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The synthesis of fourteen mono-cationic and six dicationic analogs of Hoechst 33258 is described. The monocationic benzimiazoles **7a-7g** and the dicationic benzimidazoles **9a-9c** are obtained in five steps starting from 4-acetamidobenzonitrile. The monocationic bis-benzimiazoles **12a-12g** are synthesized in four steps starting from 4-amino-3-nitrobenzonitrile. The dicationic bis-benzimiazoles **17a-17c** are obtained in six steps starting from 4-amino-3-nitrobenzonitrile.

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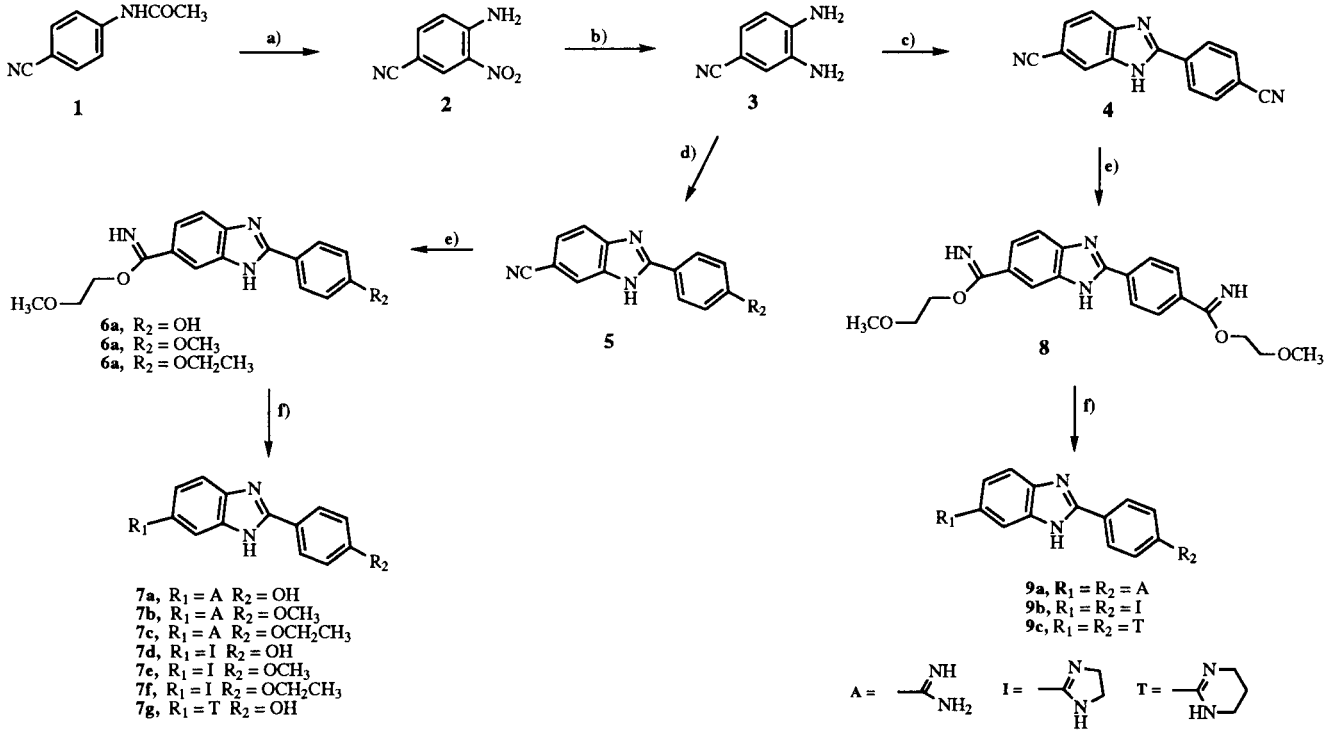
Study of the chemistry of benzimidazoles remains of considerable current interest as a result of the important biological and biophysical properties of molecules such as the bis-benzimidazoles Hoechst 33258, 33342 and related compounds [2-5]. Hoechst 33258 has been shown to bind to the minor-groove of DNA with selectively at AATT sites [6,7]. Although a considerable amount of detail is known at the molecular level about the binding interactions of these bis-benzimidazoles as a result of theoretical studies and both nmr and X-ray investigations [8-10] the AT specificity in binding of these type compounds has led to some debate over the relative importance of factors such as hydrogen bonding, electrostatic and van der Waals interactions to the binding affinity and specificity. With the compounds available it was not possible to provide an experimental determination of the relative importance of these factors. We recently reported the nucleic acid binding properties of a number of mono- and bis-benzimidazoles and the crystal structure of the complex between 5-(2-imidazolinyl)-2[2-(4-hydroxyphenyl)-5-benzimidazoyl]benzimidazole and the duplex dodecamer $d(CGCGAATTCGCG)_2$ [11,12]. For the mono-cationic benzimidazoles it was found that DNA binding affinity was increased more by the addition of a second benzimidazole unit than by a second cationic group. The studies concluded that van der Waals interactions were more important for minor-groove binding than electrostatic interactions in the benzimidazole systems investigated. The present report describes the synthesis of

Scheme I

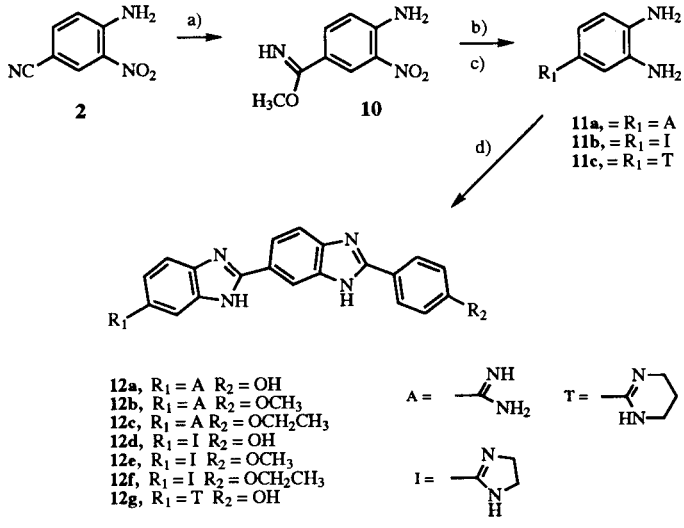


the mono- and bis-benzimidazoles employed in the analysis of benzimidazole-DNA minor-groove interactions [11].

The synthetic approach used to prepare mono- and dicationic benzimidazoles **7a-7g, 9a-9c** is outlined in Scheme I. The reactions in the sequence for conversion of **1** into **3** have been previously described by Tidwell and coworkers and were performed essentially as reported [13]. In Scheme I the key step of benzimidazole formation involves reaction of 3,4-diaminobenzonitrile **3** with a substituted benzaldehyde in the presence of a mild oxidizing agent; apparently to aromatize the dihydrobenzimidazole, or the equivalent, presumed to be initially formed. Nitrobenzene [14] was employed as the oxidant for the synthesis of 2-[4-cyanophenyl]-5-cyanobenzimidazole **4.** 1,4-Benzoquinone [15] was used in the preparation of the series of compounds **5** which have electron donors on the 2-phenyl group. Both methods of oxidation gave good yields of the desired benzimidazoles; generally, we prefer the 1,4-benzoquinone method because of the milder reaction conditions and the relative ease of solvent removal. Using classical Pinner methodology both nitriles **4** and **5** were converted into imidate esters **6** and **8** using 2-methoxyethanol saturated with hydrogen chloride. The imidate esters were converted into the corresponding amidines, imidazolines, and tetrahydropyrimidine derivatives **7** and **9** by reaction with ammonia, 1,2-ethanediamine, and 1,3-propanediamine, respectively using a well established approach [16,17].

Scheme II contains the synthetic sequence used for preparation of the monocationic bis-benzimidazoles **12a-12g**. The key intermediates, 4-subsutituted-1,2-phenylenediamines **11,** were prepared in three steps from 3-amino-4-nitrobenzonitrile **2** [13]; preparation of the latter were described in Scheme I. Condensation of the various 4-subsutituted-1,2-phenylenediamines **11** with the imidate esters derived from the 5-cyano-2-[4-substituted-phenyl]benzimidazoles **6,** the latter were also described in Scheme I, by heating in methanol yields the monocationic bis- benzimidazoles **12a-12g**.

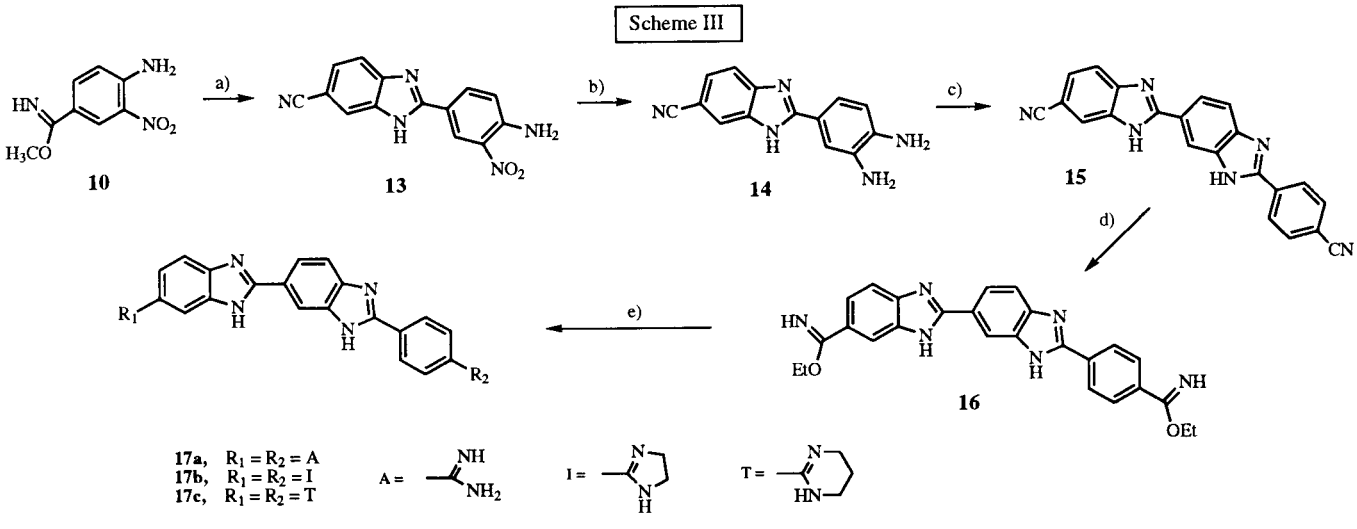
Scheme II



a) CH_3OH, HCl b) NH_3, $NH_2CH_2CH_2NH_2$, or $NH_2CH_2CH_2CH_2NH_2$ c)H_2, Pd/C d) **6a**, **6b**, or **6c** and CH_3OH, reflux

The synthetic sequence employed for preparation of the dicationic bis-benzimidazoles **17a-17c** is outlined in Scheme III. The synthetic approach begins with the condensation of 4-amino-3-nitrobenzimidate ester **10**, described in Scheme II, and 3,4-diaminobenzonitrile **3**, described in Scheme I, to yield the benzimidazole **13**. Reduction of the nitro group of **13** and condensation of the resultant diamine **14** with 4-cyanobenzaldehyde using nitrobenzene as both the solvent and oxidant yields

Scheme III



a) 3,4-diaminobenzonitrile, MeOH b) $SnCl_2$/HCl/EtOH c) 4-cyanobenzaldehyde, nitrobenzene, 125°C d) HCl, EtOH e) NH_3, $NH_2CH_2CH_2NH_2$, or $NH_2CH_2CH_2CH_2NH_2$

Table 1
Physical and Spectral Data for Compounds **7a-7g.**

Compound No.	Molecular Formula	Mp °C	Analysis Calcd./Found C	H	N	^{1}H NMR Data [a]
7a	$C_{14}H_{12}N_4O$•2HCl•0.5H_2O	345-350	50.32 50.55	4.52 4.49	16.76 16.60	7.67 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 9.18, 9.53 (s, s, NH, 2H, 2H), 10.75 (s, OH, 1H)
7b	$C_{15}H_{14}N_4O$•2HCl•0.25H_2O	305-310	52.41 52.86	4.84 4.81	16.30 16.32	3.89 (s, 3H, OCH_3), 7.22 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 8.32 (d, J = 8.8 Hz, 2H) 9.08, 9.44 (s, s, NH, 2H, 2H)
7c	$C_{16}H_{16}N_4O$•2HCl•0.66H_2O	275-280	52.61 52.41	5.34 5.37	15.34 15.20	1.38 (t, 3H, CH_3), 4.18 (q, 2H, CH_2O-), 7.21 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H) 8.18 (s, 1H), 8.32 (d, J = 8.4 Hz, 2H), 9.09, 9.45 (s, s, NH, 2H, 2H)
7d	$C_{16}H_{14}N_4O$•2HCl•H_2O	375-380	52.05 52.05	4.91 4.92	15.17 15.07	4.03 (s, 4H, NCH_2CH_2N), 7.01 (d, J = 8.8, 2H), 7.87 (m, 2H), 8.17 (d, J = 8.8 Hz, 2H), 8.33 (s, 1H), 10.50 (s, OH, 1H), 10.64 (s, NH, 2H)
7e	$C_{17}H_{16}N_4O$•2HCl•0.5H_2O	310-320	54.56 54.90	5.12 5.09	14.97 14.89	3.88 (s, 3H, OCH_3), 4.03 (s, 4H, NCH_2CH_2N), 7.20 (d, J = 8.8 Hz, 2H), 7.86-7.90 (m, 2H), 8.29 (d, J = 8.8 Hz, 2H) 8.37 (s, 1H), 10.68 (s, NH, 2H)
7f	$C_{18}H_{18}N_4O$•2HCl•0.5H_2O	280-285	55.67 56.14	5.45 5.46	14.43 14.53	1.38 (t, 3H, CH_3), 4.04 (s, 4H, NCH_2CH_2N), 4.17 (q, 2H, CH_2O), 7.21 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 8.8 Hz, 2H), 8.44 (s, 1H), 10.84 (s, NH, 2H)
7g	$C_{17}H_{16}N_4O$•2HCl•0.5H_2O	350-355	54.56 54.85	5.12 5.19	14.87 14.99	2.02 (m, 2H, CH_2), 3.53 (m, 4H, NCH_2), 7.05 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 8.09 (s, 1H), 8.26 (d, J = 8.8 Hz, 2H), 10.11 (s, NH, 2H), 10.65 (s, OH, 1H)

[a] Chemical shifts are in ppm relative to TMS; recorded in DMSO-d_6 and then deuterium oxide was added to identify the exchangeable protons.

Table 2
Physical and Spectral Data for Compounds **9a-9c** and **17a-17c.**

Compound No.	Molecular Formula	Mp °C	Analysis Calcd./Found C	H	N	^{1}H NMR Data [a]
9a	$C_{15}H_{14}N_6$•2HCl•3H_2O	351-355	44.45 44.20	5.47 5.08	20.74 20.74	7.74 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.05 (d, J =8.8 Hz, 2H), 8.24 (s, 1H), 8.52 (d, J = 8.4 Hz, 2H), 9.09, 9.28, 9.40, 9.53 (s, s, s, s, NH, 3H, 2H, 1H, 1H)
9b	$C_{19}H_{18}N_6$•3HCl•2H_2O	>400	47.96 48.17	5.29 5.37	17.66 17.61	4.03, 4.05 (s, s, 8H, NCH_2CH_2N), 4.25 (br s, 1H, 7.90 - 7.94 (m, 2H), 8.27 (d, J = 8.8 Hz, 2H), 8.50 (s, 1H), 8.58 (d, J = 8.8 Hz, 2H), 10.78, 10.98 (s, s, NH, 1H, 1H)
9c	$C_{21}H_{22}N_6$•3HCl•H_2O	280-285	51.91 52.00	5.60 5.74	17.29 17.18	2.01 (m, 4H, CH_2), 3.52 (m, 8H, NCH_2), 4.3 (br s, 1H), 7.64 (d, d, J = 8.4 and 1.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 1.2 Hz, 1H), 8.55 (d, J = 8.4 Hz, 2H), 10.09, 10.28 (s, s NH, 1H, 1H)
17a	$C_{22}H_{18}N_8$•4HCl•1.5H_2O	344-349	46.54 46.69	4.42 4.27	19.75 19.56	7.86 (d, d, J = 8.4 and 1.2 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.00 (d, J= 8.4 Hz, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.28 (s, 1H), 8.44 (dd, J = 8.8 and 1.6 Hz, 1H), 8.61 (d, J = 8.4 Hz, 2H), 8.85 (s, 1H), 9.25, 9.35, 9.51, 9.60 (s, s, s, s, NH, 2H, 2H, 2H, 2H)
17b	$C_{26}H_{22}N_8$•4HCl•2.5H_2O	>400	48.99 48.95	4.90 4.90	17.58 17.51	4.05 (s, 8H, N-CH_2CH_2N), 7.83 - 7.87 (m, 3H), 8.23 (d, J =8.8 Hz, 2H) 8.32 (dd, J = 8.8 and 1.6 Hz, 1H), 8.41 (s, 1H), 8.58 (d, J = 8.4 Hz, 2H), 8.71 (s, 1H), 10.64, 10.81 (s, s, NH, 2H, 2H)
17c	$C_{28}H_{28}N_8$•4HCl•2H_2O	315-320	51.23 51.45	5.22 5.16	17.07 17.01	2.02 (m, 4H, CH_2), 3.54 (m, 8H, N-CH_2), 7.66 (d, J = 8.4 Hz,1H), 7.87 - 7.91 (m, 2H) 7.98 (d, J = 8.8 Hz, 2H), 8.11 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 8.8 Hz, 2H), 8.72 (s, 1H), 10.05, 10.19 (s, s, NH, 2H, 2H)

[a] Chemical shifts are in ppm relative to TMS; recorded in DMSO-d_6 and then deuterium oxide was added to identify the exchangeable protons.

Table 3

Physical and Spectral Data for Compounds **12a-12g**.

Compound No.	Molecular Formula	Mp °C	Analysis Calcd./Found C	H	N	^{1}H NMR Data [a]
12a	$C_{21}H_{16}N_6O\cdot 2HCl\cdot 2H_2O$	381-385	52.83 52.62	4.65 4.55	17.61 17.43	7.10 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 8.4 and 2.0 Hz, 1H) 7.86 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.21 (s, 1H), 8.25 (br s, NH, 1H), 8.29 (d, J = 8 Hz, 2H), 8.42 (d, J = 8.0 Hz, 1H), 8.68 (s, 1H), 9.02, 9.39 (s, s, NH, 2H, 2H) 10.90 (s,OH, 1H)
12b	$C_{22}H_{18}N_6O\cdot 3HCl\cdot 2H_2O$	295-300	50.06 50.12	4.77 4.75	15.92 15.99	3.5 (br s, NH, 1H), 3.91 (s, 3H, OCH_3), 7.28 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.21 (s, 1H), 8.39-8.43 (m, 3H), 8.69 (s, 1H), 9.07, 9.42 (s, s, NH, 2H, 2H)
12c	$C_{23}H_{20}N_6O\cdot 2HCl\cdot 2.5H_2O$	301-305	53.90 53.78	5.29 5.18	16.34 16.27	1.39 (t, 3H, CH_3), 3.5 (br s, NH, 1H), 4.19 (q, 2H, CH_2-O), 7.24 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.30 - 8.40 (m, 3H), 8.62 (s, 1H), 8.97, 9.36 (s, s, NH, 2H, 2H)
12d	$C_{23}H_{18}N_6O\cdot 2HCl\cdot 2H_2O$	>400	54.87 54.68	4.80 4.92	16.69 16.50	3.4 (br s, NH, 2H), 4.04 (s, 4H, NCH_2CH_2N), 7.08 (d, J = 8.8 Hz, 2H), 7.87 (s, 2H), 7.94 (d, J = 8.8 Hz, 1H), 8.38 - 8.42 (m, 2H), 8.26 (d, J = 8.4 Hz, 2H), 8.64 (s, 1H), 10.61 (s, OH, 1H), 10.7 (brs, NH, 1H)
12e	$C_{24}H_{20}N_6O\cdot 2HCl\cdot 2H_2O$	296-300	55.71 56.02	5.06 4.76	16.26 16.10	3.6 (vbr s, NH, 2H), 3.91 (s, 3H, OCH_3), 4.05 (s, 4H, N-CH_2CH_2-N), 7.28 (d, J = 8.8 Hz, 2H), 7.88 (s, 2H), 7.94 (d, J = 8.4 Hz, 1H), 8.36-8.38 (m, 4H), 8.66 (s, 1H), 10.62 (s, NH, 1H)
12f	$C_{25}H_{22}N_6O\cdot 2HCl\cdot 2H_2O$	290-295	56.50 56.19	5.31 5.21	15.81 15.66	1.39 (t, 3H, CH_3), 3.4 (br s, NH, 2H), 4.05 (s, 4H, NCH_2CH_2N), 4.18 (q, 2H, CH_2-O, 7.22 (d, J = 9.2 Hz, 2H), 7.80 - 7.90 (m, 3H), 8.20-8.30 (m, 3H), 8.36 (s, 1H), 8.59 (s, 1H), 10.55 (s, NH, 1H)
12g	$C_{24}H_{20}N_6O\cdot 2HCl\cdot 0.33H_2O$	>400	59.14 59.29	4.69 4.67	17.24 17.24	2.02 (m, 2H, CH_2), 3.4 (br s, NH, 1H), 3.54 (bs, 4H, CH_2-N), 7.07 (d, J = 8.8 Hz, 2H), 7.61 (dd, J = 8.4 and 1.2 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.08 (s, 1H), 8.25 (d, J = 8.8 Hz, 2H), 8.37 (d, J = 8 Hz, 1H), 8.63 (s, 1H), 9.98 (brs, NH, 2H), 10.70 (brs, OH, 1H)

[a] Chemical shifts are in ppm relative to TMS; recorded in DMSO-d_6 and then deuterium oxide was added to identify the exchangeable protons.

5-cyano-2-[2-(4-cyanophenyl)-5-benzimidazoyl]benzimidazole **15**. The bis-cyano-bis-benzimidazole **15** was converted into the corresponding bis-imidate ester **16** by standard Pinner methodology. The reaction of **16** with ammonia or the appropriate diamine provides the dicationic bis-benzimidazoles **17a-17c**.

EXPERIMENTAL

Melting points were recorded using a Thomas Hoover(Uni-Melt) capillary melting point apparatus and are uncorrected. The ^{1}H nmr and ^{13}C nmr spectra were recorded employing a Varian GX400 spectrometer and chemical shifts (δ) are in ppm relative to TMS unless otherwise noted. Mass spectra were recorded on a VG Instruments 70-SE spectrometer (Georgia Institute of Technology, Atlanta, GA). The ir spectra were recorded using a Michelson 100 (Bomem, Inc.) instrument. Elemental analysis were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4 of the theoretical values. All chemicals and solvents were purchased from Aldrich Chemical Co. or Fisher Scientific.

Compounds **3** [13], **4** [18], **9a** [18], and **11a-c** [13,19] and **12a** [13] were synthesized as previously reported and each compound gave data (mp, ^{1}H and ^{13}C nmr and ir spectroscopic results) in accord with literature values and their structure.

General Procedure for Monocationic Benzimidazoles **7a-7g**.

The imidate hydrochlorides **6a-6c**, obtained from the appropriate cyano compounds using standard Pinner conditions used extensively in this laboratory [16,17], were heated at reflux for 5 hours with excess of ammonia, 1,2-ethanediamine or 1,3-propanediamine, respectively, in anhydrous ethanol. The ethanol was distilled and water was added. The resultant solid was filtered and washed with water, ether and dried. The free base was dissolved in anhydrous ethanol and treated with hydrogen chloride-saturated ethanol. After standing overnight in a refrigerator, solids were collected by filtration, washed with anhydrous ether and dried under vacuum. Data for the compounds **7a-7g** may be found in Table 1.

General Procedure for Dicationic Benzimidazoles **9a-c** and **17a-c**.

The diimidate hydrochlorides **8** and **16**, obtained from the corresponding dicyanocompounds by the standard Pinner method used extensively in this laboratory [16,17], were used for the next reaction without further purification. The imidates were heated at reflux for 5hr in the presence of excess ammonia, 1,2-ethanediamine or 1,3-propanediamine, respectively, in anhydrous ethanol. After cooling, pale yellow free bases were filtered, washed with anhydrous ether and dried. The free bases were converted into salts by conventional methods. The free bases for compounds **9b, 9c, 17a, 17c**, were dissolved in anhydrous ethanol and treated with hydrogen chloride-saturated ethanol. The free base for compound **17b** were dissolved in

warm 2*M* acetic acid and concentrated hydrochloric acid was added. After cooling, the precipitated hydrochlorides were collected by filtration, washed with anhydrous ether and dried under vacuum. Data for the compounds **7a-c** and **17a-17c** may be found in Table 1.

General Procedure for Monocationic Bisbenzimidazoles **12a-12g**.

A solution of 1mmole of the imidates **6a-6c** and 1.1 mmoles of **11a-11c** in 10 ml anhydrous methanol were heated at reflux for 5 hours. After cooling the the hydrochlorides of **12a-12g** were collected by filtration, washed with anhydrous ethanol, ether and dried. The purity of the compounds was monitored by tlc (chloroform/methanol/aqueous ammonia, 11:4:1). In two cases, **12b**, **12f**, it was necessary to purify them additionally by converting the salts into free bases with sodium carbonate solution. The free bases were filtered, washed with water and dissolved in warm 2*M* acetic acid. Concentrated hydrochloric acid was added to the acetic acid solution and after cooling the resultant solids were filtered, washed with ether and dried. Data for the compounds **12a-12g** may be found in Table 1.

5-Cyano-2-(3,4-diaminophenyl)benzimidazole **14**.

A solution of 4.6 g (20 mmoles) imidate hydrochloride **10** and 2.9 g (22 mmoles) of 3,4-diaminobenzonitrile in 100 ml of anhydrous methanol was heated under reflux for 8 hours. After cooling, an orange solid was filtered and washed with ether. Additional product was obtained by reducing the volume of solvent and a total of 4.2 g (77%) of 5-cyano-2-(4-amino-3-nitrophenyl)benzimidazole (**13**) was obtained; mp 345-350° dec; ^{1}Hnmr (400 MHz, DMSO-d_6): 7.20 (d, 1H, Ar-H), 7.59 (dd, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.90 (s, 2H, NH_2), 8.08 (s, 1H, Ar-H), 8.21 (d, 1H, Ar-H), 8.87 (d, 1H, Ar-H), 13.40 (brs, 1H, NH). Compound **13** was used directly without further characterization.

A solution of 2.78 g (10 mmoles) of **13** and 10 g of $SnCl_2$ in 15 ml of ethanol and 15 ml of concentrated hydrochloric acid was heated under reflux for 3 hours. The resultant crystalline, yellow complex was filtered and 50 ml of water was added and the mixture was made basic with ammonium hydroxide. The basic suspension was extracted with butanol and the extract was evaporated to dryness. Recrystallization from ethanol gave a pale yellow product 1.62 g (66% yield); mp 278-280° dec; ^{1}H nmr (400 MHz, DMSO-d_6): 4.72 (s, 2H, NH_2), 5.11 (s, 2H, NH_2), 6.62 (d, 1H, Ar-H), 7.27 (dd, 1H, Ar-H), 7.42 (d, 1H, Ar-H), 7.49 (dd, 1H, Ar-H), 7.60 (d, 1H, Ar-H), 7.93 (s, 1H, Ar-H); ms: m/z 249 (100%).

Anal. Calcd. for $C_{14}H_{11}N_5 \cdot 0.5H_2O$: C, 65.10; H,4.68; N, 27.12. Found: C, 65.24; H, 4.63; N, 26.91.

5-Cyano-2-[2-(4-cyanophenyl)-5-benzimidazolyl]benzimidazole **15**.

A solution of 0.3g (2.3mmole) of 4-cyanobenzaldehyde and in 20ml of nitrobenzene was heated to 120° , then 0.39 g (1.6 mmoles) of the diamine **14** was added gradually. The mixture was heated at 120°-130° for 3 hours. After cooling, the solid was filtered and washed with hexane. Recrystallization from methanol gave 0.51g (91%) of **15** compound; mp 380-390° dec; ^{1}H nmr: (400 MHz, DMSO-d_6 and DMSO-d_6/D_2O): 7.61 (dd, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 7.83 (d, 1H, Ar-H), 8.07 (d, 2H, Ar-H), 8.13-8.18 (m, 2H, Ar-H), 8.39 (d, 2H, Ar-H), 8.49 (s, 1H, Ar-H), 13.5 (brs, 2H, NH); ms: m/z 360 (100%).

Anal. Calcd. for $C_{22}H_{12}N_6 \cdot H_2O$: C, 69.83; H, 3.73; N, 22.21. Found: C, 69.88; H, 3,75; N, 22.16.

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