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Synthesis and Antifungal Activity of Novel Sclerotiorin Analogues

Long Lin,[†,‡] Nick Mulholland,[‡,§] Qiong-You Wu,[†,‡] David Beattie,[§] Shao-Wei Huang,[†] Dianne Irwin,[§] John Clough,[§] Yu-Cheng Gu,*[,§] and Guang-Fu Yang*[,†]

[†]Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. China

[§]Syngenta Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, U.K.

ABSTRACT: Sclerotiorin **1**, first isolated from *Penicillium sclerotiorum*, has weak antifungal activity and belongs to the azaphilone-type family of natural products. Several series of sclerotiorin analogues were designed and synthesized with the aim of discovering novel fungicides with improved activity. The syntheses involved two key steps, cycloisomerization and then oxidation, and used a simple and efficient Sonogashira cross-coupling reaction to construct the required functionalized precursor. With sclerotiorin as a control, the activities of the newly synthesized analogues were evaluated against seven fungal pathogens, and several promising candidates (compounds $\mathbf{3a_1}$, $\mathbf{3d_2}$, $\mathbf{3e_2}$, $\mathbf{3f_2}$ and $\mathbf{3k_2}$) with greater activity and simpler structures than sclerotiorin were discovered. In addition, preliminary structure−activity relationships were studied, which revealed that not only the chlorine or bromine substituent at the 5-position of the nucleus but also the phenyl group at the 3-position and the substituent pattern on it contributed crucially to the observed antifungal activity. Analogues with a methyl substituent at the 1-position have reduced levels of activity, while those with a free hydroxyl group in place of acetoxy at the quaternary center of the bicyclic ring system retain activity.

KEYWORDS: *sclerotiorin, azaphilone, fungicides, natural product*

1. INTRODUCTION

Natural products are well-known as one of the key sources for lead discovery in agrochemical development. Natural products with novel scaffolds always afford an opportunity to discover novel antifungal agents that operate by modes of action different from those that are already known. Consequently, the resulting new agrochemicals have the opportunity to overcome resistance to chemicals currently in use. Notable examples of the successful utilization of natural products are strobilurin-type fungicides,[1] analogues of the naturally occurring β-methoxyacrylate strobilurin A, which are inhibitors of the cytochrome bc_1 complex.[2]

Sclerotiorin **1**, first isolated from *Penicillium sclerotiorum*,[3] belongs to the azaphilone-type family of natural products which share two common characteristics, a highly oxygenated bicyclic core and a quaternary center which breaks the aromaticity of the ring system. To date, over 170 different azaphilones have been identified.[4] They have been reported to exhibit a wide range of biological activities, such as inhibition of monoamine oxidase,[5] inhibition of the formation of the P53-MDM2 complex,[6] inhibition of the gp120-CD4 binding reaction,[7] and inhibition of fatty acid synthase,[8] as well as having antifungal activity.[9,10] Because of their broad spectrum biological properties, a number of studies aimed at the synthesis of racemic azaphilones have been reported.[11−14] In general, pyronoquinones[11] and pyrylium salts[12,13] have been used as precursors. Whalley and his co-workers reported the synthesis of the bicyclic core of sclerotioirin by cyclization and then oxidation of a suitable *o*-formyl-benzyl ketone.[12,13] Recently, Porco's group described an efficient gold-catalyzed cycloisomerization of *o*-alkynylbenzaldehydes into 2-benzopyrylium salts and subsequent IBX oxidation to form the azaphilone ring system.[15] In comparison to the earlier approaches, Porco's protocol achieved the target azaphilones in higher yield and in a shorter reaction time. In particular, this approach takes advantage of readily available alkynes to construct the *o*-alkynylbenzaldehydes and results in the formation of azaphilones with diverse side chains at the 3-position which, we realized, would allow us to investigate the effect of modifications at this position on the activity of sclerotiorin analogues. Till now, little attention has been paid to the structural optimization of the antifungal activity of the azaphilones. Therefore, we envisioned that sclerotiorin, which had preciously shown weak antifungal activity in Syngenta's screens, might be a lead for the discovery of novel agricultural fungicides.

Structurally, sclerotiorin features a nine-carbon aliphatic diene side chain and a bicyclic core in which aromaticity is interrupted by a chiral quaternary center. To simplify the structure of sclerotiorin, we first synthesized compounds **2**, **3**, and **4** (Figure 1) by replacement of the long aliphatic side chain with an aromatic ring. This modification may also be helpful in improving the photostability of sclerotiorin. In the meantime, compound **5** was designed to determine the importance of conjugation in the sclerotiorin scaffold. Thus, a methylene bridge is inserted in compound **5**, to break the conjugation between the bicyclic core and the side chain. In addition, compounds **6** were designed to get further insight into the structure−activity relationships. For all of these designed compounds, the bicyclic core of sclerotiorin was retained to mimic the natural parent structure. In all of the analogues described in this paper, the

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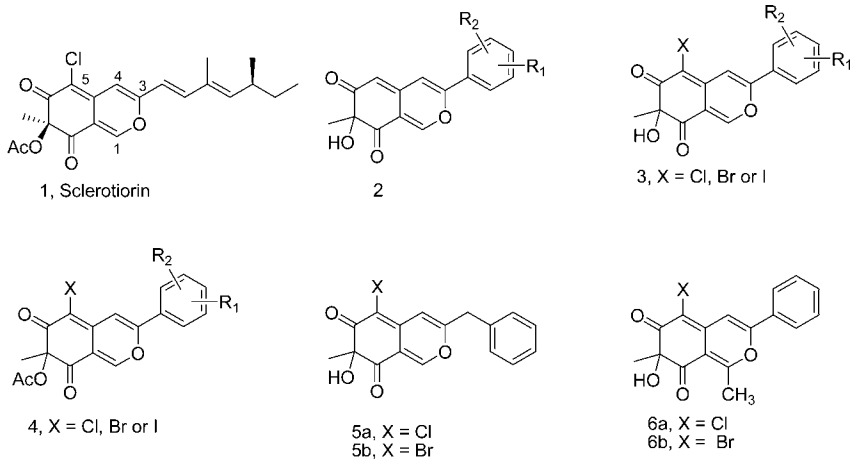


Figure 1. Sclerotiorin and the designed analogues.

absolute stereochemistry of the chiral center of the bicyclic system was ignored, and racemic compounds were prepared. Herein, we report the synthesis and characterization of these sclerotiorin analogues as well as an assessment of their antifungal activities.

MATERIALS AND METHODS

All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried and redistilled before use. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 600 spectrometer, and chemical shifts (δ) are given in ppm relative to tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 600 (150 MHz) spectrometer, and chemical shifts (δ) are given in ppm relative to the center line of a triplet at 77.0 ppm of chloroform-*d*. The following abbreviations are used to designate mutiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. HRMS were obtained on a Waters MALDI SYNAPT G2 HDMS equipped with an electrospray source (Milford, MA, USA).

General Procedure for the Preparation of 2-Alknylbenzaldehydes 9a–9s. An oven-dried two-necked flask was evacuated and backfilled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with 2-bromobenzaldehyde (500 mg, 2.16 mmol), $PdCl_2(PPh_3)_2$ (75.8 mg, 0.108 mmol, 5 mol %), and CuI (20.5 mg, 0.108 mmol, 5 mol %), followed by anhydrous DMF (20 mL) and Et_3N (654.5 mg, 6.48 mmol). The resulting suspension was stirred for 10 min, then the alkyne (2.37 mmol) was injected, and the reaction mixture was stirred at 60 °C for the indicated period of time. The resulting suspension was allowed to cool to room temperature and was then diluted with water (50 mL), neutralized with 0.1 N HCl, and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (3 × 100 mL) and brine (3 × 100 mL), dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

General Procedure for the Preparation of Azaphilones 2a–2s. To the alkynylbenzaldehyde **9** (0.5 mmol) and $AgNO_3$ (4.25 mg, 0.025 mmol) were added 2.0 mL of dichloroethane and 200 μL of trifluoroacetic acid, and the mixture was stirred at rt until TLC monitoring indicated the disappearance of the material **9** (5 min). To the resulting mixture were added *o*-iodoxybenzoic acid (IBX) (155 mg, 0.55 mmol) and tetrabutylammonium iodide (9.25 mg, 0.025 mmol), and the reaction mixture was stirred at rt for a further 1 h, then then quenched with saturated $Na_2S_2O_3$, and extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) afforded compounds **2a–2s**.

Data for ***2a***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.75 (d, J = 6.6 Hz 2H), 7.54–7.50 (m, 3H), 6.78 (s, 1H), 5.70 (s, 1H), 3.98 (br, 1H), 1.60 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 195.5, 157.3, 152.6, 143.8, 131.6, 130.0, 129.1, 125.6, 115.8, 106.8, 106.2, 83.5, 28.5. HRMS (MALDI): calcd for $C_{16}H_{12}O_4$ $[M + Na]^+$ 291.0633, found 291.0638.

Data for ***2b***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.70 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 6.67 (s, 1H), 5.66 (s, 1H), 3.97 (br, 1H), 3.89 (s, 3H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{14}O_5$ $[M + Na]^+$ 321.0739, found 321.0721.

Data for ***2c***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 5.68 (s, 1H), 3.97 (br, 1H), 2.43 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 195.6, 157.6, 152.6, 144.2, 142.4, 129.8, 127.3, 125.5, 115.8, 106.0, 105.8, 83.5, 28.6, 21.5. HRMS (MALDI): calcd for $C_{17}H_{14}O_4$ $[M + Na]^+$ 305.0790, found 305.0786.

Data for ***2d***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.79–7.75 (m, 2H), 7.22–7.17 (m, 2H), 6.75 (s, 1H), 5.70 (s, 1H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 195.4, 165.8, 163.3, 156.3, 152.4, 143.6, 127.8, 127.7, 126.3, 116.4, 116.2, 115.7, 106.5, 106.3, 83.5, 28.4. HRMS (MALDI): calcd for $C_{16}H_{11}FO_4$ $[M + Na]^+$ 309.0539, found 309.0545.

Data for ***2e***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 6.94 (s, 1H), 5.75 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 195.5, 155.0, 152.1, 142.5, 133.2, 132.5, 132.3, 125.7, 125.6, 124.1, 122.3, 115.6, 108.2, 107.3, 83.4, 27.8. HRMS (MALDI): calcd for $C_{17}H_{11}F_3O_4$ $[M + Na]^+$ 359.0507, found 359.0510.

Data for ***2f***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 5.69 (s, 1H), 3.97 (br, 1H), 1.60 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 195.6, 157.6, 155.5, 152.7, 144.1, 127.2, 126.1, 125.4, 115.8, 106.1, 105.8, 83.5, 35.0, 31.0, 28.6. HRMS (MALDI): calcd for $C_{20}H_{20}O_4$ $[M + Na]^+$ 347.1259, found 347.1265.

Data for ***2g***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, J = 8.4 Hz, 2H), 8.04 (s, 1H), 7.94 (d, J = 9.0 Hz, 2H), 6.92 (s, 1H), 5.78 (s, 1H), 1.61 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.8, 196.4, 153.1, 152.9, 148.4, 141.8, 136.1, 126.6, 124.2, 115.4, 110.1, 108.5, 83.0, 26.4. HRMS (MALDI): calcd for $C_{16}H_{11}NO_6$ $[M + Na]^+$ 336.0484, found 336.0455.

Data for ***2h***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 5.69 (s, 1H), 3.88 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 195.5, 159.9, 157.0, 152.6, 143.7, 131.3, 130.1, 117.9, 117.1, 115.7, 111.0, 107.0, 106.2, 83.5, 55.4, 28.4. HRMS (MALDI): calcd for $C_{17}H_{14}O_5$ $[M + Na]^+$ 321.0739, found 321.0701.

Data for ***2i***. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.68 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H),

7.38 (d, J = 7.8 Hz, 1H), 7.30 (s, 1H), 5.58 (s, 1H), 2.39 (s, 3H), 1.36 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{14}O_4$ $[M + Na]^+$ 305.0790, found 305.0776.

Data for ***2j***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.55−7.53 (m, 1H), 7.51−7.43 (m, 2H), 7.25−7.21 (m, 1H), 6.78 (s, 1H), 5.72 (s, 1H), 3.95 (br, 1H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 195.3, 164.1, 161.7, 155.8, 152.4, 143.2, 132.2, 132.1, 130.9, 130.8, 121.2, 118.6, 118.4, 115.8, 112.8, 112.5, 107.6, 106.9, 83.6, 28.4. HRMS (MALDI): calcd for $C_{16}H_{11}FO_4$ $[M + Na]^+$ 309.0539, found 309.0491.

Data for ***2k***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.73 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 6.78 (s, 1H), 5.72 (s, 1H), 3.93 (br, 1H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 195.3, 155.6, 152.4, 143.1, 135.3, 131.8, 131.5, 130.4, 125.6, 123.6, 115.8, 107.6, 106.9, 83.6, 28.4. HRMS (MALDI): calcd for $C_{16}H_{11}ClO_4$ $[M + Na]^+$ 325.0244, found 325.0223.

Data for ***2l***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.07 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 5.65 (s, 1H), 3.96 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.2, 195.8, 157.5, 154.4, 152.8, 144.5, 132.5, 128.4, 120.8, 118.9, 115.3, 111.6, 105.8, 83.4, 55.7, 55.6, 28.5. HRMS (MALDI): calcd for $C_{17}H_{14}O_5$ $[M + Na]^+$ 321.0739, found 321.0752.

Data for ***2m***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.43−7.41 (m, 2H), 7.31−7.30 (m, 2H), 6.43 (s, 1H), 5.65 (s, 1H), 3.96 (br, 1H), 2.44 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 195.6, 159.5, 152.7, 143.7, 136.6, 131.2, 130.9, 130.8, 128.9, 126.2, 115.6, 111.0, 105.9, 83.5, 28.3, 20.4. HRMS (MALDI): calcd for $C_{17}H_{14}O_4$ $[M + Na]^+$ 305.0790, found 305.0774.

Data for ***2n***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.76−7.72 (m, 1H), 7.52−7.49 (m, 1H), 7.31−7.28 (m, 1H), 7.25−7.22 (m, 1H), 6.97 (s, 1H), 5.71 (s, 1H), 3.96 (br, 1H), 1.61 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.2, 195.4, 161.0, 159.3, 152.5, 152.4, 152.2, 143.4, 132.9, 128.1, 124.8, 118.6, 118.5, 116.9, 116.7, 115.5, 111.8, 111.7, 106.9, 83.6, 30.8, 28.4. HRMS (MALDI): calcd for $C_{16}H_{11}FO_4$ $[M + Na]^+$ 309.0539, found 309.0511.

Data for ***2o***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 6.70 (s, 1H), 5.68 (s, 1H), 3.96 (br, 1H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 195.5, 155.7, 152.9, 143.2, 132.5, 132.0, 130.8, 130.2, 129.9, 127.2, 115.5, 112.5, 106.6, 83.6, 28.3. HRMS (MALDI): calcd for $C_{16}H_{11}ClO_4$ $[M + Na]^+$ 325.0244, found 325.0224.

Data for ***2p***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.71−7.67 (m, 2H), 7.59−7.57 (m, 1H), 6.47 (s, 1H), 5.66 (s, 1H), 3.96 (br, 1H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 195.4, 156.9, 152.6, 143.0, 132.2, 131.2, 130.8, 129.6, 128.9, 128.6, 127.1, 124.5, 121.8, 115.6, 111.7, 106.8, 83.7, 28.3. HRMS (MALDI): calcd for $C_{17}H_{11}F_3O_4$ $[M + Na]^+$ 359.0507, found 359.0490.

Data for ***2q***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.84 (s, 1H), 7.59−7.57 (m, 2H), 6.78 (s, 1H), 5.72 (s, 1H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 195.2, 154.8, 152.2, 142.9, 136.0, 133.8, 131.2, 130.0, 127.3, 124.5, 115.8, 107.8, 107.2, 83.7, 28.4. HRMS (MALDI): calcd for $C_{16}H_{10}Cl_2O_4$ $[M + Na]^+$ 358.9854, found 358.9827.

Data for ***2r***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.59−7.52 (m, 2H), 6.71 (s, 1H), 5.72 (s, 1H), 3.91 (br, 1H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}F_2O_4$ $[M + Na]^+$ 327.0445, found 327.0427.

Data for ***2s***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.40−7.37 (m, 2H), 7.35−7.33 (m, 1H), 7.26−7.25 (m, 2H), 6.05 (s, 1H), 5.50 (s, 1H), 3.89 (s, 1H), 3.73 (s, 2H), 1.54 (s, 3H). ^{13}C NMR (150 MHz $CDCl_3$): δ 196.1, 195.5, 161.3, 152.8, 143.7, 133.9, 129.0, 128.9, 127.6, 115.6, 109.1, 105.6, 83.4, 39.2, 28.3. HRMS (MALDI): calcd for $C_{17}H_{14}O_5$ $[M + Na]^+$ 321.0739, found 321.0721.

General Procedure for the Preparation of Halogenated Azaphilones 3. To a stirred solution of compound **2** (0.05 mmol) in CH_2Cl_2 was added NXS (0.055 mmol). The resulting mixture was stirred at rt until TLC analysis indicated that the starting material had disappeared. The resulting mixture was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 5:1) to give the product **3**.

Data for ***3a$_1$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.83−7.82 (m, 2H), 7.58−7.53 (m, 3H), 7.22 (s, 1H), 3.96 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{11}ClO_4$ $[M + Na]^+$ 325.0244, found 325.0240.

Data for ***3a$_2$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.59−7.53 (m, 3H), 7.26 (s, 1H), 3.96 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{11}BrO_4$ $[M + Na]^+$ 368.9738, found 368.9748.

Data for ***3a$_3$***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.85−7.83 (m, 2H), 7.59−7.54 (m, 3H), 7.27 (s, 1H), 3.96 (br, 1H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{11}IO_4$ $[M + Na]^+$ 416.9600, found 416.9604.

Data for ***3b$_2$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.16 (s, 1H), 7.03 (d, J = 7.8 Hz, 2H), 3.97 (br, 1H), 3.91 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_5$ $[M + Na]^+$ 398.9844, found 398.9808.

Data for ***3c$_1$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.20 (s, 1H), 3.95 (br, 1H), 2.45 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}ClNO_4$ $[M + Na]^+$ 339.0400, found 339.0405.

Data for ***3c$_2$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.22 (s, 1H), 3.95 (br, 1H), 2.45 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_4$ $[M + H]^+$ 361.0076, found 361.0027.

Data for ***3c$_3$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.73 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.22 (s, 1H), 3.97 (br, 1H), 2.45 (s, 3H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}IO_4$ $[M + Na]^+$ 430.9756, found 430.9765.

Data for ***3d$_1$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.84−7.82 (m, 2H), 7.24−7.21 (m, 2H), 7.16 (s, 1H), 3.91 (br, 1H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}ClFO_4$ $[M + Na]^+$ 343.0149, found 343.0126.

Data for ***3d$_2$***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.86−7.83 (m, 2H), 7.25−7.20 (m, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}BrFO_4$ $[M + Na]^+$ 386.9644, found 386.9635.

Data for ***3d$_3$***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.87−7.83 (m, 2H), 7.26−7.20 (m, 3H), 4.04 (br, 1H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}FIO_4$ $[M + Na]^+$ 434.9506, found 434.9510.

Data for ***3e$_1$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.29 (s, 1H), 3.89 (br, 1H), 1.64 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{10}ClF_3O_4$ $[M + Na]^+$ 393.0117, found 393.0107.

Data for ***3e$_2$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 3.96 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{10}BrF_3O_4$ $[M + Na]^+$ 436.9612, found 436.9595.

Data for ***3e$_3$***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (m, 3H), 7.80 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 3.94 (br, 1H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{10}IF_3O_4$ $[M + Na]^+$ 484.9474, found 484.9477.

Data for ***3f$_1$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 3.97 (br, 1H), 1.63 (s, 3H), 1.37 (s, 9H). HRMS (MALDI): calcd for $C_{20}H_{19}ClO_4$ $[M + Na]^+$ 381.0870, found 381.0875.

Data for ***3f$_2$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 3.97 (br, 1H), 1.62 (s, 3H), 1.37 (s, 9H). HRMS (MALDI): calcd for $C_{20}H_{19}BrO_4$ $[M + Na]^+$ 425.0364, found 425.0367.

Data for ***3f$_3$***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (1H, s), 7.77 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 3.97 (br, 1H), 1.61 (s, 3H), 1.37 (s, 9H). HRMS (MALDI): calcd for $C_{20}H_{19}IO_4$ $[M + Na]^+$ 473.0226, found 473.0223.

Data for ***3g₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.4 Hz, 2H), 8.04 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.38 (s, 1H), 3.89 (br, 1H), 1.64 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}BrNO_6$ $[M + Na]^+$ 413.9589, found 413.9579.

Data for ***3h₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.46–7.41 (m, 2H), 7.31 (s, 1H), 7.24 (s, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 3.90 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}ClO_5$ $[M + Na]^+$ 355.0349, found 355.0330.

Data for ***3h₂***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.48–7.39 (m, 2H), 7.31 (s, 1H), 7.24 (s, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 3.93 (br, 1H), 3.90 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_5$ $[M + Na]^+$ 398.9844, found 398.9856.

Data for ***3i₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.63–7.62 (m, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 6.6 Hz, 1H), 7.20 (s, 1H), 3.92 (br, 1H), 2.46 (s, 3H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}ClO_4$ $[M + Na]^+$ 339.0400, found 339.0410.

Data for ***3i₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.64–7.62 (m, 2H), 7.43–7.38 (m, 2H), 7.24 (s, 1H), 3.95 (br, 1H), 2.46 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_4$ $[M + Na]^+$ 382.9895, found 382.9886.

Data for ***3i₃***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.64–7.62 (m, 2H), 7.44–7.38 (m, 2H), 7.24 (s, 1H), 4.47 (s, 3H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}IO_4$ $[M + Na]^+$ 430.9756, found 430.9742.

Data for ***3j₁***. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.84–7.80 (m, 2H), 7.65–7.58 (m, 1H), 7.49–7.41 (m, 1H), 7.35 (s, 1H), 1.39 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}ClFO_4$ $[M + H]^+$ 321.0330, found 321.0319.

Data for ***3j₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.53–7.51 (m, 2H), 7.28–7.26 (m, 2H), 3.94 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}BrFO_4$ $[M + Na]^+$ 386.9644, found 386.9655.

Data for ***3j₃***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.53–7.51 (m, 2H), 7.29–7.26 (m, 2H), 3.95 (br, 1H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}IFO_4$ $[M + Na]^+$ 434.9506, found 434.9435.

Data for ***3k₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.80 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 3.91 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}Cl_2O_4$ $[M + Na]^+$ 358.9854, found 358.9854.

Data for ***3k₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.80 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.25 (s, 1H), 3.93 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}BrClO_4$ $[M + Na]^+$ 402.9349, found 402.9354.

Data for ***3k₃***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.80 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.25 (s, 1H), 3.95 (br, 1H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}IClO_4$ $[M + Na]^+$ 450.9210, found 450.9217.

Data for ***3l₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.69 (s, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.00 (s, 3H), 3.91 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}ClO_5$ $[M + Na]^+$ 355.0349, found 355.0325.

Data for ***3l₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.76–7.75 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.11–7.06 (m, 2H), 4.00 (s, 3H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_5$ $[M + Na]^+$ 398.9844, found 398.9840.

Data for ***3m₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.35–7.32 (m, 2H), 6.91 (s, 1H), 3.90 (br, 1H), 2.48 (s, 3H), 1.65 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}ClO_4$ $[M + Na]^+$ 339.0400, found 339.0383.

Data for ***3m₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.34–7.33 (m, 2H), 6.96 (s, 1H), 3.94 (br, 1H), 2.48 (s, 3H), 1.65 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_4$ $[M + Na]^+$ 382.9895, found 382.9874.

Data for ***3n₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.79–7.76 (m, 1H), 7.55–7.54 (m, 1H), 7.42 (s, 1H), 7.33–7.31 (m, 1H), 7.27–7.24 (m, 1H), 3.93 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}ClFO_4$ $[M + Na]^+$ 343.0149, found 343.0106.

Data for ***3n₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.79–7.77 (m, 1H), 7.55–7.54 (m, 1H), 7.47 (s, 1H), 7.33–7.31 (m, 1H), 7.28–7.25 (m, 1H), 3.92 (br, 1H), 1.63 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}BrFO_4$ $[M + Na]^+$ 386.9644, found 386.9616.

Data for ***3o₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.19 (s, 1H), 3.90 (br, 1H), 1.65 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}Cl_2O_4$ $[M + Na]^+$ 358.9854, found 358.9852.

Data for ***3o₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 3.91 (br, 1H), 1.65 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_{10}BrClO_4$ $[M + Na]^+$ 402.9349, found 402.9348.

Data for ***3p₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.73–7.71 (m, 2H), 7.64–7.63 (m, 1H), 6.92 (s, 1H), 3.87 (br, 1H), 1.65 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{10}ClF_3O_4$ $[M + Na]^+$ 393.0117, found 393.0110.

Data for ***3p₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.86–7.85 (m, 1H), 7.74–7.70 (m, 2H), 7.65–7.64 (m, 1H), 6.96 (s, 1H), 3.90 (br, 1H), 1.65 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{10}BrF_3O_4$ $[M + Na]^+$ 436.9612, found 436.9620.

Data for ***3q₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.90 (s, 1H), 7.65–7.62 (m, 2H), 7.19 (s, 1H), 3.92 (br, 1H), 1.64 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_9Cl_3O_4$ $[M + Na]^+$ 392.9464, found 392.9453.

Data for ***3q₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.91 (s, 1H), 7.66–7.61 (m, 2H), 7.23 (s, 1H), 3.92 (br, 1H), 1.62 (s, 3H);

Data for ***3r₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.67–7.60 (m, 2H), 7.35–7.33 (m, 1H), 7.15 (s, 1H), 3.88 (br, 1H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_9ClF_2O_4$ $[M + Na]^+$ 361.0055, found 361.0027.

Data for ***3r₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.68–7.61 (m, 2H), 7.37–7.32 (m, 1H), 7.19 (s, 1H), 3.84 (br, 1H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{16}H_9BrF_2O_4$ $[M + Na]^+$ 404.9550, found 404.9554.

General Procedure for the Preparation of Acetylated Azaphilones 4. To a stirred solution of azaphilone **3** (0.035 mmol) and acetic anhydride (7.14 mg, 0.070 mmol) in 1.5 mL of CH_2Cl_2 were added triethylamine (7.07 mg, 0.070 mmol) and 4-(dimethylamino)-pyridine (4.27 mg, 0.035 mmol). The resulting mixture was stirred at rt for 30 min and concentrated in vacuo. Purification on silica gel (hexane:EtOAc = 10:1 to 5:1) provided **4**.

Data for ***4a₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.82–8.81 (m, 2H), 7.56–7.53 (m, 3H), 7.24 (s, 1H), 2.20 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{13}ClO_5$ $[M + Na]^+$ 367.0349, found 367.0353.

Data for ***4a₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.82–7.81 (m, 2H), 7.58–7.52 (m, 3H), 7.29 (s, 1H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{13}BrO_5$ $[M + Na]^+$ 410.9844, found 410.9850.

Data for ***4b₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.18 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 3H), 2.19 (s, 3H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}BrO_6$ $[M + Na]^+$ 440.9950, found 440.9965.

Data for ***4c₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.20 (s, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}ClO_5$ $[M + Na]^+$ 381.0506, found 381.0491.

Data for ***4c₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (1H, s), 7.71 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.24 (s, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}BrO_5$ $[M + Na]^+$ 425.0001, found 425.0005.

Data for ***4c₃***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.26 (s, 1H), 2.45 (s, 3H), 2.19 (s, 3H), 1.58 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}IO_5$ $[M + Na]^+$ 472.9862, found 472.9846.

Data for ***4d₂***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.84–7.81 (m, 2H), 7.24–7.20 (m, 3H), 2.19 (s, 3H), 1.59 (s, 3H). HRMS

(MALDI): calcd for $C_{18}H_{12}FBrO_5$ $[M + Na]^+$ 428.9750, found 428.9756.

Data for ***4d₃***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.84−7.80 (m, 2H), 7.25−7.20 (m, 3H), 2.18 (s, 3H), 1.58 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}FIO_5$ $[M + Na]^+$ 476.9611, found 476.9618.

Data for ***4e₂***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.35 (s, 1H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{12}BrF_3O_5$ $[M + Na]^+$ 478.9718, found 478.9721.

Data for ***4e₃***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (m, 3H), 7.79 (m, 2H), 7.36 (s, 1H), 2.19 (s, 3H), 1.58 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{12}IF_3O_5$ $[M + Na]^+$ 526.9579, found 526.9606.

Data for ***4f₁***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.20 (s, 1H), 2.19 (s, 3H), 1.60 (s, 3H), 1.36 (s, 9H). HRMS (MALDI): calcd for $C_{22}H_{21}ClO_5$ $[M + Na]^+$ 423.0975, found 423.1004.

Data for ***4f₂***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 9.2 Hz, 2H), 7.25 (s, 1H), 2.19 (s, 3H), 1.60 (s, 3H), 1.35 (s, 9H). HRMS (MALDI): calcd for $C_{22}H_{21}BrO_5$ $[M + Na]^+$ 467.0470, found 467.0451.

Data for ***4f₃***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, s), 7.75 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.26 (s, 1H), 2.18 (s, 3H), 1.58 (s, 3H), 1.37 (s, 9H). HRMS (MALDI): calcd for $C_{22}H_{21}IO_5$ $[M + Na]^+$ 515.0331, found 515.0330.

Data for ***4h₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.44−7.41 (m, 2H), 7.30−7.26 (m, 2H), 7.10−7.09 (d, J = 7.2 Hz, 1H), 3.89 (s, 3H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}BrO_6$ $[M + Na]^+$ 440.9950, found 440.9958.

Data for ***4i₁***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.62−7.60 (m, 2H), 7.42−7.35 (m, 2H), 7.22 (s, 1H), 2.45 (s, 3H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}ClO_5$ $[M + Na]^+$ 381.0506, found 381.0498.

Data for ***4i₂***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.62−7.60 (m, 2H), 7.41−7.38 (m, 2H), 7.27 (s, 1H), 2.46 (s, 3H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}BrO_5$ $[M + Na]^+$ 425.0001, found 425.0026.

Data for ***4i₃***. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.72−7.70 (m, 2H), 7.51−7.45 (m, 2H), 7.24 (s, 1H), 2.42 (s, 3H), 2.12 (s, 3H), 1.50 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}IO_5$ $[M + Na]^+$ 472.9862, found 472.9854.

Data for ***4j₁***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.53−7.48 (m, 2H), 7.28−7.23 (m, 2H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}ClFO_5$ $[M + Na]^+$ 385.0255, found 385.0256.

Data for ***4j₂***. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.84−7.81 (m, 2H), 7.67−7.63 (m, 1H), 7.51−7.48 (m, 1H), 7.39 (s, 1H), 2.13 (s, 3H), 1.52 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}BrFO_5$ $[M + Na]^+$ 428.9750, found 428.9773.

Data for ***4j₃***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.53−7.49 (m, 2H), 7.29−7.26 (m, 2H), 2.19 (s, 3H), 1.58 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}IFO_5$ $[M + Na]^+$ 476.9611, found 476.9622.

Data for ***4k₂***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.78 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.52−7.47 (m, 2H), 7.27 (s, 1H), 2.19 (s, 3H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}BrClO_5$ $[M + Na]^+$ 444.9454, found 444.9462.

Data for ***4l₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}ClO_6$ $[M + Na]^+$ 397.0455, found 397.0459.

Data for ***4l₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.75 (s, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.10−7.05 (m, 2H), 3.99 (s, 3H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}BrO_6$ $[M + Na]^+$ 440.9950, found 440.9951.

Data for ***4m₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.33−7.32 (m, 2H), 6.93 (s, 1H), 2.47 (s, 3H), 2.20 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}ClO_5$ $[M + Na]^+$ 381.0506, found 381.0468.

Data for ***4m₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.33−7.32 (m, 2H), 6.98 (s, 1H), 2.48 (s, 3H), 2.20 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{15}BrO_5$ $[M + Na]^+$ 425.0001, found 425.0004.

Data for ***4n₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.77−7.74 (m, 1H), 7.53−7.52 (m, 1H), 7.42 (s, 1H), 7.32−7.29 (m, 1H), 7.25−7.23 (m, 1H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}ClFO_5$ $[M + Na]^+$ 385.0255, found 385.0229.

Data for ***4n₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.77−7.74 (m, 1H), 7.55−7.52 (m, 1H), 7.48 (s, 1H), 7.32−7.29 (m, 1H), 7.25−7.23 (m, 1H), 2.19 (s, 3H), 1.60 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}BrFO_5$ $[M + Na]^+$ 428.9750, found 428.9757.

Data for ***4o₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.18 (s, 1H), 2.20 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}Cl_2O_5$ $[M + Na]^+$ 400.9959, found 400.9963.

Data for ***4o₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.24 (s, 1H), 2.20 (s, 3H), 1.61 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{12}BrClO_5$ $[M + Na]^+$ 444.9454, found 444.9465.

Data for ***4p₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.84 (d, J = 6.6 Hz, 1H), 7.72−7.70 (m, 2H), 7.63 (d, J = 6.6 Hz, 1H), 6.94 (s, 1H), 2.20 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{12}ClF_3O_5$ $[M + Na]^+$ 435.0223, found 435.0222.

Data for ***4p₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.72−7.70 (m, 2H), 7.63 (d, J = 6.6 Hz, 1H), 6.99 (s, 1H), 2.20 (s, 3H), 1.62 (s, 3H). HRMS (MALDI): calcd for $C_{19}H_{12}BrF_3O_5$ $[M + Na]^+$ 478.9718, found 478.9710.

Data for ***4q₂***. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.26 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 2.13 (s, 3H), 1.52 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{11}BrCl_2O_5$ $[M + Na]^+$ 478.9065, found 478.9060.

Data for ***4r₁***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.65−7.62 (m, 1H), 7.60−7.58 (m, 1H), 7.35−7.31 (m, 1H), 7.17 (s, 1H), 2.19 (s, 3H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{11}ClF_2O_5$ $[M + Na]^+$ 403.0161, found 403.0156.

Data for ***4r₂***. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.65−7.59 (m, 2H), 7.35−7.31 (m, 1H), 7.22 (s, 1H), 2.19 (s, 3H), 1.59 (s, 3H). HRMS (MALDI): calcd for $C_{18}H_{11}BrF_2O_5$ $[M + Na]^+$ 446.9656, found 446.9647.

Preparation of 1-(2,4-Dimethoxy-3-methylphenyl)ethanone (17). To a solution of 2,6-dimethoxytoluene (3.04 g, 20 mmol) in dichloromethane (15 mL) was added $AlCl_3$ (3.2 g, 24 mmol) at 0 °C. The mixture was stirred for 0.5 h, and a solution of acetyl chloride (1.4 mL) in dichloromethane (15 mL) was added. The progress of the reaction was monitored by TLC and, when it was complete, the reaction mixture was poured into ice water and neutralized to pH 7 with a 3% solution of NaOH. The separated organic phase was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 25:1) to give pale **17** as a yellow oil (2.29 g, 59%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, J = 9 Hz, 2H), 6.68 (d, J = 9 Hz, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 2.63 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 198.8, 162.0, 159.2, 128.8, 125.4, 120.1, 105.8, 61.7, 55.6, 30.1, 8.7. ESI-MS 194.0 (M^+).

Preparation of 1-(2,4-Dimethoxy-3-methyl-5-nitrophenyl)-ethanone (18). A solution of **17** (4.85 g, 25 mmol) in 15 mL of acetic anhydride was added slowly to a mixture of $Cu(NO_3)_2{\cdot}3H_2O$ (3.62 g, 15 mmol) in 15 mL of acetic anhydride at 0 °C. The mixture was stirred vigorously, and the reaction was monitored by TLC. When it was complete, the mixture was poured into ice water, stirred for 30 min, and then extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 8:1) to provide **18** as a pale yellow solid (3.53 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 3.94 (s, 3H), 3.84 (s, 3H),

2.65 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.3, 162.2, 155.8, 139.9, 128.8, 128.6, 124.7, 62.2, 62.0, 30.2, 9.9. ESI-MS 239.1 (M^+).

Preparation of 1-(3-Amino-2-bromo-4,6-dimethoxy-5-methylphenyl)ethanone (19). To a solution of **18** (2.39 g, 10 mmol) in 18 mL of anhydrous THF was added 10% Pd/C (0.25 g), and the resulting mixture was hydrogenated under H_2 at room temperature. The progress of the reaction was monitored by TLC, and, when it was complete, the mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give the crude aniline, which was employed in the next step without further purification. The crude aniline was dissolved in 18 mL of acetic acid, and a solution of bromine (0.57 mL, 11 mmol) in 6 mL of acetic acid was slowly added at 10 °C. Monitoring the reaction by TLC indicated the disappearance of the aniline, at which point the reaction mixture was quenched by the addition of aqueous $Na_2S_2O_3$. The mixture was extracted three times with ethyl acetate and the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$, water, and brine, then dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) to give **19** as a pale yellow product (2.22 g, 77%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.13 (br, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 2.52 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.6, 146.5, 146.1, 135.6, 133.7, 124.6, 100.3, 62.6, 59.3, 31.7, 9.3. ESI-MS 287.0 (M^+).

Preparation of 1-(6-Bromo-2,4-dimethoxy-3-methylphenyl)-ethanone (20). To a solution of compound **19** (2.02 g, 7.0 mmol) in 30 mL of THF and 20 mL of distilled water was slowly added 5 mL of concentrated HCl, and the reaction mixture was cooled to −5 °C. Sodium nitrite (0.53 g, 7.68 mmol) in 2 mL of H_2O was added dropwise, and the mixture was stirred for 30 min at −5 °C before the addition of urea (0.1 g, 1.67 mmol). Aqueous hypophosphorous acid (50% w/w) (16 mL) was then added over 1 h, and the resulting mixture was allowed to warm to 0 °C, stirred for an additional 6 h, and then extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a residue, which was purified by flash chromatography (petroleum ether:ethyl acetate = 15:1) to give **20** as yellow oil (1.61 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (s, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.52 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.4, 159.4, 156.0, 130.6, 119.8, 114.3, 110.6, 62.4, 55.9, 31.8, 8.8. ESI-MS 272.0 $(M - H)^+$, 274.0 $(M + H)^+$.

Preparation of 1-(6-Bromo-2,4-dihydroxy-3-methylphenyl)-ethanone (21). To the compound **20** (0.273 g, 1.0 mmol) in 5 mL of freshly distilled toluene was added $AlCl_3$ (1.3 g, 1.0 mmol). The mixture was heated under reflux for 1 h (TLC monitoring) and then poured into ice water and extracted three times with ethyl acetate. The combined organic extracts were washed with water and brine and dried with anhydrous Na_2SO_4. The solvent was concentrated, and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 8:1) to give **21** as a yellow solid (0.18 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.49 (s, 1H), 6.76 (s, 1H), 5.43 (s, 1H), 2.86 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 202.5, 158.5, 157.1, 120.2, 116.2, 112.0, 111.4, 32.1, 8.2. ESI-MS 244.0 $(M - H)^+$, 276.0 $(M + H)^+$.

Preparation of 1-(2,4-dihydroxy-3-methyl-6-(2-phenylethynyl)phenyl)ethanone (22). To a mixture of compound **21** (98 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (2 mg, mmol) in degassed DMF (3 mL) and under an inert atmosphere were added successively phenylacetylene (49.1 mg, 0.48 mmol) and Et_3N (3 mL). The resulting mixture was heated and stirred at 50 °C for about 5 h. After cooling to room temperature, the mixture was poured into water, neutralized with 1% aqueous HCl, and then extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified directly on a column of silica gel (petroleum ether:ethyl acetate = 8:1), affording **22** as a yellow solid (90.4 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.79 (s, 1H), 10.76 (s, 1H), 7.58 (br, 2H), 7.47 (br, 3H), 6.75 (s, 1H), 2.89 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 203.6, 163.3, 160.5, 131.1, 129.3, 128.9, 122.2, 122.0, 113.8,113.2, 112.5, 95.3, 89.8, 31.5, 8.0. HRMS (MALDI): calcd for $C_{17}H_{14}O_3$ $[M + H]^+$ 267.1021, found 267.0989.

Preparation of 1-(3-Halogen-4,6-dihydroxy-5-methyl-2-(2-phenylethynyl)phenyl)ethanone (23). To a solution of compound **22** (106 mg, 0.4 mmol) in 4 mL of THF was added concentrated HX (10 equiv of concentrated HCl and HBr for **23a** and **23b**, respectively), and the mixture was stirred for 3 min. IBX (0.37 g, 1.20 mmol) and TBAI (7 mg) were added successively. Progress of the reaction was monitored by TLC, and, after 30 min, the reaction mixture was poured into water and neutralized with saturated aqueous Na_2CO_3. The resulting mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 12:1), affording yellow product **23**.

*Data for **23a**.* ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.74 (s, 1H), 7.57−7.56 (m, 2H), 7.418−7.40 (m, 3H), 6.26 (s, 1H), 3.00 (s, 3H), 2.22 (s, 3H). HRMS(MALDI): calcd for $C_{17}H_{13}ClO_3$ $[M + H]^+$ 301.0631, found 301.0581.

*Data for **23b**.* ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.72 (s, 1H), 7.57−7.56 (m, 2H), 7.418−7.40 (m, 3H), 6.24 (s, 1H), 2.99 (s, 3H), 2.22 (s, 3H). HRMS (MALDI): calcd for $C_{17}H_{13}BrO_3$ $[M + H]^+$ 345.0126, found 345.0085.

Preparation of Azaphilone 6a and 6b. A mixture of **23a** or **23b** (0.24 mmol), $Au(OAc)_3$ (4.5 mg, 0.012 mmol), and trifluoroacetic acid (1.5 mL) in 1.5 mL of 1,2-dichloroethane was stirred for 20 min at room temperature. Then IBX (75 mg) and TBAI (4.5 mg) were added. Progress of the reaction was monitored by TLC, and, when it was complete, the mixture was quenched by addition of aqueous $Na_2S_2O_3$. The reactant was extracted three times with ethyl acetate. The combined organic extracts were washed with water and brine and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 5:1) to give **6a** or **6b** as a yellow solid (32 mg, 36%).

*Data for **6a**.* ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, J = 7.2 Hz, 2H), 7.57−7.52 (m, 3H), 7.26 (s, 1H), 2.70 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (150 MHz $CDCl_3$): δ 195.8, 189.4, 165.4, 157.8, 141.4, 132.0, 130.0, 129.2, 125.9, 111.7, 108.7, 103.6, 84.3, 28.5, 19.3. HRMS (MALDI): calcd for $C_{17}H_{13}ClO_4$ $[M + Na]^+$ 339.0400, found 339.0448.

*Data for **6b**:* ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (d, J = 7.2 Hz, 2H), 7.52−7.57 (m, 3H), 7.32 (s, 1H), 4.00 (br, 1H), 2.70 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (150 MHz $CDCl_3$): δ 195.9, 189.7, 165.4, 158.1, 143.6, 132.0, 129.9, 129.2, 125.9, 112.5, 106.3, 100.5, 84.3, 28.5, 19.2. HRMS (MALDI): calcd for $C_{17}H_{13}BrO_4$ $[M + Na]^+$ 382.9895, found 382.9861.

Biological Testing. All testing was undertaken on 96-well microtiter plates. Pathogen species, rates, and number of replicates are given in Table 1 for the assays conducted on leaf pieces, and Table 2 for the assays conducted in artificial media.

Table 1. Details of the Primary-Level Leaf-Piece Assays

pathogen	host	rates[a]	replicates[b]
Phytophthora infestans	tomato	200, 60	2
Septoria tritici	wheat	100	3
Uromyces viciae-fabae	field bean	100	2

[a]Rates are given as parts per million a.i. in the formulated sample applied to the leaf piece. [b]Number of replicates plates per rate.

For the leaf-piece assays, 200−300 μL of water agar was dispensed into each well of the assay plates. Leaf pieces of the appropriate host species (6 mm diameter for tomato and bean, 6 mm length for wheat) were cut either automatically or by hand and transferred onto the surface of the agar. Dried sample of the active ingredient was formulated to the necessary rate using a robotic liquid-handling system, and 10 μL was dispensed onto the surface of each leaf piece.

Spore suspensions of the pathogen species were made up to the necessary rate (approximately 150,000 sporangia/mL for *Phytophthora*

Table 2. Details of the Primary-Level Assays Conducted in Artificial Media

pathogen	rates[a]	replicates[b]
Pythium dissimile	20, 2	2
Alternaria solani	20, 2	2
Botryotinia fuckeliana (*Botrytis cinerea*)	20, 2	2
Gibberella zeae (*Fusarium graminearum*)	20, 2	2

[a]Rates are given as parts per million a.i. in the final artificial media mixture. [b]Number of replicates plates per rate.

infestans, 1,000,000 conidia/mL for *Septoria tritici*, and 0.3 mg of spores/mL for *Uromyces viciae-fabae*), and applied to the treated leaf pieces using a hand-held spray gun. Lids were placed on the plates, and they were stored in appropriate controlled environment conditions for between 5 and 14 days, depending on the test species.

For the artificial medium assays, stock cultures of the target species were grown in appropriate conditions on artificial media in 90 mm Petri dishes. For all pathogens apart from *Pythium dissimile*, spore suspensions were prepared in water from these stock plates and made into a 3% nutrient agar (final spore concentrations of 10,000 sp/mL for *Gibberella zeae*, 15,000 sp/mL for *Botryotinia fuckeliana*, and 20,000 sp/mL for *Alternaria solani*). For *Pythium dissimile*, a water suspension of fragments of surface mycelia was made from the stock cultures and made into a 3% agar as for the other species, adjusted to a final optical density reading of 0.5 at 425 nm.

The chemicals to be tested were formulated and transferred to the assay plates using the liquid handling robot as for the leaf-piece assays, with adjustments in concentration for the high and low rate replicates. The wells of these plates were then loaded with 90 μL of the spore/agar suspensions of the appropriate species using an automated liquid handling system, to give final rates of target compound in the media of 20 ppm (high rate) or 2 ppm (low rate). The plates were then stored in controlled environments set to appropriate conditions, until assessment between 5 and 14 days later, depending on the species.

Assessment for each species was carried out by eye, with each individual well scored on a three-band pattern with additional result types for assay failure and phytotoxic activity on the leaf piece (Table 3).

Table 3. Assessment Criteria for the Biological Assays

scoring band	well condition
0	0 to 49% control of disease or pathogen
55	50 to 80% control of disease or pathogen
99	81 to 100% control of disease or pathogen
NCH	not captured (too phytotoxic)
NC	not captured (test failure)

The resulting data were collated for each compound, and averages across replicates were used to make a judgment of the overall activity level of the compound.

RESULTS AND DISCUSSION

Chemistry. According to the retrosynthetic analysis as shown in Figure 2, we planned to prepare the core structures **2**−**5** by the oxidation of the appropriate benzopyrylium salts **8**, which may be derived from the alkynylbenzaldehyde **9**, which should be readily accessible using Sonogashira coupling.

In this synthetic procedure, 2-bromobenzaldehyde **10** is a key intermediate for the Sonogashira coupling reaction. A suitable preparation of this intermediate is outlined in Scheme 1. In this route, the cheap and commercially available 2-methylresorcinol was selected as the starting material. The preparation of the dimethoxybenzaldehyde **13** was achieved by methylation of the resorcinol **11** and then formylation with $POCl_3$ in DMF under standard Vilsmeier reaction conditions. Nitration of compound **13** with $Cu(NO_3)_2$ afforded **14** in which the aldehyde was protected in situ as geminal diacetate. The nitro group of **14** was hydrogenated, and the resulting aniline was treated with bromine to give the fully substituted benzene **15**, which was deaminated by reduction of the corresponding diazonium salt with H_3PO_2, under which conditions deprotection of the geminal diacetate took place to generate **16**. The two methoxyl groups of compound **16** were deprotected using BBr_3 in dichloromethane to afford the desired 2-bromobenzaldehyde smoothly and in excellent yield. The intermediate **10** could be obtained on a multigram scale using this synthetic route.

With the key intermediate **10** in hand, we then investigated its coupling reactions with phenylacetylenes bearing diverse aromatic substituents. We initially attempted to optimize the Sonogashira coupling reaction between 2-bromobenzaldehyde and phenylacetylene by screening the catalysts [$Pd(PPh_3)_4$, $Pd(PhCN)_2Cl_2$, $Pd(PPh_3)_2Cl_2$], bases (K_2CO_3, triethylamine, etc.), and solvents (CH_3CN, THF, DMF, toluene, etc.). Optimal conditions were obtained with the cocatalyst system of $Pd(PPh_3)_2Cl_2$/CuI in the presence of triethylamine in DMF at 60 °C. A variety of aromatic terminal acetylenes were employed in this palladium/copper cocatalyzed process, and good to excellent yields were achieved in most cases (Table 4, entries **1**−**18**). It is worth noting that the presence of either electron-donating or electron-withdrawing groups on the phenylacetylene did not significantly affect the yield of the Sonogashira coupling. In addition, no noteworthy steric effects were observed (Table 4, entry **6**). However, the benzyl-acetylene 1-(prop-2-ynyl)benzene showed lower reactivity in this coupling reaction, and a much lower yield was observed (entry **19**). In this case, microwave irradiation was employed to improve the yield. The optimum reaction conditions were found to be 5% $PdCl_2(PPh_3)_2$, 5% CuI, and Et_3N (3 equiv) in a 4:1 mixture of dioxane and water at 80 °C under microwave irradiation for 15 min, and the isolated yield improved significantly to 75%.

The subsequent cycloisomerization with a Lewis acid ($AgNO_3$) at room temperature using a mixture of 1,2-dichloroethane and trifluoroacetic acid as solvent afforded the pyrylium salts, which were oxidized without isolation with *o*-iodoxybenzoic acid (IBX) to afford the azaphilones **2** in satisfactory yield. This one-pot procedure greatly simplifies the synthesis. The intermediate *o*-alkynylbenzaldehydes **9** are all tolerated in this two-step one-pot transformation, and were converted smoothly into the corresponding azaphilones. Remarkably, electron-donating or electron-withdrawing aromatic substituents on the *o*-alkynylbenzaldehydes, irrespective of their position on the benzene

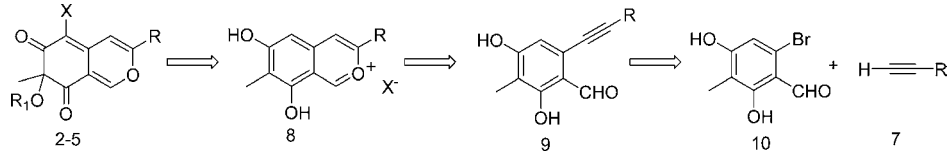
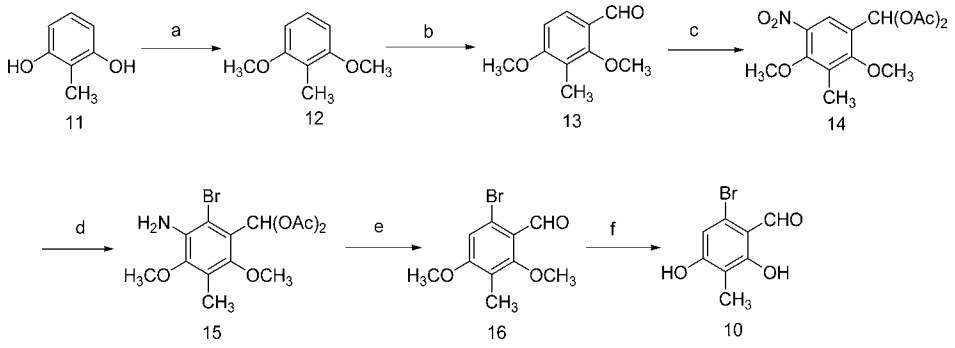


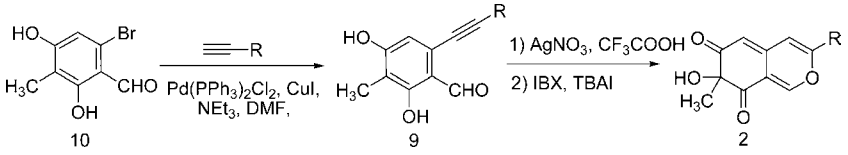
Figure 2. Retrosynthetic analysis of the designed azaphilone analogues.

Scheme 1[a]



[a]Reagents and conditions: (a) $(CH_3)_2SO_4$, K_2CO_3, 87%; (b) $POCl_3$, DMF, 88%; (c) $Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, 81%; (d) (i) Pd/C, H_2; (ii) Br_2, 88% in two steps; (e) $NaNO_2$, H_3PO_2, 83%; (f) BBr_3, CH_2Cl_2, −78 °C, 90%.

Table 4. Synthesis of 2 and 3 via the Sonogashira reaction and Subsequent Cycloisomerization



		yield[a] (%)	
no.	R	9	2
1	C_6H_5–	**9a** (78)	**2a** (63)
2	4-CH_3O–C_6H_4–	**9b** (70)	**2b** (55)
3	4-CH_3–C_6H_4–	**9c** (83)	**2c** (54)
4	4-F–C_6H_4–	**9d** (83)	**2d** (55)
5	4-CF_3–C_6H_4–	**9e** (76)	**2e** (72)
6	4-$(CH_3)_3C$–C_6H_4–	**9f** (77)	**2f** (65)
7	4-NO_2–C_6H_4–	**9g** (55)	**2g** (55)
8	3-CH_3O–C_6H_4–	**9h** (69)	**2h** (60)
9	3-CH_3–C_6H_4–	**9i** (90)	**2i** (65)
10	3-F–C_6H_4–	**9j** (73)	**2j** (61)
11	3-Cl–C_6H_4–	**9k** (63)	**2k** (65)
12	2-CH_3O–C_6H_4–	**9l** (92)	**2l** (52)
13	2-CH_3–C_6H_4–	**9m** (92)	**2m** (66)
14	2-F–C_6H_4–	**9n** (75)	**2n** (67)
15	2-Cl–C_6H_4–	**9o** (84)	**2o** (81)
16	2-CF_3–C_6H_4–	**9p** (90)	**2p** (78)
17	3,4-di-Cl–C_6H_3–	**9q** (87)	**2q** (66)
18	3,4-di-F–C_6H_3–	**9r** (86)	**2r** (42)
19	$C_6H_5CH_2$–	**9s** (48, 75[b])	**2s** (28, 48[c])

[a]Isolated yield. [b]The reaction was run in a dioxane–water mixture (4:1) at 80°C under microwave irradiation. [c]The reaction temperature was adjusted to 0 °C.

ring, did not affect the yields of azaphilones. In the case of entry **19**, only 28% isolated yield was achieved. However, when the temperature of cycloisomerization was reduced to 0 °C, the yield improved to 48%.

Selected azaphilones **2** were treated with *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) in dichloromethane to produce derivatives which were halogenated at the 5-position, and these were then converted into the corresponding acetates by treatment with acetic anhydride in the presence of triethylamine and DMAP, as shown in Table 5. Compounds **5a** and **5b** were prepared in the same way, by halogenation of the compound **2s** with NCS or NBS, respectively.

Compound **6** has a chlorine or bromine atom at the 5-position and an additional methyl group at the 1-position. It was prepared by the synthetic route illustrated in Scheme 2, which parallels the route shown in Scheme 1. Regioselective Friedel–Crafts acylation of the dimethylated compound **12** provided the intermediate **17**, which underwent nitration with $Cu(NO_3)_2$ in acetic acid to afford compound **18**. The fully substituted benzene **19** was then obtained by successive reduction and bromination of compound **18**. Compound **19** was then transformed into the key intermediate **21** by deamination and demethylation. It is worth noting that, compared with the BBr_3 method, the demethylation of **20** with $AlCl_3$ possesses many advantages, such as the low cost of the reagent, the mild reaction conditionsm, and the convenient workup procedure. Sonogashira coupling of **21** with phenylacetylene afforded compound **22**. Unfortunately, when we used the conditions previously explored to carry out the subsequent cycloisomerization

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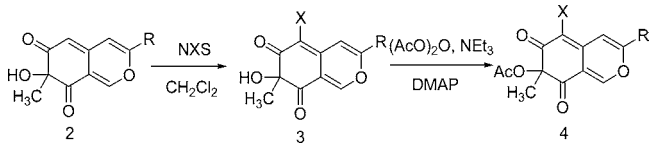
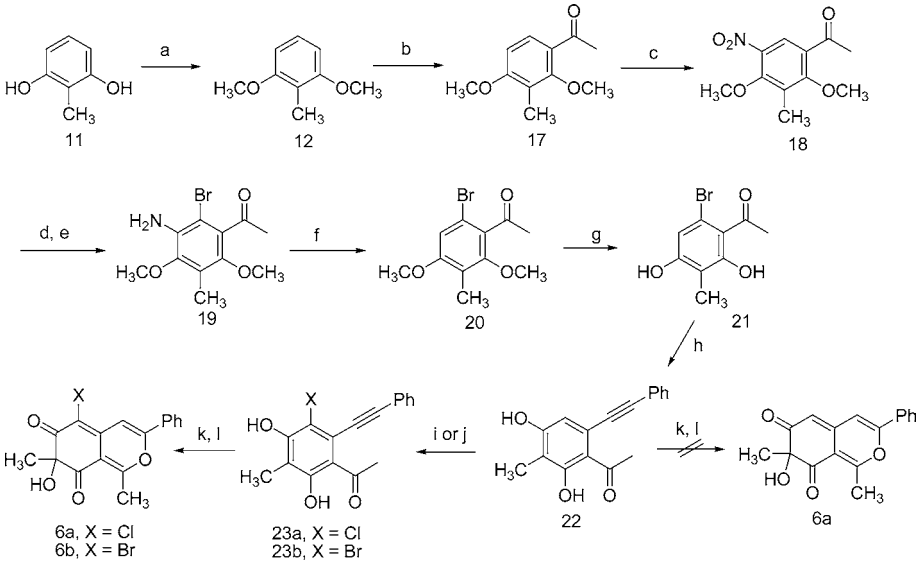
Table 5. Synthesis of Compounds 3 and 4 via Halogenation and Acetylation



			yield (%)					yield (%)	
no.	X	R	3	4	no.	X	R	3	4
1	Cl	C_6H_5–	**3a**$_1$ (60)	**4a**$_1$ (50)	22	I	3-CH_3–C_6H_4–	**3i**$_3$ (50)	**4i**$_3$ (42)
2	Br	C_6H_5–	**3a**$_2$ (70)	**4a**$_2$ (56)	23	Cl	3-F–C_6H_4–	**3j**$_1$ (63)	**4j**$_1$ (40)
3	I	C_6H_5–	**3a**$_3$ (58)		24	Br	3-F–C_6H_4–	**3j**$_2$ (66)	**4j**$_2$ (45)
4	Br	4-CH_3O–C_6H_4–	**3b**$_2$ (55)	**4b**$_2$ (50)	25	I	3-F–C_6H_4–	**3j**$_3$ (54)	**4j**$_3$ (22)
5	Cl	4-CH_3–C_6H_4–	**3c**$_1$ (52)	**4c**$_1$ (67)	26	Cl	3-Cl–C_6H_4–	**3k**$_1$ (59	
6	Br	4-CH_3–C_6H_4–	**3c**$_2$ (49)	**4c**$_2$ (43)	27	Br	3-Cl–C_6H_4–	**3k**$_2$ (71)	**4k**$_2$ (36)
7	I	4-CH_3–C_6H_4–	**3c**$_3$ (60)	**4c**$_3$ (54)	28	I	3-Cl–C_6H_4–	**3k**$_3$ (59)	**4k**$_3$ (17)
8	Cl	4-F–C_6H_4–	**3d**$_1$ (50)	**4d**$_1$ (45)	29	Cl	2-CH_3O–C_6H_4–	**3l**$_1$ (38)	**4l**$_1$ (47)
9	Br	4-F–C_6H_4–	**3d**$_2$ (80)	**4d**$_2$ (49)	30	Br	2-CH_3O–C_6H_4–	**3l**$_2$ (66)	**4l**$_2$ (67)
10	I	4-F–C_6H_4–	**3d**$_3$ (80)	**4d**$_3$ (52)	31	Cl	2-CH_3–C_6H_4–	**3m**$_1$ (63)	
11	Cl	4-CF_3–C_6H_4–	**3e**$_1$ (78)		32	Br	2-CH_3–C_6H_4–	**3m**$_2$ (70)	**4m**$_2$ (44)
12	Br	4-CF_3–C_6H_4–	**3e**$_2$ (65)	**4e**$_2$ (74)	33	Cl	2-F–C_6H_4–	**3n**$_1$ (52)	
13	I	4-CF_3–C_6H_4–	**3e**$_3$ (59)	**4e**$_3$ (21)	34	Br	2-F–C_6H_4–	**3n**$_2$ (29)	**4n**$_2$ (31)
14	Cl	4-$(CH_3)_3C$–C_6H_4–	**3f**$_1$ (74)	**4f**$_1$ (55)	35	Cl	2-Cl–C_6H_4–	**3o**$_1$ (40)	**4o**$_1$ (49)
15	Br	4-$(CH_3)_3C$–C_6H_4–	**3f**$_2$ (40)	**4f**$_2$ (38)	36	Br	2-Cl–C_6H_4–	**3o**$_2$ (67)	**4o**$_2$ (58)
16	I	4-$(CH_3)_3C$–C_6H_4–	**3f**$_3$ (74)	**4f**$_3$ (58)	37	Cl	2-CF_3–C_6H_4–	**3p**$_1$ (50)	
17	Br	4-NO_2–C_6H_4–	**3g**$_2$ (63)	**4g**$_2$ (42)	38	Br	2-CF_3–C_6H_4–	**3p**$_2$ (65)	**4p**$_2$ (83)
18	Cl	3-CH_3O–C_6H_4–	**3h**$_1$ (40)	**4h**$_1$ (27)	39	Cl	3,4-di-Cl–C_6H_3–	**3q**$_1$ (69)	
19	Br	3-CH_3O–C_6H_4–	**3h**$_2$ (50)	**4h**$_2$ (31)	40	Br	3,4-di-Cl–C_6H_3–	**3q**$_2$ (56)	**4q**$_2$ 30
20	Cl	3-CH_3–C_6H_4–	**3i**$_1$ (56)	**4i**$_1$ (55)	41	Cl	3,4-di-F–C_6H_3–	**3r**$_1$ (67)	**4r**$_1$ (38)
21	Br	3-CH_3–C_6H_4–	**3i**$_2$ (53)	**4i**$_2$ (53)	42	Br	3,4-di-F–C_6H_3–	**3r**$_2$ (63)	**4r**$_2$ (42)

Scheme 2[a]



[a]Reagents and conditions: (a) Me_2SO_4, K_2CO_3, 87%; (b) CH_3COCl, $AlCl_3$, 59%; (c) $Cu(NO_3)_2$, Ac_2O, 59%; (d) Pd/C, H_2; (e) Br_2, 77% over two steps; (f) HCl, $NaNO_2$, H_3PO_2, 84%; (g) $AlCl_3$, toluene, refluxing, 74%; (h) phenylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 85%; (i) for **31a**, 10 equiv of HCl, 3 equiv of IBX, 23%; (j) for **31b**, 10 equiv of HBr, 3 equiv of IBX, 75%; (k) $Au(OAc)_3$, DCE/TFA (10:1); (l) IBX, TBAB, 15% or 36% for X = Cl or Br in two steps, respectively.

and oxidation, we failed to obtain compound **6a**. However, compounds **6a** and **6b** were obtained successfully when we used compound **23** obtained by halogenation of compound **22** to perform the cycloisomerization reaction. This result showed that the halogen atom at the 3-position is favorable to this transformation.

Antifungal Activity. In general, antifungal activity from these compounds was limited to those assays conducted in artificial media. Activity on leaf-piece assays (particularly the *Septoria tritici* assay) was rare throughout. In general, compounds which displayed activity tended to lack potency, with activity on lower rates infrequent.

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Table 6. Antifungal Activity of Selected Compounds[a]

	hydroxyl analogues								acetyl analogues						
	Pi[b]	St	Uvf	Pd	As	Bf	Gz		Pi	St	Uvf	Pd	As	Bf	Gz
compd	200/60[c]	100	100	20/2	20/2	20/2	20/2	compd	200/60	100	100	20/2	20/2	20/2	20/2
3a$_1$	0/0	0	0	99/99	99/27	27/0	99/0	**4a$_1$**	0/−	99	0	99/77	0/0	0/0	0/0
3a$_2$	0/0	0	0	99/77	99/0	0/0	99/0	**4a$_2$**	0/−	49	0	99/99	0/0	0/0	0/0
3a$_3$	0/0	0	0	0/0	0/0	0/0	0/0								
3b$_2$	0/0	0	27	0/0	0/0	0/0	0/0	**4b$_2$**	0/0	18	NC	0/0	0/0	0/0	0/0
3c$_1$	0/77	0	55	99/49	99/0	99/0	99/0	**4c$_1$**	0/0	0	55	0/0	0/0	0/0	0/0
3c$_2$	0/0	51	99	49/49	0/0	27/27	0/0	**4c$_2$**	27/0	18	0	55/0	0/0	0/0	0/0
3c$_3$	0/0	0	0	0/0	0/0	0/0	0/0	**4c$_3$**	0/0	0	49	99/0	0/0	0/0	0/0
3d$_1$	49/27	0	55	99/0	0/0	0/0	0/0								
3d$_2$	49/0	0	0	99/0	99/0	77/0	77/0	**4d$_2$**	27/0	0	55	0/0	0/0	0/0	0/0
3d$_3$	0/0	0	0	0/0	0/0	0/0	0/0	**4d$_3$**	27/0	0	99	49/0	0/0	0/0	0/0
3e$_1$	27/0	0	77	0/0	0/0	27/0	0/0								
3e$_2$	49/0	18	NCH	99/49	99/0	99/27	99/0	**4e$_2$**	0/0	0	77	0/0	0/0	0/0	0/0
3e$_3$	0/0	0	0	0/0	0/0	0/0	0/0	**4e$_3$**	0/0	0	99	0/0	0/0	0/0	0/0
3f$_1$	0/0	0	NCH	0/0	0/0	0/49	0/0	**4f$_1$**	0/0	0	77	0/0	0/0	0/0	0/0
3f$_2$	99/49	36	55	99/0	99/0	99/0	99/0	**4f$_2$**	0/0	0	99	0/0	0/0	0/0	0/0
3f$_3$	0/0	0	27	0/0	0/0	0/0	0/0	**4f$_3$**	0/0	0	99	0/0	0/0	0/0	0/0
3g$_2$	77/27	0	27	0/0	0/0	0/0	0/0								
3h$_1$	27/49	0	0	99/0	0/0	0/0	99/0								
3h$_2$	49/55	0	0	99/55	55/0	77/0	99/0	**4h$_2$**	0/0	0	0	27/0	0/0	0/0	0/0
3i$_1$	0/49	18	55	99/0	77/0	77/0	99/0	**4i$_1$**	77/0	18	0	0/0	0/0	0/0	0/0
3i$_2$	0/49	69	55	99/0	77/0	77/0	99/0	**4i$_2$**	77/0	0	0	0/0	0/0	0/0	0/0
3j$_1$	0/0	0	0	99/0	99/0	55/0	77/0	**4j$_1$**	0/0	0	0	0/0	0/0	0/0	0/0
3j$_2$	0/0	0	0	99/49	99/0	55/0	77/0	**4j$_2$**	49/0	0	0	0/0	0/0	0/0	0/0
3j$_3$	0/0	0	0	0/0	0/0	0/0	0/0								
3k$_1$	27/49	0	49	0/49	0/0	0/0	0/0								
3k$_2$	0/0	33	27	99/49	99/0	99/0	99/0	**4k$_2$**	0/0	0	55	0/0	0/0	0/0	0/0
3k$_3$	0/0	0	27	0/0	0/0	0/0	0/0								
3l$_1$	49/0	0	0	0/0	0/0	0/0	0/0	**4l$_1$**	0/49	0	0	0/0	0/0	0/0	0/0
3l$_2$	0/0	0	0	77/27	0/0	27/0	0/0	**4l$_2$**	0/0	0	27	99/0	0/0	0/0	55/0
3m$_1$	49/49	0	0	99/99	77/0	55/0	99/0	**4m$_1$**	0/0	0	27	27/0	0/0	0/0	0/0
3m$_2$	0/55	18	0	99/27	0/0	55/0	99/0	**4m$_2$**	0/0	0	0	27/0	0/0	0/0	0/0
3n$_1$	49/49	0	0	99/49	77/0	55/0	99/0	**4n$_1$**	0/0	0	49	49/0	0/0	0/0	0/0
3n$_2$	0/0	0	0	0/0	55/0	0/0	0/0	**4n$_2$**	0/27	0	0	0/0	0/0	0/0	0/0
3o$_1$	27/77	0	0	99/0	55/0	55/0	99/0	**4o$_1$**	0/0	0	55	55/0	27/0	0/0	0/0
3o$_2$	27/0	18	55	99/49	55/0	99/0	99/0	**4o$_2$**	0/0	18	27	49/0	0/0	0/0	0/0
3p$_1$	0/0	0	0	99/77	0/0	0/0	27/0								
3p$_2$	0/27	0	0	99/55	0/0	27/0	55/0								
3q$_1$	0/0	0	0	0/0	49/0	55/0	27/0								
3q$_2$	0/0	0	0	0/0	0/0	27/27	27/0	**4q$_2$**	0/0	0	0	0/0	0/0	0/0	0/0
3r$_1$	49/0	0	0	99/0	0/0	0/0	0/0	**4r$_1$**	0/0	18	55	27/0	0/0	0/0	0/0
3r$_2$	77/49	18	0	99/0	0/0	0/0	0/0	**4r$_2$**	0/0	18	0	0/0	0/0	0/0	0/0
1	0/0	0	NCH	99/0	0/0	0/0	0/0								
2a	0/0	0	0	99/49	0/0	0/0	0/0								
5a	0/0	0	0	27/0	0/0	0/0	99/0								
5b	0/0	18	55	27/0	0/0	0/0	99/0								
6a	0/0	0	27	0/0	0/0	0/0	99/0								
6b	0/0	0	0	27/0	0/0	0/0	99/0								

[a]Equivalent hydroxyl and acetyl analogues are presented side by side for clear comparison. Values are mean assessment scores across replicates, as defined in Tables 2 and 3. Higher values indicate greater activity; NC indicates a test failure; NCH that no assessment was possible due to phytotoxic effects on the leaf pieces and "−" that the compound was not tested at that rate. [b]Pi = *Phytophthora infestans* (tested on tomato leaf pieces), St = *Septoria tritici* (tested on wheat leaf pieces), Uvf = *Uromyces viciae-fabae* (tested on bean leaf pieces); Pd = *Pythium dissimile*, As = *Alternaria solani*, Bf = *Botryotinia fuckeliana*, Gz = *Gibberella zeae* (all tested on artificial media). [c]Tested rates in ppm.

It is possible to draw some conclusions about the structure−activity relationship of the azaphilone derivatives. Initial testing of the series **2a**−**r** produced activity that was typically absent or limited to a single species on artificial media (compound **2a** is included in Table 6 as an example). Substituting a halogen at the 5-position (**3a**−**r**) improved the spectrum of activity in some cases. It was also clear that the free hydroxyl group plays an important role in activity, as compounds in which it is derivatized as the acetate (**4a**−**r**) were all found to be less active than their equivalent unprotected analogues.

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However, there was some variation in the data with regard to the relative effects of different halogens tried at the 5-position. While it is clear that substituting with iodine in this position (**3**[**n**]$_3$) results in poor activity, the effect of substitution with chlorine (**3**[**n**]$_1$) or bromine (**3**[**n**]$_2$) is dependent on the substitution on the side phenyl ring. For example, substituting a methyl group in the para position produces a broader spectrum of activity in the chloro-substituted analogue (**3c**$_1$ > **3c**$_2$), whereas a CF_3 in the para position results in broader spectrum in the bromo-substituted analogue (**3e**$_2$ > **3e**$_1$). Similarly, where the phenyl-ring substitution is a fluorine atom, placing it in the para position gave better activity in the bromo-substituted compound (**3d**$_2$ > **3d**$_1$), the meta position resulted in roughly equal activity in the two analogues (**3j**$_1$ = **3j**$_2$), while if the fluorine is placed in the ortho position the chloro-substituted analogue is clearly more active (**3n**$_1$ > **3n**$_2$). It also appears that polysubstitution on the phenyl ring is detrimental to the antifungal activity (**3q**, **3r**) regardless of the substitution at the 5-position.

Compounds with para substitutions of strongly electron-withdrawing (NO_2, compound **3g**$_2$) or electron-donating (OCH_3, compound **3b**$_2$) groups were found to have a poor spectrum of antifungal activity. However, these were only tested as bromo-substituted examples and, given the variation in spectrum produced by other combinations of substituents, firm conclusions cannot be drawn about the significance of these data. Methoxy groups were tested in other positions in combination with both halogen variants (**3h**, **3l**), but only the meta position and bromo-substituted combination (**3h**$_2$) showed broad-spectrum activity.

Further substitutions were also evaluated. Compounds with the phenyl moiety replaced with a benzyl (**5a**, **5b**), or with an additional methyl substituted at the 1-position (**6a**, **6b**), produced relatively poor levels of antifungal activity compared to the corresponding compounds **3a**$_1$ and **3a**$_2$.

In summary, we have synthesized a series of novel azaphilone analogues by replacement of the diene aliphatic side chain of sclerotiorin with aromatic substituents. Their synthesis was achieved using metal-catalyzed cycloisomerization of suitable 2-alkynylbenzaldehydes, followed by oxidation in the same pot, a sequence which allowed the preparation of azaphilone analogues with diverse side chains at the 3-position. Very interestingly, a number of these azaphilones (**3a**$_1$, **3a**$_2$, **3c**$_1$, **3d**$_2$, **3e**$_2$, **3f**$_2$, **3k**$_2$, etc.) exhibited good inhibition of the hyphal growth of various plant-pathogenic fungal pathogens. In particular, compound **3f**$_2$ displayed strong antifungal activity across a broad spectrum of the species tested.

The structure activity relationships of these compounds can be summarized: (1) The free hydroxyl at the quaternary center of azaphilones plays an important role in the antifungal activity. Acetylation of this hydroxyl group leads to a reduction in activity. (2) Substitution with halogens at the 5-position may improve the antifungal spectrum, but this is dependent on both the halogen chosen and any substitution on the side phenyl ring. Bromine and chlorine can both produce improvements in activity over unsubstituted compounds, but iodine is detrimental to the activity. (3) Antifungal activity is possible with either electron-withdrawing or electron-donating substituents on the phenyl ring. However, multiple substitutions on the phenyl ring are detrimental to activity. (4) The position of the substituent on the side phenyl ring can affect the level of antifungal activity. In general, where a derivative is active, those with substituents on the meta position of the phenyl will have better activity than those with equivalent substitutions on the para position or the ortho position but this may change with different substituents in the 5-position.

In conclusion, we have succeeded in simultaneously simplifying the structure of sclerotiorin and improving activity in the new analogues. However, the antifungal activity of these newly synthesized compounds is confined to the liquid culture assays and there is no significant activity in the leaf disk assays. The reason for this limitation is not clear at the present stage, and research to explain this difference is underway.

AUTHOR INFORMATION

Corresponding Author

*E-mail: gfyang@mail.ccnu.edu.cn (G.-F.Y.); yucheng.gu@syngenta.com (Y.-C.G.).

Author Contributions

‡Co-first authors.

Notes

The authors declare no competing financial interest.

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