INTRODUCTION OF PHARMACOPHORE GROUPS INTO BIS(INDOL-1-YL)MALEIMIDES AND 6H-PYRROLO[3,4:2,3][1,4]DIAZEPINO[6,7,1-hi]-INDOLO-8,10(7H,9H)-DIONES

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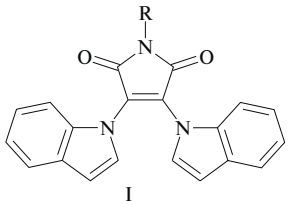
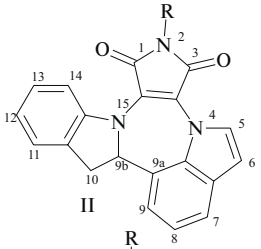
The synthesis of bis(indol-1-yl)maleimides and polycondensed [1,4]diazepines containing various functional groups, which are the analogs of biologically active indolo[2,3-à]carbazoles, is described. Functional groups were introduced directly into [1,4]diazepine and bis(indol-1-yl)maleimide molecules via electrophilic substitution reactions using precursors containing such functional groups.

Previously, we described the synthesis of bis(indol-1-yl)maleimides (I) capable of forming, [1,4]diazepines (II) containing annelated indole, indoline, and maleimide rings under the action of protonic acids [1]. Diazepines II are readily dehydrated with the formation of 6H-pyrrolo-[3,4:2,3][1,4]diazepino[6,7,1-hi]indolo-8,10(7H,9H)-diones (III). Maleimides I are the isomers of bis(indol-3-yl)-maleimides (IV), some of which exhibit high biological activity (protein kinase C and/or topoisomerase I inhibition). Diones III are the analogs of indolo[2, 3-a]carbazoles (V), which are used as initial compounds for the synthesis of various biologically active substances.



I



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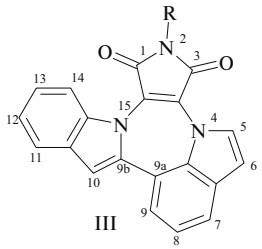

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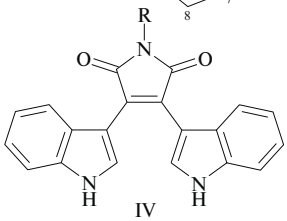

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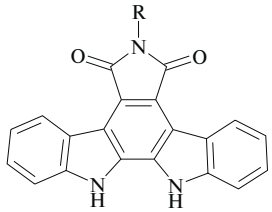
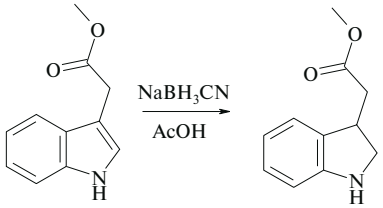


V

The aim of this study was to develop methods for the introduction of various pharmacophore groups or their precursors into bis(indol-1-yl)maleimides I and [1,4]indolodiazepines II and III.

Introduction of Pharmacophore Groups into Initial Compounds for the Synthesis of Bis(indol-1-yl)maleimides and Polycondensed [1,4]Diazepines Containing Pharmacophore Moieties

(2,3-Dihydroindol-3-yl)acetic acid methyl ester (VII) [2] was obtained via the reduction of (indol-3-yl)acetic acid methyl ester (VI) under the action of $NaBH_3CN$ in glacial acetic acid (yield, 70%):



VI VII

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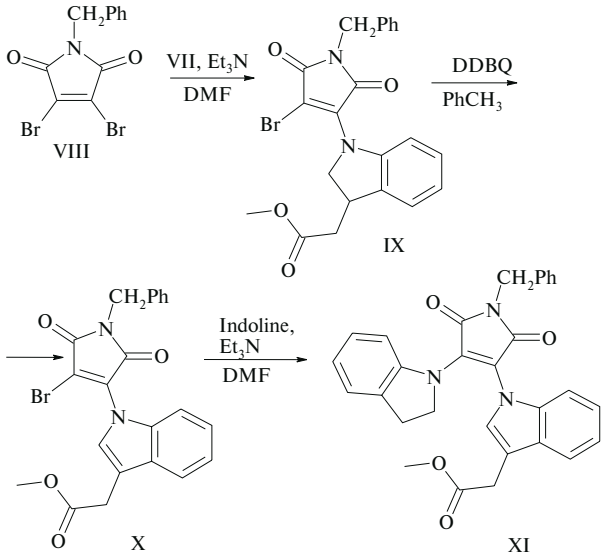
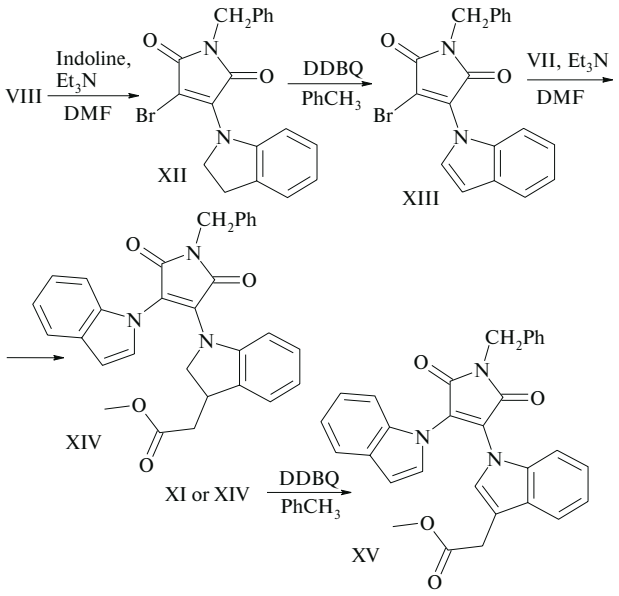
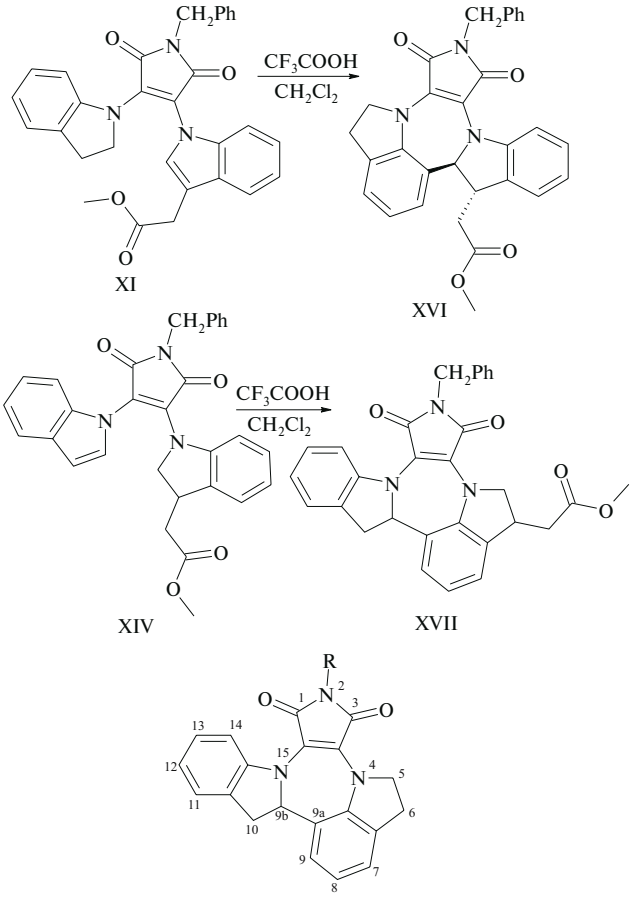
The subsequent condensation of ester VII with 1-benzyl-3,4-dibromomaleimide (VIII) in DMF in the presence of Et_3N led to the formation of methyl ester IX (yield, 72%). Then, dehydration of the indoline moiety of ester IX by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDBQ) in toluene led to compound X (yield, 70%), and the reaction of compound X with indoline in DMF in the presence of Et_3N yielded methyl ester XI (yield, 70%):



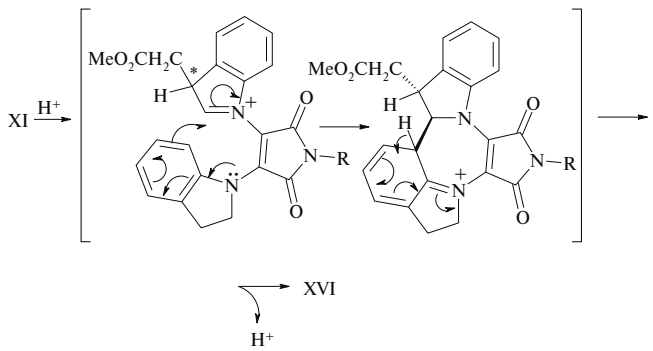
The interaction of 1-benzyl-3-bromo-4-(indol-1-yl)maleimide (XIII) with ester VII in DMF in the presence of Et_3N led to methyl ester XIV (yield, 70%), which is an isomer of ester XI. Then, fully aromatized bisindole derivative XV was obtained via dehydration of ester XI or XIV under the action of DDBQ in boiling toluene (yield, 70%).

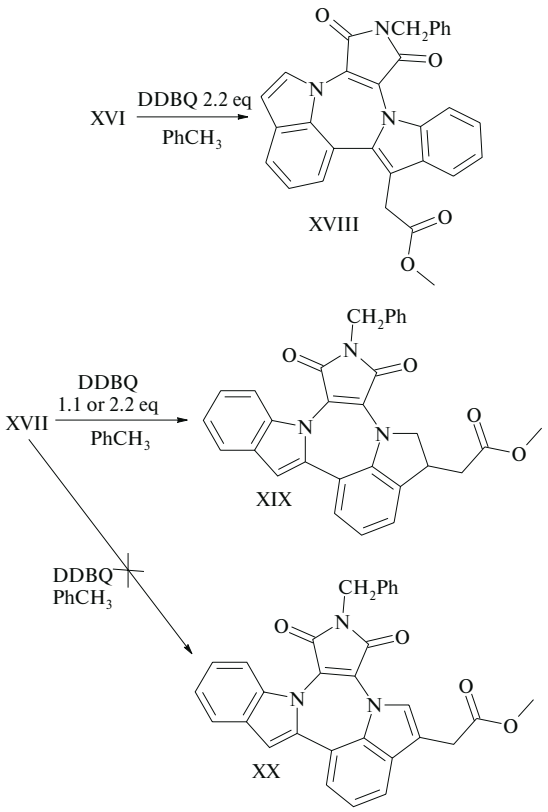


Isomers XI and XIV exhibited cyclization in the presence of CF_3COOH in CH_2Cl_2 with the formation of [1,4]diazepines containing two indoline fragments and a maleimide cycle (compounds XVI and XVII, respectively).



Compounds XVI and XVII contain two asymmetric atoms: C10, C9b (XVI) and C6, C9b (XVII). It is interesting to note that the ^1H NMR spectrum of compound XII displays two sets of signals (which is characteristic of a mixture of two racemic isomers), whereas the spectrum of compound XVI exhibits only one set of signals, which implies that the latter compound represents a single diastereomer. Protonation of the indole fragment of compound XI at position 3 leads to the formation of an indolinium ring with an asymmetric center at position 3. Closing of the seven-member cycle leads to the formation of the second indoline ring with the second asymmetric atom. It is naturally assumed that the formation of a *trans* product is preferred.



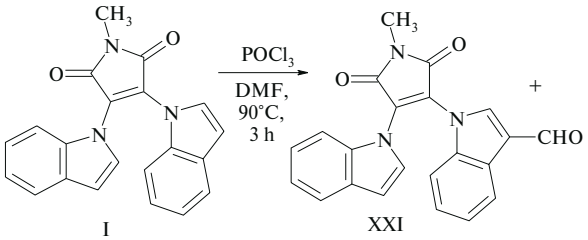


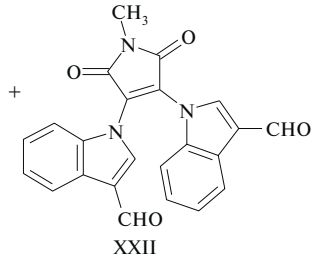
Dehydration of diindolinodiazepine XVI with DDBQ (2.2 eq.) in boiling toluene yields diindolodiazepine XVIII, while dehydration of diindolinodiazepine XVII (isomeric to XVI) leads to indoloindolinodiazepine XIX. Even in the presence of excess DDBQ, dehydration of the second indoine fragment with the formation of diazepine XX was not observed even upon 6-h boiling in toluene.

Introduction of Pharmacophore Groups or Their Precursors into Existing Polycondensed Systems

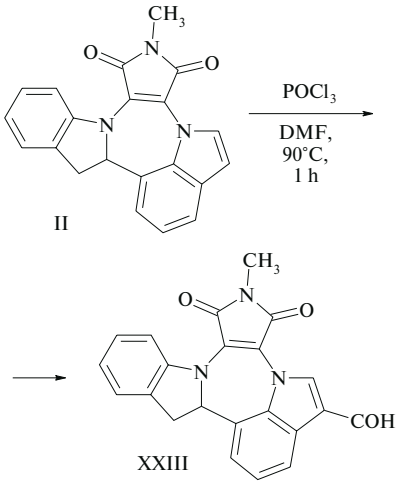
An alternative approach to the synthesis of bis(indol-1-yl)maleimides and [1,4]diazepines with annelated indole and maleimide rings is based on the introduction of pharmacophore groups or their precursors into polycondensed systems. We have used bis(indol-1-yl)maleimide (I) and [1,4]diazepines II and III (R = CH_3).

The formylation of compound I in DMF in the presence of $POCl_3$ led to the formation of a mixture of mono- and dialdehydes (XXI + XXII), which was separated into components by chromatography with a yield of 70% (XXI) and 12% (XXII).





The formylation of compound II under analogous conditions led to compound XXIII (yield, 70%).



EXPERIMENTAL CHEMICAL PART

The NMR spectra were measured using a Varian VXR-400 spectrometer operating at a working frequency of 400 MHz (^{1}H NMR) and 100.6 MHz (^{13}C NMR), using DMSO-d_6, $CDCl_3$, and $(CD_3)_2CO$ as solvents; the chemical shifts were determined relative to the solvent signals (internal standard). Analytical TLC was performed on Kieselgel F_{294} (Merck, Germany) plates, and column chromatography, on Kieselgel 60 silica gel. The melting points were determined using a Buchi SMP-20 device without corrections. The high-resolution mass spectra were obtained using a Finnigan MAT Model 8430 spectrometer equipped with a system of direct sample introduction (electron impact energy, 70 eV; ion source temperature, 250°C) and with a computer-controlled SS-300 data acquisition and processing system. The survey electron-impact mass spectra were recorded on a Finnigan SAQ Model 710 spectrometer (70 eV; 150°C).

The organic extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuum. The initial 3,4-dibromomaleimide VIII was obtained using a classical method [3], 1-methyl- and 1-benzyl-3,4-dibromomaleimides were obtained as described previously [1].

1-[4-Bromo-2, 5-dioxo-1H-pyrrol-3-yl]-(1H-2,3-dihydroindol-3-yl)acetic acid methyl ester (IX). To a solution of 2 g (10.5 mmole) of 2,3-dihydroindol-3-yl)acetic acid methyl ester (VII) and 2.29 g (8 mmole) of 1-benzyl-3,4-dibromomaleimide (VIII) in 5 ml DMF was added 2 ml

(14.2 mmole) of Et_3N. The mixture was stirred for 12 h at room temperature, diluted with 50 ml of EtOAc, washed sequentially with 1 – 2 M aqueous HCl solution (2 × 50 ml), aqueous $NaHCO_3$ solution (2 × 50 ml), and saturated NaCl solution (50 ml), dried in air, and evaporated to obtain an orange-red oil residue, which was recrystallized from ethanol to yield 2.58 g (72%) of compound IX; m.p., 62 – 63°C; R_f, 0.15 (*n*-heptane–EtOAc, 1 : 6).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 2.67 (dd, 1H, J 9.03 Hz, 16.6 Hz), 2.86 (dd, 1H, J 5.19 Hz, 18.84 Hz), 3.69 – 3.76 (m, 1H), 4.09 (dd, 1H, J 6.35 Hz, 10.99 Hz), 4.50 (dd, 1H, J 8.55 Hz, 10.80 Hz), 4.64 (s, 2H), 6.99 (t, 2H, J 7.82 Hz), 7.18 (t, 2H, J 7.76 Hz), 7.26 – 7.36 (m, 5H);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 37.2, 37.3, 41.3, 51.5, 59.2, 89.5, 116.2, 123.1, 124.0, 126.7, 127.3, 127.4, 128.4, 134.9, 136.6, 141.8, 141.7, 165.3, (C = O), 116.1 (C = O), 171.9 (COOMe);

Mass spectrum, *m/z* (I_{rel}, %): 456 (100), 380 (60).

1-[4-Bromo-2,5-dioxo-1-benzyl-1H-pyrrol-3-yl]-(1H-indol-3-yl)acetic acid methyl ester (X). To a solution of 2.58 g (5.8 mmole) of compound IX in 50 ml toluene was added 1.52 g (6.70 mmole) of DDBQ and the mixture was boiled with reflux for 1 h, cooled to room temperature, and poured into 200 ml of saturated aqueous $NaHCO_3$ solution. The mixture was stirred for 20 min and allowed to stand until phase separation. The organic layer was separated, and the aqueous phase was repeatedly extracted with 50 ml EtOAc. The organic phases were combined and washed sequentially with saturated aqueous $NaHCO_3$ solution (2 × 50 ml) and saturated NaCl solution (50 ml), dried in air, and evaporated to obtain compound X in the form of an orange oil of with a yield of 1.85 g (72%); m.p., 63 – 64 g; R_f, 0.13 (*n*-heptane – EtOAc, 6 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 67 (s, 3H), 3.89 (s, 2H), 4.77 (s, 2H), 7.25 (t, 1H, J 7.50 Hz), 7.28 – 7.32 (m, 2H), 7.35-7.42 (m, 5H, Ph), 7.49 (d, 1H, J 7.87 Hz), 7.58 (s, 1H, indole H2), 7.62 (d, 1H, J 7.63 Hz);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 29.9, 41.8, 51.6, 111.1, 113.0, 114.0, 119.2, 121.7, 122.8, 126.4, 127.4, 127.4 (2C), 128.7, 134.3, 136.0, 138.3, 164.9 (C=O), 165.3 (C=O), 171.0 (COOMe);

Mass spectrum, *m/z* (I_{rel}, %): 454 (83), 395 (100).

1-[4-(2, 3-Dihydro-1H-indol-1-yl)-2.5-dihydro-2, 5-dioxo-1-benzyl-1H-pyrrol-3-yl]-(1H-indol-3-yl)acetic acid methyl ester (XI). To a solution of 0.36 g (8.1 mmole) of methyl ester X and 0.2 ml (0.9 mmole) of indoline in 10 ml DMF was added 0.2 ml (1.4 mmole) of Et_3N. The mixture was stirred for 24 h at room temperature, diluted with 30 ml of EtOAc, washed sequentially with 1 – 2 M aqueous HCl solution (2 × 30 ml), saturated aqueous $NaHCO_3$ solution (20 ml), and saturated NaCl solution (20 ml), dried in air, and evaporated. The residue was purified by chromatography on a silica gel column eluted with an *n*-heptane – $(CH_3)_2CO$ (10 : 1) mixture. Upon recrystallization, compound XI was obtained in the form of an orange-red crystalline powder with a yield of 0.26 g (70%); m.p., 63 – 65°C; R_f, 0.40 (*n*-heptane – EtOAc, 3 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.06 (2H, t, J 7.87 Hz), 3.61 (3H, s), 3.77 (2H, s), 4.23 (2H, t, J 7.87 Hz), 4.72 (2H, s), 6.10 (1H, d, J 7.86 Hz), 6.48 (1H, t, J 7.76 Hz), 6.64 (1H, t, J 7.41 Hz), 6.91 – 7.03 (3H, m), 7.18 (1H, d, J 7.38 Hz), 7.29 (1H, m), 7.36 – 7.42 (6H, m);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 28.8, 30.2, 40.8, 51.6, 52.6, 107.2, 110.4, 111.0, 112.2, 118.7, 120.0, 122.1, 122.6, 124.2, 126.0, 127.0, 127.2, 127.4, 127.5, 128.5, 131.9, 132.9, 136.8, 136.9, 142.3, 165.9 (C = O), 167.2 (C = O), 171.5 (COOMe);

Mass spectrum, *m/z* (I_{rel}, %): 491 (100), 344 (80).

[1-(Benzyl-4-indol-1-yl)-2, 5-dioxo-2, 3-dihydro-1H-pyrrol-3-yl]-(1H-indol-3-yl)acetic acid methyl ester (XV). To a solution of 50 mg (0.1 mmole) of compound XI, in 10 ml toluene was added 45 mg (0.2 mmole) of DDBQ and the mixture was boiled with reflux for 1 h, cooled to room temperature, and poured into 50 ml of saturated aqueous $NaHCO_3$ solution. The mixture was stirred for 20 min and allowed to stand until phase separation. The organic layer was separated, and the aqueous phase was repeatedly extracted with EtOAc (2 × 10 ml). The organic phases were combined and washed sequentially with saturated aqueous $NaHCO_3$ solution (2 × 15 ml) and saturated NaCl solution (10 ml), dried in air, and evaporated. The residue was purified by chromatography on a silica gel column eluted with an *n*-heptane – EtOAc (4.5 : 1) mixture. Compound X was obtained in the form of an orange-red oil with a yield of 35 mg (70%); R_f, 0.39 (*n*-heptane – EtOAc, 3 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.65 (s, 3H), 3.87 (s, 2H), 4.83 (s, 2H), 6.55 (d, 1H, J 8.24 Hz), 6.62 (d, 1H, J 8.42 Hz), 6.69 – 6.74 (m, 2H), 6.77 (d, 1H, J 3.48 Hz), 6.91 (tt, 2H, J 7.04), 7.32 (d, 1H, J 7.33 Hz), 7.37 – 7.41 (m, 3H), 7.46 (d, 1H, J 3.48 Hz), 7.68 (s, 1H);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 30.1, 41.4, 51.8, 106.7, 111.0, 111.1, 113.1, 119.2, 120.7, 121.4, 121.5, 122.7, 122.8, 126.4, 127.6, 127.7 (2C), 128.0, 128.1, 128.2, 128.6 (2C), 135.1, 135.2, 136.4, 166.4 (2C, C=O), 171.3 (COOMe);

High-resolution mass spectrum, *m/z* (I_{rel}, %): anal. calcd. for $C_{30}H_{23}N_3O_4$, 489.1688; found, 489.1689 $[M]^+$ (100), 430 (45) $[M^+–COOMe]$, 416 (20) $[M^+–CH_2COOMe]$, 338 (10) $[M+–COOMe–C_7H_7]$.

1-[2, 5-Dihydro-4-(1H-indol-1-yl)-2.5-dioxo-1-benzyl-1H-pyrrol-3-yl]-2,3-dihydro-(1H-indol-3-yl)acetic acid methyl ester (XIV). To a solution of 0.33 g (1 mmole) of compound XIII and 0.23 ml (1.2 mmole) of compound VII in 5 ml DMF was added 0.2 ml (1.4 mmole) of Et_3N. The mixture was stirred for 24 h at room temperature, diluted with 50 ml of EtOAc, washed sequentially with 1 – 2 M aqueous HCl solution (2 × 20 ml), saturated aqueous $NaHCO_3$ solution (2 × 20 ml), and saturated NaCl solution (20 ml), dried in air, and evaporated to obtain compound

XIV in the form of an orange-red oil with a yield of 0.3 g (70%); R_f, 0.41 (*n*-heptane – EtOAc, 3 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 2.72 (dd, 1H, J 9.34 Hz, 16.84 Hz), 2.85 (dd, 1H, J 5.30 Hz, 16.66 Hz), 3.68 (s, 3H), 3.73 (m, 1H), 4.14 (dd, 1H, J 5.96 Hz, 11.25 Hz), 4.59 (dd, 1H, J 9.20 Hz, 11.16 Hz), 4.74 (s, 2H), 5.93 (d, 1H, J 6.06 Hz), 6.46 (t, 1H, J 7.73 Hz), 6.61 (d, 1H, J 3.35 Hz), 6.65 (t, 1H, J 7.41 Hz), 6.95 – 6.99 (m, 2H), 7.06 (d, 1H, J 7.33 Hz), 7.26 (d, 1H, J 7.42 Hz), 7.31 (d, 1H, J 6.81 Hz), 7.36 – 7.43 (m, 5H), 7.47 (d, 1H, J 6.15 Hz);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 37.1, 37.7, 40.9, 51.5, 104.3, 107.4, 111.3, 111.9, 120.27, 120.33, 121.9, 122.7, 123.7, 126.6, 127.4 (2C), 127.6 (2C), 128.5 (2C), 128.6, 132.4, 134.1, 136.5, 136.8, 142.1, 166.2 (C = O), 167.2 (C = O), 171.9 (COOMe);

Mass spectrum, *m/z* (I_{rel}, %): 491 (100), 344 (50).

(2-Benzyl-1,3-dioxo-2,3,5,6,9b,10-hexahydro-1H-indolo[1′,7′:4,5,6]pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-a]-indol-10-yl)acetic acid methyl ester (XVI). To a solution of 165 mg (0.37 mmole) of compound XI in 20 ml of CH_2Cl_2 was added 0.33 ml (3.7 mmole) of CF_3COOH and the reaction mixture was stirred at room temperature for three days and poured into 50 ml of EtOAc. This mixture was washed sequentially with saturated aqueous $NaHCO_3$ solution (2 × 20 ml) and saturated NaCl solution (20 ml), dried in air, and evaporated. The residue was purified by chromatography on a silica gel column eluted with an *n*-heptane – EtOAc (6 : 1) mixture. Compound XVI was obtained in the form of a dark violet oil with a yield of 100 mg (60%); R_f, 0.53 (*n*-heptane – EtOAc, 3 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 2.71 (m, 2H), 3.07 – 3.17 (m, 2H), 3.60 (s, 3H), 4.26 – 4.34 (m, 2H), 4.58 – 4.69 (m, 4H), 6.51(t, 1H, J 7.69 Hz), 6.68 (t, 1H, J 7.37 Hz), 6.88 (t, 1H, J 7.69 Hz), 7.02 (t, 1H, J 7.54 Hz), 7.18 – 7.23 (m, 2H), 7.30 (d, 1H, J 8.10 Hz), 7.34 – 7.39 (m, 5H);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 27.7, 38.5, 40.4, 50.5, 51.5, 68.3, 109.1, 112.2 (p), 118.7, 121.5, 124.58, 124.6, 124.8, 127.3, 127.4, 127.8, 127.9, 128.6, 129.3, 129.5, 133.4, 137.2, 143.5, 144.6, 164.8 (C=O), 165.7 (C=O), 171.7 (COOMe);

High-resolution mass spectrum, *m/z* (I_{rel}, %): anal. calcd. for $C_{30}H_{25}N_3O_4$, 491.1845; found, 491.1839 $[M]^+$ (100), 432 (5) $[M^+–COOMe]$, 418 (20) $[M^+–CH_2COOMe]$.

(2-Benzyl-1,3-dioxo-2,3,5,6,9b,10-hexahydro-1H-indolo[1′,7′:4,5,6]pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-a]indol-6-yl)acetic acid methyl ester (XVII).To a solution of 265 mg (0.59 mmole) of compound XIV, in 30 ml of CH_2Cl_2 was added 0.5 ml (5.7 mmole) of CF_3COOH and the mixture was stirred at room temperature for 1 h and poured into 50 ml of EtOAc. This mixture was washed sequentially with saturated aqueous $NaHCO_3$ solution (2 × 20 ml) and saturated NaCl solution (20 ml), dried in air, and evaporated. The residue was purified by chromatography on a silica gel column eluted with an *n*-heptane – EtOAc (6 : 1) mixture. Compound XVII was obtained in the form of a dark violet oil with a yield of 250 mg (80%); R_f, 0.48 (*n*-heptane – EtOAc, 3 : 1). The NMR spectrum exhibit two sets of signals, which corresponds to a mixture of two diastereomers.

High-resolution mass spectrum, *m/z* (I_{rel}, %): anal. calcd. for $C_{30}H_{25}N_3O_4$, 491.1845; found, 491.1836 $[M]^+$ (100), 432 (5)$[M^+$-COOMe], 418 (20)$[M^+$- $CH_2COOMe]$.

(2-Benzyl-1,3-dioxy-2,3-dihydro-1H-indolo[1′,7′:4,5,6]-pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-a]indol-10-yl)acetic acid methyl ester (XVIII). A solution of 200 mg (0.4 mmole) of compound XVI and 180 mg (0.8 mmole) DDBQ in 30 ml of toluene was boiled for 3 h, cooled to room temperature, poured into 50 ml of saturated aqueous $NaHCO_3$ solution, stirred for 20 min, and allowed to stand until phase separation. The organic layer was separated, and the aqueous phase was repeatedly extracted with EtOAc (30 ml). The organic phases were combined and washed sequentially with saturated aqueous $NaHCO_3$ solution (2 × 50 ml) and saturated NaCl solution (50 ml), dried in air, and evaporated. The residue was purified by chromatography on a silica gel column eluted with an *n*-heptane – EtOAc (4.5 : 1) mixture. Compound XVIII was obtained in the form of an orange-red oil with a yield of 150 mg (75%); R_f, 0.36 (*n*-heptane – EtOAc, 3 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.67 (s, 3H), 3.91 (s, 2H), 4.73 (s, 2H), 6.83 (d, 1H, J 3.6 Hz), 7.17 (t, 1H, J 7.83 Hz), 7.24 (t, 1H, J 8.04 Hz), 7.28 – 7.32 (m, 2H), 7.33 – 7.41 (m, 5H), 7.49 (d, 1H, J 8.28 Hz), 7.57 – 7.61 (m, 2H), 8.08 (d, 1H, J 3.57 Hz);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 31.0, 41.2, 52.2, 108.6, 113.9, 114.1, 116.6, 118.0, 119.1, 121.4, 121.9, 123.1, 123.2, 124.2, 127.35 (2C), 127.4, 128.4, 128.5 (2C), 130.7, 130.8, 132.8, 136.1, 136.5, 136.8, 164.1 (C=O), 165.7 (C=O), 171.2 (COOMe);

High-resolution mass spectrum, *m/z* (I_{rel}, %): anal. calcd. for $C_{30}H_{21}N_3O_4$, 487.1532; found, 491.1539 $[M]^+$ (100), 428 (50) $[M^+–COOHMe]$, 369 (10) $[M^+–C_7H_7]$.

(2-Benzyl-1,3-dioxy-2,3-dihydro-1H-indolo[1′,7′:4,5,6]-pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-a]indol-6-yl)acetic acid methyl ester (XIX) was obtained from compound XVII using a procedure analogous to that described above for compound XVIII. After purification on a silica gel column in an *n*-heptane – EtOAc (4.5 : 1) mixture, compound XIX was obtained in the form of an orange-red oil with a yield of 75 mg (75%); R_f, 0.64 (*n*-heptane – EtOAc, 6 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 2.65 (dd, 1H, J 9.28 Hz, 17.02 Hz), 2.87 (dd, 1H, J 5.15 Hz, 16.82 Hz), 3.64 (m, 4H, multiplet from C6-H of indole fragment and singlet from OCH_3), 4.11 (dd, 1H, J 6.10 Hz, 12.21 Hz), 4.55 (dd, 1H, J 9.46 Hz, 12.14 Hz), 4.66 (s, 2H), 6.90 (s, 1H, C10-H), 6.94 (t, 1H, J 7.63 Hz), 7.01 (t, 1H, J 7.02 Hz), 7.07 (t, 1H, J 7.86 Hz), 7.13 (d, 1H, J 7.39 Hz), 7.22 (d, 1H, J 8.06 Hz), 7.28 – 7.31 (m, 1H), 7.33 – 7.38 (m, 4H), 7.44 (d, 1H, J 7.86 Hz), 7.61 (d, 1H, J 7.63 Hz);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 30.6, 35.8, 38.4, 51.6, 54.5, 109.0, 110.7 (p), 113.9, 116.9 (p), 120.3, 121.2, 123.1, 123.9, 124.4, 127.0, 127.3 (2C), 127.4, 128.5 (2C), 129.6 (p), 134.9 (p), 135.0 (p), 135.7 (p), 136.9 (p), 137.0 (p), 144.2 (p), 164.0 (C=O), 164.5 (C=O), 171.9 (COOMe);

High-resolution mass spectrum, *m/z* (I_{rel}, %): anal. calcd. for $C_{30}H_{23}N_3O_4$, 487.1688; found, 489.1695 $[M]^+$ (100), 369 (120) $[M^+–C_7H_7]$.

2,5-Dihydro-2,5-dioxo-3-(3-formylindol-1-yl)-4-(indol-1-yl)-methyl-1H-pyrrole (XXI) and 2,5-dihydro-2,5-dioxo-3,4-bis(3-formylindol-1-yl)-1-methylpyrrole-2,5-dione (XXII). To a solution of 250 mg (0.73 mmole) of compound I in 10 ml DMF cooled to 0°C was gradually added with stirring 0.4 ml (4.27 mmole) of $POCl_3$ and the stirring was continued at this temperature for 10 min. Then, the reaction mass was heated to 80°C and stirred at this temperature for 1 h, cooled to room temperature, diluted with 20 ml of EtOAc, and neutralized by pouring into 50 ml of saturated aqueous Na_2CO_3 solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 20 ml). The organic extracts were combines, washed with saturated aqueous NaCl solution (2 × 20 ml), dried in air, and evaporated to obtain a mixture of products in the form of an orange-red amorphous powder. Separation of this substance on a silica gel column eluted with an *n*-heptane – EtOAc (2 : 1) yields the following individual compounds:

Compound XXI was obtained in the form of an orange crystalline powder upon recrystallization from ethanol with a yield of 170 mg (70%); m.p., 262 – 264°C; R_f, 0.30 (*n*-heptane – EtOAc, 2 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.16 (s, 3H, NCH_3), 6.68 (d, 2H, J 8.28 Hz), 6.84 (d,1H, J 3.58 Hz), 6.88 (t, 1H, J 7.32 Hz), 6.93 (t, 1H, J 7.83 Hz), 7.09 (t, 1H, J 7.83 Hz), 7.47 (d, 1H, J 7.69 Hz), 7.68 (d, 1H, J 3.48 Hz), 8.01 (d, 1H, J 7.83 Hz), 8.57 (s, 1H), 10.13 (s, 1H, CHO);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 24.35 (CH_3), 107.68, 110.88, 111.21, 120.50, 120.79, 121.01, 121.18, 122.01, 122.88, 123.75, 123.92, 124.45, 126.42, 127.84, 128.62, 134.84, 136.32, 139.60, 166.16 (C=O), 166.28 (C=O), 186.29 (CHO). $C_{22}H_{15}N_3O_3$.

Compound XXII was obtained in the form of an orange crystalline powder upon recrystallization from ethanol with a yield of 30 mg (12%); m.p., 262 – 264°C; R_f, 0.28 (*n*-heptane – EtOAc, 2 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.20 (s, 3H, NCH_3), 6.78 (d, 2H, J 8.32 Hz), 6.92 (t, 2H, J 7.23 Hz), 7.11 (t, 2H, J 7.33 Hz), 8.01 (d, 1H, J 7.77 Hz), 8.61 (s, 3H), 10.15 (s, 2H, –CHO);

^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 24.51 (CH_3), 111.19, 121.25, 121.38, 124.08, 124.12, 124.73, 136.03, 139.39, 165.76 (C = O), 186.53 (CHO). $C_{23}H_{15}N_3O_4$.

2-Methyl-1,3-dioxo-1,3,9b,10-tetrahydro-1H-in-dolo[1′,7′:4,5,6]pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-a]in-dole-6-carbaldehyde (XXIII). To a solution of 200 mg (0.58 mmole) of compound II in 20 ml DMF cooled to 0°C was gradually added with stirring 0.3 ml (3.21 mmole) of $POCl_3$ and the stirring was continued at this temperature for 10 min. Then, the reaction mass was heated to 80°C and stirred at this temperature for 2 h, cooled to room temperature, diluted with 40 ml of EtOAc, and neutralized by pouring into 60 ml of saturated aqueous Na_2CO_3 solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 20 ml). The organic extracts were combines, washed with saturated aqueous NaCl solution (2 × 20 ml), dried in air, and evaporated to obtain a mixture of products in the form of an crimson amorphous powder. Separation of this substance on a silica gel column eluted with an *n*-heptane – EtOAc (2 : 1) followed by recrystallization yields compound XXIII in the form of a crimson crystalline powder with a yield of 130 mg (31%); m.p., > 300°C; R_f, 0.37 (*n*-heptane–EtOAc, 2 : 1).

^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.03 (s, 3H), 3.82 (dd, 1H, J 17.11 Hz, 9.3 Hz), 3.92 (dd, 1H, J 18.32 Hz, 3.62 Hz), 5.47 (dd, 1H, J 4.79 Hz, 4.13 Hz), 6.88 (t, 1H, J 6.26 Hz), 7.00 (d, 1H, J 7.01 Hz), 7.07 (t, 1H, J 7.07 Hz), 7.30 (d, 1H, J 6.19 Hz), 7.39 (t, 1H, J 7.67 Hz), 7.50 (d, 1H, J 7.50 Hz), 8.21 (d, 1H, J 7.37 Hz), 9.24 (s, 1H), 10.17 (c, 1H).

Mass spectrum, *m/z* (I_{rel}, %): 369 (100), 284 (29).

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