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

Thomas P. Selby *, George P. Lahm, Thomas M. Stevenson, Kenneth A. Hughes, Daniel Cordova, I. Billy Annan, James D. Barry, Eric A. Benner, Martin J. Currie, Thomas F. Pahutski

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

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

* Corresponding author.
E-mail address: thomas.p.selby@usa.dupont.com (T.P. Selby).

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

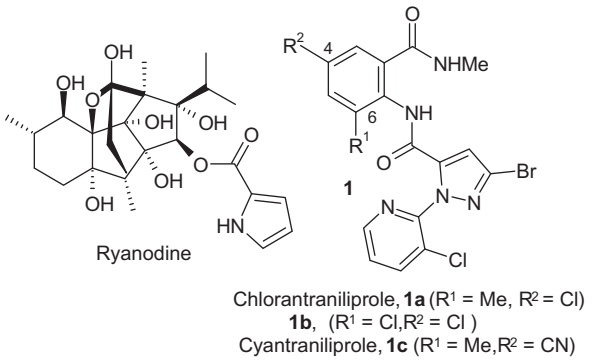


Figure 1. Ryanodine and anthranilic diamides.

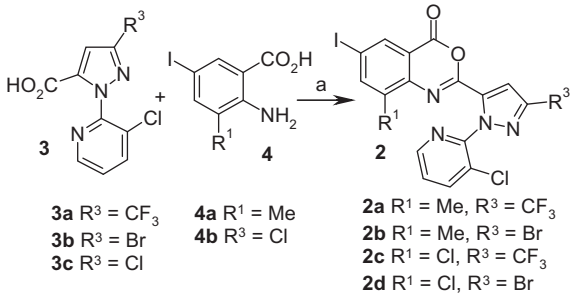
cross-coupling of a 4-iodoanthranilic diamide with cyanide. As outlined in Scheme 1, iodobenzoxazinones of formula **2** were made by sequential treatment of pyridylpyrazole acids **3** with 1.1 equiv of triethylamine and methanesulfonyl chloride, followed by one equiv of iodoanthranilic acid **4**,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

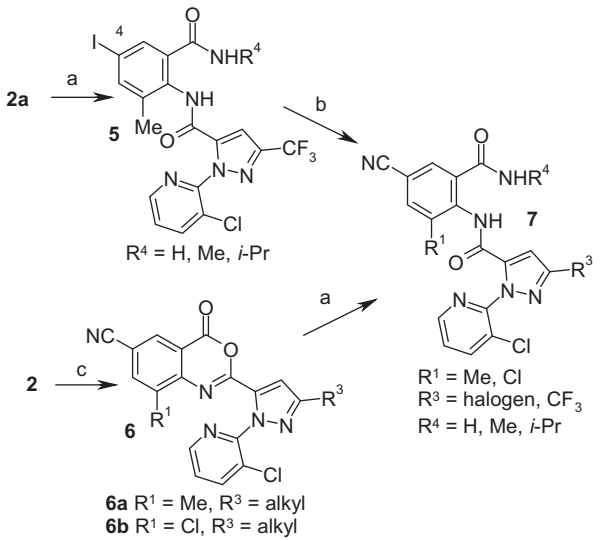
For expanded tests where larger quantities of 4-cyanoanthranilic diamides **7** were needed, an alternative synthesis of precursors **6a** was employed as outlined in Scheme 3.

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**.

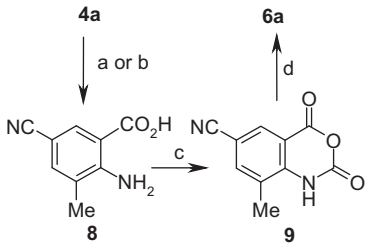
Regioisomeric 4-chloro-6-cyanoanthranilic diamides of formula **10** were made by the method in Scheme 4. Cyanide was first coupled with 4-chloro-6-iodoanthranilic acid **11** via palladium-mediation to give 4-chloro-6-cyanoanthranilic acid **12**.[27] Reacting **12** with pyrazole acids **3** in the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



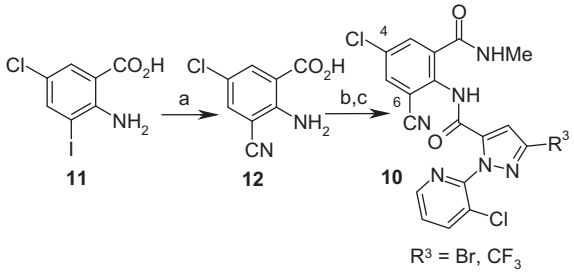
Scheme 1. Reagents and conditions: (a) (i) Compound **3** (1 equiv), $MeSO_2Cl$ (1.1 equiv), Et_3N (1.1 equiv), 0–5 °C, 10 min (ii) Compound **4** (1 equiv), 0 °C, 5 min (iii) Et_3N (2.1 equiv), MeCN, 0–10 °C, 45 min (iv) $MeSO_2Cl$ (1.1 equiv), MeCN, 0–25 °C, 12 h, 60–65%.



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