Bioorganic & Medicinal Chemistry Letters 23 (2013) 6341–6345

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of cyantraniliprole, a potent and selective anthranilic diamide ryanodine receptor activator with cross-spectrum insecticidal activity

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ARTICLE INFO

Article history:
Received 18 July 2013
Revised 17 September 2013
Accepted 23 September 2013
Available online 1 October 2013

Keywords:
Ryanodine receptor
Anthranilic diamides
Chlorantraniliprole
Cyantraniliprole
Calcium channels

ABSTRACT

Anthranilic diamides are an exceptionally active class of insect control chemistry that selectively activates insect ryanodine receptors causing mortality from uncontrolled release of calcium ion stores in muscle cells. Work in this area led to the successful commercialization of chlorantraniliprole for control of Lepidoptera and other insect pests at very low application rates. In search of lower log*P* analogs with improved plant systemic properties, exploration of cyano-substituted anthranilic diamides culminated in the discovery of a second product candidate, cyantraniliprole, having excellent activity against a wide range of pests from multiple insect orders. Here we report on the chemistry, biology and structure–activity trends for a series of cyanoanthranilic diamides from which cyantraniliprole was selected for commercial development.

Calcium channels are an attractive biological target for insect control due to the important role they play in multiple cell functions such as muscle contraction, neurotransmitter release and fertilization.[1–4] The ryanodine receptor (RyR) is a non-voltage gated calcium channel located in the sarcoplasmic reticulum of muscle cells that regulates the release of intracellular calcium stores critical for muscle function.[5,6]

The name is derived from the natural product ryanodine, a plant metabolite from *Ryania speciosa* that affects calcium release by locking channels in the partially open state.[7,8]

We previously reported on the discovery of a new synthetic class of anthranilic diamide RyR activators which led to the commercialization of chlorantraniliprole (**1a**, DPX-E2Y45, Rynaxypyr®), an insect control agent with outstanding activity against a wide range of lepidopteran pests and other 'plant-chewing' insects (Fig. 1).[9–13] Chlorantraniliprole binds to a site on the RyR distinct from that of ryanodine and its low toxicity to mammals is attributed to the high selectivity for insect versus mammalian RyRs.[14–16]

In contact-systemic screening on 'sap-feeding' pests (insects that feed on the fluids of plants and also referred to as 'sucking/piercing' pests), **1b**, a 4,6-dichloroanthranilamide analog of chlorantraniliprole, demonstrated strong activity against the hemipteran pest *Myzus persicae* (green peach aphid) while maintaining excellent potency against Lepidoptera (Fig. 1). However, in straight systemic tests where plant uptake and translocation of the compound are essential since there is no direct contact with the insect, **1b** showed reduced efficacy versus that observed in the contact-systemic screen. This result was consistent with a measured log*P* (HPLC, pH 7) of 2.9, high for plant systemic movement where a log below 2 would be preferred.[18–22] Nevertheless, the encouraging contact activity against a hemipteran insect, where **1b** was applied directly to the pest on the plant, prompted a search for lower log*P* analogs that might possess improved systemic properties.

Slightly lower log*P* fluorine-containing anthranilic diamides were subsequently reported by Clark et al. to have only a limited improvement in systemic activity.[17] However, we continued to pursue a wide range of polar groups on the anthranilic core with an emphasis on nitrile substitution. This effort culminated in the discovery of cyantraniliprole (**1c**, DPX-HGW86, Cyazypyr™), a second product candidate to emerge from this chemistry class having cross-spectrum activity against a range of insect orders, including Lepidoptera (i.e., caterpillars), Hemiptera (i.e., aphids and white flies) and Coleoptera (i.e., beetles).[23,24] This Letter focuses on the synthesis, biology and structure–activity relationships for a series of cyano-substituted anthranilic diamides that led to cyantraniliprole.

Introduction of a nitrile group at the 4-position on the anthranilamide ring was initially accomplished via palladium-catalyzed

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0960-894X/$ - see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.bmcl.2013.09.076

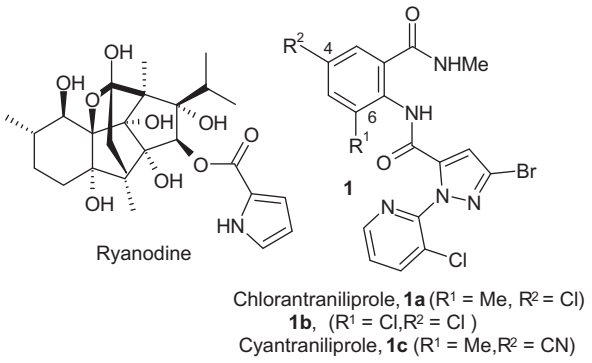


Figure 1. Ryanodine and anthranilic diamides.

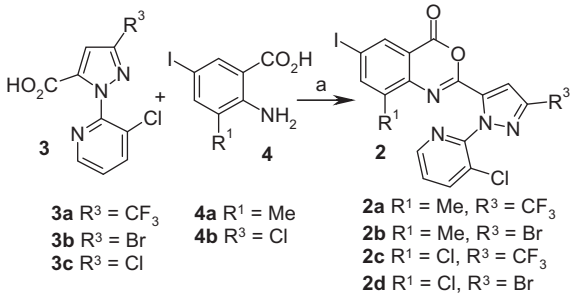
cross-coupling of a 4-iodoanthranilic diamide with cyanide. As outlined in Scheme 1, iodobenzoxazinones of formula **2** were made by sequential treatment of pyridylpyrazole acids **3** with 1.1 equiv of triethylamine and methanesulfonyl chloride, followed by one equiv of iodoanthranilic acid **4**, 2.1 equiv of triethylamine and another 1.1 equiv of methanesulfonyl chloride.[23,25]

Ring opening of iodobenzoxazinone **2a** with amines gave the respective 4-iodoanthranilic diamides **5** that were cross-coupled with cuprous cyanide by heating in the presence of Pd(PPh3)4 and cuprous iodide in THF to afford the corresponding 4-cyanoanthranilic diamides **7** in modest yields (Scheme 2). Reversing the order of these two steps was found to be preferred. Iodobenzoxazinones **2** were coupled with cyanide to afford cyanobenzoxazinones **6** that on ring opening with amines gave 4-cyanoanthranilic diamides of formula **7** (Scheme 2) in good yield.[25]

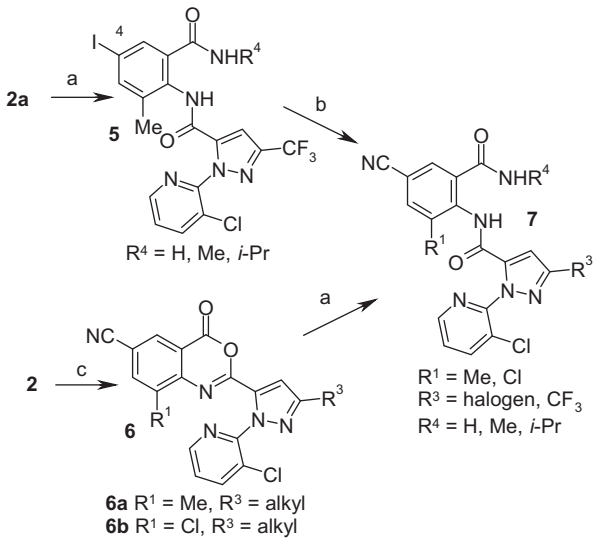
For expanded tests where larger quantities of 4-cyanoanthranilic diamides **7** were needed, an alternative synthesis of precursors **6a** was employed as outlined in Scheme 3.

Heating **4a** with cuprous cyanide under Rosenmund–von Braun conditions gave cyanoanthranilic acid **8** in moderate yield.[26] Copper-catalyzed exchange of iodide with sodium cyanide in the presence of a diamine ligand gave an improved yield. Treatment of **8** with diphosgene gave isatoic anhydride **9** which on reacting with acid chlorides of pyrazole acids **3** afforded good yields of cyanobenzoxazinones **6a**.

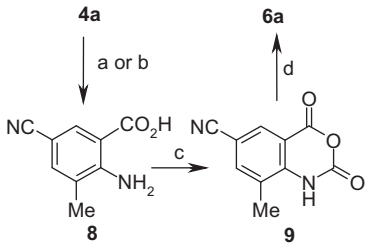
Regioisomeric 4-chloro-6-cyanoanthranilic diamides of formula **10** were made by the method in Scheme 4. Cyanide was first coupled with 4-chloro-6-iodoanthranilic acid **11** via palladium-mediation to give 4-chloro-6-cyanoanthranilic acid **12**.[27] Reacting **12** with pyrazole acids **3** in the presence of methanesulfonyl chloride and base by the same reaction sequence described in Scheme 1



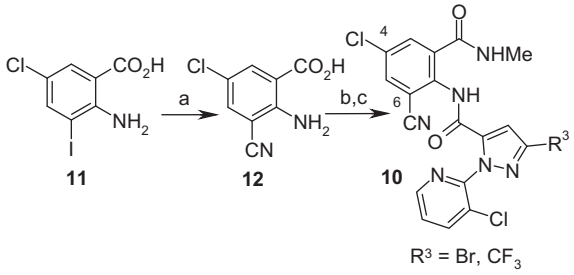
Scheme 1. Reagents and conditions: (a) (i) Compound **3** (1 equiv), $MeSO_2Cl$ (1.1 equiv), Et_3N (1.1 equiv), 0–5 °C, 10 min (ii) Compound **4** (1 equiv), 0 °C, 5 min (iii) Et_3N (2.1 equiv), MeCN, 0–10 °C, 45 min (iv) $MeSO_2Cl$ (1.1 equiv), MeCN, 0–25 °C, 12 h, 60–65%.



Scheme 2. Reagents and conditions: (a) methylamine (1 M in THF), neat isopropylamine (3 equiv) or concd NH_4OH, THF, 25 °C, 3 h, 80–85%) (b) CuCN (10 equiv), $Pd(PPh_3)_4$ (10 mol %), CuI (20 mol %), THF, reflux, 5 h, 20–35%. (c) CuCN (5 equiv), $Pd(PPh_3)_4$ (10 mol %), CuI (25–40 mol %), THF, reflux, 5 h, 50–60%.



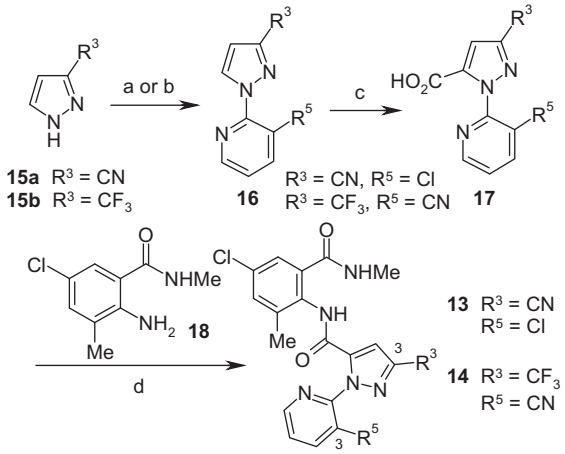
Scheme 3. Reagents and conditions: (a) CuCN (1.2 equiv), DMF, 140 °C, 18 h, 50% (b) NaCN (1.2 equiv), *N*,*N*′-dimethylethylenediamine (2 equiv), CuI (10 mol %), KI (20 mol %), PhCl, 120 °C, 24 h, 70% (c) diphosgene (1.5 equiv), dioxane, 60 °C, 85% (d) (i) Compound **3** (1 equiv), oxalyl chloride (1.5 equiv), DMF (cat.), CH_2Cl_2 (ii) Compound **9** (1 equiv), MeCN, 85 °C, 75%.



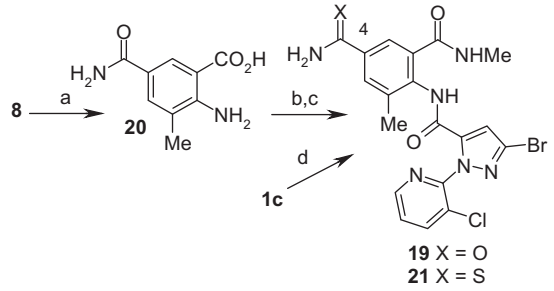
Scheme 4. Reagents and conditions: (a) CuCN (3 equiv), $Pd(PPh_3)_4$ (10 mol %), CuI (40 mol %), THF, reflux, 5 h, 40% (b) (i) Compound **3** (1 equiv), $MeSO_2Cl$ (1.1 equiv), Et_3N (1.1 equiv), 0–5 °C, 10 min (ii) Compound **12** (1 equiv), 0 °C, 5 min (iii) Et_3N (2.1 equiv), MeCN, 0–10 °C, 45 min (iv) $MeSO_2Cl$ (1.1 equiv), MeCN, 0–25 °C, 12 h, 50–55% (c) methylamine (1 M in THF) , THF, 25 °C, 3 h, 70 %.

gave the corresponding benzoxazinones that on ring opening with methylamine afforded **10**.

Preparation of cyanopyrazole and cyanopyridine containing diamides **13** and **14**, respectively, are outlined in Scheme 5. Coupling of commercially available pyrazoles **15a** and **15b** with 2,3-dichloropyridine and 2-chloro-3-cyanopyridine by heating in DMF in the presence of potassium carbonate gave the corresponding pyridylpyrazoles **16**. Lithiation of **16** followed by trapping with



Scheme 5. Reagents and conditions: (a) Compound **15a**, 2,3-dichloropyridine, potassium carbonate (2 equiv), DMF, 130–140 °C, 55% (b) Compound **15b**, 2-chloro-3-cyanopyridine, potassium carbonate (2 equiv), DMF, 130–140 °C, 60% (c) (i) Compound **16**, LDA (1.5 equiv), THF, −78 °C (ii) CO_2 (iii) HCl (aq), 50–60% (d) (i) **17**, $(COCl)_2$, DMF (cat.), CH_2Cl_2, ambient temp (ii) Compound **18**, $(i\text{-Pr})_2$EtN, THF, 0–25 °C, 40–50%.



Scheme 6. Reagents and conditions: (a) concd H_2SO_4, 25 °C, 80% (b) (i) Compound **3** (where R^3 = Br) (1 equiv), $MeSO_2Cl$ (1.1 equiv), Et_3N (1.1 equiv), 0–5 °C, 10 min (ii) Compound **20** (1 equiv), 0 °C, 5 min (iii) Et_3N (2.1 equiv), MeCN, 0–10 °C, 45 min (iv) $MeSO_2Cl$ (1.1 equiv), MeCN, 0–25 °C, 12 h, 45% (c) methylamine (1 M in THF), THF, 25 °C, 3 h, 60 %. (d) $(NH_4)_2S$ (7 equiv), MeOH, microwave, 80 °C, 30%.

CO_2 gave pyridylpyrazole acids **17** that were converted to the acid chlorides and coupled with anthranilic methylamide **18** to afford **13** and **14**, respectively.

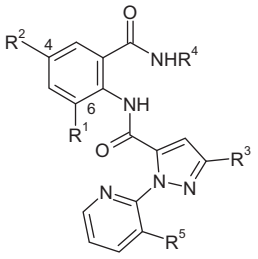
Preparation of a 4-carboxamidoanthranilic diamide (**19**) is shown in Scheme 6. Hydrolysis of the nitrile group of anthranilic acid **8** in concentrated sulfuric acid gave 4-carboxamido anthranilic acid **20** which was converted to a benzoxazinone by the same method as in Scheme 1 followed by ring opening with methylamine to afford **19**.

The 4-thiocarboxamido anthranilic diamide **21** was made by heating 4-cyanoanthranilamide **1c** with excess ammonium sulfide in a microwave (Scheme 6).

Table 1 summarizes estimated (HPLC, pH 7) and calculated log*P* values for a selection of prepared anthranilic diamides. The measured log*P* values for **1a** (chlorantraniliprole), **1b** and **1c** (cyantraniliprole) were 3.0, 2.9 and 2.6, respectively. Lipophilicity as measured (HPLC) or calculated by log*P* for cyanoanthranilic diamides **7a**–**7j**, **10a**, **10b**, **13**, and **14** varied between values of 3.6 and 2.2. Carboxamido anthranilamide **19** (R^2 = $CONH_2$) had a measured log*P* of 1.6 and thiocarboxamido anthranilamide **21** (R^2 = $CSNH_2$) had calculated log*P* of 2.3.

In shake-flask studies, the measured logP_{ow} for **1c** was 1.9 (pH7, 22 °C), significantly lower than the HPLC estimated value of 2.6 and a log unit lower than that of **1a** with a logP_{ow} of 2.9 (pH7, 20 °C).

Table 1
Log P_s of selected anthranilic diamides



Entry	R^1	R^2	R^3	R^4	R^5	Log*P* *
1a	Me	Cl	Br	Me	Cl	3.0 (m) 3.2 (c)
1b	Cl	Cl	Br	Me	Cl	2.9 (m) 3.6 (c)
1c	Me	CN	Br	Me	Cl	2.6 (m) 2.3 (c)
7a	Me	CN	CF_3	Me	Cl	3.1 (m) 2.7 (c)
7b	Me	CN	CF_3	H	Cl	2.7 (m) 2.5 (c)
7c	Me	CN	CF_3	*i*-Pr	Cl	3.6 (c)
7d	Me	CN	Br	H	Cl	2.3 (m) 2.5 (c)
7e	Me	CN	Br	*i*-Pr	Cl	3.6 (c)
7f	Me	CN	Cl	Me	Cl	2.5 (m) 2.6 (c)
7g	Me	CN	Cl	H	Cl	2.2 (m) 2.3 (c)
7h	Me	CN	Cl	*i*-Pr	Cl	3.4 (c)
7i	Cl	CN	Br	Me	Cl	2.8 (c)
7j	Cl	CN	CF_3	Me	Cl	2.8 (c)
10a	CN	Cl	Br	Me	Cl	2.9 (c)
10b	CN	Cl	CF_3	Me	Cl	2.9 (c)
13	Me	Cl	CN	Me	Cl	2.3 (c)
14	Me	Cl	CF_3	Me	CN	2.5 (c)
19	Me	$CONH_2$	Br	Me	Cl	1.6 (m) 1.3 (c)
21	Me	$CSNH_2$	Br	Me	Cl	2.3 (c)

* Log*P* numbers are measured HPLC (pH 7) values (m) or calculated values (c) from Biobyte *c*log*P* software. Measured values were determined on a Zorbax SB C18 column at 40 °C using 5 mM ammonium acetate in acetonitrile gradient. Retention times were compared to retention times of standards with known values of shake-flask octanol–water partition coefficient in the same system.

This resulted in an increase of water solubility from 2 ppm for **1a** (20 °C) to approximately 15 ppm for **1c**, thus conferring enhanced xylem mobility for upward plant movement. Although the HPLC log*P* values in Table 2 were referenced to the logP_{ow} of standards, the reason for the log unit discrepancy between the HPLC and shake-flask values for **1c** was unclear but a welcomed result.

The intrinsic activity of these compounds was measured in a functional assay where the first full length recombinant insect RyR, *Drosophila melanogaster* RyR, was stably expressed in an insect cell line (Sf9) as previously described.[14] Subsequently, RyRs from both lepidopteran and hemipteran insects were cloned and expressed in Sf9 cells.

Table 2 summarizes anthranilic diamide potency as EC_{50} values (50% effective concentrations) against the following three insect recombinant RyRs: dipteran RyR from *Drosophila melanogaster* (fruit fly), lepidopteran RyR from *Heliothis virescens* (tobacco budworm) and hemipteran RyR generated as a chimera from *Myzus persicae* (green peach aphid) and *Perigrinus maidis* (corn plant hopper).

In these recombinant cell lines, anthranilic diamides stimulated a calcium response, comprising an initial transient internal calcium store release that then triggered sustained calcium elevation from external calcium entry via voltage-independent channels. Unlike

Table 2
Intrinsic potency of anthranilic diamides on Sf9 cells expressing recombinant insect RyRs

Entry	Dipteran RyR[1]	Lepidopteran RyR[2]	Hemipteran RyR[3]
	Mean EC_{50} (μM)		
1a	0.04 (0.01)	0.05 (0.02)	0.04 (0.01)
1b	0.04 (0.01)	0.10 (0.01)	0.06 (0.01)
1c	0.09 (0.01)	0.25 (0.02)	0.09 (0.01)
7a	0.10 (0.01)	0.28 (0.03)	0.12 (0.01)
7b	0.30 (0.01)	>1	0.41 (0.04)
7c	0.33 (0.02)	>1	0.48 (0.02)
7d	0.07 (0.01)	0.30 (0.01)	0.08 (0.01)
7e	0.09 (0.01)	0.28 (0.02)	0.07 (0.01)
7f	0.13 (0.01)	0.43 (0.02)	0.13 (0.02)
7g	0.09 (0.01)	0.28 (0.01)	0.09 (0.01)
7h	0.15 (0.01)	>1	0.28 (0.05)
7i	0.07 (0.01)	0.15 (0.01)	0.06 (0.01)
7j	0.15 (0.01)	0.34 (0.01)	0.09 (0.01)
10a	0.16 (0.01)	0.45 (0.06)	0.19 (0.01)
10b	0.26 (0.02)	0.54 (0.07)	0.31 (0.03)
13	0.20 (0.01)	0.16 (0.01)	0.25 (0.01)
14	0.46 (0.01)	0.23 (0.03)	0.43 (0.05)
19	0.69 (0.12)	>1	0.52 (0.07)
21	0.09 (0.01)	0.42 (0.06)	0.09 (0.02)

[1] *Drosophila melanogaster*.
[2] *Heliothis virescens*.
[3] *Myzus persicae-Perigrinus maidis* chimera. EC50 values were determined from $n = 3$ replicates. Standard error deviations are shown in parentheses.

Table 3
Insecticidal activity of anthranilic diamides in a foliar applied test

Entry	*Sf*[1]	*Ag*[2]	*Ef*[3]
	EC_{50} Values (ppm)		
1a	<0.1	12.4[a]	1.5[a]
1b	<0.1	0.9[a]	1.4[a]
1c	0.2[a]	0.4[a]	2.0[b]
7a	0.1[a]	1.3[a]	-
7b	0.7[c]	4.7[a]	<2.0
7c	<0.1	1.5[a]	5.4[a]
7d	<0.1	4.0[b]	3.8[b]
7e	0.2[a]	2.3[a]	11[b]
7f	0.3[c]	1.9[a]	4.8[b]
7 g	0.4[c]	2.7[a]	1.1[c]
7 h	0.2[a]	1.1[c]	19[b]
7i	<0.1	1.6[b]	14[c]
7j	9.0[a]	3.7[a]	9.0[b]
10a	19[b]	>250	60[c]
10b	20[a]	>250	>250
13	5.7[a]	>50	17[c]
14	<0.1	>250	>250
19	16[a]	>250	4.3[c]
21	0.8[a]	0.4[b]	4.0[c]

[1] *Spodoptera frugiperda* (*Sf*, fall armyworm).
[2] *Aphis gossypii* (*Ag*, cotton/melon aphid).
[3] *Empoasca fabae* (*Ef*, potato leaf hopper). The EC_{50} values for *Sf* assess plant protection whereas the values for *Ag* and *Ef* represent mortality. The confidence interval ranges for reported values from probit analyses are: [a]⩽50% of calculated value, [b]⩽100% of calculated value, [c]⩽200% of calculated value.

the plant alkaloid, ryanodine, which locks calcium channels in the open position only when RyRs have already been activated, anthranilic diamide insecticides directly activate RyR channels with channels remaining open, either fully or partially, resulting in depletion of calcium stores.[14,16]

Chlorantraniliprole (**1a**) stimulated RyR-mediated calcium release with an EC_{50} range of 0.04–0.05 μM against all three insect receptors. The hemipteran lead **1b** showed similar potency with an activity range of 0.04–0.1 μM whereas **1c** (cyantraniliprole) was slightly less potent overall, falling in a range of 0.09–0.25 μM. Other nitrile analogs where R^2 = cyano (**7a**–**7j**) also gave high levels of activation with EC_{50} values between 0.06 and 0.48 μM, except for **7b**, **7c** and **7h** being over 1 μM on Lepidopteran RyR. Regioisomeric nitriles **10a** and **10b** with cyano at the 6 versus 4 anthranilic position (R^1 = CN and R^2 = Cl), **13** with cyano on the pyrazole (R^3 = CN) and **14** with cyano on the pyridine (R^5 = CN) were less potent with EC_{50} values between 0.16 and 0.54 μM. Although carboxamide **19** ($R^2 = CONH_2$) was much less active than its nitrile counterpart **1c**, the 4-thiocarboxamide **21** ($R^2 = CSNH_2$) was surprisingly much closer to **1c** in potency, falling in the 0.09–0.42 μM range. Although the cell culture was not analytically assayed, there is precedent for a thiocarbxamide group serving as a pro-form of cyano in cell culture medium so partial or full conversion of **21** to **1c** might have occurred.[28]

In comparing anthranilic diamide activation to mammalian RyRs, **1c** was found to be nearly 500-fold less potent against the most sensitive mammalian receptor isoform tested (mouse RyR1), revealing a substantial difference in insect versus mammalian target site selectivity.[29,30]

Table 3 summarizes insecticidal activity as EC_{50} values in ppm from foliar-applied tests that reflect predominantly contact activity against the lepidopteran (chewing) pest *Spodoptera frugiperda* (*Sf*, fall armyworm) and two hemipteran sap-feeding (sucking-piercing) insects: *Aphis gossypii* (*Ag*, cotton/melon aphid), and *Empoasca fabae (Ef*, potato leaf hopper). The EC_{50} values in Table 3 are the effective concentrations that gave 50% plant protection from feeding by *Sf* and 50% mortality in the case of *Ag*, and *Ef*.

Chlorantraniliprole (**1a**) had an EC_{50} value less than 0.1 ppm against *Sf* but required higher concentrations of 12.4 and 1.5 ppm for 50% mortality against *Ag* and *Ef*. On the other hand, diamide **1b** had EC_{50} values of <0.1, 0.9 and 1.4 ppm against *Sf*, *Ag* and *Ef*, respectively. The lower log*P* cyanoanthranilamide **1c** had a slightly higher EC_{50} value of 0.2 ppm on *Sf* and 2.0 ppm against *Ef* versus **1a** and **1b**, but was more active on *Ag* with an EC_{50} value of 0.4 ppm. Some of the other 4-cyanoanthranilamides (**7a**–**7j**) in Table 3 approached **1c** in overall activity but none were clearly superior. Surprisingly, switching R^1 and R^2 resulted in a considerable loss of activity as revealed for **10a** and **10b**, where R^1 = CN and R^2 = Cl. Anthranilamides **13** and **14** with a nitrile group at the pyrazole R^3 or pyridine R^5 position also had diminished activity. Paralleling the cellular receptor activity in Table 2, the 4-carboxamido anthranilamide **19** ($R^2 = CONH_2$) performed poorly but the thiocarboxamide **21** ($R^2 = CSNH_2$), which presumably is a pro-form of **1c**, was much closer to **1c** in activity.

A direct comparison of the insecticidal activity of **1c** (cyantraniliprole) versus **1a** (chlorantraniliprole) against pests from three insect orders (Hemiptera, Lepidoptera and Coleoptera) is outlined in Table 4. All of the EC_{50} values reflect insect mortality and further demonstrate the scope of cross-spectrum insect control provided by **1c**.

In advanced laboratory and greenhouse systemic tests, **1c** continued to outperform its higher log*P* counterparts on a range of sap-feeding insects. Although **1a** and **1c** had comparable potencies in activating hemipteran RyRs, physical properties

Table 4
Chlorantraniliprole versus Cyantraniliprole against pests of different insect orders.

Scientific name	Insect order	**1a**	**1c**
		EC_{50} Values (ppm)	
Myzus persicae	Hemiptera	5.00	1.10
Bemisia tabaci	Hemiptera	0.80	0.08
Plutella xylostella	Lepidoptera	0.05	0.07
Heliothis virescens	Lepidoptera	0.04	0.21
Leptinotarsa decemlineata	Coleoptera	<0.1	<0.1

These EC_{50} values represent mortality and the confidence intervals are ⩽50% of the calculated value.

clearly are crucial for the enhanced control of sucking/piercing insects by **1c** where improved systemic properties, such as lower log*P* and higher water solubility, aid in plant uptake and translocation.

Translation of activity from the greenhouse to field was confirmed where **1c** controlled a wide range of insects, including aphids, leafhoppers, planthoppers, whiteflies, leaf-feeding beetles, leafminers, fruit flies, psyllids, weevils and caterpillars at application rates generally between 10 and 200 grams of active ingredient per hectare, depending on the specific pest group. Plant protection resulted from rapid cessation of plant feeding with excellent translaminar movement into leaf tissue when foliar applied or by upward plant movement in soil applications.

In summary, cyantraniliprole (**1c**) was active against a wide range of insects on a variety of crops in worldwide field evaluations coupled with a favorable environmental-fate profile and remarkable selectivity for insect over mammalian forms of RyRs. It represents the first anthranilic diamide from the IRAC (Insecticide Resistance Action Committee) mode-of action Group 28 (Ryanodine Receptor Modulators) to target sap-feeding aphid pests with no evidence to date suggesting cross-resistance with other commercial aphid insecticides having a different mode of action.[31] Comprising a combination of favorable attributes, cyantraniliprole holds great promise as a pest management tool to growers globally.

Acknowledgment

The authors wish to thank all those who made technical contributions to this program, especially the chemists and biologists involved in the preparation, characterization and evaluation of compounds.

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