Simple amidation of unprotected phenol-containing 2-alkenoic acids

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A series of amides of 2-*E*-alkenoic acids have been synthesised through the activation of these acids with dicyclohexylcarbodiimide / pentafluorophenol and further reaction with amines under microwave irradiation. In daylight, the *E*-configured amides undergo a slow photochemical *E*/*Z*-isomerisation. Photoirradiation experiments with selected 3-(hydroxyphenyl)-2(*E*)-alkenamides were carried out using a high pressure mercury UV lamp.

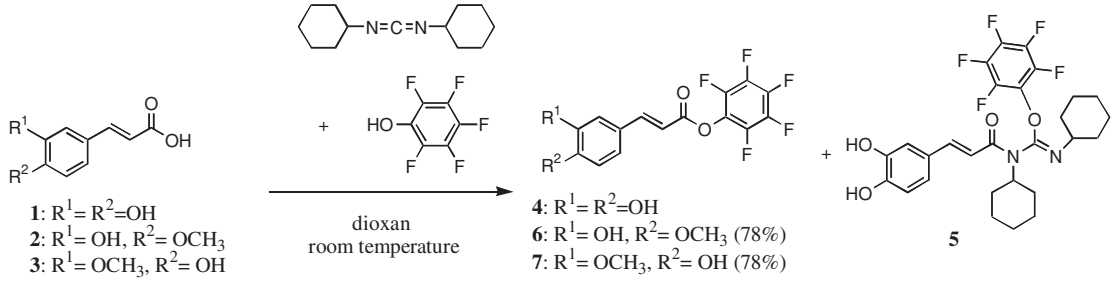
Keywords: amides, antioxidants, microwave irradiation, polyphenol, photoisomerisation

In recent years, the study of hydroxyphenylalkeneamides as antioxidants has attracted attention.[1] In our quest to use steroidal carriers as *in vivo* delivery systems for antioxidants to tissues prone to oxidative stress,[2] an efficient synthetic method was needed to link steroidal amines to *non*-protected hydroxyphenylalkenoic acids. A number of ways to activate carboxylic acids for linking to amines have been proposed previously, such as the activation with *N*,*N*-bis-[2-oxo-3-oxazolidinyl] phosphorodiamidic chloride,[3] with diphenylphosphinic chloride,[4] with (*N*,*N*-carbonyldiimidazole),[5] or with (benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate.[6] Other, more conventional, amidation reactions include the use of dicyclohexylcarbodiimide (DCC)[7] as coupling agent, and the mixed anhydride method. It is known, however, that in the case of 2-alkenoic acids, the DCC method leads to a more stable ureide (**A**) as the main product,[4b,7] thus lowering the yield of the activated acid to about 20%. Also, the reaction of 2-alkenoic acids with amines using the mixed anhydride method leads to unwanted side-products.[7] While the activation of 2-alkenoic acids with diphenylphosphinic chloride and subsequent reaction with amines has been reported to give the corresponding alkenamides in excellent yield,[4] phenol moities in phenol-containing alkenoic acids must be protected because of the oxophililicity of the phosphinic chloride. In order to avoid the protection / deprotection steps involved, the authors turned to the possibility of using pentafluorophenol (PFP) as activating agent. Pentafluorophenol (PFP) is known to give pentafluorophenyl esters which are highly electrophilic and susceptible to the nucleophilic attack of amines. Again, this method has been widely used for the activation of saturated acids for subsequent amidation reactions.[8] However, under conventional reaction conditions, once more, limitations can be expected when using this method in combination with the DCC method, where the DCC method has been reported to give large amounts of unwanted products when 2-alkenoic acids are used as starting materials.[4b]

Herein, we describe an easily performed, microwave assisted amidation of pentafluorophenylesters of unprotected phenol-containing 2-alkenoic acids, which utilises the DCC methodology.

Initially, a number of amidation procedures were carried out with the unsaturated polyphenolic ferulic and caffeic acids. The utilisation of the reagents CDI (*N*,*N*-carbonyldiimidazole), *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiami dicchloride, and diphenylphosphinic chloride yielded amides either in very low yields (CDI, diphenylphosphinic chloride) or did not work out at all [*N*,*N*-bis(2-oxo-3-oxazolidinyl) phosphorodiamidic chloride].[9] In the case of CDI, the reaction did work; however, it was difficult to purify the product. There was no precedent in the literature regarding these methods for phenol or catechol containing acids, although a large number of other carboxylic acids have been reported to give amides in good yield. In the case of the phosphorus-containing activating agents, it is most likely the preference of the phosphorus for the phenolic oxygen that hinders the activation of the carboxylic function and the subsequent amidation. Here, unidentified phosphorus containing by-products could be isolated. All of the above reactions, albeit one step procedures, necessitate anhydrous solvents, inert atmosphere, long reaction times and elaborate work-ups including extractions and complicated chromatographic separations.

Our first studies on the activation of 2-alkenoic acids bearing a polyphenolic substituent via DCC and PFP activation showed partially expected results. Thus, in the case of the activation of caffeic acid (**1**), the reaction was confirmed to lead to a by-product along with the formation of the respective activated acid (**4**). The by-product, however, was shown not to be the typical acid ureide **A** (Fig. 1), sometimes described in the literature as a by-product in the activation of acids when using DCC. Rather, it is the 1,3-dicyclohexyl-1-(3',4'-dihydroxycinnamoyl)-2-pentafluorophenyl-isourea (**5**) (Scheme 1). This by-product, which is formed in significant amounts,



1: $R^1 = R^2 = OH$
2: $R^1 = OH$, $R^2 = OCH_3$
3: $R^1 = OCH_3$, $R^2 = OH$

4: $R^1 = R^2 = OH$
6: $R^1 = OH$, $R^2 = OCH_3$ (78%)
7: $R^1 = OCH_3$, $R^2 = OH$ (78%)

5

Scheme 1

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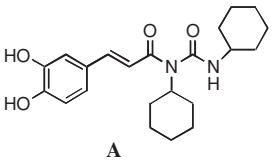


A

Fig. 1

complicates the work-up of **4**, as it possesses solubility similar to that of **4** and is also difficult to separate the compounds by column chromatography. Interestingly, in the activation of ferulic acid (**2**) and the parent *trans*-3-hydroxy-4-methoxycinnamic acid (**3**), no by-product corresponding to **5** was observed in significant amounts. Here, it was easy to obtain the respective activated acids **6** and **7** in high yields. The by-product **5** can be explained by attack of the pentafluoro-phenol on the carbonyl function of ureide **A** and subsequent dehydration. Similar products have been formulated as intermediates in the reaction of acylureas with phosphorus oxychloride ($POCl_3$)[10] and have been isolated as labile compounds from the reaction of barbituric acid and ribose 5-phosphate[11] and analogous reactions.

First attempts to obtain amides from mixtures of compounds **4** and **5** and aliphatic amines (**11**) in chloroform afforded the desired product in yields of about 20 %. Under these conditions, the by-product **5** itself was shown not to react.

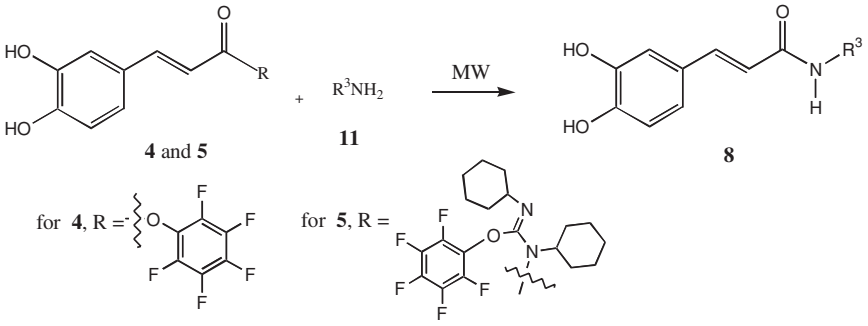
In subsequent studies the reaction was carried out under microwave irradiation[12] and mostly under solventless conditions, when the desired amides were formed in good yields (Scheme 2, Table 1). In these cases the isoureide **5** was shown to be equally reactive, so that a complete reaction of all starting materials could be achieved.

In the case of 3-hydroxy-4-methoxycinnamic acid (**2**) and ferulic acid (**3**), the activation with DCC and PFP yields only the pentafluorophenyl cinnamates **6** and **7** as mentioned above, and as pure starting materials these were subjected to the microwave-induced amidation reactions with equally good success (Scheme 3, Table 2).

In order to avoid the oxidation of the polyphenolic moiety the reactions under microwave irradiation have to be carried out under an argon atmosphere due to the high temperatures reached by the reaction mixture at the end of the reactions.

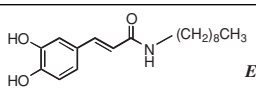
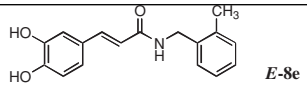
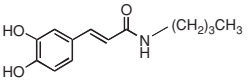
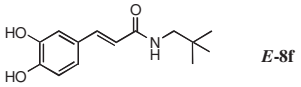
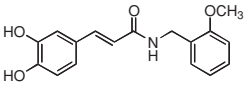
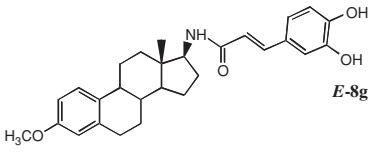
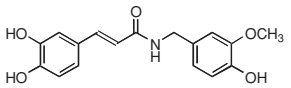
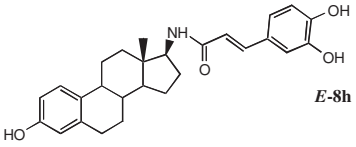
With liquid amines no additional solvent was used in the reaction. In the case of *n*-butylamine (**11b**), 6 equiv. of amine were used for 1 equiv. of activated acid because of the low boiling point of the amine. The lower yield in the case of *n*-butylamine is most likely a result of its low boiling point.

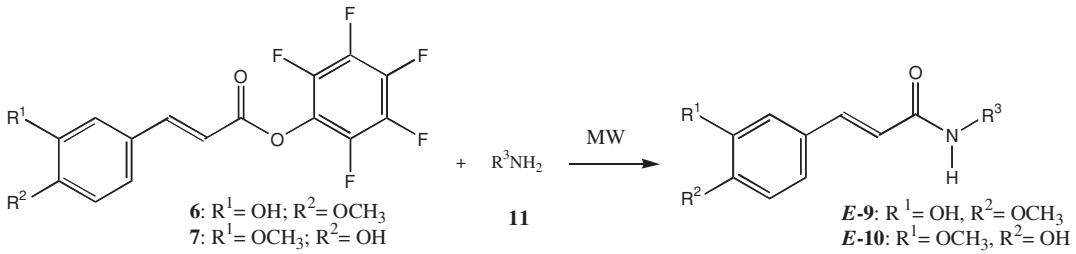
4-Hydroxy-3-methoxybenzylamine (**11d**) was introduced as its commercially available solid hydrochloride salt (3 equiv.), which was dissolved in an aliquot of chloroform, and to which triethylamine (3.1 equiv.) and the activated acid (1 equiv.) were added subsequently. Then the solvent was evaporated and the resulting mixture was subjected to microwave irradiation. In the reactions involving 3-*O*-methyl-17β-aminoestra-1,3,5(10)-trien-3-ol (**11g**) and 17β-aminoestra-1,3,5(10)-triene-3-ol (**11h**), the solid amine was dissolved in dioxan (1 ml), the activated acid was added, and the reaction mixture was subjected with the solvent to cycles of microwave irradiation of 1 min duration. After the irradiation the mixtures were cooled and transferred directly onto silica gel and subjected



Scheme 2

Table 1

Amine	Reaction time	Product	Yield/%	Amine	Reaction time	Product	Yield/%
11a	13 min	 ***E*-8a**	80	**11e**	5 min	 ***E*-8e**	55
11b	5 min	 ***E*-8b**	25	**11f**	13 min	 ***E*-8f**	74
11c	13 min	 ***E*-8c**	70	**11g**	3 min	 ***E*-8g**	55
11d	13 min	 ***E*-8d**	65	**11h**	3 min	 ***E*-8h**	76



Scheme 3

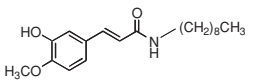
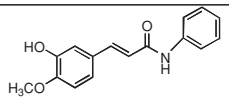
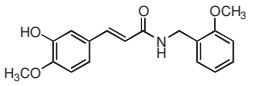
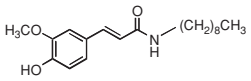
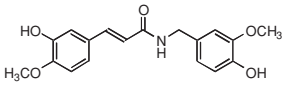
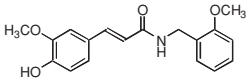
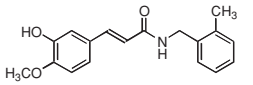
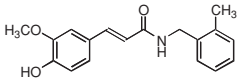
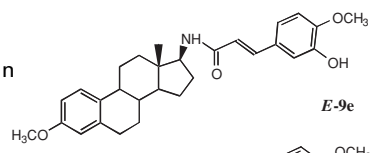
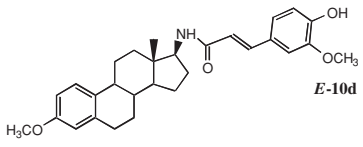
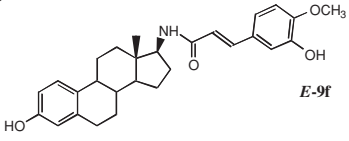
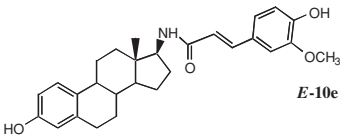
to rapid column chromatography. Evaporation of the eluent yielded pure products, which were crystallised from *n*-hexane. Only 3,4-dihydroxy-*N*-butylcinnamide (***E*-8b**) and 4-hydroxy-3-methoxy-*N*-nonylcinnamide (***E*-10a**) were isolated as oils. A microwave effect has been reported for amidation reactions previously.[13] Whether such an effect is operative in this case is not certain. It must be noted, however, that reacting a mixture of **4** and **5** with nonylamine by simply heating the mixture for 13 min. conventionally at 130 °C, which is the plateau temperature reached in the microwave irradiation with the mixtures studied, does not yield the amides in appreciable amounts. Compound **5** does not react under the conditions and can be recovered. Reacting the carboxylic acids directly[13] with amines under microwave irradiation is not possible in the case of the cinnamic acids and cinnamic acid derivatives, due to side reactions of these acids under the conditions.

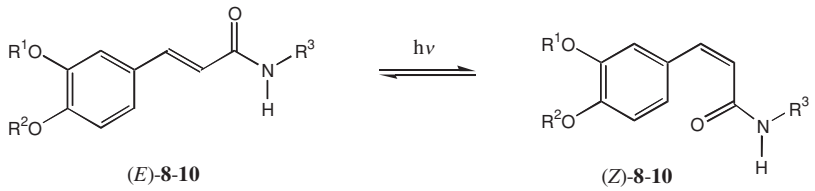
Compounds ***E*-8a**, ***E*-8g**, ***E*-9b**, ***E*-9e** and ***E*-10d** were screened as potential chemotherapeutic agents within the Developmental Therapeutics Program[14] of the National Cancer Institute, NIH (USA). In the screening only ***E*-8a** and ***E*-8g**, compounds, with both phenolic moieties unprotected, showed significant cytostatic activity.

It was noted that the *E*-alkenamides prepared above are not stable in solution, when exposed to daylight. After leaving solutions of the samples in chloroform exposed to daylight for 5h, the samples were analysed by ^{1}H NMR spectrometric measurement. New signals appeared in the spectra, which could be identified as those of the corresponding *Z*-isomers, in which the respective signal peak for the proton at the 2 position is shifted up-field and the coupling constant $^3J_{H2}/_{H3}$ is significantly smaller than that of the corresponding *E*-isomer (for compound ***Z*-9d** [DMSO-d^6, 270 MHz] δ 5.87 ppm, $^3J^Z$ = 12.9 Hz *vs*. ***E*-9d** 7.29, $^3J^E$ = 15.7 Hz).[15] To exclude the possibility of a thermal isomerisation, a sample of ***E*-9d** (5 mg, 0.5 ml, 33.6 mmol/l) in DMSO was heated at 50 °C in the dark for 22h. No *E*/*Z*-isomerisation could be observed in this case. The photoisomerisation is solvent dependent.

In the UV spectrum, alkenamides show two distinct absorption peaks, at λ 288–296 nm and at λ 321–325 nm, respectively. Solutions of alkenamides ***E*-8e** (10.1 mg, 0.9 ml, 39.6 mmol/l), ***E*-9d** (9.1 mg, 0.9 ml, 34 mmol/l), ***E*-9e** (11.3 mg, 0.7 ml, 35 mmol/l), and ***E*-10c** (10.7 mg, 0.9 ml, 40 mmol/l), as representative samples, in DMSO-d$_6$ were subjected to photoirradiation with a mercury high pressure lamp. The reactions were monitored by ^{1}H NMR spectroscopy after 10 min., 20 min., 50 min., and 110 min. In all cases rapid *E*/*Z*-isomerisation could be observed, leading towards an equilibrium after 110 min (Scheme 4).

Table 2

Amine	Reaction time	Product	Yield/%	Amine	Reaction time	Product	Yield/%
11a	5 min	 ***E*-9a**	70	**11i**	20 min	 ***E*-9g**	76
11c	10 min	 ***E*-9b**	83	**11a**	5 min	 ***E*-10a**	58
11d	5 min	 ***E*-9c**	42	**11c**	10 min	 ***E*-10b**	78
11e	5 min	 ***E*-9d**	99	**11e**	5 min	 ***E*-10c**	54
11g	1 min	 ***E*-9e**	90	**11g**	3 min	 ***E*-10d**	85
11h	3 min	 ***E*-9f**	85	**11h**	4 min	 ***E*-10e**	58



E/*Z* ratios (duration of photoirradiation)

for ***E*-8e**: $R^1 = R^2 = H$; R^3 = *o*-tolyl

for ***E*-9d**: $R^1 = H$; $R^2 = CH_3$; R^3 = *o*-tolyl

for ***E*-9e**: $R^1 = H$; $R^2 = CH_3$; R^3 = 3-methoxy-estra-1,3,5(10)-trien-17β-yl

for ***E*-10c**: $R^1 = CH_3$; $R^2 = H$; R^3 = *o*-tolyl

[***E*-8e/*Z*-8e**]: 100/0 (0 min); 63/37 (10 min); 55/45 (20 min); 53/47 (50 min)

[***E*-9d/*Z*-9d**]: 100/0 (0 min); 67/33 (10 min); 58/42 (20 min); 53/47 (50 min)

[***E*-9e/*Z*-9e**]: 100/0 (0 min); 68/32 (10 min); 64/36 (50 min); 63/37(110 min)

[***E*-10c/*Z*-10c**]: 100/0 (0 min); 82/18 (10 min); 71/29 (20 min); 64/36 (50 min) 62/38 (110 min)

Scheme 4

Photoisomerisations of ferulic acid, caffeic acid and their esters are known,[16, 17] and the photoisomerisation capability has been utilised in sun block filters. Also, the photoisomerisation of ferulates in cell walls of plants has been studied.[18] That alkenamides of this type isomerise as well, however, is a little-known fact.

The authors have shown the possibility of using the DCC/PFP activation method for amidations of 2-alkenoic acids under microwave irradiation. This novel method can even be applied to 2-alkenoic acids with a non-protected polyphenolic moiety. In the case of caffeic acid (**1**), where the initial activation reaction affords a by-product **5**, this by-product was shown to be equally reactive towards amidation. The advantages of the microwave-induced amidation are that the reaction can be carried out without a solvent, or in the case of solid amines, with the use of minimal amounts of solvent. Although high temperatures develop upon microwave irradiation, the amidation reaction does yield significant amounts of by-products, facilitating the work-up of the products. Short reaction times and the relatively low cost of the reagents complement the benefits to this an attractive amidation method.

Experimental

Melting points were measured on a Yanaco hot-stage microscope. Infrared spectra was measured with a JASCO IR-700 instrument. ^{1}H (270 MHz and 395.7 MHz) spectra were recorded with a JEOL EX-270 and a JEOL Lambda 400 FT-NMR spectrometer. ^{13}C (99.45 MHz) spectra were measured with a JEOL Lambda 400 FT-NMR spectrometer. The chemical shifts are relative to TMS. Mass spectra were measured with a JMS-01-SG-2 spectrometer. The mass spectra were taken in FAB-mode using 3-nitrobenzyl alcohol as matrix, unless noted otherwise. UV spectra were taken with a JASCO UV/VIS/NIR V-570 spectrophotometer. Column chromatography was carried out on Wakogel 300.

For the microwave irradiation experiments a domestic microwave National NE-S12 (with power settings at 170 W / 500 W and 750 W, 2450 MHz) was used. Pyrex glass beakers (20 ml) with a small opening were used. The beakers were sealed with Saran Wrap®, which allows for pressure equilibration. Temperature calibration showed that a temperature plateau of 130 °C (bulk temperature of the mixture) is reached after 3 min. The photoirradiation of the alkenamides was carried out in pyrex glass tubes (4.22 mm inner diameter, wall thickness 0.37 mm). A 1kW Rikagaku mercury high pressure lamp was used as the light source.

All chemical reagents were of reagent grade. Dioxan was dried and distilled from Na under inert atmosphere. 3-*O*-Methyl-17β-aminoestra-1,3,5(10)-trien-3-ol (**11g**) was prepared from the corresponding 17-oxime by reduction with Na in refluxing *n*-propanol analogous to a known procedure, the non-protected 17β-aminoestra-1,3,5(10)-trien-3-ol (**11h**) was prepared by the same procedure or by reduction with $LiAlH_4$.[19, 20, 21]

All the amines were liquids, except the 4-hydroxy-3-methoxybenzylamine hydrochloride (**11d**), the 3-*O*-methyl-17β-aminoestra-1,3,5(10)-trien-3-ol (**11g**) and the 17β-aminoestra-1,3,5(10)-trien-3-ol (**11h**). The reaction with these last amines was performed using an aliquot of dioxan and with microwave cycles of 1 minute each.

General procedure A

To a solution of acid (1 equiv.) was added DCC (1.1 equiv.) and pentafluorophenol (1.1 equiv.) in anhydrous dioxan. The mixture was stirred at room temperature. After a reaction time of between 4 and 24 hours, the solvent was evaporated *in vacuo* and the crude was subjected to column chromatography on silica gel (diethyl ether/*n*-hexane 1:1) to provide the respective activated acids **4**, **6**, **7**.

Pentafluorophenyl 3,4-dihydroxycinnamate (**4**): **1** (1.0 g, 5.55 mmol), DCC (1.39 g, 6.76 mmol) and PFP (1.39 g, 7.55 mmol) in dry dioxan (26 ml) were reacted according to the general procedure (reaction time 24 h) to give **4** (Found: M^+, 346.0267. $C_{15}H_7F_5O_4$ requires M 346.0265). δ_H (DMSO-d_6, 270 MHz) 7.84 (1H, d, $^3J^E$ = 15.7 Hz), 7.18 (1H, s), 7.17 (1H, d, ^3J = 8.2 Hz), 6.80 (1H, d, ^3J = 8.2 Hz), 6.61 (1H, d, $^3J^E$ = 15.7 Hz); MS (70 eV) *m/z* (%) = 346 (M^+, 2.4), 163 (100) and *1,3-dicyclohexyl-1-[3-(3,4-dihydroxy)cinnamoyl]-2-O-pentafluorophenyl-isourea* (**5**): (Found: MH^+, 553.2131. $C_{28}H_{30}O_4N_2F_5$ requires MH 553.2126). δ_H (DMSO d_6, 270 MHz) 9.62 (1H, s, OH), 9.17 (1H, s, OH), 7.52 (1H, d, $^3J^E$ = 15.3 Hz), 6.94 (1H, s), 6.88 (1H, d, ^3J = 8.1 Hz), 6.77 (1H, d, ^3J = 8.1 Hz), 6.45 (1H, d, $^3J^E$ = 15.3 Hz), 4.26 (broad m), 0.82–2.49 (22H, m); MS *m/z* (%) = 553 (MH^+, 28), 163 (100), 391 (66).

Pentafluorophenyl 3-hydroxy-4-methoxycinnamate (**6**): **2** (1.0 g, 5.15 mmol), DCC (1.26 g, 6.10 mmol) and PFP (1.07 g, 5.80 mmol) in dry dioxan (30 ml) were reacted according to general procedure A (reaction time 7h) to give **6** (1.44 g; 78%) as a colourless solid: m.p. 114–117 °C. (Found: MH^+, 361.0504. $C_{16}H_{10}F_5O_4$ requires: MH, 361.0499). (KBr)/cm^{-1} ν_{max} 3424, 1722, 1631, 1609, 1518, 1286, 1212; δ_H (DMSO d_6, 270 MHz) 9.26 (1H, s, OH), 7.88 (1H, d, $^3J^E$ = 15.9 Hz), 7.30 (1H, s), 7.26 (1H, d, ^3J = 7.9 Hz), 7.0 (1H, d, ^3J = 7.9 Hz), 6.7 (1H, d, $^3J^E$ = 15.9 Hz), 3.83 (3H, s, OCH_3); δ_C (DMSO d_6, 99.45 MHz) 163.2, 151.8, 150.8, 147.3, 126.8, 123.2, 115.4, 112.5, 111.0, 56.2; δ_F (DMSO d_6, 400 MHz) -153.61 (d, ^3J[*F*,*F*] 21.0 Hz), –158.17 (t, ^3J[*F*,*F*] 24.0 Hz), –162.61 (dd, ^3J[*F*,*F*] 21.0 Hz, ^3J[*F*,*F*] 24.0 Hz); MS *m/z* (%) = 361 (MH^+, 21%).

Pentafluorophenyl 4-hydroxy-3-methoxycinnamate (**7**): **3** (1.0 g, 5.15 mmol), DCC (1.16 g, 5.66 mmol) and PFP (1.04 g, 5.66 mmol) in dry dioxan (30 ml) were reacted according to general procedure A to give **7** (1.44 g; 78%) as a colourless solid; m.p. 110–114 °C; (Found: MH^+, 361.0493. $C_{16}H_9F_5O_4$ requires MH, 361.0499). (KBr)/cm^{-1} ν_{max} 3468, 1725, 1626, 1601, 1293, 993; δ_H (DMSO d_6, 270 MHz) 9.86 (1H, s), 7.90 (1H, d, $^3J^E$= 15.9 Hz), 7.47 (1H, s), 7.26 (1H, d, ^3J = 8.4 Hz), 6.83 (1H, d, ^3J = 8.4 Hz), 6.82 (1H, d, $^3J^E$ = 15.9 Hz), 3.83 (3H, s); MS *m/z* (%) = 361 (MH^+, 8).

General procedure B

The amine (3 equiv.) was added to the activated acid (1 equiv.) and the resulting mixture was irradiated at 500 W (2450 MHz).

The reaction was carried out under argon atmosphere. The progress of the reaction was controlled by TLC. After the reaction was complete, the mixture was directly subjected to column chromatography on silica gel (ethyl acetate/chloroform). Thereafter, the pure compound was crystallised in chloroform/*n*-hexane to provide the respective amide as a solid material.

(E)-3,4-Dihydroxy-N-nonylcinnamide (***E*-8a**)**:** (140 mg, 80 %); colourless solid; m.p. 106–110 °C; (Found: MH^+, 306.2072. $C_{18}H_{28}NO_3$ requires MH, 306.2069). (KBr)/cm^{-1} ν_{max} 3476, 3374, 2920, 2850, 1650, 1592, 1455; δ_H (DMSO-d_6, 270 MHz) 9.31 (1H, s, OH), 9.08 (1H, s, OH), 7.88 (1H, t, NH, ^3J= 5.7 Hz), 7.19 (1H, d, $^3J^E$= 15.7 Hz), 6.91 (1H, s), 6.81 (1H, d, ^3J= 8.4 Hz), 6.72 (1H, d, ^3J= 8.4 Hz), 6.30 (1H, d, $^3J^E$= 15.7 Hz), 1.24–1.41 (14H, m), 0.84 (3H, t, ^3J= 5.7 Hz). MS *m/z* = 306 (MH^+, 100).

(E)-3,4-Dihydroxy-N-butylcinnamide (***E*-8b**) (23 mg, 25 %); yellow oil; (Found: MH^+, 236.1289. $C_{13}H_{18}NO_3$ requires MH, 236.1287). (Neat)/cm^{-1} ν_{max} 3358, 2928, 2858, 1654, 1594, 1543, 1280; δ_H (DMSOd_6, 270 MHz) 7.87 (1H, s, OH), 7.68 (1H, m, NH), 7.19 (1H, d, ^3J = 15.4 Hz), 6.89 (1H, s), 6.78 (1H, d, ^3J=8.1 Hz), 6.68 (1H, d, ^3J= 8.1 Hz), 6.28 (1H, d, ^3J = 15.4 Hz), 3.13 (2H, t, ^3J 7.0 Hz), 1.22–1.46 (4H, m), 0.87 (3H, t, ^3J =6.7 Hz); MS *m/z* (%) = 236 (MH^+, 28).

(E)-3,4-Dihydroxy-N-(2′-methoxybenzyl)cinnamide (***E*-8c**): (70 mg, 70 %), light brownish solid; m.p. 154–155 °C. (Found: MH^+, 300.1241. $C_{17}H_{28}NO_4$ requires MH, 300.1236). (KBr)/cm^{-1} ν_{max} 3386, 3100, 2930, 1657, 1592, 1273; δ_H (DMSO d_6, 270 MHz) 9.30 (1H, s, OH), 9.07 (1H, s, OH), 8.23 (1H, t, NH, ^3J= 5.4 Hz), 7.71–6.28 (8H, m), 6.43 (d, 1H, $^3J^E$ = 15.6 Hz), 4.32 (2H, d, ^3J = 5.4 Hz), 3.8 (3H, s, OCH_3); δ_C (DMSO d_6, 99.45 MHz) 165.9, 157.1, 147.7, 146.0, 139.7, 137.6, 128.4, 127.3, 126.9, 120.8, 120.6, 118.9, 116.2, 114.3, 119.9, 55.8, 37.8. MS *m/z* (%) = 300 (MH^+, 33).

(E)-3,4-Dihydroxy-N-(4′-hydroxy-3′-methoxybenzyl)cinnamide (***E*-8d**): (61 mg, 65 %) yellow solid; m.p. 200–202 °C. (Found MH^+, 316.1185. $C_{17}H_{18}NO_5$ requires MH 316.1185). IR (KBr) ν 3456, 1655, 1580, 1518, 1277 cm^{-1}; δ_H (DMSO d_6, 270 MHz) 9.31 (1H, s, OH), 9.08 (1H, s, OH), 8.8 (1H, s, OH), 8.31 (1H, t, NH, ^3J= 5.9 Hz), 7.25 (1H, d, $^3J^E$ = 15.4 Hz), 6.92–6.50 (6H, m), 6.36 (1H, d, $^3J^E$= 15.4 Hz), 4.25 (2H, d, ^3J= 5.9 Hz), 3.77 (3H, s, OCH_3). MS *m/z* (%) = 316 (MH^+, 8.8).

(E)-3,4-Dihydroxy-N-(2′-methylbenzyl)cinnamide (***E*-8e**): (70 mg, 55 %) m.p. 207–208 °C (Found: MH^+, 284.1287. $C_{17}H_{18}NO_3$ requires MH, 284.1287). (KBr)/cm^{-1} ν_{max} 3348, 1649, 1620, 1586, 1260; δ_H (DMSO d_6, 270 MHz) 9.31 (1H, s, OH), 9.07 (1H, s, OH), 8.28 (1H, t, NH, ^3J = 5.5 Hz), 7.26 (1H, d, $^3J^E$= 15.6 Hz), 7.71–6.22 (7H, m), 6.41 (1H, d, $^3J^E$= 15.6 Hz), 4.34 (2H, d, ^3J= 5.5 Hz), 2.27 (3H, s, CH_3); δ_C (DMSO d_6, 99.45 MHz) 165.8, 147.7, 146.0, 139.8, 137.5, 136.2, 130.4, 128.3, 127.4, 126.8, 126.2, 120.9, 118.7, 116.2, 114.3, 40.9, 19.0. MS *m/z* (%) 284 (MH^+, 28.3).

(E)-3,4-Dihydroxy-N-neopentylcinnamide (***E*-8f**): (79 mg, 74 %); colourless solid, m.p. 202–206 °C (Found MH^+, 250.1442. $C_{14}H_{20}NO_3$ requires MH, 250.1443). (KBr)/cm^{-1} ν_{max} 3338, 3194, 2954, 1648, 1613, 1569, 1528, 1250; δ_H (DMSO-d_6, 270 MHz) 9.29 (1H, s, OH), 9.05 (1H, s, OH), 7.81 (1H, t, NH, ^3J = 6.1 Hz), 7.21 (1H, d, $^3J^E$ = 15.4 Hz), 6.93 (1H, s), 6.82 (1H, d, ^3J= 8.2 Hz), 6.75 (1H, d, ^3J= 8.2 Hz), 6.44 (1H, d, $^3J^E$= 15.4 Hz), 2.98 (2H, d, ^3J= 6.1 Hz), 0.85 (9H, s, $C(CH_3)_3$); δ_C (DMSO d_6, 99.45 MHz) 166.04, 147.6, 145.9, 139.4, 127.0, 120.7, 119.3, 116.2, 114.3, 50.2, 32.5, 27.8; MS *m/z* (%) 250 (MH^+, 43.5).

*(E)-3,4-Dihydroxy-N-(3′-O-methyl-estra-1′,3′,5′(10′)-trien-3′-ol-17*β*′-yl)cinnamide* (***E*-8g**): (85 mg, 55%); colourless solid; m.p. 165–168 °C (Found MH^+, 448.2484. $C_{28}H_{34}O_4$ requires MH^+, 448.2488). (KBr)/cm^{-1} ν_{max} 3342, 2924, 1652, 1598, 1519, 1446, 1277, 1112; δ_H ($CDCl_3$, 270 MHz) 7.56 (1H, d, $^3J^E$ = 15.4 Hz), 7.13–7.19 (2H, m), 6.97 (1H, d, ^3J = 8.4 Hz), 6.84 (1H, d, ^3J = 8.1 Hz), 6.65 (1H, d, ^3J = 8.4 Hz), 6.58 (1H, s), 6.21 (1H, d, $^3J^E$ = 15.4 Hz), 5.58 (1H, d, NH, ^3J = 8.9 Hz), 4.07 (1H, m), 3.73 (3H, s, OCH_3), 2.81 (2H, m), 1.14–2.23 (13H, m), 0.73 (3H, s, CH_3); δ_C ($CDCl_3$, 99.45 MHz) 167.1, 157.4, 146.8, 144.3, 142.4, 137.8, 132.5, 127.1, 126.4, 119.9, 117.3, 116.2, 115.4, 113.8, 111.4, 59.5, 55.2, 51.6, 43.8, 43.7, 39.0, 29.8, 28.9, 27.3, 26.2, 2.41, 12.2. MS *m/z* (%) = 448 (MH^+, 13).

*(E)-3,4-Dihydroxy-N-(3′-hydroxyestra-1′,3′,5′(10′)-trien-3′-ol-17*β*′-yl)cinnamide* (***E*-8h**): (196 mg, 76%); colourless solid; m.p. 304–306 °C. (Found: MH^+, 434.2325 [FAB^+], $C_{27}H_{31}NO_4$ requires MH^+, 434.2331). (KBr)/cm^{-1} ν_{max} 3388, 2924, 1644, 1602, 1562, 1529, 1441, 1287, 1250; δ_H (DMSO-d_6, 270 MHz) 9.31 (1H, s, OH), 9.07 (1H, s, OH), 8.95 (1H, s, OH), 7.65 (1H, d, NH, ^3J = 8.3 Hz), 7.20 (1H, d, $^3J^E$ = 15.7 Hz), 7.02 (1H, d, ^3J = 8.4 Hz), 6.92 (1H, s), 6.82 (1H, d, ^3J = 8.4 Hz), 6.73 (1H, d, ^3J = 8.4 Hz), 6.48 (1H, d, ^3J = 8.4 Hz), 6.43 (1H, d, $^3J^E$ = 15.7 Hz), 6.42 (1H, s), 3.89 (1H, dd, ^3J = 8.3 Hz, ^3J = 8.3 Hz), 2.70 (2H, m), 1.22–2.22 (13H, m), 0.68 (3H, s, CH_3); MS *m/z* (%) = 434 (MH^+, 2).

(E)-3-Hydroxy-4-methoxy-N-nonylcinnamide (***E*-9a**): (62 mg, 70%); colourless solid; m.p. 107–111°C; (Found: MH^+, 320.2228 [FAB]. $C_{19}H_{30}NO_3$ requires MH, 320.2226). (KBr)/cm^{-1} ν_{max} 3290, 2920, 2852, 1656, 1600, 1557, 1264; δ_H (DMSO-d_6, 270 MHz) 9.12 (1H, s, OH), 7.93 (1H, *t*, NH, ^3J = 5.3 Hz), 7.23 (1H, d, $^3J^E$= 16.0 Hz), 6.92–6.95 (3H, m), 6.36 (1H, d, $^3J^E$= 16.0 Hz), 3.77 (3 H, s, OCH_3), 3.12 (2H, dd, ^3J = 5.3 Hz, ^3J = 5.3 Hz), 1.42–1.24 (14H, m), 0.84 (3H, t, ^3J = 6.2 Hz, CH_3); MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* (%) = 320 (MH^+, 100). (Found: C, 71.29; H, 9.05; N 4.35. $C_{19}H_{30}NO_3$ requires C, 71.44; H, 9.15; N, 4.38).

(E)-3-Hydroxy-4-methoxy-N-(2′-methoxybenzyl)cinnamide (***E*-9b**): (117 mg, 83%); colourless solid; m.p. 153–156°C; (Found: MH^+, 314.1395. $C_{18}H_{20}NO_4$ requires MH, 314.1392). (KBr)/cm^{-1} ν_{max} 3356, 2950, 2840, 1648, 1590, 1538, 1259, 1245; δ_H (DMSO d_6, 270 MHz) 9.14 (1H, s, OH), 8.28 (1H, *t*, NH, ^3J= 5.6 Hz), 7.29 (1H, d, $^3J^E$= 15.7 Hz), 7.21 (1H, d, ^3J= 8.0 Hz), 7.17 (1H, d, ^3J= 8.0 Hz), 6.86–6.99 (5H, m), 6.49 (1H, d, $^3J^E$= 15.7 Hz), 4.33 (2H, d, ^3J= 5.6Hz), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), δ_C (DMSO d_6, 99.45 MHz) 165.8, 157.2, 149.6, 147.1, 139.4, 128.6, 128.4, 127.2, 120.7, 120.6, 119.9, 113.8, 112.6, 111.0, 56.1, 55.8, 37.8; MS *m/z* (%) = 314 (MH^+, 26).

(E)-3-Hydroxy-4-methoxy-N-(4′-hydroxy-3′-methoxy-benzyl) cinnamide (***E*-9c**): (79 mg, 42%); colourless solid; m.p. 120–124 °C; (Found: MH^+, 330.1347 [FAB]. $C_{18}H_{20}NO_5$ requires MH, 330.1341). (KBr)/cm^{-1} ν 3388, 2936, 2836, 1654, 1604, 1513, 1438, 1212, 1270; δ_H (DMSO-d_6, 270 MHz) 9.14 (1H, s, OH), 8.80 (1H, s, OH), 8.34 (1H, d, NH, ^3J= 5.8 Hz), 7.29 (1H, d, $^3J^E$= 15.9 Hz), 6.95 (3H, m), 6.84 (1H, s), 6.65–6.73 (2H, m), 6.43 (1H, d, $^3J^E$= 15.9 Hz), 4.25 (2H, d, *J*= 5.8 Hz), 3.77 (3H, s, OCH_3), 3.73 (3H, s, OCH_3); δ_C (DMSO-d_6, 99.45 MHz) 163.9, 147.9, 146.0, 144.9, 142.2, 139.7, 126.8, 120.8, 120.4, 118.9, 116.2, 115.7, 115.3, 114.3, 112.4, 56.0 (2C, OCH_3), 42.6 (NCH_2); MS *m/z* (%) = 330 (MH^+, 7).

(E)-3-Hydroxy-4-methoxy-N-(2′-methylbenzyl)cinnamide (***E*-9d**): (148 mg, 99%); colourless solid; m.p. 139–141 °C; (Found MH^+, 298.1441, $C_{18}H_{20}NO_3$ requires MH, 298.1443). (KBr)/cm^{-1} ν_{max} 3344, 1641, 1572, 1530, 1433, 1263; δ_H (DMSO d_6, 270 MHz) 9.14 (1H, s, OH), 8.32 (1H, t, NH, ^3J= 5.6 Hz), 7.3 (1H, d, $^3J^E$= 15.8 Hz), 7.21–6.90 (7H, m), 6.46 (1H, d, $^3J^E$= 15.8 Hz), 4.34 (2H, d, ^3J= 5.6 Hz), 3.78 (3H, s, OCH_3), 2.27 (3H, s, CH_3); MS *m/z* (%) = 298 (MH^+, 100).

*(E)-3-Hydroxy-4-methoxy-N-(3′-O-methyl-estra-1′,3′,5′(10′)-trien-3′-ol-17*β*′-yl)cinnamide* (***E*-9e**) (110 mg, 90%); colourless solid; m.p. 110–112 °C; (Found: MH^+, 462.2646 [FAB]; $C_{29}H_{36}NO_4$ requires MH, 462.2644). (KBr)/cm^{-1} ν 3356, 2924, 2868, 1659, 1611, 1511, 1439, 1267, 1209; δ_H NMR ($CDCl_3$, 270 MHz) 7.49 (1H, d, $^3J^E$= 15.5 Hz), 7.16 (1H, d, ^3J= 8.4 Hz), 7.08 (1H, d, ^4J = 2.1 Hz), 6.96 (1H, dd, ^3J= 8.4 Hz, ^4J = 2.1 Hz), 6.79 (1H, d, ^3J= 8.4 Hz), 6.67 (1H, dd, ^3J= 8.4 Hz, ^4J = 2.7 Hz), 6.62 (1H, d, ^4J = 2.7 Hz), 6.21 (1H, d, $^3J^E$= 15.5 Hz), 5.58 (1H, s, OH), 5.39 (1H, d, ^3J = 9.2 Hz, NH), 4.08–4.11 (1H, m), 3.88 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 2.81 (2H, m), 2.16–2.27 (2H, m), 1.65–1.80 (2H, m), 0.81–1.52 (9H, m), 0.73 (3H, s, CH_3); δ_C ($CDCl_3$, 99.45 MHz) 166.1, 157.4, 148.0, 145.8, 140.8, 137.9, 128.5, 126.4, 121.5, 118.9, 113.8, 112.5, 111.4, 110.5, 59.0, 56.0, 55.2, 51.7, 43.8, 43.7, 39.0, 37.0, 29.8, 28.9, 27.4, 26.3, 23.4, 14.1, 12.2; MS *m/z* (%) = 462 (MH^+, 10).

*(E)-3-Hydroxy-4-methoxy-N-(3′-hydroxyestra-1′,3′,5′(10′)-trien-3′-ol-17*β*′-yl)cinnamide* (***E*-9f**): (105 mg, 85%); colourless solid; m.p. 161–164 °C; (Found: MH^+, 448.2491 [FAB^+]. $C_{28}H_{34}NO_4$ requires MH, 448.2488). (KBr)/cm^{-1} ν 3442, 2924, 1655, 1609, 1510, 1440, 1267; δ_H ($CDCl_3$, 270 MHz) 7.48 (1H, d, $^3J^E$= 15.4 Hz), 7.09 (1H, d, ^3J= 8.4 Hz), 7.07 (1H, d, ^4J= 1.9 Hz), 6.95 (1H, dd, ^4J= 1.9 Hz, ^3J= 8.1 Hz), 6.78 (1H, d, ^3J= 8.1 Hz), 6.56 (1H, dd, ^4J= 2.7 Hz, ^3J= 8.4 Hz), 6.51 (1H, d, ^4J= 2.7 Hz), 6.19 (1H, d, $^3J^E$= 15.4 Hz), 5.55 (1H, s, OH), 5.36 (1H, d, NH, ^3J= 8.4 Hz), 4.51 (1H, s, OH), 4.07–4.10 (1H, m), 3.87 (3H, s, OCH_3), 2.77 (2H, m), 2.12–2.20 (2H, m), 1.79–1.84 (2H, m), 0.80–1.49 (9H, m), 0.72 (3H, s, CH_3); MS *m/z* (%) = 448 (25), 282 (92).

(E)-3-Hydroxy-4-methoxy-N-(phenyl)cinnamide (***E*-9g**): (121 mg, 76%), colourless solid; m.p. 225-227 °C; (Found: MH^+, 270.1126 [FAB], $C_{16}H_{16}NO_3$ requires MH, 270.1130). (KBr)/cm^{-1} ν_{max} 3326, 1671, 1606, 1550, 1270; δ_H (DMSO-d_6, 270 MHz) 10.0 (*s*, 1H, NH), 9.20 (*s*, 1H, OH), 7.67 (*d*, 1H, ^3J= 8.1 Hz), 7.42 (*d*, 1H, $^3J^E$= 15.4 Hz), 7.33–6.94 (*m*, 7H), 6.59 (*d*, 1H, J^E= 15.4 Hz), 3.79 (*s*, 3H); ^{13}C NMR (DMSO d_6, 99.45 MHz) δ_C 164.3, 150.0, 147.2, 140.8, 139.9, 129.2, 129.1, 128.0, 123.6, 121.1, 119.9, 119.6, 113.9, 112.6, 56.1; MS *m/z* (%) 270 (MH^+, 36).

(E)-4-Hydroxy-3-methoxy-N-nonylcinnamide (***E*-10a**): (77 mg, 58%) colourless oil; (Found: MH$^+$, 320.2228 [FAB]; $C_{19}H_{30}O_3N$ requires MH, 320.2226). (neat)/cm^{-1} (NaCl) ν_{max} 3290, 2924, 2854, 1654, 1589, 1514, 1272; δ_H (DMSO-d_6, 270 MHz) 9.36 (1H, s), 7.88 (1H, t, ^3J= 5.5 Hz), 7.28 (1H, d, $^3J^E$= 15.8 Hz), 7.09 (1H, d, ^4J= 1.6 Hz), 6.96 (1H, dd, ^4J= 1.6 Hz ^3J= 8.2 Hz), 6.77 (1H, d, ^3J= 8.2 Hz), 6.41 (1H, d, $^3J^E$= 15.8 Hz), 3.79 (3H, s, OCH_3), 3.09–3.16 (2H, m), 1.24–1.42 (14 H, m), 0.84 (3H, t, ^3J= 6.6 Hz); MS *m/z* (%) = 320 (MH$^+$, 55).

(E)-4-Hydroxy-3-methoxy-N-(2'-methoxybenzyl)cinnamide (***E*-10b**): (101 mg, 78%) colourless solid; m.p. 127–130 °C; (Found: M$^+$, 313.1310; $C_{18}H_{19}NO_4$ requires M, 313.1314). (KBr)/cm^{-1} ν_{max} 3282, 2936, 2836, 1655, 1598, 1510, 1246, 1160; δ_H (DMSO-d_6, 270 MHz) 9.39 (1H, s), 8.22 (1H, t, ^3J= 5.8 Hz), 7.33 (1H, d, $^3J^E$= 15.8 Hz), 7.16 (3H, m), 7.11 (1H, s), 6.97 (1H, d, ^3J= 8.0 Hz), 6.87–6.92 (1H, m), 6.77 (1H, d, ^3J= 8.0 Hz), 6.54 (1H, d, $^3J^E$= 15.8 Hz), 4.33 (2H, d, ^3J= 5.8 Hz), 3.80 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); MS (70 eV) *m/z* (%) = 313 (M$^+$, 31).

(E)-4-Hydroxy-3-methoxy-N-(2'-methylbenzyl)cinnamide (***E*-10c**): (91 mg, 54%) colourless solid**;** m.p. 182–184 °C; (Found: M$^+$, 297.1364. $C_{18}H_{19}NO_3$ requires M, 297.1365). (KBr)/cm^{-1} ν 3496, 3244, 2932, 1653, 1612, 1545, 1508, 1263, 1209; δ_H (DMSO-d_6, 270 MHz) 9.40 (1H, s), 8.29 (1H, t, ^3J= 5.6 Hz), 7.36 (1H, d, $^3J^E$= 15.8 Hz), 7.11–7.23 (4H, m), 7.06 (1H, d, ^4J= 1.6 Hz), 6.99 (1H, dd, ^4J= 1.6, Hz, ^3J= 8.4 Hz), 6.77 (1H, d, ^3J= 8.4 Hz), 6.53 (1H, d, $^3J^E$= 15.8 Hz), 4.36 (2H, d, ^3J= 5.6 Hz), 3.79 (3H, s, OCH_3), 2.29 (3H, s, CH_3); MS (EI, 70 eV) *m/z* (%) = 297 (M$^+$, 12).

*(E)-4-Hydroxy-3-methoxy-N-(3'-O-methyl-estra-1',3',5'(10')-trien-3'-ol-17*β*'-yl)cinnamide* (***E*-10d**): (138 mg, 85%), colourless solid; m.p. 118–121 °C; (Found: MH$^+$, 462.2650 [FAB], $C_{29}H_{36}NO_4$ requires, MH, 462.2644). IR (KBr)/cm^{-1} ν_{max} 3418, 2924, 1656, 1609, 1516, 1270, 1253; δ_H ($CDCl_3$, 270 MHz) 7.51 (1H, d, $^3J^E$= 15.4 Hz), 7.16 (1H, d, ^3J= 8.4 Hz), 7.30 (1H, d, ^3J= 8.1 Hz), 6.96 (1H, s), 6.87 (1H, d, ^3J= 8.1 Hz), 6.67 (1H, d, ^3J= 8.4 Hz), 6.59 (1H, s), 6.22 (1H, d, $^3J^E$= 15.4 Hz), 5.75 (1H, s), 5.31 (1H, d, ^3J= 9.2 Hz), 4.09–4.15 (1H, m), 3.88 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 2.81 (2H, m), 2.21–2.28 (2H, m), 1.81–1.85 (2H, m), 0.81–1.52 (9H, m), 0.74 (3H, s, CH_3); MS *m/z* (%) = 462 (MH$^+$, 12).

*(E)-4-Hydroxy-3-methoxy-N-(3'-hydroxy-estra-1',3',5'(10')-trien-3'-ol-17*β*'-yl)cinnamide* (***E*-10e**): (72 mg, 58%); colourless solid; m.p. 176–178 °C; (Found: M$^+$ 448.2484. $C_{28}H_{34}NO_4$ requires M, 448.2488). ν_{max} (KBr)/cm^{-1} 3354, 2926, 2862, 1653, 1595, 1517, 1283, 1253; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 9.37 (*s*, 1H, OH), 8.95 (*s*, 1H, OH), 7.65 (*d*, 1H, NH, *J* = 7.8 Hz), 7.28 (*d*, 1H, $^3J^E$ = 15.7 Hz), 7.10 (*s*, 1H), 7.02 (*d*, 1H, ^3J=8.4 Hz)**,** 6.96 (*d*, 1H, ^3J= 8.1 Hz), 6.85 (*d*, 1H, ^3J= 8.1 Hz), 6.54 (*d*, 1H, $^3J^E$= 15.7 Hz), 6.49 (*d*, 1H, ^3J= 8.4 Hz), 6.43 (*s*, 1H), 3.85–3.95 (*m*, 1H), 3.80 (*s*, 3H, OCH_3), 2.71 (*m*, 2H), 2.14–2.23 (m, 13H), 0.69 (s, 3H, CH_3); MS *m/z* (%) = 448 (MH$^+$, 16.5), 73 (100).

In a pyrex glass tube (4.22 mm inner diameter, wall thickness 0.37 mm), a sample of ***E*-9d** (9.1 mg, 0.9 ml, 34 mmol/l) in DMSO-d^6 was prepared and photoirradiated at room temperature with a 1KW Rikagaku mercury high pressure lamp. The sample was monitored by ^{1}H NMR spectroscopy after 10 min, 20 min, 50 min, and 110 min. After 110 min, the sample consisted of a mixture of ***E*-9d** (56.2%) and ***Z*-9d** (43.8%); δ_H (DMSO-d_6, 270 MHz) 8.90 (*s*, 1H, OH), 8.39 (1H, t, NH, *J*= 5.7 Hz), 7.36 (1H, d, ^4J= 2.2 Hz), 6.95–7.23 (5H, m), 6.82 (1H, d, ^3J= 8.4 Hz), 6.49 (1H, d, $^3J^Z$= 12.7 Hz), 5.88 (1H, d, $^3J^Z$ = 12.7 Hz), 4.30 (2H, d, *J*= 5.7 Hz), 3.76 (3H, s, OCH_3), 2.28 (3H, s, CH_3).

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