HETEROCYCLES, Vol. 58, 2002, pp. 359-369, Received, 25th March, 2002

# QUINOLONE ANALOGUES 5.[1-4] SYNTHESIS OF 1-METHYL-PYRIDAZINO[3,4-*b*]QUINOXALIN-4(1*H*)-ONES

Yoshihisa Kurasawa,[a,*] Jun Takizawa,[a] Yuka Maesaki,[a] Ayaka Kawase,[a] Yoshihisa Okamoto,[b] and Ho Sik Kim[c]

[a]School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108-8641, Japan
[b]Center for Natural Sciences, Kitasato University, Kitasato, Sagamihara, Kanagawa 228-8555, Japan
[c]Department of Chemistry, Catholic University of Taegu, Gyongsan 712-702, Korea

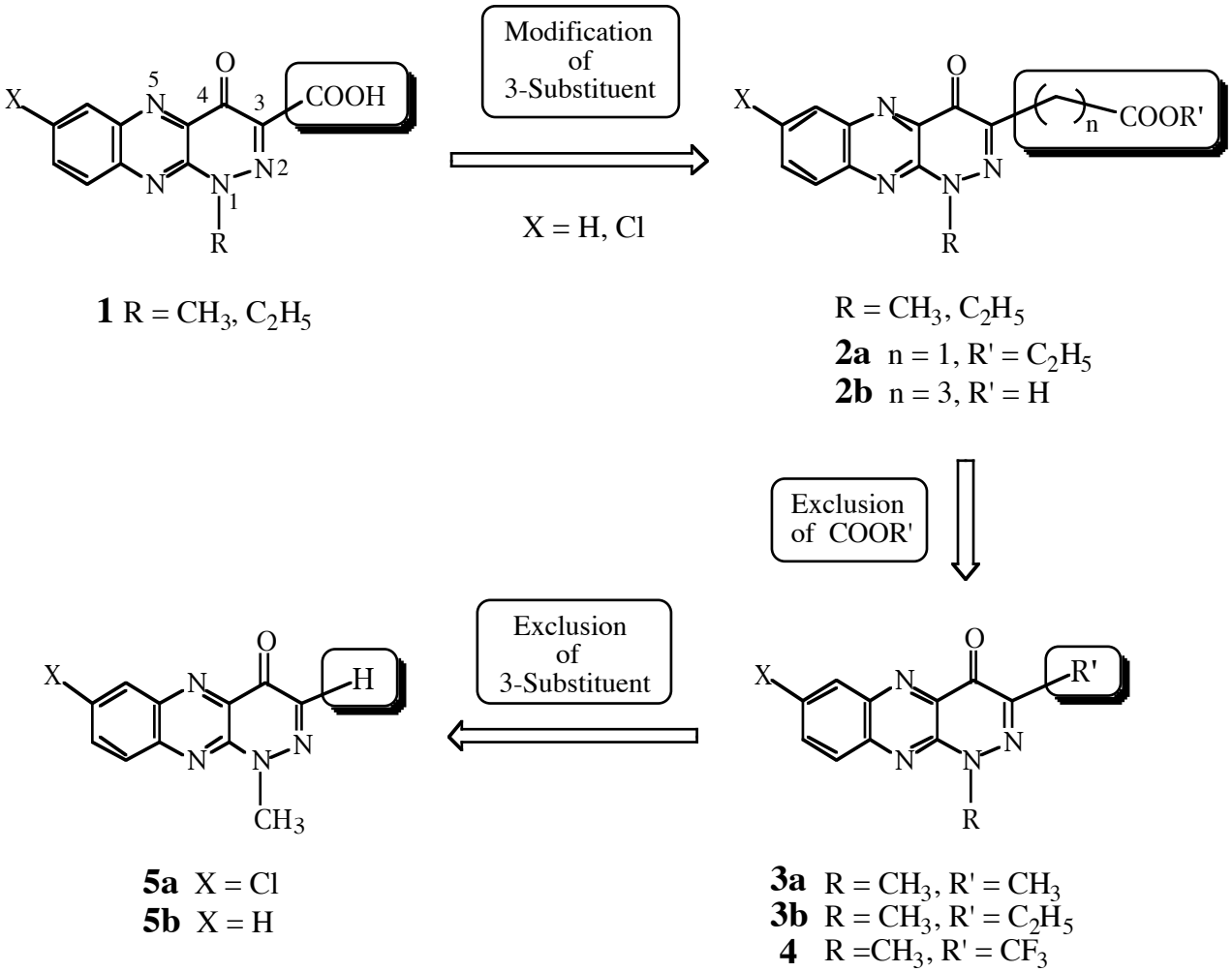
**Abstract** - The reaction of the quinoxaline *N*-oxide (**8a**) with diethyl ethoxymethylenemalonate gave the 1,4-dihydropyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate (**10c**), whose reaction with a base afforded the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylate (**6a**). The oxidation of compound (**6a**) with nitrous acid provided the 1,4-dihydro-4-hydroxypyridazino[3,4-*b*]quinoxaline-4-carboxylate (**7**), whose reaction with potassium hydroxide gave 7-chloro-1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**5a**). On the other hand, the reaction of the quinoxaline *N*-oxide (**8b**) with acetylacetaldehyde dimethyl acetal afforded 4-acetyl-1,5-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline (**6b**), whose oxidation with selenium dioxide provided 1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**5b**).

## INTRODUCTION

In a previous paper,[1] we reported the synthesis of the 1-alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids (**1**) as candidates of antibacterial quinolone analogues (Scheme 1), and compounds (**1**) were found to have weak antibacterial activities from our screening data. Then, we modified the 3-substituent of compounds (**1**) and synthesized the (1-alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)acetates (**2a**) and 4-(1-alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]-quinoxalin-3-yl)butanoic acids (**2b**) (Scheme 1) in order to improve the antibacterial activities.[2]
However, this modification was not successful in the improvement of antibacterial activities, and hence we further converted the structure of compounds (**2a,b**) and synthesized the 1,3-dialkylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**3a,b**) (Scheme 1), which had not carboxyl or carboxylate function in the 3-substituent.[3] As the result, compounds (**3a,b**) were shown to possess better antibacterial activities than

those of compounds (**1** and **2a,b**).[3] In addition, compounds (**3a,b**) were clarified to have antifungal activities.[5,6] The 3-trifluoromethyl homologues 1-methyl-3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**4**)[4] (Scheme 1) also exhibited the antibacterial and antifungal activities[6] in similar extent to those of the 1,3-dimethylpyridazino[3,4-*b*]quinoxalin-4-(1*H*)-ones (**3a**).[6] In the present investigation, we have transformed the structure of compounds (**3a,b** and **4**) and synthesized the 1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**5a,b**) (Scheme 1), which were the 3-H homologues. Since compounds (**3a,b** and **4**) without the carboxyl group at the 3-position showed antifungal activities, compounds (**5a,b**) without the carboxyl group at the 3-position were also expected to exhibit some antifungal activities.[7-9]

**Scheme 1**




**1** R = $CH_3$, $C_2H_5$

R = $CH_3$, $C_2H_5$
**2a** n = 1, R' = $C_2H_5$
**2b** n = 3, R' = H

**5a** X = Cl
**5b** X = H

**3a** R = $CH_3$, R' = $CH_3$
**3b** R = $CH_3$, R' = $C_2H_5$
**4** R = $CH_3$, R' = $CF_3$

**METHODS FOR THE SYNTHESIS OF COMPOUNDS (5a,b)**

In order to synthesize the 3-H homologues (**5a,b**), the decarboxylation of the 3-carboxylic acid homologues (**1**) would be convenient, but this attempt was not successful. Accordingly, we undertook methods shown in Scheme 2. Compound (**5a**) was synthesized *via* oxidation of compound (**6a**) with nitrous acid and then treatment of compound (**7**) with a base (route A), while compound (**5b**) was produced *via* oxidation of compound (**6b**) with selenium dioxide (route B). Compounds (**1**[1] and **4**[4]) and compounds (**2a,b**[2] and **3a,b**[3]) were also synthesized by the methods of the routes A and B, respectively.

**SYNTHESIS OF COMPOUND (5a)**

In a previous paper,[10] we reported that the reaction of the quinoxaline *N*-oxide (**8a**) with ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile gave the quinoxaline *N*-oxide (**9a** or **9b**), respectively (Chart 1). Moreover, compound (**9a**) was cyclized into the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carbonitrile (**6c**)[4,10-14] under a basic condition, while the quinoxaline *N*-oxide (**9b**) was not cyclized under the same condition. However, we found in the present investigation that the quinoxaline *N*-oxides (**9a,b**) were easily cyclized into the 1,4-dihydropyridazino[3,4-*b*]quinoxalines (**10a,b**), respectively, under reflux in acetic acid (Scheme 3). This cyclization method enabled us to synthesize the quinolone analogue (**5a**) as shown in Scheme 4.

**Scheme 2**

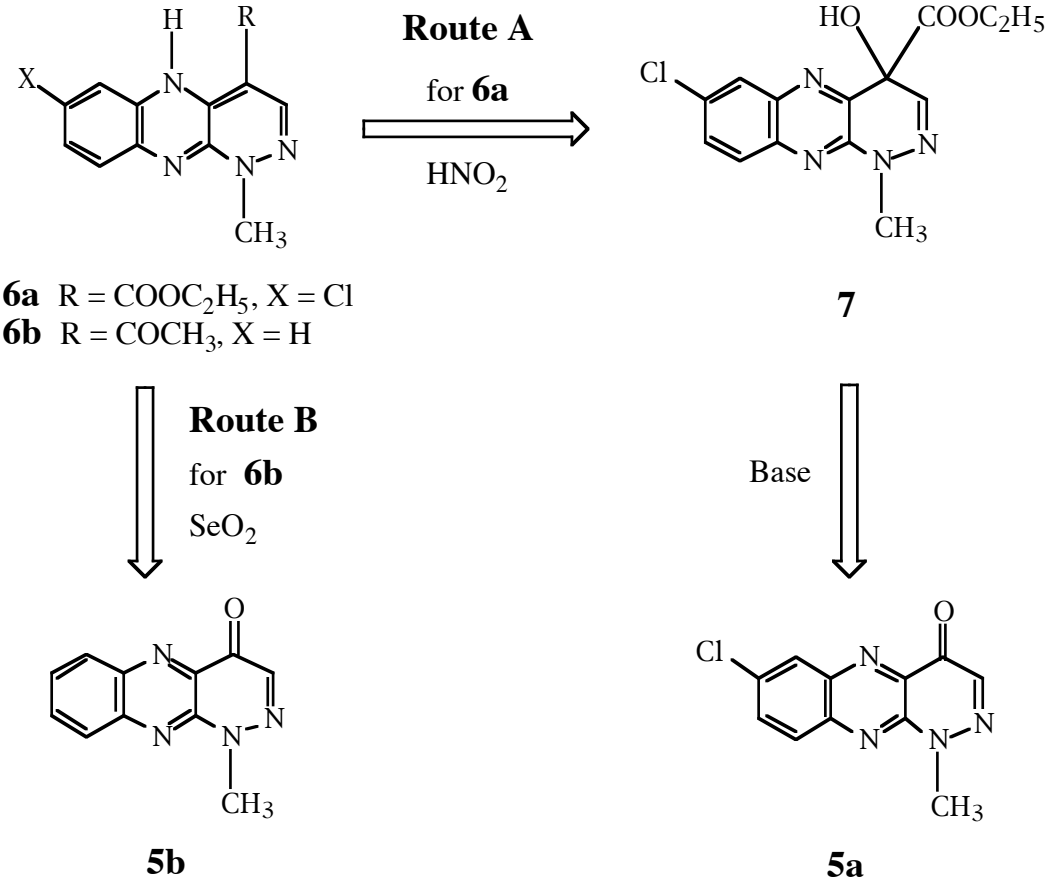
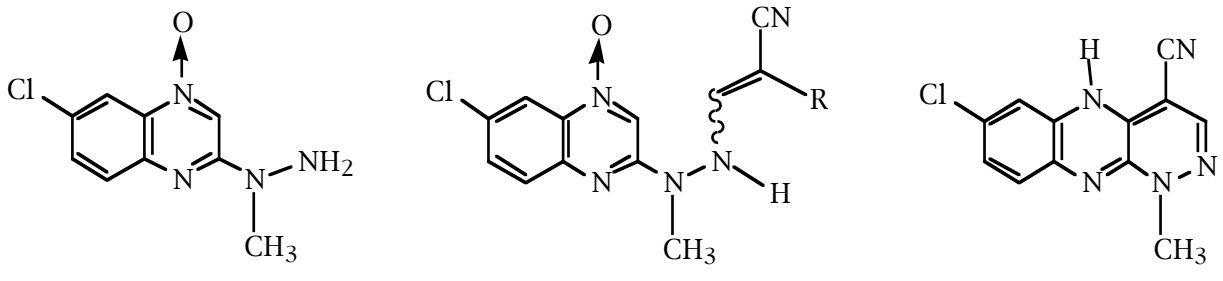



**Chart 1**



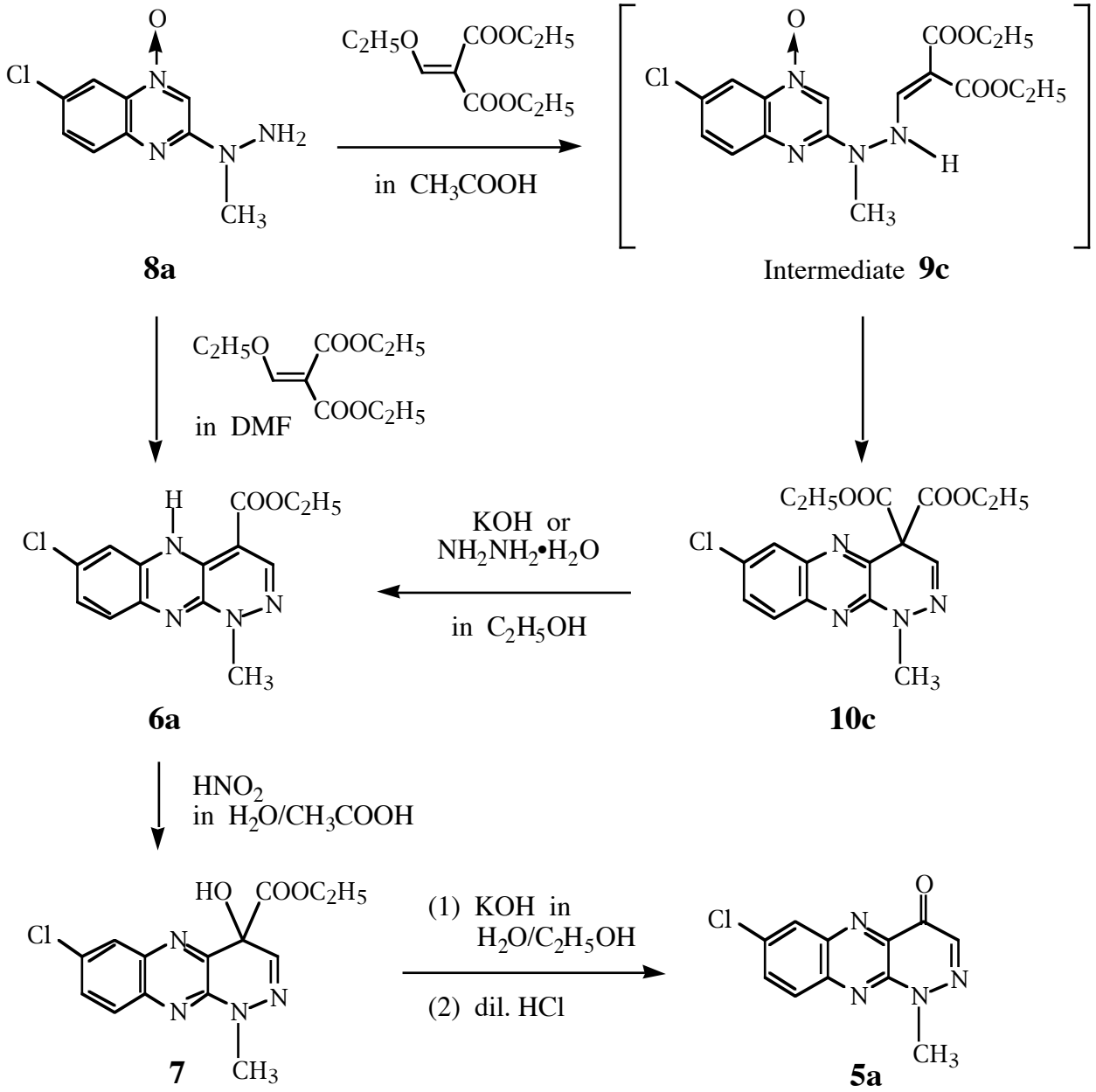
The reaction of the quinoxaline *N*-oxide (**8a**) with diethyl ethoxymethylenemalonate in acetic acid gave

**Scheme 3**


**9a** R = $COOC_2H_5$
**9b** R = CN

**10a** R = $COOC_2H_5$
**10b** R = CN

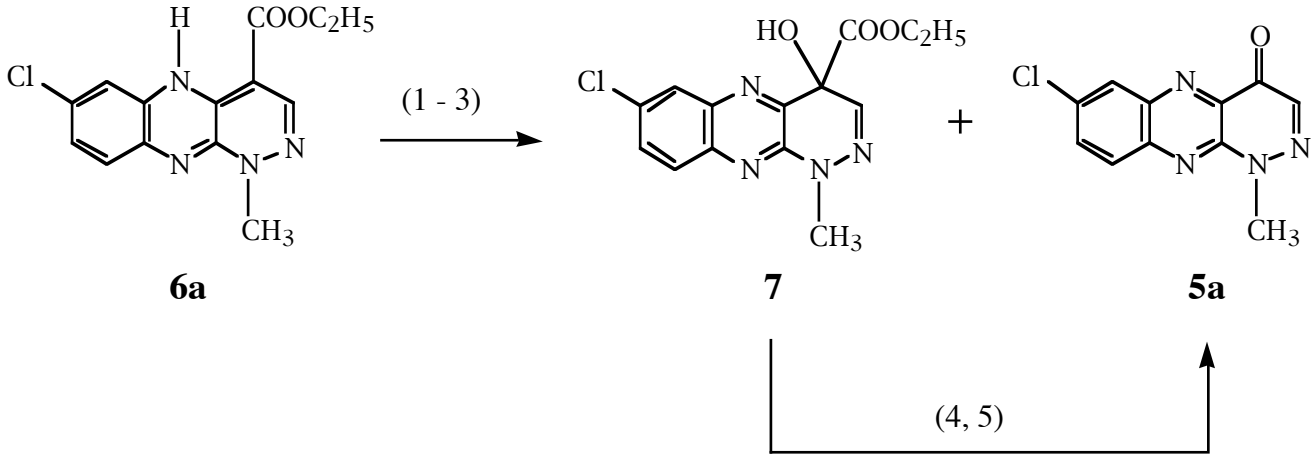
**Scheme 4**



the1,4-dihydropyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate (**10c**) presumably *via* an intermediate (**9c**) (Scheme 4), whose reaction with potassium hydroxide or hydrazine hydrate resulted in hydrolysis and decarboxylation to afford the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylate (**6a**).[4,10-14] Compound (**6a**) was also obtained directly by the reaction of the quinoxaline *N*-oxide (**8a**) with diethyl ethoxymethylenemalonate in *N,N*-dimethylformamide. The yield of compound (**6a**) was better in the direct synthesis (**8a**→**6a**, 87%) than in the synthesis *via* compound (**10c**) (**8a**→**10c**→**6a**, 71%). The reaction of compound (**6a**) with nitrous acid effected oxidation[1,2,4] to provide the 1,4-dihydro-4-hydroxypyridazino[3,4-*b*]quinoxaline-4-carboxylate (**7**), whose reaction with potassium hydroxide resulted in elimination of formate[1,2] to give the quinolone analogue (**5a**). In the Scheme 4, compound (**7**) was obtained in low yield (44%) after recrystallization,[15] which led to a low yield of compound (**5a**). Accordingly, we devised the procedure to improve the yield of compound (**5a**) from compound (**6a**) as shown in Scheme 5.

The oxidation of compound (**6a**) with nitrous acid, treatment with potassium hydroxide, and then neutralization with hydrochloric acid were carried out in the one-pot procedure to afford compound (**7**) (59%) and compound (**5a**) (35%). Further reaction of compound (**7**) with potassium hydroxide provided compound (**5a**) (73%). After all, compound (**5a**) was obtained in 77% yield from compound (**6a**) by the procedure in Scheme 5.

**Scheme 5**




**6a** **7** **5a**

(1) $HNO_2$ in $H_2O/CH_3COOH$, (2) KOH in $H_2O/C_2H_5OH$,
(3) dil. HCl, (4) KOH in $H_2O/C_2H_5OH$, (5) dil. HCl

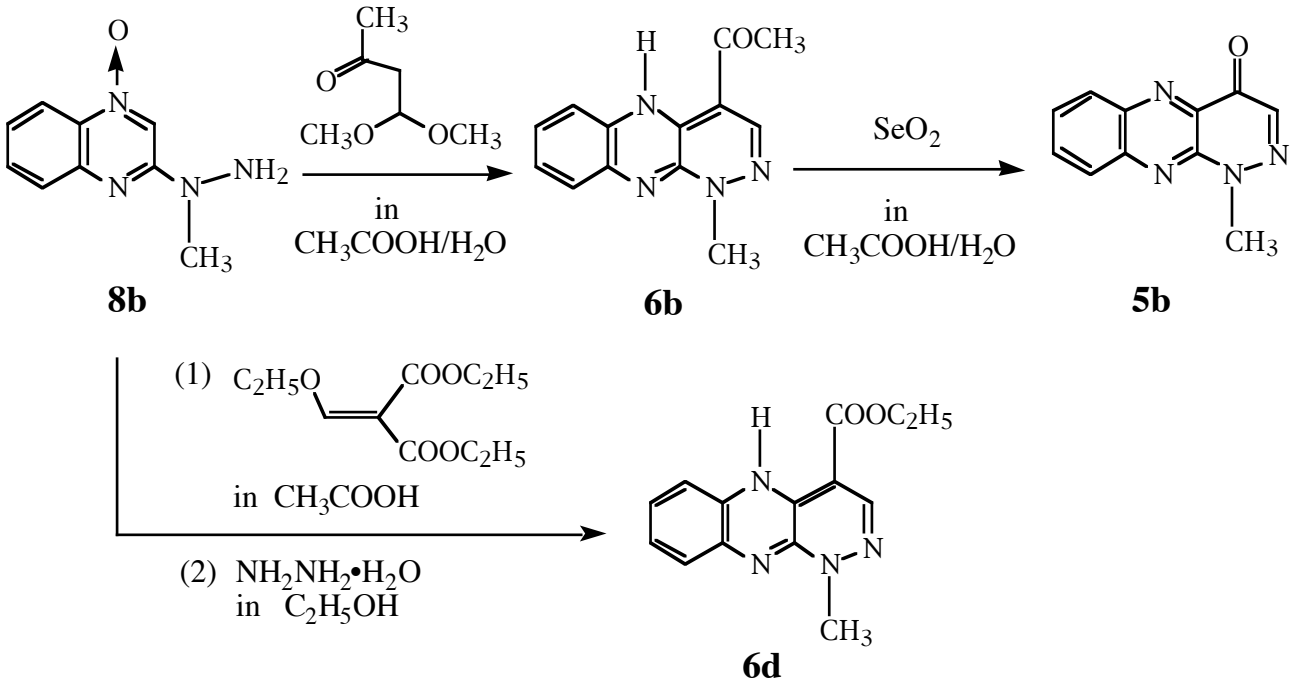
**SYNTHESIS OF COMPOUND (5b)**

The route A method shown in Scheme 2 was not suitable for the synthesis of compound (**5b**). Consequently, we adopted the route B method exhibited in Scheme 2, as described below.

The reaction of compound (**8b**) with diethyl ethoxymethylenemalonate and subsequent reaction with hydrazine hydrate provided the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylate (**6d**) (Scheme 6). The oxidation of compound (**6d**) with nitrous acid did not bring about favorable result for the synthesis of compound (**5b**).

The reaction of the quinoxaline *N*-oxide (**8b**) with acetylacetaldehyde dimethyl acetal gave 4-acetyl-1,5-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline (**6b**),[4,10-14] whose oxidation with selenium dioxide afforded 1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**5b**) (Scheme 6). Compounds (**6b** and **5b**) were obtained in low yields, and hence some alternate routes should be devised in order to improve the yields of compounds (**6b** and **5b**).

**Scheme 6**




## SCREENING DATA

Compounds (**5a,b**) showed antifungal activities *in vitro* against *Trichophyton mentagrophytes* (*T. m.*) and *Trichophyton rubrum* (*T. r.*). The minimum inhibitory concentrations of compound (**5a**) were 1 and 0.5 ppm against *T. m.* and *T. r.*, and those of compound (**5b**) were 1 ppm against *T. m.* and *T. r.*, respectively.[6]

## EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The IR spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrophotometer. The NMR spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The MS spectra were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

### Ethyl 7-Chloro-4-cyano-1,4-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline-4-carboxyl-ate (10a)

A solution of compound (**9a**) (2 g) in acetic acid (50 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* afforded yellow crystals of compound (**10a**) (1.48 g, 78%). Recrystallization from

*N,N*-dimethylformamide/ethanol/water gave yellow needles, mp 162-163 °C; IR: ν $cm^{-1}$ 2210, 2185, 1750; MS: m/z 329 ($M^+$), 331 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 8.11 (d, J = 2.0 Hz, 1H, 6-H), 7.90 (d, J = 9.0 Hz, 1H, 9-H), 7.82 (dd, J = 2.0, 9.0 Hz, 1H, 8-H), 7.32 (s, 1H, 3-H), 4.26 (dq, J = 7.0, 10.0 Hz, 1H, methylene H), 4.22 (dq, J = 7.0, 10.0 Hz, 1H, methylene H), 3.61 (s, 3H, N-$CH_3$), 1.14 (dd, J = 7.0, 7.0 Hz, 3H, $CH_3$). *Anal.* Calcd for $C_{15}H_{12}N_5O_2Cl$: C, 54.64; H, 3.67; N, 21.24. Found: C, 54.48; H, 3.71; N, 21.52.

**7-Chloro-1,4-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline-4,4-dicarbonitrile (10b)**

A solution of compound (**9b**) (2.5 g) in acetic acid (50 mL) was refluxed for 2 h to precipitate brick red needles of compound (**10b**), which were collected by filtration and then washed with ethanol/*n*-hexane to give an analytically pure sample (1.09 g, 46%), mp 294-295 °C; IR: ν $cm^{-1}$ 3090, 2200, 2190, 2170, 1590; MS: m/z 282 ($M^+$), 284 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide ): 10.38 (s, 1H, 3-H), 8.28 (d, J = 2.0 Hz, 1H, 6-H), 7.70 (d, J = 9.0 Hz, 1H, 9-H), 7.54 (dd, J = 2.0, 9.0 Hz, 1H, 8-H), 4.45 (s, 3H, N-$CH_3$). *Anal.* Calcd for $C_{13}H_7N_6Cl$: C, 55.23; H, 2.50; N, 29.73. Found: C, 55.18; H, 2.58; N, 29.43.

**Diethyl 7-Chloro-1,4-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate (10c)**

A solution of compound (**8a**) (10 g, 44.5 mmol) and diethyl ethoxymethylenemalonate (12.5 g, 57.9 mmol) in acetic acid (200 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* gave yellow crystals of compound (**10c**), which were triturated with ethanol/water and collected by filtration (13.66 g, 81%). Recrystallization from ethanol gave yellow needles, mp 105-106 °C; IR: ν $cm^{-1}$ 2980, 2930, 2900, 1760, 1730, 1605; MS: m/z 376 ($M^+$), 378 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide ): 8.03 (d, J = 2.5 Hz, 1H, 6-H), 7.90 (d, J = 9.0 Hz, 1H, 9-H), 7.78 (dd, J = 2.5, 9.0 Hz, 1H, 8-H), 7.32 (s, 1H, 3-H), 4.24 (q, J = 7.0 Hz, 4H, $CH_2$), 3.59 (s, 3H, N-$CH_3$), 1.19 (t, J = 7.0 Hz, 6H, $CH_3$). *Anal.* Calcd for $C_{17}H_{17}N_4O_4Cl$: C, 54.19; H, 4.55; N, 14.87. Found: C, 54.06; H, 4.63; N, 14.93.

**Ethyl 7-Chloro-1,5-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline-4-carboxylate (6a)**

Method 1. A solution of compound (**10c**) (10 g, 26.6 mmol) and 100% hydrazine hydrate (3.32 g, 66.4 mmol) in ethanol (300 mL) was refluxed for 1 h to precipitate orange needles of compound (**6a**), which were collected by filtration to give an analytically pure sample (7.02 g, 87%).

Method 2. A solution of compound (**10c**) (10 g, 26.6 mmol) and potassium hydroxide (1 g, 17.9 mmol) in ethanol (300 mL)/water (30 mL) was refluxed for 2 h. After the solution was cooled to rt, 1*N* hydrochloric acid (18 mL) and acetic acid (5 mL) were added to the solution. Evaporation of the solvent *in vacuo* gave orange crystals of compound (**6a**), which were triturated with water and collected by filtration (6.95 g, 86%). Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded orange needles.

Method 3. A solution of compound (**8a**) (3 g, 13.4 mmol) and diethyl ethoxymethylenemalonate (4.34 g, 20.1 mmol) in *N,N*-dimethylformamide (50 mL) was refluxed for 1 h. The solution was allowed to stand overnight at rt to precipitate orange needles of compound (**6a**), which were collected by filtration

and then washed with ethanol to provide an analytically pure sample (1.70 g, 42%).
Compound (**6a**) had mp 215-216 °C; IR: ν $cm^{-1}$ 1655, 1615; MS: m/z 304 ($M^+$), 306 ($M^+$ + 2); NMR (deuteriodimethyl sulfoxide ): 7.13 (s, 1H, 3-H), 7.07 (s, 1H, 6-H), 6.75 (d, J = 7.0 Hz, 1H, aromatic H), 6.63 (d, J = 7.0 Hz, 1H, aromatic H), 4.17 (q, J = 7.0 Hz, 2H, $CH_2$), 3.11 (s, 3H, N-$CH_3$), 1.23 (t, J = 7.0 Hz, 3H, $CH_3$). *Anal.* Calcd for $C_{13}H_{15}N_4O_3Cl$: C, 55.18; H, 4.30; N, 11.63. Found: C, 55.05; H, 4.28; N, 11.75.

**Ethyl 7-Chloro-1,4-dihydro-4-hydroxy-1-methylpyridazino[3,4-*b*]quinoxaline-4-carboxylate (7)**
A solution of sodium nitrite (1.70 g, 24.6 mmol) in water (25 mL) was added to a suspension of compound (**6a**) (5 g, 16.4 mmol) in acetic acid (200 mL)/water (25 mL) with stirring in an ice-water bath. The mixture was heated at 70-80 °C for 30 min and then at 90-110 °C for 30 min. The solvent was evaporated *in vacuo* to give yellow crystals, whose recrystallization from acetic acid/water afforded yellow needles of compound (**7**) (2.26 g, 43%), mp 150-151 °C; IR: ν $cm^{-1}$ 1750, 1605; MS: m/z 320 ($M^+$), 322 ($M^+$ + 2); NMR (deuteriodimethyl sulfoxide ): 8.01 (d, J = 2.5 Hz, 1H, 6-H), 7.88 (d, J = 9.0 Hz, 1H, 9-H), 7.77 (dd, J = 9.0, 2.5 Hz, 1H, 8-H), 7.18 (s, 1H, OH), 7.10 (s, 1H, 3-H), 4.14 (q, J = 7.0 Hz, 2H, $CH_2$), 3.67 (s, 3H, N-$CH_3$), 1.08 (t, J = 7.0 Hz, 3H, $CH_3$). *Anal.* Calcd for $C_{14}H_{13}N_4O_3Cl$: C, 52.43; H, 4.09; N, 17.47. Found: C, 52.14; H, 4.14; N, 17.41.

**7-Chloro-1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (5a)**
Method 1. A solution of compound (**7**) (2 g, 6.24 mmol) and potassium hydroxide (349 mg, 6.24 mmol) in ethanol (50 mL)/water (1 mL) was refluxed for 1 h to precipitate crystals. After cooling to rt, 5*N* hydrochloric acid (1.3 mL) was added to the reaction mixture with stirring to give yellow crystals, which were collected by filtration. Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles of compound (**5a**) (0.85 g, 74%).
Method 2. A solution of sodium nitrite (1.70 g, 24.6 mmol) in water (25 mL) was added to a solution of compound (**6a**) (5 g, 16.4 mmol) in acetic acid (200 mL)/water (25 mL) with stirring in an ice-water bath. Then, the mixture was heated at 90-100 °C for 30 min with stirring. Evaporation of the solvent *in vacuo* gave an oily substance, which was dissolved in a solution of potassium hydroxide (1.15 g, 20.5 mmol) in ethanol (130 mL)/water (1 mL). The solution was refluxed for 2 h to precipitate brown crystals of compound (**5a**). After 5*N* hydrochloric acid (4.1 mL) was added to the reaction mixture, the yellow crystals of compound (**5a**) were collected by filtration (1.40 g, 35%). Evaporation of the filtrate *in vacuo* provided yellow crystals of compound (**7**), which were triturated with water and then collected by filtration (3.1 g, 59%). Subsequently, a solution of compound (**7**) (3.1 g, 9.67 mmol) and potassium hydroxide (1.10 g, 19.7 mmol) in ethanol (130 mL)/water (1 mL) was refluxed for 2 h to precipitate yellow crystals of compound (**5a**), which were collected by filtration (1.72 g, 73%), total yield, 3.12 g (77%).
Compound (**5a**) had mp 309-310 °C; IR: ν $cm^{-1}$ 3065, 1650, 1610, 1540, 1525; MS: m/z 246 ($M^+$), 248 ($M^+$ + 2); NMR (deuteriodimethyl sulfoxide ): 8.40 (dd, J = 2.5, 0.5 Hz, 1H, 6-H), 8.16 (dd, J = 9.0, 0.5

Hz, 1H, 9-H), 8.06 (dd, J = 9.0, 2.5 Hz, 1H, 8-H), 7.94 (s, 1H, 3-H), 4.12 (s, 3H, N-$CH_3$). *Anal.* Calcd for $C_{11}H_7N_4OCl$: C, 53.56; H, 2.86; N, 22.71. Found: C, 53.41; H, 3.03; N, 22.59.

**4-Acetyl-1,5-dihydro-1-methylpyridazino[3,4-*b*]quinoxaline (6b)**

A solution of acetylacetaldehyde dimethyl acetal (5.21 g, 39.5 mmol) in acetic acid (80 mL)/water (20 mL) was heated at 90-100 °C for 30 min. Compound (**8b**) (5 g, 26.3 mmol) was then added to the solution, and the whole mixture was refluxed for 2 h with stirring. Evaporation of the solvent *in vacuo* afforded crystals, which were dissolved in chloroform and then submitted to column chromatography on silica gel, eluting with chloroform. The first fraction was collected and evaporated *in vacuo* to give red crystals of compound (**6b**) (1.18 g, 19%), IR: ν $cm^{-1}$ 1620[11], 1610, 1590; MS: m/z 240 ($M^+$).[14] This sample was used for the synthesis of compound (**5b**) without further purification.

**1-Methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (5b)**

A solution of compound (**6b**) (1 g, 4.17 mmol) and selenium dioxide (1.14 g, 10.4 mmol) in acetic acid (40 mL)/water (10 mL) was refluxed for 1 h. After precipitate was filtered off, mother liquor was evaporated *in vacuo* to give crystals, which were dissolved in chloroform/*n*-hexane (10 : 1) and then submitted to column chromatography on silica gel, eluting with chloroform/*n*-hexane (10 : 1). The first fraction was collected and evaporated *in vacuo* to give yellow crystals of compound (**5b**) (350 mg, 40%). Recrystallization from ethanol/water provided yellow needles, mp 249-250 °C; IR: ν $cm^{-1}$ 3050, 1650; MS: m/z 212 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.26 (ddd, J = 8.5, 1.5, 0.8 Hz, 1H, aromatic H), 8.12 (ddd, J = 8.5, 1.5, 0.8 Hz, 1H, aromatic H), 8.06 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H, aromatic H), 7.93 (s, 1H, 3-H), 7.92 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H, aromatic H), 4.13 (s, 3H, N-$CH_3$). *Anal.* Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.45; H, 4.00; N, 26.33.

**Ethyl 1,5-Dihydro-1-methylpyridazino[3,4-*b*]quinoxaline-4-carboxylate (6d)**

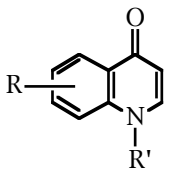
A solution of compound (**8b**) (10 g, 52.6 mmol) and diethyl ethoxymethylenemalonate (17.04 g, 78.9 mmol) in acetic acid (200 mL) was refluxed for 2 h. Evaporation of the solvent *in vacuo* gave an oily substance, which was dissolved in a solution of 100% hydrazine hydrate (5 g, 0.1 mol) in ethanol (200 mL). The solution was refluxed for 1 h to precipitate yellow needles of compound (**6d**), which were collected by filtration and washed with ethanol to provide an analytically pure sample (4.78 g). Evaporation of the filtrate *in vacuo* afforded yellow needles of compound (**6d**), total yield, 5.31 g (37%). Compound (**6d**) had mp 127-128 °C; IR: ν $cm^{-1}$ 1670, 1655, 1618; MS: m/z 270 ($M^+$); NMR (deuteriodimethyl sulfoxide ): 10.24 (s, 1H, NH), 6.93 (dd, J = 8.0, 1.5 Hz, 1H, aromatic H), 6.77 (dd, J = 7.5, 1.5 Hz, 1H, aromatic H), 6.70 (dd, J = 8.0, 1.5 Hz, 1H, aromatic H), 6.70 (dd, J = 7.5, 1.5 Hz, 1H, aromatic H), 7.04 (s, 1H, 3-H), 4.16 (q, J = 7.0 Hz, 2H, $CH_2$), 3.12 (s, 3H, N-$CH_3$), 1.23 (t, J = 7.0 Hz, 3H, $CH_3$). *Anal.* Calcd for $C_{14}H_{14}N_4O_2$: C, 62.09; H, 5.29; N, 21.01. Found: C, 62.21; H, 5.22; N, 20.73.

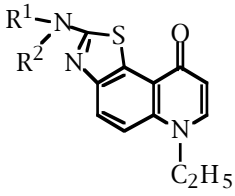
**ACKNOWLEDGEMENT**

We wish to thank Nissan Chemical Industries, Ltd. and SSP Company, Ltd. for the antimicrobial screening tests.

**REFERENCES AND NOTES**

1. Y. Kurasawa, A. Tsuruoka, N. Rikiishi, N. Fujiwara, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2000, **37**, 791.
2. Y. Kurasawa, K. Sakurai, S. Kajiwara, K. Harada, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2000, **37**, 1257.
3. Y. Kurasawa, S. Ohshima, Y. Kishimoto, M. Ogura, Y. Okamoto, and H. S. Kim, *Heterocycles*, 2001, **54**, 359.
4. Y. Kurasawa, I. Matsuzaki, W. Satoh, Y. Okamoto, and H. S. Kim, *Heterocycles,* 2002, **56**, 291.
5. For example, the minimum inhibitory concentrations of compounds (**3a,b**) were between 1.0 and 2.0 ppm against *Bacillus subtilis* (bacteria) and *Trichophyton mentagrophytes* (fungi).
6. The detailed screening data will be reported elsewhere.
7. A. Albrecht, *Prog. Drug Res.*, 1977, **21**, 9.
8. S. Kadoya, I. Takamura, N. Suzuki, and R. Dohmori, *Chem. Pharm. Bull.*, 1976, **24**, 136.
9. No or insignificant antimicrobial activities have been reported for the 3-H quinolone homologues (**11**[7] and **12**[8]) shown below.

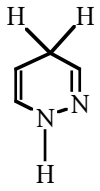


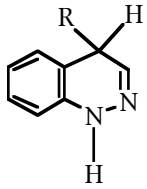

**11** **12** $R^1 = CH_3, C_2H_5,\ R^2 = CH_3, H$

10. Y. Kurasawa, A. Takada, H. S. Kim, and Y. Okamoto, *J. Heterocycl. Chem.*, 1993, **30**, 1659.
11. Y. Kurasawa, A. Takano, K. Harada, A. Takada, H. S. Kim, and Y. Okamoto, *Khim. Geterotsikl. Soedin.*, 1995, **9**, 1245.
12. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, 'Advances in Heterocyclic Chemistry, Supplement 1, The Tautomerism of Heterocycles,' ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, San Francisco, London, 1976, p. 78, and references cited therein.
13. L. S. Besford, G. Allen, and J. M. Bruce, *J. Chem. Soc.*, 1963, 2867.

14. This type of compounds were clarified by us to exist as the 1,5-dihydropyridazino[3,4-*b*]-quinoxaline form, but not the 1,4-dihydropyridazino[3,4-*b*]quinoxaline form, in solution and solid state,[11] while dihydropyridazine[12] and dihydrocinnolines[13] were reported to predominate as the 1,4-dihydro form.




Dihydropyridazine[12]




Dihydrocinnolines[13]

15. The recovery was not so good.