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ORIGINAL PAPER

An alternative way to analogues of avenanthramides and their antiradical activity

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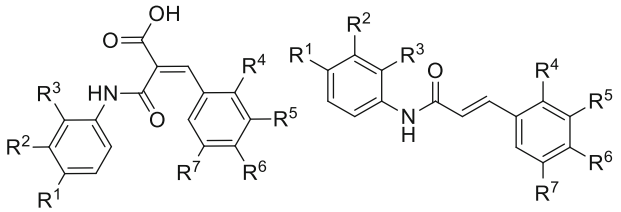
Abstract

The paper is devoted to the synthesis of arylidene malonic acid monoanilides and cinnamoyl anilines by condensation of malonic acid monoanilides with aromatic aldehydes. The presented synthetic route applies simple, cheap, and commercially available aromatic aldehydes and amines, thus overcoming traditional schemes, which involve derivatives of hydroxycinnamic acids. Besides, a mild and effective pyridine-mediated decarboxylation of carboxylic group at C_{sp}^2 in arylidene malonic acid monoanilides leading to cinnamoyl anilines is presented. The structures of obtained selected arylidene derivatives were approved additionally by X-ray analysis. The antiradical properties (2,2-diphenyl-1-picrylhydrazyl and galvinoxyl tests) and structure–activity relationships of the synthesized compounds were studied.

Graphical abstract



Keywords Aldol condensation · Antioxidant · Carbonyl compounds · Carboxylic acids · Cinnamoyl anilines · Retro reactions · X-ray structure determination

Introduction

Cinnamoyl anthranilates **1**, known as avenanthramides (Fig. 1), are found in plants, mostly in oats (*Avena sativa* L.) [1]. Avenanthramides and their synthetic analogues demonstrate wide range of biological activity. Tranilast or Rizaben (**2**, *N*-(3,4-dimethoxycinnamoyl)anthranilic acid, Fig. 1) is already used in medicine as anti-allergic drug. The compound demonstrates also antitumor potential [2]. Some studies are devoted to cinnamoyl anilines as potential selective matrix metalloproteinase [3] and influenza neuraminidase [4, 5] inhibitors, anti-cancer [6–8] and anti-narcotic agents through agonism of 5-HT1A receptor [9]. Avenanthramides are known as strong antioxidants, both in vivo and in vitro. Their antioxidant properties are up to 30 times greater than that demonstrated by other oat polyphenols, e.g., vanillic and caffeic acid derivatives [10]. Previously, we have evaluated the role of the position of carboxylic group in the aniline moiety on the antiradical properties of synthetic analogues of avenanthramides **3** (Fig. 2) [11]. On the other hand, Spasova et al. [12] have studied the impact of ferulic or sinapic acid and α-amino

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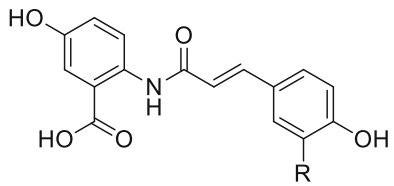

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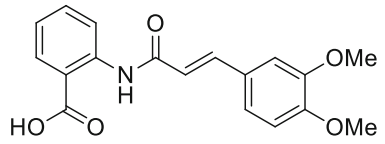

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Fig. 1 Structures of well-known cinnamoyl anthranilates **1** and **2**

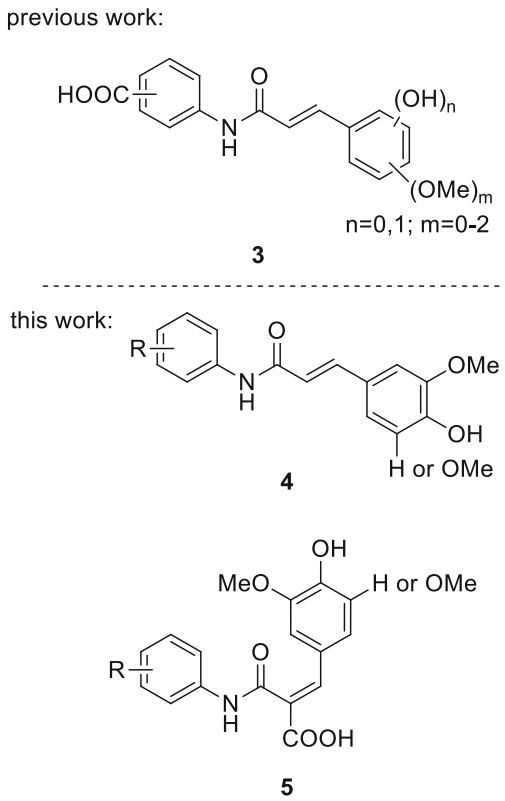


Fig. 2 Structures of the compounds **3**–**5**

acid conjugates on the oxidative stability of sunflower oil. This study is devoted to establishment of structure-antiradical activity relationships of 1) cinnamoyl anilines **4** containing mainly EDG in aniline moiety and 2) arylidenes of malonic acid monoanilides **5** (Fig. 2).

A straightforward route to cinnamoyl amines is acylation of corresponding amines with carboxylic acid chlorides [13] or acids in the presence of various condensation reagents [12]. Herein we present an alternative, cost-effective route leading to target compounds. The presented protocol involves cleavage of Meldrum's acid, Knoevenagel condensation between the obtained malonic monoamide and aromatic aldehyde, followed by decarboxylation of arylidene malonic acid.

Results and discussion

Chemistry

Typically malonic acid monoamides are synthesized from malonic acid or its derivatives and various substituted anilines. Although the procedure is effective, it is encumbered with rather expensive reagents (when unsymmetrical malonic acid derivatives are involved) or low selectivity for symmetrical malonic acid derivatives. An elegant alternative is Meldrum's acid. There are known few examples involving Meldrum's acid as acylating agent leading to malonic acid monoanilides. Mainly for aminobenzoic acids the reaction effectively may be carried out in toluene [12, 14]. Few examples involve ethanol [15] or CH_2Cl_2/THF [16] as reaction media. Besides solvent-free protocols are presented, too [17, 18]. Contrarily, in 2017 Meldrum's acid is described as an effective acylating agent for synthesis of the anilides of acetic acid or its derivatives under solvent- and catalyst-free conditions [19]. Monoamides can be obtained by cleavage of Meldrum's acid with silylated aromatic amine and sequential hydrolysis of the formed malonic silyl esters [20, 21]. However, the described procedures [12, 14–18] leading to malonic acid monoanilides did not turn out relevant for wide scope of anilines: cleavage of Meldrum's acid (**6**) with aromatic amine **7** leads to decarboxylation of target compound **8**, in some cases forming corresponding acetanilide **9** even as the major product. In order to avoid degradation of malonic acid monoanilides **8** during the reaction various solvents and temperatures were tested. The optimization of reaction was carried out with Meldrum's acid (**6**) and *p*-anisidine (**7a**) (data for various reaction conditions see in Supporting material, Table S1). The synthesis of malonic monoanilides without any remarkable decarboxylation was successfully realized by refluxing in water for 1–1.5 h and the product was easily isolated by simple filtration. Besides that these reaction conditions were applicable both for EDG and EAG containing anilines **7** (Scheme 1, Table 1). The malonic acid monoanilides **8** were effectivelly purified by sequential conversion to sodium salts and acidification with hydrochloric acid.

The next step was Knoevenagel condensation of the obtained malonic acid monoamides **8** and aromatic aldehydes **10**. Aldol condensation is straightforward route for introducing C=C double bond in the structure [22, 23]. Knoevenagel condensation is well-known method for α-functionalization of 1,3-dicarbonyl compounds [24, 25]. Besides, Knoevenagel condensation is widely used as a

Scheme 1

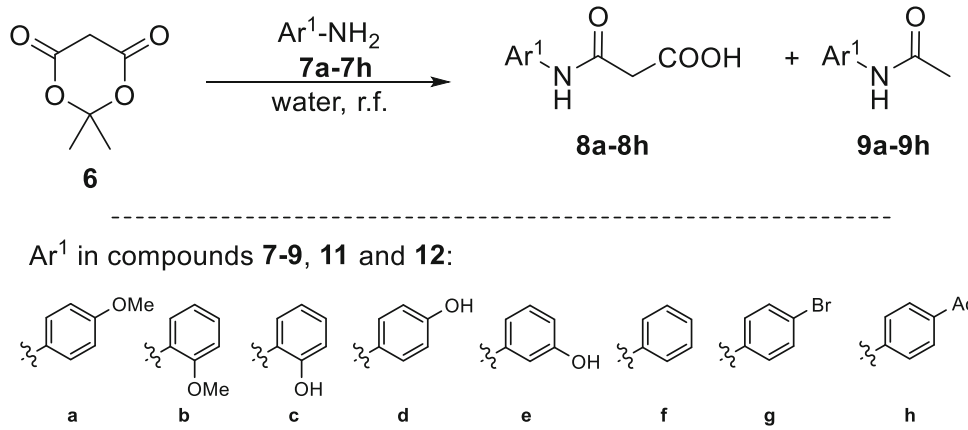


Table 1 Cleavage of Meldrum's acid (**6**) with anilines **7** under optimized reaction conditions

Entry	Abbr. for aniline **7** and product **8**	Time	Composition of product mixture/%[a]		Yield/%[b]
			Comp. **8**	Comp. **9**	
1	**a**	1 h 20 min	91	4	67
2	**b**	1 h 35 min	85	6	67
3	**c**	1 h 5 min	80	3	30
4	**d**	1 h 25 min	87	2	70
5	**e**	1 h	93	6	48
6	**f**	1 h	86	3	55
7	**g**	1 h	77	18	52
8	**h**	1 h 10 min	79	7	60

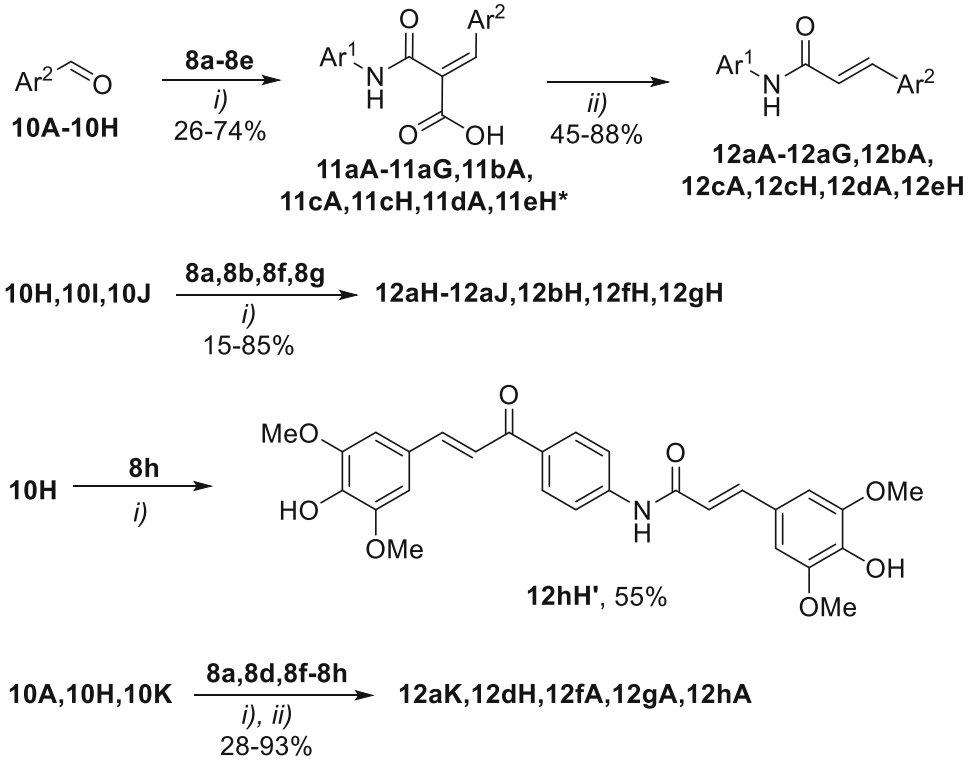
[a]The composition of crude product (HPLC data) after evaporation of reaction mixture (in most of the cases the conversion was almost quantitative)

[b]The yield of compound **8** after isolation and purification

step in different domino-reactions [26, 27]. On the other hand, only few examples are dealing with Knoevenagel condensation with unsymmetrical malonic acid derivatives containing carboxylic acid moiety. Few papers describe synthesis of cinnamoyl anilines using Knoevenagel condensation of malonic acid monoanilides with aromatic aldehydes. It is recommended to realize this condensation by heating without solvent [28] or in pyridine [29], as well as in the presence of β-alanine in toluene under reflux [30]. Condensation between aldehyde and malonic acid monoester can be mediated by piperidinium acetate in acetic acid [31] or benzene [32]. It is assumed that huge excess of aldehyde should be added [33]. Piperidinium acetate is described as useful for the synthesis of corresponding amides, too [33]. Unfortunately, our efforts to carry out this reaction with malonic acid monoanilides **8** and aromatic aldehydes **10** under the conditions described above did not give cinnamoyl anilines or the yield of the expected product was very low. The obstacle was overwhelming decarboxylation of malonic acid monoanilide **8** under heating at high temperature. Previously we have demonstrated that in case of some representative aldehydes **10** and malonic acid monoamides **8** reaction led to corresponding derivatives of cinnamic acid, when it was realized in trifluoroacetic acid. However, generally trifluoroacetic acid mediated additional intramolecular Friedel–Crafts alkylation forming 4-aryldihydroquinolin-2-one system [34]. To avoid it different reaction conditions were approbated (Scheme 2, Table 2). It was found out that when the reaction of malonic acid monoanilide **8** and aromatic aldehyde **10** was realized in acetic acid in the presence of guanidine at 75 °C, the condensation product **11** was obtained exclusively.

The optimized reaction conditions—heating in acetic acid in the presence of guanidine—were used to synthesize several malonic acid derivatives **11** and **12**. In most of the cases the condensation products **11** were isolated in medium to high yields. However, when the reaction was carried

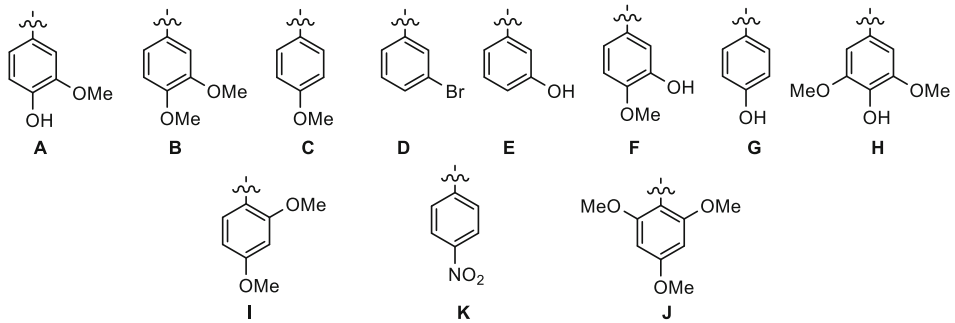
Scheme 2



i) guanidine, AcOH, 75 °C; *ii)* Py, reflux

Ar^1 residue see in Scheme 1.

Ar^2 residue:



*the first letter in the abbreviation of the compound represent the residue of aniline; the second one - the residue of aldehyde.

out with syringaldehyde (**10H**), usually corresponding cinnamoyl aniline **12** was the only product. When the condensation was carried out between syringaldehyde (**10H**) and malonic acid monoanilides **8c**–**8e** containing hydroxyl group, we managed to isolate the corresponding condensation products **11**. When the aldol condensation was realized between *N*-(4-acethylphenyl)malonic acid monoamide (**8h**) and aromatic aldehyde, the reaction occurred both with acetyl group and in the moiety of malonic acid. Compound **12hH′** was even the main product and the *N*-sinapinoyl 4-acetylaniline was the minor by-product when syringaldehyde (**10H**) was used. On the other hand, the simple aldol condensation at malonic acid monoanilide moiety was the major for monoanilide **8h** and vanillin (**10A**) and the compound 11hA was isolated. It was found out that the condensation products **11** exist as *E*-

Table 2 Condensation of *N*-(4-methoxyphenyl)malonic acid monoanilide (**8a**) with vanillin (**10a**)

Entry	Conditions of reaction				Composition of crude product/%[a]		
	Solvent	Base/mol%	Time/h	Temperature/ °C	4-Methoxy-*N*-acetylaniline (**9a**)	Compound **11a**	Compound **12a**
1	Pyridine	Piperidine (10)	2.5	116	57	0	7
2	Pyridine	Piperidine (40)	2.5	116	39	0	27
3	Pyridine	Piperidine (100)	2.5	116	38	0	31
4	Pyridine	Guanidine (10)	3.25	116	49	0	6
5	Acetic acid	Guanidine (10)	2.5	118	68	0	13
6	Acetic acid	Guanidine (10)	5	75	0	97	0
7	Water	Guanidine (10)	28	100	0	0	6
8	Water	Guanidine (10)	240	20–30	30	0	7
9	Ethanol	Guanidine (10)	9	78	59	0	27

[a]The composition was analyzed with HPLC

isomers in DMSO solution according to NOESY experiment. The analysis of NOESY spectra for compound **11aA** clearly showed nuclear Overhauser effects between the proton at *ortho*-position in the aldehyde residue and NH, as well as protons at *ortho*-positions in aldehyde and aniline residues. The same configuration of the C=C bond was approved also for solid state of compound **11aA** according to X-ray analysis (Fig. 3).

To the best of our knowledge, the only known decarboxylation of condensation product **11** took place during heating of the compound at melting point [35]. Nevertheless, there are some examples describing decarboxylation of benzylidene malonic acid derivatives under mild conditions—malonic acid arylidene undergoes decarboxylation by heating in aqueous pyridine [36] or in the presence of ammonium acetate by heating in ethanol [37]. Decarboxylation of monoester of malonic acid arylidene can be realized in benzene in the presence of piperidine [35]. Treatment of cinnamic acids with DBU under microwave irradiation leads to substituted styrenes [38]. α-Arylcinnamic acids can be transformed to *cis*-stilbenes in the presence of amine via cuprous oxide-catalyzed process [39]. Contrarily, methylimidazole promotes formation of

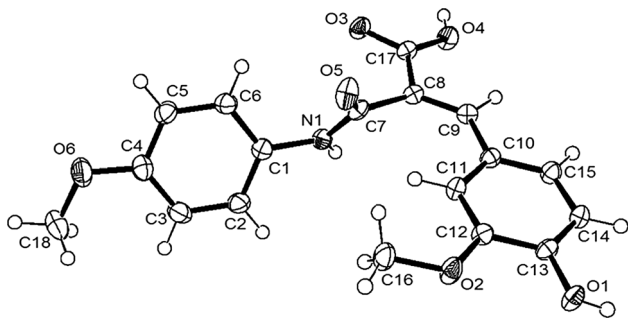


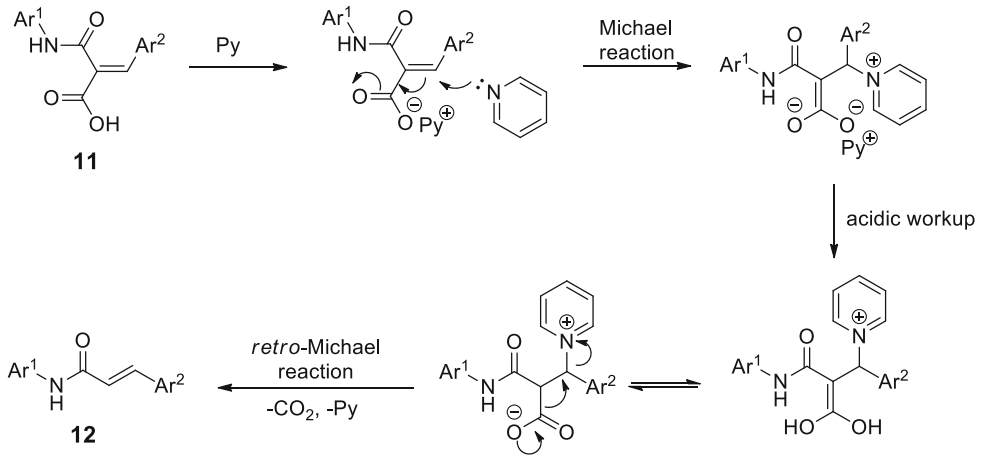
Fig. 3 ORTEP diagram of **11aA**

trans-stilbenes [40]. Taking into account these examples it seemed quite sure that heating in pyridine is sufficient to realize decarboxylation of arylidene malonic acid monoanilides **11**: refluxing in pyridine (even without any other base) for few hours resulted with formation of *E*-isomer **12** exclusively. The mechanism obviously combines Michael addition of pyridine to condensation product **11** and *retro*-Michael reaction (involving release of carbon dioxide) that gives the desired cinnamoyl aniline **12** (the plausible mechanism is given in Scheme 3). Similar decarboxylation is already described for the synthesis of styrenes from cinnamic acids [41]. Usually, the yield of transformation **11** → **12** was high and the reaction conditions were applicable for various substituents in the moiety of both cinnamic acid and aniline.

Crystal structure of arylidene malonic acid monoanilides 11 X-ray crystal structure analysis was carried out for synthesized condensation products **11aA** and **11bA**. The ORTEP diagrams [42] with thermal ellipsoids probability level of 50% for **11aA** and **11bA** are shown in Figs. 3 and 4, respectively. Stacking interactions are shown in Figs. 5 and 6. Table 3 lists crystallographic data and refinement parameters for **11aA** and **11bA**. Geometry of the hydrogen bonding is given in Table 4.

3-(4-Hydroxy-3-methoxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11aA) It was unexpectedly found that the structure **11aA** exhibits rarely encountered phenomenon—proton disorder—in carboxylic acid dimers with strong hydrogen bonds [43–46]. Proton disorder is a dynamic and temperature-dependent process when a proton migrates across a short strong hydrogen bond [46]. Geometrically it results in an alignment of C–O bonds of the carboxylic group and appearance of a hydrogen atom in two different positions with occupancy

Scheme 3



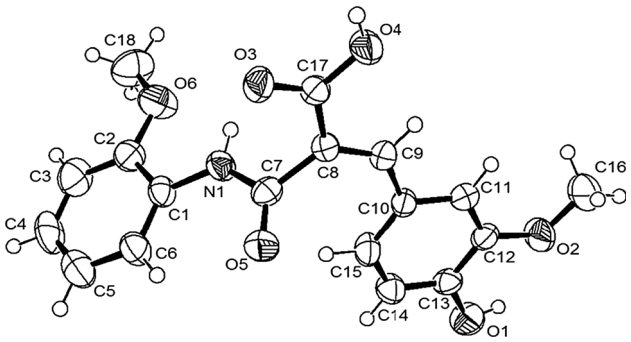


Fig. 4 ORTEP diagram of **11bA**

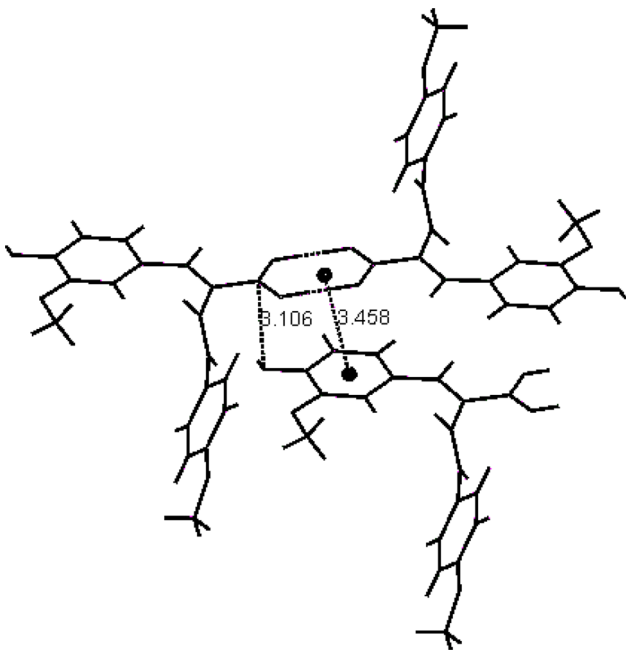


Fig. 5 π–π Stacking interactions in the structure **11aA**

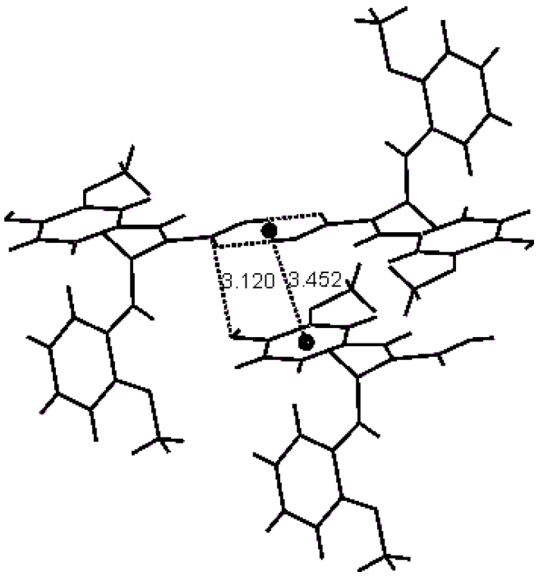


Fig. 6 π–π Stacking interactions and strong H-bonds in the structure **11bA**

factor around 0.5. In the crystal structure **11aA** there are strong H-bonds O4–H···O3 (O4–O3 = 2.545 Å) between carboxylic groups forming $R_2^2(8)$ moiety [46]. The C-O bonds are almost equal [O3–C17 = 1.272(2) Å, O4–C17 = 1.264(2) Å]. The hydrogen atom occupies two different positions (only one position is shown in Fig. 3).

Crystal packing includes also three weaker H-bonds (Table 4). In crystal the molecule **11aA** has three strictly flat fragments: 4-methoxyphenyl (plane I), N1–C7(=O5)–C8 (II) and the rest of the molecule (III). Root mean square deviations of fitted atoms for these planes are less than 0.0521 Å. A dihedral angle I/II is equal to 52.23(4)° and II/III = 70.82(5)°. Two intramolecular hydrogen bonds C9–H···O4 and C11–

Table 3 Crystallographic data and refinement parameters for compounds **11aA** and **11bA**

	Compound **11aA**	Compound **11bA**
Formula	$C_{18}H_{17}NO_6$	$C_{18}H_{17}NO_6$
M_r/g mol^{-1}	343.33	343.33
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/a$	P-1
a/Å	12.1168(3)	7.6073(5)
b/Å	8.8045(3)	8.6491(5)
c/Å	15.5246(4)	12.7187(10)
α/°	90.00	97.329(3)
β/°	98.754(2)	95.619(3)
γ/°	90.00	93.752(2)
V/Å^3	1636.91(8)	823.44(10)
$F(000)$	720	360
Z	4	2
D_x/Mg m^{-3}	1.393	1.385
Unique reflections	3755	3331
$R[F2 > 2\sigma(F2)]$	0.044	0.061
$wR(F2)$	0.115	0.154
Deposition number	CCDC 972916	CCDC 972915

Table 4 Hydrogen bond data in the compounds **11aA** and **11bA**

D–H···A	H···A	D···A	∠D–H···A
Compound **11aA**			
Intramolecular			
C9–H···O4	2.35	2.760(2)	106
C11–H···O5	2.43	3.200(2)	140
Intermolecular			
N1–H···O1	2.23	3.006(2)	150
O4–H···O3	1.75	2.545(2)	175
O1–H···O5	1.82	2.635(2)	171
C14–H···O5	2.46	3.107(2)	127
Compound **11bA**			
Intramolecular			
O1–H···O2	2.19	2.636(3)	114
N1–H···O6	2.16	2.584(3)	110
C9–H···O4	2.32	2.728(3)	106
C6–H···O5	2.30	2.901(4)	121
Intermolecular			
O4–H···O3	1.77	2.591(3)	175
N1–H···O1	2.53	3.331(4)	156
C15–H···O5	2.59	3.308(4)	135
C16–H···O3	2.51	3.447(4)	167

H···O5 were also detected in the molecule. The packing of the molecules **11aA** in the crystal exhibits π–π stacking interactions characterized by overlapping of 4-hydroxy-3-methoxybenzyl fragment by $R_2^2(8)$ motif of strong H-bonds between carboxylic groups of the homodimer (Fig. 5). The stacking distances are in the range of 3.11–3.45 Å. Packing index, or percent filled space, has high value of 69.2% [47].

3-(4-Hydroxy-3-methoxyphenyl)-2-[[(2-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11bA) In the molecule **11bA** there are two strictly flat fragments having a common C7 atom (Fig. 4). Root mean square deviations of fitted atoms for these planes are less than 0.0426 Å. A dihedral angle between the planes is 79.39(3)°. The conformation of the molecule **11bA** is stabilized by four intramolecular hydrogen bonds O1–H···O2, N1–H···O6, C6–H···O5, and C9–H···O4 (Table 4). In crystal the molecules **11bA** are associated in dimers by strong symmetric H-bonds between carboxylic groups forming $R_2^2(8)$ synthon. In contrast to structure **11aA** there is no proton disorder and carboxylic group assumes its standard geometry [48]. Besides H-bond network molecular packing exhibits π–π stacking interactions characterized by superposition of 4-hydroxy-3-methoxyphenyl fragment and $R_2^2(8)$ motif of strong H-bonds of the homodimer (Fig. 6). The stacking distances are in the range of 3.12–3.45 Å. Packing index, or filled space percentage in **11bA**, has also high value of 68.8% but less than in **11aA**.

Antiradical activity of compounds 11 and 12

All obtained compounds were tested for their antiradical activity in vitro. Wide range of model systems can be used to detect the antiradical activity [49]; nevertheless, most often stable free radicals 2,2-diphenyl-1-picrylhydrazyl (DPPH) and galvinoxyl (GO) are used to evaluate antiradical activity. Free radical tests were realized in ethanol. The general procedure for antiradical activity is as follows: free radical solution in ethanol (200 μM for DPPH and ~ 20 μM for GO) was mixed with the solution of verifiable compound. Usually the test for active compounds (their antiradical activity, when molar ratio of antioxidant and free radical is 1:1, is around 50% or more) was realized with 6–8 different concentrations of antioxidant. The disappearance of free radical was detected with spectrophotometric method, by measuring the absorbance of the solution. The selected wavelength was the absorption maximum for the free radicals. Further the inhibition of free radical was calculated according to the following equation:

$$\text{Inhibition} = \frac{\text{Absorption}_{\text{blank}} - \text{Absorption}_{\text{sample}}}{\text{Absorption}_{\text{blank}}} \times 100\%,$$

where $\text{Absorption}_{\text{blank}}$—absorption offree radical solution; $\text{Absorption}_{\text{sample}}$—absorption of the sample containing an additive of compound **11** or **12**.

In order to calculate antiradical activity (activity, when molar ratio of antioxidant and free radical was 1:1) and IC_{50} value (the concentration of antioxidant, when 50% of free radical is inhibited) graph in coordinates "concentration of antioxidant/μM" and "inhibition of free radical/%" was constructed. Obviously, higher antiradical activity and smaller IC_{50} values correspond to better antiradical agent.

In both tests antiradical activity was determined, when the reaction reached plateau. The reaction with GO was slower in comparison to the reaction with DPPH for both condensation products **11** and cinnamoyl anilines **12**: the duration of the test was 6 and 3 h, respectively. GO test was more sensitive to various structure parameters in comparison to DPPH assay: antiradical activity of anilides of ferulic acid differed even three times depending on the substituents in the aniline moiety (Table 5). Most of the compounds **11** and **12** are more active than corresponding derivatives with general structure **3**. Unfortunately, the antiradical activity only for few representatives reach the effect demonstrated by widely used antioxidant *tert*-butylhydroquinone. However, all synthesized derivatives of ferulic and sinapic acid are remarkably more active in comparison to other widely commercially used antioxidant butylated hydroxytoluene.

Hammett substituent constants are widely used to study various structure–activity relationships, including evaluation of the impact of the substituents on the oxidation processes—e.g. reactions of phenolic acids with Fenton-generated hydroxyl radicals [51]. In order to clear up the effect of the electronic factors of the substituents in the aniline moiety, correlations between Hammett substituent constants and antiradical activity (DPPH or GO) or inhibition concentration (IC_{50}) were evaluated. The position of substituents in the aniline moiety was detected with respect to the cinnamoylamino group—*ortho*-, *meta*- or *para*-, respectively. The correlations were established for anilides **12** of ferulic and sinapic acids (see the Figs. S1–S4 in Supplementary Material). Slight effect of the substituents in the aniline moiety on the antiradical activity against DPPH was observed both for sinapic and ferulic acid derivatives. There is a trend that increase of electron donating properties of substituents in aniline ring causes increase of antiradical activity. Synthesized feruloyl and sinapinoyl anilines demonstrated strong correlation between antiradical activity against free radical GO and Hammett substituent constants: increase of electron acceptor properties of the substituents caused decrease in antiradical properties of these compounds. These observations are in agreement with that what was described for polysubstituted phenolic antioxidants [52].

Conclusion

An alternative and convenient way starting from cheap and commercially available compounds for the synthesis of cinnamoyl anilines through decarboxylation of arylidene malonic acid monoanilides under mild conditions is provided. The antiradical activity of the cinnamoyl anilines and arylidene malonic acid monoanilides has been detected. It was found out that in case of the derivatives of sinapic and ferulic acid the correlation exists between antiradical activity and electronic effects in the aniline moiety—substituents with electron donor properties increase the antiradical activity.

Experimental

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on Bruker Avance 300 spectrometer. The samples were dissolved in DMSO-d_6 or $CDCl_3$ and the spectra were calibrated to the residue of DMSO [δ (^{1}H NMR) = 2.50 ppm, δ (^{13}C NMR) = 39.52 ppm] or $CHCl_3$ [δ (^{1}H NMR) = 7.26 ppm, δ (^{13}C NMR) = 77.16 ppm] [53]. The protons in the aniline moieties were numbered from 2 to 6 and in aldehyde moieties—from 2′ to 6′ (with respect to IUPAC recommendations for numbering of substituents). The protons of double bond are specified as follows: $Ar^{1}NHC(O)CH^{a}{=}CH^{b}Ar^{2}$. IR spectra were recorded on Perkin Elmer spectrometer (model: Spectrum BX, FT-IS system) for solid sample in KBr disc. Melting points were measured with STUART melting point SMP10 apparatus. Microanalysis was done with Carlo-Erba Instruments element analyzer (model: EA1108). High-resolution mass spectra were recorded on Agilent 1290 Infinity instrument with Agilent 6230 TOF LC/MS detector and electrospray ionization. Reactions were controlled with TLC. Silica plates ALUGRAM® SIL G/UV254 were eluated with $CHCl_3$:EtOH (1:0.175 v:v) for arylidene malonic acid monoanilides **11** or $CHCl_3$:EtOH (1:0.0875 v:v) for cinnamoyl anilines **12**. HPLC data were collected with Agilent Technologies apparatus (model 1200) with Phenomenex Gemini-NX C18 column (4.6 × 100 mm, 3 μm). The presented data show relative ratio of the compounds and the data are not calibrated. The eluent for the reaction mixture (**8** + **10** → **11** and/or **12**) was methanol (solvent A) and 0.01 M KH_2PO_4 containing 6% acetonitrile (solvent B). The gradient profile was: 0 to 10 min—10% A to 90% A, after that—3 min 90% A. The eluent for the reaction mixture (**6** + **7** → **8** and/or **9**) was KH_2PO_4 buffer solution containing 6% methanol (solvent A) and methanol (solvent B). The gradient profile was as follows: 90% A at 0 min, 10% A at 10 min, 10% A at 13 min and 0% A at

Table 5 Antiradical activity of arylidene malonic acid monoanilides **11** and cinnamoyl anilines **12**

Compound	DPPH test		GO test	
	Inhibition/%[a]	IC_{50}/μM[b]	Inhibition/%[a]	IC_{50}/μM[b]
11aA	42.9 ± 1.5	152.9 ± 6.6	34.9 ± 1.9	218.7 ± 30.8
11aB	0.4 ± 0.0	–	0 ± 0.1	–
11aC	1.9 ± 0.0	–	0.3 ± 0.8	–
11aD	2.8 ± 1.2	–	0.9 ± 0.3	–
11aE	7.8 ± 0.1	–	3.8 ± 0.7	–
11aF	10.2 ± 0.7	–	2.3 ± 1.3	–
11aG	0.1 ± 0.1	–	1.7 ± 2.3	–
11bA	40.6 ± 0.9	175.5 ± 18.4	37.4 ± 3.1	189.8 ± 28.4
11cA	46.3 ± 0.4	130.6 ± 6.3	44.4 ± 2.9	126.8 ± 15.8
11cH	101.0 ± 0.9	17.3 ± 2.7	78.7 ± 0.4	25.6 ± 6.2
11dA	49.9 ± 0.1	100.1 ± 0.3	35.2 ± 2.2	196.3 ± 30.9
11eH	100.1 ± 1.1	24.2 ± 0.4	81.2 ± 3.0	27.3 ± 2.1
12aA	63.4 ± 2.4	64.0 ± 1.5	34.3 ± 0.6	178.0 ± 14.8
12aB	0 ± 0.2	–	0 ± 0.2	–
12aC	0 ± 0.8	–	0 ± 0.2	–
12aD	1.2 ± 0.3	–	0.0 ± 0.3	–
12aE	3.1 ± 0.1	–	1.5 ± 0.2	–
12aF	12.4 ± 0.5	–	3.0 ± 0.3	–
12aG	2.0 ± 0.3	–	1.0 ± 0.2	–
12aH	99.6 ± 2.0	38.7 ± 0.5	80.9 ± 0.1	40.1 ± 0.9
12aI	2.7 ± 0.0	–	0 ± 0.2	–
12aJ	0 ± 0.3	–	0 ± 0.2	–
12aK	0.7 ± 0.1	–	2.6 ± 0.3	–
12bA	70.1 ± 4.5	57.5 ± 8.5	26.5 ± 1.8	262.8 ± 12.5
12bH	91.2 ± 0.9	43.1 ± 1.7	78.7 ± 1.8	58.1 ± 6.6
12cA	76.2 ± 0.5	44.1 ± 1.8	40.5 ± 1.9	156.7 ± 1.8
12cH	91.9 ± 0.2	33.9 ± 4.0	75.5 ± 3.7	56.8 ± 7.0
12dA	77.0 ± 0.9	45.3 ± 1.5	39.5 ± 0.9	145.5 ± 5.9
12dH	93.2 ± 1.2	39.3 ± 0.8	74.5 ± 1.2	53.8 ± 6.6
12eH	97.9 ± 4.1	39.0 ± 2.3	75.6 ± 1.1	60.6 ± 0.3
12fA	73.3 ± 0.2	49.8 ± 0.6	35.4 ± 0.0	176.1 ± 5.4
12fH	90.6 ± 5.0	36.9 ± 2.8	71.2 ± 4.6	69.3 ± 0.9
12gA	66.8 ± 3.1	60.8 ± 4.0	35.0 ± 1.4	188.1 ± 1.3
12gH	97.3 ± 2.0	37.7 ± 1.4	69.9 ± 5.2	64.2 ± 5.2
12hA	70.6 ± 0.9	52.7 ± 1.7	20.0 ± 0.6	375.4 ± 8.1
12hH′	75.0 ± 0.4	25.3 ± 0.4	53.9 ± 1.8	72.0 ± 4.2
Compounds **3** (ferulic acid derivatives) [11]	68–73	44–80	13–42	–
Compounds **3** (sinapic acid derivatives) [11]	96–99	21–38	64–78	48–74
Butylated hydroxytoluene [50]	37.8 ± 2.6	–	58.7 ± 1.2	–
tert-Butylhydroquinone [50]	97.9 ± 0.1	19.5 ± 2.3	81.4 ± 1.2	22.6 ± 1.6

[a]The inhibition was detected, when molar ratio of free radical and compound was 1:1, concentration 100 μM

[b]Concentration that inhibits 50% of the free radical (starting concentration of the free radical was 100 μM). The IC_{50} was calculated only for compounds demonstrating significant antiradical activity

15 min. The absorption of the solutions was measured with Camspec M501 Single Beam Scanning UV/Visible spectrophotometer. X-ray single crystal diffraction data were collected using Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Structure solution and refinement was performed with SIR2004 [54] and SHELXL97 [55]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in the Fourier difference maps and then were switched to the 'riding' model in the structure refinement process. Details are given in Table 3.

All used aromatic aldehydes, aromatic amines, Meldrum's acid and free radicals (DPPH and GO) were commercially available and were used without additional purification.

Synthesis of malonic acid monoanilides 8a–8h

Meldrum's acid (**6**, 2 g, 13.9 mmol) and aniline **7** (13.9 mmol) were refluxed in 20 cm^3 water for 1–1.5 h. When the reaction was completed, the mixture was allowed to cool to room temperature and the precipitate filtered. In order to purify the crude solid product was mixed with a small amount of cold water (ice bath), 10% KOH solution was added by mixing until the pH of solution reached pH > 7. The mixture was filtered after 15 min, the filtrate was cooled to 4–5 °C (ice bath) and 10% HCl solution was added by mixing until pH < 7. The precipitate was filtered after 15 min and air dried. For the yield see Table 1. Malonic acid monoanilides **8a** [56], **8b** [57], **8c** [58], **8d** [34], **8f** [59], and **8g** [60] are known and their spectra correspond to those in literature.

2-[(3-Hydroxyphenyl)carbamoyl]acetic acid (8e, $C_9H_9NO_4$) White powder; m.p.: 155 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.33 (2H, s, CH_2), 6.46 (1H, dd, J = 8.0, 1.4 Hz, H-4), 6.93 (1H, d, J = 8.0 Hz, H-6), 7.07 (1H, t, J = 8.0 Hz, H-5), 7.17 (1H, d, J = 1.4 Hz, H-2), 9.41 (1H, s, OH), 10.01 (1H, s, NH), 12.65 (1H, brs, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 44.1, 106.3, 109.9, 110.7, 129.6, 140.1, 157.7, 164.6, 169.4 ppm; IR (KBr): $\bar{\nu}$ = 3500, 3260, 1720, 1695, 1455 cm^{-1}; LC–MS: m/z = 196.11.

2-[(4-Acetylphenyl)carbamoyl]acetic acid (8h, $C_{11}H_{11}NO_4$) Light yellow solid; m.p.: 159 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.52 (3H, s, Ac), 3.42 (2H, s, CH_2), 7.72 (2H, d, J = 8.7 Hz, H-2,6), 7.93 (2H, d, J = 8.7 Hz, H-3,5), 10.48 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.8, 44.6, 118.8, 130.1, 132.2, 143.5, 165.8, 169.8, 197.2 ppm; IR (KBr): $\bar{\nu}$ = 3295, 2560, 1715, 1685, 1655, 1410 cm^{-1}; LC–MS: m/z = 222.32.

General procedure for the synthesis of arylidene malonic acid monoanilides 11aA–11aG, 11bA, 11cA, 11cH, 11dA, 11eH

A malonic acid monoanilide **8** (0.6 mmol), aromatic aldehyde **10** (0.6 mmol), guanidine hydrochloride (0.06 mmol), and potassium hydroxide (0.06 mmol) in 1 cm^3 acetic acid were stirred at 75 °C for 7–40 h (the reaction was monitored by TLC until full conversion of starting compounds). After the reaction was complete, the product mixture was cooled to room temperature and poured into 75 cm^3 ice. The precipitate was filtered, air-dried, and recrystallized from ethanol or mixture ethanol:water (2:1 v:v).

3-(4-Hydroxy-3-methoxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11aA) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and vanillin (**10A**) by reflux in acetic acid for 12.5 h. Crystallization led to solid material (62%) with m.p. 188–190 °C. The compound is known and its ^{1}H and ^{13}C NMR data correspond to literature [34].

3-(3,4-Dimethoxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11aB, $C_{19}H_{19}NO_6$) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 3,4-dimethoxybenzaldehyde (**10B**) by reflux in acetic acid for 13 h. Crystallization led to solid material (61%) with m.p. 204–206 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.50 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.92 (2H, d, J = 9.0 Hz, H-2,5), 6.99 (1H, d, J = 8.5 Hz, H-5′), 7.22 (1H, dd, J = 8.5, 1.8 Hz, H-6′), 7.24 (1H, d, J = 1.8 Hz, H-2′), 7.55 (1H, s, H-b), 7.61 (2H, d, J = 9.0 Hz, H-2,6), 10.36 (1H, s, NH), 12.84 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.6, 55.6, 56.0, 112.1, 112.4, 114.4, 121.0, 124.8, 126.2, 128.5, 132.1, 139.6, 149.0, 151.2, 155.9, 165.0, 166.7 ppm; IR (KBr): $\bar{\nu}$ = 3840, 3805, 3735, 3310, 2955, 2840, 2615, 2360, 2345, 2040, 1685, 1655, 1600, 1540, 1510, 1465, 1450, 1440, 1420, 1300, 1265, 1200, 1185, 1160, 1150, 1115, 1065, 1020, 960, 940, 910, 830, 805, 670, 625, 580, 525, 460 cm^{-1}; HRMS: m/z = 358.1285.

3-(4-Methoxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11aC, $C_{18}H_{17}NO_5$) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 4-methoxybenzaldehyde (**10C**) by reflux in acetic acid for 24.5 h. Crystallization led to solid material (69%) with m.p. 207–209 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.92 (2H, d, J = 9.0 Hz, H-3,5/3′,5′), 6.94 (2H, d, J = 8.9 Hz, H-3,5/3′,5′), 7.55 (1H, s, H-b), 7.52–7.64 (4H, m, H-2,6,2′,6′), 10.30 (1H, s, NH), 12.86 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 55.3, 114.0, 114.4,

120.8, 125.6, 127.9, 131.6, 132.3, 138.9, 155.5, 160.9, 164.5, 166.3 ppm; IR (KBr): $\bar{\nu}$ = 3855, 3740, 3620, 3260, 3135, 3010, 2960, 2935, 2840, 2645, 2535, 2360, 2345, 2040, 1680, 1650, 1600, 1570, 1540, 1515, 1475, 1460, 1430, 1260, 1215, 1175, 1125, 1065, 1025, 945, 915, 855, 835, 810, 780, 745, 725, 670, 615, 560, 535, 475 cm^{-1}; HRMS: *m/z* = 328.1179.

3-(3-Bromophenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]-prop-2(*E*)-enoic acid (11aD) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 3-bromobenzaldehyde (**10D**) by reflux in acetic acid for 46.5 h. Crystallization led to solid material (26%) with m.p. 200–201 °C. The compound is known and its ^{1}H and ^{13}C NMR data correspond to literature [34].

3-(3-Hydroxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11aE, $C_{17}H_{15}NO_5$) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 3-hydroxybenzaldehyde (**10E**) by reflux in acetic acid for 17 h. Crystallization led to solid material (66%) with m.p. 181 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.73 (3H, s, OCH_3), 6.81 (1H, dd, *J* = 8.0, 2.0 Hz, H-4′), 6.91 (2H, d, *J* = 9.0 Hz, H-3,5), 7.02 (1H, d, *J* = 2.0 Hz, H-2′), 7.03 (1H, d, *J* = 8.0, Hz, H-6′), 7.18 (1H, t, *J* = 8.0 Hz, H-5′), 7.50 (1H, s, H-b), 7.55 (2H, d, *J* = 9.0 Hz, H-2,6), 9.62 (1H, s, OH), 10.26 (1H, s, NH), 12.95 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 113.9, 116.1, 117.4, 120.7, 120.9, 129.8, 130.3, 132.2, 134.4, 139.3, 155.5, 157.6, 164.0, 166.2 ppm; IR (KBr): $\bar{\nu}$ = 3840, 3800, 3740, 3650, 3235, 3040, 3000, 2835, 2630, 2360, 2345, 1770, 1710, 1675, 1660, 1635, 1620, 1595, 1580, 1560, 1515, 1455, 1435, 1415, 1350, 1340, 1300, 1280, 1245, 1170, 1070, 1030, 1000, 965, 940, 920, 880, 830, 820, 810, 795, 775, 745, 695, 675, 600, 565, 520, 460 cm^{-1}.

3-(3-Hydroxy-4-methoxyphenyl)-2-[[(4-methoxyphenyl)-amino]carbonyl]prop-2(*E*)-enoic acid (11aF, $C_{18}H_{17}NO_6$) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 3-hydroxy-4-methoxybenzaldehyde (**10F**) by reflux in acetic acid for 31 h. Crystallization led to solid material (37%) with m.p. 209–210 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.85–6.98 (3H, m, H-3,5,5′), 7.03–7.12 (2H, m, H-2′,6′), 7.44 (1H, s, H-b), 7.58 (2H, d, *J* = 8.7 Hz, H-2,6), 9.16 (1H, s, OH), 10.24 (1H, s, NH), 12.79 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 55.6, 113.9, 113.9, 116.4, 120.9, 122.7, 126.0, 127.8, 132.4, 139.4, 146.4, 149.9, 155.5, 164.5, 166.4 ppm; IR (KBr): $\bar{\nu}$ = 3840, 3800, 3735, 3675, 3650, 3395, 3195, 3135, 3060, 3000, 2940, 2845, 2630, 2360, 2345, 2045, 1685, 1635, 1600, 1580, 1560, 1540, 1510, 1465, 1455, 1420, 1380, 1340, 1315, 1180, 1135, 1080, 1030, 970, 940, 910, 885, 860, 830, 800, 765, 740, 690, 630, 590, 550, 520, 495, 470, 440 cm^{-1}; HRMS: *m/z* = 344.1124.

3-(4-Hydroxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11aG, $C_{17}H_{15}NO_5$) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 4-hydroxybenzaldehyde (**10G**) by reflux in acetic acid for 18 h. Crystallization led to solid material (68%) with m.p. 208–210 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (3H, s, OCH_3), 6.76 (2H, d, *J* = 8.6 Hz, H-3′,5′), 6.91 (2H, d, *J* = 9.0 Hz, H-3,5), 7.46 (2H, d, *J* = 8.6 Hz, H-2′,6′), 7.50 (1H, s, H-b), 7.57 (2H, d, *J* = 9.0 Hz, H-2,6), 10.09 (1H, s, OH), 10.26 (1H, s, NH), 12.77 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 113.9, 115.8, 120.8, 124.1, 126.9, 131.9, 132.4, 139.4, 155.5, 159.7, 164.7, 166.4 ppm; IR (KBr): $\bar{\nu}$ = 3855, 3740, 3300, 3120, 3025, 2960, 2900, 2835, 2690, 2615, 2510, 2360, 2345, 1650, 1625, 1600, 1585, 1560, 1510, 1475, 1455, 1445, 1420, 1380, 1300, 1270, 1250, 1205, 1175, 1120, 1105, 1075, 1040, 1010, 950, 940, 915, 840, 825, 810, 790, 725, 685, 595, 575, 545, 530, 515, 485, 420 cm^{-1}.

3-(4-Hydroxy-3-methoxyphenyl)-2-[[(2-methoxyphenyl)-amino]carbonyl]prop-2(*E*)-enoic acid (11bA, $C_{18}H_{17}NO_6$) was obtained from 2-(2-methoxyphenyl)carbamoylacetic acid (**8b**) and vanillin (**10A**) by reflux in acetic acid for 7 h. Crystallization led to solid material (74%) with m.p. 187–189 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.56 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 6.78 (1H, d, *J* = 8.2 Hz, H-5′), 6.96 (1H, t, *J* = 7.6 Hz, H-5), 7.03 (1H, d, *J* = 8.2 Hz, H-6′), 7.08–7.15 (2H, m, H-3,4), 7.21 (1H, s, H-11), 7.47 (1H, s, H-b), 8.11 (1H, d, *J* = 7.9 Hz, H-6), 9.62 (1H, s, OH), 9.68 (1H, s, NH), 12.66 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.7, 56.1, 111.9, 113.4, 116.0, 120.8, 122.3, 125.0, 125.2, 125.3, 127.5, 127.6, 140.1, 147.9, 149.6, 150.2, 166.3, 166.7 ppm; IR (KBr): $\bar{\nu}$ = 3840, 3735, 3650, 3545, 3495, 3355, 3010, 2960, 2835, 2645, 2530, 2360, 2345, 1660, 1620, 1590, 1560, 1520, 1485, 1460, 1440, 1430, 1390, 1375, 1315, 1305, 1285, 1255, 1225, 1205, 1185, 1130, 1115, 1065, 1045, 1025, 930, 900, 875, 810, 780, 770, 750, 730, 685, 635, 615, 580, 560, 515, 485, 455, 430 cm^{-1}.

3-(4-Hydroxy-3-methoxyphenyl)-2-[[(2-hydroxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11cA, $C_{17}H_{15}NO_6$) was obtained from 2-(4-hydroxyphenyl)carbamoylacetic acid (**8c**) and vanillin (**10A**) by reflux in acetic acid for 28 h. Crystallization led to solid material (62%) with m.p. 174–175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.57 (3H, s, OCH_3), 6.74–6.91 (2H, m, H-3,5,5′), 6.99 (1H, td, *J* = 7.8, 1.6 Hz, H-4), 7.11 (1H, dd, *J* = 8.3, 1.8 Hz, H-6′), 7.21 (1H, d, *J* = 1.8 Hz, H-2′), 7.49 (1H, s, H-b), 7.85 (1H, dd, *J* = 7.8, 1.6 Hz, H-6), 9.73 (1H, s, NH), 9.74 (2H, s, 2OH), 12.78 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz,

DMSO-d_6): δ = 55.2, 112.7, 115.6, 115.9, 119.1, 122.1, 124.4, 125.0, 125.2, 126.1), 126.6, 140.0, 147.6, 147.9, 149.3, 165.8, 166.4 ppm; IR (KBr): $\bar{\nu}$ = 3855, 3735, 3450, 3365, 3315, 3080, 2970, 2750, 2625, 2360, 2345, 1735, 1700, 1640, 1625, 1595, 1540, 1520, 1455, 1430, 1395, 1310, 1285, 1255, 1210, 1190, 1135, 1115, 1060, 1035, 940, 910, 860, 815, 800, 755, 730, 680, 630, 580, 455 cm^{-1}; HRMS: *m/z* = 330.0995.

3-(3,5-Dimethoxy-4-hydroxyphenyl)-2-[[(2-hydroxyphenyl)-amino]carbonyl]prop-2(*E*)-enoic acid (11cH, $C_{18}H_{17}NO_7$) was obtained from 2-(2-hydroxyphenyl)carbamoylacetic acid (**8c**) and syringaldehyde (**10H**) by reflux in acetic acid for 14 h. Crystallization led to solid material (72%) with m.p. 208–210 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.61 (6H, s, 2 × OCH_3), 6.81 (1H, td, *J* = 8.0, 1.4 Hz, H-5), 6.88 (1H, dd, *J* = 8.0, 1.4 Hz, H-3), 6.92–7.02 (3H, m, H-4,2′,6′), 7.52 (1H, s, H-b), 7.88 (1H, dd, *J* = 8.0, 1.4 Hz, H-6), 9.08 (1H, s, OH), 9.73 (1H, s, NH), 12.77 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.2, 108.2, 116.3, 119.5, 122.3, 123.6, 125.5, 126.5, 127.4, 138.7, 140.6, 148.2, 166.2, 166.6 ppm; IR (KBr): $\bar{\nu}$ = 3775, 3310, 3285, 3060, 2960, 2840, 2735, 2620, 2350, 2270, 1775, 1765, 1750, 1730, 1690, 1675, 1630, 1620, 1590, 1550, 1525, 1485, 1455, 1430, 1390, 1375, 1365, 1330, 1285, 1275, 1255, 1215, 1185, 1165, 1155, 1120, 1075, 1045, 990, 945, 930, 905, 855, 820, 785, 750, 680, 630, 620, 590, 580, 550, 530, 515, 490, 455, 430, 410 cm^{-1}; HRMS: *m/z* = 360.1072.

3-(4-Hydroxy-3-methoxyphenyl)-2-[[(4-hydroxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (11dA, $C_{17}H_{15}NO_6$) was obtained from 2-(4-hydroxyphenyl)carbamoylacetic acid (**8d**) and vanillin (**10A**) by reflux in acetic acid for 47.5 h. Crystallization led to solid material (52%) with m.p. 210–212 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.54 (3H, s, OCH_3), 6.71 (2H, d, *J* = 8.2 Hz, H-3,5), 6.77 (1H, d, *J* = 8.3 Hz, H-5′), 7.07 (1H, dd, *J* = 8.3, 1.9 Hz, H-6′), 7.21 (1H, d, *J* = 1.9 Hz, H-2′), 7.43–7.51 (3H, m, H-2,6,b), 9.21 (1H, s, OH), 9.67 (1H, s, OH), 7.20 (1H, s, NH), 12.70 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 112.5, 115.1, 115.5, 120.7, 124.5, 124.9, 127.1, 130.9, 139.4, 147.5, 149.1, 153.5, 164.5, 166.4 ppm; IR (KBr): $\bar{\nu}$ = 3750, 3345, 3045, 2795, 2690, 2600, 2345, 2285, 1710, 1655, 1625, 1600, 1570, 1535, 1510, 1490, 1460, 1450, 1430, 1410, 1375, 1320, 1290, 1255, 1210, 1170, 1130, 1060, 1040, 945, 915, 840, 815, 760, 725, 665, 645, 635, 575, 530, 490, 460, 420 cm^{-1}.

3-(3,5-Dimethoxy-4-hydroxyphenyl)-2-[[(3-hydroxyphenyl)-amino]carbonyl]prop-2(*E*)-enoic acid (11eH, $C_{18}H_{17}NO_7$) was obtained from 2-(3-hydroxyphenyl)carbamoylacetic acid (**8e**) and syringaldehyde (**10H**) by reflux in acetic acid for 21.5 h. Crystallization led to solid material (67%) with m.p. 197–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.60 (6H, s, 2 × OCH_3), 6.47 (1H, d, *J* = 8.3 Hz, H-4), 6.95 (2H, s, H-2′,6′), 6.99–7.13 (2H, m, H-5,6), 7.32 (1H, s, H-2), 7.51 (1H, s, H-b), 9.08 (1H, s, OH), 9.41 (1H, s, OH), 10.35 (1H, s, NH), 12.79 (1H, br. s, COOH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.8, 106.3, 107.7, 109.9, 110.7, 123.2, 127.4, 129.5, 138.3, 139.9, 140.2, 147.8, 157.7, 165.2, 166.2 ppm; IR (KBr): $\bar{\nu}$ = 3785, 3505, 3320, 3195, 2845, 2635, 2515, 2350, 2285, 1755, 1735, 1700, 1695, 1675, 1650, 1610, 1590, 1555, 1515, 1455, 1430, 1350, 1330, 1270, 1250, 1220, 1190, 1160, 1115, 1040, 980, 970, 945, 920, 895, 870, 830, 815, 795, 750, 730, 690, 635, 630, 595, 565, 535, 460, 435, 415 cm^{-1}; HRMS: *m/z* = 360.1079.

Cinnamoyl anilines 12aA–12aG, 12bA, 12cA, 12cH, 12dA, 12eH (synthetic protocol I)

3-Arylamino-(*E*)-2-arylidene-3-oxopropanoic acid **11** (0.3 mmol) was refluxed in pyridine for 1–10 h (the reaction was monitored by TLC until full conversion of starting compounds). After the reaction was complete, the product mixture was cooled to room temperature, poured into 40 cm^3 ice, and acidified until pH < 7. The precipitate was filtered, air-dried, and recrystallized from mixture ethanol:water (2:1 v:v).

3-(4-Hydroxy-3-methoxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aA) was obtained from 3-(4-hydroxy-3-methoxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]-prop-2(*E*)-enoic acid (**11aA**) by reflux in pyridine for 1.5 h. Crystallization led to solid material (68%) with m.p. 185–188 °C. The compound is known and its ^{1}H and ^{13}C NMR data correspond to literature [34].

3-(3,4-Dimethoxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aB, $C_{18}H_{19}NO_4$) was obtained from 3-(3,4-dimethoxyphenyl)-2-[[(4-methoxyphenyl)amino]car-bonyl]prop-2(*E*)-enoic acid (**11aB**) by reflux in pyridine for 6 h. Crystallization lead to solid material (77%) with m.p. 165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 6.45 (1H, d, *J* = 15.4 Hz, H-a), 6.84–6.93 (3H, m, H-3,5,5′), 7.06 (1H, d, *J* = 1.5 Hz, H-2′), 7.12 (1H, dd, *J* = 8.3, 1.5 Hz, H-6′), 7.42 (1H, br. s, NH), 7.55 (2H, d, *J* = 8.7 Hz, H-2,6), 7.70 (1H, d, *J* = 15.4 Hz, H-b) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.6, 56.0, 56.1, 110.0, 111.2, 114.4, 118.9, 121.8, 122.2, 127.9, 131.4, 142.0, 149.3, 151.0, 156.6, 164.3 ppm; IR (KBr): $\bar{\nu}$ = 3570, 3270, 3050, 2935, 2840, 1655, 1615, 1600, 1535, 1510, 1460, 1445, 1410, 1340, 1300, 1260, 1240, 1185, 1165, 1135, 1025, 970, 840, 830, 805, 765, 680, 550, 520 cm^{-1}; HRMS: *m/z* = 314.1385.

3-(4-Methoxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aC) was obtained from 3-(4-methoxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (**11aC**) by reflux in pyridine for 9.5 h. Crystallization led to solid material (68%) with m.p. 179–182 °C (182–184 °C [61]). The compound is known and its ^{1}H and ^{13}C NMR data correspond to literature [34].

3-(3-Bromophenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aD, $C_{16}H_{14}BrNO_2$) was obtained from 3-(3-bromophenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (**11aD**) by reflux in pyridine for 3.5 h. Crystallization led to solid material (82%) with m.p. 134–136 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.73 (3H, s, OCH_3), 6.86 (1H, d, J = 15.8 Hz, H-a), 6.92 (2H, d, J = 7.9 Hz, H-3,5), 7.43 (1H, t, J = 7.8 Hz, H-5′), 7.52 (1H, d, J = 15.8 Hz, H-b), 7.56–7.68 (4H, m, H-2,6,4′,6′), 7.82 (1H, s, H-2′), 10.11 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 114.0, 120.7, 122.3, 124.2, 126.5, 130.1, 131.0, 132.1, 132.3, 137.4, 137.8, 155.4, 162.7 ppm; IR (KBr): $\bar{\nu}$ = 3325, 3010, 2955, 2835, 2220, 1665, 1630, 1600, 1560, 1535, 1510, 1305, 1250, 1195, 1180, 1030, 980, 825, 670, 520 cm^{-1}.

3-(3-Hydroxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aE, $C_{16}H_{15}NO_3$) was obtained from 3-(3-hydroxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (**11aE**) by reflux in pyridine for 3 h. Crystallization led to solid material (69%) with m.p. 187–189 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (3H, s, OCH_3), 6.73 (1H, d, J = 15.7 Hz, H-a), 6.82 (1H, dd, J = 8.0, 2.1 Hz, H-4′), 6.92 (2H, d, J = 8.9 Hz, H-3,5), 6.99 (1H, s, H-11), 7.03 (1H, d, J = 8.0 Hz, H-6′), 7.25 (1H, t, J = 8.0 Hz, H-5′), 7.46 (1H, d, J = 15.7 Hz, H-b), 7.62 (2H, d, J = 8.9 Hz, H-2,6), 9.63 (1H, s, OH), 10.07 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.6, 114.3, 114.4, 117.4, 119.3, 121.1, 122.6, 130.4, 132.9, 136.5, 140.3, 155.8, 158.2, 163.5 ppm; IR (KBr): $\bar{\nu}$ = 3250, 2840, 2360, 1655, 1595, 1510, 1445, 1415, 1360, 1295, 1235, 1175, 1110, 1030, 995, 970, 830, 790, 765, 680, 550, 520 cm^{-1}.

3-(3-Hydroxy-4-methoxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aF, $C_{17}H_{17}NO_4$) was obtained from 3-(3-hydroxy-4-methoxyphenyl)-2-[[(4-methoxyphenyl)amino]-carbonyl]prop-2(*E*)-enoic acid (**11aF**) by reflux in pyridine for 10 h. Crystallization led to solid material (85%) with m.p. 205–206 °C. ^{1}H NMR (300 MHz DMSO-d_6): δ = 3.73 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.57 (1H, d, J = 15.6 Hz, H-a), 6.90 (2H, d, J = 9.0 Hz, H-3,4), 6.94–7.06 (3H, m, H-2′,5′,6′), 7.41 (1H, d, J = 15.6 Hz, H-b), 7.61 (2H, d, J = 9.0 Hz, H-2,6), 9.24 (1H, s, OH), 9.98 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 55.6, 112.1, 113.4, 113.9, 119.6, 120.6, 127.7, 132.6, 139.9, 146.8, 149.4, 155.2, 163.4 ppm; IR (KBr): $\bar{\nu}$ = 3300, 3075, 3000, 2845, 2360, 1655, 1600, 1585, 1540, 1515, 1455, 1435, 1415, 1375, 1310, 1265, 1250, 1215, 1190, 1180, 1165, 1125, 1035, 1025, 980, 850, 800, 550 cm^{-1}; HRMS: m/z = 300.1230.

3-(4-Hydroxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aG, $C_{16}H_{15}NO_3$) was obtained from 3-(4-hydroxyphenyl)-2-[[(4-methoxyphenyl)amino]carbonyl]prop-2(*E*)-enoic acid (**11aG**) by reflux in pyridine for 5 h. Crystallization led to solid material (88%) with m.p. 193–195 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.73 (3H, s, OCH_3), 6.59 (1H, d, J = 15.6 Hz, H-a), 6.83 (2H, d, J = 8.51 Hz, H-3′,5′), 6.91 (2H, d, J = 9.0 Hz, H-3,5), 7.46 (2H, d, J = 8.51 Hz, H-2,6/2′,6′), 7.47 (1H, d, J = 15.6 Hz, H-b), 7.62 (2H, d, J = 9.0 Hz, H-2,6/2′,6′), 9.63 (1H, s, OH), 9.97 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.6, 114.4, 116.3, 119.2, 121.0, 126.3, 129.9, 133.2, 140.3, 155.6, 159.5, 164.0 ppm; IR (KBr): $\bar{\nu}$ = 3480, 3330, 3000, 2950, 2820, 1905, 1655, 1620, 1600, 1540, 1510, 1450, 1420, 1345, 1295, 1270, 1230, 1175, 1105, 1030, 980, 830, 565, 520 cm^{-1}; HRMS: m/z = 270.1140.

3-(4-Hydroxy-3-methoxyphenyl)-*N*-(2-methoxyphenyl)prop-2(*E*)-enamide (12bA, $C_{17}H_{17}NO_4$) was obtained from 3-(4-hydroxy-3-methoxyphenyl)-2-[[(2-methoxyphenyl)amino]-carbonyl]prop-2(*E*)-enoic acid (**11bA**) by reflux in pyridine for 2 h. Crystallization led to solid material (86%) with m.p. 165–166 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.82 (1H, d, J = 8.1 Hz, H-5′), 6.90–6.97 (1H, m, H-5), 7.02 (1H, d, J = 15.6 Hz, H-a), 7.05–7.09 (3H, m, H-3,4,6′), 7.23 (1H, d, J = 1.1 Hz, H-2′), 7.46 (1H, d, J = 15.6 Hz, H-b), 7.20 (1H, d, J = 7.9 Hz, H-6), 9.15 (1H, s, OH), 9.51 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 56.2, 111.2, 111.5, 116.1, 119.8, 120.8, 121.7, 122.7, 124.5, 126.9, 128.2, 141.1, 148.3, 149.1, 149.5, 164.7 ppm; IR (KBr) $\bar{\nu}$ = 3345, 3080, 2945, 2835, 2365, 1660, 1620, 1590, 1535, 1520, 1485, 1460, 1430, 1395, 1360, 1320, 1300, 1285, 1250, 1215, 1190, 1175, 1160, 1130, 1040, 1025, 985, 865, 820, 765, 745, 695, 585, 545 cm^{-1}.

3-(4-Hydroxy-3-methoxyphenyl)-*N*-(2-hydroxyphenyl)prop-2(*E*)-enamide (12cA, $C_{16}H_{15}NO_4$) was obtained from 3-(4-hydroxy-3-methoxyphenyl)-2-[[(2-hydroxyphenyl)amino]-carbonyl]prop-2(*E*)-enoic acid (**11cA**) by reflux in pyridine for 2 h. Crystallization led to solid material (45%) with m.p. 185 °C. ^{1}H NMR (300 MHz DMSO-d_6): δ = 3.84 (3H, s, OCH_3), 6.80 (1H, dt, J = 8.1, 1.6 Hz, H-4/5), 6.82 (1H, d, J = 8.2 Hz, H-5′), 6.90 (1H, dt, J = 8.1, 1.6 Hz, H-4/5), 6.97 (1H, d, J = 8.1 Hz, H-3), 6.99 (1H, d, J = 15.6 Hz, H-a), 7.06 (1H, dd, J = 8.2, 1.6 Hz, H-6′), 7.24 (1H, d, J = 1.6 Hz, H-2′), 7.50 (1H, d, J = 15.6 Hz,

H-b), 7.93 (1H, d, J = 8.1 Hz, H-4), 9.36 (1H, s, OH), 9.53 (1H, s, OH), 10.03 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.5, 110.7, 115.2, 115.8, 118.9, 119.1, 121.5, 122.3, 124.4, 126.4, 126.9, 140.8, 147.5, 147.9, 148.7, 164.5 ppm; IR (KBr): $\bar{\nu}$ = 3370, 3060, 1650, 1630, 1610 cm^{-1}; HRMS: m/z = 330.1335.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-(2-hydroxyphenyl)-prop-2(*E*)-enamide (12cH, $C_{17}H_{17}NO_5$) was obtained from 3-(4-hydroxy-3,5-dimethoxyphenyl)-2-[[(2-hydroxyphenyl)-amino]carbonyl]prop-2(*E*)-enoic acid (**11cH**) by reflux in pyridine for 4 h. Crystallization led to solid material (74%) with m.p. 199–201 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (6H, s, 2 × OCH_3), 6.79 (1H, t, J = 7.2 Hz, H-6), 6.85–6.99 (4H, m, H-3,4,2′,6′), 7.03 (1H, d, J = 15.6 Hz, H-a), 7.46 (1H, d, J = 15.6 Hz, H-b), 7.96 (1H, d, J = 7.2 Hz, H-6), 8.88 (1H, s, OH), 9.32 (1H, s, OH), 10.03 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 115.6, 115.6, 119.1, 119.3, 121.4, 124.3, 125.2, 126.9, 137.6, 141.0, 147.4, 148.1, 164.4 ppm; IR (KBr): $\bar{\nu}$ = 3385, 3105, 2840, 2710, 2590, 2240, 1655, 1615, 1590, 1560, 1535, 1515, 1450, 1425, 1375, 1350, 1325, 1280, 1260, 1240, 1210, 1185, 1155, 1105, 1040, 1000, 855, 815, 755, 670 cm^{-1}; HRMS: m/z = 316.1179.

3-(4-Hydroxy-3-methoxyphenyl)-*N*-(4-hydroxyphenyl)prop-2(*E*)-enamide (12dA, $C_{16}H_{15}NO_4$) was obtained from 3-(4-hydroxy-3-methoxyphenyl)-2-[[(4-hydroxyphenyl)amino]-carbonyl]prop-2(*E*)-enoic acid (**11dA**) by reflux in pyridine for 3.5 h. Crystallization led to solid material (50%) with m.p. 192–194 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (3H, s, OCH_3), 6.60 (1H, d, J = 15.6 Hz, H-a), 6.71 (2H, d, J = 8.8 Hz, H-3,5), 6.81 (1H, d, J = 8.1 Hz, H-5′), 7.04 (1H, d, J = 8.1 Hz, H-6′), 7.16 (1H, s, H-2′), 7.43 (1H, d, J = 15.6 Hz, H-b), 7.48 (2H, d, J = 8.8 Hz, H-2,6), 9.19 (1H, br. s, OH), 9.47 (1H, br. s, OH), 9.83 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.5, 110.8, 115.1, 115.7, 119.2, 120.7, 121.8, 126.4, 131.3, 139.8, 147.9, 148.5, 153.3, 163.4 ppm; IR (KBr): $\bar{\nu}$ = 3775, 3655, 3340, 3135, 2810, 2345, 2280, 1685, 1665, 1655, 1650, 1640, 1620, 1590, 1560, 1545, 1535, 1510, 1460, 1450, 1350, 1300, 1250, 1185, 1160, 1130, 1030, 1005, 975, 835, 820, 780, 520, 430 cm^{-1}; HRMS: m/z = 286.1075.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-(3-hydroxyphenyl)-prop-2(*E*)-enamide (12eH, $C_{17}H_{17}NO_5$) was obtained from 3-(4-hydroxy-3,5-dimethoxyphenyl)-2-[[(3-hydroxyphenyl)-amino]carbonyl]prop-2(*E*)-enoic acid (**11eH**) by reflux in pyridine for 2 h. Crystallization lead to solid material (79%) with m.p. 235–237 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (6H, s, 2 × OCH_3), 6.45 (1H, d, J = 7.5 Hz, H-4), 6.66 (1H, d, J = 15.5 Hz, H-a), 6.92 (2H, s, H-2′,6′), 7.00–7.17 (2H, m, H-5,6), 7.30 (1H, s, H-2), 7.48 (1H, d, J = 15.5 Hz, H-b), 8.88 (1H, s, OH), 9.39 (1H, s, OH), 9.95 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 105.4, 106.2, 109.9, 110.3, 119.4, 125.1, 129.4, 137.6, 140.5, 140.7, 148.1, 157.6, 163.8 ppm; IR (KBr): $\bar{\nu}$ = 3345, 3200, 2935, 2845, 2240, 1665, 1605, 1570, 1550, 1515, 1465, 1380, 1325, 1290, 1235, 1215, 1160, 1120, 970, 820, 595, 575 cm^{-1}; HRMS: m/z = 316.1177.

Cinnamoyl anilines 12aH–12aJ, 12bH, 12fH, 12gH, 12hH′ (synthetic protocol II)

were obtained according to the same procedure described for arylidene malonic acid monoanilides **11**.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-(4-methoxyphenyl)-prop-2(*E*)-enamide (12aH, $C_{18}H_{19}NO_5$) was obtained from 2-[(4-methoxyphenyl)carbamoyl]acetic acid (**8a**) and syringaldehyde (**10H**) by reflux in acetic acid for 21.5 h. Crystallization led to solid material (85%) with m.p. 186–188 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3), 6.65 (1H, d, J = 15.6 Hz, H-a), 6.91 (2H, d, J = 9.0 Hz, H-3,5), 6.92 (2H, s, H-2′,6′), 7.48 (1H, d, J = 15.6 Hz, H-b), 7.62 (2H, d, J = 9.0 Hz, H-2,6), 8.87 (1H, s, OH), 9.97 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.7, 56.4, 105.8, 114.4, 119.9, 121.0, 125.7, 133.2, 138.1, 140.9, 148.6, 155.6, 164.0 ppm; IR (KBr): $\bar{\nu}$ = 3750, 3370, 2935, 2835, 2360, 1655, 1620, 1605, 1515, 1460, 1440, 1430, 1375, 1330, 1300, 1265, 1230, 1210, 1180, 1155, 1110, 1040, 960, 835, 810, 600 cm^{-1}; HRMS: m/z = 330.1345.

3-(2,4-Dimethoxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aI, $C_{18}H_{19}NO_4$) was obtained from 2-[(4-methoxyphenyl)carbamoyl]acetic acid (**8a**) and 2,4-dimethoxybenzaldehyde (**10I**) by reflux in acetic acid for 12 h. Crystallization led to solid material (15%) with m.p. 154–156 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.59–6.68 (2H, m, H-3′,5′), 6.72 (1H, d, J = 15.9 Hz, H-a), 6.91 (2H, d, J = 7.5 Hz, H-3,5), 7.51 (1H, d, J = 7.6 Hz, H-6′), 7.62 (2H, d, J = 7.5 Hz, H-2,6), 7.71 (1H, d, J = 15.9 Hz, H-b), 9.95 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.6, 55.9, 56.1, 99.0, 106.4, 114.4, 116.6, 120.5, 121.1, 130.0, 133.2, 135.2, 155.6, 159.6, 162.4, 164.4 ppm; IR (KBr): $\bar{\nu}$ = 3305, 3005, 2945, 2835, 2360, 1650, 1605, 1575, 1520, 1510, 1465, 1435, 1410, 1335, 1290, 1265, 1230, 1195, 1170, 1160, 1120, 1030, 1000, 975, 835, 750, 580, 535 cm^{-1}; HRMS: m/z = 314.1387.

3-(2,4,6-Trimethoxyphenyl)-*N*-(4-methoxyphenyl)prop-2(*E*)-enamide (12aJ) was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 2,4,6-

trimethoxybenzaldehyde (**10J**) by reflux in acetic acid for 40 h. Crystallization led to solid material (71%) with m.p. 205–207 °C (198–200 °C [62]). The compound is known and its ^{1}H and ^{13}C NMR data correspond to literature [34].

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-(2-methoxyphenyl)-prop-2(*E*)-enamide (12bH, $C_{18}H_{19}NO_5$) was obtained from 2-[(2-methoxyphenyl)carbamoyl]acetic acid (**8b**) and syringaldehyde (**10H**) by reflux in acetic acid for 34.5 h. Crystallization led to solid material (79%) with m.p. 119–121 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (6H, s, 2 × OCH_3), 3.87 (3H, s, CH_3), 6.89–6.98 (3H, m, H-8,2′,6′), 7.01–7.10 (3H, m, H-3,4,5), 7.47 (1H, d, J = 15.5 Hz, H-b), 8.21 (1H, d, J = 7.7 Hz, H-6), 8.86 (1H, s, NH), 9.12 (1H, s, OH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.7, 56.0, 105.6, 111.0, 119.7, 120.3, 121.1, 124.0, 125.3, 127.8, 137.7, 140.9, 148.1, 149.1, 164.1 ppm; IR (KBr): $\bar{\nu}$ = 3385, 2950, 2835, 1605, 1560, 1520, 1485, 1460, 1430, 1375, 1335, 1270, 1250, 1220, 1190, 1165, 1110, 1050, 1025, 985, 915, 840, 740, 635, 600, 560, 440 cm^{-1}; HRMS: m/z = 330.1335.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-phenylprop-2(*E*)-enamide (12fH, $C_{17}H_{17}NO_4$) was obtained from 2-phenylcarbamoylacetic acid (**8f**) and syringaldehyde (**10H**) by reflux in acetic acid for 31.5 h. Crystallization led to solid material (53%) with m.p. 96–99 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (6H, s, 2 × OCH_3), 6.68 (1H, d, J = 15.6 Hz, H-a), 6.93 (2H, s, H-2′,6′), 7.05 (1H, t, J = 7.4 Hz, H-4), 7.32 (2H, t, J = 7.4 Hz, H-3,5), 7.51 (1H, d, J = 15.6 Hz, H-b), 7.70 (2H, d, J = 7.4 Hz, H-2,6), 8.90 (1H, s, OH), 10.09 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 105.4, 119.1, 119.3, 123.1, 125.1, 128.8, 137.7, 139.5, 140.9, 148.1, 164.0 ppm; IR (KBr): $\bar{\nu}$ = 3780, 3330, 3135, 3020, 2970, 2940, 2845, 2350, 2280, 1660, 1650, 1595, 1560, 1540, 1515, 1500, 1495, 1465, 1440, 1425, 1375, 1355, 1325, 1300, 1225, 1180, 1155, 1120, 1040, 1000, 990, 965, 910, 860, 850, 830, 760, 725, 695, 665, 635, 610, 570, 530, 510, 440 cm^{-1}; HRMS: m/z = 300.1230.

***N*-(4-Bromophenyl)-3-(4-hydroxy-3,5-dimethoxyphenyl)-prop-2(*E*)-enamide (12gH, $C_{17}H_{16}BrNO_4$)** was obtained from 2-[(4-bromophenyl)carbamoyl]acetic acid (**8g**) and syringaldehyde (**10H**) by reflux in acetic acid for 23.5 h. Crystallization led to solid material (79%) with m.p. 200–202 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (6H, s, 2 × OCH_3), 6.64 (1H, d, J = 15.6 Hz, H-a), 6.93 (2H, s, H-2′,6′), 7.50 (2H, d, J = 8.5 Hz, H-3,5), 7.52 (1H, d, J = 15.6 Hz, H-b), 6.68 (2H, d, J = 8.5 Hz, H-2,6), 8.89 (1H, s, OH), 10.22 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.9, 105.5, 114.6, 118.9, 120.9, 124.9, 131.5, 137.8, 138.8, 141.3, 148.1, 164.0 ppm; IR (KBr): $\bar{\nu}$ = 3750, 3510, 3450, 3275, 3095, 3030, 2940, 2840, 2280, 1650, 1635 1620, 1590, 1560, 1520, 1490, 1460, 1425, 1395, 1375, 1350, 1320, 1270, 1245, 1230, 1180, 1155, 1115, 1070, 1045, 1010, 990, 965, 905, 860, 830, 815, 780, 730, 670, 605, 590, 505, 450, 420 cm^{-1}.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-[4-[3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2(*E*)-enoyl]phenyl]prop-2(*E*)-enamide (12hH′, $C_{28}H_{27}NO_8$) was obtained from 2-(4-acetylphenyl)carbamoylacetic acid (**8h**) and syringaldehyde (**10J**) by reflux in acetic acid for 35.5 h. Purification on silica (35–70 μm; eluent—ethyl acetate:hexanes (2:3 v:v)) and following crystallization led to solid material (55%) with m.p. 192–195 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (6H, s, 2 × OCH_3), 3.86 (6H, s, 2 × OCH_3), 6.71 (1H, d, J = 15.8 Hz, H-a), 6.95 (2H, s, H-2′,6′), 7.20 (2H, s, H-2′′,6′′), 7.56 (1H, d, J = 15.7 Hz, H-b), 7.67 (1H, d, J = 15 Hz, H-a'), 7.82 (1H, d, J = 15.0 Hz, H-b'), 7.89 (2H, d, J = 9.1 Hz, H-3,5), 8.18 (2H, d, J = 9.1 Hz, H-2,6), 8.10–9.10 (2H, br. s., 2 × OH), 10.48 (1H, s, NH) ppm (both sinapinoyl moieties are indicated with the same letters and numbers, however, for the moiety in the aniline residue additional ′ is introduced); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 56.2, 105.6, 106.9, 118.4, 118.6, 118.9, 124.9, 125.2, 129.9, 132.6, 138.0, 138.6, 141.9, 143.8, 144.7, 148.08, 148.10, 164.4, 187.3 ppm; IR (KBr): $\bar{\nu}$ = 3625, 3360, 3195, 2995, 2970. 2940, 2840, 1710, 1685, 1625, 1595, 1530, 1515, 1455, 1430, 1410, 1370, 1335, 1320, 1300, 1285, 1255, 1215, 1175, 1160, 1115, 1035, 1010, 990, 970, 930, 910, 885, 865, 850, 820, 790, 780, 765, 745, 720, 690, 680, 655, 645, 635, 615, 605, 560, 550, 525, 505, 485, 475 cm^{-1}; HRMS: m/z = 506.1809.

Cinnamoyl anilines 12aK, 12dH, 12fA, 12gA, 12hA (synthetic protocol III)

A malonic acid monoanilide **8** (0.6 mmol), aromatic aldehyde **10** (0.6 mmol), guanidine hydrochloride (0.06 mmol), and potassium hydroxide (0.06 mmol) in 1 cm^3 acetic acid were stirred at 75 °C for 7–40 h. The crude product was isolated in the same way as described for arylidene malonic acid monoanilides **5**. Further the crude product was refluxed in pyridine as described for cinnamoyl anilines in the Synthetic protocol I. Both steps were monitored by TLC until full conversion of starting compounds.

***N*-(4-Methoxyphenyl)-3-(4-nitrophenyl)prop-2(*E*)-enamide (12aK)** was obtained from 2-(4-methoxyphenyl)carbamoylacetic acid (**8a**) and 4-nitrobenzaldehyde (**10K**) by reflux in acetic acid for 23.5 h and sequential reflux of crude product in pyridine for 3.5 h. Crystallization led to solid material (82%) with m.p. 214–215 °C (215.5 °C [63]). The compound is known; however, to the best of our

knowledge its spectral data are not known. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.55 (3H, s, OCH_3), 6.62 (2H, d, J = 8.4 Hz, H-3,5), 6.70 (1H, d, J = 15.4 Hz, H-a), 7.35–7.48 (5H, m, H-2,6, 2′,6′,b), 8.00 (2H, d, J = 8.7 Hz, H-12,14), 9.51 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.1, 113.6, 121.2, 123.7, 126.3, 128.0, 131.7, 137.1, 141.3, 147.5, 155.7, 162.6 ppm; IR (KBr): $\bar{\nu}$ = 3275, 3045, 2960, 2840, 2360, 1650, 1620, 1600, 1540, 1520, 1415, 1345, 1300, 1280, 1245, 1190, 1170, 1110, 1030, 970, 850, 820, 785, 735, 715, 555, 520, 505 cm^{-1}; HRMS: m/z = 299.1026.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-(4-hydroxyphenyl)-prop-2(*E*)-enamide (12dH, $C_{17}H_{17}NO_5$) was obtained from 2-(4-hydroxyphenyl)carbamoylacetic acid (**8d**) and syringaldehyde (**10H**) by reflux in acetic acid for 23.5 h and sequential reflux of crude product in pyridine for 3.5 h. Crystallization led to solid material (93%) with m.p. 261–264 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.81 (6H, s, 2 × OCH_3), 6.63 (1H, d, J = 15.6 Hz, H-a), 6.71 (2H, d, J = 8.8 Hz, H-3,5), 6.90 (2H, s, H-2′,6′), 7.44 (1H, d, J = 15.6 Hz, H-b), 7.48 (1H, d, J = 8.8 Hz, H-2,6), 8.84 (1H, s, OH), 9.19 (1H, s, OH), 9.84 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 115.3, 115.2, 119.6, 120.7, 125.2, 131.3, 137.5, 140.1, 148.1, 153.3, 163.3 ppm; IR (KBr): $\bar{\nu}$ = 3465, 3350, 3310, 2940, 2840, 2660, 2245, 1665, 1630, 1605, 1550, 1535, 1515, 1475, 1460, 1375, 1335, 1275, 1250, 1185, 1145, 1110, 1040, 900, 835, 820, 765, 555 cm^{-1}; HRMS: m/z = 316.1171.

3-(4-Hydroxy-3-methoxyphenyl)-*N*-(4-phenyl)prop-2(*E*)-enamide (12fA) was obtained from 2-phenylcarbamoylacetic acid (**8f**) and vanillin (**10A**) by reflux in acetic acid for 9 h and sequential reflux of crude product in pyridine for 3 h. Crystallization led to solid material (28%) with m.p. 142–144 °C (143–145 °C [64]). The compound is known and its ^{1}H and ^{13}C NMR data correspond to literature [65].

***N*-(4-Bromophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2(*E*)-enamide (12gA, $C_{16}H_{14}BrNO_3$)** was obtained from 2-(4-bromophenyl)carbamoylacetic acid (**8g**) and vanillin (**10A**) by reflux in acetic acid for 41 h and sequential reflux of crude product in pyridine for 4.5 h. Crystallization led to solid material (33%) with m.p. 193 °C. ^{1}H NMR (300 MHz DMSO-d_6): δ = 3.83 (3H, s, OCH_3), 6.62 (1H, d, J = 15.6 Hz, H-a), 6.83 (1H, d, J = 8.1 Hz, H-5′), 7.07 (1H, dd, J = 8.1, 1.1 Hz, H-6′), 7.19 (1H, d, J = 1.1 Hz, H-2′), 7.51 (3H, m, H-3,5,b), 7.67 (2H, d, J = 8.8 Hz, H-2,6), 9.56 (1H, s, OH), 10.23 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.5, 110.8, 114.7, 115.7, 118.5, 121.0, 122.1, 126.1, 131.6, 138.9, 141.1, 147.9, 148.9, 164.2 ppm; IR (KBr): $\bar{\nu}$ = 3240, 3110, 3050, 1655, 1620, 1595, 1535, 1515, 1490, 1430, 1395, 1295, 1270, 1250, 1210, 1180, 1160, 1120, 1070, 1030, 1010, 990, 865, 830, 805, 725, 510 cm^{-1}; HRMS; m/z = 348.0231.

***N*-(4-Acetylphenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2(*E*)-enamide (12hA, $C_{18}H_{17}NO_4$)** was obtained from 2-(4-acetylphenyl)carbamoylacetic acid (**8h**) and vanillin (**10A**) by reflux in acetic acid for 22.5 h and sequential reflux of crude product in pyridine for 3 h. The compound was purified on silica (35–70 μm; eluent—ethyl acetate:hexanes (2:3 v:v), followed by crystallization leading to solid material (38%) with m.p. 196–198 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.53 (3H, s, Ac), 3.81 (3H, s, OCH_3), 6.66 (1H, d, J = 15.6 Hz, H-a), 6.83 (1H, d, J = 8.3 Hz, H-5′), 7.09 (1H, dd, J = 8.3 Hz, 2.1 Hz, H-6′), 7.21 (1H, d, J = 2.1 Hz, H-2′), 7.54 (1H, d, J = 15.6 Hz, H-b), 7.82 (2H, d, J = 8.4 Hz, H-2,6), 7.82 (2H, d, J = 8.4 Hz, H-3,5), 9.53–9.67 (1H, brs, OH), 10.44 (1H, s, NH) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 26.5, 55.5, 110.9, 115.8, 118.4, 122.3, 126.0, 129.6, 131.6, 141.7, 143.9, 147.9, 149.0, 164.5, 196.5 ppm; IR (KBr): $\bar{\nu}$ = 3415, 3320, 3065, 3000, 2845, 1670, 1630, 1595, 1515, 1460, 1445, 1430, 1405, 1370, 1340, 1300, 1280, 1260, 1250, 1215, 1180, 1175, 1155, 1130, 1075, 1030, 1000, 965, 960, 930, 885, 850, 835, 820, 810, 780, 740, 725, 710, 685, 645, 610, 590, 560, 510, 520, 495, 460 cm^{-1}; HRMS: m/z = 312.1247.

Antiradical activity

2,2-Diphenyl-1-picrylhydrazyl test was carried out according to procedure described in literature [66]. GO test was done as follows: 2 cm^3 GO solution in EtOH (concentration 20 μM) and 2 cm^3 solution of compound **11** or **12** were mixed (concentration 200 μM). The duration of test for cinnamoyl anilines **12** was 3 h, for arylidene malonic acid monoanilides **11** 6 h; when the reaction was completed, absorption was measured at 428 nm. Samples of various concentrations of compounds were prepared similarly to the procedure described above. Both, for DPPH and GO tests the inhibition (%) and IC_{50} value (μM) is the mean (± standard deviation) of two independent experiments. All the measurements were done triple for each experiment line.

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