylates  | 137 |
| 2.7.1    | Crystal Structure of ( <i>E</i> )-Ethyl-3-[( <i>S</i> )-1-phenylethylamino]-<br>3-[4-(trifluoromethyl)- phenylamino]-2-cyanoacrylate                             | 137 |
| 2.7.2    | Characterization of Two Chiral Isomers of ( <i>E</i> )-Ethyl-3-<br>[( <i>R</i> ) or ( <i>S</i> )-1-phenylethyl amino]-3-[4-nitrophenylamino]-2-<br>cyanoacrylate | 143 |
|          | References   | 147 |
| <b>3</b> | <b>Synthesis and Antiviral Activity of Chiral Thiourea</b>   |     |
|          | <b>Derivatives</b>   | 153 |
| 3.1      | Chiral Thiourea Deravatives from Primary Amine and<br>Isocyanate   | 153 |
| 3.1.1    | Introduction   | 153 |
| 3.1.2    | Materials and Methods  | 154 |
| 3.1.3    | Results and Discussion   | 155 |

|          |   |            |
|----------|---|------------|
| 3.1.4    | Conclusions   | 160        |
| 3.2      | Chiral Thiourea Derivatives Containing $\alpha$ -Aminophosphonate<br>Moiety   | 160        |
| 3.2.1    | Introduction  | 160        |
| 3.2.2    | Materials and Methods   | 162        |
| 3.2.3    | Results and Discussion  | 163        |
| 3.2.4    | Conclusions   | 166        |
|          | References  | 166        |
| <b>4</b> | <b>The Heterocyclic Antiviral Agents</b>  | <b>169</b> |
| 4.1      | Pyrazole Derivatives Containing Oxime Ester Moiety  | 169        |
| 4.1.1    | Introduction  | 169        |
| 4.1.2    | Materials and Methods   | 170        |
| 4.1.3    | Chemistry   | 173        |
| 4.1.4    | Antiviral Activity  | 175        |
| 4.1.5    | Discussion  | 182        |
| 4.1.6    | Conclusions   | 183        |
| 4.2      | Pyrazole Derivatives Containing Oxime Ether Moiety  | 184        |
| 4.2.1    | Introduction  | 184        |
| 4.2.2    | Materials and Methods   | 186        |
| 4.2.3    | Results and Discussion  | 187        |
| 4.2.4    | Conclusions   | 191        |
| 4.3      | Quinazolinone Derivatives   | 192        |
| 4.3.1    | Introduction  | 192        |
| 4.3.2    | Materials and Methods   | 193        |
| 4.3.3    | Results and Discussion  | 195        |
| 4.3.4    | Conclusions   | 202        |
|          | References  | 202        |
| <b>5</b> | <b>Innovation and Application of Environment-Friendly Antiviral<br/>Agents for Plants</b>   | <b>207</b> |
| 5.1      | Innovation of New Antiviral Agent Dufulin[ <i>N</i> -[2-(4-methyl-<br>benzothiazol)]-2-ylamino-2-fluophenyl- <i>O,O</i> -diethyl phosphonate] | 207        |
| 5.1.1    | Product Chemistry   | 208        |

|        |  |            |
|--------|--|------------|
| 5.1.2  | Formulation of Dufulin .....   | 208        |
| 5.1.3  | Optimization of Synthetic Conditions in Lab Scale and<br>Pilot Scale ..... | 218        |
| 5.1.4  | Toxicology Test .....  | 224        |
| 5.1.5  | Field Trials .....   | 227        |
| 5.1.6  | Pesticide Residue .....  | 231        |
| 5.1.7  | Environmental toxicology .....   | 238        |
| 5.1.8  | Mode of Action .....   | 240        |
|        | References .....   | 257        |
| 5.1.9  | Photolysis and Hydrolysis .....  | 258        |
| 5.1.10 | Systemic Behaviors .....   | 273        |
|        | References .....   | 279        |
| 5.2    | GU188, 2-Cyanoacrylate Derivative, Candidate Antiviral Agent .....         | 280        |
| 5.2.1  | Synthesis .....  | 280        |
| 5.2.2  | Analytical Method .....  | 284        |
| 5.2.3  | Bioassays and Field Trials .....   | 287        |
| 5.2.4  | Toxicological Test .....   | 289        |
| 5.2.5  | Action Mechanism .....   | 290        |
| 5.3    | Studies on the Development of Novel Amino-oligosaccharide .....            | 295        |
| 5.3.1  | Introduction .....   | 295        |
| 5.3.2  | Anti-TMV and Mechanism of Action .....                                     | 296        |
| 5.3.3  | Industrialization .....  | 298        |
|        | <b>Index .....</b>   | <b>301</b> |