Synthesis of Geometrically Constrained Unsymmetrical Bis(polyamides) Related to the Antiviral Distamycin

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Keywords: Antiviral agents / DNA recognition / Distamycin / Polyamides / Unsymmetrical polyamides

Analysis of the structural and stereochemical requirements for the strict DNA base-sequence recognition of $(AT)_4$ and $(AT)_5$, respectively, for the oligopeptide minor-groove binding agents netropsin (**I**) and distamycin (**II**) leads to proposals for the rational structure modification for altered base recognition. In this paper we report the synthesis of unsymmetrical imidazo-pyrrolo-bis(polyamides), structurally related to the natural antiviral agents distamycin, and bearing either unnatural (**25**–**27**) or natural (**31**–**33**) termini linked by a flexible or rigid linker. This is the first report of the synthesis of an imidazole-bearing structure with either dimethylaminopropyl or amidinium termini in the linked bis(polyamides).

Introduction

Antiviral chemotherapy continues to be one of the most important means of controlling viral diseases.[1] One of the most challenging problems in the use of drugs in the treatment of human diseases is specificity. Recently, it has become evident that DNA-sequence selectivity is an important component contributing to the cytotoxic potency of several chemotherapeutic agents.[2] Therefore, the question arises as to whether one could tailor the binding preference of DNA binding agents to particular base sequences and thereby produce new drugs that might prove effective clinically and might complement efforts in the antisense or triple helix antigene area. Netropsin (**I**)[3] and distamycin (**II**)[4] (Figure 1) have served as prototype DNA-sequence selective minor-groove binding agents. However, in an attempt to bind longer sequences of DNA the empirical $(n + 1)$ rule[5] cannot be extended indefinitely because, as the number of repeating units increases, the mismatching becomes more severe; this is manifested by a trend of weaker binding with higher homologs.[6] One solution to this phasing problem is to synthesize extended bis(polyamides) tethered by a linker of appropriate dimensions.[7]

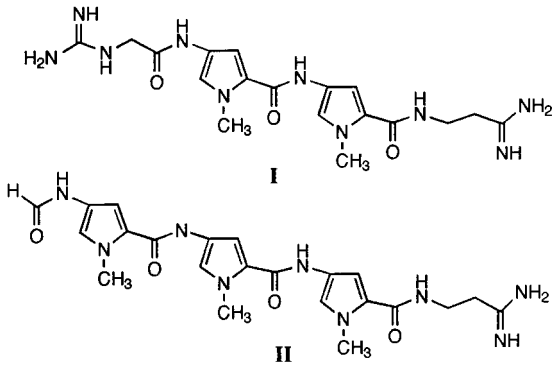

Figure 1. Netropsin (**I**), Distamycin (**II**)

Studies conducted in our group on murine leukemic retrovirus (MuLV),[8] HIV-1 integrase[9] and Okazaki fragments[10] have shown that the inclusion of a flexible polymethylene or fumaryl linker, or a *para* arrangement of distamycin moieties on either benzene or pyridine, confers in vitro inhibitory activities against HIV-1 and HIV-2 integrase in nanomolar concentrations[9] and comparable potency against the other targets. However, because of the presence of unnatural dimethylaminopropyl termini (initially employed for reasons of chemically stability), these linked polyamides have limited cellular uptake and hence low in vivo selectivity and limited clinical application. Encouraged by the high potency and selectivity in vitro, however, we have designed new unsymmetrical bis(polyamides) containing an imidazole moiety on one side of these active linkers and pyrrole on the other side so as to refine the drug targeting of the proviral U3LTR region.[9] Imidazole is introduced for the first time in the bis(polyamides) to change base-site recognition selectively from AT to GC in the minor groove of B-DNA[11] in order to permit targeting of mixed DNA sequences and to thereby investigate the effect of DNA sequence selectivity on drug efficacy. These unsymmetrical polyamides were also synthesized with either dimethylaminopropyl or amidinium termini in order to explore their potential against HIV type 1 and FIV integrase in vitro and in vivo.

Results and Discussion

Compounds **1** and **2** were synthesized by the reported procedure.[12] Subsequent condensation with 3-(dimethylamino)propylamine or 3-aminopropionitrile fumarate in

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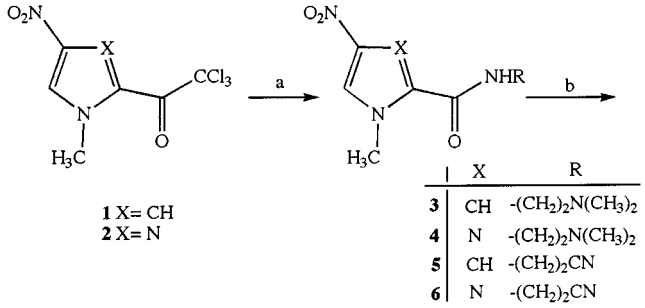
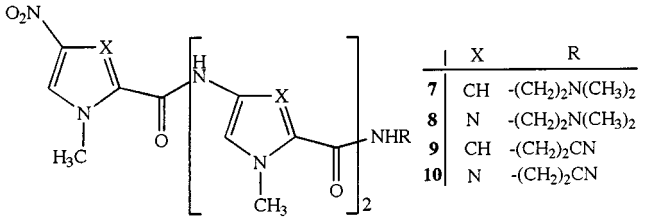
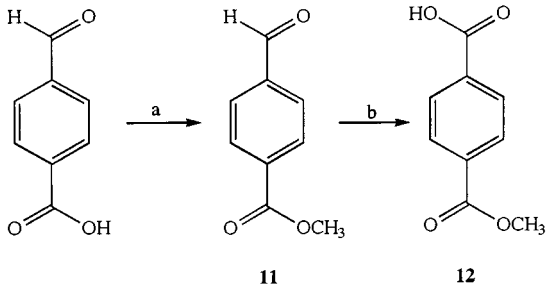




Scheme 1. a = $H_2N(CH_2)_3N(CH_3)_2$ or $H_2NCH_2CH_2CN$·0.5HOOCCH=CHCOOH, THF, 90%; b = H_2, Pd/C, MeOH, **1** or **2**, 80%

THF gave the compounds **3**–**6** (Scheme 1). A Pd/C-facilitated reduction of **3** and coupling with **1** resulted in a dipyrrole unit which was again reduced by Pd/C and coupled with **1** to give **7**. Compounds **8**–**10** were synthesized in a similar manner. Fumaric acid monoethyl ester (**III**) was



Scheme 2. a = $SOCl_2$, MeOH, 90%; b = $NaClO_2$, H_2NSO_3H, H_2O, 80%

commercially available while pyridine-2,5-dicarboxylic acid 5-methyl ester (**IV**) was synthesized by the reported procedure.[13a] Terephthalic acid monomethyl ester was synthesized by a new and convenient strategy (Scheme 2). 4-Carboxybenzaldehyde (available commercially) was converted into the 4-formylbenzoic acid methyl ester (**11**) in 90% yield by reaction with $SOCl_2$ in MeOH. This reaction was followed by sodium chlorite and sulfamic acid-mediated Swern oxidation affording terephthalic acid monomethyl ester (**12**) in 80% yield. This procedure is convenient and straightforward and proceeds with higher yields than the earlier methods.[13b]–[13d] Catalytic reduction of **8** afforded an unstable amine, which was coupled with the acid group of the linker **III**, catalyzed by DCC/HOBt in anhydrous

Table 1. Synthesis of unsymmetrical bispolyamide

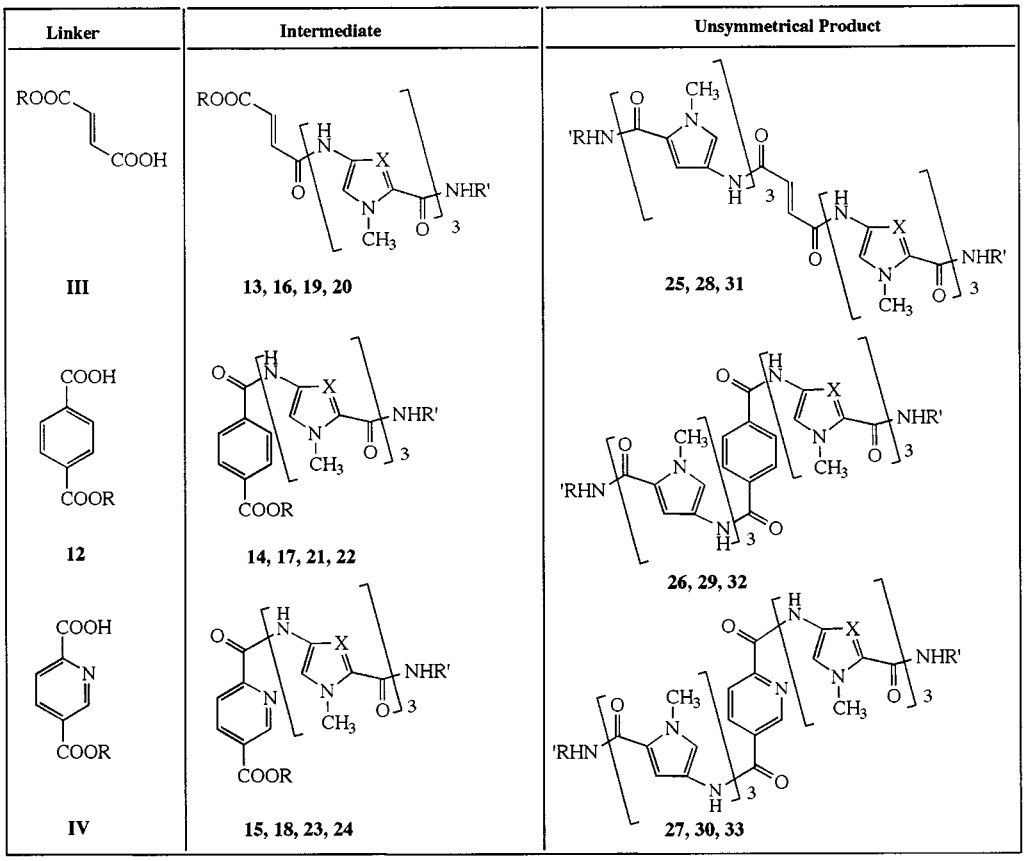


Table 2. Substitution on intermediates and unsymmetrical products

Compound	X	R	R'
13	N	Et	$-(CH_2)_3N(CH_3)_2$
14, 15	N	Me	$-(CH_2)_3N(CH_3)_2$
16	CH	Et	$-(CH_2)_2CN$
17, 18	CH	Me	$-(CH_2)_2CN$
19, 21, 23,	N	H	$-(CH_2)_3N(CH_3)_2$
20, 22, 24	CH	H	$-(CH_2)_2CN$
25, 26, 27	N	-	$-(CH_2)_3N(CH_3)_2$
28, 29, 30	N	-	$-(CH_2)_2CN$
31, 32, 33	N	-	$-(CH_2)_2C(=NH)NH_2$

DMF, to give an intermediate **13** in 40% yield. Intermediates **14** and **15** were synthesized similarly from terephthalic acid monomethyl ester (**12**) and pyridine-2,5-dicarboxylic acid monomethyl ester (**IV**), respectively (Table 1 and 2). However, when the same strategy was applied for coupling the reduced product of **10** with the acid end of the linker **III**, the coupling afforded low yields and, because of the high polarity of the intermediate, it was very difficult to purify, thereby further lowering the overall yield.

Therefore, we reduced compound **9** in a similar way and coupled the resulting amine with the acid functionalities of the linker **III** to afford intermediate **16** in 40% yield. Intermediates **17** and **18** were synthesized similarly by coupling the acid group of the linker terephthalic acid monomethyl ester (**12**) or pyridine-2,5-dicarboxylic acid monomethyl ester (**IV**), respectively. The ester linkages in **13**−**18** were then hydrolyzed with ethanolic sodium hydroxide, and the corresponding sodium salt of the acids were acidified with Dowex-H^+ resin to afford the acid intermediates **19**−**24**. The synthesis of the unsymmetrical polyamides was accomplished by coupling the appropriate unstable amine, obtained from the Pd/C reduction of **7** with the acid functionality of **19**, catalyzed by DCC/HOBt in dry DMF, to give the unsymmetrical imidazo-pyrrolo-bis(polyamide) **25**, bearing a dimethylaminopropyl terminus, in 44% yield. The bis(polyamides) **26** and **27** were synthesised similarly from **21** and **23** respectively (Table 1 and 2). The reduced amine of **10** was similarly coupled with **20** to afford the imidazo-pyrrolo-bis(polyamide) **28**, with a propionitrile terminus, as were **29** and **30** from **22** and **24** coupled with the reduced amine of **10**. Compounds **28**−**30** were subjected to a modified Pinnar reaction[14] to give **31**−**33**, respectively, with natural amidinium termini. Our observations agree with those of Baksheev et al.[14c] that the first step of the reaction of the cyano group, i.e. formation of the imino ester with an alcohol in the presence of hydrogen chloride, is completed in 90 min, and that longer reaction times promote side reactions resulting in lower yields. The imino ester reacts readily with ammonia in ethanolic solution within 1 h at ambient temperature to afford amidinium termini.

Conclusions

Encouraged by the high in vitro potency and selectivity of the symmetrical pyrrolo-bis(polyamides) with unnatural dimethylaminopropyl termini against HIV-1 and HIV-2 integrase, leukemic retrovirus (MuLv) and Okazaki fragments, we designed and synthesised imidazo-pyrrolo-bis(polyamides) **25**−**31** linked by the geometrically constrained linkers **III**, **IV** and **12**. Imidazole in the extended polyamides is incorporated for the first time for the recognition of GC sequences in the minor groove of B-DNA. These unsymmetrical bis(polyamides) are synthesised with the unnatural termini **25**−**27** and also with the natural amidinium termini **31**−**33**. In the course of this work terephthalic acid monomethyl ester (**12**) is synthesised by a new and convenient route. These compounds are currently undergoing biological evaluation at the NIH.

Experimental Section

General: Melting points were determined with an electrothermal melting point apparatus and are uncorrected. All chemicals used were of reagent grade. Dimethylformamide (DMF), methanol (MeOH) and tetrahydrofuran (THF) were of anhydrous grade pro-

cured from Aldrich Chemical Co. and were used without further purification. Freshly distilled dichloromethane was used. − The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, E. Merck TLC plates visualizing under UV light. − ^{1}H NMR spectra were recorded with a Bruker (300 MHz) spectrometer with tetramethylsilane (TMS) as internal standard on the δ scale. Multiplicity of resonance peaks are indicated as singlet (s), broad singlet (br s), doublet (d), quadruplet (q), triplet (t) and multiplet (m). − Mass-spectrometric analysis was performed by positive-mode electrospray ionization with Micromass ZapSpec Hybrid Sector-TOF.

***N*-[3-(Dimethylamino)propyl]-1-methyl-4-nitropyrrole-2-carboxamide (3). − General Procedure:** A solution of 3-dimethylaminopropylamine (0.45 mL, 3.68 mmol) in anhydrous tetrahydrofuran was added slowly to a stirred solution of **1** (1.00 g, 3.68 mmol) at 0 °C and then the temperature of the reaction was raised to room temperature after complete addition. Stirring was continued for an additional 2 h. Evaporation of the solvent and crystallization of the product in hexane/CH_2Cl_2 (3:1, v/v) afforded pure **3**, 96% yield, as pale yellow needles, m.p. 120−122 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.59 (q, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 2.15 (s, 6 H, $N(CH_3)_2$), 2.25 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.15 (dt, *J* = 6.0 Hz, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.95 (s, 3 H, $N-CH_3$), 7.45 (d, *J* = 2.0 Hz, 1 H, Py*H*), 8.15 (d, *J* = 2.0 Hz, 1 H, Py*H*), 8.45 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2$). − ^{13}C NMR ([D$_6$]DMSO): δ = 161.1 (*C*=O), 133.7, 128.1, 123.2, 107.5(Py−C), 56.3 ($NCH_2CH_2CH_2N$), 44.3 [$N(CH_3)_2$], 37.4 ($N-CH_3$), 37.1 ($CH_2CH_2CH_2N$), 26.4 [$CH_2N(CH_3)_2$]. − HRMS: calcd. for $C_{11}H_{19}N_4O_3$ 255.145; found 255.146 (M^+ + H, 100%); calcd. C 51.94, H 7.14, N 22.04; found C 51.97, H 7.15, N 22.10.

The following compounds were prepared using this procedure.

***N*-[3-(Dimethylamino)propyl]-1-methyl-4-nitroimidazole-2-carboxamide (4):** 98% yield, as pale yellow needles, m.p. 132 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.76 (q, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 2.28 [s, 6 H, $N(CH_3)_2$], 2.40 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.15 (dt, *J* = 7.0 Hz, *J* = 6.0 Hz, 2 H, $CH_2CH_2CH_2N$), 4.12 (s, 3 H, $N-CH_3$), 7.75 (s, 1 H, Im 5-*H*), 8.40 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2$). − ^{13}C NMR ([D$_6$]DMSO): δ = 157.5 (*C*=O), 144.2, 137.7, 126.3, (Im−C), 56.5 ($NCH_2CH_2CH_2N$), 44.7 [$N(CH_3)_2$], 37.1 ($CH_2CH_2CH_2N$), 36.4 ($N-CH_3$), 26.5 [$CH_2N(CH_3)_2$]. − HRMS: calcd. for $C_{10}H_{18}N_5O_3$ 256.140; found 256.140 (M^+ + H, 100%); calcd. C 47.03, H 6.72, N 27.44; found C 47.10, H 6.74, N 27.63.

***N*-(2-Cyanoethyl)-1-methyl-4-nitropyrrole-2-carboxamide (5):** Synthesized using 3-aminopropionitrile fumarate in 92% yield, as pale yellow needles, m.p. 118−120 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.75 (t, *J* = 6.0 Hz, 2 H, CH_2CH_2CN), 3.45 (q, 2 H, $NHCH_2CH_2CN$), 3.95 (s, 3 H, NCH_3), 7.45 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.17 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.85 (t, *J* = 6.0 Hz, 1 H, $CO-NHCH_2CH_2CN$). − ^{13}C NMR ([D$_6$]DMSO): δ = 171.3 (*C*=O), 133.7, 128.4, 123.4 (Py−C), 119.3 (*C*N), 107.9 (Py−C), 50.3 ($N-CH_3$), 31.8 (NCH_2CH_2CN), 21.8 (CH_2CH_2CN). − HRMS: calcd. for $C_9H_{11}N_4O_3$ 223.081; found 223.083 (M^+ + H, 100%); calcd. C 48.63, H 4.54, N 25.22; found C 48.64, H 4.57, N 26.23.

***N*-(2-Cyanoethyl)-1-methyl-4-nitroimidazole-2-carboxamide (6):** 90% yield, as pale yellow needles, m.p. 133−135 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.45 (t, *J* = 6.0 Hz, 2 H, CH_2CH_2CN), 3.25 (q, 2 H, $NHCH_2CH_2CN$), 3.85 (s, 3 H, $N-CH_3$), 8.25 (s, 1 H, Im 5-*H*), 8.85 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CN$). − ^{13}C NMR ([D$_6$]DMSO): δ = 157.8 (*C*=O), 143.3, 137.0, 126.3 (Im−C), 119.0 (*C*N), 36.4 ($N-CH_3$), 34.8 (NCH_2CH_2CN), 17.2 (CH_2CH_2CN).− HRMS: calcd. for $C_8H_{10}N_5O_3$ 224.078; found 224.078 (M^+ + H, 100%); calcd. C 41.18, H 8.21, N 30.03; found C 41.15, H 8.30, N 30.09.

***N*-[(3-(Dimethylamino)propyl]-1-methyl-4-[(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]pyrrole-2-carboxamide (7). − General Procedure:** Catalytic hydrogenation using Pd/C (10%, 400 mg) of compound **3** (1.00 g, 378 mmol) in DMF/MeOH (1:1, v/v) afforded an unstable amine which was dried, in order to remove traces of MeOH, and redissolved in dry DMF maintained at 0 °C and a solution of **1** (1.03 g, 378 mmol) in anhydrous THF (10 mL) was added to it slowly. The reaction mixture was slowly brought to room temperature and stirred at this temperature for 18 h. The solvent was removed in vacuo and the residue was purified on silica gel CH_2Cl_2/MeOH/NH_4OH (80:20:0.5).This gave a dipyrrolodicarboxamide intermediate which was again reduced and allowed to react with **1** in a similar way as above to give a crude product of the triamide which was purified on a silica gel column using CH_2Cl_2/MeOH/NH_4OH (80:20:2) as eluent to afford pure **7**, 78% yield, as a yellow powder, m.p. 118−121 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.60 (q, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 2.16 [s, 6 H, $N(CH_3)_2$], 2.28 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.18 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.78 (s, 3 H, $N-CH_3$), 3.86 (s, 3 H, $N-CH_3$), 3.90 (s, 3 H, $N-CH_3$), 6.84 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.04 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.14 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.20 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.25 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.38 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.09 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 9.90 (s, 1 H, CON*H*), 10.02 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 161.1, 158.3, 156.9 (*C*=O), 133.7, 128.1, 126.2, 123.0, 122.9, 122.0, 121.4, 118.5, 117.8, 107.6, 104.5, 104.1 (Py−C), 56.4 ($NCH_2CH_2CH_2N$), 44.2 [$N(CH_3)_2$], 37.4 ($N-CH_3$), 36.7 ($CH_2CH_2CH_2N$), 36.1, 35.9 ($N-CH_3$), 26.4 [$CH_2N(CH_3)_2$]. − HRMS: calcd. for $C_{23}H_{31}N_8O_5$ 499.241; found 499.241 (M^+ + H, 100%); calcd. C 55.40, H 6.07, N 22.48; found C 55.9, H 6.13, N 22.53.

The following compounds were prepared in a similar way.

***N*-[(3-(Dimethylamino)propyl]-1-methyl-4-[(1-methyl-4-nitroimidazole-2-carboxamido)imidazole-2-carboxamido]imidazole-2-carboxamide (8):** 80% yield, as a yellow powder, m.p. 212−215 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.70 (q, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 2.25 [s, 6 H, $N(CH_3)_2$], 2.40 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.26 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.96 (s, 3 H, $N-CH_3$), 4.05 (s, 3 H, $N-CH_3$), 4.07 (s, 3 H, $N-CH_3$), 7.50 (s, 1 H, Im 5-*H*), 7.68 (s, 1 H, Im 5-*H*), 8.40 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 8.65 (s, 1 H, Im 5-*H*), 9.70 (s, 1 H, CON*H*), 10.30 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 158.6, 155.5, 155.3 (*C*=O), 144.6, 137.3, 135.0, 134.8, 134.7, 133.7, 127.0, 116.1, 113.8 (Im−C), 56.9 ($NCH_2CH_2CH_2N$), 45.0 [$N(CH_3)_2$], 37.1 ($CH_2CH_2CH_2N$), 36.6, 35.4, 35.3 ($N-CH_3$), 26.9 [$CH_2N-(CH_3)_2$]. − HRMS: calcd. for $C_{20}H_{28}N_{11}O_5$ 502.227; found 502.227 (M^+ + H, 100%); calcd. C 47.88, H 5.43, N 30.73; found C 47.90, H 5.50, N 30.90.

***N*-(2-Cyanoethyl)-1-methyl-4-[(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]pyrrole-2-carboxamide (9):** 75% yield, as a yellow powder, m.p. 284−287 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.75 (t, *J* = 6.0 Hz, 2 H, CH_2CH_2CN), 3.45 (q, 2 H, $NHCH_2CH_2CN$), 3.81 (s, 3 H, NCH_3), 3.91 (s, 3 H, $N-CH_3$), 4.00 (s, 3 H, NCH_3), 6.92 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.15 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.22 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.31 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.60 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.21 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.25 (t, *J* = 6.0 Hz, 1 H,

CON*H*CH_2CH_2−CN), 9.95 (s, 1 H, CON*H*), 10.23 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 175.7, 172.6, 171.2 (*C*=O), 148.0, 142.4, 140.5, 137.2, 136.5, 136.4, 135.7, 133.6, 132.9, 132.6, 121.8, 118.9 (Py−C), 118.8 (*C*N), 51.7, 50.4, 50.2 (N−CH_3), 31.9 (N*C*H_2CH_2CN), 22.7 (CH_2*C*H_2CN). − HRMS: calcd. for $C_{21}H_{23}N_8O_5$ 467.1791; found 467.1788 (M^+ + H, 100%); calcd. C 54.06, H 4.76, N 24.03; found C 54.09, H 4.81, N 25.01.

***N*-(2-Cyanoethyl)-1-methyl-4-[(1-methyl-4-nitroimidazole-2-carboxamido)imidazole-2-carboxamido]imidazole-2-carboxamide (10):** 77% yield, as a yellow powder, m.p. 269−271 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.79 (t, *J* = 6.0 Hz, 2 H, CH_2C*H*$_2$CN), 3.49 (q, 2 H, NH−C*H*$_2CH_2$CN), 3.99 (s, 3 H, N−C*H*$_3$), 4.01 (s, 3 H, N−C*H*$_3$), 4.05 (s, 3 H, NC*H*$_3$), 7.55 (s, 1 H, Im 5-*H*), 7.65 (s, 1 H, Im 5-*H*), 8.55 (t, *J* = 6.0 Hz, 1 H, CON*H*CH_2CH_2CN), 8.65 (s, 1 H, Im 5-*H*), 9.55 (s, 1 H, CON*H*), 10.65 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 157.6, 155.2, 155.0 (*C*=O), 144.3, 137.0, 134.8, 134.6, 133.8, 133.4 (Im−C), 119.1 (*C*N), 116.8, 113.8, 113.1 (Im−C), 36.6 (N−CH_3), 35.2 (N*C*H_2CH_2CN), 17.4 (CH_2*C*H_2CN). − HRMS: calcd. for $C_{18}H_{20}N_{11}O_5$ 470.1648; found 470.1663 (M^+ + H, 100%); calcd. C 46.04, H 4.08, N 32.83; found C 46.14, H 4.10, N 32.89.

Methyl 4-Formylbenzoate (11): To 4-formylbenzoic acid (1.00 g, 7.24 mmol) in dry methanol (200 mL) thionyl chloride (6.00 mL, 7.24 mmol) was added dropwise at 0 °C until all of the compound dissolved. The reaction mixture was slowly brought to room temperature and then stirred for 2 h. The solvent was removed in vacuo, by coevaporation with dichloromethane (2 × 100 mL) to remove the excess of thionyl chloride to afford **11**, 90% yield, m.p. 64−65 °C (ref.[13d] 61−63 °C). −^{1}H NMR ([D$_6$]DMSO): δ = 4.00 (s, 3 H, ArCOOC*H*$_3$), 7.95 (d, *J* = 10 Hz, 2 H, Ar*H*), 8.15 (d, 2 H, *J* = 10 Hz, Ar*H*), 10.05 (s, 1 H, ArC*H*O). − ^{13}C NMR ([D$_6$]DMSO): δ = 52.7 (O*C*H$_3$), 129.7 (C-2, C-6), 129.6 (C-3, C-5), 134.2 (C-4), 134.8 (C-1), 165.5 (Ar*C*OOCH$_3$), 192.6 (*C*HO). − EI; *m*/*z* (%): 164.04 (33.45), 149.02 (100.00), 133.02 (53.26), 121.02 (19.54), 105.03 (15.16), 77.03 (12.73), 65.03 (18.62), 51.02 (11.56). − $C_9H_8O_3$: calcd. C 65.85, H 4.91, found C 65.79, H 4.97.

Methyl Terephthalate (12): To a solution of **11** (150 mg, 0.91 mmol) and sulfamic acid (150 mg, 1.09 mmol) in water (10 mL) was added a solution of sodium chlorite (98 mg, 1.09 mmol) in water (1 mL). The reaction mixture was stirred at room temperature for 1 h. The acid precipitated was collected to afford **12,** 80% yield, m.p. 218−220 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.95 (s, 3 H, ArCOOC*H*$_3$), 4.5−5.00 (br s, 1 H, ArCOO*H*), 8.03 (d, 4 H, Ar*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 52.3 (O*C*H$_3$), 129.7 (C-2, C-6), 129.6 (C-3, C-5), 133.3 (C-4), 134.7 (C-1), 165.5 (Ar*C*OOCH$_3$), 167.8 (*C*OOH). − EI; *m*/*z* (%): 180.04 (25.29), 149.02 (78.42), 133.02 (10.50), 121.02 (19.09), 104.02 (8.88), 76.03 (19.45), 69.13 (100.00), 51.02 (10.88). − $C_9H_8O_4$: calcd. C 60.0, H 4.48, found C 61.2, H 4.83.

Fumaramide 13. − General Procedure: Catalytic hydrogenation using Pd/C (10%, 0.15 g) of compound **8** (0.28 g, 0.56 mmol) in DMF/MeOH (1:1, v/v, 15 mL) afforded an unstable amine which was dried, in order to remove traces of MeOH, and redissolved in dry DMF (10 mL). Then fumaric acid monoethyl ester (81 mg, 0.56 mmol) and 1-hydroxybenzotriazole (108 mg, 0.79 mmol) were added to this solution, followed by the addition of a solution of 1,3-dicyclohexylcarbodiimide (166 mg, 0.79 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred at room temperature for 18 h under argon. TLC examination of the reaction mixture at this time showed the formation of the product. The solvent was removed in vacuo and the residue was purified on a silica gel column using CH_2Cl_2/MeOH/NH_4OH (80:20:2) as eluent to give **13**, 44.5% yield as yellow powder, m.p. 208−210 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.30 (t, *J* = 7.0 Hz, 3 H, $COOCH_2C$*H*$_3$), 1.76 (q, *J* = 7.0 Hz, 2 H, CH_2C*H*$_2CH_2$N), 2.42 [s, 6 H, N(C*H*$_3$)$_2$], 2.60 (t, *J* = 7.0 Hz, 2 H, CH_2CH_2C*H*$_2$N), 3.28 (t, *J* = 7.0 Hz, 2 H, C*H*$_2CH_2CH_2$N), 3.90 (s, 3 H, NC*H*$_3$), 4.05 (s, 3 H, NC*H*$_3$), 4.07 (s, 3 H, NC*H*$_3$), 4.20 (q, *J* = 7.0 Hz, 2 H, $COOCH_2CH_3$), 6.72 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 7.30 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 7.55 (s, 1 H, Im 5-*H*), 7.68 (s, 1 H, Im 5-*H*), 7.70 (s, 1 H, Im 5-*H*), 8.44 (t, *J* = 6.0 Hz, 1 H, CON*H*$CH_2CH_2CH_2$N), 9.68 (s, 1 H, CON*H*), 9.78 (s, 1 H, CON*H*), 11.14 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 164.5, 165.3, 158.6, 155.5, 155.3 (*C*=O), 144.6, 137.3, 135.0, 134.8, 134.7, 133.7 (Im−C), 134.5, 132.6 (*C*H=*C*H), 127.0, 116.1, 113.8 (Im−C), 60.9 (CO*C*H_2CH_3), 56.9 (N*C*$H_2CH_2CH_2$N), 45.0 [N(*C*H$_3$)$_2$], 37.1 (CH_2*C*H_2CH_2N), 36.6, 35.4, 35.3 (N−CH_3), 26.9 [*C*H_2N(CH$_3$)$_2$], 13.9 (CH_2*C*H$_3$). − HRMS: calcd. for $C_{26}H_{36}N_{11}O_6$ 598.284; found 598.286 (M^+ + H, 100%); calcd. C 52.24, H 5.91, N 25.79; found C 52.31, H 4.14, N 25.81.

The following compounds were prepared by this method.

Benzamide 14: 40% yield, as a yellow powder, m.p. 222−225 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.76 (q, *J* = 7.0 Hz, 2 H, CH_2C*H*$_2CH_2$N), 2.24 (t, *J* = 7.0 Hz, 2 H, CH_2CH_2C*H*$_2$N), 2.30 [s, 6 H, N(C*H*$_3$)$_2$], 3.20 (t, *J* = 7.0 Hz, 2 H, C*H*$_2CH_2CH_2$N), 3.92 (s, 3 H, NC*H*$_3$), 3.95 (s, 3 H, ArC−OOC*H*$_3$), 4.00 (s, 3 H, N−C*H*$_3$), 4.05 (s, 3 H, N−C*H*$_3$), 7.55 (s, 1 H, Im 5-*H*), 7.66 (s, 1 H, Im 5-*H*), 7.68 (s, 1 H, Im 5-*H*), 8.12 (dd, *J* = 10 Hz, 4 H, phenylic H), 8.40 (t, *J* = 6.0 Hz, 1 H, CON*H*−*C*$H_2CH_2CH_2$N), 9.65 (s, 1 H, CON*H*), 9.75 (s, 1 H, CON*H*), 11.02 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 167.7, 167.8, 158.6, 155.5, 155.3 (*C*=O), 144.7, 137.2, 135.0, 134.9, 134.7, 133.5 (Im−C), 133.3 (Ar C-4), 133.5 (ArC-1), 129.6 (ArC-2 and C-6), 129.4 (ArC-3 and C-5), 127.3, 116.3, 113.5 (Im−C), 56.4 (N*C*$H_2CH_2CH_2$N), 52.5 (O*C*H$_3$), 45.2 [N(*C*H$_3$)$_2$], 37.3 (CH_2*C*H_2CH_2N), 36.7, 35.3, 35.2 (N−CH_3), 26.4 [*C*H_2−N(CH$_3$)$_2$]. − HRMS: calcd. for $C_{29}H_{36}N_{11}O_6$ 634.284; found 634.284 (M^+ + H, 100%); calcd. C 54.95, H 5.57, N 24.32; found C 54.93, H 5.63, N 24.37.

Pyridinecarboxamide 15: 39% yield, as a yellow powder, m.p. 241−244 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.08 (q, *J* = 7.0 Hz, 2 H, CH_2C*H*$_2CH_2$N), 2.84 [s, 6 H, N(C*H*$_3$)$_2$], 3.15 (t, *J* = 7.0 Hz, 2 H, CH_2−CH_2C*H*$_2$N), 3.48 (t, *J* = 7.0 Hz, 2 H, C*H*$_2CH_2CH_2$N), 3.92 (s, 3 H, NC*H*$_3$), 3.95 (s, 3 H, ArCOOC*H*$_3$), 4.10 (s, 3 H, N−C*H*$_3$), 4.15 (s, 3 H, N−C*H*$_3$), 7.24 (s, 1 H, Im 5-*H*), 7.40 (s, 1 H, Im 5-*H*), 7.42 (s, 1 H, Im 5-*H*), 8.35 (d, *J* = 7.0 Hz, 1 H, pyridyl 3-*H*), 8.40 (t, *J* = 6.0 Hz, 1 H, CON*H*$CH_2CH_2CH_2$N), 8.75 (dd, *J* = 7.0 Hz and *J* = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.34 (d, *J* = 2.0 Hz, 1 H, pyridyl 6-*H*), 9.65 (s, 1 H, CON*H*), 9.75 (s, 1 H, CON*H*), 11.02 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 165.7, 164.3, 158.6, 155.5, 155.3 (*C*=O), 144.7, 137.0, 135.2, 134.9, 134.7, 133.3 (Im−C), 151.4, 150.1, 138.5, 129.1, 124.6 (pyridyl *C*), 127.3, 116.3, 113.3 (Im−C), 56.4 (N*C*$H_2CH_2CH_2$N), 53.8 (O*C*H$_3$), 45.2 [N(*C*H$_3$)$_2$], 37.2 (CH_2*C*H_2CH_2N), 36.2, 35.3, 35.2 (N−CH_3), 26.4 [*C*H_2N(CH$_3$)$_2$]. − HRMS: calcd. for $C_{28}H_{34}N_{12}O_6$ 635.280; found 635.281 (M^+ + H, 100%); calcd. C 52.97, H 5.40, N 26.49; found C 52.99, H 5.45, N 26.63.

Fumaramide 16: 47% yield, as a yellow powder, m.p. 223−225 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.30 (t, *J* = 7.0 Hz, 3 H, CO-OCH_2C*H*$_3$), 2.75 (t, *J* = 6.0 Hz, 2 H, CH_2C*H*$_2$CN), 3.45 (q, 2 H, NHC*H*$_2CH_2$CN), 3.81 (s, 3 H, N−C*H*$_3$), 3.91 (s, 3 H, N−C*H*$_3$), 4.00 (s, 3 H, N−C*H*$_3$), 4.20 (q, *J* = 7.0 Hz, 2 H, $COOCH_2$−CH_3), 6.72 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 6.92 (d, *J* = 2.0 Hz, 1 H,

Py−*H*), 7.15 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.22 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.30 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 7.31 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.60 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.21 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.25 (t, *J* = 6.0 Hz, 1 H, CON*H*−*C*H$_2$CH$_2$CN), 9.95 (s, 1 H, CON*H*), 10.23 (s, 1 H, CON*H*), 11.02 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 165.6, 165.5, 164.3, 158.5, 155.4 (*C*=O), 148.0, 142.4, 140.5, 137.4, 136.8, 136.4, 135.7 (Py−*C*), 134.6, 134.3 (*C*H=*C*H), 133.6, 132.9, 132.6, 121.6, 119.6 (Py−C), 119.8 (*C*N), 60.8 (CO*C*H$_2$CH$_3$), 51.7, 51.4, 50.4 (N−CH$_3$), 32.6 (N*C*H$_2$CH$_2$CN), 22.8 (CH$_2$*C*H$_2$CN), 13.8 (COCH$_2$*C*H$_3$). − HRMS: calcd. for $C_{27}H_{31}N_8O_6$ 563.235; found 563.237 (M^+ + H, 100%); calcd. C 57.63, H 5.38, N 19.93; found C 56.93, H 5.41, N 20.01.

Benzamide 17: 44% yield, as a yellow powder, m.p. 219−223 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.78 (t, *J* = 6.0 Hz, 2 H, CH$_2$C*H*$_2$CN), 3.49 (q, 2 H, NHC*H*$_2$CH$_2$CN), 3.83 (s, 3 H, N−C*H*$_3$), 3.92 (s, 3 H, N−C*H*$_3$), 3.97 (s, 3 H, ArCOOC*H*$_3$), 4.05 (s, 3 H, N−C*H*$_3$), 6.93 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.20 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.21 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.37 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.65 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.15 (dd, *J* = 10 Hz, 4 H, phenylic), 8.22 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.25 (t, *J* = 6.0 Hz, 1 H, CON*H*CH$_2$CH$_2$CN), 10.01 (s, 1 H, CON*H*), 10.23 (s, 1 H, CON*H*), 11.05 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 164.7, 164.5, 165.2, 158.5, 155.3 (*C*=O), 148.0, 142.4, 140.3, 137.2, 136.5, 136.4, 135.7, 133.6, 132.6, 132.4 (Py−*C*), 133.3, 132.1, 129.6, 129.4 (Ar−*C*), 121.3, 118.9 (Py−C), 118.8 (*C*N), 52.6 (O*C*H$_3$), 51.7, 50.4, 50.2 (N−CH$_3$), 31.9 (N*C*H$_2$CH$_2$CN), 22.7 (CH$_2$*C*H$_2$CN). − HRMS: calcd. for $C_{30}H_{31}N_8O_6$ 599.235; found 599.234 (M^+ + H, 100%); calcd. C 60.18, H 5.05, N 18.73; found C 60.67, H 4.95, N 17.93.

Pyridinecarboxamide 18: 37% yield, as a yellow powder, m.p. 267−271 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.77 (t, *J* = 6.0 Hz, 2 H, CH$_2$C*H*$_2$CN), 3.43 (q, 2 H, NHC*H*$_2$CH$_2$CN), 3.78 (s, 3 H, N−C*H*$_3$), 3.91 (s, 3 H, N−C*H*$_3$), 3.99 (s, 3 H, ArCOOC*H*$_3$), 4.05 (s, 3 H, N−C*H*$_3$), 6.93 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.15 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.29 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.35 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.65 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.25 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.27 (t, *J* = 6.0 Hz, 1 H, CON*H*−*C*H$_2$CH$_2$CN), 8.39 (d, *J* = 7.0 Hz, 1 H, pyridyl 3-*H*), 8.79 (dd, *J* = 7.0 Hz, *J* = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.38 (d, *J* = 2.0 Hz, 1 H, pyridyl 6-*H*), 10.01 (s, 1 H, CON*H*), 10.27 (s, 1 H, CON*H*), 11.15 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 164.6, 165.5, 164.3, 158.5, 155.4 (*C*=O), 151.3, 150.2, 137.3, 129.2, 124.6 (pyridyl *C*), 148.0, 142.3, 140.5, 137.2, 136.5, 136.4, 135.7, 133.6, 132.9, 132.6, 121.8, 118.9 (Py−C), 118.8 (*C*N), 53.6 (O*C*H$_3$), 51.7, 50.4, 50.2 (N−CH$_3$), 31.9 (N*C*H$_2$CH$_2$CN), 22.7 (CH$_2$*C*H$_2$CN). − HRMS: calcd. for $C_{29}H_{30}N_9O_6$ 600.231 found 600.231 (M^+ + H, 100%); calcd. C 58.08, H 4.88, N 21.03; found C 58.02, H 4.79, N 20.97.

Fumaramide 19. − General Procedure: An ethanolic solution of **13** (0.10 g, 0.16 mmol) was treated with 1 N aqueous sodium hydroxide (4 mL), and the mixture was stirred at reflux for 18 h. A chromatographic examination of this reaction mixture showed the formation of the corresponding sodium salt of the acid and complete disappearance of the ester. The solvent was removed in vacuo, the residue was dissolved in water (30 mL) and acidified to pH = 2 using Dowex-H$^+$ resin. The resin was collected and the aqueous phase was freeze-dried to afford 80 mg of **19**, 89% yield, as a yellow solid, m.p. 208−210 °C (dec.). − ^{1}H NMR ([D$_6$]DMSO): δ = 1.80 (q, *J* = 7.0 Hz, 2 H, CH$_2$C*H*$_2$CH$_2$N), 2.42 [s, 6 H, N(C*H*$_3$)$_2$], 2.75 (t, *J* = 7.0 Hz, 2 H, CH$_2$CH$_2$C*H*$_2$N), 3.22 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_2$CH$_2$N), 3.92 (s, 3 H, N−C*H*$_3$), 4.00 (s, 3 H, N−C*H*$_3$), 4.03 (s, 3 H, N−C*H*$_3$), 4.00−5.00 (br s, 1 H, ArCOO*H*), 6.66 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 7.06 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 7.20 (s, 1 H, Im 5-*H*), 7.65 (s, 1 H, Im 5-*H*), 7.68 (s, 1 H, Im 5-*H*), 8.40 (t, *J* = 6.0 Hz, 1 H, CON*H*CH$_2$CH$_2$CH$_2$N), 9.65 (s, 1 H, CON*H*), 9.75 (s, 1 H, CON*H*), 11.00 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 164.6, 165.3, 158.7, 155.4, 155.3 (*C*=O), 144.5, 137.3, 135.0, 134.6, 134.5, 133.7 (Im−C), 134.5, 132.6 (*C*H=*C*H), 127.2, 116.3, 113.4 (Im−C), 56.9 (N*C*H$_2$CH$_2$CH$_2$N), 45.2 [N(*C*H$_3$)$_2$], 37.3 (CH$_2$*C*H$_2$CH$_2$N), 36.6, 35.5, 35.4 (N−CH$_3$), 26.8 [*C*H$_2$N(CH$_3$)$_2$]. − HRMS: calcd. for $C_{24}H_{32}N_{11}O_6$ 570.252; found 570.251 (M^+ + H, 100%); calcd. C 50.59, H 5.49, N 27.06; found C 50.27, H 5.34, N 26.89.

The following compounds were prepared by this procedure.

Fumaramide 20: 86% yield, as light yellow solid, m.p. 265−269 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.75 (t, *J* = 6.0 Hz, 2 H, CH$_2$C*H*$_2$CN), 3.48 (q, 2 H, NHC*H*$_2$CH$_2$CN), 3.82 (s, 3 H, N−C*H*$_3$), 3.87 (s, 3 H, N−C*H*$_3$), 4.03 (s, 3 H, N−C*H*$_3$), 4.35−5.12 (s, 1 H, CHCOO*H*), 6.74 (d, *J* = 1.5 Hz, 1 H, vinylic C*H*), 6.89 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.10 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.25 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.32 (d, *J* = 1.5 Hz, 1 H vinylic C*H*), 7.33 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.59 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.26 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.29 (t, *J* = 6.0 Hz, 1 H, CON*H*CH$_2$CH$_2$CN), 9.98 (s, 1 H, CON*H*), 10.27 (s, 1 H, CON*H*), 11.07 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 165.6, 165.4, 164.3, 158.7, 155.4 (*C*=O), 148.1, 142.4, 140.2, 137.4, 136.8, 136.4, 135.7 (Py−*C*), 134.4, 134.3 (*C*H=*C*H), 133.4, 132.9, 132.4, 121.6, 119.5 (Py−C), 119.8 (*C*N), 51.7, 51.4, 50.4 (N−CH$_3$), 32.4 (N*C*H$_2$CH$_2$CN), 22.6 (CH$_2$*C*H$_2$CN). − HRMS: calcd. for $C_{25}H_{27}N_8O_6$ 535.204; found 535.207 (M^+ + H, 100%); calcd. C 56.16, H 4.91, N 20.97; found C 55.13, H 4.67, N 20.57.

Benzamide 21: 90% yield, as a yellow solid, m.p. 227−229 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.70 (q, *J* = 7.0 Hz, 2 H, CH$_2$C*H*$_2$CH$_2$N), 2.26 (t, *J* = 7.0 Hz, 2 H, CH$_2$CH$_2$C*H*$_2$N), 2.35 [s, 6 H, N(C*H*$_3$)$_2$], 3.25 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_2$CH$_2$N), 3.98 (s, 3 H, N−C*H*$_3$), 4.01 (s, 3 H, N−C*H*$_3$), 4.05 (s, 3 H, N−C*H*$_3$), 4.15−5.00 (s, 1 H, ArCOO*H*), 7.57 (s, 1 H, Im 5-*H*), 7.68 (s, 1 H, Im 5-*H*), 7.73 (s, 1 H, Im 5-*H*), 8.15 (dd, *J* = 10 Hz, 4 H, phenylic), 8.42 (t, *J* = 6.0 Hz, 1 H, CON*H*CH$_2$CH$_2$CH$_2$N), 9.71 (s, 1 H, CON*H*), 9.75 (s, 1 H, CON*H*), 11.05 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 167.7, 167.4, 158.5, 155.5, 155.1 (*C*=O), 144.6, 137.2, 135.1, 134.7, 134.6, 133.5 (Im−C), 133.3, 133.5, 129.6, 129.4 (Ar−*C*), 127.3, 116.3, 113.4 (Im−C), 56.2 (N*C*H$_2$CH$_2$CH$_2$N), 45.4 [N(*C*H$_3$)$_2$], 37.2 (CH$_2$*C*H$_2$CH$_2$N), 36.7, 35.4, 35.2 (N−CH$_3$), 26.3 [*C*H$_2$N(CH$_3$)$_2$]. − HRMS: calcd. for $C_{28}H_{34}N_{11}O_6$ 620.268; found 620.270 (M^+ + H, 100%); calcd. C 54.26, H 5.37, N 24.87; found C 53.97, H 4.99, N 24.67.

Benzamide 22: 80% yield, as a light brown solid, m.p. 281−283 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.75 (t, *J* = 6.0 Hz, 2 H, CH$_2$C*H*$_2$CN), 3.46 (q, 2 H, NHC*H*$_2$CH$_2$CN), 3.87 (s, 3 H, N−C*H*$_3$), 3.93 (s, 3 H, N−C*H*$_3$), 4.05 (s, 3 H, N−C*H*$_3$), 4.13 (s, 1 H, ArCOO*H*), 6.96 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.18 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.27 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.34 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.64 (d, *J* = 2.0−Hz, 1 H, Py−*H*), 8.15 (dd, *J* = 10 Hz, 4 H, phenylic), 8.17 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.22 (t, *J* = 6.0 Hz, 1 H, CON*H*CH$_2$CH$_2$CN), 9.93 (s, 1 H, CON*H*), 10.17 (s, 1 H, CON*H*), 11.05 (s, 1 H, CON*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 164.6, 164.5, 165.1, 158.4, 155.3 (*C*=O), 148.2, 142.4, 140.3, 137.2, 136.5, 136.2, 135.7, 133.6, 132.5, 132.4 (Py−*C*), 133.2, 132.1, 129.6, 129.4 (Ar−*C*), 121.4, 118.9 (Py−C), 118.8 (*C*N), 51.4, 50.4, 50.3 (N−CH$_3$), 31.6 (N*C*H$_2$CH$_2$CN), 22.6 (CH$_2$*C*H$_2$CN). − HRMS: calcd. for $C_{29}H_{29}N_8O_6$ 585.220; found

585.223 (M^+ + H, 100%); calcd. C 59.57, H 4.83, N 19.18; found C 58.98, H 4.64, N 19.01.

Pyridinecarboxamide 23: 75% yield, as a yellow solid, m.p. 245−247 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.06 (q, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 2.73 [s, 6 H, $N(CH_3)_2$], 3.20 [t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N(CH_3)_2$], 3.48 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2N$), 3.96 (s, 3 H, $N-CH_3$), 4.02 (s, 3 H, $N-CH_3$), 4.05 (s, 3 H, $N-CH_3$), 4.15−5.00 (s, 1 H, ArCOO*H*), 7.26 (s, 1 H, Im 5-*H*), 7.48 (s, 1 H, Im 5-*H*), 7.48 (s, 1 H, Im 5-*H*), 8.31 (d, *J* = 7.0 Hz, 1 H, pyridyl 3-*H*), 8.39 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 8.76 (dd, 7.0 Hz and *J* = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.34 (d, *J* = 2.0 Hz, 1 H, pyridyl 6-*H*), 9.68 (s, 1 H, CONH), 9.72 (s, 1 H, CONH), 11.14 (s, 1 H, CONH). − ^{13}C NMR ([D$_6$]DMSO): δ = 165.6, 164.3, 158.4, 155.5, 155.2 (*C*=O), 144.6, 137.0, 135.2, 134.8, 134.7, 133.2 (Im−C), 151.4, 150.1, 138.6, 129.1, 124.4 (pyridyl *C*), 127.3, 116.3, 113.2 (Im−C), 56.2 ($NCH_2CH_2CH_2N$), 45.3 [$N(CH_3)_2$], 37.2 ($CH_2CH_2CH_2N$), 36.2, 35.4, 35.2 ($N-CH_3$), 26.3 [$CH_2N(CH_3)_2$]. − HRMS: calcd. for $C_{27}H_{33}N_{12}O_6$ 621.263; found 621.265 (M^+ + H, 100%); calcd. C 52.24, H 5.20, N 27.09; found C 51.97, H 4.99, N 28.89.

Pyridinecarboxamide 24: 73% yield, as a light brown solid, m.p. > 300 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.73 (t, *J* = 6.0 Hz, 2 H, CH_2CH_2CN), 3.43 (q, 2 H, $NHCH_2CH_2CN$), 3.79 (s, 3 H, $N-CH_3$), 3.95 (s, 3 H, $N-CH_3$), 4.03 (s, 3 H, $N-CH_3$), 4.50 (s, 1 H, ArCOO*H*), 6.94 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.09 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.20 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.31 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.58 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.26 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 8.29 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CN$), 8.30 (d, *J* = 7.0 Hz, 1 H, pyridyl 3-*H*), 8.72 (dd, 7.0 Hz and *J* = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.32 (d, *J* = 2.0 Hz, 1 H, pyridyl 6-*H*), 9.97 (s, 1 H, CONH), 10.21 (s, 1 H, CONH), 11.04 (s, 1 H, CONH). − ^{13}C NMR ([D$_6$]DMSO): δ = 164.7, 165.6, 164.3, 158.3, 155.4 (*C*=O), 151.3, 150.5, 137.3, 129.2, 124.6 (pyridyl *C*), 148.0, 142.2, 140.5, 137.2, 136.5, 136.4, 135.4, 133.6, 132.9, 132.6, 121.8, 119.6 (Py−C), 119.8 (*C*N), 51.7, 50.2, 50.2 ($N-CH_3$), 31.9 (NCH_2CH_2CN), 22.7 (CH_2CH_2CN). − HRMS: calcd. for $C_{28}H_{28}N_8O_6$ 571.212; found 572.210 (M^+ + H, 100%); calcd. C 58.82, H 4.76, N 19.61; found C 57.98, H 4.39, N 19.23.

Dicarboxamide 25. − General Procedure: Compound **7** (55 mg, 0.11 mmol) was dissolved in DMF/methanol (1:1, v/v, 5 mL) and hydrogenated in the presence of Pd/C (10%, 25 mg). The catalyst was removed by filtration, washed with methanol and dried in high vacuum in order to remove traces of methanol. The dried amino compound was mixed with compound **19** (63 mg, 0.11 mmol) and 1-hydroxybenzotriazole (21 mg, 0.15 mmol) in DMF (15 mL). This procedure was followed by the addition of a solution of 1,3-dicyclohexylcarbodiimide (31 mg, 0.15 mmol) in DMF (1 mL). The stirring was continued at room temperature for 18 h under argon. TLC examination after 18 h confirmed formation of the product. The solvent was removed in vacuo and the crude product was purified on a silica gel column using CH_2Cl_2/MeOH/NH_4OH (8.0:2.0:0.2) as eluent to afford pure **25**; 44% yield, as a yellow powder, m.p. 195−198 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.64 (q, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2-CH_2N$), 2.12 [s, 12 H, 2 × $N(CH_3)_2$], 2.24 (t, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2CH_2N$), 3.20 (dt, *J* = 6.0 Hz, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2CH_2N$), 3.82 (s, 3 H, $N-CH_3$), 3.85 (s, 3 H, $N-CH_3$), 3.87 (s, 3 H, $N-CH_3$), 3.91 (s, 3 H, $N-CH_3$), 3.95 (s, 3 H, $N-CH_3$), 4.02 (s, 3 H, $N-CH_3$), 6.82 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 6.95 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.05 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.20 (m, 3 H, 1 H, Py−*H* and 2 H, C*H*=C*H*), 7.28 (d, *J* = 2.0 Hz, H, Py−*H*), 7.36 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.52 (s, 1 H, Im 5-H), 7.66 (s, 1 H, Im 5-H), 7.76 (s, 1 H, Im 5-H), 8.08 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 8.48 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 9.68 (s, 1 H, CONH), 9.76 (s, 1 H, CONH), 9.80 (s, 1 H, CONH), 9.90 (s, 1 H, CONH), 10.00 (s, 1 H, CONH), 11.06 (s, 1 H, CONH). − HRMS: calcd. for $C_{47}H_{62}N_{19}O_8$ 1020.502; found 1020.501 (M^+ + H, 100%).

The following compounds were prepared by this procedure.

Benzene Derivative 26: 47% yield, as a yellow powder, mp. 205−207 °C. −^{1}H NMR ([D$_6$]DMSO): δ = 1.67 (q, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2-CH_2N$), 2.20 [s, 12 H, 2 × $N(CH_3)_2$], 2.24 (t, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2CH_2N$), 3.25 (dt, *J* = 6.0 Hz, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2CH_2N$), 3.85 (s, 3 H, $N-CH_3$), 3.85 (s, 3 H, $N-CH_3$), 3.90 (s, 3 H, $N-CH_3$), 3.93 (s, 3 H, $N-CH_3$), 3.95 (s, 3 H, $N-CH_3$), 4.10 (s, 3 H, $N-CH_3$), 6.85 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 6.95 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.08 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.25 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.28 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.39 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.52 (s, 1 H, Im 5-*H*), 7.72 (s, 1 H, Im 5-*H*), 7.76 (s, 1 H, Im 5-*H*), 8.10 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 8.15 (dd, *J* = 10 Hz, 4 H, phenylic), 8.40 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 9.73 (s, 1 H, CONH), 9.76 (s, 1 H, CONH), 9.89 (s, 1 H, CONH), 9.90 (s, 1 H, CONH), 10.15 (s, 1 H, CONH), 11.06 (s, 1 H, CONH). − HRMS: calcd. for $C_{51}H_{64}N_{19}O_8$ 1070.517; found 1070.515 (M^+ + H, 100%).

Pyridine Derivative 27: 40% yield, as a light yellow fluffy solid, m.p. 227−230 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.70 (q, *J* = 7.0 Hz, 4 H, 2 × $CH_2-CH_2CH_2N$), 2.25 [s, 12 H, 2 × $N(CH_3)_2$], 2.38 (t, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2CH_2N$), 3.21 (dt, *J* = 6.0 Hz, *J* = 7.0 Hz, 4 H, 2 × $CH_2CH_2CH_2N$), 3.88 (s, 3 H, $N-CH_3$), 3.91 (s, 3 H, $N-CH_3$), 3.95 (s, 3 H, $N-CH_3$), 3.94 (s, 3 H, $N-CH_3$), 3.95 (s, 3 H, $N-CH_3$), 4.10 (s, 3 H, $N-CH_3$), 6.67 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 6.90 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.05 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.21 (d, 1 H, *J* = 2.0 Hz, Py−*H*), 7.23 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.40 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.48 (s, 1 H, Im 5-*H*), 7.73 (s, 1 H, Im 5-*H*), 7.79 (s, 1 H, Im 5-*H*), 8.15 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 8.35 (d, *J* = 7.0 Hz, 1 H, pyridyl 3-*H*), 8.39 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CH_2N$), 8.75 (dd, 7.0 Hz and *J* = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.34 (d, *J* = 2.0 Hz, 1 H, pyridyl 6-*H*), 9.83 (s, 1 H, CONH), 9.86 (s, 1 H, CONH), 9.89 (s, 1 H, CONH), 9.95 (s, 1 H, CONH), 10.17 (s, 1 H, CONH), 11.14 (s, 1 H, CONH). − HRMS: calcd. for $C_{50}H_{63}N_{20}O_8$ 1071.512; found 1071.514 (M^+ + H, 100%).

Fumaroyl Derivative 28: 48% yield, as a light brown solid, m.p. 232−235 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.78 (t, *J* = 6.0 Hz, 4 H, 2 × CH_2CH_2CN), 3.49 (q, 4 H, 2 × $NHCH_2CH_2CN$), 3.82 (s, 3 H, $N-CH_3$), 3.87 (s, 3 H, $N-CH_3$), 3.89 (s, 3 H, $N-CH_3$), 3.91 (s, 3 H, $N-CH_3$), 4.00 (s, 3 H, $N-CH_3$), 4.02 (s, 3 H, $N-CH_3$), 6.87 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 6.95 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.05 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.20 (m, 3 H, 1 H Py−*H* and 2 H C*H*=C*H*), 7.29 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.41 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 7.50 (s, 1 H, Im 5-*H*), 7.63 (s, 1 H, Im 5-*H*), 7.80 (s, 1 H, Im 5-*H*), 8.08 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CN$), 8.42 (t, *J* = 6.0 Hz, 1 H, $CONHCH_2CH_2CN$), 9.50 (s, 1 H, CONH), 9.79 (s, 1 H, CONH), 9.90 (s, 1 H, CONH), 9.98 (s, 1 H, CONH), 10.13 (s, 1 H, CONH), 11.21 (s, 1 H, CONH). − HRMS: calcd. for $C_{43}H_{46}N_{19}O_8$ 956.377; found 956.376 (M^+ + H, 100%).

Benzene Derivative 29: 47% yield, as a brown solid, m.p. > 300 °C. −^{1}H NMR ([D$_6$]DMSO): δ = 2.85 (t, *J* = 6.0 Hz, 4 H, 2 × CH_2-CH_2CN), 3.65 (q, 4 H, 2 × $NHCH_2CH_2CN$), 3.85 (s, 3 H, NCH_3), 3.87 (s, 3 H, $N-CH_3$), 3.90 (s, 3 H, $N-CH_3$), 3.94 (s, 3 H, $N-CH_3$), 4.00 (s, 3 H, $N-CH_3$), 4.05 (s, 3 H, $N-CH_3$), 6.85 (d, *J* = 2.0 Hz, 1 H, Py−*H*), 6.95 (d, *J* = 2.0 Hz, 1 H, Py−*H*),

7.12 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.24 (m, J = 2.0 Hz, 1 H, Py−*H*), 7.32 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.43 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.60 (s, 1 H, Im 5-*H*), 7.65 (s, 1 H, Im 5-*H*), 7.83 (s, 1 H, Im 5-*H*), 8.10 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2CN), 8.28 (dd, J = 10 Hz, 4 H, phenylic), 8.40 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2CN), 9.80 (s, 1 H, CON*H*), 9.85 (s, 1 H, CON*H*), 9.93 (s, 1 H, CON*H*), 9.98 (s, 1 H, CON*H*), 10.09 (s, 1 H, CON*H*), 11.14 (s, 1 H, CON*H*). − HRMS: calcd. for $C_{47}H_{48}N_{19}O_8$ 1006.393; found 1006.393 (M^+ + H, 100%).

Pyridine Derivative 30: 37% yield, as a brown powder, m.p. 300 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.67 (t, J = 6.0 Hz, 4 H, 2 × CH_2CH_2CN), 3.63 (q, 4 H, 2 × $NHCH_2CH_2CN$), 3.80 (s, 3 H, N−CH_3), 3.83 (s, 3 H, N−CH_3), 3.90 (s, 3 H, N−CH_3), 3.98 (s, 3 H, N−CH_3), 4.02 (s, 3 H, N−CH_3), 4.10 (s, 3 H, N−CH_3), 6.87 (d, J = 2.0 Hz, 1 H, Py−*H*), 6.95 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.20 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.24 (m, J = 2.0 Hz, 1 H, Py−*H*), 7.38 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.43 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.58 (s, 1 H, Im 5-*H*), 7.63 (s, 1 H, Im 5-*H*), 7.79 (s, 1 H, Im 5-*H*), 8.05 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2CN), 8.29 (d, J = 7.0 Hz, 1 H, pyridyl 3-H), 8.48 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2CN), 8.79 (dd, J =7.0 Hz, J = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.48 (d, J = 2.0 Hz, 1 H, pyridyl 6-*H*), 9.89 (s, 1 H, CON*H*), 10.01 (s, 1 H, CON*H*), 10.08 (s, 1 H, CON*H*), 10.19 (s, 1 H, CON*H*), 10.29 (s, 1 H, CON*H*), 11.31 (s, 1 H, CON*H*). − HRMS: calcd. for $C_{46}H_{47}N_{20}O_8$ 1007.388; found 1007.388 (M^+ + H, 100%).

Fumaroyl Derivative 31. − General Procedure: Compound **28** (500 mg. 0.523 mmol) in 25 mL of anhydrous ethanol was saturated with dry HCl with cooling. After 2 h at room temperature, the solvent was evaporated to dryness, and the residue was washed with dry diethyl ether (2 × 50 mL) and then dried. The residue was again dissolved in dry ethanol followed by treatment with NH_3 condensed (4.5 mL) into the reaction vessel. The reaction mixture was stirred at room temperature for 18 h. The solvent was then removed, the residue was dissolved in a large amount (100 mL) of methanol, and the impurities were collected. The solution was concentrated to a small volume (10 mL) and the pure compound **31** was collected as a dihydrochloride salt, 65% yield, m.p. > 300 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.63 [t, J = 6.00 Hz, 4 H, 2 × $CH_2CH_2C(NH_2)_2$], 3.50 (t, J = 6.00 Hz, 4 H, 2 × $CONHCH_2CH_2$), 3.80 (s, 3 H, N−CH_3), 3.83 (s, 3 H, N−CH_3), 3.84 (s, 3 H, N−CH_3), 3.95 (s, 3 H, N−CH_3), 4.11 (s, 3 H, N−CH_3), 4.15 (s, 3 H, N−CH_3), 6.89 (d, J = 2.0 Hz, 1 H, Py−*H*), 6.94 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.05 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.20 (d, 2 H, C*H*=C*H*), 7.46 (s, 1 H, Im 5-*H*), 7.50 (s, 1 H, Im 5-*H*), 7.86 (s, 1 H, Im 5-*H*), 8.34 (t, J = 6.0 Hz, 1 H, $CONHCH_2CH_2$), 8.42 (t, J = 6.0 Hz, 1 H, $CONHCH_2CH_2$), 8.65 [s, 8 H, 2 × $C(NH_2)_2$], 9.01 [s, 8 H, 2 × $C(NH_2)_2$], 9.01 (s, 1 H, CONH), 9.40 (s, 1 H, CONH), 9.64 (s, 1 H, CONH), 9.78 (s, 1 H, CONH), 9.95 (s, 1 H, CONH), 10.03 (s, 1 H, CONH), 10.57 (s, 1 H, CONH). − HRMS: calcd. for $C_{43}H_{52}N_{21}O_8$ 990.430; found 990.430 (M^+ + H, 100%).

The following compounds were prepared by this procedure.

Benzene Derivative 32: 64% yield, m.p. > 300 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.71 [t, J = 6.0 Hz, 4 H, 2 × $CH_2CH_2C(NH_2)_2$], 3.53 (t, J = 6.0 Hz, 4 H, 2 × $CONHCH_2CH_2$), 3.83 (s, 3 H, N−CH_3), 3.85 (s, 3 H, N−CH_3), 3.87 (s, 3 H, N−CH_3), 3.98 (s, 3 H, N−CH_3), 4.14 (s, 3 H, N−CH_3), 4.17 (s, 3 H, N−CH_3), 6.93 (d, J = 2.0 Hz, 1 H, Py−*H*), 6.96 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.15 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.49 (s, 1 H, Im 5-*H*), 7.54 (s, 1 H, Im 5-*H*), 7.86 (s, 1 H, Im 5-*H*), 8.32 (dd, J = 10 Hz, 4 H, phenylic), 8.38 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2), 8.49 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2), 8.65 [s, 8 H, 2 × $C(NH_2)_2$], 9.05 [s, 8 H, 2 × $C(NH_2)_2$], 9.10 (s, 1 H, CON*H*), 9.40 (s, 1 H, CON*H*), 9.70 (s, 1 H, CON*H*), 9.78 (s, 1 H, CON*H*), 9.99 (s, 1 H, CON*H*), 10.14 (s, 1 H, CON*H*), 10.78 (s, 1 H, CON*H*). − HRMS: calcd. for $C_{47}H_{54}N_{21}O_8$ 1040.446; found 1040.446 (M^+ + H, 100%).

Pyridine Derivative 33: 65% yield, m.p. > 300 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.73 [t, J = 6.0 Hz, 4 H, 2 × $CH_2CH_2C(NH_2)_2$], 3.58 (t, J = 6.0 Hz, 4 H, 2 × $CONHCH_2CH_2$), 3.84 (s, 3 H, N−CH_3), 3.88 (s, 3 H, N−CH_3), 3.92 (s, 3 H, N−CH_3), 4.00 (s, 3 H, N−CH_3), 4.10 (s, 3 H, N−CH_3), 4.17 (s, 3 H, N−CH_3), 6.97 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.00 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.15 (d, J = 2.0 Hz, 1 H, Py−*H*), 7.52 (s, 1 H, Im 5-*H*), 7.57 (s, 1 H, Im 5-*H*), 7.84 (s, 1 H, Im 5-*H*), 8.32 (d, J = 7.0 Hz, 1 H, pyridyl 3-*H*), 8.40 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2), 8.53 (t, J = 6.0 Hz, 1 H, CON*H*CH_2CH_2), 8.69 [s, 8 H, 2 × $C(NH_2)_2$], 8.83 (dd, J = 7.0 Hz, J = 2.0 Hz, 1 H, pyridyl 4-*H*), 9.52 (d, J = 2.0 Hz, 1 H, pyridyl 6-*H*), 9.10 [s, 8 H, 2 × $C(NH_2)_2$], 9.15 (s, 1 H, CON*H*), 9.44 (s, 1 H, CON*H*), 9.79 (s, 1 H, CON*H*), 9.89 (s, 1 H, CON*H*), 10.01 (s, 1 H, CON*H*), 10.14 (s, 1 H, CON*H*), 10.78 (s, 1 H, CON*H*). − HRMS: calcd. for $C_{46}H_{53}N_{22}O_8$ 1041.441; found 1041.443 (M^+ + H, 100%).

Acknowledgments

We are grateful for a research grant (to J. W. L.) from the Natural Sciences and Engineering Research Council of Canada.

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Received November 2, 1999
[O99614]