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# 含苯氧甲基、氯甲基的十元、十二元及十六元氮杂内酯化合物的合成及抑菌活性

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**摘要:** 大环内酯类化合物已被广泛应用于药物中, 为发现新型高活性抑菌化合物, 以课题组之前研究的大环内酯化合物 **WLD**、**D16-19** 等为先导化合物, 设计、合成一系列新型含苯氧甲基、氯甲基的十元、十二元及十六元氮杂内酯化合物 **C** 和 **E**, 并进行离体抑真菌活性测定。结果表明: 在 50 mg/L 质量浓度下, 大部分化合物 **C** 和 **E** 对供试的 5 种病原真菌均有一定的抑菌活性, 其中 **C5** 和 **C6** 对马铃薯早疫病菌 *Alternaria solani* 的抑制率分别为 88% 和 90%, 化合物 **C6** 对小麦赤霉病菌 *Fusarium graminearum* 的抑制率为 94%。对比 **C** 和 **E** 对 5 种真菌的抑制率, 加入氨基甲酸酯和脲结构片段对化合物活性没有明显提高; 十六元氮杂内酯化合物 **C5**、**C6** 的抑菌活性高于十元和十二元氮杂内酯化合物 **C1~C4**, 说明化合物的主体结构氮杂内酯环对化合物的活性影响较大。**C5** 对马铃薯早疫病菌的  $EC_{50}$  值为 2.95 mg/L, 与对照药剂吡唑醚菌酯活性相近, 优于先导化合物 **D16-19** 对番茄早疫病菌 *A. solani* 的活性 ( $EC_{50}$  值为 4.76 mg/L), 表明在十六元氮杂内酯中加入苯氧甲基可提高化合物对早疫病菌的活性, **C5** 可作为新型抑菌活性先导化合物进一步研究。

**关键词:** 苯氧甲基; 氯甲基; 氮杂内酯化合物; 合成; 抑菌活性

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## Synthesis and bacteriostatic activity of ten-, twelve- and sixteen-membered azalactone compounds containing phenoxymethyl and chloromethyl group

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**Abstract:** Macrolides have been extensively utilized in drug discovery to identify new and highly potent fungistatic compounds. A series of novel ten-, twelve-, and sixteen-membered azolides containing phenoxymethyl and chloromethyl compounds **C** and **E** were designed and synthesized based on the macrolide compounds **WLD** and **D16-19**, which had previously been investigated by the research group as lead compounds. Their fungistatic activities were evaluated *in vitro*. The results demonstrated that the majority of the compounds **C** and **E** exhibited inhibitory activities against the five pathogenic

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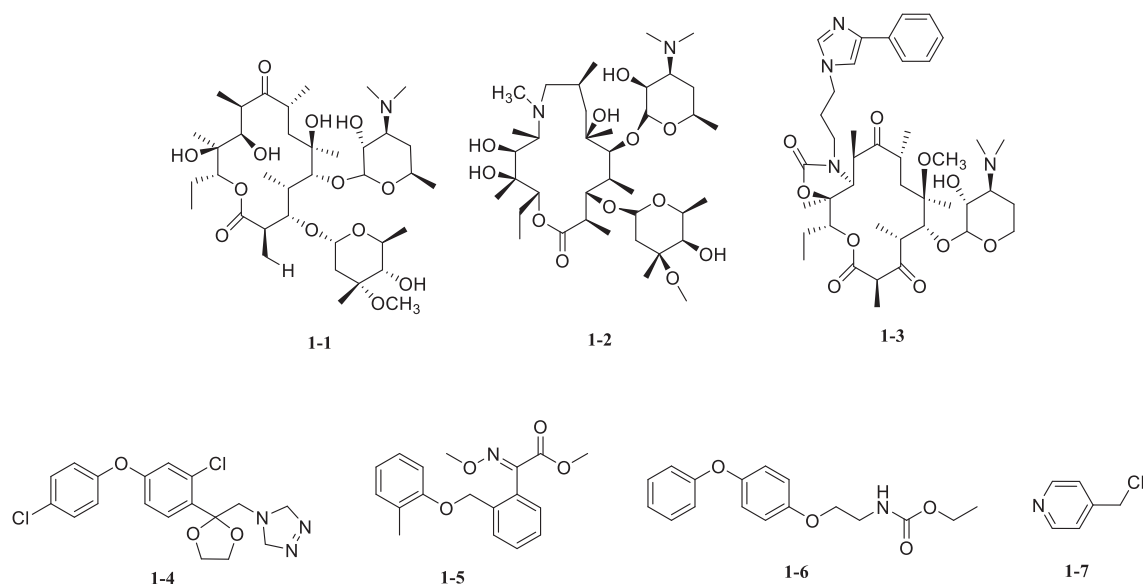


fungi tested at a concentration of 50 mg/L. Among these, **C5** and **C6** showed inhibition rates of 88% and 90% against *Alternaria solani*, respectively, while **C6** exhibited a 94% inhibition rate against *Fusarium graminearum*. Notably, the addition of structural fragments carbamate and urea did not significantly enhance the compound activity. Furthermore, hexadecyl azalactones **C5** and **C6** displayed higher inhibitory activity compared to ten- and twelve-membered azalactone **C1-C4**, indicating that the azalactone ring, as the main structural element of the compounds, had a greater impact on their activities. Compound **C5** exhibited an  $EC_{50}$  value of 2.95 mg/L against *A. solani*, similar to the activity of the control drug pyraclostrobin and superior to the lead compound **D16-19** against *A. solani* ( $EC_{50}$  value of 4.76 mg/L). This suggests that adding phenoxyethyl to hexadecyl azoguanide can enhance the compounds' activity against *A. solani*. Further investigation is warranted to determine the potential of compound **C5** as a novel bacteriostatic lead compound.

**Keywords:** phenoxyethyl; chloromethyl; azolactone compounds; synthesis; bacteriostatic activity

大环内酯类天然产物已被广泛应用于药物中, 许多大环内酯类药物具有抑菌活性<sup>[1-2]</sup>, 第一代大环内酯类抗生素红霉素类 (erythromycins, **1-1**, 图式 1)<sup>[3]</sup>, 可用于治疗球菌引起的皮肤病, 但其具有酸不稳定性, 人们很快研发了第二代大环内酯类抗生素阿奇霉素 (azithromycin) (**1-2**, 图式 1)<sup>[4]</sup>。

阿奇霉素是第一个氮杂内酯类抗生素, 在抑菌谱和耐受性方面有了很大的改善, 对革兰氏阳性菌和厌氧菌具有更好的抑制活性<sup>[3]</sup>。第三代大环内酯类抗生素中泰利霉素 (telithromycin) (**1-3**, 图式 1)<sup>[5]</sup> 具有更好的抑菌活性及更低的耐药性。



图式 1 大环内酯类化合物及含苯醚结构和氯甲基结构的化合物

Scheme 1 Macrolides and compounds containing phenyl ether and chloromethyl structures

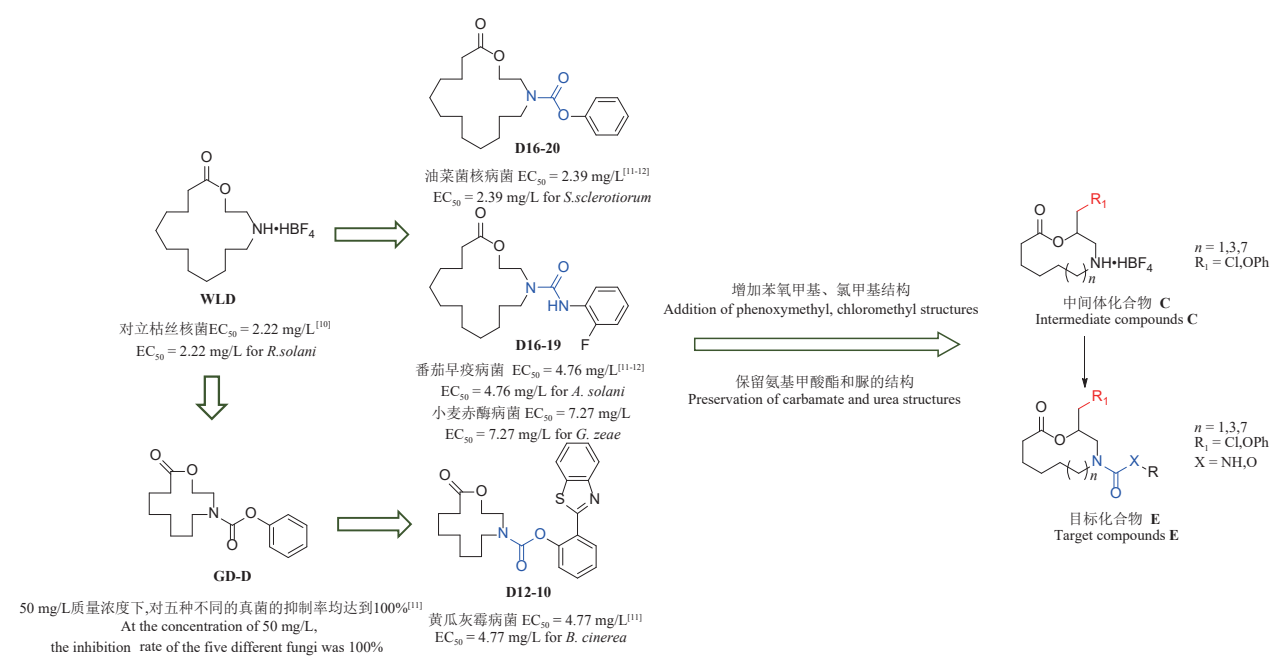
一些常见的农药分子中含有苯醚结构和氯甲基结构, 而含二芳基醚类结构的化合物是含醚结构化合物中重要的一种, 其具有强疏水性、分子柔性、极好的脂溶性、细胞膜渗透性以及代谢稳定性等优点<sup>[6-7]</sup>。苯醚甲环唑 (**1-4**, 图式 1) 具有广谱杀菌活性, 可通过抑制细胞壁甾醇合成来抑制真菌生长<sup>[8]</sup>; 醚菌酯 (**1-5**, 图式 1) 作为线粒体呼

吸抑制剂, 对梨的白粉病具有良好防效, 而且是一种广谱杀菌剂, 持效期长<sup>[8]</sup>; 苯醚威 (**1-6**, 图式 1) 影响昆虫的激素调节功能, 干扰节肢动物的免疫力, 而且对哺乳动物毒性较小<sup>[9]</sup>; 此外, 氯甲基吡啶 (**1-7**, 图式 1) 作为硝化抑制剂可以促进农作物对有机氮的吸收和利用<sup>[10]</sup>。

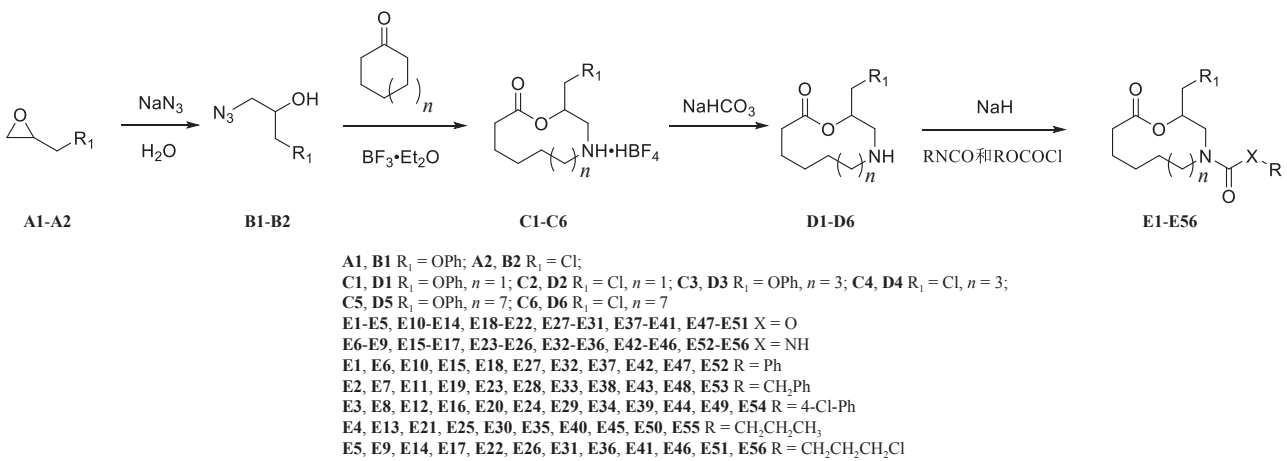
本课题组长期致力于研究大环内酯类化合

物,最先发现化合物 13-氮杂-1,15-十五内酯氟硼酸盐 (**WLD**) 对立枯丝核菌 *Rhizoctonia solani* 的  $EC_{50}$  值为 2.22 mg/L, 与对照药剂百菌清药效相当<sup>[11]</sup>。前期设计合成了十六元、十二元氮杂大环内酯化合物<sup>[12-13]</sup>。其中, **GD-D** 显示出了良好的杀真菌活性, 在 50 mg/L 下, 对 5 种不同的真菌均表现出良好的抑制活性。为了获得更高抑菌活性的新型化合物, 本研究保留了十六元、十二元氮杂内酯主体结构以及氨基甲酸酯、脲的片段结构, 设计了十元氮杂内酯主体结构, 且在主体结构中增加了苯氧甲基和氯甲基结构片段, 合成了含苯氧甲基和氯甲基的十元、十二元及十六元中

间体 **C** 系列化合物, 在 **C** 基础上, 增加了氨基甲酸酯、脲结构的 **E** 系列化合物 (目标化合物的设计思路见图式 2)。化合物合成路线见图式 3, 原料 **A** 与叠氮钠在七水合三氯化铷催化下反应生成化合物 **B**, 参考课题组之前合成氮杂大环内酯的方法<sup>[14]</sup>, 叠氮醇与环酮反应生成氮杂内酯氟硼酸盐的新化合物 **C**, 加入饱和碳酸氢钠溶液生成中间体 **D**, 氮杂内酯的仲胺活性较低, 使用强碱 NaH 夺取质子, 进一步与氯甲酸酯或异氰酸酯反应, 生成终产物 **E**。化合物 **C** 和 **E** 的结构均采用核磁共振氢谱 ( $^1\text{H}$  NMR)、碳谱 ( $^{13}\text{C}$  NMR) 和高分辨质谱 (HR-ESI-MS) 进行表征, 并对其进行了抑菌活性测定。



图式 2 目标化合物的设计思路  
Scheme 2 Design idea of the target compounds



图式 3 目标化合物的合成路线  
Scheme 3 Synthetic route of the target compounds

## 1 实验部分

### 1.1 仪器与试剂

Bruker DPX300 核磁共振仪 (500 MHz 或 300 MHz), TMS 为内标,  $\text{CDCl}_3$  为溶剂; RY-1 g 熔点仪 (天津天光光学仪器有限公司, 温度未校正); Q-Exactive 型高分辨质谱仪 (中国赛默飞世尔科技有限公司); EYELA N-1100 旋转蒸发仪; SHB-III 循环式真空泵 (郑州恒岩仪器有限公司)。

所用试剂均为市售分析纯, 无水反应中试剂均用常规方法进行无水处理; 98% 吡唑醚菌酯 (pyraclostrobin) 由浙江天一生物科技有限公司 (中国绍兴) 提供。

### 1.2 化合物的合成

1.2.1 化合物 **B1**、**B2** 的合成 根据文献 [15]、[16] 的方法进行。

1.2.2 化合物 **C** 的合成 室温氩气保护下, 将 0.05 mol 环己酮、环戊酮或环十二酮和 0.06 mol **B1** 或 **B2** 溶于 100 mL 无水二氯甲烷 ( $\text{CH}_2\text{Cl}_2$ ) 中, 冰浴下滴加 0.125 mol 47% 三氟化硼乙醚溶液, 1 h 滴加完毕。加热回流搅拌 24 h, 薄层色谱 (TLC,  $V(\text{石油醚, PE}) : V(\text{乙酸乙酯, EA}) = 3 : 1$ ) 监测至环酮反应完毕。冰浴下逐滴滴加饱和碳酸氢钠水溶液至不再有固体析出, 撤去冰浴, 室温下抽滤, 得白色固体, 即得产物氮杂内酯氟硼酸盐 **C**。

7-氮杂-9-苯氧甲基-9-壬内酯氟硼酸盐 (**C1**): 白色固体, 产率 92%, m.p. 62-63 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (m, 2H), 7.02–6.85 (m, 3H), 4.41 (s, 1H), 4.16 (s, 1H), 3.93 (m, 2H), 3.72–3.59 (m, 2H), 3.44 (d, 2H), 2.67–2.44 (m, 2H), 1.69 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  177.53, 157.41, 128.51, 120.07, 113.47, 69.09, 68.26, 52.41, 51.07, 35.99, 28.78, 27.14, 22.25; HR-ESI-MS:  $\text{C}_{15}\text{H}_{22}\text{NO}_3$   $[\text{M} + \text{H}]^+$ , 计算值 264.1594, 测试值 264.1595。

7-氮杂-9-氯甲基-9-壬内酯氟硼酸盐 (**C2**): 白色固体, 产率 88%, m.p. 125-126 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.63 (d, 1H), 4.05–3.90 (m, 1H), 3.70–3.42 (m, 6H), 2.57 (d, 2H), 1.86–1.54 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  179.48, 83.30, 54.91, 48.03, 44.88, 27.91, 26.85, 24.60, 21.03; HR-ESI-MS:  $\text{C}_9\text{H}_{17}\text{ClNO}_2$   $[\text{M} + \text{H}]^+$ , 计算值 206.0942, 测试值 206.0945。

9-氮杂-11-苯氧甲基-11-十一内酯氟硼酸盐 (**C3**): 浅黄色液体, 产率 90%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (s, 2H), 7.35–7.19 (m, 2H), 6.91 (m, 11.1 Hz, 3H), 5.56–5.34 (m, 1H), 4.13 (d, 2H), 3.16 (d, 2H), 2.79 (m, 2H), 2.58–2.25 (m,

2H), 1.91–1.33 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  174.94, 173.11, 158.76, 158.34, 129.59, 121.23, 120.52, 114.65, 70.84, 68.90, 67.52, 55.00, 49.11, 48.26, 47.83, 46.77, 33.97, 28.08, 26.23, 25.75, 24.95, 24.55, 23.46, 22.96, 21.74; HR-ESI-MS:  $\text{C}_{17}\text{H}_{26}\text{NO}_3$   $[\text{M} + \text{H}]^+$ , 计算值 292.1907, 测试值 292.1906。

9-氮杂-11-氯甲基-11-十一内酯氟硼酸盐 (**C4**): 白色固体, 产率 76%, m.p. 99-101 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.63 (m, 1H), 4.11 (m, 7H), 2.91 (m, 2H), 1.75 (m, 4H), 1.49 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  178.23, 172.50, 82.55, 69.12, 52.55, 46.90, 45.33, 44.96, 43.72, 33.74, 24.80, 24.61, 24.53, 24.17, 23.75, 22.77, 21.89, 21.17, 21.00, 20.81; HR-ESI-MS:  $\text{C}_{11}\text{H}_{21}\text{ClNO}_2$   $[\text{M} + \text{H}]^+$ , 计算值 234.1255, 测试值 234.1257。

13-氮杂-15-苯氧甲基-1,15-十五内酯氟硼酸盐 (**C5**): 白色固体, 产率 92%, m.p. 109-110 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25–7.19 (m, 2H), 6.93 (m, 1H), 6.85 (m, 2H), 5.65 (m, 1H), 4.39–4.22 (m, 3H), 4.15 (m, 1H), 3.83 (m, 1H), 3.65 (m, 1H), 2.83–2.71 (m, 2H), 1.90–1.60 (m, 4H), 1.41–1.19 (m, 14H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.34, 157.74, 129.74, 122.04, 114.81, 82.29, 66.69, 50.62, 46.56, 27.17, 26.96, 26.37, 26.02, 25.49, 25.32, 24.87, 23.31, 23.24, 23.05; HR-ESI-MS:  $\text{C}_{21}\text{H}_{34}\text{NO}_3$   $[\text{M} + \text{H}]^+$ , 计算值 347.4990, 测试值 347.4990。

13-氮杂-15-氯甲基-1,15-十五内酯氟硼酸盐 (**C6**): 白色固体, 产率 97%, m.p. 103-105 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.06 (br, 2H), 5.31 (m, 1H), 3.90 (m, 1H), 3.76 (m, 1H), 3.57–3.33 (m, 2H), 3.31–3.03 (m, 2H), 2.58–2.36 (m, 2H), 1.84–1.55 (m, 4H), 1.52–1.23 (m, 14H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  173.77, 69.16, 48.44, 48.23, 43.34, 33.45, 26.80, 26.17, 26.07, 25.96, 25.62, 25.49, 24.42, 24.05, 23.30; HR-ESI-MS:  $\text{C}_{15}\text{H}_{29}\text{ClNO}_2$   $[\text{M} + \text{H}]^+$ , 计算值 290.8515, 测试值 289.8440。

1.2.3 目标化合物 **E** 的合成 化合物 **C** 溶于二氯甲烷中, 加入过量的饱和碳酸氢钠水溶液, 室温搅拌 30 min, 用二氯甲烷萃取, 合并有机相, 干燥, 浓缩, 得到化合物 **D**, 室温氩气保护下, 将 1.9 mmol 化合物 **D** 溶于 20 mL 无水  $\text{CH}_2\text{Cl}_2$  中, 冰浴下加入 2.85 mmol 氢化钠 (NaH), 搅拌半小时后撤去冰浴, 逐滴加入 2.47 mmol 取代氯甲酸酯或异氰酸酯, 室温搅拌 24 h, TCL ( $V(\text{PE}) : V(\text{EA}) = 1 : 1$ ) 检测反应完毕。冰浴下滴加 15 mL 水停止反应,  $\text{CH}_2\text{Cl}_2$  萃取 (20 mL  $\times$  3), 合并有机相,  $\text{Na}_2\text{SO}_4$  干燥, 减压除去溶剂, 残余物经硅胶 (筛孔径 0.050~0.075 mm, 200~300 目) 柱层析 ( $V(\text{PE}) : V(\text{EA}) = 10 : 1$ ) 分离, 得产物 **E**。

7-*N*-苄氧甲酰基-9-苄氧甲基-7-氮杂-9-壬内酯 (**E1**): 白色固体, 产率 65%, m.p. 98-100 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52–7.12 (m, 7H), 6.96 (m, 3H), 5.38–5.19 (m, 1H), 4.20 (m, 2H), 3.99 (m, 1H), 3.73–3.37 (m, 3H), 2.54 (m, 2H), 1.70 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.47, 157.32, 152.22, 150.04, 128.51, 125.11, 120.33, 119.94, 113.67, 75.24, 66.22, 50.21, 47.98, 36.13, 28.82, 27.46, 22.31; HR-ESI-MS:  $\text{C}_{22}\text{H}_{26}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 384.1805, 测试值 384.1807.

7-*N*-苄氧甲酰基-9-苄氧甲基-7-氮杂-9-壬内酯 (**E2**): 浅黄色液体, 产率 30%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55–7.19 (m, 7H), 7.07–6.80 (m, 3H), 5.30–5.13 (m, 3H), 4.28–3.88 (m, 3H), 3.64–3.24 (m, 3H), 2.50 (m, 2H), 1.64 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.35, 157.37, 153.64, 134.17, 128.44, 127.47, 120.20, 113.66, 74.50, 68.74, 66.40, 50.20, 48.16, 36.09, 28.78, 27.37, 22.27; HR-ESI-MS:  $\text{C}_{23}\text{H}_{28}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 398.1962, 测试值 398.1965.

7-*N*-(4-氯苄氧甲酰基)-9-苄氧甲基-7-氮杂-9-壬内酯 (**E3**): 浅黄色液体, 产率 33%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.22 (m, 5H), 7.19–7.07 (m, 2H), 7.04–6.87 (m, 3H), 5.36–5.14 (m, 1H), 4.29–4.09 (m, 2H), 3.97 (m, 5.0 Hz, 1H), 3.75–3.38 (m, 3H), 2.54 (m, 2H), 1.70 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.68, 157.38, 151.95, 135.69, 128.52, 127.96, 127.41, 120.25, 119.06, 113.59, 70.81, 66.73, 49.56, 47.62, 36.10, 28.76, 27.36, 22.26; HR-ESI-MS:  $\text{C}_{22}\text{H}_{25}\text{ClNO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 418.1416, 测试值 418.1417.

7-*N*-丙氧甲酰基-9-苄氧甲基-7-氮杂-9-壬内酯 (**E4**): 浅黄色液体, 产率 30%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (m, 3H), 6.93 (m, 4H), 5.30–5.07 (m, 1H), 4.24–4.04 (m, 4H), 3.94 (m, 5.0 Hz, 1H), 3.57–3.41 (m, 3H), 2.52 (m, 2H), 1.69 (m, 7.1 Hz, 9H), 0.95 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  176.01, 158.04, 154.44, 129.14, 120.94, 114.34, 74.78, 69.44, 67.04, 50.86, 48.74, 36.83, 29.48, 28.10, 22.97, 21.63, 9.79; HR-ESI-MS:  $\text{C}_{19}\text{H}_{28}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 350.1962, 测试值 350.1963.

7-*N*-(2-氯乙基氧甲酰基)-9-苄氧甲基-7-氮杂-9-壬内酯 (**E5**): 浅黄色液体, 产率 50%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (m, 2H), 7.07–6.79 (m, 3H), 5.33–5.13 (m, 1H), 4.40 (m, 2H), 4.14 (m, 2H), 3.94 (m, 1H), 3.70 (m, 2H), 3.63–3.37 (m, 3H), 2.53 (m, 2H), 1.67 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.45, 157.30, 153.31, 128.48, 120.27, 113.63, 74.85, 66.29, 50.34, 48.10, 40.17, 36.14, 28.83, 27.42, 22.32; HR-ESI-MS:  $\text{C}_{18}\text{H}_{25}\text{ClNO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 370.1416, 测试值 370.1421.

7-*N*-苄氨基甲酰基-9-苄氧甲基-7-氮杂-9-壬内酯 (**E6**): 白色固体, 产率 33%, m.p. 139-140 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56–7.20 (m, 7H), 7.15–6.87 (m, 4H), 5.45–5.17 (m, 1H), 4.29–4.05 (m, 2H), 3.87 (m, 1H), 3.76–

3.31 (m, 3H), 2.54 (m, 2H), 1.68 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.56, 157.45, 151.99, 136.90, 128.50, 128.01, 122.51, 120.18, 117.84, 113.64, 70.82, 66.82, 49.57, 47.67, 36.11, 28.79, 27.41, 22.30; HR-ESI-MS:  $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 383.1965, 测试值 383.1967.

7-*N*-苄氨基甲酰基-9-苄氧甲基-7-氮杂-9-壬内酯 (**E7**): 白色固体, 产率 57%, m.p. 165-167 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46–7.12 (m, 7H), 7.04–6.76 (m, 3H), 5.48–5.12 (m, 2H), 4.53–3.96 (m, 4H), 3.87–3.16 (m, 4H), 2.47 (m, 2H), 1.64 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.33, 157.54, 154.93, 137.42, 128.44, 127.61, 126.44, 120.08, 113.68, 70.68, 66.95, 49.55, 47.78, 44.01, 36.11, 28.83, 27.43, 22.32; HR-ESI-MS:  $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 397.2122, 测试值 397.2116.

7-*N*-(4-氯苄基氨基甲酰基)-9-苄氧甲基-7-氮杂-9-壬内酯 (**E8**): 白色固体, 产率 47%, m.p. 83-84 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69 (s, 1H), 7.49–7.12 (m, 6H), 7.04–6.79 (m, 3H), 5.27 (m, 1H), 4.11 (m, 2H), 3.92–3.28 (m, 4H), 2.51 (m, 2H), 1.64 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.68, 157.38, 151.95, 135.69, 128.52, 127.96, 127.41, 120.25, 119.06, 113.59, 70.81, 66.73, 49.56, 47.62, 36.10, 28.76, 27.36, 22.26; HR-ESI-MS:  $\text{C}_{22}\text{H}_{26}\text{ClN}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 417.1576, 测试值 417.1568.

7-*N*-(2-氯乙基氨基甲酰基)-9-苄氧甲基-7-氮杂-9-壬内酯 (**E9**): 白色固体, 产率 50%, m.p. 88-89 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.16 (m, 3H), 7.06–6.80 (m, 3H), 5.56–5.04 (m, 2H), 4.24–3.99 (m, 2H), 3.78 (m, 5.2 Hz, 1H), 3.68–3.39 (m, 7H), 2.52 (m, 2H), 1.66 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.39, 157.49, 154.77, 128.49, 120.16, 113.68, 70.96, 66.87, 49.71, 47.85, 42.74, 41.84, 36.16, 28.86, 27.46, 22.35; HR-ESI-MS:  $\text{C}_{18}\text{H}_{26}\text{ClN}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 369.1576, 测试值 369.1570.

7-*N*-苄氧甲酰基-9-氯甲基-7-氮杂-9-壬内酯 (**E10**): 浅黄色液体, 产率 31%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49–7.34 (m, 2H), 7.31–7.12 (m, 3H), 5.25–5.04 (m, 1H), 3.88 (m, 2H), 3.70 (m, 1H), 3.61–3.34 (m, 3H), 2.54 (m, 2H), 1.85–1.54 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.55, 151.99, 149.96, 128.53, 125.22, 119.89, 75.69, 50.34, 48.90, 42.84, 36.08, 28.79, 27.45, 22.28; HR-ESI-MS:  $\text{C}_{16}\text{H}_{21}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 326.1154, 测试值 326.1153.

7-*N*-苄氧甲酰基-9-氯甲基-7-氮杂-9-壬内酯 (**E11**): 浅黄色液体, 产率 30%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49–7.31 (m, 5H), 5.31–4.99 (m, 3H), 3.96–3.19 (m, 6H), 2.47 (m, 2H), 1.85–1.39 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.46, 153.42, 134.02, 127.55, 75.04, 68.93, 50.34, 49.07, 43.00, 36.04, 28.75, 27.37, 22.24; HR-ESI-MS:  $\text{C}_{17}\text{H}_{23}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 340.1311, 测试值 340.1311.

7-*N*-(4-氯苯氧甲酰基)-9-氯甲基-7-氮杂-9-壬内酯 (**E12**): 浅黄色液体, 产率 29%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44–7.31 (m, 2H), 7.22–7.07 (m, 2H), 5.13 (m, 1H), 3.96–3.79 (m, 2H), 3.76–3.38 (m, 4H), 2.54 (m, 2H), 1.69 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.65, 151.71, 148.47, 130.66, 128.59, 128.25, 121.31, 76.03, 50.40, 48.93, 42.73, 36.07, 28.79, 27.46, 22.27; HR-ESI-MS:  $\text{C}_{16}\text{H}_{20}\text{Cl}_2\text{NO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 360.0764, 测试值 360.0767.

7-*N*-丙氧甲酰基-9-氯甲基-7-氮杂-9-壬内酯 (**E13**): 浅黄色液体, 产率 30%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.14–4.98 (m, 1H), 4.13 (m, 2H), 4.02–3.31 (m, 7H), 2.67–2.40 (m, 2H), 1.71 (m, 8H), 0.97 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.58, 74.79, 69.00, 50.36, 49.00, 43.08, 36.10, 28.83, 27.43, 22.30, 20.98, 9.11; HR-ESI-MS:  $\text{C}_{13}\text{H}_{23}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 292.1310, 测试值 292.1311.

7-*N*-(2-氯乙基氧甲酰基)-9-氯甲基-7-氮杂-9-壬内酯 (**E14**): 浅黄色液体, 产率 54%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.08 (m, 1H), 4.62–4.33 (m, 2H), 3.93–3.58 (m, 5H), 3.46 (m, 3H), 2.53 (m, 2H), 1.86–1.54 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.59, 153.11, 75.42, 66.52, 50.50, 49.03, 42.90, 40.18, 36.08, 28.80, 27.42, 22.29; HR-ESI-MS:  $\text{C}_{12}\text{H}_{20}\text{Cl}_2\text{NO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 312.0764, 测试值 312.0765.

7-*N*-苄氨基甲酰基-9-氯甲基-7-氮杂-9-壬内酯 (**E15**): 白色固体, 产率 67%, m.p. 144–146 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45–7.03 (m, 6H), 5.41 (s, 1H), 5.15–5.00 (m, 1H), 4.36 (m, 4.0 Hz, 2H), 3.59 (m, 6H), 2.48 (m, 2H), 1.81–1.37 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.41, 154.62, 137.28, 127.66, 126.50, 71.52, 49.72, 48.66, 44.07, 43.67, 36.08, 28.82, 27.46, 22.30; HR-ESI-MS:  $\text{C}_{17}\text{H}_{24}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 339.1470, 测试值 339.1472.

7-*N*-(4-氯苯基氨基甲酰基)-9-氯甲基-7-氮杂-9-壬内酯 (**E16**): 浅黄色液体, 产率 64%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.23 (m, 4H), 6.58 (s, 1H), 5.27 (m, 1H), 3.96–3.22 (m, 6H), 2.55 (m, 2H), 1.90–1.37 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.73, 151.62, 135.45, 128.01, 127.63, 119.07, 71.63, 49.75, 48.59, 43.41, 36.08, 28.78, 27.42, 22.26; HR-ESI-MS:  $\text{C}_{16}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 359.0924, 测试值 359.0923.

7-*N*-(2-氯乙基氨基甲酰基)-9-氯甲基-7-氮杂-9-壬内酯 (**E17**): 浅黄色液体, 产率 36%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.08 (m, 1H), 4.62–4.33 (m, 2H), 3.93–3.58 (m, 5H), 3.46 (m, 3H), 2.53 (m, 2H), 1.86–1.54 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.61, 154.50, 71.60, 49.88, 48.70, 43.58, 42.71, 41.83, 36.08, 28.83, 27.43, 22.29; HR-ESI-MS:  $\text{C}_{12}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 311.0924, 测试值 311.0928.

9-*N*-苯氧甲酰基-11-苯氧甲基-9-氮杂-11-十一内酯 (**E18**): 白色固体, 产率 97%, m.p. 81–83 °C.  $^1\text{H}$  NMR (300

MHz,  $\text{CDCl}_3$ )  $\delta$  7.46–6.78 (m, 11H), 5.51 (m, 1H), 4.35–3.63 (m, 5H), 3.19 (m, 1H), 2.45 (m, 2H), 2.01–1.28 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.50, 157.47, 154.48, 150.35, 128.36, 124.28, 120.64, 120.23, 113.70, 76.51, 76.08, 75.66, 71.73, 66.24, 48.87, 47.29, 47.00, 46.40, 32.59, 24.33, 23.60, 22.60, 22.21; HR-ESI-MS:  $\text{C}_{24}\text{H}_{30}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 412.2118, 测试值 412.2116.

9-*N*-苄氧甲酰基-11-苯氧甲基-9-氮杂-11-十一内酯 (**E19**): 白色固体, 产率 67%, m.p. 92–93 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (m, 8H), 7.01–6.69 (m, 3H), 5.41 (s, 1H), 5.09 (m, 2H), 4.29–3.94 (m, 2H), 3.73 (m, 2H), 3.12 (m, 1H), 2.60–2.30 (m, 2H), 1.71 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  173.20, 158.18, 156.01, 136.39, 129.13, 128.19, 127.68, 120.85, 114.32, 72.72, 66.98, 49.01, 46.92, 33.18, 24.47, 23.86, 23.40, 23.21, 22.94; HR-ESI-MS:  $\text{C}_{25}\text{H}_{31}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 426.2275, 测试值 426.2274.

9-*N*-(4-氯苯氧甲酰基)-11-苯氧甲基-9-氮杂-11-十一内酯 (**E20**): 浅黄色液体, 产率 84%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (m, 4H), 6.95 (m, 5H), 5.49 (m, 1H), 4.23–3.64 (m, 5H), 3.36–3.00 (m, 1H), 2.65–2.33 (m, 2H), 1.63 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.43, 157.46, 154.08, 153.42, 148.86, 129.58, 128.58, 128.22, 122.01, 121.19, 120.26, 113.62, 71.51, 66.45, 65.78, 48.81, 47.38, 47.01, 46.34, 32.58, 24.34, 23.58, 22.59, 22.20; HR-ESI-MS:  $\text{C}_{24}\text{H}_{29}\text{ClNO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 446.1729, 测试值 446.1729.

9-*N*-丙氧甲酰基-11-苯氧甲基-9-氮杂-11-十一内酯 (**E21**): 浅黄色液体, 产率 63%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (m, 2H), 7.02–6.81 (m, 3H), 5.39 (m, 1H), 4.07 (m, 4H), 3.92–3.47 (m, 3H), 3.07 (m, 1H), 2.60–2.28 (m, 2H), 1.97–1.29 (m, 13H), 0.94 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.55, 157.49, 128.45, 120.17, 113.63, 72.19, 66.58, 66.12, 48.33, 47.05, 46.38, 32.58, 23.71, 22.63, 22.22, 21.34, 9.47; HR-ESI-MS:  $\text{C}_{21}\text{H}_{32}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 378.2275, 测试值 378.2274.

9-*N*-(2-氯乙基氧甲酰基)-11-苯氧甲基-9-氮杂-11-十一内酯 (**E22**): 白色固体, 产率 57%, m.p. 91–92 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (m, 2H), 6.94 (m, 3H), 5.41 (m, 1H), 4.26 (m, 4H), 3.72 (m, 5H), 3.10 (m, 1H), 2.61–2.28 (m, 2H), 1.99–1.29 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.50, 157.42, 155.12, 128.47, 120.20, 113.63, 71.86, 66.21, 64.02, 48.50, 46.87, 46.41, 45.87, 41.24, 32.55, 28.66, 24.09, 23.83, 22.57, 22.22; HR-ESI-MS:  $\text{C}_{20}\text{H}_{29}\text{ClNO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 398.1729, 测试值 398.1729.

9-*N*-苄氨基甲酰基-11-苯氧甲基-9-氮杂-11-十一内酯 (**E23**): 白色固体, 产率 65%, m.p. 103–105 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43–7.13 (m, 7H), 6.94 (m, 1H), 6.74 (m, 2H), 5.34 (m, 1H), 5.05 (m, 1H), 4.50–4.27 (m, 2H), 4.11



(m, 2H), 3.76 (dd, 2H), 3.55–3.14 (m, 2H), 2.44 (m, 2H), 1.90–1.30 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.28, 157.56, 156.96, 138.50, 128.52, 127.57, 126.69, 126.18, 120.41, 113.52, 72.23, 65.35, 48.10, 46.40, 44.11, 32.38, 23.84, 23.40, 22.71, 22.11; HR-ESI-MS:  $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 425.2435, 测试值 425.2435.

9-*N*-(4-氯苯基氨基甲酰基)-11-苯氧甲基-9-氮杂-11-十一内酯 (**E24**): 白色固体, 产率 67%, m.p. 136–138 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (s, 1H), 7.35 (m, 6H), 7.08–6.80 (m, 3H), 5.36 (s, 1H), 4.31–4.03 (m, 2H), 3.73 (m, 3H), 3.27–3.05 (m, 1H), 2.49–2.28 (m, 2H), 1.88–1.16 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.93, 158.34, 155.55, 139.46, 129.62, 128.72, 128.15, 125.71, 121.76, 121.11, 119.99, 114.77, 73.01, 67.38, 48.18, 46.30, 33.01, 24.33, 23.86, 23.59, 22.75; HR-ESI-MS:  $\text{C}_{24}\text{H}_{30}\text{ClN}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 445.1889, 测试值 445.1882.

9-*N*-丙基氨基甲酰基-11-苯氧甲基-9-氮杂-11-十一内酯 (**E25**): 白色固体, 产率 73%, m.p. 62–64 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (m, 2H), 7.06–6.80 (m, 3H), 5.34 (m, 1H), 4.70 (m, 1H), 4.13 (m, 2.7 Hz, 2H), 3.72 (m, 2H), 3.23 (m, 4H), 2.64–2.29 (m, 2H), 1.95–1.30 (m, 13H), 0.88 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.33, 157.69, 157.12, 128.56, 120.44, 113.62, 72.39, 65.60, 48.17, 46.44, 41.70, 32.46, 23.99, 23.51, 22.43, 10.37; HR-ESI-MS:  $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 377.2435, 测试值 377.2434.

9-*N*-(2-氯乙基氨基甲酰基)-11-苯氧甲基-9-氮杂-11-十一内酯 (**E26**): 白色固体, 产率 55%, m.p. 102–104 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.19 (m, 2H), 7.08–6.81 (m, 3H), 5.44–5.27 (m, 1H), 5.16 (m, 1H), 4.13 (m, 2H), 3.93–3.09 (m, 8H), 2.45 (m, 2H), 1.95–1.30 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.35, 157.20, 128.56, 120.44, 113.65, 72.17, 65.64, 48.17, 46.51, 43.79, 41.74, 32.47, 23.92, 23.46, 22.51, 21.88; HR-ESI-MS:  $\text{C}_{20}\text{H}_{30}\text{ClN}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 397.1891, 测试值 397.1889.

9-*N*-苯氧甲酰基-11-氯甲基-9-氮杂-11-十一内酯 (**E27**): 浅黄色液体, 产率 85%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (m, 2H), 7.23–7.05 (m, 3H), 5.38 (m, 1H), 3.97–3.53 (m, 5H), 3.16 (m, 1H), 2.63–2.34 (m, 2H), 1.82 (m, 3H), 1.46 (m, 7H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.23, 150.26, 128.25, 124.36, 120.60, 114.32, 72.17, 49.30, 47.40, 42.76, 42.37, 41.98, 32.50, 24.40, 23.73, 22.64, 22.13; HR-ESI-MS:  $\text{C}_{18}\text{H}_{25}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 354.1467, 测试值 354.1469.

9-*N*-苄氧甲酰基-11-氯甲基-9-氮杂-11-十一内酯 (**E28**): 白色固体, 产率 87%, m.p. 89–90 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41–7.28 (m, 5H), 5.21 (m, 3H), 3.66 (m, 5H), 3.03 (m, 1H), 2.64–2.32 (m, 2H), 1.94–1.26 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.26, 156.00, 135.56, 127.59, 126.11, 72.46,

66.38, 49.18, 48.53, 47.09, 46.51, 42.78, 32.44, 25.11, 22.10, 22.58, 23.32, 22.10, 22.16; HR-ESI-MS:  $\text{C}_{19}\text{H}_{27}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 368.1623, 测试值 368.1624.

9-*N*-(4-氯苯氧甲酰基)-11-氯甲基-9-氮杂-11-十一内酯 (**E29**): 浅黄色液体, 产率 90%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42–7.23 (m, 2H), 7.07 (m, 2H), 5.46–5.26 (m, 1H), 4.05–3.57 (m, 5H), 3.27–3.01 (m, 1H), 2.64–2.36 (m, 2H), 1.97–1.31 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.25, 154.17, 148.76, 129.73, 128.30, 122.03, 72.00, 49.65, 49.05, 47.77, 47.22, 43.01, 42.32, 32.52, 24.41, 22.77, 22.14; HR-ESI-MS:  $\text{C}_{18}\text{H}_{24}\text{Cl}_2\text{NO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 388.1077, 测试值 388.1079.

9-*N*-丙氧甲酰基-11-氯甲基-9-氮杂-11-十一内酯 (**E30**): 浅黄色液体, 产率 67%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.26 (s, 1H), 4.05 (m, 2H), 3.88–3.43 (m, 5H), 3.15–2.86 (m, 1H), 2.63–2.33 (m, 2H), 1.94–1.29 (m, 12H), 0.95 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.33, 156.32, 155.58, 72.61, 66.25, 49.11, 46.51, 42.81, 32.51, 23.77, 22.63, 22.18, 21.35, 9.47; HR-ESI-MS:  $\text{C}_{15}\text{H}_{27}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 320.1623, 测试值 320.1618.

9-*N*-(2-氯乙基氧甲酰基)-11-氯甲基-9-氮杂-11-十一内酯 (**E31**): 浅黄色液体, 产率 75%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.29 (m, 1H), 4.35 (m, 2H), 3.87–3.44 (m, 7H), 3.16–2.89 (m, 1H), 2.65–2.30 (m, 2H), 1.95–1.20 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.32, 155.55, 154.73, 72.33, 64.14, 49.22, 48.86, 47.30, 46.66, 42.83, 41.26, 32.49, 24.13, 23.90, 22.60, 22.16; HR-ESI-MS:  $\text{C}_{14}\text{H}_{24}\text{Cl}_2\text{NO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 340.1077, 测试值 340.1081.

9-*N*-苯氨基甲酰基-11-氯甲基-9-氮杂-11-十一内酯 (**E32**): 白色固体, 产率 85%, m.p. 116–118 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (m, 7.8 Hz, 4H), 7.04 (m, 1H), 6.66 (s, 1H), 5.26 (m, 1H), 3.90–3.60 (m, 4H), 3.56–3.19 (m, 2H), 2.65–2.35 (m, 2H), 1.95–1.28 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.18, 155.00, 137.83, 127.82, 122.26, 119.09, 72.95, 49.18, 47.01, 42.78, 32.46, 24.48, 23.52, 22.61, 22.08; HR-ESI-MS:  $\text{C}_{18}\text{H}_{26}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 353.1626, 测试值 353.1627.

9-*N*-苄氨基甲酰基-11-氯甲基-9-氮杂-11-十一内酯 (**E33**): 白色固体, 产率 50%, m.p. 70–72 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42–7.15 (m, 5H), 5.24 (m, 1H), 4.88 (m, 1H), 4.41 (m, 2H), 3.90–3.53 (m, 4H), 3.40–3.07 (m, 2H), 2.45 (m, 2H), 1.96–1.22 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.21, 157.39, 138.43, 127.62, 126.40, 73.25, 49.06, 46.64, 44.01, 42.99, 32.45, 24.34, 23.56, 22.59, 22.11; HR-ESI-MS:  $\text{C}_{19}\text{H}_{28}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 367.1783, 测试值 367.1784.

9-*N*-(4-氯苯基氨基甲酰基)-11-氯甲基-9-氮杂-11-十一内酯 (**E34**): 浅黄色液体, 产率 75%.  $^1\text{H}$  NMR (300 MHz,

$\text{CDCl}_3$ )  $\delta$  7.35–7.23 (m, 4H), 6.58 (s, 1H), 5.27 (m, 1H), 3.96–3.22 (m, 6H), 2.67–2.36 (m, 2H), 1.90–1.37 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.16, 154.78, 136.56, 127.78, 127.12, 120.27, 72.83, 49.18, 47.06, 42.70, 32.46, 24.47, 23.50, 22.96, 21.97; HR-ESI-MS:  $\text{C}_{18}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 385.1091, 测试值 385.1095.

9-*N*-丙基氨基甲酰基-11-氯甲基-9-氮杂-11-十一内酯 (**E35**): 浅黄色液体, 产率 77%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.22 (m, 1H), 4.57 (m, 1H), 3.90–3.52 (m, 4H), 3.45–3.06 (m, 4H), 2.63–2.29 (m, 2H), 1.97–1.29 (m, 13H), 0.92 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.28, 170.86, 157.59, 154.32, 73.44, 69.65, 61.07, 49.00, 47.85, 46.63, 44.95, 43.03, 42.49, 41.72, 33.98, 32.51, 24.78, 24.32, 23.63, 23.30, 22.83, 22.33, 22.02, 21.12, 19.43, 10.30; HR-ESI-MS:  $\text{C}_{15}\text{H}_{28}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 319.1783, 测试值 319.1786.

9-*N*-(2-氯乙基氨基甲酰基)-11-氯甲基-9-氮杂-11-十一内酯 (**E36**): 浅黄色液体, 产率 70%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.57–5.04 (m, 2H), 4.84 (m, 1H), 4.21–3.07 (m, 8H), 2.72–2.15 (m, 3H), 2.02–1.20 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.25, 157.18, 73.06, 49.11, 46.84, 43.92, 42.92, 41.71, 32.52, 24.34, 23.61, 22.85, 22.23, 22.11; HR-ESI-MS:  $\text{C}_{14}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 339.1237, 测试值 339.1238.

13-*N*-苯氧甲酰基-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E37**): 白色固体, 产率 74%, m.p. 68–70 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.24 (m, 4H), 7.17 (m, 1H), 7.09 (m, 1H), 7.02 (m, 1H), 6.94 (m, 1H), 6.91–6.86 (m, 2H), 5.42 (m, 1H), 4.22 (m, 1H), 4.18–4.10 (m, 1H), 3.96 (m, 1H), 3.64–3.30 (m, 3H), 2.38 (m, 2H), 1.84–1.60 (m, 4H), 1.47–1.28 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.37, 158.55, 158.42, 155.27, 154.40, 151.35, 151.22, 129.50, 129.31, 129.26, 125.39, 125.29, 121.68, 121.31, 121.15, 114.73, 114.62, 71.74, 71.36, 67.79, 66.99, 48.85, 48.77, 48.34, 48.28, 33.87, 27.19, 26.53, 26.39, 26.11, 26.06, 24.75, 23.71; HR-ESI-MS:  $\text{C}_{28}\text{H}_{38}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 468.2744, 测试值 468.2749.

13-*N*-苄氧甲酰基-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E38**): 白色固体, 产率 68%, m.p. 62–64 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.10 (m, 7H), 6.86 (m, 1H), 6.79 (m, 1H), 6.66 (m, 1H), 5.23 (m, 1H), 5.12–4.90 (m, 2H), 4.17–3.71 (m, 3H), 3.43–3.27 (m, 2H), 3.22 (m, 1H), 2.26 (m, 2H), 1.73–1.45 (m, 4H), 1.37–1.16 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.34, 158.57, 158.44, 156.61, 155.88, 136.75, 136.49, 129.45, 128.52, 128.16, 128.08, 127.99, 127.74, 121.09, 114.69, 114.52, 71.72, 71.44, 67.72, 67.26, 66.95, 48.42, 48.12, 47.66, 47.60, 33.86, 27.14, 27.04, 26.51, 26.22, 26.08, 26.06, 24.69, 23.70; HR-ESI-MS:  $\text{C}_{29}\text{H}_{40}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 482.2901, 测试值 482.2903.

13-*N*-(4-氯苄氧甲酰基)-15-苯氧甲基-13-氮杂-1,15-十

五内酯 (**E39**): 白色固体, 产率 51%, m.p. 64–66 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33–7.22 (m, 5H), 7.02 (m, 1H), 6.98–6.84 (m, 4H), 5.41 (m, 1H), 4.24–4.09 (m, 2H), 3.96 (m, 1H), 3.62–3.30 (m, 3H), 2.38 (m, 2H), 1.84–1.58 (m, 4H), 1.46–1.27 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.38, 173.33, 158.52, 158.36, 154.87, 154.01, 149.86, 149.72, 130.72, 130.56, 129.60, 129.52, 129.33, 129.23, 123.08, 122.99, 121.37, 121.21, 114.71, 114.56, 71.60, 71.14, 67.73, 66.75, 48.93, 48.81, 48.38, 48.20, 33.92, 33.86, 27.20, 27.13, 26.51, 26.34, 26.11, 26.05, 24.73, 23.74, 23.69; HR-ESI-MS:  $\text{C}_{28}\text{H}_{37}\text{ClNO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 502.2355, 测试值 502.2355.

13-*N*-丙氧甲酰基-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E40**): 无色液体, 产率 50%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30–7.23 (m, 2H), 6.94 (m, 1H), 6.91–6.86 (m, 2H), 5.31 (m, 1H), 4.25–3.93 (m, 4H), 3.84 (m, 1H), 3.37 (m, 2H), 3.28 (m, 1H), 2.35 (m, 2H), 1.76 (m, 1H), 1.68–1.52 (m, 5H), 1.45–1.25 (m, 14H), 0.92 (m, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.37, 158.60, 156.94, 156.23, 129.47, 121.10, 114.71, 114.54, 71.88, 71.53, 67.82, 67.16, 66.89, 48.32, 48.09, 47.60, 33.92, 27.17, 27.00, 26.54, 26.37, 26.12, 26.09, 26.08, 24.73, 23.75, 22.36, 10.50; HR-ESI-MS:  $\text{C}_{25}\text{H}_{40}\text{NO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 434.2901, 测试值 434.2902.

13-*N*-(2-氯乙基氧甲酰基)-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E41**): 无色液体, 产率 64%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.23 (m, 2H), 6.99–6.86 (m, 3H), 5.33 (m, 1H), 4.40 (m, 1H), 4.36–4.13 (m, 3H), 4.09 (m, 1H), 3.85 (m, 1H), 3.73–3.64 (m, 2H), 3.56 (m, 1H), 3.41 (m, 2H), 3.30 (m, 1H), 2.36 (m, 2H), 1.76 (m, 1H), 1.66–1.56 (m, 3H), 1.45–1.26 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.33, 173.29, 158.53, 158.46, 156.13, 155.37, 154.43, 129.59, 129.48, 121.19, 121.13, 114.68, 114.54, 71.59, 71.33, 67.65, 67.51, 66.89, 65.04, 48.52, 48.22, 47.88, 47.69, 42.25, 41.05, 33.89, 33.84, 27.11, 26.99, 26.50, 26.22, 26.06, 26.04, 24.66, 23.75, 23.66; HR-ESI-MS:  $\text{C}_{24}\text{H}_{37}\text{ClNO}_5$   $[\text{M} + \text{H}]^+$ , 计算值 454.2355, 测试值 454.2359.

13-*N*-苯胺基甲酰基-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E42**): 白色固体, 产率 45%, m.p. 83–85 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.26 (m, 4H), 7.23–7.18 (m, 2H), 7.07 (br, 1H), 7.02–6.94 (m, 4H), 5.27 (m, 1H), 4.25 (m, 1H), 4.18 (m, 1H), 3.85 (m, 1H), 3.52 (m, 2H), 3.32 (m, 1H), 2.37 (m, 2H), 1.83–1.57 (m, 4H), 1.44–1.26 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.48, 157.93, 155.60, 139.18, 129.70, 128.76, 122.84, 121.81, 119.83, 114.87, 71.14, 66.32, 47.43, 47.34, 34.09, 27.14, 26.54, 26.40, 26.37, 26.36, 26.20, 24.63, 24.10; HR-ESI-MS:  $\text{C}_{28}\text{H}_{39}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 467.2904, 测试值 467.2909.

13-*N*-苄胺基甲酰基-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E43**): 无色液体, 产率 41%.  $^1\text{H}$  NMR (500 MHz,



$\text{CDCl}_3$ )  $\delta$  7.21–7.11 (m, 8H), 6.87 (m, 1H), 6.71 (m, 2H), 5.21–5.12 (m, 2H), 4.30–4.20 (m, 2H), 4.09 (m, 1H), 4.00 (m, 1H), 3.72 (m, 1H), 3.35 (m, 2H), 3.15 (m, 1H), 2.25 (m, 2H), 1.73–1.46 (m, 4H), 1.34–1.19 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.38, 158.02, 157.94, 139.56, 129.56, 128.54, 127.65, 127.12, 121.43, 114.54, 71.34, 66.35, 47.34, 47.26, 45.02, 33.96, 27.17, 26.50, 26.40, 26.29, 26.20, 26.16, 26.12, 24.68, 23.92; HR-ESI-MS:  $\text{C}_{29}\text{H}_{41}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 481.3061, 测试值 481.3061.

13-*N*-(4-氯苯胺基甲酰基)-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E44**): 无色液体, 产率 62%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33–7.27 (m, 2H), 7.22–7.19 (m, 2H), 7.18–7.11 (m, 3H), 7.01 (m, 1H), 6.97–6.93 (m, 2H), 5.25 (m, 1H), 4.25–4.15 (m, 2H), 3.84 (m, 1H), 3.56–3.45 (m, 2H), 3.32 (m, 1H), 2.43–2.32 (m, 2H), 1.87–1.57 (m, 4H), 1.46–1.21 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.50, 157.77, 155.41, 137.83, 129.77, 128.65, 127.68, 121.98, 121.01, 114.84, 70.88, 66.13, 47.34, 47.12, 34.08, 27.13, 26.51, 26.39, 26.37, 26.23, 26.17, 24.55, 24.13; HR-ESI-MS:  $\text{C}_{28}\text{H}_{38}\text{ClN}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 501.2515, 测试值 501.2515.

13-*N*-丙基胺基甲酰基-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E45**): 白色固体, 产率 42%, m.p. 41–43 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.25 (m, 2H), 6.97 (m, 1H), 6.91 (m, 2H), 5.22 (m, 1H), 4.89 (m, 1H), 4.19 (m, 1H), 4.10 (m, 1H), 3.79 (m, 1H), 3.42–3.31 (m, 2H), 3.24 (m, 1H), 3.10 (m, 2H), 2.36 (m, 2H), 1.82–1.55 (m, 4H), 1.45–1.24 (m, 16H), 0.85 (m, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.45, 158.07, 129.58, 121.47, 114.61, 71.38, 66.49, 47.15, 47.09, 42.69, 34.05, 27.22, 26.55, 26.41, 26.33, 26.30, 26.25, 26.17, 24.66, 24.02, 23.38, 11.38; HR-ESI-MS:  $\text{C}_{25}\text{H}_{41}\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 433.3061, 测试值 433.3066.

13-*N*-(2-氯乙基胺基甲酰基)-15-苯氧甲基-13-氮杂-1,15-十五内酯 (**E46**): 无色液体, 产率 55%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (m, 2H), 6.97 (m, 1H), 6.92 (m, 2H), 5.32 (m, 1H), 5.25 (m, 1H), 4.19 (m, 1H), 4.11 (m, 1H), 3.80 (m, 1H), 3.54 (m, 2H), 3.47 (m, 2H), 3.40 (m, 2H), 3.25 (m, 1H), 2.36 (m, 2H), 1.81–1.56 (m, 4H), 1.44–1.26 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.25, 157.53, 72.48, 48.69, 47.70, 45.00, 44.37, 42.67, 33.80, 27.19, 26.64, 26.44, 26.17, 26.14, 26.13, 24.75, 23.76; HR-ESI-MS:  $\text{C}_{24}\text{H}_{38}\text{ClN}_2\text{O}_4$   $[\text{M} + \text{H}]^+$ , 计算值 453.2515, 测试值 453.2519.

13-*N*-苯氧甲酰基-15-氯甲基-13-氮杂-1,15-十五内酯 (**E47**): 无色液体, 产率 43%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.33 (m, 2H), 7.19 (m, 1H), 7.15–7.08 (m, 2H), 5.28 (m, 1H), 3.98–3.77 (m, 2H), 3.67 (m, 1H), 3.57–3.27 (m, 3H), 2.41 (m, 2H), 1.85–1.59 (m, 4H), 1.47–1.27 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.02, 155.21, 154.14, 151.19, 151.08,

129.25, 125.37, 121.58, 72.31, 71.75, 49.63, 48.75, 48.42, 44.48, 43.77, 33.68, 33.60, 27.13, 27.04, 26.41, 26.01, 25.97, 25.92, 24.63, 23.57; HR-ESI-MS:  $\text{C}_{22}\text{H}_{33}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 410.2093, 测试值 410.2092.

13-*N*-苄氧甲酰基-15-氯甲基-13-氮杂-1,15-十五内酯 (**E48**): 无色液体, 产率 44%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.20 (m, 5H), 5.15–5.00 (m, 3H), 3.75–3.39 (m, 3H), 3.38–3.13 (m, 3H), 2.29 (m, 2H), 1.73–1.43 (m, 4H), 1.37–1.16 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.06, 156.61, 155.74, 136.58, 136.33, 128.51, 128.19, 128.01, 127.73, 72.38, 72.00, 67.43, 67.31, 49.26, 48.29, 47.82, 44.46, 43.89, 33.68, 27.13, 26.96, 26.45, 26.04, 25.99, 24.65, 23.64; HR-ESI-MS:  $\text{C}_{23}\text{H}_{35}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 424.2249, 测试值 424.2248.

13-*N*-(4-氯苯氧甲酰基)-15-氯甲基-13-氮杂-1,15-十五内酯 (**E49**): 无色液体, 产率 45%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34–7.29 (m, 2H), 7.11–7.03 (m, 2H), 5.27 (m, 1H), 3.97–3.75 (m, 2H), 3.66 (m, 1H), 3.56–3.26 (m, 3H), 2.40 (m, 2H), 1.86–1.58 (m, 4H), 1.47–1.26 (m, 14H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.07, 173.02, 154.87, 153.82, 149.74, 149.63, 130.74, 129.30, 123.01, 72.20, 71.62, 49.72, 48.89, 48.75, 48.52, 44.44, 43.68, 33.73, 33.64, 27.16, 27.11, 26.43, 26.02, 25.95, 24.67, 23.60; HR-ESI-MS:  $\text{C}_{22}\text{H}_{32}\text{Cl}_2\text{NO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 444.1703, 测试值 444.1704.

13-*N*-丙氧甲酰基-15-氯甲基-13-氮杂-1,15-十五内酯 (**E50**): 无色液体, 产率 75%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.10 (m, 1H), 3.97 (m, 2H), 3.77–3.62 (m, 2H), 3.55 (m, 1H), 3.38–3.11 (m, 3H), 2.31 (m, 2H), 1.77–1.44 (m, 6H), 1.38–1.17 (m, 14H), 0.88 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.10, 156.94, 156.10, 72.56, 72.05, 67.24, 49.17, 48.19, 48.11, 47.76, 44.53, 43.89, 33.73, 27.16, 26.91, 26.49, 26.08, 26.07, 26.04, 26.02, 24.67, 23.68, 22.34, 10.47; HR-ESI-MS:  $\text{C}_{19}\text{H}_{35}\text{ClNO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 376.2249, 测试值 376.2250.

13-*N*-(2-氯乙基氧甲酰基)-15-氯甲基-13-氮杂-1,15-十五内酯 (**E51**): 无色液体, 产率 67%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.12 (m, 1H), 4.32–4.23 (m, 2H), 3.68–3.55 (m, 4H), 3.38–3.14 (m, 3H), 2.32 (m, 2H), 1.75–1.47 (m, 4H), 1.39–1.20 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.09, 156.17, 155.24, 72.24, 71.95, 67.51, 65.14, 49.31, 48.44, 48.36, 48.03, 44.37, 44.07, 42.31, 42.25, 41.05, 33.75, 33.69, 27.16, 26.90, 26.46, 26.05, 26.00, 24.66, 23.62; HR-ESI-MS:  $\text{C}_{18}\text{H}_{32}\text{Cl}_2\text{NO}_4$   $[\text{M} + \text{H}]^+$ , 计算值 396.1703, 测试值 396.1705.

13-*N*-苯胺基甲酰基-15-氯甲基-13-氮杂-1,15-十五内酯 (**E52**): 白色固体, 产率 44%, m.p. 120–122 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41–7.37 (m, 2H), 7.31–7.27 (m, 2H), 7.03 (m, 1H), 6.77 (br, 1H), 5.17 (m, 1H), 3.86 (m, 1H), 3.78

(m, 1H), 3.70 (m, 1H), 3.50–3.41 (m, 2H), 3.34 (m, 1H), 2.41 (m, 2H), 1.83–1.59 (m, 4H), 1.43–1.27 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.32, 155.35, 138.94, 128.89, 123.19, 119.95, 72.32, 48.64, 47.86, 44.27, 33.89, 27.16, 26.86, 26.51, 26.27, 26.24, 26.18, 24.71, 23.91; HR-ESI-MS:  $\text{C}_{22}\text{H}_{34}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 409.2252, 测试值 409.2258.

13-*N*-苄胺基甲酰基-15-氯甲基-13-氮杂-1,15-十五内酯 (**E53**): 白色固体, 产率 66%, m.p. 87–89 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28–7.16 (m, 5H), 5.06 (m, 1H), 4.92 (br, 1H), 4.39–4.29 (m, 2H), 3.75(m, 1H), 3.69 (m, 1H), 3.58 (m, 1H), 3.29–3.21 (m, 2H), 3.14 (m, 1H), 2.28 (m, 2H), 1.74–1.44 (m, 4H), 1.37–1.15 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.21, 157.79, 139.45, 128.62, 127.52, 127.26, 72.65, 48.75, 47.58, 44.95, 44.43, 33.74, 27.14, 26.72, 26.44, 26.15, 26.11, 26.10, 26.07, 24.73, 23.71; HR-ESI-MS:  $\text{C}_{23}\text{H}_{36}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 423.2409, 测试值 423.2411.

13-*N*-(4-氯苄胺基甲酰基)-15-氯甲基-13-氮杂-1,15-十五内酯 (**E54**): 白色固体, 产率 88%, m.p. 113–115 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (m, 2H), 7.15 (m, 2H), 6.78 (br, 1H), 5.09 (m, 1H), 3.77 (m, 1H), 3.69 (m, 1H), 3.62 (m, 1H), 3.36 (m, 2H), 3.28 (m, 1H), 2.33 (m, 2H), 1.74–1.51 (m, 4H), 1.36–1.17 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.37, 155.14, 137.61, 128.79, 128.04, 121.13, 72.11, 48.45, 47.78, 44.16, 33.89, 27.12, 26.77, 26.47, 26.25, 26.17, 24.62, 23.94; HR-ESI-MS:  $\text{C}_{22}\text{H}_{33}\text{Cl}_2\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 443.1863, 测试值 443.1864.

13-*N*-丙基胺基甲酰基-15-氯甲基-13-氮杂-1,15-十五内酯 (**E55**): 白色固体, 产率 41%, m.p. 66–68 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.12 (m, 1H), 4.69 (m, 1H), 3.83 (m, 3.7 Hz, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.34–3.13 (m, 5H), 2.39 (m, 2H), 1.77 (m, 1H), 1.68–1.48 (m, 5H), 1.44–1.26 (m, 14H), 0.92 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.25, 157.85, 72.66, 48.50, 47.43, 44.47, 42.69, 33.82, 27.18, 26.57, 26.47, 26.24, 26.16, 26.13, 24.71, 23.79, 23.43, 11.38; HR-ESI-MS:  $\text{C}_{19}\text{H}_{35}\text{ClN}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 375.2409, 测试值 375.2414.

13-*N*-(2-氯乙基胺基甲酰基)-15-氯甲基-13-氮杂-1,15-十五内酯 (**E56**): 无色液体, 产率 46%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.18–5.07 (m, 2H), 3.82 (m, 1H), 3.75 (m, 1H), 3.69–3.63 (m, 3H), 3.62–3.51 (m, 2H), 3.37–3.29 (m, 2H), 3.24 (m, 1H), 2.40 (m, 2H), 1.83–1.55 (m, 4H), 1.42–1.25 (m, 14H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.25, 157.53, 72.48, 48.69, 47.70, 45.00, 44.37, 42.67, 33.80, 27.19, 26.64, 26.44, 26.17, 26.14, 26.13, 24.75, 23.76; HR-ESI-MS:  $\text{C}_{18}\text{H}_{33}\text{Cl}_2\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ , 计算值 395.1863, 测试值 395.1866.

### 1.3 生物活性测定

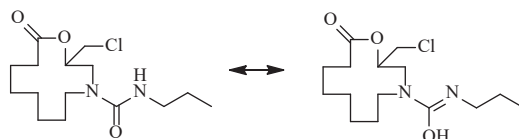
采用菌丝生长速率法<sup>[17]</sup>, 在 50 mg/L 下, 测

定目标化合物的离体抑菌活性。供试真菌包括番茄灰霉病菌 *Botrytis cinerea*、苹果腐烂病菌 *Valsa mali*、小麦赤霉病菌 *Fusarium graminearum*、马铃薯早疫病菌 *Alternaria solani* 和油菜菌核病菌 *Sclerotinia sclerotiorum*, 供试真菌均由中国农业科学院植物保护研究所提供, 以吡唑醚菌酯为对照药剂。针对 50 mg/L 下抑制率大于 80% 的化合物, 采用等比稀释, 分别测试质量浓度为 50、25、12.5、6.25 与 3.13 mg/L 时的抑菌率, 使用 SPSS 25.0 进行数据处理和分析, 每组实验设置 3 个平行。

## 2 结果与讨论

### 2.1 化合物 E 的互变异构

9-氮杂-11-氯甲基-11-十一内酯脲类系列化合物以  $\text{CDCl}_3$  为溶剂时,  $^{13}\text{C}$  NMR 出现了比例为 2 : 1 的两组峰。这是由于脲类结构中的酰胺存在互变异构的现象, 酰胺可以转变为亚胺醇, 进而形成两组互变异构体, 同类型其他化合物, 异构现象并不明显, 原因在于脲类结构连接基团不同, 互变异构的两种结构所占比例不同, **E35** 为明显的 2 : 1 (图式 4)。



图式 4 **E35** 互变异构的两种结构

Scheme 4 Two structures of **E35** reciprocal isomerism

### 2.2 离体抑菌活性

初筛结果 (表 1) 表明, 所合成的大部分化合物 **C** 和 **E** 对病原真菌均有一定的抑菌活性。比较化合物 **C1**~**C6** 的抑菌活性发现, 十六元氮杂内酯的活性高于十元和十二元的氮杂内酯活性; 化合物 **E46** 对番茄灰霉病菌、苹果腐烂病菌和马铃薯早疫病菌活性均高于 50%, 取代基为含 Cl 的碳链基团会提高十六元大环内酯类化合物的抑菌活性; 化合物 **C5** 和 **C6** 对番茄灰霉病菌、苹果腐烂病菌、小麦赤霉病菌和马铃薯早疫病菌均有良好的抑制活性, 抑制率均高于 60%, 化合物 **C6** 对小麦赤霉病菌和马铃薯早疫病菌抑菌活性较好, 抑制率均大于 90%, 而含氨基甲酸酯和脲的结构化合物 **E** 系列化合物活性不佳, 表明加入氨基甲酸酯和脲结构片段对化合物活性没有明显的提

表 1 化合物 C1~C6 和目标化合物 E1~E56 在 50 mg/L 下的离体抑菌活性

Table 1 *In vitro* inhibitory activity of compounds C1-C6 and target compounds E1-E56 at 50 mg/L

| 化合物<br>Compounds        | 抑制率 ± 标准误差 Inhibition rate ± SE/% |                          |                                 |                             |                                  |
|-------------------------|-----------------------------------|--------------------------|---------------------------------|-----------------------------|----------------------------------|
|                         | 番茄灰霉病菌<br><i>B. cinerea</i>       | 苹果腐烂病菌<br><i>V. mali</i> | 小麦赤霉病菌<br><i>F. graminearum</i> | 马铃薯早疫病菌<br><i>A. solani</i> | 油菜菌核病菌<br><i>S. sclerotiorum</i> |
| C1                      | 7 ± 1                             | 0 ± 4                    | 9 ± 2                           | 0 ± 1                       | 0 ± 1                            |
| C2                      | 3 ± 6                             | 0 ± 4                    | 0 ± 1                           | 10 ± 4                      | 0 ± 1                            |
| C3                      | 15 ± 2                            | 0 ± 2                    | 6 ± 3                           | 4 ± 3                       | 0 ± 4                            |
| C4                      | 0 ± 1                             | 0 ± 5                    | 13 ± 3                          | 6 ± 2                       | 0 ± 3                            |
| C5                      | 50 ± 2                            | 78 ± 1                   | 78 ± 4                          | 88 ± 2                      | 30 ± 5                           |
| C6                      | 61 ± 2                            | 60 ± 6                   | 94 ± 1                          | 90 ± 2                      | 30 ± 2                           |
| E1                      | 22 ± 2                            | 37 ± 7                   | 22 ± 1                          | 14 ± 1                      | 34 ± 7                           |
| E2                      | 21 ± 5                            | 29 ± 3                   | 37 ± 12                         | 42 ± 3                      | 62 ± 1                           |
| E3                      | 15 ± 1                            | 39 ± 5                   | 30 ± 3                          | 12 ± 5                      | 4 ± 1                            |
| E4                      | 5 ± 1                             | 6 ± 4                    | 18 ± 4                          | 9 ± 4                       | 6 ± 1                            |
| E5                      | 25 ± 1                            | 18 ± 2                   | 3 ± 4                           | 0 ± 2                       | 0 ± 3                            |
| E6                      | 34 ± 3                            | 38 ± 1                   | 25 ± 3                          | 25 ± 6                      | 35 ± 4                           |
| E7                      | 19 ± 3                            | 18 ± 6                   | 15 ± 3                          | 22 ± 4                      | 32 ± 2                           |
| E8                      | 31 ± 5                            | 47 ± 1                   | 31 ± 3                          | 30 ± 3                      | 37 ± 2                           |
| E9                      | 18 ± 6                            | 0 ± 3                    | 7 ± 2                           | 10 ± 5                      | 21 ±                             |
| E10                     | 3 ± 7                             | 2 ± 4                    | 0 ± 15                          | 0 ± 5                       | 0 ± 3                            |
| E11                     | 4 ± 2                             | 15 ± 5                   | 0 ± 6                           | 0 ± 2                       | 8 ± 5                            |
| E12                     | 21 ± 1                            | 29 ± 1                   | 8 ± 2                           | 0 ± 6                       | 35 ± 2                           |
| E13                     | 8 ± 1                             | 0 ± 1                    | 0 ± 4                           | 0 ± 1                       | 1 ± 4                            |
| E14                     | 14 ± 4                            | 4 ± 1                    | 8 ± 1                           | 2 ± 1                       | 17 ± 1                           |
| E15                     | 21 ± 3                            | 1 ± 5                    | 43 ± 2                          | 7 ± 1                       | 0 ± 1                            |
| E16                     | 38 ± 4                            | 47 ± 3                   | 5 ± 4                           | 16 ± 4                      | 38 ± 2                           |
| E17                     | 13 ± 4                            | 1 ± 2                    | 0 ± 5                           | 6 ± 3                       | 20 ± 4                           |
| E18                     | 28 ± 4                            | 24 ± 2                   | 21 ± 3                          | 12 ± 2                      | 0 ± 2                            |
| E19                     | 0 ± 2                             | 11 ± 5                   | 4 ± 2                           | 16 ± 2                      | 4 ± 5                            |
| E20                     | 13 ± 7                            | 10 ± 5                   | 0 ± 1                           | 3 ± 1                       | 0 ± 6                            |
| E21                     | 23 ± 6                            | 24 ± 6                   | 30 ± 1                          | 39 ± 7                      | 48 ± 3                           |
| E22                     | 26 ± 3                            | 38 ± 3                   | 18 ± 1                          | 21 ± 4                      | 39 ± 4                           |
| E23                     | 23 ± 5                            | 51 ± 3                   | 35 ± 1                          | 30 ± 4                      | 62 ± 1                           |
| E24                     | 41 ± 2                            | 53 ± 2                   | 43 ± 4                          | 3 ± 5                       | 54 ± 5                           |
| E25                     | 73 ±                              | 45 ± 4                   | 48 ± 2                          | 45 ± 3                      | 68 ± 3                           |
| E26                     | 7 ± 1                             | 6 ± 5                    | 11 ± 3                          | 0 ± 1                       | 0 ± 1                            |
| E27                     | 27 ± 4                            | 31 ± 4                   | 40 ± 2                          | 27 ± 5                      | 75 ± 1                           |
| E28                     | 6 ± 5                             | 19 ± 2                   | 25 ± 3                          | 29 ± 3                      | 78 ± 1                           |
| E29                     | 9 ± 7                             | 49 ± 1                   | 34 ± 1                          | 24 ± 6                      | 61 ± 5                           |
| E30                     | 19 ± 4                            | 49 ± 5                   | 26 ± 4                          | 14 ± 3                      | 18 ± 46                          |
| E31                     | 13 ± 2                            | 29 ± 5                   | 25 ± 5                          | 0 ± 2                       | 20 ± 2                           |
| E32                     | 21 ± 3                            | 24 ± 5                   | 0 ± 2                           | 0 ± 1                       | 30 ± 3                           |
| E33                     | 13 ± 5                            | 16 ± 3                   | 0 ± 3                           | 0 ± 3                       | 0 ± 3                            |
| E34                     | 42 ± 3                            | 69 ± 3                   | 42 ± 2                          | 40 ± 3                      | 51 ± 3                           |
| E35                     | 0 ± 3                             | 1 ± 5                    | 0 ± 4                           | 0 ± 4                       | 0 ± 2                            |
| E36                     | 10 ± 4                            | 0 ± 1                    | 7 ± 3                           | 0 ± 5                       | 0 ± 4                            |
| E37                     | 6 ± 1                             | 5 ± 1                    | 3 ± 5                           | 1 ± 6                       | 14 ± 6                           |
| E38                     | 1 ± 4                             | 1 ± 2                    | 1 ± 1                           | 1 ± 2                       | 15 ± 7                           |
| E39                     | 1 ± 4                             | 1 ± 2                    | 5 ± 4                           | 6 ± 2                       | 5 ± 1                            |
| E40                     | 5 ± 4                             | 1 ± 2                    | 7 ± 3                           | 2 ± 3                       | 8 ± 4                            |
| E41                     | 1 ± 6                             | 2 ± 3                    | 5 ± 2                           | 7 ± 5                       | 9 ± 5                            |
| E42                     | 4 ± 6                             | 12 ± 2                   | 7 ± 4                           | 7 ± 1                       | 5 ± 3                            |
| E43                     | 2 ± 3                             | 12 ± 1                   | 4 ± 3                           | 8 ± 1                       | 8 ± 1                            |
| E44                     | 1 ± 2                             | 4 ± 4                    | 3 ± 3                           | 5 ± 1                       | 11 ± 4                           |
| E45                     | 16 ± 5                            | 27 ± 1                   | 22 ± 4                          | 31 ±                        | 9 ± 2                            |
| E46                     | 85 ± 7                            | 88 ± 2                   | 26 ± 3                          | 54 ± 4                      | 7 ± 5                            |
| E47                     | 5 ± 1                             | 18 ± 3                   | 1 ± 2                           | 7 ± 4                       | 9 ± 6                            |
| E48                     | 1 ± 4                             | 2 ± 2                    | 1 ± 1                           | 6 ±                         | 8 ± 72                           |
| E49                     | 1 ± 6                             | 8 ± 1                    | 6 ± 1                           | 3 ± 2                       | 10 ± 3                           |
| E50                     | 6 ± 3                             | 20 ± 3                   | 10 ± 1                          | 8 ± 2                       | 6 ± 1                            |
| E51                     | 5 ± 5                             | 23 ± 4                   | 8 ± 4                           | 14 ± 1                      | 4 ± 1                            |
| E52                     | 13 ± 2                            | 44 ± 2                   | 13 ± 4                          | 16 ± 3                      | 10 ± 1                           |
| E53                     | 56 ± 4                            | 50 ± 2                   | 32 ± 5                          | 48 ± 4                      | 9 ± 4                            |
| E54                     | 4 ± 6                             | 25 ± 1                   | 5 ± 2                           | 10 ±                        | 7 ± 3                            |
| E55                     | 61 ± 3                            | 39 ± 1                   | 36 ± 2                          | 46 ± 2                      | 9 ± 5                            |
| E56                     | 56 ± 1                            | 45 ± 1                   | 35 ± 2                          | 47 ± 5                      | 11 ± 2                           |
| 吡唑醚菌酯<br>pyraclostrobin | 100 ± 1                           | 100 ± 3                  | 100 ± 1                         | 100 ± 3                     | 100 ± 2                          |

高, 化合物 **C1~C4** 的抑菌活性和 **E** 系列化合物抑菌活性均比先导化合物的活性均较差, 表明增加苯氧甲基和氯甲基结构对十元、十二元氮杂内酯化合物的抑菌活性没有明显影响, 化合物的主体结构氮杂内酯环对化合物活性影响较大, 十六元氮杂内酯化合物 **C5**、**C6** 抑菌活性高于十元、十二元氮杂内酯化合物, 大环内酯抑菌活性高于中环内酯, 原因可能是十六元氮杂内酯环张力较弱, 氮杂内酯环具有更好的柔性, 而十元环和十

二元环氮杂内酯环张力更大, 刚性较强, 不易与靶标结合, 不易发挥药效。

结果 (表 2) 表明, 化合物 **C5** 对马铃薯早疫病菌的 EC<sub>50</sub> 值为 2.95 mg/L, 与对照药剂吡唑醚菌酯对马铃薯早疫病菌的 EC<sub>50</sub> 值 (2.36 mg/L) 相近, 活性优于先导化合物 **D16-19** 对番茄早疫病菌 EC<sub>50</sub> 值 (4.76 mg/L)<sup>[12]</sup>, 表明在十六元氮杂内酯中加入苯氧甲基可增强化合物对早疫病菌的活性, 化合物 **C6** 与 **E46** 活性不如对照吡唑醚菌酯。

表 2 化合物 C5、C6 和目标化合物 E46 对部分病原真菌的 EC<sub>50</sub> 值  
Table 2 EC<sub>50</sub> values of compounds C5, C6 and target compound E46 against some pathogenic fungi

| 化合物<br>Compounds        | 病原真菌<br>Pathogenic fungi        | 毒力回归方程<br>Toxicity regression equation | R <sup>2</sup> | EC <sub>50</sub> /(mg/L) | 95% 置信区间<br>95% Confidence limit/(mg/L) |
|-------------------------|---------------------------------|----------------------------------------|----------------|--------------------------|-----------------------------------------|
| C5                      | 马铃薯早疫病菌<br><i>A. solani</i>     | y = 1.05 + 2.11x                       | 0.912          | 2.95                     | 0.89 ~ 4.72                             |
|                         | 马铃薯早疫病菌<br><i>A. solani</i>     | y = 2.10 + 2.09x                       | 0.992          | 9.55                     | 6.50 ~ 13.56                            |
| C6                      | 小麦赤霉病菌<br><i>F. graminearum</i> | y = 2.64 + 2.43x                       | 0.919          | 12.85                    | 6.27 ~ 28.31                            |
|                         | 番茄灰霉病菌<br><i>B. cinerea</i>     | y = 1.99 + 1.74x                       | 0.963          | 14.46                    | 12.31 ~ 17.10                           |
| E46                     | 苹果腐烂病菌<br><i>V. mali</i>        | y = 2.21 + 1.61x                       | 0.931          | 23.74                    | 14.98 ~ 51.30                           |
|                         | 苹果腐烂病菌<br><i>V. mali</i>        | y = 0.06 + 0.59x                       | 0.995          | 0.79                     | 0.03 ~ 1.71                             |
| 吡唑醚菌酯<br>pyraclostrobin | 小麦赤霉病菌<br><i>F. graminearum</i> | y = 0.13 + 0.56x                       | 0.991          | 1.43                     | 0.91 ~ 3.27                             |
|                         | 番茄灰霉病菌<br><i>B. cinerea</i>     | y = 1.74 + 1.88x                       | 0.993          | 0.12                     | 0.10 ~ 0.15                             |
|                         | 马铃薯早疫病菌<br><i>A. solani</i>     | y = 1.54 + 2.13x                       | 0.996          | 2.36                     | 0.97 ~ 4.86                             |

3 结论

本研究设计合成了 62 个新型含苯氧甲基、氯甲基的十元、十二元及十六元氮杂内酯化合物 **C** 和 **E**, 测定了目标化合物对 5 种病原真菌的离体抑菌活性。抑菌活性结果表明, 大部分化合物对 5 种病原真菌有一定的抑菌活性, 不含氨基甲酸酯和脲结构的化合物 **C5** 和 **C6** 对番茄灰霉病菌、苹果腐烂病菌、小麦赤霉病菌和马铃薯早疫病菌均有良好的抑制活性, 抑制率均高于 60%, 加入氨基甲酸酯和脲结构片段对化合物活性没有明显的提高, 化合物 **C1~C4** 的抑菌活性和 **E** 系列化合物抑菌活性对比先导化合物的活性均较差, 增加苯氧甲基和氯甲基结构对十元、十二元氮杂内酯化合物的抑菌活性没有显著提高。对化合物活性影响较大的是主体结构氮杂内酯环, 大环内酯抑菌活性高于中环内酯的抑菌活性。含苯氧甲

基十六元氮杂内酯化合物 **C5** 对马铃薯早疫病菌 EC<sub>50</sub> 值为 2.95 mg/L, 与对照药吡唑醚菌酯活性 (2.36 mg/L) 相当, 在十六元氮杂内酯中加入苯氧甲基可增强化合物对早疫病菌的抑制活性。化合物 **C5** 可作为新型抑菌活性先导化合物进一步研究。

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## · 书 讯 ·

系统阐述大环化合物立体化学方向的高水平专著

# 《大环化合物的立体化学》

王道全 编著

化学工业出版社 出版



### 内容简介:

本书在概述大环化合物的研究概况、发展趋势及展望的基础上,系统阐述了普通大环化合物的立体化学,包括大环烷、大环烯烃、大环炔烃、大环酮、大环内酯和大环内酰胺的构象,及其由环内双键和环上取代基引起的顺反异构等内容,重点分析了大环化合物的构象。此外,还介绍了大环化合物某些特有的性质以及发生在大环上的几个典型反应的构象分析。

### 图书特点:

1) 汇集团队研究成果,重点分析大环化合物构象。本书是作者科研团队多年来研究成果的集大成,是我国首部系统阐述大环化合物立体化学方向的高水平专著。

2) 系统开展基础研究,大力推动新农药创制工作。本书作者科研团队在系统开展了阿维菌素结构改造研究后,在麝香酮合成研究、环十二酮立体化学研究和大环化合物作为农药的创新研究等方面做了大量的工作,并取得了阶段性成果,可为发掘大环化合物的农药活性、推动新农药创制助力。

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