

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

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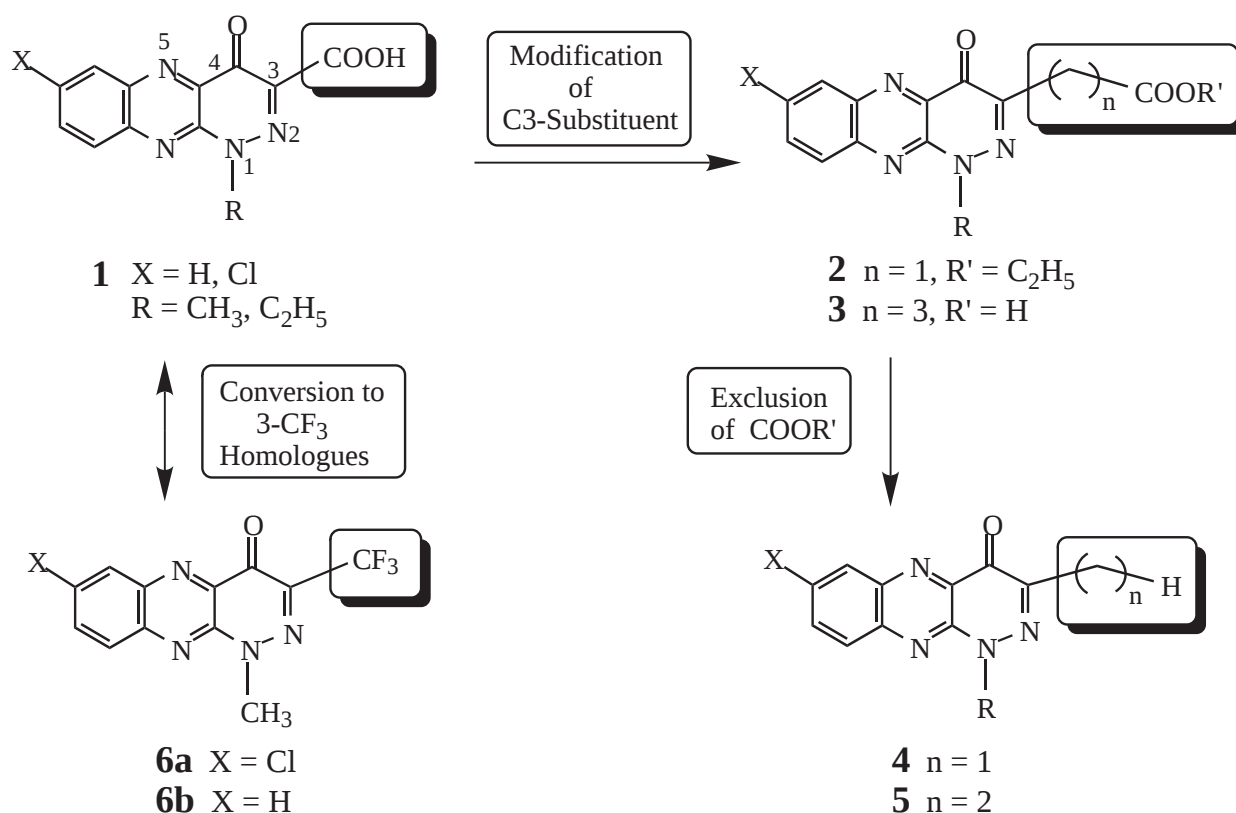
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Abstract - The reaction of the quinoxaline *N*-oxides (**7a,b**) with 4,4,4-trifluoroacetoacetate gave the 1,5-dihydro-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**15a,b**), whose oxidation with nitrous acid afforded the 1,4-dihydro-4-hydroxy-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**16a,b**), respectively. The reaction of compounds (**16a,b**) with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) provided the 1,5-dihydro-3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4-ols (**17a,b**), whose oxidation with sodium bromate produced the 1-methyl-3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**6a,b**), respectively.

In a previous paper,¹ we reported the synthesis of the pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids (**1**) (Scheme 1) as candidates of antibacterial quinolone analogues. However, the antibacterial activities of compounds (**1**) were not so high, and hence we then synthesized the 2-(pyridazino[3,4-*b*]quinoxalin-3-yl)acetates (**2**) and 4-(pyridazino[3,4-*b*]quinoxalin-3-yl)butyric acids (**3**) in order to improve the activities

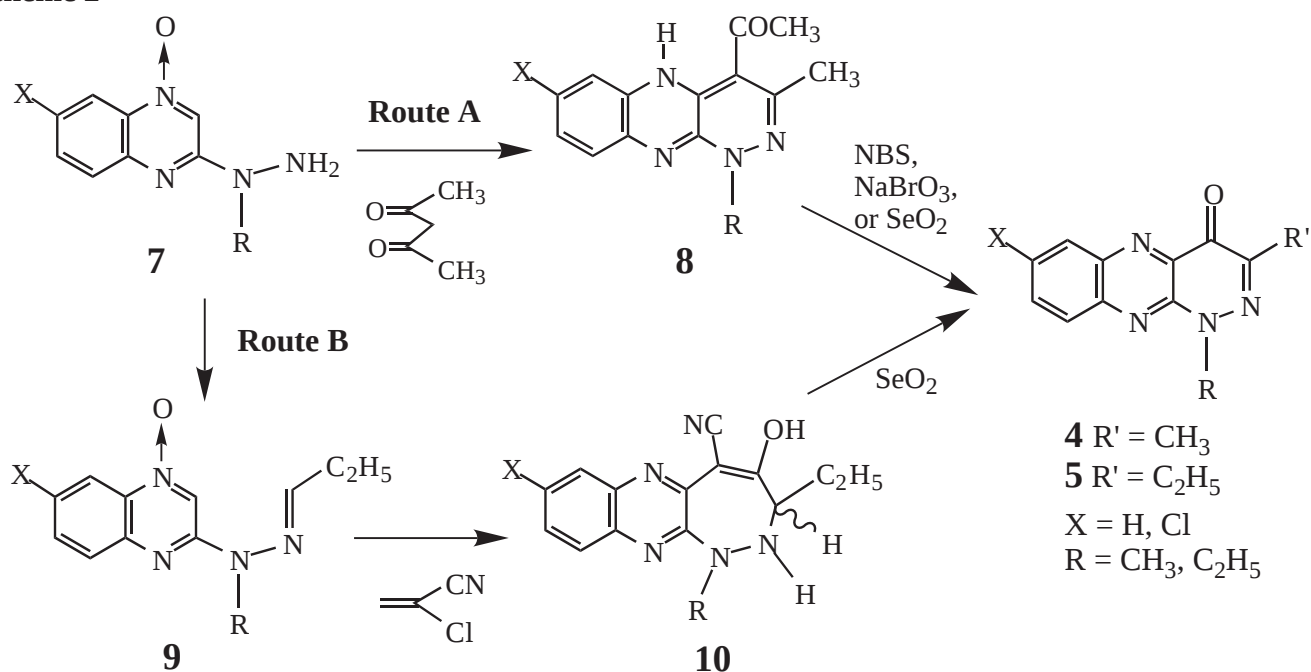
Scheme 1



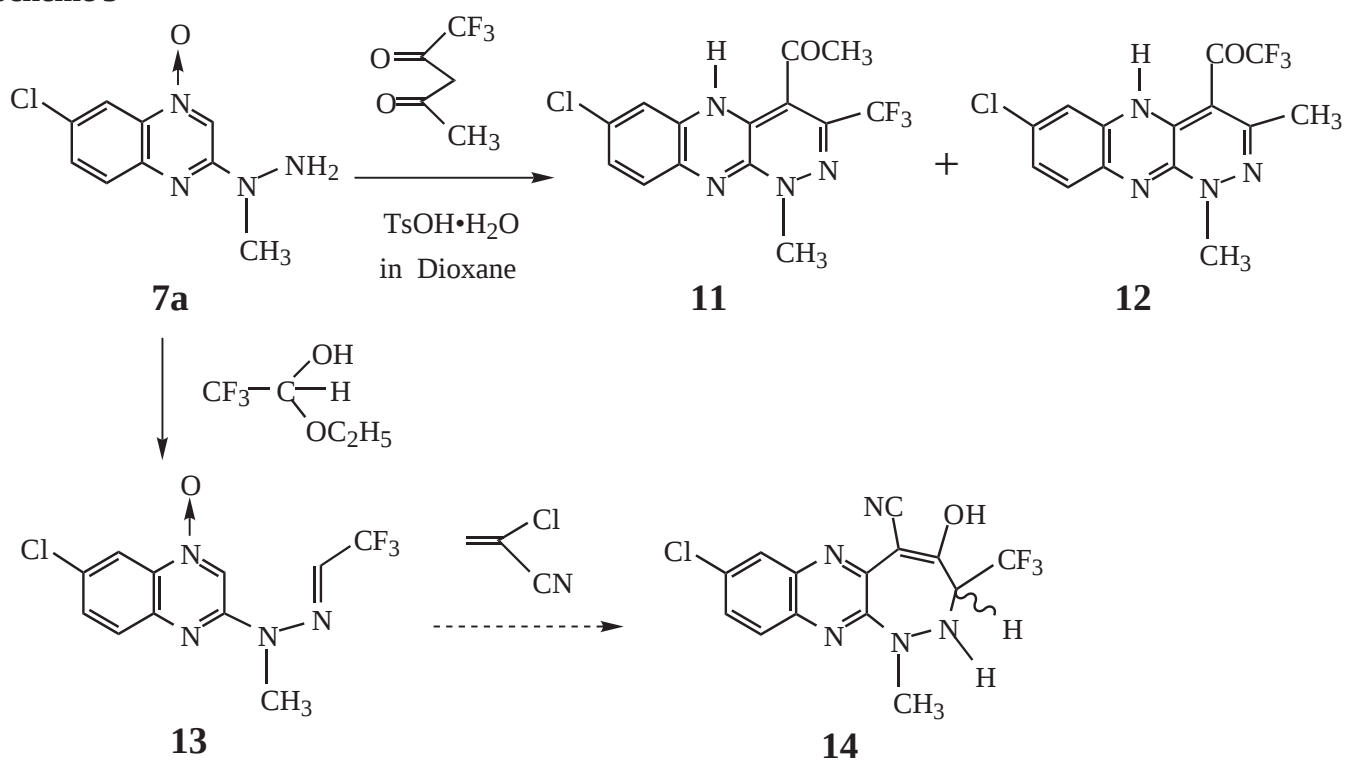
by the conversion of the C3-substituent.² Nevertheless, the screening data showed that the antibacterial activities of compounds (**2** and **3**) were similar to those of compounds (**1**) without activity improvement. These results directed us to study further structural modification, which led to the exclusion of the COOR' moiety from the C3-substituent of compounds (**2** and **3**), giving the 1,3-dialkylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**4** and **5**).³ The screening data indicated that some of compounds (**4** and **5**) exhibited a good antifungal activity as well as better antibacterial activities than compounds (**1-3**).³ Of compounds (**4** and **5**), the N1-methyl derivatives were better in the antimicrobial activities than the N1-ethyl derivatives, while the C3-methyl derivatives were similar in the antimicrobial activities to the C3-ethyl derivatives. In consideration of these substituent characteristics, we further undertook the synthesis of the 1-methyl-3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**6a,b**) (Scheme 1) in order to search for more potent compounds, since the introduction of a fluorine-including substituent has been well known to improve some biological activities. This paper describes the synthesis of the 1-methyl-3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones (**6a,b**) from the quinoxaline *N*-oxides (**7a,b**), respectively.

Scheme 2 shows two routes A and B, which synthesize the 1-alkyl-3-methyl and 1-alkyl-3-ethyl derivatives (**4** and **5**) from the quinoxaline *N*-oxides (**7**) via compounds (**8**) and compounds (**9** and **10**), respectively.³

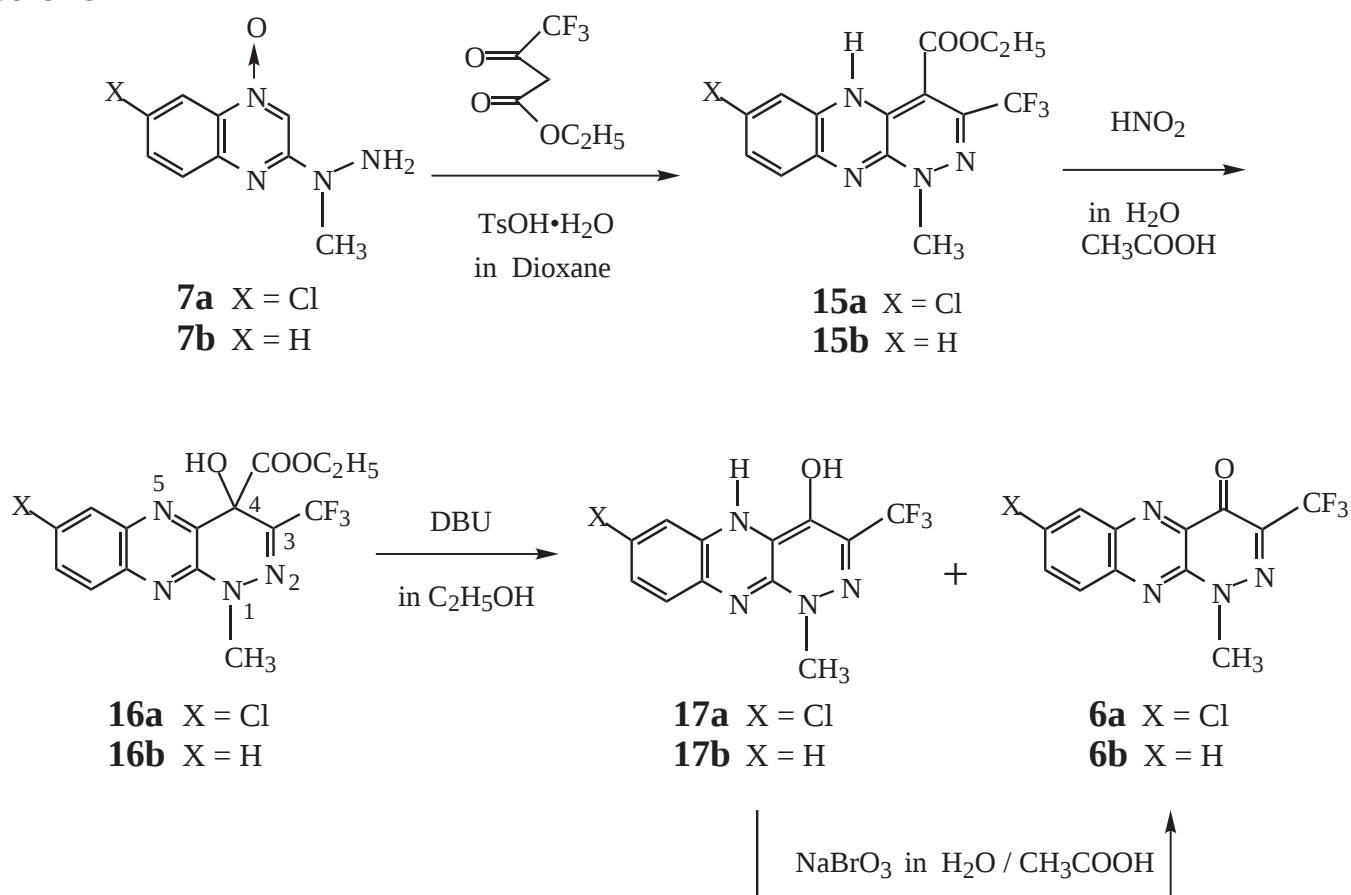
Scheme 2



Scheme 3



Scheme 4

Table 1. Yield of Compounds (**17a**) and / or (**6**)

Substrate	Yield (%)	
16a	17a (90 %)	———
16b	17b (74 %)	6b (20 %)
17b	———	6b (87 %)

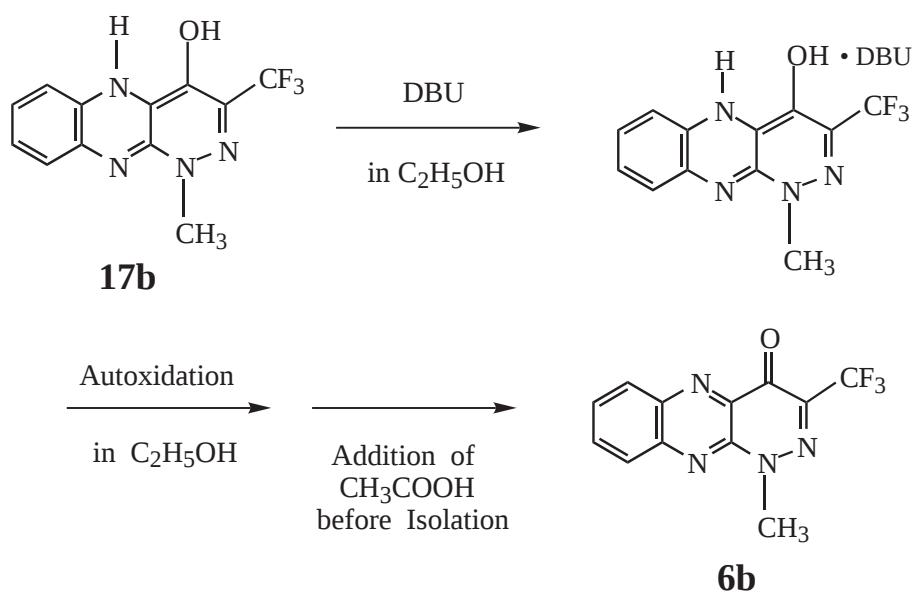
Reflux time was 1 h, and DBU was added in a 1.5-fold molar ratio.

Initially, these methods were used to produce the 1-methyl-3-trifluoromethyl derivatives (**6a,b**), but unfavorable results were obtained as follows. Namely, the reaction of compound (**7a**) with trifluoroacetylacetone gave a mixture of the 4-acetyl-3-trifluoromethyl and 3-methyl-4-trifluoroacetyl derivatives (**11** and **12**) (Scheme 3), whose separation was not so easy by column chromatography. Such chromatographic separation was not convenient for us, and compound (**12**) was not necessary for our purpose. Furthermore, the quinoxaline *N*-oxide (**13**) obtained from compound (**7a**) was hardly converted into the 3-trifluoromethyl-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile (**14**). Accordingly, we

abandoned these methods.

Thus, we had to devise an alternate route to synthesize compounds (**6a,b**), so that the 3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**15a,b**) with the 1,5-dihydro tautomeric form⁴ were obtained from the reaction of compounds (**7a,b**) with ethyl 4,4,4-trifluoroacetoacetate in the presence of *p*-toluenesulfonic acid (Scheme 4).⁵ The reaction of compounds (**15a,b**) with nitrous acid resulted in C4-oxidation^{1,2} to afford the 4-hydroxy-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**16a,b**), respectively. The reaction of compounds (**16a**) with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in ethanol effected hydrolysis and subsequent decarboxylation to provide the 3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4-ol (**17a**), while the reaction of compound (**16b**) with DBU in ethanol produced a mixture of the 3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4-ol (**17b**) and 1-methyl-3-trifluoromethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (**6b**) (Table 1). Since reflux of the 4-hydroxy derivative (**17b**) in DBU/ethanol gave the 4-oxo derivative (**6b**) (Scheme 5), the formation of the 4-oxo derivative (**6b**) in Schemes 4 and 5 was attributable to autoxidation. The reaction of the 4-hydroxy derivatives (**17a,b**) with sodium bromate gave the 4-oxo derivatives (**6a,b**), respectively.

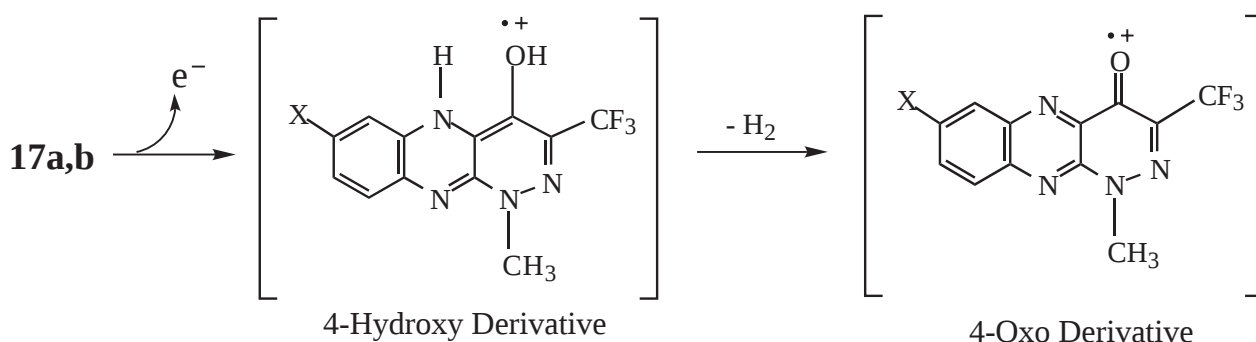
Scheme 5



The structural assignment of new compounds (**6** and **15-17**) was based on the analytical and spectral data, although the mass and NMR spectral data for the 4-hydroxy derivatives (**17a,b**) were not simple because of their susceptibility to oxidation. In the mass spectra, the 4-hydroxy derivatives (**17a,b**) did not show

the molecular ion peaks (M^+),⁶ but exhibited the $[M^+ - 2 (H_2)]$ ion peaks corresponding to the M^+ of the 4-oxo derivatives (**6a,b**) (Scheme 6).

Scheme 6



Scheme 7

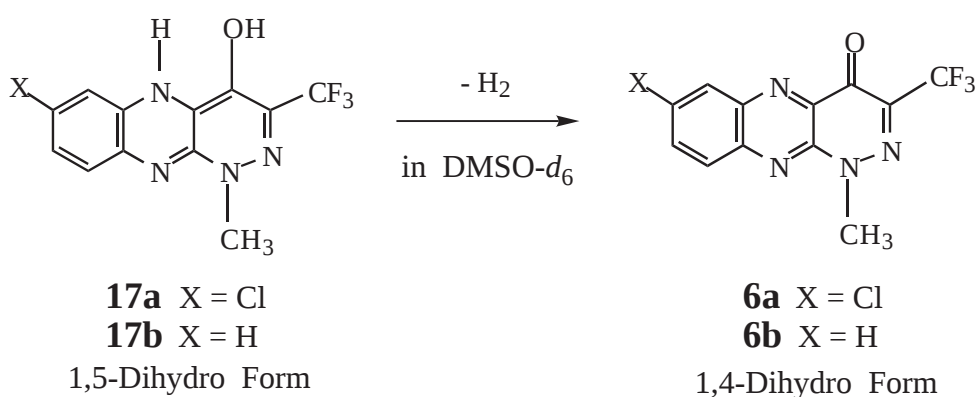


Table 2. Aromatic Proton Signals observed in the NMR Spectra of Compounds (**17a,b**) in DMSO- d_6

Compound	Aromatic Proton Signals (δ) corresponding to	
	1,5-Dihydro Form (17)	1,4-Dihydro Form (6)
17a	6.99 - 6.62	8.50, 8.23, 8.13
17b	6.99 - 6.61	8.35, 8.20, 8.13, 8.01

Moreover, in the NMR spectra, the 4-hydroxy derivatives (**17a,b**) showed the aromatic proton signals in a higher magnetic field (δ 6.99 - 6.61) and in a lower magnetic field (δ 8.50 - 8.01) (Scheme 7, Table 2),⁷ which would correspond to the aromatic proton signals of the 4-hydroxy derivatives (**17a,b**) with the 1,5-dihydro form^{1,2,8} and the 4-oxo derivatives (**6a,b**) with the 1,4-dihydro form^{1,2,8} (δ 8.50 - 8.02),

respectively (Figure, Table 3). The aromatic proton signals of compounds (**15a,b**) (δ 6.92 - 6.66) with the 1,5-dihydro form^{1,2} (Figure, Table 3) were observed in a similar magnetic field to those of the 4-hydroxy derivatives (**17a,b**) in a higher magnetic field (δ 6.99 - 6.61).

Figure

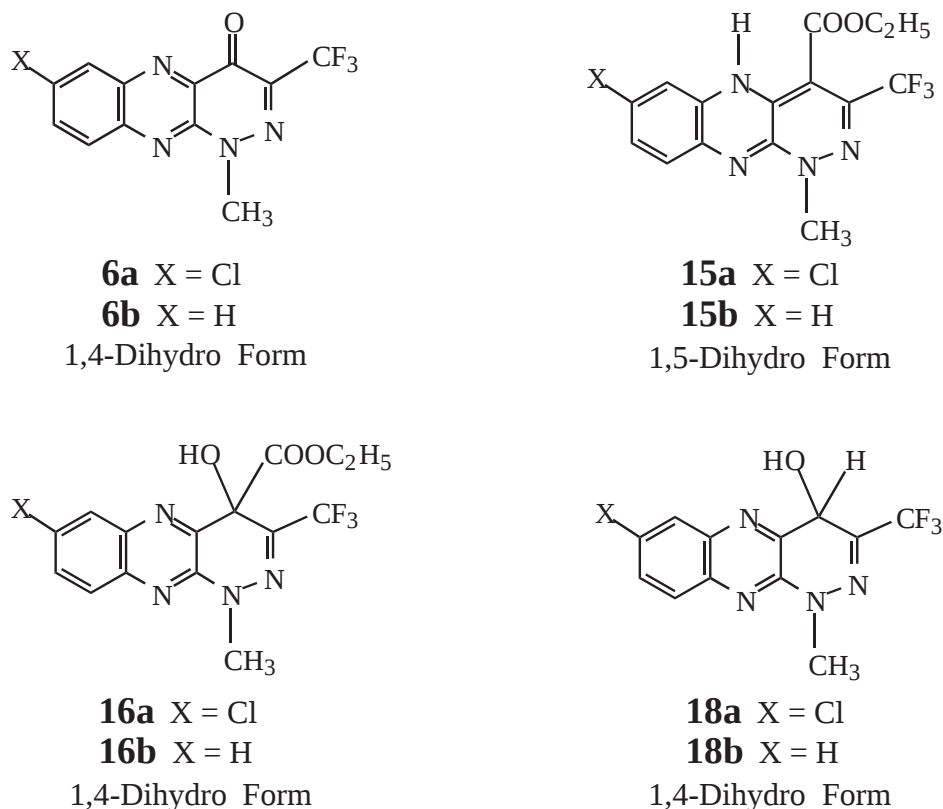


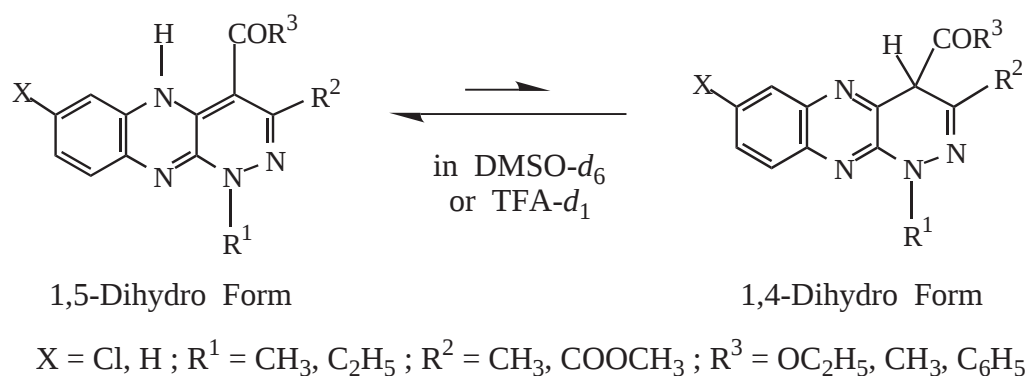
Table 3. Aromatic Proton Signals of Compounds (**6a,b**), (**15a,b**), and (**16a,b**)

Compound	Solvent	Aromatic Proton Signals (δ)
6a	DMSO- <i>d</i> ₆	8.50, 8.23, 8.13
6b	DMSO- <i>d</i> ₆	8.35, 8.20, 8.13, 8.02
15a	TFA- <i>d</i> ₁	6.71 - 6.66
15b	TFA- <i>d</i> ₁	6.92 - 6.80
16a	DMSO- <i>d</i> ₆	8.15 - 7.89
16b	DMSO- <i>d</i> ₆	8.03 - 7.74

On the other hand, the aromatic proton signals of compounds (**17a,b**) in a lower magnetic field (δ 8.50 -

8.02) would not correspond to those of compounds (**18a,b**) (Figure), since the 1,5-dihydropyridazino[3,4-*b*]quinoxalines did not tautomerize into the 1,4-dihydropyridazino[3,4-*b*]quinoxalines in deuteriodimethyl sulfoxide or deuteriotrifluoroacetic acid (Scheme 8).¹⁻⁴ Furthermore, the aromatic proton signals of compounds (**16a,b**) with the 1,4-dihydro form (δ 8.15 - 7.74) (Figure, Table 3) were observed in a slightly higher magnetic field than those of compounds (**6a,b**) (δ 8.50 - 8.02). The screening of compounds (**6a,b**) is in progress, and its data will be reported elsewhere.

Scheme 8



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 mass spectra were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

6-Chloro-2-[1-methyl-2-(2,2,2-trifluoroethylidene)hydrazino]quinoxaline 4-Oxide (**13**)

A solution of compound (**7a**) (10 g, 44.5 mmol) and trifluoroacetaldehyde ethyl hemiacetal (90% purity, 10.61 g, 66.8 mmol) in dioxane (200 mL)/concentrated hydrochloric acid (5 mL)/water (5 mL) was refluxed for 2 h. The solution was allowed to stand overnight at rt to precipitate colorless needles of compound (**13**), which were collected by filtration to obtain an analytically pure sample (8.57 g).

Evaporation of the filtrate *in vacuo* afforded crystals of compound (**13**), which were triturated with ethanol/hexane and then collected by filtration (3.70 g). Total yield, 12.27 g (90%).

Compound (**13**) had mp 210-211 °C; IR: ν cm⁻¹ 1625, 1580, 1545; MS: m/z 304 (M⁺), 306 (M⁺ + 2); NMR (deuteriodimethyl sulfoxide): 8.58 (s, 1H, C3-H), 8.26 (d, J = 2.0 Hz, 1H, C5-H), 7.88 (d, J = 8.5 Hz, 1H, C8-H), 7.82 (dd, J = 2.0, 8.5 Hz, 1H, C7-H), 7.66 (q, J = 4.0 Hz, 1H, hydrazone CH), 3.59 (s, 3H, N-CH₃). *Anal.* Calcd for C₁₁H₈N₄OCIF₃: C, 43.37; H, 2.65; N, 18.39. Found: C, 43.40; H, 2.78; N, 18.33.

Ethyl 7-Chloro-1,5-dihydro-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxaline-4-carboxylate (15a)

A suspension of compound (**7a**) (10 g, 44.5 mmol), ethyl 4,4,4-trifluoroacetoacetate (12.3 g, 66.8 mmol), and *p*-toluenesulfonic acid monohydrate (50 mg) in dioxane (200 mL) was refluxed for 3 h to give a clear solution. After cooling to rt, triethylamine (2 mL) was added to the solution. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol to provide compound (**15a**) (7.43 g, 45%). Recrystallization from *N,N*-dimethylformamide/ethanol gave brown needles, mp 150-151 °C; IR: ν cm⁻¹ 1650, 1600; MS: m/z 372 (M⁺), 374 (M⁺ + 2); NMR (deuteriotrifluoroacetic acid): 6.71 (dd, J = 1.0, 2.0 Hz, 1H, C6-H), 6.71 (dd, J = 2.0, 9.0 Hz, 1H, C8-H), 6.66 (dd, J = 1.0, 9.0 Hz, 1H, C9-H), 4.14 (q, J = 7.0 Hz, 2H, CH₂), 3.53 (s, 3H, N-CH₃), 1.11 (t, J = 7.0 Hz, 3H, CH₃). *Anal.* Calcd for C₁₅H₁₂N₄O₂ClF₃: C, 48.34; H, 3.24; N, 15.03. Found: C, 48.26; H, 3.32; N, 15.18.

Ethyl 7-Chloro-1,4-dihydro-4-hydroxy-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxaline-4-carboxylate (16a)

A solution of sodium nitrite (1.39 g, 20.1 mmol) in water (30 mL) was added to a suspension of compound (**15a**) (5 g, 13.4 mmol) in acetic acid (150 mL)/water (70 mL) with stirring at rt. The suspension was heated at 90-100 °C with stirring for 30 min to precipitate yellow needles of compound (**16a**), and the reaction mixture was allowed to stand overnight. Compound (**16a**) was collected by filtration and washed with ethanol/water (3:1) to provide an analytically pure sample (5.01 g, 96%), mp 193-194 °C; IR: ν cm⁻¹ 3300, 1765, 1620, 1605; MS: m/z 315 (M⁺), 317 (M⁺ + 2); NMR (deuteriodimethyl sulfoxide): 8.15 (dd, J = 1.0, 2.5 Hz, 1H, C6-H), 8.05 (dd, J = 1.0, 9.0 Hz, 1H, C9-H), 7.89 (dd, J = 2.5, 9.0 Hz, 1H, C8-H), 7.60 (s, 1H, C4-OH), 4.23 (dq, J = 7.0, 10.0 Hz, 1H, methylene H), 4.13 (dq, J = 7.0, 10.0 Hz, 1H, methylene H), 3.81 (s, 1H, N-CH₃), 1.06 (dd, J = 7.0, 7.0 Hz, 3H, CH₃). *Anal.* Calcd for C₁₅H₁₂N₄O₃ClF₃: C, 46.35; H, 3.11; N, 14.41. Found: C, 46.23; H, 3.16; N, 14.54.

7-Chloro-1,5-dihydro-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4-ol (17a)

A solution of compound (**16a**) (5 g, 12.9 mmol) and DBU (2.95 g, 19.4 mmol) in ethanol (200 mL) was refluxed for 1 h. After cooling to rt, acetic acid (15 mL) was added to the reaction mixture to precipitate green powders of compound (**17a**), which were collected by filtration and washed with ethanol/water (3:1) to provide an analytically pure sample (3.66 g, 90%), mp 268-269 °C; IR: ν cm⁻¹ 3200, 1640, 1620, 1600; MS: m/z 314 [$M^+ - 2$ (H₂)], 316 [$(M^+ + 2) - 2$ (2H)]; NMR (deuteriodimethyl sulfoxide): [signals for 4-hydroxy derivative (9%)] 7.14 (s, C4-OH), 6.99 (d, J = 8.0 Hz, C9-H), 6.82 (d, J = 2.0 Hz, C6-H), 6.62 (dd, J = 8.0, 2.0 Hz, C8-H) (NH proton signal was not observed); [signals for 4-oxo derivative (71%)] 8.50 (d, J = 1.8 Hz, C6-H), 8.23 (d, J = 9.5 Hz, C9-H), 8.13 (dd, J = 1.8, 9.5 Hz, C8-H), 4.20 (s, N-CH₃); [signals for unknown tautomer⁷ (20%)] 6.42 (d, J = 1.5 Hz, C6-H), 6.36 (dd, J = 1.5, 8.0 Hz, C8-H), 6.32 (d, J = 8.0 Hz, C9-H). *Anal.* Calcd for C₁₂H₈N₄OClF₃: C, 45.51; H, 2.55; N, 17.69. Found : C, 45.70; H, 2.40; N, 17.68.

7-Chloro-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4(1H)-one (6a)

A suspension of compound (**17a**) (2 g, 6.32 mmol) and sodium bromate (1.43 g, 9.48 mmol) in acetic acid (50 mL)/water (10 mL) was refluxed for 10 min to give a clear solution. Evaporation of the solvent *in vacuo* gave yellow crystals of compound (**6a**), which were collected by filtration (1.67 g, 84%). Recrystallization from acetic acid/water provided yellow crystals, mp 265-266 °C; IR: ν cm⁻¹ 1760, 1605; MS: m/z 314 (M^+), 316 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 8.50 (d, J = 1.8 Hz, 1H, C6-H), 8.23 (d, J = 9.5 Hz, 1H, C9-H), 8.13 (dd, J = 9.0 Hz, 1H, C8-H), 4.20 (s, 3H, N-CH₃). *Anal.* Calcd for C₁₂H₆N₄OClF₃: C, 45.81; H, 1.92; N, 17.81. Found : C, 45.57; H, 1.98; N, 17.88.

Ethyl 1,5-Dihydro-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxaline-4-carboxylate (15b)

A suspension of compound (**7b**) (10 g, 52.6 mmol), ethyl 4,4,4-trifluoroacetoacetate (14.5 g, 78.9 mmol), and *p*-toluenesulfonic acid monohydrate (500 mg) in dioxane (200 mL) was refluxed for 3 h to give a clear solution and then to precipitate a small amount of crystals. After cooling to rt, triethylamine (2 mL) was added to the solution. Then, evaporation of the solvent *in vacuo* afforded crystals of compound (**15b**), which were triturated with water and collected by filtration (7.18 g, 40%). Recrystallization from *N,N*-dimethylformamide/ethanol/water gave brown needles, mp 135-136 °C; IR: ν cm⁻¹ 1650; MS: m/z 338 (M^+); NMR (deuteriotrifluoroacetic acid): 6.92 (ddd, J = 1.0, 8.0, 8.0 Hz, 1H, aromatic H), 6.85 (ddd, J = 1.0, 8.0, 8.0 Hz, 1H, aromatic H), 6.80 (dd, J = 1.0, 8.0 Hz, 1H, aromatic H), 4.23 (q, J = 7.0 Hz, 2H, CH₂), 3.61 (s, 3H, N-CH₃), 1.20 (t, J = 7.0 Hz, 3H, CH₃). *Anal.* Calcd for C₁₅H₁₃N₄O₂F₃: C, 53.26; H, 3.87;

N, 16.56. Found : C, 53.06; H, 3.92; N, 16.51.

Ethyl 1,4-Dihydro-4-hydroxy-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxaline-4-carboxylate (16b)

A solution of sodium nitrite (1.53 g, 22.2 mmol) in water (30 mL) was added to a suspension of compound (15b) (5 g, 14.8 mmol) in acetic acid (150 mL)/water (70 mL) with stirring at rt. The suspension was heated at 90-100 °C with stirring for 30 min to give a clear solution. The solution was allowed to stand at rt to precipitate colorless needles of compound (16b), which were collected by filtration and washed with hexane to afford an analytically pure sample (3.84 g). Evaporation of the filtrate *in vacuo* provided additional colorless needles of compound (16b), which were collected by filtration (0.98 g). Total yield, 4.82 g (92%).

Compound (16b) had mp 140-141 °C; IR: ν cm⁻¹ 3360, 1750, 1620, MS: m/z 354 (M⁺); NMR (deuteriodimethyl sulfoxide): 8.03 (ddd, J = 1.0, 1.0, 8.0 Hz, 1H, aromatic H), 7.99 (ddd, J = 1.0, 1.0, 8.0 Hz, 1H, aromatic H), 7.88 (ddd, J = 1.0, 7.5, 7.5 Hz, 1H, aromatic H), 7.74 (ddd, J = 1.0, 7.5, 7.5 Hz, 1H, aromatic H), 7.53 (s, 1H, C4-OH), 4.23 (dd, J = 7.0, 10.0 Hz, 1H, CH₂), 4.12 (dd, J = 7.0, 10.0 Hz, 1H, CH₂), 3.82 (s, 3H, N-CH₃), 1.06 (dd, 3H, CH₃). *Anal.* Calcd for C₁₅H₁₃N₄O₃F₃: C, 50.85; H, 3.70; N, 15.81. Found : C, 50.86; H, 3.84; N, 15.83.

1,5-Dihydro-1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4-ol (17b) and 1-Methyl-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4(1H)-one (6b)

A solution of compound (16b) (4 g, 11.3 mmol) and DBU (2.58 g, 17.0 mmol) in ethanol (150 mL) was refluxed for 1 h. After cooling to rt, acetic acid (5 mL) was added to the reaction mixture to precipitate green powders of compound (17b), which were collected by filtration and washed with hexane to provide an analytically pure sample (2.36 g, 74%). Evaporation of the filtrate *in vacuo* gave yellow crystals of compound (6b), which were triturated with ethanol/water (1:4) and then collected by filtration (0.63 g, 20%). Recrystallization from acetic acid/water afforded yellow needles.

Compound (17b) had mp 220-221 °C; IR: ν cm⁻¹ 3310, 3190, 3130, 1650, 1620; MS: m/z 282 (M⁺),⁶ 280 [M⁺ - 2 (H₂)]; NMR (deuteriodimethyl sulfoxide): [signals for 4-hydroxy derivative (11%)] 7.53 (s, C4-OH), 6.99 (dd, J = 1.0, 8.0 Hz, aromatic H), 6.95 (ddd, J = 1.0, 7.0, 7.0 Hz, aromatic H), 6.89 (dd, J = 1.0, 8.0 Hz, aromatic H), 6.61 (ddd, J = 1.0, 7.0, 7.0 Hz, aromatic H) (NH proton signal was not observed); [signals for 4-oxo derivative (79%)] 8.35 (dd, J = 1.5, 9.0 Hz, aromatic H), 8.20 (dd, J = 1.5, 9.0 Hz, aromatic H), 8.13 (ddd, J = 1.5, 8.0, 8.0 Hz, aromatic H), 8.01 (ddd, J = 1.5, 8.0, 8.0 Hz,

aromatic H), 4.22 (s, N-CH₃); [signals for unknown tautomer⁷ (10%)] 6.44 - 6.34 (m, C6-, C8-, C9-H).

Anal. Calcd for C₁₂H₉F₃N₄O: C, 51.07; H, 3.21; N, 19.85. Found: C, 51.19; H, 3.02; N, 19.74.

Compound (**6b**) had mp 220-221 °C; IR: ν cm⁻¹ 1665, 1615; MS: m/z 280 (M⁺); NMR (deuteriodimethyl sulfoxide): 8.35 (dd, J = 1.5, 8.0 Hz, 1H, aromatic H), 8.20 (dd, J = 1.5, 8.0 Hz, 1H, aromatic H), 8.13 (ddd, J = 1.5, 7.5, 7.5 Hz, 1H, aromatic H), 8.02 (ddd, J = 1.5, 7.5, 7.5 Hz, 1H, aromatic H), 4.22 (s, 3H, N-CH₃). *Anal.* Calcd for C₁₂H₇N₄OF₃: C, 51.44; H, 2.52; N, 19.99. Found : C, 51.39; H, 2.62; N, 19.96.

1-Methyl-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4(1H)-one (6b)

Method 1. A suspension of compound (**17b**) (1.5 g, 5.32 mmol) and sodium bromate (1.20 g, 7.98 mmol) in acetic acid (40 mL)/water (10 mL) was refluxed for 10 min to give a clear solution. Evaporation of the solvent *in vacuo* afforded yellow crystals of compound (**6b**), which were triturated with water and then collected by filtration (1.21 g, 81%). Recrystallization from acetic acid/water provided yellow needles.

Method 2. A solution of compound (**17b**) (500 mg, 1.77 mmol) and DBU (404 mg, 2.66 mmol) in ethanol (40 mL) was refluxed for 1 h. After acetic acid (5 mL) was added to the solution, evaporation of the solvent *in vacuo* gave yellow crystals of compound (**6b**), which were triturated with ethanol/water and then collected by filtration (430 mg, 87%).

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5. This reaction failed in the absence of *p*-toluenesulfonic acid or in the use of *N,N*-dimethylformamide as

a solvent.

6. In the case of compound (**17b**), the peak of M^+ was observed at m/z 282 in a smaller ratio than that of $[M^+ - 2(H_2)]$ at m/z 280 when the MS spectra were measured at 384 °C.
7. Besides these aromatic proton signals, another group of aromatic proton signals was observed at δ 6.44 - 6.32 in a minor ratio, which would be due to an unknown third tautomer as described in the EXPERIMENTAL.
8. The aromatic proton signals of the 1,5-dihydropyridazino[3,4-*b*]quinoxalines are observed in a higher magnetic field than those of the 1,4-dihydropyridazino[3,4-*b*]quinoxalines.^{1,2}