



SYNTHESIS AND STRUCTURAL STUDY OF SOME 4-(2-ARYLIDENEHYDRAZINYL)-7-CHLOROQUINOLINE COMPOUNDS

*Le Trong Duc*¹, *Nguyen Tien Cong*^{1*}, *Nguyen Quang Tung*²

¹Ho Chi Minh City University of Education

²Hanoi University of Industry

Received: 14/02/2017; Revised: 03/3/2017; Accepted: 24/3/2017

ABSTRACT

7-Chloro-4-hydrazinylquinoline and seven hydrazone derivatives were synthesized from 4,7-dichloroquinoline. The structures of the compounds were determined by IR, ¹H-NMR, ¹³C-NMR and HR-MS spectral data

Keywords: 4-(2-arylidenehydrazinyl)-7-chloroquinoline, 7-chloro-4-hydrazinylquinoline, 4,7-dichloroquinoline.

TÓM TẮT

Tổng hợp và xác định cấu trúc một số hợp chất

4-(2-arylidenehydrazinyl)-7-chloroquinoline

7-Chloro-4-hydrazinylquinoline và bảy dẫn xuất dạng hydrazone của nó (trong đó có 3 hợp chất mới) đã được tổng hợp từ 4,7-dichloroquinoline. Cấu trúc của các chất tổng hợp được đã được xác nhận bởi các phổ IR, ¹H-NMR, ¹³C-NMR và phổ khối lượng độ phân giải cao.

Từ khóa: 4-(2-arylidenehydrazinyl)-7-chloroquinoline, 7-chloro-4-hydrazinylquinoline, 4,7-dichloroquinoline.

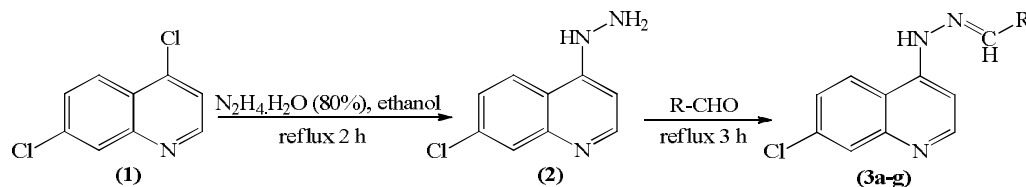
1. Introduction

Hydrazones containing quinoline heterocycle have been of great interest in medicinal chemistry for their role as anticancer, antibacterial, antifungal, anti-tubercular agents [1-7]. It has been evidenced from literature survey that the bioactivity of these compounds were affected by the presence or absence of chlorine substituent at the 7th position in quinoline heterocycle as well as the properties of some substituents in molecule of these hydrazones [4,5]. Although synthesis and bioactive of some hydrazones synthesized from 4,7-dichloroquinoline were reported, spectral data of many compounds were not published. In our research on 4-(2-arylidenehydrazinyl)-7-chloroquinoline compounds, we reported here the result of synthesis of the seven compounds and some features about spectral data including IR, ¹H-NMR, ¹³C-NMR spectra and MS of them.

* Email: congnt@hcmue.edu.vn

2. Experimental

The synthetic route for the preparation of 4-(2-arylidenehydrazinyl)-7-chloroquinoline compounds is presented in Scheme 1.



R = 4-(CH₃)₂NC₆H₄ (**3a**), 4-ClC₆H₄ (**3b**), 4-FC₆H₄ (**3c**), 2-FC₆H₄ (**3d**), 3CH₃O-4-HOC₆H₃ (**3e**), 3CH₃O-4-HO-5IC₆H₂ (**3f**), C₆H₅CH=CH (**3g**).

Scheme 1. Pathway for synthesis

Synthesis of 7-chloro-4-hydrazinylquinoline (2): compound (2) was synthesized following the previously reported procedure [1,6]. The solution of hydrazine hydrate (80%, 35 mL, 50 mmol) in ethanol absolute (30 mL) was dropped down slowly to the solution of 4,7-dichloroquinoline (10 g, 5 mmol) in ethanol absolute (20 mL). After the mixture was refluxed for 2 hours and then was maintained at room temperature overnight, the yellow precipitates were filtered and recrystallized from ethanol to give 4.66 g crystal (yield 80%, mp. 224°C matching with [1]).

Synthesis of 4-(2-arylidenehydrazinyl)-7-chloroquinoline compounds (3a-g): The (3a-g) compounds were synthesized according to the procedure for synthesis of 4-(2-benzylidenehydrazinyl)-7-chloroquinoline described in reference [1]: The (2) compound (0.19 g, 1.0 mmol) was dissolved in 10 mL of anhydrous ethanol. To this solution, a solution of appropriate aromatic aldehyde (1.0 mmol) and a few drops of acid acetic glacial in 10 mL ethanol absolute was slowly added while stirring. The mixture was refluxed for 3.0 hours. After standing overnight, the precipitate obtained was filtered off and recrystallized from suitable solvent to give the corresponding hydrazone.

IR spectra (IR) of all compounds were measured in KBr discs on a Shimadzu FTIR-8400S spectrophotometer at Faculty of Chemistry, Ho Chi Minh City University of Education and on Shimadzu FTIR Affinity - 1S at Faculty of Chemistry, University of Science – Ha Noi National University.

¹H-NMR spectra (500 MHz) and ¹³C-NMR spectra (125 MHz) were recorded on a Bruker Avance 500 MHz using DMSO-*d*₆ as solvent and tetramethylsilane as an internal standard at Faculty of Chemistry, University of Science – Ha Noi National University

HR-MS spectra were taken on a Bruker micrOTOF-Q 10187 at University of Science – Ho Chi Minh National University.

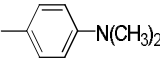
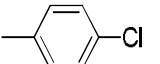
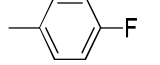
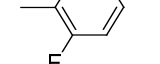
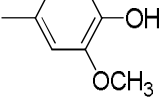
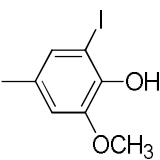
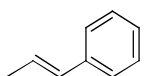
3. Result and discussion

7-Chloro-4-hydrazinylquinoline (2) was synthesized from 4,7-dichloroquinoline according to known method [1,6]. Melting point of the product is in accordance with the

melting point of 7-chloro-4-hydrazinylquinoline described in [1]. All IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ spectral data of the product are conformed with the structure of the title compound. IR: 3255 and 3258 cm^{-1} ($\nu_{\text{N-H}}$ of $-\text{NH}_2$), 3117 cm^{-1} ($\nu_{\text{N-H}}$ of $-\text{NH}-$), 3055 cm^{-1} ($\nu_{\text{Csp}^2-\text{H}}$), 2931 cm^{-1} ($\nu_{\text{Csp}^3-\text{H}}$), 1600 cm^{-1} ($\nu_{\text{C=C}}$), 1566 cm^{-1} ($\nu_{\text{C=N}}$). $^1\text{H-NMR}$: δ 8.60 (1H, *br*, NH), δ 8.39 (1H, *br*, Ar-H), δ 8.16 (1H, *d*, $J = 9.0$ Hz, Ar-H), δ 7.76 (1H, *br*, Ar-H), δ 7.39 (1H, *d-d*, $J_1 = 9.0$ Hz, $J_2 = 2.0$ Hz, Ar-H), δ 4.45 (2H, *br*, NH_2). $^{13}\text{C-NMR}$: δ 152.8, 151.8, 148.8, 133.2, 127.4, 123.8, 116.0, 115.8, 98.8. A search of the SciFinder (December 14, 2016) showed that the sufficient spectral data of 7-chloro-4-hydrazinylquinoline compound had not been found in the references.

In reaction of aromatic aldehydes with (2) compound to obtain desired hydrazone compounds (3a-g), aldehydes are activated by acid acetic. The reaction occurs easily and may be observed clearly by both changing color of reaction solution and the appearance of precipitate during and after the progress of reaction.

Table 1. Melting point, yield, IR spectral data and molecular weight of (3a-g) compounds

Com.	R	Solvent recrystallized	Mp. ($^{\circ}\text{C}$)	Yield (%)	ν (cm^{-1})			$[\text{M}+\text{H}]^+$ [M^+ Calcd.]
					C-H	NH OH	C=C C=N	
3a		DMF : H ₂ O	237	80	2978	3194	1604 1573	325.1241 [324.1142]
3b		EtOH: H ₂ O	226 [6]: 225–226	82	3078	3191	1602 1576	316.0415 [315.0330]
3c		EtOH	245 [6]: 245–246	79	3086	3194	1600 1570	300.0747 [299.0626]
3d		EtOH	234 [6]: 234–236	79	3085	3194	1601 1568	300.0711 [299.0626]
3e		EtOH: H ₂ O	224 [7]: 273 – 275	81	2924 3070	3150 3472	1610 1589	328.0875 [327.0775]
3f		DMF : H ₂ O	233	84	2980 3068	3120 3490	1608 1579	453.9837 [452.9741]
3g		EtOH	231	85	3080	3260	1610 1578	308.0988 [307.0876]

Although the synthesis of the (**3b-d**) compounds were reported in [6], (**3e**) was reported in [7], but spectral data (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$) of these compounds were not mentioned completely. Both synthesis and spectral data of three other compounds including (**3a**) and (**3f-g**) have not been reported in any references.

In IR spectra of the hydrazones, the specific vibration of amino group ($-\text{NH}_2$, double peak) at $3255 - 3258 \text{ cm}^{-1}$ was disappeared and the sharpness peak of N-H bonds still appear. IR spectra of the (**3a-g**) compounds showed stretching bands of the N-H bonds (around 3200 cm^{-1}) and C=N bonds (at $1568-1589 \text{ cm}^{-1}$), which are similar to that of the 7-chloro-4-quinolinylhydrazone compounds described in [6]. In the IR spectra, except the stretching bands of the N-H bonds, (**3e**) and (**3f**) compounds also have the peak of the vibration of O-H group at $3471 - 3645 \text{ cm}^{-1}$. In some compounds that have not the -OH group in the structure (**3a-d**, **3g**), there are some differences from the stretching bands of N-H bonds. In the (**3g**) compound, the longer conjunction in the molecule of (**3g**) than the others may be the reason of appearance of the vibration of N-H bonds at higher frequency (nearby 3260 cm^{-1}).

Compounds (**3b-d**) have the melting point matching with some references but (**3e**) is not. The result of [2] show that the melting point of (**3e**) from 273 to $275 \text{ }^\circ\text{C}$. This difference can be explain by the solvent used for recrystallization. Each solvent has their way to forming crystal so that the structure of (**3e**) may not tight and it show the melting point lower than that one presented in [7].

Table 2. Signals in the $^1\text{H-NMR}$ of hydrazones (**3a-g**) (δ , ppm and J , Hz)

V_i trí	X						
	4-N(CH ₃) ₂ (3a)	4-Cl (3b)	4-F (3c)	2-F (3d)	3-OCH ₃ -4-OH (3e)	3-OCH ₃ -4-OH-5-I (3f)	(3g)
2	8.54 (<i>br</i>)	8.60 (<i>br</i>)	8.60 (<i>br</i>)	8.62 (<i>br</i>)	8.56 (<i>br</i>)	7.86 (<i>br</i>)	8.57 (<i>d</i>) $J = 5.5$
3	7.31 (<i>br</i>)	7.42 (<i>br</i>)	7.41 (<i>br</i>)	7.43 (<i>d</i>) $J = 5.0$	7.37 (<i>br</i>)	7.41 (<i>br</i>)	7.25 (<i>d</i>) $J = 5.5$
5	8.36 (<i>d</i>) $J = 8.0$	8.39 (<i>br</i>)	8.38 (<i>d</i>) $J = 9.0$	8.38 (<i>d</i>) $J = 9.0$	8.37 (<i>d</i>) $J = 8.0$	8.43 (<i>d</i>) $J = 9.0$	8.37 (<i>d</i>) $J = 9.0$
6	7.55 (<i>br</i>)	7.61 (<i>d-br</i>)	7.60 (<i>br</i>)	7.63 (<i>d-br</i>)	7.57 (<i>br</i>)	7.62 (<i>d-br</i>) $J = 9.0$	7.60 (<i>dd</i>)

	$J = 7.5$		$J = 8.5$		$J_1 = 9.0$ $J_2 = 2.5$	
8	7.87 (<i>br</i>)	7.92 (<i>br</i>)	7.91 (<i>br</i>)	7.93 (<i>br</i>)	7.88 (<i>br</i>)	7.95 (<i>br</i>) 7.90 (<i>d</i>) $J = 2.5$
11	10.95 (<i>br</i>)	11.34 (<i>br</i>)	11.26 (<i>br</i>)	11.39 (<i>br</i>)	11.06 (<i>br</i>)	11.78 (<i>br</i>) 11.15 (<i>s</i>)
13	8.29 (<i>s</i>)	8.39 (<i>s</i>)	8.40 (<i>s</i>)	8.62 (<i>s</i>)	8.30 (<i>s</i>)	8.31 (<i>s</i>) 8.24 (<i>d</i>) $J = 9.0$
15	7.61 (<i>d</i>) $J = 8.5$	7.83 (<i>d</i>) $J = 8.5$	7.86 (<i>m</i>)	7.31 (<i>m</i>)	7.15 (<i>dd</i>) $J_1 = 8.0$ $J_2 = 1.5$	7.68 (<i>d</i>) $J = 1.5$ 7.64 (<i>d</i>) $J = 7.5$
16	6.78 (<i>d</i>) $J = 8.5$	7.53 (<i>d</i>) $J = 8.5$	7.31 (<i>dd</i>) $J_1 = 8.5; J_2 = 9.0$	7.47 (<i>dt</i>) $J_1 = J_2 = 8.0; J_3 = 4.5$	6.86 (<i>d</i>) $J = 8.0$	- 7.41 (<i>dd</i>) $J_1 = 7.5$ $J_2 = 7.5$
17	-	-	-	7.08 (<i>t</i>) $J_1 = J_2 = 8.0$	-	- 7.33 (<i>t</i>) $J = 7.5$
18	6.78 (<i>d</i>) $J = 8.5$	7.53 (<i>d</i>) $J = 8.5$	7.31 (<i>dd</i>) $J_1 = 8.5; J_2 = 8.8$	7.31 (<i>m</i>)	-	- 7.41 (<i>dd</i>) $J_1 = 7.5$ $J_2 = 7.5$
19	7.61 (<i>d</i>) $J = 8.5$	7.83 (<i>d</i>) $J = 8.5$	7.86 (<i>m</i>)	-	7.41 (<i>d</i>) $J = 1.5$	7.45 (<i>d</i>) $J = 2.0$ 7.64 (<i>d</i>) $J = 7.5$

Note: H^{13a}: δ 7.13 (*dd*), $J_1 = 16.0$ Hz, $J_2 = 9.0$ Hz; H^{13b}: δ 7.05 (*d*), $J_1 = 16.0$ Hz.

In the ¹H-NMR spectra, except the signal of NH group appeared at high field (around 11.0 ppm) and the *singlet* signals of the methyl group of (**3a**), (**3e**) and (**3f**) compounds appeared at low field (**3a** gives the signal of the -N(CH₃)₂ group at 2.99 ppm; (**3e**) and (**3f**) give the signals of the -OCH₃ groups at 3.88 ppm and 3.92 ppm, respectively), most of signals appeared in the aromatic area. H¹⁵ with H¹⁹ and H¹⁶ with H¹⁸ in the (**3a-c**) and (**3g**) molecules were pairs of equivalent protons so they appeared with intensity of 2H in the spectra. The presence of *singlet* signal at 9.46 ppm in the ¹H-NMR spectrum of (**3e**) and *singlet* signal at 10.07 ppm in the ¹H-NMR spectrum of (**3f**) was attributed to protons of the hydroxyl groups. Besides, in the ¹H-NMR spectrum of (**3g**) compound, *spin-spin* splitting between olefinic protons (H^{13a} and H^{13b}) with the coupling constants $J = 16.0$ Hz indicates that this compound exists in a *E* isomer. We assigned signals according to the structure of the hydrazone compounds and showing the result in Table 2.

In the ¹³C-NMR spectra of all the (**3a-g**) compounds also appeared fully signals as expected. However, these compounds do not dissolve well in solvent which used for taking

spectra so the signals appeared in the spectra with low resolution. (**3c**) and (**3d**) compounds have fluorine substituent so some signals of carbon atom in the aromatic area of these compounds appear as *doublets* because of *spin-spin* splitting between ^{19}F and ^{13}C with the suitable coupling constants J . In the ^{13}C -NMR spectrum of (**3a**) compound, the methyl group has the same chemical shift with the methyl groups of DMSO- d_6 solvent and these signals were assigned at 40.0 ppm. All of compounds showed the signals matching with the expected structure. The signals in the ^{13}C -NMR spectra were presented in Table 3.

The results showed that all of seven hydrazine compounds (**3a-g**) have the signal of imine protons ($-\text{N}=\text{CH}-$) at 8.24 – 8.31 ppm which are in agreement with the chemical shift of imine protons in 7-chloro-4-quinolinylhydrazone molecules described in [6].

Table 3. Signals in the ^{13}C -NMR of hydrazones (δ , ppm)

(see the structure at Table 2)

Compounds	C=C, C=N	CH ₂ CH ₃
3a	100.7, 111.9, 115.5, 122.1, 123.9, 124.5, 127.6, 128.1, 133.6, 144.5, 147.1, 149.4, 151.2, 152.0	40.0
3b	114.3, 116.0, 116.1, 122.6, 124.4, 125.5, 126.1, 128.7, 129.3, 132.7, 133.8, 134.2, 142.4, 152.5	-
3c	99.5, 101.4, (115.8, 115.9; $J = 86$), (123.9, 124.0, $J = 30.5$), 124.1, 124.9, 127.7, 128.8, (133.7, 133.8, $J = 30.0$); (142.2, 142.3, $J = 30.0$), 147.1, 152.0, 161.8, 163.7.	-
3d	101.5, 115.5, (115.9, 116.0, $J = 82.5$), (122.2, 122.3; $J = 39$), 123.8, (124.9, 125.1, $J = 85.5$), 126.1, 127.7, (131.1, 131.2, $J = 31.5$), 133.8, (135.9, 135.9, $J = 10.0$); 146.8, 149.2, 152.0, 159.3, 161.3.	-
3e	101.0, 105.8, 109.1, 115.5, 121.4, 124.0, 124.7, 126.2, 127.6, 129.3, 133.8, 144.0, 147.2, 148.1, 148.5, 152.0.	55,6
3f	84.6, 101.0, 109.2, 124.6, 125.3, 125.6, 127.8, 130.0, 131.7, 135.1, 139.8, 145.2, 147.4, 147.9, 148.2, 149.3.	56,1
3g	101.6, 117.1, 124.4, 125.3, 126.1, 127.4, 128.1, 129.0, 129.3, 131.7, 134.3, 137.6, 146.4, 147.1, 149.7, 152.4.	-

4. Conclusion

7-Chloro-4-hydrazinylquinoline and seven 4-(2-arylidenehydrazinyl)-7-chloroquinoline compounds were synthesized. The structure of the seven compounds were determined by IR, ^1H -NMR, ^{13}C -NMR and HR-MS spectral data. Three new compounds (**3a**, **3f-g**) and four other compounds (**3b-d**, **3e**) are similar in characteristic of IR, NMR spectra: in the IR spectra, absorption band of the N-H bonds appeared at 3120–3194 cm^{-1}

and absorption band of the C=N bonds appeared at 1568–1589 cm^{-1} while the $^1\text{H-NMR}$ spectra showed signal of imine protons at 8.24 – 8.31 ppm and in the $^{13}\text{C-NMR}$ spectra, signal of C=N at 149.3–163.7 ppm.

REFERENCES

- [1] Nora H. Al-Sa'alan, "Antimicrobial activity and spectral, magnetic and thermal studies of some transition metal complexes of a Schiff base hydrazone containing a quinoline moiety," *Molecules*, Vol.12, pp. 1080–1091, May.2007.
- [2] Auri R. Duval, Pedro H. Carvalho, Maieli C. Soares, Daniela P. Gouvêa, Geonir M. Siqueira, Rafael G. Lund, and Wilson Cunico, "7-Chloroquinolin-4-yl arylhydrazone derivatives: Synthesis and antifungal activity," *The Scientific World Journal*, Vol.11, pp. 1489–1495, Jul.2011.
- [3] Luisa Savini, Luisa Chiasserini, Alessandra Gaeta and Cesare Pellerano, "Synthesis and anti-tubercular evaluation of 4-quinolyhydrazones," *Bioorganic and Medicinal Chemistry*, Vol.10, pp. 2193–2198, Feb.2012.
- [4] Marcelle de L. F. Bispo, Camila C. de Alcantara, Manoel O. de Moraes, Cláudia do Ó Pessoa, Felipe A. R. Rodrigues, Carlos R. Kaiser, Solange M. S. V. Wardell, James L. Wardell, Marcus V. N. de Souza, "A new and potent class of quinoline derivatives against cancer," *Monatshefte für Chemie - Chemical Monthly*, Vol.146, pp. 2041–2052, Sep.2015.
- [5] Sandra Gemma, Luisa Savini, Maria Altarelli, Pierangela Tripaldi, Luisa Chiasserini, Salvatore Sanna Coccone, Vinod Kumar, Caterina Camodeca, Giuseppe Campiani, Ettore Novellino, Sandra Clarizio, Giovanni Delogu, Stefania Butini, "Development of antitubercular compounds based on a 4-quinolyhydrazone scaffold. Further structure-activity relationship studies," *Bioorganic and Medicinal Chemistry*, Vol. 17, pp. 6063–6072, Jun.2009
- [6] André L. P. Candéa, Marcelle de L. Ferreira, Karla C. Pais, Laura N. de F. Cardoso, Carlos R. Kaiser, Maria das Graças M. de O. Henriques, Maria C. S. Lourenço, Flávio A. F. M. Bezerra, Marcus V. N. de Souza, "Synthesis and antitubercular activity of 7-chloro-4-quinolinyhydrazones derivatives," *Bioorganic and Medicinal Chemistry Letters*, Vol.19, pp. 6272–6274, Sep.2009.
- [7] Luciana Maria Ribeiro Antinarelli, Isabela de Oliveira Souza, Nicolas Glanzmann, Ayla das Chagas Almeida, Gabriane Nascimento Porcino, Eveline Gomes Vasconcelos, Adilson David da Silva, Elaine Soares Coimbra, "Aminoquinoline compounds: Effect of 7-chloro-4-quinolinyhydrazone derivatives against *Leishmania amazonensis*," *Experimental Parasitology*, Vol.171, pp. 10–16, Oct.2016.