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The discovery of Arylex™ active and Rinskor™ active: Two novel auxin herbicides

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ABSTRACT

Multiple classes of commercially important auxin herbicides have been discovered since the 1940s including the aryloxyacetates (2,4-D, MCPA, dichlorprop, mecoprop, triclopyr, and fluroxypyr), the benzoates (dicamba), the quinoline-2-carboxylates (quinclorac and quinmerac), the pyrimidine-4-carboxylates (aminocyclopyrachlor), and the pyridine-2-carboxylates (picloram, clopyralid, and aminopyralid). In the last 10 years, two novel pyridine-2-carboxylate (or picolinate) herbicides were discovered at Dow AgroSciences. This paper will describe the structure activity relationship study that led to the discovery of the 6-aryl-picolinate herbicides Arylex™ active (2005) and Rinskor™ active (2010). While Arylex was developed primarily for use in cereal crops and Rinskor is still in development primarily for use in rice crops, both herbicides will also be utilized in additional crops.

1. Introduction

About 250 plant species currently cause enough problems in food production to be classified as weeds. Collectively, these weeds reduce crop yield and quality, harbor various pests and diseases, and interfere with the management of crops.[1] Accordingly, control of these weeds is essential for maximizing crop production and for simplifying crop management. With the discovery of the auxin herbicides 2,4-D and MCPA in the 1940s, the agricultural practice of weed management was totally transformed.[2] These auxin herbicides reduced the cost and increased the efficiency of controlling a variety of problematic weeds in many important crops.

A herbicide is classified as an auxin if it induces physiological and phenotypic effects similar to those induced by indole-3-acetic acid, a natural plant hormone of the auxin class.[3] Since synthetic auxin herbicides are typically much more stable than indole-3-acetic acid *in planta*, the phenotypic effects caused by auxin herbicides (i.e., tissue swelling, root growth inhibition, and epinasty) can be quite severe and can cause plant death. Since the discovery of 2,4-D and MCPA over 70 years ago, many other herbicides that act via an auxinic mode of action have been discovered and commercialized. The most successful commercial auxin herbicides produced to date are represented by the following classes (examples): the aryloxyacetates (2,4-D, MCPA, dichlorprop, mecoprop, triclopyr, and fluroxypyr), the benzoates (dicamba), the quinoline-2-carboxylates (quinclorac and quinmerac), the pyrimidine-4-carboxylates (aminocyclopyrachlor), and the pyridine-2-carboxylates (picloram, clopyralid, and aminopyralid).

Research efforts at Dow Chemical and Dow AgroSciences have produced all of the commercial auxin herbicides classified as

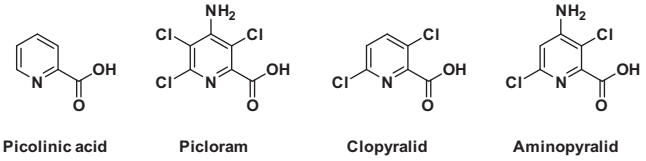

Figure 1. Picolinic acid and some closely related picolinate auxin herbicides.

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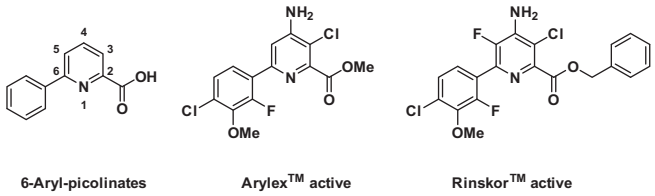


Figure 2. The 6-aryl-picolinate auxin herbicide class.

pyridine-2-carboxylates to date. The pyridine-2-carboxylate auxin herbicides are derivatives of picolinic acid (Fig. 1) and are thus also known as the picolinate auxin herbicides. Picloram (Fig. 1), the first picolinate auxin herbicide, was serendipitously discovered in the late 1950s during a Dow Chemical research study that was focused on the discovery of novel nitrification inhibitors.[4,5]

The second picolinate auxin herbicide, clopyralid (Fig. 1), was discovered in the early 1960s via a Dow Chemical structure activity relationship (SAR) study prompted by the discovery of picloram.[4,6] Almost 40 years after the discovery of picloram, the picolinate auxin herbicide aminopyralid (Fig. 1) was discovered at Dow Chemical when a new electrolysis procedure, originally developed as a method to produce clopyralid from 3,4,5,6-tetrachloropicolinic acid, was applied to picloram to determine what compounds the electrolysis reaction would produce. The major product of that reaction was aminopyralid.[4,7,8]

This second serendipitous discovery of a picolinate auxin herbicide with commercial utility catalyzed a more thorough SAR study of the herbicidal activity associated with the picolinic acid core-structure. This SAR study eventually resulted in the discovery of two more picolinate auxin herbicides with commercial utility. In the years following the discovery of aminopyralid, multiple classes of picolinate analogs were synthesized and found to exhibit potent herbicidal activity toward a large number of key weed species. One of the most potent classes produced to date is the 6-aryl-picolinate class shown in Figure 2. This report provides a brief description of the innovative steps that led to the discovery of the 6-aryl-picolinates and ultimately to the discovery of two novel auxin herbicides: Arylex™ active and Rinskor™ active (Fig. 2).

2. Results and discussion

2.1. Synthesis

All of the picolinate analogs included in this report were synthesized by the sequences shown in Schemes 1–5. As shown in Scheme 1, picloram-methyl **2** was synthesized by treating picloram **1**[5] with thionyl chloride in methanol. Methyl 4-amino-3,5-dichloro-6-aryl-picolinates **3** and **4** were synthesized by the Suzuki reaction of picloram-methyl **2** with the appropriate boronic acid or boronic ester.

As shown in Scheme 2, aminopyralid-methyl **6** was synthesized by heating aminopyralid **5**[7] in a mixture of methanol and sulfuric acid. *N*-acyl-aminopyralid-methyl **7** was synthesized by heating aminopyralid-methyl **6** in acetic anhydride. Methyl 4-acetamido-3-chloro-6-aryl-picolinates **8**–**11** were synthesized by the reaction of *N*-acyl-aminopyralid-methyl **7** with the appropriate boronic acid or boronic ester. Methyl 4-amino-3-chloro-6-aryl-picolinates **12**–**15** were synthesized by dissolving methyl 4-acetamido-3-chloro-6-aryl-picolinates **8**–**11** in methanol and treating these solutions with acetyl chloride. Bromination of methyl 4-amino-3-chloro-6-aryl-picolinate **15** with NBS afforded methyl 4-amino-5-bromo-3-chloro-6-aryl-picolinate **16**. Hydrolysis of methyl 4-acetamido-3-chloro-6-aryl-picolinates **10** and **11** with sodium hydroxide in methanol provided 4-amino-3-chloro-6-aryl-picolinic acids **17** and **18**. Finally, 5-chloro-4-amino-6-aryl-pyridine **19** was synthesized by heating 4-amino-3-chloro-6-aryl-picolinic acid **18** in dioxane.

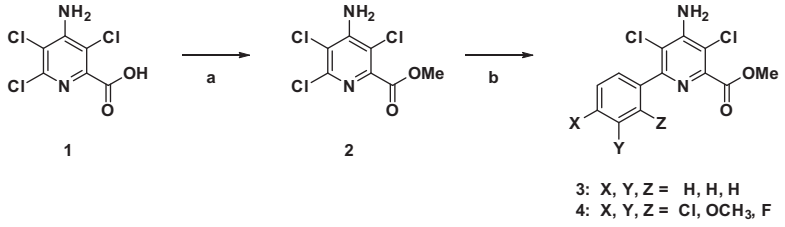
As shown in Scheme 3, methyl 4-amino-3-chloro-5-fluoro-6-aryl-picolinates **21** and **22** were synthesized by the reaction of 5-fluoro-aminopyralid-methyl **20**[9] with the appropriate boronic acid or boronic ester. Hydrolysis of methyl 4-amino-3-chloro-5-fluoro-6-aryl-picolinates **21** and **22** with sodium hydroxide in methanol provided 4-amino-3-chloro-5-fluoro-6-aryl-picolinic acids **23** and **24**. Finally, benzyl 4-amino-3-chloro-5-fluoro-6-aryl-picolinate **25** was synthesized by the reaction of 4-amino-3-chloro-5-fluoro-6-aryl-picolinic acid **24** with benzyl bromide.

As shown in Scheme 4, methyl 4-amino-6-aryl-picolinate **27** was synthesized by the reaction of methyl 6-aryl-tetrahydropyridine-2-carboxylate **26**[10] with DBU in dichloromethane. Methyl 3-bromo-6-aryl-tetrahydropyridine-2-carboxylate **28** was synthesized by treating methyl 6-aryl-tetrahydropyridine-2-carboxylate **26** with NBS in dichloromethane.[10] Methyl 3-bromo-6-aryl-tetrahydropyridine-2-carboxylate **28** was converted to methyl 4-amino-3-bromo-6-aryl-picolinate **29** by heating it in the presence of acetic acid.[10] Methyl 3-chloro-6-aryl-tetrahydropyridine-2-carboxylate **30** was synthesized by treating methyl 6-aryl-tetrahydropyridine-2-carboxylate **26** with sulfuryl chloride in dichloromethane.[10] Finally, methyl 4-amino-3-fluoro-6-aryl-picolinate **31** was synthesized by the reaction of methyl 3-chloro-6-aryl-tetrahydropyridine-2-carboxylate **30** with cesium fluoride in dimethyl sulfoxide.

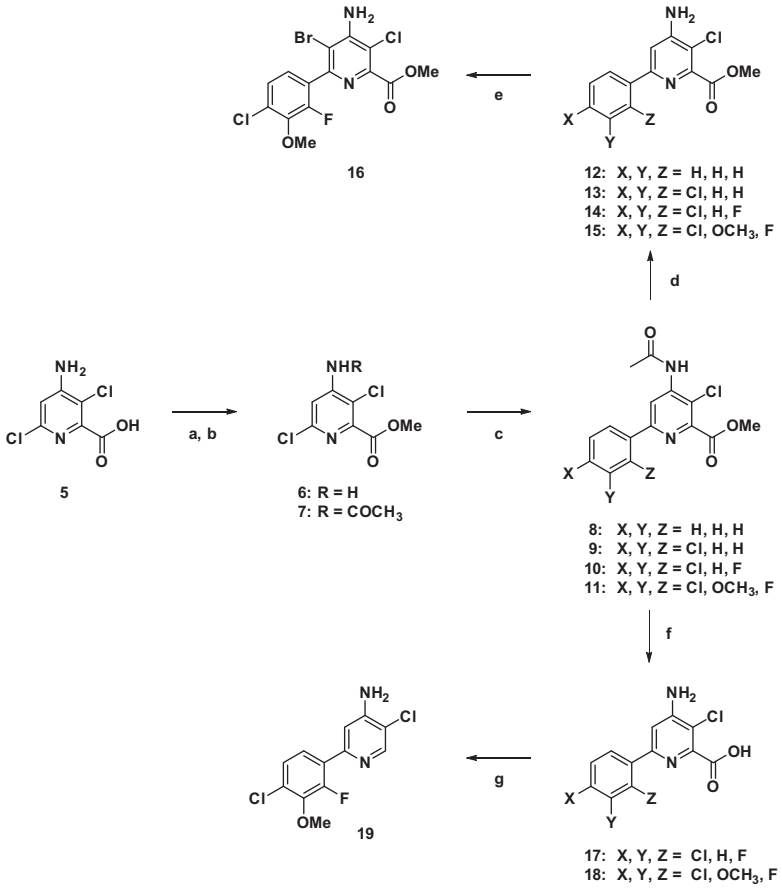
Finally, as shown in Scheme 5, methyl 3-chloro-6-aryl-picolinate **33** was synthesized by the Suzuki reaction of clopyralid-methyl **32**[11] with the appropriate boronic acid or boronic ester.

2.2. SAR study that led to first 6-aryl-picolinate auxin herbicides

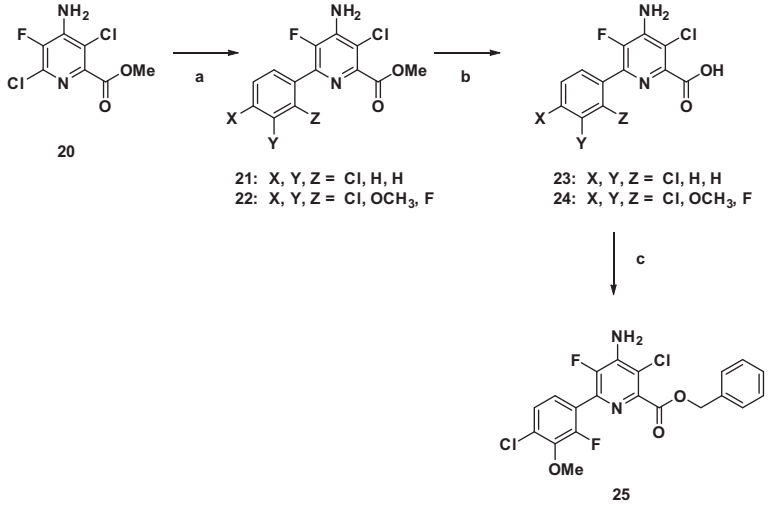
The carboxylic acid functional group of picolinate auxin herbicides is necessary for both the phloem trapping that imparts their systemic herbicidal activity and for the binding interaction that causes their herbicidal effects. Herbicides that act systemically must have some type of acidic functional group (i.e., the carboxylic acid of aminopyralid shown in Fig. 3) that can pass through the lipophilic walls of the phloem tubes and ionize in the basic (pH ~8) aqueous medium of the phloem. If the p*K*a of the acidic



Scheme 1. Synthesis of picolinate analogs **2**–**4**. Reagents and conditions: (a) MeOH, $SOCl_2$, 0–50 °C, 4 h; (b) boronic acid or boronic ester, $Pd(PPh_3)_2Cl_2$, CsF, DME/water, 150 °C, 5 min.



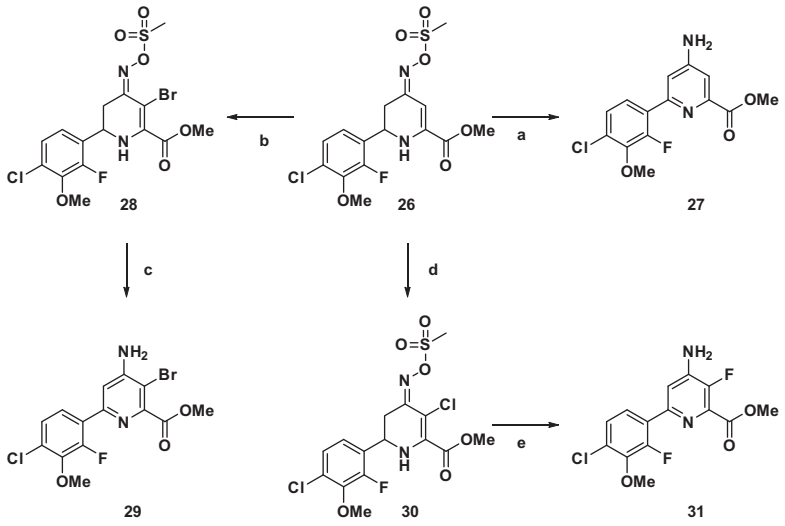
Scheme 2. Synthesis of picolinate analogs **6**–**19**. Reagents and conditions: (a) MeOH, H_2SO_4, reflux, 24 h; (b) Ac_2O, reflux, 16 h; (c) boronic acid or boronic ester, $Pd(PPh_3)_2Cl_2$, KF, ACN/water, 110 °C, 20 min; (d) acetyl chloride, MeOH, 6 h; (e) NBS, DCM, rt, 3 h; (f) NaOH, MeOH/water, rt, 16 h; (g) dioxane, 100 °C, 3 h.



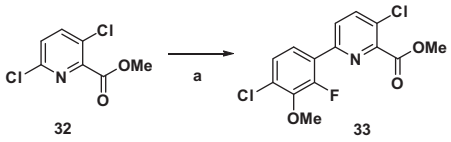
Scheme 3. Synthesis of picolinate analogs **21**–**25**. Reagents and conditions: (a) boronic acid or boronic ester, $Pd(PPh_3)_2Cl_2$, KF, ACN/water, 115 °C, 20 min; (b) NaOH, MeOH/water, rt, 16 h; (c) benzyl bromide, K_2CO_3, DMSO, rt, 3 h.

functional group is below 5, the equilibrium constant for the ionization of the acid (i.e., the deprotonation of aminopyralid shown in Fig. 3) is 10^3 or higher.

In this case (p*K*a <5), the anionic form of the herbicide predominates the neutral form by a factor of 1000:1 or higher in the phloem. Since anions cannot easily pass through the lipophilic walls of the phloem tube, the anionic form of the herbicide concentrates in the phloem in a process called phloem trapping. This process leads to relatively high concentrations of the herbicide within the phloem where the herbicide can be transported to the growing points of the plant and more effectively interfere with plant development. For picolinate auxin herbicides (i.e., clopyralid, picloram,



Scheme 4. Synthesis of picolinate analogs **27**–**31**. Reagents and conditions: (a) DBU, DCM, rt, 1 h; (b) NBS, DCM, rt, 1 h (see US8252938 for details); (c) AcOH, 150 °C, 5 min (see US8252938 for details); (d) SO_2Cl_2, DCM, 0–25 °C, 1 h (see US8252938 for details); (e) CsF, DMSO, rt, 30 min.



Scheme 5. Synthesis of picolinate analog **33**. (a) Boronic acid or boronic ester, Pd $(OAc)_2$, DPPB, CsF, ACN, reflux, 2 h.

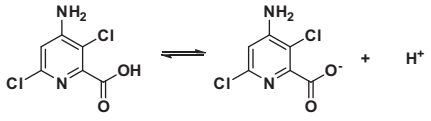


Figure 3. Ionization of aminopyralid.

aminopyralid, Arylex™ active, and Rinskor™ active), the carboxylic acid functional group is also involved in a key binding interaction at the target site for the auxin mode of action.[12]

However, it is important to note that some carboxylate esters of picolinate auxin herbicides exhibit an average herbicidal activity that is approximately equal to that exhibited by their corresponding carboxylic acids. This is true because many plants rapidly convert primary carboxylate esters (i.e., methyl esters) to their corresponding carboxylic acids[13] (see Fig. 4 for an example of this). Since the *in planta* enzymatic conversion of methyl esters to carboxylic acids is often a fast and efficient process for picolinate auxin herbicides, the herbicidal activity of a picolinate auxin methyl ester and its corresponding carboxylic acid are often very similar.

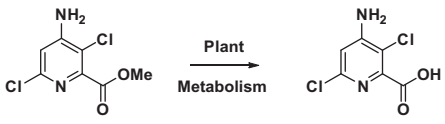


Figure 4. In many plants, conversion of aminopyralid-methyl into aminopyralid by enzymatic hydrolysis is rapid and efficient.

Two examples of this are shown in Figure 5 where the average herbicidal activity of picloram **1** and aminopyralid **5** are compared with the average herbicidal activity of their corresponding methyl esters (**2** and **6**, respectively). The fact that the average herbicidal activity for each of these herbicide pairs (i.e., picloram **1** and picloram-methyl **2**) is similar supports the assertion that picloram-methyl **2** and aminopyralid-methyl **6** are both rapidly and efficiently converted *in planta* to picloram **1** and aminopyralid **5**, respectively. Since the average herbicidal activity of the methyl esters discussed in this paper were all similar to the average herbicidal activity of their corresponding carboxylic acids, the activity data for the remaining SAR discussion was limited to that associated with the methyl esters alone.

The serendipitous discovery of aminopyralid **5** set in motion an exhaustive SAR study of the picolinate auxin herbicide class. This SAR study soon led to the discovery of the 6-aryl-picolinate auxin herbicide class. The first 6-aryl-picolinate analog synthesized was methyl 4-amino-3,5-dichloro-6-phenylpicolinate **3**. While **3** exhibited significant herbicidal activity, its average broadleaf activity was substantially less than that exhibited by aminopyralid-methyl **6** (Fig. 6). The third 6-aryl-picolinate analog synthesized, methyl 4-amino-3-chloro-6-phenylpicolinate **12**, was substantially more active than **3** but still less active than aminopyralid-methyl **6** (see Fig. 6). However, the herbicidal activity associated with **12** provided a clear focus for the SAR development. The positive direction of this focus was quickly confirmed when the sixth 6-aryl-picolinate analog synthesized, methyl 4-amino-3-chloro-6-(4-chlorophenyl)-picolinate **13**, exhibited an average herbicidal activity that was equal to that exhibited by aminopyralid-methyl **6** (Fig. 6).

2.3. SAR study that led to Arylex™ active

The 6-aryl-picolinate SAR pattern that eventually led to the discovery of Arylex™ active, a novel auxin herbicide recently launched by Dow AgroSciences, started with lead compound **13** (Fig. 7). While many compounds were synthesized in the development of the SAR, two of the most herbicidally active analogs were methyl 4-amino-3-chloro-6-(4-chlorophenyl)-5-fluoropicolinate **21** and methyl 4-amino-3-chloro-6-(4-chloro-2-fluorophenyl)picolinate **14**. As shown in Figure 7, the average herbicidal activity of **21** and **14** were both significantly higher than that associated with

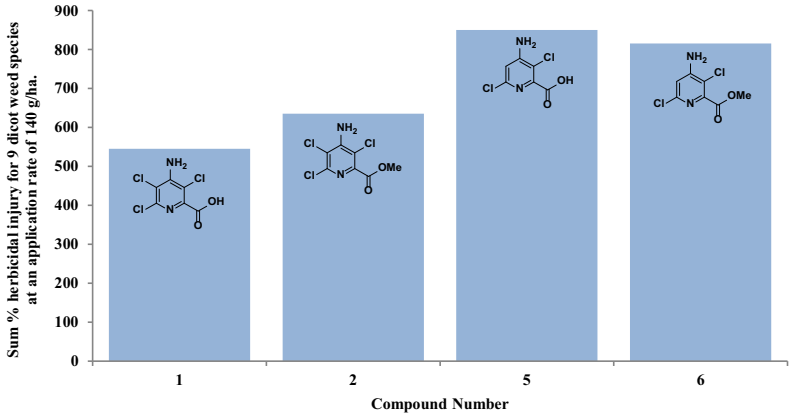


Figure 5. Herbicidal activity of picloram **1**, picloram-methyl **2**, aminopyralid **5**, and aminopyralid-methyl **6**.

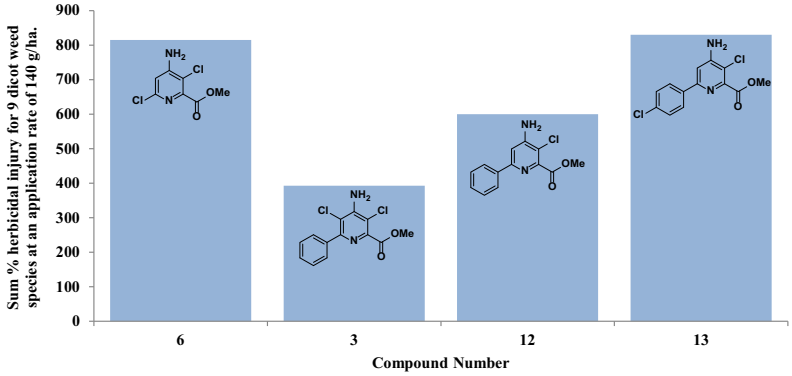


Figure 6. The discovery of aminopyralid catalyzed a thorough SAR study that uncovered the 6-aryl-picolinate auxin herbicide class via analogs **3**, **12**, and **13**.

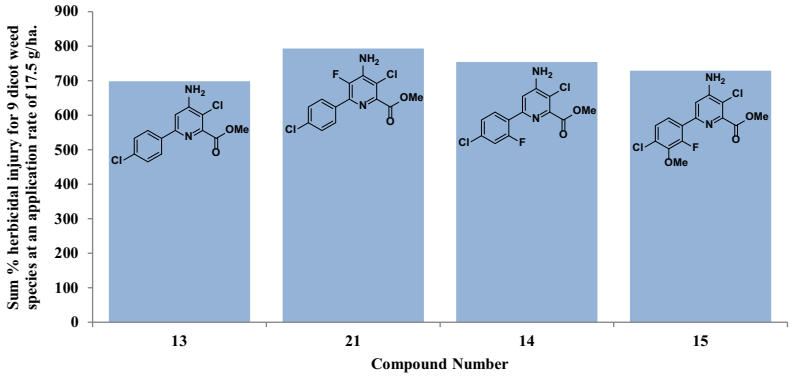


Figure 7. The SAR path that led to Arylex™ active **15**.

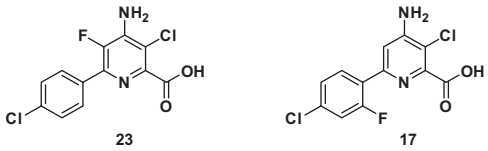


Figure 8. The carboxylic acid forms of **21** and **14** (**23** and **17**, respectively) are both highly active herbicides but probably too soil-persistent to meet regulatory requirements for the targeted commercial applications.

lead compound **13**. Accordingly, the carboxylic acid forms of **21** and **14** (compounds **23** and **17**, respectively, Fig. 8) were subjected to extensive greenhouse and field testing. While the herbicidal activity profiles of **23** and **17** were compelling for some targeted commercial applications, the soil half-life for these analogs appeared to be too long (>240 days) to meet the regulatory requirements for the targeted commercial applications.

Fortunately, an effort designed to incorporate a metabolic handle into the structure of **14** quickly led to compound **15** (Arylex™ active), a potent and broad spectrum auxin herbicide with excellent selectivity to wheat and barley.[4,14] A specific hypothesis that the introduction of a methoxy group at the phenyl tail 3-position of **14** would generate an analog with decreased soil half-life and high herbicidal potency was developed from two observations: (1) There are examples of methoxy groups serving as metabolic handles in commercial herbicides,[4] and (2) An analog of **12** with

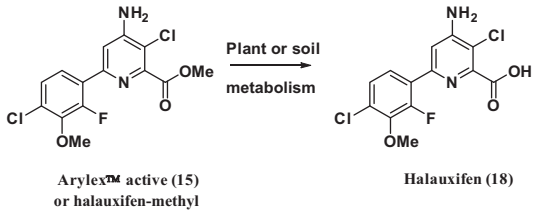


Figure 9. The plant and soil metabolic conversion of Arylex™ active **15** to its carboxylic acid form: halauxifen **18**.

a methoxy group at the phenyl tail 3-position (methyl 4-amino-3-chloro-6-(3-methoxyphenyl)picolinate) was found to be substantially more active than **12** on some key weed species (structure and data not shown).[4]

This hypothesis was confirmed when **15** (Arylex™ active) was found to exhibit herbicidal activity similar to **14**, and when its corresponding carboxylic acid form (compound **18**) was found to exhibit a significantly lower soil half-life range of 10–30 days (Fig. 9). The carboxylic acid form of Arylex (compound **18**) received the common name halauxifen in 2013. Since Arylex is the methyl ester of halauxifen, Arylex is also known commercially as halauxifen-methyl (Fig. 9). Arylex™ active was launched in 2014 for use in cereals and other crops.

2.4. SAR study that led to Rinskor™ active

While probing the SAR of Arylex™ active **15**, several important features of the Arylex picolinate head were identified. For example, the 2-methoxycarbonyl and the 4-amino functional groups of Arylex were found to be essential for the expression of its potent, broad-spectrum herbicidal activity. Accordingly, the des-2-methoxycarbonyl analog of Arylex (compound **19**) is essentially inactive at the 17.5 g/ha application rate (Fig. 10), and the des-4-amino analog of Arylex (compound **33**) is substantially less active than Arylex **15** (Fig. 10).

While less critical than the 2-methoxycarbonyl and 4-amino functional groups of Arylex, the 3-chlorine functional group of Arylex is still important for expression of its potent, broad-spectrum herbicidal activity. Thus, the des-3-chloro analog of Arylex (compound **27**) is substantially less active than Arylex **15** (Fig. 10). As shown in Figure 11, the 3-fluoro and 3-bromo analogs of Arylex (compounds **31** and **29**, respectively) were substantially more active than **27** but significantly less active than Arylex **15**.

While studying the SAR of the Arylex picolinate head 5-position, a second 6-aryl-picolinate auxin herbicide with commercial utility was discovered. Based on previous SAR work with 6-aryl-picolinate analogs (data not shown), we expected the 5-fluoro analog of Arylex (compound **22)** to be as active as Arylex **15**, and the 5-chloro and 5-bromo analogs of Arylex (compounds **4** and **16**, respectively) to be significantly less active than Arylex **15**. As depicted in Figure 12, these expectations were correct.

More importantly, the 5-fluoro analog of Arylex (compound **22**) exhibited potent and broad spectrum herbicidal activity with excellent selectivity to rice. In addition, the corresponding carboxylic acid form of **22** (compound **24)** exhibited a commercially acceptable soil half-life range of 10–30 days (Fig. 13). Optimization of the ester form of **24** eventually led to benzyl ester **25** (Rinskor™ active) as an optimal derivative of **24** (Fig. 13).[15] Initial registrations of Rinskor™ active for use in rice and other crops are anticipated in 2017–2018. Rinskor has not yet received a common name.

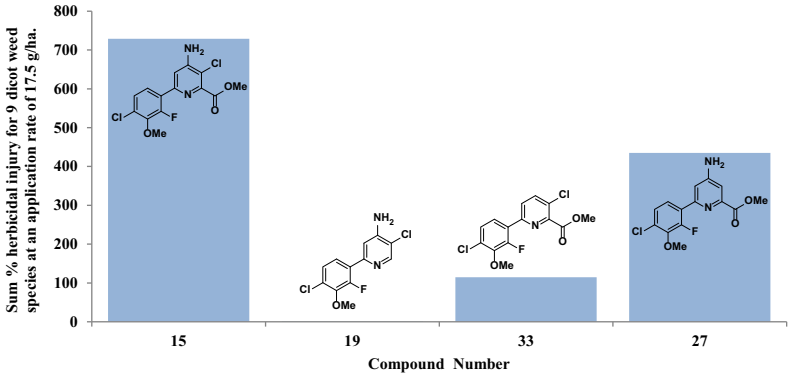


Figure 10. SAR of Arylex™ active (**15**) picolinate head.

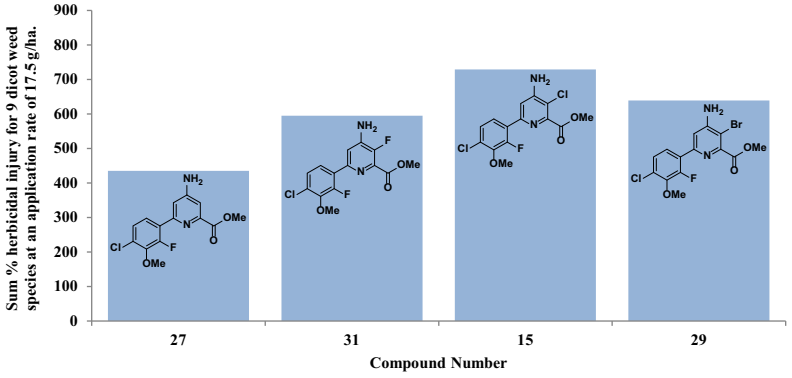


Figure 11. SAR of Arylex™ active (**15**) picolinate head 3-position.

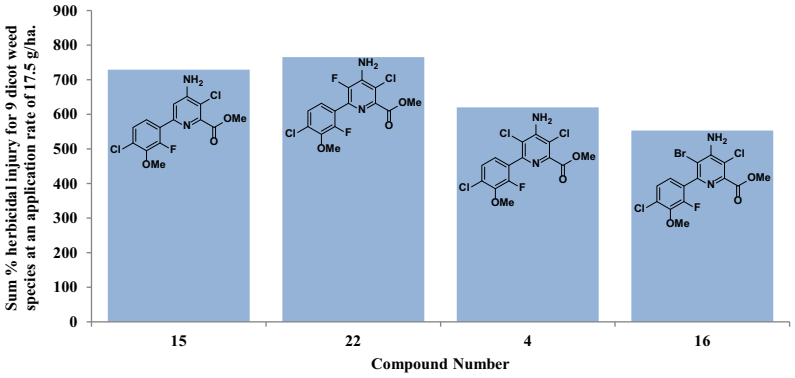


Figure 12. SAR of Arylex™ active (**15**) picolinate head 5-position.

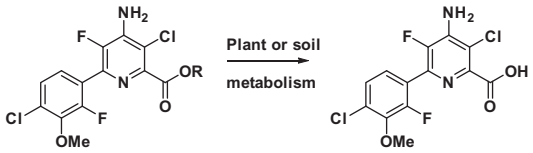


Figure 13. The plant and soil metabolic conversion of **22** and Rinskor™ active (**25**) to their common carboxylic acid form **24**.

3. Conclusion

The serendipitous discovery of the picolinate auxin herbicide aminopyralid in 1998 catalyzed an extensive SAR study that uncovered a novel class of auxin herbicides: the 6-aryl-picolinates. A SAR study of the 6-aryl-picolinates quickly identified two highly active 6-aryl-picolinate herbicides: **21** and **14**. While the activity profiles of these two herbicides were compelling, the soil half-life exhibited by the corresponding carboxylic acid forms of **21** and **14** were both >240 days and considered too long to meet regulatory requirements for the targeted commercial herbicide concepts.

To address this soil half-life issue, an analog of **14** with a methoxy group at the phenyl tail 3-position was designed and synthesized. The novel analog, Arylex™ active, exhibited potent and broad spectrum herbicidal activity with excellent safety to cereal crops, and its corresponding carboxylic acid form exhibited a commercially acceptable soil half-life range of 10–30 days. The herbicide Arylex™ active was launched by Dow AgroSciences in 2014 for use in cereals and other crops.

While conducting a SAR study of the Arylex picolinate head, the 5-fluoro analog of Arylex (compound **22**) was found to exhibit herbicidal activity equal to or better than Arylex for many key weed species. In addition, the corresponding carboxylic acid form of **22** (compound **24**) exhibited a commercially acceptable soil half-life range of 10–30 days. In a subsequent optimization study, the benzyl ester of **24** (compound **25** or Rinskor™ active) was found to exhibit potent and broad spectrum herbicidal activity with excellent safety to rice crops. Initial registrations of the herbicide Rinskor™ active for use in rice and other crops are anticipated in 2017–2018.

4. Experimental

4.1. Chemistry

4.1.1. General

All commercial reagents and solvents were used as received unless otherwise noted. Melting points were obtained on an OptiMelt Automated Melting Point System purchased from Stanford Research Systems and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR), fluorine nuclear magnetic resonance (^{19}F NMR), and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 300, 400, or 600 MHz in $CDCl_3$, DMSO-d_6, or acetone-d_6. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. Mass spectra were obtained using a Waters Micromass ZQ mass spectrometer (LC/MS) or an Agilent 6890 Gas Chromatograph (GC) equipped with an Agilent 5973N Mass Selective Detector (MSD) (GC/MS).

4.1.2. Methyl 4-amino-3,5,6-trichloropicolinate (2)

A solution of compound **1** (5 g, 20 mmol, see US3285925 for preparation) in methanol (105 mL) was cooled to 0 °C. Thionyl chloride (1.95 mL, 26 mmol) was added dropwise at 0 °C and the resulting reaction mixture was stirred at 50 °C for 4 h. The reaction mixture was then concentrated under vacuum and the residue was dissolved in EtOAc (100 mL), washed with water (50 mL), and washed with brine (50 mL). The organic phase was dried, filtered, and concentrated under vacuum to provide compound **2** as a pale yellow solid (4 g, 78% yield): mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.86, 149.03, 146.83, 144.04, 115.40, 114.73, 53.34; EIMS *m*/*z* 254.

4.1.3. Methyl 4-amino-3,5-dichloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (4)

Compound **2** (0.500 g, 1.957 mmol), 2-(4-chloro-2-fluoro-3-methoxyphenyl)-1,3,2-dioxaborinane (0.622 g, 2.54 mmol), bis (triphenylphosphine)palladium(II)-chloride (0.137 g, 0.196 mmol), and cesium fluoride (0.595 g, 3.91 mmol) were combined in 1,2-dimethoxyethane (4 mL) and water (4 mL) in a microwave reactor vessel. The reaction mixture was irradiated in a microwave reactor at 150 °C for 5 min. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried and concentrated onto Celite before purification by flash chromatography (ethyl acetate/hexanes gradient) to provide compound **4** (0.5 g, 67% yield) as a white solid: mp 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.08 (dd, *J* = 8.4, 6.8 Hz, 1H), 5.34 (s, 2H), 3.98 (d, *J* = 1.2 Hz, 3H), 3.97 (s, 3H); ESIMS *m*/*z* 379 [(M+H)$^+$].

Another compound synthesized by a similar method was:

4.1.3.1. Methyl 4-amino-3,5-dichloro-6-phenylpicolinate (3). White solid, mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.62 (m, 2H), 7.47–7.40 (m, 3H), 5.32 (s, 2H), 3.97 (s, 3H); ESIMS *m*/*z* 297 [(M+H)$^+$].

4.1.4. Methyl 4-amino-3,6-dichloropicolinate (6)

To a 2 L, 3-neck round bottom flask with overhead stirrer, temperature probe, nitrogen inlet, and condenser was added compound **5** (207 g, 1 mol, see US6352635 for preparation) and methanol (850 mL). Concentrated sulfuric acid (118 g, 1.2 mol) was added via addition funnel over a 25 min period. The reaction mixture was then heated at reflux for 24 h. At this point, a LCMS analysis indicated that the reaction was about 85% complete. The reaction mixture was allowed to cool to room temperature then transferred to a round bottom flask and concentrated under vacuum. The residue was diluted with ethyl acetate, and the pH was adjusted to about 9 with 37% ammonium hydroxide. The organic phase was collected and the aqueous phase was washed with ethyl acetate (2 × 300 mL). The organic extracts were combined, washed with water, washed with brine, dried, and filtered. The solution was concentrated and then diluted with hexanes. The product was allowed to crystallize for 1 h at room temperature then filtered and dried under vacuum to provide compound **6** (180 g, 81% yield) as a pink-purple solid: mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 4.95 (s, 2H), 3.97 (s, 3H); ESIMS m/z 221 [$(M+H)^+$].

4.1.5. Methyl 4-acetamido-3,6-dichloropicolinate (7)

Compound **6** (2.0 g, 9 mmol) was dissolved in acetic anhydride (20 mL) and heated at reflux for 16 h. The cooled reaction mixture was concentrated under vacuum to remove the excess acetic anhydride. The residue was dissolved in ethyl acetate, the solution poured slowly into water, and the phases thoroughly mixed. Brine was added to aid phase separation. The organic phase was washed with saturated sodium bicarbonate, dried, and concentrated under vacuum. The major products were determined to be mono- and di-acetylated analogs of compound **6** in roughly a 1:1 ratio. Purification by flash chromatography (1:2 ethyl acetate to hexanes) provided compound **7** (920 mg, 39% yield) as a yellow solid: mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.00 (s, 1H), 3.99 (s, 3H), 2.32 (s, 3H); ESIMS m/z 263 [$(M+H)^+$].

4.1.6. Methyl 4-acetamido-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (11)

Compound **7** (0.400 g, 1.520 mmol), 2-(4-chloro-2-fluoro-3-methoxyphenyl)-1,3,2-dioxaborinane (0.483 g, 1.977 mmol), bis (triphenylphosphine)-palladium(II) chloride (0.053 g, 0.076 mmol), and potassium fluoride (0.230 g, 3.95 mmol) were combined in acetonitrile (2.5 mL) and water (2.5 mL). The reaction mixture was irradiated in a microwave at 110 °C in a sealed vial for 20 min. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried and concentrated. The product was purified by flash chromatography (5–40% ethyl acetate in hexanes gradient) to provide compound **11** (0.397 g, 0.995 mmol, 65.4% yield) as a white solid: mp 156–159°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.68 (d, J = 1.1 Hz, 1H), 7.67–7.59 (m, 1H), 7.47 (dd, J = 8.7, 1.6 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 2.25 (s, 3H); ^{19}F NMR (376 MHz, DMSO) δ −131.54; ESIMS m/z 387 [$(M+H)^+$].

Other compounds synthesized by a similar method include:

4.1.6.1. Methyl 4-acetamido-3-chloro-6-phenylpicolinate (8). White solid, mp 155–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.71 (s, 1H), 7.96 (m, 2H), 7.52 (m, 3H), 3.96 (s, 3H), 2.26 (s, 3H); ESIMS m/z 305 [$(M+H)^+$].

4.1.6.2. Methyl 4-acetamido-3-chloro-6-(4-chlorophenyl)picolinate (9). White solid, mp 154–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.71 (s, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 2.24 (s, 3H); ESIMS m/z 339 [$(M+H)^+$].

4.1.6.3. Methyl 4-acetamido-3-chloro-6-(4-chloro-2-fluorophenyl)-picolinate (10). White solid, mp 140–143 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.93 (m, 2H), 7.22 (m, 2H), 4.01 (s, 3H), 2.32 (s, 3H); EIMS m/z 356.

4.1.7. Methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (15)

Acetyl chloride (0.8 g, 10 mmol) was slowly added to a solution of compound **11** (0.8 g, 2.0 mmol) in 150 mL of methanol and stirred for 6 h. The reaction was checked by HPLC and found to be 90% complete. Additional acetyl chloride (0.8 g, 10 mmol) was added and the reaction mixture was stirred overnight to complete the conversion. The methanol was removed under vacuum to leave a white solid. This solid was stirred with ethyl acetate (150 mL) and saturated aqueous $NaHCO_3$ (20 mL) for 1 h to allow all the solids to dissolve. About 0.5 g of K_2CO_3 was added to the aqueous phase and the resulting mixture was stirred for 20 min. The organic phase was dried, filtered, and concentrated under vacuum to provide compound **15** (0.7 g, 99% yield) as a white solid: mp 144–145 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (dd, J = 8.6, 7.9 Hz, 1H), 7.41 (dd, J = 8.7, 1.7 Hz, 1H), 7.23 (d, J = 1.7 Hz, 1H), 6.89 (s, 2H), 3.93 (d, J = 0.8 Hz, 3H), 3.88 (s, 3H); ^{19}F NMR (376 MHz, DMSO) δ −131.48; ESIMS m/z 345 [$(M+H)^+$].

Other compounds synthesized by a similar method include:

4.1.7.1. Methyl 4-amino-3-chloro-6-phenylpicolinate (12). Yellow solid, mp 131–134°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (m, 2H), 7.48 (m, 3H), 7.30 (s, 1H), 6.80 (s, 2H), 3.91 (s, 3H); ESIMS m/z 261 [$(M-H)^-$].

4.1.7.2. Methyl 4-amino-3-chloro-6-(4-chlorophenyl)picolinate (13). White solid, mp 120–122°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (m, 2H), 7.54 (m, 2H), 7.29 (s, 1H), 6.79 (s, 2H), 3.90 (s, 3H); ESIMS m/z 297 [$(M+H)^+$].

4.1.7.3. Methyl 4-amino-3-chloro-6-(4-chloro-2-fluorophenyl)-picolinate (14). White solid, mp 117–119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (t, J = 8.6 Hz, 1H), 7.57 (dd, J = 11.3, 2.1 Hz, 1H), 7.41 (m, 1H), 7.24 (d, J = 1.6 Hz, 1H), 6.88 (s, 2H), 3.89 (s, 3H); ^{19}F NMR (376 MHz, DMSO) δ −113.49; EIMS m/z 314.

4.1.8. Methyl 4-amino-5-bromo-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (16)

To a solution of compound **15** (200 mg, 0.58 mmol) in DCM was added NBS (113 mg. 0.64 mmol). The reaction mixture was stirred at ambient temp for 3 h. The reaction mixture was concentrated onto silica gel and purified by flash chromatography (0–50% ethyl acetate in petroleum ether) to provide compound **16** (212 mg, 86% yield) as a light tan solid: mp 124–125 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43 (dd, J = 8.5, 1.7, 1H), 7.16 (dd, J = 8.4, 7.1, 1H), 7.10 (s, 2H), 3.92 (d, J = 1.1, 3H), 3.87 (s, 3H); HRMS (FAB) calculated for $C_{14}H_{10}Cl_2BrFN_2O_3$ 421.923; found: m/z 422.931 [$(M+H)^+$].

4.1.9. 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinic acid (18)

To a reaction vessel containing compound **11** (0.830 g, 2.144 mmol) was added methanol (21.44 mL) and 2 N sodium hydroxide (4.29 mL, 8.57 mmol). The reaction mixture was stirred overnight at room temperature then acidified by adding a slight excess of 2 N HCl. The mixture was concentrated and the precipitate that formed was washed with water and dried under vacuum to provide compound **18** (0.700 g, 97% yield) as a white solid: mp

167–169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.42 (dd, J = 8.7, 1.6 Hz, 1H), 7.20 (d, J = 1.7 Hz, 1H), 6.81 (s, 2H), 3.93 (d, J = 0.8 Hz, 3H)^{19}F NMR (376 MHz, DMSO) δ −131.50. ESIMS m/z 331 [(M+H)$^+$].

Another compound synthesized by a similar method was:

4.1.9.1. 4-Amino-3-chloro-6-(4-chloro-2-fluorophenyl)picolinic acid (17). White solid, mp 163–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 7.93 (t, J = 8.6 Hz, 1H), 7.57 (dd, J = 11.3, 2.1 Hz, 1H), 7.41 (dd, J = 8.5, 2.1 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 6.81 (s, 2H); ^{19}F NMR (376 MHz, DMSO) δ −113.50; ESIMS m/z 301 [(M+H)$^+$].

4.1.10. 5-Chloro-2-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridin-4-amine (19)

Compound **18** (0.200 g, 0.6 mmol) was dissolved in 1,4-dioxane (12.08 mL) and heated at 100 °C for 3 h. The solvent was removed under vacuum to provide compound **19** (140 mg, 78% yield) as a white solid: mp 165–167°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.61 (dd, J = 8.7, 7.9 Hz, 1H), 7.40 (dd, J = 8.7, 1.7 Hz, 1H), 7.15 (d, J = 1.9 Hz, 1H), 6.55 (s, 2H), 3.92 (d, J = 0.9 Hz, 3H); ^{19}F NMR (376 MHz, DMSO) δ −131.63; ESIMS m/z 287 [(M+H)$^+$].

4.1.11. Methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropicolinate (22)

To a microwave reactor vessel, compound **20** (1.5 g, 6.28 mmol), 2-(4-chloro-2-fluoro-3-methoxyphenyl)-1,3,2-dioxaborinane (1.994 g, 8.16 mmol), potassium fluoride (0.948 g, 16.32 mmol) and bis(triphenylphosphine)palladium(II)chloride (0.440 g, 0.628 mmol) were combined in acetonitrile (13.5 mL) and water (4.5 mL). The reaction mixture was then irradiated in a microwave at 115 °C for 20 min. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water then concentrated onto 7 g of silica gel. The product was purified by flash chromatography (2-20% ethyl acetate in dichloromethane gradient solvent system) to provide compound **22** (1.5 g, 4.13 mmol, 65.8% yield) as a white solid: mp 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (dd, J = 8.5, 1.6 Hz, 1H), 7.31 (dd, J = 11.5, 1.4 Hz, 1H), 7.12 (s, 2H), 3.93 (d, J = 1.0 Hz, 3H), 3.87 (s, 3H); ^{19}F NMR (376 MHz, DMSO) δc −129.19 (J_{F-F} = 30 Hz), 137.67 (J_{F-F} = 30 Hz); ESIMS m/z 363 [(M+H)$^+$].

Another compound synthesized in a similar manner was:

4.1.11.1. Methyl 4-amino-3-chloro-6-(4-chlorophenyl)-5-fluoro-picolinate (21). White solid, mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.81 (m, 2H), 7.50–7.37 (m, 2H), 4.92 (s, 2H), 3.99 (s, 3H); ESIMS m/z 315 [(M+H)$^+$].

4.1.12. 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-5-fluoropicolinic acid (24)

A slurry of compound **22** (10.2 g, 28 mmol) in methanol (60 mL) was prepared in a 250 mL round bottom flask. A 50% w/w solution of sodium hydroxide (4.58 g, 57 mmol) was added followed by 10 mL water. The reaction mixture was stirred overnight. Hydrochloric acid (2 N, 29 mL, 58 mmol) was added causing precipitation of a solid which was filtered, washed with water, and dried under vacuum to provide compound **24** (8.90 g, 91% yield) as a white solid: mp 166–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.68 (s, 1H), 7.47 (dd, J = 8.5, 1.5 Hz, 1H), 7.30 (dd, J = 8.5, 7.0 Hz, 1H), 7.02 (s, 2H), 3.93 (d, J = 0.9 Hz, 3H); ^{19}F NMR (376 MHz, DMSO) δ −129.10 (J_{F-F} = 30 Hz), 138.67 (J_{F-F} = 30 Hz); ESIMS m/z 349 [(M+H$^+$].

Another compound synthesized by a similar method was:

4.1.12.1. 4-Amino-3-chloro-6-(4-chlorophenyl)-5-fluoropicolinic acid (23). Off-white solid, mp 154–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92–7.84 (m, 2H), 7.60–7.55 (m, 2H), 6.93 (s, 2H); ^{19}F NMR (376 MHz, DMSO) δ −141.03; ESIMS m/z 301 [(M+H$^+$].

4.1.13. Benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropicolinate (25)

To a solution of compound **24** (43.0 g, 123 mmol) in dimethyl sulfoxide (250 mL) was added potassium carbonate (25.5 g, 185 mmol) fairly quickly with magnetic stirring. Then benzyl bromide (23.17 g, 135 mmol) was added dropwise over a time period of about 10 min. The resulting reaction mixture was stirred for 3 h at room temperature. When LC analysis showed 2.8% starting material remained, more benzyl bromide (0.8 g) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried, filtered, and concentrated under vacuum to a volume of about 300–400 mL. Heptane was added slowly and the product crystallized out. The product crystals were collected by filtration and washed with pentane. The filtrate gave a second crop upon standing for 1 h that was also collected it by filtration. The mother liquors were combined and concentrated to about 150 mL to provide a third crop. All three crops were combined and dried under vacuum at 50 °C (<1 mm) for 3 h to provide compound **25** (51.4 g, 95% yield) as a white fluffy solid: mp 143–144.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (dd, J = 7.4, 1.2 Hz, 3H), 7.44–7.33 (m, 3H), 7.30 (dd, J = 8.5, 7.1 Hz, 1H), 7.12 (s, 2H), 5.39 (s, 2H), 3.93 (d, J = 0.9 Hz, 3H); ESIMS m/z 439 ([M+H]$^+$); Elemental Analysis: C, 54.69; H, 3.21; N, 6.38. Found: C, 54.37; H, 3.25; N, 6.27.

4.1.14. Methyl 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (27)

To a solution of compound **26** (280 mg, 0.69 mmol, synthesized as described in US8252938) in dichloromethane (5 mL) was added 1,8-diazabicycloundec-7-ene (209 mg, 1.38 mmol). The reaction was exothermic and was heated to reflux by the heat generated from the reaction. After 1 h at room temperature, the reaction mixture was applied to a silica gel column and eluted with 50% ethyl acetate in pentane to provide compound **27** (90 mg, 42% yield) as an off-white solid: mp 159–162°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (m, 1H), 7.43 (dd, J = 8.7, 1.6 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.08 (t, J = 2.1 Hz, 1H), 6.57 (s, 2H), 3.93 (d, J = 0.9 Hz, 3H), 3.84 (s, 3H); ^{19}F NMR (376 MHz, DMSO) δ −131.92; ESIMS m/z 311 [(M+H)$^+$].

4.1.15. Methyl 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-3-fluoropicolinate (31)

To a suspension of anhydrous cesium fluoride (0.228 g, 1.5 mmol) in dry dimethyl sulfoxide (2 mL) was added compound **30** (0.221 g, 0.5 mmol, synthesized as described in US8252938). After stirring at room temperature for 30 min, the reaction mixture was added to diethyl ether (50 mL) and the resulting solution was washed with water, washed with brine, dried, and concentrated. The product was purified by preparatory TLC (20% ethyl acetate in hexanes) to provide compound **31** (0.12 g, 73% yield) as an off-white solid: mp 170–175 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.70 (dd, J = 8.6, 7.9 Hz, 1H), 7.44 (dd, J = 6.3, 1.9 Hz, 1H), 7.35 (dd, J = 8.7, 1.8 Hz, 1H), 6.11 (d, J = 6.4 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H); ^{19}F NMR (376 MHz, acetone) δ −133.05, -148.61; EIMS m/z 328.

4.1.16. Methyl 3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (33)

Compound **32** (1.0 g, 4.85 mmol, see US20120100990 for preparation), 2-(4-chloro-2-fluoro-3-methoxyphenyl)-1,3,2-dioxaborinane (1.424 g, 5.82 mmol), cesium fluoride (0.737 g, 4.85 mmol),

Table 1
Broadleaf weed species utilized in post-emergent herbicide evaluations

Scientific name	Common name	Bayer code
Chenpodium album	Lambsquarter	CHEAL
Ipomea hederacea	Ivyleaf Morningglory	IPOHE
Amaranthus retroflexus	Redroot Pigweed	AMARE
Abutilon theophrasti	Velvetleaf	ABUTH
Viola tricolor	Viola	VIOTR
Polygonum convolvulus	Wild Buckwheat	POLCO
Euphorbia heterophylla	Wild Poinsettia	EPHHL
Cirsium arvense	Canadian Thistle	CIRAR
Helianthus annuus	Sunflower	HELAN

1,4-bis(diphenylphosphino) butane (0.207 g, 0.485 mmol), and palladium(II) acetate (0.109 g, 0.485 mmol) were combined in acetonitrile (48.5 mL) and heated at reflux for 2 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried, filtered, and concentrated. The product was purified by flash chromatography (ethyl acetate/hexanes gradient) to provide compound **33** (400 mg, 25% yield) as a white solid: mp 112–114°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 8.6 Hz, 1H), 8.00 (dd, J = 8.6, 2.1 Hz, 1H), 7.63 (m, 1H), 7.49 (dd, J = 8.7, 1.6 Hz, 1H), 3.95 (s, 6H);^{19}F NMR (376 MHz, DMSO) δ −131.51; ESIMS m/z 330 [(M+H)$^{+}$].

4.2. Biology

4.2.1. Herbicidal assessment of key picolinate and 6-aryl-picolinate analogs

Herbicidal activity was assessed in foliar applications for the nine dicotyledonous weed species shown in Table 1. Plants were incubated in a greenhouse and evaluated for percent visual injury 14 days after compound application. For each compound tested, the percent visual injury values were added together so that the relative activity of test compounds could be compared graphically. For these graphical comparisons, the highest possible score would be 900 and would require 100% percent visual injury (or complete control) of all nine dicotyledonous weed species tested.

4.2.2. Foliar herbicidal activity evaluation

The test plants shown in Table 1 were grown in Metro-mix 360 (SunGro Horticulture, Agawam, MA) in 133 square centimeter (cm^2) plastic pots for 7–21 days in a greenhouse with a 15 h photoperiod maintained at 23–29 °C during the day and 22–28 °C during the night. Plants were grown to the 2 to 3 leaf stage prior to applications.

The concentrated stock solutions were prepared by placing a weighed amount (determined by the highest rate to be tested) of each test compound in a 25 mL glass vial and dissolving the test compound in 4 mL of a 97:3 volume/volume (v/v) mixture of acetone and dimethyl sulfoxide (DMSO), hereafter referred to as the General Purpose Solvent (GPS). If the test compound did not dissolve readily, the mixture was warmed and/or sonicated.

The concentrated stock solutions were diluted with 20 mL of an aqueous mixture containing water, GPS, isopropyl alcohol, Atplus 411F crop oil concentrate, and Triton® X-155 surfactant in a 46:42:12:1.0:0.02 v/v ratio to obtain the spray solutions associated with the highest application rates. Additional spray solutions for the lower application rates were obtained by serial dilution of 12 mL of the high rate solution with a solution containing 2 mL of GPS and 10 mL of an aqueous mixture containing water, GPS, isopropyl alcohol, Atplus 411F crop oil concentrate, and Triton® X-155 surfactant in a 46:42:12:1.0:0.02 v/v ratio. The resulting spray solutions were 1/2X, 1/4X, 1/8X and 1/16X of the most concentrated, high rate spray solution.

Compound requirements were based upon a 12 mL application volume at a rate of 187 L/ha. Formulated compounds were applied to the plant material with an overhead Mandel track sprayer equipped with a 8002E nozzles calibrated to deliver 187 L/ha over an application area of 0.503 square meters at a spray height of 18 inches (43 cm) above the average plant canopy height. Control plants were sprayed in the same manner with the solvent blank. The treated plants and control plants were placed in a greenhouse as described above and watered by sub-irrigation to prevent wash-off of the test compounds. After 14 days, the condition of the test plants as compared with that of the control plants was determined visually and scored on a scale of 0 to 100 percent where 0 corresponds to no injury and 100 corresponds to complete kill.

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