An Influence of a Basic Side Chain Moiety on the Tautomer Ratio between the Enamine and Methylene Imine Forms in Azole Condensed Quinoxalines

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Dedicated to the memory of Dr. Roland K. Robins

The reaction of 7-chloro-4-(2-cyano-2-hydroxyvinyl)tetrazolo[1,5-*a*]quinoxaline **2a** with 4-aminopyridine, *p*-toluidine or *p*-aminophenol gave 7-chloro-4-(4-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]-quinoxaline **7a**, 7-chloro-4-(*p*-tolylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **8a** or 7-chloro-4-(*p*-hydroxyphenylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **9a**, respectively. The reaction of 7-chloro-4-(2-cyano-2-hydroxyvinyl)-1,2,4-triazolo[4,3-*a*]quinoxaline **2b** with 4-aminopyridine, *p*-toluidine or *p*-aminophenol afforded 7-chloro-4-(4-pyridylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo-[4,3-*a*]quinoxaline **7b**, 7-chloro-4-(*p*-tolylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **8b** or 7-chloro-4-(*p*-hydroxyphenylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **9b**, respectively. The reaction of compound **2a** with 2-aminopyridine or 3-aminopyridine provided 7-chloro-4-(2-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **10** or 7-chloro-4-(3-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **11**, respectively. Compounds **7a,b** (4-pyridylcarbamoyl) predominated as the enamine tautomer **A** in a trifluoroacetic acid solution, while compounds **8a,b** (*p*-tolylcarbamoyl) and compounds **9a,b** (*p*-hydroxyphenylcarbamoyl) coexisted as the enamine **A** and methylene imine **B** tautomers in a trifluoroacetic acid solution. Moreover, the ratio of the enamine tautomer **A** elevated in an order of compound **11** (3-pyridylcarbamoyl), compound **10** (2-pyridylcarbamoyl) and compound **7a** (4-pyridylcarbamoyl), reflecting an order of the increase in the pKa values of the aminopyridine side chain moieties. In general, the ratio of the enamine tautomer **A** was higher in the basic carbamoyl derivatives **7-11** than in the neutral ester derivatives **3a,b**. From these results, the basic side chain moiety of the tetrazolo[1,5-*a*]quinoxalines **7a-11** or 1,2,4-triazolo[4,3-*a*]quinoxalines **7b-9b** was found to increase the ratio of the enamine tautomer **A** in trifluoroacetic acid media.

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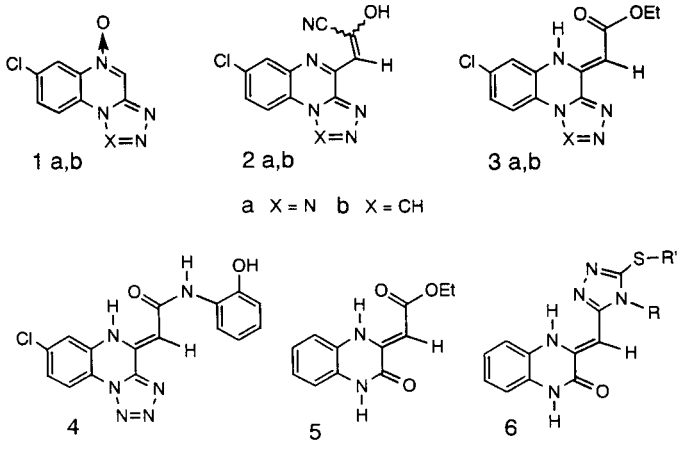
In a previous paper [1], we reported that the reaction of the tetrazolo[1,5-*a*]quinoxaline 5-oxide **1a** or 1,2,4-triazolo-[4,3-*a*]quinoxaline 5-oxide **1b** with 2-chloroacrylonitrile resulted in the 1,3-dipolar cycloaddition reaction followed by cyano group migration to give the enol type acyl cyanide **2a** or **2b**, respectively (Chart). The alcoholysis of compounds **2a,b** [1] or aminolysis of compound **2a** [2] with ethanol or *o*-aminophenol afforded the esters **3a,b** or amide **4**, respectively. These esters **3a,b** and amide **4** showed the interesting tautomeric equilibria between the enamine **A** and methylene imine **B** forms in a dimethyl sulfoxide or trifluoroacetic acid solution (Scheme 1). On the other hand, the lactam type 3-ethoxycarbonylmethylenequinoxaline **5** [3] and 3-triazolylmethylenequinoxalines **6** [4] (Chart) also exhibited the above tautomeric equilibria between two forms **A** and **B** in a dimethyl sulfoxide or trifluoroacetic acid solution. The tautomer ratio of **A** to **B** in a dimethyl sulfoxide solution was not significantly varied between compounds **3a,b** and compounds **5,6**, but the tautomer ratio of **A** to **B** in a trifluoroacetic acid solution was considerably different between compounds **3a,b** and compounds **5,6** (Table 1). Namely, the lactam type quinoxalines **5,6** predominantly existed as the **B** form in a trifluoroacetic acid solution, while the azole ring condensed quinoxaline esters **3a,b** coexisted as the **A** and **B**

Chart



Scheme 1

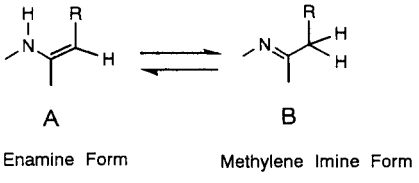


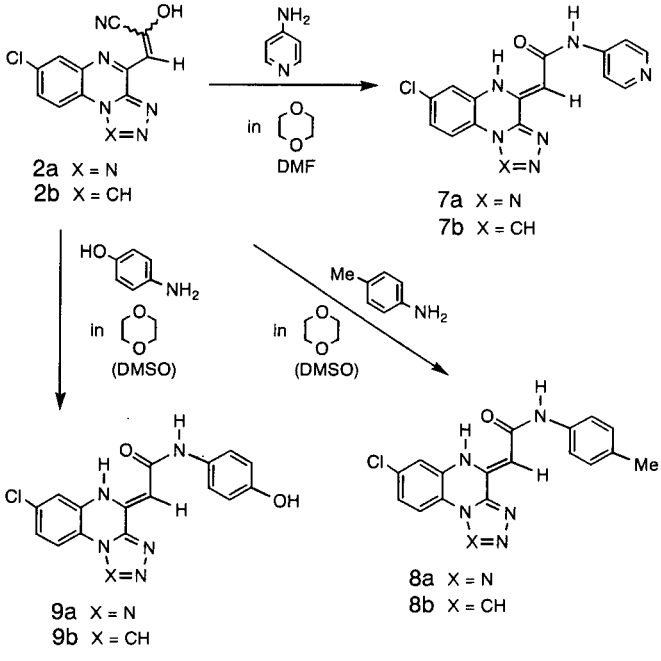
Table 1
Tautomer Ratio between the Enamine **A** and Methylene Imine **B** Forms for Compounds **3-6**

Compound	Solvent	Tautomer Ratio A	B
3a	TFA-d_1 [a]	50	50 [c]
3b	TFA-d_1	67	33 [c]
4	TFA-d_1	60	40 [d]
5	TFA [b]	0	100 [e]
6	TFA	0	100 [f]

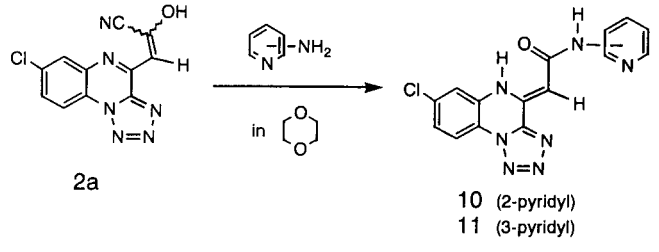
[a] Deuteriotrifluoroacetic acid. [b] Trifluoroacetic acid. [c] Reference [1]. [d] Reference [2]. [e] Reference [3]. [f] Reference [4].

forms in a trifluoroacetic acid solution. Thus, we found that the azole ring condensed quinoxalines **3a,b** was quite different from the lactam type quinoxalines **5,6** concerning the tautomerism between the **A** and **B** forms in a trifluoroacetic acid solution. Moreover, the tautomer ratio between the **A** and **B** forms varied among compounds **3a, 3b** and **4**. That is, the ratio of the tautomer **A** increased in an order of compound **3a** (50%), **4** (60%) and **3b** (67%). These data indicated that the above tautomer ratio of **A** to **B** would depend on a p*K*a value of individual compounds. Accordingly, we undertook the synthesis of the tetrazolo[1,5-*a*]quinoxalines and 1,2,4-triazolo[4,3-*a*]quinoxalines such as compounds **7-11** (Schemes 2 and 3), bearing diverse basic side chain moieties with various p*K*a values, and examined whether the side chain moiety with different p*K*a values could vary the tautomer ratio of **A** to **B**. This paper describes the synthesis of novel compounds **7-11** and the control of the tautomer ratio of **A** to **B** by the side chain moieties.

Scheme 2



Scheme 3



The reaction of 7-chloro-4-(2-cyano-2-hydroxyvinyl)tetrazolo[1,5-*a*]quinoxaline **2a** or 7-chloro-4-(2-cyano-2-hydroxyvinyl)-1,2,4-triazolo[4,3-*a*]quinoxaline **2b** with 4-aminopyridine gave 7-chloro-4-(4-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **7a** or 7-chloro-4-(4-pyridylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **7b**, respectively, while the reaction of compound **2a** or **2b** with *p*-toluidine provided 7-chloro-4-(*p*-tolylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **8a** or 7-chloro-4-(*p*-tolylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**, respectively (Scheme 2). Similarly, the reaction of compound **2a** or **2b** with *p*-aminophenol furnished 7-chloro-4-(*p*-hydroxyphenylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **9a** or 7-chloro-4-(*p*-hydroxyphenylcarbamoylmethyl-

Table 2

NMR Spectral Data of Compounds **7a, 8a** and **9a** in Deuteriotrifluoroacetic Acid

Compound	Tautomer Ratio		Chemical Shifts (δ ppm) (Coupling Constant, Hz)								
			Tautomer **A**				Tautomer **B**				
	A	**B**	C_6-H	C_8-H	C_9-H	Me	C_6-H	C_8-H	C_9-H	Me	Others
7a	100	0	7.19 (s)	6.98 (d, 9.0)	7.79 (d, 9.0)	–	–	–	–	–	8.13 (d, 7.0), 7.88 (d, 7.0)
8a	67	33	[a]	[a]	7.98 (d, 8.0)	2.17 (s)	8.22 (s)	7.82 (d, 8.0)	8.47 (d, 8.0)	2.10 (s)	7.20-6.90
9a	60	40	[a]	[a]	8.06 (d, 8.5)	–	8.30 (s)	7.91 (d, 8.5)	8.55 (d, 8.5)	–	7.35-7.10, 7.00-6.80

[a] Overlapped with other signals.

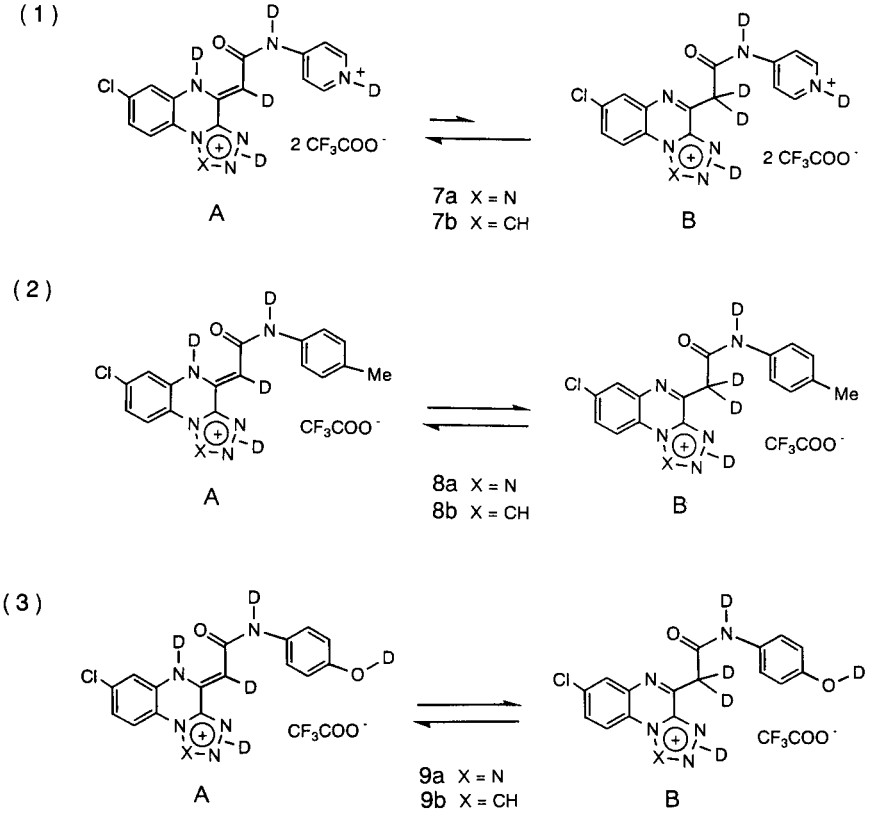
Table 3

NMR Spectral Data of Compounds **7b, 8b** and **9b** in Deuteriotrifluoroacetic Acid

Compound	Tautomer Ratio		Chemical Shifts (δ ppm) (Coupling Constant, Hz)										
			Tautomer **A**					Tautomer **B**					
	A	**B**	C_1-H	C_6-H	C_8-H	C_9-H	Me	C_1-H	C_6-H	C_8-H	C_9-H	Me	Others
7b	100	0	10.02 (s)	7.23 (s)	7.01 (d, 8.5)	7.58 (d, 8.5)	–	–	–	–	–	–	8.14 (d, 6.0), 7.91 (d, 6.0)
8b	79	21	9.94 (s)	7.48 (d, 2.0)	7.28 [a]	7.84 (d, 9.0)	2.01 (s)	10.22 (s)	8.01 (d, 2.0)	7.62 [a]	8.04 (d, 9.0)	1.95 (s)	7.10-7.02, 6.98-6.80
9b	76	24	9.96 (s)	[b]	[b]	7.54 (d, 9.0)	–	10.26 (s)	8.05 (s)	7.67 (d, 9.0)	8.09 (d, 9.0)	–	7.14-6.88, 6.80-6.60

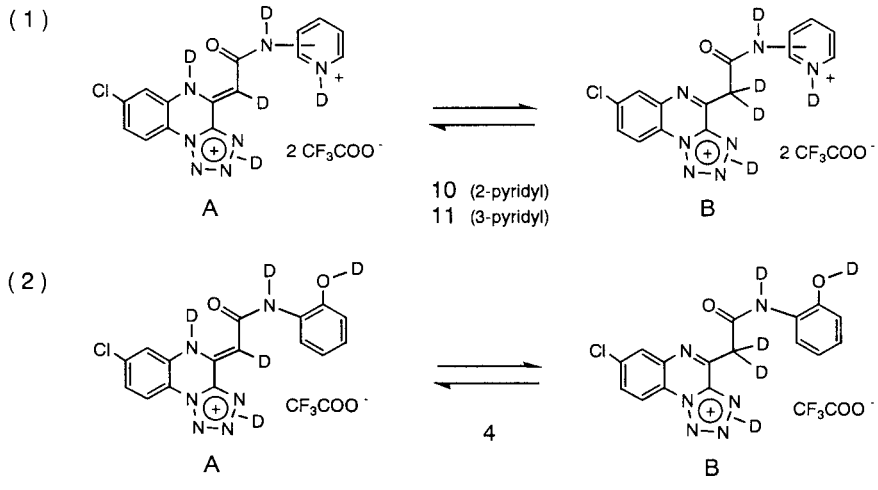
[a] (dd, 2.0, 9.0). [b] Overlapped with other signals.

Scheme 4



Deuterized Species and Tautomeric Equilibria of Compounds 7-9 in Deuteriotrifluoroacetic Acid

Scheme 5



Deuterized Species and Tautomeric Equilibria of Compounds 4, 10 and 11 in Deuteriotrifluoroacetic Acid

Table 4

NMR Spectral Data of Compounds **4**, **10** and **11** in Deuteriotrifluoroacetic Acid

Compounds	Tautomer Ratio		Chemical Shifts (δ ppm) (Coupling Constant, Hz) Tautomer A			Tautomer B			
	A	B	C_6-H	C_8-H	C_9-H	C_6-H	C_8-H	C_9-H	Others
10	83	17	7.26 (d, 2.0)	7.15 [b]	7.95 (d, 9.0)	[a]	[a]	8.24 (d, 9.0)	8.10 (d, 7.0), 7.31-7.21
11	68	32	7.21 (s)	7.03 (d, 8.5)	7.86 (d, 8.5)	8.06 (s)	[a]	8.26 (d, 8.5)	9.27 (s), 8.42-8.15, 7.78-7.65
4	60	40	[a]	[a]	8.01 (d, 8.5)	8.26 (s)	7.86 (d, 8.5)	8.50 [c] (d, 8.5)	7.40-6.80

[a] Overlapped with other signals. [b] (dd, 2.0, 9.0). [c] Already reported in reference [2].

Table 5

Tautomer Ratio between the Enamine **A** and Methylene Imine **B** Forms for Compounds **7a**, **10** and **11** in Deuteriotrifluoroacetic Acid

Compound	Aminopyridine Moiety (First p*K*a in Water) [a]	Tautomer Ratio A	B
7a	4-Aminopyridine (9.17)	100	0
10	2-Aminopyridine (6.86)	83	17
11	3-Aminopyridine (5.98)	68	32

[a] Reference [9].

ene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **9b**, respectively. The reaction of compound **2a** with 2-aminopyridine or 3-aminopyridine gave 7-chloro-4-(2-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **10** or 7-chloro-4-(3-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **11**, respectively (Scheme 3).

The structural assignment of novel compounds **7-11** was based on the spectral and analytical data. Most of compounds **7-11** were insoluble in deuteriodimethyl sulfoxide, and their nmr spectra were measured in deuteriotrifluoroacetic acid (Tables 2, 3, 4). The protonated species of 1,2,4-triazoles, imidazoles, oxazoles and other azoles in a trifluoroacetic acid solution have already been reported by some research groups [5-7], and hence the protonated species of compounds **7-11** shown in Schemes 4 and 5 would be formed in a deuteriotrifluoroacetic acid solution. The tautomer ratio of **A** to **B** was calculated from the integral ratio of the C_6-H, C_8-H or C_9-H proton signal [8] in the tetrazolo[1,5-*a*]quinoxalines **7a-11** and 1,2,4-triazolo-[4,3-*a*]quinoxalines **7b-9b**, since the vinyl and methylene proton signals were not observed because of D-H exchange as shown in Schemes 4 and 5. The integral ratio of the C_1-H (compounds **7b-9b**) or methyl (compounds **8a,b**) proton signal was also helpful for the calculation of the tautomer ratio.

The data of Tables 2 and 3 exhibited that compounds **7a,b** having a 4-pyridylcarbamoyl group predominantly

existed as the enamine tautomer **A** [**A**%: 100 (both **7a,b**)] [Scheme 4, (1)], while compounds **8a,b** bearing a *p*-tolylcarbamoyl group and compounds **9a,b** possessing a *p*-hydroxyphenylcarbamoyl group coexisted as the tautomers **A** and **B**[**A**/**B**%: 67/33 (**8a**), 79/21 (**8b**), 60/40 (**9a**), 76/24 (**9b**)] [Scheme 4, (2), (3)]. The ratio of the tautomer **A** was rather higher in compounds **8a,b** with a *p*-tolylcarbamoyl group than in compounds **9a,b** with a *p*-hydroxyphenylcarbamoyl group [**A**%: 67/60 (**8a**/**9a**); 79/76 (**8b**/**9b**)], wherein the phenol group of compounds **9a,b** might slightly lower the p*K*a in comparison with the *p*-tolyl group of compounds **8a,b**. The data of Table 4 likewise represented that the ratio of the tautomer **A** was higher in compound **10** with a 2-pyridylcarbamoyl group [Scheme 5, (1)] than in compound **4** with an *o*-hydroxycarbamoyl group [Scheme 5, (2)] [**A**%: 83/60 (**10**/**4**)]. On the other hand, the data of Table 5 showed that the ratio of the tautomer **A** augmented in an order of compound **11** (68%), compound **10** (83%) and compound **7a** (100%), which reflected an order of the increase in the p*K*a values of the aminopyridine moieties [first p*K*a: **11** (3-aminopyridine, 5.98), **10** (2-aminopyridine, 6.86), **7a** (4-aminopyridine, 9.17)] [9]. In addition, the ratio of the tautomer **A** was also higher in compounds **7-11** having a carbamoyl group than in compounds **3a,b** possessing an ester group [**A**%: 100-60/50 (**7a-11**/**3a**), 100-76/67 (**7b-9b**/**3b**)]. Thus, an increase in the p*K*a value of the azole condensed quinoxaline derivatives was found to elevate the ratio of the enamine tautomer **A** in a trifluoroacetic acid solution. In other words, the p*K*a value of the side chaine moiety might control the tautomer ratio of **A** to **B** in a trifluoroacetic acid solution.

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 IRA-1 spectrophotometer. The nmr spectra were measured in deuteriotrifluoroacetic acid with a VXR-300 spectrometer at 300 MHz. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

7-Chloro-4-(4-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo-[1,5-*a*]quinoxaline **7a**.

A solution of compound **2a** (2 g, 7.34 mmoles) and 4-aminopyridine (1.03 g, 11.0 mmoles) in dioxane (100 ml)/*N,N*-dimethylformamide (50 ml) was refluxed in an oil bath for 1 hour to give a clear solution. The solution was evaporated *in vacuo* to afford yellow needles **7a**, which were triturated with hot *N,N*-dimethylformamide/ethanol and collected by suction filtration to obtain an analytically pure sample (1.17 g, 47%), mp 290° dec; ir: ν cm^{-1} 1655, 1630, 1580, 1510; ms: m/z 339 (M^+), 341 ($M^+ + 2$).

Anal. Calcd. for $C_{16}H_{11}ClN_8O$: C, 52.40; H, 3.02; Cl, 9.67; N, 30.55. Found: C, 52.11; H, 3.03; Cl, 9.90; N, 30.60.

7-Chloro-4-(4-pyridylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **7b**.

A solution of compound **2b** (2 g, 7.37 mmoles) and 4-aminopyridine (1.04 g, 11.1 mmoles) in dioxane (100 ml)/*N,N*-dimethylformamide (50 ml) was refluxed in an oil bath for 2 hours to precipitate yellow needles **7b**, which were collected by suction filtration and washed with ethanol to give an analytically pure sample (1.17 g, 47%), mp 330° dec; ir: ν cm^{-1} 1650, 1620, 1570, 1520, 1510; ms: m/z 338 (M^+), 340 ($M^+ + 2$).

Anal. Calcd. for $C_{16}H_{11}ClN_6O$: C, 56.73; H, 3.27; Cl, 10.46; N, 24.81. Found: C, 56.65; H, 3.46; Cl, 10.55; N, 24.59.

7-Chloro-4-(*p*-tolylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **8a**.

A solution of compound **2a** (2 g, 7.34 mmoles) and *p*-toluidine (1.18 g, 11.0 mmoles) in dioxane (100 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals **8a**, which were collected by suction filtration (0.84 g, 32%). Recrystallization from dioxane/ethanol provided yellow needles, mp 270-271°; ir: ν cm^{-1} 1645, 1615, 1580, 1530, 1510; ms: m/z 352 (M^+), 354 ($M^+ + 2$).

Anal. Calcd. for $C_{17}H_{13}ClN_6B$: C, 57.88; H, 3.71; Cl, 10.05; N, 23.82. Found: C, 57.91; H, 3.92; Cl, 10.16; N, 23.59.

7-Chloro-4-(*p*-tolylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**.

A solution of compound **2b** (2 g, 7.37 mmoles) and *p*-toluidine (1.19 g, 11.1 mmoles) in dioxane (70 ml)/dimethyl sulfoxide (30 ml) was refluxed in an oil bath for 2 hours to give a clear solution. Dioxane was evaporated *in vacuo*, and ethanol and water were added to the residual dimethyl sulfoxide solution under heating on a boiling water bath. The solution was allowed to stand at room temperature to precipitate yellow needles **8b**, which were collected by suction filtration and washed with ethanol to provide an analytically pure sample (1.59 g, 61%), mp 277-278°; ir: ν cm^{-1} 1635, 1605, 1575, 1520; ms: m/z 351 (M^+), 353 ($M^+ + 2$).

Anal. Calcd. for $C_{18}H_{14}ClN_5O$: C, 61.46; H, 4.01; Cl, 10.08; N, 19.91. Found: C, 61.33; H, 4.18; Cl, 10.15; N, 20.03.

7-Chloro-4-(*p*-hydroxyphenylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **9a**.

A solution of compound **2a** (2 g, 7.34 mmoles) and *p*-aminophenol (1.20 g, 11.0 mmoles) in dioxane (100 ml) was refluxed in an oil bath for 1 hour to give a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals **9a**, which collected by suction filtration (1.60 g, 62%). Recrystallization from dioxane gave yellow needles, mp 268-269°; ir: ν cm^{-1} 3320, 1640, 1605, 1590, 1580, 1540, 1520, 1500; ms: m/z 354 (M^+), 356 ($M^+ + 2$).

Anal. Calcd. for $C_{16}H_{11}ClN_6O_2$: C, 54.17; H, 3.13; Cl, 9.99; N, 23.69. Found: C, 54.05; H, 3.04; Cl, 10.05; N, 23.53.

7-Chloro-4-(*p*-hydroxyphenylcarbamoylmethylene)-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **9b**.

A solution of compound **2b** (2 g, 7.37 mmoles) and *p*-aminophenol (1.21 g, 11.1 mmoles) in dioxane (70 ml)/dimethyl sulfoxide (30 ml) was refluxed in an oil bath for 2 hours to give a clear solution. Dioxane was evaporated *in vacuo*, and ethanol and water were added to the residual dimethyl sulfoxide solution under heating on a boiling water bath. The solution was allowed to stand at room temperature to precipitate yellow needles **9b**, which were collected by suction filtration and washed with eth-

anol to furnish an analytically pure sample (1.46 g, 56%), mp 295-296°; ir: ν cm^{-1} 1630, 1610, 1580, 1545, 1520; ms: m/z 353 (M^+), 355 ($M^+ + 2$).

Anal. Calcd. for $C_{17}H_{12}ClN_5O_2$: C, 57.72; H, 3.42; Cl, 10.02; N, 19.80. Found: C, 57.83; H, 3.61; Cl, 10.23; N, 19.93.

7-Chloro-4-(2-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **10**.

A solution of compound **2a** (2 g, 7.34 mmoles) and 2-aminopyridine (1.03 g, 11.0 mmoles) in dioxane (100 ml) was refluxed in an oil bath for 2 hours to give a clear solution, and the solvent was evaporated *in vacuo* to afford brown crystals. Recrystallization from dioxane/ethanol/water provided brown needles **10**, which were collected by suction filtration (0.45 g, 18%), mp 260-261°; ir: ν cm^{-1} 1650, 1625, 1590, 1575, 1540, 1520; ms: m/z 339 (M^+), 341 ($M^+ + 2$).

Anal. Calcd. for $C_{16}H_{11}ClN_8O$: C, 52.40; H, 3.02; Cl, 9.67; N, 30.55. Found: C, 52.53; H, 3.24; Cl, 9.84; N, 30.73.

7-Chloro-4-(3-pyridylcarbamoylmethylene)-4,5-dihydrotetrazolo-[1,5-*a*]quinoxaline **11**.

A solution of compound **2a** (2 g, 7.34 mmoles) and 3-aminopyridine (1.03 g, 11.0 mmoles) in dioxane (100 ml) was refluxed in an oil bath for 1 hour to give a clear solution. The solvent was evaporated *in vacuo* to afford yellow needles **11**, which were triturated with ethanol/hexane and collected by suction filtration to obtain an analytically pure sample (1.52 g, 61%), mp 297-298°; ir: ν cm^{-1} 1650, 1625, 1570, 1545, 1520; ms: m/z 339 (M^+), 341 ($M^+ + 2$).

Anal. Calcd. for $C_{16}H_{11}ClN_8O$: C, 52.40; H, 3.02; Cl, 9.67; N, 30.55. Found: C, 52.63; H, 3.11; Cl, 9.73; N, 30.79.

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