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Research Article

Preparation and Antibacterial Activity of Some New 4-(2-Heterylidenehydrazinyl)-7-chloroquinoline Derivatives

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N-(4-Substituted phenyl)acetamides, which were prepared from acetic anhydride and *p*-substituted anilines, were utilized as precursors for reactions to Vilsmeier-Haack reagent to form 6-substituted-2-chloroquinoline-3-carbaldehydes **3a–c**. Meanwhile, a similar reagent was applied to 1-[1-(4-substituted phenyl)ethylidene]-2-phenylhydrazines as substrates, which were synthesized from phenylhydrazine hydrochloride and *p*-substituted acetophenones, and 1,3-diarylpyrazole-4-carbaldehydes **3d–f** were observed as a result. Reactions between the aldehydes **3a–f** and 7-chloro-4-hydrazinylquinoline **2**, obtained from reaction of 4,7-dichloroquinoline **1** and hydrazine hydrate, formed six new hydrazone compounds, namely, 4-{2-[(6-substituted-2-chloroquinolin-3-yl)methylidene]hydrazinyl}-7-chloroquinolines **4a–c** and 4-(2-{[3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}hydrazinyl)-7-chloroquinolines **4d–f**. The chemical structures of all synthesized compounds were elucidated by the analysis of IR, ^{1}H, ^{13}C-NMR, and HRMS spectral data. Additionally, all of the synthesized hydrazones were evaluated in terms of cytotoxic activity against four strains of bacteria and four strains of fungus at several concentrations of substrates. As a result, three of them, **4a–c**, possess the good ability as growth inhibitor of *Bacillus subtilis* and *Aspergillus niger* at the concentration of 25 μg/mL and 50 μg/mL, respectively, while compound **4e** only shows a cytotoxic activity against *Aspergillus niger* at the concentration of 25 μg/mL.

1. Introduction

Quinoline derivatives, which widely occur in nature, especially alkaloids, have become an important skeleton in synthetic chemistry due to their variety of applications in medicinal, bioorganic, and industrial chemistry. Some hydrazone derivatives possessing a quinoline moiety have been well known as having a broad spectrum of biological activities such as antibacterial [1], anticancer [2], antitubercular [3–5], antifungal [6], anti-inflammatory [7], antimalarial [8], and antimicrobial [9, 10]. According to Ferreira et al. [11], hydrazone derivatives, which were prepared from the reaction of 7-chloro-4-hydrazinylquinoline and heteroaromatic aldehydes, showed a good antimycobacterial activity in comparison with some drugs such as ethambutol and rifampicin. Additionally, some hydrazones being born from 2-chloroquinoline-3-carbaldehyde possessed a moderate to good antibacterial activity against both Gram-positive and Gram-negative bacteria [12].

Besides, pyrazole derivatives have been of great interest in medicinal chemistry for their role as potent antiparasitic [13], antimicrobial [14], and antitumor agents [15]. (4-Chlorophenyl)-[1-(4-nitrophenyl)-3-phenylpyrazol-4-yl-methylene]amine [13] compound possesses a good activity against *L. infantum* with IC50 of 12.4 μM while 5-(3-isobutyl-1-phenyl-1*H*-pyrazol-4-yl)-2-substituted-1,3,4-oxadiazoles [15] have an anticancer activity against breast and liver cell line with IC50 of around 2–7 μM and 4–13 μM, respectively.

In this article, 7-chloro-4-hydrazinylquinoline **2** was prepared from the reaction of 4,7-dichloroquinoline **1** and hydrazine hydrate and then was utilized as the key intermediate material for the synthesis of some new

hydrazones containing 2-chloroquinoline or pyrazole moiety. The new synthesized hydrazones including 4-{2-[(6-substituted-2-chloroquinolin-3-yl)methylidene]hydrazinyl}-7-chloroquinoline **4a–c** and 4-(2-{[3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}hydrazinyl)-7-chloroquinoline **4d–f** were evaluated for antimicrobial activities against eight kinds of microorganisms. The chemical structure of the hydrazones was elucidated by IR, NMR, and HRMS spectral analysis and their biological activities were reported for the first time.

2. Materials and Methods

All chemicals were purchased from Merck or Aldrich and solvents were commercial and were used without any further purification.

Melting points were determined with a Gallenkamp digital Melting-point apparatus 5A-6797 and were uncorrected.

The IR absorption spectra were scanned on Shimadzu FTIR 8400S spectrum using potassium bromide (KBr) pellets.

All the ^{1}H, ^{13}C-NMR, HSQC, and HMBC spectra were recorded on a Bruker Advance 500 MHz model spectrometer using DMSO-d_6 as solvents and internal standard. The *spin-spin* coupling constants (J) are given in Hz. Peak multiplicity is reported as *s* (singlet), *d* (doublet), *dd* (double-doublet), *t* (triplet), *q* (quartet), *m* (multiplet), and *br* (broad).

Mass spectrometric data were recorded on a micrOTOF-QII Bruker.

Thin-layer chromatography (TLC) was performed on silica-gel sheets (silica gel 60 F254, Merck) and visualized in ultraviolet light (254 nm).

The synthesis of the hydrazones containing quinoline heterocycles was performed following the steps shown in Scheme 1.

2-Chloroquinoline-3-carbaldehydes ***3a–c*** were prepared according to the literature [16]. *p*-Substituted aniline was added to the solution of acetic anhydride in acetic acid, following by being refluxed in 2 hours. Consequently, cooling to room temperature and pouring into ice water were performed to collect *N*-(4-substituted phenyl)acetamide derivatives, which then reacted to the mixture of dimethylformamide and phosphoryl chloride (Vilsmeier-Haack reagent) to form 2-chloroquinoline-3-carbaldehyde derivatives **3a–c**.

1,3-Diarylpyrazole-4-carbaldehydes ***3d–f*** were prepared according to the literature [17]. Phenylhydrazine hydrochloride was slowly added to the mixture of 4′-substituted acetophenones and acetic acid in ethanol. The reaction mixture was stirred and then was poured into water to separate the product 1-(1-phenylethylidene)-2-phenylhydrazine, which was treated with Vilsmeier-Haack reagent at 80–90°C in 15 hours to form 1,3-diphenylpyrazole-4-carbaldehyde derivatives **3d–f**.

Preparation of 7-Chloro-4-hydrazinylquinoline ***2***. 4,7-Dichloroquinoline (10 g, 5 mmol) was dissolved in ethanol (20 mL) in which hydrazine hydrate (35 mL, 50 mmol) was slowly dropped. The reaction mixture was refluxed for 2 hours. Consequently, this mixture was cooled to room temperature and was kept overnight to separate the solid. The yellow precipitates were filtered and recrystallized from ethanol to give compound **2**. Yield: 80%; mp. 224-225°C (literature [1]: 223–225°C). IR (ν, cm^{-1}): 3255, 3258 (–NH– and –NH$_2$), 3055 (Csp^2-H), 2931 (Csp^3-H), 1600 (C=C) and 1566 (C=N); ^{1}H-NMR (500 MHz, DMSO–d_6) δ (ppm), J (Hz): 8.60 (1H, *br*, >NH), 8.39 (1H, *br*, Ar-H), 8.16 (1H, *d*, J = 9.0, Ar-H), 7.76 (1H, *s*, Ar-H), 7.39 (1H, *dd*, J_1 = 9.0, J_2 = 2.0, Ar-H), 6.87 (1H, *br*, Ar-H) and 4.45 (2H, *br*, –NH$_2$); ^{13}C-NMR (125 MHz, DMSO–d_6) δ (ppm): 152.8, 151.8, 148.8, 133.2, 127.4, 123.8, 115.9 and 98.8 (S1–S3 from Supplementary materials).

Preparation of 4-(2-Heterylidenehydrazinyl)-7-chloroquinoline Compounds ***4a–f***. Appropriate 2-chloroquinoline-3-carbaldehyde derivatives **3a–c** or 1,3-diphenylpyrazole-4-carbaldehyde derivatives **3d–f** (1 mmol) were dissolved in absolute ethanol (10 mL) with a few drops of glacial acetic acid. This mixture was stirred for 10 minutes and then compound **2** (0.19 g, 1 mmol) was added in. The reaction mixture was refluxed for 3 hours. At the completion of reaction, the mixture was cooled to room temperature to separate the solid, which was filtered and recrystallized from suitable solvent to give products **4a–f**, respectively.

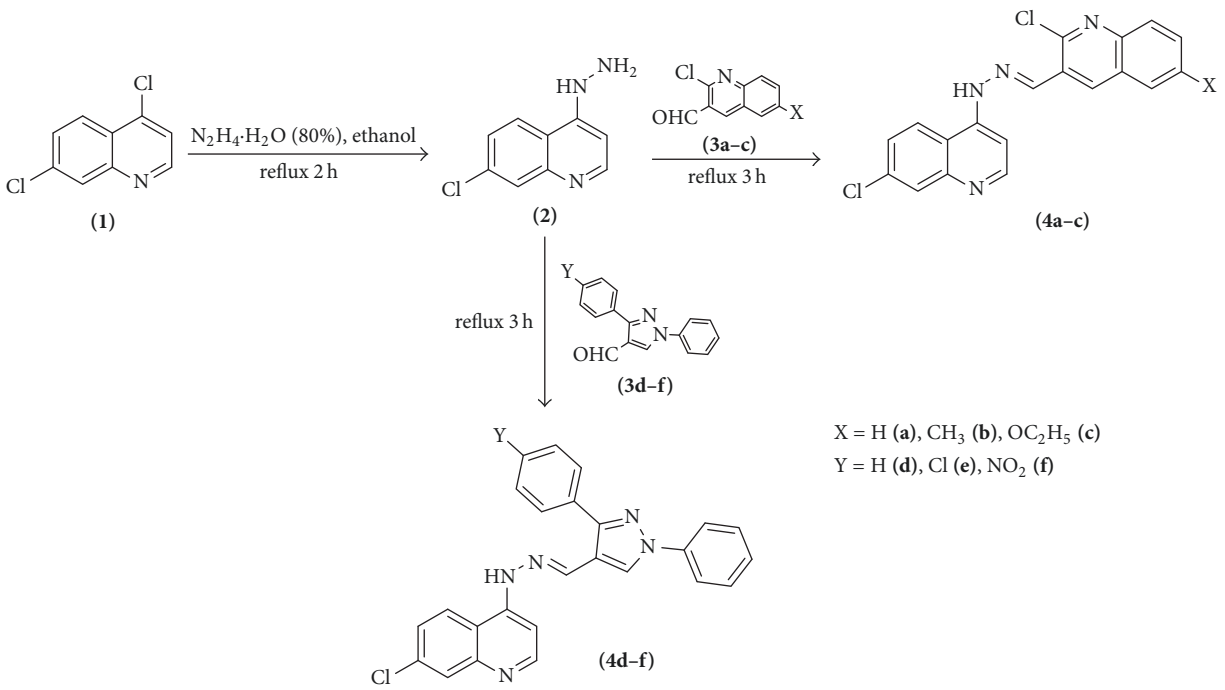
All the synthesized hydrazones were evaluated to in terms of antimicrobial activities against microorganism. The method for these experiences was based on the literature [18, 19].

3. Result and Discussion

7-Chlorohydrazinylquinoline **2** was prepared from the reaction of 4,7-dichloroquinoline **1** and hydrazine hydrate. Its ^{1}H-NMR spectrum (S2 from Supplementary materials) showed two *broad singlet* signals of hydrazine group (–NHNH$_2$) at δ_H 8.6 and 4.5. Additionally, there were a *doublet* signal at δ_H 8.16 with *spin-spin* coupling of 9.0 Hz attributed to **H5** and a *double-doublet* signal at 7.39 attributed to **H6**. Meanwhile, **H8** gave a *singlet* signal at δ_H 7.76. Two signals appearing at δ_H 8.39 and 6.87 were attributed to **H2** and **H3**, respectively. Theoretically, **H2** and **H3** usually appear as *doublet* signals due to having *spin-spin* coupling together. However, in our case, the ring system may lead to them becoming hydroxylic protons, and, so, the *broad* signals were obtained.

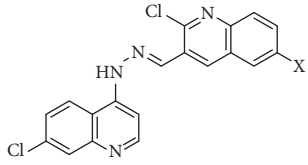
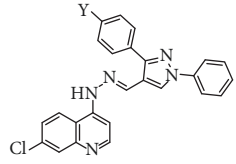
Compound **2** was utilized as a precursor for preparation of six new hydrazones according to Scheme 1. The reaction of 4,7-dichloroquinoline **1** with hydrazine hydrate formed 7-chlorohydrazinylquinoline **2**, which was treated by 2-chloroquinoline-3-carbaldehyde derivatives **3a–c** to form 4-{2-[(6-substituted-2-chloroquinolin-3-yl)methylidene]hydrazinyl}-7-chloroquinoline compounds **4a–c**. Meanwhile, 4-(2-{[3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}hydrazinyl)-7-chloroquinoline compounds **4d–f** were produced by the reaction of compound **2** and 1,3-diphenylpyrazole-4-carbaldehyde derivatives **3d–f**.

The reaction of **2** and some heteroaromatic **3a–f** occurred easily and may be observed clearly by both changing color of reaction solution and the appearance of precipitates in the progress of reaction.



Scheme 1: Pathway for preparation of 4-(2-heterylidenehydrazinyl)-7-chloroquinoline derivatives.

Table 1: The physical properties and IR spectral data of the **4a–f** compounds.

Comp.	Structure	X or Y	Solvent recrystallized	Mp. (°C)	Yield (%)	ν (cm^{-1})		
						C–H	NH	C=C C=N
4a		H	DMF : H_2O	236	83	3055	3179	1615 1566
4b		CH_3	DMF : H_2O	239	83	2895 3055	3179	1615 1566
4c		OEt	EtOH	239	81	2978 3040	3232	1620 1582
4d		H	Dioxane : H_2O	236	84	3063	3256	1651 1582
4e		Cl	DMF : H_2O	233	85	3063	3241	1613 1575
4f		NO_2	Ac : H_2O	236	83	3060	3215	1620 1555

More information can be found in Supplementary Materials.

In IR spectra, the specific vibration of amino group (–NH_2, double peak) at 3255–3258 cm^{-1} disappeared while the sharpness peak of N–H bonds still appeared around 3200 cm^{-1}; the stretching bands of the C=N bonds were recognized at 1555–1582 cm^{-1}. These data are similar to those of the 7-chloro-4-quinolinylhydrazone compounds described in literature [3].

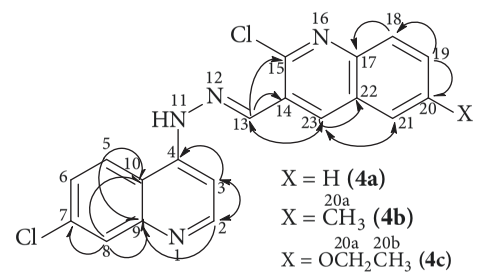
The physical properties and IR spectral data of the **4a–f** compounds were presented in Table 1.

The structures of the hydrazones were further confirmed by the HRMS data. Molecular ion peaks in the mass spectra of the products were in conformity with desired molecular formulas of them (see Tables 2 and 3).

Both the ^{1}H-NMR (500 MHz, DMSO-d_6) and ^{13}C-NMR (125 MHz, DMSO-d_6) spectra of these compounds showed all of the signals matching with the expected structures. The ^{1}H-NMR spectra of each of the compounds **4a–f** showed the *singlet* signals at δ_H 8.51–8.83 and 11.11–11.70, which were attributed to –C**H**=N– (**H13**) and –N**H**– (**H11**), respectively. Furthermore, each of the ^{13}C spectra presented a signal around 136–139 ppm, which made cross peak with the signal of **H13** in the HSQC spectra and so it was attributed to –**C**H=N– (**C13**). Besides, *singlet* signal of the methyl group in molecule of **4b** appeared at 2.54 ppm; the signals of the ethyl group in **4c** were assigned as *quartet* at 4.21 ppm (2H, J = 7.0 Hz) and *triplet* at 1.44 ppm (3H, J = 7.0 Hz). The *singlet* at

Table 2: ^{1}H, ^{13}C-NMR, and HR-MS spectral data of compounds **4a–c**.

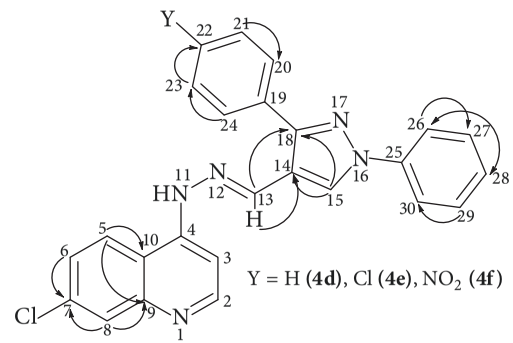
Number	X = H (**4a**)		X = CH_3 (**4b**)		X = OC_2H_5 (**4c**)	
	δ_H (ppm) *J* (Hz)	δ_C (ppm)	δ_H (ppm) *J* (Hz)	δ_C (ppm)	δ_H (ppm) *J* (Hz)	δ_C (ppm)
2	8.68 (*d*) *J* = 4.5	152.5	8.67 (*d*) *J* = 5.0	152.0	8.67 (*d*) *J* = 4.5	157.3
3	7.62 (*d*) *J* = 5.0	102.9	7.60 (*d*) *J* = 5.5	101.8	7.58 (*d*) *J* = 4.5	101.8
4	-	149.2	-	149.2	-	150.0
5	8.42 (*d*) *J* = 9.0	124.2	8.42 (*d*) *J* = 9.0	123.8	8.40 (*d*) *J* = 9.0	123.8
6	7.67 (*dd*) J_1 = 8.5; J_2 = 1.5	124.3	7.66 (*dd*) J_1 = 9.0; J_2 = 2.0	125.3	7.65 (*d*) *J* = 8.5	124.2
7	-	133.4	-	133.9	-	133.7
8	7.96 (*br*)	128.1	7.96 (*d*) *J* = 2.5	127.4	7.95 (*br*)	127.8
9	-	147.3	-	145.5	-	145.9
10	-	116.1	-	115.6	-	115.3
11	11.70 (*s*)	-	11.67 (*s*)	-	11.67 (*s*)	-
13	8.85 (*s*)	138.5	8.83 (*s*)	138.1	8.80 (*s*)	139.0
14	-	125.8	-	126.5	-	125.3
15	-	127.1	-	127.1	-	127.5
17	-	137.8	-	137.5	-	138.1
18	8.23 (*d*) *J* = 8.5	127.6	7.89 (*d*) *J* = 8.5	127.3	7.87 (*d*) *J* = 9.5	128.4
19	7.72 (*t*) *J* = 8.0	131.9	7.70 (*dd*) J_1 = 8.5; J_2 = 1.5	133.6	7.46 (*dd*) J_1 = 9.0; J_2 = 2.5	130.0
20	7.86 (*t*) *J* = 7.5	148.8	-	146.6	-	145.6
20a	-	-	2.54 (*s*)	21.2	4.21 (*q*) *J* = 7.0	63.7
20b	-	-	-	-	1.44 (*t*) *J* = 7.0	14.5
21	7.99 (*d*) *J* = 8.5	129.2	7.99 (*s*)	127.8	7.61 (*s*)	129.1
22	-	148.3	-	147.4	-	142.8
23	9.15 (*s*)	134.6	9.02 (*s*)	134.3	9.01 (*s*)	134.7
MS	367.0518 $[M + H]^+$ ($C_{19}H_{13}Cl_2N_4$ + H, 367.0512)		381.0674 $[M + H]^+$ ($C_{20}H_{15}Cl_2N_4$ + H, 381.0668)		411.0775 $[M + H]^+$ ($C_{21}H_{17}Cl_2N_4O$ + H, 411.0774)	



More information can be found in Supplementary Materials.

Table 3: ^{1}H, ^{13}C-NMR, and HR-MS spectral data of compounds **4d–f**.

Number	Y = H (**4d**)		Y = Cl (**4e**)		Y = NO_2 (**4f**)	
	δ_H (ppm) J (Hz)	δ_C (ppm)	δ_H (ppm) J (Hz)	δ_C (ppm)	δ_H (ppm) J (Hz)	δ_C (ppm)
2	8.56 (*d*) J = 5.0	152.0	8.48 (*br*)	152.3	8.49 (*br*)	152.7
3	7.51–7.58 (*m*)	101.2	7.31 (*br*)	101.8	7.28 (*br*)	102.2
4	-	149.2	-	149.2	-	147.2
5	8.33 (*d*) J = 9.0	123.9	8.36 (*d*) J = 9.0	123.0	8.34 (*d*) J = 9.0	123.4
6	7.51–7.58 (*m*)	124.8	7.60 (*br*)	125.1	7.58 (*br*)	124.8
7	-	131.6	-	131.2	-	131.2
8	7.90 (*s*)	128.6	7.84 (*br*)	128.0	7.84 (*br*)	128.6
9	-	147.0	-	146.5	-	146.6
10	-	115.4	-	115.0	-	115.0
11	11.11 (*s*)	-	11.33 (*br*)	-	11.26 (*br*)	-
13	8.51 (*s*)	136.4	8.54 (*s*)	139.0	8.57 (*s*)	138.9
14	-	117.5	-	117.5	-	117.8
15	9.11 (*s*)	127.7	9.14 (*s*)	128.7	9.17 (*s*)	127.4
18	-	151.3	-	150.0	-	148.8
19	-	133.8	-	133.9	-	133.6
20, 24	7.79 (*d*) J = 8.0	128.5	7.64 (*d*) J = 8.5	128.7	8.14 (*d*) J = 8.5	123.9
21, 23	7.51–7.58 (*m*)	129.7	7.85 (*d*) J = 8.5	129.6	8.42 (*d*) J = 8.5	129.7
22	7.37–7.41 (*m*)	132.4	-	133.4	-	132.8
25	-	139.1	-	139.7	-	139.0
26, 30	8.03 (*d*) J = 7.5	118.7	8.03 (*d*) J = 8.5	118.8	8.05 (*d*) J = 8.5	118.9
27, 29	7.51–7.58 (*m*)	128.8	7.57 (*d*) J = 8.5	130.2	7.60 (*d*) J = 8.5	129.5
28	7.37–7.41 (*m*)	127.2	7.41 (*t*) J = 8.5	127.1	7.44 (*t*) J = 8.5	127.4
MS	424.1347 $[M + H]^+$ ($C_{25}H_{18}ClN_5$ + H, 424.1323)		458.0946 $[M+H]^+$ ($C_{25}H_{17}Cl_2N_5$ + H, 458.0934)		469.1179 $[M + H]^+$ ($C_{25}H_{17}ClN_6O_2$ + H, 469.1174)	



More information can be found in Supplementary Materials.

Table 4: Antimicrobial activity of hydrazones **4a–f**.

Samp.	Minimum inhibitory concentration (MIC: μg/mL)							
	Bacterial strains				Fungal strains			
	EC	PA	BS	SA	AN	FO	SC	CA
4a	(−)	(−)	25	(−)	50	(−)	(−)	(−)
4b	(−)	(−)	25	(−)	50	(−)	(−)	(−)
4c	(−)	(−)	25	(−)	50	(−)	(−)	(−)
4d	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)
4e	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)
4f	(−)	(−)	(−)	(−)	25	(−)	(−)	(−)

(−) means negative; EC, PA, BS, and SA stand for *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus*; AN, FO, SC, and CA stand for *Aspergillus niger*, *Fusarium oxysporum*, *Saccharomyces cerevisiae*, and *Candida albicans*.

δ_H 9.01–9.15 in the ^{1}H-NMR spectra of compounds **4a–c** was assigned to proton in the 23th position (**H23**) while the *singlet* at δ_H 9.11–9.17 in the ^{1}H-NMR spectra of compounds **4d–f** was assigned to proton of the pyrazole ring (**H15**). A complete assignment of ^{1}H and ^{13}C NMR spectra of the hydrazones was based on analysis of NMR and 2D spectra (the HMBC correlations of **4b** and **4e** compounds were shown in the structures at Tables 2 and 3) and is presented in Tables 2 and 3.

The configuration of –CH=N– bonds of hydrazone compounds was identified by their NOESY spectral analysis. The supposal configuration of compound **4d** was *Z* due to the correlation between **H2** and **H22/28**, which was shown in its NOESY spectrum. Meanwhile, the NOESY spectrum of compound **4e** presented a cross peak of correlation of **H13** and **H8**, which confirmed the *E* configuration of this compound. There was a remark that the carbon signal of –**C**H=N– group in *Z* configuration appears at the higher magnetic field than in *E* configuration [20]. In our case, the same observation was collected with the carbon signal of –**C**H=N– group of compound **4d** appearing at δ_C 136.4 whereas the others were collected at δ_C 139.0. Furthermore, the ^{13}C-NMR spectrum of compound **4f** showed the signal of –**C**H=N– group at δ_C 138.9, and, thus, its configuration was supposed to be *E*. These data were presented in Table 3.

All synthesized compounds were tested for antibacterial and antifungal activities. Four kinds of bacteria including *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 25923), *Bacillus subtilis* (ATCC 11774), and *Staphylococcus aureus* (ATCC 11632) and four fungus involving *Aspergillus niger* (439), *Fusarium oxysporum* (M42), *Candida albicans* (ATCC 7754), and *Saccharomyces cerevisiae* (SH 20) were utilized for these experiments. The results were presented in Table 4.

As the data has shown, the series of 7-chloro-4-[2-(2-chloroquinolin-3-yl-methylene)hydrazinyl]quinoline compounds **4a–c** possess antibacterial and antifungal activities against *Bacillus subtilis* at the concentration of 25 μg/mL and *Aspergillus niger* at the concentration of 50 μg/mL, respectively.

Meanwhile, in the other series, there was only 7-chloro-4-(2-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)quinoline **4f** showing the antifungal activity against *Aspergillus niger* at the concentration of 25 μg/mL.

4. Conclusion

By a simple and convenient method, 7-chloro-4-hydrazinylquinoline **2** and six aldehydes including 2-chloro-6-substituted quinoline-3-carbaldehydes **3a–c** and 1,3-diarylpyrazole-4-carbaldehydes **3d–f** were prepared. The reaction of hydrazine **2** with the heteroaromatic aldehydes **3a–f** formed six new 4-(2-heterylidenehydrazinyl)-7-chloroquinoline compounds **4a–f**. Their chemical structures were elucidated by the analysis of IR, NMR, and HRMS spectral data. It was found that the configuration of hydrazones was *E* except *(Z)*-4-{2-[(1,3-diphenyl-1-phenyl-1*H*-pyrazol-4-yl)methylene]hydrazinyl}-7-chloroquinoline compound **4d**. All of them were tested for the antimicrobial activities against eight kinds of bacteria and fungus. The results showed that the hydrazones containing 2-chloroquinoline moiety **4a–c** possess good activities in growth inhibition of *Bacillus subtilis* and *Aspergillus niger* at the concentration of 25 and 50 μg/mL, respectively. In general, the hydrazones containing 1,3-diarylpyrazole moieties **4d–f** had been inactive but compound **4f** exhibited high biological activity against *Aspergillus niger* at the concentration of 25 μg/mL.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Supplementary Materials

Supplementary data associated with this article can be found in the attached file. These data include NMR (^{1}H, ^{13}C, HSQC, HMBC, and NOESY), IR, and HRMS spectra of the synthesized compounds (**2**, **3a–f**, **4a–f**): IR spectrum of compound (**2**); ^{1}H NMR spectrum of compound (**2**); ^{13}C NMR spectrum of compound (**2**); ^{1}H NMR spectrum of compound (**3a**); ^{1}H NMR spectrum of compound (**3b**); ^{1}H NMR spectrum of compound (**3c**); ^{1}H NMR spectrum of compound (**3d**); ^{1}H NMR spectrum of compound (**3e**); ^{1}H NMR spectrum of compound (**3f**); IR spectrum of compound (**4a**); ^{1}H NMR spectrum of compound (**4a**); ^{13}C NMR spectrum of compound (**4a**); HRMS spectrum of compound (**4a**); IR spectrum of compound (**4b**); ^{1}H

NMR spectrum of compound (**4b**); ^{13}C NMR spectrum of compound (**4b**); HSQC spectrum of compound (**4b**); HMBC spectrum of compound (**4b**); NOESY spectrum of compound (**4b**); HRMS spectrum of compound (**4b**); IR spectrum of compound (**4c**); ^{1}H NMR spectrum of compound (**4c**); ^{13}C NMR spectrum of compound (**4c**); HRMS spectrum of compound (**4c**); IR spectrum of compound (**4d**); ^{1}H NMR spectrum of compound (**4d**); ^{13}C NMR spectrum of compound (**4d**); HRMS spectrum of compound (**4d**); NOESY spectrum of compound (**4d**); IR spectrum of compound (**4e**); ^{1}H NMR spectrum of compound (**4e**); ^{13}C NMR spectrum of compound (**4e**); HSQC spectrum of compound (**4e**); HMBC spectrum of compound (**4e**); NOESY spectrum of compound (**4e**); HRMS spectrum of compound (**4e**); IR spectrum of compound (**4f**); ^{1}H NMR spectrum of compound (**4f**); ^{13}C NMR spectrum of compound (**4f**); HRMS spectrum of compound (**4f**). *(Supplementary Materials)*

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