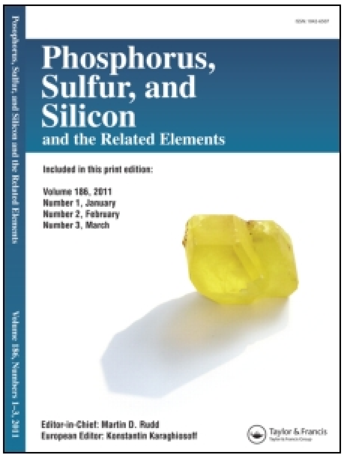


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# The Use of OP and Development of New Organophosphorus Agrochemicals in China

Hong Wu He[a]
[a] Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, Institute of Pesticide Chemistry, College of Chemistry, Central China Normal University, Wuhan, P.R. China

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# The Use of OP and Development of New Organophosphorus Agrochemicals in China

**Hong Wu He**
Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, Institute of Pesticide Chemistry, College of Chemistry, Central China Normal University, Wuhan, P.R. China

*Phosphorus-containing agrochemicals have made a major contribution to the advancement of agriculture in China. Current status about production and usages of organophosphorus agrochemicals in China is reviewed in this article. Development of new organophosphorus agrochemicals including insecticide, herbicide, and anti-TMV agent in recent years is introduced. Recent progress in research and development of α-(Substituted phenoxyacetoxy)alkylphosphonates is then described: α-(Substituted phenoxyacetoxy)alkylphosphonate II as a kind of potential agrochemicals was found on the basis of the study of a series of α-oxophosphonic acid derivatives I in our Lab. Some compounds II were demonstrated as effective inhibitors of pyruvate dehydrogenase complex from plant (in vitro) and showed notable herbicidal activity against broad-leaved weeds. Compound HW02 as a potential herbicide was evaluated and developed.*

**Keywords** Organophosphorus agrochemical; insecticide; herbicide; anti-virus agent



## INTRODUCTION

Pesticides have made great contributions to the advancement of agriculture in China. More than 600 active ingredients, 22,000 formulations and products could be produced in China. Figures 1 and 2 reflect the production and application numbers for pesticides 1995–2005. Approximately 1 million tons/year of active ingredients were produced in recent years.[40] Almost 0.25~0.27 million tons were applied to about 300 millions ha/year in China, that is to say, China ranked first in production and second in usage for pesticides in the world.

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Address correspondence to Hongwu He, Key Laboratory of Pesticide and Chemical Biology, Ministry of Education; Institute of Pesticide Chemistry, College of Chemistry, Central China Normal University, 152 Luo-yu Road, Wu Chang, Wuhan 430079, P.R.China. E-mail: he1208@mail.ccnu.edu.cn

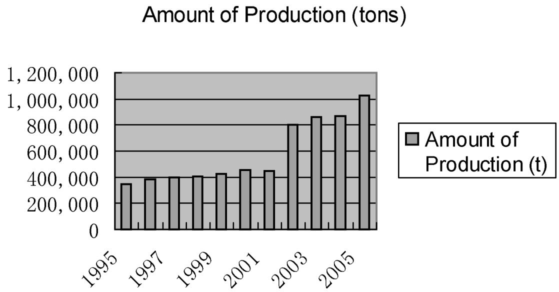



**FIGURE 1** Amount of production for pesticides 1995–2005.

China is both an import & export country and exports more pesticide products than the country imports. 30–40% yield of crop loss could be avoided due to application of pesticides. In the other words, additional yield for crop is obtained by the use of pesticides in every year, such as, 48 million tons rice; 0.6 million tons cotton, 48 million tons vegetable, 6 million tons fruit. So pesticides have made a great contribution to the advancement of agriculture in China. The production of pesticides in China can meet the domestic needs, ensure a bumper harvest and improve the living standard of the farmers. Among the pesticides, organophosphorus (OP) agrochemicals are the most important group of pesticides used in China.



## STATUS OF OP PRODUCTION AND USAGES IN CHINA

Many phosphorus-containing agrochemicals have been developed and widely used all over the world because of their high efficacy and low persistency in the natural environment.[1] OP agrochemicals also have widely used for crop protection in China and they are the most important group of pesticides for Chinese pesticide industry. Look back to 1983, where the usages of DDT and Lindane were prohibited in

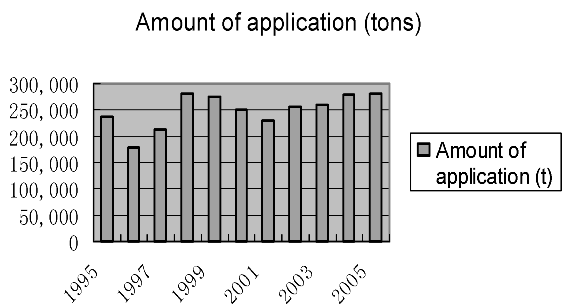
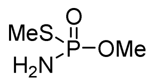
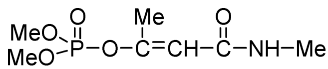
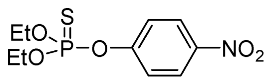
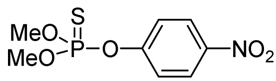
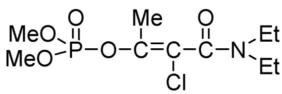



**FIGURE 2** Amount of application for pesticides during 1995–2005.

**TABLE I 5 High-Toxicity OP Insecticides**

| OP insecticides | Structure | LD50 mg/kg Acute oral (rat) | Producers |
|---|---|---|---|
| Methamidphos |  | 30 | 45 |
| Monocrotphos |  | 20 | 13 |
| Parathion |  | 5 | 15 |
| Parathion-methyl |  | 5 | 26 |
| Phosphamidan |  | 20 | |

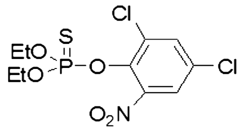
China. In that year, OP insecticides increased rapidly. More than 30 of OP agrochemicals as main products were produced and widely used for crop protection in China. Among OP agrochemicals OP insecticides have become most commercial important insecticides in China because of their high efficacy, low prices, simple technology in production, and their agricultural variability. Insecticides covered almost 70% of the whole agrochemical market and OP insecticides covered 70% of the insecticides market in China during 1990–2002. In 1990, insecticides covered 78% of the whole agrochemical market in China—OP insecticides covered 70%, while herbicides and fungicides only covered 10% and 9%, respectively. OP insecticides have great economical importance for the Chinese pesticide industry. Among OP insecticides used in China, 5 economic important OP insecticides are listed in Table I.

In the 21st century, the Chinese government has given more priority and attention to safety management. High-toxicity problems have become the reasons of withdrawing of some OP insecticides from the market of China. In order to meet the increasing requirements on food quality, food safety and environment safeguard, some policies were made by authorities in China, such as the amount of high-toxicity OP products has been limited since 2002; Highly toxic products have been prohibited for registration; Five high-toxicity OP insecticides (see Table I) have been entirely banned in China since January 1, 2007. These policies promoted the production and application of low-toxicity, high activity insecticides. High-toxicity OP products have been gradually being displaced by low-toxicity OP products or other new synthetic agrochemicals since 2002. Product structures in pesticide industry were greatly adjusted. So the amount of production for high-toxicity OP products decreased and herbicides increased rapidly: insecticides from 78% in 1990 decreased to 41.8% in 2005; and herbicides from 10% in 1990 increased to 28.6% in 2005. During 2002–2006, although the amount of production for high-toxicity OP products decreased rapidly, both low-toxicity OP insecticides and OP herbicides increased rapidly. Now OP products still cover almost 40–50% of the whole agrochemical production in China.

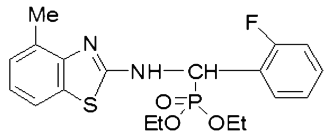
## DEVELOPMENT OF NEW ORGANOPHOSPHORUS AGROCHEMICALS IN CHINA

China has become the second largest country in pesticide usages. R&D for environment friendly agrochemicals are becoming more and more important in China. Innovation system for agrochemicals needs to be established in China. With the financial support from state government, two pesticide innovation centers were established in China during 1996–2000. One is the National Pesticide Engineering Research Center including Shenyang Research Institute of Chemical Industry and Nankai University. Another is the National Pesticide Discovery South Center, which is composed of four institutes including Shanghai Pesticide Research Institute, Jiangsu Pesticide Research Institute Co., Ltd., Hunan Pesticide Research Institute, Zhejiang Chemical Industry Science and Technology Group Company. Some universities and research institutes are also involved in pesticide discovery research. So pesticide discovery facilities and research system including molecular design, chemical synthesis, structure analysis, screening (laboratory, greenhouse and field), safety evaluation (toxicity and eco-toxicity), process research and pilot plant, registration and market development have been preliminarily established in China. R&D for new agrochemicals have made great progress in recent years, 21 new pesticides, including, 5 Insecticides, 9 Fungicides, 5 Herbicides, and 2 PGR's as patent products have been developed and got temporary registration from the ICAMA (Institute for Control of Agrochemicals Ministry of Agriculture) in China. China has started innovating new pesticides with independent intellectual property. Among those new pesticides several low-toxicity organophosphorus compounds as patent products including insecticide, herbicide, and anti-TMV agent are being developed in China. Their structures are shown in Figure 3.

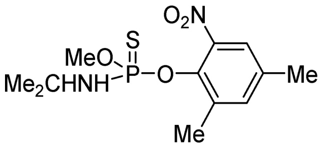
Xiaochongliulin as a novel organophosphates insecticide was found and developed by Sichuan Research Institute of Chemical Industry



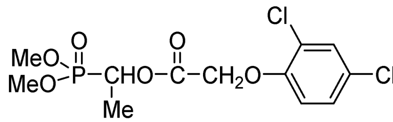
Xiao Chong Liu Lin Insecticide



Bingduxing Anti-TMV agent



H-9201 Herbicide



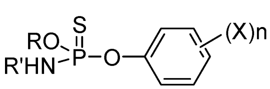
HW02 Herbicide

**FIGURE 3** OP pesticides developed in China.



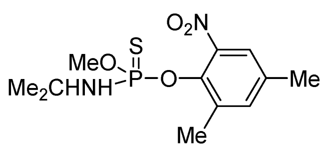
in China.[2] Its acute oral (rat, male/female) $LD_{50} > 212$ mg/kg and its 30% EC product has low toxicity, acute oral (rat, male/female) $LD_{50} > 2000$ mg/kg. Field test results showed that it was active against citrus red mite, citrus scales, cotton bollworm, diamondback moth, rice planthopper, and so on. It has got temporary registration for citrus scale control from ICAMA in China. So Xiaochongliulin can be used as a low toxicity insecticide to replace high toxicity organophosphates insecticides in China.

H-9201 as a novel organophosphates herbicide was found by the research on synthesis and bioactivity of a series of phosphoramidates compounds (I) in Figure 4 by Hua-Zheng Yang et al. in Nankai University in China.[3] H-9201 has low toxicity with acute oral (rat, male/female) $LD_{50} > 2500$ mg/kg. H-9201 exhibited good effects against a broad spectrum of monocotyledon and broadleaf weeds. H-9201 as herbicide is being developed and used for main monocotyledon and broadleaf weeds control in soybean, vegetable, wheat, and rice crops field at the rate of 450–900g/ha. H-9201 has got temporary registration from ICAMA in China.



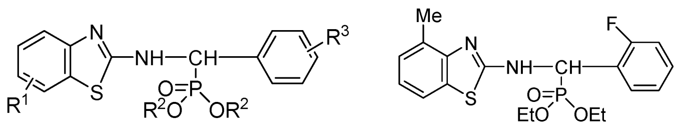
(I)

R,R' = alkyl
X = Substituent



H-9201 Herbicide

**FIGURE 4** H-9201 was found from phosphoramidates compounds (I).




(2) Bingduxing Anti-TMV agent

$R_1$=4-Me,MeO,F,Cl,$NO_2$,$CF_3$,6-Me,MeO,F,Cl,$NO_2$,$CF_3$;
$R_2$=Me,Et,n-Pr,i-Pr,n-Bu,s-Bu,i-Bu;$R_3$=2-F,$CF_3$,3-F,$CF_3$,4-F,$CF_3$

**FIGURE 5** Bingduxing was found from aminophosphonate compounds (2).



Bingduxing as a novel anti-virus agent was found on the basis of the study of a series of aminophosphonate compounds (2) containing benzothiazole by Baoan Song et al. in Guizhou University in China.[4] A series of compounds (2) in Figure 5 were synthesized and their bioactivitie for anti-tobacco mosaic virus (TMV) were screened by a Half-leaf method which was used to determine protective, curative, and inactivation effects (both in vivo and in vitro). Bingduxing with good anti-tobacco mosaic virus (TMV) was found. The result showed that Bingduxing possessed good curative effect against TMV in vivo, better than that of the control agents Ningnan mycin, Virus A, and Antofine. Bingduxing as anti-TMV agent is being developed. Field trails were completed for temporary registration. It showed good effect against TMV at the rate of 300 g/ha.

Compound HW02 as a potential herbicide was found on the basis of the study of a series of $\alpha$-(substituted phenoxyacetoxy)alkylphosphonate II in our Lab.[5] HW02 has got temporary registration recently from ICAMA in China. Recent progress in research and development of $\alpha$-(substituted phenoxyacetoxy)alkylphosphonates II are described in following section.

## Research and Development of $\alpha$-(Substituted Phenoxyacetoxy)alkyl Phosphonates with Herbicidal Activity

Pyruvate dehydrogenase complex (PDHc) is already known to be a site of pesticide action, because it plays a pivotal role in cellular metabolism catalyzing the oxidative decarboxylation of pyruvate and the subsequent acetylation of coenzyme A (CoA) to acetyl-CoA.[6–9] The complex consists of three enzymes and a number of cofactors. Decarboxylation of pyruvate is the first step in this conversion. This step is catalyzed by pyruvate decarboxylase (PDHc E1), which promotes the decarboxylation of pyruvate using thiamine pyrophosphate (TPP) and $Mg^{2+}$ as cofactors.[10–12] From the point of view of agrochemical design, PDHc E1

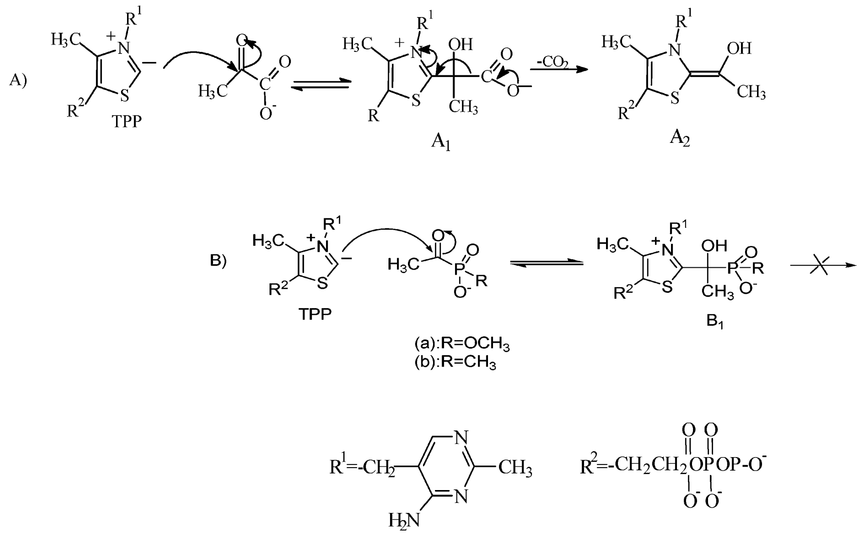


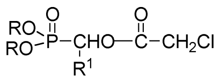
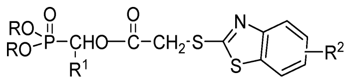
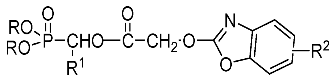
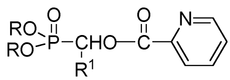
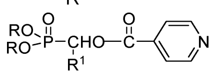
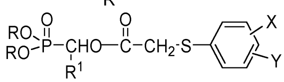
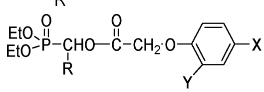
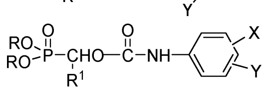
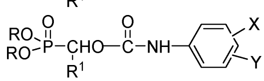
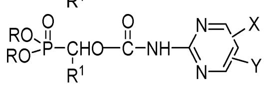

**FIGURE 6** Comparison of the reactions of Pyruvate (A) and compounds (B) with thiamine pyrophosphate catalyzed by pyruvate dehydrogenase.

is a target of interest. There are some reports about design of inhibitors of pyruvate dehydrogenase complex (PDHc) as herbicide. An attempt to design inhibitors of PDHc E1 as herbicides using biochemical reasoning was reported by Baillie et al.[13] Series of acylphosphinates and acylphosphonates as an analog of pyruvate have been prepared as mechanism-based inhibitors of PDHc. Such as methyl acetylphosphinate as an analog of pyruvate can bind with TPP to form adduct B1, but B1 can not undergo dephosphorylation to giv A2[14] (see Figure 6).

Baillie et al. demonstrated that some acetylphosphinates and acetylphosphonates showed herbicidal activity due to their inhibition against PDHc.[13] Although they were not active enough for full development as herbicides,[13–15] this provided a clue to the design of PDHc inhibitor. Therefore, one approach to design novel PDHc E1 inhibitors with phosphonate structure as potential herbicides was attempted in our laboratory. On the basis of the work of Baillie et al., the structural unit of phosphonate molecule as moiety A is kept, and an aryl or a heterocycle group as moiety B is linked with moiety A by a carboxylate ester bond to form $\alpha$-oxophosphonic acid derivatives I (see Figure 7). In order to find a lead compound with desired herbicidal activity, first, different structural unit Q was introduced into phosphonate molecule (moiety A) to obtain different series of $\alpha$-Oxophosphonic acid derivatives.

So ten series of $\alpha$-Oxophosphonic acid derivatives I-1~10 have been synthesized in our previous work and reported in the corresponding

**TABLE II Herbicidal Activities of Compounds I**

| No | Structure | Herbicidal activities[a,b] | The number of compounds tested | Literatures |
|---|---|---|---|---|
| I-1 |  | ≤30% | 8 | [16] |
| I-2 |  | ≤30% | 21 | [17] |
| I-3 |  | ≤32% | 16 | [18] |
| I-4 |  | ≤48% | 10 | [19] |
| I-5 |  | ≤48% | 10 | [20] |
| I-6 |  | ≤18% | 8 | [21] |
| I-7 |  | ≤100% | 12 | [22] |
| I-8 |  | ≤30% | 8 | [23] |
| I-9 |  | ≤30% | 40 | [24] |
| I-10 |  | 0% | 16 | [25] |

a, Growth inhibition: 0 (no effect), 100 (completely kill); Dose = 2.25Kg/ha.
b, Test plants: Monocotyledon: such as barnyard grass, wheat, chinese sorghum.
Dicotyledon: such as rape, common vetch, setose thistle, three-colored amaranth, radish.

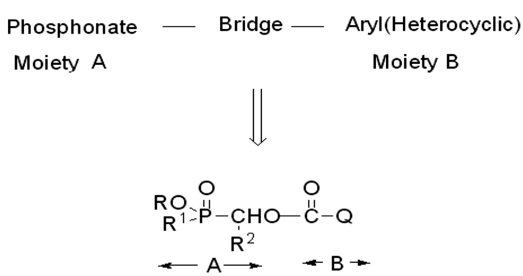



**FIGURE 7** $\alpha$-Oxophosphonic acid derivatives I.

**TABLE III Herbicidal Activity of Compounds I-7[a,b,c]**

| | | | | Monocotyledo | | | | Dicotyledo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N0 | X | Y | Z | Tri | | Ech | Ave | Bra | | Com | | Lye | Ama |
| | | | | A | B | B | A | A | B | A | B | A | B |
| I-7a | Cl | Cl | H | 45 | 9 | 42 | 0 | 99 | 100 | 100 | 100 | 100 | 80 |
| I-7b | Cl | Cl | Me | 51 | 45 | 42 | 0 | 91 | 100 | 100 | 100 | 100 | 100 |
| I-7c | Cl | Cl | Et | 35 | 48 | 0 | 42 | 100 | 100 | 100 | 77 | 100 | 100 |
| I-7d | Cl | Cl | n-Pr | 60 | 62 | 42 | 0 | 91 | 100 | 100 | 51 | 100 | 100 |
| I-7e | Cl | Cl | Ph | 66 | 30 | 42 | 0 | 91 | 100 | 41 | 66 | 100 | — |
| I-7f | Cl | H | H | 51 | 40 | 42 | 0 | 91 | 100 | 100 | 51 | 90 | 60 |
| I-7g | Cl | H | Me | 60 | 36 | 41 | 0 | 91 | 100 | 94 | 100 | 100 | 0 |
| I-7h | Cl | H | Et | 52 | 49 | 42 | 0 | 91 | 27 | 100 | 73 | 100 | 100 |
| I-7i | Cl | H | n-Pr | 45 | 30 | 71 | 3 | 91 | 100 | 100 | 22 | 100 | 100 |
| I-7j | Cl | H | Ph | 39 | 22 | 57 | 71 | 91 | 100 | 41 | 22 | 100 | 0 |
| I-7k | Cl | H | $CC_{l3}$ | 0 | 38 | 42 | 0 | 100 | 79 | 100 | 77 | 100 | 60 |
| I-7l | Me | H | $CC_{l3}$ | 0 | 30 | 42 | 0 | 100 | 0 | 41 | 66 | 0 | 60 |

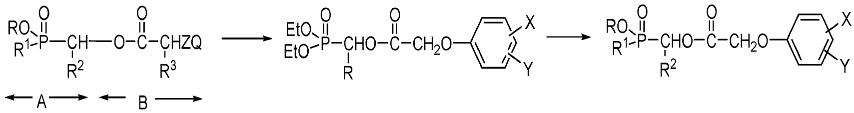
a. Dos = 2.25 Kg/ha; A = pre-emergenc; B = Post-emergence.
b. Growth inhibition 0 (no effect); 100 (completely killed) —: not tested.
c. Tri = Wheat; Ech = Barnyarcd Grass; Bra = Rape; Com = Common vetc; Ama = Three-colored amaranth; Ave = Wild oats; Lyc = Tomato.



literatures.[16–25] Their herbicidal activity was evaluated at a dose of 2.25 a.i. kg/ha in a set of experiments in a greenhouse. The general structure and comparison of herbicidal activities of compounds I-1∼10 are listed in Table II. Most series of compounds showed poor herbicidal activity. Only series I-7, O,O-diethyl $\alpha$-(substituted phenoxyacetoxy)alkylphosphonate, exhibited significant herbicidal activity. The detailed herbicidal activity data of a series of compound I-7 are given in Table III. They had significant activity against dicotyledonous plants. Therefore, we selected compound I-7 as a lead compound and attempted to optimize its structure by chemical modification.

The structure of compound I–7 could be extended to a general structure II (Figure 8). In the structure II, there are five different substituents which can be changed by chemical modifications. It is possible that the biochemical properties of compounds II will be remarkably variable by combinations of several groups or atoms attached to the structure II.

We have been very interested to get answers to some questions about $\alpha$-(substituted phenoxyacetoxy)alkylphosphonates. Would they acquire better herbicidal activity by the chemical modification of lead compounds I-7? Do they act as inhibitors of pyruvate dehydrogenase complex?




I 1-10 I-7 II

**FIGURE 8** The structure of compound I-7 extended to a general structure II.

In order to obtain higher herbicidal active compounds as powerful inhibitors of PDHc the structure of lead compound I-7 was modified. The phospho(i)nates and their salt as substrate analogs or as potential substrate analogs of the target enzyme were designed, they might well be effective as the inhibitors of PDHc. So different series of 1-(phenoxyacetoxy) alkylphospho(i)nates II were designed and synthesized[26–34] (Figure 9). Optimizing the structure of lead compound by chemical modification was carried out on the basis of the study of synthesis, biological activities, biochemistry, and structure- activity relationship.[35–37]

$\alpha$-(Substituted phenoxyacetoxy)alkylphosphonates II showed a broad structure–activity-range. According to results of evaluation for their herbicidal activity in a greenhouse, series II-2, II-3 exhibited lower herbicidal activity than that of compound I-7, however some compounds in series II-1, II-4, II-5, and II-6 showed significant herbicidal activity

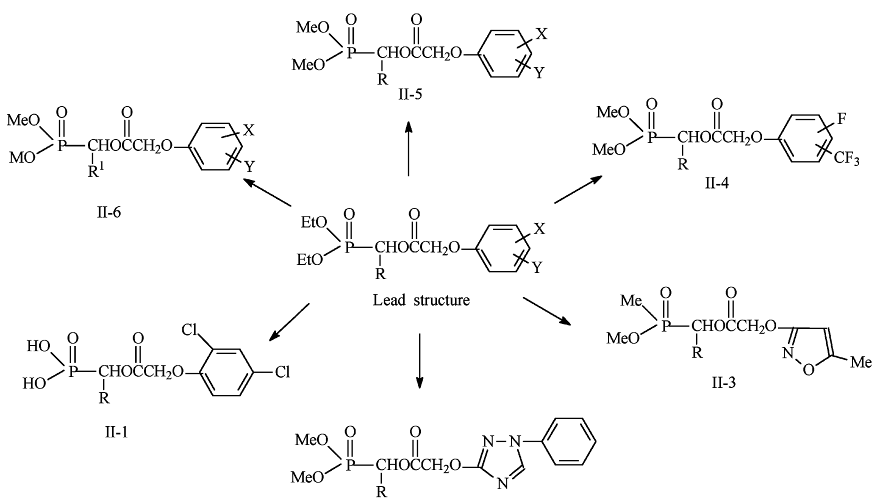



**FIGURE 9** Optimizing the structure of lead compound by chemical modification.

against dicotyledon. Substituent X and Y in the structure II can greatly affect activity, especially, compounds exhibited higher herbicidal activity when X and Y as 2, 4-Cl, Cl or 2, 4- Cl, F. It also could be found that herbicidal activity could be greatly enhanced by the chemical modification of R, $R^1$, $R^2$ in the phosphonate moiety in structure II when the X and Y is kept constant. The effect of compounds on PDHc was tested, some compounds in series II-5, II-6 were demonstrated to be effective inhibitors of PDHc in vitro.[38] It is very interesting that herbicidal activities of these compounds positively correlated with inhibition of PDHc. Herbicidal activities were enhanced with the increase in inhibitory activites of compounds on PDHc and inhibitory activities on PDHc of compounds could be increased greatly by the chemical modification of substituents in structure II. The results indicate that the improvement of herbicidal or inhibitory activity requires a reasonable combination of both phospho(i)nate and phenoxyacetic acid moieties, and the structure and position of substituents R, $R^1$, $R^2$, X, and Y are critical.

Compound HW02 with notable herbicidal activity was found by the chemical modification of substituents in parent compound II. The effect on PDHc of HW02 was tested and it was shown to be a good inhibitor of the PDHc from pea (*Pisum sativum L.*) mitochondria with an $I_{50}$ value of 18.19 $\mu$M (in vitro).[39] Its activity against PDHc from dicotyledon was much higher than that of monocotyledon. So it could be selectively inhibiting PDHc from dicotyledon. According to the data in Table IV HW02 also showed higher activities against broadleaf weeds than plants of monocotyledon and it was safe for wheat and rice.[39] The results indicate that HW02 is selectively inhibiting dicotyledonous weeds due to its selectively inhibiting the PDHc of dicotyledonous weeds. So it could be a selective herbicide to be useful in monocotyledonous corps field for dicotyledonous weeds control.

In order to evaluate the commercial potential of HW02 as herbicide, field tria, toxicity evaluation, eco-toxicity evaluation and process research for HW02 were carried out. The evaluation of toxicity and ecological effects showed that HW02 had low acute toxicity with cute oral (rat, male/female) $LD_{50}$ >1400 mg/kg and it was also low toxic to bee, birds, and fishes.[39] HW02 showed systemic biophysical property and good effects against a broad spectrum of weeds. More than forty fields trials showed that it could be as a herbicide applied to control weeds in lawn, wheat and maize field and exhibited a potent activity against broad-leaved weeds at the rate of 150–450 g/ha, and was safe for the following crops.[39] Until now, field trias in lawn and maize field for weed control have been completed for temporary registration; HW02 has got temporary registration recently from ICAMA in China.

**TABLE IV The Herbicidal Activities of HW02 (Relative Inhibition of Growth % )[a]**

| | *Brassica napus.* | *Medicago sativa L.* | *Amaranthus retroflexus* | *Daucus carota L.* | *Triticum aestivum L.* | *Oryza sativa* |
|---|---|---|---|---|---|---|
| g/ha | Post | Post | Post | Post | Post | Post |
| 150 | 42.6 | 69.8 | 59.3 | 59.9 | — | — |
| 225 | 90.0 | 80.0 | 67.9 | 94.2 | — | — |
| 300 | 100 | 86.6 | 100 | 100 | — | — |
| 450 | 100 | 95.0 | 100 | 100 | 0 | 0 |
| 600 | 100 | 100 | 100 | 100 | 0 | 0 |

[a]Evaluation in greenhouse test. Post: post-emergence; —: not tested.

As a conclusion, above results strongly support the view that a potential herbicide could be obtained by the design of inhibitor of pyruvate dehydrogenase complex.

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