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Insecticidal anthranilic diamides: A new class of potent ryanodine receptor activators

George P. Lahm,* Thomas P. Selby, John H. Freudenberger, Thomas M. Stevenson, Brian J. Myers, Gilles Seburyamo, Ben K. Smith, Lindsey Flexner, Christopher E. Clark and Daniel Cordova

DuPont Crop Protection, Stine-Haskell Research Center, 1094 Elkton Road, Newark, DE 19711, USA

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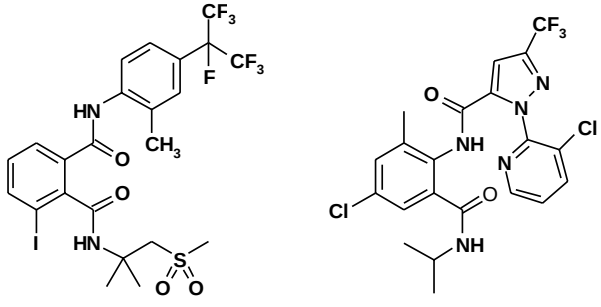
Abstract—A novel class of anthranilic diamides has been discovered with exceptional insecticidal activity on a range of Lepidoptera. These compounds have been found to exhibit their action by release of intracellular Ca^{2+} stores mediated by the ryanodine receptor. The discovery, synthesis, structure–activity, and biological results are presented.

The safe and effective use of insecticides to fight serious crop damage from harmful pests is an essential element in both defense of the food supply and prevention of disease transmission. Due to the ability of insects to rapidly develop resistance, the discovery of agents that act on new biochemical targets is an important tool for effective pest management.

Calcium channels represent a novel target for insect control. Calcium homeostasis plays a key role in multiple cell functions with particular importance in muscle control. Coordinated muscle contraction involves activation of two distinct classes of calcium channels: voltage-gated channels, which allow external calcium entry, and ryanodine receptor channels, which regulate release of internal calcium stores.[1] Ryanodine receptor channels, located in the sarcoplasmic reticulum, derive their name from the plant metabolite ryanodine, a natural insecticide found to affect calcium release by locking channels in a partially opened state.[2] A new class of insecticidal anthranilic diamides has been found which exhibit their action by binding to ryanodine receptors and activating the uncontrolled release of calcium stores.[3,4] Whole organism symptoms include feeding cessation, lethargy, paralysis, and death.

The discovery of the anthranilic diamides followed from work related to the emerging class of insecticidal phthalic diamides.[5] Flubendiamide, a new insecticide from this class, is active on a broad range of Lepidoptera (Fig. 1). Reports now indicate the mechanism of action is also that of ryanodine receptor activation, consistent with our findings for anthranilic diamides.[6] Data suggest that the phthalic diamides constitute a broad chemical class of crop protection agents. Optimum levels of activity appear to be associated with several key structural fragments. Two of these include the presence of an *ortho*-halo substituent adjacent to the alkyl amide and the presence of an *ortho*-methyl substituent on the aniline ring. The alkylsulfonylamide and heptafluoroisopropyl group are also unique features of this molecule. We



Flubendiamide **DP-23**

Figure 1. Diamide insecticides flubendiamide and **DP-23**.

Keywords: Anthranilic; Diamide; Lepidoptera; Ryanodine; Receptor; Insecticide.
* Corresponding author. Tel.: +1 302 36 65 711; fax: +1 302 36 65 738; e-mail: george.p.lahm@usa.dupont.com

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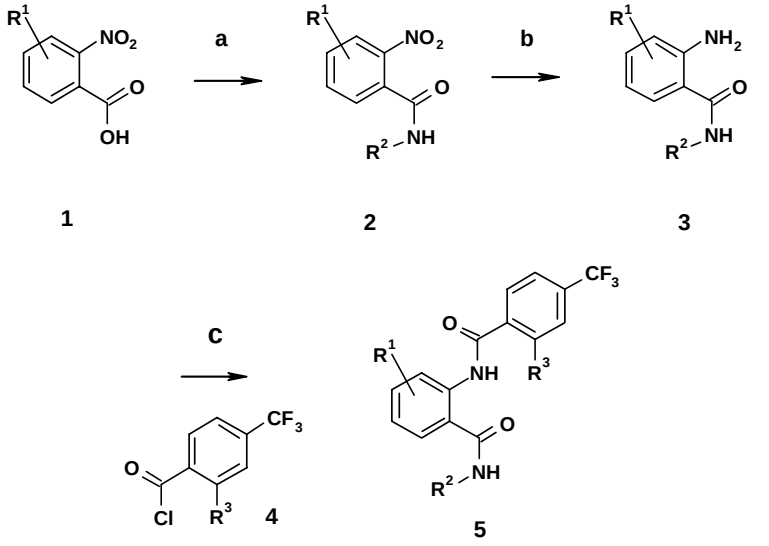
now report the discovery of a new class of insecticides, the anthranilic diamides, which exhibit their action through activation of the ryanodine receptor, culminating in exceptionally potent derivatives such as **DP-23** (see Fig. 1).

Schemes 1–7 illustrate the routes by which the anthranilic diamides were prepared. Our initial targets consisted of a set of substituted derivatives of formula **5**. They were prepared directly by coupling of an anthranilamide **3** with a substituted benzoyl chloride **4** in the presence of base (Scheme 1). Anthranilamides **3** were prepared in two steps from 2-nitrobenzoic acids by treatment with ethyl chloroformate, triethylamine, and the corresponding amines (R^2NH_2) followed by reduction of the nitro group.

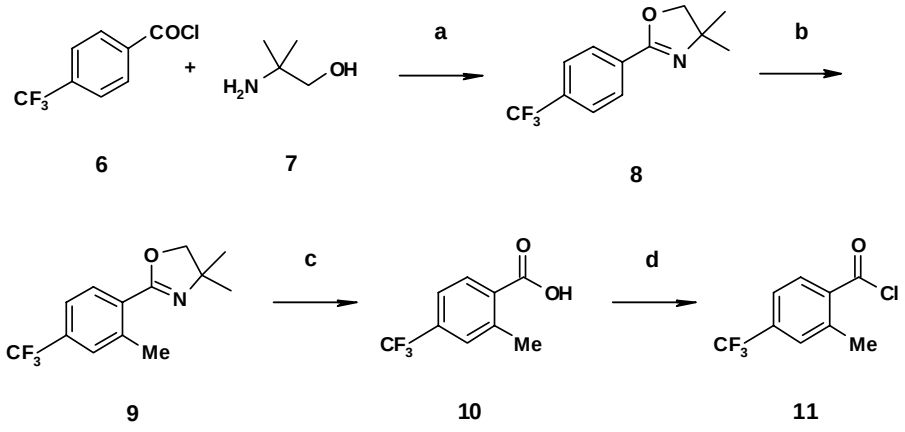
The benzoyl chloride **11** (compound **4** where R^3 is methyl) was prepared as outlined in Scheme 2. Ortho-alkylation of oxazoline **8**, by sequential treatment with *n*-butyl lithium and methyl iodide at −50 °C, followed by hydrolysis of the oxazoline, afforded 2-methyl-4-trifluoromethylbenzoic acid **10** in good yield.[7]

Pyridine analogs **17** were prepared as outlined in Scheme 3. Acetoacetate derivatives of formula **13** were condensed with 4-amino-1,1,1-trifluorobuten-2-one **12** containing an equivalent of trifluoroacetic acid in toluene to afford 2-trifluoromethyl-5-carbomethoxy-pyridines **14** by the method of Okada.[8] Results for both the ethyl and isopropyl analogs (**14**, R^3 = Et, *i*-Pr) were consistent with reported data for the methyl analog (**14**, R^3 = Me) and afforded exclusively the 2-trifluoromethyl pyridine isomers. Condensation of the acid chloride **16** with anthranilamide **3** afforded pyridine anthranilic diamides **17**.

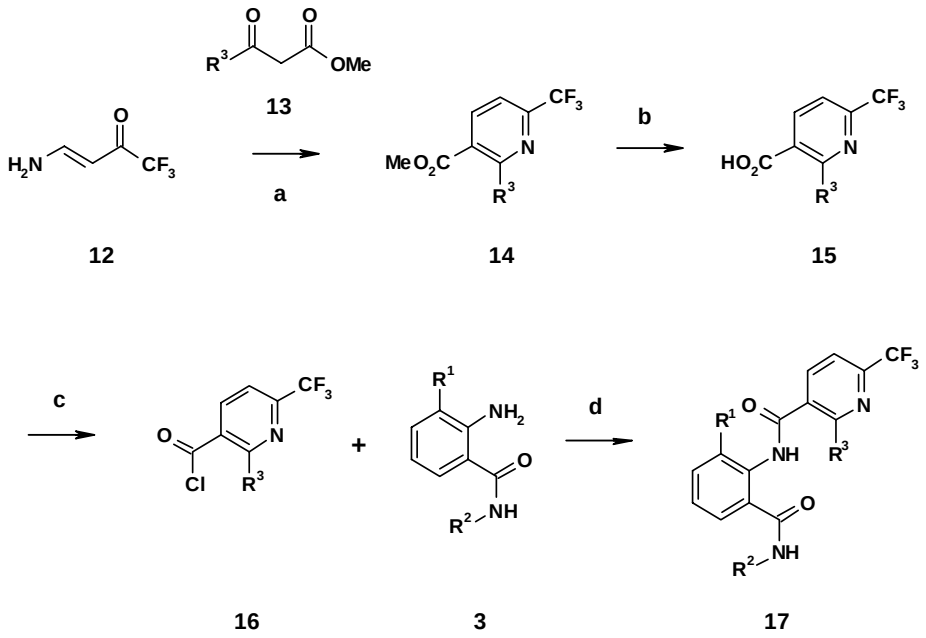
The isosteric pyrimidine analogs **23** were prepared as outlined in Scheme 4.[9] Condensation of trifluoromethyl-acetamidine **18** with methoxymethylene-β-ketoesters **19** afforded 2-trifluoromethyl-5-carbomethoxypyrimidines **20**. Condensation of the derived acid chlorides



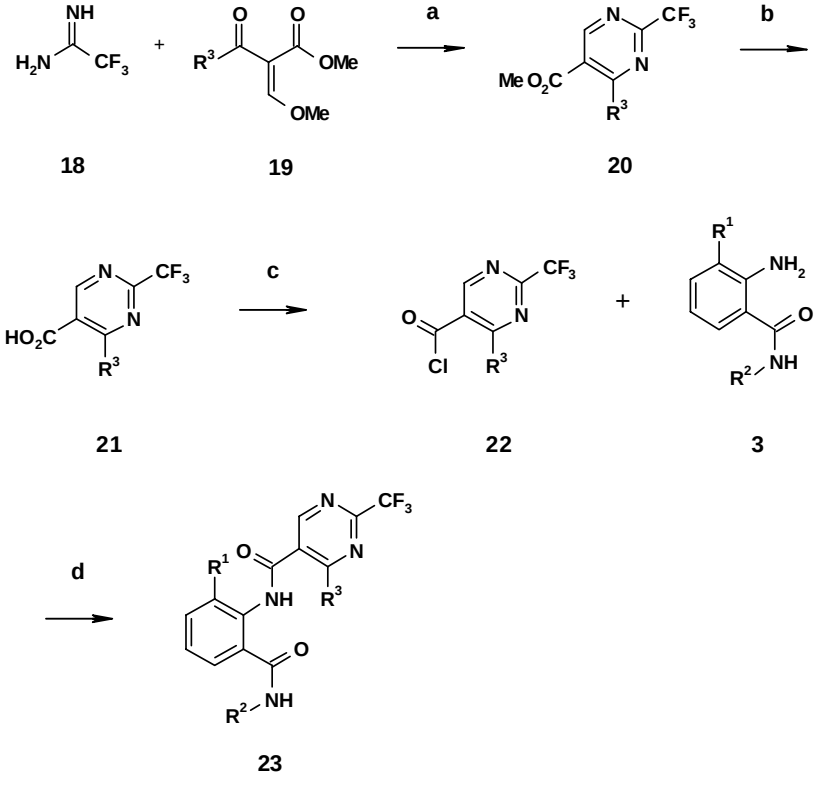
Scheme 1. Reagents and conditions: (a) (i) EtOCOCl, Et_3N, THF, 10 °C (ii) R^2NH_2, THF, 80–90%; (b) H_2, Pd/C, EtOH, 75–95%; (c) $(i\text{-Pr})_2EtN$, $CHCl_3$, 60–80%.



Scheme 2. Reagents and conditions: (a) (i) Et_3N, THF (ii) $SOCl_2$, 15 °C (iii) Et_2O, aq NaOH, 82%; (b) (i) *n*-BuLi, THF, −60 °C (ii) MeI, THF, quant.; (c) concd HCl, H_2O, reflux, 40%; (d) $SOCl_2$, PhMe, reflux, 80%.



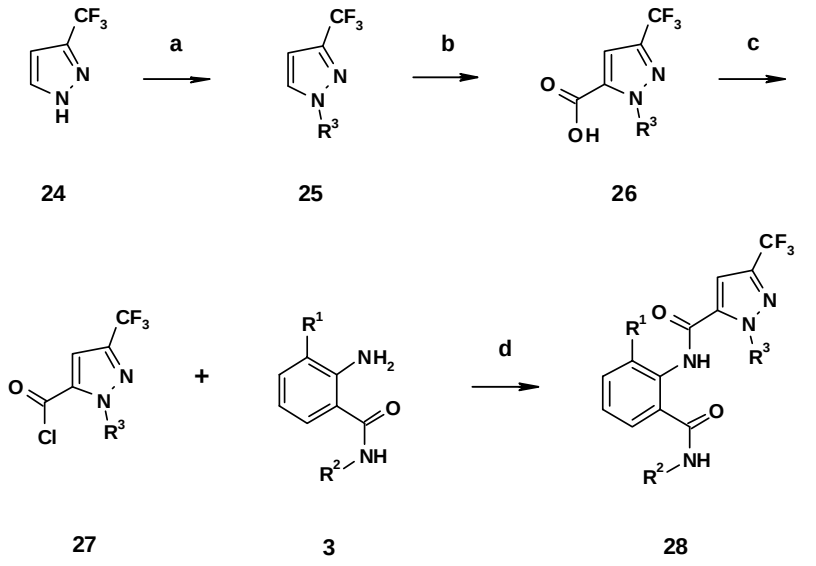
Scheme 3. Reagents and conditions: (a) TFA, toluene, reflux, 25–35%; (b) (i) aq NaOH, MeOH, (ii) HCl, 65–70%; (c) $SOCl_2$, PhMe, reflux, quant.; (d) $(i\text{-Pr})_2EtN$, $CHCl_3$, 50–65%.



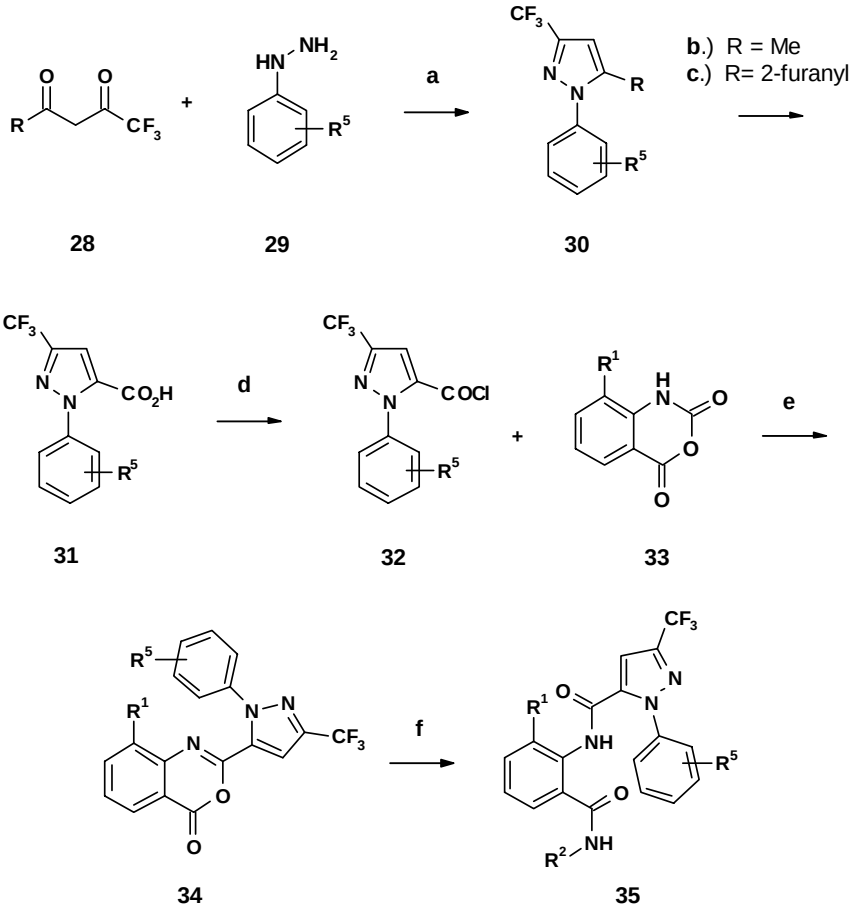
Scheme 4. Reagents and conditions: (a) MeOH, reflux, 50–60%; (b) (i) aq NaOH, MeOH, ambient temp (ii) concd HCl, H_2O, 85–90%; (c) $(COCl)_2$, CH_2Cl_2, DMF (cat.); (d) $(i\text{-Pr})_2EtN$, THF 0 °C to rt, 40–60%.

22 with anthranilamides **3** afforded pyrimidine anthranilic diamides **23**.

Five-membered heterocyclic analogs were of interest to explore the effect of ring size. Pyrazole analogs **28** were prepared as outlined in Scheme 5. Alkylation of 3-trifluoromethyl pyrazole with alkyl iodides in DMF afforded the *N*-alkyl pyrazoles **25**. Regioselective lithiation of **25** with lithium diisopropyl amide at −78 °C afforded exclusively the 5-lithio derivatives in accord with



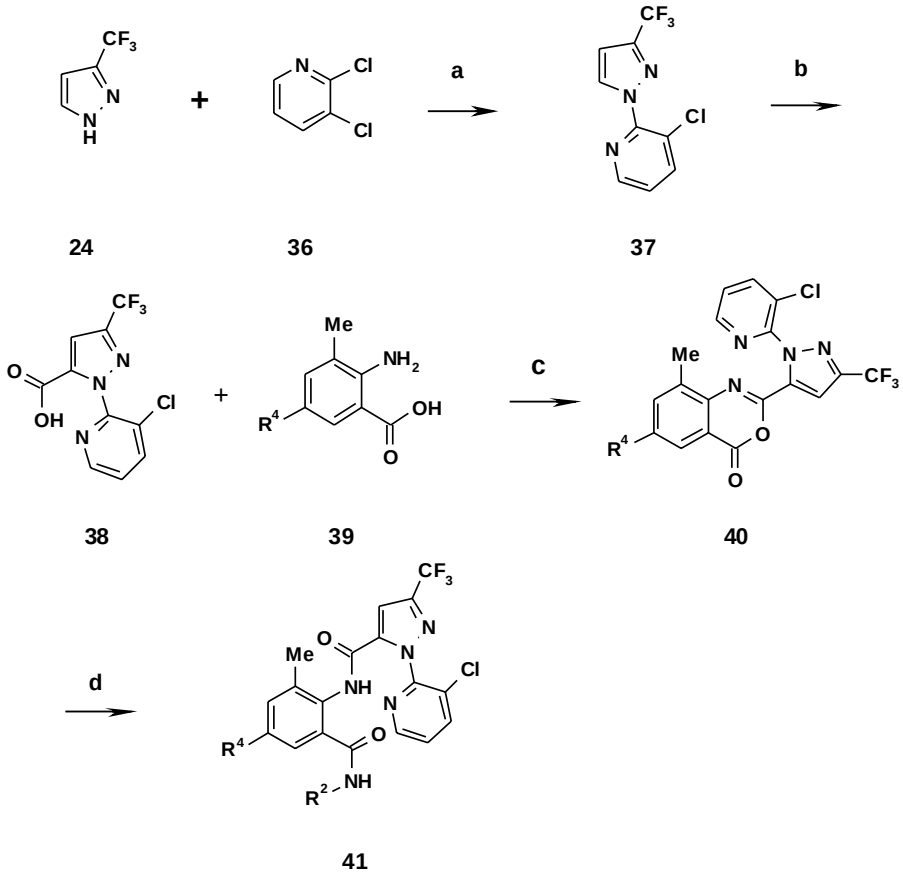
Scheme 5. Reagents and conditions: (a) R^3I, K_2CO_3, DMF, 70–75%; (b) (i) LDA, THF, −78 °C (ii) CO_2 (iii) HCl, 60–65%; (c) $(COCl)_2$, CH_2Cl_2, DMF (cat.); (d) $(i\text{-Pr})_2EtN$, THF, 40–60%.



Scheme 6. Reagents and conditions: (a) AcOH, NaOAc, reflux, 40–60%; (b) $KMnO_4$, H_2O, cetyltrimethyl-ammonium chloride, 10-20%; (c) NaOCl, $NaClO_2$, NaH_2PO_4, MeCN, H_2O, 80–90%; (d) $(COCl)_2$, CH_2Cl_2, DMF; (e) pyridine, reflux; (f) R^2NH_2, THF, 70–80% (three steps).

published results.[10] Quenching with carbon dioxide provided the 5-carboxy-pyrazoles **26** in good yield. Condensation of the derived acid chlorides **27** with anthranilamides **3** afforded the target pyrazole anthranilic diamides **28**.

The phenylpyrazole acids **31** were prepared by the method shown in Scheme 6. Condensation of 1,1,1-trifluoropentanedione with substituted phenyl hydrazines provided the 3-trifluoromethyl-1-phenyl-pyrazoles **30**, with varying amounts (20–40%) of the isomeric



Scheme 7. Reagents and conditions: (a) K_2CO_3, DMF, 125 °C, 75%; (b) (i) LDA, THF, −75 °C (ii) CO_2 (iii) HCl, quant.; (c) (i) **38**, $MeSO_2Cl$, Et_3N, MeCN (ii) **39** (iii) Et_3N, MeCN (iv) $MeSO_2Cl$, 50–60%; (d) R^2NH_2, THF, 70–90%.

5-trifluoromethyl-1-phenylpyrazoles. The acids **31** were prepared by oxidation with potassium permanganate under phase transfer conditions,[11] albeit in generally low yield (10–20%).

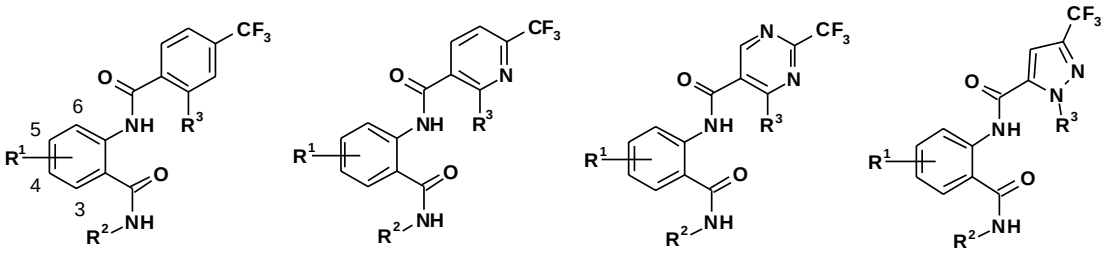
The 2-furanyl derivatives provided better results consistent with literature precedence.[12] Condensation of 4,4,4-trifluoro-1-(2-furanyl)-1,3-butanedione with substituted phenyl hydrazines afforded the 3-trifluoromethyl-1-phenylpyrazoles **30** as the principal product, with lesser amounts of the 5-trifluoromethyl-1-phenylpyrazoles (5–10%). Sodium chlorite oxidation of the furanyl group provided the acids **31** in 70–90% yield. Conversion to anthranilic diamides **35** was achieved using a two-step benzoxazinone route. Condensation of the acid chloride **32** with isatoic anhydrides **33** in pyridine afforded the benzoxazinones **34** directly.[13] Treatment of the benzoxazinone with amines in THF at room temperature afforded the *N*-phenyl pyrazole anthranilic diamides **35** in good yield.

The pyridylpyrazole analogs **41** were prepared following the sequence outlined in Scheme 7. Reaction of 3-trifluoromethyl pyrazole with 2,3-dichloropyridine in DMF afforded exclusively the pyridylpyrazole **37**. As with the alkylpyrazoles **25**, the pyridylpyrazole underwent selective lithiation at the 5-position to afford the corresponding acid upon carbon dioxide quench.

A useful procedure for benzoxazinone **40** formation was employed involving sequential treatment of **38** with one equivalent of triethylamine and methanesulfonyl chloride, followed by the anthranilic acid **39**, then followed with a second equivalent of triethylamine and methanesulfonyl chloride. The intermediate 4-chloro-6-methyl-anthranilic acid **39** (R^4 = Cl) was prepared by chlorination of 6-methylanthranilic acid with *N*-chlorosuccinimide. The benzoxazinones **40** were converted to the corresponding pyridylpyrazole anthranilic diamides **41** in good yield by treatment with amines.

The insecticidal activity of anthranilic diamides is summarized in Tables 1 and 2. Compounds were tested against a series of Lepidoptera under standard laboratory procedures.[14] Potency on diamondback moth (*Plutella xylostella*, *Px*), fall armyworm (*Spodoptera frugiperda*, *Sf*), and tobacco budworm (*Heliothis virescens*, *Hv*) was evaluated. Insecticidal potency is reported as an LC_{50} in ppm, the lethal concentration required for 50% mortality. A subset of compounds was also tested in a calcium mobilization assay, using neurons from the American cockroach, *Periplaneta americana*, to assess activity at the insect ryanodine receptor.[15] This assay demonstrates the ability of anthranilic diamides to release internal calcium stores while failing to activate voltage-gated calcium channels. Furthermore, the calcium mobilization induced by anthranilic diamides was

Table 1. Insecticidal potency and calcium mobilization threshold (CMT) of anthranilic diamides



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Entry	Series	R^1	R^2	R^3	LC_{50} (ppm)			CMT (μM)[a]
					Sf[a]	*Px*[a]	*Hv*[a]	
DP-01	I	H	*i*-Pr	Me	>500	27.3[b]	>500	39.3[c]
DP-02	I	6-Me	*i*-Pr	H	68.9	16.9	>500	
DP-03	I	6-Me	Me	Me	154.9[c]	60.1	>500	
DP-04	I	6-Me	Et	Me	210.4[b]	32.8[b]	>500	
DP-05	I	6-Me	*i*-Pr	Me	20.4	20.7	255.5[b]	
DP-06	I	3-Me	*i*-Pr	Me	>500	77.0[b]	>500	
DP-07	II	6-Me	*i*-Pr	Me	45.2	20.7	326.9[c]	
DP-08	II	6-Me	*i*-Pr	Et	51.3[b]	9.7	77.5[b]	20.6
DP-09	II	6-Me	*i*-Pr	*i*-Pr	53.0[b]	9.6	55.5	
DP-10	III	6-Me	*i*-Pr	Me	70.2	11.6	102.4	
DP-11	III	6-Me	*i*-Pr	Et	193.8[b]	9.0	41.0	
DP-12	III	6-Me	*i*-Pr	*i*-Pr	45.2	9.8	42.3	26.6
DP-13	IV	6-Me	*i*-Pr	Me	48.8[b]	29.6	130.1[b]	119.7
DP-14	IV	6-Me	*i*-Pr	Et	88.2	34.8	158.1[b]	
DP-15	IV	6-Me	*i*-Pr	*i*-Pr	22.8	11.1	36.4	

Insect LC_{50}'s (ppm) on diamondback moth (*Px*, *Plutella xylostella*), fall armyworm (*Sf*, *Spodoptera frugiperda*), and tobacco budworm (*Hv*, *Heliothis virescens*).

[a] Mortality and Ca^{2+} mobilization values were obtained for multiple test rates, each tested in replicate ($n \geqslant 16$ for LC_{50} values), ($n \geqslant 11$ for CMT values). LC_{50} and CMT calculations, with confidence intervals, were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.[16] For each of the values listed the range between the calculated LC_{50} and CMT values, and the corresponding lower or upper 90%-confidence interval value is less than 50% of the calculated value unless otherwise noted.

[b] The range for the upper and/or lower 90%-confidence interval is less than 100% of the calculated value.

[c] The range for the upper and/or lower 90%-confidence interval is less than 250% of the calculated value.

blocked following ryanodine (1 μM) treatment, consistent with action at the ryanodine receptor. The calcium mobilization threshold (CMT) is recorded in Tables 1 and 2. Insecticidal activity was found to correlate with potency in mobilizing calcium (Chart 1). These studies have confirmed the mode of action for anthranilic diamides to be RyR activation and this chemistry has been found to exhibit selectivity for insect receptors.[4]

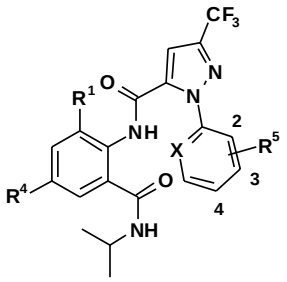
Initial studies were conducted on benzoyl anthranilamides of series I (Table 1). These compounds showed their highest levels of potency on *P. xylostella* and were only marginally effective on *H. virescens*. In fact, *P. xylostella* was consistently the most sensitive species to all anthranilic diamides of series I–V.

For the series I compounds several key structural features were identified as important for insecticidal activity. Anthranilic diamides lacking an R^1 substituent at the 6-position were found to be low in activity. The unsubstituted analog **DP-01** was effective on only the single species *Px* with an LC_{50} of 27.3 ppm. A substantial improvement was achieved by incorporation of a methyl group at the 6-position of the anthranilamide; the LC_{50} on *Px* was reduced to 16.9 ppm and *Sf* showed a greater relative improvement to 68.9 ppm. Comparison of the 3-methyl and 6-methyl positional isomers, **DP-05** and **DP-06**, provided an interesting observation relevant to the relationship with phthalic diamides such as flubendiamide. While the 6-methyl isomer was the most active of series I, the corresponding 3-methyl isomer was the weakest. This seems to contrast with phthalic diamides where the R^1 substituent appears preferentially located *ortho* to the alkyl amide, as inferred from the citations of Ref. 5, and suggests a divergent structure–activity profile for these two classes of chemistry. The presence of a methyl substituent at R^3 provides an increase in activity versus the corresponding unsubstituted analogs as can be seen by comparison of compounds **DP-02** and **DP-05**, where activity is improved better than 2-fold on *Hv* and greater than 3-fold on *Sf*. This observation appears consistent with phthalic diamide structure–activity, where incorporation of an *ortho*-methyl group on the aniline ring increases activity for this class.

The pyridines and pyrimidines of series II and III showed similar levels of activity and were also comparable to the phenyl analogs of series I. Comparison of

Table 2. Insecticidal potency and calcium mobilization threshold (CMT) of series V 1-arylpyrazolyl anthranilic diamides

V



Entry	Series	R^1	R^4	R^5	X	LC_{50} (ppm)			CMT[a] (μM)
						Sf[a]	*Px*[a]	*Hv*[a]	
DP-16	V	Me	H	H	CH	48.3	26.0	353.6[c]	
DP-17	V	Me	H	2-Cl	CH	0.2	0.05[b]	3.4	0.2
DP-18	V	Cl	H	2-Cl	CH	0.4	0.1	3.0	0.3
DP-19	V	Me	H	3-Cl	CH	>500	>500	>500	
DP-20	V	Me	H	4-Cl	CH	>500	>500	>500	
DP-21	V	Cl	H	2-Cl	N	0.1	0.1	0.4	
DP-22	V	Me	H	2-Cl	N	0.1[c]	0.1	0.4	0.3
DP-23	V	Me	Cl	2-Cl	N	0.03	0.01[b]	0.02[c]	0.1
Cypermethrin						5.3	2.1	13.5	na
Indoxacarb						0.3	0.5	1.5	na

Insect LC_{50}'s in ppm on diamondback moth (*Px*, *Plutella xylostella*), fall armyworm (*Sf*, *Spodoptera frugiperda*), and tobacco budworm (*Hv*, *Heliothis virescens*).

[a] Mortality and Ca^{2+} mobilization values were obtained for multiple test rates, each tested in replicate ($n \geqslant 16$ for LC_{50} values), ($n \geqslant 11$ for CMT values). LC_{50} and CMT calculations, with confidence intervals, were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.[16] For each of the values listed the range between the calculated LC_{50} and CMT values and the corresponding lower or upper 90%-confidence interval value is less than 50% of the calculated value unless otherwise noted (na, not applicable).

[b] Range for the upper and/or lower 90%-confidence interval is less than 100% of the calculated value.

[c] Range for the upper and/or lower 90%-confidence interval is less than 250% of the calculated value.

DP-05, **DP-07**, and **DP-10** shows the pyrimidine **DP-10** to be slightly more active on *Sf* and *Px*, and somewhat less active on *Hv*. Comparative data at the R^3 position showed improved activity with increasing size across the series methyl, ethyl, and isopropyl. This trend was confirmed for both the pyridines (**DP-07**, **DP-08**, and **DP-09**) and pyrimidines (**DP-10**, **DP-11**, and **DP-12**). On balance the isopropyl analogs **DP-09** and **DP-12** were the most active for each set by a small margin. Replacement of the heteroaryl group with a pyrazole (series IV) showed a slight net activity improvement in comparison to the pyridines and pyrimidines. The 1-isopropyl pyrazole **DP-15** was the most active alkylpyrazole, with activity comparable to those of **DP-09** and **DP-12** on both *Px* and *Hv*, and with twice the potency on *Sf*.

Activity for the series V aryl pyrazoles is shown in Table 2. The unsubstituted phenyl pyrazole **DP-16** showed relatively modest activity, but was of interest based on its departure from perceived structure–activity relationships. It was less active than the isopropyl analog **DP-15** with rates twofold higher on *Sf* and *Px*, and with a more substantial loss of activity on *Hv*. In contrast, the *ortho*-Cl-phenyl analog **DP-17** showed a remarkable 100-fold improvement in activity against all three species of Lepidoptera and a dramatic reduction in the Ca^{2+} mobilization threshold.

The 6-Cl anthranilamide **DP-18** also showed an equivalent increase in activity, confirming the trend for *ortho*-Cl-phenylpyrazoles. Activity for both **DP-17** and **DP-18** was significantly better than that of the commercial standard cypermethrin and was comparable to that of the standard indoxacarb. In contrast, the isomeric *meta*-Cl and *para*-Cl analogs, **DP-19** and **DP-20**, respectively, showed a substantial activity loss. It is possible that the large increase in activity for **DP-17** and **DP-18** is the result of an ortho steric interaction favoring a more preferred out of plane conformation.

A variety of heterocyclic derivatives of the phenyl pyrazole were investigated and optimum potency was observed for analogs containing the 2-pyridylpyrazole group, such as **DP-21** and **DP-22**. Both compounds showed significantly better activity than their phenyl pyrazole analogs **DP-17** and **DP-18**, particularly on *Hv*. Activity in the Ca^{2+} mobilization assay was comparable for all four compounds, suggesting that the increase in efficacy for pyridylpyrazoles was due in part to improved properties of leaf penetration, plant transport or other aspects of delivery.

Optimization to the 4-chloroanthranilic diamide **DP-23** produced a compound unmatched in potency and spectrum for Lepidoptera.[17,18] High levels of activity

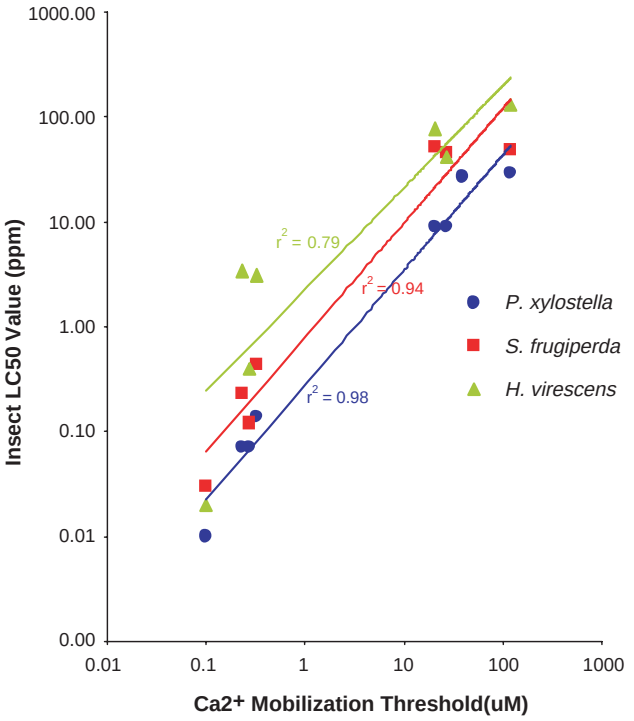


Chart 1. Calcium mobilization activity of anthranilic diamides plotted against the LC_{50} for *P. xylostella*, *S. frugiperda*, and *H. virescens*.

were observed on each of the three species of Lepidoptera at rates in the range of 0.01–0.03 ppm. Comparison of these data with the commercial standards cypermethrin and indoxacarb (Table 2) indicates a potency increase in the range of one to two orders of magnitude. Results from the Ca^{2+} mobilization assay were consistent with insect data showing an IC_{50} of 0.1 μM, the most active compound of the series by a substantial margin.

Comparison of the insecticidal activity on *P. xylostella*, *S. frugiperda*, and *H. virescens* against data from the Ca^{2+} mobilization assay (Chart 1) illustrates the strong relationship between whole organism insect activity and Ca^{2+} mobilization. The relative susceptibility of insect species follows from the trendline *P. xylostella* > *S. frugiperda* > *H. virescens*. Additionally, the clear distinction between the relative activity of series V phenyl and pyridyl pyrazoles and the remaining series I–IV anthranilic diamides is evident.

In summary a novel class of anthranilic diamides has been discovered with exceptional insecticidal activity on a broad spectrum of Lepidoptera. These compounds have been found to exhibit their action by release of intracellular Ca^{2+} stores mediated by the ryanodine receptor. The 4-chloroanthranilic diamide **DP-23** demonstrates activity on each of the three species of Lepidoptera at rates in the range of 0.01–0.03 ppm. This level of activity is significantly better than current standards with remarkable consistency across a broad insect spectrum. These compounds combine a new mode of action with outstanding insecticidal properties and promise to be a valuable addition to the chemistry of crop protection.

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14. A representative testing protocol for *Spodoptera frugiperda* is described: Experimental compounds were formulated at 500 ppm using a solution containing 10% acetone, 90% water, and 300 ppm X-77® Spreader (Loveland Industries, Inc.). Serial dilutions were made to obtain concentrations of 0.01, 0.03, 1, 3, 10, 30, 100, and 500 ppm. The formulated compounds were sprayed to run

off on 4-week-old soybean plants. Once the plants had dried, a leaf (or trifoliate) was excised from the treated plant. The leaves were cut into 24 pieces and placed singly into a 5.5 cm by 3.5 cm cell of a 16-well plastic tray (Mullinix Packages, Inc.). Each cell also contained a 2.5 square of moistened chromatography paper (Whatman No. 3MM) to prevent desiccation. One third instar larvae of *Spodoptera frugiperda* was placed into each cell. A total of 16 insects were tested per rate. Larval mortality was assessed at 96 h post-infestation. Percent control was evaluated [(#dead/total number of insects) × 100] and LC_{50}s were calculated.

15. Embryonic neurons from the American cockroach, *Periplaneta americana*, were cultured onto glass coverslips following published methods.[22] Cells grown 7–14 days in culture were treated for 30 min with the calcium fluoroprobe, Fura-2 AM, (2 μM), and 0.02% pluronic acid in saline having the following composition (mM): NaCl 190, KCl 3.1, $CaCl_2$ 9.0, and Tris 10.0, pH 7.2. Fluoroprobe loaded cells were then rinsed with saline and placed in a recording chamber perfused with saline. Calcium radioimaging studies were conducted by monitoring fluorescence emission images (510 nm) with cells alternately excited at 340 and 380 nm using a fluorescence microscope coupled with the MetaFluor™ imaging system (Universal Imaging, West Chester, PA). As a positive control, cells were treated with the ryanodine receptor agent, caffeine (20 mM), prior to test compound challenges (3 min duration). Caffeine exhibits a calcium mobilization threshold of 5.5 mM in this assay. Intracellular free calcium concentrations ($[Ca^{2+}]_i$) were calculated using the Grynkiewicz equation with calcium mobilization threshold values defined as the concentration required to stimulate a 25 nM mean increase in basal $[Ca^{2+}]_i$.[23] Only those cells responsive to caffeine were included for data analysis.
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17. All new compounds gave satisfactory spectral data consistent with their structures. Selected spectral data for compounds **DP-17**, **DP-18**, **DP-22**, **DP-23** are reported.[18–21]
18. Synthesis of **DP-23**: To a solution of 6-chloro-2-[1-(3-chloro-2-pyridinyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-8-methyl-4*H*-3,1-benzoxazin-4-one (5.0 g, 11.3 mmol) in tetrahydrofuran (35 mL) was added dropwise isopropylamine (2.9 mL, 34.0 mmol) in tetrahydrofuran (10 mL) at room temperature. The reaction mixture was warmed until all solids had dissolved and stirred an additional 5 min, at which point thin layer chromatography on silica gel confirmed completion of the reaction. The tetrahydrofuran was evaporated under reduced pressure, and the residual solid was purified by chromatography on silica gel, followed by trituration with ether/hexane to afford 4.6 g of a white solid. Yield 81 %; mp 195–196 °C; IR (Nujol) ν_{max} 3347, 1690, 1680, 1582, 1547, 1463, 1418, 1376, 1306 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 1.17 (d, 6H, J = 6.53 Hz), 2.13 (s, 3H), 4.15 (m, 1H), 5.98 (d, 1H, J = 7.90 Hz), 7.13 (s, 1H), 7.16 (s, 1H), 7.30 (dd, 1H, J = 2.25, 12.69 Hz), 7.55 (s, 1H), 7.88 (dd, 1H, 1.56, 8.10 Hz), 8.49 (dd, 1H, J = 1.46, 4.68 Hz), 10.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 18.28, 22.69, 41.58, 106.97, 121.46 (q, J_{C-F} 268.57 Hz), 126.16, 127.64, 128.54, 131.63, 131.68, 131.87, 137.24, 139.23, 139.80, 139.94, 142.36 (q, J_{C-F} 38.31 Hz), 147.80, 149.13, 156.11, 165.50; HRMS (APESI, M+) $C_{21}H_{18}Cl_2F_3N_5O_2$: *m/z* calcd 500.0868, *m/z* found 500.0851 (M^+).
19. Compound **DP-17**: mp 232–232 °C; IR (Nujol) ν_{max} 3309, 1672, 1617, 1587, 1536, 1486, 1462, 1379, 1301 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 1.20 (d, 6H, J = 6.53 Hz), 2.20 (s, 3H), 4.17 (m, 1H), 5.95 (d, 1H, J = 7.61 Hz), 7.15 (t, 1H, J = 7.61 Hz), 7.23 (m, 2H), 7.31 (s, 1H), 7.40 (m, 2H), 7.44 (m, 1H), 7.54 (m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 17.87, 22.08, 40.77, 106.39, 120.93 (q, J_{C-F} 269.68 Hz), 125.79, 126.70, 127.78, 128.93, 129.51, 130.31, 131.06, 131.60, 132.28, 134.70, 135.92, 137.59, 139.49, 141.34 (q, J_{C-F} 39.33 Hz), 155.54, 166.40; HRMS (APESI, M+) $C_{22}H_{20}ClF_3N_4O_2$: *m/z* calcd 465.1305, *m/z* found 465.1298 (M^-).
20. Compound **DP-18**: mp 232–232 °C; IR (Nujol) ν_{max} 3326, 1672, 1629, 1592, 1528, 1492, 1462, 1378, 1306 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 1.13 (d, 6H, J = 6.53 Hz), 4.13 (m, 1H), 5.96 (d, 1H, J = 7.90 Hz), 7.11 (t, 1H, J = 7.81 Hz), 7.26 (m, 2H), 7.38 (m, 2H), 7.46 (m, 2H), 7.57 (s, 1H), 10.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 22.03, 40.90, 106.71, 120.89 (q, J_{C-F} 268.01 Hz), 127.01, 127.74, 128.37, 128.94, 129.51, 130.44, 130.62, 131.07, 131.09, 132.17, 137.45, 137.57, 138.89, 141.33 (q, J_{C-F} 39.33 Hz), 155.60, 165.12; HRMS (APESI, M+) $C_{21}H_{17}Cl_2F_3N_4O_2$: *m/z* calcd 485.0759, *m/z* found 485.0755.
21. Compound **DP-22**: mp 191–192 °C; IR (Nujol) ν_{max} 3265, 1657, 1627, 1598, 1546, 1460, 1416, 1375, 1305 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 1.18 (d, 6H, J = 6.83 Hz), 2.19 (s, 3H), 4.18 (m, 1H), 5.97 (d, 1H, J = 8.78 Hz), 7.21 (m, 1H), 7.23 (m, 2H), 7.40 (m, 1H), 7.41 (s, 1H), 7.85 (dd, 1H, J = 1.76, 8.19 Hz), 8.48 (dd, 1H, J = 1.75, 4.97 Hz), 10.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 18.49, 22.77, 41.43, 106.85, 121.49 (q, J_{C-F} 267.13 Hz), 126.48, 127.54, 127.62, 128.55, 132.24, 132.69, 135.67, 136.63, 139.92, 140.02, 142.36 (q, J_{C-F} 38.72 Hz), 147.80, 149.19, 156.09, 166.96; HRMS (APESI, M+) $C_{21}H_{19}ClF_3N_5O_2$: *m/z* calcd 466.1258, *m/z* found 466.1253.
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