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Environment-Friendly Antiviral Agents for Plants

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With 110 figures

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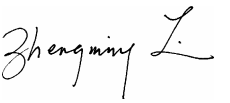
Foreword

Plant virus is often referred to as “plant cancer” which is considered to be a serious threat to agricultural production. For example, the breakout of tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV) could cause billion dollars of agricultural loss world-wide. Viruses such as the genus *Tospovirus* of the family *Bunyaviridae* and the genus *Begonovirus* of family *Geminiviridae* are also destructive to vegetable plantation. Since the mechanism of parasitism and invasion into plant cell of virus is not clear yet, it poses a difficult problem for us to study the prevention and control of plant viral diseases. In the recent innovation program of environmental friendly green pesticides initiated in China, the novel virucide research seems to be lagging behind from other areas such as herbicide, fungicide and insecticide.

During the last decade, professor Baoan Song of Guizhou University, China, has led his research group, starting from a natural lead structure, to carry out persistently a project in discovering novel virucide by studying its related molecular design, bioassay technology, mode of action, formulation, with which a new plant immune activation phenomenon was discovered and its mechanism postulated. After intensive synthesis and bio-screening practices, Song’s group has finally discovered a novel bio-active structure, which was named later as Dufulin and been granted as a new pesticide approved by the Ministry of Agriculture of China for further development. Professor Song has also pushed forward his related R&D of Dufulin to the industrialization stage. It is expected that Dufulin will play its significant role in combating the plant viral diseases in China.

In tackling such a rather difficult project conducted by professor Song’s group, this monograph has been well documented to compile all the original research data as well as its methodology throughout the whole R&D procedures of Dufulin. The monograph is hereby highly recommended to our colleagues, which will bring us an insight into the discovery of a novel virucide, deepen our

understanding to the related inter-disciplinary work, enrich our expertise and experience in our innovation of research work.



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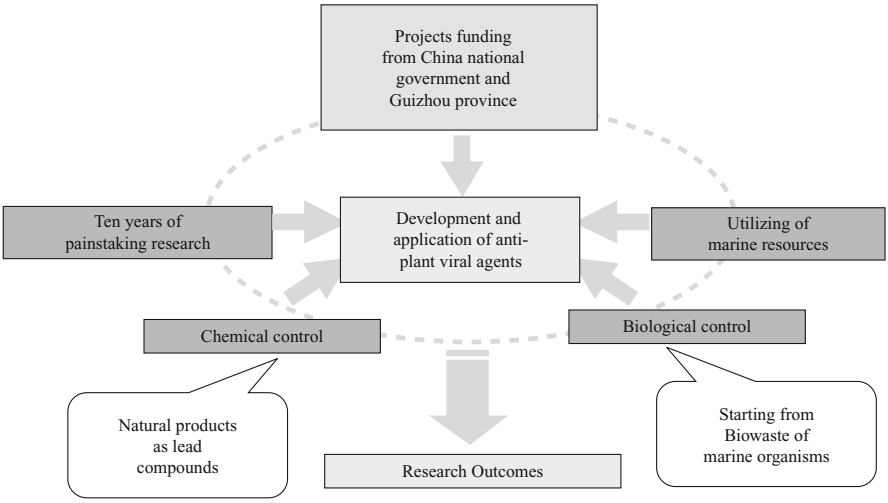
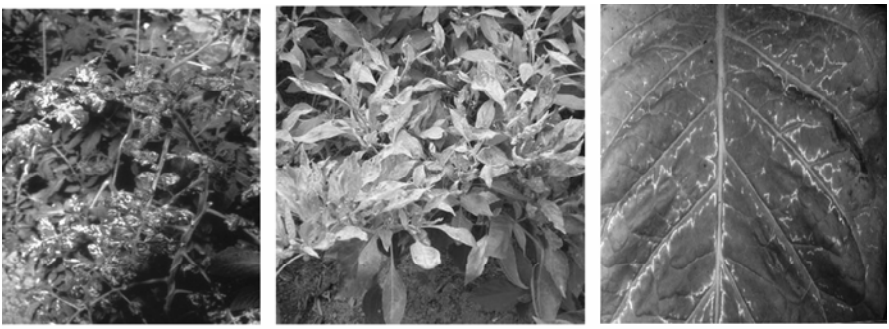
Feb. 2009

Preface

Plant viruses, generally known as “cancer of plant”, are responsible for the most common diseases occurring in the main agriculture crops as well as vegetable and tobacco that lead to serious damage and enormous economic loss. In order to protect the plant from the virus disease, various methods have been developed, including crop rotation, virus eradication, mild strain cross protection (MSCP), virus transmission control, application of antivirus agents and newly emerging genetically antivirus modified crops. However, damage from plant virus cannot be avoided effectively despite taking reasonable measures. The use of traditional chemical pesticides, on the other hand, may bring about a disastrous impact on our environment. Thus, the continuous research and development of environment-friendly antivirus agents for field application have become an important endeavor for the scientists engaged in plant protection. The authors carried out ten years of research aiming at discovering novel green antiviral agents for plants and successfully found some new compounds with excellent antivirus bioactivity. After completing systematic R&D work, one brand of new compound was industrialized and applied in the field with excellent protection effect thus avoiding huge economic loss due to the great damage caused by plant virus. Interestingly enough, it was found to exert its function through new mechanism of activating plant immune system.

As mimics of natural amino acids, the synthesis and biological studies of aminophosphonic acids and their ester derivatives have attracted wide attention in recent years. Previous research demonstrated that some aminophosphonates are associated with antiviral, growth-regulatory and antifungal activities. Taking amino phosphonic acid as the lead compound for optimization studies, more than one thousand compounds were designed and synthesized by us among which Dufulin (Bingduxing) was identified as one of the potential structures with outstanding antiviral activity. Systematic researches were conducted from basic lab research to field trial as well as field application including lab bioassay, compound synthesis optimization, field bioassay trial, residual analysis, toxicity evaluation, and environmental behavior studies that finally paved the way to the registration of new pesticide Dufulin as a new molecular antivirus agent approved





Tomato mosaic virus | Capsicum annuum Virus disease | Cucumber Mosaic disease

Tobacco mosaic disease | Rice ragged stunt disease | Rice stripe disease

by the Ministry of Agriculture. The intellectual property of Dufulin as well as its usage was approved by State Intellectual Property Office of China (SIPO). Besides studying its application, basic research on the mode of action of Dufulin was also carried out and it was found that Dufulin exerts its function through a new mechanism by activating the plant immune system. The observations were:(1) It is associated with the tobacco resistance enzymes and could cause aggregation of the virus particle thereby reducing the infecting ability of the virus.(2) This antiviral agent can also upregulate the expression of tobacco pathogenesis-related proteins PR-1 and PR-5. (3) The anti-TMV bioactivity of Dufulin is associated with the induction of cysteamine acid synthase in chloroplast, followed by activating the salicylic acid signaling pathway and thus conferring the plant the systematically acquired resistance.

Cyanoacrylates, included in our studies, have been traditionally considered as herbicides acting as Photosystem Ⅱ Inhibitors. Our research showed that these compounds also have good anti-TMV activities and are worth investigating for their potential to be employed as green anti viralagents in future. In addition, some more promising results were obtained from the research of chiral thioureas and hetercyclic compounds carried out in our center.

Although there is no dearth with regard to the scientific information or availability in terms of text books in the field of synthetic pesticides and their role in crop protection, none of them deals with the chemistry of green antiviral agents for plants.

In the context of the present inadequacy of professional book available on the anti-viral agents, we made best effort to investigate this relatively unexplored area and summarize our findings in the form of a comprehensive textbook. The present edition of Environment-Friendly Antiviral Agents for Plants has been written with an idea to keep up pace with the recent progress made in the field of environmentally benign antiviral agents for plants and encompasses five specific directions that could open new avenues for the treatment of plant virus diseases.

There are five chapters in this book. Chapter 1 describes the synthesis and antiviral activity of α-aminophosphonates. Chapter 2 introduces the synthesis and antiviral activity of cyanoacrylates. Chapter 3 talks about chiral thiourea antiviral agents. Chapter 4 discusses the heterocyclic antiviral agents, and Chapter 5 introduces the innovation and application of environment-friendly antiviral agent for plants, especially the novel antiviral chemical for plants entity Dufulin, a new antiviral agent that was granted the temporary registration by the Ministry of Agriculture of China. We made best possible effort to introduce the research progress and the research method for every kind of antivirus agent. In addition, development of green pesticides with characteristics such as high selectivity, efficiency, low toxicity and easy degradability poses enormous challenge to both synthetic chemists and biologists and we hope the book can provide some valuable

information on the chemistry of potentially novel chemicals that may be termed as green agents for the control of plant virus diseases. It would be a great comfort for the authors if this book can serve to the improvement of novel antiviral agents R&D for plants as well as their applications in plant virus disease control.

The research work introduced in this book was carried out in Key Laboratory of Green Pesticide and Agricultural Bioengineering (Guizhou University), Ministry of Education, Center for Research and Development of Fine Chemicals of Guizhou University, and was accomplished by the author together with his group members which include Xia Zhou, Song Yang, Linhong Jin, Deyu Hu, Zhuo Chen, Wei Xue, Pinaki S. Bhadury, Guiping OuYang, Rongmao Huang, Song Zeng, Yuping Zhang, etc. The scientific research results provided in this book and the publication of this book are also based on the support received from several of my master and doctoral students *e.g*. Guiping OuYang, Gang Liu, Caijun Chen, Xinwen Gao, but the names of about forty master students who made significant contribution cannot be listed here. Their experimental results, Ph. D. dissertations and master thesis, as well as the journal publications achieved by them and me are the basis of this book. The whole book was written and organized by me, Xia Zhou, Song Yang and Linhong Jin, and was finally organized by me, Xia Zhou and Dr. Pinaki who gave contributions to Chapter 5.

The research work described in this book got the financial support from the following grant funding agencies whom I would like to extend our sincere appreciation: 1) National Key Basic Research Project (973 Plan, Grant No.2003 CB114404), 2) National Key Project for International Cooperation of Science and Technology (Grant No.2005DFA30650); 3) National Nature Science Foundation of China (Grant Nos.20872002, 20662004, 20672024, 20762002, 20562003, 20362004, 20442003); 4) Foundation for New Century Talent in Universities of China (Grant No. NCET-04-0912); 5) The Special Program for Key Basic Research (Grant No.2005CCA01500); 6) National High-Tech Research and Development Plan (863 Plan, Grant Nos.2003AA2Z3542, 2002AA-64-9190, 2002AA217131); 7) Key Technologies R&D Program (Grant Nos.2006BAE01A03-5, 2006BAE01A 02-5, 2006BAE01A01-13); 8) Guizhou Talent Base Foundation (Grant No.[2008] 3); 9) Chinese University Sci & Tech Innovation Key Project (Grant Nos.706051, 705039); 10) Program Foundation of Ministry of Education of China (Grant Nos.20040657003, 20060657004); 11) Foundation for Science and Technology Excellent Talent in Guizhou Province of China (Grant No.2005 [0515]); 12) Guizhou Province Governor Foundation for Scientific Research (Grant Nos. [2007] 16, [2006] 24, [2006] 23); 13) Key Projects Supported by Department of Science and Technology of Guizhou Province (Grant Nos. NY [2008] 3020, NY [2008] 3061, G [2008] 70011, J [2008] 2025, GY [2006] 3010, J [2006] 2010, J [2007] 2010, J [2005] 2010, 2004NGY020, [2002] 1073).

Finally, I would like to thank Prof. Zhengming Li to write the foreward for

this book. I also strongly appreciate the efforts of my colleagues and students and thank them for their support in this research work. I sincerely hope that this book would be helpful for the teachers, students in the field of pesticide science, plant protection, organic chemistry, fine chemicals and applied chemistry as well as environment chemistry and agriculture science, and the researchers from both industry and academia.

Baoan Song
Feb. 2009

Contents

Introduction 1

1 Studies on α-Aminophosphonates with Antiviral Activity 7

1.1 Organocatalytic Synthesis and Antiviral Activity of Asymmetric α-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 α-Aminophosphonates Containing Amide 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 α-Aminophosphonates Containing 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 α-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 α-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 α-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 α-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 α-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 α-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 α-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 *O*,*O*-Dipropyl-α-aminophosphonate 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

2 Synthesis, Characterization and Antiviral Activity of Cyanoacrylates and Derivatives ····95
2.1 Synthesis and Antivival Activity of Cyanoacrylates Containing 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 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 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 Cyanoacylate Derivatives from Phenylethanamine ····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 Cyanoacylate 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 Cyanoacylate Derivatives Containing α-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 (*E*)-Ethyl-3-[(*S*)-1-phenylethylamino]-3-[4-(trifluoromethyl)- phenylamino]-2-cyanoacrylate ····· 137
2.7.2 Characterization of Two Chiral Isomers of (*E*)-Ethyl-3-[(*R*) or (*S*)-1-phenylethyl amino]-3-[4-nitrophenylamino]-2-cyanoacrylate ····· 143
References ····· 147

3 Synthesis and Antiviral Activity of Chiral Thiourea Derivatives ····· 153
3.1 Chiral Thiourea Deravatives from Primary Amine and 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 α-Aminophosphonate 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

4 The Heterocyclic Antiviral Agents ····· 169
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

5 Innovation and Application of Environment-Friendly Antiviral Agents for Plants ····· 207
5.1 Innovation of New Antiviral Agent Dufulin[*N*-[2-(4-methyl-benzothiazol)]-2-ylamino-2-fluophenyl-*O,O*-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 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

Index ····301