医药与日化原料

2-(4-芳氧苯氧基)丙酸衍生物的合成及除草活性

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摘要：以(*R*)-2-(4-羟基苯氧基)丙酸为原料，经醚化、酰氯化、酰胺化或酯化等步骤合成了 22 个 2-(4-芳氧苯氧基)丙酸酯或 2-(4-芳氧苯氧基)丙酰胺化合物（Ⅳa~v），其结构经 ^{1}HNMR、^{13}CNMR、MS 及 EA 表征。除草活性测试结果表明：在 75 g/hm^2 浓度下，大部分化合物对单子叶杂草具有选择性的除草活性，其中化合物Ⅳa、Ⅳc、Ⅳf、Ⅳg 和Ⅳi 对单子叶杂草（马唐、稗草、狗尾草）土壤处理和茎叶处理均具有 100%的防除效果。
关键词：2-(4-芳氧苯氧基)丙酸酯类除草剂（APP 类除草剂）；2-(4-芳氧苯氧基)丙酰胺；除草活性；构效关系；
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Synthesis and Herbicidal Activity of 2-(4-Aryloxyphenoxy) Propionic Acid Derivatives

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Abstract: Twenty-two 2-(4-aryloxyphenoxy) propionic acid derivatives were designed and synthesized from (*R*)-2-(4-hydroxyphenoxy) propanoic acid by etherification, acylation, amidation or esterification. Their structures were characterized by ^{1}HNMR, ^{13}CNMR, HRMS and elemental analysis. The bioassay results indicated that most of compounds exhibited excellent herbicidal activity and selectivity against monocotyl-edonous weeds at the dosage of 75 g/hm^2. In particular, compounds Ⅳa, Ⅳc, Ⅳf, Ⅳg and Ⅳi exhibited 100% herbicidal efficiency in both pre- and postemergence treatments against *Digitaria sanguinalis*, *Echinochloa crus-galli L* and *Setaria viridis*.
Key words: 2-(4-aryloxyphenoxy) propionate type herbicide(APP type herbicide); 2-(4-aryloxyphenoxy) propionamide; herbicidal activity; structure-activity relationship
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2-(4-芳氧苯氧基)丙酸（APP）类除草剂是一类选择性防除禾本科杂草除草剂，因具高效、低毒、高选择性和环境友好等特点[1]，自上市以来，其研究备受关注。此类除草剂经抑制禾本科杂草乙酰辅酶 A 羧化酶，阻断植株体内酯肪酸的合成[2]，选择性地防除禾本科杂草，从而对阔叶作物无影响。1991 年，诺华公司开发了第一个用于小麦田的 APP 类除草剂——炔草酯[3]，此后，陶氏化学和韩国化工技术研究院陆续开发出了两种用于水稻田的 APP 类除草剂——氰氟草酯和噁唑酰草胺[4]。

然而，由于氰氟草酯和噁唑酰草胺的大量使用，这 2 种除草剂已相继出现杂草抗性[5-6]。为解决除草剂抗性问题，寻找高效的 APP 除草剂新品种成为一种选择。因此，国内外科研工作者做了大量研究，合成了一大批高活性化合物，但在作物安全性特别是禾本科作物安全性上尚未有较大突破[7-14]。为此，本人在 2-(4-芳氧苯氧基)丙酸化合物方面做了很多工作，以炔草酯为先导物，对其改造得到 HNPC-A8169，发现其具有很好的除草活性[15]，进一步改造得到系列 A 化合物[16]，用吡啶基或噻唑基对不饱和烃进行替代，得到系列 B 化合物[17]，生物活性测定结果表明，化合物 HNPC-A11315（B1：

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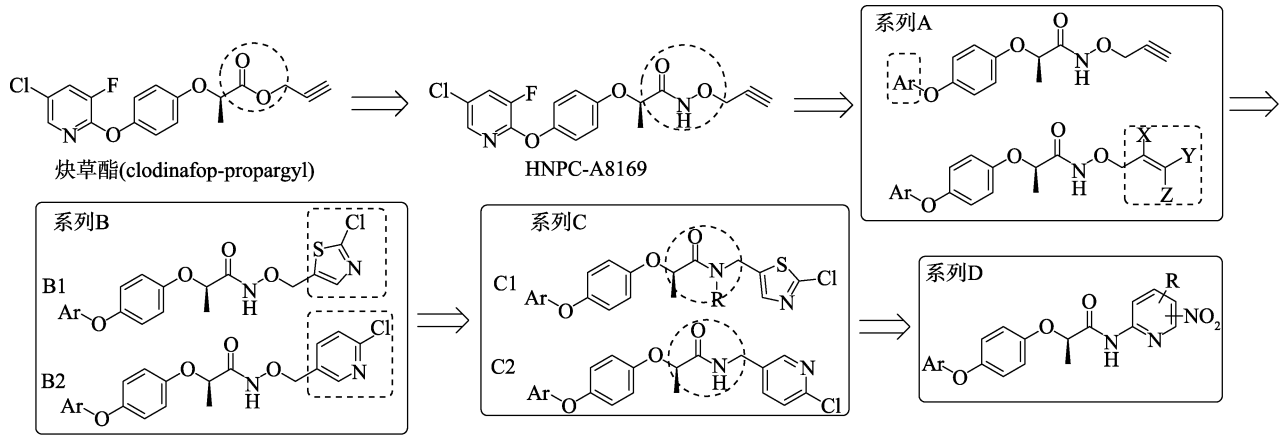
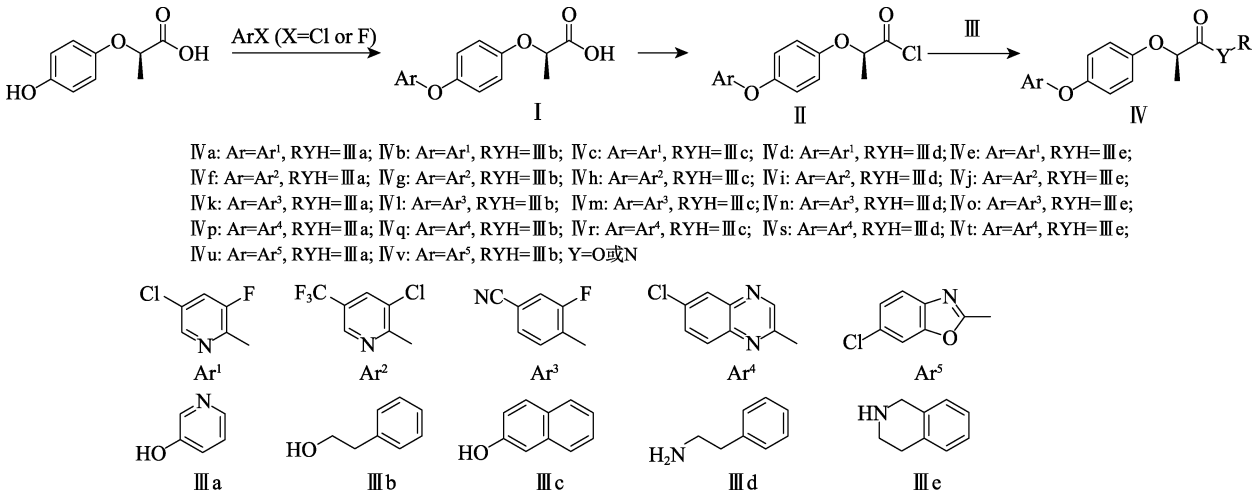
Ar=6-氯喹喔啉）除草活性远高于同类商品化除草剂炔草酯，且化合物对阔叶作物表现出安全性，但遗憾的是对禾本科作物的安全性较差。为提高化合物的作物安全性，将 *N*-杂环甲氧基中的氧原子去掉，得到系列 C 化合物[18]，活性及作物安全性测试表明，化合物 HNPC-A11211（C2: Ar=3-氯-5-三氟甲基吡啶-2-基）的除草活性高于噁唑酰草胺，且对水稻茎叶处理安全，同时对水稻田主要杂草千金子的活性远高于氰氟草酯，该化合物正在进行深入的除草活性和作物安全性的研究。进一步对其结构改造，用硝基吡啶替代芳甲基，得到系列 D 化合物，大部分化合物均具有很好的除草活性[19]。此外，鉴于该类化合物还具有抗肿瘤活性[1]，化合物在抗肿瘤活性研究方面亦取得了不错的结果[20-21]。炔草酯、HNPC-A8169 及系列 A、B、C、D 化合物结构如下所示，虚线部分为结构上的创新点。



在前期研究的基础上，本文保留田间应用主要品种（炔草酯、氰氟草酯、噁唑酰草胺、吡氟禾草灵、精喹禾灵等）的芳氧苯氧基部分，重点对羧酸衍生物部分进行改造，设计了一系列 2-(4-芳氧苯氧基)丙酸酯类和酰胺类化合物，经醚化，酰氯化，酰胺化或酯化等步骤合成了 22 个 2-(4-芳氧苯氧基)丙酸衍生物，合成路线如下：



1　实验部分

1.1　试剂与仪器

所用原料和试剂均为市售 AR 或 CP，其中(*R*)-2-(4-羟基苯氧)丙酸 e.e.值为 98%。

Bruker advance III （400 MHz）型核磁共振仪、SolariX-70FT-MS 型高分辨质谱仪，美国布鲁克公司；X-5 显微熔点测定仪，郑州南北仪器设备有限公司；ZF-2 型三用紫外分析仪，上海市安亭电子仪器厂；PE2400II-CHNS/O 型元素分析仪，美国珀金埃尔默公司。

1.2　合成步骤

1.2.1　化合物Ⅰ和Ⅱ的合成

化合物Ⅰ和Ⅱ的合成参照文献[18]。

1.2.2　目标化合物Ⅳa~v 的合成

取 2-(4-芳氧苯氧基)丙酰氯Ⅱa~e（3.3 mmol）、二氯甲烷（40 mL）、中间体Ⅲa~e（3.3 mmol）和催化量的 4-二甲基氨基吡啶（DMAP），冰浴搅拌

10 min，滴入三乙胺 1.0 g（10 mmol），继续搅拌 3 h，倒入 100 mL 冰水中，CH_2Cl_2 萃取，Na_2SO_4 干燥，减压脱溶，柱层析得到 2-(4-芳氧苯氧基)丙酸衍生物Ⅳa~v。

吡啶-3-基-(*R*)-2-[4-(3-氟-5-氯吡啶-2-氧基)苯氧基]丙酸酯（Ⅳa）：0.58 g，产率 45%，黄色油状液体，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.81 (d, *J*=6.8 Hz, 3H, CH_3), 5.00 (q, *J*=6.8 Hz, 1H, CH), 7.02 (d, *J*=9.2 Hz, 2H, PhH), 7.11 (d, *J*=9.2 Hz, 2H, PhH), 7.35 (dd, *J*= 8.4 Hz,4.4 Hz, 1H, Py-H), 7.44~7.47 (m, 1H, Py-H), 7.50 (dd, *J*= 9.2 Hz, 2.0 Hz, 1H, Py-H), 7.88 (d, *J*=2.0 Hz, 1H, Py-H), 8.39 (d, *J*=2.8 Hz, 1H, Py-H), 8.50 (dd, *J*= 4.4 Hz, 1.6 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.57, 73.19, 116.28, 122.47, 124.02, 124.90, 125.08, 129.06, 140.17, 142.94, 145.63, 147.00, 147.24, 147.40, 148.28, 154.67, 170.22。Anal. Calcd. for $C_{19}H_{14}ClFN_2O_4$，%: C 58.70, H 3.63, N 7.21, found：C 58.91, H 3.55, N 7.10。

(*R*)-2-[4-(3-氟-5-氯吡啶-2-氧基)苯氧基]丙酸苯乙基酯（Ⅳb）：0.71 g，产率 51%，无色油状液体，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.56 (d, *J*=6.8 Hz, 3H, CH_3), 2.95 (t, *J* =6.8 Hz, 2H, CH_2), 4.40 (t, *J*=6.8 Hz, 2H, CH_2), 4.68 (q, *J*=6.8 Hz, 1H, CH), 6.84 (d, *J*=9.2 Hz, 2H, PhH), 7.03 (d, *J*=9.2 Hz, 2H, PhH), 7.17~7.31 (m, 5H, PhH), 7.49(dd, *J* =9.2Hz, 2.4 Hz, 1H, Py-H), 7.85 (d, *J*=2.4 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.58, 34.94, 65.56, 73.06, 116.01, 122.25, 124.82, 125.00, 126.65, 128.52, 128.87, 137.30, 140.09, 145.64, 146.95, 148.28, 154.91, 172.02。Anal. Calcd. for $C_{22}H_{19}ClFNO_4$，%: C 63.54, H 4.61, N 3.37, found：C 63.40, H 4.49, N 3.30。

(*R*)-2-[4-(3-氟-5-氯吡啶-2-氧基)苯氧基]丙酸萘酯（Ⅳc）：0.86 g，产率 59%，淡黄色固体，熔点 125.7~126.5 ℃；^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.84 (d, *J*=6.8 Hz, 3H, CH_3), 5.02 (q, *J*=6.8 Hz, 1H, CH), 7.06 (d, *J*=9.2 Hz, 2H, PhH), 7.13~7.18 (m, 3H, PhH + Naphthol-H), 7.47~7.53 (m, 4H, Naphthol-H), 7.80 (dd, *J*=7.2Hz, 2.0 Hz, 1H, Py-H), 7.83~7.86 (m, 2H, Naphthol-H), 7.88 (d, *J*=2.4 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.67, 73.37, 116.30, 118.33, 120.54, 122.42, 124.88, 125.06, 125.91, 126.70, 127.65, 127.78, 129.56, 131.56, 133.62, 140.13, 140.19, 145.68, 147.29, 147.81, 154.89, 170.86。Anal. Calcd. for $C_{24}H_{17}ClFNO_4$，%: C 65.84, H 3.91, N 3.20, found：C 65.73, H 3.89, N 3.11。

N-苯乙基-(*R*)-2-[4-(3-氟-5-氯吡啶-2-氧基)苯氧基]丙酰胺（Ⅳd）：0.84 g，产率 61%，白色固体，熔点 108.0~109.1 ℃；^{1}HNMR ($CDCl_3$, 400 MHz)，δ:1.54 (d, *J*=6.8 Hz, 3H, CH_3), 2.71~2.85 (m, 2H, CH_2), 3.47~3.66 (m, 2H, CH_2), 4.61 (q, *J*=6.8 Hz, 1H, CH), 6.45 (br, s, 1H, NH), 6.86 (d, *J*=8.8 Hz, 2H, PhH), 7.08~7.10 (m, 4H, PhH), 7.18~7.29 (m, 3H, PhH), 7.51 (dd, *J*=8.8Hz, 2.4 Hz, 1H, Py-H), 7.85 (d, *J*=2.4 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.93, 35.67, 40.06, 75.57, 116.24, 122.55, 124.90, 125.09, 126.53, 128.64, 128.76, 138.46, 140.09, 140.15, 147.23, 150.14, 154.26, 171.92。Anal. Calcd. for $C_{22}H_{20}ClFN_2O_3$，%: C 63.69, H 4.86, N 6.75, found：C 63.55, H 4.87, N 6.56。

(*R*)-四氢异喹啉-2-基-2-[4-(3-氟-5-氯吡啶-2-氧基)苯氧基]丙酮（Ⅳe）：0.78 g，产率 55%，黄色油状液体，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.67 (d, *J*=6.8 Hz, 3H, CH_3), 2.73~2.94 (m, 2H, CH_2), 3.64~3.99 (m, 2H, CH_2), 4.66~4.96 (m, 2H, CH_2), 5.01 (q, *J*=6.8 Hz, 1H, CH), 6.91~7.20 (m, 8H, PhH), 7.48 (dd, *J*=8.8 Hz, 2.0 Hz, 1H, Py-H), 7.85 (d, *J*=2.0 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 17.87, 29.52, 44.98, 46.82, 74.91, 115.77, 122.39, 124.82, 125.00, 126.51, 128.38, 128.96, 132.72, 133.73, 140.13, 145.63, 146.93, 148.27, 151.19, 154.61, 170.03。Anal. Calcd. for $C_{23}H_{20}ClFN_2O_3$，%: C 64.72, H 4.72, N 6.56, found：C 64.52, H 4.49, N 6.69。

吡啶-3-基-(*R*)-2-[4-(3-氯-5-三氟甲基吡啶-2-氧基)苯氧基]丙酸酯（Ⅳf）：0.76 g，产率 52%，淡黄色透明液体，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.83 (d, *J*=6.8 Hz, 3H, CH_3), 5.02 (q, *J*=6.8 Hz, 1H, CH), 7.05 (d, *J*=8.8 Hz, 2H, Ph-H), 7.12 (d, *J*=8.8 Hz, 2H, Ph-H), 7.35 (dd, *J*=8.4 Hz, 4.8 Hz, 1H, Py-H), 7.44~7.48 (m, 1H, Py-H), 7.97 (d, *J*=2.4 Hz, 1H, Py-H), 8.27~8.28 (m,1H, Py-H), 8.39 (d, *J*=2.4 Hz, 1H, Py-H), 8.50 (d, *J*=4.0 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.56, 73.20, 116.10, 116.30, 119.18, 122.61, 122.86, 124.00, 129.03, 136.30, 142.61, 142.95, 147.19, 147.27, 155.03, 161.29, 170.18, 172.27。Anal. Calcd. for $C_{20}H_{14}ClF_3N_2O_4$，%: C 54.75, H 3.22, N 6.38, found：C 54.61, H 3.01, N 6.23。

(*R*)-2-[4-(3-氯-5-三氟甲基吡啶-2-氧基)苯氧基]丙酸苯乙基酯（Ⅳg）：0.73 g，产率 47%，透明黏稠状液体，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.57 (d, *J*=6.8 Hz, 3H, CH_3), 2.95 (t, *J*=6.8 Hz, 2H, CH_2), 4.41 (t, *J*=6.8 Hz, 2H, CH_2), 4.698 (q, *J*=6.8 Hz, 1H, CH), 6.87 (d, *J*=9.2 Hz, 2H, Ph-H), 7.03 (d, *J*=9.2 Hz, 2H, Ph-H), 7.17~7.31 (m, 5H, Ph-H), 7.96 (d, *J*=2.4 Hz, 1H, Py-H), 8.24 (s, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.57, 34.93, 65.58, 73.03, 116.00, 119.13, 121.48, 122.07, 122.58, 126.65, 128.52, 128.86, 136.22, 137.28, 142.56, 146.70, 155.22, 161.35, 171.95。Anal. Calcd. for $C_{23}H_{19}ClF_3NO_4$，%: C 59.30, H 4.11, N 3.01, found：C 59.12, H 4.00, N 3.19。

(*R*)-2-[4-(3-氯-5-三氟甲基吡啶-2-氧基)苯氧基]丙酸萘酯（Ⅳh）：0.73 g，产率 45%，白色固体，

m.p. 105 ~ 113 ℃, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.85 (d, J=6.8 Hz, 3H, CH_3), 5.04 (q, J=6.8 Hz, 1H, CH), 7.07 (d, J=6.8 Hz, 2H, Ph-H), 7.14~7.18 (m, 3H, Ph-H + naphthalene-H), 7.46~7.53 (m, 3H, naphthalene-H), 7.78~7.86 (m, 3H, naphthalene-H), 7.97 (d, J=2.4 Hz, 1H, Py-H), 8.27 (s, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 18.66, 73.32, 116.28, 118.32, 119.17, 120.52, 122.50, 122.79, 125.93, 126.72, 127.64, 127.78, 129.57, 131.56, 133.61, 136.25, 142.55, 142.60, 147.03, 147.78, 155.22, 161.36, 170.81。Anal. Calcd. for $C_{25}H_{17}ClF_3NO_4$, %: C 61.55, H 3.51, N 2.87, found: C 61.76, H 3.61, N 2.59。

N-苯乙基-(*R*)-2-[4-(3-氯-5-三氟甲基吡啶-2-氧基)苯氧基]丙酰胺(Ⅳi): 1.00 g, 产率 65%, 白色固体, m. p.146~148 ℃, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.59 (d, J=6.8 Hz, 3H, CH_3), 2.74~2.91 (m, 2H, CH_2), 3.48-3.57 (m, 1H, CH_2), 3.64~3.73 (m, 1H, CH_2), 4.66 (q, J=6.8 Hz, 1H, CH), 6.50 (br, 1H, NH), 6.93 (d, J=9.2 Hz, 2H, Ph-H), 7.12~7.15 (m, 3H, Ph-H), 7.24~7.33 (m, 4H, Ph-H), 8.02 (s, 1H, Py-H), 8.29 (s, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 18.93, 35.68, 40.06, 75.59, 116.25, 119.12, 122.87, 126.53, 128.64, 128.75, 136.28, 138.40, 142.51, 146.96, 154.59, 171,85; Anal. Calcd. for $C_{23}H_{20}ClF_3N_2O_3$, %: C 59.43, H 4.34, N 6.03, found: C 59.31, H 4.29, N 6.26。

(*R*)-四氢异喹啉-2-基-2-[4-(3-氯-5-三氟甲基吡啶-2-氧基)苯氧基]丙酮(Ⅳj): 1.00 g, 产率 63%, 白色固体, m.p. 47~48 ℃, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.67 (d, J=6.8 Hz, 3H, CH_3), 2.73-2.94 (m, 2H, CH_2), 3.64-4.01 (m, 2H, CH_2), 4.66-4.97 (m, 2H, CH_2), 5.03 (q, J=6.8 Hz, 1H, CH), 6.94-7.21 (m, 8H, Ph-H), 7.96 (s, 1H, Py-H), 8.24 (s, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 17.89, 29.56, 45.02, 46.86, 75.07, 115.85, 115.96, 119.18, 122.64, 122.76, 126.39, 126.55, 126.66, 127.04, 128.39, 132.75, 136.19, 142.53, 146.80, 155.01, 161.32, 170.00. Anal. Calcd. for $C_{24}H_{20}ClF_3N_2O_3$, %: C 60.45, H 4.23, N 5.87, found: C 60.59, H 4.10, N 5.98。

吡啶-3-基-(*R*)-2-[4-(4-氰基-2-氟苯氧基)苯氧基]丙酸酯(Ⅳk): 0.88 g, 产率 70%, 黄色黏液, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.85 (d, J=6.4 Hz, 3H, CH_3), 5.03 (q, J=6.4 Hz, 1H, CH), 6.91~7.09 (m, 4H, PhH), 7.30~7.51 (m, 5H, PhH, Py-H), 8.43 (s, 1H, Py-H), 8.55 (s, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 18.56, 73.13, 116.52, 116.65, 116.83, 118.81, 120.57, 120.78, 121.12, 124.13, 129.11, 129.40, 135.26, 142.82, 147.03, 147.25, 149.11, 154.69, 170.07。Anal. Calcd. for $C_{21}H_{15}FN_2O_4$, %: C 66.66, H 4.00, N 7.40, found: C 66.81, H 3.88, N 7.21。

(*R*)-2-[4-(4-氰基-2-氟苯氧基)苯氧基]丙酸苯乙基酯(Ⅳl): 0.88 g, 产率 65%, 透明油状液体, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.57 (d, J=6.8 Hz, 3H, CH_3), 2.95 (t, J=6.8 Hz, 2H, CH_2), 4.41 (t, J=6.8 Hz, 2H, CH_2), 4.67 (q, J=6.8 Hz, 1H, CH), 6.81-6.87 (m, 3H, Ph-H), 6.94 (d, J=9.2 Hz, 2H, Ph-H), 7.17-7.34 (m, 6H, Ph-H), 7.44 (dd, J=10.0 Hz, 2.0 Hz, 1H, Ph-H); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 18.52, 34.93, 65.56, 72.98, 105.93, 116.52, 118.47, 120.41, 120.62, 121.00, 126.67, 128.50, 128.82, 129.31, 137.24, 148.44, 151.08, 153.58, 154.95, 171.81。Anal. Calcd. for $C_{24}H_{20}FNO_4$, %: C 71.10, H 4.97, N 3.45, found: C 71.32, H 5.02, N 3.19。

(*R*)-2-[4-(4 氰基-2-氟苯氧基)苯氧基]丙酸萘酯(Ⅳm): 0.67 g, 产率 47%, 白色固体, 熔点 80~81 ℃, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.85 (d, J=6.8 Hz, 3H, CH_3), 5.00 (q, J=6.8 Hz, 1H, CH), 6.90 (t, J=4.0 Hz, 1H, naphthalin-H), 7.06 (s, 4H, PhH), 7.16 (dd, J=8.8 Hz, 2.4 Hz, 1H, PhH), 7.32~7.35 (m, 1H, naphthalin-H), 7.45~7.53 (m, 4H, PhH + naphthalin-H), 7.80 (dd, J=7.2 Hz, 2.0 Hz, 1H, naphthalin-H), 7.84 (d, J=8.4 Hz, 2H, naphthalin-H); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 18.63, 73.38, 106.20, 116.92, 118.26, 118.74, 120.42, 120.53, 120.74, 121.12, 126.02, 126.82, 127.63, 127.82, 129.35, 129.62, 131.62, 133.65, 147.83, 148.98, 150.46, 151.24, 154.98, 170.63。Anal. Calcd. for $C_{26}H_{18}FNO_4$, %: C 73.06, H 4.24, N 3.28, found: C 73.23, H 4.51, N 3.52。

N-苯乙基-(*R*)-2-[4-(4-氰基-2-氟苯氧基)苯氧基]丙酰胺(Ⅳn): 0.74 g, 产率 55%, 白色固体, 熔点 104~105 ℃, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.54 (d, J=6.8 Hz, 3H, CH_3), 2.71~2.84 (m, 2H, CH_2), 3.46~3.54 (m, 1H, CH_2), 3.58~3.67 (m, 1H, CH_2), 4.59 (q, J=6.8 Hz, 1H, CH), 6.43 (br s, 1H, NH), 6.84~6.90 (m, 3H, PhH), 6.99 (d, J=8.8 Hz, 2H, PhH), 7.09 (d, J=6.4 Hz, 2H, PhH), 7.19~7.28 (m, 3H, PhH), 7.34 (dt, J=8.4 Hz, 1.6Hz, 1H, PhH), 7.46 (dd, J=10.0 Hz, 2.0 Hz, 1H, PhH); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 18.88, 35.64, 40.04, 75.73, 116.86, 117.57, 118.73, 120.55, 120.77, 121.06, 126.57, 128.62, 128.71, 129.32, 129.36, 138.44, 148.99, 153.72, 154.26, 171.73。Anal. Calcd. for $C_{24}H_{21}FN_2O_3$, %: C 71.27, H 5.23, N 6.93, found: C 71.49, H 5.00, N 6.87。

(*R*)-四氢异喹啉-2-基-2-[4-(4-氰基-2-氟苯氧基)苯氧基]丙酮(Ⅳo): 0.90 g, 产率 65%, 黄色黏液, ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 1.68 (d, J=6.8 Hz, 3H, CH_3), 2.75~2.90 (m, 2H, CH_2), 3.78~4.02 (m, 2H, CH_2), 4.68~4.89 (m, 2H, CH_2), 5.05 (q, J=6.8 Hz, 1H, CH), 6.74~6.85 (m, 1H, PhH), 6.88~7.00 (m, 4H, PhH), 7.07~7.23 (m, 4H, PhH), 7.29~7.33 (m, 1H, PhH), 7.44 (dd, J=10.0 Hz,2.0 Hz, 1H, PhH); ^{13}CNMR ($CDCl_3$, 100 MHz), δ: 17.98, 29.56, 45.02, 46.88,

75.00, 106.09, 116.47, 118.63, 120.46, 120.67, 121.17, 125.93, 126.68, 127.06, 128.39, 128.98, 129.32, 132.73, 148.58, 150.47, 153.63, 154.80, 169.93。Anal. Calcd. for $C_{25}H_{21}FN_2O_3$，%: C 72.10, H 5.08, N 6.73, found：C 72.21, H 5.01, N 6.59。

吡啶-3-基-(*R*)-2-[4-(6-氯喹喔啉-2-氧基)苯氧基]丙酸酯（Ⅳp）：0.72 g，产率 51%，淡黄色固体，m.p. 81~82 ℃，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.85 (d, J=6.8 Hz, 3H, CH_3), 5.05 (d, J=6.8Hz, 1H, CH), 7.07 (d, J=9.2 Hz, 2H, PhH), 7.23 (d, J=9.2 Hz, 2H, PhH), 7.35 (dd, J=8.4 Hz, 4.8 Hz, 1H, Py-H), 7.47~7.50 (m, 1H, Py-H), 7.62 (dd, J=8.8Hz, 2.4 Hz, 1H, quinoxaline-H), 7.70 (d, J=8.8 Hz, 1H, quinoxaline-H), 8.05 (d, J=2.4 Hz, 1H, quinoxaline-H), 8.41 (d, J=2.8 Hz, 1H, Py-H), 8.52 (dd, J=4.8 Hz, 1.2 Hz, 1H, Py-H), 8.69 (s, 1H, quinoxaline-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.59, 73.14, 116.21, 122.68, 123.99, 127.93, 128.82, 129.01, 131.18, 132.91, 138.48, 139.78, 140.10, 142.96, 146.93, 146.99, 147.30, 154.82, 157.15, 170.23。Anal. Calcd. for $C_{22}H_{16}ClN_3O_4$，%: C 62.64, H 3.82, N 9.96, found：C 62.59, H 4.00, N 10.01。

(*R*)-2-[4-(6-氯喹喔啉-2-氧基)苯氧基]丙酸苯乙酯（Ⅳq）：1.12 g，产率 75%，白色固体，m.p. 78~79 ℃，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.59 (d, J=6.8 Hz, 3H, CH_3), 2.96 (t, J=7.2 Hz, 2H, CH_2), 4.38~4.44 (m, 2H, CH_2), 4.72 (q, J=6.8 Hz, 1H, CH), 6.89 (d, J=7.2 Hz, 2H, PhH), 7.12~7.31 (m, 7H, PhH), 7.59 (dd, J=7.2 Hz, 2.4 Hz, 1H, quinoxaline-H), 7.64 (d, J =7.2 Hz, 1H, quinoxaline-H), 8.04 (d, J=2.4 Hz, 1H, quinoxaline-H), 8.67 (s, 1H, quinoxaline-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.60, 34.97, 65.58, 73.00, 115.94, 122.42, 126.66, 127.92, 128.53, 128.77, 128.87, 131.11, 132.81, 137.29, 138.52, 139.74, 140.11, 146.50, 155.06, 157.22, 172.00。Anal. Calcd. for $C_{25}H_{21}ClN_2O_4$，%: C 66.89, H 4.72, N 6.24, found：C 67.02, H 4.66, N 6.19。

(*R*)-2-[4-(6-氯喹喔啉-2-氧基)苯氧基]丙酸萘酯（Ⅳr）：1.24 g，产率 79%，白色固体，m.p. 120~121 ℃。^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.87 (d, J=6.8 Hz, 3H, CH_3), 5.06 (q, J=6.8 Hz, 1H, CH), 7.11 (d, J=7.2 Hz, 2H, PhH), 7.18 (dd, J=8.8 Hz, 2.4 Hz, 1H, naphthalin-H), 7.24 (d, J=7.2 Hz, 2H, PhH), 7.45~7.52 (m, 2H, naphthalin-H), 7.55 (d, J =2.4 Hz, 1H, naphthalin-H),7.60 (dd, J=8.8 Hz, 2.0 Hz, 1H, quinoxaline-H), 7.67 (d, J=8.8 Hz, 1H, quinoxaline-H), 7.79 (dd, J=6.4 Hz, 2.8 Hz, 1H, naphthalin-H), 7.84 (dd, J=7.2 Hz, 3.2 Hz, 1H, naphthalin-H), 8.05 (d, J=2.0 Hz, 2H, quinoxaline-H), 8.69 (s, 1H, quinoxaline-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.66, 73.39, 116.31, 118.31, 120.52, 122.61, 125.93, 126.73, 127.66, 127.78, 127.96, 128.83, 129.58, 131.14, 131.59, 132.89, 133.64, 138.55, 139.82, 140.13, 146.89, 147.86, 155.08, 157.23, 170.80。Anal. Calcd. for $C_{27}H_{19}ClN_2O_4$，%: C 68.87, H 4.07, N 5.95, found：C 69.01, H 4.02, N 5.91。

N-苯乙基-(*R*)-2-[4-(6-氯喹喔啉-2-氧基)苯氧基]丙酰胺（Ⅳs）：0.88 g，产率 59%，淡黄色固体，m.p. 136~138 ℃，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.57 (d, J=8.4 Hz, 3H, CH_3), 2.71~2.88 (m, 2H, CH_2), 3.42~3.50 (m, 1H, CH_2), 3.65~3.74 (m, 1H, CH_2), 4.65 (q, J =8.4 Hz, 1H, CH), 6.46 (br s, 1H, NH), 6.91 (d, J=8.8 Hz, 2H, PhH), 7.07 (d, J=6.8 Hz, 2H, PhH), 7.18~7.29 (m, 5H, Ph-H), 7.58 (dd, J=9.2 Hz, 2.4Hz, 1H, quinoxaline-H), 7.62 (d, J=9.2 Hz, 1H, quinoxaline-H), 8.05 (d, J=2.4 Hz, 1H, quinoxaline-H), 8.69 (s, 1H, quinoxaline-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.96, 35.73, 40.07, 75.64, 116.24, 122.70, 126.54, 127.99, 128.69, 128.73, 128.79, 131.18, 132.93, 138.49, 138.51, 139.84, 140.11, 146.88, 154.47, 157.20, 171.89。Anal. Calcd. for $C_{25}H_{22}ClN_3O_3$，%: C 67.04, H 4.95, N 9.38, found：C 67.12, H 5.01, N 9.44。

(*R*)-四氢异喹啉-2-基-2-[4-(6-氯-喹喔啉-2-氧基)苯氧基]丙酮（Ⅳt）：0.99 g，产率 65%，淡黄色固体，m.p. 48~50 ℃，^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.69 (d, J=6.8 Hz, 3H, CH_3), 2.74~2.95 (m, 2H, CH_2), 3.95~4.04 (m, 2H, CH_2), 4.70~4.98 (m, 2H, CH_2), 5.06 (q, J=6.8 Hz, 1H, CH), 6.95~7.00 (m, 2H, PhH), 7.10~ 7.21 (m, 6H, Ph-H), 7.56~7.69 (m, 2H, quinoxaline-H), 8.04 (d, J=2.4 Hz, 1H, quinoxaline-H), 8.65 (s, 1H, quinoxaline-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 17.94, 29.57, 45.01, 46.87, 74.96, 115.77, 115.89, 122.43, 122.60, 125.92, 126.54, 126.68, 127.93, 128.38, 128.79, 131.10, 132.83, 138.51, 139.76, 140.09, 146.55, 154.83, 157.19, 170.06。HRMS (ESI, posotive mode): 460.1412 ($M+H^+$)。

吡啶-3-基-(*R*)-2-[4-(6-氯苯并噁唑-2-氧基)苯氧基]丙酸酯（Ⅳu）：0.93 g，产率 68%，棕黄色固体，熔点 105.2~107.4 ℃；^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.82 (d, J=6.8 Hz, 3H, CH_3), 5.02(q, J=6.8Hz, 1H, CH), 7.05 (d, J=9.2Hz, 2H, PhH), 7.24(dd, J_1=8.4Hz, J_2= 2.0 Hz, 1H,benzoxazole-H), 7.34(dd, J_1=8.4 Hz, J_2=4.4 Hz, 1H, Py-H), 7.38(d, J=9.2 Hz, 2H, PhH), 7.41 (d, J=8.4 Hz, 1H,benzoxazole-H), 7.45 (d, J= 2.0 Hz, 1H, benzoxazole-H), 7.46~7.49 (m, 1H, Py-H), 8.41 (d, J=2.8 Hz, 1H, Py-H), 8.50(dd, J_1=4.4 Hz, J_2= 1.6 Hz, 1H, Py-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.54, 73.19, 110.69, 116.48, 119.21, 121.45, 123.99, 124.37, 125.09, 128.95, 140.28, 142.98, 146.79, 146.95, 147.39, 151.73, 153.17, 153.85, 169.72。Anal. Calcd. for $C_{21}H_{15}ClN_2O_5$，%: C 61.40, H 3.68, N 6.82, found：C 61.34, H 3.77, N 6.95。

(*R*)-2-[4-(6-氯苯并噁唑-2-氧基)苯氧基]丙酸苯乙酯（Ⅳv）：0.86 g，产率 59%，棕黄色固体，熔点

65.1~67.2 ℃；^{1}HNMR ($CDCl_3$, 400 MHz)，δ: 1.57 (d, J=6.8 Hz, 3H, CH_3), 2.96 (t, J=6.8 Hz, 2H, CH_2), 4.41 (t, J=6.8 Hz, 2H, CH_2), 4.69 (q, J=6.8 Hz, 1H, CH), 6.87 (d, J=9.2 Hz, 2H, PhH), 7.19 (d, J=9.2 Hz, 2H, PhH), 7.24 (dd, J_1=8.4 Hz, J_2=2.0 Hz, 1H, benzoxazole-H), 7.27~7.33 (m, 5H, PhH), 7.39 (d, J=8.4 Hz, 1H, benzoxazole-H), 7.43 (d, J=2.0 Hz, 1H, benzoxazole-H); ^{13}CNMR ($CDCl_3$, 100 MHz)，δ: 18.54, 34.93, 65.60, 73.05, 110.64, 116.17, 119.17, 121.20, 125.03, 126.68, 128.54, 128.75, 128.86, 137.26, 139.50, 146.73, 148.44, 153.57, 155.76, 171.78。 Anal. Calcd. for $C_{24}H_{20}ClNO_5$，%: C 65.83, H 4.60, N 3.20, found：C 65.79, H 4.56, N 3.12。

1.3 除草活性测试

除草活性测试委托具有农药登记实验资质的湖南化工研究院（国家农药创制工程技术中心）参照《农药生物活性评价 SOP》进行测定，具体方法参照文献[18]。

2 结果与讨论

2.1 化合物的除草活性

在 75 g/hm^2 浓度下，对所合成化合物Ⅳa~v 进行单子叶杂草（马唐、稗草、狗尾草）和双子叶杂草（苘麻、刺苋、藜）的除草活性筛选，结果见表 1。

表 1 化合物Ⅳa~v 的除草活性

Table 1 Herbicidal activity of compound Ⅳa~v

样品	除草活性/%											
	土壤处理						茎叶处理					
	马唐	稗草	狗尾草	苘麻	刺苋	藜	马唐	稗草	狗尾草	苘麻	刺苋	藜
Ⅳa	100	100	100	0	0	0	100	100	100	0	0	0
Ⅳb	100	100	100	0	0	0	90	100	100	0	0	0
Ⅳc	100	100	100	0	0	0	100	100	100	0	0	0
Ⅳd	0	0	0	0	0	0	80	100	100	0	0	0
Ⅳe	90	90	90	0	0	0	90	95	95	0	0	0
Ⅳf	100	100	100	0	0	0	100	100	100	0	0	0
Ⅳg	100	100	100	0	0	0	100	100	100	0	0	0
Ⅳh	0	0	0	0	0	0	100	100	100	0	0	0
Ⅳi	100	100	100	0	0	0	100	100	100	0	0	0
Ⅳj	0	0	0	0	0	0	85	85	85	0	0	0
Ⅳk	0	0	0	0	0	0	50	50	50	0	0	0
Ⅳl	0	0	0	0	0	0	50	50	50	0	0	0
Ⅳm	0	0	0	0	0	0	50	50	50	0	0	0
Ⅳn	0	0	0	0	0	0	0	0	0	0	0	0
Ⅳo	0	0	0	0	0	0	0	0	0	0	0	0
Ⅳp	90	90	90	0	0	0	100	100	100	0	0	0
Ⅳq	90	90	90	0	0	0	100	100	100	0	0	0
Ⅳr	100	100	100	0	0	0	95	95	95	0	0	0
Ⅳs	70	70	70	0	0	0	90	100	100	0	0	0
Ⅳt	0	0	0	0	0	0	90	90	90	0	0	0
Ⅳu	0	0	0	0	0	0	0	0	0	0	0	0
Ⅳv	0	0	0	0	0	0	95	95	95	0	0	0

从表 1 可以看出，大部分化合物在 75 g/hm^2 实验浓度下土壤处理和茎叶处理对单子叶杂草（马唐、稗草、狗尾草）均具有较高的除草活性，而对双子叶杂草（苘麻、刺苋、藜）无除草活性，说明所测试化合物对单子叶杂草具有选择性防除效果，这与该类除草剂选择性防除禾本科杂草的作用机理一致[22]；化合物Ⅳa~c、Ⅳe~g、Ⅳi 和Ⅳp~r 对单子叶杂草（马唐、稗草、狗尾草）土壤处理和茎叶处理均具 90%及以上的除草活性，其中Ⅳa、Ⅳc、Ⅳf、Ⅳg 和Ⅳi 对单子叶杂草土壤处理和茎叶处理活性均为 100%；化合物Ⅳd、Ⅳh、Ⅳs、Ⅳt 和Ⅳv 仅在实验浓度下茎叶处理对马唐、稗草、狗尾草具有较高的除草活性，而土壤处理活性较差或无除草活性；化合物Ⅳj~o 和Ⅳu 在实验浓度下茎叶处理和土壤处理除草活性均较低或无除草活性；根据不同处理方式的活性对比发现，茎叶处理一般较土壤处理除草活性高，此结果与该类除草剂的苗后茎叶施药方式一致[22]。

基于以上除草活性结果分析，并与商品化除草剂施药浓度对比[22]，本文报道的化合物的除草抑制浓度与目前大多数该类除草剂的田间施用浓度在一个数量级上，因此本文报道的化合物特别是Ⅳa、Ⅳc、Ⅳf、Ⅳg 和Ⅳi 具有较高的除草剂应用价值，可对其苗后茎叶处理活性及作物安全性进行进一步的测试。

2.2 构效关系

生物活性测定结果表明，化合物结构对除草活

性具有显著影响，其中 Ar 基团对活性的影响最大，当 Ar 为喹喔啉和吡啶环（3-氟-5-氯吡啶和 3-氯-5-三氟甲基吡啶）时，化合物（Ⅳa~e、Ⅳf~j 和Ⅳp~t）的除草活性较高，大部分具有 90%以上活性，其中 Ar 为吡啶环时，化合物的除草活性总体较 Ar 为喹喔啉环化合物高；而当 Ar 为苯环和苯并噁唑环时，大部分化合物活性较差（Ⅳv 除外）。这与此前对该类除草剂的构效关系[18]研究一致，同时发现与苯环和苯并噁唑环对应的商品化品种分别为氰氟草酯（cyhalofop-butyl）和噁唑酰草胺（metamifop），而这两个品种均为水稻田（禾本科作物）防除禾本科杂草的除草剂品种，作为除草剂品种可能考虑更多的是其对水稻的安全性，而非活性。羧酸衍生物部分取代基对活性也有影响，当为酯类化合物（Ⅳa~c、Ⅳf~g、Ⅳi 和Ⅳp~r）时，活性普遍高于酰胺类化合物，这也能说明大部分该类除草剂为酯类化合物的原因[1]。

3　结论

本文设计并合成了 22 个 2-(4-芳氧苯氧基)丙酸衍生物。在 75 g/hm^2 浓度下，大部分化合物对单子叶杂草均具有较高的除草活性，且对单子叶杂草具有选择性，其中化合物Ⅳa、Ⅳc、Ⅳf、Ⅳg 和Ⅳi 对单子叶杂草（马唐、稗草、狗尾草）土壤处理和茎叶处理均具 100%防除效果。定性构效关系表明，Ar 基团对化合物的活性影响最大，当 Ar 为喹喔啉和吡啶环时，活性显著高于 Ar 为苯环和苯并噁唑环的化合物，同时酯类化合物总体较酰胺类化合物活性高。基于活性测试结果，化合物Ⅳa、Ⅳc、Ⅳf、Ⅳg 和Ⅳi 具有较高的除草剂应用价值，可进行进一步的活性测试及及安全评价实验。

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