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Synthesis and Bioactivity Evaluation of Novel Arylimines Containing a 3-Aminoethyl-2-[(*p*-trifluoromethoxy)anilino]-4(3*H*)-quinazolinone Moiety

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Supporting Information

ABSTRACT: Twenty-seven novel (*E*)-3-[2-arylideneaminoethyl]-2-[4-(trifluoromethoxy)anilino]-4(3*H*)-quinazolinone derivatives were synthesized by reacting various aromatic aldehydes with intermediate **6**. The target compounds were characterized by ^{1}H NMR, ^{3}C NMR, IR, and elemental analysis. Bioassay results revealed that some of the compounds have strong antifungal activities against six fungi (*Gibberella zeae*, *Fusarium oxysporum*, *Clematis mandshurica*, *Paralepetopsis sasakii*, *Phytophthora infestans*, and *Sclerotinia sclerotiorum*) and three bacteria (*Xanthomonas oryzae*, tomato bacterial wilt, and tobacco bacterial wilt). Notably, these compounds exhibited the highest activity against tomato bacterial wilt and *X. oryzae*, with 50% effective concentration (EC_{50}) values ranging from 45.96 to 93.31 μg/mL and from 20.09 to 21.33 μg/mL, respectively, which are superior to those of the commercial antibacterial agents thiodiazole-copper (99.80 μg/mL) and bismerthiazol (92.61 μg/mL). These results indicate that novel arylimine derivatives containing the 4(3*H*)-quinazolinone moiety can effectively control tobacco bacterial wilt, tomato bacterial wilt, and *X. oryzae*. Evaluation of their bactericidal properties in field studies as well as the mechanisms underlying their enhanced antibacterial activity should be interesting topics for future investigations.

KEYWORDS: *4(3H)-quinazolinone moiety, arylimine derivatives, antibacterial activities, antifungal activities*

INTRODUCTION

The 4(3*H*)-quinazolinone family is a group of high-potential, biologically active pharmacophoric nitrogen-containing heterocyclic molecules.[1,2] A large number of 4(3*H*)-quinazolinone derivatives have been reported to date, and they have received considerable attention in recent years because of their broad spectrum of biological properties, including antibacterial,[3−5] antifungal,[6] antimalarial,[7] antiviral,[8] anticancer,[9] and anticonvulsant[10−12] activities. Imines (also known as Schiff bases or azomethines), which are usually synthesized from the condensation of amines with active carbonyl groups, also exhibit a broad range of biological activities, including antifungal,[13,14] herbicidal,[15] insecticidal,[16] antibacterial,[17] and antiviral,[18] activities and inhibition of nitrification.[19] Various natural products with critical pharmacophores contain imine groups.[20] Efficient bioactivity of these compounds is mainly attributed to the alkyl/aryl/heteroaryl group at the second or third position in the quinazolin-4(3*H*)-one core or attached to the C═N moiety. For example, 2-methyl-3-[5-(4-chlorophenyl)-1,3,4-oxadiazole-2-yl]-quinazoline-4(3*H*)-ones exhibit moderate to high antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*, as well as antifungal activity against *Aspergillus niger* and *Fusarium oxysporum*, with minimal inhibitory concentrations (MICs) of 79, 75, 86, 70, 130, and 141 μg/mL, respectively.[21] Ilangovan et al.[22] reported a series of 2-aryl-3-aminoquinazoline-4(3*H*)-one semicarbazones with high inhibitory activity against *E. coli* and *Candida albicans*. Moreover, 6,8-dibromo-3-substituted phenylquinazoline-4(3*H*)-one derivatives were successfully synthesized by Mohamed et al.[23] In particular, 2-[4-(2-phenyl-6,8-dibromo-4-oxo-(4*H*)quinazolin-3-yl]-*N*-ethylamidobenzoic acid hydrazide exhibited the highest in vitro antimicrobial activity against *E. coli*, *Salmonella typhimurium*, *Listeria monocytogenes*, *S. aureus*, *P. aeruginosa*, and *Bacillus cereus*, with 1.56, 3.12, 1.56, 25, 25, and 25 μg/mL MICs, respectively. Meanwhile, 2-[4-(2-phenyl-6,8-dibromo-4-oxo-(4*H*)quinazolin-3-yl]-*N*-methylthioamidobenzoic acid hydrazide exhibited the highest in vitro antifungal activity against *C. albicans* and *Aspergillus flavus*, with 0.78 and 0.097 μg/mL MICs, respectively. In our previous work,[24,25] we showed that **I** [2-methyl-3-(2,3-dichlorobenzalamino)-4(3*H*)-quinazolinone] and **II** {(1*E*,4*E*)-1-aryl-5-[2-(quinazolin-4-yloxy)phenyl]-1,4-pentadien-3-one} exhibited high ex vivo antiviral activity against tobacco mosaic virus (TMV). Structure−activity relationship (SAR) analyses further suggested that the 4(3*H*)-quinazolinone moiety is crucial for its potent activity.

Plant bacteria, such as *Ralstonia solanacearum*, *Pseudomonas solanacearum*, and *Xanthomonas oryzae*, are extremely difficult to manage in agricultural production. The high incidence of mortality among infected plants and the lack of effective control methods make *R. solanacearum*, *P. solanacearum*, and *X. oryzae* three of the world's most destructive plant pathogens. Currently available traditional bactericides such as inorganic

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Figure 1. Schematic diagram for the synthesis of intermediate 6

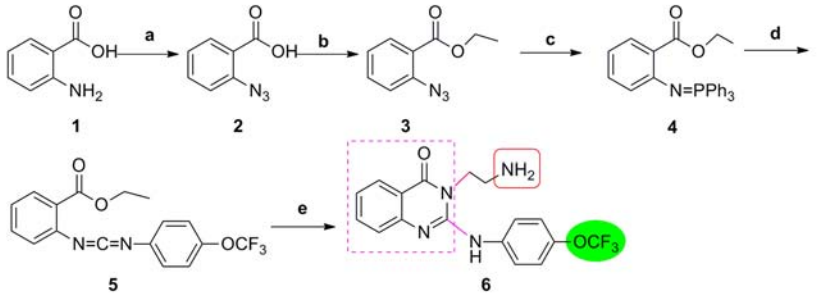

Figure 1. Schematic diagram showing the synthesis of intermediate **6**.

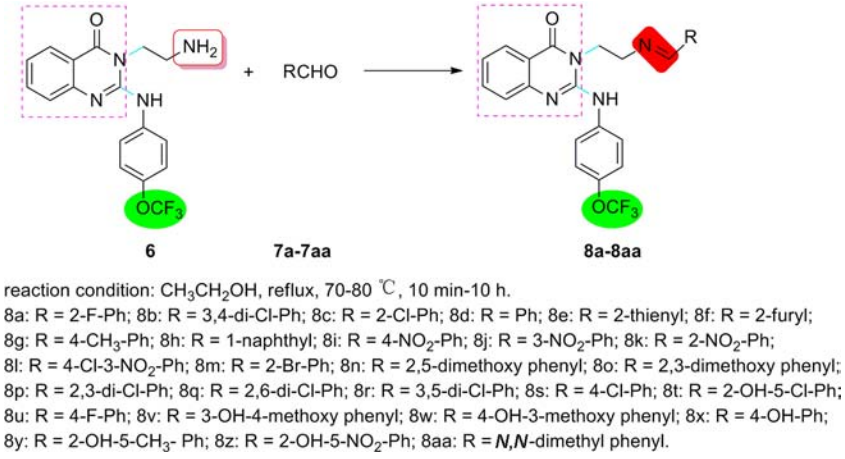

Figure 2. Schematic diagram showing the synthesis of final compounds **8a**−**8aa**.

bactericides (e.g., copper formulations) are not very effective and can even enhance resistance in host tobacco, tomato, and rice plants. Each year, pathogenic bacteria are responsible for billions of dollars in economic loss worldwide. Therefore, the search for alternative antibacterial agents remains a daunting task in pesticide science.[26]

On the basis of these considerations, a series of (*E*)-3-[2-(substituted-arylideneamino)ethyl]-2-[4-(trifluoromethoxy)-anilino]quinazolin-4(3*H*)-one derivatives were designed and synthesized (Figure 2). Biological assay revealed that some of the title compounds displayed good antibacterial and antifungal activities. For example, title compound **8f**, **8w**, and **8x** showed superior activities compared with the commercially available agricultural antibacterial agent thiodiazole-copper and bismerthiazol against tomato bacterial wilt and *X. oryzae* in vitro. The structure−activity relationship (SAR) analyses of antifungal and antibacterial and activities were also studied. To the best of our knowledge, this paper is the first to discuss the antibacterial activities of (*E*)-3-[2-arylideneaminoethyl]-2-[4-(trifluoromethoxy)anilino]quinazolin-4(3*H*)-one derivatives.

MATERIALS AND METHODS

Instruments. The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer using KBr disks. NMR was performed in a $CDCl_3$ or DMSO-d_6 solvent on a JEOL-ECX 500 NMR spectrometer operating at 500 and 125 MHz at room temperature and using TMS as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, and bs = broad singlet. All first-order splitting patterns were assigned on the basis of multiplet appearance. Splitting patterns that could not be easily interpreted were designated multiplet (m) or broad (br). Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Mass spectral studies were conducted on an Agilent 5973 organic mass spectrometer. Analytical TLC was performed on silica gel GF_{254}. Column chromatographic purification was performed using silica gel. All reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated, and redistilled prior to use.

General Procedures for the Preparation of Intermediate 6. Intermediate **6** was synthesized by a five-step process following previously reported procedures (Figure 1).[27,28] White, solid *o*-azidobenzoic acid **2** was synthesized from 13.7 g (0.1 mol) anthranilic acid via a diazotization azide reaction under a salt ice bath. A yellow, oily liquid of *o*-azidobenzoic acid ethyl ester **3** was obtained by esterification of 16.3 g (0.1 mol) *o*-azidobenzoic acid **2** with ethanol. *o*-Azidobenzoic acid ethyl ester **3** (10 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) was added to a solution of triphenylphosphine (2.62 g, 10 mmol) in anhydrous CH_2Cl_2 (20 mL). After stirring overnight and desolventizing under reduced pressure, the obtained residue was recrystallized with petroleum ether and then filtered to obtain a white, solid iminophosphorane **4**. Aromatic isocyanate (3 mmol) was added to a solution of iminophosphorane **4** (1.28 g, 3.0 mmol) in anhydrous THF (10 mL) at room temperature. The resulting mixture was stirred at 0−5 °C for 12 h to generate carbodiimide **5**, which was used directly without further purification. Afterward, **5** was added dropwise into a solution of primary diamines (3.0 mmol) in THF (10 mL). The reaction mixture was then stirred for 12 h at room temperature. Upon completion, the solvent was removed under reduced pressure, and the residue was recrystallized from CH_2Cl_2/CH_3OH (1:1, v/v) to obtain

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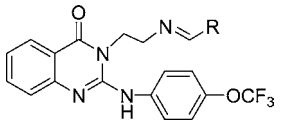
Table 1. Physical and Analytical Data of Synthesized Compounds 8a−8aa[a]



compd	R	molecular formula (MW)	time/h	mp/°C	yield[b]/%	elemental analysis (found/calcd)/% C	H	N
8a	2-F phenyl	$C_{24}H_{18}F_4N_4O_2$ (470.1)	1/2	170−171	98	61.26/61.28	3.99/3.86	12.08/11.91
8b	3,4-di-Cl phenyl	$C_{24}H_{17}Cl_2F_3N_4O_2$ (520.1)	1	160−161	95	55.60/55.29	3.23/3.29	10.52/10.75
8c	2-Cl phenyl	$C_{24}H_{18}ClF_3N_4O_2$ (486.1)	2/3	190−191	95	59.31/59.21	3.98/3.73	11.53/11.51
8d	phenyl	$C_{24}H_{19}F_3N_4O_2$ (452.2)	1	153−154	92	63.89/63.71	4.07/4.23	12.94/12.38
8e	2-thienyl	$C_{22}H_{17}F_3N_4O_2S$ (458.1)	4.5	168−169	85	57.16/57.64	3.65/3.74	12.62/12.22
8f	2-furyl	$C_{22}H_{17}F_3N_4O_3$ (442.1)	1/6	130−131	89	59.89/59.73	3.68/3.87	12.86/12.66
8g	4-CH_3 phenyl	$C_{25}H_{21}F_3N_4O_2$ (466.2)	1.5	143−144	69	64.22/64.37	4.20/4.54	12.20/12.01
8h	1-naphthyl	$C_{28}H_{21}F_3N_4O_2$ (502.2)	1.5	201−202	89	67.03/66.93	4.25/4.21	11.33/11.15
8i	4-NO_2 phenyl	$C_{24}H_{18}F_3N_5O_4$ (497.1)	3	134−135	88	57.82/57.93	3.38/3.65	14.26/14.08
8j	3-NO_2 phenyl	$C_{24}H_{18}F_3N_5O_4$ (497.1)	2	150−151	95	57.66/57.95	3.67/3.65	14.54/14.08
8k	2-NO_2 phenyl	$C_{24}H_{18}F_3N_5O_4$ (497.1)	10	136−137	88	57.59/57.95	3.62/3.65	14.52/14.08
8l	4-Cl-3-NO_2 phenyl	$C_{24}H_{17}ClF_3N_5O_4$ (531.1)	1.5	139−140	97	53.93/54.20	3.15/3.22	13.52/13.17
8m	2-Br phenyl	$C_{24}H_{18}BrF_3N_4O_2$ (530.1)	1/6	198−199	98	54.37/54.25	3.33/3.41	10.44/10.54
8n	2,5-dimethoxyl phenyl	$C_{26}H_{23}F_3N_4O_4$ (512.2)	4.5	175−176	88	61.07/60.93	4.13/4.52	11.04/10.93
8o	2,3-dimethoxyl phenyl	$C_{26}H_{23}F_3N_4O_4$ (512.2)	3	207−208	97	60.48/60.93	4.05/4.52	10.92/10.93
8p	2,3-di-Cl phenyl	$C_{24}H_{17}Cl_2F_3N_4O_2$(520.1)	1	175−176	87	55.21/55.29	3.03/3.29	11.05/10.75
8q	2,6-di-Cl phenyl	$C_{24}H_{17}Cl_2F_3N_4O_2$ (520.1)	1.5	157−158	52	55.23/55.29	3.04/3.29	11.04/10.75
8r	3,5-di-Cl phenyl	$C_{24}H_{17}Cl_2F_3N_4O_2$ (520.1)	2	186−187	90	55.44/55.29	2.93/3.29	10.98/10.75
8s	4-Cl phenyl	$C_{24}H_{18}ClF_3N_4O_2$ (486.1)	2	149−150	55	58.90/59.21	3.50/3.73	11.92/11.51
8t	2-OH-5-Cl phenyl	$C_{24}H_{18}ClF_3N_4O_3$ (502.1)	1/6	213-214	97	57.26/57.32	3.28/3.61	11.27/11.14
8u	4-F phenyl	$C_{24}H_{18}F_4N_4O_2$ (470.1)	1/4	152−153	64	61.30/61.28	3.47/3.86	12.31/11.91
8v	3-OH-4-OCH_3 phenyl	$C_{25}H_{21}F_3N_4O_4$ (498.2)	3	176−177	67	59.95/60.24	3.87/4.25	11.51/11.24
8w	4-OH-3-OCH_3 phenyl	$C_{25}H_{21}F_3N_4O_4$ (498.2)	3	156−157	50	59.87/60.24	3.77/4.25	11.20/11.24
8x	4-OH phenyl	$C_{24}H_{19}F_3N_4O_3$ (468.1)	1	186−187	40	61.70/61.54	3.63/4.09	12.11/11.96
8y	2-OH-5-CH_3 phenyl	$C_{25}H_{21}F_3N_4O_3$ (482.2)	1/6	211−212	97	62.47/62.24	4.03/4.39	12.10/11.61
8z	2-OH-5-NO_2 phenyl	$C_{24}H_{18}F_3N_5O_5$ (513.1)	1	138−139	53	63.45/63.02	4.89/4.88	14.53/14.13
8aa	*N*,*N*-dimethyl phenyl	$C_{26}H_{24}F_3N_5O_2$ (495.2)	1/4	244−246	88	56.18/56.14	3.52/3.53	13.92/13.64

[a]The reaction was performed according to the general experimental program. [b]Isolated yields based on 3-(2-aminoethyl)-2-(4-(trifluoromethoxy)-phenylamino)quinazolin-4(3*H*)-one **6**.

white, crystalline 3-aminoethyl-2-[(*p*-trifluoromethoxy)anilino]-quinazolin-4(3*H*)-one **6**: mp 159−160 °C; yield, 82%; IR (KBr, cm^{-1}) ν 3383 (N−H, NH_2), 3307 (N−H, Qu-ring-NH—Ar), 1670 (C═O), 1612 (C═N), 1562−1491 (C—C, benzene and Qu-ring); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.21 (s, 1H, Qu-ring-NH—Ar), 8.10 (t, $J_1 = J_2 = 8.0$ Hz, 1H, Qu—H), 7.40−7.58 (m, 3H, Qu—H, 1H, Ar—H), 7.19−7.28 (m, 3H, Ar—H), 4.23 (s, 2H, $-CH_2-$), 3.23 (s, 2H, $-CH_2NH_2$), 1.86 (bs, 2H, $-NH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.42, 148.95, 148.42, 144.04, 138.79, 134.43, 126.84, 125.54,123.66, 121.77, 120.94, 119.66, 118.22, 47.27, 41.47. Anal. Calcd for $C_{17}H_{15}F_3N_4O_2$: C, 56.04; H, 4.15; N, 15.38. Found: C, 55.94; H, 4.39; N, 15.61. MS (ESI) *m*/*z* 365.1 ($[M + H]^+$), 387 ($[M + Na]^+$).

General Synthetic Procedures for Title Compounds 8a−8aa. Target compounds **8a−8aa** were synthesized as schematized in Figure 2. Aromatic aldehyde (1.2 mmol) was added to a solution of 3-aminoethyl-2-[(*p*-trifluoromethoxy)anilino]quinazolin-4(3*H*)-one **6** (364 mg, 1 mmol) in anhydrous CH_3CH_2OH (15 mL) at 0−50 °C. The resulting mixture was refluxed to 75 °C with stirring for a specific reaction time (ranging from 10 min to 10 h). Upon completion of reaction (as indicated by TLC), the solvent was removed under depressurization, and the residue was recrystallized from CH_2Cl_2/CH_3CH_2OH (1:15, v/v). The product was then filtered, washed, and dried to obtain (*E*)-3-[2-(substituted-arylideneamino)ethyl]-2-[4-(trifluoromethoxy)anilino]quinazolin-4(3*H*)-one derivatives. The physical characteristics, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis data for all of the synthesized compounds are reported in the experimental protocols. The data for **8x** is shown below, and data for others can be found in the Supporting Information.

*(E)-3-[2-(4-Hydroxybenzylideneamino)ethyl]-2-[4-(trifluoromethoxy)anilino]quinazolin-4(3H)-one (**8x**):* white solid; IR (KBr, cm^{-1}) ν 3184 (N—H, Qu—ring—NH—Ar), 3041 (O—H, Ar—OH), 1678 (C═O), 1610 (C═N), 1442−1583 (C═C and N—H, benzene and Qu—ring and N—H bend), 1276 (C—N), 1222 (C—F), 1161 (Ar—C—O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H, Ar—OH), 8.23 (s, 1H, Qu—ring—NH—Ar), 8.01 (s, 1H, −N═CH−), 7.17−7.26 (m, 10H, Qu—H and Ar—H), 6.75 (s, 2H, Ar—H), 4.56 (s, 2H, ═N—CH_2-), 3.88 (s, 2H, N—CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.52, 162.38, 160.71, 148.71, 148.31, 143.93, 139.09, 130.39, 127.52, 126.92, 125.55, 123.87, 123.38, 121.78, 119.71, 118.08, 115.92, 58.71, 43.61. MS (ESI) *m*/*z* 499.1 ($[M + H]^+$), 521.1 ($[M + Na]^+$).

In Vitro Antifungal Bioassay. The antifungal activities were screened and evaluated against six pathogenic fungi, namely, *G. zeae*, *F. oxysporum*, *C. mandshurica*, *P. sasakii*, *P. infestans*, and *S. sclerotiorum*, by the poison plate technique.[29,30] All final compounds were dissolved in DMSO (1 mL) before mixing with potato dextrose agar (PDA; 90 mL). The compounds were tested at a concentration of 50 μg/mL. All fungi were cultivated in PDA at 27 ± 1 °C for 4 days to make new mycelium for the identification of antifungal activity. Then, mycelia dishes of approximately 4 mm diameter were cut from the culture medium. A mycelium was obtained using a germ-free inoculation needle and inoculated in the middle of the PDA plate aseptically. The inoculated plates were incubated at 27 ± 1 °C for 5 days. DMSO in

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Table 2. Fungicidal Activity of the Title Compounds 8a−8aa at a Concentration of 50 μg/mL

	inhibition rate[a] (%)					
compd	*G. zeae*	*F. oxysporum*	*C. mandshurica*	*P. sasakii*	*P. infestans*	*S. sclerotiorum*
8a	31.25 ± 0.97	12.73 ± 0.94	24.77 ± 1.97	16.94 ± 0.75	0.96 ± 0.93	36.57 ± 2.61
8b	37.19 ± 0.86	13.60 ± 0.97	19.88 ± 0.59	16.28 ± 0.81	5.85 ± 1.48	47.57 ± 1.84
8c	21.88 ± 0.90	0	13.76 ± 1.23	6.98 ± 0.87	0	21.04 ± 0.76
8d	46.56 ± 0.95	26.71 ± 1.98	13.76 ± 0.79	12.96 ± 1.03	3.83 ± 0.79	29.45 ± 0.98
8e	19.06 ± 0.98	3.11 ± 0.84	22.32 ± 1.17	12.29 ± 0.79	0	14.24 ± 2.06
8f	37.19 ± 0.86	8.39 ± 0.63	15.90 ± 0.52	22.59 ± 0.91	5.75 ± 0.64	39.16 ± 0.88
8g	47.50 ± 1.02	35.40 ± 1.28	10.70 ± 0.86	23.59 ± 1.11	9.58 ± 0.65	32.69 ± 2.08
8h	18.75 ± 1.01	3.42 ± 1.87	24.16 ± 1.19	7.31 ± 0.73	19.17 ± 0.69	29.45 ± 2.75
8i	40.63 ± 1.06	17.08 ± 1.00	7.03 ± 1.67	19.60 ± 0.77	2.88 ± 0.67	29.45 ± 0.88
8j	30.63 ± 1.39	0	3.36 ± 0.53	20.93 ± 1.32	13.10 ± 0.86	20.06 ± 0.71
8k	40.00 ± 1.52	7.76 ± 0.95	20.18 ± 0.63	18.94 ± 0.76	2.88 ± 0.67	28.48 ± 0.93
8l	38.75 ± 1.33	16.46 ± 0.82	13.15 ± 1.60	23.26 ± 1.24	19.81 ± 0.70	20.71 ± 0.71
8m	2.50 ± 0.84	0	21.41 ± 0.54	9.63 ± 0.72	0	25.57 ± 0.78
8n	40.00 ± 0.93	9.94 ± 0.83	3.36 ± 1.52	20.27 ± 0.99	16.61 ± 0.90	8.74 ± 0.90
8o	32.19 ± 1.65	9.63 ± 0.96	10.70 ± 0.56	17.28 ± 0.77	8.31 ± 1.25	6.47 ± 1.43
8p	35.00 ± 1.28	0	16.21 ± 0.57	8.64 ± 0.84	11.18 ± 0.70	51.78 ± 1.20
8q	35.00 ± 1.72	18.01 ± 0.91	34.25 ± 0.60	9.63 ± 0.72	8.31 ± 0.81	29.13 ± 0.99
8r	30.94 ± 1.54	0	10.09 ± 1.21	15.28 ± 0.92	12.14 ± 0.60	66.67 ± 1.55
8s	25.63 ± 0.92	42.55 ± 0.83	13.76 ± 0.79	29.24 ± 0.84	27.80 ± 1.10	20.06 ± 0.71
8t	11.25 ± 0.69	0	11.93 ± 0.78	6.31 ± 0.76	6.39 ± 0.64	27.51 ± 0.97
8u	53.88 ± 0.92	60.87 ± 0.97	10.70 ± 0.56	23.06 ± 1.50	34.82 ± 0.98	37.86 ± 1.46
8v	33.75 ± 0.99	12.11 ± 0.93	1.22 ± 0.48	19.27 ± 0.78	16.93 ± 1.14	25.89 ± 1.42
8w	36.88 ± 1.43	17.39 ± 0.87	1.25 ± 0.49	16.94 ± 0.75	12.46 ± 0.71	7.77 ± 0.71
8x	40.94 ± 0.89	7.14 ± 0.78	13.45 ± 1.45	8.97 ± 0.72	18.21 ± 1.03	9.06 ± 0.95
8y	17.50 ± 0.92	10.25 ± 1.14	2.75 ± 1.16	7.97 ± 1.09	17.89 ± 0.71	8.41 ± 0.82
8z	10.00 ± 1.00	0	21.41 ± 0.54	6.64 ± 1.29	18.85 ± 1.36	10.36 ± 1.28
8aa	36.25 ± 1.07	10.87 ± 0.80	10.70 ± 1.71	7.31 ± 1.01	16.93 ± 1.24	10.03 ± 1.10
hymexazol[b]	55.54 ± 3.90	56.12 ± 4.10	49.61 ± 7.84	51.21 ± 5.96	68.22 ± 2.41	77.51 ± 3.96
DMSO						

[a]Average of five replicates. [b]The commercial agricultural fungicide hymexazol was used for comparison of antifungal activity.

sterile distilled water served as the negative control, whereas hymexazol served as the positive control. Each treatment condition consisted of three replicates. Radial growth of the fungal colonies was measured, and the data were statistically analyzed. Inhibitory effects of the test compounds in vitro on these fungi were calculated by the formula $I\ (\%) = [(C - T)/(C - 0.4)] \times 100$, where C represents the diameter of fungal growth on untreated PDA, T represents the diameter of fungi on treated PDA, and I represents the inhibition rate.

In Vitro Antibacterial Bioassay. The antibacterial activities of some title compounds against *R. solanacearum* and *X. oryzae* were evaluated by the turbidimeter test.[26,31] The final compounds were dissolved in 150 μL of dimethylformamide (DMF) and diluted with water containing Tween-20 (0.1%) to obtain final concentrations of 200 and 100 μg/mL. DMF in sterile distilled water served as a blank control, whereas thiodiazole-copper served as a positive control. Approximately 1 mL of sample liquid was added to the nontoxic nutrient broth (NB, 1.5 g of beef extract, 2.5 g of peptone, 0.5 g of yeast powder, 5.0 g of glucose, and 500 mL of distilled water, pH 7.0 to 7.2) liquid medium in 4 mL tubes. Then, approximately 40 μL of NB containing tobacco bacterial wilt was added to 5 mL of solvent NB containing the test compounds or thiodiazole-copper. The inoculated test tubes were incubated at 30 ± 1 °C with continuous shaking at 180 rpm for 48 h. Culture growth was monitored with a spectrophotometer by measuring the optical density at 600 nm (OD_{600}) given by corrected turbidity values. The relative inhibitory rate (I%) of the circle mycelium compared with a blank assay was calculated as follows: $I\ (\%) = (C_{tur} - T_{tur})/C_{tur} \times 100$. C_{tur} is the corrected turbidity value of bacterial growth on untreated NB (blank control), and T_{tur} is the corrected turbidity value of bacterial growth on treated NB.

Similarly, the solvent for tomato bacterial wilt was SM (10.0 g of peptone, 5.0 g of glucose, 1.0 g of casein acid hydrolysate, 1000 mL of distilled water, pH 7.0−7.2), and thiodiazole-copper served as the positive control.

The solvent for *X. oryzae* was M210 (9.6 g of casein acid hydrolysate, 6.0 g of saccharose, 4.8 g of yeast powder, 3.6 g of K_2HPO_4, 0.36 g of $MgSO_4 \cdot 7H_2O$, 1200 mL of distilled water, pH 7.0−7.2), and thiodiazole-copper served as the positive control. The inoculated test tubes were incubated at 30 ± 1 °C with continuous shaking at 180 rpm for 24 h.

Some of the title compounds were tested against tobacco bacterial wilt and tomato bacterial wilt at five double-declining concentrations (e.g., 200, 100, 50, 25, and 12.5 μg/mL), and their corresponding EC_{50} values were obtained. Average EC_{50} was computed from at least three separate analyses of growth inhibition using the software package SPSS 17.0.

RESULTS AND DISCUSSION

A series of new quinazolinone analogues was synthesized with good yields within a short condensation reaction time. Their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis techniques, as shown in Table 1. The IR spectral data of compounds **8a−8aa** showed characteristic absorption bands at 3209−3517 cm^{-1}, which were assigned to N—H of Qu ring—NH—Ar. The absorption bands of the C═O and C═N groups of the skeleton stretching frequency appeared at 1690−1650 and 1600−1640 cm^{-1}, respectively. A singlet varying from 8.00 to 9.50 ppm in ^{1}H NMR belonged to Qu ring—NH—Ar and −N═CH− proton, and the singlet that appeared at δ_H 4.00 ppm to 4.99 ppm revealed the presence of ═N−CH_2− and N—CH_2−. The chemical shifts at

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Table 3. Antibacterial Activity of Compounds 8a−8aa against Tobacco Bacterial Wilt, Tomato Bacterial Wilt, and *Xanthomomu oryzae*

	inhibition rate[a] (%)					
	tobacco bacterial wilt		tomato bacterial wilt		*X. oryzae* pv. *oryzae*	
compd	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL
8a	61	29	38	27	40	14
8b	52	39	22	16	52	33
8c	33	23	39	23	27	11
8d	72	55	80	64	33	26
8e	53	24	12	7	28	11
8f	94	55	100	78	100	94
8g	100	62	54	48	79	50
8h	65	58	34	8	41	24
8i	32	12	71	55	35	26
8j	100	61	60	54	48	27
8k	91	54	59	39	36	16
8l	100	43	45	38	29	8
8m	56	43	21	0	25	15
8n	74	29	43	40	51	31
8o	28	24	42	41	11	9
8p	34	33	15	0	14	0
8q	38	24	15	7	50	11
8r	42	30	16	2	9	8
8s	28	25	55	44	30	17
8t	42	16	15	14	16	11
8u	40	31	67	63	27	12
8v	50	30	78	75	100	94
8w	76	30	100	77	100	93
8x	85	29	100	75	100	91
8y	42	35	0	0	22	10
8z	65	42	45	36	36	13
8aa	100	60	88	83	70	27
thiodiazole-copper[b]	50	30	100	67	35	29
bismerthiazol[b]					72	54
control	0	0	0	0	0	0

[a]Average of three replicates. [b]The commercial agricultural antibacterial agents thiodiazole-copper and bismerthiazol were used for comparison of antibacterial activity.

nearly 168.00, 40.00, and 55.00 ppm in ^{13}C NMR confirmed the existence of C═O, ═N—CH_2−, and Qu—N—CH_2− groups, respectively. Furthermore, all final products were confirmed by MS, which were in accordance with their molecular formulas.

Antifungal Activity Screening of Title Compounds 8a−8aa. The inhibitory effects of the synthesized (*E*)-3-[2-(substituted-arylideneamino)ethyl]-2-[4-(trifluoromethoxy)-anilino]quinazolin-4(3*H*)-one derivatives on the six phytopathogenic fungi were studied, and the mycelial growth rate method was selected for screening fungicides.[32] The results were compared with those obtained from hymexazol, a commercial fungicide with a broad spectrum of bioactivity, as indicated in Table 2. The final products **8a−8aa** against *G. zeae*, *F. oxysporum*, *C. mandshurica*, *P. sasakii*, *P. infestans*, and *S. sclerotiorum* displayed inhibition rates ranging from 2.50 to 53.88%, from 0 to 60.87%, from 1.22 to 34.25%, from 6.31 to 29.24%, from 0 to 34.82%, and from 7.77 to 66.67% at 50 μg/mL, respectively. The inhibition rates of 50 μg/mL of hymexazol on the corresponding fungi were 55.54, 56.12, 49.61, 51.21, 68.22, and 77.51%, respectively. Notably, **8u** showed potent antifungal activity compared with hymexazol against *G. zeae* (53.88 vs 55.54% inhibition) and *F. oxysporum* (60.87 vs 56.12% inhibition).

Antibacterial Biological Assay of Final Products 8a−8aa. A series of (*E*)-3-[2-(substituted-arylideneamino)ethyl]-2-[4-(trifluoromethoxy)anilino]quinazolin-4(3*H*)-ones **8a−8aa** was tested for in vitro antibacterial activity against three phytopathogenic bacteria (*X. oryzae*, tomato bacterial wilt, and tobacco bacterial wilt) by the turbidimeter test.[26] Commercial agricultural antibacterial thiodiazole-copper was used as reference, as shown in Table 3. Most of the compounds exhibited excellent antibacterial activity against tomato bacterial wilt and tobacco bacterial wilt at 100 or 200 μg/mL. Some of the compounds showed prominent activity against *X. oryzae* compared with thiodiazole-copper. In particular, compounds **8g**, **8j**, **8l**, and **8aa** and compounds **8f**, **8w**, and **8x** showed comparable antibacterial activity against tobacco bacterial wilt and tomato bacterial wilt at 200 μg/mL, respectively, compared with the standard drug thiodiazole-copper. However, the antibacterial activities of compounds **8f**, **8v**, **8w**, **8x**, and **8aa** against tomato bacterial wilt at 100 μg/mL were 78, 75, 77, 75, and 83%, respectively, exceeding that of thiodiazole-copper (67%). Most importantly, the antibacterial activities of compounds **8f**, **8v**, **8w**, and **8x** against *X. oryzae* at 200 and 100 μg/mL were 100 and 94%, 100 and 94%, 100 and 93%, and 100 and 91%, respectively, which were much higher than those

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of thiodiazole-copper (35 and 29%) or bismerthiazol (72 and 54%).

On the basis of previous bioassays, all test compounds showed moderate to excellent activity against plant pathogens (tobacco bacterial wilt and tomato bacterial wilt). The EC_{50} values of some of the synthesized compounds are listed in Table 4. Notably, compounds **8f**, **8j**, and **8aa** exhibited excellent

Table 4. Inhibitory Effect of Compounds 8f, 8g, 8j, 8l, and 8aa against Tobacco Bacterial Wilt[a]

compd	EC_{50} (μg/mL)	pEC_{50} (μM)	toxic regression eq	R
8f	78.90	3.7484	$y = 2.3702x + 0.5035$	0.9761
8g	121.36	3.5845	$y = 1.4607x + 1.9558$	0.9729
8j	65.09	3.8892	$y = 2.4076x + 0.6338$	0.9797
8l	99.81	3.7260	$y = 1.4178x + 2.1656$	0.9666
8aa	88.71	3.7468	$y = 1.6589x + 1.7685$	0.9981
thiodiazole-copper[b]	216.70		$y = 1.0312x + 2.9418$	0.9903

[a]Average of three replicates. [b]The commercial agricultural antibacterial agent thiodiazole-copper was used for comparison of antibacterial activity.

activities against tobacco bacterial wilt with EC_{50} values of 78.90, 65.09, and 88.71 μg/mL, respectively. Compounds **8d**, **8f**, **8j**, **8x**, and **8aa** showed strong activity against tomato bacterial wilt in vitro, with EC_{50} values of 80.75, 50.21, 96.08, 45.96, and 93.31 μg/mL, respectively. As indicated in Table 5,

Table 5. Inhibitory Effect of Compounds 8f, 8w, 8x, and 8aa against Tomato Bacterial Wilt[a]

compd	EC_{50} (μg/mL)	pEC_{50} (μM)	toxic regression eq	R
8f	50.21	3.9447	$y = 2.6567x + 1.1466$	0.9759
8w	51.46	3.9859	$y = 1.7045x + 2.0828$	0.9959
8x	45.96	4.0079	$y = 2.2004x + 1.3420$	0.9713
8aa	93.31	3.7249	$y = 1.6832x + 1.6842$	0.9897
thiodiazole-copper[b]	99.80		$y = 1.0301x + 2.9414$	0.9913

[a]Average of three replicates. [b]The commercial agricultural antibacterial agent thiodiazole-copper was used for comparison of antibacterial activity.

these values reflect stronger antibacterial activity of these compounds than that of the commercial bactericide thiodiazole-copper (99.80 μg/mL). Finally, compounds **8f**, **8v**, **8w**, and **8x** showed excellent antibacterial activity against *X. oryzae* in vitro, with EC_{50} values of 20.09, 20.83, 21.33, and 20.23 μg/mL, respectively. As shown in Table 6, these compounds are markedly more potent against *X. oryzae* than the commercial bactericide bismerthiazol (EC_{50} = 92.61 μg/mL).

SAR Analysis of Antifungal Activities. Results of our assessment of the antifungal activities of the synthesized compounds are shown in Table 2. Among the synthesized final compounds (**8a**–**8aa**), SAR based on activity against *G. zeae*, *F. oxysporum*, *P. sasakii*, and *P. infestans* showed that the substituent group at the 4-position of R (= CH_3 phenyl, F phenyl, Cl phenyl) had a critical effect on the antifungal activity of compounds **8g**, **8u**, and **8s**. Moreover, experiments on *C. mandshurica* and *S. sclerotiorum* indicated that the disubstituent group of R (= 2,6-di-Cl phenyl, 2,3-di-Cl phenyl, 3,5-di-Cl phenyl, and 3,4-di-Cl phenyl) was crucial for antifungal

Table 6. Inhibitory Effect of Compounds 8f, 8v, 8w, and 8x against *X. oryzae*[a]

compd	EC_{50} (μg/mL)	pEC_{50} (μM)	toxic regression eq	R
8f	20.09	4.3429	$y = 2.2590x + 2.0561$	0.9895
8v	20.83	4.3787	$y = 2.0497x + 2.2967$	0.9957
8w	21.33	4.3786	$y = 2.1413x + 2.1541$	0.9903
8x	20.23	4.3643	$y = 2.1343x + 2.2126$	0.9969
bismerthiazol[b]	92.61		$y = 1.4990x + 2.0520$	0.9800

[a]Average of three replicates. [b]The commercial agricultural antibacterial agent bismerthiazol was used for comparison of antibacterial activity.

activities of compounds **8b**, **8p**, **8r**, and **8q**. The final compounds with electron-withdrawing groups (4-F phenyl, 4-Cl phenyl, 2,6-di-Cl phenyl, 2,3-di-Cl phenyl, 3,5-di-Cl phenyl, and 3,4-di-Cl phenyl) were observed to show strong inhibition against the aforementioned fungi. Thus, our results show that electron-withdrawing substitutions are more preferable for improving the antifungal activities of these compounds.

SAR Analysis of Antibacterial Activities. Table 3 shows the results of our antibacterial bioassays. Thiodiazole-copper, a commercial agent for controlling *R. solanacearum* and *X. oryzae*, was used as a reference for comparison. Some of the compounds showed good potency against tobacco bacterial wilt. Different substituent groups were introduced into the quinazolin-4(3*H*)-one ring system to examine its SAR. Most of the final compounds showed low to high antibacterial activities against *R. solanacearum* and *X. oryzae* at 200 μg/mL. When R was substituted with phenyl, 2-furyl, 4-methylphenyl, 3-nitrophenyl, 2-nitrophenyl, 4-chloro-3-nitrophenyl, 4-hydroxyl-3-methoxyphenyl, 4-hydroxylphenyl, or 2-hydroxyl-5-nitrophenyl groups, the corresponding target compounds exhibited significant activity against tobacco bacterial wilt. Some of the compounds showed antibacterial activities comparable to that of thiodiazole-copper. The strongest activity against tomato bacterial wilt was observed when R was changed to phenyl, 2-furyl, 2-, 3- or 4-nitro substituted phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-hydroxyl-4-methoxy phenyl, 4-hydroxyl-3-methoxyphenyl, 4-hydroxylphenyl, or 2-hydroxyl-5-nitrophenyl groups. Some title compounds were found to be as potent as thiodiazole-copper. When R was substituted with 2-furyl, 4-methylphenyl, 3-hydroxyl-4-methoxyphenyl, 4-hydroxyl-3-methoxyphenyl, 4-hydroxylphenyl, or 2-hydroxyl-5-nitrylphenyl groups, the target compounds exhibited remarkable activities against *X. oryzae* that surpassed those of thiodiazole-copper or bismerthiazol. When R was changed to 2-furyl, 4-hydroxylphenyl, 4-hydroxyl-3-methoxyphenyl, or *N*,*N*-dimethyl groups, the resulting target compounds showed efficient broad-spectrum activities against all three bacteria.

On the basis of the values indicated in Tables 3–6, we could infer relationships between antibacterial activities and different aryl groups (style, position, and substituent group). Oxygen heterocyclic group of R was superior to sulfur heterocyclic and phenyl groups in terms of antibacterial activity. For example, inhibition rates of **8f** (R = 2-furyl) against tobacco bacterial wilt, tomato bacterial wilt, and *X. oryzae* were 94 and 55%, 100 and 78%, and 100 and 94%, at 200 and 100 μg/mL, respectively. By contrast, **8e** (R = 2-thienyl) displayed only 53 and 24%, 12 and 7%, and 28 and 11% inhibition rates at the same conditions. The presence of the $-NO_2$, $-CH_3$, or $-OH$ groups in a compound was found to be more effective than that of other groups in improving its antibacterial activity. For instance,

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inhibition rates of **8g** (R = 4-methylphenyl), **8j** (R = 3-nitrophenyl), **8l** (R = 4-chloro-3-nitrylphenyl), and **8aa** (R = 4-*N*,*N*-dimethylphenyl) against tobacco bacterial wilt were all 100% at 200 μg/mL. Moreover, **8w** (R = 4-hydroxyl-3-methoxyphenyl), **8x** (R = 4-hydroxyphenyl), and **8aa** (R = 4-*N*,*N*-dimethylphenyl) consistently showed 100% inhibition rates against tomato bacterial wilt with EC_{50} values of 51.46, 45.96, and 93.31 μg/mL, whereas **8v** (R = 3-hydroxyl-4-methoxyphenyl), **8w** (R = 4-hydroxyl-3-methoxyphenyl), and **8x** (R = 4-hydroxylphenyl) all exhibited 100 (94), 100 (93), and 100% (91%) inhibition rates against *X. oryzae* at 200 (100) μg/mL, respectively, with EC_{50} values ranging from 20.09 to 21.33 μg/mL.

Our antibacterial bioactivity assays and preliminary SAR data revealed that arylimine derivatives containing quinazolinone moieties had good antibacterial activity. A possible explanation for the increase in antibacterial activity of the compounds we tested is as follows: we introduced an *N*-aryl group in position 2 of the quinazolinone fragment of the target compound, resulting in retainment of the hydrogen-bonding donor group. Then, an aminoethyl group was inserted on the quinazolinone fragment at position 3, which may have enhanced the flexibility of the molecular backbone, allowing it to combine with the lowest energy and receptor protein molecular pathogenic bacteria. The nitrogen atom in the C═N bond has a lone pair of electrons due to SP^2 hybridization and can been regarded as a hydrogen bond acceptor. This perhaps is the key to improve the antibacterial activity of the target compounds.

In summary, a series of novel arylimine derivatives containing a quinazolinone nucleus was synthesized with moderate to good yields and screened for biological activity. All of the final compounds were confirmed on the basis of spectral data (^{1}H NMR, ^{13}C NMR, MS, and IR), elemental analysis, and melting points and were further subjected to various assays of biological activity including in vitro antifungal and antibacterial activities. Preliminary SAR analysis indicated that $-CH_3$, $-NO_2$, −OH or *N*,*N*-dimethyl groups on the benzene ring (substituted for R) enhanced the antifungal and antibacterial activities of the synthesized compounds. Moreover, introduction of −F, $-CH_3$, $-NO_2$, or −OH aromatic compounds resulted in moderate to good antifungal activities against *G. zeae*, *F. oxysporum*, and *S. sclerotiorum*. Antibacterial tests showed that all of the synthesized final products containing 2-furyl, −OH, or $-NO_2$ groups exhibited significant antibacterial activity against *R. solanacearum* and *X. oryzae*. In addition, our antibacterial assays demonstrated that the inhibition rates of compounds **8f**, **8w**, and **8x** were better than those of the commercial bactericides thiodiazole-copper and bismerthiazol. To our knowledge, this is the first report on the use of arylimine derivatives containing quinazolinone moieties as potential disease control agents against *R. solanacearum* and *X. oryzae*. Further evaluation of their bactericidal properties, particularly in field studies examining their biological efficacy, crop safety, and toxicity, is necessary before they can be adopted for widespread use.

■ ASSOCIATED CONTENT

Supporting Information

Results of our physical and analytical assays as well as data on the synthesis and characterization of intermediate **6** and target compounds **8a**−**8aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ABRREVIATIONS USED

TLC, thin layer chromatography; EC_{50}, 50% effective concentration; ^{1}H NMR, ^{1}H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; MS, mass spectroscopy

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