Quinolone Analogues 12: Synthesis and Tautomers of 2-Substituted 4-Quinolones and Related Compounds

Yoshihisa Kurasawa,[a]* Kiminari Yoshida,[a] Naoki Yamazaki,[a] Kotoji Iwamoto,[b] Yoshihiko Hamamoto,[b] Eisuke Kaji,[b] Kenji Sasaki,[c] and Yoshito Zamami[c]

[a]Department of Organic Chemistry, School of Pharmacy, Iwaki Meisei University, Iino, Chuodai, Iwaki, Fukushima 970-8551, Japan
[b]Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108-8641, Japan
[c]Department of Molecular Design for Medicine, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Tsushimanaka, Kita-ku, Okayama-Shi, Okayama 700-8530, Japan
*E-mail: kura77@iwakimu.ac.jp

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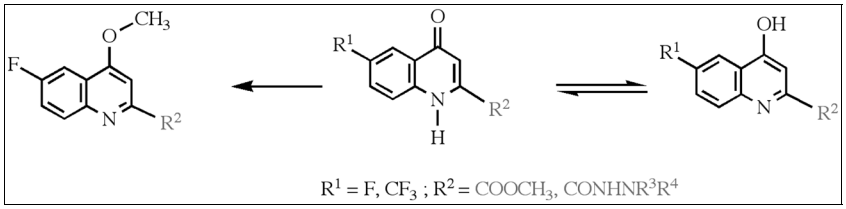

The 4-quinolone-2-carboxylates **4a,b** were converted into the 4-quinolone-2-carbohydrazides **5a,b**, hydrazones **6,7,10**, and related compounds **8,9,11**. The 4-methoxyquinoline-2-carboxylate **12** was also transformed into the 4-methoxyquinoline-2-carbohydrazide **13**, which was modified to the hydrazone **14** and related compound **15**. The antimicrobial activities of compounds **6b** and **14** are described together with the 4-oxo and 4-hydroxy tautomers of compounds **4-11** in deuteriodimethyl sulfoxide and deuteriotrifluoroacetic acid.

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INTRODUCTION

In previous articles [1–8], we reported the synthesis of the 1-methylpyridazino[3,4-*b*]quinoxalines **1a-h** as candidates of antibacterial quinolone analogues (Chart 1). The 3-alkyl **1c-e**, 3-H **1f**, and 3-halogeno **1g,h** derivatives were found to have antifungal and/or antibacterial activities [3–6,9], whereas the 3-amino **1i,j** and 3-heteroaryl **1k,l,m** derivatives were clarified to possess no antibacterial and antifungal activities [10]. Thereafter, we converted the target ring system of the pyridazino [3,4-*b*]quinoxalin-4-(1*H*)-one into the 4-quinolone in the study to search for more potent antimicrobial agents. In literatures, the 2-alkylthio-4-quinolones **2a** [11] and 2-alkylthioquinolines **2b** [11] (Chart 1) were known to have antibacterial activities, especially to MRSA, wherein the alkyl chains were composed of C_{10}~C_{15} carbons. The naturally occurring 4-quinolones **3a** [12,13], **3b** [13,14] and quinoline **3c** [13,14] (Chart 1) were also reported to possess antibiotic (**3a**), antirheumatic (**3b,c**), and antispasmodic (**3b,c**) activities. Thus, there have been many useful compounds in the 2-substituted 4-quinolones and 4-hydroxyquinolines, and hence we undertook the synthesis of some 2-substituted 4-quinolones and 4-methoxyquinolines. Moreover, since there have been a few papers on the tautomerism of the 2-substituted 4-quinolones between the 4-oxo and 4-hydroxy forms in some solvent system (Chart 2) [13,15], we have also studied to specify the 4-oxo and 4-hydroxy tautomers of our 2-substituted 4-quinolones **4–11** (Schemes 1,2) in the deuteriodimethyl sulfoxide or deuteriotrifluoroacetic acid solution using the 4-methoxyquinolines **12–15** (Scheme 3) as reference compounds. In this article, we report the synthesis and *in vitro* antimicrobial activities of the 2-substituted 4-quinolones **4-11** and 4-methoxyquinolines **12–15** together with the tautomerism of compounds **4-11** between the 4-oxoquinoline and 4-hydroxyquinoline forms in deuteriodimethyl sulfoxide or deuteriotrifluoroacetic acid media.

RESULTS AND DISCUSSION

Synthesis of compounds 4–15. The 6-substituted 4-quinolone-2-carboxylates **4a,b** were synthesized by the reaction of 4-fluoroaniline and 4-trifluoromethylaniline with dimethyl acetylenedicarboxylate, according to a known method [16] in a slight modification [17], wherein intermediary adducts were not purified before cyclization into compounds **4a,b** under reflux in diphenyl ether.

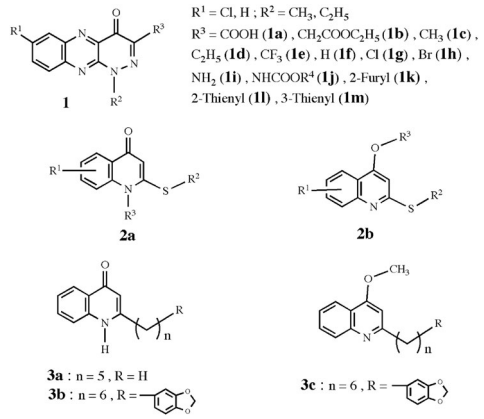
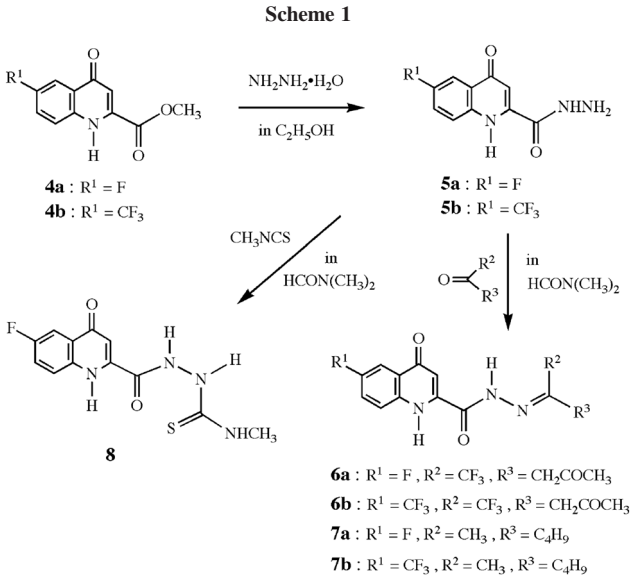


Chart 1



The reaction of compounds **4a,b** with hydrazine hydrate gave the 2-carbohydrazides **5a,b**, whose reaction with ketones afforded the hydrazones **6a,b** and **7a,b**, respectively (Scheme 1). The reaction of compound **5a** with methyl isothiocyanate furnished the thiosemicarbazide derivative **8**.

The reaction of compound **5b** with phenyl isocyanate gave the semicarbazide derivative **9**, while the reaction of compounds **5a,b** with cyclohexane-1,3-dione or hexane-2,5-dione afforded the hydrazones **10a,b** or *N*-(2,5-dimethylpyrrol-1-yl)carboxamides **11a,b**, respectively (Scheme 2).

The methylation of compound **4a** with methyl iodide and potassium carbonate effected the 4-O-methylation to provide methyl 6-fluoro-4-methoxyquinoline-2-carboxylate **12** (Scheme 3), which was supported by the NOE measurement between the 4-O-methyl and 3-H proton signals (17%). The reaction of compound **12** with hydrazine hydrate formed the 2-carbohydrazide **13**, whose reaction with 1,1,1-trifluoroacetylacetone or methyl isothiocyanate afforded the hydrazone **14** or thiosemicarbazide **15**, respectively.

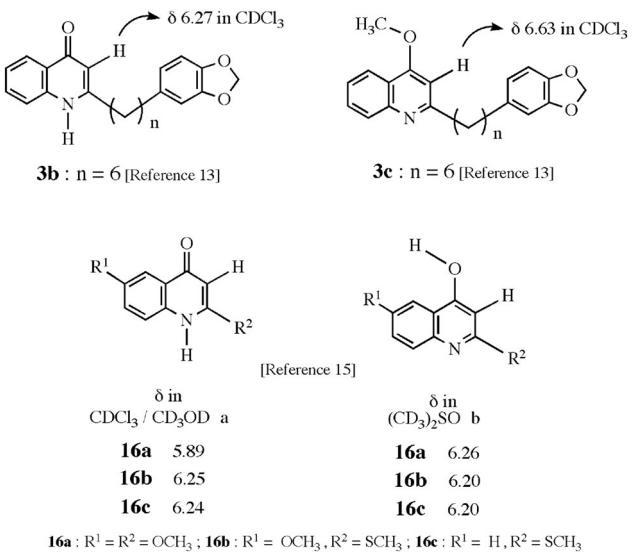


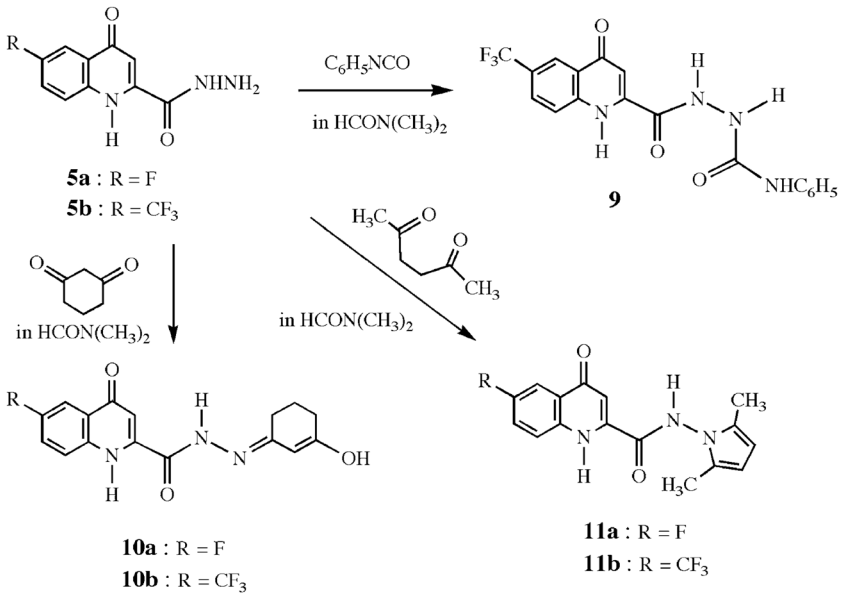
Chart 2

***In vitro* evaluation of novel compounds as antimicrobials.** The *in vitro* antimicrobial activities were evaluated for our 2-substituted 4-quinolones. As the result, compound **14** showed weak antifungal activities against five kinds of fungi (*Candida albicans, Candida crusei, Aspergillus fumigatus, Tricophyton rubrum, Tricophyton mentagrophytes*), wherein the minimum inhibitory concentrations were 8–16 ppm. On the other hand, compounds **6b** and **14** exhibited weak anti-MRSA activities against five kinds of strains (*Streptococcus aureus* ATCC 33591, 33592, 33593, 13301, 11632) at concentrations of 16–32 ppm, respectively.

4-Oxoquinoline and 4-hydroxyquinoline tautomers assigned by the ^{1}H-NMR and ^{13}C-NMR spectral data. The chemical shifts of the 3-H protons in the 2-substituted 4-quinolones and 4-methoxyquinolines have been known to vary depending on the kind of the 2-substituents and solvents used for the measurement of ^{1}H-NMR spectra. Namely, the 3-H proton signals of the 2-alkyl-4-quinolone **3b** and 2-alkyl-4-methoxyquinoline **3c** (Chart 2) were reported to appear at δ 6.27 and 6.63 in deuteriochloroform [13], respectively, while the 3-H proton signals of the 4-quinolones **16a,b,c** were observed at δ 5.89, 6.25, 6.24 in deuteriochloroform/deuteriomethanol preponderating as the 4-oxo form and at δ 6.26, 6.20, 6.20 in deuteriodimethylsulfoxide predominating as the 4-hydroxy form [15] (Chart 2), respectively.

In our 4-quinolones **4**-**7**, the 3-H proton signals in deuteriodimethyl sulfoxide (δ 6.29–6.90) were observed in higher magnetic fields than those in deuteriotrifluoroacetic

Scheme 2



acid (δ 7.64–8.31) (Table 1). Moreover, the 3-H proton signals of the 4-quinolones **4a**, **5a**, and **6a** in deuteriotrifluoroacetic acid appeared in similar magnetic fields to those of the corresponding 4-methoxyquinolines **12**, **13**, and **14** in deuteriotrifluoroacetic acid, respectively [δ (**4a**: 7.74, **12**: 7.70), (**5a**: 7.64, **13**: 7.60), (**6a**: 8.20, **14**: 8.19)] (Table 1). These data support that the 4-quinolones **4-7** preponderate as the 4-hydroxy form (**4**-**7**)-(**B**-D)$^+$ in deuteriotrifluoroacetic acid (Chart 3). While, the 3-H proton signals of the 4-quinolones **4a**, **5a**, and **6a** in deuteriodimethyl sulfoxide were observed in higher magnetic fields than those of the corresponding 4-methoxyquinolines **12**, **13**, and **14** in deuteriodimethyl sulfoxide, respectively [δ (**4a**: 6.59, **12**: 7.51), (**5a**: 6.72, **13**: 7.54), (**6a**: 6.29, **14**: 7.00)] (Table 1). These data suggest that the 4-quinolones **4-7** predominate as the 4-oxo form **A** in deuteriodimethyl sulfoxide (Chart 3).

In a deuteriodimethyl sulfoxide solution of the thiosemicarbazide derivative **8**, two kinds of 3-H proton signals were observed at δ 6.76 (major) and 7.49 (minor) together with paired NH proton signals [δ 10.88 (major)/10.57 (minor), 9.51 (major)/9.37 (minor), 8.22 (major)/7.79 (minor)], which would be due to the presence of the 4-oxo **A** and 4-hydroxy **B** tautomers in the ratio of approximately 81% to 19% [18], respectively (Scheme 4). That is, the 3-H proton signals of compound **8** at δ 6.76 (4-oxo form **A**) and 7.49 (4-hydroxy form **B**) in deuteriodimethyl sulfoxide appeared in similar magnetic fields to those of the 4-quinolones (**4**–**7**)-**A** (δ 6.29–6.90)

Scheme 3

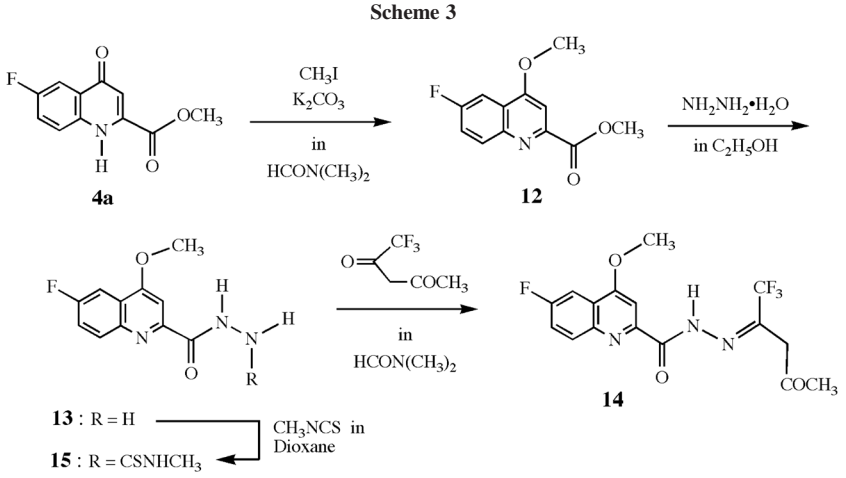


Table 1

Chemical shifts (δ) of 3-H for compounds **4–8** and **12–15**.

Substituent		4-Quinolones			4-Mcthoxyqninolincs		
C_6	C_2	Compound	δ in $(CD_3)_2SO$ 4-oxo form **A**	δ in CF_3COOD 4-hydroxy form (**B**-D)$^+$	Compound	δ in $(CD_3)_2SO$	δ in CF_3COOD
F	$COOCH_3$	**4a**	6.59	7.74	**12**	7.51	7.70
CF_3	$COOCH_3$	**4b**	6.70	7.67			
F	$CONHNH_2$	**5a**	6.72	7.64	**13**	7.54	7.60
CF_3	$CONHNH_2$	**5b**	–[a]	7.67			
F	$CONHN=C(CF_3)CH_2COCH_3$	**6a**	6.29	8.20	**14**	7.00	8.19
CF_3	$CONHN=C(CF_3)CH_2COCH_3$	**6b**	6.37	8.31			
F	$CONIHN=C(CH_3)C_4H_9$	**7a**	6.90	8.01			
CF_3	$CONHN=C(CH_3)C_4H_9$	**7b**	6.84	7.98			
F	$CONHNHCSNHCH_3$	**8**	6.76[b] 7.49[c]	7.86	**15**	7.56	7.83

[a]Insoluble in $(CD_3)_2SO$.
[b]Signal due to the 4-oxo form.
[c]Signal due to the 4-hydroxy form.

and the corresponding 4-methoxyquinoline **15** (δ 7.56) in deuteriodimethyl sulfoxide, respectively. The 3-H protion signals of the 4-hydroxy tautomer **8**-(**B**-D)$^+$ (δ 7.86) and the corresponding 4-methoxyquinoline **15**-D$^+$ (δ 7.83) in deuteriotrifluoroacetic acid were observed in similar magnetic fields. Furthermore, such a tautomerism was observed in a deuteriodimethyl sulfoxide solution of the 4-quinolone **10a**, which showed two kinds of 3-H proton signals at δ 6.69 (4-oxo tautomer **A**, major) [(**4**-**7**)-**A**: δ 6.29 – 6.90] and 7.48 (4-hydroxy tautomer **B**, minor) (**12**-**15**: δ 7.00 – 7.56) in the ratio of approximately 68% to 32% [19], respectively, together with paired NH proton signals [δ 11.03 (major)/10.74 (minor), 9.17 (major)/9.05 (minor)] (Tables 1 and 2, Scheme 4). The 3-H proton signal of the 4-hydroxy tautomer **10a**-(**B**-D)$^+$ in deuteriotrifluoroacetic acid was observed at δ 7.76 (Table 2), whose value was included in that of the 4-hydroxy tautomers (**4**-**8**)-(**B**-D)$^+$ (δ 7.64–8.31) and the 4-methoxyquinolines (**12**-**15**)-D$^+$ (δ 7.60–8.19) in deuteriotrifluoroacetic acid (Tables 1 and 2).

On the other hand, the semicarbazide derivative **9** and the 4-quinolones **10b,11a,b** were predominant as the 4-oxo tautomer **A** in deuteriodimethyl sulfoxide.

The ^{13}C-NMR spectral data [20] also supported the presence of the tautomers shown in Chart 3, as described below. Tables 3 and 4 exhibit that the respective carbon chemical shifts in deuteriotrifluoroacetic acid are similar values between compounds **4a** and **12**, compounds **5a** and **13**, and compounds **6a** and **14**. These data indicate that the 4-quinolones **4a**, **5a**, **6a,** and 4-methoxyquinolines **12**, **13**, **14** would exist as the species (**4a**, **5a**, **6a**)-(**B**-D)$^+$ and (**12**, **13**, **14**)-D$^+$ in deuteriotrifluoroacetic acid, respectively. In addition, the N1-deuteronation of compounds **4a**, **5a**, **6a** and **12**, **13**, **14** was supported in comparison of the α-, β-, and γ-carbon chemical shifts measured in deuteriodimethyl sulfoxide with those measured in deuteriotrifluoroacetic acid. Namely, after the N1-deuteronation of compounds **12**, **13**, and **14** in deuteriotrifluoroacetic acid, the α-carbons (2-C, 8a-C) and one of β-carbons (8-C) were shielded eminently (6.6–11.9 ppm), and the γ-carbons (4-C, 7-C)

Table 2

Chemical shifts (δ) of 3-H for compounds **9–11**.

Substituent			δ in $(CD_3)_2SO$		δ in CF_3COOD
C_6	C_2	Compound	4-Oxo form **A**	4-Hydroxy form **B**	4-Hydroxy form (**B**-D)$^+$
CF_3	$CONHNHCONHC_6H_5$	**9**	6.88	–	–
F	$CONHR^1$	**10a**	6.69	7.48	7.76
CF_3	$CONHR^1$	**10b**	6.81	–	–
F	$CONHR^2$	**11a**	6.87	–	–
CF_3	$CONHR^2$	**11b**	6.99	–	–

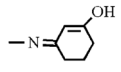
R^1 =  R^2 = 

Table 3

^{13}C-NMR spectral data for 4-quinolones **4a, 5a, 6a** measured in deuteriodimethyl sulfoxide and deuteriotrifluoroacetic acid.[a]

Carbon	**4a** $(CD_3)_2SO$	**4a**-D^+ CF_3COOD	**5a** $(CD_3)_2SO$	**5a**-D^+ CF_3COOD	**6a** $(CD_3)_2SO$	**6a**-D^+ CF_3COOD
2-C	144.0	140.5	142.8	139.6	143.6	143.1
3-C	109.1	105.8	105.8	103.5	108.2	108.3
4-C	176.5	171.3	175.7	171.4	176.0	170.4
4a-C	127.1	123.0	126.9	122.9	124.5	122.6
5-C	108.6	108.1	108.9	108.0	108.8	108.0
6-C	158.9	162.8	161.2	160.2	158.7	162.8
7-C	121.7	127.8	121.8	127.9	121.3	127.6
8-C	122.6	123.3	124.3	123.4	121.8	123.3
8a-C	137.3	136.5	138.5	136.5	136.5	135.9
2-COR	162.6	160.7	158.2	164.0	160.6	157.2
2-$COOCH_3$	55.5	55.0	–	–	–	–
Hydrazone C	–	–	–	–	91.5	94.0
Hydrazone CF_3	–	–	–	–	122.8	123.2
Hydrazone CH_2COCH_3	–	–	–	–	47.6	45.7
Hydrazone CH_2COCH_3	–	–	–	–	156.7	163.4
Hydrazone CH_2COCH_3	–	–	–	–	15.3	14.2

[a]Carbon chemical shifts were assigned by HMQC and HMBC spectral data.

were deshielded remarkably (6.0–9.9 ppm) (Table 5) [21,22]. The other β-carbon (3-C) of compounds **12**, **13**, and **14** was not shielded significantly (1.0–3.9 ppm) (Table 4) [21,22].

Concerning the tautomerism due to the prototropy in the C2-side chain moiety of our quinolones and quinolines, no obvious data were obtained to estimate the ratios (%) of some tautomeric pairs (Chart 4), since there was no diagnostic C–H signal pair such as the C3-H proton of the quinoline ring. Therefore, we refrained from the analysis of the tautomerism attributable for the prototropy in the C2-side chain moiety, which would include the oxo-hydroxy forms of the carbohydrazide moiety (Chart 4), thioxo-thiol forms of the thiosemicarbazide moiety (Chart 4), and oxo-enol forms of the cyclohexenol moiety. For example, it is hard to specify the tautomeric structures showing the paired N1-H (δ 12.28, 11.00) and CONH (δ 10.30, 9.51) proton signals of compound **5a** in deuteriodimethyl sulfoxide [23,24]. As the general characteristics ordinary observed, the vinylic proton signal in the cyclohexenol moiety of compound **10a** and the active methylene proton signals in the C2-side chain of compound **14** disappeared because of the D-H exchange in deuteriotrifluoroacetic acid.

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The IR spectra

Table 4

^{13}C-NMR spectral data for 4-methoxyquinolines **12–14** measured in deuteriodimethyl sulfoxide and deuteriotrifluoroacetic acid.[a]

Carbon	**12** $(CD_3)_2SO$	**12**-D^+ CF_3COOD	**13** $(CD_3)_2SO$	**13**-D^+ CF_3COOD	**14** $(CD_3)_2SO$	**14**-D^+ CF_3COOD
2-C	148.0	141.4	151.4	141.8	155.9	144.0
3-C	100.2	101.2	98.6	100.3	99.5	103.4
4-C	161.8	172.0	162.6	172.5	161.7	171.0
4a-C	121.8	123.9	122.1	124.1	121.3	123.3
5-C	104.8	107.9	105.5	108.4	105.4	107.7
6-C	160.2	163.2	160.3	159.2	160.1	163.1
7-C	120.4	127.5	120.8	128.2	121.1	127.1
8-C	132.3	123.6	132.2	124.3	131.9	123.4
8a-C	144.4	135.6	144.4	136.3	144.6	134.7
2-COR	164.8	160.3	162.8	165.0	165.4	156.5
2-$COOCH_3$	52.2	55.1	–	–	–	–
4-OCH_3	56.0	58.5	56.6	58.2	56.7	58.2
Hydrazone C	–	–	–	–	91.0	94.0
Hydrazone CF_3	–	–	–	–	123.1	122.3
Hydrazone CH_2COCH_3	–	–	–	–	47.9	45.1
Hydrazone CH_2COCH_3	–	–	–	–	155.2	163.5
Hydrazone CH_2COCH_3	–	–	–	–	15.3	14.1

[a]Carbon chemical shifts were assigned by HMQC and HMBC spectral data.

Table 5

Selected ^{13}C-NMR spectral data for 4-methoxyquinolines **12–14** measured in deuteriodimethyl sulfoxide and deuteriotrifluoroacetic acid.

Carbon	**12** $(CD_3)_2SO$	**12**-D^+ CF_3COOD	Difference in δ	**13** $(CD_3)_2SO$	**13**-D^+ CF_3COOD	Difference in 6	**14** $(CD_3)_2SO$	**14**-D^+ CF_3COOD	Difference in δ
2-C	148.0	141.4	6.6 (S)[a]	151.4	141.8	9.6 (S)	155.9	144.0	11.9 (S)
4-C	161.8	172.0	8.2 (D)[a]	162.6	172.5	9.9 (D)	161.7	171.0	9.3 (D)
7-C	120.4	127.5	7.1 (D)	120.8	128.2	7.4 (D)	121.1	127.1	6.0 (D)
8-C	132.3	123.6	8.7 (S)	132.2	124.3	7.9 (S)	131.9	123.4	8.5 (S)
8a-C	144.4	135.6	8.8 (S)	144.4	136.3	8.1 (S)	144.6	134.7	9.9 (S)

[a](S) and (D) mean shielding and deshielding, respectively, after deuteronation in deuteriotrifluoroacetic acid.

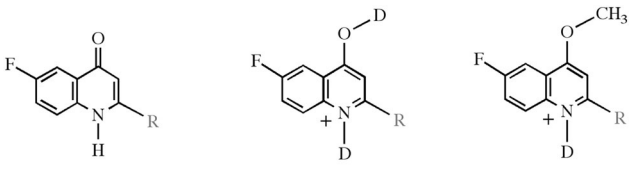


Chart 3

(potassium bromide) were recorded with a JASCO FT/IR-200 spectrometer. The NMR spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The mass spectra (ms) (DIEI) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

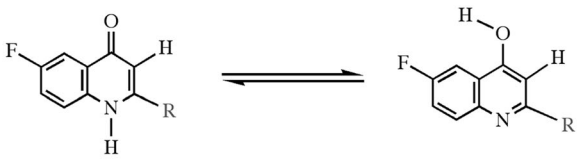
Methyl 6-Fluoro-1,4-dihydro-4-oxoquinoline-2-carboxylate 4a and Methyl 1,4-Dihydro-4-oxo-6-trifluoromethylquinoline-2-carboxylate 4b. ***General procedure.*** A suspension of the appropriate aniline derivatives (10.0 g) and dimethyl acetylenedicarboxylate (1.5-fold molar amount) in ethanol (100 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* gave an oily residue, which was dissolved in diphenyl ether (40 mL). The diphenyl ether solution was refluxed for 1 h to precipitate colorless needles **4a,b**, which were triturated with ethanol/hexane and collected by filtration. The crystals were washed with ethanol several times to provide analytically pure samples **4a** (8.32 g, 42%) and **4b** (9.42 g, 56%).

Compound **4a** had mp 250–251°; IR: ν 3100, 2960, 2920, 1740, 1610 cm^{-1}; ms: m/z 222 (M^+); NMR (deuteriodimethyl sulfoxide): 12.23 (s, 1H, NH), 7.98 (dd, J = 9.0, 4.5 Hz, 1H, 8-H), 7.68 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.61 (ddd, J = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 6.59 (s, 1H, 3-H), 3.93 (s, 3H, CH_3). Anal. Calcd. for $C_{11}H_8FNO_3$: C, 59.73; H, 3.65; N, 6.33. Found: C, 59.65; H, 3.80; N, 6.44.

Compound **4b** had mp 293–294°; IR: ν 3250, 3220, 3170, 1740, 1610 cm^{-1}; ms: m/z 272 (M^+); NMR (deuteriodimethyl sulfoxide): 12.40 (s, 1H, NH), 8.28 (d, J = 2.0 Hz, 1H, 5-H), 8.08 (d, J = 9.0 Hz, 1H, 8-H), 7.98 (dd, J = 9.0, 2.0 Hz, 1H, 7-H), 6.70 (s, 1H, 3-H), 3.95 (s, 3H, CH_3). Anal. Calcd. for $C_{12}H_8F_3NO_3$: C, 53.15; H, 2.97; N, 5.16. Found: C, 53.08; H, 3.06; N, 5.33.

6-Fluoro-1,4-dihydro-4-oxoquinoline-2-carbohydrazide 5a and 1,4-Dihydro-4-oxo-6-trifluoromethylquinoline-2-carbohydrazide 5b. ***General procedure.*** A suspension of the appropriate 4-quinolone-2-carboxylates **4a,b** (5.0 g) and hydrazine hydrate (5-fold molar amount) in ethanol (100 mL) was refluxed for 5 h to precipitate colorless needles **5a,b**, which were collected by filtration and washed with ethanol to give analytically pure samples **5a** (4.80 g, 96%) and **5b** (4.50 g, 90%).

Scheme 4



Compound	Chemical Shift for 3-H Proton (δ)		Ratio (%)	
	4-Oxo Form **A**	4-Hydroxy Form **B**	4-Oxo Form **A**	4-Hydroxy Form **B**
8	6.76	7.49	81	19
10a	6.69	7.48	68	32

8 : R = $CONHNHCSNHCH_3$; **10a** : R = CONHN= 

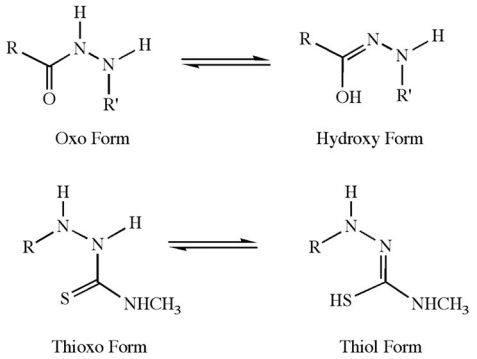


Chart 4

Compound **5a** had mp above 300°; IR: ν 3375, 3160, 1695 cm^{-1}; ms: m/z 221 (M^+); NMR (deuteriodimethyl sulfoxide): 12.28 (br), 11.00 (br) (1H, NH) [23], 10.30 (br), 9.51 (br) (1H, CONH) [23], 8.01 (dd, J = 9.0, 5.0 Hz, 1H, 8-H), 7.68 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.60 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H, 7-H), 6.72 (s, 1H, 3-H), 4.73 (br, 2H, NH_2). Anal. Calcd. for $C_{10}H_8FN_3O_2$: C, 54.30; H, 3.65; N, 19.00. Found: C, 54.13; H, 3.71; N, 19.01.

Compound **5b** had mp above 300°; IR: ν 3320, 3260, 3200, 3030, 1690, 1640 cm^{-1}; ms: m/z 271 (M^+); NMR (deuteriotrifluoroacetic acid): 8.49 (d, J = 2.0 Hz, 1H, 5-H), 8.04 (d, J = 9.0 Hz, 1H, 8-H), 7.96 (dd, J = 9.0, 2.0 Hz, 1H, 7-H), 7.67 (s, 1H, 3-H); NH and OH proton signals disappeared because of D-H exchange. Anal. Calcd. for $C_{11}H_8F_3N_3O_2$: C, 48.72; H, 2.97; N, 15.44. Found: C, 48.67; H, 3.00; N, 15.24.

6-Fluoro-1,4-dihydro-4-oxo-*N′*-(3-oxo-1-trifluoromethylbutylidene)quinoline-2-carbohydrazide 6a and 1,4-dihydro-4-oxo-*N′*-(3-oxo-1-trifluoromethylbutylidene)-6-trifluoromethylquinoline-2-carbohydrazide 6b. ***General procedure.*** A solution of the appropriate 4-quinolone-2-carbohydrazides **5a,b** (0.50 g) and 1,1,1-trifluoropentane-2,4-dione (1.5-fold molar amount) in *N,N*-dimethylformamide (20 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* gave an oily substance, which was crystallized from ethanol/water to afford yellow needles **6a** (540 mg, 76%) and **6b** (480 mg, 64%).

Compound **6a** had mp 214-215°; IR: ν 3220, 1675 cm^{-1}; ms: m/z 357 (M^+); NMR (deuteriodimethyl sulfoxide): 12.32 (br, 1H, NH), 8.34 (br, 1H, CONH), 7.82 (dd, J = 9.0, 4.0 Hz, 1H, 8-H), 7.72 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.62 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H, 7-H), 6.29 (br, 1H, 3-H), 3.54 (d, J = 19.5 Hz, 1H, CH), 3.17 (d, J = 19.5 Hz, 1H, CH), 1.97 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{11}F_4N_3O_3$: C, 50.43; H, 3.10; N, 11.76. Found: C, 50.55; H, 3.23; N, 11.59.

Compound **6b** had mp 228–229°; IR: ν 3430, 3260, 3230, 3175, 1670, 1640, 1600 cm^{-1}; ms: m/z 407 (M^+); NMR (deuteriodimethyl sulfoxide): 12.51 (s, 1H, NH), 8.38 (s, 1H, CONH), 8.33 (d, J = 2.0 Hz, 1H, 5-H), 7.98 (dd, J = 9.0, 2.0 Hz, 1H, 7-H), 7.92 (d, J = 9.0 Hz, 1H, 8-H), 6.37 (s, 1H, 3-H), 3.56 (d, J = 19.5 Hz, 1H, CH), 3.18 (d, J = 19.5 Hz, 1H, CH), 1.98 (s, 3H, CH_3). Anal. Calcd. for $C_{16}H_{11}F_6N_3O_3$: C, 47.19; H, 2.73; N, 10.32. Found: C, 47.02; H, 2.78; N, 10.12.

6-Fluoro-1,4-dihydro-*N′*-(1-methylpentylidene)-4-oxoquinoline-2-carbohydrazide 7a and 1,4-dihydro-*N′*-(1-methylpentylidene)-4-oxo-6-trifluoromethylquinoline-2-carbohydrazide 7b. ***General procedure.*** A solution of the appropriate 4-quinolone-2-carbohydrazides **5a,b** (0.50 g) and 2-hexanone (1.5-fold molar amount) in *N,N*-dimethylformamide (20 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* gave crystals **7a,b**, which were collected by filtration. Recrystallization from *N,N*-dimethylformamide/ethanol provided colorless needles **7a** (580 mg, 85%) and **7b** (460 mg, 71%).

Compound **7a** had mp 272–273°; IR: ν 3310, 3250, 1670, 1610 cm^{-1}; ms: m/z 303 (M^+); NMR (deuteriodimethyl sulfoxide): 12.10 (br, 1H, NH), 10.92 (s, 1H, CONH), 8.01 (dd, J = 9.0, 4.5 Hz, 1H, 8-H), 7.74 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.64 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H, 7-H), 6.90 (br, 1H, 3-H), 2.31 (t, J = 7.5 Hz, 2H, CH_2), 1.97 (s, 3H, CH_3), 1.51 (tt, J = 7.5, 7.5 Hz, 2H, CH_2), 1.31 (tq, J = 7.5, 7.5 Hz, 2H, CH_2), 0.89 (t, J = 7.5 Hz, 3H, CH_3). Anal. Calcd. for $C_{16}H_{18}FN_3O_2$: C, 63.35; H, 5.98; N, 13.85. Found: C, 63.09; H, 5.92; N, 13.75.

Compound **7b** had mp 293–294°; IR: ν 3310, 3250, 1670, 1640, 1605 cm^{-1}; ms: m/z 353 (M^+); NMR (deuteriodimethyl sulfoxide): 12.29 (br, 1H, NH), 10.99 (s, 1H, CONH), 8.34 (d, J = 2.0 Hz, 1H, 5-H), 8.09 (d, J = 9.5 Hz, 1H, 8-H), 7.99 (dd, J = 9.5, 2.0 Hz, 1H, 7-H), 6.84 (br, 1H, 3-H), 2.32 (t, J = 7.0 Hz, 2H, CH_2), 1.96 (s, 3H, CH_3), 1.51 (tt, J = 7.0, 7.0 Hz, 2H, CH_2), 1.31 (tq, J = 7.0, 7.0 Hz, 2H, CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{17}H_{18}F_3N_3O_2$: C, 57.79; H, 5.13; N, 11.89. Found: C, 57.58; H, 5.12; N, 11.96.

6-Fluoro-1,4-dihydro-(*N′*-methylthiocarbamoyl)-4-oxoquinoline-2-carbohydrazide 8. A solution of compound **5a** (0.50 g, 2.26 mmoles) and methyl isothiocyanate (215 mg, 2.94 mmoles) in *N,N*-dimethylformamide (20 mL) was refluxed for 1 h. Evaporation of the solvent *in vacuo* gave colorless crystals **8**, which were recrystallized from *N,N*-dimethylformamide/ethanol to afford colorless powders **8** (220 mg, 33%); mp 245–246°; IR: ν 3260, 3180, 1690, 1610 cm^{-1}; ms: m/z 294 (M^+); NMR (deuteriodimethyl sulfoxide): 12.07 (s, 1H, NH), 10.88 (s), 10.57 (s) (1H, NH), 9.51 (s), 9.37 (s) (1H, NH), 8.22 (q), 7.79 (q) (J = 4.0 Hz, 1H, NH), 8.02 (dd, J = 9.0, 4.5 Hz, 1H, 8-H), 7.70 (dd, J = 9.0, 2.5 Hz, 1H, 5-H), 7.62 (ddd, J = 9.0, 9.0, 2.5 Hz, 1H, 7-H), 7.49 (s), 6.76 (s) (1H, 3-H) [18], 2.86 (d, J = 4.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{12}H_{11}FN_4O_2S•1/2H_2O$: C, 47.52; H, 3.99; N, 18.47. Found: C, 47.37; H, 3.97; N, 18.34.

1,4-Dihydro-4-oxo-(*N′*-phenylcarbamoyl)-6-trifluoromethylquinoline-2-carbohydrazide 9. A solution of compound **5b** (0.50 g, 1.85 mmole) and phenyl isocyanate (286 mg, 2.41 mmoles) in *N,N*-dimethylformamide (20 mL) was refluxed for 1 hour. Evaporation of the solvent *in vacuo* gave colorless crystals **9**, which were recrystallized from *N,N*-dimethylformamide/ethanol/hexane to provide colorless powders **9** (150 mg, 20%); mp above 300°; IR: ν 3260, 1690, 1620, 1605 cm^{-1}; ms: m/z 390 (M^+); NMR (deuteriodimethyl sulfoxide): 12.28 (br, 1H, NH), 10.85 (s, 1H, CONH), 8.95 (s, 1H, NH), 8.44 (s, 1H, NH), 8.33 (d, J = 2.0 Hz, 1H, 5-H), 8.13 (d, J = 9.0 Hz, 1H, 8-H), 8.00 (dd, J = 9.0, 2.0 Hz, 1H, 7-H), 7.46 (dd, J = 8.0, 1.0 Hz, 2H, phenyl 2-H, 6-H), 7.25 (dd, J = 8.0, 8.0 Hz, 2H, phenyl 3-H, 5-H), 6.96 (tt, J = 8.0, 1.0 Hz, 1H, phenyl 4-H), 6.88 (br, 1H, 3-H). Anal. Calcd. for $C_{18}H_{13}F_3N_4O_3•1/2H_2O$: C, 54.14; H, 3.53; N, 14.27. Found: C, 54.04; H, 3.33; N, 14.26.

6-Fluoro-1,4-dihydro-*N′*-(3-hydroxy-2-cyclohexenylidene)-4-oxoquinoline-2-carbohydrazide 10a and 1,4-dihydro-*N′*-(3-hydroxy-2-cyclohexenylidene)-4-oxo-6-trifluoromethylquinoline-2-carbohydrazide 10b. A solution of compound **5a,b** (0.50 g) and cyclohexane-1,3-dione (1.5-fold molar amount) in *N,N*-dimethylformamide (20 mL) was refluxed for 1 h. Evaporation

of the solvent *in vacuo* gave an oily product **10a,b**, which was crystallized from ethanol/water to afford yellow powders **10a** (550 mg, 77%) and **10b** (500 mg, 70%), respectively.

Compound **10a** had mp: 234–235°; IR: ν 3300, 3250, 1685, 1610 cm^{-1}; ms: m/z 315 (M^+); NMR (deuteriodimethyl sulfoxide): 12.13 (s, 1H, NH), 11.03 (s), 10.74 (s) (1H, CONH) [19], 9.17 (s), 9.05 (s) (1H, OH), 8.00 (dd, J = 8.0, 5.0 Hz, 1H, 8-H), 7.70 (dd, J = 8.0 Hz, 1H, 5-H), 7.62 (dd, J = 8.0, 8.0 Hz, 1H, 7-H), 7.48 (s), 6.69 (s) (1H, 3-H), 4.97 (s, 1H, cyclohexene 2-H), 2.40 (t, J = 6.0 Hz, 2H, CH_2), 2.13 (t, J = 6.0 Hz, 2H, CH_2), 1.86 (tt, J = 6.0, 6.0 Hz, 2H, CH_2). Anal. Calcd. for $C_{16}H_{14}FN_3O_3 \bullet H_2O$: C, 57.65; H, 4.84; N, 12.61. Found: C, 57.78; H, 4.71; N, 12.57.

Compound **10b** had mp 292-293°; IR: ν 3440, 3200, 1680, 1640, 1600 cm^{-1}; ms: m/z 365 (M^+); NMR (deuteriodimethyl sulfoxide): 12.28 (br, 1H, NH), 11.08 (br 1H, CONH), 9.18 (s, 1H, OH), 8.33 (d, J = 2.0 Hz, 1H, 5-H), 8.11 (d, J = 9.0 Hz, 1H, 8-H), 8.00 (dd, J = 9.0, 2.0 Hz, 1H, 7-H), 6.81 (br, 1H, 3-H), 4.99 (s, 1H, cyclohexene 2-H), 2.41 (t, J = 6.0 Hz, 2H, CH_2), 2.14 (t, J = 6.0 Hz, $2HCH_2$), 1.86 (tt, J = 6.0, 6.0 Hz, 2H, CH_2). Anal. Calcd. for $C_{17}H_{14}F_3N_3O_3 \bullet 1/2H_2O$: C, 54.55; H, 4.04; N, 11.23. Found: C, 54.49; H, 3.76; N, 11.51.

6-Fluoro-1,4-dihydro-*N′*-(2,5-dimethylpyrrol-1-yl)-4-oxoquinoline-2-carbohydrazide 11a and 1,4-Dihydro-*N′*-(2,5-dimethylpyrrol-1-yl)-4-oxo-6-trifluoromethylquinoline-2-carbohydrazide 11b. A solution of compound **5a,b** (0.50 g) and hexane-2,5-dione (1.5-fold molar amount) in *N,N*-dimethylformamide (20 mL) was refluxed for 1 h. Evaporation of the solvent *in vacuo* gave crystals **11a,b**, which were recrystallized from *N,N*-dimethylformamide/ethanol/water to afford yellow needles **11a** (620 mg, 84%) and **11b** (610 mg, 95%), respectively.

Compound **11a** had mp: 280–281° (decompose); IR: ν 3250, 3210, 3000, 1690, 1610 cm^{-1}; ms: m/z 299 (M^+); NMR (deuteriodimethyl sulfoxide): 12.24 (br, 1H, NH), 11.76 (s, 1H, CONH), 8.04 (dd, J = 8.5, 4.5 Hz, 1H, 8-H), 7.76 (dd, J = 8.0 Hz, 1H, 5-H), 7.67 (dd, J = 8.5, 8.0 Hz, 1H, 7-H), 6.87 (br, 1H, 3-H), 5.72 (s, 2H, pyrrole 3-H, 4-H), 2.04 (s, 6H, pyrrole 2-CH_3, 5-CH_3). Anal. Calcd. for $C_{16}H_{14}FN_3O_2$: C, 64.21; H, 4.71; N, 14.04. Found: C, 64.27; H, 4.82; N, 13.96.

Compound **11b** had mp 292–293° (decompose); IR: ν 3250, 1690, 1640, 1610 cm^{-1}; ms: m/z 349 (M^+); NMR (deuteriodimethyl sulfoxide): 12.40 (br, 1H, NH), 11.85 (s 1H, CONH), 8.36 (d, J = 2.0 Hz, 1H, 5-H), 8.13 (d, J = 8.0 Hz, 1H, 8-H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H, 7-H), 6.99 (br, 1H, 3-H), 5.73 (s, 2H, pyrrole 3-H, 4-H), 2.05 (s, 6H, pyrrole 2-CH_3, 5-CH_3). Anal. Calcd. for $C_{17}H_{14}F_3N_3O_2 \bullet 1/2H_2O$: C, 56.98; H, 4.22; N, 11.73. Found: C, 57.16; H, 4.27; N, 11.56.

Methyl 6-Fluoro-4-methoxyquinoline-2-carboxylate 12. A mixture of compound **4a** (5.0 g, 22.6 mmoles), methyl iodide (5mL) and potassium carbonate (5 g) in *N,N*-dimethylformamide (100 mL) was heated at 120–140° for 3 h. After cooling to room temperature, the solution was filtrated, and the filtrate was evaporated *in vacuo* to give crystals **12**. Recrystallization from ethanol/water provided colorless needles **12** (4.30 g, 81%); mp 134–135°; IR: ν 3050, 3010, 1720, 1600 cm^{-1}; ms: m/z 236 (M^+); NMR (deuteriodimethyl sulfoxide): 8.13 (dd, J = 9.0, 5.5 Hz, 1H, 8-H), 7.75 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.72 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H, 7-H), 7.51 (s, 1H, 3-H), 4.08 (s, 1H, 4-OCH_3), 3.92 (s, 3H, $COOCH_3$). Anal. Calcd. for $C_{12}H_{10}FNO_3$: C, 61.28; H, 4.29; N, 5.95. Found: C, 61.25; H, 4.39; N, 6.04.

6-Fluoro-4-methoxyquinoline-2-carbohydrazide 13. A solution of compound **12** (5.0 g) and hydrazine hydrate (5 mL) in ethanol (150 mL) was refluxed for 2 h to precipitate colorless needles **13**, which were collected by filtration and washed with ethanol to give an analytically pure sample (3.65 g, 73%); mp 215–216°; IR: ν 3310, 3260, 1680, 1620, 1600 cm^{-1}; ms: m/z 235 (M^+); NMR (deuteriodimethyl sulfoxide): 9.95 (s, 1H, CONH), 8.06 (dd, J = 9.0, 5.0 Hz, 1H, 8-H), 7.76 (dd, J = 9.5, 3.0 Hz, 1H, 5-H), 7.72 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H, 7-H), 7.54 (s, 1H, 3-H), 4.65 (br, 2H, NH_2), 4.12 (s, 3H, 4-OCH_3). Anal. Calcd. for $C_{11}H_{10}FN_3O_2$: C, 56.17; H, 4.29; N, 17.86. Found: C, 55.89; H, 4.31; N, 17.80.

6-Fluoro-4-methoxy-*N′*-(3-oxo-1-trifluoromethylbutylidene)-quinoline-2-carbohydrazide 14. A solution of compound **13** (0.50 g, 2.13 mmoles) and 1,1,1-trifluoropentane-2,4-dione (0.49 g, 3.20 mmoles) in *N,N*-dimethylformamide (20 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* afforded an oily substance, which was crystallized from ethanol/water to provide reddish orage needles **14** (420 mg, 53%); mp; 159-160°; IR: ν 3100, 1600 cm^{-1}; ms: m/z 371 (M^+); NMR (deuteriodimethyl sulfoxide): 8.24 (br, 1H, CONH), 8.04 (dd, J = 9.0, 5.5 Hz, 1H, 8-H), 7.78 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.69 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H, 7-H), 7.02 (s, 1H, 3-H), 4.06 (s, 3H, 4-OCH_3), 3.51 (d, J = 19.5 Hz, 1H, CH), 3.13 (d, J = 19.5 Hz, 1H, CH), 1.85 (s, 3H, CH_3). Anal. Calcd. for $C_{16}H_{13}F_4N_3O_3$: C, 51.76; H, 3.53; N, 11.32. Found: C, 51.74; H, 3.56; N, 11.22.

6-Fluoro-4-methoxy-*N′*-(methylthiocarbamoyl)quinoline-2-carbohydrazide 15. A solution of methyl isothiocyanate (2.34 g, 32.0 mmoles) in dioxane (20 mL) was added to a refluxing solution of compound **13** (5.0 g, 21.3 mmoles) in dioxane (80 mL) to precipitate colorless needles **15** while 1-h reflux. The colorless needles were collected by filtration and washed with ethanol to give an analytically pure sample (6.95 g, 99%); mp: 245-246°; IR: ν 3360, 3180, 1700, 1690 cm^{-1}; ms: m/z 294 (M^+); NMR (deuteriodimethyl sulfoxide): 10.70 (br, 1H, CONH), 8.10 (dd, J = 9.0, 5.0 Hz, 1H, 8-H), 8.02 (q, J = 5.0 Hz, 1H, NH), 7.82 (dd, J = 9.5, 3.0 Hz, 1H, 5-H), 7.76 (ddd, J = 9.5, 9.0, 3.0 Hz, 1H, 7-H), 7.56 (s, 1H, 3-H), 4.11 (s, 3H, 4-OCH_3), 2.84 (d, J = 5.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{13}H_{13}FN_4O_2S$: C, 50.64; H, 4.25; N, 18.17. Found: C, 50.51; H, 4.33; N, 18.22.

REFERENCES AND NOTES

[1] Kurasawa, Y.; Tsuruoka, N.; Rikiishi, N.; Fujiwara, N.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2000, 37, 791.

[2] Kurasawa, Y.; Sakurai, K.; Kajiwara, S.; Harada, K.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2000, 37, 1257.

[3] Kurasawa, Y.; Ohshima, S.; Kishimoto, Y.; Ogura, M.; Okamoto, Y.; Kim, H. S. Heterocycles 2001, 54, 359.

[4] Kurasawa, Y.; Matsuzaki, I.; Satoh, W.; Okamoto, Y.; Kim, H. S. Heterocycles 2002, 56, 291.

[5] Kurasawa, Y.; Takizawa, J.; Maesaki, Y.; Kawase, A.; Okamoto, Y.; Kim, H. S. Heterocycles 2002, 58, 359.

[6] Kurasawa, Y.; Satoh, W.; Matsuzaki, I.; Maesaki, Y.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2003, 40, 837.

[7] Kurasawa, Y.; Kawase, A.; Takizawa, J.; Maesaki, Y.; Kaji, E.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2005, 42, 551.

[8] Kurasawa, Y.; Kaji, E.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2005, 42, 249.

[9] Kurasawa, Y.; Kim, H. S. J Heterocycl Chem, 2005, 42, 387.

[10] Kurasawa, Y.; unpublished results. References 7 and 8.

[11] Narita, K.; Izumi, Y.; Nishino, H.; Yoshida, T.; Takahashi, Y.; Nagata, O.; Katoh, H. 121st Conference of the Pharmaceutical Society of Japan, Sapporo, Japan, Abstract-3 No. 29 [PB] I-042 (2001).

[12] Wratten, S. J.; Wolfe, M. S.; Andersen, R. J.; Faulkner, D. J. Antimicrob Agents Chemother 1977, 11, 411.

[13] Back, T. G.; Parvez, M.; Wulff, J. E. J Org Chem 2003, 68, 2223.

[14] Back T. G.; Wulff, J. E. J Chem Soc Chem Commun 2002, 1710.

[15] Wentrup, C.; Rao, V. V. R.; Frank, W.; Fulloon, B. E.; Moloney, D. W. J.; Mosandl, T. J Org Chem 1999, 64, 3608.

[16] Erickson, E. H.; Lappi, L. R.; Rice, T. K.; Swingle, K. F.; Winkle, M. V. J Med Chem 1978, 21, 984; the yields are not so high (2 ~ 50%), and this paper includes no nmr spectral data.

[17] In our experiment, the yields of compounds **4a** and **4b** were 42% and 47%, respectively.

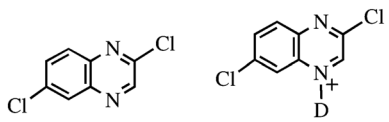
[18] Estimated from the integral curves of the 3-H proton signals at δ 6.76 and 7.49.

[19] Estimated from the integral curves of the paired NH proton signals at δ 11.03 and 10.74.

[20] All carbon chemical shifts were assigned by the HMQC and HMBC spectral data.

[21] Kim, H. S.; Okamoto, Y.; Kurasawa, Y. J Heterocycl Chem 1997, 34, 1029.

[22] The shielding and deshielding data between 4-methoxyquinolines **12**-**14** and [(**12**–**14**)-D]$^+$ were similar to those between 2,6-dichloroquinoxaline and N^4-deuterio-2,6-dichloroquinoxalinium ion reported in our previous paper [21].



[23] Paired NH proton signals were observed in deuteriodimethyl sulfoxide at δ 12.28 (br, minor)/11.00 (br, major) and 10.30 (br, major)/ 9.51 (br, minor).

[24] There have hardly been literatures dealing with the specification and estimation of the oxo-hydroxy and thioxo-thiol tautomers in open chain carbohydrazides and thiosemicarbazides, respectively.