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24   **ABSTRACT**

25   A series of *N*-aryl-pyridine-4-ones derivatives were designed and synthesized by using maltol and

26   antidesmone as lead compounds, and then their fungicidal/bactericidal activities and possible

27   mechanism of action against *Colletotrichum musae* were explored. Most of these compounds

28   exhibited significant fungicidal activity *in vitro*. Especially, compound **23** has more than 90%

29   inhibitory activity against 9 plant pathogenic fungi at 50 μg mL^{-1}, which is superior to azoxystrobin.

30   Moreover, *in vivo* bioassay also demonstrated that compound **23** exhibited high-efficiency broad-

31   spectrum antifungal activity and can effectively control postharvest diseases of mango. In addition,

32   it was found that compounds **22** and **23** can also effectively control rice bacterial leaf blight in pot

33   experiments, which was even more effective than zhongshengmycin. Preliminary mechanism

34   studies revealed that compound **23** maybe cause cell membrane and mitochondria destruction. These

35   findings indicate that compound **23** can be used to develop potential agrochemical fungicides and

36   bactericides.

37

38   **KEYWORDS:**   maltol,   *N*-aryl-pyridine-4-ones,   fungicidal   activity,   bactericidal   activity,

39   postharvest diseases, action mechanism

INTRODUCTION

40

41   Plant diseases pose a serious threat to the safety and stability of crop production. In plant

42   diseases, most of the diseases are caused by pathogenic fungi[1] and bacteria infection[2]. A variety of

43   chemical fungicides and antibiotics are used to reduce plant diseases in agriculture. However, some

44   fungicides and bactericides have caused environmental pollutions[3-4], pesticide residues in

45   agricultural products[5-7], at the same time, resistant plant-pathogenic fungi[8] and bacteria[9] isolates

46   have been reported around the world, such as azoxystrobin-resistant isolates[10-14] and streptomycin-

47   resistant isolates[15-17]. These problems have promoted pesticide researchers to find broad-spectrum,

48   high-effective and low-risk fungicides and bactericides with no cross-resistance to current

49   commercial products.

50   It is well known that using natural products as lead compounds is an effective method for the

51   discovery of pesticides. Antidesmone (**Figure 1**) is an antifungal quinoline alkaloids isolated from

52   *Waltheria indica* in our lab and exhibited broad-spectrum antifungal activities against

53   phytopathogenic fungi[18]. Maltol (3-hydroxy-2-methyl-4-pyrone, **Figure 1**) is a natural flavor which

54   is widely used as a food additive and a potent antioxidative agent[19]. At the same time, it has been

55   reported that maltol and its derivatives have certain antifungal and antibacterial activity[20-21]. In order

56   to identify the pharmacophore and simplify the structure of antidesmone, a series of *N*-substituted-

57   pyridine-4-ones (compounds **6-38**) were designed and synthesized based on the chemical structure

58   of antidesmone and maltol (**Figure 1, Scheme 1**). Furthermore, *in vitro* and *in vivo* antifungal and

59   antibacterial activity of compounds **6-38** were evaluated and the structure-activity relationship was

60   also discussed. Furthermore, preliminary mechanism against *Colletotrichum musae* of compound

61   **23** was also investigated.

62   **MATERIALS AND METHODS**

63   **Chemicals.** All commercially available chemicals can be used directly.

64   **Fungal strains.** Fungal strains were obtained from ACCC (Agricultural Culture Collection of China)

65   or College of Plant Protection, Hainan University.

66   **Instruments.** Thin layer chromatography (TLC) was used to monitor the reactions on the silica gel

67   GF254 (Qingdao Ocean Chemical Limited Company, China). Flash column chromatography

68   purification was achieved on the silica gel (300-400 mesh, Qingdao Ocean Chemical Limited

69   Company, China). The melting point was measured on the X-4 microscopic melting point

70   instrument (Beijing Taike Instruments Co., Ltd., China). ^1H and ^{13}C NMR spectra were measured

71   by using the Bruker 500 MHz or 600 MHz NMR spectrometer (Bruker Co., Switzerland) in

72   deuterium solvents with tetramethylsilane (TMS) as the internal standard. HRMS data was obtained

73   by using the MALDI-TOF / TOF mass spectrometer (Bruker Co., Switzerland).

74   **Synthesis.** The synthetic routes of the target compounds **6-38** were outlined in **Scheme 1.**

75   *General procedure for synthesizing target compounds 6-7*

76   Maltol (10 mmol) was dissolved in 10 mL H_2O and excess of ammonia or methylamine (15

77   mmol) was added into the solution. The reaction solution was heated to reflux and kept for 10 h.

78   The solvent and ammonia or methylamine were removed in vacuo. The residue was purified by

79   falsh silica gel column chromatography (CH_2Cl_2/CH_3OH = 50:1) to afford compounds **5-6**[22].

80   *3-Hydroxy-2-methylpyridin-4(1H)-one* (**6**). Gray solid, mp 285-287 °C, yield = 85%. ^{1}H NMR

81   (600 MHz, DMSO-d_6) δ 8.01 (d, J = 5.5 Hz, 1H, pyridinone), 6.33 (d, J = 5.5 Hz, 1H, pyridinone),

82   2.23 (s, 3H, CH$_3$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.6, 154.6, 149.2, 143.0, 113.6, 14.0.

83   *3-Hydroxy-1,2-dimethylpyridin-4(1H)-one* (**7**). White solid, mp 259-260 °C, yield = 69%. [1]H

84   NMR (600 MHz, DMSO-d_6) δ 7.55 (d, J = 7.2 Hz, 1H, pyridinone), 6.08 (d, J = 7.2 Hz, 1H,

85   pyridinone), 3.62 (s, 3H, N-CH$_3$), 2.26 (s, 3H, pyridinone-CH$_3$). ^{13}C NMR (150 MHz, DMSO-d_6) δ

86   168.7, 145.3, 138.0, 129.4, 110.2, 40.9, 11.7.

87   *General procedure for the synthesis of the target compounds 8-38*

88   Pyrone analogues (**2-5**) (20 mmol) and an excess of the appropriate primary arylamine (30

89   mmol) were added to an acidic solution (pH = 5.0) containing water (18.0 mL), con. HCl (0.4 mL,

90   12 mol/L) and ethanol (2.0 mL). And the mixture was heated and maintained at 160 °C for 12 h in

91   an autoclave. After the reaction was completed, the reaction mixture was adjusted to pH7.0 using

92   sodium hydroxide solution (2 N) and the mixture was extracted with CH$_2$Cl$_2$ (50 mL) for three

93   times, then the organic phase was merged and dried with anhydrous MgSO$_4$. The crude product was

94   obtained by removing solvent under vacuum and then purified by flash silica gel column

95   chromatography (CH$_2$Cl$_2$/CH$_3$OH = 50:1) to afford compounds **8-38**[23-24].

96   *3-Hydroxy-2-methyl-1-phenylpyridin-4(1H)-one* (**8**). White solid, mp 206-207 °C, yield = 83%.

97   ^{1}H NMR (500 MHz, Chloroform-d) δ 7.53 (m, J = 4.8, 1.8 Hz, 3H, Ph), 7.30 (d, J = 7.3 Hz, 1H,

98   pyridinone), 7.29 – 7.26 (m, 2H, Ph), 6.46 (d, J = 7.3 Hz, 1H, pyridinone), 2.10 (s, 3H, CH$_3$). [13]C

99   NMR (125 MHz, Chloroform-d) δ 170.3, 145.8, 141.9, 137.6, 130.0, 129.7, 128.5, 126.9, 111.0,

100   13.8. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{12}$H$_{12}$NO$_2$]: 202.0863; found: 202.0858.

101   *3-Hydroxy-1-(4-hydroxyphenyl)-2-methylpyridin-4(1H)-one* (**9**). Gray solid, mp 311-312 °C,

102   yield = 69%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.48 (d, J = 7.3 Hz, 1H, pyridinone), 7.23 − 7.20

103   (m, 2H, Ph), 6.89 − 6.86 (m, 2H, Ph), 6.18 (d, J = 7.3 Hz, 1H, pyridinone), 1.95 (s, 3H, CH$_3$). ^{13}C

104   NMR (150 MHz, DMSO-d_6) δ 169.4, 157.8, 145.0, 138.2, 133.1, 129.3, 128.0, 115.8, 110.6, 13.3.

105   ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{12}$H$_{12}$NO$_3$]: 218.0812; found: 218.0807.

106   *1-([1,1'-Biphenyl]-4-yl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**10**). Grayish white solid, mp

107   264-266 °C, yield = 65%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.85 (d, J = 8.3 Hz, 2H, Ph), 7.75 (d, J

108   = 7.5 Hz, 2H, Ph), 7.60 (d, J = 7.3 Hz, 1H, pyridinone), 7.55 (d, J = 8.3 Hz, 2H, Ph), 7.51 (t, J = 7.6

109   Hz, 2H, Ph), 7.42 (t, J = 7.3 Hz, 1H, Ph), 6.23 (d, J = 7.3 Hz, 1H, pyridinone), 2.02 (s, 3H, CH$_3$).

110   ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.7, 145.1, 140.9, 138.8, 137.9, 129.1, 128.6, 128.0, 127.8,

111   127.5, 126.9, 110.9, 13.4. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{18}$H$_{16}$NO$_2$]: 278.1176; found:

112   278.1182.

113   *1-(4-Fluorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**11**). Grayish white solid, mp 191-

114   192 °C, yield = 79%. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.31 − 7.28 (m, 2H, Ph), 7.27 (s, 1H,

115   pyridinone), 7.25 − 7.20 (m, 2H, Ph), 6.46 (d, J = 7.3 Hz, 1H, pyridinone), 2.10 (s, 3H, CH$_3$). ^{13}C

116   NMR (125 MHz, Chloroform-d) δ 170.4, 163.7, 162.7 (d, J = 251.0 Hz), 145.8, 137.6 (d, J = 3.4

117   Hz), 128.8 (d, J = 8.9 Hz), 117.2, 117.0 (d, J = 23.1 Hz), 111.2, 13.7. ESI-HRMS: m/z [M+H]$^+$

118   calcd. for [C$_{12}$H$_{11}$FNO$_2$]: 220.0768; found: 220.0765.

119   *1-(4-Chlorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**12**). White solid, mp 210-212 °C,

120   yield = 74%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.63 (d, J = 8.6 Hz, 2H, Ph), 7.55 (d, J = 7.3 Hz,

121   1H, pyridinone), 7.51 (d, J = 8.6 Hz, 2H, Ph), 6.21 (d, J = 7.3 Hz, 1H, pyridinone), 1.96 (s, 3H,

122   CH$_3$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.7, 145.0, 140.4, 137.9, 133.7, 129.6, 129.0, 128.5,

123 111.0, 13.3. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{12}$H$_{11}$ClNO$_2$]: 236.0473; found: 236.0479.

124 *1-(4-Bromophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**13**). White solid, mp 216-217 ^{o}C,

125 yield = 63%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.76 (d, *J* = 8.6 Hz, 2H, Ph), 7.54 (d, *J* = 7.3 Hz,

126 1H, pyridinone), 7.44 (d, *J* = 8.6 Hz, 2H, Ph), 6.21 (d, *J* = 7.3 Hz, 1H, pyridinone), 1.96 (s, 3H,

127 CH$_3$). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.7, 140.8, 137.8, 132.5, 129.3, 128.4, 122.2, 118.5,

128 111.0, 13.3. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{12}$H$_{11}$BrNO$_2$]: 279.9968; found: 279.9971.

129 *1-(3-Chlorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**14**). Light brown solid, mp 173-

130 175 ^{o}C, yield = 61%. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.50 (dt, *J* = 15.4, 7.8 Hz, 2H, Ph), 7.33

131 (s, 1H, Ph), 7.28 (d, *J* = 5.0 Hz, 1H, Ph), 7.21 (d, *J* = 6.9 Hz, 1H, pyridinone), 6.47 (d, *J* = 7.0 Hz,

132 1H, pyridinone), 2.13 (s, 3H, CH$_3$). ^{13}C NMR (150 MHz, Chloroform-d) δ 170.4, 145.9, 142.7,

133 137.2, 135.7, 131.0, 130.0, 128.4, 127.4, 125.3, 111.4, 13.8. ESI-HRMS: m/z [M+H]$^+$ calcd. for

134 [C$_{12}$H$_{11}$ClNO$_2$]: 236.0473; found: 236.0471.

135 *1-(2-Chlorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**15**). Reddish brown solid, mp

136 180-182 ^{o}C, yield = 60%. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.66 – 7.40 (m, 4H, Ph), 7.17 (s,

137 1H, pyridinone), 6.48 (s, 1H, pyridinone), 2.03 (s, 3H, CH$_3$). ^{13}C NMR (150 MHz, Chloroform-d)

138 δ 170.5, 145.6, 139.0, 137.1, 132.5, 131.3, 130.9, 129.1, 128.7, 111.3, 29.7, 12.8. ESI-HRMS: m/z

139 [M+H]$^+$ calcd. for [C$_{12}$H$_{11}$ClNO$_2$]: 236.0473; found: 236.0475.

140 *1-(2-Fluorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**16**). Brown solid, mp 158-159 ^{o}C,

141 yield = 60%. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.52 (s, 1H, Ph), 7.32 (d, *J* = 5.5 Hz, 2H, Ph),

142 7.29 (d, *J* = 9.0 Hz, 1H, Ph), 7.24 (d, *J* = 7.2 Hz, 1H, pyridinone), 6.48 (d, *J* = 7.1 Hz, 1H, pyridinone),

143 2.09 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz, Chloroform-d) δ 170.7, 156.4 (d, *J* = 252.9 Hz), 145.7,

144 137.7, 131.9 (d, *J* = 7.5 Hz), 129.0 (d, *J* = 12.9 Hz), 128.9, 128.8 (d, *J* = 4.3 Hz), 125.5 (d, *J* = 4.0

145   Hz), 117.4 (d, J = 19.4 Hz), 111.5, 12.9. ESI-HRMS: m/z [M+H]$^+$ calcd. for [$C_{12}H_{11}FNO_2$]:

146   220.0768; found: 220.0773.

147   *1-(2,6-Difluorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**17**). Brown solid, mp 185-187

148   ^{o}C, yield = 53%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 – 7.45 (m, 1H, pyridinone), 7.22 – 7.09

149   (m, 3H, Ph), 6.50 (d, J = 6.3 Hz, 1H, pyridinone), 2.10 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz,

150   Chloroform-*d*) δ 171.0, 158.2 (d, J = 254.7 Hz), 145.7, 138.0, 131.7, 128.8, 118.7, 112.7 (d, J =

151   19.8 Hz), 111.9, 12.4. ESI-HRMS: m/z [M+H]$^+$ calcd. for [$C_{12}H_{10}F_2NO_2$]: 238.0674; found:

152   238.0679.

153   *3-Hydroxy-2-methyl-1-(p-tolyl)pyridin-4(1H)-one* (**18**). Light brown solid, mp 256-257 ^{o}C,

154   yield = 83%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 (d, J = 8.0 Hz, 2H, Ph), 7.24 (d, J = 2.5 Hz,

155   1H, pyridinone), 7.11 (d, J = 8.2 Hz, 2H, Ph), 6.42 (d, J = 7.3 Hz, 1H, pyridinone), 2.42 (s, 3H, Ph-

156   CH$_3$), 2.07 (s, 3H, pyridinone-CH$_3$). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 170.2, 145.8, 139.8,

157   139.4, 137.6, 130.5, 128.8, 126.6, 110.9, 21.3, 13.7. ESI-HRMS: m/z [M+H]$^+$ calcd. for

158   [$C_{13}H_{14}NO_2$]: 216.1019; found: 216.1023.

159   *1-(4-Ethylphenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**19**). Light brown solid, mp 121-122

160   ^{o}C, yield = 79%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (d, J = 7.5 Hz, 2H, Ph), 7.28 (d, J = 6.8

161   Hz, 1H, pyridinone), 7.16 (d, J = 7.6 Hz, 2H, Ph), 6.44 (d, J = 6.6 Hz, 1H, pyridinone), 2.73 (q, J =

162   7.6 Hz, 2H, CH$_2$), 2.09 (s, 3H, pyridinone-CH$_3$), 1.29 (t, J = 7.6 Hz, 3H, CH$_3$). ^{13}C NMR (125 MHz,

163   Chloroform-*d*) δ 170.2, 145.7, 139.5, 137.6, 129.3, 128.8, 126.7, 110.9, 28.6, 15.5, 13.7. ESI-HRMS:

164   m/z [M+H]$^+$ calcd. for [$C_{14}H_{16}NO_2$]: 230.1176; found: 230.1184.

165   *3-Hydroxy-2-methyl-1-(4-propylphenyl)pyridin-4(1H)-one* (**20**). Light brown solid, mp 146-

166   148 ^{o}C, yield = 76%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (s, 3H, Ph and pyridinone), 7.15

167   (s, 2H, Ph), 6.44 (s, 1H, pyridinone), 2.66 (t, J = 6.9 Hz, 2H, CH_2), 2.09 (s, 3H, pyridinone-CH_3),

168   1.72 – 1.64 (m, 2H, CH_2), 0.97 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, Chloroform-d) δ

169   170.1, 145.6, 144.5, 139.4, 137.6, 129.8, 128.7, 126.5, 110.8, 37.6, 24.4, 13.8, 13.7. ESI-HRMS:

170   m/z $[M+H]^+$ calcd. for $[C_{15}H_{18}NO_2]$: 244.1332; found: 244.1335.

171   *3-Hydroxy-1-(4-isopropylphenyl)-2-methylpyridin-4(1H)-one* (**21**). Light brown solid, mp

172   193-194 ℃, yield = 76%. ^1H NMR (500 MHz, Chloroform-d) δ 7.35 (d, J = 7.9 Hz, 2H, Ph), 7.28

173   (d, J = 7.1 Hz, 1H, pyridinone), 7.16 (d, J = 8.0 Hz, 2H, Ph), 6.44 (d, J = 7.0 Hz, 1H, pyridinone),

174   2.99 (hept, J = 6.9 Hz, 1H, CH), 2.10 (s, 3H, pyridinone-CH_3), 1.29 (d, J = 6.9 Hz, 6H, Ph-

175   CH(C$\underline{H}_3$)$_2$). ^{13}C NMR (125 MHz, Chloroform-d) δ 170.2, 150.6, 145.7, 139.5, 137.6, 128.9, 127.9,

176   126.7, 110.9, 34.0, 24.0, 13.8. ESI-HRMS: m/z $[M+Na]^+$ calcd. for $[C_{15}H_{17}NO_2Na]$: 266.1151;

177   found: 266.1155.

178   *1-(4-Butylphenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**22**). Light brown solid, mp 167-169

179   ℃, yield = 71%. ^1H NMR (600 MHz, Chloroform-d) δ 7.32 (s, 3H, Ph and pyridinone), 7.16 (s, 2H,

180   Ph), 6.45 (s, 1H, pyridinone), 2.70 (t, J = 6.9 Hz, 2H, CH_2), 2.10 (s, 3H, pyridinone-CH_3), 1.65 (s,

181   2H, CH_2), 1.43 – 1.36 (m, 2H, CH_2), 0.96 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, Chloroform-

182   d) δ 170.1, 145.6, 144.7, 139.4, 137.6, 129.7, 128.8, 126.5, 110.8, 35.2, 33.4, 22.3, 13.9, 13.6. ESI-

183   HRMS: m/z $[M+H]^+$ calcd. for $[C_{16}H_{20}NO_2]$: 258.1489; found: 258.1485.

184   *1-(4-(Tert-butyl)phenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**23**). White solid, mp 197-198

185   ℃, yield = 74%. ^1H NMR (500 MHz, Chloroform-d) δ 7.51 (d, J = 8.4 Hz, 2H, Ph), 7.29 (d, J = 7.2

186   Hz, 1H, pyridinone), 7.17 (d, J = 8.4 Hz, 2H, Ph), 6.44 (d, J = 7.2 Hz, 1H, pyridinone), 2.10 (s, 3H,

187   pyridinone-CH_3), 1.37 (s, 9H, Ph-C(C$\underline{H}_3$)$_3$). ^{13}C NMR (125 MHz, Chloroform-d) δ 170.2, 153.0,

188   145.7, 139.3, 137.7, 128.8, 126.9, 126.4, 110.9, 35.0, 31.4, 13.8. ESI-HRMS: m/z [M+H]$^+$ calcd.

189   for [$C_{16}H_{20}NO_2$]: 258.1489; found: 258.1491.

190   *1-(4-(Dimethylamino)phenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**24**). Dark brown solid,

191   mp 214-215 ^{o}C, yield = 66%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 7.0 Hz, 1H,

192   pyridinone), 7.06 (d, *J* = 8.1 Hz, 2H, Ph), 6.72 (d, *J* = 8.1 Hz, 2H, Ph), 6.42 (d, *J* = 6.8 Hz, 1H,

193   pyridinone), 3.02 (s, 6H, N-(C$\underline{H}_3$)$_2$), 2.09 (s, 3H, pyridinone-CH$_3$). ^{13}C NMR (125 MHz,

194   Chloroform-*d*) δ 170.0, 150.7, 145.6, 138.2, 130.6, 129.5, 127.3, 112.2, 110.7, 40.5, 13.7. ESI-

195   HRMS: m/z [M+H]$^+$ calcd. for [$C_{14}H_{17}N_2O_2$]: 245.1285; found: 245.1282.

196   *2-(4-(3-Hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)phenyl)-2-methylpropanenitrile*   (**25**).

197   Grayish white solid, mp 229-230 ^{o}C, yield = 68%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 (d, *J*

198   = 8.2 Hz, 2H, Ph), 7.30 (d, *J* = 8.3 Hz, 2H, Ph), 7.24 (s, 1H, pyridinone), 6.44 (d, *J* = 7.2 Hz, 1H,

199   pyridinone), 2.09 (s, 3H, pyridinone-CH$_3$), 1.77 (s, 6H, Ph-C(C$\underline{H}_3$)$_2$CN). ^{13}C NMR (125 MHz,

200   Chloroform-*d*) δ 170.4, 145.9, 143.2, 141.4, 137.4, 128.3, 127.5, 126.9, 123.9, 111.2, 37.2, 29.2,

201   13.8. ESI-HRMS: m/z [M+H]$^+$ calcd. for [$C_{16}H_{17}N_2O_2$]: 269.1285; found: 269.1284.

202   *3-Hydroxy-2-methyl-1-(m-tolyl)pyridin-4(1H)-one* (**26**). Light brown solid, mp 142-143 ^{o}C,

203   yield = 61%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (s, 1H, pyridinone), 7.34 − 7.26 (m, 2H,

204   Ph), 7.08 (s, 2H, Ph), 6.46 (s, 1H, pyridinone), 2.44 (s, 3H, Ph-CH$_3$), 2.11 (s, 3H, pyridinone-CH$_3$).

205   ^{13}C NMR (125 MHz, Chloroform-*d*) δ 170.2, 145.7, 141.8, 140.3, 137.4, 130.3, 129.7, 128.7, 127.4,

206   123.8, 110.9, 21.4, 13.7. ESI-HRMS: m/z [M+Na]$^+$ calcd. for [$C_{13}H_{13}NO_2Na$]: 238.0838; found:

207   238.0831.

208   *1-(3-(Tert-butyl)phenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**27**). Grayish white solid, mp

209   185-186 ^{o}C, yield = 60%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 8.7 Hz, 1H, Ph), 7.44

210   (t, J = 7.8 Hz, 1H, Ph), 7.31 (d, J = 7.3 Hz, 1H, pyridinone), 7.23 (t, J = 1.9 Hz, 1H, Ph), 7.06 (d, J

211   = 8.8 Hz, 1H, Ph), 6.46 (d, J = 7.3 Hz, 1H, pyridinone), 2.09 (s, 3H, CH$_3$), 1.34 (s, 9H, Ph-C(C$\underline{H}_3$)$_3$).

212   ^{13}C NMR (125 MHz, Chloroform-d) δ 170.2, 153.8, 145.8, 141.7, 137.6, 129.6, 128.6, 126.6, 123.9,

213   123.8, 110.9, 35.1, 31.3, 13.8. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{16}$H$_{20}$NO$_2$]: 258.1489; found:

214   258.1482.

215   *3-Hydroxy-2-methyl-1-(3-(trifluoromethyl)phenyl)pyridin-4(1H)-one* (**28**). Brown solid, mp

216   188-190 ^{o}C, yield = 59%. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.81 (s, 1H, Ph), 7.78 – 7.68 (m,

217   1H, Ph), 7.59 (s, 1H, pyridinone), 7.57 – 7.49 (m, 1H, Ph), 7.29 (d, J = 10.9 Hz, 1H, Ph), 6.49 (s,

218   1H, pyridinone), 2.12 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz, Chloroform-d) δ 170.5, 146.0, 142.2,

219   137.3, 132.6 (q, J = 33.2 Hz), 130.8, 130.4, 128.2, 126.5 (q, J = 3.6 Hz), 124.1 (q, J = 271.2 Hz),

220   124.0 (q, J = 3.6 Hz), 111.6, 13.8. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{13}$H$_{11}$F$_3$NO$_2$]: 270.0736;

221   found: 270.0737.

222   *1-(3,5-Dimethylphenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**29**). Light brown solid, mp

223   193-195 ^{o}C, yield = 59%. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.28 (d, J = 7.6 Hz, 1H, pyridinone),

224   7.13 (s, 1H, Ph), 6.87 (s, 2H, Ph), 6.44 (d, J = 7.2 Hz, 1H, pyridinone), 2.39 (s, 6H, Ph-CH$_3$), 2.11

225   (s, 3H, pyridinone-CH$_3$). ^{13}C NMR (150 MHz, Chloroform-d) δ 170.2, 145.7, 141.7, 139.9, 137.4,

226   131.1, 128.8, 124.4, 110.9, 21.3, 13.7. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{14}$H$_{16}$NO$_2$]: 230.1176;

227   found: 230.1172.

228   *1-(3,5-Dichlorophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**30**). Brown solid, mp 195-196

229   ^{o}C, yield = 60%. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.53 (s, 1H, pyridinone), 7.23 (s, 3H, Ph),

230   6.45 (d, J = 5.9 Hz, 1H, pyridinone), 2.14 (s, 3H, CH$_3$). ^{13}C NMR (150 MHz, Chloroform-d) δ 170.6,

231   145.9, 143.2, 137.1, 136.4, 130.2, 127.9, 125.9, 111.6, 13.8. ESI-HRMS: m/z [M+H]⁺ calcd. for

232   [$C_{12}H_{10}Cl_2NO_2$]: 270.0083; found: 270.0086.

233   *1-(3,5-Dichloro-4-methylphenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**31**). Brown solid,

234   mp 205-207 ⁰C, yield = 69%. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.27 (s, 2H, Ph), 7.25 (s, 1H,

235   pyridinone), 6.46 (s, 1H, pyridinone), 2.55 (s, 3H, Ph-CH₃), 2.14 (s, 3H, pyridinone-CH₃). ¹³C NMR

236   (150 MHz, Chloroform-*d*) δ 170.5, 145.9, 140.0, 137.2, 136.7, 136.5, 128.1, 126.3, 111.5, 17.5, 13.7.

237   ESI-HRMS: m/z [M+H]⁺ calcd. for [$C_{13}H_{12}Cl_2NO_2$]: 284.0240; found: 284.0237.

238   *1-(3-Fluoro-4-morpholinophenyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**32**). Grayish white

239   solid, mp 220-221 ⁰C, yield = 68%. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 2.0 Hz, 1H,

240   pyridinone), 7.02 − 6.98 (m, 3H, Ph), 6.44 (d, *J* = 7.3 Hz, 1H, pyridinone), 3.92 − 3.87 (m, 4H,

241   morpholine), 3.19 − 3.14 (m, 4H, morpholine), 2.12 (s, 3H, CH₃). ¹³C NMR (150 MHz, Chloroform-

242   *d*) δ 170.2, 154.81 (d, *J* = 251.1 Hz), 145.7, 141.2 (d, *J* = 8.0 Hz), 137.6, 135.26 (d, *J* = 9.4 Hz),

243   128.8, 123.2 (d, *J* = 3.4 Hz), 119.0 (d, *J* = 4.1 Hz), 115.5 (d, *J* = 23.1 Hz), 111.1, 66.9, 50.6 (d, *J* =

244   3.7 Hz), 13.7. ESI-HRMS: m/z [M+H]⁺ calcd. for [$C_{16}H_{18}FN_2O_3$]: 305.1296; found: 305.1299.

245   *1-(2,3-Dihydro-1H-inden-5-yl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**33**). Brown solid, mp

246   182-183 ⁰C, yield = 79%. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 7.5 Hz, 1H, pyridinone),

247   7.27 (d, *J* = 6.9 Hz, 1H, Ph), 7.08 (s, 1H, Ph), 6.98 (d, *J* = 7.4 Hz, 1H, Ph), 6.43 (d, *J* = 6.7 Hz, 1H,

248   pyridinone), 2.97 (t, *J* = 7.1 Hz, 4H, Ar-CH₂), 2.16 (p, *J* = 6.8 Hz, 2H, Ar-CH₂), 2.10 (s, 3H, CH₃).

249   ¹³C NMR (150 MHz, Chloroform-*d*) δ 170.1, 146.4, 145.9, 145.6, 134.0, 137.6, 128.8, 125.3, 124.5,

250   122.7, 110.7, 32.9, 32.6, 25.6, 13.7. ESI-HRMS: m/z [M+H]⁺ calcd. for [$C_{15}H_{16}NO_2$]: 242.1176;

251   found: 242.1180.

252   *1-(9,9-Dimethyl-9H-fluoren-2-yl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**34**). Brown solid,

253   mp 243-244 °C, yield = 78%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 7.6 Hz, 1H, Ph),

254   7.78 – 7.76 (m, 1H, Ph), 7.49 – 7.47 (m, 1H, Ph), 7.41 – 7.37 (m, 3H, Ph), 7.30 (s, 1H, Ph), 7.22 (d,

255   *J* = 7.3 Hz, 1H, pyridinone), 6.49 (d, *J* = 7.1 Hz, 1H, pyridinone), 2.14 (s, 3H, pyridinone-CH$_3$),

256   1.52 (s, 6H, Ar-(CH$_3$)$_2$). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 170.1, 155.5, 153.8, 145.7, 140.6,

257   140.5, 137.7, 137.4, 128.6, 128.4, 127.4, 125.6, 122.8, 121.2, 120.9, 120.6, 110.8, 47.3, 27.0, 13.7.

258   ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{21}$H$_{20}$NO$_2$]: 318.1489; found: 318.1481.

259   *1-(4-(Tert-butyl)benzyl)-3-hydroxy-2-methylpyridin-4(1H)-one* (**35**). Grayish white solid, mp

260   190-191 °C, yield = 80%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.1 Hz, 2H, Ph), 7.31

261   (d, *J* = 6.4 Hz, 1H, pyridinone), 6.95 (d, *J* = 8.2 Hz, 2H, Ph), 6.43 (d, *J* = 6.5 Hz, 1H, pyridinone),

262   5.05 (s, 2H, CH$_2$), 2.29 (s, 3H, pyridinone-CH$_3$), 1.30 (s, 9H, Ph-C(CH$_3$)$_3$). ^{13}C NMR (150 MHz,

263   Chloroform-*d*) δ 170.0, 151.8, 146.5, 137.8, 132.3, 128.6, 126.3, 125.9, 111.3, 57.1, 34.7, 31.4,

264   12.3. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{17}$H$_{22}$NO$_2$]: 272.1645; found: 272.1639.

265   *1-(4-(Tert-butyl)phenyl)-3-methoxy-2-methylpyridin-4(1H)-one* (**36**). Light yellow solid, mp

266   172-174 °C, yield = 93%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.4 Hz, 2H, Ph), 7.23

267   (d, *J* = 7.5 Hz, 1H, pyridinone), 7.15 (d, *J* = 8.4 Hz, 2H, Ph), 6.41 (d, *J* = 7.5 Hz, 1H, pyridinone),

268   3.89 (s, 3H, pyridinone-OCH$_3$), 2.05 (s, 3H, pyridinone-CH$_3$), 1.34 (s, 9H, Ph-C(CH$_3$)$_3$). ^{13}C NMR

269   (150 MHz, Chloroform-*d*) δ 173.8, 152.9, 147.5, 140.8, 139.3, 138.8, 126.9, 126.4, 117.0, 59.5, 35.0,

270   31.3, 14.2. ESI-HRMS: m/z [M+Na]$^+$ calcd. for [C$_{17}$H$_{21}$NO$_2$Na]: 294.1465; found: 294.1461.

271   *1-(4-(Tert-butyl)phenyl)-2-ethyl-3-hydroxypyridin-4(1H)-one* (**37**). White solid, mp 198-200

272   °C, yield = 70%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.4 Hz, 2H, Ph), 7.23 (d, *J* = 7.3

273   Hz, 1H, pyridinone), 7.20 (d, *J* = 8.4 Hz, 2H, Ph), 6.42 (d, *J* = 7.3 Hz, 1H, pyridinone), 2.53 (q, *J* =

274   7.5 Hz, 2H, CH$_2$), 1.37 (s, 9H, Ph-C(CH$_3$)$_3$), 1.01 (t, J = 7.5 Hz, 3H, CH$_3$). ^{13}C NMR (150 MHz,

275   Chloroform-d) δ 170.4, 153.1, 145.4, 139.1, 137.8, 134.5, 126.7, 126.6, 110.9, 35.0, 31.4, 20.5,

276   12.6. ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{17}$H$_{22}$NO$_2$]: 272.1645; found: 272.1649.

277   *1-(4-(Tert-butyl)phenyl)-2,6-dimethylpyridin-4(1H)-one* (**38**). Light yellow solid, mp 209-210

278   ℃, yield = 86%. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.52 (d, J = 8.3 Hz, 2H, Ph), 7.10 (d, J = 8.3

279   Hz, 2H, Ph), 6.34 (s, 2H, pyridinone), 1.91 (s, 6H, pyridinone-CH$_3$), 1.36 (s, 9H, Ph-C(CH$_3$)$_3$). ^{13}C

280   NMR (150 MHz, Chloroform-d) δ 179.2, 153.2, 149.6, 136.8, 127.3, 127.2, 117.2, 35.0, 31.4, 21.7.

281   ESI-HRMS: m/z [M+H]$^+$ calcd. for [C$_{17}$H$_{22}$NO]: 256.1696; found: 256.1698.

282   **In vitro antifungal and antibacterial bioassay.** The antifungal activity was evaluated by the

283   mycelial growth inhibitory rate method according to previously reported procedures[25-26], and the

284   antibacterial activity against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) was determined using the

285   turbidimeter test[27].

286   **In vivo antifungal bioassay.**

287   *Potted plant experiment*

288   Evaluation of antifungal activity of compound **23** on potted plants by literature method[28].

289   *In vivo protective activity against postharvest diseases of mango*

290   Compound **23** was dissolved in DMF and diluted to 200 μg mL^{-1} with water containing 0.5%

291   (v/v) Tween 80. The mango fruits were immersed in the solution for 5 minutes, and dried naturally,

292   15 fruits per treatment, repeated 3 times[29]. Stilled water containing DMF and Tween 80 was used

293   as a control, and azoxystrobin (200 μg mL^{-1}) was used as a positive control. The treated fruit were

294   stored in a moisture chamber at 28 °C and 80% RH. The disease was observed and graded every

295   two days.

296   The classification grades are as follows:

297   Grade 0: no lesion.

298   Grade 1: lesion area $\leq$ 5%.

299   Grade 3: 5% $<$ lesion area $\leq$ 10%.

300   Grade 5: 10% $<$ lesion area $\leq$ 25%.

301   Grade 7: 25% $<$ lesion area $\leq$ 50%.

302   Grade 9: lesion area $>$ 50%.

303     $$\text{Disease index} = \frac{\sum(\text{incidence number of all grades} \times \text{grade value of this level})}{\text{total number of mango fruit} \times \text{highest grade value}} \times 100$$

304     $$\text{Control effect} = \frac{\text{control disease index} - \text{treatment disease index}}{\text{control disease index}} \times 100\%$$

305   ***In vivo* antibacterial bioassay.** The curative and protection activities of compounds **22** and **23**

306   against *Xoo* were measured by Schaad's method[30-31]. Zhongshengmycin (Yuanye, Shanghai, China)

307   served as the positive control.

308   **Hyphal morphology observation of *C. musae*.** Compound **23** was added in sterilized Czapek

309   media which had incubated *C. musae* for 4 days, and the final concentration was 15 μg mL^{-1}. Then

310   incubated together at 27 ^{0}C. After 24h, observed under microscope (OLYMPUS BX53). Acetone

311   (1.0 mL) served as the control[32].

312   **Detection of cellular oxygen content.** The mycelium of *C. musae* which had been cultured for 4

313   days was filtered and washed three times with double distilled water. Hyphae (1 g) treated with

314   compound **23** at 7.5, 15, and 30μg mL^{-1} were placed in 20 mL centrifuge tube, azoxystrobin was

315   used as the positive control, and then measured the cellular oxygen at 0, 1, 3 and 6 h gradually by

316   optical oxygen dissolution meter (STRARTER 400D)[33].

317   The experimental methods for transmission electron microscopy, detecting cell membrane

318   permeability, soluble protein content and reducing sugar content refer to the literature method

319   previously published by our research group[34].

320   All the detail experimental methods were given in the **Supporting Information**.

321   **RESULTS AND DISCUSSION**

322   **Synthesis.** The chemical structure and synthetic method are shown in **Scheme 1**. All compounds

323   are obtained by one-step reaction of pyrone and the corresponding amine, and compounds **6-7** can

324   be obtained with a normal pressure reaction, while the reaction for producing compounds **8-38** can

325   be carried out only in an autoclave to obtain a higher yield, 33 target compounds were obtained with

326   yields of 53-93%, and all of the target compounds were characterized by HRMS, ^{1}H NMR and ^{13}C

327   NMR data.

328   *In vitro* **antifungal activities of compounds 6-38 and structure-activity relationships analysis.**

329   The fungicidal activities of 33 target compounds are shown in **Table 1** and **Table 2**. **Table 1** showed

330   the preliminary screening of antifungal activities of the target compounds **6-38** at 50 μg mL^{-1}, and

331   the EC$_{50}$ values of selected compounds with excellent fungicidal activities were determined (**Table**

332   **2**).

333   The structure-activity relationship (SAR) shown in **Table 1** and **Table 2** was obvious. Firstly,

334   the antifungal acitivities of compounds **1** (maltol), **6**, **7** and **8** showed that *N*-phenyl group on the

335   pyridinone ring was beneficial to antifungal activity. In addition, the substituents on the benzene

336   ring were crucial to antifungal activity and ortho-substituents were unfavorable for the antifungal

337   activity, for example, compound **12** (4-Cl) and compound **18** (4-CH$_3$) exhibited more broad-

338   spectrum antifungal activities than compound **9** (4-OH), **11** (4-F), **13** (4-Br), **15** (2-Cl), **16** (2-F) and

339   **17** (2,6-di-F). However, meta-substituents displayed different SAR, for example, the antifungal

340   activities of compound **14** (3-Cl) were much better than that of compound **12** (4-Cl), whereas

341   compound **26** (3-CH$_3$) showed comparable antifungal activities with compound **18** (4-CH$_3$).

342   Secondly, it was showed that the antifungal activities of target compounds increased gradually with

343   increase in carbon chain or steric hindrance by comparing the fungicidal activities of compounds **18**

344   (4-methyl), **19** (4-ethyl), **20** (4-*n*-propyl), **21** (4-*iso*-propyl), **22** (4-*n*-butyl) and **23** (4-*tert*-butyl).

345   Especially, compound **23** achieved more than 94% inhibition against 9 species of plant pathogenic

346   fungi at 50 μg mL^{-1} and the EC$_{50}$ values ranged from 1.911 to 18.192 μg mL^{-1} (**Table 2**), and

347   compound **23** presented much better fungicidal activities than azoxystrobin (**Table 1** and **Table 2**,

348   EC$_{50}$ values distributed between 5.268 and 147.136 μg mL^{-1}). When the carbon atom of alkyl group

349   on phenyl ring replaced with nitrogen atom, the fungicidal activities of target compounds such as

350   compound **24** (4-dimethylamino) and **32** (4-morpholinyl) decreased significantly in comparison

351   with compound **21** (4-*iso*-propyl), and C-N bond decomposition in the fungi may be responsible for

352   the lower fungicidal activity. Furthermore, it was found that the replacement of *tert*-butyl group

353   (compound **23**) with an electron-withdrawing group (2-cyanopropan-2-yl group, compound **25**) on

354   the phenyl ring led to a sharp decrease in the antifungal activity, and the introduction of

355   trifluoromethyl group on the phenyl ring (compound **28**) could enhance the fungicidal activity by

356   comparing with compound **26** (3-CH$_3$). Thirdly, meta-position di-substituted groups on the phenyl

357   ring enhanced the fungicidal activity significantly, for instance, the fungicidal activities of

358   compounds **29** (3,5-di-CH$_3$) and **30** (3,5-di-Cl) were superior to compound **26** (3-CH$_3$) and **14** (3-

359   Cl). Moreover, compound **31** (3,5-di-Cl-4-CH$_3$) showed excellent and broad-spectrum antifungal

360   activity, which proved that the combination of chlorine atom and alkyl group contributed to the

361   improvement of antifungal activity. Both the para and meta-alkyl substitutions were favorable for

362   antifungal activity, so the indane (compound **33**) and 9,9-dimethylfluorene (compound **34**) groups

363   were introduced to the molecules and both compounds presented good antifungal activity (**Table 1**

364   and **Table 2**). The antifungal acitivities of compounds **23** and **35** showed that the insertion of a

365   methylene group between the benzene ring and the pyridinone ring reduced the antifungal activity,

366   and which proved that phenyl ring and the pyridinone ring conjugation was important to the

367   antifungal activity. Finally, the hydroxyl and methyl substituents on the pyridinone ring were critical

368   to fungicidal activity, for instance, the fungicidal activities of compounds **36**, **37** and **38** decreased

369   sharply in comparison with compound **23** (**Table 1**).

370   ***In vitro* antibacterial activity.** Since compounds **22** and **23** have excellent antifungal activity, their

371   antibacterial activity continued to be studied. Compounds **22** and **23** exhibited excellent *in vitro*

372   antibacterial activity (84.54% and 83.93% respectively) against *Xoo* at concentration of 100 μg mL^{-1},

373   which was comparable to zhongshengmycin (86.09%). The corresponding EC$_{50}$ values of

374   compounds **22** and **23** were 29.567 μg mL^{-1} and 26.398 μg mL^{-1} (**Table 3**).

375   ***In vivo* antifungal activities of compound 23.**

376   *Potted plant experiment*

377   In order to further investigate the potential antifungal activities *in vivo* of compound **23**, the *in*

378   *vivo* protective activity on potted plant were carried out. The bioassay results showed that compound

379   **23** could control plant fungal diseases (*Corynespora cassiicola*, *Pseudoperonospora cubensis*,

380   *Fusarium graminearum*, *Rhizoctonia solani* and *Botrytis cinerea*) effectively (**Table 4**). Compound

381   **23** has an above 95% control effect against other plant pathogenic fungi except   *Rhizoctonia solani*

382   (control effect was 75%).

383   *Control effect of compound 23 against postharvest diseases of mango*

384   In view of compound **23** presented excellent *in vivo* protective activity against *Botryodiplodia*

385   *theobromae* and *Colletotrichum musae*, the efficacy of compound **23** to control postharvest diseases

386   of mango fruits were investigated. As shown in **Table 5**, on day 14, the control effect of compound

387   **23** (200 μg mL^{-1}) on postharvest diseases of mango was 87.91%, while azoxystrobin was only

388   28.57%. The mango treated with compound **23** showed no odor, and the taste was not different from

389   the control. Therefore, compound **23** had no effect on the quality of mango and prolonged the

390   storage time of mango fruits.

391   ***In vivo* antibacterial activity.** The data showed in **Table 6** indicated that compounds **22** and **23**

392   exerted a better *in vivo* curative activity (49.30% and 52.42%) and protective activity (50.37% and

393   52.70%) in controlling rice bacterial leaf blight at 200 μg mL^{-1} than zhongshengmycin (42.90%,

394   200 μg mL^{-1}).

395   **Preliminary action mode of compound 23 against *C. musae***

396   *Hyphae morphology observation*

397   From **Figure 2**, we can see that the hyphal in the control treatment was usually slippy and had

398   normal branches. The color and the endosome of hypha were evenly distributed. However, after 24

399   h treatment with compound **23** at 15 μg mL^{-1}, almost all hyphal of *C. musae* became coarser,

400   distorted and deformed.

401   *Transmission electron microscope analysis*

402   From **Figure 3**, we can find that the cell structure in control treatment is clear with complete

403   cell wall (CW) and plasma membrane (PM), uniform cytoplasm, mitochondria and other organelles

404   (panels a and c). Meanwhile, some cell structures treated with compound **23** were damaged, for

405   example folds in cell membranes, blurred and even disappeared mitochondria, the disintegrated

406   organelles in the cell and a large number of vesicles in the cytoplasm (panels d and f).

407   *Cell membrane permeability*

408   With the extension of treatment time, the relative seepage ratio of the cell membrane treated

409   with compound **23** (7.5, 15, 30 μg mL^{-1}) were much higher than the control treatment. For example,

410   treatments with compound **23** (7.5, 15, 30μg mL^{-1}) for 6 h, the relative permeability rates were

411   27.64%, 39.60% and 50.42% respectively, while control treatment was 17.38%. The results showed

412   that the cell membrane treated with compound **23** was destroyed quickly. This proved that the cell

413   membrane of *C. musae* was damaged by compound **23 (Figure 4A)**.

414   *Cellular oxygen content*

415   When *C. musae* was treated with compound **23** (7.5, 15, 30 μg mL^{-1}) and azoxystrobin (15 μg

416   mL^{-1}), the cellular oxygen content was shown in **Figure 4B**. Different concentrations of compound

417   **23** have different inhibition rates on the mycelium oxygen consumption of *C. musae* After 5 h

418   treatment, the inhibition rates of compound **23** (7.5, 15, 30 μg mL^{-1}) were 10.46%, 15.27% and

419   18.03%, the inhibition rates of azoxystrobin was 16.75%. Therefore there were no significant

420   difference between compound **23** (15 μg mL^{-1}) and azoxystrobin (15 μg mL^{-1}). The results proved

421   that compound **23** may interfere with the respiration of *C. musae* like azoxystrobin. What interesting

422   is that there are two natural products containing pyridone substructures named ilicicolin H and

423   funicolosin, which are proven inhibitors of complex III in the respiration chain[35-36].

424   *Soluble protein content*

425   From **Figure 4C**, the soluble protein content in mycelium of *C. musae* which was treated with

426   compound **23 (**7.5, 15 and 30 μg mL^{-1}) was higher than the control. After 24 h treatment, the soluble

427   protein content of treated were 1.145, 1.132 and 1.128 mg/mL, which were about 30% higher than

428   the control.*Mycelial reducing sugar content*

429   Throughout the experiment, the mycelial reducing sugar content in mycelium of *C. musae*

430   which was treated with compound **23** was lower than the control (**Figure 4D**). When the mycelium

431   of *C. musae* was treated with compound **23** (7.5, 15 and 30 μg mL^{-1}) for 24 h, the contents were

432   15.57%, 7.55%, and 9.91% lower than the control.

433   In summary, a series of *N*-aryl-pyridine-4-ones were designed and synthesized, and then their

434   fungicidal, bactericidal activities and preliminary action mechanism against *C. musae* were

435   investigated. The results showed that compound **23** displayed significant fungicidal activity *in vitro*

436   and *in vivo*. In addition, this study also found that compounds **22** and **23** can effectively control rice

437   bacterial leaf blight. The preliminary action mechanism investigation indicated that compound **23**

438   exerted its fungicidal activity through two ways. On the one hand, compound **23** may attack on the

439   mycelium cell membranes of *C. musae* and affected their relative permeability. On the other hand,

440   compound **23** may attack on the mitochondria of *C. musae* and affected its respiratory pathways. In

441   addition, hyphal respiratory oxygen consumption was not significantly associated with mycelial

442   growth. The dependence of hyphae on vegetative growth and respiration is weak. Therefore, the

443   author speculates that in addition to the energy metabolism of fungi, compound **23** may also affect

444   other aspects (such as soluble protein content and reducing sugar content) of fungal metabolism,

445   and further research is needed on this aspect. These findings indicated that this series of *N*-aryl-

446   pyridine-4-ones can be used to develop as potential agrochemical fungicides and bactericides. In

447   addition, toxicity studies and action site of compound **23** need to go further approach.

448   **ACKNOWLEGEMENT**

452   **SUPPORTING INFORMATION**

453   The Supporting Information is available free of charge at https://pubs.acs.org/doi/ XXXX.

454   HRMS, ^{1}H NMR and ^{13}C NMR spectra for the target compounds **6-38**, EC_{50} values of target

455   compounds **21-23**, **27** and **30-35**   against phytopathogens, detailed bio-assay methods and *in vivo*

456   fungicidal effect pictures of compound **23**.

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559

560   **Table 1.** *In vitro* fungicidal activity data of target compounds at 50 μg mL^{-1}

Compound	inhibition rate (%)								
	B.T[a]	*F.G*	*N.D*	*P.O*	*F.O*	*C.M*	*P.C*	*B.C*	*S.S*
6	35.5±0.2	24.0±0.1	26.3±0.2	29.0±0.3	12.1±0.7	11.0±0.4	32.3±0.5	25.5±0.1	15.4±0.2
7	37.1±0.7	36.1±0.4	39.4±0.1	32.5±0.2	14.9±0.5	24.9±0.5	33.7±0.8	39.6±0.3	25.7±0.6
8	40.0±0.6	45.3±0.2	40.4±0.3	69.7±0.2	39.7±0.0	30.2±0.4	52.0±0.4	42.1±0.2	36.6±0.2
9	44.2±0.1	10.8±0.2	10.8±0.1	7.9±0.6	10.9±0.4	79.9±0.7	20.2±0.4	19.3±0.5	21.3±0.7
10	65.5±0.1	8.4±1.1	9.2±0.7	11.1±0.4	8.8±0.5	80.0±0.6	29.4±0.9	29.0±0.9	6.3±1.2
11	14.3±0.8	26.9±0.8	11.2±0.2	21.9±0.7	25.2±0.1	34.5±0.4	37.9±0.7	22.9±0.8	31.8±0.9
12	49.6±0.5	36.4±0.5	16.5±0.2	25.8±1.2	36.4±0.9	38.3±0.8	47.9±0.6	31.2±0.6	33.1±0.9
13	48.5±0.7	21.2±0.8	14.2±0.5	16.4±0.5	29.0±0.3	34.6±0.4	38.2±0.3	17.0±0.4	17.0±0.2
14	60.3±0.6	100±0.0	73.0±0.7	41.0±0.4	100±0.0	54.5±0.4	72.5±0.4	54.9±0.7	24.6±0.4
15	30.2±0.8	51.5±0.8	21.8±0.8	32.8±0.7	35.5±0.2	48.6±0.2	43.7±0.4	48.2±0.4	23.5±0.7
16	25.9±0.2	17.5±0.2	4.9±0.4	15.2±0.5	22.4±0.5	45.9±0.4	37.6±0.6	14.3±0.7	19.0±0.8
17	33.1±0.3	21.6±0.2	10.2±0.1	18.7±0.7	25.3±0.5	68.9±0.5	45.8±0.8	18.1±0.8	21.4±0.2
18	68.1±0.6	25.5±0.7	30.8±0.3	28.4±0.4	42.5±0.7	49.2±0.0	48.3±0.2	27.4±0.2	38.2±0.2
19	89.6±0.7	31.2±0.7	63.1±0.2	67.3±0.1	100±0.0	75.0±0.6	53.7±0.9	23.6±0.6	71.7±0.6
20	100±0.0	47.2±0.3	74.2±0.6	80.9±0.6	100±0.0	79.8±0.4	60.3±0.7	27.5±0.4	78.6±0.1
21	100±0.0	78.0±0.2	91.4±0.8	88.6±0.8	100±0.0	82.8±0.5	100±0.0	70.9±0.3	73.8±0.2
22	100±0.0	70.9±0.7	82.5±0.7	100±0.0	100±0.0	100±0.0	84.8±0.3	75.2±0.8	100±0.0
23	100±0.0	100±0.0	94.0±0.3	100±0.0	100±0.0	99.0±0.3	100±0.0	95.0±0.4	100±0.0
24	30.9±0.7	14.2±0.8	13.3±0.9	28.0±0.9	63.4±0.8	20.2±0.8	42.8±0.8	21.9±0.7	9.5±0.2
25	40.6±0.1	23.5±0.3	1.6±0.3	9.1±0.4	15.9±0.5	10.0±0.4	44.6±0.5	6.3±0.3	6.5±0.8
26	45.5±0.5	29.6±0.2	38.1±0.8	13.8±0.3	67.2±0.7	44.9±0.5	61.3±0.5	21.0±0.5	35.4±0.4
27	86.5±0.4	78.5±0.7	100±0.0	69.2±0.3	100±0.0	100±0.0	78.5±0.6	85.9±0.2	83.6±0.6
28	47.7±0.4	80.3±0.8	40.4±0.4	15.9±0.1	74.1±0.7	86.5±0.8	74.8±0.7	49.7±0.5	47.6±0.4
29	66.1±0.1	73.7±0.1	77.9±0.7	70.1±0.1	100±0.0	84.0±0.5	68.8±0.5	58.6±0.6	79.9±0.8
30	64.3±0.4	100±0.0	76.1±0.8	53.6±0.5	100±0.0	55.5±0.4	100±0.0	71.9±0.7	70.0±0.7
31	82.5±0.8	100±0.0	100±0.0	100±0.0	100±0.0	100±0.0	100±0.0	79.3±0.7	76.8±0.8
32	20.7±0.4	23.7±0.4	48.8±0.7	11.0±0.1	10.5±0.1	9.6±0.1	35.7±0.7	9.8±0.5	14.1±0.5
33	100±0.0	100±0.0	79.8±0.6	63.3±0.6	100±0.0	66.4±0.6	100±0.0	78.4±0.4	76.2±0.4
34	84.1±0.8	100±0.0	86.1±0.8	40.1±0.4	49.3±0.1	75.4±0.5	49.5±0.3	80.5±0.4	100±0.0
35	82.5±0.8	100±0.0	87.0±0.2	100±0.0	100±0.0	100±0.0	60.0±0.6	72.8±0.8	68.9±0.2
36	67.0±0.6	21.7±0.2	46.8±0.6	18.5±0.1	17.9±0.1	100±0.0	55.4±0.5	32.0±0.6	37.4±0.3
37	69.4±0.6	23.8±0.2	75.1±0.6	65.1±0.6	60.4±0.6	65.6±0.4	49.7±0.4	44.5±0.5	60.3±0.5
38	30.6±0.7	29.1±0.7	6.2±0.0	12.2±0.4	55.8±0.5	68.5±0.5	47.9±0.4	40.6±0.4	33.3±0.2
2(maltol)	30.4±0.7	14.1±0.9	16.6±0.9	7.0±0.6	39.0±0.2	13.3±0.1	23.7±0.2	17.2±0.1	14.6±0.8
Azoxystrobin	43.6±0.4	68.0±0.2	68.3±0.2	59.0±0.5	70.0±0.8	51.1±0.8	69.0±0.3	33.0±0.3	95.0±0.5

561   [a] ***B.T***: *Botryodiplodia theobromae;* ***F.G***: *Fusarium graminearum;* ***N.D***: *Neoscytalidium dimidiatum;* ***P.O***:

562   *Pyricularia oryae;* ***F.O***: *Fusarium oxysporum;* ***C.M***: *Colletotrichum musae;* ***P.C***: *Phytophthora capsici;* ***B.C***:

563   *Botrytis cinerea;* ***S.S***: *Sclerotinia sclerotiorum.*

564   **Table 2.** EC_{50} value of target compounds against plant pathogenic fungi

Compound	EC_{50} (μg mL^{-1})								
	B.T[a]	**F.G**	**N.D**	**P.O**	**F.O**	**C.M**	**P.C**	**B.C**	**S.S**
21	2.749	25.433	11.473	14.113	18.160	13.038	16.588	24.871	8.051
22	3.601	26.183	5.479	12.214	12.542	14.487	21.617	19.617	11.058
23	1.911	18.192	3.928	9.984	14.554	12.840	10.781	12.783	6.977
27	12.549	21.644	8.154	14.596	8.604	13.846	18.637	8.534	17.299
30	44.376	17.046	35.106	43.893	16.583	43.338	24.242	15.571	14.995
31	6.858	8.942	6.601	17.694	4.210	9.533	21.427	10.888	15.078
33	19.200	23.738	13.187	20.207	10.824	14.882	32.147	20.465	21.135
34	6.581	18.215	10.065	62.095	51.987	1.181	50.537	40.454	16.293
35	22.238	31.755	19.755	15.351	10.054	22.040	46.558	18.454	20.825
Azoxystrobin	147.136	5.268	18.946	17.897	11.830	52.509	18.807	102.728	11.497

565   [a] **B.T**: *Botryodiplodia theobromae*; **F.G**: *Fusarium graminearum*; **N.D**: *Neoscytalidium dimidiatum*; **P.O**:

566   *Pyricularia oryae*; **F.O**: *Fusarium oxysporum*; **C.M**: *Colletotrichum musae*; **P.C**: *Phytophthora capsici*; **B.C**:

567   *Botrytis cinerea*; **S.S**: *Sclerotinia sclerotiorum*.

568

569

570   **Table 3.** *In vitro* antibacterial activity of compounds against *Xanthomonas oryzae* pv. *oryzae*

treatment	inhibition rate (%) (100 μg mL^{-1})	EC_{50} (μg mL^{-1})	toxic regression eq	R^2
Compound **22**	84.54±0.41	29.567	y=-5.25+3.54x	0.992
Compound **23**	83.93±0.27	26.398	y=-4.90+3.42x	0.976
Zhongshengmycin	86.09±0.52	14.496	y=-3.03+2.56x	0.957

571

572

573   **Table 4.** Potted plant experiment of compound **23** (% Control) (400 μg mL^{-1})

Compound	**C.C**[a]	**P.C**	**F.G**	**R.S**	**B.C**
23	98±1	100±0	98±1	75±3	95±3

574   **C.C**: *Corynespora cassiicola*; **P.C**: *Pseudoperonospora cubensis*; **F.G**: *Fusarium graminearum*; **R.S**: *Rhizoctonia*

575   *solani*; **B.C**: *Botrytis cinerea*.

576

577

578 **Table 5.** Control effect of compound **23** against postharvest diseases of mango (Day 14)

treatment	concentration (μg mL^{-1})	protective effect	
		disease index[a] ($\pm$SE)	control efficacy (%)
Compound **23**	200	8.15$\pm$0.18Aa[b]	87.91
Azoxystrobin	200	48.15$\pm$0.06Bb	28.57
Control	0	67.41$\pm$0.70Cc	

579 [a] Values are the average of 3 replicates. [b] 'A' means the difference is significant at the 0.01 level; 'a' means the

580 difference is significant at the 0.05 level.

581

582

583 **Table 6.** *In vivo* control effect of compounds against rice bacterial leaf blight (200 μg mL^{-1})

treatment	14 days after processing					
	curative effect			protection effect		
	morbidity (%)	disease index ($\pm$SE)[a]	control efficiency (%)	morbidity (%)	disease index ($\pm$SE)	control efficiency (%)
Compound **22**	100	38.24$\pm$1.29Bb[b]	49.30	100	36.44$\pm$0.75Bb	50.37
Compound **23**	100	35.89$\pm$0.37Aa	52.42	100	34.73$\pm$0.52Aa	52.70
Zhongshengmycin	100	43.07$\pm$0.65Cc	42.90	100	43.47$\pm$0.60Cc	40.80
Control	100	75.43$\pm$1.60Dd		100	73.43$\pm$0.65Dd	

584 [a] Values are the average of 5 replicates. [b] 'A' means the difference is significant at the 0.01 level; 'a' means the

585 difference is significant at the 0.05 level.

586   **FIGURE CAPTIONS**

587   **Scheme 1.** General synthetic route for compounds **6-38**

588   **Figure 1.** Design strategies of target pyridinone derivatives

589   **Figure 2.** Microphotograph of the hyphal morphology of *C. musae* treated with compound **23** (200×)

590   **Figure 3.** Transmission electron micrographs of *C. musae* hyphae in (a-c) control and treatment (d-f)

591   containing 15 μg mL^{-1} of compound **23**: cell walls (CW), plasma membrane (PM), and nucleus (N);

592   mitochondria (M).

593   **Figure 4.** Effect of compound **23** on the intracellular levels of relative seepage ratio (**A**), dissolved

594   oxygen (**B**), soluble protein (**C**), and reducing sugar (**D**) of *C. musae* hyphae

(1) S:H$_2$O,reflux,10h

or (2) R:HCl,S:H$_2$O,S:C$_2$H$_5$OH,160 °C,in autoclave,12h

2-5

6-38
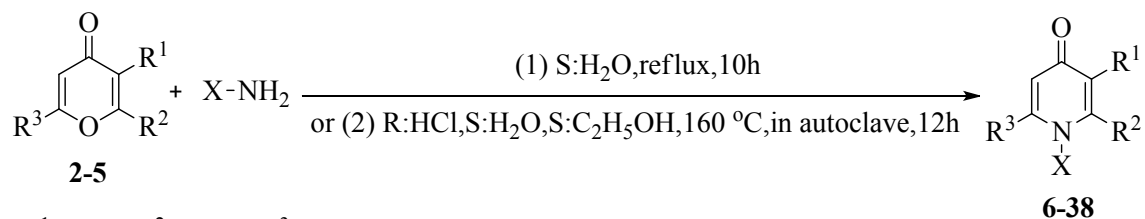
2. R^1 = OH, R^2 = CH$_3$, R^3 = H

3. R^1 = OCH$_3$, R^2 = CH$_3$, R^3 = H

4. R^1 = OH, R^2 = C$_2$H$_5$, R^3 = H

5. R^1 = H, R^2 = CH$_3$, R^3 = CH$_3$

6. R^1 = OH, R^2 = CH$_3$, R^3 = H, X = H

7. R^1 = OH, R^2 = CH$_3$, R^3 = H, X = CH$_3$

8-35. R^1 = OH, R^2 = CH$_3$, R^3 = H,

X =

8   **9**   **10**   **11**   **12**   **13**

14   **15**   **16**   **17**   **18**   **19**

20   **21**   **22**   **23**   **24**   **25**

26   **27**   **28**   **29**   **30**   **31**

32   **33**   **34**   **35**
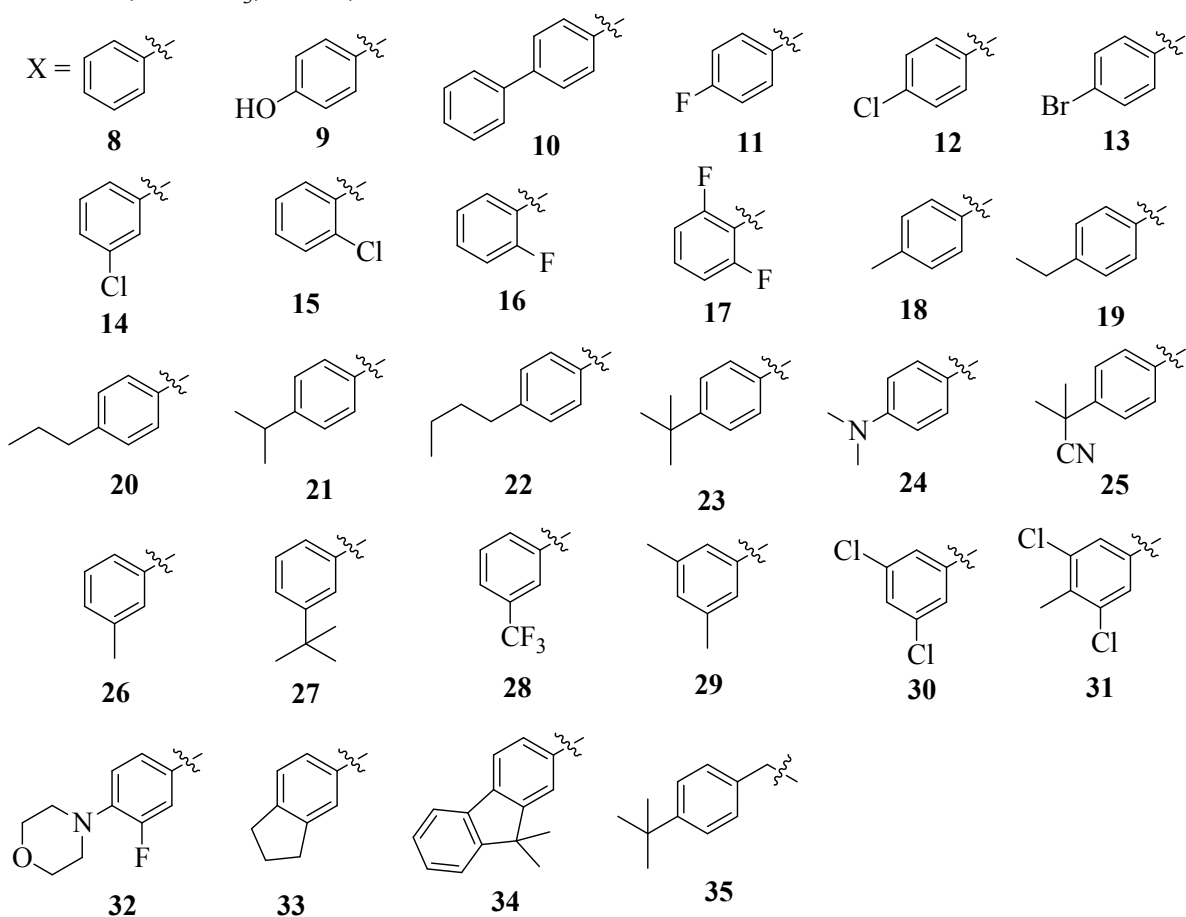
36. R^1 = OCH$_3$, R^2 = CH$_3$, R^3 = H   **37.** R^1 = OH, R^2 = C$_2$H$_5$, R^3 = H   **38.** R^1 = H, R^2 = CH$_3$, R^3 = CH$_3$
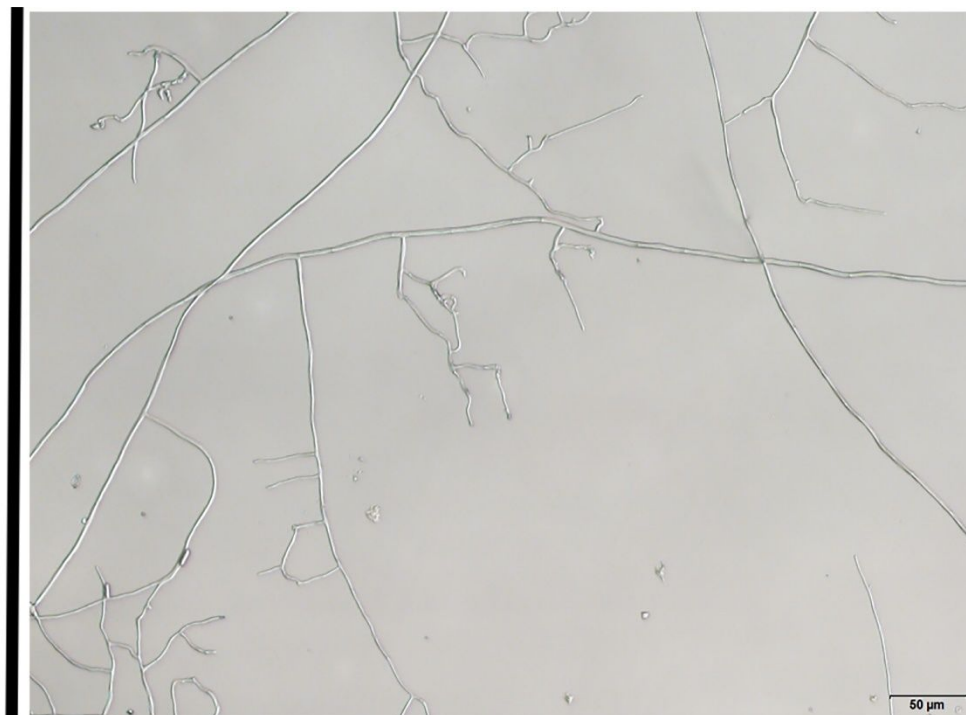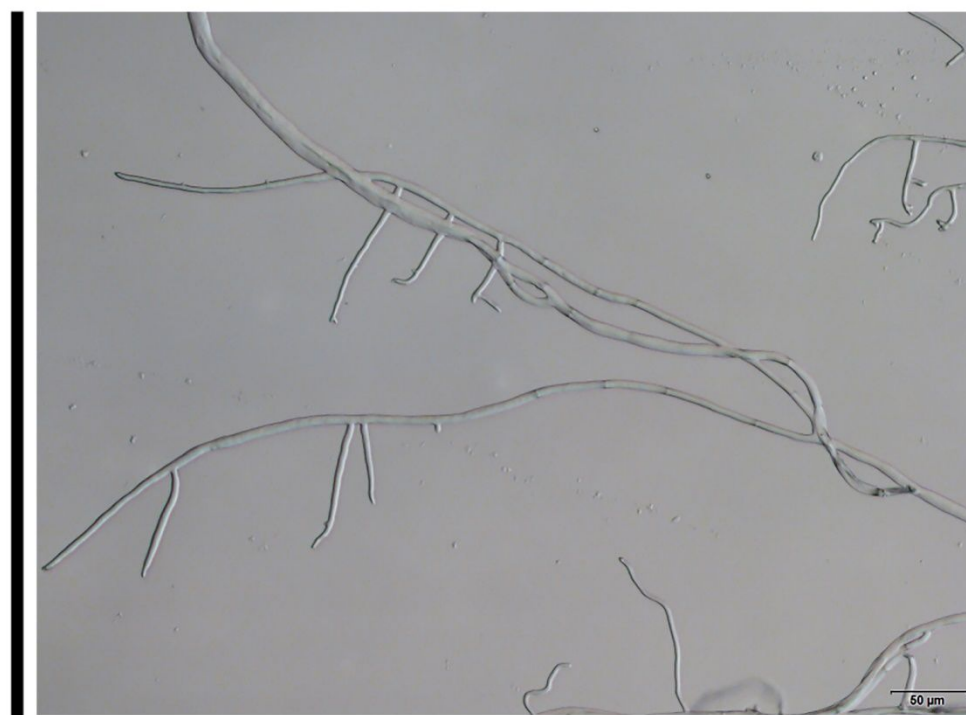
X =   X =   X =
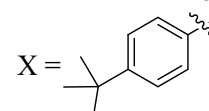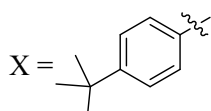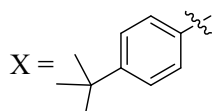
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596   **Scheme 1.** General synthetic route for compounds **6-38**
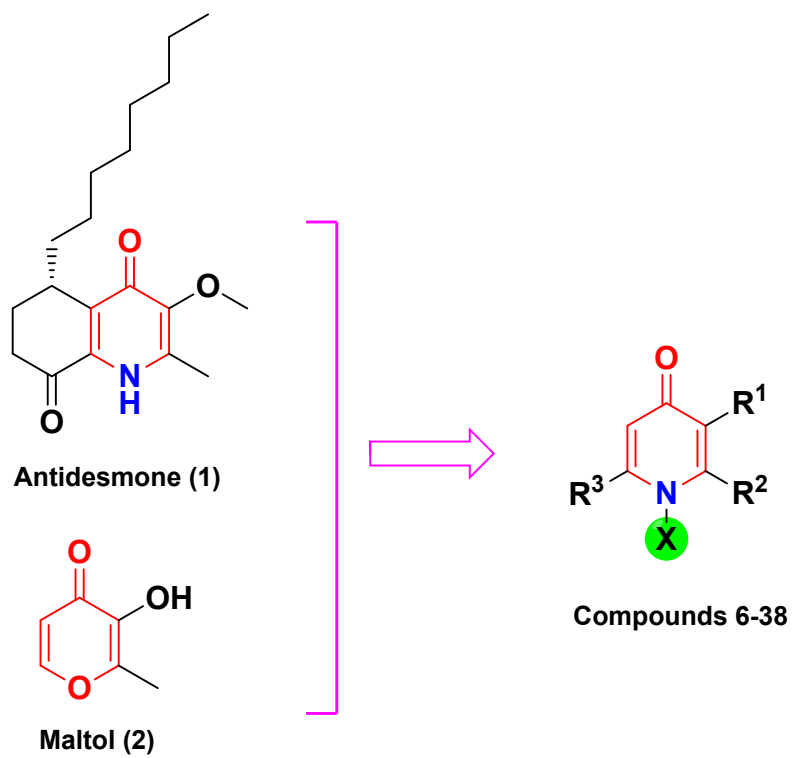
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598
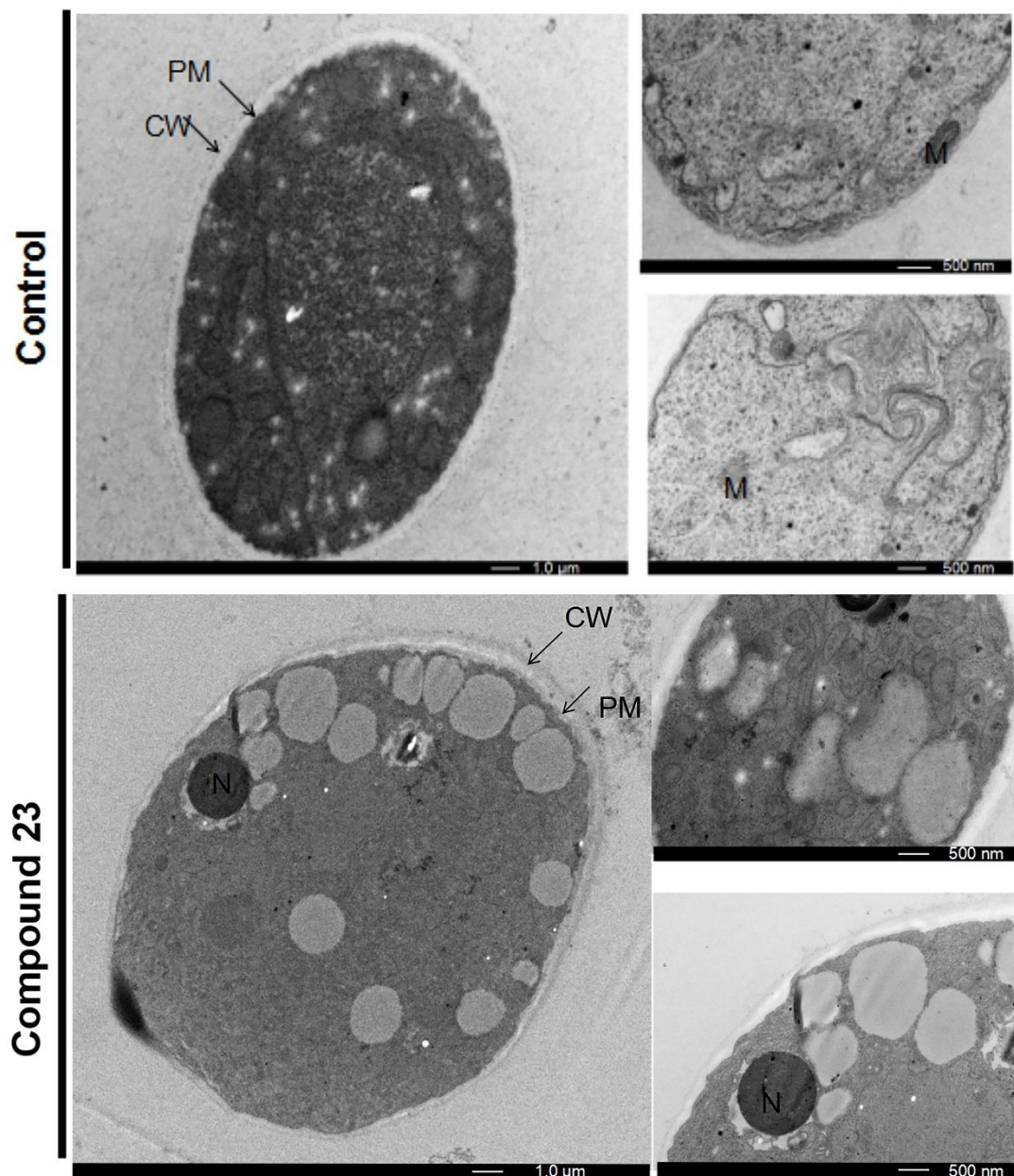
599 **Figure 1.** Design strategies of target pyridinone derivatives
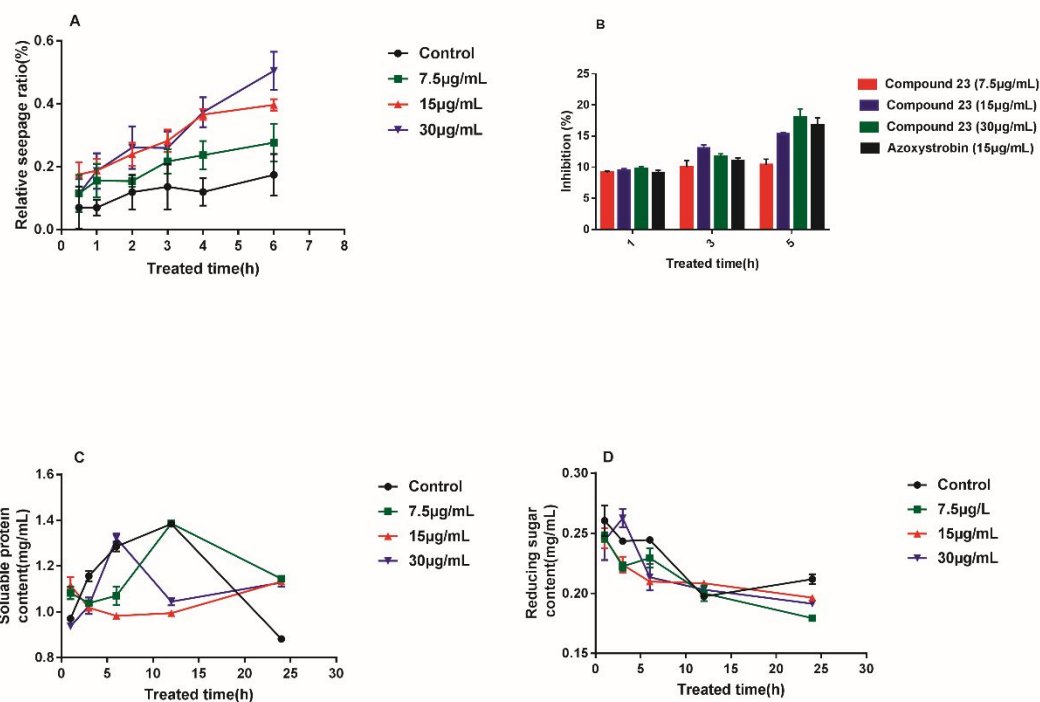
Figure 2. Microphotograph of the hyphal morphology of *C. musae* treated with compound **23** (200×)

Figure 3. Transmission electron micrographs of *C. musae* hyphae in (a-c) control and treatment (d-f) containing 15 μg mL^{-1} of compound **23**: cell walls (CW), plasma membrane (PM), and nucleus (N); mitochondria (M).
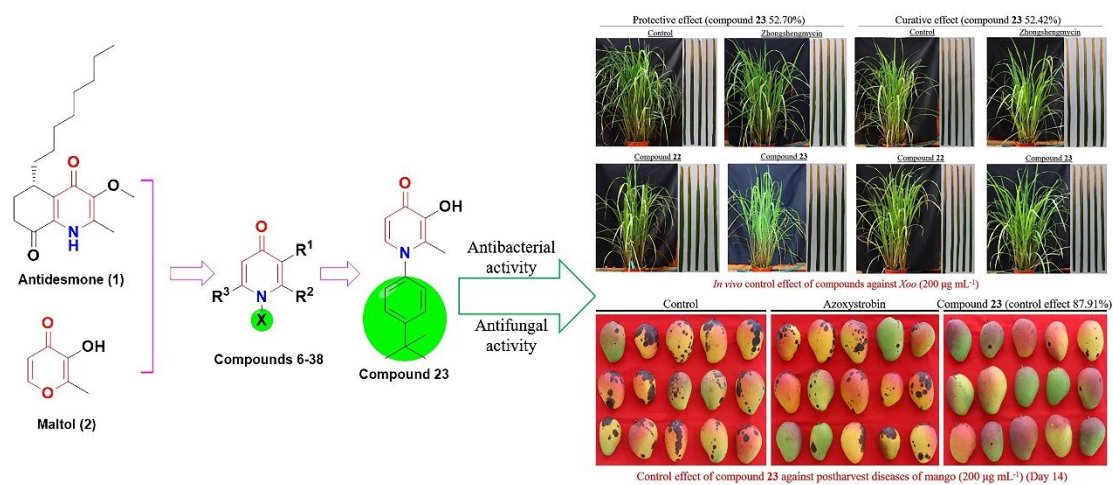
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Figure 4. Effect of compound **23** on the intracellular levels of relative seepage ratio (**A**), dissolved
oxygen (**B**), soluble protein (**C**), and reducing sugar (**D**) of *C. musae* hyphae. Results are presented
as the mean ± SD (n=3). Data at the same time point with different superscripts indicate significant
difference ($P<0.05$).

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TOC graphic

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