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·专论与综述·

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手性农药对映选择活性及机制研究进展

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摘 要：手性农药对映体在防除各类有害生物时常表现出不同的生物活性，关注手性农药对映体的选择活性对于促进农药减施增效、发展绿色农业具有重要意义。本文综述了手性农药对映体选择活性研究现状，并将对映体的选择活性机制研究归纳为两方面：一方面大多数研究采用计算机模拟技术，分析对映体与靶标分子活性位点之间的结合能力，仅有少部分研究通过生物试验验证了分子对接的结果；另一方面研究则通过放射性同位素示踪法以及定量分析代谢物等手段，探究手性农药对映体在生物系统内吸收、运输和代谢的差异。本文旨在为识别高活性手性农药单体、开发高效低风险新型绿色农药提供参考。

关键词: 手性农药；对映体；立体选择性；生物活性；机制
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Advances on enantioselective activity and it's mechanism of chiral pesticides

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Abstract: Chiral pesticide enantiomers often show different bioactivity in controlling harmful organisms. It is of great significance to pay attention to the selective activity of chiral pesticide enantiomers to promote the reduction and efficiency of pesticides and to develop green agriculture. In this paper, according to the research status of enantioselective activity of chiral pesticides, the research on enantioselective activity mechanism is summarized into two aspects: On the one hand, computer simulation technology is used to analyze the binding ability between enantiomers and active sites of target molecules, and a few of them have also carried out biological experiments; on the other hand, the study explored the differences in absorption, transportation and metabolism of chiral pesticide enantiomers in biological systems by means of radioisotope tracing and quantitative analysis of metabolites. This paper aims to provide reference for the identification of highly active activity chiral pesticide monomers and the development of new green pesticides with high efficiency and low risk.

Keywords: chiral pesticides; enantiomers; enantioselective activity; bioactivity; mechanism

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自然界中几乎所有生物分子都具有手性，如脱氧核糖核酸 (DNA)、构成糖类的糖单元、组成蛋白质的 20 种氨基酸等[1]。在非手性环境下，手性分子对映体的物理化学性质几乎完全相同，但在手性环境下则表现出不同的性质[2]。当手性对映体进入生物体内时，由于对映体与酶和其他手性分子之间存在相互选择作用，会表现出截然相反的生物效应[3-5]。由于对映异构体的存在，手性农药在靶标生物活性、非靶标生物毒性及环境归趋方面常表现出对映体选择性。近年来，手性农药在农药商品中的比例迅速上升[6]，2017 年的统计数据显示，在 759 种现代农药活性成分中，手性化合物有 227 种，占 30%，且该比例呈不断上升趋势[7]。前人关于手性农药的综述多集中于论述手性农药的合成、药效、环境安全性等方面存在的对映体选择性。如李云等对手性农药的合成、拆分及选择性差异特征研究进行了总结[8]；张利强等总结了手性农药的选择性环境行为研究进展[9]；董丰收等分析了手性三唑类杀菌剂的立体选择性生物活性、毒性及富集行为研究现状[10]；郭铭浩等重点综述了手性农药对映体的生物活性、毒性和环境风险差异[11]。但针对手性农药对映体选择活性机制的研究状况尚未见综述报道。鉴于此，笔者调研了近 10 年的相关研究，拟对目前国内外主要几类手性农药对映体的选择活性机制研究展开综述，旨在为高效、环境友好型手性农药光学纯单体的开发和应用提供参考。

1 手性农药对映体对靶标生物的选择活性

手性农药对映体对靶标生物的选择活性主要存在以下几种形式[12]：1) 一种异构体高活性，而另一种异构体无活性或活性低，如戊唑醇、草铵膦；2) 两种异构体活性稍有差别 (10 倍以内)，如保松噻、丙硫磷、甲霜灵、萘氧丙草胺等；3) 两种对映体具有同等活性，如三唑酮，无需生产和使用光学纯异构体；4) 对映体的活性类型不同，如烯效唑、氰戊菊酯等。目前已有部分手性农药品种是以高活性的光学纯单体形式进行生产、登记、销售和使用，如精异丙甲草胺、精甲霜灵、精喹禾灵和精草铵膦等[11,13-17]，但多数农药仍是以外消旋混合物形式出售和使用[5]。

1.1 手性除草剂对映体的选择性除草活性

自 1974 年德国巴斯夫股份有限公司开发了芳氧羧酸类除草剂高 2-甲-4-氯丙酸以来，手性除草化合物成为研发热点，现已相继开发成功数十个具有不同生物活性的手性商品化合物[18]。目前，市场上主要的 19 大类 300 多个除草剂品种中，有 14 类具有手性中心，约包含 73 个品种[17]，例如苯氧羧酸类、芳氧苯氧丙酸酯类、咪唑啉酮类、酰胺类、脲类以及二苯醚类等。这些手性除草剂的对映体通常表现出不同的生物活性，存在具有靶标活性的高效体和无活性/活性较低的无效体/低效体。我国目前登记的手性除草剂产品中，有 70 多个具有手性结构，且多具有一个手性中心[19]。表 1 列举比较了常见的手性除草剂对映体间的除草活性差异。

表 1 手性除草剂对映体的除草活性

Table 1 Herbicidal activity of enantiomers of chiral herbicides

除草剂种类 Types of herbicide	除草剂名称 Herbicide name	对映体的除草活性差异 Difference of herbicidal activity of enantiomers	参考文献 Reference
苯氧羧酸类 Phenoxyalkanoic acid	2,4-滴丙酸 dichlorprop	仅 *R* 体具有活性 Only *R*-dichlorprop efficient	[20]
	2-甲-4-氯丙酸 mecoprop	*S* 体几乎无活性 *S*-mecoprop is almost inactive	[21]
芳氧苯氧丙酸酯类 Aryloxyphenoxypropionates	禾草灵 diclofop-methyl	*R* 体活性为 *S* 体的 10 倍 The herbicidal activity of *R*-diclofop-methyl was decuple that of *S*-diclofop-methyl	[22]
	噁唑禾草灵 fenoxaprop-ethyl	*S* 体几乎无活性 *S*-fenoxaprop-ethyl is almost inactive	[23]
	吡氟禾草灵 fluazifop-butyl	*R* 体活性较 *S* 体高 The herbicidal activity of *R*-fluazifop-butyl is higher than that of *S*-fluazifop-butyl	[24]
	氟吡甲禾灵 haloxyfop	*R* 体活性为 *S* 体的 1000 倍 The herbicidal activity of *R*-haloxyfop was 1000 times that of *S*-haloxyfop	[25]
	氟吡乙禾灵 haloxyfop-ethyl	*R* 体活性为 *S* 体的 1000 倍 The herbicidal activity of *R*-haloxyfop-ethyl was 1000 times that of *S*-haloxyfop-ethyl	[26]

续表 1

Table 1 (Continued)

除草剂种类 Types of herbicide	除草剂名称 Herbicide name	对映体的除草活性差异 Difference of herbicidal activity of enantiomers	参考文献 Reference
芳氧苯氧丙酸酯类 Aryloxyphenoxypropionates	氰氟草酯 cyhalofop-butyl	*R* 体是活性异构体 *R*-cyhalofop-butyl is an active isomer	[17]
	喹禾灵 quizalofop-ethyl	*R* 体活性为 *S* 体的 65 倍 The herbicidal activity of *R*-quizalofop-ethyl was 65 times that of *S*- quizalofop-ethyl	[27]
	喔草酯 propa-quizafop	*R* 体高效 *R*-propa-quizafop efficient	[28]
	炔草酯 clodinafop-propargyl	*S* 体几乎无活性 *S*-clodinafop-propargyl is almost inactive	[29]
	喹禾糠酯 quizalofop-p-tefuryl	*R* 体活性远高于 *S* 体 The herbicidal activity of *R*-quizalofop-p-tefuryl is much higher than that of *S*-quizalofop-p-tefuryl.	[27]
酰胺类 Acetanilides	异丙甲草胺 metolachlor	除草活性排序为：*SS* > *SR* > *RS* > *RR* The order of weeding herbicidal activity is: *SS* > *SR* > *RS* > *RR*	[30]
	异丙草胺 propisochlor	*R* 体活性为 *S* 体的 2 倍 The herbicidal activity of *R*-propisochlor was 2 times that of *S*-propisochlor	[31]
	敌草胺 napropamide	*R* 体活性为 *S* 体的 8 倍 The herbicidal activity of *R*-napropamide was 8 times that of *S*-napropamide	[32]
	乙草胺 acetochlor	*R* 体活性为 *S* 体的 1.64 倍 The herbicidal activity of *R*-acetochlor was 1.64 times that of *S*-acetochlor	[31]
	氟丁酰草胺 beflubutamid	*S* 体活性比 *R* 体高 1000 倍 The herbicidal activity of *S*-beflubutamid was 1000 times that of *R*-beflubutamid	[33]
	二甲吩草胺 dimethenamid	*S* 体活性比 *R* 体高 30 倍 The herbicidal activity of *S*-dimethenamid was 30 times that of *R*-dimethenamid	[34]
咪唑啉酮类 Imidazolones	灭草烟 imazapyr	(+) 灭草烟对靶标酶的抑制效果是 (−) 灭草烟的 4 倍 The inhibitory effect of (+) imazapyr on target enzyme was 4 times that of (−) imazapyr	[35]
	咪唑乙烟酸 imazethapyr	*R* 体活性为 *S* 体的 25 倍 The herbicidal activity of *R*-imazethapyr was 25 times that of *S*-imazethapyr	[36]
	甲氧咪草烟 imazamox	*R* 体活性为 *S* 体的 6.69 倍 The herbicidal activity of *R*-imazamox was 6.69 times that of *S*-imazamox	[37]
二苯醚类 Diphenyl ethers	乙羧氟草醚 fluoroglycofen	*R* 体高效 *R*-fluoroglycofen efficient	[12]
	乳氟禾草灵 lactofen	*R* 体和 *S* 体均具有活性，但 *R* 体活性略高 Both *R*-lactofen and *S*-lactofen have herbicidal activity, but the activity of *R*-lactofen is slightly higher	[38]
	氟氟草醚 ethoxyfen-ethyl	*S* 体高效 *S*-ethoxyfen-ethyl efficient	[17]
有机磷类 Organophosphorus	草铵膦 glufosinate	仅 *L*-草铵膦有活性 Only *L*-glufosinate efficient	[39]
	草特磷 zytron	(−) 草特磷调节植物生长的活性比 (+) 草特磷高 24 倍多 The activity of (−) zytron in regulating plant growth was 24 times greater than (+) zytron	[12]
三嗪类 Triazines	三嗪氟草胺 triaziflam	*R* 体活性为 *S* 体的 100 倍 The herbicidal activity of *R*-triaziflam was 100 times that of *S*-triaziflam	[40]
脲类 Ureas	杀草隆 daimuron	*S* 体高效 *S*-daimuron efficient	[41]
三唑啉酮类 Triazolinones	唑酮草酯 carfentrazone-ethyl	*S* 体活性为 *R* 体的 2.04 倍 The herbicidal activity of *S*-carfentrazone-ethyl was 2.04 times that of *R*-carfentrazone-ethyl	[42]
其他 Others	呋草酮 flurtamone	*R* 体活性为 *S* 体 的 6.3~35.6 倍 The herbicidal activity of *R*-flurtamone was 6.3-35.6 times that of *S*-flurtamone	[43]
	乙氧呋草黄 ethofumesate	(−) 乙氧呋草黄的活性为 (+) 乙氧呋草黄活性的 3.5 倍 The herbicidal activity of (−) ethofumesate was 3.5 times that of (+) ethofumesate	[44]

1.2 手性杀虫剂对映体的选择性杀虫活性

手性杀虫剂目前主要包括拟除虫菊酯类、有机磷类、苯基吡唑类、新烟碱类等，其中研究较早的为有机磷类。Ohkawa 等在 1978 年研究了苯腈磷对映体对家蝇和水稻螟虫幼虫的杀虫活性，发现 *R*-(+)-苯腈磷对两种供试生物的活性较 *S*-(−)-苯腈磷的高[45]。此后相关研究人员陆续揭示了多种手性杀虫剂的对映体选择活性 (表 2)。随着对手性化合物研究的逐步深入，手性杀虫剂品种已经从毒性高、持留性强的有机氯类和有机磷类发展到了低毒性、易降解的合成拟除虫菊酯类和新烟碱类[46]。

表 2 手性杀虫剂对映体的杀虫活性

Table 2 Insecticidal activity of enantiomers of chiral insecticide

杀虫剂种类 Types of insecticide	杀虫剂名称 Insecticide name	对映体的杀虫活性差异 Difference of insecticidal activity of enantiomers	参考文献 Reference
有机磷类 Organophosphorus	水胺硫磷 isocarbophos	*S* 体的活性为 *R* 体的 13.2~55.6 倍 The activity of *S*-isocarbophos was 13.2-55.6 times that of *R*-isocarbophos	[47]
	甲基异硫磷 isofenphos-methyl	*S* 体活性为 *R* 体活性的 3.7~22.3 倍 The activity of *S*-isofenphos-methyl was 3.7-22.3 times that of *R*-isofenphos-methyl	[48]
	蔬果磷 salithion	*S* 体的活性为 *R* 体的 2 倍 The activity of *S*-salithion was 2 times that of *R*-salithion	[49]
	丙溴磷 profenofos	(−) 丙溴磷的活性为 (+) 丙溴磷的 4~12 倍 The activity of (−) profenofos was 4-12 times that of (+) profenofos	[50]
	苯硫磷 epn	(+) 苯硫磷的活性为 (−) 苯硫磷活性的 2.9~4.0 倍 The activity of (+) epn was 2.9-4.0 times that of (−) epn	[51]
	苯腈磷 cyanofenphos	(+) 苯腈磷的活性为 (−) 苯腈磷的 2.7~25 倍 The activity of (+) cyanofenphos was 2.7-25 times that of (−) cyanofenphos	[45]
	甲胺磷 methamidophos	(+) 甲胺磷的活性为 (−) 甲胺磷的 1.04~6.25 倍 The activity of (+) methamidophos was 1.04-6.25 times that of (+) methamidophos	[52]
	乙酰甲胺磷 acephate	(+) 乙酰甲胺磷的活性为 (−) 乙酰甲胺磷的 1.07~5 倍 The activity of (+) acephate was 1.07-5 times that of (−) acephate	[52]
	苯线磷 fenamiphos	(+) 苯线磷对靶标酶的抑制效果是 (−) 苯线磷的 18.9 倍 The inhibitory effect of (+) fenamiphos on target enzyme was 18.9 times that of (−) fenamiphos	[53]
	噻唑膦 fosthiazate	(1*S*,3*R*) 噻唑膦和 (1*S*,3*S*) 噻唑膦的活性比 (1*R*,3*S*) 噻唑膦和 (1*R*,3*R*) 噻唑膦高出 100 倍 The activity of (1*S*,3*R*) fosthiazate and (1*S*,3*S*) fosthiazate is 100 times higher than that of (1*R*,3*S*) fosthiazate and (1*R*,3*R*) fosthiazate	[54]
	地虫磷 chlorethoxyfos	*R* 体的活性为 *S* 体的 1.8~3.96 倍 The activity of *R*-chlorethoxyfos was 1.8-3.96 times that of *S*-chlorethoxyfos	[55]
	巴毒磷 crotoxyphos	(+) 巴毒磷对靶标酶的抑制效果为 (−) 巴毒磷的 11 倍 The inhibitory effect of (+) crotoxyphos on target enzyme was 11 times that of (−) crotoxyphos	[56]
	马拉硫磷 malathion	*R* 体的活性为 *S* 体的 2.7~11.3 倍 The activity of *R*-malathion was 2.7-11.3 times that of *S*-malathion	[57]
拟除虫菊酯类 Pyrethroids	七氟菊酯 tefluthrin	(1*R*,3*R*) 七氟菊酯的活性是 (1*S*,3*S*) 七氟菊酯的 28.4~350.8 倍 The activity of (1*R*,3*R*) tefluthrin was 28.4-350.8 times that of (1*S*,3*S*) tefluthrin	[58]
	联苯菊酯 bifenthrin	(1*R*-*cis*) 联苯菊酯的活性是 (1*S*-*cis*) 联苯菊酯的 209.8~352.94 倍 The activity of (1*R*-*cis*) bifenthrin was 209.8-352.94 times that of (1*S*-*cis*) bifenthrin	[59]
	氰戊菊酯 fenvalerate	(2*S*-α*S*) 氰戊菊酯为活性对映体，而 (2*R*-α*R*) 氰戊菊酯几乎无活性 (2*S*-α*S*) fenvalerate was an active enantiomer, while (2*R*-α*R*) fenvalerate was almost inactive	[60]
	氟胺氰菊酯 fluvalinate	*S* 体高效 *S*-fluvalinate efficient	[12]
	氯氰菊酯 cypermethrin	1*R*,3*R*-(+)-顺式 (酸)-(*S*)-醇活性最高 (1*R*,3*R*)-(+)-*cis*-α*S* alcohol has the highest activity	[61]
	氟氯氰菊酯 cyfluthrin	1*R*-顺式-α*S* 和 1*R*-反式-α*S* 的活性是其他异构体的 50~100 倍 The activity of 1*R*-*cis*-α*S* and 1*R*-*trans*-α*S*-cyfluthrin is 50-100 times that of other isomers	[62]
	氯菊酯 permethrin	顺式异构体的活性是反式异构体的 2.33 倍 The activity of *cis*-permethrin is 2.33 times that of *trans*-permethrin.	[63]
	苯醚菊酯 phenothrin epno	*R* 体活性为 *S* 体活性的 11.9~14.5 倍 The activity of *R*-phenothrin epno is 11.9-14.5 times that of *S*-phenothrin epno	[64]
氨基甲酸酯类 Carbamatepesticides	仲丁威 fenobucarb	*R* 体活性为 *S* 体活性的 1.8~2.7 倍 The activity of *R*-fenobucarb is 1.8-2.7 times that of *S*-fenobucarb	[65]
	茚虫威 indoxacarb	*S* 体活性为 *R* 体活性的 114.68 倍 The activity of *S*-indoxacarb is 114.68 times that of *R*-indoxacarb	[66]

续表 2

Table 2 (Continued)

杀虫剂种类 Types of insecticide	杀虫剂名称 Insecticide name	对映体的杀虫活性差异 Difference of insecticidal activity of enantiomers	参考文献 Reference
苯基吡唑类 Phenyl pyrazoles	丁虫腈 flufiprole	*R* 体活性为 *S* 体活性的 1.8~5.1 倍 The activity of *R*-flufiprole is 1.8-5.1 times that of *S*-flufiprole	[67]
	氟虫腈 fipronil	*R* 体活性为 *S* 体活性的 1.02~1.4 倍 The activity of *R*-fipronil is 1.02-1.4 times that of *S*-fipronil	[68]
	乙虫腈 ethiprole	*R* 体活性为 *S* 体活性的 2.43~4.27 倍 The activity of *R*-ethiprole is 2.43-4.27 times that of *S*-ethiprole	[69]
新烟碱类 Neonicotinoids	呋虫胺 dinotefuran	*S* 体活性为 *R* 体活性的 3.2~3.3 倍 The activity of *S*-dinotefuran is 3.2-3.3 times that of *R*-dinotefuran	[70]
异噁唑啉类 Isoxazoline	氟噁唑酰胺 fluxametamide	*S*-(+)-体活性为 *R*-(−)-体活性的 52.1~304.4 倍 The activity of *S*-(+)-fluxametamide is 52.1-304.4 times that of *R*-(−)-fluxametamide	[71]
	氟雷拉纳 fluralaner	*S* 体活性为 *R* 体活性的 33~39 倍 The activity of *S*-fluralaner is 33-39 times that of *R*-fluralaner	[72]

1.3 手性杀菌剂对映体的选择性杀菌活性

在我国目前登记的手性杀菌剂中，有 60 种具有手性中心[11]，其中三唑类是应用广泛且大量使用的手性杀菌剂，而约有 84% 的三唑类品种属于手性化合物[73]，此外还有酰胺类和苯基吡唑类。1987 年，Burden 等研究发现，三唑醇和多效唑的手性 *R* 异构体较 *S* 异构体能更显著地抑制真菌生长[74]。此后，研究人员对手性杀菌剂的对映体选择活性进行了广泛而深入的研究，表 3 列举了常见手性杀菌剂的对映体选择活性差异。

表 3 手性杀菌剂对映体的杀菌活性

Table 3 Fungicidal activity of enantiomers of chiral fungicides

杀菌剂种类 Types of fungicide	杀菌剂名称 Fungicides name	对映体的杀菌活性差异 Difference of fungicidal activity of enantiomers	参考文献 Reference
三唑类 Triazole	三唑酮 triadimefon	*R* 体与 *S* 体活性无差别 There is no difference in activity between *R*-triadimefon and *S*-triadimefon	[75]
	戊菌唑 penconazole	*R* 体活性较 *S* 体高 1.795~4.419 倍 The activity of *R*-penconazole is 1.795-4.419 times higher than that of *S*-penconazole	[76]
	多效唑 paclobutrazol	2*S*,3*R* 和 2*R*,3*R* 体的活性是 2*R*,3*S* 和 2*S*,3*S* 体的 25~125 倍 The activity of 2*S*,3*R* and 2*R*,3*R*-paclobutrazol is 25-125 times that of 2*R*,3*S* and 2*S*,3*S*-paclobutrazol	[74]
	粉唑醇 flutriafol	*R* 体活性较 *S* 体高 2.17~3.52 倍 The activity of *R*-flutriafol is 2.17-3.52 times higher than that of *S*-flutriafol	[77]
	烯唑醇 diniconazole	*R* 体活性较 *S* 体高 48.3~100 倍 The activity of *R*-diniconazole is 48.3-100 times higher than that of *S*-diniconazole	[78]
	戊唑醇 tebuconazole	*S* 体活性较 *R* 体高 43.7 倍 The activity of *S*-tebuconazole is 43.7 times higher than that of *R*-tebuconazole	[13]
	四氟醚唑 tetraconazole	(+)-四氟咪唑的活性为 (−)-四氟咪唑的 1.49~4.11 倍 The activity of (+)-tetraconazole is 1.49-4.11 times that of (−)-tetraconazole	[79]
	氯氟醚菌唑 mefentrifluconazole	*R* 体活性较 *S* 体高 11~113 倍 The activity of *R*-mefentrifluconazole is 11-113 times higher than that of *S*-mefentrifluconazole	[14]
	腈菌唑 myclobutanil	(+)-腈菌唑的活性是 (−)-腈菌唑的 1.79~1.96 倍 The activity of (+)-myclobutanil is 1.79-1.96 times that of (−)-myclobutanil	[80]
	灭菌唑 triticonazole	*R* 体活性较 *S* 体高 3.11-82.89 倍 The activity of *R*-triticonazole is 3.11-82.89 times higher than that of *S*-triticonazole	[81-82]
	丙硫菌唑 prothioconazole	*R* 体活性较 *S* 体高 6~262 倍 The activity of *R*-prothioconazole is 6-262 times higher than that of *S*-prothioconazole	[83]
	联苯三唑醇 bitertanol	(1*S*,2*R*)-联苯三唑醇是最有效的立体异构体，对 8 种目标致病真菌的生物活性是其他异构体的 4.3~314.7 倍 (1*S*,2*R*)-bitertanol was the most effective stereoisomer, showing 4.3-314.7 times more potent bioactivity than other stereoisomers against eight target pathogenic fungi	[84]
	氟环唑 epoxiconazole	*R*,*S*-(+)-氟环唑活性较 *S*,*R*-(−)-氟环唑高 1.3~7.25 倍 *R*,*S*-(+)-epoxiconazole bioactivity was 1.3-7.25 times higher than *S*,*R*-(−)-epoxiconazole	[85]
	三唑醇 triadimenol	1*S*,2*R*-三唑醇活性是 1*R*,2*R*-三唑醇的 5 倍，是 1*S*,2*S* 和 1*R*,2*S*-三唑醇的 125 倍 The activity of 1*S*,2*R*-triadimenol is 5 times that of 1*R*,2*R*- triadimenol, and 125 times that of 1*S*,2*S* and 1*R*,2*S*-triadimenol	[74]
	己唑醇 hexaconazole	(−)-己唑醇的活性是 (+)-己唑醇的 11~13 倍 The activity of (−)-hexaconazole was about 11-13 times more than (+)-hexaconazole for the fungi	[86]

续表 3

Table 3 (Continued)

杀菌剂种类 Types of fungicide	杀菌剂名称 Fungicides name	对映体的杀菌活性差异 Difference of fungicidal activity of enantiomers	参考文献 Reference
三唑类 Triazole	环丙唑醇 cyproconazole	*R,S*-环吡唑醇活性高于其他 3 种立体异构体，比 *S,S*-环吡唑醇高 273.9 倍 The activity of *R,S*-cyproconazole higher than the other three stereoisomers, which is 273.9 times higher than that of *S,S*-cyproconazole	[87]
	苯醚甲环唑 difenoconazole	(2*R*,4*S*)-苯醚甲环唑的活性比 (2*S*,4*S*)-苯醚甲环唑高约 24.2 倍 The activity of (2*R*,4*S*)-difenoconazole being about 24.2 times higher than that of (2*S*,4*S*)-difenoconazole	[88]
	乙环唑 etaconazole	(2*S*,4*R*)-乙环唑活性最高，比 (2*R*,4*R*)-乙环唑体高 100 多倍 (2*S*,4*R*)-etaconazole had the highest fungicidal activity, which is more than 100 times higher than that of (2*R*,4*R*)-etaconazole	[89]
	叶菌唑 metconazole	(1*S*,5*R*)-叶菌唑的活性是 (1*R*,5*S*) 叶菌唑的 13.9~23.4 倍 The activity of (1*S*,5*R*)-metconazole was 13.9-23.4 times of (1*R*,5*S*)-metconazole	[90]
	苯酰菌胺 zoxamide	*R* 体活性较 *S* 体高 34.5~140 倍 The activity of *R*-zoxamide is 34.5-140 times higher than that of *S*-zoxamide	[91]
	氟唑菌苯胺 penflufen	*S* 体活性较 *R* 体高 41.2~46.8 倍 The activity of *S*-penflufen is 41.2-46.8 times higher than that of *R*-penflufen	[92]
	氟唑菌酰羟胺 pydiflumetofen	*R* 体活性较 *S* 体高 797~960 倍 The activity of *R*-pydiflumetofen is 797-960 times higher than that of *S*-pydiflumetofen	[93]
	吡噻菌胺 penthiopyrad	*S* 体活性较 *R* 体高 5.07~22.8 倍 The activity of *S*-penthiopyrad is 5.07-22.8 times higher than that of *R*-penthiopyrad	[94]
	双炔酰菌胺 mandipropamid	*S* 体活性较 *R* 体高 233~592 倍 The activity of *S*-mandipropamid is 233-592 times higher than that of *R*-mandipropamid	[16]
	苯丙烯氟菌唑 benzovindiflupyr	1*S*,4*R*-(−)-苯并烯氟菌唑的活性较 1*R*,4*S*-(+)-苯并烯氟菌唑高 1.7~54.5 倍 The activity of 1*S*,4*R*-(−)-benzovindiflupyr is 1.7-54.5 times higher than that of 1*R*,4*S*-(+)-benzovindiflupyr	[95]
咪唑类 Imidazole	抑霉唑 imazalil	*S*-(+)-抑霉唑活性较 *R*-(−)-抑霉唑高 3~6.59 倍 The activity of *S*-(+)-imazalil is 3-6.59 times higher than that of *R*-(−)-imazalil	[96]
噁唑啉类 Isoxazolidine	啶菌噁唑 pyrisoxazole	*R,S*-啶菌噁唑的活性较 *S,S*-啶菌噁唑高 99~3545.3 倍 The activity of *R,S*-pyrisoxazole is 99-3545.3 times higher than that of *S,S*-pyrisoxazole	[97]

2 手性农药对映体的选择活性机制

2.1 对映体与靶标位点结合的选择性

研究靶标蛋白与药物分子的相互作用方式，对探究药物作用机理具有重要意义。分子对接技术已成为探索手性农药对映体选择性效应潜在机制的有力工具[83, 98-99]。分子对接是将小分子配体置于预定的结合区域，利用空间匹配和能量匹配，模拟小分子与大分子之间相互作用，选取最佳取向和构象，进而评估分子间作用模式[100]。小分子与蛋白之间的相互作用包括：静电作用、范德华力和氢键作用，最终两者之间的结合能力强弱和打分函数高低都取决于相互作用力[101]。手性农药对映体因具有不同的立体空间结构，与作用靶标的结合方式存在显著差异，从而导致不同的生物活性。在对映体选择性机制探究中，通常可利用同源建模的方法构建靶标蛋白的三维结构模型。同源建模主要包括：模板选择、序列对比、构建模型、能量优化和模型评估[100]。除分子对接结果之外，仍需通过生物试验寻找更多证据，以解析手性农药对映体与靶标位点结合时存在的差异。

2.1.1 手性除草剂对映体与靶标位点结合的选择性 近年来，有关除草剂分子靶标的种类、生物化学功能和三维结构的研究均有了重要突破。除草剂分子靶标或作用机制的发现，是从分子水平研究手性除草剂对映体选择活性的基础。除草剂的作用靶标多为植物生命活动代谢途径中的各种酶，如解偶联蛋白是二磷酸腺苷 (ADP) 生成三磷酸腺苷 (ATP) 氧化磷酸化过程的催化酶，而原卟啉原氧化酶可催化亚铁血红素和叶绿素的合成，这些酶是植物生长所必需的酶，若缺失或阻断这些酶的合成途径，将会导致植物出现不同症状的死亡[102]。

咪唑啉酮类除草剂几乎都具有手性。为探究其机制，Xie 等研究了 3 种咪唑啉酮类除草剂对稗草的活性，结果发现，*R*-咪唑啉酮的活性高于 *S*-咪唑啉酮；他们采用分子对接技术研究了其对映体与乙酰羟基酸合酶结合的差异，发现其对映体上异丙基取代基的指向相反，并且几个关键残基的位置不同，如 *R*-咪唑啉酮与 Asp365 和 Leu 形成氢键，而 *S*-咪唑啉酮与 Arg373 及 Leu375 形成氢键，从而从对映体与靶标位点结合的角度解

释了其除草活性的差异[103]。Zhang 等通过计算机模拟，探索了八氢番茄红素脱氢酶 (phytoene desaturase，PDS) 与呋草酮 (flurtamone) 对映体结合的方式，发现 *R*-呋草酮与 PDS 的结合能低于 *S*-呋草酮；分子对接结果显示，*R*-呋草酮的苯环分别与 PDS 的 PHE202 和 PHE301 形成 π-π 堆叠，而 *S*-呋草酮不存在 π-π 堆叠，从而推测，*R*-呋草酮与靶标分子活性位点的结合较 *S*-呋草酮更为稳定，可能是其存在对映体选择活性差异的机制 (图 1)[43]。Duan 等发现，*S*-唑酮草酯 (carfentrazone-ethyl) 和 *R*-唑酮草酯与靶标位点活性腔的结合方式虽然没有显著差异，但前者的结合能较低，认为这也可能是唑酮草酯具有对映体选择性生物活性的机制[104]。

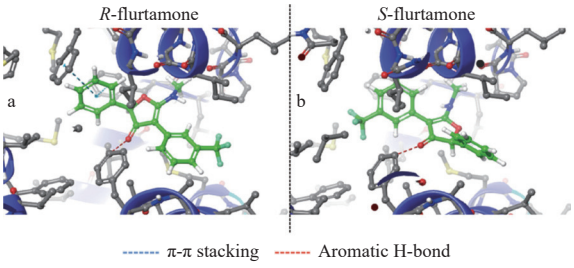


图 1 呋草酮对映体 (a、b) 与八氢番茄红素脱氢酶的对接姿态[43]

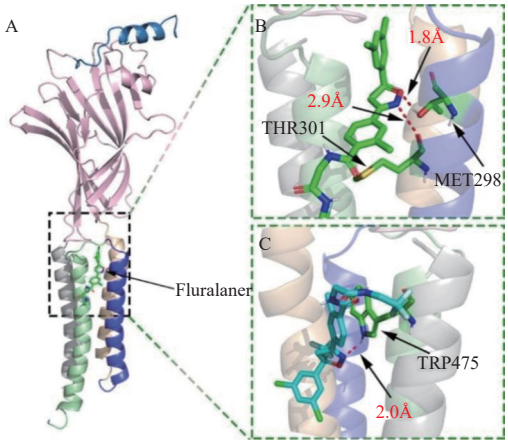
Fig. 1 Docking posture of flurtamone enantiomers (a, b) with phytoene desaturase (PDS)[43]

为更加全面深入地阐明手性除草剂的对映体选择性机制，Guo 等以 2,4-滴丙酸 (dichlorprop-*p*，DCPP) 和 2-甲-4-氯丙酸 (mecoprop-*p*，MCPP) 为研究对象，在分子对接的基础上，结合体外 H^3-IAA (indole-3-acetic acid) 结合测定、表面等离子体共振分析等技术手段，探究了手性苯氧羧酸类除草剂的对映选择性机制。结果显示：*R*-DCPP 和 *R*-MCPP 与受体 TIR1-IAA7 的结合能较 *S*-DCPP、*S*-MCPP 低；H^3-IAA 结合测定结果显示，*R*-MCPP 表现出最高的结合亲和力，其次是 *R*-DCPP，而两种 *S* 异构体几乎不与受体结合；表面等离子体共振分析显示，*R* 异构体能更多更快地结合受体蛋白且缔合稳定，不易解离。因此可以推断，苯氧羧酸类手性除草剂的对映体选择性机制是 *R* 型比 *S* 型异构体更有利于与受体 TIR1-IAA7 结合[105]。

2.1.2 手性杀虫剂对映体与靶标位点结合的选择性 对手性杀虫剂对映体选择性研究较为深入的杀虫剂品种主要为有机磷类、拟除虫菊酯类和苯基吡唑类。有机磷类杀虫剂多含有手性碳、磷及硫原子等，常存在较大的立体选择性差异。例如甲丙硫磷的对映体中，*S*-甲丙硫磷对家蝇的杀虫效果显著高于 *R*-甲丙硫磷[56]。拟除虫菊酯类杀虫剂中至少含有 1 个手性中心，且存在顺反异构体，因此该类杀虫剂是异构体数量最多的农药之一，但目前有关对映体杀虫活性差异的报道并不多。苯基吡唑类手性杀虫剂中含有手性硫原子，具有较强的杀虫活性，其作用机理是与昆虫中枢神经系统细胞膜上的 γ-氨基丁酸受体 (GABAR) 结合，干扰昆虫神经信号传导[106]。目前关于手性杀虫剂对映体与靶标蛋白之间相互结合的研究报道主要集中于苯基吡唑类杀虫剂。

Tian 等为解析苯基吡唑类手性杀虫剂丁虫腈 (flufiprole) 的立体选择性活性机制，选取果蝇 RDL 受体为研究对象，利用同源建模的方法，构建了果蝇 RDL 同源五聚体跨膜区三维结构模型，通过分子对接技术考查了丁虫腈对映体与作用靶标间的相互作用。结果显示：与 *S*-丁虫腈相比，*R*-丁虫腈与结合口袋内的氨基酸残基之间具有更强的疏水作用，与靶标位点的结合能力更强，并且从 3D 图中可看出，*R*-丁虫腈能够结合于氯离子通道的孔道中间位置，而 *S*-丁虫腈却相对偏离。该研究从分子水平说明了 *R*-丁虫腈具有更强的生物活性，揭示了丁虫腈具有立体选择活性差异的潜在机制[67]。氟噁唑酰胺 (fluxametamide) 是一种新型的配体门控氯离子通道 (LGCC) 拮抗剂，主要作用于害虫 γ-氨基丁酸门控氯离子通道 (GABACls)，作用方式新颖，有助于延缓害虫抗药性的发展[107]。Li 等为准确评价氟噁唑酰胺对映体的杀虫活性，测定了其对小菜蛾、夜蛾、棉蚜和朱砂叶螨 4 种目标害虫的对映体选择性，结果表明：*S*-(+)-氟噁唑酰胺的杀虫活性是其异构体 *R*-(−)-氟噁唑酰胺的 52.1~304.4 倍；将氟噁唑酰胺与受体 GABAR 进行分子对接，发现 *S*-(+)-氟噁唑酰胺与结合位点的亲和性更强[71]。类似的结果也见于 Zhang 等对氟雷拉纳 (fluralaner) 对映体选择活性机制的探究中，氟雷拉纳跟氟噁唑酰胺都属于手性异噁唑啉类杀虫剂，作用机制相同，*S*-氟雷拉纳抑制螟蛾和纹状线虫的活性是 *R*-氟雷拉纳的 33~39 倍；同源建模和分子对接结果表明，*S*-氟雷拉纳与 GABAR 具有较好的结合亲和力，结合能较低。据此可以得出结论：氟雷拉纳的对映体选

择性杀虫活性可能是由于其与 GABAR 的结合亲和力差异所导致 (图 2)[72]。



注：红色虚线表示氢键。

Note: The red dotted line represents a hydrogen bond.

图 2 同源性建模所得蜈蚣 γ-氨基丁酸受体 (GABAR) 的三维结构 (A)，以及 GABAR 与 *S*-(+)-氟雷拉纳 (B) 或 *R*-(−)-氟雷拉纳 (C) 的结合模式[72]

Fig. 2 Representation of the three-dimensional structure of *C. suppressalis* GABAR by homology modeling (A) and the combination modes between GABAR and *S*-(+)-fluralaner (B) or *R*-(−)-fluralaner (C)[72]

2.1.3 手性杀菌剂对映体与靶标位点结合的选择性 近 5 年来，计算机化学、化工合成、生物信息学等学科的飞速发展，对手性杀菌剂对映体选择性活性分子机制的研究起到了巨大的推动作用，其中对三唑类杀菌剂对映体选择活性的研究最为广泛且深入。Zhang 等通过同源性建模和分子对接研究表明，灭菌唑对映体在与靶标酶 CYP51b 结合时，由于形成氢键和 Pi-Pi 堆叠的能力不同，以及 Pi 阳离子相互作用、金属配位以及疏水效应的差别，*R*-灭菌唑和 *S*-灭菌唑表现出了结合活性的差异，由此得出灭菌唑对映体的不同生物活性源于其与 CYP51b 结合亲和力和结合方式不同的结论[81]。与 *S*,*R*-(−)-氟环唑相比，*R*,*S*-(+)-氟环唑与 CYPs 酶的结合能低并且与血红素铁离子之间的氢键距离短，说明 *R*,*S*-(+)-氟环唑的结合亲和能力较强[85]。Li 等研究发现，与 *R*-(−)-抑霉唑相比，*S*-(+)-抑霉唑与蛋白位点具有更强的疏水作用和更低的结合能构象[96]。Zhang 等的研究指出，*R*-丙硫菌唑与靶标 CYP51b 的结合模式优于 *S*-丙硫菌唑[83]。Li 等对结合模式及亲和力大小、对接结合模式、作用力及对接结合自由能的分析表明，*S*-(−)-戊菌唑与靶标真菌蛋白 CYP51 的亲和力高于 *R*-(+)-戊菌唑[76]。

除三唑类外，酰胺类手性杀菌剂也受到了广泛的关注。Pan 等报道，苯酰菌胺对映体与靶标分子结合位点残基之间的范德华力是导致 *R*-苯酰菌胺与 *S*-苯酰菌胺生物活性差异达到 9.9~140 倍的重要原因[91]。Wang 等的研究表明，*R*-氟唑菌酰羟胺的生物活性是 *S*-氟唑菌羟胺的 9.0~958.8 倍，表明 *R*-氟唑菌酰羟胺与 SDH 复合物具有更好的亲和力[93]。Zhang 等发现，双炔酰菌胺的对映体都能与 CesA3 的活性腔紧密结合，但与 *R*-双炔酰菌胺的 LYS 693 和 SER 694 等残基形成的氢键相比，*S*-双炔酰菌胺与 HIS693 残基形成了较强的卤素键，具有较低的结合能[16]。氟唑菌苯胺对映体与靶标蛋白结合袋中的活性位点结合时，*S*-(+)-氟唑菌苯胺能够与立枯丝核菌 *Rhizoctonia solani* 的琥珀酸脱氢酶 (SDH) 的氨基酸残基 Leu300 形成强氢键，通过对比结合模式和对接得分，发现 *S*-(+)-氟唑菌苯胺比 *R*-(−)-氟唑菌苯胺对结合位点的亲和力更强，对立枯丝核菌表现出较高的抑菌活性[92]。

目前，针对手性杀菌剂对映体选择活性机制的研究主要依靠计算机同源建模技术，生物验证相对较少，其主要原因可能是现阶段已解析出晶体结构的靶标蛋白数量有限。然而，也有研究通过分析靶标酶活性 (蛋白含量) 等验证了分子对接的结果。例如，董丰收等利用分子对接技术，研究了苯丙烯氟菌唑对映体与琥珀酸脱氢酶 (SDH) 的结合能力，结果表明，1*S*,4*R*-(−)-苯丙烯氟菌唑与 SDH 之间的亲和力更强；接着，他们测定了经苯丙烯氟菌唑对映体处理后炭疽菌 *Colletotrichum gloeosporioides* 的 SDH 活性，发现与 1*R*,4*S*-(+) 苯丙烯氟菌唑处理组和对照组相比，1*S*,4*R*-(−)-苯丙烯氟菌唑处理组 SDH 的活性显著受到了抑制；同时发现，1*S*,4*R*-(−)-苯丙烯氟菌唑处理组中琥珀酸 (succinate acid) 含量显著升高，而其下游产物富马酸 (fumaric acid) 和苹果酸 (*L*-malic acid) 的含量显著降低[95]。该研究也为其他手性农药对映体选择活性机制的研究提供了新思路。

2.2 手性农药对映体吸收、转运、代谢的选择性

手性农药不同对映异构体在生物系统中的吸收、分布、代谢和排泄等方面均存在选择性差异[108]。其中在代谢方面存在差异的潜在机制如下：1) 代谢对映体的酶不同；2) 代谢对映体的酶相同，能同时代谢对映体，但是代谢速率不同；3) 代谢酶按顺序代谢对映体，在优先代谢的异构

体完全转化之后再代谢另一种异构体；4) 部分代谢酶选择性代谢一个对映异构体，而酶的异构体可代谢另一个异构体[108]。代谢组学为评价手性农药的对映体选择活性以及从代谢角度剖析和探索其潜在机制提供了一种强大而可行的工具。

2.2.1 手性除草剂对映体的吸收、转运、代谢差异机制 异丙甲草胺的分子结构中同时含有手性碳原子和旋转阻碍的手性轴两个手性中心，存在4个立体异构体。据研究报道，异丙甲草胺可能通过抑制杂草中超长链脂肪酸和赤霉素的合成而发挥除草效果[109-110]。Zhao 等以稗草为对象，研究比较了异丙甲草胺 4 个异构体的除草活性，发现其活性差异表现为：*SS* > *SR* > *RS* > *RR*，手性碳在异构体的除草活性差异中起到了主要作用，异丙甲草胺的 *SS* 体和 *SR* 体更容易被杂草吸收并且对赤霉素合成的相对抑制率大于 90%，而 *RR* 和 *RS* 异构体对赤霉素合成的相对抑制率小于 20%，推测对赤霉素合成的选择性抑制是异丙甲草胺产生选择性除草活性的一个重要原因[30]。放射性同位素化学标记、合成、示踪技术是研究动植物体内农药代谢情况的重要手段[111]。常江海等以 ^{14}C-MCPP 对映体为示踪剂，研究了不同手性构型的 MCPP 在拟南芥中的吸收、转运以及亚细胞分布特征，结果表明：拟南芥对 ^{14}C-*R*-MCPP 和 ^{14}C-*S*-MCPP 的吸收效率分别为 90.45% 和 85.75%，二者差异显著；计算其在植株不同部位以及亚细胞中的分布比率后发现，拟南芥叶组织细胞壁对 ^{14}C-*S*-DCPP 具有更强的固定能力，而 ^{14}C-*R*-DCPP 则更易富集于叶组织的细胞器中，在相同施药浓度下，后者与靶标蛋白的接触频率更高；由此可从吸收、转运及亚细胞分布的角度，解释 *R*-MCPP 较 *S*-MCPP 具有更强除草活性的机制[112]。同年，Zhang 等通过组学分析发现，*R*-DCPP 对拟南芥叶片代谢，包括乳糖代谢、淀粉和蔗糖代谢、TCA 循环、脂肪酸生物合成途径和戊糖磷酸途径均有显著影响，并且在植物叶片中积累了大量的抗氧化剂，而 *S*-DCPP 处理组的氨基酸和部分萜类物质有所增加，表明 *R*-DCPP 对拟南芥叶片代谢的干扰程度高于 *S*-DCPP[113]。以上研究结果从吸收、转运及代谢层面，为解析手性除草剂对映体的选择活性差异提供了证据。

2.2.2 手性杀虫剂对映体的吸收、转运、代谢差异机制 目前有关手性杀虫剂对映体在吸收、转运、代谢方面存在选择性差异的研究报道还较少。2017 年，张青在探究手性苯基吡唑类杀虫剂乙虫腈的立体选择性活性机制时，通过测定乙虫腈对映体对 *γ*-氨基丁酸受体 RDL 亚基中电流的抑制作用，发现其与靶标相互结合以及对电流的抑制效果均不存在立体选择性结合差异，因此只能初步推测，可能是由于手性农药乙虫腈进入昆虫体内的途径具有立体选择性，或者由于异构体在生物体内的代谢速率不同，导致了对映体与靶标结合的量不一样，从而表现出立体选择性活性[114]。虽然具体的代谢机制还有待进一步探究，但可以确定的是，对映体吸收、转运、代谢等方面的差异是研究手性杀虫剂对映体选择活性机制的新切入点。

2.2.3 手性杀菌剂对映体的代谢差异机制 手性杀菌剂对映体的选择性生物活性及抑菌机制可通过对代谢物的定量代谢组学分析加以阐明[93, 115-116]。He 等测定了叶菌唑 (metconazole) 立体异构体的抑菌活性，结果表明：(1*S*,5*R*)-叶菌唑对禾谷镰刀菌的抑菌活性是 (1*R*,5*S*)-叶菌唑的 13.9~23.4 倍；分子对接结果显示：与另外 3 种异构体相比，(1*S*,5*R*)-叶菌唑与 CYP51B 的结合能最强、结合距离最短；核磁共振代谢组学研究结果也表明：(1*R*,5*S*)-叶菌唑处理组的禾谷镰刀菌中，丙氨酸、精氨酸、乙酸、乙醇的生成量明显高于 (1*S*,5*R*)-叶菌唑处理组，而葡萄糖、甘油、谷氨酸、蛋氨酸和三甲胺的生成量却远低于 (1*S*,5*R*)-叶菌唑处理组[90]。通过对叶菌唑立体异构体的系统研究，在立体异构水平上对叶菌唑的生物活性、代谢行为和抑菌机制形成了新的认知，所得结果从代谢角度揭示了手性杀菌剂存在对映体选择活性差异的机制。

3 小结与展望

研究手性农药不同对映异构体的选择活性，对于发展高效、安全的绿色农药具有非常重要的意义[17]。本文聚焦手性农药异构体对靶标生物的对映体选择活性，侧重阐明了选择活性的机制。总结现有的研究结果可看出，手性农药的活性普遍存在对映体选择性，其机制总体可概括为以下两方面：1) 异构体与生物体内靶标酶的结合存在差异；2) 生物体对异构体的吸收、转运和代谢能力存在差异。

基于对映体与靶标酶结合的差异，探索手性农药对映体选择性的研究，目前大多停留在计算机模拟分子对接水平。对于尚未解析 3D 蛋白结构的靶标酶，仍只能通过同源建模的方式进行对接，所得到的结论虽可在一定程度上解析手性农药对映体与靶标酶结合的差异，但还需通过体外测定、同位素标记体内测定及细胞试验等方法进一步进行验证。此外，手性农药对映体与靶标生物受体选择性地结合后，所导致的一系列生理反应与相关途径之间的联系也还有待探索。

手性农药对映体的选择性与其在生物体内的吸收、转运和代谢等过程密切相关，因此在探索手性农药对映体的选择活性时，首先要明确对映体是选择性地进入靶标生物体内还是在生物体内发生了选择性降解和代谢，或是两者兼有。目前可结合分子生物学、生物分析传感等技术解析手性农药的对映体选择活性机制。现有研究多采用代谢组学分析等技术手段，推测手性农药对映体的选择性代谢过程，但是对代谢物的鉴定还存在一定技术瓶颈，同时具体的代谢过程也还需进一步研究明确。

上述对手性农药对映体选择性活性及机制研究的总结，由浅入深地阐明了存在对映体选择性差异的原因，可为手性化合物的结构优化以及新化合物的开发提供理论参考。应对目前传统农药面临的抗性、生态风险和剂型/制剂老化等问题，深入了解手性农药活性对映体分子与作用靶标间的相互作用机制，将大幅减少化合物生产投入，降低研发成本，提高新农药创制效率，但目前仅明晰了一小部分手性农药对映体的选择性活性机制，关于更多手性农药异构体的选择性及其机制仍有待深入研究揭示。

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