Agricultural Research Service
Natural Products Utilization Research Unit

USDA

New Pesticide Modes of Action from Natural Products

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National Center for Natural Products Research

Why new pesticide target sites?

- Pesticide resistance management
- More toxicologicaly benign pesticides
- In some cases, more specificity

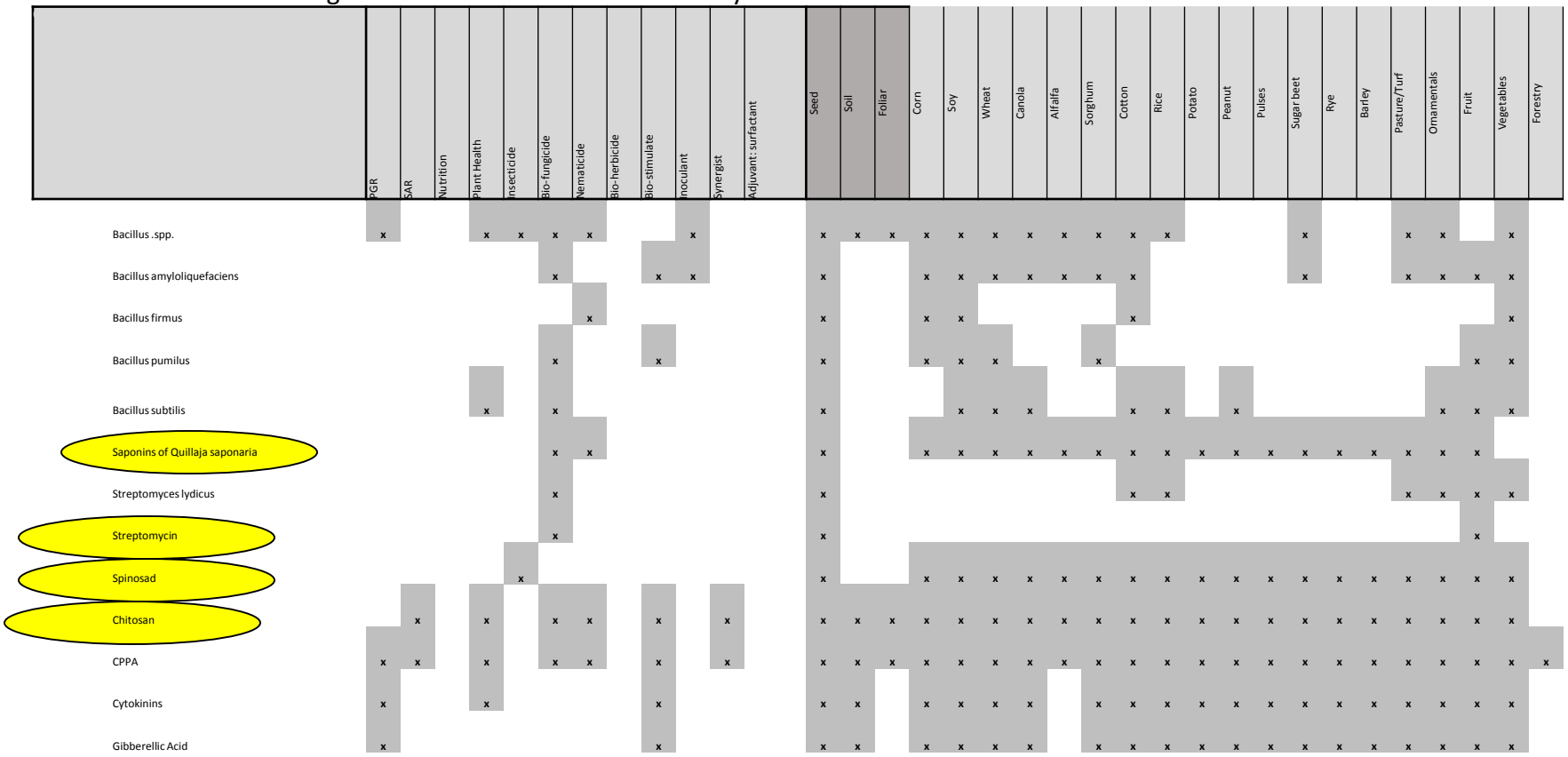
Why biopesticides?

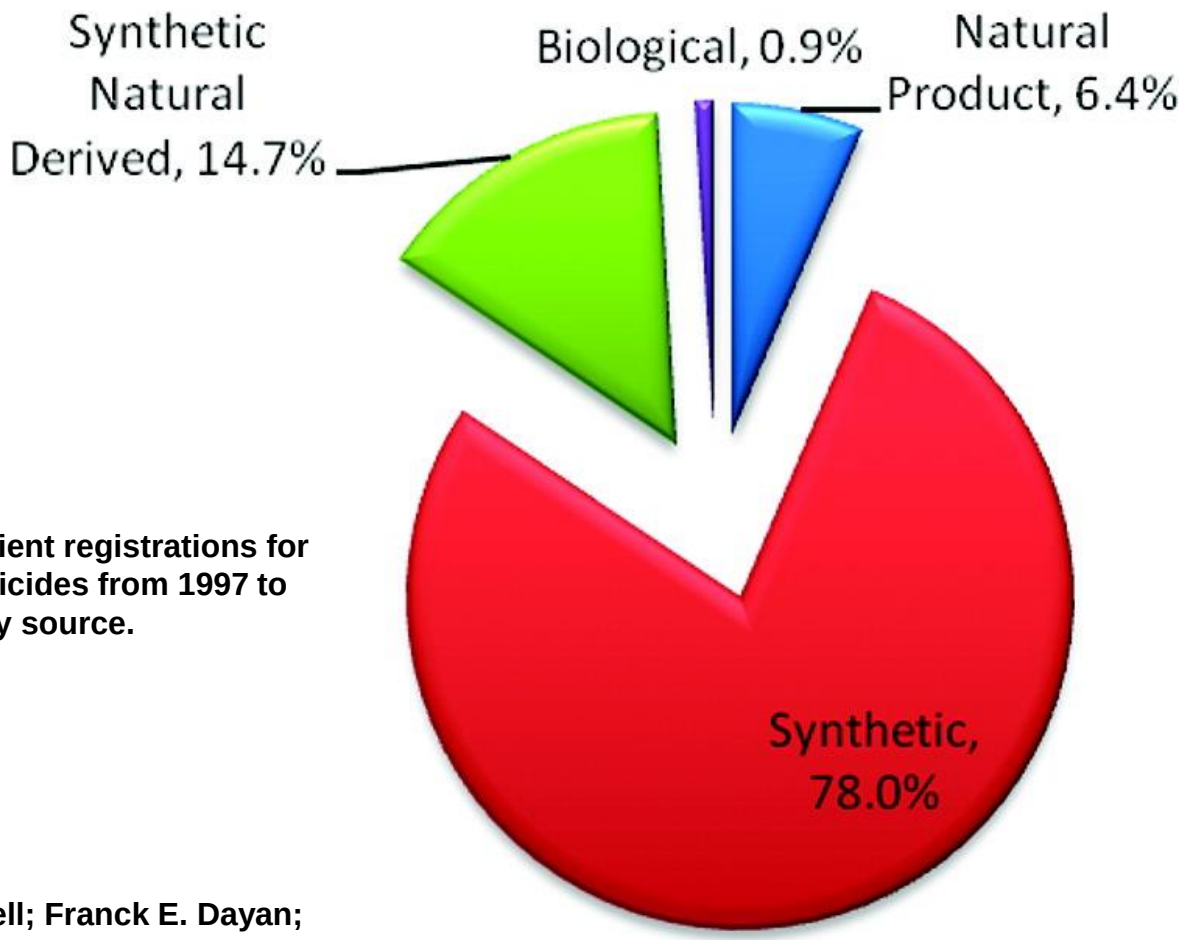
- Good source of compounds with novel molecular targets
- A way of leveraging biopesticide research

AGRITHORITY
Science without Borders

From Richard Shaw

Partial List of Biologicals and Natural Products Curently Used as Seed Treatments.





New active ingredient registrations for conventional pesticides from 1997 to 2010, organized by source.

Charles L. Cantrell; Franck E. Dayan; Stephen O. Duke; *J. Nat. Prod.* 2012, 75, 1231-1242.
DOI: 10.1021/np300024u

Perspective

SCI

Received: 4 November 2013 Revised: 22 January 2014 Accepted article published: 29 January 2014 Published online in Wiley Online Library:

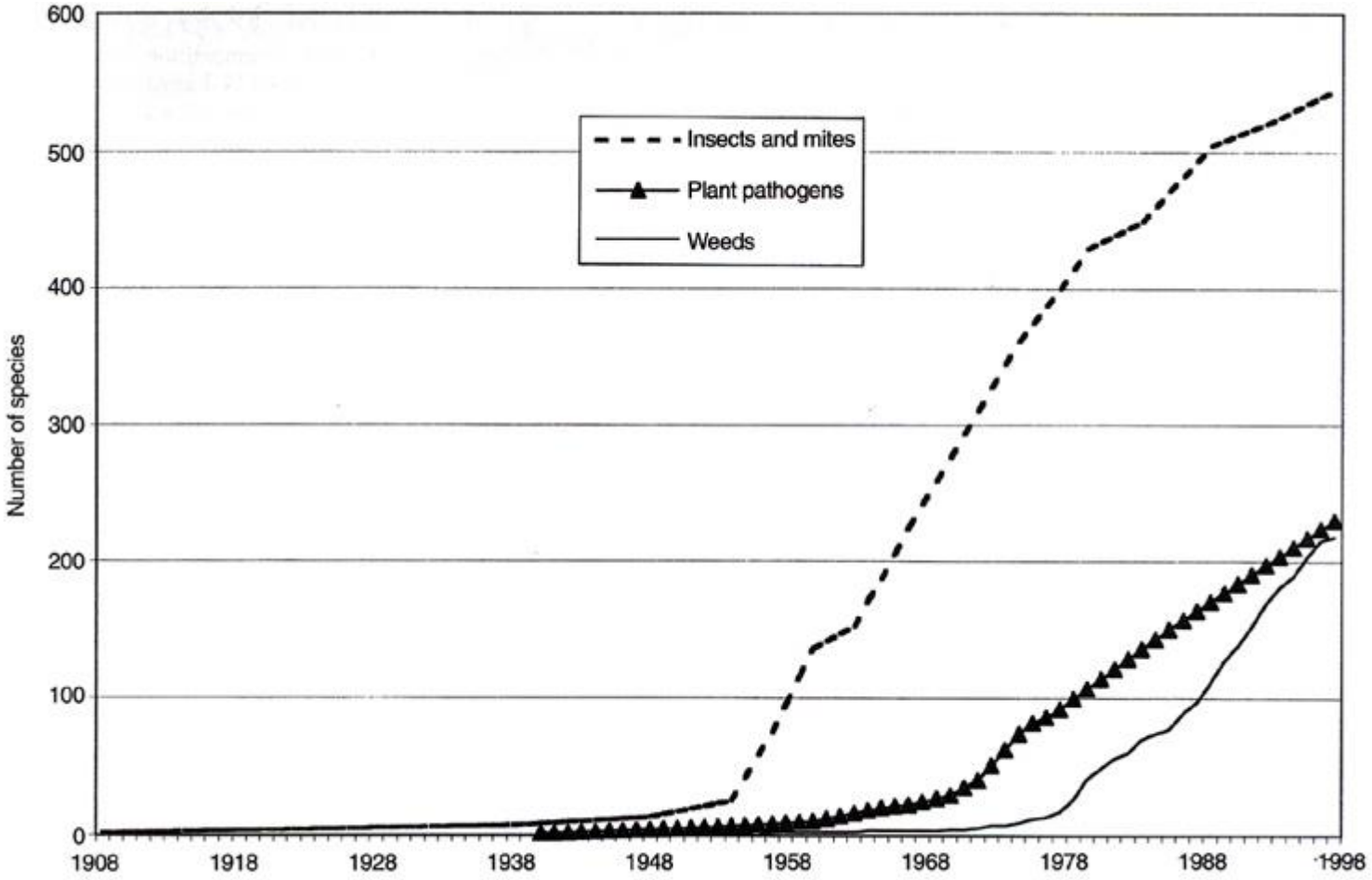
(wileyonlinelibrary.com) DOI 10.1002/ps.3744

Natural products for pest control: an analysis of their role, value and future

B Clifford Gerwick* **and Thomas C Sparks**

Pest Management Science **2014**, *70*, 1169-1185.

- Natural compounds used directly – biochemical biopesticides
- Natural product-inspired synthetic pesticides
- Synthetic pesticides that could have been inspired by natural product mode of action and/or structure



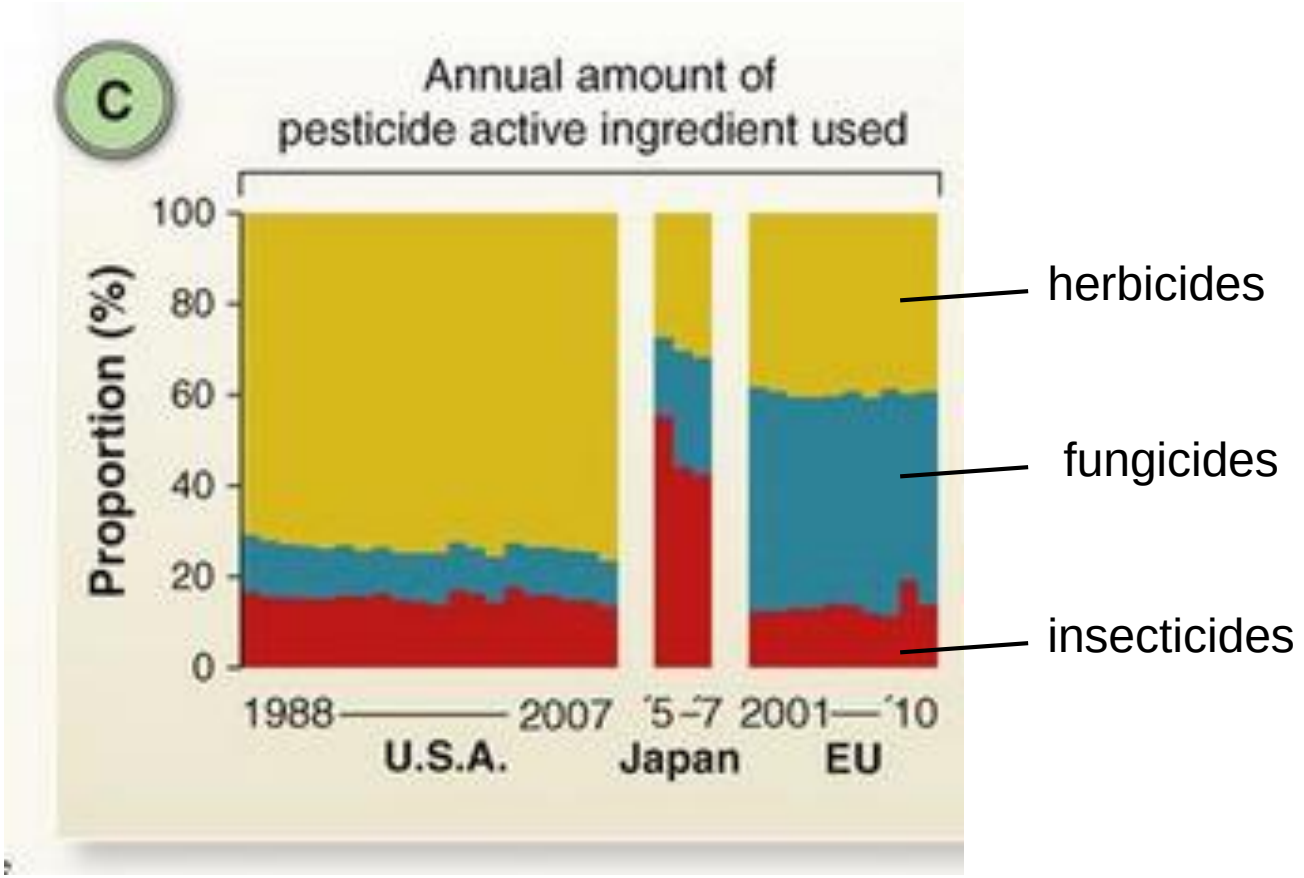
Number of pesticide-resistant species, 1908 to 1998.

Number of modes of action for commercial products (from HRAC, FRAC, and IRAC)

- Herbicides – 21
- Insecticides – 28
- Fungicides – 41

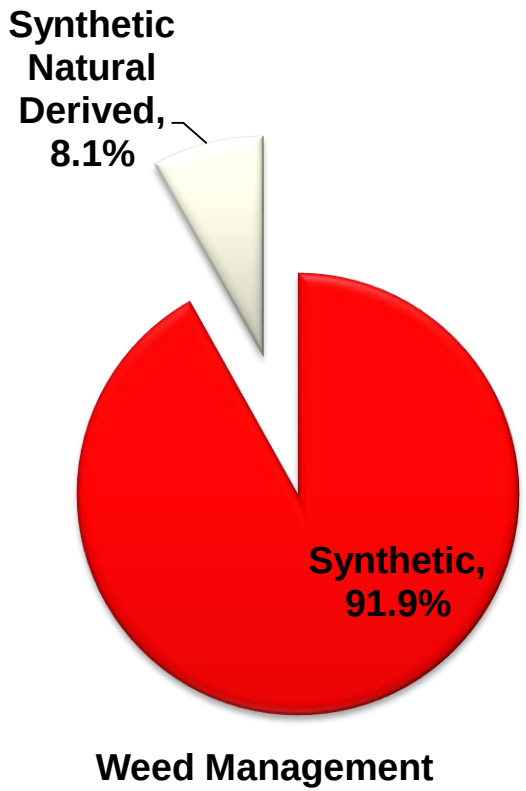
Herbicides

Köhler & Triebskorn – 2013 – Science 341: 759

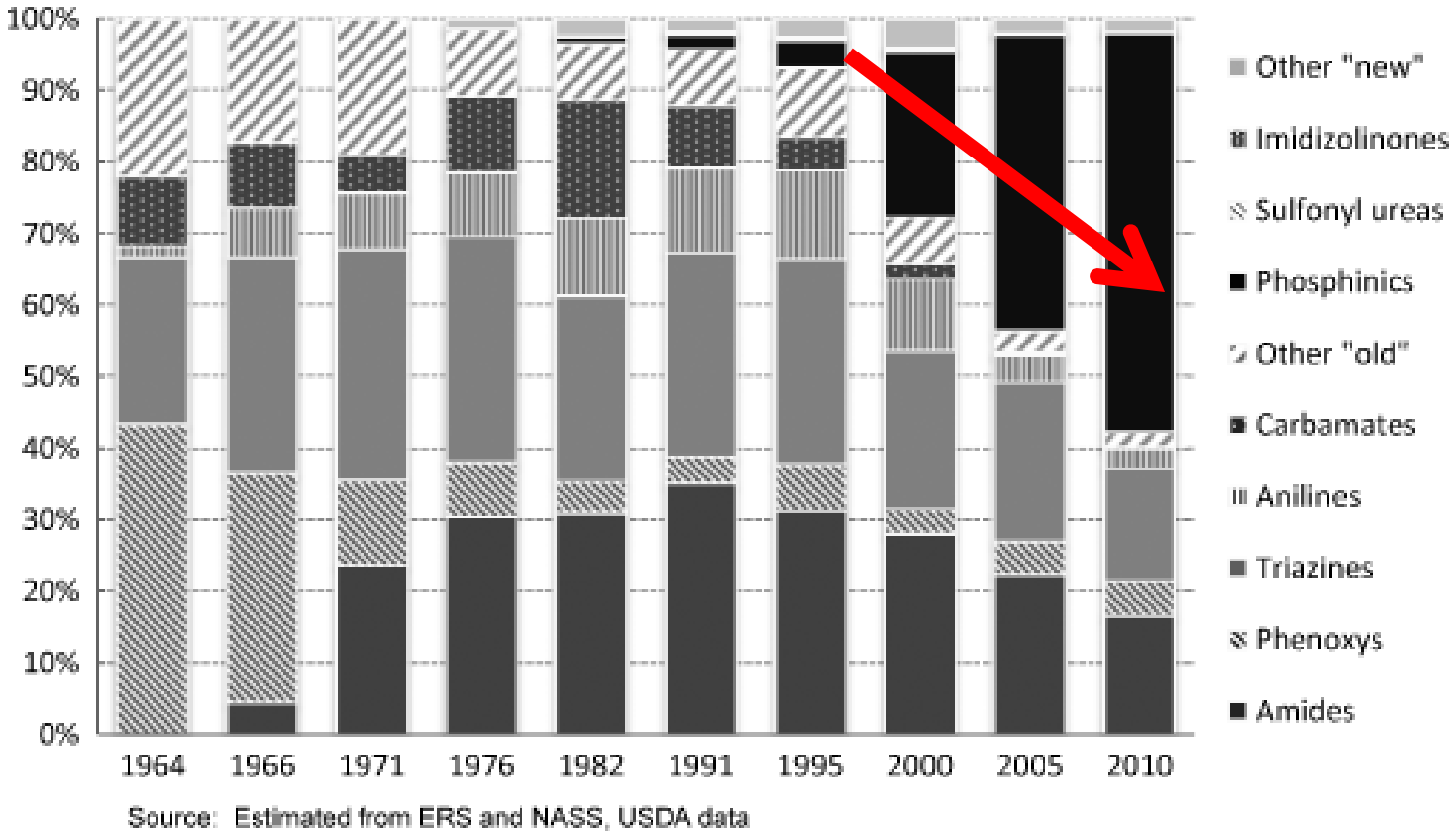


United States Department of Agriculture – Agricultural Research Service

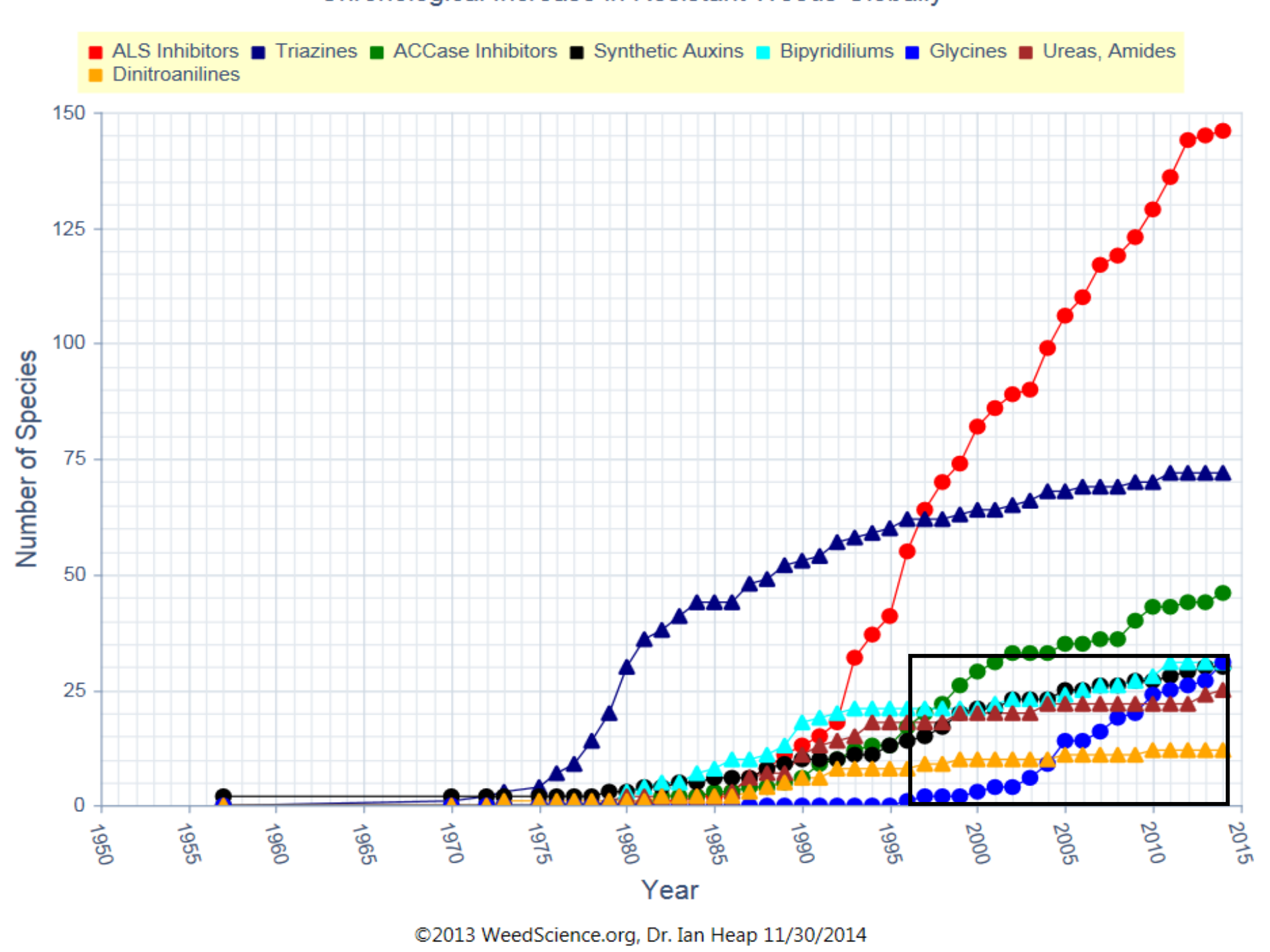
Active ingredient registrations for conventional herbicides from 1997-2010



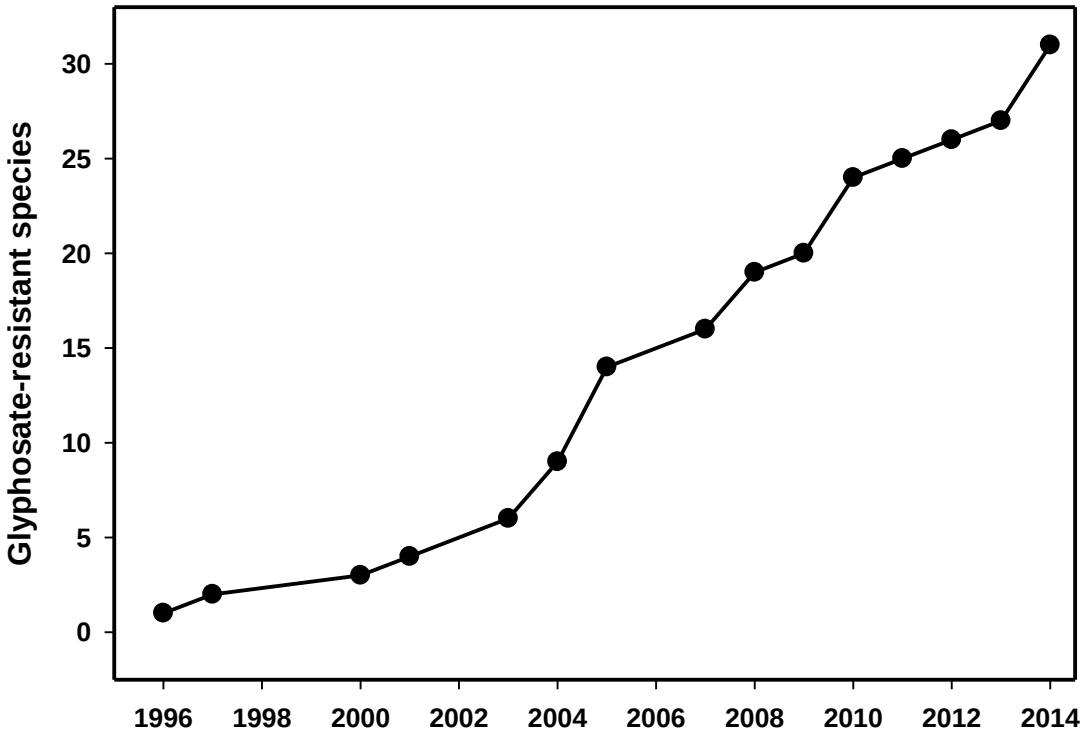
Share of total herbicide quantity use in the US.



Pest Management Science
Volume 69, Issue 9, pages 1001-1025, 6 JUN 2013 DOI: 10.1002/ps.3529
http://onlinelibrary.wiley.com/doi/10.1002/ps.3529/full#ps3529-fig-0007


Chronological Increase in Resistant Weeds Globally
ALS Inhibitors
Triazines
ACCase Inhibitors
Synthetic Auxins
Bipyridiliums
Glycines
Ureas, Amides
Dinitroanilines
Number of Species
150
125
100
75
50
25
0
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
Year
©2013 WeedScience.org, Dr. Ian Heap 11/30/2014

Global evolved glyphosate-resistant weed species



From: Heap, International Survey of Herbicide Resistant Weeds. Online; http://www.weedscience.org.

New modes of action?

Perspective

Received: 2 September 2011 Revised: 21 September 2011 Accepted article published: 12 October 2011 Published online in Wiley Online Library: 22 December 2011

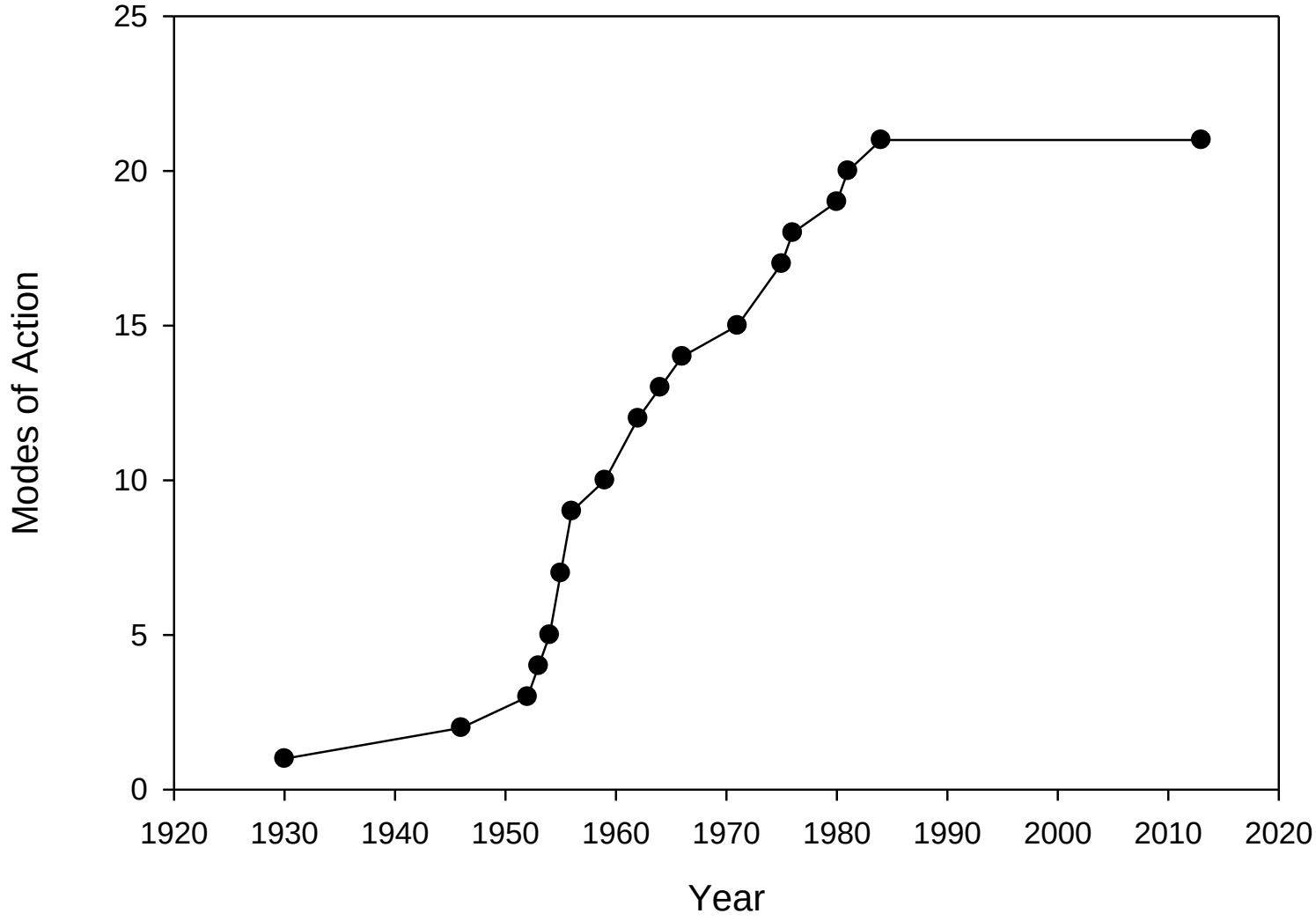
(wileyonlinelibrary.com) DOI 10.1002/ps.2333

Why have no new herbicide modes of action appeared in recent years?

Stephen O Duke*

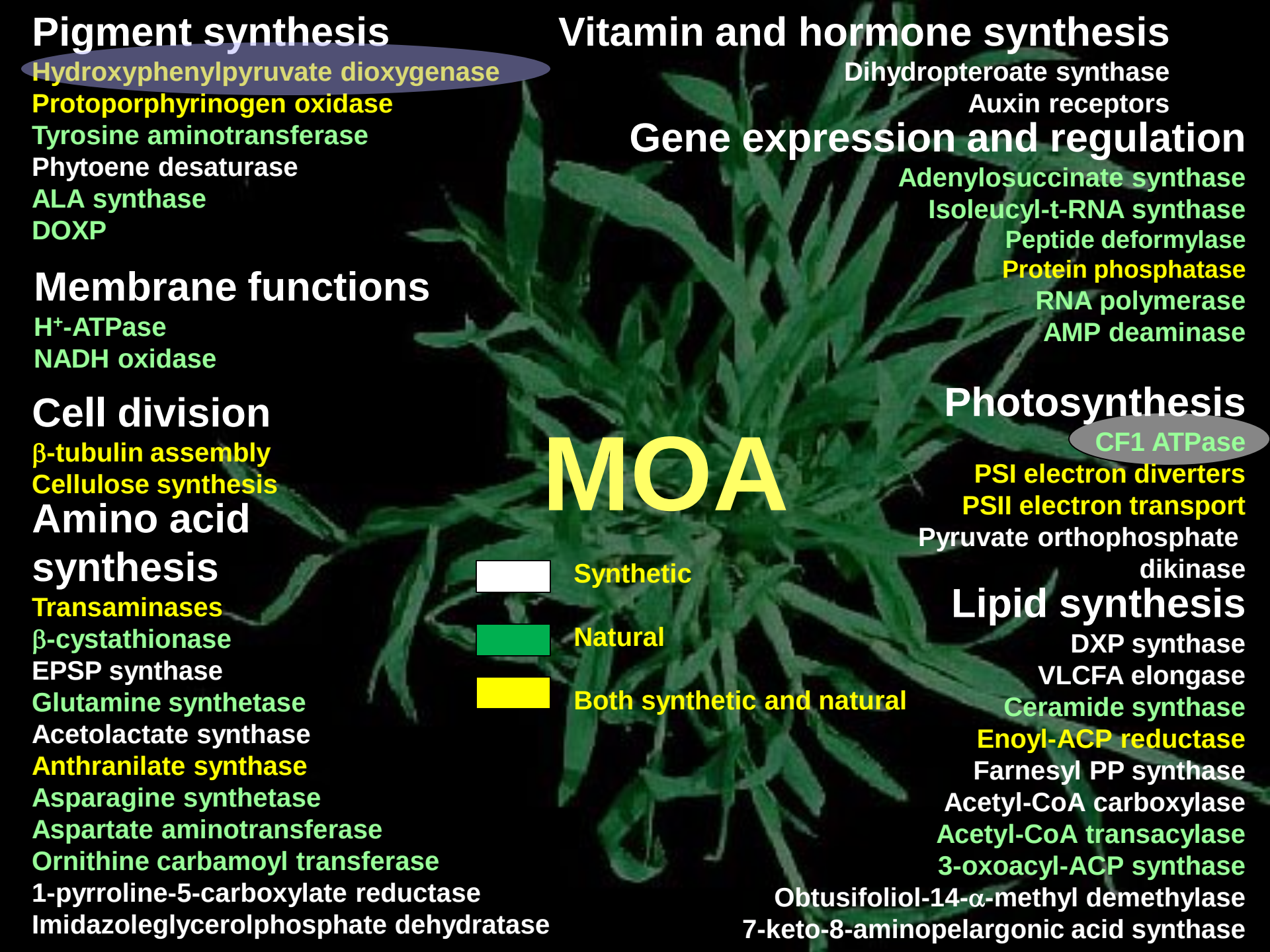
Pest Management Science **2012**, *68*, 505-512.

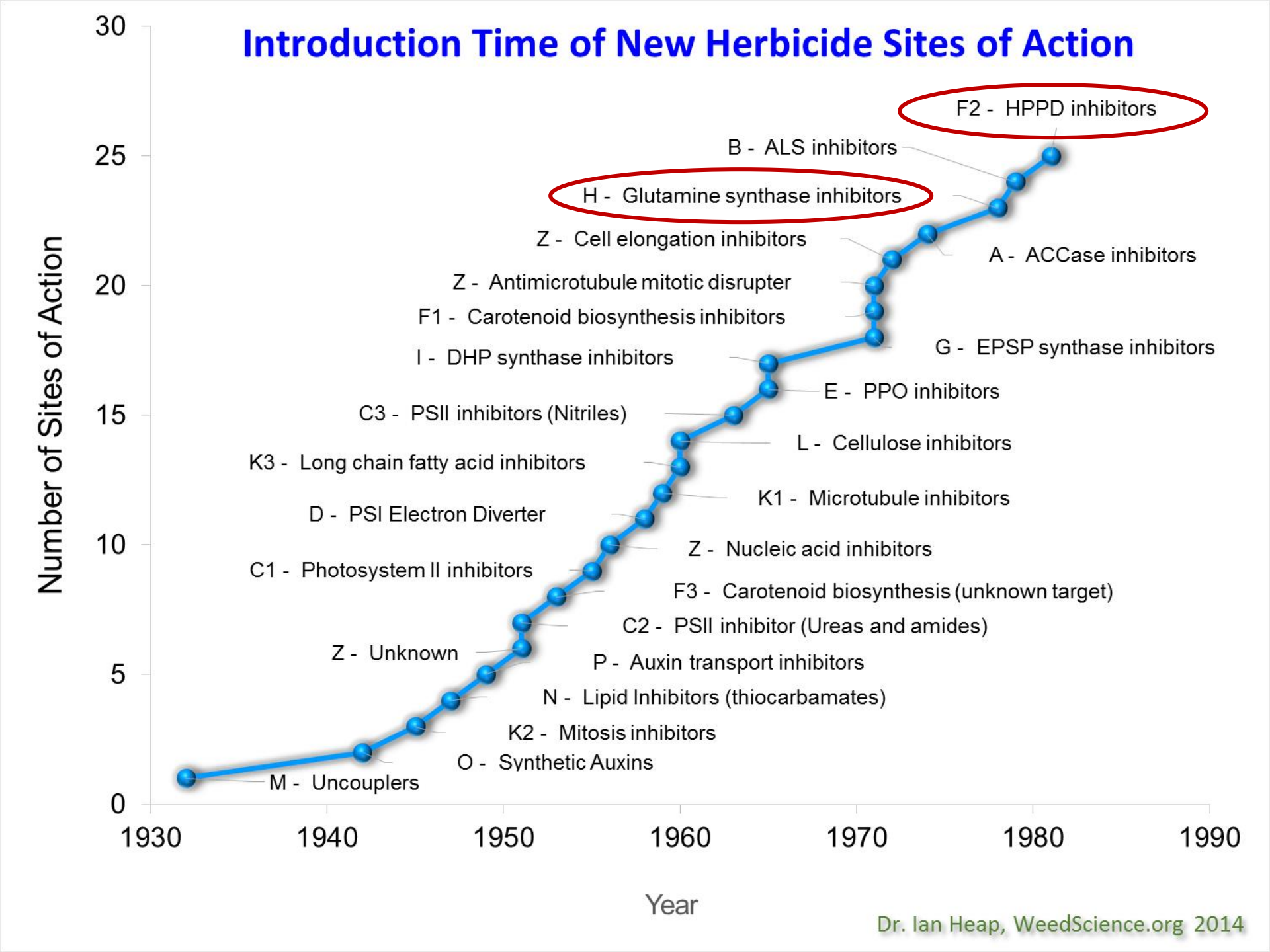
Data from: Timmons, 1970; Appleby, 2005, and HRAC



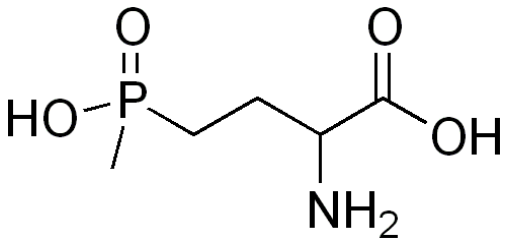
Is there a shortage of good herbicide target sites?

- Natural product research suggests no

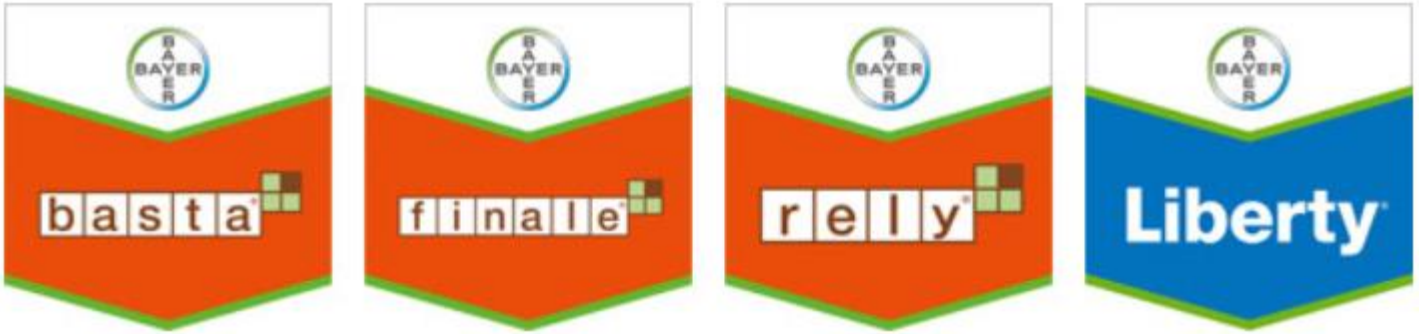

Pigment synthesis
Hydroxyphenylpyruvate dioxygenase
Protoporphyrinogen oxidase
Tyrosine aminotransferase
Phytoene desaturase
ALA synthase
DOXP
Membrane functions
H+-ATPase
NADH oxidase
Cell division
β-tubulin assembly
Cellulose synthesis
Amino acid synthesis
Transaminases
β-cystathionase
EPSP synthase
Glutamine synthetase
Acetolactate synthase
Anthranilate synthase
Asparagine synthetase
Aspartate aminotransferase
Ornithine carbamoyl transferase
1-pyrroline-5-carboxylate reductase
Imidazoleglycerolphosphate dehydratase
Vitamin and hormone synthesis
Dihydropteroate synthase
Auxin receptors
Gene expression and regulation
Adenylosuccinate synthase
Isoleucyl-t-RNA synthase
Peptide deformylase
Protein phosphatase
RNA polymerase
AMP deaminase
Photosynthesis
CF1 ATPase
PSI electron diverters
PSII electron transport
Pyruvate orthophosphate dikinase
Lipid synthesis
DXP synthase
VLCFA elongase
Ceramide synthase
Enoyl-ACP reductase
Farnesyl PP synthase
Acetyl-CoA carboxylase
Acetyl-CoA transacylase
3-oxoacyl-ACP synthase
Obtusifoliol-14-α-methyl demethylase
7-keto-8-aminopelargonic acid synthase
MOA
Synthetic
Natural
Both synthetic and natural


Introduction Time of New Herbicide Sites of Action
Number of Sites of Action
Year
0
5
10
15
20
25
30
1930
1940
1950
1960
1970
1980
1990
F2 - HPPD inhibitors
B - ALS inhibitors
H - Glutamine synthase inhibitors
Z - Cell elongation inhibitors
A - ACCase inhibitors
Z - Antimicrotubule mitotic disrupter
F1 - Carotenoid biosynthesis inhibitors
I - DHP synthase inhibitors
G - EPSP synthase inhibitors
E - PPO inhibitors
C3 - PSII inhibitors (Nitriles)
L - Cellulose inhibitors
K3 - Long chain fatty acid inhibitors
K1 - Microtubule inhibitors
D - PSI Electron Diverter
Z - Nucleic acid inhibitors
C1 - Photosystem II inhibitors
F3 - Carotenoid biosynthesis (unknown target)
C2 - PSII inhibitor (Ureas and amides)
Z - Unknown
P - Auxin transport inhibitors
N - Lipid Inhibitors (thiocarbamates)
K2 - Mitosis inhibitors
O - Synthetic Auxins
M - Uncouplers
Dr. Ian Heap, WeedScience.org 2014

Target: Glutamine synthetase

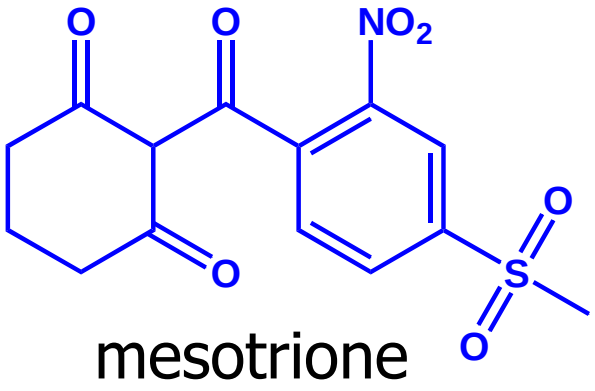


glufosinate

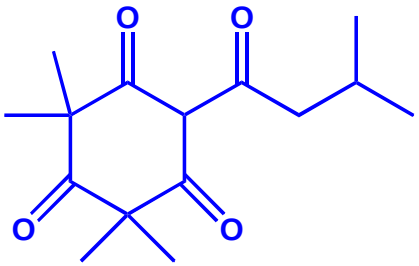


Herbicide inspired by a natural compound

Callistemon spp.
bottlebrush plant



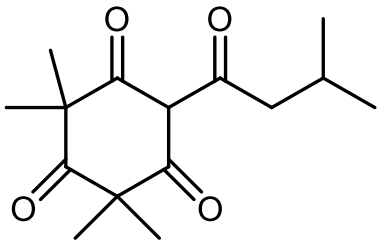
mesotrione



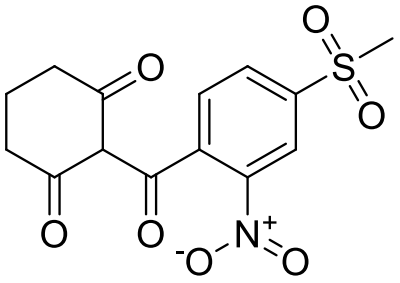
leptospermone

Callisto®
Herbicide

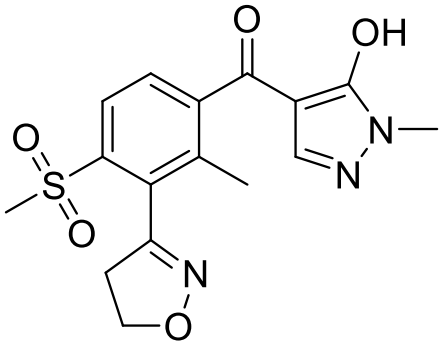
Examples of triketon active ingredient registrations derived from phytochemicals for conventional herbicides from 1997-2010



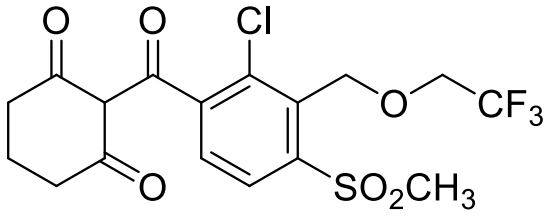
leptospermone



mesotrione

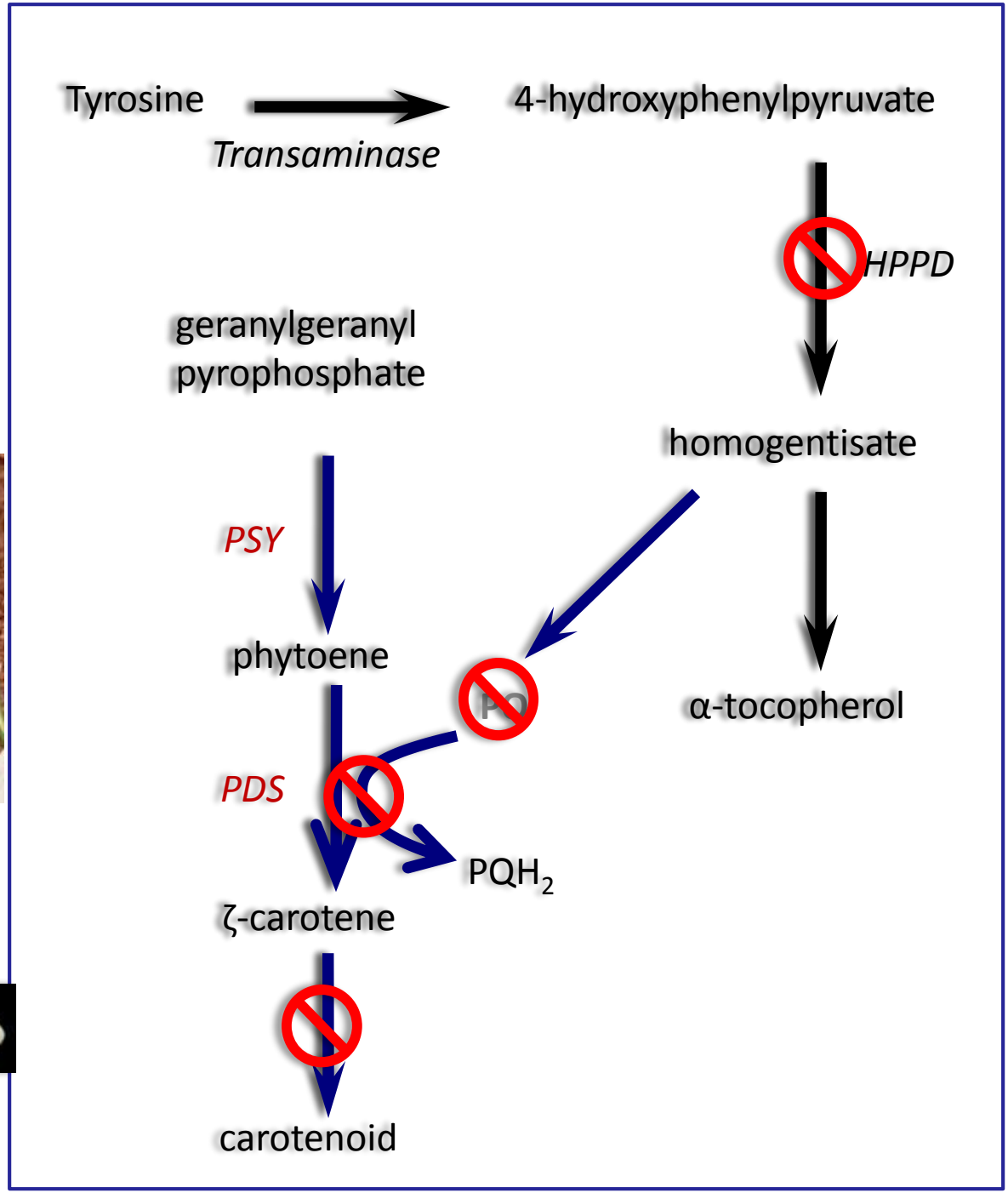


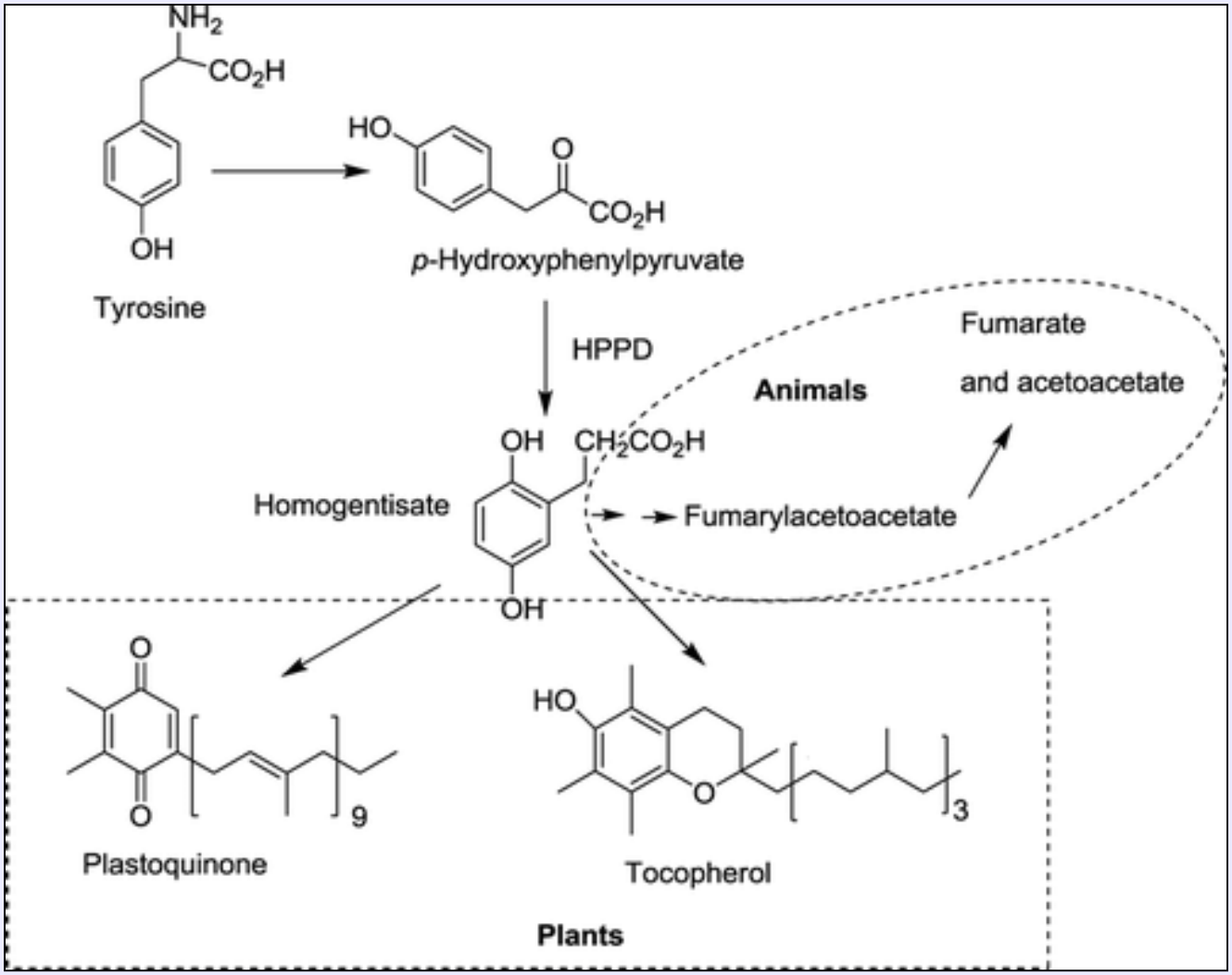
topramezone

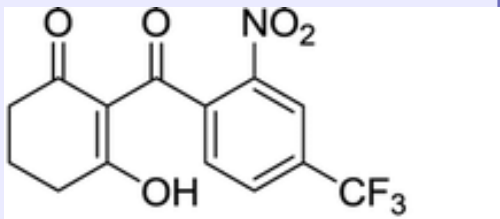


tembotrione

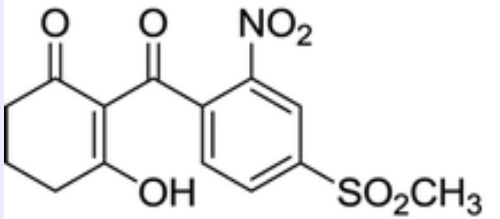
Triketone herbicides







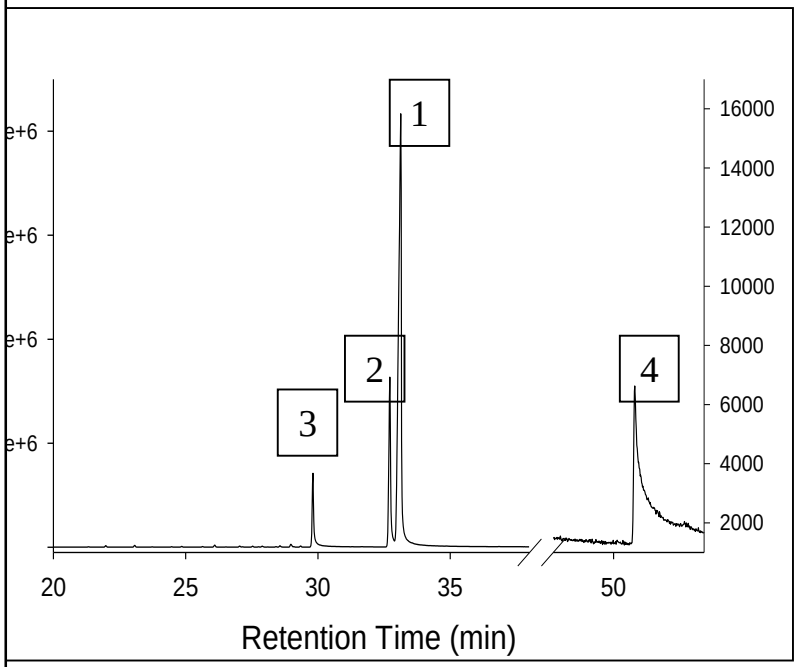
NTBC



mesotrione

Isolation and purification of β-triketones

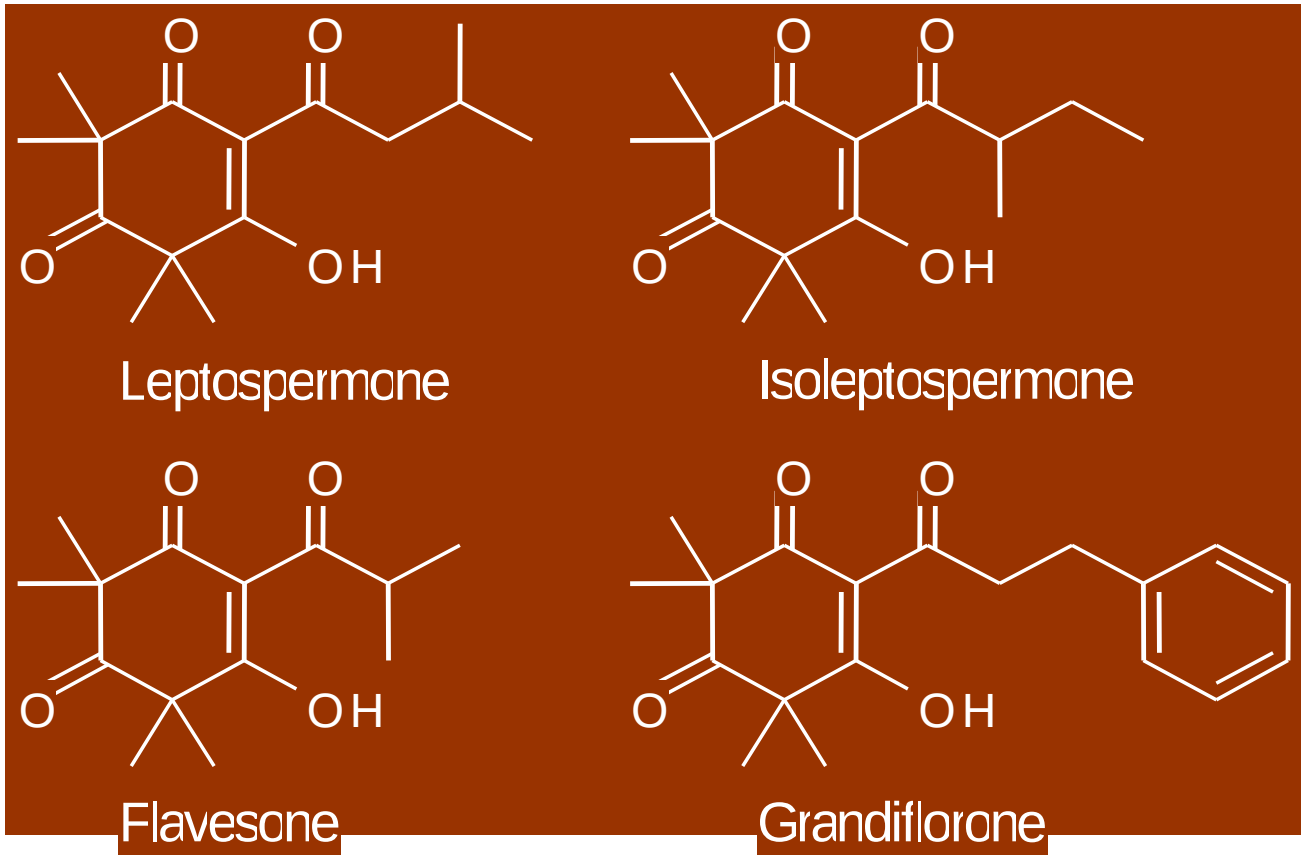
- Manuka oil was di
Et_2O
- 99.4% of the triket
extracted by liquid p
partitioning
- It contained 72.9%
leptospermone, 18.4
isoleptospermone, 7
flavensone and <1%
grandiflorone



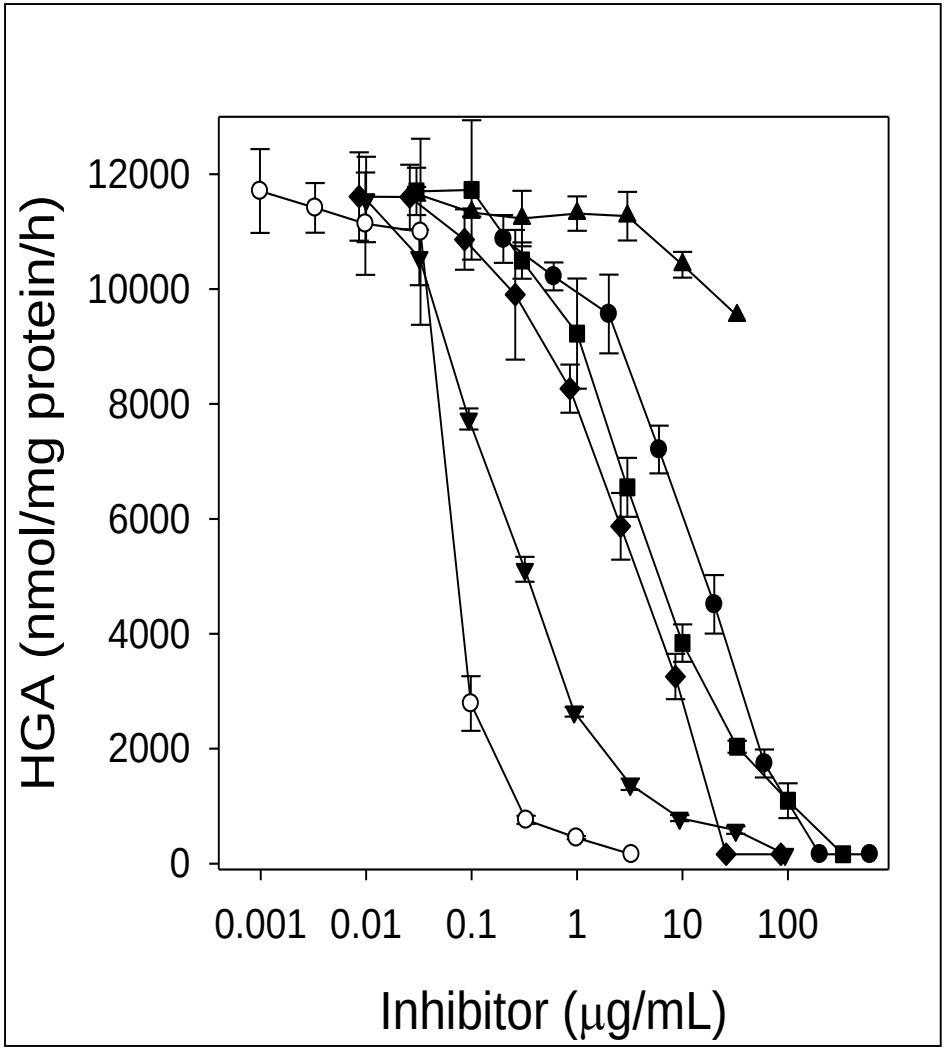
from *Leptospermum scoparium*

Leptospermum spp. (tea tree)

Manuka oil is about 40% natural triketones



Effect of Manuka oil and its components on HPPD activity



Pigweed (*Amaranthus retroflexus*)

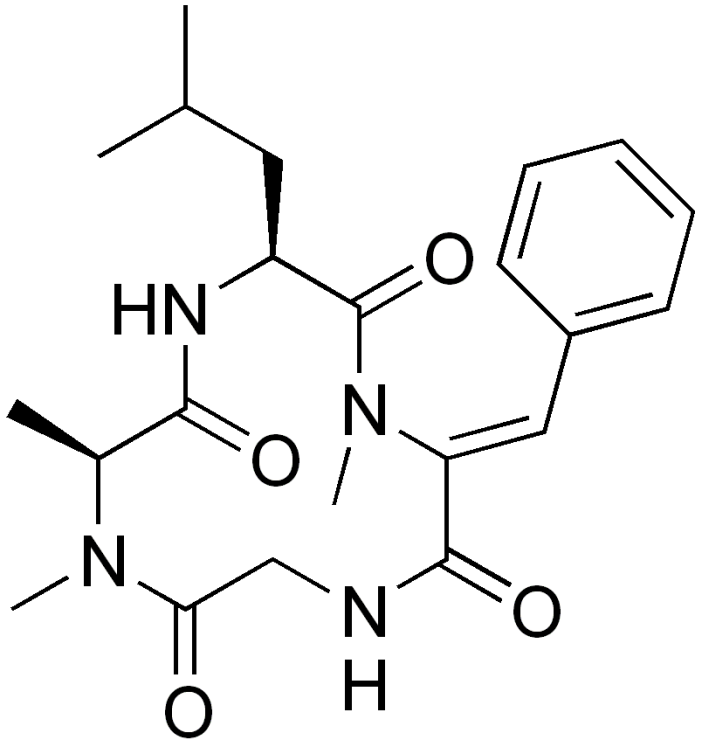
0.5% Agridex

0.5% Agridex + 0.5% manuka oil

Barnyard grass (*Echinocloa crus-galli*)

0 0.1 0.25 0.5 1

Manuka oil (% v/v)

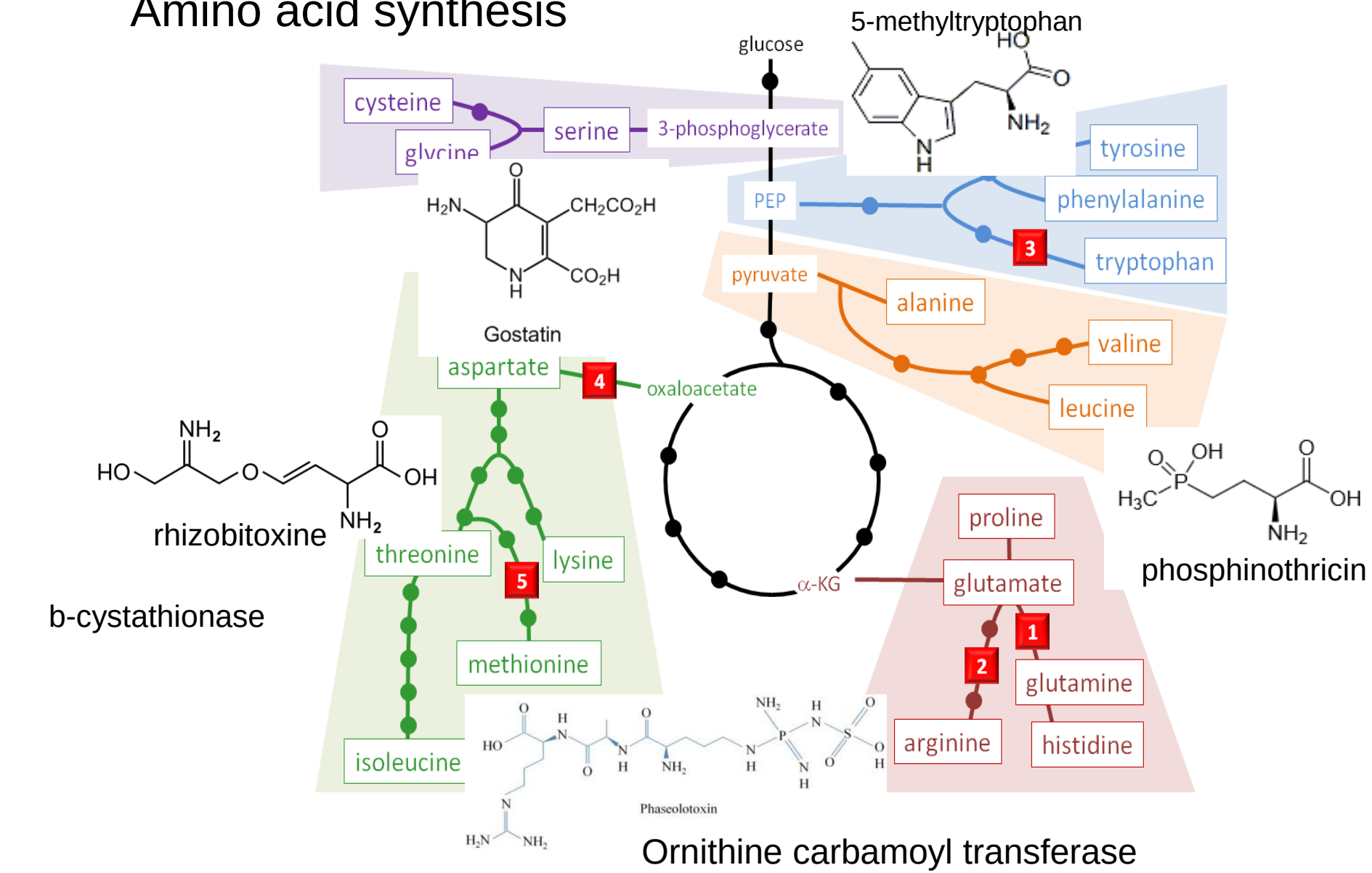


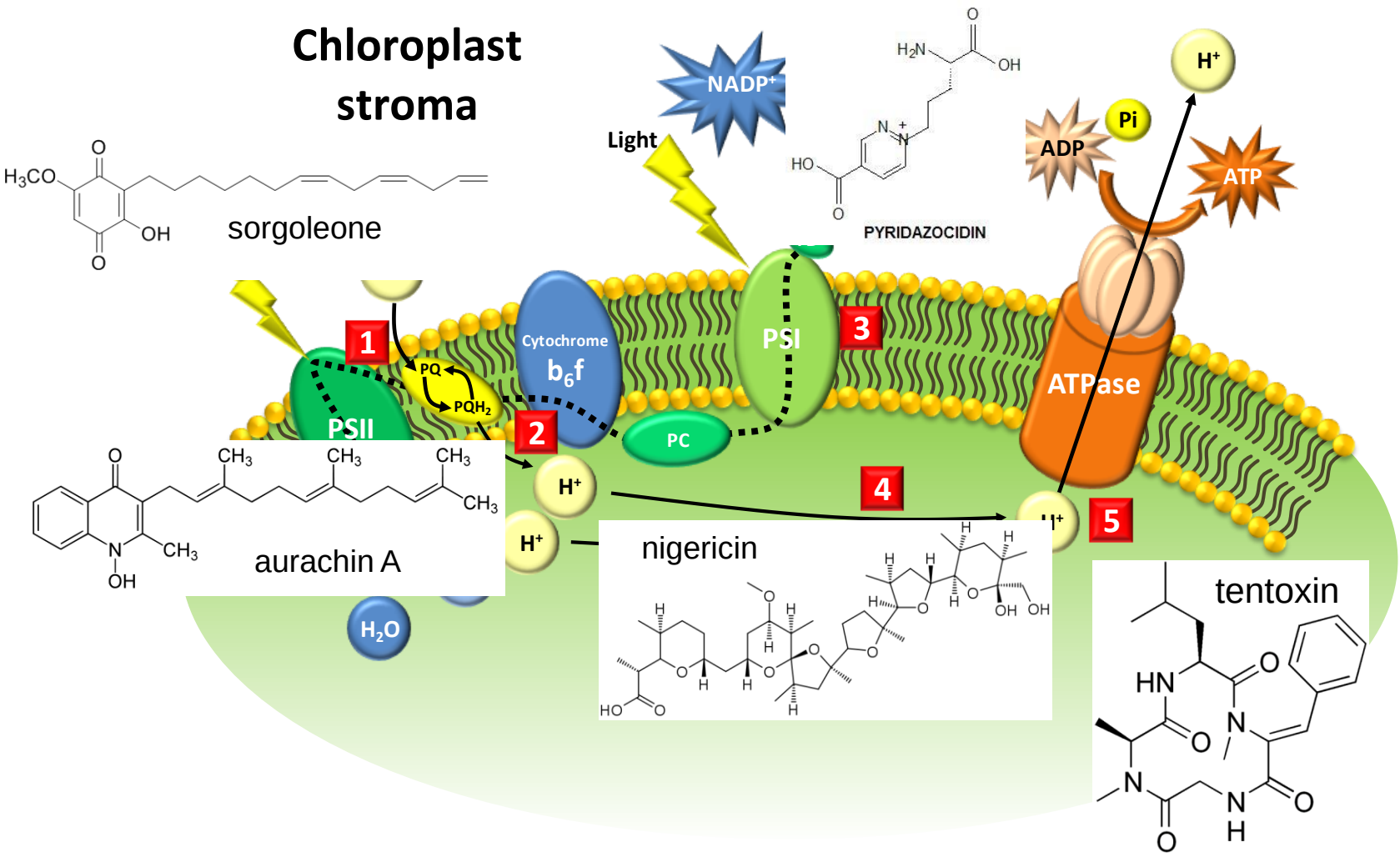
Tentoxin

- from *Alternaria alternata*
- excellent selectivity
- novel molecular target - CF_1 ATPase

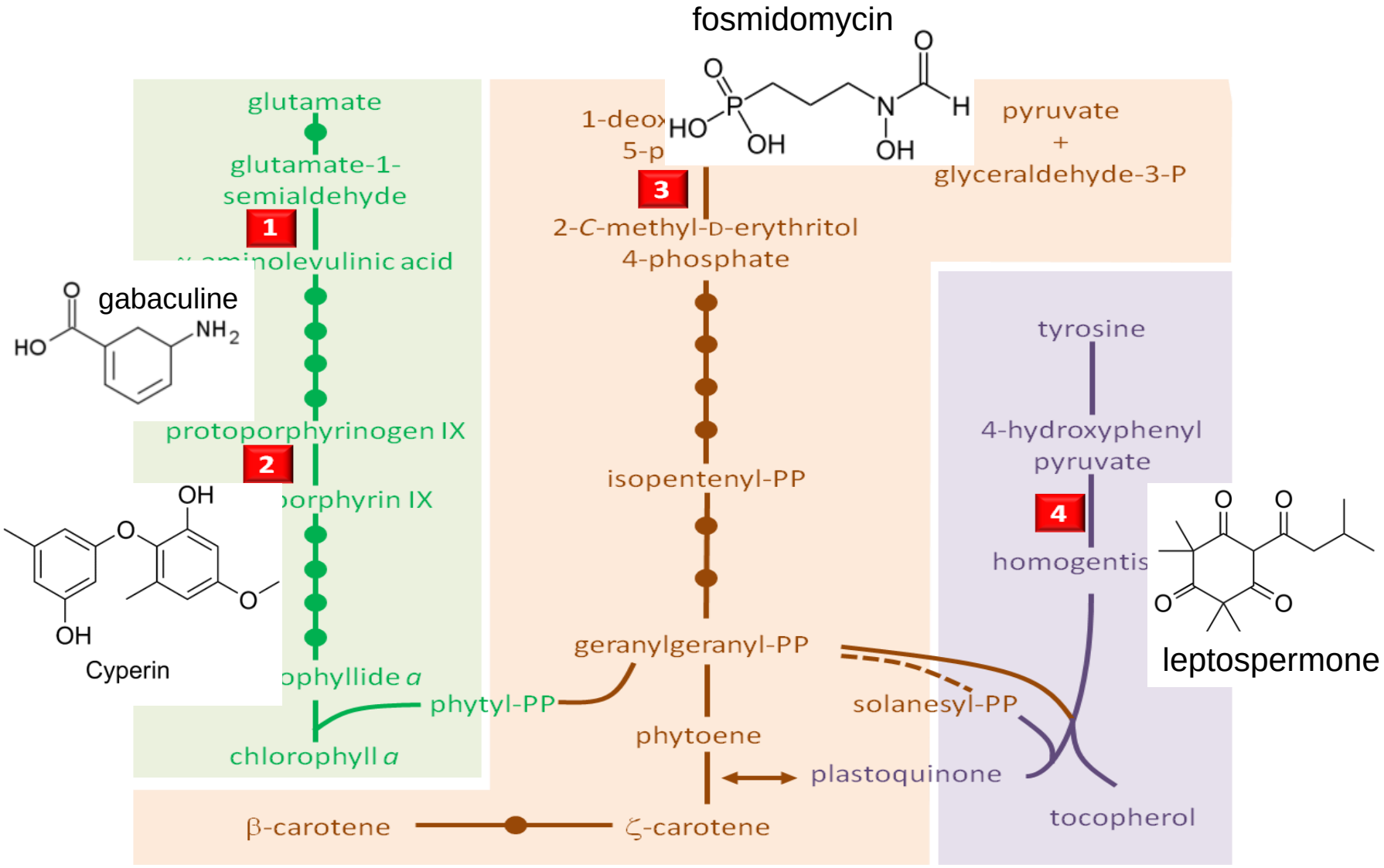
- ca. $200/mg

Amino acid synthesis

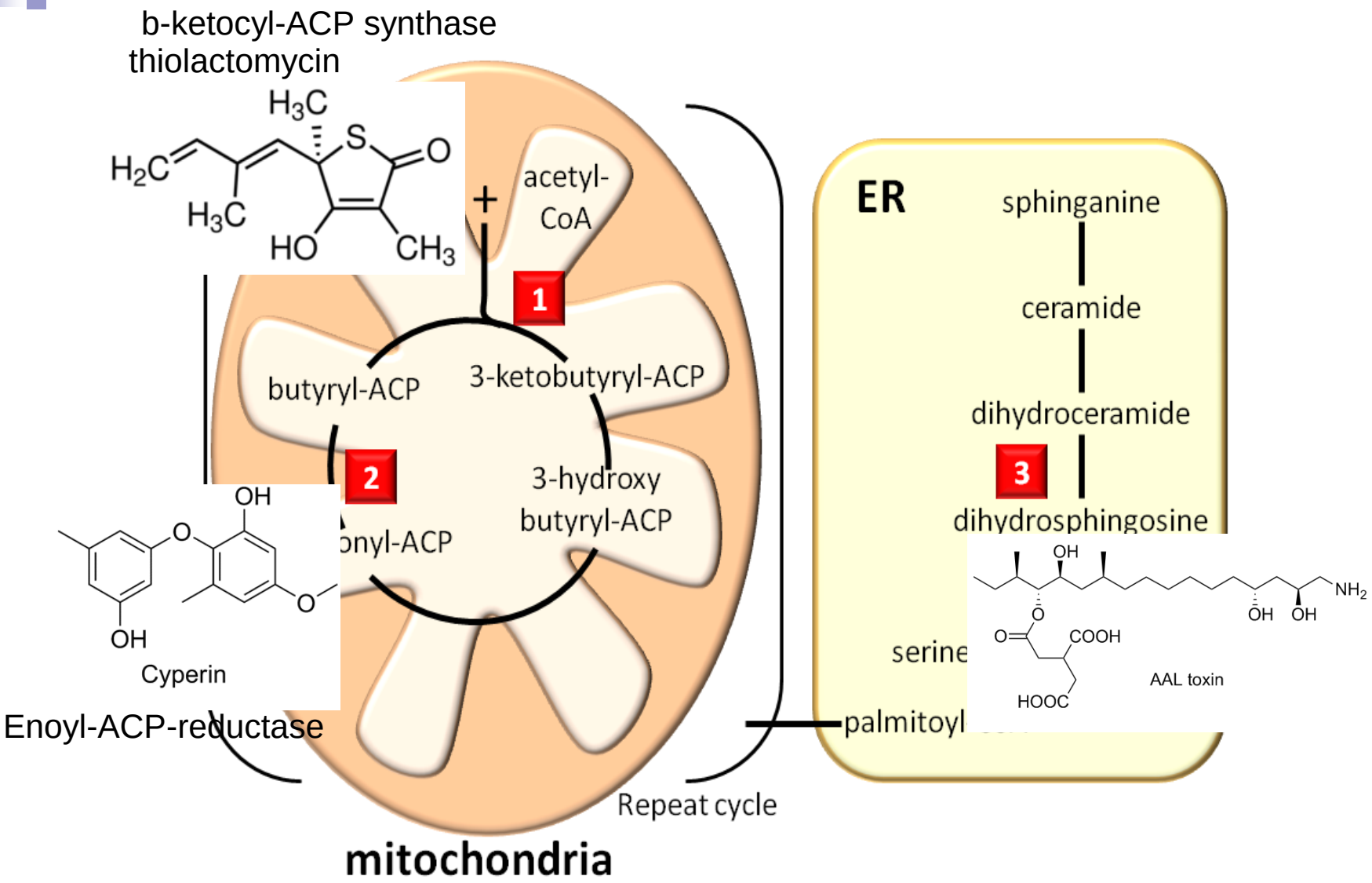




Photosynthetic energy transduction

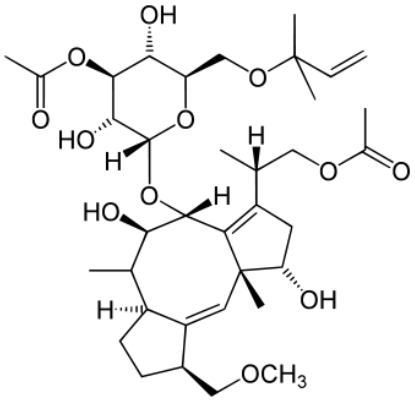


Photosynthetic pigment synthesis

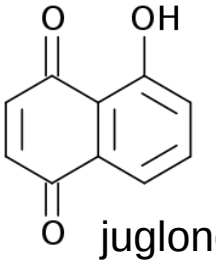


Lipid synthesis

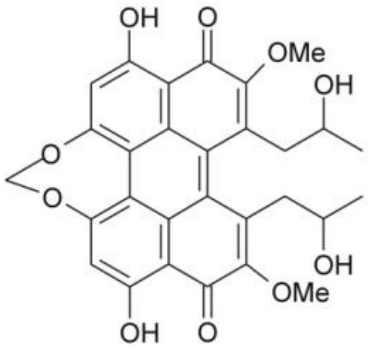
Plasma membrane functions and integrity



fusicoccin



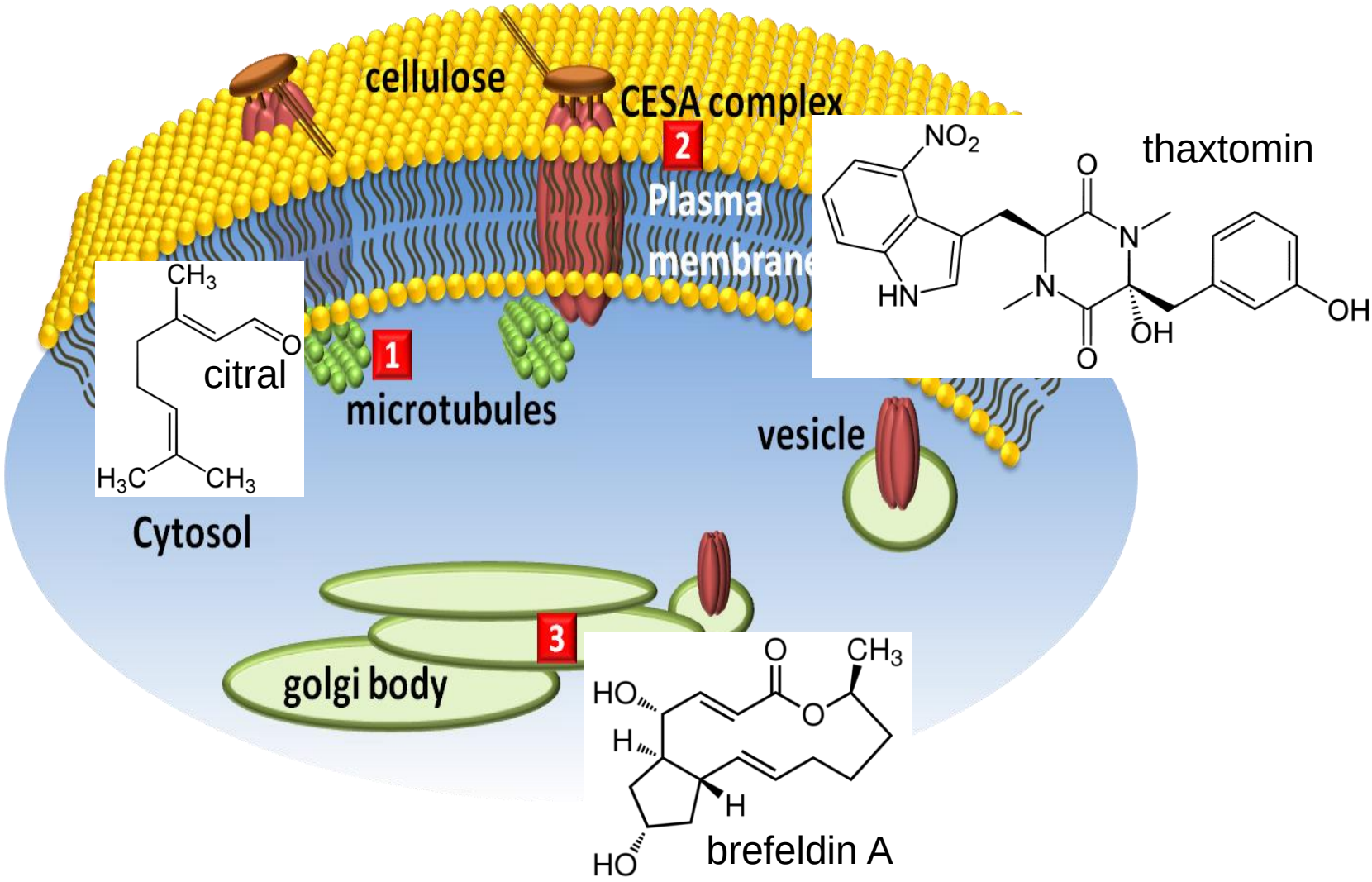
juglone



cercosporin

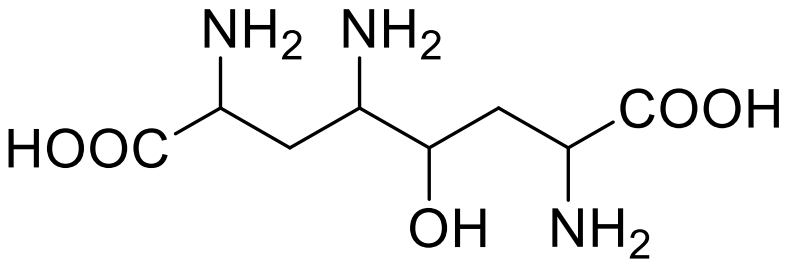
syringomycin

Macrostructure synthesis and integrity



See: Dayan, F.E. and S.O. Duke. 2014. Natural compounds as next generation herbicides. *Plant Physiology* 166: 1090-1105 DOI:10.1104/pp.114.239061.

Ascaulitoxin aglycone
2,4,7-triamino-5-hydroxy-octandioyl acid

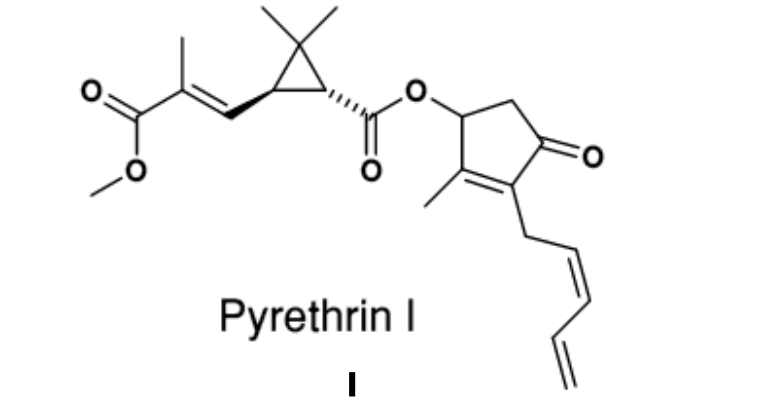


- MW 218

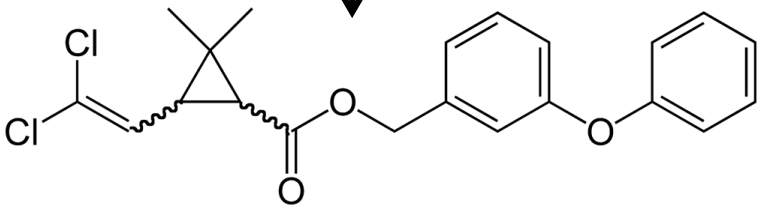
- **From *Ascochyta caulina*, a mycoherbide for lambsquarters (Evidente *et al*., 1998)**
- **Occurs as both an *N*-glucoside and an aglycone**
- **Highly potent phytotoxin against host and non-host species**
- **Nothing is known about the mode of action**
- **Duke et al. 2011. , *Pestic. Biochem. Physiol*. 100: 41-50.**

Insecticides

Pyrethrins or pyrethrum and the pyrethroids Sodium channel inhibitors

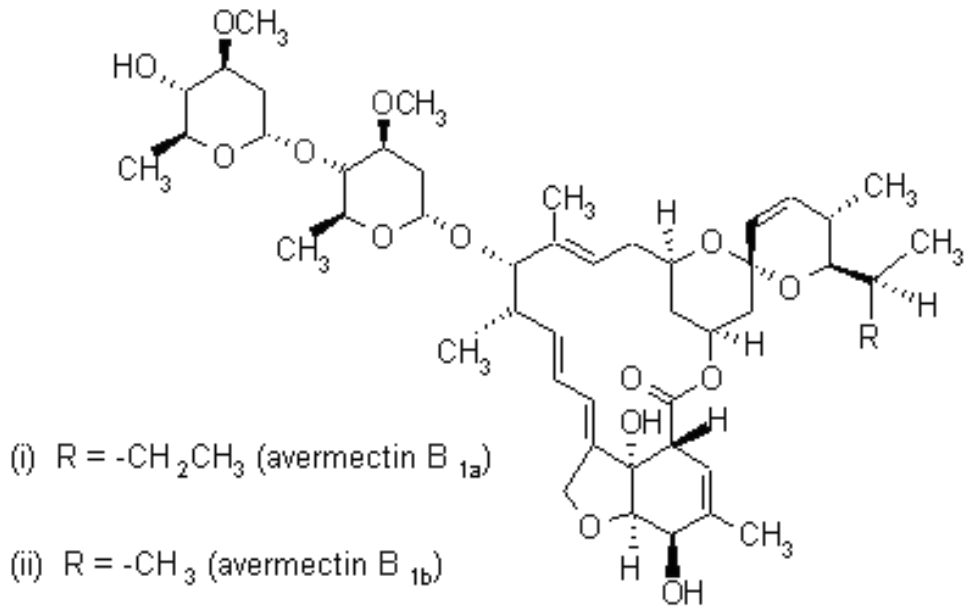


Pyrethrin I

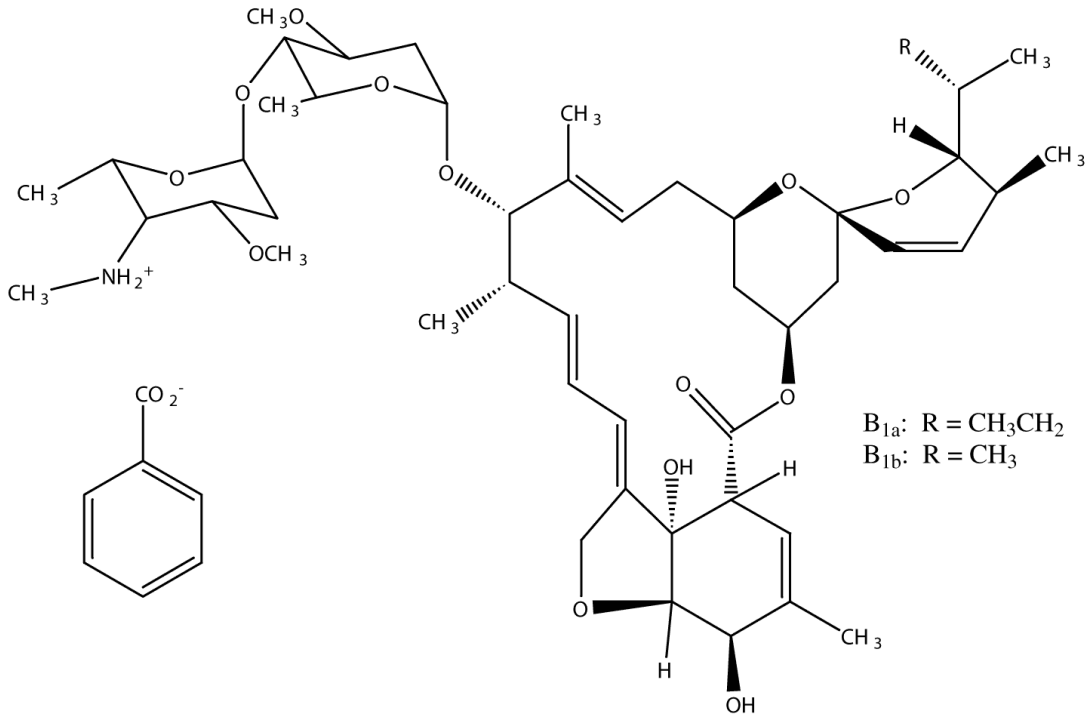


Permethrin

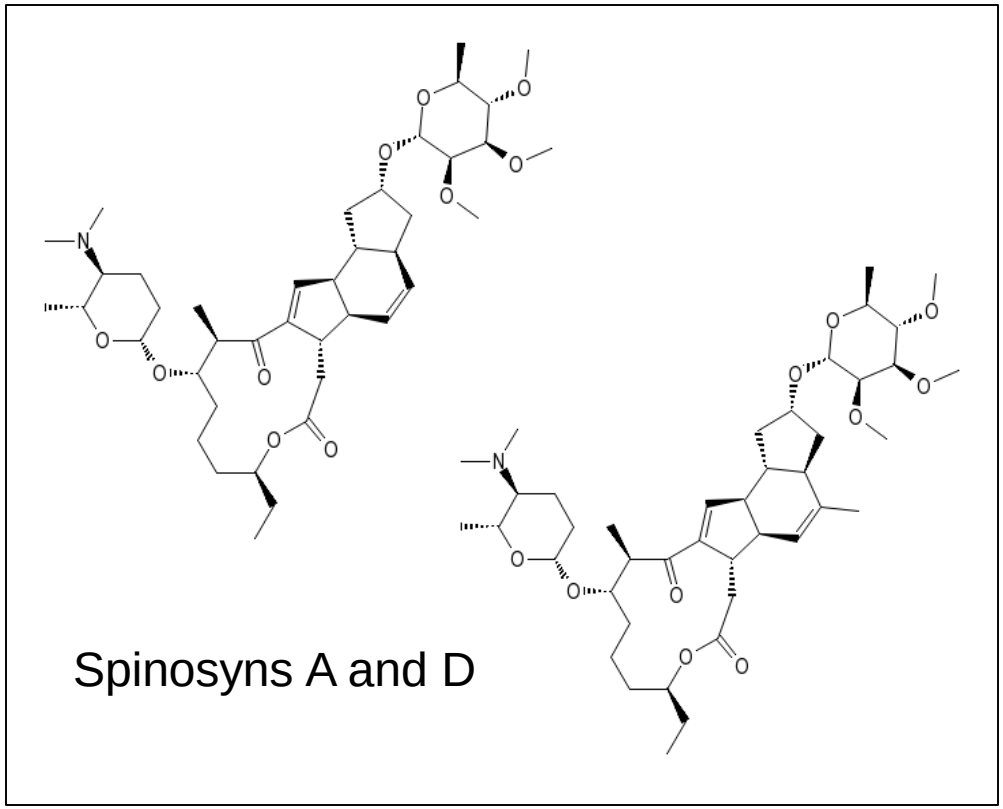
Natural GABA/glutamate-gated chloride channel inhibitors
Streptomyces avermitilis



Emamectin benzoate is semi-synthetic derivative so avermectins – same mode of action



Spinosad is composed of a mixture of spinosyns from an Actinomycete – targets the nicotinic acetylcholine receptor



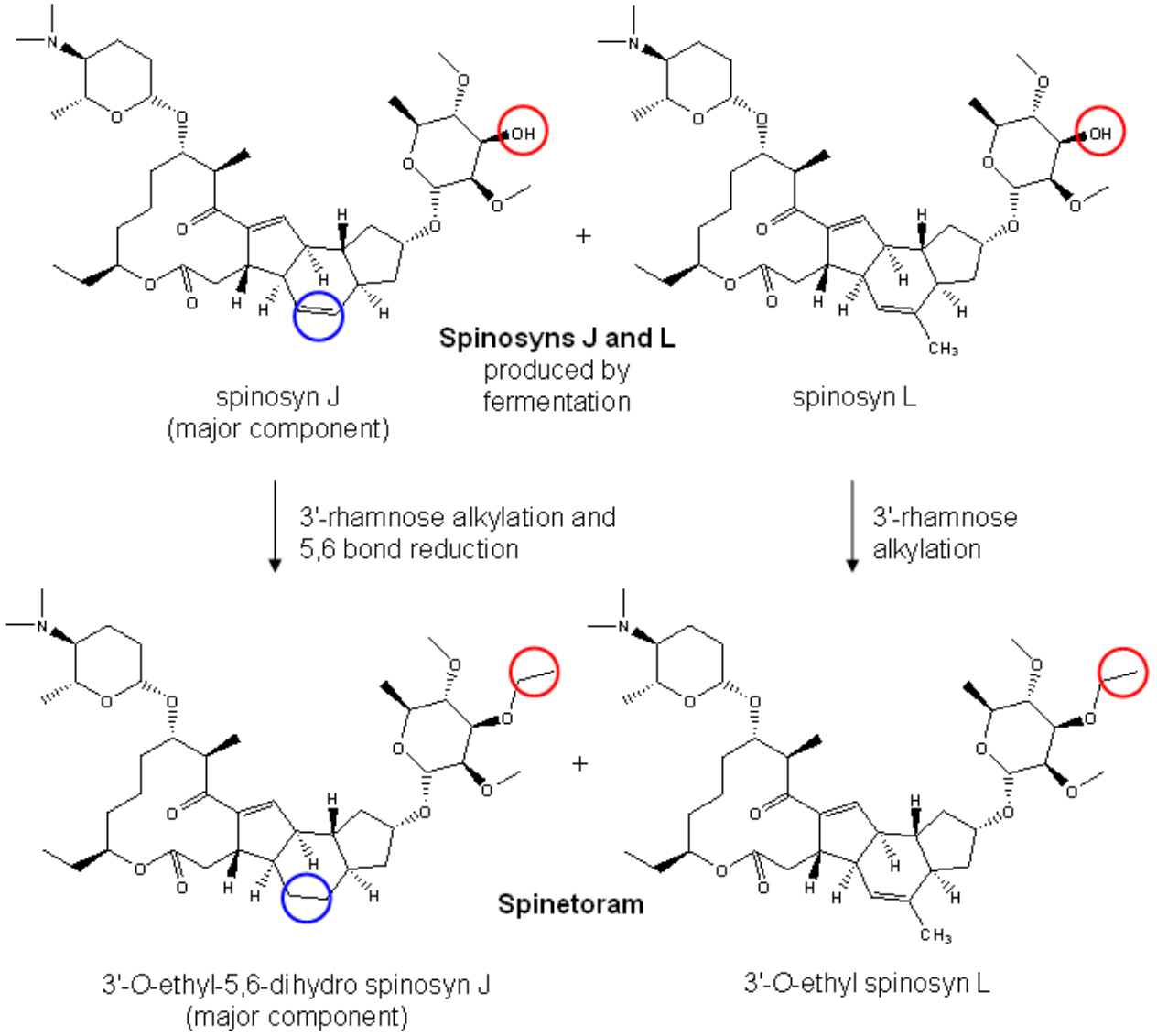
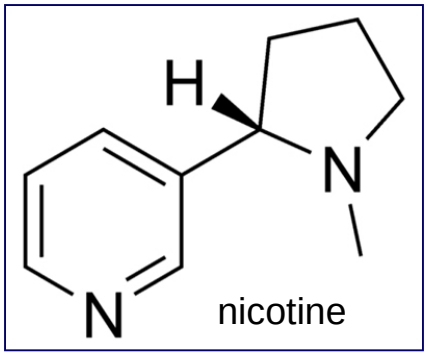
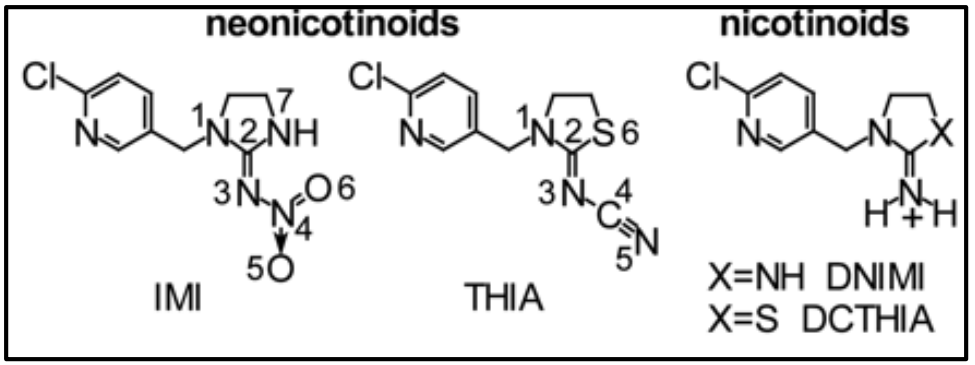


Image from *Plant Health Progress* article:
Spinetoram: How Artificial Intelligence Combined Natural Fermentation with Synthetic Chemistry to Produce a New Spinosyn Insecticide

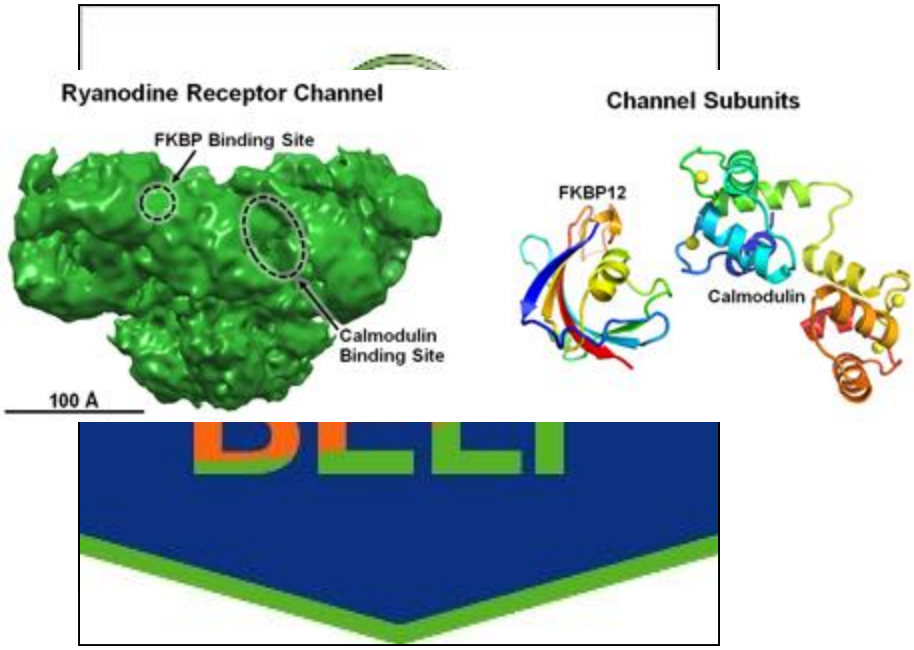
Neonicotinoids – nicotinic acetylcholine receptor



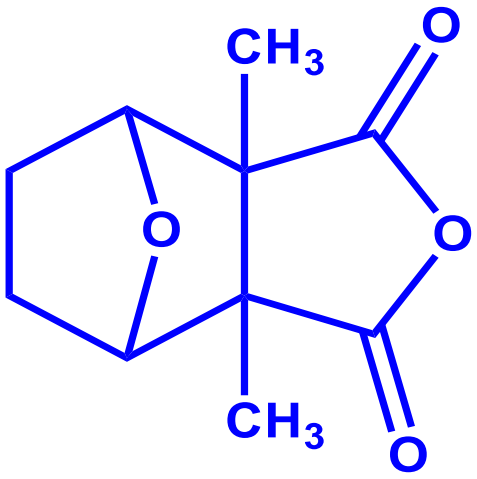


Natural products as clues to new modes of action

Ryania speciosa



flubendiamide



Cantharidin
"Spanish fly"

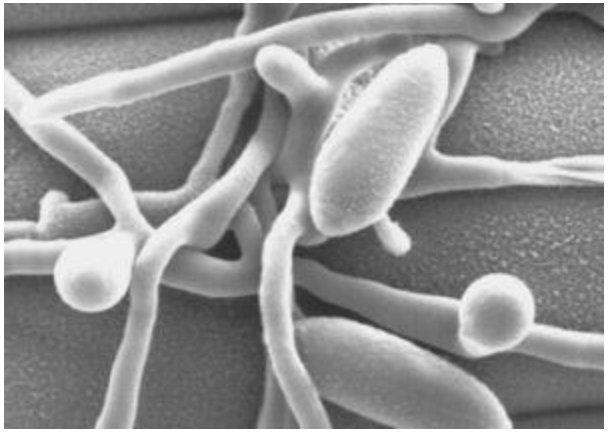
Rashid et al. *J. Econ. Entomol*. (2013) 106:2177-82.

Insecticides	LC_{50} (mg/cm^2)		
	Musca domestica	*Blatella germanica*	*Sitophilus oryzae*
Decaleside I	**0.033** (0.029–0.037)	**0.077** (0.067–0.088)	**0.044** (0.031–0.059)
Decaleside II	**0.023** (0.013–0.030)	**0.070** (0.06–0.078)	**0.032** (0.03–0.036)
Endosulfan	**0.036** (0.029–0.044)	**0.069** (0.053–0.076)	**0.031** (0.029–0.034)
Monocrotophos	**0.03** (0.027–0.039)	**0.112** (0.105–0.121)	**0.027** (0.023–0.032)
Deltamethrin	**0.029** (0.021–0.032)	**0.098** (0.088–0.107)	**0.02** (0.017–0.024)

Rajashekar et al. *Naturwissenschaten* (2012) 99: 832-852

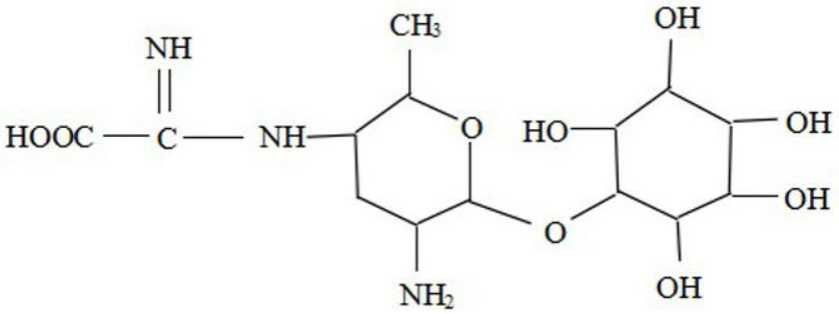
Targets tarsal gustatory sites

Fungicides

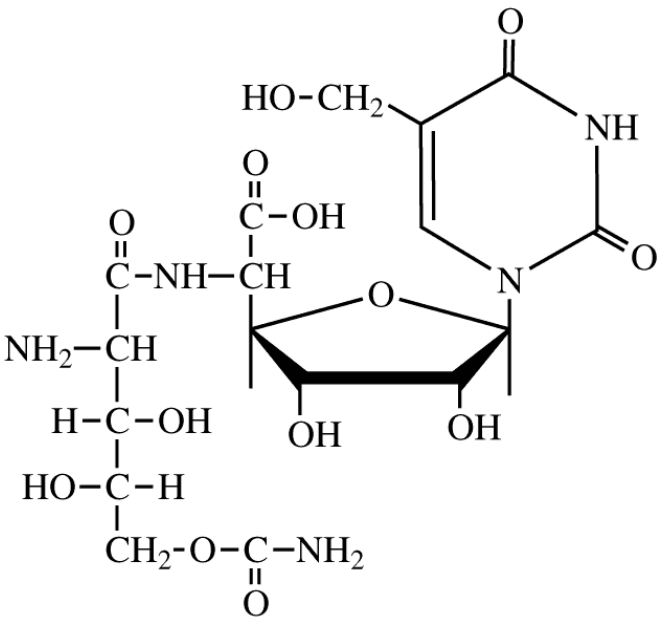


Kasugamycin

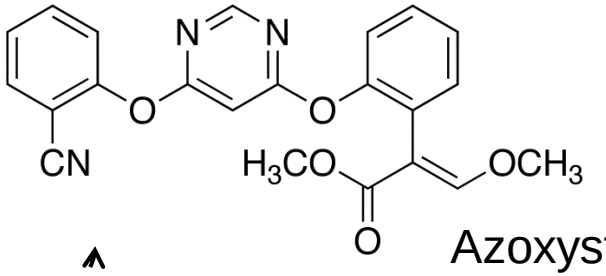
It inhibits protein synthesis



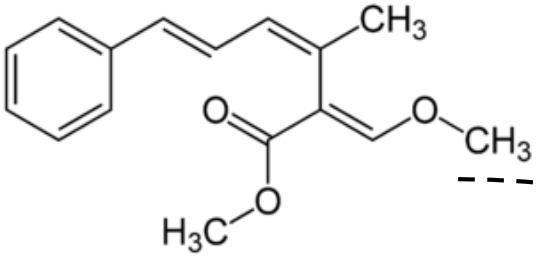
Polyoxin D
Chitin synthesis inhibitor



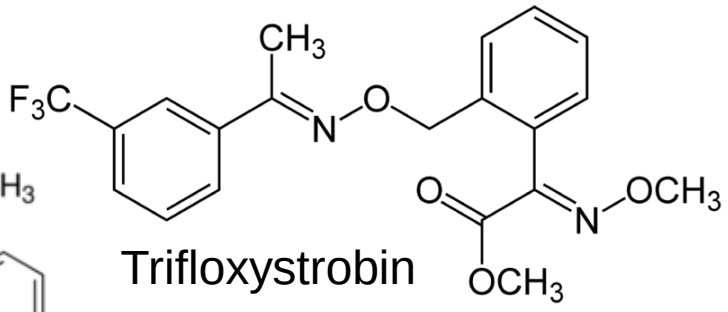
Strobilurins – 30% of commercial fungicides
Act at Q_o site of complex III of mitochondrial electron transport



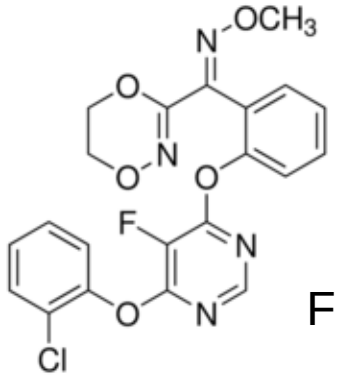
Azoxystrobin



Strobilurin A



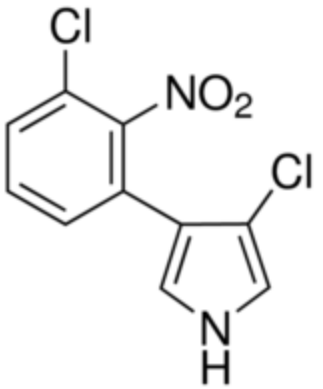
Trifloxystrobin



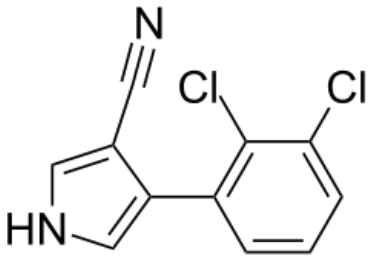
Fluoxastrobin

Phenypyrrole fungicides
Act on MAP/histidine kinase in osmotic signal transduction

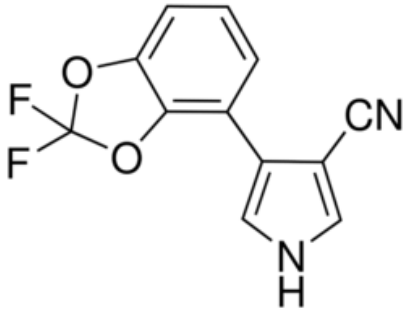
From *Pseudomonas* sp.



Pyrrolnitrin

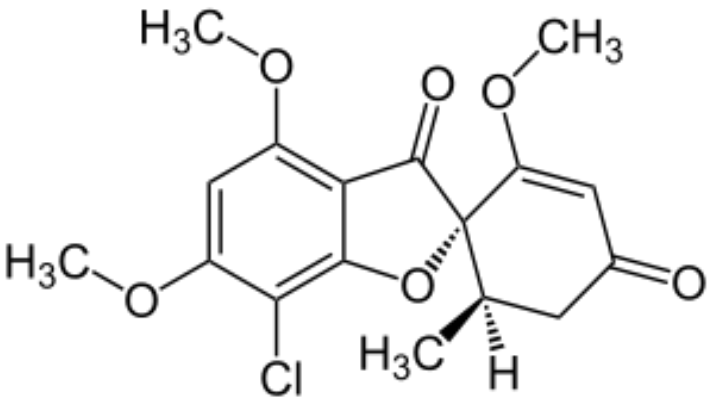


Fenpiclonil



Fludioxonil

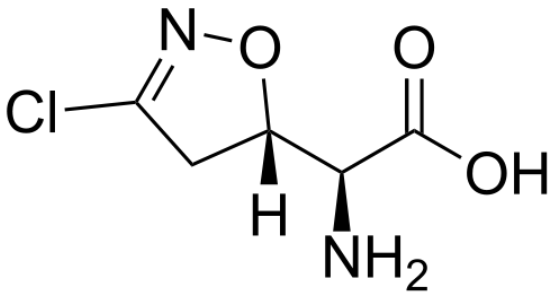
Natural product that could have led to β-tubulin-binding fungicides like benomyl



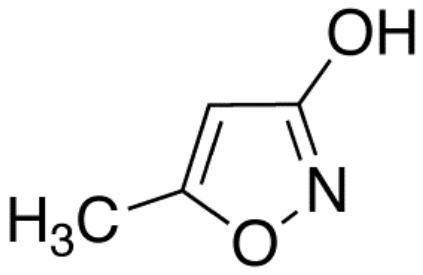
griseofulvin

Penicillium griseofulvin

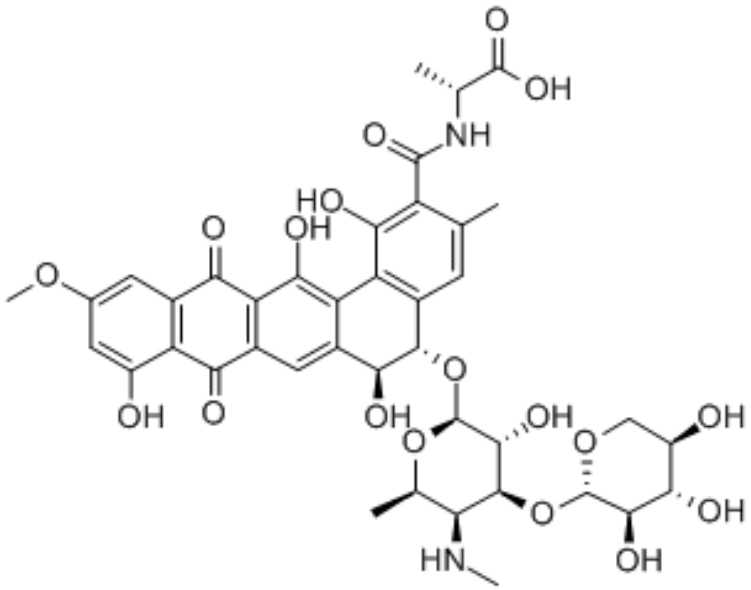
A DNA/RNA synthesis inhibitor that could have been the inspiration for hymexazol fungicide



Acividin
From *Streptomyces sviceus*



hymexazol



Antifungal through carbohydrate binding

Pradimicin A
From *Actinomadura hibisca*

Zilke and Hall, *Eur. J. Org. Chem*. (2012) 2012:4153-4163

Perspective

SCI

Received: 4 November 2013 Revised: 22 January 2014 Accepted article published: 29 January 2014 Published online in Wiley Online Library:

(wileyonlinelibrary.com) DOI 10.1002/ps.3744

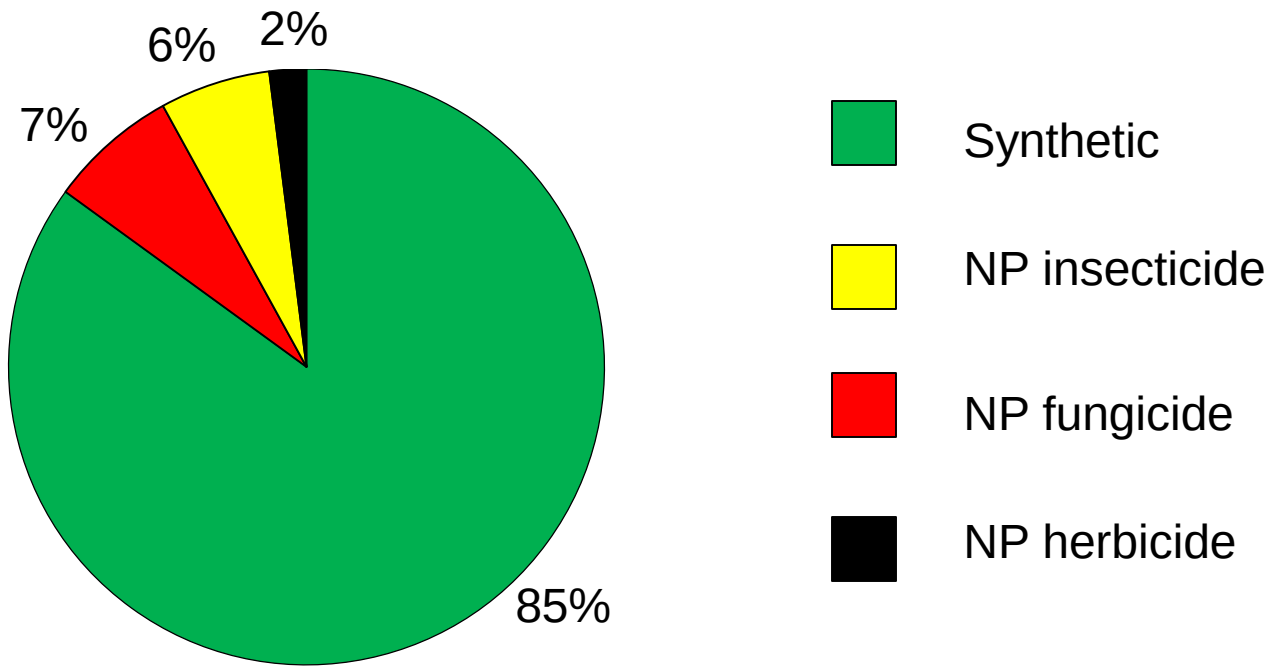
Natural products for pest control: an analysis of their role, value and future

B Clifford Gerwick* **and Thomas C Sparks**

Pest Management Science **2014**, *70*, 1169-1185.

- Natural compounds used directly – biochemical biopesticides
- Natural product-inspired synthetic pesticides
- Synthetic pesticides that could have been inspired by natural product mode of action and/or structure

Percentage of known commercial modes of action – (HRAC/IRAC/FRAC)



NP = natural products only

Natural products for pest control: an analysis of their role, value and future – Gerwick & Sparks

Pest Management Science
3 MAR 2014 DOI: 10.1002/ps.3744
http://onlinelibrary.wiley.com/doi/10.1002/ps.3744/full#ps3744-fig-0002

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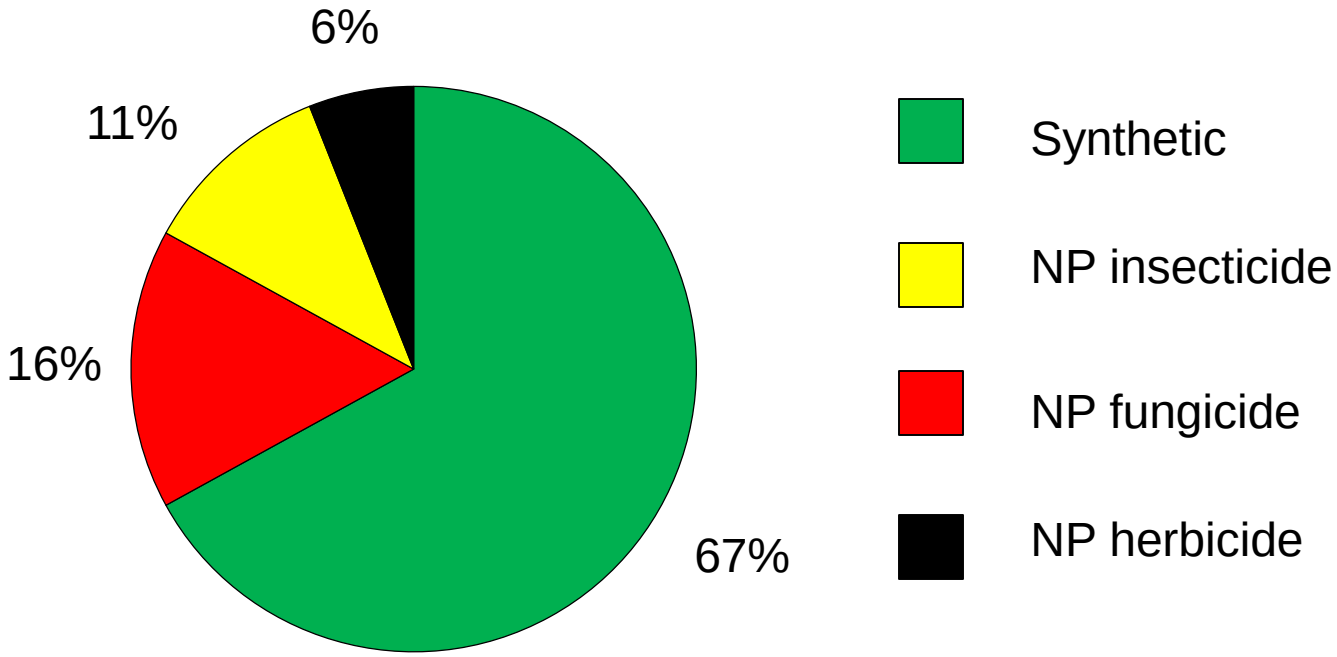

NP = natural products + natural product inspired

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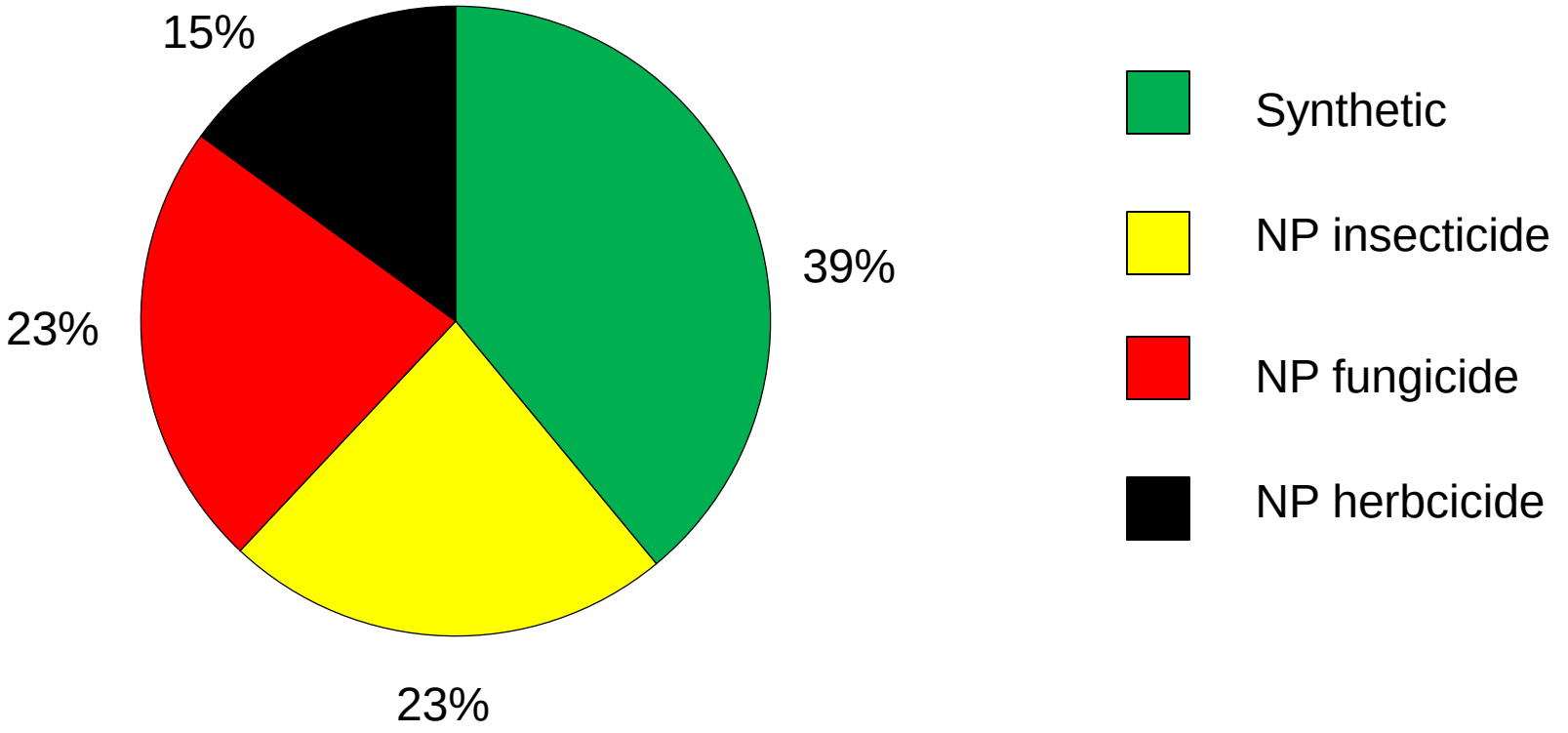

NP = natural products + natural product inspired + natural product model

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Some parting thoughts

- Natural compounds are still excellent sources of novel pesticide chemistries with new target sites
- Natural compounds can still inspire new pesticides chemistries with old or new target sites
- Natural compounds can lead to discovery of effective target sites for in vitro screening of effective inhibitors – both natural compound structure inspired and inhibitors with very different structures


THANK
YOU
FOR
LISTENING