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ABSTRACT

A novel class of mesoionic pyrido[1,2-*a*]pyrimidinones has been discovered with exceptional insecticidal activity controlling a number of insect species. In this communication, we report the part of the optimization program that led to the identification of dicloromezotiaz as a potent insecticide to control a broad range of lepidoptera. Our efforts in discovery, synthesis, structure-activity relationship elucidation, and biological activity evaluation are also presented.

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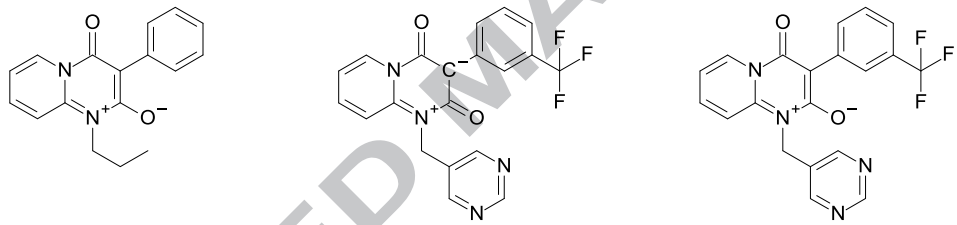
Nicotinic acetylcholine receptors (nAChRs) are well-established targets for insect control with a number of successful commercial insecticide products developed. This includes traditional neonicotinoid insecticides, as well as the more recently discovered sulfoximines and butenolides.[3,4]

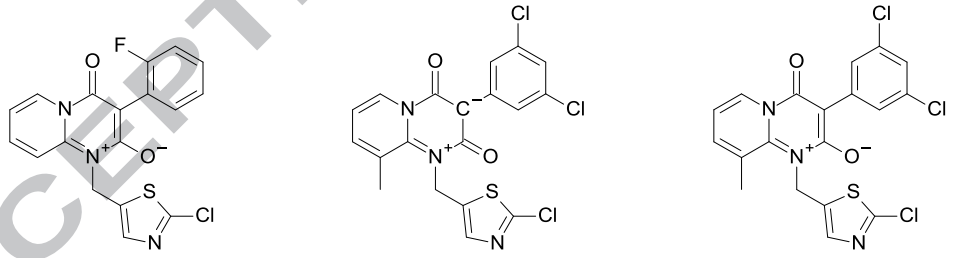
We recently reported our discovery of mesoionic insecticides originating from DuPont internal compound **1** (see Fig. 1).[1,5] As a result of the optimization effort in this area, triflumezopyrim (**2**, ISO common name approved in August, 2013, DuPont Pyraxalt®) was identified as a novel and highly potent hopper insecticide for Asian rice market.[2,6]

It has been established that traditional neonicotinoids, sulfoximines, and butenolides bind to the orthosteric (acetylcholine binding) site stimulating nAChR activation which results in acute excitatory poisoning in insects.[7] Mode of action studies of representative mesoionic analogs showed that this novel class of insecticides also binds to the orthosteric site of the nicotinic acetylcholine (nAChR) receptor, but acts primarily via inhibition of the binding site and leads to lethargic poisoning among different insect species.[8] Despite of the concise mode-of-action difference of neonicotinoids, sulfoximines, butenolides, and triflumezopyrim, all are potent insecticides controlling primarily hemipteran insect species, particularly hoppers. In general, neonicotinoids, such as acetamiprid and thiacloprid, offer limited utility for lepidopteran pest control.[9]

contain a 2-chlorothiazol-5-yl group connected to the 1-position of mesoionic core ring via a methylene linkage. Such compounds possess exceptional biological activity against a number of hopper species, including corn planthopper (*Peregrinus maidis* (Ashmead), CPH), potato leafhopper (*Empoasca fabae* (Harris), PLH), brown planthopper (*Nilaparvata lugens* (Stål), BPH), and rice green leafhopper (*Nephotettix virescens* (Distant), GLH).[1] Interestingly, **3** also shows very potent activity against two representative lepidopteran species diamondback moth (*Plutella xylostella* (Linnaeus), DBM) and fall armyworm (*Spodoptera frugiperda* (J.E. Smith), FAW).

Lepidoptera is a large order of insect species with significant importance in global agriculture. Based on the observed lepidoptera activity of **3**, the DuPont research team dedicated efforts to find a mesoionic insecticide providing highly efficacious control of lepidopteran pests. Ultimately, dicloromezotiaz (**4**, ISO common name approved in Dec. 2014) was identified.[10] In this communication, we present our efforts in this optimization program, focusing on varying the substituents on the mesoionic core ring and on the 3-phenyl group, leading to the discovery of dicloromezotiaz. We will report our efforts in discovery, synthesis, structure-activity relationship elucidation, and biological activity evaluation related to dicloromezotiaz.



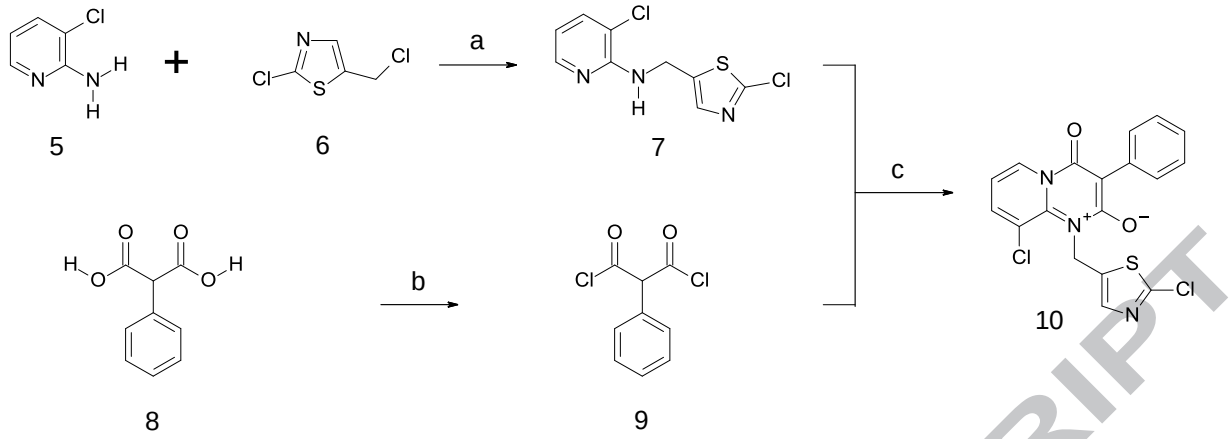


In the mesoionic insecticide optimization program, we prepared analogs, such as compound **3** (see Fig. 1), which

Figure 1. Mesoionic insecticides, triflumezopyrim (**2**), dicloromezotiaz (**4**), and alternative representations of **2** and **4** (**2a** and **4a**)

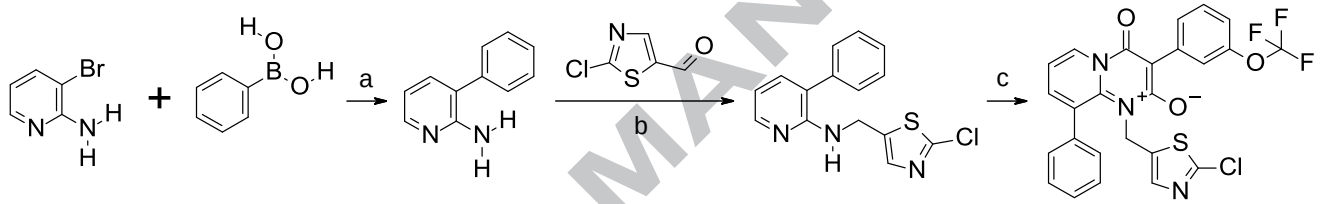
Triflumezopyrim (**2**) and dicloromezotiaz (**4**) are represented in the SciFinder® database as structure **2** and **4** shown in Fig. 1, with the negative charge located on the carbon at the 3-position of the mesoionic core. However, it is worth noting that mesoionic compounds cannot be satisfactorily represented by any single covalent or ionic structure.[11] The authors have been using the drawing pattern as shown for compounds **1**, **2a (**alternative drawing of triflumezopyrim), and **4a** (alternative drawing of dicloromezotiaz). This drawing pattern has been employed in the patent application cases filed by DuPont and has been adopted in the SciFinder® database to represent all other mesoionic compounds. The drawing pattern of **2a** and **4a** will be used throughout this article.

In our previous reports,[1,2] a number of synthetic routes have been presented for accessing mesoionic pyrido[1,2-*a*]pyrimidinones. Over the course of the optimization program, more straightforward routes and more efficient methods have been developed as described in Schemes 1-6. Analogs with various substitution at 6- to 9-postions were the first set of molecules prepared and their synthesis is outlined in Scheme 1. Substituted pyridine **7** was prepared by direct alkylation onto the 2-amino group of compound **5** with chlorothiazole alkylating agent **6** at high temperature in a microwave apparatus. Malonic acid **8** was converted to malonyl chloride **9** which was then combined with aminopyridine **7** in the presence of triethylamine to generate the desired product **10** in good overall yield.



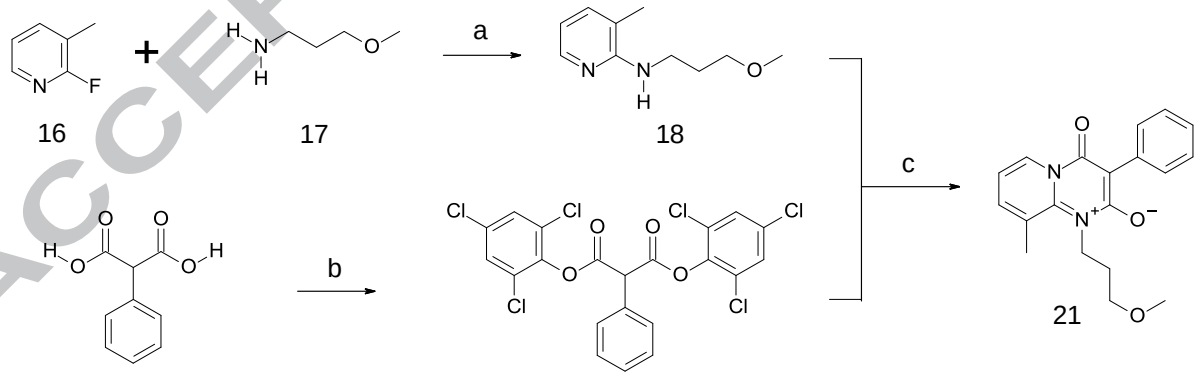
Scheme 1. Reagents and conditions: (a) NMP, 220 °C (microwave), 33%; (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 25 °C; (c) TEA, CH_2Cl_2, 25 °C, 79% for two steps.

Preparation of compound **15** is outlined in Scheme 2. Reaction between 3-bromo-2-aminopyridine (**11**) and boronic acid **12** under standard microwave Suzuki reaction conditions provided coupling product **13** in very good yield. **13**, in turn, was converted to amine **14** through a stepwise reductive amination reaction.[12] Similar cyclization reaction provided mesoionic compound **15** in reasonable yield. Lower yield in this case is likely due to imposed steric hindrance upon cyclization.



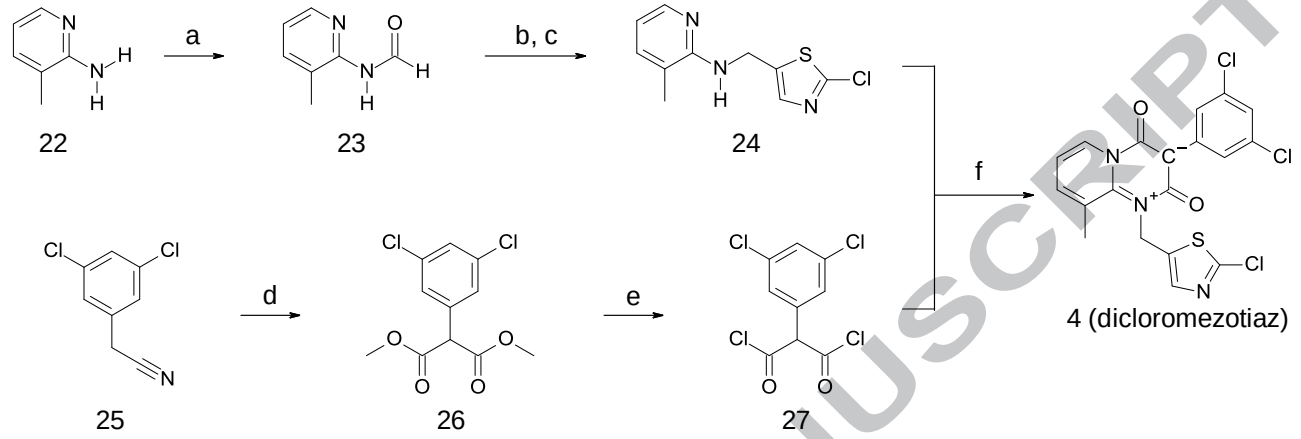
Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, Na_2CO_3, H_2O, 150 °C (microwave), 79%; (b) 2-Chlorothiazole-5-carbaldehyde, CH_2Cl_2, 90 °C (rotavapor); $NaBH_4$, MeOH, 25 °C, 99% (overall); (c) 2-[3-(Trifluoromethoxy)phenyl]propanedioyl dichloride, TEA, CH_2Cl_2, 25 °C, 36%.

Substituted 2-aminopyridines were also prepared via substitution reaction of 2-fluoropyridine (**16**), as depicted in Scheme 3. Reaction between **16** and amine **17** in NMP under microwave radiation at 220 °C produced the desired amine **18** in good yield. In this case, malonic acid was activated as the bis(2,4,6-trichlorophenyl) ester **20** which reacted with amine **18** in toluene and at elevated temperature to form compound **21** in good yield.



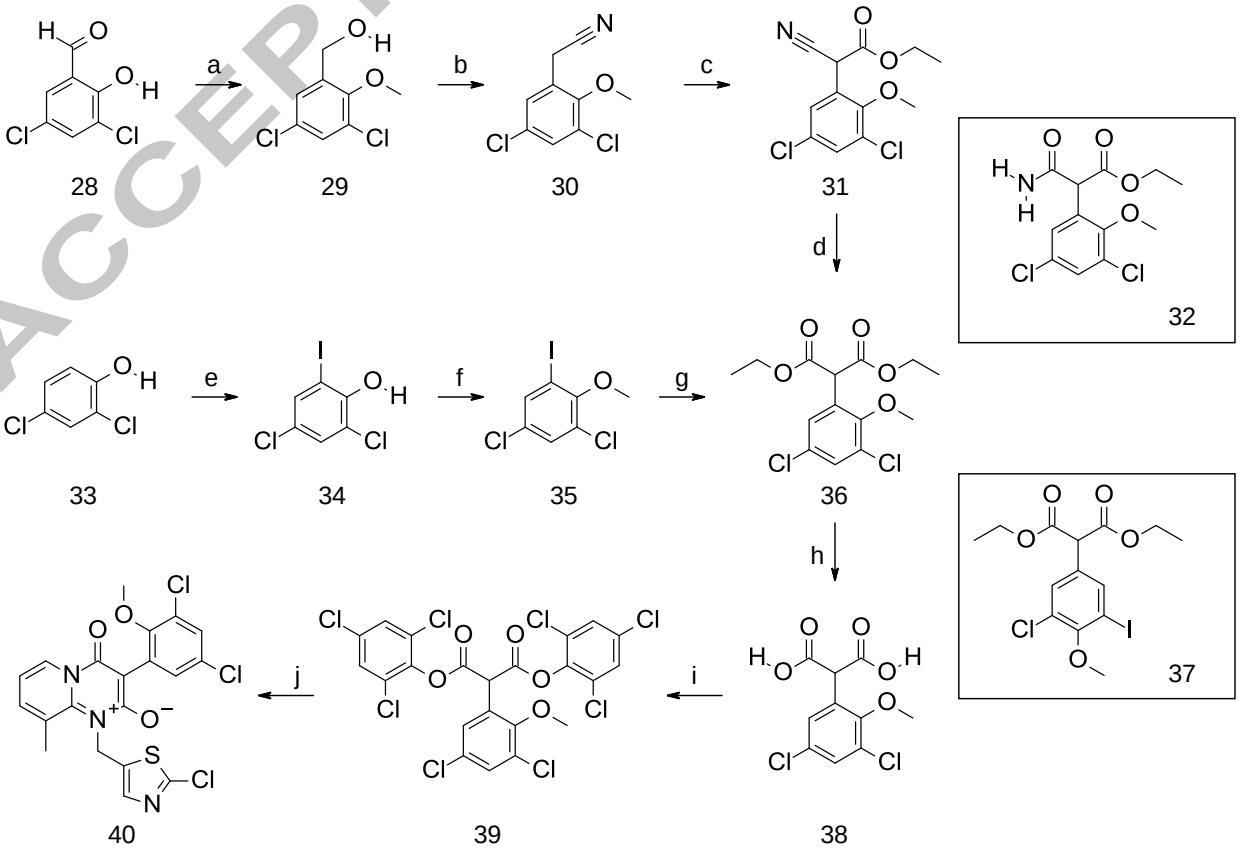
Scheme 3. Reagents and conditions: (a) NMP, 220 °C (microwave), 52%; (b) 2,4,6-Trichlorophenol, $POCl_3$, 100 °C; (c) Toluene, 100 °C, 62%.

Synthesis of dicloromezotiaz (**4**) starts from 3-methyl-2-aminopyridine (**22**) as showed in Scheme 4. Compound **22** was first formylated to generate compound **23** in excellent yield. **23** was alkylated with the desired 2-chloro-5-(chloromethyl)thiazole and then treated with sodium hydroxide to remove the formyl group and produce product **24** in very good overall yield.[13,14] Treatment of aryl acetonitrile (**25**) with sodium methoxide and in the presence of dimethyl carbonate afforded the desired cyanoacetate which was then transformed to malonate **26** through imidate formation and subsequent methanolysis. Malonate **26** was converted to the corresponding malonic acid potassium salt in the presence of potassium hydroxide. An excellent yield of the salt was obtained after removal of solvent water.[15] The resulting potassium salt was converted to the malonic chloride **27** which, in turn, reacted with amine **24** to form dicloromezotiaz (**4**) in excellent overall yield.[16]



Scheme 4. Reagents and conditions: (a) HCO_2H, Ac_2O, EtOAc, 25 to 48 °C, 90%; (b) 2-Chloro-5-(chloromethyl)thiazole, K_2CO_3, *n*-Bu_4NBr (cat.), *i*-PrOH, rt to 75 °C; (c) aq. NaOH, 50 to 10 °C , 77% for 2 steps; (d) NaOMe, $CO(OMe)_2$, toluene-MeOH, 50 °C; HCl in MeOH, H_2O, 45-50 °C, 60%; (e) aq. KOH, 30 °C, drying; $(COCl)_2$, DMF (cat.), toluene, rt; (f) TEA, toluene, 3 °C to rt, 92% for 2 steps.

Besides optimizing the substituents on the mesoionic core and sidechain at the 1-position, analogs with various substitutions on the phenyl ring were also prepared and evaluated. Synthesis of 3,5-dichloro-2-methoxy-phenyl analog **40** is outlined in Scheme 5. Subsequent *O*-methylation and reduction of aldehyde **28** provided benzyl alcohol **29** in high yield. This alcohol was then converted into benzyl chloride which, in turn, was transformed to the corresponding aryl acetonitrile **30** in good yield.[17] **30** underwent ethoxycarbonylation to form cyanoacetate **31** which was subjected to alcoholysis in the presence of hydrogen chloride to form the desired diethyl malonate **36**. Amide **32** was also isolated as a by-product from this reaction. One alternative synthesis of **36** is also presented in Scheme 5. Iodonation of phenol **33** and subsequent *O*-methylation provided anisole **35** in good overall yield.[18] **35** underwent a copper-catalyzed coupling reaction with diethyl malonate to produce aryl malonate **36** in reasonable yield.[19] Low reactivity of the C-1 site of iodobenzene **35** is evident and 30% of **35** was recovered even after prolonged



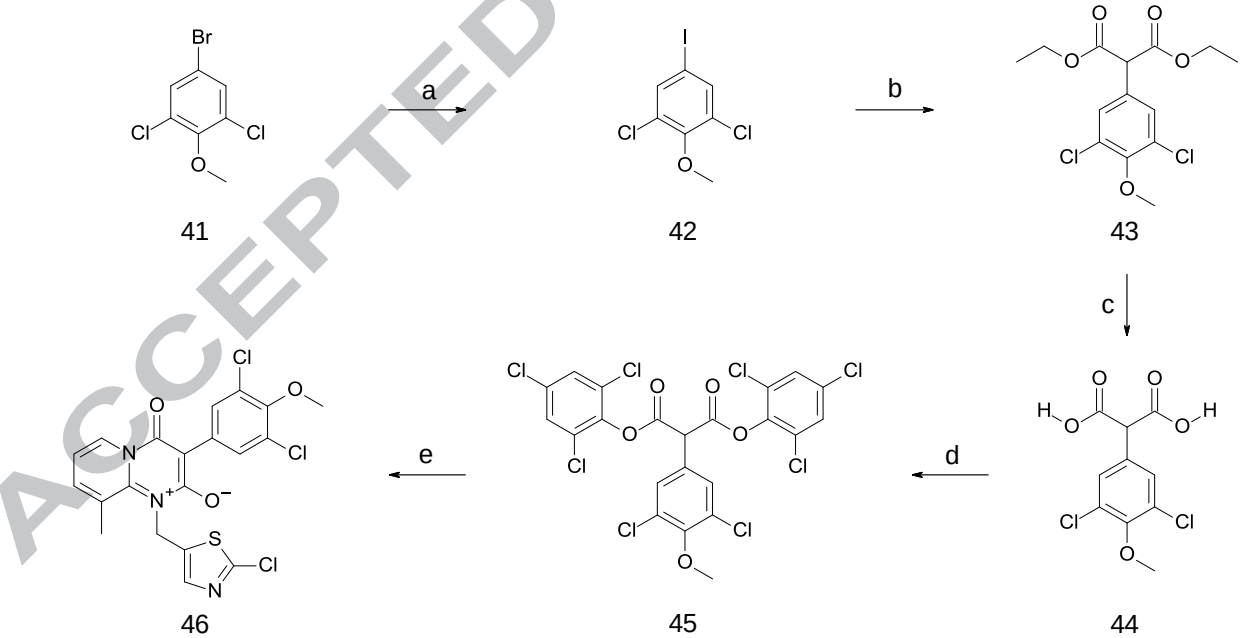
heating at 80 °C. Malonate **37** was also isolated as a side product, derived from arylation at the *para*-position of anisole **35**. The remaining steps took place uneventfully. Malonate **36** was hydrolyzed to form malonic acid **38** which was further converted to activated ester **39** in excellent overall yield. Heating a mixture of **39** and aminopyridine **24** led to formation of product **40** in reasonable yield.

Scheme 5. Reagents and conditions: (a) MeI, K_2CO_3, DMF, 25 °C; $NaBH_4$, EtOH, 0 °C, 88% (overall); (b) $SOCl_2$, $CHCl_3$, 25 0 °C; NaCN, NaI, tetrabutylammonium iodide, benzene, H_2O, 70 °C, 75% (overall); (c) NaH, diethyl carbonate, THF, 0 to 70 °C, 80%; (d) $SOCl_2$, EtOH, 25 °C; H_2O, 71% (**36**:**32** = 1:1); (e) I_2, KI, NaOH, H_2O, 0 °C; (f) K_2CO_3, MeI, CH_3CN, 25 °C, 75% for 2 steps; (g) diethyl malonate, CuI, picolinic acid, Cs_2CO_3, dioxane, 80 °C, 48% (**36**:**37** = 2:1); (h) 20% NaOH, H_2O, 60 °C; HCl; (i) $(COCl)_2$, 2,4,6-trichlorophenol, DMF (cat.), CH_2Cl_2, 25 °C, 94%; (j) Aminopyridine **24**, toluene, 110 °C, 48%.

Compound **46**, with the extra methoxy group at the 4-position of the phenyl ring, was prepared according to Scheme 6. Bromobenzene **41** underwent copper-catalyzed halogen exchange to generate iodobenzene **42** in excellent yield. **42** was then subjected to copper-catalyzed arylation of malonate to produce aryl malonate **43** in good yield. The same sequence of saponification, activated ester formation, and cyclization gave product **46** in good yield.

Insecticidal activity of the mesoionic compounds is summarized in Table 1-3. Test compounds were formulated using a solution containing 10% acetone, 90% water and 300 ppm of X-77® spreader surfactant (Loveland industries, Inc. Greeley, Colorado, USA). The formulated compounds were sprayed on the foliage of plants at 2–5 rates and tests were replicated three times. Efficacy was evaluated on corn planthopper (*Peregrinus maidis* (Ashmead), CPH); potato leafhopper (*Empoasca fabae* (Harris), PLH); diamondback moth (*Plutella xylostella* (Linnaeus), DBM); fall armyworm (*Spodoptera frugiperda* (J.E. Smith), FAW); beet armyworm (*Spodoptera exigua* (Hübner), BAW); and corn earworm (Helicoverpa zea (Boddie), HZ).[1,20] Mortality was evaluated 6 days after application for all insects. Insecticidal activity is reported as an LC_{50} (the lethal concentration required for 50% mortality) in ppm (mg/kg).

Insecticidal activity of mesoionic compounds with various substituents on the pyridine ring moiety is showed in Table 1. In general, compounds with a substituent at 6-, 7- , or 8-position of the mesoionic core show no activity for compounds **10a-f** or very limited biological activity for **10g**. For 9-substituted analogs, observed activity depends on both the substituent at the 9-position and the sidechain at the 1-position. 9-Chloro-1-*n*-propyl analog **10h** and 9-methyl-1-(3-methoxypropyl) analog **21** show no insecticidal activity while 1-(2-chlorothiazol-5-yl)methyl analogs with a substituent at the 9-position, such as **10i** (9-Me) and **10** (9-Cl), possess good to strong activity against lepidoptera species DBM and FAW. 9-Methyl analog **10i** also gives very potent activity against two hopper species CPH and PLH.



41 42 43 44 45 46

Scheme 6. Reagents and conditions: (a) NaI, CuI, *N*,*N*-dimethylethylenediamine, dioxane, 117 °C, 97%; (b) Diethyl malonate, CuI, picolinic acid, Cs_2CO_3, dioxane 80 °C, 56%; (c) 20% NaOH, H_2O, 60 °C; HCl; (d) $(COCl)_2$, 2,4,6-trichlorophenol, DMF (cat.), CH_2Cl_2, 25 °C; (e) Aminopyridine **24**, toluene, 110 °C, 75%.

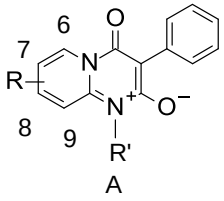
Table 2 presents 1-(2-chlorothiazol-5-yl)methyl analogs with various substitution at the 9-position. The parent hydrogen compound **15a** shows balanced potent activity against all four insect species.[1] 9-Halo analogs and methoxy compound **15b-e** and **10j** are less active than the unsubstituted compound **15a**. This is in contrast to the 9-methyl analog **10i** (see Table 1.) which is more potent than the 9-hydro compound **15a**. Replacing hydrogen atoms on the 9-methyl group with 1-3 fluorine atoms (**15f-h**) results in loss of activity. Analogs with larger substituents (**15i-k** and **15**) also lead to diminished activity.

Analogs with different substituents on the 3-phenyl group were also prepared and evaluated. As close analogs of dicloromezotiaz (**4**), compounds **40** and **46** are attractive targets from a process standpoint. Insecticidal potency of both analogs is presented on Table 3, in comparison with dicloromezotiaz (**4**)

and corresponding 9-hydrogen analog **4b**. **4b** shows strong biological activity against CPH, DBM, and FAW but Dicloromezotiaz (**4**) is significantly more potent, particularly on controlling lepidopteran species DBM and FAW. Further evaluations show that dicloromezotiaz (**4**) also possesses potent activity against other lepidopteran species, such as beet armyworm (BAW) and corn earworm (HZ). Compounds **40** and **46**, unfortunately, showed only limited insecticidal activity. Dicloromezotiaz (**4**) was eventually selected for further development evaluation due to its insecticidal potency against a broad range of insect species.

In summary, a novel class of mesoionic pyrido[1,2-*a*]pyrimidinone compounds have been discovered as potent insecticides, with triflumezopyrim (**2**) and dicloromezotiaz (**4**) identified for controlling hopper and lepidopteran insect species, respectively. This class of compounds bind to the orthosteric site of the nicotinic acetylcholine (nAChR) receptor, and modulate receptors function through potent inhibition with very weak activation at high concentrations.[8,21] Triflumezopyrim (**2**) promises to be a powerful insecticide for control of susceptible and resistant rice hopper species throughout Asia. Given that orthosteric-binding nicotinic insecticides represent an underutilized mode of action for lepidopteran insect species,[21] dicloromezotiaz (**4**) may prove be a useful control tool for these pests.

Table 1. Insecticidal potency of mesoionic compounds with various substituent on the pyridine ring moiety[a]



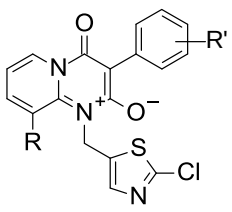
A

Entry	R	R'	CPH	PLH	DBM	FAW
10a	6-Me	n-Pr	>250	>250	>250	No data
10b	6-Cl	n-Pr	>250	>250	>250	No data
10c	7-Me	n-Pr	>250	>250	>250	No data
10d	7-Cl	n-Pr	>250	>250	>250	No data
10e	8-Me	n-Pr	>250	>250	>250	No data
10f	8-Me	(2-chlorothiazol-5-yl)methyl	>50	>50	>50	>50
10g	8-Cl	(2-chlorothiazol-5-yl)methyl	10	>250	>250	>250
10h	9-Cl	n-Pr	>250	>250	>250	>250
21	9-Me	3-methoxypropyl	>50	>50	>10	>10
10i	9-Me	(2-chlorothiazol-5-yl)methyl	<0.4	<0.4	<0.4	10
10	9-Cl	(2-chlorothiazol-5-yl)methyl	>250	10	10	>10

Insect LC_{50} values (ppm) are shown for corn planthopper (*Peregrinus maidis* (Ashmead), CPH); potato leafhopper (*Empoasca fabae* (Harris), PLH); diamondback moth (*Plutella xylostella* (Linnaeus), DBM); and fall armyworm (*Spodoptera frugiperda* (J.E. Smith), FAW).

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geq 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm. "<2" means that, at 2 ppm the mortality was 100%, however no LC_{50} value was calculated; ">250" means that, at 250 ppm the compound showed no activity, therefor no LC_{50} value was calculated, etc.

Table 2. Insecticidal potency of 9-substituted mesoionic compounds[a]



B

Entry	R	R'	CPH	PLH	DBM	FAW
15a[b]	H	H	<2	<2	<2	6.4

15b	F	4-F	50	50	<10	>250
10j	Cl	H	>10	10	10	>10
15c	Br	3-CF_3	50	50	2	10
15d	I	H	10	10	10	>50
15e	OMe	4-F	>50	>50	10	>50
15f	CFH_2	H	>50	>50	>50	>50
15g	CF_2H	H	50	30	>50	>50
15h	CF_3	4-F	50	50	250	>250
15i	Et	3-Br	>50	>50	50	50
15j	vinyl	H	>50	10	>50	>50
15	Ph	3-OCF_3	>50	>50	>50	>50
15k	CH=CH—CH=CH[c]	H	>50	>50	50	>50

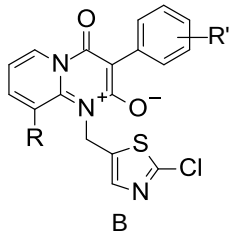
Insect LC_{50} values (ppm) are shown for corn planthopper (*Peregrinus maidis* (Ashmead), CPH); potato leafhopper (*Empoasca fabae* (Harris), PLH); diamondback moth (*Plutella xylostella* (Linnaeus), DBM); and fall armyworm (*Spodoptera frugiperda* (J.E. Smith), FAW).

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geq 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm. "<2" means that, at 2 ppm the mortality was 100%, however no LC_{50} value was calculated; ">250" means that, at 250 ppm the compound showed no activity, therefor no LC_{50} value was calculated, etc.

[b] Data has been reported in literature.[1]

[c] Tied back to 8-position to form an isoquinoline ring moiety.

Table 3. Insecticidal potency of 3-aryl mesoionic compounds[a]



B

Entry	R'	R	CPH	PLH	DBM	FAW	BAW	HZ
4b	3,5-Cl_2	H	10	>50	10	10	No data	No data
4	3,5-Cl_2	Me	2	5	<0.4	0.28	1.47	0.87
40	3,5-Cl_2-2-MeO	Me	>50	30	>10	>10	No data	No data
46	3,5-Cl_2-4-MeO	Me	>50	>50	>10	10	No data	No data

Insect LC_{50} values (ppm) are shown for corn planthopper (*Peregrinus maidis* (Ashmead), CPH); potato leafhopper (*Empoasca fabae* (Harris), PLH); diamondback moth (*Plutella xylostella* (Linnaeus), DBM); fall armyworm (*Spodoptera frugiperda* (J.E. Smith), FAW); beet armyworm (*Spodoptera exigua* (Hübner), BAW); and corn earworm (Helicoverpa zea (Boddie), HZ).

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geq 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm. "<2" means that, at 2 ppm the mortality was 100%, however no LC_{50} value was calculated; ">250" means that, at 250 ppm the compound showed no activity, therefor no LC_{50} value was calculated, etc.

References and notes

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Mesoionic pyrido[1,2-*a*]pyrimidinones: Discovery of dicloromezotiaz as a lepidoptera insecticide acting on nicotinic acetylcholine receptors

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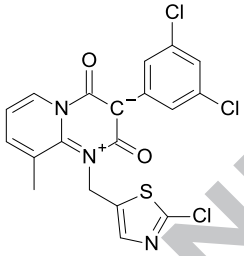

4 (dicloromezotiaz)