

# Synthesis of 1,2-Diazepino[3,4-*b*]quinoxalines by 1,3-Dipolar Cycloaddition Reaction and Their Ring Transformation to Pyridazino[3,4-*b*]quinoxalines

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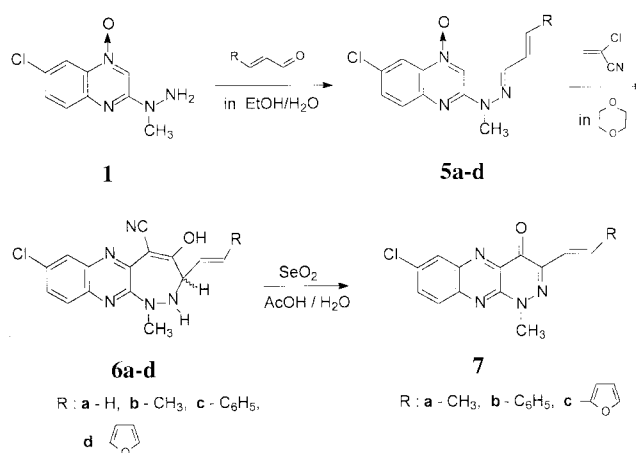
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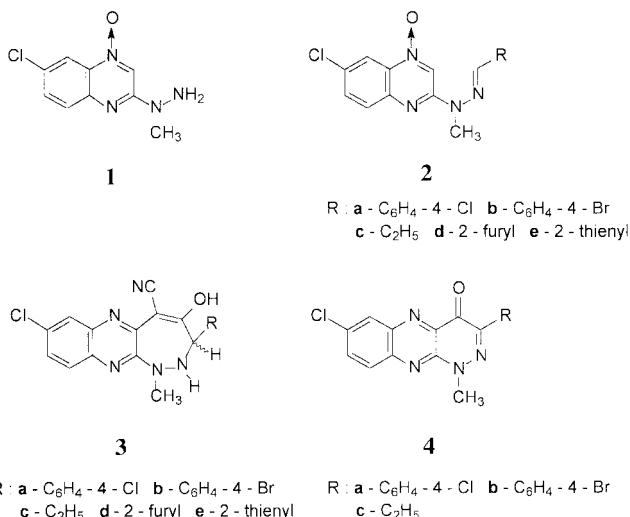
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Fused heterocyclic systems containing a quinoxaline ring were largely investigated because they were effective in pharmacological and agrochemical areas.<sup>1,2</sup>

In previous papers,<sup>3-8</sup> we reported the synthesis of the 1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **3a-e** from the quinoxaline *N*-oxide **1** via the hydrazones **2a-e** and then the oxidative ring transformation of **3a-c** with *N*-bromosuccinimide/water or selenium dioxide conveniently produced the pyridazino[3,4-*b*]quinoxalines **4a-c**, respectively. From the data of the screening test, it was found that compound **3d** showed a weak antibacterial activity against *Xanthomonas oryzae*, but compound **3e** did not show antibacterial activity.<sup>8</sup> Compound **4c** exhibited antibacterial activity against *Bacillus subtilis*.<sup>6</sup>



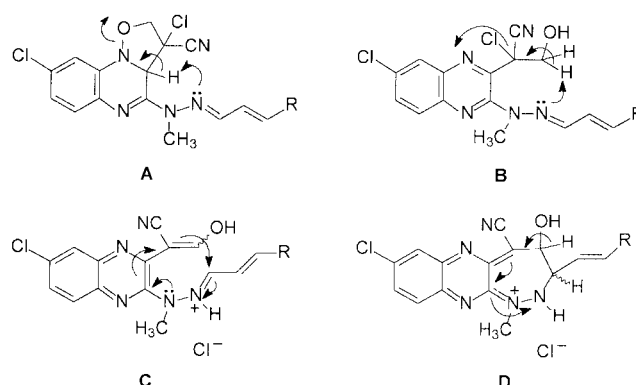
Scheme 1



In this note, we undertook the synthesis of 1,2-diazepino[3,4-*b*]quinoxalines **6** possessing the  $\alpha,\beta$ -unsaturated moieties at the 3-position from compounds **5** and the synthesis of pyridazino[3,4-*b*]quinoxalines **7** by the oxidative ring transformation of compounds **6** (Scheme 1). We, also, tested *in vitro* antibacterial activity of these compounds.

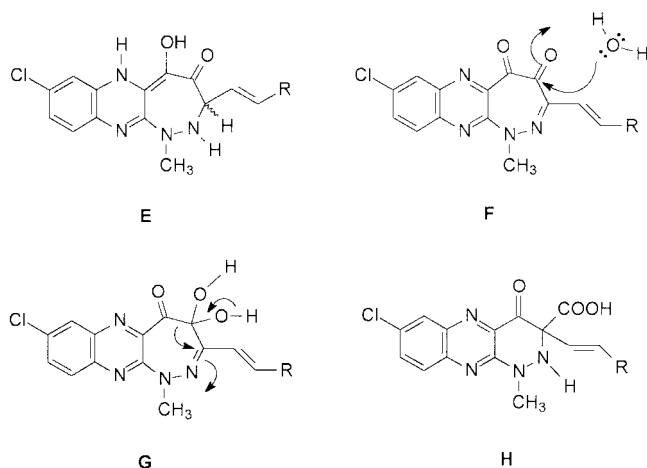
The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** with  $\alpha,\beta$ -unsaturated aldehydes such as acrolein, crotonaldehyde, *trans*-cinnamaldehyde and 3-(2-furyl)acrolein gave 6-chloro-2-[1-methyl-2-(vinylmethylene)hydrazino]quinoxaline 4-oxide **5a**, 6-chloro-2-[1-methyl-2-(methylvinyl-

methylene)hydrazino]quinoxaline 4-oxide **5b**, 6-chloro-2-[1-methyl-2-(phenylvinylmethylene)hydrazino]quinoxaline 4-oxide **5c** and 6-chloro-2-[(2-furylvinylmethylene)-1-methylhydrazino]quinoxaline 4-oxide **5d**, respectively. The reaction of compounds **5** with 2-chloroacrylonitrile afforded 6-chloro-2,3-dihydro-4-hydroxy-1-methyl-3-vinyl-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6a**, 6-chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(methylvinyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6b** and 6-chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(phenylvinyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6c** and 6-chloro-3-(2-furylvinyl)-2,3-dihydro-4-hydroxy-1-methyl-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6d**, respectively.



pino[3,4-*b*]quinoxaline-5-carbonitrile **6d**, respectively, presumably *via* intermediates **A-D**.<sup>3,4,6</sup>

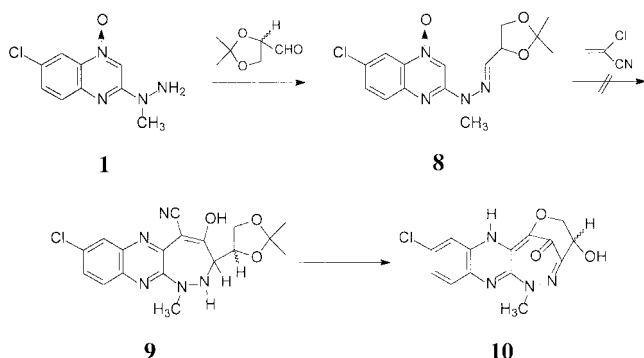
The reaction of the 1,2-diazepino[3,4-*b*]quinoxalines **6** with selenium dioxide in acetic acid/water resulted in oxidative ring transformation to provide 7-chloro-1-methyl-3-(methylvinyl)-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline **7a**, 7-chloro-1-methyl-3-(phenylvinyl)-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline **7b** and 7-chloro-3-(2-furylvinyl)-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline **7c**, respectively, presumably *via* intermediates **E-H**.<sup>5,6</sup>



We transformed compound **1** into the hydrazone **8** so as to synthesize new condensed quinoxaline **10** by 1,3-dipolar cycloaddition reaction and an intramolecular alcoholysis.<sup>7,9,10</sup> The reaction of compound **1** with 2,3-*O*-isopropylidene-D-glyceraldehyde<sup>11,12</sup> gave 6-chloro-2-[1-methyl-2-[4-(2,2-dimethyl-1,3-dioxolanylmethylene)]hydrazino]quinoxaline 4-oxide **8** (Scheme 2). Efforts to obtain compound **9** and **10** from the reaction of compound **8** with 2-chloroacrylonitrile were unsuccessful.

The structure of new compounds **6** and **7** was supported by the spectral and analytical data. The 2,3-dihydro-4-hydroxy form of compounds **6** have already been clarified by the measurement of the NOE between the N<sub>2</sub>-H and C<sub>3</sub>-H protons in previous papers.<sup>3,4</sup>

All the compounds (**6** and **7**) were tested for their antibacterial activity following paper disc method<sup>13</sup> against



Scheme 2

Table 1. *In Vitro* antibacterial activity of the compounds

Strains	Compounds	6a	6b	6c	6d	7a	7b	7c
		Gram-positive bacteria	<i>L. monocytogenes</i>	14 <sup>a</sup>	15	15	15	15
	<i>S. aureus</i>	15	12	13	13	14	12	11
	<i>B. cereus</i>	12	11	13	13	16	9	13
Gram-negative bacteria	<i>E. coli</i>	11	12	11	15	12	11	12
	<i>S. typhimurium</i>	13	15	11	13	14	14	12
	<i>P. fluorescens</i>	12	12	12	14	13	12	13

<sup>a</sup>Diameter of inhibition zone (mm)

*Listeria monocytogenes* ATCC 19111, *Staphylococcus aureus* ATCC 29737, *Bacillus cereus* ATCC 21366, *Escherichia coli* ATCC 11775, *Salmonella typhimurium* ATCC 29737 and *Pseudomonas fluorescens* ATCC 21541. Paper disc were placed on the Tryptic soy agar spreaded with each bacteria. The plates were incubated at 37 °C for 24 hrs. The activity was recorded by measuring the diameter of inhibition zones in mm<sup>14,15</sup> and results obtained are shown in Table 1. All the compounds showed inhibitory effect against tested bacteria.

## Experimental Section

All melting points were determined on a Haake Buchler melting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a Mattson Polaris FT/IR spectrophotometer. The nmr spectra were measured with a Varian Gemini-200 spectrometer at 200 MHz. The chemical shifts are given in the  $\delta$  scale. The mass spectra (ms) were determined with a shimadzu GC/MS QP-5050 spectrometer. Elemental analyses were performed on an Elementar Vario EL instrument.

### General procedure for the preparation of the quinoxaline 4-oxides (5a-d)

To a stirred and ice cooled suspension of compound **1** (1 g, 4.45 mmol) and ethanol (30 mL)/water(10 mL) was added dropwise the appropriate  $\alpha,\beta$ -unsaturated aldehydes (5.34 mmol, 1,2-fold molar amount) and concentrated sulfuric acid (4 mL). The reaction mixture was stirred at room temperature for 16 hours under nitrogen to precipitate yellow crystals, which were collected by suction filtration. Washing with ethanol and then *n*-hexane gave an analytically pure samples.

**6-Chloro-2-[1-methyl-2-(vinylmethylene)hydrazino]-quinoxaline 4-Oxide (5a)**. Yield 60%, mp 154-156 °C; IR(KBr): 3086, 1577, 1536, 1491, 1386, 1221, 1096 cm<sup>-1</sup>; MS: m/z 262 (M<sup>+</sup>), 264 (M<sup>+</sup>+2); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 8.75 (s, 1H, C<sub>3</sub>-H), 8.23 (s, 1H, C<sub>5</sub>-H), 7.80-7.74 (m, 3H, C<sub>7</sub>-H, C<sub>8</sub>-H and hydrazone CH), 6.75-6.52 (m, 1H, N=CH-CH=CH<sub>2</sub>), 5.82-5.60 (m, 2H, N=CH-CH=CH<sub>2</sub>), 3.59 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>12</sub>H<sub>11</sub>ClN<sub>4</sub>O: C, 54.87; H, 4.22; N, 21.33. Found: C, 54.76; H, 4.23; N, 21.28.

**6-Chloro-2-[1-methyl-2-(methylvinylmethylene)hydrazino]quinoxaline 4-Oxide (5b)**. Yield 88%, mp 207-209; IR

(KBr): 3088, 1577, 1536, 1485, 1098  $\text{cm}^{-1}$ ; MS:  $m/z$  276 ( $M^+$ ), 278 ( $M^+ + 2$ );  $^1\text{H NMR}$  (DMSO- $d_6$ ): 8.73 (s, 1H, C<sub>3</sub>-H), 8.24 (s, 1H, C<sub>5</sub>-H), 7.85-7.62 (m, 3H, C<sub>7</sub>-H, C<sub>8</sub>-H and hydrazone CH), 6.48-6.15 (m, 2H,  $\text{CH}=\text{CHCH}_3$ ), 3.57 (s, 3H, N-CH<sub>3</sub>), 1.88 (d,  $J = 5.5$  Hz, 3H, CH<sub>3</sub>). Anal. calcd. for C<sub>13</sub>H<sub>13</sub>ClN<sub>4</sub>O: C, 56.43; H, 4.74; N, 20.25. Found: C, 56.53; H, 4.78; N, 20.24.

**6-Chloro-2-[1-methyl-2-(phenylvinylmethylene)hydrazino]quinoxaline 4-Oxide (5c).** Yield 94%, mp 262-264 °C; IR (KBr): 3027, 1580, 1531, 1491, 1216, 1091  $\text{cm}^{-1}$ ; MS:  $m/z$  338 ( $M^+$ ), 340 ( $M^+ + 2$ );  $^1\text{H NMR}$  (CDCl<sub>3</sub>): 9.02 (s, 1H, C<sub>3</sub>-H), 8.45 (d,  $J = 2.2$  Hz, 1H, C<sub>5</sub>-H), 7.80-7.29 (m, 8H, C<sub>7</sub>-H, C<sub>8</sub>-H, aromatic and hydrazone CH), 7.10-6.82 (m, 2H,  $\text{CH}=\text{CHPh}$ ), 3.68 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>18</sub>H<sub>15</sub>ClN<sub>4</sub>O: C, 63.81; H, 4.46; N, 16.54. Found: C, 63.69; H, 4.41; N, 16.40.

**6-Chloro-2-[(2-furylvinylmethylene)-1-methylhydrazino]quinoxaline 4-Oxide (5d).** Yield 97%, mp 247-249 °C; IR (KBr): 3107, 1575, 1528, 1488, 1219, 1089  $\text{cm}^{-1}$ ; MS:  $m/z$  328 ( $M^+$ ), 330 ( $M^+ + 2$ );  $^1\text{H NMR}$  (CDCl<sub>3</sub>): 9.00 (s, 1H, C<sub>3</sub>-H), 8.43 (s, 1H, C<sub>5</sub>-H), 7.75-7.50 (m, 3H, C<sub>7</sub>-H, C<sub>8</sub>-H and furan C<sub>5</sub>-H), 7.46 (s, 1H, hydrazone CH), 6.95-6.60 (m, 2H, N=CH-CH=CH-), 6.50-6.40 (m, 2H, furan C<sub>3</sub>-H and C<sub>4</sub>-H), 3.66 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>16</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 58.46; H, 3.99; N, 17.04. Found: C, 58.38; H, 3.87; N, 16.88.

**General procedure for the preparation of the 1,2-diazepino[3,4-*b*]quinoxalines (6a-d)**

A suspension of the appropriate compounds **5** (3.82 mmol) and 2-chloroacrylonitrile (15.28 mmol) in dioxane (50 mL) was refluxed in an oil bath for 2 hours. After cooling to room temperature, the precipitate was filtered off and the filtrate was evaporated *in vacuo*. The oily residue was crystallized from ethanol/water to reddish brown crystals, which were collected by suction filtration and then washed with water to give an analytically pure samples.

**6-Chloro-2,3-dihydro-4-hydroxy-1-methyl-3-vinyl-1H-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile (6a).** Yield 63%, mp 124-126 °C; IR (KBr): 2220, 1599, 1558, 1525, 1486  $\text{cm}^{-1}$ ; MS:  $m/z$  313 ( $M^+$ ), 315 ( $M^+ + 2$ );  $^1\text{H NMR}$  (DMSO- $d_6$ ): 13.89 (brs, 1H, OH), 8.03 (s, 1H, C<sub>7</sub>-H), 7.58-7.30 (m, 2H, C<sub>9</sub>-H and C<sub>10</sub>-H), 6.20-6.02 (m, 2H, C<sub>3</sub>-H and  $\text{CH}=\text{CH}_2$ ), 5.38-5.00 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 4.64 (s, 1H, NH), 3.23 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>15</sub>H<sub>12</sub>ClN<sub>5</sub>O: C, 57.42; H, 3.86; N, 22.32. Found: C, 57.22; H, 3.80; N, 21.97.

**6-Chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(methylvinyl)-1H-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile (6b).** Yield 71%, mp 118-120 °C; IR (KBr): 2223, 1598, 1558, 1529, 1486  $\text{cm}^{-1}$ ; MS:  $m/z$  327 ( $M^+$ ), 329 ( $M^+ + 2$ );  $^1\text{H NMR}$  (DMSO- $d_6$ ): 13.86 (brs, 1H, OH), 8.03 (s, 1H, C<sub>7</sub>-H), 7.58-7.32 (m, 2H, C<sub>9</sub>-H and C<sub>10</sub>-H), 5.96 (s, 1H, C<sub>3</sub>-H), 5.90-5.38 (m, 2H,  $\text{CH}=\text{CHCH}_3$ ), 4.57 (s, 1H, NH), 3.22 (s, 3H, N-CH<sub>3</sub>), 1.66 (d,  $J = 5.6$  Hz, 3H, CH<sub>3</sub>). Anal. calcd. for C<sub>16</sub>H<sub>14</sub>ClN<sub>5</sub>O: C, 58.63; H, 4.31; N, 21.37. Found: C, 58.74; H, 4.21; N, 21.06.

**6-Chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(phenylvinyl)-1H-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile (6c).** Yield 72%, mp 168-170 °C; IR (KBr): 2225, 1598, 1557,

1527, 1486  $\text{cm}^{-1}$ ; MS:  $m/z$  389 ( $M^+$ ), 391 ( $M^+ + 2$ );  $^1\text{H NMR}$  (DMSO- $d_6$ ): 13.92 (brs, 1H, OH), 8.06 (s, 1H, C<sub>7</sub>-H), 7.60-7.15 (m, 7H, C<sub>9</sub>-H, C<sub>10</sub>-H and aromatic), 6.62-6.32 (m, 2H, C<sub>3</sub>-H and  $\text{CH}=\text{CHPh}$ ), 6.09 (d,  $J = 11.8$  Hz, 1H,  $\text{CH}=\text{CHPh}$ ), 4.81 (s, 1H, NH), 3.25 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>21</sub>H<sub>16</sub>ClN<sub>5</sub>O: C, 64.70; H, 4.14; N, 17.97. Found: C, 64.19; H, 3.98; N, 17.62.

**6-Chloro-3-(2-furylvinyl)-2,3-dihydro-4-hydroxy-1-methyl-1H-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile (6d).** Yield 86%, mp 132-134 °C; IR (KBr): 2227, 1598, 1557, 1526, 1486  $\text{cm}^{-1}$ ; MS:  $m/z$  379 ( $M^+$ ), 381 ( $M^+ + 2$ );  $^1\text{H NMR}$  (DMSO- $d_6$ ): 13.92 (brs, 1H, OH), 8.07 (s, 1H, C<sub>7</sub>-H), 7.88-7.32 (m, 3H, C<sub>9</sub>-H, C<sub>10</sub>-H and furan C<sub>5</sub>-H), 6.58-6.20 (m, 4H, C<sub>3</sub>-H,  $\text{CH}=\text{CHfuran}$ , furan C<sub>3</sub>-H and C<sub>4</sub>-H), 6.08 (d,  $J = 12.0$  Hz, 1H,  $\text{CH}=\text{CHfuran}$ ), 4.81 (s, 1H, NH), 3.23 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>2</sub>: C, 60.09; H, 3.72; N, 18.44. Found: C, 59.18; H, 3.57; N, 18.87.

**General procedure for the preparation of the pyridazino[3,4-*b*]quinoxalines (7a-c)**

A solution of the appropriate compounds **6** (3.06 mmol) and selenium dioxide (6.12 mmol) in acetic acid (20 mL)/water (10 mL) was refluxed in an oil bath for 1 hour. The reaction mixture was filtered, and the filtrate was evaporation *in vacuo* to give brick red crystals, which were triturated with water and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded violet needles.

**7-Chloro-1-methyl-3-(methylvinyl)-4-oxo-1,4-dihydro-pyridazino[3,4-*b*]quinoxaline (7a).** Yield 58%, mp 174-176 °C; IR (KBr): 1645, 1537, 1467  $\text{cm}^{-1}$ ; MS:  $m/z$  286 ( $M^+$ ), 288 ( $M^+ + 2$ );  $^1\text{H NMR}$  (CDCl<sub>3</sub>): 8.35 (d,  $J = 1.8$  Hz, 1H, C<sub>6</sub>-H), 8.02 (d,  $J = 9.4$  Hz, 1H, C<sub>9</sub>-H), 7.83 (dd,  $J = 2.1$ , 9.0 Hz, 1H, C<sub>8</sub>-H), 7.22-7.02 (m, 1H,  $\text{CH}=\text{CHCH}_3$ ), 6.79 (d,  $J = 15.8$  Hz, 1H,  $\text{CH}=\text{CHCH}_3$ ), 4.26 (s, 3H, N-CH<sub>3</sub>), 1.99 (d,  $J = 6.7$  Hz, 3H, CH<sub>3</sub>). Anal. calcd. for C<sub>14</sub>H<sub>11</sub>ClN<sub>4</sub>O: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.33; H, 3.72; N, 19.32.

**7-Chloro-1-methyl-3-(phenylvinyl)-4-oxo-1,4-dihydro-pyridazino[3,4-*b*]quinoxaline (7b).** Yield 56%, mp 273-275 °C; IR (KBr): 1632, 1536, 1461  $\text{cm}^{-1}$ ; MS:  $m/z$  348 ( $M^+$ ), 350 ( $M^+ + 2$ );  $^1\text{H NMR}$  (CDCl<sub>3</sub>): 8.37 (d,  $J = 2.2$  Hz, 1H, C<sub>6</sub>-H), 8.06-7.28 (m, 9H C<sub>8</sub>-H, C<sub>9</sub>-H, aromatic and vinylic H), 4.33 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>13</sub>ClN<sub>4</sub>O: C, 65.43; H, 3.76; N, 16.06. Found: C, 65.57; H, 3.62; N, 15.87.

**7-Chloro-3-(2-furylvinyl)-1-methyl-4-oxo-1,4-dihydro-pyridazino[3,4-*b*]quinoxaline (7c).** Yield 71%, mp 257-259 °C; IR (KBr): 1644, 1535, 1462  $\text{cm}^{-1}$ ; MS:  $m/z$  338 ( $M^+$ ), 340 ( $M^+ + 2$ );  $^1\text{H NMR}$  (CDCl<sub>3</sub>): 8.33 (d,  $J = 2.1$  Hz, 1H, C<sub>6</sub>-H), 8.02 (d,  $J = 9.1$  Hz, 1H, C<sub>9</sub>-H), 7.92-7.72 (m, 2H, C<sub>8</sub>-H and furan C<sub>5</sub>-H), 7.51-7.22 (m, 2H,  $\text{CH}=\text{CHfuran}$ ), 6.52 (d,  $J = 3.3$  Hz, 1H, furan C<sub>3</sub>-H), 6.45 (dd,  $J = 1.5$ , 3.2 Hz, 1H, furan C<sub>4</sub>-H), 4.31 (s, 3H, N-CH<sub>3</sub>). Anal. calcd. for C<sub>17</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 60.28; H, 3.27; N, 16.54. Found: C, 60.12; H, 3.38; N, 16.37.

**6-Chloro-2-[1-methyl-2-[4-(2,2-dimethyl-1,3-dioxolan-ylmethylene)]hydrazino]quinoxaline 4-Oxide (8).** A suspension of compound **1** (10 g, 44.5 mmol) and 2,3-*O*-isopropylidene-D-glyceraldehyde (8.7 g, 66.9 mmol) in dry

benzene (300 mL) was refluxed on a boiling water bath for 4 hours to give a clear solution. Evaporation of the solvent *in vacuo* gave yellow crystals, which were collected by suction filtration and washed with ethanol and then *n*-hexane to give an analytically pure sample (8.12 g). Evaporation of the solvent *in vacuo* afforded yellow crystals of compound **8**, which were collected by suction filtration and washed with ethanol (5.51 g), total yield, 13.63 g (91%).

Compound **8** had mp 153-155 °C; IR (KBr) 3073, 2922, 1575, 1540, 1486, 1402, 1227, 1069 cm<sup>-1</sup>; MS: m/z 336 (M<sup>+</sup>), 338 (M<sup>+</sup>+2); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 8.76 (s, 1H, C<sub>3</sub>-H), 8.26 (s, 1H, C<sub>5</sub>-H), 7.80 (s, 2H, C<sub>7</sub>-H and C<sub>8</sub>-H), 7.22 (d, *J* = 6.1 Hz, 1H, hydrazone CH), 4.79 (q, *J* = 6.3 Hz, dioxolane C<sub>4</sub>-H), 4.26-3.92 (m, 2H, dioxolane C<sub>5</sub>-H), 3.56 (s, 3H, N-CH<sub>3</sub>), 1.42 (s, 3H, dioxolane C<sub>2</sub>-CH<sub>3</sub>), 1.36 (s, 3H, dioxolane C<sub>2</sub>-CH<sub>3</sub>).

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