

Concise syntheses of 5-substituted pyridazino[4,5-*b*]indolones and -diones

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Dedicated to Professor Guy Quéguiner on the occasion of his 70th birthday

Abstract

A series of 5-alkyl-4-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones (**3**) was prepared from 2-acetylindole-2-carboxylic acid by a one-pot reaction (*N*-alkylation, followed by ring closure with hydrazine). Similarly, various new 5-alkyl-2,3-dihydro-1*H*-pyridazino[4,5-*b*]indole-1,4(5*H*)-diones (**6**) were obtained by alkylation and subsequent hydrazinolysis of dimethyl indole-2,3-dicarboxylate. A 5-alkyl representative (**10**) of the 3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one system was made available by two alternative pathways.

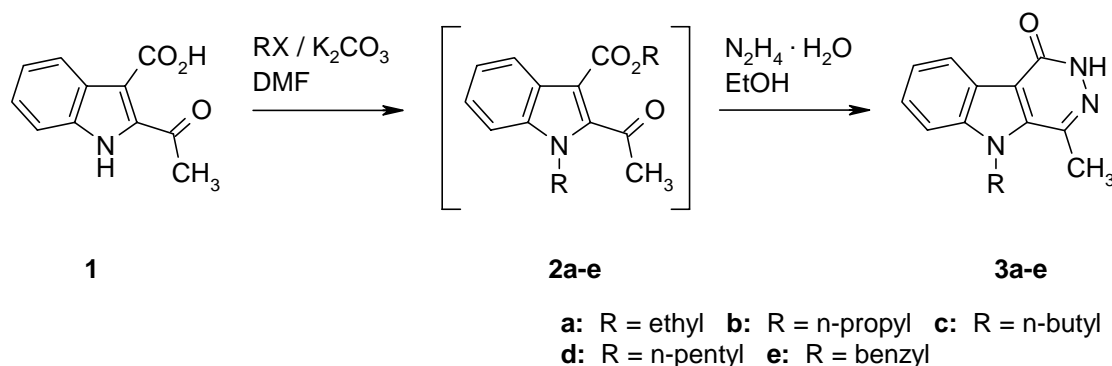
Keywords: Pyridazino[4,5-*b*]indoles, aza-carbolines, *N*-alkylation, hydrazinolysis

Introduction

The pyridazino[4,5-*b*]indole scaffold, due to its bio-isosterism with β -carboline as well as γ -carboline, has found considerable pharmaceutical interest as the core structure of a wide variety of bio-active compounds.¹⁻⁹ 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.¹⁰⁻¹² The title ring system now became interesting also in the context of an ongoing program in search of new and selective inhibitors of copper-containing amine oxidases.¹³ Based on preliminary structure-activity information,¹⁴ the need arose to prepare a focused compound library of indole-fused pyridazinones and pyridazinediones bearing various alkyl substituents at the indole nitrogen. Despite their simplicity, surprisingly few representatives of this general structure have been known so far.^{10,15-18} Here, we wish to report on short and convenient methods for the synthesis of such tricyclic compounds.

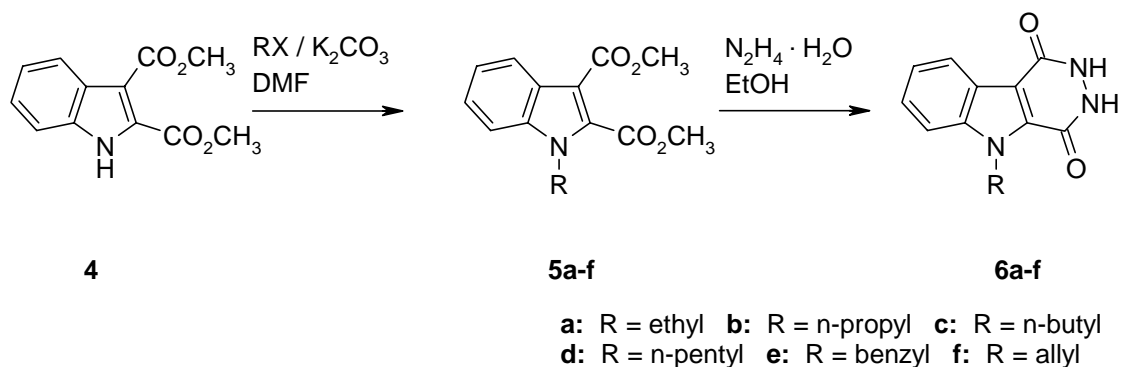
Results and Discussion

5-Alkyl-4-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones, representing one of the envisaged target structures, in principle can be prepared by selective monoalkylation of N-5 in the parent compound with stoichiometric amounts of alkylating agents, as we had shown recently.¹⁰ However, yields are low and cannot be improved by employment of excess reagent, as this would result in the formation of 2,5-disubstituted products.¹⁰ Therefore, introduction of the desired alkyl residues at the indole nitrogen is preferentially accomplished before the pyridazinone unit is formed, using the precursor, 2-acetylindole-3-carboxylic acid¹⁹ (**1**) as the substrate (Scheme 1). Here, a larger excess of alkylating agent (generally an alkyl iodide, with the exception of benzyl bromide) can be safely employed, effecting N-alkylation and esterification of the carboxylic group at the same time. The resulting ester functionality, in turn, offers the additional advantage of facilitating the subsequent ring-closure reaction with hydrazine, because free carboxylic acids of this type have been known to undergo concurrent decarboxylation very easily.²⁰ Although also this procedure gives only low to moderate yields, the sequence can be carried out very conveniently in a one-pot manner and opens a simple and short access to compounds of type **3** which are free of any contamination by 2,5-disubstituted derivatives.



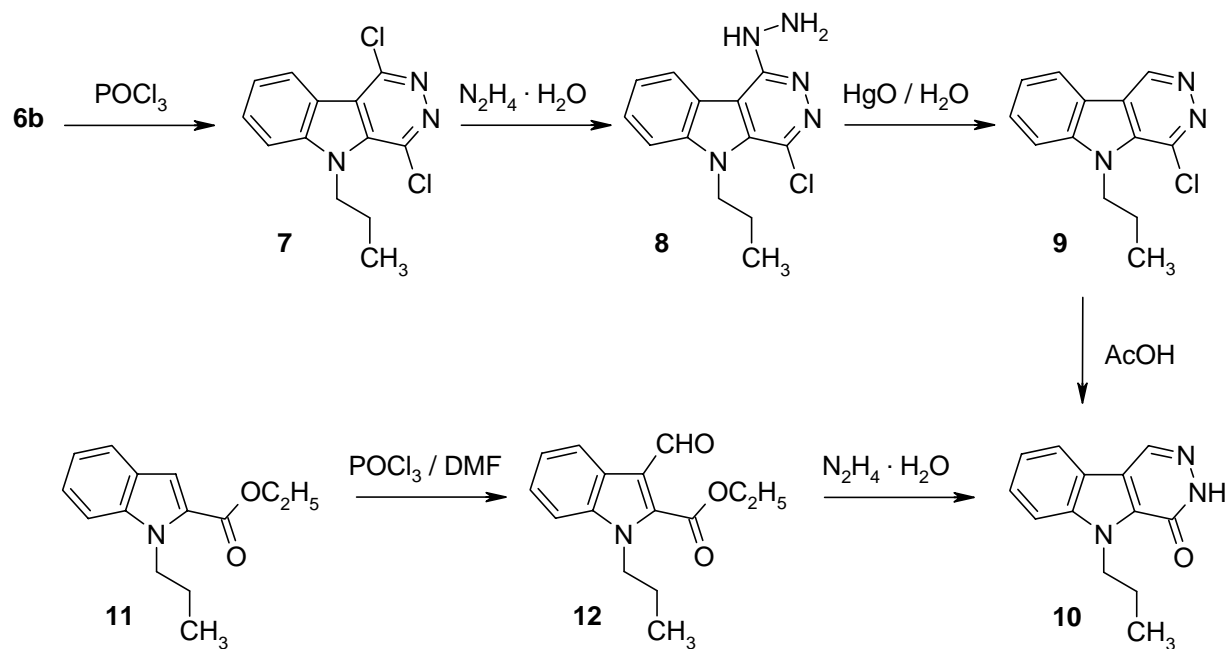
Scheme 1

For the preparation of a series of 5-alkyl-substituted 1,4-dihoxypyridazino[4,5-*b*]indoles (or their oxo tautomers, respectively), an analogous strategy was chosen. Thus, dimethyl indole-2,3-dicarboxylate²¹ was first N-alkylated with an excess of the appropriate alkyl iodide (or benzyl bromide or allyl bromide, respectively) in the presence of potassium carbonate in dimethylformamide solution. Here, the intermediate N-alkyl esters **5** were extractively isolated prior to condensation with hydrazine hydrate which then gave the pyridazino-indole derivatives **6a-f** in satisfactory yields.



Scheme 2

From the pyridazinediones (tautomeric dihydroxypyridazines or hydroxypyridazinones, respectively) of type **6**, also mono-oxygenated compounds should be easily accessible by a sequence involving transformation of **6** into the corresponding dichloropyridazine, followed by monosubstitution with hydrazine, oxidative dehydrazination, and finally hydrolysis of the remaining chloro function. This approach was successfully exemplified, starting from the *N*-propyl derivative **6b**, as shown in Scheme 3. Heating with phosphorus oxychloride smoothly afforded the dichloro compound **7** in 82% yield. Hydrazinolysis of **7** indeed gave a mono-hydrazino-monochloro product regioselectively. An analogous transformation of the 5-unsubstituted dichloro congener, leading to a 1-chloro-4-hydrazino compound, had been previously reported by Monge and coworkers.²² Interestingly, in our case the regioselectivity of this substitution was found to be completely reversed, leading to the 4-chloro-1-hydrazino derivative **8** exclusively. Obviously, steric shielding of the 4-position by the adjacent *N*-alkyl residue is responsible for the observed preferential attack of the nucleophile at C-1 rather than at C-4 (as in Monge's 5-unsubstituted compound). The position of the newly introduced hydrazino group was firmly established after its replacement by hydrogen (compound **9**) which is ideally suited for an NOE experiment, thus proving the close distance between H-9 and this pyridazine H atom. The transformation of **8** into **9** was accomplished by treatment with mercuric oxide in aqueous suspension in analogy to previous protocols.^{23,24} The final hydrolysis step, affording the new pyridazinone **10**, succeeded by heating the chloropyridazine in acetic acid.²⁵ As a more convenient synthesis of **10**, which moreover avoids the use of toxic mercuric oxide, we elaborated a sequence starting from *N*-propylindole-2-carboxylic acid ethyl ester²⁶ (**11**). This compound could be easily formylated at C-3 with Vilsmeier–Haack reagent under the conditions reported for similar substrates.²⁷ As expected, the formyl ester **12** was found to cyclize smoothly with hydrazine hydrate in ethanolic solution to afford the tricycle **10** in good yield.



Scheme 3

In conclusion, a variety of new indole-fused pyridazinones and pyridazinediones bearing small to medium-sized alkyl residues at the indole nitrogen were made accessible by short and convenient synthetic pathways. Preliminary *in-vitro* tests for inhibition of certain amine oxidases showed only weak activity of the new compounds, further screenings for 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 1605 FT-IR instrument. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Varian Unityplus 300 (300 MHz, 75 MHz) and on a Bruker Avance DPX 200 (200 MHz, 50 MHz) spectrometer (δ values in ppm). Mass spectra were obtained on a Shimadzu QP 5050A DI 50 instrument, high-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 8230 spectrometer at the Institute of Organic Chemistry, University of Vienna. For column chromatography, Merck Kieselgel 60 (0.063–0.200 mm) was used. Microanalyses were performed at the Microanalytical Laboratory, Faculty of Chemistry, University of Vienna.

5-Alkyl-4-methyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-ones (3). General procedure. To a solution of 2-acetylindole-3-carboxylic acid¹⁹ (0.203 g, 1 mmol) in dry DMF (10 mL) was added K_2CO_3 (0.280 g, 2 mmol) and the appropriate alkyl iodide (25–35 mmol; for **3e**, benzyl

bromide was used), and the mixture was stirred at RT in a closed vessel for the time given below. The volatile components were removed under reduced pressure and the residue was taken up in a mixture of hydrazine monohydrate (3 mL, 60 mmol) and EtOH (10 mL). The solution was refluxed for 24 h, then it was poured into ice-water (100 mL), acidified (pH 2-3) and kept in the refrigerator for at least 0.5 h. The precipitate was collected by filtration, washed with water, and dried. Recrystallisation from EtOH gave the products as almost colorless crystals.

5-Ethyl-4-methyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-one (3a). Reaction time: 200 h, yield: 0.045 g (20%), mp 285°C; Anal. Calcd. C₁₃H₁₃N₃O: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.53; H, 5.58; N, 18.63. IR (KBr, cm⁻¹) 3222, 2977, 2924, 1651, 1456, 1399, 1212, 752; ¹H NMR (300 MHz, DMSO-d₆) δ 12.48 (s, 1H, NH), 8.25 (d, *J* = 8.2 Hz, 1H, 9-H), 7.79 (d, *J* = 8.2 Hz, 1H, 6-H), 7.57–7.50 (m, 1H, 7-H), 7.38–7.32 (m, 1H, 8-H), 4.63 (q, *J* = 7.2 Hz, 2H, NCH₂CH₃), 2.75 (s, 3H, 4-CH₃), 1.38 (t, *J* = 7.2 Hz, 3H, NCH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 159.3, 138.3, 136.2, 134.1, 126.3, 122.0, 121.9, 111.5, 110.9, 20.0, 15.8; MS *m/z*: 228 (10%), 227 (M⁺, 64), 212 (48), 183 (10), 149 (8), 114 (18), 95 (16), 81 (54), 69 (100), 57 (29), 55 (31).

4-Methyl-5-propyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-one (3b). Reaction time: 120 h, yield: 0.108 g (45%), mp 268°C; Anal. Calcd. C₁₄H₁₅N₃O: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.59; H, 6.22; N, 17.41. IR (KBr, cm⁻¹) 3071, 2922, 1643, 1456, 1399, 1206, 1117, 767; ¹H NMR (300 MHz, DMSO-d₆) δ 12.49 (s, 1H, NH), 8.25 (dd, *J* = 7.3 Hz, 0.5 Hz, 1H, 9-H), 7.82 (d, *J* = 8.4 Hz, 1H, 6-H), 7.56–7.50 (m, 1H, 7-H), 7.35 (t, *J* = 7.4 Hz, 1H, 8-H), 4.53 (t, *J* = 7.6 Hz, 2H, NCH₂CH₂CH₃), 2.73 (s, 3H, 4-CH₃), 1.80 (sextet, *J* = 7.4 Hz, 2H, NCH₂CH₂CH₃), 0.93 (t, *J* = 7.4 Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 159.3, 138.8, 136.4, 134.0, 126.2, 121.9, 121.8, 121.7, 111.5, 111.2, 45.4, 24.0, 20.1, 10.9; MS *m/z*: 241 (M⁺, 41%), 212 (74), 149 (10), 115 (16), 95 (17), 81 (49), 69 (100), 57 (40), 55 (34).

5-Butyl-4-methyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-one (3c). Reaction time: 120 h, yield: 0.125 g (49%), mp 245°C; Anal. Calcd. C₁₅H₁₇N₃O: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.31; H, 6.58; N, 16.37. IR (KBr, cm⁻¹) 3146, 3070, 2956, 2920, 1642, 1524, 1456, 1399, 1193, 1118, 767; ¹H NMR (300 MHz, DMSO-d₆) δ 12.49 (s, 1H, NH), 8.25 (d, *J* = 8.1 Hz, 1H, 9-H), 7.78 (d, *J* = 8.1 Hz, 1H, 6-H), 7.56–7.49 (m, 1H, 7-H), 7.35 (t, *J* = 7.5 Hz, 1H, 8-H), 4.55 (t, *J* = 7.8 Hz, 2H, NCH₂CH₂CH₂CH₃), 2.73 (s, 3H, 4-CH₃), 1.75 (quintet, *J* = 7.8, 2H, NCH₂CH₂CH₂CH₃), 1.37 (sextet, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₂CH₃), 0.91 (t, *J* = 7.5 Hz, 3H, NCH₂CH₂CH₂CH₃); ¹³C NMR (75 MHz, DMSO-d₆) δ 159.2, 138.7, 136.3, 133.9, 126.1, 121.9, 121.7, 111.5, 111.0, 43.9, 32.7, 20.0, 19.5, 13.5; MS *m/z*: 255 (M⁺, 21%), 212 (42), 115 (8), 95 (6), 81 (21), 71 (14), 69 (38), 58 (100).

4-Methyl-5-pentyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-one (3d). Reaction time: 120 h, yield: 0.116 g (43%), mp 229°C; Anal. Calcd. C₁₆H₁₉N₃O: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.46; H, 7.22; N, 15.60. IR (KBr, cm⁻¹) 3069, 2924, 2863, 1643, 1456, 1397, 1172, 768; ¹H NMR (300 MHz, DMSO-d₆) δ 12.49 (s, 1H, NH), 8.25 (d, *J* = 8.2 Hz, 1H, 9-H), 7.80 (d, *J* = 8.2 Hz, 1H, 6-H), 7.56–7.50 (m, 1H, 7-H), 7.35 (t, *J* = 7.3 Hz, 1H, 8-H), 4.56 (t, *J* = 7.9 Hz, 2H, NCH₂CH₂CH₂CH₂CH₃), 2.74 (s, 3H, 4-CH₃), 1.77 (quintet, *J* = 7.5 Hz, 2H,

NCH₂CH₂CH₂CH₂CH₃), 1.37–1.31 (m, 4H, NCH₂CH₂CH₂CH₂CH₃), 0.85 (t, $J = 7.1$ Hz, 3H, NCH₂CH₂CH₂CH₂CH₃); ¹³C NMR (75 MHz, DMSO-d₆) δ 159.2, 138.7, 136.3, 133.9, 126.1, 121.9, 121.7, 111.5, 111.0, 44.0, 30.3, 28.3, 21.7, 20.0, 13.8; MS m/z : 270 (10%), 269 (M⁺, 51), 241 (19), 213 (16), 212 (100), 183 (13), 155 (10), 115 (12), 71 (13), 57 (21), 55 (13).

5-Benzyl-4-methyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-one (3e). Reaction time: 96 h, yield: 0.058 g (20%), mp 243°C; Anal. Calcd. C₁₈H₁₅N₃O: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.47; H, 5.41; N, 14.37. IR (KBr, cm⁻¹) 3160, 2985, 2916, 1644, 1452, 1394, 1169, 753; ¹H NMR (300 MHz, DMSO-d₆) δ 12.57 (s, 1H, NH), 8.31 (dd, $J = 7.8$ Hz, 0.8 Hz, 1H, 9-H), 7.74 (dd, $J = 7.8$ Hz, 0.9 Hz, 1H, 6-H), 7.53–7.47 (m, 1H, 7-H), 7.38 (t, $J = 7.0$ Hz, 1H, 8-H), 7.33–7.21 (m, 3H, phenyl-H), 6.93 (d, $J = 7.2$ Hz, 2H, phenyl-H), 5.92 (s, 2H, PhCH₂), 2.54 (s, 3H, 4-CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 159.3, 139.3, 138.0, 136.9, 134.1, 129.0, 127.4, 126.6, 125.2, 122.2, 121.9, 121.8, 112.0, 111.1, 47.1, 19.6; MS m/z : 290 (13%), 289 (M⁺, 57), 255 (3), 212 (6), 199 (9), 140 (5), 115 (12), 92 (24), 91 (100), 65 (23).

5-Alkyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-diones (6). **General procedure.** To a solution of dimethyl indole-2,3-dicarboxylate²¹ (0.233 g, 1 mmol) in dry DMF (10 mL) was added K₂CO₃ (0.420 g, 3 mmol) and the appropriate alkyl iodide (25–35 mmol; for **6e**: benzyl bromide; for **6f**: allyl bromide), and the mixture was stirred at RT in a closed vessel for 120 h. The mixture was poured into water (200 mL) and it was extracted with CH₂Cl₂ (3 x 50 mL). The combined extracts were dried over Na₂SO₄ and evaporated, then the residue was taken up in a mixture of hydrazine monohydrate (3 mL, 60 mmol) and EtOH (10 mL). The solution was refluxed for 24 h, then it was poured into ice-water (100 mL), acidified (pH 2–3) and kept in the refrigerator for at least 0.5 h. The precipitate was collected by filtration, washed with water, and dried. Recrystallisation from EtOH gave the products as almost colorless crystals.

5-Ethyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione (6a). Yield: 0.158 g (69%), mp > 310°C. Anal. Calcd. C₁₂H₁₁N₃O₂: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.60; H, 4.61; N, 18.25. IR (KBr, cm⁻¹) 2984, 2880, 1653, 1617, 1549, 1335, 1296, 1108, 738; ¹H NMR (300 MHz, DMSO-d₆) δ 11.57–11.51 (br s, 2H, NH), 8.13 (d, $J = 8.1$ Hz, 1H, 9-H), 7.79 (d, $J = 8.1$ Hz, 1H, 6-H), 7.56–7.50 (m, 1H, 7-H), 7.37–7.31 (m, 1H, 8-H), 4.77 (q, $J = 6.9$ Hz, 2H, NCH₂CH₃), 1.35 (t, $J = 6.9$ Hz, 3H, NCH₂CH₃); ¹³C NMR (75 MHz, DMSO-d₆) δ 153.9, 151.8, 138.3, 130.2, 126.3, 122.1, 121.7, 120.9, 111.0, 110.9, 39.0, 15.8; MS m/z : 229 (M⁺, 7%), 201 (7), 149 (6), 143 (7), 121 (6), 95 (13), 81 (46), 69 (100), 68 (17), 67 (17), 57 (29), 55 (34).

5-Propyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione (6b). Yield: 0.170 g (70%), mp 292°C. Anal. Calcd. C₁₃H₁₃N₃O₂: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.29; H, 5.40; N, 17.28. IR (KBr, cm⁻¹) 2963, 1653, 1551, 1470, 1292, 1158, 1113, 860, 737; ¹H NMR (300 MHz, DMSO-d₆) δ 11.56–11.53 (br s, 2H, NH), 8.13 (d, $J = 8.2$ Hz, 1H, 9-H), 7.79 (d, $J = 8.2$ Hz, 1H, 6-H), 7.52 (t, $J = 7.5$ Hz, 1H, 7-H), 7.34 (t, $J = 7.5$ Hz, 1H, 8-H), 4.71 (t, $J = 7.2$ Hz, 2H, NCH₂CH₂CH₃), 1.80 (sextet, $J = 7.2$ Hz, 2H, NCH₂CH₂CH₃), 0.82 (t, $J = 7.2$ Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 138.9, 130.7, 126.3, 122.1, 121.7, 120.8, 111.3, 45.3, 23.5, 10.8; MS m/z : 244 (6%), 243 (M⁺, 43), 214 (36), 201 (100), 170 (16), 143 (54), 129 (13), 115 (25), 114 (21), 89 (18), 77 (17), 45 (26), 31 (35).

5-Butyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione (6c). Yield: 0.159 g (62%), mp 290°C. Anal. Calcd. C₁₄H₁₅N₃O₂: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.38; H, 5.79; N, 16.17. IR (KBr, cm⁻¹) 2959, 1653, 1553, 1472, 1294, 1113, 735; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.55 (br s, 2H, NH), 8.13 (d, *J* = 8.2 Hz, 1H, 9-H), 7.77 (d, *J* = 8.2 Hz, 1H, 6-H), 7.56–7.49 (m, 1H, 7-H), 7.34 (t, *J* = 7.3 Hz, 1H, 8-H), 4.77–4.71 (m, 2H, NCH₂CH₂CH₂CH₃), 1.81–1.70 (m, 2H, NCH₂CH₂CH₂CH₃), 1.32–1.19 (m, 2H, NCH₂CH₂CH₂CH₃), 0.86 (t, *J* = 7.2 Hz, 3H, NCH₂CH₂CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 153.8, 151.7, 138.8, 130.6, 126.2, 122.1, 121.6, 120.8, 111.2, 111.0, 43.7, 32.3, 19.3, 13.6; MS *m/z*: 258 (12%), 257 (M⁺, 69), 240 (49), 228 (30), 215 (35), 214 (57), 201 (100), 170 (18), 143 (48), 115 (23), 89 (15).

5-Pentyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione (6d). Yield: 0.192 g (71%), mp 309°C. Anal. Calcd. C₁₅H₁₇N₃O₂: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.51; H, 6.14; N, 15.22. IR (KBr, cm⁻¹) 2956, 2930, 1653, 1550, 1472, 1294, 1156, 1113, 736; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.56–11.52 (br s, 2H, NH), 8.13 (d, *J* = 8.3 Hz, 1H, 9-H), 7.77 (d, *J* = 8.3 Hz, 1H, 6-H), 7.55–7.49 (m, 1H, 7-H), 7.34 (t, *J* = 7.6 Hz, 1H, 8-H), 4.73 (t, *J* = 7.0 Hz, 2H, NCH₂CH₂CH₂CH₂CH₃), 1.82–1.72 (m, 2H, NCH₂CH₂CH₂CH₂CH₃), 1.30–1.20 (m, 4H, NCH₂CH₂CH₂CH₂CH₃), 0.80 (t, *J* = 7.0 Hz, 3H, NCH₂CH₂CH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 138.8, 130.6, 126.3, 122.1, 121.7, 120.9, 111.3, 111.0, 43.9, 29.9, 28.2, 21.8; MS *m/z*: 272 (8%), 271 (M⁺, 42), 254 (48), 228 (24), 215 (30), 214 (53), 201 (100), 170 (19), 143 (43), 115 (23), 114 (23), 43 (33), 41 (40).

5-Benzyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione (6e). Yield: 0.204 g (70%), mp 315°C. Anal. Calcd. C₁₇H₁₃N₃O₂: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.92; H, 4.62; N, 14.23. IR (KBr, cm⁻¹) 3028, 2923, 1653, 1551, 1471, 1293, 1153, 1118, 739; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.68 (s, 2H, NH), 8.14 (d, *J* = 8.2 Hz, 1H, 9-H), 7.70 (d, *J* = 8.2 Hz, 1H, 6-H), 7.50–7.44 (m, 1H, 7-H), 7.36–7.30 (m, 1H, 8-H), 7.30–7.17 (m, 5H, phenyl-H), 6.00 (s, 2H, PhCH₂); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 138.8, 137.8, 130.6, 128.6, 127.4, 126.9, 126.6, 122.2, 122.0, 121.0, 111.7, 111.2, 47.0; MS *m/z*: 291 (M⁺, 12%), 214 (4), 92 (12), 91 (95), 65 (17), 46 (22), 45 (57), 43 (17), 31 (100).

5-Allyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione (6f). Yield: 0.205 g (85%), mp 278°C. Anal. Calcd. C₁₃H₁₁N₃O₂: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.42; H, 4.80; N, 17.37. IR (KBr, cm⁻¹) 2975, 1653, 1544, 1472, 1297, 1149, 1111, 937, 736; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.60 (s, 2H, NH), 8.14 (d, *J* = 8.2 Hz, 1H, 9-H), 7.70 (d, *J* = 8.2 Hz, 1H, 6-H), 7.54–7.48 (m, 1H, 7-H), 7.37–7.31 (m, 1H, 8-H), 6.10–5.96 (m, 1H, allyl 2'-H), 5.41 (d, *J* = 5.4 Hz, 2H, allyl 1'-H), 5.10 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H, allyl 3'-H), 4.89 (dd, *J* = 17.4 Hz, 1.5 Hz, 1H, allyl 3'-H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 138.8, 134.0, 130.5, 126.4, 122.1, 121.9, 120.9, 116.4, 111.5, 111.3, 46.1, 23.5, 10.8; MS *m/z*: 243 (35%), 241 (M⁺, 90), 224 (59), 214 (36), 201 (100), 170 (23), 154 (36), 143 (62), 114 (46).

1,4-Dichloro-5-propyl-5H-pyridazino[4,5-*b*]indole (7). A mixture of compound **6b** (0.486 g, 2 mmol) and POCl₃ (12 mL, 128 mmol) was heated to 100°C for 4 h. After cooling, the solution was slowly poured onto ice and it was basified with conc. ammonia. The precipitate was collected by filtration, washed with water, and dried to afford **7** as pale yellow crystals (0.459 g,

82%), mp 159°C. Anal. Calcd. C₁₃H₁₁Cl₂N₃·0.2 H₂O: C, 55.03; H, 4.05; N, 14.81. Found: C, 55.01; H, 3.80; N, 14.69. IR (KBr, cm⁻¹) 2960, 2873, 1619, 1553, 1493, 1425, 1331, 1237, 1079, 751; ¹H NMR (300 MHz, DMSO-d₆) δ 8.52 (d, *J* = 8.2 Hz, 1H, 9-H), 8.07 (d, *J* = 8.2 Hz, 1H, 6-H), 7.88–7.82 (m, 1H, 7-H), 7.58 (t, *J* = 7.7 Hz, 1H, 8-H), 4.79 (t, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₃), 1.87 (sextet, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₃), 0.94 (t, *J* = 7.5 Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 148.5, 141.0, 139.6, 133.1, 130.2, 123.0, 122.5, 118.6, 117.5, 112.0, 45.5, 23.8, 10.8; MS *m/z*: 283 (M⁺, 2%), 281 (M⁺, 22), 279 (M⁺, 27), 252 (63), 250 (100), 180 (57), 138 (19), 99 (18), 63 (17).

4-Chloro-1-hydrazino-5-propyl-5H-pyridazino[4,5-*b*]indole (8). A mixture of compound **7** (0.560 g, 2 mmol) and 100% hydrazine monohydrate (20 mL, 400 mmol) was refluxed under an argon atmosphere for 6 h. After cooling, the precipitate was collected by filtration, washed with water, and dried to afford **8** (0.253 g, 46%) as pale yellow crystals, mp 159–160°C. Anal. Calcd. C₁₃H₁₄ClN₅: C, 56.63; H, 5.12; N, 25.40. Found: C, 56.56; H, 5.11; N, 25.28. IR (KBr, cm⁻¹) 3288, 2961, 2874, 1616, 1566, 1413, 1331, 1200, 1060, 1003, 751; ¹H NMR (300 MHz, DMSO-d₆) δ 8.49 (d, *J* = 8.4 Hz, 1H, 9-H), 8.05 (d, *J* = 8.4 Hz, 1H, 6-H), 7.86–7.80 (m, 1H, 7-H), 7.57 (t, *J* = 7.7 Hz, 1H, 8-H), 4.77 (t, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₃), 3.32 (br, 3H, NH), 1.86 (sextet, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₃), 0.93 (t, *J* = 7.5 Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 148.5, 141.0, 139.6, 133.1, 130.2, 123.0, 122.5, 118.6, 117.5, 112.0, 45.5, 23.7, 10.7; MS *m/z*: 277 (M⁺, 16%), 275 (M⁺, 49), 245 (43), 216 (100), 180 (50), 168 (56), 153 (48), 126 (31), 114 (31), 77 (88), 51 (47).

4-Chloro-5-propyl-5H-pyridazino[4,5-*b*]indole (9). To a stirred suspension of yellow HgO (0.432 g, 2 mmol) in water (10 mL) was added compound **8** (0.275 g, 1 mmol) in small portions at RT. Stirring was continued for 2 h, then the mixture was extracted several times with AcOEt. The combined extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The dark oily residue was subjected to column chromatography (AcOEt) to afford **9** (0.073 g, 30%) as a yellow-orange solid, mp 125–126°C, which was used for the following step without further purification. ¹H NMR (300 MHz, DMSO-d₆) δ 9.97 (s, 1H, 1-H, shows positive NOE on irradiation at 8.43 ppm), 8.43 (d, *J* = 8.2 Hz, 1H, 9-H), 7.96 (d, *J* = 8.2 Hz, 1H, 6-H, shows positive NOE on irradiation at 4.75 ppm), 7.78–7.72 (m, 1H, 7-H), 7.49 (t, *J* = 7.5 Hz, 1H, 8-H), 4.75 (t, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₃), 1.86 (sextet, *J* = 7.5 Hz, 2H, NCH₂CH₂CH₃), 0.92 (t, *J* = 7.5 Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 144.2, 140.9, 139.6, 132.0, 129.7, 122.2, 121.4, 118.5, 111.6, 45.4, 23.8, 10.8; MS *m/z*: 247 (M⁺, 15%), 245 (M⁺, 44%), 218 (30), 216 (100), 180 (41), 153 (26), 126 (22), 75 (20), 63 (21), 51 (15).

Ethyl 1-propyl-1H-indole-2-carboxylate²⁶ (11). A mixture of ethyl indole-2-carboxylate (0.189 g, 1 mmol), K₂CO₃ (0.420 g, 3 mmol), and propyl iodide (3.0 mL, 31 mmol) in DMF (10 mL) was stirred at RT for 120 h, then it was poured into water (100 mL) and extracted repeatedly with Et₂O. The combined extracts were washed with water, dried over Na₂SO₄, and evaporated to give **11** (0.162 g, 70%) as a yellow oil. ¹H NMR (300 MHz, DMSO-d₆) δ 7.66 (d, *J* = 8.2 Hz, 1H, 4-H), 7.57 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H, 7-H), 7.34–7.28 (m, 1H, 6-H), 7.26 (s, 1H, 3-H), 7.13–7.07 (m, 1H, 5-H), 4.50 (t, *J* = 7.4 Hz, 2H, NCH₂CH₂CH₃), 4.30 (q, *J* = 7.2 Hz, 2H,

OCH₂CH₃), 1.69 (sextet, $J = 7.4$ Hz, 2H, NCH₂CH₂CH₃), 1.32 (t, $J = 7.2$ Hz, 3H, OCH₂CH₃), 0.81 (t, $J = 7.4$ Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (50 MHz, DMSO-d₆) δ 161.1, 138.7, 127.0, 125.3, 124.7, 122.2, 120.3, 111.9, 110.0, 60.2, 45.3, 23.4, 14.0, 10.2; MS m/z : 232 (8%), 231 (M⁺, 48), 202 (68), 174 (100), 143 (25), 130 (22), 116 (24), 115 (30), 89 (40), 77 (14), 63 (14); HRMS Calcd. C₁₄H₁₇NO₂: 231.1259. Found: 231.1256.

Ethyl 3-formyl-1-propyl-1H-indole-2-carboxylate (12). To a stirred solution of POCl₃ (0.3 mL, 3.3 mmol) in dry DMF (4 mL) was added dropwise a solution of compound **11** (0.231 g, 1 mmol) in dry DMF (2 mL), then the mixture was heated to 110°C for 1 h. It was then poured into water (100 mL), made alkaline with Na₂CO₃, and extracted with Et₂O. The combined extracts were washed with water, dried over Na₂SO₄, and evaporated to afford **12** (0.218 g, 84%) as a yellow oil. ¹H NMR (300 MHz, DMSO-d₆) δ 10.42 (s, 1H, formyl-H), 8.30 (d, $J = 8.0$ Hz, 1H, 4-H), 7.74 (d, $J = 8.0$ Hz, 1H, 7-H), 7.47–7.40 (m, 1H, 6-H), 7.36–7.30 (m, 1H, 5-H), 4.51–4.42 (m, 4H, NCH₂CH₂CH₃, OCH₂CH₃), 1.76 (sextet, $J = 7.4$ Hz, 2H, NCH₂CH₂CH₃), 1.38 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃), 0.86 (t, $J = 7.4$ Hz, 3H, NCH₂CH₂CH₃). ¹³C NMR (50 MHz, DMSO-d₆) δ 187.4, 160.2, 137.1, 134.0, 125.8, 123.7, 123.7, 122.3, 118.5, 111.7, 62.1, 46.3, 23.2, 13.8, 10.8; MS m/z : 259 (M⁺, 18%), 230 (100), 188 (23), 172 (26), 170 (67), 143 (13), 116 (31), 115 (31), 114 (27), 89 (28), 77 (13), 63 (12); HRMS Calcd. C₁₅H₁₇NO₃: 259.1208. Found: 259.1214.

5-Propyl-3,5-dihydro-4H-pyridazino[4,5-*b*]indol-4-one (10).

Method A. A solution of the chloro compound **9** (0.245 g, 1 mmol) in AcOH (16 mL) was refluxed for 8 h, then it was evaporated under reduced pressure. The residue was triturated with water, filtered off and dried to give **10** (0.068 g, 30%) as pale yellow crystals.

Method B. A solution of compound **12** (0.227 g, 1 mmol) and 100% hydrazine monohydrate (3 mL, 60 mmol) in EtOH (3 mL) was refluxed for 3 h. The volatile components were removed under reduced pressure and the residue was taken up in water (20 mL), acidified (pH 2-3) and kept in the refrigerator for 0.5 h. Then the precipitate was collected by filtration, washed with water and dried to give **10** (0.175 g, 77%) as almost colorless crystals, mp 207°C. Anal. Calcd. C₁₃H₁₃N₃O: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.48; H, 5.83; N, 18.49. IR (KBr, cm⁻¹) 3166, 2960, 1649, 1520, 1462, 1343, 959, 736; ¹H NMR (300 MHz, DMSO-d₆) δ 12.9–12.5 (br s, 1H, NH), 8.74 (s, 1H, 1-H), 8.18 (d, $J = 8.2$ Hz, 1H, 9-H), 7.78 (d, $J = 8.2$ Hz, 1H, 6-H), 7.58–7.52 (m, 1H, 7-H), 7.37–7.31 (m, 1H, 8-H), 4.74 (t, $J = 7.2$ Hz, 2H, NCH₂CH₂CH₃), 1.80 (sextet, $J = 7.5$ Hz, 2H, NCH₂CH₂CH₃), 0.80 (t, $J = 7.2$ Hz, 3H, NCH₂CH₂CH₃); ¹³C NMR (75 MHz, DMSO-d₆) δ 155.9, 139.2, 133.1, 130.0, 127.0, 121.5, 121.4, 120.0, 117.3, 111.4, 45.5, 23.5, 10.7; MS m/z : 227 (M⁺, 32%), 198 (43), 185 (100), 129 (29), 128 (21), 115 (25), 101 (34), 75 (25).

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