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Research Article

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The role of carboxylic group position on the antiradical activity of synthetic analogues of oat antioxidants

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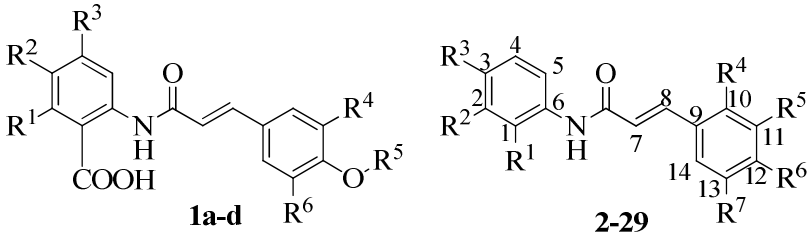
ABSTRACT

The aim of our research was to establish structure-antiradical activity relationships of the synthetic analogues of naturally occurring antioxidants - avenanthramides. We studied the influence of the position of carboxylic group in aniline moiety and substituents in the cinnamic acid moiety. It was found out that the position of carboxylic group did not have any significant impact on the antiradical activity of compounds in DPPH test; opposite situation was observed in case of feruloyl anilines in GO assay.

Keywords: Avenanthramides, *N*-cinnamoyl anilines, antiradical activity, 2,2-diphenyl-1-picrylhydrazyl (DPPH), galvinoxyl (GO)

INTRODUCTION

Avenanthramides **1** (avenanthramides A (**1a**), B (**1b**) and C (**1c**) are the most available) – cinnamamides of substituted anthranilic acid (Fig. 1) – are present mainly in oats (*Avena Sativa*) [1]; a few avenanthramides have been isolated from clove pink (*Dianthus caryophyllus*) [2], large white cabbage butterfly (*Pieris brassicae*) [3] and floating grass *Hygroryza aristata* [4]. These compounds raise interest due to their biological activity: avenanthramides exhibit antioxidant and free radical scavenging activity [5-13], demonstrate antiatherogenic [10, 14, 15], anti-inflammatory [4, 16-22], anti-itching [17, 19], anti-irritant, antiallergic [22], antigenotoxic [6], antiproliferative [7, 17, 20, 21] and anticancer [17, 18, 21] properties, and increase NO production [17, 20, 21]. Oat extracts containing avenanthramides exhibit antiradical activity [23]; they are used as cosmetic agents for the inhibition of histamine release [19], in pharmaceutical compositions for treatment or prophylaxis of disorders associated with inflammatory states [20, 22] and for inhibition of proliferation of human colon adenocarcinoma cells [21]. Synthetic analogue of avenanthramides – Tranilast (or Rizaben) (**1d**) - was developed as antiallergic drug for treatment of bronchial asthma, rhinitis and atopic dermatitis [24-26]. Tranilast has therapeutic potential as an antifibrotic agent [27, 28] and is promising drug to prevent from scarring after glaucoma filtration surgery [29]; besides that it has been studied as antimetastatic agent for treatment of breast cancer [30]. Synthesis and biological activity of *N*-((*E*)-3-aryl-2-propenoyl)aminobenzoic acids containing carboxylic function at *m*- or *p*-positions of aniline ring have been studied [31-41] less than corresponding derivatives of anthranilic acid: this encouraged us to synthesize and to test antiradical activity of a range of *N*-cinnamoylaminobenzoic acids **2**-**29**, which can be considered as analogues of avenanthramides.



1a-d **2-29**

a R^1=R^3=R^4=R^5=R^6=H, R^2=OH

b R^1=R^3=R^5=R^6=H, R^2=OH, R^4=OMe

c R^1=R^3=R^5=R^6=H, R^2=R^4=OH

d R^1=R^2=R^3=R^6=H, R^4=OMe, R^5=Me

Fig. 1. Avenanthramides and their synthetic analogues

EXPERIMENTAL SECTION

The IR spectra were recorded with Perkin Elmer FT-IR System Spectrum BX spectrometer (KBr disc). NMR spectra were registered with Brucker Advance spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. All spectra were recorded in DMSO-d_6 and chemical shifts were reported in ppm from residual peak of DMSO. The progress of reaction was monitored with TLC using Macherey-Nagel pre-coated TLC sheets Alugram® SIL G/UV_{254}; eluent – $CHCl_3$:EtOAc (4:1) or 96% EtOH. HPLC analysis was carried out with Agilent Technologies 1200 Series chromatograph using WaterXBridge C18 column (3.5 µk, 4.6×150 mm) with the solvent system acetonitrile (A) and 0.01 M KH_2PO_4 containing 6% acetonitrile (B). The eluation was done using linear gradient from 10 to 90% B within 13 min (flow rate 1 ml/min). The absorbance of the solutions was measured with Camspec M501 single beam scanning UV/Visible spectrophotometer for DPPH and GO assays. Microanalysis was done with Carlo-Erba Instruments element analyzer (model: EA1108).

All used aromatic aldehydes, Meldrum`s acid, solvents, free radicals (DPPH and GO) and catalysts (*β*-alanine and piperidine) were commercially available and were used without further purification.

The optimization of yield of products was not carried out.
N-Aryl malonic monoamides **30** were obtained by refluxing commercially available Meldrum`s acid **33** and corresponding aminobenzoic acid **32** in toluene [42]. *N*-Aryl malonic monoamides **30a** [43] and **30c** [42] are known and their spectra corresponded to the literature data.

*3-(2-Carboxyacetamido)benzoic acid (**30b**).* White solid, yield 55%. Mp 243-244 °C. IR (KBr) υ (cm^{-1}) 3295, 3085, 2990, 2830, 2680, 2575, 1730, 1695, 1670, 1595, 1550, 1455, 1440, 1310, 1275, 1255, 1200, 1170, 1115, 1085, 1000, 945, 900, 825, 755, 690, 590, 560, 530, 485, 465; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.37 (2H, s, CH_2), 7.44 (1H, t, *J* 7.9 Hz, H-4), 7.64 (1H, dd, *J* 7.9 Hz, J 1.7 Hz, H-5), 7.79 (1H, dd, J 7.9 Hz, *J* 1.7 Hz, H-3), 8.23 (1H, t, *J* 1.7 Hz, H-1), 10.33 (1H, s, NH), 12.79 (2H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 44.7 (CH_2), 120.0 (C-1), 123.2 (C-5), 124.9 (C-3), 129.2 (C-4), 132.2 (C-2), 139.9 (C-6), 165.2 (C-3), 167.6 (COOH), 169.8 (CONH). Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.76; H, 3.95; N, 6.26.

*General procedure for the synthesis of N-cinnamoyl anilines **1d**, **2-29***
Method 1
Corresponding *N*-aryl malonic monoamide **30a-c** (0.2 g, 0.9 mmol), aromatic aldehyde **31** (0.9 mmol) and *β*-alanine (25 mol-%, 20 mg) were dissolved in pyridine (2 mL) and refluxed for appropriate time (about 1.5 h, TLC control). After the completion of reaction the product mixture was cooled and acidified with concentrated hydrochloric acid (1.5-2 mL). The resulting precipitate was filtered and washed with water until neutral reaction. The obtained crude product was dried and purified with column chromatography (eluent: $CHCl_3$:EtOAc (10:1 or 2:1).

Method 2
*Step 1: Synthesis of piperidinium salts of N-cinamoyl anilines **2**×Pi-**5**×Pi, **20**×Pi, **21**×Pi, **23**×Pi, **24**×Pi, **26**×Pi, **28**×Pi and **29**×Pi*
The mixture of *N*-aryl malonic monoamide **30a-c** (2 g, 9 mmol), aromatic aldehyde **31** (9 mmol) and piperidine (0.9 mL, 9 mmol) was refluxed in toluene (9 mL) for 2 h; the flask was equipped with stirring bar and Dean-Stark apparatus. The product mixture was cooled to room temperature. The precipitate was filtered, air-dried and crystallized from mixture acetone:ethanol.

*Step 2: Synthesis of N-cinnamoyl anilines **2-5**, **20**, **21**, **23**, **24**, **26**, **28** and **29***
Corresponding piperidinium salt of benzoic acids **2-5**, **20**, **21**, **23**, **24**, **26**, **28** or **29** (1 g) was mixed with 10% hydrochloric acid (20 mL) at room temperature for 20 min. The mixture was filtered and washed with water (~50 mL) until disappearance of chloride ion in filtrate (detection with $AgNO_3$). The obtained *N*-cinnamoyl aniline was air-dried and crystallized from mixture acetone:ethanol.

Spectral data of N-cinnamoyl anilines
N-Cinnamoyl anilines **1d** [42], **10** [43], **11** [35], **21** [42], **22** [42], **23** [44], **25** [13], **26** [2], **27** [42] and **28** [42] are known and their spectra corresponded to literature data.

*4-[(2E)-3-(4-Hydroxy-3-methoxyphenyl)prop-2-eneamido]benzoic acid (**2**)*. Beige powder. Yield: method 1 - 50% (54% crude product); method 2 – 94%. Mp 236-241 °C. IR (KBr) υ (cm^{-1}) 3380, 2990, 2660, 2540, 1695, 1595, 1510, 1465, 1410, 1350, 1255, 1220, 1175, 1125, 1035, 1005, 980, 840, 820, 800, 770, 715, 695, 630, 605, 575, 545, 510; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.83 (3H, s, CH_3), 6.65 (1H, d, *J* 15.7 Hz, H-8), 6.83 (1H, d, *J* 8.0 Hz, H-13), 7.08 (1H, d, *J* 8.0 Hz, H-14), 7.19 (1H, s, H-10), 7.51 (1H, d, *J* 5.7 Hz, H-7), 7.80 (2H, d, *J* 8.8 Hz, H-1,5), 7.91 (2H, d, *J* 8.8 Hz, H-2,4), 9.6 (1H, bs, OH), 10.37 (1H, s, NH), 12.67 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.0 (CH_3), 111.4 (C-10), 116.1 (C-13), 118.9 (C-1,5,7), 122.6 (C-14), 125.4 (C-3), 126.5 (C-9), 130.9 (C-2,4), 141.9 (C-8), 144.0 (C-12), 148.3 (C-11), 149.3 (C-6), 164.8 (CONH), 167.4 (COOH). Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.36; H, 4.24; N, 4.58.

*4-[(2E)-3-(3-Hydroxy-4-methoxyphenyl)prop-2-eneamido]benzoic acid (**3**)*. White powder. Yield: method 2 - 60%. Mp 261-263 °C. IR (KBr) υ (cm^{-1}) 3300, 2930, 2850, 2665, 2550, 2365, 1670, 1610, 1525, 1430, 1410, 1375, 1320, 1295, 1265, 1175, 1130, 1020, 1000, 975, 855, 800, 770, 720, 600, 550, 505; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.81 (3H, s, CH_3), 6.63 (1H, d, *J* 15.6 Hz, H-8), 6.97 (1H, d, *J* 8.9 Hz, H-13), 7.03-7.10 (2H, m, H-10,14), 7.49 (1H, d, *J* 15.6 Hz, H-7), 7.80 (2H, d, *J* 8.6 Hz, H-1,5), 7.92 (2H, d, *J* 8.6 Hz, H-2,4), 9.27 (1H, s, OH), 10.41 (1H, s, NH), 12.70 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.1 (CH_3), 112.6 (C-10), 114.0 (C-13), 118.9 (C-1,5), 119.5 (C-14), 121.4 (C-7), 125.5 (C-3), 127.9 (C-9), 130.9 (C-2,4), 141.7 (C-8), 144.0 (C-11), 147.3 (C-12), 150.3 (C-6), 164.7 (CONH), 167.4 (COOH). Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H,4.83; N, 4.47. Found: C, 64.54; H, 4.82; N, 4.24.

*4-[(2E)-3-(4-Hydroxyphenyl)prop-2-eneamido]benzoic acid (**4**)*. Beige powder. Yield: method 1 - 41% (53% crude product); method 2 – 80%. Mp 295-296 °C. IR (KBr) υ (cm^{-1}) 3315, 2670, 2550, 1680, 1625, 1605, 1515, 1425, 1410, 1380, 1320, 1295, 1245, 1200, 1170, 1130, 1000, 970, 935, 855, 825, 800, 770, 730, 700, 660, 550, 530, 505; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 6.63 (1H, d, *J* 15.6 Hz, H-8), 6.83 (2H, d, *J* 8.3 Hz, H-11,13), 7.48 (1H, d, *J* 8.2 Hz, H-10,14), 7.53 (1H, d, *J* 15.6 Hz, H-7), 7.79 (2H, d, *J* 8.7 Hz, H-1,5), 7.90 (2H, d, *J* 8.7 Hz, H-2,4), 9.97 (1H, bs, OH), 10.39 (1H, s, NH), 12.69 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 116.3 (C-11,13), 118.5 (C-7), 118.9 (C-1,5), 125.5 (C-3), 126.1 (C-9), 130.2 (C-10,14), 130.9 (C-2,4), 141.6 (C-8), 143.9 (C-12), 159.8 (C-6), 164.9 (CONH), 167.4 (COOH).

*4-[(2E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)prop-2-eneamido]benzoic acid (**5**)*. Beige powder. Yield: method 1 - 39% (49% crude product); method 2 – 60%. Mp 264-266 °C. IR (KBr) υ (cm^{-1}) 3365, 2945, 2845, 1665, 1545, 1680, 1625, 1605, 1515, 1460, 1425, 1335, 1305, 1285, 1255, 1210, 1175, 1155, 1110, 1005, 990, 960, 910, 865, 830, 800, 775, 695, 665, 595, 545, 505, 475; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.82 (6H, s, 2×CH_3), 6.69 (1H d, *J* 15.5 Hz, H-7), 6.94 (2H, s, H-10,14), 7.55 (1H, d, *J* 15.5 Hz, H-8), 7.81 (2H, d, *J* 8.5 Hz, H-1,5), 7.92 (2H, d, *J* 8.5 Hz, H-2,4), 8.93 (1H, s, OH), 10.41 (1H, s, NH), 12.71 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.5 (CH_3), 106.0(C-10,14), 118.8 (C-1,5), 119.4 (C-7), 125.4 (C-3,9), 131.0 (C-2,4), 138.5 (C-12), 142.4 (C-8), 143.9 (C-11,13), 148.5 (C-6), 164.9 (CONH), 167.4 (COOH). Anal. Calcd. for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C,62.50; H, 5.11; N, 4.19.

*4-[(2E)-3-(4-Amyloxyphenyl)prop-2-eneamido]benzoic acid (**6**)*. White powder. Yield: method 1 - 13% (48% crude product). Mp 275-277 °C. IR (KBr) υ (cm^{-1}) 3325, 2955, 2940, 2870, 2665, 2545, 1680, 1625, 1606, 1575, 1515, 1470, 1425, 1410, 1320, 1290, 1250, 1170, 1130, 1110, 1060, 1020, 995, 970, 870, 855, 830, 820, 805, 770, 730, 700, 645, 570, 550, 525, 5085; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 0.88 (3H, t, *J* 7.0 Hz, $O(CH_2)_4C\underline{H}_3$), 1.28-1.44 (4H, m, $O(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.71 (2H, p, *J* 7.0 Hz, $OCH_2C\underline{H}_2(CH_2)_2CH_3$), 4.00 (2H, t, *J* 7.0 Hz, $OC\underline{H}_2(CH_2)_3CH_3$), 6.77 (1H, d, *J* 15.5 Hz, H-7), 6.99 (2H, d, *J* 8.6 Hz, H-11,13), 7.52-7.61 (3H, m, H-8,10,14), 7.82 (2H, d, *J* 8.7 Hz, H-1,5), 7.91 (2H, d, *J* 8.7 Hz, H-2,4), 10.58 (1H, s, NH), 12.70 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 13.9 ($O(CH_2)_4\underline{C}H_3$), 21.9 ($O(CH_2)_3\underline{C}H_2CH_3$), 27.7 ($O(CH_2)_2\underline{C}H_2CH_2CH_3$), 28.3 ($OCH_2\underline{C}H_2(CH_2)_2CH_3$), 67.6 ($O\underline{C}H_2(CH_2)_3CH_3$), 115.0 (C-11,13), 118.4 (C-1,5), 119.3 (C-7), 125.0 (C-3), 127.1 (C-9), 129.5 (C-10,14), 130.4 (C-2,4), 140.6 (C-8), 143.6 (C-12), 160.2 (C-6), 164.3 (CONH), 167.0 (COOH). Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.21; H, 6.56; N, 3.86.

*4-[(2E)-3-(3-Hydroxyphenyl)prop-2-eneamido]benzoic acid (**7**).* Pale yellow powder. Yield: method 1 - 64% (78% crude product). Mp 273-277 °C. IR (KBr) υ (cm^{-1}) 3320, 2925, 2680, 2555, 1700, 1680, 1665, 1630, 1610, 1560, 1435, 1455, 1430, 1410, 1330, 1295, 1245, 1175, 1130, 1120, 1000, 970, 935, 870, 850, 820, 785, 770, 730, 695, 650, 555, 505, 450, 430; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 6.77 (1H, d, *J* 15.7 Hz, H-7), 6.83 (1H, d, *J* 7.9 Hz, H-12), 7.01 (1H, s, H-10), 7.06 (1H, d, *J* 7.9 Hz, H-14), 7.24 (1H, t, *J* 7.9 Hz, H-13), 7.53 (1H, d, *J* 15.7 Hz, H-8), 7.80 (2H, d, *J* 8.7 Hz, H-1,5), 7.92 (2H, d, *J* 8.7 Hz, H-2,4), 9.66 (1H, bs, OH), 10.48 (1H, s, NH), 12.70 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 114.3 (C-10), 117.7 (C-12), 119.0 (C-1,5), 119.5 (C-7), 122.1 (C-14), 125.7 (C-3), 130.5 (C-13), 130.9 (C-2,4), 136.2 (C-9), 141.6 (C-8), 143.8 (C-6), 158.2 (C-11), 164.4 (CONH), 167.4 (COOH). Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.18; H, 4.44; N, 4.84.

*4-[(2E)-3-(2,4-Dimethoxyphenyl)prop-2-eneamido]benzoic acid (**8**).* Beige powder. Yield: method 1 - 48% (65% crude product). Mp 249-251 °C. IR (KBr) υ (cm^{-1}) 3300, 2945, 2840, 2660, 2540, 1685, 1660, 1605, 1520, 1460, 1420, 1335, 1290, 1265, 1250, 1210, 1170, 1160, 1120, 1030, 1000, 975, 920, 870, 855, 835, 800, 775, 740, 705, 670, 640, 695, 555, 515, 465, 450, 415; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.82 (3H, s, CH_3), 3.89 (3H, s, CH_3), 6.59-6.66 (2H, m, H-11,13), 6.77 (1H, d, *J* 16.0 Hz, H-7), 7.52 (1H, d, *J* 8.4 Hz, H-14), 7.72-7.83 (3H, m, H-1,5,8), 7.91 (2H, d, *J* 8.9 Hz, H-2,4), 10.38 (1H, s, NH), 12.70 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.0 (CH_3), 56.2 (CH_3), 99.0 (C-11), 106.6 (C-13), 116.3 (C-3), 118.8 (C-1,5), 119.9 (C-7), 125.4 (C-9), 130.4 (C-14), 130.9 (C-2,4), 136.7 (C-8), 144.0 (C-6), 159.8 (C-10), 162.7 (C-12), 165.2 (CONH), 167.4 (COOH). Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.49; H, 5.15; N, 4.17.

*4-[(2E)-3-(4-Dimethylaminophenyl)prop-2-eneamido]benzoic acid (**9**).* Pale yellow powder. Yield: method 1 - 40%. Mp 250-252 °C. IR (KBr) υ (cm^{-1}) 3180, 3890, 2810, 2660, 2535, 2365, 1680, 1595, 1525, 1410, 1350, 1315, 1295, 1250, 1160, 1125, 1065, 1035, 1000, 975, 950, 855, 810, 770, 705, 585, 545, 535, 505, 470; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.96 (6H, s, $N(CH_3)_2$), 6.59 (1H, d, *J* 15.5 Hz, H-7), 6.73 (2H, d, *J* 8.8 Hz, H-11,13), 7.46 (2H, d, *J* 8.8 Hz, H-10,14), 7.52 (1H, d, *J* 15.5 Hz, H-8), 7.82 (2H, d, *J* 8.8 Hz, H-1,5), 7.92 (2H, d, *J* 8.8 Hz, H-2,4), 10.32 (1H, s, NH), 12.12-13.07 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 40.2 ($N(CH_3)_2$), 112.4 (C-11,12), 116.4 (C-7), 118.8 (C-1,5), 122.4 (C-9), 125.3 (C-3), 129.8 (C-10,14), 131.0 (C-2,4), 142.1 (C-8), 144.2 (C-6), 151.9 (C-12), 165.2 (CONH), 167.5 (COOH). Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.35; H, 5.71; N, 9.01.

*3-[(2E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)prop-2-eneamido]benzoic acid (**12**).* Beige powder. Yield: method 1 - 27% (29% crude product). Mp 256-257 °C. IR (KBr) υ (cm^{-1}) 3480, 3315, 3070, 2995, 2940, 2840, 2590, 1695, 1655, 1615, 1595, 1535, 1515, 1490, 1460, 1430, 1415, 1370, 1325, 1305, 1265, 1235, 1190, 1155, 1110, 1040, 1015, 990, 970, 900, 865, 850, 815, 750, 680, 660, 640, 600, 580, 560, 520, 445; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.82 (6H, s, 2×CH_3), 6.66 (1H, d, *J* 15.6 Hz, H-7), 6.93 (2H, s, H-10,14), 7.45 (1H, t, *J* 7.8 Hz, H-4), 7.52 (1H, d, *J* 15.6 Hz, H-8), 7.62 (1H, d, *J* 7.6 Hz, H-5) 7.92 (1H, d, *J* 8.3 Hz, H-3), 8.33 (1H, s, H-1), 8.91 (1H, s, OH), 10.29 (1H, s, NH), 12.95 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.5 (CH_3), 106.0 (C-10,14), 119.4 (C-7), 120.3 (C-1), 123.6 (C-5), 124.4 (C-3), 125.4 (C-9), 129.5 (C-4), 131.8 (C-2), 138.3 (C-12), 140.2 (C-11,13), 141.8 (C-8), 148.5 (C-6), 164.6 (CONH), 167.7 (COOH). Anal. Calcd. for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 62.67; H, 4.97; N, 3.94.

*3-[(2E)-3-(4-Hydroxyphenyl)prop-2-eneamido]benzoic acid (**13**).* Pale orange powder. Yield: method 1 - 41%, (44% crude product). Mp 270-273 °C. IR (KBr) υ (cm^{-1}) 3395, 3130, 2665, 1892, 1910, 1685, 1665, 1585, 1545, 1510, 1445, 1410, 1380, 1345, 1285, 1270, 1235, 1185, 1165, 1100, 1005, 995, 980, 955, 940, 900, 870, 825, 815, 785, 755, 695, 675, 665, 580, 550, 525, 515, 460, 425; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 6.60 (1H, d, *J* 15.8 Hz, H-7), 6.83 (2H, d, *J* 9.16 Hz, H-11,13), 7.42-7.55 (5H, m, H-4,5,8,10,14), 7.94 (1H, d, *J* 8.5 Hz, H-3), 8.29 (1H, s, H-1), 9.98 (1H, bs, OH), 10.28 (1H, s, NH), 12.96 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 116.3 (C-11,13), 118.8 (C-7), 120.3 (C-1), 123.6 (C-5), 124.4 (C-3), 126.1 (C-9), 129.5 (C-4), 130.1 (C-10,14), 131.2 (C-2), 140.2 (C-12), 141.2 (C-8), 159.8 (C-6), 164.7 (CONH), 167.7 (COOH). Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.61; H, 4.45; N, 4.88.

*3-[(2E)-3-(2,4-Dimethoxyphenyl)prop-2-eneamido]benzoic acid (**14**).* Pale yellow powder. Yield: method 1 - 55% (66% crude product). Mp 237-238 °C. IR (KBr) υ (cm^{-1}) 3275, 3020, 2945, 2840, 2600, 2365, 1695, 1655, 1610, 1575, 1530, 1505, 1465, 1440, 1420, 1330, 1310, 1295, 1270, 1240, 1215, 1180, 1165, 1120, 1085, 1035, 1005, 975, 935, 895, 850, 840, 820, 805, 755, 745, 720, 675, 665, 635, 595, 555, 510, 470, 415; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.82 (3H, s, CH_3), 3.89 (3H, s, CH_3) 6.58-6.66 (2H, m, H-11,13), 6.75 (1H, d, *J* 15.9 Hz, H-7), 7.44 (1H, t, *J* 7.9 Hz, H-4), 7.51 (1H, d, *J* 8.8 Hz, H-14), 7.62 (1H, d, *J* 7.2 Hz, H-5), 7.74 (1H, d, *J* 15.9 Hz, H-8), 7.95 (1H, d, *J* 8.1 Hz, H-3), 8.31 (1H, s, H-1), 10.27 (1H, s, NH), 12.99 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 55.9 (CH_3), 56.2 (CH_3), 99.0 (C-11), 106.5 (C-13), 116.4 (C-9), 120.1 (C-7), 120.3 (C-1), 123.6 (C-5), 124.3

(C-3), 129.5 (C-4), 130.3 (C-14), 131.8 (C-2), 136.2 (C-8), 140.2 (C-6), 159.8 (C-10), 162.6 (C-12), 165.1 (CONH), 167.7 (COOH). Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.96; H, 5.14; N, 4.24.

*3-[(2E)-3-(3-Hydroxy-4-methoxyphenyl)prop-2-eneamido]benzoic acid (**15**).* Pale brown powder. Yield: method 1 - 42% (43% crude product). Mp 232-235 °C. IR (KBr) υ (cm^{-1}) 3315, 3215, 2845, 2570, 2030, 1905, 18115, 1695, 1670, 1630, 1605, 1560, 1520, 1485, 1435, 1355, 1300, 1215, 1190, 1160, 1130, 1020, 1005, 995, 980, 970, 910, 850, 810, 785, 760, 735, 700, 680, 665, 610, 565, 530, 500, 450, 425; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.81 (3H, s, CH_3), 6.59 (1H, d, *J* 15.9 Hz, H-7), 6.97 (1H, d, *J* 8.6 Hz, H-13), 7.02-7.08 (2H, m, H-10,14) 7.41-7.51 (2H, m, H-4,8), 7.63 (1H, d, *J* 7.6 Hz, H-5), 7.94 (1H, d, *J* 8.2 Hz, H-9), 8.31 (1H, s, H-1), 9.27 (1H, bs, OH), 10.33 (1H, s, NH), 13.00 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.1 (CH_3), 112.6 (C-10), 113.9 (C-13), 119.7 (C-14), 120.3 (C-7), 121.3 (C-1), 123.7 (C-5), 124.4 (C-3), 128.0 (C-2), 129.5 (C-4), 131.9 (C-9), 140.2 (C-6), 141.2 (C-8), 147.2 (C-11), 150.1 (C-12), 164.6 (CONH), 167.7 (COOH). Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.68; H, 4.67; N, 4.39.

*3-[(2E)-3-(4-Hydroxy-3-methoxyphenyl)prop-2-eneamido]benzoic acid (**16**).* Pale yellow powder. Yield: method 1 - 33% (36% crude product). Mp 249-250 °C. IR (KBr) υ (cm^{-1}) 3320, 3270, 3060, 3000, 2965, 2925, 2585, 1680, 1650, 1590, 1550, 1520, 1495, 1465, 1450, 1415, 1380, 1350, 1280, 1245, 1205, 1185, 1155, 1125, 1080, 1025, 995, 965, 930, 915, 865, 845, 810, 800, 760, 720, 670, 650, 615, 575, 540, 505, 460, 435; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.85 (3H, s, CH_3), 6.64 (1H, d, *J* 15.5 Hz, H-7), 6.83 (1H, d, *J* 8.5 Hz, H-13), 7.08 (1H, d, *J* 7.9 Hz, H-14), 7.20 (1H, s, H-10), 7.44 (1H, t, *J* 8.14 Hz, H-4), 7.51 (1H, d, *J* 15.5 Hz, H-8), 7.63 (1H, d, *J* 7.6 Hz, H-5), 7.93 (1H, d, *J* 8.5 Hz, H-3), 8.32 (1H, s, H-1), 9.55 (1H, bs, OH), 10.28 (1H, s, NH), 12.94 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 56.0 (CH_3), 111.4 (C-10), 116.2(C-13), 119.0 (C-7), 120.3 (C-5), 122.6 (C-14), 123.6 (C-1), 124.4 (C-3), 126.6 (C-9), 129.5 (C-4), 131.8 (C-2), 140.2 (C-12), 141.5 (C-8), 148.4 (C-11), 149.3 (C-6), 164.7 (CONH), 167.7 (COOH). Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.50; H, 4.81; N, 4.37.

*3-[(2E)-3-(4-Amyloxyphenyl)prop-2-eneamido]benzoic acid (**17**).* White powder. Yield: method 1 - 37% (45% crude product). Mp 250-251 °C. IR (KBr) υ (cm^{-1}) 3260, 3135, 3065, 2955, 2872, 2675, 2565, 1690, 1660, 1605, 1575, 1550, 1515, 1490, 1475, 1445, 1425, 1415, 1350, 1310, 1290, 1260, 1240, 1185, 1170, 1115, 1080, 1050, 1025, 1000, 980, 920, 900, 865, 830, 810, 795, 755, 680, 660, 640, 605, 590, 570, 555, 515, 485, 420; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 0.89 (3H, t, *J* 7.5 Hz, $O(CH_2)_4C\underline{H}_3$), 1.28-1.42 (4H, m, $O(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.71 (2H, p, *J* 6.9 Hz, $OCH_2C\underline{H}_2(CH_2)_2CH_3$), 4.00 (2H, t, *J* 6.4 Hz, $OC\underline{H}_2(CH_2)_3CH_3$), 6.67 (1H, d, *J* 15.8 Hz, H-7), 6.99 (2H, d, *J* 8.7 Hz, H-11,13), 7.39-7.63 (5H, m, H-4,5,8,10,14), 7.94 (1H, d, *J* 8.1 Hz, H-3), 8.31 (1H, s, H-1), 10.30 (1H, s, NH), 12.96 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 14.4 ($O(CH_2)_4\underline{C}H_3$), 22.4 ($O(CH_2)_3\underline{C}H_2CH_3$), 28.1 ($O(CH_2)_2\underline{C}H_2CH_2CH_3$), 28.8 ($OCH_2\underline{C}H_2(CH_2)_2CH_3$), 68.1 ($OCH_2(CH_2)_3CH_3$), 115.4 (C-11,13), 119.8 (C-7), 120.3 (C-1), 123.7 (C-5), 124.4 (C-3), 127.5 (C-2), 129.5 (C-4), 129.9 (C-10,14), 131.8 (C-9), 140.1 (C-12), 140.8 (C-8), 160.6 (C-6), 164.6 (CONH), 167.6 (COOH). Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.40; H, 6.04; N, 4.04.

*3-[(2E)-3-(3-Hydroxyphenyl)prop-2-eneamido]benzoic acid (**18**).* Beige powder. Yield: method 1 - 54% (60% crude product). Mp 250-251 °C. IR (KBr) υ (cm^{-1}) 3555, 3280, 3080, 2575, 1980, 1910, 1805, 1690, 1630, 1595, 1540, 1490, 1455, 1310, 1275, 1185, 1115, 1085, 1040, 1005, 995, 965, 935, 900, 850, 820, 785, 755, 730, 680, 615, 565, 530, 470, 450, 420; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 6.75 (1H, d, *J* 15.5 Hz, H-7), 6.82 (1H, d, *J* 7.9 Hz, H-12), 7.00 (1H, s, H-10), 7.05 (1H, d, *J* 7.7 Hz, H-14), 7.24 (1H, t, *J* 7.9 Hz, H-4), 7.41-7.57 (2H, m, H-8,13), 7.65 (1H, d, *J* 7.9 Hz, H-5), 7.95 (1H, d, *J* 8.8 Hz, H-3), 8.32 (1H, s, H-1), 9.65 (1H, bs, OH), 10.39 (1H, s, NH), 12.99 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 114.3 (C-10), 117.6 (C-2), 119.5 (C-7), 120.4 (C-1), 122.2 (C-14), 123.7 (C-5), 124.6 (C-3), 129.6 (C-13), 130.5 (C-4), 131.8 (C-2), 136.3 (C-9), 140.0 (C-6), 141.2 (C-8), 158.2 (C-11), 164.2 (CONH), 167.6 (COOH). Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.80; H, 4.59; N, 4.55.

*3-[(2E)-3-(3,4-Dimethoxyphenyl)prop-2-eneamido]benzoic acid (**19**).* Pale powder. Yield: method 2 – 59%. Mp 222-223 °C. IR (KBr) υ (cm^{-1}) 3270, 3135, 3065, 3015, 2960, 2910, 2840, 2670, 2590, 1695, 1655, 1625, 1595, 1540, 1515, 1490, 1560, 1440, 1410, 1345, 1305, 1260, 1240, 1185, 1165, 1140, 1080, 1020, 1000, 970, 950, 920, 895, 865, 845, 805, 785, 755, 735, 720, 690, 680, 660, 550, 520, 430, 415; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 3.80 (3H, s, CH_3), 3.82 (3H, s, CH_3), 6.70 (1H, d, *J* 15.4 Hz, H-7), 7.02 (1H, d, *J* 8.2 Hz, H-13), 7.20 (1H, d, *J* 8.2 Hz, H-14), 7.22 (1H, s, H-10), 7.45 (1H, t, *J* 7.7 Hz, H-4), 7.55 (1H, d, *J* 15.4 Hz, H-8), 7.63 (1H, d, *J* 7.7 Hz, H-5), 7.93 (1H, d, *J* 7.7 Hz, H-5), 8.33 (1H, s, H-1) 10.33 (1H, s, NH), 12.99 (1H, s, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 55.4 (CH_3), 55.6 (CH_3), 110.0 (C-10), 111.8 (C-13), 119.6 (C-7), 119.8 (C-1), 121.9 (C-14), 123.2 (C-3), 124.0 (C-5), 127.4 (C-2), 129.1 (C-4), 131.4 (C-9), 139.7 (C-6), 140.7 (C-8), 149.0 (C-12), 150.5 (C-11), 164.1

(CONH), 167.2 (COOH). Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.36; H, 4.65; N, 4.19.

*3-[(2E)-3-(4-Dimethylaminophenyl)prop-2-eneamido]benzoic acid (**20**)*. Brown powder. Yield: method 2 – 40%. Mp 229-230 °C. IR (KBr) υ (cm^{-1}) 3255, 2810, 2570, 1700, 1655, 1600, 1525, 1485, 1445, 1350, 1305, 1275, 1245, 1180, 1165, 1065, 1005, 970, 945, 855, 815, 750, 700, 675, 665, 595, 555, 530, 515, 410; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.96 (6H, s, 2×CH_3), 6.56 (1H, d, *J* 15.5 Hz, H-7), 6.75 (2H, d, *J* 8.9 Hz, H-11,12), 7.40-7.55 (4H, m, H-4,8,10,14), 7.62 (1H, dt, *J* 7.8, 1.3 Hz, H-5), 7.94 (1H, d, *J* 7.8 Hz, H-3), 8.32 (1H, t, *J* 1.3 Hz, H-1), 10.21 (1H, s, NH), 12.81-13.13 (1H, bs, COOH), ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 39.8 ($N(CH_3)_2$), 112.0 (C-11,13), 116.1 (C-7), 119.8 (C-1), 122.0 (C-9), 123.1 (C-3), 123.7 (C-5), 129.1(4), 129.3 (C-10,14), 131.3 (C-4), 139.9 (C-6), 141.2 (C-8), 151.4 (C-12), 164.6 (CONH), 167.3 (COOH). Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.74; H, 5.86; N, 8.59.

*2-[(2E)-3-(4-Dimethylaminophenyl)prop-2-eneamido]benzoic acid (**24**)*. Brown powder. Yield: method 2 – 60%. Mp 219 °C. IR (KBr) υ (cm^{-1}) 2890, 2600, 1685, 1655, 1585, 1525, 1450, 1395, 1375, 1345, 1325, 1285, 1230, 1180, 1165, 1085, 1003, 980, 950, 905, 880, 850, 810, 795, 765, 695, 655, 600, 555, 530, 510, 465, 420; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.95 (6H, s, 2×CH_3), 6.59 (1H, d, *J* 15.5 Hz, H-7), 6.81 (2H, d, *J* 8.3 Hz, H-11,12), 7.15 (1H, td, *J* 7.7, 1.0 Hz, H-3), 7.48-7.65 (4H, m, H-4,8,10,14), 8.01 (1H, dd, *J* 7.7, 1.0 Hz, H-2), 8.65 (1H, d, *J* 7.7 Hz, H-5), 11.27 (1H, s, NH), 12.70-14.64 (1H, bs, COOH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 39.8 ($N(CH_3)_2$), 111.9 (C-11,13), 116.2 (C-1), 116.3 (C-7), 120.2 (C-5), 121.9 (C-3), 122.4 (C-9), 129.8 (C-10,14), 131.2 (C-2), 134.1 (C-4), 141.5 (C-6), 142.2 (C-8), 151.4 (C-12), 164.6 (CONH), 169.6 (COOH). Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 68.89; H, 5.74; N, 8.84.

Spectral data of piperidinium salts of N-cinnamoyl anilines

*Piperidinium salt of 4-[(2E)-3-(3-metoxy-4-hydroxyphenyl)prop-2-eneamido]benzoic acid (**2**×Pi)*. Yellow powder. Yield – 48%. Mp 156-157 °C. IR (KBr) υ (cm^{-1}) 3435, 2965, 2740, 2540, 2450, 1675, 1600, 1520, 1445, 1365, 1340, 1320, 1300, 1280, 1235, 1165, 1125, 1035, 1000, 985, 870, 850, 795, 720, 630, 560, 475, 440. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.58-1.50 (2H, m, Pi), 1.68-1.58 (4H, m, Pi), 3.00-2.88 (4H, m, Pi), 3.83 (3H, s, OCH_3), 5.97-4.91 (3H, bs, $R^1R^2N^+H_2$, OH), 6.71 (1H, d, *J* 15.6 Hz, H-8), 6.86 (1H, d, *J* 8.2 Hz, H-13), 7.07 (1H, d, *J* 8.2 Hz, H-14), 7.21 (1H, d, *J* 1.3 Hz, H-10), 7.50 (1H, d, *J* 15.6 Hz, H-7), 7.69 (2H, d, *J* 8.6 Hz, H-1,5), 7.86 (2H, d, *J* 8.6 Hz, H-2,4), 10.35 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 23.0 (Pi), 23.6 (Pi), 44.3 (Pi), 56.0 (CH_3), 111.3 (C-10), 116.2 (C-13), 118.3 (C-1,5), 119.2 (C-7), 122.6 (C-14), 126.5 (C-9), 130.3 (C-2,4), 132.7 (C-3), 141.3 (C-8), 141.6 (C-6), 148.5 (C-12), 149.6 (C-11), 164.7 (NHCO), 169.9 (COO^-). Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.50; H, 6.55; N, 6.95.

*Piperidinium salt of 4-[(2E)-3-(3-hydroxy-4-methoxyphenyl)prop-2-eneamido]benzoic acid (**3**×Pi)*. White powder. Yield – 54%. Mp 236-239 °C. IR (KBr) υ (cm^{-1}) 3400, 3345, 2965, 2845, 2785, 2545, 2450, 1675, 1630, 1600, 1555, 1515, 1470, 1455, 1400, 1380, 1300, 1265, 1195, 1180, 1160, 1130, 1050, 1025, 995, 945, 860, 805, 790, 760, 725, 595, 560, 525, 450, 470, 440; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.56-1.48 (2H, m, Pi), 1.68-1.57 (4H, m, Pi), 2.98-2.86 (4H, m, Pi), 3.81 (3H, s, OCH_3), 6.38-4.31 (3H, bs, $R^1R^2N^+H_2$, OH), 6.65 (1H, d, *J* 15.6 Hz, H-8), 6.97 (1H, d, *J* 8.4 Hz, H-13), 7.04 (1H, dd, *J* 8.4, 1.8 Hz, H-14), 7.09 (1H, d, *J* 1.8 Hz, H-10), 7.45 (1H, d, *J* 15.6 Hz, H-7), 7.68 (2H, d, *J* 8.7 Hz, H-1,5), 7.86 (2H, d, *J* 8.7 Hz, H-2,4), 10.31 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 23.1 (Pi), 23.7 (Pi), 44.4 (Pi), 56.1 (CH_3), 112.6 (C-13), 114.0 (C-10), 118.4 (C-1,5), 119.9 (C-7), 121.1 (C-14), 128.1 (C-9), 130.3 (C-2,4), 132.8 (C-3), 141.0 (C-8), 141.5 (C-6), 147.4 (C-11), 150.0 (C-12), 164.4 (NHCO), 169.8 (COO^-). Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 65.91; H, 6.78; N, 7.18.

*Piperidinium salt of 4-[(2E)-3-(4-hydroxyphenyl)prop-2-eneamido]benzoic acid (**4**×Pi).* Beige powder. Yield – 53%. Mp 143-144 °C. IR (KBr) υ (cm^{-1}) 3320, 3015, 2950, 2810, 2745, 2530, 2450, 1670, 1655, 1605, 1515, 1475, 1445, 1370, 1345, 1285, 1240, 1185, 1170, 1105, 1030, 1000, 985, 970, 945, 865, 830, 790, 775, 735, 705, 690, 675, 630, 585, 555, 540, 525, 485, 465, 445, 440, 420; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.59-1.46 (2H, m, Pi), 1.73-1.55 (4H, m, Pi), 3.03-2.91 (4H, m, Pi), 6.67 (1H, d, *J* 15.6 Hz, H-8), 5.53-6.58 (3H, bs, $R^1R^2N^+H_2$, OH), 6.85 (2H, d, *J* 8.55 Hz, H-11,13), 7.45 (2H, d, *J* 8.55 Hz, H-10,14), 7.50 (1H, d, *J* 15.6 Hz, H-7), 7.71 (2H, d, *J* 8.6 Hz, H-1,5), 7.88 (2H, d, *J* 8.6 Hz, H-2,4), 10.37 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.2 (Pi), 22.7 (Pi), 43.5 (Pi), 116.0 (C-11,13), 118.0 (C-1,5), 118.5 (C-7), 125.5 (C-9), 129.6 (C-2,4), 129.9 (C-3), 131.8 (C-10,14), 140.7 (C-8), 141.4 (C-6), 159.7 (C-12), 164.3 (NHCO), 169.5 (COO^-). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 67.95; H, 6.46; N, 7.48.

*Piperidinium salt of 4-[(2E)-3-(3,5-dimethoxy-4-hydroxyphenyl)prop-2-eneamido]benzoic acid (**5**×Pi)*. Bright yellow powder. Yield - 27%. Mp 150-152 °C. IR (KBr) υ (cm^{-1}) 3475, 3240, 3045, 3000, 2970, 2935, 2845, 2735,

2540, 2450, 1595, 1575, 1530, 1515, 1460, 1430, 1405, 1370, 1325, 1300, 1240, 1225, 1190, 1165, 1120, 1025, 1000, 985, 950, 915, 875, 845, 820, 790, 780, 740, 705, 605, 560, 505, 475, 440; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.58-1.47 (2H, m, Pi), 1.70-1.58 (4H, m, Pi), 3.02-2.86 (4H, m, Pi), 3.80 (6H, s, 2×OCH_3), 6.58-5.60 (3H, bs, $R^1R^2N^+H_2$, OH), 6.79 (1H, d, *J* 15.6 Hz, H-8), 6.94 (2H, s, H-10,14), 7.51 (1H, d, *J* 15.6 Hz, H-7), 7.71 (2H, d, *J* 8.8 Hz, H-1,5), 7.87 (2H, d, *J* 8.8 Hz, H-2,4), 10.49 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.6 (Pi), 23.2 (Pi), 43.9 (Pi), 55.9 (2×CH_3), 105.5 (C-10,14), 117.9 (C-1,5), 119.3 (C-7), 124.9 (C-9), 129.8 (C-2,4), 132.3 (C-3), 137.9 (C-12), 141.0 (C-8), 141.2 (C-6), 148.1 (C-11,13), 164.2 (NHCO), 169.5 (COO^-). Anal. Calcd. for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.62; H, 6.55; N, 6.48.

*Piperidinium salt of 4-[(2E)-3-(4-methoxyphenyl)prop-2-eneamido]benzoic acid (**11**×Pi).* Beige powder. Yield - 26%. Mp 212-215 °C. IR (KBr) υ (cm^{-1}) 3380, 3260, 3040, 2950, 2845, 2540, 2440, 1665, 1625, 1605, 1575, 1515, 1470, 1445, 1425, 1400, 1380, 1355, 1310, 1295, 1250, 1175, 1110, 1025, 1000, 985, 865, 825, 790, 730, 700, 635, 555, 510, 440; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.59-1.48 (2H, m, Pi), 1.71-1.59 (4H, m, Pi), 3.04-2.90 (4H, m, Pi), 3.80 (s, 3H, OCH_3), 6.25-4.82 (2H, bs, $R^1R^2N^+H_2$), 6.78 (1H, d, *J* 16.1 Hz, H-8), 7.00 (2H, d, *J* 8.3 Hz, H-11,13), 7.61-7.51 (3H, m, H-7,10,14), 7.72 (2H, d, *J* 8.3 Hz, H-1,5), 7.89 (2H, d, *J* 8.3 Hz, H-2,4), 10.48 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.4 (Pi), 22.8 (Pi), 43.6 (Pi), 55.3 (CH_3), 114.5 (C-11,13), 118.0 (C-1,5), 119.8 (C-7), 127.3 (C-9), 129.5 (C-2,4), 129.9 (C-10,14), 132.4 (C-3), 140.0 (C-8), 141.1 (C-6), 160.6 (C-12), 164.1 (NHCO), 169.6 (COO^-). Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.04; H, 6.66; N, 7.15.

*Piperidinium salt of 2-[(2E)-3-(3-hydroxyphenyl)prop-2-eneamido]benzoic acid (**21**×Pi).* Yellow powder. Yield – 30%. Mp 217-220 °C. IR (KBr) υ (cm^{-1}) 3000, 2940, 2855, 2800, 2550, 2455, 1670, 1625, 1590, 1500, 1475, 1435, 1370, 1330, 1285, 1245, 1180, 1155, 1045, 1030, 995, 970, 955, 845, 805, 770, 765, 705, 670, 575, 560, 535, 490, 455; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.62-1.51 (2H, m, Pi), 1.73-1.63 (4H, m, Pi), 3.10-3.00 (4H, m, 4H, Pi), 6.59 (1H, d, *J* 15.7 Hz, H-8), 6.86 (1H, dd, *J* 7.8, 1.4 Hz, H-12), 7.02 (1H, dt, *J* 7.7, Hz, H-3), 7.12-7.05 (2H, m, H-10,14), 7.23 (1H, t, *J* 7.8 Hz, H-13), 7.36 (1H, dt, *J* 7.7, 1.5 Hz, H-4), 7.50 (1H, d, *J* 15.7 Hz, H-7), 8.06 (1H, dd, *J* 7.7, 1.5 Hz, H-5), 8.63 (1H, d, *J* 7.7 Hz, H-2), 10.25-8.99 (3H, bs, $R^1R^2N^+H_2$, OH), 14.19 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.3 (Pi), 22.8 (Pi), 44.0 (Pi), 114.6 (C-12), 117.5 (C-10), 119.1 (C-7), 119.3 (C-5), 122.2 (C-14), 123.7 (C-3), 124.4 (C-1), 130.4 (C-13), 131.0 (C-2), 131.8 (C-4), 136.3 (C-9), 140.5 (C-8), 141.3 (C-6), 158.4 (C-11), 163.7 (NHCO), 171.3 (COO^-). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.34; H, 6.56; N, 7.49.

*Piperidinium salt of 2-[(2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-eneamido]benzoic acid (**23**×Pi).* Pale yellow powder. Yield - 53%. Mp 207-210 °C. IR (KBr) υ (cm^{-1}) 3425, 3035, 2945, 2835, 2715, 2535, 2360, 2345, 1665, 1625, 1595, 1505, 1475, 1445, 1435, 1365, 1330, 1310, 1280, 1250, 1225, 1180, 1165, 1125, 1035, 995, 965, 945, 875, 835, 810, 755, 720, 700, 670, 595, 535, 500, 465, 435, 415; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.61-1.51 (2H, m, Pi), 1.74-1.62 (4H, m, Pi), 3.09-3.02 (4H, m, Pi), 3.84 (3H, s, OCH_3), 6.52 (1H, d, *J* 15.7 Hz, H-8), 6.85 (1H, d, *J* 8.0 Hz, H-13), 6.98 (1H, dt, *J* 7.8, 1.6 Hz, H-3), 7.09 (1H, dd, *J* 8.0, 1.7 Hz, H-14), 7.27 (1H, d, *J* 1.7 Hz, H-10), 7.33 (1H, dt, *J* 7.8, 1.6 Hz, H-4), 7.49 (1H, d, *J* 15.7 Hz, H-7), 8.02 (1H, dd, *J* 7.8, 1.6 Hz, H-5), 8.62 (1H, d, *J* 7.8 Hz, H-2), 9.79-9.02 (3H, bs, $R^1R^2N^+H_2$, OH), 14.12 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.3 (Pi), 22.8 (Pi), 44.0 (Pi), 56.1 (CH_3), 111.5 (C-10), 116.1 (C-13), 119.1 (C-7), 120.6 (C-5), 121.8 (C-14), 122.6 (C-3), 124.6 (C-1), 126.5 (C-9), 130.8 (C-2), 131.7 (C-4), 140.7 (C-8), 141,5 (C-6), 148.4 (C-12), 149.3 (C-11), 164.3 (NHCO), 171.1 (COO^-). Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.38; H, 6.57; N, 6.93.

*Piperidinium salt of 2-[(2E)-3-(4-dimethylaminophenyl)prop-2-eneamido]benzoic acid (**24**×Pi).* Brown powder. Yield – 61%. Mp 183-187 °C. IR (KBr) υ (cm^{-1}) 3430, 3000, 2945, 2860, 2755, 2525, 2420, 1670, 1600, 1555, 1505, 1435, 1365, 1290, 1280, 1225, 1180, 1165, 1090, 1060, 1040, 995, 985, 945, 850, 815, 760, 705, 665, 600, 560, 525, 460, 445; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.63-1.51 (2H, m, Pi), 1.75-1.63 (4H, m, Pi), 2.94 (6H, s, $N(CH_3)_2$), 3.11-3.01 (4H, m, Pi), 6.39 (1H, d, *J* 15.9 Hz, H-8), 6.70 (2H, d, *J* 8.7 Hz, H-11,13), 6.98 (1H, t, *J* 7.7 Hz, H-3), 7.33 (1H, dt, *J* 7.7, 1.6 Hz, H-4), 7.53-7.43 (3H, m, H-7,10,14), 8.03 (1H, dd, *J* 7.7, 1.6 Hz, H-5), 8.63 (1H, d, *J* 7.7 Hz, H-2), 9.98-9.08 (2H, bs, $R^1R^2N^+H_2$), 13.96 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.4 (Pi), 22.8 (Pi), 40.2 (CH_3), 43.9 (Pi), 112.4 (C-11,13), 118.1 (C-7), 119.0 (C-5), 121.7 (C-3), 122.5 (C-9), 124.2 (C-1), 129.8 (C-10,14), 130.9 (C-2), 131.7 (C-4), 140.9 (C-8), 141.6 (C-6), 151.7 (C-12), 164.5 (NHCO), 171.3 (COO^-). Anal. Calcd. for $C_{23}H_{29}N_3O_3$: C, 69.66; H, 7.39; N, 10.62. Found: C, 69.39; H, 7.36; N, 10.44.

*Piperidinium salt of 2-[(2E)-3-(4-hydroxyphenyl)prop-2-eneamido]benzoic acid (**26**×Pi).* Beige powder. Yield – 21%. Mp 221-222 °C. IR (KBr) υ (cm^{-1}) 3060, 2945, 2860, 2760, 2540, 1680, 1655, 1625, 1585, 1505, 1470, 1435, 1370, 1325, 1280, 1230, 1200, 1175, 1040, 1030, 995, 950, 870, 830, 755, 705, 670, 555, 515, 470, 435; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.63-1.51 (2H, m, Pi), 1.75-1.63 (4H, m, Pi), 3.09-2.99 (4H, m, Pi), 6.44 (1H, d, *J*

15.7 Hz, H-8), 6.84 (2H, d, *J* 8.6 Hz, H-11,13), 6.98 (1H, t, *J* 7.7 Hz, H-3), 7.33 (1H, t, *J* 7.7 Hz, H-4), 7.54-7.44 (3H, m, H-7,10,14), 8.02 (1H, dd, *J* 7.7, 1.3 Hz, H-5), 8.61 (1H, d, *J* 7.7 Hz, H-2), 10.34-9.08 (3H, bs, $R^1R^2N^+H_2$, OH), 14.13 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 21.8 (Pi), 22.3 (Pi), 43.5 (Pi), 115.8 (C-11,13), 118.5 (C-7), 119.3 (C-5), 121.4 (C-3), 124.0 (C-9), 125.5 (C-1), 129.7 (C-10,14), 130.4 (C-2), 131.3 (C-4), 140.0 (C-8), 141.0 (C-6), 159.4 (C-12), 163.8 (NHCO), 170.7 (COO^-). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.42; H, 6.58; N, 7.46.

*2-[(2E)-3-(3-Hydroxy-4-methoxyphenyl)prop-2-eneamido]benzoic acid piperidinium salt (**28**×Pi).* Yellow powder. Yield – 39%. Mp 217-220 °C. IR (KBr) υ (cm^{-1}) 3055, 3005, 2945, 2845, 2735, 2655, 2540, 2440, 2355, 1675, 1650, 1620, 1590, 1560, 1505, 1465, 1455, 1435, 1390, 1365, 1325, 1300, 1285, 1260, 1225, 1180, 1165, 1155, 1130, 1020, 995, 970, 95, 875, 840, 805, 790, 760, 730, 705, 665, 600, 555, 540, 500, 460, 440; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.62-1.51 (2H, m, Pi), 1.75-1.63 (4H, m, Pi), 3.11-3.01 (4H, m, Pi), 3.80 (3H, s, OCH_3), 6.41 (1H, d, *J* 15.6 Hz, H-8), 7.03-6.92 (2H, m, H-3,13), 7.07 (1H, dd, *J* 8.3, 1.9 Hz, H-14), 7.12 (1H, d, *J* 1.9 Hz, H-10), 7.34 (1H, dt, *J* 7.8, 1.6 Hz, H-4), 7.44 (1H, d, *J* 15.6 Hz, H-7), 8.03 (1H, dd, *J* 7.8, 1.6 Hz, H-5), 8.61 (1H, d, *J* 7.8 Hz, H-2), 10.08-9.03 (3H, bs, $R^1R^2N^+H_2$, OH), 14.16 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 22.3 (Pi), 22.8 (Pi), 44.0 (Pi), 56.1 (CH_3), 112.6 (C-13), 114.2 (C-10), 119.0 (C-7), 121.0 (C-5), 121.2 (C-14), 122.0 (C-3), 124.5 (C-9), 128.0 (C-1), 130.9 (C-2), 131.7 (C-4), 140.5 (C-8), 141.5 (C-6), 147.3 (C-11), 150.0 (C-12), 164.0 (CONH), 171.2 (COO^-). Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.18; H, 6.57; N, 6.97.

*Piperidinium salt of 2-[(2E)-3-(4-amyloxyphenyl)prop-2-eneamido]benzoic acid (**29**×Pi).* White powder. Yield – 33%. Mp 116-117 °C. IR (KBr) υ (cm^{-1}) 2955, 2860, 2775, 2545, 2440, 1675, 1625, 1600, 1505, 1480, 1425, 1370, 1340, 1275, 1260, 1170, 1150, 1115 1010, 990, 980, 950, 890, 870, 830, 805, 760, 740, 710, 665; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 0.90 (3H, t, *J* 6.5 Hz, $(CH_2)_4C\underline{H}_3$), 1.43-1.27 (4H, m, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.6-1.47 (2H, m, Pi), 1.77-1.60 (6H, m, $CH_2C\underline{H}_2(CH_2)_2CH_3$, Pi), 3.14-2.95 (4H, m, Pi), 3.99 (2H, t, *J* 6.5 Hz, $CH_2(CH_2)_3CH_3$), 6.51 (1H, d, *J* 15.7 Hz, H-8), 7.01-6.92 (3H, m, H-3,11,13), 7.32 (1H, dt, *J* 1.6, 7.7 Hz, H-4), 7.52 (1H, d, *J* 15.7 Hz, H-7), 7.61 (2H, d, *J* 8.7 Hz, H-10,14), 8.02 (1H, dd, *J* 1.6 Hz, 7.7 Hz, H-5), 8.60 (1H, d, *J* 7.7 Hz, H-2), 9.45-9.07 (2H, bs, $R^1R^2N^+H_2$), 14.27 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6,) δ (ppm) 14.0 ($(CH_2)_4\underline{C}H_3$), 21.9 (Pi), 21.9 (Pi), 22.4 ($(CH_2)_3\underline{C}H_2CH_3$), 28.3 ($(CH_2)_2\underline{C}H_2CH_2CH_3$), 40.2 ($CH_2\underline{C}H_2(CH_2)_2CH_3$), 43.6 (Pi), 67.6 ($\underline{C}H_2(CH_2)_3CH_3$), 114.8 (C-11,13), 118.5 (C-7), 120.9 (C-5), 121.4 (C-3), 124.3 (C-9), 127.1 (C-1), 129.5 (C-10,14), 130.3 (C-2), 131.2 (C-4), 139.5 (C-6), 141.0 (C-8), 160.0 (C-12), 163.6 (NHCO), 170.5 (COO^-). Anal. Calcd. for $C_{26}H_{34}N_2O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.07; H, 7.85; N, 6.33.

Antiradical activity of N-cinnamoyl anilines and their salts

DPPH test was carried out according to the procedure described previously [44].

GO test was carried out as follows: 200 μM solution of cinnamoyl aniline or its piperidinium salt in EtOH (2 mL) and 20 μM solution of GO in EtOH (2 mL) were mixed and kept in dark for 2 h. When the reaction was completed, absorption was measured at 428 nm. Samples, containing other concentration of compounds, were prepared similarly to the procedure described above. The antiradical activity (%) and IC_{50} value (μM) detected by DPPH and GO test is expressed as mean (±standard deviation) of two independent experiments. All the measurements were done triple for each series of experiments.

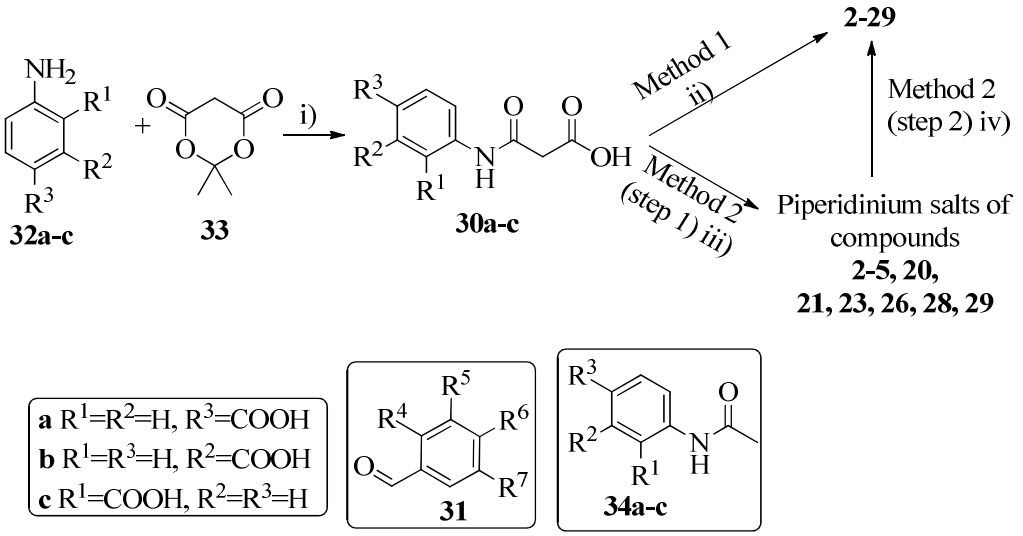
RESULTS AND DISCUSSION

Synthesis of the analogues of the avenanthramides

Most often *N*-((*E*)-3-aryl-2-propenoyl)aminobenzoic acids are synthesized by acylation of corresponding aminobenzoic acids with activated derivatives of substituted cinnamic acids, e.g., (*E*)-3-aryl-2-propenoyl halogenides [7, 19, 31, 33-36, 38, 40, 41, 45-48]. Sometimes base hydrolysis of *N*-((*E*)-3-aryl-2-propenoyl)aminobenzoates (which usually are prepared by acylation of corresponding aminobenzoates with (*E*)-3-aryl-2-propenoyl halogenides or with derivatives of cinnamic acid in the presence of amide coupling reagents) [31, 37, 46, 49, 50] has been used [37, 41]. Acylation of anthranilic acid with monoester of arylidene malonic acids followed by hydrolysis of ester group and decarboxylation lead to target compounds [25]. Several authors created olefinic bound by reaction of aromatic aldehydes with phosphorous ylides (obtained from corresponding 2-haloacetanilides) [32, 37]. Olefinic bond can be formed by aldol condensation of aromatic aldehydes with acetylaminobenzoic acids [51] or carboxyacetamidobenzoic acids [42, 45, 52], as well as by condensation of aromatic aldehydes with 2-methyl-3,1-benzoxazin-4-ones followed by hydrolysis of (*E*)-2-styryl-4*H*-benzo[d][1,3]oxazin-4-ones [1, 8, 13, 19, 45, 48, 53]. There is one example of modified Kolbe-Schmitt carboxylation of *N*-cinnamoyl-2-aminoresorcinol which provided corresponding 3-(*N*-cinnamoyl)aminobenzoic acid

[39]. Microbial synthesis of Tranilast and several avenanthramides in the presence of yeast *Saccharomyces cerevisiae* [26, 54] or *Escherichia coli* [55] is described, too.

Our investigation was aimed to clear up the influence of the position of COOH group in aniline ring on the antiradical activity of *N*-((*E*)-3-aryl-2-propenoyl)aminobenzoic acids **2**-**29**. The most convenient way to prepare the target compounds seemed creation of double bond by aldol condensation of carboxyacetamidobenzoic acids **30a-c** and aromatic aldehydes **31** (Scheme 1) analogously to the method described previously [42]. In order to obtain monoanilides of malonic acid **30a-c**, we acylated aminobenzoic acids **32a-c** with Meldrum`s acid (**33**). The reaction was carried out in toluene under reflux within 4-5 h.



i) toluene, reflux; ii) aldehyde **31**, 25 mol-% β-alanine, Py, reflux (method 1);
iii) aldehyde **31**, 1 eq. piperidine (Pi), toluene, reflux (method 2, step 1);
iv) 10% hydrochloric acid, RT (method 2, step 2).

Scheme 1. Synthesis of the *N*-cinnamoyl anilines

With the key intermediates **30a-c** in hands, we were ready to compounds **2**-**29** *via* Knoevenagel-Doebner reaction, which was carried out in pyridine, at the presence of *β*-alanine under reflux (method 1). Kamat [42] *et al.* suggested these conditions as suitable for the synthesis of *N*-cinnamoyl anthranilates **1d**, **21**-**28**; unfortunately we found out that the yield of the amides of *p*-aminobenzoic acid **2**-**11** was moderate (in the most of the cases the yield achieved 50-70%). The yield of 3-[(2*E*)-phenylprop-2-eneamido]benzoic acids **12**-**20** was even worth (for the most of the prepared compounds the yield did not exceed 30-40%). The target compounds **2**-**29** were isolated by acidification (pH < 7) of reaction mixture and filtration; the crude product contained mainly desired *N*-cinnamoyl anilines **2**-**20** and up to 10% of corresponding acetanilides **34**, but the filtrates contained mainly corresponding acetanilide **34a**-**c**, unreacted aromatic aldehyde **31** and a little (no more than 8%, according to ^{1}H NMR spectra of crude product) amount of *N*-cinnamoyl aniline **2**-**20**. In order to clarify the stability of malonic monoamide **30b** against decarboxylation at the applied conditions, the reaction mixture (malonic monoanilide **30b** and vanillin (**31**, R^4=R^7=H, R^5=OMe, R^6=OH)) was analyzed with ^{1}H NMR - the spectra were taken after 0, 15, 30 and 45 min. Product of decarboxylation **34b** was the main compound already after 15 min (it formed nearly 50% of the product mixture). We have established that about 80% of malonic monoanilide **30b** undergo decarboxylation at the reaction conditions suggested in literature [42].

In order to improve this method and the yield of synthetic analogues of avenanthramides we examined the same reaction in the presence of piperidine as a catalyst and cleared up the impact of temperature (Table 1). Unfortunately, when *β*-alanine was used as catalyst (entry 1-4) we did not obtain satisfactory yield of compound **16** even when temperature was reduced - this dramatically increased duration of the reaction. Slightly better yield was obtained when the malonic monoanilide **30b** was added portion-wise (entry 2). The highest yield (54%) of compound **16** was obtained when piperidine (Pi) was employed as catalyst instead of *β*-alanine (entry 5); the application of piperidine as catalyst allowed obtaining moderate yield even when the reaction was carried out in pyridine under reflux. Aldol condensation realized in the presence of equivalent amount of piperidine in toluene under reflux (at conditions described by Matsumoto *et al.* [56]), did not increase the yield remarkably, too. Unlike the authors [56] which obtained only *N*-cinnamoyl anthranilates under these conditions, we were able (in most of the cases) to isolate in medium yields the piperidinium salts of *N*-cinnamoyl aminobenzoic acids **2**-**5**, **11**, **21**, **23**, **24**, **26**, **28** and **29**. The obtained piperidinium salts were easily converted to corresponding *N*-cinnamoyl anilines in high

yields by treatment with hydrochloric acid (method 2). Both methods gave comparable yields of *N*-cinnamoyl anilines.

Studies of structure-antiradical activity relationships of N-cinnamoyl anilines

The antiradical activity (AA) of cinnamoyl anthranilates is well known [8, 13]. Nevertheless to the best of our knowledge the impact of the position of the carboxylic group in the ring of aniline has not been evaluated. In order to clear up this problem, the antiradical activity (2,2-diphenyl-1-picrylhydrazyl (DPPH) and galvinoxyl (GO) tests) [57] of all synthesized compounds was tested in ethanol solution. AA of all the compounds strongly depended on the substituents in the moiety of cinnamic acid; only compounds containing hydroxyl group and at least one methoxy group next to it in the aromatic ring demonstrated antiradical activity. The arrangement of methoxy and hydroxyl groups varied AA dramatically.

Table 1. Optimization of the synthesis of compound 16[a]

Entry	Catalyst	Temperature, °C	Duration, min	Yield, %[c]
1	*β*-alanine	111	75	22
2[b]	*β*-alanine	111	120	35
3	*β*-alanine	90	180	27
4	*β*-alanine	70	510	28
5	Pi	111	175	54

*[a]Reaction was carried out in Py, molar ratio of amide **30b** and vanillin (**31**, R^4=R^7=H, R^5=OMe, R^6=OH) - 1:1, amount of catalyst – 25 mol-%.*
*[b]Molar ratio of amide **30b** and vanillin (**31**) was 2:1 (amide was added portion-wise).*
[c]HPLC data.

Table 2. Antiradical activity of *N*-cinnamoyl anilines 1d, 2-29

Compound	Substituents in the aniline (R^1-R^3) and cinnamic acid (R^4-R^7) moieties							DPPH test		GO test	
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	AA (%)[a]	IC_{50} (μM)[b]	AA (%)[a]	IC_{50} (μM)[b]
2	H	H	COOH	H	OMe	OH	H	73.2±1.1	44.8±0.1	13.6±0.3	738.8±12.9
3	H	H	COOH	H	OH	OMe	H	13.6±0.1	-	1.7±0.1	-
4	H	H	COOH	H	H	OH	H	4.7±0.6	-	-2.7±0.6	-
5	H	H	COOH	H	OMe	OH	OMe	96.4±0.0	38.0±0.1	78.3±1.8	54.4±1.9
6	H	H	COOH	H	H	OAm	H	6.5±0.0	-	1.4±0.1	-
7	H	H	COOH	H	OH	H	H	2.1±0.2	-	0.2±0.2	-
8	H	H	COOH	OMe	H	OMe	H	2.5±0.4	-	-0.5±0.1	-
9	H	H	COOH	H	H	NMe_2	H	4.3±0.2	-	-1.3±0.2	-
10	H	H	COOH	H	OMe	OMe	H	3.7±1.1	-	2.2±1.1	-
11	H	H	COOH	H	H	OMe	H	6.8±0.4	-	0.7±0.4	-
12	H	COOH	H	H	OMe	OH	OMe	97.8±0.0	21.1±1.1	64.8±2.3	74.3±4.1
13	H	COOH	H	H	H	OH	H	4.2±0.3	-	-0.5±0.6	-
14	H	COOH	H	OMe	H	OMe	H	7.3±0.7	-	0.6±0.4	-
15	H	COOH	H	H	OH	OMe	H	12.3±0.3	-	3.6±0.3	-
16	H	COOH	H	H	OMe	OH	H	71.0±0.4	51.6±1.4	19.9±0.3	447.9±3.8
17	H	COOH	H	H	H	OAm	H	6.4±0.8	-	-0.8±0.4	-
18	H	COOH	H	H	OH	H	H	6.2±0.3	-	2.4±0.2	-
19	H	COOH	H	H	OMe	OMe	H	4.3±0.1	-	2.3±0.0	-
20	H	COOH	H	H	H	NMe_2	H	4.5±0.3	-	-3.0±0.0	-
1d	COOH	H	H	H	OMe	OMe	H	14.5±0.3	-	-3.5±0.1	-
21	COOH	H	H	H	OH	H	H	18.5±1.2	-	0.6±0.1	-
22	COOH	H	H	OMe	H	OMe	H	5.7±0.4	-	0.2±0.2	-
23	COOH	H	H	H	OMe	OH	H	68.9±0.2	80.0±1.4	42.6±2.8	128.1±17.1
24	COOH	H	H	H	H	NMe_2	H	4.9±1.9	-	-1.4±0.4	-
25	COOH	H	H	H	OMe	OH	OMe	98.6±0.0	21.9±0.3	79.5±0.6	48.3±0.6
26	COOH	H	H	H	H	OH	H	15.0±0.1	-	-2.6±0.1	-
27	COOH	H	H	H	H	OMe	H	13.2±0.3	-	0.2±0.2	-
28	COOH	H	H	H	OH	OMe	H	15.9±0.5	-	1.8±0.1	-
29	COOH	H	H	H	H	OAm	H	4.8±0.0	-	2.2±0.4	-

*[a] Antiradical activity (AA) was determined when molar ratio of free radical (DPPH or GO) and cinnamoyl aniline **1d**, **2-29** was 1:1.*
[b] Concentration of cinnamoyl aniline that inhibits 50% of free radical (DPPH or GO) was determined when remarkable AA was observed; the concentration of the free radical was 100 μM.

Such situation was observed in case of compounds **2**, **16** and **23** synthesized from vanillin and compounds **3**, **15** and **28** (obtained from 3-hydroxy-4-methoxy-benzaldehyde (isovanillin)): the first group exhibited good antiradical activity, while the second one did not show any significant AA (see Table 2). The most active were compounds **5**, **12** and **25** containing moiety of syringaldehyde (R^4=H, R^5=R^7=OMe, R^6=OH). We compared AA of neutral *N*-cinnamoyl anilines and their piperidinium salts (see Table 3). Compounds containing syringaldehyde moiety did not show significant difference, but AA of salts **2**×Pi and **23**×Pi obtained from vanillin was 10-20% weaker in comparison with corresponding neutral benzoic acids **2** and **23**. In most of the cases (both for *N*-cinnamoyl

aminobenzoic acids and their salts) the antiradical activity in DPPH test was at least twice higher than in GO test. DPPH and GO tests gave comparable results only in case of sinapic acid anilides **5**, **12** and **25** (the difference did not exceed 1.5 times). The position of carboxylic group was not determining for AA - only slight changes were observed in DPPH test. AA increased in following order: *p*- > *m*- > *o*-carboxy anilides (in case of vanillin derivatives). AA of derivatives of sinapic acid changed according to the sequence: *m*- > *o*- > *p*-carboxy anilides (correspondingly compounds **12**, **25** and **5**). Remarkable difference was observed for GO radical scavenging activity - the position of the carboxylic group influenced AA of ferulic acid derivatives: it increased in the range: *o*- > *m*- > *p*-carboxy anilides (**23** > **16** > **2**). AA of sinapic acid anilides **5**, **12** and **25** (as well as salt **5**×Pi) was similar in all cases, but their IC_{50} values had the same order as feruloyl anilines

Table 3. Antiradical activity of piperidinium salts of *N*-cinnamoyl anilines

Compound	DPPH test		GO test	
	AA, %[a]	IC_{50}, μM[b]	AA, %[a]	IC_{50}, μM[b]
2×Pi	61.0±0.0	68.1±0.2	13.0±1.1	593.7±12.1
3×Pi	6.4±1.1	-	1.8±0.1	-
4×Pi	2.7±0.9	-	2.8±0.1	-
5×Pi	90.2±0.8	39.1±0.6	74.1±7.3	58.6±13.6
11×Pi	0.0±0.2	-	-0.1±0.1	-
21×Pi	0.0±0.0	-	-0.5±0.0	-
23×Pi	59.9±0.1	72.0±1.8	24.9±0.5	310.6±5.9
24×Pi	0.1±0.1	-	-1.1±0.2	-
26×Pi	1.7±0.6	-	0.1±0.2	-
28×Pi	8.0±0.7	-	2.1±0.3	-
29×Pi	0.4±0.0	-	2.0±0.2	-

[a]Antiradical activity (AA) was determined when molar ratio of free radical (DPPH or GO) and piperidinium salt of N-cinnamoyl aniline was 1:1.
[b]Concentration of piperidinium salt of N-cinnamoyl aniline that inhibits 50% of free radical (DPPH or GO) was determined when remarkable AA (in comparison to other piperidinium salts of N-cinnamoyl anilines) was observed; the concentration of the free radical was 100 μM.

Immediate reaction with free radicals is highly desirable property of antioxidant. The reaction of cinnamoyl anilines with DPPH achieved the plateau within few minutes, but the reaction of corresponding piperidinium salts - even in few seconds. Contrary, the reaction of GO with cinnamoyl anilines (or their salts) reached plateau only within 2 h. Our results approve that the synthetic analogues of avenanthramides may act as powerful and quick antioxidants, especially with nitrogen radicals.

CONCLUSION

Various *N*-cinnamoyl anilines have been obtained by aldol condensation of malonic acid monoanilides with aromatic aldehydes. Benzoic acid derivatives **2**-**9**, **12**-**20**, **24** and **29** and piperidinium salts of *N*-cinnamoyl anilines **2**-**5**, **20**, **21**, **23**, **24**, **26**, **28** and **29** have been synthesized for the first time. To the best of our knowledge the impact of the position of carboxylic group in the aniline moiety on the antiradical activity of *N*-cinnamoyl anilines and their piperidinium salts is established for the first time. It has been found out that the position of carboxylic group does not have exhibit significant effect on the antiradical activity in DPPH assay, but it has strong impact on the antiradical activity of feruloyl anilines in GO test.

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