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Nucleophilic substitution and cyclization reactions involving quaternized 3-dimethylaminomethyl derivatives of 3,4-bis(indol-1-yl)maleimide and 3-(indol-1-yl)-4-(indolin-1-yl)maleimide

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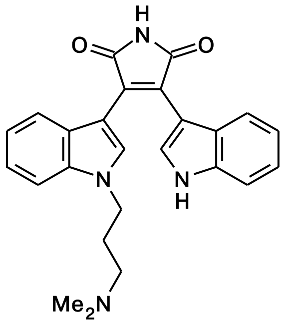
A dialkylaminomethylation reaction (the Mannich reaction) of 3,4-bis(indol-1-yl)-maleimides and 3-(indol-1-yl)-4-(indolin-1-yl)maleimides leads to mono- and di(dimethylamino) derivatives at position 3 of one or two indole rings. A series of 3,4-bis(indol-1-yl)-maleimides and 3-(indol-1-yl)-4-(indolin-1-yl)maleimides containing ω-hydroxyalkyloxymethyl substituents at position 3 of the indole ring was obtained by the reaction of iodomethylates of these compounds with ethylene glycol and other α,ω-alkanediols. The reaction of quaternary salts of bis(3-dimethylaminomethylindol-1-yl)maleimides with α,ω-alkanediols resulted in the isolation of 3,4-bis(3-ω-hydroxyalkyloxymethylindol-1-yl)maleimides. Upon heating iodomethylate of 3-(3-dimethylaminoindol-1-yl)-4-(indolin-1-yl)maleimide in pyridine, 5,6-dihydro-10-methyl-1*H*-indolo[1´,7a´,7´:4,5,6]pyrrolo[3´,4´:2,3]-[1,4]diazepino[1,7-*a*]-indole-1,3(2*H*)-dione was obtained due to the intramolecular alkylation and formation of the bond between position 2 of the indole and position 7 of the indoline rings.

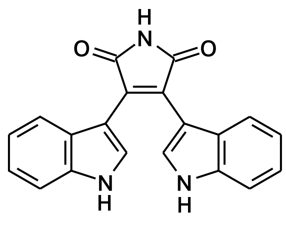
Key words: bisindolylmaleimides, the Mannich reaction, polyannulated diazepinoindoles.

Development and study of new proteinkinase inhibitors is an important direction in the search for efficient pharmaceutical drugs. There are known highly active proteinkinase inhibitors of the class of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles,[1] such as alkaloid staurosporin and related structures, many of which are in the different steps of clinical studies as antitumor medicines.[2] These compounds are built based on 3,4-bis(indol-3-yl)maleimide (Bis-IV), which, as 3,4-bis(indol-3-yl)maleimide derivatives containing an aminoalkyl substituent at one of the nitrogen atoms, for example Bis-I, is highly efficient proteinkinase C inhibitor (see Refs 3 and 4).

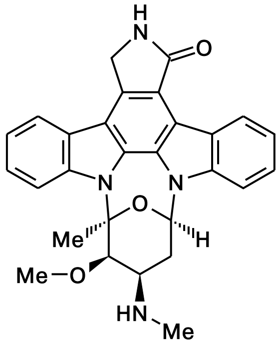
Earlier, there have been described 3,4-bis(indol-1-yl)-maleimides isomeric to the structures of the type Bis (3,4-bis(indol-3-yl)maleimides), among which efficient proteinkinase inhibitors have been also found.[5] We have developed a method for the introduction of hydroxyalkyloxymethyl residues at position 3 of 3,4-bis(indol-1-yl)maleimide and 3-(indol-1-yl)-4-(indolin-1-yl)maleimide molecules. Such hydroxyalkyloxymethyl substituents can be considered as acyclic analogs of C-deoxyglycosides containing fragment of a carbohydrate ring C—O—(C)$_n$—OH (as it is described for acyclonucleosides[6]).



Bis-I



Bis-IV



Staurosporine

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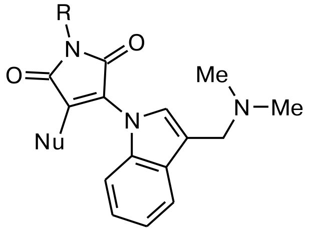
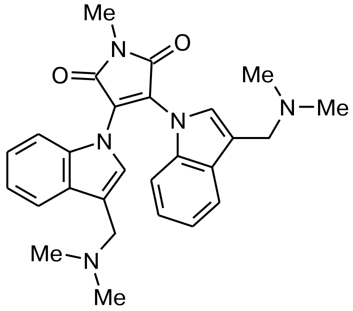
Results and Discussion

3-(3-Dimethylaminomethylindol-1-yl)maleimides containing 2,3-dihydroindole (**1a**,**b**) or indole (**2a**,**b**) residues at position 4 of the maleimide ring, as well as 3,4-bis(3-dialkylaminomethylindol-1-yl)maleimide derivatives (**3**), were obtained by aminomethylation of the corresponding 3,4-substituted maleimides.[5]



1a,b, **2a,b**



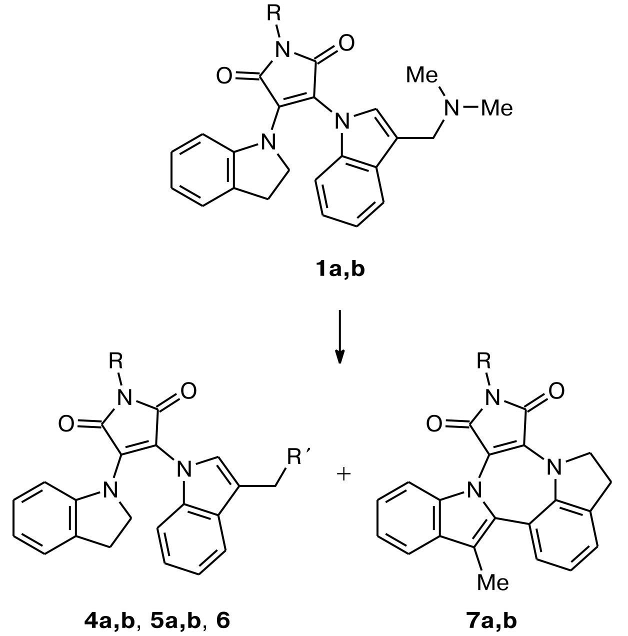
3

Compound	R	Nu
1a	H	2,3-Dihydroindol-1-yl
1b	Me	2,3-Dihydroindol-1-yl
2a	H	Indol-1-yl
2b	Me	Indol-1-yl

The present work is aimed on the structural modification of the dialkylaminomethyl fragment in compounds **1**—**3**. A possibility of replacement of activated dimethylaminomethyl group with the ω-hydroxy residue (using ethylene glycol, 1,3-propanediol, 1,4-butanediol, diethylene glycol), as well as further structural modification of the terminal hydroxy group, have been studied.

To activate the dimethylaminomethyl group of compounds **1**—**3**, quaternization was performed with methyl iodide at room temperature in THF. Condensation of **1a**,**b** with glycols or mercaptoethanol upon heating in pyridine yielded hydroxyalkoxymethyl derivatives **4**—**6** in 35—50% yields. In addition to the products of substitution of the dimethylamino group **4a** and **4b**, cyclization products **7a** and **7b**, respectively, were also isolated in about 15% yield (Scheme 1). The cyclization products **7a** and **7b** were also obtained under analogous conditions in about 15% yield without addition of glycols into the reaction mixture.

Scheme 1

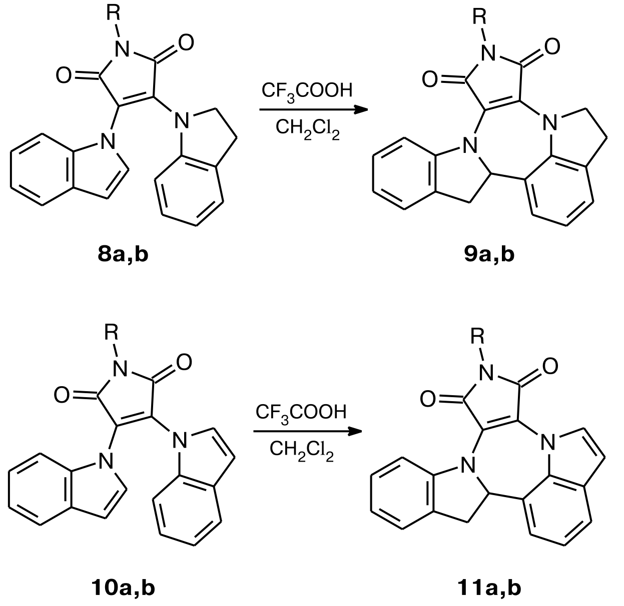


R = H (**a**), Me (**b**); R′ = $O(CH_2)_3OH$ (**4**), $O(CH_2)_2OH$ (**5**), $S(CH_2)_2OH$ (**6**)

Reagents and conditions: 1) MeI, THF; 2) R′H, pyridine, reflux.

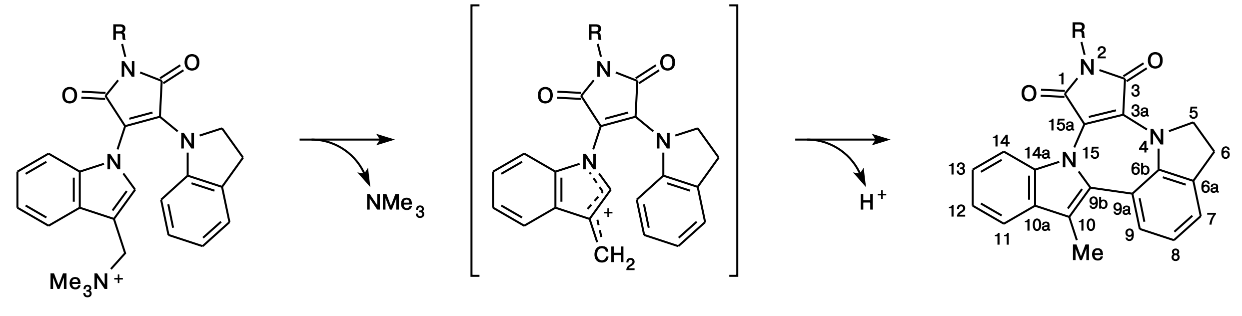
Diazepines[1,4] containing a maleimide ring annulated with the indoline **9a**,**b** or indole and indoline rings **11a**,**b** have been obtained earlier[7,8] by the cyclization of 3-(indol-1-yl)-4-(indolin-1-yl)maleimides **8a**,**b** or bis(indol-1-yl)maleimides **10a**,**b** upon the action of acids (Scheme 2). It should be noted that cyclization of maleimides **1a**,**b**

Scheme 2



R = H (**a**), Me (**b**)

Scheme 3



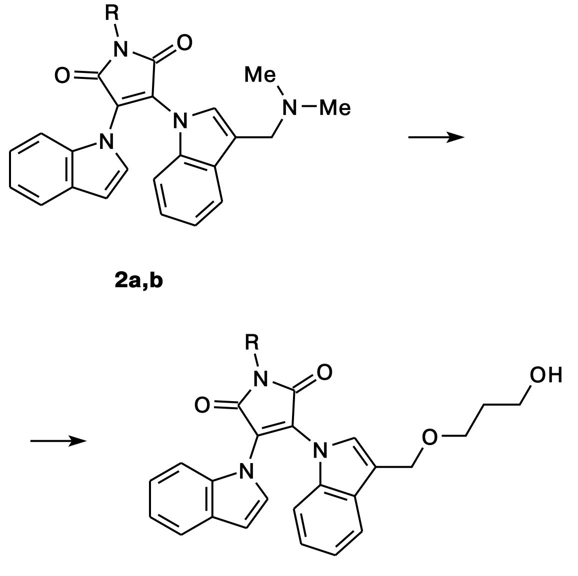
1a,b

7a,b

containing a quaternized aminomethyl fragment in the presence of pyridine does not lead to the loss of aromaticity of the indole ring (Scheme 3).

Monosubstituted 3-dimethylaminomethyl derivatives of 3,4-bis(indol-1-yl)maleimide **2a,b** upon condensation with propane-1,3-diol give compounds **12a,b** in 45% yields (Scheme 4).

Scheme 4



2a,b

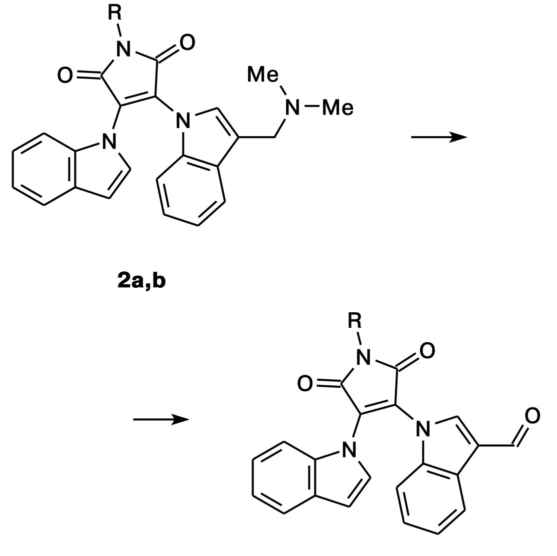
12a,b

R = H (**a**), Me (**b**)

Reagents and conditions: 1) MeI, THF; 2) $HO(CH_2)_3OH$, pyridine, reflux.

The cyclization products of compounds **2a,b**, analogous to compounds **7**, were not obtained. A prolonged reflux of their quaternary iodomethylates in pyridine for 6 days led only to the oxidation products **13a**,**b** in 15—20% yields. Compound **13b** completely corresponds to the earlier described 1-[4-(1*H*-indol-1-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indol-3-carbaldehyde (Scheme 5).[7]

Scheme 5



2a,b

13a,b

R = H (**a**), Me (**b**)

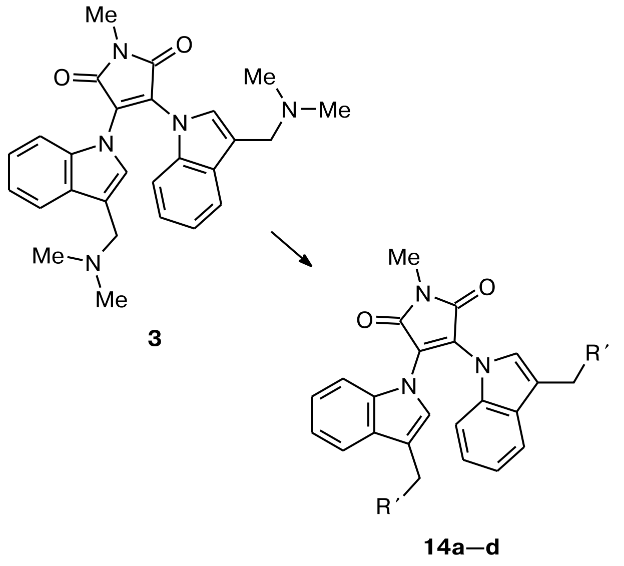
Reagents and conditions: 1) MeI, THF; 2) pyridine, reflux 140 h.

A quaternized derivative of 3,4-bis(3-dialkylaminomethylindol-1-yl)-1-methylmaleimide **3** gives the condensation reaction with glycols under more drastic conditions. The reaction was carried out in boiling collidine and led to the symmetric derivatives **14** in 30—35% yields (Scheme 6).

No product of intramolecular cyclization with the simultaneous replacement of both trimethylamine residues with terminal hydroxy groups of α,ω-diols was obtained.

The terminal hydroxy group of compounds **4a**,**b** and **5b** was activated with methanesulfonyl chloride (MsCl) in

Scheme 6

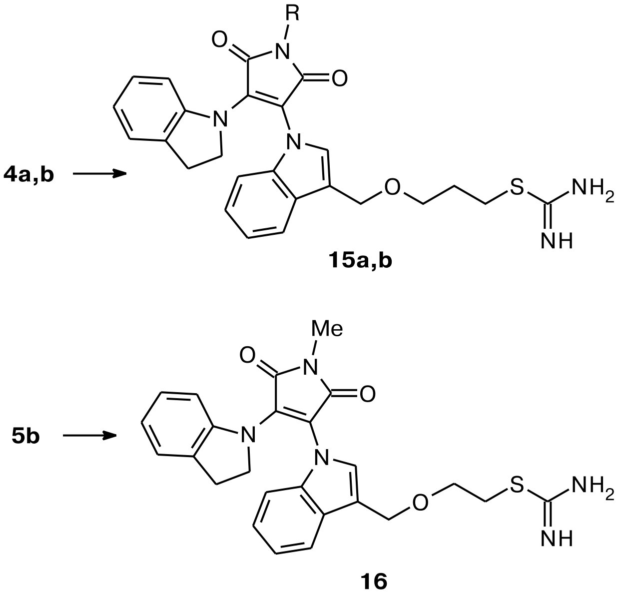


14	R′	14	R′
a	$O(CH_2)_2OH$	**c**	$O(CH_2)_4OH$
b	$O(CH_2)_3OH$	**d**	$O(CH_2)_2O(CH_2)_2OH$

Reagents and conditions: 1) MeI, THF; 2) R′H, collidine, reflux.

THF and replaced with thiourea, that resulted in obtaining compounds **15a,b** and **16** in 50—55% yields (Scheme 7).

Scheme 7



R = H (**a**), Me (**b**)

Reagents and conditions: 1) MsCl, THF; 2) $(NH_2)_2CS$, DMF.

Physico-chemical and spectroscopic characteristics of compounds obtained are given in Tables 1—3. ^{1}H and ^{13}C NMR spectra, as well as high resolution mass spectra confirm the structures of new compounds obtained.

The ^{1}H NMR spectra of compounds **4a,b**, **5b**, **6b**, as well as **15a,b** and **16**, exhibit signals characteristic of positions 2 and 3 of the indoline ring (two triplets with δ = = 3.06—3.08 and 4.20—4.25), of position 2 of the indole ring (a singlet at δ = 7.3—7.4). For the symmetric compounds **14a**,**b**,**c**,**d**, the downfield signals have the double intensity. The ^{13}C NMR spectra of the compounds exhibit signals (δ = 166 and 167) characteristic of the carbonyl groups of the maleimide ring, a characteristic signal of the carbon atom of the thiourea residue (δ = 169—170) is present in compounds **15a**,**b** and **16**. The ^{1}H NMR spectra of compounds **7a,b** exhibit signals for the methyl group at position 3 of the indole ring (a singlet at δ 2.27—2.30, position 10 of the polyannulated system) and no signal for the proton at position 2 of the indole ring. Two characteristic signals of the dihydroindole ring are observed in the high field (triplets at δ = 3.04—3.09 and 4.33—4.39), which correspond to positions 5 and 6. The detailed ^{1}H NMR spectra of compounds **7a,b** are given in Table 3.

Experimental

NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR), using the signal for $SiMe_4$ as a reference. High resolution mass spectra ESI were recorded on a micrOTOF-Q II instrument (Bruker Daltonics GmbH, Germany). Solutions of the samples (0.1 mg mL^{-1} in MeOH or MeCN) were injected directly into the ESI source using a syringe pump with the flow rate 3 μL min^{-1}. The positively and negatively charged ions were analyzed under the following conditions: the voltage on the capillary was –4.5 and +4 kV, respectively, the pressure of nitrogen in the sprayer was 0.4 Bar (5.8 psi), the flow rate of a drying gas was 4.0 L min^{-1}, and the temperature of the source was 180 °C. The instrument was calibrated using a 1% calibrating solution for ESI (Sigma-Aldrich, Switzerland) in 95% aqueous MeCN. The accuracy of measurements was 0.43 ppm in the range of masses between 118.086255 and 2721.894829. Solvents containing more than 98% of the main substance and purposed for the liquid mass spectrometry were used for the measurements.

Mass spectra were recorded on a Finnigan SAQ 710 instrument (70 eV) (direct injection, the temperature of a source of ions was 150 °C) using electron impact method (EI).

Analytical TLC was performed on Silica Gel F254 plates (Merck), column chromatography on Silica Gel Merck 60 silica gel. Extracts were dried with anhydrous Na_2SO_4 and concentrated at reduced pressure. Individuality of compounds obtained was confirmed by the HPLC data. Analytical HPLC was performed on a Shimadzu LC10 chromatograph using a 4.6×250-mm Gemini 110A-C18 column with the particle size of 5 μm (Phenomenex, USA). A Shimadzu UV-VIS 10A spectrophotometer was used for detection at the wavelengths corresponding to the absorption maxima (see Table 1). The eluent consisted of 0.2% $HCOONH_4$ pH 4.5 and acetonitrile. Elution was performed in

Table 1. Physico-chemical characteristics of compounds obtained

Compound	Molecular formula	MW[a]	HRMS[b] (ESI)		MS m/z ($I_{\rm rel}$ (%))	HPLC R_t/min (C (%))[c]
			Calculated for ion	Found		
4a	$C_{24}H_{23}N_3O_4$	417.45	440.1586 $[C_{24}H_{23}N_3O_4 + Na]^+$	440.1573	417 $[M]^+$ (55), 342 $[M - O(CH_2)_3OH]^+$ (100)	12.92 (93.0)
4b	$C_{25}H_{25}N_3O_4$	431.48	454.1742 $[C_{25}H_{25}N_3O_4 + Na]^+$	454.1715	431 $[M]^+$ (80), 356 $[M - O(CH_2)_3OH]^+$ (100)	15.4 (95.7)
5b	$C_{24}H_{23}N_3O_4$	417.46	440.1586 $[C_{24}H_{23}N_3O_4 + Na]^+$	440.1564	417 $[M]^+$ (100), 356 $[M - O(CH_2)_2OH]^+$ (65)	14.35 (97.7)
6b	$C_{24}H_{23}N_3O_3S$	433.52	456.1357 $[C_{24}H_{23}N_3O_4 + Na]^+$	456.1302	433 $[M]^+$ (20), 356 $[M - S(CH_2)_2OH]^+$ (100)	17.56 (97.6)
7a	$C_{21}H_{15}N_3O_2$	341.36	—	—	—	486.0 (3.56)
7b	$C_{22}H_{17}N_3O_2$	355.39	—	—	—	500.0 (3.46)
12a	$C_{24}H_{21}N_3O_4$	415.44	438.1429 $[C_{24}H_{21}N_3O_4+Na]^+$	438.1391	415 $[M]^+$ (10), 340 $[M - O(CH_2)_3OH]^+$ (100)	12.69 (95.5)
12b	$C_{25}H_{23}N_3O_4$	429.46	452.1586 $[C_{25}H_{23}N_3O_4+Na]^+$	452.1612	429 $[M]^+$ (10), 354 $[M - O(CH_2)_3OH]^+$ (100)	17.28 (99.4)
13a	$C_{21}H_{13}N_3O_3$	355.35				
14a	$C_{27}H_{27}N_3O_6$	489.52	512.1797 $[C_{27}H_{27}N_3O_6 + Na]^+$	512.1751	489 $[M]^+$ (5), 428 $[M - O(CH_2)_2OH]^+$ (20), 367 $[M - 2(O(CH_2)_2OH)]^+$ (100)	8.88 (95.0)
14b	$C_{29}H_{31}N_3O_6$	517.57	540.2110 $[C_{29}H_{31}N_3O_6 + Na]^+$	540.2086	517 $[M]^+$ (5), 442 $[M - O(CH_2)_3OH]^+$ (15), 367 $[M - 2\ (O(CH_2)_3OH)]^+$ (100)	10.52 (93.1)
14c	$C_{31}H_{35}N_3O_6$	545.63	568.2423 $[C_{31}H_{35}N_3O_6 + Na]^+$	568.2483	545 $[M]^+$ (5), 456 $[M - O(CH_2)_3OH]^+$ (15), 367 $[M - 2(O(CH_2)_3OH)]^+$ (100)	12.46 (98.5)
14d	$C_{31}H_{35}N_3O_8$	577.62	600.2321 $[C_{31}H_{35}N_3O_8 + Na]^+$	600.2300	577 $[M]^+$ (5), 472 [M – $O(CH_2)_2O(CH_2)_2OH]^+$ (10), 367 $[M - 2\ (O(CH_2)_2O(CH_2)_2OH)$ (100)	9.42 (95.6)
15a	$C_{25}H_{25}N_5O_3S$	475.5627	475.1751 $[C_{25}H_{25}N_5O_3S]^+$	475.1710	433 $[M - CNHNH_2]^+$ (5), 342 $[M - O(CH_2)_3SCNHNH_2]^+$ (100)	4.16 (98.5)
15b	$C_{26}H_{27}N_5O_3S$	489.59	490.1912 $[C_{26}H_{28}N_5O_3S]^+$	490.1902	447 $[M - CNHNH_2]^+$ (15), 356 $[M - O(CH_2)_3SCNHNH_2]^+$ (100)	10.45 (95.1)
16	$C_{25}H_{25}N_5O_3S$	475.56	476.1756 $[C_{25}H_{26}N_5O_3S]^+$	476.1804	433 $[M - CNHNH_2]^+$ (15), 356 $[M - O(CH_2)_2SCNHNH_2]$ (100)	9.20 (95.3)

[a] MW is the molecular weight.

[b] HRMS is the high resolution mass spectrum.

[c] The content of the target compound in the sample studied.

a gradient regime, with the percentage of acetonitrile changing from 40 to 75% over 20 min at the flow rate 1 mL min^{-1}. The volume of the injector loop was 10 μL, the injection concentrations of samples were 0.05—0.1 mg mL^{-1}. Reagents and solvents were obtained from commercial sources. 3-(3-Dialkylaminomethylindol-1-yl)-4-(indolin-1-yl)maleimide **1a**,**b**, 3-(3-dialkylaminomethylindol-1-yl)-4-(indol-1-yl)maleimide **2a**,**b**, as well as 3,4-bis(3-dialkylaminomethylindol-1-yl)maleimide **3** were obtained according to the procedures described earlier.[5]

3-(2,3-Dihydro-1*H*-indol-1-yl)-4-{3-[(3-hydroxypropoxy)-methyl]-1*H*-indol-1-yl}-1*H*-pyrrole-2,5-dione (4a) and 10-methyl-5,6-dihydro-1*H*-indolo[1´,7a´,7´:4,5,6]pyrrolo[3´,4´:2,3]-[1,4]diazepino[1,7-*a*]indole-1,3(2*H*)-dione (7a). Methyl iodide (50 μL, 1 mmol) was added to a solution of **1a** (220 mg, 0.55 mmol) in THF (20 mL). The mixture was stirred for 30 min, concentrated *in vacuo*, and dried. Further, it was suspended in pyridine (20 mL), followed by addition of ethylene glycol (1 mL, 24 mmol). The mixture was refluxed for 6 h, cooled to room temperature, diluted with EtOAc (50 mL), washed with water (3×50 mL) and brine (50 mL), dried, and concentrated. The products were separated by column chromatography in the system *n*-heptane—EtOAc (5 : 1) to obtain **4a** (0.11 g, 50%) as amorphous reddish orange powder, R_f 0.34 (*n*-heptane—EtOAc, 1 : 1) and **7a** (30 mg, 15%) as violet powder, m.p. >250 °C (from propan-2-ol), R_f 0.50 (*n*-heptane—EtOAc, 5 : 1).

3-(2,3-Dihydro-1*H*-indol-1-yl)-4-{3-[(3-hydroxypropoxy)-methyl]-1*H*-indol-1-yl}-1-methyl-1*H*-pyrrole-2,5-dione (4b) and 2,10-dimethyl-5,6-dihydro-1*H*-indolo[1´,7a´,7´:4,5,6]pyrrolo-[3´,4´:2,3][1,4]diazepino[1,7-a]indole-1,3(2*H*)-dione (7b). Compounds were obtained from **1b** using the method described for

Table 2. The elemental analysis data for compounds **7a,b** and **13a**

Compound	Found / Calculated (%)		
	C	H	N
7a	<u>73.96</u> 73.89	<u>4.64</u> 4.43	<u>11.81</u> 12.31
7b	<u>74.21</u> 74.35	<u>5.12</u> 4.82	<u>11.84</u> 11.82
13a	<u>70.62</u> 70.98	<u>3.72</u> 3.69	<u>11.90</u> 11.83

Table 3. The UV and ^{1}H and ^{13}C NMR spectroscopic data (DMSO-d$_6$) for compounds obtained

Compound	UV (EtOH) λ_{max}/nm (logε)	NMR, δ (*J*/Hz) ^{1}H*	NMR, δ (*J*/Hz) ^{13}C
4a	448.0 (3.88)	1.65—1.68 (m, 2 H, CH$_2$); 3.06 (t, 2 H, CH$_2$-indoline, *J* = 8.02); 3.42—3.48 (m, 4 H, 2 CH$_2$); 4.21 (t, 2 H, CH$_2$-indoline, *J* = 8.06); 4.44 (t, 1 H, OH, *J* = 5.12); 4.59 (s, 2 H, CH$_2$); 6.10 (d, 1 H, Ind, *J* = 8.04); 6.48 (t, 1 H, Ind, *J* = 7.51); 6.62 (t, 1 H, Ind, *J* = 7.47); 6.95 (t, 1 H, Ind, *J* = 7.01); 7.00 (t, 1 H, Ind, *J* = 7.69); 7.02 (d, 1 H, Ind, *J* = 7.29); 7.14 (d, 1 H, Ind, *J* = 7.50); 7.39 (s, 1 H, H(2)-indole); 7.48 (d, 1 H, Ind, *J* = 6.91); 11.03 (s, 1 H, NH)	28.9, 32.8, 52.5, 58.0, 63.8, 66.1, 108.6, 111.1, 111.9, 114.9, 119.1, 120.1, 122.32, 122.39, 124.3, 126.0, 126.8, 127.7, 131.9, 132.9, 137.2, 142.6, 167.5, 168.5
4b	457.0 (3.89)	1.66—1.71 (m, 2 H, CH$_2$); 3.01 (s, 3 H, CH$_3$); 3.07 (t, 2 H, CH$_2$-indoline, *J* = 8.02); 3.43—3.49 (m, 4 H, 2 CH$_2$); 4.22 (t, 2 H, CH$_2$-indoline, *J* = 8.05); 4.43 (t, 1 H, OH, *J* = 5.13); 4.60 (s, 2 H, CH$_2$); 6.11 (d, 1 H, Ind, *J* = 8.01); 6.50 (t, 1 H, Ind, *J* = 7.32); 6.64 (t, 1 H, Ind, *J* = 7.43); 6.96 (t, 1 H, Ind, *J* = 7.14); 7.01 (t, 1 H, Ind, *J* = 7.69); 7.03 (d, 1 H, Ind, *J* = 6.30); 7.17 (d, 1 H, Ind, *J* = 7.33); 7.37 (s, 1 H, H(2)-indole); 7.50 (d, 1 H, Ind, *J* = 6.77)	23.7, 28.8, 32.8, 52.5, 58.0, 63.7, 66.1, 107.8, 111.0, 112.0, 115.0, 119.1, 120.1, 122.3, 122.5, 124.3, 126.0, 126.8, 127.5, 131.9, 132.9, 137.2, 142.4, 166.3, 167.6
5b	457.0 (3.62)	3.01 (s, 3 H, CH$_3$); 3.07 (t, 2 H, CH$_2$-indoline, *J* = 8.05); 3.40—3.43 (m, 2 H, CH$_2$); 3.51—3.55 (m, 2 H, CH$_2$); 4.22 (t, 2 H, CH$_2$-indoline, *J* = 8.01); 4.65 (s, 2 H, CH$_2$); 4.67 (t, 1 H, OH, *J* = 5.49); 6.11 (t, 1 H, Ind, *J* = 8.06); 6.51 (t, 1 H, Ind, *J* = 7.69); 6.64 (t, 1 H, Ind, *J* = 7.36); 6.97 (t, 1 H, Ind, *J* = 7.04); 7.01 (t, 1 H, Ind, *J* = 6.55); 7.03 (d, 1 H, Ind, *J* = 7.22); 7.15 (d, 1 H, Ind, *J* = 7.50); 7.39 (s, 1 H, H(2)-indole); 7.52 (d, 1 H, Ind, *J* = 6.82)	23.7, 28.8, 52.6, 60.3, 63.8, 70.8, 107.8, 111.0, 112.0, 114.9, 119.2, 120.2, 122.3, 122.5, 124.4, 126.1, 126.8, 127.7, 132.0, 132.9, 137.2, 142.5, 166.3, 167.6
6b	460.0 (3.87)	2.49—2.52 (m, 2 H, CH$_2$); 3.01 (s, 3 H, CH$_3$); 3.08 (t, 2 H, CH$_2$-indoline, *J* = 7.91); 3.55—3.60 (m, 2 H, CH$_2$); 3.92 (s, 2 H, CH$_2$); 4.25 (t, 2 H, CH$_2$-indoline, *J* = 8.05); 4.83 (t, 1 H, OH, *J* = 5.49); 6.09 (d, 1 H, Ind, *J* = 7.92); 6.52 (t, 1 H, Ind, *J* = 7.33); 6.64 (t, 1 H, Ind, *J* = 7.33); 6.95 (t, 1 H, Ind, *J* = 7.03); 6.98 (t, 1 H, Ind, *J* = 7.69); 7.03 (t, 1 H, Ind, *J* = 7.29); 7.12 (d, 1 H, Ind, *J* = 7.33); 7.37 (s, 1 H, H(2)-indole); 7.54 (d, 1 H, Ind, *J* = 6.81)	23.7, 25.7, 28.8, 33.2, 52.5, 60.6, 107.9, 111.1, 111.9, 114.1, 119.2, 119.9, 122.3, 122.5, 124.3, 126.1, 126.4, 127.1, 131.9, 132.5, 137.2, 142.5, 166.4, 167.6
7a	486.0 (3.56)	2.27 (s, 3 H, CH$_3$); 3.04 (t, 2 H, H(5), *J* = 8.40); 4.33 (t, 2 H, H(6), *J* = 8.42); 7.03 (t, 1 H, H(12), *J* = 7.55); 7.06 (t, 1 H, H(13), *J* = 7.40); 7.12 (t, 1 H, H(8), *J* = 7.73); 7.13 (d, 1 H, H(11), *J* = 7.11); 7.30 (d, 1 H, H(7), *J* = 8.60); 7.33 (d, 1 H, H(14), *J* = 8.03); 7.51 (d, 1 H, H(9), *J* = 7.70); 10.82 (s, 3 H, NH)	11.09, 27.6, 47.9, 113.0, 113.3, 114.9, 116.4, 118.5, 120.5, 123.0, 123.4, 124.1, 128.5, 130.4, 131.1, 132.6, 135.8, 136.4,146.6, 165.6, 166.0

(*to be continued*)

Table 3 (*continued*)

Compound	UV (EtOH) λ_{max}/nm (logε)	NMR, δ (*J*/Hz)	
		^{1}H*	^{13}C
7b	500.0 (3.46)	2.30 (s, 3 H, CH$_3$); 2.93 (s, 3 H, NSH$_3$); 3.09 (t, 2 H, H(5), *J* = 8.28); 4.39 (t, 2 H, H(6), *J* = 8.23); 7.06 (t, 1 H, H(12), *J* = 7.55); 7.07 (dt, 1 H, H(13), *J* = 7.93, *J* = 1.05); 7.13 (dt, 1 H, H (8), *J* = 8.28, *J* = 1.28); 7.17 (dd, 1 H, H(11), *J* = 7.29, *J* = 1.02); 7.32 (d, 1 H, H(7), *J* = 8.29); 7.37 (d, 1 H, H(14), *J* = 7.83); 7.53 (d, 1 H, H(9), *J* = 7.65)	11.5, 23.5, 27.7, 48.1, 112.5, 113.4, 115.0, 116.5, 118.6, 120.6, 123.2, 123.4, 124.3, 128.6, 130.5, 131.1, 132.8, 136.1, 136.5, 146.7, 164.6, 165.2
12a	423.0 (3.68)	1.62—1.68 (m, 2 H, CH$_2$); 3.43—3.45 (m, 4 H, 2 CH$_2$); 4.44 (t, 1 H, OH, *J* = 5.03); 4.59 (s, 2 H, CH$_2$); 6.49 (d, 1 H, Ind, *J* = 8.38); 6.57 (d, 1 H, Ind, *J* = 8.34); 6.67 (t, 2 H, Ind, *J* = 5.94); 6.71 (d, 1 H, Ind, *J* = 3.48); 6.86 (t, 1 H, Ind, *J* = 7.14); 6.87 (t, 1 H, Ind, *J* = 6.96); 7.42 (t, 2 H, Ind, *J* = 8.42); 7.60 (d, 1 H, Ind, *J* = 3.30); 7.61 (s, 1 H, H (2)-indole); 11.56 (s, 1 H, NH)	
12b	432.0 (3.70)	1.67—1.73 (m, 2 H, CH$_2$); 3.12 (s, 3 H, CH$_3$); 3.46—3.50 (m, 4 H, 2 CH$_2$); 4.48 (t, 1 H, OH, *J* = 5.03); 4.65 (s, 2 H, Ind, CH$_2$); 6.55 (d, 1 H, Ind, *J* = 8.38); 6.62 (d, 1 H, Ind, *J* = 8.34); 6.73 (t, Ind, 2 H, Ind, *J* = 5.94); 6.78 (d, 1 H, Ind, *J* = 3.48); 6.92 (t, 1 H, Ind, *J* = 7.14); 6.94 (t, 1 H, Ind, *J* = 6.96); 7.48 (t, 2 H, Ind, *J* = 8.42); 7.62 (d, 1 H, Ind, *J* = 3.30); 7.62 (s, 1 H, H(2))	24.2, 32.8, 58.0, 63.7, 66.4, 106.8, 110.91, 110.93, 117.4, 117.5, 119.5, 120.8, 121.52, 121.55, 122.5, 122.8, 123.0, 126.3, 127.6, 127.9, 128.3, 135.0, 135.5, 166.6, 166.7
13a	—	6.69 (d, 1 H, Ind, *J* = 6.67); 6.70 (d, 1 H, Ind, *J* = 6.41); 6.75 (t, 1 H, Ind, *J* = 7.06); 6.81 (d, 1 H, Ind, *J* = 3.50); 6.87 (t, 1 H, Ind, *J* = 7.18); 6.92 (t, 1 H, Ind, *J* = 6.71); 7.09 (t, 1 H, Ind, *J* = 7.06); 7.47 (d, 1 H, Ind, *J* = 7.83); 7.70 (d, 1 H, Ind, *J* = 3.58); 8.01 (d, 1 H, Ind, *J* = 7.83); 8.60 (s, 1 H, H(2)); 10.13 (s, 1 H, COH); 11.80 (br.s, 1 H, NH)	107.4, 110.9, 111.2, 120.6, 120.8, 120.9, 121.1, 121.9, 122.8, 123.7, 123.9, 124.4, 126.5, 128.0, 128.6, 134.8, 136.3, 139.8, 167.1, 167.2, 186.2
14a	434.0 (3.70)	3.11 (s, 3 H, CH$_3$); 3.43—3.46 (m, 4 H, 2 CH$_2$); 3.52—3.55 (m, 4 H, 2 CH$_2$); 4.43 (t, 2 H, 2 OH, *J* = 5.30); 4.68 (s, 4 H, 2 CH$_2$); 6.56 (d, 2 H, Ind, *J* = 8.20);6.73 (t, 2 H, Ind, *J* = 8.23); 6.93 (t, 2 H, Ind, *J* = 7.13); 7.50 (d, 2 H, Ind, *J* = 7.82); 7.63 (s, 2 H, 2 H(2))	24.2, 60.3 (2 C); 63.8 (2 C), 71.0 (2 C); 110.9 (2 C); 117.3 (2 C); 119.5 (2 C); 121.4 (2 C); 122.80 (2 C); 122.89 (2 C); 126.4 (2 C); 127.6 (2 C); 135.5 (2 C); 166.6 (2 C)
14b	434.0 (3.74)	1.65—1.71 (m, 4 H, 2 CH$_2$); 3.12 (s, 3 H, CH$_3$); 3.45—3.49 (m, 8 H, 4 CH$_2$); 4.64 (s, 4 H, 2 CH$_2$); 6.58 (d, 2 H, Ind, *J* = 8.28); 6.45 (t, 2 H, Ind, *J* = 8.24); 6.94 (t, 2 H, Ind, *J* = 7.10); 7.49 (d, 2 H, Ind, *J* = 7.87); 7.62 (s, 2 H, 2 H(2))	24.2, 32.8 (2 C), 58.0 (2 C), 63.7 (2 C), 66.3 (2 C), 110.9 (2 C), 117.4 (2 C), 119.5 (2 C), 121.4 (2 C), 122.81 (2 C), 122.87 (2 C), 126.3 (2 C), 127.6 (2 C), 135.5 (2 C), 166.6 (2 C)
14c	435.0 (3.79)	1.41—1.48 (m, 4 H, 2 CH$_2$); 1.51—1.58 (m, 4 H, 2 CH$_2$); 3.10 (s, 3 H, CH$_3$); 3.36—3.43 (m, 8 H, 4 CH$_2$); 4.42 (t, 2 H, OH, *J* = 5.30); 4.63 (s, 4 H, 2 CH$_2$); 6.57 (d, 2 H, Ind, *J* = 8.40); 6.71 (t, 2 H, Ind, *J* = 7.30); 6.93 (t, 2 H, Ind, *J* = 7.90); 7.47 (d, 2 H, Ind, *J* = 7.77); 7.60 (s, 2 H, 2 H(2))	24.2, 25.9 (2 C), 29.3 (2 C), 32.8 (2 C), 60.6 (2 C), 63.5 (2 C), 69.0 (2 C), 110.9 (2 C), 117.4 (2 C), 119.5 (2 C), 121.4 (2 C), 122.8 (2 C), 126.3 (2 C), 127.6 (2 C), 135.5 (2 C), 166.6 (2 C)
14d	435.0 (3.77)	3.12 (s, 3 H, CH$_3$); 3.41—3.49 (m, 8 H, 4 CH$_2$); 3.49—3.57 (m, 8 H, 4 CH$_2$); 4.64 (t, 2 H, OH, *J* = 5.50); 4.64 (s, 4 H, 2 CH$_2$); 6.58 (d, 2 H, Ind, *J* = 8.28); 6.75 (t, 2 H, Ind, *J* = 8.28); 6.94 (t, 2 H, Ind, *J* = 7.20); 7.51 (d, 2 H, Ind, *J* = 7.88); 7.63 (s, 2 H, 2 H(2))	24.2, 60.2 (2 C), 63.7 (2 C), 68.4 (2 C), 69.7 (2 C), 72.3 (2 C), 110.9 (2 C), 117.1 (2 C), 119.5 (2 C), 121.5 (2 C), 122.8 (2 C), 122.9 (2 C), 126.5 (2 C), 127.5 (2 C), 135.5 (2 C), 166.6 (2 C)

(*to be continued*)

Table 3 (*continued*)

Compound	UV (EtOH) λ_{max}/nm (logε)	NMR, δ (*J*/Hz)	
		^{1}H*	^{13}C
15a	445 (3.74)	1.82—1.88 (m, 2 H, CH_2); 3.06 (t, 2 H, CH_2-indoline, *J* = 7.92); 3.17—3.23 (m, 4 H, 2 CH_2); 4.21 (t, 2 H, CH_2-indoline, *J* = 7.91); 4.62 (s, 2 H, CH_2); 6.08 (d, 1 H, Ind, *J* = 7.92); 6.47 (t, 1 H, Ind, *J* = 7.65); 6.62 (t, 1 H, Ind, *J* = 7.37); 6.96 (t, 1 H, Ind, *J* = 7.04); 6.99 (t, 1 H, Ind, *J* = 7.73); 7.02 (d, 1 H, Ind, *J* = 7.29); 7.15 (d, 1 H, Ind, *J* = 7.51); 7.40 (s, 1 H, H(2)); 7.50 (d, 1 H, Ind, *J* = 7.50); 9.35 (br.s, 3 H, SCNHNH$_2$); 10.54 (s, 1 H, NH)	27.4, 28.6, 48.6, 52.5, 63.8, 66.6, 108.4, 111.1, 112.0, 114.4, 119.0, 120.2, 122.4 (2 S), 124.4, 126.0, 126.8, 128.0, 132.0, 133.0, 137.1, 142.6, 167.5, 168.5, 170.1
15b	455.0 (3.81)	1.83—1.89 (m, 2 H, CH_2); 3.01 (s, 3 H, CH_3); 3.08 (t, 2 H, CH_2-indoline, *J* = 7.95); 3.18—3.24 (m, 2 H, CH_2); 3.30—3.48 (m, 2 H, CH_2); 4.22 (t, 2 H, CH_2-indoline, *J* = 7.87); 4.63 (s, 2 H, CH_2); 6.11 (d, 1 H, Ind, *J* = 8.05); 6.48 (t, 1 H, Ind, *J* = 7.36); 6.65 (t, 1 H, Ind, *J* = 7.32); 6.97 (t, 1 H, Ind, *J* = 7.14); 7.02 (t, 1 H, Ind, *J* = 7.14); 7.04 (d, 1 H, Ind, *J* = 5.21); 7.17 (d, 1 H, Ind, *J* = 7.40); 7.39 (s, 1 H, H (2)); 7.50 (d, 1 H, Ind, *J* = 6.96); 9.40 (br.s, 3 H, SCNHNH$_2$)	23.8, 27.4, 28.6, 28.9, 52.6, 63.8, 66.6, 107.7, 111.2, 112.1, 114.5, 119.1, 120.3, 122.4, 122.6, 124.4, 126.1, 126.8, 127.9, 132.1, 133.1, 137.2, 142.4, 166.3, 167.6, 169.9
16	454.0 (3.73)	3.01 (s, 3 H, CH_3); 3.08 (t, 2 H, CH_2-indoline, *J* = 7.97); 3.40—3.46 (m, 2 H, CH_2); 3.54—3.60 (m, 2 H, CH_2); 4.23 (t, 2 H, CH_2-indoline, *J* = 7.91); 4.70 (s, 2 H, CH_2); 6.08 (d, 1 H, *J* = 7.91); 6.48 (t, 1 H, Ind, *J* = 7.69); 6.66 (t, 1 H, Ind, *J* = 7.32); 6.98 (t, 1 H, Ind, *J* = 6.22); 7.03 (t, 1 H, Ind, *J* = 8.01); 7.04 (d, 1 H, Ind, *J* = 8.65); 7.17 (d, 1 H, Ind, *J* = 7.59); 7.41 (s, 1 H, H (2)); 7.52 (d, 1 H, Ind, *J* = 7.10); 9.32 (br.s, 3 H, SCNHNH$_2$)	23.8, 28.9, 30.7, 52.7, 63.8, 66.5, 107.5, 111.2, 112.1, 114.0, 119.1, 120.4, 122.5, 122.7, 124.5, 126.1, 126.7, 128.2, 132.1, 133.1, 137.2, 142.4, 166.4, 167.6, 170.4

* Ind is an indole or indoline fragment.

compounds **4a** and **7a**. The products were separated by column chromatography in the system *n*-heptane—EtOAc (5 : 1) to obtain **4b** (310 mg, 51%) as amorphous reddish orange powder, R_f 0.20 (*n*-heptane—EtOAc, 1 : 1) and **7b** (53 mg, 15%) as violet powder, m.p. 222 °C (from propan-2-ol), R_f 0.40 (*n*-heptane—EtOAc, 5 : 1).

3-(2,3-Dihydro-1*H*-indol-1-yl)-4-{3-[(2-hydroxyethoxy)-methyl]-1*H*-indol-1-yl}-1-methyl-1*H*-pyrrole-2,5-dione (5b). Compound was obtained from **1b** using the method described for compound **4a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (1 : 1) to obtain **5b** (520 mg, 51%) as amorphous reddish orange powder, R_f 0.30 (*n*-heptane—EtOAc, 1 : 1).

3-(2,3-Dihydro-1*H*-indol-1-yl)-4-(3-{[(2-hydroxyethyl)-sulfanyl]methyl}-1*H*-indol-1-yl)-1-methyl-1*H*-pyrrole-2,5-dione (6b). Compound was obtained from **1b** using the method described for compound **4a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (3 : 1) to obtain **6b** (190 mg, 51%) as amorphous reddish orange powder, R_f 0.40 (*n*-heptane—EtOAc, 1 : 1).

3-{3-[(3-Hydroxypropoxy)methyl]-1*H*-indol-1-yl}-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione (12a). Compound was obtained from **2a** using the method described for compound **4a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (3 : 1) to obtain **12a** (230 mg, 52%) as amorphous reddish orange powder, R_f 0.40 (*n*-heptane—EtOAc, 1 : 1).

3-{3-[(3-Hydroxypropoxy)methyl]-1*H*-indol-1-yl}-4-(1*H*-indol-1-yl)-1-methyl-1*H*-pyrrole-2,5-dione (12b). Compound was obtained from **2b** using the method described for compound **4a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (3 : 1) to obtain **12b** (225 mg, 50%) as amorphous reddish orange powder, R_f 0.30 (*n*-heptane—EtOAc, 1 : 1).

1-[4-(1*H*-Indol-1-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indole-3-carbaldehyde (13a). Methyl iodide (100 μL, 2 mmol) was added to a solution of **2a** (500 mg, 1.3 mmol) in THF (50 mL). The mixture was stirred for 30 min, concentrated *in vacuo*, and dried. Further, it was suspended in pyridine (20 mL). The suspension was refluxed for 6 days, cooled to room temperature, diluted with EtOAc (50 mL), washed with water (3×50 mL) and brine (50 mL), dried, and concentrated. The product was purified by column chromatography in the system *n*-heptane—EtOAc (2 : 1) to obtain **13a** (70 mg, 15%) as amorphous reddish orange powder, m.p. >250 °C (from propan-2-ol), R_f 0.30 (*n*-heptane—EtOAc, 1 : 1).

1-[4-(1*H*-Indol-1-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indole-3-carbaldehyde (13b). Compound was obtained from **2b** using the method described for compound **13a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (2 : 1) to obtain **13b** (100 mg, 20%) as amorphous reddish orange powder.

3,4-Bis{3-[(2-Hydroxyethoxy)methyl]-1*H*-indol-1-yl}-1-methyl-1*H*-pyrrole-2,5-dione (14a). Methyl iodide (150 μL, 3 mmol) was added to a solution of **3** (600 mg, 1.3 mmol) in THF (50 mL). The mixture was stirred for 8 h., concentrated *in vacuo*, and dried. Further, it was suspended in 2,4,6-trimethylpyridine (20 mL), followed by addition of ethylene glycol (300 μL, 4.8 mmol). The mixture was refluxed for 20 h, cooled to room temperature, diluted with EtOAc (100 mL), washed with water (3×50 mL) and brine (50 mL), dried, and concentrated. The product was purified by column chromatography in the system *n*-heptane—EtOAc (1 : 1) to obtain **14a** (220 mg, 35%) as amorphous reddish orange powder, R_f 0.45 (EtOAc).

3,4-Bis{3-[(3-hydroxypropoxy)methyl]-1*H*-indol-1-yl}-1-methyl-1*H*-pyrrole-2,5-dione (14b). Compound was obtained from **3** using the method described for compound **14a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (1 : 1) to obtain **14b** (210 mg, 35%) as amorphous reddish orange powder, R_f 0.50 (EtOAc).

3,4-Bis{3-[(4-hydroxybutoxy)methyl]-1*H*-indol-1-yl}-1-methyl-1*H*-pyrrole-2,5-dione (14c). Compound was obtained from **3** using the method described for compound **14a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc (1 : 0.5) to obtain **14c** (215 mg, 35%) as amorphous reddish orange powder, R_f 0.50 (EtOAc).

3,4-Bis(3-{[2-(2-hydroxyethoxy)ethoxy]methyl}-1*H*-indol-1-yl)-1-methyl-1*H*-pyrrole-2,5-dione (14d). Compound was obtained from **3** using the method described for compound **14a**. The product was purified by column chromatography in the system *n*-heptane—EtOAc to obtain **14d** (220 mg, 30%) as amorphous reddish orange powder, R_f 0.30 (EtOAc).

3-({1-[4-(2,3-Dihydro-1*H*-indol-1-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indol-3-yl}methoxy)propyl imidothiocarbamate (15a). Methanesulfonyl chloride (50 μL, 0.64 mmol) was added to a solution of **4a** (0.2 g, 0.47 mmol) in THF (10 mL). The mixture was stirred for 20 min and diluted with EtOAc (50 mL), washed with water (3×50 mL) and brine (50 mL), dried, and concentrated. The residue was dissolved in DMF (10 mL), followed by addition of thiourea (500 mg, 6.6 mmol) and stirring for 10 h at 50 °C. Then, it was cooled to room temperature, diluted with BuOH (50 mL), washed with water (3×50 mL) and brine (50 mL), and concentrated. The product was purified by column chromatography in the system CH_2Cl_2—MeOH (20 : 1) to obtain **15a** (120 mg, 55%) as amorphous reddish orange powder, R_f 0.30 (CH_2Cl_2—MeOH, 5 : 1).

4-({1-[4-(2,3-Dihydro-1*H*-indol-1-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indol-3-yl}methoxy)propylimidothiocarbamate (15b). Compound was obtained from **4b** using the method described for compound **15a**. The product was purified by column chromatography in the system CH_2Cl_2—MeOH (20 : 1) to obtain **15b** (98 mg, 55%) as amorphous reddish orange powder, R_f 0.40 (CH_2Cl_2—MeOH, 5 : 1).

2-({1-[4-(2,3-Dihydro-1*H*-indol-1-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indol-3-yl}methoxy)ethylimidothiocarbamate (16). Compound was obtained from **5b** using the method described for compound **15a**. The product was purified by column chromatography in the system CH_2Cl_2—MeOH (20 : 1) to obtain **16** (110 mg, 54%) as amorphous reddish orange powder, R_f 0.40 (CH_2Cl_2—MeOH, 5 : 1).

References

1. U. Pindur, Y. Kim, F. Meharbani, *Curr. Med. Chem.*, 1999, **6**, 29.
2. S. Omura, Y. Yawai, A. Hirano, A. Nakagawa, J. Awaya, Y. Tsuchiya, R. Masuma, *J. Antibiot.*, 1977, **30**, 275.
3. A. J. Bridges, *Chem. Rev.*, 2001, **101**, 2541.
4. P. G. Goekjian, M. R. Jirousek, *Expert Opin. Invest. Drugs*, 2001, **10**, 2117.
5. A. Yu. Simonov, S. A. Lakatosh, Yu. N. Luzikov, M. I. Reznikova, O. Yu. Susova, A. A. Shtil´, S. M. Elizarov, V. N. Danilenko, M. N. Preobrazhenskaya, *Izv. Akad. Nauk*, *Ser. Khim.*, 2008, 1977 [*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 2011].
6. A. Gueiffier, M. Lhassani, A. Elhakmaoui, R. Snoeck, A. Graciela, O. Chavignon, J. Teulade, A. Kerbal, E. Essassi, J. Debouzy, M. Witvrouw, Y. Blache, J. Balzarini, E. De Clercq, J. Chapat, *J. Med. Chem.*, 1996, **39**, 2856.
7. S. A. Lakatosh, A. Yu. Simonov, Yu. N. Luzikov, M. N. Preobrazhenskaya, *Khim. Farm. Zh.*, 2006, **40**, 29 [*Pharm. Chem. J.* (*Engl. Transl.*), 2006, **40**, 435].
8. S. A. Lakatosh, Y. N. Luzikov, M. N. Preobrazhenskaya, *Org. Biomol. Chem.*, 2003, **1**, 826.

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