1,2,3,6-Tetrahydropyrrolo[1,2-*d*][1,4]diazocines. Reactions of 1-methyl-2-R-tetrahydropyrrolo[1,2-*a*]pyrazines with alkynes

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The reactions of 6-formyl- and 6-trifluoroacetyl-1-methyl-2-R-tetrahydropyrrolo[1,2-*a*]-pyrazines with activated alkynes in methanol and acetonitrile have been studied. Terahydropyrrolo[1,2-*d*][1,4]diazocine derivatives were synthesized at the first time.

Key words: tetrahydropyrrolo[1,2-*a*]pyrazines, pyrrolo[1,2-*d*][1,4]diazocines, tandem transformation, ring expansion.

Recently we have reported a novel tandem transformations involving expansion and cleavage of the terahydropyridine ring fused at the *c*-edge with the heterocyclic or benzene moiety under the action of alkynes activated by the electron-withdrawing substituents in protic and aprotic solvents.[1—4] Thus, the tandem transformations of 2-R-tetrahydropyrrolo[3,2-*c*]pyridines[1] and 2,3,5-trimethyl-7-trifluoroacetylpyrrolo[1,2-*c*]pyrimidine[2] have been studied. The pathways of transformations of these compounds governed by the electronic effects of the substituents in the α-position, the nature of the solvent and substituents at the nitrogen atoms of the pyrrole and the tetrahydropyridine rings as well as the character of fusion of the latter.

In aprotic solvents, unsubstituted at the N(1) atom as well as 1-vinyl-4,5,7-trimethyltetrahydropyrrolo[3,2-*c*]-pyridines **1** (R^1 = H; R^2 = H, CH=CH_2) under the action of acetylenedicarboxylic acid ester (dimethyl acetylenedicarboxylate, DMAD) furnished exclusively 3-vinylpyrroles **2**, while 2-trifluoroacetyl-, formyl-, and dicyanovinyl-substituted derivatives gave the mixtures of 3-vinylpyrroles **2** and azocines **3**. In methanol, tetrahydropyridine ring underwent the cleavage involving one molecule of methanol to give the mixture of diastereomeric 3-methoxyethylpyrroles **4** (Scheme 1).

The reaction of 7-trifluoroacetyl-substituted pyrrolo-[1,2-*c*]pyrimidine with alkynes followed another pattern (Scheme 2).

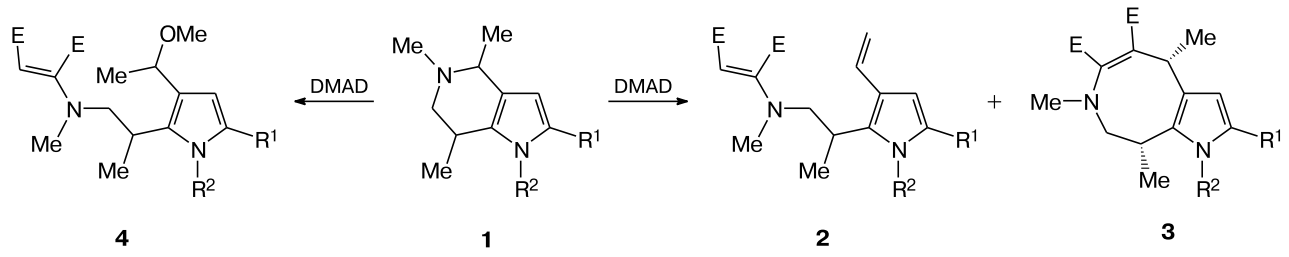
In methanol, the ring opening in the presence of DMAD involved only the aminal moiety to give pyrroles **5**. If the reaction was carried out either in ethanol or acetonitrile in the presence of methyl propiolate, the cleavage of the aminal moiety as well as the N(2)—C(3) bond took place, which led to the mixtures of pyrroles **5** and **6**.

It was of interest to study the reactivity of tetrahydropyrrolo[1,2-*a*]pyrazines in this reaction as the fusion mode of the azine and azole rings in the latter differed from that in the compounds described above.

In the present work the reaction pattern of 1-methyl-2-methyl(ethyl)-6-R-tetrahydropyrrolo[1,2-*a*]pyrazines **7—10** with alkynes in methanol and acetonitrile was studied.

The starting 1-methyl-3,4-dihydropyrrolo[1,2-*a*]-pyrazine was synthesized from acetylfuran by the known

Scheme 1



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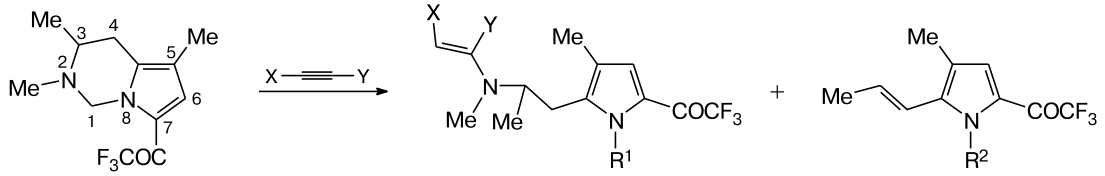
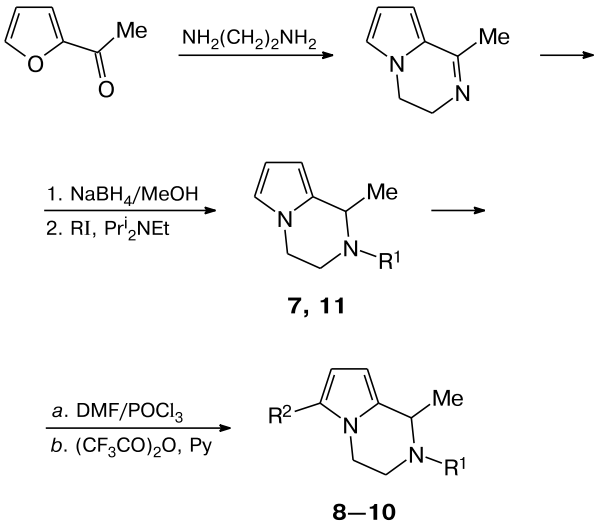
Scheme 2



X = Y = CO_2Me, R^1 = H, CH_2OMe; X = CO_2Et, Y = H, R^1 = H; R^2 = H, CH_2—NMe—CH=CH—CO_2Et

procedure.[5–7] The reduction of acetylfuran and subsequent alkylation of the intermediate with methyl and ethyl iodide in the presence of Hünig´s base furnished 2-alkylated tetrahydropyrrolo[1,2-*a*]pyrazines (TGPP) **7** and **11**, which were converted into 6-formyl-substituted TGPP **9** and **8** by the Vilsmeier—Haack reaction (Scheme 3).

Scheme 3



Compound	R^1	R^2
7	Et	H
8	Me	CHO
9	Et	CHO
10	Et	CF_3CO
11	Me	H

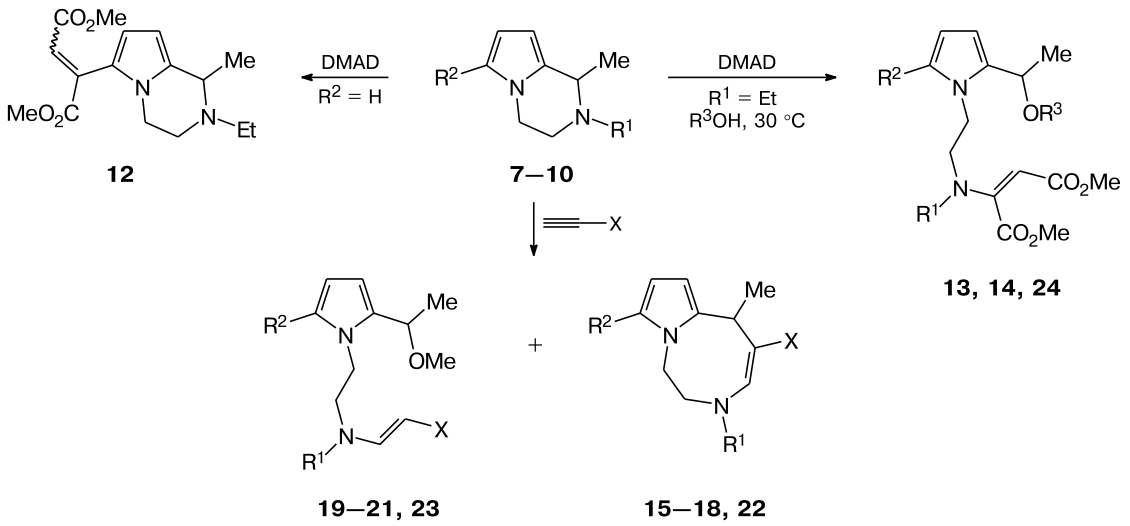
Treatment of compound **7** with trifluoroacetic anhydride afforded 6-trifluoroacetyl derivative **10**. Introduction of the acyl groups in the position 6 of TGPP **7** is could be explained by the fact that the reaction of compound **7** with DMAD in acetonitrile at 50 °C, in contrast with the previously described tetrahydropyrrolo[3,2-*c*]pyridines,[1] resulted in the α-vinylation of the pyrrole ring instead of the tetrahydropyridine fragment transformations. (Scheme 4). Vinyl-substiuted TGPP **12** was isolated as the mixture of *Z*- and *E*-isomers in 1 : 1 ratio (according to the ^{1}H NMR spectra) in 36% total yield. (see Scheme 4).

No reaction of formyl-substituted TGPP **8** and **9** with even 3—7-fold excess of DMAD was observed in acetonitrile upon reflux. In methanol, reaction of 2-ethyl-substituted TGPP **9** with DMAD at 30 °C for 7 days furnished 2-(1-methoxyethyl)substituted pyrrole **13** in 47% yield. Compound **13** is the result of the cleavage process involving one molecule of methanol. The similar cleavage of compound **8** took place in aqueous acetonitrile. Hydroxyethyl-substituted pyrrole **14** was isolated in 7% yield (see Scheme 4).

The reaction of formyl-substituted derivatives **8** and **9** with terminal alkynes, methyl propiolate, and *p*-tosylacetylene at 30 °C for 7 and 14 days, respectively, resulted in the multi-component mixtures, from which pyrrolodiazocines **15—17** were isolated. Compound **9** reacted with acetylacetylene only upon reflux (14 days) giving pyrrolodiazocine **18** in the 31% yield. The reaction of compounds **8** and **9** with methyl propiolate and acetyl acetylene in MeOH at 30 °C afforded 2-(1-methoxyethyl)-substituted pyrroles **19**, **20**, and **21** in the yields of 9, 25, and 54%, respectively. No reaction of 6-trifluoromethyl-substituted TGPP **10** with methyl propiolate was found in acetonitrile upon reflux. If this reaction was carried out in methanol at 30 °C, pyrrolodiazocine **22** and 2-methoxyethyl-substituted pyrrole **23** were formed in 1 : 1.5 ratio. The reaction of compound **10** with DMAD in methanol led to the tetrahydropyrazine ring cleavage affording pyrrole **24** in 89% yield. The attempts to obtain pyrrolodiazocines from 2-methoxyethyl-substituted pyrroles **13**, **14**, **19—21**, and **24** applying the conditions, which were used in the case of 3-methoxymethyl(methoxyethyl)pyrroles, namely, boron trifluoride-mediated cyclization, failed. In contrast with studied previously pyrrolopyridines and pyrrolopyrimidines, pyrrolopyrazines reacted with alkynes mainly upon heating and the reactions accompanied by a significant resinification. Column chromatography has to be used for the isolation of the products.

The structures of synthesized pyrrolodiazocines **15—18**, **22** and substituted pyrroles **13**, **14**, **19—21**, and **23**, **24** were confirmed by the IR, ^{1}H NMR, and mass spectroscopic data. The mass spectra of all compounds revealed

Scheme 4



Compound	R^1	R^2	X (R^3)	Compound	R^1	R^2	X (R^3)
13	Et	CHO	(Me)	**19**	Me	CHO	CO_2Me
14	Me	CHO	(H)	**20**	Et	CHO	CO_2Me
15	Me	CHO	CO_2Me	**21**	Et	CHO	Ac
16	Et	CHO	CO_2Me	**22**	Et	CF_3CO	CO_2Me
17	Et	CHO	Ts	**23**	Et	CF_3CO	CO_2Me
18	Et	CHO	Ac	**24**	Et	CF_3CO	(Me)

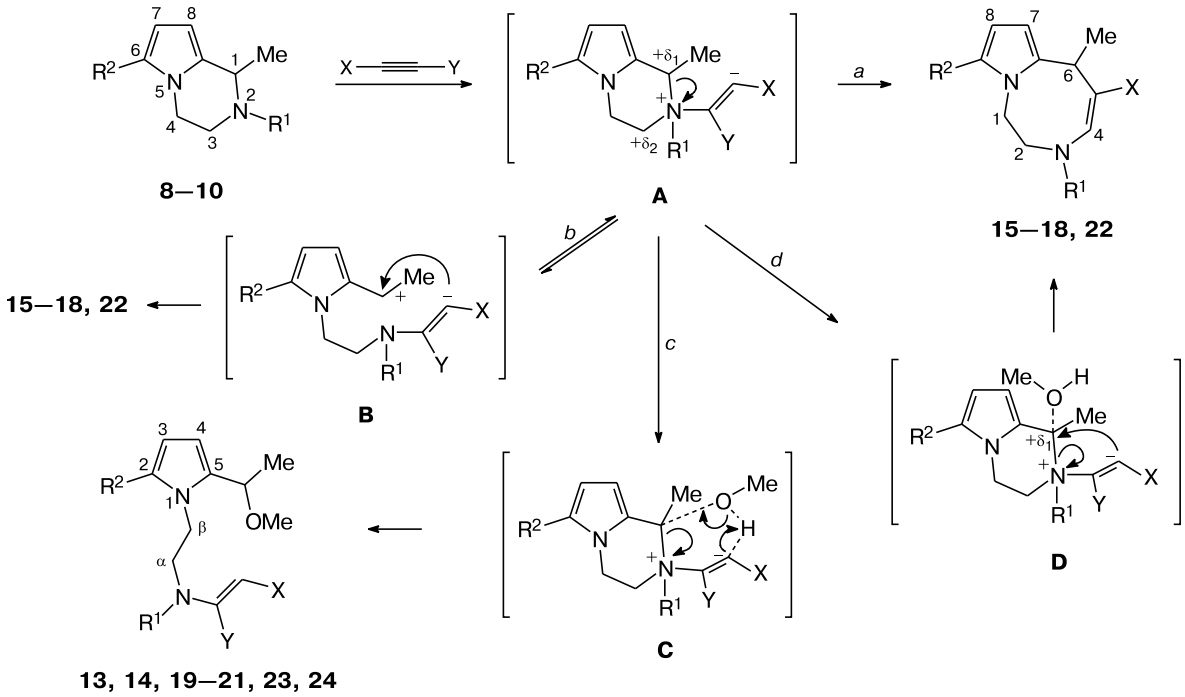
the peaks of different intensity attributed to the molecular ions. In the IR spectra, the stretching vibrations of the carbonyl group, which were attributed to the formyl (1641—1660 cm^{-1}), acetyl (1683—1689 cm^{-1}), trifluoroacetyl (1680—1681 cm^{-1}), and ester (1702—1750 cm^{-1}) fragments, were observed. The ^1H NMR spectra contained the signals for all protons of compounds **12—24** with reasonable chemical shifts and coupling constant values. The ^1H NMR spectra of pyrrolodiazocines **15—18** and **22** exhibited the singlet signals at δ 7.20—7.52 characteristic of the H(4) protons. The ^1H NMR spectra of pyrroles **13**, **14**, and **24** contained characteristic signals of the vinyl fragment at δ 4.79—4.91. In the case of pyrroles **19—21** and **23**, the characteristic signals are broadened singlets in the range of δ 4.67—5.08 and doublet signals in the range of δ 7.36—7.43 (J = 13.1—13.2 Hz), which indicated the *trans*-configuration of the vinyl group. The reactions of pyrrolopyrazines **8—10** with alkynes proceeded similarly to that for other fused tetrahydropyridazines studied by us (Scheme 5).

The initial step of the reaction is the formation of the zwitterion **A**. In such a process, the accessibility of the lone electron pair of the nitrogen atom is important. The latter depended on the bulkiness of the substituents R^1, as well as the geometry of the hydrogenated azine ring. Apparently, these facts explained the significant decrease in the reactivity of pyrrolopyrazines in the tandem transformations as compared with tetrahydropyrrolopyridines.[1]

In the aprotic solvent, the C(1)—N bond in the zwitterion **A** is loosened, which facilitated the nucleophilic attack of the C(1) atom by the anionic center, thus favoring the formation of pyrrolodiazocines **15—18** and **22** (pathway *a*). Therefore, one cannot exclude the cleavage of the C(1)—N bond of the zwitterion **A** to form the second intermediate zwitterion **B** (pathway *b*), which, from one hand, could underwent ring closure to give diazocines, and, from the other hand, could be involved in many transformations typical of carbocations. In our opinion, the formation of the multi-component mixtures could be regarded as indirect evidence of the formation of the zwitterion **B**. In methanol, the zwitterion **A** gave substituted pyrroles **13**, **14**, **19—21**, **23**, and **24**. The latter compounds formed *via* the transition state **C**, which is the result of the cleavage of the C(1)—N bond of the zwitterion **A** involving one molecule of methanol (pathway *c*). The methanol nucleophilic assistance favored the formation of pyrrolodiazocines *via* the transition state **D** (pathway *d*).

In summary, the possibility of the transformation of tetrahydropyrrolo[1,2-*a*]pyrazines into tetrahydropyrrolo[1,2-*d*][1,4]diazocines and 2-R-5-methoxyethylpyrroles with the vinylaminoethyl substituent at the nitrogen atom in the presence of alkynes was demonstrated. The effects of the solvents, the substituents at the nitrogen atom of the piperazine ring as well as the nature of the fused aromatic system[1,2] on the facility and the direction of the transformations was demonstrated.

Scheme 5



Experimental

The IR spectra were recorded on an Infralum FT-801 Fourier-transform IR spectrometer in KBr pellets or films (in the case of liquid samples). The mass spectra were obtained on a Finnigan MAT 95 XL instrument (EI, 70 eV). The LC/MS was performed on a Agilent 1100 Series chromatograph coupled with an Agilent Technologies LC/MSD VL mass spectrometer (electrospray ionization, APCI), ELSD Sedex 75. The ^{1}H NMR were recorded on a Bruker-400 instrument in $CDCl_3$ using Me_4Si as internal standard. TLC was performed on precoated plates Silufol UV-254 and Alufol (the spots were visualized in an iodine chamber). Column chromatography was performed with neutral aluminum oxide (Fluka, Brockmann II, 60 mesh).

1-Methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine. To a solution of 1-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine[5,6] (16.5 g, 0.12 mol) in MeOH (70 mL), sodium borohydride (5.14 g, 0.14 mol) was added portionwise at 20 °C. After 3 days (TLC monitoring), the solvent was removed *in vacuo*. The residue was diluted with water (40 mL), the mixture that formed was extracted with diethyl ether (3×150 mL), the combined extract was dried with $MgSO_4$, and the solvent was removed *in vacuo*. Purification of the residue by column chromatography afforded the title compound in a yield of 8.17 g (49%). Found (%): C, 70.54; H, 8.89; N, 20.50. $C_8H_{12}N_2$. Calculated (%): C, 70.59; H, 8.82; N, 20.59. ^{1}H NMR, δ: 1.45 (d, 3 H, 1-Me, J = 6.7 Hz); 3.15—3.22 (m, 1 H, C(4)H); 3.34 (dt, 1 H, C(4)H, J = 3.3 Hz, J = 12.7 Hz); 3.90—3.96 (m, 2 H, C(3)H_2); 4.06 (q, 1 H, C(1)H, J = 6.7 Hz); 5.88—5.92 (m, 1 H, C(8)H); 6.14—6.18 (m, 1 H, C(7)H); 6.55—6.66 (m, 1 H, C(6)H). MS, m/z (I_{rel} (%)): 136 $[M]^+$ (10), 135 (12), 121 (100), 94 (14), 65 (9), 42 (9), 41 (9), 39 (12).

1,2-Dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (11). A solution of 1-methyl-1,2,3,4-tetrahydropyrrolopyrazine (8.17 g, 0.06 mol), Hünig's base (17.41 g, 0.14 mol), and methyl iodide (14.02 g, 0.1 mol) in MeCN (30 mL) was kept at 20 °C for 3 days under argon (TLC monitoring). The solvent was removed *in vacuo*, the residue was diluted with CH_2Cl_2 (20 mL) and extracted with water (3×20 mL), the organic layer was dried with $MgSO_4$. Removal of the solvent and purification of the residue by column chromatography (aluminum oxide) afforded compound **11** (2.44 g, 30%), brown oil. Found (%): C, 71.97; H, 9.42; N, 20.35. $C_9H_{14}N_2$. Calculated (%): C, 72.00; H, 9.33; N, 18.66. ^{1}H NMR, δ: 1.45 (d, 3 H, Me, J = 6.0 Hz); 2.46 (s, 3 H, NMe); 2.75 (ddd, 1 H, C(4)H, J = 4.5 Hz, J = 11.6 Hz, J = 16.0 Hz); 3.05 (dq, 1 H, C(3)H, J = 6.6 Hz, J = 12.1 Hz); 3.36 (q, 1 H, J = 6.0 Hz); 3.93 (dq, 1 H, C(3)H, J = 6.2 Hz, J = 12.1 Hz); 4.09 (ddd, 1 H, C(4)H, J = 4.5 Hz, J = 11.6 Hz, J = 16.0 Hz); 5.89 (t, 1 H, C(8)H, J = 3.4 Hz); 6.17 (t, 1 H, C(7)H, J = 3.4 Hz); 6.54 (br.s, 1 H, C(6)H). MS, m/z: 151 $[M + 1]^+$.

2-Ethyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (7) was obtained analogously to compound **11** from NH-pyrrolopyrazine (5.97 g, 0.04 mol), Hünig's base (8.51 g, 0.07 mol), and ethyl iodide (7.55 g, 0.05 mol) in MeCN (50 mL). Yield of pyrrolopyrazine **7** was 3.90 g (54%) **7**, brown oil. Found (%): C, 73.25; H, 9.81; N, 17.05. $C_{10}H_{16}N_2$. Calculated (%): C, 73.17; H, 9.77; N, 17.26. ^{1}H NMR, δ: 1.15 (t, 3 H, NCH$_2$<u>Me</u>, J = 7.4 Hz); 1.43 (d, 3 H, Me, J = 6.7 Hz); 2.50—2.54 (m, 1 H, NC<u>H</u>$_2$Me); 2.75 (ddd, 1 H, C(4)H, J = 4.7 Hz, J = 9.4 Hz, J = 12.3 Hz); 2.89—2.92 (m, 1 H, NC<u>H</u>$_2$Me); 3.20 (dt, 1 H, C(4)H, J = 4.7 Hz, J = 12.3 Hz); 3.73 (q, 1 H, C(1)H, J = 6.7 Hz); 3.93—4.04 (m, 2 H, C(3)H_2); 5.86—5.93 (m, 1 H, C(8)H); 6.13—6.17 (m, 1 H, C(7)H); 6.51—6.55 (m, 1 H, C(6)H). MS, m/z (I_{rel} (%)): 164 $[M]^+$ (5), 163 (6), 149 (100), 121 (10), 106 (9), 94 (9), 92 (7), 65 (6), 42 (10).

1-Methyl-2-R-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carbaldehyde 8 and 9 (general procedure). To DMF (7.01 g, 0.096 mol) phosphorus oxychloride (4.91 g, 0.032 mol) was added dropwise at −5 °C. The mixture was heated to room temperature and stirred for 40 min. To a resulting mixture, a solution of pyrrolopyrazine **7** or **11** (0.016 mol) in DMF (5 mL) was added dropwise. After completion of the reaction (TLC monitoring), the reaction mixture was alkalized with 10% aqueous NaOH to pH 10, extracted with diethyl ether (3×50 mL), and the combined extract was dried with $MgSO_4$. Removal of the solvent *in vacuo* and purification of the residue by column chromatography (aluminum oxide) afforded the target compound.

1,2-Dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (8). Yield 82%, brown oil. Found (%): C, 67.48; H, 7.90; N, 15.62. $C_{10}H_{14}N_2O$. Calculated (%): C, 67.42; H, 7.87; N, 15.73. IR, ν/cm^{-1}: 1655 (CHO). ^{1}H NMR, δ: 1.45 (d, 3 H, Me, J = 6.5 Hz); 2.44 (s, 3 H, NMe); 2.71 (ddd, 1 H, C(4)H, J = 4.0 Hz, J = 11.1 Hz, J = 12.4 Hz); 3.01 (ddd, 1 H, C(3)H, J = 2.6 Hz, J = 4.6 Hz, J = 13.4 Hz); 3.41 (q, 1 H, C(1)H, J = 6.5 Hz); 4.21 (ddd, 1 H, C(4)H, J = 4.0 Hz, J = 11.1 Hz, J = 12.4 Hz); 4.59 (ddd, 1 H, C(3)H, J = 2.6 Hz, J = 4.6 Hz, J = 13.4 Hz); 6.02 (d, 1 H, C(8)H, J = 4.1 Hz); 6.89 (d, 1 H, C(7)H, J = 4.1 Hz); 9.44 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 178 [M]$^+$ (6), 163 (100), 56 (7), 54 (6), 43 (8), 42 (59), 40 (12).

2-Ethyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (9). Yield 64%, brown oil. Found (%): C, 68.82; H, 8.37; N, 14.69. $C_{11}H_{16}N_2O$. Calculated (%): C, 68.75; H, 8.33; N, 14.58. IR, ν/cm^{-1}: 1655 (CHO). ^{1}H NMR, δ: 1.14 (t, 3 H, Me$\underline{\text{Me}}$CH$_2$, J = 7.2 Hz); 1.41 (d, 3 H, Me, J = 6.6 Hz); 2.51 (dq, 1 H, C$\underline{\text{H}}_2$Me, J = 7.2 Hz, J = 14.2 Hz); 2.71 (ddd, 1 H, C(4)H, J = 4.3 Hz, J = 8.8 Hz, J = 12.8 Hz); 2.85 (dq, 1 H, C$\underline{\text{H}}_2$Me, J = 7.2 Hz, J = 14.2 Hz); 3.17 (dt, 1 H, C(4)H, J = 4.5 Hz, J = 12.8 Hz); 3.78 (q, 1 H, C(1)H, J = 6.6 Hz); 4.25 (ddd, 1 H, C(3)H, J = 4.5 Hz, J = 8.8 Hz, J = 13.5 Hz); 4.49 (dt, 1 H, C(3)H, J = 4.5 Hz, J = 13.5 Hz); 6.00 (d, 1 H, C(8)H, J = 4.0 Hz); 6.86 (d, 1 H, C(7)H, J = 4.0 Hz); 9.42 (s, 1 H, CHO). MS, m/z: 193 [M + 1]$^+$.

1-(2-Ethyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazin-6-yl)-2,2,2-trifluotoethanone (10). To a solution of pyrrolopyrazine **7** (2.0 g, 0.012 mol) and pyridine (2.0 g, 0.029 mol) in anhydrous CH_2Cl_2 (40 mL), trifluoroacetic anhydride (5.12 g, 0.024 mol) was added dropwise at 35 °C. After completion of the reaction (TLC monitoring), water (40 mL) was added and the mixture alkalized by aqueous $NaHCO_3$ to pH 10. The organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (2×20 mL), the combined organics was dried with $MgSO_4$. Removal of the solvent *in vacuo* and purification of the residue by column chromatography afforded compound **10** in a yield of 1.87 g (60%), brown oil. Found (%): C, 55.44; H, 5.81; N, 10.85. $C_{12}H_{15}F_3N_2O$. Calculated (%): C, 55.38; H, 5.77; N, 10.77. IR, ν/cm^{-1}: 1660 ($COCF_3$). ^{1}H NMR, δ: 1.14 (t, 3 H, CH$_2$$\underline{\text{Me}}$, J = 7.9 Hz); 1.44 (d, 3 H, Me, J = 6.6 Hz); 2.55 (ddd, 1 H, C$\underline{\text{H}}_2$Me, J = 6.6 Hz, J = 7.9 Hz, J = 14.4 Hz); 2.75 (dq, 1 H, C(3)H, J = 7.9 Hz, J = 13.1 Hz); 2.86 (ddd, 1 H, C$\underline{\text{H}}_2$Me, J = 6.6 Hz, J = 7.9 Hz, J = 14.4 Hz); 3.22 (dt, 1 H, C(3)H, J = 5.3 Hz, J = 13.1 Hz); 3.83 (q, 1 H, C(1)H, J = 6.6 Hz); 4.27—4.33 (m, 1 H, C(4)H); 4.50 (dt, 1 H, C(4)H, J = 5.3 Hz, J = 14.4 Hz); 6.09 (d, 1 H, C(8)H, J = 3.4 Hz); 7.20 (br.s, 1 H, C(7)H). MS, m/z (I_{rel} (%)): 260 [M]$^+$ (3), 245 (100), 163 (7), 147 (7), 91 (7), 69 (88), 65 (18), 56 (40), 55 (11), 54 (14), 43 (21), 42 (72), 41 (19).

(*Z*)- and (*E*)-Dimethyl 2-(2-ethyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-6-yl)-2-butenedioate (12). A solution of pyrrolopyrazine **7** (0.4 g, 2.4 mmol) and DMAD (0.77 g, 5.4 mmol) in MeCN (15 mL) was heated at 50 °C (TLC monitoring). The solvent was removed and the residue was purified by column chromatography (aluminum oxide). Yield 0.26 g (36%), yellow oil. Found (%): C, 63.00; H, 6.95; N, 9.25. $C_{16}H_{22}N_2O_4$. Calculated (%): C, 62.85; H, 7.22; N, 9.20. IR, ν/cm^{-1}: 1735 (CO_2Me). ^{1}H NMR, δ: 1.08 (t, 3 H, CH$_2$$\underline{\text{Me}}$, J = 7.2 Hz); 1.12 (t, 3 H, CH$_2$$\underline{\text{Me}}$, J = 7.2 Hz); 1.39 (d, 3 H, Me, J = 6.7 Hz); 1.42 (d, 3 H, Me, J = 6.7 Hz); 2.50—2.55 (m, 2 H, C$\underline{\text{H}}_2$Me); 2.68—2.73 (m, 2 H, C(3)H$_2$); 2.85—2.90 (m, 2 H, C$\underline{\text{H}}_2$Me); 3.13—3.18 (m, 2 H, C(3)H$_2$); 3.66 (s, 3 H, OMe); 3.68—3.73 (m, 2 H, C(1)H); 3.73 (s, 3 H, OMe); 3.74—3.77 (m, 2 H, C(4)H$_2$); 3.80 (s, 3 H, OMe); 3.96 (s, 3 H, OMe); 4.03—4.07 (m, 2 H, C(4)H$_2$); 5.85 (s, 1 H, CH=); 5.92 (d, 1 H, C(8)H, J = 3.7 Hz); 5.97 (d, 1 H, C(8)H, J = 4.1 Hz); 6.25 (d, 1 H, C(7)H, J = 3.7 Hz); 6.41 (d, 1 H, C(7)H, J = 4.1 Hz); 6.86 (s, 1 H, CH=). MS, m/z: 307 [M + 1]$^+$.

Reaction of pyrrolopyrazines 8—10 with dimethyl acetylenedicarboxylate (general procedure). A solution of pyrrolopyrazine **9** or **10** (2.8 mmol) and DMAD (5.6 mmol) in MeOH (20 mL) was kept at 30 °C. In the case of pyrrolopyrazoline **8**, a solution of **8** (2.8 mmol) and DMAD (9.6 mmol) in MeCN (20 mL) was refluxed. After completion of the reaction (TLC monitoring), the solvent was removed *in vacuo*. Purification of the residue by column chromatography (aluminum oxide, eluent — ethyl acetate—heptane, 1 : 10) afforded pyrroles **13**, **14**, and **24**.

Dimethyl 2-(*N*-ethyl-{2-[2-formyl-5-(1-methoxyethyl)-1*H*-pyrrol-1-yl]ethyl}amino)maleate (13). Yield 47%, yellow oil. Found (%): C, 60.10; H, 6.91; N, 7.49. $C_{18}H_{26}N_2O_6$. Calculated (%): C, 59.02; H, 7.10; N, 7.65. IR, ν/cm^{-1}: 1650 (CHO); 1737 (CO_2Me). ^{1}H NMR, δ: 1.10 (t, 3 H, CH$_2$$\underline{\text{Me}}$, J = 7.1 Hz); 1.54 (d, 3 H, CH$\underline{\text{Me}}$, J = 6.5 Hz); 3.04—3.13 (m, 1 H, C$_\beta$H); 3.15—3.22 (m, 1 H, C$_\beta$H); 3.30 (s, 3 H, OMe); 3.39—3.48 (m, 2 H, C$\underline{\text{H}}_2$Me); 3.65 (s, 3 H, CO_2Me); 3.95 (s, 3 H, CO_2Me); 4.41—4.52 (m, 2 H, C$_\alpha$H$_2$); 4.59 (q, 1 H, C$\underline{\text{H}}$Me, J = 6.5 Hz); 4.84 (br.s, 1 H, CH=); 6.26 (d, 1 H, C(4)H, J = 4.1 Hz); 6.93 (d, 1 H, C(3)H, J = 4.1 Hz); 9.49 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 366 [M]$^+$ (5), 335 (6), 334 (7), 247 (5), 213 (6), 201 (9), 200 (100), 179 (8), 164 (7), 158 (9), 154 (29), 126 (9), 122 (10), 112 (11), 96 (51), 94 (11), 82 (16), 68 (16), 59 (49), 56 (9), 45 (41), 42 (12), 41 (8).

Dimethyl 2-(*N*-methyl-{2-[2-formyl-5-(1-hydroxyethyl)-1*H*-pyrrol-1-yl]ethyl}amino)maleate (14). Yield 7%, yellow oil. Found (%): C, 56.89; H, 6.32; N, 8.07. $C_{16}H_{22}N_2O_6$. Calculated (%): C, 56.80; H, 6.51; N, 8.28. IR, ν/cm^{-1}: 1661 (CHO); 1743 (CO_2Me). ^{1}H NMR, δ: 1.63 (d, 3 H, CH$\underline{\text{Me}}$, J = 6.0 Hz); 2.87 (s, 3 H, NMe); 3.39—3.49 (m, 1 H, C$_\beta$H); 3.50—3.59 (m, 1 H, C$_\beta$H); 3.65 (s, 3 H, CO_2Me); 3.94 (s, 1 H, CO_2Me); 4.33 (q, 1 H, C$\underline{\text{H}}$Me, J = 6.0 Hz); 4.63—4.74 (m, 2 H, C$_\alpha$H$_2$); 4.94 (br.s, 1 H, CH=); 6.28 (d, 1 H, C(4)H, J = 4.0 Hz); 6.92 (d, 1 H, C(3)H, J = 4.0 Hz); 9.49 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 338 [M]$^+$ (3), 307 (10), 306 (15), 279 (20), 199 (22), 188 (32), 186 (100), 140 (19), 126 (16), 108 (11), 182 (90), 68 (19), 59 (73), 45 (53).

Dimethyl 2-(*N*-ethyl-{2-[2-(2′,2′,2′-trifluoroacetyl)-5-(1-methoxyethyl)-1*H*-pyrrol-1-yl]ethyl}amino)maleate (24). Yield 89%, yellow oil. Found (%): C, 52.28; H, 6.00; N, 6.30. $C_{19}H_{25}F_3N_2O_6$. Calculated (%): C, 52.53; H, 5.76; N, 6.45. IR, ν/cm^{-1}: 1648 (CO); 1750 (CO_2Me). ^{1}H NMR, δ: 1.12 (t, 3 H,

$CH_2\underline{Me}$, J = 7.2 Hz); 1.56 (d, 3 H, $CH\underline{Me}$, J = 6.5 Hz); 3.09—3.26 (m, 2 H, $C_\beta H_2$); 3.33 (s, 3 H, OMe); 3.43 (q, 2 H, $C\underline{H}_2Me$, J = 7.2 Hz); 3.65 (s, 3 H, CO_2Me); 3.95 (s, 3 H, CO_2Me); 4.43—4.50 (m, 1 H, $C\underline{H}Me$); 4.56—4.64 (m, 2 H, $C_\alpha H_2$); 4.79 (s, 1 H, CH=); 6.34 (d, 1 H, C(4)H, J = 4.5 Hz); 7.27 (d, 1 H, C(3)H, J = 4.5 Hz). MS, m/z (I_{rel} (%)): 434 $[M]^+$ (16), 419 (15), 403 (17), 402 (31), 232 (8), 201 (20), 200 (100), 172 (7), 154 (10), 112 (11), 96 (26), 59 (10), 45 (17).

Reaction of tetrahydropyrrolo[1,2-*a*]pyrazines 8—10 with terminal alkynes (general procedure). To a solution of compound **8—10** (2.4 mmol) in MeCH (20 mL) or MeOH (15 mL), methyl propiolate or *p*-tosylacetylene (4.8 mmol) was added at 30 °C The reaction mixture was stirred at 30 °C, or refluxed in the case of the reaction of compound **9** with acetyl acetylene. After completion of the reaction (TLC monitoring), the solvent was removed *in vacuo*, the residue was purified by column chromatography. Pyrrolodiazocines **15—18** were obtained by the reaction in MeCN, the reaction of **8** and **9** with methyl propiolate in MeOH afforded pyrroles **19—21**. Pyrrolopyrazine **10** gave in methanol a mixture of pyrrolodiazocine **22** and pyrrole **23**.

Methyl 9-formyl-3,6-dimethyl-1,2,3,6-tetrahydropyrrolo-[1,2-*d*][1,4]diazocine-5-carboxylate (15). Yield 13%, yellow crystals, m.p. 122—124 °C (from ethyl acetate—hexane). Found (%): C, 63.90; H, 7.00; N, 10.78. $C_{14}H_{18}N_2O_3$. Calculated (%): C, 64.12; H, 6.87; N, 10.69. IR, ν/cm^{-1}: 1641 (CHO); 1710 (CO_2Me). ^{1}H NMR, δ: 1.55 (d, 3 H, Me, J = 7.4 Hz); 3.00 (s, 3 H, NMe); 3.60 (dt, 1 H, C(2)H, J = 4.5 Hz, J = 15.6 Hz); 3.69 (s, 3 H, CO_2Me); 3.89 (ddd, 1 H, C(1)H, J = 4.5 Hz, J = 11.4 Hz, J = 15.4 Hz); 4.41 (dt, 1 H, C(2)H, J = 4.5 Hz, J = 15.6 Hz); 4.68 (q, 1 H, C(6)H, J = 7.4 Hz); 5.38 (ddd, 1 H, J = 4.5 Hz, J = 11.4 Hz, J = 15.4 Hz); 6.07 (d, 1 H, C(7)H, J = 4.0 Hz); 6.86 (d, 1 H, C(8)H, J = 4.0 Hz); 7.47 (s, 1 H, C(4)H); 9.38 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 262 $[M]^+$ (82), 247 (73), 261 (29), 219 (12), 215 (18), 204 (18), 203 (42), 188 (18), 187 (47), 172 (30), 159 (20), 152 (21), 146 (42), 132 (20), 118 (24), 117 (26), 94 (25), 93 (19), 80 (22), 77 (20), 65 (23), 57 (70), 53 (22), 42 (100), 41 (27), 39 (37).

Methyl 3-ethyl-9-formyl-6-methyl-1,2,3,6-tetrahydropyrrolo[1,2-*d*][1,4]diazocine-5-carboxylate (16). Yield 11%, yellow crystals, m.p. 104—106 °C (from ethyl acetate—hexane). Found (%): C, 65.07; H, 7.31; N, 10.00. $C_{15}H_{20}N_2O_3$. Calculated (%): C, 65.22; H, 7.25; N, 10.14. IR, ν/cm^{-1}: 1656 (CHO); 1716 (CO_2Me). ^{1}H NMR, δ: 1.10 (t, 3 H, $CH_2\underline{Me}$, J = 7.2 Hz); 1.53 (d, 3 H, Me, J = 7.4 Hz); 3.19—3.26 (m, 2 H, $C\underline{H}_2Me$); 3.68 (s, 3 H, CO_2Me); 3.74 (br.s, 1 H, C(1)H); 3.84 (ddd, 1 H, C(2)H, J = 4.1 Hz, J = 9.2 Hz, J = 15.3 Hz); 4.44 (dt, 1 H, C(2)H, J = 4.1 Hz, J = 15.3 Hz); 4.68 (q, 1 H, C(6)H, J = 7.4 Hz); 5.35—5.41 (m, 1 H, C(1)H); 6.05 (d, 1 H, C(7)H, J = 4.0 Hz); 6.85 (d, 1 H, C(8)H, J = 4.0 Hz); 7.52 (s, 1 H, C(4)H); 9.36 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 276 $[M]^+$ (100), 261 (98), 245 (27), 229 (12), 217 (46), 201 (17), 176 (12), 173 (16), 172 (26), 160 (14), 148 (14), 147 (21), 146 (43), 130 (15), 122 (23), 118 (22), 117 (22), 108 (17), 104 (12), 94 (13), 80 (17), 77 (21), 71 (51), 65 (20), 59 (28), 58 (25), 56 (32), 54 (15), 53 (25), 42 (31), 41 (31), 40 (25), 39 (37).

3-Ethyl-6-methyl-5-tosyl-1,2,3,6-tetrahydropyrrolo[1,2-*d*]-[1,4]diazocine-9-carbaldehyde (17). Yield 16%, colorless crystals, m.p. 117—119 °C (from ethyl acetate—hexane). Found (%): C, 64.77; H, 6.28; N, 7.48. $C_{20}H_{24}N_2O_3S$. Calculated (%): C, 64.52; H, 6.45; N, 7.53. IR, ν/cm^{-1}: 1165 (SO); 1340 (SO); 1655 (CHO). ^{1}H NMR, δ: 1.17 (t, 3 H, $CH_2\underline{Me}$, J = 7.3 Hz); 1.53 (d, 3 H, Me, J = 7.2 Hz); 2.43 (s, 3 H, CH_3—Ar); 3.28—3.35 (m, 2 H, $C\underline{H}_2Me$); 3.65 (dt, 1 H, C(2)H, J = 3.9 Hz, J = 15.0 Hz); 3.90—3.97 (m, 1 H, C(1)H); 4.09 (q, 1 H, C(6)H, J = 7.2 Hz); 4.45 (dt, 1 H, C(2)H, J = 3.9 Hz, J = 15.0 Hz); 5.20 (d, 1 H, C(7)H, J = 3.9 Hz); 5.28—5.35 (m, 1 H, C(1)H); 7.26 (d, 2 H, H arom., J = 8.3 Hz); 7.58 (s, 1 H, C(4)H); 7.67 (d, 2 H, H arom., J = 8.3 Hz); 9.34 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 372 $[M]^+$ (89), 357 (31), 261 (17), 218 (30), 217 (73), 216 (100), 215 (49), 202 (34), 188 (21), 172 (25), 168 (15), 161 (27), 158 (37), 146 (35), 131 (27), 122 (19), 108 (23), 94 (15), 78 (20), 64 (23).

5-Acetyl-3-ethyl-6-methyl-1,2,3,6-tetrahydropyrrolo[1,2-*d*]-[1,4]diazocine-9-carbaldehyde (18). Yield 31%, brown oil. Found (%): C, 69.03; H, 7.82; N, 10.64. $C_{15}H_{20}N_2O_2$. Calculated (%): C, 69.23; H, 7.69; N, 10.77. IR, ν/cm^{-1}: 1589 (CO); 1658 (CHO). ^{1}H NMR, δ: 1.12 (t, 3 H, $CH_2\underline{Me}$, J = 7.2 Hz); 1.49 (d, 3 H, Me, J = 7.3 Hz); 2.20 (s, 3 H, MeCO); 3.25—3.33 (m, 2 H, $C\underline{H}_2Me$); 3.65 (ddd, 1 H, C(2)H, J = 3.0 Hz, J = 5.8 Hz, J = 15.9 Hz); 3.95 (ddd, 1 H, C(1)H, J = 4.7 Hz, J = 11.9 Hz, J = 16.2 Hz); 4.30—4.37 (m, 1 H, C(2)H); 4.95 (q, 1 H, C(6)H, J = 7.3 Hz); 5.47 (ddd, 1 H, C(1)H, J = 4.7 Hz, J = 16.2 Hz); 6.00 (d, 1 H, C(7)H, J = 3.9 Hz); 6.82 (d, 1 H, C(8)H, J = 3.9 Hz); 7.37 (s, 1 H, C(4)H); 9.35 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 260 $[M]^+$ (100), 245 (42), 231 (8), 217 (55), 203 (27), 188 (19), 174 (15), 172 (29), 160 (13), 149 (11), 147 (21), 146 (28), 118 (10), 108 (10), 96 (9), 71 (13), 43 (17).

Methyl 3-ethyl-9-(2,2,2-trifluoroacetyl)-6-methyl-1,2,3,6-tetrahydropyrrolo[1,2-*d*][1,4]diazocine-5-carboxylate (22). Yield 35%, yellow oil. Found (%): C, 56.00; H, 5.31; N, 8.00. $C_{16}H_{19}F_3N_2O_3$. Calculated (%): C, 55.81; H, 5.52; N, 8.14. IR, ν/cm^{-1}: 1681 (CO); 1702 (CO_2Me). ^{1}H NMR, δ: 1.13 (t, 3 H, $CH_2\underline{Me}$, J = 7.2 Hz); 1.55 (d, 3 H, Me, J = 7.3 Hz); 3.21—3.29 (m, 2 H, $C\underline{H}_2Me$), 3.73 (t, 1 H, C(2)H, J = 4.9 Hz); 3.70 (s, 3 H, CO_2Me); 3.82 (ddd, 1 H, C(1)H, J = 5.3 Hz, J = 9.2 Hz, J = 15.1 Hz); 4.55 (dt, 1 H, C(2)H, J = 4.5 Hz, J = 15.5 Hz); 4.70 (q, 1 H, C(6)H); 5.26 (ddd, 1 H, C(1)H, J = 5.3 Hz, J = 9.2 Hz, J = 15.1 Hz); 6.13 (d, 1 H, C(7)H, J = 4.3 Hz); 7.22 (d, 1 H, C(8)H, J = 4.3 Hz); 7.53 (s, 1 H, C(4)H). MS, m/z (I_{rel} (%)): 344 $[M]^+$ (66), 329 (100), 313 (21), 297 (29), 285 (69), 269 (16), 243 (23), 214 (23), 188 (10), 154 (7), 144 (9), 122 (13), 118 (8), 108 (9).

(*E*)-Methyl 3-(*N*-methyl-{2-[2-formyl-5-(1-methoxyethyl)-1*H*-pyrrol-1-yl]ethyl}amino)acrylate (19). Yield 9%, yellow oil. Found (%): C, 61.37; H, 7.19; N, 9.37. $C_{15}H_{22}N_2O_4$. Calculated (%): C, 61.22; H, 7.48; N, 9.52. IR, ν/cm^{-1}: 1656 (CHO); 1692 (CO_2Me). ^{1}H NMR, δ: 1.54 (d, 3 H, $\underline{Me}CH$, J = 6.2 Hz); 2.17 (s, 3 H, NMe); 3.45—3.53 (m, 2 H, $C_\alpha H_2$); 3.67 (s, 3 H, OMe); 3.71 (s, 3 H, CO_2Me); 4.27—4.35 (m, 2 H, $C_\beta H_2$); 4.49 (q, 1 H, $C\underline{H}Me$, J = 6.2 Hz); 4.67 (d, 1 H, CH=CH, J = 13.2 Hz); 6.26 (d, 1 H, C(4)H, J = 3.8 Hz); 6.93 (d, 1 H, C(3)H, J = 3.8 Hz); 7.36 (d, 1 H, CH=CH, J = 13.2 Hz); 9.49 (s, 1 H, CHO). MS, m/z: 295 $[M + 1]^+$.

(*E*)-Methyl 3-(*N*-ethyl-{2-[2-formyl-5-(1-methoxyethyl)-1*H*-pyrrol-1-yl]ethyl}amino)acrylate (20). Yield 25%, yellow oil. Found (%): C, 62.41; H, 8.00; N, 9.13. $C_{16}H_{24}N_2O_4$. Calculated (%): C, 62.34; H, 7.79; N, 9.09. IR, ν/cm^{-1}: 1655 (CHO); 1689 (CO_2Me). ^{1}H NMR, δ: 1.06 (t, 3 H, $CH_2\underline{Me}$, J = 7.1 Hz); 1.49 (d, 3 H, Me, J = 6.7 Hz); 3.07—3.16 (m, 2 H, $C_\beta H_2$); 3.28 (s, 3 H, OMe); 3.36—3.45 (m, 2 H, $C\underline{H}_2Me$); 3.40—3.49 (m, 2 H, $C_\alpha H_2$); 3.62 (s, 3 H, CO_2Me); 4.32 (q, 1 H, $C\underline{H}Me$, J = 6.7 Hz); 4.78 (br.s, 1 H, CH=CH); 6.21 (d, 1 H, C(4)H, J = 4.0 Hz); 6.88 (d, 1 H, C(3)H, J = 4.0 Hz); 7.36 (d, 1 H,

CH=CH, J = 13.2 Hz); 9.44 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 308 $[M]^+$ (12), 293 (26), 276 (45), 261 (25), 142 (100), 96 (27), 82 (13), 59 (24), 55 (9).

1-(2-{*N*-Ethyl-[5-(1-methoxyethyl)-(*E*)-3-oxobut-1-en-1-yl]amino}ethyl)-1*H*-pyrrol-2-carbaldehyde (21). Yield 54%, yellow oil. Found (%): C, 65.79; H, 8.31; N, 9.43. $C_{16}H_{24}N_2O_3$. Calculated (%): C, 65.75; H, 8.22; N, 9.59. IR, ν/cm^{-1}: 1655 (CHO); 1683 (CO). ^{1}H NMR, δ: 1.03 (t, 3 H, $CH_2\underline{Me}$, J = 6.9 Hz); 1.45 (d, 3 H, $\underline{Me}CH$, J = 6.6 Hz); 2.50 (s, 3 H, MeCO); 3.15 (q, 2 H, $C\underline{H}_2Me$, J = 6.9 Hz); 3.34 (s, 3 H, OMe); 3.40—3.49 (m, 2 H, $C_\beta H_2$); 4.35—4.46 (m, 2 H, $C_\alpha H_2$); 4.58 (q, 1 H, $C\underline{H}Me$, J = 6.6 Hz); 5.08 (br.s, 1 H, CH=CH); 6.30 (d, 1 H, C(4)H, J = 3.9 Hz); 7.07 (d, 1 H, C(3)H, J = 3.9 Hz); 7.40 (d, 1 H, CH=CH, J = 13.5 Hz); 9.48 (s, 1 H, CHO). MS, m/z: 293 $[M + 1]^+$.

(*E*)-Methyl 3-(*N*-ethyl-{2-[5-(2,2,2-trifuoroacetyl)-2-(1-methoxyethyl)-1*H*-pyrrol-1-yl]ethyl}amino)acrylate (23). Yield 35%, yellow oil. Found (%): C, 54.03; H, 6.30; N, 7.24. $C_{17}H_{23}F_3N_2O_4$. Calculated (%): C, 54.26; H, 6.12; N, 7.45. IR, ν/cm^{-1}: 1680 (CF_3CO); 1710 (CO_2Me). ^{1}H NMR, δ: 1.13 (t, 3 H, $CH_2\underline{Me}$, J = 7.1 Hz); 1.55 (d, 3 H, $CH\underline{Me}$, J = 6.5 Hz); 3.19 (q, 2 H, $C\underline{H}_2Me$, J = 7.1 Hz); 3.35 (s, 3 H, OMe); 3.44 (d, 2 H, $C_\beta H_2$, J = 7.4 Hz); 3.67 (s, 3 H, CO_2Me); 4.38 (q, 1 H, $C\underline{H}Me$, J = 6.5 Hz); 4.55 (ddd, 2 H, $C_\alpha H_2$, J = 7.4 Hz, J = 13.9 Hz); 5.26 (br.s, 1 H, CH=CH); 6.31 (d, 1 H, C(4)H, J = 4.4 Hz); 7.27 (d, 1 H, C(3)H, J = 4.4 Hz); 7.40 (d, 1 H, CH=CH, J = 13.1 Hz). MS, m/z (I_{rel} (%)): 376 $[M]^+$ (8), 361 (14), 345 (12), 344 (39), 329 (23), 313 (10), 232 (11), 216 (8), 143 (7), 142 (100), 96 (7), 82 (11), 45 (11).

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