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TRANSFORMATION OF 4-SUBSTITUTED TETRAHYDROPYRROLOBENZODIAZEPINES IN A THREE-COMPONENT REACTION WITH METHYL PROPIOLATE AND INDOLE

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The three-component reaction of 4-phenyl-, p-methoxyphenyl-, and thienylpyrrolo[1,2-a][1,4]benzodiazepines with methyl propiolate and indole in dichloromethane proceeds through opening of the diazepine ring. The major transformation products isolated are substituted pyrroles, namely, 1-(2-aminomethylphenyl)-5-(arylmethyl)-2-(indol-1(3)-yl)pyrroles and 1-(2-aminomethylphenyl)-2-aryl-(indol-3-yl)-methylpyrroles.

Keywords: pyrrolylindoles, tetrahydropyrrolo[1,2-*a*][1,4]benzodiazepines, domino reactions, multicomponent reaction, opening of the diazepine ring.

The domino reaction of [*c*]-condensed tetrahydropyridines **1** with alkynes discovered in our previous work [1-3] has led to the development of methods for the synthesis of condensed azocines **2** and methoxymethyl derivatives of heterocyclic compounds.

The nucleophilic attack of the anionic site of the initial ammonium zwitter-ion **A** at the C-1 atom as the result of expansion of the tetrahydropyridine ring leads to condensed azocines **2**, whose ring cleavage by a methanol molecule gives methoxymethyl derivative **3**. Electron-donor substituents R in the methine group facilitate cleavage of the aryl- or hetarylmethylammonium fragment at the $-N^{+}CHR-$ bond and formation of zwitterion **B**, which opens a new transformation pathway, namely, to spiro compounds **4** [4]. The existence of the open zwitterion was demonstrated using the three-component reaction of benzothienopyridine and β-carboline with methyl propiolate and indole. The corresponding triarylmethanes **5** were obtained in 76-85% yield [5, 6].

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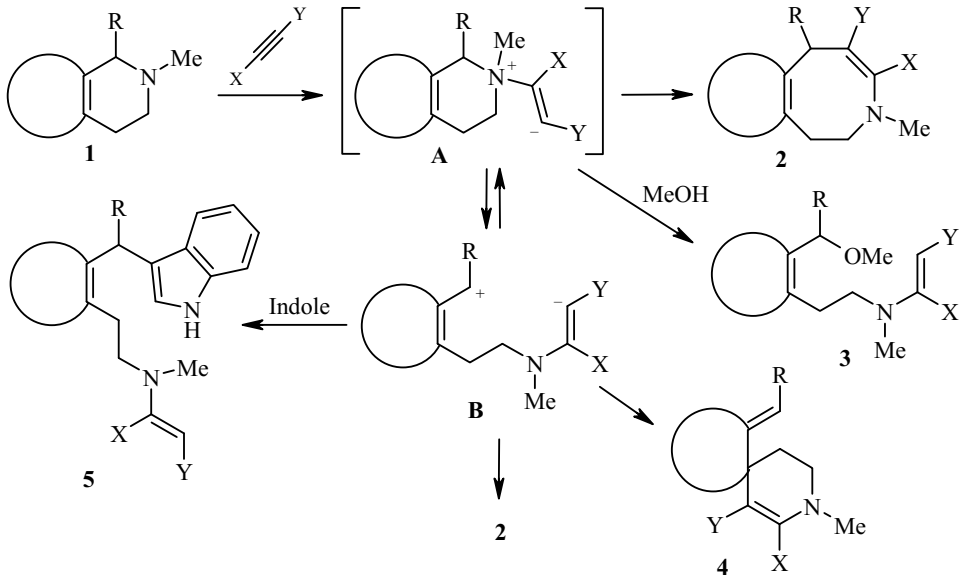
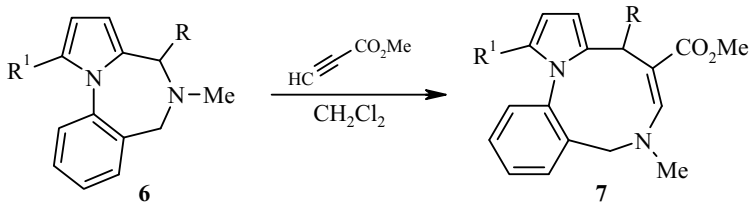


Condensed azepines and 1,4-diazepines demonstrate unique behavior in domino reactions with alkynes. While the azepine ring in the tetrahydroindoloazepines readily expands by two carbon atoms by the action of alkynes to give indoloazonines [7], the diazepine ring in benzodiazepines does not undergo any transformation by the action of alkynes [8]. Tetrahydrobenzodiazepinones react with alkynes through multiple pathways to give a multicomponent mixtures, from which Stevens rearrangement products of C- and N-vinylation are separated by chromatography [8].

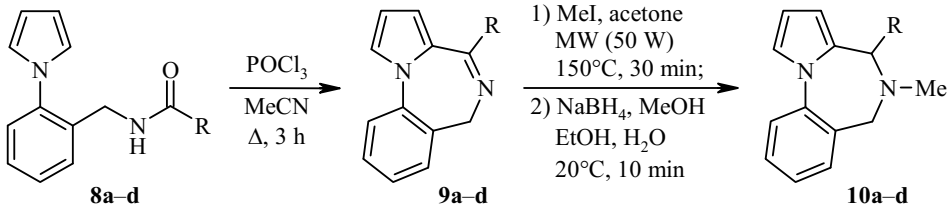
Pyrrolo[1,2-*a*][1,4]benzodiazepines **6** react with methyl propiolate in dichloromethane to give multicomponent mixtures, from which products of the expansion of the diazepine ring at the C(4)–N bond, namely, pyrrolobenzodiazonines **7** were isolated [9]. In this case, products of the transformation of the diazepine fragment at the N–C(6) bond were not isolated.



R = Ph, 2-thienyl, Me; R^1 = H, Me

In order to confirm the cleavage of the diazepine ring in benzodiazepines **6** in domino reactions with alkynes and obtain new pyrrolylindolylmethane derivatives **5** holding biological interest, we studied the transformation of 4-aryl-5-methyldihydropyrrolobenzodiazepines **10a-d** by the action of methyl propiolate in three-component reactions with indole. The synthesis of benzodiazepines **10a-d** was carried out according to the procedure described in our previous work [9] from the corresponding pyrrolobenzylamides **8a-d**. Pyrrolobenzodiazepines **10a**,**b** were described in the same work [9].

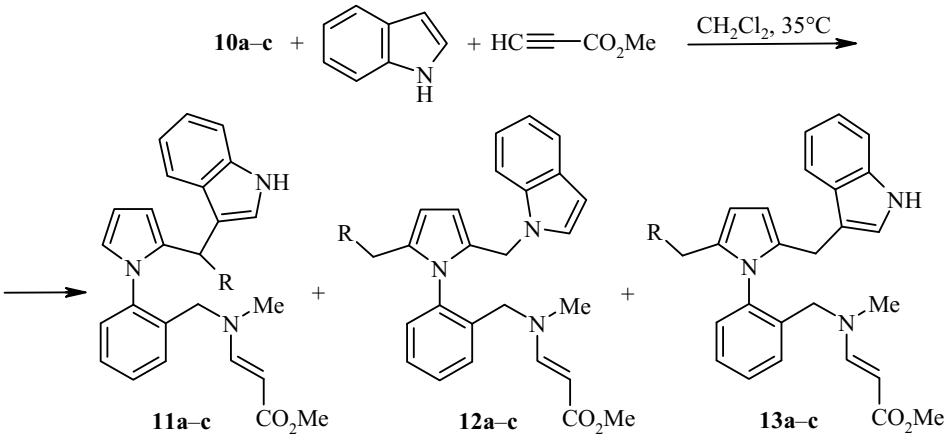
Multicomponent mixtures were obtained in three-component reactions of pyrrolobenzodiazepines **10a-c** with methyl propiolate and indole. Only products of opening of the diazepine ring at the C(4)–N bond were obtained chromatographically in 8.4-28.3% yield, namely, substituted *N*-arylpyrroles **11a-c**, **12a-c**, and **13a**,**b**. Pyrrole **13c** was not isolated from the reaction mixture.



8a–d **9a–d** **10a–d**

a R = Ph, **b** R = 2-thienyl, **c** R = 4-$MeOC_6H_4$, **d** R = 4-$O_2NC_6H_4$

Products of the alternative cleavage at the C(6)–N bond could not be detected. In our opinion, pyrroles **12a-c** are the most unusual of the isolated pyrroles. These products may be seen as products of formal nucleophilic substitution at the α-position of the pyrrole ring. Similar formal nucleophilic substitution in pyrroles using *N*-halosuccinimides was described by De Rosa et al. [10], who proposed that this reaction proceeds through 2,5-addition of the haloimides to the pyrrole ring.

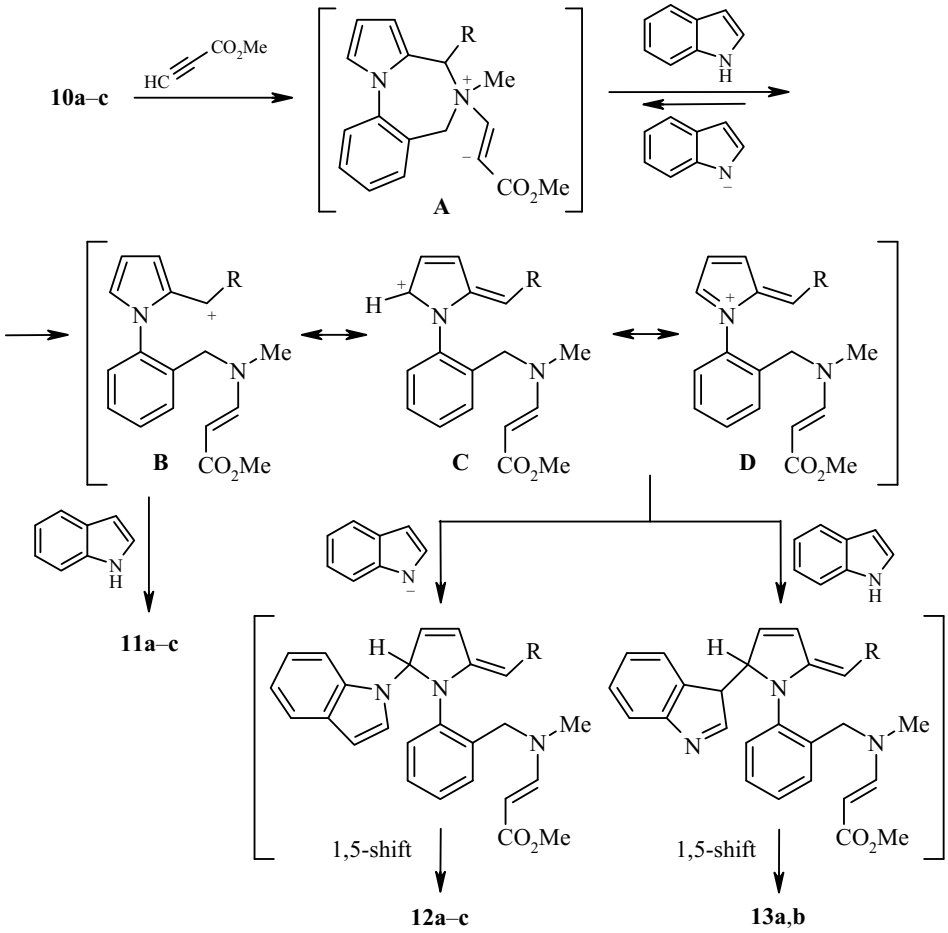


Pyrrolobenzo-diazepine	R	Pyrrole yield, %			
		11	**12**	**13**	Total yield
10a	Ph	1.6	10.5	2.0	14.1
10b	2-Thienyl	18.3	4.0	6.0	28.3
10c	4-$MeOC_6H_4$	4.8	3.6	—	8.4

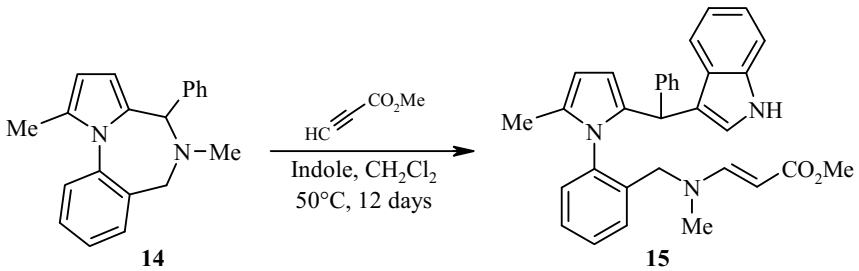
The mechanism for formation of pyrroles **11-13** is given in the scheme below. The initially-formed ammonium zwitterion **A** deprotonates the indole nitrogen atom by means of its anionic site and undergoes cleavage to give the open form **B**. This cation is more stable than the alternative form, which might have been formed upon opening of zwitterion **A** at the N^+–C(6) bond. The structure of the open form may be described using three resonance structures **B**, **C**, and **D**. The electrophilic reaction of form **B** with indole leads to the formation of pyrrolyl(indol-3-yl)arylmethanes **11a-c**. The reaction of resonance forms **C** and **D**, which have an electron-deficient site at position 2 in the pyrrole ring, with the *N*-indolyl anion through the 2,5-addition adduct and a subsequent 1,5-sigmatropic shift results in formation of 1-(indol-1-yl)pyrroles **12a-c**. (Indol-3-yl)-pyrroles **13a**,**b** are likely formed in the reaction of resonance forms **C** and **D** with indole or the indol-3-yl anion. The impossibility of forming cation **B** in the case of *p*-nitrophenyl derivative **10d** probably is the reason for the failure of this compound to undergo domino reactions with alkynes and indole.

The structures of substituted pyrroles **11a-c, 12a-c**, and **13a**,**b** were confirmed spectroscopically. The structures of pyrroles **12a** and **13a** were unequivocally established by X-ray diffraction structural analysis. The mass spectra of all the substituted pyrroles have molecular ion peaks corresponding to their empirical formulas. The ^{1}H NMR spectra of pyrroles **12** and **13** show signals for pyrrole ring protons H-3,4 at 6.25-6.62 ppm

(^3J = 3.2 Hz). The methylene group protons are seen as two AB systems at 2.97-3.58 (CH_2R, J = 16.0-17.4 Hz) and 3.63-3.95 ppm (CH_2N, J = 15.8-16.5 Hz) for pyrroles **12a-c** and at 2.95-3.60 (CH_2R, J = 16.1-16.8 Hz) and 3.66-3.99 ppm (CH_2N, J = 15.6-16.5 Hz) for pyrroles **13a**,**b**. A singlet for the indole NH proton is found in the spectra of pyrroles **13a**,**b** downfield at 7.87-7.97 ppm. The spectra of all the pyrroles obtained have a downfield doublet for the vinyl group proton overlapped with the aromatic proton signals, while a broad upfield singlet is observed at 4.30-4.65 ppm.



Pyrroles **11a-c**, which have two chiral sites, namely, a chirality axis (atropoisomeric site due to hindered rotation of the pyrrole and phenyl rings) and an asymmetric triarylmethyl site, are formed, as expected as a 0.7:1 diastereomer mixture for pyrrole **11a**, 0.9:1 mixture for compound **11b**, and 0.8:1 mixture for compound **11c** as indicated by ^{1}H NMR spectroscopy. Thus, the spectra of these compounds have a double set of signals for each of the protons. The ^{1}H NMR spectrum of pyrrole **11a** in DMSO at 90°C shows only set of signals related to the disappearance of axial chirality due to rapid rotation of the pyrrole and phenyl rings.



The ^{1}H NMR spectrum of 1-methylpyrrole **15**, obtained by the multicomponent reaction of 1-methyl-4-phenylpyrrolobenzodiazepine **14** [11] with methyl propiolate and indole, has only one set of signals for each proton, indicating the pyrrole **15** is formed as a single isomer.

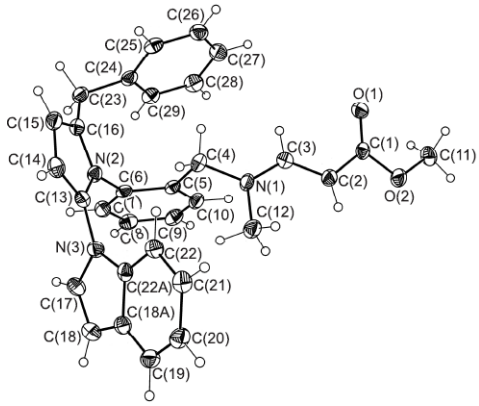


Fig. 1. Molecular structure of pyrrole **12a** with representation of the atoms by thermal vibration ellipsoids of 50% probability.

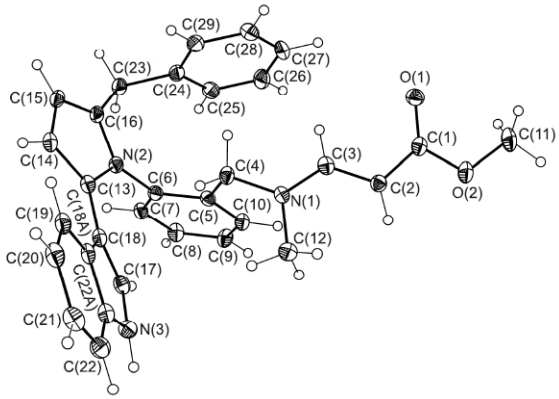


Fig. 2. Molecular structure of pyrrole **13a** with representation of the atoms by thermal vibration ellipsoids of 50% probability.

The X-ray diffraction structural analysis data illustrated in Figures 1 and 2 for pyrroles **12a** and **13a** show that these molecules differ only in the attachment of the indole substituent to the pyrrole ring, namely, through the nitrogen atom or through a carbon atom, respectively. The benzene, indole, and phenyl fragments are twisted relative to the central pyrrole ring in pyrrole **12a** by 87.54(7), 61.89(6), and 72.75(7)° and in pyrrole **13a** by 72.89(8), 23.77(9), and 89.72(8)°, respectively. The observed conformation of these molecules is apparently stabilized by intramolecular C–H···π hydrogen bonds. The methylaminopropenoate fragment $–CH_2–N(CH_3)–CH=CH–(=O)–OCH_3$ in both compounds has (*E*)-configuration and takes a flattened conformation due to the long conjugated bond chain. All the nitrogen atoms in pyrrole **12a** and N(1) and N(2) in pyrrole **13a** have trigonal-plane geometry (the sum of the valence angles are 359.7, 359.6, 359.3, 358.8, and 360.0°, respectively). On the other hand, the atom N(3) in pyrrole **13a** has a slightly pyramidal configuration (the sum of the valence angles is 357.3°) due to the formation of intermolecular hydrogen bond N(3)–H(3)···O(1) (-0.5+ *x*, 0.5-*y*, -0.5+*z*) (N···O, 2.861(3) Å; H···O, 2.04(3) Å; N–H···O, 147(2)°).

Thus, we have shown that cleavage of the N^+–C(Ar) bond occurs in the initially-formed ammonium zwitterion during the transformation of 4-arylpyrrolobenzodiazepines in a three-component reaction with methyl propiolate and indole. The resultant cation then reacts through various pathways to give different indolylpyrroles.

EXPERIMENTAL

IR spectra were recorded on an Infralum-801 Fourier spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker WP-400 (400 MHz) spectrometer in $CDCl_3$, internal standard was TMS. LG mass spectra were recorded on a system comprising an Agilent 1100 liquid chromatograph, an Agilent Technologies LC/MSD VL mass spectrometer (atmospheric pressure ESI), and Sedex 75 ELSD detector (compounds **8d**, **9d**, **12b**). Mass spectra were recorded on a Thermo Scientific MAT 95XL chromato-mass spectrometer with direct sample insertion (electron ionization, 70 eV, compounds **10d**, **12a**) or on a JEOL JMS-T100LP-DART 100 instrument (DART ionization, all other compounds). Elemental analysis was carried out on a Carlo Erba 1106 instrument. Melting points were determined on a SMP 10 apparatus. Sorbfil and Alufol plates were used for TLC (visualization by iodine vapor, $KMnO_4$ and H_2SO_4 solutions). Silica gel from Acros (0.04-0.06 mm, 60 Å) was used for column chromatography.

All the solvents were purified by distillation. Methyl propiolate from Acros Organics was used without additional purification. Microwave-activated quaternization of pyrrolobenzodiazepines was performed in an Anton Paar Monowave 300 oven.

4-Methoxy-*N*-[2-(1*H*-pyrrol-1-yl)benzyl]benzamide (8c). *p*-Methoxybenzoyl chloride (10.9 g, 64 mmol) was added dropwise to calcinated K_2CO_3 (10.5 g, 75 mmol) and 2-(pyrrol-1-yl)benzylamine (10.0 g, 58 mmol) in abs. MeCN (20 ml) at 20°C. The reaction mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC (Sorbfil, EtOAc–hexane, 1:2). The solvent was removed *in vacuo*. Water (40 ml) was added to the residue. The precipitate was filtered off and recrystallized from EtOAc–hexane, 1:2. Yield 13.3 g (92%), colorless crystals, mp 159-161°C. IR spectrum, ν, cm^{-1}: 3343 (NH), 1631 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, OCH_3); 4.56 (2H, d, *J* = 6.0, CH_2N); 5.92 (1H, br. s, NH); 6.39 (2H, t, *J* = 2.3, H-3,4 pyrrole); 6.83 (2H, t, *J* = 2.3, H-2,5 pyrrole); 6.86 (2H, d, *J* = 8.7, H-3,5 COAr); 7.27-7.40 (2H, m, H Ar); 7.49-7.58 (2H, m, H Ar); 7.60 (2H, d, *J* = 8.7, H-2,6 COAr). Mass spectrum, *m*/*z*: 307 $[M+H]^+$. Found, %: C 74.40; H 5.72; N 9.50. $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.49; H 5.92; N 9.14.

4-Nitro-*N*-[2-(1*H*-pyrrol-1-yl)benzyl]benzamide (8d) was obtained similarly to compound **8c** from calcinated K_2CO_3 (10.5 g, 75 mmol), 2-(pyrrol-1-yl)benzylamine (10.0 g, 58 mmol), and *p*-nitrobenzoyl chloride (11.9 g, 64 mmol). Yield 12.1 g (65%), colorless crystals, mp 162-163°C. IR spectrum, ν, cm^{-1}: 3324 (NH), 1633 (CO), 1542, 1343 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.54 (2H, d, *J* = 6.4, CH_2N); 5.80 (1H, br. s, NH); 6.41 (2H, t, *J* = 2.4, H-3,4 pyrrole); 6.85 (2H, t, *J* = 2.4, H-2,5 pyrrole); 7.34-7.38 (2H, m, H Ar); 7.40 (1H, t, *J* = 4.6, H Ar); 7.52-7.54 (1H, m, H Ar); 7.76 (2H, d, *J* = 8.7, H-2,6 COAr); 8.23 (2H, d, *J* = 8.7, H-3,5 COAr). Mass spectrum, *m*/*z*: 322 $[M+H]^+$. Found, %: C 67.37; H 4.58; N 13.12. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.28; H 4.71; N 13.08.

4-(4-Methoxyphenyl)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (9c). $POCl_3$ (30.0 g, 196 mmol) was added dropwise to a solution of amide **8c** (15.0 g, 49 mmol) in abs. MeCN (80 ml) under argon atmosphere. The reaction mixture was refluxed for 3 h. The reaction was monitored by TLC (Alufol, EtOAc–hexane, 1:3). The residue, (a dark oil) was poured into 25% ammonia solution (25 ml) and extracted with EtOAc (400 ml). The extract was dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was triturated with Et_2O, the resulting precipitate was filtered off. Yield 10.2 g (81%), yellow crystals, mp 79-81°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.81 (3H, s, OCH_3); 4.41 (1H, br. s) and 4.77 (1H, br. s, 6-CH_2); 6.38 (1H, t, *J* = 3.7, H-3); 6.49 (1H, dd, *J* = 2.3, *J* = 3.7, H-2); 6.86 (2H, d, *J* = 8.7, H-3',5'); 7.26-7.30 (1H, m, H Ar); 7.33 (1H, dd, *J* = 2.3, *J* = 1.8, H-1); 7.35-7.39 (2H, m, H Ar); 7.47 (1H, d, *J* = 7.3, H Ar); 7.66 (2H, d, *J* = 8.7, H-2',6'). Mass spectrum, *m*/*z*: 289 $[M+H]^+$. Found, %: C 79.31; H 5.46; N 9.68. $C_{19}H_{16}N_2O$. Calculated, %: C 79.14; H 5.59; N 9.71.

4-(4-Nitrophenyl)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (9d) was obtained similarly to compound **9c** from amide **8d** (15.7 g, 49 mmol) and $POCl_3$ (30.0 g, 196 mmol). Yield 13.5 g (91%), beige crystals, mp 165-167 °C. IR spectrum, ν, cm^{-1}: 1577 (C=N), 1514, 1347 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.72 (2H, br. s, 6-CH_2); 6.42-6.47 (2H, m, H-2,3); 7.33 (1H, t, *J* = 6.0, H-8); 7.38-7.44 (3H, m, H-1,7,9); 7.50 (1H, d,

J = 7.3, H-10); 7.90 (2H, d, *J* = 8.7, H-2',6'); 8.21 (2H, d, *J* = 8.7, H-3',5'). Mass spectrum, *m*/*z*: 304 $[M+H]^+$. Found, %: C 71.41; H 4.28; N 13.79. $C_{18}H_{13}N_3O_2$. Calculated, %: C 71.28; H 4.32; N 13.85.

4-(4-Methoxyphenyl)-5-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (10c). A mixture of benzodiazepine **9c** (0.68g, 2.7 mmol) and MeI (1.9 g, 13.6 mmol) in absolute acetone (10 ml) was irradiated with microwaves (50 W) at 150°C for 0.5 h. The solvent was removed *in vacuo*. The residue was dissolved in a mixture of MeOH (16 ml) and 60% EtOH (24 ml), and $NaBH_4$ (0.09 g, 2.5 mmol) was added. After 10 min at 20°C, a precipitate started to form. To this mixture, H_2O (50 ml) was added, and the precipitated crystals were filtered off and dried in air. Yield 0.70 g (86%), beige crystals, mp 96-98°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (3H, s, NCH_3); 3.51 (1H, d, *J* = 13.7, 6-CH_A); 3.81 (3H, s, OCH_3); 3.87 (1H, s, 4-CH); 4.11 (1H, d, *J* = 13.7, 6-CH_B); 5.50 (1H, br. s, H-3); 6.13-6.15 (1H, m, H-2); 6.87 (2H, d, *J* = 7.8, H-3',5'); 6.95 (1H, m, H-1); 7.28-7.33 (2H, m, H Ar); 7.38 (2H, d, *J* = 7.8, H-2',6'); 7.41-7.46 (2H, m, H Ar). Mass spectrum, *m*/*z*: 305 $[M+H]^+$. Found, %: C 78.79; H 6.48; N 9.13. $C_{20}H_{20}N_2O$. Calculated, %: C 78.92; H 6.62; N 9.20.

5-Methyl-4-(4-nitrophenyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (10d) was obtained similarly to compound **10c** from benzodiazepine **9d** (0.82 g, 2.7 mmol) and MeI (1.90 g, 13.6 mmol). Yield 0.72 g (83%), beige crystals, mp 150-152°C. IR spectrum, ν, cm^{-1}: 1523, 1349 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24 (3H, s, NCH_3); 3.49 (1H, d, *J* = 13.7) and 4.08 (1H, d, *J* = 13.7, 6-CH_2); 4.12 (1H, s, 4-CH); 5.41-5.45 (1H, m, H-3); 6.17 (1H, t, *J* = 3.2, H-2); 6.99-7.02 (1H, m, H-1); 7.26-7.36 (2H, m, H Ar); 7.37-7.48 (2H, m, H Ar); 7.63 (2H, d, *J* = 8.7, H-2',6'); 8.17 (2H, d, *J* = 8.7, H-3',5'). Mass spectrum, *m*/*z* (I_{rel}, %): 319 $[M]^+$ (22), 197 (100), 154 (20), 42 (8). Found, %: C 71.60; H 5.49; N 13.10. $C_{19}H_{17}N_3O_2$. Calculated, %: C 71.46; H 5.37; N 13.16.

Methyl (2*E*)-3-[(2-{2-[1*H*-Indol-3-yl(phenyl)methyl]-1*H*-pyrrol-1-yl}benzyl)(methyl)amino]acrylate (11a), Methyl (2*E*)-3-[{2-[2-Benzyl-5-(1*H*-indol-1-yl)-1*H*-pyrrol-1-yl]benzyl}(methyl)amino]acrylate (12a), Methyl (2*E*)-3-[{2-[2-Benzyl-5-(1*H*-indol-3-yl)-1*H*-pyrrol-1-yl]benzyl}(methyl)amino]acrylate (13a). A solution of pyrrolobenzodiazepine **10a** (0.5 g, 1.8 mmol), methyl propiolate (0.2 g, 2.2 mmol), and indole (0.3 g, 2.2 mmol) in CH_2Cl_2 (15 ml) was kept at 35°C for 42 h. The reaction was monitored by TLC (Alufol, EtOAc–hexane, 1:5). The solvent was removed *in vacuo*. The residue was purified by column (1.8×18 cm) chromatography on silica gel, eluent EtOAc–hexane, 1:5. The products were eluted in order **12a**, **11a** and **13a**.

Compound 11a. Yield 0.014 g (1.6%), colorless crystals, mp 145-147°C (Et_2O–hexane). According to its ^{1}H NMR spectrum, the product is a mixture of diastereomers in a ration of 0.7:1.

Minor Isomer. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.42 (3H, s, NCH_3); 3.10 (1H, d, *J* = 16.2) and 3.78 (1H, d, *J* = 16.2, CH_2N); 3.66 (3H, s, OCH_3); 4.47 (1H, br. s, =C<u>H</u>CO_2Me); 5.21 (1H, s, C<u>H</u>Ph); 5.97 (1H, br. s, H-4 pyrrole); 6.22 (1H, d, *J* = 3.7, H-2 indole); 6.57 (1H, br. s, H-3 pyrrole); 6.66 (1H, br. s, H-5 pyrrole); 6.90-7.47 (14H, m, N(Me)–C<u>H</u>=, H-4,5,6,7 indole, H Ar); 8.18 (1H, br. s, NH).

Major Isomer. IR spectrum, ν, cm^{-1}: 1692 (C=O), 1621 (NC=CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, NCH_3); 3.52 (1H, d, *J* = 16.2) and 3.93 (1H, d, *J* = 16.2, CH_2N); 3.66 (3H, s, OCH_3); 4.49 (1H, br. s, =C<u>H</u>CO_2Me); 5.21 (1H, s, C<u>H</u>Ph); 6.02 (1H, br. s, H-4 pyrrole); 6.21 (1H, d, *J* = 3.7, H-2 indole); 6.51 (1H, br. s, H-3 pyrrole); 6.60 (1H, br. s, H-5 pyrrole); 6.90-7.47 (14H, m, N(Me)–C<u>H</u>=, H-4,5,6,7 indole, H Ar); 7.91 (1H, br. s, NH). Mass spectrum, *m*/*z*: 476 $[M+H]^+$. Found, %: C 78.39; H 6.30; N 8.58. $C_{31}H_{29}N_3O_2$. Calculated, %: C 78.29; H 6.15; N 8.84.

Compound 12a. Yield 0.09 g (10.5%), colorless crystals, mp 123-125°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1691 (C=O), 1619 (NC=CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76 (3H, s, NCH_3); 2.97 (1H, d, *J* = 16.0) and 3.46 (1H, d, *J* = 16.0, C<u>H</u>$_2$Ph); 3.61 (3H, s, OCH_3); 3.63 (1H, d, *J* = 16.0) and 3.79 (1H, d, *J* = 16.0, CH_2N); 4.30 (1H, br. s, =C<u>H</u>CO_2Me); 6.25 (1H, d, *J* = 3.2, H-3 pyrrole); 6.28 (1H, d, *J* = 3.6, H-3 indole); 6.34 (1H, d, *J* = 3.2, H-4 pyrrole); 6.71 (1H, br. d, *J* = 7.3, H Ar); 6.72 (1H, d, *J* = 3.6, H-2 indole); 6.75 (1H, t, *J* = 8.2, H-5 indole); 6.84 (2H, br. s, *J* = 6.9, H Ar); 6.95 (1H, br. s, N(Me)–C<u>H</u>=); 7.05 (1H, t, *J* = 7.3, H Ar); 7.16-7.22 (3H, m, H Ar); 7.26-7.34 (3H, m, H-6 indole, H Ar); 7.38 (1H, d, *J* = 8.2, H-4 indole); 7.46 (1H, d, *J* = 8.2, H-7 indole). Mass spectrum, *m*/*z* (I_{rel}, %): 475 $[M]^+$ (91), 369 (86), 269 (42), 244 (100), 154 (22). Found, %: C 78.39; H 6.05; N 8.69. $C_{31}H_{29}N_3O_2$. Calculated, %: C 78.29; H 6.15; N 8.84.

Compound 13a. Yield 0.017 g (2.0%), colorless crystals, mp 171-173°C (Et_2O). IR spectrum, ν, cm^{-1}: 1695 (C=O), 1617 (NC=CO_2CH_3). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.92 (3H, s, NCH_3); 2.95 (1H, d, *J* = 16.8) and 3.41 (1H, d, *J* = 16.8, C<u>H</u>$_2$Ph); 3.59 (3H, s, OCH_3); 3.66 (1H, s, *J* = 15.6) and 3.84 (1H, d, *J* = 15.6, CH_2N); 4.63 (1H, br. s, =C<u>H</u>CO_2Me); 6.17 (1H, d, *J* = 2.5, H-2 indole); 6.32 (1H, d, *J* = 3.1, H-4 pyrrole); 6.60 (1H, d, *J* = 3.1, H-3 pyrrole); 6.83 (1H, t, *J* = 8.1, H Ar); 6.85-6.89 (2H, m, H Ar); 6.97 (1H, br. s, N(Me)–C<u>H</u>=); 7.10-7.20 (6H, m, H Ar, H-6,5 indole); 7.26-7.29 (1H, m, H Ar); 7.32-7.39 (1H, m, H Ar); 7.40 (1H, d, *J* = 8.1, H-7 indole); 7.87 (1H, s, NH); 7.88 (1H, d, *J* = 8.1, H-4 indole). Mass spectrum, *m*/*z*: 476 $[M+H]^+$. Found, %: C 78.39; H 6.09; N 8.58. $C_{31}H_{29}N_3O_2$. Calculated, %: C 78.29; H 6.15; N 8.84.

Methyl (2*E*)-3-[(2-{2-[1*H*-Indol-3-yl(2-thienyl)methyl]-1*H*-pyrrol-1-yl}benzyl)(methyl)amino]-acrylate (11b), Methyl (2*E*)-3-[{2-[2-(1*H*-Indol-1-yl)-5-(2-thienylmethyl)-1*H*-pyrrol-1-yl]benzyl}(methyl)-amino]acrylate (12b), Methyl (2*E*)-3-[{2-[2-(1*H*-Indol-1-yl)-5-(2-thienylmethyl)-1*H*-pyrrol-1-yl]benzyl}-(methyl)amino]acrylate (13b). A solution of benzodiazepine **10b** (0.40 g, 1.4 mmol), methyl propiolate (0.14 g, 1.7 mmol), and indole (0.20 g, 1.7 mmol) in CH_2Cl_2 (15 ml) was kept at 35°C for 4 days. The reaction was monitored by TLC (Alufol, EtOAc–hexane, 1:10). The solvent was removed *in vacuo*. The residue was purified by column (1.8×30 cm) chromatography on silica gel, eluent EtOAc–hexane, 1:15. The products were eluted in order **12b**, **11b** and **13b**.

Compound 11b. Yield 0.15 g (18.3%), orange crystals, mp >155°C (decomp., EtOAc–hexane). According to its ^1H NMR spectrum, the product is a mixture of diastereomers in a ratio of 0.9:1.

Minor Isomer. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.55 (3H, s, NCH_3); 3.50 (1H, d, *J* = 16.1) and 3.83 (1H, d, *J* = 16.1, CH_2N); 3.68 (3H, s, OCH_3); 4.44 (1H, br. s, =C<u>H</u>CO_2Me); 5.49 (1H, s, Pyrr–C<u>H</u>–Ind); 6.09 (1H, dd, *J* = 1.4, *J* = 3.2, H-3 pyrrole); 6.27 (1H, br. s, H-2 indole); 6.63 (1H, d, *J* = 3.2, H-5 pyrrole); 6.73-6.75 (1H, m, H-4 pyrrole); 6.75-6.76 (1H, m, H-3 thienyl); 6.85-6.89 (1H, m, H-4 thienyl); 7.01-7.05 (1H, m, H Ar); 7.11 (1H, br. s, H-5 thienyl); 7.13-7.19 (3H, m, H Ar); 7.24-7.42 (5H, m, =C<u>H</u>NCH_3, H Ar); 8.37 (1H, br. s, NH).

Major Isomer. IR spectrum, ν, cm^{-1}: 1689 (C=O), 1623 (NC=CO_2CH_3). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, NCH_3); 3.23 (1H, d, *J* = 17.0) and 3.95 (1H, d, *J* = 17.0, CH_2N); 3.68 (3H, s, OCH_3); 4.54 (1H, br. d, *J* = 12.8, =C<u>H</u>CO_2Me); 5.47 (1H, s, Pyrr–C<u>H</u>–Ind); 6.24 (1H, t, *J* = 3.2, H-3 pyrrole); 6.28 (1H, br. s, H-2 indole); 6.57 (1H, br. s, H-4 pyrrole); 6.61 (1H, br. s, H-5 pyrrole); 6.70-6.73 (1H, m, H-3 thienyl); 6.85-6.89 (1H, m, H-4 thienyl); 6.94-6.97 (1H, m, H Ar); 6.98 (1H, br. s, H-5 thienyl); 7.13-7.19 (3H, m, H Ar); 7.24-7.42 (5H, m, H Ar, N(Me)–C<u>H</u>=); 8.02 (1H, br. s, NH). Mass spectrum, *m*/*z*: 482 $[M+H]^+$. Found, %: C 72.45; H 5.82; N 8.75. $C_{29}H_{27}N_3O_2S$. Calculated, %: C 72.32; H 5.65; N 8.72.

Compound 12b. Yield 0.032 g (4.0%), colorless crystals, mp 116-117°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 1691 (C=O), 1617 (NC=CO_2CH_3). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.90 (3H, br. s, NCH_3); 3.29 (1H, d, *J* = 17.4) and 3.58 (1H, d, *J* = 17.4, C<u>H</u>$_2$Het); 3.63 (3H, s, OCH_3); 3.90 (1H, d, *J* = 16.5) and 3.95 (1H, d, *J* = 16.5, CH_2N); 4.35 (1H, br. s, =C<u>H</u>CO_2Me); 6.32 (1H, d, *J* = 3.2, H-3 pyrrole); 6.34 (1H, d, *J* = 4.1, H-3 indole); 6.39 (1H, d, *J* = 3.2, H-4 pyrrole); 6.40-6.42 (1H, m, H-3 thienyl); 6.75 (1H, d, *J* = 4.1, H-2 indole); 6.81 (1H, d, *J* = 6.9, H Ar); 6.85 (1H, dd, *J* = 3.7, *J* = 5.0, H-4 thienyl); 7.08 (2H, t, *J* = 7.3, H Ar); 7.15-7.20 (2H, m, H-5 indole, H-5 thienyl); 7.28-7.31 (3H, м, H-6 indole, N(Me)–C<u>H</u>=, H Ar); 7.42 (1H, d, *J* = 8.2, H-4 indole); 7.50 (1H, d, *J* = 7.8, H-7 indole). Mass spectrum, *m*/*z*: 482 $[M+H]^+$. Found, %: C 72.65; H 5.44; N 8.48. $C_{29}H_{27}N_3O_2S$. Calculated, %: C 72.32; H 5.65; N 8.72.

Compound 13b. Yield 0.050 g (6.0%), beige crystals, mp 133-135°C (Et_2O). IR spectrum, ν, cm^{-1}: 1671 (C=O), 1608 (NC=CO_2CH_3). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.98 (3H, s, NCH_3); 3.23 (1H, d, *J* = 16.1) and 3.50 (1H, d, *J* = 16.1, C<u>H</u>$_2$Het); 3.60 (3H, s, OCH_3); 3.93 (1H, d, *J* = 16.5) and 3.99 (1H, d, *J* = 16.5, CH_2N); 4.35 (1H, br. s, =C<u>H</u>CO_2Me); 6.19 (1H, d, *J* = 2.3, H-2 indole); 6.38 (1H, d, *J* = 3.2, H-4 pyrrole); 6.39 (1H, br. s, H-3 thienyl); 6.62 (1H, d, *J* = 3.2, H-3 pyrrole); 6.81 (1H, t, *J* = 4.2, H-4 thienyl); 6.90 (1H, d, *J* = 7.3, H Ar); 7.05 (1H, br. s, N(Me)–C<u>H</u>=); 7.10 (1H, d, *J* = 5.0, H-5 thienyl); 7.14-7.20 (2H, m, H-5,6 indole); 7.26-7.28 (1H, m, H-7 indole); 7.35-7.44 (3H, m, H Ar); 7.90 (1H, d, *J* = 7.8, H-4 indole); 7.97 (1H, s, NH). Mass spectrum, *m*/*z*: 482 $[M+H]^+$. Found, %: C 72.48; H 5.71; N 8.79. $C_{29}H_{27}N_3O_2S$. Calculated, %: C 72.32; H 5.65; N 8.72.

Methyl (2*E*)-3-[(2-{2-[1*H*-Indol-3-yl(4-methoxyphenyl)methyl]-1*H*-pyrrol-1-yl}benzyl)(methyl)-amino]acrylate (11c), Methyl (2*E*)-3-[{2-[2-(1*H*-Indol-1-yl)-5-(4-methoxybenzyl)methyl-1*H*-pyrrol-1-yl]-benzyl}(methyl)amino]acrylate (12c). A solution of pyrrolobenzodiazepine **10c** (0.50 g, 1.64 mmol), methyl propiolate (0.31 g, 3.61 mmol), and indole (0.23 g, 1.97 mmol) in CH_2Cl_2 (25 ml) was kept at 35°C for 3 weeks. The reaction was monitored by TLC (Alufol, EtOAc–hexane, 1:5). The solvent was removed *in vacuo*. The residue was purified by column (1.8×18 cm) chromatography on silica gel, eluent EtOAc–hexane, 1:7. The product **12c** was eluted first, then product **11c**.

Compound 11c. Yield 0.04 g (4.8%), yellow crystals, mp 99-101°C (EtOAc–hexane). According to its ^{1}H NMR spectrum, the product is a mixture of diastereomers in a ratio of 0.8:1.

Minor Isomer. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, br. s, NCH_3); 3.66 (3H, s, OCH_3); 3.69 (1H, d, *J* = 16.5) and 3.97 (1H, d, *J* = 16.5, CH_2N); 3.76 (3H, s, CO_2CH_3); 4.49 (1H, br. s, =C<u>H</u>CO_2Me); 5.16 (1H, s, C<u>H</u>C_6H_4OMe); 6.00 (1H, d, *J* = 3.1, H-3 pyrrole); 6.22 (1H, t, *J* = 3.1, H-4 pyrrole); 6.55 (1H, br. s, H-2 indole); 6.64 (1H, br. s, H-5 pyrrole); 6.76 (2H, d, *J* = 7.8, H Ar); 6.95 (2H, d, *J* = 7.8, H Ar); 6.94-6.96 (1H, m, H Ar); 7.00-7.08 (2H, m, H Ar); 7.11 (1H, t, *J* = 7.3, H Ar); 7.15 (1H, d, *J* = 7.8, H Ar); 7.17-7.40 (4H, м, N(Me)–C<u>H</u>=, H Ar); 8.22 (1H, br. s, NH).

Major Isomer. IR spectrum, ν, cm^{-1}: 1698 (C=O), 1631 (NC=CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, br. s, NCH_3); 3.49 (1H, d, *J* = 16.5) and 3.92 (1H, d, *J* = 16.5, CH_2N); 3.65 (3H, s, OCH_3); 3.75 (3H, s, CO_2CH_3); 4.49 (1H, br. s, =C<u>H</u>CO_2Me); 5.15 (1H, s, C<u>H</u>C_6H_4OMe); 5.94 (1H, d, *J* = 3.1, H-3 pyrrole); 6.20 (1H, t, *J* = 3.1, H-4 pyrrole); 6.50 (1H, br. s, H-2 indole); 6.59 (1H, br. s, H-5 pyrrole); 6.76 (2H, d, *J* = 7.8, H Ar); 6.95 (2H, d, *J* = 7.8, H Ar); 6.94-6.96 (1H, m, H Ar); 7.00-7.08 (2H, m, H Ar); 7.11 (1H, t, *J* = 7.3, H Ar); 7.15 (1H, d, *J* = 7.8, H Ar); 7.17-7.40 (4H, m, N(Me)–C<u>H</u>=, H Ar); 7.93 (1H, br. s, NH). Mass spectrum, *m*/*z*: 506 $[M+H]^+$. Found, %: C 76.19; H 6.01; N 8.50. $C_{32}H_{31}N_3O_3$. Calculated, %: C 76.02; H 6.18; N 8.31.

Compound 12c. Yield 0.03 g (3.6%), colorless crystals, mp 129-131°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1695 (C=O), 1621 (NC=CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (3H, s, NCH_3); 3.19 (1H, d, *J* = 16.5) and 3.52 (1H, d, *J* = 16.5, C<u>H</u>$_2$C$_6$H$_4$OMe); 3.57 (1H, d, *J* = 15.8) и 3.69 (1H, d, *J* = 15.8, NCH_2); 3.61 (3H, s, ArOC<u>H</u>$_3$); 3.77 (3H, s, CO_2CH_3); 4.33 (1H, br. s, CH=C<u>H</u>CO_2CH_3); 6.21 (1H, d, *J* = 2.8, H-4 pyrrole); 6.30 (1H, d, *J* = 2.8, H-3 pyrrole); 6.34 (1H, d, *J* = 3.7, H-3 indole); 6.70-6.76 (3H, m, H Ar); 6.77-6.84 (3H, m, H Ar); 7.00 (1H, br. s, H-2 indole); 7.06 (1H, t, *J* = 7.8, H-5 indole); 7.15 (1H, t, *J* = 7.8, H-6 indole); 7.22-7.23 (3H, m, N(Me)–C<u>H</u>=, H Ar); 7.39 (1H, d, *J* = 7.8, H-4 indole); 7.48 (1H, d, *J* = 7.8, H-7 indole). Mass spectrum, *m*/*z*: 506 $[M+H]^+$. Found, %: C 76.12; H 6.28; N 8.20. $C_{32}H_{31}N_3O_3$. Calculated, %: C 75.99; H 6.16; N 8.29.

Methyl (2*E*)-3-[(2-{2-[1*H*-Indol-3-yl(phenyl)methyl]-5-methyl-1*H*-pyrrol-1-yl}benzyl)(methyl)-amino]acrylate (15). A solution of pyrrolobenzodiazepine **14** (0.50 g, 1.70 mmol), methyl propiolate (0.40 g, 5.20 mmol), and indole (0.24 g, 2.08 mmol) in CH_2Cl_2 (30 ml) was kept at 50°C for 12 days. The reaction was monitored by TLC (Alufol, EtOAc–hexane, 1:8). The solvent was removed *in vacuo*. The residue was purified by column (1.8×18 cm) chromatography on silica gel, eluent EtOAc–hexane, 1:6. Yield 0.17 g (20%), beige crystals, mp 195-197°C (Et_2O). IR spectrum, ν, cm^{-1}: 1671 (C=O), 1614 (NC=CO_2CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.94 (3H, s, CH_3); 2.44 (3H, s, NCH_3); 3.00 (1H, d, *J* = 17.0, CH_2N); 3.64 (1H, d, *J* = 17.0, CH_2N); 3.67 (3H, s, OCH_3); 4.49 (1H, br. s, =C<u>H</u>CO_2Me); 5.08 (1H, s, H Ph); 5.85-5.89 (1H, m, H-3 pyrrole); 5.93-5.98 (1H, m, H-4 pyrrole); 6.49 (1H, br. s, H-2 indole); 7.00-7.11 (4 H, m, H-4,5,6,7 indole); 7.12-7.20 (2H, m, H Ar); 7.22-7.43 (8H, m, N(Me)–C<u>H</u>=, H Ar); 7.89 (1H, br. s, NH). Mass spectrum, *m*/*z*: 490 $[M+H]^+$. Found, %: C 78.58; H 6.43; N 8.65. $C_{32}H_{31}N_3O_2$. Calculated, %: C 78.50; H 6.38; N 8.58.

X-ray Structure Investigation of Compounds 12a and 13a. Crystal of compound **12a** was grown from EtOAc–hexane ($C_{31}H_{29}N_3O_2$, *M* 475.57). Crystal structure parameters at 100 K: crystal system triclinic, space group *P*1. Unit cell dimensions: *a* 8.2348(7), *b* 10.2414(9), *c* 15.3342(14) Å; α 104.142(2), β 99.437(2), γ 90.052(2)°; *V* 1235.92(19) Å^3; *Z* 2; d_{calc} 1.278 g/cm^3; *F*(000) 504; μ 0.081 mm^{-1}. Crystal of compound **13a** was grown from EtOAc–hexane ($C_{31}H_{29}N_3O_2$, *M* 475.57). Crystal structure parameters at 100 K: crystal system monoclinic, space group $P2_1/n$. Unit cell dimensions: *a* 17.5997(18), *b* 7.3471(7), *c* 20.602(2) Å; α 90, β 110.045(2), γ 90°; *V* 2502.6(4) Å^3; *Z* 4; d_{calc} 1.262 g/cm^3; *F*(000) 1008; μ 0.080 mm^{-1}. The unit cell parameters

and reflection intensities for compounds **12a** and **13a** were measured on an automatic three circle diffractometer Bruker SMART APEX-II CCD with a two-coordinated detector (MoKα radiation, graphite monochromator, φ- and ω-scanning). The obtained data were corrected for X-ray absorption using SADABS software [12]. The structures were solved by the direct method and refined with the full-matrix least-squares method on F^2 with anisotropic thermal parameters for all the non-hydrogen atoms. The hydrogen atom on the amino group of compound **13a** was identified objectively from Fourier difference syntheses and refined isotropically. The positions of other hydrogen atoms in both compounds were calculated geometrically and included in the refinement with the fixed positional (the "rider" model) and thermal ($U_{iso}(H) = 1.5U_{eq}(C)$ for the methyl groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for all other groups) parameters. All calculations were performed using SHELXTL software [13]. The atom coordinate, bond length, valence angle, and anisotropic thermal parameter tables for compounds **12a** and **13a** have been deposited at the Cambridge Crystallographic Data Center (deposits CCDC 931405 and CCDC 931404).

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