Synthesis of 3-azaharman and other new azacarbolines of the pyridazino[4,5-*b*]indole type

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Dedicated with best wishes to Professor Branko Stanovnik on his 65th birthday

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Abstract

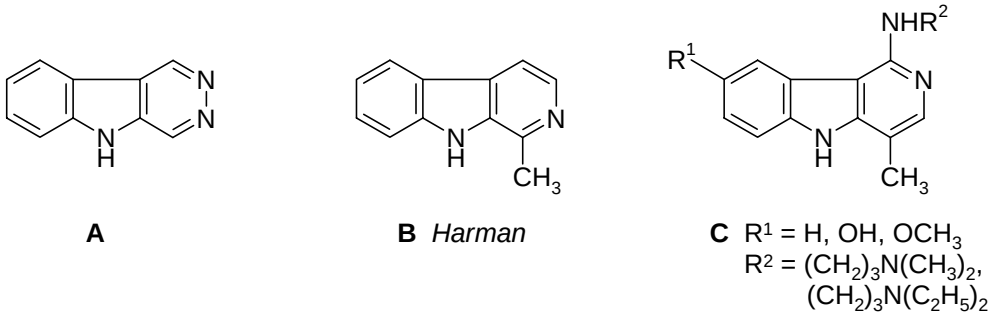
Starting from the indole-fused pyridazinone **3**, a series of new pyridazino[4,5-*b*]indoles, functionalized at positions 1, 2, or 5 was prepared, including the two tetracyclic compounds **12** and **13**, which represent new ring systems. Reductive dehalogenation of the chloro compound **8** gave a 3-aza isoster of the natural product, harman.

Keywords: Pyridazino[4,5-*b*]indoles, azacarbolines, azaharman, antitumor agents

Introduction

The pyridazino[4,5-*b*]indole ring system (**A**) has been known for several decades and so far a variety of biological activitiy has been reported for a large number of its derivatives, such as antihypertensive,[1] antiarrhythmic,[2] positive inotropic,[3] thromboxane A_2 synthetase inhibitory,[4] MAO inhibitory,[5] serotonine antagonistic,[6] antihistaminic,[7] anxiolytic,[8] or HIV-1 reverse transcriptase inhibitory[9] activities. Moreover, the pyridazino[4,5-*b*]indole ring system can be regarded as an aza analog of β-carboline as well as γ-carboline which both, in turn, are the parent systems of many other bio-active natural and synthetic compounds. In this context, the 1-methyl-β-carboline, *harman* (**B**),[10] and its cytotoxic congeners as well as the antitumor γ-carbolines of type **C** (Figure 1) should be particularly mentioned. The latter compounds[11] had been designed as tricyclic analogs of tetracyclic anticancer agents of the *ellipticine* type, and they had been found to exhibit significant cytotoxic activity despite "shrinking" the pyrido[4,3-*b*]carbazole into a pyrido[4,3-*b*]indole scaffold. As we had previously demonstrated that also pyridazino[4,5-*b*]carbazoles (3-azaellipticines) bearing appropriate substituents show comparable activity in

antitumor assays,[12] we became interested in the synthesis of 4-methylpyridazino[4,5-*b*]indoles as tricyclic analogs of these 3-azaellipticines, representing another new type of potential antitumor agents.

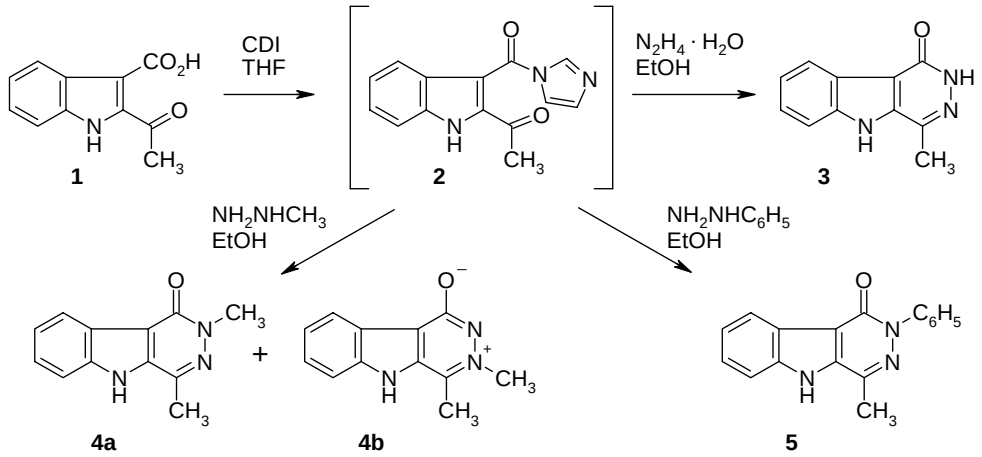


A **B** *Harman* **C** R^1 = H, OH, OCH_3; R^2 = $(CH_2)_3N(CH_3)_2$, $(CH_2)_3N(C_2H_5)_2$

Figure 1

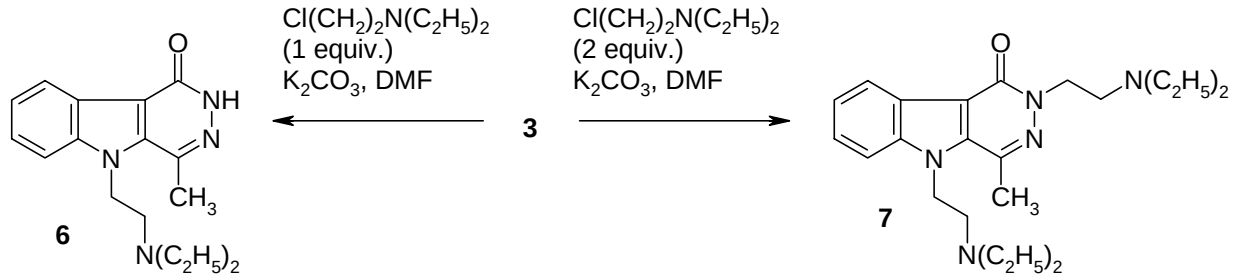
Results and Discussion

The key intermediate **3** (Scheme 1) had been prepared previously by Zhungietu et al.[13] by condensation of 2-acetylindole-3-carboxylic acid **1** with hydrazine hydrate at elevated temperature. This reaction, however, suffers from poorly reproducible yields which reflect the high decarboxylation tendency[14] of the starting material, causing a significant side reaction (formation of 2-acetylindole or its hydrazone, respectively). We now could substantially improve this step by first transforming the keto acid **1** into a suitable activated derivative under mild conditions and subsequent treatment of this intermediate with hydrazine hydrate. For this purpose, the imidazolide **2** was found to be a good choice, as it can be easily prepared in an inert solvent at room temperature by treatment of **1** with 1,1'-carbonyldiimidazole (CDI), and without isolation this compound smoothly undergoes hydrazinolysis to afford the pyridazinone **3**. Also monosubstituted hydrazines can be employed in the cyclization reaction with **2** to afford the 2-substituted products **4a** and **5**, although yields are somewhat lower and, in the case of methylhydrazine, formation of small amounts of an isomeric side product **4b** was observed.



Scheme 1

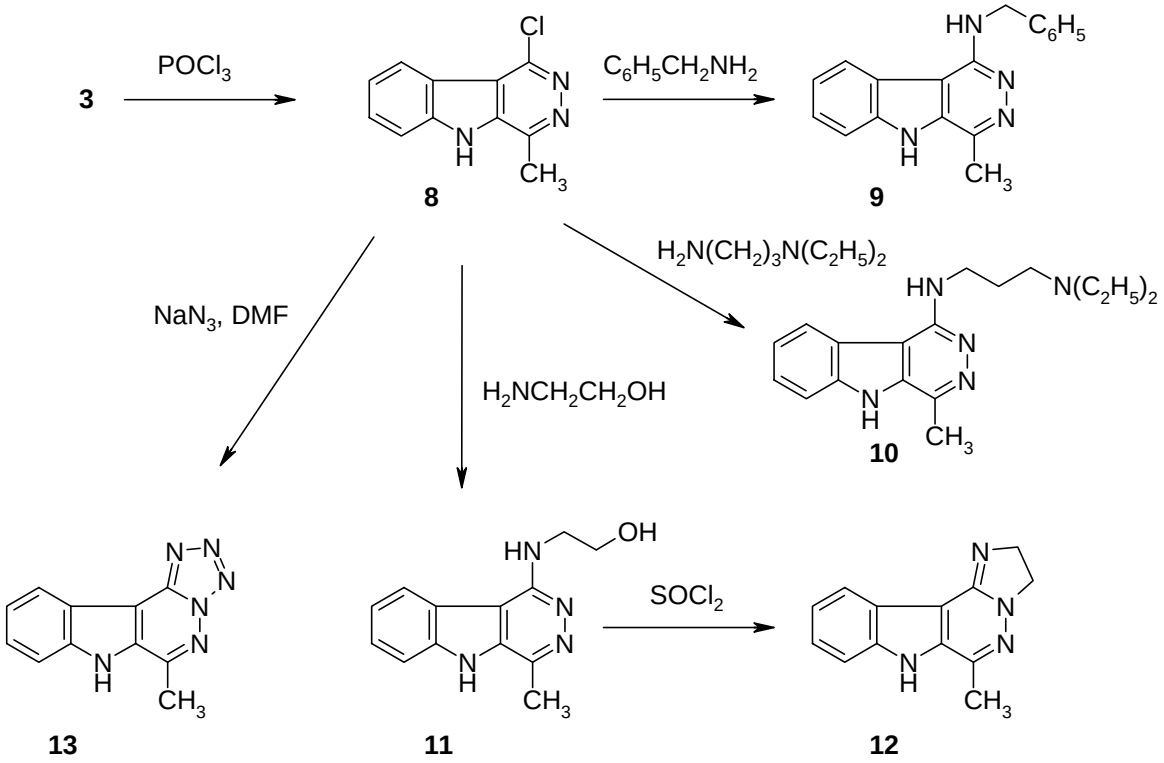
On the other hand, it was found that alkylation of the condensed pyridazinone **3** preferentially takes place at the indole nitrogen. Thus, reaction of **3** with one equivalent of diethylaminoethyl chloride in the presence of potassium carbonate in dimethylformamide solution gives the 5-substituted product **6** in moderate yield, whereas employment of two equivalents of the alkylating agent affords the 2,5-disubstituted compound **7** (Scheme 2).



Scheme 2

As an intermediate for functionalization at the 1-position, the chloropyridazine **8** was prepared in excellent yield by heating **3** in phosphorus oxychloride (Scheme 3). This compound turned out to be remarkably inert towards nucleophilic attack. For instance, **8** can be easily recrystallized from boiling ethanol/acetonitrile (2:1) without noticeable solvolysis. Obviously, this lack of reactivity is mainly caused by considerable steric shielding of the chloro function by the 9-H atom at the benzene ring, in addition to electronic factors (annulation of an electron-rich indole system onto the chloropyridazine moiety). Nucleophilic substitution of the chloro function in **8** with amines requires relatively harsh conditions, e.g. heating in a high-boiling amine in the absence of a solvent. By this method, the benzylamino compound **9** could be obtained in good yield. Likewise, the potential anticancer agent **10**, bearing a 3-(diethylamino)propylamino side chain as well as the hydroxyethylamino derivative **11** were prepared, albeit in lower yields owing

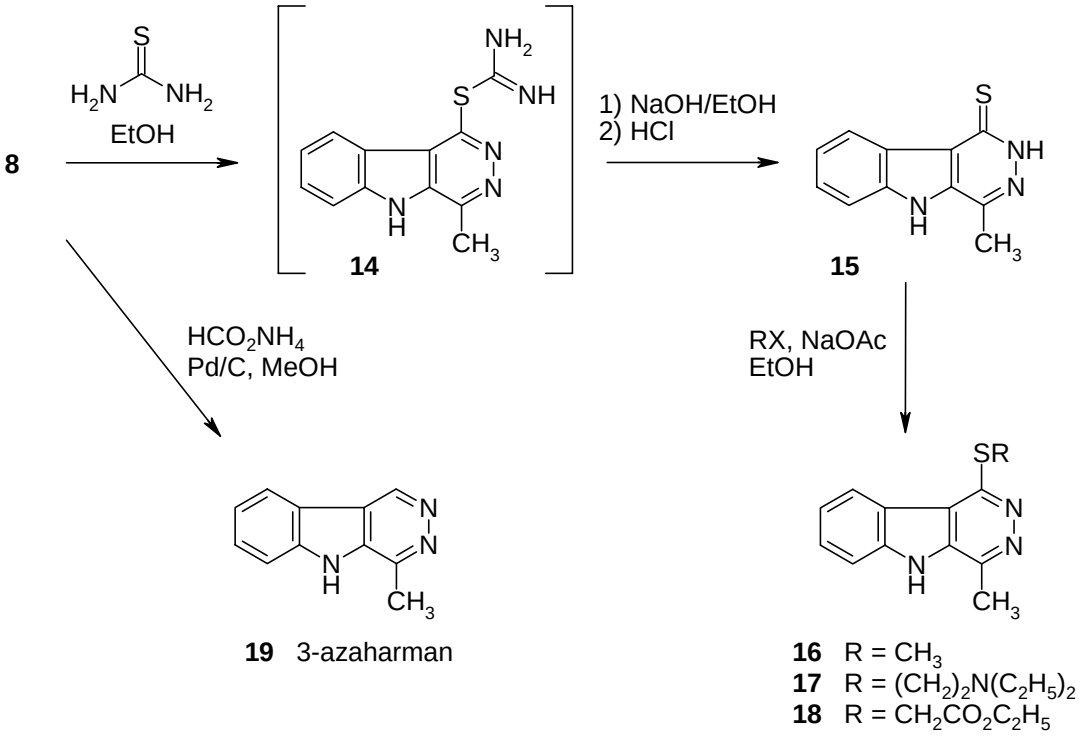
to work-up losses and some decomposition during the substitution reaction. The alcohol **11**, when heated in thionyl chloride, is transformed into the corresponding chloro derivative which spontaneously cyclizes into the imidazo[2',1':6,1]pyridazino[4,5-*b*]indole **12** (obtained as the hydrochloride), which represents a new ring system. Another representative of a hitherto unknown ring system, the tetrazolo[5',1':6,1]pyridazino[4,5-*b*]indole **13**, was prepared from **8** in a single step by refluxing with excess sodium azide in dimethylformamide solution.



Scheme 3

Attempts to convert the pyridazinone **3** into the corresponding thione by refluxing with phosphorus pentasulfide in pyridine gave only a very low yield of the desired compound, whereas employment of Lawesson's reagent met with a complete failure. However, reaction of the chloropyridazine **8** with thiourea in ethanol, followed by alkaline hydrolysis of an intermediate isothiourea derivative (**14**) was found to afford the pyridazinethione **15** in satisfactory yield (Scheme 4). Expectedly, reaction of this compound with alkylating agents takes place at the sulfur atom exclusively, as demonstrated by the transformation of **15** into the alkylsulfanyl compounds **16-18**, which are obtained by treatment of the thione with methyl iodide, diethylaminoethyl chloride, or ethyl bromoacetate, respectively, in ethanolic solution in the presence of a weak base (sodium acetate). The position of the newly introduced substituent clearly follows from NOE difference spectra which confirm the proximity of the S-alkyl residue and the 9-H proton.

In contrast to the sluggish nucleophilic displacement reactions with the chloropyridazine **8**, reductive dehalogenation takes place very smoothly when **8** is subjected to catalytic transfer hydrogenation in refluxing methanol, employing ammonium formate as the hydrogen source and palladium on carbon as the catalyst. Thus, the 1-unsubstituted tricycle **19** which represents an aza isoster of the natural product, *harman*, is obtained in 64% yield.



Scheme 4

In a preliminary *in-vitro* screening of the new azacarbolines, only compounds **6**, **7**, **9**, **10**, **11**, and **13** showed weak to moderate antitumor activity, with cell-growth inhibitory activities generally not exceeding 50% at a fixed sample concentration of 3.16 μg/mL. Further investigations aiming at the synthesis of new functionalized and/or annulated derivatives of the pyridazino[4,5-*b*]indole system with potential biological activity are in progress.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage microscope. IR spectra (KBr pellets) were recorded on a Perkin–Elmer Spectrum 1000 FT-IR instrument. ^{1}H NMR spectra were recorded on a Varian Unity*plus* 300 (300 MHz) and on a Bruker Avance DPX 200 (200 MHz) spectrometer (DMSO-d_6 as solvent unless otherwise stated, TMS as

internal reference, δ values in ppm). Mass spectra were obtained on a Shimadzu QP 5050A DI 50 instrument, high-resolution (HR) and fast-atom-bombardment (FAB) mass spectra were recorded on a Finnigan MAT 8230 spectrometer at the Department of Organic Chemistry, University of Vienna. For column chromatography, Merck Kieselgel 60 (0.063-0.200 mm) was used. Light petroleum refers to the fraction of bp 50–70 °C. Microanalyses were performed at the Department of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

2,5-Dihydro-4-methyl-1*H*-pyridazino[4,5-*b*]indol-1-one[13] **(3).** A mixture of 2-acetylindole-3-carboxylic acid **1**[15] (203 mg, 1 mmol) and *N*,*N*´-carbonyldiimidazole (243 mg, 1.5 mmol) in dry THF (10 mL) was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue (crude imidazolide **2**) was refluxed with hydrazine hydrate (1 mL, 50 mmol) in ethanol (10 mL) for 24 h. The solvent was removed in vacuo and the residue was triturated with water. The solid product was collected by filtration and recrystallized from ethanol to give **3** as buff crystals (140 mg, 70%), mp 295–297 °C (Lit.[13] 64%, mp. 295 °C).

2,4-Dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**4a**) and **3,4-dimethyl-5*H*-pyridazino[4,5-*b*]indol-3-ium-1-olate (4b).** A mixture of the carboxylic acid **1**[15] (203 mg, 1 mmol) and *N*,*N*´-carbonyldiimidazole (243 mg, 1.5 mmol) in dry THF (10 mL) was stirred at room temperature for 2 h, then the solvent was removed in vacuo and the residue (crude imidazolide **2**) was dissolved in ethanol (10 mL). Methylhydrazine (2 mL, 38 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was purified by short-column chromatography (dichloromethane/methanol, 9:1). The eluate was evaporated and the residue was recrystallized from ethanol to give **4a** as buff crystals (88 mg, 40%), mp. 331–333 °C. ^{1}H NMR δ 12.24 (s, 1H, NH, shows positive NOE on irradiation at 2.52 ppm), 8.20–8.17 (m, 1H, 9-H), 7.64–7.61 (m, 1H, 6-H), 7.49–7.43 (m, 1H, 7-H), 7.33–7.28 (m, 1H, 8-H), 3.72 (s, 3H, 2-CH_3), 2.52 (s, 3H, 4-CH_3); IR: 3187, 3158, 3086, 2942, 1632, 1621, 1584, 1558, 1452, 1384, 1324, 1247, 1200, 895, 753, 769, 658, 625 cm^{-1}; MS *m/z*: 213 (M^+, 7%), 191 (14), 190 (100), 172 (13), 91 (27); Anal. calcd. for $C_{12}H_{11}N_3O \cdot 0.35\ H_2O$ (219.55): C, 65.65; H, 5.37; N, 19.14. Found: C, 65.49; H, 5.22; N, 19.43. From the material insoluble in hot ethanol, compound **4b** was obtained as colorless crystals (16 mg, 7%), mp. >350 °C. ^{1}H NMR δ 12.37 (s, 1H, NH), 8.31 (d, *J* = 7.8 Hz, 1H, 9-H), 7.62 (d, *J* = 8.4 Hz, 1H, 6-H), 7.52–7.47 (m, 1H, 7-H), 7.31–7.26 (m, 1H, 8-H), 4.12 (s, 3H, 3-CH_3, shows positive NOE on irradiation at 2.97 ppm), 2.97 (s, 3H, 4-CH_3, shows positive NOE on irradiation at 4.12 ppm); IR: 3419, 3066, 2954, 2660, 1621, 1584, 1563, 1521, 1495, 1448, 1303, 1328, 1221, 1194, 1022, 791, 701, 665 cm^{-1}.

2,5-Dihydro-4-methyl-2-phenyl-1*H*-pyridazino[4,5-*b*]indol-1-one (5). A mixture of the carboxylic acid **1**[15] (203 mg, 1 mmol) and *N*,*N*´-carbonyldiimidazole (243 mg, 1.5 mmol) in dry THF (10 mL) was stirred at room temperature for 2 h, then the solvent was removed in vacuo and the residue (crude imidazolide **2**) was dissolved in ethanol (10 mL). Phenylhydrazine (119 mg, 1.1 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was evaporated and the residue was subjected to column chromatography (ethyl acetate/light petroleum, 1:1). Evaporation of the main fraction, followed by recrystallization of the residue from ethanol gave **5** as buff crystals (87 mg, 29%), mp. 312–314 °C. ^{1}H NMR δ 12.47 (s, 1H,

NH), 8.20 (d, *J* = 8.1 Hz, 1H, 9-H), 7.69 (d, *J* = 8.1 Hz, 1H, 6-H), 7.60–7.56 (m, 2H, phenyl 2'-H, 6'-H), 7.54–7.47 (m, 3H, 7-H, phenyl 3'-H, 5'-H), 7.42–7.32 (m, 2H, 8-H, phenyl 4'-H), 2.62 (s, 3H, CH_3); IR: 3136, 2967, 2925, 1621, 1539, 1501, 1419, 1380, 1247, 1232, 1137, 751, 736, 663 cm^{-1}; MS *m/z*: 276 (M^++1, 19%), 275 (M^+, 100), 274 (M^+-1, 93), 205 (6), 170 (6), 140 (21), 137 (11), 115 (56), 114 (29), 89 (12), 77 (32), 63 (13), 51 (32); Anal. calcd. for $C_{17}H_{13}N_3O \cdot 1.1\ H_2O$ (295.13): C, 69.19; H, 5.19; N, 14.24. Found: C, 69.32; H, 5.17; N, 13.94.

5-[2-(Diethylamino)ethyl]-4-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (6). To a mixture of the pyridazinone **3** (199 mg, 1 mmol) and K_2CO_3 (414 mg, 3 mmol) in dry DMF (15 mL) was added 2-diethylaminoethyl chloride hydrochloride (172 mg, 1 mmol), and the mixture was refluxed for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in water and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The solid product was recrystallized from ethanol/ether (3:1) to give compound **6** as pale yellow needles (106 mg, 34%), mp. 171–173 °C. ^{1}H NMR ($CDCl_3$) δ 10.60 (s, 1H, NH), 8.51 (d, *J* = 7.8 Hz, 1H, 9-H), 7.58–7.51 (m, 2H, 6-H, 7-H, shows positive NOE on irradiation at 4.60 ppm), 7.43–7.38 (m, 1H, 8-H), 4.60 (t, *J* = 7.2 Hz, 2H, $NC\underline{H}_2CH_2NEt_2$), 2.85 (s, 3H, 4-$CH_3$, shows positive NOE on irradiation at 4.60 ppm), 2.85–2.81 (m, 2H, $NCH_2C\underline{H}_2NEt_2$), 2.55 (q, *J* = 7.2 Hz, 4H, $NC\underline{H}_2CH_3$), 0.97 (t, *J* = 7.2 Hz, 6H, $NCH_2C\underline{H}_3$); IR: 3223, 3153, 3075, 2966, 2927, 2865, 2813, 1648, 1472, 1399, 1298, 1201, 785, 761, 587, 516 cm^{-1}; MS *m/z*: 299 (M^++1, 1%), 99 (5), 86 (100), 58 (12); Anal. calcd. for $C_{17}H_{22}N_4O \cdot 0.35\ C_2H_5OH$ (314.51): C, 67.60; H, 7.72; N, 17.81. Found: C, 67.32; H, 7.55; N, 17.97.

2,5-Bis-[2-(diethylamino)ethyl]-4-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (7). To a mixture of the pyridazinone **3** (199 mg, 1 mmol) and K_2CO_3 (414 mg, 3 mmol) in dry DMF (15 mL) was added 2-diethylaminoethyl chloride hydrochloride (344 mg, 2 mmol), and the mixture was refluxed for 24 h. The solvent was removed under reduced pressure and the oily residue was taken up in water and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The semi-solid product was purified by column chromatography (dichloromethane/methanol, 9:1) to afford compound **7** as a buff wax-like material (200 mg, 50%), mp. 48–50 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (d, *J* = 7.5 Hz, 1H, 9-H), 7.52–7.46 (m, 2H, 6-H, 7-H, shows positive NOE on irradiation at 4.54 ppm), 7.40–7.34 (m, 1H, 8-H), 4.54 (t, *J* = 7.3 Hz, 2H, $N_{(5)}C\underline{H}_2CH_2NEt_2$), 4.43 (t, *J* = 7.3 Hz, 2H, $N_{(2)}C\underline{H}_2CH_2NEt_2$), 3.01 (t, *J* = 7.35 Hz, 2H, $N_{(2)}CH_2C\underline{H}_2NEt_2$, shows positive NOE on irradiation at 4.43 ppm), 2.82–2.80 (m, 5H, 4-CH_3, $N_{(5)}CH_2C\underline{H}_2NEt_2$, shows positive NOE on irradiation at 4.54 ppm), 2.73 (q, *J* = 7.2 Hz, 4H, $N_{(2)}CH_2CH_2N(C\underline{H}_2CH_3)_2$, shows positive NOE on irradiation at 4.43 ppm), 2.54 (q, *J* = 7.1 Hz, 4H, $N_{(5)}CH_2CH_2N(C\underline{H}_2CH_3)_2$), 1.12 (t, *J* = 7.2 Hz, 6H, $N_{(2)}CH_2CH_2N(CH_2C\underline{H}_3)_2$), 0.96 (t, *J* = 7.1 Hz, 6H, $N_{(5)}CH_2CH_2N(CH_2C\underline{H}_3)_2$); IR: 2965, 2929, 2803, 1659, 1552, 1458, 1395, 1206, 1120, 1068, 782, 756, 724 cm^{-1}. MS *m/z*: 398 (M^++1, 7%), 326 (8), 300 (9), 299 (44), 100 (22), 99 (91), 86 (100), 71 (15), 58 (19); HRMS calcd. for $C_{23}H_{35}N_5O$ (M^+): 397.2842. Found: 397.2856.

1-Chloro-4-methyl-5*H*-pyridazino[4,5-*b*]indole (8). A mixture of the pyridazinone **3** (1.26 g, 6.3 mmol) and $POCl_3$ (10 mL) was heated to 100 °C for 4 h. After cooling, excess reagent was removed under reduced pressure and the residue was poured into a mixture of ice (50 g) and 20% ammonia (10 mL). The precipitate was collected by filtration and recrystallized from ethanol/acetonitrile (2:1) to give compound **8** as colorless crystals (1.35 g, 98%), mp. 283–285 °C. ^{1}H NMR δ 12.68 (s, 1H, NH), 8.34 (d, *J* = 7.8 Hz, 1H, 9-H), 7.75 (d, *J* = 8.1 Hz, 1H, 6-H), 7.70–7.64 (m, 1H, 7-H), 7.46–7.39 (m, 1H, 8-H), 2.86 (s, 3H, CH_3); IR: 3133, 2817, 1624, 1546, 1499, 1404, 1380, 1326, 1283, 1233, 1137, 1112, 918, 736, 664 cm^{-1}; MS *m/z*: 220 (M^++1, 10%), 219 (M^+, 74), 218 (M^++1, 29), 217 (M^+, 100), 188 (28), 154 (47), 128 (13), 127 (20), 114 (13), 77 (24), 63 (11); Anal. calcd. for $C_{11}H_8N_3Cl$ (217.66): C, 60.70; H, 3.70; N, 19.31. Found: C, 60.68; H, 3.70; N, 19.30.

***N*-Benzyl-*N*-(4-methyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)amine (9).** A mixture of the chloro compound **8** (217 mg, 1 mmol) and benzylamine (4.95 g, 45.8 mmol) was heated to 120 °C for 48 h. The reagent was removed by Kugelrohr distillation and the residue was triturated with diethyl ether to afford a buff solid. This material was subjected to column chromatography (dichloromethane/methanol, 95:5), followed by recrystallization from ethanol/diethyl ether (2:1) to give the amine **9** as yellowish-brown crystals (288 mg, 87%), mp. 173–175 °C. ^{1}H NMR δ 12.08 (br s, 1H, NH), 8.53 (d, *J* = 7.8 Hz, 1H, 9-H), 7.68 (d, *J* = 8.1 Hz, 1H, 6-H), 7.55 (t, *J* = 7.65 Hz, 1H, 7-H), 7.45–7.41 (m, 2H, phenyl 2'-H, 6'-H, shows positive NOE on irradiation at 4.91 ppm), 7.36 (t, *J* = 7.7 Hz, 1H, 8-H, shows positive NOE on irradiation at 8.53 ppm), 7.32–7.17 (m, 3H, phenyl 3'-H, 4'-H, 5'-H), 7.13 (t, *J* = 6.0 Hz, 1H, N<u>H</u>CH_2, shows positive NOE on irradiation at 4.91 ppm), 4.91 (d, *J* = 6.0 Hz, 2H, CH_2), 2.69 (s, 3H, CH_3); IR: 3253, 3061, 2939, 2882, 1630, 1576, 1562, 1454, 1405, 1353, 1250, 1212, 1022, 770, 748, 693, 601 cm^{-1}; MS *m/z*: 288 (M^+, 1%), 107 (60), 106 (100), 91 (18), 79 (37), 78 (17), 77 (27), 65 (7), 51 (29), 50 (19); HRMS calcd. for $C_{18}H_{16}N_4$ (M^+): 288.1375. Found: 288.1369. Anal. calcd. for $C_{18}H_{16}N_4 \cdot 0.95$ C_2H_5OH (332.12): C, 71.97; H, 6.59; N, 16.87. Found: C, 71.94; H, 6.19; N, 16.50.

***N*1,*N*1-Diethyl-*N*3-(4-methyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)propane-1,3-diamine (10).** A mixture of the chloro compound **8** (217 mg, 1 mmol) and *N*,*N*-diethylpropane-1,3-diamine (3 mL, 19 mmol) was heated to 120 °C for 10 h. The reagent was removed by Kugelrohr distillation and the residue was dissolved in ethanol (2 mL). Concentrated HCl (0.5 mL) was added, then the volatile components were removed in vacuo and the residue was dried. It was then triturated with little abs. ethanol and placed in the refrigerator for 16 h. The precipitate was collected by filtration, washid with little abs. ethanol and dried to afford the dihydrochloride-dihydrate of compound **10** as colorless crystals (118 mg, 28%), mp 185 °C. ^{1}H NMR δ 14.50–14.10 (br, 1H, NH), 13.61 (s, 1H, 5-NH, shows positive NOE on irradiation at 2.79 ppm), 10.85–10.45 (br, 1H, NH), 8.85 (d, *J* = 8.1 Hz, 1H, 9-H), 8.80–8.50 (br, 1H, NH), 7.85 (d, *J* = 8.1 Hz, 1H, 6-H), 7.71–7.65 (m, 1H, 7-H), 7.53–7.46 (m, 1H, 8-H, shows positive NOE on irradiation at 8.85 ppm), 3.82–3.80 (m, 2H, NHC<u>H$_2$</u>$CH_2CH_2NEt_2$), 3.24–3.15 (m, 2H, $NHCH_2CH_2C$<u>H$_2$</u>NEt_2), 3.21–3.00 (m, 4H, NC<u>H$_2$</u>CH_3), 2.79 (s, 3H, 4-CH_3), 2.20–2.04 (m, 2H, $NHCH_2C$<u>H$_2$</u>CH_2NEt_2), 1.23 (t, *J* = 7.2 Hz, 6H, NCH_2C<u>H$_3$</u>); IR: 3378, 3057, 2945, 1633, 1563, 1465, 1414, 1210, 1033, 756 cm^{-1};

MS (free base) *m/z*: 311 (M^+, 10%), 282 (35), 239 (55), 225 (69), 212 (100), 211 (35), 199 (76), 198 (30), 183 (72), 168 (22), 156 (18), 142 (18), 98 (22), 86 (81), 84 (28), 58 (29); Anal. calcd. for $C_{18}H_{25}N_5 \cdot 2\ HCl \cdot 2\ H_2O$ (420.371): C, 51.43; H, 7.43; N, 16.66. Found: C, 51.19; H, 7.58; N, 16.51.

2-[(4-Methyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)amino]ethanol (11). A mixture of the chloro compound **8** (217 mg, 1 mmol) and ethanolamine (5.06 g, 82.8 mmol) was heated to 120 °C for 28 h. The reagent was removed by Kugelrohr distillation and the residue was subjected to column chromatography (dichloromethane/methanol, 9:1), followed by recrystallization from ethanol/diisopropyl ether (1:1) to give **11** as buff crystals (118 mg, 49%), mp. 250–252 °C. ^{1}H NMR δ 8.55 (d, *J* = 8.1 Hz, 1H, 9-H), 7.76 (d, *J* = 8.1 Hz, 1H, 6-H), 7.62–7.58 (m, 1H, 7-H), 7.46–7.40 (m, 1H, 8-H), 7.32 (s, 1H, NH), 3.75–3.70 (m, 4H, CH_2), 2.74 (s, 3H, CH_3); IR: 3363, 3298, 3061, 2950, 2790, 1640, 1588, 1563, 1418, 1239, 1055, 1020, 756, 636 cm^{-1}; MS *m/z*: 242 (M^+, 4%), 223 (14), 211 (10), 198 (100), 183 (9), 169 (39), 168 (17), 155 (12), 142 (23), 140 (18), 115 (24), 114 (21), 88 (9), 63 (11); HRMS calcd. for $C_{13}H_{14}N_4O$ (M^+): 242.1168. Found: 242.1165.

6-Methyl-2,7-dihydro-3*H*-imidazo[2',1':6,1]pyridazino[4,5-*b*]indole (12). A suspension of compound **11** (90 mg, 0.37 mmol) in $SOCl_2$ (10 mL) was heated to 80 °C for 48 h. The volatile components were removed under reduced pressure and the residue was recrystallized from ethanol to afford the hydrochloride of **12** as pale yellow needles (30 mg, 26%), mp. 319–321 °C. ^{1}H NMR δ 13.63 (br s, 1H, 7-NH, shows positive NOE on irradiation at 2.72 ppm), 10.18 (s, 1H, 1-NH, shows positive NOE on irradiation at 8.53 ppm), 8.53 (d, *J* = 7.8 Hz, 1H, 11-H), 7.83 (d, *J* = 8.4 Hz, 1H, 8-H), 7.67 (t, *J* = 7.8 Hz, 1H, 9-H), 7.50 (t, *J* = 7.6 Hz, 1H, 10-H), 4.74 (t, *J* = 9.8 Hz, 2H, CH_2), 4.12 (t, *J* = 9.8 Hz, 2H, CH_2), 2.72 (s, 3H, CH_3); IR: 3403, 3113, 2955, 2831, 2775, 1674, 1618, 1533, 1443, 1383, 1317, 1286, 1264, 1199, 943 778, 760, 618 cm^{-1}; MS (free base) *m/z*: 225 (M^++1, 17%), 224 (M^+, 100), 223 (M^+-1, 84), 182 (23), 168 (13), 155 (12), 140 (9), 128 (8), 112 (12), 101 (7), 98 (8); Anal. calcd. for $C_{13}H_{12}N_4 \cdot 1.8\ HCl \cdot 0.4\ C_2H_5OH$ (308.32): C, 53.76; H, 5.30; N, 18.17. Found: C, 53.74; H, 5.48; N, 18.11.

6-Methyl-7*H*-tetrazolo[5',1':6,1]pyridazino[4,5-*b*]indole (13). To a solution of the chloro compound **8** (217 mg, 1 mmol) in DMF (10 mL) was added sodium azide (195 mg, 3 mmol), and the mixture was refluxed for 48 h. The solvent was removed under reduced pressure and the solid residue was triturated with water. The product was collected by filtration and recrystallized from DMSO to give **13** as colorless crystals (140 mg, 62%), mp. 311–313 °C. ^{1}H NMR δ 13.18 (br, 1H, NH), 8.34 (d, *J* = 8.1 Hz, 1H, 11-H), 7.87 (d, *J* = 8.1 Hz, 1H, 8-H), 7.74–7.69 (m, 1H, 9-H), 7.57-7.51 (m, 1H, 10-H), 2.97 (s, 3H, CH_3); IR: 3147, 3141, 3111, 3014, 2928, 1637, 1612, 1540, 1501, 1441, 1394, 1324, 1247, 1098, 778, 759, 666 cm^{-1}; MS *m/z*: 224 (M^+, 6%), 168 (100), 167 (26), 141 (23), 140 (62), 115 (30), 114 (40), 100 (10), 88 (20), 75 (13), 71 (14), 63 (21), 57 (16), 51 (19); Anal. calcd. for $C_{11}H_8N_6$ (224.22): C, 58.92; H, 3.60; N, 37.48. Found: C, 59.20; H, 3.77; N, 37.24.

2,5-Dihydro-4-methyl-1*H*-pyridazino[4,5-*b*]indole-1-thione (15). A solution of the chloro compound **8** (217 mg, 1 mmol) and thiourea (228 mg, 3 mmol) in ethanol (15 mL) was refluxed

until the starting material was consumed (ca. 8 h; TLC monitoring). The solvent was removed under reduced pressure and the residue (crude isothiourea **14**) was refluxed in a mixture of 10% NaOH (3 mL) and ethanol (10 mL) for 1 h. The solvent was evaporated and the solid residue was redissolved in water. The solution was acidified with 2*N* HCl, then the precipitate thus formed was collected by filtration and recrystallized from ethanol to give **15** as fine colorless crystals (129 mg, 55%), mp. 321–323 °C. ^{1}H NMR δ 13.94 (s, 1H, 2-NH), 12.66 (s, 1H, 5-NH, shows positive NOE on irradiation at 2.67 ppm), 8.98 (d, *J* = 8.1 Hz, 1H, 9-H), 7.73 (d, *J* = 8.4 Hz, 1H, 6-H), 7.63–7.58 (m, 1H, 7-H), 7.45–7.40 (m, 1H, 8-H), 2.67 (s, 3H, CH_3); IR: 3379, 3143, 3064, 2891, 1621, 1565, 1525, 1380, 1252, 1098, 996, 754, 731, 633 cm^{-1}; MS *m/z*: 216 (M^++1, 13%), 215 (M^+, 100), 186 (40), 154 (6), 142 (7), 140 (6), 128 (6), 115 (13), 108 (5), 93 (9), 89 (10), 69 (12), 63 (9), 52 (12); Anal. calcd. for $C_{11}H_9N_3S \cdot H_2O$ (233.29): C, 56.63; H, 4.75; N, 18.01. Found: C, 56.74; H, 4.65; N, 17.70.

4-Methyl-1-(methylsulfanyl)-5*H*-pyridazino[4,5-*b*]indole (16). To a stirred mixture of the thione **15** (108 mg, 0.5 mmol) and sodium acetate (164 mg, 2 mmol) in ethanol (15 mL) was added methyl iodide (71 mg, 0.5 mmol) and the mixture was stirred at room temperature until there was no starting material left (ca. 24 h; TLC monitoring). The solvent was removed under reduced pressure and the solid residue was recrystallized from ethanol to afford buff crystals (78 mg, 68%), mp. 238–240 °C. ^{1}H NMR δ 12.98 (br s, 1H, NH), 8.28 (d, *J* = 8.1 Hz, 1H, 9-H, shows positive NOE on irradiation at 2.85 ppm), 7.82 (d, *J* = 8.4 Hz, 1H, 6-H, shows positive NOE on irradiation at 12.98 ppm), 7.75–7.69 (m, 1H, 7-H), 7.53–7.48 (m, 1H, 8-H), 2.98 (s, 3H, 4-CH_3, shows positive NOE on irradiation at 12.98 ppm), 2.85 (s, 3H, SCH_3); IR: 3112, 3063, 2967, 1621, 1539, 1419, 1373, 1325, 1233, 1137, 1111, 918, 750, 663 cm^{-1}; MS *m/z*: 229 (M^+, 100%), 228 (M^+-1, 38), 196 (23), 186 (16), 184 (22), 168 (37), 142 (45), 128 (31), 115 (50), 114 (34), 100 (18), 93 (44), 89 (23), 79 (12), 63 (12); HRMS calcd. for $C_{12}H_{11}N_3S$ (M^+): 229.0674. Found: 229.0669.

***N*,*N*-Diethyl-*N*-{2-[(4-methyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)sulfanyl]ethyl}amine (17).** A mixture of the thione **15** (215 mg, 1 mmol), sodium acetate (492 mg, 6 mmol), and 2-diethylaminoethyl chloride hydrochloride (190 mg, 1.1 mmol) in ethanol (15 mL) was refluxed for 14 h. The solvent was removed under reduced pressure and the residue was triturated with water and extracted with dichloromethane (3 × 50 mL). The organic layer was washed with water (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed and the crude product was purified by column chromatography (dichloromethane/methanol, 9:1), followed by recrystallization from ethanol to afford **17** as brownish-yellow crystals (150 mg, 48%), mp. 78–80 °C. ^{1}H NMR δ 8.35 (d, *J* = 7.8 Hz, 1H, 9-H), 7.65 (d, *J* = 8.4 Hz, 1H, 6-H), 7.57–7.51 (m, 1H, 7-H), 7.42–7.36 (m, 1H, 8-H), 3.66 (t, *J* = 7.2 Hz, 2H, $SC\underline{H}_2CH_2N$), 3.00 (t, *J* = 7.2 Hz, 2H, $SCH_2C\underline{H}_2N$), 2.90 (s, 3H, 4-CH_3); 2.64 (q, *J* = 7.2 Hz, 4H, $NC\underline{H}_2CH_3$), 1.04 (t, *J* = 7.2 Hz, 6H, $NCH_2C\underline{H}_3$); IR: 3136, 2967, 2925, 1621, 1539, 1419, 1380, 1327, 1247, 1137, 1097, 751, 668, cm^{-1}; MS *m/z*: 242 (2%), 215 (19), 186 (5), 115 (4), 99 (100), 86 (87), 71 (55), 56 (24); FAB-MS: 315 (M^++1, 100%), 242 (25), 100 (42).

Ethyl 2-[(4-methyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)sulfanyl]acetate (18). A mixture of the thione **15** (215 mg, 1 mmol), sodium acetate (246 mg, 3 mmol) and ethyl bromoacetate (167 mg, 1 mmol) in ethanol (15 mL) was refluxed for 18 h. The solvent was removed under reduced pressure and the residue was triturated with water and extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with water (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethanol to give **18** as fine yellow crystals (144 mg, 48%), mp. 288–290 °C. ^{1}H NMR δ 12.44 (br s, 1H, NH), 8.20 (d, *J* = 9.0 Hz, 1H, 9-H, shows positive NOE on irradiation at 4.37 ppm), 7.74 (d, *J* = 8.0 Hz, 1H, 6-H), 7.67–7.61 (m, 1H, 7-H), 7.47–7.41 (m, 1H, 8-H), 4.37 (s, 2H, SCH_2), 4.12 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 2.82 (s, 3H, 4-CH_3), 1.19 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$); IR: 3107, 3083, 2981, 2822, 2814, 1738, 1621, 1541, 1422, 1382, 1362, 1281, 1152, 1113, 1026, 983, 727, 662 cm^{-1}; MS *m/z*: 301 (M^+, 19%), 256 (10), 229 (25), 228 (100), 215 (7), 211 (8), 185 (10), 167 (17), 159 (12), 142 (18), 140 (14), 128 (8), 115 (27), 114 (25), 100 (13), 89 (17), 69 (8), 63 (10), 58 (9); Anal. calcd. for $C_{15}H_{15}N_3O_2S$ (301.35): C, 59.78; H, 5.01; N, 13.94. Found: C, 59.77; H, 5.21; N, 13.88.

4-Methyl-5*H*-pyridazino[4,5-*b*]indole (19). To a stirred solution of the chloro compound **8** (217 mg, 1 mmol) in methanol (100 mL) was added ammonium formate (252 mg, 4 mmol) and 10% palladium on carbon (55 mg). The mixture was heated to reflux under an argon atmosphere. Further portions of ammonium formate were added until the starting material was completely consumed (ca. 24 h; TLC monitoring: dichloromethane/methanol, 4:1). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. Water (15 mL) was added to the residue, the product was collected by filtration, washed with water, dried, and recrystallized from ethanol to afford **19** as colorless crystals (117 mg, 64%), mp. >320 °C (decomp.; sublimation above 280 °C). ^{1}H NMR δ 12.26 (br s, 1H, NH), 9.75 (s, 1H, 1-H, shows positive NOE on irradiation at 8.33–8.28 ppm), 8.33–8.28 (m, 1H, 9-H), 7.72–7.68 (m, 1H, 6-H), 7.65–7.57 (m, 1H, 7-H), 7.40–7.33 (m, 1H, 8-H, shows positive NOE on irradiation at 8.33-8.28 ppm), 2.88 (s, 3H, CH_3); IR: 3050, 2962, 2907, 2783, 2749, 2669, 1623, 1601, 1553, 1508, 1451, 1333, 1231, 919, 752, 724, 569 cm^{-1}; MS *m/z*: 183 (M^+, 100%), 155 (10), 154 (40), 140 (5), 128 (17), 127 (19), 114 (8), 101 (10), 88 (8), 77 (29), 75 (15), 63 (14), 51 (18); HRMS calcd. for $C_{11}H_9N_3$ (M^+): 183.0796. Found: 183.0792. Anal. calcd. for $C_{11}H_9N_4 \cdot 0.25\ C_2H_5OH$ (194.73): C, 70.93; H, 5.44; N, 21.58. Found: C, 71.19; H, 5.28; N, 21.48.

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