The discovery of fluazaindolizine: A new product for the control of plant parasitic nematodes

George P. Lahm, Johan Desaeger, Ben K. Smith, Thomas F. Pahutski, Michel A. Rivera, Tony Meloro, Roman Kucharczyk, Renee M. Lett, Anne Daly, Brenton T. Smith, Daniel Cordova, Tim Thoden, John A. Wiles

PII: S0960-894X(17)30161-0
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.02.029
Reference: BMCL 24701

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 20 January 2017
Revised Date: 13 February 2017
Accepted Date: 14 February 2017

Please cite this article as: Lahm, G.P., Desaeger, J., Smith, B.K., Pahutski, T.F., Rivera, M.A., Meloro, T., Kucharczyk, R., Lett, R.M., Daly, A., Smith, B.T., Cordova, D., Thoden, T., Wiles, J.A., The discovery of fluazaindolizine: A new product for the control of plant parasitic nematodes, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.02.029

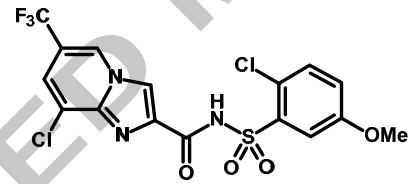
The discovery of fluazaindolizine: A new product for the control of plant parasitic nematodes

George P. Lahm,[a]* Johan Desaeger,[a] Ben K. Smith,[a] Thomas F. Pahutski,[a] Michel A. Rivera,[a] Tony Meloro,[a] Roman Kucharczyk,[a] Renee M. Lett,[a] Anne Daly,[a] Brenton T. Smith,[a] Daniel Cordova,[a] Tim Thoden,[b] John A. Wiles[c]

[a]*DuPont Crop Protection, Stine-Haskell Research Center, 1090 Elkton Rd., Newark, DE 19714, USA*
[b]*DuPont de Nemours (France) S.A.S., European Research Center, 68740 Nambsheim, France*
[c]*DuPont (U.K.) Limited, 4th Floor, Kings Court, London Road, Stevenage, SG1 2NG, United Kingdom*

Abstract - Fluazaindolizine is a new highly effective and selective product for the control of plant parasitic nematodes. Specificity for nematodes coupled with absence of activity against the target sites of commercial nematicides suggests that fluazaindolizine has a novel mode of action. The discovery, structure-activity development and biological properties for this new class of nematicides are presented.

The discovery and development of new nematicides that are highly effective against the target pest, work by new modes of action, and meet societal demands of safety to humans and the environment are essential in the defense of crops. Soil dwelling nematodes are responsible for significant crop damage and yield loss in agricultural production. Furthermore, many current nematicidal products are under regulatory pressure due to a range of toxicological and environmental issues. Herein we describe the discovery of fluazaindolizine (**1**), a new product for the control of plant parasitic nematodes.[1]



1

Figure 1. Chemical structure of fluazaindolizine.

Plant-parasitic nematodes are ubiquitous microscopic soil pests that feed on plant roots resulting in severe crop losses. The damage often goes unnoticed due to the hidden nature of nematodes and the non-specific damage symptoms, which can be confused with soil fertility, drought or other soil pest or pathogen problems. The most recent nematode damage survey valued global crop losses at $100 billion annually.[2] The increasing need for food production and the growing pressure on agricultural land will likely cause crop losses to increase.

More than 4,000 species of plant-parasitic nematodes have been described but only a fraction of these cause economic damage to crops.[3] The most important nematode pest worldwide is the root-knot nematode (*Meloidogyne* spp.), which is estimated to account for greater than 50% of all nematicide use and 5% of crop loss globally.[4] Other agriculturally important plant-parasitic nematodes include cyst nematodes (*Globodera* and *Heterodera* spp.), lesion nematodes (*Pratylenchus* spp.), reniform nematodes (*Rotylenchulus* spp.) and sting nematodes (*Belonolaimus* spp.).

Soil fumigants account for about 50% of all commercial nematicides, with organophosphates and carbamates comprising nearly all of the remaining nematicides.[5] Many of these products are under regulatory pressure, and certain fumigants and organophosphates have been banned. Despite increasing regulatory pressure and limited choice, the global nematicide market continues to grow. Valued at $1 billion in 2011, the market is estimated to