Bioorganic & Medicinal Chemistry Letters 26 (2016) 5444–5449

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

# Mesoionic pyrido[1,2-*a*]pyrimidinones: A novel class of insecticides inhibiting nicotinic acetylcholine receptors

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ARTICLE INFO

*Article history:*
Received 22 September 2016
Revised 10 October 2016
Accepted 11 October 2016
Available online 13 October 2016

*Keywords:*
Mesoionic
Pyrido[1,2-*a*]pyrimidinone
Insecticide
Acetylcholine receptor
Inhibitor

ABSTRACT

A novel class of mesoionic pyrido[1,2-*a*]pyrimidinones has been discovered with exceptional insecticidal activity controlling a number of insect species, particularly hemiptera and lepidoptera. Mode-of-action studies showed that they act on nicotinic acetylcholine receptors (nAChRs) primarily as inhibitors. Here we report the discovery, evolution, and preparation of this class of chemistry. Our efforts in structure–activity relationship elucidation and biological activity evaluation are also presented.



Worldwide population growth, urbanization, demand for better quality food diet more rich in protein, and yet limits of arable land and freshwater supplies provide opportunities and challenges for farmers of tomorrow. The agrochemical tools growers currently utilize are also under continuous pressure, due to a number of factors which contribute to loss of existing products. Such factors include the continuing development of resistance, the desire for products with more favored toxicological and environmental profiles, and the need for effective control options for integrated pest management.

The discovery and development of novel pesticides involves a number of different approaches, ranging from investigations of known chemical scaffolds,[1–3] to the high throughput screening of collections of compounds in the attempt to find new or previously unknown chemical scaffolds with desired biological activities.[4] A novel class of mesoionic pyrido[1,2-*a*]pyrimidinones has been discovered as potent insecticides originated from screen of DuPont internal collection of compounds.[5] In this communication, we report the initial discovery of this class of insecticides. We will also present the optimization efforts in this area that revealed analogs such as **29** that shows potent insecticidal activities against a number of insect species and acts on nicotinic acetylcholine receptors primarily as inhibitors.

In the early 1990s, DuPont Crop Protection had devoted efforts to optimizing pyrido[1,2-*a*]pyrimidinone fungicides **A** (see Fig. 1), which led to the discovery of proquinazid (**1**) and its launch in 2005 as a potent fungicide for powdery mildew control.[6] At the lead optimization stage, one variation of structure **A** pursued was a compound replacing the allyl group in **A** with a phenyl group while changing the methyl group to a more desired *n*-propyl group, i.e., compound **2** shown in Figure 1. As depicted in Scheme 1, **2** was prepared in good yield by an alkylation reaction of the corresponding parent pyrido[1,2-*a*]pyrimidinone **3**. However, one by-product was also isolated out of this reaction and identified as mesoionic pyrido[1,2-*a*]pyrimidinone **4**,[7] resulting from unexpected N-alkylation of the pyrido[1,2-*a*]pyrimidinone ring nitrogen atom.[8] Compound **4** and its close analogs were tested and showed no interesting pesticidal activity in the screen at the time. However, in follow-up tests in 2005 against an expanded species list, **4** displayed insecticidal activity against corn planthopper (*Peregrinus maidis* (ashmead), CPH) and diamondback moth (*Plutella xylostella* (Linnaeus), DBM). Interesting insecticidal activity of compound **4** combined with an uncommon yet very intriguing chemical structure prompted us to further explore its analogs.

There are two methods commonly employed for building up pyrido[1,2-*a*]pyrimidinone mesoionic rings. The first one is N-alkylation of parent pyrido[1,2-*a*]pyrimidinone ring as shown in Scheme 1. Alternatively, the reaction between *N*-substituted 2-aminoamidines with malonic esters at high temperature also

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http://dx.doi.org/10.1016/j.bmcl.2016.10.031
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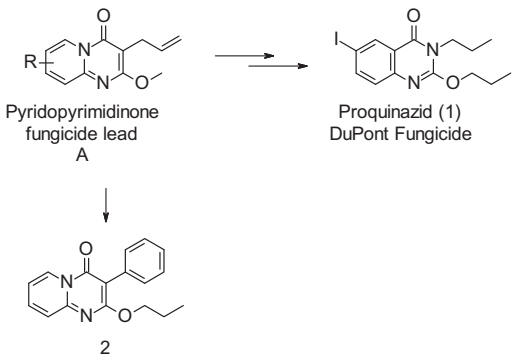


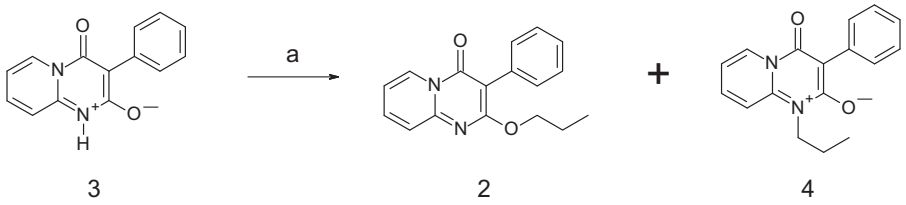

**Figure 1.** Pyrido[1,2-*a*]pyrimidinone fungicide and proquinazid.

generates desired mesoionic compounds.[9] This method was applied for preparation of compound **4** and its analogs. The compounds shown in Tables 1–4 were prepared as described in Schemes 2–6. Synthesis of 1-alkyl compounds is outlined in Scheme 2. 2-(Propylamino)pyridine (**7**) was prepared in two steps from *N*-formyl-2-aminopyridine (**5**) by treatment with sodium hydride, 1-iodopropane followed by deformylation under acidic conditions.[10] Required diethyl phenylmalonate (**8**) and its analogs with various substituents on the phenyl ring were prepared according to literature.[11] Cyclization between 2-aminopyridine **7** and diethyl phenylmalonate (**8**) produced desired mesoionic compound **4** in reasonable yield. Other 1-alkyl analogs **4a**–**4j** in Table 1 and oxygen-containing analogs **11g**–**11i** in Table 2 were prepared in a similar fashion.

Mesoionic compounds containing 1-alkoxycarbonylalkyl groups were prepared as depicted in Scheme 3. 2-Aminopyridine (**9**) was mixed with aqueous glyoxal in the presence of ethanol as co-solvent. The resulting mixture was treated with triflic acid at elevated temperature to generate the expected product **10** in one-pot in good overall yield.[12] The use of triflic acid is an improvement of a similar reaction reported previously in which explosive concentrated perchloric acid was utilized as promoter.[13] Cyclization between 2-aminopyridine **10** and malonate **8** gave mesoionic compound **11b** in low yield.

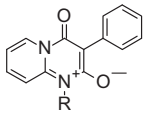
We then shifted our interest to the preparation of 2,2,2-trifluoroethyl analog **14**. Its synthesis is outlined in Scheme 4. 2-Aminopyridine (**9**) was first treated with trifluoroacetic anhydride to convert to *N*-trifluoroacetamide **12**, which, in turn, was reduced by diborane in THF to generate 2-(2′,2′,2′-trifluoroethylamino)-pyridine (**13**).[14] Cyclization between **13** and malonate **8** produced mesoionic compound **14**.

Analogs containing a 5-membered heterocycle ring moiety presented in Table 3 were prepared starting from modification of commercially available heterocycle starting materials. 2-Chlorooxazol-5-yl analog **21** was prepared as outlined in Scheme 5. Ethyl oxazole-5-carboxylate **15** was first converted to 5-hydroxymethyl oxazole **16** via DIBAL-H reduction.[15] **16** was then transformed to 5-(bromomethyl)oxazole **17** which further reacted as an alkylating agent with *N*-Boc-protected 2-aminopyridine **18** to form **19**.[16] Cleavage of the Boc group of **19** was achieved through treatment




**Scheme 1.** Reagents and conditions: (a) *n*-PrI, $K_2CO_3$, 25 °C, ~70% (**3**), <10% (**4**).

**Table 1**
Insecticidal potency of 1-alkyl mesoionic compounds[a]




| Entry | R | CPH | PLH | BPH | GLH | DBM | FAW |
|---|---|---|---|---|---|---|---|
| **4a** | Me | 106.6 | >50 | No data | No data | >250 | No data |
| **4b** | Et | <50 | >50 | >50 | No data | 84.2 | No data |
| **4** | *n*-Pr | 10.4 | 33.4 | >10 | No data | 28.1 | >50 |
| **4c** | Allyl | 50.4 | <50 | No data | No data | 111.8 | >250 |
| **4d** | *i*-Pr | <50 | <50 | No data | No data | 64.3 | >250 |
| **4e** | *n*-Bu | 19.5 | >250 | >10 | No data | 92.1 | >250 |
| **4f** | *i*-Bu | 52.3 | <50 | >50 | No data | 92.1 | No data |
| **4g** | $CH_2$-*c*-Pr | 13.5 | <50 | >10 | No data | 19.2 | >250 |
| **4h** | n-Pent | <250 | >250 | No data | No data | 92.1 | >250 |
| **4i** | Bn | <50 | >250 | No data | No data | >250 | No data |
| **4j** | Ph | >250 | >250 | No data | No data | >250 | No data |

Insect $LC_{50}$ values (ppm) are shown for corn planthopper (*Peregrinus maidis* (Ashmead), CPH); potato leafhopper (*Empoasca fabae* (Harris), PLH); brown planthopper (*Nilaparvata lugens* (Stål), BPH, imidacloprid-resistant); rice green leafhopper (*Nephotettix virescens* (Distant), GLH); 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 ($n \geqslant 3$). $LC_{50}$ calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm. '<50' means that, at 50 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.