Synthesis and functionalization of some new pyridazino[4,5-*b*]indole derivatives

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.763

Abstract
Starting from the indole-fused pyridazinone **5**, a series of new pyridazino[4,5-*b*]indoles of potential pharmaceutical interest (**9**-**18**), was prepared. Compounds **20** and **21** were obtained by nucleophilic displacement of the chlorine atom of **19.** Thionation of the chloro derivative **19** gave the thione compound **23,** while its reaction with sodium azide gave a tetracyclic system, namely the tetrazolopyridazinoindole **22**. Dehalogenation of the chloro compound **19** gave a 3-aza analogue of the natural product, harman.

Keywords: Pyridazino[4,5-*b*]indoles, aza-carbolines, alkylation, antitumor agents

Introduction

The pyridazino[4,5-*b*]indole scaffold has attracted considerable pharmaceutical interest due to its bio-isosterism with β-carboline as well as γ-carboline, as the core structure of a wide variety of bio-active compounds.[1-9] Morover, various 5*H*-pyridazino[4,5-*b*]indole derivatives show promising *in vitro* inhibitory activities against PI3Ka, significant anti-proliferative effects in various cell types[10,11] and antimicrobial activity.[12] Recently, it was reported that some pyridazino[4,5-*b*]indole derivatives containing alkyl-, benzyl- and phenacyl-substituted 1,2,3-triazolylmethyl units exhibit potent cancer cell growth inhibition activity at lower micromolar concentrations.[13] Furthermore, the title ring system became interesting in the context of an ongoing program in search of new and selective inhibitors of copper-containing amine oxidases.[14] During the past few years, we have investigated the synthesis and biological activity of various new representatives of this “aza-carboline" ring system, mainly focusing on potential antitumor agents.[15-17] Encouraged by the pharmaceutical importance of these ring systems, we decided to

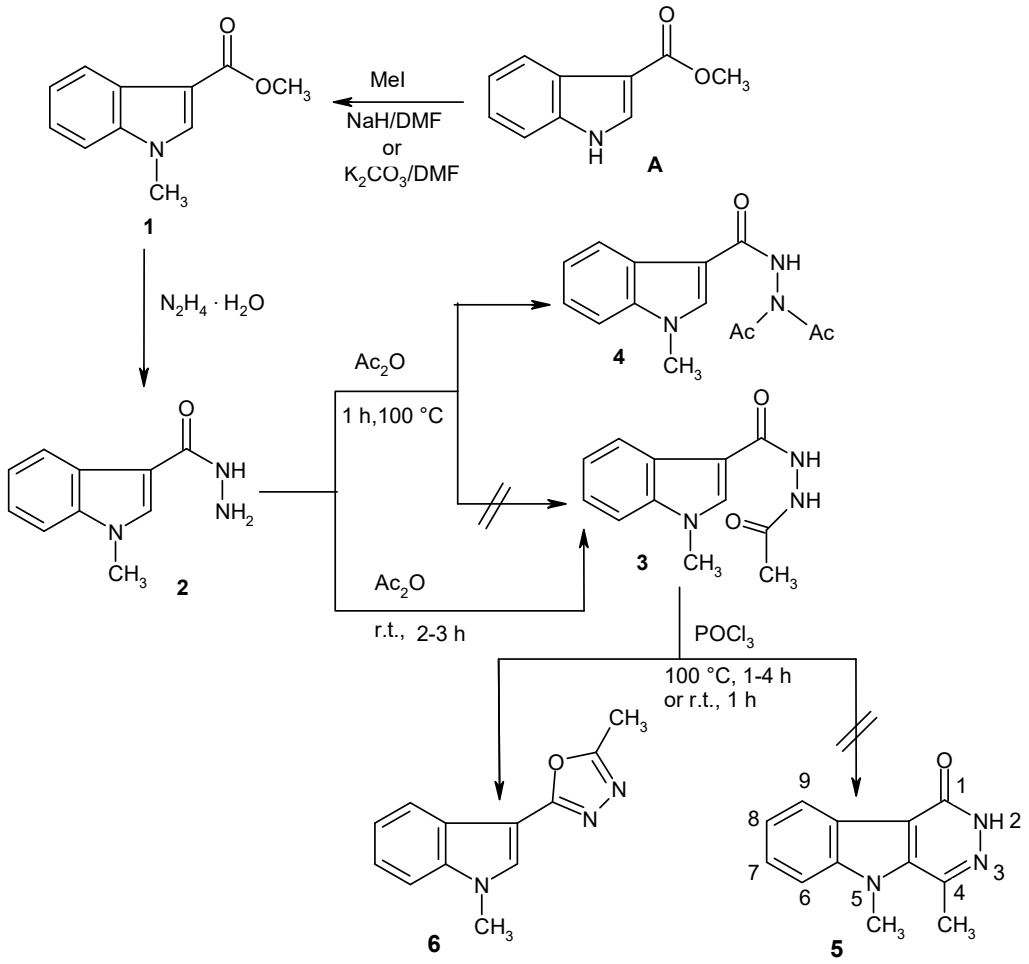
probe a new approach towards the synthesis of new pyridazino[4,5-*b*]indole derivatives of potential pharmaceutical interest.

Results and Discussion

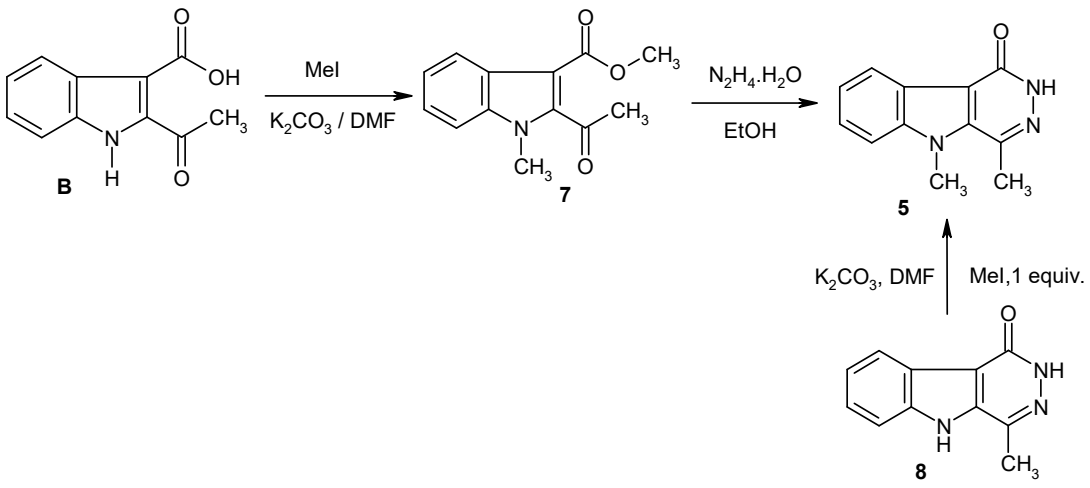
In the present work, the cyclisation behaviour of 1-methyl-*N*'-acetylindole-3-carbohydrazide **3** has been studied. The preparation of this intermediate **3** is straightforward: it has been reported that reaction of methyl indole-3-carboxylate **A** with methyl iodide in dry DMF in the presence of sodium hydride affords the N-methylated ester **1** in 81% yield.[18] We have carried out a slight modification of this procedure, using potassium carbonate as a base, instead of sodium hydride, where the yield was improved to 85%. Heating of the ester **1** in neat hydrazine hydrate under reflux gave the corresponding hydrazide **2**. Acetylation of **2** by treatment with acetic anhydride at 100 °C for 1 hour did not give the monoacetyl derivative **3**, but afforded the diacetyl derivative **4**. However, the monoacetyl compound **3** was obtained by reaction of the hydrazide **2** with acetic anhydride at room temperature for 2-3 hours, giving **3** in a good yield (72%). This latter compound has been prepared previously by treatment of the hydrazide **2** with dimethyl acetamide.[19] The ^{1}H-NMR spectrum of compound **4** shows a singlet at δ 2.34 ppm with the relative intensity of six protons (two CH_3CO groups), and NOE difference experiments revealed positive NOE's at δ 10.41 ppm (NH), δ 8.13 ppm (H-2) and δ 8.06 ppm (H-4) on irradiation of the acetyl singlet at δ 2.34 ppm.

Treatment of **3** with $POCl_3$ under various conditions (at room temperature or at 100 °C for 1-4 hours) did not give the corresponding pyridazinone **5** but afforded the oxadiazole derivative **6**[19] in 77% yield. ^{1}H-NMR NOE difference experiments provide evidence for the oxadiazole structure **6** and permit exclusion of the pyridazinone structure **5**: saturation of the N-CH_3 resonance at δ 3.88 ppm leads to positive NOE's at δ 8.13 ppm (H-2) and at δ 7.59-7.56 ppm (H-7), thus proving that position 2 of the indole skeleton is unsubstituted (Scheme 1).

However, the key intermediate 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**5**) was easily prepared *via* a different route (Scheme 2). Thus, reaction of the N-unsubstituted pyridazinoindole **8**[15] with an equimolar amount of methyl iodide in dry DMF in the presence of potassium carbonate afforded only the corresponding pyridazino[4,5-*b*]indole **5**, and no 2-substitution was observed. The structure of compound **5** was confirmed by ^{1}H-NMR NOE difference experiments which proved the vicinity of the N-CH_3 and the C-CH_3 groups, thus the CH_3 moiety must be attached to N-5 and not to N-2. Furthermore, the structure of **5** was also proven chemically by an unequivocal synthesis: refluxing of the N-methylated keto ester **7** with hydrazine hydrate in ethanol gave a product which is identical with **5** in all respects. Compound **7**, in turn, was obtained according to a known procedure[18] by N-methylation and simultaneous esterification of 2-acetylindole-3-carboxylic acid **B**[20] in a one-pot synthesis using methyl iodide and potassium carbonate in DMF. The literature procedure was slightly modified by using potassium carbonate instead of sodium hydride as a base (Scheme 2).

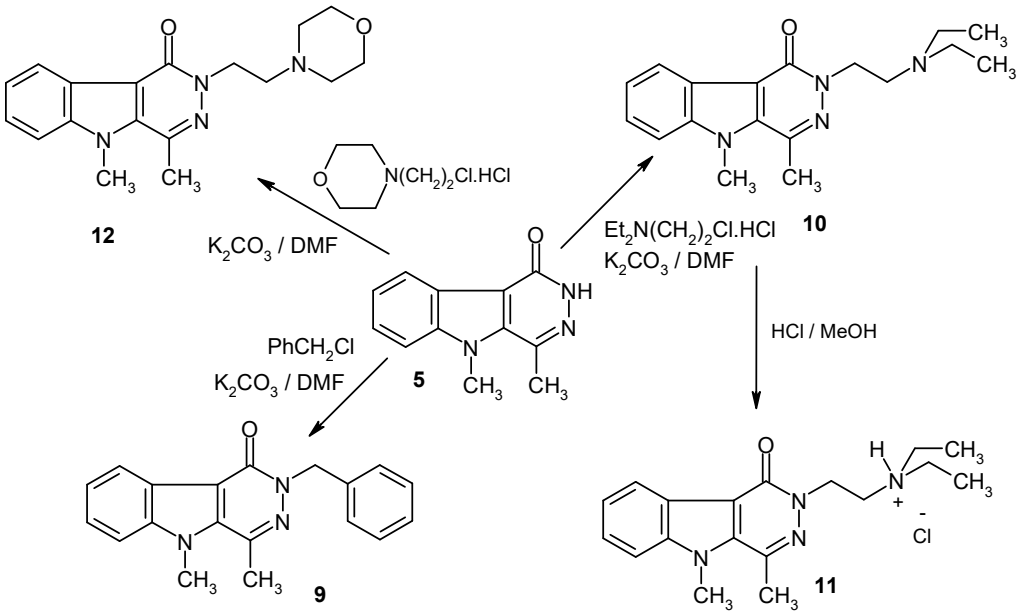


Scheme 1. Attempts to synthesize the key intermediate pyridazinoindole **5**.



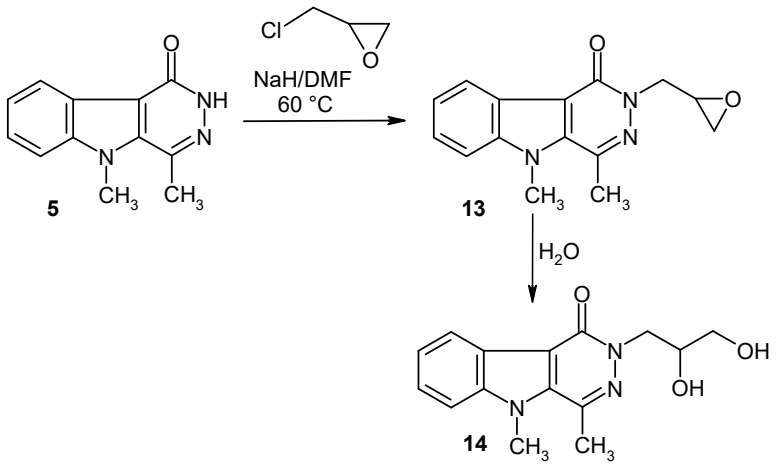
Scheme 2. Synthesis of the pyridazino[4,5-*b*]indol-1-one **5**.

The introduction of a variety of different alkyl groups into position 2 of 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-b]indol-1-one (**5**) appeared interesting from a pharmaceutical point of view. Thus, **5** was allowed to react with some alkylating agents such as benzyl chloride, 2-diethylaminoethyl chloride, or 4-(2-chloroethyl)morpholine. The reactions were performed in dry DMF in the presence of potassium carbonate to afford the corresponding pyridazinoindole derivatives **9**, **10**, and **12** as colorless solids in yields of 49–55%. The hydrochloride **11** was obtained in 60% yield by dissolving the free base **10** (which is difficult to recrystallize) in methanolic hydrogen chloride (freshly prepared from acetyl chloride and methanol). The structures of the new compounds (Scheme 3) were established by elemental analyses, IR, MS, HRMS, and ^{1}H-NMR spectra.



Scheme 3. Synthesis of pyridazinoindole derivatives **9**, **10**, and **12**

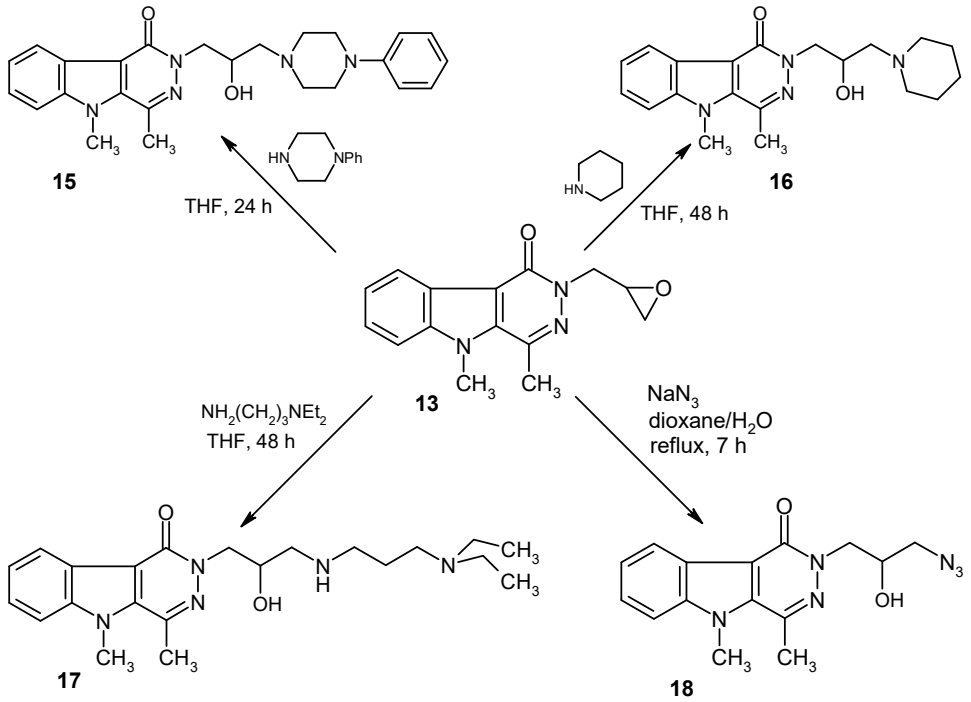
Also, the high reactivity of epoxides and their usefulness for further functionalisation reactions prompted us to synthesize and investigate the epoxide **13**, which could be prepared by treatment of the pyridazinone **5** with an excess of epichlorohydrin in the presence of sodium hydride in dry DMF solution at 60 °C (Scheme 4). Under these conditions, the epoxide **13** is formed in high yield and in sufficient purity for further transformations, i.e. ring-opening reactions with nitrogen nucleophiles. The ^{1}H-NMR signal pattern of the newly introduced side chain is in agreement with the spectral data reported for similar structures.[21] During work-up of **13**, contact with water must be reduced to a minimum, otherwise the sensitive epoxide ring undergoes hydrolysis. In this manner, the dihydroxypropyl derivative **14** was obtained in 25% yield and its structure was spectroscopically confirmed.



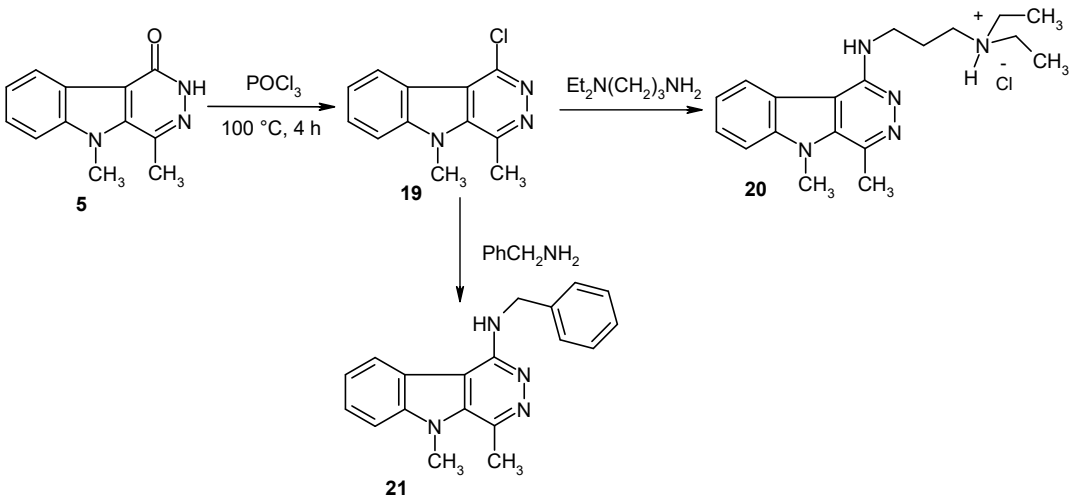
Scheme 4. Reaction of pyridazinone **5** with epichlorohydrin.

Regioselective ring opening of **13** with various nitrogen nucleophiles was anticipated to afford a series of new amino alcohols that might exhibit interesting pharmacological properties (Scheme 5). Thus, opening of the oxirane ring of **13** with primary or secondary amines was performed in tetrahydrofuran solution at reflux temperature to afford the corresponding amino alcohols **15-17** in 49-80% yield. The reactions were carried out using three molar equivalents of the nucleophilic reagent (*N*-phenylpiperazine, piperidine, or 3-diethylamino-1-propylamine, respectively). For the synthesis of the azido alcohol **18**, the epoxide was opened regioselectively with sodium azide in aqueous dioxane analogously to a known procedure.[21] The structure of the alcohols **15-18** was confirmed by elemental analyses, IR, MS and ^{1}H-NMR spectra, the latter spectra showed a characteristic signal of the C<u>H</u>(OH) moiety. The appearance of an absorption band at ν 2104 cm^{-1} in the IR spectrum of compound **18** is due to the azido group.

On the other hand, heating compound **5** in boiling $POCl_3$ gave the corresponding chloro derivative **19**. The chlorine atom of the latter compound is labile and could be easily substituted by nitrogen nucleophiles such as 3-diethylaminopropylamine and benzylamine in the absence of a solvent, giving the corresponding pyridazinoindoles **20** and **21**, respectively. Analytical data showed that the diethylamino compound **20** was obtained in its hydrochloride form. The IR spectrum showed two bands at ν 3457 and 3387 cm^{-1}, attributable to the two NH groups. The ^{1}H-NMR spectrum of compound **21** shows a singlet at δ 4.89 ppm (2H, NCH_2) and a triplet at δ 7.03 ppm (NH) which gives a positive NOE on irradiation at δ 8.52 (H-9) and at δ 4.89 (NCH_2) (Scheme 6).



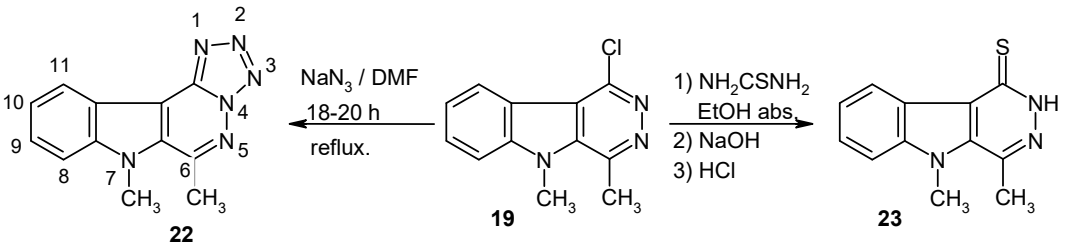
Scheme 5. Ring opening of **13** with various nitrogen nucleophiles.



Scheme 6. Reactions of chloro compound **19** with some nitrogen nucleophiles.

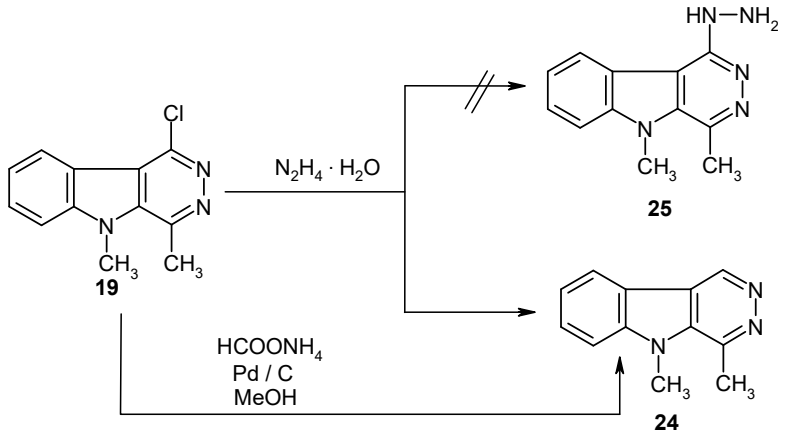
Moreover, reaction of the chloro derivative **19** with sodium azide in dry DMF gave the tetrazolo compound **22** in 82% yield *via* nucleophilic displacement of chlorine by azide, followed by intramolecular tetrazole ring closure. On the other hand, reaction of **19** with thiourea, followed by saponification of an intermediate isothiourea derivative with sodium hydroxide and subsequent acidification afforded the corresponding thione **23**. ^{1}H-NMR data (absence of a noticeable NOE

for the exchangeable signal at δ 13.95 ppm on saturation of the H-9 resonance at δ 9.11 ppm) as well as IR data (appearance of a new absorption band at ν 3280 cm^{-1} due to NH, in addition to C=S absorption bands at ν 1550 and 1269 cm^{-1}) support the thione structure rather than its thiol tautomer (Scheme 7).



Scheme 7. Synthesis of tetrazolo compound **22** and thione derivative **23**.

Finally, hydrazinolysis of **19** resulted in dechlorination giving **24** rather than the corresponding hydrazino derivative **25** (Scheme 8). The formation of **24** can be attributed most probably to an oxidative dehydrazination reaction of the unstable hydrazino compound **25** in the presence of air oxygen. This behaviour is not surprising, as we had previously observed an analogous transformation with a similar pyridazinoindole.[15,16] The 1-unsubstituted pyridazine **24** could be prepared alternatively by catalytic transfer hydrogenation of **19** using ammonium formate as the hydrogen source and Pd/C as a catalyst in refluxing methanol, affording analytically pure **24** in 68% yield. In agreement with the proposed structure, the ^{1}H-NMR spectrum showed a new singlet at δ 9.68 ppm which is assigned to the pyridazine proton (H-1), thus proving the successful removal of the chloro substituent.



Scheme 8. Hydrazinolysis of **19** and formation of the 1-unsubstituted pyridazine **24.**

Conclusions

Syntheses of a number of new pyridazino[4,5-*b*]indole derivatives were successfully accomplished, using 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**5**) as the key intermediate. Various functionalisations were achieved at positions 1 and 2 of the azacarboline system, including the annulation of a tetrazole ring. The new compounds were characterized by spectroscopic data and elemental analyses

Experimental Section

General. Melting points (uncorrected) were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. IR spectra were recorded for KBr pellets on a Perkin-Elmer 1605 FTIR 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 (TMS as internal reference, δ values in ppm). Mass spectra were obtained with a Hewlett-Packard 5890A/5970B-GC/MSD or with a Shimadzu QP5050 DI 50 spectrometer. HRMS spectra were taken on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna. For thin layer chromatography, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used (detection using UV_{254} and UV_{366} light). Column chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm. Elemental analyses were carried out at the Microanalytical Laboratory, Department of Chemistry, University of Vienna and Assiut University. Methyl indole-3-carboxylate (**A**) is commercially available, 2-acetyl-1*H*-indole-3-carboxylic acid (**B**),[20] methyl 1-methyl-1*H*-indole-3-carboxylate (**1**),[18,22] 1-methyl-1*H*-indole-3-carbohydrazide (**2**),[23] *N*′-acetyl-1-methyl-1*H*-indole-3-carbohydrazide (**3**),[19] 2-methyl-5-(1-methyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (**6**)[19] and 2,5-dihydro-4-methyl-1*H*-pyridazino[4,5-*b*]indol-1-one (**8**)[15] have been reported before.

***N*′,*N*′-Diacetyl-1-methyl-1*H*-indole-3-carbohydrazide** (**4**). A mixture of the hydrazide **2** (500 mg, 2.5 mmol) and acetic anhydride (10 ml) was heated to 100 °C for 1 h. After cooling, the excess of acetic anhydride was removed under reduced pressure and the residue was washed with water, filtered off, and recrystallized from ethanol to afford 368 mg (53 %) of compound **4** as colorless crystals, mp 168-170 °C. IR: ν 3212, 3117, 3006, 1738, 1730, 1641, 1538, 1576, 1503, 1468, 1422, 1389, 1252, 1188, 1102, 1103, 987, 888, 783, 779, 676 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1H, NH, shows positive NOE on irradiation at 2.34 ppm), 8.13 (s, 1H, H-2, shows positive NOE on irradiation at 2.34 ppm), 8.06 (d, $J_{4\text{-}5}$ 8.1 Hz, 1H, H-4, shows positive NOE on irradiation at 2.34 ppm), 7.54 (d, $J_{6\text{-}7}$ 7.8 Hz, 1H, H-7), 7.29-7.16 (m, 2H, H-5, H-6), 3.86 (s, 3H, CH_3), 2.34 (s, 6H, CH_3CO). MS (EI): *m/z* (%) 273 (M^+,7%), 159 (13), 158 (100), 130 (9), 103 (8), 77 (11). Anal. Calcd. for $C_{14}H_{15}N_3O_3$ (273.29): C, 60.53; H, 5.53; N, 15.38. Found; C, 60.41; H, 5.40; N, 15.33.

4,5-Dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (5). **Method (a).** To a suspension of the pyridazinone **8** (50 mg, 0.25 mmol) and K_2CO_3 (70 mg, 0.5 mmol) in dry DMF (5 ml) was added an equimolar amount of methyl iodide (35.5 mg, 0.25 mmol). The mixture was stirred at r.t. for 22-24 h. The solvent was removed under reduced pressure and the solid residue was triturated with water. The crude product was collected and recrystallized from ethanol to give 18 mg (33%) of **5** as colorless crystals, mp 322-324 °C.

Method (b). To a mixture of the acid **B** (202 mg, 1 mmol) and K_2CO_3 (280 mg, 2 mmol) in DMF (10 ml) was added an excess of methyl iodide (3 ml). The mixture was stirred at r.t. for 2 h, then the solvent was removed under reduced pressure and the dark brown residue was triturated with water and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over Na_2SO_4. The solvent was removed and the brown solid residue (compound **7**) was refluxed with hydrazine hydrate (3 ml, 60 mmol) in ethanol (10 ml) for 24 h. The solvent was concentrated and the solid product was filtered off and recrystallized from ethanol to afford 185 mg (85%) of **5** as colorless crystals, mp 322-324 °C. IR: ν 3219, 3148, 3069, 2925, 1645, 1564, 1564, 1468, 1392, 1292, 1226, 1105, 980, 761, 783, 569, 548 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.43 (s, 1H, NH), 8.26 (d, J 8.1 Hz, 1H, H-9), 7.79 (d, J 8.4 Hz, 1H, H-6, shows positive NOE on irradiation at 4.13 ppm), 7.57-7.52 (m, 1H, H-7), 7.38-7.33 (m, 1H, H-8), 4.13 (s, 3H, NCH_3, shows positive NOE on irradiation at 2.78 ppm), 2.78 (s, 3H, CH_3, shows positive NOE on irradiation at 4.13 ppm). MS (EI): *m/z* (%) 214 (15%), 213 (M^+, 100), 197 (14), 184 (10), 170 (10), 154 (18), 140 (12), 128 (23), 115 (16), 107 (7), 102 (9), 89 (11), 86 (9), 77 (19), 75 (9), 63 (17), 55 (9), 51 (12). Anal. Calcd. for $C_{12}H_{11}N_3O$ (213.23): C, 67.59; H, 5.20; N, 19.71. Found: C, 67.51; H, 5.27; N, 19.58.

Methyl 2-Acetyl-1-methyl-1*H*-indole-3-carboxylate (7). To a mixture of the carboxylic acid **B** (202 mg, 1 mmol) and K_2CO_3 (420 mg, 3 mmol) in dry DMF (15 ml) was added methyl iodide (2 ml, 32 mmol). The mixture was stirred at r.t. until the starting material was completely alkylated (ca. 5-6 h; TLC monitoring). The solvent was removed *in vacuo* and the residue was triturated with water and extracted with dichloromethane (3 x 50 ml). The combined extracts were washed with water, dried over Na_2SO_4 and evaporated to give a brown oil which was subjected to column chromatography (light petroleum/ethyl acetate, 4:1) to give 200 mg (87%) of **7** as yellow oil which solidified on standing: semi-solid yellow crystals, mp 53-55 °C. IR: ν 3055, 2948, 2851, 1700, 1663, 1611, 1517, 1486, 1457, 1375, 1276, 1207, 1158, 1107, 1016, 788, 740, 668 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.05 (d, J 7.2 Hz, 1H, H-9), 7.67 (d, $J_{6,7}$ 8.2 Hz, 1H, H-6), 7.43-7.29 (m, 2H, H-7, H-8), 3.87 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 2.69 (s, 3H, CH_3). MS (EI): *m/z* (%) 231 (M^+, 100%), 216 (44), 201 (8), 199 (59), 186 (31), 171 (25), 158 (50), 143, (55), 129 (30), 114 (29), 102 (25), 89 (39), 77 (43), 69 (18), 63 (24), 51 (21). Anal. Calcd. for $C_{13}H_{13}NO_3$ (231.24): C , 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.63; N, 6.02.

2-Benzyl-4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (9). To a mixture of the pyridazinone 5 (213 mg, 1 mmol) and K_2CO_3 (414 mg, 3 mmol) in dry DMF (10 ml) was added benzyl chloride (139 mg, 1.1 mmol). The mixture was heated under reflux for 21 h. After cooling, the solvent was removed under reduced pressure and the residue was triturated with water, then

the product was extracted with dichloromethane (3 x 50 ml). The combined extracts were washed with water (3 x 50 ml), dried over Na_2SO_4, and concentrated under reduced pressure to give a buff solid product which was recrystallized from ethyl acetate/light petroleum to afford 147 mg (49%) of **9** as colorless needles mp 220-222 °C. IR: ν 3446, 3052, 2947, 1645, 1616, 1551, 1464, 1429, 1388, 1352, 1260, 1177, 1107, 925, 780, 753, 709 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.50-8.47 (m, 1H, H-9), 7.51-7.46 (m, 3H, H-7, phenyl-H), 7.39-736 (m, 2H, H-6, H-8), 7.34-7.21 (m, 3H, phenyl-H), 4.47 (s, 2H, CH_2), 4.02 (s, 3H, CH_3-5), 2.76 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 304 (15%), 303 (M^+, 63), 288 (26), 200 (13), 199 (100), 198 (24), 183 (15), 170 (5), 157 (12), 128 (9), 91 (17), 77 (5), 65 (8). Anal. Calcd. for $C_{19}H_{17}N_3O$ (303.35): C, 75.22; H, 5.65; N, 13.85. Found: C, 75.08; H, 5.73; N, 13.79.

2-[2-(Diethylamino)ethyl]-4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (10). To a stirred mixture of the pyridazinone **5** (213 mg, 1 mmol) and K_2CO_3 (276 mg, 2 mmol) in dry DMF (15 ml) was added diethylaminoethyl chloride hydrochloride (200 mg, 1.16 mmol). The mixture was heated to 140 °C for 30 h, and the reaction was monitored by TLC. The solvent was removed under reduced pressure and the solid residue was purified by column chromatography (dichloromethane/methanol, 9:1). The first fraction was discarded and the second fraction afforded 157 mg (50%) of **10** as yellow crystals mp 110-112 °C. IR: ν 3048, 2966, 2925, 2815, 2797, 1645, 1554, 1464, 1430, 1382, 1205, 1099, 920, 780, 750 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.52 (d, $J_{8\text{-}9}$ 7.7 Hz, 1H, H-9), 7.55-7.37 (m, 3H, H-6, H-7, H-8), 4.43 (t, J 7.5 Hz, 2H, $NC\underline{H}_2CH_2NEt_2$), 4.09 (s, 3H, CH_3-5), 2.98 (t, J 7.5 Hz, 2H, $NCH_2C\underline{H}_2NEt_2$), 2.82 (s, 3H, CH_3-4), 2.71 (q, J 7.1 Hz, 4H, $NCH_2CH_2N(C\underline{H}_2CH_3)_2$), 1.13 (t, J 7.1 Hz, 6H, $NCH_2CH_2N(CH_2C\underline{H}_3)_2$). MS (EI): *m/z* (%) 312 (M^+, 1%), 214 (9), 99 (63), 87 (7), 86 (100), 84 (6), 71 (13), 58 (13), 56 (8). Anal. Calcd. for $C_{18}H_{24}N_4O$ (312.37): C, 69.20; H, 7.74; N, 17.93. Found: C, 69.13; H, 7.66; N, 17.87. HRMS calcd for $C_{18}H_{24}N_4O$ (M^+): 312.1950; found: 312.1942 $\pm$ 0.00156.

2-[2-(Diethylamino)ethyl]-4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one hydrochloride (11). The free base **10** (50 mg, 0.16 mmol) was dissolved in methanolic HCl (freshly prepared by mixing 0.1 ml of acetyl chloride and 5 ml of abs. methanol) and this solution was evaporated. The hydrochloride **11** was obtained as a pale yellow solid which was recrystallized from ethanol to afford 24 mg (40%) of **11** as colorless crystals, mp 268-270°C. IR: ν 3382, 2938, 2658, 2584, 2456, 1644, 1616, 1552, 1464, 1358, 1328, 1247, 1023, 780, 751, 715 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.26 (s, 1H, NH), 8.28 (d, $J_{8\text{-}9}$ 7.8 Hz, 1H, H-9), 7.85 (d, $J_{6\text{-}7}$ 8.4 Hz, 1H, H-6), 7.62-7.56 (m, 1H, H-7), 7.43-7.37 (m, 1H, H-8), 4.57 (t, J 6.8 Hz, 2H, $NC\underline{H}_2CH_2NEt_2$), 4.17 (s, 3H, CH_3-5), 3.48 (t, unresolved, 2H, $NCH_2C\underline{H}_2NEt_2$), 3.24 (q, unresolved, 4H, $NCH_2CH_2N(C\underline{H}_2CH_3)_2$), 2.83 (s, 3H, CH_3-4), 1.24 (t, J 7.3 Hz, 6H, $NCH_2CH_2N(CH_2C\underline{H}_3)_2$). MS (EI): *m/z* (%) 312 (M^+, 1%), 214 (7), 183 (5), 157 (5), 99 (38), 86 (100), 71 (16), 58 (21), 57 (10), 56 (15). Anal. Calcd. for $C_{18}H_{25}N_4OCl$ (348.87): C, 61.97, H, 7.22; Cl, 10.16; N, 16.06. Found: C, 61.85; H, 7.31; Cl, 10.09; N, 16.17.

4,5-Dimethyl-2-(2-morpholinoethyl)-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (12). To a stirred mixture of the pyridazinone **5** (213 mg, 1 mmol) and K_2CO_3 (276 mg, 2 mmol) in dry DMF (15 ml) was added 4-(2-chloroethyl)morpholine hydrochloride (186 mg, 1 mmol). The mixture

was refluxed for 17 h, and the reaction was monitored by TLC. The mixture was concentrated *in vacuo*, the residue was poured into water and the product was extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness, followed by recrystallization from ethyl acetate/methanol (9:1) to give 180 mg (55%) of **12** as colorless crystals, mp 170-172 °C. IR: ν 3445, 2957, 2848, 2806, 1647, 1555, 1466, 1390, 1356, 1297, 1244, 1119, 1117, 1035, 923, 845, 782, 783 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, $J_{8\text{-}9}$ 8.1 Hz, 1H, H-9), 7.57-7.51 (m, 1H, H-7), 7.46 (d, $J_{6\text{-}7}$ 6.0 Hz, 1H, H-6), 7.42-7.36 (m, 1H, H-8), 4.47 (t, *J* 7.0 Hz, 2H, $NC\underline{H}_2CH_2N_{mor.}$), 4.09 (s, 3H, CH_3-5), 3.74-3.70 (m, 4H, OCH_2), 2.88 (t, *J* 7.0 Hz, 2H, $NCH_2C\underline{H}_2N_{mor}$), 2.80 (s, 3H, CH_3-4), 2.65-2.60 (m, unresolved, 4H, NCH_2). MS (EI): *m/z* (%) 327 (M^++1, 1%), 308 (8), 214 (56), 198 (4), 183 (5), 128 (5), 113 (100), 100 (65), 69 (11), 56 (25). Anal. Calcd. for $C_{18}H_{22}N_4O_2$ (326.40): C, 66.24; H, 6.79; N, 17.16. Found: C, 66.17; H, 6.71; N, 17.14.

4,5-Dimethyl-2-(oxiran-2-ylmethyl)-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (13). To an ice-cooled suspension of 60% NaH (60 mg, 1.5 mmol) in dry DMF (5 ml) was added dropwise a solution of the pyridazinone **5** (213 mg, 1 mmol) in dry DMF (5 ml). The mixture was stirred at r.t. for 1 h, then epichlorohydrin (465 mg, 5 mmol) was added, and stirring was continued at 60 °C for 72 h. The solvent was removed under reduced pressure and the residue was taken up in water and extracted with dichloromethane (3 x 30 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography (dichloromethane/ethyl acetate, 95:5) to afford 263 mg (93%) of **13** as a light brown solid which was recrystallized from ethyl acetate to give almost colorless crystals, mp 170-172 °C. IR: ν 3441, 3056, 2996, 2942, 1653, 1635, 1551, 1523, 1469, 1422, 1393, 1356, 1265, 1245, 1111, 1016, 920, 748, 688 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.53-8.50 (m, 1H, H-9), 7.60-7.514 (m, 1H, H-7), 7.49 (d, $J_{6\text{-}7}$ 6.0 Hz, 1H, H-6, shows positive NOE on irradiation at 4.12 ppm), 7.45-7.40 (m, 1H, H-8, shows positive NOE on irradiation at 8.53-8.50 ppm), 4.58 (dd, *J* 4.5 and 13.8 Hz, 1H, H-1′), 4.41 (dd, *J* 5.4 and 13.8 Hz, 1H, H-1′), 4.12 (s, 3H, CH_3-5), 3.51-3.48 (m, 1H, H-2′), 2.89 (t, *J* 4.4 Hz, 1H, H-3′), 2.84 (s, 3H, CH_3-4), 2.80 (dd, *J* 2.6 and 5.0 Hz, 1H, H-3′). MS (EI): *m/z* (%) 270 (9%), 269 (M^+, 31%), 238 (17), 226 (19), 214 (25), 213 (100), 200 (18), 199 (100), 198 (35), 184 (23), 183 (39), 170 (19), 157 (25), 155 (14), 128 (18), 57 (9). Anal. Calcd. for $C_{15}H_{15}N_3O_2$ (269.31): C, 66.90: H, 5.61; N, 15.60. Found: C, 66.82: H, 5.54; N, 15.51.

2-(2,3-Dihydroxypropyl)-4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (14). This compound was obtained as a side product from the alkylation reaction described above when the mixture was in contact with water for some time before extraction with dichloromethane; buff crystals (70 mg, 25%), mp. 202-204 °C. IR: ν 3403, 2924, 2853, 1636, 1550, 1464, 1437, 1393, 1350, 1247, 1245, 1109, 1034, 761,753, 550 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.48 (m, $J_{8\text{-}9}$ 7.8 Hz, 1H, H-9), 7.62-7.56 (m, 1H, H-7), 7.49 (d, $J_{6\text{-}7}$ 8.4 Hz, 1H, H-6), 7.46-7.41 (m, 1H, H-8), 4.54 (d, *J* 5.1 Hz, 2H, CH_2-1′, shows positive NOE on irradiation at 3.62 ppm), 4.18-4.14 (m, 1H, H-2′, shows positive NOE on irradiation at 4.54 ppm), 4.11 (s, 3H, CH_3-5), 3.62 (d, *J* 4.2 Hz, 2H, CH_2-3′), 2.84 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 287 (M^+, 3%), 269 (39), 256 (45), 227 (18), 226 (33), 214 (74), 213 (100), 199 (61), 198 (30), 197 (13), 183 (21), 157 (29), 154 (15), 128 (28), 115

(13), 114 (18), 61 (32). Anal. Calcd. for $C_{15}H_{17}N_3O_3$ (287.32): C, 62.71: H, 5.96; N, 14.63. Found: C, 62.79: H, 6.86; N, 14.53.

2-[2-Hydroxy-3-(4-phenylpiperazino)propyl]-4,5-dimethyl-2,5-dihydro-1*H*-pyrid-azino[4,5-*b*]indol-1-one (15). To a solution of the epoxide **13** (269 mg, 1 mmol) in dry THF (10 ml) was added 1-phenylpiperazine (487 mg, 3 mmol). The mixture was stirred at reflux for 24 h, then it was diluted with water (20 ml) and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow solid which was recrystallized from ethanol to afford pale yellow crystals (350 mg, 80%), mp. 220-222 °C. IR: ν 3419, 2943, 2823, 1645, 1599, 1554, 1496, 1465, 1391, 1243, 1230, 1142, 1110, 1010, 928, 753, 716, 689 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.52 (d, $J_{8\text{-}9}$ 8.1 Hz, 1H, H-9), 7.61-7.55 (m, 1H, H-7), 7.50 (d, $J_{6\text{-}7}$ 8.1 Hz, 1H, H-6), 7.46-7.40 (m, 1H, H-8), 7.30-7.25 (m, 2H, phenyl H-3′, H-5′, shows positive NOE on irradiation at 6.95 ppm), 6.95 (d, J 7.8 Hz, 2H, phenyl H-2′, H-6′, shows positive NOE on irradiation at 3.23 ppm), 6.89-6.85 (m, 1H, phenyl H-4′), 4.58-4.33 (m, 3H, $N_{pyr.}CH_2$ and C<u>H</u>OH), 4.13 (s, 3H, CH_3-5), 3.23 (t, J 4.8 Hz, 4H, PhNC<u>H</u>$_2$, shows positive NOE on irradiation at 6.95 ppm), 2.86 (s, 3H, CH_3-4), 2.81 (t, J 5.1 Hz, 2H, $N_{pip.}C$<u>H</u>$_2$CHOH, shows positive NOE on irradiation at 3.23 ppm), 2.72-2.61 (m, 4H, $N_{pip.}CH_2$). MS (EI): *m/z* (%) 431 (M^+, 1%), 416 (6), 313 (11), 299 (84), 256 (72), 214 (21), 201 (16), 199 (26), 176 (38), 175 (100), 160 (19), 132 (68), 105 (23), 104 (35), 77 (21), 70 (73), 56 (28). Anal. Calcd. for $C_{25}H_{29}N_5O_2$ (431.54): C, 69.58; H, 6.77; N, 16.23. Found: C, 69.49; H, 6.71; N, 16.14.

2-(2-Hydroxy-3-piperidinopropyl)-4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]ind-ol-1-one (16). This compound was obtained following the procedure described above for the preparation of **15**, employing piperidine (255 mg, 3 mmol) as the amine component. The product was recrystallized from ethyl acetate/methanol (9:1) to give 175 mg (49%) of **16** as colorless crystals, mp 158-160 °C. IR: ν 3411, 3050, 2935, 2854, 1634, 1616, 1553, 1465, 1441, 1393, 1352, 1246, 1112, 1092, 1036, 782, 751, 687 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.50 (d, $J_{8\text{-}9}$ 7.8 Hz, 1H, H-9), 7.59-7.53 (m, 1H, H-7), 7.47 (d, $J_{6\text{-}7}$ 8.1 Hz, 1H, H-6), 7.44-7.38 (m, 1H, H-8), 4.51-4.27 (m, 3H, $N_{pyr.}CH_2$ and C<u>H</u>OH), 4.10 (s, 3H, CH_3-5), 2.84 (s, 3H, CH_3-4), 2.63-2.57 (m, 2H, $N_{pip.}CH_2$, shows positive NOE on irradiation at 1.64-1.43 ppm), 2.51-2.48 (m, 2H, $N_{pip.}C$<u>H</u>$_2$CHOH), 2.44-2.41 (m, 2H, $N_{pip.}CH_2$, shows positive NOE on irradiation at 1.64-1.43 ppm), 1.64-1.43 (m, 6H, CH_2). MS (EI): *m/z* (%) 355 (M^++1, 0.13%), 256 (14), 253 (7), 124 (8), 99 (18), 98 (100), 55 (9). Anal. Calcd. for $C_{20}H_{26}N_4O_2$ (354.46): C, 67.77; H, 7.39; N, 15.81. Found: C, 67.55; H, 7.33; N, 15.64.

2-(3-{[3-(Diethylamino)propyl]amino}-2-hydroxypropyl)-4,5-dimethyl-2,5-di-hydro-1*H*-pyridazino[4,5-*b*]indol-1-one (17). This compound was obtained following the procedure described above for the preparation of **15**, employing *N,N*-diethyl-1,3-propanediamine (2.5 g, 19 mmol) as the amine component. The product was purified by trituration with diethyl ether and recrystallization from ethyl acetate to afford 220 mg (55%) of **17** as colorless crystals mp 137-139 °C. IR: ν 3423, 3309, 3056, 2964, 2931, 2817, 1647, 1465, 1557, 1447, 1381, 1242, 1112, 1112, 1067, 918, 780, 754, 715, 715 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, $J_{8\text{-}9}$ 7.8 Hz, 1H, H-9), 7.60-7.55 (m, 1H, H-7), 7.49 (d, $J_{6\text{-}7}$ 7.5 Hz, 1H, H-6), 7.45-7.40 (m, 1H, H-8), 4.54-4.40 (m,

2H, $N_{pyr.}CH_2$), 4.27-4.19 (m, 1H, C<u>H</u>OH), 4.11 (s, 3H, CH_3-5), 2.83 (s, 3H, CH_3-4), 2.81-2.64 (m, 4H, CH(OH)C<u>H</u>$_2$NH and C<u>H</u>$_2$NEt$_2$; C<u>H</u>$_2$NEt$_2$ shows positive NOE on irradiation at 1.73-1.64 ppm), 2.58-2.49 (m, 6H, NHC<u>H</u>$_2$CH$_2$CH$_2$NEt$_2$ and N(C<u>H</u>$_2$CH$_3$)$_2$; NHC<u>H</u>$_2$CH$_2$CH$_2$NEt$_2$ shows positive NOE on irradiation at 1.73-1.64 ppm), 1.73-1.64 (m, 2H, NHCH$_2$C<u>H</u>$_2$CH$_2$NEt$_2$), 1.04 (t, *J* 7.1 Hz, 6H, N(CH$_2$C<u>H</u>$_3$)$_2$). MS (EI): *m/z* (%) 400 (M^++1, 0.4%), 282 (6), 270 (6), 256 (11), 214 (29), 213 (24), 183 (6), 143 (37), 129 (6), 113 (32), 100 (16), 98 (25), 86 (100), 84 (11), 72 (18), 58 (17), 56 (10). Anal. Calcd. for $C_{22}H_{33}N_5O_2$ (399.54): C, 66.14; H, 8.33; N, 17.53. Found: C, 66.07; H, 8.24; N, 17.40.

2-(3-Azido-2-hydroxypropyl)-4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (18). The epoxide **13** (269 mg, 1 mmol) was dissolved in dioxane (4 ml) and a solution of sodium azide (91 mg, 1.39 mmol) in water (2 ml) was added. The mixture was heated to reflux for 7 h, cooled, and the solvent was removed *in vacuo*. The residue was partitioned between water and dichloromethane. The aqueous layer was further extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to give 162 mg (52%) of **18** as buff crystals, mp 160-162 °C. IR: ν 3383, 2926, 2872, 2104, 1636, 1616, 1550, 1465, 1437, 1394, 1247, 1092, 1045, 920, 781, 753, 723 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.46 (d, $J_{8\text{-}9}$ 8.1 Hz, 1H, H-9), 7.60-7.55 (m, 1H, H-7), 7.57 (d, $J_{6\text{-}7}$ 8.4 Hz, 1H, H-6), 7.44-7.39 (m, 1H, H-8), 4.49 (d, *J* 4.8 Hz, 2H, $N_{pyr.}CH_2$), 4.29-4.24 (m, 1H, C<u>H</u>OH), 4.10 (s, 3H, CH_3-5), 3.87-3.85 (br m, 1H, OH; disappears on addition of D_2O), 3.61-3.58 (m, 1H, CH_2N_3), 3.42-3.35 (m, 1H, CH_2N_3), 2.82 (s, 3H, CH_3-4). Anal. Calcd. for $C_{15}H_{16}N_6O_2$ (312.33): C, 57.68: H, 5.16; N, 26.91. Found: C, 57.61: H, 5.09; N, 26.83.

1-Chloro-4,5-dimethyl-5*H*-pyridazino[4,5-*b*]indole (19). A mixture of compound **5** (639 mg, 3 mmol) and $POCl_3$ (5 ml) was heated to 100 °C for 4 h. After cooling, the excess of $POCl_3$ was removed under reduced pressure. The residue was triturated with ice water and neutralized with 2 *N* ammonia to give a brown precipitate which was filtered off and recrystallized from ethanol to give colorless crystals (450 mg, 63%), mp 240-242 °C. IR ν 3065, 2983, 1618, 1576, 1541, 1494, 1465, 1379, 1344, 1288, 1247, 1154, 1095, 745, 778, 668 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (d, $J_{8\text{-}9}$ 8.1 Hz, 1H, H-9), 7.92 (d, $J_{6\text{-}7}$ 8.4 Hz, 1H, H-6), 7.79-7.74 (m, 1H, H-7), 7.52-7.46 (m, 1H, H-8), 4.21 (s, 3H, CH_3-5), 3.13 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 234 (5), 233 (M^+, 34), 232 (25), 231 (M^+, 100), 230 (35), 202 (19), 168 (19), 167 (27), 153 (16), 126 (12), 114 (14), 84 (25), 63 (12), 51 (10). Anal. Calcd. for $C_{12}H_{10}N_3Cl$ (231.69): C, 62.21: H, 4.35; Cl, 15.30; N, 14.14. Found: C, 62.15: H, 4.30; Cl, 15.24; N, 14.18.

***N*1-(4,5-Dimethyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)-*N*3,*N*3-diethylpropane-1,3-diamine hydrochloride (20).** A suspension of the chloro compound **19** (231 mg, 1 mmol) and 3-diethylaminopropylamine (10 ml, 64 mmol) was heated under argon atmosphere at 160 °C until the starting material was consumed (TLC monitoring). After cooling, the volatile components were removed by Kugelrohr distillation and the residue was subjected to column chromatography (dichloromethane/methanol/triethylamine, 90:7:3), followed by recrystallization from ethyl acetate/ether (1:2) to give 150 mg (38%) of **20** as buff crystals, mp 168-170 °C. IR: ν 3457, 3387,

2940, 2712, 2678, 2481, 1617, 1582, 1468, 1430, 1384, 1338, 1236, 1113, 750, 736, 654 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.87 (d, J_{8-9} 7.8 Hz, 1H, H-9), 7.62-7.56 (m, 1H, H-7), 7.53-7.48 (m, 1H, H-8), 7.46 (d, J_{6-7} 2.7 Hz, 1H, H-6, shows positive NOE on irradiation at 4.09 ppm), 7.26-7.21 (b, 1H, NH), 4.09 (s, 5H, $NCH_2CH_2CH_2NEt_2$ and CH_3-5), 3.25-3.17 (m, 6H, $NCH_2CH_2CH_2N(CH_2CH_3)_2$ and CH_2-b), 3.04 (s, 3H, CH_3-4, shows positive NOE on irradiation at 4.09 ppm), 2.42 (quint, J 6.5 Hz, 2H, $NCH_2CH_2CH_2NEt_2$; 1.47 (t, J 7.3 Hz, 6H, $NCH_2CH_2CH_2N(CH_2CH_3)_2$). MS (EI): *m/z* (%) 325 (M^+,7%), 296 (41), 253 (36), 239 (60226 (100), 225 (28), 213 (63197 (34), 182 (19), 156 (21), 114 (13), 98 (20), 86 (60), 84 (20), 58 (28), 56 (21). Anal. Calcd. for $C_{19}H_{27}N_5 \cdot 1.9$ HCl (394.74): C, 57.81; H, 7.38; N, 17.74. Found: C, 57.78; H, 7.50; N, 17.58. HRMS (for the free base): calcd for $C_{19}H_{27}N_5$ (M^+): 325.2266; found: 325.2271 $\pm$ 0.00121.

***N*-Benzyl-*N*-(4,5-dimethyl-5*H*-pyridazino[4,5-*b*]indol-1-yl)amine (21).** A mixture of the chloro compound **19** (231 mg, 1 mmol) and benzylamine (4.95 g, 45.77 mmol) was heated to 170 °C until the starting material was consumed (ca. 20 h; TLC monitoring). The reagent was removed by Kugelrohr distillation and the brown residue was triturated with diethyl ether to afford a solid material which was purified by column chromatography (dichloromethane/ methanol, 90:10), followed by recrystallization from ethyl acetate/light petroleum (1:1) to give 226 mg (75%) of **21** as yellow crystals, mp 226-228 °C. IR: ν 3394, 3053, 2925, 1616, 1576, 1485, 1469, 1448, 1411, 1356, 1325, 1246, 1108, 1142, 1060, 962, 843, 785, 759, 757, 693 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.52 (d, J_{8-9} 8.1 Hz, 1H, H-9), 7.78 (d, J_{6-7} 8.4 Hz, 1H, H-6), 7.61-7.56 (m, 1H, H-7), 7.41-7.32 (m, 3H, H-8, phenyl H-2′, H-6′, shows positive NOE on irradiation at 4.89 ppm and on irradiation at 8.52 ppm), 7.29-7.24 (m, 2H, phenyl H-3′, H-5′), 7.19-7.14 (m, 1H, phenyl H-4′), 7.03 (t, J 6.38 Hz, 1H, NH, show positive NOE on irradiation at 8.52 and on irradiation at 4.89 ppm), 4.89 (d, J 6.0 Hz, 2H, CH_2), 4.12 (s, 3H, CH_3-5), 2.93 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 303 (26%), 302 (M^+, 100), 198 (7), 197 (16), 196 (20), 182 (40), 168 (7), 156 (28), 155 (14), 142 (10), 128 (8), 106 (68), 104 (6), 91 (28), 79 (7), 77 (13), 65 (22), 63 (7). Anal. Calcd. for $C_{19}H_{18}N_4$ (302.38): C, 75.47; H, 6.00; N, 18.53. Found: C, 75.32; H, 6.08; N, 18.38.

6,7-Dimethyl-7*H*-tetrazolo[5',1':6,1]pyridazino[4,5-*b*]indole (22). To a solution of the chloro compound **19** (231 mg, 1 mmol) in DMF (10 ml) was added sodium azide (195 mg, 3 mmol), and the mixture was heated under reflux for 18-20 h (TLC monitoring). The solvent was removed *in vacuo*, the residue was triturated with water, and the resulting solid was collected by filtration and dried. Recrystallization from DMSO afforded 195 mg (82%) of **22** as colorless crystals, mp 265-267 °C. IR: ν 3059, 2948, 2933, 1638, 1607, 1519, 1500, 1460, 1418, 1388, 1345, 1274, 1217, 1114, 1066, 980, 946, 864, 760, 647 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.32 (d, J_{8-9} 7.8 Hz, 1H, H-9), 7.99 (d, J_{6-7} 8.4 Hz, 1H, H-6), 7.77-7.71 (m, 1H, H-7), 7.56-7.51 (m, 1H, H-7), 4.32 (s, 3H, CH_3-5), 3.17 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 239 (6%), 238 (M^+, 23), 183 (15), 182 (100), 181 (96), 179 (11), 167 (11), 155 (49), 154 (43), 140 (38), 129 (12), 127 (24), 114 (12), 77 (45), 74 (7), 64 (14), 63 (24). Anal. Calcd. for $C_{12}H_{10}N_6$ (238.25): C, 60.50; H, 4.23; N, 35.27. Found: C, 60.62; H, 4.18; N, 35.21.

4,5-Dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-thione (23). A mixture of the chloro compound **19** (231 mg, 1 mmol) and thiourea (456 mg, 6 mmol) in abs. ethanol (15 ml) was heated under reflux for 48 h, and the reaction was followed by TLC. The solvent was evaporated *in vacuo* and the residue was boiled with 10% sodium hydroxide (2 ml) and ethanol (10 ml) for 1 h. The mixture was concentrated and the resulting salt was dissolved in water and acidified with 2 *N* HCl, then the solid product thus formed was filtered off and recrystallized from ethanol to afford 166 mg (69%) as buff crystals, mp 335-337 °C. IR: ν 3280, 3135, 3019, 2916, 1663, 1616, 1558, 1512, 1465, 1392, 1269, 1197, 1130, 1078, 1015, 961, 753, 728, 631 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.95 (s, 1H, NH), 9.11 (d, $J_{8\text{-}9}$ 7.5 Hz, 1H, H-9), 7.85 (d, $J_{6\text{-}7}$ 8.1 Hz, 1H, H-6), 7.67-7.62 (m, 1H, H-7), 7.46-7.41 (m, 1H, H-8, shows positive NOE on irradiation at 9.11 ppm), 4.17 (s, 3H, CH_3-5), 2.67 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 229 (M^+, 5), 107 (52), 106 (100), 104 (5), 91 (17), 89 (6), 80 (5), 79 (55), 78 (20), 77 (32), 65 (7), 63 (6), 53 (7), 52 (11), 51 (25), 50 (14). Anal. Calcd. for $C_{12}H_{11}N_3S$ (229.31): C, 62.86; H, 4.84; N, 18.33; S, 13.98. Found: C, 62.79; H, 4.75; N, 18.27; S, 13.86.

Dimethyl-5*H*-pyridazino[4,5-*b*]indole (24). *4,5-* To a stirred suspension of the chloro compound **19** (231 mg, 1 mmol) in methanol (20 ml) was added ammonium formate (252 mg, 3.98 mmol) and 10% palladium/carbon (80 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: dichlromethane/methanol, 9:1). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. Water (50 ml) was added to the residue, the product was collected by filtration, washed with water, dried and recrystallized from ethyl acetate/light petroleum (1:1) to give 135 mg (69%) of **24** as colorless crystals, mp 193-195 °C . IR: ν 3046, 2987, 2916, 1653, 1619, 1548, 1473, 1452, 1337, 1295, 1231, 1128, 1038, 1018, 918, 839, 757, 738, 617, 516 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, H-1), 8.21 (d, $J_{8\text{-}9}$ 9.0 Hz, 1H, H-9), 7.73-7.68 (m, 1H, H-7), 7.76 (d, $J_{6\text{-}7}$ 8.4 Hz, 1H, H-6), 7.47-7.42 (m, 1H, H-8), 4.22 (s, 3H, CH_3-5), 2.88 (s, 3H, CH_3-4). MS (EI): *m/z* (%) 198 (15%), 197 (M^+, 100), 196 (71), 168 (34), 167 (43), 153 (13), 139 (6), 128 (13), 127 (18), 101 (6), 98 (5), 84 (9), 77 (7), 75 (12), 70 (7), 63 (10), 51 (12). Anal. Calcd. for $C_{12}H_{11}N_3$ (197.24): C, 73.07; H, 5.62; N, 21.30. Found: C, 72.92; H, 5.63; N, 21.24.

Acknowledgements

This research project is supported in part by deanship of scientific research, Jazan University, 6th program, Project Number 2399/6/36.

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