European Journal of Medicinal Chemistry 77 (2014) 65–74

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis, and antibacterial activity of novel Schiff base derivatives of quinazolin-4(3*H*)-one

Xiang Wang [a,b], Juan Yin [a], Li Shi [a], Guoping Zhang [a], Baoan Song [a,*]

[a] State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research, and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, People's Republic of China
[b] College of Chemistry and Materials Engineering, Kaili University, Kaili 556011, People's Republic of China

Keywords:
Schiff base derivative
Quinazolin-4(3*H*)-one
Synthesis
Ralstonia solanacearum
Antibacterial activity

A B S T R A C T

Novel imine derivatives of quinazolin-4(3*H*)-one were designed and synthesized by using aminoethyl moieties to increase the amine bridge of quinazolin-4(3*H*)-one amine and then introducing various aromatic aldehydes. The target compounds were characterized by proton nuclear magnetic resonance spectroscopy (^{1}H NMR), carbon nuclear magnetic resonance spectroscopy (^{13}C NMR), mass spectrometry (MS), infrared spectroscopy (IR), elemental analysis, and X-ray diffraction crystallography. Bioassay results indicated that some of the compounds showed good to excellent antibacterial activities against tobacco bacterial wilt and tomato bacterial wilt. The 50% effective concentrations (EC_{50}) of the compounds against tobacco and tomato bacterial wilts ranged from 63.73 μg/mL to 201.52 μg/mL and 38.64 μg/mL to 81.39 μg/mL, respectively, which are lower than that the positive control thiodiazole copper (216.70 and 99.80 μg/mL). These results indicated that novel Schiff base derivatives containing the 4(3*H*)-quinazolinone moiety can effectively control tobacco and tomato bacterial wilts.

1. Introduction

Ralstonia solanacearum (*R. solanacearum*), one of the highest destructive and widespread soil-borne phytopathogenic bacteria. The hosts of *R. solanacearum* include economically important plants, such as tomato, tobacco, potato, banana, pepper, and peanut. *R. solanacearum* can enter plant roots through wounds and multiply in the cortical tissue before invading the xylem elements [1–5]. The high incidence of plant mortality and the lack of effective control methods make *R. solanacearum* the world's most destructive plant pathogen. Currently available traditional bactericides, such as inorganic bactericides (e.g., copper formulations), are not highly effective and can even enhance resistance in host tobacco and tomato plants. Each year, pathogenic bacteria are responsible for billions of dollars of economic losses worldwide. Therefore, the search for alternative antibacterial agents remains a daunting task in pesticide science [6,7].

The Schiff base family is composed of natural products with critical pharmacophores [8]. It can be used as ideal lead structures to develop agrochemicals and medicines, including fungicide [9,10], bactericide [11], antiviral agent [12], herbicide [13], insecticide [14], antioxidant agent [15], antiproliferative [16,17], and antimicrobial drug [18,19]. Various natural alkaloids with critical pharmacophores contain quinazolinone groups. For example, febrifugine, isofebrifugine, thiabutazide, (−)-benzomalvin A, 2-(4-hydroxybutyl) quinazolin-4-one, and luotonin F was found in the plants, animals, and microorganisms (Fig. 1) [20–22], Luotonins A, B, C, D, E, and F are novel alkaloids that have been isolated from the aerial parts of *Peganum nigellastrum* Bunge, which has a long history in Chinese medicine for the treatment of rheumatism, inflammation, abscesses, and other maladies [23]. Meanwhile, 4(3*H*)-quinazolinone derivatives have attracted considerable attention in recent years because of their broad-spectrum biological properties, such as antiinflammatory [24], antifungal [25], antibacterial [26,27], anticoccidial [28], antiviral [29–31], and antimicrobial [32] activities. The efficient bioactivity of these compounds is mainly attributed to the alkyl/aryl/heteroaryl group with multi-substituents in the quinazolin-4(3*H*)-one core or attached to the C=N moiety. The current research on the activity of imine derivatives of quinazolin-4(3*H*)-one

Abbreviations: TLC, thin layer chromatography; mp, melting point; IR, Infrared; ^{1}H NMR, proton nuclear magnetic resonance; ^{13}C NMR, carbon nuclear magnetic resonance; MS, mass spectroscopy; EC_{50}, 50% effective concentration; SAR, structure–activity relationship; *R. solanacearum*, *Ralstonia solanacearum*.

* Corresponding author.
E-mail address: songbaoan22@yahoo.com (B. Song).

http://dx.doi.org/10.1016/j.ejmech.2014.02.053
0223-5234/

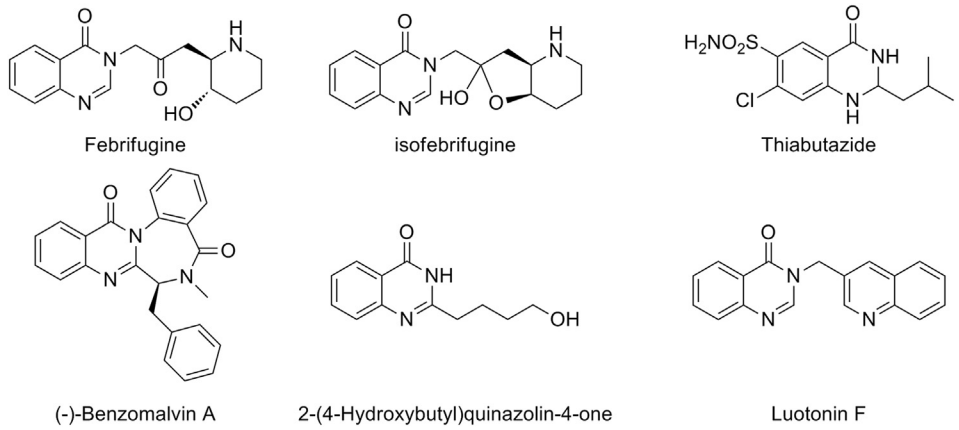
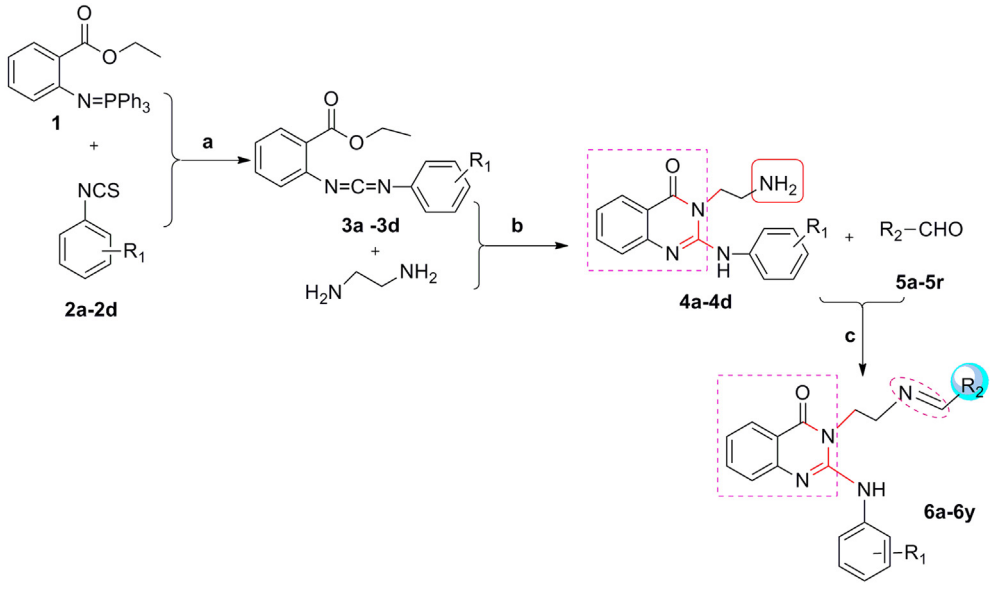


Fig. 1. Examples of natural products bearing quinazolin-4-one skeleton.

and their analogues has mainly focused on antimicrobial inhibition of *Escherichia coli*, *Salmonella typhimurium*, *Candida albicans* and *Aspergillus flavus* [33], antibacterial and antifungal activities [34]. In our previous work, we reported that some quinazolin or C=N containing compounds elicited antiviral activities against tobacco mosaic virus and cucumber mosaic virus [29,31]. We also found that a series of arylimine derivatives containing a 3-aminoethyl-2-[(p-trifluoromethoxy)anilino]-4(3*H*)-quinazolinone moiety could inhibit the growth of *R. solanacearum* and *Xanthomonas oryzae* [35]. We proposed that an *N*-aryl group in position 2 and an aminoethyl group in position 3 on the quinazolinone core might sufficiently enhance the flexibility of the molecular backbone.

On the basis of these considerations, a series of new (*E*)-3-[2-(substituted-arylideneamino) ethyl]-2-[substituted-anilino]quinazolin-4(3*H*)-one derivatives were designed and synthesized from 4(3*H*)-quinazolinone derivatives and various aromatic aldehydes via condensation reaction (Scheme 1), and their antibacterial activities against tobacco and tomato bacterial wilts were systematically evaluated for the first time. Results of bioassays indicate that most synthesized compounds exhibit strong antibacterial activities



reaction condition: **a**: R^1ArNCO, THF, 0-5 ℃, 10 h; **b**: $H_2NCH_2CH_2NH_2$, THF, 10 h; **c**: CH_3CH_2OH, reflux, 70-80 ℃, 12 min-8 h.

6a: R^1 = H, R^2 = 2,6-di-Cl-Ph; **6b**: R^1 = H, R^2 = 2-F-Ph; **6c**: R^1 = H, R^2 = 1-naphthyl; **6d**: R^1 = H, R^2 = 3,4-di-Cl-Ph; **6e**: R^1 = H, R^2 = 2-Cl-Ph; **6f**: R^1 = H, R^2 = 2-OH-5-CH_3-Ph; **6g**: R^1 = H, R^2 = 2-OH-5-OCH_3-Ph; **6h**: R^1 = H, R^2 = 4-*N*,*N*-di-CH_3-Ph; **6i**: R^1 = 4-CH_3, R^2 = 2-F-Ph; **6j**: R^1 = 4-CH_3, R^2 = 3-OH-4-OCH_3-Ph; **6k**: R^1 =4-CH_3, R^2 = 1-naphthyl; **6l**: R^1 = 4-CH_3, R^2 = 4-Br-Ph; **6m**: R^1 = 4-CH_3, R^2 = 2-NO_2-Ph; **6n**: R^1 = 4-CH_3, R^2 = 3-NO_2-Ph; **6o**: R^1 =4-CH_3, R^2 = 4-Cl-Ph; **6p**: R^1 = 3-CH_3, R^2 = 4-*N*,*N*-di-CH_3-Ph; **6q**: R^1 = 3-CH_3, R^2 = 2,6-di-Cl-Ph; **6r**: R^1 = 3-CH_3, R^2 = 4-F-Ph; **6s**: R^1 = 3-CH_3, R^2 = 4-OH-Ph; **6t**: R^1 =4-Cl, R^2 = 4-Cl-3-NO_2-Ph; **6u**: R^1 = 4-Cl, R^2 = Ph; **6v**: R^1 = 4-Cl, R^2 = 3-NO_2-Ph; **6w**: R^1 = 4-Cl, R^2 = 3-OCH_3-Ph; **6x**: R^1 = 4-Cl, R^2 = 3-OH-4-OCH_3-Ph; **6y**: R^1 = 4-Cl, R^2 = 4-*N*,*N*-di-CH_3-Ph.

Scheme 1. Schematic for the synthesis of final compounds **6a**–**6y**.

against tobacco and tomato bacterial wilts. In particular, the EC_{50} values of compound **6x** against tobacco and tomato bacterial wilts were 84.72 and 49.26 μg/mL, respectively. Notably, compound **6x** showed much higher than thiodiazole copper (EC_{50} 216.70 and 99.80 μg/mL).

2. Results and discussion

2.1. Chemistry

A series of new Schiff base derivatives containing the 4(3*H*)-quinazolinone moiety were rapidly synthesized with good yields by condensation reactions. The structures of the compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, IR, elemental analysis, and X-ray diffraction crystallography. Spectral data are provided in Tables 1 and 2. The compounds were screened for their *in vitro* antimicrobial activities against tobacco and tomato bacterial wilts. The EC_{50} of some of the synthesized compounds were also determined.

2.2. Analytical spectral data of compounds *6a–6y*

The IR spectral data of compounds **6a–6y** showed characteristic absorption bands at 3531 cm^{-1}–3184 cm^{-1}, which were assigned to the N–H of Qu–**NH**–Ar. The absorption bands of the C=O and C=N groups of the skeletal stretching frequency appeared at 1678 cm^{-1}–1654 cm^{-1} and 1631 cm^{-1}–1604 cm^{-1}, respectively. The absorption bands at 1598 cm^{-1}–1471 cm^{-1} belonged to the stretching frequency of C=C on benzene and to the bending of N–H on Qu–**NH**–Ar. A singlet varying from 9.45 ppm–8.16 ppm in the ^{1}H NMR spectra belonged to Qu–N**H**–Ar and –N=C**H**–, and the singlet or triplet that appeared at δ_H 4.68 ppm–4.01 ppm revealed the presence of =N–C**H$_2$**– and Qu–C**H$_2$**–. The chemical shifts from 169.91 ppm–158.21 ppm and at nearly 45.00 ppm and 59.00 ppm in the ^{13}C NMR spectra confirmed the existence of **C**=O or **C**=N and = N–**C**H_2– and Qu–**C**H_2–, respectively. All the final products were confirmed by MS according to their molecular formulae. All the spectra exhibited parent peaks because of molecular ions (M+1), and the halogen-substituted compounds produced the (M+2) peak. The structure of (*E*)-3-[2-((4-chloro-3-nitrobenzylidene)amino)ethyl]-2-[(4-chlorophenyl)-amino]quinazolin-4(3*H*)-one **6t** was also confirmed by X-ray diffraction (Fig. 2). Crystallographic data (excluding structure factors) for the structure had been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-971755 [38].

2.3. In vitro antibacterial bioassay

The antibacterial activity of all the test compounds were determined by performing a turbidimeter test as previously described [35,36]. The commercial plant bactericide thiodiazole copper was used to compare the antibacterial activities of the compounds (Table 3). The title compounds with excellent antibacterial activities were tested against tobacco and tomato bacterial wilts at five double-declining concentrations (e.g., 200, 100, 50, 25, and 12.5 μg/mL), and their corresponding EC_{50} values were obtained. The average EC_{50} was computed from at least three separate analyses of growth inhibition using the software package SPSS 17.0. Screening results are summarized in Tables 4 and 5.

As shown in Table 3, the primary *in vitro* bioassay results revealed that all test compounds at 100 μg/mL or 200 μg/mL exhibited moderate to excellent antibacterial activities against tobacco and tomato bacterial wilts. In particular, compounds **6g**, **6h**, **6k**, **6l**, **6n**, **6o**, **6p**, **6t**, and **6x** at 200 μg/mL showed comparable antibacterial activities against tobacco bacterial wilt compared with the standard drug thiodiazole copper. The inhibition rates of compounds **6g**, **6l**, **6o**, **6p**, and **6w** at 100 μg/mL were 67%, 79%, 68%, 66%, and 61%, respectively, which were much higher than those of thiodiazole copper (50%) at 200 μg/mL. In addition, the inhibition rates of compounds **6q**, **6t**, **6v**, and **6x** at 200 μg/mL against tomato bacterial wilt were all 100%, which was equivalent to that of the standard drug thiodiazole copper. Compounds **6f**, **6q**, **6v**, and **6x** at 100 μg/mL showed 81%, 91%, 71%, and 78% inhibition rates, respectively, which exceeded that of thiodiazole copper (67%).

Basing on previous *in vitro* bioassays, we found that some of the compounds showed excellent activities against plant pathogens, including tobacco and tomato bacterial wilts. The EC_{50} values for some of the synthesized compounds are calculated and summarized in Tables 4 and 5. Most of the evaluated compounds exhibited

Table 1
Physical and analytical date of synthesized compounds **6a–6y**.[a]

Compd.	Molecular formular (M.W)	Time (h)	Yield (%)[b]	Elemental analysis (%): found/calcd.		
				C	H	N
6a	$C_{23}H_{18}Cl_2N_4O$ (436.1)	1	92	63.30/63.17	4.37/4.15	12.47/12.81
6b	$C_{23}H_{19}FN_4O$ (386.2)	1.5	95	71.62/71.49	5.04/4.96	14.64/14.50
6c	$C_{27}H_{22}N_4O$ (418.2)	0.5	90	77.19/77.49	5.53/5.30	13.53/13.39
6d	$C_{23}H_{18}Cl_2N_4O$ (436.1)	1	92	63.16/63.17	3.99/4.15	12.73/12.81
6e	$C_{23}H_{19}ClN_4O$ (402.1)	0.3	88	68.53/68.57	4.50/4.75	13.84/13.91
6f	$C_{24}H_{22}N_4O_2$ (398.2)	0.5	95	71.99/72.34	5.54/5.57	14.22/14.06
6g	$C_{24}H_{22}N_4O_3$ (414.2)	0.5	90	69.53/69.55	4.96/5.35	13.45/13.52
6h	$C_{25}H_{25}N_5O$ (411.2)	0.5	88	72.84/72.97	5.91/6.12	17.14/17.02
6i	$C_{24}H_{21}FN_4O$ (400.2)	0.2	89	72.00/71.98	5.58/5.29	13.93/13.99
6j	$C_{25}H_{24}N_4O_3$ (428.2)	1	93	70.34/70.08	5.77/5.65	13.05/13.08
6k	$C_{28}H_{24}N_4O$ (432.2)	0.5	84	77.83/77.75	5.67/5.59	12.96/12.95
6l	$C_{24}H_{21}BrN_4O$ (460.1)	1	94	62.30/62.48	4.86/4.59	12.09/12.14
6m	$C_{24}H_{21}N_5O_3$ (427.2)	4	94	67.13/67.44	5.05/4.95	16.19/16.38
6n	$C_{24}H_{21}N_5O_3$ (427.2)	4	92	67.06/67.44	4.97/4.95	16.78/16.38
6o	$C_{24}H_{21}ClN_4O$ (416.2)	8	84	69.47/69.14	5.14/5.08	13.64/13.44
6p	$C_{26}H_{27}N_5O$ (425.2)	1	87	73.79/73.39	6.53/6.40	16.09/16.46
6q	$C_{24}H_{20}Cl_2N_4O$ (450.1)	8	88	63.98/63.87	4.19/4.47	12.45/12.41
6r	C24H21FN4O (400.2)	3	58	72.02/71.98	4.99/5.29	14.12/13.99
6s	$C_{24}H_{22}N_4O_2$ (398.2)	3	89	72.08/72.34	5.19/5.57	14.37/14.06
6t	$C_{23}H_{17}Cl_2N_5O_3$ (481.1)	1.5	88	57.35/57.27	3.58/3.55	14.25/14.52
6u	$C_{23}H_{19}ClN_4O$ (402.1)	1.5	84	68.54/68.57	4.58/4.75	13.58/13.91
6v	$C_{23}H_{18}ClN_5O_3$ (447.1)	1.5	93	61.29/61.68	4.23/4.05	15.39/15.64
6w	$C_{24}H_{21}ClN_4O_2$ (432.1)	2	99	66.24/66.59	4.78/4.89	13.01/12.94
6x	$C_{24}H_{21}ClN_4O_3$ (448.1)	2	87	64.57/64.21	4.82/4.72	12.88/12.48
6y	$C_{25}H_{24}ClN_5O$ (445.2)	0.7	99	67.43/67.33	5.04/5.42	15.77/15.70

[a] The reaction was performed according to general experimental program.
[b] Isolated yields based on Intermediate **4a–4d**.

Table 2
Crystal structure data collection and handling of synthesized compound **6t**.

Entry	Items	Data collection and handling
1	Crystal system	Monoclinic, yellow crystal
2	Crystal Size	0.23 × 0.20 × 0.20 mm^3
3	Wavelength	Mo K_α radiation (0.71073 Å)
4	μ	2.11 cm^{-1}
5	Diffractometer, scan mode	Bruker APEX-II CCD, φ and ω
6	$2\theta_{max}$	52°
7	$N(hkl)_{measured}$, $N(hkl)_{unique}$	16092, 4231
8	Criterion for I_{obs}, $N(hkl)_{gt}$	$I_{obs} > 2\ s(I_{obs})$, 3581
9	$N(param)_{refined}$	291
10	Programs	SHELX-97
11	Spatial configuration	*E*

favourable inhibitory activities against tobacco and tomato bacterial wilts. Notably, compounds **6g**, **6h**, **6l**, **6n**, **6p**, and **6x** exhibited excellent activities against tobacco bacterial wilt, with EC_{50} values of 63.73, 76.46, 89.43, 99.37, 87.04, and 84.72 μg/mL, respectively. As indicated in Table 4, these compounds had stronger antibacterial activities than the commercial bactericide thiodiazole copper (216.70 μg/mL). Compounds **6q**, **6t**, **6v**, and **6x** showed strong activities against tomato bacterial wilt *in vitro*, with EC_{50} values of 38.64, 81.39, 50.18, and 49.26 μg/mL, respectively. As shown in Table 5, these compounds had stronger antibacterial activities against tomato bacterial wilt than the commercial bactericide thiodiazole copper (99.80 μg/mL). Particularly, compound **6x** showed a comparable or stronger antibacterial activity against tobacco and tomato bacterial wilts compared with thiodiazole copper. Thus, compound **6x** was regarded as the most promising antibacterial agent and chosen for further evaluation.

2.4. SAR of the Schiff base derivatives of quinazolinones

A SAR for test compounds **6a**–**6y** can be drawn from the above antibacterial bioassay evaluation as follows. Most of the final compounds at 200 μg/mL showed moderate to good antibacterial activities against tobacco and tomato bacterial wilts. Stronger activities against tobacco bacterial wilt compared with thiodiazole copper were demonstrated by the compounds having R^1 substituted with H and R^2 substituted with the 2-OH-5-CH_3-Ph, 2-OH-5-OCH_3-Ph, or 4-*N*,*N*-di-CH_3-Ph group; R^1 substituted with 4-CH_3 and the corresponding R^2 substituted with the 2-F-Ph, 3-OH-4-OCH_3-Ph, 1-naphthyl, 4-Br-Ph, 3-NO_2-Ph, or 4-Cl-Ph group; R^1 substituted with 3-CH_3 and the corresponding R^2 substituted with the 4-F-Ph, 4-OH-Ph, or 4-*N*,*N*-di-CH_3-Ph group; R^1 substituted with 4-Cl and the corresponding R^2 substituted with the 3-NO_2-Ph, 4-Cl-3-NO_2-Ph, 3-OH-4-OCH_3-Ph, or 4-*N*,*N*-di-CH_3-Ph group. The strongest activity against tomato bacterial wilt was observed when R^1 was adjusted to 3-CH_3, 4-Cl was substituted with an anilino group, and R^2 was substituted with the 2,6-di-Cl-Ph, 4-Cl-3-NO_2-Ph, 3-OH-4-OCH_3-Ph, or 3-NO_2-Ph group. These compounds were found to be as potent as thiodiazole copper. The resulting compounds revealed efficient broad-spectrum activities against the two plant bacteria when R^1 was 4-Cl and R^2 was changed to the 4-Cl-3-NO_2-Ph, 3-OH-4-OCH_3-Ph, or 3-NO_2-Ph group.

The data in Tables 3–5 show the relationships between antibacterial activities against tobacco and tomato bacterial wilts and different aryl groups (style and position) of aromatic aldehydes. A close analysis of the screening results and structures of the active compounds revealed that the electron-donating substituents of the phenyl ring (**6f**, **6g**, **6h**, **6j**, **6k**, **6p**, **6s**, **6x**, and **6y**) can increase antimicrobial activity. Compared with the compounds bearing electron-withdrawing groups, compounds **6q**, **6t**, **6v**, and **6x** with chlorine-substituted ring exhibited more potent antibacterial activities against tomato bacterial wilt. The presence of the $-NO_2$, $-CH_3$, −Cl, −Br, or −OH group in a compound was more effective in improving antibacterial activity than that of other groups. For instance, compounds **6g** (R^1 = H, R^2 = 2-OH-5-OCH_3-Ph), **6h** (R^1 = H, R^2 = 4-*N*,*N*-di-CH_3-Ph), **6k** (R^1 = 4-CH_3, R^2 = 1-naphthyl), **6l** (R^1 = 4-CH_3, R^2 = 4-Br-Ph), **6n** (R^1 = 4-CH_3, R^2 = 3-NO_2-Ph), **6o** (R^1 = 4-CH_3, R^2 = 4-Cl-Ph), **6p** (R^1 = 3-CH_3, R^2 = 4-*N*,*N*-di-CH_3-Ph), **6t** (R^1 = 4-Cl, R^2 = 4-Cl-3-NO_2-Ph), and **6x** (R^1 = 4-Cl, R^2 = 3-OH-4-OCH_3-Ph) at 200 μg/mL showed 100% inhibition rate against tobacco bacterial wilt. These compounds had EC_{50} values ranging from 63.73 μg/mL to 201.52 μg/mL, which were superior to that of the commercial plant antibacterial agent thiodiazole copper (216.70 μg/mL). Moreover, compounds **6q** (R^1 = 4-CH_3, R^2 = 2,6-di-Cl-Ph), **6t** (R^1 = 4-Cl, R^2 = 4-Cl-3-NO_2-Ph), **6v** (R^1 = 4-Cl, R^2 = 3-NO_2-Ph), and **6x** (R^1 = 4-Cl, R^2 = 4-*N*,*N*-di-CH_3-Ph) at 200 μg/mL consistently showed 100% inhibition rate against tomato bacterial wilt. These compounds had EC_{50} values of 38.64, 81.39, 50.18, and 45.96 μg/mL, which were superior to that of the commercial plant antibacterial agent thiodiazole copper (99.80 μg/mL). Notably,

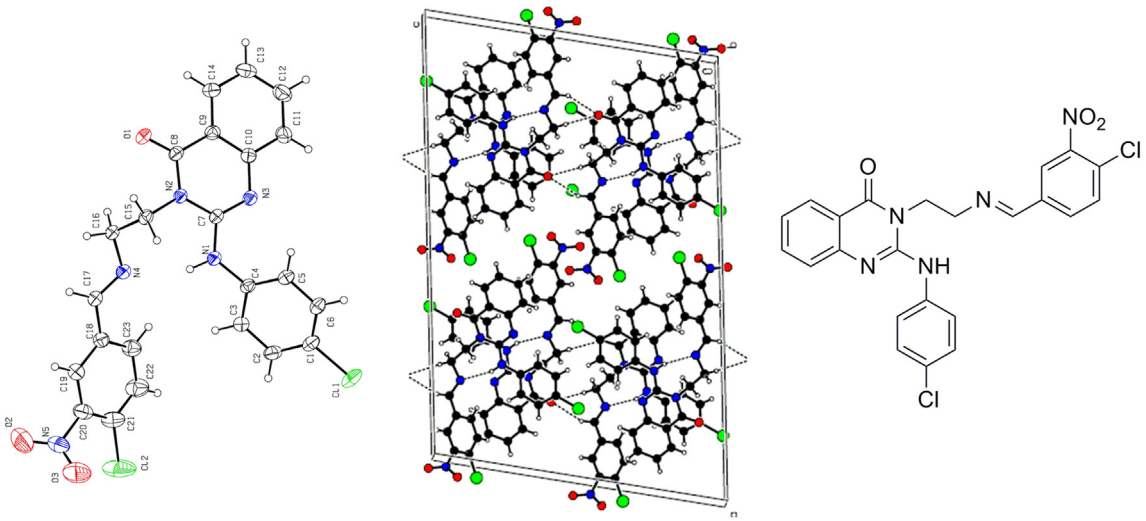


Fig. 2. Crystal structure of **6t**.

Table 3
Antibacterial activity of compounds **6a**–**6y** against tobacco and tomato bacterial wilts.

Compd.	R^1	R^2	Inhibition rate (%)[a]			
			Tobacco bacterial wilt		Tomato bacterial wilt	
			200 (μg/mL)	100 (μg/mL)	200 (μg/mL)	100 (μg/mL)
6a	H	2,6-di-Cl-Ph	89	40	60	40
6b	H	2-F-Ph	73	34	70	37
6c	H	1-naphthyl	66	58	61	33
6d	H	3,4-di-Cl-Ph	93	52	63	55
6e	H	2-Cl-Ph	66	26	81	41
6f	H	2-OH-5-CH_3-Ph	98	59	85	81
6g	H	2-OH-5-OCH_3-Ph	100	67	67	58
6h	H	4-*N*,*N*-di-CH_3-Ph	100	56	48	26
6i	4-CH_3	2-F-Ph	93	39	60	48
6j	4-CH_3	3-OH-4-OCH_3-Ph	93	42	53	19
6k	4-CH_3	1-naphthyl	100	51	45	25
6l	4-CH_3	4-Br-Ph	100	79	54	28
6m	4-CH_3	2-NO_2-Ph	86	31	74	27
6n	4-CH_3	3-NO_2-Ph	100	44	55	52
6o	4-CH_3	4-Cl-Ph	100	68	78	51
6p	3-CH_3	4-*N*,*N*-di-CH_3-Ph	100	66	46	15
6q	3-CH_3	2,6-di-Cl-Ph	44	21	100	91
6r	3-CH_3	4-F-Ph	90	14	58	29
6s	3-CH_3	4-OH-Ph	97	32	48	32
6t	4-Cl	4-Cl-3-NO_2-Ph	100	46	100	61
6u	4-Cl	Ph	85	50	74	62
6v	4-Cl	3-NO_2-Ph	93	41	100	71
6w	4-Cl	4-OCH_3-Ph	81	61	65	54
6x	4-Cl	3-OH-4-OCH_3-Ph	100	52	100	78
6y	4-Cl	4-*N*,*N*-di-CH_3-Ph	96	47	50	21
thiodiazole copper[b]			50	30	100	67
CK			0	0	0	0

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

compound **6x** at 200 and 100 μg/mL exhibited 100% (52%) and 100% (78%) inhibition rates against tobacco and tomato bacterial wilts, with EC_{50} values 84.72 and 45.96 μg/mL, respectively.

The results of primary *in vitro* antibacterial bioactivity assay and preliminary SAR analysis revealed that the Schiff base derivatives containing 4(3*H*)-quinazolinone cores had good antibacterial activity. We can infer that these compounds were introduced with an *N*-aryl group in position 2 of the quinazolinone fragment of the target compounds, resulting in the retainment of the hydrogen-bonding donor group. An aminoethyl group was then inserted on the quinazolinone fragment in position 3, which might enhance 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 having a lone pair of electrons caused by SP^2 hybridization can be regarded as a hydrogen-bond acceptor, which was perhaps the key to improve the antibacterial activity of the target compounds.

3. Conclusion

In the present study, twenty-five novel Schiff base ramifications containing quinazolinone nucleus were synthesized and their biological activities were preliminary evaluated *in vitro*. Compound **6x** exhibited stronger antibacterial activities against tobacco and tomato bacterial wilts compared with the commercial plant bactericide thiodiazole copper. Preliminary SAR analysis indicated that the $-CH_3$, $-NO_2$, $-OH$, $-Cl$, or *N*, *N*-di-methyl group on the benzene ring (substituted for R^2) enhanced the antibacterial activity of the synthesized compounds. Further evaluation of the *in vivo* antibacterial activity properties of the compounds, particularly the mechanisms underlying their enhanced antibacterial activity, should be performed in future investigations.

Table 4
Inhibitory effect of compounds **6g**, **6h**, **6k**, **6l**, **6n**, **6o**, **6p**, **6t** and **6x** against tobacco bacterial wilt.[a]

Compd.	EC_{50} (μg/mL)	pEC_{50} (μM)	$Y = Bx + A$	*R*
6g	63.73	3.8129	$y = 2.3409x + 0.7616$	0.9849
6h	76.46	3.7250	$y = 1.6289x + 1.9321$	0.9950
6k	179.93	3.3806	$y = 1.3939x + 1.8566$	0.9911
6l	89.43	3.7114	$y = 2.2979x + 0.5157$	0.9838
6n	99.37	3.6334	$y = 1.7781x + 1.4487$	0.9829
6o	110.03	3.5778	$y = 2.0650x + 0.7843$	0.9784
6p	87.04	3.6889	$y = 1.5888x + 1.9182$	0.9945
6t	201.52	3.3779	$y = 1.1613x + 2.3240$	0.9710
6x	84.72	3.7234	$y = 2.0091x + 0.9530$	0.9753
Thiodiazole copper[b]	216.70	/	$y = 1.0312x + 2.9418$	0.9903

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

4. Experimental

4.1. General methods

Unless noted, all solvents and reagents were freshly distilled or purified according to standard procedures. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in KBr disk. ^1H NMR and ^{13}C NMR were performed using deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO)-d_6 as a solvent on a JEOL-ECX 500 NMR spectrometer at room temperature operating at 500 and 125 MHz, respectively, with trimethylsilyl (TMS) as an internal standard. X-ray data for **6t** were collected using a Bruker Smart Apex CCD area detector diffractometer with Mo-Ka radiation. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Mass spectral studies were conducted on an Agilent 5973 organic mass spectrometer. Melting points were uncorrected and determined with an XT-4 binocular microscope (Beijing Tech Instrument Co., China). 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 based on the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as m or br. Analytical thin layer chromatography (TLC) was performed on silica gel GF_{254}. Flash column chromatography was carried out on a 200–300 mesh silica gel.

4.2. General procedure for the preparation of intermediates *4a*–*4d*

According to the reported procedures [23,37], the key intermediates **4a**–**4d** were synthesized by a two-step process, as

Table 5
Inhibition effect of the compounds **6q**, **6t**, **6v** and **6x** against tomato bacterial wilt.[a]

Compd.	EC_{50} (μg/mL)	pEC_{50} (μM)	Toxic regression equation	*R*
6q	38.64	4.0665	$y = 2.2748x + 1.3896$	0.9859
6t	81.39	3.7721	$y = 1.9813x + 2.2146$	0.9690
6v	50.18	3.9508	$y = 2.3448x + 1.0125$	0.9497
6x	49.26	3.9586	$y = 2.5260x + 0.7247$	0.9322
Thiodiazole copper[b]	99.80	/	$y = 1.0301x + 2.9414$	0.9913

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

shown in Scheme 1. Different aromatic isocyanates **2a**–**2d** (3 mmol) were added to a solution of iminophosphorane **1** (1.28 g, 3.0 mmol) in anhydrous tetrahydrofuran (THF, 10 mL) at room temperature. The resulting mixture was stirred at 0 °C–5 °C for 10 h–12 h to generate carbodiimides **3a**–**3d**, which were used directly without further purification. Subsequently, **3a**–**3d** were added dropwise into a solution of ethanediamine (3.0 mmol) in THF (10 mL), and the reaction mixture was stirred for 6 h–10 h at room temperature. The solvent was removed under reduced pressure, and the residue was recrystallized from CH_2Cl_2/CH_3OH (1:1, v:v) to yield 63%–80% of intermediates **4a**–**4d**. The data for **4a**–**4d** are shown below.

4.2.1. 3-Aminoethyl-2-anilinoquinazolin-4(3H)-one (**4a**)

White solid; m.p. 159 °C–160 °C (literature [1], 160 °C–161 °C); yield, 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 11.14 (s, 1H, Qu-ring–N**H**–Ar), 8.12 (d, J = 8.0 Hz, 1H, Qu–**H**), 7.02–7.58 (m, 3H, Qu–**H** and 5H, Ar–**H**), 4.20 (t, J = 4.6 Hz 2H, Qu–C**H$_2$**), 3.18 (t, J = 4.6 Hz 2H, C**H$_2$**NH$_2$), 1.82 (s, 2H, CH_2N**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.56, 149.20, 148.73, 139.99, 134.32, 128.92, 126.83, 125.54, 123.37, 122.71, 120.11, 118.17, 47.36, and 41.44. MS (ESI) m/z: 281.1 ($[M+H]^+$), 303 ($[M+Na]^+$).

4.2.2. 3-Aminoethyl-2-[4-methylanilino]quinazolin-4(3H)-one (**4b**)

White solid; m.p. 179 °C–180 °C; yield, 71%; ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 10.92 (s, 1H, Qu-ring–N**H**–Ar), 8.13 (d, J = 8.0 Hz, 1H, Qu–**H**), 7.55–7.59 (m, 1H, Qu–**H**), 7.12–7.45 (m, 3H, Qu–**H** and 4H, Ar–**H**), 4.26 (t, J = 4.6 Hz 2H, Qu–C**H$_2$**), 3.25 (t, J = 4.6 Hz 2H, C**H$_2$**NH$_2$), 2.30 (s, 3H, Ar–C**H$_3$**), 1.78 (bs, 2H, –CH_2N**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.64, 149.42, 148.90, 137.30, 134.26, 132.33, 129.42, 126.82, 125.57, 123.18, 120.35, 118.05, 47.33, 41.49, and 20.97. MS (ESI) m/z: 295.1 ($[M+H]^+$), 317.1 ($[M+Na]^+$).

4.2.3. 3-Aminoethyl-2-[3-methylanilino]quinazolin-4(3H)-one (**4c**)

White solid; m.p. 177 °C–178 °C; yield, 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 10.94 (s, 1H, Qu-ring–N**H**–Ar), 8.14 (d, J = 8.0 Hz, 1H, Qu–**H**), 7.59 (t, J = 7.2 Hz, 1H, Qu–**H**), 7.35–7.45 (m, 2H, Qu–**H**), 7.20–7.24 (m, 3H, Ar–**H**), 6.88 (d, J = 7.5 Hz, 1H, Ar–**H**), 4.29 (t, J = 4.6 Hz 2H, Qu–C**H$_2$**), 3.29 (t, J = 4.6 Hz, 2H, –C**H$_2$**NH$_2$), 2.36 (s, 3H, Ar–C**H$_3$**), 1.81 (bs, 2H, CH_2N**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.61, 149.25, 148.78, 139.85, 138.70, 134.28, 128.79, 126.83, 125.60, 123.64, 123.30, 120.77, 118.12, 117.41, 47.38, 41.48, and 21.73. MS (ESI) m/z: 295.1 ($[M+H]^+$), 317.1 ($[M+Na]^+$).

4.2.4. 3-Aminoethyl-2-[4-chlorineanilino]quinazolin-4(3H)-one (**4d**)

White solid; m.p. 152 °C–153 °C (literature [1], 151 °C–153 °C); yield, 63%; ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 11.21 (s, 1H, Qu-ring–N**H**–Ar), 8.10 (t, J = 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, Qu–C**H$_2$**), 3.23 (s, 2H, C**H$_2$**NH$_2$), 1.86 (bs, 2H, CH_2N**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.47, 148.96, 148.48, 138.59, 134.42, 128.83, 127.43, 126.85, 125.54, 123.61, 121.35, 118.16, 47.26, and 41.46. MS (ESI) m/z: 313 ($[M-H]^+$).

4.3. General procedure for the preparation of title compounds **6a**–**6y**

Target Compounds **6a**–**6y** were synthesized as shown in Scheme 1. Aromatic aldehyde (1.2 mmol) was added to a solution of intermediates **4a**–**4d** (1 mmol) in anhydrous CH_3CH_2OH (15 mL) at 0 °C–50 °C. The resulting mixture was heated up to 75 °C with stirring and refluxing for a specific reaction time (ranging from 12 min–8 h). Upon completion of the reaction 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 obtained product was filtered, washed, and then dried to produce title compounds **6a**–**6y**.

4.3.1. (E)-3-[2-((2,6-dichlorobenzylidene)amino)ethyl]-2-anilinoquinazolin-4(3H)-one (**6a**)

White solid; IR (KBr, cm^{-1}) ν: 3246 (N–H, Qu-ring–**NH**–Ar), 3034 (Ar–**C**–**H**), 1666 (C=O), 1608 (C=N), 1473–1581 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1444 (C–H), 1350 (C–N), 727–779 (C–Cl); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.02 (s, 1H, Qu-ring–N**H**–Ar), 8.54 (s, 1H, –N=C**H**–Ar), 8.18 (d, 1H, J = 8.00 Hz, Qu–**H**), 7.60 (t, 1H, J = 7.72 Hz, Qu–**H**), 7.14–7.44 (m, 9H, Ar–**H** and Qu–**H**), 6.97 (t, 1H, J = 6.87 Hz, Ar–**H**), 4.64 (s, 2H, C=N–C**H$_2$**–), 4.21 (s, 2H, Qu-ring–C**H$_2$**–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.70, 160.53, 148.86, 148.65, 139.48, 134.60, 134.37, 132.41, 131.13, 128.77, 128.63, 126.78, 125.81, 123.59, 122.83, 120.54, 118.22, 59.90, and 44.90; MS (ESI) m/z: 437.2 ($[M+H]^+$), 459.2 ($[M+Na]^+$).

4.3.2. (E)-3-(2-((2-fluorobenzylidene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6b**)

White solid; IR (KBr, cm^{-1}) ν: 3460 (N–H, Qu-ring–**NH**–Ar), 3059 (Ar–**C**–**H**), 1674 (C=O), 1610 (C=N), 1473–1585 (C=C and N–H, benzene and Qu-ring and bending of N–H), 1444 (C–H), 1278 (C–N), 1172–1253 (C–F); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.83 (s, 1H, Qu-ring–N**H**–Ar), 8.68 (s, 1H, –N=C**H**–Ar), 8.19 (d, 1H, J = 8.05 Hz, Ar–**H**), 7.90 (t, 1H, J = 6.87 Hz, Ar–**H**), 7.43–7.62 (m, 5H, Ar–**H**), 7.03–7.30 (m, 6H, Ar–**H** and Qu–**H**), 4.63 (s, 2H, =N–C**H$_2$**–Ar), 4.12 (s, 2H, Qu-ring –C**H$_2$**–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.58, 158.56, 148.75, 148.48, 139.33, 134.36, 133.56, 133.49, 128.89, 128.03, 126.82, 125.76, 124.49, 123.76, 123.05, 120.50, 118.33, 116.38, 116.22, 60.17, and 45.21; MS (ESI) m/z: 387.3 ($[M+H]^+$), 409.3 ($[M+Na]^+$).

4.3.3. (E)-3-(2-((naphthalen-1-ylmethylene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6c**)

White solid; IR (KBr, cm^{-1}) ν: 3278 (N–H, Qu-ring–**NH**–Ar), 3059 (Ar–**C**–**H**), 1666 (C=O), 1614 (C=N), 1473–1587 (C=C and N–H, benzene and Qu-ring and bending of N–H), 1444 (C–H), 1307 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.11 (s, 1H, Qu-ring–N**H**–Ar), 9.01 (s, 1H, –N=C**H**–Ar), 8.56 (d, 1H, J = 8.60 Hz, Ar–**H**), 8.20 (d, 1H, J = 7.70 Hz, Ar–**H**), 7.91–7.98 (m, 3H, Ar–**H**), 7.40–7.59 (m, 5H, Ar–**H**), 7.08–7.25 (m, 5H, Ar–**H** and Qu–**H**), 7.90 (t, 1H, J = 7.45 Hz, Ar–**H**), 4.68 (s, 2H, =N–C**H$_2$**–Ar), 4.23 (s, 2H, Qu-ring –C**H$_2$**–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.71, 148.93, 148.58, 139.11, 134.39, 133.86, 132.18, 131.30, 130.79, 128.98, 128.67, 128.31, 127.64, 126.81, 126.45, 125.78, 125.25, 123.67, 123.45, 122.88, 120.65, 118.32, 60.70, and 45.45; MS (ESI) m/z: 419.3 ($[M+H]^+$), 441.3 ($[M+Na]^+$).

4.3.4. (E)-3-(2-((3,4-dichlorobenzylidene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6d**)

White solid; IR (KBr, cm^{-1}) ν: 3321 (N–H, Qu-ring–**NH**–Ar), 3136 (Ar–**C**–**H**), 1668 (C=O), 1610 (C=N), 1475–1591 (C=C and N–H, benzene and Qu-ring and bending of N–H), 1446 (C–H), 1348 (C–N), 692–761 (C–Cl); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.54 (s, 1H, Qu-ring–N**H**–Ar), 8.29 (s, 1H, –N=C**H**–Ar), 8.18 (d, 1H, J = 6.85 Hz, Ar–**H**), 7.91 (d, 1H, J = 5.75 Hz, Ar–**H**), 7.23–7.61 (m, 9H, Ar–**H** and Qu–**H**), 7.09 (t, 1H, J = 6.85 Hz, Ar–**H**), 4.63 (s, 2H, =N–C**H$_2$**–Ar), 4.12 (s, 2H, Qu-ring –C**H$_2$**–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.53, 162.44, 148.58, 148.44, 139.07, 136.04, 136.04, 134.70, 134.48, 133.65, 131.01, 129.55, 129.10, 127.88, 126.78, 125.78, 123.81, 123.36, 120.61, 118.24, 59.93, and 45.00; MS (ESI) m/z: 437.2 ($[M+H]^+$), 459.2 ($[M+Na]^+$).

*4.3.5. (E)-3-(2-((2-chlorobenzylidene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6e**)*

White solid; IR (KBr, cm^{-1}) ν: 3263 (N–H, Qu-ring–**NH**–Ar), 3062 (Ar–**C**–**H**), 1674 (C=O), 1610 (C=N), 1473–1587 (C=C and N–H, benzene and Qu-ring and bending of N–H), 1444 (C–H), 1303 (C–N), 551–754 (C–Cl); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.90 (s, 1H, Qu-ring–N**H**–Ar), 8.82 (s, 1H, –N=C**H**–Ar), 8.19 (d, 1H, J = 8.05 Hz, Ar–**H**), 7.97 (d, 1H, J = 7.40 Hz, Ar–**H**), 7.23–7.62 (m, 10H, Ar–**H** and Qu–**H**), 7.03 (t, 1H, J = 7.15 Hz, Ar–**H**), 4.63 (s, 2H, =N–C**H$_2$**–Ar), 4.15 (s, 2H, Qu-ring –C**H$_2$**–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.59, 161.85, 148.74, 148.49, 139.29, 135.71, 134.42, 132.69, 132.25, 130.28, 128.88, 128.54, 127.12, 126.83, 125.76, 123.76, 123.04, 120.50, 118.32, 59.87, and 45.21; MS (ESI) m/z: 403.2 ($[M+H]^+$), 425.2 ($[M+Na]^+$).

*4.3.6. (E)-3-(2-((2-hydroxy-5-methylbenzylidene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6f**)*

Yellow solid; IR (KBr, cm^{-1}) ν: 3417 (N–H and O–H, Qu-ring–**NH**–Ar and Ar–**OH**), 3053 (Ar–**C**–**H**), 2916 (=CH), 1668 (C=O), 1606 (C=N), 1473–1562 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1442 (C–H), 1282 (C–N), 1024–1282 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 12.24 (s, 1H, Ar–O**H**), 8.31 (s, 1H, Qu-ring–N**H**–Ar), 8.18 (d, 1H, J = 7.75 Hz, –N=C**H**–Ar), 7.60 (t, 1H, J = 7.40 Hz, Ar–**H**), 7.390 (t, 4H, J = 6.85 Hz, Ar–**H**), 6.86–7.15 (m, 6H, Ar–**H** and Qu–**H**), 6.72 (s, 1H, Ar–**H**), 4.56 (s, 2H, =N–C**H$_2$**–Ar), 4.14 (s, 2H, Qu-ring –C**H$_2$**–), 2.23 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 169.19, 158.21, 148.20, 138.41, 134.78, 134.61, 1334.46, 132.27, 130.24, 128.89, 128.76, 128.66, 126.81, 125.86, 124.00, 123.75, 122.41, 121.22, 118.18, 117.92, 116.91, 59.63, 44.68, and 20.35; MS (ESI) m/z: 399.3 ($[M+H]^+$), 421.3 ($[M+Na]^+$).

*4.3.7. (E)-3-(2-((2-hydroxy-5-methoxybenzylidene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6g**)*

Yellow solid; IR (KBr, cm^{-1}) ν: 3400 (N–H and O–H, Qu-ring–**NH**–Ar and Ar–**OH**), 3061 (Ar–**C**–**H**), 2961 (=CH), 1658 (C=O), 1604 (C=N), 1471–1562 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1444 (C–H), 1273 (C–N), 1031–1228 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 12.03 (s, 1H, Ar–O**H**), 8.32 (s, 1H, Qu-ring–N**H**–Ar), 8.18 (d, 1H, J = 8.00 Hz, –N=C**H**–Ar), 6.87–7.62 (m, 11H, Ar–**H** and Qu–**H**), 6.67 (s, 1H, Ar–**H**), 4.56 (t, 2H, J = 5.00 Hz, =N–C**H$_2$**–Ar), 4.12 (t, 2H, J = 5.00 Hz, Qu-ring –C**H$_2$**–), 3.71 (s, 3H, Ar–OC**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 168.86, 166.09, 163.31, 154.64, 152.53, 148.25, 147.72, 138.37, 134.63, 130.24, 128.90, 126.81, 125.87, 124.01, 123.77, 122.40, 121.22, 121.01, 118.06, 117.85, 115.11, 59.66, 55.94, and 44.60; MS (ESI) m/z: 415.3 ($[M+H]^+$), 437.3 ($[M+Na]^+$).

*4.3.8. (E)-3-(2-((4-(dimethylamino)benzylidene)amino)ethyl)-2-anilinoquinazolin-4(3H)-one (**6h**)*

Grey solid; IR (KBr, cm^{-1}) ν: 3444 (N–H, Qu-ring–**NH**–Ar), 3053 (Ar–**C**–**H**), 1676 (C=O), 1604 (C=N), 1496–1583 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1444 (C–H), 1165–1305 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.33 (s, 1H, Qu-ring–N**H**–Ar), 6.62–8.19 (m, 14H, –CH_2=C**H**, Ar–**H** and Qu–**H**), 4.57 (s, 2H, =N–C**H$_2$**–Ar), 4.01 (s, 2H, Qu-ring –C**H$_2$**–), 3.00 (s, 6H, Ar–N(C**H$_3$**)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 164.42, 163.66, 152.66, 149.15, 148.62, 139.66, 134.26, 130.22, 128.85, 126.81, 125.72, 123.54, 122.88, 122.78, 120.62, 118.35, 111.51, 59.85, 45.68, and 40.25; MS (ESI) m/z: 412.2 ($[M+H]^+$), 434.1 ($[M+Na]^+$).

*4.3.9. (E)-3-(2-((2-fluorobenzylidene)amino)ethyl)-2-(4-methylanilino)quinazolin-4(3H)-one (**6i**)*

White solid; IR (KBr, cm^{-1}) ν: 3253 (N–H, Qu-ring–**NH**–Ar), 3037 (Ar–**C**–**H**), 1674 (C=O), 1610 (C=N), 1473–1585 (C=C and N–H, benzene and Qu-ring and bending of N–H), 1456 (C–H), 1309 (C–N), 1024–1384 (C–F); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.70 (s, 1H, Qu-ring–N**H**–Ar), 8.66 (s, 1H, –N=C**H**–Ar), 8.17 (d, 1H, J = 6.90 Hz, Ar–**H**), 7.89 (d, 1H, J = 5.70 Hz, Ar–**H**), 7.07–7.58 (m, 10H, Ar–**H** and Qu–**H**), 4.61 (s, 2H, =N–C**H$_2$**–Ar), 4.11 (s, 2H, Qu-ring –C**H$_2$**–), 2.31 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.61, 161.37, 158.42, 149.05, 148.64, 136.65, 134.35, 133.45, 132.72, 129.41, 128.03, 126.81, 125.71, 124.48, 123.54, 122.85, 120.87, 118.20, 116.20, 60.23, 45.16, and 20.94; MS (ESI) m/z: 401.3 ($[M+H]^+$), 423.3 ($[M+Na]^+$).

*4.3.10. (E)-3-[2-((3-hydroxy-4-methoxybenzylidene)amino)ethyl]-2-(4-methylanilino)quinazolin-4(3H)-one (**6j**)*

White solid; IR (KBr, cm^{-1}) ν: 3365 (N–H and O–H, Qu-ring–**NH**–Ar and Ar–**OH**), 2845 (Ar–**C**–**H**), 1664 (C=O), 1614 (C=N), 1475–1583 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1438 (C–H), 1273 (C–N), 1020–1242 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.77 (s, 1H, –O**H**), 8.21 (s, 1H, –N=C**H**–Ar), 8.16 (d, 1H, J = 7.45 Hz, Ar–**H**), 7.10–7.56 (m, 9H, Ar–**H** and Qu–**H**), 6.83 (d, 1H, J = 8.00 Hz, Ar–**H**), 5.75 (s, 1H, Qu-ring–N**H**–Ar), 4.59 (s, 2H, =N–C**H$_2$**–Ar), 4.04 (s, 2H, Qu-ring –C**H$_2$**–), 3.91 (s, 3H, Ar–OC**H$_3$**), 2.31 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 164.07, 163.69, 149.63, 149.30, 148.71, 146.12, 136.67, 134.29, 132.65, 129.43, 128.70, 126.77, 125.70, 123.44, 122.20, 121.12, 118.17, 111.53, 110.36, 59.91, 56.14, 45.38, and 20.95; MS (ESI) m/z: 429.3 ($[M+H]^+$), 451.3 ($[M+Na]^+$).

*4.3.11. (E)-3-(2-((naphthalen-1-ylmethylene)amino)ethyl)-2-(4-methylanilino)quinazolin-4(3H)-one (**6k**)*

White solid; IR (KBr, cm^{-1}) ν: 3228 (N–H, Qu-ring–**NH**–Ar), 3030 (Ar–**C**–**H**), 1666 (C=O), 1614 (C=N), 1475–1587 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1435 (C–H), 1024–1290 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.08 (s, 1H, Qu-ring–N**H**–Ar), 8.86 (s, 1H, –N=C**H**–Ar), 8.55 (d, 1H, J = 6.85 Hz, Ar–**H**), 8.19 (d, 1H, J = 8.00 Hz, Ar–**H**), 7.90–7.97 (m, 3H, Ar–**H**), 7.37–7.58 (m, 5H, Ar–**H** and Qu–**H**), 7.25 (dd, 1H, $^4J_{HH}$ = 6.85 Hz, $^3J_{HH}$ = 9.20 Hz, Ar–**H**), 7.07 (d, 1H, J = 8.05 Hz, Ar–**H**), 6.91 (d, 1H, J = 8.00 Hz, Ar–**H**), 4.66 (s, 2H, =N–C**H$_2$**–Ar), 4.22 (s, 2H, Qu-ring –C**H$_2$**–), 2.24 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.76, 163.60, 149.19, 148.74, 136.44, 134.32, 133.85, 132.50, 132.14, 131.30, 130.80, 129.17, 128.97, 128.34, 127.63, 126.78, 126.44, 125.76, 125.25, 123.48, 123.46, 120.95, 118.20, 60.75, 45.39, and 20.87; MS (ESI) m/z: 433.3 ($[M+H]^+$), 455.3 ($[M+Na]^+$).

*4.3.12. (E)-3-(2-((4-bromobenzylidene)amino)ethyl)-2-(4-methylanilino)quinazolin-4(3H)-one (**6l**)*

White solid; IR (KBr, cm^{-1}) ν: 3265 (N–H, Qu-ring–**NH**–Ar), 3053 (Ar–**C**–**H**), 1666 (C=O), 1610 (C=N), 1473–1589 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1444 (C–H), 1008–1311 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.60 (d, 1H, J = 8.60 Hz, Qu-ring–N**H**–Ar), 8.30 (d, 1H, J = 9.15 Hz, N=C**H**–Ar), 8.16 (t, 1H, J = 8.30 Hz, Ar–**H**), 7.09–7.58 (m, 11H, Ar–**H** and Qu–**H**), 4.60 (s, 2H, =N–C**H$_2$**–Ar), 4.07 (s, 2H, Qu-ring –C**H$_2$**–), 2.33 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.42, 148.79, 148.63, 136.56, 134.20, 133.79, 132.93, 132.18, 132.00, 129.92, 129.73, 129.50, 129.30, 126.78, 126.19, 125.74, 123.55, 123.35, 120.90, 120.71, 118.14, 59.92, 45.06, and 20.59; MS (ESI) m/z: 463.2 ($[M+2+H]^+$), 483.2 ($[M+Na]^+$).

*4.3.13. (E)-3-[2-((2-nitrobenzylidene)amino)ethyl]-2-(4-methylanilino)quinazolin-4(3H)-one (**6m**)*

Yellow solid; IR (KBr, cm^{-1}) ν: 3246 (N–H, Qu-ring–**NH**–Ar), 3032 (Ar–**C**–**H**), 1674 (C=O), 1610 (C=N), 1473–1587 (C=C, N=O and N–H, benzene and Qu-ring and bending of **N**–**H** and $-NO_2$ of **N**=**O**), 1446 (C–H), 1020–1290 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$)

δ in ppm: 8.84 (s, 2H, Qu-ring–N**H**–Ar and –N=C**H**–Ar), 8.18 (d, 1H, *J* = 8.05 Hz, Ar–**H**), 8.12 (t, 1H, *J* = 3.45 Hz, Ar–**H**), 7.90 (*t*, 1H, *J* = 5.75 Hz, Ar–**H**), 7.58–7.65 (m, 3H, Ar–**H**), 7.44 (d, 1H, *J* = 8.00 Hz, Qu–**H**), 7.20–7.26 (m, 3H, Qu–**H**), 7.03 (d, 2H, *J* = 8.00 Hz, Ar–**H**), 4.63 (s, 2H, =N–C**H$_2$**–Ar), 4.18 (s, 2H, Qu-ring –C**H$_2$**–), 2.29 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.59, 161.36, 148.80, 148.58, 136.59, 134.43, 134.00, 132.61, 131.69, 130.67, 130.02, 129.37, 126.86, 125.70, 124.90, 123.63, 120.48, 118.20, 59.56, 44.92, and 20.91; MS (ESI) *m*/*z*: 428.3 ($[M+H]^+$), 450.3 ($[M+Na]^+$).

4.3.14. (E)-3-[2-((3-nitrobenzylidene)amino)ethyl]-2-(4-methylanilino)quinazolin-4(3H)-one (**6n**)

Yellow crystal; IR (KBr, cm^{-1}) ν: 3292 (N–H, Qu-ring–**NH**–Ar), 2914 (Ar–**C**–**H**), 1662 (C=O), 1612 (C=N), 1473–1587 (C=C, N=O and N–H, benzene and Qu-ring and bending of **N**–**H** and $-NO_2$ of **N=O**), 1436 (C–H), 1352 (N=O), 1033–1284 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.67 (s, 1H, Qu-ring–N**H**–Ar), 8.42 (s, 1H, –N=C**H**–Ar), 8.31 (d, 1H, *J* = 9.70 Hz, Ar–**H**), 8.24 (s, 1H, Ar–**H**), 8.16 (d, 1H, *J* = 6.30 Hz, Ar–**H**), 7.96 (d, 1H, *J* = 7.45 Hz, Ar–**H**), 7.59 (t, 2H, *J* = 7.72 Hz, Ar–**H**), 7.40 (d, 3H, *J* = 8.00 Hz, Qu–**H**), 7.24 (t, 1H, *J* = 8.00 Hz, Qu–**H**), 7.12 (d, 2H, *J* = 8.55 Hz, Ar–**H**), 4.66 (s, 2H, =N–C**H$_2$**–Ar), 4.17 (s, 2H, Qu-ring –C**H$_2$**–), 2.31 (s, 3H, –Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.53, 162.44, 148.67, 148.64, 148.55, 136.44, 136.30, 134.47, 134.45, 133.06, 130.11, 129.59, 126.75, 126.08, 125.74, 123.67, 122.65, 120.72, 118.11, 60.20, 44.81, and 20.92; MS (ESI) *m*/*z*: 428.3 ($[M+H]^+$), 450.3 ($[M+Na]^+$).

4.3.15. (E)-3-[2-((4-chlorobenzylidene)amino)ethyl]-2-(4-methylanilino)quinazolin-4(3H)-one (**6o**)

White solid; IR (KBr, cm^{-1}) ν: 3261 (N–H, Qu-ring–**NH**–Ar), 3030 (Ar–**C**–**H**), 1664 (C=O), 1637 (C=N), 1473–1587 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1436 (C–H), 1033–1294 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.61 (s, 1H, Qu-ring–N**H**–Ar), 8.33 (s, 1H, –N=C**H**–Ar), 8.16 (d, 1H, *J* = 8.05 Hz, Ar–**H**), 7.65 (d, 2H, *J* = 8.60 Hz, Ar–**H**), 7.60 (t, 1H, *J* = 6.85 Hz, Ar–**H**), 7.34–7.41 (m, 5H, Ar–**H** and Qu–**H**), 7.23 (d, 1H, *J* = 7.40 Hz, Qu–**H**), 7.12 (d, 1H, *J* = 8.00 Hz, Ar–**H**), 4.61 (s, 2H, =N–C**H$_2$**–Ar), 4.09 (s, 2H, Qu-ring –C**H$_2$**–), 2.33 (s, 3H, –Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.60, 163.49, 149.00, 148.63, 137.88, 136.56, 134.39, 133.39, 132.92, 129.75, 129.49, 129.22, 126.77, 125.74, 123.56, 120.92, 118.14, 59.92, 45.10, and 20.59; MS (ESI) *m*/*z*: 417.3 ($[M+H]^+$), 43 9.3 ($[M+Na]^+$).

4.3.16. (E)-3-[2-((4-(dimethylamino)benzylidene)amino)ethyl]-2-(3-methylanilino)quinazolin-4(3H)-one (**6p**)

White solid; IR (KBr, cm^{-1}) ν: 3263 (N–H, Qu-ring–**NH**–Ar), 1668 (C=O), 1610 (C=N), 1473–1587 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1448 (C–H), 1033–1296 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.19 (s, 1H, Qu-ring–N**H**–Ar), 8.20 (s, 1H, –N=C**H**–Ar), 8.17 (d, 1H, *J* = 8.00 Hz, Ar–**H**), 7.18–7.60 (m, 8H, Ar–**H** and Qu–**H**), 6.86 (d, 1H, *J* = 7.45 Hz, Qu–**H**), 6.65 (d, 1H, *J* = 8.60 Hz, Ar–**H**), 4.57 (s, 2H, =N–C**H$_2$**–Ar), 4.01 (s, 2H, Qu-ring –C**H$_2$**–), 3.01 (s, 6H, Ar–N(C**H$_3$**)$_2$), 2.31 (s, 3H, Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 164.36, 163.69, 152.66, 149.33, 148.70, 139.42, 138.54, 134.23, 130.27, 128.68, 126.79, 125.74, 123.74, 123.46, 122.97, 121.51, 118.25, 111.53, 59.97, 45.66, 40.25, and 21.54; MS (ESI) *m*/*z*: 426.4 ($[M+H]^+$), 448.4 ($[M+Na]^+$).

4.3.17. (E)-3-[2-((2,6-dichlorobenzylidene)amino)ethyl]-2-(3-methylanilino)quinazolin-4(3H)-one (**6q**)

White solid; IR (KBr, cm^{-1}) ν: 3566 (N–H, Qu-ring–**NH**–Ar), 3039 (Ar–**C**–**H**), 1664 (C=O), 1610 (C=N), 1473–1591 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1436 (C–H), 1033–1296 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.00 (s, 1H, Qu-ring–N**H**–Ar), 8.52 (s, 1H, –N=C**H**–Ar), 8.17 (d, 1H, *J* = 6.00 Hz, Ar–**H**), 7.60 (t, 1H, *J* = 7.80 Hz, Ar–**H**), 7.06–7.46 (m, 7H, Ar–**H** and Qu–**H**), 6.83 (s, 1H, Qu–**H**), 6.78 (d, 1H, *J* = 8.00 Hz, Ar–**H**), 4.61 (s, 2H, =N–C**H$_2$**–Ar), 4.19 (s, 2H, Qu-ring –C**H$_2$**–), 2.14 (s, 3H, –Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.72, 160.43, 148.92, 148.72, 134.65, 134.32, 132.51, 131.10, 128.76, 128.50, 128.30, 126.77, 125.84, 123.87, 123.70, 123.49, 121.08, 118.17, 117.95, 59.95, 44.87, and 21.50; MS (ESI) *m*/*z*: 451.1 ($[M+H]^+$), 473.1 ($[M+Na]^+$).

4.3.18. (E)-3-[2-((4-fluorobenzylidene)amino)ethyl]-2-(3-methylanilino)quinazolin-4(3H)-one (**6r**)

White solid; IR (KBr, cm^{-1}) ν: 3363 (N–H, Qu-ring–**NH**–Ar), 3029 (Ar–**C**–**H**), 1664 (C=O), 1610 (C=N), 1471–1560 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1448 (C–H), 1029–1280 (C–N and C–F); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.89 (s, 1H, Qu-ring–N**H**–Ar), 8.33 (s, 1H, –N=C**H**–Ar), 8.17 (d, 1H, *J* = 6.30 Hz, Ar–**H**), 7.06–7.74 (m, 10H, Ar–**H** and Qu–**H**), 6.88 (d, 1H, *J* = 7.45 Hz, Ar–**H**), 4.60 (s, 2H, =N–C**H$_2$**–Ar), 4.09 (t, 2H, *J* = 5.15 Hz, Qu-ring –C**H$_2$**–), 2.28 (s, 3H, –Ar–C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.91, 163.58, 163.38, 148.88, 148.56, 139.10, 138.72, 134.38, 131.35, 130.71, 130.64, 128.81, 126.79, 125.78, 124.07, 123.66, 121.28, 118.24, 118.05, 116.18, 116.01, 59.93, 45.18, and 21.55; MS (ESI) *m*/*z*: 401.2 ($[M+H]^+$), 423.1 ($[M+Na]^+$).

4.3.19. (E)-3-[2-((4-hydroxybenzylidene)amino)ethyl]-2-(3-methylanilino)quinazolin-4(3H)-one (**6s**)

White solid; IR (KBr, cm^{-1}) ν: 3363 (N–H and O–H, Qu-ring–**NH**–Ar and Ar–**OH**), 3023 (Ar–**C**–**H**), 1654 (C=O), 1608 (C=N), 1473–1558 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1442 (C–H), 1039–1280 (C–N and C–O); ^{1}H NMR (500 MHz, DMSO-d_6) δ in ppm: 10.01 (s, 1H, Ar–O**H**), 8.83 (s, 1H, Qu-ring–N**H**–Ar), 8.27 (s, 1H, –N=C**H**–Ar), 8.01 (d, 1H, *J* = 6.90 Hz, Ar–**H**), 7.56–7.64 (m, 3H, Ar–**H**), 7.47 (d, 1H, *J* = 8.60 Hz, Ar–**H**), 7.19–7.28 (m, 4H, Qu–**H**), 6.89 (d, 1H, *J* = 7.45 Hz, Ar–**H**), 6.78 (d, 2H, *J* = 8.60 Hz, Ar–**H**), 4.53 (t, 2H, *J* = 5.70 Hz, =N–C**H$_2$**–Ar), 3.91 (t, 2H, *J* = 6.30 Hz, Qu-ring –C**H$_2$**–), 2.26 (s, 3H, –Ar–C**H$_3$**); ^{13}C NMR (125 MHz, DMSO-d_6) δ in ppm: 163.80, 162.53, 160.83, 149.10, 148.64, 139.57, 138.13, 134.87, 130.56, 128.81, 127.20, 126.88, 125.52, 124.32, 123.57, 122.76, 119.57, 117.93, 115.93, 59.05, 44.01, and 21.54; MS (ESI) *m*/*z*: 399.2 ($[M+H]^+$), 421.1 ($[M+Na]^+$).

4.3.20. (E)-3-[2-((4-chloro-3-nitrobenzylidene)amino)ethyl]-2-[(4-chlorophenyl)amino]quinazolin-4(3H)-one (**6t**)

Yellow crystal; IR (KBr, cm^{-1}) ν: 3265 (N–H, Qu-ring–**NH**–Ar), 3057 (Ar–**C**–**H**), 1674 (C=O), 1606 (C=N), 1471–1581 (C=C, N=O and N–H, benzene and Qu-ring and bending of **N**–**H** and $-NO_2$ of **N=O**), 1442 (C–H), 1357 (N=O), 1024–1284 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.36 (s, 1H, Qu-ring–N**H**–Ar), 8.31 (s, 1H, –N=C**H**–Ar), 8.28 (s, 1H, Ar–**H**), 8.16 (d, 1H, *J* = 7.45 Hz, Ar–**H**), 7.24–7.74 (m, 9H, Qu–**H** and Ar–**H**), 4.64 (s, 2H, =N–C**H$_2$**–Ar), 4.15 (s, 2H, Qu-ring –C**H$_2$**–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.32, 161.61, 148.41, 148.12, 148.07, 137.53, 134.67, 134.58, 132.72, 132.56, 130.23, 129.13, 128.35, 126.82, 125.74, 124.41, 124.14, 121.62, 118.24, 60.03, and 44.72; MS (ESI) *m*/*z*: 482.2 ($[M+H]^+$), 504.2 ($[M+Na]^+$).

4.3.21. (E)-3-[2-(benzylideneamino)ethyl]-2-[(4-chlorophenyl)amino]quinazolin-4(3H)-one (**6u**)

White solid; IR (KBr, cm^{-1}) ν: 3271 (N–H, Qu-ring–**NH**–Ar), 3088 (Ar–**C**–**H**), 1672 (C=O), 1606 (C=N), 1475–1587 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1435 (C–H), 1022–1350 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.00 (s, 1H, Qu-ring–N**H**–Ar), 8.38 (s, 1H, –N=C**H**–Ar), 8.18 (d, 1H, *J* = 6.85 Hz, Ar–**H**), 7.39–7.69 (m, 9H, Ar–**H** and Qu–**H**), 7.22–7.25 (m, 3H, Ar–

H and Qu–**H**), 4.60 (s, 2H, =N–C**H**$_2$–Ar), 4.09 (s, 2H, Qu-ring –C**H**$_2$–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 165.03, 163.49, 148.68, 148.29, 137.98, 134.87, 134.49, 131.96, 128.96, 128.82, 128.54, 127.85, 126.86, 125.71, 123.93, 121.86, 118.35, 59.84, 45.27; MS (ESI) *m*/*z*: 403.3 ([M+H]$^+$), 425.3 ([M+Na]$^+$).

4.3.22. (E)-2-[(4-chlorophenyl)amino]-3-[2-((3-nitrobenzylidene)amino)ethyl]quinazolin-4(3H)-one (**6v**)

White solid; IR (KBr, cm^{-1}) ν: 3271 (N–H, Qu-ring–**NH**–Ar), 2875 (Ar–**C**–**H**), 1672 (C=O), 1606 (C=N), 1475–1587 (C=C, N=O and N–H, benzene and Qu-ring and bending of **N**–**H** and –NO$_2$ of **N**=**O**), 1435 (C–H), 1350 (N=O), 1022–1303 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 8.65 (s, 1H, Qu-ring–N**H**–Ar), 8.44 (s, 2H, –N=C**H**–Ar and Ar–**H**), 8.32 (d, 1H, J = 8.55 Hz, Ar–**H**), 8.17 (d, 1H, J = 6.90 Hz, Ar–**H**), 7.94 (d, 1H, J = 8.00 Hz, Ar–**H**), 7.62 (dd, 2H, $^4J_{HH}$ = 8.60 Hz, $^3J_{HH}$ = 8.00 Hz, Ar–**H**), 7.51 (d, 2H, J = 8.60 Hz, Ar–**H**), 7.41 (d, 1H, J = 8.00 Hz, Qu–**H**), 7.41 (dd, 3H, $^4J_{HH}$ = 2.30 Hz, $^3J_{HH}$ = 8.00 Hz, Ar–**H** and Qu–**H**), 4.66 (s, 2H, =N–C**H**$_2$–Ar), 4.17 (s, 2H, Qu-ring –C**H**$_2$–); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 163.37, 162.70, 148.70, 148.18, 148.14, 137.63, 136.34, 134.64, 134.44, 130.22, 129.05, 128.15, 126.82, 126.19, 125.72, 124.12, 122.47, 121.60, 118.29, 60.06, 44.85; MS (ESI) *m*/*z*: 448.3 ([M+H]$^+$), 470.2 ([M+Na]$^+$).

4.3.23. (E)-2-[(4-chlorophenyl)amino]-3-[2-((4-methoxybenzylidene)amino)ethyl]quinazolin-4(3H)-one (**6w**)

White solid; IR (KBr, cm^{-1}) ν: 3184 (N–H, Qu-ring–**NH**–Ar), 3034 (Ar–**C**–**H**), 1670 (C=O), 1604 (C=N), 1473–1585 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1436 (C–H), 1259 (C–N), 1037–1165 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.13 (s, 1H, Qu-ring–N**H**–Ar), 8.28 (s, 1H, –N=C**H**–Ar), 8.18 (d, 1H, J = 8.00 Hz, Ar–**H**), 7.23–7.63 (m, 9H, Ar–**H** and Qu–**H**), 6.90 (d, 2H, J = 8.55 Hz, Ar–**H** and Qu–**H**), 4.58 (s, 2H, =N–C**H**$_2$–Ar), 4.04 (s, 2H, Qu-ring –C**H**$_2$–), 3.84 (s, 3H, Ar–OC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 164.19, 163.49, 162.58, 148.75, 148.30, 138.10, 134.46, 130.28, 128.83, 127.78, 127.75, 126.85, 125.69, 123.89, 121.83, 118.36, 114.30, 59.77, 55.58, 45.38; MS (ESI) *m*/*z*: 433.1 ([M+H]$^+$), 455.1 ([M+Na]$^+$).

4.3.24. (E)-2-[(4-chlorophenyl)amino]-3-[2-((3-hydroxy-4-methoxybenzylidene)amino)ethyl]quinazolin-4(3H)-one (**6x**)

Grey solid; IR (KBr, cm^{-1}) ν: 3531 (N–H and O–H, Qu-ring–**NH**–Ar and Ar–**OH**), 3205 (Ar–**C**–**H**), 2904 (=CH), 1670 (C=O), 1604 (C=N), 1473–1585 (C=C and N–H, benzene and Qu-ring and bending of N–H), 1436 (C–H), 1278 (C–N), 1020–1209 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.01 (s, 1H, Ar–O**H**), 8.21 (s, 1H, Qu-ring–N**H**–Ar), 8.16 (s, 1H, –N=C**H**–Ar), 7.11–7.59 (m, 10H, Ar–**H** and Qu–**H**), 6.82 (d, 1H, J = 7.45 Hz, Ar–**H**), 5.87 (s, 1H, Ar–**H**), 4.57 (s, 2H, =N–C**H**$_2$–Ar), 4.02 (s, 2H, Qu-ring –C**H**$_2$–), 3.91 (s, 3H, Ar–OC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 164.27, 163.47, 149.75, 148.80, 148.32, 146.20, 137.99, 134.46, 128.84, 128.53, 127.79, 126.84, 125.67, 123.87, 122.20, 122.01, 118.33, 113.38, 110.39, 59.77, 56.16, 45.39; MS (ESI) *m*/*z*: 449.1 ([M+H]$^+$), 471.0 ([M+Na]$^+$).

4.3.25. (E)-2-[(4-chlorophenyl)amino]-3-[2-((4-(dimethylamino)benzylidene)amino)ethyl]quinazolin-4(3H)-one (**6y**)

Grey solid; IR (KBr, cm^{-1}) ν: 3246 (N–H, Qu-ring–**NH**–Ar), 3034 (Ar–**C**–**H**), 1678 (C=O), 1631 (C=N), 1473–1598 (C=C and N–H, benzene and Qu-ring and bending of **N**–**H**), 1438 (C–H), 1031–1365 (C–N); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm: 9.45 (s, 1H, Qu-ring–N**H**–Ar), 8.20 (s, 1H, –N=C**H**–Ar), 8.18 (d, 1H, J = 7.45 Hz, Ar–**H**), 7.61 (t, 1H, J = 6.85 Hz, Ar–**H**), 7.56 (q, 3H, $^4J_{HH}$ = $^3J_{HH}$ = 8.60 Hz, Ar–**H**), 7.43 (d, 1H, J = 8.05 Hz, Ar–**H**), 7.23 (t, 4H, J = 7.72 Hz, Ar–**H** and Qu–**H**), 6.64 (d, 2H, J = 9.15 Hz, Ar–**H** and Qu–**H**), 4.57 (s, 2H, =N–C**H**$_2$–Ar), 4.01 (s, 2H, Qu-ring –C**H**$_2$–), 3.03 (s, 6H, Ar–N(C**H**$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ in ppm: 164.52, 163.55, 152.71, 148.97, 148.38, 138.31, 134.37, 130.18, 128.77, 127.54, 126.87, 125.66, 123.78, 122.69, 121.88, 118.39, 111.48, 59.79, 45.63, 40.28; MS (ESI) *m*/*z*: 446.1 ([M+H]$^+$), 468.1 ([M+Na]$^+$).

Acknowledgement

We gratefully acknowledge assistance from the National Key Technologies R&D Program (No. 2011BAE06B05-6).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.02.053.

References

[1] M. Salanoubat, S. Genin, F. Artiguenave, J. Gouzy, S. Mangenot, M. Arlat, A. Billaultk, P. Brottier, J.C. Camus, L. Cattolico, M. Chandler, N. Choisne, C. Claudel-Renard, S. Cunnac, N. Demange, C. Gaspin, M. Lavie, A. Moisan, C. Robert, W. Saurin, T. Schiex, P. Siguier, P. Thébault, M. Whalen, P. Wincker, M. Levy, J. Weissenbach, C.A. Boucher, Genome sequence of the plant pathogen *Ralstonia solanacearum*, Nature 415 (2002) 497–502.

[2] M. Shinohara, N. Nakajima, Y. Uehara, Purification and characterization of a novel esterase (*β*-hydroxypalmitate methyl ester hydrolase) and prevention of the expression of virulence by *Ralstonia solanacearum*, Journal of Applied Microbiology 103 (2007) 152–162.

[3] P. Lefeuvrel, G. Cellier, B. Remenant, F. Chiroleu, P. Prior, Constraints on genome dynamics revealed from gene distribution among the *Ralstonia solanacearum* species, PloS One 8 (2013) e63155–e63165.

[4] W. Yim, S. Seshadri, K. Kim, G. Lee, T. Sa, Ethylene emission and PR protein synthesis in ACC deaminase producing methylobacterium spp. inoculated tomato plants (*Lycopersicon esculentum* mill.) challenged with *Ralstonia solanacearum* under greenhouse conditions, Plant Physiology & Biochemistry 67 (2013) 95–104.

[5] A. Kiba, M. Nakano, P. Vincent-Pope, H. Takahashi, T. Sawasaki, Y. Endo, K. Ohnishid, H. Yoshioka, Y. Hikichi, A novel Sec14 phospholipid transfer protein from *Nicotiana benthamiana* is up-regulated in response to *Ralstonia solanacearum* infection, pathogen associated molecular patterns and effector molecules and involved in plant immunity, Journal of Plant Physiology 169 (2012) 1017–1022.

[6] A.M. Wu, J.H. Liu, A. Herp, D. Sudakevitz, N. Gilboa-Garber, Relative intensities of recognition factors at two combining sites of *Ralstonia solanacearum* lectin (RSL) for accommodating $_L$Fucα1→, $_D$Manα1→ and Galβ1→3/4GlcNAc glycotopes, FEBS Letters 586 (2012) 1294–1299.

[7] W.M. Xu, F.F. Han, M. He, D.Y. Hu, J. He, S. Yang, B.A. Song, Inhibition of tobacco bacterial wilt with sulfone derivatives containing an 1,3,4-oxadiazole moiety, Journal of Agricultural and Food Chemistry 60 (2012) 1036–1041.

[8] P. Przybylski, A. Huczynski, K. Pyta, B. Brzezinski, F. Bartl, Biological properties of Schiff bases and azo derivatives of phenols, Current Organic Chemistry 13 (2009) 124–148.

[9] N. Aggarwal, R. Kumar, P. Dureja, S. Diwan, D.S. Rawat, Schiff bases as potential fungicides and nitrification inhibitors, Journal of Agricultural and Food Chemistry 57 (2009) 8520–8525.

[10] A.M. Isloor, B. Kalluraya, P. Shetty, Regioselective reaction: synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1,2,4-triazoles, European Journal of Medicinal Chemistry 44 (2009) 3784–3787.

[11] L. Shi, H.M. Ge, S.H. Tan, H.Q. Li, Y.C. Song, H.L. Zhu, R.X. Tan, Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde, European Journal of Medicinal Chemistry 42 (2007) 558–564.

[12] D. Sriram, P. Yogeeswari, N.S. Myneedu, V. Saraswat, Abacavir prodrugs: microwave-assisted synthesis and their evaluation of anti-HIV activities, Bioorganic & Medicinal Chemistry Letters 16 (2006) 2127–2129.

[13] C.E. Ward, R.V. Berthold, J.F. Koerwer, J.B. Tomlin, D.T. Manning, Synthesis and herbicidal activity of 1,2,3,4-tetrahydro-1,3,5-triazino[1,2-a]benzimidazoles, Journal of Agricultural and Food Chemistry 34 (1986) 1005–1010.

[14] A.B. DeMilo, R.E. Redfern, New insect juvenile hormone mimics: aromatic Schiff bases and related compounds against the large milkweed bug and yellow mealworm, Journal of Agricultural and Food Chemistry 27 (1979) 760–762.

[15] N. Gumrukcuoglu, B.B. Sokmen, S. Ugras, H.I. Ugras, R. Yanardag, Synthesis, antibacterial, antielastase, antiurease and antioxidant activities of new 1, 4-butylene bridged bis-1,2,4-triazole derivatives, Journal of Enzyme Inhibition and Medicinal Chemistry 28 (2013) 89–94.

[16] K. Sztanke, A. Maziarka, A. Osinka, M. Sztanke, An insight into synthetic Schiff bases revealing antiproliferative activities *in vitro*, Bioorganic & Medicinal Chemistry 21 (2013) 3648–3666.

[17] K.N. Mohana, L. Mallesha, Synthesis and antiproliferative activity of some new fluorinated Schiff bases derived from 1,2,4-triazoles, Journal of Fluorine Chemistry 156 (2013) 15–20.

[18] A.M. Vijesh, A.M. Isloor, P. Shetty, S. Sundershan, H.K. Fun, New pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents, European Journal of Medicinal Chemistry 62 (2013) 410–415.
[19] P.T. Pudota, R.S.M. Purohit, G.V. Pujar, Synthesis, in vitro antimicrobial and cytotoxic activities of some novel bis-1,3,4-oxadiazoles, Journal of Applied Chemical Research 7 (2013) 7–18.
[20] S.B. Mhaske, N.P. Argade, The chemistry of recently isolated naturally occurring quinazolinone alkaloids, Tetrahedron 62 (2006) 9787–9826.
[21] I. Philipova, G. Dobrikov, K. Krumova, J. Kaneti, Convenient synthesis of some 2 substituted 4(3*H*)quinazolinone derivatives, Journal of Heterocyclic Chemistry 43 (2006) 1057–1063.
[22] B.V. Subba Reddy, A. Venkateswarlu, Ch Madan, A. Vinu, Cellulose-SO_3H: an efficient and biodegradable solid acid for the synthesis of quinazolin-4(1H)-ones, Tetrahedron Letters 52 (2011) 1891–1894.
[23] Y.P. Zhu, Z. Fei, M.C. Liu, F.C. Jia, A.X. Wu, Direct one-pot synthesis of Luotonin F and analogues via rational logical design, Organic Letters 15 (2013) 378–381.
[24] B. Maggio, G. Daidone, D. Raffa, S. Plescia, L. Mantione, V.M.C. Cutuli, N.G. Mangano, A. Caruso, Synthesis and pharmacological study of ethyl 1-methyl-5-(substituted 3,4-dihydro-4-oxoquinazolin-3-yl)-1H-pyrazole-4-acetates, European Journal of Medicinal Chemistry 36 (2001) 737–742.
[25] J. Bartroli, E. Turmo, M. Algueró, E. Boncompte, M.L. Vericat, L. Conte, J. Ramis, M. Merlos, J. Gracía-Rafanell, J. Forn, New azole antifungals. 3. synthesis and antifungal activity of 3-substituted-4(3*H*)-quinazolinones, Journal of Medicinal Chemistry 41 (1998) 1869–1882.
[26] F. Li, Y.Q. Feng, Q.Q. Meng, W.H. Li, Z.M. Li, Q.R. Wang, F.G. Tao, An efficient construction of 4(3*H*)-quinazolinones under microwave irradiation, Arkivoc 1 (2007) 40–50.
[27] M. Carpintero, M. Cifuentes, R. Ferritto, R. Haro, M.A. Toledo, Automated liquid-liquid extraction workstation for library synthesis and its use in the parallel and chromatography-free synthesis of 2-alkyl-3-alkyl-4-(3*H*)-quinazolinones, Journal of Combinatorial Chemistry 9 (2007) 818–822.
[28] P. Panneerselvam, B.A. Rather, D.R. S Reddy, N. Ramesh Kumar, Synthesis and anti-microbial screening of some Schiff bases of 3-amino-6,8-dibromo-2-phenylquin- azolin-4(3*H*)-ones, European Journal of Medicinal Chemistry 44 (2009) 2328–2333.
[29] X.W. Gao, X.J. Cai, K. Yan, B.A. Song, L.L. Gao, Z. Chen, Synthesis and antiviral bioactivities of 2-aryl- or 2-methyl-3-(substituted-benzalamino)-4(3*H*)-quinazolinone derivatives, Molecules 12 (2007) 2621–2642.
[30] Z.W. Wang, M.X. Wang, X. Yao, Y. Li, J. Tan, L.Z. Wang, W.T. Qiao, Y.Q. Geng, Y.X. Liu, Q.M. Wang, Design, synthesis and antiviral activity of novel quinazolinones, European Journal of Medicinal Chemistry 53 (2012) 275–282.
[31] H. Luo, J.J. Liu, L.H. Jin, D.Y. Hu, Z. Chen, S. Yang, J. Wu, B.A. Song, Synthesis and antiviral bioactivity of novel (1*E*, 4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy) phenyl)-1,4-pentadien-3 -one derivatives, European Journal of Medicinal Chemistry 63 (2013) 662–669.
[32] V. Gupta, S.K. Kashaw, V. Jatav, P. Mishra, Synthesis and antimicrobial activity of some new 3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-2-styrylquinazoline-4(3*H*)-ones, Medicinal Chemistry Research 17 (2008) 205–211.
[33] M.S. Mohamed, M.M. Kamel, E.M.M. Kassem, N. Abotaleb, S.I. Abd El-moez, M.F. Ahmed, Novel 6,8-dibromo-4(3*H*)-quinazolinone derivatives of antibacterial and anti-fungal activities, European Journal of Medicinal Chemistry 45 (2010) 3311–3319.
[34] N.B. Patel, J.C. Patel, Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3*H*)-one, Arabian Journal of Chemistry 4 (2011) 403–411.
[35] X. Wang, Z.N. Li, J. Yin, M. He, W. Xue, Z.W. Chen, B.A. Song, Synthesis and bioactivity evaluation of novel arylimines containing 3-aminoethyl-2-[(p-trifluoromethoxy)anilino]-4(3H)- quinazolinone moiety, Journal of Agricultural and Food Chemistry 61 (2013) 9575–9958.
[36] J.Y. Lee, S.S. Moon, B.K. Hwang, Isolation and in vitro and *in vivo* activity against phytophthora capsici and colletotrichum orbiculare of phenazine-1-carboxylic acid from pseudomonas aeruginosa strain GC-B26, Pest Management Science 59 (2003) 872–882.
[37] X.H. Yang, M.H. Wu, S.F. Sun, M.W. Ding, J.L. Xie, Q.H. Xia, Synthesis of 3-amino- alkyl-2-arylaminoquinazolin-4(3*H*)-ones and 3,3'-disubstituted bis-2-arylamino quinazolin-4(3*H*)- ones *via* reactions of 1-aryl-3-(2-ethoxycarbonylphenyl) carbodi- imides with diamines, Journal of Heterocyclic Chemistry 45 (2008) 1365–1369.
[38] The structure of 6t, which was recrystallized from EtOH, was determined by single-crystal X-ray diffraction analysis. Data collection: SMART (Bruker, 2001); cell refinement: SAINT (Bruker, 2001); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: PLATON (Spek, 2003). Crystal data: $C_{24}H_{21}ClN_4O_3$, M = 448.90, Monoclinic, P2(1)/c, a = 8.0890(12) Å, b = 12.6753(19) Å, c = 21.141(3) Å, $\alpha = 90^\circ$, $\beta = 93.923(2)^\circ$, $\gamma = 90^\circ$, V = 2162.5(6) Å3, Z = 4, Dcalcd = 1.379 g/cm^3, 16092 collected reflections, 4321 independent (Rint = 0.0193), R1 = 0.0370, wR2 = 0.1020.