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Synthesis of Schiff Bases and Isoindolyl- and Thiazolyl-Substituted Quinolines from 6-Amino-2-methylquinolin-4-ol

I. L. Aleqsanyan[a],* and L. P. Hambardzumyan[a]

[a] *Yerevan State University, Yerevan, 375025 Armenia*

**e-mail: ialeksanyan@ysu.am*

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Abstract—Reactions of 6-amino-2-methylquinolin-4-ol with salicylaldehyde, phthalic anhydride, phenyl isothiocyanate, and ammonium thiocyanate afforded 6-[(2-hydroxybenzylidene)amino]-2-methylquinolin-4-ol, 2-(4-hydroxy-2-methylquinolin-6-yl)-1*H*-isoindole-1,3(2*H*)-dione, *N*-(4-hydroxy-2-methylquinolin-6-yl)-*N*′-phenylthiourea, and 1-(4-hydroxy-2-methylquinolin-6-yl)thiourea, respectively. Heterocyclizations of the latter with ethyl bromoacetate and bromacetophenone led to the formation of 2-[(4-hydroxy-2-methylquinolin-6-yl)-imino]-1,3-thiazolidin-4-one and 2-methyl-6-[(4-phenyl-1,3-thiazol-2(3*H*)-ylidene)amino]quinolin-4-ol, respectively.

Keywords: quinoline, thiourea, phenylthiourea, aminoquinoline, phenyl isothiocyanate, phthalic anhydride, bromoacetophenone, ethyl bromoacetate, isoindole, thiazolidine

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INTRODUCTION

Quinoline and its derivatives constitute an important class heterocyclic compounds that are promising for the design of new drugs, including those for the treatment of COVID-19 [1–6]. The quinoline scaffold could give rise to a broad spectrum of biological activity [7–9], such as antimicrobial, antiviral, antiprotozoal, antimalarial, antitumor, cardiovascular, psychotropic, antioxidant, anticonvulsant, analgesic, anti-inflammatory, anthelminthic, etc. [8]. Numerous methods have been developed for the synthesis of quinoline and its derivatives. The goal of the present work was to synthesize new quinoline derivatives containing five-membered heterocyclic fragments starting from 6-amino-2-methylquinolin-4-ol.

RESULTS AND DISCUSSION

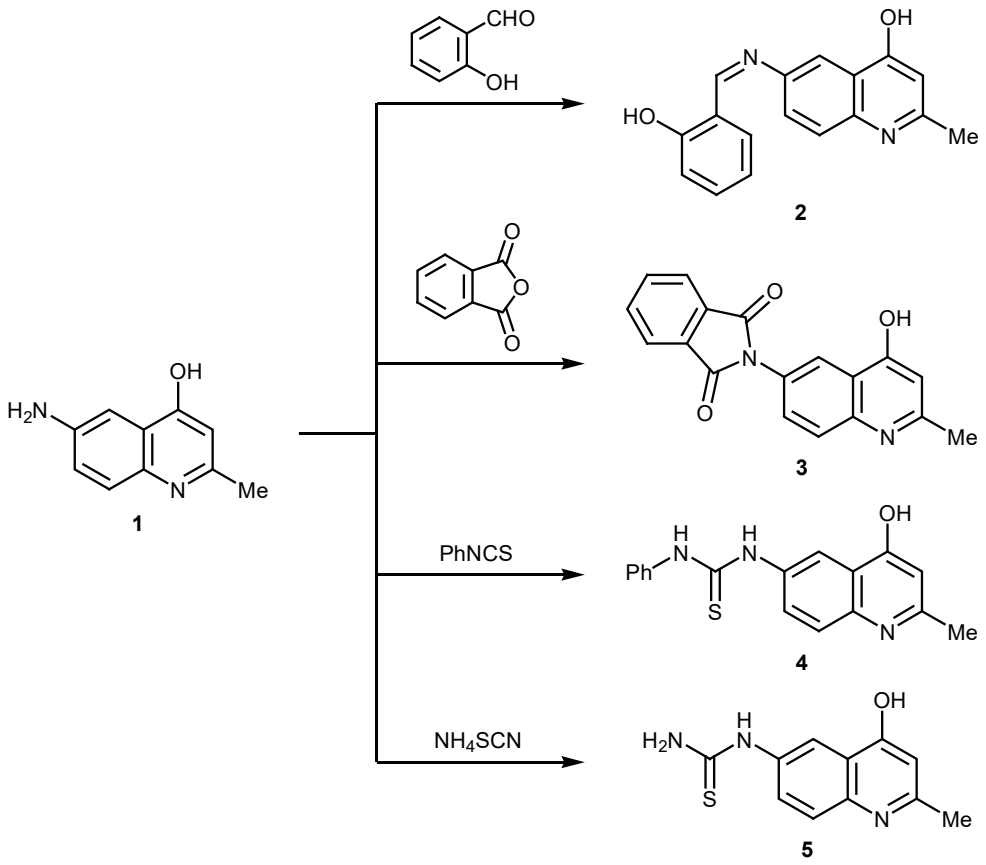
In continuation of our studies on the synthesis of biologically active compounds, herein we report the synthesis of new Schiff bases and isoindole-1,3-dione and thiazole derivatives containing a quinoline ring using 6-amino-2-methylquinolin-4-ol (**1**) as starting material. The reaction of aminoquinoline **1** with salicylaldehyde in boiling ethanol gave 6-[(2-hydroxybenzylidene)amino]-2-methylquinolin-4-ol (**2**). Compound **1** reacted with phthalic anhydride in dioxane–acetic acid (5:1) under reflux conditions to produce 2-(4-hydroxy-2-methylquinolin-6-yl)-1*H*-isoindole-1,3(2*H*)-dione (**3**). *N*-(4-Hydroxy-2-methylquinolin-6-yl)-*N*′-phenylthiourea (**4**) was synthesized in a good yield by the reaction of aminoquinoline **1** with an equimolar amount of phenyl isothiocyanate in boiling ethanol. The reaction of **1** with ammonium thiocyanate in aqueous medium in the presence of concentrated aqueous HCl at 150°C for 5–6 h afforded *N*-(4-hydroxy-2-methylquinolin-6-yl)thiourea (**5**) (Scheme 1).

Taking into account functional potential of thiourea **5**, it was reacted with ethyl bromoacetate and bromoacetophenone in the presence of sodium acetate in anhydrous ethanol. These reactions led to the formation of 2-[(4-hydroxy-2-methylquinolin-6-yl)imino]-1,3-thiazolidin-4-one (**6**) and 2-methyl-6-{[4-phenyl-1,3-thiazol-2(3*H*)-ylidene]amino}quinolin-4-one (**7**), respectively (Scheme 2).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 spectrometer (Germany) in DMSO-d_6–CCl_4 (1:3). The progress of reactions and the purity of the isolated compounds were monitored

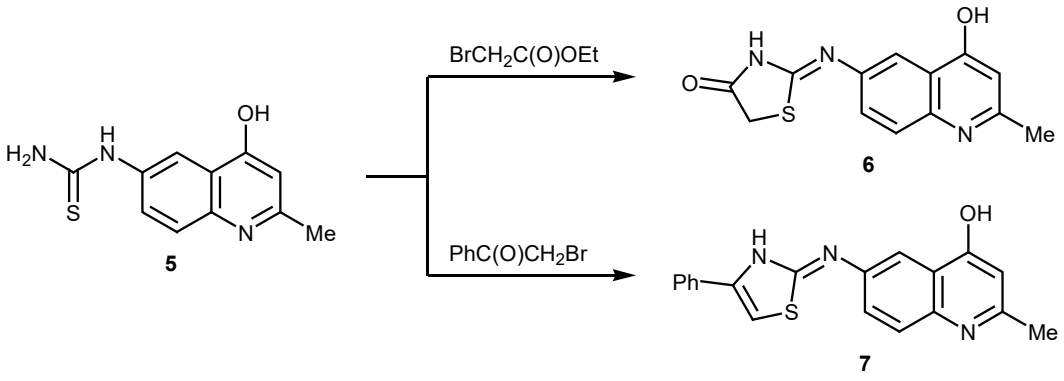
Scheme 1.



by TLC on Alugram® XtraSIL G UV254 plates (Germany) using iodine vapor for visualization. All solvents were distilled just before use, and commercially available reagents were purchased from Merck (Darmshtadt, Germany) and/or its branches.

6-[(2-Hydroxybenzylidene)amino]-2-methylquinolin-4-ol (2). A mixture of 0.174 g (1 mmol) of compound **1** [10], 10 mL of methanol, 0.122 g (1 mmol) of salicylaldehyde, and one drop of concentrated aqueous HCl was refluxed with stirring for 7 h. The solvent was distilled off, the residue was dissolved in a dilute alkali solution, the solution was filtered, and the filtrate was acidified to pH 5.0–5.5. The precipitate was filtered off and washed with water. Yield 0.20 g (72%), mp 326–327°C, R_f 0.52 (EtOH–xylene, 1:1). ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3), 6.73 s (1H, H_{arom}), 7.11–7.16 m (2H, H_{arom}), 7.34 d (1H, H_{arom}, J = 2.4 Hz), 7.43 d.d (1H, H_{arom}, J = 9.0, 2.5 Hz), 7.51–7.59 m (2H, H_{arom}), 7.88 d (1H, H_{arom}, J = 9.0 Hz), 8.01 d (1H, H_{arom}, J = 8.3 Hz), 9.82 s (1H,

Scheme 2.



NH), 10.83 br.s (1H, OH). Found, %: C 73.20; H 5.14.; N 10.23. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.38; H 5.04; N 10.07.

2-(4-Hydroxy-2-methylquinolin-6-yl)-1*H*-isoindole-1,3(2*H*)-dione (3) was synthesized according to the procedure described in [11]. A mixture of 0.174 g (1 mmol) of compound **1** [10], 10 mL of dioxane, 2 mL of acetic acid, and 0.18 g (1.2 mmol) of phthalic anhydride was refluxed with stirring for 3 h. After cooling, the precipitate was filtered off and washed with dioxane. Yield 0.27 g (89%), mp 350°C (decomp.), R_f 0.57 (EtOH–xylene, 1:1.5). ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 5.92 s (1H, H_{arom}), 7.36 d (1H, H_{arom}, J = 8.9 Hz), 7.43 d.d (2H, H_{arom}, J = 11.1, 3.9 Hz), 7.74–7.87 m (2H, H_{arom}), 7.97 s (1H, H_{arom}), 8.41 d (1H, H_{arom}, J = 2.3 Hz), 11.89 br.s (1H, OH). Found, %: C 71.18; H 3.79; N 9.37. $C_{18}H_{12}N_2O_3$. Calculated, %: C 71.05; H 3.95; N 9.21.

***N*-(4-Hydroxy-2-methylquinolin-6-yl)-*N*′-phenylthiourea (4).** A mixture of 0.87 g (5 mmol) of compound **1** [10], 10 mL of ethanol, and 0.675 g (0.6 mL, 5 mmol) of phenyl isothiocyanate was refluxed with stirring for 6 h. After cooling, the precipitate was filtered off and washed with ethanol. Yield 1.30 g (85%), mp 325°C (decomp.), R_f 0.60 (EtOH–xylene, 1:2.5). ^{1}H NMR spectrum, δ, ppm: 2.35 d (3H, CH_3, J = 0.7 Hz), 5.81 s (1H, H_{arom}), 7.06–7.12 m (1H, H_{arom}), 7.26–7.34 m (2H, H_{arom}), 7.43 d (1H, H_{arom}, J = 8.8 Hz), 7.52–7.57 m (2H, H_{arom}), 7.88 d.d (2H, H_{arom}, J = 8.8, 2.2 Hz), 7.97 d (1H, H_{arom}, J = 2.5 Hz), 9.87 br.s (2H, NH), 11.39 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.23, 39.49, 107.67, 117.16, 118.42, 123.13, 123.69, 124.50, 127.81, 128.26, 134.39, 137.07, 139.30, 148.25, 176.09, 179.43. Found, %: C 66.18; H 4.71; N 13.43; S 10.20. $C_{17}H_{15}N_3OS$. Calculated, %: C 66.02; H 4.85; N 13.59; S 10.36.

***N*-(4-Hydroxy-2-methylquinolin-6-yl)thiourea (5).** A mixture of 1.74 g (10 mmol) of compound **1** [10], 30 mL of water, 2.5 mL of aqueous HCl (pH ~ 2.0), and 2.28 g (30 mmol) of ammonium thiocyanate was heated with stirring at ~150°C for 5–6 h. After cooling, the precipitate was filtered off and washed with water. Yield 1.51 g (65%), mp 242–243°C, R_f 0.52 (EtOH–xylene, 1:2). ^{1}H NMR spectrum, δ, ppm: 2.74 s (3H, CH_3), 6.95 s (1H, H_{arom}), 7.62 br.s (2H, NH_2), 7.99 d (1H, H_{arom}, J = 9.1 Hz), 8.16 d.d (1H, H_{arom}, J = 9.1, 2.5 Hz), 8.52 d (1H, H_{arom}, J = 2.5 Hz), 10.50 s (1H, NH), 14.72 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.59, 39.39, 39.78, 40.06, 40.33, 95.45, 105.54, 113.44, 118.95, 119.72, 129.42, 135.85, 138.25. Found, %: C 56.78; H 4.69; N 18.12; S 13.87. $C_{11}H_{11}N_3OS$: Calculated, %: C 56.65; H 4.72; N 18.03; S 13.73.

2-[(4-Hydroxy-2-methylquinolin-6-yl)imino]-1,3-thiazolidin-4-one (6). A mixture of 0.233 g (1 mmol) of compound **5**, 10 mL of anhydrous ethanol, 0.246 g (3 mmol) of anhydrous sodium acetate, and 0.22 g (0.15 mL, 1.3 mmol) of ethyl bromoacetate was refluxed with stirring for 5–6 h. After cooling, the precipitate was filtered off, washed with ethanol, and dried. Yield 0.23 g (85%), mp 375°C (decomp.), R_f 0.50 (EtOH–xylene, 1:3). ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 3.96 t (2H, CH_2, J = 19.1 Hz), 5.89 s (1H, H_{arom}), 7.20–7.70 m (2H, H_{arom}), 7.93 d (1H, H_{arom}, J = 8.4 Hz), 11.26 br.s (1H, NH), 11.60 br.s (1H, OH). Found, %: C 57.26; H 4.89; N 15.23; S 11.59. $C_{13}H_{11}N_3O_2S$. Calculated, %: C 57.14; H 4.72; N 15.38; S 11.72.

2-Methyl-6-{[4-phenyl-1,3-thiazol-2(3*H*)-ylidene]amino}quinolin-4-ol (7). A mixture of 0.233 g (1 mmol) of compound **5**, 10 mL of anhydrous ethanol, 0.246 g (3 mmol) of anhydrous sodium acetate, and 0.199 g (1 mmol) of bromoacetophenone was refluxed with stirring for 6–7 h. After cooling, the precipitate was filtered off, washed with ethanol, and dried. Yield 0.31 g (93%), mp 305–306°C, R_f 0.67 (EtOH–PhMe, 1:1). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 5.82 s (1H, H_{arom}), 7.25–7.34 m (2H, H_{arom}), 7.40 d.d (2H, H_{arom}, J = 10.3, 4.7 Hz), 7.49 d (1H, H_{arom}, J = 8.9 Hz), 7.89 d.d (1H, H_{arom}, J = 8.9, 2.7 Hz), 7.92–7.97 m (2H, H_{arom}), 8.46 d (1H, H_{arom}, J = 2.6 Hz), 10.41 s (1H, NH), 11.58 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.26, 39.23, 40.06, 40.33, 102.85, 107.45, 110.46, 118.54, 122.29, 125.23, 125.66, 127.50, 128.53, 134.50, 135.07, 136.72, 148.52, 149.99, 162.94, 176.21. Found, %: C 68.32; H 4.68; N 12.49; S 9.72. $C_{19}H_{15}N_3OS$. Calculated, %: C 68.48; H 4.50; N 12.61; S 9.61.

CONCLUSIONS

The reactions of 6-amino-2-methylquinolin-4-ol with salicylaldehyde, phthalic anhydride, phenyl isothiocyanate, and ammonium thiocyanate have been found to produce 6-[(2-hydroxybenzylidene)amino]-2-methylquinolin-4-ol, 2-(4-hydroxy-2-methylquinolin-6-yl)-1*H*-isoindole-1,3(2*H*)-dione, *N*-(4-hydroxy-2-methylquinolin-6-yl)-*N*′-phenylthiourea, and *N*-(4-hydroxy-2-methylquinolin-6-yl)thiourea, respectively. Methods have been developed for the synthesis of

2-[(4-hydroxy-2-methylquinolin-6-yl)imino]-1,3-thiazolidin-4-one and 2-methyl-6-{[4-phenyl-1,3-thiazol-2(3*H*)-ylidene]amino}quinolin-4-ol via heterocyclizations of *N*-(4-hydroxy-2-methylquinolin-6-yl)thiourea with ethyl bromoacetate and bromoacetophenone, respectively.

AUTHOR INFORMATION

I.L. Aleqsanyan, ORCID: https://orcid.org/0000-0002-4039-2323

L.P. Hambardzumyan, ORCID: https://orcid.org/0000-0003-1210-0052

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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