

according to methods described previously.<sup>31</sup>

**Effects on the Firing Rate of Substantia Nigra DA Neurons.**<sup>12</sup> The action potential of zona compacta DA cells was recorded in chloral-anesthetized rats by using standard extracellular recording techniques. DA cells were identified by waveform and firing pattern, and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Base line firing rate was calculated by averaging the rate over the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

**Inhibition of spontaneous locomotor activity and motor coordination**<sup>14,15</sup> were carried out according to methods described previously.<sup>31</sup>

**Inhibition of GBL-Stimulated DA Synthesis.**<sup>13</sup> Compounds were administered to male Long-Evans rats (Blue Spruce Farms, Altamont, NY) 1 h before sacrifice and GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 min and 25 min, respectively, before sacrifice. Brain striatal levels of DOPA were measured by HPLC with electrochemical detection.<sup>32</sup>

**Effects on Spontaneous Locomotion in Reserpinized Rats.**<sup>17</sup> Drugs were administered subcutaneously to normal rats treated with 5 mg/kg reserpine 24 h prior to testing. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.<sup>15,31</sup>

**Stereotypy in Rats.** Compounds were administered sc to naive rats and the animals were observed at 10, 20, and 30 min

postdose for the presence of repetitive rearing, head-swaying, sniffing, licking, and gnawing of at least 5-s duration. Data were expressed as percentage of rats showing signs of stereotypy.

**Effects on Spontaneous Locomotion in 6-OHDA-Lesioned Rats.**<sup>23</sup> Drugs were administered subcutaneously to rats treated at least 1 month previously with central injections of 6-OHDA (200 µg icv) and systemic injections of pargyline (50 mg/kg ip) and desmethylimipramine (25 mg/kg ip) as described previously.<sup>33</sup> This treatment produced large selective depletion of brain DA (approximately 90%) as described previously<sup>33</sup> and as determined by brain DA determinations in representative animals. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.<sup>15,31</sup> Data are reported as the ED<sub>200</sub> value, the dose of compound needed to increase the locomotor activity of the animals to twice the level of control (unlesioned) animals.

**Acknowledgment.** We thank C. L. Christoffersen, L. L. Coughenour, S. Myers, A. E. Williams, and in particular J. N. Wiley for biological data.

**Registry No.** 3, 108351-93-5; 3-2HCl, 118371-15-6; 4a, 108351-94-6; 4a-2HCl, 108351-95-7; 4b, 108351-96-8; 4c, 108351-90-2; 4d, 108351-92-4; 4d-2HCl, 108351-97-9; 4e, 108351-98-0; 4e-2HBr, 108351-99-1; 4f, 108352-00-7; 4f-2HCl, 108352-01-8; 4g, 108352-02-9; 4g-2HCl, 108352-03-0; 4h, 108352-04-1; 4h-2HCl, 108352-05-2; 4i, 108351-91-3; 4j, 108352-06-3; 4j-2HCl, 108352-07-4; 4k, 108352-11-0; 4l, 122845-19-6; 4l-2HCl, 122845-22-1; 5, 5006-62-2; 6, 100050-04-2; 7, 118371-33-8; 7-HCl, 122845-36-7; 9, 6221-12-1; 10a, 30235-27-9; 10b, 56541-06-1; 11a, 113259-07-7; 11b, 122845-24-3; 11c, 113259-08-8; 11d, 122845-25-4; 11e, 122845-26-5; 11f, 122845-27-6; 11g, 122845-28-7; 11h, 122845-29-8; 11i, 122845-30-1; 11j, 122845-31-2; 11k, 122845-32-3; 11l, 122845-33-4; 14-HCl, 112534-17-5; 15-HCl, 122845-34-5; 16, 122845-20-9; 17, 122845-35-6; 18, 122845-21-0; 18-2HCl, 122845-23-2.

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## Synthesis and Cardiotoxic Activity of Novel Biimidazoles

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A series of substituted 2,2'-bi-1H-imidazoles and related analogues was synthesized and evaluated for inotropic activity. Structure-activity relationship studies based on a nonclassical bioisosteric approach indicated the necessity of a cyano group on one of the imidazole rings to obtain the desired pharmacological profile. 4(5)-Cyano-2,2'-bi-1H-imidazole (15a) was the most potent inotropic agent in the series. It produced a 25% increase in left ventricular dP/dt at 0.16 mg/kg iv (ED<sub>25%</sub> = 0.16 mg/kg) and increased left ventricular contractile force 60% at 1 mg/kg iv in anesthetized dogs. Compound 15a is a good inhibitor of type IV cyclic nucleotide phosphodiesterase isolated from dog heart having a potency similar to that of amrinone. Neither 5'-cyano-2,4'-bi-1H-imidazole (44) nor 4-cyano-2,4'-bi-1H-imidazole (48) demonstrated inotropic activity. In addition, the two possible 1,1'-dimethylcyano-2,2'-bi-1H-imidazoles (24 and 25) were inactive, indicating that an acidic NH as well as a cyano group are essential for inotropic activity.

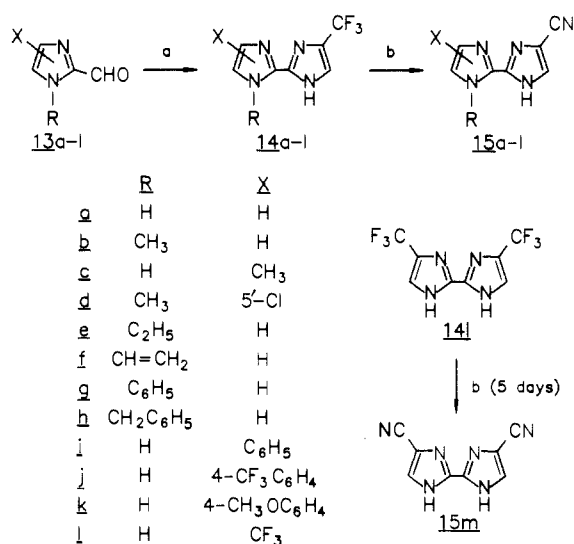
For a number of years there has been a search for safe, orally active, inotropic agents for the treatment of congestive heart failure (CHF).<sup>1,2</sup> The disease is widespread and is on the rise due, in part, to the increasing longevity of the population. Until recently, the only inotropic agents available for the treatment of congestive heart failure were the sympathomimetic agents dobutamine and dopamine and the cardiac glycosides. Milrinone is now available for use, and other agents are currently undergoing clinical evaluation.<sup>3-5</sup>

We wish to report a new structural class of orally effective cardiotoxic agents represented by 4(5)-cyano-2,2'-bi-1H-imidazole (15a). During our investigation of the pharmacology of a potential dopamine β-hydroxylase

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**Scheme I. Preparation of 4-Cyano-2,2'-bi-1*H*-imidazoles<sup>a</sup>**

<sup>a</sup> (a) CF<sub>3</sub>COCHBr<sub>2</sub>/NaOAc/NH<sub>4</sub>OH. (b) 5% NH<sub>4</sub>OH.

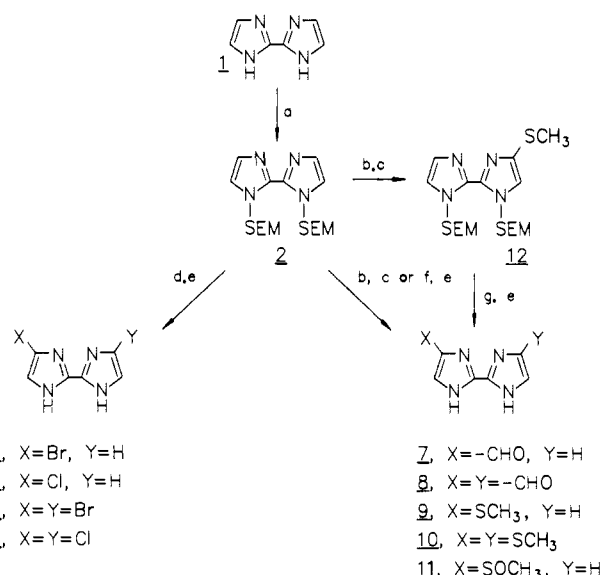
(DβH) inhibitor, 2,2'-bi-1*H*-imidazole (1),<sup>6,7</sup> cardiotoxic activity was observed.<sup>8</sup> After the administration of a single 10 mg/kg oral dose to conscious monkeys, inotropic activity as measured by  $dP/dt_{max}$  increased 78%. Additional studies indicated the inotropic effects were attributable to a metabolite of 1, of unknown structure. These observations and the report that imidazole increases myocardial contractility<sup>9</sup> prompted us to further investigate substituted biimidazoles as potential cardiotoxic agents.

**Chemistry**

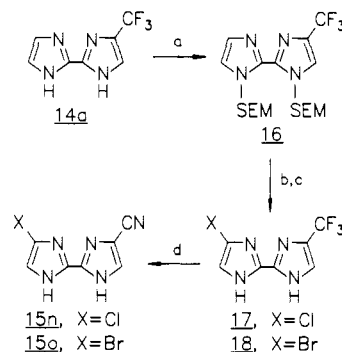
In contrast to imidazoles, few chemical transformations have been reported on the 2,2'-bi-1*H*-imidazole ring system. The selective mononitration and dinitration of 1 with 99% nitric acid have been accomplished.<sup>10</sup> Bromination of 1 yields tetrabromo-2,2'-bi-1*H*-imidazole.<sup>11</sup> N-Alkylation of 1 with dimethyl sulfate<sup>10</sup> as well as with 1,2-dihaloethanes and 1,3-dihalopropanes has been reported.<sup>12</sup>

The synthesis of 4(5)-cyano-2,2'-bi-1*H*-imidazole (15a) was accomplished by our recently reported method<sup>13</sup> (see Scheme I). 4(5)-Trifluoromethyl-2,2'-bi-1*H*-imidazole (14a) was treated with warm 5% ammonium hydroxide to transform the trifluoromethyl group to a cyano group in 87% yield. A number of analogues (15b-m) were synthesized by this route. The trifluoromethyl starting materials (14a-l) were prepared by using Baldwin's method,<sup>14</sup> by treating imidazole-2-carboxaldehydes (13a-l) with 1,1-dibromo-3,3,3-trifluoroacetone,<sup>15</sup> sodium acetate, and ammonium hydroxide.

In order to mono- and difunctionalize the very insoluble 1, the NH groups were protected with [2-(trimethyl-

**Scheme II. Preparation of Mono- and Disubstituted 2,2'-Biimidazoles from 2,2'-Bi-1*H*-imidazole (1)<sup>a</sup>**

<sup>a</sup> (a) NaH/DMF; SEM-Cl. (b) 2.5 equiv of *n*-BuLi/TMEDA. (c) CH<sub>3</sub>SSCH<sub>3</sub>. (d) NXS. (e) H<sub>3</sub>O<sup>+</sup>. (f) DMF. (g) MCPBA.

**Scheme III. Preparation of 4'-Chloro- and 4'-Bromo-4-cyano-2,2'-bi-1*H*-imidazoles<sup>a</sup>**

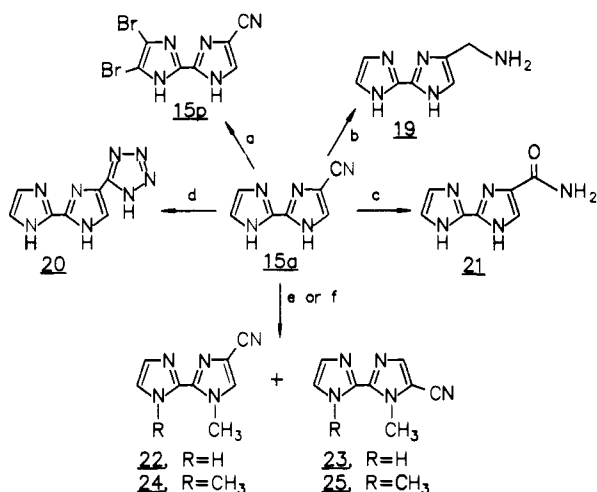
<sup>a</sup> (a) NaH/DMF; SEM-Cl. (b) NXS. (c) H<sub>3</sub>O<sup>+</sup>. (d) 5% NH<sub>4</sub>OH.

silyl)ethoxy]methyl<sup>16</sup> (SEM) to provide 2 in high yield<sup>17</sup> (see Scheme II). This protecting group is easily introduced and removed from imidazole rings.<sup>17</sup> Metalation of 2 with 2.5 equiv of *n*-butyllithium in THF with TMEDA, followed by addition of DMF or methyl disulfide, provided, after deprotection, the monoaldehyde 7 and dialdehyde 8, or the (methylthio)- and bis(methylthio)bi-1*H*-imidazoles 9 and 10, respectively. Oxidation of the SEM-protected mono(methylthio)bi-1*H*-imidazole 12 with 3-chloroperbenzoic acid followed by removal of the SEM groups gave the methyl sulfoxide 11.

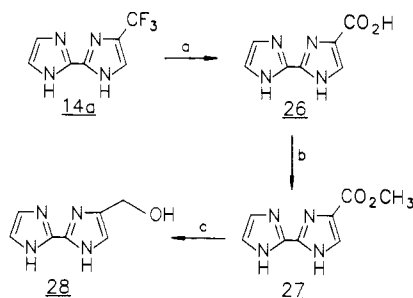
Chlorination or bromination of 2 with the corresponding *N*-halosuccinimide yielded the monochloro or monobromo derivatives 3 and 4, respectively, as well as small amounts of the dihalo derivatives 5 and 6, as outlined in Scheme II.<sup>18</sup> Selective monohalogenation of the bis-SEM-protected 4(5)-(trifluoromethyl)-2,2'-bi-1*H*-imidazole 16 on the

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**Scheme IV.** Preparation of Biimidazoles from 4(5)-Cyano-2,2'-bi-1*H*-imidazole (15a)<sup>a</sup>

<sup>a</sup> (a) Br<sub>2</sub>. (b) H<sub>2</sub>; Pd/C. (c) Concentrated HCl. (d) NaN<sub>3</sub>/NH<sub>4</sub>Cl/LiCl. (e) NaH/DMF/CH<sub>3</sub>I. (f) 20% NaOH/(CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>.

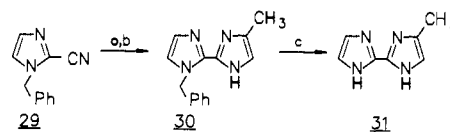
**Scheme V.** Preparation of 4-Substituted 2,2'-Biimidazoles from 14a<sup>a</sup>

<sup>a</sup> (a) 1 N NaOH. (b) CH<sub>3</sub>OH/HCl. (c) Na/NH<sub>3</sub>.

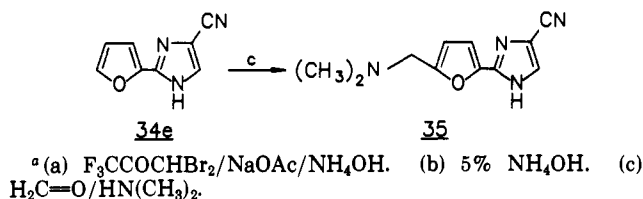
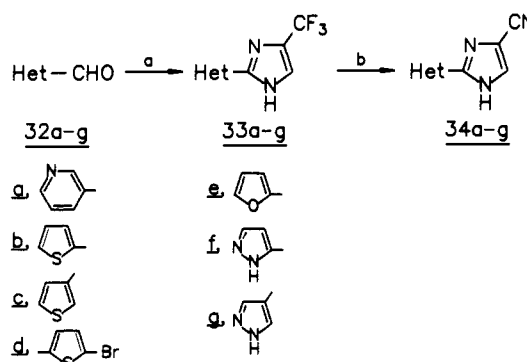
unsubstituted ring was accomplished with *N*-chloro- or *N*-bromosuccinimide (see Scheme III). Deprotection gave 17 or 18, which were converted to the chlorocyno (15n) and bromocyno (15o) analogues as outlined above with 5% ammonium hydroxide. Direct bromination of 15a yielded 4',5'-dibromo-4(5)-cyanobi-1*H*-imidazole (15p) (see Scheme IV). Compound 15a served as a pivotal intermediate for a number of additional bi-1*H*-imidazoles including the methylamine (19), tetrazole (20), and amide (21).

All five possible *N*-monomethyl and *N,N'*-dimethyl analogues of 15a were prepared. Monomethylation (1 equiv of sodium hydride and methyl iodide in DMF) provided both 4-cyano-1-methyl-2,2'-bi-1*H*-imidazole (22) (40%) and 5-cyano-1-methyl-2,2'-bi-1*H*-imidazole (23) (8%). Comparison of 22 and 23 with the *N*-methyl analogue 15b, prepared unambiguously (see Scheme I), confirmed that methylation occurred on the ring containing the cyano group. The site of *N*-alkylation on the cyano-containing imidazole ring was assigned on the basis of <sup>1</sup>H NMR spectroscopy. Takenchi<sup>19</sup> has demonstrated that the H-5 proton on 4-substituted imidazoles is downfield from the H-4 proton on 5-substituted imidazoles (DMSO-*d*<sub>6</sub>). The proton adjacent to the cyano group on 22 appears at δ 8.24 (DMSO-*d*<sub>6</sub>) and at δ 7.97 in 23. Structural assignments for 24 and 25 were based on the same NMR arguments. Compounds 24 and 25 were prepared by the treatment of 15a with excess dimethyl sulfate and 20% aqueous sodium hydroxide in ethanol.

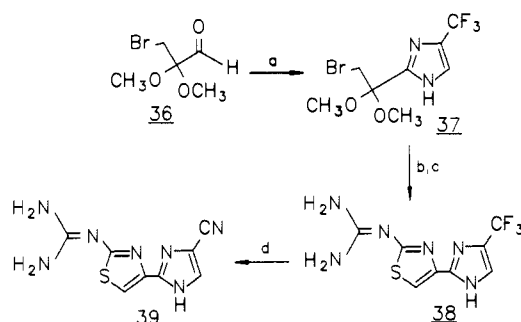
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**Scheme VI.** Preparation of 4(5)-Methyl-2,2'-bi-1*H*-imidazole (31) from 1-Benzyl-2-cyanoimidazole (29)<sup>a</sup>

<sup>a</sup> (a) S<sub>8</sub>/H<sub>2</sub>NCH<sub>2</sub>CH(CH<sub>3</sub>)NH<sub>2</sub>. (b) MnO<sub>2</sub>. (c) Na/NH<sub>3</sub>.

**Scheme VII.** Preparation of 2-Heterocyclo-4(5)-cyanoimidazoles<sup>a</sup>

<sup>a</sup> (a) F<sub>3</sub>CCOCHBr<sub>2</sub>/NaOAc/NH<sub>4</sub>OH. (b) 5% NH<sub>4</sub>OH. (c) H<sub>2</sub>C=O/HN(CH<sub>3</sub>)<sub>2</sub>.

**Scheme VIII.** Preparation of 39<sup>a</sup>

<sup>a</sup> (a) CF<sub>3</sub>COCHBr<sub>2</sub>/NaOAc/NH<sub>4</sub>OH. (b) HCO<sub>2</sub>H. (c) (H<sub>2</sub>N)<sub>2</sub>C=NC=SNH<sub>2</sub>. (d) 5% NH<sub>4</sub>OH.

4(5)-(Trifluoromethyl)-2,2'-bi-1*H*-imidazole (14a) served as an intermediate to the carboxylic acid (26), methyl ester (27), and methyl alcohol (28) (see Scheme V). 4(5)-Methyl-2,2'-bi-1*H*-imidazole (31) (see Scheme VI) was prepared from *N*-benzyl-2-cyanoimidazole (29)<sup>20</sup> by conversion of the cyano group to a methylimidazole ring, followed by debenzylation. A series of 2-heterocyclic-4(5)-cyanoimidazoles (34a-g) was prepared by using the same synthetic sequence used to obtain 15a (see Scheme VII). 2-[5-[(Dimethylamino)methyl]-2-furanyl]-1*H*-imidazole-4-carbonitrile (35) (Scheme VII) was prepared from the corresponding furanyl compound 34e by using Mannich reaction conditions.

The synthesis of (2-guanidinothiazolyl)cianoimidazole 39 (see Scheme VIII) required selective functional group manipulation and started with 3-bromo-2,2-dimethoxypropionaldehyde (36).<sup>21</sup> Treatment of 36 with 1,1-di-

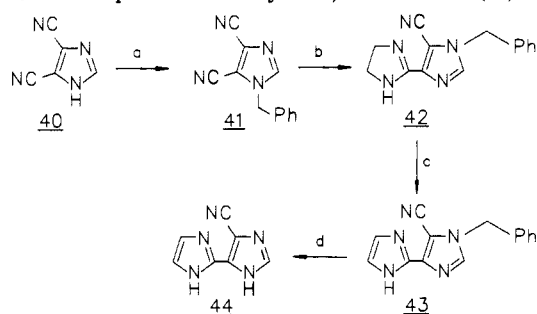
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Table I. Inotropic Activity of Biimidazoles

compd	R <sub>1</sub>	R <sub>2</sub>	X	Y	prepn method, ref	dP/dt, anesthetized rat <sup>a</sup> ED <sub>25%</sub> , mg/kg	n <sup>b</sup>	anesthetized dog <sup>c</sup> peak % ΔCF	n <sup>b</sup>
1 <sup>d</sup>	H	H	H	H	6	0.24	5		
2	SEM	SEM	H	H	17	NA	3		
3	H	H	H	Br	18	5.5	5	51 <sup>f</sup>	4
4	H	H	H	Cl	18	NA	2		
5	H	H	Br	Br	18	NA	2		
6	H	H	Cl	Cl	18	0.7	3		
7 <sup>d</sup>	H	H	H	CH=O	17	NA	2		
8	H	H	CH=O	CH=O	17	NA	3		
9	H	H	H	SCH <sub>3</sub>	17			4	2
10	H	H	SCH <sub>3</sub>	SCH <sub>3</sub>	17	<i>e</i>			
11	H	H	H	SOCH <sub>3</sub>	17			1	2
12	SEM	SEM	H	SCH <sub>3</sub>	17				
14a	H	H	H	CF <sub>3</sub>	13	NA	2		
15a	H	H	H	CN	<i>g</i>	4.8	3	60	4
17	H	H	Cl	CF <sub>3</sub>	<i>g</i>				
18	H	H	Br	CF <sub>3</sub>	<i>g</i>	NA	2		
19	H	H	H	CH <sub>2</sub> NH <sub>2</sub>	<i>g</i>	NA	2		
20	H	H	H		<i>g</i>	NA	2	0	1
21	H	H	H	CONH <sub>2</sub>	<i>g</i>	NA	2		
26	H	H	H	CO <sub>2</sub> H	<i>g</i>	NA	2		
27 <sup>d</sup>	H	H	H	CO <sub>2</sub> Me	<i>g</i>	NA	3		
28	H	H	H	CH <sub>2</sub> OH	<i>g</i>			0	2
31	H	H	H	CH <sub>3</sub>	<i>g</i>	NA	2		
47					<i>g</i>			0	1
enoximone						1.4	6	73 ± 32	3
milrinone						0.3 mg/kg = 13 ± 3% †; higher doses caused decrease	3	52 ± 4	3

<sup>a</sup> Effective dose of compound (mg/kg iv) that produces a 25% increase in left ventricular dP/dt<sub>max</sub>. ED<sub>25%</sub> values were obtained from three to five dose-response curves. NA = not active at 3 mg/kg. Data not available for all compounds. <sup>b</sup> n = number of animals. <sup>c</sup> Peak percent change in contractile force produced by 1 mg/kg administered iv. <sup>d</sup> Dihydrochloride salt. <sup>e</sup> Insoluble. <sup>f</sup> At 10 mg/kg. <sup>g</sup> See Experimental Section of this work.

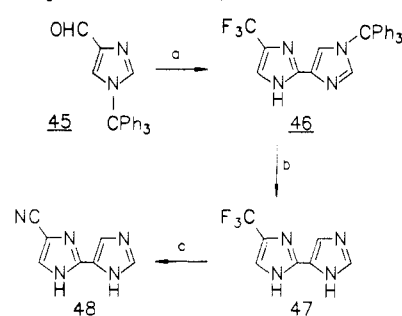
## Scheme IX. Preparation of 5'-Cyano-2,4'-biimidazole (14)



<sup>a</sup> (a) NaH/PhCH<sub>2</sub>Br. (b) H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>/S<sub>8</sub>. (c) MnO<sub>2</sub>. (d) Na/NH<sub>3</sub>.

bromo-3,3,3-trifluoroacetone as in the synthesis of 14a–1 provided the 2-substituted-4(5)-(trifluoromethyl)imidazole 37 in 67% yield. Hydrolysis of the dimethyl acetal group, followed by treatment with amidinothiourea in refluxing acetone, gave the thiazolyimidazole 38 in 35% yield. The trifluoromethyl group was converted to the nitrile in 84% yield by the above method.

The synthesis of 5-cyano-2,4'-bi-1*H*-imidazole (44) was carried out as outlined in Scheme IX. The intermediate

Scheme X. Preparation of 4(5)-Cyano-2,4'-biimidazole (48)<sup>a</sup>

<sup>a</sup> (a) F<sub>3</sub>CCOCHBr<sub>2</sub>/NaOAc/NH<sub>4</sub>OH. (b) 2 N HCl. (c) 5% NH<sub>4</sub>OH.

*N*-benzylcyanobiimidazole was isolated as a 7:1 mixture of the 5-cyano isomer 43 and the 4-cyano isomer.<sup>22</sup> De-

(22) Structural assignments for 43 and ii (isolated as a 7 to 1 mixture) were made on the basis of the positions of the benzylic methylene protons in the <sup>1</sup>H NMR spectrum (DMSO-*d*<sub>6</sub>) of model compounds 19 and i<sup>23</sup> vs 43 and ii.

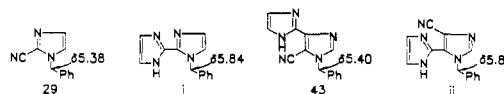


Table II. Physical Properties and Inotropic Activity of Cyanobiimidazoles

compd	R <sub>1</sub>	R <sub>2</sub>	X	Y	yield, %	method	mp, °C	recrystn solvent	anesthetized dog				
									ED <sub>25%</sub> , mg/kg <sup>a</sup>	n <sup>b</sup>	peak % ΔCF <sup>c</sup>	n <sup>b</sup>	
15a	H	H	H	H	93	B <sup>f</sup>	>260 <sup>d</sup>	HOAc	0.16	4	60	4	
15b	CH <sub>3</sub>	H	H	H	94	B	>270 <sup>d</sup>	MeO(CH <sub>2</sub> ) <sub>2</sub> OH			29	1	
15c	H	H	CH <sub>3</sub>	H	45	B	>260	<i>i</i> -PrOH	0.63	3			
15d	CH <sub>3</sub>	H	5'-Cl	H	55	B	259-261	<i>i</i> -PrOH			11	2	
15e	C <sub>2</sub> H <sub>5</sub>	H	H	H	52	B	215-216	<i>i</i> -PrOH			41	2	
15f	CH=CH <sub>2</sub>	H	H	H	15	B	>260	MeO(CH <sub>2</sub> ) <sub>2</sub> OH			41	2	
15g	C <sub>6</sub> H <sub>5</sub>	H	H	H	38	B	222-225	EtOH			0	2	
15h	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	69	B	239-241 <sup>d</sup>	MeO(CH <sub>2</sub> ) <sub>2</sub> OH/H <sub>2</sub> O			2	2	
15i	H	H	C <sub>6</sub> H <sub>5</sub>	H	42	B	>260	<i>i</i> -PrOH	0.89	3			
15j	H	H	4-(CF <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>	H	53	B	>250	<i>i</i> -PrOH/H <sub>2</sub> O	0.26	2			
15k	H	H	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub>	H	61	B	>260	<i>i</i> -PrOH	0.36	3	106	1	
15l	H	H	CF <sub>3</sub>	H	35	B	>250	<i>i</i> -PrOH	0.33	3			
15m	H	H	CN	H	70	B	>250 <sup>d</sup>	EtOH/H <sub>2</sub> O	0.18	3			
15n	H	H	Cl	H	48	<i>g</i>	>250				95	2	
15o	H	H	4'-Br	H	43	<i>g</i>	>260	EtOAc	0.20	3			
15p	H	H	4',5'-Br <sub>2</sub>	H	17	<i>g</i>	>260				96	2	
22	H	CH <sub>3</sub>	H	H	40	<i>g</i>	237-239	PhCH <sub>3</sub> / <i>i</i> -PrOH	0.17	1			
23	H	CH <sub>3</sub>	H	CN <sup>e</sup>	8	<i>g</i>	238-239	PhCH <sub>3</sub> / <i>i</i> -PrOH			3	2	
24	CH <sub>3</sub>	CH <sub>3</sub>	H	H	21	<i>g</i>	119-120						
25	CH <sub>3</sub>	CH <sub>3</sub>	H	CN <sup>e</sup>	8	<i>g</i>	127-130	PhCH <sub>3</sub> /Hex			13 <sup>f</sup>	3	
44					83	<i>g</i>	>285					0	1
48					63	B <sup>f</sup>	>260	MeO(CH <sub>2</sub> ) <sub>2</sub> OH/H <sub>2</sub> O				25	4
49					65	B	>250 <sup>a</sup>	MeO(CH <sub>2</sub> ) <sub>2</sub> OH/H <sub>2</sub> O				17	3
50					48	B	>250 <sup>a</sup>	DMF				8	2
enoximone									0.46	3	73 ± 32	3	
milrinone									0.06	3	52 ± 4	3	

<sup>a</sup> Effective dose of compound (mg/kg iv) that produces a 25% increase in left ventricular  $dP/dt_{max}$ . ED<sub>25%</sub> values were obtained from one to four dose-response curves. Data not available for all compounds. <sup>b</sup> *n* = number of dogs. <sup>c</sup> Peak percent change in contractile force produced by 1 mg/kg administered iv. <sup>d</sup> Initially reported in ref 13. <sup>e</sup> CN group at 5-position. <sup>f</sup>  $dP/dt$ , anesthetized rat at 1 mg/kg. <sup>g</sup> See Experimental Section of this work.

benzylation with sodium liquid ammonia gave pure **44** in 85% yield. 4(5)-Cyano-2,2'-bi-1*H*-imidazole (**48**) was obtained from **45**<sup>24</sup> via a similar procedure used to obtain **15a-l** (see Scheme X).

### Results and Discussion

The positive inotropic activities of the compounds in Tables I-III were derived from experiments performed on anesthetized, acutely instrumented rats and dogs. The rats were prepared according to the method of Hayes<sup>25</sup> as described under Experimental Section (Experiments in Anesthetized Rats). The dogs were prepared as described under Experimental Section (Experiments in Anesthetized Dogs). Isoproterenol was administered prior to drug administration to verify inotropic responsiveness of each preparation.

The finding that **1** demonstrated inotropic activity in the conscious monkey led to a synthetic program to determine the structural features of 2,2'-bi-1*H*-imidazole

necessary for inotropic activity. Early in our synthetic program, 4(5)-bromo-2,2'-bi-1*H*-imidazole (**3**) demonstrated inotropic activity in the anesthetized dog (see Table I). However, the increase in contractile force was partially blocked by atenolol, suggesting a  $\beta$ -adrenergic component. Surprisingly, the classical chloro isostere analogue **4** was inactive (see Table I). Thornber<sup>26</sup> has reported trifluoromethyl and cyano to be nonclassical isosteres for bromine, which prompted our synthesis of these analogues. Although the trifluoromethyl analogue **14a** was devoid of inotropic activity, the 4(5)-cyano-2,2'-bi-1*H*-imidazole (**15a**) was found to be a potent inotropic agent with a moderate duration of action (Table I and Figure 2). A number of other 4(5)-monosubstituted analogues were prepared which were inactive; these included methylthio (**9**), methyl sulfide (**11**), aminomethyl (**19**), carboxamide (**21**), carboxylic acid (**26**), methyl ester (**27**), hydroxymethyl (**28**), and methyl-substituted analogues (**31**) (Table I).

Since the cyano group was necessary for activity, a number of substituted cyanobi-1*H*-imidazoles were prepared (Table II). The symmetrical dicyano compound **15m**

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Table III. Physical Properties and Inotropic Activity of 2-Heterocyclic-4(5)-cyanoimidazoles<sup>a</sup>

compd	Het	yield, %	mp, °C	recrystn solvent	dP/dt, anesthetized rat <sup>b</sup> ED <sub>25%</sub> , mg/kg	n <sup>c</sup>	anesthetized dog <sup>d</sup> peak % ΔCF	n <sup>c</sup>
34a		88	215–218	PhCH <sub>3</sub> / <i>i</i> -PrOH	NA	2	31	1
34b		40	209–212	PhCH <sub>3</sub>	NA	2		
34c		13	198–202	PhCH <sub>3</sub>	NA	2		
34d		26	214–216	PhCH <sub>3</sub>	NA	2		
34e		77	229–332 <sup>e</sup>	MeOH/H <sub>2</sub> O	NA	3		
34f		80	259–261 <sup>e</sup>	<i>i</i> -PrOH/H <sub>2</sub> O	NA	2	-4	1
34g		94	259–259 <sup>e</sup>	<i>i</i> -PrOH/H <sub>2</sub> O	NA	2	NA	1
35		30	168–170	EtOAc/EtOH			NA	1
39		84	>250	EtOH/Hex			NA	1
enoximone					1.4	6	73 ± 32	3
milrinone					0.3 mg/kg = 13 ± 3% †; higher doses caused decrease	3	52 ± 4	3

<sup>a</sup> Prepared by method in ref 13 from the corresponding (trifluoromethyl)imidazole with the exception of 35; Experimental Section contains procedures for 35 and 39. <sup>b</sup> See footnote a in Table I. <sup>c</sup> n = number of animals. <sup>d</sup> See footnote c in Table I. <sup>e</sup> Initially reported in ref 16.

Table IV. Physical Properties of (Trifluoromethyl)biimidazoles<sup>a</sup>

compd	R	X	yield, %	mp, °C	recrystn solvent
14a	H	H	59	239–241 <sup>a</sup>	xylene
14b	CH <sub>3</sub>	H	27	192–194 <sup>a</sup>	toluene
14c	H	CH <sub>3</sub>	28	230–232	xylene
14d	CH <sub>3</sub>	5'-Cl	37	217–219	toluene
14e	C <sub>2</sub> H <sub>5</sub>	H	40	126–127	EtOH/H <sub>2</sub> O
14f	CH=CH <sub>2</sub>	H	34	166–169	PhCH <sub>3</sub>
14g	C <sub>6</sub> H <sub>5</sub>	H	63	184–186	EtOH/H <sub>2</sub> O
14h	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	32	169–170	CH <sub>3</sub> CN/H <sub>2</sub> O
14i	H	C <sub>6</sub> H <sub>5</sub>	43	234–238	EtOH/H <sub>2</sub> O
14j	H	4-(CF <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>	43	138–140	<i>i</i> -PrOH/H <sub>2</sub> O
14k	H	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub>	77	240–245 dec	EtOH/H <sub>2</sub> O
14l	H	CF <sub>3</sub>	59	>260 <sup>a</sup>	EtOH/H <sub>2</sub> O

<sup>a</sup> See Experimental Section and supplementary material of ref 13 for examples of this conversion (method B). This methodology was originally reported by Baldwin and co-workers (ref 14). The experimental procedure for the synthesis of 13l is found in the supplementary material of ref 13 and is representative of the method used to introduce the aldehyde group in the 2-position.

was approximately equipotent to 15a. Substitution of other electron-withdrawing groups on the non-cyano-containing ring, as exemplified by trifluoromethyl (15l), *p*-(trifluoromethyl)phenyl (15j), and bromo (15o and 15p), retained most of the inotropic activity of the parent molecule 15a. Methyl (15c) and phenyl (15i) substitution greatly diminished the activity whereas *p*-methoxyphenyl

substitution (15k) led to retention of activity. 1-Methyl-4-cyano-2,2'-bi-1*H*-imidazole (22) was equipotent with 15a, whereas the positional isomer 1-methyl-5-cyano-2,2'-bi-1*H*-imidazole (23) was inactive. In addition, the two possible 1,1'-dimethylcyano-bi-1*H*-imidazoles 24 and 25 were also inactive, indicating that an acidic NH is essential for activity.

**Table V.** Comparison of the Effects of 15a, Enoximone, and Amrinone on Type IV PDE from Dog Hearts and Kidneys

drug	IC <sub>50</sub> of type IV PDE, $\mu\text{M}^a$	
	cardiac	kidney
15a	36.7 $\pm$ 4.1	339 $\pm$ 23
enoximone	2.9 $\pm$ 0.2	>150 (34 $\pm$ 6%)
amrinone	41.0 $\pm$ 2.1	>150 (24 $\pm$ 5%)

<sup>a</sup>IC<sub>50</sub> values were determined by using Dixon plots (1/*v* vs inhibitor concentration). Three or four separate enzyme preparations were used for each determination and are reported as means  $\pm$  SEM. Values in parentheses indicate percent inhibition at the drug concentration shown. Substrate concentration was 0.5  $\mu\text{M}$  cAMP.

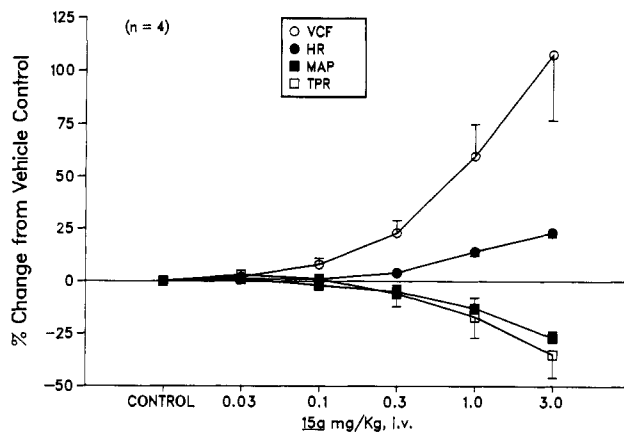
Changing from 2,2'-bi-1*H*-imidazole to 2,4'-bi-1*H*-imidazole with the cyano group in either the 5'-position (44) or the 4-position (48) led to complete loss of inotropic activity. Replacement of the unsubstituted imidazole ring in 15a with other heteroaromatic rings (34a-g) (Table III) also caused complete loss of activity. A phenyl ring spacer has been successfully used by other groups in designing active cardiotoxic agents.<sup>27</sup> However, compounds 49 and 50 (Table II) which incorporate this approach proved inactive as inotropes.

The elegant design of ranitidine<sup>28</sup> and tiotidine<sup>29</sup> in which the imidazole ring present in cimetidine was replaced with [(dimethylamino)methyl]furan and 2-guanidinothiazole, respectively, suggested that these bioisosteres for the unsubstituted imidazole ring in 15a might be possible. Replacement of this imidazole ring with [(dimethylamino)methyl]furan and 2-guanidinothiazole provided 35 and 39, both devoid of inotropic activity (see Table III).

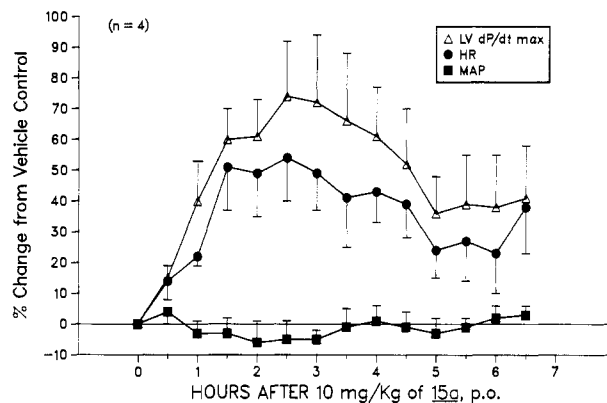
On the basis of its ED<sub>25%</sub> value in dogs, 15a, the most active compound of the series, was evaluated as a cardiotoxic agent (see Table II). Testing included determining its ability to inhibit cyclic nucleotide phosphodiesterase (PDE) by the method of Thompson.<sup>30</sup> It is a weak inhibitor of type I and type II PDE<sup>31</sup> isolated from dog heart and kidney, respectively, causing 10% inhibition of these isoenzymes at concentrations up to 200  $\mu\text{M}$ . The effect of 15a on type IV PDE (high-affinity PDE, PDE III)<sup>30</sup> depends upon the tissue from which the isoenzyme is isolated. It is a good inhibitor of type IV PDE isolated from dog heart, having a potency similar to that of amrinone but less than that of enoximone (Table V). However, 15a is a very weak inhibitor of type IV PDE isolated from dog kidney. These results indicate that 15a is a selective inhibitor of the subtype of type IV PDE present in dog heart.

It has recently been shown that there are two subtypes of type IV PDE,<sup>32</sup> one that is strongly inhibited by low concentrations of cGMP and one that is not inhibited by cGMP. Cardiac tissue contains predominately the former

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- (32) Strada, S. J.; Shen, C.-C.; Thompson, W. J. VIth International Conference on Cyclic Nucleotides, Calcium and Protein Phosphorylation, Abstract 115, 1986.



**Figure 1.** Dose-dependent effects of 15a on ventricular contractile force (VCF), heart rate (HR), mean arterial pressure (MAP), and total peripheral resistance (TPR) in pentobarbital-anesthetized (*n* = 4) dogs. The compound was administered in 20-min intervals following a 20-min vehicle control period. Data points are mean values for each 20-min period. Control MAP and HR were 110  $\pm$  8 mmHg and 133  $\pm$  10 beats/min.



**Figure 2.** Effect of 15a (10 mg/kg po) on left ventricular  $dP/dt_{\text{max}}$ , heart rate (HR), and mean arterial pressure (MAP) in conscious instrumented (*n* = 4) dogs. Data points are mean values for thirteen 30-min periods which followed two 30-min vehicle control periods. Control MAP and HR were 103  $\pm$  3 mmHg and 83  $\pm$  9 beats/min.

subtype, while kidney contains almost exclusively the latter subtype. Enoximone and amrinone have been shown to be selective inhibitors of the cGMP-inhibitable form of type IV PDE, with very little effect on the cGMP-noninhibitable form.<sup>33</sup> The data presented indicate that 15a is also specific for the cGMP-inhibitable subtype of type IV PDE.

The cardiovascular response of four anesthetized dogs to the iv administration of 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg 4(5)-cyano-2,2'-bi-1*H*-imidazole (15a) is shown in Figure 1. The figure illustrates the percent change from predose base-line value of mean arterial pressure (MAP), heart rate (HR), peak ventricular contractile force (VCF), and calculated total peripheral resistance (TPR) following the administration of 15a. The doses were administered 20 min apart and produced dose-related increases in VCF and HR and decreases in MAP. The changes were statistically significant after the 1.0 and 3.0 mg/kg doses. The decreases in MAP were associated with decreases in calculated total peripheral resistance. Figure 2 illustrates the response of four conscious, chronically instrumented dogs which were dosed orally with 10 mg/kg of 15a. The dose increased left ventricular (LV)  $dP/dt_{\text{max}}$  by more than 70%

(33) Kariya, T.; Dage, R. C. *Fed. Proc.* 1987, 46, 373.

(2117 ± 531 mmHg/s) and increased HR by 45 ± 12 beats/min but had little effect on MAP. The increase in  $LV\ dP/dt_{max}$  was significant within 30 min following dosing and was still above base line 6 $\frac{1}{2}$  h after dosing. The values returned to predose levels 24 h after dosing. While mean arterial pressure did not decrease following dosing of the conscious dogs, it decreased in parallel with a decrease in PPR in the anesthetized dogs.

In anesthetized dogs a 0.3 mg/kg intravenous dose of **15a** increased contractility 23 ± 6% while the same dose of milrinone, RO 13-6438, and amrinone increased contractility 110%, 47%, and 19%, respectively. A 3 mg/kg intravenous dose of milrinone increased contractility approximately 105% while the same dose of **15a** increased contractility 108 ± 31%.<sup>34-36</sup> In conscious dogs a 10 mg/kg oral dose of **15a** increased contractility more than 70% while the same dose of RO 13-6438 and amrinone increased contractility 44% and 57%; 6 h after dosing contractility was still elevated 40%, 28%, and 20%, respectively. A 1 mg/kg oral dose of milrinone increased contractility 99%, with duration of action exceeding 5 h.<sup>34-36</sup> A detailed description of the methods used in these studies may be found under Experimental Section.

The dog studies reported here demonstrate that 4(5)-cyano-2,2'-bi-1*H*-imidazole (**15a**) increased myocardial contractility and reduced calculated total peripheral resistance and MAP. It possesses, therefore, a cardiovascular profile that may prove useful in the treatment of clinical conditions arising from reduced myocardial contractility and elevated vascular tone. Compound **15a** was also studied in the propranolol-failed dog model and caused marked improvement in cardiac output and left ventricular contractile force. These results will be reported separately.

We have demonstrated that inotropic activity of the series studied is confined to cyano-substituted 2,2'-bi-1*H*-imidazoles containing an acidic NH group. Compound **15a** represents a new class of potent, orally active inotropic agents with good duration of action. The pharmacological studies on **15a** suggest its potential utility in the treatment of congestive heart failure.

### Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were determined on either a Varian EM-360 or a Varian XL-300 instrument and are reported in ppm downfield from (CH<sub>3</sub>)<sub>4</sub>Si internal standard ( $\delta$ ). Mass spectra were obtained on a Finnegan 4000 spectrometer interfaced to an Incos 2000 data system. Elemental analyses were provided by the Analytical Chemistry Department, Merrell Dow Research Institute, Cincinnati, OH.

**4(5)-(Trifluoromethyl)-2,2'-bi-1*H*-imidazole (14a) (Method A).** 1,1-Dibromo-3,3,3-trifluoroacetone<sup>15</sup> (252 g, 140 mL, 0.94 mol) was added to a solution of sodium acetate (138 g, 1.6 mol) in water (700 mL). The solution was heated on a steam bath for 30 min. To the cooled solution (ice bath) was added imidazole-2-carboxaldehyde (**13a**; 75 g, 0.78 mol) and methanol (3 L), followed by concentrated ammonium hydroxide (1 L) (Caution: The NH<sub>4</sub>OH addition is mildly exothermic). A homogeneous reaction mixture was obtained, and after 1 h product began to crystallize. After stirring overnight at room temperature, **14a** was collected by filtration and dried (77.7 g, 49.3%). This material was sufficiently pure to carry on to the next step. Recrystallization of a small sample from xylene provided an analytical sample: mp 239–241 °C; UV max (CH<sub>3</sub>OH) 270 nm ( $\epsilon$  21600); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  5.6 (br s, exchangeable), 7.1 (s, 2), 7.6 (s, 1); MS

(Cl/CH<sub>4</sub>) *m/z* 203 (M + 1, base peak), 183 (M + 1 - HF). Anal. (C<sub>7</sub>H<sub>5</sub>F<sub>3</sub>N<sub>4</sub>) C, H, N.

**4(5)-Cyano-2,2'-bi-1*H*-imidazole (15a) (Method B).** A mixture of 4(5)-(trifluoromethyl)-2,2'-bi-1*H*-imidazole (**14a**; 2.5 g, 1.4 mmol) and 5% aqueous NH<sub>4</sub>OH (200 mL) was warmed to 60 °C. The progress of the reaction was followed by TLC (EtOAc) and HPLC (particle 10 ODS C18 column) (1:2.5:2.5 acetonitrile/0.04 M sodium dihydrogen phosphate/0.04 M sodium hydrogen phosphate, 1.5 mL/min). After 1 h, the cooled reaction was carefully neutralized with glacial acetic acid to give **15a** (1.71 g, 87%) as a light tan solid. Recrystallization (HOAc) gave analytically pure material: mp >260 °C; UV max (CH<sub>3</sub>OH) 273 nm ( $\epsilon$  38160); IR (Nujol) 2200 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO)  $\delta$  7.13 (s, 2), 8.08 (s, 1); MS (EI at 70 eV) *m/z* 159 (M<sup>+</sup>, base peak), 132 (M<sup>+</sup> - HCN). Anal. (C<sub>7</sub>H<sub>5</sub>N<sub>5</sub>) C, H, N.

**4-Chloro-4'-(cyano-2,2'-bi-1*H*-imidazole (15n).** Using method B, **15n** was isolated in 48% yield: mp >250 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.36 (s, 1), 8.20 (s, 1); MS (EI at 70 eV) *m/z* 193 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>4</sub>ClN<sub>5</sub>) C, H, N.

**4-Bromo-4'-(cyano-2,2'-bi-1*H*-imidazole (15o).** A sample of **18** (1.52 g, 5.4 mmol) was treated as in method B. The reaction was neutralized with HOAc, and **15o** (0.55 g, 43%) was collected as a white solid: mp >260 °C (EtOAc); IR (Nujol) 2240 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.35 (s, 1), 8.15 (s, 1); MS (EI at 70 eV) *m/z* 237 (M<sup>+</sup>), 158 (M<sup>+</sup> - Br), 131 (M<sup>+</sup> - Br - HCN). Anal. (C<sub>7</sub>H<sub>4</sub>BrN<sub>5</sub>) C, H, N.

**4',5'-Dibromo-4-cyano-2,2'-bi-1*H*-imidazole (15p).** To **15a** (0.6 g, 3.8 mmol) in CCl<sub>4</sub> (80 mL) was added 1.2 g (7.5 mmol) of Br<sub>2</sub>. After 2 days, the solid was collected and purified by flash chromatography (EtOAc) to yield **15p** (200 mg, 17%) as a tan solid: mp >260 °C; IR (KBr) 2245 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  8.23 (s, 1); MS (CI/CH<sub>4</sub>) *m/z* 318 (MH<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>3</sub>Br<sub>2</sub>N<sub>5</sub>) C, H, N.

**4-(Trifluoromethyl)-1,1'-bis[[2-(trimethylsilyl)ethoxy]methyl]-2,2'-bi-1*H*-imidazole (16).** To 14.4 g (0.03 mol) of 50% NaH (washed 3× with hexane) and 300 mL of DMF was slowly added **14a** (26.3 g, 0.13 mmol) as a solid. The reaction was stirred for 2 h at room temperature and then heated at 40 °C for 2 h. SEM-Cl (50 g, 0.3 mol) was added dropwise. After 1 h, the reaction was quenched with water (1 L) and the product was extracted into EtOAc (3 × 150 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration, 51.2 g of crude product was obtained. Purification by preparative HPLC (37% EtOAc/63% hexane) gave **16** (16.7 g, 28%) as a tan oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  -0.14 (s, 18), 0.61–1.0 (m, 4), 3.25–3.70 (m, 4), 5.76 (s, 2), 5.81 (s, 2), 6.91–7.06 (m, 2), 7.36 (br s, 1); MS (CI/CH<sub>4</sub>) *m/z* 463 (MH<sup>+</sup>).

**4-Chloro-4'-(trifluoromethyl)-2,2'-bi-1*H*-imidazole (17).** By use of a procedure similar to that described for **18**, **17** was obtained in 77% yield: MS (EI at 70 eV) 236 (M<sup>+</sup>).

**4-Bromo-4'-(trifluoromethyl)-2,2'-bi-1*H*-imidazole (18).** A mixture of **16** (11.1 g, 0.024 mol) and 250 mL of CCl<sub>4</sub> was treated with 4.89 g (0.028 mol) of NBS. The reaction was refluxed for 3 h, cooled, filtered, and concentrated to an oil (12.5 g). Flash chromatography (5% EtOAc/hexane) gave 5.56 g (43%) of the bis-SEM-protected product as a tan oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  -0.14 (s, 18), 0.65–1.00 (m, 4), 3.25–3.60 (m, 4), 5.70 (s, 2), 5.72 (s, 2), 7.00 (s, 1), 7.31 (s br, 1); MS (CI/CH<sub>4</sub>) *m/z* 541 (MH<sup>+</sup>). A mixture of 4.9 g of the tan oil, 40 mL of 40% HBr, 40 mL of water, and 200 mL of EtOH was heated at 80 °C for 3 h. The EtOH was removed under vacuum, and the resulting slurry was neutralized with aqueous K<sub>2</sub>CO<sub>3</sub>. The white solid **18** (2.42 g, 96%) was collected: mp >260 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.45 (s, 1), 7.95 (s br, 1); MS (EI at 70 eV) *m/z* 280 (M<sup>+</sup>), 261 (M<sup>+</sup> - F), 201 (M<sup>+</sup> - Br). Anal. (C<sub>7</sub>H<sub>4</sub>BrF<sub>3</sub>N<sub>4</sub>) C, H, N.

**2,2'-Bi-1*H*-imidazole-4-methanamine (19).** Compound **15a** (2.0 g, 0.0126 mol), 1.0 g 10% Pd/C, 50 mL EtOH, and 10 mL of EtOH were saturated with HCl and hydrogenated at 50 psi. After 48 h, 10 mL of H<sub>2</sub>O was added and the catalyst was removed by filtration. The filtrate was concentrated to give **19** (2.56 g, 80%) as a white solid: mp 259–262 °C (aqueous 2-propanol); <sup>1</sup>H NMR (D<sub>2</sub>O/DSS)  $\delta$  4.27 (s, 2), 7.58 (s, 3); MS (CI/CH<sub>4</sub>) *m/z* 164 (MH<sup>+</sup>), 147 (MH<sup>+</sup> - NH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>9</sub>N<sub>5</sub>·2.5HCl) C, H, N.

**5-(2,2'-Bi-1*H*-imidazol-4-yl)-1*H*-tetrazole (20).** A mixture of **15a** (2.0 g, 0.0126 mol), NaN<sub>3</sub> (0.91 g, 0.014 mol), LiCl (0.17 g, 0.004 mol), NH<sub>4</sub>Cl (0.75 g, 0.014 mol), and DMF (50 mL) was heated at 50 °C for 3 days. After cooling, the reaction was diluted

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with 800 mL of water and the off-white solid was collected and washed with water. After drying, 1.86 g (73%) of **20** was obtained: mp >250 °C (2-propanol/water, 1/4); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.18 (s, 2), 7.85 (s, 1); MS (CI/CH<sub>4</sub>) *m/z* 203 (MH<sup>+</sup>), 175 (MH<sup>+</sup> - N<sub>2</sub>). Anal. (C<sub>7</sub>H<sub>8</sub>N<sub>6</sub>) by exact mass.

**2,2'-Bi-1*H*-imidazole-4-carboxamide Hemihydrochloride (21)**. A sample of **15a** (2.0 g, 0.0126 mol) in 100 mL of concentrated HCl was warmed at 45 °C for 2 h and cooled and the pale yellow solid collected. After washing with cold EtOH and Et<sub>2</sub>O, 2.0 g (63%) of **21** was obtained: mp >265 °C; IR (Nujol) 3400, 3350, 1685 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O/DSS) δ 7.62 (s, 2), 8.02 (s, 1); MS (EI at 70 eV) *m/z* 177 (MH<sup>+</sup>), 160 (MH<sup>+</sup> - NH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>7</sub>N<sub>6</sub>O·0.5HCl) C, H, N.

**4-Cyano-1-methyl-2,2'-bi-1*H*-imidazole (22) and 5-Cyano-1-methyl-2,2'-bi-1*H*-imidazole (23)**. Under nitrogen, a mixture of 0.92 g (0.023 mol) of 60% sodium hydride (washed with hexane) and DMF (150 mL) was charged with **15a** (3.4 g, 0.021 mol). The reaction was warmed at 50 °C for 15 min and cooled to room temperature, and 1.3 mL (0.021 mol) of iodomethane was added. After 18 h, the reaction was diluted with water and extracted with EtOAc (3 × 200 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration, 4.6 g of an oily solid was obtained. The two isomers were separated by flash chromatography (hexane/ethyl acetate, 1:1) to provide 1.5 g (40.5%) of **22** (slower moving band) and 0.3 g (8.1%) of **23** (faster moving band).

**22**: mp 237–239 °C (toluene/2-propanol); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 4.08 (s, 3), 7.12 (br s, 1), 7.29 (br s, 1), 8.24 (s, 1); MS (EI at 70 eV) *m/z* 173 (M<sup>+</sup>), 172 (M<sup>+</sup> - H). Anal. (C<sub>8</sub>H<sub>7</sub>N<sub>5</sub>) C, H, N.

**23**: mp 238–239 °C (toluene/2-propanol); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 4.16 (s, 3), 7.17 (br s, 1), 7.32 (br s, 1), 7.97 (s, 1); MS (EI at 70 eV) *m/z* 173 (M<sup>+</sup>), 172 (M<sup>+</sup> - H). Anal. (C<sub>8</sub>H<sub>7</sub>N<sub>5</sub>) C, H, N.

**4-Cyano-1,1'-dimethyl-2,2'-bi-1*H*-imidazole (24) and 5-Cyano-1,1'-dimethyl-2,2'-bi-1*H*-imidazole (25)**. A mixture of **15a** (2.4 g, 0.015 mol), dimethyl sulfate (6.6 mL), 11.5 mL of 20% NaOH, and 40 mL of EtOH was refluxed for 7 h. After cooling and neutralization with dilute HCl, the reaction mixture was extracted with EtOAc (3 × 25 mL). The EtOAc layers were washed with 10% NaOH to remove any monomethylated products. After drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration, a 0.86-g mixture of **24** and **25** was obtained as a pale yellow oil which rapidly crystallized. Recrystallization from 40 mL 1:1 toluene/hexane gave 0.22 g of **25**. The filtrate was concentrated to give 0.6 g of **24**, which was purified by flash chromatography (EtOAc). **25**: mp 127–130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.08 (s, 3), 4.11 (s, 3), 7.00 (m, 1), 7.11 (m, 1), 7.47 (s, 1); MS (EI at 70 eV) *m/z* 187 (M<sup>+</sup>). Anal. (C<sub>9</sub>H<sub>9</sub>N<sub>5</sub>) C, H, N. **24**: mp 119–120 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.05 (s, 3), 4.18 (s, 3), 7.00 (s, 1), 7.13 (s, 1), 7.68 (s, 1); MS (EI at 70 eV) *m/z* 187 (M<sup>+</sup>). Anal. (C<sub>9</sub>H<sub>9</sub>N<sub>5</sub>) C, H, N.

**2,2'-Bi-1*H*-imidazole-4-carboxylic Acid (26)**. According to a procedure similar to that of Baldwin and co-workers,<sup>14</sup> **14a** (4.35 g, 0.0215 mol) and 250 mL 1 N NaOH were heated at 90 °C for 2 h, cooled, and acidified with concentrated HCl. The white solid was collected and washed with EtOH and then Et<sub>2</sub>O to give **26** as a tan powder: mp 265 °C (HOAc); IR (KBr) 1650, 1605, 1380 cm<sup>-1</sup>; <sup>1</sup>H NMR (TFA) δ 7.82 (s, 2), 8.38 (br s, 1); MS (EI at 70 eV) *m/z* 178 (M<sup>+</sup>), 160 (M<sup>+</sup> - H<sub>2</sub>O). Anal. (C<sub>7</sub>H<sub>6</sub>N<sub>4</sub>O<sub>2</sub>·H<sub>2</sub>O) C, H, N.

**2,2'-Bi-1*H*-imidazole-4-carboxylic Acid Methyl Ester Hydrochloride (27)**. A 2.1-g (0.0118-mol) sample of **26** in 300 mL of absolute MeOH was saturated with HCl gas. After 5 days, the pale yellow solid was collected and dried to give **27** (2.7 g, 100%): mp 214–217 °C (2-propanol); <sup>1</sup>H NMR (D<sub>2</sub>O/DSS) δ 4.00 (s, 3), 7.18 (s, 2), 8.15 (s, 1); MS (CI/CH<sub>4</sub>) *m/z* 193 (MH<sup>+</sup>). Anal. (C<sub>8</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>·1.75HCl) C, H, N.

**2,2'-Bi-1*H*-imidazole-4-methanol (28)**. Sodium metal (1.5 g, 6.4 mmol) was added to liquid NH<sub>3</sub> (100 mL). After 15 min, **27** (1.6 g, 6 mmol) was added as a solid in small portions. After 10 min, MeOH was added to dissipate the blue color. NH<sub>4</sub>Cl (4.0 g) was added to the pale yellow solution, and the NH<sub>3</sub> was allowed to evaporate. The reaction was heated with 100 mL of 2-propanol and filtered hot. The filtrate was concentrated to give 0.85 g (86%) of **28** as a waxy brown hygroscopic solid (MeOH/H<sub>2</sub>O): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 4.45 (s, 2), 7.00 (s, 1), 7.11 (s, 2); MS (CI/CH<sub>4</sub>) *m/z* 165 (MH<sup>+</sup>), 147 (MH<sup>+</sup> - H<sub>2</sub>O).

**1-(Phenylmethyl)-4'(5')-methyl-2,2'-bi-1*H*-imidazole (30)**. A mixture of 1-benzyl-2-cyanoimidazole (**29**)<sup>20</sup> (5.49 g, 0.03 mol),

sulfur (100 mg), and methoxyethanol (10 mL) was stirred under nitrogen and heated at 90 °C for 0.5 h. 1,2-Diaminopropane (2.96 g, 0.04 mol) was added and the mixture heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature and then partitioned between H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> phase was washed with H<sub>2</sub>O (2×) and dried (MgSO<sub>4</sub>). The CH<sub>2</sub>Cl<sub>2</sub> solution was treated with 15 g of activated MnO<sub>2</sub> at room temperature. The progress of the reaction was followed by TLC (30% MeOH in CH<sub>2</sub>Cl<sub>2</sub>). After 18 h, an additional 5 g of activated MnO<sub>2</sub> was added and the mixture stirred for 144 h. The reaction was filtered through Celite, and the pad was washed with CHCl<sub>3</sub>. The filtrate was evaporated in vacuo to yield an amber-colored viscous oil. Flash chromatography on silica gel (10% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) gave 3.1 g (43%) of **30** as a straw-colored solid: mp 120–122 °C; MS (EI at 70 eV) *m/z* 238 (M<sup>+</sup>), 161 (M<sup>+</sup> - Ph).

**4(5)-Methyl-2,2'-bi-1*H*-imidazole (31)**. To a 500-mL flask containing a dry ice condenser and submerged in an 2-propanol/dry ice bath was placed **30** (2.8 g, 0.0118 mol) and liquid ammonia (ca. 250 mL). The solution was stirred, and tiny pieces of Na were added every 3 min until the blue color persisted. After 15 min, NH<sub>4</sub>Cl (10 g) was added. The ammonia was allowed to evaporate overnight. The white solid residue was treated with 150 mL of H<sub>2</sub>O, filtered, washed with H<sub>2</sub>O, dried, and washed with Et<sub>2</sub>O. Analytically pure **31** (1.5 g, 86%) was obtained as an off-white solid: mp >260 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>/2 drops of TFA, 300 MHz) δ 2.54 (s, 3), 7.48 (s, 1), 7.75 (s, 2); MS (CI/CH<sub>4</sub>) *m/z* 149 (MH<sup>+</sup>, base peak). Anal. (C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>) C, H, N.

**2-[5-(Dimethylamino)methyl]-2-furanyl]-1*H*-imidazole-4-carbonitrile Bis(4-methylbenzenesulfonate) (35)**. A mixture of **34e** (50 mg, 0.314 mmol), paraformaldehyde (17 mg, 0.547 mmol), dimethylamine hydrochloride (40 mg, 0.493 mmol), and 620 μL of ethanol was heated at reflux for 24 h under a nitrogen atmosphere. An additional 17 mg (0.547 mmol) of paraformaldehyde and 40 mg (0.493 mmol) of dimethylamine hydrochloride were added, and the reaction was continued at reflux. After 24 h, the reaction was concentrated under reduced pressure, diluted with 300 μL of water, treated with K<sub>2</sub>CO<sub>3</sub>, and extracted into EtOAc (3 × 5 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration under reduced pressure gave 20 mg (30%) of **35** (free base) as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.25 (s, 6), 3.48 (s, 2), 6.27 (d, *J* = 3 Hz, 1), 6.80 (d, *J* = 3 Hz, 1), 7.59 (s, 1), 9.60 (br s, 1); IR (neat) 2240 cm<sup>-1</sup>; MS (EI at 70 eV) *m/z* 217 (MH<sup>+</sup>, base peak). A 120-mg (0.555-mmol) sample of the yellow oil was dissolved in ether/methanol and treated with 1 N 4-toluenesulfonic acid (EtOH). The resulting white solid was collected and dried to yield **35** (120 mg, 39%): mp 168–170 °C (EtOAc/EtOH). Anal. (C<sub>25</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>) C, H, N.

**2-(2-Bromo-1,1-dimethoxyethyl)-4-(trifluoromethyl)-1*H*-imidazole (37)**. A mixture of sodium acetate (3.2 g, 0.0388 mol), 1,1-dibromo-3,3,3-trifluoroacetone<sup>15</sup> (5.3 mL, 0.0353 mol), and 25 mL of water was warmed on a steam bath for 30 min. After cooling, the solution was added to a mixture of MeOH (115 mL) and **36**<sup>21</sup> (6.3 g, 0.0320 mol) and concentrated NH<sub>4</sub>OH (30 mL). After stirring overnight, the methanol was removed under reduced pressure to give 6.5 g (67%) of **37** as a white solid: mp 181–182 °C dec; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>/CDCl<sub>3</sub>) δ 3.21 (s, 6), 3.82 (s, 2), 7.29 (br s, 1); MS (CI/CH<sub>4</sub>) *m/z* 305 (MH<sup>+</sup>), 285 (MH<sup>+</sup> - HF), 273 (MH<sup>+</sup> - MeOH). Anal. (C<sub>8</sub>H<sub>10</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

**2-[2-[(Diaminomethylene)amino]-4-thiazolyl]-4-(trifluoromethyl)-1*H*-imidazole (38)**. A solution of **37** (10.0 g, 33.0 mmol) and 180 mL of 98% formic acid was heated at reflux for 1 h. After cooling, the solution was concentrated under reduced pressure, diluted with Et<sub>2</sub>O (300 mL), and filtered. The ethereal solution was concentrated under reduced pressure and the resulting off-white solid dissolved in 300 mL of acetone and treated with amidinothiourea (3.3 g, 27.6 mmol). After heating at reflux for 1 h, the reaction was cooled, filtered, and concentrated under reduced pressure. The resulting orange-brown solid was treated with 50 mL of 5 N NaOH, extracted into EtOAc (3 × 75 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure to give **38** (6.2 g, 98.7%) as a dark orange solid. Flash chromatography (20% EtOAc/hexane) gave 2.7 g (35.4%) of **38** as a light orange solid: mp 217–220 °C dec (insert at 215 °C) (EtOAc/hexane); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 6.84 (br s, 5), 7.20 (s, 1), 7.81 (d, *J* = 1.1 Hz, 1); MS (CI/CH<sub>4</sub>) *m/z* 277 (M<sup>+</sup>, base peak), 257 (MH<sup>+</sup> - HF). Anal. (C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>N<sub>6</sub>S) C, H, N.

**2-[2-[(Diaminomethylene)amino]-4-thiazolyl]-4-cyano-1H-imidazole (39).** A solution of **38** (730 mg, 2.64 mmol) and 5% NH<sub>4</sub>OH (75 mL) was warmed at 60 °C. After 4 days, the solution was cooled to room temperature and the ammonia removed under reduced pressure. The off-white solid that formed was collected and dried to yield 520 mg (84%) of **39**: mp >250 °C (EtOH/hexane). Anal. (C<sub>8</sub>H<sub>7</sub>N<sub>7</sub>S·H<sub>2</sub>O) C, H, N. Hydrochloride salt (MeOH): mp >260 °C; NMR (D<sub>2</sub>O/DSS) δ 7.60 (s, 1), 7.90 (s, 1); MS (EI 70 eV) *m/z* 234 (MH<sup>+</sup>, base peak).

**4,5-Dicyano-1-(phenylmethyl)-1H-imidazole (41).** To a mixture of 99% NaH (2.0 g, 0.085 mmol) and DMF (150 mL) was added **40**<sup>37</sup> (10.0 g, 0.085 mol). After 30 min, 14.5 g (0.085 mol) of benzyl bromide was added, and the reaction was stirred at room temperature for 2 h and then quenched with 1 L water. The white precipitate was collected and recrystallized (toluene) to yield 9.9 g (56%) of **41**: mp 124–127 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.20 (s, 2), 7.10–7.52 (m, 5), 7.62 (s, 1); MS (EI at 70 eV) *m/z* 208 (M<sup>+</sup>). Anal. (C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>) C, H, N.

**5'-Cyano-4,5-dihydro-1'-(phenylmethyl)-2,4'-bi-1H-imidazole (42).** A mixture of **41** (23.5 g, 0.113 mol), sulfur (1.9 g, 0.06 mol), 2-methoxyethanol (100 mL), and ethylenediamine (8.4 g, 0.14 mol) was heated at 130 °C for 5 h. The reaction was diluted with 1 N HCl and the product extracted with EtOAc. The aqueous layer was neutralized (K<sub>2</sub>CO<sub>3</sub>) and the product extracted into EtOAc. After drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration, 28.1 g of oily solid was obtained. Flash chromatography (200:10:1 CHCl<sub>3</sub>/MeOH/concentrated NH<sub>4</sub>OH) gave 8.85 g (31%) of **42**: mp 168–169.5 °C (2-propanol); IR (Nujol) 2220 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.80 (s, 4), 5.25 (s, 2), 7.12–7.45 (m, 5), 7.58 (s, 1). Anal. (C<sub>14</sub>H<sub>13</sub>N<sub>5</sub>) C, H, N.

**5'-Cyano-1'-(phenylmethyl)-2,4'-bi-1H-imidazole (43).** A 75 g (0.85 mol) sample of MnO<sub>2</sub> was refluxed with 500 mL of benzene for 2 h and any water present collected in a Dean-Stark trap. The benzene was decanted after cooling and a CH<sub>2</sub>Cl<sub>2</sub> (800-mL) solution of **42** (18.2 g, 0.072 mol) added. The reaction was mechanically stirred for 6 days and filtered. The MnO<sub>2</sub> was extracted with CH<sub>2</sub>Cl<sub>2</sub> in a Soxhlet apparatus for 24 h. The combined CH<sub>2</sub>Cl<sub>2</sub> solutions gave 14.2 g of material after concentration. Flash chromatography (EtOAc, then 10% MeOH/EtOAc) gave 10.9 g (61%) of **43** as a pale yellow powder: mp 209–210 °C; IR (Nujol) 2220 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 5.45 (s, 2), 7.05–7.47 (m, 7), 8.35 (s, 1).

**5'-Cyano-2,4'-bi-1H-imidazole (44).** A solution of **43** (4.0 g, 0.016 mol) in liquid NH<sub>3</sub> (100 mL) was treated with 2 equiv of sodium metal. The NH<sub>3</sub> was allowed to evaporate after quenching the reaction with solid NH<sub>4</sub>Cl. Water was added, and the slurry was neutralized with HOAc. After collection and drying, 2.1 g (83%) of **44** was obtained as a white solid: mp >285 °C; IR (Nujol) 2220 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.17 (s, 2), 7.98 (s, 1); MS (CI/CH<sub>4</sub>) *m/z* 160 (MH<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>5</sub>N<sub>5</sub>) C, H, N.

**4-(Trifluoromethyl)-1'-(triphenylmethyl)-2,4'-bi-1H-imidazole (46).** A mixture of 6.7 mL (0.045 mol) of 1,1-dibromo-3,3,3-trifluoroacetone, 5 g (0.061 mol) of NaOAc, and 50 mL of water was warmed on a steam bath for 0.5 h. After cooling, this solution was mixed with 13.5 g (0.04 mol) of **45**,<sup>24</sup> MeOH (200 mL), and 28% NH<sub>4</sub>OH (400 mL). The reaction was stirred for 3 days at room temperature, and the yellow solid was collected and dried to yield 9.1 g (51%) of **46**: mp 261–263 °C (2-propanol); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 6.97–7.65 (m, 18); MS (EI at 70 eV) *m/z* 444 (M<sup>+</sup>). Anal. (C<sub>26</sub>H<sub>19</sub>F<sub>3</sub>N<sub>4</sub>) C, H, N.

**4-(Trifluoromethyl)-2,4'-bi-1H-imidazole (47).** A mixture of **46** (8.8 g, 0.02 mol) and 100 mL of 2 N HCl was warmed on a steam bath for 1 h. The white solid (triphenylcarbinol) was collected by filtration and washed with hot water (2 × 50 mL). The filtrate was neutralized (K<sub>2</sub>CO<sub>3</sub>) and extracted with EtOAc (3 × 200 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration, 2.95 g (74%) of **47** was obtained as a white solid: mp 207–209 °C (EtOAc); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.57 (br s, 2), 7.71 (s, 1); MS (EI at 70 eV) *m/z* 202 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>5</sub>F<sub>3</sub>N<sub>4</sub>) C, H, N.

**4-Cyano-2,4'-bi-1H-imidazole (48) (Method B).** A mixture of **47** (2.2 g, 0.011 mol) and 150 mL of 5% NH<sub>4</sub>OH was warmed at 60 °C for 17 h. The reaction was placed on a rotary evaporator to remove the NH<sub>3</sub>. The tan solid **48** (1.1 g, 63%) was collected

and recrystallized (2-methoxyethanol/water): mp >260 °C; IR (Nujol) 2240 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.57 (s, 1), 7.75 (s, 1), 8.00 (s, 1); MS (EI at 70 eV) *m/z* 159 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>5</sub>N<sub>5</sub>) C, H, N.

**Experiments in Anesthetized Rats.** Most rats were prepared according to the method of Hayes.<sup>25</sup> They were anesthetized with sodium pentobarbital, 65 mg/kg ip, and atropine sulfate, 1 mg/kg, was also administered ip. The trachea was cannulated, and the rat was allowed to respire voluntarily. A carotid or femoral artery was cannulated for measurement of arterial blood pressure, and a branch of the jugular or a femoral vein was cannulated for administration of test compounds and additional sodium pentobarbital. A saline-filled 22-gauge hypodermic needle connected to a pressure transducer was inserted through the chest wall and into the left ventricle to measure ventricular pressure while *dP/dt*<sub>max</sub> was derived electronically. In some cases, left ventricular pressure was measured by passing a saline-filled catheter (PE 50) down the right carotid artery and into the left ventricle. The catheter was then connected to a pressure transducer. All doses of test drug(s) were administered in 0.2-mL volumes.

**Experiments in Anesthetized Dogs.** Mongrel dogs of either sex (19–22 kg) were anesthetized with sodium pentobarbital, 32.5 mg/kg iv, and were maintained under anesthesia with a continuous pentobarbital infusion of 5 mg/kg per hour. Following tracheal intubation, the dogs were ventilated with a Harvard respirator. The rate of ventilation was set at 16 cycles/min, and tidal volume was adjusted to 10–15 mL/kg of body weight. A heat pad was used to maintain body temperature. A polyethylene catheter filled with heparinized saline was advanced into the abdominal aorta via a femoral artery and was connected to a Statham pressure transducer for measurement of arterial blood pressure. Both femoral veins were cannulated: one for administration of test drug, and the other for continuous infusion of pentobarbital. Heart rate was recorded by means of a Gould biotachometer triggered by the arterial pressure pulse. Cardiac output was estimated by measuring ascending aortic flow with a Carolina Medical Electronics electromagnetic flow probe. The left chest was opened through the fifth intercostal space, and a precalibrated Walton-Brodie strain gauge arch was sutured to the surface of the left ventricle to measure cardiac contractile force. The strain gauge was adjusted so predrug peak contractile force produced a pen deflection of approximately 1 cm. All parameters were continuously recorded as 1-min averages with a microprocessor-based data logger. When stable base-line values were obtained, test compound was administered as a slow (1–2-min) iv injection in doses of 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg. Doses were administered in this order every 20 min following a 20-min vehicle control period. Fresh solutions of test compound were prepared immediately prior to an experiment.

The ED<sub>25%</sub> values listed in the tables represent the dose of drug required to increase left ventricular *dP/dt*<sub>max</sub> by 25% in rats or to increase contractile force by 25% in dogs. Values were the average of two to six dose-response curves. Each curve was constructed by using 0.3, 1.0, and 3.0 mg/kg iv doses. The peak percent change values of dogs represent the average change in contractile force produced by 1 mg/kg drug.

**Experiments in Conscious Instrumented Dogs.** Four mongrel dogs of either sex weighing 15–25 kg were used in this study. They were conditioned to wear a mesh jacket (Alice King Chatham) for 1 week prior to and during recovery from surgery and throughout the study. Surgical preparation occurred in two steps. First, a previously calibrated Konigsberg pressure transducer was advanced into the left ventricle through a surgical opening near the apex and was anchored in the myocardium to measure left ventricular pressure. The transducer was held in place with opposing purse string sutures. Ten to fourteen days later, a Silastic cannula (0.045 × 0.080 in.) was inserted into the dorsal aorta via a femoral artery to measure arterial blood pressure. Both procedures incorporated aseptic techniques. The cannula was exteriorized near the exit site of the Konigsberg cable, and both were stored in a pocket of the jacket. The animals were allowed to recover from surgery for at least 2 weeks prior to undergoing testing. On the day of the study, the Konigsberg cable and the cable from a pressure transducer (which had been connected to the arterial cannula) were connected to a Buxco signal conditioner and interfaced with a digitizer/recorder. Heart rate,

(37) U.S. Patent 2,534,331; *Chem. Abstr.* 1951, 45, 5191d.

aortic blood pressure, and left ventricular blood pressure were measured directly; left ventricular contractility was assessed by deriving  $dP/dt_{max}$  from left ventricular pulse pressure. The study consisted of fifteen 30-min periods. The first two periods were control periods prior to dosing, while the remaining thirteen periods were postdose experimental periods. Compound 15a, 10 mg/kg, was administered as a dry powder in a gelatin capsule.

**PDE Assays.** Three isoenzymes of PDE were isolated from dog heart and dog kidney by chromatography on DEAE-cellulose.<sup>30</sup> These were labeled type I (calmodulin sensitive), type II (cGMP sensitive), and type IV (high-affinity PDE, PDE III) phosphodiesterase as recommended by the Committee on Nomenclature.<sup>31</sup> Assays for PDE activity were done by the two-step method of Thompson et al.,<sup>30</sup> using [<sup>3</sup>H]cAMP as the substrate. Enzyme activity was initiated by addition of substrate to tubes containing buffer (pH 7.4) and sufficient enzyme to hydrolyze less than 20% of the substrate in 10 min at 30 °C. Dimethyl sulfoxide was used to dissolve compounds, and control assays containing identical concentrations of the solvent (1%) were run.

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101226-47-5; 9, 101226-50-0; 10, 101226-51-1; 11, 101226-52-2; 12, 123124-76-5; 13a, 10111-08-7; 13b, 13750-81-7; 13c, 113825-16-4; 13d, 37050-18-3; 13e, 111851-98-0; 13f, 69767-96-0; 13g, 6002-15-9; 13h, 10045-65-5; 13i, 56248-10-3; 13j, 123125-08-6; 13k, 123125-09-7; 13l, 102808-02-6; 14a, 102807-85-2; 14b, 102807-87-4; 14c, 123125-01-9; 14d, 111851-99-1; 14e, 123125-02-0; 14f, 123125-03-1; 14g, 123125-04-2; 14h, 102807-88-5; 14i, 123125-05-3; 14j, 123125-06-4; 14k, 123125-07-5; 14l, 102807-86-3; 15a, 102807-93-2; 15b, 102807-95-4; 15c, 111851-87-7; 15d, 111851-93-5; 15e, 111851-88-8; 15f, 111851-91-3; 15g, 111851-90-2; 15h, 102807-96-5; 15i, 111851-92-4; 15j, 111851-79-7; 15k, 111851-80-0; 15l, 111851-78-6; 15m, 102807-94-3; 15n, 111851-86-6; 15o, 111852-14-3; 15p, 111851-81-1; 16, 111852-11-0; 16 (4'-Br), 111851-12-1; 17, 123124-77-6; 18, 111852-13-2; 19, 123124-78-7; 20, 123124-79-8; 21, 123124-80-1; 22, 111851-82-2; 23, 111851-83-3; 24, 123124-81-2; 25, 123124-82-3; 26, 111928-57-5; 27, 123125-12-2; 27·2HCl, 123124-83-4; 28, 123124-84-5; 29, 46323-27-7; 30, 111851-95-7; 31, 111851-97-9; 32a, 500-22-1; 32b, 98-03-3; 32c, 498-62-4; 32d, 4701-17-1; 32e, 98-01-1; 32f, 3920-50-1; 32g, 35344-95-7; 33a, 33468-84-7; 33b, 33468-72-3; 33c, 123125-10-0; 33d, 81654-10-6; 33e, 33468-88-1; 33f, 102807-89-6; 33g, 102807-90-9; 34a, 123124-97-0; 34b, 123124-98-1; 34c, 123124-99-2; 34d, 123124-00-8; 34e, 102807-99-8; 34f, 102807-97-6; 34g, 102807-98-7; 35, 123124-85-6; 35·2Ts-OH, 123124-86-7; 36, 81371-82-6; 37, 123124-87-8; 38, 123124-88-9; 39, 123124-89-0; 39·HCl, 123125-11-1; 40, 1122-28-7; 41, 123124-90-3; 42, 123124-91-4; 43, 123124-92-5; 44, 123124-93-6; 45, 33016-47-6; 46, 123124-94-7; 47, 123124-95-8; 48, 123124-96-9; 49, 102807-91-0; 50, 102807-92-1; 1,1-dibromo-3,3,3-trifluoroacetone, 431-67-4.

## N-Phenyl-2-pyridinecarbothioamides as Gastric Mucosal Protectants

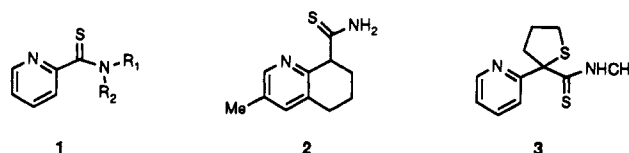
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A series of substituted 2-pyridinecarbothioamides was synthesized and evaluated for gastric mucosal protectant activity in the rat. Out of this investigation *N*-(3,5-difluorophenyl)-2-pyridinecarbothioamide (**23**, AY-31,574) was identified. This compound was much more potent than sucralfate and ranitidine against ethanol-induced lesions. Compound **23** was equipotent with ranitidine against gastric injury caused by stress. Unlike ranitidine, **23** was found to be devoid of antisecretory activity in the pylorus-ligated rat model, making it a selective mucosal protectant. Such a potent selective mucosal protectant may provide a novel clinical approach in treating ulcers.

In recent years interest has grown in discovering therapeutic agents which prevent ulcers by increasing defensive forces present in the gut. The property of a drug protecting the integrity of the mucosa against aggressors such as acid, ethanol, and NSAID's without affecting the aggressor has been coined cytoprotection.<sup>1</sup> The primary approach toward curing ulcers clinically has been to decrease the aggressive forces injuring the ulcer. For instance, the H<sub>2</sub>-antagonists cimetidine<sup>2</sup> and ranitidine<sup>3</sup> and the proton pump inhibitor omeprazole<sup>4</sup> have been used to reduce acid secretion, which successfully accelerates healing. However, omeprazole has an excessive duration of antisecretory action (>24 h) and like long-acting H<sub>2</sub> antagonists, it causes dysplasia when administered long-term in rats.<sup>5</sup> Therefore, the total elimination of gastric acid secretion (aggressive factors) appears to cause de-

Scheme I



leterious side effects. The potential advantage of purely cytoprotective agents such as sucralfate, which is an aluminum complex, has been demonstrated in the clinic by lower ulcer recurrence rates.<sup>6</sup> In the course of efforts to discover a novel type of antiulcer agent, thioamides of general structure 1 (Scheme I) were identified, which were potent cytoprotective agents with no antisecretory activity. In contrast, thioamides such as tiquinamide (**2**)<sup>7</sup> and picartamide (**3**),<sup>8</sup> on which 1 was based, are potent antisecretory agents. Because it was expected that a selective

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