

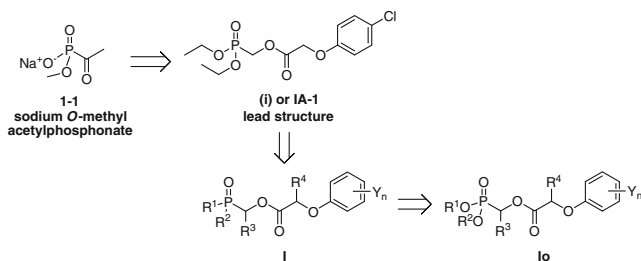
Chapter 2

Alkylphosphonates

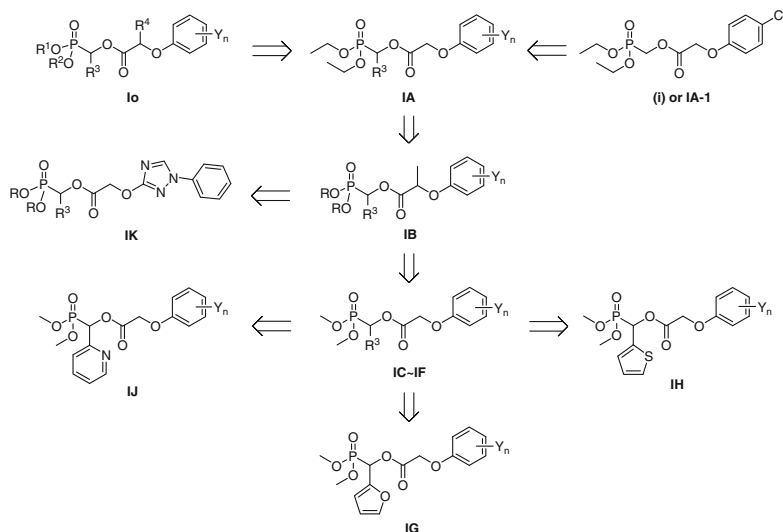
As stated in Chap. 1, through the modification of hit compound, sodium *O*-methylacetylphosphonate **1-1**, ten series of 1-oxophosphonic acid derivatives (**i**)–(**x**) (Table 1.7) were synthesized to examine their herbicidal activity at an early stage of our work. The results showed that only a few *O,O*-diethyl 1-(substituted phenoxyacetoxy)alkylphosphonates (**i**) (Scheme 2.1) exhibited significant herbicidal activity at 2.25 kg ai/ha in the greenhouse. In our continued work, the alkylphosphonates (**i**) were identified as the lead structure of a new class of herbicides. Therefore it was further extended to a general structure **I** which could be modified to form more than thirty series of compounds including alkylphosphonates, alkylphosphinates, cyclic phosphate, caged bicyclic phosphates and relative derivatives (Scheme 1.20).

According to the work of Baillie et al. [1] the structural unit of phosphonate was important for the inhibition against plant PDHc, therefore the study on structure **I** was firstly focused on the phosphonate scaffold **Io** by the modification of lead compound **IA-1** (Scheme 2.1). Different groups of R^1 , R^2 , R^3 , R^4 and Y_n were introduced into the general structure **Io** to form different series of alkylphosphonates **IA-1K** (Scheme 2.2), in an attempt to find compounds with better herbicidal activities.

In **IA** series, optimization was focused on the modification of substituents R^3 and Y_n . Most **IA** showed good herbicidal activity against dicotyledonous plants at 2.25 kg ai/ha. In order to examine the effect of R^1 , R^2 and R^4 in the



Scheme 2.1 Optimization of hit compound **1-1**



Scheme 2.2 Design of alkylphosphonates **IA–IK**

alkylphosphonates **Io** on herbicide activity, **IA** was modified to form **IB** (Scheme 2.2). Results of study on **IB** series suggested that R^1 , R^2 and R^4 with smaller groups in structure **Io** would show better herbicidal activity. Therefore, the structure **IB** was further optimized to produce *O,O*-dimethyl 1-(substituted phenoxyacetoxo)alkylphosphonates **IC–IF** (Scheme 2.2).

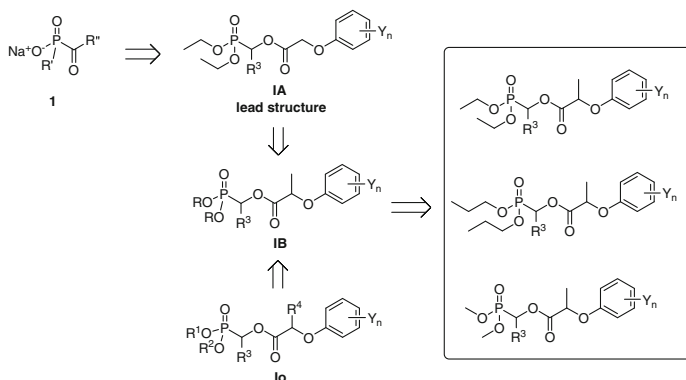
As shown in Scheme 2.2, the introduction of heterocyclic groups in R^3 of **IC–IF** led to the phosphonates **IG** (R^3 =fur-2-yl), **IH** (R^3 =pyrid-2-yl) and **IJ** (R^3 =thien-2-yl), respectively. The replacement of the substituted phenoxy moiety by the triazole ring in **IB** gave 1-(1-phenyl-1,2,4-triazol-3-yloxyacetoxo) alkylphosphonates **IK**. Several compounds in **IC** and **IG** series were found to be herbicidally active compounds against broadleaf weeds by systematic study of alkylphosphonates **IA–IK**.

In this chapter, we describe the synthesis, herbicidal activity and structure-activity relationship (SAR) of alkylphosphonates **IA–IK**. Herbicidal activity of **IC-22** and **IG-21** will be discussed in detail.

2.1 (Alkyl or Substituted Phenyl)Methylphosphonates IA–IF

2.1.1 Introduction

In order to systematically examine the herbicidal activity of lead structure (i), a series of *O,O*-diethyl 1-(substituted phenoxyacetoxo)alkylphosphonates as **IA** was further designed and prepared by the modification of lead compound **IA-1**.

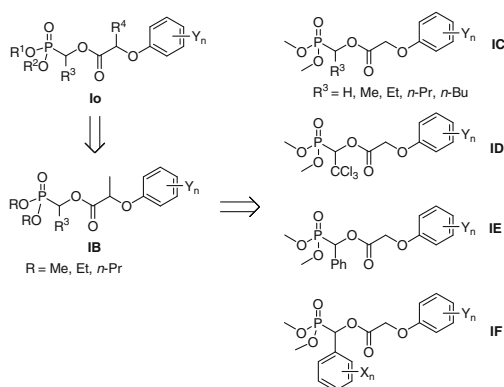


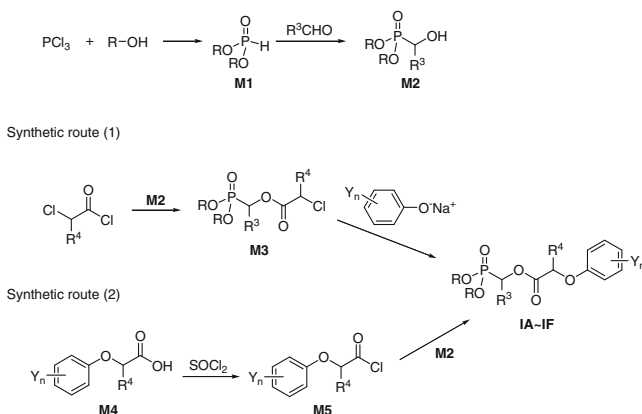
Scheme 2.3 Design of 1-(substituted phenoxyacetoxy)alkylphosphonates **IB**

According to the study on acylphosphonates by Baillie et al., substituent R^1 in monosodium acylphosphonates **1** (Scheme 2.3) greatly affected both enzyme inhibitory activity and herbicide activity of compounds. Therefore, R^1 and R^2 in structure **Io** were firstly modified to examine their effect on herbicidal activity. Me, Et or *n*-Pr as R^1 and R^2 was introduced into the structure **Io** to form **IB** (Scheme 2.3). In the **IB** series, where Me as R^4 was kept, further optimization was focused on the modification of R^3 and Y_n .

It was found that when smaller R (or Me as R^1 and R^2 in the structure **Io**) was introduced into the structure **IB**, the herbicidal activity of the compound could be significantly increased. Therefore, structure **IB** was further optimized to produce a series of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IC–IF** (Scheme 2.4). In the **IC–IF** series, Me as R^1 and R^2 , H as R^4 in the structure **Io** were kept, optimization was focused on the modification of substituents R^3 . In the **IC** series, H, Me, Et, *n*-Pr, and *n*-Bu as R^3 ; In the **ID** series, CCl_3 as R^3 ; In the **IE** series, Ph as R^3 ; In the **IF** series, substituted Ph as R^3 . When R^3 was kept, further

Scheme 2.4 Design of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IC–IF**





Scheme 2.5 Synthetic route of *O,O*-dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA–IF**

optimization was focused on the modification of Y_n . It was expected that herbicidal activity would be improved by the chemical modifications of **IB**.

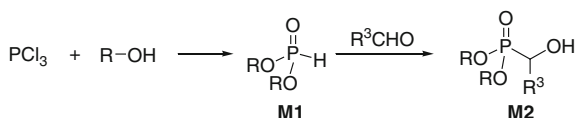
Based on the above consideration, six series of 1-(substituted phenoxyacetoxy) alkylphosphonate derivatives **IA–IF** were prepared. The synthesis and herbicidal activity of **IA–IF**, and their SAR are summarized in this Sect. 2.1.

We chose the following synthetic routes (1) or (2) to obtain *O,O*-dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA–IF** (Scheme 2.5). In the synthetic route (1), the title compounds can be synthesized by the reaction of substituted phenol sodium with corresponding 1-(chloroacetoxy)alkylphosphonates **M3** in the presence of sodium iodide. In the synthetic route (2), the title compounds can be synthesized by the condensation of *O,O*-dialkyl 1-hydroxyalkylphosphonates **M2** and substituted phenoxyacetyl chlorides **M5** (Scheme 2.5).

The synthetic yields of **IA–IF** using the method of route (2) were better than that of route (1). Therefore, we mainly chose the synthetic route (2) to obtain **IA–IF**. *O,O*-Dialkyl 1-hydroxyalkylphosphonates **M2**, substituted phenoxyacetic acids **M4** and substituted phenoxyacetyl chlorides **M5** are the important intermediates for the synthesis of **IA–IF**. The preparation of **M2**, **M4** and **M5** is described in Sects. 2.1.2 and 2.1.3, respectively.

2.1.2 Synthesis of *O,O*-Dialkyl 1-Hydroxyalkylphosphonates **M2**

O,O-Dialkyl 1-hydroxyalkylphosphonates **M2** are key intermediates for the preparation of title compounds **IA–IF**. **M2** could be prepared by the nucleophilic addition of dialkyl phosphonates to several kinds of aldehydes (Scheme 2.6).

**Scheme 2.6** Synthesis of *O,O*-dialkyl 1-hydroxyalkylphosphonates **M2**

Some *O,O*-dialkyl 1-hydroxyalkylphosphonates have been prepared by the addition of dialkyl phosphonates to aldehydes under different reaction conditions [2], which can be summarized as follows: (1) non-catalytic thermal addition [3, 4], (2) base-catalysis addition [5], and (3) solvent-free catalytic process using potassium fluoride, calcium fluoride, aluminum oxide, or others, as a catalyst [6–8].

The method of base-catalyzed addition is a simple procedure, however, in this case the yield is not always good, and a mixture of products is sometimes obtained. In a strong alkaline medium, 1-hydroxyalkylphosphonates are easily cleaved to regenerate the starting carbonyl compounds [3]. Texier-Boullet reported a convenient solvent-free catalyzed addition using a mixture of potassium fluoride and alumina, or a mixture of potassium fluoride and aluminum oxide [6, 7]. This method had an advantage of higher yield, and the catalytic effect of the mixture of aluminum oxide and potassium fluoride was better than that of using only potassium fluoride or aluminum oxide.

In our work the methods (2) and (3) were chosen to prepare 1-hydroxyalkylphosphonates. *O,O*-Diethyl 1-hydroxyalkylphosphonates **M2-1–M2-16** and *O,O*-dimethyl 1-hydroxyalkylphosphonates **M2-17–M2-40** were prepared by the reaction of diethyl or dimethyl phosphonates **M1** with several kinds of aldehydes using triethylamine as a catalyst in the range of 58–93 % yields (method **M2-A**, Tables 2.1 and 2.2). If the above reaction was using a mixture of potassium fluoride and aluminum oxide (mass ratio 1:1) as a catalyst the yields were in the range of 68–98 % (method **M2-B**, Tables 2.1 and 2.2). The structures of compounds **M2-1–M2-40** are listed in Tables 2.1 and 2.2.

2.1.3 Synthesis of Substituted Phenoxyacetic Acids **M4** and Substituted Phenoxyacetyl Chlorides **M5**

According to the Ref. [9], substituted phenoxyacetic acids were prepared by the condensation of corresponding substituted phenols with chloroacetic acid in the presence of alkali, such as sodium hydroxide (method **M4-A**). The synthetic route is shown in Scheme 2.7. Substituted phenoxyacetic acids **M4-1–M4-16** prepared by this method **M4-A** are summarized in Table 2.3.

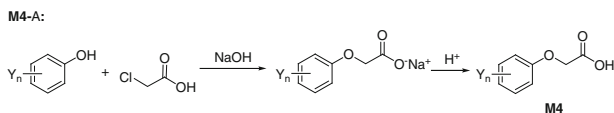
**Scheme 2.7** Synthesis of substituted phenoxyacetic acids **M4**

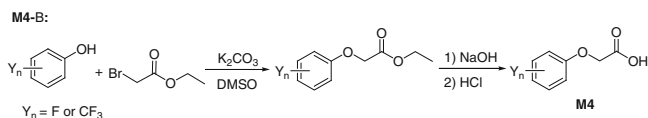
Table 2.1 Structure of *O,O*-diethyl 1-hydroxyalkylphosphonates **M2-1–M2-16**

Compound	R ³	Method	Compound	R ³	Method
M2-1	H	M2-A	M2-9	4-MeOPh	M2-A ^a M2-B ^b
M2-2	Me	M2-A	M2-10	4-FPh	M2-A M2-B
M2-3	Et	M2-A	M2-11	2-ClPh	M2-A M2-B
M2-4	<i>n</i> -Pr	M2-A	M2-12	3-ClPh	M2-A M2-B
M2-5	<i>i</i> -Pr	M2-A	M2-13	4-ClPh	M2-A M2-B
M2-6	Ph	M2-A M2-B	M2-14	2,4-Cl ₂ Ph	M2-A M2-B
M2-7	4-MePh	M2-A M2-B	M2-15	3,4-Cl ₂ Ph	M2-A M2-B
M2-8	3-NO ₂ Ph	M2-A M2-B	M2-16	3,4-OCH ₂ OPh	M2-A M2-B

^a Method **M2-A**: Et₃N as a catalyst

^b Method **M2-B**: KF/Al₂O₃ as a catalyst

In the reaction of chloroacetic acid with fluoro-substituted phenols or trifluoromethyl-substituted phenols in the presence of sodium hydroxide, products had low yields because of a strong electron-withdrawing nature of the substituent. However, by using the method of Brayer et al. [10], fluoro-substituted phenoxyacetic acids and trifluoromethyl-substituted phenoxyacetic acids **M4-17–M4-27** (Table 2.4) could be prepared in satisfactory yields by the reaction of fluoro-substituted phenols or trifluoromethyl-substituted phenols with ethyl bromoacetate in the presence of K₂CO₃ in DMSO followed by alkaline hydrolysis (Scheme 2.8, method **M4-B**). Thus, a series of substituted phenoxyacetic acids **M4-1–M4-27** was prepared by method **M4-A** or **M4-B**.



Scheme 2.8 Synthesis of fluoro and trifluoromethyl-substituted phenoxyacetic acids **M4**

In order to condense with 1-hydroxyalkylphosphonates in a highly effective way, substituted phenoxyacetic acids were converted to the corresponding substituted phenoxyacetyl chlorides **M5** by using thionyl chloride in high yields (>90 %).

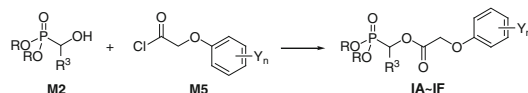
Table 2.2 Structure of *O,O*-dimethyl 1-hydroxyalkylphosphonates **M2-17–M2-40**

Compound	R ³	Method	Compound	R ³	Method
M2-17	H	M2-A	M2-29	4-MeOPh	M2-A ^a M2-B ^b
M2-18	Me	M2-A M2-B	M2-30	4-FPh	M2-A M2-B
M2-19	Et	M2-A	M2-31	2-ClPh	M2-A M2-B
M2-20	<i>n</i> -Pr	M2-A	M2-32	3-ClPh	M2-A M2-B
M2-21	<i>i</i> -Pr	M2-A	M2-33	4-ClPh	M2-A M2-B
M2-22	<i>n</i> -Bu	M2-A	M2-34	3-BrPh	M2-A
M2-23	CCl ₃	M2-A M2-B	M2-35	2,4-Cl ₂ Ph	M2-A M2-B
M2-24	Ph	M2-A M2-B	M2-36	3,4-Cl ₂ Ph	M2-A M2-B
M2-25	4-MePh	M2-A M2-B	M2-37	Fur-2-yl	M2-A M2-B
M2-26	3-NO ₂ Ph	M2-B	M2-38	Thien-2-yl	M2-39
M2-27	4-NO ₂ Ph	M2-A	M2-39	Pyrid-2-yl	M2-A M2-B
M2-28	2-HOPh	M2-A	M2-40	3,4-OCH ₂ OPh	M2-A M2-B

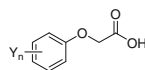
^a Method: **M2-A**: Et₃N as a catalyst^b Method: **M2-B**: KF/Al₂O₃ as a catalyst

2.1.4 Synthesis of IA–IF

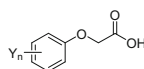
O,O-Dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA–IF** could be conveniently synthesized by the condensation of 1-hydroxyalkylphosphonates **M2** with substituted phenoxyacetyl chlorides **M5** in the presence of pyridine as a base (Scheme 2.9).

**Scheme 2.9** Synthesis of *O,O*-dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA–IF**

Considering that 1-hydroxyalkylphosphonates **M2** are easily regenerated to the starting carbonyl compounds in strong alkaline medium [3], pyridine, a weak base,

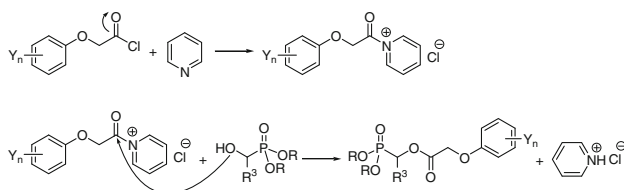
Table 2.3 Structure of substituted phenoxyacetic acids **M4-1–M4-16**

Compound	Y _n	Method	Compound	Y _n	Method
M4-1	H	M4-A	M4-9	2-Me,4-Cl	M4-A
M4-2	3-Me	M4-A	M4-10	3-Me,4-Cl	M4-A
M4-3	4-Me	M4-A	M4-11	2-Cl,5-Me	M4-A
M4-4	2-NO ₂	M4-A	M4-12	2,3-Cl ₂	M4-A
M4-5	4-NO ₂	M4-A	M4-13	2,4-Cl ₂	M4-A
M4-6	4-Cl	M4-A	M4-14	2,6-Cl ₂	M4-A
M4-7	4-Br	M4-A	M4-15	2,4-Br ₂	M4-A
M4-8	2,3-Me ₂	M4-A	M4-16	2-NO ₂ ,4-Cl	M4-A

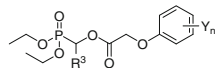
Table 2.4 Structure of substituted phenoxyacetic acids **M4-17–M4-27**

Compound	Y _n	Method	Compound	Y _n	Method
M4-17	3-CF ₃	M4-B	M4-23	3,5-F ₂	M4-B
M4-18	4-CF ₃	M4-B	M4-24	2-F,4-Cl	M4-B
M4-19	2-F	M4-B	M4-25	2-Cl,4-F	M4-B
M4-20	3-F	M4-B	M4-26	3-Cl,4-F	M4-B
M4-21	4-F	M4-B	M4-27	2-NO ₂ ,4-CF ₃	M4-B
M4-22	2,4-F ₂	M4-B			

was chosen for this reaction. It not only acted as an acid-binding agent but also was a catalyzer. The catalytic mechanism of pyridine is shown in Scheme 2.10.

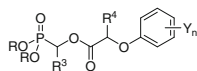
**Scheme 2.10** Catalytic mechanism of pyridine

Since 1-hydroxyalkylphosphonates are easy to decompose at high temperature [3] and **IA–IF** contain a carboxylic ester group which is sensitive to acid or base, the reaction required a temperature near room temperature in anhydrous solvents. We performed the reaction in two steps: first, the reaction was carried out at room temperature for several hours, and then at a higher temperature under mild reaction conditions. All **IA–IF** were conveniently synthesized in the presence of pyridine and anhydrous trichloromethane. The structures of **IA–IF** are listed in Tables 2.5, 2.6, 2.7, 2.8, 2.9, 2.10 and 2.11, respectively.

Table 2.5 Structure of *O,O*-diethyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA**^a

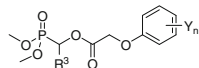
Compound	R ³	Y _n	Compound	R ³	Y _n
IA-1	H	4-Cl	IA-13	Ph	2,4-Cl ₂
IA-2	H	2,4-Cl ₂	IA-14	4-MePh	2,4-Cl ₂
IA-3	Me	4-Cl	IA-15	3-NO ₂ Ph	3-CF ₃
IA-4	Me	2,4-Cl ₂	IA-16	4-MeOPh	3-CF ₃
IA-5	CCl ₃	2-Me	IA-17	4-FPh	3-CF ₃
IA-6	CCl ₃	4-Cl	IA-18	2-ClPh	2,4-Cl ₂
IA-7	Et	4-Cl	IA-19	3-ClPh	3-CF ₃
IA-8	Et	2,4-Cl ₂	IA-20	4-ClPh	3-CF ₃
IA-9	<i>n</i> -Pr	4-Cl	IA-21	4-ClPh	2,4-Cl ₂
IA-10	<i>n</i> -Pr	2,4-Cl ₂	IA-22	2,4-Cl ₂ Ph	3-CF ₃
IA-11	Ph	3-CF ₃	IA-23	3,4-Cl ₂ Ph	3-CF ₃
IA-12	Ph	2-Cl	IA-24	3,4-OCH ₂ OPh	3-CF ₃

^a Synthesis of **IA-1–IA-4** and **IA-7–IA-10** [11, 12]; **IA-5**, **IA-6**, **IA-11** and **IA-12** [11, 13]; **IA-11**, **IA-17** and **IA-19** [14]; **IA-15**, **IA-22** and **IA-23** [15]; **IA-18** [16]; **IA-20** and **IA-24** [17]

Table 2.6 Structure of 1-(substituted phenoxyacetoxy)alkylphosphonates **IB**^a

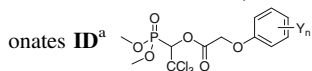
Compound	R	R ³	R ⁴	Y _n	Compound	R	R ³	R ⁴	Y _n
IB-1	Me	Me	Me	2-F	IB-9	Me	4-MePh	Me	2-Cl,4-F
IB-2	Me	Me	Me	2-Cl,4-F	IB-10	Me	4-FPh	Me	2-F
IB-3	Me	Me	Me	2,4-Cl ₂	IB-11	Me	4-FPh	Me	2-Cl,4-F
IB-4	Me	Pr	Me	2,4-Cl ₂	IB-12	Et	Me	Me	2,4-Cl ₂
IB-5	Me	CCl ₃	Me	2-F	IB-13	Et	Ph	Me	2,4-Cl ₂
IB-6	Me	CCl ₃	Me	2-Cl,4-F	IB-14	<i>n</i> -Pr	Me	Me	2,4-Cl ₂
IB-7	Me	Ph	Me	2,4-Cl ₂	IB-15	<i>n</i> -Pr	Ph	Me	2,4-Cl ₂
IB-8	Me	4-MePh	Me	2-F	IB-16	<i>n</i> -Pr	2-ClPh	Me	2,4-Cl ₂

^a Synthesis of for compounds: **IB-1**, **IB-2**, **IB-5**, **IB-6**, and **IB-8–IB-11** [18]; **IB-3**, **IB-4**, **IB-7**, **IB-12**, **IB-13** and **IB-14** [19]; **IB-15** [20]; **IB-16** [16]

Table 2.7 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)alkylphosphonates **IC**^a

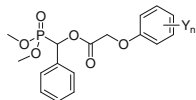
Compound	R ³	Y _n	Compound	R ³	Y _n
IC-1	H	2,4-Cl ₂	IC-18	Me	2-F,4-Cl
IC-2	Me	H	IC-19	Me	2-Cl,4-F
IC-3	Me	3-Me	IC-20	Me	3-Cl,4-F
IC-4	Me	4-Me	IC-21	Me	2,3-Cl ₂
IC-5	Me	3-CF ₃	IC-22	Me	2,4-Cl ₂
IC-6	Me	4-CF ₃	IC-23	Me	2,6-Cl ₂
IC-7	Me	2-F	IC-24	Me	2,4-Br ₂
IC-8	Me	3-F	IC-25	Me	2-NO ₂ ,4-Cl
IC-9	Me	4-F	IC-26	Et	3-CF ₃
IC-10	Me	4-Cl	IC-27	Et	2,4-Cl ₂
IC-11	Me	4-Br	IC-28	Et	2-NO ₂ ,4-CF ₃
IC-12	Me	2,3-Me ₂	IC-29	<i>n</i> -Pr	3-CF ₃
IC-13	Me	2-Me,4-Cl	IC-30	<i>n</i> -Pr	2-NO ₂
IC-14	Me	3-Me,4-Cl	IC-31	<i>n</i> -Pr	4-NO ₂
IC-15	Me	2-Cl,5-Me	IC-32	<i>n</i> -Pr	2,4-Cl ₂
IC-16	Me	2,4-F ₂	IC-33	<i>n</i> -Pr	2-NO ₂ ,4-CF ₃
IC-17	Me	3,5-F ₂	IC-34	<i>n</i> -Bu	2,4-Cl ₂

^a Synthesis of **IC-1** [21]; **IC-2** and **IC-5** [17]; **IC-4**, **IC-7**, **IC-11**, **IC-12**, **IC-20**, **IC-22**, **IC-24**, **IC-25**, **IC-27** and **IC-32** [21, 22]; **IC-6** and **IC-19** [15]; **IC-8**, **IC-9**, **IC-10**, **IC-13**, **IC-14**, **IC-15**, **IC-21** and **IC-23** [23]; **IC-16** and **IC-17** [14]; **IC-34** [16]

Table 2.8 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)-2,2,2-trichloroethylphosphonates **ID**^a

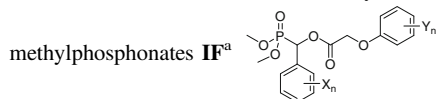
Compound	Y _n	Compound	Y _n
ID-1	4-CF ₃	ID-8	2,4-F ₂
ID-2	3-F	ID-9	3,5-F ₂
ID-3	4-F	ID-10	2-Cl,4-F
ID-4	4-Cl	ID-11	3-Cl,4-F
ID-5	2-Me,4-Cl	ID-12	2,3-Cl ₂
ID-6	3-Me,4-Cl	ID-13	2,4-Cl ₂
ID-7	2-Cl,5-Me	ID-14	2,6-Cl ₂

^a Synthesis of **ID-1** and **ID-10** [5]; **ID-2**–**ID-7**, **ID-12** and **ID-14** [23]; **ID-8** and **ID-9** [4]; **ID-11** and **ID-13** [22]

Table 2.9 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)benzylphosphonates **IE**^a

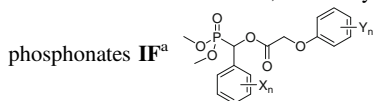
Compound	Y _n	Compound	Y _n	Compound	Y _n
IE-1	H	IE-9	3-F	IE-17	2,4-F ₂
IE-2	3-Me	IE-10	4-F	IE-18	2-F,4-Cl
IE-3	4-Me	IE-11	4-Cl	IE-19	2-Cl,4-F
IE-4	3-CF ₃	IE-12	4-Br	IE-20	3-Cl,4-F
IE-5	4-CF ₃	IE-13	2,3-Me ₂	IE-21	2,3-Cl ₂
IE-6	2-NO ₂	IE-14	2-Me,4-Cl	IE-22	2,4-Cl ₂
IE-7	4-NO ₂	IE-15	3-Me,4-Cl	IE-23	2,6-Cl ₂
IE-8	2-F	IE-16	2-Cl,5-Me	IE-24	2-NO ₂ ,4-CF ₃

^a Synthesis of compounds: **IE-1–IE-3**, **IE-5**, **IE-6**, **IE-13**, **IE-17**, **IE-19**, **IE-20** and **IE-24** [22]; **IE-8** [14]; **IE-9**, **IE-10**, **IE-14–IE-16**, **IE-21** and **IE-23** [23]; **IE-22** [21, 24]

Table 2.10 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(substituted phenyl) methylphosphonates **IF**^a

Compound	X _n	Y _n	Compound	X _n	Y _n
IF-1	4-Me	3-CF ₃	IF-22	4-F	2,4-Cl ₂
IF-2	4-Me	4-F	IF-23	2-Cl	3-CF ₃
IF-3	4-Me	4-Cl	IF-24	2-Cl	2,4-Cl ₂
IF-4	4-Me	4-Br	IF-25	3-Cl	3-CF ₃
IF-5	4-Me	2-Me,4-Cl	IF-26	3-Cl	2,4-Cl ₂
IF-6	4-Me	2,4-F ₂	IF-27	4-Cl	3-CF ₃
IF-7	4-Me	2-F,4-Cl	IF-28	4-Cl	2-Me,4-Cl
IF-8	4-Me	2-Cl,4-F	IF-29	4-Cl	2-F,4-Cl
IF-9	4-Me	2,4-Cl ₂	IF-30	4-Cl	2-Cl,4-F
IF-10	2-OH	4-Cl	IF-31	4-Cl	2,4-Cl ₂
IF-11	2-OH	2-Cl,4-F	IF-32	3-Br	2,4-Cl ₂
IF-12	4-MeO	3-CF ₃	IF-33	2,3-Cl ₂	2,4-Cl ₂
IF-13	4-MeO	4-F	IF-34	2,4-Cl ₂	H
IF-14	4-MeO	4-Cl	IF-35	2,4-Cl ₂	3-CF ₃
IF-15	4-MeO	4-Br	IF-36	2,4-Cl ₂	2,4-Cl ₂
IF-16	4-MeO	2-Me,4-Cl	IF-37	3,4-Cl ₂	H
IF-17	4-MeO	2,4-F ₂	IF-38	3,4-Cl ₂	3-CF ₃
IF-18	4-MeO	2-F,4-Cl	IF-39	3,4-Cl ₂	2,4-Cl ₂
IF-19	4-MeO	2-Cl,4-F	IF-40	3,4-OCH ₂ O	3-CF ₃
IF-20	4-MeO	2,4-Cl ₂	IF-41	3,4-OCH ₂ O	2,4-Cl ₂
IF-21	4-F	3-CF ₃			

^a Synthesis of **IF-1**, **IF-23**, **IF-27** and **IF-40** [17]; **IF-5**, **IF-7** and **IF-8** [21]; **IF-24** [16]; **IF-9**, **IF-20**, **IF-22**, **IF-26**, **IF-33**, **IF-36**, **IF-39** and **IF-41** [24]; **IF-10**, **IF-11** and **IF-32** [22]; **IF-21** and **IF-25** [14]; **IF-35** and **IF-38** [15]

Table 2.11 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(nitrophenyl)methyl-

Compound	X _n	Y _n	Compound	X _n	Y _n
IF-42	3-NO ₂	H	IF-53	3-NO ₂	2-Cl,5-Me
IF-43	3-NO ₂	3-CF ₃	IF-54	3-NO ₂	2,4-F ₂
IF-44	3-NO ₂	4-CF ₃	IF-55	3-NO ₂	2-Cl,4-F
IF-45	3-NO ₂	2-NO ₂	IF-56	3-NO ₂	3-Cl,4-F
IF-46	3-NO ₂	4-NO ₂	IF-57	3-NO ₂	2,3-Cl ₂
IF-47	3-NO ₂	2-F	IF-58	3-NO ₂	2,4-Cl ₂
IF-48	3-NO ₂	3-F	IF-59	3-NO ₂	2,6-Cl ₂
IF-49	3-NO ₂	4-F	IF-60	3-NO ₂	2-NO ₂ ,4-CF ₃
IF-50	3-NO ₂	4-Cl	IF-61	4-NO ₂	2-NO ₂
IF-51	3-NO ₂	2-Me,4-Cl	IF-62	4-NO ₂	2,4-F ₂
IF-52	3-NO ₂	3-Me,4-Cl	IF-63	4-NO ₂	2,4-Cl ₂

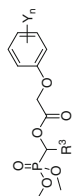
^a Synthesis of **IF-43**, **IF-44**, **IF-50–IF-54**, **IF-55**, **IF-56**, **IF-57**, **IF-59** and **IF-60** [22]; **IF-47** and **IF-48** [14]; **IF-45** and **IF-46** [25]; **IF-49** [15]; **IF-58**, and **IF-63** [21]

All of **IA–IF** could be prepared according to the general synthetic procedure of *O,O*-dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA–IJ** in the Sect. 9.1.7. **IA–IF** are soluble in a variety of organic solvents such as benzene, diethyl ether, ethyl acetate, and so on. They are stable to light and air at room temperature but easily decompose under the acidic or basic conditions. The structures of **IA–IF** were characterized by ¹H NMR, IR, and confirmed by elementary analysis. Several compounds were also characterized by MS and ³¹P NMR spectra. Spectroscopic analysis of some representative **IA–IF** are given in the next section.

2.1.5 Spectroscopic Analysis of **IA–IF**

All main functional groups were characterized in IR spectra which showed normal stretching absorption bands indicating the existence of benzene ring (1,453–1,615 cm⁻¹), P–O–C (1,029–1,061 cm⁻¹), and P–C (705–833 cm⁻¹). A strong absorption near 1,760 cm⁻¹ (1,738–1,794 cm⁻¹) was identified for the absorption C=O. A sharp and weak band at 3,010–3,098 cm⁻¹ accounted for the C–H stretching of aromatic hydrocarbon. A strong peak at 1,213–1,261 cm⁻¹ accounted for P=O in phosphonates. Two strong peaks near 1,525 and 1,344 cm⁻¹ were the evidence for the NO₂ stretching in NO₂-containing compounds, such as **IC-28**, **IC-31**, **IE-24**, and **IF-45** (Table 2.12).

The IR spectrum of **IC-22** is shown in Fig. 2.1. A sharp and weak band 3,098–3,074 cm⁻¹ accounted for the C–H stretching of the aromatic hydrocarbon in

Table 2.12 IR spectra of **IC-28**, **IC-31**, **IE-24**, and **IF-45**

Compound	R^3	Y_n	$\nu_{\text{Ar-H}}$	$\nu_{\text{R-H}}$	$\nu_{\text{C=O}}$	$\nu_{\text{ArC-C}}$	$\nu_{\text{P=O}}$	$\nu_{\text{Ar-O-C}}$	$\nu_{\text{C-O-C}}$	$\nu_{\text{P-O-C}}$	$\nu_{\text{P-C}}$	ν_{NO_2}	$\nu_{\text{Ar-CF}_3}$
IC-28	Et	2-NO ₂ , 4-CF ₃	3,061	2,952 2,852	1,767	1,629 1,458	1,261	1,233	1,193	1,054	824	1,544	1,330
IC-31	<i>n</i> -Pr	4-NO ₂	3,084	2,960 2,855	1,767	1,593 1,496	1,261		1,178	1,032	751	1,516 1,344	
IE-24	Ph	2-NO ₂ , 4-CF ₃	3,070	2,947 2,857	1,763	1,630 1,483	1,264	1,230	1,194	1,033	833	1,506	1,335
IF-45	3-NO ₂ Ph	2-NO ₂	3,046	2,951 2,856	1,787	1,590 1,497	1,253		1,178	1,037	745	1,528 1,350	

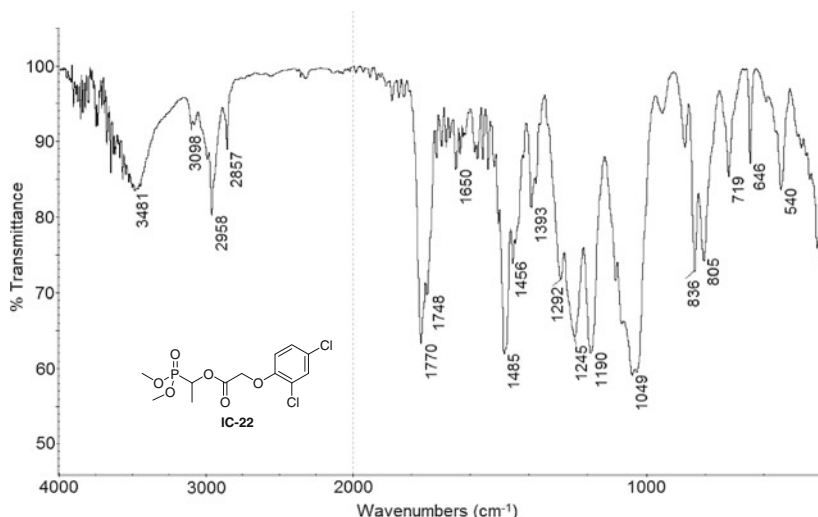
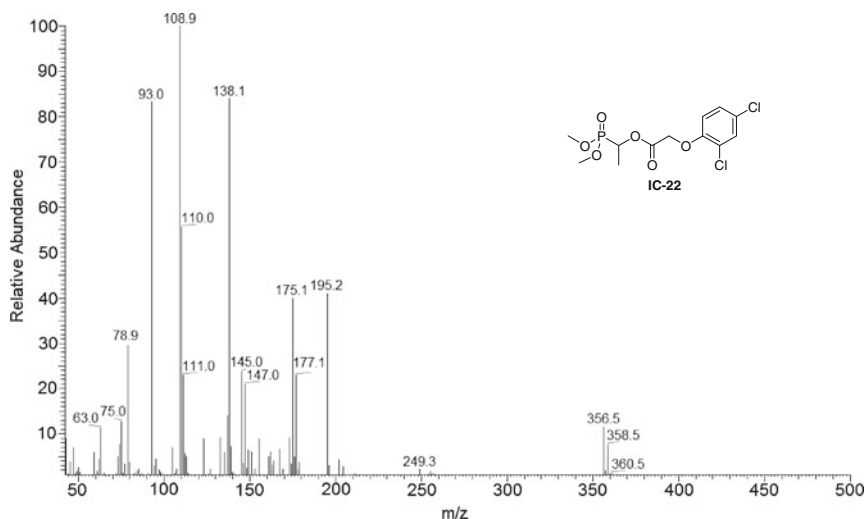


Fig. 2.1 IR spectrum of **IC-22**

IC-22. Peaks at 1,587, 1,485 cm^{-1} accounted for vibration of the skeleton of the benzene ring. Peaks at 866, 836, 719 cm^{-1} accounted for C–H flexural vibration of the benzene ring. Peaks at 2,993, 2,958, 2,857 cm^{-1} accounted for C–H stretching vibration of the saturated alkyl. Peaks at 1,456, 1,446, 1,393 cm^{-1} accounted for C–H flexural vibration of the saturated alkyl. A peak at 1,393 cm^{-1} also accounted for Me which existed in the molecule. A strong absorption at 1,770 cm^{-1} was identified for stretching vibration of C=O. A peak at 1,190 cm^{-1} accounted for stretching vibration of C–O–C and 1,292 cm^{-1} accounted for stretching vibration of Ar–O–C. A peak at 805 cm^{-1} accounted for the stretching vibration of C–Cl. A strong peak at 1,245 cm^{-1} accounted for P=O in phosphonates. Peaks at 1,049 and 646 cm^{-1} were identified for the stretching vibration of P–O–C and P–C, respectively.

The EI mass spectra of most **IC–IF** gave weak molecular ion peaks. The fragmentation ions of **IC–IF** were consistent with the structure. For example, **IC-22** ($\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{O}_6\text{P}$) was characterized by MS spectra, EI-MS m/z (%): 356(M^+ , 11.4), 195(41.1), 175(40.3), 145(23.8), 138(83.9), 109(100), 93(83.3), 79(29.5). The MS spectrum of **IC-22** is shown in Fig. 2.2. In the EI mass spectra, **IC-22** gave weak molecular ion peak 356 with 11.4 % relative abundance. All fragmentation ions of **IC-22** were consistent with its structure.

In the ^1H NMR spectra of **IC**, **ID**, **IE**, and **IF**, the proton signals in both the P–C moiety and P–OMe moiety displayed as two doublets due to couplings to the phosphorus. In the *O,O*-dimethyl 1-(substituted phenoxyacetoxy)alkylphosphonates series, the proton signals corresponding to the two methoxy groups attached to phosphorus appeared as two doublets are caused by the phosphorus nucleus. ^1H NMR spectra of **IC-1**, **IC-8**, **ID-5**, **ID-12**, **IE-22**, **IF-24**, and **IF-32** are listed in Table 2.13. It was also noticed that the signals of methoxy protons attached to

Fig. 2.2 EI-MS spectrum of **IC-22**Table 2.13 ^1H NMR spectra of representative compounds

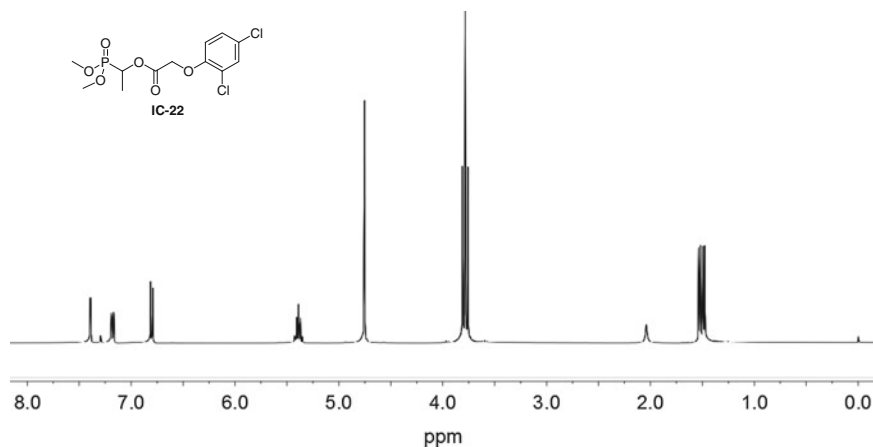
Compound	R^3	Y_n	δ/ppm
IC-1	H	2,4- Cl_2	3.85 (d, 6H, $J = 10.8$ Hz, $2 \times \text{OMe}$), 4.30 (d, 2H, $J = 11.6$ Hz, CH_2P), 4.75 (s, 2H, OCH_2CO), 6.8–7.5 (m, 3H, C_6H_3)
IC-5	Me	3- CF_3	1.43–1.74 (d, 3H, Me), 3.50–3.55 (dd, 6H, $2 \times \text{OMe}$), 4.79 (s, 2H, OCH_2CO), 5.39 (m, 1H, OCHP), 7.04–7.39 (m, 4H, C_6H_4)
IC-22	Me	2,4- Cl_2	1.48–1.60 (t, 3H, Me), 3.76–3.85 (dd, 6H, $2 \times \text{OMe}$), 4.75 (s, 2H, OCH_2CO), 5.25–5.40 (m, 1H, CH), 6.80–7.50 (m, 3H, C_6H_3)
IC-28	Et	2- NO_2 , 4- CF_3	0.95–1.13 (t, 3H, Me), 1.83–1.99 (m, 2H, CH_2), 3.72–3.82 (dd, 6H, $2 \times \text{OMe}$), 4.96 (s, 2H, OCH_2), 5.19–5.28 (m, 1H, CHP), 7.10–8.12 (m, 3H, C_6H_3)
IC-33	<i>n</i> -Pr	2- NO_2 , 4- CF_3	0.88–0.95 (t, 3H, Me), 1.30–1.85 (m, 4H, $2 \times \text{CH}_2$), 3.73–3.81 (dd, 6H, $2 \times \text{OMe}$), 4.84 (s, 2H, OCH_2), 5.33–5.36 (m, 1H, CHP), 7.06–8.10 (m, 3H, C_6H_3)
IC-34	<i>n</i> -Bu	2,4- Cl_2	0.90 (t, 3H, Me), 1.25–1.85 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.80–3.90 (d, 6H, $J = 10.8$ Hz, $2 \times \text{OMe}$), 4.80 (s, 2H, OCH_2CO) (s, 2H, CH_2), 5.25–5.45 (m, 1H, CHP), 6.80–7.40 (m, 3H, C_6H_3)

(continued)

Table 2.13 (continued)

Compound	R ³	Y _n	δ/ppm
ID-5	CCl ₃	2-Me,4-Cl	2.28 (s, 3H, PhMe), 3.85–3.88 (d, 6H, <i>J</i> = 10.8 Hz, 2 × OMe), 4.86 (s, 2H, OCH ₂ CO), 5.97 (d, 1H, <i>J</i> = 11.6 Hz, OCHP), 6.65–7.27 (m, 3H, C ₆ H ₃)
ID-12	CCl ₃	2,3-Cl ₂	3.86–3.93 (d, 6H, <i>J</i> = 10.8 Hz, 2 × OMe), 4.95 (s, 2H, OCH ₂ CO), 5.97 (d, 1H, <i>J</i> = 11.6 Hz, OCHP), 6.79–7.16 (m, 3H, C ₆ H ₃)
IE-22	Ph	2,4-Cl ₂	3.70 (d, 6H, <i>J</i> = 10.8 Hz, 2 × OMe), 4.80 (s, 2H, OCH ₂ CO), 6.24 (d, 1H, <i>J</i> = 11.6 Hz, CHP), 6.72–7.42 (m, 8H, C ₆ H ₃ + C ₆ H ₅)
IF-24	2-ClPh	2,4-Cl ₂	3.85 (d, 6H, <i>J</i> = 10.8 Hz, 2 × OMe), 4.80 (s, 2H, OCH ₂ CO), 6.40 (d, 1H, <i>J</i> = 11.6 Hz, CHP), 6.80–7.40 (m, 7H, C ₆ H ₃ + 6H ₄)
IF-32	3-BrPh	2,4-Cl ₂	3.7–3.8 (d, 6H, <i>J</i> = 10.8 Hz, 2 × OMe), 4.75 (s, 2H, OCH ₂ CO), 6.20 (d, 6H, <i>J</i> = 12.0 Hz, CHP), 6.7–7.5 (m, 7H, C ₆ H ₃ + C ₆ H ₄)

phosphorus appeared as two doublets. For instance, the signals of both methyls (dd, 6H, 2 × CH₃O) in **IC-22** split into two doublets at δ 3.76 and 3.85, respectively, the difference in the chemical shifts of the two methyl groups was attributed to a stereogenic center of carbon in the molecule. When R³ in structure **ID**, **IE** or **IF** is Ph, substituted Ph or CCl₃, the proton signal corresponding to the moiety of OCHP attached to phosphorus appeared as a doublet split only by the phosphorus nucleus. ¹H NMR spectra of **ID-5**, **ID-12**, **IE-22**, **IF-24**, and **IF-32** are listed in Table 2.13. However, when R³ in structure **IB** or **IC** is Me, Et, *n*-Pr or *n*-Bu, the proton signal of the moiety of OCHP was split into a multiplet, which was caused

**Fig. 2.3** ¹H NMR spectrum of **IC-22** (CDCl₃, 400 MHz)



No (C) ^a	1	2	3	4	5	6
δ (ppm)	53.29	53.37	65.17	14.92	166.95	66.10
	d	d	d	s	d	s
	² J _{P-C} = 7.7	² J _{P-C} = 7.1	¹ J _{P-C} = 170.0		³ J _{P-C} = 6.8	
No (C) ^a	7	8	9	10	11	12
δ (ppm)	152.10	124.12	130.24	127.16	127.47	114.68
	s	s	s	s	s	s

^a Sequence number of C atom

by the effect of magnetic nucleus from both phosphorus and proton in R^3 . 1H NMR spectra of **IC-1**, **IC-5**, **IC-22**, **IC-28**, **IC-33**, and **IC-34** are also listed in Table 2.13.

In 1H NMR spectra of most compounds, the signal corresponding to the methylene group (OCH_2CO) between a phenoxy and a carbonyl group appeared as a singlet (see Table 2.13). As an example, 1H NMR spectrum of **IC-22** is shown in Fig. 2.3.

In 1H NMR spectrum of **IC-22**, the proton signal corresponding to the two methoxy groups attached to phosphorus appeared as two doublets was caused by the phosphorus nucleus. The signals of both methyls (dd, 6H, $2 \times CH_3O$) in **IC-22** were split into two doublets at δ 3.77 and 3.80, respectively. The proton signal of the moiety of OCHP in **IC-22** was split into a multiplet, which was caused by the effect of the magnetic nucleus from both phosphorus and proton in Me as R^3 . The signal corresponding to the methylene group (OCH_2CO) between a phenoxy and a carbonyl group in **IC-22** appeared at δ 4.75 as a singlet.

IC-22 was also characterized by ^{13}C NMR spectroscopic data (Table 2.14). The ^{13}C NMR spectrum of **IC-22** is shown in Fig. 2.4.

^{31}P NMR spectra of some **IC-IF** showed a singlet between δ 12 and 24 ppm. In the ^{31}P NMR spectrum of **IC-22**, its chemical shifts appeared as a singlet at δ 23.18 ppm which was consistent with the characterization of phosphonate. The ^{31}P NMR spectrum of **IC-22** is shown in Fig. 2.5.

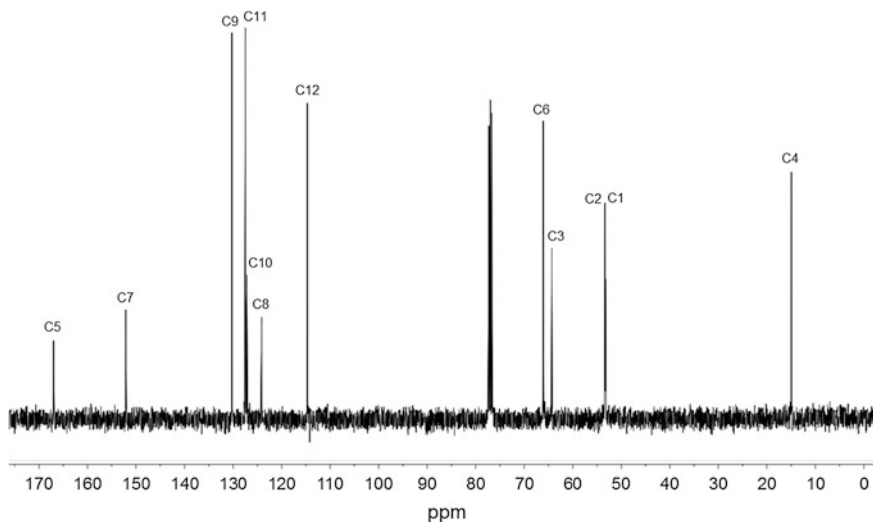


Fig. 2.4 ^{13}C NMR spectrum of **IC-22** ($DMSO-d_6$, 150 MHz)

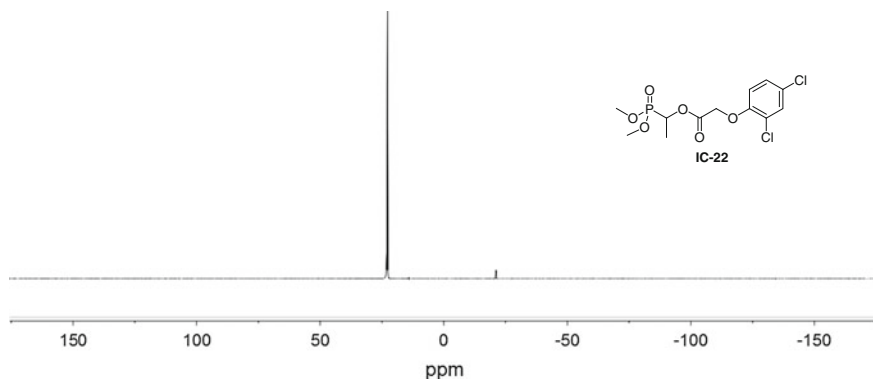


Fig. 2.5 ^{31}P NMR spectrum of **IC-22** (CDCl_3 , 162 MHz)

2.1.6 Crystal Structure Analysis of **IC-7**

The molecular structure of **IC-7** is shown in Fig. 2.6. The packing diagram of the unit cell of **IC-7** is shown in Fig. 2.7. Selected bond lengths and angles are presented in Table 2.15. As can be seen from the X-ray single crystal structure of **IC-7**, all bond lengths and angles show normal values. The P(1)–O(5) bond length of 1.4649(11) Å is significantly shorter than the P(1)–O(4) and P(1)–O(6) distances of 1.553(4) and 1.5688(13) Å, respectively. The molecules are connected by

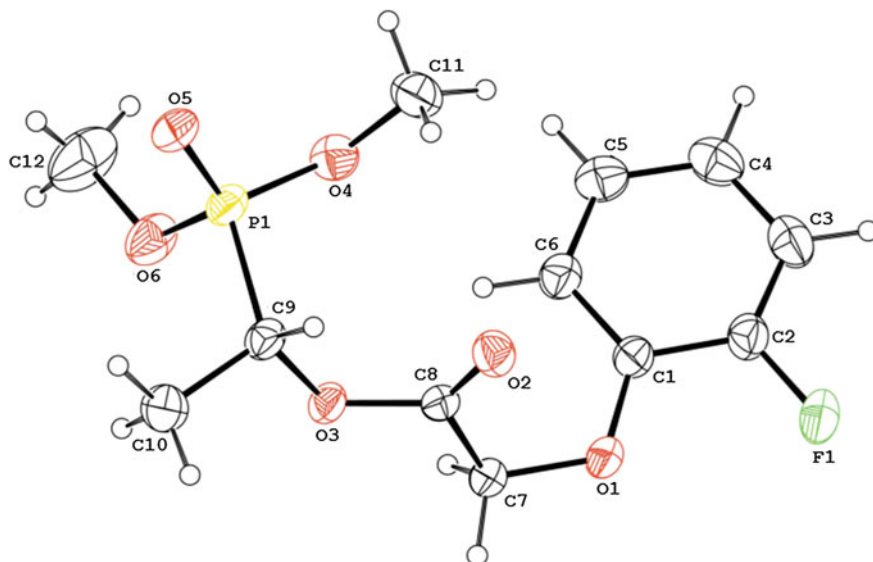
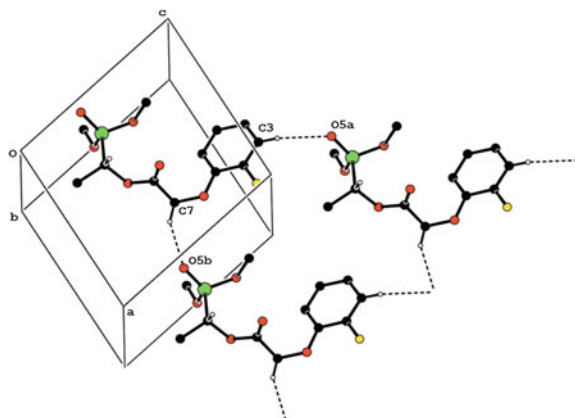


Fig. 2.6 Molecular structure of **IC-7**

Fig. 2.7 Packing diagram of **IC-7**

intermolecular C–H–O hydrogen bonds (Table 2.16), forming a layer parallel to (010) plane [26].

IC-7 was recrystallized from petroleum ether/dichloromethane (4/1, v/v) to give colorless crystals (0.30 mm × 0.30 mm × 0.20 mm) suitable for X-ray single-crystal diffraction. The crystal structure of **IC-7** was recorded on a Smart Apex CCD diffractometer using graphite monochromated MoK α radiation (λ = 0.071073 nm). In the range of $2.2^\circ \leq \theta \leq 28.2^\circ$, 9,060 independent reflections (R_{int} = 0.018), of which 3,314 contributing reflection had $I > 2\sigma(I)$, and all data were corrected using SADABS program. The structure was solved by direct methods using SHELXS-97, all other calculations were performed with the Bruker SAINT system and Bruker

Table 2.15 Selected bond distance (Å) and angles (°) for **IC-7**

Bond	Distance	Bond	Angles deg.
C(1)–O(1)	1.3704(19)	O(5)–P(1)	1.4649(11)
C(7)–O(1)	1.4178(18)	O(6)–P(x1)	1.5688(13)
C(8)–O(2)	1.1927(17)	O(1)–C(1)–C(6)	126.52(14)
C(8)–O(3)	1.3454(17)	O(3)–C(8)–C(7)	108.99(12)
C(9)–O(3)	1.4573(16)	C(1)–O(1)–C(7)	116.99(12)
C(9)–P(1)	1.8110(15)	C(8)–O(3)–C(9)	117.31(11)
C(11)–O(4)	1.447(2)	O(5)–P(1)–O(6)	116.09(7)
O(4)–P(1)	1.5682(13)	O(4)–P(1)–O(6)	102.03(8)

Table 2.16 Hydrogen bond for **IC-7**

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
C(3)–H(3)...O(5) ^a	0.93	2.51	3.416(2)	165
C(7)–H(7A)...O(5) ^b	0.97	2.39	3.2793(19)	152
C(9)–H(9)...O(2)	0.98	2.33	2.7241(19)	103

Symmetry codes: ^a x + 1; y; z + 1; ^b x + 1; y; z

SMART programs. All non-hydrogen atoms were refined on F^2 anisotropically by full-matrix least squares method. Hydrogen atoms were observed and refined with a fixed isotropic displacement parameter. Full-matrix least-squares refinement gave final values of $R = 0.039$ and $R_w = 0.109$. The max and min difference between peaks and holes was 330 and -280 e nm^{-3} , respectively.

2.1.7 Herbicidal Activity of IA–IF

O,O-diethyl 1-(4-chlorophenoxyacetoxy)methylphosphonate **IA-1** with significant herbicidal activity was firstly found in our previous study. Further, a series of *O,O*-diethyl 1-(substituted phenoxyacetoxy) alkylphosphonates **IA** was prepared by the modification of **IA-1** and their herbicidal activity were examined systematically at 2.25 kg ai/ha in the green house.

The herbicidal activity data of **IA** are given in Table 2.17. Most **IA** exhibited significant herbicidal activity at 2.25 kg ai/ha against rape (*Brassica campestris*), pea (*Pisum sativum*), Chinese spinach (*Amaranthus tricolor*), and tomato (*Lycopersicon esculentum*) and had weaker activity against wheat (*Triticum aestivum*), barnyard grass (*Echinochloa crusgalli*), and wild oats (*Avena fatua*).

The data in Table 2.17 showed that most **IA** exhibited good post-emergence herbicidal activity against dicotyledon. Therefore structure **IA** was identified as the lead structure of a new herbicide and this lead structure was first extended to a phosphonate structure **Io** for further chemical modification (Scheme 2.11).

In order to examine the effect of size of R^1 , R^2 and R^4 on herbicidal activity, Me, Et and Pr as R^1 and R^2 , H as R^4 were introduced into structure **Io** to design a series of 1-(substituted phenoxyacetoxy)alkylphosphonates **IB**.

The IC_{50} values of some **IB** and **IA** against cucumber (*Cucumis sativa*) were tested to compare the effect of R^1 , R^2 , and R^4 on herbicidal activity. The results are listed in Table 2.18.

From the assay results in Table 2.18, it can be found that inhibitory potency against cucumber decreases with the increase in the size of R^1 , R^2 , and R^4 . When Et as R^1 and R^2 were replaced by *n*-Pr group in structure **Io**, the inhibitory potency of compounds were greatly decreased. For example, inhibitory potency against the root of cucumber: **IB-14** ($R^1 = R^2 = \text{Pr}$) < **IB-12** ($R^1 = R^2 = \text{Et}$); **IB-12** ($R^1 = R^2 = \text{Et}$, $R^4 = \text{Me}$) < **IA-4** ($R^1 = R^2 = \text{Et}$, $R^4 = \text{H}$).

The inhibitory potency against cucumber could be greatly improved when the *n*-Pr as R^1 and R^2 was replaced by the Me group in structure **Io**. Comparing the inhibitory activity of tested **IB** in Table 2.18, it can be found that when R^3 and R^4 are kept unchanged, compounds with Me as R^1 and R^2 group displayed higher inhibitory potency against cucumber than that of *n*-Pr as R^1 and R^2 group. For example, inhibitory potency against the stem of cucumber: **IB-3** ($R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Me}$) > **IB-14** ($R^1 = R^2 = \text{n-Pr}$, $R^3 = R^4 = \text{Me}$); **IB-7** ($R^1 = R^2 = \text{Me}$, $R^3 = \text{Ph}$, $R^4 = \text{Me}$) > **IB-15** ($R^1 = R^2 = \text{n-Pr}$, $R^3 = \text{Ph}$, $R^4 = \text{Me}$).

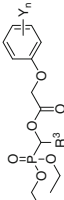
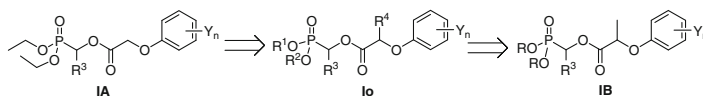
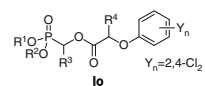


Table 2.17 Herbicidal activity of *O,O*-diethyl 1-(substituted phenoxyacetoxymethyl)alkylphosphonates **IA^a**

Compound	R ³	Y _n	Pre-emergence			Post-emergence		
			Monocotyledon		Dicotyledon		Monocotyledon	Dicotyledon
			Tri ^b	Ave ^b	Bra ^b	Pis ^b		
IA-1	H	4-Cl	51	0	91	100	40	42
IA-2	H	2,4-Cl ₂	45	0	99	100	9	42
IA-3	Me	4-Cl	60	0	91	94	36	41
IA-4	Me	2,4-Cl ₂	51	0	91	100	45	42
IA-5	CCl ₃	4-Me	0	0	100	41	30	42
IA-6	CCl ₃	4-Cl	0	0	100	100	38	42
IA-7	Et	4-Cl	52	0	91	100	49	42
IA-8	Et	2,4-Cl ₂	35	42	100	100	48	0
IA-9	<i>n</i> -Pr	4-Cl	45	3	91	100	30	71
IA-10	<i>n</i> -Pr	2,4-Cl ₂	60	0	91	100	62	42
IA-12	Ph	4-Cl	39	71	91	41	22	57
IA-13	Ph	2,4-Cl ₂	66	0	91	41	30	42

^a Inhibitory potency (%) against the growth of plants at a rate of 2.25 kg ai/ha in the green house, 0 (no effect), 100 % (completely kill), NT (not tested)

^b Tri: wheat; Ave: wild oat; Bra: rape; Pis: pea; Lyc: tomato; Ech: barnyard grass; Amt: Chinese spinach

**Scheme 2.11** Design of 1-(substituted phenoxyacetoxymethyl)alkylphosphonates **IB****Table 2.18** IC_{50} values of some **IB** and **IA** against cucumber^a


Compound	R ¹ , R ²	R ³	R ⁴	Stem length IC_{50} (μ M)	Compound	R ¹ , R ²	R ³	R ⁴	Root length IC_{50} (μ M)
IB-3	Me	Me	Me	6.74	IA-4	Et	Me	H	0.300
IB-14	<i>n</i> -Pr	Me	Me	18.0	IB-12	Et	Me	Me	1.08
IB-7	Me	Ph	Me	30.1	IB-14	<i>n</i> -Pr	Me	Me	2.44
IB-15	<i>n</i> -Pr	Ph	Me	44.3	IB-15	<i>n</i> -Pr	Ph	Me	4.52

^a IC_{50} is effective dose that provides 50% inhibition against the growth of cucumber (root or stem)

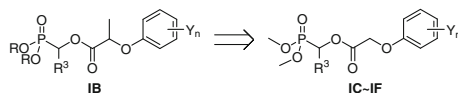
When H as R⁴ in structure **Io** was replaced by Me to form **IB**, the inhibitory potency of **IB** greatly decreased. For example, inhibitory potency against the root of cucumber: **IB-12** (R¹ = R² = Et, R³ = Me, R⁴ = Me) < **IA-4** (R¹ = R² = Et, R³ = Me, R⁴ = H).

Above bioassay results of **IB** showed that inhibitory potency could be greatly improved when the *n*-Pr or Et group as R¹ and R² was replaced by the Me group. Meanwhile, it showed that the compound with H as R⁴ had higher inhibitory potency than that of Me as R⁴. This suggested that smaller R¹, R², and R⁴ groups in the structure **Io** would be beneficial to herbicidal activity.

Therefore, the structure **IB** was further optimized to produce *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)alkylphosphonates **IC–IF** (Scheme 2.12).

Several series of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)alkylphosphonates **IC–IF** were prepared to examine their herbicidal activity. It was expected that better herbicidal activities could be achieved by keeping a small methoxyl group which link with the phosphorus atom and H for R⁴ in the structure **Io**.

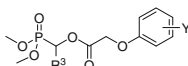
The herbicidal activity of **IC–IF** including **IA** and **IB** were evaluated at different rates in the greenhouse. Substituted phenoxyacetic acid as a structure unit of auxin-type herbicide was contained in the structure of **IA–IF**, therefore an auxin-type herbicide 2,4-D was used as a positive control for the test in the greenhouse. Considering 2,4-D against broadleaved weeds for post-emergence at a recommended rate of 0.2–2.0 kg ai/ha, a preliminary bioassay was first carried out at

**Scheme 2.12** Design of alkylphosphonates **IC–IF**

1.5 kg ai/ha. Pre-emergence and post-emergence inhibitory effect against rape (*Brassica campestris*), common amaranth (*Amaranthus retroflexus*), clover (*Medicago sativa*), barnyard grass (*Echinochloa crusgalli*), and crab grass (*Digitaria sanguinalis*) were examined in this preliminary bioassay.

Based on the preliminary bioassays, inhibition against some plants was further evaluated at a lower rate for pre-emergence and post-emergence herbicidal activity. The results are listed in Tables 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30 and 2.31. The herbicidal activity of IC–IF are reviewed as follows.

Table 2.19 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)alkylphosphonates IC^a



Compound	R ³	Y _n	Pre-emergence				
			Dicotyledon			Monocotyledon	
			Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IC-1	H	2,4-Cl ₂	A	A	A	B	B
IC-2	Me	H	D	D	D	D	D
IC-4	Me	4-Me	B	B	B	C	D
IC-5	Me	3-CF ₃	A	B	A	B	A
IC-6	Me	4-CF ₃	D	D	D	D	D
IC-7	Me	2-F	D	D	D	D	D
IC-8	Me	3-F	D	D	D	D	D
IC-9	Me	4-F	B	C	B	C	A
IC-10	Me	4-Cl	A	A	A	A	A
IC-11	Me	4-Br	D	D	D	D	D
IC-12	Me	2,3-Me ₂	A	B	B	B	D
IC-13	Me	2-Me,4-Cl	A	A	A	A	A
IC-14	Me	3-Me,4-Cl	A	B	B	B	B
IC-15	Me	2-Cl,5-Me	D	D	D	D	D
IC-16	Me	2,4-F ₂	D	D	C	D	B
IC-17	Me	3,5-F ₂	D	D	D	D	D
IC-18	Me	2-F,4-Cl	D	D	D	D	D
IC-19	Me	2-Cl,4-F	A	A	A	A	A
IC-20	Me	3-Cl,4-F	D	D	B	C	C
IC-21	Me	2,3-Cl ₂	D	D	D	D	D
IC-22	Me	2,4-Cl ₂	A	A	A	B	B
IC-23	Me	2,6-Cl ₂	D	D	D	D	D
IC-24	Me	2,4-Br ₂	D	D	B	D	D
IC-25	Me	2-NO ₂ ,4-Cl	D	D	D	D	D
IC-27	Et	2,4-Cl ₂	A	A	A	D	A
IC-28	Et	2-NO ₂ ,4-CF ₃	D	D	D	D	D
IC-31	<i>n</i> -Pr	4-NO ₂	D	D	D	D	D
IC-32	<i>n</i> -Pr	2,4-Cl ₂	A	A	A	B	B

(continued)

Table 2.19 (continued)

Compound	R ³	Y _n	Pre-emergence				
			Dicotyledon			Monocotyledon	
			Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IC-33	<i>n</i> -Pr	2-NO ₂ ,4-CF ₃	D	D	D	D	D
IC-34	<i>n</i> -Bu	2,4-Cl ₂	A	A	A	D	B
2,4-D			A	A	A	B	A

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.20 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted

phenoxyacetoxy)alkylphosphonates **IC^a**

Compound	R ³	Y _n	Post-emergence				
			Dicotyledon			Monocotyledon	
			Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IC-1	H	2,4-Cl ₂	A	A	A	C	C
IC-2	Me	H	D	D	D	D	D
IC-4	Me	4-Me	C	C	C	C	D
IC-5	Me	3-CF ₃	D	C	A	D	D
IC-6	Me	4-CF ₃	D	B	D	D	D
IC-7	Me	2-F	D	D	D	D	D
IC-8	Me	3-F	D	D	D	D	D
IC-9	Me	4-F	C	B	C	C	D
IC-10	Me	4-Cl	B	A	C	D	D
IC-11	Me	4-Br	B	C	C	D	D
IC-12	Me	2,3-Me ₂	B	C	C	C	D
IC-13	Me	2-Me,4-Cl	A	A	C	C	B
IC-14	Me	3-Me,4-Cl	C	C	C	D	D
IC-15	Me	2-Cl,5-Me	D	D	D	D	C
IC-16	Me	2,4-F ₂	B	B	C	D	C
IC-17	Me	3,5-F ₂	D	D	D	D	D
IC-18	Me	2-F,4-Cl	D	C	D	D	D
IC-19	Me	2-Cl,4-F	A	A	A	B	B
IC-20	Me	3-Cl,4-F	B	B	B	D	D
IC-21	Me	2,3-Cl ₂	D	C	D	D	D
IC-22	Me	2,4-Cl ₂	A	A	A	C	C
IC-23	Me	2,6-Cl ₂	D	C	D	D	D
IC-24	Me	2,4-Br ₂	A	A	A	D	D
IC-25	Me	2-NO ₂ ,4-Cl	D	D	D	D	D
IC-27	Et	2,4-Cl ₂	A	A	A	C	B
IC-28	Et	2-NO ₂ ,4-CF ₃	D	D	D	D	D

(continued)

Table 2.20 (continued)

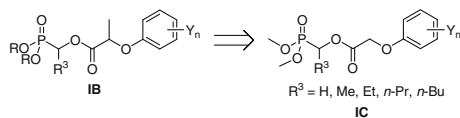
Compound	R ³	Y _n	Post-emergence				
			Dicotyledon			Monocotyledon	
			Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IC-31	<i>n</i> -Pr	4-NO ₂	D	D	D	D	D
IC-32	<i>n</i> -Pr	2,4-Cl ₂	A	A	A	C	C
IC-33	<i>n</i> -Pr	2-NO ₂ ,4-CF ₃	D	D	D	D	D
IC-34	<i>n</i> -Bu	2,4-Cl ₂	A	A	A	C	C
2,4-D			A	A	A	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

2.1.7.1 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)Alkylphosphonates **IC**

Thirty-four of **IC** were prepared to test their herbicidal activity. Further optimization was focused on the substituents Y_n (Scheme 2.13). The herbicidal activity of **IC** is listed in Tables 2.19 and 2.20.

**Scheme 2.13** Design of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IC**

(A) Pre-emergence herbicidal activity of **IC**

As shown in Table 2.19, **IC-10** (R³ = Me, Y_n = 4-Cl), **IC-13** (R³ = Me, Y_n = 2-Me,4-Cl) and **IC-19** (R³ = Me, Y_n = 2-Cl,4-F) exhibited pre-emergence herbicidal activity against dicotyledons and crab grass comparable to that of 2,4-D, and they showed better activities than 2,4-D against barnyard grass at 1.5 kg ai/ha. Those compounds with 2,4-Cl₂ as Y_n, such as **IC-1**, **IC-22**, **IC-27**, **IC-32**, **IC-34** exhibited notable herbicidal activity against dicotyledons for pre-emergence application comparable to 2,4-D. Other compounds showed no significant pre-emergence herbicidal activity at 1.5 kg ai/ha.

(B) Post-emergence herbicidal activity of **IC**

As shown in Table 2.20, **IC-1**, **IC-22**, **IC-27**, **IC-32**, **IC-34** (Y_n = 2,4-Cl₂), **IC-19** (Y_n = 2-Cl,4-F), and **IC-24** (Y_n = 2,4-Br₂) exhibited notable herbicidal activity against dicotyledons for post-emergence application comparable to 2,4-D at 1.5 kg ai/ha. When 2,4-Cl₂; 2-Cl,4-F or 2,4-Br₂ as Y_n was on the phenoxy-benzene ring, all those compounds showed good herbicidal activity.

(C) SAR analyses for **IC**

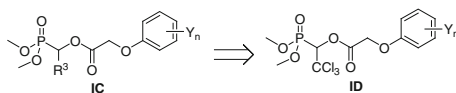
The substitutions of 4-Cl (**IC-10**), 2-Me,4-Cl (**IC-13**), and 2-Cl,4-F (**IC-19**) on the phenoxy-benzene ring were most promotive for pre-emergence herbicidal activity against dicotyledons and monocotyledons at 1.5 kg ai/ha. The substitutions of 2,4-Cl₂; 2-Cl,4-F and 2,4-Br₂ on the phenoxy-benzene ring were most promotive for post-emergence herbicidal activity against dicotyledons followed by 2-Me,4-Cl (**IC-13**). All compounds with 2,4-Cl₂ as Y_n (**IC-1**, **IC-22**, **IC-27**, **IC-32**, **IC-34**) or 2-Cl,4-F as Y_n (**IC-19**) exhibited notable herbicidal activity against dicotyledons for pre-emergence and post-emergence applications comparable to 2,4-D at 1.5 kg ai/ha, irrespective of H, Me, Et, *n*-Pr or *n*-Bu as R³, respectively. The introduction of 2,4-F₂ or 2-F,4-Cl as Y_n resulted in a sharp decrease in herbicidal activity. **IC-2** with no substituent on the phenoxy-benzene ring was completely inactive. Those compounds with 4-CF₃ (**IC-6**), 2-F (**IC-7**), 3-F (**IC-8**), 2-Cl,5-Me (**IC-15**), 3,5-F₂ (**IC-17**), 2,3-Cl₂ (**IC-21**), 2,6-Cl₂ (**IC-23**), 4-NO₂ (**IC-31**), 2-NO₂,4-Cl (**IC-25**), and 2-NO₂,4-CF₃ (**IC-28** and **IC-33**) as Y_n on the phenoxy-benzene ring, were almost inactive against both tested monocotyledons and dicotyledons.

2.1.7.2 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)-2,2,2-Trichloroethylphosphonates **ID**

The bioassays of **IC** showed that herbicidal activity could be greatly affected by different substituents Y_n on the phenoxy-benzene ring. However, the difference in the R³ moiety including H, Me, Et, *n*-Pr and *n*-Bu seems to have no significant change on herbicidal activity at 1.5 kg ai/ha. On the basis of structure **IC**, the structure of R³ was changed to CCl₃ to form a series of **ID** (Scheme 2.14), further modification was only focused on substituents Y_n. Fourteen of **ID** were prepared and their herbicidal activity was tested. The herbicidal activity of **ID** is listed in Tables 2.21 and 2.22.

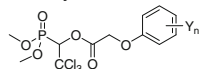
(A) Pre-emergence herbicidal activity of **ID**

As shown in Table 2.21, **ID-4** (Y_n = 4-Cl), **ID-5** (Y_n = 2-Me,4-Cl) and **ID-10** (Y_n = 2-Cl,4-F) exhibited pre-emergence herbicidal activity against dicotyledons and crab grass comparable to 2,4-D, and they showed better activity than 2,4-D against barnyard grass at 1.5 kg ai/ha. Compounds **ID-13** (Y_n = 2,4-Cl₂) also exhibited good herbicidal activity against dicotyledons and crab grass for pre-emergence application comparable to 2,4-D, while other compounds showed weak pre-emergence herbicidal activity at 1.5 kg ai/ha.



Scheme 2.14 Design of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-2,2,2-trichloroethylphosphonates **ID**

Table 2.21 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxo)-2,2,2-trichloroethylphosphonates **ID**^a

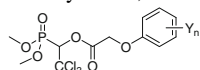


Compound	Y _n	Pre-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
ID-1	4-CF ₃	D	D	D	D	D
ID-2	3-F	D	D	D	D	D
ID-3	4-F	C	C	C	C	A
ID-4	4-Cl	A	A	A	A	A
ID-5	2-Me,4-Cl	A	A	A	A	A
ID-6	3-Me,4-Cl	C	C	C	C	C
ID-7	2-Cl,5-Me	D	D	D	D	D
ID-8	2,4-F ₂	D	D	B	D	B
ID-9	3,5-F ₂	D	D	D	D	D
ID-10	2-Cl,4-F	A	A	A	A	A
ID-11	3-Cl,4-F	D	C	C	C	B
ID-12	2,3-Cl ₂	D	D	D	D	D
ID-13	2,4-Cl ₂	A	A	A	C	A
ID-14	2,6-Cl ₂	D	D	D	D	D
2,4-D		A	A	A	B	A

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.22 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxo)-2,2,2-trichloroethylphosphonates **ID**^a



Compound	Y _n	Post-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
ID-1	4-CF ₃	D	B	D	D	D
ID-2	3-F	D	D	D	D	D
ID-3	4-F	C	B	C	C	D
ID-4	4-Cl	B	A	B	D	C
ID-5	2-Me,4-Cl	A	A	C	C	B
ID-6	3-Me,4-Cl	C	D	D	D	D
ID-7	2-Cl,5-Me	D	D	D	D	D
ID-8	2,4-F ₂	C	B	C	D	C
ID-9	3,5-F ₂	D	D	D	D	D
ID-10	2-Cl,4-F	B	A	A	B	B

(continued)

Table 2.22 (continued)

Compound	Y _n	Post-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
ID-11	3-Cl,4-F	B	A	C	C	D
ID-12	2,3-Cl ₂	D	D	D	D	D
ID-13	2,4-Cl ₂	A	A	A	D	D
ID-14	2,6-Cl ₂	D	B	D	D	D
2,4-D		A	A	A	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

(B) *Post-emergence herbicidal activity of ID*

As shown in Table 2.22, only **ID-13** (Y_n = 2,4-Cl₂) exhibited notable post-emergence herbicidal activity against dicotyledons comparable to 2,4-D followed by **ID-10** (Y_n = 2-Cl,4-F) and **ID-4** (Y_n = 4-Cl). Most **ID** had no significant herbicidal activity against monocotyledons for post-emergence application, except that **ID-10** (Y_n = 2-Cl,4-F) had medium activity against monocotyledons and it was better than 2,4-D.

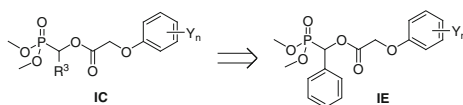
(C) *SAR analyses for ID*

Like SAR analyses for **IC**, the substitutions of 4-Cl (**ID-4**), 2-Me,4-Cl (**ID-5**) and 2-Cl,4-F (**ID-10**) on the phenoxy-benzene ring were most promotive for pre-emergence herbicidal activity against dicotyledons and monocotyledons. They were not only comparable to 2,4-D, but also were better than that of 2,4-D against barnyard grass at 1.5 kg ai/ha. The substitution of 2,4-Cl₂ (**ID-13**) on the phenoxy-benzene ring was very promotive for post-emergence herbicidal activity against dicotyledons comparable to 2,4-D. Noticed that 2-Cl,4-F substitution (**ID-10**) was most promotive for pre- and post-emergence herbicidal activity against both dicotyledons and monocotyledons at 1.5 kg ai/ha.

Herbicidal activity of compounds with 3-Cl,4-F (**ID-11**), 2,4-F₂ (**ID-8**), 3-Me, 4-Cl (**ID-6**), and 4-F (**ID-3**) substitutions was very weak. Compounds with 4-CF₃ (**ID-1**), 2-Cl,5-Me (**ID-7**), 2,3-Cl₂ (**ID-12**), 2,6-Cl₂ (**ID-14**), 3-F (**ID-2**), and 3,5-F₂ (**ID-9**) substitutions were almost inactive for pre- and post-emergence herbicidal activity against both dicotyledons and monocotyledons at 1.5 kg ai/ha.

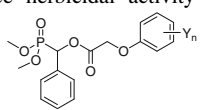
2.1.7.3 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)Benzylphosphonates **IE**

On the basis of structure **IC**, Ph was introduced at R³ to form a series of **IE** (Scheme 2.15), further modification was only focused on substituents Y_n. Twenty-four **IE** were prepared to test their herbicidal activity. The herbicidal activity of **IE** is listed in Tables 2.23 and 2.24.



Scheme 2.15 Design of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)benzylphosphonates **IE**

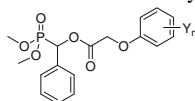
Table 2.23 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)benzylphosphonates **IE**^a



Compound	Y _n	Pre-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IE-1	H	D	D	D	D	D
IE-2	3-Me	B	B	B	D	D
IE-3	4-Me	B	B	B	D	D
IE-5	4-CF ₃	D	D	D	D	D
IE-6	2-NO ₂	D	D	D	D	D
IE-8	2-F	D	D	D	D	D
IE-9	3-F	D	D	D	D	D
IE-10	4-F	D	B	B	C	A
IE-11	4-Cl	A	A	A	A	A
IE-13	2,3-Me ₂	A	C	B	B	D
IE-14	2-Me,4-Cl	A	A	A	A	A
IE-15	3-Me,4-Cl	B	B	A	C	B
IE-16	2-Cl,5-Me	D	D	D	D	D
IE-17	2,4-F ₂	D	C	C	B	D
IE-19	2-Cl,4-F	A	A	A	A	A
IE-20	3-Cl,4-F	A	A	B	B	A
IE-21	2,3-Cl ₂	D	D	D	D	D
IE-22	2,4-Cl ₂	A	A	A	D	D
IE-23	2,6-Cl ₂	D	D	D	D	D
IE-24	2-NO ₂ ,4-CF ₃	D	D	D	D	D
2,4-D		A	A	A	B	A

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.24 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)benzylphosphonates **IE**^a

Compound	Y _n	Post-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IE-1	H	D	D	D	D	D
IE-2	3-Me	C	C	C	D	D
IE-3	4-Me	C	C	C	D	D
IE-5	4-CF ₃	D	D	D	D	D
IE-6	2-NO ₂	D	D	D	D	D
IE-8	2-F	D	D	D	D	D
IE-9	3-F	D	D	D	D	D
IE-10	4-F	C	B	C	C	C
IE-11	4-Cl	B	A	B	B	C
IE-13	2,3-Me ₂	B	D	C	C	D
IE-14	2-Me,4-Cl	A	A	A	B	C
IE-15	3-Me,4-Cl	B	B	C	D	D
IE-16	2-Cl,5-Me	D	D	D	D	D
IE-17	2,4-F ₂	D	A	D	D	D
IE-19	2-Cl,4-F	B	A	B	B	C
IE-20	3-Cl,4-F	B	B	C	C	D
IE-21	2,3-Cl ₂	D	D	D	D	D
IE-22	2,4-Cl ₂	A	A	A	D	D
IE-23	2,6-Cl ₂	D	B	D	D	D
IE-24	2-NO ₂ ,4-CF ₃	D	D	D	D	D
2,4-D		A	A	A	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

(A) Pre-emergence herbicidal activity of **IE**

The data in Table 2.23 showed that **IE-11** (Y_n = 4-Cl), **IE-14** (Y_n = 2-Me,4-Cl) and **IE-19** (Y_n = 2-Cl,4-F) exhibited pre-emergence herbicidal activity against dicotyledons and crab grass comparable to 2,4-D, and they showed better activity than 2,4-D against barnyard grass at 1.5 kg ai/ha. **IE-20** (Y_n = 3-Cl,4-F) and **IE-15** (Y_n = 3-Me,4-Cl) had medium activity. **IE-22** (Y_n = 2,4-Cl₂) exhibited good herbicidal activity against dicotyledons comparable to 2,4-D for pre-emergence, but it had no significant herbicidal activity against monocotyledons. **IE-10** (Y_n as 4-F) had significant herbicidal activity against crab grass. **IE-20** (Y_n = 3-Cl,4-F) exhibited pre-emergence herbicidal activity against monocotyledons comparable to

2,4-D. Other compounds showed weak herbicidal activity against dicotyledons and monocotyledons for pre-emergence at 1.5 kg ai/ha.

(B) *Post-emergence herbicidal activity of IE*

The data in Table 2.24 show that **IE-14** ($Y_n = 2\text{-Me}, 4\text{-Cl}$) and **IE-22** ($Y_n = 2, 4\text{-Cl}_2$) exhibited notable post-emergence herbicidal activity against dicotyledons comparable to 2,4-D followed by **IE-11** ($Y_n = 4\text{-Cl}$), **IE-19** ($Y_n = 2\text{-Cl}, 4\text{-F}$), **IE-15** ($Y_n = 3\text{-Me}, 4\text{-Cl}$), and **IE-20** ($Y_n = 3\text{-Cl}, 4\text{-F}$). Most **IE** had no significant herbicidal activity against monocotyledons for post-emergence application, but **IE-11** ($Y_n = 4\text{-Cl}$), **IE-14** ($Y_n = 2\text{-Me}, 4\text{-Cl}$), and **IE-19** ($Y_n = 2\text{-Cl}, 4\text{-F}$) showed better herbicidal activity against barnyard grass than 2,4-D at 1.5 kg ai/ha.

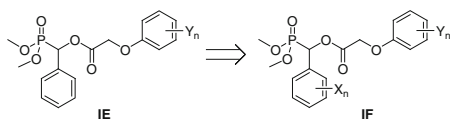
(C) *SAR analyses for IE*

Compounds with no substituent on the phenoxy-benzene ring (**IE-1**) had no herbicidal activity. When 4-Cl, 2-Me, 4-Cl, 2-Cl, 4-F and 2,4-Cl₂ were introduced as Y_n , respectively, **IE-11**, **IE-14**, **IE-19**, and **IE-22** showed good herbicidal activity against dicotyledons for pre-emergence and post-emergence applications at 1.5 kg ai/ha. Especially, compounds with 4-Cl (**IE-11**), 2-Me, 4-Cl (**IE-14**) and 2-Cl, 4-F (**IE-19**) substitutions on the phenoxy-benzene ring not only exhibited notable herbicidal activity against dicotyledons for pre-emergence and post-emergence applications, but also exhibited good herbicidal activity against monocotyledons for pre-emergence application. The herbicidal activity of compounds was almost lost when 4-CF₃; 2-NO₂; 2-F; 3-F; 2,4-F₂; 2-NO₂, 4-CF₃; 2-Cl, 5-Me; 2,3-Cl₂ or 2,6-Cl₂ as Y_n on the phenoxy-benzene ring, while 3-Me, 4-Cl; 3-Cl, 4-F; 3-Me; 4-Me; 4-F; 2,3-Me₂ as Y_n resulted in a decrease in herbicidal activity.

IC-IE with Y_n as 4-Cl, 2-Me, 4-Cl and 2-Cl, 4-F as Y_n exhibited good herbicidal activity against dicotyledons and monocotyledons for pre-emergence application, irrespective of H, Me, Et, *n*-Pr, *n*-Bu, CCl₃, or Ph as R³, respectively.

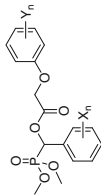
2.1.7.4 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)-1-(Substituted Phenyl)methylphosphonates **IF**

On the basis of structure **IE**, substituted phenyls were introduced to form a series of **IF**. Further modification was focused on substituents Y_n and X_n (Scheme 2.16). Sixty-three compounds of **IF** were prepared to test their herbicidal activity. The herbicidal activity of **IF** is listed in Tables 2.25 and 2.26.



Scheme 2.16 Design of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(substituted phenyl)methylphosphonates **IF**

Table 2.25 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(substituted phenyl)methylphosphonates **IF**^a



Compound	X _n	Y _n	Pre-emergence					Monocotyledon	
			Dicotyledon		Amr ^b	Med ^b	Ech ^b		
			Br ^a						
IF-1	4-Me	3-CF ₃	C		A	C		C	B
IF-10	2-OH	4-Cl	D		D	A		D	C
IF-11	2-OH	2-Cl,4-F	A		A	A		C	A
IF-20	4-MeO	2,4-Cl ₂	D		D	D		A	A
IF-21	4-F	3-CF ₃	B		A	A		C	A
IF-22	4-F	2,4-Cl ₂	A		A	A		A	A
IF-23	2-Cl	3-CF ₃	D		A	A		B	A
IF-24	2-Cl	2,4-Cl ₂	A		A	A		A	A
IF-25	3-Cl	3-CF ₃	A		A	A		C	D
IF-26	3-Cl	2,4-Cl ₂	A		A	A		A	A
IF-27	4-ClPh	3-CF ₃	C		D	A		C	C
IF-31	4-Cl	2,4-Cl ₂	A		A	A		A	A
IF-32	3-Br	2,4-Cl ₂	A		A	A		C	A
IF-33	2,3-Cl	2,4-Cl ₂	A		A	A		A	A
IF-35	2,4-Cl ₂	3-CF ₃	D		A	A		A	A
IF-36	2,4-Cl ₂	2,4-Cl ₂	A		A	A		A	A
IF-38	3,4-Cl ₂	3-CF ₃	B		A	A		B	A
IF-39	3,4-Cl ₂	2,4-Cl ₂	B		B	B		A	A
IF-40	3,4-OCH ₂ O	3-CF ₃	B		A	A		A	A
IF-41	3,4-OCH ₂ O	2,4-Cl ₂	A		A	A		A	A
IF-43	3-NO ₂	3-CF ₃	C		C	C		D	D

(continued)

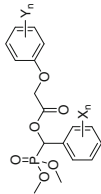
Table 2.25 (continued)

Compound	X _n	Y _n	Pre-emergence				
			Dicotyledon		Monocotyledon		
			Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IF-44	3-NO ₂	4-CF ₃	D	D	D	D	D
IF-45	3-NO ₂	2-NO ₂	D	D	D	D	D
IF-46	3-NO ₂	4-NO ₂	D	D	D	D	D
IF-47	3-NO ₂	2-F	D	D	D	D	D
IF-48	3-NO ₂	3-F	D	D	D	D	D
IF-49	3-NO ₂	4-F	D	B	B	C	B
IF-50	3-NO ₂	4-Cl	A	A	A	A	A
IF-51	3-NO ₂	2-Me,4-Cl	C	B	B	A	A
IF-52	3-NO ₂	3-Me,4-Cl	C	B	B	D	C
IF-53	3-NO ₂	2-Cl,5-Me	D	D	D	D	D
IF-54	3-NO ₂	2,4-F ₂	D	D	C	D	C
IF-55	3-NO ₂	2-Cl,4-F	A	A	A	A	A
IF-56	3-NO ₂	3-Cl,4-F	D	C	C	C	B
IF-57	3-NO ₂	2,3-Cl ₂	D	D	D	D	D
IF-58	3-NO ₂	2,4-Cl ₂	A	A	A	C	D
IF-59	3-NO ₂	2,6-Cl ₂	D	D	D	D	D
IF-60	3-NO ₂	2-NO ₂ ,4-CF ₃	D	D	D	D	D
IF-62	4-NO ₂	2-NO ₂	D	D	D	D	D
IF-63	4-NO ₂	2,4-Cl ₂	A	A	A	C	D
2,4-D			A	A	A	B	A

^a Inhibitory potency(%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales: A—90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr:common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.26 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(substituted phenyl)methylphosphonates **IF**^a



Compound	X _n	Y _n	Post-emergence				
			Dicotyledon		Monocotyledon		
			Bra ^b	Amr ^b	Med ^b	Echl ^b	Dig ^b
IF-1	4-Me	3-CF ₃	A	D	B	D	D
IF-10	2-OH	4-Cl	B	B	B	D	D
IF-11	2-OH	2-Cl,4-F	A	A	A	C	D
IF-20	4-MeO	2,4-Cl ₂	D	D	D	D	D
IF-21	4-F	3-CF ₃	C	A	B	D	D
IF-22	4-F	2,4-Cl ₂	B	B	B	D	D
IF-23	2-Cl	3-CF ₃	C	A	B	D	D
IF-24	2-Cl	2,4-Cl ₂	A	A	A	D	D
IF-25	3-Cl	3-CF ₃	D	A	B	D	D
IF-26	3-Cl	2,4-Cl ₂	A	A	A	D	D
IF-27	4-Cl	3-CF ₃	B	A	D	C	D
IF-31	4-Cl	2,4-Cl ₂	A	A	A	D	D
IF-32	3-Br	2,4-Cl ₂	A	A	A	C	D
IF-33	2,3-Cl ₂	2,4-Cl ₂	A	A	A	C	D
IF-35	2,4-Cl ₂	3-CF ₃	C	A	B	D	D
IF-36	2,4-Cl ₂	2,4-Cl ₂	A	A	A	D	D
IF-38	3,4-Cl ₂	3-CF ₃	D	A	B	D	D
IF-39	3,4-Cl ₂	2,4-Cl ₂	A	A	A	D	D
IF-40	3,4-OCH ₂ O	3-CF ₃	D	B	B	D	D
IF-41	3,4-OCH ₂ O	2,4-Cl ₂	B	B	B	D	D

(continued)

Table 2.26 (continued)

Compound	X _n	Y _n	Post-emergence				
			Dicotyledon			Monocotyledon	
			Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IF-43	3-NO ₂	3-CF ₃	C	D	D	C	D
IF-44	3-NO ₂	4-CF ₃	D	C	D	D	D
IF-45	3-NO ₂	2-NO ₂	D	D	D	D	D
IF-46	3-NO ₂	4-NO ₂	D	D	D	D	D
IF-47	3-NO ₂	2-F	D	D	D	A	D
IF-48	3-NO ₂	3-F	D	D	D	D	D
IF-49	3-NO ₂	4-F	C	B	C	D	C
IF-50	3-NO ₂	4-Cl	B	B	B	B	C
IF-51	3-NO ₂	2-Me,4-Cl	B	A	C	B	D
IF-52	3-NO ₂	3-Me,4-Cl	D	B	B	D	D
IF-53	3-NO ₂	2-Cl,5-Me	D	D	D	D	D
IF-54	3-NO ₂	2,4-F ₂	B	B	C	D	C
IF-55	3-NO ₂	2-Cl,4-F	B	A	C	B	C
IF-56	3-NO ₂	3-Cl,4-F	C	B	C	C	D
IF-57	3-NO ₂	2,3-Cl ₂	D	D	D	D	D
IF-58	3-NO ₂	2,4-Cl ₂	A	A	A	D	D
IF-59	3-NO ₂	2,6-Cl ₂	D	D	D	D	D
IF-60	3-NO ₂	2-NO ₂ ,4-CF ₃	D	D	D	D	D
IF-62	4-NO ₂	2-NO ₂	D	D	D	D	D
IF-63	4-NO ₂	2,4-Cl ₂	A	A	A	D	D
2,4-D			A	A	A	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scale—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

(A) Pre-emergence herbicidal activity of IF

The data in Table 2.25 show **IF-22**, **IF-24**, **IF-26**, **IF-31**, **IF-33**, **IF-36**, **IF-41**, **IF-50** and **IF-55** exhibited pre-emergence herbicidal activity against dicotyledons and crab grass comparable to 2,4-D, and they showed better pre-emergence herbicidal activity against barnyard grass than that of 2,4-D at 1.5 kg ai/ha. **IF-32**, **IF-58** and **IF-63** only had pre-emergence herbicidal activity against dicotyledons comparable to 2,4-D. **IF-20**, **IF-35**, **IF-39**, **IF-40** and **IF-51** had significant pre-emergence herbicidal activity against monocotyledons. They showed activity against crab grass comparable to 2,4-D, against barnyard grass better than that of 2,4-D at 1.5 kg ai/ha. Other compounds showed weak herbicidal activity against dicotyledons and monocotyledons for pre-emergence application at 1.5 kg ai/ha.

(B) Post-emergence herbicidal activity of IF

As shown in Table 2.26, **IF-11**, **IF-24**, **IF-26**, **IF-31–IF-33**, **IF-36**, **IF-39**, **IF-58** and **IF-63** exhibited good herbicidal activity against dicotyledons for post-emergence application. Most **IF** had no significant herbicidal activity against monocotyledons for post-emergence application except **IF-47**, **IF-50**, **IF-51**, and **IF-55**, which had activity against barnyard grass.

(C) SAR analyses for IF

The data in Tables 2.25 and 2.26 showed that compounds with 2,4-Cl₂, 2-Cl,4-F or 4-Cl as Y_n on the phenoxy-benzene ring were most beneficial for pre-emergence herbicidal activity against dicotyledons and crab grass. While compounds with 2,4-Cl₂ or 2-Cl,4-F as Y_n were most beneficial for post-emergence herbicidal activity against dicotyledons. Compounds with 2-F,4-Cl; 2-Me,4-Cl; 4-Cl or 4-F as Y_n were beneficial for post-emergence herbicidal activity against barnyard grass at a rate of 1.5 kg ai/ha. Introduction of other substituents as Y_n led to a sharp decrease in herbicidal activity or loss of activity completely.

Herbicidal activity was also greatly affected by X_n even 2,4-Cl₂, 2-Cl,4-F or 4-Cl as Y_n were kept the same. Introduction of 4-MeO (**IF-20**), 4-F (**IF-22**), 3,4-OCH₂O (**IF-41**) or 3,4-Cl₂ (**IF-39**) as X_n into **IF** led to a decrease in herbicidal activity against dicotyledons for pre-emergence or post-emergence application. Particularly for **IF-20** (X_n = 4-MeO, Y_n = 2,4-Cl₂), its herbicidal activity against dicotyledons for both pre-emergence and post-emergence applications was completely lost.

All compounds with 2,4-Cl₂ as Y_n exhibited better pre-emergence herbicidal activity against barnyard grass than that of 2,4-D except compounds with NO₂ as X_n. Introduction of 3-NO₂ and 4-NO₂ as X_n led to a sharp decrease in pre-emergence herbicidal activity against monocotyledons, such as **IF-58** (X_n = 3-NO₂, Y_n = 2,4-Cl₂) and **IF-63** (X_n = 4-NO₂, Y_n = 2,4-Cl₂). However, compounds with 3-NO₂ as X_n, 2-Cl,4-F or 4-Cl as Y_n displayed good pre-emergence herbicidal activity against monocotyledons. **IF-10** (X_n = 2-OH, Y_n = 4-Cl) was almost inactive to monocotyledons and dicotyledons except clover for pre-emergence application at 1.5 kg ai/ha. Above SAR analyses indicated that improvement of herbicidal activity required a reasonable combination of both X_n and Y_n. Both the structure and position of Y_n, and the structure of X_n are critical for herbicidal activity.

2.1.7.5 Further Herbicide Activity Assay of Some 1-(Substituted Phenoxyacetoxy)Alkylphosphonates

Based on the preliminary bioassays, some 1-(substituted phenoxyacetoxy)-alkylphosphonates were further evaluated in greenhouse at a lower rate for pre-emergence and post-emergence herbicidal activity. Chingma abutilon (*Abutilon theophrasti*), spiny amaranth (*Amaranthus spinosus*), goosefoot (*Chenopodium album*), crab grass (*Digitaria Sanguinalis*), and green bristlegrass (*Setaria viridis*) were chosen as test species.

(A) Pre-emergence herbicide activity of some 1-(substituted phenoxyacetoxy)-alkylphosphonates

In order to confirm the pre-emergence herbicidal activity of 1-(substituted phenoxyacetoxy)alkylphosphonates, seven compounds were chosen for further herbicide activity assay at a lower rate for pre-emergence herbicidal activity. As shown in Table 2.27, they displayed very poor herbicidal activity against tested plants for pre-emergence application except **IA-4** and **IC-2** with 48–53 % inhibitory potency against dicotyledonous plants at 450 g ai/ha. All tested compounds had no pre-emergence herbicidal activity against tested plants at 150 or 75 g ai/ha, irrespective of difference in structure.

Table 2.27 Structure and pre-emergence herbicidal activity of some 1-(substituted phenoxyacetoxy)alkylphosphonates^a

Compound	R	R ³	Y _n	Rate (g ai/ha)	Abu ^b	Ams ^b	Che ^b	Dig ^b	Set ^b
IA-4	Et	Me	2,4-Cl ₂	75	0	0	0	0	0
				150	0	0	0	0	0
				450	48	50	53	10	6
IC-2	Me	Me	H	75	0	0	0	0	0
				150	0	0	0	0	0
				450	48	53	53	0	5
IC-5	Me	Me	3-CF ₃	75	0	0	0	0	0
				150	0	0	0	0	0
				450	0	0	0	36	36
IC-13	Me	Me	2-Me,4-Cl	150	0	0	0	0	0
				450	0	30	0	16	0
IC-22	Me	Me	2,4-Cl ₂	75	0	0	0	0	0
				150	0	0	0	0	0
				450	0	0	0	45	35
IE-22	Me	Ph	2,4-Cl ₂	75	0	0	0	0	0
				150	0	0	0	0	0
				450	0	0	0	45	30

(continued)

Table 2.27 (continued)

Compound	R	R ³	Y _n	Rate (g ai/ha)	Abu ^b	Ams ^b	Che ^b	Dig ^b	Set ^b
IF-58	Me	3-NO ₂ Ph	2,4-Cl ₂	75	0	0	0	0	0
				150	0	0	0	0	0
				450	0	0	0	0	0
2,4-D				75	0	0	0	0	0
				150	0	0	0	10	6
				450	0	0	0	65	65

^a Inhibitory potency (%) against the growth of plants in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Abu: chingma abutilon; Ams: spiny amaranth; Che: goosefoot; Dig: crab grass; Set: green bristlegrass

(B) *Post-emergence herbicide activity of some 1-(substituted phenoxyacetoxy)-alkylphosphonates*

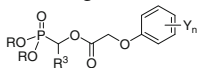
In order to confirm the post-emergence herbicide activity of 1-(substituted phenoxyacetoxy)alkylphosphonates, seven compounds were further evaluated at a lower rate for post-emergence herbicidal activity. The result showed that tested compounds displayed much higher herbicidal activity against dicotyledonous plants than monocotyledons for post-emergence application. All tested compounds exhibited excellent post-emergence herbicidal activity (with 90–100 % inhibitory potency) against tested dicotyledonous plants; however, they displayed very poor herbicidal activity (only with 0–37 % inhibitory potency) against monocotyledons, crab grass, and green bristlegrass at 450 g ai/ha.

The data in Table 2.28 showed that compounds with 2,4-Cl₂ as Y_n had higher herbicidal activity than that of compounds with 2-Me,4-Cl or 3-CF₃ as Y_n. The compounds with 2,4-Cl₂ as Y_n exhibited potent herbicidal activity against dicotyledons for post-emergence application at 75 g ai/ha. It was found that **IC-22** with the *O,O*-dimethyl group exhibited better herbicidal activity than **IA-4** with the *O,O*-diethyl group at 75 g ai/ha. When 2,4-Cl₂ as Y_n stay the same, R³ as Me was much more beneficial than R³ as Ph or 3-NO₂Ph for post-emergence herbicidal activity. Among **IA–IF**, **IC-22** displayed the best post-emergence herbicide activity having >90 % inhibitory potency against dicotyledons better than or comparable to 2,4-D.

2.1.7.6 Inhibition on Growth of Cucumber

The IC₅₀ values of some **IC–IF** against cucumber (*Cucumis sativa*) were measured in order to further confirm the effect of substituent on herbicidal activity (Tables 2.29, 2.30 and 2.31).

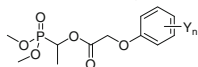
Inhibitory potency shown by IC₅₀ values in Tables 2.29 and 2.30 corresponded well to the SAR analyses base on the herbicidal effect of those compounds in the greenhouse.

Table 2.28 Structure and post-emergence herbicidal activity of some 1-(substituted phenoxyacetoxymethyl)alkylphosphonates^a

Compound	R	R ³	Y _n	Rate (g ai/ha)	Abu ^b	Ams ^b	Che ^b
IA-4	Et	Me	2,4-Cl ₂	75	98	53	63
				150	98	83	93
IC-2	Me	Me	H	75	83	63	83
				150	99	93	100
IC-5	Me	Me	3-CF ₃	75	28	0	33
				150	42	0	42
IC-13	Me	Me	2-Me,4-Cl	150	82	10	60
IC-22	Me	Me	2,4-Cl ₂	75	98	90	93
				150	100	100	96
IE-22	Me	Ph	2,4-Cl ₂	75	83	63	83
				150	93	70	93
IF-58	Me	3-NO ₂ Ph	2,4-Cl ₂	75	50	50	53
				150	90	100	83
2,4-D				75	73	60	73
				150	100	93	93

^a Inhibitory potency (%) against the growth of plants in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Abu: chingma abutilon; Ams: spiny amaranth; Che: goosefoot

Table 2.29 IC₅₀ values of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)alkylphosphonates against cucumber

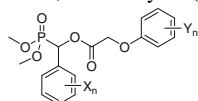
Compound	Y _n	Root length IC ₅₀ (μM) ^a	R
IC-22	2,4-Cl ₂	0.0025	0.9868
IC-19	2-Cl,4-F	0.2836	0.9902
IC-10	4-Cl	0.427	0.9903
IC-13	2-Me,4-Cl	0.4363	0.9543
IC-20	3-Cl,4-F	1.123	0.9936
IC-9	4-F	1.517	0.9908
IC-16	2,4-F ₂	1.838	0.9918
IC-14	3-Me,4-Cl	2.957	0.9961
IC-15	2-Cl,5-Me	48.59	0.9964
IC-2	H	89.10	0.9965
IC-23	2,6-Cl ₂	99.97	0.9975
IC-8	3-F	111.1	0.9934
IC-21	2,3-Cl ₂	207.5	0.9997
IC-6	4-CF ₃	246.9	0.9956

(continued)

Table 2.29 (continued)

Compound	Y _n	Root length IC ₅₀ (μM) ^a	R
IC-17	3,5-F ₂	287.0	0.9976
IC-7	2-F	376.5	0.9880
2,4-D		0.2280	0.9918

^a IC₅₀ is effective dose that provides 50 % inhibition against the growth of cucumber root

Table 2.30 IC₅₀ values of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-arylmethylphosphonates against cucumber

Compound	X _n	Y _n	Root length IC ₅₀ (μM) ^a	R
IE-22	H	2,4-Cl ₂	0.0142	0.9868
IE-19	H	2-Cl,4-F	0.3198	0.9905
IE-14	H	2-Me,4-Cl	0.3526	0.9916
IE-11	H	4-Cl	0.3964	0.9954
IE-20	H	3-Cl,4-F	0.5840	0.9989
IE-15	H	3-Me, 4-Cl	1.731	0.9970
IE-10	H	4-F	2.050	0.9868
IE-17	H	2,4-F ₂	3.246	0.9836
IE-9	H	3-F	64.23	0.9933
IE-16	H	2-Cl,5-Me	72.71	0.9982
IE-23	H	2,6-Cl ₂	85.11	0.9863
IE-6	H	2-NO ₂	223.0	0.9982
IE-21	H	2,3-Cl ₂	228.4	0.9951
IE-8	H	2-F	625.3	0.9963
IF-59	3-NO ₂	2,4-Cl ₂	0.0034	0.9868
IF-51	3-NO ₂	2-Me,4-Cl	0.3258	0.9836
IF-45	3-NO ₂	2-NO ₂	297.0	0.9982
IF-46	3-NO ₂	4-NO ₂	>11400	0.9863
2,4-D			0.2280	0.9918

^a IC₅₀ is effective dose that provides 50 % inhibition against the growth of cucumber root.

As shown in Table 2.29, substituent Y_n on the phenoxy-benzene ring had greater influence on inhibitory potency against the growth of the root of cucumber. Compared with **IC-2** which had no substituent on the phenoxy-benzene ring, inhibitory potency could be greatly enhanced by introducing 2,4-Cl₂; 2-Cl,4-F; 2-Me,4-Cl and 4-Cl on the phenoxy-benzene ring. Whereas the introduction of 2,3-Cl₂; 2,6-Cl₂; 2,3-F₂; 4-CF₃ or 3,5-F₂ as Y_n resulted in a sharp decrease in inhibitory potency against cucumber.

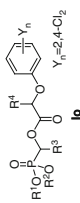


Table 2.31 IC₅₀ values of *O,O*-dialkyl 1-(substituted phenoxyacetoxymethyl)alkylphosphonates against cucumber

Compound	R ¹ , R ²	R ³	R ⁴	Stem Length IC ₅₀ (μM) ^a	Compound	R ¹ , R ²	R ³	R ⁴	Root Length IC ₅₀ (μM) ^a
IF-58	Me	3-NO ₂ Ph	H	5.02	IC-22	Me	Me	H	0.0025
IB-3	Me	Me	Me	6.74	IF-58	Me	3-NO ₂ Ph	H	0.0034
IC-22	Me	Me	H	7.56	IC-32	Me	Pr	H	0.0075
IC-1	Me	H	H	7.79	IE-22	Me	Ph	H	0.0142
IE-22	Me	Ph	H	8.95	IA-13	Et	Ph	H	0.0488
IC-32	Me	<i>n</i> -Pr	H	9.34	IC-1	Me	H	H	0.0577
2,4-D				10.1	2,4-D				0.228
IA-2	Et	H	H	13.4	IA-4	Et	Me	H	0.300
IB-4	Me	<i>n</i> -Pr	Me	13.7	IA-8	Et	Et	H	0.310
IC-27	Me	Et	H	14.0	IC-27	Me	Et	H	0.327
IB-14	<i>n</i> -Pr	Me	Me	18.0	IB-12	Et	Me	Me	1.08
IA-18	Et	2-ClPh	H	21.1	IB-3	Me	Me	Me	1.42
IA-8	Et	Et	H	25.7	IA-18	Et	2-ClPh	H	1.49
IB-7	Me	Ph	Me	30.1	IB-14	<i>n</i> -Pr	Me	Me	2.44
IB-15	<i>n</i> -Pr	Ph	Me	44.3	IB-4	Me	<i>n</i> -Pr	Me	2.98
IA-13	Et	Ph	H	109	IB-15	<i>n</i> -Pr	Ph	Me	4.52
IB-16	<i>n</i> -Pr	2-ClPh	Me	164	IB-16	<i>n</i> -Pr	2-ClPh	Me	12.1

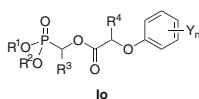
^a IC₅₀ is effective dose that provides 50 % inhibition against the growth of cucumber (root or stem)

As shown in Table 2.30, compounds with 2,4-Cl₂; 2-Cl,4-F; 2-Me,4-Cl and 4-Cl as Y_n on the phenoxy-benzene ring displayed higher inhibitory potency against the growth of the root of cucumber. Whereas the compounds with 2,3-Cl₂; 2,6-Cl₂; 2-Cl,5-Me; 2,3-F₂ or NO₂ on the phenoxy-benzene ring showed poor inhibitory potency. As a typical example, the introduction of a nitro group as Y_n on the phenoxy-benzene ring resulted in a sharp decrease in inhibitory potency, such as **IF-45** (IC₅₀ = 297 μM) and **IF-46** (IC₅₀ > 11,400 μM). However, the introduction of 3-NO₂ group into the benzene ring at X_n had a favorable effect on inhibitory potency when 2,4-Cl₂ was as Y_n, such as **IF-59** (IC₅₀ = 0.0034 μM).

The above results showed 2,4-Cl₂ as Y_n on the phenoxy-benzene ring to be most beneficial for herbicidal activity. In order to confirm the effect of R¹, R², R³, and R⁴ in structure **Io** on activity, the inhibitory potency of some compounds against cucumber was examined when 2,4-Cl₂ as Y_n was kept constant (Table 2.31).

As shown in Table 2.31, great differences for cucumber toxicity could be made due to a change of R¹, R², R³, and R⁴ in the phosphonate **Io** when 2,4-Cl₂ as Y_n were kept unchanged. Inhibitory activity decreased with the increase in the size of R¹, R², and R⁴. When *n*-Pr or Et was replaced by a smaller group (Me), inhibitory potency was greatly improved. Compounds with Me as R¹, R², and H as R⁴ displayed higher inhibitory potency, such as **IC-1**, **IC-22**, **IC-32**, **IE-22**, and **IF-58** displayed higher activity against the growth of root and stem of cucumber than that of 2,4-D. However several compounds with Et or *n*-Pr as R¹ and R², showed lower activity against the growth of cucumber than that of 2,4-D. These results indicated that the phosphonates **Io** themselves were responsible for the inhibitory potency against cucumber, not the possible metabolic product 2,4-D.

2.1.8 Structure-Herbicidal Activity Relationships



Io

On the scaffold of the phosphonate **Io**, the effects of substituents R¹, R², R³, R⁴, and Y_n on herbicidal activity can be summarized as follows:

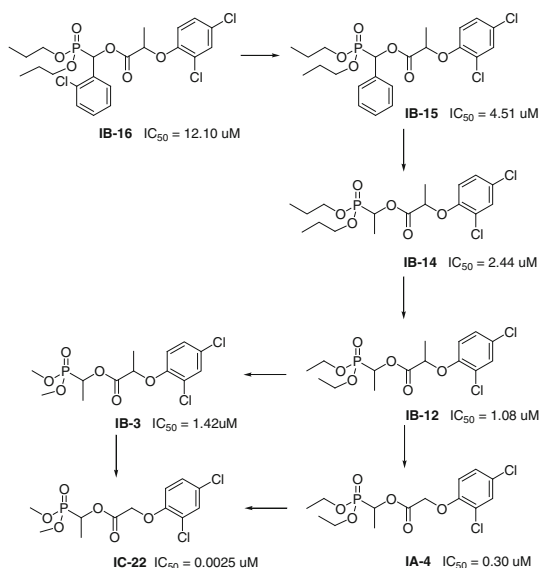
- (A) Herbicidal activity was highly dependent upon the structure and position of substituent Y_n on the phenoxy-benzene ring. Herbicidal activities of compounds against dicotyledons for post-emergence application could be greatly enhanced by introducing 2,4-Cl₂ or 2-Cl,4-F into the phenoxy-benzene ring compared with that of other substituents. Herbicidal activities of compounds would be weak or lost when 2-F, 3-F; 2,3-F₂; 3,5-F₂; 2-Cl,5-Me; 2,3-Cl₂; 2,6-Cl₂; 4-CF₃; 2-NO₂; 4-NO₂; 2-NO₂,4-Cl or 2-NO₂,4-CF₃ as Y_n were introduced into the phenoxy-benzene ring. Compounds with no substituent on the phenoxy-benzene ring were inactive.

- (B) Substituents R^1 , R^2 , and R^4 played a very important role in herbicidal activity. Herbicidal activity decreased with the increase in the size of R^1 , R^2 , and R^4 . Compounds with Me as R^1 and R^2 , H as R^4 displayed higher inhibitory potency than those of Et and *n*-Pr as R^1 and R^2 , and H or Me as R^4 even when 2,4-Cl₂ as Y_n was kept unchanged. This finding accorded with the SAR analyses for acylphosphonates by Baillie et al. They found that when a smaller substituent with weaker electronegativity was introduced to link with the phosphorus atom in the skeleton of acylphosphonates, herbicide activity of compound significantly increased.
- (C) When Y_n , R^1 , R^2 , and R^4 were kept unchanged in the phosphonate **Io**, the different substituent of R^3 also had great influence on the herbicidal activity. **IF-20** ($R^3 = 4\text{-MeOPh}$) exhibited low inhibitory potency (<50 %) against the tested plants, but **IF-31** ($R^3 = 4\text{-ClPh}$) exhibited 100 % post- or pre-emergence inhibitory potency against all tested dicotyledons in greenhouse (Tables 2.25 and 2.26). However, the effect of R^3 depends on structures of Y_n , R^1 , R^2 , and R^4 . As a typical example, the herbicidal activity of **IF-58** ($R^1 = R^2 = \text{Me}$, $R^3 = 3\text{-NO}_2\text{Ph}$, $R^4 = \text{H}$, $Y_n = 2,4\text{-Cl}_2$) was much higher than that of **IF-46** ($R^1 = R^2 = \text{Me}$, $R^3 = 3\text{-NO}_2\text{Ph}$, $R^4 = \text{H}$, $Y_n = 4\text{-NO}_2$).
- (D) There were remarkably different effects on herbicidal activity by introducing a nitro group as R^3 and/or Y_n . The introduction of a nitro group as Y_n on the phenoxy-benzene ring resulted in much lower herbicidal activity (such as compounds with 2-NO₂; 4-NO₂; 2-NO₂,4-Cl or 2-NO₂,4-CF₃ as Y_n). However, the introduction of a nitro group in R^3 had a favourable effect on herbicidal activity. Good herbicidal activity against dicotyledons was observed in the compounds **IF-58** ($R^1 = R^2 = \text{Me}$, $R^3 = 3\text{-NO}_2\text{Ph}$, $R^4 = \text{H}$, $Y_n = 2,4\text{-Cl}_2$) and **IF-63** ($R^1 = R^2 = \text{Me}$, $R^3 = 4\text{-NO}_2\text{Ph}$, $R^4 = \text{H}$, $Y_n = 2,4\text{-Cl}_2$). This indicated that introduction of a nitro group as Y_n on the phenoxy-benzene ring was not beneficial to herbicidal activity. Satisfactory herbicidal activity of the phosphonate **Io** could be achieved by introducing a nitro group in R^3 with a reasonable combination of Y_n , R^1 , R^2 , and R^4 .

The above SAR analyses indicated that improvement of herbicidal activity required a reasonable combination of both phosphorus-containing moiety and phenoxyacetate moiety. Herbicidal activity was remarkably variable by chemical modification of R^1 , R^2 , R^3 , R^4 , and Y_n . As shown in Scheme 2.17, when 2,4-Cl₂ were kept unchanged as Y_n , inhibitory potency against the growth of the root of cucumber was greatly enhanced by the chemical modification of substituents in the phosphorus-containing moiety.

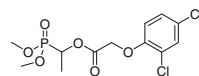
IC-22 with notable inhibitory potency was found by optimizing the structure of R^1 , R^2 , R^3 and R^4 in **Io** [22]. It also exhibited promising post-emergence herbicidal activity against dicotyledons better than or comparable to 2,4-D.

Scheme 2.17 Increase of inhibitory potency against the growth of the root of cucumber



2.1.9 Herbicidal Activity of IC-22

In order to confirm the practicality, **IC-22** (code number for development: HW02) was selected for further evaluation for its herbicidal activity and herbicidal spectrum at 18.75–450 g ai/ha in greenhouse. **IC-22** tested for post-emergence activity against a range of weed species including white eclipta (*Eclipta prostrata*), common amaranth (*Amaranthus retroflexus*), siberian cocklebur (*Xanthium strumarium*), hairy bittercress (*Cardamine hirsute*), purslane (*Portulaca oleracea*), clover (*Medicago sativa*) barnyard grass (*Echinochloa crusgalli*), and crab grass (*Digitaria sanguinalis*). As shown in Table 2.32, **IC-22** exhibited excellent herbicidal activity against broadleaf weeds by post-emergence application at 18.75–450 g ai/ha. However, no post emergence activity was seen against monocot weeds, barnyard grass, and crab grass at 450–18.75 g ai/ha. Crop selectivity of **IC-22** at 37.5–600 g ai/ha was further examined. Rape (*Brassica campestris*), carrot (*Daucus carota*), wheat (*Triticum aestivum*), maize (*Zea mays*), and rice (*Oryza sativa*) were chosen as representative crops to test IC-22's selectivity (Table 2.32). Among tested crops, rape and carrot as dicotyledonous crop were very susceptible at a rate as low as 37.5 g ai/ha, whereas wheat, maize, and rice exhibited a higher tolerance to **IC-22** even at 600 g ai/ha. The data in Tables 2.32 and 2.33 further showed all tested broadleaf plants were highly sensitive to **IC-22** by post-emergence application at a lower rate. **IC-22** tested showed an indication of broad spectrum herbicide activity against broadleaf weeds and a higher level of selectivity between broadleaf weeds and wheat, maize, or rice.

Table 2.32 Herbicidal activity of **IC-22** for post-emergence application^a

Rate (g ai/ha)	Amr ^b	Car ^b	Ecl ^b	Por ^b	Med ^b	Xan ^b	Dig ^b	Ech ^b
18.75	65	75	56	50	60	50	0	0
37.5	83	84	72	65	72	60	0	0
75	90	88	82.5	75	84	72	0	0
150	96	90	90	85	90	90	15	0
225	96	95	96	90	95	95	23	10
300	100	100	100	95	97	100	32	20
450	100	100	100	100	100	100	37.5	35

^a Evaluation in greenhouse. Inhibitory potency (%) against the growth of plants, 0 (no effect), 100 % (completely kill)

^b Ecl: white eclipta; Amr: common amaranth; Xan: siberian cocklebur; Car: hairy bittercress; Por: purslane; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.33 Crop selectivity of **IC-22** for post-emergence application^a

Rate (g ai/ha)	Dau ^b	Bra ^b	Tri ^b	Ory ^b	Zea ^b
37.5	85	90	NT	NT	NT
75	90	93	NT	NT	NT
150	95	97	NT	NT	0
225	97	100	0	0	0
300	100	100	0	0	0
450	100	100	0	0	0
600	100	100	0	0	0

^a Inhibitory potency (%) against the growth of plants in the greenhouse, 0 (no effect), 100 % (completely kill), NT (not tested)

^b Dau: carrot; Bra: rape; Tri: wheat; Ory: rice; Zea: maize

2.1.10 Summary

O,O-Dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates **IA–IF** including 103 compounds as potential PDHc inhibitors were conveniently synthesized by the condensation of 1-hydroxyalkylphosphonates **M2** and substituted phenoxyacetyl chlorides **M5** in the presence of base under mild reaction conditions.

Some alkylphosphonates showed much higher herbicidal activity against dicotyledons than monocotyledons for post-emergence and pro-emergence applications in greenhouse. Their post-emergence herbicidal activity against dicotyledons was much better than pre-emergence herbicidal activity.

Bioassay results showed that satisfactory herbicidal activity of *O,O*-dialkyl 1-(substituted phenoxyacetoxy)alkylphosphonates could be achieved by a reasonable combination of both phosphorus-containing moiety and phenoxyacetate moiety. The herbicidal activity could be increased greatly by optimizing R, R³, R⁴, and Y_n in the parent structure **Io**. One requirement was *O*-methyl, rather than *O*-ethyl or *O*-*n*-propyl attached to phosphorus atom. The other was that two chlorine atoms or chlorine and fluorine atoms as Y_n should be substituted at the 2- and 4-positions on a phenoxy-benzene ring. Besides, smaller groups H as R⁴ and Me as R³ were beneficial to herbicidal activity. *O,O*-Dimethyl 1-(2,4-dichlorophenoxyacetoxy)ethylphosphonate **IC-22** was thus found to be the most effective against broadleaf weeds, better than or comparable to 2,4-D in post-emergence application at 18.75–450 g ai/ha.

IC-22 showed much higher herbicidal activity than that of those reported plant PDHc inhibitors, acylphosphinates and acylphosphonates [1, 27]. Those compounds exhibited 80–100 % inhibition against weeds at 2.8 kg/ha; but at this rate they had shown unacceptable phytotoxicity to the crops. Compared with acylphosphinates and acylphosphonates, **IC-22** exhibited promising herbicidal activity and selectivity for development as a selective post-emergence herbicide which may be used for broadleaf weed control in monocot crop fields.

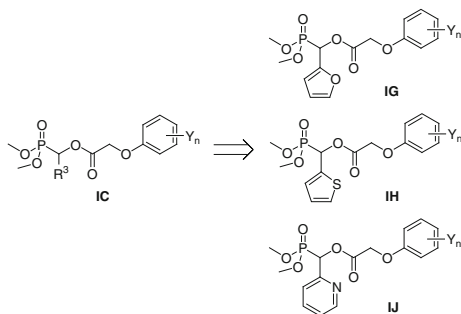
2.2 Heterocyclylmethylphosphonates IG–IJ

2.2.1 Introduction

Through the optimization of lead structures **IA**, *O,O*-dimethyl 1-(2,4-dichlorophenoxyacetoxy)ethylphosphonate (**IC-22**) was found to be a potential herbicide [22], with an effective inhibition against plant PDHc E1 (see Chap. 7).

The further synthetic strategy was thus focused on the modifications of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)alkylphosphonates scaffold. As many heterocyclic compounds had shown remarkable biological properties, we were interested in the design of heterocycle-containing 1-(substituted phenoxyacetoxy)alkylphosphonates. Different heterocyclic group such as furyl, thienyl, or pyridyl group as R³ was introduced to **IC** to form *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(fur-2-yl)methylphosphonates **IG**, *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphosphonates **IH** and *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(pyrid-2-yl)methylphosphonates **IJ** (Scheme 2.18).

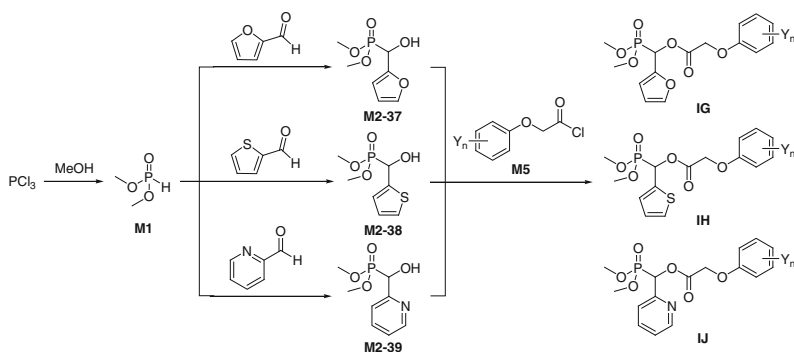
In this section we describe the synthesis, herbicidal activity, and SAR analyses of heterocyclylmethylphosphonates **IG–IJ**. It has been found that **IG–21** and some of its analogs have shown potential utility as an herbicide against broadleaf weeds.



Scheme 2.18 Design of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-heterocyclymethylphosphonates **IG–IJ**

2.2.2 Synthesis of **IG–IJ**

Heterocyclymethylphosphonates **IG–IJ** were synthesized by the condensation of *O,O*-dimethyl 1-hydroxyl-1-heterocyclymethylphosphonates **M2** (**M2-37**, **M2-38** and **M2-39**) and substituted phenoxyacetyl chloride **M5**. The synthetic route in Scheme 2.19 was carried out for preparations of **IG–IJ**.



Scheme 2.19 Synthetic route of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-heterocyclymethylphosphonates **IG–IJ**

O,O-dimethyl 1-hydroxyl-1-heterocyclymethylphosphonates **M2-37**, **M2-38** and **M2-39** were prepared by a base-catalyzed nucleophilic addition of *O,O*-dimethyl phosphonate **M1** (or dimethyl phosphite) to corresponding heterocyclaldehydes using triethylamine as a catalyst in the range of 81–90 % yields. The method for the preparation of *O,O*-dimethyl 1-hydroxyl-1-heterocyclymethylphosphonates **M2** has

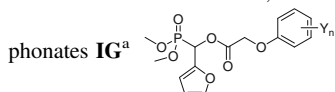
been discussed in Sect. 2.1.2. The yields and physicochemical data of **M2-37**, **M2-38** and **M2-39** are listed in Table 9.2.

The method for preparations of substituted phenoxyacetic acids **M4** and substituted phenoxyacetyl chlorides **M5** has been discussed in Sect. 2.1.3. **M5** were prepared from corresponding substituted phenoxyacetic acids **M4**. **M4-1–M4-3**, **M4-6–M4-8**, and **M4-9–M4-14** which were used to prepare **IG–IJ** are shown in Table 2.7. **M4** could be prepared according to the general synthesis procedure of **M4** in Sect. 9.1.5.

The synthetic reaction of **IG–IJ** required a temperature near room temperature using a weak base because **IG–IJ** contained a carboxylic ester group which was sensitive to acid or base. A large number of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)phosphonates have been prepared by the condensation of 1-hydroxyalkylphosphonates with substituted phenoxyacetyl chlorides in the presence of pyridine as an acid-binding agent. In the synthesis study of **IG–IJ**, triethylamine was also found to be a good acid-binding agent and as a catalyst for the condensation of **M2** and **M5**. In order to prevent hydrolysis of **M2** and **M5**, this condensation should be carried out in anhydrous solvent, such as anhydrous CH_2Cl_2 or CHCl_3 . The structures of **IG–IJ** are listed in Tables 2.34, 2.35 and 2.36.

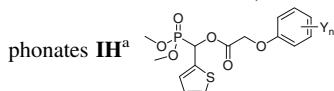
The general synthesis procedure of heterocyclylmethylphosphonates **IG–IJ** is introduced in Sect. 9.1.7. **IG–IJ** were soluble in a variety of organic solvents such as benzene, diethyl ether, ethyl acetate, and so on. They were stable to light and air at room temperature but easily decomposed under the acidic or basic conditions. Their structures were characterized by ^1H NMR, ^{31}P NMR, IR and MS, and confirmed by elementary analysis. Spectroscopic analysis of some representative **IG–IJ** are given in the next section.

Table 2.34 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxymethyl)-1-(fur-2-yl)methylphosphonates **IG^a**



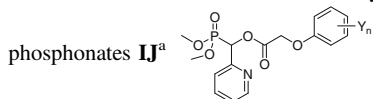
Compound	Y _n	Compound	Y _n	Compound	Y _n
IG-1	H	IG-9	2-Cl	IG-17	2,4-F ₂
IG-2	3-Me	IG-10	4-Cl	IG-18	2-F,4-Cl
IG-3	4-Me	IG-11	4-Br	IG-19	2-Cl,4-F
IG-4	3-CF ₃	IG-12	4-CN	IG-20	2,3-Cl ₂
IG-5	4-CF ₃	IG-13	2,3-Me ₂	IG-21	2,4-Cl ₂
IG-6	2-F	IG-14	2-Me,4-Cl	IG-22	2,6-Cl ₂
IG-7	3-F	IG-15	3-Me,4-Cl	IG-23	2,4,5-Cl ₃
IG-8	4-F	IG-16	2-Cl,5-Me		

^a Synthesis of **IG-1–IG-6**, **IG-9**, **IG-11–IG-13**, **IG-17–IG-19** and **IG-23** [28]; **IG-7**, **IG-8**, **IG-10**, **IG-14**, **IG-16**, **IG-20**, **IG-21** and **IG-22** [23]

Table 2.35 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphos-

Compound	Y _n	Compound	Y _n	Compound	Y _n
IH-1	3-CF ₃	IH-8	4-Br	IH-15	2-F,4-Cl
IH-2	4-CF ₃	IH-9	4-CN	IH-16	2-Cl,4-F
IH-3	2-F	IH-10	2,3-Me ₂	IH-17	2,3-Cl ₂
IH-4	3-F	IH-11	2-Me,4-Cl	IH-18	2,4-Cl ₂
IH-5	4-F	IH-12	3-Me,4-Cl	IH-19	2,6-Cl ₂
IH-6	2-Cl	IH-13	2-Cl,5-Me	IH-20	2,4,5-Cl ₃
IH-7	4-Cl	IH-14	2,4-F ₂		

^a Synthesis of **IH-4**, **IH-5**, **IH-7**, **IH-11**, **IH-13**, **IH-17**, **IH-18** and **IH-19** [23]; **IH-2**, **IH-6**, **IH-8**, **IH-9**, **IH-10**, **IH-14**, and **IH-15** [28]; **IH-1**, **IH-3**, **IH-12**, and **IH-16** [29]

Table 2.36 Structure of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(pyrid-2-yl)methyl-

Compound	Y _n	Compound	Y _n	Compound	Y _n
IJ-1	3-CF ₃	IJ-6	4-Cl	IJ-11	2-Cl,4-F
IJ-2	4-CF ₃	IJ-7	2-Me,4-Cl	IJ-12	2,3-Cl ₂
IJ-3	2-F	IJ-8	3-Me,4-Cl	IJ-13	2,4-Cl ₂
IJ-4	3-F	IJ-9	2-Cl,5-Me	IJ-14	2,6-Cl ₂
IJ-5	4-F	IJ-10	2,4-F ₂		

^a Synthesis of **IJ-1–IJ-14** [29]

2.2.3 Spectroscopic Analysis of **IG–IJ**

All main functional groups in **IG–IJ** were characterized by IR which showed normal stretching absorption bands indicating the existence of benzene ring (1,450–1,615 cm⁻¹), P–O–C (1,026–1,054 cm⁻¹), P–C (730–750 cm⁻¹), and C–O–C (1,149–1,200 cm⁻¹). A strong absorption near 1,750–1,770 cm⁻¹ was identified for the absorption C=O. A sharp and weak band at 3,040–3,100 cm⁻¹ accounted for the C–H stretching of the benzene ring. A strong peak at 1,250–1,260 cm⁻¹ accounted for P=O in phosphonates. The IR spectrum of **IJ-8** is shown in Fig. 2.8.

The EI mass spectra of most **IG–IJ** gave molecular ion peaks. The fragment ions of **IG–IJ** were consistent with the structure and could be assigned. The primary fragmentations of most compounds **IG–IJ** were associated with the cleavages of C–O bond.

The MS spectrum of **IG-21** is shown in Fig. 2.9. The fragmentation of **IG-21** is shown in Scheme 2.20.

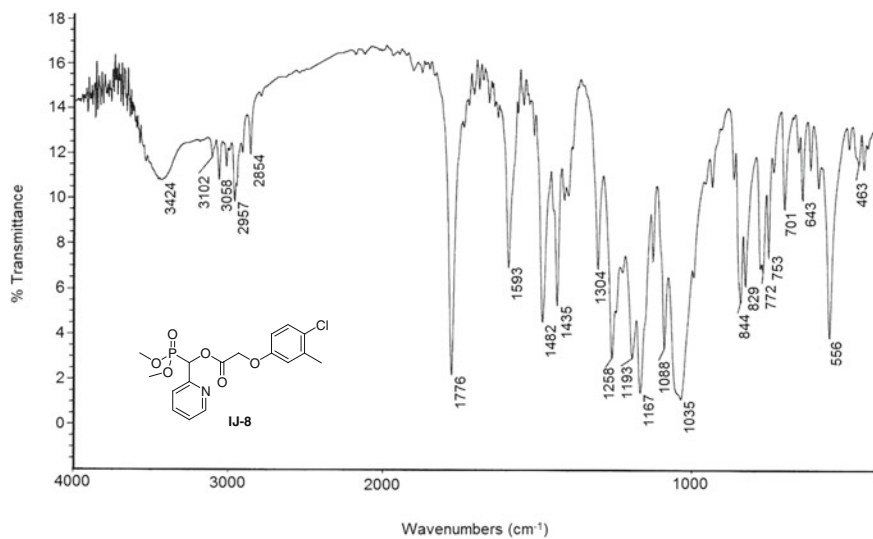


Fig. 2.8 IR spectrum of IJ-8

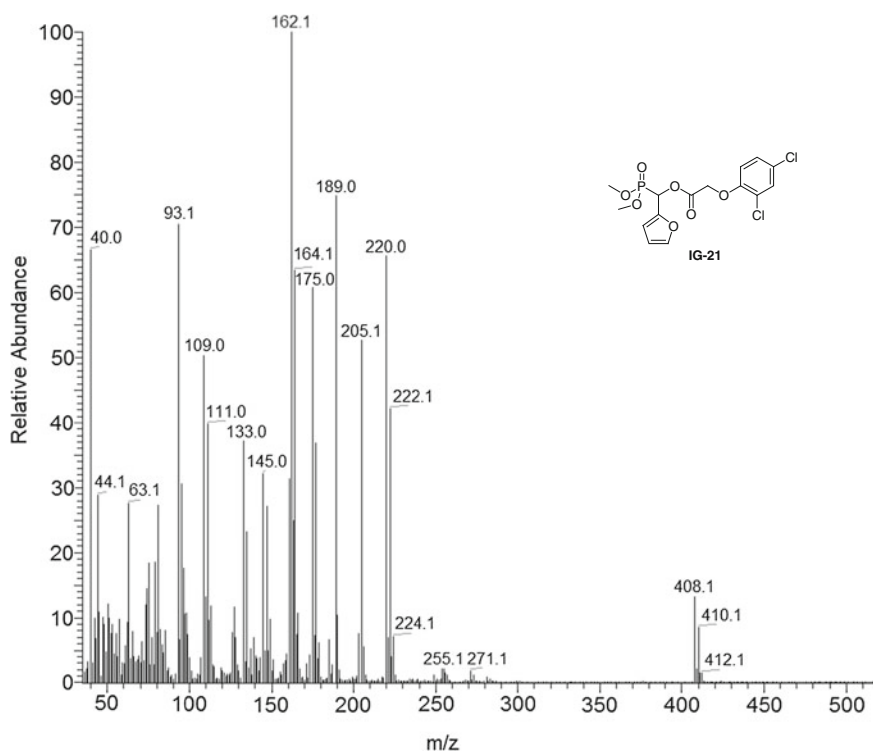
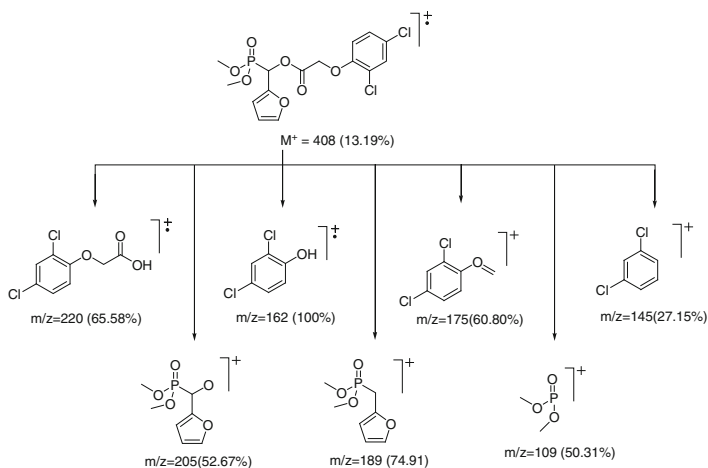


Fig. 2.9 EI-MS spectrum of IG-21



Scheme 2.20 Fragmentation of **IG-21**

In the ^1H NMR spectra of **IG–IJ**, it could be observed that both the proton signals in the P–C–H moiety and P–OMe moiety displayed as two doublets due to couplings to the phosphorus. In the ^1H NMR spectra of **IG–IJ**, the proton signals corresponding to the two methoxyl groups attached to phosphorus appeared as two doublets at δ 3.65–3.85. The difference in the chemical shift of two methyl hydrogens due to the low rate of environmental exchange was caused by the slow rotation of P–C bond, and the magnetic nucleus phosphorus made the signals of both methyls split into two doublets. It was also noticed that the signal of methyl protons (MeO) attached to phosphorus in **IG-7**, **IG-8**, **IG-16**, **IH-4**, and **IH-5** appeared as two doublets. For instance, the signals of both methyls (dd, 6H, $2 \times \text{OCH}_3$) in **IG-16**, **IH-13**, and **IJ-13** split into two doublets at δ 3.73 and 3.84; δ 3.70 and 3.80; δ 3.73 and 3.79, respectively, the difference in chemical shift of the two methyl groups was attributed to a stereogenic center of α -carbon in the molecule.

In most of the compounds with alkyl as R^3 , the signal corresponding to the methylene group (OCH_2CO) between the phenoxy and carbonyl group appeared as a singlet. Noticeably the signal corresponding to the methylene group (CH_2) in some **IG** and **IH** flanked by the phenoxy group and carbonyl group appeared as a quartet. In this case, outside lines were smaller in size, which belonged to the AB system with a difference in chemical shift between the two mutually coupled protons A and B, at δ 4.72 ± 0.08 and 4.73 ± 0.08 in **IG-7** and **IG-8**, at δ 4.94 ± 0.06 and 4.98 ± 0.06 in **IH-4**, respectively. In **IG-7**, the methylene protons (OCH_2CO) were observed at δ 4.67 and 4.71 ppm, respectively, but in the extreme case, when A and B had exactly the same chemical shift, the outside lines disappeared, and the inside lines merged into a singlet. It can be exemplified by **IG-10**,

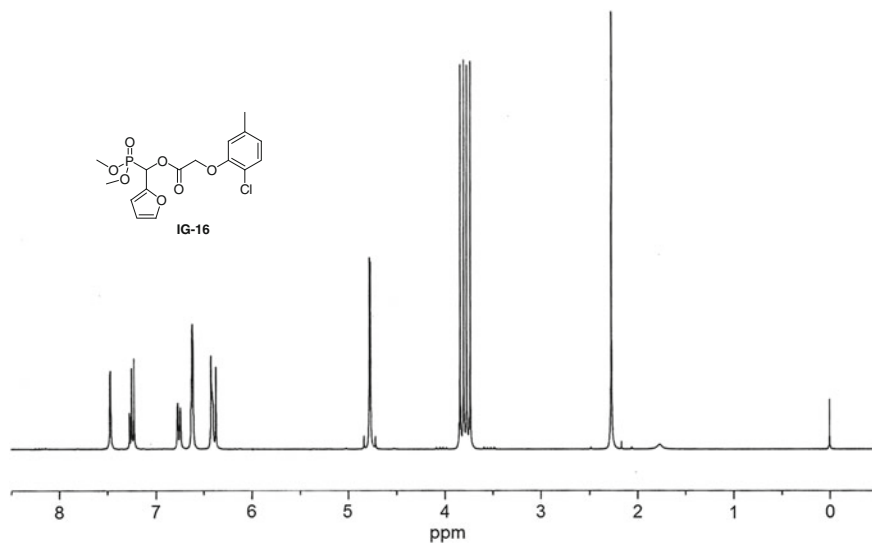


Fig. 2.10 ^1H NMR spectrum of **IG-16** (CDCl_3 , 300 MHz)

IG-16, **IG-22**, and **IH-4**. However, most of **IJ**, the signal of (OCH_2CO) between a phenoxy and carbonyl group appeared as a singlet. ^1H NMR spectra of **IG-16**, **IH-13** and **IJ-13** are shown in Figs. 2.10, 2.11 and 2.12, respectively.

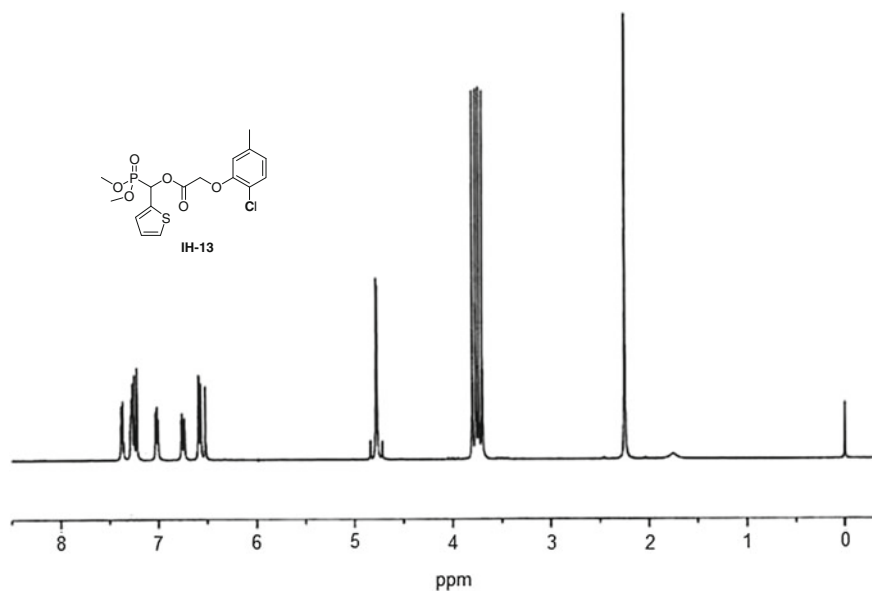


Fig. 2.11 ^1H NMR spectrum of **IH-13** (CDCl_3 , 300 MHz)

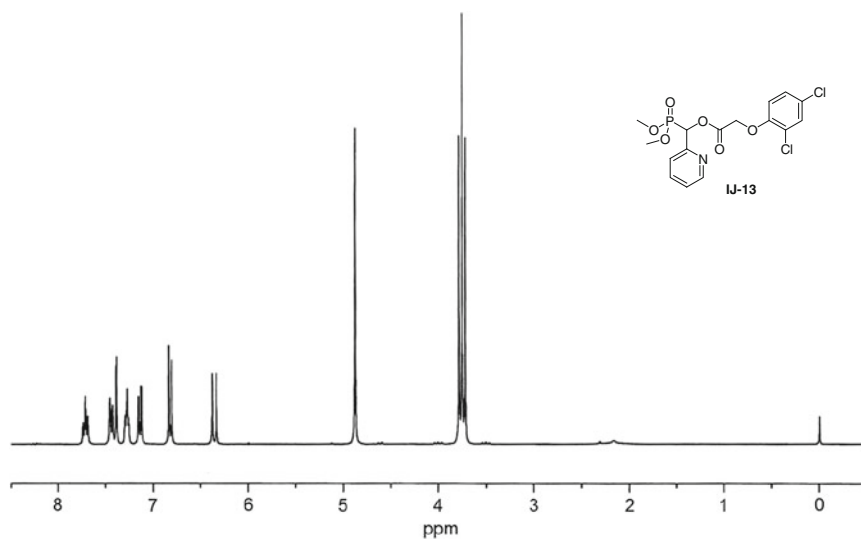


Fig. 2.12 ^1H NMR spectrum of **IJ-13** (CDCl_3 , 300 MHz)

2.2.4 Crystal Structure Analysis of **IH-18** and **IG-21**

2.2.4.1 Crystal Structure Analysis of **IH-18**

The molecular structure of **IH-18** is shown in Fig. 2.13. The packing diagram of the unit cell of **IH-18** is shown in Fig. 2.14. Selected bond lengths and angles are

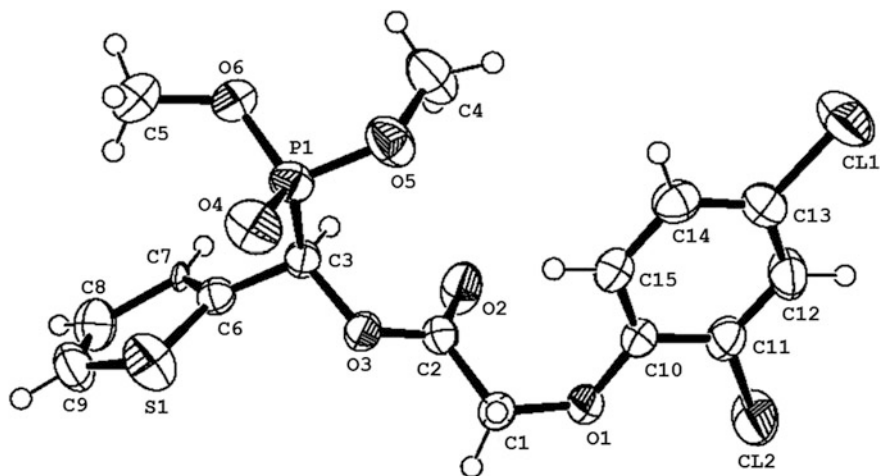


Fig. 2.13 Molecular structure of **IH-18**

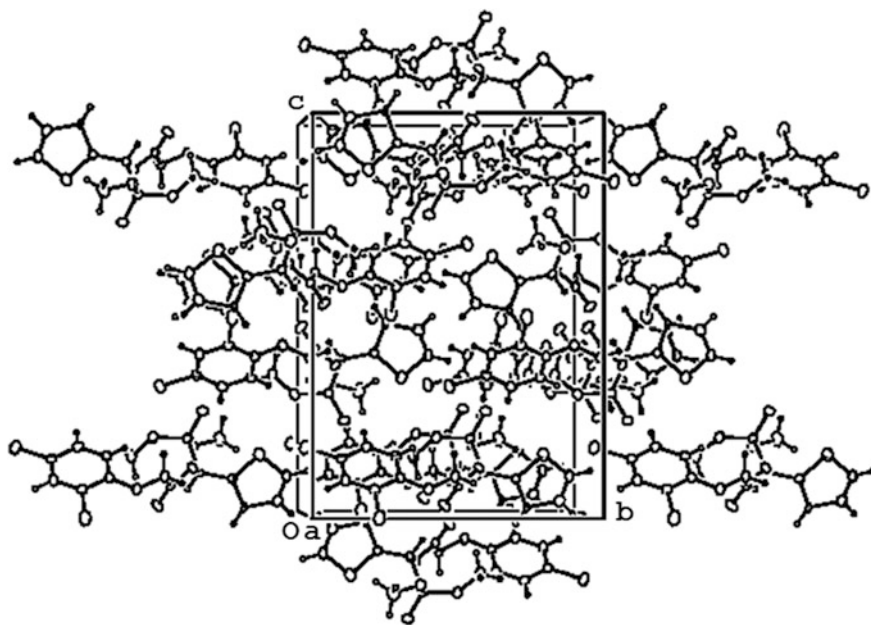


Fig. 2.14 Packing diagram of **IH-18**

presented in Table 2.37. As it can be seen from the X-ray single crystal structure of **IH-18**, all bond lengths and angles show normal values. The P(1)–O(4) bond length of 1.466(4) Å is significantly shorter than the P(1)–O(5) and P(1)–O(6) distances of 1.553(4) and 1.578(4) Å, respectively. O(4)–P(1)–O(5) and O(4)–P(1)–O(6) bond angles of **IH-18** are much larger than the O(5)–P(1)–O(6) bond angle, which indicates the phosphorus adopts a four-coordinate distorted-tetrahedral environment composed by three oxygen atoms and one carbon atom. The benzene and furan rings form a dihedral angle of 73.54°. The title molecule is mainly stabilized by van der Waals' force so that the construction of the single crystal is difficult.

IH-18 was recrystallized from trichloromethane and petroleum ether to give colorless crystals (0.10 mm × 0.25 mm × 0.30 mm) suitable for X-ray single-crystal

Table 2.37 Selected bond distance (Å) and angles (°) for **IH-18**

Bond	Dist.	Bond	Angles deg.
O(4)–P(1)	1.466(4)	C(6)–O(3)–C(3)	117.1(3)
O(5)–P(1)	1.553(4)	C(5)–O(6)–P(1)	121.6(4)
O(6)–C(5)	1.434(7)	O(4)–P(1)–O(5)	112.6(2)
O(6)–P(1)	1.578(4)	O(4)–P(1)–O(6)	116.2(2)
O(2)–C(6)	1.192(5)	O(5)–P(1)–O(6)	104.5(2)
P(1)–C(3)	1.821(4)	O(4)–P(1)–C(3)	113.6(2)

diffraction. The crystal structure of **IH-18** was recorded on a Smart Apex CCD diffractometer using graphite monochromated MoK α radiation ($\lambda = 0.071073$ nm). In the range of $2.32^\circ \leq \theta \leq 25.03^\circ$, 7,622 independent reflections ($R_{\text{int}} = 0.0282$), of which 3,294 contributing reflection had $I > 2\sigma(I)$, and all data were corrected using SADABS program. The structure was solved by direct methods using SHELXS-97; all other calculations were performed with Bruker SAINT system and Bruker SMART programs. All non-hydrogen atoms were refined on F^2 anisotropically using full-matrix least squares method. Hydrogen atoms were observed and refined with a fixed isotropic displacement parameter. Full-matrix least-squares refinement gave final values of $R = 0.0646$, $R_w = 0.1954$. The max and min difference between peaks and holes was 1,281 and -851 e nm $^{-3}$, respectively.

Crystallographic parameters of **IH-18**: $a = 0.8544(3)$, $b = 1.7536(5)$, $c = 1.2620(4)$ nm, $\alpha = 90.000$, $\beta = 98.963(5)$, $\gamma = 90.000(8)$, $V = 1.8678(9)$ nm 3 , $Mr = 425.22$, $Z = 7$, $D_c = 1.512$ mg/m 3 , $\mu = 0.573$ mm $^{-1}$, $F(000) = 872$. The summary of data collection statistics for the X-ray structure of **IH-18** was reported in literature [23].

2.2.4.2 Crystal Structure Analysis of IG-21

The molecular structure of **IG-21** is shown in Fig. 2.15. The packing diagram of the unit cell of **IG-21** is shown in Fig. 2.16. Hydrogen bonds are presented in Table 2.38. The crystal structure belongs to the monoclinic system with space group $P 2_1/c$, $a = 8.5380(7)$ Å, $b = 17.3111(14)$ Å, $c = 12.4003(10)$ Å, $\alpha = 90^\circ$, $\beta = 98.475(1)^\circ$, $\gamma = 90^\circ$, $V = 1812.8(3)$ Å 3 , $Z = 4$, $D_c = 1.499$ mg/m 3 , $\mu = 0.48$ mm $^{-1}$, $F(000) = 840$. It can be seen from the crystal structure, **IG-21** forms a racemate crystal with monoclinic ($P 2_1/c$) symmetry. The benzene and furan rings are non-planar, and the dihedral angle between two rings is $73.54(1)^\circ$. In the crystal structure, weak intermolecular C–H...O hydrogen bonds (Table 2.38) link the

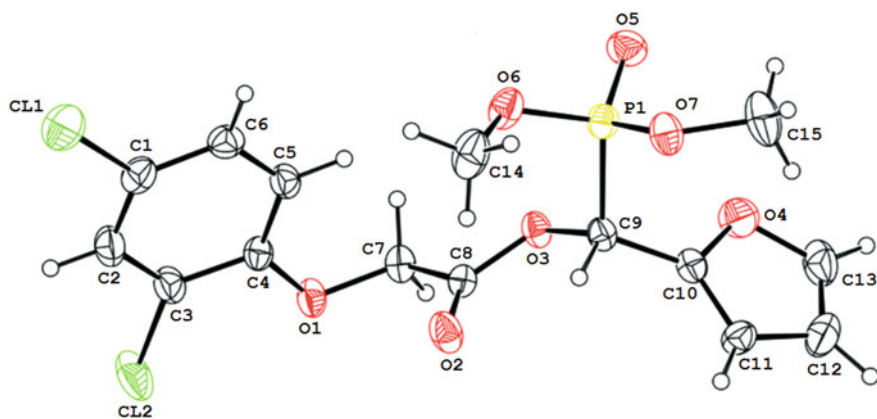
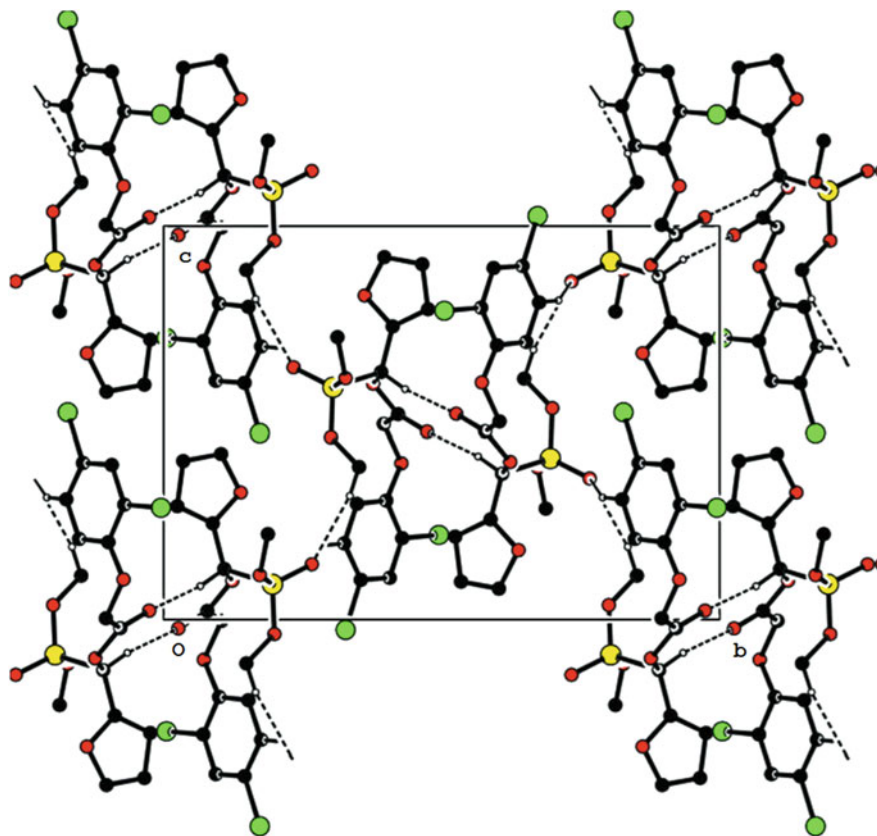


Fig. 2.15 Molecular structure of **IG-21**

Fig. 2.16 Packing diagram of **IG-21**Table 2.38 Hydrogen bonds of **IG-21**

<i>D</i> –H... <i>A</i>	<i>D</i> –H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> –H... <i>A</i>
C(6)–H(6)...O(5) ^a	0.93	2.50	3.322(3)	148
C(9)–H(9)...O(2) ^b	0.98	2.35	3.270(2)	157
O(14)–H(14B)...O(5) ^a	0.96	2.44	3.379(3)	165

Symmetry code: ^a $x, -y + 1/2, z - 1/2$; ^b $-x + 2, -y + 1, -z + 1$

molecules into layers parallel to the (100) plane. Weak C–H... π interaction (C15...Cg1 = 3.690(3) Å, C15–H15...Cg1 = 137°, Cg1 is the centroid defined by atoms O4/C10–C13) is also observed in the crystal structure.

IG-21 was recrystallized from ethyl acetate to give colorless crystals (0.30 mm × 0.20 mm × 0.20 mm) suitable for X-ray single-crystal diffraction. The crystal structure of **IG-21** was recorded on a Smart Apex CCD diffractometer using graphite monochromated MoK α radiation (λ = 0.071073 nm). In the range of

$2.4^{\circ} \leq \theta \leq 28.2^{\circ}$, 4,135 independent reflections ($R_{\text{int}} = 0.048$), of which 3,158 contributing reflection had $I > 2\sigma(I)$, and all data were corrected using SADABS program. The structure was solved by direct methods using SHELXS-97, all other calculations were performed with Bruker SAINT system and Bruker SMART programs. All non-hydrogen atoms were refined on F^2 anisotropically using full-matrix least squares method. Hydrogen atoms were observed and refined with a fixed isotropic displacement parameter. Full-matrix least-squares refinement gave final values of $R = 0.049$, $R_w = 0.133$. The summary of data collection statistics for the X-ray structure of **IG-21** was reported in Ref. [30].

2.2.5 Herbicidal Activity of IG-IJ

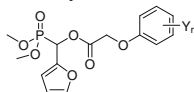
The herbicidal activities of heterocyclylmethylphosphonates **IG-IJ** including **IC-22** were evaluated at a different rate in a set of experiments in the greenhouse. These compounds were first tested at 1.5 kg ai/ha for pre- and post-emergence activity against a range of weed species including rape (*Brassica campestris*), common amaranth (*Amaranthus retroflexus*), clover (*Medicago sativa*), barnyard grass (*Echinochloa Crusgalli*), and crab grass (*Digitaria Sanguinalis*). Post-emergence activity against rape (*Brassica campestris*), chingma abutilon (*Abutilon theophrasti*), common amaranth (*Amaranthus retroflexus*), white eclipta (*Eclipta prostrata*) and giant foxtail (*Setaria faberi*) was further evaluated at 450 or 150 g ai/ha in the greenhouse. The results are listed in Tables 2.39, 2.40, 2.41, 2.42, 2.43, 2.44, 2.45, 2.46 and 2.47. The herbicidal activity of **IG-IJ** including **IC-22** are reviewed as follows.

2.2.5.1 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)-1-(Fur-2-yl)methylphosphonates **IG**

Twenty-three of **IG** were prepared to test their herbicidal activity. The data of herbicidal activity of **IG** are listed in Tables 2.39, 2.40 and 2.41.

Table 2.39 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted

phenoxyacetoxy)-1-(fur-2-yl)methylphosphonates **IG^a**



Compound	Y _n	Pre-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IG-4	3-CF ₃	D	D	D	D	D
IG-6	2-F	D	D	D	D	D
IG-7	3-F	C	D	D	D	D

(continued)

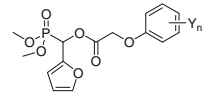
Table 2.39 (continued)

Compound	Y _n	Pre-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IG-8	4-F	B	B	C	D	A
IG-10	4-Cl	A	B	B	B	A
IG-14	2-Me,4-Cl	D	D	C	D	C
IG-15	3-Me,4-Cl	A	C	B	B	B
IG-16	2-Cl,5-Me	D	D	D	D	D
IG-19	2-Cl,4-F	A	A	A	A	A
IG-20	2,3-Cl ₂	D	D	D	D	D
IG-21	2,4-Cl ₂	A	B	A	A	A
IG-22	2,6-Cl ₂	D	D	D	D	D
2,4-D		A	A	A	B	A

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.40 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetox)-1-(fur-2-yl)methylphosphonates IG^a



Compound	Y _n	Post-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IG-4	3-CF ₃	D	D	D	D	D
IG-6	2-F	D	D	D	D	D
IG-7	3-F	D	D	D	D	D
IG-8	4-F	D	C	C	D	C
IG-10	4-Cl	C	C	C	C	C
IG-14	2-Me,4-Cl	C	C	D	D	C
IG-15	3-Me,4-Cl	C	C	C	D	C
IG-16	2-Cl,5-Me	B	D	D	D	D
IG-19	2-Cl,4-F	A	A	A	C	B
IG-20	2,3-Cl ₂	D	D	D	D	D
IG-21	2,4-Cl ₂	A	A	A	D	C
IG-22	2,6-Cl ₂	D	D	D	D	D
2,4-D		A	A	A	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

(A) *Pre-emergence herbicidal activity of IG*

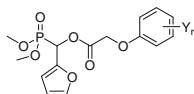
The data in Table 2.39 showed that **IG-19** ($Y_n = 2\text{-Cl}, 4\text{-F}$) and **IG-21** ($Y_n = 2, 4\text{-Cl}_2$) exhibited significant herbicidal activity against dicotyledons and monocotyledons for pre-emergence application comparable to 2,4-D at 1.5 kg ai/ha followed by **IG-10** ($Y_n = 4\text{-Cl}$) and **IG-15** ($Y_n = 3\text{-Me}, 4\text{-Cl}$). However all other compounds showed weak or no herbicidal activity against dicotyledons and monocotyledons for pre-emergence application at 1.5 kg ai/ha.

(B) *Post-emergence herbicidal activity of IG*

The data in Table 2.40 showed that only **IG-19** ($Y_n = 2\text{-Cl}, 4\text{-F}$) and **IG-21** ($Y_n = 2, 4\text{-Cl}_2$) exhibited significant herbicidal activity against dicotyledons for post-emergence application comparable to 2,4-D at 1.5 kg ai/ha. All tested **IG** had no significant herbicidal activity against monocotyledons for post-emergence application.

On the basis of the preliminary bioassay, post-emergence herbicidal activity of most **IG** was further examined at 150 g ai/ha in the greenhouse. The results of post-emergence herbicidal activity against rape, chingma abutilon, common amaranth, and white eclipta are listed in Table 2.41.

Table 2.41 Structure and post-emergence herbicidal activities of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(fur-2-yl)methylphosphonates **IG^a**



Compound	Y_n	Post-emergence			
		Bra ^b	Abu ^b	Amr ^b	Ecl ^b
IG-1	H	28	22	6	31
IG-2	3-Me	37	39	36	30
IG-3	4-Me	36	32	23	30
IG-4	3-CF ₃	0	0	0	0
IG-5	4-CF ₃	0	0	0	0
IG-6	2-F	75	40	60	60
IG-9	2-Cl	40	0	40	30
IG-10	4-Cl	75	75	70	70
IG-11	4-Br	75	40	60	60
IG-12	4-CN	40	40	50	30
IG-13	2,3-Me ₂	40	50	50	30
IG-14	2-Me,4-Cl	85	80	80	60
IG-15	3-Me,4-Cl	80	80	80	75
IG-17	2,4-F ₂	60	40	50	40
IG-18	2-F,4-Cl	75	70	60	70
IG-19	2-Cl,4-F	85	75	90	75
IG-20	2,3-Cl ₂	30	20	25	35

(continued)

Table 2.41 (continued)

Compound	Y _n	Post-emergence			
		Bra ^b	Abu ^b	Amr ^b	Ecl ^b
IG-21	2,4-Cl ₂	95	95	95	90
IG-23	2,4,5-Cl ₃	85	75	75	80
IC-22 (Clacyfos)	2,4-Cl ₂	92	95	91	90
2,4-D		93	93	92	90

^a Inhibitory potency (%) against the plant growth at a rate of 150 g ai/ha in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Bra: rape; Abu: chingma abutilon; Amr: common amaranth; Ecl: white eclipia

It was found that **IG-21** exhibited the best inhibition followed by **IG-19** at 150 g ai/ha. **IG-21** exhibited herbicidal activity comparable to **IC-22** and 2,4-D. **IG-10** (Y_n = 4-Cl), **IG-14** (Y_n = 2-Me,4-Cl), **IG-15** (Y_n = 3-Me,4-Cl), **IG-18** (Y_n = 2-F,4-Cl) and **IG-23** (Y_n = 2,4,5-Cl₃) had medium activity against tested dicotyledons with 60–85 % inhibition. However, other compounds had weak herbicidal activities or were almost inactive at 150 g ai/ha.

(C) SAR analyses for **IG**

IG-21 (Y_n = 2,4-Cl₂) exhibited the best herbicidal activity against dicotyledons for post-emergence application at 150 g ai/ha followed by **IG-19** (Y_n = 2-Cl,4-F).

Compounds **IG** with 2,4,5-Cl₃; 2-Me,4-Cl; 3-Me,4-Cl; 4-Cl and 2-F,4-Cl as Y_n showed modest herbicidal activity. However, **IG** with other groups as Y_n or no substituent on the phenoxy-benzene ring had weak herbicidal activity or almost inactive. Especially, **IG** with 3-CF₃ or 4-CF₃ as Y_n completely lost activity.

The results of SAR analysis for **IG** were similar to those for **IC-IF**, i.e., substituents Y_n on the phenoxy-benzene ring greatly affected the herbicidal activity, and 2- and 4-positions in the phenoxy-benzene ring were the most essential. It showed that the fur-2-yl group was beneficial to herbicidal activity when the compound had Y_n as 2,4-Cl₂ in structure **IG**.

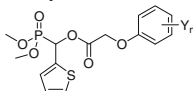
2.2.5.2 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)-1-(Thien-2-yl)Methylphosphonates **IH**

Twenty of **IH** were prepared to test their herbicidal activity. The data of herbicidal activity of **IH** are listed in Tables 2.42, 2.43, 2.44 and 2.45.

(A) Pre-emergence herbicidal activity of **IH**

The data in Table 2.42 showed that **IH-7** (Y_n = 4-Cl), **IH-11** (Y_n = 2-Me,4-Cl), **IH-16** (Y_n = 2-Cl,4-F) and **IH-18** (Y_n = 2,4-Cl₂) exhibited significant herbicidal activities against dicotyledons and monocotyledons for pre-emergence application comparable to 2,4-D followed by **IH-9** (Y_n = 4-CN) and **IH-12** (Y_n = 3-Me,4-Cl)

Table 2.42 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphosphonates **IH^a**

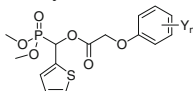


		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IH-1	3-CF ₃	C	B	C	D	B
IH-2	4-CF ₃	D	D	D	D	B
IH-3	2-F	D	D	D	D	D
IH-4	3-F	D	D	D	A	D
IH-5	4-F	B	C	C	C	A
IH-6	2-Cl	D	D	C	D	D
IH-7	4-Cl	A	A	A	B	A
IH-8	4-Br	D	D	D	D	D
IH-9	4-CN	A	A	A	D	D
IH-10	2,3-Me ₂	D	D	D	D	D
IH-11	2-Me,4-Cl	A	A	A	A	A
IH-12	3-Me,4-Cl	B	B	A	C	B
IH-13	2-Cl,5-Me	D	D	D	D	D
IH-16	2-Cl,4-F	A	A	A	A	A
IH-17	2,3-Cl ₂	D	D	D	D	D
IH-18	2,4-Cl ₂	A	A	A	A	A
IH-19	2,6-Cl ₂	D	D	D	D	D
2,4-D		A	A	A	B	A

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.43 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphosphonates **IH^a**



Compound	Y _n	Post-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IH-1	3-CF ₃	B	C	B	D	C
IH-2	4-CF ₃	D	D	D	D	C
IH-3	2-F	D	D	D	D	D
IH-4	3-F	D	D	D	D	D
IH-5	4-F	A	A	C	D	D
IH-6	2-Cl	C	C	D	D	D
IH-7	4-Cl	A	A	A	D	C

(continued)

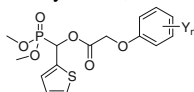
Table 2.43 (continued)

Compound	Y _n	Post-emergence				
		Dicotyledon			Monocotyledon	
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b
IH-8	4-Br	B	D	D	D	D
IH-9	4-CN	A	A	A	D	D
IH-10	2,3-Me ₂	D	D	D	D	C
IH-11	2-Me,4-Cl	A	A	A	C	D
IH-12	3-Me,4-Cl	C	C	D	D	D
IH-13	2-Cl,5-Me	D	D	D	D	C
IH-16	2-Cl,4-F	A	A	A	D	C
IH-17	2,3-Cl ₂	D	D	D	D	D
IH-18	2,4-Cl ₂	A	A	A	C	C
IH-19	2,6-Cl ₂	D	D	D	D	D
IH-20	2,4,5-Cl ₃	A	A	A	C	C
2,4-D		A	A	A	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 1.5 kg ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass

Table 2.44 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(thien-2-yl)methylphosphonates **IH^a**



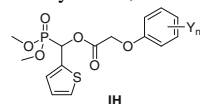
Compound	Y _n	Rate (g ai/ha)	Post-emergence			
			Bra ^b	Abu ^b	Amr ^b	Ecl ^b
IH-6	2-Cl	450	30	40	50	60
IH-7	4-Cl	450	90	85	80	85
IH-8	4-Br	450	75	70	60	70
IH-9	4-CN	450	40	40	40	30
IH-10	2,3-Me ₂	450	0	0	40	0
IH-11	2-Me,4-Cl	450	95	90	100	85
IH-12	3-Me,4-Cl	450	60	60	60	70
IH-14	2,4-F ₂	450	80	75	70	60
IH-15	2-F,4-Cl	450	75	75	75	70
IH-16	2-Cl,4-F	450	95	90	100	90
IH-17	2,3-Cl ₂	450	40	40	60	50
IH-18	2,4-Cl ₂	450	100	100	100	100
IH-20	2,4,5-Cl ₃	450	95	85	90	85
IC-22 (Clacyfos)		450	100	100	100	100

^a Inhibitory potency (%) against the plant growth in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Bra: rape; Abu: chingma abutilon; Amr: common amaranth; Ecl: white eclipta

Table 2.45 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted

phenoxyacetoxy)-1-(thien-2-yl)methylphosphonates **IH**^a



IH

Compound	Y _n	Post-emergence			
		Bra ^b	Abu ^b	Amr ^b	Ecl ^b
IH-1	3-CF ₃	30	20	20	15
IH-2	4-CF ₃	20	15	20	30
IH-6	2-Cl	0	0	0	0
IH-7	4-Cl	70	70	70	70
IH-8	4-Br	70	50	50	60
IH-9	4-CN	30	30	40	0
IH-10	2,3-Me ₂	0	0	40	0
IH-11	2-Me,4-Cl	80	60	80	75
IH-12	3-Me,4-Cl	0	0	50	50
IH-14	2,4-F ₂	70	60	60	60
IH-15	2-F,4-Cl	70	70	70	70
IH-16	2-Cl,4-F	75	71	90	80
IH-17	2,3-Cl ₂	0	0	40	40
IH-18	2,4-Cl ₂	90	90	90	90
IH-20	2,4,5-Cl ₃	80	80	80	80
2,4-D		93	93	92	90
IC-22 (Clacyfos)		92	95	91	90

^a Inhibitory potency (%) against the plant growth at a rate of 150 g ai/ha in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Bra: rape; Abu: chingma abutilon; Amr: common amaranth; Ecl: white eclipta

which only had herbicidal activity against dicotyledons for pre-emergence application at 1.5 kg ai/ha. **IH-11**, **IH-16**, and **IH-18** showed better pre-emergence herbicidal activity against barnyard grass than that of 2,4-D at 1.5 kg ai/ha. All other compounds showed weak or no herbicidal activity against dicotyledons and monocotyledons for pre-emergence application at 1.5 kg ai/ha.

(B) Post-emergence herbicidal activity of **IH**

The data in Table 2.43 showed that **IH-7** (Y_n = 4-Cl), **IH-11** (Y_n = 2-Me,4-Cl), **IH-16** (Y_n = 2-Cl,4-F), **IH-18** (Y_n = 2,4-Cl₂) and **IH-20** (Y_n = 2,4,6-Cl₃) exhibited significant herbicidal activity against dicotyledons for post-emergence application comparable to 2,4-D. All tested **IH** had no significant post-emergence herbicidal activity against monocotyledons at 1.5 kg ai/ha.

On the basis of preliminary bioassay, post-emergence herbicidal activity of most **IH** was further examined at 450 and 150 g ai/ha in the greenhouse. The results of post-emergence herbicidal activity against rape, chingma abutilon, common amaranth, and white eclipta are listed in Tables 2.44 and 2.45. The data in

Table 2.44 show that **IH-7**, **IH-11**, **IH-16**, **IH-18**, and **IH-20** still exhibited significant herbicidal activity against dicotyledons for post-emergence application at 450 g ai/ha.

Only **IH-16**, **IH-18**, and **IH-20** showed >70 % inhibition against dicotyledons for post-emergence at 150 g ai/ha (Table 2.45). **IH-18** had the best herbicidal activity at 150 g ai/ha comparable to **IC-22** and 2,4-D.

(C) SAR analyses for **IH**

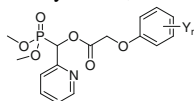
Like the results of SAR analyses for **IG**, substituents Y_n on the benzene ring of the phenoxy moiety greatly affected the activity as well. **IH-18** ($Y_n = 2,4\text{-Cl}_2$) exhibited the best herbicidal activity against dicotyledons for post-emergence at 150 g ai/ha followed by **IH-16** ($Y_n = 2,4,5\text{-Cl}_3$) and **IH-20** ($Y_n = 2\text{-Cl},4\text{-F}$). Compounds **IH** with 3- CF_3 ; 4- CF_3 ; 2- Cl ,4- CN ; 2,3- Me_2 ; 3- Me ,4- Cl and 2,3- Cl_2 as Y_n had only 0–50 % inhibition against tested dicotyledons at 150 g ai/ha. It showed that 2,4- Cl_2 as Y_n was most beneficial to post-emergence herbicidal activity, and the thienyl group was also beneficial to herbicidal activity when the compounds had Y_n as 2,4- Cl_2 in the structure **IH**.

2.2.5.3 Herbicidal Activity of *O,O*-Dimethyl 1-(Substituted Phenoxyacetoxy)-1-(Pyrid-2-yl)methylphosphonates **IJ** in Greenhouse

It was also very interesting to examine the effect on herbicidal activity by the introduction of pyridyl group as R^3 into the structure **IC** to form a new series of **IJ**. In the series of **IJ**, further modification was only focused on substituents Y_n . The data of herbicidal activity of some **IJ** are listed in Tables 2.46 and 2.47.

Table 2.46 Structure and pre-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted

phenoxyacetoxy)-1-(pyrid-2-yl)methylphosphonates **IJ**^a



Compound	Y_n	Pre-emergence					
		Dicotyledon			Monocotyledon		
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b	Sef ^b
IJ-1	3- CF_3	B	C	C	C	C	C
IJ-3	2-F	B	C	B	A	D	A
IJ-5	4-F	A	A	A	B	B	B
IJ-6	4-Cl	A	C	A	C	C	C
IJ-8	3-Me,4-Cl	A	D	B	C	C	C
IJ-9	2-Cl,5-Me	D	D	D	C	D	D
IJ-10	2,4- F_2	D	D	D	D	D	D
IJ-12	2,3- Cl_2	D	D	D	D	D	D

(continued)

Table 2.46 (continued)

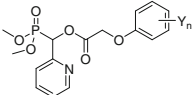
Compound	Y _n	Pre-emergence					
		Dicotyledon			Monocotyledon		
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b	Sef ^b
IJ-13	2,4-Cl ₂	A	B	B	C	B	B
IJ-14	2,6-Cl ₂	D	D	D	D	D	D
2,4-D		A	A	A	C	C	C

^a Inhibitory potency (%) against the growth of plants at a rate of 900 g ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass; Sef: giant foxtail

Table 2.47 Structure and post-emergence herbicidal activity of *O,O*-dimethyl 1-(substituted

phenoxyacetoxy)-1-(pyrid-2-yl)methylphosphonates **IJ^a**



Compound	Y _n	Post-emergence					
		Dicotyledon			Monocotyledon		
		Bra ^b	Amr ^b	Med ^b	Ech ^b	Dig ^b	Sef ^b
IJ-1	3-CF ₃	C	C	C	C	C	B
IJ-3	2-F	A	A	B	B	B	B
IJ-5	4-F	C	C	B	B	B	C
IJ-6	4-Cl	D	D	D	D	D	D
IJ-8	3-Me,4-Cl	C	C	C	D	D	D
IJ-9	2-Cl,5-Me	D	D	D	D	D	D
IJ-10	2,4-F ₂	D	D	D	D	D	D
IJ-12	2,3-Cl ₂	D	D	D	D	D	D
IJ-13	2,4-Cl ₂	A	B	B	C	B	B
IJ-14	2,6-Cl ₂	D	D	D	D	D	D
2,4-D		A	A	A	B	A	C

^a Inhibitory potency (%) against the growth of plants at a rate of 900 g ai/ha in the greenhouse was expressed as four scales—A: 90–100 %, B: 75–89 %, C: 50–74 %, D: <50 %

^b Bra: rape; Amr: common amaranth; Med: clover; Ech: barnyard grass; Dig: crab grass; Sef: giant foxtail

(A) Pre-emergence herbicidal activity of **IJ**

The data in Table 2.46 showed that **IJ-5** (Y_n = 4-F) exhibited pre-emergence activity against dicotyledons comparable to 2,4-D, and better pre-emergence activity against monocotyledons than that of 2,4-D at 900 g ai/ha. **IJ-3** (Y_n = 2-F) and **IJ-13** (Y_n = 2,4-Cl₂) also exhibited better pre-emergence activity against monocotyledons than that of 2,4-D, but weaker pre-emergence activity against dicotyledons than that of 2,4-D. All other compounds showed weak or no herbicidal activity against dicotyledons and monocotyledons for pre-emergence application at 900 g ai/ha.

(B) *Post-emergence herbicidal activity of IJ*

The data in Table 2.47 showed that **IJ-3** ($Y_n = 2\text{-F}$) and **IJ-13** ($Y_n = 2,4\text{-Cl}_2$) exhibited post-emergence herbicidal activity against dicotyledons and monocotyledons at 900 g ai/ha, but a little weaker than that of 2,4-D. Other tested **IJ** had no significant herbicidal activity against dicotyledons and monocotyledons at 900 g ai/ha.

(C) *SAR analyses for IJ*

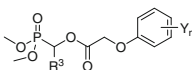
The introduction of apyridyl group as R^3 in **IC** resulted in a decrease in herbicidal activity against dicotyledons for pre-emergence and post-emergence applications even when 2,4- Cl_2 as Y_n . However, **IJ-5** ($Y_n = 4\text{-F}$) exhibited good pre-emergence herbicidal activity against dicotyledons comparable to 2,4-D. **IJ-3** ($Y_n = 2\text{-F}$), **IJ-5** ($Y_n = 4\text{-F}$) and **IJ-13** ($Y_n = 2,4\text{-Cl}_2$) showed better pre-emergence activity against monocotyledons than that of 2,4-D at 900 g ai/ha. These findings showed that **IJ** had a different SAR with **IG** and **IH**.

The results showed that pyridyl group as R^3 was beneficial to the pre-emergence herbicidal activity when 4-F as Y_n . Among the **IJ**, **IJ-5** exhibited the best pre-emergence herbicidal activity at 900 g ai/ha.

2.2.6 Structure-Herbicidal Activity Relationships

Structure-herbicidal activity relationships of **IG**, **IH**, and **IJ** can be summarized as follows: Similarly to the SAR analyses for **IA-IF**, herbicidal activity was highly dependent upon the structure and position of substituents Y_n in the phenoxyacetyl substructure and R^3 .

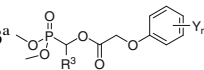
- (A) For post-emergence herbicidal activity: When fur-2-yl or thien-2-yl group as R^3 , 2,4- Cl_2 as Y_n were most beneficial to post-emergence herbicidal activity against dicotyledons, such as **IG-21** and **IH-13**. However when the pyrid-2-yl as R^3 , Compounds with 2-F as Y_n exhibited the best post-emergence herbicidal activity against dicotyledons, such as **IJ-3**, but it was not good as 2,4-D.
- (B) For pre-emergence herbicidal activity: When pyrid-2-yl group as R^3 compounds with 4-F as Y_n exhibited the best pre-emergence herbicidal activity against dicotyledons and monocotyledon, such as **IJ-5** was comparable to or better than 2,4-D at 900 g ai/ha. Whereas when fur-2-yl or thien-2-yl group as R^3 , compounds with 4-F as Y_n showed very weak or lower activity against dicotyledons and monocotyledon, such as **IG-8** and **IH-5**. However **IJ-13** with 2,4- Cl_2 as Y_n exhibited medium herbicidal activity for both pre- and post emergence application, it was not as good as 2,4-D.
- (C) Compounds with 2,3- Cl_2 or 2,6- Cl_2 as Y_n completely lost post-emergence herbicidal activity, irrespective of the fur-2-yl, thien-2-yl or pyrid-2-yl group as R^3 . Pre-emergence and post-emergence herbicidal activity of **IG-21**, **IH-13**,

Table 2.48 Pre-emergence herbicidal activity of **IG-21**, **IH-13**, and **IJ-13**^a

Compound	R ³	Y _n	Pre-emergence					
			Dicotyledon			Monocotyledon		
			Brj ^b	Amr ^b	Che ^b	Ech ^b	Dig ^b	Sef ^b
IG-21	Fur-2-yl	2,4-Cl ₂	60	60	10	0	50	0
IH-13	Thien-2-yl	2,4-Cl ₂	50	50	40	0	50	0
IJ-13	Pyrid-2-yl	2,4-Cl ₂	50	50	40	10	40	0
IC-22 (Clacyfos)	Me	2,4-Cl ₂	70	70	70	0	10	0

^a Inhibitory potency (%) against the growth of plants at a rate of 300 g ai/ha in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Brj: leaf mustard; Amr: common amaranth; Che: goosefoot; Ech: barnyard grass; Dig: crab grass; Sef: giant foxtail

Table 2.49 Post-emergence herbicidal activity of **IG-21**, **IH-13**, and **IJ-13**^a

Compound	R ³	Y _n	Post-emergence					
			Dicotyledon			Monocotyledon		
			Brj ^b	Amr ^b	Che ^b	Ech ^b	Dig ^b	Sef ^b
IG-21	Fur-2-yl	2,4-Cl ₂	100	100	95	40	70	10
IH-13	Thien-2-yl	2,4-Cl ₂	100	100	80	50	50	0
IJ-13	Pyrid-2-yl	2,4-Cl ₂	100	100	85	20	30	0
IC-22 (Clacyfos)	Me	2,4-Cl ₂	100	100	95	20	50	10

^a Inhibitory potency (%) against the growth of plants at a rate of 300 g ai/ha in the greenhouse, 0 (no effect), 100 % (completely kill)

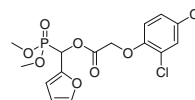
^b Brj: leaf mustard; Amr: common amaranth; Che: goosefoot; Ech: barnyard grass; Dig: crab grass; Sef: giant foxtail

IJ-13, and **IC-22** were further compared at 300 g ai/ha. The results of herbicidal activity against leaf mustard, common amaranth, goosefoot, barnyard grass, crab grass, and giant foxtail are listed in Tables 2.48 and 2.49.

As shown in Tables 2.48 and 2.49, **IG-21** exhibited notable post-emergence herbicidal activity comparable to **IC-22**. Its herbicidal activity seems better than that of **IH-13** and **IJ-13**. Both **IC-22** and **IG-21** would be promising for further development as post-emergence herbicides, and **IG-21** also displayed modest pre-emergence herbicidal activity against dicotyledons.

2.2.7 Herbicidal Activity of **IG-21**

The herbicidal activity and crop selectivity of **IG-21** (code number for development: HWS) were further examined at 1,200–50 g ai/ha. **IG-21** was tested for post-emergence activity against a range of plant species including purslane (*Portulaca oleracea*), slender amaranth (*Amaranthus ascendens*), goosefoot (*Chenopodium album*), spiny amaranth (*Amaranthus spinosus*), sugarbeet (*Beta vulgaris*), maize (*Zea mays*) and rice (*Oryza sativa*). Results are shown in Table 2.50.

Table 2.50 Post-emergence herbicidal activity of **IG-21**^a

Rate (g ai/ha)	Por ^b	Ama ^b	Che ^b	Ams ^b	Bet ^b	Zea ^b	Ory ^b
50	70	100	80	60	80	NT	NT
100	83	100	90	90	80	NT	NT
200	85	100	100	98	98	0	NT
300	91	100	100	98	98	0	0
450	100	100	100	100	100	0	0
900	100	100	100	100	100	0	0
1,200	100	100	100	100	100	10	20

^a Inhibitory potency (%) against the growth of plants in the greenhouse, 0 (no effect), 100 % (completely kill), NT (not tested)

^b Por: purslane; Ama: slender amaranth; Che: goosefoot; Ams: spiny amaranth; Bet: sugarbeet; Zea: maize; Ory: rice

IG-21 exhibited excellent herbicidal activity against broadleaf weeds by post-emergence application. Dicotyledonous crop sugarbeet was susceptible to **IG-21** at 50 or >50 g ai/ha, whereas the monocot crops maize and rice displayed high tolerance to **IG-21** even at the rates of 900–1200 g ai/ha. **IG-21** was safe for maize and rice and was selected for development as a useful selective herbicide for broadleaf weed control in monocot crop fields. Post-emergence herbicidal activity of **IG-21** and **IC-22** was further examined against common amaranth (*Amaranthus retroflexus*), goosefoot (*Chenopodium album*), leaf mustard (*Brassica juncea*), and morning glory (*Ipomoea nil*) compared with 2,4-D and glyphosate at 75–18.75 g ai/ha. Results are shown in Table 2.51.

Table 2.51 Post-emergence herbicidal activity of **IG-21** and **IC-22**^a

Compound	Rate (g ai/ha)	Post-emergence			
		Amr ^b	Che ^b	Brj ^b	Ipo ^b
IG-21	75	95	85	100	100
	37.5	95	80	100	90
	18.75	80	70	100	85
IC-22	75	100	85	100	100
	37.5	100	80	100	100
	18.75	90	70	100	100
2,4-D	75	95	95	100	100
	37.5	90	80	100	100
	18.75	70	75	80	90
glyphosate	75	75	80	80	75
	37.5	60	70	75	60
	18.75	60	50	70	50

^a Inhibitory potency (%) against the growth of plants in the greenhouse, 0 (no effect), 100 % (completely kill)

^b Ama: common amaranth; Che:goosefoot; Bra: leaf mustard; Ipo: morning glory

The effects of **IG-21** and **IC-22** including 30 % HW02 (**IC-22**) EC compared with 2,4-D and glyphosate against leaf mustard and morning glory for post-emergence application at 75 g ai/ha in the greenhouse were shown in Figs. 2.17, 2.18, 2.19 and 2.20.



Fig. 2.17 Effect against leaf mustard for post-emergence application at 75 g ai/ha (after 1 day)



Fig. 2.18 Effect against leaf mustard for post-emergence application at 75 g ai/ha (after 7 days)



Fig. 2.19 Effect against leaf mustard for post-emergence application at 75 g ai/ha (after 20 days)



Fig. 2.20 Effect against morning glory for post-emergence application at 75 g ai/ha (after 20 days)

As shown in Table 2.51 and Figs. 2.17, 2.18, 2.19 and 2.20, both **IG-21** and **IC-22** exhibited good effects against broadleaf weeds by post-emergence application at 75–18.75 g ai/ha. Both **IG-21** and **IC-22** exhibited notable post-emergence herbicidal activity comparable to 2,4-D and glyphosate and they exhibited better effects against tested broadleaf weeds than that of glyphosate at 18.75 g ai/ha.

2.2.8 Summary

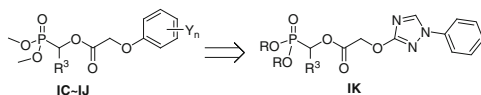
O,O-dialkyl 1-(substituted phenoxyacetoxy)-1-heterocyclylmethyl phosphonates **IG–IJ** including 57 compounds were synthesized by the condensation of *O,O*-dimethyl 1-hydroxy-1-heterocyclylmethylphosphonates **M2** and substituted phenoxyacetyl chlorides **M5** using a weak base.

The *O,O*-dimethyl heterocyclylmethylphosphonates **IG–IJ** with fur-2-yl or thien-2-yl group as R³ and 2,4-Cl₂ as Y_n as well as that with pyrid-2-yl group as R³ and 2-F or 4-F as Y_n were most beneficial to herbicidal activity. *O,O*-Dimethyl 1-(2,4-dichlorophenoxyacetoxy)-1-(fur-2-yl)methylphosphonate **IG-21** was found to be the most effective compound with excellent herbicidal activity against broadleaf weeds at 37.5 g ai/ha. **IG-21** showed a good selectivity and safe for monocotyledonous crops, such as maize and rice even at 0.9–1.2 kg ai/ha. **IG-21** is promising for development as a selective post-emergence herbicide.

2.3 (1-Phenyl-1,2,4-Triazol-3-yloxyacetoxy) Alkylphosphonates **IK**

2.3.1 Introduction

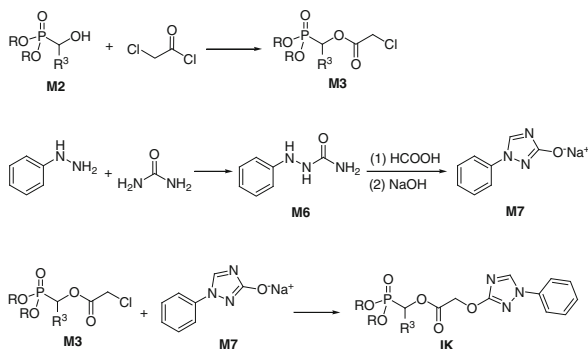
Compounds containing a triazole ring in the molecule are known to display diverse and useful biological properties [31, 32]. Some of them have been developed as fungicides, herbicides or plant growth regulators (PGRs) [33]. We were interested in the synthesis of a novel series of compounds which incorporated a triazole ring into the phenoxyacetoxy moiety in the molecule. A series of *O,O*-dialkyl 1-(1-phenyl-1,2,4-triazol-3-yloxyacetoxy)alkylphosphonates **IK** was thus prepared to examine biological effect by the introduction of a triazole ring into the phenoxyacetoxy moiety in **IC–IJ** (Scheme 2.21). In this section we describe the synthesis and the biological activity of **IK**.



Scheme 2.21 Design of 1-(1-phenyl-1,2,4-triazol-3-yloxyacetoxy)alkylphosphonates **IK**

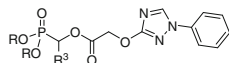
2.3.2 Synthesis of **IK**

IK could be synthesized by the reaction of 1-(chloroacetoxy)alkylphosphonate **M3** with the sodium salt of 1-phenyl-3-hydroxy-1,2,4-triazole **M7** (Scheme 2.22).

**Scheme 2.22** Synthesis of 1-(1-phenyl-1,2,4-triazol-3-yloxyacetoxy)alkylphosphonates **IK**

As shown in Scheme 2.22, phenyl hydrazine reacted with urea to give phenylhydrazide **M6**. Condensation of **M6** with formic acid followed by addition of concentrated sulfuric acid gave 1-phenyl-3-hydroxy-1,2,4-triazole **M6** which was converted to the sodium salt of 1-phenyl-3-hydroxy-1,2,4-triazole **M7**. 1-(Chloroacetoxy)alkylphosphonates **M3** were prepared from *O,O*-dialkyl 1-hydroxyalkylphosphonate **M2** and chloroacetyl chloride in the presence of pyridine. **IK-1–IK-7** in Table 2.52 could be obtained by the reaction of **M7** with **M3** in acetonitrile using tetrabutylammonium bromide as a catalyst. The synthetic procedures of **M3** and **M7** are introduced in the Sects. 9.1.4 and 9.1.8, respectively.

The presence of catalytic tetrabutylammonium bromide was necessary for the reaction of sodium salt of 1-phenyl-3-hydroxy-1,2,4-triazole **M7** with 1-(chloroacetoxy)alkylphosphonates **M3** to get better yields. The experiment also showed that this reaction was affected by reaction temperature, base, and water. We observed that both the carboxylate ester bond and phosphonate ester bond in compounds **M3** or **IK** were easy to cleave by hydrolysis in the presence of base and water at a higher temperature. It was found that the carboxylate ester bond was easier to cleave than the phosphonate ester bond in diethyl phosphonate; however, the phosphonate ester bond was easier to cleave than the carboxylate ester bond in

Table 2.52 Structure of 1-(1-phenyl-1,2,4-triazol-3-yloxyacetoxy)alkylphosphonates **IK**^a

Compound	R	R ³	Compound	R	R ³
IK-1	Me	Ph	IK-5	Me	Et
IK-2	Me	3-NO ₂ Ph	IK-6	Me	<i>n</i> -Pr
IK-3	Me	2-ClPh	IK-7	Et	Ph
IK-4	Me	4-ClPh			

^a Synthesis of **IK-1–IK-7** [34]

dimethyl phosphonate under a harsh reaction condition. In this case the reaction of **M3** and **M7** was rationalized and carried out in dry acetonitrile at 40–50 °C using tetrabutylammonium bromide as a catalyst. Thus **IK-1–IK-7** could be obtained in 66–85 % yields.

The synthestic procedures of **IK-1–IK-7** are introduced in the Sect. 9.1.9. **IK-1–IK-7** were soluble in a variety of organic solvents such as CH₂Cl₂, CHCl₃, benzene, ethyl ether, acetonitrile, ethyl acetate, and so on. They were stable to light and air at room temperature but easy to decompose under the acidic or basic conditions. The structures of **IK-1–IK-7** were characterized by ¹H NMR, IR and confirmed by elementary analysis. The structures of some compounds were also confirmed by mass spectra.

2.3.3 Spectroscopic Analysis of *IK*

All main functional groups were characterized by IR spectra, which showed normal stretching absorption bands indicating the existence of benzen ring (1,460–1,640 cm⁻¹), P–O–C (1,030 and 950 cm⁻¹), and P–C (755–760 cm⁻¹). A strong absorption near 1,760–1,772 cm⁻¹ was identified for absorption C=O. A band near 3,050 cm⁻¹ accounted for C–H stretching of the benzene ring and the triazole ring. A strong band at 2,800–2,900 cm⁻¹ accounted for C–H stretching of the alkyl group. A strong peak near 1,250 cm⁻¹ accounted for P=O in phosphonates. A strong peak near 1,340 cm⁻¹ evidenced for C–N stretching in **IK-1–IK-7**.

EI mass spectra of **IK-1** gave stronger molecular ion peaks. Fragment ions of **IK-1** were consistent with the structure and could be assigned.

In the ¹H NMR spectra of **IK-1–IK-7**, the proton signals of the phenyl-triazol-3-yl group could be observed as follows: one proton in the triazol-3-yl moiety appeared as a multiplet at δ 7.2–7.6 ppm and five protons in the Ph moiety appeared as a multiplet near δ 8.2 ppm. The signal corresponding to the methylene group (OCH₂CO) flanked by the phenoxy group and the carbonyl group appeared as a singlet for **IK-1–IK-7**. Like **IA** and **IB**, the proton signals corresponding to the two methoxy groups attached to phosphorus appeared as two doublets split by the phosphorus nucleus. Two methyl groups in the CH₃CH₂O moiety of **IK-7** displayed as a multiplet, in fact it should be two triplets due to couplings to the CH₂ in the CH₃CH₂O moiety and couplings to the phosphorus. The proton signals corresponding to the group OCHP attached to phosphorus in compounds with Ph or substituted Ph as R³ appeared as a doublet split only by phosphorus nucleus.

However, protons (OCHP) in compounds with Et and *n*-Pr as R³ appeared as multiplets which were split by the effect of the magnetic nucleus from both phosphorus and proton in R³, such as **IK-5** and **IK-6**. The chemical shifts of proton signal in the OCHP could be affected by the structure of R³. For compounds with Et as R³, its signal in the OCHP appeared at δ 5.1–5.4 ppm, while for compounds with Ph or substituted Ph as R³, proton signals in the OCHP appear at 6.2–6.6 ppm. This

indicated that their chemical shifts moved to a lower field due to the effect of the attenuation on magnetic shielding caused by the electronegativity of Ph or substituted Ph.

2.3.4 Herbicidal Activity of **IK**

The herbicidal activity of *O,O*-dialkyl 1-(1-phenyl-1,2,4-triazol-3-yl oxyacetoxy) alkylphosphonates **IK** were evaluated at 2.25 kg ai/ha in the greenhouse. They were tested for pre- and post-emergence inhibitory effects against barnyard grass (*Echinochloa Crusgalli*), crab grass (*Digitaria Sanguinalis*), rape (*Brassica campestris*), setose thistle (*Cirsium japonicum*), cucumber (*Cucumis sativa*), and lettuce (*Lactuca sativa*). However, all of **IK** only showed less than 20 % inhibition against the above tested plants at 2.25 kg ai/ha, but they showed plant growth regulatory activity [34].

2.3.5 Summary

O,O-dialkyl 1-(1-phenyl-1,2,4-triazol-3-yloxyacetoxy)alkylphosphonates **IK** including 7 compounds were synthesized by the reaction of sodium salt of 1-phenyl-3-hydroxy-1,2,4-triazole **M7** with 1-(chloroacetoxy)alkylphosphonates **M3** using tetrabutylammonium bromide as a catalyst in acetonitrile.

All of **IK** showed very weak inhibitory activity (<20 % inhibition) against barnyard grass, crab grass, rape, setose thistle, cucumber, and lettuce for pre-emergence and post-emergence applications. It is noteworthy that there is no substituent on the benzene ring of 1-phenyl-3-hydroxy-1,2,4-triazole moiety in **IK**.

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