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

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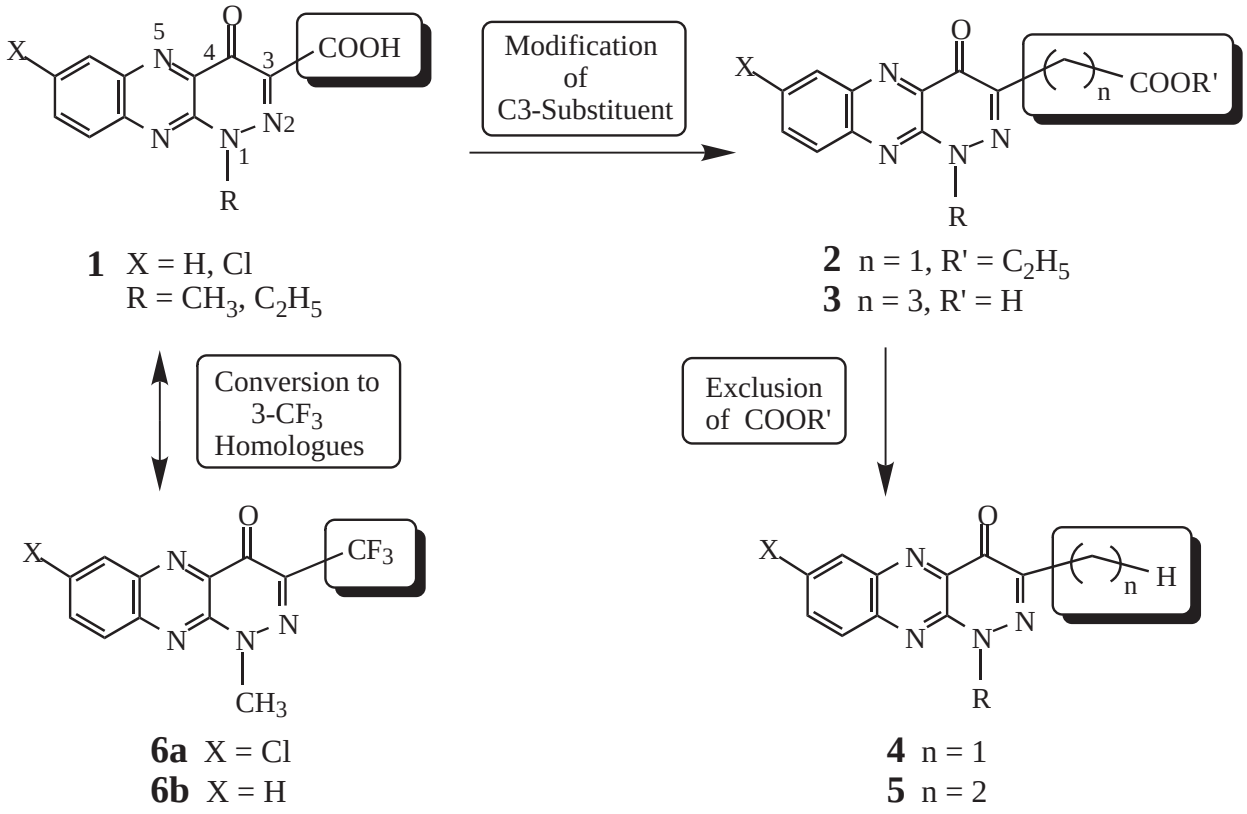
Abstract - The reaction of the quinoxaline *N*-oxides (**7a,b**) with 4,4,4-trifluoroacetoacetate gave the 1,5-dihydro-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**15a,b**), whose oxidation with nitrous acid afforded the 1,4-dihydro-4-hydroxy-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates (**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

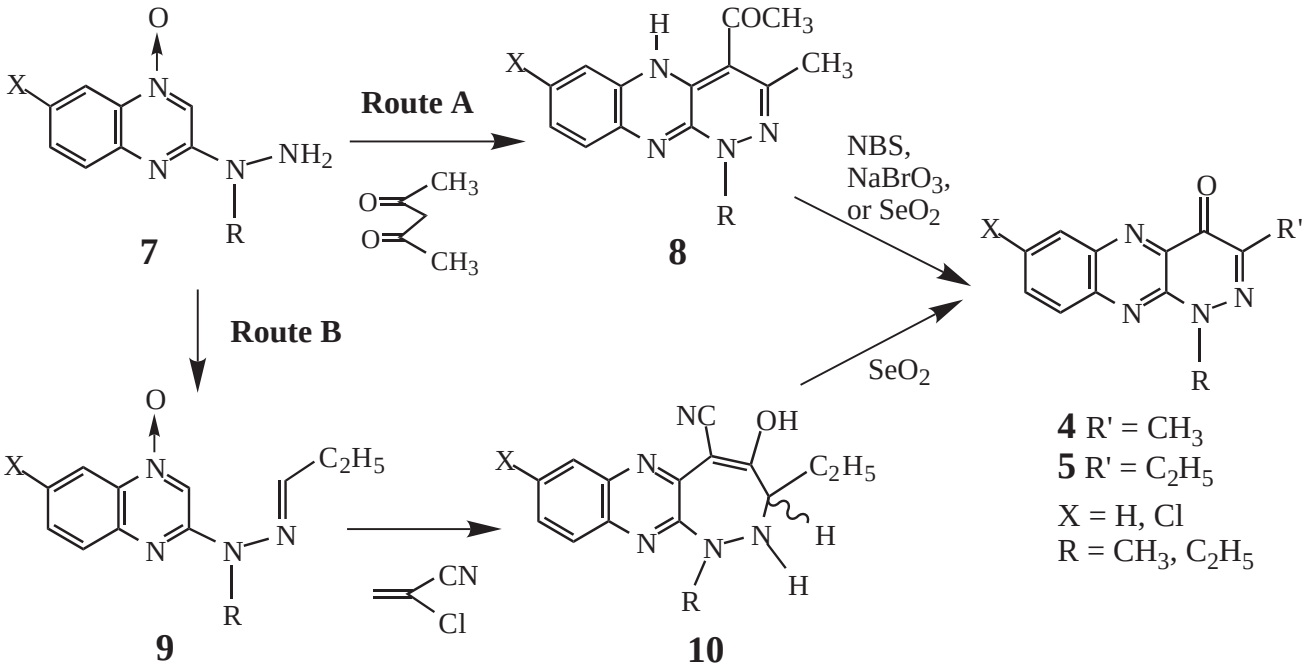
Scheme 1



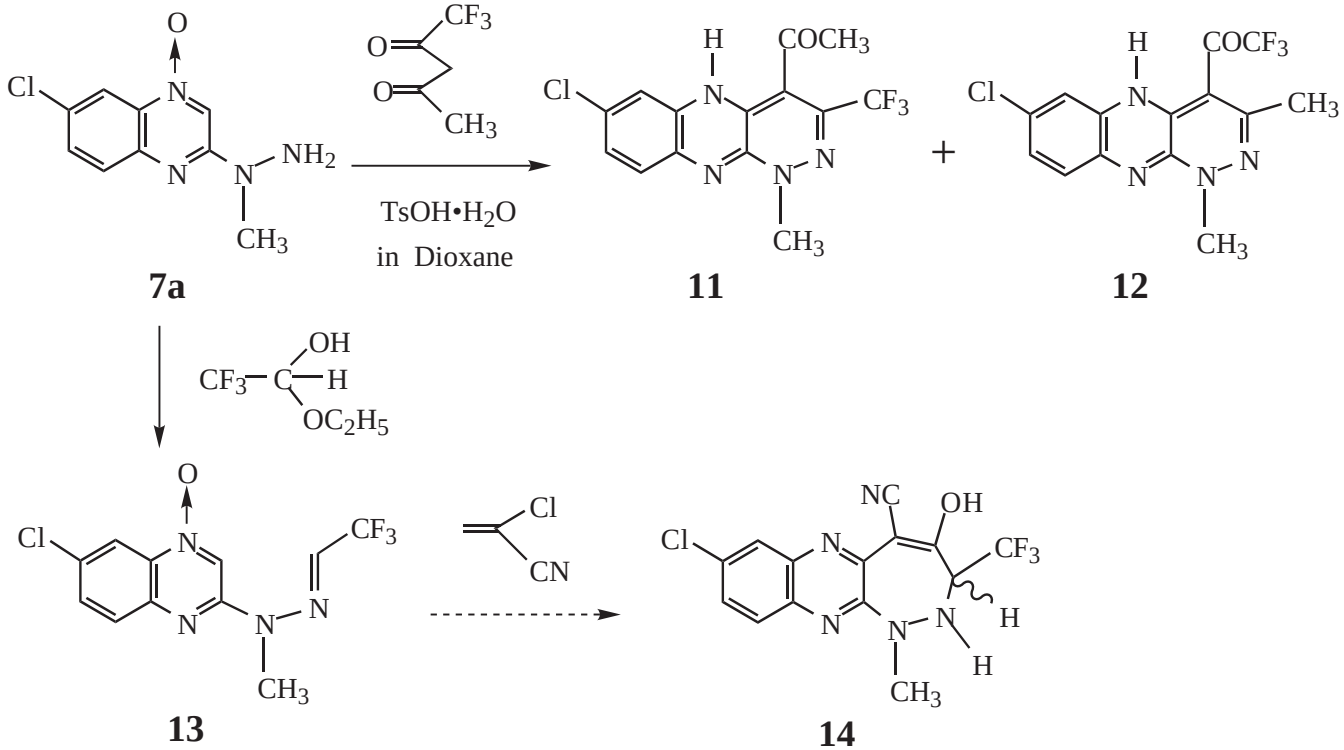
by the conversion of the C3-substituent.[2] Nevertheless, the screening data showed that the antibacterial activities of compounds (**2** and **3**) were similar to those of compounds (**1**) without activity improvement. These results directed us to study further structural modification, which led to 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

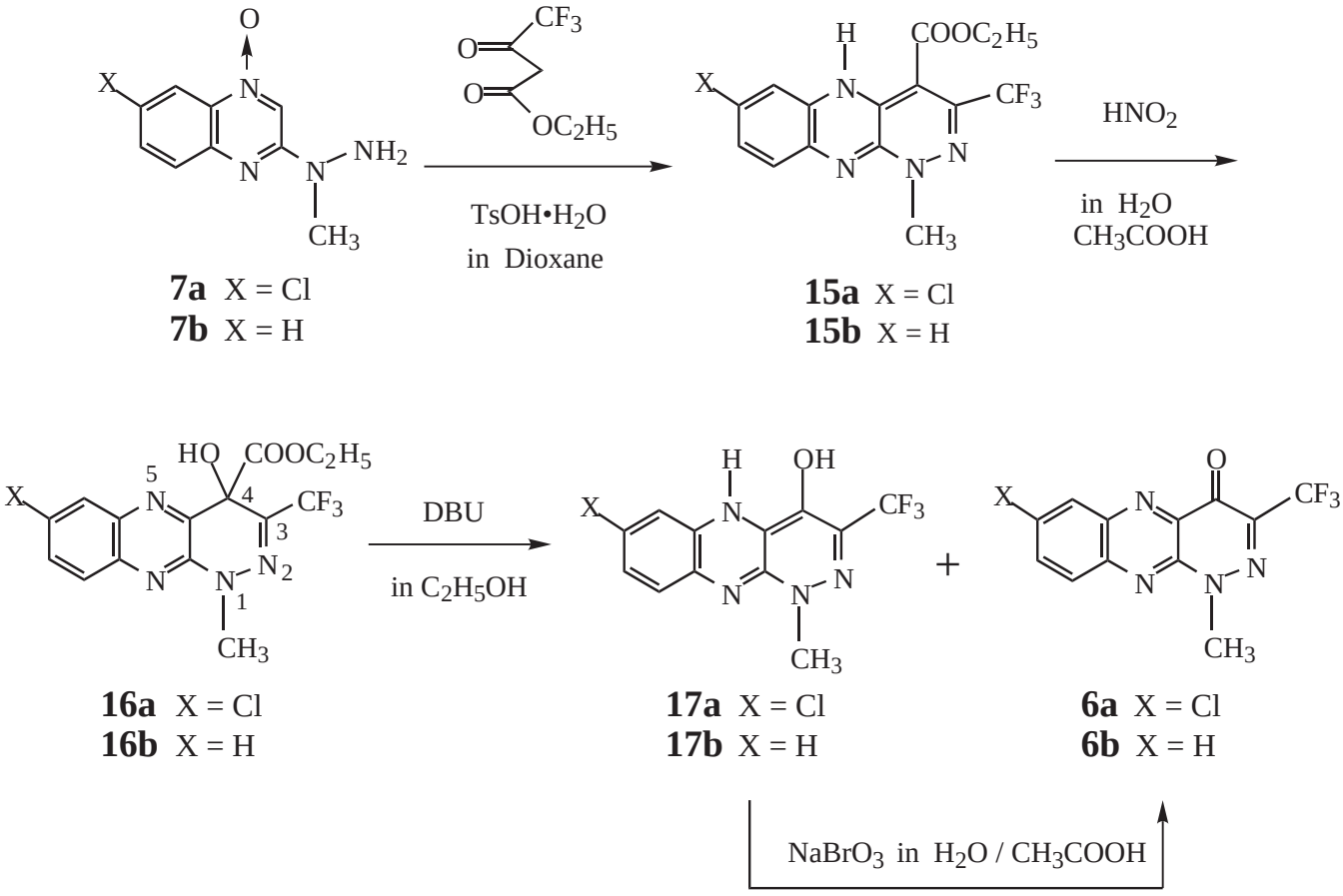


Table 1. Yield of Compounds (**17a**) and / or (**6**)

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

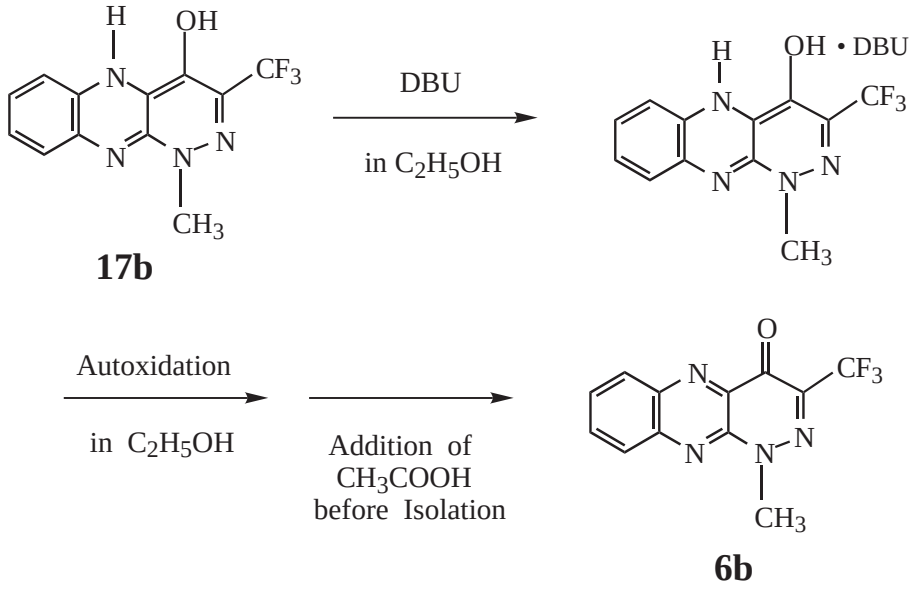
Reflux time was 1 h, and DBU was added in a 1.5-fold molar ratio.

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 form[4] 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



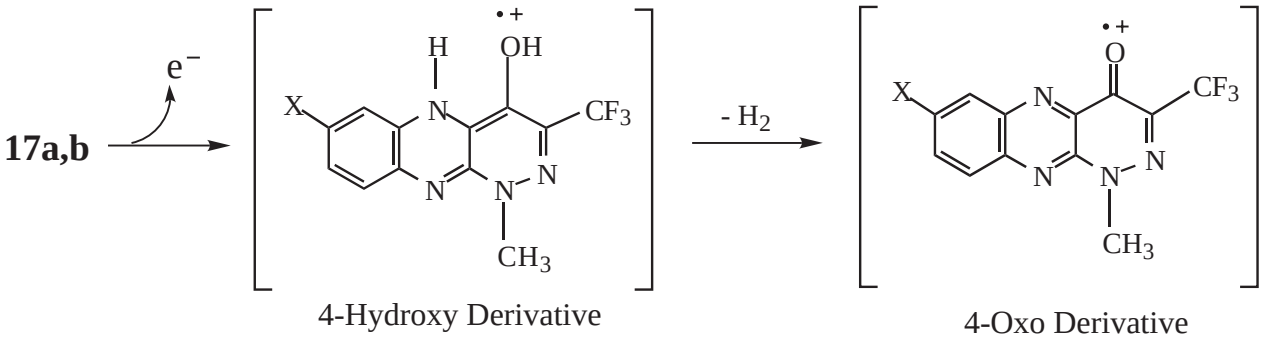
17b

6b

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).

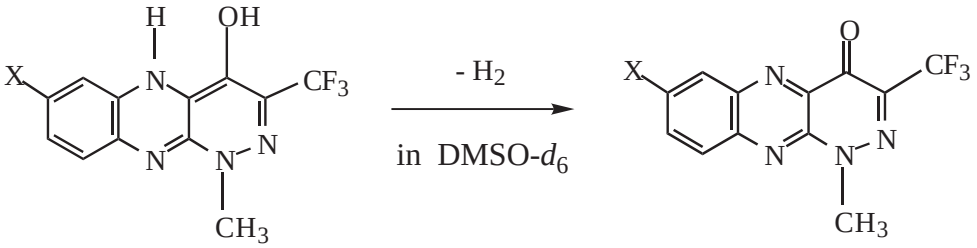
Scheme 6



4-Hydroxy Derivative

4-Oxo Derivative

Scheme 7



17a X = Cl
17b X = H
1,5-Dihydro Form

6a X = Cl
6b X = H
1,4-Dihydro Form

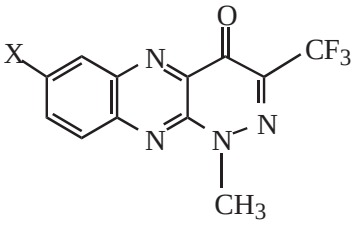
Table 2. Aromatic Proton Signals observed in the NMR Spectra of Compounds (**17a,b**) in DMSO-d_6

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

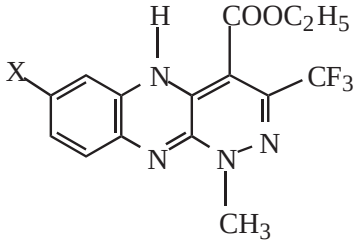
Moreover, in the NMR spectra, the 4-hydroxy derivatives (**17a,b**) showed the aromatic proton signals in a higher magnetic field (δ 6.99 - 6.61) and in a lower magnetic field (δ 8.50 - 8.01) (Scheme 7, Table 2),[7] which would correspond to the aromatic proton signals of the 4-hydroxy derivatives (**17a,b**) 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 the1,5-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).

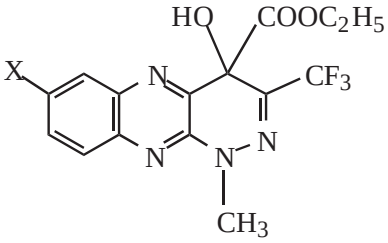
Figure



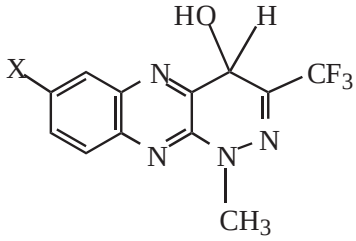
6a X = Cl
6b X = H
1,4-Dihydro Form



15a X = Cl
15b X = H
1,5-Dihydro Form



16a X = Cl
16b X = H
1,4-Dihydro Form



18a X = Cl
18b X = H
1,4-Dihydro Form

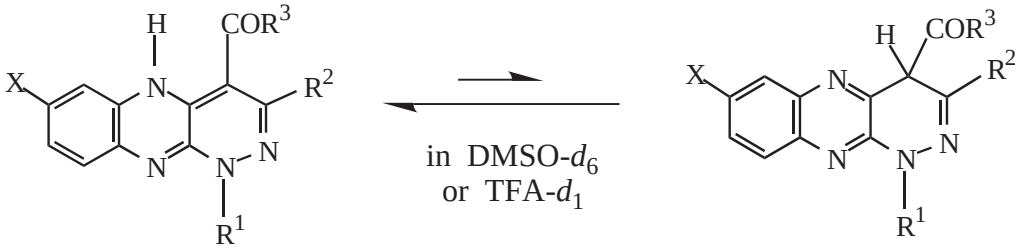
Table 3. Aromatic Proton Signals of Compounds (**6a,b**), (**15a,b**), and (**16a,b**)

Compound	Solvent	Aromatic Proton Signals (δ)
6a	DMSO-d_6	8.50, 8.23, 8.13
6b	DMSO-d_6	8.35, 8.20, 8.13, 8.02
15a	TFA-d_1	6.71 - 6.66
15b	TFA-d_1	6.92 - 6.80
16a	DMSO-d_6	8.15 - 7.89
16b	DMSO-d_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



1,5-Dihydro Form 1,4-Dihydro Form

X = Cl, H ; R^1 = CH_3, C_2H_5 ; R^2 = CH_3, $COOCH_3$; R^3 = OC_2H_5, CH_3, C_6H_5

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-CH_3). *Anal.* Calcd for $C_{11}H_8N_4OClF_3$: 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, CH_2), 3.53 (s, 3H, N-CH_3), 1.11 (t, J = 7.0 Hz, 3H, CH_3). *Anal.* Calcd for $C_{15}H_{12}N_4O_2ClF_3$: 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-CH_3), 1.06 (dd, J = 7.0, 7.0 Hz, 3H, CH_3). *Anal.* Calcd for $C_{15}H_{12}N_4O_3ClF_3$: 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 (H_2)], 316 [(M^+ + 2) - 2 (2H)]; NMR (deuteriodimethyl sulfoxide): [siganls 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-CH_3); [signals for unknown tautomer[7] (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 $C_{12}H_8N_4OClF_3$: 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-CH_3). *Anal.* Calcd for $C_{12}H_6N_4OClF_3$: 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, CH_2), 3.61 (s, 3H, N-CH_3), 1.20 (t, J = 7.0 Hz, 3H, CH_3). *Anal.* Calcd for $C_{15}H_{13}N_4O_2F_3$: 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, CH_2), 4.12 (dd, J = 7.0, 10.0 Hz, 1H, CH_2), 3.82 (s, 3H, N-CH_3), 1.06 (dd, 3H, CH_3). *Anal.* Calcd for $C_{15}H_{13}N_4O_3F_3$: 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-trifluoro-methylpyridazino[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 yelllow 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 needlles.

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 (H_2)]; NMR (deuteriodimethyl sulfoxide): [siganls 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-CH_3); [signals for unknown tautomer[7] (10%)] 6.44 - 6.34 (m, C6-, C8-, C9-H). *Anal.* Calcd for $C_{12}H_9F_3N_4O$: 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-CH_3). *Anal.* Calcd for $C_{12}H_7N_4OF_3$: 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 neeldes.

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]