

1,5-Dimethyl-6H-pyridazino[4,5-*b*]carbazole, a 3-Aza Bioisoster of the Antitumor Alkaloid *Olivacine*

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A series of *b*-fused carbazoles structurally related to pyrido[4,3-*b*]carbazole-type alkaloids was prepared, utilizing the Diels–Alder reaction of 1-methylpyrano[3,4-*b*]indol-3(9*H*)-one with electron-deficient acetylenic dienophiles as the key step. The title compound (14) thus obtained in only four steps represents a new 3-aza analog of the antitumor natural product, *olivacine*.

Key words 3-aza-olivacine; pyridazino[4,5-*b*]carbazole; antitumor agent

Olivacine (1,5-dimethyl-6H-pyrido[4,3-*b*]carbazole) is a member of the pyridocarbazole family of alkaloids. It was first isolated from the bark and stem of *Aspidosperma olivaceum*²⁾ and it has been found to possess similar antitumor activity as its 5,11-dimethyl isomer, *ellipticine*, and related compounds like 9-methoxyellipticine.^{3,4)} As the main mechanism of these agents' antineoplastic action, a stabilization of the "cleavable complex" which is formed between DNA and the enzyme, *topoisomerase II*,⁵⁾ is generally accepted, although additional mechanisms have been discussed for some pyridocarbazoles, e.g. reactivation of the lost functionality of the p53 protein.⁶⁾ Based on the naturally occurring lead compounds, numerous modifications of this system have been studied,⁷⁾ leading to the development of drugs like *elliptinium*,⁸⁾ *datelliptium*,⁹⁾ *retelliptine*,¹⁰⁾ or *pazelliptine*.¹¹⁾ More recently, the highly potent *olivacine* analog, S16020-2,^{12,13)} has attracted considerable attention due to its apparent ability to circumvent P-glycoprotein-mediated multidrug resistance.¹⁴⁾

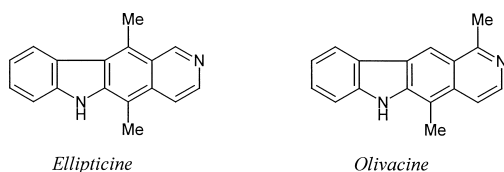


Chart 1

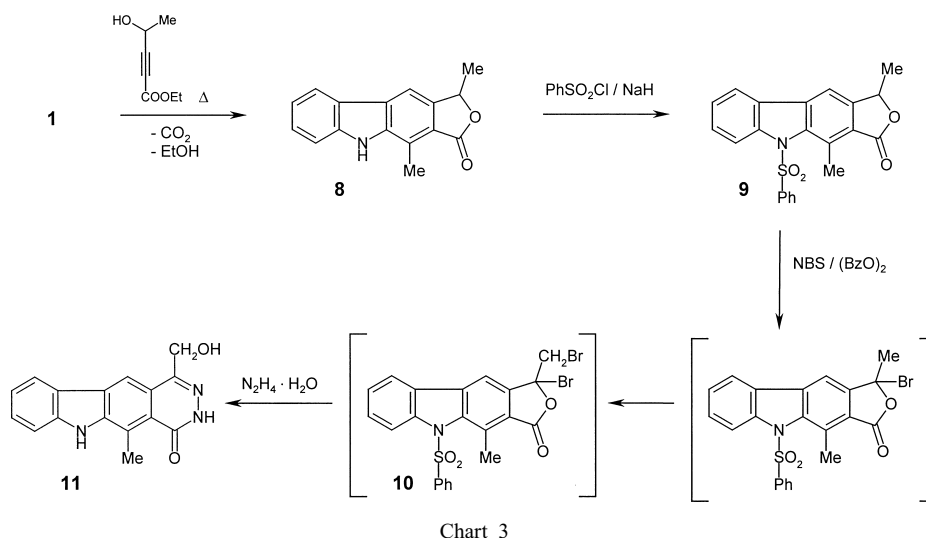
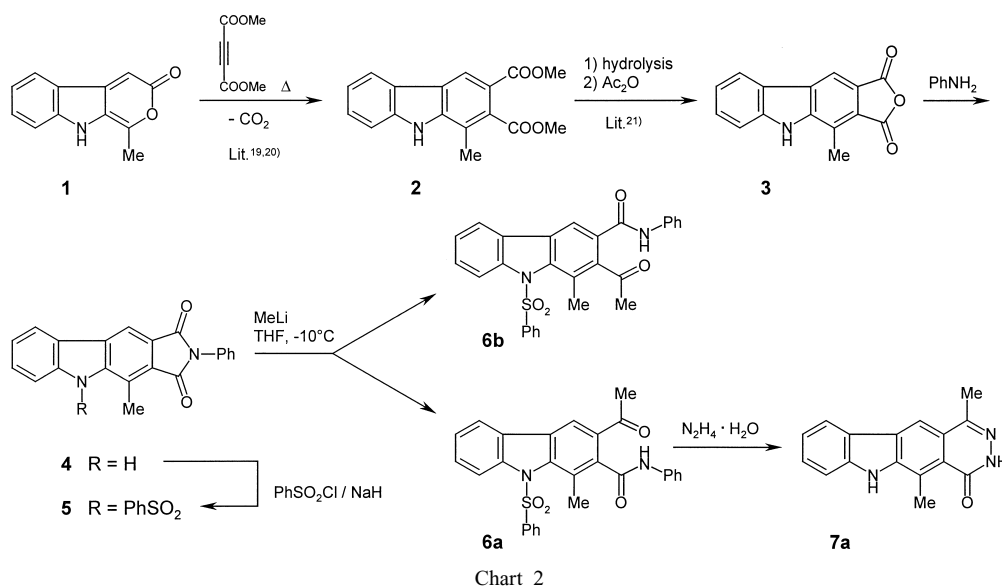
Among the structural variations which have been described so far, there are several examples for incorporation of an additional nitrogen atom into the tetracyclic skeleton, like in the case of 9-aza-*ellipticine*¹⁵⁾ or *pazelliptine*.^{11,16)} Based on previous investigations in the 3-aza-*ellipticine* series by Landelle *et al.*,¹⁷⁾ we recently reported the synthesis of several pyridazino[4,5-*b*]carbazoles, some of which exhibited significant antitumor activity.¹⁸⁾ In the course of our ongoing research in this field, we now became interested in the synthesis of the hitherto unknown title molecule, 1,5-dimethyl-6H-pyridazino[4,5-*b*]carbazole, as a 3-aza isoster of *olivacine*, which was required as a reference compound. Until now, only one method for the preparation of 1,5-dialkyl-6H-pyridazino[4,5-*b*]carbazoles has been described, which is based on a ring transformation of 5-acyl-11H-pyrido[4,3-*a*]carbazoles under Wolff-Kishner conditions.¹⁹⁾ However, this sequence inherently leads to 5-ethyl-substituted pyri-

dazino[4,5-*b*]carbazoles and thus cannot be adopted to the synthesis of our target structure. Here, we wish to report on a short synthesis of 3-aza-*olivacine* and on the results of an initial *in-vitro* testing for antitumor activity.

In a first approach to the 1,5-disubstituted pyridazino[4,5-*b*]carbazole skeleton, we investigated the selective addition of methylolithium to an appropriate 1-methylcarbazole-2,3-dicarboxylic acid derivative. After some unsuccessful attempts with the corresponding anhydride, we employed the protected *N*-phenylimide (**5**) as the electrophile. This compound can be easily prepared starting from commercially available 1-methylpyrano[3,4-*b*]indol-3(9*H*)-one²⁰⁾ (**1**) by Diels–Alder reaction with dimethyl acetylenedicarboxylate which gives the diester (**2**),^{20,21)} followed by ester hydrolysis and subsequent formation of the cyclic anhydride (**3**).²²⁾ Heating of the latter with excess aniline, followed by protection of the carbazole nitrogen with a benzenesulfonyl group gives **5** in good overall yield. For steric reasons, attack of a carbanionic reagent could be expected to take place preferentially at the less hindered CO group of the cyclic imide structure. Indeed, this was found to be the case: treatment of **5** with methylolithium in tetrahydrofuran at -10°C afforded the two acetylcarbazolecarboxamides **6a** and **6b** in a ratio of 1.6 : 1 in favor of the desired isomer **6a**; structural assignment is based on nuclear Overhauser enhancement (NOE) difference spectroscopy. Whereas the moderate regioselectivity of this transformation is compensated to some extent by the high combined yield (90%), the separation of the two isomers turned out to be very difficult, requiring multiple runs of medium-pressure liquid chromatography. Refluxing of the main product (**6a**) in hydrazine hydrate for 24 h smoothly effected the desired pyridazinone ring closure as well as deprotection of the carbazole nitrogen to afford the key intermediate (**7a**) in high yield. However, in view of the cumbersome **6a/6b** separation, we decided to investigate alternative routes to this fused pyridazinone in such a manner that all of the required carbon atoms should be introduced already at the stage of the initial Diels–Alder reaction with the pyrone (**1**).

Based on findings previously reported by Moody²³⁾ who had used similar reagents, we succeeded in transforming the diene **1** regiospecifically into the lactone **8** in high yield (92%), using ethyl 4-hydroxy-2-pentynoate as the dienophile in refluxing bromobenzene solution. In order to introduce the required ketone functionality, an attempt was made to selectively brominate the C1 atom of the fused system in analogy

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to syntheses of other benzo-fused bromo lactones,^{24,25} by treatment of **8** with *N*-bromosuccinimide (NBS) and dibenzoyl peroxide in refluxing chloroform. However, we were not able to obtain the desired bromo lactone: employment of one equivalent of NBS resulted in the formation of a 1 : 1 mixture of unreacted starting material and a compound which must be a dibrominated derivative. The yield of this dibromo compound for which structure **10** is proposed (*cf.* Chart 3) could be raised to about 80% by increasing the NBS amount to 2.2 eq. Although the unstable dibromo lactone could not be isolated and purified, it could be easily transformed into a stable crystalline product by prolonged refluxing in hydrazine hydrate. Under these conditions, the protecting group is split off and the pyridazinone ring is formed. Interestingly, the latter was found to bear a hydroxymethyl substituent at position 1.

Although reductive transformation of the CH₂OH group in **11** into the required methyl substituent could be envisaged, a more direct route to the target structure was sought by a modified pathway which should avoid the need to oxidize any carbon atom. This could be accomplished by employ-

ment of ethyl 4-oxo-2-pentynoate as the dienophile in the Diels–Alder reaction with **1**, however at the expense of an almost complete loss of regioselectivity, which is not surprising in view of previous observations with similar reagents.²³ The ratio of the isomeric keto esters (**12a, b**) thus formed was determined by ¹H-NMR as 1.2 : 1 in favor of the desired isomer (**12a**). Whereas the combined yield is very high and the cycloaddition proceeds smoothly within only 2 h of refluxing in bromobenzene solution, the main problem turned out to be the complete failure to separate the isomers by any means. Moreover, hydrazinolysis of the ester mixture by refluxing in ethanolic hydrazine hydrate for 18 h expectedly gave the fused pyridazinones **7a** and **7b** in excellent combined yield, but again all attempts failed to separate **7a** from its isomer at this stage. However, careful reaction monitoring of this cyclocondensation step by ¹H-NMR revealed that the desired pyridazinone (**7a**) is formed from its precursor (**12a**) much faster than the isomer (**7b**) from the corresponding keto ester (**12b**). Taking advantage of this kinetic aspect and of the low solubility of the tetracyclic product in the reaction medium, a convenient method for the preparation of pure **7a**

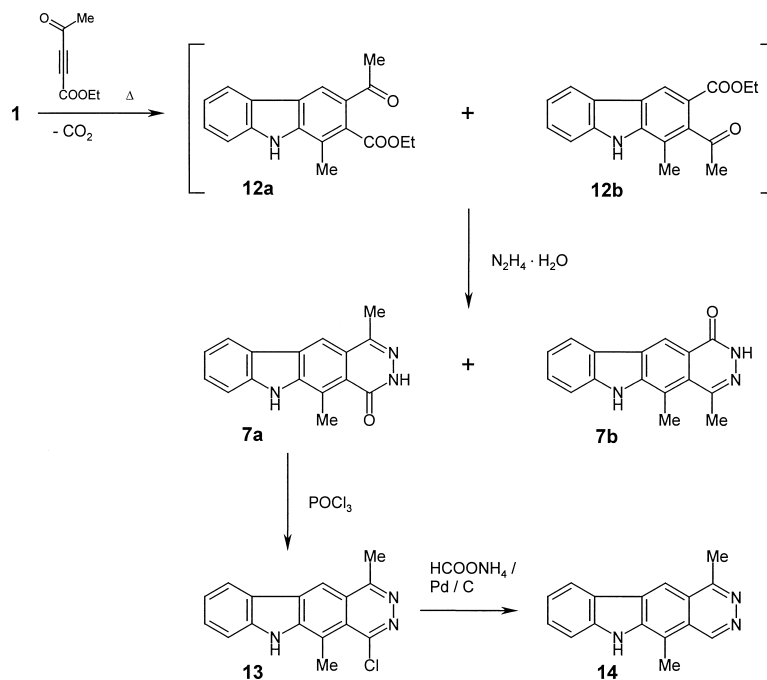


Chart 4

Table 1. Cytotoxic Activity of 3-aza-olivacine (**14**) and 5-Methyl-6H-pyridazino[4,5-*b*]carbazole¹⁸ (**15**) (% Inhibition of Cell Growth) at a Fixed Concentration of 3.16 $\mu\text{g/ml}$

Compound	Cell line ^{a)}			
	KB	L-1210	SK-OV-3	MCF-7
14 (R=Me)	71.2	88.2	69.5	41.9
15 (R=H)	51.0	73.0	43.3	n.d. ^{b)}

a) Cell lines: KB, cervical carcinoma; L-1210, lymphatic leukemia; SK-OV-3, ovarian carcinoma; MCF-7, mamma carcinoma. b) Not detectable.

was developed, simply by interrupting the hydrazinolysis process after only 10 min of refluxing, followed by isolation of the precipitate thus formed (see Experimental). The one-pot sequence **1**→**12a, b**→**7a** thus affords the key intermediate in 30% yield based on the commercially available starting material. After isolation of **7a**, refluxing of the remaining reaction mixture was continued for 18 h to give another precipitate which was found to be a mixture of **7a** and **7b** in a ratio of 0.6 : 1 from which a pure sample of the latter pyridazinone could be isolated by fractional crystallization.

The last two steps to the target compound are straightforward: first, the pyridazinone (**7a**) was converted into the chloro compound (**13**) in very good yield by refluxing in phosphorus oxychloride, and finally the chloro substituent was reductively removed by catalytic transfer hydrogenation, using ammonium formate as the hydrogen source. Work-up by continuous extraction with ethyl acetate of an aqueous suspension of the crude product gave analytically pure **14** in satisfactory yield.

Preliminary evaluation of the cytotoxic activity of 3-aza-olivacine (**14**) towards four human tumor cell lines, using the XTT²⁶ assay (Table 1), showed significant effects only at a relatively high concentration of 3.16 $\mu\text{g/ml}$ (approx. 10^{-5} M), whereas at lower concentrations (10^{-6} to 10^{-9} M) no dose-dependent activity was observed. For all cell lines, growth inhibitory activity of **14** was found to exceed that of the 5-monomethyl congener (**15**), the synthesis of which we had reported recently.¹⁸

In conclusion, a series of *b*-fused carbazoles could be made available, utilizing the Diels–Alder reaction of 1-methylpyrano[3,4-*b*]indol-3(9H)-one (**1**) with electron-deficient acetylenic dienophiles as the key step. Employment of a 4-oxo-2-pentynoic acid ester in this cycloaddition reaction thus permits the synthesis of the title compound (**14**) as a new 3-aza bioisoster of the natural product, *olivacine*, in only four steps from commercially available material. Further structural modifications of this compound type will be carried out, aiming at an enhancement of antineoplastic activity.

Experimental

Melting points (uncorrected) were determined on a Kofler hot-stage microscope (Reichert). ¹H-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer (300 MHz). IR spectra were recorded on a Perkin–Elmer 1605 FTIR or on a Perkin–Elmer Spectrum 1000 FTIR instrument. Mass spectra were recorded on a Shimadzu QP5050A spectrometer, high-resolution mass spectra were obtained on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna, and on a Micromass Autospec instrument at the Department of Organic Chemistry, University of Santiago de Compostela. Elemental analyses were carried out at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna. Column chromatography was performed on Merck Kieselgel 60 (0.063–0.200 mm). Medium-pressure liquid chromatography (MPLC) was done on Merck Lobar columns filled with LiChroprep Si 60 (0.040–0.063 mm), with UV detection at 280 nm. For TLC, Merck aluminium sheets pre-coated with Kieselgel 60 F₂₅₄ were used.

Compounds **1**,²⁰ **2**,^{20,21} and **3**²² were prepared by known procedures. Solvent names are abbreviated as follows: tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO).

3,5-Dihydro-4-methyl-2-phenylpyrrolo[3,4-*b*]carbazole-1(2H),3-

dione²⁷⁾ (**4**) A mixture of 1-methylcarbazole-2,3-dicarboxylic acid anhydride (**3**) (1.0 g, 3.98 mmol) and aniline (20 ml) was refluxed for 2 h. After cooling, it was poured into ice-water (50 ml). The pH was adjusted to 1–2 by addition of concd hydrochloric acid and the product was collected by filtration, washed with water, and dried. Recrystallization from methanol afforded the imide **4** (1.17 g, 90%) as colorless crystals, mp 312–313 °C (lit.²⁷⁾ mp 297–298 °C).

5-Benzenesulfonyl-3,5-dihydro-4-methyl-2-phenylpyrrolo[3,4-*b*]carbazole-1(2*H*),3-dione (**5**) To a stirred, ice-cooled solution of the imide **4** (2.0 g, 6.13 mmol) in a 1 : 1 mixture of toluene and DMF (50 ml) was added sodium hydride (80% suspension; 0.28 g, 9.3 mmol) in small portions. After 10 min, benzenesulfonyl chloride (1.42 g, 8.04 mmol) was added, and the mixture was stirred at room temperature for 4 h. Excess sodium hydride was then decomposed with 7% sulfuric acid, and the product was extracted with toluene. The extract was washed with water, dried, and evaporated. Recrystallization of the residue from acetonitrile gave compound **5** (2.63 g, 92%) as colorless crystals, mp 257–259 °C. ¹H-NMR (DMSO-*d*₆) δ: 3.04 (3H, s, 4-CH₃), 7.20–7.31 (4H, m, phenyl-H), 7.40–7.63 (8H, m, 7-H, 8-H, phenyl-H), 8.11 (1H, d, *J*=8.1 Hz, 6-H), 8.16 (1H, d, *J*=7.2 Hz, 9-H; shows positive NOE on irradiation at 8.53 ppm), 8.53 (1H, s, 10-H). IR (KBr) cm⁻¹: 1762, 1712, 1502, 1446, 1374, 1362, 1224, 1168, 1104, 750, 692, 588. MS *m/z* (rel. int.): 466 (M⁺, 10%), 402 (4), 326 (29), 325 (82), 297 (12), 242 (20), 178 (19), 123 (38), 95 (20), 77 (100), 51 (34). *Anal.* Calcd for C₂₇H₁₈N₂O₄S·0.15H₂O: C, 69.11; H, 3.93; N, 5.97. Found: C, 69.04; H, 4.15; N, 6.27.

Reaction of the Imide 5 with Methylolithium A 1.4 M solution of methylolithium in diethyl ether (1.1 ml, 1.54 mmol) was added dropwise at –10 °C to a stirred suspension of the imide **5** (620 mg, 1.33 mmol) in dry THF (40 ml) under an atmosphere of nitrogen. The mixture was stirred at –10 °C for 30 min and then at room temperature for 1 h. The volatile components were removed under reduced pressure and the solid residue was purified by short-column chromatography (eluent: ethyl acetate/light petroleum, 1 : 1). The mixture of the two isomeric products **6a** and **6b** was separated by repeated MPLC with recycling of mixed fractions (eluent: ethyl acetate/light petroleum, 1 : 1).

Evaporation of the first fraction afforded *N*-phenyl-3-acetyl-1-methyl-9-benzenesulfonyl-9*H*-carbazole-2-carboxamide (**6a**) as colorless crystals (360 mg, 55%), mp 130–131 °C (ethyl acetate/light petroleum). ¹H-NMR (DMSO-*d*₆) δ: 1.57 (3H, s, COCH₃), 3.03 (3H, s, 1-CH₃), 6.72 (1H, s, NH), 7.11–7.15 (2H, m, phenyl-H), 7.22–7.28 (2H, m, phenyl-H), 7.36–7.58 (8H, m, 6-H, 7-H, phenyl-H), 8.00 (1H, d, *J*=7.8 Hz, 5-H), 8.07 (1H, d, *J*=8.1 Hz, 8-H), 8.16 (1H, s, 4-H). IR (KBr) cm⁻¹: 1700, 1676, 1496, 1368, 1186, 1172, 770, 756, 576. MS *m/z* (rel. int.): 482 (M⁺, 1%), 464 (9), 400 (6), 341 (7), 326 (10), 324 (24), 323 (100), 308 (30), 293 (11), 191 (7), 77 (34), 51 (15). HR-MS *m/z*: 482.1301 (Calcd for C₂₈H₂₂N₂O₄S: 482.1300). *Anal.* Calcd for C₂₈H₂₂N₂O₄S·0.5H₂O: C, 68.42; H, 4.72; N, 5.70. Found: C, 68.34; H, 4.93; N, 5.41.

Evaporation of the second fraction gave *N*-phenyl-2-acetyl-1-methyl-9-benzenesulfonyl-9*H*-carbazole-3-carboxamide (**6b**) as colorless crystals (225 mg, 35%), mp 186–188 °C (ethyl acetate/light petroleum). ¹H-NMR (DMSO-*d*₆) δ: 1.71 (3H, s, COCH₃), 2.95 (3H, s, 1-CH₃), 6.90 (1H, s, NH), 7.09–7.13 (2H, m, phenyl-H), 7.22–7.28 (2H, m, phenyl-H), 7.34–7.59 (8H, m, 6-H, 7-H, phenyl-H), 8.04 (1H, d, *J*=7.8 Hz, 5-H; shows positive NOE on irradiation at 8.23 ppm), 8.07 (1H, d, *J*=8.9 Hz, 8-H), 8.23 (1H, s, 4-H). IR (KBr) cm⁻¹: 1684, 1676, 1496, 1448, 1370, 1178, 722, 688, 576. MS *m/z* (rel. int.): 482 (M⁺, 6%), 467 (8), 464 (10), 400 (16), 399 (13), 326 (20), 324 (26), 323 (100), 308 (29), 293 (35), 249 (16), 147 (14), 77 (64), 51 (25). HR-MS *m/z*: 482.1310 (Calcd for C₂₈H₂₂N₂O₄S: 482.1300). *Anal.* Calcd for C₂₈H₂₂N₂O₄S: C, 69.69; H, 4.60; N, 5.81. Found: C, 69.35; H, 4.71; N, 5.59.

3,6-Dihydro-1,5-dimethyl-4*H*-pyridazino[4,5-*b*]carbazol-4-one (**7a**) A mixture of compound **6a** (241 mg, 0.5 mmol) and hydrazine hydrate (5 ml) was refluxed for 24 h. The excess reagent was removed under reduced pressure and the residue was triturated with 1 M hydrochloric acid (10 ml). The solid was collected by filtration, washed with water, and dried. Recrystallization from ethanol afforded the product (116 mg, 88%) as colorless crystals, mp 312–314 °C (decomp). ¹H-NMR (DMSO-*d*₆) δ: 2.62 (3H, s, 1-CH₃), 3.16 (3H, s, 5-CH₃), 7.25–7.31 (1H, m, 9-H), 7.52–7.58 (1H, m, 8-H), 7.61 (1H, d, *J*=8.1 Hz, 7-H), 8.38 (1H, d, *J*=7.8 Hz, 10-H), 8.58 (1H, s, 11-H; shows positive NOE on irradiation at 2.62 ppm), 11.71 (1H, s, carbazole-NH; shows positive NOE on irradiation at 3.16 ppm), 11.88 (1H, s, pyridazine-NH). IR (KBr) cm⁻¹: 3415, 3239, 3052, 1642, 1498, 1387, 1364, 1267, 1247, 789, 745, 726. MS *m/z* (rel. int.): 264 (15%), 263 (M⁺ 100), 218 (5), 204 (4), 163 (4), 132 (3), 91 (12), 84 (7), 72 (7), 71 (13), 55 (11). *Anal.*

Calcd for C₁₆H₁₃N₃O: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.65; H, 4.90; N, 15.95.

1,4-Dimethyl-1,5-dihydro-3*H*-furo[3,4-*b*]carbazol-3-one (**8**) A solution of 1-methylpyrano[3,4-*b*]indol-3(9*H*)-one (**1**) (1.0 g, 5 mmol) and ethyl 4-hydroxy-2-pentynoate²⁸⁾ (1.42 g, 10 mmol) in bromobenzene (50 ml) was refluxed under argon for 72 h. After cooling, the mixture was diluted with ethyl acetate (50 ml) and filtered through a short column of silica (complete elution with ethyl acetate). The residue obtained on evaporation of the volatile components was recrystallized from toluene to give the lactone **8** (1.16 g, 92%) as almost colorless crystals, mp 233–234 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.61 (3H, d, *J*=6.6 Hz, 1-CH₃), 2.86 (3H, s, 4-CH₃), 5.68 (1H, q, *J*=6.6 Hz, 1-H), 7.19–7.25 (1H, m, 8-H), 7.46–7.52 (1H, m, 7-H), 7.54–7.59 (1H, m, 6-H), 8.16 (1H, s, 10-H; shows positive NOE on irradiation at 1.61 ppm), 8.21 (1H, d, *J*=7.8 Hz, 9-H), 11.59 (1H, s, NH). IR (KBr) cm⁻¹: 3289, 3058, 2973, 2926, 1729, 1628, 1511, 1349, 1325, 1306, 1249, 1033, 747. MS *m/z* (rel. int.): 252 (12%), 251 (M⁺, 69), 237 (13), 236 (80), 209 (15), 208 (100), 180 (42), 152 (15), 118 (11), 90 (15), 77 (18), 76 (22). *Anal.* Calcd for C₁₆H₁₃NO₂: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.09; H, 5.14; N, 5.48.

5-Benzenesulfonyl-1,4-dimethyl-1,5-dihydro-3*H*-furo[3,4-*b*]carbazol-3-one (**9**) To a stirred, ice-cooled solution of the lactone **8** (200 mg, 0.8 mmol) in a 1 : 1 mixture of toluene and DMF (10 ml) was added sodium hydride (80% suspension; 45 mg, 1.5 mmol) in small portions. After 10 min, benzenesulfonyl chloride (176 mg, 1 mmol) was added and the mixture was stirred at room temperature for 4 h. Excess sodium hydride was then decomposed with 7% sulfuric acid, and the product was extracted with toluene. The extract was washed with water, dried, and evaporated. Recrystallization of the residue from acetonitrile gave compound **9** (260 mg, 83%) as colorless crystals, mp 235–239 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.59 (3H, d, *J*=6.9 Hz, 1-CH₃), 2.97 (3H, s, 4-CH₃), 5.68 (1H, q, *J*=6.9 Hz, 1-H), 7.07–7.12 (2H, m, phenyl 2-H, 6-H; shows positive NOE on irradiation at 2.97 ppm), 7.18–7.24 (2H, m, phenyl 3-H, 5-H), 7.39–7.48 (2H, 8-H, phenyl 4-H), 7.55–7.61 (1H, m, 7-H), 7.93 (1H, d, *J*=7.5 Hz, 9-H), 8.04 (1H, s, 10-H), 8.08 (1H, d, *J*=8.4 Hz, 6-H; shows positive NOE on irradiation at 7.07–7.12 ppm). IR (KBr) cm⁻¹: 3079, 2975, 2930, 1753, 1448, 1363, 1339, 1183, 1029, 772, 762, 690, 576, 559. MS *m/z* (rel. int.): 391 (13%), 327 (9), 251 (18), 250 (100), 208 (79), 207 (20), 180 (31), 179 (24), 178 (16), 152 (11), 77 (29), 51 (14). *Anal.* Calcd for C₂₂H₁₇NO₄S: C, 67.50; H, 4.38; N, 3.58. Found: C, 67.70; H, 4.47; N, 3.50.

3,6-Dihydro-1,5-dihydroxymethyl-5-methyl-4*H*-pyridazino[4,5-*b*]carbazol-4-one (**11**) A solution of the lactone **9** (196 mg, 0.5 mmol) and *N*-bromosuccinimide (196 mg, 1.1 mmol) in dry chloroform (10 ml) was heated to reflux. Dibenzoyl peroxide (70%; 10 mg, 0.03 mmol) was added, and refluxing was continued for 3 h. The solvent was evaporated under reduced pressure, the residue of crude dibromo compound **10** was taken up in hydrazine hydrate (5 ml) and the mixture was refluxed for 18 h. It was then diluted with water (20 ml) and the precipitate was collected by filtration, washed with water, and dried. The material was washed several times with boiling methanol to afford the pure product (130 mg, 93%) as pale yellow crystals, mp >320 °C (decomp). ¹H-NMR (DMSO-*d*₆) δ: 3.16 (3H, s, 5-CH₃), 4.80 (2H, d, *J*=5.7 Hz, CH₂OH), 5.43 (1H, t, *J*=5.7 Hz, CH₂OH), 7.25–7.31 (1H, m, 9-H), 7.52–7.58 (1H, m, 8-H), 7.62 (1H, d, *J*=8.1 Hz, 7-H), 8.29 (1H, d, *J*=7.8 Hz, 10-H), 8.73 (1H, s, 11-H; shows positive NOE on irradiation at 4.80 ppm), 11.72 (1H, s, carbazole NH; shows positive NOE on irradiation at 3.16 ppm), 12.00 (1H, s, pyridazine NH). IR (KBr) cm⁻¹: 3415, 3335, 3251, 3062, 2926, 1627, 1495, 1453, 1417, 1376, 1337, 1239, 1026, 822, 768, 754. MS *m/z* (rel. int.): 280 (18%), 279 (M⁺, 100), 278 (21), 263 (15), 250 (40), 233 (24), 205 (20), 192 (11), 164 (8), 140 (12), 102 (19), 98 (18), 88 (12), 81 (28). *Anal.* Calcd for C₁₆H₁₃N₃O₂: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.53; H, 4.77; N, 15.21.

One-Pot Synthesis of the Pyridazinones 7a and 7b from the Pyranoidole 1 A solution of 1-methylpyrano[3,4-*b*]indol-3(9*H*)-one (**1**) (398 mg, 2 mmol) and ethyl 4-oxo-2-pentynoate²⁹⁾ (560 mg, 4 mmol) in bromobenzene (30 ml) was refluxed under argon for 2 h. The volatile components were removed under reduced pressure and the oily residue consisting of the two isomeric esters **12a** and **12b** was dissolved in ethanol (8 ml). After addition of hydrazine hydrate (300 mg, 6 mmol), the solution was refluxed for 10 min, then it was immediately chilled. The precipitate was collected by filtration, washed with ethanol, and dried to afford pure **7a** (160 mg, 30%). The filtrate was refluxed for another 18 h. The precipitate thus obtained was filtered off, washed with ethanol, and dried to afford a mixture of **7a** and **7b** (225 mg, 43%) in a ratio of 0.6 : 1. Fractional crystallization from ethanol gave pure 2,6-dihydro-4,5-dimethyl-1*H*-pyridazino[4,5-*b*]carbazol-1-one (**7b**) as colorless crystals, mp >350 °C (decomp). ¹H-NMR (DMSO-*d*₆) δ: 2.79 (3H, s,

4-CH₃; shows positive NOE on irradiation at 2.99 ppm), 2.99 (3H, s, 5-CH₃), 7.23–7.29 (1H, m, 9-H), 7.50–7.56 (1H, m, 8-H), 7.60 (1H, d, *J*=8.1 Hz, 7-H), 8.34 (1H, d, *J*=7.8 Hz, 10-H), 8.99 (1H, s, 11-H), 11.69 (1H, s, carbazole NH); shows positive NOE on irradiation at 2.99 ppm), 12.13 (1H, s, pyridazine NH). IR (KBr) cm⁻¹: 3284, 3064, 2987, 1642, 1625, 1603, 1551, 1455, 1386, 1353, 1293, 1234, 1176, 795, 742, 731, 557. MS *m/z* (rel. int.): 264 (18%), 263 (100), 234 (19), 219 (11), 218 (26), 206 (20), 205 (12), 204 (22), 191 (15), 102 (11), 88 (8). HR-MS *m/z*: 263.1071 (Calcd for C₁₆H₁₃N₃O: 263.1059). *Anal.* Calcd for C₁₆H₁₃N₃O·0.1H₂O: C, 72.49; H, 5.02; N, 15.85. Found: C, 72.46; H, 4.81; N, 15.88.

4-Chloro-1,5-dimethyl-6H-pyridazino[4,5-*b*]carbazole (13) A mixture of the pyridazinone **7a** (263 mg, 1 mmol) and POCl₃ (25 ml) was refluxed for 3 h. The excess reagent was distilled off under reduced pressure and the residue was treated with crushed ice (20 g). The mixture was basified by addition of concd ammonia and the precipitate was collected by filtration, washed with water, and dried to afford the product (260 mg, 92%) as a yellow solid, mp >300 °C (decomp). ¹H-NMR (DMSO-*d*₆) δ: 3.01 (3H, s, 1-CH₃), 3.20 (3H, s, 5-CH₃), 7.31–7.37 (1H, m, 9-H), 7.59–7.67 (2H, m, 7-H, 8-H), 8.49 (1H, d, *J*=8.1 Hz, 10-H), 9.02 (1H, s, 11-H; shows positive NOE on irradiation at 3.01 ppm). IR (KBr) cm⁻¹: 3236, 3063, 2922, 1627, 1609, 1496, 1467, 1400, 1360, 1310, 1260, 745, 591. MS *m/z* (rel. int.): 283 (M⁺, 4%), 281 (M⁺, 10), 264 (18), 263 (100), 246 (7), 234 (9), 218 (15), 204 (13), 191 (10), 132 (11), 121 (16), 109 (14), 102 (22), 95 (22), 91 (15), 83 (16), 57 (29), 55 (29). HR-MS *m/z*: 281.0712 (Calcd for C₁₆H₁₃ClN₃: 281.0720). *Anal.* Calcd for C₁₆H₁₂ClN₃·0.6H₂O: C, 65.69; H, 4.55; N, 14.36. Found: C, 65.56; H, 4.29; N, 14.50.

1,5-Dimethyl-6H-pyridazino[4,5-*b*]carbazole (14) A mixture of the chloro compound **13** (281 mg, 1 mmol), ammonium formate (630 mg, 10 mmol), and 10% Pd/C catalyst (60 mg) in methanol (60 ml) was refluxed under argon for 1 h. After addition of another portion of ammonium formate (315 mg, 5 mmol), refluxing was continued for 2 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (200 ml) and the mixture was basified by addition of concd ammonia (2 ml). The suspension was continuously extracted with ethyl acetate (400 ml) for 24 h, using a rotary perforator. The extract was kept in the refrigerator for 16 h, then the separated solid was collected by filtration, washed with cold ethyl acetate, and dried to afford the pure product (150 mg, 61%) as pale yellow crystals, mp >340 °C (decomp). ¹H-NMR (DMSO-*d*₆) δ: 2.95 (3H, s, 5-CH₃; shows positive NOE on irradiation at 9.73 ppm), 3.03 (3H, s, 1-CH₃; shows positive NOE on irradiation at 8.92 ppm), 7.27–7.33 (1H, m, 9-H), 7.55–7.64 (2H, m, 7-H, 8-H), 8.45 (1H, d, *J*=7.8 Hz, 10-H), 8.92 (1H, s, 11-H), 9.73 (1H, s, 4-H), 11.75 (1H, s, NH). IR (KBr) cm⁻¹: 3059, 2924, 2874, 2765, 1611, 1498, 1467, 1416, 1401, 1379, 1315, 1253, 1228, 865, 745, 590, 554. MS *m/z* (rel. int.): 248 (20%), 247 (M⁺, 100), 246 (17), 219 (14), 205 (13), 189 (51), 178 (10), 151 (13), 134 (17), 124 (11), 109 (20), 102 (24), 96 (21), 94 (23), 88 (14), 82 (16), 70 (20). *Anal.* Calcd for C₁₆H₁₃N₃: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.57; H, 5.43; N, 17.02.

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