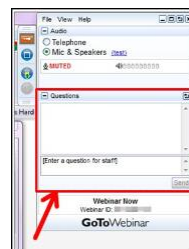


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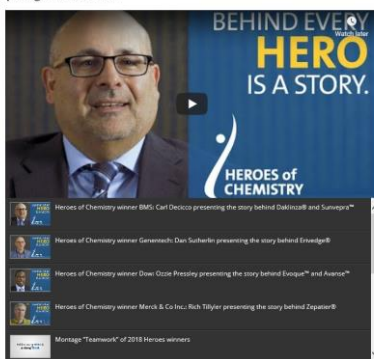
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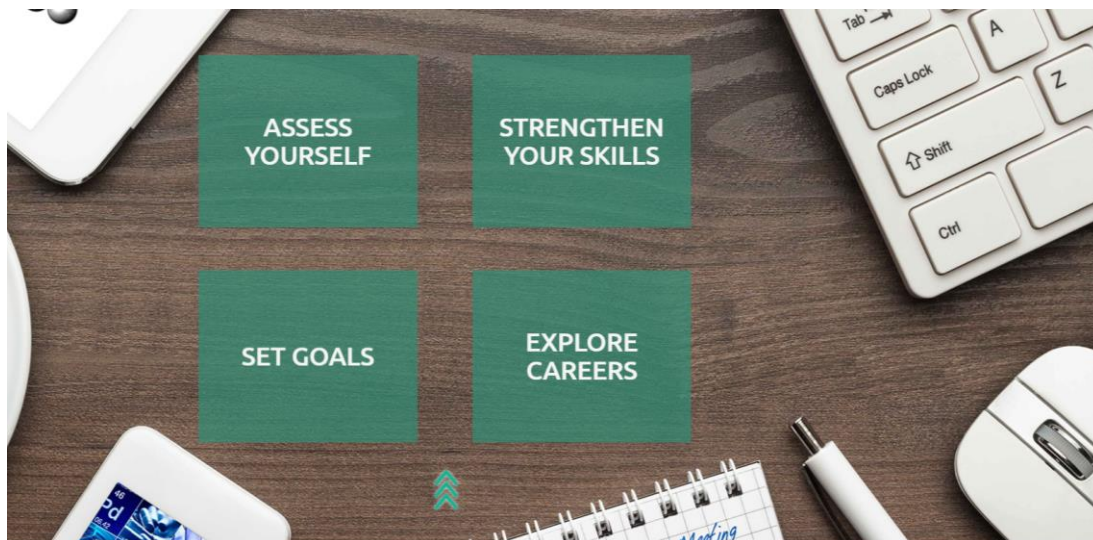
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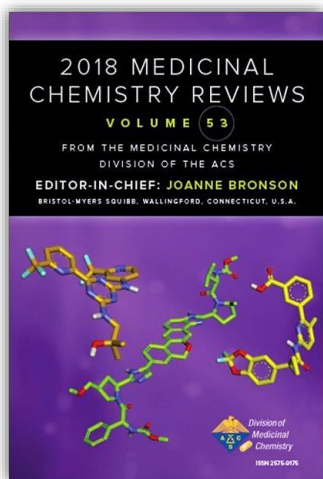
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Nathan Turley - Pfizer Peter Senter - Seattle Genetics</p> <p>Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides Paul Smith - Amgen Richard Dixon - BMS</p> <p>Crystallography as a Drug Design and Delivery Tool (Special Topic) Robert Harrison - Crystal Pharmaceut Vincent Scott - Amgen Andrew Bryant - Merck</p> <p>III - Pharmacology Revisited</p> <p>Dealing with Receptor Drug Modulators in Drug Discovery: Can We Predict Toxicities of Drug Candidates that Have Receptor Modulators? Doreen O'Neil - Pfizer Frederic Pezet - Guangcheng - Vanderbilt University</p> <p>Rational Design of Small Molecules Targeting RNA Matt Dring - Scripps MI Florida Amanda Garner - University of Michigan</p> <p>Cell Penetrating Peptides to Improve Cellular Drug Uptake Dehua Wu - The Ohio State University Scott Hill - Bristol-Myers Squibb</p>	<p>I - Fighting Cancer</p> <p>Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors Timothy P. Heffron - Genentech Mark Witzman - Bristol-Myers Squibb</p> <p>Fighting Cancer: Epigenetic Targets for Oncology Stuart Conway - Oxford Shivan Bagai - AstraZeneca</p> <p>Fighting Cancer: Allosyn and Targeting Cancer Cell Metabolism Stefan Greber - Agos Scott Edmundson - AstraZeneca</p> <p>Social Broadcast</p> <p>Cyclic Peptides: Discovery of CTRP Modulators Peter Groppe - Vertex Nick Sheehan - Bristol-Myers Squibb</p> <p>II - Anti-Infectives</p> <p>Anti-Infective: Rational Approaches to the Design and Optimization Jason Sells - Brown University Courtney Alzrich - University of Minnesota</p> <p>Tuberculosis: An Introduction for Medicinal Chemists Carl Hansen - Hoff-La Roche Christopher Byers - Merck</p> <p>Viral Infections: The Search for a Cure Mike Saffa - AbbVie Stephen Mason - Coriander Corporation</p> <p>Social Broadcast</p> <p>Spiral Muscular Atrophy Kevin Hodges - Haverly Medical School Aayan Heemayat - ACS Publications</p> <p>III - Immunology</p> <p>Psoriasis: Treatment and Novel Approaches Frank Hargreaves - AstraZeneca John Morrison - Bristol-Myers Squibb</p> <p>Usher: Treatment and Novel Approaches Laurence Menard - Bristol-Myers Squibb Mary Smothers - Bristol-Myers Squibb</p>	<p>A New Strategy in Drug Discovery: Protein-Induced Protein Degradation Ian Church - BenevolenceBio Aaron Bag - Bristol-Myers Squibb</p> <p>Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry Arnette Bas - AstraZeneca Donna Kuehn - University of Pittsburgh Erika Araya - Bristol-Myers Squibb Naoufel Zarem - AstraZeneca</p> <p>A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles Marlene Varon Arista - AstraZeneca Dennis Luong - Genentech</p> <p>Nanomaterials for Fighting Antibiotic Resistant Bacteria Vincent Rotello - University of Massachusetts at Amherst Christopher England - American Chemical Society</p> <p>Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance Manoj Arora - Northeastern University Venkat Krishnamurthy - AstraZeneca</p> <p>Pitfalls and Promises of Central Nervous System Drug Discovery Vincent Rotello - University of Massachusetts at Amherst Nicholas Maxwell - Bristol-Myers Squibb</p> <p>How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows Craig Lindner - Vanderbilt Center for Neuroscience Drug Discovery Amy Newman - Intramural Research Program, NIH</p> <p>A New Strategy for the Treatment of Chronic Pain: Antagonizing P2X7 with a Monoclonal Antibody Peter Thornton - AstraZeneca Naoufel Zarem - AstraZeneca</p> <p>How to Predict Human CNS PK/PD: Practical Experiments and Advanced Mathematical Modeling Elizabeth de Lange - Leiden Academic Center for Drug Research Alexander Kopturin - AstraZeneca</p> <p>Human Exosomes: An Ideal Vehicle for Delivery of Therapeutic RNAs to Cells and Organs Hani Vahedi - University of Gothenburg Alexander Kopturin - AstraZeneca</p>

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Jan 31 **How to Succeed in Drug Discovery: Insight from Medicinal Chemists (1.5 hrs.)**
John Lowe III - JIL3 Pharm
Mark Murcko - Relay Therapeutics
Ann Weber - Kallyope
William Greenlee - MedChem Discovery Consulting



Feb 28 **Cosolvent Molecular Dynamics: Mapping Protein Surfaces to Discover Allosteric Sites**
Heather Carlson - University of Michigan
Rommie Amaro - UC San Diego



Mar 28 **Women at the Interface of Computational Chemistry and Drug Discovery (1.5 hrs)**
Zoe Cournia - Biomedical Research Foundation and JCM
Kate Holloway - Gfree Bio
Yvonne C. Martin - Previously of Abbott Laboratories
Shana Posy - Bristol-Myers Squibb



Apr 18 **Effective Exploration of Chemical Space in Hit-Finding**
Hanneke Jansen - Novartis Institutes for Biomedical Research
Zoe Cournia - Biomedical Research Foundation and JCM



May 30 **Widening the Therapeutic Window: Kinetic Selectivity and Target Vulnerability**
Peter Tonge - Stony Brook University and ACS Infectious Diseases
Stewart Fisher - C4 Therapeutics



Jun 27 **Precision Control of CRISPR-Cas9**
Amit Choudhary - Broad Institute of Harvard and MIT
Venkat Krishnamurthy - AstraZeneca



Aug 8 **Transformation of Recombinant Cells to FDA Approved Products: Clinical Development to Marketplace (New Date)**
Rodney Ho - University of Washington
Venkat Krishnamurthy - AstraZeneca



Aug 22 **The Evolving Outsourcing Landscape in Pharma R&D: Pros and Cons of Different Models**
Bart DeCorte - MercachemSyncom
Allen Reitz - Fox Chase Chemical Diversity Center



Sep 19 **Thinking Outside the Pillbox: Lead Generation and Optimization in Crop Protection Research**
Fides Benfatti - Syngenta

Oct 24 **Treating Diabetes: Designing the Once-Weekly and Oral GLP-1 Semaglutide**
Jesper Lau - Novo Nordisk A/S

Nov 28 **Prodrugs**
Jarkko Rautio - University of Eastern Finland

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

THIS ACS WEBINAR WILL BEGIN SHORTLY...

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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



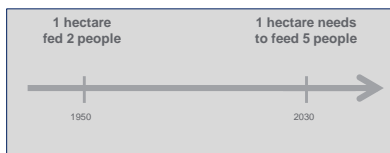

Fides Benfatti
 Senior Team Leader Chemical Research

Syngenta Crop Protection
fides.benfatti@syngenta.com

Classification: PUBLIC

Why do we need new Crop Protection products?

➤ Growing more with less



Source: UNEP, Cline, Syngenta

➤ Climate change

World stress map
Climate change is already reducing water and arable land

Climate change impact

- High
- Medium
- Low



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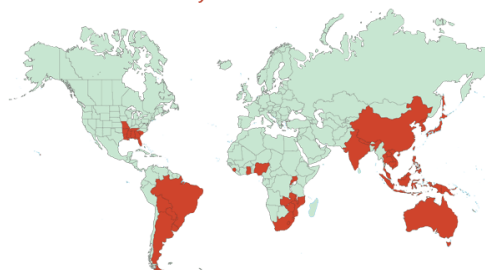


Why do we need new Crop Protection products?

➤ Resistance development and shifting pest populations



Asian Soybean Rust World Wide



➤ Changing regulatory landscape

Source: www.plantmanagementnetwork.org



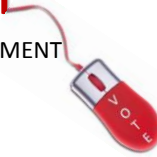
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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



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!*

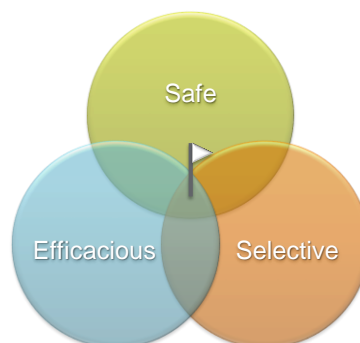
Sources:
 1. OECD-FAO Agricultural Outlook 2012
 2. FAO Losses Report
 3. Davis, 2005
 4. <https://pubs.cifor.org/science.com/doi/full/10.1039/c2cc31919a>



How are crop protection products discovered and optimized

Outline

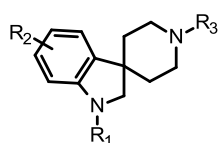
- ❖ Discovery of insecticidal spiroindolines
- ❖ Bioavailability-guided design of new aphicides
- ❖ Modern crop protection products targeting ion channels



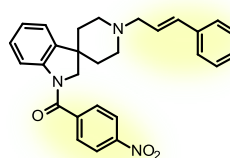
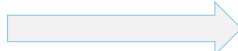
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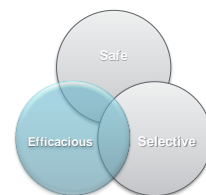
Discovery of insecticidal spiroindolines



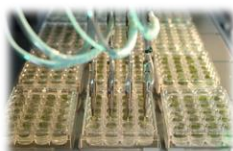
Spiro[indoline-3,4'-piperidine]



Insecticidal Hit!



- 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



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Hughes, D. J.; Worthington, P. A.; Russell, C. A.; Clarke, E. D.; Peace, J. E.; Ashton, M. R.; Coulter, T. S.; Roberts, R. S.; Molleyres, L.-P.; Cederbaum, F.; Cassayre, J.; Maierfisch, P. **WO2003106457**

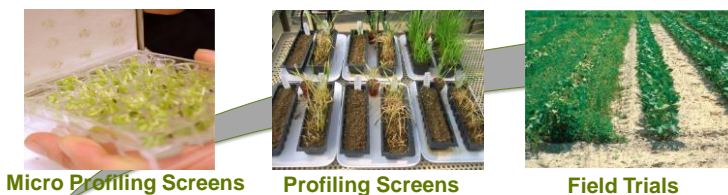
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Agrochemical research: screening cascade

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



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



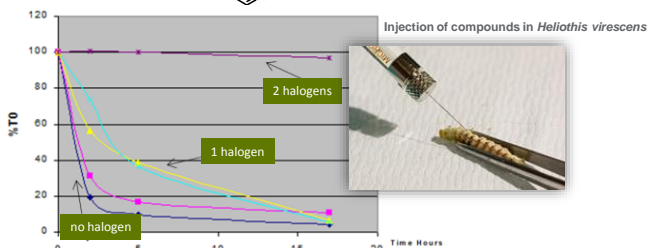
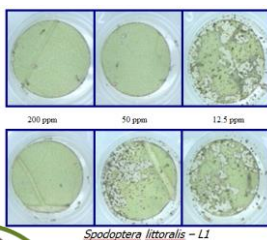
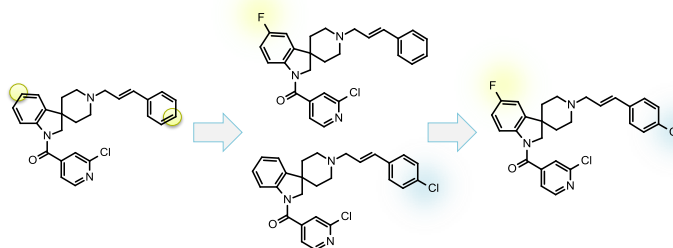
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Discovery of insecticidal spiroindolines: Hit-to-Lead Optimization

Block metabolically weak positions
 → improved potency
 → cumulative effect



26

Hughes, D. J.; Worthington, P. A.; Russell, C. A.; Clarke, E. D.; Peace, J. E.; Ashton, M. R.; Coulter, T. S.; Roberts, R. S.; Molleyres, L.-P.; Cederbaum, F.; Cassayre, J.; Maiefisch, P. WO2003106457
 Sluder A.; Shah, S.; Cassayre, J.; Clover R.; Maiefisch, P.; Molleyres, L.-P. et al *PLoS One* 2012, 7(5), e34712

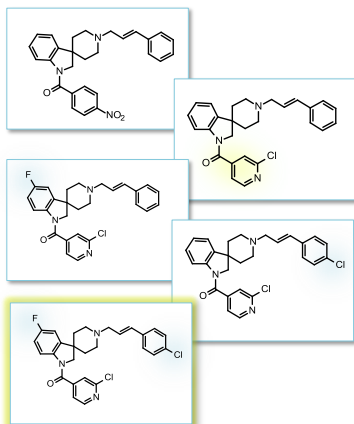
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Discovery of insecticidal spiroindolines: Hit-to-Lead Optimization

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

	<i>Spodoptera littoralis</i>	<i>Heliothis virescens</i>	<i>Plutella xylostella</i>
	Spodoptera littoralis L1	Heliothis virescens L1	Plutella xylostella L2
	> 500	> 500	>500
	200	200	200
	200	50	200
	50	≤12	<50
	12	0.8	3
Primary screening [EC80-100 in ppm (mg/L)]			



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Classification: PUBLIC

Properties and insecticidal activity of spiroindoline lead

 Spiroindoline Lead	Melting Point (M.p.)	168-170°C
	Aqueous solubility	5 ppm@pH 6.5
	Log P	5.94
	pKa	7.88
	Photostability _{T50}	114 mins
Rat acute toxicity	MLD ₅₀ > 200 mg/Kg	

Lepidopteran control (activity given as effective concentration EC₈₀ in ppm (mg / L))

effective concentration EC ₈₀ in ppm (mg / L)	<i>Spodoptera littoralis</i> L1	<i>Heliothis virescens</i> L1	<i>Plutella xylostella</i> L3	<i>Cydia pomonella</i> L1
Spiroindoline 6b	12	0.8	6	3
Spinosad	0.8	0.8	0.2	12
Indoxacarb	3	3	3	12



Check



Spinosad 10 g / hl*



Spiroindoline 8 g / hl*

Diamondback moth, *Plutella xylostella*, on cabbage

28

Classification: PUBLIC

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 disfunction

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

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

A database of *Caenorhabditis elegans* behavioral phenotypes, E. Yemini *et al* *Nature Methods*, 2013, 10, 877-879



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Classification: PUBLIC

Symptomology in *C. elegans*

- Spiroindolines induces characteristic symptoms in *C. elegans*



Symptom resembles phenotype

Hypothesis: Spiroindolines affect cholinergic signaling



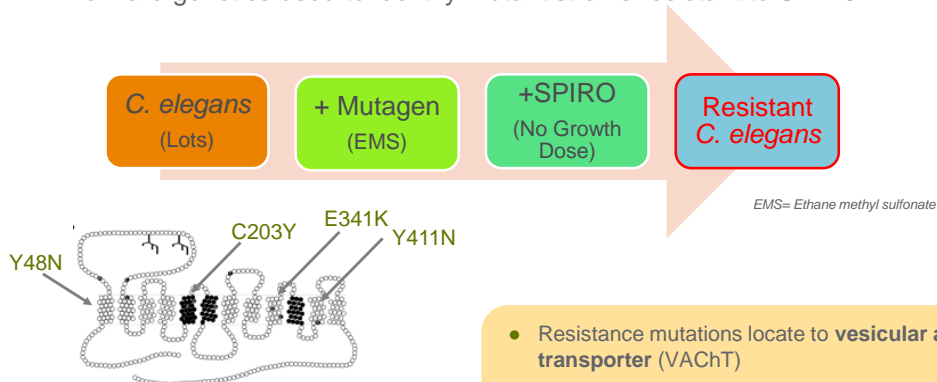
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PLoS ONE 2012, 7, e34712.

Classification: PUBLIC

Confirming the hypothesis

- Forward genetics used to identify mutant strains resistant to SPIRO



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*



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Classification: PUBLIC

Bioavailability-guided design of new aphicides



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Classification: PUBLIC

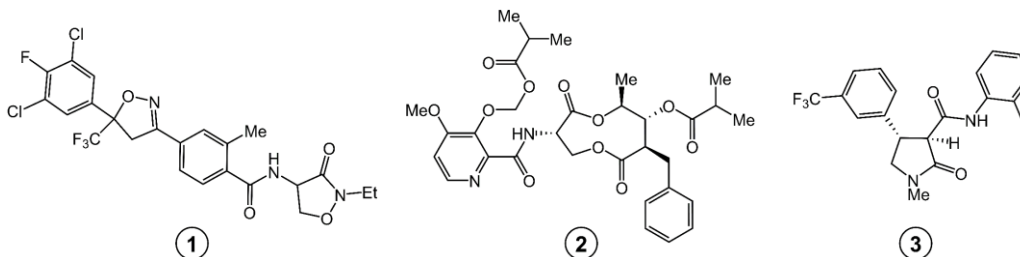
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



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

(Select all that apply)



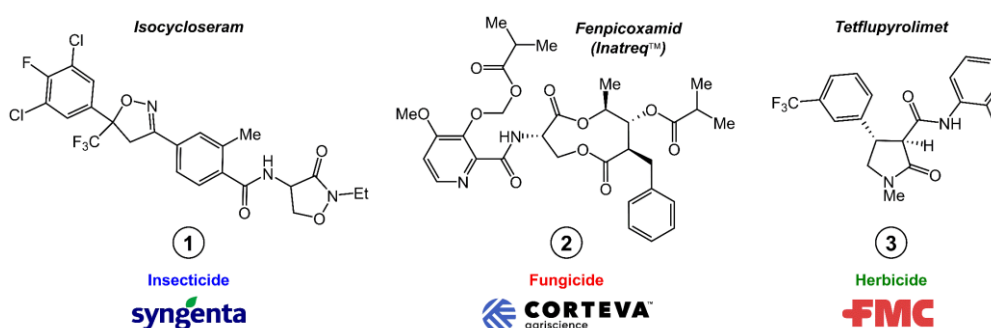
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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

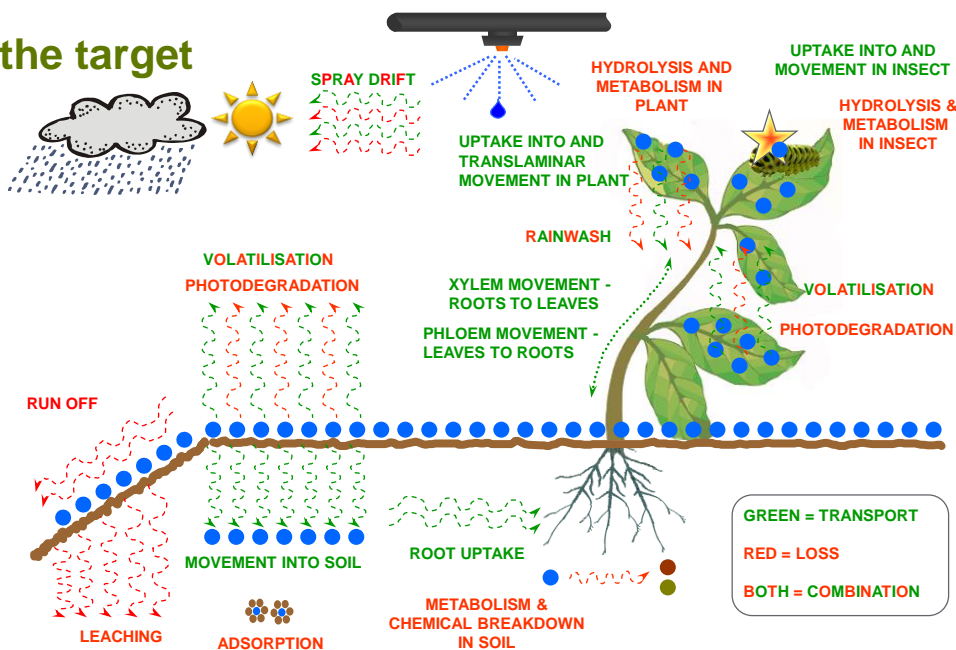


Which of these molecules is an or are agrochemical(s)?



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

How to reach the target

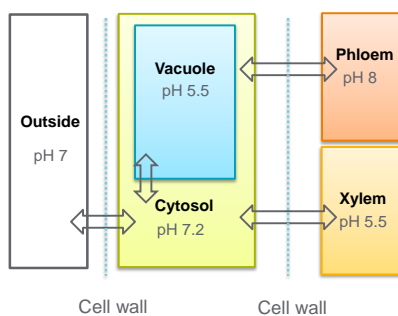


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Influence of physical chemical properties on the uptake into plants



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

Trapp S. 2009 in J. Devillers, Ed.: Ecotoxicology Modeling. Springer, Dordrecht
 Buchholz, A.; O'Sullivan, A. C.; Trapp, S. In *Discovery and Synthesis of Crop Protection Products*; American Chemical Society: 2015; Vol. 1204, p 93.

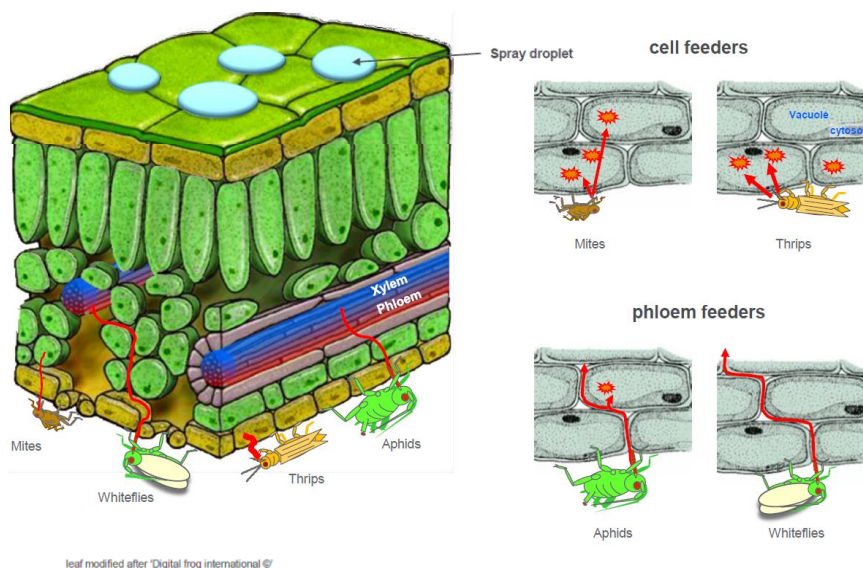


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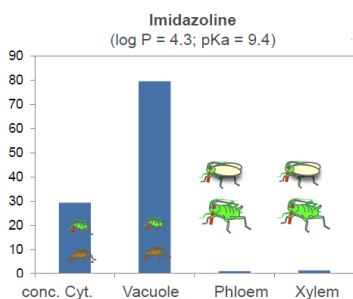
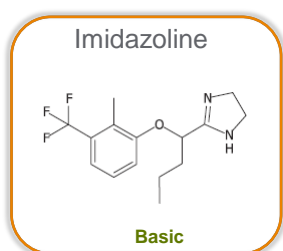
Feeding behaviour of insect pests



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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)

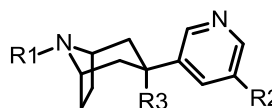
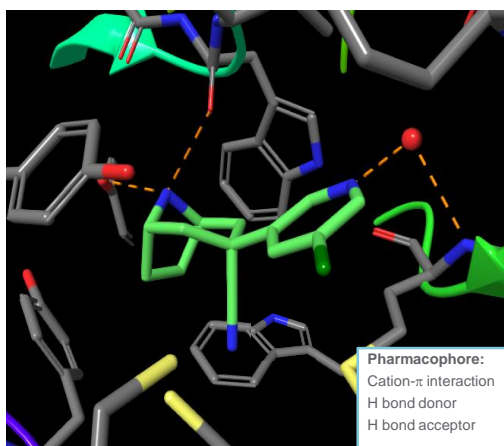
Buchholz, A., Trapp, S., Pest Manag. Sci. (2016); 72: 929–939



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nAChR agonists for aphids control



Our target

- Low lipophilicity ($\log P < 2.5$)
- ✓ Low molecular volume
- Non-basic

AChBP co-crystal structure with lead

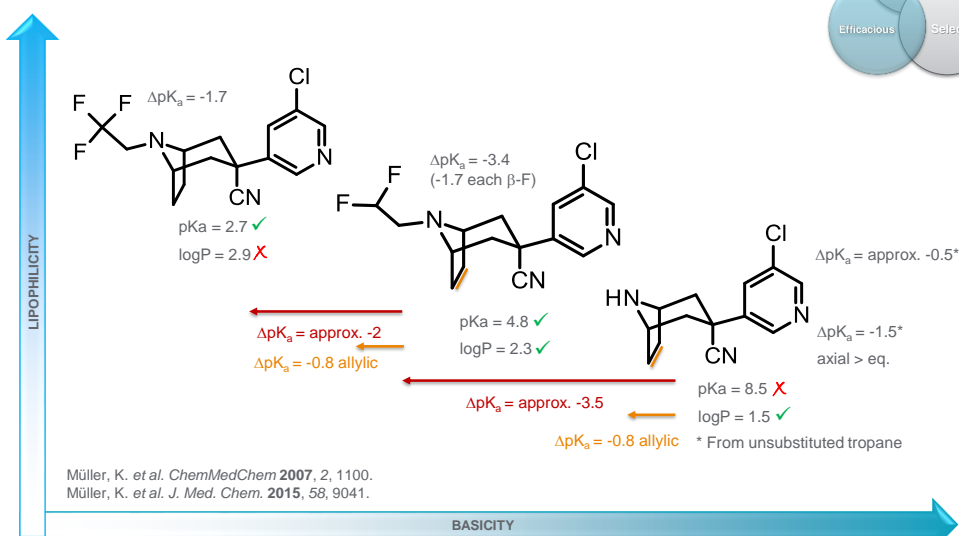
Proc. Brighton Crop Protection Conf: Pest and Diseases 2002, 1, 145 – 152.



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Tuning physicochemical properties



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Modern crop protection products targeting ion channels



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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

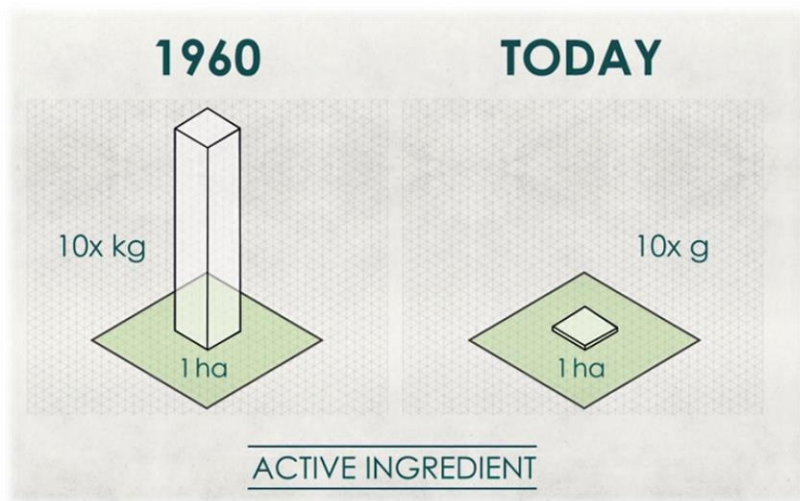


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The crop science in the 1960's used 10 Kgs of active ingredient per hectare to protect crops (1 hectare is almost 2.5 acres). How much active ingredient is used today in comparison?

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

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



<https://croplife.org/crop-protection/innovation-in-crop-protection-products/>



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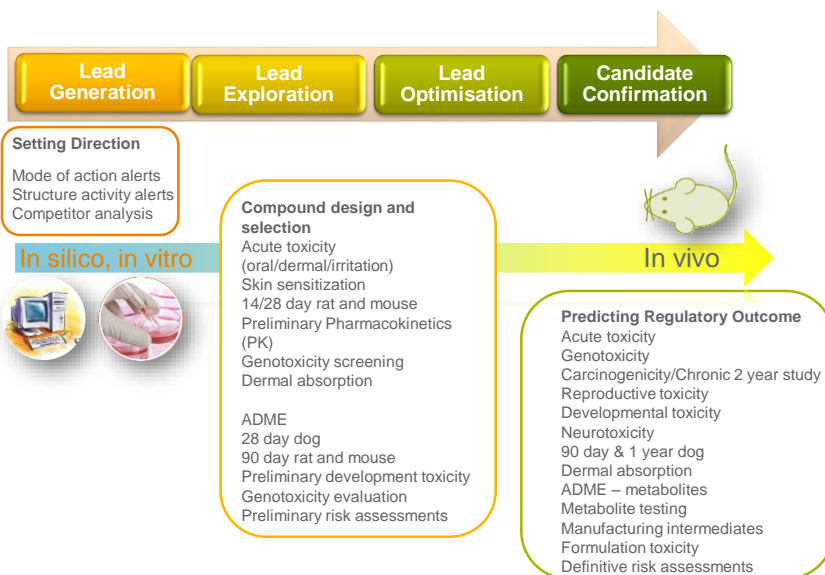
Product Safety – Who is being protected?



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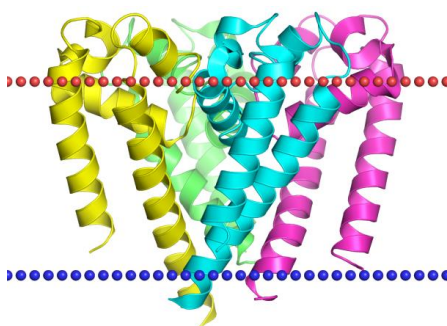
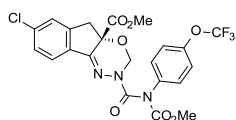
Product safety: studies per stage



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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)

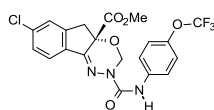
Channels **2008**, 2, 100.
Bioorg. Med. Chem. Lett. **2014**, 24, 3690.
J. Med. Chem. **2015**, 58, 7093–7118



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Mammalian safety of Indoxacarb

Differential binding

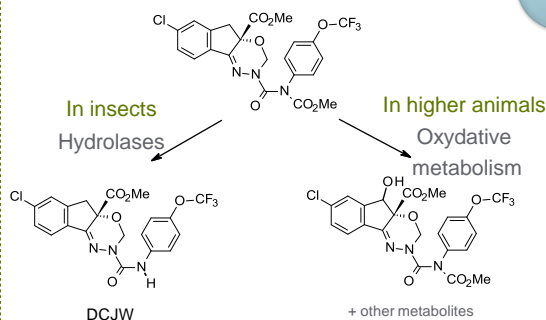


DCJW Active ingredient

$IC_{50} = 1000 \text{ nM}$ on rat $Na_V 1.4$
 $IC_{50} = 25 \text{ nM}$ on Bg $Na_V 1-1a$
 (Bg = *Blattella Germanica*)

Pestic. Biochem. Physiol. **2010**, 97, 87.

Selective metabolism



Crop Protection **2000**, 19, 537.

Indoxacarb, *JMPR* Evaluation report 2005.

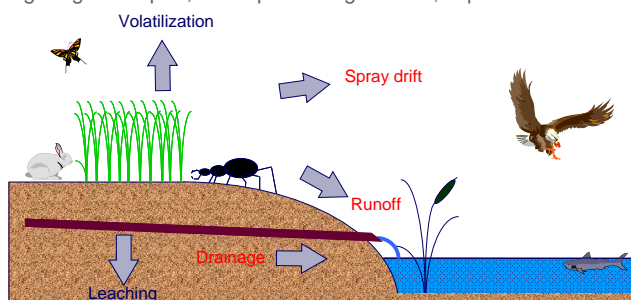


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Environmental Safety – What is being protected?

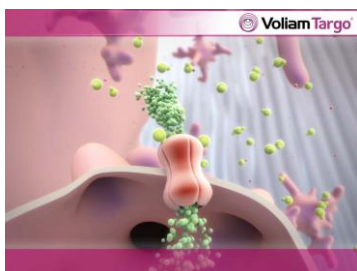
- **Groundwater** – Drinking water (human exposure), irrigation water, the aquifer itself as an entity
- **Surface Water** – Drinking water, irrigation water, aquatic organisms (fish and aquatic plants)
- **Soil** – Persistence in soil, topsoil erosion, carry-over into follow on crops
- **Non target 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



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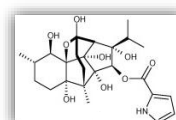
Efficacious, safe and selective: Anthranilic amides

Anthranilic amides bind to the insect ryanodine receptor in muscle cells



Intrinsic target-based selectivity:
Insect vs. Mammal

	EC50 (nM)
Cockroach	36
Fruit Fly	48
Mouse	14'000
Rat	> 100'000



Ryanodine (plant metabolite)



VOLIAM TARGO

Untreated



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

Crop: Cauliflower
Source: Taiwan, Syngenta trials 2007

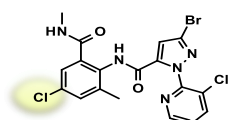


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Pest Manage. Sci. 2013, 69, 7.; *Invert. Neurosci.* 2008, 8, 107-19; *Biochemistry*, 2009, 48, 10342

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Modulation of soil persistence



Chlorantraniliprole (DuPont)

M.p. (°C) 208-210

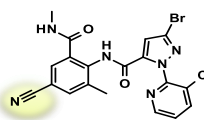
logP 2.76

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)

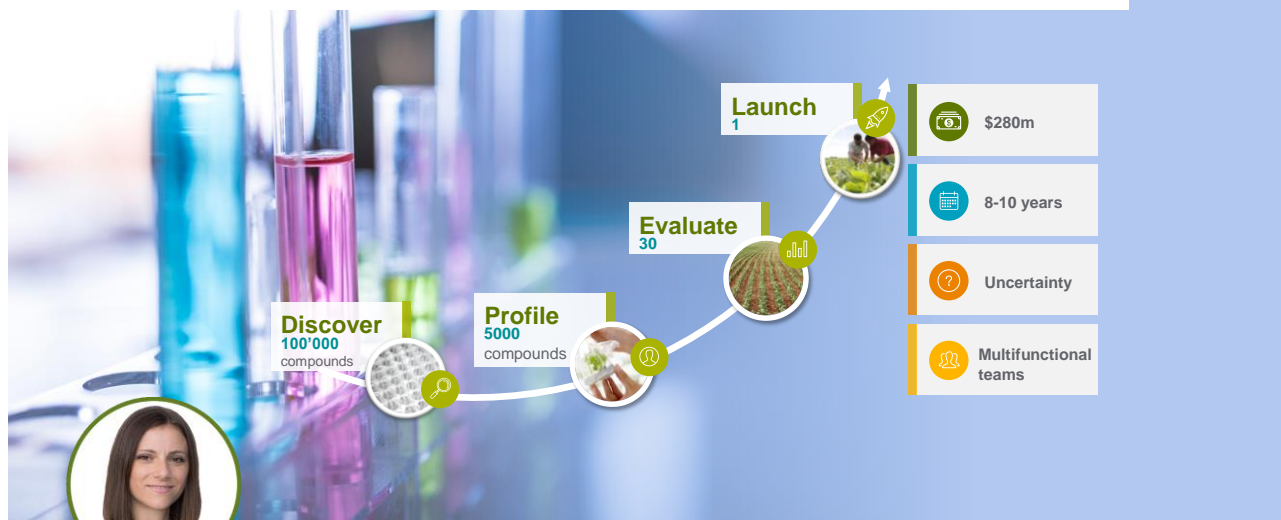


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CP Research & Development



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Acknowledgements

Chemistry

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Biokinetics

Myriam Daniels and team
Rob Lind

Electrophysiology

Jim Goodchild
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Prof. Richard Baines*

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Penny Cutler
Janet Phillips

Genetics

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



Bringing plant potential to life

* University of Manchester

** Cambria Biosciences

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Bringing plant potential to life

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Webinar Additional Resource!

150 Most Recent Crop Protection Active Ingredients



150 Most Recent Crop Protection Active Ingredients									

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<p>148</p> <p>Pinoxaden (Acetyl)</p> <p>Me, Me</p> <p>2017 Launched</p> <p>syngenta</p> <p>Herbicide</p>	<p>149</p> <p>Flucetosulfuron</p> <p>OMe</p> <p>2002 Launched</p> <p>LG Life Sciences</p> <p>Herbicide</p>	<p>150</p> <p>Aminopyralid (Mitsunuma)</p> <p>2002 Launched</p> <p>CORTEVA agriculture</p> <p>Herbicide</p>
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<https://www.acs.org/content/dam/acsorg/events/drug-discovery/slides/2019-09-19-recent-crop-protection-poster.pdf>

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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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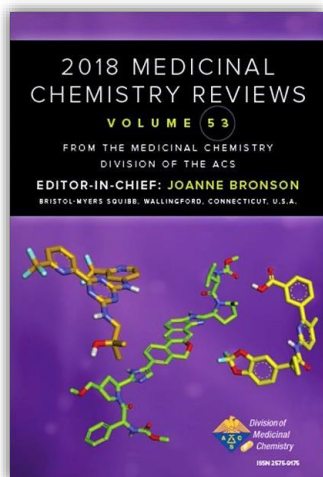
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