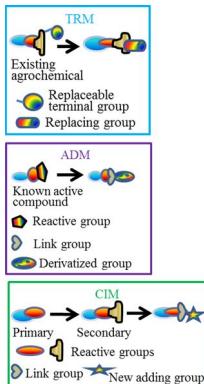


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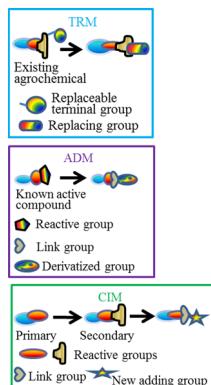
Application of the Intermediate Derivatization Approach in Agrochemical Discovery

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1. INTRODUCTION

1.1. Agrochemical Discovery

Agrochemicals, including insecticides/acaricides, herbicides, and fungicides, play an important role in modern agriculture by increasing both crop quality and yield while reducing labor costs in major crops such as rice, corn, fruits, and vegetables.¹ To meet the increasing demand for food supply due to a growing population as well as increasingly stringent regulatory

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80 requirements for protecting the environment and ensuring food
81 safety, new agrochemicals that are more efficacious, and possess
82 novel modes of action and better safety profiles are
83 continuously sought.^{1a,2} Typically, a novel agrochemical is
84 invented initially by the discovery of a bioactive lead compound
85 through chemical synthesis followed by modification of the
86 chemical structure and optimization of the biological activity;
87 selection of the commercial candidate may involve consid-
88 eration of cost, efficacy, selectivity, and safety factors.³ This
89 approach requires an integrated multidisciplinary team of
90 chemists, chemical engineers, computational chemists, toxicol-
91 ogists, and biologists to work closely together.⁴ However, a
92 downward trend in agrochemical discovery is occurring.
93 Because of continually increasing requirements that new
94 agrochemicals must meet to be successful, the typical discovery
95 process is significantly longer, while the success rate for
96 commercial development is declining. As a result of this trend,
97 the financial investment required for the discovery of a new
98 agrochemical discovery is significantly greater.⁵ Thus, it is
99 important for sustainability of the agrochemical industry that
100 improved approaches to the discovery of new agrochemicals are
101 developed.^{4,5}

102 Usually, new agrochemicals may be obtained by following up
103 an initial bioactive lead compound. The methods for
104 discovering agrochemical lead compounds may be classified
105 as^{5c,6} Random Synthesis and Screening,^{6a,7} Modification of
106 Natural Compounds,^{5,8} "Me Too Chemistry" (molecules with
107 similar structures to existing products),⁹ Combinatorial
108 Chemistry,¹⁰ and Rational Design.^{6a,11} Statistical data of
109 agrochemical discovery methods show that Random Synthesis
110 and Screening and "Me Too Chemistry" have been the two
111 most successful approaches for new product discovery.⁷ For
112 example, chlorosulfuron, diflufenican, and flonicamid were
113 discovered by Random Synthesis and Screening, whereas
114 haloxyfop, pyraoxystrobin, and thiamethoxam were discovered
115 via "Me Too Chemistry". However, these two discovery
116 methods require more substantial resources in the form of
117 manpower, funding, and time, and their success rates for
118 discovery of new agrochemicals are declining, although they are
119 still better than the other methods mentioned above. Recently,
120 novel approaches, such as Chemical Genetics,^{2b,12} Fragment-
121 based or Molecule-based Design,¹³ Target-oriented Synthesis
122 (TOS), and Diversity-oriented Synthesis (DOS),¹⁴ for lead
123 discovery have been proposed in the pharmaceutical field.
124 However, these approaches have not yet been proven successful
125 in the discovery of new pharmaceuticals or agrochemicals.^{11e}
126 Additionally, due to increasing competition in a mature
127 market and a heightened awareness of competitors' activities,
128 many companies are strengthening their intellectual property
129 assets, particularly for their promising development candidates.
130 These factors make it more difficult for companies to discover
131 new agrochemicals by capitalizing on gaps in their competitors'
132 patents. This situation places enormous pressure on researchers
133 to remain competitive by exploring innovative approaches that
134 can reduce the investment cost and maximize the return for
135 their discovery efforts. Furthermore, it is necessary to shorten
136 the time of research phases to be able to respond quickly to
137 changing market demands. Overall, in the discovery of
138 biological active compounds, the conventional methods
139 described above lack the required efficiency for sustained
140 success, and the recent novel methods that have been reported
141 in pharmaceutical field have not yet been successful for
142 discovering agrochemicals. Therefore, a more practically useful

143 and efficient strategy for discovering novel bioactive com-
144 pounds with excellent marketable potential is needed. We had
145 introduced improved methods for the discovery of new
146 agrochemicals, which we called Intermediate Derivatization
147 Methods (IDMs), in our previous reports.^{7b,15} In this Review,
148 we describe each of the methods and provide numerous
149 examples demonstrating their application.

1.2. Description of Intermediate Derivatization Methods for Agrochemical Discovery

The IDM approach to agrochemical discovery may be
151 considered to fit between the conventional methods used in
152 agrochemical discovery and the recent novel methods reported
153 in the pharmaceutical field. The basic idea behind IDM is to
154 apply a wide variety of synthetic methodology on key
155 intermediates resulting in an efficient route to innovative
156 chemical structures, which, in conjunction with biological
157 screening, become patentable leads or target compounds. There
158 are three types of IDMs depending mainly on the functionality
159 in the key intermediate:

- Common Intermediate Method (CIM): modification of
key intermediates used as building blocks that possess
functionality amenable to preparing a diverse set of
structures, for example, derivatization of β -keto esters
- Terminal Group Replacement Method (TRM): mod-
ification of key intermediates that possess functionality
amenable to replacing terminal moieties of existing
agrochemicals, for example, replacement of the o-
chlorophenyl terminal group of chlorsulfuron with varied
structures
- Active compound Derivatization Method (ADM): mod-
ification of known active compounds possessing
functionality amenable to derivatization, for example,
derivatization of the carbofuran amide group

The Common Intermediate Method (CIM) may be used to
175 synthesize new compounds by applying various chemical
176 reactions starting with intermediates that have been used to
177 prepare known agrochemicals, pharmaceuticals, or natural
178 products. These intermediates are often commercially available
179 on a large scale and therefore readily available. The key to the
180 success of this method is to apply new chemical reactions or
181 new synthesis routes to obtain novel structures that are totally
182 different from previously known agrochemicals, pharmaceut-
183 icals, or natural products. These newly synthesized compounds
184 can be screened and each optimized to obtain new lead
185 compounds, ultimately leading to the discovery of new
186 agrochemicals. In contrast with the conventional methods
187 described previously, CIM is mainly based on suitably
188 functionalized and commercially available chemical intermedi-
189 ates rather than based on random design. Therefore, this
190 strategy increases the efficiency of reaching commercialization
191 by simplifying the research stage and reducing the cost of
192 development.

The Terminal Group Replacement Method (TRM) focuses
194 on novel key intermediates that have the potential to replace
195 terminal moieties of known agrochemicals, pharmaceuticals, or
196 natural products. These unique intermediates are synthesized
197 through chemical reactions starting from raw chemicals. These
198 structurally de novo compounds are further optimized to obtain
199 new lead compounds and develop novel products with 200
excellent bioactivity. The concept is designed to directly
201 mimic known bioactive molecules via a similar strategy used in
202 the "Me Too Chemistry" or Bioisosterism approach but with a
203

204 greater emphasis on the role of the key intermediates. In this
205 way, the bioactivity of the original compounds may be
206 maintained or improved, resulting in a high success rate of
207 discovering patentable structures.

208 Active compound Derivatization Method (ADM) uses
209 agrochemicals, or noncommercial compounds with known
210 biological activity, as intermediates and transforms them into
211 novel bioactive molecules through various chemical reactions.
212 Typically, the agrochemical products used as intermediates
213 have been on the decline and/or possess low biological activity,
214 high toxicity, or some other drawback. Biological screening and
215 optimization of the leads generated by this method result in the
216 discovery of new crop protection products. It should also be
217 mentioned that these new compounds do not necessarily
218 possess the same biological activity spectrum as the
219 intermediates from which they are derived.

220 The purpose of IDM is to enhance the efficiency of
221 discovering lead compounds through the synthesis of key
222 intermediates via the application of developed and advanced
223 organic reactions.¹⁶ IDM focuses on the strategic role of key
224 intermediates in the discovery and development of new
225 agrochemicals. In this regard, the IDM approach differs
226 somewhat from that of other existing discovery methods. It
227 has been demonstrated that lead compounds can be derived
228 from the selected raw materials via a variety of organic
229 reactions, followed by optimization using bioisosteric replace-
230 ment and other common modification methods. By particularly
231 focusing on key intermediates, IDM encompasses novel
232 chemistry as well as “Me Too Chemistry” to discover new
233 agrochemicals with improved biological activity while providing
234 the required proprietary intellectual property. The success of
235 the IDM approach depends on key participation of organic
236 chemists in the entire process of the bioactive compound
237 discovery, although scientists with strong backgrounds in other
238 areas are also absolutely needed.

239 It is well-known that the discovery of patentable compounds
240 with promising biological activity is the most important goal of
241 the R&D section in any agrochemical or drug development
242 company. By analyzing the discovery process of known
243 agrochemicals and reviewing their synthetic approaches, we
244 have identified IDM, a unique development approach to
245 discover novel biologically active compounds. We have
246 practically applied this approach in our discovery program at
247 Shenyang Research Institute of Chemical Industry (SYRICI)
248 and concluded that this approach is fast, efficient, straightfor-
249 ward, and logically fluent. Finding suitable intermediates is key
250 to the success of IDM. As compared to the current methods of
251 discovering lead compounds, there are several advantages of
252 IDM regarding structure innovation and the ability to obtain
253 international and domestic patents. IDM covers both lead
254 discovery and lead optimization and holds great potential for
255 discovering patentable compounds. IDM is an improvement on
256 the classical lead discovery approaches such as Random
257 Synthesis and Screening and “Me Too Chemistry”, which
258 typically use “active group combination” and “bioisosterism”
259 strategies, respectively.^{7b,17} In fact, “active group combination”,
260 which largely relies on the finding of novel active substructures,
261 was an efficient approach 20 years ago, but now it is not very
262 successful because it has become more difficult to discover
263 patentable and highly active compounds in this way. Although
264 “Me Too Chemistry” has been successfully used in the past,
265 currently most of the possible structural analogues of a new
266 agrochemical suggested by bioisosterism have been patented by

267 its primary inventors, leaving little room for further 268 modifications by other researchers. Therefore, it is more 269 difficult to discover novel compounds with improved bioactivity 270 beyond the claims of patents in prior arts by utilizing 271 conventional bioisosterism replacement. 271

272 Combinatorial chemistry had flourished for quite a while in 273 the 1990s. This novel technique applied the solid-phase 274 synthesis used in polymer chemistry and was expected to 275 improve the efficiency and innovation of biologically active 276 compound discovery. However, the number of quality leads 277 found by this method has been disappointing as indicated by a 278 follow-up survey.¹⁸ The compounds resulting from early 279 combinatorial libraries did not meet their designer’s expect- 280 ations. The problem seemed to stem from limitations in use of 281 solid-phase polymers, which were lacking in diversity of 282 functional groups in each set, thus limiting the diversity of 283 the resultant chemical entities. 283

284 Modification of natural compounds also had led to many 285 excellent agrochemical discoveries, but the limited number and 286 variety of commercial natural products has made modification 287 of these compounds more difficult to achieve. It is well-known 288 that isolation of the active components of a complex mixture of 289 compounds in a natural source is a daunting task. One of the 290 challenges encountered when attempting the purification of a 291 natural source is that changes or usually loss of the original 292 biological activity often occur after multiple rounds of 293 extractions and chromatography. The pure compounds isolated 294 from the plants or other natural sources are often either 295 biologically inactive or much less active than original mixtures. 296 In addition, characterization of a complex natural compound 297 structure itself can be a laborious and challenging task. 297

298 Rational design or molecule design based on structure 299 including fragment-based or molecule-based design for lead 300 discovery relies largely on advances in the fields of biochemistry 301 and computer science. As far as we are aware, there have not 302 been any significant examples of agrochemicals discovered 303 using these approaches since the 1980s.^{11e} 303

304 At first glance, there appear to be similarities between CIM 304 and Random Synthesis and Screening, between TRM and 305 isosterisms, and between ADM and “Me Too Chemistry” 306 approaches. However, upon close examination, there are key 307 differences among these approaches. CIM is similar to Random 308 Synthesis and Screening from the perspective of the entire 309 process, but the key intermediates used in CIM are selected on 310 the basis of the presence of appropriate functionality that 311 permits the synthesis of a diverse set of structures, while 312 Random Synthesis or Screening may use any possibly available 313 starting compounds. TRM seems to be similar to bioisosterism; 314 however, in TRM the terminal group may be replaced with 315 groups that not necessarily similar in size and therefore go 316 beyond the strict definition of bioisosters. In contrast with “Me 317 Too Chemistry”, which simply attempts to mimic active 318 molecules, ADM generates innovative structures by performing 319 chemical reactions on reactive groups in known agrochemicals. 320

321 Novel drug development concepts such as chemical genetics, 321 DOS, and TOS, etc., have boomed recently in the 322 pharmaceutical field. Chemical genetics, based on modern 323 solid-phase synthesis, has been adopted by the scientific 324 community for drug design. Chemical genetics has not yet 325 been found to be successfully applied in agrochemical 326 discovery. DOS is a new term for a method of library 327 construction in chemical genetics. It has attracted attention in 328 drug discovery for its great potential in generating valuable lead 329

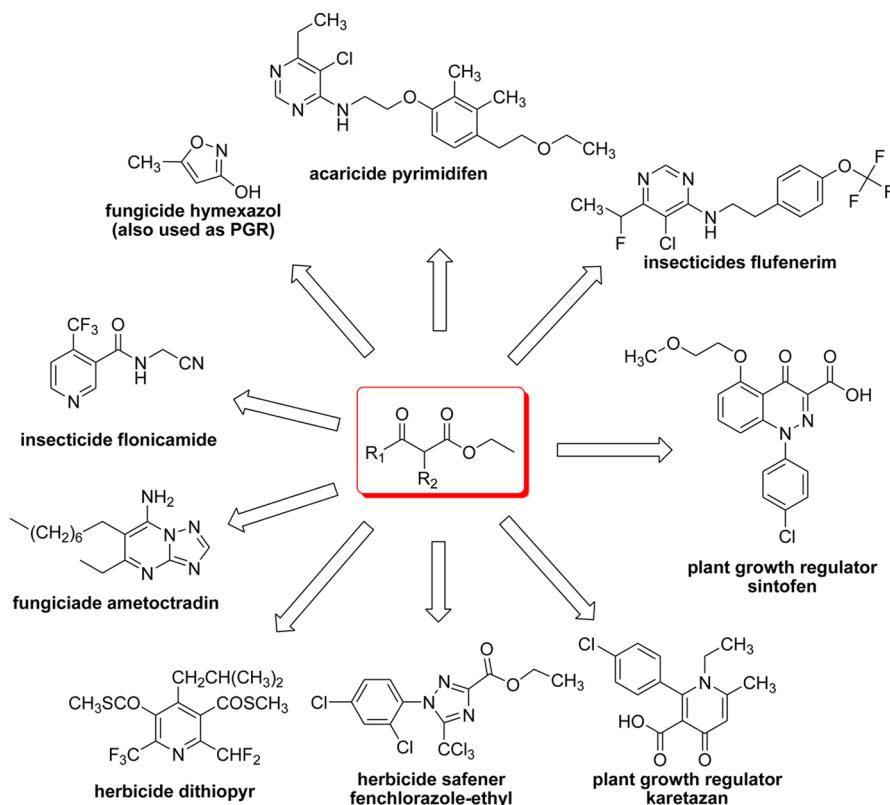


Figure 1. Some agrochemicals synthesized by derivatization of a common intermediate.

discoveries. However, this method has largely failed to deliver the promised drugs so far. TOS shows a clear picture of the preselected target protein structures and final chemical structures being designed. The chemical structures are either in silico predicted or rationally designed. Theoretically, this method should deliver a better success rate for lead discovery because it uses a rational design. However, as is evident from the above discussion, the efficiency of the non-IDM methods to discover biological active compounds has greatly diminished. Only when new lead compounds with novel structures have been discovered would other optimization methods including bioisosteric replacement be useful in designing new agrochemicals; in other words, it is very difficult to find new patentable agrochemicals using current methods.

2. APPLICATION OF THE INTERMEDIATE DERIVATIZATION APPROACH IN AGROCHEMICAL DISCOVERY

The success of IDM depends on the exploitation of key intermediates to generate agrochemical leads. Rapid biological screening is necessary to expedite the identification of new lead molecules. New compounds could be obtained by chemical synthesis or by exploiting other approaches such as fermentation or biological catalysis. Differences among the three methods, CIM, TRM, and ADM, exist with respect to the complexity of the key intermediate and the time period required to progress from the initial to the optimal compound. The shorter time period for reaching the successful compound also is key to patentability. The greatest opportunity to discover compounds with novel structures should be attributed to CIM, but usually this method also takes the greatest effort; TRM and ADM generally focus on new compounds with structures similar to known ones but with improved bioactivity, although

novel compounds may also be discovered. The combination of TRM and ADM significantly contributes to innovation in chemical structures as well.

Comparing the success rate for the three methods by the length of time required to discover a successful product, we estimate that TRM and ADM require a shorter time to achieve the final target compound than does CIM. For example, for developing and developed products at SYRICI, which are described in the following sections, a few hundred analogues were synthesized within 2–3 years using TRM and ADM to complete the optimization of the lead compounds with very high success rates. In the case of CIM, it is expected that the time required to discover the initial lead compound, which relies largely on chance or serendipity, may vary greatly from one project to the next, and this uncertainty would impact the time required to discover a successful product.

The selection of starting material plays a critical role in the successful application of IDM. With an appropriate starting point, use of IDM can significantly improve the discovery process for highly active compounds leading to greater success. A useful strategy involves selecting an appropriate starting material from naturally occurring small molecules with known biological properties or from existing agrochemical and/or pharmaceutical products.

In the following sections, we provide examples of the successful application of IDM in the discovery and development of new agrochemicals.

2.1. Common Intermediate Method (CIM)

As we described above, CIM focuses a modification of key intermediates possessing functionality amenable to preparing a diverse set of structures. Through analyzing and summarizing the discovery of the commercial agrochemicals, we found that

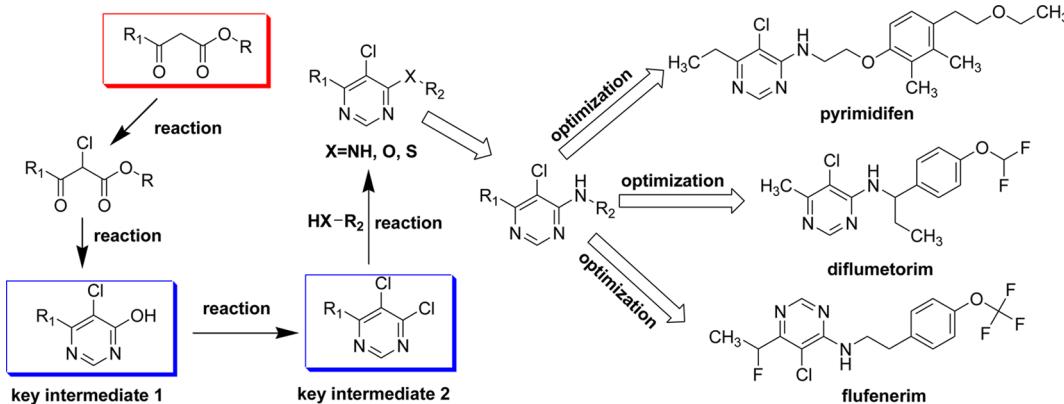


Figure 2. Discovery of pyrimidifen, diflumetorim, and flufenirim.

there are many instances in which substituted β -keto esters were used as starting materials, indicating that the substituted β -keto esters are common intermediates in the synthesis of a wide variety of agrochemicals. Other common intermediates to commercial agrochemicals include substituted pyridines such as 2,3-dichloro-5-(trifluoromethyl)pyridine,¹⁹ 2-chloronicotinic acid,^{19b,20} substituted benzoic acid,²¹ substituted aniline,²² etc. Substituted β -keto esters can be used to react with many other types of intermediates, including amidines, hydroxylamines, 2-cyanoacetamides, benzoyl chlorides, 1-(phenyl)ethanones, hydrazines, and aldehydes, to afford a diverse set of commercially unavailable intermediates, which upon further reaction yield new target compounds. Therefore, substituted β -keto esters possess the functionality required to synthesize a diverse set of structures leading to novel agrochemicals with excellent biological activity via CIM. Figure 1 demonstrates the range of commercial agrochemicals that have been developed from β -keto esters using this strategy.

In sections 2.1.1–2.1.8, we provide detailed examples of the application of CIM in the discovery of agrochemicals using substituted β -keto esters.

2.1.1. Discovery of Pyrimidifen, Diflumetorim, and Flufenirim. In Figure 2, we present synthetic routes to three commercial agrochemicals starting from substituted β -keto esters. Key intermediate 2 was obtained via chlorination of key intermediate 1 using phosphoryl trichloride, which was in turn prepared from substituted α -chloro- β -keto esters. We could classify substituted β -keto esters as primary key intermediates and intermediates 1 and 2 as secondary key intermediates.²³ 2 then was further reacted with other available intermediates containing reactive groups such as hydroxyl, primary or secondary amine, hydrazinyl, thiol, etc., to obtain new derivatives that were analyzed and summarized by bioassays to discover substituted pyrimidinamine compounds with promising bioactivity. Thus, by nucleophilic substitution, a series of pyrimidinamine analogues were synthesized from 2 reacting with various substituted amines. Following additional rounds of bioactive screening and/or chemical structure optimization, flufenirim, diflumetorim, and pyrimidifen were obtained.^{24–26} These three compounds have excellent acaricidal/insecticidal, fungicidal, and insecticidal activity, respectively.

Pyrimidifen is the first commercial pyrimidinamine acaricide/insecticide developed by Sankyo Co., Ltd. and UBE Industries in 1995 with high activity against all stages of spider mites on apples, pears, vegetables, and tea, spider mites and rust mites on

citrus fruit, and diamond-back moth on vegetables.²⁷ Diflumetorim invented by UBE Industries and developed in cooperation with Nissan Chemical Industries Ltd.,²⁸ the second commercialized compound in this series, can control powdery mildew and rust on ornamentals. Flufenirim, the third developed pyrimidinamine compound, is structurally similar to pyrimidifen. This compound was found by UBE Industries via chemical modifications as well as biological screening.²⁹ Interestingly, this compound has a surprising insecticidal activity mainly against aphids and plant hoppers with unknown mode of action.²⁹ These products are evidence that similar

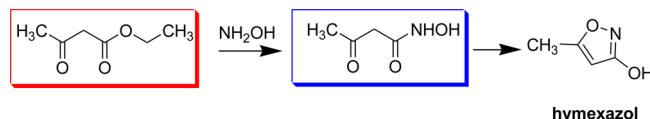


Figure 3. Discovery of hymexazol.

chemical structures do not necessarily possess similar biological properties.

2.1.2. Discovery of Hymexazol. In Figure 3, we present the synthetic route to the fungicide hymexazol starting from a β -keto ester. Ethyl 3-oxobutanoate (ethyl acetoacetate) was reacted with hydroxylamine to yield the amide derivative followed by cyclization reaction to afford the target product hymexazol.³⁰

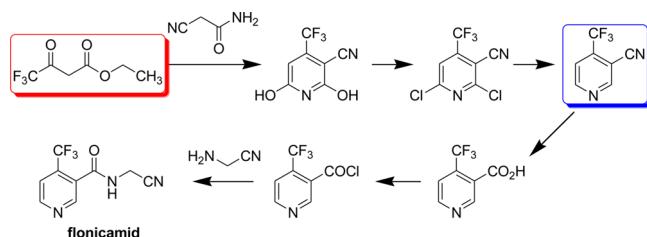


Figure 4. Discovery of flonicamid.

Hymexazol was developed by Sankyo Co., Ltd. in 1970, and it is a systemic fungicide that also exhibits some plant growth stimulation activity with no toxicity to soil microorganisms.³¹

2.1.3. Discovery of Flonicamid. In Figure 4, we present the synthetic route to the insecticide flonicamid starting from a β -keto ester. The highlighted key intermediate

463 (trifluoromethyl)nicotinonitrile, to flonicamid, was prepared
 464 from ethyl 4,4,4-trifluoro-3-oxobutanoate and 2-cyanoaceta-
 465 mide by cyclization, chlorination, and hydrodechlorination
 466 reactions. Further reaction through hydrolysis to the carboxylic
 467 acid, conversion to the acid chloride, and then condensation
 468 with aminoacetonitrile yielded the target compound flonica-
 469 mid.³² It is clear that a diversity of chemical reactions has been
 470 applied to obtain this final product. In this case, 4-
 471 (trifluoromethyl)nicotinonitrile could be classified as a
 472 secondary key intermediate as well.

473 Flonicamid discovered by Ishihara Sangyo Kaisha, Ltd. is a
 474 selective aphicide with systemic, translaminar activity, gives
 475 long-term control, and is effective against some other sucking
 476 insects. It is worthwhile to note that flonicamid appears to

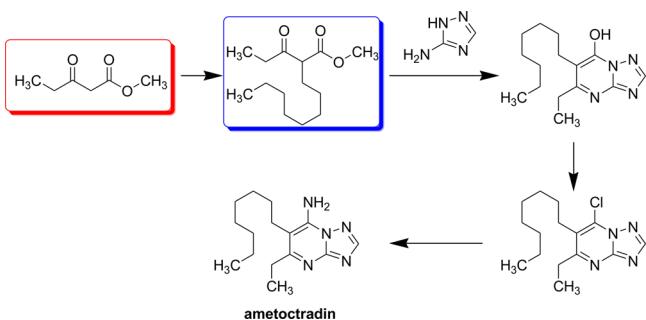


Figure 5. Discovery of ametoctradin.

477 possess a novel mode of action that is differentiated from other
 478 insecticides commonly used.³³ However, it has been shown that
 479 flonicamid targets the insect potassium A-type channel.^{33h}

480 **2.1.4. Discovery of Ametoctradin.** In Figure 5, we
 481 present the synthetic route to the fungicide ametoctradin
 482 starting from a β -keto ester. Methyl 3-oxopentanoate was
 483 alkylated to yield the highlighted octyl derivative, followed by
 484 condensation with 2H-1,2,4-triazol-3-amine, chlorination, and
 485 aminated to afford the target ametoctradin.³⁴

486 Ametoctradin is a mitochondrial respiration inhibitor acting
 487 at Complex III with high fungicidal activity against all major
 488 Oomycete diseases, for example, downy mildew (*Plasmopara*

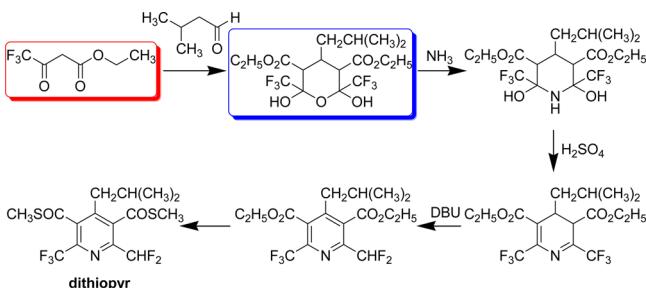


Figure 6. Discovery of dithiopyr.

489 *viticola*) in grapes and late blight (*Phytophthora infestans*) in
 490 potatoes and tomatoes and late blights in vegetables (e.g.,
 491 cucurbits, brassicas, onions, and lettuce).³⁵

492 **2.1.5. Discovery of Dithiopyr.** In Figure 6, we present the
 493 synthetic route to the herbicide dithiopyr starting from a β -keto
 494 ester. Ethyl 4,4,4-trifluoro-3-oxobutanoate was reacted with 3-
 495 methylbutyraldehyde to yield the highlighted pyran derivative
 496 followed by amination to the piperidine derivative, and then by
 497 dehydration and dehydrofluorination to the pyridine-3,5-

498 dicarboxylate, and finally conversion to the thioester target
 499 dithiopyr.³⁶

500 Dithiopyr is a herbicide discovered by Monsanto Co.,
 501 developed by Rohm & Haas (now Dow AgroSciences LLC),
 502 which is applied to pre-emergence and early postemergence

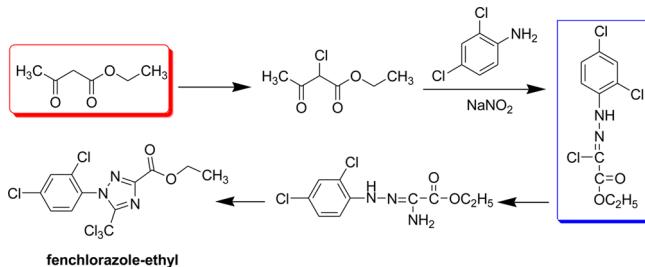


Figure 7. Discovery of fenchlorazole-ethyl.

503 control annual grass and broad-leaved weeds in turf by
 504 inhibiting cell division via disrupting spindle microtubule
 505 formation.³⁷

506 **2.1.6. Discovery of Fenchlorazole-ethyl.** In Figure 7, we
 507 present the synthetic route to the herbicide safener
 508 fenchlorazole-ethyl starting from a β -keto ester. Ethyl 3-
 509 oxobutanoate (ethyl acetoacetate) was chlorinated and then
 510 reacted with the aryl diazonium chloride to yield the highlighted
 511 intermediate, which was aminated and then reacted with
 512 trichloroacetyl chloride to provide the target fenchlorazole-
 513 ethyl.³⁸

514 Biologically different from the products synthesized from β -
 515 keto esters mentioned before, fenchlorazole-ethyl is used as a
 516 safener for herbicide fenoxaprop-ethyl or fenoxaprop-P-ethyl in

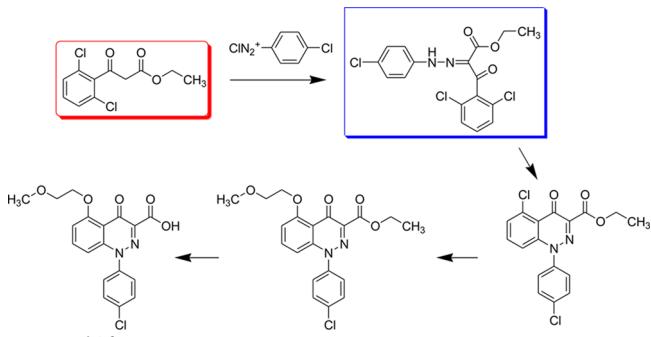


Figure 8. Discovery of sintofen.

517 postemergence control of grass weeds in wheat, durum wheat,
 518 rye, and triticale by combination with the grass herbicide
 519 fenoxaprop-ethyl or fenoxaprop-P-ethyl.³⁹

520 **2.1.7. Discovery of Sintofen.** In Figure 8, we present the
 521 synthetic route to the plant growth regulator sintofen starting
 522 from a β -keto ester, ethyl 3-(2,6-dichlorophenyl)-3-oxopropo-
 523 noate, being reacted with an aryl diazonium chloride to obtain
 524 the highlighted intermediate, and then cyclization, substitution
 525 with 2-methoxyethanol, and hydrolysis were carried out to
 526 achieve the target sintofen.⁴⁰

527 Sintofen is used as a hybridizing agent, for sterilizing spring
 528 and winter wheat.⁴¹

529 **2.1.8. Discovery of Karetazan.** In Figure 9, we present the
 530 synthetic route to the plant growth regulator karetazan starting
 531 from a β -keto ester. The condensation of ethyl 3-(4-
 532 chlorophenyl)-3-oxopropanoate with ethyl amine led to the

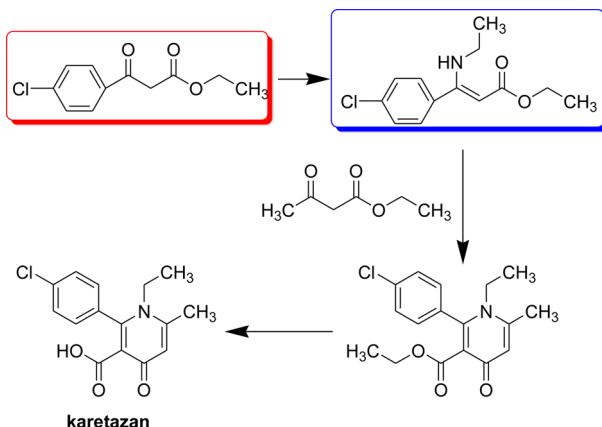


Figure 9. Discovery of karetazan.

2.2. Terminal Group Replacement Method (TRM)

Many successful crop protection products have been discovered by replacing groups situated on the ends of known active molecules. For example, new sulfonylurea herbicides were obtained by replacement of the terminal groups in chlorosulfuron, new aryloxyphenoxypropionic acid herbicides by replacement of terminal groups in diclofop, and new methoxyacrylate fungicides or acaricides by replacement of terminal groups of azoxystrobin or kresoxim-methyl.⁴³ In sections 2.2.1–2.2.4, we provide detailed examples of the application of TRM in the discovery of new agrochemicals starting from existing active leads. Recently, the TRM has been widely applied at SYRICI of China as described separately in section 3.1.

2.2.1. Discovery of Sulfonylurea Herbicides. In Figure 10, we present the range of sulfonylurea herbicides prepared by replacing the terminal groups (2-chlorophenyl and triazine) of the highlighted sulfonylurea chlorosulfuron. Chemical Abstracts Service registry numbers were added as an indicator of relative order of discovery with the most recently discovered compounds represented by the largest CAS number. Chlorosulfuron was the first commercial sulfonylurea herbicide introduced in the U.S. in 1982 by DuPont Co.⁴⁴ On the basis of this structure, many sulfonylurea herbicides were discovered and developed mainly by replacement of the terminal phenyl

highlighted intermediate, which was reacted with ethyl 3-oxobutanoate to obtain the cyclized compound, then hydrolyzed to form the target compound karetazan.⁴²

Utilization of β -keto esters twice makes the synthesis of karetazan different from other products described above. Karetazan is a plant growth regulator used in corn as a chemical hybridizing substance.

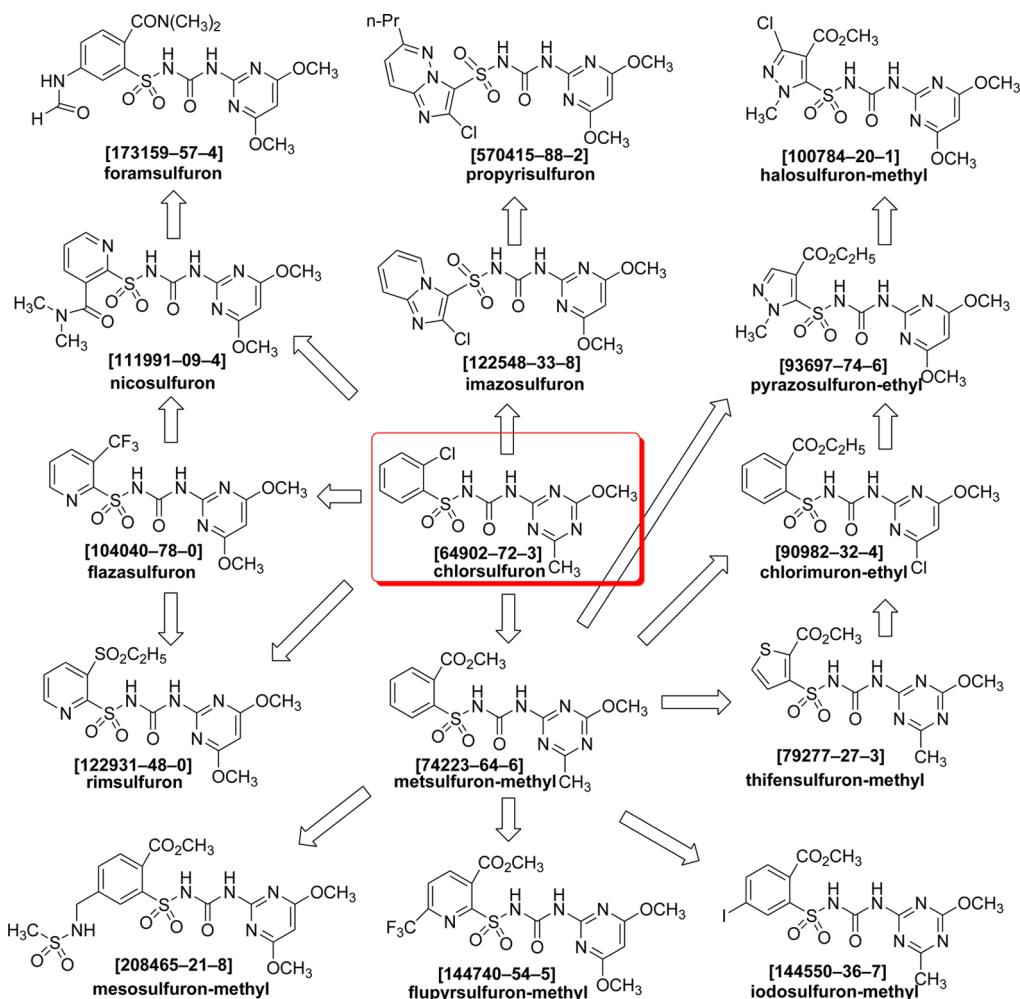
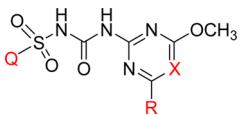


Figure 10. Discovery of sulfonylurea herbicides.

Table 1. Replacement of Terminal Groups in Sulfonyleurea Herbicides

Name	CAS No.	Q-	X	-R
chlorsulfuron	64902-72-3		N	CH ₃
metsulfuron-methyl	74223-64-6		N	CH ₃
iodosulfuron-methyl	144550-36-7		N	CH ₃
thifensulfuron-methyl	79277-27-3		N	CH ₃
chlorimuron-ethyl	90982-32-4		CH	Cl
mesosulfuron-methyl	208465-21-8		CH	OCH ₃
fluprysulfuron-methyl	144740-54-5		CH	OCH ₃
imazosulfuron	122548-33-8		CH	OCH ₃
pyrazosulfuron-ethyl	93697-74-6		CH	OCH ₃
propyrisulfuron	570415-88-2		CH	OCH ₃
flazasulfuron	104040-78-0		CH	OCH ₃
nicosulfuron	111991-09-4		CH	OCH ₃
foramsulfuron	173159-57-4		CH	OCH ₃
rimsulfuron	122931-48-0		CH	OCH ₃
halosulfuron-methyl	100784-20-1		CH	OCH ₃

⁵⁶⁴ ring as well as triazinyl ring.⁴⁵ Three examples in which the ⁵⁶⁵ phenyl ring alone was replaced and 11 examples in which both ⁵⁶⁶ the phenyl and the triazine rings were replaced are presented as ⁵⁶⁷ a tabular comparison of replacement structures in Table 1 and ⁵⁶⁸ discussed below.

2.2.1.1. Replacement of 2-Chlorophenyl Terminal Group. ⁵⁶⁹

Metsulfuron-methyl: Replacement of –Cl on the phenyl ring of ⁵⁷⁰ chlorsulfuron with –CO₂CH₃ led to metsulfuron-methyl, which ⁵⁷¹ showed good control of a wide range of grass and broad-leaved ⁵⁷² weeds in wheat, barley, rice, oats, and triticale by ⁵⁷³ postemergence application.⁴⁶ However, this modification did ⁵⁷⁴ not improve its safety to succeeding crops due to its long ⁵⁷⁵ residue time in soil.⁵⁷⁶

Iodosulfuron-methyl: Modification of metsulfuron-methyl by ⁵⁷⁷ introducing iodine gave iodosulfuron-methyl showing superior ⁵⁷⁸ safety to succeeding cereal crops such as wheat, durum wheat, ⁵⁷⁹ and rye.⁴⁷⁵⁸⁰

Thifensulfuron-methyl: When the phenyl ring of chlorsulfur- ⁵⁸¹ on was replaced by thiophene to form thifensulfuron-methyl, or ⁵⁸² modification of metsulfuron-methyl by replacing the phenyl ⁵⁸³ ring with a thiophene ring to give thifensulfuron-methyl, it ⁵⁸⁴ showed excellent safety to corn and soybean besides wheat ⁵⁸⁵ crops.^{45d,48}⁵⁸⁶

2.2.1.2. Replacement of Both 2-Chlorophenyl and Triazine Terminal Groups. **2.2.1.2.1. Chlorimuron-ethyl.** Replacement ⁵⁸⁷ of the triazine ring of metsulfuron-methyl with a pyrimidine ⁵⁸⁸ ring led to chlorimuron-ethyl, or replacing –Cl on phenyl ring ⁵⁸⁹ of chlorsulfuron with –CO₂C₂H₅ and the triazine ring of ⁵⁹¹ chlorsulfuron with a pyrimidine ring gave chlorimuron-ethyl, ⁵⁹² which is a postemergence herbicide used for control of ⁵⁹³ important broad-leaved weeds, such as cockleburs, pigweed, ⁵⁹⁴ sunflower, and annual morning glory, in soya beans and ⁵⁹⁵ peanuts.^{45e,49}⁵⁹⁶

2.2.1.2.2. Mesosulfuron-methyl, Fluprysulfuron-methyl.⁵⁹⁷ Modification of metsulfuron-methyl by replacing the triazine ⁵⁹⁸ ring with a pyrimidine ring and introducing a methylsulfonyl- ⁵⁹⁹ laminomethyl group on the phenyl ring gave mesosulfuron- ⁶⁰⁰ methyl. Modification of metsulfuron-methyl by replacing the ⁶⁰¹ triazine ring with a pyrimidine ring and replacing the phenyl ⁶⁰² ring with a pyridine ring produced fluprysulfuron-methyl.⁶⁰³ Mesosulfuron-methyl and fluprysulfuron-methyl are effective ⁶⁰⁴ herbicides in cereals such as wheat field.^{45f,i-k} For example, ⁶⁰⁵ fluprysulfuron-methyl-sodium is a selective herbicide for ⁶⁰⁶ postemergence controlling grass (primarily black-grass) and ⁶⁰⁷ broad-leaved weeds in cereals with excellent safety on ⁶⁰⁸ succeeding crops due to its fast degradation speed.⁵⁰⁶⁰⁹

2.2.1.2.3. Imazosulfuron, Pyrazosulfuron-ethyl, and Propyrisulfuron. Modification of chlorsulfuron by replacement of ⁶¹⁰ the phenyl ring by an imidazopyridine ring and the triazine ring ⁶¹¹ by a pyrimidine ring gave imazosulfuron. Modification of ⁶¹² chlorsulfuron by replacing the triazine ring with a pyrimidine ⁶¹⁴ ring and replacing the phenyl ring with a pyrazole ring ⁶¹⁵ generated pyrazosulfuron-ethyl. Modification of chlorsulfuron ⁶¹⁶ by replacing the triazine ring with a pyrimidine ring and ⁶¹⁷ replacing the phenyl ring with a imidazopyridazine ring ⁶¹⁸ generated propyrisulfuron (another way to describe the TRM ⁶¹⁹ is modification of imazosulfuron by replacing the imidazopyr- ⁶²⁰ idine ring with a imidazopyridazine ring generated propyr- ⁶²¹ isulfuron). Imazosulfuron, pyrazosulfuron-ethyl, and propyr- ⁶²² isulfuron are all good herbicides used in rice field.^{45f-h}⁶²³ Imazosulfuron, developed by Takeda Chemical Industries ⁶²⁴ Ltd. (now Sumitomo Chemical Company Ltd.) in 1994, and ⁶²⁵ pyrazosulfuron-ethyl, introduced by Nissan Chemical Industries ⁶²⁶ Ltd. in 1990, both provide pre- or postemergence control of ⁶²⁷ annual and perennial broad-leaved weeds and sedges also in ⁶²⁸ wet-sown and transplanted rice crops with no damage to rice in ⁶²⁹ normal use.^{51,52} Another herbicide used for rice with innovative ⁶³⁰ structure is propyrisulfuron launched in Japan in 2011. Its ⁶³¹

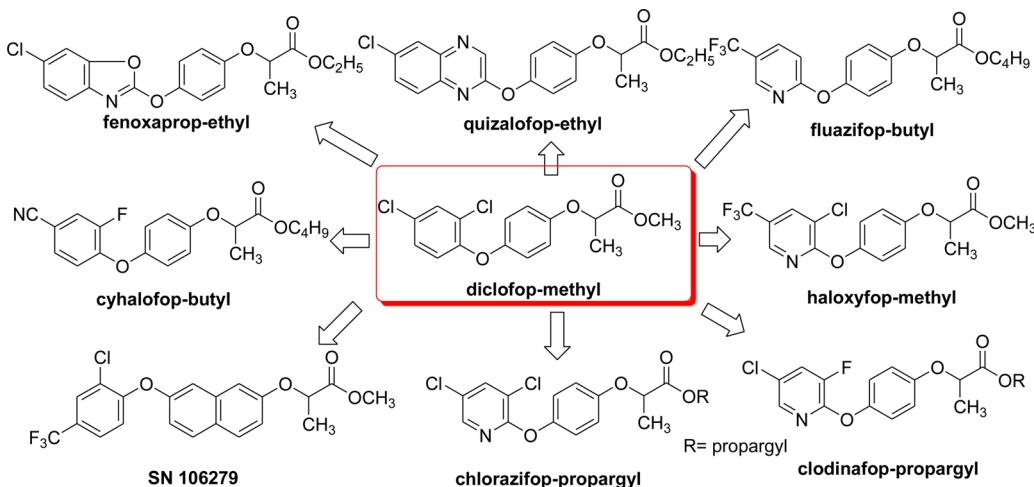


Figure 11. Discovery of aryloxyphenoxypropionic acid herbicides.

632 structure is very similar to that of imazosulfuron, but
633 propyrisulfuron has an advantage over imazosulfuron by
634 providing excellent herbicidal activity against weeds that show
635 resistance to other commercialized sulfonylurea herbicides.⁵³
636 **2.2.1.2.4. Flazasulfuron.** Modification of chlorsulfuron by
637 replacement of the phenyl ring by a pyridine ring and the
638 triazine ring by a pyrimidine ring gave flazasulfuron.
639 Flazasulfuron is mainly used for pre- and postemergence
640 control of grass and broad-leaved weeds and sedges in warm-
641 season turf.^{19a,54} Halosulfuron-methyl, another herbicide, is
642 used in turf as well.⁵⁵

643 **2.2.1.2.5. Nicosulfuron, Foramsulfuron, Rimsulfuron, and**
644 **Halosulfuron-methyl.** Modification of chlorsulfuron by re-
645 placement of the phenyl ring by a pyridine ring and the triazine
646 ring by a pyrimidine ring gave nicosulfuron (another way to
647 describe the TRM is modification of flazasulfuron by replacing
648 the $-CF_3$ group with a $-CON(CH_3)_2$ group gave nicosulfur-
649 on).

650 Modification of chlorsulfuron by replacement of the phenyl
651 ring by a pyridine ring and the triazine ring by a pyrimidine ring
652 gave rimsulfuron (another way to describe the TRM is
653 modification of flazasulfuron by replacing the $-CF_3$ group
654 with a $-SO_2C_2H_5$ group gave rimsulfuron).

655 Modification of chlorsulfuron by replacement of the 2-chloro
656 substituent on the phenyl ring by 5-formamido-2-dimethylcar-
657 bamoyl substituents and the triazine ring by a pyrimidine ring
658 gave foramsulfuron (another way to describe the TRM is
659 modification of nicosulfuron by replacing the 3-
660 (dimethylcarbamoyl)pyridine-2-yl group with a 5-(dimethyl-
661 carbamoyl)-2-formamidophenyl group gave rimsulfuron).

662 Modification of chlorsulfuron by replacing the triazine ring
663 with a pyrimidine ring and replacing the phenyl ring with a
664 pyrazole ring generated halosulfuron-methyl (another way to
665 describe the TRM is modification of pyrazosulfuron-ethyl by
666 introducing a chlorine atom on the pyrazole ring and replacing
667 the $CO_2C_2H_5$ group with a CO_2CH_3 group to give
668 halosulfuron-methyl).

669 Nicosulfuron, foramsulfuron, rimsulfuron, and halosulfuron-
670 methyl are all used in maize. Nicosulfuron is a selective
671 postemergence herbicide, developed by Ishihara Sangyo Kaisha,
672 Ltd. to control annual grass weeds, broad-leaved weeds, and
673 perennials.⁵⁶ Rimsulfuron, which was introduced by DuPont
674 Co. and first marketed in Europe in 1991, displays good safety
675 on maize, especially spring maize with no effect on succeeding

676 crops. Rimsulfuron is applied postemergence to effectively 677 control most annual and perennial grasses and several broad- 677 leaved weeds in maize.⁵⁷ It is also used in tomatoes and 678 potatoes. Foramsulfuron, another herbicide applied in maize, 679 was first synthesized in 1995 and developed by Aventis 680 CropScience (now Bayer AG) for postemergence control of 681 grasses and broad-leaved weeds.⁵⁸ When mixed with 682 iodosulfuron-methyl-sodium, the broad-leaved weed spectrum 683 is enhanced. The active ingredient is usually used in 684 combination with the safener isoxadifen-ethyl. Halosulfuron- 685 methyl, which differs from pyrazosulfuron-ethyl only in 686 possessing a chlorine atom on the pyrazole ring and a methyl 687 ester group in place of the ethyl ester group on the pyrazole 688 ring, has application to a wider range of crops for the 689 f11 postemergence control of annual broad-leaved weeds and 690 nutsedge species, in maize, sugar cane, rice, sorghum, nuts, and 691 turf,^{45f,h,55} illustrating the potential advantages of small changes 692 in structure. 693

2.2.2. Discovery of Aryloxyphenoxypropionic Acid 694
Herbicides. In Figure 11, we present a range of 695 f11 aryloxyphenoxypropionic acid herbicides prepared by replacing 696 the terminal groups (2,4-dichlorophenoxy group and carbon 697 chain in ester group) of the highlighted herbicide diclofop- 698 methyl. After the first aryloxyphenoxypropionic acid herbicide, 699 diclofop-methyl, was released,⁵⁹ many herbicides having the 700 same scaffold structure were discovered by employing the 701 t2 terminal group replacement approach.⁶⁰ Two examples in 702 which only the 2,4-dichlorophenoxy group of diclofop-methyl 703 was replaced and six examples in which both the 2,4- 704 dichlorophenoxy group and the carbon chain in the ester of 705 diclofop-methyl were replaced are presented as a tabular 706 comparison of replacement structures in Table 2 and discussed 707 t2 below. 708

2.2.2.1. Replacement of 2,4-Dichlorophenoxy Terminal 709
Group. **2.2.2.1.1. Haloxifop-methyl.** Replacement of the 2,4- 710 dichlorophenoxy group in diclofop-methyl with a 3-chloro-5- 711 trifluoromethyl-2-pyridinyloxy group gave haloxifop-methyl.⁶¹ 712

2.2.2.1.2. SN 106279. Replacement of the 2,4-dichlorophe- 713 noxy group in diclofop-methyl with a 2-chloro-4-trifluorome- 714 thylphenoxy group gave SN 106279.⁶² 715

2.2.2.2. Replacement of Both 2,4-Dichlorophenoxy Group 716
and Carbon Chain in the Ester Terminal Goup. 717
2.2.2.2.1. Chlorazifop-propargyl. Replacement of the 2,4- 718 dichlorophenoxy group in diclofop-methyl with a 3,5-dichloro- 719

Table 2. Replacement of Terminal Groups in Aryloxyphenoxypropionic Acid Herbicides

Name	CAS No.	Q-	-R
diclofop-methyl	51388-27-3		CH ₃
haloxyfop-methyl	69806-40-2		CH ₃
SN 106279	103055-25-0		CH ₃
chlorazifop-propargyl	74267-69-9		CH ₂ C≡CH
fenoxaprop-ethyl	82110-72-3		C ₂ H ₅
quizalofop-ethyl	76578-14-8		C ₂ H ₅
cyhalofop-butyl	122008-85-9		C ₄ H ₉ -n
fluazifop-butyl	69335-91-7		C ₄ H ₉ -n
clodinafop-propargyl	105512-06-9		CH ₂ C≡CH

2-pyridinyloxy group and a two-carbon with a triple bond extension of the carbon chain in the ester of diclofop-methyl gave chlorazifop-propargyl.⁶³

2.2.2.2. Fenoxaprop-ethyl. Replacement of the 2,4-dichlorophenoxy group in diclofop-methyl with a 6-chloro-2-benzoxazolyloxy group and a one-carbon extension of the carbon chain in the ester of diclofop-methyl gave fenoxaprop-ethyl.⁶⁴

2.2.2.3. Quizalofop-ethyl. Replacement of the 2,4-dichlorophenoxy group in diclofop-methyl with a 6-chloro-2-quinazolinylloxy group and a one-carbon extension of the carbon chain in the ester of diclofop-methyl gave quizalofop-ethyl.⁶⁵

2.2.2.4. Cyhalofop-butyl. Replacement of the 2,4-dichlorophenoxy group in diclofop-methyl with a 2-fluoro-4-

cyanophenoxy group and a three-carbon extension of the carbon chain in the ester of diclofop-methyl gave cyhalofop-butyl, showing fast action (grass weeds cease growth immediately after treatment, death of the whole plant within 2–3 weeks) and excellent safety on grass crops such as rice due to rapid metabolism to the inactive diacid.⁶⁶

2.2.2.5. Fluazifop-butyl. Replacement of the 2,4-dichlorophenoxy group in diclofop-methyl with a 5-trifluoromethyl-2-pyridinyloxy group and a three-carbon extension of the carbon chain in the ester of diclofop-methyl gave fluazifop-butyl.^{61h,67}

2.2.2.6. Clodinafop-propargyl. Replacement of the 2,4-dichlorophenoxy group in diclofop-methyl with a 5-chloro-3-fluoro-2-pyridinyloxy group and a two-carbon with a triple bond extension of the carbon chain in the ester of diclofop-methyl gave clodinafop-propargyl.⁶⁸ Interestingly, clodinafop-propargyl did not show improvement in herbicidal activity or safety on graminaceous crops as compared to the lead compound diclofop-methyl. However, clodinafop-propargyl is nonphytotoxic to broad-leaved crops with roughly the same postemergence control characteristics of annual and perennial grass weeds in broad-leaved crops as compared to diclofop-methyl. Furthermore, clodinafop-propargyl shows low toxicity to spring and winter wheat plus relatively low dosage of 30–60 g/ha for killing the weeds.⁷⁵⁸

All aryloxyphenoxypropionic acid herbicides described above except SN 106279 and chlorazifop-propargyl have been commercialized.⁷⁶¹

2.2.3. Discovery of Diacylhydrazine Insecticides. In Figure 12, we present a range of diacylhydrazine insecticides prepared by replacing the terminal phenyl groups of the highlighted diacylhydrazine lead compound RH 5849, which showed good activity against Lepidopteran pests. After the first diacylhydrazine insecticide, RH 5849, was discovered by Rohm & Haas (now Dow AgroSciences LLC),⁶⁹ several insecticides having the same scaffold structure were discovered by employing the terminal group replacement approach. One example in which only one phenyl group of RH 5849 was replaced and four examples in which both phenyl groups of RH 5849 were replaced are presented as a tabular comparison of replacement structures in Table 3 and discussed below.^{774 t3}

2.2.3.1. Replacement of One Phenyl Terminal Group.

2.2.3.1.1. Halofenozide. Replacement of one phenyl group by a 4-chlorophenyl group gave halofenozide with activity on both Lepidopteran and Coleopteran pests.^{69b,70}

2.2.3.2. Replacement of Both Phenyl Terminal Groups.

2.2.3.2.1. Tebufenozide. Replacement of one phenyl group by

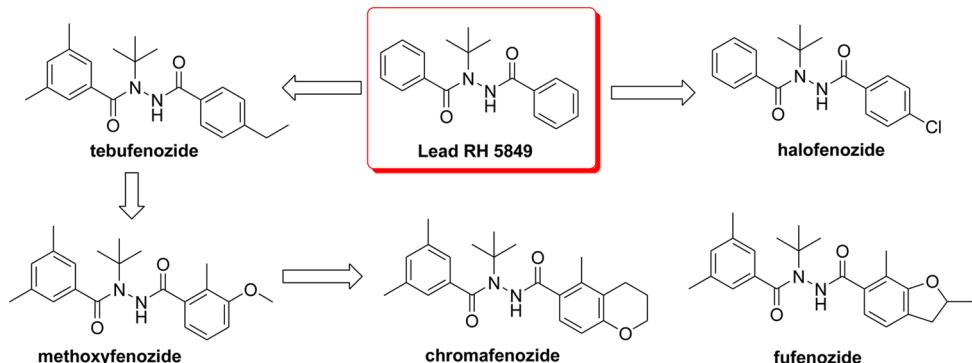
**Figure 12.** Discovery of diacylhydrazine insecticides.

Table 3. Replacement of Terminal Groups in Diacylhydrazine Insecticides

Name	CAS No.	Q_1^-	$-Q_2$
Lead RH 5849	112225-87-3		
halofenozide	112226-61-6		
tebufenozide	112410-23-8		
methoxyfenozide	161050-58-4		
chromafenozide	143807-66-3		
fufenozone	467427-81-1		

⁷⁸¹ a 3,5-dimethylphenyl group and the other phenyl group by a 4-
⁷⁸² ethylphenyl group gave tebufenozide.^{70,71}

⁷⁸³ 2.2.3.2. *Methoxyfenozide*. Replacement of one phenyl
⁷⁸⁴ group by a 3,5-dimethylphenyl group and the other phenyl
⁷⁸⁵ group by a 3-methoxy-2-methylphenyl group gave methox-
⁷⁸⁶ yfenozide.⁷²

⁷⁸⁷ 2.2.3.2.3. *Chromafenozide*. Replacement of one phenyl
⁷⁸⁸ group by a 3,5-dimethylphenyl group and the other phenyl
⁷⁸⁹ group by a 5-methyl-6-benzopyranyl group gave chromafen-
⁷⁹⁰ zide. Chromafenozide was developed jointly by Nippon Kayaku
⁷⁹¹ Co., Ltd. and Sankyo Co., Ltd. (now Mitsui Chemicals Inc.).
⁷⁹² This compound was first registered in Japan in 1999.⁷³

⁷⁹³ 2.2.3.2.4. *Fufenozone*. Replacement of one phenyl group by
⁷⁹⁴ a 3,5-dimethylphenyl group and the other phenyl group by a
⁷⁹⁵ 2,7-dimethyl-6-benzofuranyl group gave fufenozone. Fufenozone
⁷⁹⁶ was developed by Jiangsu Pesticide Research Institute in China
⁷⁹⁷ and showed good insecticidal activity as well.⁷⁴

⁷⁹⁸ 2.2.4. **Discovery of Carboxanilide Fungicides**. In Figure
⁷⁹⁹ 13, we present the range of carboxanilide fungicides prepared
⁸⁰⁰ by replacing the terminal phenyl group and oxathiin ring of the
⁸⁰¹ highlighted carboxanilide carboxin. Chemical Abstracts Service
⁸⁰² registry numbers indicate an approximate chronological order
⁸⁰³ of discovery of carboxanilide fungicides. Carboxin is a selective
⁸⁰⁴ and systemic fungicide introduced by Uniroyal Chemical Co.,
⁸⁰⁵ Inc. (now Chemtura Corp.) in 1966 that is used as a seed
⁸⁰⁶ treatment for control of smuts and bunts on barley, wheat, and
⁸⁰⁷ oats, and for seedling diseases of barley, wheat, oats, rice,
⁸⁰⁸ cotton, peanuts, soya beans, vegetables, maize, sorghum, and
⁸⁰⁹ other crops.⁷⁵ After the first carboxanilide fungicide, carboxin,
⁸¹⁰ was discovered, several fungicides having the same scaffold
⁸¹¹ structure were discovered by employing the terminal group
⁸¹² replacement approach. Four examples in which either the
⁸¹³ terminal oxathiin ring or the phenyl ring was replaced and 13
⁸¹⁴ examples in which both the oxathiin ring and the phenyl ring of
⁸¹⁵ carboxin were replaced are presented as a tabular comparison of
⁸¹⁶ replacement structures in Table 4 and discussed below.

2.2.4.1. Replacement of Either the Oxathiin Ring or the Phenyl Ring Terminal Group. 2.2.4.1.1. *F-427*. Replacement of the phenyl ring by a biphenyl group gave F-427, a Uniroyal Chemical Co. fungicide lead.^{81,82}

2.2.4.1.2. Mebenil. Replacement of the oxathiin ring by a phenyl ring gave mebenil. Mebenil, discovered by BASF, is effective against Basidiomycetes and for the control of *Puccinia* spp. on cereals at 1.7–2.5 kg/ha, and for treating seed potatoes against *Rhizoctonia* spp. at 0.30–0.37 g/kg seed.⁷⁷

2.2.4.1.3. Fenfuram. Replacement of the oxathiin ring by a furan ring gave fenfuram. Fenfuram, discovered by Shell Research Ltd. and developed by KenoGard VT AB (now Bayer AG), which mainly controls smuts in cereals.⁷⁸

2.2.4.1.4. Metsulfovax. Replacement of the oxathiin ring by a thiazole ring gave metsulfovax. Metsulfovax, evaluated by Uniroyal Chemical Co., Inc., provided control of *Puccinia*, *Ustilago*, *Rhizoctonia solani*, *Tilletia* spp., and other Basidiomycetes in cereals, cotton, potatoes, and ornamentals with a broad spectrum.^{76b,79}

2.2.4.2. Replacement of Both Oxathiin Ring and Phenyl Ring Terminal Groups. 2.2.4.2.1. *Thifluzamide*. Replacement of the oxathiin ring by a thiazole ring and the phenyl ring by a 2,6-dibromo-4-trifluoromethoxyphenyl ring gave Thifluzamide. The discovery of Thifluzamide could also be considered as the TRM modification of metsulfovax by replacing the methyl group with a trifluoromethyl group and by replacing the phenyl group with a 2,6-dibromo-4-trifluoromethoxyphenyl group as well. Thifluzamide was initially developed by Monsanto Co., and sold to Rohm & Haas Co. (now Dow AgroSciences LLC) in 1994. This product was first marketed in South Korea in 1997. Nissan Chemical Industries Ltd. acquired worldwide business for this compound from Dow in January, 2010. Thifluzamide has broad spectrum fungicidal activity primarily on Basidiomycetes, in particular diseases caused by *Rhizoctonia* spp., on rice, potatoes, maize, and amenity grass.⁸⁰

2.2.4.2.2. Tiadinil. Replacement of the oxathiin ring by a thiadiazole ring and the phenyl ring by a 3-chloro-4-methylphenyl ring gave tiadinil. Similar to the case of Thifluzamide, the finding of tiadinil could be considered as the TRM modification of metsulfovax by replacing the phenyl group with a 3-chloro-4-methylphenyl group and by replacing the 2,4-dimethylthiazole group with a 4-methyl-1,2,3-thiadiazole group. Tiadinil, discovered by Nihon Nohyaku Co., Ltd. and registered in Japan in 2003, has control of rice blast, bacterial leaf blight, and bacterial grain rot.⁸¹

2.2.4.2.3. Mepronil. Replacement of the oxathiin ring by a 2-methylphenyl ring and the phenyl ring by a 3-(1-methylethoxy)phenyl ring gave mepronil. The discovery of mepronil could also be regarded as the TRM modification of mebenil by replacing the phenyl group with a 3-(1-methylethoxy)phenyl group. Mepronil with good control of diseases caused by Basidiomycetes in rice, cereals, potatoes, vegetables, cucumbers, sugar beet, fruit, vines, tobacco, turf grass, ornamentals, etc., was introduced by Kumiai Chemical Industries Co., Ltd. in 1981.⁸²

2.2.4.2.4. Flutolanil. Replacement of the oxathiin ring by a (trifluoromethyl)phenyl ring and the phenyl ring by a 3-(1-methylethoxy)phenyl ring gave flutolanil. The discovery of flutolanil could also be regarded as the TRM modification of mepronil by replacing the 2-methylphenyl group with a (trifluoromethyl)phenyl group. Flutolanil with good systemic bioactivity was discovered by Nihon Nohyaku Co., Ltd. and introduced in 1986 for controlling the following pathogens:⁸³

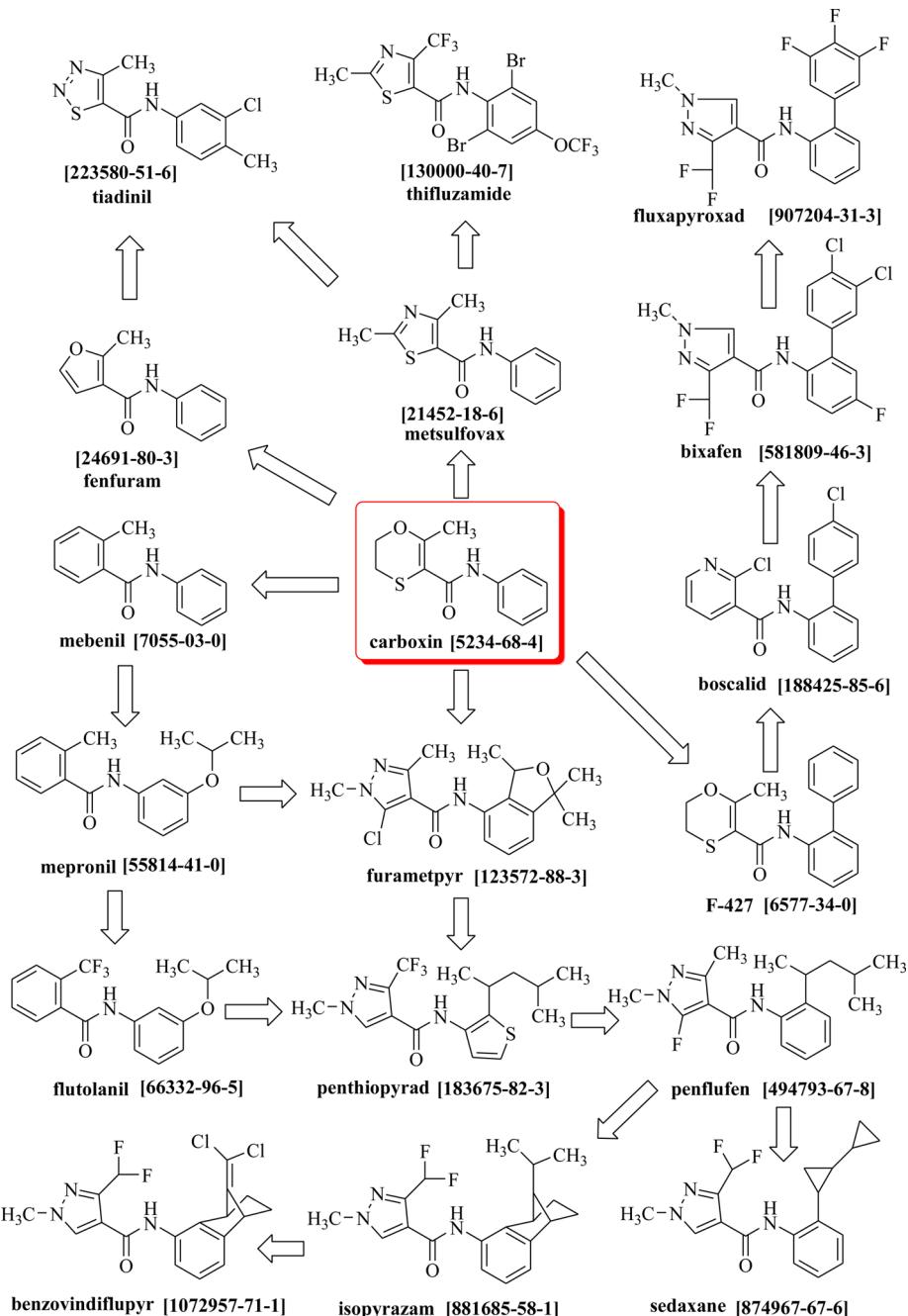


Figure 13. Discovery of some carboxanilide fungicides.

880 *Rhizoctonia solani* on rice; *Typhula* spp. and *R. cerealis* on
 881 cereals; *R. solani* on potatoes; *Corticium rolfsii* and *R. solani* on
 882 sugar beet; *R. solani* on vegetables; *Sclerotium rolfsii* on peanuts;
 883 *Gymnosporangium* spp. on pome fruit; *R. solani* and *S. rolfsii* on
 884 ornamentals; and *R. solani*, *S. rolfsii*, *R. cerealis*, and *Lepista* spp.
 885 on turf, especially against rice sheath blight. It also has an
 886 advantage of nonphytotoxicity to cereals, rice, vegetables, and
 887 fruits, even applied directly.⁸³

888 2.2.4.2.5. **Boscalid.** Replacement of the oxathiin ring by a
 889 pyridine ring and the phenyl ring by a 4'-chloro-1,1'-biphenyl-
 890 2-yl ring gave boscalid. The discovery of boscalid could also be
 891 regarded as the TRM modification of F-427 by replacing the
 892 oxathiin group with a pyridine group. Boscalid, discovered by
 893 BASF, was applied to control sclerotinia disease, rust, potato
 894 early blight, gray mold, etc.⁸⁴

2.2.4.2.6. **Bixafen.** Replacement of the oxathiin ring by a
 895 pyrazole ring and the phenyl ring by a 3',4'-dichloro-5-fluoro-
 896 1,1'-biphenyl-2-yl ring gave bixafen. The discovery of bixafen
 897 could also be regarded as the TRM modification of boscalid by
 898 replacing the pyridine group with a pyrazole group. Bixafen,
 899 discovered by Bayer CropScience, first marketed in 2011 in UK,
 900 Germany, Ireland, and France, demonstrates good to excellent
 901 activity against *Septoria tritici*, *Puccinia triticina*, *Puccinia*
 902 *striiformis*, *Oculimacula* spp., and *Pyrenophora tritici-repentis* in
 903 wheat and against *Pyrenophora teres*, *Ramularia collo-cygni*,
 904 *Rhynchosporium secalis*, and *Puccinia hordei* in barley.⁸⁵

2.2.4.2.7. **Fluxapyroxad.** Replacement of the oxathiin ring by a
 906 pyrazole ring and the phenyl ring by a 3',4',S'-trifluoro-
 907 1,1'-biphenyl-2-yl ring gave fluxapyroxad. The discovery of
 908 fluxapyroxad could also be considered as the TRM modification

Table 4. Replacement of Terminal Groups in Carboxanilide Fungicides

Name	CAS No.	Q ₁ -	-Q ₂
carboxin	5234-68-4		
F-427	6577-34-0		
mebenil	7055-03-0		
fentfuram	24691-80-3		
metsulfovax	21452-18-6		
thifluzamide	130000-40-7		
tiadinil	223580-51-6		
mepronil	55814-41-0		
flutolanil	66332-96-5		
boscalid	188425-85-6		
Name	CAS No.	Q ₁ -	-Q ₂
bixafen	581809-46-3		
fluxapyroxad	907204-31-3		
furametpyr	123572-88-3		
penthiopyrad	183675-82-3		
penflufen	494793-67-8		
sedaxane	874967-67-6		
isopyrazam	881685-58-1		
benzovindiflupyr	1072957-71-1		

⁹¹⁰ of bixafen by replacing the 3',4'-dichloro-5-fluorobiphenyl-2-yl
⁹¹¹ group with a 3',4',5'-trifluorobiphenyl-2-yl group. Fluxapyroxad
⁹¹² controls several fungal development stages for a broad range of
⁹¹³ pathogens belonging to the following major classes: *Ascomy-*
⁹¹⁴ *cetes*, *Basidiomycetes*, *Deuteromycetes*, and *Zygomycetes*. Like
⁹¹⁵ other SDH (succinate dehydrogenase) inhibitors, it does not
⁹¹⁶ control *Peronosporomycetes*.^{85d,86}

⁹¹⁷ **2.2.4.2.8. Furametpyr.** Replacement of the oxathiin ring by a
⁹¹⁸ pyrazole ring and the phenyl ring by an isobenzofuran ring gave
⁹¹⁹ furametpyr. The discovery of furametpyr could also be
⁹²⁰ considered as the modification of mepronil by replacing 2-
⁹²¹ methylphenyl group with 5-chloro-1,3-dimethylpyrazole group
⁹²² and replacing 3-(1-methylethoxy)phenyl ring with an iso-
⁹²³ benzofuran ring. Sumitomo Chemical Co., Ltd. in 1989
⁹²⁴ discovered this fungicide, which shows excellent fungicidal

active on rice sheath blight on rice, and was first registered in Japan in 1996.^{84e,87}

925
926

⁹²⁷ **2.2.4.2.9. Penthiopyrad.** Replacement of the oxathiin ring by a pyrazole ring and the phenyl ring by a thiophene ring gave penthiopyrad. The discovery of penthiopyrad could also be considered as the TRM modification of furametpyr by replacing the isobenzofuran group with a thiophene group. Penthiopyrad was developed by Mitsui Chemicals Inc. and used mainly to control gray mold and powdery mildew.⁸⁸

933

⁹³⁴ **2.2.4.2.10. Penflufen.** Replacement of the oxathiin ring by a pyrazole ring and the phenyl ring by a 2-(1,3-dimethylbutyl)-phenyl ring gave penflufen. The discovery of penflufen could also be considered as the TRM modification of penthiopyrad by replacing the thiophene group with a phenyl group. Penflufen was launched by Bayer in 2012 with registrations in UK (2011),

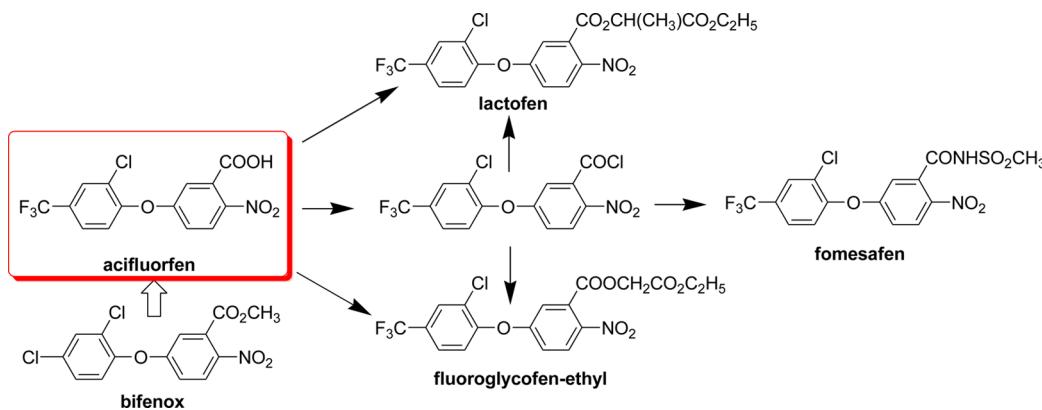


Figure 14. Discovery of fluoroglycofen-ethyl, fomesafen, and lactofen.

940 Canada, and the U.S. (2012). This compound shows potent
 941 activity at low dose rates against a wide spectrum of
 942 *Basidiomycetes* and *Ascomycetes* fungi. Under development as a
 943 seed treatment, potato tuber/seed treatment, penflufen is
 944 suggested to be used as a soil applied fungicide providing a high
 945 level of protection to seedlings against seedborne and soilborne
 946 diseases caused by the basidiomycete *Rhizoctonia solani* in crops
 947 such as corn, soybeans, canola, potatoes, cotton, ground nuts,
 948 onions, succulent peas, and beans. It is also active against cereal
 949 diseases caused by *Tilletia*, *Ustilago*, *Rhizoctonia*, and
 950 *Cochliobolus*, and has shown activity against rice sheath blight
 951 and rice false smut (*Ustilaginoidea virens*).⁸⁹

952 **2.2.4.2.11. Sedaxane.** Replacement of the oxathiin ring by a
 953 pyrazole ring and the phenyl ring by a 2-(2-
 954 cyclopropylcyclopropyl)phenyl ring gave sedaxane. The discov-
 955 ery of sedaxane could also be regarded as the TRM
 956 modification of penflufen by replacing the 2-(1,3-
 957 dimethylbutyl)phenyl ring group with a 2-(2-
 958 cyclopropylcyclopropyl)phenyl group. Sedaxane is the first
 959 Syngenta carboxanilide compound that is being evaluated for
 960 global registration under the new concept of a Global Joint
 961 Review. This fungicide provides longer-lasting protection
 962 against difficult-to-control seedborne, soilborne, and airborne
 963 pathogens and improves the quality of roots.^{85d,86c,87b,90}

964 **2.2.4.2.12. Isopyrazam.** Replacement of the oxathiin ring by
 965 a pyrazole ring and the phenyl ring by a 1,2,3,4-tetrahydro-9-(1-
 966 methylethyl)-1,4-methanonaphthalen-5-yl ring gave isopyra-
 967 zam. The discovery of isopyrazam could also be considered
 968 as the TRM modification of penflufen by replacing the 2-(1,3-
 969 dimethylbutyl)phenyl group with a 1,2,3,4-tetrahydro-9-(1-
 970 methylethyl)-1,4-methanonaphthalen-5-yl group. Isopyrazam
 971 is a broad spectrum fungicide from Syngenta against the wheat
 972 diseases leaf blotch (*Septoria tritici*), brown rust (*Puccinia*
 973 *recondita*), and yellow rust (*Puccinia striiformis*); and against the
 974 barley diseases net blotch (*Pyrenophora teres*), *Rhynchosporium*
 975 *secalis*, and *Ramularia collo-cygni*. Isopyrazam is also active
 976 against diseases in other crops including pome fruit (*Venturia*
 977 *inaequalis*, *Podosphaera leucotricha*), vegetables (powdery
 978 mildews, leaf spots, rusts), oil seed rape (both *sclerotinia* and
 979 *Phoma*), and banana (*Mycosphaerella fijiensis*).^{86c,91}

980 **2.2.4.2.13. Benzovindiflupyr.** Replacement of the oxathiin
 981 ring by a pyrazole ring and the phenyl ring by a 9-(
 982 dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphtha-
 983 len-5-yl ring gave benzovindiflupyr. The discovery of
 984 benzovindiflupyr could also be considered as the TRM
 985 modification of isopyrazam by replacing the 1,2,3,4-tetrahy-
 986 dro-9-(1-methylethyl)-1,4-methanonaphthalen-5-yl group with

a 9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaph- 987
 thalen-5-yl group. Benzovindiflupyr (SYN545192) is under 988
 development by Syngenta.⁹² 989

2.3. Active Compound Derivatization Method (ADM)

As described above, ADM is a strategy to discover a novel 990 biological active compound based on existing active compounds 991 possessing chemically active functional groups amenable to 992 derivatization. In most cases, only one chemically reactive 993 functional group is modified from starting compound to final 994 product. New compounds may be prepared via one step or 995 multiple-step chemical reactions using known or existing 996 commercially available compounds as starting materials. 997

ADM has been widely used in discovering novel biologically 998 active compounds. In this Review, we will mainly focus on the 999 derivatization of agrochemicals rather than the entire bio- 1000 logically active discovery field. There are many successful 1001 agrochemicals prepared by employing ADM. Generally, once a 1002 structurally de novo biologically active compound is identified, 1003 its derivatives based on the reactive functional group will be 1004 investigated. Common reactive groups include hydroxyl, 1005 primary or secondary amine, nitro, nitrile, carboxyl or ester, 1006 etc., which can undergo a series of reactions to afford new 1007 compounds. Finding a compound with improved biological 1008 activities including increased selectivity, increased potency, 1009 and/or enhanced crop safety as compared to those of starting 1010 native compound is the key to the success of this approach. 1011 f14

In sections 2.3.1–2.3.7, we provide detailed examples of the 1012 application of ADM in the discovery of new agrochemicals 1013 starting from existing agrochemicals. We present examples in 1014 the herbicide, fungicide, and insecticide areas. 1015

2.3.1. From Acifluorfen to Fluoroglycofen-ethyl, 1016 Fomesafen, and Lactofen. In Figure 14, we present a 1017 f14 range of diphenyl ether herbicides prepared from highlighted 1018 herbicide acifluorfen. Three examples in which the carboxylic 1019 acid function of acifluorfen is derivatized are presented below. 1020

Herbicide fluoroglycofen-ethyl was discovered by reacting 1021 acifluorfen with ethyl 2-chloroacetate in the presence of 1022 potassium carbonate in dimethyl sulfoxide.⁹³ An alternative 1023 synthesis route is the conversion of acifluorfen into its acyl 1024 chloride and then esterification of the acyl chloride using ethyl 1025 glycolate to give fluoroglycofen-ethyl. Fluoroglycofen-ethyl, 1026 developed by Rohm & Haas Co. (now Dow AgroSciences 1027 LLC), has better biological activity and selectivity than native 1028 acifluorfen.^{93–96} 1029

Fomesafen is obtained from acifluorfen via its acyl chloride 1030 reacting with methanesulfonamide. Fomesafen introduced by 1031

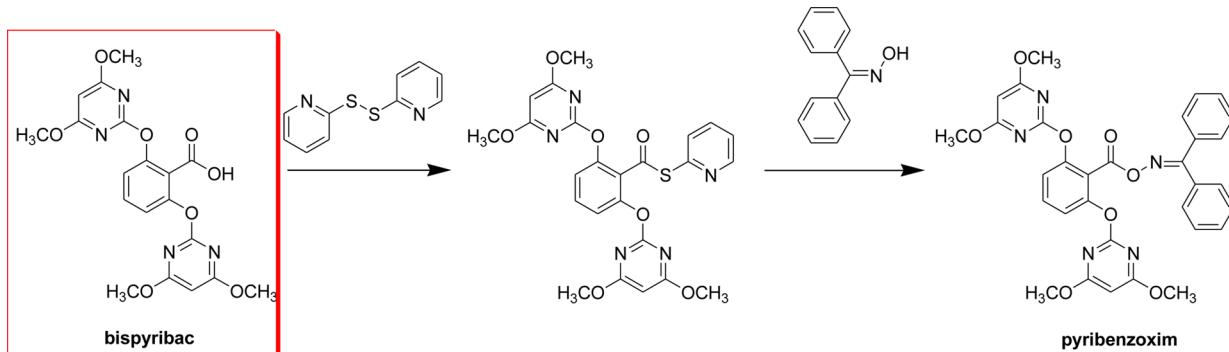


Figure 15. Discovery of pyribenzoxim.

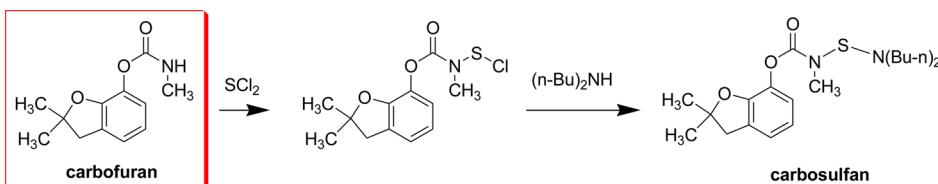


Figure 16. Discovery of carbosulfan.

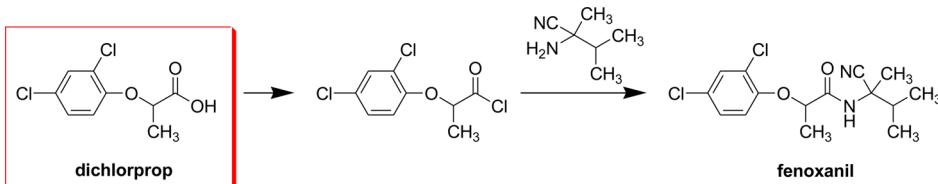


Figure 17. Discovery of fenoxanil.

1032 ICI Plant Protection Division (now Syngenta AG) is effective
1033 on early postemergence control of broad-leaved weeds in soya
1034 beans with better biological activity and selectivity than native
1035 acifluorfen.^{94–97}

1036 The same acyl chloride intermediate of acifluorfen can be
1037 used to obtain lactofen by esterification with another
1038 complicated alcohol, HO–CH(CH₃)CO₂C₂H₅.⁹⁷ Of course,
1039 lactofen could be directly obtained from acifluorfen via the
1040 reaction with ethyl 2-chloropropanoate. Lactofen, introduced
1041 by PPG Industries in 1987, exhibits postemergence herbicidal
1042 activity for control of broad-leaved weeds in cotton, soya beans,
1043 and snap beans, at 0.2 lb/a.

1044 Interestingly, acifluorfen can be considered as a derivative of
1045 herbicide bifenoxy by using TRM. In this case, we do not count
1046 that from bifenoxy to acifluorfen is developed by ADM because
1047 acifluorfen could not be directly obtained using bifenoxy as a
1048 starting material.^{94–96,98}

1049 **2.3.2. From Bispyribac to Pyribenzoxim.** In Figure 15,
1050 we present a pyrimidinyloxybenzoic acid oxime ester herbicide
1051 prepared from highlighted herbicide bispyribac. Bispyribac,
1052 developed jointly by Kumai and Ihara Chemical Industries Co.,
1053 Ltd., is a selective, systemic postemergence herbicide for
1054 control of grasses, sedges, and broad-leaved weeds in direct-
1055 seeded rice, at rates of 15–45 g/ha. It is also used to stunt
1056 growth of weeds in noncrop situations.⁹⁹ Pyribenzoxim is an
1057 example in which the carboxylic acid function of bispyribac is
1058 derivatized to obtain a new biologically active compound.
1059 Pyribenzoxim can be directly obtained via two steps as
1060 illustrated in Figure 14. Although there was little difference in
1061 herbicidal properties between bispyribac and pyribenzoxim, the

1062 f16 structure of pyribenzoxim is an innovative derivative of 1062 f16
1063 bispyribac.¹⁰⁰ Pyribenzoxim developed by LG Life Sciences 1063
1064 Ltd. is also a postemergence herbicide, and used to control 1064
1065 barnyard grass (*Echinochloa* spp.), blackgrass (*Alopecurus* 1065
myosuroides), and polygonums in rice, wheat, and zoysiagrass, 1066
1067 at 30 g/ha.¹⁰¹

1068 f16 **2.3.3. From Carbofuran to Carbosulfan.** In Figure 16, 1068 f16
we present a carbamate insecticide prepared from highlighted 1069
insecticide carbofuran. Although carbofuran is a mature 1070
commercially available insecticide, the presence of chemically 1071
reactive carbamate group provides an opportunity for 1072
derivatization.¹⁰²

1073 The successive reactions of carbofuran with SCl₂ and then 1074
with dibutylamine led to carbosulfan. Carbosulfan has lower 1075
mammalian toxicity as compared to the native compound, 1076
carbofuran.¹⁰² Carbofuran and carbosulfan are both insecticides 1077
introduced by FMC Corp. for broad spectrum control of soil- 1078
dwelling and foliar-feeding insects such as wireworms, white 1079
grubs, millipedes, symphylids, fruit flies, bean seed flies, root 1080
flies, flea beetles, weevils, sciarid flies, aphids, thrips, and 1081 f17
nematodes in vegetables, ornamentals, beet, maize, sorghum, 1082
sunflowers, oilseed rape, potatoes, alfalfa, peanuts, soya beans, 1083
sugar cane, rice, cotton, coffee, cucurbits, tobacco, lavender, 1084
citrus, vines, strawberries, bananas, mushrooms, and other 1085
crops.¹⁰³

1086 **2.3.4. From Dichlorprop to Fenoxanil.** In Figure 17, we 1087 f17
present a phenoxypropionamide fungicide prepared from 1088
highlighted herbicide dichlorprop. Fenoxanil is an example in 1089
which the carboxylic acid function of dichlorprop is derivatized 1090
to obtain a new biologically active compound. Dichlorprop is a 1091

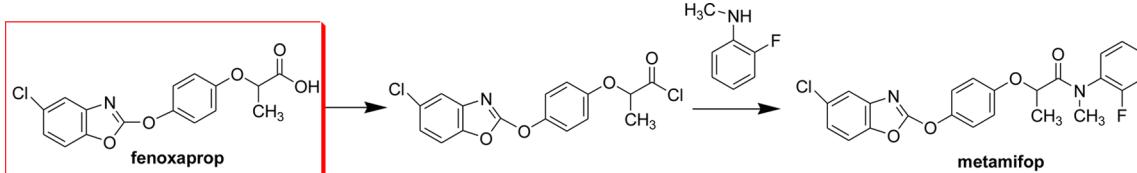


Figure 18. Discovery of metamifop.

1092 postemergence herbicide for controlling annual and perennial
1093 broad-leaved weeds in cereals and grassland.

1094 By derivatizing the carboxylic acid group to an amide, the
1095 herbicide dichlorprop was converted into fenoxanil, which is a
1096 fungicide for controlling rice blast by foliar or into-water
1097 application.¹⁰⁴

1098 **2.3.5. From Fenoxaprop to Metamifop.** In Figure 18, we
1099 present an aryloxyphenoxypropionamide herbicide prepared
1100 from highlighted herbicide fenoxaprop. Metamifop is an
1101 example in which the carboxylic acid function of fenoxaprop
1102 is derivatized to obtain a new biologically active compound.
1103 Fenoxaprop is used for postemergence control of many annual
1104 and perennial grass weeds in broadleaf crop field such as soya
1105 beans, cotton, sugar beet, peanuts, potatoes, beans, sunflowers,
1106 and vegetables.

1107 By derivatizing the carboxylic acid group to an amide, the
1108 herbicide fenoxaprop was converted into the herbicide
1109 metamifop.¹⁰⁵ The derivatization of fenoxaprop to metamifop

1127 neonicotinoid insecticide NTN32692. NTN32692 is an 1127
insecticide lead in the neonicotinoid chemistry field.¹⁰⁹ 1128

1129 NTN32692 was reacted with succinaldehyde to obtain 1129
1130 cycloxaiprid with both innovative structure and good insecticidal 1130
activity.¹¹⁰ A recent study has demonstrated that cycloxaiprid 1131
1132 has a strong binding affinity to nicotinic acetylcholine receptor 1132
in house fly and honeybee head membranes, and mouse brain 1133
membranes as well.¹¹¹ 1134

2.4. Combination of Terminal Group Replacement Method and Active Compound Derivatization Method (TRM and ADM)

1137 TRM and ADM can be applied either alone or both in one 1137
1138 agrochemical discovery process. In sections 2.4.1–2.4.4, we 1138 f21
1139 provide detailed examples of the application of TRM and ADM 1139
1140 in combination in the discovery of new agrochemicals starting 1140
from active molecules. 1141

1142 **2.4.1. From Metsulfuron-methyl to Pyrazosulfuron-
ethyl, Tribenuron-methyl, Metazosulfuron, Halosulfur-
on-methyl, and Azimsulfuron.** In Figure 21, we present a 1142 f21
1143 range of sulfonylurea herbicides prepared from highlighted 1143
1144 sulfonyleurea herbicide metsulfuron-methyl by a combination of 1144
1145 TRM and ADM approaches. 1145

1146 Tribenuron-methyl is prepared by the replacement of N–H 1146
1147 on metsulfuron-methyl by N–CH₃ by using TRM. Tribenuron- 1147
1148 methyl discovered by DuPont Co. was mainly used for 1148
1149 postemergence control broad-leaved weeds in cereal crops, 1149
1150 including wheat, barley, oats, rye, and triticale at 7.5–30 g/ 1150
1151 ha.^{45d,46,112} 1152

1153 Pyrazosulfuron-ethyl and halosulfuron-methyl are both 1153
1154 prepared by the replacement of the phenyl ring of 1155
1155 metsulfuron-methyl with a pyrazole ring and replacement of 1156
1156 triazine ring with a pyrimidine ring via TRM.^{52,55} 1157

1157 Pyrazosulfuron-ethyl may also be converted to halosulfuron- 1158
1158 methyl by replacement of H on the pyrazole ring with a 1159
1159 chlorine atom using TRM. 1160

1161 Halosulfuron-methyl was discovered by Nissan Chemical 1161
1162 Industries Ltd. and developed jointly by Monsanto Co. and 1162
1163 Nissan Chemical Industries Ltd. and registered in the U.S. in 1163
1994. Halosulfuron-methyl shows good activity controlling 1164
1165 annual broad-leaved weeds and nutsedge species in maize, sugar 1165
cane, rice, sorghum, nuts, and turf.^{45d,55} The uses of 1166
1167 metsulfuron-methyl, pyrazosulfuron-ethyl, and metazosulfuron 1167
have previously been discussed in section 2.2.1 on the discovery 1168
of sulfonylurea herbicides.¹¹⁶⁹

1170 Pyrazosulfuron-ethyl and halosulfuron-methyl may be 1170
1171 converted to azimsulfuron and metazosulfuron, respectively, 1171
1172 by derivatization of the ester function on the pyrazole ring to 1172
1173 tetrazole and dioxazine heterocyclic groups using ADM.^{113,114} 1173

1174 Azimsulfuron, which was introduced by DuPont Co., is also a 1174
1175 postemergence herbicide in Southern European rice with good 1175
1176 selectivity and high activity against annual and perennial broad- 1176
leaved and sedge weeds at 20–25 g/ha.^{45d,113} 1177 f22

1178 Metazosulfuron, developed by Nissan Chemical Industries 1178
1179 Ltd. in 2004 and first registered in Korea in 2011, was used for 1179

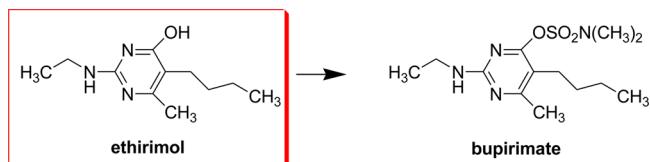


Figure 19. Discovery of bupirimate.

1110 greatly improves the safety on gramineous crops such as rice;
1111 this improvement allows metamifop to be applied in various
1112 crops, including rice to postemergence control annual and
1113 perennial grass weeds.¹⁰⁶

1114 **2.3.6. From Ethirimol to Bupirimate.** In Figure 19, we
1115 present a pyrimidine fungicide prepared from highlighted
1116 pyrimidine fungicide ethirimol. Bupirimate is an example in
1117 which the hydroxyl group of ethirimol is derivatized to obtain a
1118 new biologically active compound.

1119 The hydroxyl group of ethirimol was derivatized into
1120 dimethylsulfamate group, resulting in the discovery of
1121 bupirimate.¹⁰⁷ Bupirimate is a superior fungicide to ethirimol
1122 by providing low doses, high efficacy, and low toxicity. It is a
1123 major fungicide for powdery mildew control with improved
1124 systemic property including protective and curative action.¹⁰⁸

1125 **2.3.7. From NTN32692 to Cycloxaiprid.** In Figure 20, we
1126 present a neonicotinoid insecticide prepared from highlighted

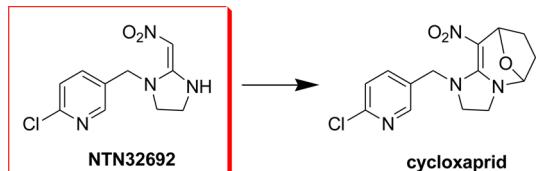


Figure 20. Discovery of cycloxaiprid.

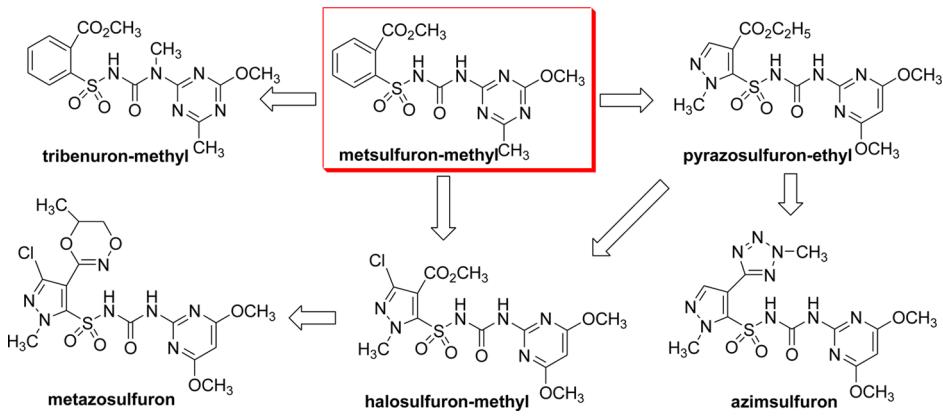


Figure 21. Discovery of pyrazosulfuron-ethyl and others.

1180 pre- and postemergence control annual and perennial weeds in
1181 transplanted rice with high efficacy of at 60–100 g/ha.¹¹⁴

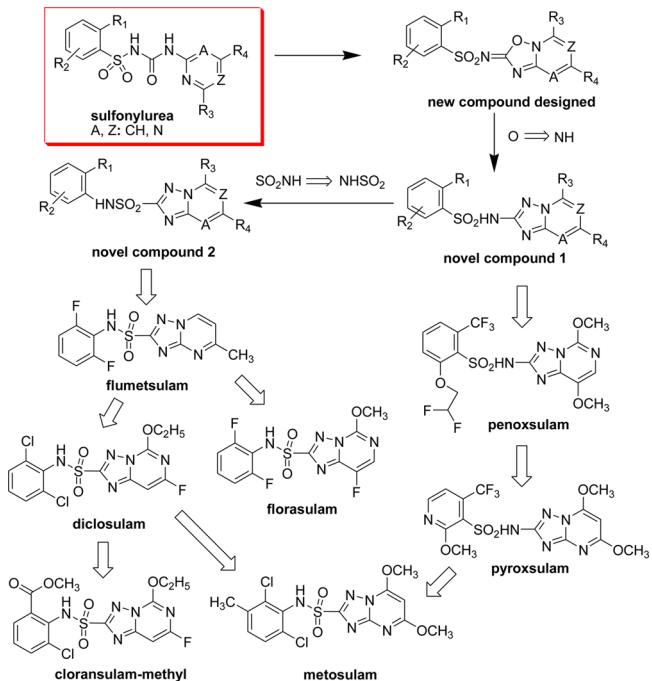


Figure 22. Discovery of triazolopyrimidine sulfonamides.

2.4.2. From Sulfonylurea to Triazolopyrimidine 1182

Sulfonamides. In Figure 22, we present a range of 1183 f22 triazolopyrimidine herbicides prepared from highlighted 1184 sulfonlurea herbicides by a combination of TRM and ADM 1185 approaches. 1186

The discovery of triazolopyrimidine sulfonamides including 1187 flumetsulam, penoxsulam, diclosulam, florasulam, cloransulam- 1188 methyl, metosulam, and pyroxulam (Figure 22) was achieved 1189 through the imaginative use of both TRM and ADM, starting 1190 from well-known sulfonlurea structures. Sulfonlureas were 1191 cyclized to afford triazolopyrimidines by ADM, and then 1192 replacements of O by NH and SO₂NH by NHSO₂ were 1193 successively applied to obtain structurally de novo lead 1194 compounds 1 and 2, respectively. These two lead compounds 1195 are major scaffolds of triazolopyrimidine sulfonamides. After 1196 further refinements in the phenyl ring on the left and fused 1197 heterocycle on the right, several triazolopyrimidine sulfona- 1198 mides were achieved successfully.^{7b,115} Pyroxulam can be 1199 obtained by replacement of the phenyl ring of penoxsulam by a 1200 pyridinyl ring. 1201

The triazolopyrimidine compounds have shown very good 1202 herbicidal activity, as follows. 1203

Cloransulam-methyl may be applied to the soil surface or 1204 incorporated pre-emergence or postemergence in soy beans, to 1205 control broad-leaved weeds.¹¹⁶ 1206

Diclosulam displays pre-emergence, preplant, and preplant 1207 incorporated control of broad-leaved weed in peanuts and soy 1208 beans.^{116b,c,117} 1209

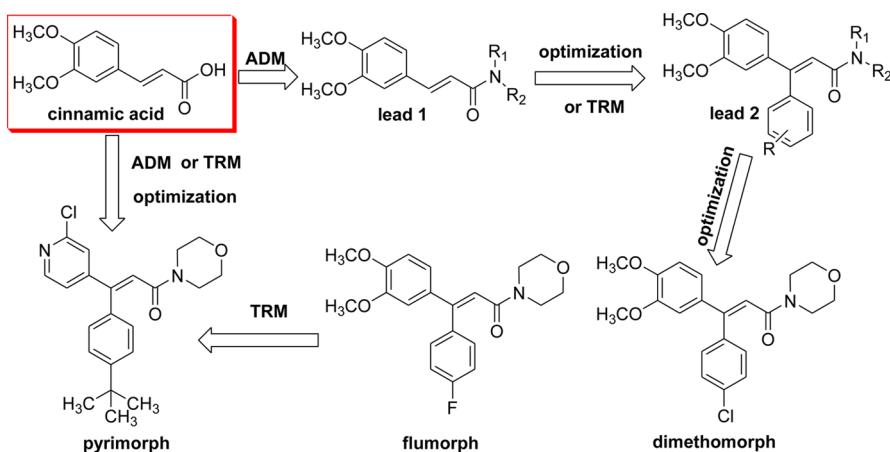


Figure 23. Discovery of morpholine fungicides dimethomorph, flumorph, and pyrimorph.

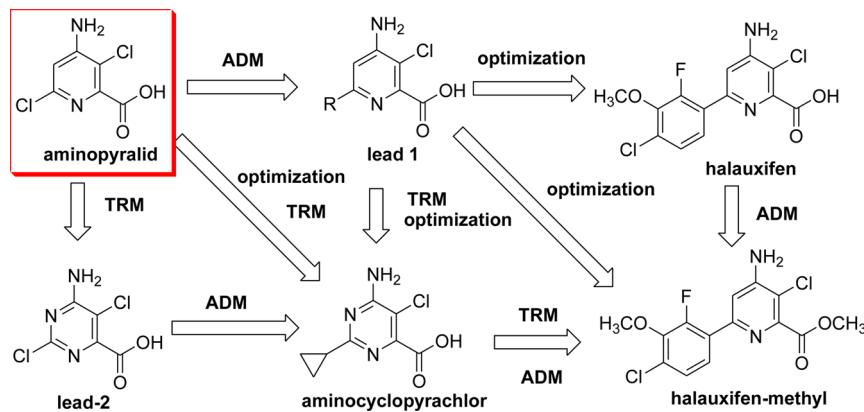


Figure 24. Discovery of halauxifen, aminocyclopyrachlor, and halauxifen-methyl.

1210 Flumetsulam can be used both alone and in combination
1211 with trifluralin or metolachlor for control of broad-leaved weeds
1212 and grasses in soy beans, field peas, and maize.¹¹⁸

1213 Florasulam is used for postemergence control of broad-
1214 leaved weeds, in cereals and maize.^{116b,119}

1215 Metosulam with nonphytotoxic effects on recommended
1216 crops can provide postemergence control of many important
1217 broad-leaved weeds in wheat, barley, and rye, and pre- or
1218 postemergence control of many important broad-leaved weeds
1219 in maize. Metosulam can be used in lupins as well.¹²⁰

1220 Penoxsulam demonstrates control of many broad-leaved,
1221 sedge, and aquatic weeds in rice and is able to provide long
1222 residual weed control, depending on soil type and use rate.¹²¹

1223 Pyroxysulam shows broad spectrum postemergence annual
1224 grass and broad-leaved weed control in cereals. In the presence
1225 of a safener, pyroxysulam can be applied in spring and winter
1226 wheat, winter rye, and winter triticale, and is useful for short
1227 soil residual control of newly emerging annual weeds.^{121f,122}

2.4.3. From Natural Product Cinnamic Acid to Fungicides Dimethomorph, Flumorph, and Pyrimorph.

1228 In Figure 23, we present a range of morpholine fungicides
1229 prepared from highlighted fungicidal cinnamic acid by a
1230 combination of TRM and ADM approaches.

1231 The discovery of morpholine fungicides including dimetho-
1232 morph, flumorph, and pyrimorph was achieved through the
1233 imaginative use of both TRM and ADM, starting from cinnamic
1234 acid (Figure 23). The fungicidal natural product, cinnamic
1235 acid,¹²³ was used as the starting material to obtain lead 1
1236 through ADM by derivatizing the carboxylic group into an
1237 amide group. Lead 1 was further optimized to yield novel lead 2
1238 by replacing one hydrogen atom at double bond of lead 1 with
1239 a phenyl group. Further optimizations then were carried out by
1240 varying substituents R₁, R₂ at amine group and R at phenyl
1241 group of lead 2 using TRM. Through these optimizations, two
1242 fungicides, dimethomorph and flumorph, were obtained.^{124,125}
1243 Furthermore, by replacing the 3,4-dimethoxyphenyl group of
1244 either flumorph or dimethomorph with a 2-chloropyridin-4-yl
1245 group and the halogen atom with a *tert*-butyl group, pyrimorph
1246 was obtained.¹²⁶ The discovery of pyrimorph could also be
1247 considered to be obtained directly from cinnamic acid by
1248 means of ADM, TRM, and several optimizations.

1249 **2.4.4. From Aminopyralid to Halauxifen, Amino-
1250 cyclopyrachlor, and Halauxifen-methyl.** In Figure 24, we
1251 present a range of pyridine and pyrimidine herbicides prepared
1252 from known herbicide, highlighted aminopyralid,¹²⁷ by a
1253 combination of TRM and ADM approaches.

The chlorine atom at the 2-position of pyridine in aminopyralid could be derivatized by various substituents via ADM. For example, 4-chloro-2-fluoro-3-methoxyphenyl was introduced via this strategy to obtain halauxifen. Halauxifen was further improved by ADM via changing carboxylic group into ester group to afford halauxifen-methyl. Another route from lead 1 to halauxifen-methyl was envisioned via TRM optimization to form aminocyclopyrachlor first, and then by another TRM plus ADM to form halauxifen-methyl.¹²⁸ The transformation from aminopyralid into aminocyclopyrachlor could be achieved through replacement of the pyridine ring of aminopyralid by a pyrimidine ring and further derivatization at the 2-position of the pyrimidine ring. The first step is a typical TRM to obtain lead 2, and the second step is achieved by a novel Suzuki reaction as ADM. However, the derivatization from aminocyclopyrachlor to halauxifen-methyl can be also considered as a combined approach using both TRM and ADM because the esterification of the carboxylic acid function employs ADM and the replacements of pyrimidinyl group into pyridinyl group and cyclopropyl into trisubstituted phenyl group use TRM.¹²⁹

Aminopyralid was developed by Dow AgroSciences LLC, which is a systemic herbicide with an auxinic mode of action. It can be absorbed by both foliage and roots, and is systemic with mobility in phloem and xylem for selective control of annual and perennial broad-leaved weeds including many invasive and noxious plants in grassland when used in combination with fluoroxypr.¹³⁰

Aminocyclopyrachlor, a newly discovered pyridine synthetic auxin herbicide, is under development by DuPont for control of perennial broad-leaved weeds.¹³¹

Halauxifen-methyl is a novel pyridine synthetic auxin herbicide being developed by Dow AgroSciences LLC for postemergence broadleaf weed control in several crops. Halauxifen-methyl readily degrades in plant tissues and exhibits selectivity to multiple crops including cereals, brassicas, turf and forage grasses, etc.^{129b–d,132}

3. AGROCHEMICAL DISCOVERY AT SYRICI USING INTERMEDIATE DERIVATIZATION METHODS

We have used the IDM strategy to develop novel biologically active compounds, particularly agrochemicals, at the Shenyang Research Institute of Chemical Industry (SYRICI) for more than 10 years.^{7b,133} These methods are now firmly established in our research programs. In sections 3.1 and 3.2, we provide practical examples of the application of IDM at SYRICI in the

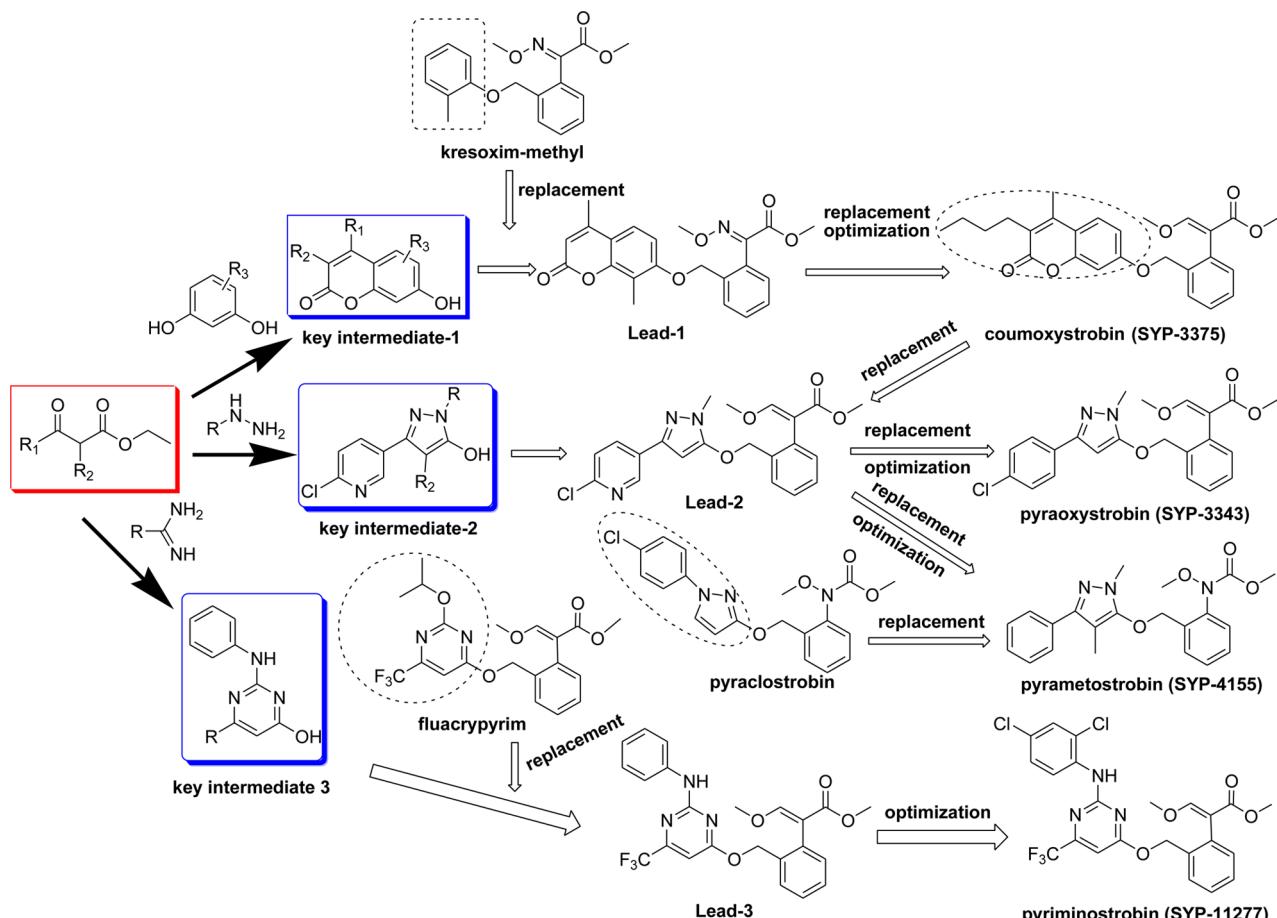


Figure 25. Discovery of coumoxystrobin, pyraoxystrobin, pyrametostrobin, and pyriminostrobin. Reprinted with permission from refs 137a and 137b. Copyright 2010 and 2011 John Wiley and Sons.

discovery of agrochemicals. We are sharing this information with the scientific community in the hope that it will enhance the discovery of biologically active compounds. Although we have so far discussed three major approaches including CIM, TRM, and ADM, we will mainly discuss the terminal moiety replacement method (TRM) in this section because it is the most frequently used method at SYRICI.

3.1. Discovery of Coumoxystrobin, Pyraoxystrobin, Pyrametostrobin, and Pyriminostrobin

In Figure 25, we present a range of methoxyacrylate fungicides and acaricides prepared from highlighted key intermediates 1–3 by using TRM. The key intermediates were in turn prepared by CIM from highlighted β -keto ester.

Recently, the TRM has been successfully applied at SYRICI to develop methoxyacrylate fungicides coumoxystrobin (SYP-3375), pyraoxystrobin (SYP-3343), pyrametostrobin (SYP-4155), and acaricide pyriminostrobin (SYP-11277) shown in Figure 25. Various β -keto esters (primary key intermediates, highlighted in red) were cyclized with phenols such as resorcinol, amidines, and hydrazines to form secondary key intermediates (highlighted in blue) 1 (coumarins), 2 (pyrazoles), and 3 (pyrimidines). Replacement of the 2-methylphenyl terminal group of methoxyacrylate fungicide kresoxim-methyl by key intermediate 1 gave lead-1, which led to the discovery of coumoxystrobin (SYP-3375).¹³⁴ Similarly, using key intermediate 2 as the replacement group of the coumarin terminal group of coumoxystrobin provided lead-2, followed by further optimization that led to the discovery of

pyraoxystrobin (SYP-3343).¹³⁵ During the optimization process of pyraoxystrobin, considering the unique structural component of pyraclostrobin, we also obtained pyrametostrobin (SYP-4155).¹³⁶ Next, high-active target compound pyriminostrobin (SYP-11277) was synthesized by replacement of the isopropoxy terminal group in methoxyacrylate acaricide fluacrypyrim by the phenylamino group initially giving Lead-3 followed by optimization of the phenyl group.¹³⁷ Certainly, the three new leads lead-1, lead-2, and lead-3 obtained from the corresponding three secondary key intermediates 1, 2, 3 showed promising fungicidal/acaricidal activity, and were key milestones in the discovery of the target compounds. Fungicides pyraoxystrobin, coumoxystrobin, and pyrametostrobin, which were discovered within 2–3 years from the first synthesized compound by TRM, represented an important intellectual property, and were successfully launched in China over the period 2009–2011.

The four products mentioned above are successful models using the strategy of IDM, and have shown advantages over existing commercial standards. Three fungicides, coumoxystrobin, pyraoxystrobin, and pyrametostrobin, have a broad spectrum of fungicidal activity providing crop and vegetable protection. There are, however, interesting differences among them: Coumoxystrobin is the most effective agent on apple valsa canker.^{134a,138} Pyraoxystrobin is particularly active against cucumber downy mildew and rice blast with interesting insecticidal activity as well.^{135a,b,d,e} Pyrametostrobin shows excellent fungicidal activity controlling wheat powdery mildew

1355 in cereals and has very good systemic activity.¹³⁶ Currently, 1356 most of the commercialized methoxyacrylate agrochemicals are 1357 fungicides. However, pyriminostrobin is an acaricide in 1358 methoxyacrylate class developed by our group. This acaricide 1359 has shown better bioactivity than competing acaricides 1360 fluacrypyrim, spirodiclofen, and propargite.^{137a–c}

1361 Patents for coumoxystrobin, pyraoxystrobin, pyrametostro- 1362 bin, and pyriminostrobin have been granted in China, Japan, 1363 the U.S., and other countries.

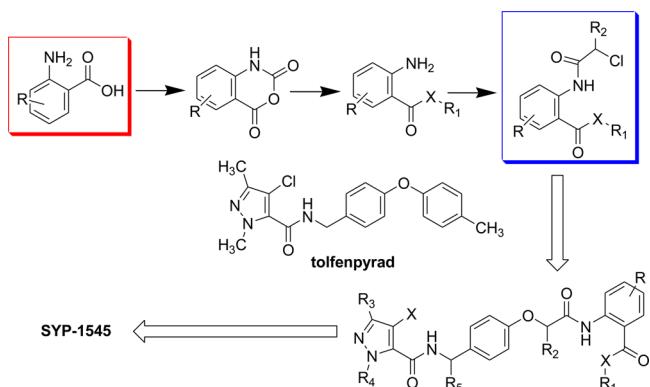


Figure 26. Discovery of advanced fungicidal lead SYP-1545.

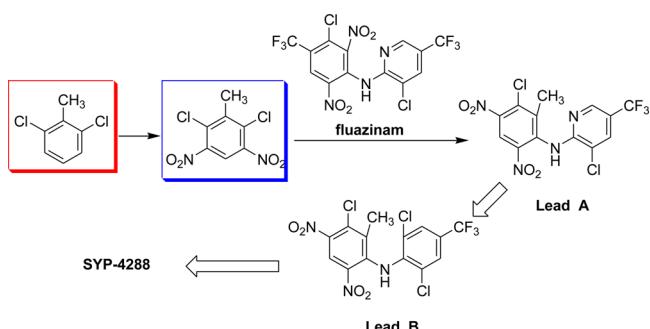


Figure 27. Discovery of advanced fungicidal lead SYP-4288.

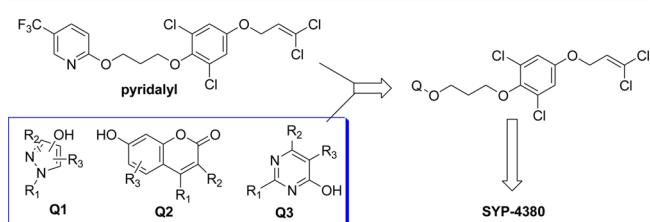


Figure 28. Discovery of advanced insecticidal lead SYP-4380.

3.2. Discovery of Advanced Candidates SYP-1545, SYP-4288, and SYP-4380

1364 In Figures 26–28, we present fungicides SYP-1545 and SYP- 1365 4288 and insecticide SYP-4380, which were discovered by 1366 TRM and ADM and are currently under development. Their 1367 discoveries are summarized below. Because of their early patent 1368 stage, the exact structures of SYP-1545, SYP-4288, and SYP- 1369 4380 cannot be disclosed.

1370 As shown in Figure 26, using the red-highlighted substituted 1371 2-aminobenzoic acid as a primary key intermediate, the 1372 substituted 1*H*-benzo[*d*][1,3]oxazine-2,4-dione compound 1373 was formed. Ring-opening followed by acylation of the amino 1374 group gave the blue-highlighted key intermediate, which was 1375

1376 used to replace the terminal *p*-methylphenyl group of 1377 tolafenpyrad. Further optimization gave the advanced lead 1378 compound SYP-1545, which was excellent in preventing and 1379 controlling plant diseases, such as cucumber downy mildew, 1380 corn rust, rice blast, etc.¹³⁹ The discovery of the advanced 1381 fungicide lead SYP-1545 was unexpected because we assumed 1382 that combining the two moieties from acaricidal pyrazol-4- 1383 amides (e.g., tolafenpyrad) with insecticidal ryanodine receptor 1384 activator diamides (e.g., chlorantraniliprole) would have 1385 produced a new insecticide and/or acaricide with improved 1386 bioactivity. However, bioassay results surprisingly showed that 1387 this novel target compound had fungicidal activity.^{133d} 1387

1388 As shown in Figure 27, the key intermediate 2,4-dichloro-3- 1389 methyl-1,5-dinitrobenzene (highlighted in blue) was prepared 1390 from 2,6-dichlorotoluene, which is a raw material of low cost 1391 and commercial availability. The terminal substituted phenyl 1392 group of fluazinam was replaced with this intermediate, 1393 resulting in the discovery of lead A showing no control against 1393 cucumber downy mildew (CDM), southern corn rust (CSR), 1394 wheat powdery mildew (WPM), cucumber gray mold (CGM), 1395 but had weak activity against rice blast (RB). The results 1396 prompted the authors to improve its fungicidal activity by 1397 replacement of pyridine with benzene and subtle structural 1398 refinement to afford lead B, which had a much wider spectrum 1399 activity than lead A. Further optimization around lead B was 1400 performed to achieve SYP-4288 with broader spectrum and 1401 higher fungicidal activity, especially against cucumber downy 1402 mildew, rice blast, and gray mold of vegetables at very low 1403 doses. These improvements suggested that this compound was 1404 a promising commercial fungicide candidate.¹⁴⁰ 1405

1406 As shown in Figure 28, the highlighted novel intermediates, 1407 substituted pyrazoles Q1, coumarins Q2, or pyrimidines Q3, 1408 which were derived from β -keto esters, replaced the terminal 1409 pyridinyl ring of the known insecticide pyridalyl. Following 1410 further substituent modifications, SYP-4380 was discovered 1411 with excellent insecticidal activity against lepidopterous pests at 1412 very low doses, much better than pyridalyl.¹⁴¹ 1412

4. CONCLUSION

1413 In this Review, we described Intermediate Derivatization 1414 Methods useful for agrochemical discovery. By providing 86 1414 successful examples, we demonstrated that these methods are 1415 f29 effective for the discovery of new biologically active molecules. 1416 We believe that Intermediate Derivatization Methods are more 1417 efficient than traditional discovery methods by reducing the 1418 ever increasing time and cost of the discovery process. These 1419

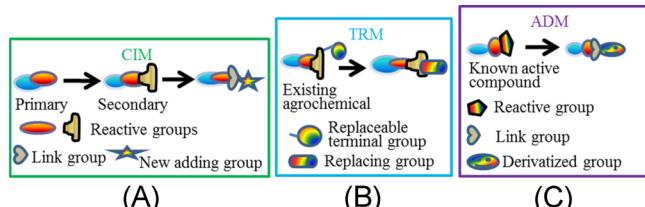


Figure 29. Schematic description of CIM, TRM, and ADM: CIM (A) starts from primary intermediate with relatively simple structure and undergoes multiple chemical modification processes with adding link and new reactive groups; TRM (B) starts directly from highly selective but modifiable existing agrochemical with very well-designed terminal group replacement; and ADM (C) starts from known active compound. After several chemical modifications, final target compounds will be found with bioassay screens.

1420 three comprehensive but distinct approaches of IDM can be
1421 expressed in Figure 29A–C.

1422 We will continue to improve the Intermediate Derivatization
1423 Methods in agrochemical discovery via selection of inter-
1424 mediates with more varied functionalities, and application of
1425 more efficient organic synthesis routes. One approach we are
1426 considering is to combine IDM with the recently reported
1427 “click chemistry” concept for discovery of biologically active
1428 compounds.¹⁴² We believe that by enabling greater efficiency to
1429 the discovery process of new agrochemicals, and conceivably
1430 also to the discovery of new pharmaceuticals, IDM will enhance
1431 the prospects of sustainable new product development.

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1439 Notes

1440 The authors declare no competing financial interest.

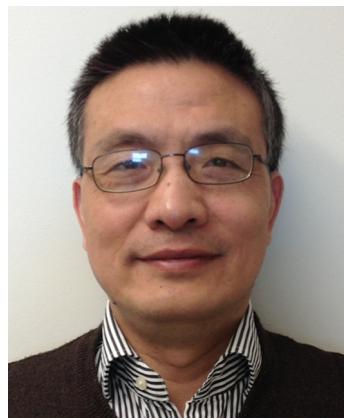
1441 Biographies



1442 Aiying Guan was born in Liaoning Province, China, in 1978. She has
1443 been working in the laboratory of Professor Changling Liu since she
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1446 Biochemistry from Shenyang Agricultural University of China in 2008.
1447 Her research work focuses on the design, synthesis, and optimization
1448 of novel agrochemicals. Up to now, she has 6 peer-reviewed SCI
1449 articles and more than 60 patents filed in China and other countries. In
1450 2003, she discovered fungicide coumoxystrobin under the supervision
1451 of Dr. Changling Liu. This compound was launched in China in 2010
1452 and granted patents ZL200480020125.S, US7642364, and
1453 JP2007510674. Currently, she is a senior scientist in charge of several
1454 National Key Technologies of R&D Programs of China.



1455 Changling Liu was born in Henan Province, China, in 1963. He 1456
1456 received his Ph.D. in pesticide science in 2005 from Nankai University 1457
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is Director of R&D at Shenyang Research Institute of Chemical 1459
Industry, Vice Director of State Key Laboratory of the Discovery and 1460
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SINOCHEM GROUP. He is a Secretary-General of the Chinese 1461
Pesticide Society, Chief-Editor of the Chinese Journal of Agro- 1462
chemicals, a member of the American Chemical Society, and a visiting 1463
professor in many universities such as Nankai University, Zhengzhou 1464
University, Guizhou University, etc. From 1995 to 2004, he worked at 1465
Rohm & Haas Co. and Dow AgroSciences Ltd. for cooperative 1466
research program for nearly 2 years. Up to now, he has more than 160 1467
patents filed in China and other countries including US, EP, JP, KR, 1468
AU, BR, and AR, and one-half of them have been granted. He has also 1469
published more than 20 peer-reviewed SCI papers. In 1994, he 1470
discovered a fungicide “flumorph”. This is the first commercial 1471
fungicide with independent intellectual property rights in China and 1472
was launched in China at the end of 1999. Three other fungicides, 1473
coumoxystrobin, pyraoxystrobin, and pyrametostrobin, discovered by 1474
him were launched in China during 2009–2011 as well. He has 1475
received many awards, such as expert entitled to Government Special 1476
Allowance, the gold prize of the Seventh National invention patent, 1477
the first prize of National Petro-chemical Technology Invention 1478
(2001), the second prize of National Technical Invention (2002), the 1479
eighth Science & Technology Award for Chinese Youth in 2004, a 1480
member of the National New Century Excellent Talents Project 1481
(2007), the scientific and technical innovation prize of Chinese 1482
Pesticides (2008), National Outstanding Professional and Technical 1483
Personnel, and the prize for Outstanding Contributor to Chinese 1484
Pesticide Industry at the 60th anniversary of the founding of PRC 1485
(2009).



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 1499 been a research instructor in the Division of Cardiothoracic Surgery,
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1507 Mark Dekeyser was born in Ypres, Belgium, in 1953. He is currently
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 1510 Waterloo in 1976, Mark joined Chemtura Co. (then known as
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 1512 division. While conducting research at Chemtura, he received his
 1513 Ph.D. in biology in 1994 from the University of Waterloo under the
 1514 supervision of Dr. Roger Downter. Mark was promoted to Research
 1515 Fellow in 2003 and remained at Chemtura until 2007. In 2008, he
 1516 accepted a position with Apotex Pharmachem Inc. in Regulatory
 1517 Affairs. Mark holds 36 U.S. patents and has authored or coauthored 25
 1518 peer-reviewed journal articles and delivered 13 conference presenta-
 1519 tions, all in the field of agrochemical research. He is coinventor of the
 1520 acaricide bifenazate. Mark is also a reviewer for the American Chemical
 1521 Society.

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