

1-芳基-3-(3-(4-氧香豆素基)苯基)硫脲  
衍生物的合成及抑菌活性

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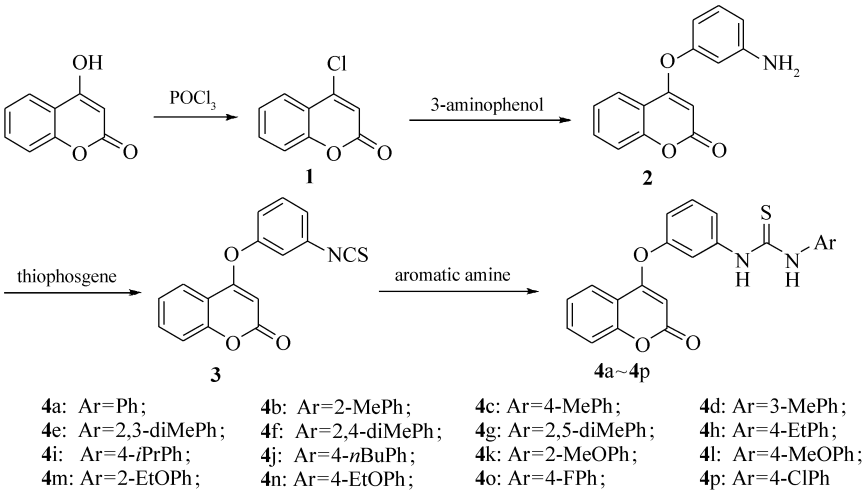
**摘 要** 为了筛选出具有较高抑菌活性的含香豆素的硫脲类衍生物,本文以 4-羟基香豆素为原料,经氯化、醚化、异硫氰酸化和加成反应合成了一系列 1-芳基-3-(3-(4-氧香豆素基)苯基)硫脲衍生物,其结构经红外光谱(IR)、核磁共振谱(NMR)和质谱(MS)等技术手段进行了表征。结果表明,目标化合物对水稻白叶枯菌和柑橘溃疡菌均具有较好的抑制活性。其中化合物 **4k**、**4l**、**4m** 和 **4n** 抑制水稻白叶枯菌活性 EC<sub>50</sub> 值分别为 137.42、131.05、129.23 和 117.43 mg/L,优于对照药剂噻菌铜的活性(195.24 mg/L);化合物 **4k**、**4l**、**4m** 和 **4n** 抑制柑橘溃疡菌活性 EC<sub>50</sub> 值分别为 97.02、94.31、102.28 和 90.52 mg/L,优于噻菌铜的活性(120.25 mg/L)。

**关键词** 香豆素;硫脲类衍生物;合成;抑菌活性

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近年来,农作物细菌性病害已成为严重影响农业生产的主要病害之一,严重影响农作物的产量和品质,给农户造成重大经济损失。细菌性病害是由细菌病原菌侵染所致的病害,如软腐病、溃疡病、青枯病等,这些侵害植物的细菌可通过自然孔口(气孔、皮孔、水孔等)和伤口侵入,借流水、雨水、昆虫等传播,在病残体、种子、土壤中过冬,在高温、高湿条件下容易发病<sup>[1]</sup>。目前,防治农作物细菌性病害的农药种类还比较少,现有农药品种如农用链霉素、叶青双和铜制剂(噻菌铜、硫酸铜、氧氯化铜)等药剂<sup>[2]</sup>。硫



Scheme 1 Synthetic routes of the title compounds (**4a~4p**)

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脲类衍生物具有抑菌<sup>[3-4]</sup>、抗病毒<sup>[5]</sup>、抗肿瘤<sup>[6]</sup>、抗寄生虫<sup>[7]</sup>等生物活性。近年来,有大量的文献报道了具有抗菌活性的硫脲类衍生物<sup>[8-10]</sup>。此外,4-羟基香豆素及其衍生物具有抗菌<sup>[11]</sup>、除草<sup>[12]</sup>、抗癌<sup>[13]</sup>、抗HIV<sup>[14]</sup>等生物活性,同时也是合成医药、农药、染料的重要中间体<sup>[15]</sup>。研究发现大多数4-羟基香豆素衍生物具有优良的抑菌活性,如:徐翠莲等<sup>[16]</sup>报道了含有香豆素骨架的缩氨基硫脲化合物对革兰氏阳性菌和阴性菌均有比较显著的抑菌活性。我们课题组<sup>[17]</sup>前期发现了具有抑制水稻白叶枯菌和柑橘溃疡病菌活性含香豆素的席夫碱类衍生物。为了筛选出更高抗菌活性的含香豆素类衍生物,以4-羟基香豆素为原料,经氯化、醚化异硫氰酸化和加成等反应合成了一系列1-芳基-3-(3-(4-氧香豆素基)苯基)硫脲衍生物,并对目标化合物进行抑制水稻白叶枯菌和柑橘溃疡病菌活性测试。目标化合物(4a~4p)的合成路线如 Scheme 1 所示。

## 1 实验部分

### 1.1 仪器和试剂

IR Affinity-1S 型傅里叶变换分光光度计(日本岛津公司);JEOL-ECX500 型500 MHz核磁共振仪(日本电子株式会社);X-4 型数字显微熔点测定仪(北京泰克仪器有限公司);RE-52AA 型旋转蒸发仪(上海亚荣生化有限公司);IKA RCT 型基本型磁力搅拌器(广州仪科实验技术有限公司);QY-20 型三用紫外分析仪(上海市安亭电子仪器厂)。

4-羟基香豆素( $\geq 98\%$ ,天津希恩思生化科技有限公司);对氨基酚( $\geq 98\%$ ,Aladdin-上海阿拉丁生化科技股份有限公司);硫光气( $\geq 95\%$ ,天津希恩思生化科技有限公司)。其余试剂均为分析纯。

### 1.2 实验方法

1.2.1 中间体1的合成 中间体1的制备参考文献[18]的合成方法。

1.2.2 中间体2的合成 将9.0 g(0.05 mol)中间体1、5.45 g(0.05 mol)间氨基酚和13.8 g(0.1 mol)无水碳酸钾溶于250 mL 乙腈中,在80℃下,回流反应6 h,冷却至室温,过滤除去不溶性盐,减压蒸去溶剂,剩余物中加无水乙醇溶解并重结晶,得到白色固体4-(3-氨基苯氧基)-香豆素(2),产率:81%,mp 124~126℃。<sup>1</sup>H NMR(500 MHz, DMSO- $d_6$ ), $\delta$ :8.17(d,  $J$ =7.0 Hz, 1H, coumarin-5-H), 7.60(t,  $J$ =5.0 Hz, 1H, coumarin-7-H), 7.34~7.30(m, 2H, coumarin-6,8-H); 7.18(d,  $J$ =8.5 Hz, 2H, Ar—H), 6.95(d,  $J$ =8.5 Hz, 2H, Ar—H), 5.26(s, 1H, coumarin-3-H); <sup>13</sup>C NMR(125 MHz, DMSO- $d_6$ ), $\delta$ :166.37, 161.83, 153.64, 151.52, 133.86, 131.13, 125.04, 123.49, 117.14, 112.72, 107.86, 106.08, 93.06。

1.2.3 中间体3的合成 将2.53 g(10 mmol)4-(3-氨基苯氧基)-香豆素(2)溶于50.0 mL 氯苯中,加入1.0 mL 三乙胺,加热,当温度为升高到35℃时,缓慢滴加1.02 mL(12 mmol)硫光气和50.0 mL 氯苯的混合溶液,并保持35℃,搅拌8 h。反应结束后,冷却至室温,减压除去溶剂,加入200 mL 水,过滤,干燥,再用无水乙醇重结晶,得到白色固体4-(4-异硫氰酸酯苯氧基)香豆素(3),产率:86%,mp 147~148℃。<sup>1</sup>H NMR(500 MHz, DMSO- $d_6$ ), $\delta$ :8.03(d,  $J$ =8.5 Hz, 1H, coumarin-5-H), 7.74(t,  $J$ =8.0 Hz, 1H, coumarin-7-H), 7.48~7.43(m, 2H, coumarin-6,8-H), 7.16(d,  $J$ =8.0 Hz, 2H, Ar—H), 6.98(d,  $J$ =8.0 Hz, 2H, Ar—H), 5.26(s, 1H, coumarin-3-H); <sup>13</sup>C NMR(125 MHz, DMSO- $d_6$ ), $\delta$ :165.93, 161.35, 154.16, 151.52, 136.69, 133.35, 131.16, 128.22, 125.10, 123.48, 122.31, 117.25, 115.31, 93.21。

1.2.4 1-芳基-3-(3-(4-氧香豆素基)苯基)硫脲(4a~4p)的合成 将0.295 g(1.0 mmol)4-(4-异硫氰酸酯苯氧基)香豆素(3)和1.1 mmol 芳香胺溶于10 mL 四氢呋喃中,室温反应,反应1~3 h后停止搅拌,减压除去溶剂,再用甲醇重结晶,得到目标化合物1-芳基-3-(3-(4-氧香豆素基)苯基)硫脲衍生物(4a~4p)。

1-苯基-3-(3-(4-氧香豆素基)苯基)硫脲(4a):白色固体,mp 163~165℃,产率80%;<sup>1</sup>H NMR(500 MHz, DMSO- $d_6$ ), $\delta$ :5.26(s, 1H, coumarin-3-H), 6.69(d,  $J$ =7.5 Hz, 1H, Ar—H), 7.12(d,  $J$ =7.0 Hz, 1H, Ar—H), 7.30~7.48(m, 7H, coumarin-6,8-H, Ar—H), 7.60(d,  $J$ =8.0 Hz, 2H, Ar—H), 7.74(t,  $J$ =8.5 Hz, 1H, coumarin-7-H), 8.03(d,  $J$ =8.0 Hz, 1H, coumarin-5-H), 9.81(s, 1H, OPhN—H), 9.90(s, 1H, ArN—H); <sup>13</sup>C NMR(125 MHz, DMSO- $d_6$ ), $\delta$ :93.34, 115.26, 117.07, 121.81, 123.47,

124.36, 125.09, 126.09, 128.93, 133.87, 138.37, 139.83, 148.92, 153.56, 161.65, 166.46, 181.29; IR (KBr),  $\sigma/\text{cm}^{-1}$ : 3323, 3159, 1716, 1606, 1541, 1388, 1224, 1145; MS (ESI) 计算值 ( $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ )  $[\text{M} + \text{Na}]^+$ : 403.0, 测量值: 403.9。

1-(2-甲基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4b**): 白色固体, mp 167 ~ 169 °C, 产率 78%;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 2.25 (s, 3H,  $\text{CH}_3$ ), 5.26 (s, 1H, coumarin-3-H), 6.69 (d,  $J = 7.0$  Hz, 1H, Ar—H), 7.12 (d,  $J = 7.5$  Hz, 1H, Ar—H), 7.30 ~ 7.49 (m, 6H, coumarin-6,8-H, Ar—H), 7.61 (d,  $J = 7.5$  Hz, 2H, Ar—H), 7.75 (t,  $J = 8.0$  Hz, 1H, coumarin-7-H), 8.05 (d,  $J = 8.0$  Hz, 1H, coumarin-5-H), 9.76 (s, 1H, OPhN—H), 9.98 (s, 1H, ArN—H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 21.36, 93.17, 115.10, 116.94, 121.44, 121.67, 123.35, 124.75, 124.86, 125.71, 126.01, 128.67, 133.75, 137.75, 138.26, 139.52, 148.75, 153.42, 161.54, 166.34, 180.05; IR (KBr),  $\sigma/\text{cm}^{-1}$ : 3334, 3153, 1707, 1606, 1560, 1386, 1276, 1145; MS (ESI) 计算值 ( $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ )  $[\text{M} + \text{Na}]^+$ : 425.5, 测量值: 425.7。

1-(4-甲基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4c**): 白色固体, mp 167 ~ 169 °C, 产率 83%;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 2.21 (s, 3H,  $\text{CH}_3$ ), 5.26 (s, 1H, coumarin-3-H), 6.68 (d,  $J = 7.5$  Hz, 1H, Ar—H), 7.12 (d,  $J = 7.0$  Hz, 1H, Ar—H), 7.30 ~ 7.48 (m, 6H, coumarin-6,8-H, Ar—H), 7.60 (d,  $J = 8.0$  Hz, 2H, Ar—H), 7.74 (t,  $J = 7.5$  Hz, 1H, coumarin-7-H), 8.03 (d,  $J = 7.0$  Hz, 1H, coumarin-5-H), 9.36 (s, 1H, OPhN—H), 9.75 (s, 1H, ArN—H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 19.02, 94.02, 115.93, 117.74, 122.52, 124.16, 125.66, 127.07, 127.27, 127.74, 129.24, 131.48, 134.53, 136.09, 139.99, 149.69, 154.24, 162.34, 167.15, 181.72; IR (KBr),  $\sigma/\text{cm}^{-1}$ : 3323, 3159, 1716, 1606, 1541, 1388, 1224, 1145; MS (ESI) 计算值 ( $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ )  $[\text{M} + \text{Na}]^+$ : 425.1, 测量值: 425.5。

1-(3-甲基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4d**): 白色固体, mp 169 ~ 171 °C, 产率 86%;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 2.25 (s, 3H,  $\text{CH}_3$ ), 5.26 (s, 1H, coumarin-3-H), 6.69 (d,  $J = 7.0$  Hz, 1H, Ar—H), 7.11 (d,  $J = 7.5$  Hz, 1H, Ar—H), 7.33 ~ 7.48 (m, 6H, coumarin-6,8-H, Ar—H), 7.60 (d,  $J = 7.5$  Hz, 2H, Ar—H), 7.74 (t,  $J = 7.5$  Hz, 2H, coumarin-7-H, Ar—H), 8.03 (d,  $J = 7.5$  Hz, 1H, coumarin-5-H), 9.38 (s, 1H, OPhN—H), 9.96 (s, 1H, ArN—H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 18.34, 93.80, 115.69, 117.51, 121.98, 122.36, 123.92, 125.42, 126.98, 127.22, 128.67, 130.67, 132.66, 134.30, 134.90, 138.72, 140.18, 149.64, 154.00, 162.14, 166.91, 181.41; IR (KBr),  $\sigma/\text{cm}^{-1}$ : 3322, 3132, 1714, 1606, 1543, 1386, 1226, 1147; MS (ESI) 计算值 ( $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ )  $[\text{M} + \text{Na}]^+$ : 425.1, 测量值: 425.1。

1-(2,3-二甲基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4e**): 白色固体, mp 175 ~ 176 °C, 产率 74%;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 2.15 (s, 3H,  $\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 5.26 (s, 1H, coumarin-3-H), 6.69 (d,  $J = 7.0$  Hz, 1H, Ar—H), 7.08 ~ 7.30 (m, 4H, Ar—H), 7.45 ~ 7.49 (m, 2H, coumarin-6,8-H), 7.60 (d,  $J = 9.0$  Hz, 2H, Ar—H), 7.73 (t,  $J = 8.0$  Hz, 1H, coumarin-7-H), 8.03 (d,  $J = 8.0$  Hz, 1H, coumarin-5-H), 9.41 (s, 1H, OPh—NH), 9.75 (s, 1H, ArN—H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 15.07, 20.87, 93.67, 115.62, 117.42, 122.09, 123.84, 125.34, 126.25, 126.82, 128.93, 134.22, 134.61, 137.98, 138.36, 149.33, 153.93, 162.01, 166.84, 181.52; IR (KBr),  $\sigma/\text{cm}^{-1}$ : 3325, 3163, 1712, 1606, 1533, 1388, 1224, 1145; MS (ESI) 计算值 ( $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ )  $[\text{M} + \text{Na}]^+$ : 439.3, 测量值: 439.5。

1-(2,4-二甲基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4f**): 白色固体, mp 176 ~ 178 °C, 产率 72%;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 2.23 (s, 3H,  $\text{CH}_3$ ), 2.29 (s, 3H,  $\text{CH}_3$ ), 5.26 (s, 1H, coumarin-3-H), 7.00 ~ 7.31 (m, 5H, Ar—H), 7.44 ~ 7.48 (m, 2H, coumarin-6,8-H), 7.61 (d,  $J = 8.0$  Hz, 2H, Ar—H), 7.73 (t,  $J = 8.0$  Hz, 1H, coumarin-7-H), 8.03 (d,  $J = 8.5$  Hz, 1H, coumarin-5-H), 9.48 (s, 1H, OPh—NH), 9.86 (s, 1H, ArN—H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ),  $\delta$ : 18.04, 20.80, 93.02, 114.96, 116.81, 121.59, 123.23, 124.75, 126.19, 126.93, 128.01, 128.18, 131.13, 133.63, 134.96, 136.01, 138.07, 148.68, 153.28, 161.44, 166.25, 180.77; IR (KBr),  $\sigma/\text{cm}^{-1}$ : 3324, 3155, 1707, 1606, 1560, 1386, 1276, 1145; MS (ESI) 计算值 ( $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ )  $[\text{M} + \text{Na}]^+$ : 439.3, 测量值: 439.5。

1-(2,5-二甲基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4g**): 白色固体, mp 177 ~ 179 °C, 产率

70% ;  $^1\text{H}$  NMR ( 500 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 2. 20 ( s, 3H,  $\text{CH}_3$  ), 2. 26 ( s, 3H,  $\text{CH}_3$  ), 5. 26 ( s, 1H, coumarin-3-H ), 6. 98 ( d,  $J = 7. 5$  Hz, 1H, Ar—H ), 7. 11 ( d,  $J = 7. 5$  Hz, 1H, Ar—H ), 7. 31 ~ 7. 49 ( m, 6H, coumarin-6, 8-H, Ar—H ), 7. 61 ( d,  $J = 7. 5$  Hz, 2H, Ar—H ), 7. 73 ( t,  $J = 8. 5$  Hz, 1H, coumarin-7-H ), 8. 03 ( d,  $J = 7. 5$  Hz, 1H, coumarin-5-H ), 9. 45 ( s, 1H, OPhN—H ), 9. 89 ( s, 1H, ArN—H );  $^{13}\text{C}$  NMR ( 125 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 17. 89, 20. 87, 93. 26, 115. 19, 117. 02, 121. 78, 123. 43, 126. 40, 126. 40, 127. 73, 128. 87, 130. 60, 132. 18, 133. 82, 135. 61, 138. 28, 148. 94, 153. 50, 161. 63, 166. 44, 180. 87; IR ( KBr ),  $\sigma/\text{cm}^{-1}$ : 3327, 3149, 1703, 1605, 1560, 1392, 1219, 1184; MS ( ESI ) 计算值 (  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$  ) [ M + Na ]  $^+$ : 439. 3, 测量值: 439. 6。

1-(4-乙基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4h**): 白色固体, mp 172 ~ 174  $^{\circ}\text{C}$ , 产率 87% ;  $^1\text{H}$  NMR ( 500 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 1. 18 ( t,  $J = 7. 5$  Hz, 3H,  $\text{CH}_3$  ), 2. 51 ~ 1. 54 ( m, 2H,  $\text{CH}_2$  ), 5. 26 ( s, 1H, coumarin-3-H ), 6. 69 ( d,  $J = 7. 5$  Hz, 1H, Ar—H ), 7. 16 ( d,  $J = 8. 0$  Hz, 2H, Ar—H ), 7. 31 ~ 7. 49 ( m, 6H, coumarin-6, 8-H, Ar—H ), 7. 60 ( d,  $J = 8. 0$  Hz, 2H, Ar—H ), 7. 61 ( d,  $J = 8. 5$  Hz, 2H, Ar—H ), 7. 74 ( t,  $J = 8. 0$  Hz, 1H, coumarin-7-H ), 8. 03 ( d,  $J = 7. 5$  Hz, 1H, coumarin-5-H ), 9. 87 ( s, 1H, OPhN—H ), 9. 95 ( s, 1H, ArN—H );  $^{13}\text{C}$  NMR ( 125 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 16. 51, 28. 55, 93. 74, 115. 68, 117. 17, 122. 17, 123. 89, 124. 99, 125. 41, 126. 49, 128. 64, 134. 29, 137. 81, 138. 89, 141. 15, 149. 26, 153. 98, 162. 07, 166. 88, 180. 68; IR ( KBr ),  $\sigma/\text{cm}^{-1}$ : 3329, 3174, 1685, 1606, 1541, 1384, 1222, 1145; MS ( ESI ) 计算值 (  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$  ) [ M + Na ]  $^+$ : 439. 1, 测量值: 439. 9。

1-(4-异丙基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4i**): 白色固体, mp 186 ~ 188  $^{\circ}\text{C}$ , 产率 77% ;  $^1\text{H}$  NMR ( 500 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 1. 20 ( s, 6H,  $\text{CH}_3$  ), 2. 88 ~ 2. 30 ( m, 1H, CH ), 5. 26 ( s, 1H, coumarin-3-H ), 6. 69 ( d,  $J = 7. 5$  Hz, 1H, Ar—H ), 7. 12 ( d,  $J = 7. 5$  Hz, 2H, Ar—H ), 7. 21 ~ 7. 46 ( m, 6H, coumarin-6, 8-H, Ar—H ), 7. 62 ( d,  $J = 8. 5$  Hz, 2H, Ar—H ), 7. 73 ( t,  $J = 8. 0$  Hz, 1H, coumarin-7-H ), 8. 03 ( d,  $J = 8. 5$  Hz, 1H, coumarin-5-H ), 9. 75 ( s, 1H, OPhN—H ), 9. 94 ( s, 1H, ArN—H );  $^{13}\text{C}$  NMR ( 125 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 24. 30, 33. 33, 93. 17, 115. 11, 116. 98, 121. 69, 123. 37, 124. 43, 124. 91, 125. 93, 126. 66, 133. 79, 137. 35, 138. 35, 145. 23, 148. 71, 153. 44, 161. 57, 166. 38, 180. 07; IR ( KBr ),  $\sigma/\text{cm}^{-1}$ : 3325, 3116, 1701, 1606, 1541, 1386, 1219, 1186; MS ( ESI ) 计算值 (  $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$  ) [ M + Na ]  $^+$ : 453. 1, 测量值: 453. 2。

1-(4-丁基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4j**): 白色固体, mp 196 ~ 198  $^{\circ}\text{C}$ , 产率 71% ;  $^1\text{H}$  NMR ( 500 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 1. 14 ( t,  $J = 7. 0$  Hz, 3H,  $\text{CH}_3$  ), 1. 56 ~ 1. 59 ( m, 2H,  $\text{CH}_2$  ), 2. 55 ( t,  $J = 7. 5$  Hz, 2H,  $\text{CH}_2$  ), 5. 26 ( s, 1H, coumarin-3-H ), 6. 68 ( d,  $J = 7. 0$  Hz, 1H, Ar—H ), 7. 14 ( d,  $J = 8. 0$  Hz, 2H, Ar—H ), 7. 31 ~ 7. 46 ( m, 6H, coumarin-6, 8-H, Ar—H ), 7. 61 ( d,  $J = 9. 0$  Hz, 2H, Ar—H ), 7. 73 ( t,  $J = 7. 0$  Hz, 1H, coumarin-7-H ), 8. 03 ( d,  $J = 8. 0$  Hz, 1H, coumarin-5-H ), 9. 68 ( s, 1H, OPhN—H ), 9. 98 ( s, 1H, ArN—H );  $^{13}\text{C}$  NMR ( 125 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 14. 19, 22. 15, 33. 56, 34. 72, 93. 27, 115. 21, 117. 02, 121. 71, 123. 42, 124. 42, 124. 94, 126. 03, 128. 69, 133. 82, 137. 32, 138. 40, 139. 26, 148. 80, 153. 51, 161. 60, 166. 41, 180. 17; IR ( KBr ),  $\sigma/\text{cm}^{-1}$ : 3327, 3124, 1715, 1606, 1547, 1384, 1225, 1145; MS ( ESI ) 计算值 (  $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$  ) [ M + Na ]  $^+$ : 467. 1, 测量值: 467. 3。

1-(2-甲氧基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4k**): 白色固体, mp 175 ~ 176  $^{\circ}\text{C}$ , 产率 80% ;  $^1\text{H}$  NMR ( 500 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 3. 89 ( s, 3H,  $\text{OCH}_3$  ), 5. 26 ( s, 1H, coumarin-3-H ), 6. 98 ( d,  $J = 7. 5$  Hz, 1H, Ar—H ), 7. 20 ( d,  $J = 8. 0$  Hz, 1H, Ar—H ), 7. 31 ~ 7. 49 ( m, 4H, coumarin-6, 8-H, Ar—H ), 7. 61 ( d,  $J = 8. 0$  Hz, 2H, Ar—H ), 7. 74 ( t,  $J = 7. 5$  Hz, 1H, coumarin-7-H ), 7. 80 ( d,  $J = 8. 0$  Hz, 2H, Ar—H ), 8. 03 ( d,  $J = 8. 0$  Hz, 1H, coumarin-5-H ), 9. 41 ( s, 1H, OPhN—H ), 9. 96 ( s, 1H, ArN—H );  $^{13}\text{C}$  NMR ( 125 MHz,  $\text{DMSO-d}_6$  ),  $\delta$ : 56. 51, 93. 66, 112. 36, 115. 60, 117. 41, 120. 66, 122. 08, 123. 82, 125. 33, 126. 38, 126. 97, 128. 39, 134. 22, 138. 68, 149. 21, 152. 99, 153. 92, 161. 98, 166. 79, 180. 48; IR ( KBr ),  $\sigma/\text{cm}^{-1}$ : 3331, 3136, 1708, 1606, 1538, 1388, 1219, 1145; MS ( ESI ) 计算值 (  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$  ) [ M + Na ]  $^+$ : 431. 2, 测量值: 431. 5。

1-(4-甲氧基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(**4l**): 白色固体, mp 178 ~ 179  $^{\circ}\text{C}$ , 产率 83% ;

$^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ) ,  $\delta$ : 3. 75 ( s, 3H,  $\text{OCH}_3$  ) , 5. 26 ( s, 1H, coumarin-3-H ) , 6. 96 ( d,  $J$  = 8. 5 Hz, 1H, Ar—H ) , 7. 43 ~ 7. 48 ( m, 6H, coumarin-6, 8-H, Ar—H ) , 7. 61 ( d,  $J$  = 8. 0 Hz, 2H, Ar—H ) , 7. 73 ( t,  $J$  = 8. 0 Hz, 1H, coumarin-7-H ) , 8. 03 ( d,  $J$  = 8. 0 Hz, 1H, coumarin-5-H ) , 9. 56 ( s, 1H,  $\text{OPhN—H}$  ) , 9. 88 ( s, 1H,  $\text{ArN—H}$  ) ;  $^{13}\text{C}$  NMR ( 125 MHz, DMSO- $d_6$  ) ,  $\delta$ : 55. 88, 93. 49, 114. 34, 115. 43, 117. 23, 121. 92, 123. 63, 125. 15, 126. 33, 126. 86, 132. 70, 134. 03, 138. 62, 149. 02, 153. 72, 157. 34, 161. 82, 166. 63, 180. 73; IR ( KBr ) ,  $\sigma/\text{cm}^{-1}$ : 3337, 3116, 1710, 1606, 1541, 1386, 1222, 1145; MS ( ESI ) 计算值 (  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$  ) [  $\text{M} + \text{Na}$  ]  $^+$ : 431. 2, 测量值: 431. 3。

1-(2-乙氧基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(4m): 白色固体, mp 174 ~ 176  $^{\circ}\text{C}$ , 产率 73%;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ) ,  $\delta$ : 1. 41 ( t,  $J$  = 6. 5 Hz, 3H,  $\text{CH}_3$  ) , 4. 14 ~ 4. 18 ( m, 2H,  $\text{OCH}_2$  ) , 5. 26 ( s, 1H, coumarin-3-H ) , 6. 98 ( d,  $J$  = 8. 0 Hz, 1H, Ar—H ) , 7. 10 ( d,  $J$  = 7. 0 Hz, 1H, Ar—H ) , 7. 16 ~ 7. 48 ( m, 6H, coumarin-6, 8-H, Ar—H ) , 7. 61 ( d,  $J$  = 8. 5 Hz, 2H, Ar—H ) , 7. 73 ( t,  $J$  = 8. 5 Hz, 1H, coumarin-7-H ) , 7. 80 ( d,  $J$  = 8. 0 Hz, 2H, Ar—H ) , 8. 03 ( d,  $J$  = 8. 0 Hz, 1H, coumarin-5-H ) , 9. 31 ( s, 1H,  $\text{OPhN—H}$  ) , 9. 85 ( s, 1H,  $\text{ArN—H}$  ) ;  $^{13}\text{C}$  NMR ( 125 MHz, DMSO- $d_6$  ) ,  $\delta$ : 15. 03, 64. 21, 93. 18, 112. 82, 115. 09, 116. 91, 120. 09, 121. 68, 123. 32, 124. 83, 125. 98, 126. 37, 128. 39, 129. 33, 132. 26, 133. 75, 138. 04, 148. 81, 151. 69, 153. 41, 161. 47, 166. 28, 179. 76; IR ( KBr ) ,  $\sigma/\text{cm}^{-1}$ : 3332, 3119, 1705, 1606, 1548, 1387, 1219, 1145; MS ( ESI ) 计算值 (  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$  ) [  $\text{M} + \text{Na}$  ]  $^+$ : 455. 2, 测量值: 455. 4。

1-(4-乙氧基苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(4n): 白色固体, mp 172 ~ 174  $^{\circ}\text{C}$ , 产率 84%;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ) ,  $\delta$ : 1. 38 ( t,  $J$  = 8. 0 Hz, 3H,  $\text{CH}_3$  ) , 4. 02 ~ 4. 05 ( m, 2H,  $\text{OCH}_2$  ) , 5. 26 ( s, 1H, coumarin-3-H ) , 6. 96 ( d,  $J$  = 9. 5 Hz, 1H, Ar—H ) , 7. 31 ( d,  $J$  = 8. 0 Hz, 4H, Ar—H ) , 7. 44 ~ 7. 47 ( m, 2H, coumarin-6, 8-H ) , 7. 61 ( d,  $J$  = 8. 0 Hz, 2H, Ar—H ) , 7. 74 ( t,  $J$  = 7. 0 Hz, 1H, coumarin-7-H ) , 8. 04 ( d,  $J$  = 7. 0 Hz, 1H, coumarin-5-H ) , 9. 43 ( s, 1H,  $\text{OPhN—H}$  ) , 9. 82 ( s, 1H,  $\text{ArN—H}$  ) ;  $^{13}\text{C}$  NMR ( 125 MHz, DMSO- $d_6$  ) ,  $\delta$ : 15. 15, 63. 59, 93. 27, 114. 60, 115. 21, 117. 07, 121. 80, 123. 47, 125. 00, 126. 19, 126. 68, 132. 36, 133. 88, 138. 42, 148. 81, 153. 52, 156. 40, 161. 68, 166. 49, 180. 43; IR ( KBr ) ,  $\sigma/\text{cm}^{-1}$ : 3329, 3117, 1701, 1606, 1537, 1389, 1226, 1145; MS ( ESI ) 计算值 (  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$  ) [  $\text{M} + \text{Na}$  ]  $^+$ : 455. 1, 测量值: 455. 3。

1-(4-氟苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(4o): 白色固体, mp 177 ~ 179  $^{\circ}\text{C}$ , 产率 65%;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ) ,  $\delta$ : 5. 26 ( s, 1H, coumarin-3-H ) , 7. 12 ( d,  $J$  = 8. 0 Hz, 2H, Ar—H ) , 7. 31 ( d,  $J$  = 6. 5 Hz, 2H, Ar—H ) , 7. 44 ~ 7. 49 ( m, 4H, coumarin-6, 8-H, Ar—H ) , 7. 61 ( d,  $J$  = 7. 5 Hz, 2H, Ar—H ) , 7. 74 ( t,  $J$  = 8. 5 Hz, 1H, coumarin-7-H ) , 8. 03 ( d,  $J$  = 8. 0 Hz, 1H, coumarin-5-H ) , 9. 68 ( s, 1H,  $\text{OPhN—H}$  ) , 9. 89 ( s, 1H,  $\text{ArN—H}$  ) ;  $^{13}\text{C}$  NMR ( 125 MHz, DMSO- $d_6$  ) ,  $\delta$ : 93. 61, 115. 51, 115. 92, 117. 36, 122. 17, 123. 76, 125. 28, 126. 52, 127. 22, 127. 28, 134. 16, 136. 41, 138. 52, 149. 28, 153. 83, 161. 95, 166. 74, 180. 92; IR ( KBr ) ,  $\sigma/\text{cm}^{-1}$ : 3335, 3125, 1707, 1606, 1541, 1376, 1218, 1145; MS ( ESI ) 计算值 (  $\text{C}_{22}\text{H}_{15}\text{FN}_2\text{O}_3\text{S}$  ) [  $\text{M} + \text{Na}$  ]  $^+$ : 429. 0, 测量值: 429. 2。

1-(4-氯苯基)-3-(3-(4-氧香豆素基)苯基)硫脲(4p): 白色固体, mp 183 ~ 185  $^{\circ}\text{C}$ , 产率 61%;  $^1\text{H}$  NMR ( 500 MHz, DMSO- $d_6$  ) ,  $\delta$ : 5. 26 ( s, 1H, coumarin-3-H ) , 7. 33 ~ 7. 48 ( m, 7H, coumarin-6, 8-H, Ar—H ) , 7. 61 ( d,  $J$  = 8. 0 Hz, 2H, Ar—H ) , 7. 73 ( t,  $J$  = 8. 0 Hz, 2H, coumarin-7-H, Ar—H ) , 8. 03 ( d,  $J$  = 8. 0 Hz, 1H, coumarin-5-H ) , 9. 45 ( s, 1H,  $\text{OPhN—H}$  ) , 9. 87 ( s, 1H,  $\text{ArN—H}$  ) ;  $^{13}\text{C}$  NMR ( 125 MHz, DMSO- $d_6$  ) ,  $\delta$ : 93. 78, 115. 68, 117. 50, 122. 32, 123. 59, 123. 90, 124. 92, 125. 42, 126. 67, 131. 71, 132. 00, 133. 36, 133. 95, 134. 30, 138. 59, 139. 41, 149. 49, 153. 99, 162. 08, 166. 86, 180. 76; IR ( KBr ) ,  $\sigma/\text{cm}^{-1}$ : 3336, 3151, 1730, 1606, 1539, 1382, 1220, 1176; MS ( ESI ) 计算值 (  $\text{C}_{22}\text{H}_{15}\text{ClN}_2\text{O}_3\text{S}$  ) [  $\text{M} + \text{Na}$  ]  $^+$ : 445. 1, 测量值: 445. 4。

### 1.3 抑菌生物活性测试

#### 1.3.1 目标化合物的初步抑菌生物活性测试

采用浑浊度法<sup>[19]</sup>, 在药剂质量浓度为 200 和 100 mg/L 时, 以水稻白叶枯菌和柑橘溃疡菌为供试菌株, 对目标化合物 4a ~ 4p 进行了抑菌活性的测定, 以商品药剂噻唑酮为对照药剂。

1.3.2 部分目标化合物的抑菌活性  $EC_{50}$  值测定 采用质量浓度倍减法将部分供试化合物用溶剂配制成 5 个质量浓度(200、100、50、25 和 12.5 mg/L),采用浊度法测定各个质量浓度抑制率,每处理重复 3 次,计算药剂对病原菌的有效抑制中浓度( $EC_{50}$ )值,结果见表 2 所示。

2 结果与讨论

2.1 目标化合物的合成

以关键中间体 3 的合成为例,探讨了不同溶剂、温度和时间对其收率的影响,结果见表 1。

表 1 优化中间体 3 的合成条件  
Table 1 Optimization of the synthesis conditions of intermediate 3

No	Solvent	Temperature/℃	Time/h	Yield/%
1	Ether	r. t.	8	18
2	Dichloromethane	r. t.	8	27
3	Chloroform	r. t.	8	40
4	1,4-Dioxane	r. t.	8	45
5	Chlorobenzene	r. t.	8	70
6	Chlorobenzene	0	8	52
7	Chlorobenzene	20	8	64
8	Chlorobenzene	35	8	85
9	Chlorobenzene	50	8	81
10	Chlorobenzene	35	4	48
11	Chlorobenzene	35	6	74
12	Chlorobenzene	35	10	83

Note;r. t. means room temperature.

由表 1 可以看出,当溶剂为氯苯,室温下反应 8 h,收率最高为 70%。然后,用氯苯为溶剂,反应 8 h,反应温度升高至 35 ℃,收率增加至 85%。最后,用氯苯为溶剂,反应温度为 35 ℃,分别缩短或增加反应时间(4、6、10 h),其收率分别为 48%、74% 和 83%。因此,合成 4-(4-异硫氰酸酯苯氧基)香豆(3)的最佳反应条件为:氯苯作溶剂、反应温度为 35 ℃,反应时间为 8 h。

2.2 目标化合物的图谱解析

所有化合物的结构均经过 IR、 $^1\text{H}$  NMR、 $^{13}\text{C}$  NMR 和 MS 等手段进行了表征。在 IR 谱图中,3116 ~ 3334  $\text{cm}^{-1}$  是  $\text{—NH—C=S—NH—}$  中 NH 的伸缩振动引起的;官能团  $\text{—O—C=O—}$  和  $\text{—NH—C=S—NH—}$  中  $\text{C=S}$  伸缩振动吸收峰则出现在 1701 ~ 1730 和 1145 ~ 1186  $\text{cm}^{-1}$  处。在  $^1\text{H}$  NMR 谱图中,硫脲基团的质子的化学位移在 9.31 ~ 9.98 处; $\delta$  5.6 是香豆素环上 3 位的质子的化学位移。在  $^{13}\text{C}$  NMR 谱图中, $\delta$  179.76 ~ 181.72 是  $\text{—NH—C=S—NH—}$  中碳的化学位移。

2.3 目标化合物的抑菌活性

采用浑浊度法,在药剂质量浓度为 200 和 100 mg/L 时,以水稻白叶枯菌和柑橘溃疡病菌为供试菌株,测定目标化合物 4a ~ 4p 的抑菌活性,其结果如表 2 所示。

表 2 标化合物 4a ~ 4p 的抑菌活性  
Table 2 Antibacterial activities of the title compounds 4a ~ 4p

Compound	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i>		<i>Xanthomonas citri</i> subsp. <i>Citri</i>	
	200 mg/L	100 mg/L	200 mg/L	100 mg/L
4a	71.2 ± 2.3	40.4 ± 2.8	77.2 ± 2.3	38.6 ± 1.4
4b	72.3 ± 2.4	43.5 ± 2.4	77.4 ± 1.8	39.2 ± 2.6
4c	79.0 ± 1.5	44.3 ± 1.7	75.2 ± 2.2	40.2 ± 1.5
4d	80.4 ± 1.7	47.2 ± 1.6	75.7 ± 2.7	37.0 ± 1.7
4e	78.1 ± 2.1	46.4 ± 2.4	80.1 ± 1.2	48.1 ± 1.6

Continued on next page

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Compound	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i>		<i>Xanthomonas citri</i> subsp. <i>Citri</i>	
	200 mg/L	100 mg/L	200 mg/L	100 mg/L
4f	82.7 ± 1.6	44.3 ± 1.2	83.8 ± 2.0	50.1 ± 2.7
4g	80.5 ± 2.1	42.3 ± 1.2	85.6 ± 2.2	55.3 ± 1.5
4h	80.3 ± 2.5	49.6 ± 3.1	84.1 ± 2.1	57.4 ± 2.4
4i	82.5 ± 2.8	43.5 ± 2.7	79.2 ± 1.6	44.1 ± 2.2
4j	78.7 ± 1.2	43.5 ± 1.7	76.8 ± 2.6	44.2 ± 2.0
4k	90.1 ± 1.4	48.2 ± 2.1	93.1 ± 2.4	50.2 ± 2.3
4l	94.1 ± 2.3	55.1 ± 1.7	96.3 ± 1.6	58.7 ± 1.5
4m	87.3 ± 1.5	52.7 ± 2.6	90.7 ± 2.2	51.3 ± 2.1
4n	92.2 ± 2.6	57.9 ± 1.8	94.5 ± 1.8	53.9 ± 2.0
4o	41.2 ± 3.1	22.1 ± 1.0	51.6 ± 2.0	39.2 ± 1.9
4p	43.4 ± 2.7	24.8 ± 2.3	49.5 ± 1.1	28.1 ± 1.3
Thiodiazole-copper	66.3 ± 1.2	40.6 ± 2.1	76.4 ± 1.5	46.8 ± 1.8

由表 2 可以看出,目标化合物具有以水稻白叶枯菌和柑橘溃疡病菌活性。当药剂质量浓度为 200 mg/L 时,化合物 4d、4f、4g、4h、4i、4k、4l、4m 和 4n 对水稻白叶枯菌的抑制率分别为 80.4%、82.7%、80.5%、80.3%、82.5%、90.1%、94.1%、87.3% 和 92.2%, 优于对照药剂噻菌铜(66.3%);当药剂质量浓度为 100 mg/L,化合物 4d、4e、4h、4k、4l、4m 和 4n 对烟草青枯菌的抑制率分别为 47.2%、46.4%、49.6%、48.2%、55.1%、52.7% 和 57.9%, 均优于对照药剂噻菌铜(40.6%)。此外,当质量浓度为 200 mg/L 时,化合物 4d、4e、4f、4h、4k、4l、4m 和 4n 对柑橘溃疡病菌的抑制率分别为 80.1%、83.8%、85.6%、84.1%、93.1%、96.3%、90.7% 和 94.5%, 优于对照药剂噻菌铜的活性(76.4%)。当质量浓度为 100 mg/L 时,化合物 4d、4e、4f、4h、4k、4l、4m 和 4n 对柑橘溃疡病菌的抑制率分别为 48.1%、50.1%、55.3%、55.3%、50.2%、58.7%、51.3% 和 53.9%, 优于对照药剂噻菌铜的活性(46.8%)。

选择抑菌活性高的 4 个目标化合物 4k、4l、4m 和 4n 测定抑制水稻白叶枯菌和柑橘溃疡病菌活性 EC<sub>50</sub> 值,结果见表 3。

表 3 部分化合物的抗菌活性 EC<sub>50</sub> 值  
Table 3 EC<sub>50</sub> values of Antibacterial activities of the part of title compounds

Compound	EC <sub>50</sub> /(mg·L <sup>-1</sup> )	
	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i>	<i>Xanthomonas citri</i> subsp. <i>Citri</i>
4k	137.42 ± 1.8	97.02 ± 1.9
4l	131.05 ± 2.2	94.31 ± 2.4
4m	129.23 ± 2.9	102.28 ± 2.0
4n	117.43 ± 1.3	90.52 ± 1.3
Thiodiazole-copper	195.24 ± 1.8	120.25 ± 1.7

从表 3 可以看出,目标化合物衍生物对水稻白叶枯菌和柑橘溃疡病菌均具有较好的抑制活性。其中化合物 4k、4l、4m 和 4n 抑制烟草青枯菌活性 EC<sub>50</sub> 值分别为 137.42、131.05、129.23 和 117.43 mg/L, 优于对照药剂噻菌铜(195.24 mg/L);化合物 4k、4l、4m 和 4n 抑制番茄青枯菌活性 EC<sub>50</sub> 值和 97.02、94.31、102.28 和 90.52 mg/L, 优于对照药剂噻菌铜的活性(120.25 mg/L)。初步构效关系表明:当目标化合物中的 Ar 为 2-甲氧基苯基(2-MeOPh)、4-甲氧基苯基(4-MeOPh)、2-乙氧基苯基(2-EtOPh) 和 4-乙氧基苯基(4-EtOPh) 时,相对应的目标化合物对水稻白叶枯菌和柑橘溃疡病菌具有较优的抑制活性,均优于对照药剂噻菌铜的活性。此外,大多数目标化合物抑制柑橘溃疡病菌的活性优于抑制水稻白叶枯菌的活性。

3 结 论

以 4-羟基香豆素为先导,采用结构多样性衍生,设计合成了 16 个 1-芳基-3-(3-(4-氧香豆素基)苯基)硫脲衍生物。采用浑浊度法,以水稻白叶枯菌和柑橘溃疡病菌为供试菌株,测定目标化合物的抑菌

活性。测试结果表明:大多数目标化合物具有较好的抑菌活性。其中化合物**4k**、**4l**、**4m**和**4n**对水稻白叶枯菌和柑橘溃疡病菌具有较优的抑制活性,均优于对照药剂噻菌铜的活性。对其结构进一步修饰和改造,有可能得到活性更高的化合物,该研究工作正在进行中。

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## Synthesis and Antibacterial Activity of 1-Aryl-3-(3-((2-oxo-2H-Chromen-4-yl)oxy)phenyl)thiourea Derivatives

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**Abstract** In order to develop thiourea derivatives with antibacterial activities, a series of novel 1-aryl-3-(3-((2-oxo-2H-chromen-4-yl)oxy)phenyl)thiourea derivative was synthesized from 4-hydroxycoumarin *via* chlorination, etherification, isothiocyanate formation and addition reactions. The structures of the title compounds were characterized by infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS). The results show that title compounds exhibit excellent antibacterial activities against *Xanthomonas oryzae pv. oryzae* (Xoo) and *Xanthomonas citri subsp. Citri* (Xcc). Among of them, compounds **4k**, **4l**, **4m** and **4n** show excellent antibacterial activities against Xoo, with the EC<sub>50</sub> values 137.42, 131.05, 129.23 and 117.43 mg/L, respectively, which were better than that of the control agent thiodiazole-copper (195.24 mg/L). Compounds **4k**, **4l**, **4m** and **4n** display considerable antibacterial activities against Xcc, with the EC<sub>50</sub> values of 97.02, 94.31, 102.28 and 90.52 mg/L, respectively, which are better than that of thiodiazole-copper (120.25 mg/L).

**Keywords** coumarin; thiourea derivatives; synthesis; antibacterial activities

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