Synthesis of tetra- and pentacyclic carbazole-fused imides as potential antitumor agents

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Dedicated to Professor Henk C. van der Plas on the occasion of his 80th birthday

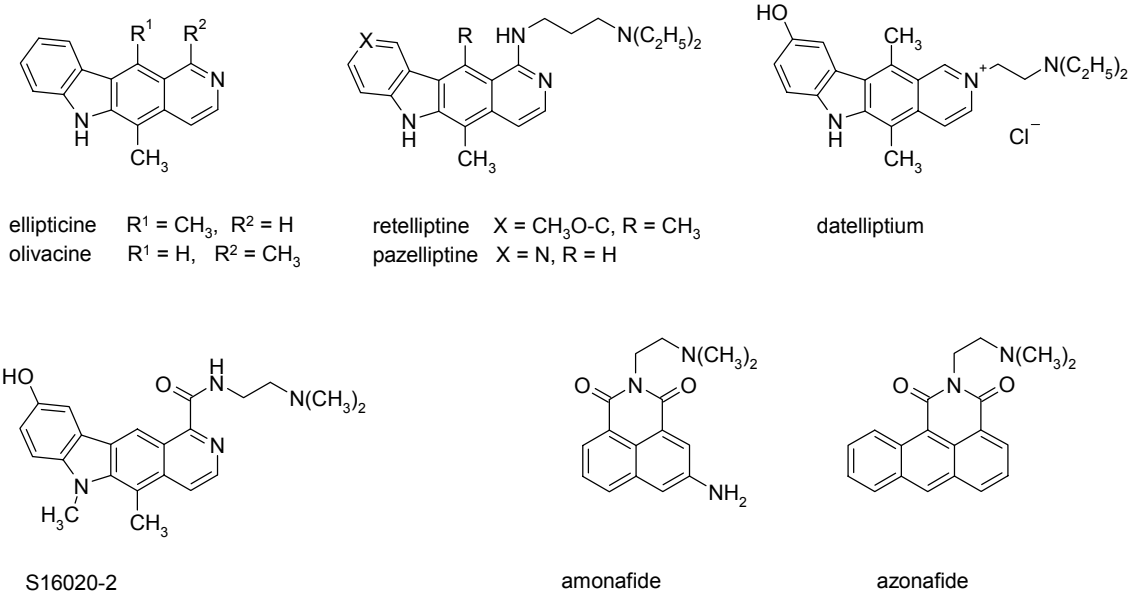
Abstract
A series of tetra- and pentacyclic imides with a carbazole skeleton and a basic side chain at the imide nitrogen was synthesized by cyclization of carbazole-2,3-dicarboxylic acid esters with an appropriate amine or *via* an *N*-aminoimide as a reactive intermediate. The target compounds **6** and **9** were tested *in vitro* for tumor cell-growth inhibition

Keywords: Carbazole, pyrrolo[3,4-*b*]carbazole, imides, antitumor activity

Introduction

Based on the planar, aromatic tetracyclic skeleton of the antitumor alkaloids, *ellipticine* and *olivacine*,[1] a number of drug candidates with enhanced antineoplastic properties has been developed in the past decades.[2] Examples include compounds like *retelliptine*,[3] *pazelliptine*,[4] *datelliptium*,[5] or S16020-2.[6] It has been shown that the presence of a basic side chain of the *N*,*N*-dialkylaminoalkyl type enhances the drugs' DNA affinity.[3] The latter is essential for the biochemical mode of action, through stabilisation of the complex formed between DNA and the enzyme, topoisomerase II.[7] Among the numerous drugs targeting topoisomerase II, also a group of compounds featuring a naphthalene (or higher annulated) ring system fused to a six-membered cyclic imide structure with a basic *N*-substituent has received considerable attention. The drug molecules, *amonafide*[8] and *azonafide*[9] can be regarded as prototypes for this type of agent. Remarkably, *amonafide* as well as the pyrido[4,3-*b*]carbazole derivative, S16020-2 have been found to escape the P-glycoprotein-mediated multi-drug resistance,[10,11] the latter being a common problem in tumor chemotherapy. As it has been claimed that certain carbazoles fused to a *N*-substituted cyclic imide also exhibit pronounced antitumor properties,[12,13] we became interested in the combination of some structural features of *ellipticine*-type and *amonafide*-type

agents, in continuation of our previous studies aimed at the synthesis and antitumor activity of heterocycle-annulated carbazoles.[14,15] Here, we wish to report on the preparation of a series of new tetra- and pentacyclic compounds with a carbazole-2,3-dicarboximide core structure and their *in-vitro* tumor cell-growth inhibitory activity.

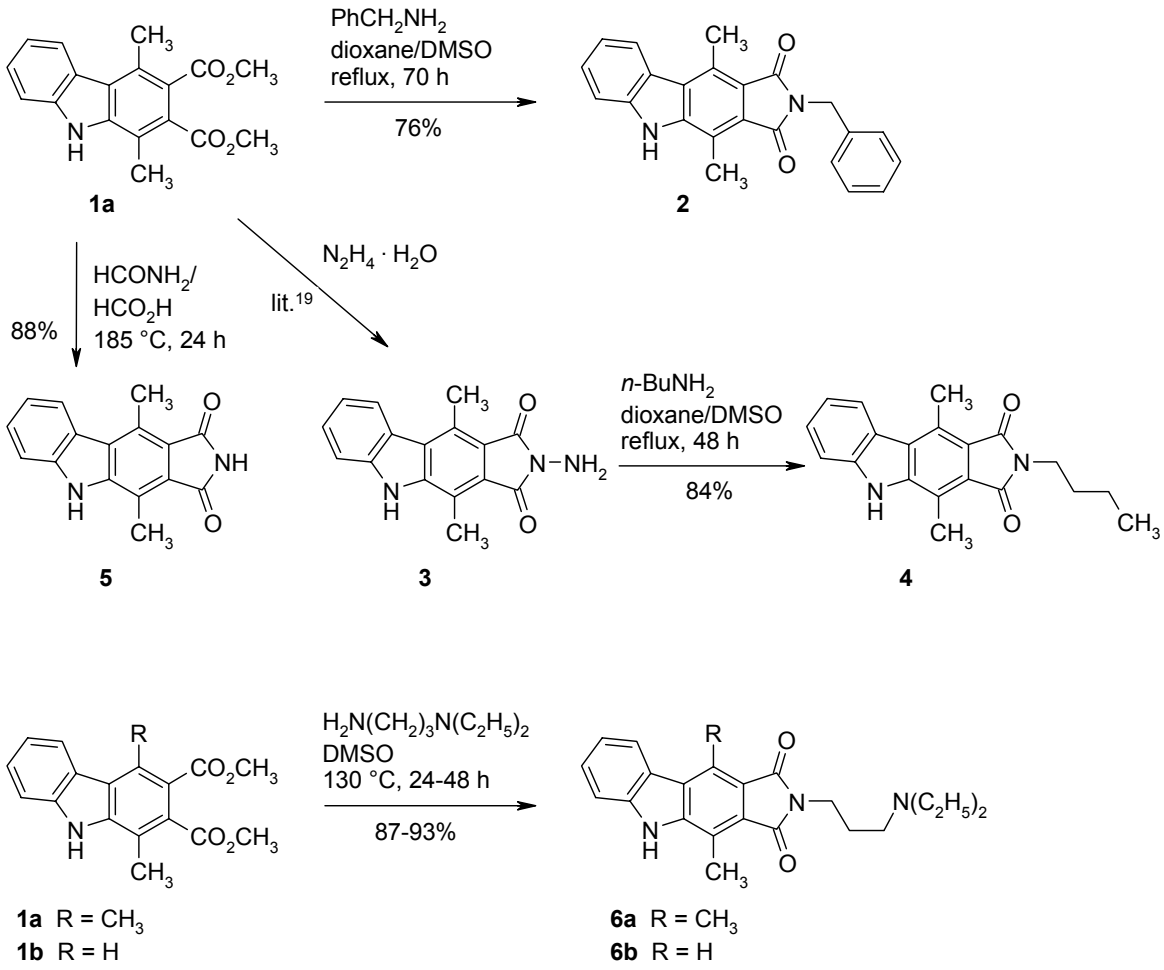


Scheme 1

Results and Discussion

The easily accessible diester **1a**[17] (Scheme 2) was chosen as a synthon featuring the 1,4-dimethylcarbazole motif of *ellipticine* as well as the required functional groups which should be suitable for the construction of an imide unit. Initial experiments showed that **1a** can be transformed into a *N*-substituted carbazole-2,3-dicarboximide derivative simply by heating with an excess of a high-boiling amine such as benzylamine (affording compound **2**), but reacts much more sluggishly with low-boiling amines. In the latter case, e.g. for the preparation of the *N*-butyl substituted imide **4**, employment of a reactive intermediate is necessary.[18] For this purpose, the *N*-aminoimide **3**[19] which is easily formed on treatment of **1a** with hydrazine hydrate, can be conveniently used as an "anhydride equivalent", thus giving **4** in good yield upon refluxing in excess *n*-butylamine. The formation of the five-membered cyclic imide structure is clearly evidenced by the characteristic IR absorption bands of the products at 1740–1750 cm^{-1} and 1680–1700 cm^{-1}, apart from their mass spectra and microanalytical data. For the preparation of the *N*-unsubstituted parent compound **5**, heating of **1a** in formamide/formic acid was found to be the method of choice, affording **5** in 88% yield. Introduction of the desired basic side chain was accomplished by prolonged heating of the diester **1a** with excess *N*,*N*-diethyl-1,3-

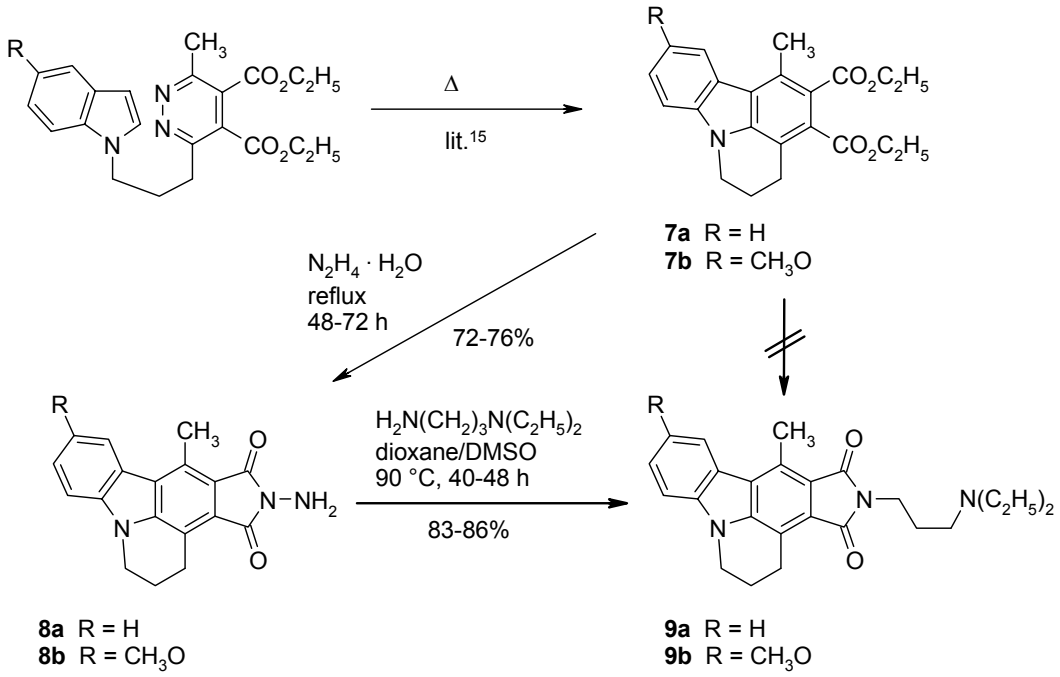
propanediamine in DMSO solution under argon atmosphere. This method, which is similar to that described for the preparation of carbazole-1,2-dicarboximides from the corresponding diesters,[13] gave the diethylaminopropyl-substituted target compound **6a** in high yield. In an analogous fashion, the mono-methyl-substituted carbazole-2,3-diester **1b**[20] (lacking the methyl group at position 4) was smoothly cyclized into the imide **6b**.



Scheme 2

Enlarging the tetracyclic skeleton into a pentacyclic one, introduction of a three-carbon bridge between the indole nitrogen and the adjacent ring C was envisaged, thus adding a structural feature of the cytotoxic *canthine* alkaloids.[21] The requisite carbazolediesters of type **7** (Scheme 3) had been made available by us previously,[15] making use of an intramolecular inverse-electron-demand Diels-Alder reaction of appropriately substituted 3-[3-(indol-1-yl)propyl]pyridazine-4,5-dicarboxylates. A similar cycloaddition approach had been used by Snyder's group for the construction of bridged β-carbolines.[16] Interestingly, the tetracyclic esters **7a,b** did not undergo direct cyclization into the target imides by heating with excess primary

amine under various conditions, despite their steric and electronic similarity to the ester **1a**. However, **7a,b** could be easily transformed into the pentacyclic *N*-aminoimides **8a,b**. Like in the case of compund **3**, these structures were found to be sufficiently reactive in order to undergo an exchange reaction with excess amine, thus furnishing the desired *N*-substituted imides **9a,b** in good yields.



Scheme 3

The target compounds **6a,b** and **9a,b** as well as the *N*-unsubstituted imide **5** which represents the core structure were tested *in vitro* for tumor cell-growth inhibition, using the XTT assay.[22] The results are summarized in Table 1, they show that **6a** is superior as compared to **6b**, the latter lacking the second methyl group at the aromatic scaffold. Likewise, when **9a** is compared to its methoxy derivative **9b**, the latter structural modification is clearly beneficial. Expectedly, the reference compound **5** with an unsubstituted imide nitrogen shows only very weak activity, which demonstrates the importance of the basic side chain in this type of agent. At concentrations lower than 3.16 μg/mL, also compounds **6a,b** and **9a,b** exhibited only weak to moderate effect.

Table 1. *In-vitro* antitumor activity (XTT assay; tumor cell growth inhibition in %) of compounds **5**, **6a**, **6b**, **9a**, and **9b** at a fixed sample concentration of 3.16 μg/mL

5	**6a**	**6b**	**9a**	**9b**
KB-HeLa: 1%	KB-HeLa: 99%	KB-HeLa: 31%	KB-HeLa: 14%	KB-HeLa: 35%
SK-OV-3: *n.v.*	SK-OV-3: 85%	SK-OV-3: 42%	SK-OV-3: 12%	SK-OV-3: 11%
L1210: 44%	L1210: 100%	L1210: 100%	SF-268: 17%	SF-268: 72%
MCF-7: *n.v.*	MCF-7: 72%	MCF-7: 32%	NCI-H460: 47%	NCI-H460: 94%
(n.v.: not valid)			RKOp27: 21%	RKOp27: 100%

Cell lines used:

KB-HeLa:	cervical carcinoma	SF-268:	CNS cancer
L1210:	lymphatic leukemia (mouse)	NCI-H460:	non-small-cell lung cancer
SK-OV-3:	ovarial carcinoma	RKOp27:	colon adenocarcinoma
MCF-7:	mamma carcinoma		

In conclusion, a series of tetra- and pentacyclic imides with a carbazole skeleton and a basic side chain attached to the imide nitrogen has been made conveniently available either by direct cyclization of a carbazole-2,3-diester with an appropriate primary amine or by a two-step sequence involving an *N*-aminoimide as a more reactive intermediate. The target compounds show significant tumor cell-growth inhibition *in vitro* at a concentration of about 10 μmol/L.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage microscope. IR spectra (KBr pellets) were recorded on a Perkin–Elmer 1605 FT-IR instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Unity*plus* 300 spectrometer (δ values in ppm). Mass spectra were obtained on a Shimadzu QP 5050A DI 50 instrument, high-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 8230 spectrometer at the Institute of Organic Chemistry, University of Vienna. For column chromatography, Merck Kieselgel 60 (0.063-0.200 mm) was used. Microanalyses[23] were performed at the Microanalytical Laboratory, Faculty of Chemistry, University of Vienna.

2-Benzyl-4,10-dimethylpyrrolo[3,4-*b*]carbazole-1,3(2*H*,5*H*)-dione (2). A mixture of dimethyl 1,4-dimethyl-9*H*-carbazole-2,3-dicarboxylate (**1a**)[17] (155 mg, 0.50 mmol), benzylamine (10.0 mL, 92.0 mmol), dioxane (10 mL) and DMSO (3 mL) was heated under reflux for 70 h. The volatile components were removed under reduced pressure and the residue was recrystallized from MeOH/AcOEt to give **2** (135 mg, 76%) as colorless crystals, mp 313°C. Anal. Calcd. $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 78.33; H, 5.02; N, 7.85. IR (KBr, cm^{-1}) 3378, 3063, 3032, 2941, 1739, 1687, 1433, 1394, 1337, 749, 730, 698; ^{1}H NMR (DMSO-d_6) δ 12.08

(br s, 1H, NH, shows positive NOE on irradiation at 2.84 ppm), 8.24 (d, J_{8-9} = 8.1 Hz, 1H, 9-H, shows positive NOE on irradiation at 3.12 ppm), 7.63 (d, J_{6-7} = 8.1 Hz, 1H, 6-H), 7.53–7.47 (m, 1H, 7-H), 7.37–7.24 (m, 6H, 8-H, phenyl-H), 4.70 (s, 2H, NCH_2), 3.12 (s, 3H, 10-CH_3), 2.84 (s, 3H, 4-CH_3); MS *m/z*: 354 (M^+, 100%), 263 (47), 248 (24), 221 (13), 192 (30), 191 (27), 165 (15), 106 (23), 104 (24), 91 (89), 78 (39), 77 (62), 65 (53), 51 (59).

2-Butyl-4,10-dimethylpyrrolo[3,4-*b*]carbazole-1,3(2*H*,5*H*)-dione (4). A mixture of 2-amino-4,10-dimethylpyrrolo[3,4-*b*]carbazole-1,3(2*H*,5*H*)-dione (**3**)[19] (100 mg, 0.36 mmol), *n*-butylamine (10.0 mL, 101.0 mmol), dioxane (10 mL) and DMSO (3 mL) was heated under reflux for 48 h. The volatile components were removed under reduced pressure and the residue was purified by short-column chromatography (light petroleum/AcOEt, 4+1), followed by recrystallization from 2-PrOH to afford **4** (98 mg, 84%) as pale yellow crystals, mp 286–288°C. Anal. Calcd. $C_{20}H_{20}N_2O_2$ • 0.25 H_2O: C, 73.94; H, 6.36; N, 8.62. Found: C, 74.14; H, 6.19; N, 8.56. IR (KBr, cm^{-1}) 3347, 2957, 1748, 1677, 1435, 1401, 1367, 747, 729; ^{1}H NMR (DMSO-d_6) δ 11.93 (br s, 1H, NH), 8.23 (d, J_{8-9} = 8.1 Hz, 1H, 9-H, shows positive NOE on irradiation at 3.11 ppm), 7.63 (d, J_{6-7} = 8.4 Hz, 1H, 6-H), 7.54–7.47 (m, 1H, 7-H), 7.32–7.24 (m, 1H, 8-H), 3.52 (t, J = 7.3 Hz, 2H, $NC\underline{H}_2CH_2CH_2CH_3$), 3.11 (s, 3H, 10-$CH_3$), 2.84 (s, 3H, 4-$CH_3$), 1.58 (quint, J = 7.3 Hz, 2H, $NCH_2C\underline{H}_2CH_2CH_3$), 1.37–1.24 (m, 2H, $NCH_2CH_2C\underline{H}_2CH_3$), 0.91 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_2C\underline{H}_3$); MS *m/z*: 320 ($M^+$, 66%), 278 (51), 277 (100), 264 (26), 193 (16), 192 (15), 191 (10); HRMS Calcd. $C_{20}H_{20}N_2O_2$: 320.1525. Found: 320.1519.

4,10-Dimethylpyrrolo[3,4-*b*]carbazole-1,3(2*H*,5*H*)-dione (5). A mixture of dimethyl 1,4-dimethyl-9*H*-carbazole-2,3-dicarboxylate (**1a**)[17] (311 mg, 1.00 mmol), formic acid (2 mL) and formamide (30 mL) was heated to 185°C for 24 h. After cooling, the precipitate was collected by filtration, washed with water and dried to give **5** (235 mg, 88%) as pale yellow crystals, mp > 350°C. Anal. Calcd. $C_{16}H_{12}N_2O_2$ • 0.2 H_2O: C, 71.74; H, 4.67; N, 10.46. Found: C, 71.66; H, 4.74; N, 10.31. IR (KBr, cm^{-1}) 3327, 3170, 3049, 1744, 1700, 1365, 1330, 761, 730, 652; ^{1}H NMR (DMSO-d_6) δ 12.01 (br s, 1H, NH), 10.88 (br s, 1H, NH), 8.23 (d, J_{8-9} = 8.1 Hz, 1H, 9-H, shows positive NOE on irradiation at 3.10 ppm), 7.62 (d, J_{6-7} = 8.1 Hz, 1H, 6-H), 7.53–7.47 (m, 1H, 7-H), 7.30–7.24 (m, 1H, 8-H), 3.10 (s, 3H, 10-CH_3), 2.82 (s, 3H, 4-CH_3); ^{13}C NMR (DMSO-d_6) δ 170.4, 170.0, 141.9, 140.8, 131.4, 126.4, 125.8, 124.1, 123.0, 122.8, 120.1, 119.4, 118.8, 111.8, 14.2, 11.6; MS *m/z*: 264 (M^+, 100%), 193 (38), 95 (50), 83 (54), 69 (32), 57 (38), 55 (32).

2-[3-(Diethylamino)propyl]-4,10-dimethylpyrrolo[3,4-*b*]carbazole-1,3(2*H*,5*H*)-dione (6a). A solution of dimethyl 1,4-dimethyl-9*H*-carbazole-2,3-dicarboxylate (**1a**)[17] (311 mg, 1.00 mmol) and *N*,*N*-diethyl-1,3-propanediamine (1302 mg, 10.00 mmol) in DMSO (5 mL) was stirred at 130°C for 24 h under an argon atmosphere. Another portion of *N*,*N*-diethyl-1,3-propanediamine (1302 mg, 10.00 mmol) was added and heating was continued for further 24 h. The volatile components were removed under reduced pressure and the residue was triturated with MeOH. The almost colorless, crystalline material was collected by filtration and the filtrate was subjected to column chromatography (AcOEt/light petroleum/Et_3N, 95+95+10) to afford another portion of the product. The combined crops were recrystallized from AcOEt to give **6a** (337 mg, 87%) as colorless crystals, mp 232–235°C. Anal. Calcd. $C_{23}H_{27}N_3O_2$ • 0.6 H_2O: C, 71.15; H,

7.32; N, 10.82. Found: C, 71.19; H, 7.02; N, 10.77. IR (KBr, cm^{-1}) 3343, 2968, 1745, 1676, 1437, 1401, 1364, 1032, 746, 730, 628; ^{1}H NMR (DMSO-d_6) δ 12.03 (br s, 1H, NH), 8.23 (d, $J_{8–9}$ = 8.1 Hz, 1H, 9-H), 7.62 (d, $J_{6–7}$ = 8.1 Hz, 1H, 6-H), 7.54–7.46 (m, 1H, 7-H), 7.31–7.24 (m, 1H, 8-H), 3.54 (t, J = 7.2 Hz, 2H, $NC\underline{H}_2CH_2CH_2N(CH_2CH_3)_2$), 3.11 (s, 3H, 10-$CH_3$), 2.83 (s, 3H, 4-$CH_3$), 2.46–2.37 (m, 6H, $NCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 1.74–1.63 (m, 2H, $NCH_2C\underline{H}_2CH_2N(CH_2CH_3)_2$), 0.90 (t, J = 7.2 Hz, 6H, $N(CH_2C\underline{H}_3)_2$); ^{13}C NMR (DMSO-$d_6$) δ 168.8, 168.4, 141.6, 140.7, 131.3, 126.2, 124.6, 123.8, 122.9, 122.6, 120.0, 118.8, 118.2, 111.7, 50.0, 46.1, 35.4, 25.7, 14.2, 11.7, 11.6; MS *m/z*: 377 (M^+, 2%), 348 (5), 305 (3), 277 (7), 193 (3), 192 (3), 181 (4), 139 (3), 112 (3), 87 (5), 86 (100), 84 (8), 72 (26), 58 (21); HRMS Calcd. $C_{23}H_{27}N_3O_2$: 377.2103. Found: 377.2112.

2-[3-(Diethylamino)propyl]-4-methylpyrrolo[3,4-*b*]carbazole-1,3(2*H*,5*H*)-dione (6b). A solution of dimethyl 1-methyl-9*H*-carbazole-2,3-dicarboxylate (**1b**)[20] (297 mg, 1.00 mmol) and *N*,*N*-diethyl-1,3-propanediamine (1302 mg, 10.00 mmol) in DMSO (5 mL) was stirred at 130°C for 24 h under an argon atmosphere. The volatile components were removed under reduced pressure and the residue was purified by column chromatography (AcOEt/light petroleum/Et_3N, 95+95+10), followed by recrystallization from AcOEt to give **6b** (338 mg, 93%) as almost colorless crystals, mp 203–207°C. Anal. Calcd. $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.91; H, 7.15; N, 11.64. IR (KBr, cm^{-1}) 3332, 2968, 2800, 1752, 1689, 1460, 1397, 1361, 1248, 1040, 750, 730; ^{1}H NMR (DMSO-d_6) δ 12.01 (br s, 1H, NH), 8.46 (s, 1H, 10-H), 8.29 (d, $J_{8–9}$ = 7.8 Hz, 1H, 9-H), 7.59 (d, $J_{6–7}$ = 8.4 Hz, 1H, 6-H), 7.52–7.46 (m, 1H, 7-H), 7.28–7.22 (m, 1H, 8-H), 3.56 (t, J = 7.4 Hz, 2H, $NC\underline{H}_2CH_2CH_2N(CH_2CH_3)_2$), 2.86 (s, 3H, 4-$CH_3$), 2.45–2.35 (m, 6H, $NCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 1.75–1.64 (m, 2H, $NCH_2C\underline{H}_2CH_2N(CH_2CH_3)_2$), 0.89 (t, J = 7.1 Hz, 6H, $NCH_2CH_2CH_2N(CH_2C\underline{H}_3)_2$); ^{13}C NMR (DMSO-$d_6$) δ 169.0, 168.1, 142.2, 140.9, 127.2, 124.8, 124.7, 122.6, 122.2, 121.3, 121.1, 120.1, 114.0, 111.8, 50.0, 46.1, 35.7, 25.7, 12.0, 11.6; MS *m/z*: 363 (M^+, 2%), 348 (2), 334 (7), 291 (5), 263 (7), 179 (3), 178 (4), 174 (7), 132 (2), 112 (4), 87 (7), 86 (100), 84 (7), 72 (32), 58 (12).

11-Amino-9-methyl-2,3-dihydropyrido[1,2,3-*lm*]pyrrolo[3,4-*b*]carbazole-10,12(1*H*, 11*H*)-dione (8a). A mixture of diethyl 1-methyl-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (**7a**)[15] (117 mg, 0.32 mmol) and hydrazine monohydrate (4.0 mL, 82.0 mmol) was refluxed for 48 h. After cooling, EtOH (4 mL) was added and the precipitate was collected by filtration and washed several times with boiling MeOH to give **8a** (76 mg, 76%) as pale yellow crystals, mp 295–300°C (decomp). Anal. Calcd. $C_{18}H_{15}N_3O_2$ • 0.4 H_2O: C, 69.17; H, 5.10; N, 13.44. Found: C, 69.14; H, 4.95; N, 13.44. IR (KBr, cm^{-1}) 3322, 3046, 2929, 1756, 1703, 1617, 1518, 1413, 1333, 1303, 1253, 748; ^{1}H NMR (DMSO-d_6) δ 8.29 (d, $J_{7–8}$ = 7.8 Hz, 1H, 8-H), 7.72 (d, $J_{5–6}$ = 8.1 Hz, 1H, 5-H), 7.64–7.54 (m, 1H, 6-H), 7.40–7.30 (m, 1H, 7-H), 4.85 (s, 2H, NH_2), 4.36 (t, $J_{2–3}$ = 5.7 Hz, 2H, 3-H), 3.38 (t, $J_{1–2}$ = 6.1 Hz, 2H, 1-H), 3.14 (s, 3H, CH_3), 2.36–2.20 (m, 2H, 2-H); MS *m/z*: 305 (M^+, 100%), 289 (23), 260 (50), 244 (22), 232 (33), 217 (50), 204 (30), 190 (22), 163 (16), 152 (83), 145 (40), 138 (18), 123 (28), 115 (17), 109 (76), 102 (35), 95 (39), 82 (16); HRMS Calcd. $C_{18}H_{15}N_3O_2$: 305.1164. Found: 305.1171.

11-Amino-7-methoxy-9-methyl-2,3-dihydropyrido[1,2,3-*lm*]pyrrolo[3,4-*b*]carbazole-10,12(1*H*,11*H*)-dione (8b). A mixture of diethyl 10-methoxy-1-methyl-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (**7b**)[15] (121 mg, 0.31 mmol) and hydrazine monohydrate (4.0 mL, 5.0 mmol) was refluxed for 72 h. After cooling, EtOH (4 mL) was added and the precipitate was collected by filtration and washed with EtOH to give **8b** (77 mg, 72%) as pale yellow crystals, mp 247–252°C. Anal. Calcd. $C_{19}H_{17}N_3O_3 \cdot 0.5\ H_2O$: C, 66.27; H, 5.27; N, 12.20. Found: C, 66.14; H, 5.13; N, 12.01. IR (KBr, cm^{-1}) 3334, 2942, 2832, 1748, 1696, 1612, 1481, 1411, 1283, 1226, 1144, 1033, 748, 677; ^{1}H NMR (DMSO-d_6) δ 7.68 (d, $J_{6–8}$ = 2.4 Hz, 1H, 8-H), 7.62 (d, $J_{5–6}$ = 9.0 Hz, 1H, 5-H), 7.22 (dd, $J_{5–6}$ = 9.0 Hz, $J_{6–8}$ = 2.4 Hz, 1H, 6-H), 4.81 (br s, 2H, NH_2), 4.28 (t, $J_{2–3}$ = 5.8 Hz, 2H, 3-H), 3.88 (s, 3H, OCH_3), 3.32 (t, $J_{1–2}$ = 6.0 Hz, 2H, 1-H), 3.09 (s, 3H, 9-CH_3), 2.30–2.16 (m, 2H, 2-H); MS *m/z*: 335 (M^+, 100%), 320 (49), 290 (26), 275 (9), 262 (9), 247 (11), 234 (12), 204 (10), 168 (12), 138 (23), 124 (31), 102 (36), 95 (26), 82 (11); HRMS Calcd. $C_{19}H_{17}N_3O_3$: 335.1270. Found: 335.1261.

11-[3-(Diethylamino)propyl]-9-methyl-2,3-dihydropyrido[1,2,3-*lm*]pyrrolo[3,4-*b*]carbazole-10,12(1*H*,11*H*)-dione (9a). A mixture of **8a** (98 mg, 0.32 mmol), *N*,*N*-diethyl-1,3-propanediamine (2.0 mL, 12.7 mmol), dioxane (2 mL) and DMSO (2 mL) was heated in a closed vessel to 90°C for 48 h under an argon atmosphere. The volatile components were removed under reduced pressure and the residue was triturated with MeOH. The crystalline material was collected by filtration and washed with MeOH to give **9a** (108 mg, 83%) as colorless crystals, mp 174–177°C. Anal. Calcd. $C_{25}H_{29}N_3O_2$: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.19; H, 7.07; N, 10.47. IR (KBr, cm^{-1}) 2967, 2798, 1746, 1684, 1416, 1375, 1332, 747; ^{1}H NMR (DMSO-d_6) δ 8.28 (d, $J_{7–8}$ = 7.8 Hz, 1H, 8-H), 7.71 (d, $J_{5–6}$ = 8.1 Hz, 1H, 5-H, shows positive NOE on irradiation at 4.34 ppm), 7.62–7.53 (m, 1H, 6-H), 7.38–7.29 (m, 1H, 7-H), 4.34 (t, $J_{2–3}$ = 5.8 Hz, 2H, 3-H), 3.57 (t, *J* = 7.2 Hz, 2H, $NC\underline{H}_2CH_2CH_2N(CH_2CH_3)_2$), 3.37 (t, $J_{1–2}$ = 6.0 Hz, 2H, 1-H), 3.13 (s, 3H, 9-CH_3), 2.50–2.35 (m, 6H, $NCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 2.33–2.20 (m, 2H, 2-H), 1.79–1.62 (m, 2H, $NCH_2C\underline{H}_2CH_2N(CH_2CH_3)_2$), 0.91 (t, *J* = 7.0 Hz, 6H, $NCH_2CH_2CH_2N(CH_2C\underline{H}_3)_2$); MS *m/z*: 403 ($M^+$, 2%), 374 (9), 331 (4), 303 (5), 218 (6), 112 (6), 86 (100), 72 (21), 58 (12).

11-[3-(Diethylamino)propyl]-7-methoxy-9-methyl-2,3-dihydropyrido[1,2,3-*lm*]pyrrolo[3,4-*b*]carbazole-10,12(1*H*,11*H*)-dione (9b). A mixture of **8b** (100 mg, 0.30 mmol), *N*,*N*-diethyl-1,3-propanediamine (2.0 mL, 12.7 mmol), dioxane (2 mL) and DMSO (2 mL) was heated in a closed vessel to 90°C for 40 h under an argon atmosphere. The volatile components were removed under reduced pressure and the residue was triturated with MeOH. The crystalline material was collected by filtration and washed with MeOH to give **9b** (113 mg, 86%) as pale yellow crystals, mp 173–177°C. Anal. Calcd. $C_{26}H_{31}N_3O_3 \cdot 0.4\ H_2O$: C, 70.85; H, 7.27; N, 9.53. Found: C, 70.81; H, 7.07; N, 9.78. IR (KBr, cm^{-1}) 2966, 2938, 2804, 1745, 1687, 1484, 1411, 1310, 1230, 1145, 1030, 832; ^{1}H NMR (DMSO-d_6) δ 7.64 (d, $J_{6–8}$ = 2.2 Hz, 1H, 8-H), 7.60 (d, $J_{5–6}$ = 8.8 Hz, 1H, 5-H), 7.21 (dd, $J_{5–6}$ = 8.8 Hz, $J_{6–8}$ = 2.2 Hz, 1H, 6-H), 4.25 (t, $J_{2–3}$ = 5.5 Hz, 2H, 3-H), 3.87 (s, 3H, OCH_3), 3.52 (t, *J* = 7.3 Hz, 2H, $NC\underline{H}_2CH_2CH_2N(CH_2CH_3)_2$), 3.30 (t, $J_{1–2}$ = 6.0 Hz, 2H, 1-H), 3.05 (s, 3H, 9-CH_3), 2.50–2.33 (m, 6H, $NCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 2.30–2.12 (m, 2H, 2-

H), 1.77–1.59 (m, 2H, $NCH_2C\underline{H}_2CH_2N(CH_2CH_3)_2$), 0.91 (t, J = 7.0 Hz, 6H, $NCH_2CH_2CH_2N(CH_2C\underline{H}_3)_2$); MS *m/z*: 433 ($M^+$, 2%), 404 (8), 361 (3), 333 (6), 112 (7), 86 (100), 72 (20), 58 (11); HRMS Calcd. $C_{26}H_{31}N_3O_3$: 433.2365. Found: 433.2374.

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23. For some of the new compounds, microanalytical data indicated partial hydration. In all of these cases, residual water could not be removed even on prolonged drying *in vacuo* over P_2O_5.