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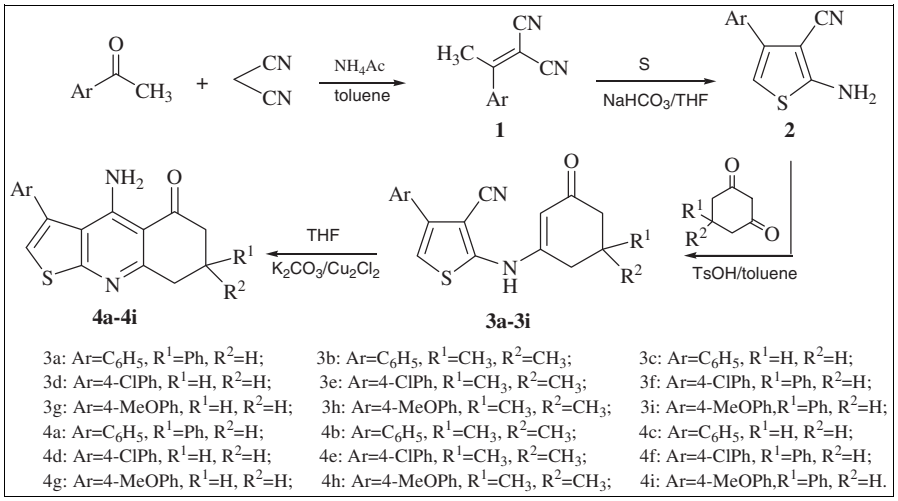

The Knoevenagel reactions of malononitrile with acetophenone or 4-substituted acetophenons were carried to give the corresponding 2-(1-aryle thylidene)malononitriles, which was further cyclized with sulfur using $NaHCO_3$ as catalysts to generate 2-amino-5-arylthiophene-3-carbonitrile **2**. The intermediate enamines **3** were prepared by refluxing of **2** with 5-substituted-1,3-cyclohexanedione using *p*-toluenesulfonic acid as catalyst. The title compounds 4-amino-3-aryl -7-substituted-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one were synthesized by cyclization of **3** in the presence of K_2CO_3 and Cu_2Cl_2. The structures of all compounds were characterized by elemental analysis, IR, MS, and ^{1}H-NMR spectra.

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INTRODUCTION

The substantial growth in the number of investigations in the field of the organosulfur compounds observed in recent years, in particular, for condensed heteroaromatic systems including a thiophene ring, has been due to an expanded application in the medical field and has been shown to exert diverse biological effects such as antioxidant effects, anti-inflammatory properties, inhibition of platelet aggregation, reduction of systolic blood pressure, reduction of cholesterol levels, and anticardiovascular disease [1,2]. Rashad reported several novel analogs of dihydronaphthothiophenes, naphthothiophenes, thieno [2,3-*d*]pyrimidines, and their fused heterocyclic thienotriazolo[4,3-*a*] pyrimidine derivatives, which including a thiophene ring showed higher anti-H5N1 activity [3].

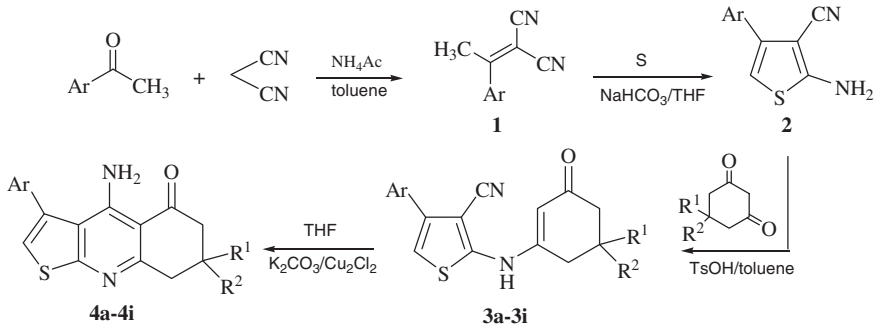
Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products and biologically active compounds. Quinoline derivatives are utilized as potential antitumoral, antituberculosis, anticonvulsant, antibreast cancer, and anti-HIV agents [4–8]. At the same time, quinoline derivatives are the important fine chemicals for the synthesis of drug molecules, dyes, pesticides, *etc*. [9].

In view of the above information and to continue our research program concerned with structural modification of certain biologically active heterocyclic nuclei with the purpose of enhancing their biological activity, we report here the synthesis of several novel analogs of thieno[2,3-*b*]quinolinone derivatives hoping that they can have some chemical and biological interests.

RESULT AND DISCUSSION

As shown in Scheme 1, the intermediates 2-(1-arylethylidene)malononitriles **1** were prepared from acetophenone or substituted acetophenone, malononitrile in dry toluene with NH_4Ac as catalyst, followed by the cyclization with sulfur in the presence of $NaHCO_3$ as catalyst in THF to give the thiophenes **2**. This process was achieved in high yield. The intermediate enamines **3** were obtained by condensation reaction of compounds **2** with 5-substituted-1,3-cyclohexanedione using *p*-toluenesulfonic acid as catalyst in toluene. 4-Amino-3-aryl-7-substituted-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-ones **4** were synthesized by cyclization of the intermediate enamines **3** in the presence

Scheme 1



3a: Ar=C_6H_5, R^1=Ph, R^2=H; 3b: Ar=C_6H_5, R^1=CH_3, R^2=CH_3; 3c: Ar=C_6H_5, R^1=H, R^2=H;
3d: Ar=4-ClPh, R^1=H, R^2=H; 3e: Ar=4-ClPh, R^1=CH_3, R^2=CH_3; 3f: Ar=4-ClPh, R^1=Ph, R^2=H;
3g: Ar=4-MeOPh, R^1=H, R^2=H; 3h: Ar=4-MeOPh, R^1=CH_3, R^2=CH_3; 3i: Ar=4-MeOPh,R^1=Ph, R^2=H;
4a: Ar=C_6H_5, R^1=Ph, R^2=H; 4b: Ar=C_6H_5, R^1=CH_3, R^2=CH_3; 4c: Ar=C_6H_5, R^1=H, R^2=H;
4d: Ar=4-ClPh, R^1=H, R^2=H; 4e: Ar=4-ClPh, R^1=CH_3, R^2=CH_3; 4f: Ar=4-ClPh, R^1=Ph, R^2=H;
4g: Ar=4-MeOPh, R^1=H, R^2=H; 4h: Ar=4-MeOPh, R^1=CH_3, R^2=CH_3; 4i: Ar=4-MeOPh,R^1=Ph, R^2=H.

of K_2CO_3 and Cu_2Cl_2 [10]. The melting points and yields of compounds **3** and **4** are shown in Tables 1 and 2.

In our initial experiments, we noted that the substituted functional groups at 4-position of acetophenone, including electron-donating to electron-withdrawing groups, was tolerated under the same conditions. However, the reaction yields for these compounds differ from each other and correlated to electronic effects of their substituents. The presence of an electron-withdrawing group such as chlorine atom on an acetophenone tends to speed up the reaction and gave higher yields. However, if there is an electron-donating group such as methoxyl group on an acetophenone tends to slow down the reaction and gave lower yields of the compounds **2**. On the other hand, substitutions on the 1,3-cyclohexanedione appear to have effect on the yields. The presence of two methyl groups or a phenyl group in 1,3-cyclohexanedione appears to have a positive effect on the yield of the intermediate enamines **3**.

The data of ^{1}H-NMR, MS, and IR shown in the Experimental section are in accordance with the chemical structures of the target compounds. The ^{1}H-NMR spectra of compounds **3a** and **4a** were recorded in $CDCl_3$, CD_3OD, or DMSO-d_6. The ^{1}H-NMR spectra of **3a** showed single signal at δ 7.00 corresponding to the proton attached to thiophene ring and additional single peak at δ 5.98 ascribed to the typical proton peak olefin proton bonded to the enamine moiety. In the ^{1}H-NMR spectrum of compound **4a**, two broad single peaks at δ 5.39 and δ 9.63 were observed. They disappeared after D_2O exchange and, therefore, were attributed to the two N-H of the amino group. Because of the existence of intramolecular hydrogen bond between one proton of the amino group and the oxygen atom of the carbonyl group nearby, its proton peak was drifted to δ 9.63. A sharp single peaks at 7.01 was observed. It was attributed to the C_2-H of the thiophene ring. The structures of these compounds were further supported by their IR spectra. The spectrum of compound **3a** showed the absorption bands at 2215 and 3452 cm^{-1} for the cyano group and amino group, respectively. However, an absorption band of cyano group disappeared in the IR spectrum of compound **4a**.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. Microanalysis was performed by the PerkinElmer 2400 microanalytical service. Infrared spectra were

Table 1

The melting point and yield of 2-amino-5-arylthiophene-3-carbonitrile derivatives.

Entries	R^1	R^2	Ar	MP (°C)	Yield (%)
3a	Ph	H	Ph	190–192	85.4
3b	CH_3	CH_3	Ph	156–158	89.5
3c	H	H	Ph	146–148	79.3
3d	H	H	4-ClPh	228–230	92.1
3e	CH_3	CH_3	4-ClPh	190–192	93.1
3f	Ph	H	4-ClPh	178–180	89.5
3g	H	H	4-OCH_3	202–204	90.5
3h	CH_3	CH_3	4-OCH_3	172–174	91.3

Table 2

The melting point and yield of thieno[2,3-*b*]quinolinone derivatives.

Entries	R^1	R^2	Ar	MP (°C)	Yield (%)
4a	Ph	H	Ph	194–196	49.6
4b	CH_3	CH_3	Ph	226–228	50.1
4c	H	H	Ph	200–202	46.4
4d	H	H	4-ClPh	>270	58.6
4e	CH3	CH3	4-ClPh	>270	64.1
4f	Ph	H	4-ClPh	216–218	60.2
4g	H	H	4-OCH3	176–178	62.1
4h	CH_3	CH_3	4-OCH3	178–180	65.3
4i	Ph	H	4-OCH3	204–206	63.1

recorded as KBr pellets on PerkingElmer 1700 spectrophotometer. The ^{1}H-NMR spectra were recorded by a Bruker ARX-300 or VARIAN-400 spectrometer. Sample solutions were prepared in $CDCl_3$, CD_3OD, or DMSO-d_6, and the chemical shifts are expressed δ ppm using TMS, as an internal standard. Mass spectra were recorded by JMS-DX300 at 70eV.

All chemical reagents were commercially available and purified with standard methods before use. The solvents were dried in routine ways and redistilled. 5-Substituted-1,3-cyclohexanedione were prepared in good yield from aromatic aldehyde, acetone, and diethyl malonate according to the literature [11] method with slightly modification.

General procedure for the synthesis of 2-(1-arylethylidene) malononitrile (1). Toluene (50 mL) was added to a mixture of 4-substituted acetophenone (5 mmol), malononitrile (6 mmol), and ammonium (6 mmol). The solution was stirred at 105°C for 2–3 h. Using a Dean-Stark trap [12], the condensed water was removed from the reaction system. The solvent was evaporated, and the resulting solution was cooled to room temperature. The separated solid was collected, washed with water, and then recrystallized from 95% ethanol to afford 2-(1-arylethylidene) malononitrile.

General procedure for the synthesis of 2-amino-4-arylthiophene-3-carbonitrile (2). 2-(1-Arylethylidene)malononitrile **1** (5 mmol) and elemental sulfur (6.5 mmol) are suspended in 16 mL THF and warmed to an internal temperature of 35°C. A solution of sodium bicarbonate (0.8 g in 16 mL H_2O) is added over 1 h [13]. The mixture is stirred at 35°C for 35 min before the solution is transferred to a separatory funnel. Then, the organic layers were separated, and the water phase was extracted with ethyl acetate by combining the organic phase. After removal of the solvent, the residue was recrystallized from 95% ethanol to give 2-amino-4-arylthiophene-3-carbonitrile.

General procedure for the synthesis of 2-(3-oxo-5-substituted-cyclohex-1-enylamino)-4-arylthiophene-3-carbonitrile(3). To a three-neck flask with a Dean-Stark trap, 50 mL of dry and redistilled toluene, *p*-toluenesulfonic acid (0.1 g) were added. The mixture was stirred at 110°C for 30 min, then 2-amino-4-arylthiophene-3-carbonitrile (5 mmol) and 5-substituted-1,3-cyclohexanedione (7.5 mmol) were added. The reaction was monitored by TLC. When the reaction was completed, the mixture was cooled to room temperature, then evaporated under reduced pressure, and the crude product was recrystallized from 95% ethanol.

General procedure for the synthesis of 4-amino-3-aryl-7-substituted-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one(4). 2-(3-oxo-5-phenylcyclohex-1-enylamino)-4-phenylthiophene-3-carbonitrile(5 mmol) was added to THF (1 mL/mmol) containing potassium carbonate (2.5 mmol) and cuprous chloride (0.5 mmol). The reaction mixture was refluxed for 6 h, and then the hot mixture was filtered into ice hexane. The precipitate was collected and washed with ethanol. The gray powder was purified by silica gel flash chromatography using ethyl acetate/hexane mixture(1:4) as eluent to afford pure compounds. Compounds **4a**–**4i** were synthesized by the same procedure. Data of compounds are shown below.

2-(3-Oxo-5-phenylcyclohex-1-enylamino)-4-phenylthiophene-3-carbonitrile (3a). Yield: 85.4%, m.p. 190–192°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.64–2.75 (m, 3H, 4′-, 6′-H), 2.91–2.96 (m, 1H, 4′-H), 3.47–3.51 (m, 1H, 5′-H), 5.98 (s, 1H, 2′-H), 7.00 (s, 1H, 5-H), 7.27–7.60 (m, 10H, Ph-H); IR (KBr) υ: 3452 (NH), 1656 (C=O), 2214 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 371.2 (M+1, 100); *Anal*. Calcd. for $C_{23}H_{18}N_2OS$: C 74.57, H 4.90, N 7.56; found C 74.60, H 4.91, N 7.44.

2-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)-4-phenylthiophene-3-carbonitrile (3b). Yield: 89.5%, m.p. 156–158°C; ^{1}H-NMR (CD_3OD, 400 MHz) δ:1.15 (s, 6H, 2×CH_3), 2.28 (s, 2H, 6′-H), 2.55 (s, 2H, 4′-H), 7.44–7.51 (m, 4H, 5-H, and Ph-H), 7.63–7.65 (m, 2H, Ph-H); IR (KBr) υ: 3429 (NH), 1685 (C=O), 2232 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 323.1 (M+1, 100); *Anal*. Calcd. for $C_{19}H_{18}N_2OS$: C 70.78, H 5.63, N 8.69; found C 70.71, H 5.58, N 8.64.

2-(3-Oxocyclohex-1-enylamino)-4-phenylthiophene-3-carbonitrile (3c). Yield: 79.3%, m.p. 146–148°C; ^{1}H-NMR(CD_3OD, 300 MHz) δ: 2.01–2.10 (m, 2H, 6′-H), 2.30–2.39 (m, 2H, 5′-H), 2.63–2.67 (m, 2H, 4′-H), 5.50 (s, 1H, 2′-H), 7.38–7.48 (m, 4H, 5-H, and Ph-H), 7.60–7.62 (d, *J* = 6.9 Hz, 2H, Ph-H); IR (KBr) υ: 3472 (NH), 1714 (C=O), 2225 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 295.1 (M+1, 100); *Anal*. Calcd. for $C_{17}H_{14}N_2OS$: C 69.36, H 4.79, N 9.52; found C 69.22, H 4.88, N 9.54.

4-(4-Chlorophenyl)-2-(3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile (3d). Yield: 92.1%, m.p. 228–230°C; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.91–1.94 (m, 2H, 6′-H), 2.21–2.24 (m, 2H, 5′-H), 2.57–2.59 (m, 2H, 4′-H), 5.38 (s, 1H, 2′-H), 7.57–7.65 (m, 5H, 5-H, and Ph-H); IR (KBr) υ: 3464 (NH), 1687 (C=O), 2219 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 329.1 (M+1, 100); *Anal*. Calcd. for $C_{17}H_{13}ClN_2OS$: C 62.10, H 3.98, N 8.52; found C 62.17, H 3.87, N 8.76.

4-(4-Chlorophenyl)-2-(5,5-dimethyl-3-oxocyclohex-1-enylamino) thiophene-3-carb-onitrile (3e). Yield: 93.1%, m.p. 190–192°C; ^{1}H-NMR($CDCl_3$, 400 MHz) δ: 1.13 (s, 6H, 2×CH_3), 2.28 (s, 2H, 6′-H), 2.43 (s, 2H, 4′-H), 5.87 (s, 1H, 2′-H), 6.93 (s, 1H, 5-H), 7.41–7.43 (d, *J* = 6.8 Hz, 2H, Ph-H), 7.49–7.51 (d, *J* = 6.8 Hz, 2H, Ph-H); IR (KBr) υ: 3418 (NH), 1696 (C=O), 2218 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 357.1 (M+1, 100); *Anal*. Calcd. for $C_{19}H_{17}ClN_2OS$: C 63.95, H 4.80, N 7.85; found C 64.16, H 4.82, N 7.86.

4-(4-Chlorophenyl)-2-(3-oxo-5-phenylcyclohex-1-enylamino) thiophene-3-carbonit-rile (3f). Yield: 89.5%, m.p. 178–180°C; ^{1}H-NMR(DMSO-d_6, 400 MHz) δ: 2.58–2.92 (m, 3H, 6-H, and 4-H), 545 (s, 1H, 2′-H), 7.22–7.65 (m, 6H, 5-H, and Ph-H), 7.64 (d, *J* = 8.8 Hz, 2H, Ph-H), 7.58 (d, *J* = 8.8 Hz, 2H, Ph-H); IR (KBr) υ: 3439 (NH), 1635 (C=O), 2248 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 405.1 (M+1, 100); *Anal*. Calcd. for $C_{23}H_{17}ClN_2OS$: C 68.22, H 4.23, N 6.92; found C 68.50, H 4.30, N 6.89.

4-(4-Methoxyphenyl)-2-(3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile(3g). Yield: 90.5%, m.p. 202–204°C; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 2.03–2.09 (m, 2H, 6′-H), 2.34–2.39 (t, *J* = 6.3 Hz, *J* = 6.0 Hz, 2H, 5′-H), 2.62–2.66 (t, *J* = 6.3 Hz, 2H, 4′-H), 3.82 (s, 3H, OCH_3), 5.54 (s, 1H, 2′-H), 6.99–7.01 (d, *J* = 8.7 Hz, 2H, Ph-H), 7.32 (s, 1H, 5-H), 7.53–7.56 (d, *J* = 8.7 Hz, 2H, Ph-H); IR (KBr) υ: 3442 (NH), 1654 (C=O), 2223 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 325.1 (M+1, 100); *Anal*. Calcd. for $C_{18}H_{16}N_2O_2S$: C 66.64, H 4.97, N 8.64; found C 66.50, H 4.77, N 8.35.

2-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)-4-(4-methoxyphenyl) thiophene-3-ca-rbonitrile(3h). Yield: 91.3%, m.p. 172–174°C; ^{1}H-NMR(DMSO-d_6, 400 MHz) δ: 1.02 (s, 6H, 2×CH_3), 2.098 (s, 2H, 6′-H), 2.43 (s, 2H, 4′-H), 3.80 (s, 3H, OCH3), 5.28 (s, 1H, 2′-H), 7.03–7.05 (d, *J* = 8.8 Hz, 2H, Ph-H), 7.49 (s, 1H, 5-H), 7.52–7.55 (d, *J* = 8.8 Hz, 2H, Ph-H); IR (KBr) υ: 3453 (NH), 1710 (C=O), 2238 (C≡N) cm^{-1}; MS (70eV) *m/z* (%): 353.1 (M+1, 100); *Anal*. Calcd. for $C_{20}H_{20}N_2O_2S$: C 68.16, H 5.72, N 7.95; found C 68.20, H 5.45, N 7.54.

4-Amino-3,7-diphenyl-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4a). Yield: 49.6%. m.p. 194–196°C; ^{1}H-NMR($CDCl_3$, 400 MHz) δ: 2.86–2.95 (m, 2H, 8-H), 3.25–3.42 (m, 2H, 6-H), 3.47–3.54 (m, 1H, 7-H), 5.39 (br, s, 1H, N-H), 7.01 (s, 1H, 2-H), 7.29–7.48 (m, 10H, Ph-H), 9.63 (br, s, 1H, N-H); IR (KBr) υ: 3443 (NH), 1750 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 371.1 (M+1, 100); *Anal*. Calcd. for $C_{23}H_{18}N_2OS$: C 74.57, H 4.90, N 7.56; found C 74.44, H 4.95, N 7.66.

4-Amino-7,7-dimethyl-3-phenyl-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4b). Yield: 50.1%. m.p. 226–228°C; ^{1}H-NMR($CDCl_3$, 300 MHz) δ: 1.02 (s, 6H, 2×CH_3), 1.98 (s, 1H, 8-H), 2.88 (s, 3H, 8-H and 6-H), 5.40 (br, s, 1H, N-H), 7.35 (s, 1H, 2-H), 7.50 (s, 5H, Ph-H), 9.43 (br,s, 1H, N-H); IR (KBr) υ: 3426 (NH), 1765 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 323.1 (M+1, 100); *Anal*. Calcd. for $C_{19}H_{18}N_2OS$: C 70.78, H 5.63, N 8.69; found C 70.64, H 5.65, N 8.76.

4-Amino-3-phenyl-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4c). Yield: 46.4%. m.p. 200–202°C; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 1.99–2.08 (m, 2H, 8-H), 2.28–2.26 (m, 2H, 7-H), 2.61–2.65 (m, 2H, 6-H), 5.49 (br, s, 1H, N-H), 7.30 (s, 1H, 2-H), 7.38–7.60 (m, 5H, Ph-H), 9.43 (br, s, 1H, N-H); IR (KBr) υ: 3478 (NH), 1753 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 295.1 (M+1, 100); *Anal*. Calcd. for $C_{17}H_{14}N_2OS$: C 69.36, H 4.79, N 9.52; found C 69.44, H 4.75, N 9.66.

4-Amino-3-(4-chlorophenyl)-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4d). Yield: 58.6%. m.p. > 270°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.05–2.08 (m, 2H, 8-H), 2.19–2.22 (m, 2H, 7-H), 2.48–2.56 (m, 2H, 6-H), 5.43 (br, s, 1H, N-H), 7.42–7.44 (d, *J* = 8.2 Hz, 2H, Ph-H), 7.65 (s, 1H, 2-H), 7.72–7.75 (d, *J* = 8.2 Hz, 2H, Ph-H), 9.39 (br, s, 1H, N-H); IR (KBr) υ: 3460 (NH), 1735 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 329.1 (M+1, 100); *Anal*. Calcd. for $C_{17}H_{13}ClN_2OS$: C 62.10, H 3.98, N 8.52; found C 62.24, H 3.95, N 8.66.

4-Amino-3-(4-chlorophenyl)-7,7-dimethyl-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4e). Yield: 64.1%. m.p. > 270°C; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 1.02 (s, 6H, 2×CH_3), 2.18 (s, 2H, 8-H), 2.26 (s, 2H, 6-H), 5.50 (br, s, 1H, N-H), 7.38 (s, 1H, 2-H), 7.48–7.50 (d, *J* = 8.2 Hz, 2H, Ph-H), 7.55–7.57 (d, *J* = 8.2 Hz, 2H, Ph-H), 9.45 (br, s, 1H, N-H); IR (KBr) υ: 3466 (NH), 1758 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 357.1 (M+1, 100); *Anal*. Calcd. for $C_{19}H_{17}ClN_2OS$: C 63.95, H 4.80, N 7.85; found C 63.64, H 4.75, N 7.96.

4-Amino-3-(4-chlorophenyl)-7-phenyl-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-on-e(4f). Yield: 60.2%. m.p. 216–218°C; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 2.73–2.79 (m, 2H, 8-H), 2.97–3.06 (m, 2H, 8-H), 3.13–3.18 (m, 1H, 6-H), 5.57 (br, s, 1H, N-H), 7.24–7.58 (m, 5H, 2-H, and Ph-H), 9.48 (br, s, 1H, N-H); IR (KBr) υ: 3462 (NH), 1733 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 405.1 (M+1, 100); *Anal*. Calcd. for $C_{23}H_{17}ClN_2OS$: C 68.22, H 4.23, N 6.92; found C 68.34, H 4.15, N 6.96.

4-Amino-3-(4-methoxyphenyl)-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4g). Yield: 62.1%. m.p. 176–178°C; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 1.99 (s, 2H, 8-H), 2.59 (s, 2H, 7-H), 2.96 (s, 2H, 6-H), 3.81 (s, 3H, OCH_3) 5.50 (br, s, 1H, N-H), 7.05–7.07 (d, *J* = 7.7 Hz, 2H, Ph-H), 7.26 (s, 1H, 2-H), 7.37–7.39 (d, *J* = 7.7 Hz, 2H, Ph-H), 9.44 (br, s, 1H, N-H); IR (KBr) υ: 3410 (NH), 1754 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 325.1 (M+1, 100); *Anal*. Calcd. for $C_{18}H_{16}N_2O_2S$: C 66.64, H 4.97, N 8.64; found C 66.44, H 4.85, N 8.66.

4-Amino-3-(4-methoxyphenyl)-7,7-dimethyl-7,8-dihydrothieno[2,3-b]quinolin-5-(6H)-one(4h). Yield: 65.3%. m.p. 178–180°C; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 1.02 (s, 6H, 2×CH_3), 1.98 (s, 2H, 8-H), 2.87 (s, 2H, 6-H), 3.82 (s, 3H, OCH_3) 5.50 (br, s, 1H, N-H), 7.05–7.07 (d, *J* = 6.6 Hz, 2H, Ph-H), 7.27 (s, 1H, 2-H), 7.38–7.40 (d, *J* = 6.6 Hz, 2H, Ph-H), 9.40 (br, s, 1H, N-H); IR (KBr) υ: 3448 (NH), 1741 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 353.1 (M+1, 100); *Anal*. Calcd. for $C_{20}H_{20}N_2O_2S$: C 68.16, H 5.72, N 7.95; found C 68.24, H 5.75, N 7.86.

4-Amino-3-(4-methoxyphenyl)-7-phenyl-7,8-dihydrothieno[2,3-b]quinolin-5(6H)-one(4i). Yield: 63.1%. m.p. 204–206°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.72–2.78 (m, 2H, 6-H), 2.96–3.05 (m, 2H, 8-H), 3.12–3.17 (m, 1H, 7-H), 3.82 (s, 3H, OCH_3), 5.56 (br, s, 1H, N-H), 7.06–7.40 (m, 10H, 2-H, and Ph-H), 9.45 (br, s, 1H, N-H); IR (KBr) υ: 3476 (NH), 1728 (C=O) cm^{-1}; MS (70eV) *m/z* (%): 401.1 (M+1, 100); *Anal*. Calcd. for $C_{24}H_{20}N_2O_2S$: C 71.98, H 5.03, N 6.99; found C 71.84, H 5.15, N 6.86.

CONCLUSIONS

In summary, we have provided a method for the synthesis of a series of novel compounds 4-amino-3-aryl-7-substituted-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one derivatives. The effect of the temperature on the reactions of malononitrile with 4-substituted acetophenone was also investigated. We found that the reaction temperature was determined to be 35°C in the presence of $NaHCO_3$, significantly degrading the byproducts, which is easier to be removed during the crystallization of the desired product **1**. In addition, the reaction of thiophenes **2** (5 mmol) with 5-substituted-1,3-cyclo-hexanedione in the presence of *p*-toluenesulfonic acid (0.1 g) was also performed in excellent yield. The molar ratio of 5-substituted-1,3-cyclohexanediones and compound **2** is 1.5:1, and the optimal reaction time is 2∼3 h.

REFERENCES AND NOTES

[1] Rose, P.; Whiteman, M.; Moore, P. K. Nat Prod Rep 2005, 22, 351.

[2] Marcela, A. V. P.; Roberto, M. M. Mol A Med 2010, 31, 540.

[3] Rashad, A. E.; Shamroukh, A. H.; Abdel-Megeid, R. E. Eur J Med Chem 2010, 45, 5251.

[4] O'Donnell, F.; Smyth, T. J. P.; Ramachandran, V. N. Int J Antimicrob Agents 2010, 35, 30.

[5] Nayyar, A.; Monga, V.; Malde, A. Bioorg Med Chem 2007, 15, 626.

[6] Guo, L. J.; Wei, C. X.; Jia, J. H. Eur J Med Chem 2009, 44, 954.

[7] Shi, A.; Nguyen, T. A.; Battina, S. K. Bioorg Med Chem Lett 2008, 18, 3364.

[8] Ahmed, N.; Brahmbhatt, K. G.; Sabde, S. Bioorg Med Chem 2010, 18, 2872.

[9] Wang, L. Y.; Chen, Q. W.; Zhai, G. H. Dyes Pigm 2007, 72, 357.

[10] Han, G. F.; Wang, R. H.; Zhang, W. T. Synth Commun 2009, 39, 2492.

[11] Han, G. F.; Wang, J. J.; Jiang, G. J. Chin J Org Chem 2003, 23, 1004 (in Chinese).

[12] Yen, M. S.; Wang, I. S. Dyes Pigm 2004, 61, 243.

[13] Barnes, D. M.; Haight, A. R.; Hameury, T. Tetrahedron 2006, 62, 11311.