CYCLIZATION REACTIONS OF 2,2'-BIS-*N*-METHYLINDOLYL TO POTENTIAL PROTEIN KINASE C INHIBITORS

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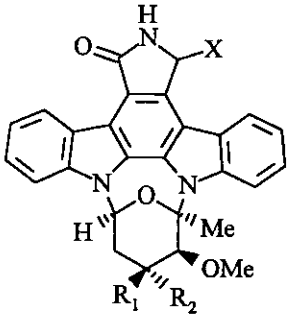
Abstract —— 2,2'-Bis-*N*-methylindolyl (**4**) was used as the starting material in the syntheses of some indolo[2,3-*a*]carbazoles (**6**, **7**, and **10a,b**). Compounds of this type represent the subunit of the staurosporine group of substances, a natural class of protein kinase C inhibitors. Reaction of the bisindolyl (**4**) with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate – in the sense of a Diels-Alder reaction with inverse electron demand – gave rise to the pyridazino[*b*]indoles (**11b, 11b'**) as an isolable mixture of diastereomers and additionally to a rearranged product (**13**).

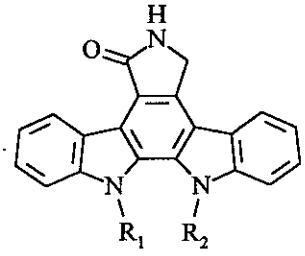
INTRODUCTION

The activation of protein kinase C (PKC) is involved in signal transduction for a variety of biologically active substances which activate cell functions and proliferation.[1,2] Among the various types of PKC inhibitors,[3-10] staurosporine, the related bacterial metabolites (**1, 2**), and some synthetic aglycone analogues (**2, 3**) have been shown to be potent inhibitors that interact with ATP binding sites. Furthermore, PKC has attracted attention as a potential target for the development of novel antitumor[11] and anti-inflammatory[12] agents. Thus, an increasing number of reports on synthetic elaborations of several indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole aglycones as well as bisindolyl derivatives and analogues, some of which included investigations on structure-activity relationships, has appeared in the past few years.[13-19] It is interesting to note that bisindolylmaleimides exhibiting a close electronic relationship to the staurosporine aglycone have been detected in several species of marine algae.[20] Since some derivatives of the common aglycones of natural microbial metabolites exert pronounced PKC inhibiting effects, the development of further syntheses of closely related systems will be of general interest. In continuation of our investigations on indole functionalization, including cycloaddition reactions,[21,22] we now report on some derivatization and cyclization reactions of the readily available 2,2'-bis-*N*-methylindolyl[22] with a series of the electrophilic reagents generally employed in Diels-Alder reactions for the construction of some substructures of the staurosporine family. A related strategy has been described by Somei and Kodama.[23]



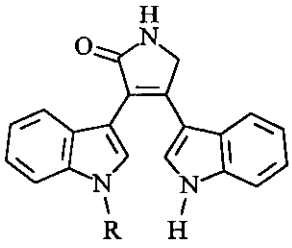
1a - 1d

a) Staurosporine[4] : X = R_2 = H; R_1 = NHMe
b) TAN-1030 A[5] : X = H; R_1, R_2 = =NOH
c) RK-286 C[6] : X = R_2 = H; R_1 = OH
d) UCN-01 and 02[7] : X = OH; R_2 = H; R_1 = NHMe



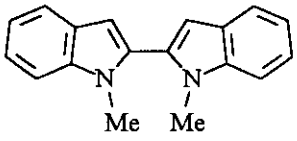
2a, 2b

a) K-252c[8,9] : R_1 = R_2 = H
b) Gö 6976[10] : R_1 = Me; R_2 = -$(CH_2)_2$-CN



3a, 3b

a) B[11] R = H
b) C[11] R = -$(CH_2)_3NMe_2$



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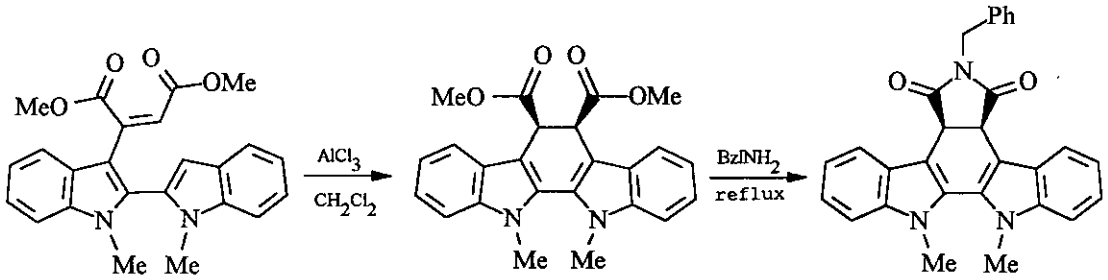
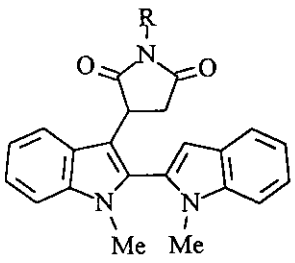
RESULTS AND DISCUSSION

2,2'-Bis-*N*-methylindolyl (**4**) reacted with dimethyl acetylenedicarboxylate in dichloromethane under $AlCl_3$ catalysis to furnish, among other isomers,[22b] *via* 3-(2-dimethoxymaleoyl)-1-methyl-2-(1-methylindol-2-yl)indole (**5**; 34% yield),[22] the indolo[2,3-*a*]carbazole (**6**; 62% yield) *cis*-stereospecifically. Reaction of compound (**6**) with benzylamine (reflux, 19 h) smoothly gave rise to the novel indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoledione (**7**) in 40% yield.

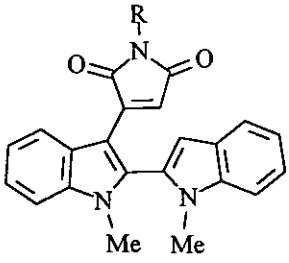


5 **6** (62%) **7** (40%)

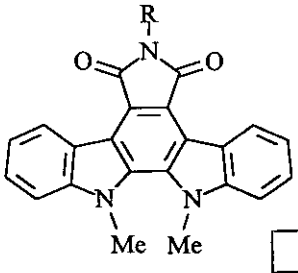
The bisindolyl (**4**) also reacted with maleimide and *N*-phenylmaleimide in the presence of $AlCl_3$ to furnish the Michael-type adducts (**8a,a'**) and (**8b,b'**), respectively. As a consequence of the combination of central and axial chirality elements (estimated barrier to rotation of the indolyl residue at C3 > 23 kcal mol^{-1}), the existence of two long life-time diastereomers (**a,a'/b,b'**) was deduced in each case by nmr spectroscopy at 20 °C from the presence of double sets of signals as well as by $^1H,^1H$-NOE experiments. In the case of **8a,a'**, one of the two diastereomers could be separated preparatively. On the other hand, addition of Pd/C to **8a,a'** or **8b,b'** gave rise to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazolediones (**10a** and **10b**) directly. The hexacyclic products (**10**) are also accessible through a two-step procedure in which compounds (**8**) are first dehydrogenated to **9** using DDQ while the products (**9**) are subsequently oxidatively cyclized to **10a** or **10b** by means of Pd/C catalyst in refluxing *o*-dichlorobenzene.



8a, 8a' (43 %)
8b, 8b' (87 %)



9a (10 %)
9b (20 %)

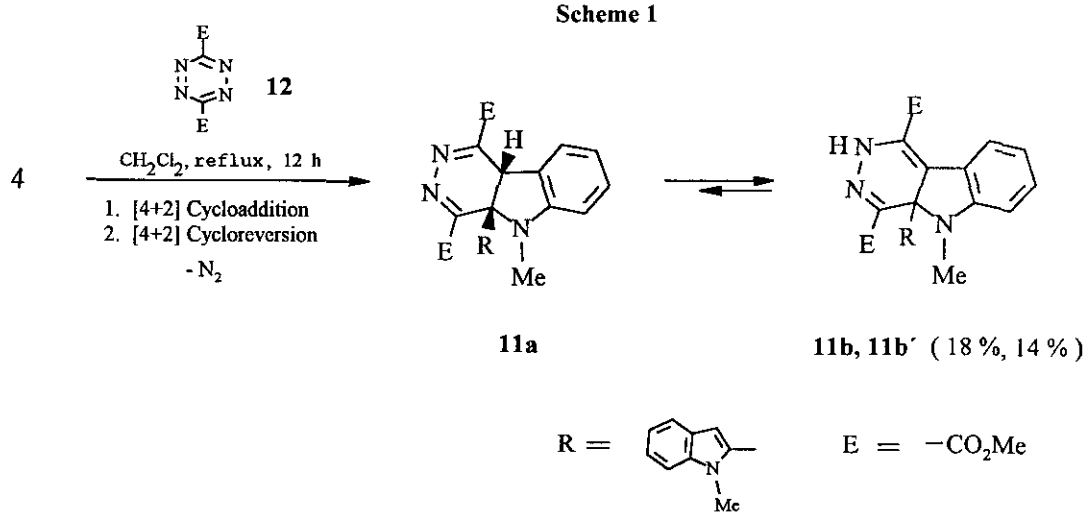


10a (10 %)
10b (21 %)

8 - 10	R
a (a')	H
b (b')	Ph

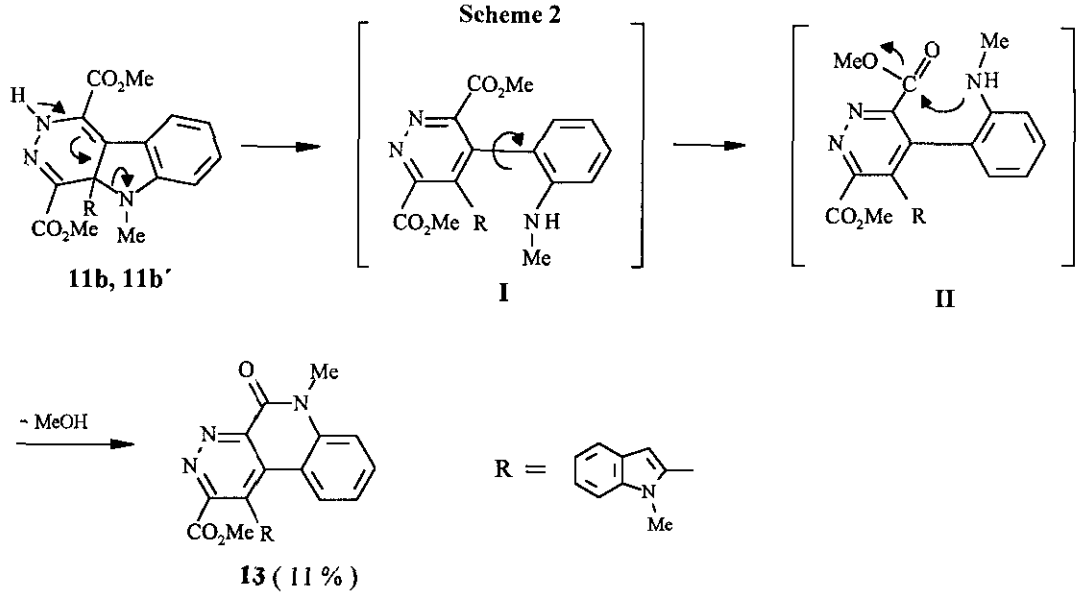
On the basis of our experience of Diels-Alder reactions with inverse electron demand[24] in the vinylindole series,[25] we investigated the reactivity of the electron-rich indole derivative (**4**) towards dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**12**) as a conformationally fixed *s-cis*-diazadiene (Scheme 1). According to AM1 calculations[26] on **4** and the respective tetrazine (**12**), a HOMO(bisindolyl)-LUMO(tetrazine)-controlled [2πs + 4πs] cycloaddition was predicted on the basis of the FMO concept. However, upon involvement of the two indole enamine π-systems in **4**, a [4πs + 4πs] process or a double [2πs + 4πs] combination would also seem feasible. In fact, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**12**) only reacted with one enamine double bond in **4** in a [4 + 2] cycloaddition/[4 + 2] cycloreversion sequence to yield the dihydropyridazino[4,5-*b*]indole (**11a**) as the primary product (Scheme 1). Subsequent tautomerization of **11a** in the reaction mixture then furnished the more stable isomers (**11b,11b'**). The compounds (**11b,11b'**) are the preparatively isolable products and could, in this case, be separated completely by flash chromatography. Inspection of Dreiding models and MMX force field calculations[27] in combination with NOE measurements allow the conclusion that the existence of stable (isolable) diastereomers is more likely due to the central chirality at C4a and, especially, to the very slow N2 inversion and/or ring inversion of the diazine ring[28] rather than to a slow rotation of the indolyl ring at C4a. However, on account of the reactive diazadiene unit in **11a**, this intermediate should be susceptible to trapping by a further molecule of **4** to produce isomeric, bridged 1,2-diazine derivatives.

Scheme 1



Indeed, during the chromatographic work-up required to obtain a sufficient amount of **11b,11b'**, two further substances were isolated. One of these compounds could only be characterized by electron-impact mass spectrometry (*m/z* = 690) because of its very low yield (<2%) and instability. We suggest in this case a double Diels-Alder product probably formed by reaction of **11a** with a further molecule of **12**. However, the other reaction product was unambiguously characterized by X-ray crystallography and assigned as compound (**13**) (Scheme 2, Figure 1). The tricyclic diazine monoester (**13**) is probably formed from **11b,b'** by heterolytic cleavage and ring closure *via* an intermediate with the appropriate conformation **II**. Related reactions of anellated diazines have been reported.[29]

Scheme 2



For the crystal structure analysis of **13**, monoclinic crystals with the space group $P2_1/n$ were obtained from a dimethyl sulfoxide solution. All geometrical parameters showed the normal values. The conformation of the molecule in the solid state can be described by the torsion angles C24-C25-C12-C11 (−74.7(3)°) and O1-C15-C11-C12 (130.4(3)°). The indole fragment is almost planar within 0.026 Å. The angle between the phenyl and pyridazine rings is 18.1°.

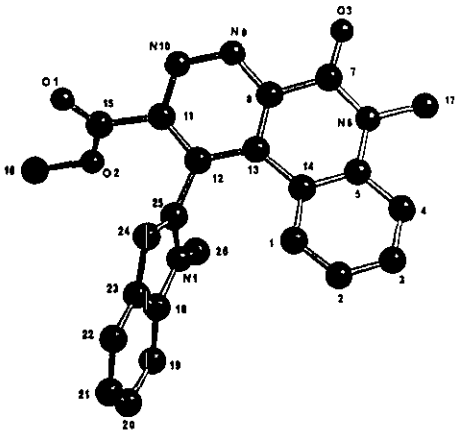


Figure 1. SCHAKAL plot of the X-ray structure of compound (**13**). The numbering scheme shown does not correspond to that of the IUPAC nomenclature.

Biochemical investigations of the new compounds prepared as potential protein kinase C inhibitors are in progress.[30]

EXPERIMENTAL

The ir (KBr) spectra were recorded with a Perkin Elmer 1310 instrument. The ^{1}H nmr spectra (δ, ppm; *J* Hz) were recorded at 200 and 400 MHz and the ^{13}C-nmr spectra at 100.6 MHz on Bruker AC 200 and AMX 400 spectrometers. The electron impact (70 eV) mass spectra were obtained using a Varian MAT CH 7 spectrometer. Elemental analyses were performed with a Carlo Erba Strumentazione 1106 apparatus. Melting points were measured with an Electrothermal 8200 instrument. Flash chromatography was performed on Merck 60 silica gel (particle size: 0.040-0.063 mm). The petroleum ether used had the boiling range 40-60 °C. All reactions were carried out in highly pure, anhydrous solvents under an argon atmosphere. The synthesis of compound (**6**) is described in Ref.[22b]

12-Benzyl-5,6-dimethyl-10c,13a-dihydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-11,13-dione (7). Compound (**6**) (210 mg, 0.52 mmol) was dissolved in 6 ml (54.93 mmol) of benzylamine and the solution was heated under reflux for 19 h. The reaction mixture was then allowed to cool to room temperature and concentrated. The residue was dried over silica gel and then separated by flash chromatography (petroleum ether/ethyl acetate, 2/1). Yield: 93 mg (40%); mp 246-248 °C (colorless crystals from petroleum ether/ethyl acetate); ir: ν 3300, 3060, 2920, 1710, 1640, 1550, 1420, 1330, 1265, 1160, 1020, 735, 700; ^{1}H nmr (400 MHz, CD_2Cl_2): δ

2.61 (s, 2 H), 3.98 (s, 6 H, 2 × N-CH_3), 4.39 (s, 2 H), 7.07-7.26 (m, 9 H, aromatic H), 7.34-7.40 (m, 2 H, aromatic H), 7.54 (d, J = 7.4 Hz, 2 H, 1-H and 10-H); EI-ms *m/z* (rel. int. %) 445 (M^+, 27), 421 (32), 420 (100), 286 (20), 285 (64), 284 (41), 271 (39), 270 (19), 269 (24), 268 (12), 256 (28), 255 (19), 241 (10). Anal. Calcd for $C_{29}H_{23}N_3O_2$: C, 78.18; H, 5.20; N, 9.43. Found: C, 77.93 ; H, 5.44 ; N, 9.50.

3-(1,4-Dioxo-2,3-dihydromaleimido)-1-methyl-2-(1-methylindol-2-yl)indole (8a, 8a') (mixture of diastereomers). Anhydrous aluminum trichloride (500 mg, 3.37 mmol) and maleimide (500 mg, 5.15 mmol) were dissolved in 60 ml of anhydrous xylene. The mixture was stirred at room temperature for 45 min. Compound (**4**) (450 mg, 1.73 mmol) was then added, the mixture was stirred for 48 h at room temperature, and then poured into water. The organic layer was separated and the aqueous phase was washed twice with dichloromethane. The combined organic phases were dried with sodium sulfate, concentrated, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3/1) to furnish the mixture of diastereomers (**8a/8a'**). Yield: 263 mg (43%); mp 237 °C (colorless crystals from petroleum ether/ethyl acetate); ir: ν 3040, 1700, 1465, 1350, 1325, 1190, 750; ^{1}H nmr (400 MHz, DMSO-d_6, mixture of diastereomers **8a/8a'** integrating in the ratio **a:a'** = 1:1): δ 2.63 (dd, J = 18.1, 5.5 Hz, 1 H, 3"-H, **a**), 2.80 (dd, J = 18.1, 5.4 Hz, 1 H, 3"-H, **a'**), 3.03 (dd, J = 18.1, 9.8 Hz, 1 H, 3"-H, **a**), 3.12 (dd, J = 18.1, 9.9 Hz, 1 H, 3"-H, **a'**), 3.52 (s, 6 H, 2 × N-CH_3), 3.53 (s, 3 H, N-CH_3), 3.62 (s, 3 H, N-CH_3), 4.10 (dd, J = 9.8, 5.5 Hz, 1 H, 2"-H, **a**), 4.21 (dd, J = 9.8, 5.4 Hz, 1 H, 2"-H, **a'**), 6.66 (s, 1 H, 3'-H, **a**), 6.74 (s, 1 H, 3'-H, **a'**), 7.10-7.15 (m, 4 H, aromatic H), 7.23-7.30 (m, 4 H, aromatic H), 7.35 (d, J = 7.95 Hz, 1 H, aromatic H), 7.41 (d, J = 7.94 Hz, 1 H, aromatic H), 7.52-7.57 (m, 4 H, aromatic H), 7.64 (d, J = 7.9 Hz, 2 H, 2 × 4-H, **a** and **a'**), 11.31 (s, 1 H, NH), 11.43 (s, 1 H, NH); EI-ms *m/z* (rel. int. %) 358 (M^+ + 1, 25), 357 (M^+, 100), 286 (28), 285 (20), 271 (14), 256 (10), 143 (11). Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.35; H, 5.52; N, 11.27.

3-(1,4-Dioxo-5-phenyl-2,3-dihydromaleimido)-1-methyl-2-(1-methylindol-2-yl)indole (8b,8b'). A suspension of *N*-phenylmaleimide (420 mg, 2.43 mmol) and aluminum trichloride (480 mg, 3.60 mmol) in 40 ml of anhydrous xylene was stirred at room temperature for 30 min. The 2,2'-bisindolyl (**4**) (520 mg, 2.00 mmol) was then added, the reaction mixture was heated under reflux for 10 min, and then allowed to cool to room temperature. The cooled mixture was poured into water, the organic layer was separated, and the aqueous phase washed with dichloromethane. The combined organic layers were dried with sodium sulfate, concentrated, and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 1.5/1). Yield (**8b,8b'**): 754 mg (87%); mp 203-204 °C (colorless crystals from petroleum ether/ethyl acetate); ir: ν 3050, 2925, 1710, 1500, 1470, 1390, 1180, 800, 750, 690; ^{1}H nmr (400 MHz, CD_2Cl_2; mixture of diastereomers **8b,8b'** integrating in the ratio **b:b'** = 6.2:5): δ 3.03 (dd, J = 18.5, 5.8 Hz, 1 H, 3"-H, **b'**), 3.11 (dd, J = 18.5, 5.6 Hz, 1 H, 3"-H, **b**), 3.25 (dd, J = 18.6, 10.0 Hz, 1 H, 3"-H, **b'**), 3.33 (dd, J = 18.5, 10.0 Hz, 1 H, 3"-H, **b**), 3.52 (s, 3 H, N-CH_3, **b**), 3.58 (s, 3 H, N-CH_3, **b**), 3.59 (s, 3 H, N-CH_3, **b'**), 3.67 (s, 3 H, N-CH_3, **b'**), 4.31 (dd, J = 10.0, 5.9 Hz, 1 H, 2"-H, **b'**), 4.48 (dd, J = 10.0, 5.6 Hz, 1 H, 2"-H, **b**), 6.68 (s, 1 H, 3'-H, **b'**), 6.74 (m, 1 H, phenyl-H, **b'**), 6.76 (m, 1 H, phenyl-H, **b**), 6.78 (s, 1 H, 3'-H, **b**), 7.20-7.50 (m, 21 H, aromatic H), 7.58 (d, J = 8.0 Hz, 1 H, **b**), 7.70 (d, J

= 7.7 Hz, 2 H, **b** and **b'**); ^{1}H nmr (200 MHz, $CDCl_3$; pure **8b**): δ 3.10 (dd, *J* = 18.5, 5.5 Hz, 1 H, 3"-H), 3.34 (dd, *J* = 18.5, 9.8 Hz, 1 H, 3"-H), 3.52 (s, 3 H, N-CH_3), 3.56 (s, 3 H, N-CH_3), 4.48 (dd, *J* = 9.8, 5.6 Hz, 1 H, 2"-H), 6.63-6.68 (m, 2 H, 2 × phenyl H), 6.76 (s, 1 H, 3-H), 7.15-7.23 (m, 3 H, 2 × and 1 × phenyl H), 7.25-7.31 (m, 1 H, aromatic H), 7.32-7.47 (m, 5 H, aromatic H), 7.56 (d, *J* = 7.8 Hz, 1 H, aromatic H), 7.68 (d, *J* = 7.8 Hz, 1 H, 4-H); EI-ms *m/z* (rel. int. %) 433 (M^+, 100), 286 (33), 285 (26), 271 (29), 270 (31), 256 (14), 255 (12). Anal. Calcd for $C_{28}H_{23}N_3O_2$: *C, 77.58; H, 5.35; N, 9.69. Found: C, 77.85; H, 5.30; N, 9.68.*

3-(Maleimido-2-yl)-1-methyl-2-(1-methylindol-2-yl)indole (9a) and 5,6-Dimethylindolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-11,13-dione (10a). Compound (**8a/8a'**) (200 mg, 0.56 mmol) was dissolved in 9 ml of *o*-dichlorobenzene and stirred for 30 min at room temperature. 10% Pd/C (160 mg) was added and the mixture was heated overnight under reflux. The reaction mixture was concentrated, the residue was dried over silica gel and then separated by flash chromatography (petroleum ether/ethyl acetate, 3/1) until **9a** was separated. After separation of **9a**, the column was washed with 1 l of dichloromethane. The dichloromethane fraction was concentrated and the residue crystallized. Compound (**10a**) recrystallized from dichloromethane as yellow, filmy plates.

Yield of **9a**: 20 mg (10%); mp 218-220 °C (orange-colored crystals from petroleum ether/ethyl acetate); ir: ν 3180, 3050, 1700, 1610, 1460, 1330, 750; ^{1}H nmr (400 MHz, $CDCl_3$): δ 3.61 (s, 3 H, N-CH_3 or N'-CH_3), 3.63 (s, 3 H, N'-CH_3 or N-CH_3), 6.17 (s, 1 H, maleimide 3-H), 6.60 (s, 1 H, 3-H), 7.16-7.20 (m, 1 H, aromatic H), 7.21 (br s, 1 H, maleimide NH), 7.30-7.35 (m, 2 H, aromatic H), 7.38-7.45 (m, 3 H, aromatic H), 7.65 (d, *J* = 7.9 Hz, 1 H, 7-H or 4'-H), 7.97 (d, *J* = 8.0 Hz, 1 H, 4-H); ^{13}C nmr (100.6 MHz, $CDCl_3$): δ 30.8 and 31.0 (2 × N-CH_3), 106.2 (C_t), 107.1 (C_q), 109.9 (C_t), 110.18 (C_t) 120.4 (C_t), 121.2 (C_t); 122.1 (C_t), 123.0 (C_t), 123.1 (C_t), 123.9 (2 × C_t, one C_t overlapping), 125.9 (C_q), 127.6 (C_q), 129.3 (C_q), 134.2 (C_q), 138.0 (C_q), 138.2 (C_q), 142.2 (C_q), 170.0 and 170.7 (2 × CO); EI-ms *m/z* (rel. int. %) 355 (M^+, 100), 338 (12), 284 (22), 283 (17), 269 (21), 268 (18). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.00; H, 4.81; N, 11.57.

Yield of **10a**: 20 mg (10%); mp > 300 °C; ir: ν 3200, 1750, 1690, 1570, 1450, 1340, 1315, 1240, 1155, 1100, 740; ^{1}H-nmr (400 MHz, DMSO-d_6): δ 4.28 (s, 6 H, 2 × N-CH_3), 7.38-7.45 (m, 2 H, 5-H or 6-H), 7.62-7.69 (m, 2 H, 6-H or 5-H), 7.80 (d, *J* = 8.2 Hz, 2 H, 7-H, 7'-H), 9.13 (d, *J* = 7.9 Hz, 2 H, 4-H, 4'-H), 11.11 (s, 1 H, NH); EI-ms *m/z* (rel. int. %) 354 (M^+ + 1, 21), 353 (M^+, 100), 338 (29), 292 (19), 280 (14), 268 (13), 267 (97), 266 (82), 265 (41), 240 (40), 239 (12), 238 (19). Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.56; H, 4.21; N, 11.77.

3-(1,4-Dioxo-5-phenylmaleimido)-1-methyl-2-(1-methylindol-2-yl)indole (9b) and 5,6-Dimethyl-12-phenylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-11,13-dione (10b). Compound (**8b, 8b'**) (300 mg, 0.69 mmol) was dissolved in 10 ml of *o*-dichlorobenzene and the solution was stirred for 30 min at room temperature. After addition of 10% Pd/C (195 mg), the mixture was heated overnight under reflux. The reaction mixture was concentrated and the residue was dried over silica gel prior to separation by flash chromatography (petroleum

ether/ethyl acetate, 3/1). After separation of **9b**, the column was washed with 1 l of dichloromethane. The dichloromethane fraction was concentrated to furnish **10b** which was recrystallized from dichloromethane to furnish yellow, filmy plates.

Yield of **9b**: 60 mg (20%); mp 180-185 °C (orange-red crystals from petroleum ether/ethyl acetate); ir: ν 2920, 1700, 1465, 1380, 750, 730; ^{1}H nmr (400 MHz, $CDCl_3$): δ 3.63 (s, 3 H, N-CH_3), 3.64 (s, 3 H, N-CH_3), 6.27 (s, 1 H, phenylmaleimide H), 6.65 (s, 1 H, 3-H), 7.12-7.23 (m, 2 H, aromatic H), 7.26-7.46 (m, 9 H, aromatic H), 7.67 (d, J = 7.9 Hz, 1 H, aromatic H), 8.06 (d, J = 7.9 Hz, 1 H, 4-H); EI-ms *m/z* (rel. int. %) 432 (M^+ + 1, 28), 431 (M^+, 87), 414 (11), 339 (11), 312 (18), 311 (69), 310 (10), 297 (13), 285 (17), 284 (67), 283 (74), 282 (14), 281 (11), 271 (10), 270 (27), 269 (100), 268 (83), 267 (28), 266 (10), 254 (10), 253 (13), 241 (16). Anal. Calcd for $C_{28}H_{21}N_3O_2$: C, 77.94; H, 4.91; N, 9.74. Found: C, 77.98; H, 4.90; N, 9.72.

Yield of **10b**: 61 mg (21 %); mp > 340 °C; ir: ν 1735, 1690, 1560, 1465, 1360, 1310, 1230, 1100, 1080, 735, 705; ^{1}H-nmr (400 MHz, $CDCl_3$): δ 4.25 (s, 6 H, N-CH_3, N'-CH_3), 7.41-7.45 (m, 3 H, aromatic H), 7.53-7.66 (m, 8 H, aromatic H), 9.31 (d, J = 7.9 Hz, 2 H, 4-H, 4'-H); EI-ms *m/z* (rel. int. %) 430 (M^+ + 1, 31), 429 (M^+, 100), 414 (14), 267 (16). Anal. Calcd for $C_{28}H_{19}N_3O_2$: C, 78.31; H, 4.46; N, 9.78. Found: C, 78.23; H, 4.37; N, 9.61.

4a-(Methylindol-2-yl)-5-methyl-2,4a-dihydropyridazino[4,5-*b*]indole (11b and 11b'). Compound **(4)** (130 mg, 0.5 mmol) and the tetrazine (110 mg, 0.56 mmol) were dissolved in 10 ml of anhydrous dichloromethane, and the solution was stirred at room temperature for 30 min. Then the mixture was heated overnight under reflux, subsequently concentrated, and the residue was separated by flash chromatography to furnish the selectively isolated diastereomers **(11b)** and **(11b')** (petroleum ether/ethyl acetate, 2/1) and the compound **(13)** (petroleum ether/ethyl actetate, 1/5).

Yield of **11b**: 39 mg (18%); mp 144-150 °C (yellow-colored crystals from petroleum ether/ethyl acetate); ir: ν 2950, 1740, 1520, 1460, 1430, 1380, 1330, 1310, 1280, 1240, 1200, 1180, 1110, 750; ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.95 (s, 3 H, N-CH_3 or O-CH_3), 3.50 (s, 3 H, N-CH_3 or O-CH_3), 3.53 (s, 3 H, N-CH_3 or O-CH_3), 3.81 (s, 3 H, N-CH_3 or O-CH_3), 6.68 (s, 1 H, 3-H), 7.17-7.19 (m, 1 H, aromatic H), 7.32-7.43 (m, 5 H, aromatic H), 7.67 (d, J = 7.9 Hz, 1 H, 4-H or 4'-H), 7.92 (s, 1 H, NH), 8.56 (d, J = 7.8 Hz, 1 H, 4'-H or 4-H); ^{13}C nmr (100.6 MHz, $CDCl_3$): δ 30.6 (s, N-CH_3), 30.8 (s, N-CH_3), 51.6 (s, O-CH_3), 52.3 (s, O-CH_3), 107.5, 109.8, 109.9, 110.4, 120.3, 121.1, 122.9, 123.2, 124.0, 124.5, 125.8, 127.0, 127.4, 137.0, 137.8, 138.0, 149.5, 161.7, 163.7 (CO), 164.2 (CO); EI-ms *m/z* (rel. int. %) 430 (M^+, 13), 345 (12), 344 (50), 312 (24), 286 (13), 285 (59), 284 (100), 271 (20), 270 (27). Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.79; H, 5.20; N, 12.92.

Yield of **11b'**: 30 mg (14%); mp 150-154 °C (orange-colored crystals from petroleum ether/ethyl acetate); ir: ν 3250, 2975, 1725, 1700, 1600, 1475, 1430, 1340, 1315, 1290, 1240, 1195, 1160, 1135, 1060, 950, 825, 780, 760; ^{1}Hnmr (400 MHz, CD_2Cl_2): δ 2.96 (s, 3 H, O-CH_3), 3.13 (s, 3 H, O-CH_3), 3.90 (s, 3 H, N-CH_3), 3.95 (s, 3 H, N-CH_3), 6.47 (s, 1 H, 3-H), 6.74 (d, J = 8.1 Hz, 1 H, aromatic H), 6.85-6.89 (m, 1 H, aromatic H), 7.00-7.04 (m, 1 H, aromatic H), 7.15-7.16 (m, 2 H, aromatic H), 7.37-7.41 (m, 1 H, aromatic H), 7.49 (d, J = 7.9

Hz, 1 H, aromatic H), 8.37 (dd, J = 7.9, 0.6 Hz, 1 H, 4-H or 4'-H), 9.43 (s, 1 H, NH); ^{13}C nmr (100.6 MHz, CD_2Cl_2): δ 31.8 (N-CH_3), 33.4 (N-CH_3), 52.8 (O-CH_3), 52.9 (O-CH_3), 105.7, 108.3, 109.6, 118.9, 119.8, 120.1, 120.8, 121.1, 122.2, 122.8, 123.9, 126.6, 126.7, 131.9, 132.4, 139.6, 154.5, 162.1 (CO), 163.9 (CO), one signal is overlapped; EI-ms *m/z* (rel. int. %) 430.2 (M^+, 6), 372 (24), 371 (97), 345 (29), 344 (23), 339 (12), 312 (14), 300 (13), 287 (21), 286 (100), 285 (20), 284 (339), 271 (24), 270 (30), 269 (12), 143 (13), 59 (12), 54 (11). Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.72; H, 5.30; N, 12.84.

Methyl 6-Methyl-1-[1-methyl-1*H*-indol-2-yl]-5-oxo-5,6-dihydropyridazino[3,4-*c*]quinoline-2-carboxylate (13). Compound (**13**) was obtained in the preparation of **11b** and **11b'** as described above and separated by flash chromatography (petroleum ether/ethyl acetate, 1/5) as yellow-colored needles in approx. 11% yield; mp 245-249 °C (petroleum ether/ethyl acetate); ir: ν 1730, 1665, 1425, 1275, 1215, 760, 740; ^1H-nmr (400 MHz, *DMSO-d_6*): δ 3.29 (s, 3 H, O-CH_3 or N-CH_3), 3.64 (s, 3 H, O-CH_3 or N-CH_3), 3.78 (s, 3 H, O-CH_3 or N-CH_3), 6.70 (s, 1 H, indole C3-H), 6.74 (m, 1 H, aromatic H), 6.85-6.89 (m, 1 H, aromatic H), 7.16-7.20 (m, 1 H, aromatic H), 7.29-7.33 (m, 1 H, aromatic H), 7.57 (d, J = 8.2 Hz, 1 H, aromatic H), 7.64-7.71 (m, 3 H, aromatic H); EI-ms *m/z* (rel. int. %) 399 (M^+ + 1, 27), 398 (M^+, 100), 340 (12), 339 (M^+ – CO-OCH_3). Anal. Calcd for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.17; H, 4.48; N, 13.69.

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