引用:韩世博,陈珂,王淑敏,等. 含马来酰亚胺结构的 5-(1-氨基-2-苯氧丁烯基)巴比妥酸衍生物的合成及除草活性研究[J]. 聊城大学学报(自然科学版),2025,38(6):976-987.

Citation: HAN Shibo, CHEN Ke, WANG Shumin, FU Shuyue, GAO Wei, LEI Kang. Synthesis and herbicidal activity of 5-(1-Amino-2-phenoxybutylidene) barbituric acid derivatives containing a maleimide moiety[J]. Journal of Liaocheng University (Natural Science Edition),2025,38(6):976-987.

文章编号 1672-6634(2025)06-0976-12 **DOI** 10.19728/j.issn1672-6634.2025020003

含马来酰亚胺结构的 5-(1-氨基-2-苯氧丁烯基)巴比妥酸衍生物的合成及除草活性研究

韩世博,陈珂,王淑敏,付书悦,高卫,雷康

(聊城大学 药学与食品工程学院,山东 聊城 252059)

摘要 为寻找结构新颖、活性更高的除草剂先导化合物,设计、合成了 19 个含马来酰亚胺结构的 5-(1-氨基-2-苯氧丁烯基)巴比妥酸类化合物。温室盆栽除草活性结果表明,在苗后处理、1 200 g/ha 的剂量下,大部分目标化合物具有较好的除草活性。其中,目标化合物 BTA-13 在 150 g/ha 剂量下对杂草的总抑制率为 293%,与商品化除草剂-氟胺草酯相当。除草谱和作物安全性研究发现,在苗后处理、150 g/ha 的剂量下,目标化合物 BTA-13 具有较宽的除草谱并且对玉米和小麦相对安全,这说明该化合物具有开发成为除草剂的潜力。目前的研究表明,化合物 BTA-13 可以作为新型除草剂的先导化合物。

关键词 巴比妥酸;马来酰亚胺;烯胺二酮;除草剂

中图分类号 TQ457.2 **文献标志码** A **开放科学(资源服务)标识码(OSID)**

Synthesis and herbicidal activity of 5-(1-Amino-2-phenoxybutylidene) barbituric acid derivatives containing a maleimide moiety

HAN Shibo, CHEN Ke, WANG Shumin, FU Shuyue, GAO Wei, LEI Kang

(School of Pharmaceutical Sciences and Food Engineering, Liaocheng University, Liaocheng 252059, China)

Abstract In order to discover herbicide lead compounds with novel structure and high activity, nineteen 5-(1-amino-2-phenoxybutyliene) barbituric acid derivatives containing a maleimide moiety were designed and synthesized, and their herbicidal activities were evaluated in the greenhouse. The bioassay data showed that most of the target compounds exhibited moderate to good growth inhibition against the tested weeds at the dose of 1 200 g/ha under the post-emergence condition. Among them, the target compound BTA-13 exhibited excellent herbicidal activity against the weeds tested with sum inhibition rate 293%, even at a dosage of 150 g/ha, which was comparable to the commercial herbicide-Fluminate. The studies of herbicidal spectrum and crop safety revealed that the target compound BTA-13 had a broad herbicidal spectrum, and it was determined to be safe for maize and wheat at a dose of 150 g/ha under the post-emergence condi-

收稿日期:2025-02-10

基金项目:国家自然科学基金青年项目(31701827, 32402430);山东省自然科学基金项目(ZR2023MC095)资助

通信作者:雷康,男,汉族,博士,副教授,研究方向:绿色农药,E-mail:leikang@lcu.edu.cn。

tion, which indicated that the target compound BTA-13 had the potential to be developed into herbicide. The present work demonstrates that the target compound BTA-13 can serve as a lead compound for further development of novel herbicides.

Keywords　barbituric acid; maleimide; enamino diketone; herbicides

0　引言

杂草通过争夺光、水、空间和养分等资源影响农作物生长,造成粮食大幅减产[1]。除草剂在治理农田草害,保障粮食安全方面发挥着举足轻重的作用[2]。然而,长期大量使用除草剂引发严重的环境污染及抗性杂草出现等问题[3]。因此,迫切需要开发环境友好、低抗性和结构新颖的新型除草剂。开发新型除草剂的关键环节是除草先导化合物的发现,而开发具有除草活性的先导化合物的主要技术之一是活性亚结构拼接法[4]。目前,基于活性亚结构拼接法成功开发新型除草剂先导化合物的例子已有报道[5-13]。例如,华中师范大学杨光富课题组将硝磺草酮的三酮结构片段与天然喹唑啉酮结构片段进行活性亚结构拼接,成功开发出商业化除草剂喹草酮[14-15]。受此启发,本课题组在前期工作中利用活性亚结构拼接策略,设计、合成了一系列 5-(1-氨基-2-苯氧亚乙基)巴比妥酸衍生物[16]。其中,化合物**I** 被确定为潜在的除草剂先导化合物(图 1)。为继续开发结构新颖、活性更高的除草剂先导化合物,本文将对先导化合物**I** 做进一步的结构改造。

马来酰亚胺是一些天然生物碱和生物活性分子的重要母核结构(图 1)[17]。研究发现,含有马来酰亚胺结构的化合物具有抗惊厥[18]、抗炎[19]、抗菌[20-21]、抗癌[22-23]、抗结核[24]等药理活性。此外,含有马来酰亚胺结构的化合物还具除草[25]、杀虫[26]和杀菌[27]等农用活性。基于上述,本文将在前期工作的基础上,将马来酰亚胺结构引入到先导化合物**I** 的苯环上,构建含有马来酰亚胺结构的新型 5-(1-氨基-2-苯氧亚乙基)巴比妥酸类化合物(BTA),并进行除草活性和构效关系(SAR)研究,以期发现一种含有马来酰亚胺结构的新型除草剂先导化合物。

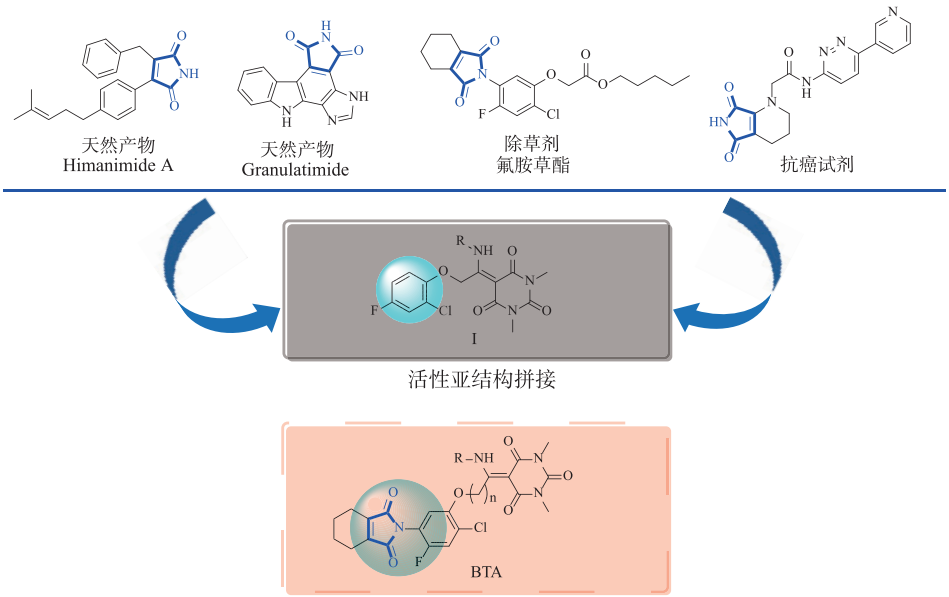

图 1　目标化合物 BTA 的设计

Fig. 1　Design of target compounds BTA

1　结果与讨论

1.1　目标化合物的合成

目标化合物 BTA-1～BTA-19 按照图 2 所示的路线合成。首先,以 2-氯-4-氟-5-硝基苯酚为原料,在碱性条件下,与 4-溴丁酸乙酯反应,经过亲核取代反应得到 2-氯-4-氟-5-硝基苯氧丁酸乙酯(化合物 1);化合物 1 在钯/碳催化条件下,与氢气反应,经过氢化还原得到 2-氯-4-氟-5-氨基苯氧丁酸乙酯(化合物 2);化合物 2

在碱性条件下经过水解得到 2-氯-4-氟-5-氨基苯氧丁酸(化合物 3)。然后,将化合物 3 与四氢邻苯二甲酸酐在冰醋酸中进行缩合反应得到化合物 4;将化合物 4 与草酰氯进行酰化反应得到化合物 5,并进一步与 1,3-二甲基巴比妥酸反应得到重要的三酮类中间体 6。最后,在碱性条件下,将化合物 6 与各种 R 取代的胺在乙醇中进行亲核反应,得到终产物 BTA-1～BTA-19。终产物 BTA-1～BTA-19 的结构通过核磁共振氢谱(^{1}HNMR)、核磁共振碳谱(^{13}CNMR)和高分辨质谱(HRMS)确证。

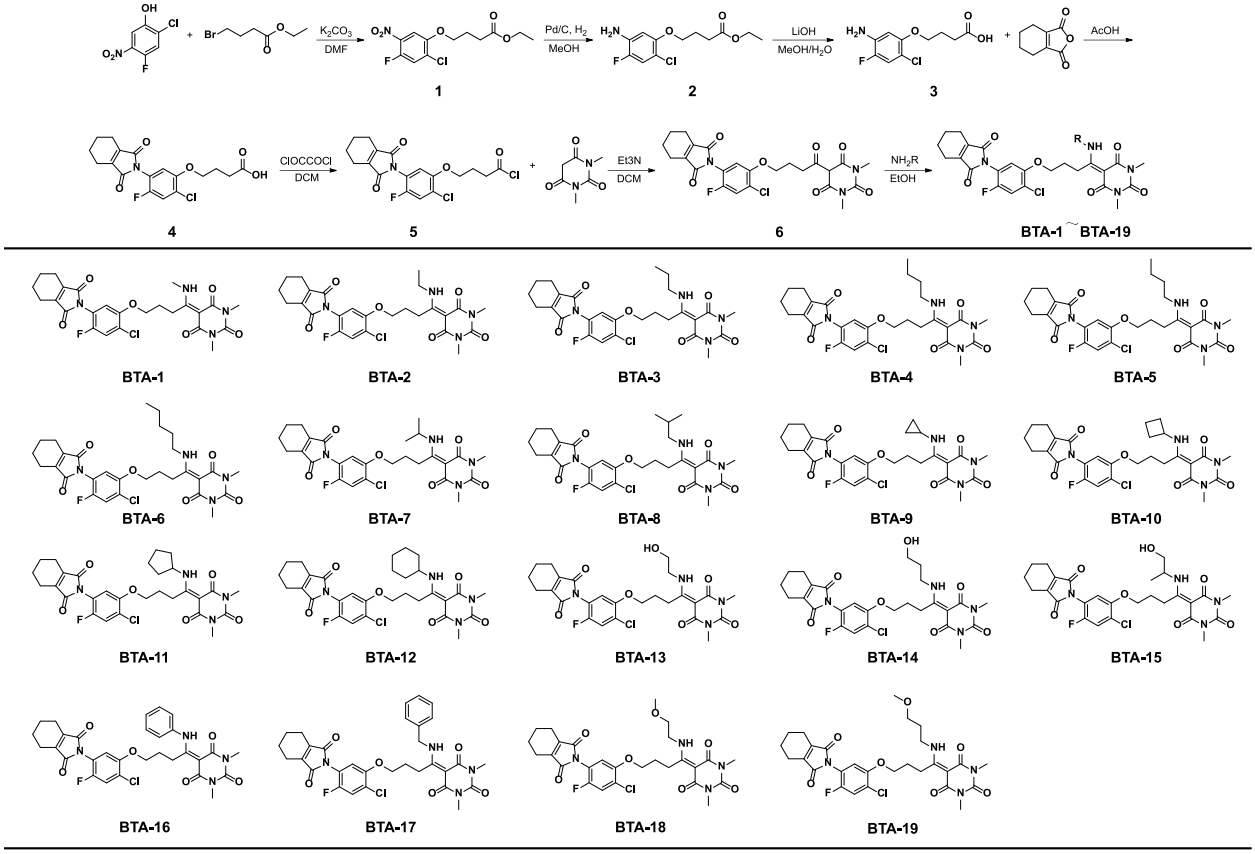

图 2 目标化合物 BTA-1～BTA-19 的合成路线

Fig. 2 Synthetic route of target compounds BTA-1～BTA-19

1.2 目标化合物的除草活性研究

首先采用温室盆栽法,在苗后处理、1 200 g/ha 剂量条件下,对目标化合物 BTA-1～BTA-19 的除草活性进行第一轮测试。如图 3 所示,大部分目标化合物对被测杂草均有较好的生长抑制作用,例如,化合物 BTA-1、BTA-2、BTA-13、BTA-14、BTA-15、BTA-18 和 BTA-19 对四种被测杂草的生长总抑制率均大于 300%,其中,化合物 BTA-13 对四种被测杂草的生长总抑制率为 400%,与商品化的除草剂-氟胺草酯(FP)的抑制效果相同。此外,根据图 3 所示结果发现,目标化合物对双子叶植物油菜(蓝色)和苋菜(红色)的抑制效果整体优于对单子叶植物稗草(黄色)和马唐(绿色)的抑制效果,这说明目标化合物对双子叶植物具有选择性。

通过结构-活性关系对比研究发现,当 R 基团为直链烷基时,目标化合物 BTA-1～BTA-6 的除草活性随着碳链的伸长,活性逐渐降低。推测可能的原因是,随着碳链的伸长,目标化合物的脂水分配系数(*C*log P)变大,脂溶性增强,造成目标化合物在植物体内的吸收传导受阻,从而使目标化合物的除草活性降低。平行比较目标化合物(BTA-2, BTA-3 和 BTA-7)与目标化合物(BTA-13, BTA-14 和 BTA-15)的除草活性证实了这一推测。当在直链烷基的末端引入羟基时,目标化合物 BTA-13(R=羟乙基),BTA-14(R=羟丙基)和 BTA-15(R=羟异丙基)的 *C*log *P* 值分别为 3.40, 3.71 和 3.78,对测试杂草的生长总抑制率分别为 400%, 368%和 331%,整体优于含烷基的目标化合物 BTA-2(R=乙基,*C*log *P* = 4.75,总抑制率 304%),BTA-3(R=丙基,*C*log *P* = 5.28,总抑制率 226%)和 BTA-7(R=异丙基,*C*log *P* = 5.81,总抑制率 160%)。这些

研究结果说明,在目标化合物中引入亲水性基团,增加目标化合物的水溶性,有利于提高除草活性。这一结论通过比较目标化合物(BTA-13 和 BTA-14)与目标化合物(BTA-18 和 BTA-19)的除草活性得到进一步的证实。当目标化合物 BTA-13(总抑制率 400%)和 BTA-14(总抑制率 368%)的羟基被亲脂性的甲氧基取代,化合物 BTA-18 和 BTA-19 的除草总抑制率分别降至 343%和 315%。

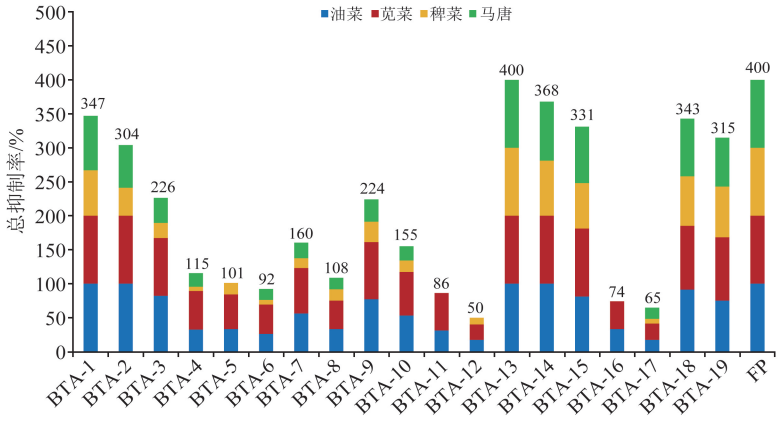

图 3　目标化合物 BTA-1～BTA-19 在苗后处理、1 200 g/ha 剂量下的温室盆栽的除草活性(总抑制率/%)

Fig. 3　The herbicidal activity of target compounds BTA-1～BTA-19 at the dosage of 1200 g/ha under the post-emergence condition in greenhouse testing (sum inhibition rate/%)

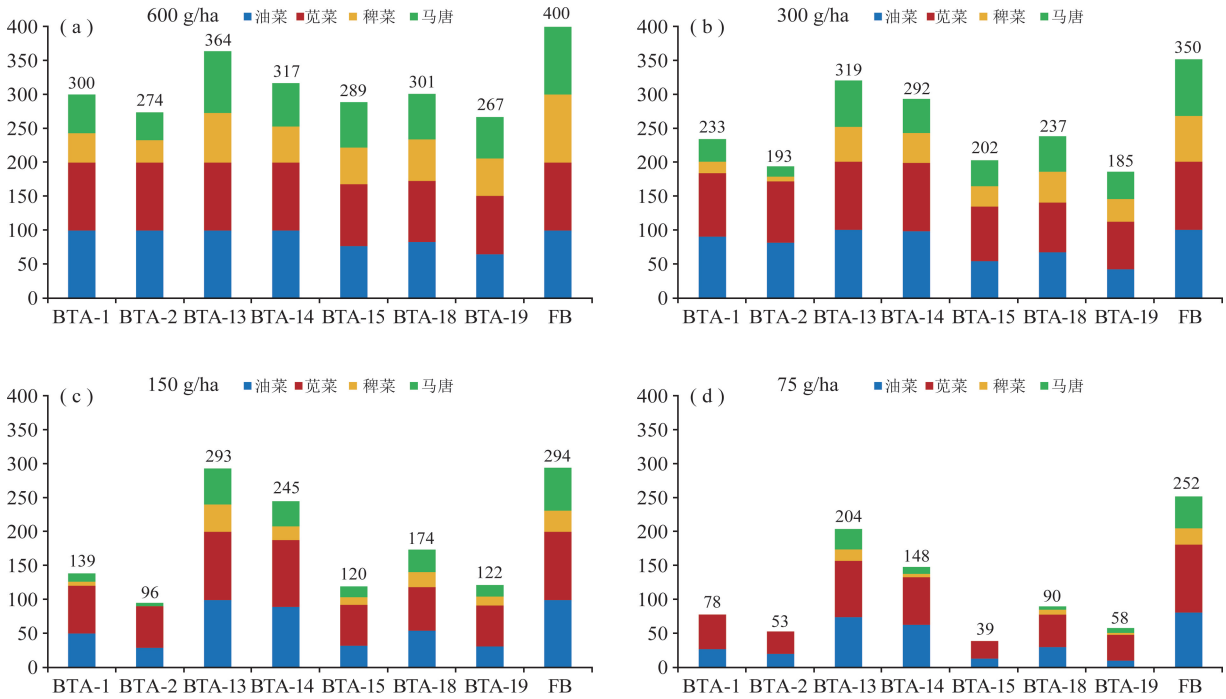

图 4　目标化合物 BTA-1～BTA-19 在不同剂量下的温室盆栽除草活性(总抑制率/%)

Fig. 4　The herbicidal activity of target compounds BTA-1～BTA-19 at a different dosage in greenhouse testing (sum inhibition rate/%)

当 R 基团为支链烷烃时,目标化合物的除草活性低于相应的含有直链烷基的化合物的除草活性。例如,化合物 BAT-7(*R*=异丙基)和 BAT-8(*R*=异丁基)对被测杂草的生长总抑制率分别为 160%和 108%,而相应的化合物 BAT-7(*R*=丙基)和 BAT-8(*R*=丁基)对被测杂草的生长总抑制率分别为 226%和 115%。此外,当 *R* 基团为环烷基时,随着环的扩大,目标化合物 BTA-9～BTA-12 的除草活性逐渐下降。这些结果说明,*R* 基团的空间位阻效应对化合物的除草活性具有一定的影响,*R* 基团的空间位阻越大,化合物的除草活性越低。值得注意的是,目标化合物 BAT-10(*R*=环丁基,总抑制率 155%)的空间位阻大于 BAT-4(*R*=

丁基,总抑制率115%),但BAT-10(R=环丁基)的除草活性高于BAT-4,这一结果可能是因为化合物BAT-10($C\log P$= 5.13)的水溶性高于BAT-4($C\log P$= 5.81)。这一发现说明,目标化合物的除草活性不仅受到R基团空间位阻的影响,同时也受到化合物$C\log P$的影响,且化合物的$C\log P$比R基团的空间位阻效应对除草活性的影响更大。

为了进一步评价目标化合物的除草活性,在苗后处理条件下,采用半剂量降浓度法,对总抑制率高于300%的目标化合物BTA-1,BTA-2,BTA-13~BTA-15,BTA-18和BTA-19进行第二轮温室盆栽活性测试。如图4所示,随着剂量从600 g/ha降至75 g/ha,目标化合物BTA-1,BTA-2,BTA-13~BTA-15,BTA-18,BTA-19和商品化除草剂-氟胺草酯对被测杂草的生长总抑制率逐渐降低。值得注意的是,当剂量降至150 g/ha时,目标化合物BTA-13对被测杂草的生长总抑制率为293%,与商品化除草剂-氟胺草酯的活性相当。因此,目标化合物BTA-13可以作为最优先导化合物进行进一步的研究。

1.3 目标化合物BTA-13的除草谱和作物安全性研究

为了进一步评价目标化合物BTA-13是否具有开发除草剂的潜力,在苗后处理、150 g/ha剂量条件下,测试了目标化合物BTA-13的除草谱及作物安全性。除草谱实验结果表明(图5),化合物BTA-13对8种双子叶杂草均具有大于95%的除草活性,其中,对油菜、反枝苋、马齿苋、藜、翅果菊和蒲公英的生长抑制率均为100%。然而,化合物BTA-13对单子叶杂草的生长抑制率较低。此外,通过评价化合物BTA-13的作物安全性发现(表1),化合物BTA-13对大豆和花生具有较高的损伤率,分别为90%和83%,而对玉米和小麦的损伤率分别为13.3%和7%。基于上述的结果可以看出,化合物BTA-13具有较宽的除草谱,且对作物玉米和小麦相对安全,可以作为一个选择性的除草剂先导化合物进行进一步的优化。

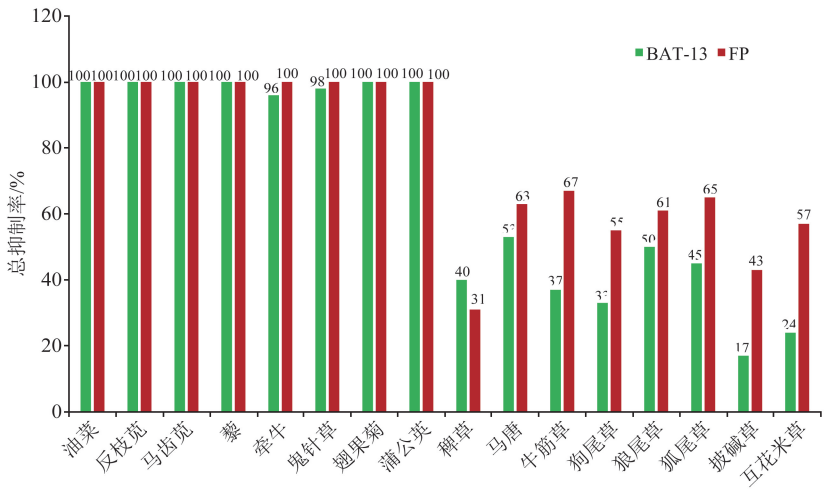

图5 目标化合物BTA-13在苗后处理、150 g/ha剂量条件下的除草谱

Fig. 5 The herbicidal spectrum testing of compound BTA-13 under the post-emergence condition at the dosage of 150 g/ha

表1 在苗后处理、150 g/ha剂量条件下,化合物BTA-13对农作物的损伤率(%)[a]

Tab. 1 Injury rate (%) of compound BTA-13 under postcrop treatment, 150 g / ha dosea

化合物	玉米	小麦	花生	大豆
BTA-13	13.3	7	83	90
氟胺草酯	60	53	100	100

注:a数据为三次平行实验的平均值。

2 实验部分

2.1 仪器与试剂

本实验所用试剂均为分析纯或化学纯,购于安耐吉化学试剂有限公司和TCI化学试剂公司,使用前均经过蒸馏并干燥;硅胶(200~300目)购于青岛海洋化工厂;核磁检测采用Bruker 500型核磁共振仪,TMS

为内标,氘代氯仿作溶剂;熔点测试采用北京台克熔点仪(X-4;北京泰克,北京,中国);高分辨率质谱检测采用 Ionspec 7.0 T 光谱仪(Varian, Palo Alto, CA)电喷雾电离傅立叶变换离子回旋共振技术;药物喷施采用实验室喷雾器(3WP-2000;中国农业部南京农业机械化研究所)。

2.2　实验方法

2.2.1　化合物1 的合成。在 1 000 mL 圆底烧瓶中依次加入 2-氯-4-氟-5-硝基苯酚(19.1 g, 0.1 mol)、4-氯丁酸乙酯(38.8 g, 0.2 mol)、碳酸钾(27.6 g, 0.2 mol)和 *N*, *N*-二甲基甲酰胺(DMF, 500 mL),并在 50℃下搅拌 12 h。薄层层析法(TLC)跟踪反应,待反应结束后,将反应液倒入 500 mL 冰水中,水相用乙酸乙酯(EA, 300 mL)萃取 3 次。合并有机相,用 500 mL 饱和 NaCl 洗涤 3 次,并用无水 Na_2SO_4 干燥 2 h。然后,减压除去乙酸乙酯,得到黄色油状物。以乙酸乙酯/石油醚(体积比, 1:100～1:20)的混合液为洗脱剂,经硅胶柱层析法纯化黄色油状物,得到化合物1 为淡黄色油状物(28.1 g,产率 92%)。

2.2.2　化合物2 的合成。在 500 mL 圆底烧瓶中依次加入中间体1(28.1 g, 92.1 mmol)、钯/碳(Pd/C, 5%, 2.81 g)和甲醇(MeOH, 300 mL),然后向反应体系中通入氢气,室温搅拌 12 h。反应完成后,过滤,收集滤液,用旋转蒸发器除去甲醇,得到棕色油状物。以乙酸乙酯/石油醚(体积比, 1∶20～1∶5)的混合液为洗脱剂,经硅胶柱层析法纯化棕色油状物,得到化合物2 为淡黄色油状物(24.0 g,产率 95%)。

2.2.3　化合物3 的合成。将化合物2(24.0 g, 87.3 mmol)溶于 500 mL 的甲醇中,然后依次加入氢氧化锂(LiOH, 21.0 g, 873 mmol)和 10 mL 水。反应体系在室温下搅拌 12 h。反应结束后,用旋转蒸发器除去甲醇,用 1 M 稀盐酸(HCl)调至 pH=1,此时有大量白色固体析出。过滤,收集析出的固体,水洗,并在真空干燥箱中干燥 6 h,得到化合物3 为白色固体(15.7 g,产率 73%)。

2.2.4　化合物4 的合成。在 500 mL 圆底烧瓶中依次加入化合物3(15.7 g, 63.6 mmol)、四氢邻苯二甲酸酐(9.7 g,63.6 mmol)和冰醋酸(AcOH,250 mL),并在 120 ℃下搅拌 6 h。反应完成后,将反应液冷却至 0 ℃,有大量白色固体析出。过滤,收集析出的固体,水洗,并在真空干燥箱中干燥 6 h,得到化合物4 为白色固体(17.0 g,产率 77%)。

2.2.5　化合物6 的合成。将化合物4(17.0 g,44.6 mmol)溶于二氯甲烷(DCM,300 mL)中,然后加依次加入草酰氯($(COCl)_2$,30 mL)和 1 滴 *N*, *N*-二甲基甲酰胺。反应体系在室温下搅拌 12 h 后,用旋转蒸发器除去二氯甲烷,得到化合物5。然后,将化合物5 溶于 300 mL 二氯甲烷中,依次加入三乙胺(Et_3N,10 mL)和 1, 3-二甲基巴比妥酸。反应体系在室温下搅拌 72 h 后,依次用 1 mol/L 的稀盐酸、水、饱和氯化钠溶液洗涤,无水硫酸钠干燥。用旋转蒸发器除去二氯甲烷得到黄色固体,以乙酸乙酯/石油醚(体积比, 1∶30)的混合液为洗脱剂,经硅胶柱层析法纯化黄色固体,得到化合物6 为淡黄色固体(14.1 g,产率 61%)。

2.2.6　目标化合物 BTA-1～BTA-19 的合成。将化合物6(519 mg,1 mmol)溶于 10 mL 乙醇中,然后加入甲胺(62 mg,2 mmol)。反应体系在 90 ℃下搅拌 2 h。反应结束后,冷却至室温,析出大量固体。过滤,收集固体,乙醇洗涤,真空干燥后得到目标化合物BTA-1(388 mg,产率 73%)。其它目标化合物BTA-2～BTA-19 的合成方法与BTA-1 相同。

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(甲胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-1):白色固体;产率 73.0%;熔点 253～255 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.56 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.14 (t, J = 5.4 Hz, 2H), 3.42～3.35 (m, 2H), 3.32 (s, 3H), 3.30 (s, 3H), 3.25 (d, J = 5.1 Hz, 3H), 2.44 (s, 4H), 2.18～32.13 (m, 2H), 1.84 (s, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 177.32 (s), 168.79 (s), 166.72 (s), 162.53 (s), 151.65 (d, J = 248.4 Hz), 151.36 (s), 150.70 (d, J = 2.6 Hz), 123.41 (d, J = 9.5 Hz), 118.38 (d, J = 24.3 Hz), 118.31 (d, J = 14.6 Hz), 113.60 (s), 89.94 (s), 68.93 (s), 30.06 (s), 27.93 (s), 27.65 (s), 26.70 (s), 26.60 (s), 21.26 (s), 20.30 (s);HRMS: calcd for $C_{25}H_{27}ClFN_4O_6^+$ $[M+H]^+$ 533.159 77, found 533.160 52.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(乙胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-2):白色固体;产率 67.2%;熔点 249～252 ℃;^{1}H NMR (500 MHz,

$CDCl_3$) δ12.56 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.4 Hz, 1H), 4.13 (t, J = 5.5 Hz, 2H), 3.69～3.61 (m, 2H), 3.39～3.28 (m, 8H), 2.44 (s, 4H), 2.16 (td, J = 11.7, 5.8 Hz, 2H), 1.84 (s, 4H), 1.38 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ176.08 (s), 168.78 (s), 166.74 (s), 162.57 (s), 151.64 (d, J = 248.3 Hz), 151.37 (s), 150.70 (d, J = 2.7 Hz), 142.51 (s), 123.35 (d, J = 9.5 Hz), 118.36 (d, J = 24.3 Hz), 118.32 (d, J = 14.6 Hz), 113.58 (s), 89.59 (s), 68.94 (s), 38.37 (s), 27.93 (s), 27.64 (s), 27.14 (s), 26.77 (s), 21.26 (s), 20.29 (s), 14.89 (s); HRMS: calcd for $C_{26}H_{29}ClFN_4O_6^+[M+H]^+$ 547.175 42, found 547.176 39.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(丙胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-3):白色固体;产率 70.5%;熔点 261～262 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ12.63 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d,J = 6.4 Hz, 1H), 4.13 (t, J = 5.5 Hz, 2H), 3.56 (dd, J = 12.6, 7.0 Hz, 2H), 3.42～3.27 (m, 8H), 2.45～2.43 (m, 4H), 2.15 (td, J = 11.7, 5.8 Hz, 2H), 1.87～1.81 (m, 4H), 1.76 (dd, J = 14.4, 7.2 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ176.21 (s), 168.77 (s), 166.77 (s), 162.57 (s), 151.64 (d, J = 248.3 Hz), 151.38 (s), 150.70 (d, J = 2.6 Hz), 142.51 (s), 123.36 (d, J = 9.2 Hz), 118.36 (d, J = 24.3 Hz), 118.32 (d, J = 14.6 Hz), 113.57 (s), 89.64 (s), 68.91 (s), 45.17 (s), 27.92 (s), 27.64 (s), 27.11 (s), 26.79 (s), 22.88 (s), 21.26 (s), 20.29 (s), 11.38 (s); HRMS: calcd for $C_{27}H_{31}ClFN_4O_6^+[M+H]^+$ 561.191 07, found 561.192 08.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(丁胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-4):白色固体;产率 65.7%;熔点 260～262 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ12.61 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.4 Hz, 1H), 4.13 (t, J = 5.5 Hz, 2H), 3.59 (dd, J = 12.6, 7.0 Hz, 2H), 3.36 (dd, J = 9.3, 6.2 Hz, 2H), 3.33 (s, 3H), 3.30 (s, 3H), 2.45～2.43 (m, 4H), 2.15 (td, J = 11.7, 5.8 Hz, 2H), 1.88～1.80 (m, 4H), 1.75～1.66 (m, 2H), 1.63 (s, 4H), 1.52～1.40 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ176.16 (s), 168.79 (s), 166.77 (s), 162.58 (s), 151.64 (d, J = 248.3 Hz), 151.40 (s), 150.71 (d, J = 2.5 Hz), 142.52 (s), 123.37 (d, J = 9.4 Hz), 118.36 (d, J = 24.3 Hz), 118.32 (d, J = 14.6 Hz), 113.58 (s), 89.64 (s), 68.94 (s), 43.29 (s), 31.55 (s), 27.93 (s), 27.66 (s), 27.12 (s), 26.83 (s), 21.26 (s), 20.29 (s), 20.04 (s), 13.67 (s); HRMS: calcd for $C_{28}H_{33}ClFN_4O_6^+[M+H]^+$ 575.206 72, found 575.207 64.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(戊胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-5):白色固体;产率 60.5%;熔点 261～263 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ12.61 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.4 Hz, 1H), 4.13 (t, J = 5.4 Hz, 2H), 3.57 (dd, J = 12.7, 7.1 Hz, 2H), 3.40～3.27 (m, 8H), 2.44 (s, 4H), 2.15 (td, J = 11.7, 5.8 Hz, 2H), 1.84 (t, J = 2.4 Hz, 4H), 1.77～1.68 (m, 2H), 1.44～1.34 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ176.12 (s), 168.79 (s), 166.76 (s), 162.58 (s), 151.64 (d, J = 248.3 Hz), 151.39 (s), 150.71 (d, J = 2.5 Hz), 142.52 (s), 123.35 (d, J = 9.3 Hz), 118.36 (d, J = 24.3 Hz), 118.32 (d, J = 14.6 Hz), 113.52 (s), 89.62 (s), 68.90 (s), 43.57 (s), 29.24 (s), 28.91 (s), 27.94 (s), 27.67 (s), 27.10 (s), 26.84 (s), 22.28 (s), 21.26 (s), 20.30 (s), 13.89 (s); HRMS: calcd for $C_{29}H_{35}ClFN_4O_6^+[M+H]^+$ 589.222 37, found 589.223 69.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(己胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-6):白色固体;产率 63.0%;熔点 252～255 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ12.61 (s, 1H), 7.28 (d, J = 9.1, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.13 (t, J = 5.4 Hz, 2H), 3.59～3.55 (m, 2H), 3.38～3.34 (m, 2H), 3.33 (s, 3H), 3.30 (s, 3H), 2.44 (s, 4H), 2.18～2.13 (m, 2H), 1.84 (s, 4H), 1.76～1.68 (m, 2H), 1.48～1.38 (m, 2H), 1.34～1.31 (m, 4H), 0.95

～0.84 (m, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.11 (s), 168.76 (s), 166.76 (s), 162.57 (s), 151.64 (d, J = 248.3 Hz), 151.39 (s), 150.71 (d, J = 2.7 Hz), 142.51 (s), 123.37 (d, J = 9.4 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.58 (s), 89.62 (s), 68.94 (s), 43.59 (s), 31.32 (s), 29.53 (s), 27.91 (s), 27.64 (s), 27.12 (s), 26.82 (s), 26.48 (s), 22.44 (s), 21.26 (s), 20.29 (s), 13.94 (s);HRMS: calcd for $C_{30}H_{37}ClFN_4O_6^+$[M+H]$^+$ 603.238 02, found 603.239 01.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(异丙胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-7):白色固体;产率 54.6%;熔点 314～315 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.64 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.32～4.22 (m, 1H), 4.13 (t, J = 5.4 Hz, 2H), 3.41～3.28 (m, 8H), 2.44 (s, 4H), 2.22～2.10 (m, 2H), 1.84 (s, 4H), 1.35 (d, J = 6.4 Hz, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 174.64 (s), 168.79 (s), 166.78 (s), 162.57 (s), 151.63 (d, J = 248.2 Hz), 151.39 (s), 150.67 (d, J = 2.7 Hz), 142.52 (s), 123.28 (d, J = 9.2 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.52 (s), 89.26 (s), 68.86 (s), 45.58 (s), 27.94 (s), 27.78 (s), 27.64 (s), 26.60 (s), 23.58 (s), 21.26 (s), 20.29 (s);HRMS: calcd for $C_{27}H_{31}ClFN_4O_6^+$[M+H]$^+$ 561.191 07, found 561.192 32.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(异丁胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-8):白色固体;产率 55.1%;熔点 281～283 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.13 (t, J = 5.4 Hz, 2H), 3.43～3.39 (m, 2H), 3.38～3.28 (m, 8H), 2.44 (s, 4H), 2.17～2.12 (m, 2H), 2.03～1.95 (m, 1H), 1.84 (s, 4H), 1.06 (s, 3H), 1.04 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.23 (s), 168.76 (s), 166.80 (s), 162.57 (s), 151.60 (d, J = 248.2 Hz), 151.37 (s), 150.66 (d, J = 2.6 Hz), 142.50 (s), 123.32 (d, J = 9.4 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.50 (s), 89.66 (s), 68.83 (s), 50.88 (s), 28.72 (s), 27.92 (s), 27.66 (s), 27.03 (s), 26.78 (s), 21.25 (s), 20.28 (s), 20.13 (s);HRMS: calcd for $C_{28}H_{33}ClFN_4O_6^+$[M+H]$^+$ 575.206 72, found 575.207 70.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(环丙胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-9):白色固体;产率 53.0%;熔点 259～262 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.27 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 6.4 Hz, 1H), 4.17 (t, J = 5.5 Hz, 2H), 3.66～3.50 (m, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 3.08～3.03 (m, 1H), 2.44 (d, J = 5.8 Hz, 4H), 2.24～2.19 (m, 2H), 1.88～1.81 (m, 4H), 1.07～0.99 (m, 2H), 0.85～0.77 (m, 2H);^{13}C NMR (125 MHz, $CDCl_3$) δ 178.54 (s), 168.78 (s), 166.64 (s), 162.31 (s), 151.60 (d, J = 248.4 Hz), 151.30 (s), 150.76 (d, J = 2.7 Hz), 142.51 (s), 123.30 (d, J = 9.3 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.60 (s), 89.96 (s), 69.14 (s), 27.92 (s), 27.89 (s), 27.63 (s), 26.88 (s), 25.62 (s), 21.26 (s), 20.29 (s), 8.08 (s);HRMS: calcd for $C_{27}H_{29}ClFN_4O_6^+$[M+H]$^+$ 559.175 42, found 559.176 39.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(环丁胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-10):白色固体;产率 47.3%;熔点 289～290 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.73 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 8.9 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.51～4.41 (m, 1H), 4.13 (t, J = 5.4 Hz, 2H), 3.37～3.24 (m, 8H), 2.53～2.47 (m, 2H), 2.44 (s, 4H), 2.23～2.08 (m, 4H), 1.93～1.79 (m, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 174.90 (s), 168.79 (s), 166.71 (s), 162.55 (s), 151.61 (d, J = 248.4 Hz), 151.35 (s), 150.72 (d, J = 2.7 Hz), 142.52 (s), 123.26 (d, J = 9.3 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.47 (s), 89.55 (s), 68.92 (s), 47.94 (s), 31.37 (s), 27.93 (s), 27.66 (s), 27.29 (s), 21.26 (s), 20.29 (s), 15.35 (s);HRMS: calcd for $C_{28}H_{31}ClFN_4O_6^+$[M+H]$^+$ 573.191 07, found 573.192 08.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(环戊胺)丁烯基)-1,3-二甲

基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-11):白色固体;产率 50.2%;熔点 302～303 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.76 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.39～4.31 (m, 1H), 4.14 (t, J = 5.4 Hz, 2H), 3.38 (dd, J = 9.5, 6.1 Hz, 2H), 3.32 (s, 3H), 3.30 (s, 3H), 2.44 (s, 4H), 2.23～2.07 (m, 4H), 1.84 (dd, J = 5.3, 2.9 Hz, 6H), 1.75～1.61 (m, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 175.01 (s), 168.78 (s), 166.77 (s), 162.54 (s), 151.61 (d, J = 248.5 Hz), 151.40 (s), 150.68 (d, J = 2.3 Hz), 142.52 (s), 123.24 (d, J = 9.6 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.48 (s), 89.40 (s), 68.88 (s), 54.91 (s), 34.20 (s), 27.93 (s), 27.65 (s), 27.47 (s), 27.07 (s), 23.97 (s), 21.26 (s), 20.29 (s);HRMS: calcd for $C_{29}H_{33}ClFN_4O_6^+$ $[M+H]^+$ 587.206 72, found 587.207 58.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(环己胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-12):白色固体;产率 45.3%;熔点 309～311 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.75 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.13 (t, J = 5.4 Hz, 2H), 3.94～3.73 (m, 1H), 3.39～3.29 (m, 8H), 2.44 (s, 4H), 2.20～2.11 (m, 2H), 1.92 (dd, J = 8.7, 3.9 Hz, 2H), 1.84 (s, 4H), 1.79 (dd, J = 9.2, 4.1 Hz, 2H), 1.64 (d, J = 4.2 Hz, 2H), 1.47 (td, J = 12.9, 2.9 Hz, 2H), 1.41～1.26 (m, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 174.59 (s), 168.77 (s), 166.81 (s), 162.55 (s), 151.61 (d, J = 248.1 Hz), 151.41 (s), 150.66 (d, J = 2.4 Hz), 142.52 (s), 123.30 (d, J = 9.3 Hz), 118.35 (d, J = 24.5 Hz), 118.34 (d, J = 14.8 Hz), 113.44 (s), 89.30 (s), 68.79 (s), 33.59 (s), 27.94 (s), 27.90 (s), 27.66 (s), 26.64 (s), 25.04 (s), 24.11 (s), 21.26 (s), 20.29 (s);HRMS: calcd for $C_{30}H_{35}ClFN_4O_6^+$ $[M+H]^+$ 601.222 37, found 601.222 96.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-((2-羟乙基)胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-13):白色固体;产率 62.3%;熔点 252～255 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.81 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.14 (t, J = 5.4 Hz, 2H), 3.90 (t, J = 5.1 Hz, 2H), 3.75 (dd, J = 10.4, 5.3 Hz, 2H), 3.38 (dd, J = 11.0, 4.4 Hz, 2H), 3.31 (s, 6H), 2.44 (s, 4H), 2.17 (td, J = 11.9, 5.9 Hz, 2H), 1.83 (s, 5H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.57 (s), 168.84 (s), 166.74 (s), 162.56 (s), 151.67 (d, J = 248.9 Hz), 151.36 (s), 150.58 (d, J = 2.5 Hz), 142.56 (s), 123.36 (d, J = 9.2 Hz), 118.39 (d, J = 24.4 Hz), 118.31 (d, J = 14.7 Hz), 113.69 (s), 89.99 (s), 68.80 (s), 60.80 (s), 45.39 (s), 27.96 (s), 27.72 (s), 26.96 (s), 26.81 (s), 21.25 (s), 20.29 (s);HRMS: calcd for $C_{26}H_{29}ClFN_4O_7^+$ $[M+H]^+$ 563.170 33, found 563.171 51.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-((3-羟丙基)胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-14):白色固体;产率 63.5%;熔点 265～268 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.66 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.3 Hz, 1H), 4.14 (t, J = 5.5 Hz, 2H), 3.77 (t, J = 5.9 Hz, 1H), 3.74～3.68 (m, 1H), 3.42～3.35 (m, 2H), 3.33～3.28 (m, 6H), 2.44 (s, 4H), 2.17 (td, J = 12.1, 5.9 Hz, 2H), 2.02～1.90 (m, 2H), 1.83 (t, J = 2.4 Hz, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.41 (s), 168.88 (s), 166.76 (s), 162.54 (s), 151.63 (d, J = 251.8 Hz), 151.37 (s), 150.58 (d, J = 2.5 Hz), 142.55 (s), 123.47 (d, J = 9.7 Hz), 118.38 (d, J = 24.3 Hz), 118.31 (d, J = 14.6 Hz), 113.67 (s), 89.77 (s), 68.85 (s), 59.40 (s), 40.38 (s), 31.78 (s), 27.95 (s), 27.68 (s), 27.03 (s), 26.73 (s), 21.25 (s), 20.29 (s);HRMS: calcd for $C_{27}H_{31}ClFN_4O_7^+$ $[M+H]^+$ 577.185 98, found 577.187 07.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-((1-羟丙-2-基)胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-15):白色固体;产率 67.2%;熔点 269～271 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.84 (s, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.79 (d, J = 6.3 Hz, 1H), 4.18～

4.07 (m, 3H), 3.69～3.65 (m, 1H), 3.53～3.44 (m, 1H), 3.37 (t, J = 7.1 Hz, 2H), 3.32 (s, 3H), 3.31 (s, 3H), 2.44 (s, 4H), 2.17 (dd, J = 12.8, 6.6 Hz, 2H), 1.83 (s, 5H), 1.30 (d, J = 6.3 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.35 (s), 168.84 (s), 166.72 (s), 162.57 (s), 151.65 (d, J = 248.8 Hz), 151.38 (s), 150.56 (d, J = 2.5 Hz), 142.56 (s), 123.32 (d,J = 9.1 Hz), 113.62 (s), 118.38 (d, J = 24.7 Hz), 118.32 (d, J = 13.5 Hz), 89.97 (s), 68.68 (s), 66.23 (s), 50.21 (s), 27.97 (s), 27.75 (s), 26.94 (s), 26.83 (s), 21.25 (s), 21.19 (s), 20.30 (s);HRMS: calcd for $C_{27}H_{31}ClFN_4O_7^+$ $[M+H]^+$ 577.185 98, found 577.186 89.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-(苯胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-16):白色固体;产率 42.8%;熔点 249～252 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 14.14 (s, 1H), 7.39 (t, J = 6.9 Hz, 2H), 7.34 (d, J = 6.6 Hz, 1H), 7.17 (d, J = 8.1 Hz, 3H), 6.74～6.61 (m, 1H), 4.00 (t, J = 5.3 Hz, 2H), 3.37 (d, J = 1.1 Hz, 3H), 3.33 (d, J = 1.2 Hz, 3H), 3.26～3.19 (m, 2H), 2.43 (s, 4H), 2.12～2.04 (m, 2H), 1.83 (s, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.50 (s), 168.80 (s), 167.02 (s), 162.32 (s), 151.43 (d, J = 247.8 Hz), 151.27 (s), 150.49 (d, J = 2.5 Hz), 142.46 (s), 136.02 (s), 129.70 (s), 128.35 (s), 126.27 (s), 123.50 (d, J = 9.4 Hz), 118.21 (d, J = 24.6 Hz), 117.99 (d, J = 14.5 Hz), 113.30 (s), 90.49 (s), 68.88 (s), 28.04 (s), 27.91 (s), 27.81 (s), 27.67 (s), 21.27 (s), 20.27 (s);HRMS: calcd for $C_{30}H_{29}ClFN_4O_6^+$ $[M+H]^+$ 595.175 42, found 595.176 45.

5-(1-(苄胺)-4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2H-异吲哚-2-基)-4-氟苯氧)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-17):白色固体;产率 55.5%;熔点 275～278 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.97 (s, 1H), 7.39 (t, J = 7.3 Hz, 2H), 7.35～7.29 (m, 3H), 7.26 (d, J = 9.0 Hz, 1H), 6.79 (d, J = 6.3 Hz, 1H), 4.80 (d, J = 5.8 Hz, 2H), 4.13 (t, J = 5.4 Hz, 2H), 3.43 (dd, J = 9.2, 6.3 Hz, 2H), 3.32 (s, 3H), 3.31 (s, 3H), 2.44 (s, 4H), 2.18 (td, J = 11.7, 5.8 Hz, 2H), 1.83 (s, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.47 (s), 168.79 (s), 166.77 (s), 162.54 (s), 151.66 (d, J = 248.1 Hz), 151.33 (s), 150.69 (d, J = 2.6 Hz), 142.52 (s), 135.62 (s), 129.23 (s), 128.28 (s), 127.28 (s), 123.40 (d, J = 9.4 Hz), 118.37 (d, J = 24.5 Hz), 118.30 (d, J = 14.1 Hz), 113.57 (s), 90.17 (s), 68.96 (s), 47.31 (s), 27.99 (s), 27.72 (s), 27.20 (s), 26.96 (s), 21.26 (s), 20.30 (s);HRMS: calcd for $C_{31}H_{31}ClFN_4O_6^+$ $[M+H]^+$ 609.191 07, found 609.192 20.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-((2-甲氧乙基)胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-18):白色固体;产率 67.2%;熔点 253～255 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.73 (s, 1H), 7.28 (d, J = 10.0 Hz, 1H), 6.80 (d, J = 6.1 Hz, 1H), 4.12 (t, J = 5.0 Hz, 2H), 3.79 (dd, J = 9.6, 4.7 Hz, 2H), 3.63 (t, J = 4.8 Hz, 2H), 3.43 (s, 3H), 3.42～3.35 (m, 2H), 3.33 (s, 3H), 3.30 (s, 3H), 2.44 (s, 4H), 2.17 (d, J = 6.0 Hz, 2H), 1.84 (s, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.35 (s), 168.78 (s), 166.66 (s), 162.61 (s), 151.65 (d, J = 248.4 Hz), 151.41 (s), 150.69 (d, J = 2.8 Hz), 142.52 (s), 123.32 (d, J = 9.1 Hz), 118.36 (d, J = 24.3 Hz), 118.30 (d, J = 14.1 Hz), 113.60 (s), 89.96 (s), 70.27 (s), 68.89 (s), 59.23 (s), 43.39 (s), 27.94 (s), 27.71 (s), 27.03 (s), 26.85 (s), 21.26 (s), 20.29 (s);HRMS: calcd for $C_{27}H_{31}ClFN_4O_7^+$ $[M+H]^+$ 577.185 98, found 577.186 83.

5-(4-(2-氯-5-(1,3-二氧-1,3,4,5,6,7-六氢-2*H*-异吲哚-2-基)-4-氟苯氧)-1-((3-甲氧丙基)胺)丁烯基)-1,3-二甲基嘧啶-2,4,6(1*H*,3*H*,5*H*)-三酮(BTA-19):白色固体;产率 63.2%;熔点 251～253 ℃;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.65 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 6.4 Hz, 1H), 4.13 (t, J = 5.5 Hz, 2H), 3.70 (dd, J = 12.4, 6.7 Hz, 2H), 3.49 (t, J = 5.8 Hz, 2H), 3.40～3.34 (m, 5H), 3.32 (s, 3H), 3.30 (s, 3H), 2.44 (s, 4H), 2.15 (td, J = 12.0, 5.8 Hz, 2H), 2.01～1.93 (m, 2H), 1.86～1.79 (m, 4H);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.29 (s), 168.80 (s), 166.70 (s), 162.59 (s),

151.62 (d, J = 248.4 Hz), 151.41 (s), 150.74 (d, J = 2.3 Hz), 142.51 (s), 123.42 (d, J = 9.1 Hz), 118.34 (d, J = 24.5 Hz), 118.27 (d, J = 14.5 Hz), 113.55 (s), 89.75 (s), 69.25 (s), 68.93 (s), 58.82 (s), 40.81 (s), 29.53 (s), 27.94 (s), 27.66 (s), 27.09 (s), 26.66 (s), 21.26 (s), 20.30 (s); HRMS: calcd for $C_{28}H_{33}ClFN_4O_7^+[M+H]^+$ 591.201 63, found 591.202 70.

2.3 除草活性测试[6-8]

将 150 g 砂质粘土置于长×宽×高为 8 cm × 7 cm × 7 cm 的塑料方盒中,用水湿润。然后将 15 颗发芽种子种植至 1～2 cm 深,放置在温度为 28～30 ℃、光照/黑暗时间为 12 h/12 h 的温室中培养。当幼苗长到两叶一心期时,使用实验室喷雾器进行茎叶喷雾处理。药物浓度设置为 1 200 g/ha, 600 g/ha, 300 g/ha, 150 g/ha 和 75 g/ha,以未经处理的幼苗为对照组。每个实验组设置三个平行。21 天后称重每盆植株地上部鲜重,以鲜重抑制百分数来表示药效。抑制率计算公式为 $\rho_{抑制率}(\%)=(M_{空白对照草的鲜重}-M_{处理盆草的鲜重})/M_{空白对照草的鲜重}\times 100\%$。

3 结论

以 2-氯-4-氟-5-硝基苯酚为原料,经七步反应合成了 19 个含马来酰亚胺结构的 5-(1-氨基-2-苯氧亚乙基)巴比妥酸衍生物,其结构经核磁共振氢谱、碳谱和高分辨质谱的确证。通过三轮温室盆栽活性筛选发现,在苗后处理、150 g/ha 施药量情况下,目标化合物 BTA-13 对双子叶植物油菜、反枝苋、马齿苋、藜、牵牛、鬼针草、翅果菊和蒲公英具有优异的除草活性,抑制率均大于 95%。通过结构-活性关系研究发现,目标化合物的 Clog P 对除草活性具有较大的影响。在目标化合物的结构中引入亲水性的基团,提高化合物的水溶性有利于提高化合物的除草活性。同时,结构-活性关系研究还发现,目标化合物中 R 基团的空间位阻对除草活性也具有一定的影响。当在目标化合物的结构中引入体积较大的 R 基团时,不利于提高目标化合物的除草活性。这些构效关系结果为今后化合物的改造提供了有用的信息。此外,通过作物安全性评价发现,化合物 BTA-13 对玉米和小麦相对安全。因此,化合物 BTA-13 可以作为新型除草剂先导化合物进行进一步的优化。

参 考 文 献

[1] LAMBERTH C, JEANMART S, LUKSCH T, et al. Current challenges and trends in the discovery of agrochemicals[J]. Science, 2013, 341: 742-746.

[2] ZHANG P, DUAN C B, JIN B, et al. Recent advances in the natural products-based lead discovery for new agrochemicals[J]. Advanced Agrochem, 2023, 2: 324-339.

[3] PETERSON M A, COLLAVO A, OVEJERO R, et al. The challenge of herbicide resistance around the world: a current summary[J]. Pest Management Science, 2018, 74: 2246-2259.

[4] JIA L, GAO S, ZHANG Y Y, et al. Fragmenlt recombination design, synthesis, and safener activity of novel ester-substituted pyrazole derivatives[J]. Journal of Agricultural and Food Chemistry, 2021, 69: 8366-8379.

[5] LI K J, QU R Y, LIU Y C, et al. Design, synthesis, and herbicidal activity of pyrimidine-biphenyl hybrids as novel acetohydroxyacid synthase inhibitors[J]. Journal of Agricultural and Food Chemistry, 2018, 66: 3773-3782.

[6] WANG S M, LI N, HAN S B, et al. Synthesis, herbicidal activity, and molecular mode of action evaluation of novel quinazolinone-phenoxypropionate hybrids containing a diester moiety[J]. Agronomy, 2024, 14: 2124.

[7] LI N, CHEN K, HAN S B, et al. Synthesis, herbicidal activity, and molecular mode of action evaluation of novel aryloxyphenoxypropionate/amide derivatives containing a quinazolinone moiety[J]. Journal of Agricultural and Food Chemistry, 2024, 72: 9445-9456.

[8] WANG C C, CHEN K, LI N, et al. Design, synthesis, mode of action and herbicidal evaluation of quinazolin-4(3H)-one derivatives based on aryloxyphenoxypropionate motif[J]. Agronomy, 2022, 12: 1840.

[9] SUN S S, KOU S, WANG W F, et al. Synthesis of novel propionamide-methylpyrazole carboxylates as herbicidal candidates[J]. Journal of Agricultural and Food Chemistry, 2024, 72: 21401-21409.

[10] WANG D W, ZHANG R B, YU S Y, et al. Discovery of novel N-isoxazolinylphenyltriazinones as promising protoporphyrinogen IX oxidase inhibitors[J]. Journal of Agricultural and Food Chemistry, 2019, 67: 12382-12392.

[11] YANG Z K, LI Q B, YIN J M,et al. Design, synthesis and mode of action of novel 3-chloro-6-pyrazolyl picolinate derivatives as herbicide candidates[J]. Pest Management Science, 2021, 77: 2252-2263.

[12] ZHAO L X, WANG Z X, ZOU Y L,et al. Phenoxypyridine derivatives containing natural product coumarins with allelopathy as novel and promising proporphyrin IX oxidase-inhibiting herbicides: design, synthesis and biological activity study[J]. Pesticide Biochemistry and Physiology, 2021, 177: 104897.

[13] FENG T, LIU Q, XU Z Y,et al. Design, synthesis, herbicidal activity, and structure-activity relationship study of novel 6-(5-aryl-substituted-1-pyrazolyl)-2-picolinic acid as potential herbicides[J]. Molecules, 2023, 28: 1431.

[14] WANG D W, LIN H Y, CAO R J, et al. Synthesis and herbicidal evaluation of triketone-containing quinazoline-2,4-diones[J]. Journal of Agricultural and Food Chemistry, 2014, 62: 11786-11796.

[15] WANG D W, LIN H Y, CAO R J, et al. Design, synthesis and herbicidal activity of novel quinazoline-2,4-diones as 4-hydroxyphenylpyruvate dioxygenase inhibitors[J]. Pest Management Science, 2015, 71: 1122-1132.

[16] LEI K, Li P,ZHOU X Y, et al. Design, synthesis and herbicidal activity of 5-acylbarbituric acid derivatives and study of molecular mode of action[J]. Chinese Journal of Organic Chemistry, 2020, 40: 2788-2797.

[17] PANOV A A, SIMONOV A Y, LAVRENOV S N, et al. 3,4-Disubstituted maleimides: synthesis and biological activity[J]. Chemistry of Heterocyclic Compounds, 2018, 54: 103-113.

[18] KORNET M J, CRIDER A M. Potential long-acting anticonvulsants. 1. Synthesis and activity of succinimides containing an alkylating group at the 2 position[J]. Journal of Medicinal Chemistry, 1977, 20: 405-409.

[19] CHIEN S C, CHEN M L, KUO H T,et al. Anti-inflammatory activities of new succinic and maleic derivatives from the fruiting body of Antrodia camphorata[J]. Journal of Agricultural and Food Chemistry, 2008, 56: 7017-7022.

[20] MAHBOOBJ S, EICHHORN E, POPP A,et al. 3-Bromo-4-(1*H*-3-indolyl)-2,5-dihydro-1*H*-2,5-pyrroledione derivatives as new lead compounds for antibacterially active substances[J]. European Journal of Medicinal Chemistry, 2006, 41: 176-191.

[21] YANG K, CHEN Y F, TO K, et al. Alectinib (CH5424802) antagonizes ABCB1-and ABCG2-mediated multidrug resistance in vitro, in vivo and ex vivo[J]. Experimental and Molecular Medicine, 2017, 49: e303.

[22] HO S Y, ALAM J, JEYARAJ D A, et al. Scaffold hopping and optimization of maleimide based porcupine inhibitors[J]. Journal of Medicinal Chemistry, 2017, 60: 6678-6692.

[23] FABBRO D, COWAN-JACOB S W, MOBITZ H, et al. Targeting cancer with small-molecular-weight kinase inhibitors[J]. Methods in Molecular Biology, 2012, 795: 1-9.

[24] KUMAR M M K, NAIK J D, SATYAVATHI K, et al. Denigrins A-C: new antitubercular 3,4-diarylpyrrole alkaloids from Dendrilla nigra[J]. Natural Product Research, 2014, 28: 888-894.

[25] ZHAO L X, JIANG M J, HU J J,et al. Design, synthesis, and herbicidal activity of novel diphenyl ether derivatives containing fast degrading tetrahydrophthalimide[J]. Journal of Agricultural and Food Chemistry, 2020, 68: 3729-3741.

[26] GENG W, ZHANG Q, LIU L, et al. Design, synthesis, and herbicidal activity of novel tetrahydrophthalimide derivatives containing oxadiazole/thiadiazole moieties[J]. Journal of Agricultural and Food Chemistry, 2024, 72: 17191-17199.

[27] ZHANG L, CHEN R J, LI X Y, et al. Synthesis, insecticidal activities, and 3D-QASR of N-pyridylpyrazole amide derivatives containing a phthalimide as potential ryanodine receptor activators[J]. Journal of Agricultural and Food Chemistry, 2022, 70: 12651-12662.

(责任编辑:刘庆松)