Inhibition of Tobacco Bacterial Wilt with Sulfone Derivatives Containing 1, 3, 4-Oxadiazole Moiety

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Supporting Information

1 General Information: The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in KBr disk. ^{1}H, and ^{13}C NMR (solvent $CDCl_3$ or Acetone-d_6 or DMSO-d_6) spectral analyses were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet, Splitting patterns that could not be easily interpreted were designated as multiplet (m) or broad (br). Elemental analysis was performed on an Elementar Vario-III CHN analyzer.

Analytical TLC was performed on silica gel GF_{254}. Column chromatographic purification was carried out using silica gel. Commercial reagents were used as received, unless otherwise indicated. Reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. DCM was freshly distilled from CaH_2.

2 Synthesis of the Intermediates 1-3: Starting from the carboxylic acids, following the reported method (*1-2*), intermediates **3** were synthesized in three steps employing esterification, hydrazidation, and cyclization. Specifically, intermediates **3** (2-thiol-5-substituted-1, 3, 4-oxadiazole) were prepared by the reaction of intermediates **2** (substitutedphenylhydride), potassium hydroxide, and carbon disulfide in ethanol under reflux condition. Intermediates **2** were synthesized from intermediates **1** and hydrazine hydrate in methanol under reflux condition. Intermediates **1** (substituted benzoic acid ester) were made through esterification reactions from starting material acids.

3 General Procedure for the Preparation of the Intermediates 4: To a solution of 2-thiol-5-substituted-1, 3, 4-oxadiazole **3** (2 mmol) and sodium hydroxide (0.08 g, 2 mmol) in water (20 mL), dimethyl sulfate(0.32 g, 2.5 mmol)/diethyl sulfate(0.38 g, 2.5 mmol) was added dropwisely. After stirred for 5 h at room temperature (20 ˚C-23 ˚C), for solid products, the precipitate was filtered off, washed with 5% Na_2CO_3 solution and distilled water, dried and recrystallized from ethanol to afford corresponding solid products **4**; for liquid products, 5% Na_2CO_3 solution was added into the reaction mixture, and then extracted with ethyl ether (4 × 20 mL), the ethyl ether layer was dried with anhydrous Na_2SO_4, after removal of the organic solvent under reduced pressure, oil products **4** were obtained.

Characterization of the intermediates **4**

2-(methylthio)-5-(3-nitro-4-chlorophenyl)-1, 3, 4-oxadiazole (4a). Yield 86.5%; white solid; mp 76-78 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.89-7.42 (m, 3 H, phenyl-H), 2.73 (s, 3 H, SCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.3, 161.0, 145.4, 141.3, 133.3, 131.2, 129.4, 122.7 14.7; Anal. Calcd. for $C_9H_6ClN_3O_3S$: C 39.79, H 2.23, N 15.47; found: C 39.41, H 2.48, N 15.05.

2-(ethylthio)-5-(3-nitro-4-chlorophenyl)-1, 3, 4-oxadiazole (4'a). Yield 81.5%; white solid; mp 137-139˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.59-8.13 (m, 3 H, ArH), 4.31 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.51 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

2-(methylthio)-5-(3, 4-dimethoxyphenyl)-1, 3, 4-oxadiazole (4b). Yield 76.3%; oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.57-6.93 (m, 3 H, phenyl-H), 3.96 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 2.77 (s, 3 H, SCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.8, 164.4, 151.9, 149.3, 120.2, 116.3, 111.1, 109.1, 56.2, 56.1, 14.7; Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C 52.37, H 4.79, N 11.10; found: C 52.71, H 4.63, N 11.38.

2-(ethylthio)-5-(3, 4-dimethoxyphenyl)-1, 3, 4-oxadiazole (4'b). Yield 77.2%; oil; 7.82-7.24 (m, 3 H, phenyl-H), 3.93 (s, 6 H, 2 OCH_3), 3.61 (q, *J* = 7.45 Hz, 2 H, CH_2CH_3), 1.53(t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

2-(ethylthio)-5-phenyl-1, 3, 4-oxadiazole (4'c). Yield 84.5%; oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.89-7.27 (m, 5 H, phenyl-H), 4.34 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.52 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.7, 164.4, 131.7, 129.4, 129.1, 126.7, 27.1, 14.8.

2-(methylthio)-5-(3, 4-difluorophenyl)-1, 3, 4-oxadiazole (4d). Yield 85.3%; oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.54-7.07 (m, 3 H, phenyl-H), 2.78 (s, 3 H, SCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 166.6, 161.8, 134.3, 133.7, 129.4, 112.4, 111.7, 102.3, 14.6; Anal. Calcd. for $C_9H_6F_2N_2OS$: C 47.37, H 2.65, N 12.27; found: C 47.70, H 2.13, N 12.51.

2-(ethylthio)-5-(3, 4-difluorophenyl)-1, 3, 4-oxadiazole (4'd). Yield 85.5%; oil; 7.53-7.07 (m, 3 H, phenyl-H), 4.33 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.53 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

2-(methylthio)-5-(4-chlorobenzyl)-1, 3, 4-oxadiazole (4e). Yield 90.2%; white solid; mp 32-34 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.32-7.22 (m, 4 H, benzyl-H), 4.13 (s, 2 H, CH_2), 2.68 (s, 3 H, SCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.9, 165.8, 133.7, 132.1, 130.4, 130.2, 129.3, 129.1, 31.3, 14.6.

2-(ethylthio)-5-(4-chlorobenzyl)-1, 3, 4-oxadiazole (4'e). Yield 90.2%; white solid; mp 43-45 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.32-7.23 (m, 4 H, benzyl-H), 4.35 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 4.13 (s, 2 H, CH_2), 1.45 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3).

2-(methylthio)-5-(2-bromophenyl)-1, 3, 4-oxadiazole (4f). Yield 85.3%; oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.81-7.44 (m, 4 H, phenyl-H), 3.03(s, 3 H, SCH_3)

2-(ethylthio)-5-(4-methylphenyl)-1, 3, 4-oxadiazole (4'g). Yield 86.1%; white solid; mp 35-37

˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.86-7.26 (m, 4 H, phenyl-H), 4.31 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.53 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

2-(ethylthio)-5-(2, 4-difluorophenyl)-1, 3, 4-oxadiazole (4'h). Yield 83.2%; mp 35-37 ˚C; 7.84-7.27 (m, 3 H, phenyl-H), 4.34 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.57 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

2-(ethylthio)-5-(3-fluorophenyl)-1, 3, 4-oxadiazole (4'i). Yield 76.5%; white solid; mp 45-47 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.83-7.24 (m, 4 H, phenyl-H), 4.45 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.55 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

2-(ethylthio)-5-(4-fluorophenyl)-1, 3, 4-oxadiazole (4'j). Yield 84.7%; white solid; mp 37-38 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.73-7.65 (m, 3 H, phenyl-H), 4.31 (q, *J* = 6.85 Hz, 2 H, CH_2CH_3), 1.51 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3).

4 General Procedure for the Preparation of the Title Compounds 5.

A solution of 2-(methylthio/ethylthio)-5-substituted-1, 3, 4-oxadiazole **4** (3.83 mmol) in glacial acetic acid (10 mL) was treated dropwise at 10 ˚C with potassium permanganate (0.78 g, 4.98 mmol) as a 5% aqueous solution over 0.5 h. The reaction was allowed to proceed for an additional 0.5 h, 40% sodium hydrogen sulphite aqueous solution was subsequently added until the mixture was decolorized, and diluted with 50 mL water. The product was filtered and recrystallized from ethanol give the title compounds **5**.

Characterization of Compounds **5**

2-(methylsulfonyl)-5-(3-nitro-4-chlorophenyl)-1, 3, 4-oxadiazole (5a). Yield 79.9%; white solid; mp 131-132 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.35-8.04 (m, 3 H, ArH), 3.45 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.7, 161.0, 145.4, 130.3, 126.6, 125.4, 120.2, 111.3, 40.1; IR (KBr, cm^{-1}) *v:* 3030, 2981, 1616, 1575, 1558, 1373, 1130; Anal. Calcd. for $C_9H_6ClN_3O_5S$: C 35.60, H 1.99, N 13.84; found: C 35.45, H 2.04, N 13.95.

2-(ethylsulfonyl)-5-(3-nitro-4-chlorophenyl)-1, 3, 4-oxadiazole (5'a). Yield 79.2%; white solid, mp 121-123˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.41-7.91 (m, 3 H, ArH), 3.63 (q, *J* = 7.45 Hz, 2 H, CH_2), 1.54 (t, *J* = 7.45 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 161.7, 161.1, 145.3, 131.1, 126.0, 124.9, 120.2, 112.4, 50.1, 7.1; IR (KBr, cm^{-1}) *v:* 3043, 2971, 1601, 1575, 1558, 1353, 1131;

Anal. Calcd. for $C_{10}H_8ClN_3O_5S$: C 37.80, H 2.54, N 13.23; found: C 37.43, H 2.53, N 13.01.

2-(methylsulfonyl)-5-(3, 4-dimethoxyphenyl)-1, 3, 4-oxadiazole (5b). Yield 84.7%; white solid; mp 112-114 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.73-6.99 (m, 3 H, ArH), 3.98 (s, 6 H, 2 OCH_3), 3.53 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 166.7, 161.7, 153.4, 149.6, 121.8, 114.4, 111.3, 109.8, 56.3, 56.2, 43.0; IR (KBr, cm^{-1}) *v:* 3030, 2997, 2912, 1608, 1558, 1340, 1143; Anal. Calcd. for $C_{11}H_{12}N_2O_5S$: C 46.47, H 4.25, N 9.85; found: C 46.25, H 4.19, N 9.45.

2-(ethylsulfonyl)-5-(3, 4-dimethoxyphenyl)-1, 3, 4-oxadiazole (5'b). Yield 82.3%; white solid; mp 107-109˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.91-7.11 (m, 3H, ArH), 3.98 (s, 6 H, 2 OCH_3), 3.62 (q, *J* = 7.45 Hz, 2 H, CH_2CH_3), 1.57 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.1, 160.2, 149.7, 147.2, 121.0, 114.1, 110.7, 107.4, 56.4, 56.1, 51.0, 6.8; IR (KBr, cm^{-1}) *v:* 3037, 2987, 2912, 1608, 1558, 1347, 1153; Anal. Calcd. for $C_{12}H_{14}N_2O_5S$: C 48.31, H 4.73, N 9.39; found: C 48.01, H 4.44, N 9.08.

2-(ethylsulfonyl)-5-phenyl-1, 3, 4-oxadiazole (5'c). Yield 88.6%; white solid; mp.134-135˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.41-7.51 (m, 5 H, benzyl-H), 3.60 (q, *J* = 7.45 Hz, 2 H, CH_2CH_3) 1.48 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 167.1, 163.2, 137.5, 132.1, 130.7, 128.0, 50.4, 7.2; IR (KBr, cm^{-1}) *v:* 3043, 2933, 1616, 1558, 1351, 1137; Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C 50.43, H 4.23, N 11.76; found: C 50.31, H 3.98, N 12.01.

2-(methylsulfonyl)-5-(3, 4-difluorophenyl)-1, 3, 4-oxadiazole (5d). Yield 83.5%; white solid; mp 132-134 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.99-7.36 (m, 3 H, ArH), 3.53 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 164.9, 162.4, 124.8, 119.0, 118.9, 118.4, 117.4, 115.3, 43.0; IR (KBr, cm^{-1}) *v:* 3008, 2914, 1597, 1558, 1541, 1346, 1172; Anal. Calcd. for $C_9H_6F_2N_2O_3S$: C 41.54, H 2.32, N 10.77; found: C 41.88, H 2.61, N 10.43.

2-(ethylsulfonyl)-5-(3, 4-difluorophenyl)-1, 3, 4-oxadiazole (5'd). Yield 77.3%; white solid; mp 115-117˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.03-7.56 (m, 3 H, ArH), 3.62 (q, *J* = 7.45 Hz, 2 H, CH_2), 1.54 (t, *J* = 7.45 Hz, 3 H, CH_3); ^{13}C NMR(125 MHz, $CDCl_3$) *δ:* 163.9, 161.4, 124.4, 119.6, 118.7, 118.0, 117.2, 50.1, 6.8; IR (KBr, cm^{-1}) *v:* 3028, 2922, 1601, 1506, 1435, 1342, 1157; Anal. Calcd. for $C_{10}H_8F_2N_2O_3S$: C 43.80, H 2.94, N 10.21; found: C 43.67, H 2.89, N 10.61.

2-(methylsulfonyl)-5-(4-chlorobenzyl)-1, 3, 4-oxadiazole (5e). Yield 82.9%; white solid; mp 131-132 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.36-7.26 (m, 4 H, ArH), 4.27 (s, 2 H, CH_2), 3.44 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 167.4, 162.9, 134.3, 130.5, 130.4, 129.4, 42.9, 31.3; IR

(KBr, cm^{-1}) *v:* 3030, 2927, 1604, 1558, 1373, 1175; Anal. Calcd. for $C_{10}H_9ClN_2O_3S$: C 44.04, H 3.33, N 10.27; found: C 44.45, H 3.35, N 10.56.

2-(ethylsulfonyl)-5-(4-chlorobenzyl)-1, 3, 4-oxadiazole (5'e). Yield 85.3%; white solid; mp 125-126˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.35-7.26 (m, 4 H, ArH), 4.27 (s, 2 H, CH_2), 3.53(q, *J* = 7.45 Hz, 2 H, CH_2), 1.47 (t, *J* = 7.45 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 167.4, 162.1, 134.3, 130.6, 130.3, 129.4, 50.0, 31.3, 6.8; IR (KBr, cm^{-1}) *v:* 3057, 2928, 1601, 1558, 1345, 1153; Anal. Calcd. for $C_{11}H_{11}ClN_2O_3S$: C 46.08, H 3.87, N 9.77; found: C 46.15, H 3.72, N 9.43.

2-(methylsulfonyl)-5-(2-bromophenyl)-1, 3, 4-oxadiazole (5f). Yield 78.8%; white solid; mp 134-135 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.00-7.46 (m, 4 H, ArH), 3.54 (s, 3 H, CH_3);^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.5, 162.5, 135.0, 133.8, 132.2, 127.9, 123.5, 122.2, 43.0; IR (KBr, cm^{-1}) *v:* 3028, 2943, 1615 1557, 1516, 1443, 1373, 1155; Anal. Calcd. for $C_9H_7BrN_2O_3S$: C 35.66, H 2.33, N 9.24; found: C 35.87, H 2.44, N 9.61.

2-(ethylsulfonyl)-5-(4-methylphenyl)-1, 3, 4-oxadiazole (5'g). Yield 85.9%; white solid; mp 106-108˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.01-7.45 (m, 4 H, ArH), 3.67 (q, *J* = 7.45 Hz, 2 H, CH_2CH_3), 2.49 (s, 3 H, CH_3), 1.53 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 164.9, 161.9, 145.0, 131.2, 128.6, 120.2, 51.2, 21.8, 6.9; IR (KBr, cm^{-1}) *v:* 3010, 2924, 1616, 1558, 1506, 1489, 1340, 1153; Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C 52.37, H 4.79, N 11.10; found: C 52.14, H 4.61, N 11.34.

2-(ethylsulfonyl)-5-(2, 4-difluorophenyl)-1, 3, 4-oxadiazole (5'h). Yield 83.1%; white solid; mp 113-114˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.77-7.56 (m, 3 H, benzyl-H); 3.62 (q, *J* = 7.45 Hz, 2 H, CH_2CH_3), 1.51 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR(125 MHz, $CDCl_3$) *δ:* 167.3, 166.4, 139.9, 138.7, 131.4, 130.8, 127.8, 126.2, 50.3, 7.2; IR (KBr, cm^{-1}) *v:* 3013, 2981, 1597, 1561, 1457, 1407, 1357, 1153; Anal. Calcd. for $C_{10}H_8F_2N_2O_3S$: C 43.80, H 2.94, N 10.21; found: C 43.49, H 2.69, N 9.72.

2-(ethylsulfonyl)-5-(3-fluorophenyl)-1, 3, 4-oxadiazole (5'i). Yield 84.4%; white solid; mp 119–121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.14–7.50 (m, 4 H, ArH), 3.63 (q, *J* = 7.45 Hz, 2 H, CH_2CH_3), 1.55 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 165.5, 161.5, 135.7, 133.4, 130.8, 127.7, 125.9, 123.7, 50.1, 6.9; IR (KBr, cm^{-1}) *v:* 3031, 2973, 1517, 1555, 1473, 1351, 1143; Anal. Calcd. for $C_{10}H_9FN_2O_3S$: C 46.87, H 3.54, N 10.93; found: C 46.77, H 3.82, N 10.65.

2-(ethylsulfonyl)-5-(4-fluorophenyl)-1, 3, 4-oxadiazole(5'j). Yield 80.3%; white solid; mp 127-129˚C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 8.15-7.75 (m, 4 H, ArH), 3.53(q, *J* = 7.45 Hz, 2 H, CH_2CH_3), 1.47 (t, *J* = 7.45 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 167.4, 163.3, 135.3, 130.6, 131.3, 129.6, 50.3, 6.7; IR (KBr, cm^{-1}) *v:* 3038, 2913, 1605, 1557, 1357, 1153; Anal. Calcd. for $C_{10}H_9FN_2O_3S$: C 46.87, H 3.54, N 10.93; found: C 46.62, H 3.81, N 10.59.

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