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Thinking outside the Pillbox
Lead Generation and Optimization in Crop Protection Research

T H I S   A C S   W E B I N A R   W I L L   B E G I N   S H O R T L Y ...
Thinking Outside the Pillbox: Lead Generation and Optimization in Crop Protection Research

Tejas Shah
Research Investigator, Corteva Agriscience

Fides Benfatti
Team Leader, Research Chemistry, Syngenta Crop Protection

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Thinking Outside the Pillbox: Lead Generation and Optimization in Crop Protection Research

Fides Benfatti
Senior Team Leader Chemical Research
Syngenta Crop Protection
fides.benfatti@syngenta.com

Classification: PUBLIC
Why do we need new Crop Protection products?

- Growing more with less

---

1 hectare fed 2 people  
1 hectare needs to feed 5 people

Source: UNEP, Cline, Syngenta

- Climate change

---

Climate change is already reducing water and arable land

Agriculture uses 70% of the world’s fresh water withdrawals

Source: www.plantmanagementnetwork.org

---

Why do we need new Crop Protection products?

- Resistance development and shifting pest populations

---

Changing regulatory landscape

Source: www.plantmanagementnetwork.org
Approximately how much was lost in billions (USD) to plant diseases and infestations from 2005 to 2015?

- 1 billion
- 3.5 billion
- 5 billion
- 7 billion
- 9.5 billion

* If your answer differs greatly from the choices above tell us in the chat!
How are crop protection products discovered and optimized

Outline

- Discovery of insecticidal spiroindolines
- Bioavailability-guided design of new aphicides
- Modern crop protection products targeting ion channels

Discovery of insecticidal spiroindolines

- Screening of a chemical library (obtained from Oxford Asymmetry, now Evotec)
- Insecticidal hit compound identified by high throughput screening
- Activity on Drosophila melanogaster, Plutella xylostella and Heliothis virescens at 1000 ppm
- Only compounds possessing a cinnamyl group displayed insecticidal activity

Hughes, D. J.; Worthington, P. A.; Russell, C. A.; Clarke, E. D.; Peace, J. E.; Ashton, M. R.; Coulter, T. S.; Roberts, R. S.; Moloney, L. P.; Cederbaum, F.; Cassayre, J.; Mainfisch, P. WO2003106457
**Agrochemical research:** screening cascade

- *In vivo* on-target test from day 1

![Insecticide HTS](image1)
![Fungicide HTS](image2)
![Herbicide HTS](image3)

- Increase in tests size parallel to project stage (HTS >>> field)

![Micro Profiling Screens](image4)
![Profiling Screens](image5)
![Field Trials](image6)

**Discovery of insecticidal spiroindolines:** Hit-to-Lead Optimization

*Block metabolically weak positions*

→ improved potency
→ cumulative effect

![Diagram](image7)

Discovery of insecticidal spiroindolines: Hit-to-Lead Optimization

- Cumulative effect observed cross lepidopteran target species
- Lead shows promising activity at low dose

<table>
<thead>
<tr>
<th>Spodoptera littoralis L1</th>
<th>Heliothis virescens L1</th>
<th>Plutella xylostella L2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500</td>
<td>&gt; 500</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>200</td>
<td>200</td>
<td>200</td>
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<tr>
<td>200</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>50</td>
<td>≤ 12</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>12</td>
<td>0.8</td>
<td>3</td>
</tr>
</tbody>
</table>

Primary screening [EC80-100 in ppm (mg/L)]

Properties and insecticidal activity of spiroindoline lead

- Melting Point (M.p.) 168-170°C
- Aqueous solubility 5 ppm@pH 6.5
- Log P 5.94
- pKa 7.88
- Photostability T<sub>50</sub> 114 mins
- Rat acute toxicity MLD<sub>50</sub> > 200 mg/Kg

<table>
<thead>
<tr>
<th>Lepidopteran control (activity given as effective concentration EC&lt;sub&gt;80&lt;/sub&gt; in ppm (mg/L))</th>
</tr>
</thead>
<tbody>
<tr>
<td>effective concentration EC&lt;sub&gt;80&lt;/sub&gt; in ppm (mg/L)</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Spiroindoline 6b</td>
</tr>
<tr>
<td>Spinosad</td>
</tr>
<tr>
<td>Indoxacarb</td>
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</tbody>
</table>

Check: Spinosad 10 g / hl*  Spirodindoline 8 g / hl*
Symptomology – insights into the mode of action

- Exploiting genetic model systems – C. elegans and Drosophila

Decades of academic work linking phenotype (visible effects) to genetic dysfunction

- Comparing chemical symptoms to genetic phenotypes identifies candidate target proteins e.g. Spiroindolines

For a recent extensive analysis of C. elegans behavioral phenotype:

Symptomology in C. elegans

- Spiroindolines induces characteristic symptoms in C. elegans

Symptom resembles phenotype

Hypothesis: Spiroindolines affect cholinergic signaling
Confirming the hypothesis

- Forward genetics used to identify mutant strains resistant to SPIRO

Resistant *C. elegans*

Locate resistance mutations using genetic mapping and sequencing

- Resistance mutations locate to vesicular acetylcholine transporter (VACHT)
- Binding of spiroindoline to VACHT can now be confirmed using standard biochemical approaches *in vitro*

**Bioavailability-guided design of new aphicides**
**Audience Survey Question**

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which of these molecules is an or are agrochemical(s)?
(Select all that apply)

1. ![Molecule 1](image1)
2. ![Molecule 2](image2)
3. ![Molecule 3](image3)

*If your answer differs greatly from the choices above tell us in the chat!*

---

**Audience Survey Question**

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which of these molecules is an or are agrochemical(s)?

1. **Isocloseram**
   - Insecticide
   - Syngenta
   - ![Isocloseram](image1)
2. **Fenpicaroxamid**
   - Fungicide
   - Corteva
   - ![Fenpicaroxamid](image2)
3. **Tetruypolimet**
   - Herbicide
   - FMC
   - ![Tetruypolimet](image3)

*If your answer differs greatly from the choices above tell us in the chat!*
How to reach the target

Influence of physical chemical properties on the uptake into plants

The logP and pKa of agrochemicals dictate their distribution in plants

- Weak acids with intermediate lipophilicity get trapped in phloem
- Basic molecules get trapped in vacuoles
- Caveat: carrier proteins, channels can provide active transport

Buchholz, A.; O'Sullivan, A. C.; Trapp, S. In Discovery and Synthesis of Crop Protection Products; American Chemical Society: 2015; Vol. 1204, p 93.
Feeding behaviour of insect pests

Which compound won’t be efficacious for aphids control?

Remember:

- Aphids are phloem and xylem feeders
- Weak acids get trapped in phloem
- Basic molecules get trapped in vacuoles (i.e. cells)

nAChR agonists for aphids control

AChBP co-crystal structure with lead

Pharmacophore:
- Cation-π interaction
- H bond donor
- H bond acceptor


Our target
- Low lipophilicity (logP < 2.5)
- Low molecular volume
- Non-basic

Tuning physicochemical properties

ΔpK_a = -2
ΔpK_a = -0.8 allylic
ΔpK_a = -1.7

ΔpK_a = -3.4
(-1.7 each β-F)

ΔpK_a = -0.3
logP = 2.3

ΔpK_a = approx. -2

ΔpK_a = -1.5*
axial > eq.

ΔpK_a = approx. -0.5*

ΔpK_a = approx. -3.5

ΔpK_a = -0.8 allylic

* From unsubstituted tropane

Modern crop protection products targeting ion channels

The crop science in the 1960’s used 10 Kgs of active ingredient per hectare to protect crops (1 hectare is almost 2.5 acres). How much active ingredient is used today in comparison?

- 1 kilogram
- 500 grams
- 100 grams
- 10 grams
- 1 gram

* If your answer differs greatly from the choices above tell us in the chat!
Product Safety – Who is being protected?

Product safety: studies per stage

### Lead Generation
- Setting Direction
- Mode of action alerts
- Structure activity alerts
- Competitor analysis

### Lead Exploration
- Compound design and selection
  - Acute toxicity (oral/dermal/irritation)
  - Skin sensitization
  - 14/28 day rat and mouse
  - Preliminary Pharmacokinetics (PK)
  - Genotoxicity screening
  - Dermal absorption
  - ADME
  - 28 day dog
  - 90 day rat and mouse
  - Preliminary development toxicity
  - Genotoxicity evaluation
  - Preliminary risk assessments

### Lead Optimisation
- Predicting Regulatory Outcome
  - Acute toxicity
  - Genotoxicity
  - Carcinogenicity/Chronic 2 year study
  - Reproductive toxicity
  - Developmental toxicity
  - Neurotoxicity
  - 90 day & 1 year dog
  - Dermal absorption
  - ADME – metabolites
  - Metabolite testing
  - Manufacturing intermediates
  - Formulation toxicity
  - Definitive risk assessments

### Candidate Confirmation
- Setting Direction
- Mode of action alerts
- Structure activity alerts
- Competitor analysis

### In vivo
- channels
- 2008, 2, 100.
- J. Med. Chem. 2015, 58, 7093–7118

Efficacious, safe and selective: Indoxacarb

- Indoxacarb (DuPont) is an insecticide that exerts its mode of action by targeting the Voltage-gated Sodium channel
- It is active against Lepidoptera (moths)
Mammalian safety of Indoxacarb

Differential binding

\[
\text{IC}_{50} = 1000\ \text{nM} \text{ on rat Na}_\text{V} 1.4 \\
\text{IC}_{50} = 25\ \text{nM} \text{ on Bg Na}_\text{V} 1-1a \\
(\text{Bg} = \text{Blattella Germanica})
\]

Selective metabolism

In insects

Hydrolases

In higher animals

Oxidative metabolism

+ other metabolites


Crop Protection 2000, 19, 537.

Environmental Safety – What is being protected?

- **Groundwater** – Drinking water (human exposure), irrigation water, the aquifer itself as an entity
- **Surface Water** – Drinking water, irrigation water, aquatic organisms (fish and aquatic plants)
- **Soil** – Persistence in soil, topsoil erosion, carry-over into follow on crops
- **Non target insects, plants and the organisms**
  - Bees, beneficial insects, worms, off target plant species, birds, field dwelling mammals
- **Air** – long range transport, atmospheric degradation, vapour movement
Efficacious, safe and selective: Anthranilic amides

Anthranilic amides bind to the insect ryanodine receptor in muscle cells

<table>
<thead>
<tr>
<th>Intrinsic target-based selectivity: Insect vs. Mammal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EC50 (nM)</strong></td>
</tr>
<tr>
<td>Cockroach</td>
</tr>
<tr>
<td>Fruit Fly</td>
</tr>
<tr>
<td>Mouse</td>
</tr>
<tr>
<td>Rat</td>
</tr>
</tbody>
</table>

Ryanodine (plant metabolite)

Voliam Targo

Crop: Cauliflower
Source: Taiwan, Syngenta trials 2007

Active in the field at rates as low as 5 g/ha!
(typical rate for organophosphates = 1 Kg/ha)


Modulation of soil persistance

Chlorantraniliprole (DuPont)
M.p. (°C) 208-210
logP 2.76
pKa (acid) 10.8

Water solubility (mg/l, 20-25 °C) 1.0
Water DT50 10 d (pH 9, 25 °C)
Soil DT50 < 2–12 mo

Cyantraniliprole (DuPont/Syngenta)
M.p. (°C) 224
logP 1.94
pKa (acid) 8.8

Water solubility (mg/l, 20-25 °C) 14.24
Water DT50 < 1 d (pH 9, 25 °C)
Soil DT50 average 32 d

Improved plant mobility
Increased spectrum of insect control (aphids and leafhoppers)

(Data from BCPC Pesticide Manual)
CP Research & Development

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Prof. Richard Baines*

Biochemistry
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Liz Hirst
Penny Cutler
Janet Phillips

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Ann Sluder**
Sheetal Shah
Ralph Clover**
Min Shi

Product Safety
Steve Hadfield
Caroline Winn
Mark Slater
Tony Seville

C. elegans biology
Anthony Flemming and team

* University of Manchester
** Cambria Biosciences

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