DOI: 10.1002/ejoc.201000620

Chemo-, Regio- and Stereospecific Synthesis of Unnatural, Fluorescent Amino Acids by Condensation of L-Lysine and 1-Vinylpyrrole-2-carbaldehydes

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Keywords: Amino acids / Aldehydes / Nitrogen heterocycles / Schiff bases / Fluorescence

A new family of unnatural, optically active amino acids containing the pyrrole moiety have been synthesized by condensation of 1-vinylpyrrole-2-carbaldehydes with L-lysine under mild conditions (EtOH, room temp., 2.5–3 h, 0.5 wt.-% of CF_3CO_2H) in up to 90 % yields. Unlike non-vinylated analogues, 1-vinylpyrrole-2-carbaldehydes react chemo-, regio- and stereospecifically with an ε-amino group only to afford products of exclusively (*E*) configuration. The amino acids synthesized containing aromatic or condensed aromatic substitutents in the pyrrole ring fluoresce in the UV/Vis region (λ_{max} = 350–382 nm, Stokes shifts 6150–7800 cm^{-1}).

Introduction

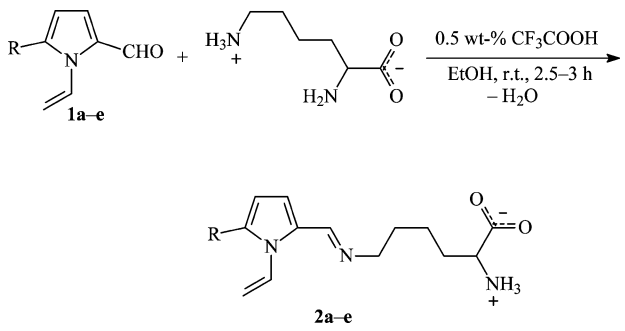
Lysine is known to play key structural and functional roles in proteins.[1] The basic side chains of the lysine residues are essential in the DNA–protein recognition. Their almost ubiquitous presence in the interface of DNA–protein complexes makes lysine an attractive target for chemical modifications.[2] Chemical transformations of the lysine amino groups are employed in the synthesis of antitumor drugs[3] and virus suppressors.[4] Similar lysine derivatives are isolated from natural sources.[5] Such modifications provide important information of the protein properties, e.g. about the sweetness of lysozyme.[6] The lysine moiety offers a convenient way of incorporating various chemical groups onto the protein surfaces.[7] The development of new methodologies to increase the sensitivity of biological imaging in living cells is now considered as one of the cardinal research challenges.[8] Therefore, one important application of the lysine modifications is the labelling of synthetic peptides for monitoring enzyme activity. The introduction of fluorescent moieties into the lysine molecules is an alternative to the use of radioactive labels.[9] One of the most expedient and useful approaches to lysine modifications involves its condensation with carbonyl compounds to deliver Schiff bases.[10] However, to the best of our knowledge, no example of a lysine condensation with pyrrole-2-carbaldehydes has been so far reported, though such a combination could lead to lysine derivatives possessing fluorescent properties that might be promising for the design of biological labels.

1-Vinylpyrrole-2-carbaldehydes, particularly those having aromatic, condensed aromatic or heteroaromatic substituents, now available[11] by formylation of the corresponding 1-vinylpyrroles (also accessible[12] compounds) represent highly reactive[13] building blocks for the introduction of diverse pyrrole chromophores to the lysine molecules.

Here we report on the synthesis of the hitherto unknown family of unnatural amino acids **2a**–**f** by condensation of L-lysine with 1-vinylpyrrole-2-carbaldehydes **1a**–**f**.

Results and Discussion

The reaction of L-lysine with 1-vinylpyrrole-2-carbaldehydes **1a**–**f** proceeds smoothly (EtOH, 0.5 wt.-% of CF_3COOH, room temperature, 2.5–3 h) to give amino acids **2a**–**f** in a chemo-, regio- and stereospecific mode involving the ε-amino group only (Scheme 1). Schiff bases **2a**–**f** are formed exclusively in the (*E*) configuration in 69–90% yields (Table 1).



Scheme 1. Synthesis of unnatural amino acids **2**.

Likewise, amino acid **2f** containing an annulated dihydronaphthalene moiety has been synthesized from 1-vinyl-4,5-dihydrobenz[*g*]indole-2-carbaldehyde (**1f**) (Scheme 2).

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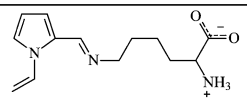
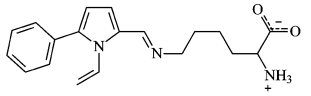
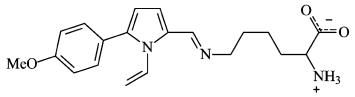
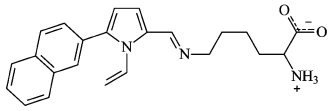
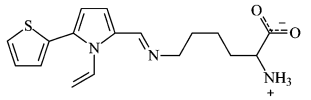
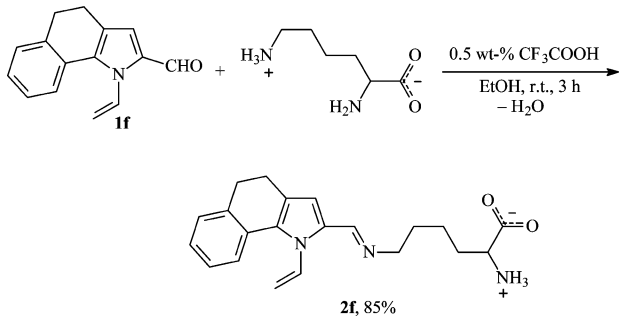
Table 1. Substituents and isolated yields of amino acids **2**.

Entry	Product	Isolated yield
2a		69 %
2b		78 %
2c		89 %
2d		77 %
2e		90 %

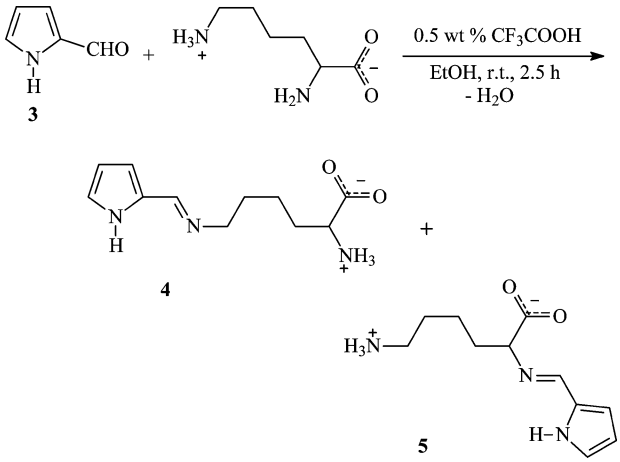


Scheme 2.

The 1-vinylpyrroles with aromatic, condensed aromatic and heteroaromatic substitutents have been specially selected having in mind their better chromophoric properties due to the conjugation between the substituents and the pyrrole ring. This should improve the expected fluorescent properties of the target amino acids.

For the condensation of L-lysine with 1-vinylpyrrole-2-carbaldehydes **1a**–**f**, we have employed trifluoroacetic acid (CF_3COOH) as catalyst, because our previous investigations have shown[13c] that this acid efficiently and selectively catalyzes the transformations of 1-vinylpyrrole-2-carbaldehydes to the corresponding Schiff bases, the acidophobic *N*-vinyl group being preserved. The reaction does not occur without catalyst (GLC data).

Lysine is known to participate in a variety of reactions (including Schiff base formation) involving both its α- and ε-amino groups.[7b,8,14] As a rule, to selectively conduct the reaction by exploiting just one amino group, it is needed to protect the second one.[8,10d,14b,14c] In agreement with these data, when non-vinylated 1-*H*-pyrrole-2-carbaldehyde **3** reacts with L-lysine under the above conditions (Scheme 1), both expected Schiff bases **4** and **5** were isolated in a yield of 80% (Scheme 3), the ratio **4**/**5** being 3:1 (^{1}H NMR spectroscopy).



Scheme 3. Behaviour of non-vinylated pyrrole-2-carbaldehyde **3** under the conditions studied.

In contrast to *N*-unsubstituted pyrrole-2-carbaldehyde **3**, in the case of 1-vinylpyrrole-2-carbaldehydes **1a**–**f**, the possible alternative isomers formed with the participation of the α-amino group of lysine are not detected, even in trace concentrations (^{1}H NMR spectroscopy). Since the electronic effect of the *N*-vinyl group on the carbonyl function transmitted through the pyrrole ring proves to be negligible (^{13}C NMR chemical shifts of the carbonyl carbon atoms in **1a** and **3**: δ = 178.8 and 178.6 ppm, respectively), a probable reason of the observed regiospecificity of the Schiff base formation is the steric hindrance from the *N*-vinyl group to the attack of the lysine α-amino group on the carbonyl function.

All amino acids **2a**–**f** exist exclusively as the (*E*) isomers. This was confirmed by 2D NOESY experiments, which show NOE correlations between the HC=N proton and 3-H of the pyrrole moiety, as well as between the HC=N proton and the N–CH_2 group of the lysine fragment (Figure 1).

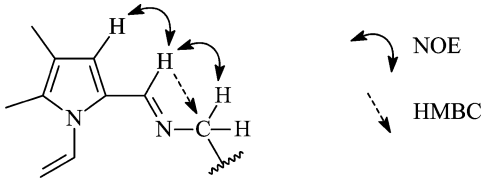


Figure 1. Cross-peaks in the 2D NOESY and HMBC spectra of the amino acids **2**.

The (*E*)/(*Z*) isomerism around the C=N bond makes these amino acids potential optical molecular switches due to (*E*)/(*Z*) isomerisation under UV irradiation.

A zwitterionic form of the amino acid **2** is supported by its IR (KBr) spectrum, where a broad strong absorption in the region of 3300–2500 cm^{-1} is observed. This absorption is commonly assigned to the $^+NH_3$ group.[15] In the spectrum, a band at 2150–2100 cm^{-1} is attributable to the same $^+NH_3$ moiety. The CO_2^- anion was spectroscopically con-

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firmed by a broad absorption in the region of 1650–1550 cm^{-1}, obviously overlapping with the band of the C=N and C=C stretching-vibration bands.

Amino acids **2a**–**f** are soluble in DMSO and DMSO/water (1:1) and scarcely soluble in benzene, acetone, chloroform and acetonitrile.

All the amino acids containing aromatic and condensed aromatic substituents (**2b**–**e**) fluoresce in the near-UV region (350–362 nm); the amino acid with a naphthyl substutient (**2d**) emits in a visible spectral region (382 nm). Their Stokes shifts range from 6150 to 7800 cm^{-1} (Table 2).

Table 2. UV/Vis and fluorescence spectra of amino acids **2b**–**d**,**f** (MeCN).

Amino acid	Absorption[a] λ_{max} [nm]	Emission λ_{max} [nm]	Stokes shift [cm^{-1}]
2b	292	356	6150
2c	286	350	6400
2d[b]	279	357, 382(sh.)	7800
2f	292	362	6600

[a] The values are derived from excitation spectra. [b] The emission spectrum has a vibration structure.

Conclusions

A general methodology for the synthesis of a new family of unnatural amino acids, containing hydrophobic pyrrole-based chromophores, has been developed. The methodology consists of the chemo-, regio- and stereospecific condensation of L-lysine with 1-vinylpyrrole-2-carbaldehydes catalyzed by CF_3COOH under mild conditions (EtOH, room temp.). The amino acids synthesized exhibit promising fluorescent properties and are prospective in the search for novel biological labels. The methodology allows the fluorescence parameters to be controlled by employing diverse aryl-, hetaryl- and condensed aromatic substituted 1-vinylpyrroles readily available from ketones and acetylene by the Trofimov reaction.[12] The amino acids synthesized according to the above methodology represent a rare combination of pharmacophoric pyrrole and amino acid moieties and hence can also be used as flexible building blocks for drug design. The reactive *N*-vinyl group in the molecules of the amino acids synthesized is of a particular structural advantage. This makes these compounds promising monomers, which are prone to various addition reactions across the double bond.[16] A possible combination of vinyl polymerization (or cross-linking) with peptide synthesis may extend considerably the scope of application of these novel amino acids.

Experimental Section

General: ^1H (400.13 MHz) and ^{13}C (101.6 MHz) NMR spectra were recorded with Bruker DPX 400 or AV-400 spectrometers by using hexamethyldisiloxane (HMDS) as an internal standard. In order to attribute ^1H and ^{13}C peaks, 2D homonuclear COSY and NOESY routines, as well as 2D heteronuclear HSQC and HMBC techniques were used. IR spectra were recorded with a Bruker IFS 25 spectrometer. All melting points were taken with a Kofler micro hot stage. Optical rotations were measured with a Polamat A polarimeter at 23 °C. 1-Vinylpyrrole-2-carbaldehydes were obtained according to ref.[11b] Other chemicals (Aldrich) and solvents were of commercial grade.

Synthesis of 2-Amino-6-{[(1-vinylpyrrol-2-yl)methylene]amino}-hexanoic Acids 2a–f: A mixture of 1-vinylpyrrole-2-carbaldehyde **1** (1 mmol), L-lysine monohydrate (0.16 g, 1 mmol) and CF_3COOH (0.5 wt.-% with respect to the whole mass) in EtOH (7 mL) was stirred at room temperature for 2.5–3 h. The residue precipitated was filtered off, washed with cold water and EtOH and dried.

2-Amino-6-{[(1-vinylpyrrol-2-yl)methylene]amino}hexanoic Acid (2a): From 0.12 g (1 mmol) of **1a** 0.17 g (69%) of **2a** was obtained. Beige crystals. M.p. 150–153 °C (decomp.). $[\alpha]_D^{23}$ = +11.3 (c = 0.02, CH_3CN). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.12 (s, 1 H, CH=N), 7.85 (dd, $^3J_{A\text{-}X}$ = 8.7, $^3J_{B\text{-}X}$ = 15.5 Hz, 1 H, H_X), 7.18 (m, 1 H, 5-H), 6.54 (m, 1 H, 3-H), 6.32 (m, 1 H, 4-H), 5.00 (d, $^3J_{B\text{-}X}$ = 15.5 Hz, 1 H, H_B), 4.90 (d, $^3J_{A\text{-}X}$ = 8.7 Hz, 1 H, H_A), 3.42 (m, 2 H, NCH_2), 3.40 (br. s, 3 H, NH_2, OH), 3.11 (m, 1 H, CH), 1.73 (m, 2 H, CH_2), 1.58 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.8 (1 C, C=O), 150.8 (1 C, C=N), 133.2 (1 C, C_α), 129.4 (1 C, C-2), 120.5 (1 C, C-5), 115.4 (1 C, C-3), 110.3 (1 C, C-4), 105.5 (1 C, C_β), 60.2 (1 C, NCH_2), 54.4 (1 C, CH), 31.6 (1 C, CH_2), 29.9 (1 C, CH_2), 23.5 (1 C, CH_2) ppm. $C_{13}H_{19}N_3O_2$ (249.31): calcd. C 62.63, H 7.68, N 16.85; found C 63.00, H 7.50, N 16.66.

2-Amino-6-{[(5-phenyl-1-vinylpyrrol-2-yl)methylene]amino}hexanoic Acid (2b): From 0.20 g (1 mmol) of **1b** 0.25 g (78%) of **2b** was obtained. Beige crystals. M.p. 192–195 °C (decomp.). $[\alpha]_D^{23}$ = +5.0 (c = 0.02, CH_3CN). IR (KBr): $\tilde{\nu}$ = 3444, 3030, 2988, 2855, 2821, 1629, 1601, 1514, 1464, 1450, 1400, 1352, 1328, 1288, 1232, 1199, 1156, 1116, 1074, 1043, 1005, 957, 915, 864, 784, 758, 698, 660, 598, 543, 512, 494, 453 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.23 (s, 1 H, CH=N), 7.49 (dd, $^3J_{A\text{-}X}$ = 8.6, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_X), 7.41 (m, 4 H, H_o, H_m, Ph), 7.32 (m, 1 H, H_p, Ph), 6.71 (d, $^3J_{3\text{-}4}$ = 3.6 Hz, 1 H, 3-H), 6.34 (d, $^3J_{3\text{-}4}$ = 3.6 Hz, 1 H, 4-H), 5.09 (d, $^3J_{A\text{-}X}$ = 8.6 Hz, 1 H, H_A), 4.72 (d, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_B), 3.46 (m, 2 H, NCH_2), 3.40 (br. s, 3 H, NH_2, OH), 3.12 (m, 1 H, CH), 1.74 (m, 2 H, CH_2), 1.58 (m, 2 H, CH_2), 1.37 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.9 (1 C, C=O), 151.9 (1 C, C=N), 136.8 (1 C, C-5), 132.3 (1 C, C_i), 132.0 (1 C, C_α), 131.5 (1 C, C-2), 128.6 (2 C, C_o), 128.4 (2 C, C_m), 127.3 (1 C, C_p), 114.9 (1 C, C-3), 111.5 (1 C, C-4), 111.3 (1 C, C_β), 61.0 (1 C, NCH_2), 54.2 (1 C, CH), 31.0 (1 C, CH_2), 30.7 (1 C, CH_2), 23.1 (1 C, CH_2) ppm. $C_{19}H_{23}N_3O_2$ (325.41): calcd. C 70.13, H 7.12, N 12.91; found C 70.15, H 7.06, N 12.72.

2-Amino-6-{[5-(4-methoxyphenyl)-1-vinylpyrrol-2-yl)methylene]-amino}hexanoic Acid (2c): From 0.23 g (1 mmol) of **1c** 0.32 g (89%) of **2c** was obtained. Orange crystals. M.p. 179–183 °C (decomp.). $[\alpha]_D^{23}$ = +4.9 (c = 0.02, CH_3CN). IR (KBr): $\tilde{\nu}$ = 3439, 3036, 2988, 2853, 1628, 1610, 1581, 1516, 1468, 1432, 1406, 1352, 1329, 1309, 1288, 1251, 1199, 1179, 1158, 1130, 1111, 1043, 1029, 973, 959, 919, 857, 837, 795, 769, 736, 721, 698, 663, 631, 606, 591, 530, 451 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.21 (s, 1 H, CH=N), 7.48 (dd, $^3J_{A\text{-}X}$ = 8.8, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_X), 7.34 (m, 2 H, H_o, Ph), 6.98 (m, 2 H, H_m, Ph), 6.68 (d, $^3J_{3\text{-}4}$ = 3.6 Hz, 1 H, 3-H), 6.25 (d, $^3J_{3\text{-}4}$ = 3.6 Hz, 1 H, 4-H), 5.07 (d, $^3J_{A\text{-}X}$ = 8.6 Hz, 1 H, H_A), 4.73 (d, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_B), 3.78 (s, 3 H, OMe), 3.46 (m, 2 H, NCH_2), 3.30 (br. s, 3 H, NH_2, OH), 3.09 (m, 1 H, CH), 1.75 (m, 2 H, CH_2), 1.56 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.7 (1 C, C=O),

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160.3 (1 C, C_i), 154.9 (1 C, C=N), 138.2 (1 C, C-5), 134.3 (1 C, C_i), 132.1 (1 C, C_α), 131.9 (2 C, C_m), 131.7 (1 C, C-2), 115.7 (2 C, C_o), 114.6 (1 C, C-3), 112.1 (1 C, C-4), 111.7 (1 C, C_β), 61.2 (1 C, NCH_2), 56.4 (1 C, OMe), 54.5 (1 C, CH), 31.2 (1 C, CH_2), 30.5 (1 C, CH_2), 22.9 (1 C, CH_2) ppm.

2-Amino-6-[(5-naphthalen-2-yl-1-vinylpyrrole-2-ylmethylidene)-amino]hexanoic Acid (2d): From 0.25 g (1 mmol) of **1d** 0.29 g (77%) of **2d** was obtained. Beige crystals. M.p. 208–211 °C (decomp.). $[\alpha]_D^{23}$ = +3.2 (c = 0.02, CH_3CN). IR (KBr): $\tilde{\nu}$ = 3441, 3050, 2934, 2858, 1636, 1582, 1515, 1452, 1407, 1355, 1325, 1302, 1273, 1257, 1215, 1195, 1158, 1130, 1046, 1016, 977, 959, 948, 926, 892, 858, 817, 779, 761, 742, 681, 665, 651, 632, 590, 552, 533, 474, 450 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (s, 1 H, CH=N), 7.99 (s, 1 H, H_{ar}), 7.90 (m, 3 H, H_{ar}), 7.61 (dd, $^3J_{A\text{-}X}$ = 8.6, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_X), 7.55 (m, 3 H, H_{ar}), 6.75 (d, $^3J_{3\text{-}4}$ = 3.8 Hz, 1 H, 3-H), 6.48 (d, $^3J_{3\text{-}4}$ = 3.8 Hz, 1 H, 4-H), 5.11 (d, $^3J_{A\text{-}X}$ = 8.6 Hz, 1 H, H_A), 4.74 (d, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_B), 3.48 (m, 2 H, NCH_2), 3.40 (br. s, 3 H, NH_2, OH), 3.10 (m, 1 H, CH), 1.76 (m, 2 H, CH_2), 1.57 (m, 2 H, CH_2), 1.38 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.7 (1 C, C=O), 152.0 (1 C, C=N), 136.8 (1 C, C-5), 132.8, 132.4 (2 C, C_{ar}), 132.2 (1 C, C_α), 131.9 (1 C, C_{ar}), 131.8 (1 C, C-2), 129.8 (1 C, C_{ar}), 126.6–128.2 (7 C, C_{ar}), 115.1 (1 C, C-3), 112.0 (1 C, C-4), 111.4 (1 C, C_β), 60.6 (1 C, NCH_2), 54.4 (1 C, CH), 30.7 (1 C, CH_2), 29.5 (1 C, CH_2), 22.9 (1 C, CH_2) ppm. $C_{23}H_{25}N_3O_2$ (375.47): calcd. C 73.58, H 6.71, N 11.19; found C 73.78, H 6.65, N 11.36.

2-Amino-6-({[5-(2-thienyl)-1-vinylpyrrol-2-yl]methylene}amino)-hexanoic Acid (2e): From 0.20 g (1 mmol) of **1e** 0.30 g (90%) of **2e** was obtained. Beige crystals. M.p. 221–225 °C (decomp.). $[\alpha]_D^{23}$ = +7.9 (c = 0.015, CH_3CN). IR (KBr): $\tilde{\nu}$ = 3437, 3056, 2987, 2925, 2858, 2821, 2132, 1624, 1583, 1517, 1473, 1452, 1414, 1352, 1327, 1290, 1222, 1198, 1157, 1121, 1033, 1001, 959, 909, 864, 846, 822, 772, 745, 687, 592, 532, 518, 493 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.19 (s, 1 H, CH=N), 7.56 (d, $^3J_{3'\text{-}4'}$ = 5.1 Hz, 1 H, 3′-H), 7.34 (dd, $^3J_{A\text{-}X}$ = 8.6, $^3J_{B\text{-}X}$ = 15.9 Hz, 1 H, H_X), 7.20 (d, $^3J_{5'\text{-}4'}$ = 3.4 Hz, 1 H, 5′-H), 7.10 (dd, $^3J_{3'\text{-}4'}$ = 5.1, $^3J_{5'\text{-}4'}$ = 3.4 Hz, 1 H, 4′-H), 6.71 (d, $^3J_{3\text{-}4}$ = 3.9 Hz, 1 H, 3-H), 6.42 (d, $^3J_{3\text{-}4}$ = 3.9 Hz, 1 H, 4-H), 5.33 (d, $^3J_{A\text{-}X}$ = 8.6 Hz, 1 H, H_A), 5.08 (d, $^3J_{B\text{-}X}$ = 15.9 Hz, 1 H, H_B), 3.46 (m, 2 H, NCH_2), 3.40 (br. s, 3 H, NH_2, OH), 3.08 (m, 1 H, CH), 1.73 (m, 2 H, CH_2), 1.55 (m, 2 H, CH_2), 1.35 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 169.7 (1 C, C=O), 151.9 (1 C, C=N), 133.8 (1 C, C-2′), 132.1 (1 C, C_α), 132.0 (1 C, C-5), 129.9 (1 C, C-2), 127.7 (1 C, C-3′), 127.5 (1 C, C-4′), 126.7 (1 C, C-5′), 114.1 (1 C, C-3), 113.9 (1 C, C_β), 112.1 (1 C, C-4), 61.1 (1 C, NCH_2), 54.3 (1 C, CH), 31.1 (1 C, CH_2), 30.6 (1 C, CH_2), 23.2 (1 C, CH_2) ppm. $C_{17}H_{21}N_3O_2S$ (331.43): calcd. C 61.61, H 6.39, N 12.68; found C 61.89, H 6.11, N 12.82.

2-Amino-6-{[(1-vinyl-4,5-dihydrobenzo[*g*]indol-2-yl)methylene]-amino}hexanoic Acid (2f): From 0.22 g (1 mmol) of **1f** 0.30 g (85%) of **2f** was obtained. Beige crystals. M.p. 206–210 °C (decomp.). $[\alpha]_D^{23}$ = +5.5 (c = 0.01, CH_3CN). IR (KBr): $\tilde{\nu}$ = 3446, 3055, 2931, 1628, 1603, 1583, 1515, 1478, 1439, 1407, 1358, 1324, 1308, 1294, 1254, 1194, 1158, 1135, 1097, 1046, 1026, 980, 916, 808, 775, 757, 736, 712, 668, 652, 509, 467, 442, 421 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.18 (s, 1 H, CH=N), 7.55 (dd, $^3J_{A\text{-}X}$ = 8.3, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_X), 7.59 (m, 1 H, H_{ar}), 7.27 (m, 1 H, H_{ar}), 7.18 (m, 1 H, H_{ar}), 7.10 (m, 1 H, H_{ar}) 6.60 (s, 1 H, 3-H), 5.38 (d, $^3J_{A\text{-}X}$ = 8.3 Hz, 1 H, H_A), 5.18 (d, $^3J_{B\text{-}X}$ = 15.6 Hz, 1 H, H_B), 3.46 (m, 2 H, NCH_2), 3.40 (br. s, 3 H, NH_2, OH), 3.10 (m, 1 H, CH), 2.78 (m, 2 H, CH_2), 2.54 (m, 2 H, CH_2), 1.72 (m, 2 H, CH_2), 1.54 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.7 (1 C, C=O), 152.0 (1 C, C=N), 136.2 (1 C, C_{ar}), 133.2 (1 C, C_α), 132.0 (1 C, C-2), 131.9 (1 C, C_{ar}), 130.9 (1 C, C-5), 128.3, 127.2, 126.1, 125.6 (4 C, CH_{ar}), 125.4 (1 C, C-4), 111.4 (1 C, C-3), 111.0 (1 C, C_β), 60.4 (1 C, NCH_2), 54.5 (1 C, CH), 30.8 (1 C, CH_2), 29.9 (1 C, CH_2), 29.6 (1 C, CH_2), 23.1 (1 C, CH_2), 21.8 (1 C, CH_2) ppm. $C_{21}H_{25}N_3O_2$ (351.45): calcd. C 71.77, H 7.17, N 11.96; found C 71.88, H 7.21, N 11.86.

Acknowledgments

This work has been carried out under financial support of leading scientific schools by the President of the Russian Federation (Grant NSH-3230.2010.3)

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Received: May 4, 2010
Published Online: July 16, 2010

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