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# QUINOLONE ANALOGUES 3. SYNTHESIS OF 1,3-DIALKYL-4-OXO-1,4-DIHYDROPYRIDAZINO[3,4 -*b*]QUINOXALINES

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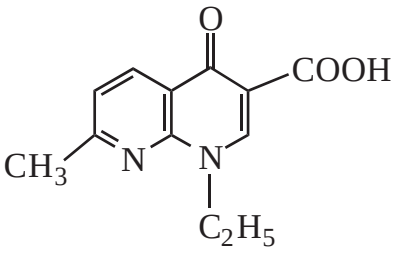
*Abstract* - The 1-alkyl-3-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxalines (**10a-d**) were synthesized from the quinoxaline *N*-oxides (**8a-d**) *via* the oxidation of the 4-acetyl-1-alkyl-3-methyl-1,5-dihydro-pyridazino[3,4-*b*]quinoxalines (**9a-d**) with *N*-bromosuccinimide/water, sodium bromate, or selenium dioxide, while the 1-alkyl-3-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines (**13a-d**) were synthesized from the quinoxaline *N*-oxides (**8a-d**) *via* the oxidative ring trans-formation of the 1-alkyl-3-ethyl-2,3-dihydro-4-hydroxy-1*H*-1,2-diaz-epino[3,4-*b*]quinoxalines (**12a-d**), respectively.

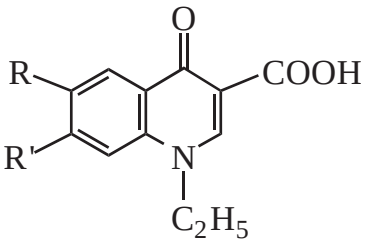
Since the discovery of nalidixic acid (Chart 1) in 1962[1] and its introduction in the treatment of urinary tract infections in 1963, many research groups have developed quinolone antibacterials[2] such as oxolinic acid,[2] resoxacin,[2] pipemidic acid,[2] cinoxacin,[2,3] pyrimido[4,5-*c*]pyridazines,[2,4] and pyrido[2,3-*b*]quinoxalines,[5] and new quinolones such as ofloxacin,[6] enoxacin,[7] ciprofloxacin,[8] flumequine,[2] norfloxacin,[9] sitafloxacin,[10] sparfloxacin,[11] and

tosufloxacin.[12]

**Chart 1**

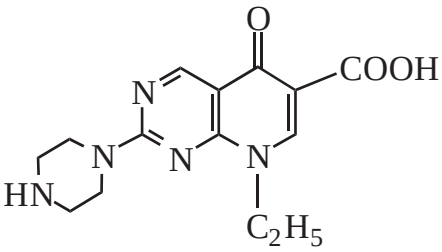


Nalidixic Acid

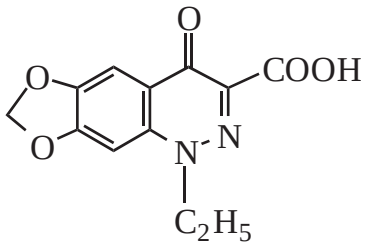


Oxolinic Acid
R, R' = $OCH_2O$

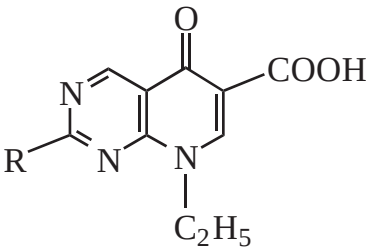
Resoxacin
R = H, R' = 4-Pyridyl



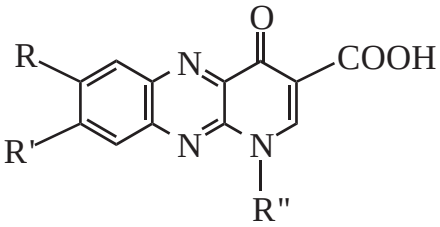
Pipemidic Acid



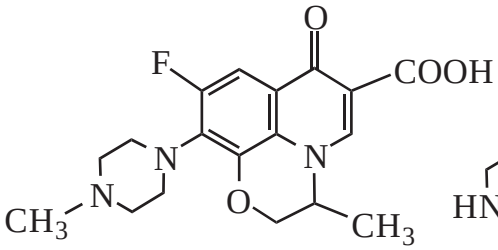
Cinoxacin



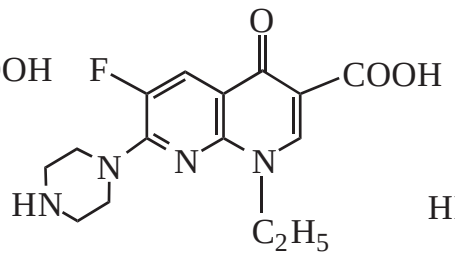
Pyrimido[4,5-*c*]pyridazines



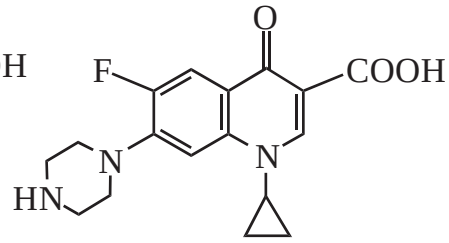
Pyrido[2,3-*b*]quinoxalines



Ofloxacin



Enoxacin



Ciprofloxacin

Recently, we have also reported the synthesis of the 1-alkyl-4-oxo-1,4-dihydro-pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids (**1**)[13] (Chart 2) as the candidates of antibacterial quinolone analogues, which are provided by the structural hybridization among nalidixic acid, cinoxacin, and pyrido[2,3-*b*]quinoxalines. However, compounds (**1**) were found to be inferior to nalidixic acid and cinoxacin in the antibacterial activity, and hence we then carried out the modification of the $C_3$-substituent as shown in Chart 3, since there was a successful example for the $C_3$-substituent alteration in one of quinolone

analogues such as the 3-quinolinecarboxamide (**5**) (Chart 4) having the excellent antiherpetic activity.[14] Namely, an improvement of antimicrobial activities is expected in the structural change of compounds (**1**) into the 2-(1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)acetates (**2**) and 4-(1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-

**Chart 2**

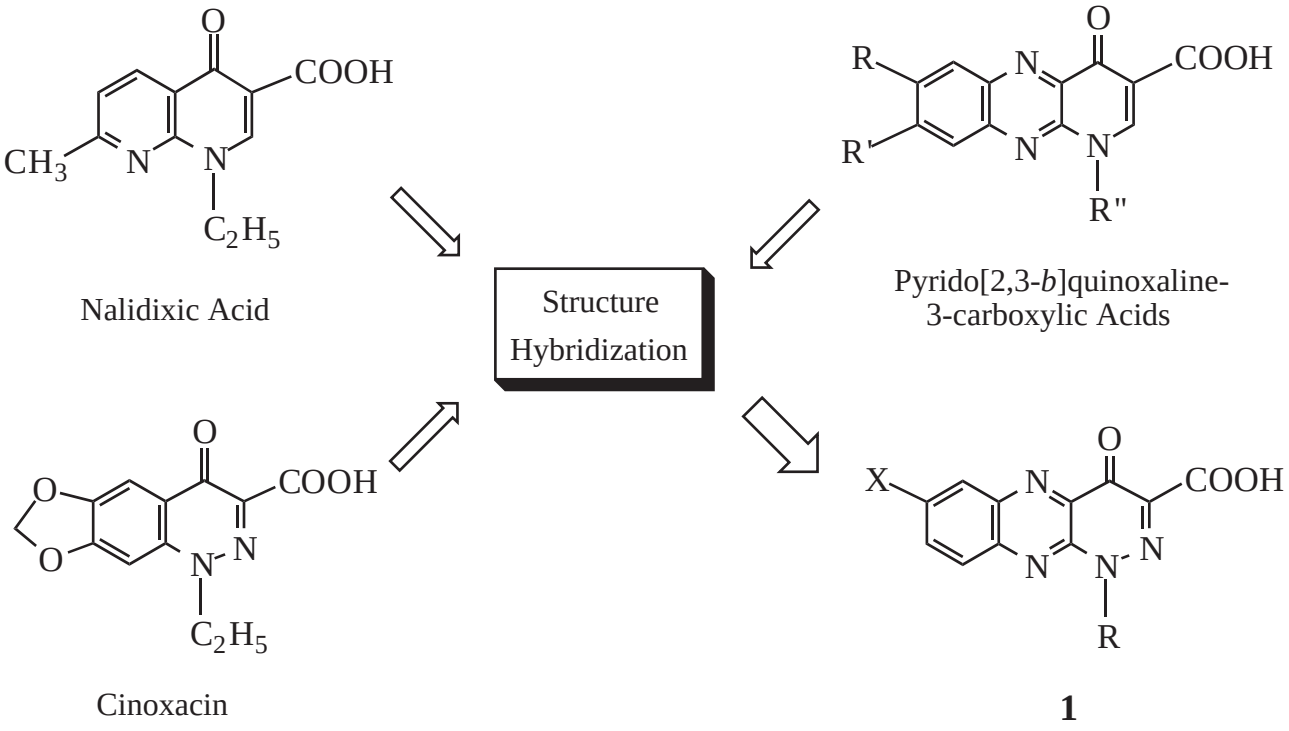
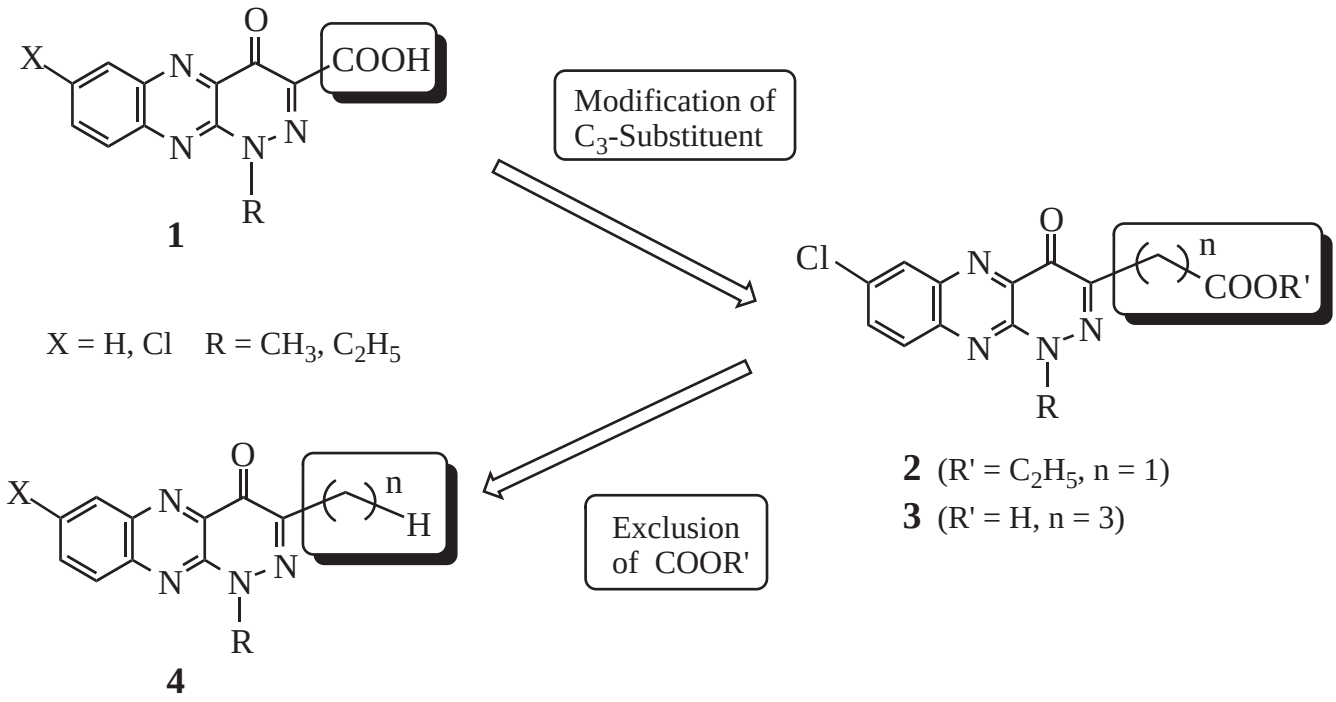
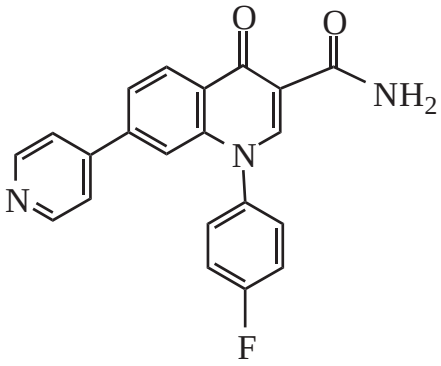



**Chart 3**

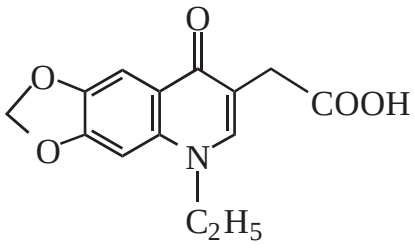


3-yl)butyric acids (**3**).[15] The synthesis and subsequent screening test of compounds (**2** and **3**) were carried out, indicating that the antimicrobial activities of compounds (**2** and **3**) were similar to those of compounds (**1**). These results manifested that the insertion of the methylene group between the $C_3$ carbon and the $C_3$-carboxyl (or its ester) group did not lower the antimicrobial activities. One of oxolinic acid homologues, the methylene-inserted carboxylic acid (**6**) (Chart 4), has also been reported to have antibacterial activities.[2]

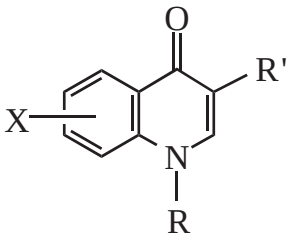
**Chart 4**




**5**




**6**




**7**

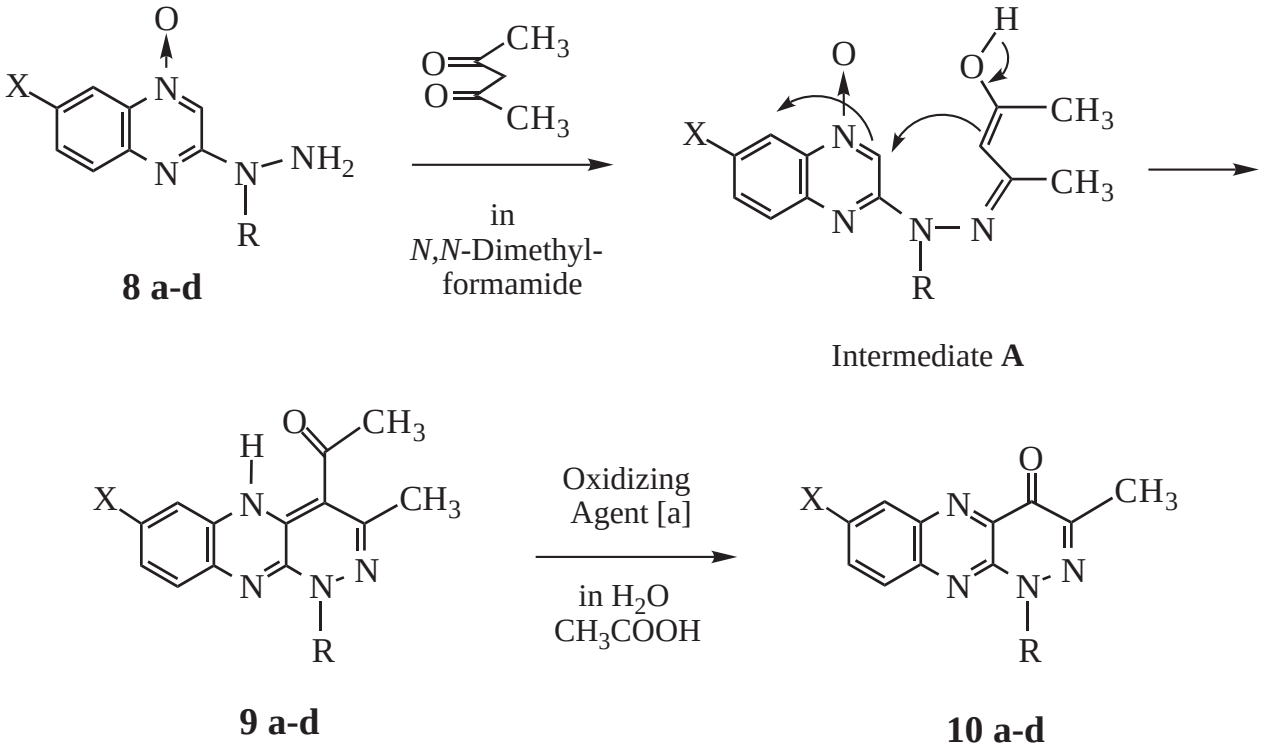
| R' |
|---|
| H, $CH_2OR''$, CHO, COR'' |
| $NH_2$, $NHCOCH_3$, $NO_2$ |
| $SOCH_3$, $SO_2CH_3$, $SO_2NHR'$ |
| $PO_3H_2$, $PO(OC_2H_5)_2$ |

On the other hand, in a series of quinolone compounds (**7**) (Chart 4), various derivatives with diverse $C_3$-functional groups have been synthesized and bioassayed for many kinds of bacteria.[2] However, $C_3$-alkyl derivatives have not been synthesized yet in quinolone analogues. Accordingly, we have synthesized a series of $C_3$-alkyl compounds (**4**) (Chart 3) in the present investigation and examined whether the carboxyl (or its ester) group is indispensable for the antimicrobial activity of the 4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline derivatives. As the result, the screening data for compounds (**4**) showed that some of compounds (**4**) were found to be more excellent than compounds (**1**, **2**, and **3**) in an antimicrobial activity. This paper describes the synthesis of the 1-alkyl-3-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines (**10a-d**) from the quinoxaline *N*-oxides (**8a-d**) *via* the oxidation of the 1,5-dihydropyridazino[3,4-*b*]quinoxalines (**9a-d**)[16] (Scheme 1) together with the synthesis of the 1-alkyl-3-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines

(**13a-d**) from the quinoxaline *N*-oxides (**8a-d**) *via* the oxidative ring transformation of the 1,2-diazepino[3,4-*b*]quinoxalines (**12a-d**) (Scheme 2).[17-21]

(1) *Synthesis of 1-Alkyl-3-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxalines (**10a-d**)*
The reaction of the quinoxaline *N*-oxides (**8a-d**) with acetylacetone gave the 4-acetyl-1-alkyl-3-methyl-1,5-dihydropyridazino[3,4-*b*]quinoxalines (**9a-d**), respectively, presumably *via* an intermediate (**A**) (Scheme 1).[22] Oxidation of compounds (**9a-d**) with *N*-bromosuccinimide/water, sodium bromate, or selenium dioxide afforded the 1-alkyl-3-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines (**10a-d**), respectively, presumably *via* an intermediate (**B**) (Chart 5).[15]

**Scheme 1**



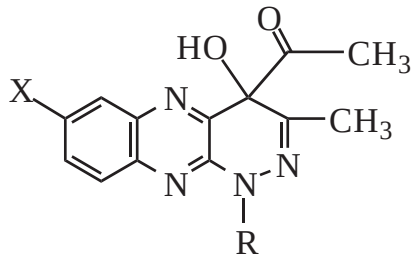

**a** : X = Cl, R = $CH_3$ ; **b** : X = Cl, R = $C_2H_5$ ; **c** : X = H, R = $CH_3$ ; **d** : X = H, R = $C_2H_5$

[a] *N*-Bromosuccinimide, $NaBrO_3$, or $SeO_2$

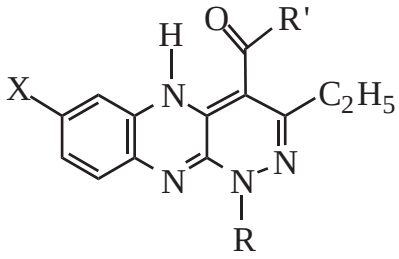
(2) *Synthesis of 1-Alkyl-3-ethyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxalines (**13a-d**)*
Since there was not a facile method for the synthesis of the $C_3$-ethyl homologue (**9e**) (Chart 5) utilizing a commercially available reagent, compounds (**13a-d**) were synthesized *via* the

oxidative ring transformation of compounds (**12a-d**) as follows.

**Chart 5**

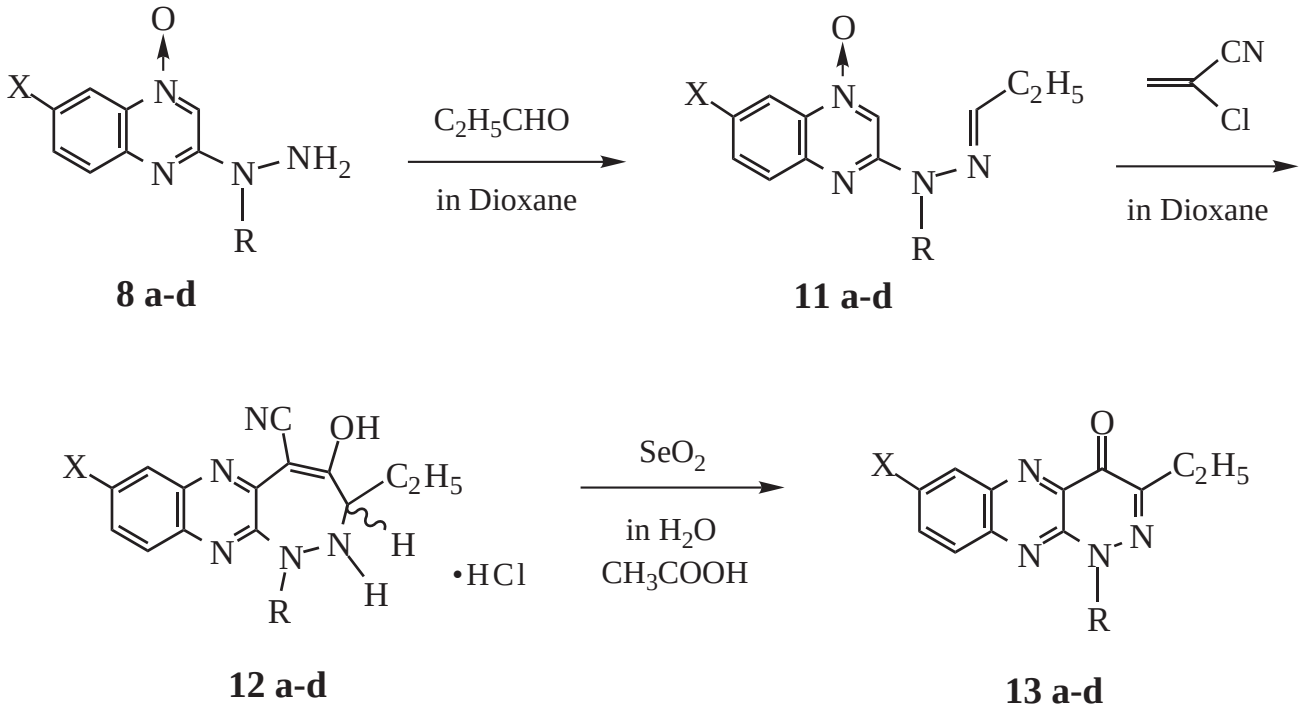


Intermediate **B**



**9e**

**Scheme 2**



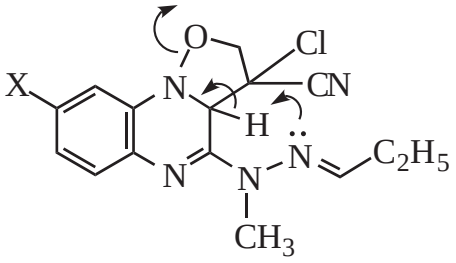

**8 a-d** **11 a-d** **12 a-d** **13 a-d**

**a** : X = Cl, R = $CH_3$ ; **b** : X = Cl, R = $C_2H_5$ ; **c** : X = H, R = $CH_3$ ; **d** : X = H, R = $C_2H_5$

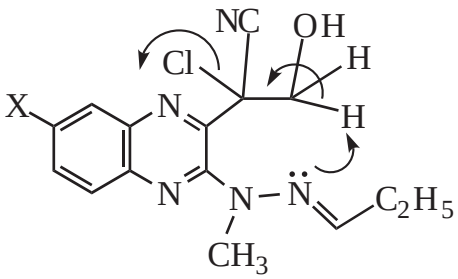
The reaction of the quinoxaline *N*-oxides (**8a-d**) with propionaldehyde provided the 2-(1-alkyl-2-propylidenehydrazino)-6-chloroquinoxaline 4-oxides (**11a,b**) and 3-(1-alkyl-2-propylidenehydrazino)quinoxaline 1-oxides (**11c,d**), whose reaction with 2-chloro-acrylonitrile gave the 1-alkyl-3-ethyl-2,3-dihydro-4-hydroxy-1*H*-1,2-diazepino[3,4-*b*]quino-xaline-5-carbonitrile hydrochlorides (**12a-d**), respectively (Scheme 2), presumably *via*

intermediates (**C**-**F**) (Chart 6). The reaction of compounds (**12a-d**) with selenium dioxide resulted in oxidative ring transformation to afford the 1-alkyl-3-ethyl-4-oxo-1,4-dihydro-pyridazino[3,4-*b*]quinoxalines (**13a-d**), respectively, presumably *via* intermediates (**G**-**J**) (Chart 7).[21,23]

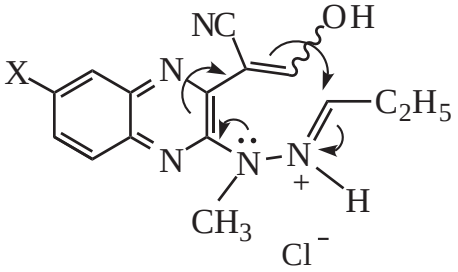
**Chart 6**



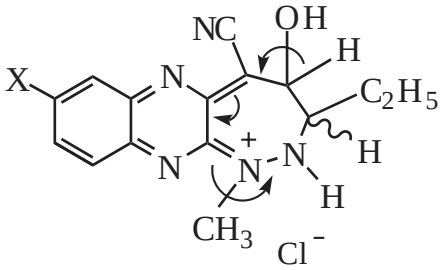
Intermediate **C**



Intermediate **D**

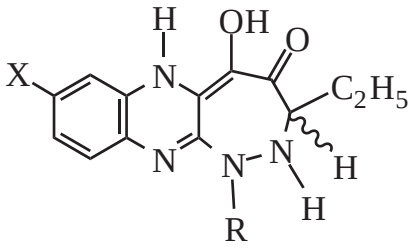


Intermediate **E**

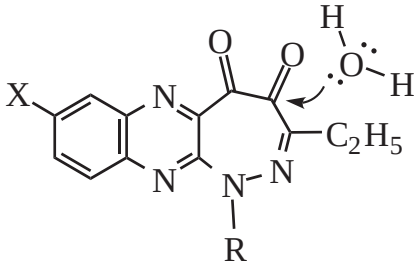


Intermediate **F**

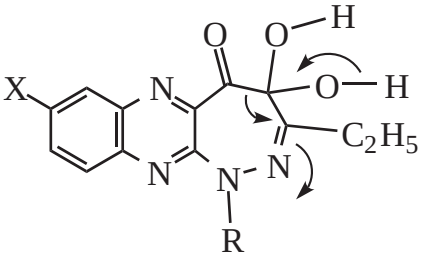
**Chart 7**



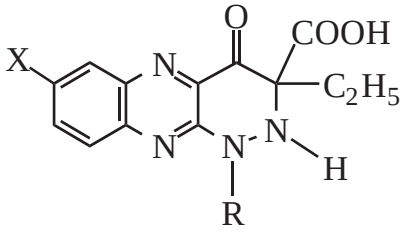
Intermediate **G**



Intermediate **H**



Intermediate **I**



Intermediate **J**

(3) *Screening Data*

The minimum inhibitory concentration (MIC) of the 1-methyl-3-alkyl derivatives (**10a**) and (**13a**) to *Bacillus subtilis* was 2.0 ppm,[24] which was superior to the MIC of the 3-carboxylic acids (**1**), methylene-inserted carboxylates (**2**), and methylene-inserted carboxylic acids (**3**) (15.6 ppm).

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

The synthesis of compound (**9a**) has already been reported by us.[16]

*4-Acetyl-7-chloro-1-ethyl-3-methyl-1,5-dihydropyridazino[3,4-b]quinoxaline (**9b**)*

A solution of compound (**8b**) (3 g, 12.6 mmol) and acetylacetone (3.14 g, 31.4 mmol) in *N,N*-dimethylformamide (30 mL) was refluxed in an oil bath for 3 h. The solution was allowed to stand overnight to precipitate orange to red needles of compound (**9b**), which were collected by suction filtration and washed with ethanol to afford an analytically pure sample (1.36 g, 36%), mp 184-185°C; IR: ν $cm^{-1}$ 1590, 1580; MS: m/z 302 ($M^+$), 304 ($M^+ + 2$); $^1H$ NMR (deuteriotrifluoroacetic acid): 6.97 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 6.96 (d, J = 2.0 Hz, 1H, $C_6$-H), 6.88 (d, J = 9.0 Hz, 1H, $C_9$-H), 4.04 (q, J = 7.0 Hz, 2H, $N_1$-ethyl $CH_2$), 2.64 (s, 3H, $C_4$-acetyl $CH_3$), 2.45 (s, 3H, $C_3$-$CH_3$), 1.39 (t, J = 7.0 Hz, 3H, $N_1$-ethyl $CH_3$). The $N_5$-H proton signal was not observed because of D - H exchange. *Anal*. Calcd for $C_{15}H_{15}N_4OCl$: C, 59.51; H, 4.99; N, 18.51; Cl, 11.71. Found: C, 59.21; H, 4.95; N, 18.54; Cl, 11.83.

*4-Acetyl-1,3-dimethyl-1,5-dihydropyridazino[3,4-b]quinoxaline (**9c**)*

A solution of compound (**8c**) (4 g, 21.1 mmol) and acetylacetone (5.28 g, 52.8 mmol) in *N,N*-dimethylformamide (30 mL) was refluxed in an oil bath for 3 h. The solution was allowed to stand overnight to precipitate orange needles of compound (**9c**), which were collected by

suction filtration and washed with ethanol to afford an analytically pure sample (2.15 g, 40%), mp 206-207°C; IR: ν $cm^{-1}$ 1600, 1585, 1535, 1505; MS: m/z 254 ($M^+$); $^1H$ NMR [deuteriodimethyl sulfoxide-deuteriotrifluoroacetic acid (1:1)]: 6.98 (m, 1H, aromatic H), 6.83-6.75 (m, 3H, aromatic H), 3.51 (s, 3H, $N_1$-$CH_3$), 2.35 (s, 3H, $C_4$-acetyl $CH_3$), 2.08 (s, 3H, $C_3$-$CH_3$). The $N_5$-H proton signal was not observed because of D - H exchange. *Anal*. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.91; H, 5.49; N, 21.92.

*4-Acetyl-1-ethyl-3-methyl-1,5-dihydropyridazino[3,4-b]quinoxaline (**9d**)*

A solution of compound (**8d**) (4 g, 19.6 mmol) and acetylacetone (4.90 g, 49.0 mmol) in *N*,*N*-dimethylformamide (30 mL) was refluxed in an oil bath for 3 h. The solution was allowed to stand overnight to precipitate red needles of compound (**9d**), which were collected by suction filtration and washed with ethanol to give an analytically pure sample (1.66 g, 32%), mp 139-140°C; IR: ν $cm^{-1}$ 1585, 1580; MS: m/z 268 ($M^+$); $^1H$ NMR (deuteriodimethyl sulfoxide): 12.88 (br, 1H, $N_5$-H), 6.91 - 6.70 (m, 4H, aromatic H), 3.64 (q, J = 7.0 Hz, 2H, $N_1$-ethyl $CH_2$), 2.39 (s, 3H, $C_4$-acetyl $CH_3$), 2.09 (s, 3H, $C_3$ -$CH_3$), 1.12 (t, J = 7.0 Hz, 3H, $N_1$-ethyl $CH_3$). *Anal*. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.17; H, 6.02; N, 20.76.

*7-Chloro-1,3-dimethyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**10a**)*

A solution of compound (**9a**) (1 g, 3.47 mmol) and *N*-bromosuccinimide (1.55 g, 8.68 mmol) in acetic acid (20 mL)/water (10 mL) was refluxed in an oil bath for 2 h. The reaction mixture was allowed to stand overnight to precipitate orange cottony needles of compound (**10a**), which were collected by suction filtration and washed with ethanol/hexane (1:1) to provide an analytically pure sample (0.74 g, 82%), mp 229-230°C; IR: ν $cm^{-1}$ 1650; MS: m/z 260 ($M^+$), 262 ($M^+$ + 2); $^1H$ NMR (deuteriotrifluoroacetic acid): 8.27 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.20 (d, J = 9.0 Hz, 1H, $C_9$-H), 8.02 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 4.54 (s, 3H, $N_1$-$CH_3$), 2.62 (s, 3H, $C_3$-$CH_3$). *Anal.* Calcd for $C_{12}H_9N_4OCl$: C, 55.29; H, 3.48; N, 21.49; Cl, 13.60. Found: C, 55.09; H, 3.50; N, 21.52; Cl, 13.60.

*7-Chloro-1-ethyl-3-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**10b**)*

A solution of compound (**9b**) (1 g, 3.31 mmol) and sodium bromate (1.0 g, 6.61 mmol) in acetic acid (20 mL)/water (10 mL) was refluxed in an oil bath for 2 h to precipitate orange prismic needles. After the reaction mixture was allowed to stand overnight, the orange

prismic needles of compound (**10b**) were collected by suction filtration and washed with ethanol/hexane (1:1) to provide an analytically pure sample (0.57 g, 63%), mp 200-201°C; IR: ν $cm^{-1}$ 1640; MS: m/z 274 ($M^+$), 276 ($M^+$ + 2); $^1$H NMR (deuteriodimethyl sulfoxide): 8.35 (dd, J = 2.0, 0.5 Hz, 1H, $C_6$-H), 8.10 (dd, J = 9.0, 0.5 Hz, 1H, $C_9$-H), 8.01 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 4.60 (q, J = 7.0 Hz, 2H, $N_1$-ethyl $CH_2$), 2.32 (s, 3H, $C_3$-$CH_3$), 1.41 (t, J = 7.0 Hz, 3H, $N_1$-ethyl $CH_3$). *Anal.* Calcd for $C_{13}H_{11}N_4OCl$: C, 56.84; H, 4.04; N, 20.39; Cl, 12.91. Found: C, 56.56; H, 3.96; N, 20.21; Cl, 12.85.

*1,3-Dimethyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**10c**)*

A solution of compound (**9c**) (5 g, 19.7 mmol) and sodium bromate (5.95 g, 39.4 mmol) in acetic acid (100 mL)/water (30 mL) was refluxed in an oil bath for 2 h. The solution was allowed to stand overnight to precipitate yellow needles of compound (**10c**), which were collected by suction filtration and washed with ethanol to give an analytically pure sample (2.73 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals of compound (**10c**), which were collected by suction filtration (0.97 g), total yield, 3.70 g (83%).

Compound (**10c**) had mp 247-248°C; IR: ν $cm^{-1}$ 1635, 1610; MS: m/z 226 ($M^+$); $^1$H NMR [deuteriodimethyl sulfoxide-deuteriotrifluoroacetic acid (1:1)]: 8.10 (ddd, J = 8.5, 1.5, 0.8 Hz, 1H, aromatic H), 7.95 (ddd, J = 8.5, 1.5, 0.8 Hz, 1H, aromatic H), 7.83 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H, aromatic H), 7.68 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H, aromatic H), 4.03 (s, 3H, $N_1$-$CH_3$) 2.23 (s, 3H, $C_3$-$CH_3$). *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.59; H, 4.55; N, 24.81.

*1-Ethyl-3-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**10d**)*

A solution of compound (**9d**) (2 g, 7.46 mmol) and selenium dioxide (1.66 g, 14.9 mmol) in acetic acid (50 mL)/water (10 mL) was refluxed in an oil bath for 1 h. Evaporation of the solvent *in vacuo* gave an oily residue, whose crystallization from ethanol/water afforded yellow needles of compound (**10d**) (0.81 g, 45%), mp 160-161°C; IR: ν $cm^{-1}$ 1645; MS: m/z 240 ($M^+$); $^1$H NMR (deuteriodimethyl sulfoxide): 8.24 (dd, J = 8.0, 1.5 Hz, 1H, aromatic H), 8.07 (dd, J = 8.0, 1.5 Hz, 1H, aromatic H), 8.01 (ddd, J = 8.0, 7.0, 1.5 Hz, 1H, aromatic H), 7.87 (ddd, J = 8.0, 7.0, 1.5 Hz, 1H, aromatic H), 4.62 (q, J = 7.0 Hz, 2H, $N_1$-ethyl $CH_2$), 2.33 (s, 3H, $C_3$-$CH_3$), 1.42 (t, J = 7.0 Hz, 3H, $N_1$-ethyl $CH_3$). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.82; H, 5.05; N, 23.21.

*6-Chloro-2-(1-methyl-2-propylidenehydrazino)quinoxaline 4-Oxide (**11a**)*

A solution of compound (**8a**) (10 g, 44.5 mmol) and propionaldehyde (6.44 g, 111 mmol) in *N,N*-dimethylformamide (200 mL) was refluxed in an oil bath for 2 h. Evaporation of the solvent *in vacuo* afforded yellow crystals of compound (**11a**). Recrystallization from *N,N*-dimethylformamide/ethanol/waterr provided yellow needles (11.31 g, 96%), mp 128-129°C; IR: ν $cm^{-1}$ 1580, 1540, 1500; MS: m/z 264 ($M^+$), 266 ($M^+$ + 2); $^1$H NMR (deuteriodimethyl sulfoxide): 8.68 (s, 1H, $C_3$-H), 8.20 (dd, J = 2.0, 1.0 Hz, 1H, $C_5$-H), 7.74 (dd, J = 8.5, 1.0 Hz, 1H, $C_8$-H), 7.72 (dd, J = 2.0, 8.5 Hz, 1H, $C_7$-H), 7.34 (t, J = 4.5 Hz, 1H, propylidene CH), 3.48 (s, 3H, N-$CH_3$), 2.38 (qd, J = 7.0, 4.5 Hz, 2H, propylidene $CH_2$), 1.11 (t, J = 7.0 Hz, 3H, propylidene $CH_3$). *Anal.* Calcd for $C_{12}H_{13}N_4OCl$: C, 54.45; H, 4.95; N, 21.17; Cl, 13.39. Found: C, 54.40; H, 4.98; N, 21.14; Cl, 13.42.

*6-Chloro-2-(1-ethyl-2-propylidenehydrazino)quinoxaline 4-Oxide (**11b**)*

A solution of compound (**8b**) (5 g, 21.0 mmol) and propionaldehyde (3.04 g, 52.4 mmol) in *N,N*-dimethylformamide (100 mL) was refluxed in an oil bath for 2 h. Evaporation of the solvent *in vacuo* gave yellow crystals of compound (**11b**). Recrystallization from ethanol afforded brown prismic needles (4.92 g, 84%), mp 119-120°C; IR: ν $cm^{-1}$ 1575, 1530, 1485; MS: m/z 278 ($M^+$), 280 ($M^+$ + 2); $^1$H NMR (deuteriodimethyl sulfoxide): 8.64 (d, J = 0.5 Hz, 1H, $C_3$-H), 8.20 (ddd, J = 2.0, 1.0, 0.5 Hz, 1H, $C_5$-H), 7.74 (dd, J = 8.5, 1.0 Hz, 1H, $C_8$-H), 7.71 (dd, J = 2.0, 8.5 Hz, 1H, $C_7$-H), 7.42 (t, J = 4.5 Hz, 1H, propylidene CH), 4.21 (q, J = 7.0 Hz, 2H, N-ethyl $CH_2$), 2.38 (qd, J = 7.0, 4.5 Hz, 2H, propylidene $CH_2$), 1.11 (t, J = 7.0 Hz, 3H, propylidene $CH_3$), 1.08 (t, J = 7.0 Hz, 3H, N-ethyl $CH_3$). *Anal.* Calcd for $C_{13}H_{15}N_4OCl$: C, 56.02; H, 5.42; N, 20.10; Cl, 12.72. Found: C, 55.92; H, 5.40; N, 19.98; Cl, 12.69.

*3-(1-Methyl-2-propylidenehydrazino)quinoxaline 1-Oxide (**11c**)*

A solution of compound (**8c**) (5 g, 26.3 mmol) and propionaldehyde (2.29 g, 39.5 mmol) in *N,N*-dimethylformamide (100 mL) was refluxed in an oil bath for 2 h. Evaporation of the solvent *in vacuo* gave yellow crystals of compound (**11c**). Recrystallization from ethanol/water provided yellow needles (5.50 g, 91%), mp 120-121°C; IR: ν $cm^{-1}$ 1610, 1585, 1545, 1505; MS: m/z 230 ($M^+$); $^1$H NMR (deuteriodimethyl sulfoxide): 8.68 (s, 1H, $C_2$-H), 8.24 (ddd, J = 8.5, 2.5, 1.5 Hz, 1H, aromatic H), 7.74-7.68 (m, 2H, aromatic H), 7.45 (ddd, J = 8.5, 5.5, 2.5 Hz, 1H, aromatic H), 7.30 (t, J = 4.5 Hz, 1H, propylidene CH), 3.48 (s, 3H, N-

$CH_3$), 2.37 (qd, J = 7.0, 4.5 Hz, 2H, propylidene $CH_2$), 1.11 (t, J = 7.0 Hz, 3H, propylidene $CH_3$). *Anal.* Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.53; H, 5.94; N, 24.37.

*3-(1-Ethyl-2-propylidenehydrazino)quinoxaline 1-Oxide (**11d**)*

A solution of compound (**8d**) (5 g, 24.5 mmol) and propionaldehyde (2.13 g, 36.8 mmol) in *N,N*-dimethylformamide (100 mL) was refluxed in an oil bath for 2 h. Evaporation of the solvent *in vacuo* gave yellow crystals of compound (**11d**). Recrystallization from ethanol/water provided yellow needles (4.39 g, 90%), mp 95-96°C; IR: ν $cm^{-1}$ 1610, 1580, 1535, 1490; MS: m/z 244 ($M^+$); $^1H$ NMR (deuteriodimethyl sulfoxide): 8.65 (s, 1H, $C_2$-H), 8.24 (ddd, J = 8.5, 1.5, 0.5 Hz, 1H, aromatic H), 7.74 (ddd, J = 8.5, 2.0, 0.5 Hz, 1H, aromatic H), 7.70 (ddd, J = 8.5, 6.5, 1.5 Hz, 1H, aromatic H), 7.45 (ddd, J = 8.5, 6.5, 2.0 Hz, 1H, aromatic H), 7.39 (t, J = 4.5 Hz, 1H, propylidene CH), 4.22 (q, J = 7.0 Hz, 2H, N-ethyl $CH_2$), 2.38 (qd, J = 7.0, 4.5 Hz, 2H, propylidene $CH_2$), 1.11 (t, J = 7.0 Hz, 3H, propylidene $CH_3$), 1.08 (t, J = 7.0 Hz, 3H, N-ethyl $CH_3$). *Anal.* Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93. Found: C, 63.76; H, 6.54; N, 22.90.

*8-Chloro-3-ethyl-2,3-dihydro-4-hydroxy-1-methyl-1H-1,2-diazepino[3,4-b]quinoxaline-5-carbonitrile Hydrochloride (**12a**)*

A solution of compound (**11a**) (3 g, 11.4 mmol) and 2-chloroacrylonitrile (2.49 g, 28.5 mmol) in dioxane (90 mL) was refluxed in an oil bath for 30 min. The reaction mixture was allowed to stand overnight to precipitate brown crystals of compound (**12a**), which were collected by suction filtration and washed with hexane (2.10 g, 53%), IR: ν $cm^{-1}$ 3400, 3180, 2220, 1650, 1590, 1570; MS: m/z 315 ($M^+$), 317 ($M^+$ + 2). This sample was used for the ring transformation into the pyridazino[3,4-*b*]quinoxaline (**13a**).

*8-Chloro-1,3-diethyl-2,3-dihydro-4-hydroxy-1H-1,2-diazepino[3,4-b]quinoxaline-5-carbonitrile Hydrochloride (**12b**)*

A solution of compound (**11b**) (4 g, 14.4 mmol) and 2-chloroacrylonitrile (3.14 g, 35.9 mmol) in dioxane (120 mL) was refluxed in an oil bath for 30 min to precipitate brown crystals of compound (**12b**). After the reaction mixture was cooled to rt, the hydrochloride (**12b**) was collected by suction filtration and washed with hexane (1.92 g, 37%), IR: ν $cm^{-1}$ 3120, 2220, 1640, 1620, 1590, 1540; MS: m/z 329 ($M^+$), 331 ($M^+$ + 2). This sample was employed for

the ring transformation into the pyridazino[3,4-*b*]quinoxaline (**13b**).

*3-Ethyl-2,3-dihydro-4-hydroxy-1-methyl-1H-1,2-diazepino[3,4-b]quinoxaline-5-carbonitrile Hydrochloride (**12c**)*

A solution of compound (**11c**) (4 g, 17.4 mmol) and 2-chloroacrylonitrile (3.81 g, 43.5 mmol) in dioxane (100 mL) was refluxed in an oil bath for 30 min to precipitate brown crystals of compound (**12c**). After the reaction mixture was cooled to rt, the hydrochloride (**12c**) was collected by suction filtration and washed with hexane (3.65 g, 66%).

Evaporation of the filtrate *in vacuo* gave an oily residue, which was crystallized from dioxane/hexane to provide orange prisms [free base of compound (**12c**)] (170 mg, 5%). Compound (**12c**) [IR: ν $cm^{-1}$ 3400, 3170, 2200, 15650; MS: m/z 281 ($M^+$)] was used for the ring transformation into the pyridazino[3,4-*b*]quinoxaline (**13c**).

Free base of compound (**12c**) had mp 195-196°C; IR: ν $cm^{-1}$ 3210, 1600, 1565; MS: m/z 281 ($M^+$); $^1$H NMR (deuteriodimethyl sulfoxide): 14.21 (br, 1H, OH), 7.74 (dd, J = 8.0, 1.0 Hz, 1H, aromatic H), 7.52 (dd, J = 8.0, 1.0 Hz, 1H, aromatic H), 7.42 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, aromatic H), 7.32 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, aromatic H), 5.82 (d, J = 2.0 Hz, 1H, $N_2$-H), 3.79 (ddd, J = 10.0, 5.0, 2.0 Hz, 1H, $C_3$-H), 3.24 (s, 3H, $N_1$-$CH_3$), 1.70 (qdd, J = 14.0, 10.0, 7.0 Hz, 1H, methylene CH of $C_3$-ethyl), 1.50 (qdd, J = 14.0, 7.0, 5.0 Hz, 1H, methylene CH of $C_3$-ethyl), 1.02 (dd, J = 7.0, 7.0 Hz, 3H, $C_3$-ethyl $CH_3$). *Anal.* Calcd for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.89. Found: C, 63.87; H, 5.48; N, 24.54.

*1,3-Diethyl-2,3-dihydro-4-hydroxy-1H-1,2-diazepino[3,4-b]quinoxaline-5-carbonitrile Hydrochloride (**12d**)*

A solution of compound (**11d**) (3 g, 12.3 mmol) and 2-chloroacrylonitrile (2.70 g, 30.8 mmol) in dioxane (100 mL) was refluxed in an oil bath for 1 h. The solution was allowed to stand overnight to precipitate brown crystals of compound (**12d**), which were collected by suction filtration and washed with hexane (1.96 g, 48%). Evaporation of the filtrate *in vacuo* provided an oily residue, which was crystallized from dioxane/hexane to provide brown needles [free base of compound (**12d**)] (370 mg, 10%).

Compound (**12d**) [IR: ν $cm^{-1}$ 3400, 3100, 2220, 1640, 1620; MS: m/z 295 ($M^+$)] was employed for the ring transformation into the pyridazino[3,4-*b*]quinoxaline (**13d**).

Free base of compound (**12d**) had mp 164-165°C; IR: n $cm^{-1}$ 3245, 2975, 2940, 2215, 1600;

MS: m/z 295 ($M^+$); $^1$H NMR (deuteriodimethyl sulfoxide): 14.23 (br, 1H, OH), 7.72 (dd, J = 8.0, 1.0 Hz, 1H, aromatic H), 7.49 (dd, J = 8.0, 1.0 Hz, 1H, aromatic H), 7.41 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, aromatic H), 7.30 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, aromatic H), 5.77 (d, J = 2.5 Hz, 1H, $N_2$-H), 3.81 (qd, J = 14.0, 7.0 Hz, 1H, methylene CH of $N_1$-ethyl), 3.78 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H, $C_3$-H), 3.62 (qd, J = 14.0, 7.0 Hz, 1H, methylene CH of $N_1$-ethyl), 1.69 (qdd, J = 14.0, 10.0, 7.0 Hz, 1H, methylene CH of $C_3$-ethyl), 1.46 (qdd, J = 14.0, 7.0, 5.0 Hz, 1H, methylene CH of $C_3$-ethyl), 1.18 (dd, J = 7.0, 7.0 Hz, 3H, $N_1$-ethyl $CH_3$), 1.03 (dd, J = 7.0, 7.0 Hz, 3H, $C_3$-ethyl $CH_3$). *Anal.* Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.12; H, 5.71; N, 23.65.

*7-Chloro-3-ethyl-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**13a**)*

A solution of the hydrochloride (**12a**) (1 g, 2.84 mmol) and selenium dioxide (0.95 g, 8.56 mmol) in acetic acid (30 mL)/water (2 mL) was refluxed in an oil bath for 1 h. After the solution was filtered, the filtrate was evaporated *in vacuo* to give yellow crystals, which were triturated with ethanol/water and then collected by suction filtration (0.68 g, 87%). Recrystallization from ethanol provided brown prisms of compound (**13a**), mp 173-174°C; IR: ν $cm^{-1}$ 1645; MS: m/z 274 ($M^+$), 276 ($M^+$ + 2); $^1$H NMR (deuteriodimethyl sulfoxide): 8.34 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.09 (d, J = 9.0 Hz, 1H, $C_9$-H), 8.00 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 4.09 (s, 3H, $N_1$-$CH_3$ ), 2.74 (q, J = 7.0 Hz, 2H, $C_3$-ethyl $CH_2$), 1.20 (t, J = 7.0 Hz, 3H, $C_3$-ethyl $CH_3$). *Anal.* Calcd for $C_{13}H_{11}N_4OCl$: C, 56.84; H, 4.04; N, 20.39; Cl, 12.91. Found: C, 56.70; H, 4.09; N, 20.51; Cl, 13.05.

*7-Chloro-1,3-diethyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**13b**)*

A solution of the hydrochloride (**12b**) (1.5 g, 4.10 mmol) and selenium dioxide (0.91 g, 8.20 mmol) in acetic acid (30 mL)/water (5 mL) was refluxed in an oil bath for 1 h. Evaporation of the solvent *in vacuo* afforded brown crystals of compound (**13b**), which were recrystallized from ethanol to give brown prismic needles of compound (**13b**) (0.64 g, 54%), mp 188-189°C; IR: ν $cm^{-1}$ 1640, 1610; MS: m/z 288 ($M^+$), 290 ($M^+$ + 2); $^1$H NMR (deuteriodimethyl sulfoxide): 8.33 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.09 (d, J = 9.0 Hz, 1H, $C_9$-H), 8.00 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 4.61 (q, J = 7.0 Hz, 2H, $N_1$-ethyl $CH_2$), 2.76 (q, J = 7.0 Hz, 2H, $C_3$-ethyl $CH_2$), 1.42 (t, J = 7.0 Hz, 3H, $N_1$-ethyl $CH_3$), 1.21 (t, J = 7.0 Hz, 3H, $C_3$-ethyl $CH_3$). *Anal.* Calcd for $C_{14}H_{13}N_4OCl$: C, 58.24; H, 4.54; N, 19.40; Cl, 12.28. Found: C, 58.03; H, 4.61; N, 19.20; Cl, 12.33.

*3-Ethyl-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**13c**)*

A solution of compound (**12c**) (2 g, 6.30 mmol) and selenium dioxide (1.75 g, 15.8 mmol) in acetic acid (50 mL)/water (10 mL) was refluxed in an oil bath for 1 h. Evaporation of the solvent *in vacuo* gave brown crystals of compound (**13c**), which were recrystallized from ethanol/water to afford brown needles of compound (**13c**) (0.86 g). Evaporation of the filtrate *in vacuo* provided brown crystals of (**13c**), which were collected by suction filtration (0.12 g), total yield (0.98 g, 65%).

Compound (**13c**) had mp 182-183°C; IR: ν $cm^{-1}$ 1640, 1540, 1485; MS: m/z 240 ($M^+$); $^1H$ NMR (deuteriodimethyl sulfoxide): 8.22 (ddd, J = 7.5, 1.5, 0.5 Hz, 1H, aromatic H), 8.05 (ddd, J = 7.5, 1.5, 0.5 Hz, 1H, aromatic H), 8.00 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, aromatic H), 7.86 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, aromatic H), 4.09 (s, 3H, $N_1$-$CH_3$), 2.74 (q, J = 7.0 Hz, 2H, $C_3$-ethyl $CH_2$), 1.20 (t, J = 7.0 Hz, 3H, $C_3$-ethyl $CH_3$). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.83; H, 5.11; N, 23.15.

*1,3-Diethyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline (**13d**)*

A solution of compound (**12d**) (1.5 g, 4.52 mmol) and selenium dioxide (1.25 g, 11.3 mmol) in acetic acid (50 mL)/water (10 mL) was refluxed in an oil bath for 1 h. Evaporation of the solvent *in vacuo* gave brown crystals of compound (**13d**), which were recrystallized from ethanol/water to afford brown needles of compound (**13d**) (0.69 g, 60%), mp 146-147°C; IR: ν $cm^{-1}$ 1640, 1615, 1555, 1530; MS: m/z 254 ($M^+$); $^1H$ NMR (deuteriodimethyl sulfoxide): 8.22 (ddd, J = 7.5, 1.5, 0.5 Hz, 1H, aromatic H), 8.06 (ddd, J = 7.5, 1.5, 0.5 Hz, 1H, aromatic H), 8.00 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, aromatic H), 7.86 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, aromatic H), 4.61 (q, J = 7.0 Hz, 2H, $N_1$-ethyl $CH_2$), 2.75 (q, J = 7.0 Hz, 2H, $C_3$-ethyl $CH_2$), 1.43 (t, J = 7.0 Hz, 3H, $N_1$-ethyl $CH_3$), 1.21 (t, J = 7.0 Hz, 3H, $C_3$-ethyl $CH_3$). *Anal.* Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.25; H, 5.71; N, 22.22.

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23. There are several reports treating with the ring contraction of 1,2-diketones (for example, the ring contraction from an intermediate **H** to an intermediate **J** in Chart 7): H. C. Van Der Plas, 'Ring Transformation of Heterocycles,' Vol. 2, ed. by H. C. Van Der Plas, Academic Press, London, New York, 1973, pp. 146-147, 266-267, 272, 292-294, and references cited therein.
24. Other screening data for compounds (**10a**) and (**13a**) will be reported elsewhere.