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Anti-*Pneumocystis carinii* pneumonia activity of dicationic carbazoles

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Summary — A series of 2,7- and 3,6-bis cationic carbazoles was synthesized and evaluated for activity against a rat model of *Pneumocystis carinii* pneumonia (PCP). The compounds were also tested for inhibition of topoisomerase II and binding to DNA. Several of the compounds proved to be more potent and less toxic than a standard anti-PCP drug (pentamidine). While no quantitative correlation was seen between anti-PCP activity, topoisomerase inhibition and DNA binding, a minimal level of DNA binding was found to be necessary for antimicrobial activity.

***Pneumocystis carinii* pneumonia / carbazoles / dications / DNA / amidines**

Introduction

This work is a continuation of studies designed to develop novel dicationic molecules (pentamidine related) as therapeutic agents for the treatment of opportunistic infections (OIs) associated with the Acquired Immune Deficiency Syndrome (AIDS). Previous work in our laboratory related to the antimicrobial activity of dicationic molecules has: (1) led to an understanding of the effect of metabolism on the biological activity of pentamidine and related compounds [1–5]; (2) provided evidence for potential mechanisms of antimicrobial activity of this class of compounds [6–11]; (3) shown the compounds to be active against a number of pathogenic organisms [6, 9, 10, 12–22]; (4) led to the preclinical and clinical development of new agents for the treatment of the important AIDS related OI, *Pneumocystis carinii* pneumonia (PCP) [20].

Previous studies suggested an important link between the ability of dicationic molecules to bind in the minor groove on DNA, inhibit topoisomerases and exert antimicrobial activity [6–10]. The past work clearly indicated that the DNA binding and antimicrobial potency and specificity were dependent on the nature and size of the spacer between the cationic moieties. While the current study, using the carbazole ring as the spacer unit, failed to show a quantitative relationship between anti-PCP activity, DNA binding, and topoisomerase inhibition, several compounds were identified with potent anti-PCP activity. In addition, the importance of DNA binding to antimicrobial activity was confirmed.

Chemistry

The 3,6-disubstituted carbazoles **1–9** (scheme 1) were all synthesized from carbazole. The major dibromination product of carbazole, intermediate **16** [23, 24], underwent *N*-methylation to **17** with iodomethane using phase-transfer catalysis [25] or sodium hydride in DMF. *N*-Alkylation of **16** with cyclohexylmethyl bromide using the latter conditions gave **18**. Dibromocarbazoles **16–18** were reacted with copper(I) cyanide (Rosenmund–von Braun reaction) [26, 27] in refluxing

Abbreviations – BOC: *tert*-butoxycarbonyl; DIBAL: di-*iso*-butyl aluminum hydride; DMF: *N,N*-dimethylformamide; DMSO: dimethylsulfoxide; HPLC: high-performance liquid chromatography; TBDMS: *tert*-butyl dimethylsilyl; TFA: trifluoroacetic acid; THF: tetrahydrofuran.

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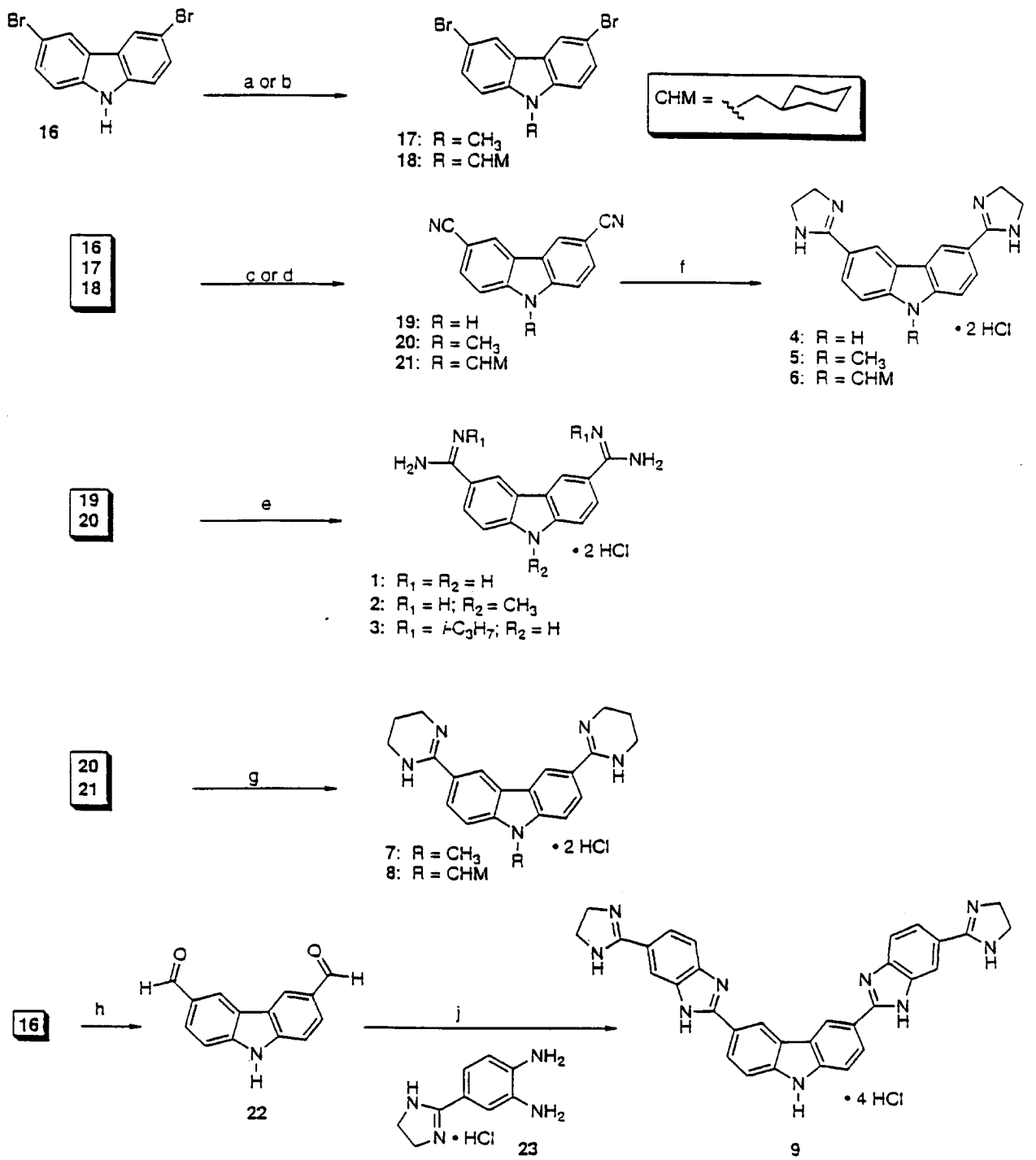
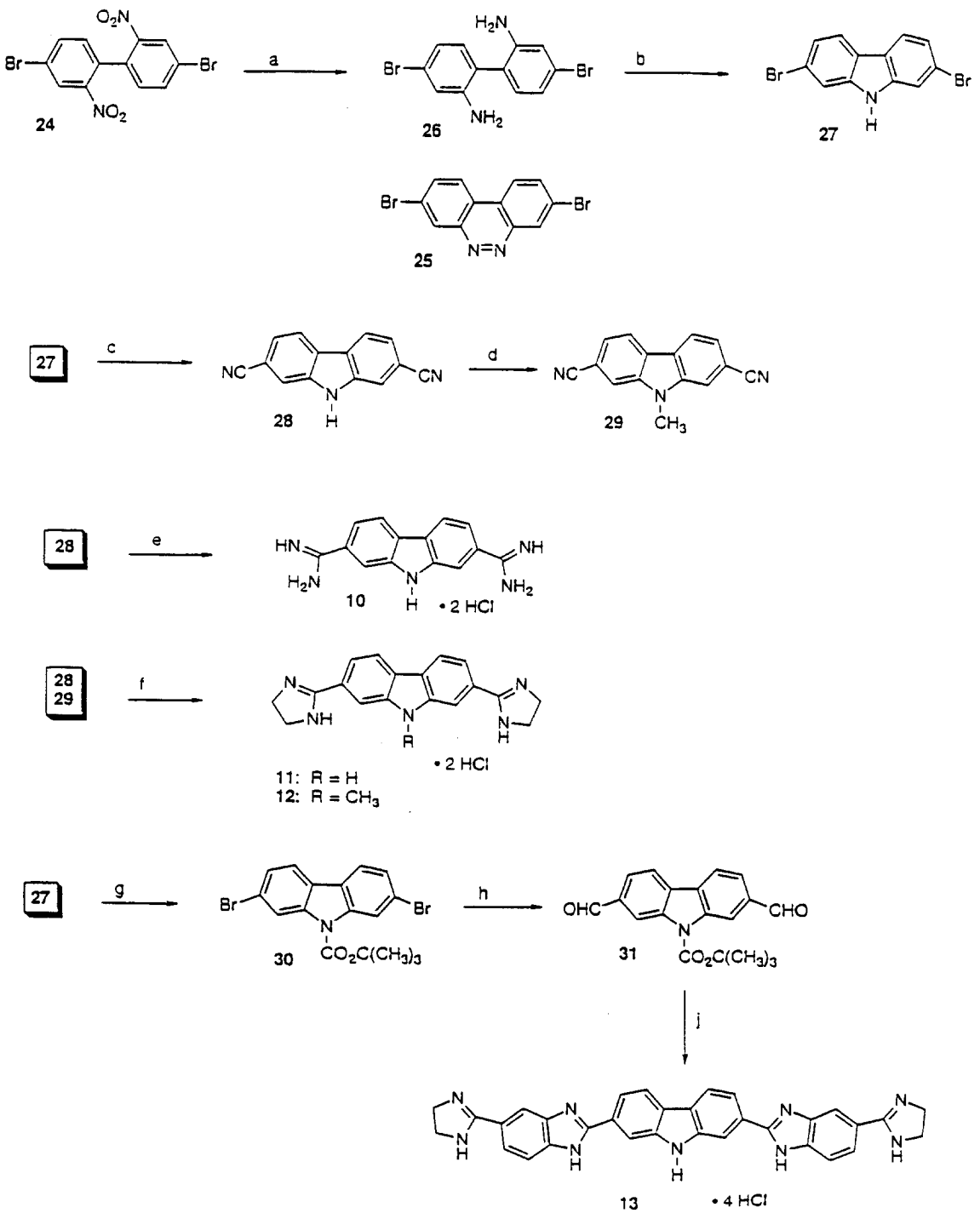


Scheme 1. Synthesis of 3,6-substituted carbazoles. Key: (a) NaH, alkyl halide, DMF, Δ; (b) CH_3I, benzyl triethylammonium chloride, CH_2Cl_2/50% aq NaOH; (c) CuCN, quinoline, Δ, 2 h; (d) CuCN, DMF, Δ, 71 h; (e) (i) EtOH, HCl, 1,4-dioxane, −5 to 25 °C, 17–21 d, (ii) appropriate amine, EtOH, Δ; (f) $NH_2(CH_2)_2NH_2$•2HCl, 310–320 °C, 15 min; (g) $NH_2(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$•2HCl, 300–310 °C, 15–30 min; (h) (i) KH, THF, 0 °C, (ii) *t*-BuLi, −78 to 25 °C, (iii) DMF, −78 to 25 °C, (iv) 1 M H_3PO_4; (j) (i) 1,4-benzoquinone, EtOH, Δ, 3.5 h, (ii) aq HCl.

DMF [28] or quinoline to give the dinitriles **19–21**. Diamidines **1–3** were prepared by the reaction of diimidate derivatives of **19** and **20** with ammonia or isopropyl amine, respectively, in ethanol (Pinner synthesis) [14, 29–32]. While the reaction of the diimidate with the amine was complete after several hours, the formation of the diimidate proved to be much slower. In a typical experiment, unreacted dinitrile **19** was detectable by IR analysis after a three weeks' reaction time. The introduction of an electron-withdrawing protecting group on the nitrogen atom of **19** was considered as a means of enhancing the formation of the diimidate, but to no avail. For example, when the *N*-tosyl [33] derivative of **19** was subjected to Pinner conditions, the diimidate was formed after only four days. Unfortunately, the tosyl group of the diamidine product could not be removed (to give **1**) without affecting the amidino groups, nor could the *N*-tosyl diamidine be purified. The diimidazoline **4** can be prepared by the Pinner route, or more conveniently, by neat fusion of **19** with the dihydrochloride salt of ethylenediamine at 300 °C. The reaction of dinitriles **20** and **21** with a mixture of ethylenediamine and its dihydrochloride salt at 300 °C gave diimidazolines **5** and **6,** respectively. Analogous treatment of **20** and **21** with 1,3-diaminopropane and its dihydrochloride salt gave bis-tetrahydropyrimidines **7** and **8**, respectively. The attempted reaction of the diimidate derivative of **19** with the known phenylene diamine **23** [14] to prepare bis-benzimidazole **9** proved to be unsuccessful. Another strategy employed for the preparation of **9** involved the acid-catalyzed coupling of **23** with the dicarboxyl analogue of **19** by established methodology [34]. Unfortunately, both the acid- and base-catalyzed hydrolyses of **19** to the diacid analogue were unsuccessful. Another strategy involved the quinone-catalyzed oxidative coupling [35] of **23** with dialdehyde **22**. No information concerning the preparation, isolation, or physical data supporting the structure of **22** is given in what appears to be the only reference to **22** in the literature [36] or in the references cited therein. Attempted reduction of **19** with DIBAL [37] using various solvents failed to give the expected dialdehyde. Examples of Vilsmeir formylations of carbazole derivatives (both with and without substituents on the nitrogen atom) to give the respective 3,6-diformylcarbazoles have been reported [38, 39]. However, in our laboratory, when both carbazole and *N*-benzyl carbazole [25] were subjected to analogous reaction conditions, only the monoaldehyde product was formed. A convenient one-pot preparation of dialdehyde **22** from dibromide **16** was achieved following the procedure of Moyer et al [40]. This procedure, reported as a synthesis of indole aldehydes, involves forming the anion of **16** using potassium hydride, a lithium–bromine exchange effected by *tert*-butyllithium, and formylation by treatment of the dilithio intermediate with DMF followed by acidic hydrolysis. Dialdehyde **22** was isolated in low yield (27%). Apparently, the lithium–bromine exchange failed to go to completion under the conditions employed; and the other product detected by HPLC was presumably the 3-bromo-6-formyl analogue. Dialdehyde **22** readily underwent quinone-catalyzed oxidative coupling with diamine **23** to give bis-benzimidazole **9** as the dihydrochloride salt. The dihydrochloride salt proved to be insufficiently soluble for in vivo assays and was subsequently treated with aqueous HCl to form the tetrahydrochloride salt.

The 2,7-substituted compounds **10–13** (scheme 2) were prepared, analogously, from dibromocarbazole **27**. A published three-step synthesis of this compound involves an Ullmann [41, 42] reaction of 2,5-dibromonitrobenzene to give biphenyl **24**, reduction of the nitro groups of **24** with tin/hydrochloric acid to give diamine **26**, and a deaminative ring closure catalyzed by Nafion®-H [43] to form carbazole **27** [44]. While the nitro groups of **24** were readily reduced by the tin/hydrochloric acid method, isolation and purification of the product **26** proved difficult in our laboratory. Reduction of **24** with stannous chloride dihydrate in refluxing ethanol gave diamine **26** of the highest purity, with a melting point nearly 20 °C higher than the literature value [44], and in a yield of 63%, only slightly less than that obtained from the tin/HCl reduction either in our laboratory or the literature. 3,8-Dibromobenzo[*c*]cinnoline **25** [45] was isolated as a minor product by either the stannous chloride or tin/HCl reduction (yields of 17 and 3%, respectively). The reduction of **24** using 5% ruthenium on carbon and hydrazine hydrate in refluxing ethanol [46] gave decreased amounts of **26** and increased amounts of **25**. Formation of **25** under these conditions is not surprising since this compound and related analogues have been prepared by reduction of nitro compounds under a variety of conditions [45, 47–51]. The Nafion-catalyzed cyclization reaction of **26** to **27** failed to go to completion in our laboratory. The cyclization was achieved using 85% phosphoric acid at 200 °C [52]. The melting point of product **27** is about 25 °C higher than the literature value [44]. The reaction of dibromide **27** with copper(I) cyanide in refluxing DMF to give dinitrile **28** was complete within 24 h (compared to 70 h reaction time for the 3,6-regioisomer **16**). Intermediate **28** readily underwent *N*-methylation to **29** using iodomethane and sodium hydride in DMF. Dinitrile **28** was much more reactive to Pinner synthesis conditions than regioisomer **19**; the formation of the diimidate derivative of **28** was complete after 5 days. Reaction of the diimidate derivative of **28** with ammonia gave diamidine **10**. The neat fusion of **28** and **29** with ethylenediamine dihydrochloride gave



Scheme 2. Synthesis of 2,7-dicationically substituted carbazoles. Key: (a) $SnCl_2 \cdot 2H_2O$, EtOH, Δ, 3 h; (b) 85% H_3PO_4, 200 °C, 44 h; (c) CuCN, DMF, Δ, 9 h; (d) CH_3I, NaH, DMF; (e) (i) EtOH, HCl, 1,4-dioxane, –5 to 25 °C, 5 d, (ii) EtOH/NH_3, 40 °C, 16 h; (f) $NH_2(CH_2)_2NH_2 \cdot 2HCl$, NH, 310–320 °C, 30–75 min; (g) di-*tert*-butyldicarbonate, benzyltriethylammonium chloride, toluene/30% aq NaOH, 0 °C, 1 h; (h) (i) *tert*-butyllithium, THF, –78 °C, 70 min, (ii) DMF, –78 to 25 °C, 2 h; (j) (i) TFA, 25 °C, 1 h, (ii) **23**, 1,4-benzoquinone, EtOH, Δ, 8 h, (iii) aq HCl.

diimidazolines **11** and **12**, respectively. The preparation of 2,7-bis-benzimidazole **13** from dibromo precursor **27** was somewhat less straightforward than that of **9** from **16**. As was the case with dibromide **9**, the sequential reaction of **27** with potassium hydride, *tert*-butyllithium, and DMF gave a mixture of the desired dialdehyde, the bromoaldehyde, and carbazole. Unfortunately, the two aldehydes could not be readily separated. The use of protecting groups on the nitrogen atoms was investigated for two reasons: (1) possible enhancement of the exchange of both bromine atoms by lithium if the acidic carbazole NH were replaced by a group covalently bound to the nitrogen atom; and (2) facilitated separation of dialdehyde and bromoaldehyde products bearing a lipophilic substituent on the nitrogen atom. A TBDMS group was readily attached to the nitrogen atom of **27** in 92% yield. However, lithiation–formylation of this silylated dibromide gave both the dialdehyde and bromoaldehyde products, which were not readily separable. Dibromide **27** readily underwent reaction with di-*tert*-butyl dicarbonate using phase-transfer catalysis [25] to give the BOC-dibromide **30**. While the lithiation–formylation reaction of **30** did give a mixture of **31**, its bromoaldehyde analogue, and carbazole, the BOC-dialdehyde **31** was readily purified by recrystallization. This compound underwent facile deprotection in neat TFA at room temperature. The resulting crude 2,7-diformylcarbazole was reacted immediately with phenylene diamine **23** in the presence of 1,4-benzoquinone to give the 2,7-bis-benzimidazole **13**, isolated as the tetrahydrochloride salt.

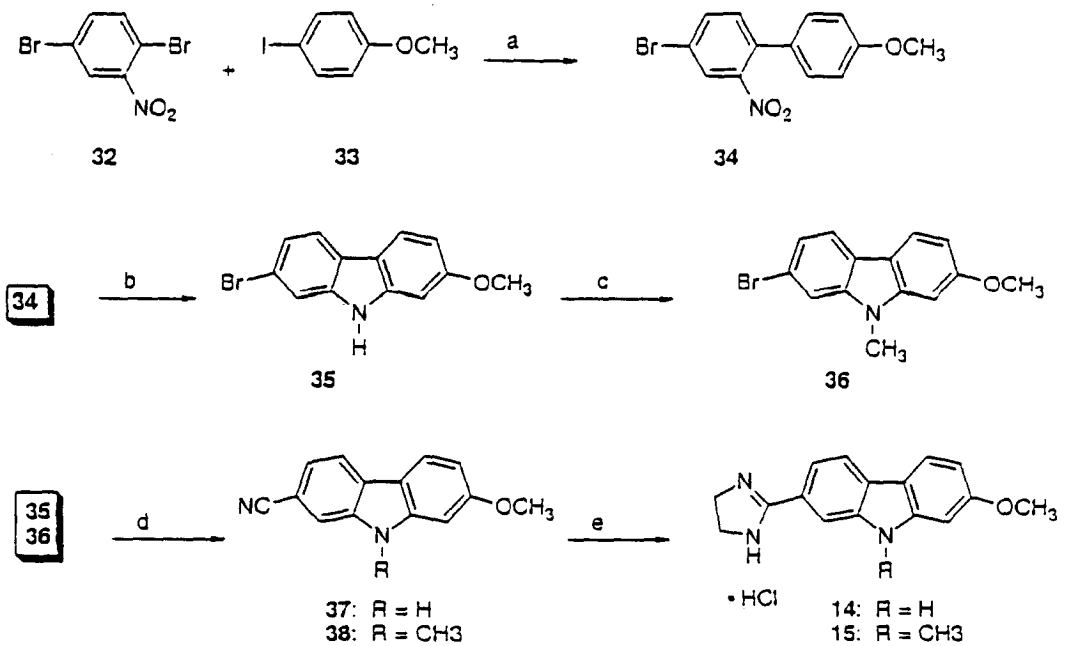
The syntheses of 2-(2-imidazolinyl) and 7-methoxycarbazoles **14** and **15** are depicted in scheme 3. For this synthesis it was necessary to construct the carbazole ring de novo. The crucial step was the preparation of intermediate **34** by the crossed Ullmann reaction from commercially available aryl halides **32** and **33**. The success of this reaction was dependent upon reaction conditions. When **32** and **33** were treated with Copper Bronze in DMF at 120 °C [44] the major product was **24**, the self-condensation product. However, when the two halides were reacted neat with Copper Bronze at the same temperature or at 175 °C [53], the cross-condensation product **32** was obtained in yields of 30 or 60%, respectively. The treatment of nitrobiphenyl **34** with triethyl phosphite at 160 °C [47, 54] readily gave the desired carbazole **35**. The attempted *N*-methylation of **35** to **36** with iodomethane using the phase-transfer catalysis method of Nishi et al [25] proved to be sluggish, presumably due the low solubility of the starting material in toluene. However, the methylation of **35** to **36** using iodomethane and sodium hydride in DMF proved to be expedient. Reaction of bromocarbazoles **35** and **36** with cuprous cyanide gave the expected cyanocarbazoles **37** and **38**, respectively. The monoethyl imidate derivatives of nitriles **37** and **38** were reacted with ethylenediamine to give imidazolines **14** and **15**, respectively. The crude product **14** proved (by microanalysis) to be the free base rather than the expected hydrochloride salt. Therefore crude products **14** and **15** were treated with aqueous HCl to generate the water-soluble mono-hydrochloride salts.

Results and discussion

Activity against P carinii pneumonia

The activity of the compounds against PCP in the rat model of disease is shown in table I. The activity is expressed as the percent of cysts counted in treated groups as compared to untreated controls. All of the compounds in the initial screen were given by tail vein injection at a dose of 5 mg/kg/day for 14 days. The test compounds were compared for efficacy with the standard anti-PCP compound, pentamidine, at one-half the dose of pentamidine. Ten of the fifteen compounds tested were found to be more potent than the standard drug. It is also noteworthy that only two of the compounds (**5**, **13**) exhibited significant toxicity in the rat model at the screening dose (5 mg/kg). Nine of the compounds (**1–5**, **7** and **10–12**) proved to be highly potent against the organism by producing over a 99% reduction in parasite load. There was no significant difference in activity between the 2,7-substituted carbazoles and the 3,6-substituted derivatives. Likewise, with the exception of one cyclohexylmethyl-derivative **6** and the 5-(2-imidazolynyl-2-benzimidazolyl substituted analogues **9** and **13**, all of the dicationic substituents exhibited excellent activity. The most notable structure–activity observation was the absence of anti-PCP activity exhibited by the two monocations **14** and **15**. This finding is consistent with our previous observations, using other spacer groups, indicating that both cations are essential for antimicrobial activity (unpublished results). It is also noteworthy that the two compounds with extended length **9** and **13** were excellent DNA binders but one had poor anti-PCP activity while the other was highly toxic. Four compounds **1**, **2**, **10**, **11** from the initial screen were tested in a dose response study.

The results from the dose–response study are shown in table II. All of the compounds had greatly reduced activity when given below 1 mg/kg/day. However, two of the compounds (**1** and **2**) were equally as active as pentamidine down to 1.6 mg/kg/day (approximately 1/6 the dose of pentamidine). Two of the compounds (**2** and **10**) tested at higher dose levels, approaching the dose of pentamidine, were found to exhibit less toxicity than the standard drug.



Scheme 3. Synthesis of 2-(2-imidazolinyl)-7-methoxycarbazoles. Key: (a) Cu, 175 °C, 3.5 h; (b) triethyl phosphite, Δ, 10 h; (c) CH_3I, NaH, DMF, 2 h; (d) CuCN, DMF, Δ, 8–11 h; (e) (i) EtOH, HCl, 1,4-dioxane, –5 to 25 °C, 5 d, (ii) $NH_2(CH_2)_2NH_2$, EtOH, Δ, 3–5 h.

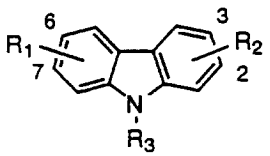
Inhibition of topoisomerase II and DNA binding

Previous studies on dicationic molecules having different spacer groups and tested against other organisms indicated that there was a strong relationship between inhibition of topoisomerase II and antimicrobial activity [6, 9, 10]. This relationship was especially significant for several series of dicationic molecules tested against *Giardia lamblia*. From the topoisomerase II inhibition data in table I it is apparent that this series of carbazoles, despite most members of the group having potent anti-PCP activity, show only modest inhibition toward the enzyme. Also there appears to be no definable structure–activity relationship for the compounds against topoisomerase.

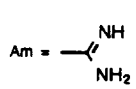
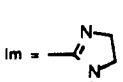
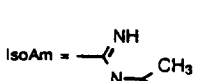
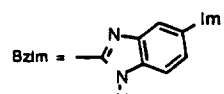
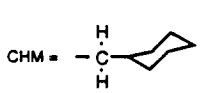
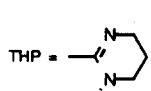
All but two of the compounds exhibited potent binding to the minor groove of DNA as measured by the increase in melting point of calf thymus DNA. The two compounds with weakest affinity for calf thymus DNA **14** and **15** also showed the poorest activity against PCP. Our past studies indicated that the strength of DNA binding for dicationic molecules does not exhibit a quantitative correlation with the strength of anti-PCP activity [14, 21, 22]. This lack of correlation can be seen for compounds **3** and **6**. Compound **3** is more potent than **6** in the PCP rat model while showing less affinity for DNA. Several factors may contribute to the finding that some strong DNA-binding compounds are not potent antimicrobial agents. The most likely factors are the inability of these molecules to be transported into the parisite and/or the lack of specificity (ie, the number and nature of base pairs bound) with regard to DNA binding. While a quantitative relationship could not be established between DNA binding and anti-PCP activity, the previous studies did show that a minimum level of DNA affinity ($\Delta T_m > 5.0$) was necessary to achieve antimicrobial activity [14, 21, 22]. From table I it can be seen that this observation also holds true for the dicationic carbazoles. The interactions of the dicationic carbazoles with the minor groove of DNA and the role of minor groove binding to antimicrobial activity is detailed in a separate manuscript [55].

In conclusion, this series of carbazoles contained a number of compounds with potent activity in the rat model of PCP. Additionally, several of the compounds proved to be less toxic and more potent than the anti-PCP drug, pentamidine. This series contains some of

Table I. Activity against *Pneumocystis carinii* pneumonia (PCP), inhibition of topoisomerase type II, and DNA binding by novel dicationic carbazoles.



Compound	R_1,R_2	R_1[a]	R_2[a]	R_3[a]	*Pneumocystis carinii*			*Topoisomerase: type II* IC_{50} *(μM)*	*DNA binding* ΔT_m *(°C)*[f]
					Dose[b]	*Toxicity*[c]	*% Saline control ± std error*[d]		
Saline ctrl	–	–	–	–	–	0	100.00 ± 10.00	–	–
Pentamidine	–	–	–	–	10.0	++	3.09 ± 1.60	> 100	10.7
1	3,6	Am	Am	H	5.0	0	0.56 ± 0.26	100	17.2
2	3,6	Am	Am	CH_3	5.0	0	0.43 ± 0 30	–	19 5
3	3,6	IsoAm	IsoAm	H	5.0	+	0.10 ± 0.07	5–10	9.6
4	3,6	Im	Im	H	5.0	0	0.04 ± 0.02	100	19.5
5	3,6	Im	Im	CH_3	5.0	+++	0.12 ± 0.08	5–10	24.0
6	3,6	Im	Im	CHM	5.0	0	25.23 ± 3.44	5–10	16.8
7	3,6	THP	THP	CH_3	5.0	+	0.10 ± 0.04	10–50	13.6
8	3,6	THP	THP	CHM	5.0	+	2.89 ± 1.12	1000	7.3
9	3,6	Bzlm	Bzlm	H	5.0	0	43.64 ± 10.19	50	22.0
10	2,7	Am	Am	H	5.0	0	0.12 ± 0.03	10	19.0
11	2,7	Im	Im	H	5.0	0	0.35 ± 0.24	25	18.6
12	2,7	Im	Im	CH_3	5.0	0	0.35 ± 0.10	50	19.1
13	2,7	Bzlm	Bzlm	H	5.0	++++	NA[e]	25	23.6
14	2,7	Im	OCH_3	H	5.0	0	321.04 ± 76.47	–	3.3
15	2,7	Im	OCH_3	CH_3	5.0	0	200.60 ± 35.20	–	3.9

[a] Am =  Im =  IsoAm =  Bzlm =  CHM =  THP = 

[b]Dose units are mg/kg/day. Each compound was given iv via tail vein to at least 8 rats once daily for 14 days. [c]Toxicity scores are subjective evaluations of overt toxicity in dexamethasone immunosuppressed rats. A score of '0' indicates no observable deleterious effects from dosing whereas '++++', the highest score, indicates death of all animals before completion of dosing. [d]Cysts/g lung counts were 51.53 (x 10^6) for the saline control group and 1.59 (x 10^6) for the pentamidine group. These scores were pooled across experiments involving compounds **1–15**. Saline: $n = 72$; pentamidine: $n = 67$. [e]Not available as all animals died due to toxic effect of the compound. [f]Change in melting point determined on calf thymus DNA.

the most potent anti-PCP compounds we have tested in over 9 years of research in this area. The anti-PCP activity did not quantitatively correlate with DNA binding or topoisomerase II inhibition. However, the current results were in agreement with earlier findings suggesting that DNA binding was necessary for the antimicrobial activity. Studies are currently under way to determine the role of DNA binding in the anti-PCP activity of the carbazole compounds.

Biological studies

The anti-PCP activity of the compounds was determined using a standard procedure [20]. Likewise, the binding of the molecules to DNA as determined by thermal melting of calf thymus DNA [56] and their topoisomerase inhibition [6] were carried out according to reported methods.

Experimental protocols

Uncorrected melting points were measured on a Thomas Hoover capillary melting point apparatus or a Mel-Temp II apparatus. IR spectra were recorded in Nujol mulls or KBr pellets on a Perkin-Elmer 1320 or a Michelson 100 FTIR (Bomen, Inc) spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Jeol GX-270, Bruker AC 300, Varian Gemini 300 and XL 400 spectrometers. Chemical shifts are expressed in parts per million relative to tetramethylsilane or

Table II. Dose response of selected carbazoles.

Compound	*Dose*[a]		*Toxicity*[b]	*% Saline control ± std error*
	mg/kg/day	*μmol/kg/day*		
Saline cntrl	–	–	0	100.00 ± 10.00
Pentamidine	10.0	22.0	++	3.09 ± 1.60
1	5.0	14.6	0	0.56 ± 0.26
	1.6	4.6	0	2.08 ± 0.59
	0.5	1.5	0	64.49 ± 27.66
2	7.0	20.0	0	0.06 ± 0.03
	5.0	14.3	0	0.43 ± 0.30
	1.6	4.6	0	2.99 ± 1.81
	0.5	1.5	0	42.87 ± 10.84
10	8.5	26.2	+	0.12 ± 0.03
	5.0	15.4	0	0.12 ± 0.03
	2.5	7.7	0	2.85 ± 0.99
	1.5	4.6	0	15.23 ± 6.67
	0.5	1.5	0	110.05 ± 21.43
11	5.0	12.9	0	0.35 ± 0.24
	1.8	4.6	0	6.25 ± 2.29
	0.6	1.5	0	55.48 ± 22.14

[a]Each compound was given iv via tail vein to at least 8 rats once daily for 14 days. [b]Toxicity scores are subjective evaluations of overt toxicity in dexamethasone immunosuppressed rats. A score of '0' indicates no observable deleterious effects from dosing whereas '++++', the highest score, indicates death of all animals before completion of dosing.

sodium 3-(trimethylsilyl)propionate. Anhydrous ethanol was distilled over Mg immediately prior to use. Reaction products were dried over P_2O_5 at 77 or 110 °C at 0.2 mm Hg. Unless stated otherwise, reactions were monitored by TLC on silica or by reverse-phase HPLC. HPLC chromatograms were recorded on a Hewlett-Packard 1090 chromatograph using a Dupont Zorbax Rx C8 column (4.6 mm x 25 cm) and UV detection (230 nm). Mobile phases consisted of mixtures of acetonitrile (3.75–67.5% v/v) in water containing 10 mM tetramethylammonium chloride, 10 mM sodium heptanesulfonate, and 2.2 mM phosphoric acid. The concentration of acetonitrile was maintained at 3.75% for 0.5 min, increased to 45% following a linear gradient over 19.5 min, increased immediately to 67.5% following a linear gradient over 5 min, then maintained at 67.5% for 7 min. Chromatographic data were recorded and analyzed with a Hewlett-Packard 3396 integrator. Electron impact mass spectra were recorded on a VG 70-SE or a VG 70-SEQ Hybrid spectrometer. FAB mass spectra were recorded on a VG 70-SEQ Hybrid spectrometer (cesium ion gun, 30 KV). Microanalyses were performed by Atlantic Microlab, Norcross, GA, and were within ±0.4% of calculated values. Carbazole and compounds **32** and **33** were purchased from Aldrich Chemical Co, Milwaukee, WI. Compound **16** was purchased from Aldrich Chemical Co, or was prepared from carbazole [23]. Compounds **23** [14] and **24** [44] were prepared by established methods.

*3,6-Diamidinocarbazole dihydrochloride **1***

A stirred suspension of 3,6-dicyanocarbazole (**19**, 2.48 g, 11.4 mmol) in anhydrous EtOH (3.0 mL, 51 mmol) and dry 1,4-dioxane (150 mL) was cooled in an ice–salt bath and was saturated with HCl gas at such a rate that the reaction temperature was maintained below 5 °C. The flask was then tightly sealed and the mixture was maintained at room temperature for 21 days, until only a small nitrile band (2220 cm^{-1}) was detected by IR analysis. The reaction mixture was purged with N_2 gas and diluted with ether (200 mL). The crude diimidate was filtered off under N_2 and was immediately suspended in anhydrous ethanol (100 mL). The suspension was diluted with a solution of NH_3 (3.97 g, 233 mmol) in ethanol (100 mL). The resulting solution was stirred overnight at 35–50 °C in a tightly stoppered flask. The reaction mixture was filtered through Celite 545 and evaporated. The residue was dissolved in a mixture of hot water and ethanol, filtered, and diluted with acetone to give a precipitate. The precipitate was collected and recrystallized several times from water–acetone to give white crystals (0.39 g, 11%): mp > 360 °C; ^{1}H-NMR (300 MHz, DMSO–d_6) δ 12.61 (br s, 1 H), 9.44 (br s, 4 H), 9.16 (br s, 4 H), 8.82 (d, J = 1.2 Hz, 2 H), 7.99 (dd, J = 8.6 and 1.2 Hz, 2 H), 7.79 (d, J = 8.6 Hz, 2 H); FAB-MS m/z 252 (MH^+ of free base); HPLC t_R 13.10 min (99.0 area %). Anal $C_{14}H_{13}N_5 \cdot 2HCl \cdot H_2O$ (C, H, N).

*3,6-Diamidino-9-methylcarbazole dihydrochloride **2***

A stirred suspension of 3,6-dicyano-9-methylcarbazole (**20**, 2.01 g, 8.70 mmol) in anhydrous EtOH (5.2 mL, 89 mmol) and dioxane (100 mL) was saturated with HCl gas as described above. The crude diimidate (3.15 g) was collected after 22 days. A portion of the crude imidate (1.61 g) was stirred in a

solution of ammonia (4.66 g, 274 mmol) in anhydrous ethanol (80 mL) at 45–50 °C for 20 h. The crude product (0.89 g) was filtered off and dissolved in hot water (50 mL). The turbid solution was filtered through Celite 545. The filtrate was concentrated to ca 25 mL and diluted with acetone (150 mL) to give an ivory colored powder (0.70 g, 49%): mp > 300 °C, ^{1}H-NMR (400 MHz, DMSO–d_6) δ 9.47 (br s, 3.5 H), 9.00 (br s, 3.5 H), 8.85 (s, 2 H), 8.06 (d, J = 8.6 Hz, 2 H), 7.94 (d, J = 8.6 Hz, 2 H), 4.03 (s, 3 H); FAB-MS m/z 266 (MH^+ of free base); HPLC t_R 14.14 min (97.1 area %). Anal $C_{15}H_{15}N_5$•2HCl•0.7H_2O (C, H, N).

3,6-Bis(N-isopropylamidino)carbazole dihydrochloride ***3***
A stirred suspension of 3,6-dicyanocarbazole (**19**, 1.65 g, 7.59 mmol) in anhydrous EtOH (3.0 mL, 51.4 mmol) and dioxane (130 mL) was saturated with HCl gas as described above. The crude diimidate was collected after 17 days. To a stirred suspension of the crude diimidate in anhydrous ethanol (40 mL) isopropylamine (25 mL, 290 mmol) was added, and the mixture was refluxed under nitrogen for 20.5 h. The solvent was evaporated to give an oily residue, from which a solid was obtained after alkalinization, acidification, and multiple evaporations. The material was recrystallized several times from ethanol–water–acetone to give a white powder (0.37 g, 12%): mp 317–318 °C; ^{1}H-NMR (400 MHz, DMSO–d_6) δ 12.59 (br s, 1 H), 9.61 (br s, 2 H), 9.49 (br s, 2 H), 9.11 (br s, 2 H), 8.70 (d, J = 1.5 Hz, 2 H), 7.84 (dd, J = 8.6 and 1.5 Hz, 2 H), 7.75 (d, J = 8.6, 2 H), 4.14 (m, 2 H), 1.33 (s, 6 H), 1.31 (s, 6 H); FAB-MS m/z 336 (MH^+ of free base); HPLC t_R 15.96 min (97.3 area %). Anal $C_{20}H_{25}N_5$•2HCl (C, H, N).

3,6-Bis(2-imidazolinyl)carbazole dihydrochloride ***4***
A mixture of 3,6-dicyanocarbazole (**19**, 2.01 g, 9.27 mmol) and ethylenediamine dihydrochloride (8.36 g, 62.9 mmol) was pulverized in an agate mortar and heated for 15 min at 310–320 °C in a sand bath. The reaction mixture was dissolved in boiling water (150 mL). Insoluble solids were filtered off through Celite 545. The filtrate was concentrated to ca 25 mL, and the crude product was precipitated out by dilution with ethanol (75 mL). The material was recrystallized several times from mixtures of ethanol and methanol or from mixtures of the same diluted with ether to give a pale yellow powder (0.31 g, 8.9%): mp > 320 °C (dec); ^{1}H-NMR (300 MHz, TFA–d) δ 8.44 (s, 2 H), 7.93 (d, J = 8.6 Hz, 2 H), 7.75 (d, J = 8.6 Hz, 2 H), 4.26 (s, 8 H); FAB-MS m/z 304 (MH^+ of free base); HPLC t_R 14.18 min (98.0 area %). Anal $C_{18}H_{17}N_5$•2HCl•0.5H_2O (C, H, N).

General procedure for the preparation of compounds ***5–8***

The reactions of dicyanoaromatic compounds **20** and **21** (6 mmol) and diaminoalkanes (75 mmol of the base and 80 mmol of the appropriate dihydrochloride) to give cyclic amidines **5–8** were effected in a sand bath at 300–310 °C (15–30 min). When the reaction was completed by TLC, the unreacted dinitrile was extracted with chloroform or acetone. The product was crystallized from boiling water. The hydrochlorides of the methyl derivatives are more soluble in water than the cyclohexylmethyl amidines. It was preferable to remove unchanged or decomposed material by filtration. The base was precipitated by means of 2 M sodium hydroxide solution and the hydrochloride was then prepared using ethanolic hydrogen chloride. The analytical and spectral data are contained below.

3,6-Bis(2-imidazolinyl)-9-methylcarbazole dihydrochloride ***5***
White crystals (1.6 g, 65%): mp > 300 °C; IR (KBr) 3496, 3433, 3103, 2984, 1599, 1491, 1406, 1355, 1317, 1285 cm^{-1}; ^{1}H-NMR (300 MHz, D_2O): δ 7.25 (d, J = 8.3 Hz, 2 H), 7.16 (s, 2 H), 6.98 (d, J = 8.3 Hz, 2 H), 3.95 (s, 8 H), 3.30 (s, 3 H); ^{13}C-NMR (75 MHz, D_2O) δ 166.5, 145.9, 127.9, 123.2, 122.7, 114.1, 112.3, 47.0, 31.8; EIMS (75 eV, 0.3 mA) m/z 317 (M^+ of free base); HPLC t_R 15.2 min (99.9 area %). Anal $C_{19}H_{19}N_5$•2HCl•H_2O (C, H, N).

3,6-Bis(2-imidazolinyl)-9-(cyclohexylmethyl)carbazole dihydrochloride ***6***
White crystals (2.16 g, 71%): mp > 300 °C; IR (KBr) 3096, 2925, 2844, 1603, 1493, 1418, 1361, 1319, 1288, 1251 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO–d_6) δ 10.79 (br s, 4 H), 8.97 (s, 2 H), 8.19 (d, J = 8.8 Hz, 2 H), 8.09 (d, J = 8.8 Hz, 2 H), 4.40 (d, J = 7.0 Hz, 2 H), 4.06 (s, 8 H), 1.93 (m, 1 H), 1.62 (m, 3 H), 1.47 (m, 2 H), 1.13 (m, 5 H); ^{13}C-NMR (75 MHz, DMSO–d_6) δ 166.1, 145.0, 126.7, 122.3, 121.8, 113.3, 111.7, 50.3, 45.4, 38.4, 31.3, 26.6, 26.1; EIMS (75 eV, 0.3 mA) m/z 399 (M^+ of free base); HPLC t_R 20.10 min (99.1 area %). Anal $C_{25}H_{29}N_5$•2HCl•$2H_2O$ (C, H, N).

3,6-Bis[2-(1,4,5,6-tetrahydropyrimidinyl)]-9-methylcarbazole dihydrochloride ***7***
White crystals (1.9 g, 70%): mp > 300 °C; IR (KBr) 3403, 3161, 3020, 1631, 1599, 1493, 1443, 1370, 1316, 1263 cm^{-1}; ^{1}H-NMR (300 MHz, D_2O) δ 8.04 (s, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H), 3.72 (br s, 8 H), 3.52 (s, 3 H), 2.24 (br s, 4 H); ^{13}C-NMR (75 MHz, D_2O) δ 162.0, 146.1, 127.0, 124.0, 121.9, 121.1, 112.7, 42.1, 31.8, 21.0; EIMS (75 eV, 0.3 mA) m/z 345 (M^+ of free base); HPLC t_R 15.33 min (98.3 area %). Anal $C_{21}H_{23}N_5$•2HCl•1.75H_2O (C, H, N).

3,6-Bis[2-(1,4,5,6-tetrahydropyrimidinyl)]-9-(cyclohexylmethyl)carbazole dihydrochloride ***8***
White crystals (1.89 g, 61%): mp > 300 °C, IR (KBr) 3146, 3016, 2919, 2849, 1631, 1598, 1445, 1375, 1320 cm^{-1}; ^{1}H-NMR (270 MHz, DMSO–d_6) δ 10.20 (br s, 4 H), 8.79 (s, 2 H), 7.99 (d, J = 8.8 Hz, 2 H), 7.85 (d, J = 8.8 Hz, 2 H), 4.37 (m, 2 H), 3.54 (m, 8 H), 2.02 (m, 5 H), 1.65 (m, 5 H), 1.14 (m, 5 H); ^{13}C-NMR (67.5 MHz, DMSO–d_6) δ 159.1, 143.6, 125.8, 121.7, 120.7, 120.5, 110.6, 48.9, 39.2, 37.7, 30.3, 25.8, 25.2, 18.4; EIMS (75 eV, 0.3 mA) m/z 427 (M^+ of free base); HPLC t_R 20.32 min (96.0 area %). Anal $C_{27}H_{33}N_5$•2HCl•H_2O (C, H, N).

3,6-Bis[5-(2-imidazolinyl)-2-benzimidazoyl]carbazole tetrahydrochloride ***9***
A mixture of 3,6-diformylcarbazole (**22**, 0.24 g, 1.5 mmol), 4-(2-imidazolinyl)-1,2-phenylenediamine hydrochloride (**23**, 0.64 g, 3.00 mmol), and 1,4-benzoquinone (0.39 g, 3.6 mmol) in ethanol (100 mL) was stirred at reflux for 3.5 h while exposed to the atmosphere. The precipitated product (as the dihydrochloride salt) was filtered off. This material was dissolved in hot water (30 mL), and the solution was diluted with a 4 N HCl solution (15 mL) to give the tetrahydrochloride salt as a chartreuse powder (0.50 g, 49%): mp > 360 °C; ^{1}H-NMR (300 MHz, TFA–d) δ 9.25 (s, 2 H), 8.74 (s, 2 H), 8.40 (d, J = 8.3 Hz, 2 H), 8.11 (s, 4 H), 7.89 (d, J = 8.3 Hz, 2 H), 4.32 (s, 8 H); FAB-MS m/z 536 (MH^+ of free base); HPLC t_R 17.90 min (100 area %). Anal $C_{32}H_{25}N_9$•4HCl•3.25H_2O (C, H, N).

2,7-Diamidinocarbazole dihydrochloride ***10***
A stirred suspension of 2,7-dicyanocarbazole (**28**, 1.68 g, 7.74 mmol) in anhydrous ethanol (3.0 mL, 51 mmol) and dry

1,4-dioxane (100 mL) was saturated with HCl gas as described in the synthesis of compound **1**. The crude diimidate was collected after 5 days reaction time. A suspension of the diimidate in anhydrous ethanol (15 mL) was diluted with an ethanolic ammonia solution (7.26 g NH_3 in 85 mL of solution). The resulting solution was stirred overnight at 40 °C in a stoppered flask. The cooled reaction mixture was poured into cold ether (125 mL), and the resulting precipitate was filtered off. The material was recrystallized once from water–ethanol–acetone and four times from water–acetone to give a light yellow powder (0.48 g, 19%): mp > 360 °C (dec); ^{1}H-NMR (400 MHz, DMSO–d_6) δ 12.53 (s, 1 H), 9.52 (s, 4 H), 9.27 (s, 4 H), 8.49 (d, J = 8.8 Hz, 2 H), 8.08 (s, 2 H), 7.65 (d, J = 8.8 Hz, 2 H); FAB-MS *m/z* 252 (MH^+ of free base); HPLC t_R 13.32 min (98.0 area %). Anal $C_{14}H_{13}N_5$•2HCl (C, H, N).

2,7-Bis(2-imidazolinyl)carbazole dihydrochloride ***11***
A mixture of 2,7-dicyanocarbazole (**28**, 0.99 g, 4.6 mmol) and ethylenediamine dihydrochloride (3.00 g, 22.6 mmol) was pulverized in an agate mortar and heated at 320 °C for 30 min. The reaction mixture was dissolved in hot water (100 mL) and filtered through Celite 545. The filtrate was concentrated to ca 5 mL. The precipitate which formed was collected and dissolved in methanol. The methanolic solution was filtered through Norit-A (3 mm layer), concentrated, and diluted with ether to give a yellow solid. The solid was recrystallized from hot water–EtOH (20 mL each) to give yellow microcrystals (0.39 g, 2.3%): mp > 360 °C; ^{1}H-NMR (300 MHz, TFA–*d*) δ 8.36 (d, J = 8.2 Hz, 2 H), 8.19 (s, 2 H), 7.67 (d, J = 8.2 Hz, 2 H), 4.27 (s, 8 H); FAB-MS *m/z* 304 (MH^+ of free base); HPLC t_R 14.28 min (98.4 area %). Anal $C_{18}H_{17}N_5$•2HCl•0.6H_2O (C, H, N).

2,7-Bis(2-imidazolinyl)-9-methylcarbazole dihydrochloride ***12***
A mixture of 2,7-dicyano-9-methylcarbazole (**29**, 1.33 g, 5.76 mmol) and ethylenediamine dihydrochloride (5.50 g, 41.4 mmol) was treated as above and maintained at 300 °C for a total of 75 min. The reaction mixture was dissolved in hot water and filtered through a layer of Norit-A (40 x 3 mm) over a pad of Celite 545. The filtrate was concentrated to 150 mL to give amber needles (0.78 g). The crystals were dissolved in hot water and the solution was concentrated to 30 mL to give fine chartreuse needles (0.42 g, 19%): mp > 360 °C (dec); ^{1}H-NMR (300 MHz, TFA–*d*) δ 8.48 (d, J = 7.5 Hz, 2 H), 8.17 (s, 2 H), 7.79 (d, J = 7.5 Hz, 2 H), 4.36 (s, 8 h), 4.10 (s, 3 H); FAB-MS *m/z* 318 (MH^+ of free base); HPLC t_R 14.59 min (98.2 area %). Anal $C_{19}H_{19}N_5$•2HCl•H_2O (C, H, N).

2,7-Bis[5-(2-imidazolinyl)-2-benzimidazoyl]carbazole tetrahydrochloride ***13***
9-(*tert*-Butoxycarbonyl)-2,7-diformylcarbazole (**31**, 0.50 g, 1.55 mmol) was dissolved in TFA (10 mL) and stirred at 25 °C for 1 h. Within a few minutes a precipitate formed. The TFA was removed under reduced pressure, and the crude 2,7-diformylcarbazole was reacted with 4-(2-imidazolinyl)-1,2-phenylenediamine hydrochloride (**23**, 0.85 g, 4.01 mmol) and 1,4-benzoquinone (0.43 g, 3.98 mmol) in refluxing ethanol (100 mL) for a total of 7.5 h, while exposed to the atmosphere. The crude dihydrochloride product was filtered off, dissolved in hot water (50 mL), and diluted with 4 N HCl (15 mL). The resulting precipitate was filtered off and washed with ethanol and ether to give dark green microcrystals (0.63 g, 60%): mp > 360 °C; ^{1}H-NMR (300 MHz, DMSO–d_6) δ 12.21 (s, 1 H), 10.67 (s, 4 H), 8.53 (s, 2 H), 8.44 (d, J = 8.6 Hz, 2 H), 8.42 (s, 2 H), 8.19 (d, J = 8.6 Hz, 2 H), 7.90 (s, 4 H), 4.05 (s, 8 H); FAB-MS *m/z* 536 (MH^+ of free base); HPLC t_R 17.2 min (100 area %). Anal $C_{32}H_{25}N_9$•4HCl•1.2H_2O (C, H, N).

2-(2-Imidazolinyl)-7-methoxycarbazole hydrochloride ***14***
A solution of 2-cyano-7-methoxycarbazole (**37**, 1.89 g, 8.52 mmol) and dry ethanol (5.0 mL, 87 mmol) in dry 1,4-dioxane (100 mL) was saturated with HCl gas as described in the preparation of **1**. After 5 days the crude imidate was collected (1.38 g, 53.2% recovery) and reacted immediately with ethylenediamine (1.85 g, 30.8 mmol) in dry ethanol (50 mL) at reflux under nitrogen for 5 h. The precipitated imidazoline base was collected and dried (0.63 g, 28 % recovery from nitrile). An aliquot (0.40 g) was dissolved with heat in a total of ethanol (20 mL) and water (10 mL). The solution was diluted with 4 N HCl to give green crystals (0.43 g, 93% recovery from crystallization, est 26% total yield from nitrile): mp 226–228 °C; ^{1}H-NMR (400 MHz, DMSO–d_6) δ 11.91 (s, 1 H), 10.62 (s, 2 H), 8.26 (d, J = 8.2 Hz, 1 H), 8.15 (d, J = 1.5 Hz, 1 H), 8.12 (d, J = 8.6 Hz, 1 H), 7.74 (dd, J = 8.2 and 1.5 Hz, 1 H), 7.04 (d, J = 2.2 Hz), 6.88 (dd, J = 8.6 and 2.2 Hz, 1 H), 4.03 (s, 4 H), 3.88 (s, 3 H); FAB MS *m/z* 266 (MH^+ of free base); HPLC t_R 18.21 min (99.1 area %). Anal $C_{16}H_{15}N_3O$•HCl•0.7H_2O (C, H, N).

2-(2-Imidazolinyl)-7-methoxy-9-methylcarbazole hydrochloride ***15***
A stirred solution of 2-cyano-7-methoxy-9-methylcarbazole (**38**, 1.78 g, 7.55 mmol) and dry ethanol (5.0 mL, 86 mmol) in dry 1,4-dioxane (100 mL) was saturated with HCl gas as described above. After 5 days the crude imidate (2.17 g, 90.1% recovery) was collected and reacted with ethylenediamine (2.15 g, 35.8 mmol) in dry ethanol (50 mL) at reflux under N_2 for 3 h. The precipitated imidazoline base was filtered off (1.59 g, 75.4% recovery from nitrile). An aliquot (0.51 g) was dissolved in a mixture of hot ethanol (10 mL) and water (5 mL). The solution was diluted with 4 N HCl (10 mL) to give the hydrochloride salt as yellow needles (0.47 g, 83% recovery from crystallization, est 63% total yield from nitrile): mp 327–330 °C (dec); ^{1}H-NMR (400 MHz, DMSO–d_6) δ 10.67 (s, 2 H), 8.42 (s, 1 H), 8.29 (d, J = 8.1 Hz, 1 H), 8.15 (d, J = 8.5 Hz, 1 H), 7.79 (d, J = 8.1 Hz, 1 H), 7.23 (d, J = 1.8 Hz), 6.91 (dd, J = 8.5 and 1.8 Hz, 1 H), 4.05 (s, 4 H), 3.93 (s, 3 H), 3.93 (s, 3 H); FAB MS *m/z* 280 (MH^+ of free base); HPLC t_R 19.40 min (99.3 area %). Anal $C_{17}H_{17}N_3O$•HCl•0.2H_2O (C, H, N).

3,6-Dibromo-9-methylcarbazole ***17***
A mixture of 3,6-dibromocarbazole (**16**, 20 g, 60 mmol), sodium hydride (2.75 g of 60% oil dispersion, 70 mmol), iodomethane (12 g, 80 mmol) and DMF (50 mL) was heated for 6 h at 60 °C and poured into water. The resulting precipitate was filtered off, washed several times with water, and then extracted with chloroform in a Soxhlet apparatus. The product was recrystallized from ethanol to give white crystals (18.90 g, 91%): mp 160 °C; IR (KBr) 2929, 1474, 1440, 1416, 1357, 1318, 1284, 1239, 1146, 850, 828, 801; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 8.02 (s, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.14 (d, J = 8.8 Hz, 2 H), 3.68 (s, 3 H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 139.9, 129.1, 123.4, 123.2, 112.1, 110.1, 29.2; EIMS (75 eV, 0.3 mA) *m/z* 341, 339 (M^+).

3,6-Dibromo-9-(cyclohexylmethyl)carbazole ***18***
Sodium hydride (2.75 g of 60% oil dispersion, 70 mmol) was added to a solution of 3,6-dibromocarbazole (**16**, 20 g, 60 mmol) in DMF (50 mL). The mixture was stirred for 0.5 h before the addition of cyclohexylmethyl bromide (14 g, 80 mmol). The mixture was heated at 100 °C for another 2 h and was worked up as above to give white crystals (2.13 g, 82%): mp 157 °C; IR (KBr) 2920, 2846, 1472, 1437, 1344,

1291, 1206, 1146, 1056, 1016, 959, 830, 801 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.11 (d, J = 2.0 Hz, 2 H), 7.53 (dd, J = 8.8 and 2.0 Hz, 2 H), 7.25 (d, J = 8.8 Hz, 2 H), 4.03 (d, J = 6.8 Hz, 2H), 1.75–1.55 (m, 5 H), 1.94 (m, 1 H), 1.12 (m, 5 H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 139.8, 129.0, 123.2, 111.9, 110.8, 49.8, 38.2, 31.4, 26.2, 25.7; EIMS (75 eV, 0.3 mA) *m/z* 423, 421 (M^+).

3,6-Dicyanocarbazole ***19***

A mixture of 3,6-dibromocarbazole (**16**, 32.02 g, 95.2 mmol) and dried copper(I) cyanide (32.45 g, 329.4 mmol, 3.34 equiv) in dry DMF (500 mL) was heated at reflux under nitrogen for 70 h. The reaction mixture was poured into ice-water. The precipitate which formed was filtered off and washed with water. The solid was stirred in water containing ethylenediamine (50 mL) for 1 h, then filtered off and washed with water. The solid was stirred in a solution of sodium cyanide (40 g) in water (700 mL) for 1.5 h. The dinitrile was filtered off, washed with water, and dried to give a tan powder (21.36 g, 99%): mp > 360 °C; IR (KBr) 3300, 3120, 2960, 2020, 2860, 2220, 1600, 1455, 1405, 1300, 1260, 1070, 805 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO–d_6) δ 12.39 (br s, 1 H), 8.81 (s, 2 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H); HPLC t_R 22.21 min (93.1 area %). Anal $C_{14}H_7N_3 \cdot 0.2H_2O$ (C, H, N).

3,6-Dicyano-9-methylcarbazole ***20***

A mixture of 3,6-dibromo-9-methylcarbazole (**17**, 18 g, 50 mmol) copper(I) cyanide (10 g, 110 mmol), and quinoline (50 mL) was refluxed for 2 h. The reaction mixture was allowed to cool and diluted with ether. The complex of the nitrile and cuprous halide was filtered off and washed with ether. The complex was decomposed by heating at 60–80 °C in a solution of hydrated ferric chloride (40 g) and concentrated hydrochloric acid (10 mL) in water (60 mL). The crude dinitrile was filtered off, extracted with acetone in a Soxhlet apparatus, and then recrystallized from methanol to give white crystals (9.9 g, 86%): mp > 300 °C; IR (KBr) 3058, 2220, 1634, 1596, 1485, 1366, 1300 cm^{-1}; ^{1}H-NMR (270 MHz, DMSO–d_6) δ 8.82 (s, 2 H), 7.95 (d, J = 8.6 Hz, 2 H), 7.87 (d, J = 8.6 Hz, 2 H), 3.98 (s, 3 H); ^{13}C-NMR (67.5 MHz, DMSO–d_6) δ 142.8, 129.5, 125.6, 121.2, 119.3, 110.7, 101.8, 29.2; EIMS (75 eV, 0.3 mA) *m/z* 231 (M^+). Anal $C_{15}H_9N_3$ (C, H, N).

3,6-Dicyano-9-(cyclohexylmethyl)carbazole ***21***

A mixture of 3,6-dibromo-9-(cyclohexylmethyl)carbazole (**18**, 20 g, 50 mmol), copper(I) cyanide (10 g, 110 mmol), and quinoline (50 mL) was refluxed for 2 h, then worked up as above. The crude dinitrile was filtered off, washed with water, and purified by column chromatography eluting with chloroform: hexane (1:1). The product was recrystallized from ethanol to give white crystals (11.18 g, 75%): mp 244 °C; IR (KBr) 2921, 2849, 2220, 1632, 1595, 1484, 1455, 1387, 1354, 1299 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.39 (s, 2 H), 7.78 (d, J = 8.3 Hz, 2 H), 7.53 (d, J = 8.3 Hz, 2 H), 4.18 (d, J = 7.3 Hz, 2 H), 1.98 (m, 1 H), 1.80–1.50 (m, 5 H), 1.17 (m, 5 H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 143.2, 130.2, 125.6, 122.0, 119.8, 110.7, 103.4, 50.1, 38.2, 31.4, 26.1, 25.6; EIMS (75 eV, 0.3 mA) *m/z* 313 (M^+). Anal $C_{21}H_{19}N_3$ (C, H, N).

3,6-Diformylcarbazole ***22***

3,6-Dibromocarbazole (**16**, 2.03 g, 6.24 mmol) was added to a stirred suspension of potassium hydride (0.26 g, 6.5 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred under nitrogen for 40 min before the temperature was lowered to –78 °C. *tert*-Butyllithium (20 mL of a 1.7 M solution in pentane, 34 mmol) was added by a syringe over 3 min. The mixture was allowed to warm to room temperature over 1 hour before being cooled again to –78 °C. DMF (5 mL, 65 mmol) was introduced via a syringe. The mixture was allowed to warm to room temperature and was stirred for 1.5 h before it was poured into a 1 M H_3PO_4 solution (200 mL), forming a fine precipitate. The precipitate was filtered off (Celite 545). The product was extracted from the Celite in hot pyridine (100 mL), and the solution was diluted with water (100 mL) to give a tan powder (0.38 g, 27%): mp > 300 °C (dec); ^{1}H-NMR (400 MHz, DMSO–d_6) δ 12.35 (br s, 1 H), 10.07 (s, 2 H), 8.86 (d, J = 1.5 Hz, 2 H), 8.00 (dd, J = 8.5 and 1.5 Hz), 7.70 (d, J = 8.5 Hz); EIMS *m/z* 223 (M^+), 222 (M – H^+), 194 (M – CHO^+); HPLC t_R 19.19 min (99.3 area %). Anal $C_{14}H_9NO_2 \cdot 0.7H_2O$ (C, H, N).

3,8-Dibromobenzo[c]cinnoline ***25***

A mixture of 2,2'-dinitro-4,4'-dibromobiphenyl (**24**, 32.5 g, 80.84 mmol) and stannous chloride dihydrate (200.0 g, 886.4 mmol) in ethanol (400 mL) was heated to reflux. Reactants went into solution within minutes, and the mixture was stirred at reflux for 3 h. The alkalinized (NaOH) reaction mixture was poured (in portions) into large volumes of ice-water mixtures, and the aqueous mixtures were extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The crude product residue was recrystallized from a mixture of boiling ethanol (500 mL) and ethyl acetate (350 mL) to give greenish-yellow needles (4.75 g, 17.4%): mp 242–243 °C (lit [45] 237 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.93 (d, J = 2.0 Hz, 2 H), 8.42 (d, J = 8.8 Hz, 2 H), 8.03 (dd, J = 8.8 and 2.0 Hz, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.72, 135.39, 133.78, 123.39, 122.96, 119.17; HPLC t_R 26.99 min (97.6 area %). Anal $C_{12}H_6Br_2N_2 \cdot 0.2EtOH$ (C, H, N).

2,2'-Diamino-4,4'-dibromobiphenyl ***26***

The mother liquor from above was diluted with ethanol, warmed, filtered through Norit-A (1 cm thick). The filtrate was concentrated to 300 mL and was diluted with water (150 mL). The product crystallized out as ivory crystals (17.47 g, 63.18%): mp 119–120 °C (lit [44] 99–105 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 6 H), 3.76 (br s, 4 H); HPLC t_R 25.98 min (99.2 area %).

2,7-Dibromocarbazole ***27***

A solution of 2,2'-diamino-4,4'-dibromobiphenyl (**26**, 17.93 g, 52.41 mmol) in 85% H_3PO_4 (90 mL) was stirred at 190–200 °C for 26 h. The precipitate which had formed was filtered off, washed with water, and dried. Unreacted diamine which was recovered from the filtrate by extraction with ethyl acetate was reacted with fresh H_3PO_4 (50 mL) for 18 h to form more product. A solution of the crude product in toluene was filtered through Celite 545, and the concentrated filtrate was diluted with hexane to give beige crystals (14.50 g, 85.2%): mp 233–234 °C (lit [44] 198–203 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1 H), 7.89 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 1.7 Hz, 2 H), 7.37 (dd, J = 8.3 and 1.7 Hz, 2 H); HPLC t_R 27.75 min (99.6 area %). Anal $C_{12}H_7Br_2N$ (C, H, N).

2,7-Dicyanocarbazole ***28***

Copper(I) cyanide (14.7 g, 164.3 mmol) was added to a stirred solution of 2,7-dibromocarbazole (**27**, 12.28 g, 37.75 mmol) in DMF (150 mL). The solution was maintained at reflux under nitrogen for 22.5 h. The reaction mixture was worked up as in the preparation of **19**, except that 40 mL of ethylenediamine and 20 g of NaCN were used, to give a beige powder (7.92 g,

96.6%): mp 279–281 °C; ^{1}H-NMR (400 MHz, DMSO–d_6) δ 12.18 (br s, 1 H), 8.46 (d, J = 8.0 Hz, 2 H), 8.08 (s, 2 H), 7.62 (d, J = 8.0 Hz, 2 H); HPLC t_R 23.13 min (96.3%). Anal $C_{14}H_7N_3$ (C, H, N).

2,7-Dicyano-9-methylcarbazole ***29***
Sodium hydride (0.31 g of a 60% dispersion in mineral oil, 7.71 mmol) was washed with hexane 3 times and dried under reduced pressure. To a stirred suspension of the hydride in DMF (40 mL) at 0 °C 2,7-dicyanocarbazole (**28**, 1.47 g, 6.74 mmol) was added. The mixture was heated in an oil bath maintained at 60 °C for 30 min before the addition of iodomethane (3.39 g, 23.9 mmol). The mixture was maintained at the same temperature for 2 h before being poured into a mixture of ice and water (300 mL). The precipitated product was filtered off and dried to give an ivory powder (1.49 g, 95.6%): mp 333–334 °C (dec); ^{1}H-NMR (300 MHz, TFA–*d*) δ 8.26 (d, J = 8.2 Hz, 2 H), 7.88 (s, 2 H), 7.60 (d, J = 8.2 Hz), 3.94 (s, 3 H). Anal $C_{15}H_9N_3$ (C, H, N).

9-BOC-2,7-dibromocarbazole ***30***
A solution of sodium hydroxide (10.0 g in 30 mL of water) was added to a stirred suspension of 2,7-dibromocarbazole (**27**, 1.95 g, 6.00 mmol) and benzyltriethylammonium chloride (0.05 g, 0.23 mmol) in toluene (15 mL). The two-phase mixture was cooled to 0 °C before the addition of di-*tert*-butyl dicarbonate (2.49 g, 11.42 mmol). A precipitate began to form in the toluene layer within minutes, and after 30 min the ice bath was removed. After another 30 min the reaction mixture was poured into water (250 mL) and extracted with ethyl acetate (2 x 50 mL). Combined extracts were washed with sat NaCl solution, dried ($MgSO_4$), and evaporated to a white powder. The crude material was dissolved in hot toluene, and the solution was concentrated to 20 mL to give white microcrystals (2.17 g, 85.1%): mp 175 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 2 H), 7.79 (d, J = 8.1 Hz, 2 H), 7.48 (d, J = 8.1 Hz, 2 H), 1.77 (s, 9 H). Anal $C_{17}H_{15}BrNO_2$ (C, H, N).

9-BOC-2,7-diformylcarbazole ***31***
tert-Butyllithium (17.0 mL of a 1.7 M solution in pentane, 28.9 mmol) was added to a stirred solution of 9-BOC-2,7-dibromocarbazole (**30**, 2.00 g, 4.72 mmol) in dry THF (50 mL) maintained at –78 °C under nitrogen. After 70 min dry DMF (4.0 mL, 51.7 mmol) was added. The mixture was allowed to warm to ambient temperature over 2 h, and was poured into and shaken with an ammonium chloride solution (20 g in 100 mL of water) after 2 h. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). Combined organic layers were washed with water (100 mL), dried ($MgSO_4$), and evaporated. The crude product was recrystallized first from acetone (20 mL), then from ethanol (50 mL) to give pale yellow microcrystals (0.52 g, 34.0%): mp 170 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 2 H), 8.89 (s, 2 H), 8.19 (d, J = 8.1 Hz, 2 H), 7.96 (d, J = 8.1 Hz, 2 H), 1.83 (s, 9 H); HPLC t_R 27.50 min (100 area %). Anal $C_{19}H_{17}NO_4$ (C, H, N).

4-Bromo-4'-methoxy-2-nitrobiphenyl ***34***
Copper powder (Aldrich no 29,258-3, 9.57 g, 151 mg atoms) was added over 40 min to a stirred molten mixture of 2,5-dibromonitrobenzene (**32**, 14.05 g, 50.03 mmol) and 4-iodoanisole (**33**, 14.47 g, 61.81 mmol) maintained at 175 °C. The reaction mixture was maintained for another 3.5 h. The reaction mixture was extracted into hot toluene and filtered through Celite 545. The filtrate (ca 500 mL) was washed with water (400 mL), dried ($MgSO_4$), and evaporated. The crude material was recrystallized from ethanol (325 mL) to give yellow needles (9.28 g, 60.2%): mp 125–127 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 2.0 Hz, 1 H), 7.72 (dd, J = 8.3 and 2.0 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2 H), 6.96, (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H); high-resolution EIMS calc 306.984404, found 306.983085; HPLC t_R 26.84 min (96.4 area %). Anal $C_{13}H_{10}BrNO_3$ (C, H, N).

2-Bromo-7-methoxycarbazole ***35***
A solution of 4-bromo-4'-methoxy-2-nitrobiphenyl (**34**, 9.02 g, 29.24 mmol) in triethyl phosphite (25 mL, 150 mmol) was stirred at reflux under nitrogen for a total of 8.5 h. The solvent (containing triethyl phosphate) was distilled off under reduced pressure. The residue was suspended in ethanol (100 mL) with sonication and stirring. The solid was filtered off. The filtrate was evaporated, and the residue was diluted with ethanol and sonicated to give more solid. The combined solids were suspended in boiling ethanol and diluted with toluene (60 mL) until all material dissolved. The resulting solution was evaporated to 225 mL to give ivory crystals (5.86 g, 72.6%): mp 286 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.25 (2, 1 H), 7.97 (d, J = 8.6 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 1 H), 7.58 (d, J = 1.7 Hz, 1 H), 7.23 (dd, J = 8.2 and 1.7 Hz, 1 H), 6.98 (d, J = 2.3 Hz, 1 H), 6.78 (dd, J = 8.6 and 2.3 Hz, 1 H), 3.83 (s, 3 H); high-resolution EIMS calc 274.994575, found 274.994214; HPLC t_R 26.01 min (100 area %). Anal $C_{13}H_{10}BrNO$ (C, H, N).

2-Bromo-7-methoxy-9-methylcarbazole ***36***
Sodium hydride (0.63 g of a 60% dispersion in mineral oil, 16 mmol) was washed with hexane (3 x 10 mL) under nitrogen in a dry flask, dried under vacuum, and suspended in dry DMF (50 mL) at 0 °C with stirring under nitrogen. 2-Bromo-7-methoxycarbazole (**35**, 2.76 g, 10.0 mmol) was added, and the temperature was increased to 50 °C. Iodomethane (3.03 g, 21.4 mmol) was added. The mixture was maintained at 50 °C for 3 h, then overnight at room temperature. The reaction mixture was poured into ice-water (300 mL). The precipitated product was collected by filtration and dried to give white powder (2.68 g, 92.2%): mp 137–138 °C; ^{1}H-NMR (400 MHz, DMSO–d_6) δ 8.00 (d, J = 8.5 Hz, 1 H), 7.96 (d, J = 8.2 Hz, 1 H), 7.77 (d, J = 1.6 Hz, 1 H), 7.27 (dd, J = 8.2 and 1.6 Hz, 1 H), 7.13 (d, J = 2.1 Hz, 1 H), 6.82 (dd, J = 8.5 and 2.1 Hz, 1 H), 3.87 (s, 3 H), 3.87 (s, 3 H); HPLC t_R 27.49 min (98.3 area %). Anal $C_{14}H_{12}BrNO$ (C, H, N).

2-Cyano-7-methoxycarbazole ***37***
A stirred solution of 2-bromo-7-methoxycarbazole (**35**, 2.97 g, 10.8 mmol) and copper(I) cyanide (3.97 g, 33.0 mmol) in dry DMF (50 mL) was maintained at reflux under nitrogen for a total of 10 h. The reaction mixture was poured into ice and water (total volume 500 mL). The resulting precipitate was collected and stirred in a mixture of ethylenediamine (25 mL), water (300 mL), and ethyl acetate (400 mL). Layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate solutions were washed with a solution of sodium cyanide (5.0 g in 100 mL of water), followed by water (100 mL), dried ($MgSO_4$), and evaporated to a solid. The solid was recrystallized from ethanol–water to give light tan microcrystals (1.95 g, 81.8%): mp 164–166 °C; ^{1}H-NMR (400 MHz, DMSO–d_6) δ 11.59 (s, 1 H), 8.17 (d, J = 8.1 Hz, 1 H), 8.08 (d, J = 8.7 Hz, 1 H), 7.88 (d, J = 1.4 Hz, 1 H), 7.47 (dd, J = 8.1 and 1.4 Hz, 1 H), 7.02 (d, J = 2.1 Hz, 1 H), 6.84 (dd, J = 8.7 and 2.1 Hz, 1 H), 3.85 (s, 3 H); HPLC t_R 23.72 min (97.4 area %). Anal $C_{14}H_{10}N_2O$ (C, H, N).

2-Cyano-7-methoxy-9-methylcarbazole ***38***

A stirred solution of 2-bromo-7-methoxy-9-methylcarbazole (**36**, 2.97 g, 10.8 mmol) and copper(I) cyanide (1.95 g, 21.80 mmol) in dry DMF was maintained at reflux for a total of 11 h and was worked up as above. The dried extracts were evaporated and dried to give a white powder (1.95 g, 91.9%): mp 148–149 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.22 (d, J = 8.1 Hz, 1 H), 8.14 (d, J = 8.6 Hz, 1 H), 8.11 (d, J = 1.3 Hz, 1 H), 7.53 (dd, J = 8.1 and 1.3 Hz, 1 H), 7.20 (d, J = 2.1 Hz, 1 H), 6.90 (dd, J = 8.6 and 2.1 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H); HPLC t_R 25.53 min (100 area %). Anal $C_{15}H_{12}N_2O$ (C, H, N).

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