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Synthesis and biological evaluation of novel tamoxifen analogues

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ABSTRACT

A collection of compounds, structurally related to the anticancer drug tamoxifen, used in breast cancer therapy, were designed and synthesized as potential anticancer agents. McMurry coupling reaction was used as the key synthetic step in the preparation of these analogues and the structural assignment of *E*, *Z* isomers was determined on the basis of 2D-NOESY experiments. The compounds were evaluated for their antiproliferative activity on breast cancer (MCF-7), cervix adenocarcinoma (HeLa) and biphasic mesothelioma (MSTO-211H) human tumor cell lines. The estrogen like properties of the novel compounds were compared with those of the untreated controls using an estrogen responsive element-based (ERE) luciferase reporter assay and compared to 17β-estradiol (E2). Finally, with the aim to correlate the antiproliferative activity with an intracellular target(s), the effect on relaxation activity of DNA topoisomerases I and II was assayed.

1. Introduction

Tamoxifen (**1**, Fig. 1) is a triarylethylene compound that has been widely used in the treatment of breast cancer.[1,2] In addition to acute cancer therapy, tamoxifen is used as a preventative treatment[3] for high risk women as well as in long-term adjuvant therapy.[4] However, the use of tamoxifen has also been associated with increased risk of endometrial[5,6] and uterine[7] cancers as well as increased possibility of suffering a pulmonary embolism, stroke, or deep vein thrombosis.[8] Tamoxifen is converted to the active metabolite 4-hydroxytamoxifen (**2**, Fig. 1) which acts primarily through inhibition of the estrogen receptor transcriptional activity.[9] Furthermore, other mechanisms have been documented which may or may not be estrogen receptor dependent[10] and include induction of apoptosis,[11] interference with the insulin-like growth factor I receptor,[12] and suppression of telomerase activity by inhibition of protein kinase C.[13]

As a follow-up to our interest in the synthesis of anticancer compounds,[14] we describe in the present study, the synthesis of novel tamoxifen derivatives (Fig. 1) via McMurry reaction coupling.[15] The novel derivatives (Fig. 1), maintain the triarylethylene skeleton of tamoxifen, bearing OH groups in position 4 of the phenyl moieties of tamoxifen and substitute the side chain of tamoxifen with an amide side chain. The in vitro antiproliferative activity of these compounds was evaluated against three human tumor cell lines, MCF-7 (breast cancer), HeLa (cervix adenocarcinoma) and MSTO-211H (biphasic mesothelioma). Furthermore, we evaluated the estrogen like properties of the novel compounds using an ERE luciferase assay in HC11 cells (mouse mammary epithelial cells). The ERE luciferase reporter construct which is stably integrated into these cells harbors a transgene composed of 3 consensus ERE driving the expression of firefly luciferase protein, which allows the detection of estrogen activity by light produced by the luciferase enzyme. Finally, the effect on topoisomerases I and II was assayed to determine the potential intracellular target(s).

2. Results and discussion

2.1. Chemistry

The synthesis of the crucial keto-amides **6** is outlined in Scheme 1. Specifically, various *N*-(4-bromophenyl)amides (**4**), were reacted with 4-(benzyloxy)benzaldehyde (**3**) to produce the hydroxy-amides (**5**) from moderate to good yields (25–55%).

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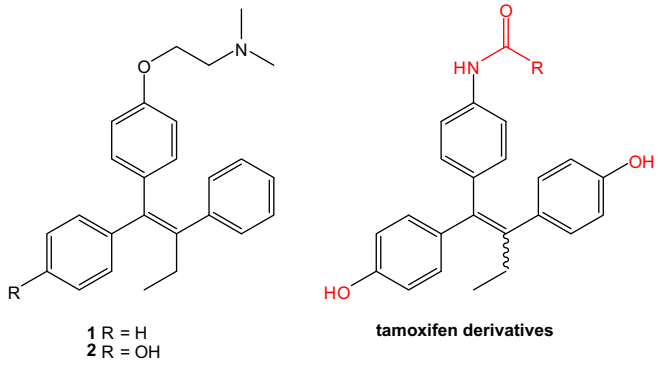


Figure 1. Structures of tamoxifen (**1**), 4-hydroxytamoxifen (**2**) and novel tamoxifen derivatives.

Oxidation of hydroxy-amides **5**, in the presence of Jones reagent, furnished the corresponding keto-amides **6**, in almost quantitative yields (90–95%).

Subsequently, keto-amides **6**, were treated under McMurry olefination conditions with 1-(4′-(benzyloxy)phenyl)propan-1-one (Scheme 2), to provide a mixture of *E*/*Z* isomers (**7** and **8**) in 1:1 ratio, that were separated by flash column chromatography in good yields (50–65%). Finally, deprotection of compounds **7** and **8** with BBr_3 at −78 °C (Scheme 2), afforded the target tamoxifen derivatives **9** and **10** in quantitative yields (90–95%).

The stereochemical assignments of the *E*, *Z* isomers were determined on the basis of 2D-NOESY experiments. For example the stereochemistry of compound **7d** (Scheme 2) was determined on its 2D-NOESY spectrum (Supplementary data), obtained at 400 MHz. The CH_2CH_3 protons at 2.50 ppm demonstrate NOE cross peaks with the proton at 7.07 ppm (H-2‴′) and the CH_2CH_3 protons at 0.96 ppm with the proton at 7.17 ppm (H-2‴). These NOE data establish the stereochemical assignment of compound **7d** to be in the *E* configuration. Similarly, the stereochemistry of compound **8d** was determined to be in the *Z* configuration based on its 2D-NOESY spectrum (Supplementary data), obtained at 400 MHz. The CH_2CH_3 protons at 0.94 ppm demonstrate NOE cross peaks with the proton at 7.17 ppm (H-3′) and the CH_2CH_3 protons at 2.48 ppm with the proton at 7.06 ppm (H-2‴′). A similar strategy using 2D-NOESY data was employed for the stereochemical assignment of compounds **7** and **8**.

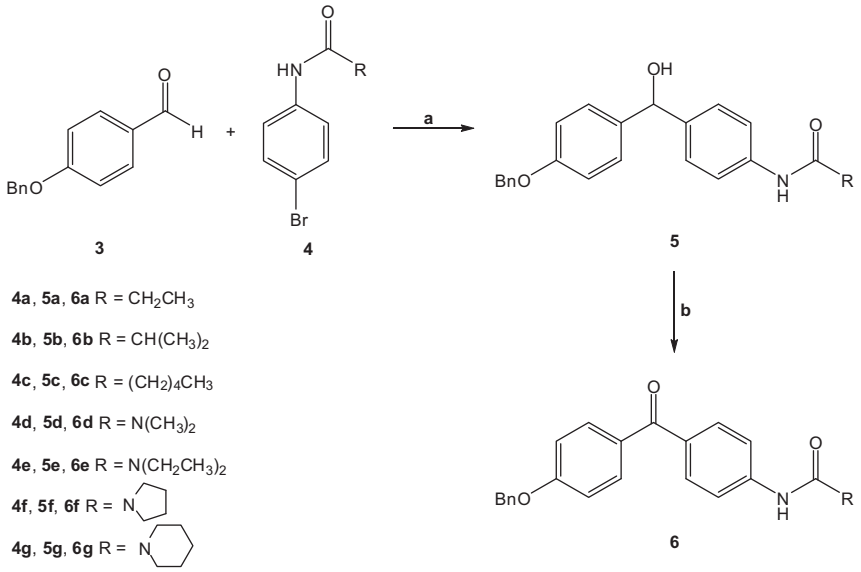
2.2. Antiproliferative activity

The solubility of compounds **9** and **10** has been evaluated theoretically by *c*log*P*[16] and have been compared to tamoxifen and 4-hydroxytamoxifen (Table 1). The theoretical calculations for the new compounds, showed values that are generally lower than that of tamoxifen, which indicates that compounds **9** and **10** present a reduced lipophilicity.

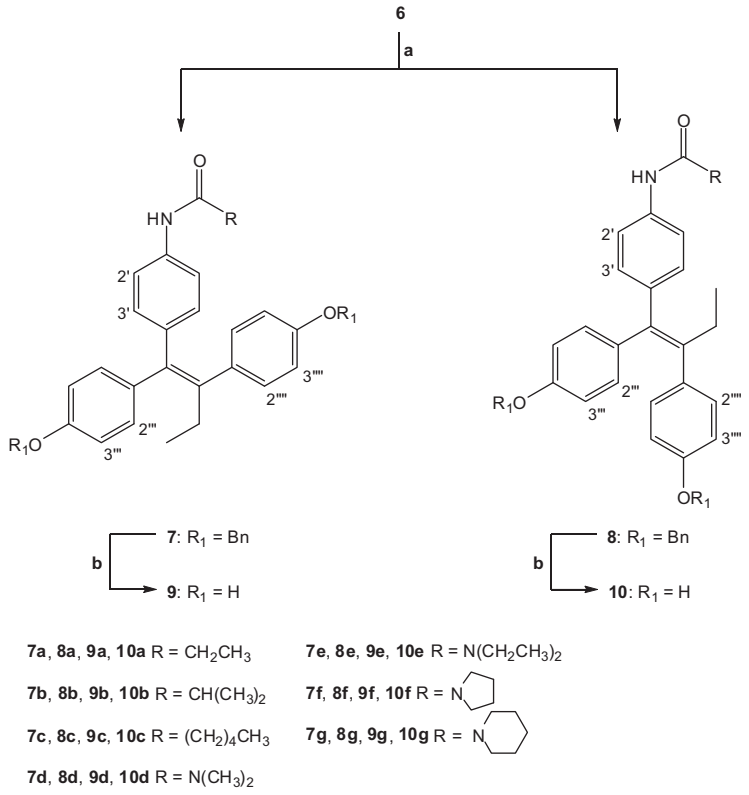
The novel compounds were evaluated by an in vitro assay performed on three human cancer cell lines comprised of breast cancer (MCF-7), which is known to overexpress the estrogen receptor,[17] cervix adenocarcinoma (HeLa) and biphasic mesothelioma (MSTO-211H), using tamoxifen and 4-hydroxytamoxifen as reference compounds. The results, expressed as GI_{50} values, are shown in Table 1.

As regard the estrogen sensitive MCF-7 cells, the obtained results highlighted for the compounds carrying in R a branched group (**b**, **d** and **e** series) or the piperidine (**9g** and **10g**) an antiproliferative activity comparable or even higher with respect to that of tamoxifen (Scheme 2). In particular, the most active compound is **10b** that shows an antiproliferative activity about 4 times higher with respect to the reference drug. Nevertheless, the comparison with 4-hydroxytamoxifen underlined for all new derivatives a significantly lower cytotoxicity. In this connection, it seems that the addition of a further 4-hydroxyl group in the triarylethylene moiety could play a crucial role in the occurrence of cytotoxic effect. As regard the compounds characterized in R by a linear substituent (**a** and **c** series) or by a pyrrolidine (**9f** and **10f**), they are practically ineffective. Moreover, taking into consideration the stereochemistry, *Z* isomers seem generally slightly more active toward MCF-7 cells, showing GI_{50} values from 1.8 (compounds **d**) to 3.6 times (compounds **g**) lower with respect to *E* isomers.

The investigation of the antiproliferative effect on two estrogen-independent human tumor cell lines, HeLa and MSTO-211H, shows, as expected, a significant decrease of the sensitivity toward tamoxifen. In contrast, for the novel derivatives the GI_{50} values obtained for HeLa and MSTO-211H remain practically unchanged with respect to those obtained for MCF-7, with the exception of **10b**. Indeed, interestingly, for this latter compound a decrease in



Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF, −50 °C, 2 h; (b) Jones reagent, acetone, 0 °C, 30 min.



Scheme 2. Reagents and conditions: (a) Zn, $TiCl_4$, 1-(4′-(benzyloxy)phenyl)propan-1-one, THF, −10 °C to reflux, 5 h; (b) BBr_3, DCM, −78 °C, 1 h.

Table 1
Cell growth inhibition in the presence of examined compounds

Compound	Cell lines GI_{50}[a] (μM)			$c\log P$[b]
	MCF-7	HeLa	MSTO-211H	
9a	>20	14.1 ± 1.6	12.3 ± 0.3	5.076
10a	>20	17.1 ± 1.1	15.5 ± 1.5	5.076
9b	6.7 ± 1.5	6.7 ± 1.6	10.9 ± 1.3	5.320
10b	2.9 ± 0.4	7.4 ± 1.4	8.4 ± 1.3	5.320
9c	>20	29.9 ± 1.6	18.1 ± 3.4	6.646
10c	>20	27.2 ± 1.2	16.6 ± 1.4	6.646
9d	17.9 ± 1.1	15.2 ± 3.2	17.8 ± 3.2	4.382
10d	9.9 ± 3.4	8.0 ± 0.8	8.7 ± 0.8	4.382
9e	9.1 ± 1.3	9.1 ± 1.8	8.3 ± 1.1	5.524
10e	11.2 ± 1.4	10.7 ± 2.5	8.3 ± 0.3	5.524
9f	>20	26.7 ± 0.9	>30	5.175
10f	⩾20	22.4 ± 3.9	18.5 ± 0.7	5.175
9g	16.5 ± 1.2	15.4 ± 3.1	9.1 ± 1.3	5.680
10g	4.5 ± 1.1	8.2 ± 1.5	2.3 ± 1.2	5.680
Tamoxifen	12.0 ± 1.6	32.6 ± 2.1	23.3 ± 2.5	6.064
4-OH Tamoxifen	0.107 ± 0.081[c]	nd	nd	5.585

[a] Values are the mean ± SD of at least three independent experiments.
[b] $c\log P$ = calculated octanol–water partition coefficient.
[c] Taken from Ref. 18.

cytotoxic effect of 2.5 and 2.8 times is observed in HeLa and MSTO-211H, respectively.

2.3. Estrogen like properties of the compounds

To assess the estrogenic activities of selected compounds, we used HC11 (mouse mammary epithelial cell line) with an integrated 3×ERE-Luciferase construct in their genome.[19] Luciferase activation, measured as amount of emitted light in the luciferase assay, is proportional to the activation of gene transcription by ERs and is, therefore, considered a measurement of classical genomic estrogen receptor response to agonists or antagonists. To determine if the novel compounds were estrogenic, HC11 cells were treated with E2 (10 nM, = 100%) in addition to 1 μM concentration of the tested compounds (Fig. 2). Overall, compounds **9a**, **9b**, **10e**, and **9f** displayed agonist activity (108%, 96%, 80% and 73% respectively), same as E2, with compound **9a** to be the most potent. Compound **9g** showed reduced agonistic activity (51% activation compared to estradiol), while compounds **10b**, **9d**, **9e**, **10f**, and **10g** (18%, 25%, 27%, 20% and 15% respectively) were not able to activate reporter gene expression.

2.4. Effect on topoisomerase relaxation activity

In a previous paper it was demonstrated the ability of tamoxifen to inhibit the relaxation activity of topoisomerases I and II.[20] In this connection, and with the aim to establish the possible molecular target(s) accountable for the cytotoxicity of the new derivatives, we investigate their effect on the catalytic activity of both topoisomerase I and II. Figure 3A shows the effect of some representative compounds (**9b**, **10b**, **10d**, **9e**, **10g** and **9a**) on the relaxation of plasmid pBR322 DNA, mediated by topoisomerase II. The supercoiled DNA (DNA) was converted into relaxed forms by the enzyme (topo II). At 50 μM concentration both **9b** and **10b** exert a partial inhibitory effect, as demonstrated by the appearance of supercoiled DNA and by the concurrent decrease in relaxed products, while the other compounds do not affect the enzymatic activity. Nevertheless, by increasing the concentration up to 100 μM (Fig. 3B), a complete inhibition is observed for all the derivatives, apart from **9a**. Indeed in this latter experimental condition, **9a** induces a significant, but only partial effect on topoisomerase II relaxation. Taking into account that **9a** exerts the lower antiproliferative capacity, these data could suggest the contribution of the inhibition on topoisomerase II to the cytotoxicity. Otherwise, experiments performed with topoisomerase

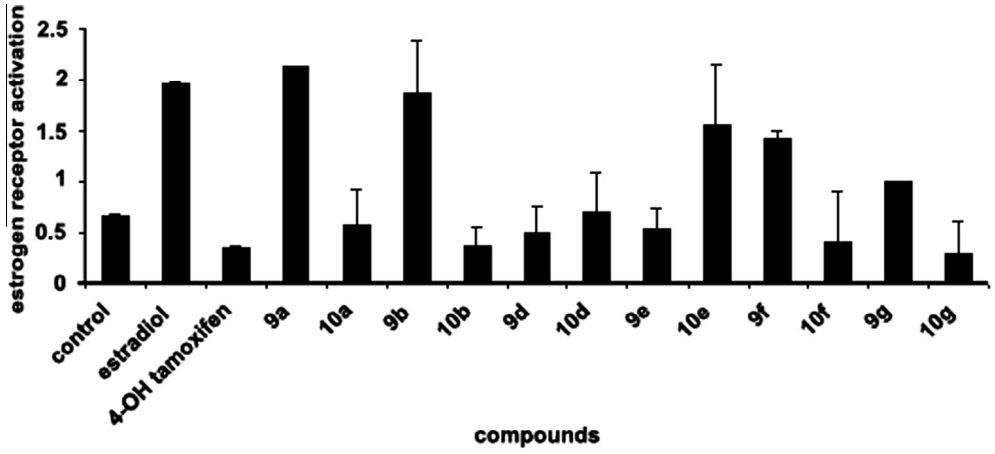


Figure 2. Activity of selective compounds in HC11 cell line. HC11 cells stably transfected with 3×ERE–Luc construct were seeded in 24-well plates and after the cells reached 50–60% confluence, were treated with 1 μM (final) tested compounds, 10 nM E2 or ethanol (control). After 24 h the percentage of estrogen activity was determined (see experimental part). Data are presented as % to one of the arbitrary selected compounds of three independent experiments, performed in duplicates.

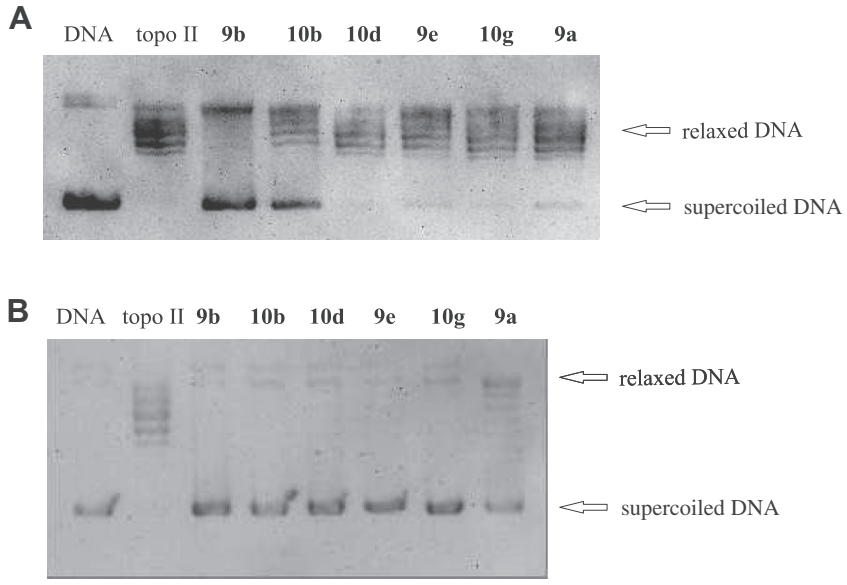


Figure 3. Effect on topoisomerase II-mediated DNA relaxation. Supercoiled pBR322 DNA (DNA) was incubated with topoisomerase II in the absence (topo II) and presence of indicated compounds at 50 μM (A) or 100 μM (B) concentration.

I highlighted the inability of all derivatives to affect the enzymatic activity, even at the higher tested concentration (100 μM, data not shown).

3. Conclusions

The synthesis through McMurry coupling reaction of some derivatives structurally related to the well known anti-estrogen anticancer drug tamoxifen, clinically used to treat breast cancer, is described. The investigation of the antiproliferative effect on human breast cancer cell line MCF-7 showed for some derivatives an interesting cytotoxic activity, in some cases significantly higher with respect to that obtained for tamoxifen. Nevertheless, in most cases a comparable effect is obtained also on two estrogen independent human tumor cell lines, HeLa (cervix adenocarcinoma) and MSTO-211H (biphasic mesothelioma), thus suggesting the ability to exert the antiproliferative effect through a mechanism of action independent from the estrogen receptor. These results could be also in agreement with the difference in cytotoxicity between the new derivatives and 4-hydroxytamoxifen that acts primarily through inhibition of the estrogen receptor transcriptional activity. Indeed, the study on the molecular mechanism responsible for cytotoxicity highlighted the ability of compounds to inhibit relaxation activity mediated by topoisomerase II, thus suggesting the nuclear enzyme as a potential intracellular target.

Among the novel derivatives, **10b** appears as the most interesting. Indeed, this compound induces the highest antiproliferative effect on MCF-7 cells, about 4 times higher with respect to the reference drug. In addition, both HeLa and MSTO-211H cell lines show a significant less sensitivity toward **10b**. On the whole, these properties render this new triarylethylene-based compound a lead structure that deserves to be further studied to obtain more specific drugs for the treatment of breast cancer.

4. Experimental section

4.1. General experimental conditions

All reactions were carried out in oven-dried glassware under argon atmosphere. All starting materials were purchased from

Aldrich, while the solvents used were purified by distillation prior to use. Solvent mixtures employed in chromatography were reported as volume to volume ratios. Thin layer chromatography (TLC) was performed on Merck precoated aluminium sheets of Silica Gel 60 F_{254}, visualization of products being accomplished by UV absorbance at 254 nm and by an alcohol solution of anisaldehyde with heating. Flash column chromatography was performed on a SDS silica gel (35–70 μm). All tested compounds possessed a purity of >98% confirmed via elemental analyses (CHN). Melting points were determined on a Stuart apparatus (SMP3) and are uncorrected. IR spectra were recorded on a Thermo electron corporation Nicolet 6700 FT-IR spectrometer using CH_2Cl_2 in ZnSe round windows. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600, 400, and 100, 50 MHz respectively on Bruker DRX-600, DRX-400 and DRX-200 spectrometers in the indicated solvents. Chemical shifts (δ) for proton and carbon resonances are quoted in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as an internal standard. MS spectra were recorded using electrospray ionization (ESI) technique on a Thermo Accela LC TSQ Quantum Access MS–MS spectometer.

4.2. Synthesis

4.2.1. General procedure for the synthesis of analogues 5

4.2.1.1. Synthesis of *N*-(4-((4′(benzyloxy)phenyl)(hydroxy)-methyl)phenyl) propionamide (5a). To a cold at −50 °C solution of amide **4a** (1.2 g, 5.2 mmol) in THF (60 mL), *n*-BuLi (9.7 mL, 1.6 M in hexane, 16 mmol) was added dropwise and the new solution was stirred for 10 min at the same temperature. Then, a solution of 4-(benzyloxy)benzaldehyde (**3**) (1.0 g, 4.7 mmol) in THF (10 mL) was added and the resulted solution was stirred for another 2 h at −50 °C. After the completion of the reaction, the solvent was evaporated in vacuum, EtOAc was added and the organic layer was washed with 5% NH_4Cl, water and brine, dried with Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (Hex/EtOAc 1:1) to provide hydroxy-amide **5a** as oil (40% yield). R_f = 0.26 (Hex/EtOAc 1:1); IR (film) ν: 1665, 1013 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 9.06 (1H, s, N*H*), 7.60 (2H, d, *J* 8.4 Hz, H-2), 7.47 (2H, d, *J* 7.2 Hz, H-2′), 7.39 (1H, t, *J* 8.0 Hz, Ph*H*-para), 7.37–7.30 (6H, m, Ph*H*-ortho, Ph*H*-meta and H-3), 6.96 (2H, d, *J* 7.2 Hz, H-3′), 5.75 (1H, d, *J* 3.6 Hz, C*H*OH), 5.01 (2H, s, CH_2O), 4.71 (1H, s, O*H*), 2.35 (2H, q, *J* 7.6 Hz, CH_2CH$_3$), 1.12 (3H, t, *J* 7.6 Hz, CH$_2$CH_3); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 171.6 (NHCO), 157.9 (C-4′), 140.5 (C-4), 138.4 (C-1), 138.2 (PhCCH$_2$O), 137.6 (C-1′), 128.4 (C-2′), 127.6 (Ph*C*-meta and Ph*C*-para), 127.4 (Ph*C*-ortho), 126.7 (C-3), 118.8 (C-2), 114.3 (C-3′), 74.5 (CHOH), 69.5 (Ph-*C*H$_2$O), 28.5 (*C*H$_2$CH$_3$), 9.0 (CH$_2$*C*H$_3$); MS: 362.47 (M+H$^+$), 384.48 (M+Na$^+$).

4.2.1.2. Synthesis of *N*-(4-((4′-(benzyloxy)phenyl)(hydroxy)-methyl)phenyl) isobutyramide (5b). According to the general procedure, hydroxy-amide **5b** was obtained from amide **4b** after purification by flash column chromatography (Hex/EtOAc 6:4) and evaporation of the solvent as oil (25% yield). R_f = 0.19 (Hex/EtOAc 6:4); IR (film) ν: 1663, 1019 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 9.03 (1H, s, N*H*), 7.61 (2H, d, *J* 8.4 Hz, H-2), 7.47 (2H, d, *J* 7.2 Hz, H-2′), 7.39 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.37–7.30 (6H, m, Ph*H*-ortho, Ph*H*-meta and H-3), 6.96 (2H, d, *J* 7.2 Hz, H-3′), 5.74 (1H, s, C*H*OH), 5.10 (2H, s, CH_2O), 4.71 (1H, s, O*H*), 2.60 (1H, m, C*H*(CH$_3$)$_2$), 1.15 (6H, d, *J* 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 174.9 (NHCO), 157.8 (C-4′), 138.4 (C-4), 138.2 (C-1), 137.6 (PhCCH$_2$O), 128.4 (C-2′), 127.6 (Ph*C*-meta and Ph*C*-para), 127.5 (Ph*C*-ortho), 126.6 (C-3), 120.9 (C-1′), 118.9 (C-2), 114.3 (C-3′), 74.5 (CHOH), 69.5 (Ph-*C*H$_2$O), 35.7 (*C*H(CH$_3$)$_2$), 19.0 (CH(*C*H$_3$)$_2$); MS: 376.37 (M+H$^+$), 398.37 (M+Na$^+$).

4.2.1.3. Synthesis of *N*-(4-((4′-(benzyloxy)phenyl)(hydroxy)-methyl)phenyl) hexanamide (5c). According to the general procedure, hydroxy-amide **5c** was obtained from amide **4c** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (30% yield). R_f = 0.22 (Hex/EtOAc 1:1); IR (film) ν: 1655, 1021 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 9.08 (1H, s, N*H*), 7.60 (2H, d, *J* 8.4 Hz, H-2), 7.47 (2H, d, *J* 7.2 Hz, H-2′), 7.39 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.37–7.30 (6H, m, Ph*H*-ortho, Ph*H*-meta and H-3), 6.96 (2H, d, *J* 7.2 Hz, H-3′), 5.74 (1H, d, *J* 4.0 Hz, C*H*OH), 5.10 (2H, s, CH_2O), 4.70 (1H, d, *J* 4.0 Hz, O*H*), 2.34 (2H, t, *J* 7.2 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.67 (2H, m, CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.33 (4H, m, CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.90 (3H, t, *J* 7.2 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 170.2 (NHCO), 157.8 (C-4′), 138.4 (C-4), 138.2 (C-1), 137.6 (PhCCH$_2$O), 128.4 (C-2′), 127.6 (Ph*C*-meta and Ph*C*-para), 127.4 (Ph*C*-ortho), 126.6 (C-3), 120.8 (C-1′), 118.8 (C-2), 114.3 (C-3′), 74.5 (CHOH), 69.5 (Ph-*C*H$_2$O), 36.8 (*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.3 (CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_3$), 25.1 (CH$_2$CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.2 (CH$_2$CH$_2$CH$_2$*C*H$_2$CH$_3$), 13.34 (CH$_2$CH$_2$CH$_2$CH$_2$*C*H$_3$); MS: 404.57 (M+H$^+$), 426.68 (M+Na$^+$).

4.2.1.4. Synthesis of 3-(4′-((4″-(benzyloxy)phenyl)(hydroxy)-methyl)phenyl)-1,1-dimethylurea (5d). According to the general procedure, hydroxy-amide **5d** was obtained from amide **4d** after purification by flash column chromatography (Hex/EtOAc 1:9) and evaporation of the solvent as foam (55% yield). R_f = 0.19 (Hex/EtOAc 1:9); IR (film) ν: 1645, 1019 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.72 (1H, s, N*H*), 7.47 (6H, m, H-2′, Ph*H*-ortho and Ph*H*-meta), 7.39 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.31 (2H, d, *J* 8.0 Hz, H-3′), 7.24 (2H, d, *J* 8.4 Hz, H-2″), 6.95 (2H, d, *J* 8.4 Hz, H-3″), 5.72 (1H, s, C*H*OH), 5.10 (2H, s, CH_2O), 4.71 (1H, s, O*H*), 2.97 (6H, s, N(CH_3)$_2$); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 157.8 (C-4″), 155.8 (NHCO), 139.5 (C-1′), 139.2 (PhCCH$_2$O), 138.3 (C-4′), 137.6 (C-1″), 128.4 (C-2″), 127.6 (Ph*C*-meta and Ph*C*-para), 127.5 (Ph*C*-ortho), 126.4 (C-3′), 119.2 (C-2′), 114.3 (C-3″), 74.6 (CHOH), 69.5 (Ph-*C*H$_2$O), 35.6 (N(*C*H$_3$)$_2$); MS: 377.39 (M+H$^+$), 399.40 (M+Na$^+$).

4.2.1.5. Synthesis of 3-(4′-((4″-(benzyloxy)phenyl)(hydroxy)-methyl)phenyl)-1,1-diethylurea (5e). According to the general procedure, hydroxy-amide **5e** was obtained from amide **4e** after purification by flash column chromatography (Hex/EtOAc 4:6) and evaporation of the solvent as oil (35% yield). R_f = 0.21 (Hex/EtOAc 4:6); IR (film) ν: 1642, 1012 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.62 (1H, s, N*H*), 7.49–7.47 (4H, m, H-2′ and Ph*H*-meta), 7.39 (1H, t, *J* 7.6 Hz, Ph*H*-para), 7.37–7.30 (4H, m, H-3′ and Ph*H*-ortho), 7.24 (2H, d, *J* 7.6 Hz, H-2″), 6.95 (2H, d, *J* 7.6 Hz, H-3″), 5.72 (1H, s, C*H*OH), 5.10 (2H, s, CH_2O), 4.70 (1H, s, O*H*), 3.41 (4H, q, *J* 6.8 Hz, N(CH_2CH$_3$)$_2$), 1.15 (6H, t, *J* 6.8 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 157.8 (C-4″), 154.5 (NHCO), 139.6 (C-1′), 139.2 (PhCCH$_2$O), 138.3 (C-4′), 137.6 (C-1″), 128.4 (C-2″), 127.6 (Ph*C*-meta and Ph*C*-para), 127.5 (Ph*C*-ortho), 126.4 (C-3′), 119.4 (C-2′), 114.3 (C-3″), 74.6 (CHOH), 69.5 (Ph-*C*H$_2$O), 40.9 (N(*C*H$_2$CH$_3$)$_2$), 13.4 (N(CH$_2$*C*H$_3$)$_2$); MS: 405.24 (M+H$^+$), 427.24 (M+Na$^+$).

4.2.1.6. Synthesis of *N*-(4′-((4″-(benzyloxy)phenyl)(hydroxy)-methyl)phenyl) pyrrolidine-1-carboxamide (5f). According to the general procedure, hydroxy-amide **5f** was obtained from amide **4f** after purification by flash column chromatography (Hex/EtOAc 4:6) and evaporation of the solvent as white solid (35% yield). R_f = 0.13 (Hex/EtOAc 4:6); mp 164–165 °C; IR (film) ν: 1646, 1024 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.52–7.49 (4H, m, H-2′ and Ph*H*-meta), 7.39 (1H, t, *J* 7.6 Hz, Ph*H*-para), 7.34–7.30 (4H, m, H-3′ and Ph*H*-ortho), 7.23 (2H, d, *J* 7.6 Hz, H-2″), 6.95 (2H, d, *J* 7.6 Hz, H-3″), 5.71 (1H, d, *J* 4.0 Hz, C*H*OH), 5.10 (2H, s, CH_2O), 4.62 (1H, d, *J* 4.0 Hz, OH), 3.43 (4H, t, *J* 6.4 Hz,

N(CH_2)$_2$(CH_2)$_2$), 1.92 (4H, t, *J* 6.4 Hz, N(CH_2)$_2$(CH_2)$_2$); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 157.9 (C-4″), 153.9 (NHCO), 139.6 (C-1′), 139.1 (PhCCH_2O), 138.3 (C-4′), 137.8 (C-1″), 128.4 (C-2″), 127.6 (PhC-ortho, PhC-meta, and PhC-para), 126.4 (C-3′), 118.8 (C-2′), 114.3 (C-3″), 74.6 (CHOH), 69.5 (Ph-CH_2O), 45.5 (N(CH_2)$_2$(CH_2)$_2$), 25.2 (N(CH_2)$_2$(CH_2)$_2$); MS: 403.50 (M+H$^+$), 425.49 (M+Na$^+$).

4.2.1.7. Synthesis of *N*-(4′-((4″-(benzyloxy)phenyl)(hydroxy)-methyl)phenyl) piperidine-1-carboxamide (5g). According to the general procedure, hydroxy-amide **5g** was obtained from amide **4g** after purification by flash column chromatography (Hex/EtOAc 3:7) and evaporation of the solvent as white solid (35% yield). R_f = 0.30 (Hex/EtOAc 3:7); mp 166–167 °C; IR (film) *v*: 1643, 1027 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.85 (1H, s, N*H*), 7.48–7.45 (4H, m, H-2′ and Ph*H*-meta), 7.39 (1H, t, *J* 7.6 Hz, Ph*H*-para), 7.34–7.30 (4H, m, H-3′ and Ph*H*-ortho), 7.24 (2H, d, *J* 8.8 Hz, H-2″), 6.95 (2H, d, *J* 8.8 Hz, H-3″), 5.71 (1H, d, *J* 4.0 Hz, C*H*OH), 5.10 (2H, s, CH_2O), 4.62 (1H, d, *J* 4.0 Hz, OH), 3.47 (4H, t, *J* 6.4 Hz, N(CH_2)$_2$(CH_2)$_2$$CH_2$), 1.62 (4H, m, N($CH_2$)$_2$($CH_2$)$_2$$CH_2$), 1.53 (2H, m, N($CH_2$)$_2$($CH_2$)$_2$$CH_2$); ^{13}C NMR (acetone-$d_6$, 50 MHz): δ = 157.6 (C-4″), 153.7 (NHCO), 139.3 (C-1′), 139.2 (PhCCH_2O), 138.1 (C-4′), 137.9 (C-1″), 128.3 (C-2″), 127.6 (PhC-meta and PhC-para), 127.5 (PhC-ortho), 126.4 (C-3′), 119.0 (C-2′), 114.3 (C-3″), 74.6 (CHOH), 69.5 (Ph-CH_2O), 44.9 (N(CH_2)$_2$(CH_2)$_2$$CH_2$), 25.7 (N($CH_2$)$_2$($CH_2$)$_2$$CH_2$), 24.4 (N($CH_2$)$_2$($CH_2$)$_2$$CH_2$); MS: 417.46 (M+H$^+$), 439.47 (M+Na$^+$).

4.2.2. General procedure for the synthesis of analogues 6

4.2.2.1. Synthesis of *N*-(4-(4′-(benzyloxy)benzoyl)phenyl)propionamide (6a). To a cold at 0 °C solution of hydroxy-amide **5a** (0.20 g, 0.55 mmol) in acetone (22 mL), Jones reagent (4.3 mL) was added and the new solution was stirred for 30 min at the same temperature. After the completion of the reaction, 2-propanol was added and the solvent was evaporated in vacuum. Then, EtOAc was added and the organic layer was washed with water and brine, dried with Na_2SO_4, filtered and evaporated in vacuum till dryness to provide keto-amide **6a** as white solid (90% yield). R_f = 0.36 (Hex/EtOAc 1:1); mp 162–163 °C; IR (film) *v*: 1657, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.2 (1H, s, N*H*), 7.78–7.69 (6H, m, H-2, H-3 and H-2′), 7.49 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.42 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.36 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.17 (2H, d, *J* 7.2 Hz, H-3′), 5.22 (2H, s, CH_2O), 2.39 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 1.11 (3H, t, *J* 7.6 Hz, CH$_2$CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 173.0 (NHCO), 162.2 (C-4′), 143.5 (C-1), 137.0 (PhCCH_2O), 132.4 (C-3), 132.2 (C-4), 131.2 (C-2′), 130.5 (C-1′), 129.0 (PhC-ortho), 128.5 (PhC-para), 128.3 (PhC-meta), 118.6 (C-2), 115.0 (C-3′), 67.0 (Ph-CH_2O), 30.1 (CH_2CH$_3$), 10.0 (CH$_2$$CH_3$); MS: 360.47 (M+H$^+$), 382.48 (M+Na$^+$).

4.2.2.2. Synthesis of *N*-(4-(4′-(benzyloxy)benzoyl)phenyl)isobutyramide (6b). According to the general procedure, keto-amide **6b** was obtained from hydroxy-amide **5b** as white solid (95% yield). R_f = 0.41 (Hex/EtOAc 1:1); mp 165–166 °C; IR (film) *v*: 1698, 1635 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.2 (1H, s, N*H*), 7.80–7.68 (6H, m, H-2, H-3 and H-2′), 7.49 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.42 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.36 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.16 (2H, d, *J* 7.2 Hz, H-3′), 5.22 (2H, s, CH_2O), 2.65 (1H, m, C*H*(CH$_3$)$_2$), 1.13 (6H, d, *J* 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 176.3 (NHCO), 162.2 (C-4′), 143.6 (C-1), 137.0 (PhCCH_2O), 132.4 (C-3), 132.2 (C-4), 131.2 (C-2′), 130.5 (C-1′), 129.0 (PhC-ortho), 128.5 (PhC-para), 128.3 (PhC-meta), 118.7 (C-2), 115.0 (C-3′), 70.0 (Ph-CH_2O), 35.5 (*C*H(CH$_3$)$_2$), 19.9 (CH(*C*H$_3$)$_2$); MS: 374.47 (M+H$^+$), 396.48 (M+Na$^+$).

4.2.2.3. *N*-(4-(4′-(benzyloxy)benzoyl)phenyl)hexanamide (6c). According to the general procedure, keto-amide **6c** was obtained from hydroxy-amide **5c** as white solid (95% yield). R_f = 0.24 (Hex/EtOAc 7:3); mp 168–169 °C; IR (film) *v*: 1638, 1596 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.3 (1H, s, N*H*), 7.79–7.68 (6H, m, H-2, H-3 and H-2′), 7.50 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.43 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.36 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.17 (2H, d, *J* 7.2 Hz, H-3′), 5.23 (2H, s, CH_2O), 2.34 (2H, t, *J* 7.2 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.62 (2H, m, CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.32 (4H, m, CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.89 (3H, t, *J* 7.2 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 172.4 (NHCO), 162.2 (C-4′), 143.5 (C-1), 137.0 (PhCCH_2O), 132.4 (C-3), 132.2 (C-4), 131.2 (C-2′), 130.5 (C-1′), 129.0 (PhC-ortho), 128.5 (PhC-para), 128.3 (PhC-meta), 118.6 (C-2), 115.0 (C-3′), 70.0 (Ph-CH_2O), 37.0 (*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.3 (CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_3$), 25.2 (CH$_2$CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.4 (CH$_2$CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.3 (CH$_2$CH$_2$CH$_2$CH$_2$*C*H$_3$); MS: 402.57 (M+H$^+$), 424.59 (M+Na$^+$).

4.2.2.4. 3-(4′-(4″-(Benzyloxy)benzoyl)phenyl)-1,1-dimethylurea (6d). According to the general procedure, keto-amide **6d** was obtained from hydroxy-amide **5d** as white solid (90% yield). R_f = 0.13 (Hex/EtOAc 1:1); mp 159–160 °C; IR (film) *v*: 1643, 1599 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.75 (1H, s, N*H*), 7.76–7.68 (6H, m, H-2′, H-3′ and H-2″), 7.50 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.45 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.40 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.19 (2H, d, *J* 7.2 Hz, H-3″), 5.25 (2H, s, CH_2O), 2.99 (6H, s, N(CH_3)$_2$); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 162.0 (C-4″), 155.7 (NHCO), 145.4 (C-1′), 137.0 (PhCCH_2O), 132.2 (C-3′), 131.0 (C-2″), 130.8 (C-4′), 130.7 (C-1″), 129.0 (PhC-ortho), 128.5 (PhC-para), 128.3 (PhC-meta), 118.7 (C-2′), 115.0 (C-3″), 70.0 (Ph-CH_2O), 36.7 (N(*C*H$_3$)$_2$); MS: 375.35 (M+H$^+$), 397.34 (M+Na$^+$).

4.2.2.5. 3-(4′-(4″-(Benzyloxy)benzoyl)phenyl)-1,1-diethylurea (6e). According to the general procedure, keto-amide **6e** was obtained from hydroxy-amide **5e** as white solid (95% yield). R_f = 0.27 (Hex/EtOAc 1:1); mp 162–163 °C; IR (film) *v*: 1644, 1597 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.60 (1H, s, N*H*), 7.75–7.65 (6H, m, H-2′, H-3′ and H-2″), 7.51 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.44 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.38 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.19 (2H, d, *J* 7.6 Hz, H-3″), 5.24 (2H, s, CH_2O), 3.41 (4H, q, *J* 6.4 Hz, N(CH_2CH$_3$)$_2$), 1.13 (6H, t, *J* 6.4 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 162.0 (C-4″), 154.4 (NHCO), 145.5 (C-1′), 137.0 (PhCCH_2O), 132.2 (C-3′), 131.0 (C-2″), 130.8 (C-4′), 130.7 (C-1″), 129.0 (PhC-ortho), 128.5 (PhC-para), 128.3 (PhC-meta), 118.8 (C-2′), 115.0 (C-3″), 70.0 (Ph-CH_2O), 41.0 (N(CH_2CH$_3$)$_2$), 13.3 (N(CH$_2$CH_3)$_2$); MS: 403.26 (M+H$^+$), 425.34 (M+Na$^+$).

4.2.2.6. *N*-(4′-(4″-(Benzyloxy) benzoyl)phenyl)pyrrolidine-1-carboxamide (6f). According to the general procedure, keto-amide **6f** was obtained from hydroxy-amide **5f** as white solid (90% yield). R_f = 0.47 (Hex/EtOAc 3:7); mp 178–179 °C; IR (film) *v*: 1645, 1598 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.54 (1H, s, N*H*), 7.74–7.71 (6H, m, H-2′, H-3′ and H-2″), 7.48 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.42 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.36 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.17 (2H, d, *J* 7.6 Hz, H-3″), 5.22 (2H, s, CH_2O), 3.80 (2H, t, *J* 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 3.40 (2H, t, *J* 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 2.67 (2H, t, *J* 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 2.00 (2H, t, *J* 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 162.0 (C-4″), 154.6 (NHCO), 145.5 (C-1′), 137.0 (PhCCH_2O), 132.2 (C-3′), 131.0 (C-2″), 130.8 (C-4′), 130.7 (C-1″), 129.0 (PhC-ortho), 128.5 (PhC-para), 128.3 (PhC-meta), 118.6 (C-2′), 115.0 (C-3″), 70.0 (Ph-CH_2O), 45.5 (N(CH_2)$_2$(CH_2)$_2$), 25.3 (N(CH_2)$_2$(CH_2)$_2$).; MS: 401.39 (M+H$^+$), 423.39 (M+Na$^+$).

4.2.2.7. *N*-(4′-(4″-(Benzyloxy)benzoyl)phenyl)piperidine-1-carboxamide (6g). According to the general procedure, keto-amide **6g** was obtained from hydroxy-amide **5g** as white solid (90% yield). R_f = 0.30 (Hex/EtOAc 1:1); mp 205–206 °C; IR (film) *ν*: 1644, 1599 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.89 (1H, s, N*H*), 7.78 (2H, d, *J* 7.6 Hz, H-2′), 7.74–7.66 (6H, m, H-3′ and H-2″), 7.51 (2H, d, *J* 7.2 Hz, Ph*H*-ortho), 7.44 (2H, t, *J* 7.2 Hz, Ph*H*-meta), 7.38 (1H, t, *J* 7.2 Hz, Ph*H*-para), 7.18 (2H, d, *J* 7.6 Hz, H-3″), 5.24 (2H, s, CH_2O), 3.47 (4H, t, *J* 6.4 Hz, N(CH_2)$_2$(CH$_2$)$_2$CH$_2$), 1.61 (2H, m, N(CH$_2$)$_2$(CH_2)$_2$CH$_2$), 1.53 (4H, m, N(CH$_2$)$_2$(CH_2)$_2$CH$_2$ and N(CH$_2$)$_2$(CH$_2$)$_2$CH_2); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 193.7 (CO), 162.0 (C-4″), 154.8 (NHCO), 145.6 (C-1′), 137.0 (Ph*C*CH$_2$O), 132.2 (C-3′), 131.1 (C-2″), 130.8 (C-4′), 130.6 (C-1″), 129.0 (Ph*C*-ortho), 128.5 (Ph*C*-para), 128.3 (Ph*C*-meta), 118.5 (C-2′), 115.0 (C-3″), 70.0 (Ph-CH_2O), 45.2 (N(CH_2)$_2$(CH$_2$)$_2$CH$_2$), 26.0 (N(CH$_2$)$_2$(CH_2)$_2$CH$_2$), 24.5 (N(CH$_2$)$_2$(CH$_2$)$_2$CH_2); MS: 415.44 (M+H$^+$), 437.49 (M+Na$^+$).

4.2.3. General procedure for the synthesis of analogues 7 and 8

4.2.3.1. Synthesis of (*E*)-*N*-(4-(1′,2′-bis(4″,4‴-(benzyloxy)phenyl)but-1′-enyl)phenyl)propionamide (7a) and (*Z*)-*N*-(4-(1′,2′-bis(4″,4‴-(benzyloxy) phenyl)but-1′-enyl)phenyl) propionamide (8a). To a cold at −10 °C suspension of Zn (0.21 g, 3.2 mmol) in THF (3.1 mL), $TiCl_4$ (0.14 mL, 1.3 mmol) was added dropwise and the new mixture was stirred for another 10 min in the same temperature and after was refluxed for 2 h. Then, a solution of keto-amide **6a** (0.12 g, 0.33 mmol) and 1-(4′-(benzyloxy)phenyl)propan-1-one (0.086 g, 0.36 mmol) in THF (6.6 mL), was added to the cooled suspension of the titanium reagent at 0 °C, and the reaction mixture was refluxed for 2.5 h. After the completion of the reaction, the reaction mixture was cooled to rt and poured into a 10% aq K_2CO_3 solution (10 mL). Vigorous stirring was maintained for 5 min, and the dispersed insoluble material was removed by vacuum filtration using celite. The organic layer was separated and the aqueous layer was extracted 3 times with EtOAc. The combined EtOAc extracts were washed with water and brine, dried with Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (Hex/EtOAc 6:4) to provide analogue **7a** as white solid and analogue **8a** as oil (50% total yield). Compound **7a**: R_f = 0.43 (Hex/EtOAc 6:4); mp 154–155 °C; IR (film) *ν*: 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.46–7.31 (10H, m, Ph*H* and PhH′), 7.18 (2H, d, *J* 8.4 Hz, H-2), 7.13 (2H, d, *J* 8.4 Hz, H-2″), 7.02 (2H, d, *J* 8.4 Hz, H-2‴), 7.00 (1H, s, N*H*), 6.95 (2H, d, *J* 8.4 Hz, H-3″), 6.83 (2H, d, *J* 8.4 Hz, H-3), 6.78 (2H, d, *J* 8.4 Hz, H-3‴), 5.07 (2H, s, C4″-OCH_2), 4.99 (2H, s, C4‴-OCH_2), 2.47 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 2.32 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 1.20 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.940 (3H, t, *J* 7.2 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.7 (CO), 157.6 (C-4″), 157.2 (C-4‴), 141.3 (C-2′), 139.6 (C-4), 137.3 (C-1), 137.2 (Ph*C*CH$_2$O and Ph*C*′CH$_2$O), 136.4 (C-1′), 136.0 (C-1″), 135.4 (C-1‴), 131.5 (C-3), 130.8 (C-2‴), 130.7 (C-2″), 128.6 (Ph*C*′-ortho), 128.5 (Ph*C*-ortho), 128.0 (Ph*C*′-para), 127.9 (Ph*C*-para), 127.6 (Ph*C*′-meta), 127.5 (Ph*C*-meta), 118.6 (C-2), 114.4 (C-3″), 114.3 (C-3‴), 70.1 (C4″-OCH$_2$), 70.0 (C4‴-OCH$_2$), 30.8 (COCH$_2$CH$_3$), 29.7 (CH$_2$CH$_3$), 13.7 (CH$_2$CH$_3$), 9.7 (COCH$_2$CH$_3$); MS: 568.45 (M+H$^+$), 590.44 (M+Na$^+$). Compound **8a**: R_f = 0.35 (Hex/EtOAc 6:4); IR (film) *ν*: 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.52 (2H, d, *J* 8.4 Hz, H-2), 7.43–7.29 (10H, m, Ph*H* and PhH′), 7.18 (3H, m, H-3 and NH), 7.04 (2H, d, *J* 8.4 Hz, H-2‴), 6.80 (2H, d, *J* 8.4 Hz, H-3‴), 6.78 (2H, d, *J* 8.4 Hz, H-2″), 6.64 (2H, d, *J* 8.4 Hz, H-3″), 5.01 (2H, s, C4‴-OCH_2), 4.93 (2H, s, C4″-OCH_2), 2.45 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 2.40 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 1.26 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.928 (3H, t, *J* 7.2 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.9 (CO), 157.1 (C-4″), 156.8 (C-4‴), 141.0 (C-2′), 140.0 (C-4), 137.2 (Ph*C*CH$_2$O and Ph*C*′CH$_2$O), 136.4 (C-1′), 136.0 (C-1″), 134.9 (C-1‴), 132.0 (C-2″), 130.6 (C-2‴), 130.1 (C-3), 129.9 (C-1), 128.5 (Ph*C*′-ortho and Ph*C*-ortho), 127.9 (Ph*C*′-para and Ph*C*-para), 127.5 (Ph*C*′-meta and Ph*C*-meta), 119.4 (C-2), 114.3 (C-3‴), 113.8 (C-3″), 69.9 (C4‴-OCH$_2$), 69.9 (C4″-OCH$_2$), 30.8 (COCH$_2$CH$_3$), 28.9 (CH$_2$CH$_3$), 13.7 (CH$_2$CH$_3$), 9.7 (COCH$_2$CH$_3$); MS: 568.45.44 (M+H$^+$), 590.44 (M+Na$^+$).

4.2.3.2. Synthesis of (*E*)-*N*-(4-(1′,2′-bis(4″,4‴-(benzyloxy)phenyl)but-1′-enyl)phenyl)isobutyramide (7b) and (*Z*)-*N*-(4-(1′,2′-bis(4″,4‴-(benzyloxy) phenyl) but-1′-enyl)phenyl)isobutyramide (8b). According to the general procedure, analogues **7b** and **8b** were obtained from keto-amide **6b** after purification by flash column chromatography (Hex/EtOAc 6:4) and evaporation of the solvent as white solid and oil respectively (65% total yield). Compound **7b**: R_f = 0.69 (Hex/EtOAc 6:4); mp 156–157 °C; IR (film) *ν*: 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.47–7.35 (10H, m, Ph*H* and PhH′), 7.20 (2H, d, *J* 8.4 Hz, H-2), 7.14 (2H, d, *J* 8.4 Hz, H-2″), 7.03 (2H, d, *J* 8.4 Hz, H-2‴), 7.00 (1H, s, N*H*), 6.95 (2H, d, *J* 8.4 Hz, H-3″), 6.83 (2H, d, *J* 8.4 Hz, H-3), 6.79 (2H, d, *J* 8.4 Hz, H-3‴), 5.07 (2H, s, C4″-OCH_2), 5.00 (2H, s, C4‴-OCH_2), 2.49 (2H, q, *J* 7.8 Hz, CH_2CH$_3$), 2.46–2.41 (1H, m, C*H*(CH$_3$)$_2$), 1.21 (6H, d, *J* 6.6 Hz, CH(CH_3)$_2$), 0.945 (3H, t, *J* 7.8 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 175.0 (CO), 157.6 (C-4″), 157.2 (C-4‴), 141.2 (C-2′), 140.0 (C-4), 137.3 (C-1), 137.2 (Ph*C*CH$_2$O and Ph*C*′CH$_2$O), 136.5 (C-1′), 136.0 (C-1″), 135.6 (C-1‴), 131.6 (C-3), 130.8 (C-2‴), 130.7 (C-2″), 128.6 (Ph*C*′-ortho and Ph*C*-ortho), 128.0 (Ph*C*′-para and Ph*C*-para), 127.6 (Ph*C*′-meta and Ph*C*-meta), 118.6 (C-2), 114.4 (C-3″), 113.4 (C-3‴), 70.1 (C4″-OCH$_2$), 70.0 (C4‴-OCH$_2$), 36.7 (CH(CH$_3$)$_2$), 28.7 (CH$_2$CH$_3$), 19.7 (CH(CH$_3$)$_2$), 13.7 (CH$_2$CH$_3$); MS: 582.54 (M+H$^+$), 604.53 (M+Na$^+$). Compound **8b**: R_f = 0.62 (Hex/EtOAc 6:4); IR (film) *ν*: 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.51 (2H, d, *J* 8.4 Hz, H-2), 7.46–7.29 (10H, m, Ph*H* and PhH′), 7.19 (2H, d, *J* 8.4 Hz, H-3), 7.16 (1H, s, N*H*), 7.04 (2H, d, *J* 8.4 Hz, H-2‴), 6.80 (2H, d, *J* 8.4 Hz, H-3‴), 6.78 (2H, d, *J* 8.4 Hz, H-2″), 6.64 (2H, d, *J* 8.4 Hz, H-3″), 5.01 (2H, s, C4‴-OCH_2), 4.93 (2H, s, C4″-OCH_2), 2.53–2.48 (1H, m, C*H*(CH$_3$)$_2$), 2.44 (2H, q, *J* 7.8 Hz, CH_2CH$_3$), 1.27 (6H, d, *J* 6.6 Hz, CH(CH_3)$_2$), 0.935 (3H, t, *J* 7.8 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 175.2 (CO), 157.1 (C-4‴), 156.7 (C-4″), 141.0 (C-2′), 139.9 (C-4), 137.2 (Ph*C*CH$_2$O and Ph*C*′CH$_2$O), 136.4 (C-1′), 136.0 (C-1″), 134.9 (C-1‴), 132.0 (C-2″), 130.8 (C-1), 130.7 (C-2‴), 130.1 (C-3), 128.5 (Ph*C*′-ortho and Ph*C*-ortho), 127.9 (Ph*C*′-para and Ph*C*-para), 127.5 (Ph*C*′-meta and Ph*C*-meta), 119.4 (C-2), 114.3 (C-3‴), 113.7 (C-3″), 69.9 (C4‴-OCH$_2$), 69.8 (C4″-OCH$_2$), 36.8 (CH(CH$_3$)$_2$), 29.7 (CH$_2$CH$_3$), 19.6 (CH(CH$_3$)$_2$), 13.7 (CH$_2$CH$_3$); MS: 582.50 (M+H$^+$), 604.54 (M+Na$^+$).

4.2.3.3. Synthesis of (*E*)-*N*-(4-(1′,2′-bis(4″,4‴-(benzyloxy)phenyl)but-1′-enyl)phenyl)hexanamide (7c) and (*Z*)-*N*-(4-(1′,2′-bis(4″,4‴-(benzyloxy)phenyl) but-1′-enyl)phenyl) hexanamide (8c). According to the general procedure, analogues **7c** and **8c** were obtained from keto-amide **6c** after purification by flash column chromatography (Hex/EtOAc 8:2) and evaporation of the solvent as white solid and oil respectively (50% total yield). Compound **7c**: R_f = 0.33 (Hex/EtOAc 8:2); mp 162–163 °C; IR (film) *ν*: 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.48–7.35 (10H, m, Ph*H* and PhH′), 7.22 (2H, d, *J* 8.4 Hz, H-2), 7.16 (2H, d, *J* 8.4 Hz, H-2″), 7.05 (2H, d, *J* 8.4 Hz, H-2‴), 7.04 (1H, s, N*H*), 6.98 (2H, d, *J* 8.4 Hz, H-3″), 6.85 (2H, d, *J* 8.4 Hz, H-3), 6.81 (2H, d, *J* 8.4 Hz, H-3‴), 5.09 (2H, s, C4″-OCH_2), 5.02 (2H, s, C4‴-OCH_2), 2.45 (2H, q, *J* 7.8 Hz, CH_2CH$_3$), 2.30 (2H, t, *J* 7.2 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.72–1.69 (2H, m, CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.36–1.32 (4H, m, CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.960–0.900 (6H, m, CH$_2$CH_3 κ∝I CH$_2$CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz):

δ = 171.3 (CO), 157.6 (C-4″), 157.2 (C-4‴), 141.0 (C-2′), 139.6 (C-4), 137.3 (C-1), 137.2 (PhCCH$_2$O and PhC′CH$_2$O), 136.4 (C-1′), 136.0 (C-1″), 135.4 (C-1‴), 131.5 (C-3), 130.8 (C-2‴), 130.7 (C-2″), 128.6 (PhC′-ortho and PhC-ortho), 128.0 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 118.6 (C-2), 114.4 (C-3″), 114.3 (C-3‴), 70.0 (C4″-OCH$_2$), 69.9 (C4‴-OCH$_2$), 37.9 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.5 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 28.9 (CH$_2$CH$_3$), 25.4 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 22.5 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 14.0 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$) 13.7 (CH$_2$CH$_3$); MS: 610.84 (M+H$^+$), 632.89 (M+Na$^+$). Compound **8c**: R_f = 0.31 (Hex/EtOAc 8:2); IR (film) ν: 1657 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.52 (2H, d, J 8.4 Hz, H-2), 7.46–7.32 (10H, m, PhH and PhH′), 7.20 (2H, d, J 8.4 Hz, H-3), 7.19 (1H, s, NH), 7.07 (2H, d, J 8.4 Hz, H-2‴), 6.84 (2H, d, J 8.4 Hz, H-3‴), 6.80 (2H, d, J 8.4 Hz, H-2″), 6.67 (2H, d, J 8.4 Hz, H-3″), 5.03 (2H, s, C4‴-OCH$_2$), 4.96 (2H, s, C4″-OCH$_2$), 2.47 (2H, q, J 7.8 Hz, CH$_2$CH$_3$), 2.38 (2H, t, J 7.2 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.79–1.75 (2H, m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.42–1.38 (4H, m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 0.980–0.920 (6H, m, CH$_2$CH$_3$ and CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 171.4 (CO), 157.1 (C-4‴), 156.8 (C-4″), 141.3 (C-2′), 140.0 (C-4), 137.2 (PhCCH$_2$O and PhC′CH$_2$O), 136.4 (C-1′), 136.0 (C-1″), 134.9 (C-1‴), 132.0 (C-2″), 130.8 (C-1), 130.7 (C-2‴), 130.1 (C-3), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.5 (PhC′-meta and PhC-meta), 119.4 (C-2), 114.3 (C-3‴), 113.7 (C-3″), 69.9 (C4‴-OCH$_2$), 69.8 (C4″-OCH$_2$), 37.9 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.5 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 28.9 (CH$_2$CH$_3$), 25.4 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 22.5 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 14.0 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$) 13.7 (CH$_2$CH$_3$); MS: 610.85 (M+H$^+$), 632.88 (M+Na$^+$).

4.2.3.4. Synthesis of (*E*)-3-(4′-(1″,2″-bis(4‴,4⁗-(benzyloxy)phenyl)but-1″-enyl)phenyl)-1,1-dimethylurea (7d) and (*Z*)-3-(4′-(1″,2″-bis(4‴,4⁗-(benzyloxy)phenyl)but-1″-enyl)phenyl)-1,1-dimethylurea (8d).

According to the general procedure, analogues **7d** and **8d** were obtained from keto-amide **6d** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as white solid and oil respectively (50% total yield). Compound **7d**: R_f = 0.23 (Hex/EtOAc 1:1); mp 174–175 °C; IR (film) ν: 1646 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.49–7.33 (10H, m, PhH and PhH′), 7.17 (2H, d, J 8.8 Hz, H-2‴), 7.07 (2H, d, J 8.8 Hz, H-2⁗), 7.05 (2H, d, J 8.8 Hz, H-2′), 6.98 (2H, d, J 8.8 Hz, H-3‴), 6.82 (2H, d, J 8.8 Hz, H-3′), 6.81 (2H, d, J 8.8 Hz, H-3⁗), 6.20 (1H, s, NH), 5.09 (2H, s, C4‴-OCH$_2$), 5.01 (2H, s, C4⁗-OCH$_2$), 2.98 (6H, s, N(CH$_3$)$_2$), 2.50 (2H, q, J 7.2 Hz, CH$_2$CH$_3$), 0.960 (3H, t, J 7.2 Hz, CH$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.5 (C-4‴), 157.1 (C-4⁗), 155.6 (CO), 140.9 (C-2″), 138.3 (C-4′), 137.4 (C-1″), 137.2 (PhCCH$_2$O and PhC′CH$_2$O), 136.4 (C-1′ and C-1‴), 135.0 (C-1⁗), 131.4 (C-3′), 130.8 (C-2⁗), 130.7 (C-2‴), 128.6 (PhC′-ortho and PhC-ortho), 128.0 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 118.6 (C-2′), 114.4 (C-3‴), 114.2 (C-3⁗), 70.0 (C4‴-OCH$_2$), 69.9 (C4⁗-OCH$_2$), 36.5 (N(CH$_3$)$_2$), 29.0 (CH$_2$CH$_3$), 13.7 (CH$_2$CH$_3$); MS: 583.64 (M+H$^+$), 605.64 (M+Na$^+$). Compound **8d**: R_f = 0.13 (Hex/EtOAc 1:1); IR (film) ν: 1643 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.46–7.32 (12H, m, PhH, PhH′ and H-2′), 7.17 (2H, d, J 8.8 Hz, H-3′), 7.06 (2H, d, J 8.8 Hz, H-2⁗), 6.82 (2H, d, J 8.8 Hz, H-3⁗), 6.81 (2H, d, J 8.8 Hz, H-2‴), 6.66 (2H, d, J 8.8 Hz, H-3‴), 6.34 (1H, s, NH), 5.03 (2H, s, C4⁗-OCH$_2$), 4.95 (2H, s, C4‴-OCH$_2$), 3.06 (6H, s, N(CH$_3$)$_2$), 2.48 (2H, q, J 7.2 Hz, CH$_2$CH$_3$), 0.940 (3H, t, J 7.2 Hz, CH$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.0 (C-4‴), 156.7 (C-4⁗), 155.7 (CO), 140.7 (C-2″), 138.8 (C-1′), 137.5 (C-1″), 137.3 (C-4′), 137.1 (PhCCH$_2$O and PhC′CH$_2$O), 136.1 (C-1‴), 135.0 (C-1⁗), 132.0 (C-2‴), 130.8 (C-2⁗), 130.0 (C-3′), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.5 (PhC′-meta and PhC-meta), 119.5 (C-2′), 114.2 (C-3⁗), 113.7 (C-3‴), 69.9 (C4⁗-OCH$_2$), 69.8 (C4‴-OCH$_2$), 36.5 (N(CH$_3$)$_2$), 29.7 (CH$_2$CH$_3$), 13.7 (CH$_2$CH$_3$); MS: 583.65 (M+H$^+$), 605.64 (M+Na$^+$).

4.2.3.5. Synthesis of (*E*)-3-(4′-(1″,2″-bis(4‴,4⁗-(benzyloxy)phenyl)but-1″-enyl)phenyl)-1,1-diethylurea (7e) and (*Z*)-3-(4′-(1″,2″-bis(4‴,4⁗-(benzyloxy)phenyl)but-1″-enyl)phenyl)-1,1-diethylurea (8e).

According to the general procedure, analogues **7e** and **8e** were obtained from keto-amide **6e** after purification by flash column chromatography (Hex/EtOAc 6:4) and evaporation of the solvent as white solid and oil respectively (65% total yield). Compound **7e**: R_f = 0.38 (Hex/EtOAc 6:4); mp 177–178 °C; IR (film) ν: 1645 cm^{-1}; ^{1}H NMR (CDCl$_3$, 600 MHz): δ = 7.47–7.31 (10H, m, PhH and PhH′), 7.15 (2H, d, J 8.8 Hz, H-2‴), 7.07 (2H, d, J 8.8 Hz, H-2⁗), 7.06 (2H, d, J 8.8 Hz, H-2′), 6.95 (2H, d, J 8.8 Hz, H-3‴), 6.80 (2H, d, J 8.8 Hz, H-3′), 6.79 (2H, d, J 8.8 Hz, H-3⁗), 6.12 (1H, s, NH), 5.07 (2H, s, C4‴-OCH$_2$), 5.00 (2H, s, C4⁗-OCH$_2$), 3.32 (4H, q, J 7.2 Hz, N(CH$_2$CH$_3$)$_2$), 2.48 (2H, q, J 7.2 Hz, CH$_2$CH$_3$), 1.18 (6H, t, J 7.2 Hz, N(CH$_2$CH$_3$)$_2$), 0.943 (3H, t, J 7.2 Hz, CH$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.6 (C-4‴), 157.2 (C-4⁗), 154.5 (CO), 140.8 (C-2″), 138.1 (C-4′), 137.5 (C-1″), 137.2 (C-1′ and C-1‴), 136.7 (PhCCH$_2$O and PhC′CH$_2$O), 135.0 (C-1⁗), 131.4 (C-3′), 130.8 (C-2⁗), 130.7 (C-2‴), 128.5 (PhC′-ortho and PhC-ortho), 128.0 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 118.6 (C-2′), 114.4 (C-3‴), 114.2 (C-3⁗), 70.1 (C4‴-OCH$_2$), 69.9 (C4⁗-OCH$_2$), 41.6 (N(CH$_2$CH$_3$)$_2$), 28.9 (CH$_2$CH$_3$), 13.9 (N(CH$_2$CH$_3$)$_2$), 13.7 (CH$_2$CH$_3$); MS: 611.57 (M+H$^+$), 633.55 (M+Na$^+$). Compound **8e**: R_f = 0.33 (Hex/EtOAc 6:4); IR (film) ν: 1644 cm^{-1}; ^{1}H NMR (CDCl$_3$, 600 MHz): δ = 7.49–7.30 (12H, m, PhH, PhH′ and H-2′), 7.15 (2H, d, J 8.8 Hz, H-3′), 7.04 (2H, d, J 8.8 Hz, H-2⁗), 6.80 (2H, d, J 8.8 Hz, H-3⁗), 6.79 (2H, d, J 8.8 Hz, H-2‴), 6.64 (2H, d, J 8.8 Hz, H-3‴), 6.33 (1H, s, NH), 5.01 (2H, s, C4⁗-OCH$_2$), 4.93 (2H, s, C4‴-OCH$_2$), 3.39 (4H q J 7.2 Hz, N(CH$_2$CH$_3$)$_2$), 2.46 (2H, q, J 7.2 Hz, CH$_2$CH$_3$), 1.24 (6H, t, J 7.2 Hz, N(CH$_2$CH$_3$)$_2$), 0.920 (3H, t, J 7.2 Hz, CH$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.1 (C-4‴), 156.7 (C-4⁗), 154.1 (CO), 140.8 (C-2″), 139.0 (C-1′), 137.3 (C-1″ καI C-4′), 137.1 (PhCCH$_2$O and PhC′CH$_2$O), 136.1 (C-1‴), 135.0 (C-1⁗), 132.0 (C-2‴), 130.8 (C-2⁗), 130.1 (C-3′), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 119.5 (C-2′), 114.3 (C-3⁗), 113.7 (C-3‴), 69.9 (C4‴-OCH$_2$), 69.8 (C4⁗-OCH$_2$), 41.7 (N(CH$_2$CH$_3$)$_2$), 29.7 (CH$_2$CH$_3$), 14.0 (N(CH$_2$CH$_3$)$_2$) 13.7 (CH$_2$CH$_3$); MS: 611.58 (M+H$^+$), 633.55 (M+Na$^+$).

4.2.3.6. Synthesis of (*E*)-*N*-(4′-(1″,2″-bis(4‴,4⁗-(benzyloxy)phenyl)but-1″-enyl)phenyl)pyrrolidine-1-carboxamide (7f) and (*Z*)-*N*-(4′-(1″,2″-bis(4‴,4⁗-(benzyloxy)phenyl)but-1″-enyl)phenyl)pyrrolidine-1-carboxamide (8f).

According to the general procedure, analogues **7f** and **8f** were obtained from keto-amide **6f** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as white solid and oil respectively (50% total yield). Compound **7f**: R_f = 0.32 (Hex/EtOAc 1:1); mp 185–186 °C; IR (film) ν: 1641 cm^{-1}; ^{1}H NMR (CDCl$_3$, 600 MHz): δ = 7.46–7.31 (10H, m, PhH and PhH′), 7.16 (2H, d, J 8.8 Hz, H-2‴), 7.07 (2H, d, J 8.8 Hz, H-2⁗), 7.03 (2H, d, J 8.8 Hz, H-2′), 6.95 (2H, d, J 8.8 Hz, H-3‴), 6.79 (2H, d, J 8.8 Hz, H-3′), 6.78 (2H, d, J 8.8 Hz, H-3⁗), 6.09 (1H, s, NH), 5.07 (2H, s, C4‴-OCH$_2$), 5.00 (2H, s, C4⁗-OCH$_2$), 3.43 (4H, m, N(CH$_2$)$_2$(CH$_2$)$_2$), 2.42 (2H, q, J 7.2 Hz, CH$_2$CH$_3$), 1.94 (4H, m, N(CH$_2$)$_2$(CH$_2$)$_2$), 0.913 (3H, t, J 7.2 Hz, CH$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.5 (C-4‴), 157.0 (C-4⁗), 153.9 (CO), 140.7 (C-2″), 138.1 (C-4′), 137.5 (C-1″), 137.1 (C-1′ καI C-1‴),136.7 (PhCCH$_2$O and PhC′CH$_2$O), 135.4 (C-1⁗), 131.4 (C-3′), 130.8 (C-2⁗), 130.7 (C-2‴), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 118.3 (C-2′), 114.3 (C-3‴), 114.2 (C-3⁗), 70.0 (C4‴-OCH$_2$), 69.9 (C4⁗-OCH$_2$), 45.8 (N(CH$_2$)$_2$(CH$_2$)$_2$), 28.9 (CH$_2$CH$_3$), 25.6 (N(CH$_2$)$_2$(CH$_2$)$_2$), 13.7 (CH$_2$CH$_3$); MS: 609.65 (M+H$^+$), 631.63 (M+Na$^+$). Compound **8f**: R_f = 0.24 (Hex/EtOAc 1:1); IR (film) ν: 1642 cm^{-1}; ^{1}H NMR (CDCl$_3$, 600 MHz): δ = 7.49–7.30 (12H, m, PhH, PhH′ and H-2′), 7.14 (2H, d,

J 8.8 Hz, H-3′), 7.03 (2H, d, *J* 8.8 Hz, H-2‴′), 6.79 (2H, d, *J* 8.8 Hz, H-3‴′), 6.78 (2H, d, *J* 8.8 Hz, H-2″′), 6.64 (2H, d, *J* 8.8 Hz, H-3″′), 6.17 (1H, s, N*H*), 5.00 (2H, s, C4‴′-OC*H*$_2$), 4.93 (2H, s, C4″′-OC*H*$_2$), 3.48 (4H, m, N(C*H*$_2$)$_2$(CH$_2$)$_2$), 2.46 (2H, q, *J* 7.2 Hz, C*H*$_2$CH$_3$), 1.98 (4H, m, N(CH$_2$)$_2$(C*H*$_2$)$_2$), 0.922 (3H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.6 (C-4″′), 156.9 (C-4‴′), 154.1 (CO), 140.7 (C-2″), 138.6 (C-1′), 137.5 (C-1″), 137.4 (C-4′), 137.1 (PhCCH$_2$O and PhC′CH$_2$O), 136.2 (C-1″′), 135.1 (C-1‴′), 132.0 (C-2″′), 130.8 (C-2‴′), 130.0 (C-3′), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 119.2 (C-2′), 114.3 (C-3‴′), 113.7 (C-3″′), 69.9 (C4″′-OCH$_2$), 69.8 (C4‴′-OCH$_2$), 45.8 (N(*C*H$_2$)$_2$(CH$_2$)$_2$), 29.7 (*C*H$_2$CH$_3$), 25.6 (N(CH$_2$)$_2$(*C*H$_2$)$_2$) 13.7 (CH$_2$CH$_3$); MS: 609.67 (M+H$^+$), 631.67 (M+Na$^+$).

4.2.3.7. Synthesis of (*E*)-*N*-(4′-(1″,2″-bis(4‴,4″′-(benzyloxy)phenyl)but-1″-enyl)phenyl)piperidine-1-carboxamide (7g) and (*Z*)-*N*-(4′-(1″,2″-bis(4‴,4″′-(benzyloxy)phenyl)but-1″-enyl)-phenyl)piperidine-1-carboxamide (8g). According to the general procedure, analogues **7g** and **8g** were obtained from keto-amide **6g** after purification by flash column chromatography (Hex/EtOAc 7:3) and evaporation of the solvent as white solid and oil respectively (50% total yield). Compound **7g**: R_f = 0.28 (Hex/EtOAc 7:3); mp 210–211 °C; IR (film) *v*: 1644 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.49–7.34 (10H, m, Ph*H* and PhH′), 7.16 (2H, d, *J* 8.8 Hz, H-2″′), 7.06 (2H, d, *J* 8.8 Hz, H-2‴′), 7.04 (2H, d, *J* 8.8 Hz, H-2′), 6.97 (2H, d, *J* 8.8 Hz, H-3″′), 6.80 (4H, d, *J* 8.8 Hz, H-3′ and H-3‴′), 6.23 (1H, s, N*H*), 5.09 (2H, s, C4″′-OC*H*$_2$), 5.01 (2H, s, C4‴′-OC*H*$_2$), 3.40 (4H, t, *J* 6.4 Hz, N(C*H*$_2$)$_2$(CH$_2$)$_2$CH$_2$), 2.49 (2H, q, *J* 7.2 Hz, C*H*$_2$CH$_3$), 1.60 (6H, m, N(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_2$ and N(CH$_2$)$_2$(CH$_2$)$_2$C*H*$_2$), 0.957 (3H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.5 (C-4″′), 157.1 (C-4‴′), 154.9 (CO), 140.8 (C-2″), 138.2 (C-4′), 137.4 (C-1″), 137.1 (PhCCH$_2$O and PhC′CH$_2$O), 136.7 (C-1′), 136.6 (C-1″′), 135.0 (C-1‴′), 131.4 (C-3′), 130.8 (C-2‴′), 130.7 (C-2″′), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 118.6 (C-2′), 114.3 (C-3″′), 114.2 (C-3‴′), 70.0 (C4″′-OCH$_2$), 69.9 (C4‴′-OCH$_2$), 45.2 (N(*C*H$_2$)$_2$(CH$_2$)$_2$CH$_2$), 29.7 (*C*H$_2$CH$_3$), 25.7 (N(CH$_2$)$_2$(CH$_2$)$_2$CH$_2$), 24.4 (N(CH$_2$)$_2$(CH$_2$)$_2$C*H*$_2$), 13.7 (CH$_2$C*H*$_3$); MS: 623.87 (M+H$^+$), 645.81 (M+Na$^+$). Compound **8g**: R_f = 0.22 (Hex/EtOAc 7:3); IR (film) *v*: 1642 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.46–7.32 (12H, m, Ph*H*, PhH′ and H-2′), 7.16 (2H, d, *J* 8.8 Hz, H-3′), 7.05 (2H, d, *J* 8.8 Hz, H-2‴′), 6.82 (2H, d, *J* 8.8 Hz, H-3‴′), 6.81 (2H, d, *J* 8.8 Hz, H-2″′), 6.66 (2H, d, *J* 8.8 Hz, H-3″′), 6.38 (1H, s, N*H*), 5.03 (2H, s, C4‴′-OC*H*$_2$), 4.95 (2H, s, C4″′-OC*H*$_2$), 3.48 (4H, t, *J* 6.4 Hz, N(C*H*$_2$)$_2$(CH$_2$)$_2$CH$_2$), 2.48 (2H, q, *J* 7.2 Hz, C*H*$_2$CH$_3$), 1.66 –1.61 (6H, m, N(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_2$ and N(CH$_2$)$_2$(CH$_2$)$_2$C*H*$_2$), 0.940 (3H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 157.0 (C-4″′), 156.7 (C-4‴′), 155.7 (CO), 140.7 (C-2″), 138.7 (C-4′), 137.6 (C-1′), 137.4 (C-1″), 137.1 (PhCCH$_2$O and PhC′CH$_2$O), 136.1 (C-1″′), 135.1 (C-1‴′), 132.0 (C-2″′), 130.8 (C-2‴′), 130.0 (C-3′), 128.5 (PhC′-ortho and PhC-ortho), 127.9 (PhC′-para and PhC-para), 127.6 (PhC′-meta and PhC-meta), 119.4 (C-2′), 114.2 (C-3‴′), 113.7 (C-3″′), 69.9 (C4″′-OCH$_2$), 69.8 (C4‴′-OCH$_2$), 45.3 (N(CH$_2$)$_2$(CH$_2$)$_2$CH$_2$), 29.7 (*C*H$_2$CH$_3$), 25.7 (N(CH$_2$)$_2$(*C*H$_2$)$_2$CH$_2$), 24.4 (N(CH$_2$)$_2$(CH$_2$)$_2$C*H*$_2$), 13.7 (CH$_2$C*H*$_3$); MS: 623.84 (M+H$^+$), 645.81 (M+Na$^+$).

4.2.4. General procedure for the deptotection of analogues 7 and 8

4.2.4.1. Synthesis of (*E*)-*N*-(4-(1′,2′-bis(4″,4‴′-hydroxyphenyl)-but-1′-enyl) phenyl)propionamide (9a). To a cold at −78 °C solution of analogue **7a** (0.018 g, 0.032 mmol) in CH$_2$Cl$_2$ (2.2 mL), BBr$_3$ (0.07 mmol, 1.0 M in CH$_2$Cl$_2$, 5 equiv per bond, 3.6 mL) was added dropwise and the reaction was kept for another 1 h at the same temperature. Then, the solution was cooled at 0 °C, neutralized with MeOH and HCl 1 N was added. The organic phase was extracted twice with EtOAc. The combined organic extracts were washed with water and brine, dried with Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash column chromatography (Hex/EtOAc 1:1) to provide analogue **9a** as oil (90% yield). R_f = 0.20 (Hex/EtOAc 1:1); IR (film) *v*: 1689 cm^{-1}; ^{1}H NMR (CD$_3$OD-d_4, 400 MHz): δ = 7.20 (2H, d, *J* 8.6 Hz, H-2), 7.02 (2H, d, *J* 8.6 Hz, H-2″), 6.94 (2H, d, *J* 8.6 Hz, H-2‴′), 6.81 (2H, d, *J* 8.6 Hz, H-3″), 6.78 (2H, d, *J* 8.6 Hz, H-3), 6.60 (2H, d, *J* 8.6 Hz, H-3‴′), 2.47 (2H, q, *J* 7.5 Hz, C*H*$_2$CH$_3$), 2.33 (2H, q, *J* 7.6 Hz, COC*H*$_2$CH$_3$), 1.19 (3H, t, *J* 7.8 Hz, COCH$_2$C*H*$_3$), 0.936 (3H, t, *J* 7.8 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CD$_3$OD-d_4, 100 MHz): δ = 173.8 (CO), 155.8 (C-4″), 155.4 (C-4‴′), 141.2 (C-2′), 139.8 (C-4), 137.5 (C-1), 135.9 (C-1″′), 135.0 (C-1″), 133.4 (C-1′), 130.9 (C-3), 130.5 (C-2‴′), 130.2 (C-2″), 118.7 (C-2), 114.5 (C-3″), 114.3 (C-3‴′), 29.6 (COC*H*$_2$CH$_3$), 28.4 (*C*H$_2$CH$_3$), 12.6 (CH$_2$*C*H$_3$), 8.8 (COCH$_2$*C*H$_3$); MS: 388.35 (M+H$^+$), 410.33 (M+Na$^+$). Anal. Calcd for C$_{25}$H$_{25}$NO$_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 81.40; H, 6.22; N, 3.38.

4.2.4.2. Synthesis of (*Z*)-*N*-(4-(1′,2′-bis(4″,4‴′-hydroxyphenyl)but-1′-enyl) phenyl)propionamide (10a). According to the general procedure, analogue **10a** was obtained from analogue **8a** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (90% yield). R_f = 0.18 (Hex/EtOAc 1:1); IR (film) *v*: 1690 cm^{-1}; ^{1}H NMR (CD$_3$OD-d_4, 400 MHz): δ = 7.53 (2H, d, *J* 8.5 Hz, H-2), 7.15 (2H, d, *J* 8.5 Hz, H-3), 6.94 (2H, d, *J* 8.6 Hz, H-2″′), 6.69 (2H, d, *J* 8.6 Hz, H-2″), 6.61 (2H, d, *J* 8.6 Hz, H-3″′), 6.46 (2H, d, *J* 8.6 Hz, H-3″), 2.48–2.40 (4H, m, C*H*$_2$CH$_3$ and COC*H*$_2$CH$_3$), 1.23 (3H, t, *J* 7.6 Hz, COCH$_2$C*H*$_3$), 0.932 (3H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CD$_3$OD-d_4, 100 MHz): δ = 174.0 (CO), 155.3 (C-4″′), 154.9 (C-4″), 140.6 (C-2′), 140.1 (C-4), 137.4 (C-1′), 136.9 (C-1), 134.8 (C-1″), 133.5 (C-1″′), 131.7 (C-2″), 130.6 (C-2″′), 129.5 (C-3), 119.6 (C-2), 114.3 (C-3″′), 113.8 (C-3″), 29.7 (COC*H*$_2$CH$_3$), 28.3 (*C*H$_2$CH$_3$), 12.6 (CH$_2$*C*H$_3$), 8.9 (COCH$_2$*C*H$_3$); MS: 388.36 (M+H$^+$), 410.35 (M+Na$^+$). Anal. Calcd for C$_{25}$H$_{25}$NO$_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 81.42; H, 6.24; N, 3.36.

4.2.4.3. Synthesis of (*E*)-*N*-(4-(1′,2′-bis(4″,4‴′-hydroxyphenyl)-but-1′-enyl) phenyl)isobutyramide (9b). According to the general procedure, analogue **9b** was obtained from analogue **7b** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (95% yield). R_f = 0.30 (Hex/EtOAc 1:1); IR (film) *v*: 1665 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz): δ = 7.35 (2H, d, *J* 8.4 Hz, H-2), 7.05 (2H, d, *J* 8.4 Hz, H-2″), 6.97 (2H, d, *J* 8.4 Hz, H-2‴′), 6.83 (2H, d, *J* 8.4 Hz, H-3″), 6.80 (2H, d, *J* 8.4 Hz, H-3), 6.65 (2H, d, *J* 8.4 Hz, H-3‴′), 2.54 (1H, m, C*H*(CH$_3$)$_2$), 2.45 (2H, q, *J* 7.8 Hz, C*H*$_2$CH$_3$), 1.10 (6H, d, *J* 6.6 Hz, CH(C*H*$_3$)$_2$), 0.915 (3H, t, *J* 7.8 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 174.8 (CO), 156.1 (C-4″), 155.7 (C-4‴′), 140.8 (C-2′), 138.9 (C-4), 137.6 (C-1′), 137.2 (C-1), 135.1 (C-1″), 133.4 (C-1″′), 130.9 (C-3), 130.7 (C-2″′), 130.4 (C-2″), 118.1 (C-2), 114.9 (C-3″), 114.8 (C-3‴′), 35.7 (*C*H(CH$_3$)$_2$), 28.8 (*C*H$_2$CH$_3$ from HSQC), 19.6 (CH(*C*H$_3$)$_2$), 13.1 (CH$_2$*C*H$_3$); MS: 402.38 (M+H$^+$), 424.36 (M+Na$^+$). Anal. Calcd for C$_{26}$H$_{27}$NO$_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 81.82; H, 6.43; N, 3.12.

4.2.4.4. Synthesis of (*Z*)-*N*-(4-(1′,2′-bis(4″,4‴′-hydroxyphenyl)-but-1′-enyl) phenyl)isobutyramide (10b). According to the general procedure, analogue **10b** was obtained from analogue **8b** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (95% yield). R_f = 0.29 (Hex/EtOAc 1:1); IR (film) *v*: 1665 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz): δ = 7.67 (2H, d, *J* 8.4 Hz, H-2), 7.13 (2H, d, *J* 8.4 Hz, H-3), 6.97 (2H, d, *J* 8.4 Hz, H-2‴′), 6.71 (2H, d, *J* 8.4 Hz, H-2″), 6.66 (2H, d, *J* 8.4 Hz, H-3‴′), 6.50 (2H, d, *J* 8.4 Hz, H-3″), 2.63 (1H, m, C*H*(CH$_3$)$_2$), 2.43 (2H, q, *J* 7.8 Hz, C*H*$_2$CH$_3$), 1.17 (6H, d, *J* 6.6 Hz,

CH(CH_3)$_2$), 0.920 (3H, t, *J* 7.8 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6): δ = 171.8 (CO), 155.6 (C-4‴), 155.3 (C-4″), 140.4 (C-2′), 139.2 (C-4), 138.2 (C-1′), 137.6 (C-1), 134.8 (C-1″), 133.4 (C-1‴), 131.8 (C-2″), 130.7 (C-2‴), 129.6 (C-3), 118.9 (C-2), 114.7 (C-3‴), 114.2 (C-3″), 36.0 ($CH(CH_3)_2$), 28.9 (CH_2CH_3 from HSQC), 19.0 ($CH(CH_3)_2$), 13.1 (CH_2CH_3); MS: 402.37 (M+H$^+$), 424.37 (M+Na$^+$). Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 81.84; H, 6.42; N, 3.11.

4.2.4.5. Synthesis of (*E*)-*N*-(4-(1′,2′-bis(4″,4‴-hydroxyphenyl)-but-1′-enyl)phenyl) hexanamide (9c). According to the general procedure, analogue **9c** was obtained from analogue **7c** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (90% yield). R_f = 0.31 (Hex/EtOAc 1:1); IR (film) *v*: 1658 cm^{-1}; ^{1}H NMR (CD_3OD-d_4, 400 MHz): δ = 7.20 (2H, d, *J* 8.8 Hz, H-2), 7.02 (2H, d, *J* 8.8 Hz, H-2″), 6.93 (2H, d, *J* 8.4 Hz, H-2‴), 6.81 (2H, d, *J* 8.8 Hz, H-3), 6.77 (2H, d, *J* 8.8 Hz, H-3″), 6.60 (2H, d, *J* 8.4 Hz, H-3‴), 2.47 (2H, q, *J* 7.4 Hz, CH_2CH_3), 2.31 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2CH_2CH_3$), 1.68–1.63 (2H, m, $CH_2CH_2CH_2CH_2CH_3$), 1.38–1.33 (4H, m, $CH_2CH_2CH_2CH_2CH_3$), 0.933 (6H, t, *J* 7.4 Hz, CH_2CH_3 and $CH_2CH_2CH_2CH_2CH_3$); ^{13}C NMR (CD_3OD-d_4, 100 MHz): δ = 173.8 (CO), 156.5 (C-4″), 156.0 (C-4‴), 141.8 (C-2′), 140.5 (C-4), 138.1 (C-1′), 136.5 (C-1), 135.7 (C-1″), 134.1 (C-1‴), 131.5 (C-3), 131.2 (C-2‴), 130.9 (C-2″), 119.4 (C-2), 115.1 (C-3″), 115.0 (C-3‴), 37.2 ($CH_2CH_2CH_2CH_2CH_3$), 31.8 ($CH_2CH_2CH_2CH_2CH_3$), 29.1 (CH_2CH_3), 25.9 ($CH_2CH_2CH_2CH_2CH_3$), 22.7 ($CH_2CH_2CH_2CH_2CH_3$), 13.2 ($CH_2CH_2CH_2CH_2CH_3$ and CH_2CH_3); MS: 430.57 (M+H$^+$), 461.57 (M+Na$^+$). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 83.13; H, 6.98; N, 2.88.

4.2.4.6. Synthesis of (*Z*)-*N*-(4-(1′,2′-bis(4″,4‴-hydroxyphenyl)-but-1′-enyl)phenyl) hexanamide (10c). According to the general procedure, analogue **10c** was obtained from analogue **8c** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (90% yield). R_f = 0.29 (Hex/EtOAc 1:1); IR (film) *v*: 1658 cm^{-1}; ^{1}H NMR (CD_3OD-d_4, 400 MHz): δ = 7.53 (2H, d, *J* 8.8 Hz, H-2), 7.15 (2H, d, *J* 8.8 Hz, H-3), 6.94 (2H, d, *J* 8.8 Hz, H-2‴), 6.68 (2H, d, *J* 8.8 Hz, H-2″), 6.61 (2H, d, *J* 8.8 Hz, H-3‴), 6.45 (2H, d, *J* 8.8 Hz, H-3″), 2.47 (2H, q, *J* 7.4 Hz, CH_2CH_3), 2.37 (2H, t, *J* 7.7 Hz, $CH_2CH_2CH_2CH_2CH_3$), 1.75–170 (2H, m, $CH_2CH_2CH_2CH_2CH_3$), 1.41–1.38 (4H, m, $CH_2CH_2CH_2CH_2CH_3$), 0.933 (6H, t, *J* 7.4 Hz, CH_2CH_3 and $CH_2CH_2CH_2CH_2CH_3$); ^{13}C NMR (CD_3OD-d_4, 100 MHz): δ = 173.8 (CO), 157.0 (C-4‴), 155.5 (C-4″), 141.3 (C-2′), 140.8 (C-4), 137.5 (C-1′), 135.7 (C-1), 135.4 (C-1″), 134.1 (C-1‴), 132.3 (C-2″), 131.2 (C-2‴), 130.1 (C-3), 120.2 (C-2), 115.0 (C-3‴), 114.4 (C-3″), 37.2 ($CH_2CH_2CH_2CH_2CH_3$), 32.1 ($CH_2CH_2CH_2CH_2CH_3$), 29.0 (CH_2CH_3), 25.9 ($CH_2CH_2CH_2CH_2CH_3$), 22.7 ($CH_2CH_2CH_2CH_2CH_3$), 13.5 ($CH_2CH_2CH_2CH_2CH_3$ and CH_2CH_3); MS: 430.58 (M+H$^+$), 461.56 (M+Na$^+$). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 83.12; H, 6.99; N, 2.87.

4.2.4.7. Synthesis of (*E*)-3-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)-but-1″-enyl) phenyl)-1,1-dimethylurea (9d). According to the general procedure, analogue **9d** was obtained from analogue **7d** after purification by flash column chromatography (EtOAc) and evaporation of the solvent as oil (95% yield). R_f = 0.44 (EtOAc); IR (film) *v*: 1647 cm^{-1}; ^{1}H NMR (CD_3OD-d_4, 400 MHz): δ = 7.03 (2H, d, *J* 8.4 Hz, H-2′), 7.02 (2H, d, *J* 8.4 Hz, H-2‴), 6.94 (2H, d, *J* 8.4 Hz, H-2⁗), 6.78 (2H, d, *J* 8.4 Hz, H-3‴), 6.76 (2H, d, *J* 8.4 Hz, H-3′), 6.58 (2H, d, *J* 8.4 Hz, H-3⁗), 2.98 (6H, s, N(CH_3)$_2$), 2.46 (2H, q, *J* 7.2 Hz, CH_2CH_3), 0.930 (3H, t, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR (CD_3OD-d_4, 50 MHz): δ = 157.5 (CO), 155.3 (C-4‴), 154.8 (C-4⁗), 140.8 (C-2″), 138.8 (C-4′), 137.6 (C-1″), 136.9 (C-1′), 135.2 (C-1‴), 133.5 (C-1⁗), 130.7 (C-3′), 130.5 (C-2⁗), 130.2 (C-2‴), 119.8 (C-2′), 114.4 (C-3‴), 114.3 (C-3⁗), 35.3 (N(CH_3)$_2$), 28.4 (CH_2CH_3), 12.6 (CH_2CH_3). MS: 403.51 (M+H$^+$), 425.52 (M+Na$^+$). Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 79.73; H, 6.18; N, 6.55.

4.2.4.8. Synthesis of (*Z*)-3-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)-but-1″-enyl) phenyl)-1,1-dimethylurea (10d). According to the general procedure, analogue **10d** was obtained from analogue **8d** after purification by flash column chromatography (EtOAc) and evaporation of the solvent as oil (95% yield). R_f = 0.41 (EtOAc); IR (film) *v*: 1644 cm^{-1}; ^{1}H NMR (CD_3OD-d_4, 400 MHz): δ = 7.35 (2H, d, *J* 8.4 Hz, H-2′), 7.11 (2H, d, *J* 8.4 Hz, H-3′), 6.94 (2H, d, *J* 8.4 Hz, H-2⁗), 6.68 (2H, d, *J* 8.4 Hz, H-2‴), 6.61 (2H, d, *J* 8.4 Hz, H-3⁗), 6.44 (2H, d, *J* 8.4 Hz, H-3‴), 3.05 (6H, s, N(CH_3)$_2$), 2.46 (2H, q, *J* 7.2 Hz, CH_2CH_3), 0.930 (3H, t, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR (CD_3OD-d_4, 50 MHz): δ = 157.7 (CO), 155.7 (C-4‴), 155.2 (C-4⁗), 140.4 (C-2″), 137.2 (C-1′), 136.8 (C-1″), 135.2 (C-4′), 133.5 (C-1‴), 131.4 (C-1⁗), 130.7 (C-2‴), 130.6 (C-2⁗), 130.3 (C-3′), 119.7 (C-2′), 114.4 (C-3⁗), 114.3 (C-3‴), 35.3 (N(CH_3)$_2$), 28.4 (CH_2CH_3), 12.6 (CH_2CH_3); MS: 403.50 (M+H$^+$), 425.50 (M+Na$^+$). Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 79.77; H, 6.20; N, 6.58.

4.2.4.9. Synthesis of (*E*)-3-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)-but-1″-enyl) phenyl)-1,1-diethylurea (9e). According to the general procedure, analogue **9e** was obtained from analogue **7e** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as foam (95% yield). R_f = 0.15 (Hex/EtOAc 1:1); IR (film) *v*: 1646 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz): δ = 7.41 (1H, s, N*H*), 7.21 (2H, d, *J* 8.4 Hz, H-2′), 7.05 (2H, d, *J* 8.4 Hz, H-2‴), 6.96 (2H, d, *J* 8.4 Hz, H-2⁗), 6.83 (2H, d, *J* 8.4 Hz, H-3‴), 6.73 (2H, d, *J* 8.4 Hz, H-3′), 6.65 (2H, d, *J* 8.4 Hz, H-3⁗), 3.36 (4H, q, *J* 7.2 Hz, N(CH_2CH_3)$_2$), 2.45 (2H, q, *J* 7.2 Hz, CH_2CH_3), 1.11 (6H, t, *J* 7.2 Hz, N(CH_2CH_3)$_2$), 0.911 (3H, t, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 156.1 (CO), 155.6 (C-4‴), 154.3 (C-4⁗), 140.3 (C-2″), 138.3 (C-4′), 137.8 (C-1″), 137.4 (C-1′), 135.3 (C-1‴), 133.6 (C-1⁗), 130.7 (C-3′), 130.6 (C-2⁗), 130.4 (C-2‴), 118.4 (C-2′), 114.7 (C-3‴ and C-3⁗), 40.9 (N(CH_2CH_3)$_2$), 28.9 (CH_2CH_3 from HSQC), 13.4 (N(CH_2CH_3)$_2$), 13.1 (CH_2CH_3); MS: 431.39 (M+H$^+$), 453.40 (M+Na$^+$). Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 80.87; H, 6.69; N, 6.04.

4.2.4.10. Synthesis of (*Z*)-3-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)-but-1″-enyl) phenyl)-1,1-diethylurea (10e). According to the general procedure, analogue **10e** was obtained from analogue **8e** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (95% yield). R_f = 0.14 (Hex/EtOAc 1:1); IR (film) *v*: 1643 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz): δ = 7.62 (1H, s, N*H*), 7.54 (2H, d, *J* 8.4 Hz, H-2′), 7.07 (2H, d, *J* 8.4 Hz, H-3′), 6.97 (2H, d, *J* 8.4 Hz, H-2⁗), 6.71 (2H, d, *J* 8.4 Hz, H-2‴), 6.65 (2H, d, *J* 8.4 Hz, H-3⁗), 6.50 (2H, d, *J* 8.4 Hz, H-3‴), 3.43 (4H, q, *J* 7.2 Hz, N(CH_2CH_3)$_2$), 2.44 (2H, q, *J* 7.2 Hz, CH_2CH_3), 1.17 (6H, t, *J* 7.2 Hz, N(CH_2CH_3)$_2$), 0.911 (3H, t, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 157.1 (CO), 155.6 (C-4‴), 154.4 (C-4⁗), 140.1 (C-2″), 137.8 (C-1′), 137.2 (C-1″), 135.0 (C-4′), 133.6 (C-1‴), 131.8 (C-1⁗), 130.7 (C-2‴), 130.4 (C-2⁗), 129.2 (C-3′), 119.2 (C-2′), 114.7 (C-3⁗), 114.1 (C-3‴), 40.9 (N(CH_2CH_3)$_2$), 29.0 (CH_2CH_3 from HSQC), 13.4 (N(CH_2CH_3)$_2$), 13.1 (CH_2CH_3); MS: 431.38 (M+H$^+$), 453.40 (M+Na$^+$). Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 80.86; H, 6.66; N, 6.08.

4.2.4.11. Synthesis of (*E*)-*N*-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)but-1″-enyl)phenyl)pyrrolidine-1-carboxamide (9f). According to the general procedure, analogue **9f** was obtained from analogue **7f** after purification by flash column

chromatography (Hex/EtOAc 4:6) and evaporation of the solvent as oil (90% yield). R_f = 0.11 (Hex/EtOAc 4:6); IR (film) ν: 1640 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz): δ = 7.23 (2H, d, J 8.4 Hz, H-2′), 7.05 (2H, d, J 8.4 Hz, H-2‴), 6.96 (2H, d, J 8.4 Hz, H-2⁗), 6.83 (2H, d, J 8.4 Hz, H-3‴), 6.73 (2H, d, J 8.4 Hz, H-3′), 6.64 (2H, d, J 8.4 Hz, H-3⁗), 3.38 (4H, t, J 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 2.44 (2H, q, J 7.2 Hz, CH_2CH_3), 1.88 (4H, t, J 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 0.909 (3H, t, J 7.2 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 156.1 (C-4‴), 155.4 (C-4⁗), 154.8 (CO), 140.1 (C-2″), 138.3 (C-4′), 137.9 (C-1″), 137.1 (C-1′), 135.5 (C-1‴), 133.2 (C-1⁗), 130.5 (C-3′), 130.2 (C-2⁗), 130.1 (C-2‴), 118.4 (C-2′), 114.9 (C-3‴), 114.8 (C-3⁗), 45.4 (N(CH_2)$_2$(CH_2)$_2$), 29.0 (CH_2CH_3 from HSQC), 25.2 (N(CH_2)$_2$(CH_2)$_2$), 13.3 (CH_2CH_3); MS: 429.40 ($M+H^+$), 451.39 ($M+Na^+$). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 80.12; H, 6.22; N, 6.18.

4.2.4.12. Synthesis of (*Z*)-*N*-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)but-1″-enyl)phenyl)pyrrolidine-1-carboxamide (10f).

According to the general procedure, analogue **10f** was obtained from analogue **8f** after purification by flash column chromatography (Hex/EtOAc 4:6) and evaporation of the solvent as oil (90% yield). R_f = 0.10 (Hex/EtOAc 4:6); IR (film) ν: 1642 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz): δ = 7.55 (2H, d, J 8.4 Hz, H-2′), 7.52 (1H, s, N*H*), 7.07 (2H, d, J 8.4 Hz, H-3′), 6.96 (2H, d, J 8.4 Hz, H-2⁗), 6.71 (2H, d, J 8.4 Hz, H-2‴), 6.65 (2H, d, J 8.4 Hz, H-3⁗), 6.50 (2H, d, J 8.4 Hz, H-3‴), 3.45 (4H, t, J 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 2.44 (2H, q, J 7.2 Hz, CH_2CH_3), 1.93 (4H, t, J 7.2 Hz, N(CH_2)$_2$(CH_2)$_2$), 0.910 (3H, t, J 7.2 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 50 MHz): δ = 155.6 (C-4‴), 155.3 (C-4⁗), 153.9 (CO), 140.0 (C-2″), 137.8 (C-1′), 137.6 (C-1″), 135.9 (C-4′), 135.0 (C-1‴), 131.8 (C-1⁗), 130.7 (C-2‴), 129.3 (C-2⁗ and C-3′), 118.7 (C-2′), 114.7 (C-3⁗), 114.1 (C-3‴), 45.5 (N(CH_2)$_2$(CH_2)$_2$), 29.0 (CH_2CH_3 from HSQC), 25.3 (N(CH_2)$_2$(CH_2)$_2$), 13.2 (CH_2CH_3); MS: 429.43 ($M+H^+$), 451.41 ($M+Na^+$). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 80.10; H, 6.21; N, 6.17.

4.2.4.13. Synthesis of (*E*)-*N*-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)but-1″-enyl) phenyl)piperidine-1-carboxamide (9g).

According to the general procedure, analogue **9g** was obtained from analogue **7g** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (90% yield). R_f = 0.18 (Hex/EtOAc 1:1); IR (film) ν: 1645 cm^{-1}; ^1H NMR (CD_3OD-d_4, 400 MHz): δ = 7.01 (2H, d, J 8.4 Hz, H-2′), 7.00 (2H, d, J 8.4 Hz, H-2‴), 6.94 (2H, d, J 8.4 Hz, H-2⁗), 6.77 (2H, d, J 8.4 Hz, H-3‴), 6.76 (2H, d, J 8.4 Hz, H-3′), 6.59 (2H, d, J 8.4 Hz, H-3⁗), 3.45 (4H, t, J 6.4 Hz, N(CH_2)$_2$(CH_2)$_2$$CH_2$), 2.46 (2H, q, J 7.2 Hz, CH_2CH_3), 1.66 (4H, m, N(CH_2)$_2$(CH_2)$_2$$CH_2$), 1.58 (2H, m, N($CH_2$)$_2$($CH_2$)$_2$$CH_2$), 0.929 (3H, t, J 7.2 Hz, CH_2CH_3); ^{13}C NMR (CD_3OD-d_4, 50 MHz): δ = 155.9 (C-4‴), 155.2 (C-4⁗), 154.9 (CO), 142.0 (C-2″), 138.7 (C-4′), 138.0 (C-1″), 137.8 (C-1′), 135.1 (C-1‴), 133.6 (C-1⁗), 131.6 (C-3′), 130.5 (C-2⁗), 130.2 (C-2‴), 120.5 (C-2′), 114.4 (C-3‴), 114.3 (C-3⁗), 44.8 (N(CH_2)$_2$(CH_2)$_2$$CH_2$), 29.3 ($CH_2CH_3$), 25.5 (N($CH_2$)$_2$($CH_2$)$_2$$CH_2$ and N(CH_2)$_2$(CH_2)$_2$$CH_2$), 12.8 ($CH_2CH_3$); MS: 443.59 ($M+H^+$), 465.54 ($M+Na^+$). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 80.17; H, 6.49; N, 5.99.

4.2.4.14. Synthesis of (*Z*)-*N*-(4′-(1″,2″-bis(4‴,4⁗-hydroxyphenyl)but-1″-enyl) phenyl)piperidine-1-carboxamide (10g).

According to the general procedure, analogue **10g** was obtained from analogue **8g** after purification by flash column chromatography (Hex/EtOAc 1:1) and evaporation of the solvent as oil (90% yield). R_f = 0.17 (Hex/EtOAc 1:1); IR (film) ν: 1643 cm^{-1}; ^1H NMR (CD_3OD-d_4, 400 MHz): δ = 7.32 (2H, d, J 8.4 Hz, H-2′), 7.11 (2H, d, J 8.4 Hz, H-3′), 6.94 (2H, d, J 8.4 Hz, H-2⁗), 6.68 (2H, d, J 8.4 Hz, H-2‴), 6.61 (2H, d, J 8.4 Hz, H-3⁗), 6.44 (2H, d, J 8.4 Hz, H-3‴), 3.53 (4H, t, J 6.4 Hz, N(CH_2)$_2$(CH_2)$_2$$CH_2$), 2.46 (2H, q, J 7.2 Hz, CH_2CH_3), 1.70 (4H, m, N(CH_2)$_2$(CH_2)$_2$$CH_2$), 1.64 (2H, m, N($CH_2$)$_2$($CH_2$)$_2$$CH_2$), 0.931 (3H, t, J 7.2 Hz, CH_2CH_3); ^{13}C NMR (CD_3OD-d_4, 50 MHz): δ = 156.9 (C-4‴), 155.7 (C-4⁗), 152.7 (CO), 140.8 (C-2″), 139.0 (C-1′), 137.6 (C-1″), 137.0 (C-4′), 135.2 (C-1‴), 133.5 (C-1⁗), 131.6 (C-2‴), 130.2 (C-2⁗), 129.3 (C-3′), 119.6 (C-2′), 114.3 (C-3⁗), 113.7 (C-3‴), 44.9 (N(CH_2)$_2$(CH_2)$_2$$CH_2$), 29.3 ($CH_2CH_3$), 25.6 (N($CH_2$)$_2$($CH_2$)$_2$$CH_2$ and N(CH_2)$_2$(CH_2)$_2$$CH_2$), 12.6 ($CH_2CH_3$); MS: 443.58 ($M+H^+$), 465.52 ($M+Na^+$). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 80.15; H, 6.47; N, 6.01.

4.3. Biological assays

4.3.1. Inhibition growth assay

MCF-7 (human mammary gland adenocarcinoma cells), MSTO-211H (human biphasic mesothelioma cells) and HeLa (human cervix adenocarcinoma cells) were grown in Dulbecco's Modified Eagle's Medium (Sigma Chemical Co.), in RPMI 1640 (Sigma Chemical Co.) supplemented with 2.38 g/L Hepes, 0.11 g/L pyruvate sodium and in Nutrient Mixture F-12 [HAM] (Sigma Chemical Co.), respectively. 10% Heat-inactivated fetal calf serum (Invitrogen), 100 U/mL penicillin, 100 μg/mL streptomycin, and 0.25 μg/mL amphotericin B (Sigma Chemical Co.) were added to the media. The cells were cultured at 37 °C in a moist atmosphere of 5% carbon dioxide in air. MCF-7 and MSTO-211H ($3–4 \times 10^4$) were seeded into each well of a 24-well cell culture plate. After incubation for 24 h, various concentrations of the test agents were added to the complete medium and cells were incubated for a further 72 h. HeLa ($3–4 \times 10^4$) were seeded into each well of a 24-well cell culture plate. After incubation for 24 h, the medium was replaced with an equal volume of fresh medium, and various concentrations of the test agents were added. The cells were then incubated in standard conditions for a further 72 h. A trypan blue assay was performed to determine cell viability. Cytotoxicity data were expressed as GI_{50} values, that is, the concentration of the test agent inducing 50% reduction in cell growth compared with control cultures.

4.3.2. Estrogenic activity: luciferase assay (HC11 cells)

HC11 cells (mouse mammary breast epithelial cells) stably transfected with 3×ERE–Luc construct were seeded in 24-well plates and after the cells reached 50–60% confluence, were treated with 1 μM (final) tested compounds, 1 μM 4-OH tamoxifen and 10 nM E2 or ethanol (control). After 24 h cells were collected in 1× Passive Lysis Buffer (Promega) according to manufacturer's instructions, and luciferase activity was measured using BioThema Luciferase Assay. Protein concentration of samples was determined using Bradford assay. The luciferase values were correlated to the protein concentration of each sample. Data are indicated as % of E2 activity above bars of three independent experiments, performed in duplicates.

4.3.3. DNA topoisomerase relaxation assay

Supercoiled pBR322 plasmid DNA (0.25 μg, Fermentas Life Sciences) was incubated with 1U topoisomerase II (USB Corporation) or 2U topoisomerase I (Topogen) and the test compounds as indicated, for 60 min at 37 °C in 20 μL reaction buffer.

Reactions were stopped by adding 4 μL stop buffer (5% SDS, 0.125% bromophenol blue and 25% glycerol), 50 μg/mL proteinase K (Sigma) and incubating for a further 30 min at 37 °C. The samples were separated by electrophoresis on a 1% agarose gel at room temperature. The gels were stained with ethidium bromide 1 μg/mL in TAE buffer, transilluminated by UV light, and fluorescence emission was visualized by a CCD camera coupled to a Bio-Rad Gel Doc XR apparatus.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.05.012. These data include MOL files and InChiKeys of the most important compounds described in this article.

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