Bioorganic & Medicinal Chemistry 17 (2009) 4127–4133

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

New and selective ryanodine receptor activators for insect control

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ARTICLE INFO

Article history:
Received 3 October 2008
Revised 6 January 2009
Accepted 9 January 2009
Available online 15 January 2009

Keywords:
Ryanodine
Insecticide
Flubendiamide
Chlorantraniliprole
Rynaxypyr

ABSTRACT

Diamide insecticides have emerged as one of the most promising new classes of insecticide chemistry owing to their excellent insecticidal efficacy and high margins of mammalian safety. Chlorantraniliprole and flubendiamide, the first two insecticides from this class, demonstrate exceptional activity across a broad range of pests in the order Lepidoptera. This chemistry has been confirmed to control insects via activation of ryanodine receptors which leads to uncontrolled calcium release in muscle. The high levels of mammalian safety are attributed to a strong selectivity for insect over mammalian receptors.

1. Introduction

The ryanodine receptor (RyR) derives its name from the plant metabolite ryanodine **1**, a natural insecticide from *Ryania speciosa*, known to modify calcium channels[1] (Fig. 1). The insecticidal activity of *Ryania* extracts were first described by Rogers and coworkers in 1946 for a range of lepidopteran and hemipteran pests.[2,3] As a family the ryanoids consist of a diverse array of natural products with ryanodine as the principle active constituent. Derivatives including 3-pyridyl ryanodine **2** and the hydrolysis derivative ryanodol **3** have been determined to be essentially void of insecticidal activity.

The structure of ryanodine was determined by Wiesner, Valenta, and Findlay in 1966, and revised by Srivastava and Przybylska through an X-ray on the ryanodol *p*-bromobenzyl ether, correcting for the orientation of the isopropyl group.[4,5] The first syntheses of (+)-ryandol **2**, and *epi*-ryanodine were completed by Deslongchamps in 1979 and 1993, respectively.[6,7] However, there has yet to be a total synthesis of ryanodine principally due to difficulty with esterification of the 3-hydroxy group.[8] At its peak, approximately 200 metric tons were used annually, primarily for the control of thrips, *Cydia pomonella* (codling moth) and *Ostrinia nubilalis* (European corn borer). This amount decreased over time as more effective pesticides were introduced with ryanodine's registration and use eventually discontinued in 1993.[9]

The ryanodine receptor is a non-voltage-gated calcium channel that regulates the release of intracellular calcium stores critical for muscle contraction. As ryanodine is a potent natural insecticide, it has been conjectured that RyRs would provide an excellent target for insect control. However, prior to recent developments, no synthetic molecules targeting this receptor have been commercialized. The phthalic diamides[10–12] from Nihon Nohyaku, and the anthranilic diamides[13–16] from DuPont, are the first synthetic classes of potent activators of insect RyRs. The recent commercial introduction of the RyR insecticides flubendiamide **4** and chlorantraniliprole (Rynaxypyr®) **5**, is significant in the field of crop protection, particularly important in light of the ability of insects to rapidly develop resistance and the need for safe and effective pesticides that act at new biochemical targets[10,14] (Fig. 2).

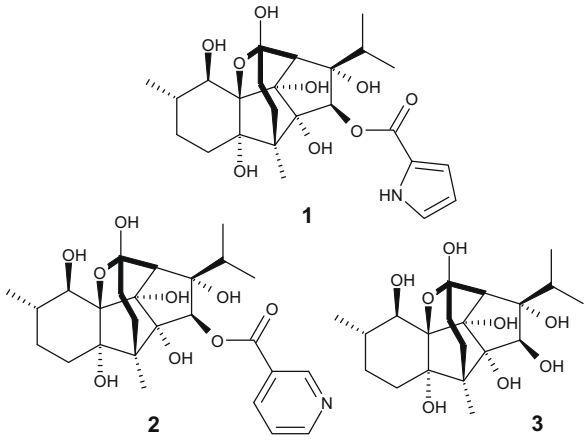

Figure 1. Ryanodine (**1**), 3-pyridyl ryanodine (**2**) and ryanodol (**3**).

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doi:10.1016/j.bmc.2009.01.018

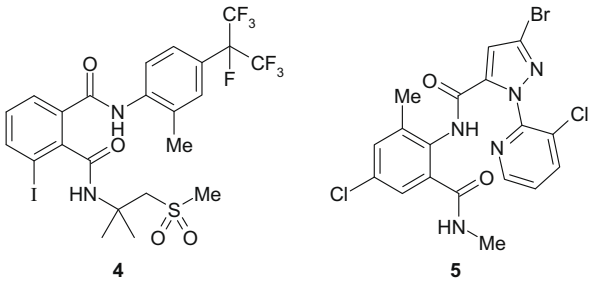


Figure 2. RyR insecticides, flubendiamide (**4**) and chlorantraniliprole (**5**).

2. Discovery

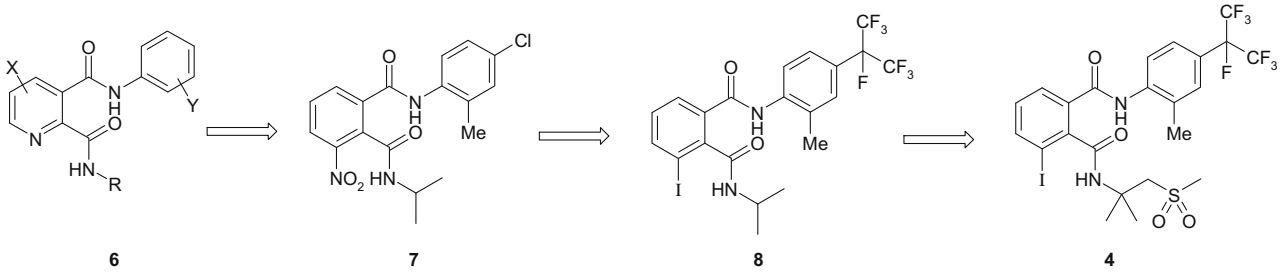
The discovery of initial leads to flubendiamide had its origins at Nihon Nohyaku in 1993 in a pyridine dicarboxamide herbicide program around compounds of type **6** (Scheme 1).[17] Through the course of this work the phthalic diamide **7** was serendipitously discovered to have surprising Lepidopteran activity in the range of 10–100 ppm on larvae of both *Spodoptera litura* ('fall armyworm') and *Plutella xylostella* (diamondback moth). Optimization to the 4-heptafluoroisopropyl and 2-iodo substituents of compound **8**, resulted in a substantial increase in insecticidal activity. Extensive modification of the amide identified the methylsulfonylalkylamide residue of flubendiamide **4** as optimum with activity on *S. litura* and *P. xylostella* in the range of 0.03–0.10 ppm and three orders of magnitude more active than the initial lead **7**.[10,17]

DuPont's discovery of the anthranilic diamides originated from compounds containing the 2-methyl-4-trifluoromethyl phthalic diamide group of structure **9**. Compound **9** was disclosed to control three species of Lepidoptera at the rate of 500 ppm, *S. litura*, *P. xylostella*, and *Cnaphalocrocis medinalis* (rice leaf roller).[11] The discovery of compound **10** resulted from the observation that reversing the amide orientation found in **9** to that of the anthranilic diamide in **10** required location of the aryl methyl substituent to be in a position ortho to the benzamide group in order for compounds to retain significant levels of insecticidal activity (Scheme 2).[13] This was in direct contrast to the phthalic amides where the aryl substituent was located preferentially ortho to the smaller isopropyl amide. Optimization to the *N*-(2-chlorophenyl)-pyrazole of structure **11** produced a 200-fold increase in insecticidal activity. The 3-chloropyridyl group, bromo pyrazole, and 4-halo substituent of the anthranilic diamide **5** were discovered to be optimal with compounds possessing activity at 0.01–0.05 ppm across a broad spectrum of Lepidoptera.[14,18] Additionally, the methyl amide of chlorantraniliprole offered the optimal properties of plant protection coupled with excellent safety and environmental attributes. Despite the relationship of starting leads **7** and **10** there remained no apparent continuation in the ensuing structure-activity trends between the phthalic and anthranilic diamide classes of chemistry.

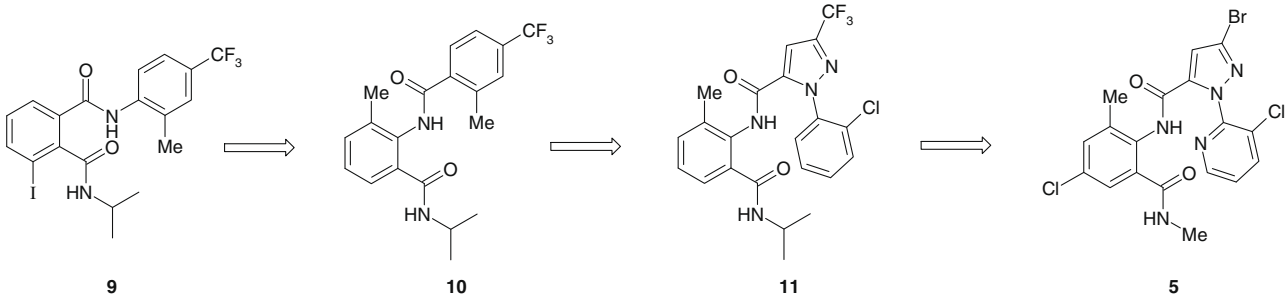
3. Chemistry

An expeditious synthesis of flubendiamide is described in Scheme 3.[12,19] The 2-thioalkylamide is introduced through a regioselective addition of 1,1-dimethyl-2-(methylthio)ethylamine to 3-iodophthalic anhydride **12** to produce the phthalamic acid **13** in 89% yield. The phthalamic acid is then cyclized to the phthalisoimide **14** through activation with trifluoracetic anhydride and opened with 2-methyl-4-heptafluoroisopropyl aniline in acetonitrile to provide the phthalic diamide **16** in 90% yield over the two steps (b) and (c). Oxidation of the thio group with *m*-chloroperbenzoic acid in methylene chloride affords flubendiamide **4** in 95% yield. The 2-methyl-4-heptafluoroisopropyl aniline **15** can be prepared by the regiospecific alkylation of *o*-toluidine with 2-iodoheptafluoropropane in the presence of sodium dithionite in 96% yield.[20] Efficient syntheses of 1,1-dimethyl-2-(methylthio)ethylamine have also been reported from 1,1-dimethylethylene glycol.[21–23]

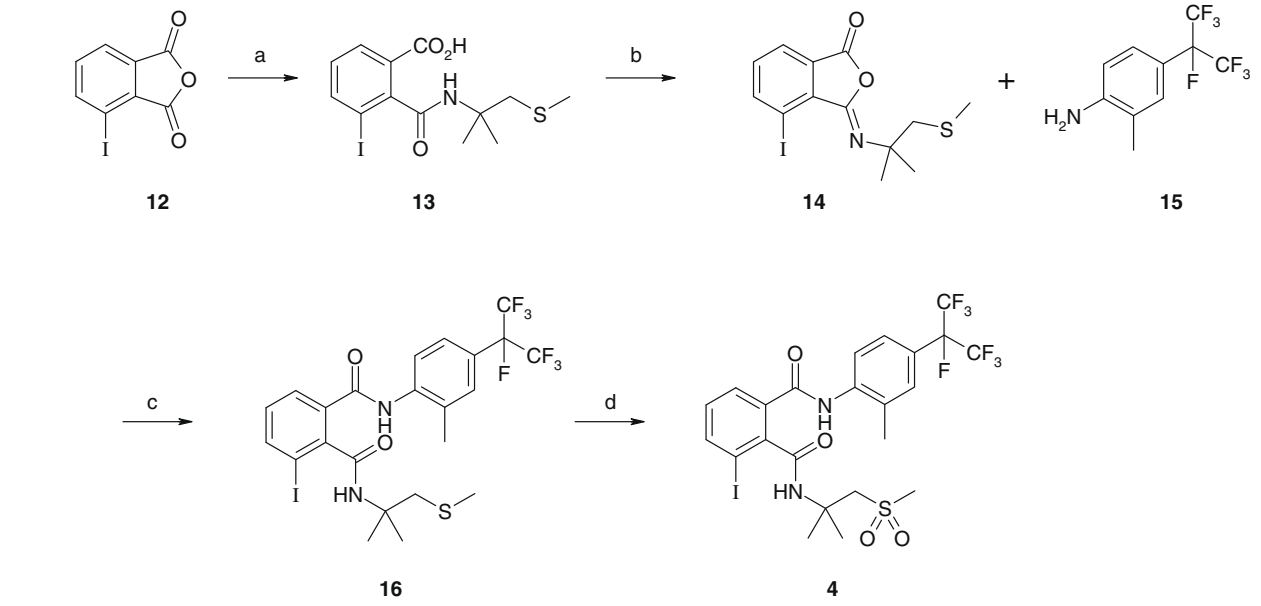
A number of efficient syntheses for the preparation of chlorantraniliprole were developed including that described in Scheme 4.[14,16] The reaction of 3-chloro-2-hydrazinopyridine **17** with diethylmaleate **18** in the presence of sodium ethoxide affords the pyrazolone **19** in 55% yield. Subsequent treatment of **19** with phosphoryl



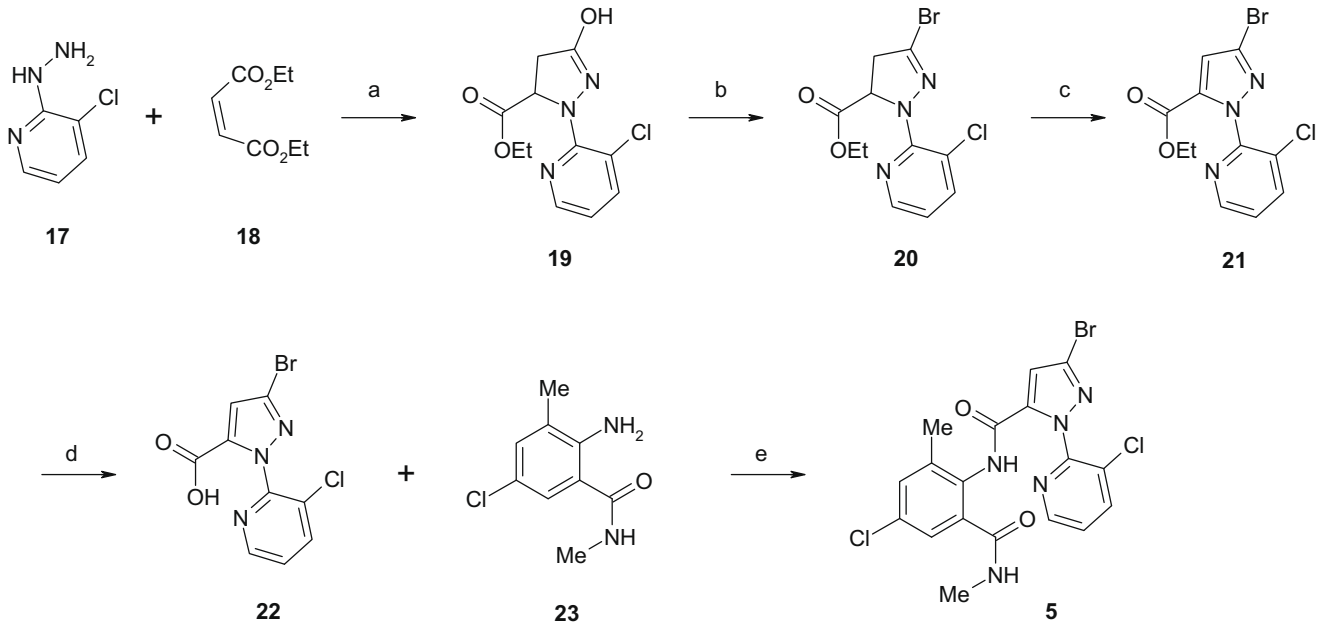
Scheme 1. Lead discovery and optimization for the phthalic diamide class of RyR insecticides.



Scheme 2. Lead discovery and optimization for the anthranilic diamide class of RyR insecticides.



Scheme 3. (a) $H_2NC(Me)_2CH_2SCH_3$, CH_3CN, 0–20 °C , 89% (b) $(CF_3CO_2)O$, K_2CO_3 , toluene, RT (c) CF_3CO_2H, CH_3CN, 90% two steps (d) m-CPBA, CH_2Cl_2, RT, 95%.



Scheme 4. (a) NaOEt, EtOH, reflux, 55% (b) $POBr_3$, MeCN, 83 °C, 95% (c) MeCN, H_2SO_4, $K_2S_2O_8$, reflux, 90% (d) (i) aq NaOH, MeOH (ii) aq HCl, 91% (e) $MeSO_2Cl$, picoline, MeCN, 0-5 °C 97%.

bromide in acetonitrile at 80 °C afforded the bromopyrazoline **20** in 95% yield. Oxidation of **20** to the pyrazole **21** can be accomplished with potassium persulfate as the oxidant in 90% yield.[24] The derived acid **22** can then be coupled with 2-amino-3-methyl-5-chloro-*N*-methylbenzamide **23** in 97% yield using methanesulfonyl chloride and picoline in acetonitile.[25]

The physical and chemical properties for flubendiamide and chlorantraniliprole are summarized in Table 1.[9,26]

Table 1
Physical and chemical properties for flubendiamide and chlorantraniliprole

Physical/chemical properties	Flubendiamide	Chlorantraniliprole
Chemical class	Phthalic diamide	Anthranilic diamide
Empirical formula	$C_{22}H_{23}IF_7N_2O_4S$	$C_{18}H_{14}BrCl_2N_5O_2$
Molecular weight	682.4 g/mol	483.15 g/mol
Physical form	Colorless crystals	Off-white crystalline powder
Odor	None	None
Melting point	217.5–220.7 °C	208–210 °C
Water solubility (20 °C)	0.03 mg/L	1.0 mg/L
log P_{ow}	4.20 at 24.9 °C	2.86 at 20 °C
Density (20 °C)	1.66 g/mL	1.51 g/mL

4. Biological profile

Flubendiamide and chlorantraniliprole have extremely potent and broad spectrum activity within the insect order Lepidoptera (butterflies and moths). The global insecticide market for controlling this order is valued at ~$2.5 billion annually. In general, these insecticides provide rapid plant protection through the cessation of

Table 2
Formulations of flubendiamide and chlorantraniliprole

Active ingredient	Trade name	Amount in formulation (g a.i./L or kg)[a]	Formulation	Commercial use rate (g a.i./ha)[b]
Flubendiamide	Belt®	480	SC	70–175/application 316–526/season
	Fame™	480	SC	Not available
	Fenos™	480	SC	Not available
	Synapse®	240	WDG	34–50/application 67–151/season
Chlorantraniliprole	Altacor®	350	WDG	49–110/application 224/season
	Coragen®	200	SC	29–110/application 224/season
	Ferterra™	0.4	GR	Not available
	Prevathon™	51.5	SC	Not available

g a.i., grams of active ingredient; GR, granules; SC, suspension concentrate; WDG, water-dispersible granules.
[a] g a.i./L for SC formulations; g a.i./kg for GR and WDG formulations.
[b] Based on labels registered in the United States in 2008.

larval feeding, which happens soon after consumption.[27] The resulting mortality generally occurs after 1–3 days. Flubendiamide is highly active, with EC_{50} values ranging between 0.004 and 0.58 ppm for the larvae of eight Lepidopteran pests of cabbage, rice, and tea.[10] For chlorantraniliprole, reported EC_{50} values for larvae were 0.02 ppm for *S. frugiperda* (fall armyworm); 0.01 ppm for *P. xylostella*; and 0.05 ppm for *Heliothis virescens* (tobacco budworm).[14] Flubendiamide activity has been limited to Lepidopteran larvae.[28] In addition to larvicidal activity, chlorantraniliprole has been found to have significant ovicidal activity among some Lepidopteran pests.[26] At sub-lethal concentrations of chlorantraniliprole, a reduction in the proportion of mating *C. pomonella* females has been reported.[29] This may reflect broad behavioral effects resulting from weak muscle poisoning, however, elucidating the specific physiological mechanisms associated with mating reduction requires further investigation.

Limited systemic activity has been claimed for both compounds, although there are differences, attributed in part to the log*P* values for chlorantraniliprole and flubendiamide.[19,26] Flubendiamide has loco-systemic properties, that is a small amount of absorption into the leaf cuticle or deeper leaf tissues occurrs very close to the application area[30]; however there are currently no registered uses for systemic application. The lower log*P* value for chlorantraniliprole accounts for some systemic movement, and as such, there are registered uses that take advantage of this feature including application by drip (trickle) chemigation. Translaminar activity has been demonstrated for both flubendiamide and chlorantraniliprole, against *P. xylostella* in cabbage.[30,31] Translaminar mobility into the leaf helps explain the good residual activity against pests, as these compounds are more protected from ultraviolet degradation and precipitation.

To date, neither flubendiamide nor chlorantraniliprole has been found to exhibit cross-resistance with other commercial insecticides. Flubendiamide has been shown to be effective on resistant strains of *P. xylostella*, *S. exigua* (beet armyworm), and *Helicoverpa armigera* ('American bollworm').[10] Compounds with a novel mode of action, such as flubendiamide and chlorantraniliprole, are excellent selections for use in Integrated Pest Management (IPM) programs where insecticide rotations are needed to slow resistance development, as well as in regions where commercial standards are no longer effective because of resistance.

For flubendiamide, no significant activity has been reported for insects outside the order Lepidoptera, as field trials have focused on evaluating only these pests.[27,30,32,33] Chlorantraniliprole, in contrast, has broader insecticidal activity, controlling pests in other orders, including Coleoptera (Colorado potato beetle – *Leptinotarsa decemlineata*), Diptera (leafminers – *Liriomyza* spp.), and Isoptera (sugar cane termites – *Microtermes obesi* and *Odontotermes obesus*); as well as suppression of several pests in the order Hemiptera (whiteflies – *Bemisia* spp.).[34–36] Larval control of several scarab beetle pests has also been observed when chlorantraniliprole was applied with entomopathogenic nematodes.[37]

4.1. Registration, crop use, and formulations

Flubendiamide first acquired registration in 2006 (Philippines), with chlorantraniliprole receiving its first registration the following year in the same country. By the end of 2008 both compounds will have registrations in 10–15 countries with use in a broad range of crops. Flubendiamide and chlorantraniliprole obtained US registration for use on the following crop groups: tree fruit, grape, cotton, and vegetables (Brassica, Cucurbits, fruiting, and leafy). In addition, flubendiamide is registered on corn, tobacco, and tree nuts; and chlorantraniliprole is registered on potato.

The crop use and application method can vary based on country and type of formulation. Several formulations have been developed for each commercial compound (Table 2). Other formulation types are also being evaluated, as evidenced by chlorantraniliprole being

Table 3
Toxicological profile for flubendiamide and chlorantraniliprole technical

Toxicological test	Flubendiamide[a]	Chlorantraniliprole[a]
Acute oral toxicity, LD_{50}	$\geqslant$2000 mg/kg (toxicity category III)	$\geqslant$5000 mg/kg (toxicity category IV)
Acute dermal toxicity, LD_{50}	$\geqslant$2000 mg/kg (toxicity category III)	$\geqslant$5000 mg/kg (toxicity category IV)
Inhalation LC_{50}	$\geqslant$0.0685 mg/L (toxicity category II)	$\geqslant$5.1 mg/L (Toxicity category IV)
Dermal irritation	No skin irritation (toxicity category IV)	No skin irritation (toxicity category IV)
Eye irritation	Acceptable (toxicity category IV)	Acceptable (toxicity category IV)
Dermal sensitization	Not a sensitizer	Not a sensitizer
Mutagenicity	Acceptable	Acceptable
Carcinogenicity	Acceptable	Acceptable
Reproductive Toxicity	Acceptable	Acceptable
Developmental Toxicity	Acceptable	Acceptable
Neurotoxicity	Acceptable	Acceptable
Acute reference dose[b]	0.995 mg/kg/day based on eye effects in offspring	None based on the absence of adverse effects attributable to a single exposure
Chronic reference dose[c]	0.024 mg/kg/day based on liver toxicity across multiple species	1.58 mg/kg/day based on liver effects in mice

[a] Obtained from US Environmental Protection Agency Human Heath Risk Assessments for flubendiamide and chlorantraniliprole.[39,40]
[b] Acute reference dose is the estimated daily oral exposure of 24 h or less that is likely to be without appreciable risk of adverse health effects over a lifetime.
[c] Chronic reference dose is the estimated daily oral exposure over a lifetime that is likely to be without appreciable risk of adverse health effects.

approved for use in rice seed treatment in the United States under a Section 18 emergency exemption.

4.2. Toxicology and ecotoxicology

Chlorantraniliprole and flubendiamide have excellent acute toxicological profiles with low toxicity to mammals in oral, dermal, inhalation and eye tests (Table 3). Results are also very favorable in a range of tests including mutagenicity, carcinogenicity, neurotoxicity, and reproductive toxicity. The principal differences observed between the two insecticides can be seen in the acute and chronic reference doses.

The eco-toxicological profile is also favorable, with field use rates of both flubendiamide and chlorantraniliprole posing low risk to parasitic wasps, predatory mites, predatory bugs (*Orius* spp.), green lacewings, and lady beetles.[10,38]

5. Mode of action and selectivity

Both anthranilic and phthalic diamide insecticides impair muscle function in lepidopteran larvae with poisoning symptoms that include: rapid feeding cessation, regurgitation, lethargy, and contractile paralysis.[13,41–45] Interestingly, no significant effects on the central nervous system function have been reported. Rapid action on cardiac function, coupled with poisoning symptomology similar to that observed with ryanodine, directed mode of action elucidation efforts toward calcium homeostasis mechanisms. A strong correlation was reported between lepidopteran toxicity of anthranilic diamides and calcium mobilization in *Periplaneta americana* (American cockroach) neurons (Chart 1).[13,41]

As mentioned earlier, muscle contraction relies upon regulated release of intracellular calcium stores via RyR activation. The RyR is composed of four identical subunits that form a non-voltage gated calcium channel. These channels, coupled with various accessory proteins, are localized in the sarcoplasmic reticulum of muscle and endoplasmic reticulum of non-muscle cells (Fig. 3). Insects possess a single form of the RyR;[46] therefore activity on insect neuronal RyRs would be similar to that of insect muscle receptors.

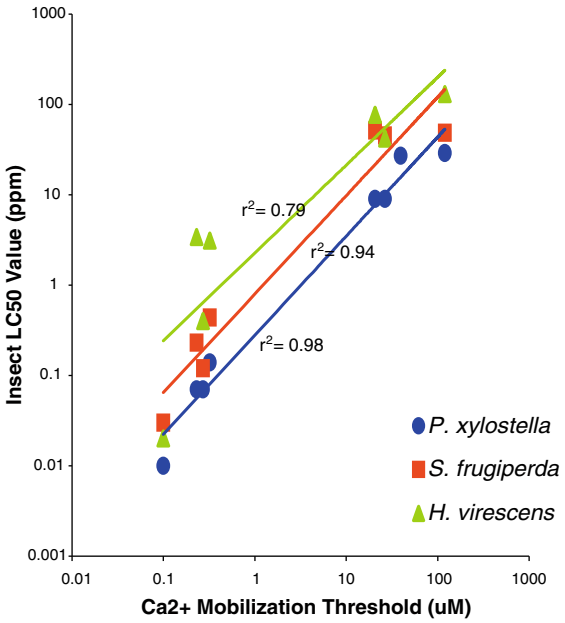


Chart 1. Calcium mobilization activity of anthranilic diamides plotted against the LC_{50} for *P. xylostella, S. frugiperda,* and *H. virescens.* (Adapted with permission from Lahm et al. 2005 Bioorg. Med. Chem. Lett. *15*, 4898–4906.).

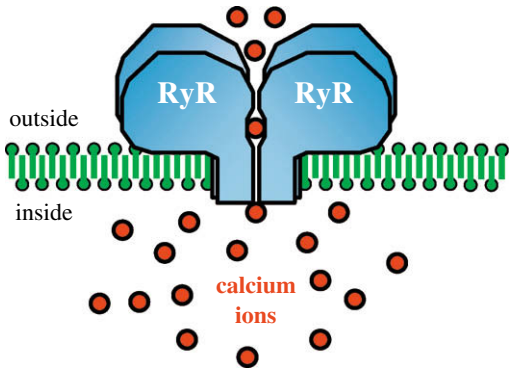


Figure 3. Schematic representation of the ryanodine receptor. The receptor is a tetramer of four identical subunits (blue) that regulates flow of calcium ions (red) out of the sarcoplasmic reticulum in muscle and endoplasmic reticulum in non-muscle cells. For simplicity, associated proteins that interact directly with the RyR are not shown.

Using neurons from *H. virescens*, flubendiamide was found to release RyR-mediated calcium stores with an EC_{50} value of 690 nM.[42,43] Significantly greater RyR potency is reported for chlorantraniliprole with EC_{50} values of 40–50 nM obtained using *P. americana* neurons and recombinant RyRs from *H. virescens* or *Drosophila melanogaster* ('laboratory fruit fly').[14,18,47] As anthranilic and phthalic diamide sensitivity is conferred upon cells only when RyRs are expressed, it can be concluded that these insecticides act directly on the receptor rather than on an accessory protein.

In addition to ryanodine, various modulators of mammalian and insect RyRs have been investigated including caffeine, ruthenium red, and dantrolene. These have been previously reviewed.[48–50] Although the binding site for caffeine is unclear, most of the exogenous modulators share the same binding site as ryanodine. Biochemical studies using [^{3}H]ryanodine, [^{3}H]flubendiamide, and the labeled anthranilic diamide, [^{3}H]DP-010 ([^{3}H]1-(2-fluorophenyl)-*N*-[2-methyl-6-[[(1-methylethyl)amino] carbonyl]phenyl]-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide), revealed that phthalic and anthranilic diamides bind to a novel site on the RyR, distinct from ryanodine and caffeine.[41–45] In *H. virescens* thoracic muscle membranes, the B_{max} value for [^{3}H]flubendiamide was at least four times greater than that observed with ryanodine.[42,43,51] This finding suggests that a flubendiamide molecule binds to each of the four receptor subunits. However, further studies are needed to confirm this. In the presence of flubendiamide (1 μM), affinity for [^{3}H]ryanodine increased in a positive allosteric fashion and no longer exhibited a dependence on calcium concentration.[42,43,51] Such results are consistent with flubendiamide shifting RyR channels from a closed conformational state to a calcium-conducting conformational state. In contrast to flubendiamide binding studies, the B_{max} value for the radiolabeled anthranilic diamide, [^{3}H]DP-010 was roughly similar to that obtained for ^{3}H-ryanodine suggesting a 1:1 stoichiometry with the tetramer.[41,45] As this binding study included the presence of ryanodine (10 μM) to enhance binding and was conducted on a different preparation (*P. americana* muscle membranes) than the ^{3}H-flubendiamide studies, one cannot conclude whether the two diamide classes bind differently to the RyR. To date, there have been no published reports as to whether chlorantraniliprole and flubendiamide compete for a single binding site on the insect RyR.

A key attribute of flubendiamide and chlorantraniliprole is their superb mammalian safety, as shown in Table 3. A major factor contributing to this safety is their selectivity for insect RyRs over those of mammals. Unlike insects, mammals possess three isoforms of the RyR. RyR1 and RyR2 are predominately localized in skeletal and cardiac muscle, respectively, whereas the more heteroge-

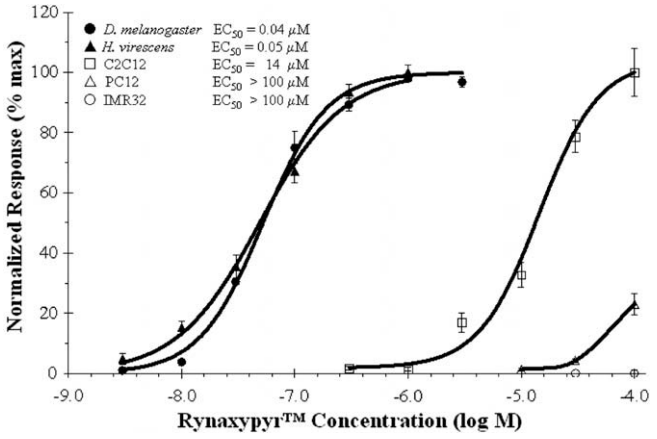


Chart 2. Differential receptor selectivity of Chlorantraniliprole in insect and mammalian cell lines expressing ryanodine receptors. (Copied with permission from Lahm et al. 2007 Bioorg. Med. Chem. Lett. *17*, 6274–6279.).

neously distributed RyR3 can be found in brain and smooth muscle.[51–53] Ebbinghaus-Kintscher and colleagues reported that micromolar concentrations of flubendiamide or its sulfoxide analog were ineffective in stimulating calcium release from cells that naturally express the three isoforms, either individually, or in combination.[42,43] As the aqueous solubility for phthalic diamides is extremely low (see Table 1), flubendiamide's potency against mammalian RyRs is unclear. Nevertheless, the ability of sub-micromolar concentrations of flubendiamide to activate insect but not mammalian RyRs clearly reveals an intrinsic target-based selectivity.

Chlorantraniliprole exhibits outstanding mammalian safety (Table 3) along with exceptional safety on avian and aquatic organisms.[14,35] As with flubendiamide, chlorantraniliprole was found to be inactive at concentrations below 1 μM against mammalian cell lines that express the various RyR isoforms. As chlorantraniliprole has a higher aqueous solubility (Table 2), receptor activity could be evaluated at high micromolar concentrations. Chlorantraniliprole was found to be ~300- and >2000-fold less potent against mouse RyR1 and rat RyR2, respectively (Chart 2).[14,18] Interestingly, no receptor activation was observed in the human cell line, IMR32, in the presence of chlorantraniliprole (100 μM).

6. Prospects

The announcement of DuPont's new RyR insecticide cyantraniliprole (Cyazypyr™), marks the second entry from the anthranilic diamide class of insecticides (Fig. 4).[54] Cyantraniliprole promises to be a strong new addition based on its properties of improved plant mobility, activity on Lepidopteran pests, and an increased spectrum of insect control in the order Hemiptera to include aphids and leafhoppers.

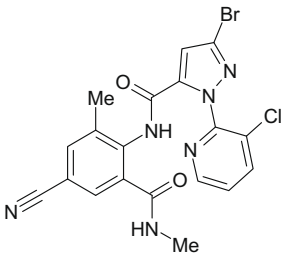


Figure 4. Cyazypyr™.

At the time of this writing there were nine global crop protection companies that have filed in excess of fifty novel compound patents in the area of ryanodine receptor insecticides of the anthranilic and phthalic diamide class. This underscores the broad interest in the search for new chemistry that works through this mode of action. Prospects are also raised for finding new chemical classes, beyond the diamides, owing to the availability of screens directed against insect RyRs.[55] One can anticipate that the low use rate, broad spectrum, and potential for high mammalian safety will continue to make new chemistry targeting insect RyRs attractive in the field of crop protection.

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