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SYNTHESIS, BIOLOGICAL ACTIVITIES, AND TAUTOMERISM OF 4-QUINOLONES AND RELATED COMPOUNDS

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Abstract – This review describes the synthesis, biological activities, and tautomerism of various 4-quinolones together with related compounds including 4-oxopyridazino[3,4-*b*]quinoxalines (bioisostere of 4-quinolones).

CONTENTS

1. INTRODUCTION

We have reported the reaction of quinoxaline 1-oxides (Figure 1) providing various condensed quinoxalines,[1] which include isoxazolo[2,3-*a*]quinoxalines,[2-6] pyrrolo[1,2-*a*]quinoxalines,[2-6] pyridazino-

[3,4-*b*]quinoxalines,[7-9] pyrazolo[3,4-*b*]quinoxalines,[10] 1,2-diazepino[3,4-*b*]quinoxalines,[11,12] 1,5,6-benzoxadiazocino[3,4-*b*]quinoxalines,[13] 1,2,4-triazolo[4,3,2-*o*,*p*][1,3]diazocino[4,5-*b*]quinoxalines,[14] 1,3,4-thiadiazino[3,4-*b*]quinoxalines,[15-18] and 1,3,4-oxadiazino[3,4-*b*]quinoxalines.[17,19] In continuation of the above works, we found the conversion of some pyridazino[3,4-*b*]quinoxalines into the 4-oxopyridazino-[3,4-*b*]quinoxaline-3-carboxylic acids (**1**)[20] (Scheme 1), which would be regarded as bioisostere of antibacterial 4-quinolones as well as cinoxacin[21-23] and pyrido[2,3-*b*]quinoxaline-3-carboxylic acids[24] (Scheme 1). Namely, the structure hybridization of nalidixic acid,[25,26] cinoxacin, and pyrido[2,3-*b*]-quinoxaline-3-carboxylic acids led to the synthesis of compounds **1**. However, compounds **1** did not exhibit excellent antibacterial activity so that C3-modified compounds (**2**-**15**) (Scheme 2) were elaborated to search for more biologically active compounds.

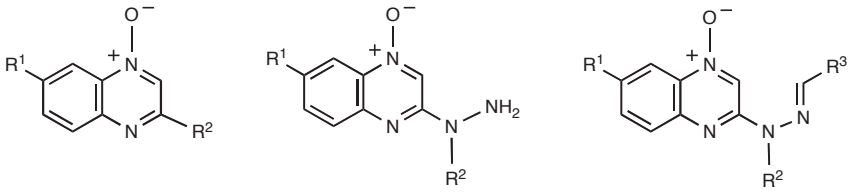
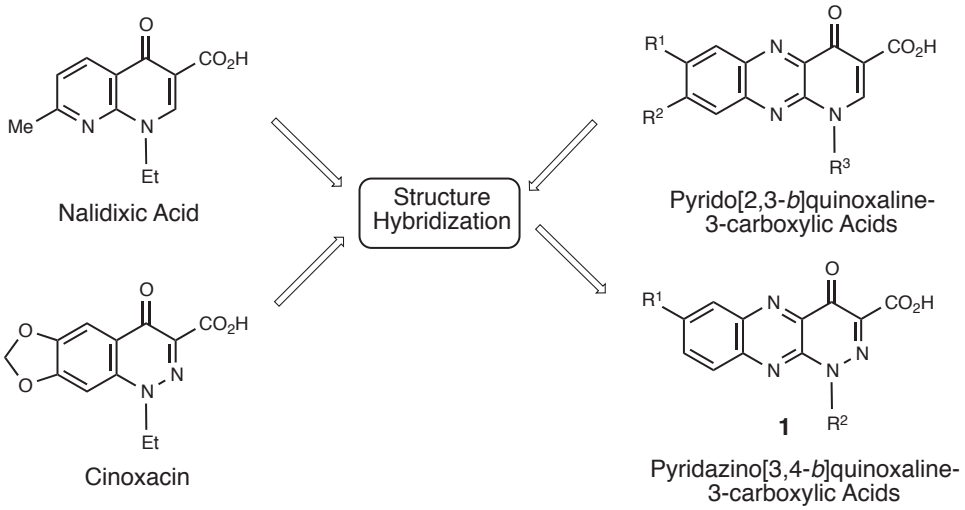


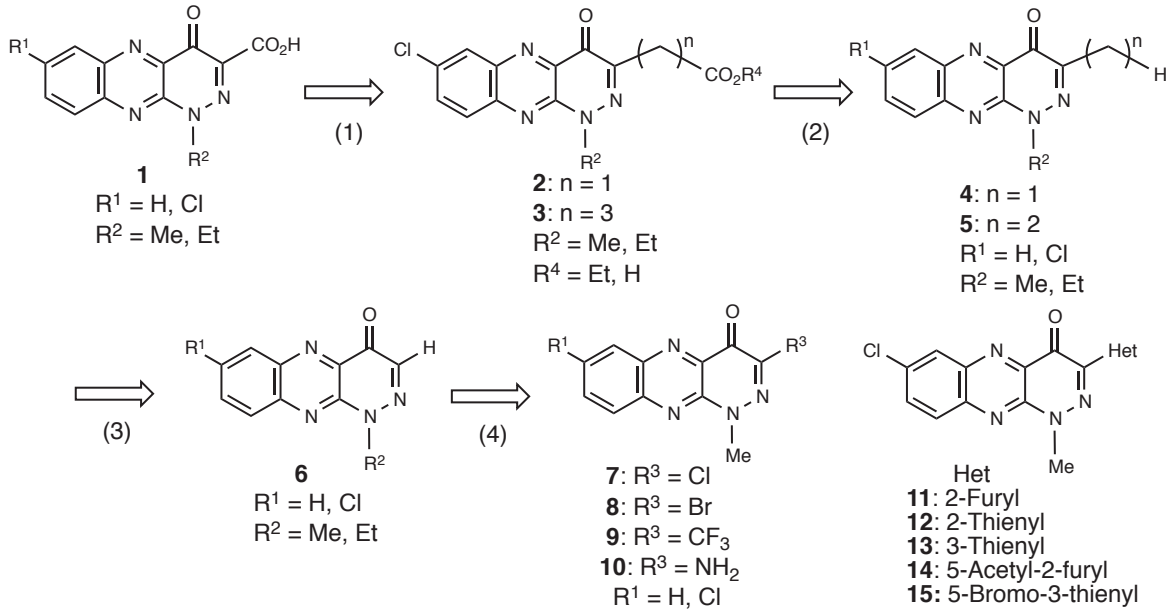
Figure 1. Quinoxaline 1-Oxides



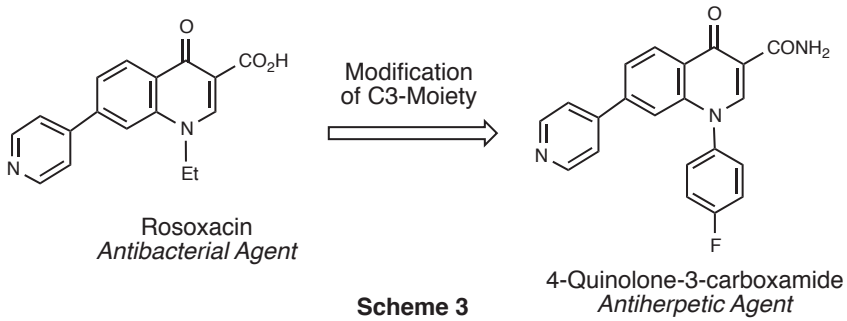
Scheme 1. Structure Hybridization Leading to Pyridazino[3,4-*b*]quinoxaline-3-carboxylic Acids **1**

On the other hand, the modification of the C3-carboxyl into C3-carboxamide group in antibacterial rosoxacin has been known to provide the antiherpetic 4-quinolone-3-carboxamide (Scheme 3).[27] Consequently, we synthesized 2- or 3-substituted 4-quinolones aiming at some biological activities such as antimicrobial and/or antimalarial activities (Figure 2). Furthermore, when the N1 of the 4-quinolones has no substituent such as the alkyl or aryl group, there would be the tautomeric equilibria between the 4-oxo and 4-hydroxy forms for 4-quinolones. In such cases, the tautomer assignment of the 4-quinolones is an important matter for the chemists or biologists dealing with sundry quinolone

derivatives. This review describes the synthesis, biological activities, and tautomeric equilibria of the above 4-quinolones and related compounds.



Scheme 2. (1) Insertion of Methylene Group; (2) Exclusion of CO_2R^4; (3) Exclusion of Alkyl Group; (4) Synthesis of Various C3-Derivatives.



Scheme 3

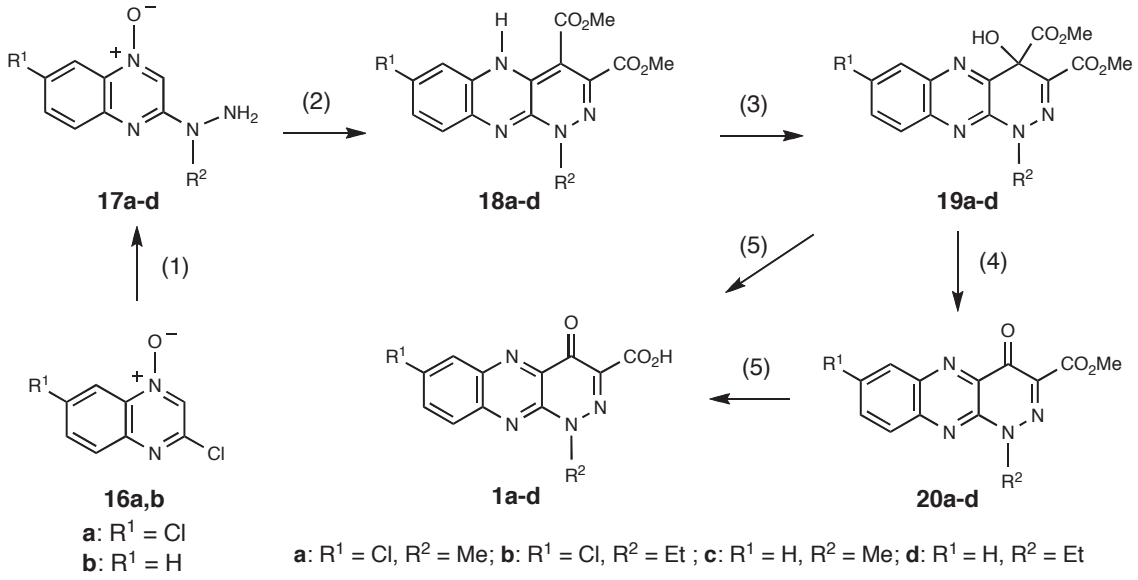
Figure 2

2. SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 3-SUBSTITUTED 4-OXOPYRIDAZINO-[3,4-*b*]QUINOXALINES AS BIOISOSTERE OF 4-QUINOLONES

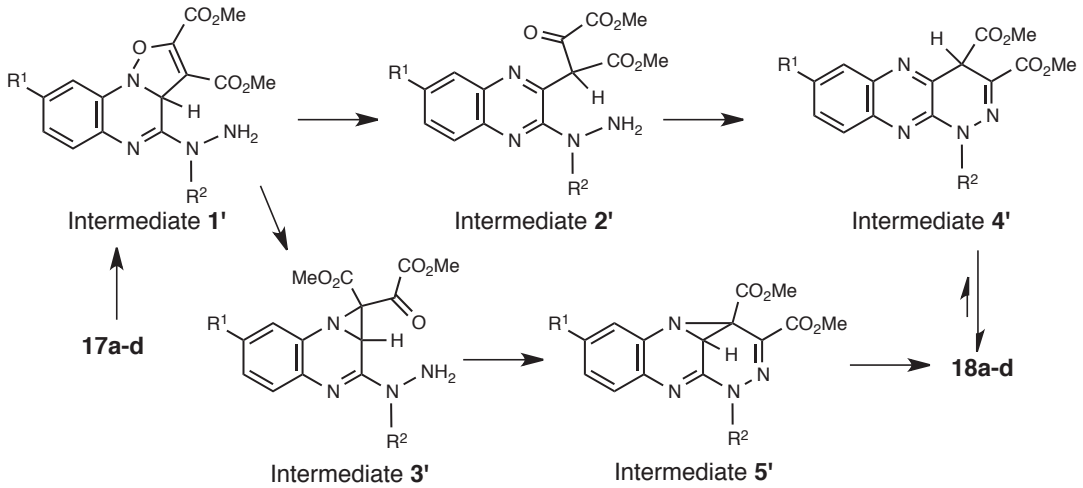
2-1. Synthesis of 1,4-Dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic Acids

The reaction of the 3-chloroquinoxaline 1-oxides (**16a,b**) with alkylhydrazines gave the 3-(1-alkylhydrazino)quinoxaline 1-oxides (**17a-d**), whose 1,3-dipolar cycloaddition reaction with acetylenedicarboxylate afforded the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates (**18a-d**) (Scheme 4) pre-

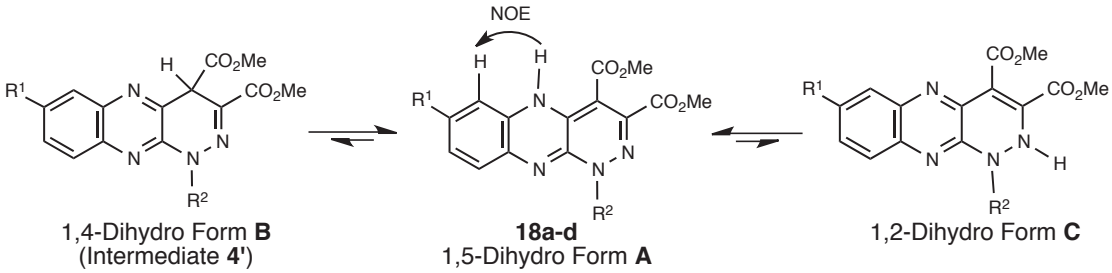
sumably *via* intermediates (**1'-5'**) (Scheme 5).[20] The tautomeric structure of compounds **18a-d** was assigned as the 1,5-dihydro form in solution and solid state (Scheme 6),[28] while dihydropyridazine[29] and dihydrocinnolines[30] have been known to exist as the 1,4-dihydro form (Figure 3). The oxidation of **18a-d** with nitrous acid provided the 4-hydroxy derivatives (**19a-d**), whose reaction with DBU or KOH produced the 4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylates (**20a-d**) or 4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **1a-d**, respectively. The 3-carboxylic acids **1a-d** and 3-carboxylates **20a-d** showed weak antimicrobial activities to bacteria [*Mycobacterium ranae*, *Staphylococcus aureus*, *Staphy-*



Scheme 4. Reagents: (1) Alkylhydrazines in EtOH; (2) Dimethyl Acetylenedicarboxylate in EtOH; (3) HNO_2 in $AcOH/H_2O$; (4) DBU in EtOH; (5) KOH in H_2O/EtOH



Scheme 5



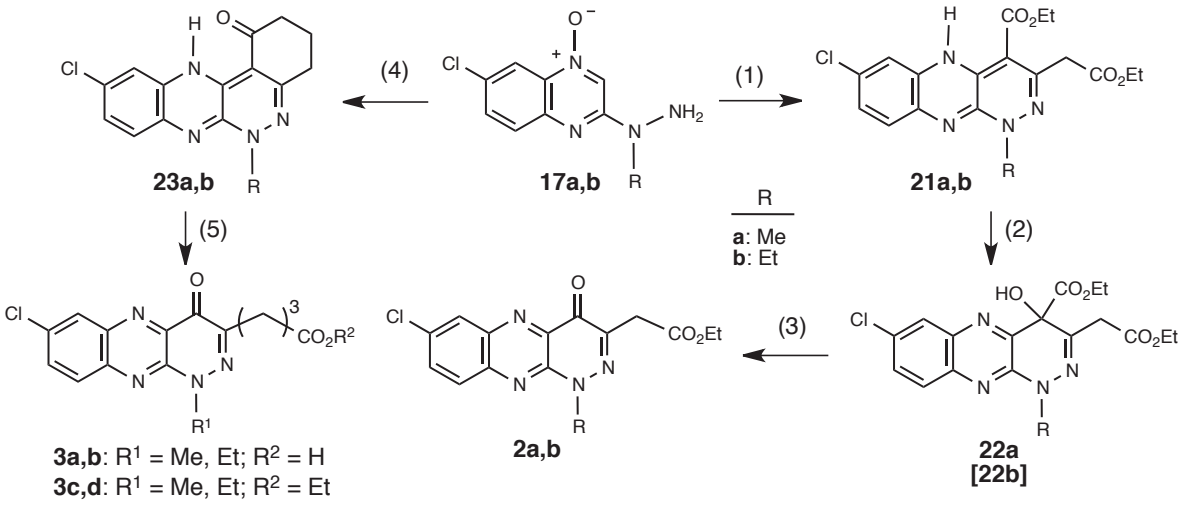
Scheme 6

Figure 3

lococcus epidermis, Klebsiella pneumoniae: minimum inhibitory concentration (MIC) 12.5-25.0 ppm (μg/mL); *Bacillus subtilis*: (MIC) 2.0-15.6 ppm] and fungi [*Candida albicans*: (MIC) 12.5-50.0 ppm].[31] Accordingly, the modification of the C3-substituent was planned for compounds **1**, and the (4-oxo-pyridazino[3,4-*b*]quinoxalin-3-yl)alkylcarboxylates (**2**, **3**) were synthesized in the next section **2-2**.

2-2. Synthesis of (1,4-Dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)acetates and 4-(1,4-Dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)butanoates

The reaction of the quinoxaline 1-oxides **17a,b** with acetone-1,3-dicarboxylate in sulfuric acid/acetic acid gave the (1,5-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)acetates (**21a,b**), whose oxidation with nitrous acid or MCPBA afforded the 1,4-dihydro-4-hydroxy derivatives (**22a,b**), respectively (Scheme 7).[32] The oxidation in this step resulted in good yields [compound **22a** (80%); compound **21b** to compound **2b** (82%)] (compound **22b** was not isolated). Subsequent reaction of compound **22a** with a base provided the (1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)acetate **2a**. In the meantime, the reaction of the quinoxaline 1-oxides **17a,b** with cyclohexane-1,3-dione produced the quinoxalino[2,3-*c*]cinnolines (**23a,b**), whose oxidation with NBS in water/acetic acid furnished the 4-(1,4-dihydro-4-oxo-pyridazino[3,4-*b*]quinoxalin-3-yl)butanoic acids (**3a,b**) (79-90%), respectively. Compounds **3a,b** were converted into the ethyl esters (**3c,d**), respectively. The conversion of the quinoxaline 1-oxides **17a,b** into compounds **21a,b** and **23a,b** would proceed *via* intermediates (**6'** and **7'**), and the oxidation of compounds **23a,b** formed compounds **3a,b** presumably *via* an intermediate (**8'**) (Figure 4). Compounds **3c,d** exhibited weak antibacterial activity to *Bacillus subtilis* (MIC, 7.8 ppm), while compounds **2a,b** and **3a,b** represented no antibacterial activity to the above bacteria.[31]



Scheme 7. Reagents: (1) Acetone-1,3-dicarboxylate in H_2SO_4/AcOH; (2) (for R = Me) HNO_2 in AcOH/H_2O; (for R = Et) MCPBA in EtOH; (3) (for R = Me) DBU in EtOH; (for R = Et) Na_2CO_3 in H_2O/EtOH; (4) Cyclohexane-1,3-dione in AcOH; (5) NBS in AcOH/H_2O

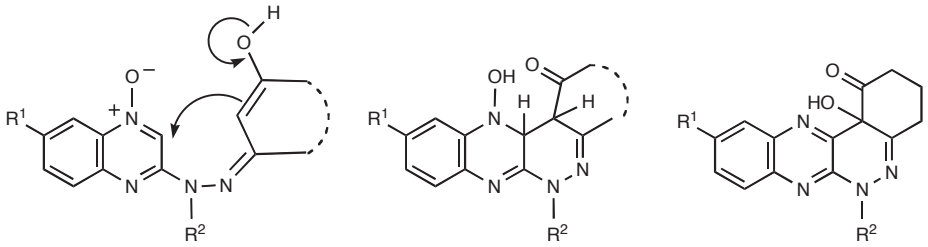
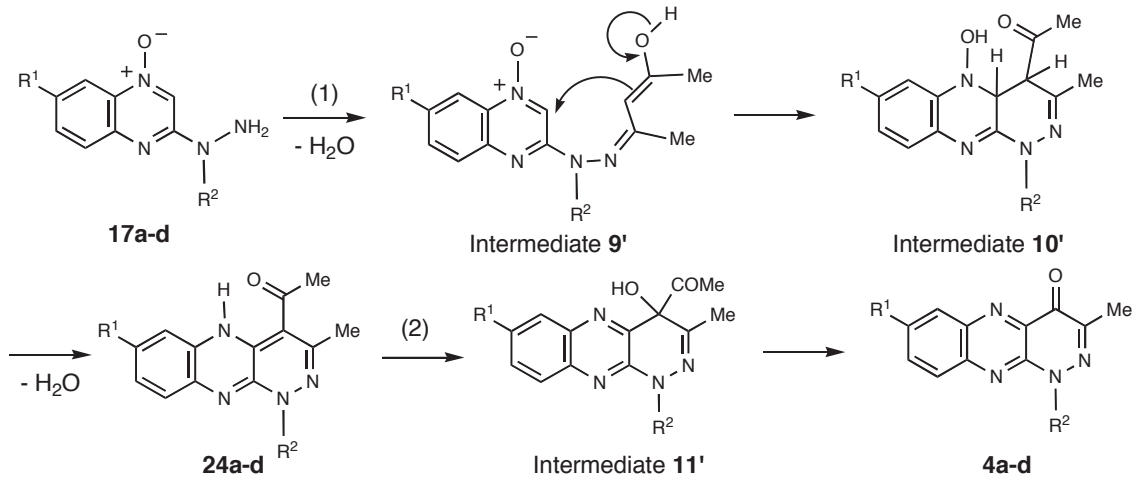


Figure 4

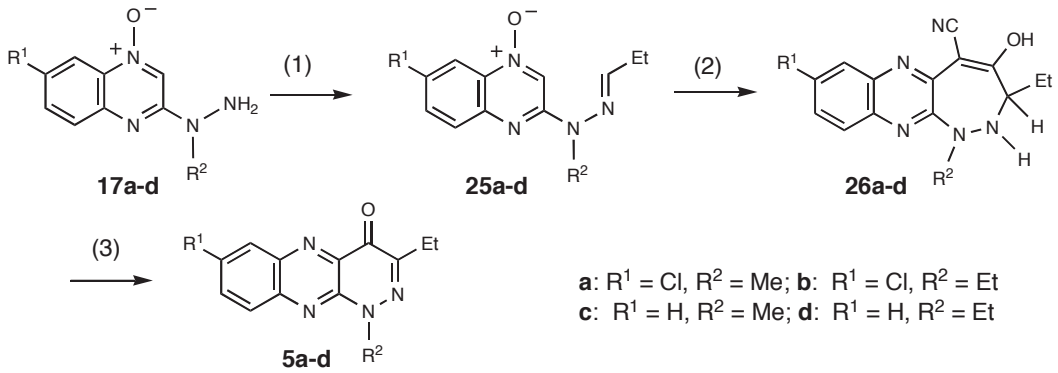
2-3. Synthesis of 3-Methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones and 3-Ethylpyridazino[3,4-*b*]-quinoxalin-4(1*H*)-ones

The reaction of the quinoxaline 1-oxides **17a-d** with acetylacetone gave the 4-acetyl-1,5-dihydropyrida-



a: R^1 = Cl, R^2 = Me; **b**: R^1 = Cl, R^2 = Et; **c**: R^1 = H, R^2 = Me; **d**: R^1 = H, R^2 = Et

Scheme 8. Reagents: (1) Acetylacetone in DMF; (2) NBS/H_2O for **24a**, $NaBrO_3$ for **24b,c**, SeO_2 for **24d** in AcOH



Scheme 9. Reagents: (1) Propanal in Dioxane; (2) 2-Chloroacrylonitrile in Dioxane; (3) SeO_2 in H_2O/AcOH

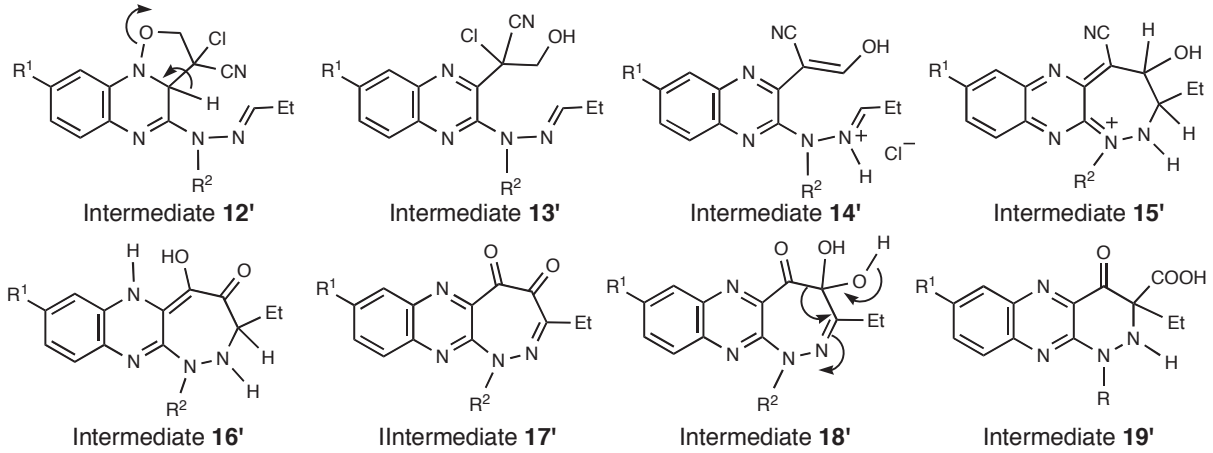


Figure 5

zino[3,4-*b*]quinoxalines (**24a-d**) presumably *via* intermediates (**9'** and **10'**) (Scheme 8).[28] The oxidation of compounds **24a**, **24b,c**, or **24d** with *N*-bromosuccinimide/water, sodium bromate, or selenium dioxide afforded the 3-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**4a-d**) presumably *via* an intermediate (**11'**).[32] On the other hand, the reaction of the quinoxaline 1-oxides **17a-d** with propanal provided the hydrazone derivatives (**25a-d**), whose reaction with 2-chloroacrylonitrile produced the racemic 1,2-diazepino[3,4-*b*]quinoxalines (**26a-d**), respectively (Scheme 9), presumably *via* intermediates (**12'-15'**) (Figure 5).[32] The initial 1,3-dipolar cycloaddition reaction giving an intermediate **12'**, subsequent ring cleavage of the isoxazolidine ring to an intermediate **13'**, and then recyclization would furnish compounds **26a-d**. The oxidative ring transformation of compounds **26a-d** with selenium dioxide resulted in the formation of the 3-ethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**5a-d**), respectively, presumably *via* intermediates (**16'-19'**) (Figure 5). Compounds **4a,c** showed antibacterial, antifungal, and algicidal activities to various microbials in the concentration of 2-8 ppm (Table 1).[33]

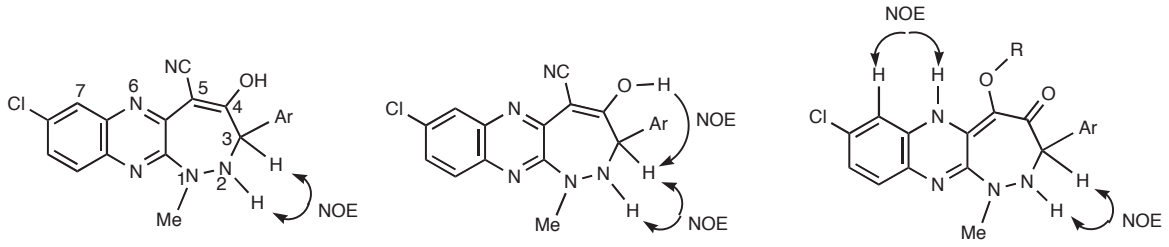
The tautomeric structure of compounds **26a-d** (Scheme 9) and an intermediate **16'** (Figure 5) exhibited above was supported by the NOE spectral data in DMSO-d_6 as shown in Figure 6.[10,11] Their tautomeric structures were found to depend on the nature of the C5-substituent. Namely, a series of compounds **26**

Table 1. *In vitro* Screening Data of Compounds **4a,c** to Several Fungi, Bacteria, and Algae

Compound	Minimum Inhibitory Concentration (ppm)					
	Fungi					
	C. alb.	*C. kru.*	*A. fla.*	*A. fumi.*	*T. ment.*	*T. rub.*
4a	4	4	8	8	2	2
4c	2	4	8	8	2	2

	Bacteria				Algae	
	B. sub.	*C. clad.*	*C. glob.*	*S. aur.*	*A. falc.*	*S. cap.*
4a	2	2	---	2	2	2
4c	3.9	---	2	---	---	---

C. alb. (Candida albicans), C. kru. (Candida krusei), A. fla. (Aspergillus flavus), A. fumi. (Aspergillus fumigatus), T. ment. (Trichophyton mentagrophytes), T. rub. (Trichophyton rubrum), B. sub. (Bacillus subtilis), C. clad. (Cladosporium cladosporioides), C. glob. (Chaetonium globosum), S. aur. (Staphylococcus aureus), A. falc. (Ankistrodesmus falcatus), S. cap. (Selenastrum capricorunutum)



26e-A
2,3-Dihydro-4-hydroxy Form
(Ar: Ph-4-R')

26f-A
2,3-Dihydro-4-hydroxy Form
(Ar: 3-Methylthiophen-2-yl)

26g-B
2,3,4,6-Tetrahydro-4-oxo Form
(R: Alkyl; Ar: Ph-4-R')

Figure 6

existed as the 2,3-dihydro-4-hydroxy form **26-A** or 2,3,4,6-tetrahydro-4-oxo form **26-B** when the C5-substituent was cyano or alkoxyl group, respectively. The crucial NOE was observed in the tautomer **26f-A** (NOE between C4-OH and C3-H) or in the tautomer **26g-B** (NOE between N6-H and C7-H).

2-4. Synthesis of Pyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones

Compounds **1a-d** have the β-keto acid moiety (A) as shown in Figure 7, and hence compounds **1a-d** are seemed to undergo the decarboxylation easily, producing compounds (**6a,b**) (Schemes 10 and 11). However, the presence of the α-hydrazono moiety (B) would suppress the decarboxylation by the electron-donating nature of the N1-nitrogen (C). Accordingly, the alternate methods for the synthesis of compounds **6a,b** were devised as displayed in Schemes 10 and 11.

The reaction of the quinoxaline 1-oxide **17a** with diethyl ethoxymethylenemalonate gave the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylate (**27**), whose oxidation with nitrous acid provided the 4-hydroxypyridazino[3,4-*b*]quinoxaline-4-carboxylate (**28**) (Scheme 10).[34] The reaction of compound

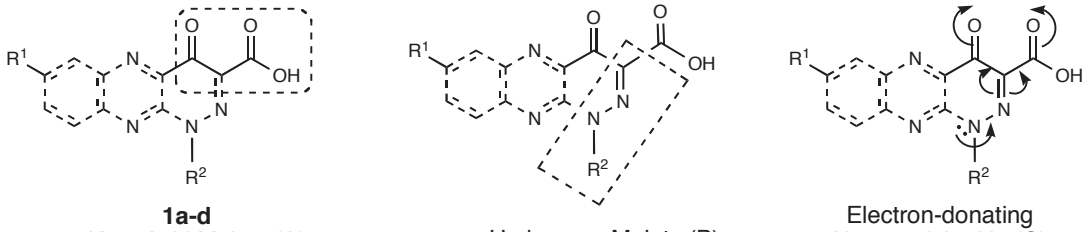
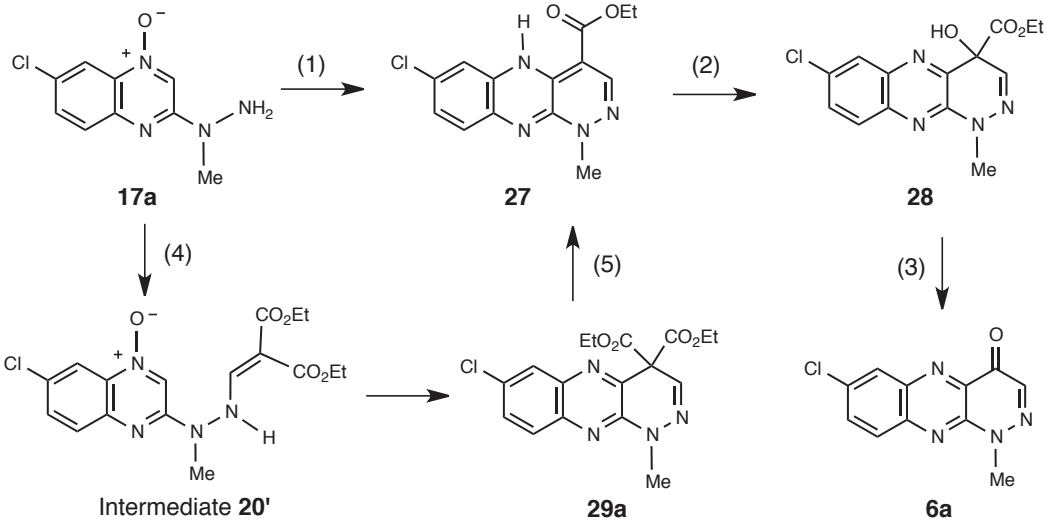
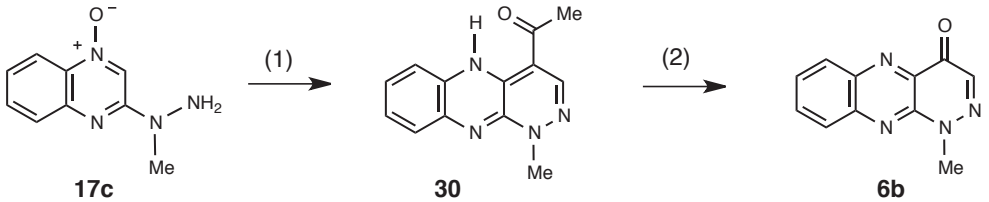


Figure 7



Scheme 10. Reagents: (1) Diethyl Ethoxymethylenemalonate in DMF; (2) HNO_2 in AcOH/H_2O; (3) KOH in EtOH/H_2O, then dil.HCl; (4) Diethyl Ethoxymethylenemalonate in AcOH; (5) KOH in EtOH/H_2O or NH_2NH_2•H_2O in EtOH

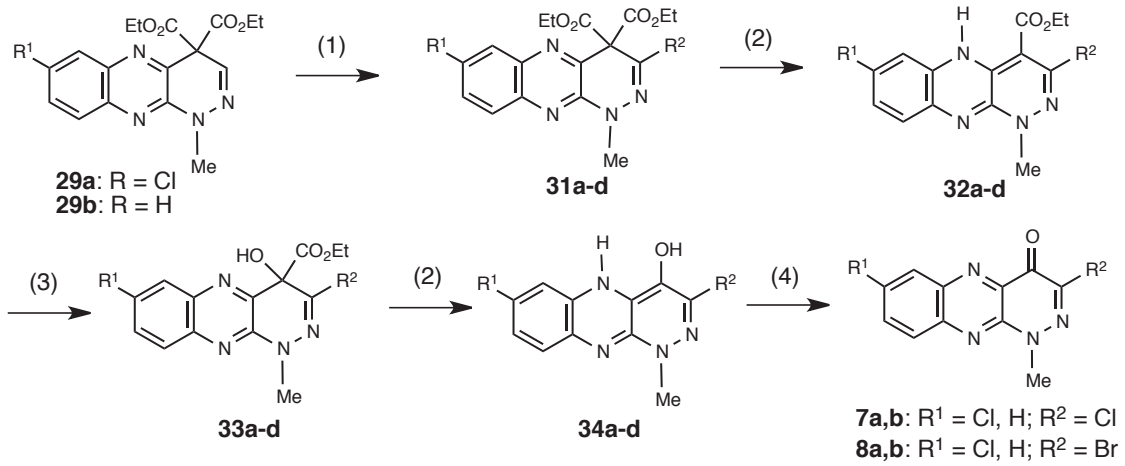
28 with potassium hydroxide afforded 7-chloro-1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**6a**). On the other hand, the reaction of the quinoxaline 1-oxide **17a** with diethyl ethoxymethylenemalonate in acetic acid produced the pyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate (**29a**) presumably *via* an intermediate (**20'**). The reaction of compound **29a** with a base resulted in hydrolysis and decarboxylation to furnish compound **27**. 1-Methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**6b**) was synthesized by a similar method *via* the oxidation of the 4-acetyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline (**30**) (Scheme 11). Compound **6a** showed antifungal activity to *Candida albicans*, *Aspergillus flavus*, *Aspergillus fumigatus* (MIC, 4 ppm), *Candida krusei* (MIC, 2 ppm), *Trichophyton mentagrophytes* (MIC, 1 ppm), and *Trichophyton rubrum* (MIC, 0.5 ppm).[33]



Scheme 11. Reagents: (1) Acetoacetaldehyde Dimethyl Acetal in AcOH/H_2O; (2) SeO_2 in AcOH/H_2O

2-5. Synthesis of 3-Halogenopyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones

The reaction of the pyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylates **29a,b** with NCS or NBS gave the 3-halogenopyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylates (**31a-d**), whose reaction with hydrazine hydrate provided the 3-halogenopyridazino[3,4-*b*]quinoxaline-4-carboxylates (**32a-d**), respectively (Scheme 12).[35] The oxidation of compounds **32a-d** with nitrous acid afforded the derivatives (**33a-d**), whose reaction with hydrazine hydrate produced the 4-hydroxy derivatives (**34a-d**), respectively. The oxidation of compounds **34a-d** with NCS or NBS in water furnished the 3-halogenopyridazino-[3,4-*b*]quinoxalin-4(1*H*)-ones (**7a,b**) or (**8a,b**), respectively. Compound **7a** (R^1 = Cl) exhibited antibacterial activity to *Aureobacididium pullulans*, *Bacillus subtilis*, *Cladosporium cladosporioides*, *Chaetonium globosum*, *Micrococcus luteus*, *and Staphylococcus aureus* (MIC, 2 ppm) and algicidal activity to *Ankistrodesmus falcatus* and *Selenastrum capricorunutum* (MIC, 2 ppm).[33] Moreover, compounds **7a,b** and **8a,b** represented antifungal activity to *Candida albicans*, *Candida krusei*, *Trichophyton mentagrophytes*, *and Trichophyton rubrum* (MIC, 0.5-4 ppm).[33]



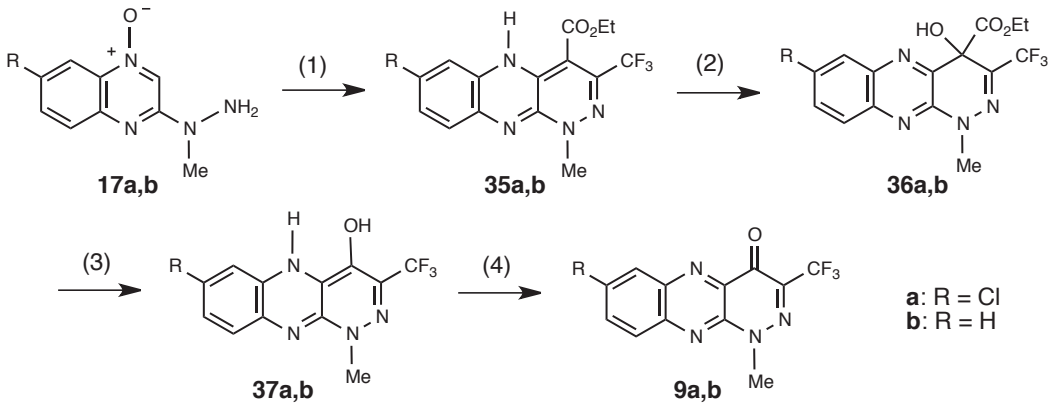
31a-d - 34a-d: **a**: R^1 = Cl, R^2 = Cl; **b**: R^1 = H, R^2 = Cl; **c**: R^1 = Cl, R^2 = Br; **d**: R^1 = H, R^2 = Br

Scheme 12. Reagents: (1) NCS, NBS or Br_2 in AcOH; (2) $NH_2NH_2 \cdot H_2O$ in EtOH; (3) HNO_2 in H_2O/AcOH; (4) NCS or NBS in H_2O/AcOH

2-6. Synthesis of 3-Trifluoromethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones

The reaction of the quinoxaline 1-oxides **17a,b** with ethyl 4,4,4-trifluoro-3-oxobutanoate gave the 3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**35a,b**), whose oxidation with nitrous acid produced the 4-hydroxy-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**36a,b**), respectively (Scheme 13).[36] The reaction of compound **36a** with a base afforded the 4-hydroxy derivative (**37a**, 90%), while the reaction of compound **36b** with a base produced the 4-hydroxy (**37b**, 74%) and 4-oxo (**9b**, 20%) derivatives. The oxidation of compounds **37a,b** with sodium bromate furnished compounds **9a,b**, respectively. Compound **9a** showed antibacterial activity to *Bacillus subtilis*, *Chaetonium*

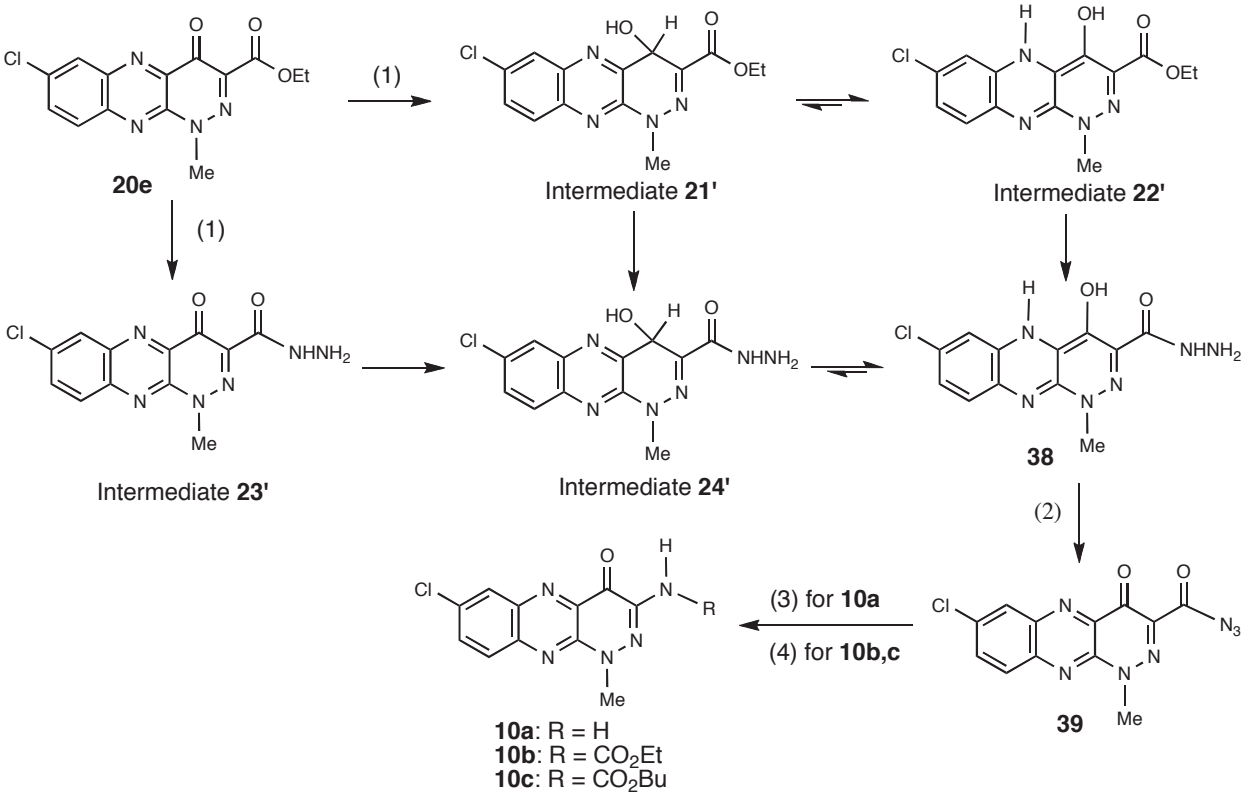
globosum, *Micrococcus luteus*, and *Staphylococcus aureus* (MIC, 2 ppm) and algicidal activity to *Ankistrodesmus falcatus* (MIC, 2 ppm).[33]



Scheme 13. Reagents: (1) Ethyl 4,4,4-Trifluoro-3-oxobutanoate, TsOH•H_2O in Dioxane; (2) HNO_2 in AcOH/H_2O; (3) DBU in EtOH; (4) $NaBrO_3$ in H_2O/AcOH

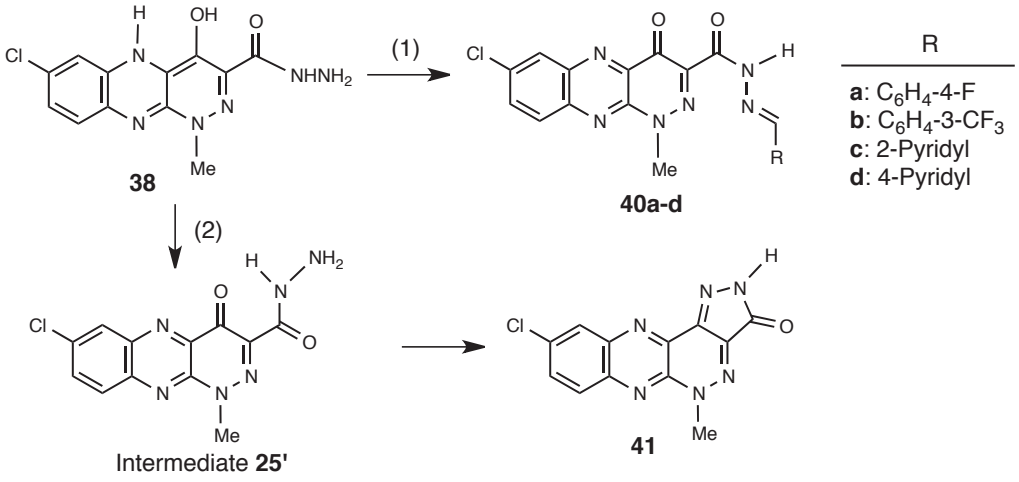
2-7. Synthesis of 3-Aminopyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones and Related Compounds

The reaction of the 4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylate (**20e**) with an excess of hydrazine hydrate furnished the 4-hydroxypyridazino[3,4-*b*]quinoxaline-3-carbohydrazide (**38**) presumably *via* intermediates (**21'-24'**) accompanied by reduction and replacement (Scheme 14).[37] The reaction of com-



Scheme 14. Reagents: (1) NH_2NH_2•H_2O (13-Fold Molar Amount) in Dioxane; (2) $NaNO_2$ in H_2O/AcOH; (3) NEt_3, H_2O in DMF; (4) NEt_3 in EtOH (for **10b**) or 1-BuOH (for **10c**)

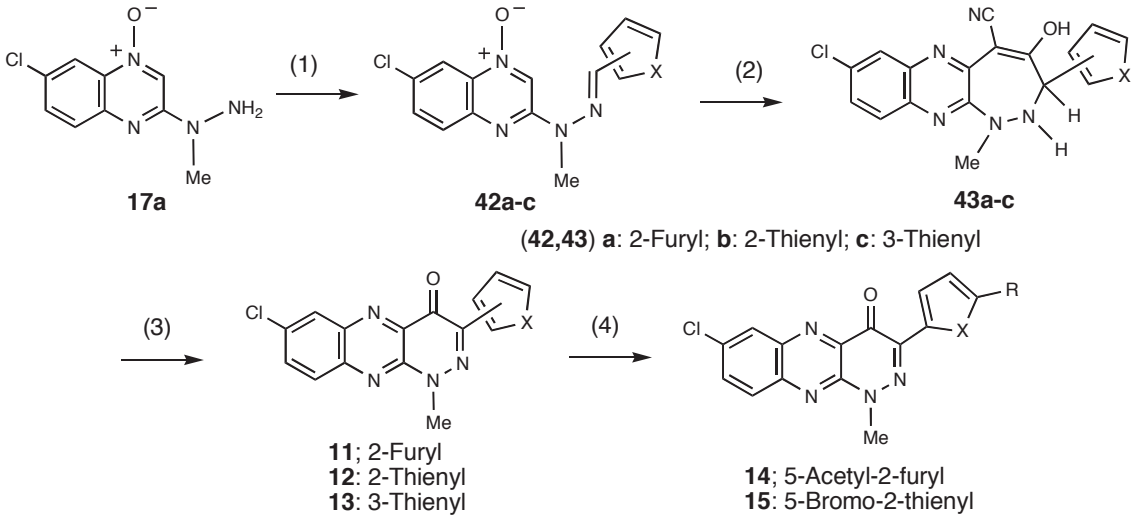
pound **38** with nitrous acid gave the 4-oxopyridazino[3,4-*b*]quinoxaline-3-carbonylazide (**39**), which was converted into the 3-aminopyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**10a**) and *N*-(pyridazino[3,4-*b*]-quinoxalin-3-yl)carbamates (**10b,c**). Compound **38** was also transformed into the hydrazones (**40a-d**), and the heating of compound **38** in DMSO produced the pyrazolo[3',4':5,6]pyridazino[3,4-*b*]quinoxalin-3(5*H*)-one (**41**) presumably *via* an intermediate (**25'**). The *in vitro* screening data was not obtained for compounds shown in Schemes 14 and 15.



Scheme 15. Reagents: (1) RCHO, Reflux in DMF for 2 h; (2) Heat in DMSO

2-8. Synthesis of 3-Heteroarylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones

The reaction of the quinoxaline 1-oxide **17a** with arylcarbaldehydes provided the hydrazones (**42a-c**), whose reaction with 2-chloroacrylonitrile afforded the 1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles (**43a-c**), respectively (Scheme 16).[38] The reaction of compounds **43a-c** with selenium dioxide/water re-



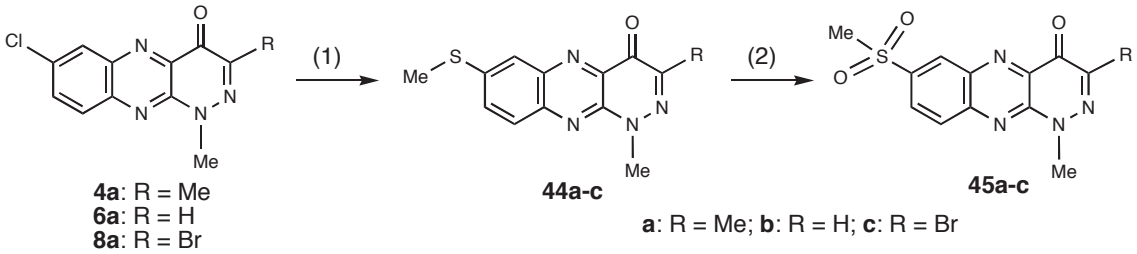
Scheme 16. Reagents: (1) Furfural, Thiophene-2-carbaldehyde, and Thiophene-3-carbaldehyde in Dioxane; (2) 2-Chloroacrylonitrile in Dioxane; (3) SeO_2 in H_2O/AcOH; (4) $Ac_2O/ZnCl_2$ for **11**; NBS in AcOH for **12**

sulted in the oxidation and ring transformation to produce the 3-hetroarylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**11-13**), respectively. Compounds **11** and **12** were converted into the 5'-substituted derivatives (**14** and **15**), respectively. Concerning the formation of compounds **43a-c** and **11-13**, the reaction would proceed *via* similar intermediates shown in Figure 5 (section **2-3**).

2-9. Synthesis of 7-Methylsulfonylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones

The reaction of the 7-chloropyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones **4a**, **6a**, and **8a** with sodium methylthiolate furnished the 7-methylsulfanyl derivatives (**44a-c**), whose oxidation with MCPBA gave the 7-methylsulfonylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**45a-c**), respectively (Scheme 17).[39] Compounds **44a-c** and **45b,c** represented *in vitro* antimicrobial activities to bacteria and algae (Table 2).[39] Compounds **44a-c** showed antibacterial activity to *Micrococcus luteus* and *Chaetonium globosum* (MIC, 2 ppm), and compounds **45b,c** exhibited antibacterial activity to *Bacillus subtilis* and *Staphylococcus aureus* (MIC, 2-3.9 ppm). In addition, compounds **44a**, **45b**, and **45c** represented algicidal activity to *Ankistrodesmus falcatus* (MIC, 2 ppm).

The 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines were found to exist as the N5-ammonium form in TFA-d_1,[40] while the 4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalines predominated as the zwitterionic form of the N10-ammonium form in DMSO-d_6 (Figure 8).[41] On the other hand, compounds **44a,b** were found to be

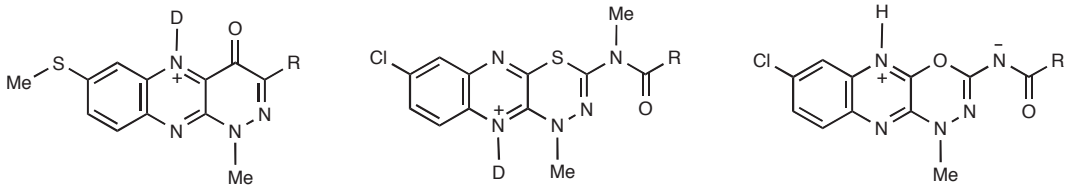


Scheme 17. Reagents: (1) MeSNa in Dioxane; (2) MCPBA in AcOH

Table 2. *In vitro* Screening Data of Compounds **44a-c** and **45b,c** to Several Bacteria and Algae

Compound	Minimum Inhibitory Concentration (ppm)				
	Bacteria				Algae
	M. lut.	*C. glob.*	*S. aur.*	*B. sub.*	*A. falc.*
44a	2	2	---	7.8	2
44b	2	2	7.8	7.8	---
44c	2	2	---	2	---
45b	7.8	6.3	2	3.9	2
45c	7.8	2	3.9	3.9	2

M. lut. (Micrococcus luteus), C. glob. (Chaetonium globosum), S. aur. (Staphylococcus aureus), B. sub. (Bacillus subtilis), A. falc. (Ankistrodesmus falcatus)



44a,b

in TFA-d_1

4*H*-1,3,4-Thiadiazino[5,6-*b*]-quinoxalines (R = Me, CF_3)

in TFA-d_1

4*H*-1,3,4-Oxadiazino[5,6-*b*]-quinoxalines (R = OR', Me, CF_3)

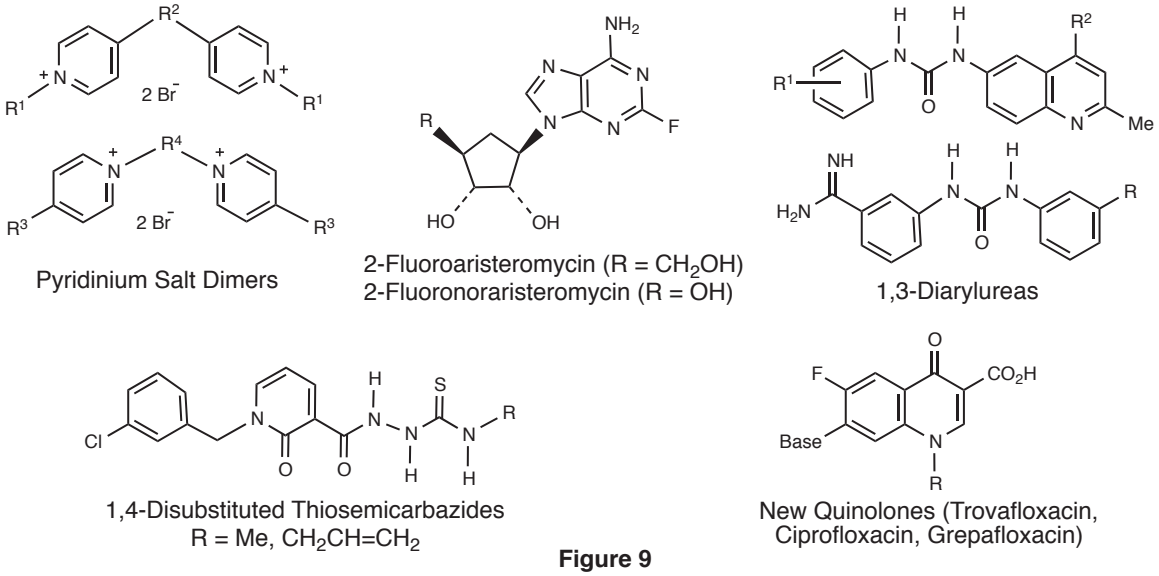
in DMSO-d_6

Figure 8. Deuteronation or Protonation Sites of Compounds **44a,b**, 4*H*-1,3,4-Thiadiazino[5,6-*b*]quinoxalines, and 4*H*-1,3,4-Oxadiazino[5,6-*b*]quinoxalines in TFA-d_1 or in DMSO-d_6

present in the N5-ammonium form in TFA-d_1.[39] The structures of these ammonium forms were assigned by the comparison of the carbon chemical shifts in $CDCl_3$ with those in TFA-d_1.

3. SOME ANTIMALARIAL AGENTS INCLUDING NEW QUINOLONES IN 2000-2010

Quinine and chloroquine have been known as antimalarial agents for the clinical use, and many research groups have synthesized various heterocyclic compounds as candidates of antimalarial agents, which are described in a review by Jain *et al*.[42] In 2000-2010, there have been many reports on the synthesis of the antimalarial agents: for example, pyridinium salt dimers [*N,N'*-hexamethylenebis(1-aryl-4-carbamoyl-pyridinium bromides), (IC_{50}, 10 nM); 1,1'-(1,12-dodecanediyl)bis(4-butylaminocarbonyl)pyridinium bromides, (ED_{50}, 8.2 mg/kg)],[43-45] carbocyclic nucleosides (2-fluoroaristeromycin and 2-fluoronor-aristeromycin, inhibiting *Plasmodium falciparum S*-adenosyl-L-homocysteine hydrolase),[46-49] 1,4-disubstituted thiosemicarbazides and 1,3-diarylureas {(4-alkyl-1-[1-(3-chlorobenzyl)-2-pyridone-3-carbonyl]thiosemicarbazides), 1-aryl-3-(quinolin-6-yl)ureas, 3-(3-amidinophenyl)-1-arylureas, inhibiting the wild-type and resistant mutant *Plasmodium falciparum* dihydrofolate reductase}[50-52] (Figure 9). Some of



Pyridinium Salt Dimers

2-Fluoroaristeromycin (R = CH_2OH)
2-Fluoronoraristeromycin (R = OH)

1,3-Diarylureas

1,4-Disubstituted Thiosemicarbazides
R = Me, $CH_2CH{=}CH_2$

New Quinolones (Trovafloxacin, Ciprofloxacin, Grepafloxacin)

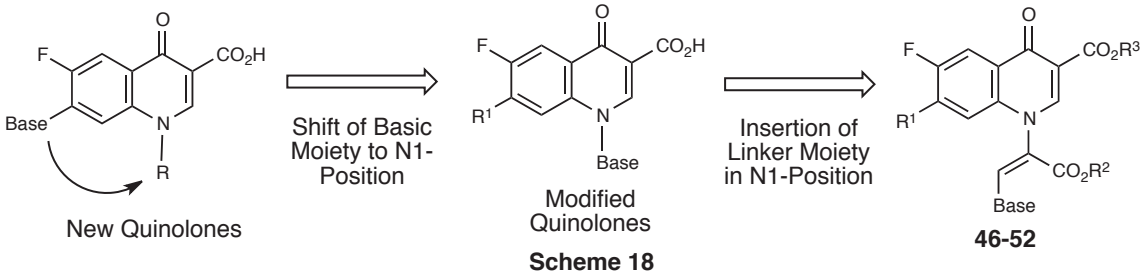
Figure 9

new quinolones were also found to possess antimalarial activity,[53,54] and the synthetic approaches were carried out to search for a new type of antimalarial 4-quinolones as described below. The literatures of antibacterial new quinolones are not introduced in this review, since there have already been numerous theses, reviews, and monographs on the antibacterial new (and old) quinolones.

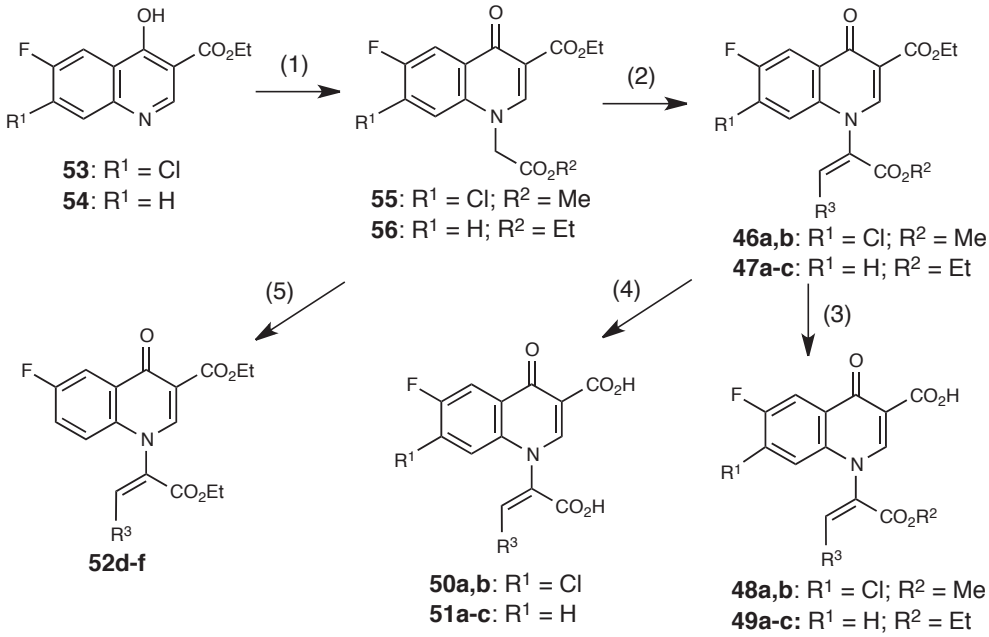
4. SYNTHESIS OF ANTIMALARIAL 4-QUINOLONES

4-1. Synthesis of 4-Quinolone-3-carboxylates with Heteroaryl Moiety in N1-Side Chain

The structural conversion of new quinolone antibacterials was carried out as shown in Scheme 18.[55] Namely, ordinary new quinolone antibacterials have the N1-(alkyl or aryl) moiety, C3-carboxyl group, 4-oxo group, C6-fluoro group, and C7-basic moiety in the quinoline ring. Although the C7-basic moiety acts an important role for the antibacterial activity, compounds (**46-52**) produced by shifting the basic moiety to N1-side chain from C7-position of new quinolones were found to show antimalarial activity.



Scheme 18



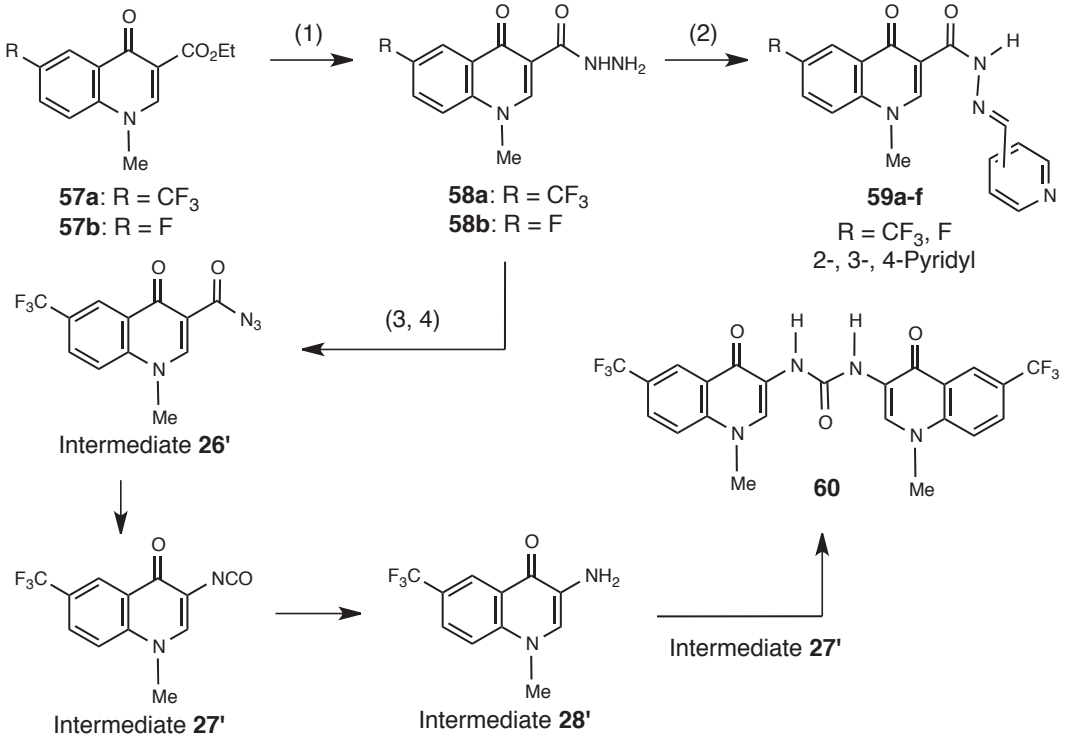
R^3: **a**: 4-Pyridyl; **b**: 3-Pyridyl; **c**: 2-Pyridyl; **d**: 2-Furyl; **e**: 2-Thienyl; **f**: 3-Thienyl

Scheme 19. Reagents: (1) $BrCH_2CO_2R^2$, K_2CO_3 in DMF; (2) Pyridinecarbaldehydes, DBU in DMF; (3) H_2SO_4, H_2O in AcOH, then NaOH; (4) NaOH, H_2O in EtOH, then HCl; (5) Heteroarylcarbaldehydes, DBU in DMF

The reaction of the 4-hydroxyquinoline-3-carboxylates (**53, 54**) with bromoacetate effected the alkylation in the N1 of quinoline to give the (4-quinolon-1-yl)acetates (**55, 56**), whose reaction with pyridine-carbaldehydes provided the 1-[1-alkoxycarbonyl-2-(2-, 3- and 4-pyridyl)vinyl]-4-quinolone-3-carboxylates (**46, 47**), respectively (Scheme 19).[55] The 1-[1-ethoxycarbonyl-2-(2-furyl, 2-thienyl, and 3-thienyl)vinyl]-4-quinolone-3-carboxylates (**52**) and 1-[2-(2-, 3- and 4-pyridyl)vinyl]-4-quinolone-3-carboxylic acids (**48-51**) were also synthesized from compounds **55, 56** and **46, 47**, respectively. The *in vitro* screening to antimalarial activity exhibited that compound **47a** (R^1 = H, R^2 = Et, R^3 = 4-pyridyl) represented the IC_{50} of 8.2 μM to *Plasmodium falciparum* and the IC_{50} of above 24 μM to mouse FM3A cell F28-7 strain (chemotherapeutic coefficient: 2.9). The IC_{50} of other compounds to *Plasmodium falciparum* was above 21 μM.

4-2. Synthesis of 4-Quinolones with Pyridyl Moiety in C3-Side Chain

In continuation of the works exhibited in the above section **4-1**, the pyridyl moiety was shifted to the C3-side chain, and the 7-chloro atom was excluded. Compounds (**57a,b**) obtained from the corresponding 4-hydroxyquinoline-3-carboxylates were converted into the 4-quinolone-3-carbohydrazides (**58a,b**), whose reaction with pyridine-2-, 3-, and 4-carbaldehydes provided the hydrazones (**59a-f**) (Scheme 20).[56] The reaction of compound **58a** (R = CF_3) with nitrous acid precipitated an azide intermediate (**26'**), and then heating of the reaction mixture gave the 1,3-bis(4-quinolon-3-yl)urea (**60**) presumably *via* intermedi-

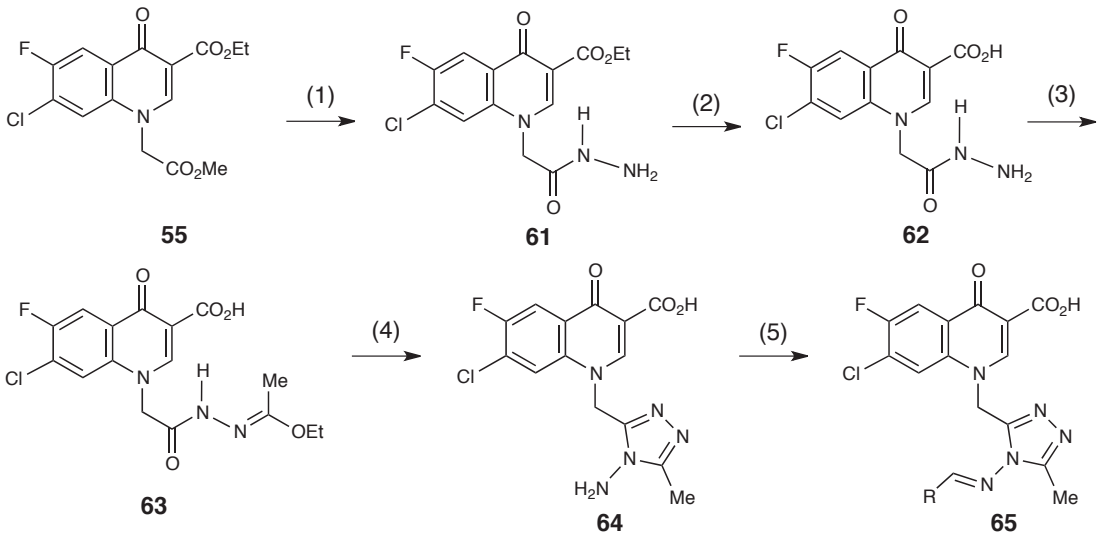


Scheme 20. Reagents: (1) $NH_2NH_2 \cdot H_2O$ in EtOH; (2) Pyridine-2-, 3-, 4-carbaldehydes in DMF; (3) $NaNO_2/H_2O$/AcOH at rt; (4) Heat

ates (**27'** and **28'**). Compounds **58b** and **59a,b** (**a**: R = CF_3, 2-pyridyl; **b**: R = F, 2-pyridyl) represented antimalarial activity to chloroquine-sensitive *Plasmodium falciparum* (IC_{50}, 8.7, 6.2, and 3.3 μM, respectively).

4-3. Synthesis of 1-(1,2,4-Triazolylmethyl)-4-quinolone-3-carboxylic Acids

The reaction of compound **55** with hydrazine hydrate gave the 1-hydrazinocarbonylmethyl-4-quinolone-3-carboxylate (**61**), whose alkaline hydrolysis provided the 1-hydrazinocarbonylmethyl-4-quinolone-3-carboxylic acid (**62**) (Scheme 21).[57] Compound **62** was transformed into the 1-[(4-amino-1,2,4-triazol-3-yl)methyl]-4-quinolone-3-carboxylic acid (**64**) *via* the 1-(1-ethoxyethylidene)hydrazinocarbonylmethyl-4-quinolone-3-carboxylic acid (**63**). The reaction of compound **64** with arylaldehydes afforded the 1-[(4-arylmethyleneamino-1,2,4-triazol-3-yl)methyl]-4-quinolone-3-carboxylic acids (**65**). Although compounds **64** and **65** did not show antimalarial activity, the 4-quinolones having the (thio)semicarbazide moiety at the 3-position of compound **64** exhibited antimalarial activity as described in the next section **4-4**.

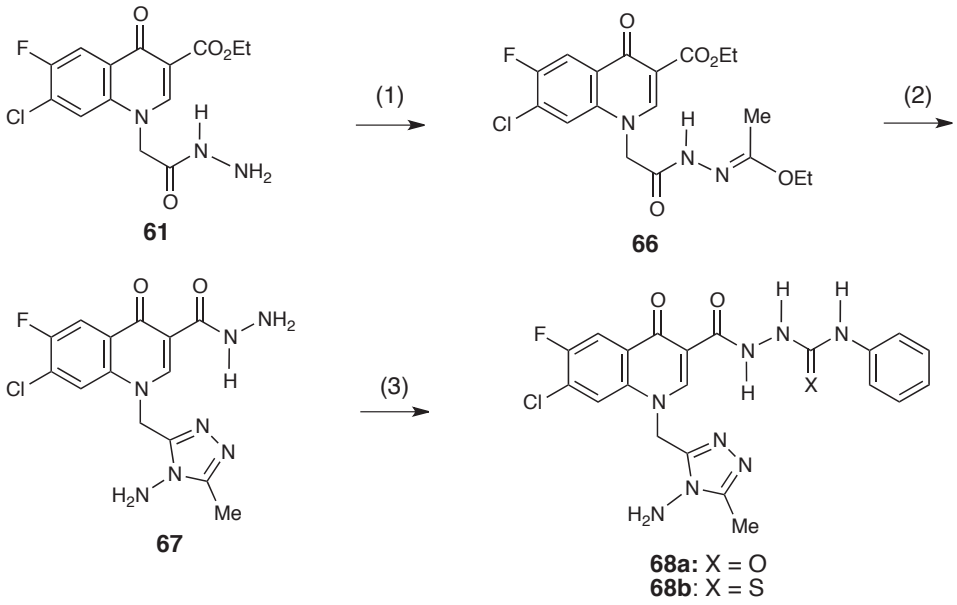


R: 2-Thienyl, 2-Furyl, 2-Pyridyl, 3-Trifluoromethylphenyl, 3-Thienyl, 5-Methyl-2-furyl, 5-Methyl-2-thienyl

Scheme 21. Reagents: (1) $NH_2NH_2 \cdot H_2O$ in DMF-EtOH; (2) KOH in EtOH, then 1*N* HCl; (3) $MeC(OEt)_3$ in DMF; (4) DBU, $NH_2NH_2 \cdot H_2O$ in EtOH; (5) Arylcarbaldehydes, H_2SO_4 in AcOH

4-4. Synthesis of 1-(4-Quinolon-3-ylcarbonyl)-4-phenylsemicarbazide and -4-phenylthiosemicarbazide

Compound **61** was converted into the 1-(1-ethoxyethylidene)hydrazinocarbonylmethyl derivative (**66**), whose reaction with hydrazine hydrate in the presence of DBU furnished the 1-(4-amino-1,2,4-triazol-3-ylmethyl)-4-quinolone-3-carbohydrazide (**67**) (Scheme 22).[57] The reaction of compound **67** with phenyl isocyanate or phenyl isothiocyanate gave the 1-(4-quinolon-3-ylcarbonyl)-4-phenylsemicarbazide (**68a**)

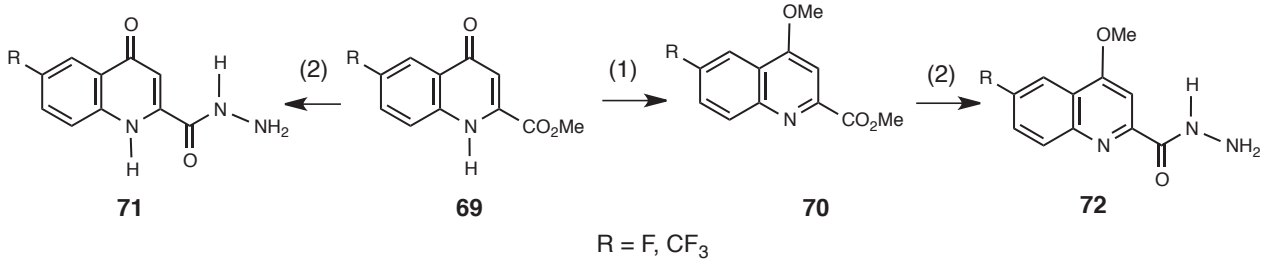


Scheme 22. Reagents: (1) $MeC(OEt)_3$ in DMF; (2) DBU, $NH_2NH_2 \cdot H_2O$ in EtOH; (3) Phenyl Isocyanate or Phenyl Isothiocyanate in DMF

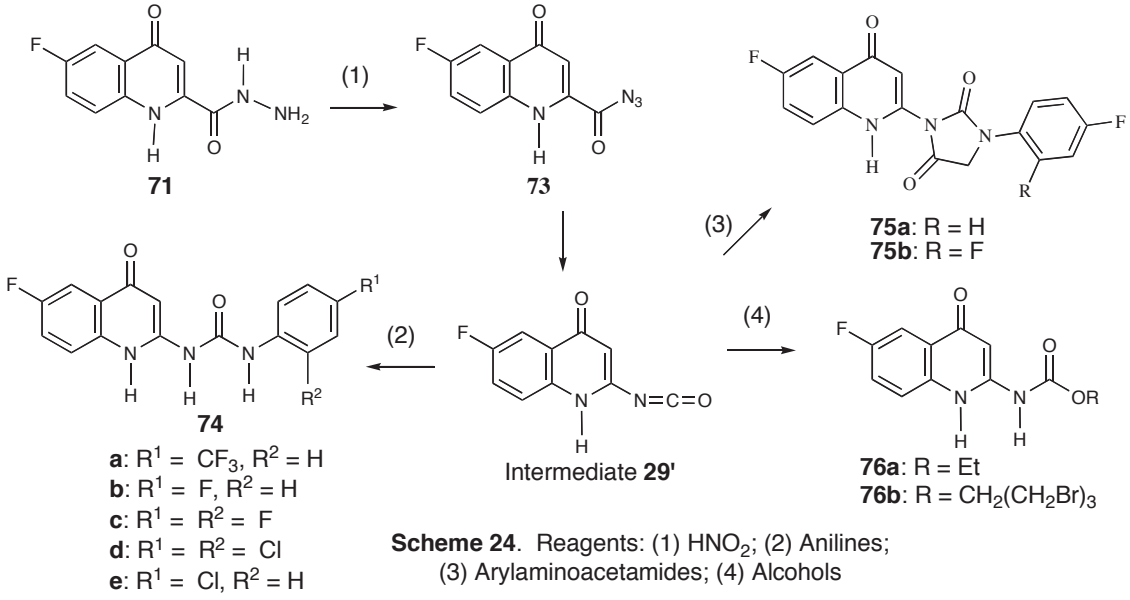
or -4-phenylthiosemicarbazide (**68b**), respectively. Compounds **68a,b** represented *in vitro* antimalarial activity to chloroquine-resistant *Plasmodium falciparum* (IC_{50}: **68a**, 3.89 μM; **68b**, 3.91 μM). Diverse 1,4-disubstituted thiosemicarbazides (Figure 9) have been known to show antimalarial activity by inhibiting *Plasmodium falciparum* dihydrofolate reductase, owing to the thiosemicarbazide moiety (hydrogen bond donor and accepter) and aromatic ring (hydrophobic moiety).[50, 51]

4-5. Synthesis of 4-Quinolones and 4-Methoxyquinolines Possessing N-Functional Group at 2-Position

The synthesis of the starting materials (**71, 72**) is shown in Scheme 23.[58] The 4-quinolone-2-carboxylate (**69**) was methylated with methyl iodide/potassium carbonate to provide the 4-methoxy derivative (**70**). Compounds **69** and **70** were converted into the 2-carbohydrazide derivatives (**71**) and (**72**), respectively. The reaction of compound **71** with nitrous acid gave the 4-quinolone-2-carbonylazide (**73**), whose heating would produce a 4-quinolon-2-yl isocyanate intermediate (**29'**) (Scheme 24).[59] The reaction of an intermediate **29'** with aniline derivatives, arylaminoacetamides, or alcohols formed the 1-aryl-3-(4-quinolon-2-yl)ureas (**74a-e**), 1-aryl-3-(4-quinolon-2-yl)imidazolidine-2,4-diones (**75a,b**), or *N*-(4-quinolon-2-



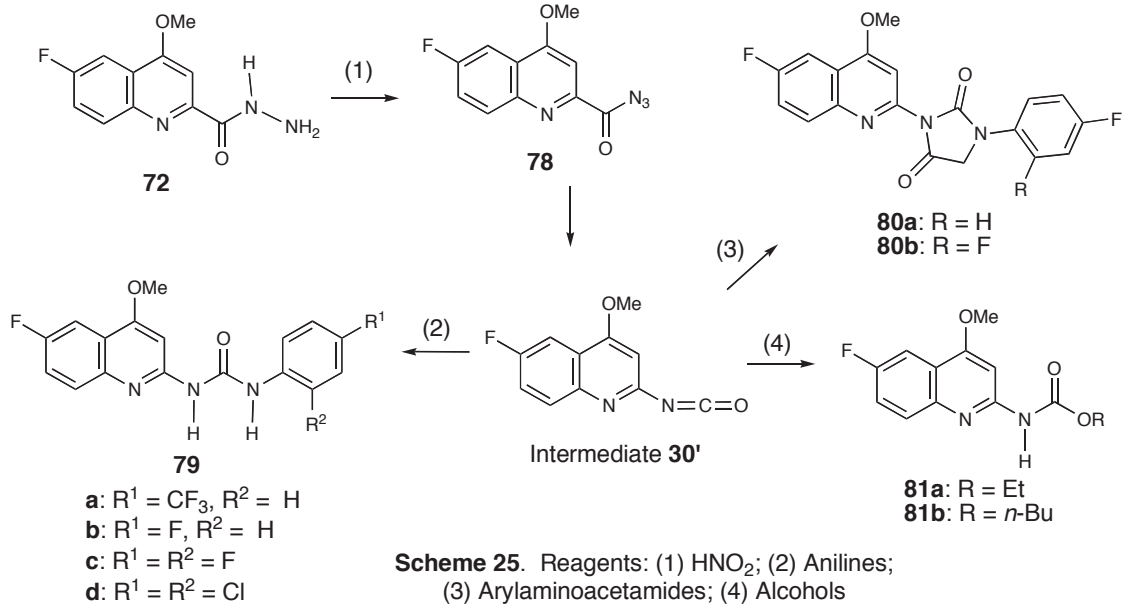
Scheme 23. Reagents: (1) MeI/K_2CO_3 in DMF; (2) $NH_2NH_2 \cdot H_2O$ in EtOH



Scheme 24. Reagents: (1) HNO_2; (2) Anilines; (3) Arylaminoacetamides; (4) Alcohols

Table 3. *In vitro* Antimalarial Activity for Compounds **74a-e**

Compound	Substituent		*Plasmodium falciparum* IC50 (μM)
	R^1	R^2	
74a	CF_3	H	0.93
74b	F	H	1.35
74c	F	F	4.00
74d	Cl	Cl	3.70
74e	Cl	H	1.50



Scheme 25. Reagents: (1) HNO_2; (2) Anilines; (3) Arylaminoacetamides; (4) Alcohols

yl)carbamates (**76a,b**), respectively. Compounds **74a-e** exhibited antimalarial activity *in vitro* to chloroquine-resistant *Plasmodium falciparum* (Gambia Cl D-3, ATCC-50037) (IC_{50}, 0.93-4.00 μM)

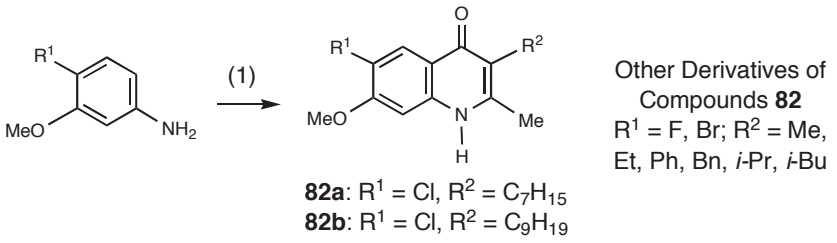
(Table 3), and these compounds would inhibit *Plasmodium falciparum* dihydrofolate reductase in a similar manner to that of the 1,3-diarylureas shown in Figure 9 (section **3**).

The reaction of the 4-methoxyquinoline-2-carbohydrazide (**72**) with nitrous acid would produce the 4-methoxyquinoline-2-carbonylazide (**78**) and then an intermediate (**30'**), whose reaction with various anilines, arylaminoacetamides, or alcohols gave the 1-aryl-3-(4-methoxyquinolin-2-yl)ureas (**79a-d**), 1-aryl-3-(4-methoxyquinolin-2-yl)imidazolidine-2,4-diones (**80a,b**), or *N*-(4-methoxyquinolin-2-yl)carbamates (**81a,b**), respectively (Scheme 25). Compounds **79-81** did not represent antimalarial activity.

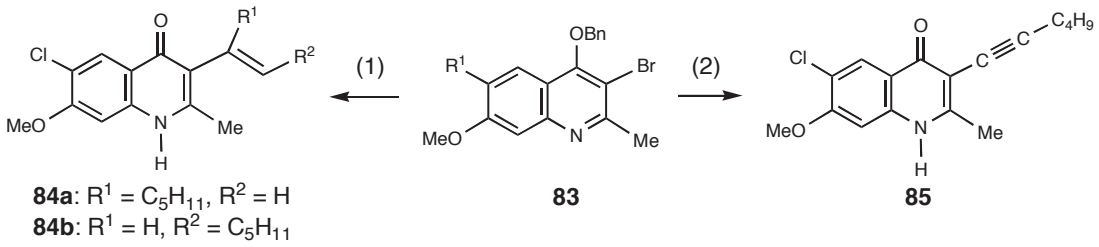
4-6. Synthesis of 3-Substituted 2-Methyl-4-quinolones

The 3-alkyl-2-methyl-4-quinolones (**82a,b**) and other derivatives were synthesized by the reaction of 4-substituted 3-methoxyanilines with 2-substituted ethyl acetoacetates (Scheme 26).[60] Compounds **82a,b** were most active in the series of compounds **82**, showing antimalarial activity to *Plasmodium falciparum* W2 (EC_{50}: **82a**, 12.3 nM; **82b**, 6.03 nM) and *Plasmodium falciparum* TM90-C2B (EC_{50}: **82a**, 2.95 nM; **82b**, 1.59 nM).

Compound (**83**) was also converted into the 3-alkenyl-2-methyl-4-quinolones (**84a,b**) and 3-alkynyl-2-methyl-4-quinolone (**85**), as shown in Scheme 27.[60] Compounds **84a,b** exhibited weaker activity than those of compounds **82a,b** [W2 (EC_{50}: **84a**, 39.4 nM; **84b**, 31.5 nM); TM90-C2B (EC_{50}: **84a**, 14.8 nM; **84b**, 10.6 nM)].



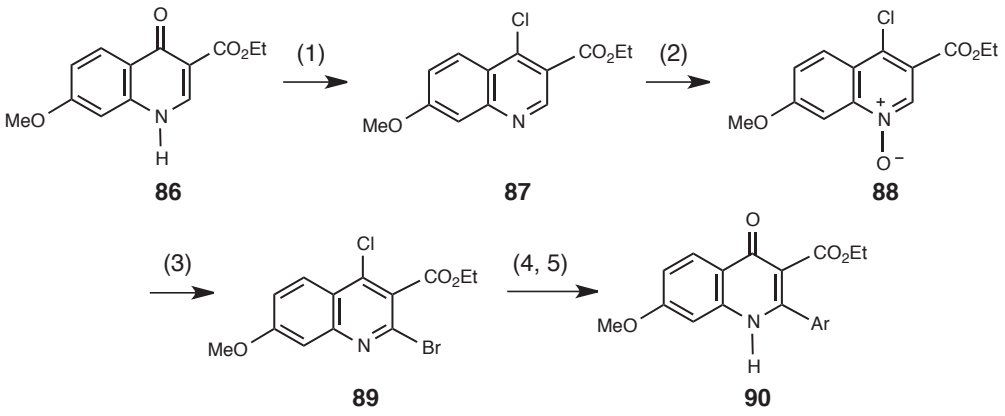
Scheme 26. Reagents: (1) 2-Substituted Ethyl Acetoacetates in AcOH/Benzene, Dean-Stark Trap, then Reflux in Ph_2O for 15 min



Scheme 27. Reagents: (1) $Pd_2(dba)_3$, XPhos (Biaryl Phosphane Ligand), TEA, Toluene, Alkenes; (2) $PdCl_2(PPh_3)_2$, CuI, TEA, DMF, 1-Hexyne, 130 °C

4-7. Synthesis of 2-Aryl-4-quinolone-3-carboxylates

The reaction of the 7-methoxy-4-quinolone-3-carboxylate (**86**) with phosphoryl chloride gave the 4-chloroquinoline-3-carboxylate (**87**), whose reaction with MCPBA gave the 1-oxide derivative (**88**) (Scheme 28).[61] The reaction of compound **88** with phosphoryl bromide provided the 2-bromo-4-chloroquinoline-3-carboxylate (**89**), whose cross-coupling and then hydrolysis afforded the 2-aryl-4-quinolone-3-carboxylates (**90**). One of compounds **90** (Ar = Ph-*m*-OMe) was most promising analogue, showing antimalarial activity to *Plasmodium falciparum* chloroquine-resistant strain K1 (EC_{50}: 0.13 μM) and 3D7 (EC_{50}: 0.10 μM). In ωmpounds **90**, it was found that (1) the 3-carboxylate derivatives were superior to the 3-carboxylic acid derivatives, (2) the 7-methoxy derivatives favored over the 5-methoxy derivatives, and (3) the substituent of the 2-aryl group was better in the 3-position than in the 2- or 4-position.



90 (Ar: Ph-3,4-methylenedioxy, Ph, 2-Thienyl, Ph-3-OMe, Ph-3-CF_3, Ph-3-Cl, Ph-3-F, Ph-3-NO_2, Ph-4-OMe, Ph-4-(*t*-Bu), Ph-4-CF_3, Ph-4-Cl, Ph-3,4-diCl, Ph-2-Me, Ph-2-Cl)

Scheme 28. Reagents: (1) $POCl_3$, 1,4-Dioxane, 120 °C for 1 h; (2) MCPBA in $CHCl_3$, rt for 4 h; (3) $POBr_3$ in $CHCl_3$, rt for 1 h; (4) $ArB(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3 in 1,4-Dioxane/H_2O, 75 °C for 3 h; (5) AcOH/H_2O (4:1), 120 °C for 1 h

5. DIVERSE 4-QUINOLONES WITH VARIOUS BIOLOGICAL ACTIVITIES

There have been many reports on the naturally occurring 4-quinolones, some of which are shown in Fig-

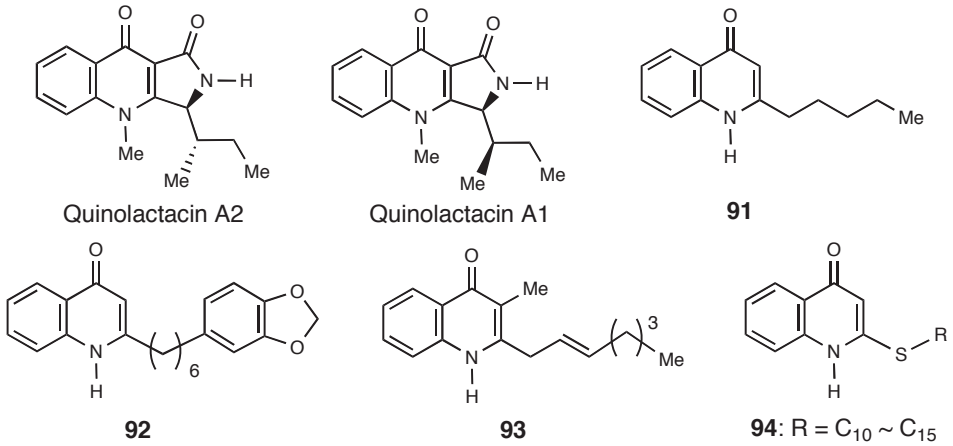
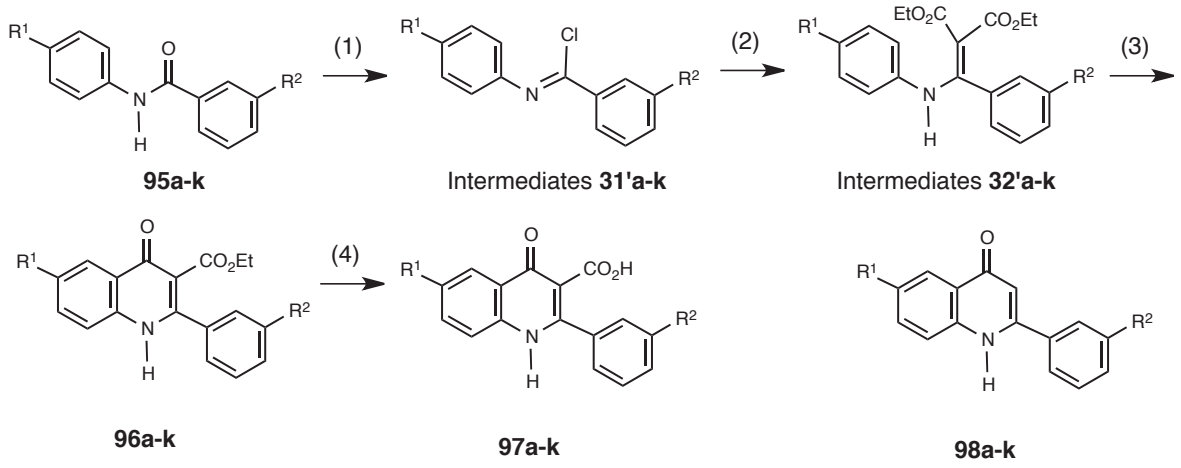


Figure 10. Biologically Active 4-Quinolones

ure 10. Quinolactacin A2 is the C1' diastereomer of quinolactacin A1, and quinolactacin A2 has exhibited 14 times higher anti-acetylcholinesterase activity than its diastereomer quinolactacin A1.[62,63] The 2-alkyl-4-quinolones (**91**),[64,65] (**92**),[65,66] and (**93**)[67] represented the antibiotic (**91**), antirheumatic (**92**), antisparsmodic (**92**), and antifungal/red pepper growth promoting (**93**) activities. The 2-alkyl-thio-4-quinolones (**94**) are artificial compounds and known to exhibit antibacterial activities, especially to MRSA.[68]

5-1. Synthesis of 2,6-Disubstituted 4-Quinolones with Anticancer Activity

The reaction of the *N*-arylbenzamides (**95a-k**) with phosphorus pentachloride gave imidoyl chloride intermediates (**31'a-k**), whose reaction with sodium diethyl malonate produced dicarboxylate intermediates (**32'a-k**), respectively (Scheme 29).[69] The heating of intermediates **32'a-k** at 170 °C afforded the 6-substituted 2-arylquinolone-3-carboxylates (**96a-k**), whose reaction with 10% sodium hydroxide provided the 4-quinolone-3-carboxylic acids (**97a-k**), respectively. Compounds (**98a-k**) were also formed together with compounds **96a-k**, presumably due to the hydrolysis and decarboxylation during the cyclization of intermediates **32'a-k**. One of compounds **97a-k** (R^1 = OMe, R^2 = F) had the highest *in vitro* cytotoxic activity to A549 lung cancer cells (ED_{50}, 0.19 μg/mL).

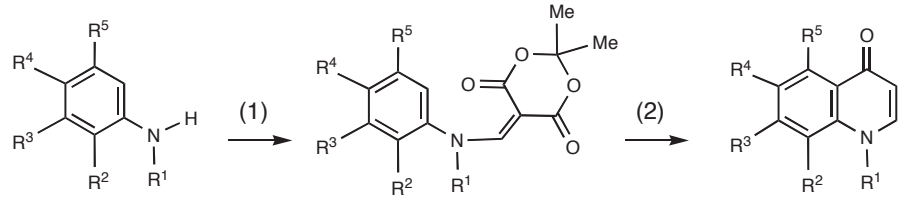


R^1 = F, Cl, OMe; R^2 = H, F, Cl, OMe

Scheme 29. Reagents: (1) PCl_5, 110-140 °C; (2) Sodium Diethylmalonate in Toluene, Reflux; (3) Heat at 170 °C; (4) 10% NaOH

5-2. Synthesis of 5,8-Disubstituted 4-Quinolones with Antitumor Activity

The reaction of the substituted anilines (**99**) with Meldrum's acid and trimethyl orthoformate gave the 5-arylaminomethylene-2,2-dimethyl-1,3-dioxane-4,6-diones (**100**), whose heating in diphenyl ether provided the 4-quinolones (**101**) (Scheme 30).[70] One of compounds **101** (5-hydroxy-8-methoxy-4-quinolone) exhibited the potent antitumor activity for HL60 (IC_{50}, 1.7 μM).



99 **100** **101**

R^1 = H, Me, OMe; R^2 = H, Me, OMe, Cl; R^3 = H, OMe, CF_3, OH;
R^4 = H, OMe; R^5 = H, OMe, OH, CF_3

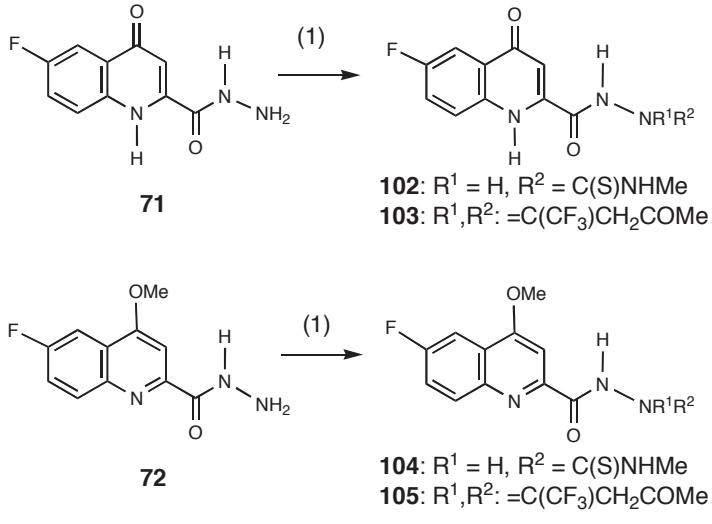
Scheme 30. Reagents: (1) Meldrum's Acid, $HC(OMe)_3$; (2) Ph_2O, Reflux

5-3. Synthesis of 4-Quinolones and Related Compounds Aiming at Antibacterial and Other Biological Activities

Since the 4-quinolones with the long chain substituent at the 2-position such as compounds **91-94** (Figure 10) showed various biological activities, the 6-fluoro-4-quinolones (**102, 103**) and 6-fluoroquinolines (**104, 105**) having the long chain at the 2-position were synthesized by the reaction of compounds **71** and **72** with methyl isothiocyanate or 1,1,1-trifluoropentane-2,4-dione, respectively (Scheme 31).[58] Compounds **103** and **105** represented weak anti-MRSA activity to five kinds of strains (ATCC 33591, 33592, 33593, 13301, 11632) at concentrations of 16-32 ppm, and compound **105** showed weak antifungal activity to five kinds of fungi (*Candida albicans, Candida krusei, Aspergillus fumigatus, Tricophyton rubrum, Tricophyton mentagrophytes*) at concentrations of 8-16 ppm.[58]

The reaction of the 2-arylquinolines (**106a-d**)[71] with methyl trifluoromethanesulfonate followed by oxidation with potassium ferricyanide gave the 2-arylquinolone alkaloids (**107a-d**), respectively (Scheme 32),[72] which were synthesized to investigate the antibacterial and other pharmacological activities.

The reaction of 4-chloro-*N*-(2-hydroxyphenyl)anthranilic acid (**108**) with various acyl chlorides provided



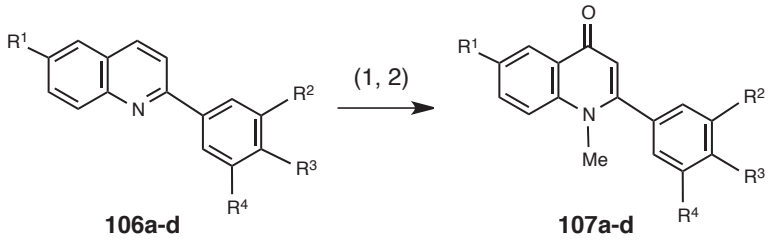
71

102: R^1 = H, R^2 = C(S)NHMe
103: R^1,R^2: =$C(CF_3)CH_2COMe$

72

104: R^1 = H, R^2 = C(S)NHMe
105: R^1,R^2: =$C(CF_3)CH_2COMe$

Scheme 31. Reagents: (1) MeNCS or 1,1,1-Trifluoropentane-2,4-dione in DMF

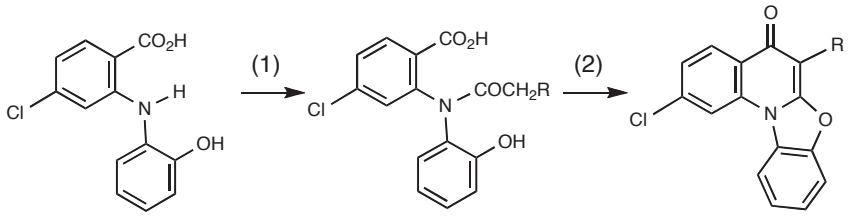


106a-d **107a-d**

a: $R^1 = R^2 = R^3 = R^4 = H$; **b**: $R^1 = R^4 = H$, $R^2R^3 = OCH_2O$;
c: $R^1 = R^2 = R^4 = H$, $R^3 = OMe$; **d**: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$

Scheme 32. Reagents: (1) CF_3SO_3Me, 150 °C for 1 h; (2) $K_3Fe(CN)_6$ in 20% NaOH, rt for 2 h

the *N*-acylated compounds (**109**), whose treatment with hot acetic anhydride furnished the 6-substituted 2-chlorobenzoxazolo[3,2-*a*]quinolin-5-ones (**110**), respectively (Scheme 33). These compounds **110** were synthesized to search for potential quinolone antibacterial agents.[73]

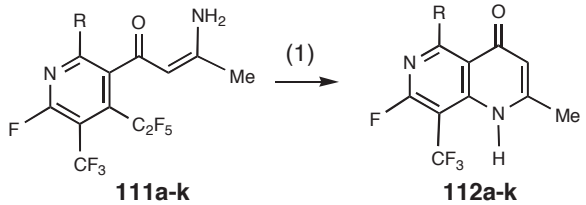


108 **109** **110**

R = Me, Et, CO_2Et, Ph, Bn, OPh, OMe, OC_6H_{11}

Scheme 33. Reagents: (1) $ClCOCH_2R$, Imidazole (3 Eq.), in CH_2Cl_2, rt; (2) Ac_2O, 80 °C

The reaction of the substituted pyridines (**111a-k**)[74-76] with various bases produced the 1,6-naphthyridin-4-ones (**112a-k**), respectively (Scheme 34),[77] which were synthesized as candidates of antibacterial quinolone analogues.

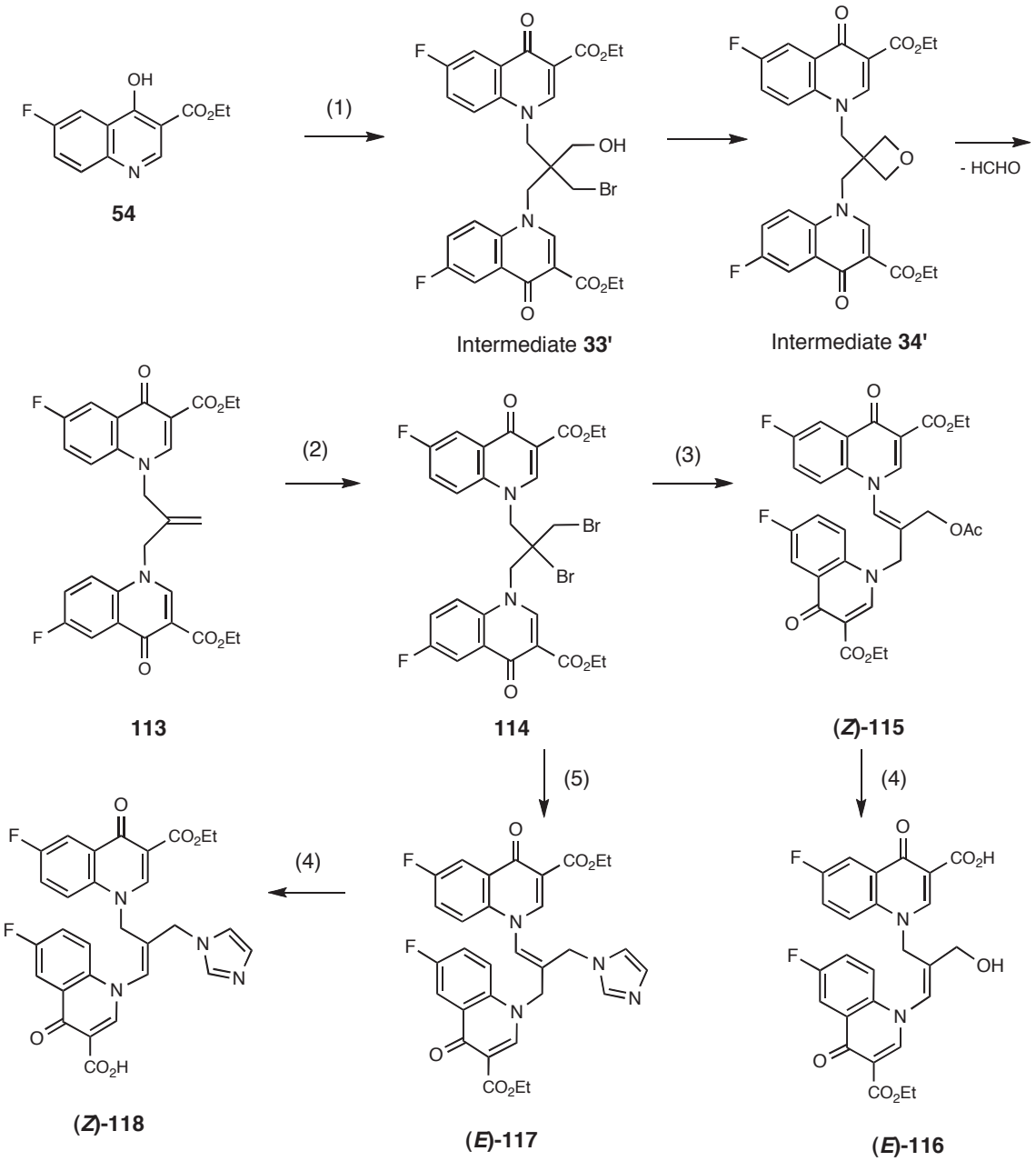


111a-k **112a-k**

R = C_6H_4-4-R' (6 Derivatives), 2-Py, 4-Py, MOM, Et, 1,3-Dioxolan-2-yl

Scheme 34. Reagents: (1) Various Bases, in THF, rt, 24 h

The reaction of the quinoline-3-carboxylate **54** with pentaerythritol tribromide gave the 1,1'-(propane-1,-3-diyl)di(4-quinolone-3-carboxylate) (**113**) presumably *via* intermediates (**33'** and **34'**) (Scheme 35), but the 1-(2,2-bisbromomethyl-3-hydroxypropyl)-4-quinolone-3-carboxylate (Figure 11) was not obtained.[78] The bromination of compound **113** gave the 1,1'-(2-bromo-2-bromomethylpropane-1,3-diyl)di(4-quinol-



Scheme 35. Reagents: (1) Pentaerythritol Tribromide, K_2CO_3 in DMF; (2) Br_2 in AcOH; (3) AcONa in AcOH; (4) 1. KOH in EtOH, 2. HCl; (5) Imidazole in DMF

one-3-carboxylate) (**114**), whose reaction with sodium acetate furnished the 1,1'-(2-acetoxymethyl-propene-1,3-diyl)di(4-quinolone-3-carboxylate) (***Z*-115**). This conversion mechanism is shown in Figure 11, wherein compound **114** would favor the *anti* conformation of two quinolone rings. Subsequent hydrolysis of compound ***Z*-115** with sodium hydroxide gave the 1,1'-(2-hydroxymethyl-propene-1,3-diyl)di(4-quinolone-3-carboxylic acid) (***E*-116**), which would be produced *via* an anion intermediate (**35'**) (Figure 11). The abstraction of the N1-methylene proton with sodium hydroxide and then the π–π stacking between two quinolone rings might promote the transformation of compound ***Z*-115** into compound ***E*-116**. The reaction of compound **114** with imidazole provided the 1,1'-[2-(imidazol-1-

ylmethyl)propene-1,3-diyl]di(4-quinolone-3-carboxylate) (***E*-117**), whose hydrolysis with sodium hydroxide also resulted in the *E*/*Z* conversion to form the 1,1'-[2-(imidazol-1-ylmethyl)propene-1,3-diyl]di(4-quinolone-3-carboxylic acid) (***Z*-118**). The geometry for (***E*-116**, ***E*-117**) and (***Z*-115**, ***Z*-118**) was supported by the NOE spectral data. Biological activity is not found in the above 4-quinolone dimers yet.

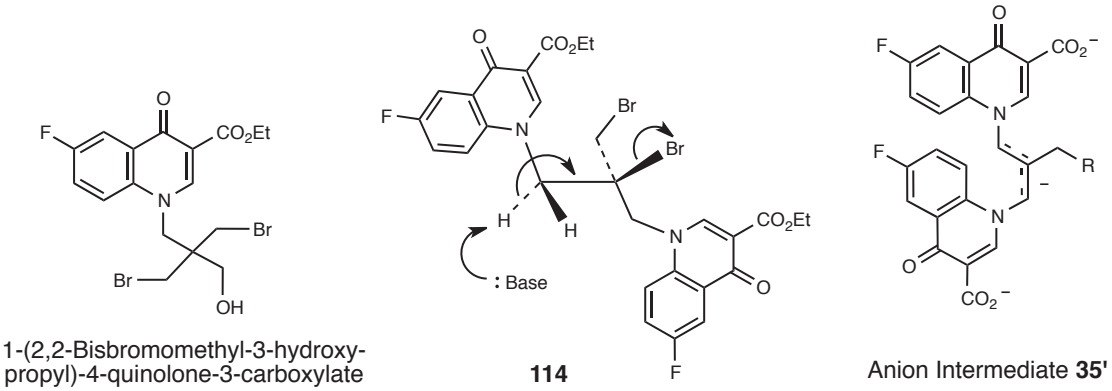
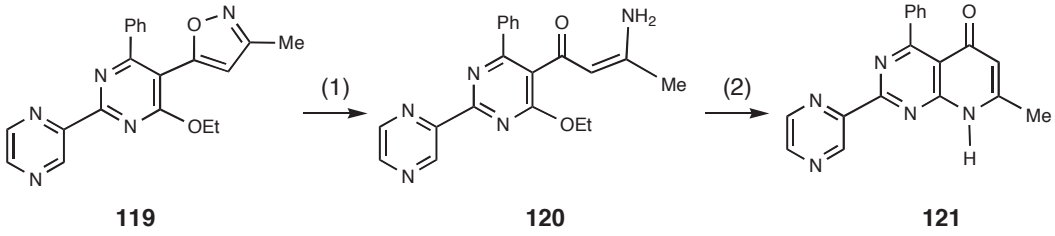


Figure 11

The reductive ring opening of the 5-(isoxazol-5-yl)-2-(pyrazin-2-yl)pyrimidine (**119**) with catalytic amount of $Mo(CO)_6$ gave the 2-(pyrazin-2-yl)pyrimidine (**120**), whose reaction with potassium *t*-butoxide resulted in the cyclization to produce the 1,3,8-triazanaphthalen-5(8*H*)-one (**121**) (Scheme 36).[79]



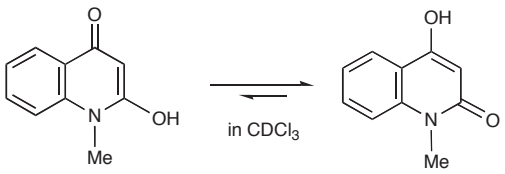
Scheme 36. Reagents: (1) $Mo(CO)_6$, $MeCN/H_2O$, Reflux, 2 h; (2) *t*-BuOK, THF, Reflux, 36 h

6. TAUTOMERISM OF QUINOLONES: TAUTOMERIC STRUCTURES BETWEEN 4-OXO AND 4-HYDROXY FORMS IN SOLUTION

There have been some literatures on the tautomeric structures of the 4-quinolones in solution and solid state, as described below. The tautomerism of the 4-quinolones between the 4-oxo and 4-hydroxy forms depends on the kind of solvents, substituents in the quinoline ring, and/or temperature of the solution, when the N1 of the 4-quinolones is not blocked with the alkyl or other substituent. Several investigations are exhibited below concerning the tautomerism or tautomeric structures of various 4-quinolones in $CDCl_3$, CD_3OD, DMSO-d_6, TFA-d_1, and/or other solvents.

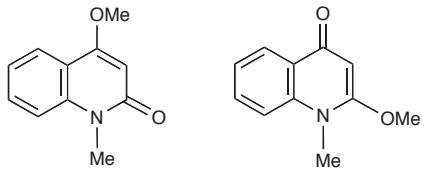
6-1. Quinolones with Enolcarbonyl Function and Related Compounds (in $CDCl_3$, DMSO-d_6)

The tautomeric structure of the hydroxyquinolone (**122**) was assigned as the 4-hydroxy-2-oxo form in $CDCl_3$ from the comparison of the ^{13}C-NMR spectral data among compound **122**, 4-methoxy-1-methyl-2-quinolone (**123**), and 2-methoxy-1-methyl-4-quinolone (**124**) (Scheme 37).[80,81] The C4 and C4a chemical shifts of compound **122** [δ 161.3 (C4), 116.3 (C4a)] are similar to those of 2-oxo compound



2-Hydroxy-4-oxo Form — 4-Hydroxy-2-oxo Form

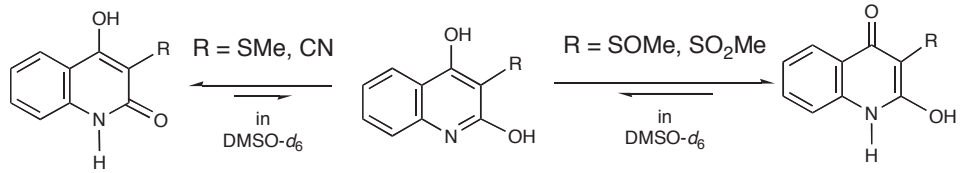
Scheme 37. 4-Hydroxy-2-oxo Tautomer of Compound **122** in $CDCl_3$



123 **124**

Compound	δ C4	C4a	C8a
122	161.3	116.3	140.1
123	162.5	116.3	139.6
124	178.3	124.7	139.6

Solvent: **122** ($CDCl_3$), **123** (DMSO-d_6), **124** ($CDCl_3$)



4-Hydroxy-2-oxo Form **125a,b** — 2,4-Dihydroxy Form **125a-d** — 2-Hydroxy-4-oxo Form **125c,d**

R: **a**-SMe, **b**-CN, **c**-SOMe, **d**-SO_2Me

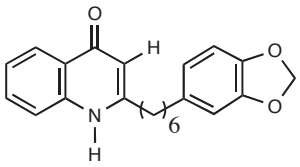
Scheme 38. 4-Hydroxy-2-oxo and 2-Hydroxy-4-oxo Tautomers of Compounds **125a-d** in DMSO-d_6

123 [δ 162.5 (C4), 116.3 (C4a)], while the C4 signal of the 1-methyl-4-quinolone **124** (δ 178.3) was observed in a lower magnetic field. The C8a chemical shifts are similar values among compounds **122**, **123**, and **124** (δ 139.6-140.1).

The tautomeric structures of the 3-substituted 2,4-dihydroxyquinolines (**125a-d**) depended on the C3-substituents (Scheme 38).[80] Namely, the 4-hydroxy-2-oxo form was preferred in DMSO-d_6 when the C3-substituent was the methylsulfanyl or cyano group (**125a,b**), while the 2-hydroxy-4-oxo form was predominant in DMSO-d_6 when the C3-substituent was the methylsulfinyl or methylsulfonyl group (**125c,d**).

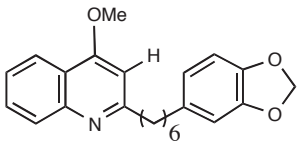
6-2. 2-Substituted 4-Quinolones and Related Compounds (in $CDCl_3$, $CDCl_3$-CD_3OD, DMSO-d_6)

The tautomeric structure of compound **92** was assigned as the 4-oxo form **A** in $CDCl_3$ from the comparison with the C3-H chemical shift of the 4-methoxyquinoline (**126**) (Figure 12).[82] The 2-methoxy derivative (**127**) and 2-methylsulfanyl derivatives (**128** and **129**) were predominant as the 4-oxo form **A** in $CDCl_3$-CD_3OD and as the 4-hydroxy form **B** in DMSO-d_6.[83]



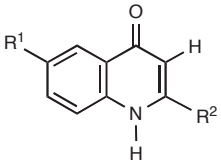
92: 4-Oxo Form **A**

δ C3-H in $CDCl_3$ 6.27



126

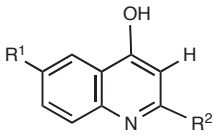
δ C3-H in $CDCl_3$ 6.63



4-Oxo Form **A**

δ C3-H in $CDCl_3$-CD_3OD

127 5.89
128 6.25
129 6.24



4-Hydroxy Form **B**

δ C3-H in DMSO-d_6

127 6.26
128 6.20
129 6.20

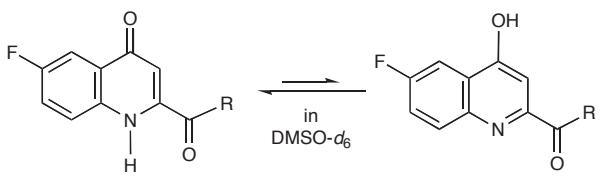
Figure 12. Chemical Shifts of C3-H in Quinoline Ring in $CDCl_3$, $CDCl_3$-CD_3OD, or DMSO-d_6

127: $R^1 = R^2$ = OMe; **128**: R^1 = OMe, R^2 = SMe; **129**: R^1 = H, R^2 = SMe

6-3. 4-Quinolone-2-carboxylate and Related Compounds (in DMSO-d_6)

The 4-quinolone-2-carboxylate **69** and 4-quinolone-2-carbohydrazide **71** were found to exist as the 4-oxo form **A** in DMSO-d_6 (Scheme 39).[58]

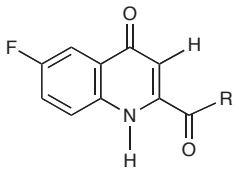
The C4 chemical shifts were similar values between the 4-quinolones **69** and **71** (δ 175.7-178.5 in DMSO-d_6) and the 1-methyl-4-quinolone **124** (Scheme 37) (δ 178.3 in $CDCl_3$),[80,81] other 4-quinolones **93** (Figure 10),[67] **112** (R = Ph) (Scheme 34)[77] (δ 176.6-177.3 in $CDCl_3$). The C4 signals of the 4-methoxyquinolines **70** and **72** (δ 161.8-162.6 in DMSO-d_6) appeared in higher magnetic fields than those of the 4-quinolones.



4-Oxo Form **A** ⇌ (in DMSO-d_6) 4-Hydroxy Form **B**

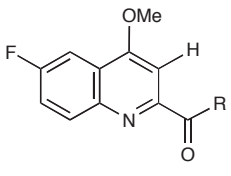
69: R = OMe
71: R = $NHNH_2$

Scheme 39. 4-Oxo Tautomer **A** of Compounds **69** and **71** in DMSO-d_6



69
71

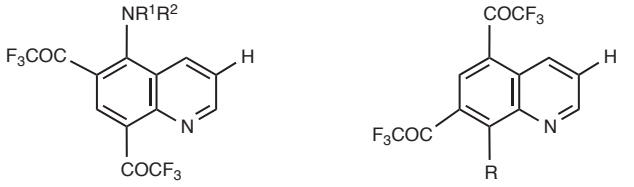
δ in DMSO-d_6
C4: 175.7 - 178.5
C4a: 126.9 - 127.1
C8a: 137.3 - 138.5
C3-H: 6.59 - 6.72



70: R = OMe
72: R = $NHNH_2$

δ in DMSO-d_6
C4: 161.8 - 162.6
C4a: 121.8 - 122.1
C8a: 144.4
C3-H: 7.51- 7.54

On the other hand, the C3-H chemical shifts were close values between the 4-quinolones **69** and **71** (δ 6.59-6.72 in DMSO-d_6) and the 1-methyl-4-quinolones **107** (Scheme 32) (δ 6.29-6.38 in $CDCl_3$),[71] other 4-quinolones **101** (Scheme 30) (δ 5.80-6.25 in $CDCl_3$ or DMSO-d_6),[70] **98** (Scheme 29),[69] **112** (Scheme 34)[77] (δ 6.10-6.47 in $CDCl_3$ or DMSO-d_6). These C3-H signals of the 4-quinolones (δ 5.80-6.72) were observed in higher magnetic fields than those of the 4-methoxyquinolines **70** and **72** (δ 7.51-7.54 in DMSO-d_6), whose values were similar to those of the quinolines **106** (Scheme 32)[71] (δ 7.54-7.85 in $CDCl_3$), 5-substituted 6,8-bistrifluoroacetylquinolines (**130**) (δ 7.23-7.72 in $CDCl_3$ or CD_3CN),[84] and 8-substituted 5,7-bistrifluoroacetylquinolines (**131**) (δ 7.48-7.79 in $CDCl_3$)[85] (Figure 13).



130
6 Derivatives
δ C3-H
in $CDCl_3$ or CD_3CN
7.23 - 7.72

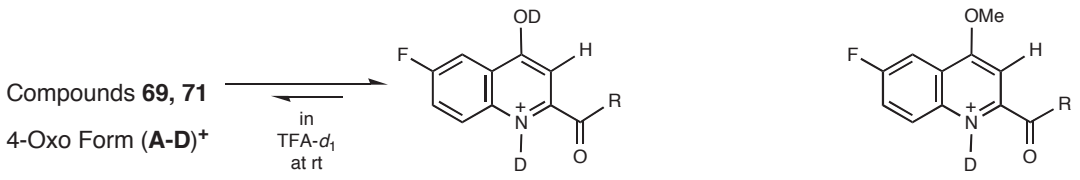
131
R = NR^1R^2, SR^3, OR^4
δ C3-H
in $CDCl_3$
7.48 - 7.79

Figure 13

6-4. 4-Quinolone-2-carboxylate and Related Compounds (in TFA-d_1 at Room Temperature)

Compounds **69** and **71** were found to present as the 4-hydroxy form (**B-D**)$^+$ in TFA-d_1, which was supported by the carbon and proton NMR spectral data (Scheme 40).[58]

The C4, C4a, C8a, and C3-H chemical shifts were similar values between compounds **69, 71** [4-hydroxy form (**B-D**)$^+$] and the 4-methoxyquinolines [(**70, 72**)-**D**]$^+$ in TFA-d_1. Furthermore, the deuteronation site was found to be the quinoline N1 by the comparison of the C2, C4, C7, and C8a chemical shifts in DMSO-d_6 with those in TFA-d_1 (Table 4). Namely, the deuteronation of the quinoline N1 resulted in the



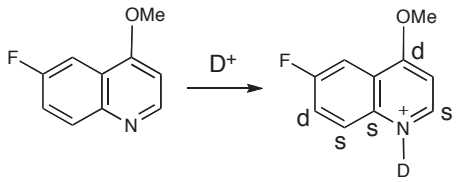
69, 71
4-Hydroxy Form (**B-D**)$^+$
δ in TFA-d_1
C4: 171.3 - 171.4
C4a: 122.9 - 123.0
C8a: 137.3 - 138.5
C3-H: 7.64 - 7.74

(**70-D**)$^+$
(**72-D**)$^+$
δ in TFA-d_1
C4: 172.0 - 172.5
C4a: 123.9 - 124.1
C8a: 135.6 - 136.3
C3-H: 7.60 - 7.70

Scheme 40. 4-Hydroxy Tautomer (**B-D**)$^+$ of Compounds **69** and **71** in TFA-d_1 at rt

Table 4. Eminent Alteration of Carbon Chemical Shifts After Deuteronation of Quinoline N1 for Compounds **70** and **72**

Carbon	δ in DMSO-d_6 **70, 72**	δ in TFA-d_1 **70, 72**	Difference in δ
C2	148.0, 151.4	141.4, 141.8	6.6 - 9.6 (s)
C4	161.8, 162.6	172.0, 172.5	8.2 - 9.9 (d)
C7	120.4, 120.8	127.5, 128.2	7.1 - 7.4 (d)
C8	132.3, 132.2	123.6, 124.3	7.9 - 8.7 (s)
C8a	144.4, 144.4	135.6, 136.3	8.1 - 8.8 (s)



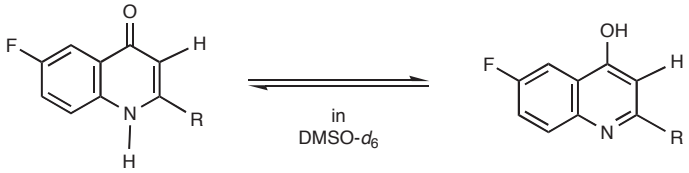
Abbreviations (s) and (d) mean (shielded) and (deshielded), respectively.

shielding of the C2, C8, and C8a and the deshielding of the C4 and C7, wherein the differences were 6.6 or more in δ values. Similar shielding and deshielding were confirmed in pyridinium salt,[86] 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines (Figure 8),[40] and pyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones[41] (Figure 8).

6-5. 4-Quinolone-2-carbohydrazide Derivatives (in DMSO-d_6)

The 4-quinolone-2-carbohydrazide derivatives **102** (Scheme 31) and (**132**) showed the tautomeric equilibria between the 4-oxo **A** and 4-hydroxy **B** forms in DMSO-d_6 (Scheme 41).[58]

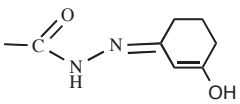
Two kinds of the C3-H signals were observed in compounds **102** and **132** (4-oxo form **A**: δ 6.69-6.76; 4-hydroxy form **B**: δ 7.48-7.49), wherein the 4-oxo tautomer **A** was predominant (68-81%).



4-Oxo Form **A** 4-Hydroxy Form **B**

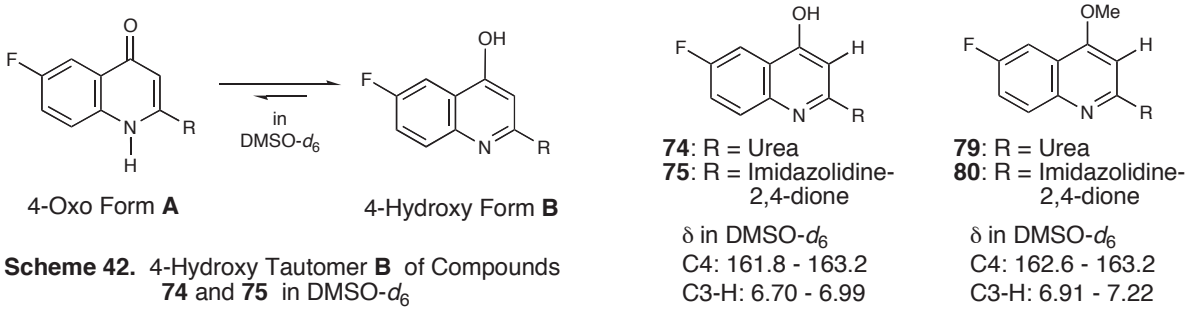
Scheme 41. Tautomeric Equilibria of Compounds **102** and **132** between 4-Oxo **A** and 4-Hydroxy **B** Forms in DMSO-d_6

Compound	Chemical Shift for C3-H (δ) 4-Oxo Form **A**	4-Hydroxy Form **B**	Tautomer Ratio (%) 4-Oxo Form **A**	4-Hydroxy Form **B**
102	6.76	7.49	81	19
132	6.69	7.48	68	32

102: R = CONHNHC(S)NHMe; **132**: R = 

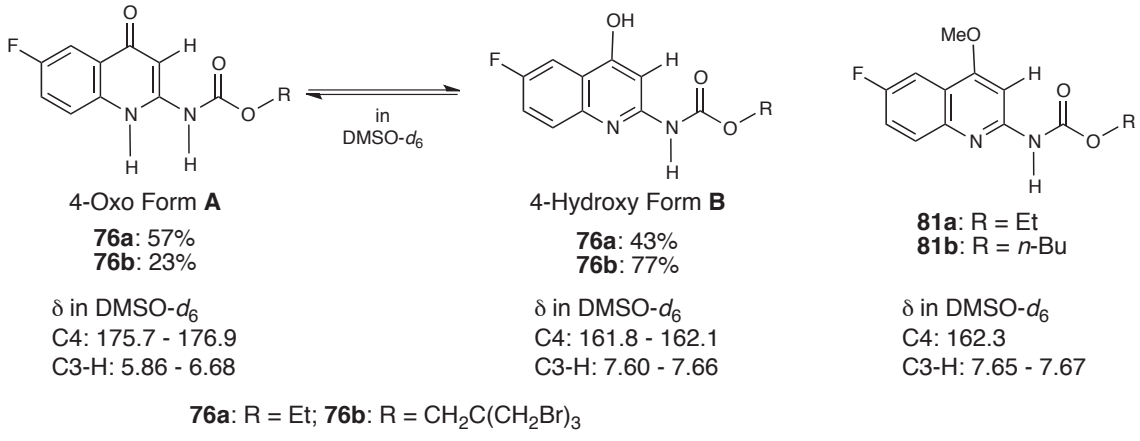
6-6. 4-Quinolones and Related Compounds with Nitrogen Function at 2-Position (in DMSO-d_6)

The 1-aryl-3-(quinolin-2-yl)ureas **74** and 1-aryl-3-(quinolin-2-yl)imidazolidine-2,4-diones **75** (Scheme 24) were found to exist as the 4-hydroxyquinoline form **B** in DMSO-d_6 (Scheme 42).[59] Namely, the C4



Scheme 42. 4-Hydroxy Tautomer **B** of Compounds **74** and **75** in DMSO-d_6

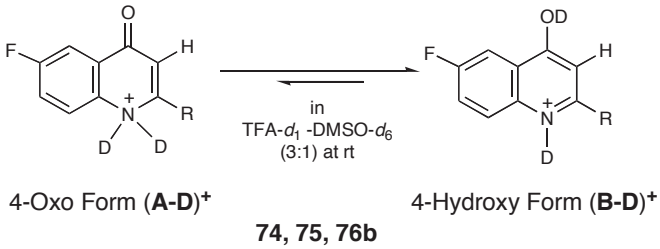
and C3-H chemical shifts were similar values between compounds **74,75** [δ 161.8-163.2 (C4), 6.70-6.99 (C3-H)] and the corresponding 4-methoxyquinolines **79,80** [δ 162.6-163.2 (C4), 6.91-7.22 (C3-H)]. However, the *N*-(quinolin-2-yl)carbamates **76a,b** (Scheme 24) showed the tautomeric equilibria between the 4-quinolone **A** and 4-hydroxyquinoline **B** forms in DMSO-d_6 (Scheme 43).[59] Two kinds of the C4 and C3-H signals were confirmed and assigned to the 4-quinolone tautomer **A** [δ 175.7-176.9 (C4), 5.86-6.68 (C3-H)] and the 4-hydroxyquinoline tautomer **B** [δ 161.8-162.1 (C4), 7.60-7.66 (C3-H)]. The C4 and C3-H chemical shifts for the 4-hydroxy form **B** of compounds **76a,b** were similar to those of the corresponding 4-methoxyquinolines **81a,b** (Scheme 25) [δ 162.3 (C4), 7.65-7.67 (C3-H)] (Scheme 43).



Scheme 43. Tautomeric Equilibria of 4-Quinolones **76a,b** between 4-Oxo **A** and 4-Hydroxy **B** Forms in DMSO-d_6

6-7. 4-Quinolones and Related Compounds with Nitrogen Function at 2-Position [in TFA-d_1-DMSO-d_6 (3:1) at Room Temperature]

The 1-aryl-3-(quinolin-2-yl)ureas **74**, 1-aryl-3-(quinolin-2-yl)imidazolidine-2,4-diones **75**, and *N*-(quinolin-2-yl)carbamate **76b** (Scheme 24) were found to present as the 4-hydroxyquinoline form $(\mathbf{B\text{-}D})^+$ in TFA-d_1–DMSO-d_6 (3:1) (Scheme 44).[59,87] That is, the C3-H chemical shifts were similar values between compounds $[(\mathbf{74, 75, 76})\text{-}(\mathbf{B\text{-}D})]^+$ and the corresponding 4-methoxyquinolines $[(\mathbf{79, 80, 81})\text{-}\mathbf{D}]^+$ (Table 5). The C4 chemical shifts were also close values between compounds $[(\mathbf{74, 75, 76})\text{-}(\mathbf{B\text{-}D})]^+$ (δ 171.6-174.9)

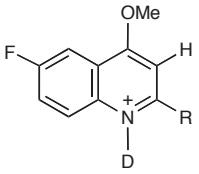


Scheme 44. 4-Hydroxy Tautomer (**B-D**)$^+$ of 4-Quinolones **74, 75, and 76b** in TFA-d_1-DMSO-d_6 (3:1) at rt

74,79: R = Urea
75,80: R = Imidazolidine -2,4-dione
76,81: R = Carbamate

Table 5. Comparison of C3-H Chemical Sfifts between Compounds **74-76** and **79-81** at rt.

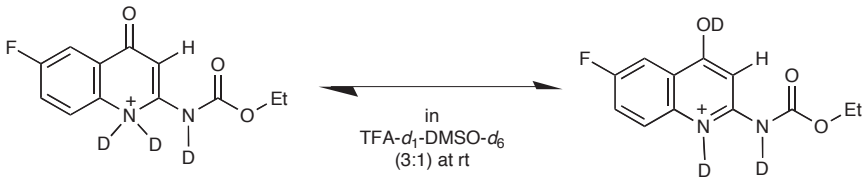
δ C3-H in TFA-d_1-DMSO-d_6 (3:1)			
74	6.42 -6.55	**79**	6.27 - 6.33
75	7.91 - 7.97	**80**	7.93 - 7.98
76	6.55 - 6.64	**81**	6.32 - 6.46



[(**79, 80, 81**)-**D**]$^+$

and the corresponding 4-methoxyquinolines [(**79, 80, 81**)-**D**]$^+$ (δ 172.3-174.4), wherein the C4 chemical shifts underwent the deshielding (about 10-11 in δ values) because of the deuteronation to the quinoline N1, as described in the section **6-4** (Table 4).

On the contrary, the ethyl *N*-(quinolin-2-yl)carbamate **76a** (Scheme 24) exhibited the tautomeric equilibria between the 4-oxo (**A-D**)$^+$ and 4-hydroxy (**B-D**)$^+$ forms in TFA-d_1–DMSO-d_6 (3:1) (Scheme 45).[87] Two kinds of the C3-H signals of compound **76a** were confirmed and assigned to the 4-quinolone tautomer (**A-D**)$^+$ (δ 7.52) and the 4-hydroxyquinoline tautomer (**B-D**)$^+$ (δ 6.55). The chemical shift of the (**B-D**)$^+$ (δ 6.55) is similar to the values of compounds **76b** and **81** in Table 5 (δ 6.32-6.64).

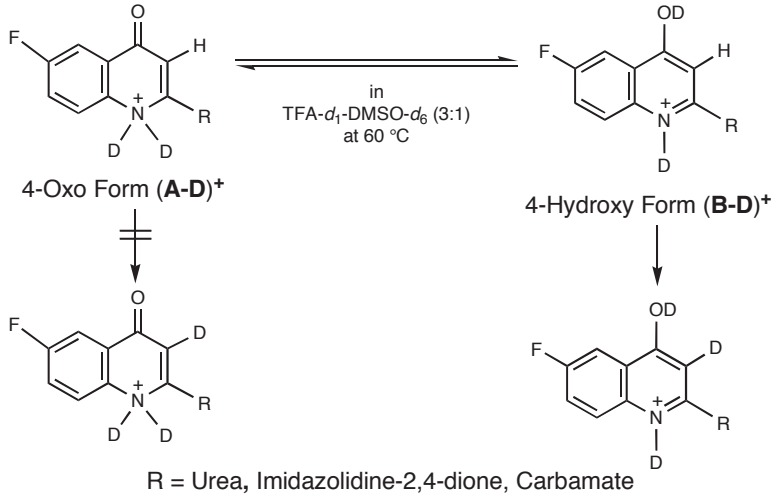


δ C3-H in TFA-d_1-DMSO-d_6 (3:1)			
(**A-D**)$^+$	7.52	(**B-D**)$^+$	6.55

Scheme 45. Tautomeric Equilibria of 4-Quinolone **76a** between 4-Oxo (**A-D**)$^+$ and 4-Hydroxy (**B-D**)$^+$ Forms in TFA-d_1-DMSO-d_6 (3:1) at rt

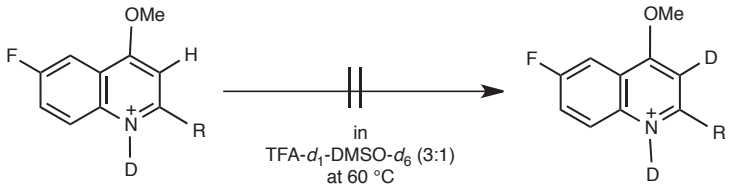
6-8. D-H Exchange for C3-H of 4-Quinolones with Nitrogen Function at 2-Position [in TFA-d_1-DMSO-d_6 (3:1) at 60 °C]

The D-H exchange of the C3-H was observed for compounds **74-76** with the C2-nitrogen function in TFA-d_1–DMSO-d_6 (3:1) at 60 °C (Scheme 46), whereas this D-H exchange did not take place in the 4-quinolone-2-carbonyl compounds **69,71** and 4-methoxyquinolines **70,72,79-81** (Scheme 47).[87] More-



Scheme 46

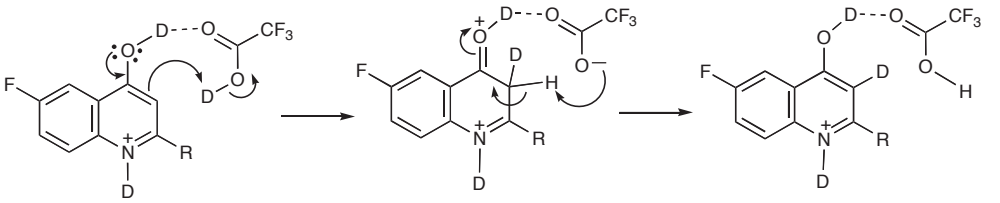
over, the D-H exchange was clarified to occur *via* the 4-hydroxy tautomer (**B-D**)$^+$, but not *via* the 4-oxo tautomer (**A-D**)$^+$, from the data on the tautomerism of the ethyl *N*-(quinolin-2-yl)carbamate **76a** (Scheme 46). Namely, the integral intensity for the C3-H signal of the 4-hydroxy tautomer (**B-D**)$^+$ (**76a**: δ 6.55) diminished with the laps of time, while the integral intensity for the C3-H signal of the 4-oxo tautomer (**A-D**)$^+$ (**76a**: δ 7.52) remained unchanged. The D-H exchange rate of the C3-H was faster in the stronger electron-donating 2-substituent than in the weaker electron-donating 2-substituent, that is, in the order of urea > carbamate > imidazolidinedione. The electron-donating nature of the C2-substituent to the C3 would augment the electron density of the C3, which seemed to be an important factor for the D-H exchange of the C3-H.



Scheme 47

6-9. Postulated D-H Exchange Mechanism for C3-H of 4-Quinolones with Nitrogen Function at 2-Position [in TFA-d_1-DMSO-d_6 (3:1) at 60 °C]

The postulated D-H exchange mechanism of the C3-H in the quinoline ring is shown in Scheme 48, wherein the crucial step would be the hydrogen bonding between the C4-OD group of the quinoline ring and the carbonyl group of deuteriotrifluoroacetic acid.[87] Such a convenient mechanism for the cyclic D-H exchange of the C3-H lacks in the 4-methoxyquinolines [(**79-81**)-**D**]$^+$ and the 4-oxo tautomer (**A-D**)$^+$ (Figure 14).



Scheme 48. Postulated Mechanism of D-H Exchange for C3-H of Compounds **74, 75,** and **76** in TFA-d_1-DMSO-d_6 (3:1) at 60 °C

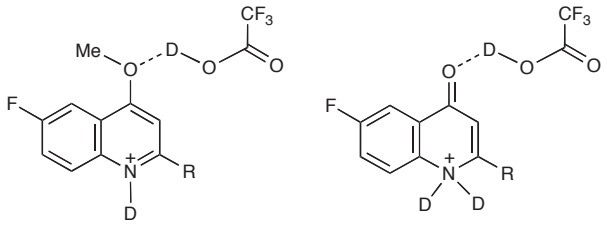


Figure 14

7. POSTSCRIPT

As described above, the synthesis and biological activities of numerous 4-quinolones and related compounds have been reported up to date in the journal, patent, and monograph literatures. Some of these literatures are introduced in this review, whose volume is however inadequate for the quinolone researchers engaged in the development of a new synthetic methodology and/or clinically available medicaments. The computer research on the synthesis and biological activities of 4-quinolones manifests the presence of more than hundred review articles in 2000-2013, and the utilization of the suitable articles is recommended to the quinolone investigators for the aid of various studies. For instance, the following publications have appeared as the review articles except for the category of antibacterial new quinolones: skeletal construction, modification, and biological activities of 4-quinolones,[88] synthesis and biological activities of 4-quinolone-metal complexes,[89,90] synthesis, transformation, structural properties, and biological activities of 2-aryl-4-quinolones.[91] At last, this review describes the tautomeric equilibria (tautomeric structures) between the 4-oxo and 4-hydroxy forms in solution together with their proton and carbon NMR spectral data indicating the crucial and diagnostic chemical shifts. The authors will be delightful if these spectral data are useful and available for the future investigations of the quinolone researchers.

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