Inatreq™ Active – a new fungicide molecule derived from fermentation

Shortlisted Candidate for the 2017 Bernard Blum Award

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Dow AgroSciences
Solutions for the Growing World

™ Trademark of The Dow Chemical Company (“Dow”) or an affiliated company of Dow.
Sources of Natural Product Screening at Dow AgroSciences

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


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

Av $285MM: cost new active registration global

Av 11.3 years: 1st EU approval
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

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 biocontrol 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

Other natural products acting on complex III

- Myxothiazol
- Antimycin A
- Strobilurin A
- Oudemansin 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

<table>
<thead>
<tr>
<th>Compound</th>
<th><em>Z. tritici</em> (leaf blotch)</th>
<th><em>P. triticina</em> (brown rust)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1DP</td>
<td>3DC</td>
</tr>
<tr>
<td>UK-2A</td>
<td>6.04</td>
<td>83.7</td>
</tr>
<tr>
<td>Inatreq</td>
<td>0.49</td>
<td>1.32</td>
</tr>
<tr>
<td>EC$_{50}$ ratio UK-2A/Inatreq</td>
<td>12.33</td>
<td>63.41</td>
</tr>
</tbody>
</table>
2017 Bernard Blum Award Nomination

POWERED BY NATURE FOR CONTROL OF CEREAL DISEASES

Derived from a natural compound produced by Streptomyces spp. through fermentation. Unique mode of action and new target site in cereals will be essential as growers are confronted with resistance and regulatory challenges to many current solutions.
Inatreq Efficacy against *Z. tritici* (STB)

Efficacy of Inatreq vs conventional standards against STB: % Control  Leaf 1&2  34 DAA (22 trials Maritime EPPO EU 2014 (11) and 2015 (11))

- **Untreated**: 9.0%
- **Prothioconazole 198 g a.i./ha**: 87.9%
- **Bixafen + Prothioconazole 281 g a.i./ha**: 87.0%

* % infection in untreated mean leaf 1+leaf 2
Inatreq Summary

● 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

Research Article

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

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Abstract

BACKGROUND: The development of novel highly efficacious fungicides that lack cross-resistance is extremely desirable. Fenpicoxamid (Inatrex™ 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 (EC₅₀, 0.051 mg L⁻¹). Fenpicoxamid is converted by Z. tritici to UK-2A, a 15-fold stronger inhibitor of Z. tritici growth (EC₅₀, 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, 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

Crop Protection
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• 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
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