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Synthesis of insecticidal fluorinated anthranilic diamides

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Abstract—A series of highly active fluorinated anthranilic diamide insecticides have been prepared and their biological activity assessed on two aphid species in the search for systemically active compounds that control Hemiptera. In addition, we have demonstrated a new synthesis of *N*-aryl 3-fluoropyrazoles.
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1. Introduction

Modern agricultural practice demands protection of large monocultures from insect pests and diseases which can otherwise severely reduce crop yields. The continual search for new methods of insect control for crop protection is driven by the ability of large, rapidly breeding populations of insects to develop resistance to current insecticides. Improved off-target safety and environmental profiles are also key goals of pesticide research. The identification of potent and selective insect toxins with new sites of action is therefore of high importance.

Rynaxypyr™ (**1**, Fig. 1), is a new insecticide for the control of lepidopteran (caterpillar) and coleopteran (beetle) pests of agriculturally significant crops.[1] It is representative of a new class of anthranilic diamides that act at the ryanodine receptor, a site of action that is currently commercially unexploited. Anthranilic diamides act on the sarcosplasmic reticulum of cardiac and skeletal muscle cells to open internal calcium stores causing muscle contraction, paralysis, and death.[2] Rynaxypyr™ demonstrates field use-rates that are significantly less than current commercial standards, varying from 50 g/ha to less than 1 g/ha and with good safety toward beneficial insects. In addition to possessing extremely high levels of potency on insects, Rynaxypyr™ shows remarkable safety to mammals as a result of poor intrinsic activity on mammalian ryanodine receptors with a margin of selectivity of the order of 10^3.

In the course of the discovery program, indications of activity on Hemiptera, or sucking insects, were noted. Indeed, compound **2** shows levels of activity on aphid and hopper species that approach commercial standards. Populations of hemipteran insect pests, which are mobile and feed on plant sap, are typically most effectively controlled by compounds having physical properties favoring penetration and systemic transport in plants. As part of a broader effort to improve the physical properties of these compounds in order to optimize their plant systemic behavior, we sought to reduce lipophilicity by replacing each of the halogens with fluorine, both individually and collectively (Fig. 2).

2. Results and discussion

Introduction of fluorine onto the phenyl ring was accomplished as shown in Scheme 1. Electrophilic chlorination of 4-fluoroanthranilic acid **3** introduces the 2-substituent, a group that is critical to the biological

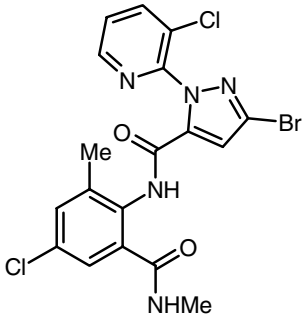

Figure 1. Rynaxypyr™ (1).

Keywords: Fluorination; Ryanodine receptor; Systemic insecticide.
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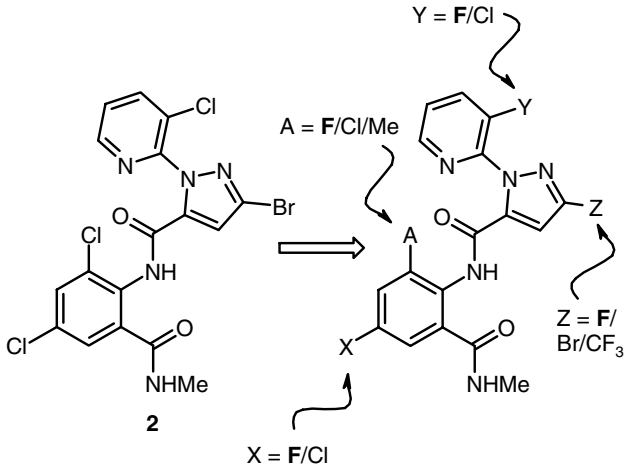
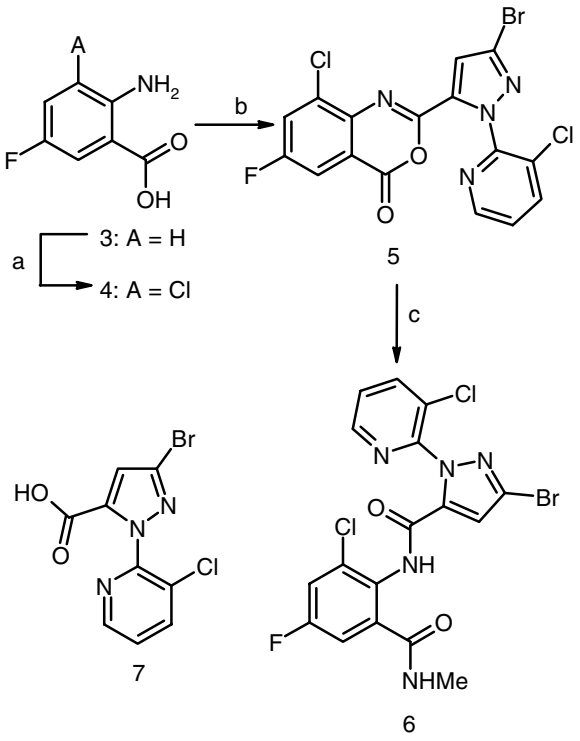


Figure 2. Desired sites of fluorination.

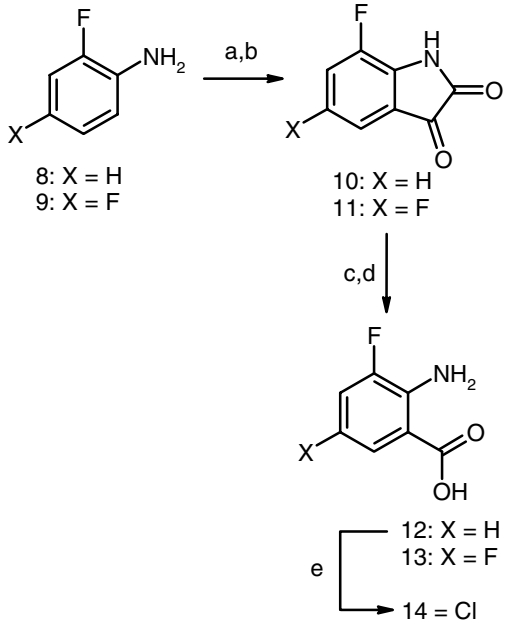


Scheme 1. Reagents and conditions: (a) 1.0 equiv NCS, DMF, rt, 14 h, 82%; (b) **7**, 1 equiv MsCl, 1 equiv NEt_3, CH_3CN, rt, 15 min then 1 equiv **4**, 2 equiv NEt_3, rt, 2 h, then 1 equiv MsCl, rt, 14 h, 47%; (c) 1.3 equiv $MeNH_2$, THF, reflux, 15 min, 59%.

activity of these compounds.[1] Coupling to the pyridylpyrazole acid **7**[1b] is followed by cyclization to the benzoxazinone **5** which can then be opened with a variety of amines to prepare the target diamides.

2-Fluoroanthranilic acids were prepared in modest yield from commercially available fluoroanilines via the isatins **10/11** (Scheme 2).

Compounds in which Y = F (Fig. 2) were prepared by a Balz-Schiemann reaction of the aminopyridines **16** (Scheme 3). Lithiation of the pyrazole **17** was followed



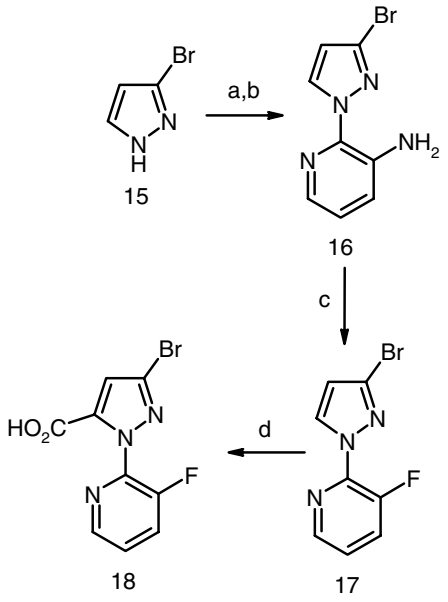
Scheme 2. Reagents and conditions: (a) 1.13 equiv $Cl_3CCH(OH)_2$, 5 equiv $NH_2OH{\cdot}HCl$, 1.25 equiv HCl, 6.7 equiv Na_2SO_4, H_2O, 75 °C, 3 h, X = H, 75%; X = F, 79%; (b) H_2SO_4, 65 °C, 3 h, X = H, 58%; X = F, 13%; (c) 1.3 equiv H_2O_2, HOAc, 2 drops H_2SO_4, 75–100 °C, 20 min, X = H, 34%; X = F, 9%; (d) 5 equiv NaOH, THF, H_2O, rt, 20 min, then 1 N HCl, X = H 30%, X = F, 60%; (e) 1 equiv NCS, DMF, rt, 3 h, 72%.

by carboxylation with CO_2 to give the requisite pyridylpyrazole acid **18** in good yield.

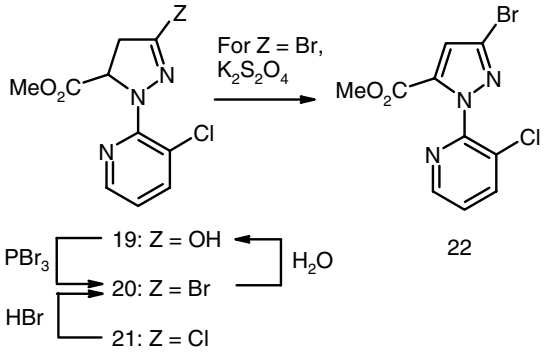
Our standard synthesis of the pyridylpyrazole portion of the molecules is analogous to that shown in Scheme 3 employing 2,3-dichloropyridine in place of 2-chloro-3-nitropyridine. By this route, the synthesis of the 3-fluoropyrazole analog **24** shown in Scheme 5 required the preparation of 3-fluoropyrazole itself.[1] This known pyrazole, however, is prepared in rather low yield by the photochemical decomposition of the corresponding diazo-compound in HBF_4.[3] This route appeared unattractive and an alternative was sought.

An improved synthetic route to the acid **7** via the corresponding ester **22** was developed by Freudenberger et al.[4a] and involves bromination of the pyrazolinone **19** followed by persulfate oxidation of bromopyrazoline **20** as shown in Scheme 4. This bromopyrazoline is somewhat sensitive toward hydrolysis and the corresponding chloropyrazoline **21** can undergo halogen exchange in HBr to give **20**.[4b] It therefore seemed reasonable that the target fluoropyrazole might be obtained from **20** or **21** via halogen exchange followed by oxidation.

Initial experiments with CsF in DMF or DMSO were promising but gave only small amounts of desired product. However, treatment of **20** with AgF in refluxing CH_3CN gave the desired fluoropyrazoline **23** in good yield (Scheme 5). Silver fluoride has been used on occasion for the fluorination of active halides, especially cyanuric chloride, but has not seen widespread use.[5]



Scheme 3. Reagents and conditions: (a) K_2CO_3, 2-chloro-3-nitropyridine, DMF, rt, 14 h; (b) 1 atm H_2, PtO_2, EtOH, rt, 14 h, 78% for 2 steps; (c) $NOBF_4$, PhCl, rt, 14 h then 90 °C, 1.5 h, 24%; (d) LDA, THF, −78 °C, 0.5 h, then CO_2, −78 °C to rt, 10 min, 90%.



Scheme 4. Alternative synthesis of bromopyrazole **22**.

Concomitant with fluorination, AgF also effected oxidation of the pyrazolines to the corresponding pyrazoles. Unfortunately, no standard method of preparative purification was found to be able to separate this mixture of fluoro and bromo pyrazoles. The reaction therefore had to be run to incomplete conversion and the fluoropyrazoline separated from the starting material before being re-subjected to the same conditions in order to prepare the pyrazole **24**, free of the biologically active bromo-analog **22**. The fluoride exchange proceeded equally well on the free base as well as the hydrobromide salt of bromopyrazoline **20**. Using 3 equivalents of AgF in refluxing CH_3CN for 1 hour provides 2:2:3:1 ratio of **20**:**22**:**23**:**24** with an isolated yield of **23** of 33%. Having fluoropyrazole **24** in hand, standard manipulations of hydrolysis, benzoxazinone formation, and ring opening with various amines proceeded smoothly to give the desired anthranilamides.

Calculated and measured logP's for a select group of *N*-methyl anthranilamides are displayed in Table 1. Calculated values have been calibrated with empirical values for 6 compounds representative of A, X, Y, and Z = F and the chloro standard **2**, and are typically higher by ~0.4 log units. The fluorinated analogs possess the desired increase in hydrophilicity and fall within the optimal logP range of 1–3 for a systemic insecticide.[6]

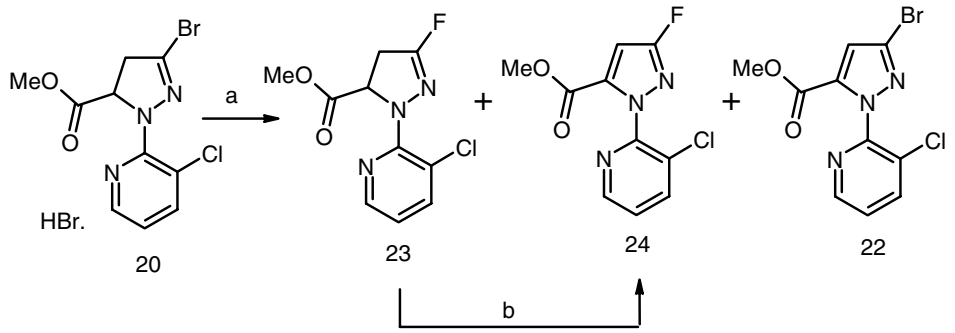
Selected biological data for this series of anthranilamides are displayed in Table 2. The EC_{50} of cotton/melon aphid (CMA; *Aphis gossypii* Glover) and green peach aphid (GPA; *Myzus persicae* (Sulzer)), two agriculturally significant pests of fruit and vegetables, was determined using a combined contact/systemic plant assay (CON/SYS). Also shown is the percent mortality of GPA in systemic only (SYS) plant assay.

Compounds **25** and **2**, anthranilamide benchmarks of hemipteran control, possess activity on aphids approaching that of the commercial standard imidacloprid, an agonist of the nicotinic receptor. They show little difference between each other, indicating that the bromo- and trifluoromethylpyrazoles are essentially equivalent. A comparison of compounds **26** and **25** and of **6** and **2** indicates that replacement of X = Cl for X = F diminishes aphicidal activity, albeit only slightly (1–3×). It can also be seen that the single substitution of A = Cl for A = Me provides compounds with reduced activity (contrast compounds **27** and **28** with **26** and **6**, respectively). Likewise, a comparison of compounds **29** and **36** with the chloro analog **2** and close analogs **25**, **26**, **6**, and **30** indicates that introduction of A = F provides compounds that are similarly inferior to those in which A = Cl, especially on GPA. The fluoropyridyl compounds as represented by compounds **30** and **31** (Y = F) possessed equivalent if not better activity on GPA as compared with compounds **25** and **2**. Compound **30** also possesses activity on CMA comparable to that of the standards. The activity of the fluoropyrazole **32** showed disappointing results with greatly diminished potency on both aphids relative to analogs **26** and **6**.

Despite the threefold lower contact activity of compound **26**, it did display 100% control of GPA in a plant systemic test at 250 ppm. This single piece of data appears to be an improvement over the chloro- analog **25** with 74% control in the same test. However, systemic control of GPA was not observed at 50 ppm for compound **26** and the remaining analogs did not show any significant progress toward the goal of a truly systemic insecticide.

3. Conclusion

In conclusion, a series of highly active fluorinated anthranilamide insecticides have been prepared and their biological activity assessed on two aphid species in the search for systemically active compounds that control Hemiptera. Although possessing excellent levels of contact activity, these compounds failed to show significant improvement in activity over their chloro analogs. This is likely due to a reduction in intrinsic



Scheme 5. Reagents and conditions: (a) 3 equiv AgF, CH_3CN, reflux, 1 h, 33%; (b) AgF, 3 equiv, CH_3CN, reflux, 1 h, 40%.

Table 1. Calculated and measured Log *P*'s for select analogs

Compound	X[a]	A[a]	Y[a]	Z[a]	Calculated log *P*	Measured log *P*
25	Cl	Cl	Cl	CF_3	3.7	
2	Cl	Cl	Cl	Br	3.6	3.0
26	F	Cl	Cl	CF_3	3.1	
6	F	Cl	Cl	Br	3.1	2.6
27	F	Me	Cl	CF_3	3.1	
28	F	Me	Cl	Br	3.0	
29	Cl	F	Cl	Br	3.3	2.9
30	Cl	Cl	F	Br	3.1	2.7
31	Cl	Cl	F	CF_3	3.1	
32[d]	F	Cl	Cl	F	2.3	
33	Cl	Cl	Cl	F	2.9	2.6
34	Cl	Me	Cl	F	2.9	
35	Cl	Me	F	Br	3.0	
36	F	F	Cl	Br	2.7	
37	F	F	Cl	F	2.0	
Rynaxypyr™ (1)	Cl	Me	Cl	Br	3.6	3.0

[a] Refer to Figure 3.

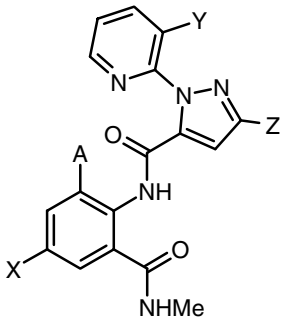


Figure 3.

activity owing to weaker hydrophobic interactions with the receptor. In the cases where A = F, a lessening of the twist angle in the neighboring amide might also be responsible for the decrease in potency.[1] In addition, we have demonstrated a new synthesis of *N*-aryl 3-fluoropyrazoles.[7]

4. Experimental

4.1. General techniques

Reactions were carried out under an atmosphere of dry nitrogen using commercially available anhydrous solvents where appropriate. Amine bases were dried and stored over potassium hydroxide. Glassware was oven-dried before use. Reactions were monitored by TLC on E. Merck silica gel plates (0.25 mm) and visualized under UV light (254 nm) and/or heating with phosphomolybdic acid ethanol solution. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040–0.063 mm except where noted). Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.

NMR spectra were recorded at 25 °C. ^{1}H NMR spectra were recorded at 300 MHz. ^{13}C spectra were recorded at 75 MHz. ^{19}F shifts were recorded at 282 MHz and are reported relative to $CFCl_3$ as an internal standard. IR samples were prepared by evaporation of a solution of the compound from $CDCl_3$ onto a NaCl plate under a stream of nitrogen. Mass spectra were recorded under FAB conditions. Melting points are uncorrected.

Ethyl 1-(3-chloro-2-pyridinyl)-3-fluoro-4,5-dihydro-1*H*-pyrazole-5-carboxylate **23**: To a solution of bromopyrazoline hydrobromide **20** (12.3 g, 29.8 mmol) in CH_3CN (100 mL) was added anhydrous AgF (11.3 g, 89.4 mmol) and the mixture was heated at reflux for 1 h. The mixture was cooled in an ice bath, diluted with EtOAc, and washed with a saturated aqueous solution of $NaHCO_3$. The mixture was filtered through a pad of Celite®, the aqueous phase was separated and ex-

Table 2. Insecticidal activity for compounds evaluated on cotton/melon aphid (CMA) and green peach aphid (GPA)

Compound	Cotton/melon aphid-EC_{50} (CON/SYS)[a]	Green peach aphid-EC_{50} (CON/SYS)[a]	GPA-% *mortality* (SYS)[b]
25	**2.1** (1.4,3.5)	**3.4** (2.7, 4.6)	74
2	**1.6** (0.9, 2.4)	**2.1** (1.4, 3.2)	22
26	**5.5** (4.0, 8.1)	**9.2** (7.2, 12.9)	100
6	**2.5** (1.1, 4.7)	**7.8** (4.0, 23.2)	2
27	**63.4** (26, 201)	**30.8** (6.7, 84.3)	8
28	**11.3** (7.2, 18.5)	**>300**	<80
29	**5.5** (3.0, 9.5)	**>300**	NT
30	**<2**[c]	**1.8**	29
31	**9.1** (5.8, 16.3)	**3.4** (1.5, 7.0)	58
32	**<100**[d]	**<100**[d]	NT
33	**6.2** (4.4, 8.9)	**20.6** (15.9, 26.8)	2
34	**>100**	**>300**	NT
35	**3.7** (2.0, 6.4)	**11.3** (8.7, 15.2)	29
36	**<50**[e]	**<250**[f]	**14**
37	**<250**[g]	**<250**[h]	**NT**
Imidacloprid	**0.4** (0.3, 0.6)	**0.3** (0.2, 0.3)	
Rynaxypyr™ (1)	**3.1** (2.0,4.7)	**12.4** (6.0, 27.2)	12

[a] Upper and lower bounds (95% confidence limits) are shown in parentheses for contact/systemic (CON/SYS) plant assay. All data in ppm.
[b] Percent mortality of GPA at 250 ppm in a systemic-only (SYS) plant assay. NT, not tested.
[c] At 2 ppm the mortality was 89%, no EC_{50} was calculated.
[d] At 100 ppm the mortality was 65% for GPA and 89% for CMA, no EC_{50} was calculated.
[e] At 50 ppm the mortality was 85%, no EC_{50} was calculated.
[f] At 250 ppm the mortality was 90%, no EC_{50} was calculated.
[g] At 250 ppm the mortality was 70%, no EC_{50} was calculated.
[h] At 250 ppm the mortality was 100%, at 50 ppm the mortality was less than 80%, no EC_{50} was calculated.

tracted with EtOAc. The organic phases were combined, washed with saturated solutions of $NaHCO_3$ and then NaCl, and dried ($MgSO_4$). After concentration, the material was purified by flash chromatography (silica gel, 15–40 μ, 9:1 to 4:1 hexane:EtOAc) to afford the fluoropyrazoline **23** as a colorless oil (2.31 g, 33% accounting for 1.24 g of recovered bromopyrazoline **20** as its free base). Colorless oil. R_f 0.27 (silica gel, 4:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 8.08 (dd, $J = 4.8$, 1.5 Hz, 1H); 7.64 (dd, $J = 7.8$, 1.5 Hz, 1H); 7.44 (dd, $J = 7.8$, 4.8 Hz, 1H); 5.41 (dd, $J = 9.3$, 11.7 Hz, 1H); 4.19 (q, $J = 7.2$ Hz, 2H); 3.32 (ddd, $J = 17.1$, 11.7, 6.3 Hz, 1H); 3.17 (ddd, $J = 17.1$, 9.3, 5.4 Hz, 1H); 1.21 (t, $J = 7.2$ Hz, 3H). F^{19} NMR ($CDCl_3$) −105.77 ($J = 5.1$ Hz). C^{13} NMR ($CDCl_3$) δ 168.2, 160.9, 157.3, 150.6, 143.2, 138.1, 118.8, 116.9, 60.7 (d, $J = 102$ Hz), 30.14 (d, $J = 26$ Hz), 12.4. HRMS calcd for $C_{11}H_{12}N_3O_2ClF$ 272.0602; Found 272.0595. IR (film) ν_{max} 2983, 1744, 1672, 1580, 1460, 1373, 1197, 1094, 1032 cm^{-1}. Elemental analysis calcd for $C_{11}H_{11}N_3O_2ClF$: C, 48.63; H, 4.08; N, 15.47; Cl, 13.05; F, 6.99. Found C, 48.42; H, 3.96; N, 15.39; Cl, 12.89; F, 6.68.

Ethyl 1-(3-chloro-2-pyridinyl)-3-fluoro-1*H*-pyrazole-5-carboxylate **24**: To a solution of fluoropyrazoline **23** (1.17 g, 4.31 mmol) in CH_3CN (30 mL) was added anhydrous AgF (2.74 g, 21.6 mmol) and the mixture was heated at reflux for 14 h in the dark. The mixture was cooled, diluted with CH_2Cl_2, and a saturated solution of $NaHCO_3$ was added. The mixture was filtered through a pad of Celite®, the phases were separated, and the organic phase was dried ($MgSO_4$). After concentration, the residue was purified by flash chromatography (silica gel, 4:1 to 7:3 hexane:EtOAc) to afford the fluoropyrazole **24** as a white solid (0.47 g, 40%). mp 54–56 °C. R_f 0.27 (silica gel, 7:3 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 8.50 (dd, $J = 4.8$, 1.6 Hz, 1H); 7.91 (dd, $J = 8.1$, 1.6 Hz, 1H); 7.44 (dd, $J = 8.1$, 4.8 Hz, 1H); 6.59 (d, $J = 6.0$ Hz, 1H); 4.23 (q, $J = 7.2$ Hz, 2H); 1.21 (t, 3H, $J = 7.2$Hz, 3H). F^{19} NMR ($CDCl_3$) −127.65 ($J = 5.9$ Hz). C^{13} NMR ($CDCl_3$) δ 163.5, 160.2, 156.3, 147.3, 145.4, 137.4, 134.2, 128.0, 124.3, 94.1 (d, $J = 23$ Hz), 60.2, 12.4. LRMS (M + H+) 269.99, 271.98. HRMS calcd for $C_{11}H_{10}N_3O_2ClF$: 270.0446; Found: 270.0435. IR (film) ν_{max} 2984, 1732, 1575, 1551, 1479, 1426, 1304, 1248 cm^{-1}. Elemental analysis calcd for $C_{11}H_9N_3O_2ClF$: C, 49.00; H, 3.36; N, 15.58; Cl, 13.15; F, 7.05. Found C, 48.97; H, 3.22; N, 15.45; Cl, 13.03; F, 6.88.

1-(3-Chloro-2-pyridinyl)-3-fluoro-1*H*-pyrazole-5-carboxylic acid (**38**). To a solution of ester **24** (2.45 g, 9.0 mmol) in 1,4-dioxane (90 mL) was added NaOH (9.9 mL, 1.0 N aqueous solution) and the mixture was stirred at ambient temperature overnight. The mixture was diluted with 1 N NaOH (50 mL) and extracted twice with Et_2O. The aqueous phase was acidified with concd HCl (~7 mL) and extracted twice with CH_2Cl_2. This extract was dried ($MgSO_4$) and concentrated to provide the acid as a white solid (2.17 g, 99%). mp 192–194 °C. R_f 0.08 (silica gel, 1:4 MeOH: CH_2Cl_2). ^1H NMR (DMSO-d_6) δ 14.0 (br s, 1H), 8.55 (dd, $J = 4.8$, 1.6 Hz, 1H); 8.24 (dd, $J = 8.1$, 1.6 Hz, 1H); 7.67 (dd, $J = 8.1$, 4.8 Hz, 1H); 6.90 (d, $J = 5.7$ Hz, 1H). C^{13} NMR (THF d_8) δ 163.1, 159.8, 156.6, 147.3, 145.1, 137.0, 134.6, 127.3, 124.2, 93.3 (d, $J = 22.5$ Hz). MS ($M+H^+$) 242.02, 244.00; ($M-H^+$) 240.08, 242.08. IR

(film) ν_{max} 3152, 2922, 2594, 1728, 1556, 1480, 1433, 1305, 1251 cm^{-1}.

2-[1-(3-Chloro-2-pyridinyl)-3-fluoro-1*H*-pyrazol-5-yl]-6,8-dichloro-4*H*-3,1-benzoxazin-4-one (**39**): To a solution of acid **38** (74 mg, 0.31 mmol) in CH_3CN (3 mL) was added $MeSO_2Cl$ (24 μL, 0.31 mmol) followed by NEt_3 (43 μL, 0.31 mmol) and the mixture was stirred at ambient temperature for 10 min. 2,5-Dichloroanthranilic acid (63 mg, 0.31 mmol) was then added, followed by NEt_3 (86 μL, 0.62 mol), and the mixture was stirred at ambient temperature for a further 2 h. $MeSO_2Cl$ (24 μL, 0.31 mmol) was then added and the mixture was stirred at ambient temperature overnight. Concentration of the mixture and purification by flash column chromatography (silica gel, 9:1 to 4:1 hexane:EtOAc) provided benzoxazinone **39** as a yellow solid (64 mg, 32%). R_f 0.22 (silica gel, 4:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 8.53 (dd, $J = 4.8$, 1.6 Hz, 1H); 8.05 (d, $J = 2.3$ Hz, 1H); 7.96 (dd, $J = 8.1$, 1.6 Hz, 1H); 7.72 (d, $J = 2.3$ Hz, 1H); 7.47 (dd, $J = 8.1$, 4.8 Hz, 1H); 6.85 (d, $J = 5.7$ Hz). F^{19} NMR ($CDCl_3$) −127.05 ($J = 6.2$ Hz). C^{13} NMR ($CDCl_3$) δ 163.8, 160.5, 154.7, 146.9, 145.7, 139.7, 137.8, 135.3, 133.2, 133.1, 131.4, 128.3, 125.4, 124.5, 117.7, 94.2 (d, $J = 25$ Hz). MS ($M+H^+$) 411, 413, 415, IR (film) ν_{max} 3120, 1778, 1639, 1542, 1485, 1424, 1300, 1265, 1054, 1017 cm^{-1}.

N-[2,4-Dichloro-6-[(methylamino)carbonyl]phenyl]-1-(3-Chloro-2-pyridinyl)-3-fluoro-1*H*-pyrazole-5-carboxamide (**33**): To a solution of benzoxazinone **39** (64 mg, 0.14 mmol) in THF (2 mL) was added $MeNH_2$ (1 mL, 2.0 M solution in THF) and the mixture was stirred at ambient temperature for 15 min. The mixture was concentrated and triturated with 1-chlorobutane to provide anthranilamide **33** as a white solid (52 mg, 76%). Mp 215–217 °C. R_f 0.34 (silica gel, 1:4 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 9.65 (s, 1H), 8.45 (dd, $J = 4.8$, 1.6 Hz, 1H); 7.85 (dd, $J = 8.1$, 1.6 Hz, 1H); 7.39–7.34 (m, 2H); 7.27 (d, 1H); 6.77 (d, 5.7 Hz, 1H), 6.27 (br q, $J = 4.8$ Hz, 1H), 2.91 (d, $J = 4.8$ Hz, 3H). F^{19} NMR ($CDCl_3$) −127.06 ($J = 5.6$ Hz). C^{13} NMR ($CDCl_3$) δ 165.8, 155.5, 147.5, 145.2, 137.3, 135.9, 133.5, 130.9, 130.8, 129.2, 127.9, 127.6, 124.8, 124.1, 106.4, 92.5 (d, $J = 24$ Hz), 25.5. LRMS ($M+H^+$) 442, 444, 446 ($M-H^+$) 440, 442, 444. HRMS calcd for $C_{17}H_{12}N_5O_2Cl_3F$: 442.0041; Found :442.0030. IR (film) ν_{max} 3251, 1666, 1643, 1549, 1470, 1307 cm^{-1}. Elemental analysis calcd for $C_{17}H_{11}N_5O_2Cl_3F$: C, 46.13; H, 2.50; N, 15.82. Found C, 46.13; H, 2.16; N, 15.64.

3-Amino-2-(3-bromopyrazolyl)pyridine **16**: 3-Bromopyrazole (10 g, 68 mmol), 2-chloro-3-nitropyridine (10.8 g, 68 mmol), and K_2CO_3 (14 g, 101 mmol) were combined in DMF (60 mL) and stirred overnight at ambient temperature. Water (300 mL) was added and the precipitated white solid was collected by filtration. 19.9 g. ^1H NMR ($CDCl_3$)δ 8.60 (dd, 1H), 8.28 (d, 1H), 8.07 (dd, 1H), 7.41 (dd, 1H), 6.53 (d, 1H). The solid was dissolved in ethanol (300 mL) and PtO_2 (200 mg) was added. The vessel was evacuated and purged with N_2 (3×) and H_2 (2×), and then stirred under a balloon of H_2 overnight. After evacuating excess hydrogen, the reaction mixture was filtered through a pad of silica gel and concentrated. The residue was dissolved in hot hexanes, filtered and pale yellow needles were collected upon cooling. 12.6 g, 78% over 2 steps. NMR ($CDCl_3$) δ 8.43 (d, 1H), 7.80 (dd, 1H), 7.13 (dd, 1H), 7.05 (dd, 1H), 6.47 (d, 1H), 5,43 (br s, 2H).

2-(3-Bromopyrazolyl)-3-fluoropyridine **17**: Aminopyridine **16** (12.6 g, 52.7 mmol) was dissolved in chlorobenzene (150 mL) and cooled in an ice bath. $NOBF_4$ (6.8 g, 57.8 mmol) was added and the mixture was allowed to warm to ambient temperature and stirred overnight before being heated at 90 °C for 1.5 h. The cooled mixture was treated with aqueous $NaHCO_3$ and extracted with Et_2O. Non-soluble material was treated with NaOH (1 N) and extracted with Et_2O. The combined ether extracts were dried and concentrated, and the residue was purified by distillation (0.5 mmHg, 162–178 °C) followed by flash chromatography of the distillate (silica gel, 10% to 20% ethyl acetate in hexanes) to give a yellow/orange solid. 3.1 g, 24%. ^1H NMR ($CDCl_3$) δ 8.33 (ddd, 1H), 8.21 (dd, 1H), 7.64 (ddd, 1H), 7.30 (ddd, 1H), 6.54 (d, 1H). F^{19} NMR ($CDCl_3$) −127.13 (dd).

3-Bromo-1-(3-fluoro-2-pyridinyl)-1*H*-pyrazole-5-carboxylic acid **18**: *n*-BuLi (2.5 M in hexanes, 5.4 mL, 13.4 mmol) was added to *i*-Pr_2NH (1.96 mL, 14.1 mmol) in THF (100 mL) at −20 to 0 °C. The mixture was stirred for 15 min before being cooled to −70 °C. Pyrazole **17** (3.1 g, 12.8 mmol) in THF (10 mL) was added via cannula such that the reaction temperature did not exceed −63 °C. After stirring at −78 °C for 0.5 h, CO_2 was introduced for several minutes. The reaction was quenched by the cautious addition of NaOH (1 N) and the reaction mixture was allowed to warm to ambient temperature. The mixture was extracted with Et_2O (2×) which was discarded. The aqueous layer was acidified with conc. HCl, extracted with CH_2Cl_2 (2×), and the combined extracts were dried ($MgSO_4$) and concentrated to afford acid **18** as a white solid. 3.3 g, 90%. ^1H NMR (DMSO-d_6) δ 14.02 (br s, 1H), 8.44 (ddd, 1H), 8.07 (ddd, 1H), 7.73 (ddd, 1H), 7.27 (s, 1H). F^{19} NMR (DMSO-d_6) −127.13 (dd).

The following compounds were obtained by the procedure described above for the synthesis of **33** from the respective anthranilic acid and pyrazole 5-carboxylic acid:

25: ^1H NMR ($CDCl_3$) δ 9.89 (br s, 1H), 8.48 (dd, 1H), 7.89 (dd, 1H), 7.51 (s, 1H), 7.42 (dd, 1H), 7.39 (d, 1H), 7.28 (d, 1H), 6.21 (q, 1H), 2.92 (d, 3H).

2: ^1H NMR ($CDCl_3$) δ 9.65 (s, 1H), 8.46 (dd, 1H), 7.85 (dd, 1H), 7.38 (m, 2H), 7.27 (m, 1H), 7.19 (s, 1H), 6.26 (q, 1H), 2.92 (d, 3H).

26: ^1H NMR ($CDCl_3$) δ 9.73 (br s, 1H), 8.48 (dd, 1H), 7.89 (dd, 1H), 7.53 (s, 1H), 7.42 (dd, 1H), 7.13 (dd, 1H), 7.03 (dd, 1H), 6.23 (q, 1H), 2.91 (d, 3H). ^{19}F NMR ($CDCl_3$) δ −62.90, (s), −111.13 (t).

6: ^1H NMR ($CDCl_3$) δ 9.49 (br s, 1H), 8.46 (dd, 1H), 7.86 (dd, 1H), 7.38 (dd, 1H), 7.19 (s, 1H), 7.14 (dd,

1H), 7.03 (dd, 1H), 6.28 (q, 1H), 2.91 (d, 3H). ^{19}F NMR ($CDCl_3$) δ −111.35 (t).

27: ^{1}H NMR ($CDCl_3$) δ 10.04 (br s, 1H), 8.48 (dd, 1H), 7.88 (dd, 1H), 7.42 (dd, 1H), 7.39 (s, 1H), 6.95 (m, 2H), 6.15 (q, 1H), 2.91 (d, 3H), 2.19 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −62.83, (s), −114.94 (t).

28: ^{1}H NMR ($CDCl_3$) δ 9.89 (br s, 1H), 8.45 (dd, 1H), 7.85 (dd, 1H), 7.37 (dd, 1H), 7.10 (s, 1H), 6.95 (m, 2H), 6.17 (q, 1H), 2.94 (d, 3H), 2.19 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −115.08 (t).

29: ^{1}H NMR ($CDCl_3$) δ 10.04 (br s, 1H), 8.46 (dd, 1H), 7.87 (dd, 1H), 7.38 (dd, 1H), 7.25–7.20 (m, 2H), 7.04 (s, 1H), 6.21 (q, 1H), 2.98 (d, 3H). ^{19}F NMR ($CDCl_3$) δ −109.35 (d).

30: ^{1}H NMR (DMSO-d_6) δ 10.8–10.6, (br s, 1H), 8.42 (m, 1H), 8.4 (br m, 1H), 8.03 (ddd, 1H), 7.85 (d, 1H), 7.75 (s, 1H), 7.72 (m, 1H), 7.52 (d, 1H), 2.66 (d, 3H). ^{19}F NMR (DMSO-$_{d6}$) δ −60.71, −126.83 (d, J = 9.9 Hz).

31: ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 1H), 8.38 (d, 1H), 8.34 (br s, 1H); 7.98 (ddd, 1H), 7.85 (d, 1H), 7.66 (ddd, 1H), 7.51 (d, 1H), 7.40 (s, 1H), 2.66 (d, 3H). ^{19}F NMR ($CDCl_3$) δ −126.67 (d).

32: ^{1}H NMR ($CDCl_3$) δ 9.39 (br s, 1H), 8.45 (dd, 1H), 7.86 (dd, 1H), 7.38 (dd, 1H), 7.19 (dd, 1H), 7.06 (dd, 1H), 6.72 (d, 1H), 6.21 (br s, 1H), 2.92 (d, 3H). ^{19}F NMR ($CDCl_3$) δ −111.46 (t), −127.13 (d).

34: ^{1}H NMR ($CDCl_3$) δ 10.05, (br s, 1H), 8.45 (dd, 1H), 7.85 (dd, 1H), 7.37 (dd, 1H), 7.27 (d, 1H), 7.23 (d, 1H), 6.66 (d, 1H), 6.13 (br m, 1H), 2.96 (d, 3H), 2.20 (s, 3H).

35: ^{1}H NMR (DMSO-d_6) δ 10.31, (s, 1H), 8.37 (m, 1H), 8.25 (br m, 1H), 7.98 (ddd, 1H), 7.65 (ddd, 1H), 7.48 (d, 1H), 7.34 (d, 1H), 7.33 (s, 1H), 2.67 (d, 3H), 2.17 (s, 3H). ^{19}F NMR (DMSO-$_{d6}$) δ −60.66, −127.01 (dd).

36: ^{1}H NMR ($CDCl_3$) δ 9.83, (s, 1H), 8.46 (dd, 1H), 7.87 (dd, 1H), 7.38 (dd, 1H), 7.04 (s, 1H), 7.01–6.92 (m, 2H), 6.27–6.16 (br s, 1H), 2.97 (d, 3H), 2.20 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −107.87 (m), −111.05 (m).

37: ^{1}H NMR ($CDCl_3$) δ 9.84, (s, 1H), 8.45 (dd, 1H), 7.86 (dd, 1H), 7.37 (dd, 1H), 7.00-6.91 (m, 2H), 6.63 (d, 1H), 6.26 (br q, 1H), 2.95 (d, 3H), 2.20 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −108.22 (t), −110.98 (q), −127.18 (d).

Log P's were calculated using Biobyte c log P software. Measured values were determined on a 2.1 mm × 50 mm Zorbax SB C18 column at 40 °C using a flow rate of 1.0 mL/min with a gradient from 99% 5 mM ammonium acetate, pH 7, buffer to 99% 5 mM ammonium acetate in acetonitrile over 5 min. Retention times were compared with a calibration curve created from retention times of compounds with known values of shake-flask octanol–water partition coefficients (P) in the same system.

4.2. Assessment of biological activity

Control of cotton/melon aphid (*Aphis gossypii* Glover). An open container containing a 6–7-days old cotton plant was infested with 30–40 aphids and the soil was subsequently covered with a layer of sand. Compounds were formulated in a solvent comprising 10% acetone, 90% water, and 300 ppm X-77® Spreader Low-Foam Formula non-ionic surfactant and applied in 1 mL volumes through an atomizing sprayer to the test unit. Good foliar and soil coverage was achieved to allow for assessment of contact and soil systemic activity, respectively. Each test was performed in triplicate and when possible with a 3–5× factor of dilution between rates. The units were allowed to dry for 1 h before being capped and held for 6 days at 19–21 °C and 50–70% relative humidity. The units were then visually inspected with a stereomicroscope to assess mortality. Probit analyses of the mortality data were used to generate EC_{50}'s (Table 2). The mortality in the untreated control and solvent check was ~1% and ~10%, respectively.

Green peach aphids (*Myzus persicae* (Sulzer)) were treated in the same manner using a 12–15 days old radish plant in place of the cotton plant. In the systemic-only assay, formulated compounds were applied directly to the soil, avoiding any direct contact with test species. The mortality in the untreated control and that in the solvent check were both ~2%.

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