# Inatreq™ Active – a new fungicide molecule derived from fermentation

Shortlisted Candidate for the 2017 Bernard Blum Award

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INATREQ™ ACTIVE

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DOW®

**Dow AgroSciences**

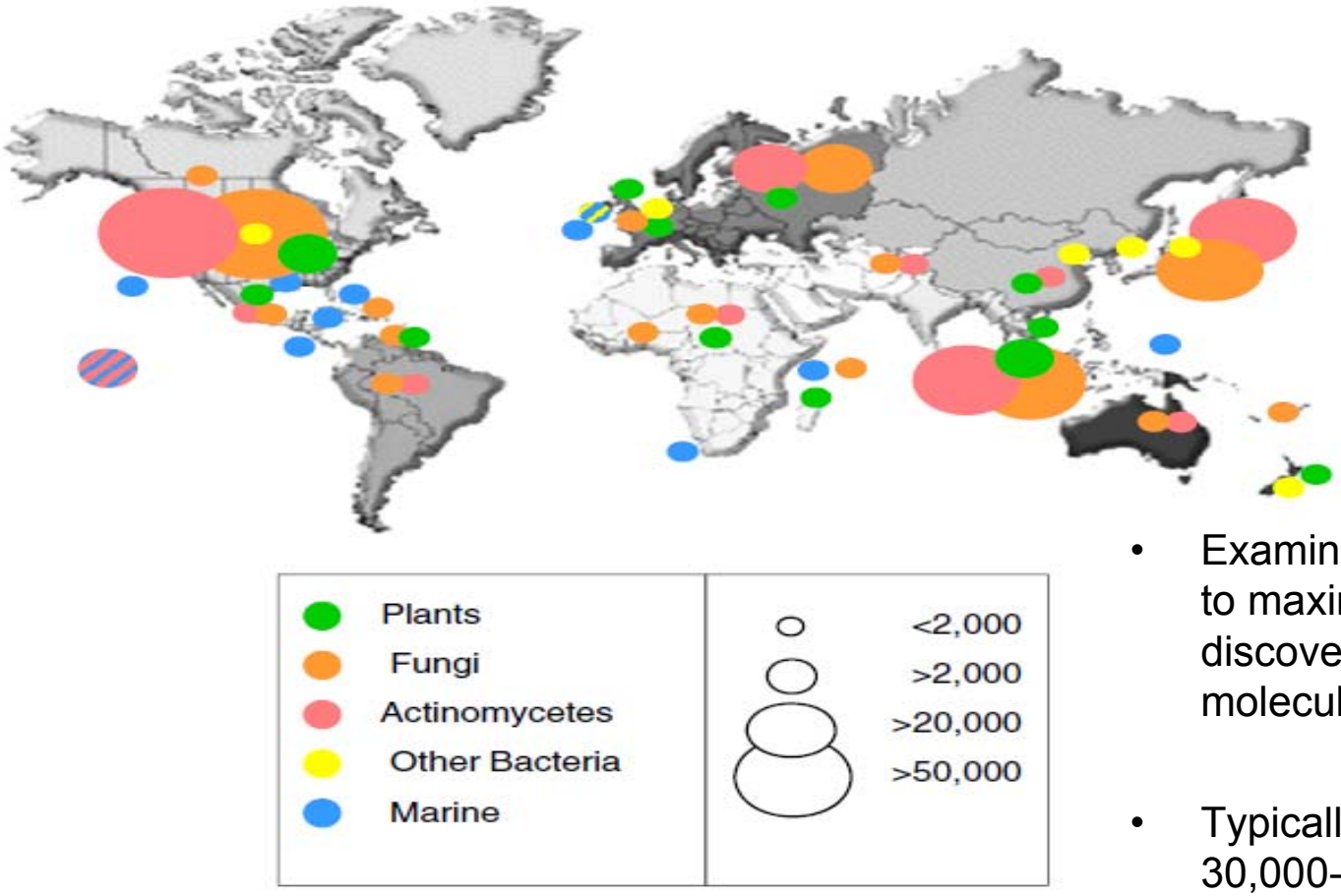
*Solutions for the Growing World*

# Sources of Natural Product Screening at Dow AgroSciences

INATREQ ACTIVE

Av $285MM: cost new active registration global

Av 11.3 years: 1st EU approval




- Examine bio diverse inputs to maximize opportunity to discover novel active molecules
- Typically evaluating 30,000-40,000 inputs/year

Loso et al: Lead generation in crop protection research: Pest *Manag Sci* **73**

Sparks & Lorsbach: Perspectives on the agrochemical industry and agrochemical discovery. Pest *Manag Sci* **73**: 672-677

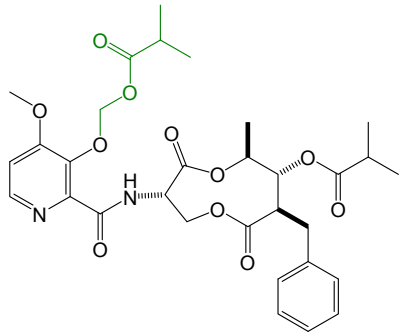
# What is Inatreq?

**INATREQ™ ACTIVE** (fenpicoxamid) is an innovative new fungicide for the control of key diseases in cereals with additional development in banana. The active is of natural origin with outstanding biological performance with a unique target site for cereal fungicides.

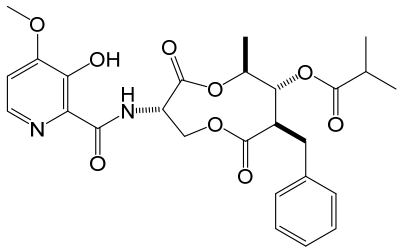
*Zymoseptoria tritici (septoria tritici blotch) in wheat*

*Mycosphaerella fijiensis* (black Sigatoka) in banana

# Inatreq™ Active Summary
# A natural product based fungicide



Inatreq™ Active



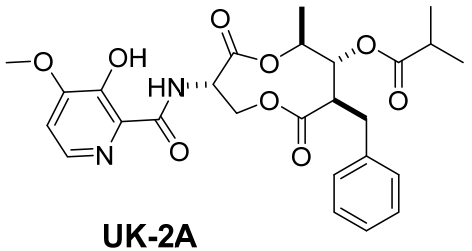
UK-2A

*Streptomyces* 517-02

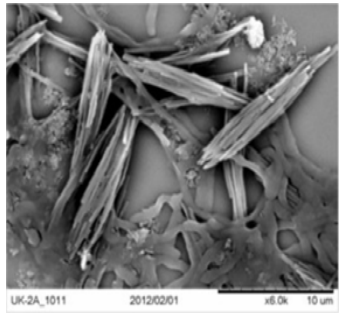
- ISO common name: Fenpicoxamid
- Derived from the natural product (UK-2A), produced by fermentation of Streptomyces sp. 517-02
- Inatreq is produced from UK-2A by a single modification step post fermentation
- Optimized version of UK-2A for improved stability and efficacy by increased bio-availability
- Inatreq converts back to the natural product UK-2A in fungi and plants
- Novel mode of action for cereal fungicides - complex III inhibition at the Qi site
- No target site based cross resistance to current chemistries used in cereals
- Outstanding biological performance on major pathogen *Zymoseptoria tritici* (Septoria wheat leaf blotch) that can cause yield losses of 20% and limited biolocontrol solutions

# Natural product UK-2A

- Isolated from soil sample containing the actinomycete Streptomyces sp. 517-02 (1996 in Osaka, Japan)
- UK-2A has broad spectrum activity in *in vitro* fungal growth inhibition assays and greenhouse tests
- Inhibits energy production in mitochondria.
  Action on complex III in the electron transport chain
- Mode of action appears commonly used in nature providing microorganisms with a competitive advantage

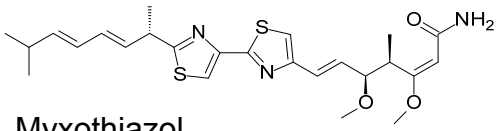


**UK-2A**

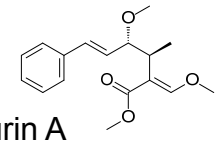


*UK-2A crystals*

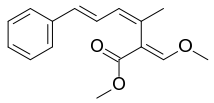
Other natural products acting on complex III



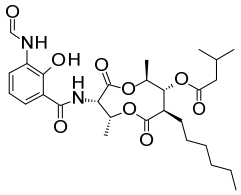
Myxothiazol



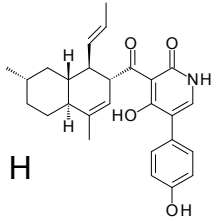
Strobilurin A



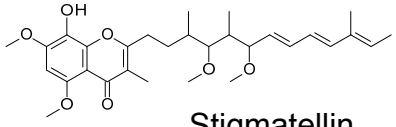
Oudemansin A



Antimycin A



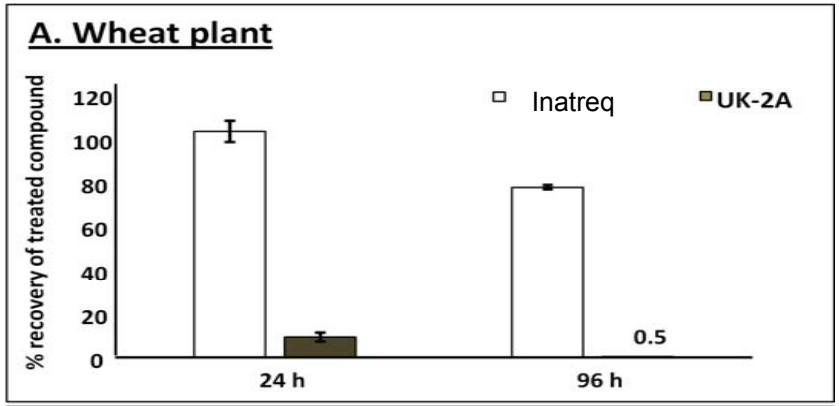
Ilicicolin H

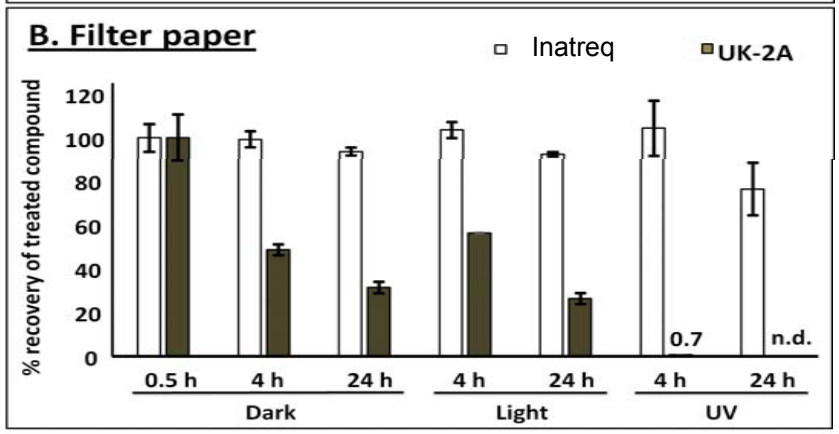


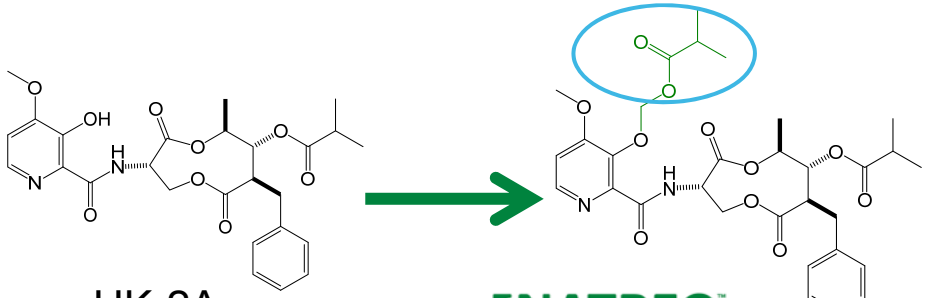
Stigmatellin

# Invention of Inatreq

- UK-2A very active when tested *in-vivo*
- Greenhouse and field efficacy of UK-2A is limited by oxidation and UV instability
- Single step modification stabilizes the molecule on plant surface and improves control



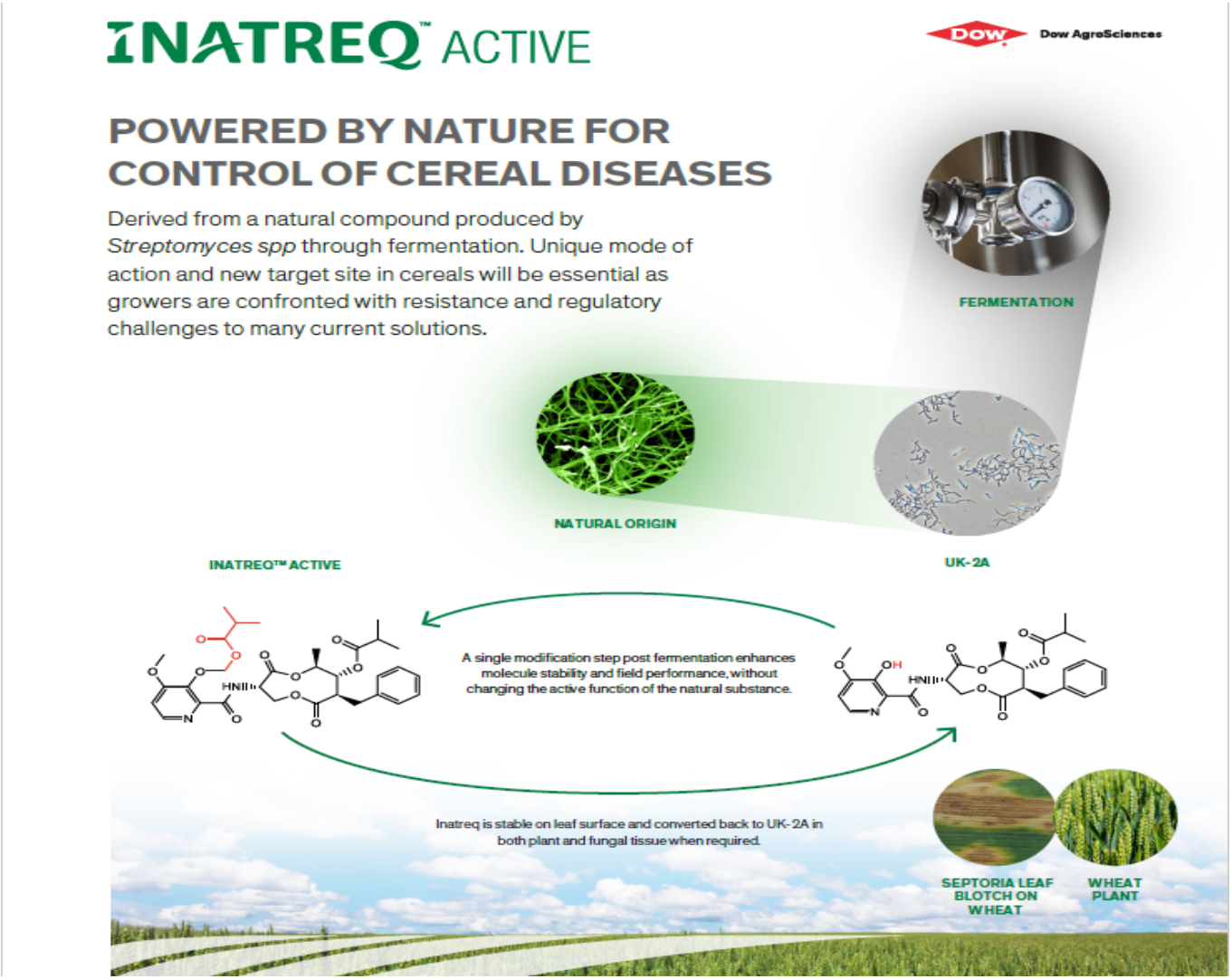



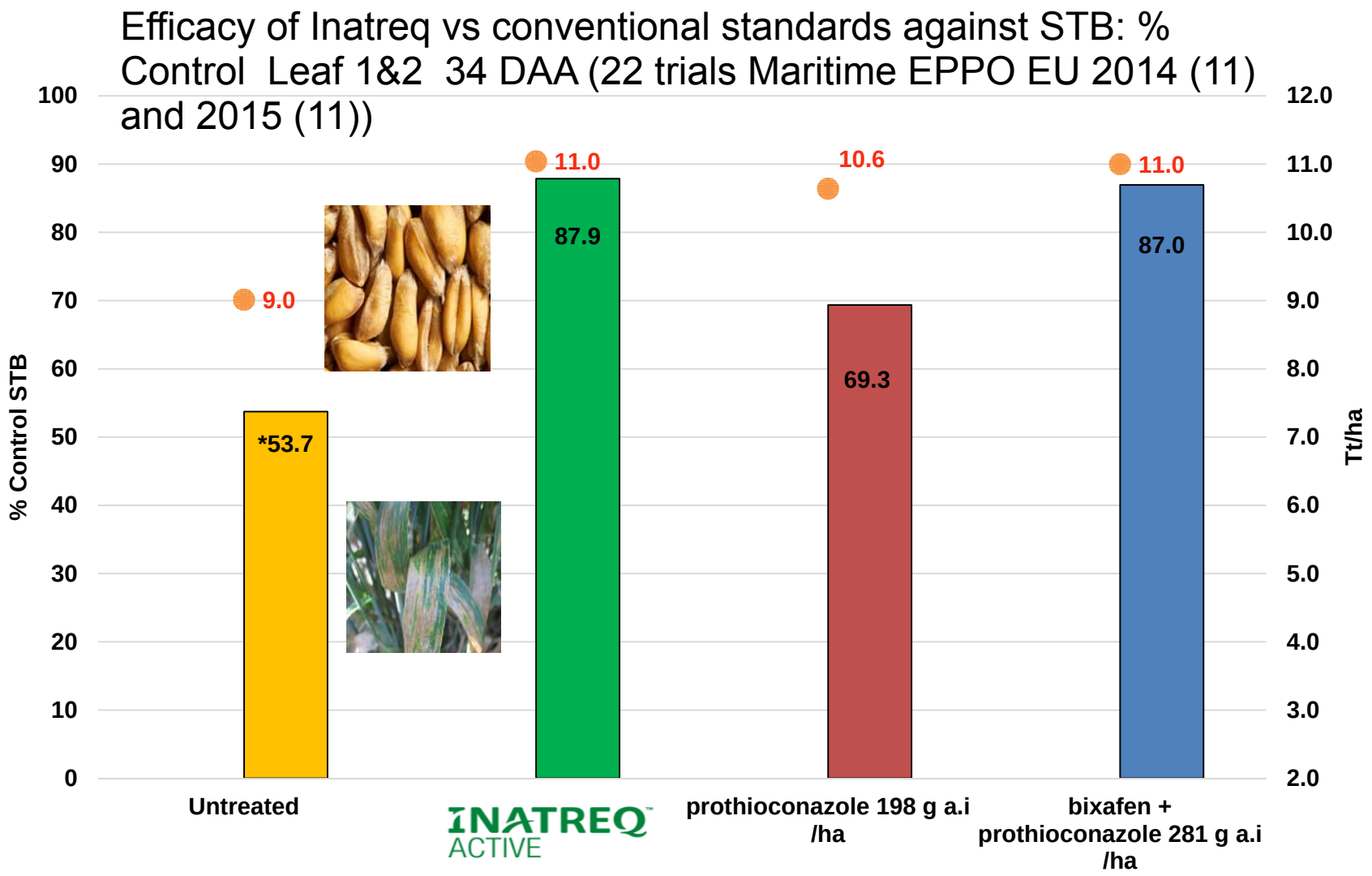

| Compound | *Z. tritici* (leaf blotch) | | *P. triticina* (brown rust) | |
|---|---|---|---|---|
| | 1DP | 3DC | 1DP | 3DC |
| UK-2A | 6.04 | 83.7 | 3.71 | 36.05 |
| Inatreq | 0.49 | 1.32 | 0.16 | 0.82 |
| $EC_{50}$ ratio UK-2A/ Inatreq | 12.33 | 63.41 | 23.19 | 43.96 |

# 2017 Bernard Blum Award Nomination

INATREQ™ ACTIVE



# Inatreq Efficacy against *Z. tritici* (STB)




* % infection in untreated mean leaf 1+leaf 2

# Inatreq Summary

INATREQ™ ACTIVE

- Derived from the natural product UK-2A and produced by fermentation
- Simple single step modification of UK-2A post fermentation to form Inatreq
  - Improves stability and hence maximizes efficacy by increasing bio-availability
  - Modification does NOT impact the environmental or toxicology profile compared to UK-2A.
- Fungicidal activity requires conversion of Inatreq back to the natural product UK-2A,
  - Occurs in both fungi and plants without changing active function of UK-2A
- Innovative fungicide to address resistance and regulatory challenges for cereal growers
  - Inatreq is a Qi inhibitor fungicide and provides a new target site in cereals
  - No cross-resistant to existing chemistries:
  - Resistance management: Inatreq should only be used alone
- Inatreq has a favourable toxicological profile comparable to UK-2A
- Inatreq can provide a biocontrol solution to cereal farmers for disease control alongside other natural products: limited effective bio-control solutions available today for STB control in cereals and many conventional solutions are under regulatory and resistance pressure

# First Published Scientific Paper

INATREQ ACTIVE

Research Article

SCI

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(wileyonlinelibrary.com) DOI 10.1002/ps.4588

## Biological characterization of fenpicoxamid, a new fungicide with utility in cereals and other crops

W John Owen,* Chenglin Yao, Kyung Myung, Greg Kemmitt, Andrew Leader, Kevin G Meyer, Andrew J Bowling, Thomas Slanec and Vincent J Kramer

### Abstract

**BACKGROUND:** The development of novel highly efficacious fungicides that lack cross-resistance is extremely desirable. Fenpicoxamid (Inatreq™ active) possesses these characteristics and is a member of a novel picolinamide class of fungicides derived from the antifungal natural product UK-2A.

**RESULTS:** Fenpicoxamid strongly inhibited *in vitro* growth of several ascomycete fungi, including *Zymoseptoria tritici* ($EC_{50}$, 0.051 mg $L^{-1}$). Fenpicoxamid is converted by *Z. tritici* to UK-2A, a 15-fold stronger inhibitor of *Z. tritici* growth ($EC_{50}$, 0.0033 mg $L^{-1}$). Strong fungicidal activity of fenpicoxamid against driver cereal diseases was confirmed in greenhouse tests, where activity on *Z. tritici* and *Puccinia triticina* matched that of fluxapyroxad. Due to its novel target site ($Q_i$ site of the respiratory cyt bc1 complex)

Open availability on-line on Wiley Press
Other papers are planned

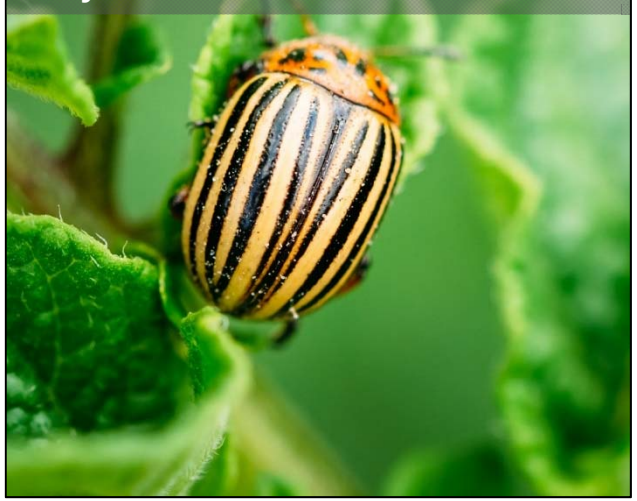
# Dow AgroSciences Open to Collaborations

## Thank you

INATREQ™ ACTIVE

### Crop Protection

- Natural or synthetic pest control actives with novel modes of action
- Improved formulation & delivery systems



### Seed & Traits

- Germplasm with improved agronomics, e.g., stress tolerance, nutrient use, yield, pest resistance
- Pest resistance & herbicide tolerant traits, genes, markers
- Advanced breeding tools, e.g., genomic selection, markers, double haploid technologies

### Enabling Technology

- Expression tools or novel trait delivery systems
- Field enabled high throughput phenotyping, nucleic acid or protein detection tools
- Engineering/synthetic biology, genome editing, microbial strain improvement
- Advanced decision making tools, e.g., predictive ag, data analytics

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