Microwave Induced Synthesis of 3-Aryl-6-(6-/8-substituted 4-chloroquinoline-3-yl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles

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The condensation of 4-amino-3-aryl-5-mercapto-1, 2, 4-triazoles (1a—f) with 6-/8-substituted 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids (2a—d) in the presence of phosphorus oxychloride on refluxing or under microwave irradiation gave twenty four novel 3-aryl-6-(6-/8-substituted 4-chloroquinoline-3-yl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (4a—x), Considerable increase in the reaction rate has been observed with improved yields under microwave irradiation. The structures of the compounds synthesized were determined by elemental analyses, IR, ^{1}H NMR and MS spectra. Their spectral properties and the reaction mechanism were also discussed. The preliminary biological test showed that some of compounds had moderate antibacterial activities.

Keywords 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole, quinoline, microwave irradiation

Introduction

In earlier papers,[1] we reported that 3,6-disubstituted *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives have been attracting much attention in recent decades because of their broad spectrum of biological activities, such as antifungal, antibacterial, antiperiodic, antiinflammatory, analgesic and anthelmintic activities. It is doubtless that the basic structure of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole ring system results in the broad spectrum of biological activities. However, the structure and position of the substituent have a major influence on a melioration of medicinal efficacy and reduction of toxicity. It is worthwhile to study the relationship between the modification of the substituent and the potentially biological activities of the fused heterocycles.

In order to improve the solvency of the fused heterocycles, the charge distribution and conjugation of the fused heterocycles and sterically hinder influence on their biological activities, alkyl, aryl and heterocyclic groups have been incorporated into the 3- and 6-position of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives.[2-4] Previousely we described a series of 3,6-disubstituted *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives which exhibited inhibiting effect on cucumber grey mold, cotton damping off, apple black rot and corn big speck.[5-7] In contrast, few *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives have been synthesized, in which heterocyclic nuclei were in 6-position.[8] Many natural plants contain quinoline derivatives that existed in the form of alkaloids which have very important pharmacological values, such as insecticidal, anti-cancer, cure cardiovascular disease. It is well known that quinoline derivatives were associated with broad-spectrum, high-efficacy, low-toxic antibacterial activities.[10-11] Quinoline derivatives have been incorporated into cephalosporin to widen antibacterial property.[12] In order to investigate the structure-activity relationship of this ring system, encouraged by the above observations and as a proceeding part of our work, we synthesized a series of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives in which quinoline moiety has been incorporated into the 6-position to obtain better biologically active agents.

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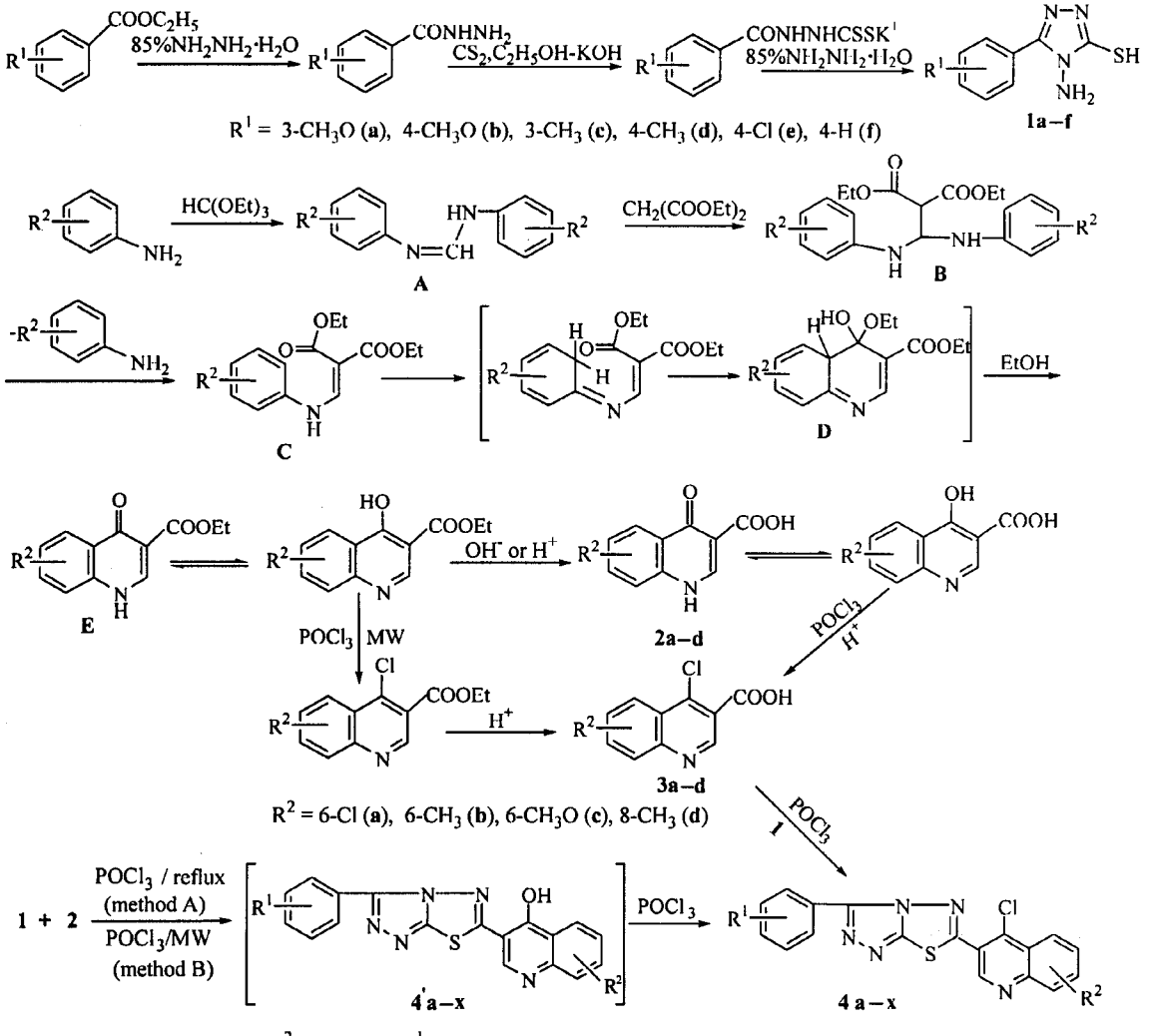
Recently, there has been much interest in the use of microwave irradiation (MWI) in synthesis due to substantial reduction in reation period.[13] Our experimental results exhibited that MWI reduced the reaction time and improved yields in the synthesis of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles derivatives.

Results and discussion

Synthesis

The key of synthesis was the preparation of quinoline acids **2a—d** and the condensation conditions of **1a—f** with **2a—d** because the conditions reported in previous paper[5] were not adapted to the condensation of all heterocyclic acids with **1a—f**. The synthons **2a—d** were synthesized by the Gould-Jacbs's method (Scheme 1).

Scheme 1



4a—f R^2 = 6-CH_3O, R^1=3-CH_3O (**a**), 4-CH_3O (**b**), 3-CH_3 (**c**), 4-CH_3 (**d**), 4-Cl (**e**), 4-H (**f**)

4g—l R^2 = 6-CH_3, R^1=3-CH_3O (**g**), 4-CH_3O (**h**), 3-CH_3 (**i**), 4-CH_3 (**j**), 4-Cl (**k**), 4-H (**l**)

4m—r R^2 = 8-CH_3, R^1=3-CH_3O (**m**), 4-CH_3O (**n**), 3-CH_3 (**o**), 4-CH_3 (**p**), 4-Cl (**q**), 4-H (**r**)

4s—x R^2 = 6-Cl, R^1=3-CH_3O (**s**), 4-CH_3O (**t**), 3-CH_3 (**u**), 4-CH_3 (**v**), 4-Cl (**w**), 4-H (**x**)

The cyclocondensation of **1a—f** with **2a—d** on refluxing or under microwave irradiation afforded bridgeheaded nitrogen heterocycles **4a—x**. Substituted aniline reacted with ethyl orthoformate to produce the Schiff bases **A**. Then **A** reacted with diethyl malonate via additive reaction to form the intermediate **B** in the presence of $BF_3 \cdot OEt_2$. The intermediate **B** eliminated substituted aniline to give the stable intermediate **C** at the raised temperature. In the liquid paraffin (255—265℃), the hydrogen atom (NH) of the intermediate **C** underwent 1,3-H migration to form the active intermediate **D**, which cyclized into 6-/8-substituted 1,4-dihydro-4-oxo-quinoline-3-carboxylates **E** accompanied by loss of ethanol molecule. Compounds **2a—d** were obtained by hydrolysis in the presence of acid or base when compound **E** was carried out. The condensation of **2** and **1** in the presence of $POCl_3$, 3-aryl-6-(6-/8-substituted 4-chloroquinoline-3-yl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**4a—x**) were obtained instead of the expected 3-aryl-6-(6-/8-substituted 4-hydroxyquinoline-3-yl)-*s*-triazolo-[3,4-*b*]-1,3,4-thiadiazoes (**4'a—x**). Although other condensed agents, such as H_2SO_4, PCC, PPA and PPE were used, the cyclic products were not obtained. It showed that phosphorus oxychloride was necessary for this condensation reaction, which not only activated the carbonyl group of **2**, but also was effective dehydrating solvent. Refluxing of **1** and **2** over oil-bath or irradiation under microwave in the presence of $POCl_3$, afforded **4a—x** instead of **4'a—x**. The reason might be that **4'a—x** were initially formed and reacted with excess $POCl_3$, or 6-/8-substituted 4-chloro-quinoline-3-carboxylic acids (**3a—d**) were initially formed and reacted with **1** to give **4a—x**. The mechanism was confirmed by **3a—d** which were obtained from **E** or **2a—d** condensed with **1** to produce **4a—x**.

Spectral properties

The structures of **4a—x** were characterized by elemental analyses, IR, ^1H NMR and mass spectral data (Tables 1, 2 and 3).

The compounds **4a—x**, which contained benzene ring, *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole and quinoline cyclic systems, were multi-π electron system. Compared with the monocyclic system, the IR absorption should exhibit bathochromic effect. But the vibratory absorption of the quinoline ring and the benzene ring of **4a—x** showed absorption bands at 1584—1673 cm^{-1}, which coincided with the skeleton vibration of benzene nucleus and quinoline nucleus. Their IR spectra displayed three characteristic absorption bands at 1584—1617 cm^{-1} for $\nu_{C=N}$, 1211—1280 cm^{-1} for ν_{N-N}, and 680—699 cm^{-1} for ν_{C-S-C}, respectively. It may be that *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole and quinoline ring systems had prominent-C effect[14] which made them not conjugate effectually and the electron could not flow freely in the molecule.

Although multi-π electron conjugation system could not be formed effectively because *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole heterocycle, 3-position aryl ring and 6-position substituted quinoline nucleus were aggregated in a molecule, as a whole, the intramolecular functional groups were interrelated and the withdrawing inductive effect of benzene ring and quinoline ring resulted in shifting to downfield (δ: 7.11—8.81) than the usual proton of benzene ring and the quinoline ring systems.[15] The chemical shift of 2-position proton of the quinoline ring was δ 9.26—9.54 which was in agreement with literature.[16] The reason described as above is that the chemical shifts of the aromatic ring methyl and methoxyl which were deshielded by *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole fused heterocycle nucleus were located further downfield. The ^1H NMR spectra of **4a—x** dispalyed singlet at δ 2.43—2.46 and δ 3.86—3.88, which were as signed to CH_3 and CH_3O of phenyl, respectively. The signal of quinoline ring CH_3 and CH_3O exhibited at δ 2.60—2.81 and δ 4.00—4.02, respectively.

By analyzing the electron impact mass spectra of the representative compounds, it was found that the compounds had intense molecular ion peaks, which were or closed to base peak. The fragment of A and F showed strong peaks and some of them were base peak, such as **4n**, **4s**, **4u**, **4v** and **4x**. The molecular ion peaks or the fragment containing chlorine exhibit isotope peaks in their mass spectra. The fragmentation pattern of these compounds followed three pathways corresponding to the fission of the fused nucleus (Scheme 2).

The compounds synthesized were screened for their antibacterial activities *in vitro* against *E. coli*, *S. aureaus* and *Ps. aeruginosa* at the concentration of 100 μg/mL using cupplate diffussion method. The preliminary results indicated that representative compounds **4a**, **4b**, **4e**, **4k**, **4h**, **4n**, **4s** and **4w** exhibited moderate antibacterial activities. Further research works are in

progress.

Table 1 Physical properties and elementary analyses of compounds **4a—x**

Compd.	Formula	Yield (%) (MW)	m.p. (℃)	Elementary analyses (Calcd.) (%)		
				C	H	N
4a	$C_{20}H_{14}N_5SO_2Cl$	71(82)	227—228	56.61(56.67)	3.37 (3.33)	16.49 (16.52)
4b	$C_{20}H_{14}N_5SO_2Cl$	63(78)	234—235	56.69 (56.67)	3.38 (3.33)	16.48 (16.52)
4c	$C_{20}H_{14}N_5SOCl$	65(80)	235—236	58.90 (58.90)	3.47 (3.46)	17.14 (17.17)
4d	$C_{20}H_{14}N_5SOCl$	68(72)	234—235	58.88 (58.90)	3.43 (3.46)	17.15 (17.17)
4e	$C_{19}H_{11}N_5SOCl_2$	50(61)	243—244	55.93 (56.09)	2.48 (2.59)	16.27 (16.35)
4f	$C_{19}H_{12}N_5SOCl$	55(65)	237—238	57.94 (57.94)	3.09 (3.01)	17.68 (17.78)
4g	$C_{20}H_{14}N_5SOCl$	58(64)	241—243	58.95 (58.90)	3.50 (3.46)	17.19 (17.17)
4h	$C_{20}H_{14}N_5SOCl$	56(71)	242—243	58.97 (58.90)	3.49 (3.46)	17.16 (17.17)
4i	$C_{20}H_{14}N_5SCl$	53(65)	218—220	61.19 (61.30)	3.57 (3.60)	17.94 (17.87)
4j	$C_{20}H_{14}N_5SCl$	54(67)	218—220	61.20 (61.30)	3.54 (3.60)	17.92 (17.87)
4k	$C_{19}H_{11}N_5SCl_2$	43(56)	258—260	55.51 (55.35)	2.73 (2.69)	17.03 (16.99)
4l	$C_{19}H_{12}N_5SCl$	48(54)	252—253	60.28 (60.40)	3.29 (3.20)	18.32 (18.53)
4m	$C_{20}H_{14}N_5SOCl$	60(78)	220—223	58.88 (58.90)	3.51 (3.46)	17.00 (17.17)
4n	$C_{20}H_{14}N_5SOCl$	63(80)	216—217	59.12 (5890)	3.54 (3.46)	17.10 (17.17)
4o	$C_{20}H_{14}N_5SCl$	50(64)	214—215	61.13 (61.30)	3.53 (3.60)	17.94 (17.87)
4p	$C_{20}H_{14}N_5SCl$	53(63)	242—243	61.31 (61.30)	3.68 (3.60)	17.72 (17.87)
4q	$C_{19}H_{11}N_5SCl_2$	44(56)	257—258	55.31 (55.35)	2.75 (2.69)	17.13 (16.99)
4r	$C_{19}H_{12}N_5SCl$	50(68)	268—269	60.44 (60.40)	3.23 (3.20)	18.62 (18.53)
4s	$C_{19}H_{11}N_5SOCl_2$	62(81)	247—248	53.24 (53.28)	2.49 (2.59)	16.31 (16.35)
4t	$C_{19}H_{11}N_5SOCl_2$	58(64)	248—249	53.38 (53.28)	2.74 (2.59)	16.28 (16.35)
4u	$C_{19}H_{11}N_5SCl_2$	55(65)	247—248	55.24(55.35)	2.58 (2.68)	16.67 (16.78)
4v	$C_{19}H_{11}N_5SCl_2$	57(68)	249—250	55.17(55.35)	2.50 (2.68)	16.39 (16.78)
4w	$C_{18}H_8N_5SCl_3$	50(65)	260—262	49.81 (49.97)	2.01 (1.86)	16.04 (16.18)
4x	$C_{18}H_9N_5SCl_2$	52(72)	247—248	54.08 (54.29)	2.37 (2.28)	17.46 (17.59)

Scheme 2

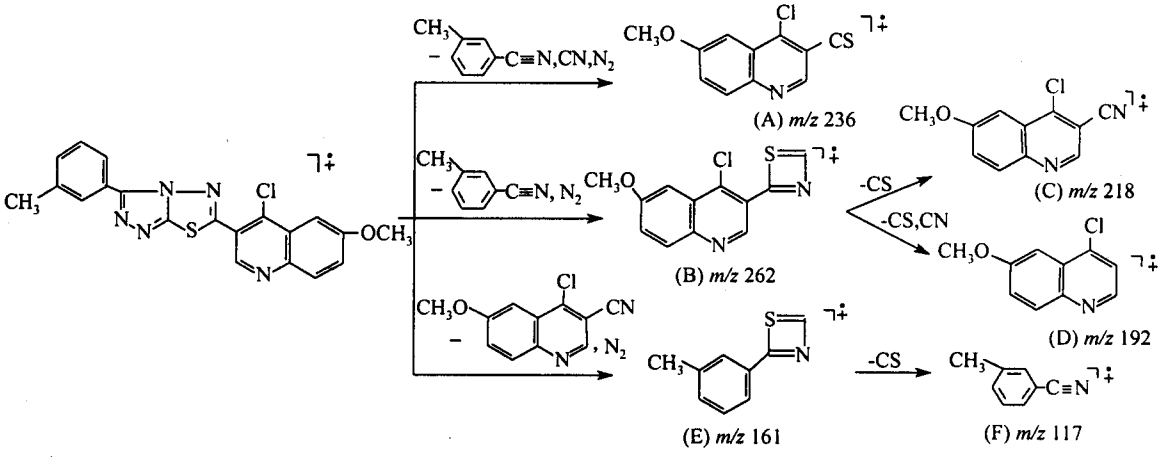


Table 2 ^{1}H NMR and IR data of compounds **4a—x**

Compd.	^{1}H NMR (DMSO-d_6, δ)	IR (ν_{max}/cm^{-1}, KBr disc)		
		C=N	N—N	C—S—C
4a	3.87 (s, 3H, 3-CH_3O), 4.02 (s, 3H, 6′-CH_3O), 7.11—8.20 (m, 7H, ArH), 9.27 (s, 1H, 2′-H)	1616 m	1233 m	699 w
4b	3.86 (s, 3H, 4-CH_3O), 4.02 (s, 3H, 6′-CH_3O), 7.14—8.20 (m, 7H, ArH), 9.28 (s, 1H, 2′-H)	1613 m	1224 m	681 w
4c	2.43 (s, 3H, CH_3), 4.00 (s, 3H, CH_3O), 7.42—8.10 (m, 7H, ArH), 9.26 (s, 1H, 2′-H)	1615 m	1245 m	694 m
4d	2.43 (s, 3H, CH_3), 4.01 (s, 3H, CH_3O), 7.40—8.12 (m, 7H, ArH), 9.26 (s, 1H, 2′-H)	1616 m	1234 m	680 m
4e	4.03 (s, 3H, CH_3O), 7.55—8.41 (m, 7H, ArH), 9.28 (s, 1H, 2′-H)	1616 m	1229 m	691 m
4f	4.02 (s, 3H, CH_3O), 7.58—8.38 (m, 7H, ArH), 9.28 (s, 1H, 2′-H)	1598 m	1232 m	695 m
4g	2.62 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 7.10—8.17 (m, 7H, ArH), 9.36 (s, 1H, 2′-H)	1598 m	1230 m	698 m
4h	2.62 (s, 3H, CH_3), 3.87 (s, 3H, CH_3O), 7.08—8.16 (m, 7H, ArH), 9.36 (s, 1H, 2′-H)	1610 m	1254 m	679 m
4i	2.44 (s, 3H, 3-CH_3), 2.60 (s, 3H, 6′-CH_3), 7.50—8.42 (m, 7H, ArH), 9.39 (s, 1H, 2′-H)	1584 m	1211 m	696 m
4j	2.43 (s, 3H, 4-CH_3), 2.61 (s, 3H, 6′-CH_3), 7.56—8.49 (m, 7H, ArH), 9.39 (s, 1H, 2′-H)	1583 m	1218 m	696 m
4k	2.63 (s, 3H, CH_3), 7.61—8.51 (m, 7H, ArH), 9.43 (s, 1H, 2′-H)	1582 m	1275 m	671 w
4l	2.62 (s, 3H, CH_3), 7.45—8.61 (m, 8H, ArH), 9.40 (s, 1H, 2′-H)	1584 m	1263 m	696 m
4m	2.80 (s, 3H, CH_3), 3.87 (s, 3H, CH_3O), 7.11—8.22 (m, 7H, ArH), 9.48 (s, 1H, 2′-H)	1610 m	1280 m	699 m
4n	2.78 (s, 3H, CH_3), 3.86 (s, 3H, CH_3O), 7.11—8.31 (m, 7H, ArH), 9.48 (s, 1H, 2′-H)	1611 m	1254 m	681 w
4o	2.44 (s, 3H, 3-CH_3), 2.78 (s, 3H, 8′-CH_3), 7.42—8.29 (m, 7H, ArH), 9.52 (s, 1H, 2′-H)	1613 m	1267 w	696 m
4p	2.46 (s, 3H, 4-CH_3), 2.79 (s, 3H, 8′-CH_3), 7.38—8.29 (m, 7H, ArH), 9.52 (s, 1H, 2′-H)	1596 m	1263 w	709 m
4q	2.73 (s, 3H, CH_3), 7.62—8.15 (m, 7H, ArH), 9.55 (s, 1H, 2′-H)	1673 m	1259 w	679 w
4r	2.81 (s, 3H, CH_3), 7.58—8.34 (m, 7H, ArH), 9.54 (s, 1H, 2′-H)	1611 m	1262 m	686 m
4s	3.88 (s, 3H, CH_3O), 7.21—8.45 (m, 7H, ArH), 9.47 (s, 1H, 2′-H)	1676 m	1227 m	699 m
4t	3.87 (s, 3H, CH_3O), 7.23—8.49 (m, 7H, ArH), 9.47 (s, 1H, 2′-H)	1614 m	1267 m	694 m
4u	2.41 (s, 3H, CH_3), 7.35—8.34 (m, 7H, ArH), 9.48 (s, 1H, 2′-H)	1663 m	1268 m	695 m
4v	2.40 (s, 3H, CH_3), 7.58—8.43 (m, 7H, ArH), 9.48 (s, 1H, 2′-H)	1610 w	1261 m	712 m
4w	7.61—8.45 (m, 7H, ArH), 9.48 (s, 1H, 2′-H)	1677 m	1259 m	680 m
4x	7.48—8.37 (m, 8H, ArH), 9.48 (s, 1H, 2′-H)	1673 m	1257 m	682 m

Table 3 Mass spectral data of representative compounds

Compd.	M^+ (%)	Other fragments (%)
4a	423 (100)	262 (2), 236 (68), 218 (6), 192 (13), 177 (7), 133 (44)
4c	407 (100)	262 (2), 236 (86), 218 (9), 192 (15), 161 (12), 117 (47)
4e	427 (100)	262 (3), 236 (98), 218 (10), 192 (18), 181 (11), 137 (65)
4f	393 (100)	262 (3), 236 (76), 218 (9), 192 (17), 147 (10), 103 (54)
4g	407 (100)	246 (2), 220 (94), 202 (10), 177 (6), 176 (3), 133 (57)
4I	391 (100)	246 (3), 220 (85), 202 (7), 176 (4), 161 (7), 177 (53)
4k	411 (100)	246 (3), 220 (73), 202 (8), 181 (10), 176 (6), 137 (58)
4l	377 (100)	246 (3), 220 (75), 202 (5), 176 (5), 147 (13), 103 (57)
4m	407 (100)	246 (3), 220 (75), 202 (8), 177 (6), 176 (3), 133 (52)
4n	407 (96)	246 (2), 220 (59), 202 (8), 177 (7), 176 (4), 133 (100)
4o	391 (100)	246 (4), 220 (82), 202 (10), 176 (6), 161 (12), 117 (47)
4p	391 (100)	246 (3), 220 (73), 202 (7), 176 (15), 161 (11), 117 (56)
4s	427 (94)	266 (2), 240 (90), 222 (10), 196 (2), 177 (24), 133 (100)
4u	411 (95)	266 (3), 240 (100), 222 (9), 196 (3), 161 (26), 117 (93)
4v	411 (92)	266 (2), 240 (90), 222 (8), 196 (6), 161 (22), 117 (100)
4x	397 (96)	266 (3), 240 (100), 222 (10), 196 (3), 147 (31), 103 (90)

Experimental

The melting points were determined on an X-4 melting point apparatus and were uncorrected. Elemental analyses were carried out on an Elementar Vario EL analyzer. IR spectra were obtained in KBr disc on a Nicolet AVATAR 360 FT-IR spectrometer. MS were taken on a VG ZAB-HS instrument (EI at 70 eV). ^{1}H NMR spectra (DMSO-d_6) were performed on a Bruker AC-80 spectrometer with TMS as an internal standard.

4-Amino-5-mercapto-3-substituted 1,2,4-triazoles (**1a—f**)

1a—f were prepared according to the literature method.[17] Their structures were confirmed by elemental analyses.

1a, R^1 = 3-CH_3O, yield 68%, m.p. 217—218 ℃ (lit.[17] 216—219℃).

1b, R^1 = 4-CH_3O, yield 52%, m.p. 204—205℃ (lit.[17] 216—219℃).

1c, R^1 = 3-CH_3, yield 63%, m.p. 219—220℃ (lit.[17] 219—220℃).

1d, R^1 = 4-CH_3, yield 54%, m.p. 214—215℃ (lit.[17] 213—214℃).

1e, R^1 = 4-Cl, yield 58%; m.p. 150—152℃ (lit.[17] 151—152℃).

1f, R^1 = 4-H, yield 67%, m.p. 204—205℃ (lit.[17] 204—206℃).

6-/8-Substituted 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids (**2a—d**)

2a—d were obtained according to the literature method.[18]

2a, R^2 = 6-Cl, yield 53%, m.p. 261—262℃.

2b, R^2 = 6-CH_3, yield 45%, m.p. 262—264℃.

2c, R^2 = 6-CH_3O, yield 25%, m.p. 272—273℃.

2d, R^2 = 8-CH_3, yield 34%, m.p. 263—264℃.

3-Aryl-6-(6-/8-substituted 4-chloroquinoline-3-yl)-s-triazolo[3,4-b]-1,3,4-thiadiazoles **4a—x**

Method A: A mixture of **1** (1 mmol) and **2** (1 mmol) in the presence of $POCl_3$ (5 mL) was refluxed over oil-bath for 8 h. After removal of the excess of $POCl_3$ under reduced pressure, distilled water (50 mL) was added to the residue. The resulting solid was filtered, treated with 10% aqueous sodium hydroxide, and then washed with water. The crude product was finally recrystallized from DMF to analytical purity.

Method B: A mixture of **1** (1 mmol) and **2** (1 mmol) in $POCl_3$ (5 mL) was irradiated under microwave for 1—3 min. The work up was similar to that of method A.

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