

Preface

With the human population explosion, the safeguarding of the world's present and future food supplies is a major problem facing mankind. Therefore enhancing the crop yields is becoming increasingly necessary. Herbicides as one of the important tools for crop protection have made a major contribution to the advancement of agriculture around the world including China. The widespread and overuse of herbicides for weed control over the past few decades has resulted in the rapid development and proliferation of herbicide-resistant weeds. It is worthy noting that there are more than 290 commercial herbicides on the market, but only a limited number (only 25) of target sites for those herbicides to work on. Biotypes of numerous susceptible weed species are now resistant to one or more herbicides. The advent of genetic engineering is currently revolutionizing this paradigm by enabling the use of nonselective herbicides on crops, that have been genetically altered to be resistant to certain compounds. The benefit, such as ease of use is obvious. However agricultural practices relying on the use of herbicide-resistant crops are leading to shifts in weed populations to naturally resistant species and the transgenic crops are not generally accepted by some countries. Therefore, the need to discover new herbicides continues to be urgent.

To cope with the increasing resistant weeds problem, numerous compounds were generated by modifying the commercial products and hope some of analogs are more potent than their parents. Unfortunately, these new compounds still target on the same sites as their parents do. New herbicides with novel mechanisms of action are hence highly desired to combat with the evolution of resistance in weeds. Finding an environment-friendly herbicide with a novel structure and new target is another challenge.

The pyruvate dehydrogenase complex (PDHc) is one of the most important oxidoreductases in organisms. It catalyzes the oxidative decarboxylation of pyruvate to form acetyl CoA, which is a pivotal process in cellular metabolism. Therefore, targeting on plant PDHc is an interesting approach from the biorational design point of view. PDHc has been reported to be one of the target enzymes affected by some herbicidal compounds. Some acetylphosphinates and acetylphosphonates, which were prepared as potential mechanism-based inhibitors for

plant PDHc E1, showed modest herbicidal activity. However, none of these PDHc inhibitors have been further developed as a herbicide due to either lack of activity, poor selectivity, or unfavorable human toxicity.

Attempts to design desirable PDHc inhibitors as herbicides have been performed in my laboratory for more than 15 years. Previous research showed that some OP compounds could be a powerful PDHc inhibitor. *O,O*-diethyl 1-(substituted phenoxyacetoxy)alkylphosphonates were later identified as the scaffolds for lead structures. Different kinds of alkylphosphonate derivatives including their optically active isomers were then synthesized and tested for their inhibitory potency against PDHc and herbicidal activities. Some alkylphosphonates with excellent herbicidal activity were then found. The binding modes of the alkylphosphonates to PDHc are in good agreement with the theoretical study reported earlier. Through the systematic R&D work, clacyfos, *O,O*-dimethyl 1-(2,4-dichlorophenoxyacetoxy)ethylphosphonate turned out to be the best herbicide candidate against broadleaf weeds and with a safe toxicity profile for mammals and non-target species. Clacyfos received the temporary registration from ICAMA of China in 2007.

This book presents many years of research on environment-friendly alkylphosphonate herbicides designed to inhibit the plant PDHc using biochemical reasoning. The most recent research on pyruvate dehydrogenase complex inhibitors is discussed in this book. Systematic studies from basic research to field application of the novel alkylphosphonate herbicidal candidates are also discussed in this book. It contains certain details about the molecule design, synthesis, biological screening, structure–activity relationship analysis, structural optimization, biochemical mechanism, field trial results, residual analysis, toxicology, and environmental fate. Data suggested that clacyfos could be an environment-friendly herbicide with low toxicity, low residue, and desirable selectivity. The R&D of clacyfos exemplifies how to use biorational design and traditional method to come up with a novel herbicide targeting on plant's PDHc. We hope this book can provide you some valuable information on chemistry, chemical biology, and practical application of alkylphosphonates.

The research introduced in this book was carried out in the Key Laboratory of Pesticide and Chemical Biology, Ministry of Education; Institute of Pesticide Chemistry, College of Chemistry, Central China Normal University, by my research team that includes Associate Professor Xiao song Tan and Dr. Hao Peng. Associate Professor Junlin Yuan, Dr. Shuqing Wan, and Ms. Aihong Lu. Many data cited in this book are from my students' dissertations, including doctoral students: Tao Wang, Ting Chen, Hao Peng, Wei Wang, Chubei Wang, Chuanfei Jin, and Junbo He; and Master students: Xia Hong, Jun Wang, Siquan Wang, Liang Xu, Xufeng Liu, Liping Mong, Meiqiang Li, Guihong Liao, Gangliang Huang, Ping Shen, Yanjun Li, Na Zuo, Xijun Sheng, Gao Ling and Xu Chao. The contributions from my colleagues and students to this book are highly appreciated.

I gratefully acknowledge the financial support for my research work from the following grant funding agencies:

1. National Basic Research Program of China (“973” Program No: 2003CB114400; 2010CB126100).
2. National Natural Science Foundation of China (No: 29572045; 20072008; 20372023; 20772042 and 21172090).
3. National Key Technologies R&D Program of China (No: 97-563-02-05, 2001BA308A02-15; 2004BA308A22-9; 2004BA308A24-9; 2006BAE01A04-07; 2006BAE01A02-9; 2006BAE01A01-10 and 2011BAE06B03).
4. Science and Technology Research Project of Ministry of Education (No. 214607 and 230532).
5. Natural Science Foundation of Hubei Province (No. 90J26; 94J40).

Finally, I am greatly indebted to Prof. Zhaojie Liu for his guidance, advice and encouragement for my research in Central China Normal University. I am very grateful to Prof. Morifusa Eto, who was my advisor when I studied at Laboratory of Pesticide Chemistry, Kyushu University, Japan in 1989. His kind encouragement, guidance, and advice on research work continue to inspire my life. I wish to express my heartfelt appreciation to Prof. Eiichi Kuwano from the Laboratory of Pesticide Chemistry, Kyushu University for his kind suggestions and guidance for my doctoral thesis.

Here I would like to thank Prof. Mitsuru Sasaki from the Department of Bio-functional Chemistry, Kobe University, Japan for his contributive advice for revising the manuscript. I wish to express special appreciation to Prof. Philip W. Lee from DuPont Crop Protection (1978–2008) for his advice on the organization of this book. Many thanks to Prof. Eddie Chio from Eli Lilly and Company (1977–2006) and Prof. Adam Hsu from Rohm and Haas (1982–2002) for their very helpful suggestions for revising the manuscript. Last but not least, my special thanks go to Ms. Carol Ashman (USA) for her efforts in revising and editing the manuscript.

The author hopes that this book would be helpful to researchers, teachers, and students in organic chemistry, pesticide science, and other related fields.

May 2014

Hong-Wu He

Environmentally Friendly Alkylphosphonate Herbicides

He, H.-W.; Peng, H.; Tan, X.-S.

2014, XXIV, 455 p. 441 illus., Hardcover

ISBN: 978-3-662-44430-6