第四届中国农药高层论坛

顺式构型：新烟碱杀虫剂创制的新尝试

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华东理工大学

北京, 2011年9月24日

怎样实现Me-Too到Me-Firt？

Me－Too是农药创制的利器！

- 创新药→me too药: me-too药引领创新药出现后的研究方向
- 1975-1994：1000多个新化学实体, 76%为me-too性创新;
- 仿制大国到创制强国，日本验证了新药研究十分成功的策略

农药创制四阶段（瓢和葫芦）：

初级阶段：依葫芦画葫芦　　发展阶段：依葫芦画瓢

高级阶段：依瓢画葫芦　　最高境界：无瓢画葫芦

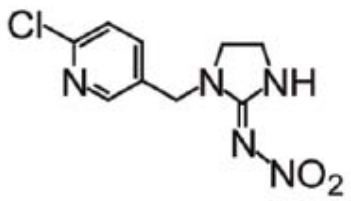
研究策略：

Me Too → Me Better → Me First ⇒ 新农药

三个方面：结构创新---活性创新-----机制创新

新烟碱杀虫剂概况

Shinzo Kagabu

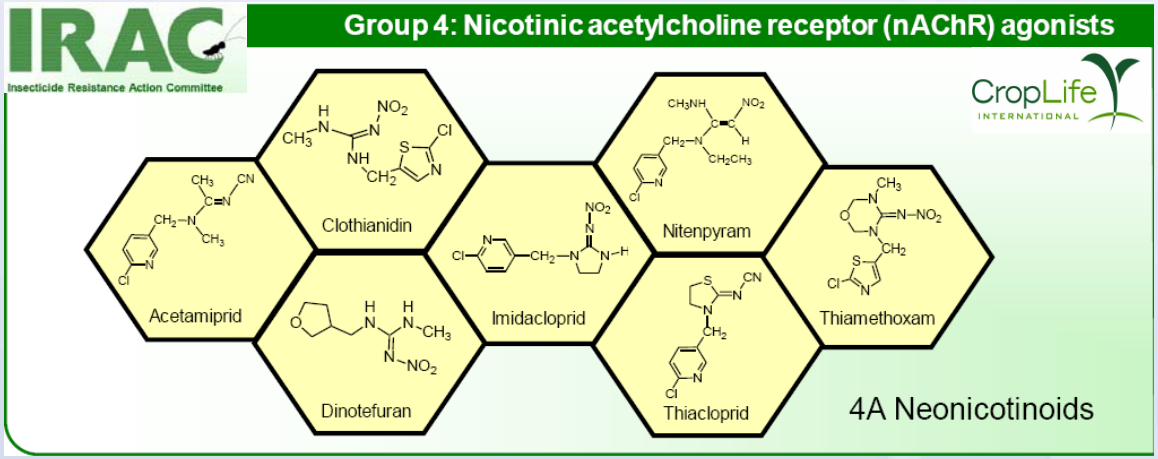


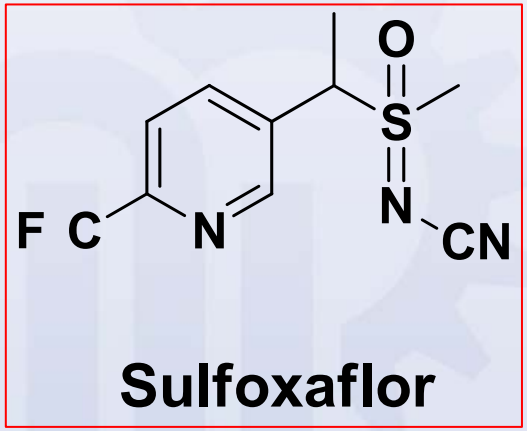
imidacloprid (1991)

新烟碱:

2009 年：全球26 亿美元
占23.7% 杀虫剂 市场

杀虫剂销售额前两位：
吡虫啉：（11亿美元）
噻虫嗪：（7亿美元）

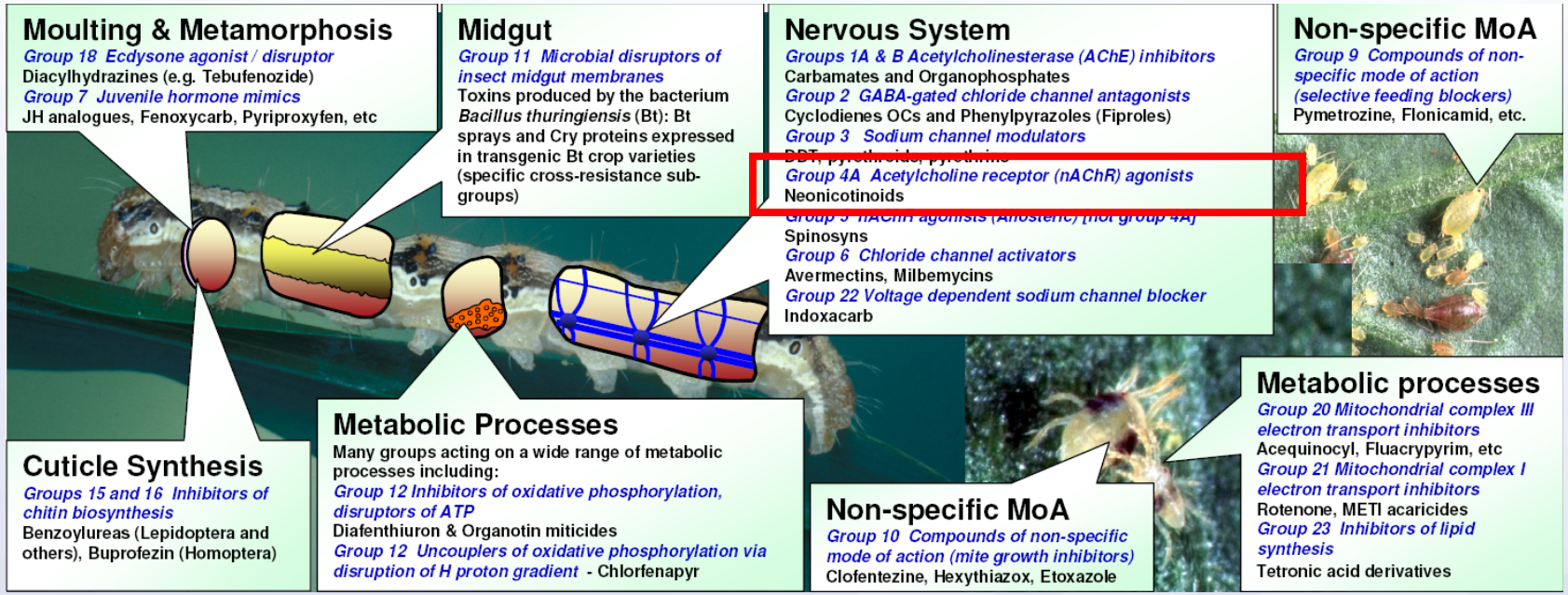




高效低毒、作用机制新颖、环境友好

2011年, 陶氏
未来5年： 4亿美元

新烟碱：nAChRs激动剂







新烟碱在中国

吡虫啉: 产能： 25000 吨;
产量t: 12500 吨; 占世界产量的2/3; 出口: 8000 吨

56 家生产企业：

啶虫脒: 产能： 20000吨;
产量: 800吨; 出口: 5000吨

29家生产企业

烯啶虫胺: 产量: 500吨; 11家生产企业；

噻虫啉: 4家生产企业；

噻虫嗪: 1家生产企业；

噻虫胺: 1家生产企业；

新烟碱发展的瓶颈（抗性和蜂毒）

抗性和交互抗性


今秋稻飞虱防控形势严峻

人民日报
2006-09-24

褐飞虱

烟粉虱


2006，居民区

2006，2007年中国褐飞虱对吡虫啉的抗性400倍！
粮食减产，几乎无药可治！造成严重社会恐慌！

蜜蜂毒性


美1/4蜜蜂神秘死亡 引发食物短缺担忧

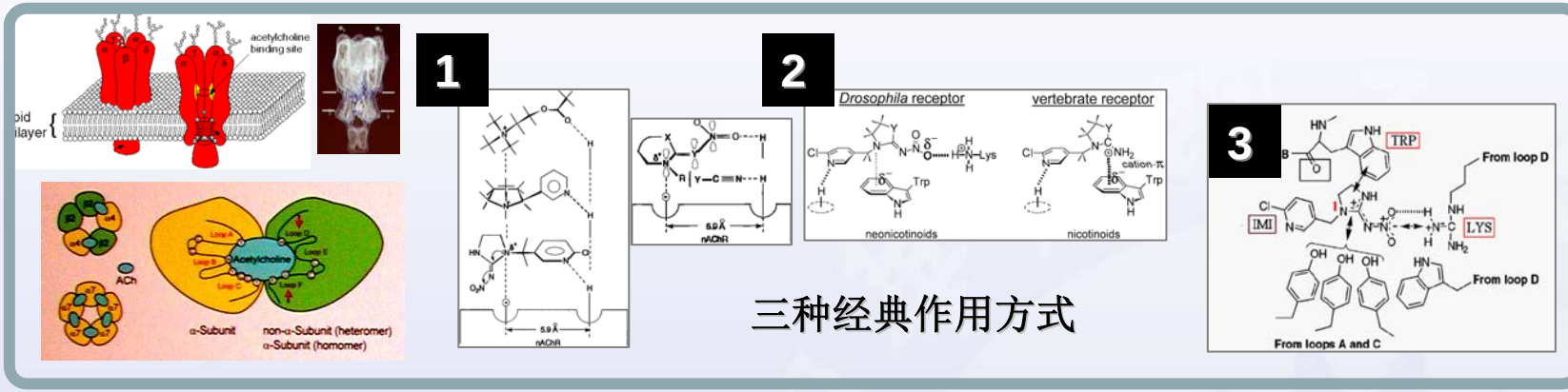
悪魔の新・農薬
Neonicotinoid
ネオニコチノイド
この神経毒が、もう食卓に出回っている！

中南欧、北美、日本均报道吡虫啉蜜蜂毒性，蜜蜂虫口降低25-40%

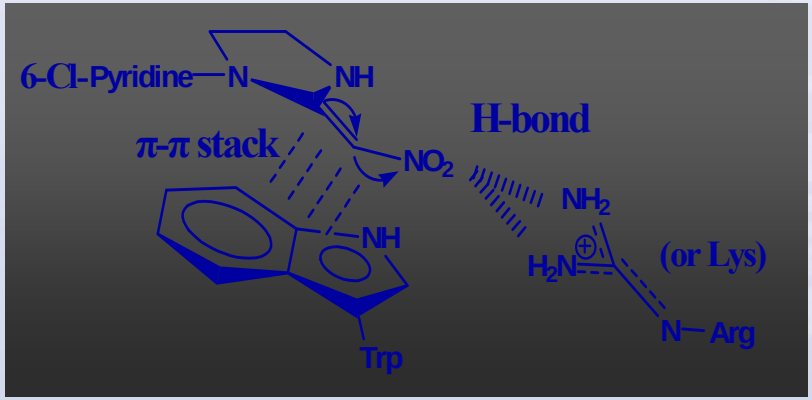
存在问题：抗性及峰毒问题的解决。 新先导和作用机制的发现

1. 新的作用机制研究及分子设计

新作用机制 — π-π 堆积作用

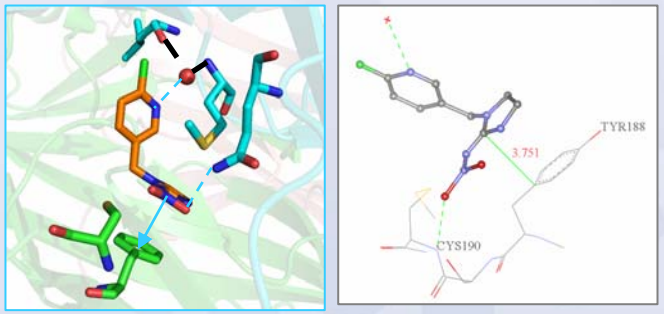


氢键诱导的π-π 堆积作用



Bioorg. Med. Chem., 2007, *15*, 2624

得到AChBP-IMI 复合物晶体结构的支持

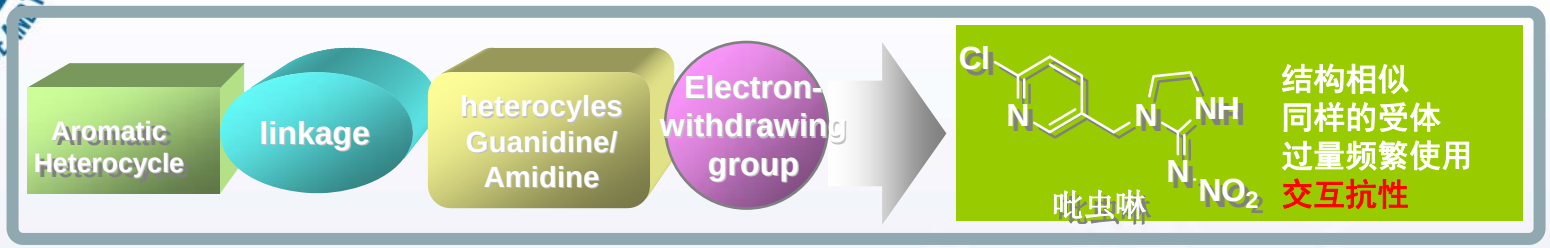


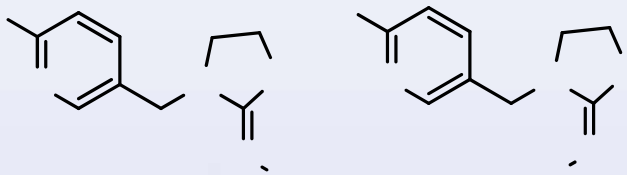
D. B. Sattelle *Invert Neurosci*, 2008, *8*, 71

J. E. Casida *PNAS*, 2008, *105*,7606

分子设计

一 新烟碱化合物的构型

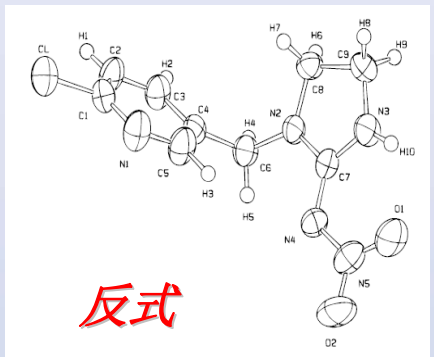




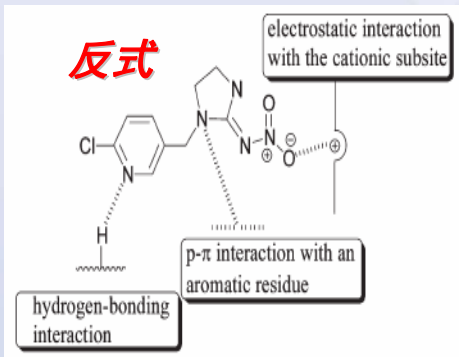
晶体结构 *反式*

量子化学 >99.99% *反式*

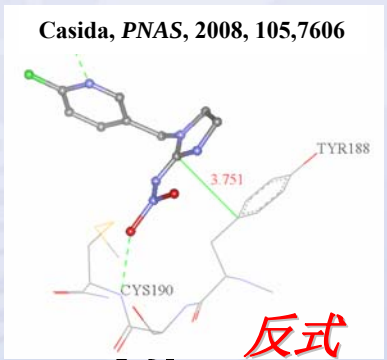
可能的作用模式 *反式*

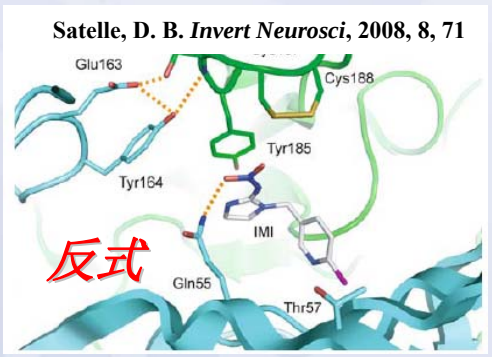


晶体结构



作用模式



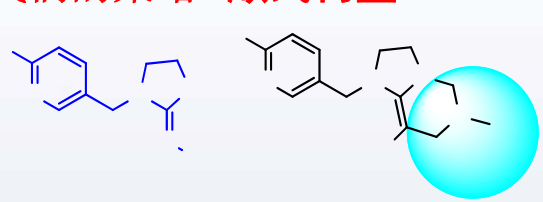


乙酰胆碱结合蛋白—吡虫啉复合物晶体结构

能否从顺式构型入手?

新烟碱的分子设计

我们的策略: **顺式构型**



JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

J. Agric. Food Chem. **2011,** *59*, 2943-2949 ARTICLE

pubs.acs.org/JAFC

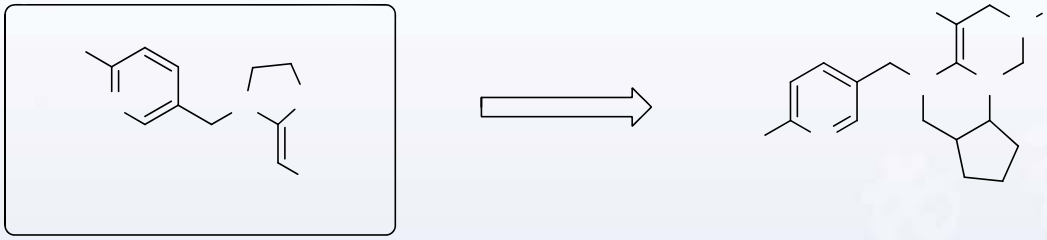
cis-Configuration: A New Tactic/Rationale for Neonicotinoid Molecular Design

Xusheng Shao,[‡] Philip W. Lee,[‡] Zewen Liu,[§] Xiaoyong Xu,[‡] Zhong Li,[*,‡] and Xuhong Qian[‡]

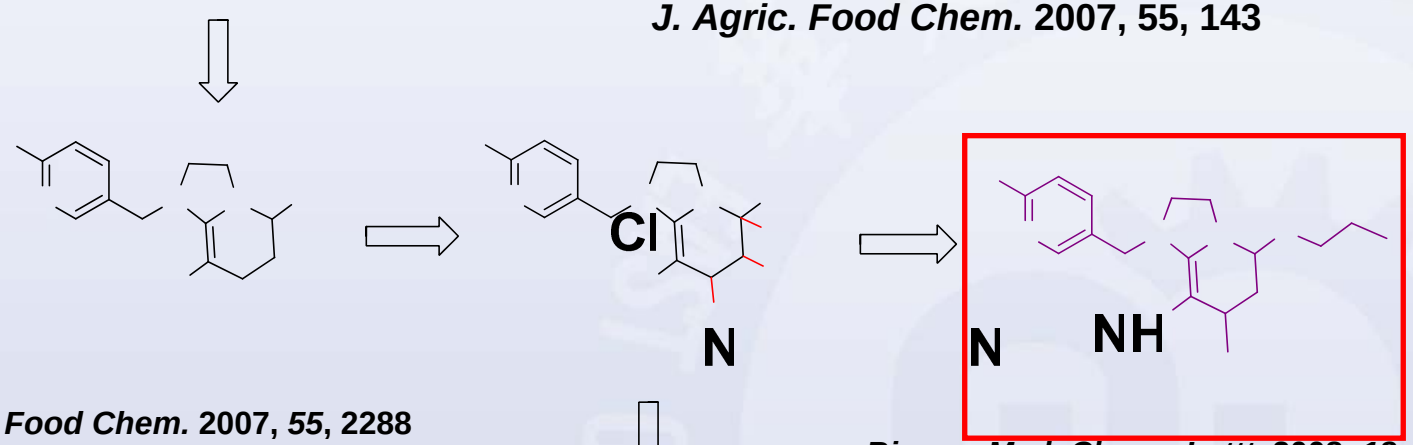
[‡]Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

我们在顺式新烟碱创制的综述

① 四氢吡啶固定顺式构型新烟碱化合物



J. Agric. Food Chem. 2007, 55, 143



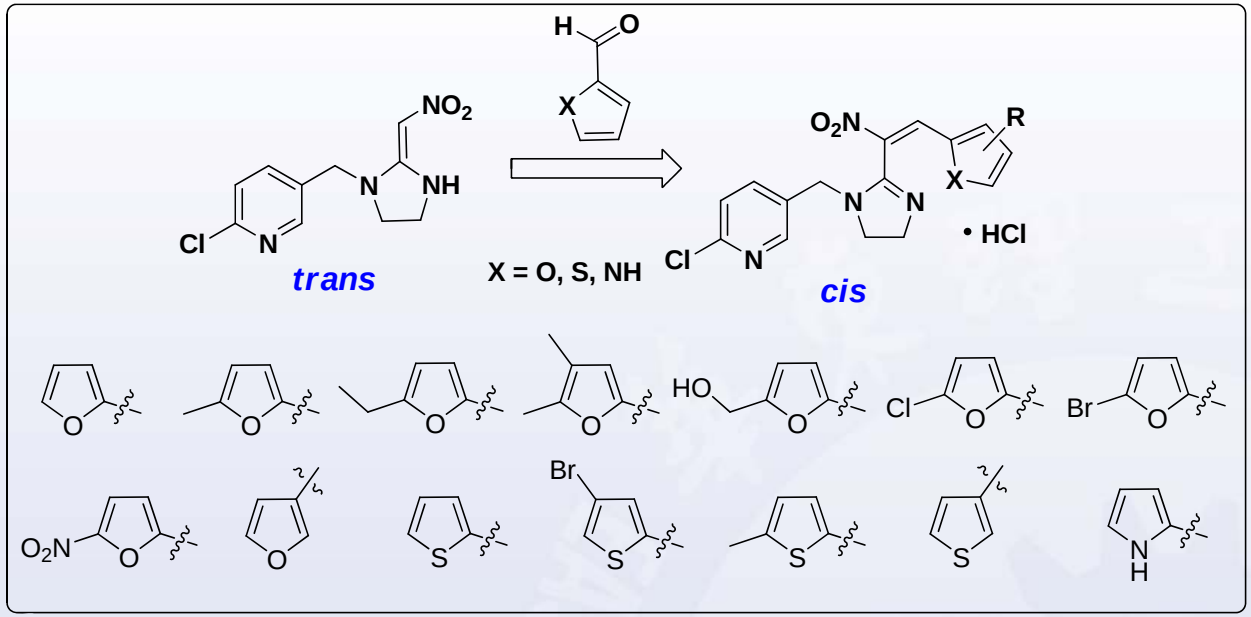
J. Agric. Food Chem. 2007, *55*, 2288
ZL 200410084457.1, WO05745204.7,
US11/751,836，EP1826209A1,
JP2007-541642

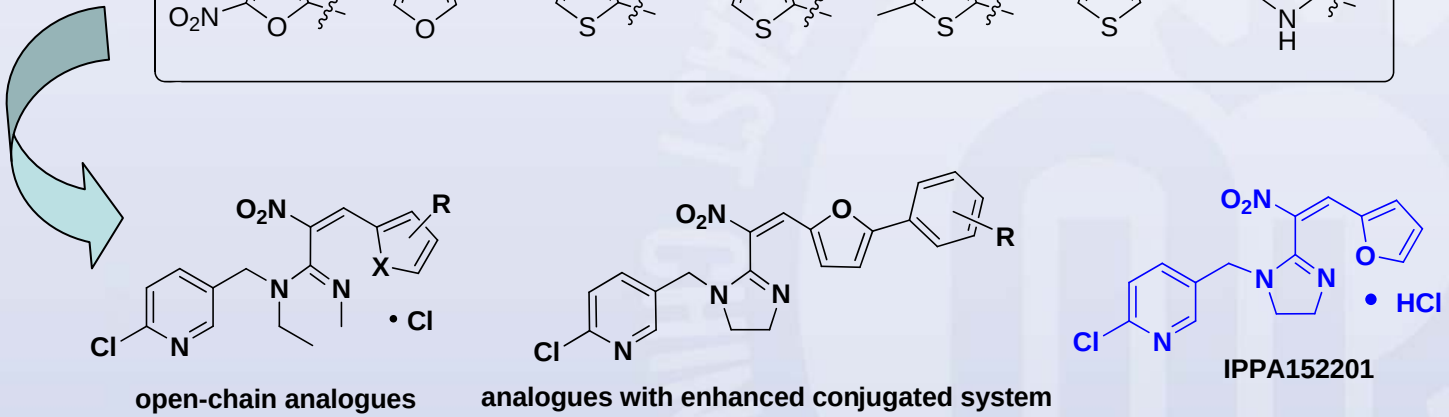
Bioorg. Med. Chem., Lettt. 2008, *18*, 6513-6516

CN101045728, WO2007101369A1,
EP1997820, US12/206,840

trans

② 大位阻基团固定顺式构型的新烟碱化合物

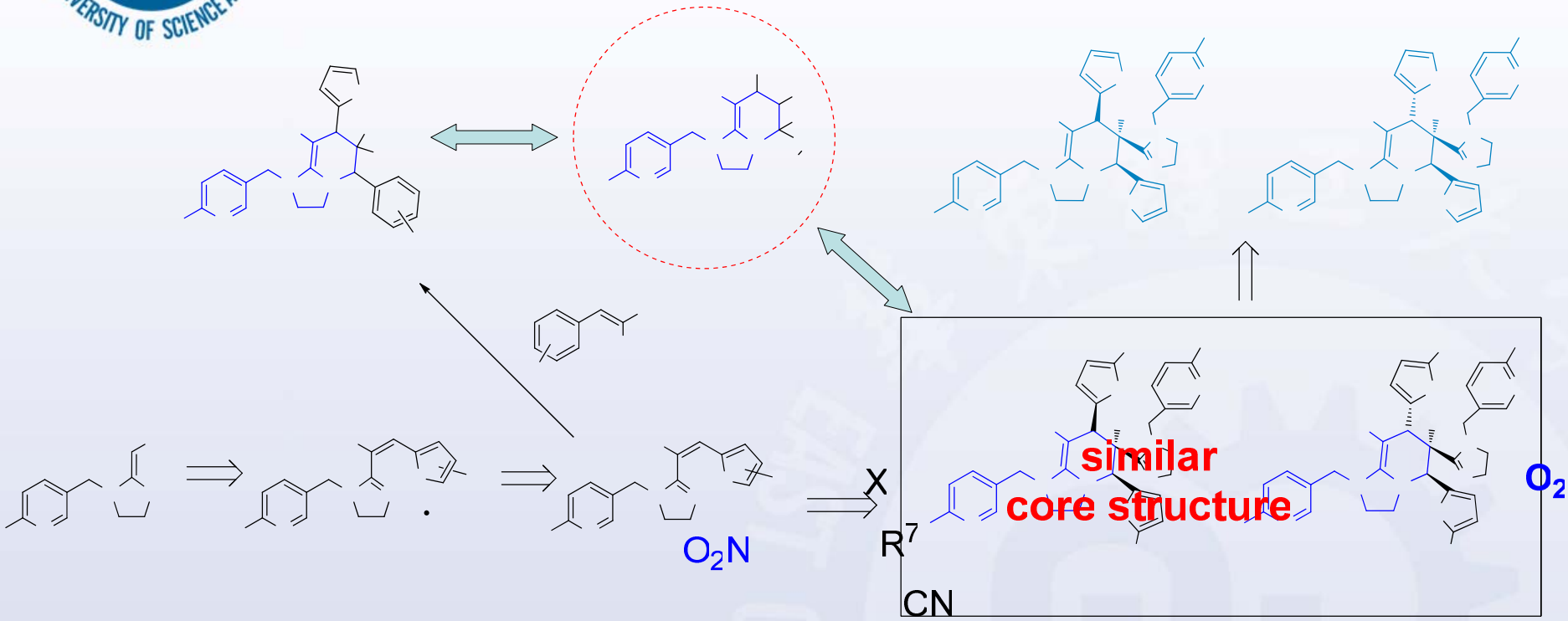




J. Agric. Food Chem. 2009, *57*, 951-957

WO 2009/094867; CN 200810032949; EP 2281812; AU 2008349040; US 12864410

③ DA反应构建的顺式构型新烟碱类似物

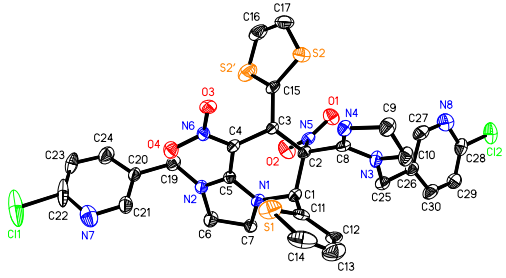


J. Agric. Food Chem. 2010, *58*, 2690–2695
J. Agric. Food Chem. **2010,** *58*, 6296–6299
WO2010/124619 A1
CN200910050137.7

cis

R^7 = CN, COOEt, NO

IPPA152311



R^1

O_2N

N N

N

cis

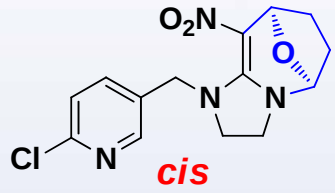
CN

R^7

sir
core s

④ 氧桥杂环固定顺式构型的新烟碱杀虫剂

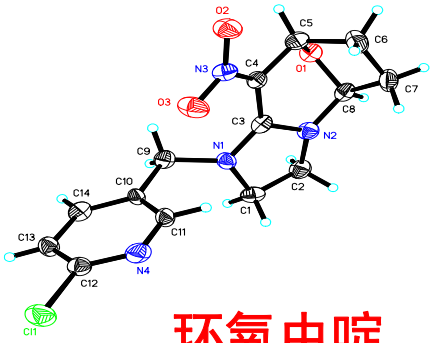
高活性



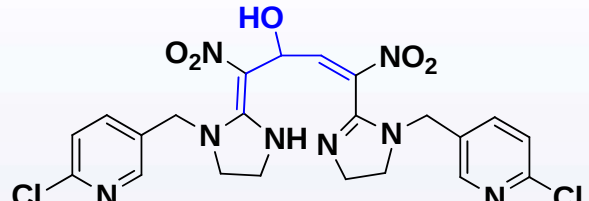
cis

Cowpea aphis: LC_{50} = 0.00471 ppm
Armyworm: LC_{50} = 0.03873 ppm

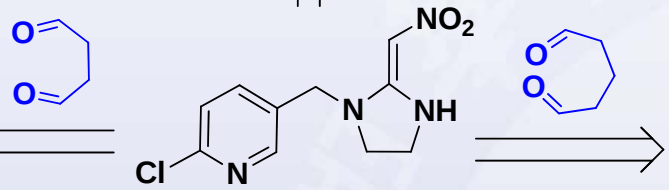
Brown planthopper
resistant: LC_{50} = 0.4925 ng/pest
sensitie: LC_{50} = 0.0742 ng/pest



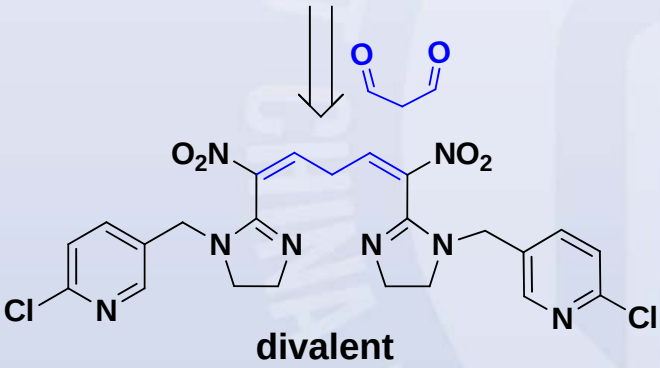
环氧虫啶



divalent

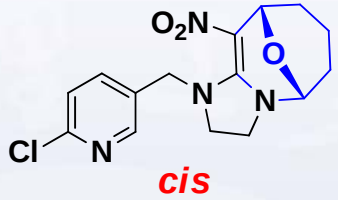


6-Cl-PMNI *trans*



divalent

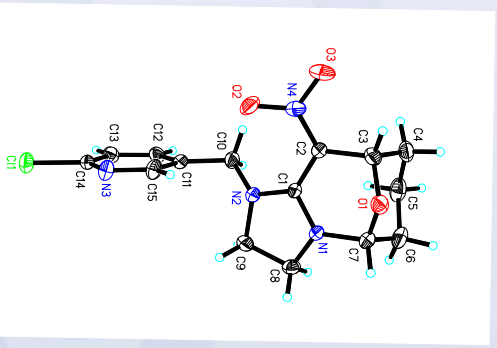
低活性



cis

Cowpea aphis:
87% mortality at 500 mgl/L
Armyworm: no activity

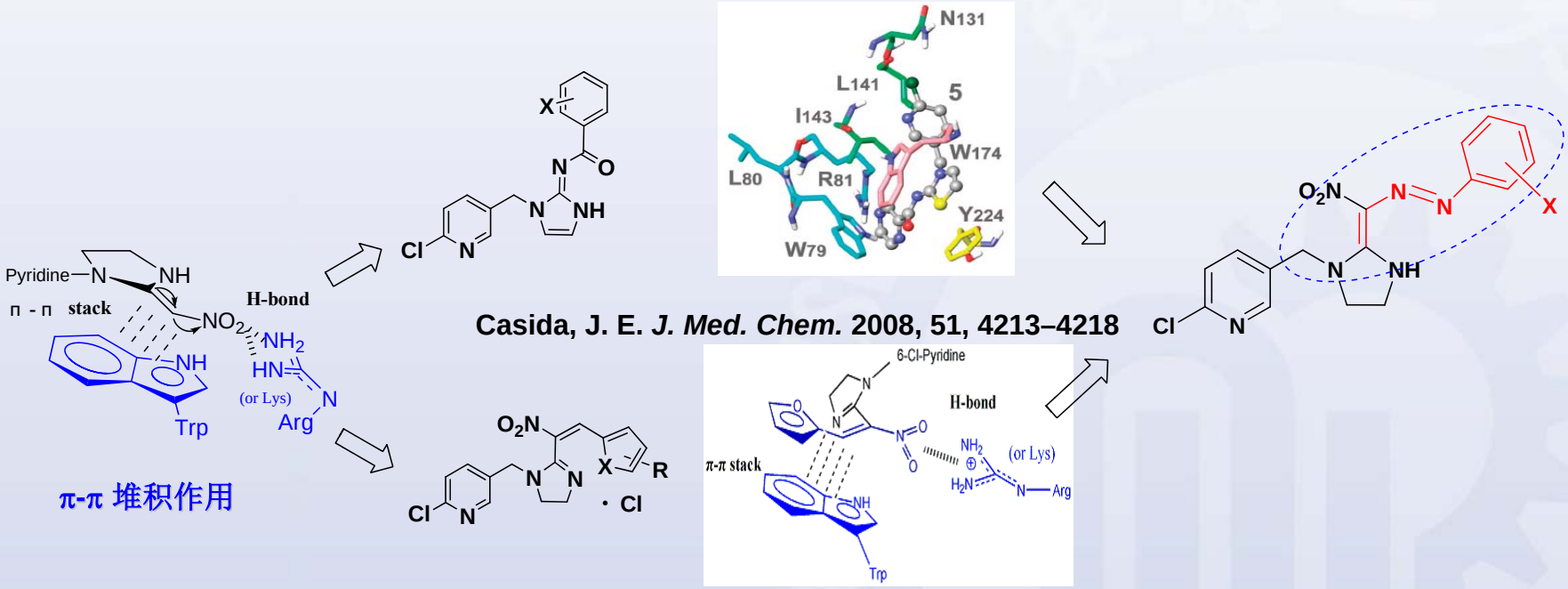
Brown planthopper
resistant: LC_{50} = 18.9795 ng/pest
sensitie: LC_{50} = 4.1440 ng/pest



J. Agric. Food Chem. 2010, *58*, 2696–2702
WO2011069456; CN102093389; WO2010/069266; CN101747320

其它相关研究

① 偶氮新烟碱—增强π-π 堆积作用

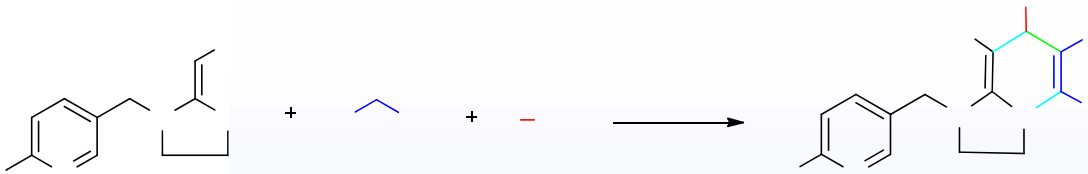


π-π 堆积作用

Casida, J. E. *J. Med. Chem.* 2008, 51, 4213–4218

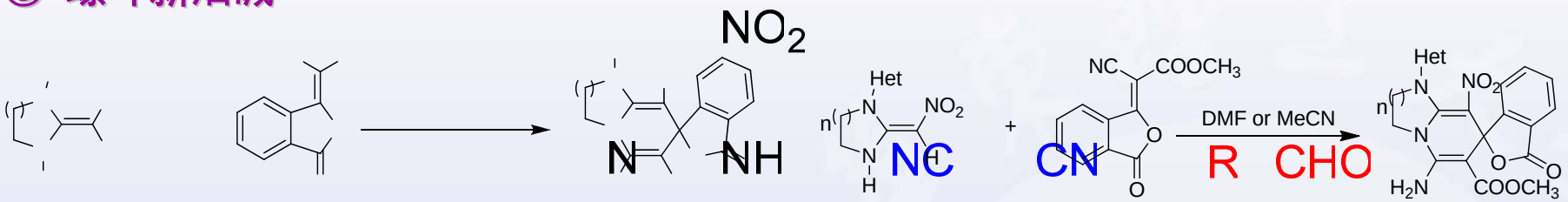
Zhong Li *J. Agric. Food Chem.*, 2009, *57*: 951–957.

② 二氢吡啶固定顺式构型的新烟碱杀虫剂

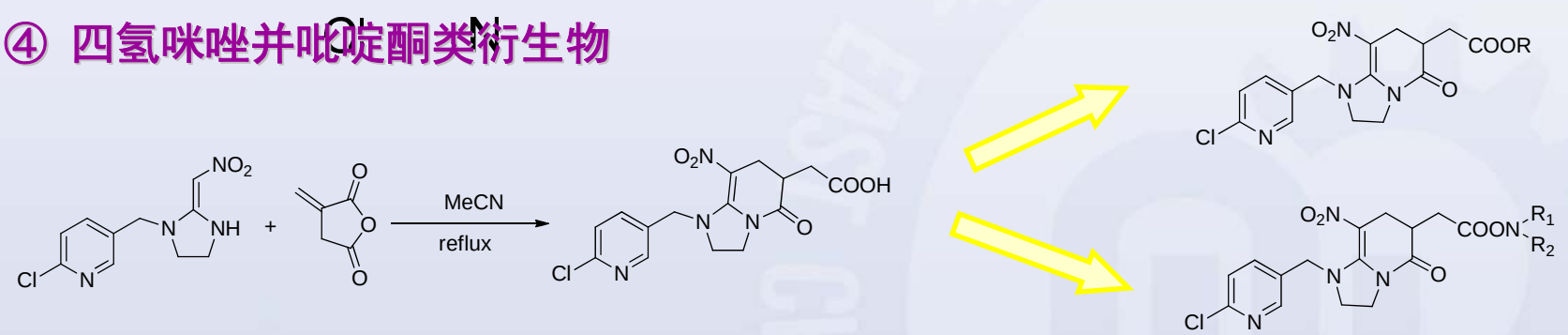


J. Agric. Food Chem.
2010, *58*, 2741-2745

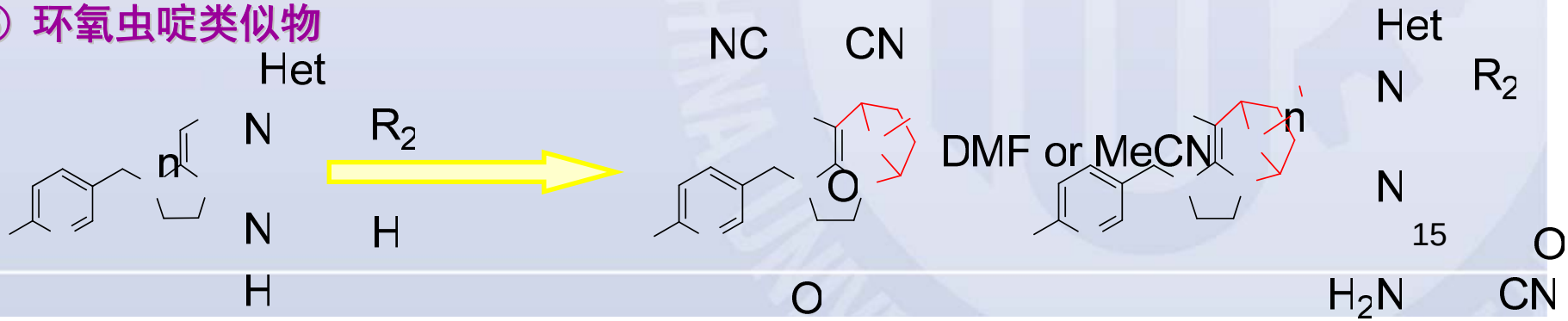
③ 螺环新烟碱



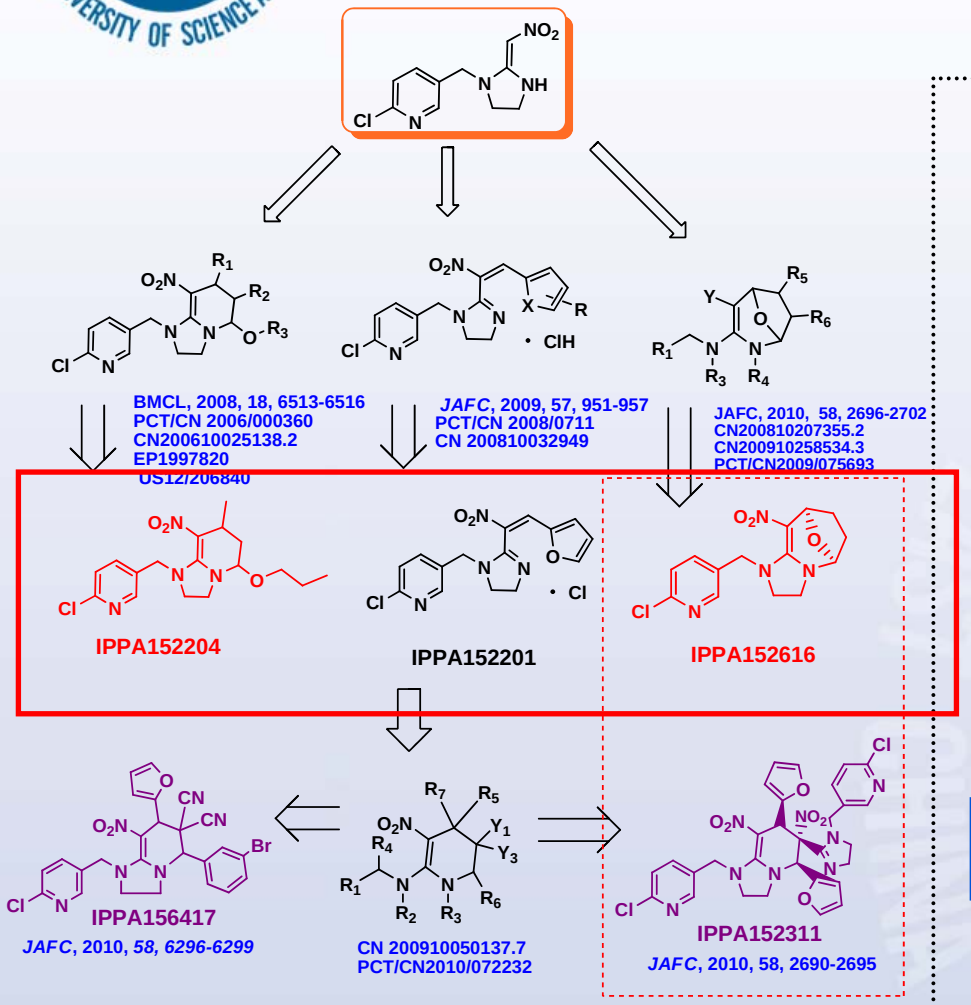
④ 四氢咪唑并吡啶酮类衍生物



⑤ 环氧虫啶类似物



2. 活性多样性及具有商品化前景的化合物



国际上首次系统的进行顺硝烯类新烟碱杀虫剂的创制研究，发现了多个系列高活性化合物。

代表性成果

商品化杀虫剂：哌虫啶

专利使用权转让给江苏克胜基团
2011年上市，克胜三大支柱品种之一

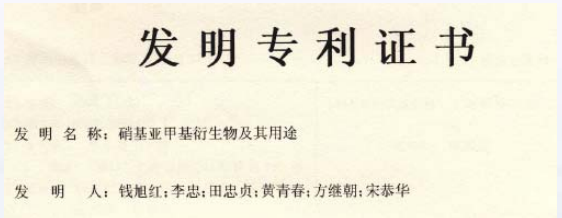
潜在兽药： IPPA152201

对羊、兔的绦虫和球虫的驱虫活性，
现与兰州兽医研究所合作开发

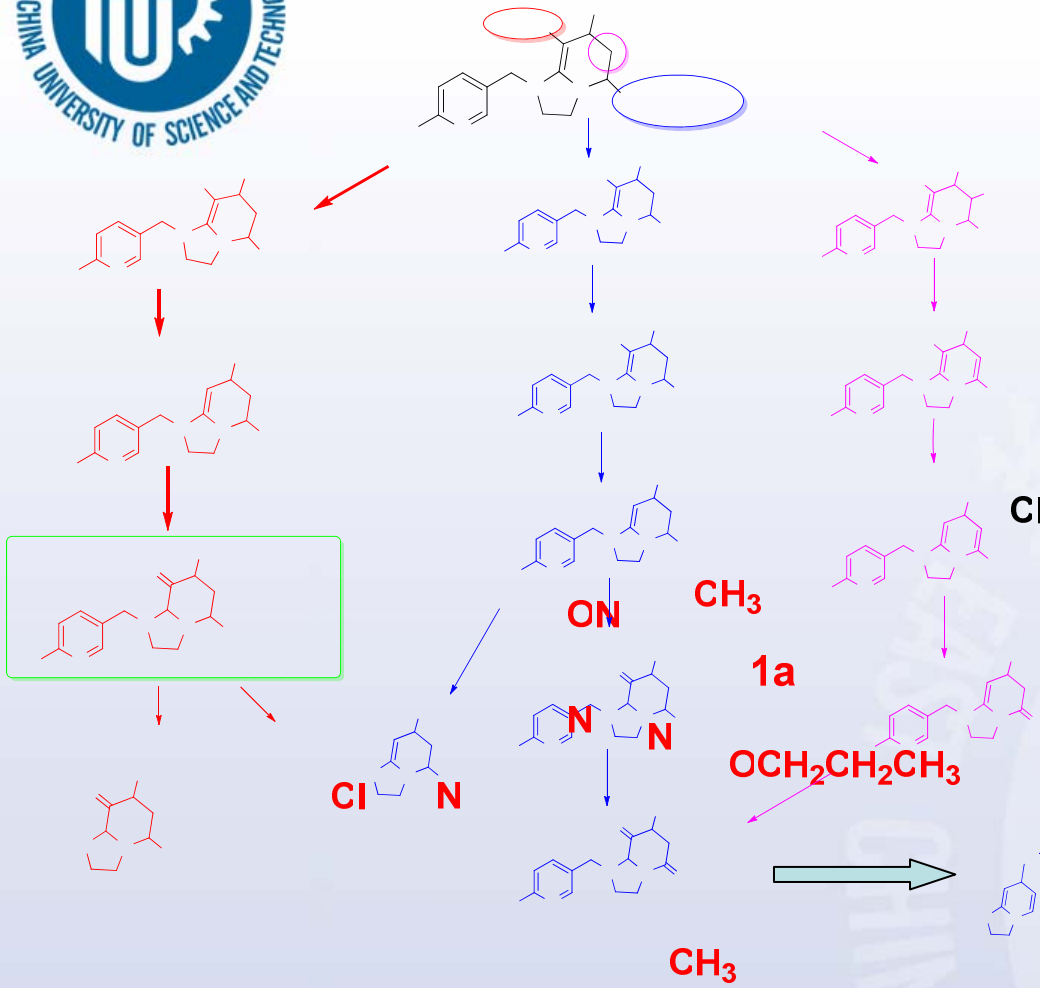
首例拮抗剂： 环氧虫啶

国际上首例具有超高活性的nAChRs拮抗剂
专利转让给上海生农生化制品有限公司

① Paichongding, 哌虫啶®



哌虫啶的光降解途径推测

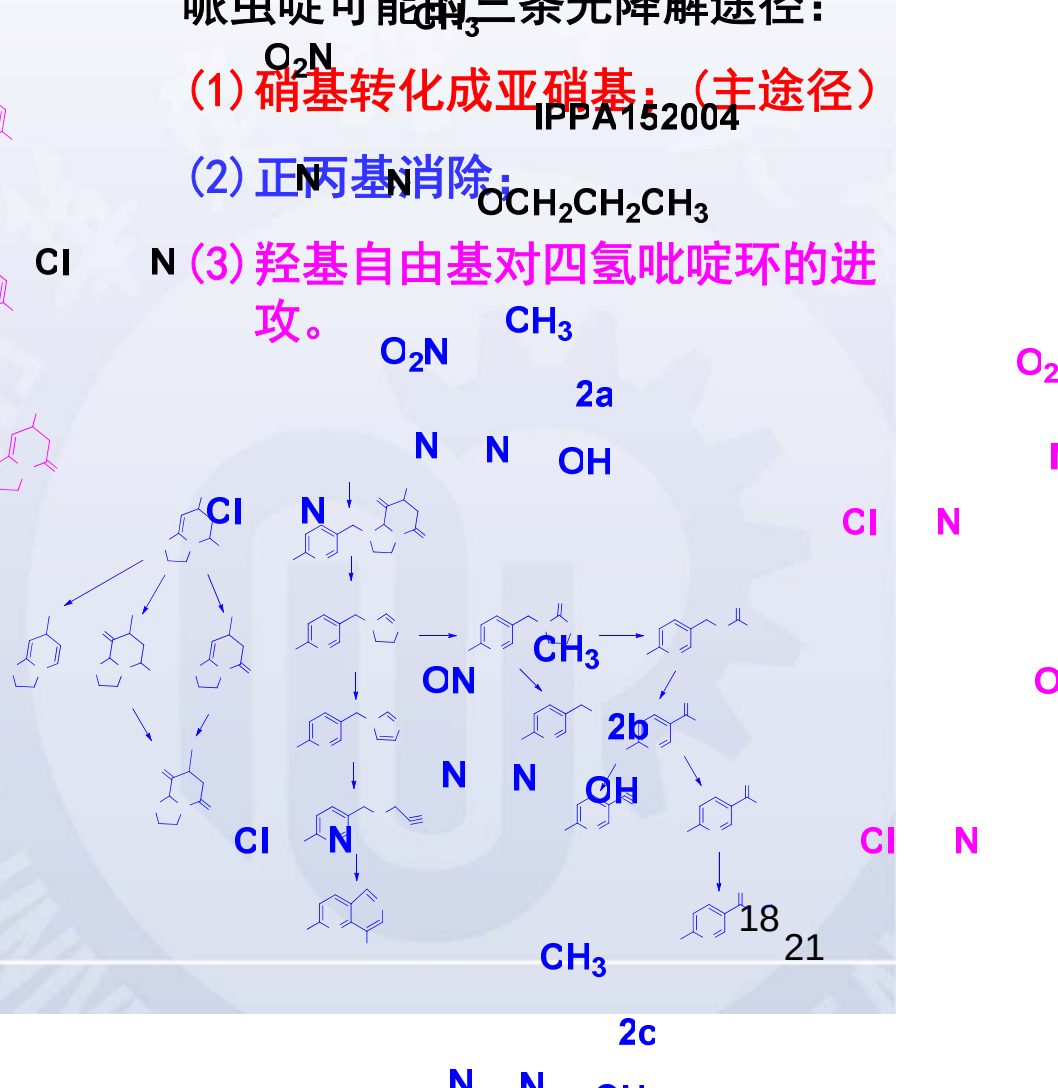


哌虫啶可能的三条光降解途径：

(1) 硝基转化成亚硝基；（主途径）

(2) 正丙基消除；

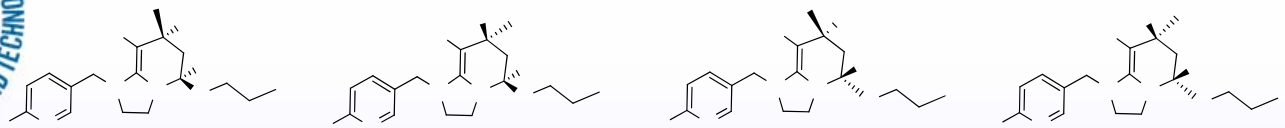
(3) 羟基自由基对四氢吡啶环的进攻。



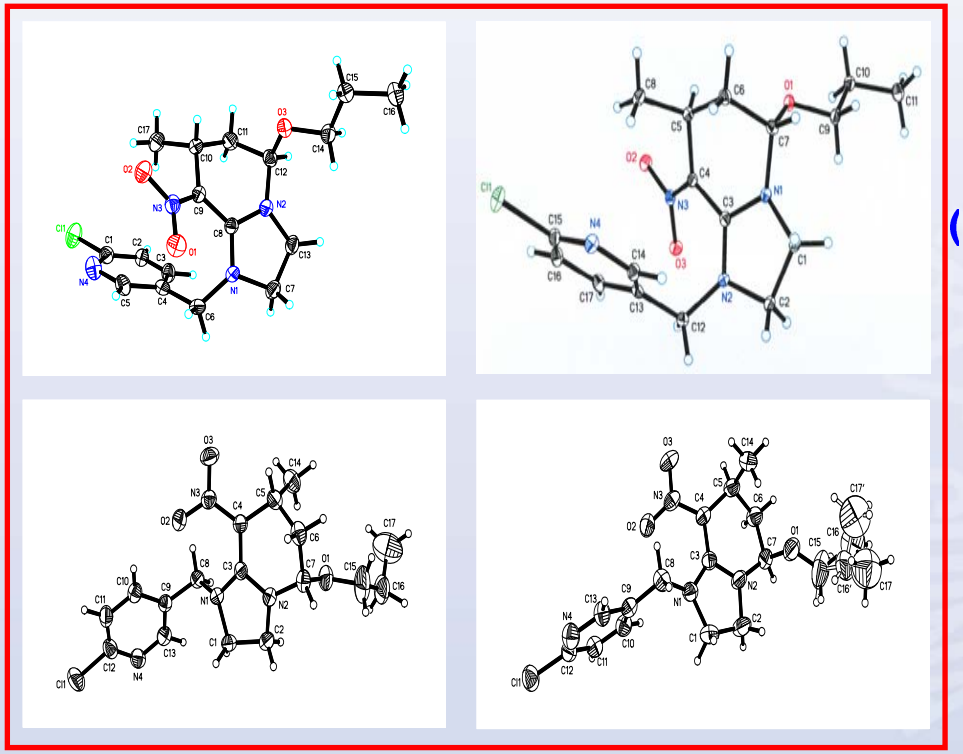
X. Y. Xu，*J. Agric. Food Chem*. 2010, 58:2746

为后期的环境代谢途径研究奠定基础！

光学异构体的拆分

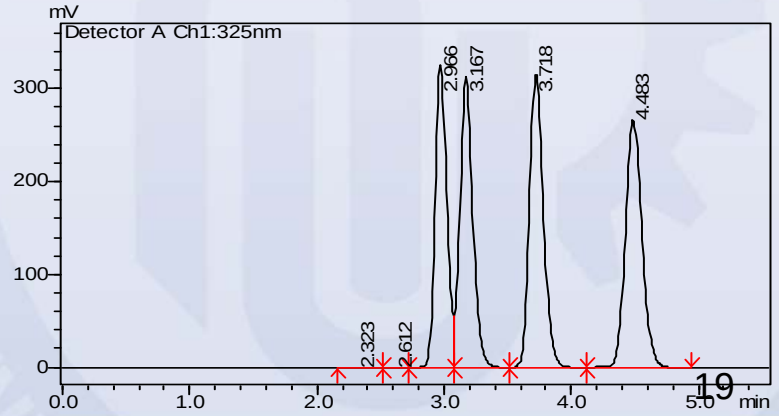


哌虫啶四个异构体的晶体结构

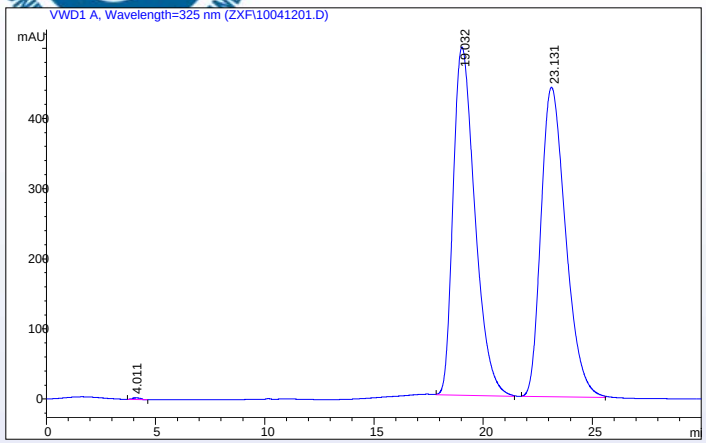


哌虫啶四个异构体活性有差异

compound	LC_{50}（mg/L）	95% confidential level
Peak1	288.139	246.395 -340.344
Peak2	50.090	42.460 - 59.330
Peak3	57.183	28.443 - 266.272
Peak4	14.364	9.679 - 21.455
SH01	21.518	15.843 - 28.277
imidacloprid	0.893	0.710 - 1.110



哌虫啶差向构体的拆分



哌虫啶四个异构体
（P1，P2，P3，P4）

混合溶剂A+B

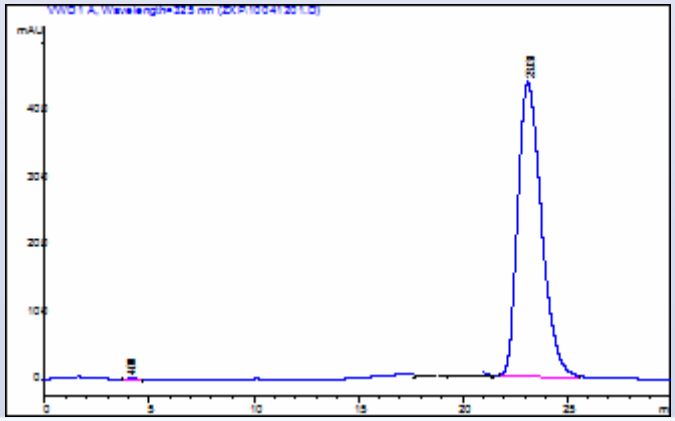
P3和P4析出

母液

哌虫啶P3和P4

哌虫啶
P1,P2,P3,P4

得到高活性
的差向异构体



P3和P4析出

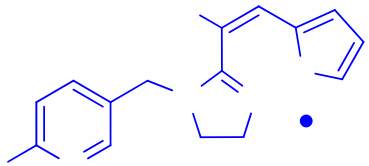
母液

溶剂C+试剂D
+试剂E回流

混合溶剂A+B

哌虫啶四个异构体
（1：1：1：1）

② IPPA152201



褐飞虱（ ***Nilaparvata lugens*** ）：

南京农大 刘泽文

Toxicity of different neonicotinoids against susceptible (Sus) and resistant (Res) strains of *N. lugens*.

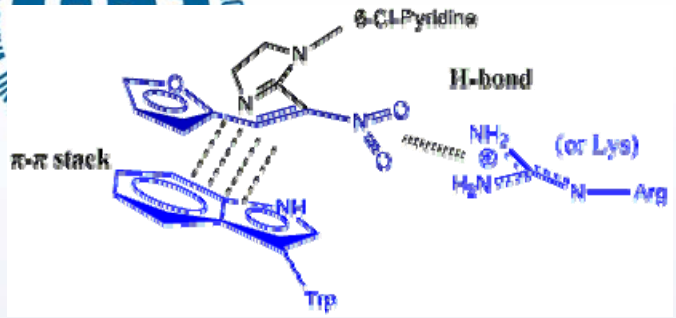
Strain	Neonicotinoids	Insect number	Slope ± SE	LD_{50} (95% FL) (ng/pest)	Relative toxicity[a]	RR factor[b]
Sus	Imidacloprid	103	3.232 ± 0.271	0.151 (0.122–0.186)	1.00	1.00
	Clothianidin	88	2.673 ± 0.351	0.240 (0.207–0.279)	1.59	1.00
	IPPA152201	117	1.833 ± 0.226	0.121 (0.093–0.162)	0.80	1.00
Res	Imidacloprid	85	1.793 ± 0.368	22.161 (14.585–36.227)	1.00	146.8
	Clothianidin	105	1.427 ± 0.276	5.664 (4.952–7.139)	0.26	23.6
	IPPA152201	124	1.560 ± 0.325	0.731 (0.486–1.052)	0.03	6.1

日本大冢公司

compound	浓度 μg/头	抗性品系	敏感品系
环氧虫啶	LD_{50}	0.007	0.000039
	R/S	18	1
吡虫啉	LD_{50}	0.071	0.000055
	R/S	1291	1

没有或低的交互抗性！

IPPA152201



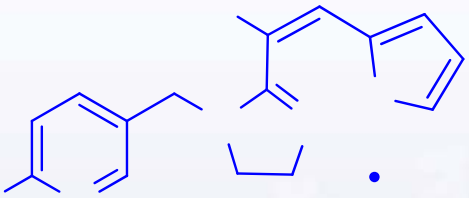
Laodelphasx striatellus	IPPA152201: 2.66 mgL^{-1} Imidacloprid:12.7 mgL^{-1}
Aphis craccivora	IPPA152201 ： 1.37 mgL^{-1}
P. separate Walker	IPPA152201 ： 9.09 mgL^{-1}
Plutella xylostella	IPPA152201： 26.03 mgL^{-1}
Nephotettix bipunctatus	IPPA152201： 0.48 mgL^{-1} Imidacloprid： 5.32 mgL^{-1} (48h)
Aphis Fabae	IPPA152201： 5.15 mgL^{-1} Imidacloprid： 21.88 mgL^{-1} (24h)

日本大冢

compound	LC50(ppm)								LD50(μg/g)	
	Common cutworm	Diamondback moth	Green peach aphid	Two-spotted spider mite Adult	Two-spotted spider mite egg	Brown winged green bug	Western flower thrips	Silver leaf whitefly	Brown rice planthopper sensitive	Brown rice planthopper resistance
IPPA152201	19.8	26.6	0.18	>500	>500	2.3	26.5	12.1	0.018	0.28
									R/S= 16	
Imidacloprid		14.6	0.2				56.1		0.025	28.8
									R/S= 1152	

对半翅目、鳞翅目和抗性品系害虫活性都有提升 ！

潜在兽药



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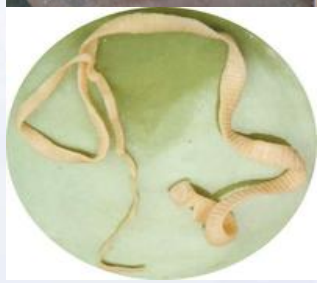
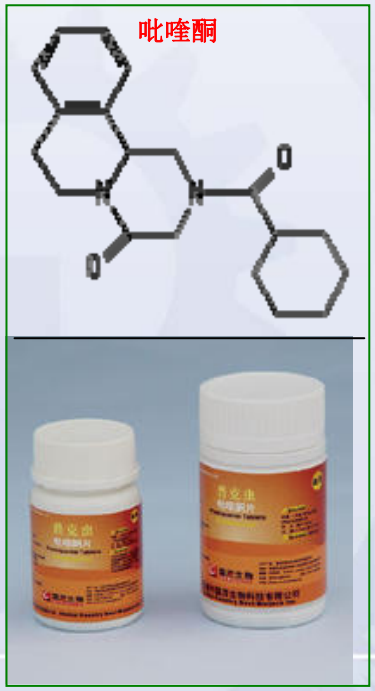


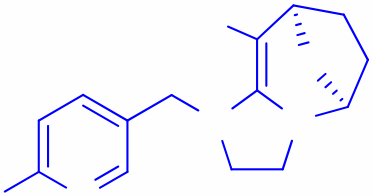
IPPA152201 无论注射还是口服对羊球虫和绦虫都有很高的活性

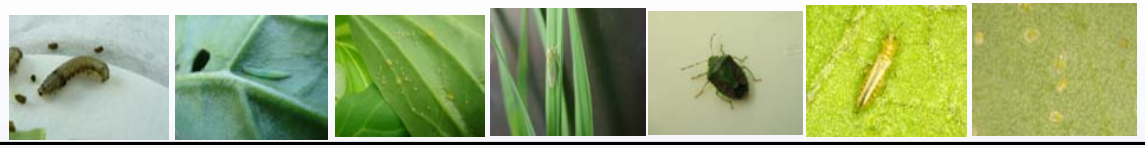
合作伙伴: 兰州兽医研究所



Cl

③ Cycloxaprid-环氧虫啶®





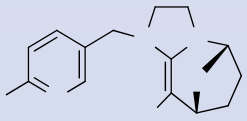
Compound	LC_{50}(ppm)								LD_{50}(μg/g)	
	Common cutworm	Diamondback moth	Green peach aphid	Green rice leafhopper	Brownwinged green bug	Western flower thrips	Sweetpotate whitefly Biotype-B	Sweetpotate whitefly Biotype-Q	Brown planthopper Susceptible	Brown planthopper Resistant
IPPA152616	34	>100	0.66	0.12	1.17	52	1.1	29	0.19	2.8
							R/S= 26		R/S= 15	
IPPA157F11	>500	>500	2.7	0.53	146	>500	26.3	>100		
							R/S= -			
Sulfoxaflor	>500	>500	0.093	0.35	<500	≒30	6.8	>100		
							R/S= -			
Imidacloprid	84	>100	0.10	0.08	5.0	44	1.9	52.5	0.057	40.9
							R/S= 28		R/S= 718	

抗性品系高活性

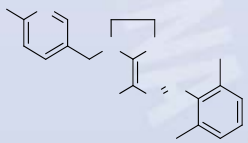
Common cutworm= *Spodoptera litura*
Diamondback moth= *Plutella xylostella*
Green peach aphid= *Myzus persicae*
Western flower thrips= *Frankliniella occidentalis*
Sweetpotate whitefly= *Bemisia tabaci*
Brownwinged green bug= *Plautia stali*
Green rice leafhopper= *Nephotettix cincticeps*
Brown rice planthopper= *Nilaparvata lugens*

Foliar spray to leaf disc
Dipping
Drench
Topical application

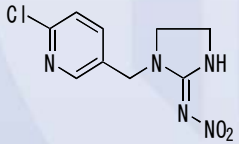
活性优于 sulfoxaflor



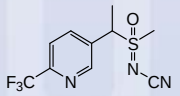
IPPA152616



IPPA157F11



Imidacloprid



Sulfoxaflor

对半翅目、鳞翅目和抗性品系害虫活性优异!

环氧虫啶田间药效

测试了安徽等10地田间药效，分别对褐飞虱、稻纵卷叶螟、蔬菜烟粉虱、葡萄斑叶蝉和黄瓜蚜虫等农业重要害虫进行防效试验。

防治褐飞虱 处理药剂	用量 （g/亩）	药后1天	药后3天	药后7天	药后15天
		平均校正防效(%)			
25%环氧虫啶WP	1	65.53ABb	75.04Dc	83.73Cc	79.72Dc
25%环氧虫啶WP	2	68.46ABab	80.38BCb	88.23BCbc	87.28BCb
25%环氧虫啶WP	4	70.97Aa	85.18Aa	93.08ABab	92.42ABa
25%吡蚜酮WP	6	70.04ABa	82.01ABab	96.30Aa	95.70Aa
10%吡虫啉WP	4	34.51Cc	34.09Ed	38.27Dd	34.06Ed
25%噻虫嗪WG	1	64.58Bb	76.54CDc	86.26BCc	82.87CDbc

防治褐飞虱：同等浓度下25%环氧虫啶WP的防效显著优于吡虫啉、噻嗪酮，与噻虫嗪、吡蚜酮相当。

防治烟粉虱：室内对B型烟粉虱敏感品系成虫的LC_{50}为3.49mg/L，显著高于噻虫嗪的毒力（LC_{50}为18.06mg/L）。

室内防治葡萄斑叶蝉：LC_{50}值与吡虫啉接近，但其LC_{90}明显低于吡虫啉。

防治黄瓜蚜虫、麦蚜：同等浓度下防效与吡虫啉和吡蚜酮相当！

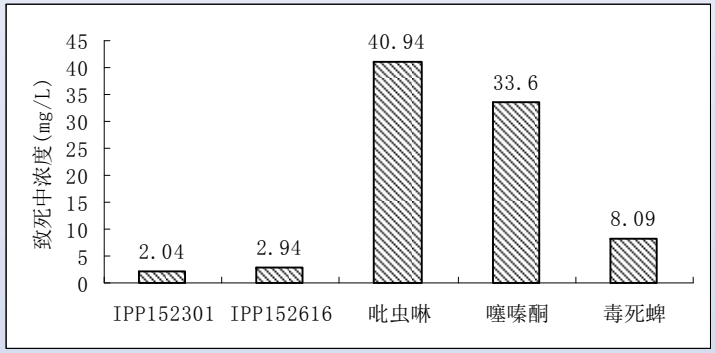
环氧虫啶等田间药效及抗性筛选

对褐飞虱雌雄成虫的活性

药剂	雄成虫		雌成虫	
	LC-P 线	LC_{50}(95%CL) (mg/L)	LC-P 线	LC_{50}(95%CL) (mg/L)
70%IPP152616	Y=2.8621+1.5380x	24.6(15.2~39.2)	Y=2.7721+2.0771x	11.8(6.11~17.1)
25%IPP152616	Y=3.5464+1.5063x	9.23(3.07~15.2)	Y=4.2108+0.7177x	12.6(0.12~29.0)
吡虫啉	Y=2.4011+1.3899x	74.1(46.2~160.5)	Y=2.9598+1.0844x	76.1(42.1~235.6)

两药剂对雌成虫的活性比吡虫啉分别高6.45和6.03倍，对雄成虫的活性比吡虫啉分别高3.01和8.03倍，剂型间差异不显著。

灰飞虱活性



比吡虫啉高20倍和14倍，比噻嗪酮高16倍和11倍，比毒死蜱高4倍和3倍

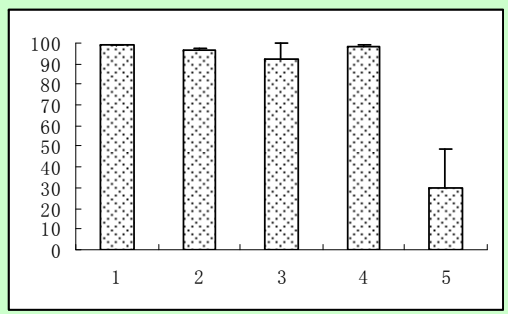
对白背飞虱的活性

药剂	LC-P 线	LC_{50}(95%CL) (mg/L)
烯啶虫胺	Y=4.9044+8.5537x	1.03 (0.59~1.33)
吡虫啉	Y=7.0221+2.127x	0.11 (0.069~0.15)
噻虫嗪	Y=6.9664+3.2126x	0.24 (0.20~0.30)
70%IPP152616WG	Y=5.0484+4.2666x	0.97 (0.58~1.29)
25%IPP152616WP	Y=4.9264+3.5187x	1.05 (0.66~1.37)

致死中浓度相当，均为1mg/L左右，与烯啶虫胺差异不显著，但是显著低于吡虫啉和噻虫嗪

环氧虫啶等田间药效及抗性筛选

环氧虫啶持效性



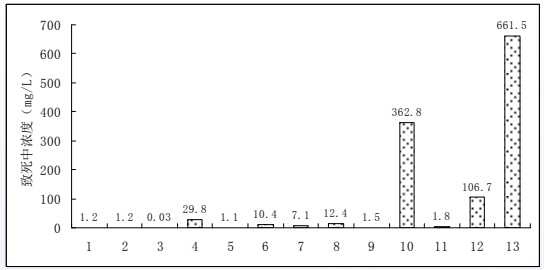
环氧虫啶4g/亩剂量15天防效为92%。
该剂量下15天的防效与噻虫嗪、吡虫啉、烯啶虫胺差异不显著，但远高于丙溴磷。

对灰飞虱的抗性筛选

代数	吡虫啉	IPP152616	IPP152301	噻嗪酮	毒死蜱
F0	40.94	2.94	2.04	33.6	8.09
F2	44.33	8.98	5.95	88.19	15.52
F3	50.73	9.02	6.35	86.75	35.12
F6	57.42	7.52	8.95	--	29.2
F12	50	8.98	5.5	2117.86	147.61
F14	96.67	19.62	5.8	2095.9	872.62
F16	107.02	17.66	6.65	2024.17	--

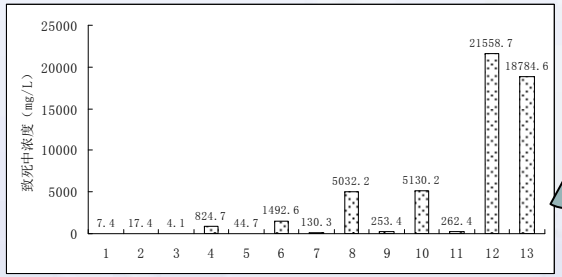
经16代连续筛选后灰飞虱对IPP152301、环氧虫啶的抗性仅提高3.3和6倍，说明灰飞虱对这两种药剂的抗性风险可能都较低。

对大螟初孵幼虫的毒力



LC_{50}=10.4mg/L

对大螟3龄幼虫的毒力



LC_{50}为1492.6mg/L

毒力高于丁烯氟虫腈、烯啶虫胺、杀虫单和毒死蜱，低于其他药剂

环氧虫啶的蜜蜂毒性

Compounds	μg a.i./adult	Motality(%) 4[a]	24	48	96	Number of honey bee
IPPA152616	0.4	3	27	70	89	30
	0.2	10	17	48	68	30
	0.1	0	0	14	48	30
	0.04	0	0	0	14	30
	0.02	0	0	0	0	30
	24h-LD_{50} 96h-LD_{50}	>0.4		0.117		μg./Adult
		>4.04		1.1934		μg./g
Imidacloprid	0.4	100	100	100	100	30
	0.2	86	88	90	79	29
	0.1	20	89	80	50	30
	0.04	0	63	43	29	30
	0.02	0	14	3	3	30
	0.01	0	0	0	4	30
	24h-LD_{50} 96h-LD_{50}	0.035		0.109		μg./Adult
		0.357		1.1118		μg./g
Dinotefuran	2	93	100	100	100	30
	1	42	100	100	100	30
	0.4	43	59	59	63	31
	0.2	0	63	60	57	30
	0.1	0	43	47	41	30
	0.04	0	7	7	0	30
	24h-LD_{50} 96h-LD_{50}	0.19		0.228		μg./Adult
		1.938		2.3256		μg./g

Compounds		μg a.i./adult	Motality(%) 4[a]	24	48	96	Number of honey bee
Sulfoxaflor		0.4	40	90	90	97	30
		0.2	7	43	55	56	30
		0.1	0	20	24	21	30
		0.04	0	0	0	0	30
		0.02	0	0	3	0	30
	24h-LD_{50} 96h-LD_{50}	0.19			0.163		μg./Adult
		1.938			1.6626		μg./g
Thiacloprid		2	0	17	23	23	30
		1	0	0	0	0	30
	24h-LD_{50} 96h-LD_{50}	>2			>2		μg./Adult
		>20.1			>20.1		μg./g
	Dilution ratio						
Dimethoate EC	1000	0.43	70	100	100	100	30
Dimethoate43%	2000	0.215	37	90	97	100	30
Lot No.EA006F	4000	0.108	0	53	77	89	30
	8000	0.054	0	23	38	32	30
	16000	0.027	0	0	3	14	30
	24h-LD_{50} 96h-LD_{50}	0.093			0.063		μg./Adult
		0.9486			0.6426		μg./g
acetone			(0)	(0)	(0)	(6)	30

a:Hour after treatment
Note: Technical materials were used for the testing except for Dimethoate EC, which is a formulated product.

日本大冢：环氧虫啶24小时对蜜蜂安全性是吡虫啉的10倍以上

中国农业大学数据：48小时，环氧虫啶急性摄入LC_{50}19.18mg/l, 吡虫啉4.94mg/l,明显低于吡虫啉。

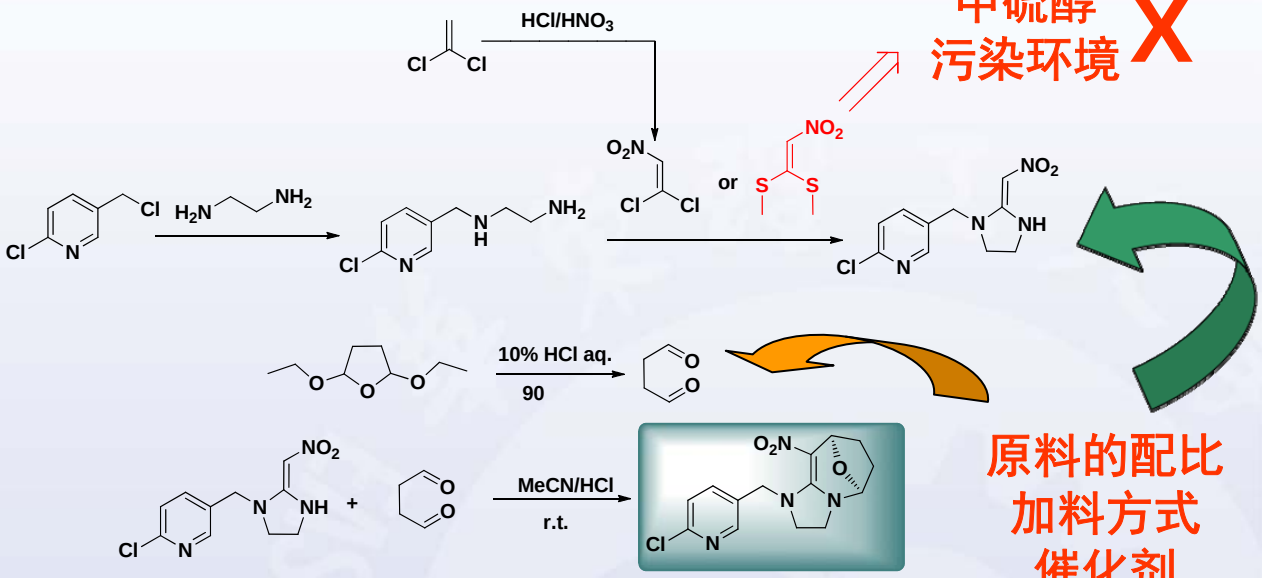
环氧虫啶农药登记前期准备

环氧虫啶工艺及优化

甲硫醇
污染环境 X

1. 改进工艺，降低成本

2.已获得大于97%的环氧虫啶45公斤



原料的配比
加料方式
催化剂

环氧虫啶毒理学试验

环氧虫啶：97%原药，25%WP， 2012.6.30完成

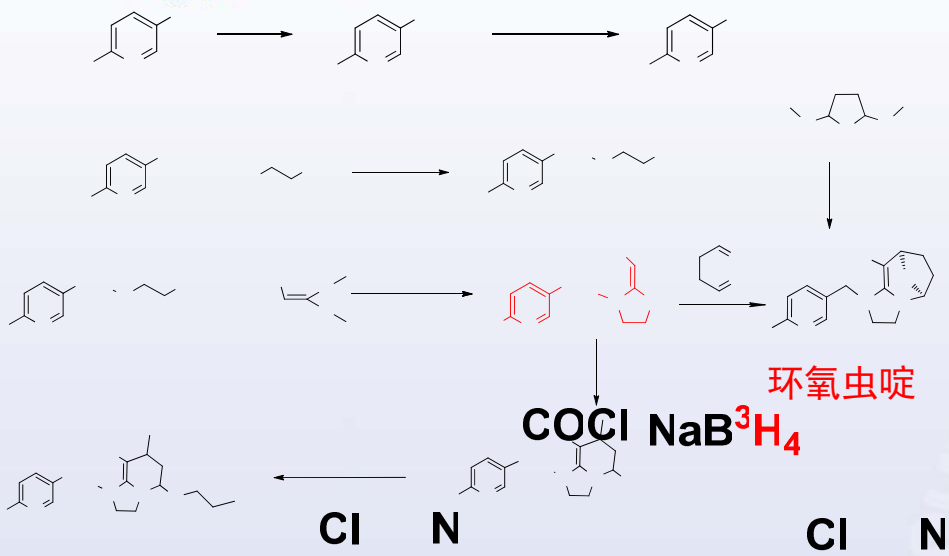
毒理学试验(LS)：急性6项 ， 亚慢性毒性试验 ， 致突变性试验4项
环境影响试验(LS) ： 环境行为试验8项，环境毒性试验9项（蜂，鸟、鱼、蚕） ，
环境行为试验1项，环境毒性试验4项（赤眼蜂、蛙、蚯蚓、土壤微生物）

环氧虫啶：97%原药，25%WP， 2014.4.30完成

毒理学试验(LS)：生殖毒性、致畸、慢性和致癌性及代谢试验4项

同位素标记物合成

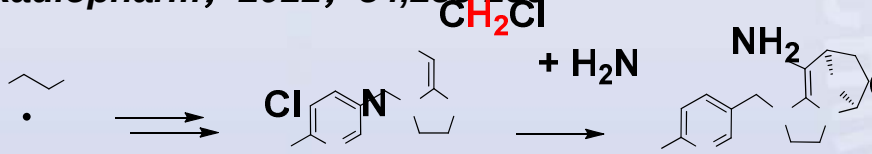
哌虫啶、环氧虫啶的^{3}H标记



环氧虫啶

哌虫啶

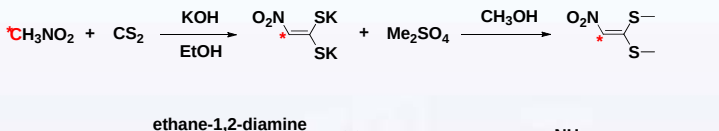
C. Li, X. Y. Xu, Z. Li, J. Label Compd. Radiopharm，2011，54,256-259

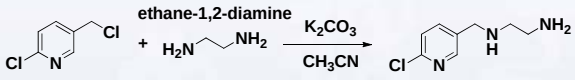


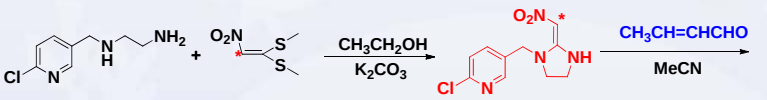
标记合成：作用机制研究

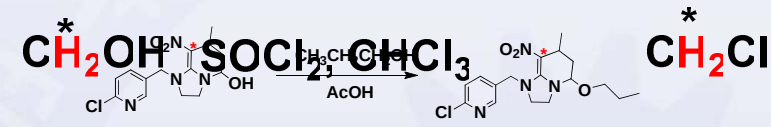
土壤代谢与植物代谢研究

哌虫啶的^{14}C标记



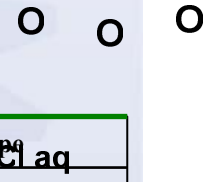






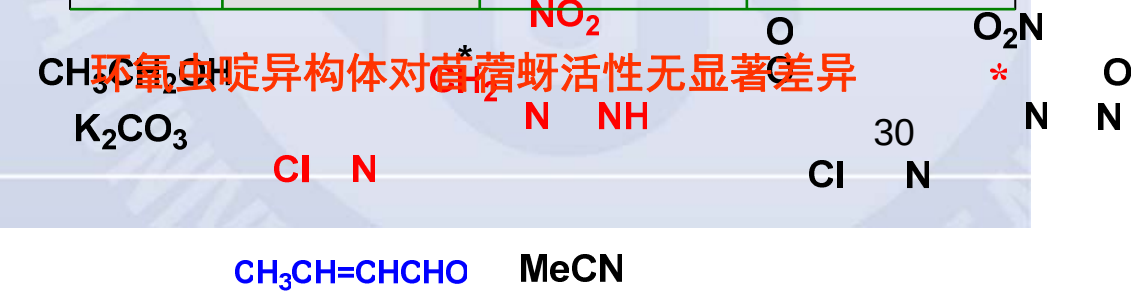
环氧虫啶

C. Li, X. Y. Xu, Z. Li, J. Label Compd. Radiopharm，2011，in press



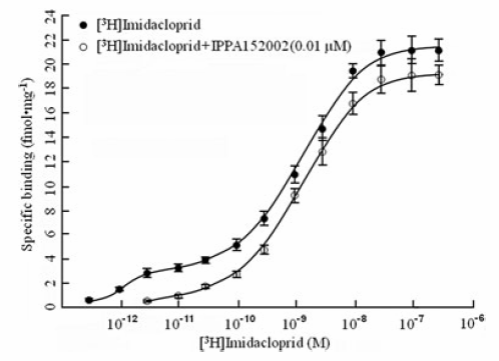
化合物	LC_{50}（mg/L）	95%置信限	Slope
Peak1	2.252	1.179 - 8.485	1.665±0.191
Peak2	1.407	1.188 -1.685	3.007±0.282

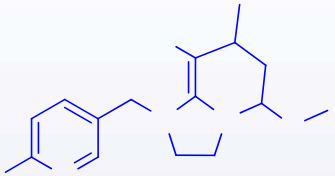
环氧虫啶异构体对蓝蛎活性无显著差异



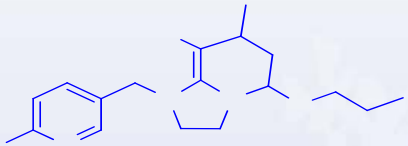
4. 作用机制多样性

① 哌虫啶—nAChRs激动剂

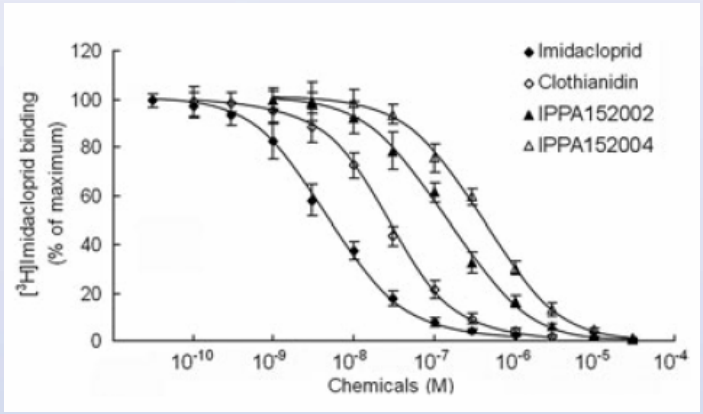


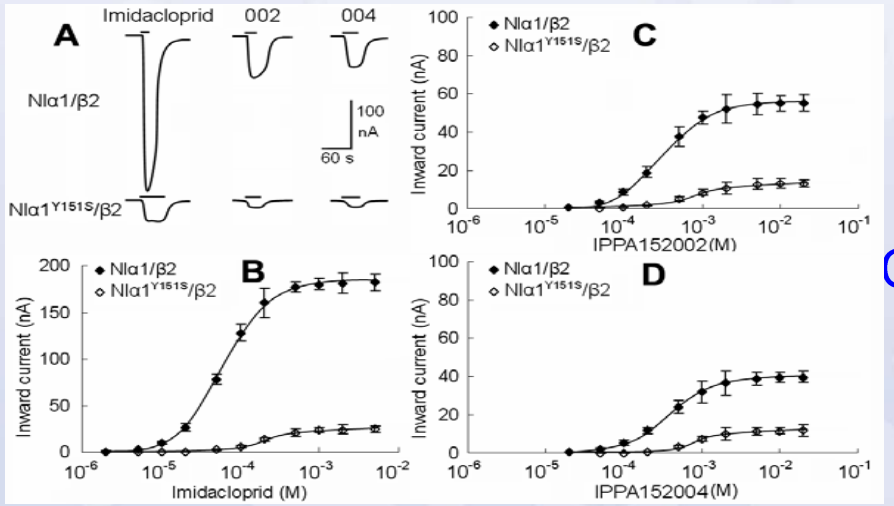


IPPA152002



哌虫啶 IPPA152004

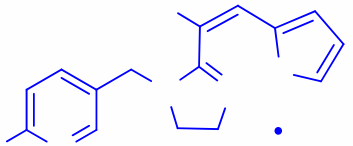


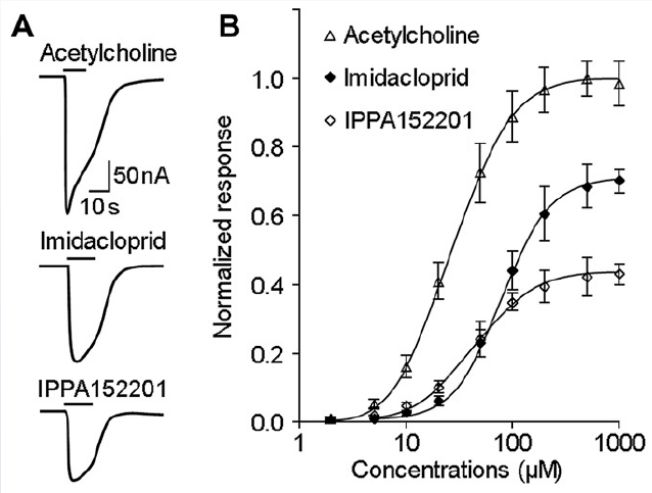


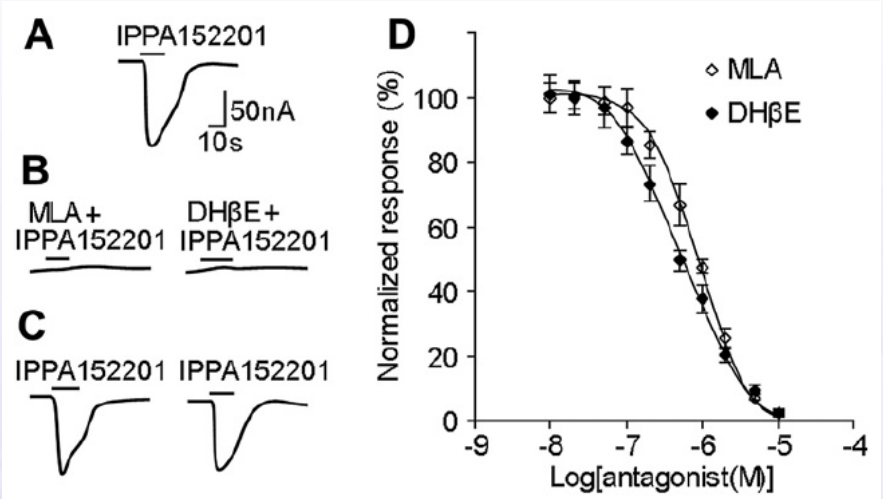
神经活性低于吡虫啉，但受吡虫啉抗性靶标变异Y151S影响较小，交互抗性小。

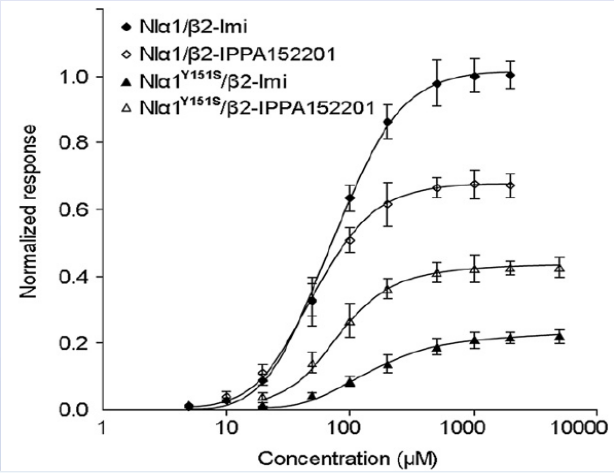
X.Y. Xu *et al*，*Insect Mol. Biol*, 2010, *19*, 1–8

②IPPA152201— nAChRs激动剂







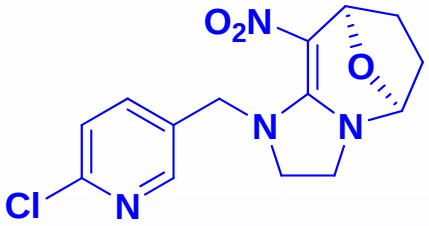


Nla1 突变(Y151S)的影响

比吡虫啉更强的昆虫神经系统激动剂，且受吡虫啉抗性靶标变异Y151S影响小，与吡虫啉无明显交互抗性。

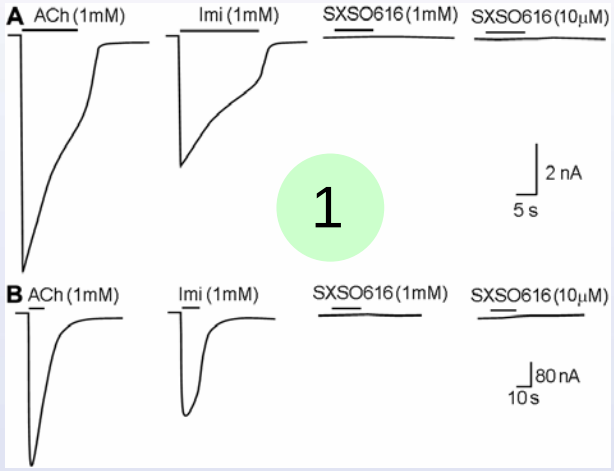
Insect Biochem. Mol. Biol. 2011, 41, 440-445

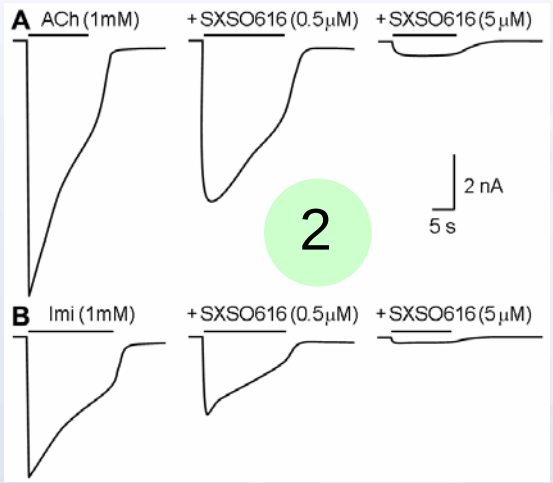
③ 环氧虫啶— nAChRs拮抗剂

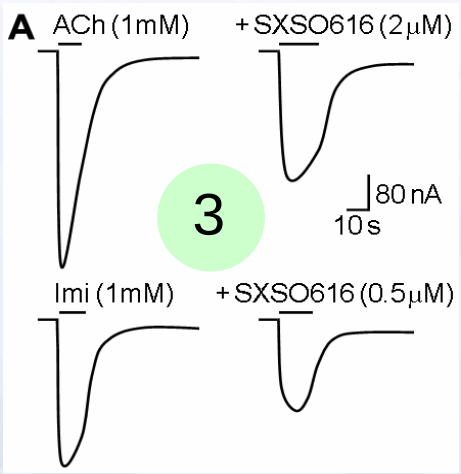


拮抗剂

拮抗剂的三条标准







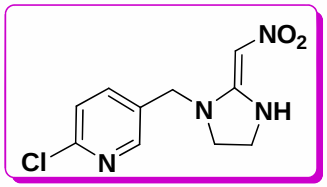
与受体高亲和力结合

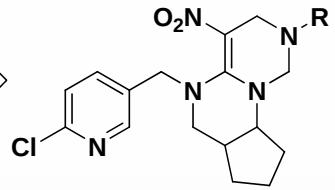
不具有激动剂效应

可以抑制激动剂的反应

国际上首例报道对nAChRs有明显拮抗作用的高活性化合物！

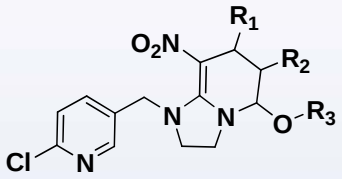
目前所有商品化的新烟碱杀虫剂都是激动剂！





Me-too

总



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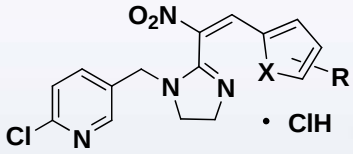

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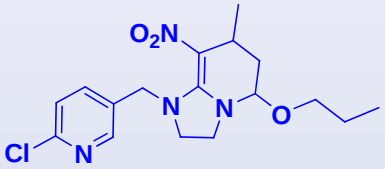
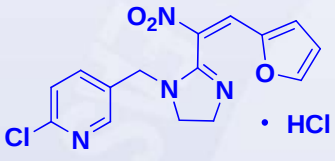


IPPA152204



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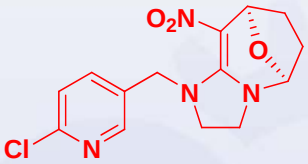
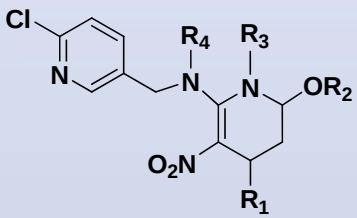


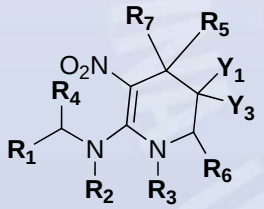
IPPA152616

Me-better

Me-First



Me-too



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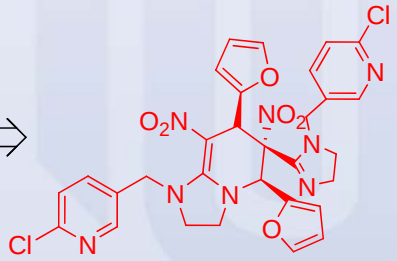

IPPA152311

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硕士生

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