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Environmentally Friendly Alkylphosphonate Herbicides

环境友好型烃基膦酸酯类除草剂

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本书以植物丙酮酸脱氢酶系（PDHc）为靶标的烃基膦酸酯类除草剂的设计、研究与应用为主线，系统介绍了PDHc抑制剂研究的新进展、以烃基膦酸酯为基本骨架设计环境友好型除草剂的分子设计理念，研究思路，从基础研究到田间应用的研究过程和结果。重点介绍了几类烃基膦酸酯的分子设计、合成、表征、除草活性研究以及相关方法学，包括烃基膦酸酯类光学异构体的不对称合成及生物活性研究。其内容涉及分子设计，先导化合物的发现、先导结构修饰，化学合成，结构表征，生物筛选、构效关系分析、分子对接研究、结构优化、活性化合物生物学特性等。本书还介绍了烃基膦酸酯作为植物PDHc抑制剂的生物化学作用机理研究，高活性化合物(包括氯酰草膦和HWS)作为除草剂应用的生物学特性,田间药效、残留、毒性、对环境生态的影响等多个环节的研究与评价结果。

本书可供从事化学，有机合成，有机磷化学，化学生物学，分子生物学，农药化学，新农药创制研究等领域研究者、科技人员参考，也可供高等院校农药、植保、农学等专业高年级本科生、研究生及教师使用。

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Foreword

Agrochemicals are used to safeguard our agricultural products from damages caused by weeds, diseases, or insects. The use of herbicides enables us to optimize the labor utilization and to ensure both high yields and good quality of crops. After repetitive application of herbicides over many years, the appearance of herbicide-resistant weeds has become a difficult problem confronting us. Currently, hundreds of herbicides have been available on the market, but their modes of action toward target weed species are rather limited. This situation calls for further research to discover highly active, environmentally friendly herbicides with novel modes of action.

Pyruvate dehydrogenase complex (PDHc) is one of the most important oxido-reductases in living organisms. It catalyzes the oxidative decarboxylation of pyruvate to form acetyl CoA, which is a pivotal process in cellular metabolism. PDHc has been reported as a potential target enzyme affected by some herbicidally active compounds. Regrettably, the PDHc inhibitors reported so far were not as active as other commercial herbicides. Therefore PDHc as a potential herbicidal target needs further investigation.

Professor Hong-Wu He is a renowned scientist in the field of pesticide science in China. She is an expert in phosphorus chemistry and pesticide innovation, for which she has received many national honors. She is the first one in China to initiate research projects in the field of novel PDHc inhibitors as potential herbicides. Through the systematic studies on molecular design, synthetic methodology, structural optimization, bioscreening, modeling etc., Professor He's group discovered a new environmentally friendly herbicide, namely clacyfos (HW02), which has the characteristics of low toxicity, low residue, and is highly safe to bees, birds, fishes, and silkworm etc. As a new PDHc inhibitor, clacyfos exhibits a different mode of action and shows no cross-resistance toward other conventional herbicides. Clacyfos has been approved in 2007 as a new post-emergence herbicide by the Ministry of Agriculture of China. It is expected that clacyfos will play a significant role in weed control.

In this book, Prof. Hong-Wu He and co-authors systematically introduce their work on the PDHc inhibitor clacyfos, from its discovery, development to commercialization. This monograph is hereby highly recommended to our colleagues and graduate students in the fields of pharmaceutical and pesticide research, phosphorus chemistry, chemical biology, life sciences, and etc. It will bring new insights into the discovery of a novel herbicide, and the complex interdisciplinary work involved. I thank the authors for sharing their expertize and experience with us, which will surely be valuable for our future research.

April 2013

Zheng-Ming Li
Nankai University

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.

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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 Biofunctional 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

Abbreviations

Abbreviations	Common Name	Latin name
Abu	Chingma abutilon	*Abutilon theophrasti*
Aca	Asian copperleaf	*Acalypha australis*
Ach	Pig's knee	*Achyranthes bidentata*
Alj	Japanese alopecurus	*Alopecurus japonicus*
Alo	Shortawn foxtail	*Alopecurus aequalis*
Alt	Alligatorweed	*Alternanthera philoxeroides*
Ama	Slender amaranth	*Amaranthus blitum*
Amm	Monarch redstem	*Ammannia baccifera*
Amr	Common amaranth	*Amaranthus retroflexus*
Ams	Spiny amaranth	*Amaranthus spinosus*
Amt	Chinese spinach	*Amaranthus tricolor*
Ave	Wild oat	*Avena fatua*
Bec	American sloughgrass	*Beckmannia syzigachne*
Bet	Sugar beet	*Beta vulgaris*
Bra	Rape	*Brassica campestris*
Brc	Field mustard	*Brassica rapa*
Brj	Leaf mustard	*Brassica juncea*
Brn	Cabbage type rape	*Brassica napus*
Bro	Ball cabbage	*Brassica oleracea*
Brp	Chinese cabbage	*Brassica pekinensis*
Caa	Chili	*Capsicum annuum*
Cap	Shepherd's purse	*Capsella bursa-pastoris*
Car	Hairy bittercress	*Cardamine hirsute*
Cas	Sickle senna	*Cassia tora*
Cay	Japanese cayratia	*Cayratia japonica*
Cer	field chickweed	*Cerastium arvense*
Che	Goosefoot	*Chenopodium album*
Chl	Feather finger grass	*Chloris virgata*

Abbreviations	Common Name	Latin name
Chs	Small goosefoot	*Chenopodium serotinum*
Cir	Setose thistle	*Cirsium japonicum*
Cis	Creeping thistle	*Cirsium setosum*
Com	Dayflower	*Commelina communis*
Con	Field bindweed	*Convolvulus arvensis*
Cuc	Cucumber	*Cucumis sativus*
Cyp	Ricefield flatsedge	*Cyperus iria*
Cym	Asian flatsedge	*Cyperus microiria*
Cyn	Bermudagrass	*Cynodon dactylon*
Cyr	Nut grass	*Cyperus rotundus*
Dap	Water flea	*Daphnia magna*
Dau	Carrot	*Daucus carota*
Des	Flixweed tansymustard	*Descurainia Sophia*
Dic	Southern crabgrass	*Digitaria ciliaris*
Dig	Crab grass	*Digitaria sanguinalis*
Ech	Barnyard grass	*Echinochloa crusgalli*
Ecl	White eclipta	*Eclipta prostrata*
Ele	Goose grass	*Eleusine indica*
Eri	Flaxleaved fleabane	*Erigeron bonariensis*
Esc	Colon bacillus	*Escherichia coli*
Eul	Aper spurge	*Euphorbia lathyris*
Eum	Spotted spurge	*Euphorbia maculata*
Eup	Wolf's milk	*Euphorbia humifusa*
Fes	Tall fescue	*Festuca arundinacea*
Gal	Cleavers	*Galium aparine*
Gly	Soybean	*Glycine max*
Gos	Cotton	*Gossypium hirsutum*
Ipn	Morning glory	*Ipomoea nil*
Ipo	Lobedleaf pharbitis	*Ipomoea hederacea*
Ixe	Chinese ixeris	*Ixeris chinensis*
Lac	Lettuce	*Lactuca sativa*
Lam	Henbit deadnettle	*Lamium amplexicaule*
Lap	Common nipplewort	*Lapsanastrum apogonoides*
Lin	Prostrate false pimpernel	*Lindernia procumbens*
Lyc	Tomato	*Lycopersicon esculentum*
Mal	Water chickweed	*Malachium aquaticum*
Med	Clover	*Medicago sativa*
Mon	Pickerel weed	*Monochoria vaginalis*
Oen	Water dropwort	*Oenanthe javanica*
Ory	Rice	*Oryza sativa*
Oxa	Creeping woodsorrel	*Oxalis corniculata*

Abbreviations	Common Name	Latin name
Pis	Pea	*Pisum sativum*
Poa	Annual bluegrass	*Poa annua*
Pob	Bunge's smartweed	*Polygonum bungeanum*
Poc	Pinkhead smartweed	*Polygonum capitatum*
Pof	Asia minor bluegrass	*Polypogon fugax*
Pol	Knotgrass	*Polygonum aviculare*
Pop	Water pepper	*Polygonum flaccidum*
Por	Common purslane	*Portulaca oleracea.*
Ran	Tall buttercup	*Ranunculus japonicus*
Rap	Radish	*Raphanus sativus*
Rot	Indian toothcup	*Rotala indica*
Rum	Curled dock	*Rumex crispus*
Sef	Giant foxtail	*Setaria faberi*
Sep	Yellow bristlegrass	*Setaria pumila*
Set	Green bristlegrass	*Setaria viridis*
Sin	White mustard	*Sinapis alba*
Sol	Black nightshade	*Solanum nigrum*
Ste	Bog chickweed	*Stellaria alsine*
Stm	Chickweed	*Stellaria media*
Tri	Wheat	*Triticum aestivum*
Trp	Cucumber-herb	*Trigonotis peduncularis*
Ver	Gray field speedwell	*Veronica polita*
Vic	Common vetch	*Vicia sativa*
Vig	Wild vetch	*Vicia gigantea*
Vir	Mung bean	*Vigna radiata*
Xan	Siberian cocklebur	*Xanthium strumarium*
Zea	Maize	*Zea mays*

About the Authors

Hong-Wu He obtained her Doctoral Degree in Agricultural Science from Kyushu University, Japan. She is currently a full-time Professor at the Key Laboratory of Pesticide and Chemical Biology, Ministry of Education of China, and the Director of Institute of Pesticide Chemistry, College of Chemistry, Central China Normal University, Wuhan, China. She is also a Member of the Council of Pesticide Society of China and the Director of Pesticide Professional Committee and Chemical Industry Society of Hubei province.

Prof. He has more than 33 years of teaching and research experience in the field of pesticide chemistry, especially in the design, synthesis, and development of novel herbicide based on pyruvate dehydrogenase. She has devoted herself to the research and development of novel herbicide named clacyfos and several other OP insecticides. She is the author of more than 230 scientific articles and 6 books. Besides that Prof. He holds more than 30 patents related to pesticide chemistry. She has received multiple Scientific and Technological Progress Awards and Technological Invention Awards in agrochemical research from the Ministry of Education of China and the Government of Hubei province. She was the winner for the award of Outstanding Contribution to the Pesticide Industry of China in 2009 and the title "National Outstanding Scientific and Technological Worker" in 2001.

Hao Peng currently is an Associate Professor at the Key Laboratory of Pesticide and Chemical Biology, Ministry of Education of China, College of Chemistry, Central China Normal University (CCNU), Wuhan, China. He obtained his Ph.D. in Pesticide Science from CCNU under the supervision of Prof. Hong-Wu He.

His current research focuses on the research and development of novel agrochemicals, especially on the design of organophosphorus compounds with herbicidal and fungicidal activity based on pyruvate dehydrogenase and pyrroline-5-carboxylate reductase. He has been involved in the research and development of novel herbicide clacyfos since 2003. He has received two Scientific and Technological Progress Awards and Technological Invention Awards in agrochemical research from the Government of Hubei province and Wuhan city. He has published more than 45 scientific articles and serves as an active reviewer for a number of scientific journals.

Xiao-Song Tan currently is an Associate Professor at the Key Laboratory of Pesticide and Chemical Biology, Ministry of Education of China, College of Chemistry, Central China Normal University (CCNU), Wuhan, China. He obtained his M.S. degree in Chemistry from CCNU.

He has worked on the synthesis, structural identification, and analysis of new bioactive chemicals for 30 years including the development of novel herbicide clacyfos since 2000. He has received multiple Scientific and Technological Progress Awards and Technological Invention Awards in agrochemical research from the Ministry of Education of China and Government of Hubei province. He has co-authored more than 50 scientific articles and several book chapters in the field of pesticide chemistry.

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