SYNTHESIS OF PYRIDAZINO[4,5-*b*]CARBAZOLES AS POTENTIAL ANTITUMOR AGENTS

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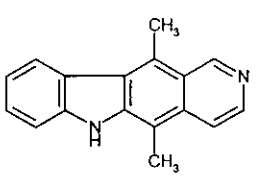
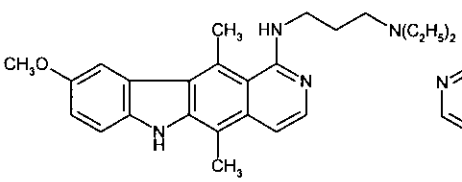
Abstract - The synthesis of a series of new pyridazino[4,5-*b*]carbazoles (**8**, **9**, **12-14**), representing 3-aza analogs of pyrido[4,3-*b*]carbazole antitumor agents, is described. The key intermediates, *d*-fused dichloropyridazines of type **5**, were subjected to nucleophilic displacement reactions and/or to reductive dehalogenation.

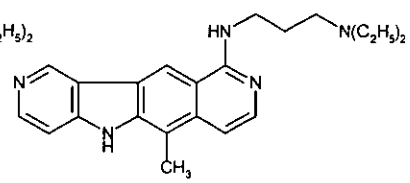
Since the discovery of the promising antitumor properties of the alkaloid *ellipticine* (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole), tetracyclic compounds of the pyridocarbazole type have been attracting considerable interest.[1,2] In order to overcome some limitations, such as low water solubility or cardiovascular side effects in the therapeutic use of *ellipticine* and early congeners, a number of analogs has been synthesized and evaluated so far. Besides quaternization of the pyridine nitrogen atom, like in the case of 9-hydroxy-2-methylellipticinium acetate (*elliptinium*),[3] the introduction of a basic side chain into position 1 of the tetracyclic system can effect the desired solubility enhancement and it has been shown that such a (*N*,*N*-dialkylamino)alkylamino substructure significantly enhances the molecule's affinity to the phosphate backbone of DNA.[4] Typical representatives of this type of *ellipticine* analogs are the drug candidates *retelliptine*[4] and *pazelliptine*[5,6] (see below).



Ellipticine



Retelliptine



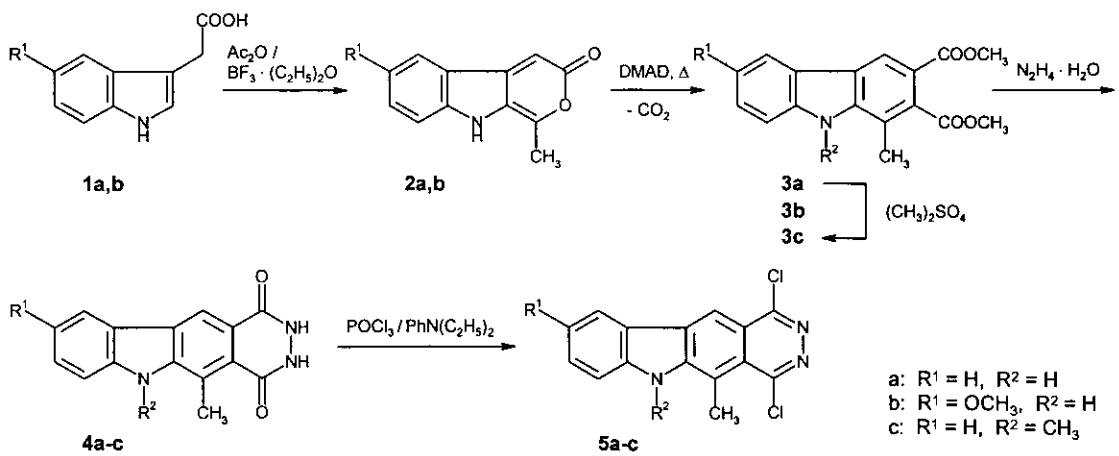
Pazelliptine

Dedicated with our very best wishes to Professor Gottfried Heinisch on the occasion of his 60th birthday.

Besides 6,11-dimethyl-5*H*-pyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinoline (9-azaellipticine)[7] and the highly active derivative, *pazelliptine*,[5,6] a series of pyridazino[4,5-*b*]carbazoles which had been prepared by Landelle *et al.*,[8] can be regarded as aza analogs of *ellipticine*. The latter 3-azaellipticines, however, bearing alkoxy substituents at positions 1 and 4, had been found to be almost inactive in an *in-vivo* antitumor screening, most probably as a consequence of their very low solubility.[8] In the framework of our ongoing research in the field of condensed pyridazines, we became interested in a reinvestigation of the pyridazino[4,5-*b*]carbazole system as the basic skeleton of new potential antineoplastic agents. Here, we wish to report on the synthesis of a series of new representatives of this ring system which combine some of the structural features of the drug molecules shown above.

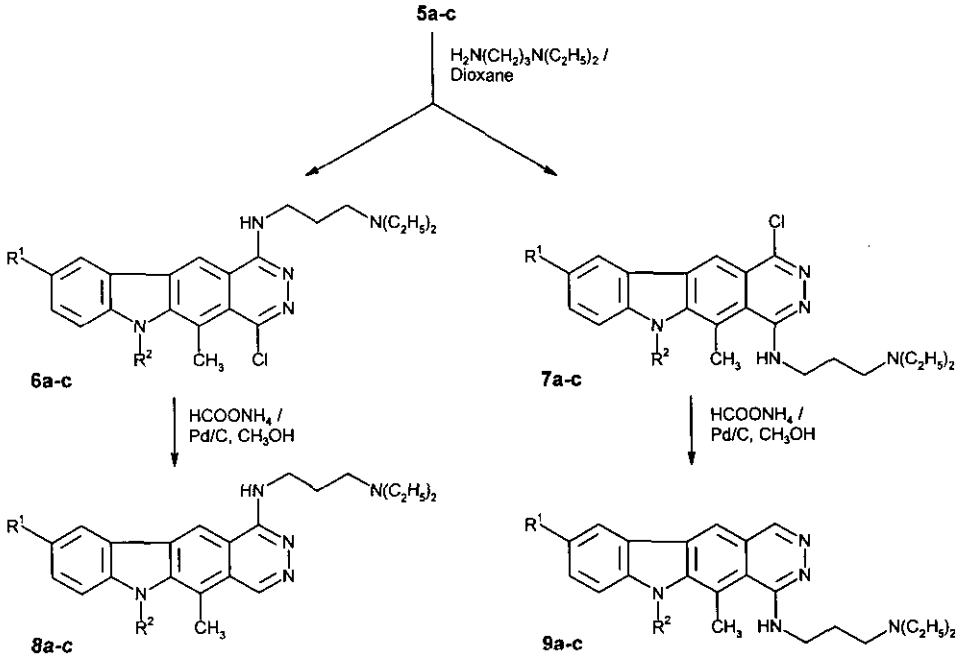
As key intermediates, we utilized the dichloropyridazines of type **5** (Scheme 1). Compounds (**5a**) and (**5c**) were prepared in several steps from 3-indoleacetic acid (**1a**) as described in the literature.[8-10] For the conversion of the pyridazinedione (**4a**) into **5a**, the procedure given in lit.,[8] was slightly modified by using *N*,*N*-diethylaniline as a base instead of pyridine. Thus, the yield could be improved from 53% to 81% and, moreover, the reaction takes place very smoothly at reflux temperature, in contrast to the more drastic conditions (heating in a sealed tube) required previously.[8] In an analogous manner, the new 1,4-dichloro-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**5b**) was prepared in 31% overall yield from 5-methoxy-3-indoleacetic acid. Not surprisingly, the presence of an electron-donating methoxy group in the fused pyrone (**2b**) was found to facilitate the Diels-Alder reaction with dimethyl acetylene-dicarboxylate (DMAD), as compared to the 6-unsubstituted compound (**2a**).

Scheme 1



When the dichloropyridazines (**5a-c**) were heated with excess *N,N*-diethyl-1,3-propanediamine in dry dioxane until complete consumption (TLC monitoring), mixtures of the two isomeric monosubstitution products of type **6** and **7** were obtained, which could be separated by column chromatography. In all cases, the yield of the 4-substituted product (**7**) was slightly higher than that of the 1-substituted isomer (**6**). For reductive removal of the chloro substituents in **6** and **7**, catalytic transfer hydrogenation, using ammonium formate as the hydrogen source and palladium/carbon as catalyst in refluxing methanol was found to be the method of choice. Thus, the potential antineoplastic agents (**8a-c**) and (**9a-c**) were prepared in reasonable yields. Structural assignment for the isomers of type **6/7** and **8/9** rests on NOE difference spectroscopy experiments, employing the resonances of H-11, CH_3-5, or the NH function of the substituent as irradiation points (see Experimental).

Scheme 2

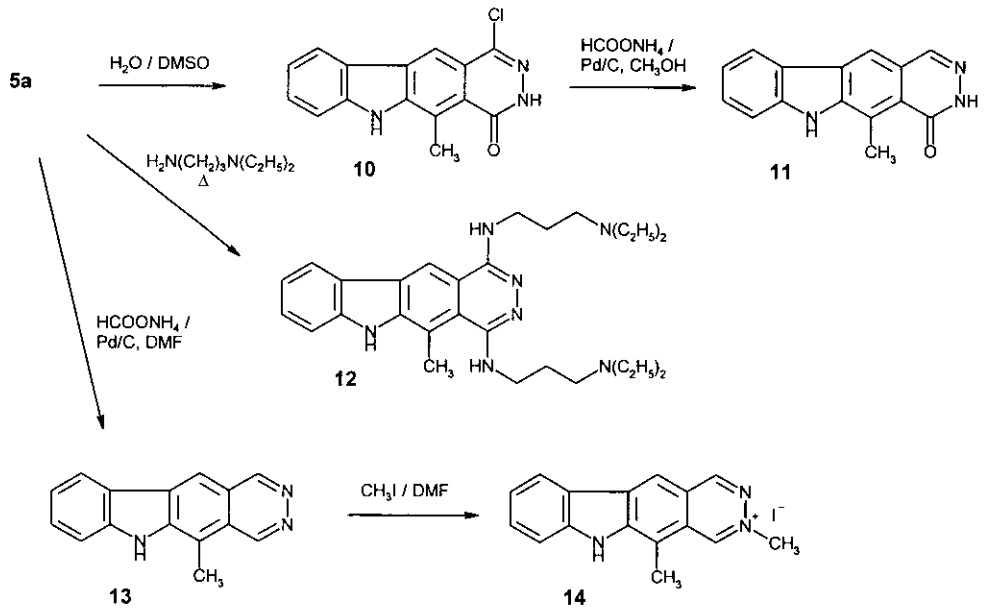


a: R^1 = H, R^2 = H; b: R^1 = OCH_3, R^2 = H; c: R^1 = H, R^2 = CH_3

Although position 1 in the chloro compounds of type **5** is sterically less hindered than position 4, the latter carbon atom is preferentially attacked by the amine, obviously for electronic reasons. This phenomenon becomes even more pronounced when water is employed as a (very small) nucleophile: the fused 1-chloro-4(3*H*)-pyridazinone (**10**) is formed almost exclusively upon treatment of **5a** with water in DMSO solution. The structure of the hydrolysis product (**10**) was established by reductive removal of the

1-chloro substituent, which afforded the pyridazinone (**11**) (Scheme 3). NOE difference spectroscopy with the latter compound clearly showed the vicinity between the pyridazine proton at position 1 and H-11.

Scheme 3



Treatment of the dichloropyridazine (**5a**) with *N*,*N*-diethyl-1,3-propanediamine under more drastic conditions than those employed for the conversion **5** → **6**, **7** furnished a 1,4-disubstituted compound (**12**) in moderate yield, which is also of interest as a potential antitumor agent. On the other hand, initial attempts to remove both chloro substituents in compound (**5a**) by catalytic transfer hydrogenation in refluxing methanol, as used for the preparation of **8a-c**, **9a-c**, and **11**, met with no success. It was found that under these conditions, the starting material undergoes hydrolysis/solvolysis considerably faster than reductive dehalogenation. However, employment of an aprotic solvent (DMF) and optimization of the reaction temperature (75°C) finally permitted the transformation of **5a** into 5-methyl-6*H*-pyridazino-[4,5-*b*]carbazole (**13**), which can be regarded as a 3-aza-11-norellipticine.

As it is known that quaternized derivatives of *ellipticine* (such as *elliptinium*[3]) show superior biological activity as compared to the parent compound, we also investigated the reaction behavior of **13** towards methyl iodide in DMF solution. Interestingly, the main product (yield: 60%) which precipitates as an orange solid from the reaction mixture, was found to be the 3,5-dimethyl compound (**14**).[11] The position of the *N*-methyl substituent clearly follows from NOE experiments (Figure 1).

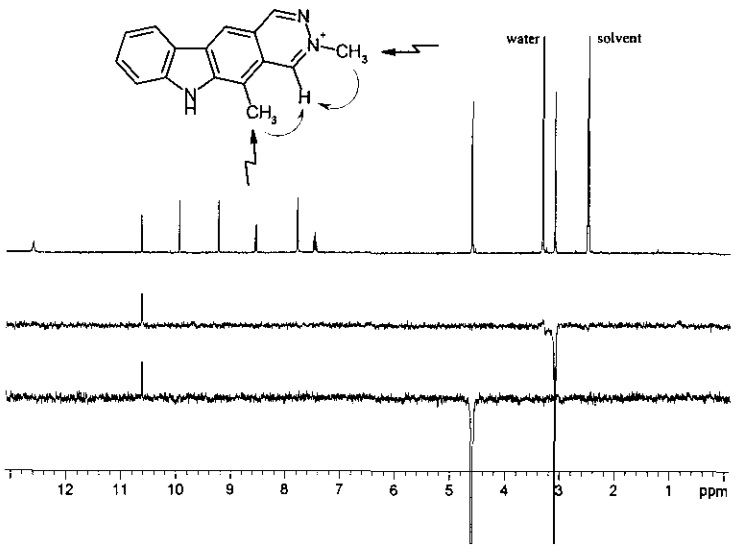


Figure 1. 300 MHz ^{1}H-NMR spectrum (upper trace) and NOE difference spectra of **14** (DMSO-d_6, 28°C), with the resonances of CH_3-5 (3.09 ppm; middle trace) and CH_3-3 (4.61 ppm; lower trace) as irradiation points.

Preliminary investigations (NCI *in-vitro* screening) of the antitumor properties of compounds (**8a,b**) and (**9a,b**) revealed an interesting activity of the 1-substituted pyridazines (**8a,b**), in particular towards several leukemia, melanoma, and breast cancer cell lines, whereas the 4-substituted isomers (**9a,b**) were found to be considerably less active. More detailed studies on the antineoplastic activity of the new compounds are to be carried out.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded for KBr pellets on a Perkin-Elmer 1605 FT-IR instrument; ^{1}H-NMR spectra were recorded on a Varian Unity*plus* 300 (300 MHz) spectrometer (TMS as internal reference, δ values in ppm). MS spectra were obtained with a Hewlett-Packard 5890A/5970B-GC/MSD or with a Shimadzu QP5000 DI 50 spectrometer. HRMS spectra were taken on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna. Column chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm, medium pressure liquid chromatography (MPLC) was carried out on Merck LiChroprep Si 60, 0.040-0.063 mm (detection at 280 nm). Light petroleum refers to the fraction of bp 50-70°C. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

1,4-Dichloro-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole[8] (**5a**)

To a suspension of 1,4-dioxo-1,2,3,4-tetrahydro-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole[8] (**4a**) (1.060 g, 4 mmol) in *N,N*-diethylaniline (4.69 g, 31 mmol) was added phosphorus oxychloride (60 mL, 644 mmol), and the mixture was heated to reflux for 2 h. Work-up as described in lit.,[8] afforded 0.978 g (81%) of a pale yellow solid, mp > 350°C (lit.,[8] mp > 350°C).

6-Methoxy-1-methylpyrano[3,4-*b*]indol-3(9*H*)-one (**2b**)

Freshly distilled boron trifluoride-diethyl ether (7.0 mL, 55 mmol) was added dropwise over 45 min to a stirred suspension of 5-methoxy-3-indolylacetic acid (**1b**) (8.208 g, 40 mmol) in acetic anhydride (18 mL) at 0°C. During the addition, the starting material dissolved and a clear, dark-red colored solution was obtained. The cooling bath was removed, and a red precipitate started to separate. After stirring at rt for 30 min, the mixture was chilled again, diluted with ether (50 mL), and filtered. The product was washed consecutively with ether, toluene, water, saturated aqueous $NaHCO_3$, then again with water. After drying, compound (**2b**) (6.923 g, 73%) was obtained as orange-red crystals, mp 193-195°C (ethanol/triethylamine, 97:3). *Anal.* Calcd for $C_{13}H_{11}NO_3 \cdot 0.5\ H_2O$: C, 65.54; H, 5.08; N, 5.88. Found: C, 65.65; H, 4.95; N, 5.74. HRMS Calcd for $C_{13}H_{11}NO_3$: 229.0739. Found: 229.0740. MS: *m/z* (rel. int.) 229 (M^+, 97%), 201 (52), 186 (100), 158 (83), 130 (21), 115 (30), 101 (24), 86 (98), 77 (26), 63 (23), 62 (24), 58 (50). IR (cm^{-1}): 3197, 1699. ^{1}H-NMR (DMSO-d_6) δ: 10.16 (s, 1 H, NH), 7.56-7.54 (m, unresolved, 1 H, H-5), 7.19-7.12 (m, unresolved, 2 H, H-7, H-8), 6.52-6.49 (m, unresolved, 1 H, H-4), 3.78 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3-1).

Dimethyl 6-Methoxy-1-methyl-9*H*-carbazole-2,3-dicarboxylate (**3b**)

A solution of **2b** (6.876 g, 30 mmol) and dimethyl acetylenedicarboxylate (19.90 g, 140 mmol) in bromobenzene (250 mL) was refluxed for 1.5 h under an argon atmsophere. The solvent was removed under reduced pressure and the residue was triturated with light petroleum (50 mL). The brown solid was purified by column chromatography (ethyl acetate/light petroleum, 2:3) to give **3b** (5.598 g, 57%) as almost colorless crystals, mp 229°C (ethyl acetate/light petroleum). *Anal.* Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.78; H, 5.37; N, 4.26. MS: *m/z* (rel. int.) 327 (M^+, 100%), 312 (21), 296 (41), 295 (46), 281 (46), 280 (66), 238 (29), 237 (63), 217 (34), 210 (24), 209 (89), 195 (31), 194 (35), 174 (52), 167 (37), 166 (41), 148 (70), 146 (25), 140 (30), 139 (22), 119 (33), 83 (40), 76 (20), 69 (45), 57 (28), 55 (34). IR (cm^{-1}): 3341, 1717. ^{1}H-NMR (DMSO-d_6) δ: 11.64 (s, 1 H, NH), 8.67 (s, 1 H, H-4), 7.87 (d, $J_{5,7}$= 2.4 Hz, 1 H, H-5), 7.48 (d, $J_{7,8}$= 9.0 Hz, 1 H, H-8), 7.10 (dd, $J_{5,7}$= 2.4 Hz, $J_{7,8}$= 9.0 Hz, 1 H, H-7), 3.85 (s, 9 H, OCH_3, $COOCH_3$), 2.45 (s, 3 H, CH_3-1).

1,4-Dioxo-1,2,3,4-tetrahydro-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**4b**)

A mixture of **3b** (1.637 g, 5 mmol) and 100% hydrazine hydrate (30 mL, 618 mmol) was refluxed for 2 h. The reagent was removed under reduced pressure, the residue was taken up in ethanol and the mixture was evaporated again. The residue was suspended in ice-cold water, a few drops of concd hydrochloric acid were added, and the mixture was kept in the refrigerator for 30 min. The precipitate was filtered off, washed with cold water, and dried to give **4b** (1.330 g, 86%) as yellow crystals, mp > 350°C. *Anal.* Calcd for $C_{16}H_{13}N_3O_3 \cdot 0.75\ H_2O$: C, 62.23; H, 4.73; N, 13.61. Found: C, 62.18; H, 4.76; N, 13.88. HRMS Calcd for $C_{16}H_{13}N_3O_3$: 295.0957. Found: 295.0942. MS: *m/z* (rel. int.) 296 (20%), 295 (M^+, 100), 281 (10), 280 (52), 209 (8), 194 (8), 166 (5), 147 (7), 118 (6), 57 (5), 55 (5). ^{1}H-NMR (DMSO-d_6) δ: 11.54 (s, 1 H, carbazole-NH), 11.2-11.0 (br, 2 H, pyridazine-NH), 8.73 (s, 1 H, H-11), 7.95 (d, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-10), 7.51 (d, $J_{7\text{-}8}$ = 9.0 Hz, 1 H, H-7), 7.17 (dd, $J_{7\text{-}8}$ = 9.0 Hz, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-8), 3.87 (s, 3 H, OCH_3), 3.09 (s, 3 H, CH_3-5).

1,4-Dichloro-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**5b**)

To a suspension of **4b** (1.181 g, 4 mmol) in *N*,*N*-diethylaniline (4.69 g, 31 mmol) was added phosphorus oxychloride (60 mL, 644 mmol), and the mixture was heated to reflux for 2 h. The volatile components were removed under reduced pressure and the residue was taken up in ice-cold 1*N* ammonia. The product was filtered off, washed with cold water, and dried. The material thus obtained was washed several times with ether to afford **5b** (1.170 g, 88%) as yellow crystals, mp > 310°C (decomp, dioxane). HRMS Calcd for $C_{16}H_{11}N_3OCl_2$: 331.0279. Found: 331.0294. MS: *m/z* (rel. int.) 335 (M^+, 12%), 334 (12), 333 (M^+, 68), 332 (21), 331 (M^+, 100), 318 (38), 316 (63), 315 (18), 313 (50), 298 (31), 261 (20), 246 (39), 218 (25), 130 (23), 63 (15), 52 (15). ^{1}H-NMR (DMSO-d_6) δ: 9.08 (s, 1 H, H-11), 8.09 (d, $J_{8\text{-}10}$= 2.3 Hz, 1 H, H-10), 7.58 (d, $J_{7\text{-}8}$= 8.8 Hz, 1 H, H-7), 7.27 (dd, $J_{7\text{-}8}$= 8.8 Hz, $J_{8\text{-}10}$= 2.3 Hz, 1 H, H-8), 3.89 (s, 3 H, OCH_3), 3.15 (s, 3 H, CH_3-5).

General Procedure for the Preparation of Compounds (**6a-c**) and (**7a-c**)

To a suspension of the dichloro compound (**5a**, **5b**, or **5c**[8]) (2 mmol), respectively, in dry dioxane (40 mL) was added *N*,*N*-diethyl-1,3-propanediamine (8 mL, 51 mmol), and the mixture was refluxed under an argon atmosphere until the starting material was completely dissolved. The solution was kept at this temperature for 30 min, then it was cooled and the volatile components were removed under reduced pressure. The residue was taken up in dichloromethane and it was washed several times with 2*N* ammonia. After drying with Na_2SO_4, the organic layer was evaporated and the residue was subjected to column chromatography (dichloromethane/methanol/triethylamine, 95:5:2, for compounds **6a,b**/**7a,b**) or

MPLC (dichloromethane/ethyl acetate/triethylamine, 45:5:1, for compounds **6c/7c**). After elution of the first fraction (compounds of type **6**), a gradient was applied by addition of increasing amounts of methanol to the eluent, thus affording compounds (**7**) in the second fraction.

4-Chloro-1-[3-(diethylamino)propylamino]-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**6a**)

Yield: 238 mg (30%), yellow crystals, mp 225-228°C (dioxane). *Anal.* Calcd for $C_{22}H_{26}N_5Cl$: C, 66.74; H, 6.62; N, 17.69. Found: C, 66.66; H, 6.72; N, 17.45. MS: *m/z* (rel. int.) 397 (M^+, 1%) , 395 (M^+, 2), 360 (16), 324 (59), 323 (88), 322 (100), 321 (49), 309 (24), 296 (61), 295 (75), 289 (27), 288 (23), 283 (28), 249 (14), 232 (56), 205 (14), 161 (12), 112 (50), 100 (21), 98 (22), 86 (74), 59 (63), 57 (65). ^{1}H-NMR (DMSO-d_6) δ: 11.75 (s, 1 H, carbazole-NH), 8.96 (s, 1 H, H-11), 8.21 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.68 (t, J = 4.8 Hz, 1 H, $N\underline{H}CH_2$, shows positive NOE on irradiation at 8.96 ppm), 7.65-7.53 (m, 2 H, H-7, H-8), 7.37-7.28 (m, 1 H, H-9), 3.63-3.53 (m, 2 H, $NHC\underline{H}_2$), 3.14 (s, 3 H, CH_3-5), 2.59-2.47 (m, 6 H, $NHCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 1.86 (quintet, J = 6.9 Hz, 2 H, $NHCH_2C\underline{H}_2CH_2N$), 0.98 (t, J = 7.1 Hz, 6 H, $NCH_2C\underline{H}_3$).

1-Chloro-4-[3-(diethylamino)propylamino]-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**7a**)

Yield: 269 mg (34%), yellow crystals, mp 247-249°C (ethanol). *Anal.* Calcd for $C_{22}H_{26}N_5Cl$: C, 66.74; H, 6.62; N, 17.69. Found: C, 66.71; H, 6.69; N, 17.62. MS: *m/z* (rel. int.) 397 (M^+, 1%), 395 (M^+, 3), 325 (23), 324 (40), 323 (70), 322 (80), 293 (18), 289 (21), 232 (30), 112 (80), 86 (46), 59 (100), 57 (53). ^{1}H-NMR (DMSO-d_6) δ: 11.80 (s, 1 H, carbazole-NH), 8.77 (s, 1 H, H-11), 8.44 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.66-7.54 (m, 2 H, H-7, H-8), 7.34-7.26 (m, 1 H, H-9), 6.69 (t, J = 4.5 Hz, 1 H, $N\underline{H}CH_2$), 3.58-3.49 (m, 2 H, $NHC\underline{H}_2$), 3.13 (s, 3 H, CH_3-5, shows positive NOE on irradiation at 6.69 ppm), 2.60-2.45 (m, 6 H, $NHCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 1.86 (quintet, J = 6.7 Hz, 2 H, $NHCH_2C\underline{H}_2CH_2N$), 0.96 (t, J = 7.1 Hz, 6 H, $NCH_2C\underline{H}_3$).

4-Chloro-1-[3-(diethylamino)propylamino]-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**6b**)

Yield: 237 mg (27%), yellow crystals, mp >180°C decomp (dichloromethane/ether). *Anal.* Calcd for $C_{23}H_{28}N_5OCl \cdot 0.65\ H_2O$: C, 63.12; H, 6.75; N, 16.00. Found: C, 63.47; H, 6.67; N, 15.57. HRMS Calcd for $C_{23}H_{28}N_5OCl$: 425.1982. Found: 425.1962. MS: *m/z* (rel. int.) 427 (M^+, 2%), 425 (M^+, 4), 354 (25), 353 (44), 352 (49), 351 (32), 339 (40), 327 (37), 326 (54), 325 (93), 319 (34), 318 (29), 313 (40), 262 (52), 113 (25), 112 (53), 100 (21), 98 (21), 86 (100), 84 (23), 72 (24), 58 (72), 56 (25). ^{1}H-NMR (DMSO-d_6) δ: 11.61 (s, 1 H, carbazole-NH), 8.98 (s, 1 H, H-11), 7.70 (d, $J_{8\text{-}10}$ = 2.6 Hz, 1 H, H-10), 7.67 (br t, 1 H, $N\underline{H}CH_2$, shows positive NOE on irradiation at 8.98 ppm), 7.54 (d, $J_{7\text{-}8}$ = 8.8 Hz, 1 H, H-7), 7.23

(dd, $J_{7\text{-}8}$ = 8.8 Hz, $J_{8\text{-}10}$ = 2.6 Hz, 1 H, H-8), 3.89 (s, 3 H, OCH_3), 3.60 (q, J = 2.4 Hz, 2 H, $NHCH_2CH_2$), 3.11 (s, 3 H, CH_3-5), 2.80-2.60 (m, unresolved, 6 H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 1.98-1.85 (m, unresolved, 2 H, $NHCH_2CH_2CH_2N$), 1.04 (t, J = 6.9 Hz, 6 H, NCH_2CH_3).

1-Chloro-4-[3-(diethylamino)propylamino]-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**7b**)

Yield: 374 mg (44%), yellow crystals, mp 129-131°C (ethanol). HRMS Calcd for $C_{23}H_{28}N_5OCl$: 425.1982. Found: 425.2002. MS: *m/z* (rel. int.) 427 (M^+, 2%), 425 (M^+, 5), 354 (44), 353 (44), 352 (100), 351 (27), 339 (21), 337 (37), 262 (20), 112 (36), 86 (23), 58 (49). ^{1}H-NMR (DMSO-d_6) δ: 11.71 (s, 1 H, carbazole-NH), 8.82 (s, 1 H, H-11), 8.05 (d, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-10), 7.53 (d, $J_{7\text{-}8}$ = 8.7 Hz, 1 H, H-7), 7.21 (dd, $J_{7\text{-}8}$ = 8.7 Hz, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-8), 6.68 (br t, 1 H, $NHCH_2$), 3.89 (s, 3 H, OCH_3), 3.57 (q, J = 2.1 Hz, 2 H, $NHCH_2CH_2$), 3.12 (s, 3 H, CH_3-5, shows positive NOE on irradiation at 6.68 ppm), 3.05-2.60 (m, unresolved, 6 H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 2.08-1.92 (m, unresolved, 2 H, $NHCH_2CH_2CH_2N$), 1.18-1.03 (m, unresolved, 6 H, NCH_2CH_3).

4-Chloro-1-[3-(diethylamino)propylamino]-5,6-dimethyl-6*H*-pyridazino[4,5-*b*]carbazole (**6c**)

Yield: 280 mg (34%), yellow oil. HRMS Calcd for $C_{23}H_{29}N_5Cl$ (MH^+): 410.2111. Found: 410.2067. MS: *m/z* (rel. int.) 409 (M^+, 3%), 374 (15), 373 (18), 337 (47), 336 (42), 335 (39), 323 (36), 310 (41), 309 (100), 303 (33), 302 (30), 301 (21), 297 (44), 263 (14), 261 (14), 246 (50), 112 (69), 100 (21), 98 (28), 86 (100), 59 (61), 57 (45). ^{1}H-NMR (DMSO-d_6) δ: 8.94 (s, 1 H, H-11), 8.20 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.72-7.60 (m, 3 H, NH, H-7, H-8; NH part shows positive NOE on irradiation at 8.94 ppm), 7.40-7.33 (m, 1 H, H-9), 4.13 (s, 3 H, NCH_3), 3.63-3.52 (m, 2 H, $NHCH_2$), 3.22 (s, 3 H, CH_3-5), 2.62-2.50 (m, 6 H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 1.87 (quintet, J = 6.9 Hz, 2 H, $NHCH_2CH_2CH_2N$), 0.99 (t, J = 7.2 Hz, 6 H, NCH_2CH_3).

1-Chloro-4-[3-(diethylamino)propylamino]-5,6-dimethyl-6*H*-pyridazino[4,5-*b*]carbazole (**7c**)

Yield: 352 mg (43%), yellow oil. HRMS Calcd for $C_{23}H_{29}N_5Cl$ (MH^+): 410.2111. Found: 410.2060. MS: *m/z* (rel. int.) 411 (M^+, 2%), 409 (M^+, 6), 374 (10), 337 (18), 336 (22), 335 (27), 323 (11), 303 (24), 297 (15), 295 (22), 246 (13), 245 (11), 112 (100), 86 (46). ^{1}H-NMR (DMSO-d_6) δ: 8.72 (s, 1 H, H-11), 8.45 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.74-7.62 (m, 2 H, H-7, H-8), 7.38-7.30 (m, 1 H, H-9), 6.70 (br s, 1 H, NH), 4.15 (s, 3 H, NCH_3), 3.59 (t, J = 6.6 Hz, 2 H, $NHCH_2CH_2$), 3.24 (s, 3 H, CH_3-5, shows positive NOE on irradiation at 6.70 ppm), 3.03-2.83 (m, 6 H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 2.04 (quintet, J = 6.6 Hz, 2 H, $NHCH_2CH_2CH_2N$), 1.14 (t, J = 7.2 Hz, 6 H, NCH_2CH_3).

General Procedure for the Preparation of Compounds (**8a-c**) and (**9a-c**)

To a solution of the chloro compound (**6a**, **7a**, **6b**, **7b**, **6c**, or **7c**, 0.5 mmol), respectively, in methanol (10 mL) was added ammonium formate (158 mg, 2.5 mmol) and 10% palladium/carbon (60 mg), and the mixture was heated to reflux under an argon atmosphere. If necessary, further portions of ammonium formate were added until the starting material was completely consumed (5-10 h; TLC monitoring: dichloromethane/2-propanol, 9:1). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in aqueous K_2CO_3 solution and it was extracted with dichloromethane. After drying of the extract with Na_2SO_4, the solvent was removed under reduced pressure.

1-[3-(Diethylamino)propylamino]-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**8a**)

The crude product was purified by column chromatography (dichloromethane/methanol/triethylamine, 45:5:1) and subsequent recrystallization from acetonitrile to give **8a** (159 mg, 88%) as pale yellow needles, mp 243-245°C. *Anal.* Calcd for $C_{22}H_{27}N_5$: C, 73.10; H, 7.53; N, 19.37. Found: C, 72.81; H, 7.53; N, 19.29. MS: *m/z* (rel. int.) 361 (M^+, 10%), 332 (24), 289 (33), 288 (36), 287 (31), 275 (50), 262 (68), 261 (100), 249 (42), 233 (34), 232 (27), 205 (17), 112 (17), 100 (15), 98 (22), 86 (48), 84 (20), 59 (35), 57 (19). ^{1}H-NMR (DMSO-d_6) δ: 11.65 (s, 1 H, carbazole-NH), 9.16 (s, 1 H, H-4, shows positive NOE on irradiation at 2.88 ppm), 8.91 (s, 1 H, H-11), 8.19 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.63-7.52 (m, 3 H, H-7, H-8, N<u>H</u>CH_2), 7.34-7.26 (m, 1 H, H-9), 3.64 (t, J = 6.9 Hz, 2 H, NHC<u>H</u>$_2CH_2$), 2.88 (s, 3 H, CH_3-5), 2.67-2.52 (*m*, *6* H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 1.90 (*quintet*, J = 6.9 Hz, 2 H, $NHCH_2CH_2CH_2N$), 1.02 (t, J = 7.2 Hz, 6 H, NCH_2CH_3).

4-[3-(Diethylamino)propylamino]-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**9a**)

The crude product was recrystallized from ethanol to afford **9a** (156 mg, 86%) as yellow crystals, mp 275-278°C (decomp). *Anal.* Calcd for $C_{22}H_{27}N_5$: C, 73.10; H, 7.53; N, 19.37. Found: C, 72.96; H, 7.74; N, 19.38. MS: *m/z* (rel. int.) 361 (M^+, 19%), 332 (15), 331 (12), 289 (49), 288 (50), 287 (43), 275 (88), 262 (100), 249 (37), 248 (29), 247 (56), 233 (55), 232 (36), 205 (25), 192 (12), 191 (11), 112 (72), 98 (35), 86 (76), 84 (33), 59 (53), 57 (30). ^{1}H-NMR (DMSO-d_6) δ: 11.59 (s, 1 H, carbazole-NH), 8.90 (s, 1 H, H-1), 8.55 (s, 1 H, H-11, shows positive NOE on irradiation at 8.90 ppm), 8.29 (d, $J_{9\text{-}10}$ = 7.5 Hz, 1 H, H-10), 7.63-7.51 (m, 2 H, H-7, H-8), 7.31-7.23 (m, 1 H, H-9), 6.50 (t, J = 6.1 Hz, 1 H, N<u>H</u>CH_2), 3.56 (q, J = 6.1 Hz, 2 H, NHC<u>H</u>$_2CH_2$), 3.13 (s, 3 H, CH_3-5), 2.60-2.46 (m, 6 H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 1.87 (quintet, J = 6.1 Hz, 2 H, $NHCH_2CH_2CH_2N$), 0.97 (t, J = 7.2 Hz, 6 H, NCH_2CH_3).

1-[3-(Diethylamino)propylamino]-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**8b**)

The crude product was recrystallized from acetonitrile to afford **8b** (122 mg, 62%) as pale brown needles, mp 227-228°C. *Anal.* Calcd for $C_{23}H_{29}N_5O$: C, 70.56; H, 7.47; N, 17.89. Found: C, 70.29; H, 7.44; N, 17.69. MS: *m/z* (rel. int.) 391 (M^+, 2%), 362 (10), 319 (15), 318 (18), 317 (14), 305 (33), 292 (48), 291 (83), 279 (35), 278 (17), 277 (12), 264 (11), 263 (29), 262 (12), 248 (21), 192 (10), 152 (13), 138 (12), 124 (11), 113 (14), 112 (25), 110 (15), 100 (21), 98 (40), 96 (19), 86 (100), 85 (13), 84 (68), 73 (10), 72 (19), 71 (18), 70 (19), 69 (12), 58 (99), 57 (32), 56 (66), 55 (21). ^{1}H-NMR (DMSO-d_6) δ: 11.43 (s, 1 H, carbazole-NH), 9.13 (s, 1 H, H-4, shows positive NOE on irradiation at 2.84 ppm), 8.86 (s, 1 H, H-11), 7.67 (d, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-10), 7.51 (d, $J_{7\text{-}8}$ = 8.7 Hz, 1 H, H-7), 7.45 (t, J = 5.1 Hz, 1 H, NHCH$_2$), 7.19 (dd, $J_{7\text{-}8}$ = 8.7 Hz, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-8), 3.89 (s, 3 H, OCH$_3$), 3.62 (q, J = 6.5 Hz, 2 H, NHCH$_2$CH$_2$), 2.84 (s, 3 H, CH$_3$-5), 2.58-2.48 (m, 6 H, NHCH$_2$CH$_2$CH$_2$N(CH$_2$CH$_3$)$_2$), 1.87 (quintet, J = 6.5 Hz, 2 H, NHCH$_2$CH$_2$CH$_2$N), 0.99 (t, J = 7.2 Hz, 6 H, NCH$_2$CH$_3$).

4-[3-(Diethylamino)propylamino]-9-methoxy-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**9b**)

The crude product was recrystallized from acetonitrile/ethanol to afford **9b** (147 mg, 75%) as pale brown crystals, mp 259-261°C (decomp). *Anal.* Calcd for $C_{23}H_{29}N_5O$: C, 70.56; H, 7.47; N, 17.89. Found: C, 70.20; H, 7.29; N, 17.63. MS: *m/z* (rel. int.) 391 (M^+, 2%), 319 (14), 318 (36), 305 (22), 303 (23), 292 (31), 279 (15), 278 (14), 277 (24), 263 (21), 262 (15), 248 (16), 192 (10), 124 (12), 113 (20), 112 (81), 110 (18), 100 (14), 98 (31), 96 (24), 86 (88), 84 (36), 82 (23), 73 (15), 72 (21), 71 (14), 70 (18), 58 (100), 57 (25), 56 (55), 55 (15). ^{1}H-NMR (DMSO-d_6) δ: 11.40 (s, 1 H, carbazole-NH), 8.86 (s, 1 H, H-1), 8.53 (s, 1 H, H-11, shows positive NOE on irradiation at 8.86 ppm), 7.87 (d, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-10), 7.49 (d, $J_{7\text{-}8}$ = 8.7 Hz, 1 H, H-7), 7.18 (dd, $J_{7\text{-}8}$ = 8.7 Hz, $J_{8\text{-}10}$ = 2.4 Hz, 1 H, H-8), 6.47 (br t, 1 H, NHCH$_2$), 3.87 (s, 3 H, OCH$_3$), 3.54 (br q, 2 H, NHCH$_2$CH$_2$), 3.10 (s, 3 H, CH$_3$-5), 2.58-2.46 (m, 6 H, NHCH$_2$CH$_2$CH$_2$-N(CH$_2$CH$_3$)$_2$), 1.85 (quintet, J = 6.6 Hz, 2 H, NHCH$_2$CH$_2$CH$_2$N), 0.96 (t, J = 7.2 Hz, 6 H, NCH$_2$CH$_3$).

1-[3-(Diethylamino)propylamino]-5,6-dimethyl-6*H*-pyridazino[4,5-*b*]carbazole (**8c**)

The crude product was purified by MPLC (dichloromethane/methanol/triethylamine, 95:5:2) to give **8c** (161 mg, 86%) as a yellow solid which slowly became dark, mp 210-219°C. *Anal.* Calcd for $C_{23}H_{29}N_5$: C, 73.57; H, 7.78; N, 18.65. Found: C, 73.31; H, 8.02; N, 18.42. MS: *m/z* (rel. int.) 375 (M^+, 10%), 346 (25), 345 (19), 303 (30), 302 (28), 289 (52), 288 (42), 276 (79), 275 (100), 263 (51), 247 (27), 246 (27), 151 (12), 112 (15), 98 (22), 86 (46), 84 (21), 59 (27), 57 (18). ^{1}H-NMR (DMSO-d_6) δ: 9.23 (s, 1 H, H-4, shows positive NOE on irradiation at 3.13 ppm), 8.96 (s, 1 H, H-11), 8.20 (d, $J_{9\text{-}10}$ = 7.5 Hz, 1 H, H-10), 7.72-7.56 (m, 2 H, H-7, H-8), 7.57 (br s, 1 H, NHCH$_2$), 7.38-7.30 (m, 1 H, H-9), 4.22 (s, 3 H, NCH$_3$),

3.68-3.59 (m, unresolved, 2 H, $NHCH_2CH_2$), 3.13 (s, 3 H, CH_3-5), 2.70-2.51 (m, 6 H, $NHCH_2CH_2CH_2$-$N(CH_2CH_3)_2$), 1.97-1.84 (m, 2 H, $NHCH_2CH_2CH_2N$), 1.03 (t, J = 6.9 Hz, 3 H, NCH_2CH_3), 0.99 (t, J = 6.9 Hz, 3 H, NCH_2CH_3).

4-[3-(Diethylamino)propylamino]-5,6-dimethyl-6*H*-pyridazino[4,5-*b*]carbazole (**9c**)

The crude product was purified by MPLC (dichloromethane/methanol/triethylamine, 95:5:2) to give **9c** (159 mg, 82%) as a yellow solid which slowly became dark, mp 110-118°C. *Anal.* Calcd for $C_{23}H_{29}N_5 \cdot 0.7\ H_2O$: C, 71.18; H, 7.89; N, 18.04. Found: C, 71.28; H, 8.07; N, 17.60. HRMS Calcd for $C_{23}H_{29}N_5$: 375.2423. Found: 375.2424. MS: *m/z* (rel. int.) 375 (M^+, 25%), 346 (14), 303 (34), 302 (31), 301 (30), 289 (86), 276 (80), 275 (43), 263 (40), 261 (100), 247 (22), 246 (27), 219 (18), 151 (11), 112 (82), 98 (29), 86 (73), 84 (28), 59 (36), 57 (22). ^{1}H-NMR (DMSO-d_6) δ: 8.88 (s, 1 H, H-1), 8.54 (s, 1 H, H-11, shows positive NOE on irradiation at 8.88 ppm), 8.30 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.71-7.58 (m, 2 H, H-7, H-8), 7.35-7.28 (m, 1 H, H-9), 6.49 (br s, 1 H, $NHCH_2$), 4.13 (s, 3 H, NCH_3), 3.57 (t, J = 6.6 Hz, 2 H, $NHCH_2CH_2$), 3.23 (s, 3 H, CH_3-5), 2.71-2.51 (m, 6 H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$), 1.90 (quintet, J = 6.6 Hz, 2 H, $NHCH_2CH_2CH_2N$), 1.01 (t, J = 7.1 Hz, 6 H, NCH_2CH_3).

1-Chloro-4,6-dihydro-5-methyl-3*H*-pyridazino[4,5-*b*]carbazol-4-one (**10**)

A solution of **5a** (302 mg, 1 mmol) in DMSO (20 mL) and water (2 mL) was heated to 100°C for 1 h. The solvents were removed by Kugelrohr distillation and the residue was triturated with little methanol. The product was filtered off, washed with cold methanol, and dried to afford **10** (233 mg, 77%) as pale yellow crystals, mp >330°C (decomp, methanol). *Anal.* Calcd for $C_{15}H_{10}N_3OCl \cdot H_2O$: C, 59.71; H, 4.01; N, 13.93. Found: C, 60.10; H, 3.90; N, 13.93. MS: *m/z* (rel. int.) 285 (M^+, 33%), 283 (M^+, 100), 248 (25), 226 (14), 191 (12), 190 (13). IR (cm^{-1}): 3265, 1627. ^{1}H-NMR (DMSO-d_6) δ: 12.32 (s, 1 H, NH), 11.93 (s, 1 H, NH), 8.67 (s, 1 H, H-11), 8.42 (d, $J_{9\text{-}10}$ = 7.7 Hz, 1 H, H-10), 7.68-7.54 (m, 2 H, H-7, H-8), 7.34-7.26 (m, 1 H, H-9), 3.16 (s, 3 H, CH_3-5).

4,6-Dihydro-5-methyl-3*H*-pyridazino[4,5-*b*]carbazol-4-one (**11**)

To a suspension of **10** (142 mg, 0.5 mmol) in methanol (10 mL) was added ammonium formate (158 mg, 2.5 mmol) and 10% palladium/carbon (50 mg), and the mixture was heated to reflux under an argon atmosphere. Further portions of ammonium formate were added until the starting material was completely consumed (TLC monitoring: dichloromethane/methanol, 9:1). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. Water (10 mL) was added to the residue, the product was collected by filtration, washed with water, and dried to afford **11** (112 mg, 88%) as pale yellow crystals,

mp 312-315°C (methanol). *Anal.* Calcd for $C_{15}H_{11}N_3O \cdot 0.3\ H_2O$: C, 70.74; H, 4.59; N, 16.50. Found: C, 70.79; H, 4.67; N, 16.54. HRMS Calcd for $C_{15}H_{11}N_3O$: 249.0902. Found: 249.0887. MS: *m/z* (rel. int.) 250 (18%), 249 (M^+, 100), 192 (28), 191 (15), 110 (17), 96 (20), 83 (48), 69 (15). IR (cm^{-1}): 3258, 1642. ^{1}H-NMR (DMSO-d_6) δ: 12.09 (s, 1 H, NH), 11.76 (s, 1 H, NH), 8.53 (s, 1 H, H-11), 8.31 (s, 1 H, H-1, shows positive NOE on irradiation at 8.53 ppm), 8.28 (d, $J_{9\text{-}10}$ = 7.5 Hz, 1 H, H-10), 7.64-7.52 (m, 2 H, H-7, H-8), 7.31-7.25 (m, 1 H, H-9), 3.16 (s, 3 H, CH_3-5).

1,4-Bis[3-(diethylamino)propylamino]-5-methyl-6*H*-pyridazino[4,5-*b*]carbazole (**12**)

A mixture of **5a** (423 mg, 1.4 mmol) and *N*,*N*-diethyl-1,3-propanediamine (15 mL, 95 mmol) was heated under an argon atmosphere to 150°C for 2 h. The reagent was removed by Kugelrohr distillation and the residue was taken up in water (20 mL). The mixture was made weakly alkaline with saturated aqueous $NaHCO_3$, then it was extracted with dichloromethane. The extract was concentrated and subjected to preparative TLC (dichloromethane/methanol/triethylamine, 41:6:3) to give **12** (172 mg, 25%) as a yellow solid which slowly became dark, mp 85-90°C (methanol). HRMS Calcd for $C_{29}H_{43}N_7$: 489.3580. Found 489.3555. MS: *m/z* (rel. int.) 489 (M^+, 10%), 460 (31), 417 (31), 416 (72), 330 (33), 316 (39), 304 (41), 289 (28), 232 (35), 112 (28), 86 (100), 58 (40). ^{1}H-NMR (DMSO-d_6) δ: 11.55 (s, 1 H, carbazole-NH), 8.75 (s, 1 H, H-11), 8.17 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.62-7.48 (m, 2 H, H-7, H-8), 7.30-7.24 (m, 1 H, H-9), 6.80 (br s, 1 H, $N\underline{H}CH_2$), 5.75 (br s, 1 H, $N\underline{H}CH_2$), 3.48 (t, J = 6.6 Hz, 2 H, $NHC\underline{H}_2CH_2$), 3.39 (t, J = 6.6 Hz, 2 H, $NHC\underline{H}_2CH_2$), 2.60-2.47 (m, 12 H, $NHCH_2CH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$), 1.87-1.79 (m, 4 H, $NHCH_2C\underline{H}_2CH_2N$), 1.00 (t, J = 7.2 Hz, 6 H, $NCH_2C\underline{H}_3$), 0.97 (t, J = 7.2 Hz, 6 H, $NCH_2C\underline{H}_3$).

5-Methyl-6*H*-pyridazino[4,5-*b*]carbazole (**13**)

To a stirred solution of ammonium formate (630 mg, 10 mmol) in dry DMF (40 mL), kept at 75°C under an argon atmosphere, was added 10% palladium/carbon (100 mg), followed by a solution of **5a** (302 mg, 1 mmol) in dry DMF (20 mL; slow addition in 2 mL portions). Stirring was continued at the same temperature and further portions of ammonium formate were gradually added, until the starting material could no longer be detected by TLC (dichloromethane/methanol, 9:1). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (200 mL) and the resulting suspension was continuously extracted with ethyl acetate. After drying, the solvent was removed and the residue was purified by column chromatography (dichloromethane/methanol, 93:7), followed by sublimation (10^{-2} mbar, 230°C) to afford **13** as pale yellow crystals (160 mg, 69%), mp 303-305°C. *Anal.* Calcd for $C_{15}H_{11}N_3 \cdot 0.35\ H_2O$: C, 75.20; H, 4.92; N, 17.54. Found: C, 75.20; H, 4.87; N, 17.56. HRMS Calcd for $C_{15}H_{11}N_3$: 233.0953. Found: 233.0940. MS: *m/z* (rel. int.) 234 (15%), 233 (M^+, 100), 205 (11),

106 (24), 105 (11), 92 (14), 91 (45), 57 (12). ^{1}H-NMR (DMSO-d_6) δ: 11.85 (s, 1 H, NH), 9.87 (s, 1 H, H-4, shows positive NOE on irradiation at 2.96 ppm), 9.62 (s, 1 H, H-1, shows positive NOE on irradiation at 8.80 ppm), 8.80 (s, 1 H, H-11), 8.37 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1 H, H-10), 7.66-7.55 (m, 2 H, H-7, H-8), 7.34-7.28 (m, 1 H, H-9), 2.96 (s, 3 H, CH_3-5).

3,5-Dimethyl-6*H*-pyridazino[4,5-*b*]carbazol-3-ium Iodide (**14**)

To a solution of **13** (58 mg, 0.25 mmol) in dry DMF (7 mL) was added methyl iodide (1 mL, 16 mmol), and the mixture was stirred at rt for 1 h. The precipitate was filtered off, washed with little DMF and recrystallized from acetonitrile/water to give **14** (57 mg, 60%) as orange crystals, mp >310°C (decomp). *Anal.* Calcd for $C_{16}H_{14}N_3I$: C, 51.22; H, 3.76; N, 11.20. Found: C, 50.93; H, 3.58; N, 11.14. ^{1}H-NMR (DMSO-d_6) δ: 12.61 (s, 1 H, NH), 10.64 (s, 1 H, H-4, shows positive NOE on irradiation at 4.61 ppm or at 3.09 ppm), 9.95 (s, 1 H, H-1), 9.24 (s, 1 H, H-11), 8.55 (d, $J_{9\text{-}10}$ = 7.8 Hz, H-10), 7.81-7.74 (m, 2 H, H-7, H-8), 7.50-7.44 (m, 1 H, H-9), 4.61 (s, 3 H, NCH_3), 3.09 (s, 3 H, CH_3-5).

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11. The mother liquor contains a mixture of **14** and another reaction product (most probably the 2,5-disubstituted isomer, according to ^{1}H-NMR) which could not be isolated in a pure form.

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