1 Overview

1.1 Introduction

1.1.1 Mode of Action of Herbicide
1.1.2 Herbicide Resistance
1.1.3 New Opportunity for Novel Herbicides
1.1.4 Basic Methodology for Discovery of Hit/Lead Compounds

1.2 Pyruvate Dehydrogenase Complex (PDHc)

1.2.1 Function of PDHc
1.2.2 Distribution of PDHc
1.2.3 Plant PDHc E1 as Site of Action of Herbicide

1.3 Progress in the Research of PDHc Inhibitors

1.3.1 OP Compounds as Inhibitors of E. coli PDHc
1.3.2 OP Compounds as Inhibitors of Plant PDHc
1.3.3 Enzyme-Selective Inhibition of OP Compounds

1.4 Design of Novel PDHc E1 Inhibitors as Herbicides

1.4.1 Selecting Plant PDHc E1 as Target of New Herbicide
1.4.2 PDHc E1 Inhibitor Acylphosphonate as Hit Compound
1.4.3 Finding Lead Structure IA
1.4.4 Optimization Strategy

1.5 Book Chapter Organization

References

2 Alkylphosphonates

2.1 (Alkyl or Substituted Phenyl)Methylphosphonates IA–IF

2.1.1 Introduction

2.1.2 Synthesis of O,O-Dialkyl 1-Hydroxyalkylphosphonates M2
2.1.3 Synthesis of Substituted Phenoxyacetic Acids M4 and Substituted Phenoxyacetyl Chlorides M5 49
2.1.4 Synthesis of IA–IF 51
2.1.5 Spectroscopic Analysis of IA–IF 56
2.1.6 Crystal Structure Analysis of IC-7 63
2.1.7 Herbicidal Activity of IA–IF 65
2.1.8 Structure-Herbicidal Activity Relationships 87
2.1.9 Herbicidal Activity of IC-22 89
2.1.10 Summary 90
2.2 Heterocyclylmethylphosphonates IG–IJ 91
2.2.1 Introduction 91
2.2.2 Synthesis of IG–IJ 92
2.2.3 Spectroscopic Analysis of IG–IJ 94
2.2.4 Crystal Structure Analysis of IH-18 and IG-21 98
2.2.5 Herbicidal Activity of IG–IJ 102
2.2.6 Structure-Herbicidal Activity Relationships 111
2.2.7 Herbicidal Activity of IG-21 112
2.2.8 Summary 116
2.3 (1-Phenyl-1,2,4-Triazol-3-yloxyacetoxy) Alkylphosphonates IK 116
2.3.1 Introduction 116
2.3.2 Synthesis of IK 116
2.3.3 Spectroscopic Analysis of IK 118
2.3.4 Herbicidal Activity of IK 119
2.3.5 Summary 119
3 Salts of Alkylphosphonates 123
3.1 Alkali Metal Salts of O-Alkyl Alkylphosphonic Acids IIA–IIE 125
3.1.1 Introduction 125
3.1.2 Synthesis of IIA–IIE 126
3.1.3 Spectroscopic Analysis of IIA–IIE 130
3.1.4 Crystal Structure Analysis of IIB-20 133
3.1.5 Herbicidal Activity of IIA–IIE 133
3.1.6 Summary 149
3.2 Alkali Metal Salts of Alkylphosphonic Acids IIF, IIG and IIH 154
3.2.1 Introduction 154
3.2.2 Synthesis of IIF, IIG and IIH 155
3.2.3 Spectroscopic Analysis of IIF, IIG and IIH 157
3.2.4 Herbicidal Activity of IIF, IIG and IIH 159
3.2.5 Summary 166
References 119
5.2 Cyclic Alkylphosphonates IVC–IVF ........................................... 230
  5.2.1 Introduction ........................................................................ 230
  5.2.2 Synthesis of IVC–IVF ....................................................... 231
  5.2.3 Spectroscopic Analysis of IVC–IVF ................................. 234
  5.2.4 Crystal Structure Analysis of IVC-19 ............................... 239
  5.2.5 Herbicidal Activity of IVC–IVF ........................................ 241
  5.2.6 Summary .......................................................................... 259

5.3 Caged Bicyclic Phosphates IVG and IVH ................................. 261
  5.3.1 Introduction ........................................................................ 261
  5.3.2 Synthesis of IVG and IVH .................................................. 261
  5.3.3 Spectroscopic Analysis of IVG and IVH ............................ 264
  5.3.4 Crystal Structure Analysis of IVG-10 ............................... 266
  5.3.5 Herbicidal Activity of IVG and IVH .................................. 268
  5.3.6 Summary .......................................................................... 273

References .................................................................................. 275

6 Optically Active Alkylphosphonates ........................................ 279
  6.1 Optically Active 1-Hydroxyalkylphosphonates IVB and M2 . 281
    6.1.1 Introduction ....................................................................... 281
    6.1.2 Asymmetric Synthesis of 1-Hydroxyalkylphosphonates
       IVB and M2 via Hydrophosphonylation ................................. 282
    6.1.3 Asymmetric Synthesis of 1-Hydroxyalkylphosphonates
       M2 via Hydroxylation .......................................................... 289
    6.1.4 Summary .......................................................................... 291

  6.2 Optically Active (Substituted Phenyl)methylphosphonates IA,
     IE and IF .............................................................................. 292
    6.2.1 Introduction ....................................................................... 292
    6.2.2 Synthesis of Optically Active IA, IE and IF ..................... 292
    6.2.3 Herbicidal Activity of Optically Active IA,
       IE and IF ............................................................................. 296
    6.2.4 Summary .......................................................................... 308

  6.3 Optically Active Substituted Ethylphosphonates IA and IC ... 310
    6.3.1 Introduction ....................................................................... 310
    6.3.2 Synthesis of Optically Active IA and IC ............................ 310
    6.3.3 Herbicidal Activity of Optically Active IA and IC .......... 314
    6.3.4 Aquatic Toxicity of Optically Active IA and IC ............... 316
    6.3.5 Summary .......................................................................... 318

References .................................................................................. 319
## Biochemical Mechanism of Alkylphosphonates

### 7.1 Molecular Docking and 3D-QSAR Studies

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1.1 Introduction</td>
<td>324</td>
</tr>
<tr>
<td>7.1.2 Binding Conformational Analysis</td>
<td>325</td>
</tr>
<tr>
<td>7.1.3 CoMFA and CoMSIA Analysis</td>
<td>325</td>
</tr>
<tr>
<td>7.1.4 Validation of the 3D-QSAR Models</td>
<td>330</td>
</tr>
<tr>
<td>7.1.5 Molecular Docking</td>
<td>330</td>
</tr>
<tr>
<td>7.1.6 Molecular Alignment and 3D-QSAR Modeling</td>
<td>331</td>
</tr>
<tr>
<td>7.1.7 CoMFA Analysis and CoMSIA Analysis Modeling</td>
<td>331</td>
</tr>
<tr>
<td>7.1.8 PLS Calculations and Validations</td>
<td>334</td>
</tr>
<tr>
<td>7.1.9 Summary</td>
<td>334</td>
</tr>
</tbody>
</table>

### 7.2 Enzyme Inhibition

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2.1 Introduction</td>
<td>335</td>
</tr>
<tr>
<td>7.2.2 Inhibitory Potency Against Plant PDHc</td>
<td>336</td>
</tr>
<tr>
<td>7.2.3 Kinetic Experiment of PDHc</td>
<td>338</td>
</tr>
<tr>
<td>7.2.4 Selective Enzyme Inhibition</td>
<td>339</td>
</tr>
<tr>
<td>7.2.5 Structure-Activity Relationships</td>
<td>341</td>
</tr>
<tr>
<td>7.2.6 Assay of PDHc from Plant</td>
<td>350</td>
</tr>
<tr>
<td>7.2.7 Assay of PDHc from <em>E. coli</em> and Pig Heart</td>
<td>352</td>
</tr>
<tr>
<td>7.2.8 Assay of Other Enzymes</td>
<td>354</td>
</tr>
<tr>
<td>7.2.9 Summary</td>
<td>354</td>
</tr>
</tbody>
</table>

## Evaluation and Application of Clacyfos and HWS

### 8.1 Evaluation of Clacyfos

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1.1 Introduction</td>
<td>359</td>
</tr>
<tr>
<td>8.1.2 Physiochemical Properties</td>
<td>360</td>
</tr>
<tr>
<td>8.1.3 Stability of Clacyfos</td>
<td>361</td>
</tr>
<tr>
<td>8.1.4 Herbicidal Activity in Greenhouse</td>
<td>363</td>
</tr>
<tr>
<td>8.1.5 Systemic Property of Clacyfos</td>
<td>366</td>
</tr>
<tr>
<td>8.1.6 Rainfast Characteristics of Clacyfos</td>
<td>366</td>
</tr>
<tr>
<td>8.1.7 Field Trials of Clacyfos</td>
<td>367</td>
</tr>
<tr>
<td>8.1.8 Toxicity Evaluation</td>
<td>377</td>
</tr>
<tr>
<td>8.1.9 Environmental Fate</td>
<td>378</td>
</tr>
<tr>
<td>8.1.10 Residues</td>
<td>379</td>
</tr>
<tr>
<td>8.1.11 Adsorption of Clacyfos on Soils</td>
<td>379</td>
</tr>
<tr>
<td>8.1.12 Ecological Effects</td>
<td>380</td>
</tr>
<tr>
<td>8.1.13 Summary</td>
<td>380</td>
</tr>
</tbody>
</table>

### 8.2 Evaluation of HWS

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2.1 Introduction</td>
<td>381</td>
</tr>
<tr>
<td>8.2.2 Physiochemical Properties</td>
<td>381</td>
</tr>
<tr>
<td>8.2.3 Herbicidal Activity in Greenhouse</td>
<td>382</td>
</tr>
<tr>
<td>8.2.4 Systemic Property of HWS</td>
<td>385</td>
</tr>
<tr>
<td>8.2.5 Rainfast Characteristics of HWS</td>
<td>385</td>
</tr>
</tbody>
</table>
9 General Methodology ................................................. 391
9.1 General Synthetic Procedure. ................................. 391
9.1.1 Chemicals, Reagents, and Solvents ...................... 391
9.1.2 \( \textit{O,O-Dialkyl Phosphonates M1} \) ....................... 391
9.1.3 \( \textit{O,O-Dialkyl 1-Hydroxyalkylphosphonates M2} \) ....... 392
9.1.4 \( \textit{O,O-Dialkyl 1-(Chloroacetoxy)-Alkylphosphonates M3} \) ... 393
9.1.5 Substituted Phenoxyacetic Acids M4 ..................... 393
9.1.6 Substituted Phenoxyacetyl Chlorides M5 .................. 396
9.1.7 \( \textit{O,O-Dialkyl 1-(Substituted Phenoxyacetoxy)-Alkylphosphonates IA–IJ} \) .... 398
9.1.8 Phenylhydrazinecarboxamide M6 and Sodium Triazol-3-olate M7 ......................................... 405
9.1.9 (1-Phenyl-1,2,4-Triazol-3-yloxyacetoxy)-Alkylphosphonates IK ................... 406
9.1.10 Alkali Metal Salts of \( \textit{O-Alkyl Alkylphosphonic Acids IIA–IIE} \) .................. 407
9.1.11 \( \textit{O,O-Bis(Trimethylsilyl) Alkylphosphonates M8 and Alkylphosphonic Acids M9} \) .... 410
9.1.12 Alkali Metal Salts of Alkylphosphonic Acids II F–II H ................. 411
9.1.13 \( t\)-Butylaminium Salts of Alkylphosphonates II J ............ 413
9.1.14 Dichloro(Methyl)Phosphine M10 .......................... 414
9.1.15 \( \textit{O-Methyl Methylphosphinate M11} \) .................. 415
9.1.16 \( \textit{O-Methyl (1-Hydroxyalkyl)Methylphosphinates M12} \) ........... 415
9.1.17 Alkylphosphinates IIIA–IIIG .............................. 416
9.1.18 Sodium Salts of Alkylphosphinic Acids III H .................. 419
9.1.19 3-Hydroxy-5-Methylisoxazole Derivatives M13–M16 .................... 420
9.1.20 \( \textit{O-Methyl [1-(5-Methylisoxazol-3-yloxyacetoxy)-Alkyl]Methylphosphinates IIIJ} \) .... 421
9.1.21 1-Phenyl-2,2-Dimethyl-1,3-Propanediol M17 .................. 422
9.1.22 Cyclic Phosphonates M18 .................................. 423
9.1.23 Cyclic 1-Hydroxyalkylphosphonates IVA and IV B .................. 423
9.1.24 Substituted Phenoxypropionic Acids M19 .................. 425
9.1.25 Substituted Phenoxypropionyl Chlorides M20 .............. 425
9.1.26 Cyclic Alkylphosphonates IVC–IVF ........................ 426
9.1.27 4-(Hydroxymethyl)-2,6,7-Trioxa-1-Phosphabicyclo-
[2.2.2]Octane-1-One/Thione M21/M22 .......................... 429
9.1.28 Caged Bicyclic Phosphates IVG and IVH .............. 429
9.1.29 Optically Active Cyclic 1-Hydroxyalkylphosphonates
IVB ................................................................. 431
9.1.30 O,O-Diethyl (Substituted Benzyl)Phosphonates
M23 ................................................................. 432
9.1.31 Optically Active 1-Hydroxyalkylphosphonates M2 ... 433
9.1.32 Optically Active (Substituted Phenyl)-
Methylphosphonates IA, IE, and IF ......................... 435
9.1.33 1-Keto Phosphonates M24 and Vinylphosphonates
M25 ................................................................. 437
9.1.34 Optically Active 1-Substituted Ethylphosphonates
IA and IC .......................................................... 441
9.2 General Information of Structural Characterization .... 442
9.3 Herbicidal Activity Assay .................................. 443
9.3.1 Test in Petri Dishes ..................................... 444
9.3.2 Test in Greenhouse ..................................... 445
References ......................................................... 446

Index .............................................................. 449