8. Locoselective [4 + 2] Cycloadditions of Vinylindoles with Inverse Electron Demand: A New Access of Indolyl-Substituted and Annellated Pyridazines

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Dedicated to Prof. Dr. *C. H. Brieskorn* (Würzburg, FRG) on the occasion of his 75th birthday

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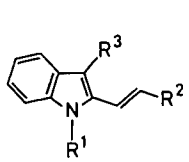
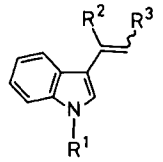
2-Vinylindole (**1a**) and its donor- and acceptor-substituted (*E*)-derivatives **1b–e** react highly locoselectively with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**3**) to form the novel (indol-2-yl)-1,4-dihydropyridazines **4a** and **7** as well as the heterocyclic annellated pyridazines **4b**, **5**, and **6**. The reactions of the structurally related 3-vinylindoles **2a–e** with **3** also gave rise to new indol-3-ylpyridazines **8**, **9**, and **10**. The locoselectivities of these *Diels-Alder* reactions were controlled mainly by steric effects.

Introduction. – 2- and 3-Vinylindoles **I** and **II** are heterocyclic dienes and, thus, represent synthetically attractive building blocks for the regio- and stereocontrolled [*b*]annellation of the indole skeleton [1–5]. In these cases, in particular, the *Diels-Alder* reaction with usual electron demand offers a valuable synthetic concept for the preparation of numerous pharmacologically interesting lead substances [5] and alkaloids [6] [7].



I

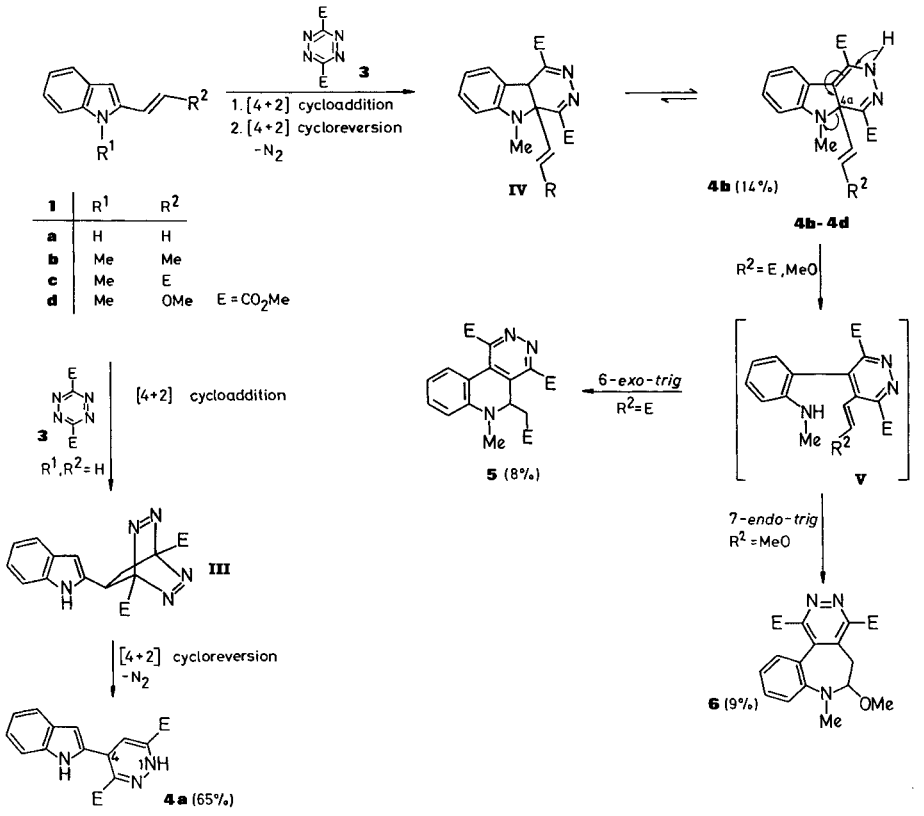


II

As a consequence of their 4π-donor reactivity, 2- and 3-vinylindoles **I** and **II** ($E_{HOMO} \approx -7$ to -8 eV) [8] should also participate in [4 + 2] cycloaddition reactions with inverse electron demand [9] with electron-poor dienes. In reactions of this type, the question concerning the locoselectivity (or periselectivity) at the aminobutadiene moiety of the vinylindole arises. In the light of the *Diels-Alder* reactions of indole [10] and *N*-substituted indoles [11] with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate and derivatives, high dienophilicities of **I** and **II** should also be expected as the consequence of the $LUMO_{diene} - HOMO_{dienophile}$ controlled reactions. In continuation of our preliminary reports [12] [13], we present here more details and include full experimental data together with further new results from the cycloadditions of vinylindoles **I** and **II** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**3**) as a highly reactive and s-*cis*-fixed 2,3-diazadiene enophile. The method reported here also lead to new annellated and/or functionalized pyridazines, compounds of pharmacological interest as antihypertensive or antithrombotic drugs [14] [15], respectively.

Results and Discussion. – The parent compound **1a** [4] reacts highly locoselectively (and periselectively) with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**3**), under very mild conditions, to furnish exclusively the 4-(indol-2-yl)-substituted dimethyl 1,4-dihydropyridazinedicarboxylate **4a** *(Scheme 1)*. The reaction probably proceeds *via* a [4 + 2] cycloaddition/[4 + 2] cycloreversion sequence by way of the bicyclic intermediate **III**

Scheme 1



which cannot be isolated (*cf.* [10–13]). The highly selective reaction at the 2-aminobutadiene moiety in **1a** is, according to models *(Büchi-Dreiding)*, the result of steric interactions, *i.e.* tetrazine **3** undergoes addition to the sterically less hindered 2-vinyl functional group more rapidly than to the C(2)=C(3) bond.

The locoselectivity of this reaction can be displaced from the 2-vinyl group to the indole enamine system by the specific introduction of substituents into **1a** at the vinyl function. Thus, the dimethylated 2-vinylindole **1b** reacts with the tetrazine **3** to yield exclusively the dihydropyridazinoindole **4b**. Within the limits of the 400-MHz ^{1}H-NMR detection, the tautomeric equilibrium lies completely upon the side of **4a** and **4b**[1]). This

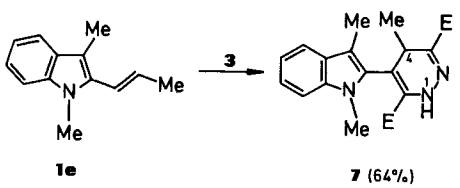
[1]) These and some of our further results demonstrate that the 4,5-dihydropyridazine tautomer (*e.g.* **IV**) is the less stable isomer in the series of cycloaddition products from vinylindoles with **3** (see also [9c]).

shift of the equilibrium position in favor of **4a** and **4b** is also in accord with the products of *Diels-Alder* reactions of styrenes with **3** [9c].

If a π-donor or π-acceptor substituent is introduced on to the vinyl group of **1**, further transformation of **4** occurs during the reaction with **3**. The primary cycloadducts **4c** and **4d**, obtained from the reactions of **1c** and **1d**, respectively, with **3**, are very unstable and decompose in the course of the further purification (EI-MS: **4c**: 385 (M^+), **4d**: 357 (M^+)). Thus, we additionally isolated the stable tricyclic compound **5** from the cycloaddition of **1c** with **3** and the new pyridazino[*d*]benzazepine **6** from that of **1d** with **3**. From a mechanistic point of view, **4c** and **4d** undergo initial oxidative heterolysis at the N–C(4a) bonds [12] to furnish the postulated intermediates **V**. Depending on the charge distribution at the vinyl moiety, intermediates **V** undergo cyclization *via* two different routes. When R = CO_2Me, a *Michael*-type addition to give the pyridazino[*c*]dihydroquinoline **5** occurs, whereas, when R = MeO, the new benzazepine derivative **6** is formed. The orientations of the two cyclizations are plausible in terms of the electrostatic model and are allowed processes according to *Baldwin*'s rules [16].

As a further example, we have also tested the reaction of the trimethylated 2-vinylindole **1e** with **3**, in order to determine the influence of a Me group at C(3) of the indole moiety on the results of the reaction *(Scheme 2)*.

Scheme 2



1e **7** (64%)

Similar to **1a**, the 2-vinylindole **1e** also reacted under mild conditions with high locoselectivity at the vinyl moiety to yield the 5-(indol-2-yl)dihydropyridazine **7** as a consequence of steric control by the additional, space-filling indolic 3-Me group in the transition state. According to ^{1}H- and ^{13}C-NMR, **7** exists in solution (CD_2Cl_2 or (D_6)DMSO) preferentially in the formulated constitution. The presence of two *ortho*-Me groups on the indole skeleton in comparison to **4a** favors a shift of the tautomeric equilibrium to **7**.

The ^{1}H- and ^{13}C-NMR spectra (400 and 100.6 MHz, respectively) of **7** at 20° reveal double sets of signals which, in (D_6)DMSO, begin to coalesce at 110°. In accordance with model *(Büchi-Dreiding)*, compound **7** (axial and central chirality) should exist as a diastereoisomeric mixture of atropisomeric forms ((PR)/(MS) and (PS)/(MR)). The ^{1}H{^{1}H}-NOE measurements of **7** demonstrate that the population of the two diastereoisomeric conformers **VI** and **VII** predominates within the range of the NMR time scale and the limits of ^{1}H-NMR detection *(Fig.)*.

MNDO calculations [18] performed for 2-vinylindole (**1a**) do indeed predict a $LUMO_{diene}$ – $HOMO_{dienophile}$-controlled reaction [19] of **1** with the tetrazine **3** tested (E_{HOMO} (**1a**) = –8.25 eV, E_{LUMO} (**3**) = –1.11 eV). However, the magnitudes of the HOMO coefficients at the 2-aminobutadiene moiety in **1a** do not allow an unambiguous prediction of the locoselectivity 'vinyl function *vs.* indole-enamine' (coefficients: C(2) = 0.405,

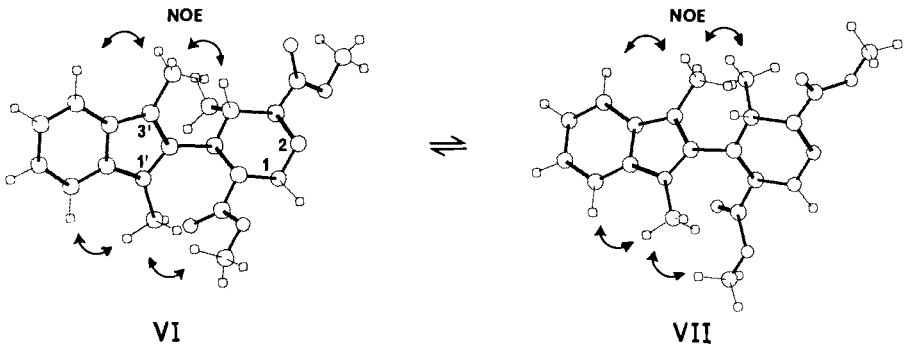


Figure. *Computer-simulated stereorepresentations of the atropisomeric forms* **VI** *and* **VII** *of* 7 *with the largest population*[2]) *as determined from* $^1H\{^1H\}$*-NOE experiments* (NOE's: 3′-Me of indole to H–C(4) of pyridazine (in **VI**); 3′-Me of indole to 4-Me of pyridazine (in **VII**); 1′-Me of indole to 6-COOMe of pyridazine (in **VI** and **VII**); the reverse NOE's were observed in all cases)

C(3) = 0.502, C(1′) = −0.157, C(2′) = −0.289). Hence, the preferred orientations of the tetrazine tested here towards the 2-aminobutadiene moiety of the 2-vinylindoles in the [4 + 2] transition state should be controlled less by electronic and more by steric effects.

In the 3-vinylindole series, we investigated the cycloadditions of the *N*-methylated compound **2a** and of some selected donor- and acceptor-substituted compounds **2b–e** with the tetrazine **3** *(Scheme 3)*. In these cases also, the question of the locoselectivity 'vinyl function *vs.* indole-enamine group' arises. The tested 3-vinylindoles **2** react with **3** under mild conditions exclusively at the 3-vinyl function.

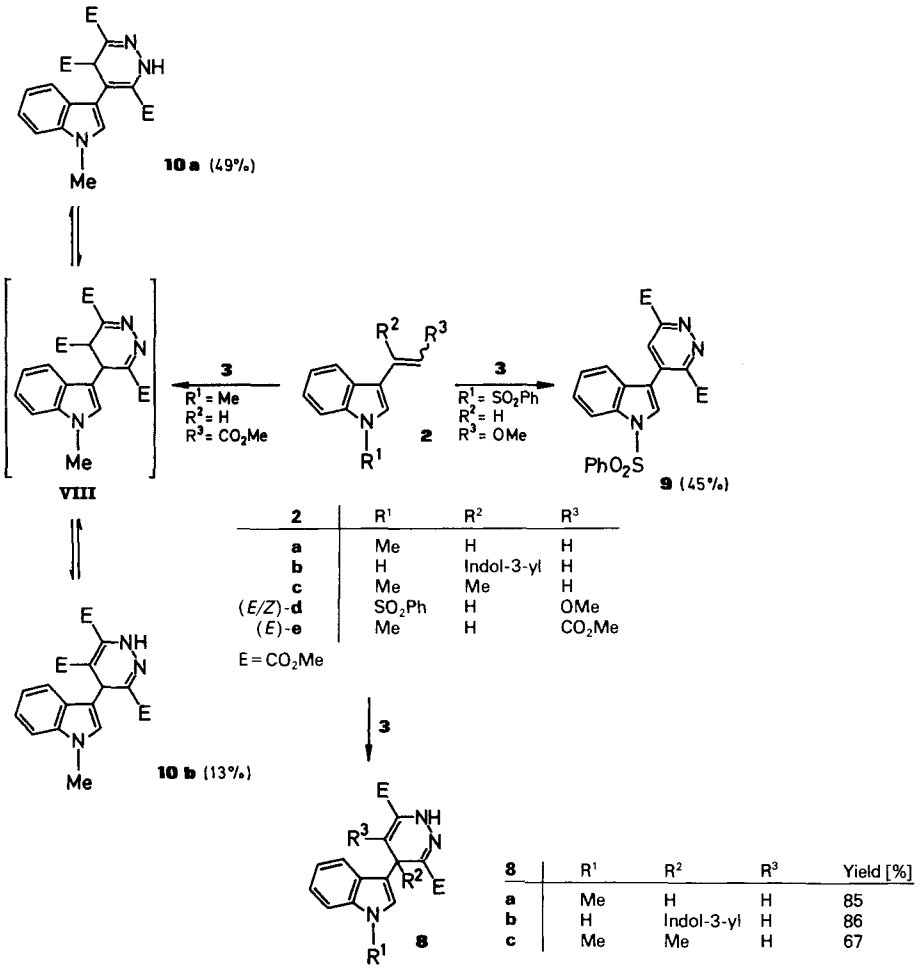
The reactions of **2a**, **2b**, and **2c** with **3** yield exclusively the novel 4-indolyl-substituted 1,4-dihydropyridazines **8a**, **8b**, and **8c**, respectively. Within the limits of the 400-MHz ^{1}H-NMR detection and in all three cases, only the tautomeric compounds **8** were detected.

The tetrazine **3** also undergoes cycloaddition to the vinyl function of (*E*/*Z*)-**2d** to furnish the 4-(indol-3-yl)-1,2-pyridazine **9** as the only stable reaction product. From a mechanistic point of view, the reaction sequence comprises [4 + 2] cycloaddition, [4 + 2] cycloreversion, and elimination of MeOH. The driving force for the formation of the 6π-heteroaromatic product is most probably the gain of energy of aromatization (see [9c]). The reaction of **2e** with **3** yields a mixture of the new indolyl-substituted 1,4-dihydro-1,2-pyridazines **10a** and **10b** which can be separated. This reaction probably also proceeds through [4 + 2] cycloaddition and [4 + 2] cycloreversion to form the intermediate **VIII** which subsequently undergoes stabilization by way of [1,3]-prototropic shifts to furnish the two tautomers **10a** and **10b**. The products **10a** and **10b** were separated by flash chromatography and are thermodynamically very stable; they do not undergo equilibration in solution within the limits of the 400-MHz ^{1}H-NMR detection.

In analogy to the reaction of **1** with **3**, MNDO calculations performed with the parent compound of the series **2** also predict a $LUMO_{diene} - HOMO_{dienophile}$-controlled cycloaddi-

[2]) The geometries used for the computer-aided graphical representation (*Atari mega ST* computer; *Chem Graph* programme) were deduced from *Büchi-Dreiding* models and X-ray crystallographic data of structurally related compounds [17]. The 1,4-dihydropyridazine ring has the boat conformation. The torsional angles around the central C(2′)–C(5) bond were taken as −40° and +40°.

Scheme 3



2	R^1	R^2	R^3
a	Me	H	H
b	H	Indol-3-yl	H
c	Me	Me	H
(*E*/*Z*)-**d**	SO_2Ph	H	OMe
(*E*)-**e**	Me	H	CO_2Me

8	R^1	R^2	R^3	Yield [%]
a	Me	H	H	85
b	H	Indol-3-yl	H	86
c	Me	Me	H	67

tion [9] ($E_{HOMO} = -8.16$ eV[3])). In the 3-vinylindole series, the locoselectivity found should be controlled mostly by the more electron-rich vinyl group[4]) in comparison to the enamine and proceed in the same direction as a result of steric effects.

The constitutions of the new pyridazines described here were elucidated basically by 200- or 400-MHz ^{1}H-NMR spectroscopy including NOE measurements and selective decoupling experiments. In some cases, 100.6-MHz ^{13}C-NMR spectroscopy including use of the *J*-modulated ^{13}C-spin-echo technique, the DEPT-pulse sequence method, and registration of the 'gated' spectra was also applied.

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[3]) This value correlates with the first vertical ionization potential obtained from He(I)α PE spectra [8].

[4]) MNDO calculation of the parent compound of **2**: HOMO coefficients: C(2) = 0.370; C(3) = 0.473; C(1′) = −0.227; C(2′) = −0.387; net atomic charges of the 2-aminobutadiene moiety. N(1) = −0.2403; C(2) = +0.0427; C(3) = −0.1250; C(1′) = −0.0245; C(2′) = −0.0933.

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Experimental Part

General. All reactions were performed in highly pure, anh. solvents under inert-gas atmospheres. Flash chromatography (FC): silica gel *60* (*Merck*, 0.040–0.063-mm particle size). M.p.: *Büchi SMP-20*; not corrected. ^{1}H- and ^{13}C-NMR spectra: *Bruker WM 400* and *Bruker AC 200* spectrometers, δ [ppm] scale, coupling constants J in Hz, TMS as internal standard. EI-MS (70 eV): *Varian MAT 7*, data given as *m/z* (%). FD-MS: *Varian MAT 312*. C,H,N Analyses: *Carlo Erba Strumentazione Analyser 1106*.

Dimethyl 1,4-Dihydro-4-(indol-2-yl)pyridazine-3,6-dicarboxylate (**4a**). *2-Vinylindole* (**1a**; 0.430 g, 3 mmol) was dissolved in CH_2Cl_2 (30 ml) and the 1,2,4,5-*tetrazine-3,6-dicarboxylate* (**3**; 0.595 g, 3 mmol) was added slowly in portions. The mixture was stirred at –75° for 1 h and then at 20° for 4 h. The org. solvent was evaporated under reduced pressure, and the residue was separated by FC using petroleum ether (40–60°)/AcOEt 1:1: 611 mg (65%) of **4a**. Colorless crystals. M.p. 152° (petroleum ether (40–60°)). ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.68 (*s*, $COOCH_3$); 3.76 (*s*, $COOCH_3$); 4.89 (*d*, ^3J = 5.9, H–C(4)); 6.00 (*s*, H–C(3′)); 6.05 (*dd*, ^3J = 5.9, ^4J = 2.2, H–C(5)); 6.92 (*t*, ^3J = 7.2, 7.6, H–C(6)); 7.12 (*t*, ^3J = 7.3, H–C(5′)); 7.35 (*d*, ^3J = 8.0, H–C(7′)); 7.40 (*d*, ^3J = 7.8, H–C(4′)); 10.78 (*d*, ^4J = 2.2, pyridazine NH); 10.92 (*s*, indole NH). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 30.82 (C(4)); 52.79 ($COOCH_3$); 52.81 ($COOCH_3$); 101.70 (C(5)); 106.76 (C(3′)); 110.94 (C(7′)); 119.88 (C(6′)); 120.41 (C(4′)); 122.12 (C(5′)); quaternary sp^2-C: 128.20 (C(3a′)); 129.23 (C(2′)); 130.81 (C(7a′)); 136.30 (C(6)); 137.44 (C(3)); 161.63 (CO); 165.58 (CO). MS: 313 (26, M^+), 149 (100). Anal. calc. for $C_{16}H_{15}N_3O_4$ (313.31): C 61.34, H 4.83, N 13.41; found: C 60.93, H 4.92, N 12.99.

*Dimethyl 2,4a-Dihydro-5-methyl-4a-(1-propenyl)-5*H*-pyridazino[4,5-b]indole-1,4-dicarboxylate* (**4b**). *1-Methyl-2-(1-propenyl)indole* (**1b**; 0.514 g, 3 mmol) was dissolved in CH_2Cl_2 (30 ml) and cooled to –75°. To this soln., **3** (0.594 g, 3 mmol) in CH_2Cl_2 (30 ml) was slowly added in several portions. The resultant mixture was stirred at –75° for 2 h and then at 10° for 3 h. The org. solvent was evaporated and the residue separated by FC using petroleum ether (40–60°)/AcOEt 1:1:143 mg (14%) of **4b**. Colorless crystals. M.p. 131° (Et_2O/petroleum ether). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.58 (*dd*, ^3J = 6.5, ^4J = 1.6, =CHCH_3); 3.13 (*s*, $COOCH_3$); 3.85 (*s*, CH_3N); 3.96 (*s*, $COOCH_3$); 4.74 (*dd*, ^3J = 15.4, ^4J = 1.6, C*H*=CHCH$_3$); 5.31 (*dq*, ^3J = 6.5, 15.4, CH=C*H*CH$_3$); 6.69 (*d*, ^3J = 8, H–C(6)); 6.80 (*ddd*, ^3J = 8, ^4J = 0.8, H–C(8)); 7.30 (*ddd*, ^3J = 8, ^4J = 1.2, H–C(7)); 8.34 (*d*, ^3J = 8, H–C(9)); 9.14 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 17.35 (=CH*C*H$_3$); 34.39 (CH_3N); 52.31 (CH_3O); 52.41 (CH_3O); 109.35 (=*C*HCH$_3$); 118.74 (*C*H=CHCH$_3$); 121.76 (indole C(7)); 127.04 (indole C(6)); 128.59 (indole C(4)); 131.87 (indole C(5)); quaternary sp^2-C: 69.79 (C(4a)); 118.47; 120.16; 123.39; 124.54; 155.14; 161.66 (CO); 163.83 (CO). MS: 341 (19, M^+), 282 (98), 59 (100). Anal. calc. for $C_{18}H_{19}N_3O_4$ (341.37): C 63.33, H 5.61, N 12.31; found: C 63.16, H 5.50, N 12.54.

Dimethyl 5,6-Dihydro-5-[(methoxycarbonyl)methyl]-6-methylpyridazino[4,5-c]quinoline-1,4-dicarboxylate (**5**). *Methyl 3-(1-methylindol-2-yl)-2-propenoate* (**1c**; 0.430 g, 2 mmol) was dissolved in dioxane (30 ml). To this soln., **3** (0.396 g, 2 mmol) in dioxane (20 ml) was added slowly. The resultant mixture was stirred at 100° for 81 h. The org. solvent was evaporated, and the residue was separated by FC using petroleum ether (40–60°)/AcOEt 5:5: 61 mg (8%) of **5**. Colorless crystals. M.p. 235° (acetone). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.52 (*dd*, ^2J = 17.4, ^3J = 12.6, CH_2); 3.63 (*dd*, ^2J = 17.4, ^3J = 5, CH_2); 3.69 (*s*, CH_3N); 3.74 (*s*, $COOCH_3$); 3.80 (*s*, $COOCH_3$); 3.91 (*s*, $COOCH_3$); 4.15 (*dd*, ^3J = 12.6, 5, H–C(5)); 7.11 (*dt*, ^3J = 7.3, ^4J = 1.1, H–C(9)); 7.20 (*mc*, H–C(7), H–C(8), H–C(10)). ^{13}C-NMR ($CDCl_3$): 30.31 (CH_3N); 52.67 (*C*H$_3$OCO–C(5)); 53.03 (COO*C*H$_3$); 53.24 (COO*C*H$_3$); 28.53 (CH_2); 39.42 (C(5)); sp^2-CH: 109.34 (C(9)); 119.35 (C(8)); 121.29 (C(10)); 122.84 (C(7)); quaternary sp^2-C: 102.75 (C(4a)); 126.45 (C(10b)); 137.09 (C(10a)); 138.38 (C(6a)); 140.80 (C(4)); 144.23 (C(1)); 164.43, 169.59, 169.90 (3 CO). MS: 385 (43, M^+), 241 (100). Anal. calc. for $C_{19}H_{19}N_3O_6$ (385.38): C 59.22, H 4.97, N 10.90; found: C 58.90, H 4.99, N 10.87.

*Dimethyl 6,7-Dihydro-6-methoxy-7-methyl-5*H*-benzo[b]pyridazino[4,5-d]azepine-1,4-dicarboxylate* (**6**). *2-(2-Methoxyvinyl)-1-methylindole* (**1d**; 0.337 g, 1.8 mmol) was dissolved in CH_2Cl_2 (30 ml). The soln. was cooled to – 75° and **3** (0.396 g, 2 mmol) in CH_2Cl_2 (20 ml) was added slowly at this temp. The mixture was stirred at –75° for 3 h and then at 20° for 18 h. The org. solvent was evaporated and the residue separated by FC using petroleum ether (40–60°)/AcOEt 1:1: 58 mg (9%) of **6**. Colorless crystals. M.p. 145° (CH_2Cl_2/petroleum ether (40–60°)). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.91 (*s*, CH_3O–C(6)); 3.30 (*dd*, ^2J = 16, ^3J = 1.5, H–C(5)); 3.50 (*s*, $COOCH_3$); 3.65 (*dd*, ^2J = 16, ^3J = 4.2, H–C(5)); 3.71 (*s*, CH_3N); 4.01 (*s*, $COOCH_3$); 5.73 (*q*, ^3J = 1.5, 4.2, H–C(6)); 7.29 (*mc*,

H–C(8), H–C(9), H–C(10)); 8.16 (*d*, ^3J = 8.9, H–C(11)). ^{13}C-NMR ($CDCl_3$): 29.67 (CH_3N); 52.79 ($COOCH_3$); 53.24 ($COOCH_3$); 56.07 (CH_3O); 28.30 (C(5)); 90.66 (C(6)); sp^2-CH: 109.45; 120.31; 121.07; 122.19; quaternary sp^2-C: 102.14; 124.04; 132.06; 137.94; 145.55; 166.94; 193.03 (CO); 199.26 (2 CO). FD-MS: 357 (3, M^+), 240 (100). EI-MS: 325 (100, $M^+ - OCH_3$). Anal. calc. for $C_{18}H_{19}N_3O_5$ (357.37): C 60.50, H 5.36, N 11.76; found: C 60.22, H 5.16, N 11.79.

Dimethyl 1,4-Dihydro-5-(1,3-dimethylindol-2-yl)-4-methylpyridazine-3,6-dicarboxylate (**7**). *1,3-Dimethyl-2-(1-propenyl)indole* (**1e**; 0.278 g, 1.5 mmol) was dissolved in CH_2Cl_2 (30 ml) and cooled to −75°. At this temp. **3** (0.396 g, 2 mmol) in CH_2Cl_2 (20 ml) was added slowly. The resultant mixture was stirred at 40° for 7 h. The org. solvent was evaporated and the residue separated by FC using petroleum ether (40–60°)/AcOEt 1:1: 338 mg (63%) of **7**. Colorless crystals. M.p. 141° (CH_2Cl_2/petroleum ether (40–60°)). ^{1}H-NMR (400 MHz, CD_2Cl_2, 20°, mixture of atropisomers): 1.06 (*dd*, ^3J = 6.9, CH_3–C(5)); 2.10, 2.24 (2*s*, CH_3–C(3′)); 3.51, 3.64 (2*s*, CH_3–C(1′)); 3.60 (*s*, $COOCH_3$); 3.69 (*q*, ^3J = 6.9, H–C(5)); 3.84 (*s*, $COOCH_3$); 7.08 (2*t*, ^3J = 6.8, ^4J = 0.9, H–C(6′)); 7.19 (2*t*, ^3J = 7.2, ^4J = 0.9, H–C(5′)); 7.28 (*dd*, ^3J = 8, H–C(7′)); 7.52 (*m*, H–C(4′)); 8.81 (*s*, NH). ^{13}C-NMR (CD_2Cl_2): 9.23, 9.94 (CH_3–C(3′)); 15.69, 16.12 (CH_3–C(5)); 30.44, 31.22 (CH_3N); 33.39, 34.47 (C(5)); 57.70, 53.02, 53.08 (4 CH_3O); sp^2-CH: 109.33; 109.47; 118.81; 119.06; 119.19; 119.21; 121.72; 122.12; quaternary sp^2-C: 112.35; 113.96; 114.04; 128.53; 128.87; 129.88; 129.99; 132.24; 134.52; 135.78; 135.81, 137.33; 137.97; 161.86 (CO); 162.18 (CO); 164.44 (CO); 164.61 (CO). MS: 355 (3, M^+), 84 (100). Anal. calc. for $C_{19}H_{21}N_3O_4$ (355.39): C 64.21, H 5.96, N 11.82; found: C 64.28, H 5.77, N 12.02.

Dimethyl 1,4-Dihydro-4-(1-methylindol-3-yl)pyridazine-3,6-dicarboxylate (**8a**). Indole **2a** (0.472 g, 3 mmol) was dissolved in CH_2Cl_2 (30 ml) and cooled to −75°. At this temp., **3** (0.594 g, 23 mmol) was added in portions. The resultant mixture was stirred for 1 h at −75° to 0°. The org. solvent was evaporated and the residue separated by FC using petroleum ether (40–60°)/AcOEt 1:1: 830 mg (85%) of **8a**. Colorless crystals. M.p. 150° (petroleum ether (40–60°)). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.70 (*s*, CH_3N); 3.74 (*s*, $COOCH_3$); 3.80 (*s*, $COOCH_3$); 5.03 (*d*, ^3J = 6, H–C(4)); 6.11 (*dd*, ^3J = 6, ^4J = 1.4, H–C(5)); 6.85 (*s*, H–C(2′)); 7.12 (*t*, ^3J = 7.9, H–C(6′)); 7.23 (*mc*, H–C(6′), H–C(7′)); 7.67 (*d*, ^3J = 7.9, H–C(4′)); 8.38 (br. *s*, NH). MS: 327 (21, M^+), 268 (100). Anal. calc. for $C_{17}H_{17}N_3O_4$ (327.34): C 62.38, H 5.23, N 12.84; found: C 62.77, H 5.55, N 13.10.

Dimethyl 4,4-Bis(indol-3-yl)-1,4-dihydropyridazine-3,6-dicarboxylate (**8b**). To a soln. of **2b** (1.0 g, 3.9 mmol) in dioxane (25 ml) was added, at r.t., **3** (0.92 g, 4.6 mmol) in one portion. After 10 min, the resultant mixture was poured on to ice and then extracted with CH_2Cl_2 (5 × 20 ml). The org. layer was dried ($CaCl_2$) and then concentrated. The residue was separated by FC using petroleum ether (40–60°)/AcOEt 6:4: 1.43 g (86%) of **8b**. Colorless crystals. M.p. 165° (petroleum ether/AcOEt). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.49 (*s*, $COOCH_3$); 3.71 (*s*, $COOCH_3$); 6.41 (*d*, ^4J = 2.2, H–C(5)); 6.90 (*s*, H–C(2′)); 6.92 (*s*, H–C(2′)); 7.00 (ψt, H–C(5′) or H–C(6′)); 7.15 (ψt, H–C(6′) or H–C(5′)); 7.31 (*d*, ^3J = 8.0, H–C(7′)); 7.51 (*d*, ^3J = 7.9, H–C(4′)); 8.19 (br. *s*, indole NH); 8.47 (*d* ^4J = 2.2, pyridazine NH). MS: 428 (1, M^+), 43 (100). Anal. calc. for $C_{24}H_{20}N_4O_4$ (428.15): C 67.28, H 4.71, N 13.08; found: C 67.66, H 4.56, N 12.99.

Dimethyl 1,4-Dihydro-4-methyl-4-(1-methylindol-3-yl)pyridazine-3,6-dicarboxylate (**8c**). A mixture of **2c** (0.3 g, 1.75 mmol) and **3** (0.42 g, 2.1 mmol) in CH_2Cl_2 (29 ml) was stirred at r.t. for 5 min. The further workup was as described for **8b**: 0.40 g (67%) of **8c**. Colorless crystals. M.p. 179° (AcOEt). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.94 (*s*, CH_3–C(4)); 3.58 (*s*, CH_3N); 3.75 (*s*, $COOCH_3$); 3.76 (*s*, $COOCH_3$); 5.61 (*d*, ^4J = 2.2, H–C(5)); 6.93 (*s*, H–C(2′)); 7.05 (ψt, H–C(5′) or H–C(6′)); 7.19 (ψt, H–C(6′) or H–C(5′)); 7.28 (*d*, ^3J = 8.2, H–C(7′)); 7.46 (*d*, ^3J = 8.0, H–C(4′)); 8.33 (br. *s*, ^4J not resolved, NH). MS: 341 (9, M^+), 282 (100). Anal. calc. for $C_{18}H_{19}N_3O_4$ (341.14): C 63.32, H 5.61, N 12.32; found: C 63.41, H 5.54, N 12.39.

Dimethyl 4-[1-(Phenylsulfonyl)indol-3-yl]pyridazine-3,6-dicarboxylate (**9**). A mixture of (*E*/*Z*)-**2d** (1:1; 0.45 g, 1.4 mmol) and **3** (0.28 g, 1.4 mmol) was dissolved in CH_2Cl_2 (20 ml) at −65°, and the mixture was then stirred at r.t. for 8 h. The solvent was evaporated under reduced pressure, the residue was triturated with some toluene, and filtered. The solid obtained was recrystallized from MeOH: 0.28 g (45%) of **9**. Colorless crystals. M.p. 207–209° (MeOH, dec.). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.79 (*s*, $COOCH_3$); 4.09 (*s*, $COOCH_3$); 7.31 (ψt, 1 arom. H); 7.41 (ψt, 1 arom. H); 7.48 (ψt, H–C(3), H–C(5) of Ph); 7.47 (ψd, 1 arom. H); 7.58 (ψt, 1 arom. H); 7.89 (*s*, H–C(2′)); 7.93 (*d*, ^3J = 8.2, H–C(2), H–C(6) of Ph); 8.06 (*d*, ^3J = 8.4, 1 arom. H); 8.38 (*s*, H–C(5)). MS: 451 (94, M^+), 77 (100). Anal. calc. for $C_{22}H_{17}N_3O_6S$ (451.09): C 58.52, H 3.80, N 9.32; found: C 58.12, H 3.84, N 9.27.

Trimethyl 1,4-Dihydro-5-(1-methylindol-3-yl)pyridazine-3,4,6-tricarboxylate (**10a**) *and Trimethyl 1,4-Dihydro-4-(1-methylindol-3-yl)pyridazine-3,5,6-tricarboxylate* (**10b**). Indole **2e** (0.430 g, 2 mmol) and **3** (0.396 g, 2 mmol) were dissolved in CH_2Cl_2 (30 ml), and the mixture was stirred at 20° for 4 h. The org. solvent was evaporated, and the residue was separated by FC using petroleum ether (40–60°)/AcOEt 1:1. The first fraction gave 378 mg (49%) of **10a**. The following eluate was concentrated, and the residue subjected to renewed FC: 100 mg (13%) of **10b**.

10a: Yellow crystals. M.p. 206° (petroleum ether (40–60°)). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.49 (*s*, $COOCH_3$); 3.72 (*s*, CH_3N); 3.83 (*s*, $COOCH_3$); 3.86 (*s*, $COOCH_3$); 4.92 (*s*, H–C(4)); 7.09 (*t*, ^3J = 8, 7, H–C(6′)); 7.18 (*t*, ^3J = 8, H–C(5′)); 7.22 (*d*, ^3J = 7, H–C(7′)); 7.31 (*d*, ^3J = 8, H–C(4′)); 7.62 (*s*, H–C(2′)); 9.20 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 33.13 (CH_3N); 52.36 (CH_3O); 52.71 (CH_3O); 52.81 (CH_3O); 44.87 (C(4)); 109.75 (C(7′)); 119.87 (C(6′)); 120.47 (C(4′)); 122.24 (C(5′)); 132.69 (C(2′)); quaternary sp^2-C: 107.01; 113.67; 123.97; 124.48; 126.56; 136.56; 163.62 (CO); 164.33 (CO); 170.20 (CO). MS: 385 (27, M^+), 326 (95), 294 (100). Anal. calc. for $C_{19}H_{19}N_3O_6$ (385.38): C 59.22, H 4.97, N 10.90; found: C 59.33, H 5.18, N 11.14.

10b: Colorless crystal. M.p. 156° (petroleum ether (40–60°)). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.66 (*s*, $COOCH_3$); 3.69 (*s*, CH_3N); 3.77 (*s*, $COOCH_3$); 3.87 (*s*, $COOCH_3$); 5.33 (*s*, H–C(4)); 6.87 (*s*, H–C(2′)); 7.16 (*mc*, H–C(5′), H–C(6′), H–C(7′)); 7.76 (*dd*, ^3J = 7.1, ^4J = 1.1, H–C(4′)); 8.62 (*s*, NH). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 28.43 (C(4)); 32.80 (CH_3N); 52.14 (CH_3O); 52.70 (CH_3O); 53.30 (CH_3O); sp^2-CH: 109.27; 119.66; 119.75; 121.83; 128.56; quaternary sp^2-C: 106.08; 114.91; 126.20; 134.15; 137.09; 137.36; 163.38 (CO); 164.07 (CO); 165.95 (CO). MS: 385 (28, M^+), 326 (100), 294 (40). Anal. calc. for $C_{19}H_{19}N_3O_6$ (385.38): C 59.22, H 4.97, N 10.90; found: C 59.28, H 5.20, N 10.95.

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