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4-Azolylphenyl isoxazoline insecticides acting at the GABA gated chloride channel

George P. Lahm *, Daniel Cordova, James D. Barry, Thomas F. Pahutski, Ben K. Smith, Jeffrey K. Long, Eric A. Benner, Caleb W. Holyoke, Kathleen Joraski, Ming Xu, Mark E. Schroeder, Ty Wagerle, Michael J. Mahaffey, Rejane M. Smith, My-Hahn Tong

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

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ABSTRACT

Isoxazoline insecticides have been shown to be potent blockers of insect GABA receptors with excellent activity on a broad pest range, including Lepidoptera and Hemiptera. Herein we report on the synthesis, biological activity and mode-of-action for a class of 4-heterocyclic aryl isoxazoline insecticides.

Effective pest management aims to limit the onset of resistance through reduction of selection pressure. This is accomplished through the use of pesticide rotation strategies. Therefore, the discovery of new classes of chemistry that work either by new biochemical mechanisms or known mechanisms that display minimal cross resistance is of great importance in the defense of crops.

New isoxazoline insecticides of type **1**, characterized by a 4-carboxamide group on the phenyl, were recently reported by Nissan, along with work concurrent to our studies on 4-heterocyclic phenyl isoxazolines (see Fig. 1).[1] Here we describe a new class of 4-azolylphenyl isoxazoline insecticides as potent blockers of insect GABA receptors culminating in the identification of exceptionally potent 3-cyano-4-triazolyl analogs such as **2** (**DP-12**).[2]

The isoxazolines appear to trace their history through the discovery of the insecticidal phthalic diamides **3** from Nihon Nohyaku (1999) and the anthranilic diamides from DuPont (2001) (see Fig. 2).[3,4] The diamides as a class exhibit their action through selective activation of insect ryanodine receptors (RyRs).[5]

Incorporation of a 3-trifluoromethylisoxazoline group into the phthalic diamides **3** as a replacement for the trifluoromethyl substituent produced the first trifluoromethyl isoxazoline **5** (Nissan, 2004).[6] Compound **5** contained an inverted orientation of the isoxazoline ring with respect to those found in type **1** along with an inverted orientation of the amide group. A similar orientation of the embedded oxime in **1** along with the corresponding orientation for the amide could be found in anthranilic diamides of type **6**, where the oxime residue was explored as a replacement for the trifluoromethyl substituent. (Nissan, 2003).[7] The combination of these substituent modifications by Nissan in 2003–4 appears to have set the stage for the functionality leading to the discovery of the 4-phenyl carboxamide isoxazoline insecticides **1** in 2005. Perhaps the most surprising aspect of this new class is identification of the site of action as blockers of the GABA gated chloride channel in contrast to their diamide precursors that work as activators of the ryanodine receptor.[8]

The compounds of Tables 1–3 were prepared as described in Schemes 1–4. Isoxazolines 11 containing a range of ortho groups (R^1) were prepared as outlined in Scheme 1. Treatment of aldehydes **7** with hydroxyl amine produced oximes **8**. Cycloaddition to produce the isoxazoline **10** was accomplished by treatment of **8** with sodium hypochlorite in the presence of the 1-trifluoromethyl-1-aryl styrenes **9** in yields of 39–56%.[2,9] While the azole group could be introduced in the first step of the synthesis we found the most expeditious route to be displacement of fluorine from the 4-fluorophenyl-1-isoxazolines **10** with azoles affording the 4-azolylisoxazolines **11** in good yield.[10] The styrenes **9** were prepared by Suzuki cross-coupling of arylboronic acids with 2-bromo-3,3,3-trifluoropropene.[11]

Isoxazolines **16** containing a 4-pyridyl group at the 5-position of the isoxazoline could be prepared from the pyridylstyrene derivatives **15** as outlined in Scheme 2. Direct C–H borylation by treatment of 2,6-disubstituted pyridines with bis(pinacolato)diborane, $[IrCl(COD)]_2$, and bipyridyl ligand provided exclusively the 4-pridylboronates **13** in good yield.[12] Palladium catalyzed coupling

* Corresponding author.
E-mail address: george.p.lahm@dupont.com (G.P. Lahm).

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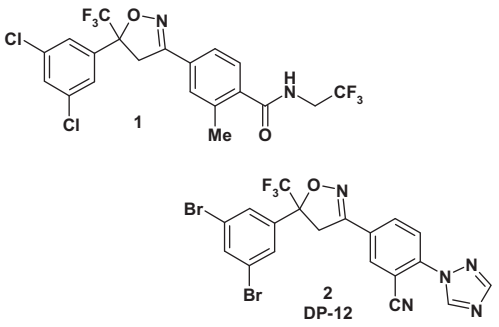


Figure 1. Isoxazoline insecticides.

of **13** with 2-bromo-3,3,3-trifluoropropene afforded fair yields of the styrenes **15**. Cycloaddition with oximes **8**, followed by azole displacement as described in Scheme 1, provided the 4-pyridyl isoxazolines **16**.

Isoxazolines **20** containing a 5-Cl-3-pyridyl group could be prepared as outlined in Scheme 3. Reduction of 5,6-dichloronicotinic acid to the corresponding aldehyde by treatment of the acid chloride with lithum tri-*t*-butoxyaluminum hydride afforded a modest yield of **18**.[13] Formation of the oxamyl chloride, cycloaddition with the styrene and triazole displacement, as in Scheme 1, afforded the target isoxazoline **20**.

Isoxazolines **24** containing a 5-cyano-3-pyridyl group could be prepared as outlined in Scheme 4. The required 3-pyridinecarboxaldhyde **22** was available in a single step from 2-cyano crotonitrile **21** by a Vilsmeier reaction.[14] The yield of **22** could be improved over literature methods by reduction in the amount of phosphorus oxychloride to 2.2 equivalents and use of dichloroethane as solvent (vs neat) at 80 °C affording **22** in 33% yield. Formation of the oxamyl chloride, cycloaddition with the styrene and triazole displacement afforded low yields of the target isoxazoline **24**, although in sufficient quantity for biological evaluation.

Insecticidal activity of the isoxazolines is summarized in Tables 1–3. Compounds were tested against a series of insects under standard laboratory procedures.[14] Potency was evaluated on fall armyworm (*Spodoptera frugiperda, Sf*), corn earworm (*Helicoverpa zea, Hz*), potato leafhopper (*Empoasca fabae*, *Ef*), and western flower thrips (*Frankliniella occidentalis*, *Fo*). Insecticidal activity is reported as an LC_{50} in ppm, the lethal concentration required for 50% mortality. As a general rule all new compounds showed higher potency against the two species of Lepidoptera.

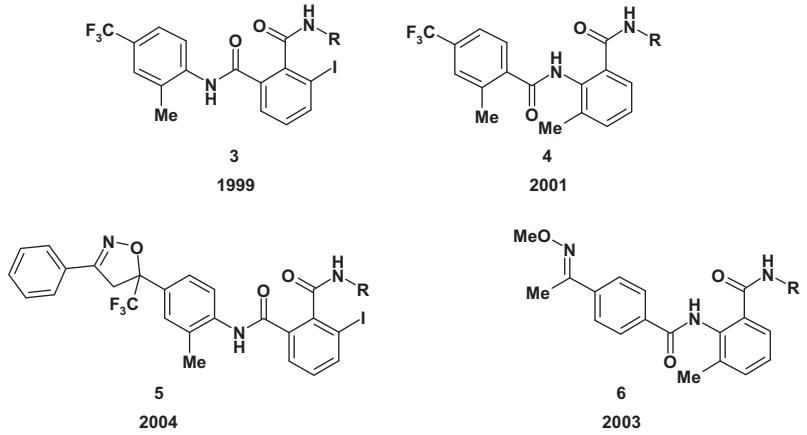
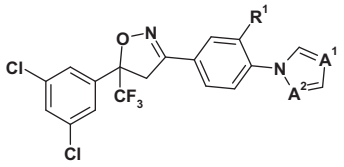


Figure 2. Isoxazolines trace their history through the diamide insecticides.

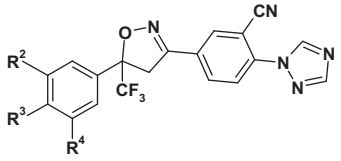
Table 1
Insecticidal potency of isoxazolines. Insect LC_{50} (ppm) are on fall armyworm (*Sf*, *Spodoptera frugiperda*), corn earworm (*Hz*, *Helicoverpa zea*), and potato leafhopper (*Ef*, *Empoasca fabae*), and western flower thrips (*Fo*, *Frankliniella occidentalis*)



Entry	R^1	A^1	A^2	*Sf*[a] LC_{50} ppm	*Hz*[a] LC_{50} ppm	*Ef*[a] LC_{50} ppm	*Fo*[a] LC_{50} ppm
DP-1	H	CH	N	>50	>50	>250	>250
DP-2	H	N	CH	45.8	31.2	>250	>250
DP-3	H	N	N	1.0	4.5	7.1	26.3
DP-4	Me	N	N	1.2	>10	7.5	33.6
DP-5	CF_3	N	N	>10	>10	15.8	11.9
DP-6	Cl	N	N	4.0	9.6	7.5	9.1
DP-7	Br	N	N	2.6	9.6	6.0	9.1
DP-8	NO_2	N	N	2.5	5.5	15.4	8.0
DP-9	CN	N	N	0.2	8.9	0.68	1.4
DP-10	OMe	N	N	26.9	>100	>250	>250
DP-11	SO_2Me	N	N	>100	>100	>250	8.4

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geqslant 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.

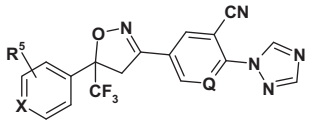
Table 2
Insecticidal potency of isoxazolines. Insect LC_{50} (ppm) are on fall armyworm (*Sf*, *Spodoptera frugiperda*), corn earworm (*Hz*, *Helicoverpa zea*), potato leafhopper (*Ef*, *Empoasca fabae*), and western flower thrips (*Fo*, *Frankliniella occidentalis*)



Entry	R^2	R^3	R^4	*Sf*[a] LC_{50} ppm	*Hz*[a] LC_{50} ppm	*Ef*[a] LC_{50} ppm	*Fo*[a] LC_{50} ppm
DP-12	Br	H	Br	0.25	0.87	2.0	0.8
DP-13	CF_3	H	CF_3	0.3	0.4	2.2	3.5
DP-14	Cl	Cl	Cl	0.11	1.41	0.7	0.5
DP-15	Cl	F	Cl	0.08	1.20	0.8	0.6
DP-16	Cl	Cl	CN	>100	>100	>50	60.0
DP-17	Cl	Cl	OMe	2.8	>10	>50	29.2
DP-18	Cl	CN	Cl	4.9	>10	6.6	4.7
DP-19	Cl	Me	Cl	3.0	>10	17.2	9.2

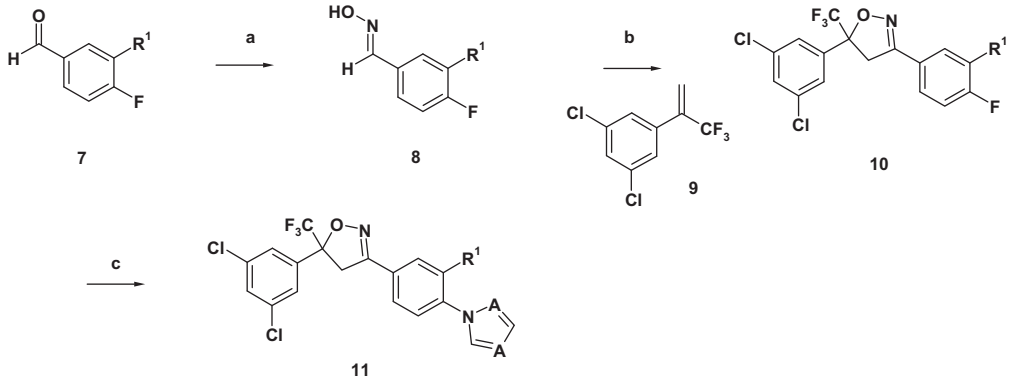
[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geqslant 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.

Table 3
Insecticidal potency of isoxazolines. Insect LC_{50} (ppm) are on fall armyworm (*Sf*, *Spodoptera frugiperda*), corn earworm (*Hz*, *Helicoverpa zea*), and potato leafhopper (*Ef*, *Empoasca fabae*), and western flower thrips (*Fo*, *Frankliniella occidentalis*)



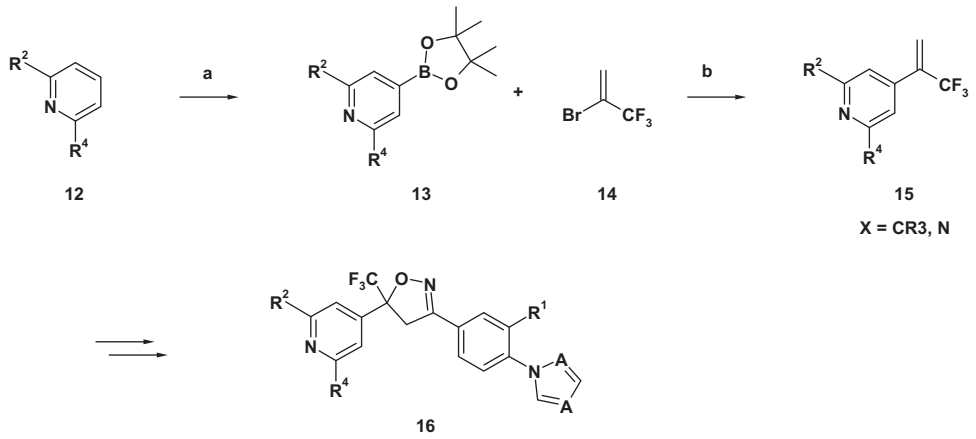
Entry	R^5	X	Q	*Sf*[a] EC_{50} ppm	*Hz*[a] EC_{50} ppm	*Ef*[a] EC_{50} ppm	*Fo*[a] EC_{50} ppm
DP-20	3-Cl	N	CH	>100	>100	>250	13.1
DP-21	3,5-diCl	N	CH	30.0	>100	>250	>250
DP-22	3,5-di-CF_3	N	CH	2.7	1.7	1.9	3.6
DP-23	3,5-diCl	CH	N	1.1	>10	19.8	33.0
DP-24	3,5-diBr	CH	N	0.7	3.3	4.5	2.3
DP-25	3,4,5-triCl	CH	N	0.7	4.3	45.9	142.5
DP-26	3-Cl, 4-F, 5-Cl	CH	N	0.5	1.1	5.7	5.1

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geqslant 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.

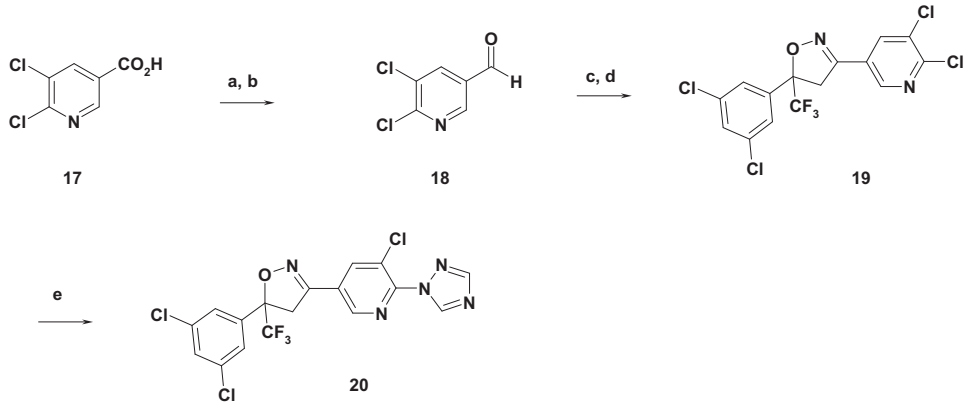


Scheme 1. Reagents and conditions: (a) NH_2OH, MeOH, 25 °C, 87–95%; (b) 6–13% NaOCl, THF, 0–25 °C, 39–56%; (c) K_2CO_3, CH_3CN, azole, 80 °C, 27–80%.

DP-1 through **DP-3** were initially prepared to investigate insecticidal activity for the azole groups pyrazole, imidazole and triazole at the 4-position of the aryl ring. While both the pyrazole **DP-1** and imidazole **DP-2** displayed only weak levels of activity, the triazole **DP-3** was quite active on both lepidopteran pests and demonstrated fair activity on *Ef* and *Fo*. Based on the activity of the triazole **DP-3** we turned our attention to an investigation of R^1 substituent groups (compounds **DP-4** to **DP-11**). The ortho-methyl group was of particular interest as this substituent appeared to maximize activity for the Nissan isoxazoline 4-carboxamides (i.e., **1**). For the triazoles, however, we observed a modest reduction in activity when methyl was introduced at R^1 as in **DP-4**. On the other hand, compound **DP-9**, containing a cyano group at R^1 demonstrated exceptionally high levels of insecticidal activity and for



Scheme 2. Reagents and conditions: (a) $Ir_2(COD)_2Cl_2$ (10 mol %), bipyidyl (10 mol %,), bis(pinacolato)diborane (0.6 equiv), heptanes, 98 °C, 82–93%; (b) $Pd(Ph_3P)_4$ (10 mol %), 4 N aq KOH, DME/THF, 75 °C, 49–79%.



Scheme 3. Reagents and conditions: (a) oxalyl chloride, DMF (cat) CH_2Cl_2; (b) $LiAlH(O\text{-}tBu)_3$, CuI, THF/acetonitrile, −78 °C, 15% (steps a–b); (c) $NH_2OH{\cdot}H_2O$, MeOH, 25 °C, 76%; (d) 6% NaOCl, THF, 25 °C, 39%; (e) K_2CO_3, CH_3CN, triazole, 80 °C, 24%.

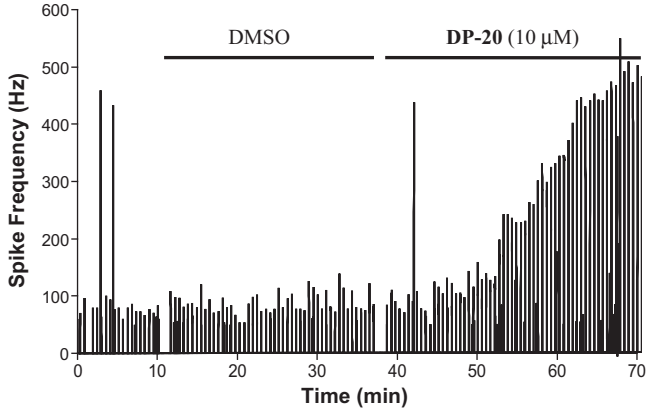


Figure 3. Nerve activity of **DP-20** in the *P. americana* cercal-reflex-N5 assay. A suction electrode attached to motor nerve, N5, recorded the air puff-induced efferent signals. In the presence of saline or DMSO air puffs induced action potentials with a spike frequency below 150 Hz. Following application of **DP-20** (10 μM) a strong increase in the air-puff response is observed.

certain insect species, including *Sf*, *Ef* and *Fo*, activity was equal or superior to commercial standards.

Compounds containing ortho halogen groups, chloro **DP-6** and bromo **DP-7**, as well as the nitro derivative **DP-8** were moderately active, although somewhat less than the unsubstituted parent **DP-3**. The trifluoromethyl substituent of compound **DP-5** showed a significant reduction in activity, somewhat surprising based on analogy with halogen substituents. Other R^1 groups including methoxy **DP-10** and methylsulfonyl **DP-11** were very weak.

Table 4
Mortality of beet armyworm exposed to treated soybean leaf material collected at different intervals after spraying[a]

Treatment	Mortality (%)			
	g ai/ha[b]	0 DAT[b]	10 DAT[b]	17 DAT[b]
DP-9 (10SE)[c]	25	100	91	58
	50	100	97	97
	100	100	100	100
DP-12 (10SE)[c]	25	100	100	94
	50	100	100	98
	100	100	100	100
Chlorantraniliprole (coragen 20SC)[c]	25	100	100	100
	50	100	100	100
Indoxacarb (steward 1.25SC)[c]	73	100	100	97
Untreated check	n/a	0	0	0

[a] A total of 64 larvae were used to assess each treatment on each date.
[b] g ai/ha = grams active per hectare; DAT = days after treatment.
[c] SE = suspo-emulsion; SC = suspension concentrate.

Table 5
Control of *Caliothrips indicus* nymphs and adults 15 days after treatment

Treatment	Rate (g ai/ha)	Number of insects	
		Nymphs	Adults
DP-9 (10SE)	25	21cd	6b
	50	20cd	7ab
	150	15d	6b
DP-12 (10SE)	25	16cd	8ab
	50	22cd	6b
	150	8d	4b
Acephate (orthene 90S)	250	14d	5b
Aldicarb (temik 15G)	410	56bc	7ab
Untreated check	n/a	142a	8ab

Means within columns followed by the same letter are not significantly different (fisher's least significant difference test, $P = 0.05$).
g ai/ha = grams active per hectare.
SE = suspo-emulsion, S = solution, G = granular.

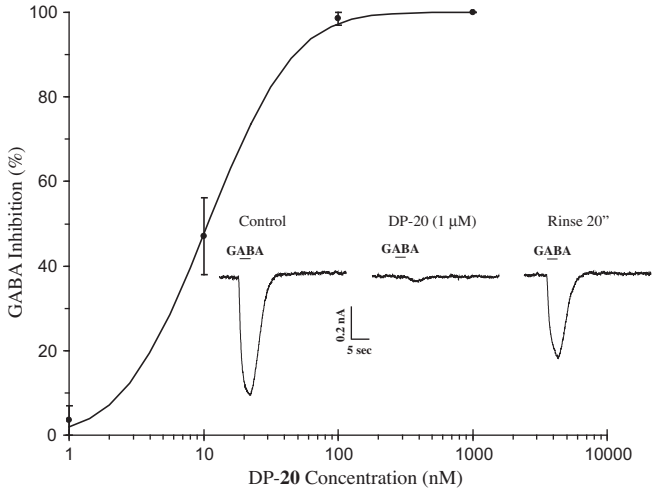


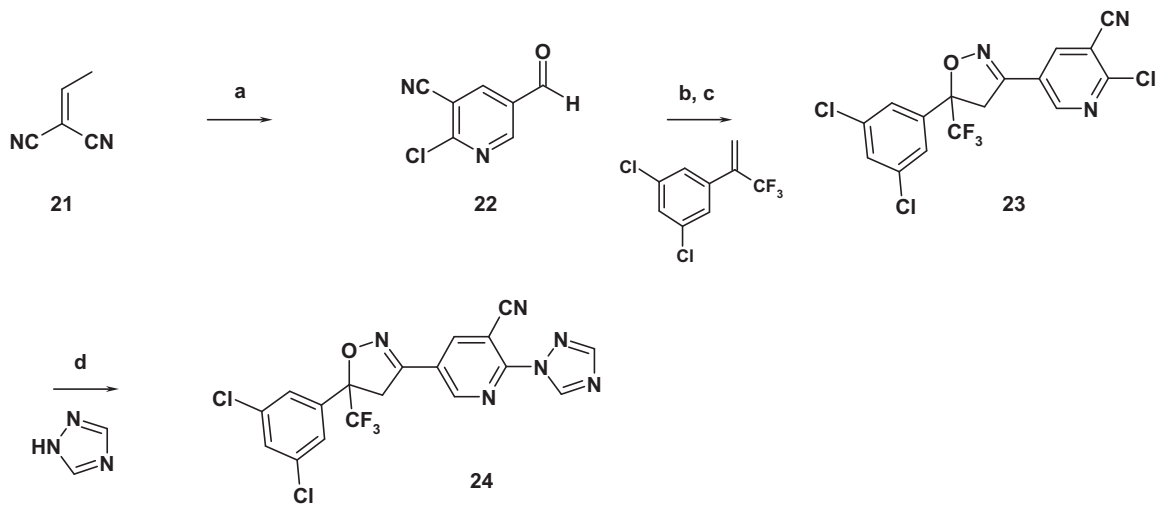
Figure 4. The isoxazoline, **DP-20** inhibits GABA gated currents in *P. americana* neurons. Dissociated neurons were voltage clamped at a holding potential of −60 mV and repeatedly stimulated with pulses of 100 μM GABA (inset left trace). Perfusion of **DP-20** inhibited the GABA response (inset middle trace) in a dose-dependent manner with an IC_{50} = 10.8 nM. Following saline rinse a partial recovery of the GABA response was observed (inset right trace).

Based on the activity of the 2-cyanophenyl triazole **DP-9**, a series of analogs containing a range of terminal aryl substituents was investigated (Table 2). Compounds **DP-12** through **DP-15** containing halogen and/or trifluoromethyl groups in positions R^2–R^4 showed an increase in activity versus **DP-9** and were among the most active compounds explored comparing favorably with standards on many key pest species. Substituent groups such as cyano and methoxy (**DP-16 and DP-17**) each resulted in a dramatic loss in activity. Replacement of the central substituent R^3 with groups such as methyl and cyano (i.e., **DP-18, DP-19**) provided moderately active compounds although somewhat less than their trihalo counterparts.

Based on an insecticidal spectrum that included hemipteran pests there was significant interest in lower log*P* analogs to improve systemic properties and increase availability to pests that feed on plant juices. Pyridine derivatives incorporating nitrogen on either of the phenyl rings were explored as one approach to reduce log*P*. These compounds were, however, less active than their carbon analogs. The terminal 4-pyridyl derivatives **DP-20** through **DP-22** showed a dramatic loss in activity for the chloro derivatives **DP-20** and **DP-21** and a more modest loss in activity for the bis-trifluoromethyl derivative **DP-22**. Specifically, for **DP-22** there was observed an approximate order of magnitude reduction in activity on the lepidopteran pests *Sf* and *Hz*, while the activity was comparable on *Ef* and *Fo*. Incorporating nitrogen ortho to the azole in **DP-23** through **DP-26** resulted in a similar although less severe, loss in activity. Of this group **DP-22** and **DP-24** were most active across the four insect species, although with less activity than standards on major hemipteran pests.

Compounds **DP-9** and **DP-12** were evaluated in several trials to determine if laboratory efficacy translated to acceptable levels of control in the field. In one trial, soybean was sprayed in the field and leaf samples were periodically collected, brought into the laboratory, and exposed to larvae of beet armyworm (*Spodoptera exigua*). Both compounds resulted in control equivalent to commercial standards indoxacarb and chlorantraniliprole (Rynaxypyr®) at 17 days after treatment; although, rates of at least 25 and 50 g ai/ha were needed for **DP-12** and **DP-9**, respectively (Table 4).

In a cotton trial in Louisiana, **DP-9** and **DP-12** provided effective control of cotton thrips (*Caliothrips indicus*) nymphs with equivalent efficacy to acephate and better control than aldicarb at much lower rates (Table 5). None of the treatments were effective at controlling adult thrips, although numbers of adults were quite low.



Scheme 4. Reagents and conditions: (a) $POCl_3$, DMF, $ClCH_2CH_2Cl$, 80 °C, 33%; (b) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, 25 °C, 81%; (c) NCS, DMF, 25 °C; (d) K_2CO_3, CH_3CN, DMF, 80 °C, 4% (steps c–d).

Table 6
Activity of select isoxazolines on toxicity and GABA response of thoracic neurons from adult *P. americana*

Cpd	P. americana LD_{50} (μg/roach)	GABAR IC_{50} (nM)
DP-1	16.7	850
DP-5	4.4	49.2
DP-20	0.4	10.8

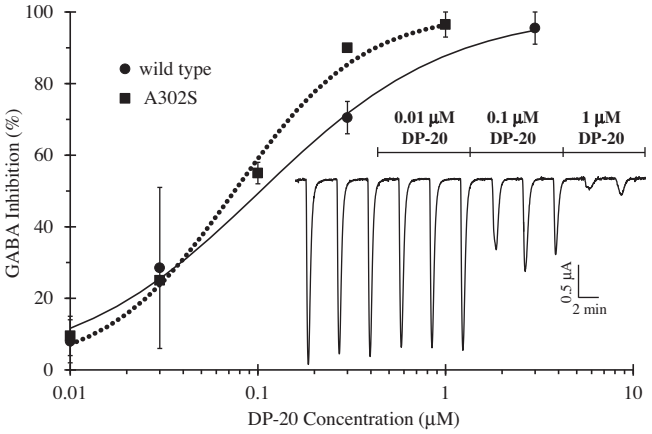


Figure 5. Dose-dependent inhibitory effect of **DP-20** on the GABA-induced currents of *Xenopus* oocytes expressing wild type (circle) and A302S (square) RDL GABA receptors. The inset shows a typical response of **DP-20** on oocytes expressing the A302S RDL GABA receptor. For all oocytes the membrane potential held at −60 mV.

S. frugiperda Larvae injected with isoxazolines exhibited symptoms which included periodic body wall contractions and hypersensitivity to mechanical stimulation. This was indicative of neuro/muscular poisoning though distinct from those observed with diamide insecticides.[15] When adult cockroach, *Periplaneta americana,* were injected, poisoning began as brief periodic wing fluttering that progressed until insects became uncoordinated with difficulty remaining upright. Once prostrate insects displayed periodic volleys of leg tremors and eventually died. The KD_{50} (50% knockdown concentration) values were determined for **DP-1**, **DP-5** and **DP-20** having values of 16.7, 4.4 and 0.4 μg/roach, respectively. These analogs were selected for in vitro studies as they provided a range of insecticidal potency and their increased aqueous solubility allowed for testing at micromolar concentrations.

To determine whether isoxazoline insecticides were active against insect RyRs, analogs were tested against native *P. americana* and recombinant *Drosophila melanogaster* RyRs as described previously, and were found to be inactive at concentrations up to 30 μM (data not shown).[15] As poisoning was neuro/muscular in nature, extracellular recordings were conducted on nerve 5 (N5) of *P. americana* metathoracic ganglia. Bath perfusion of **DP-20** (10 μM) induced a strong increase in the air puff-induced (cercus stimulation) nerve frequency while spontaneous nerve activity remained unaffected (Fig. 3). This suggested that the target was more likely a ligand-gated receptor than a voltage-gated ion channel.

Neurotransmission in the cercal reflex-N5 pathway entails both excitatory nicotinic acetylcholine receptors (nAChRs) and inhibitory GABA gated chloride channels[16]; therefore action of **DP-20** was investigated on both systems. No effect was observed on nAChRs (data not shown); however, GABA-induced currents in *P. americana* thoracic neurons were potently blocked. The isoxazoline, **DP-20**, inhibited GABA-induced chloride currents with an IC_{50} value of 10.8 nM (Fig. 4). Further evaluation showed that roach toxicity for **DP-1**, **DP-5** and **DP-20** correlates well with GABA gated chloride channel inhibition (Table 6).

The *D. melanogaster* strain, RDL (resistance-to-dieldrin), is a strain of laboratory-selected flies with resistance to dieldrin and other cyclodienes. Resistance is associated with a single amino acid substitution of serine for alanine at residue 302 of the *rdl* gene which encodes for a GABA receptor subunit.[17,18] To evaluate for cyclodiene cross-resistance, **DP-20** was tested on *Xenopus laevis* oocytes expressing the *D. melanogaster* rdl GABA receptor. Perfusion with **DP-20** produced a dose-dependent inhibition in the GABA response with IC_{50} values of 75 and 97 nM for wild type and mutant (A302S) receptors, respectively (Fig. 5). Studies using expressed GABA receptors from the housefly, *Musca domestica*, found the antiparasitic isoxazoline, A1443, to similarly block wild-type and the A299S homologs of the rdl receptor.[8] The absence of differential potency indicates that cross-resistance between isoxazoline and cyclodienes would not be expected.

In summary, a series of 4-azolylphenyl isoxazoline insecticides have been discovered which exert their action as potent blockers of the GABA gated chloride channel and importantly lack evidence of cyclodiene cross-resistance. Optimization of this class has identified 4-cyano triazoles, such as **DP-9** and **DP-12**, to be highly effective in field trials and competitive with standards, offering the potential for a new class of chemistry in the defense of crops.

References and notes

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