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Novel series of substituted biphenylmethyl urea derivatives as MCH-R1 antagonists for the treatment of obesity

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Abstract—We have designed and synthesized two novel series of MCH-R1 antagonists based on a substituted biphenylmethyl urea core. SAR was explored, suggesting that optimal binding with the receptor was achieved when the biphenylmethyl group and the linker were substituted on the same nitrogen of the urea moiety. Compound 1-(3′-cyano-4-biphenylmethyl)-3-(2-hydroxy-1,1-dimethylethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea **2t** showed the best antagonist binding activity to the MCH-R1 with a 43 nM K_i.

1. Introduction

Obesity is a worldwide epidemic.[1] Its rising prevalence throughout the world, together with its increased associated morbidity,[2] has become a real health challenge in this century and therefore, the treatment of obesity is now of great importance. Identified by WHO as one of the top ten global earth problems, current estimates hold that over 30% of adults in the United States suffer from obesity. The lack of efficacy of the available obesity drugs makes obesity one of the most attractive therapeutic targets.[3]

Melanin concentrating hormone (MCH) is a cyclic 19-amino acid neuropeptide, expressed throughout the brain, predominantly in mammalian neurons in the lateral hypothalamus and the *zona incerta*.[4] MCH is believed to play a critical role as a regulator of feeding behavior and energy balance based on several lines of evidence. Intracerebroventricular injection of MCH stimulates feeding in rats and mice, and MCH mRNA levels are up-regulated by fasting in both leptin deficient *ob*/*ob* and wild type mice.[5] MCH knockout mice result in a lean and hyperphagic phenotype and have an increased metabolism.[6] In contrast, overexpression of MCH peptide leads to obesity and insulin resistance.[7] Two G-protein-coupled receptors bind to MCH namely MCH-R1 and MCH-R2.[8] Although it is not yet clear what role MCH-R2 plays in vivo, recent research suggests that MCH-R1 is implicated in mediating the orexigenic effects of MCH. MCH-R1 knock-out mice are hyperactive, hypermetabolic, have reduced fat mass, insulin, and leptin levels, and are mildly hyperphagic.[9,10] Thus, antagonists of MCH-R1 may provide a novel target for developing potential agents for treatment of obesity.[11]

Several companies have published their attempts to identify small molecule MCH receptor antagonists with a wide range of structural types[12–15] (Fig. 1). Among them, aminotetralin T-226296 (compound **I**), which exhibited high affinity for the MCH-R1 receptor (IC_{50} value of 5.5 nM) and >90% suppression of MCH stimulated food intake at 30 mpk in lean rats, was the first reported MCH-R1 antagonist. SNAP-7941 (**II**) has also been identified as a potent antagonist at MCH-R1, showing a $pA_2 = 9.24$ in a phosphoinositide accumulation assay. In vivo studies with SNAP-7941 demonstrated that the compound, after systematic administration, was able to inhibit the effects of centrally administered MCH, and had a moderate effect on palatable consumption when compared with fenfluramine. At 1 or 10 mg_kg ip SNAP 7941 antagonized MCH-stimulated food intake in rats. However, in rats with DIO, SNAP7941 produced a sustained reduction in body

Keywords: MCH; MCH-R1 antagonist; Obesity; Biphenylmethyl urea.
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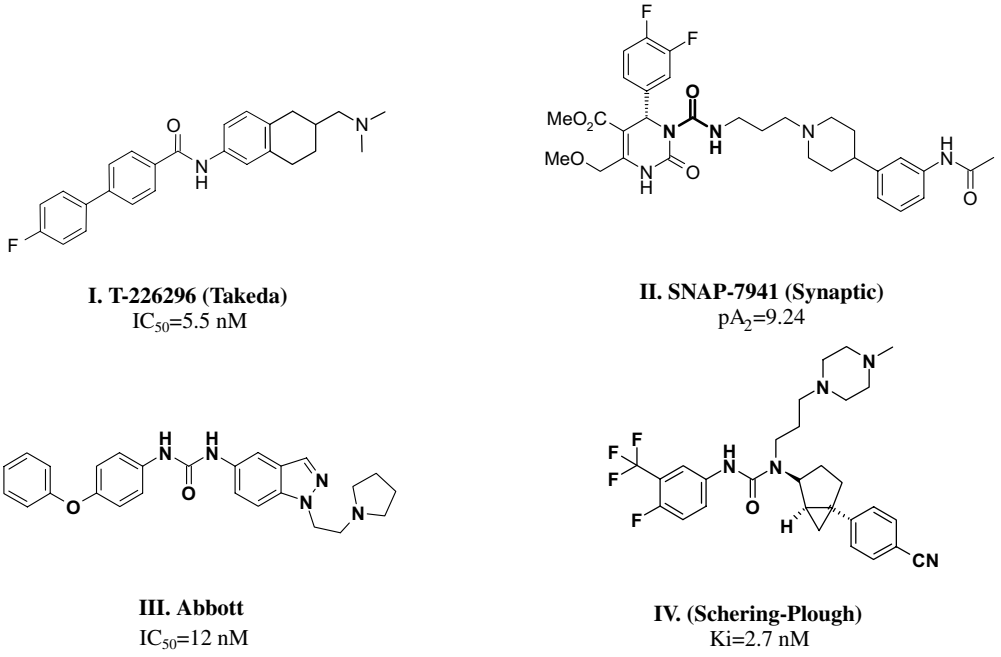


Figure 1. Small molecule MCH-R1 antagonists.

weight that was greater than that elicited by fenfluramine, an effective anorectic agent, in humans.[16] Abbot has reported the discovery of a series of MCH-R1 antagonists based upon indazoles such as compound **III** with potential bindings. Recently, Schering-Plough reported biarylurea derivatives such as compound **IV** which exhibited in vivo efficacy in rodent obesity models.

In spite of the overall structural diversity, most of these templates share a key pharmacophore that contains four common parts: an aromatic region attached to a carboxamide/urea core, which in turn is connected via a linker to a basic amine (Fig. 2).

As part of our research of antiobesity drugs and based on the pharmacophore, we have designed a novel structure (series **1** and **2**) in order to find potential MCH-R1 antagonists. Our strategy included three-component approach as delineated in Figure 3: introduction of substituted biphenylmethyl scaffold in the aromatic region (C1 region); introduction of an urea moiety as the central core (C2 region), and incorporation of a basic amine via a linker in the form of a substituted piperidine ring (C3 region). Furthermore, one of the nitrogens of the urea group would be trisubstituted (Fig. 3).

Herein, we report the synthesis and SAR studies at MCH-R1 of two novel series of substituted biphenylmethyl urea derivatives.

2. Chemistry

Preparation of series **1** derivatives is outlined in Scheme 1. Carbamate derivative **5** was synthesized in three steps from commercially available *N*-Boc-aminopiperidine via: (i) alkylation with 4-methylbenzyl bromide; (ii) *N*-Boc deprotection of the amine via urethane hydrolysis; and (iii) reaction with *p*-nitrophenyl chloroformate **5**. The preparation of amine derivatives involves a four-step procedure starting from commercially available 3-hydroxy-3-methyl-2-butanone **6**. Treatment of **6** with *N*-bromosuccinimide in the presence of the previously prepared catalyst '$NaHSO_4{\cdot}SiO_2$' provided the methylketone bromide **7**. Conversion of the bromide to the corresponding amines (**13**–**17**) was accomplished via treatment with 4-biphenylmethyl amine derivatives **8**–**12** previously prepared via a Suzuki coupling between *p*-bromobenzylamine and a variety of substituted arylboronic acids.[17] Condensation of amines **13**–**17** with *p*-nitrophenylcarbamate derivative **5** in methanol and triethylamine led to the desired urea derivatives **1f**–**j**. The direct reaction of carbamate **5** with 4-biphenylmethyl amine derivatives **8**–**12** yielded compounds **1a**–**e**.

Compounds of series **2** were synthesized by the general route shown in Scheme 2. Condensation of commercially available 4-piperidine ethanol with *p*-methylbenzylbromide under reflux in acetonitrile gave compound **18**, which was converted to aldehyde **19** by

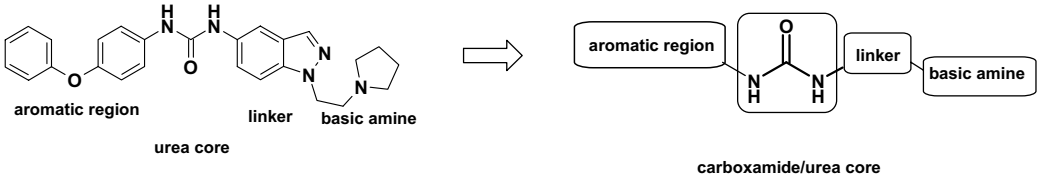


Figure 2. Example of common features of one of the reported MCH-R1 antagonist molecules.

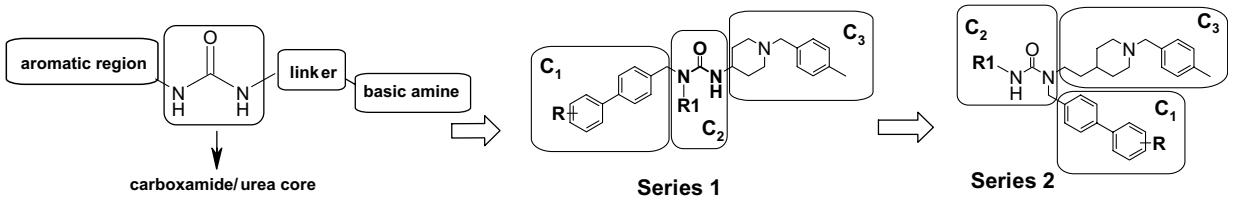
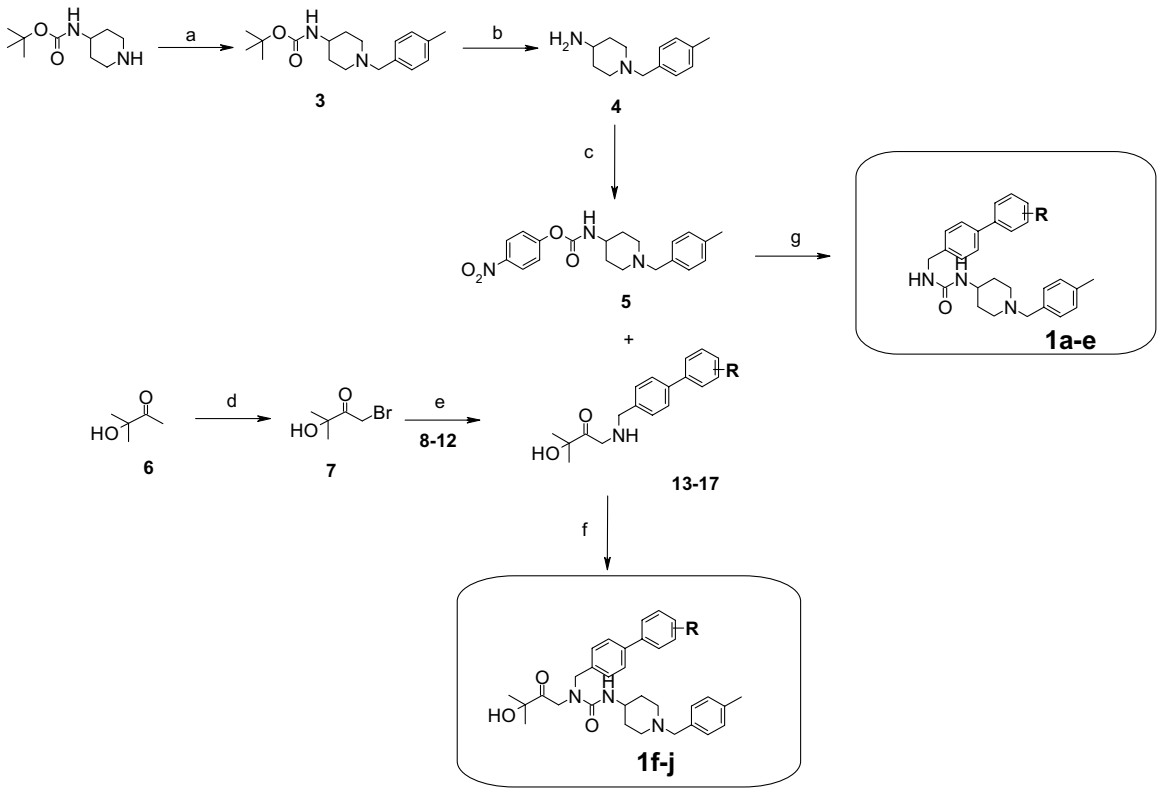


Figure 3. Design of our MCH-R1 antagonist structures.



Scheme 1. Reagents and conditions: (a) *p*-methylbenzylbromide, EtOH, DIEA, N_2, rt, 4 h, 66%; (b) DCM, 4 N HCl, dioxane, 1 N NaOH, rt, 2 h, 98%; (c) *p*-nitrophenylchloroformate, THF, 0 °C, N_2, DIEA, 4 h, 36%; (d) i—$NaHSO_4{\cdot}H_2O$, H_2O, SiO_2, 15 min, 120 °C, 48 h; ii—CCl_4, NBS, $NaHSO_4{\cdot}SiO_2$, 80 °C, 2 h, 75% in two steps; (e) i—arylboronic acid, *p*-bromobenzylamine, CH_3CN, 1 N K_2CO_3, reflux, N_2, $Pd(PPh_3)_4$, 12 h, 80%; ii—MeOH, NEt_3, rt, 6 h; (f) N_2, 6 h, rt, 9%; (g) MeOH, NEt_3, 6 h, 1 M HCl, 36%.

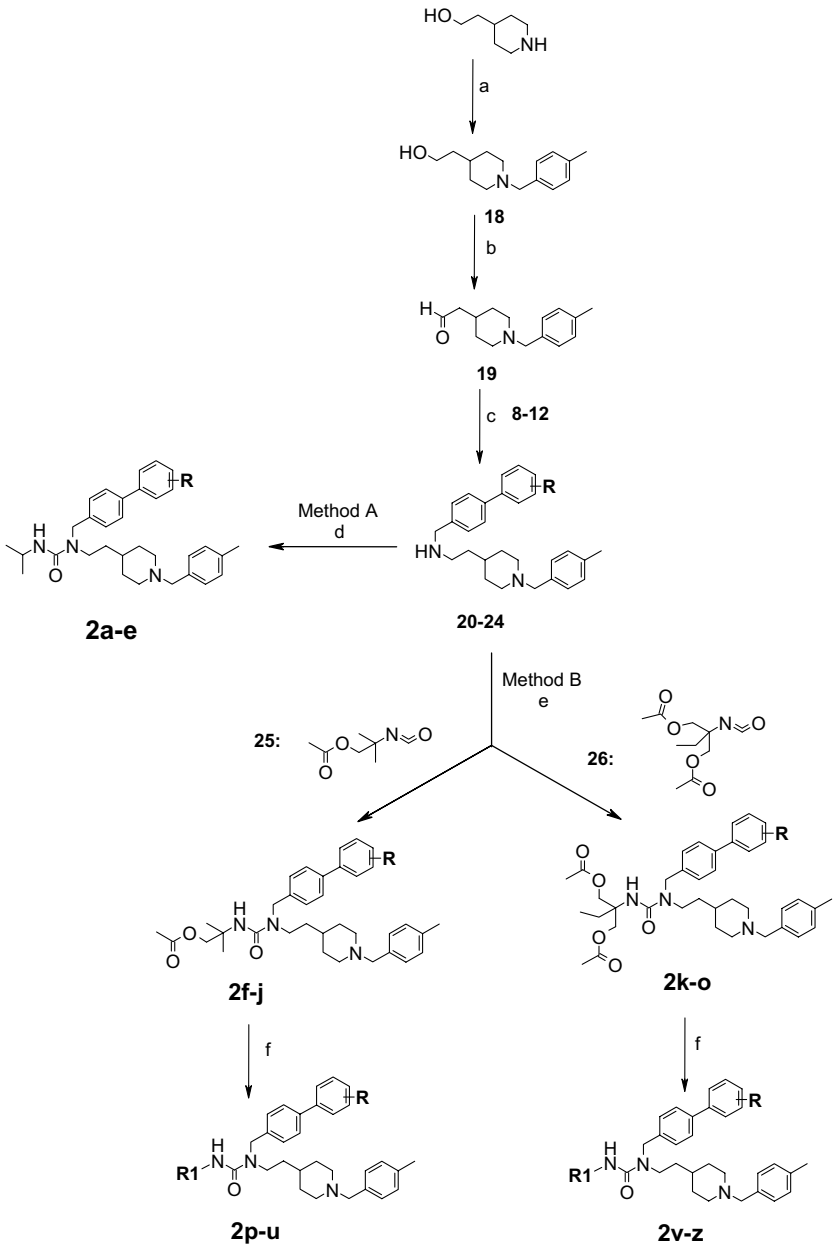
Swern oxidation with dimethylsulfoxide (DMSO) and oxalyl chloride.[18] Suzuki coupling in order to obtain 4-phenylbenzylamine derivatives **8**–**12**, as described in Scheme 1, followed by reductive amination of the aldehyde **19** afforded compounds **20**–**24**. Treatment of resulting amines with appropriate isocyanates via Curtius rearrangement[19] using diphenylphosphorylazide (DPPA) in the presence of triethylamine provided the desired urea derivatives **2a**–**e**. In cases where the isocyanate contains hydroxy groups, they were protected by conversion to an ester group (**2f**–**o**), coupled with the corresponding isocyanates and then deprotected to give the final urea analogs **2p**–**z**, as outlined in Schemes 2 and 3.

3. Results and discussion

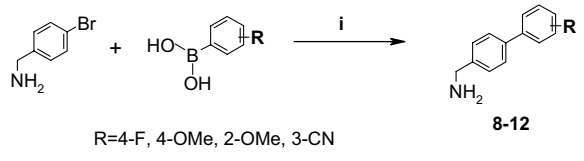
In vitro MCH-R1 binding data for compounds **1a**–**j** are summarized in Table 1. In general, series **1** ureas showed moderate potency. The disubstituted urea compounds **1a**–**e** displayed higher in vitro affinity than the corresponding trisubstituted analogs **1f**–**j**. The disubstituted urea analogs (entries **1a**–**e**) displayed modest affinity for MCH-R1, the most potent urea derivatives of this series being **1d** and **1c** (K_i = 186 and 425 nM, respectively). However, substitution of R1 with 3-hydroxy-3-methyl-2-butanone in the urea moiety (entries **1f**–**j**) was much less tolerated by the receptor.

Furthermore, the substitution of biphenylmethyl group in C1 region resulted in improved affinity (**1a**–**d**). In addition, as demonstrated by compounds **1c** and **1d**, compounds with 2-methoxy and 3-cyano substitution were more potent than the 4-methoxy and 4-fluoro analogs **1b** and **1a**.

In an attempt to improve the MCH-R1 in vitro activity, we examined the effect of modifying the position of the biaryl substituent and changing the distance between the urea scaffold and the piperidine group of the pharmacophore, as can be observed in Figure 3.



Scheme 2. Reagents and conditions: (a) *p*-methylbenzylbromide, CH_3CN, N_2, Cs_2CO_3, rt, 1–2 h, 66%; (b) DMSO, DCM, $(CO)_2Cl_2$, NEt_3, N_2, −78 °C, 4 h, 87%; (c) i—arylboronic acid, *p*-bromobenzylamine, CH_3CN, 1 N K_2CO_3, reflux, N_2, $Pd(PPh_3)_4$, 12 h, 80%; ii—MeOH, molecular sieves, N_2, rt, 12 h, $NaBH(OAc)_3$, 4–8 h, 45% in two steps; (d) Method A. DCM, 0 °C, isopropylisocyanate, 2–3 h, 5%; (e) Method B. i—AcCl, heat; ii—DPPA, NEt_3, toluene, N_2, 50% in two steps; iii—DCM, 0 °C, N_2, 84%; (f) MeOH, rt, K_2CO_3, N_2, 3 h, 15%.

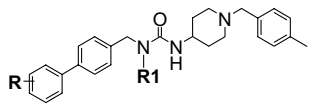


Scheme 3. Reagents and conditions: (i) CH_3CN, 1 N K_2CO_3, reflux, N_2, $Pd(PPh_3)_4$, 12 h, 80%.

The MCH-R1 in vitro affinity of **2a**–**z** is shown in Table 2. In general, the introduction of a hydroxymethyl moiety in R1 resulted in a large increase in affinity at MCH-R1, significantly better than with the isopropyl analog, as exemplified by entries **2p** (96.6 nM) versus **2a** (314 nM) and **2z** (173 nM) versus **2e** (258 nM), due to increased polar character. Compounds **2t** and **2p** were the most potent ureas in this series, with $K_i = 43$ and 96.6 nM, respectively, at MCH-R1. Replacing the hydroxy with an ester led to a drop in potency, as shown when the entry **2i** (254 nM) is compared with **2t** (43 nM) and **2m** (1200 nM) with **2x** (167 nM).

The SAR suggested that better affinity was obtained at MCH-R1 when biphenylmethyl scaffold was substituted on the same nitrogen of the urea moiety as the linker. This statement was confirmed by activity data (**2t**: $K_i = 43$ nM; $K_b = 84$ nM).

Table 1. Binding affinities of urea derivatives **1a–j** (series **1**) toward MCH-R1 receptor



Compound	R	R1	K_b[a] (nM) (pK_b ± SEM) (I_{max} %) h-MCH-R1	K_i[b] (nM) (pK_i ± SEM) h-MCH-R1
1a	4-F	H	198 (6.705) (*n* = 2) (105)	545 (6.265 ± 0.145) (*n* = 2)
1b	4-OMe	H	443 (6.355 ± 0.108) (*n* = 4) (93.5)	1460 (5.84) (*n* = 1)
1c	2-OMe	H	642 (6.19) (*n* = 2) (99.5)	425 (6.37 ± 0.03) (*n* = 2)
1d	3-CN	H	411 (6.385) (*n* = 2) (98)	186 (6.73 ± 0.15) (*n* = 2)
1e	−H	H	1060 (5.975) (*n* = 2) (124)	2640 (5.575 ± 0.055) (*n* = 2)
1f	4-F		4530 (5.343 ± 0.063) (*n* = 3) (79)	5860 (5.23 ± 0.06) (*n* = 2)
1g	4-OMe		>10,000 (<5) (*n* = 3)	ND
1h	2-OMe		3730 (5.428 ± 0.236) (*n* = 4) (68.25)	6050 (5.22) (*n* = 1)
1i	3-CN		5000 (5.30 ± 0.094) (*n* = 4) (84.5)	6380 (5.195 ± 0.075) (*n* = 2)
1j	−H		>10,000	ND

SEM is the standard error of the media. *n* is the number of experiments. ND, no data.

[a] MCH1(h)/GTPgS(-)/HEK-RF8-3Kb is the equilibrium dissociation constant for a competitive antagonist: the concentration that occupies 50% of the receptors at the equilibrium. I_{max} is the current evoked by the concentration of agonist eliciting a maximal response.

[b] MCH1(h)/[3H]SNAP-7941/HEK/SPA-BF136-1. K_i is the in vitro inhibition constant.

In summary, we have designed and synthesized two novel series of MCH-R1 antagonists based on an substituted biphenylmethyl urea core. SAR was explored, suggesting that optimal binding with the receptor was achieved when the biphenylmethyl group and the linker were substituted on the same nitrogen of the urea moiety. Compound **2t** showed the best antagonist binding activity to MCH-R1 with a 43 nM K_i.

4. Pharmacology

All of the urea derivatives described were assayed for their ability to displace radiolabeled [^{35}S]GTPγS in a competitive binding assay. The assay was initiated with the membrane preparations. CHO cells stably expressing human MCH-R1 receptors grown at confluency (in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin, and 100 μg/mL streptomycin) were harvested in PBS containing EDTA 2 mM and then centrifuged at 1000*g* for 5 min (4 °C). The resulting pellet was suspended in HEPES 20 mM (pH 7.5) containing EGTA 5 mM and then homogenized using a Kinematica polytron. The homogenate was then centrifuged (95,000*g*, 30 min, 4 °C) and the resulting pellet was suspended in 50 mM HEPES (pH 7.5), 10 mM $MgCl_2$, and 2 mM EGTA. Aliquots of membrane preparations were stored at −80 °C until use. For [^{35}S]GTPγS binding on membrane preparations, these were diluted in binding buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 3 μM GDP, 5 mM $MgCl_2$, BSA 0.1%, and saponin 10 μg/mL). Incubation was started by the addition of 0.2 mM [^{35}S]GTPγS to the membrane (25 μg/mL) and drugs, and then followed by 45 min at room temperature. For experiments with antagonists, the membranes were preincubated with both the agonist and the antagonist (MCH1(h)/[^{3}H]SNAP-7941/HEK/SPA-BF136-1) for 30 min prior to the addition of [^{35}S]GTPγS. Non-specific binding was defined by using cold GTPγS (10 μM). Reaction was stopped by rapid filtration through GF/B filters, followed by three successive washes with ice cold buffer. Microscint 20 was added to the GF/B filters which were counted using a TopCount (Packard). The results are expressed in K_i and are summarized in Tables 1 and 2.

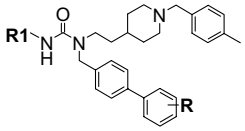
5. Experimental

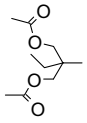
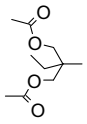
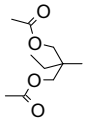
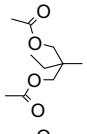
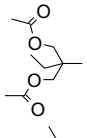
5.1. Chemistry

All reagents and solvents were purchased from commercial sources. E. Merck (Darmstadt, Germany), Scharlau (F.E.R.O.S.A., Barcelona, Spain), Panreac Química S.A. (Montcada i Reixac, Barcelona, Spain), Sigma–Aldrich Química, S.A., (Alcobendas, Madrid), Acros Organics (Janssen Pharmaceuticalaan 3a, 2440 Geel, België), and Lancaster (Bischheim-Strasbourg, France).

Melting points were determined with a Mettler FP82+FP80 apparatus (Greifense, Switzerland) and have not been corrected. The ^{1}H NMR spectra were recorded on a Bruker 400 Ultrashield™ (Bruker BioSpin GmbH, Rheinstetten, Germany), using TMS as the internal standard and with DMSO-d_6 as the solvent; the chemical shifts are reported in ppm (δ) and the coupling constant (J) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), br s (broad singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet). The IR spectra were recorded on Thermo Nicolet FT-IR Nexus Euro (Madison, USA) using

Table 2. Binding affinities of urea derivatives **2a**–**z** (series **2**) toward MCH-R1 receptor



Compound	R1	R	K_b[a] (nM) (pK_b ± SEM) (I_{max} %) h-MCH-R1	K_i[b] (nM) (pK_i ± SEM) h-MCH-R1
2a		4-F	383 (6.42) (*n* = 2) (113)	314 (6.505 ± 0.155) (*n* = 2)
2b		4-OMe	467 (6.335) (*n* = 2) (91.5)	273 (6.56 ± 0.13) (*n* = 3)
2c		2-OMe	>10,000 (<5) (*n* = 2)	ND
2d		3-CN	1010 (5.995) (*n* = 2) (97)	509 (6.29 ± 0.12) (*n* = 2)
2e		–H	220	258 (6.59 ± 0.84) (*n* = 3)
2f		4-F	409 (6.39 ± 0.142) (*n* = 3) (92.33)	421 (6.375 ± 0.175) (*n* = 2)
2g		4-OMe	647 (6.19 ± 0.191) (*n* = 3) (111.67)	595 (6.225 ± 0.125) (*n* = 2)
2h		2-OMe	721 (6.145) (*n* = 2) (97.5)	215 (6.668 ± 0.135) (*n* = 4)
2i		3-CN	233 (6.63) (*n* = 2) (103)	254 (6.595 ± 0.055) (*n* = 2)
2j		–H	366 (6.435) (*n* = 2) (101.5)	947 (6.02 ± 0.14) (*n* = 2)
2k		4-F	196 (6.71 ± 0.104) (*n* = 4) (111.75)	214 (6.67 ± 0.05) (*n* = 2)
2l		4-OMe	139 (6.857 ± 0.243) (*n* = 3) (93.67)	170 (6.77 ± 0.01) (*n* = 2)
2m		2-OMe	ND	1200
2n		3-CN	ND	1080
2o		–H	260 (6.585 ± 0.074) (*n* = 4) (114)	388 (6.41 ± 0.03) (*n* = 2)
2p		4-F	41.4 (7.385) (*n* = 2) (101.5)	96.6 (7.015 ± 0.135) (*n* = 2)

(*continued on next page*)

Table 2 (*continued*)

Compound	R1	R	K_b[a] (nM) (pK_b ± SEM) (I_{max} %) h-MCH-R1	K_i[b] (nM) (pK_i ± SEM) h-MCH-R1
2r		4-OMe	93 (7.06) (*n* = 2) (99)	204 (6.69) (*n* = 1)
2s		2-OMe	134 (6.875) (*n* = 2) (100)	251 (6.6 ± 0.04) (*n* = 2)
2t		3-CN	84 (7.077 ± 0.252) (*n* = 3) (99.33)	43 (7.36 ± 0.01) (*n* = 2)
2u		–H	122 (6.197 ± 0.195) (*n* = 3) (105)	144 (6.84 ± 0.015) (*n* = 2)
2v		4-F	293 (6.535) (*n* = 2) (111)	149 (6.825 ± 0.145) (*n* = 2)
2w		4-OMe	117 (6.93 ± 0.278) (*n* = 3) (108)	143 (6.84 ± 0.12) (*n* = 3)
2x		2-OMe	225 (6.647 ± 0.119) (*n* = 3) (94)	167 (6.78 ± 0.1) (*n* = 2)
2y		3-CN	3900 (5.41) (*n* = 1) (108)	769 (6.11 ± 0.04) (*n* = 2)
2z		–H	147 (6.835) (*n* = 2) (93.5)	173 (6.76 ± 0.01) (*n* = 2)

SEM is the standard error of the media. *n* is the number of experiments. ND, no data.

[a] MCH1(h)/GTPgS(-)/HEK-RF8-3Kb is the equilibrium dissociation constant for a competitive antagonist: the concentration that occupies 50% of the receptors at the equilibrium. Imax is the current evoked by the concentration of agonist eliciting a maximal response.

[b] MCH1(h)/[3H]SNAP-7941/HEK/SPA-BF136-1. K_i is the in vitro inhibition constant.

KBr pellets; the frequencies are expressed in cm^{-1}. Signal intensities are expressed by: vs (very strong), s (strong), m (medium), and w (weak). Elemental microanalyses were obtained on an Elemental Analyzer LECO CHN-900 (Michigan, USA) from vacuum-dried samples. The analytical results for C, H, and N were within ±0.4 of the theoretical values. Mass spectra were measured on a Agilent Technologies Model MSD/DS 5973N (mod. G2577A) mass spectrometer with direct insertion probe (DIP) (Waldbronn, Germany) and the ionization method was electron impact (EI, 70 eV).

The progress of the reactions was followed by thin-layer chromatography and silica gel 60 (0.040–0.063 mm) Alugram® SIL G/UV_{254} (Layer: 0.2 mm) (Macherey-Nagel GmbH & Co. KG. Postfach 101352. D-52313 Düren, Germany). Flash column chromatography was carried out using (Merck). HPLC conditions: Column Lichrospher 100 RP18 E.C. 5 μm (20 × 0.46), Ref. TR011567, NS N23892; mobile phase: MeOH/H_2O 60/40; flux: 1 mL/min.

5.2. Procedure for the preparation of *N*-[1-(4-methylbenzyl)-4-piperidinyl]-*tert*-butylcarbamate (3)

To a solution of *N*-Boc-aminopiperidine (10 g, 50 mmol) in 100 mL of ethanol was added dropwise under N_2 atmosphere 4-methylbenzylbromide (9.41 g, 50.9 mmol). Diisopropylethylamine (14.48 g, 112 mmol) was then added and helped to dissolve the compounds. The reaction mixture was stirred under N_2 atmosphere for 3–4 h, filtered, and concentrated to dryness in vacuo. The residue was recrystallized by ethanol in order to give **3** (6.21 g, yield: 66%) as a white solid. IR (KBr) *v*: 3361 (N–H), 1684 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) *δ*: 1.33 (d, 2H); 1.37 (s, 9H); 1.65 (d, 2H); 1.91 (t, 2H); 2.27 (s, 3H); 2.72 (d, 2H); 3.20 (s, 1H); 3.42 (s, 2H); 6.75 (s, 1H); 7.11 (d, 2H); 7.15 (d, 2H). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.05%; H, 9.21%; N, 9.21%. Found: C, 71.30%; H, 9.49%; N, 9.26%.

5.3. Procedure for the preparation of 1-(4-methylbenzyl)-4-piperidinamine (4)

Compound **3** (4 g, 13.18 mmol) was diluted in CH_2Cl_2 (50 mL) and submitted to dioxane (60 mL) and HCl 4 N, and stirred for 3 h. The reaction mixture was then filtered and the solid was washed with a solution of 1 N NaOH. The organic layer was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to yield compound **4** (2.63 g, yield: 98%) as a white oil. IR (KBr) *v*: 3355 (N–H_2), 1292 (C–N) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) *δ*: 1.20 (m, 2H); 1.63 (d, 2H); 1.89 (t, 2H); 2.27 (s, 3H); 2.43 (s, 2H); 2.49 (m, 1H);

2.69 (d, 2H); 7.09 (d, 2H); 7.14 (d, 2H). MS (EI, 70 eV): *m/z* (%) = 205 ([M]$^+$, 10), 189 (75), 113 (100), 99 (52), 85 (45).

5.4. Procedure for the preparation of *N*-[1-(4-methylbenzyl)-4-piperidinyl]-4-nitrophenylcarbamate (5)

To a solution of compound **4** (2 g, 9.80 mmol) in anhydrous THF (50 mL) was added *p*-nitrophenylchloroformate (2.17 g, 10.80 mmol) and was stirred at 0 °C, under N_2 atmosphere. Finally, DIEA (1.39 g, 10.80 mmol) was added to the reaction mixture, which was stirred at this temperature for about 4 h. The reaction mixture was filtered to obtain compound **5** (1.30 g, yield: 36%) as a white solid. Mp 195–196 °C. IR (KBr) *v*: 3217 (N–H), 1752 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.90 (t, 2H); 2.02 (d, 2H); 2.33 (s, 3H); 3.00 (d, 2H); 3.31 (d, 2H); 3.59 (s, 1H); 4.19 (d, 2H); 7.26 (d, 2H); 7.40 (d, 2H); 7.48 (d, 2H); 8.35 (d, 2H); 10.73 (s, 1H). Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.04%; H,6.23%; N, 11.38%. Found: C, 65.20%; H, 6.40%; N, 11.35%. MS (EI, 70 eV): *m/z* (%) = 369 ([M]$^+$, 5), 323 (2), 230 (40), 202 (3), 105 (100).

5.5. Procedure for the preparation of 1-bromo-3-hydroxy-3-methyl-2-butanone (7)

5.5.1. Preparation of $NaHSO_4{\cdot}SiO_2$ catalyst. SiO_2 (1.00 equiv) was added to a solution of $NaHSO_4{\cdot}H_2O$ (1.00 equiv) in water and the reaction mixture was stirred for 15 min. The mixture was then heated slowly until the formation of a white solid. Finally, this solid was dried at 120 °C for 48 h in a stove.

5.5.2. Synthesis of 1-bromo-3-hydroxy-3-methyl-2-butanone (7). *N*-Bromosuccinimide (NBS) (4.18 g, 23.48 mmol) was added to a solution of 3-hydroxy-3-methyl-2-butanone **6** (2.00 g, 19.58 mmol) in CCl_4 (100 mL). The mixture was stirred and $NaHSO_4{\cdot}SiO_2$ was added (1.76 g, 9.79 mmol). The mixture was then stirred under reflux to 80 °C for 2 h. The reaction mixture was filtered and then evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 99:1) in order to obtain **6** (2.63 g, yield: 75%) as a beige oil. IR (KBr) *v*: 3441 (O–H), 1710 (C=O)cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.24 (s, 6H); 4.71 (s, 2H). MS (EI, 70 eV): *m/z* (%) = 181 ([M]$^+$, 5), 142 (18), 135 (10), 105 (100), 97 (30).

5.6. General procedure for the preparation of 4-biphenylmethylamine derivatives (8–11)

In a 250 mL tricol, *p*-bromobenzylamine (8.64 g, 0.046 mmol) was added to a solution of the appropriate arylboronic acid (6.5 g, 0.046 mmol) in dry acetonitrile (90 mL). Then, a solution of 1 N K_2CO_3 (93 mL) was added and the mixture was stirred and heated at reflux under N_2 atmosphere. After 15 min, tetrakis(triphenylphosphine)palladium (0) (2.68 g, 0.002 mmol) was added. The reaction was found completed after 8 h. The mixture was then filtered and evaporated in vacuo. After adding HCl, the crude product was obtained and washed with CH_2Cl_2 and MeOH in order to afford **8**–**11** derivatives.

5.6.1. Procedure for the preparation of (4′-fluoro-4-biphenyl)methylamine (8). The title compound was synthesized from *p*-bromobenzylamine and *p*-fluorophenylboronic acid according to the experimental procedure of Section 5.6 in order to provide **8** (7.2 g, yield: 77%) as a beige solid. Mp 270–272 °C. IR (KBr) *v*: 3413 (NH_2) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.05 (d, 2H); 7.27–7.31 (m, 2H); 7.60 (d, 2H, *J* = 8.3 Hz); 7.71–7.75 (m, 4H); 8.60 (br s, 2H). Anal. Calcd for $C_{13}H_{12}FN$: C, 77.61%; H, 5.97%; N, 6.96%. Found: C, 77.25%; H, 6.30%; N, 6.51%.

5.6.2. Procedure for the preparation of (4′-methoxy-4-biphenyl)methylamine (9). The title compound was synthesized from *p*-bromobenzylamine and *p*-methoxyphenylboronic acid according to the experimental procedure of Section 5.6 in order to provide **9** (8.5 g, yield: 88%) as a beige solid. Mp 273–275 °C. IR (KBr) *v* 3416 (NH_2); 1251 (C–O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.79 (s, 3H); 4.01 (s, 2H); 7.03 (d, 2H, *J* = 8.7 Hz); 7.56 (d, 2H, *J* = 8.6 Hz); 7.59–7.69 (m, 4H); 8.56 (s, 2H). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.87%; H, 7.04%; N, 6.57%. Found: C, 78.95%; H, 7.16%; N, 6.25%.

5.6.3. Procedure for the preparation of (2′-methoxy-4-biphenyl)methylamine (10). The title compound was synthesized from *p*-bromobenzylamine and *o*-methoxyphenylboronic acid according to the experimental procedure of Section 5.6 in order to provide **10** (7.68 g, yield: 80%) as a beige solid. Mp 240–245 °C. IR (KBr) *v*: 3406 (NH2); 1259 (C–O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.76 (s, 3H); 4.04 (s, 2H); 7.04 (t, 1H, *J* = 7.4 Hz); 7.12 (d, 1H, *J* = 8.3 Hz); 7.28 (d, 1H, *J* = 6.0 Hz); 7.34 (t, 1H, *J* = 4.2 Hz); 7.45–7.53 (m, 4H); 8.46 (s, 2H). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.87%; H, 7.04%; N, 6.57%. Found: C, 78.55%; H, 7.01%; N, 6.87%.

5.6.4. Procedure for the preparation of (3′-cyano-4-biphenyl)methylamine (11). The title compound was synthesized from *p*-bromobenzylamine and *m*-cyanophenylboronic acid according to the experimental procedure of Section 5.6 in order to provide **11** (5.95 g, yield: 85%) as a beige solid. Mp 187–189 °C. IR (KBr) *v*: 3372 (NH_2); 2225 (CN) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.97–4.08 (m, 2H); 7.48 (d, 1H); 7.60–7.70 (m, 3H); 7.80–7.86 (m, 2H); 8.06 (d, 1H, *J* = 7.9 Hz); 8.19 (s, 1H). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74%; H, 5.81%; N, 13.45%. Found: C, 80.96%; H, 5.91%; N, 13.28%.

5.7. General procedure for the preparation of 1-(4-biphenylmethyl)-3-[1-(4-methyl benzyl)-4-piperidinyl]urea derivatives (1a–e)

The appropriate 4-biphenylmethyl amine derivatives **8**–**12** (1.20 equiv) and compound **5** (1.00 equiv) was dissolved in methanol (30 mL) and triethylamine (1.00 equiv) were added to the reaction medium. After 6 h of stirring, the solvent was evaporated and the reaction mixture washed with $NaHCO_3$ and extracted with dichloromethane, then washed with HCl 1 M and extracted with dichloromethane. The organic layer was

dried with anhydrous Na_2SO_4 and the solvent evaporated and dried. The white solid obtained was stirred in a solution of 1 M NaOH and extracted with CH_2Cl_2. The new organic layer was dried with anhydrous Na_2SO_4 and the solvent evaporated in order to obtain the desired urea derivatives **1a**–**e**.

5.7.1. Procedure for the preparation of 1-(4′-fluoro-4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1a). The title compound was synthesized from **8** and **5** according to the experimental procedure of Section 5.7 in order to provide **1a** (0.18 g, yield: 77%) as a white solid. Mp 270–272 °C. IR (KBr) *v*: 3309 (NH_2); 1626 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.32 (q, 2H); 1.74 (d, 2H); 2.00 (t, 2H); 2.28 (s, 3H); 2.68 (d, 2H); 3.38 (s, 2H); 4.23 (d, 2H); 5.90 (d, 1H); 6.26 (t, 1H); 7.11 (d, 2H); 7.16 (d, 2H); 7.26 (d, 2H); 7.31 (d, 2H); 7.58 (d, 2H); 7.68 (m, 2H). Anal. Calcd for $C_{27}H_{30}FN_3O$: C, 77.61%; H, 5.97%; N, 6.96%. Found: C, 77.25%; H, 6.30%; N, 6.51%. MS (EI, 70 eV): *m*/*z* (%) = 431 ($[M]^+$, 45), 416 (2), 326 (15), 246 (7), 185 (100).

5.7.2. Procedure for the preparation of 1-(4′-methoxy-4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1b). The title compound was synthesized from **9** and **5** according to the experimental procedure of Section 5.7 in order to provide **1b** (0.05 g, yield: 14%) as a white solid. Mp 189–191 °C. IR (KBr) *v*: 3321 (N–H); 1619 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.31 (q, 2H); 1.73 (d, 2H); 1.99 (t, 2H); 2.27 (s, 3H); 2.67 (d, 2H); 3.38 (s, 2H); 3.78 (s, 3H); 4.21 (d, 2H); 5.90 (d, 1H); 6.25 (t, 1H); 7.01 (d, 2H); 7.11 (d, 2H); 7.16 (d, 2H); 7.28 (d, 2H); 7.57 (m, 4H). Anal. Calcd for $C_{28}H_{33}N_3O_2{\cdot}1/2H_2O$: C, 74.33%; H, 7.52%; N, 9.29 %. Found: C, 73.81%; H, 7.71%; N, 9.21%. MS (EI, 70 eV): *m*/*z* (%) = 443 ($[M]^+$, 44), 182 (12), 159 (15), 146 (38), 105 (100).

5.7.3. Procedure for the preparation of 1-(2′-methoxy-4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1c). The title compound was synthesized from **10** and **5** according to the experimental procedure of Section 5.7 in order to provide **1c** (0.02 g, yield: 2%) as a brown oil. IR (KBr) *v*: 3312 (N–H); 1631 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.36 (m, 2H); 1.73 (br s, 2H); 1.99 (br s, 2H); 2.28 (s, 3H); 2.68 (br s, 2H); 3.34 (s, 2H); 3.75 (s, 3H); 4.21 (d, 2H); 5.91 (d, 1H); 6.25 (m, 1H); 7.02 (t, 1H); 7.11 (d, 2H); 7.18 (m, 2H); 7.25 (d, 2H); 7.33 (m, 1H); 7.39 (d, 2H); 7.49 (d, 1H). Anal. Calcd for $C_{28}H_{33}N_3O_2{\cdot}1/2\ H_2O$: C, 74.33%; H, 7.52%; N, 9.29 %. Found: C, 74.40%; H, 7.60%; N, 9.24%. MS (EI, 70 eV): *m*/*z* (%) = 443 ($[M]^+$, 32), 338 (7), 239 (25), 197 (40), 105 (100).

5.7.4. Procedure for the preparation of 1-(3′-cyano-4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1d). The title compound was synthesized from **11** and **5** according to the experimental procedure of Section 5.7 in order to provide **1d** (0.11 g, yield: 47%) as a white solid. IR (KBr) *v*: 3314 (N–H); 1627 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) 1.34 (q, 2H); 1.75 (d, 2H); 2.08 (br s, 2H); 2.28 (s, 3H); 2.71 (br s, 2H); 3.42 (s, 2H); 4.24 (d, 2H); 5.95 (d, 1H); 6.30 (t, 1H); 7.12 (d, 2H); 7.19 (t, 2H); 7.35 (d, 2H); 7.65 (d, 1H); 7.69 (d, 2H); 7.81 (d, 1H); 8.00 (dd, 1H); 8.13 (s, 1H). Anal. Calcd for $C_{28}H_{30}N_4O$: C, 76.71 %; H, 6.85%; N, 12.78%. Found: C, 76.54%; H, 6.75%; N, 12.84 %. MS (EI, 70 eV): *m*/*z* (%) = 438 ($[M]^+$, 5), 333 (4), 234 (10), 192 (12), 105 (100).

5.7.5. Procedure for the preparation of 1-(4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1e). The title compound was synthesized from **12** and **5** according to the experimental procedure of Section 5.7 in order to provide **1e** (0.14 g, yield: 40%) as a white solid. Mp 173–175 °C. IR (KBr) *v*: 3334 (N–H); 1625 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) 1.32 (m, 2H); 1.74 (d, 2H); 1.99 (m, 2H); 2.28 (s, 3H); 2.68 (d, 2H); 3.38 (s, 2H); 3.49 (s, 1H); 4.23 (d, 2H); 5.90 (d, 1H, J = 7.9 Hz); 6.27 (t, 1H); 7.11 (d, 2H, J = 8.0 Hz); 7.16 (d, 2H, J = 7.9 Hz); 7.32 (d, 2H, J = 7.6 Hz); 7.36 (t, 1H); 7.69 (d, 2H); 7.45 (t, 2H, J = 7.6 Hz); 7.61 (d, 2H, J = 8.0 Hz); 7.64 (d, 2H, J = 8.2 Hz). Anal. Calcd for $C_{27}H_{31}N_3O$: C, 78.45%; H, 7.51%; N, 10.17%. Found: C, 78.41%; H, 7.59%; N, 9.99%. MS (EI, 70 eV): *m*/*z* (%) = 413 ($[M]^+$, 7), 308 (5), 248 (3), 167 (33), 146 (26), 105 (100).

5.8. General procedure for the preparation of 1-(4-biphenylmethyl)-1-(3-hydroxy-3-methyl-2-oxobutyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea derivatives (1f–j)

The formation of 1-(4-biphenylmethylamino)-3-hydroxy-3-methyl-2-butanone derivatives **13**–**17** was first achieved from the reaction of the appropriate 4-biphenylmethyl amine derivatives **8**–**12** (1.00 equiv) with compound **7** (1.00 equiv). When the reaction had finished, compound **5** (1.00 equiv) was added to the same medium of reaction, without isolation of the intermediates **13**–**17**. After 6 h of stirring in N_2 atmosphere, the solvent was evaporated and the product was extracted with CH_2Cl_2 and was eliminated and the final product was purified by silica gel preparative thin layer and flash chromatography (CH_2Cl_2/MeOH 90:10) to obtain **1f**–**j**.

5.8.1. Procedure for the preparation of 1-(4′-fluoro-4-biphenylmethyl)-1-(3-hydroxy-3-methyl-2-oxobutyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1f). The title compound was synthesized from **7**, **8**, and **5** according to the same procedure of Section 5.8 in order to afford **1f** (0.19 g, yield: 13%) as a beige solid. Mp 77–79 °C. IR (KBr) *v*: 3332 (N–H); 1663 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.02–1.06 (m, 6H); 1.54 (s, 2H); 1.68 (s, 2H); 1.91 (s, 2H); 2.28 (s, 3H); 2.85 (m, 2H); 3.26 (d, 1H); 3.43 (d, 2H); 4.12–4.39 (m, 2H); 4.55 (d, 2H); 5.83 (s, 1H); 7.13 (d, 2H, J = 7.1 Hz); 7.17 (br s, 2H); 7.29 (m, 4H); 7.53 (d, 1H); 7.61 (t, 2H); 7.70 (m, 2H). Anal. Calcd for $C_{32}H_{38}N_3O_3F$: C, 72.32%, H, 7.15%; N, 7.91%. Found: C, 72.39%; H, 7.17%; N, 7.86%. MS (EI, 70 eV): *m*/*z* (%) = 532 ($[M]^+$, 2), 513 (4), 363 (4), 326 (4), 186 (100).

5.8.2. Procedure for the preparation of 1-(3-hydroxy-3-methyl-2-oxobutyl)-1-(4′-methoxy-4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1g). The title compound was synthesized from **7**, **9**, and **5** according to the same procedure of Section 5.8 in order to afford

1g (0.03 g, yield: 7%) as a beige solid. Mp 73–75 °C. IR (KBr) *v*: 3330 (N–H); 1667 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.04 (d, 6H); 1.58 (s, 2H); 1.72 (s, 2H); 1.91 (s, 2H); 2.29 (s, 3H); 2.88 (m, 2H); 3.26 (d, 1H); 3.36 (d, 2H); 3.78 (s, 3H); 4.18–4.37 (dd, 2H); 4.56 (s, 2H); 5.85 (s, 1H); 7.01 (d, 2H, J = 8.8 Hz); 7.14 (d, 2H); 7.20 (m, 4H); 7.27 (d, 2H); 7.59 (m, 4H); 7.70 (m, 2H). Anal. Calcd for $C_{33}H_{41}N_3O_4$: C, 72.93%, H, 7.55%; N, 7.73%. Found: C, 72.68%; H, 7.48%; N, 7.89%. MS (EI, 70 eV): *m/z* (%) = 544 ($[M]^+$, 2), 525 (4), 486 (3), 339 (4), 197 (100).

5.8.3. Procedure for the preparation of 1-(3-hydroxy-3-methyl-2-oxobutyl)-1-(2′-methoxy-4-biphenylmethyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1h). The title compound was synthesized from **7**, **10**, and **5** according to the same procedure of Section 5.8 in order to afford **1h** (0.08 g, yield: 5%) as a beige solid. Mp 89–90 °C. IR (KBr) *v*: 3299 (N–H); 1665 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.06 (m, 6H); 1.57 (br s, 2H); 1.76 (br s, 2H); 1.91 (br s, 2H); 2.29 (s, 3H); 2.92–3.01 (dd, 2H); 3.26 (d, 1H); 3.54 (d, 2H); 3.75 (s, 3H); 4.23–4.34 (dd, 2H); 4.57 (s, 2H); 5.88 (s, 1H); 7.01 (t, 1H); 7.18 (m, 4H); 7.26 (m, 3H); 7.32 (d, 1H); 7.43 (d, 2H); 7.53 (d, 1H). Anal. Calcd for $C_{33}H_{41}N_3O_4$: C, 72.93%, H, 7.55%; N, 7.73%. Found: C, 72.75%; H, 7.51%; N, 7.79%. MS (EI, 70 eV): *m/z* (%) = 524 (2), 507 (5), 327 (4), 200 (32), 186 (100).

5.8.4. Procedure for the preparation of 1-(3′-cyano-4-biphenylmethyl)-1-(3-hydroxy-3-methyl-2-oxobutyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1i). The title compound was synthesized from **7**, **11**, and **5** according to the same procedure of Section 5.8 in order to afford **1i** (0.06 g, yield: 13%) as a beige solid. Mp 128–130 °C. IR (KBr) *v*: 3229 (N–H); 1668 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.06 (m, 6H); 1.26 (m, 2H); 1.75 (br s, 2H); 1.91 (br s, 2H); 2.33 (s, 3H); 2.94–3.02 (dd, 2H); 3.26 (d, 1H); 3.69 (br s, 2H); 4.29 (m, 2H); 4.64 (s, 2H); 5.96 (s, 1H); 7.26 (br s, 2H); 7.34 (d, 4H); 7.53 (d, 1H); 7.67 (t, 1H); 7.74 (d, 2H); 7.83 (d, 1H); 8.03 (d, 1H) Anal. Calcd for $C_{33}H_{38}N_4O_3 \cdot HCl$: C, 68.93%, H, 6.79%; N, 9.75%. Found: C, 68.85%; H, 6.69%; N, 9.67%. MS (EI, 70 eV): *m/z* (%) = 538 ($[M]^+$, 2), 508 (5), 479 (3), 370 (5), 186 (100).

5.8.5. Procedure for the preparation of 1-(4-biphenylmethyl)-1-(3-hydroxy-3-methyl-2-oxobutyl)-3-[1-(4-methylbenzyl)-4-piperidinyl]urea (1j). The title compound was synthesized from **7**, **12**, and **5** according to the same procedure of Section 5.8 in order to afford **1j** (0.10 g, yield: 7%) as a beige solid. Mp 121–122 °C. IR (KBr) *v*: 3383 (N–H); 1672 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.06 (d, 6H); 1.38 (s, 2H); 1.66 (s, 2H); 1.81 (s, 2H); 2.39 (s, 3H); 2.99 (d, 2H); 3.29 (d, 2H); 3.58 (d,1H); 4.22–4.39 (dd, 2H); 4.65 (d, 2H); 5.76 (s, 1H); 5.96 (s, 1H); 7.20 (s, 2H); 7.31 (m, 4H); 7.36 (t, 1H); 7.46 (t, 2H); 7.66 (t, 4H). Anal. Calcd for $C_{32}H_{39}N_3O_3$: C, 74.85%, H, 7.60%; N, 8.18%. Found: C, 74.54%; H, 7.46%; N, 7.95%. MS (EI, 70 eV): *m/z* (%) = 495 (10), 436 (23), 372 (4), 310 (9), 186 (100).

5.9. Procedure for the preparation of 2-[1-(4-methylbenzyl)-4-piperidinyl]ethanol (18)

4-Piperidine ethanol (5.19 g, 40.17 mmol) in acetonitrile (125 mL) was treated under N_2 atmosphere with *p*-methylbenzylbromide (7.43 g, 40.17 mmol) and cesium carbonate (13.09 g, 40.17 mmol). The reaction mixture was stirred under reflux for 1–2 h, filtered, and concentrated to dryness in vacuo. The residue was taken up with diethyl ether (20 mL). The obtained precipitate was filtered and the liquid fraction was evaporated in order to give **18** (6.21 g, yield: 66%) as a yellow oil. IR (KBr) *v*: 3354 (O–H); 1285 (C–N) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.06–1.15 (m, 2H); 1.32–1.35 (m, 3H); 1.58 (d, 2H); 1.81–1.87 (m, 2H); 2.27 (s, 3H); 2.74 (d, 2H); 3.38–3.44 (s, 2H); 3.49 (d, 2H); 4.32 (t, 1H, J = 5.1 Hz); 7.10 (d, 2H, J = 8.0 Hz); 7.15 (d, 2H, J = 8.0 Hz). MS (EI, 70 eV): *m/z* (%) = 233 ($[M]^+$, 10), 216 (15), 202 (8), 142 (75), 105 (100).

5.10. Procedure for the preparation of [1-(4-methylbenzyl)-4-piperidinyl]acetaldehyde (19)

DMSO (4.15 mL, 58.64 mmol) in 5 mL CH_2Cl_2 was added dropwise to a solution of oxalyl chloride (9.13 g, 71.96 mmol) in CH_2Cl_2 (40 mL) and then stirred at −78 °C under N_2 atmosphere. After 5 min of stirring, compound **18** (6.21 g, 26.65 mmol) was diluted in CH_2Cl_2 (50 mL) and stirred for 30 min at −78 °C. Finally, triethylamine (27.44 mL, 197.23 mmol) was added dropwise and the mixture was stirred at this temperature for approximately 10 min. The reaction mixture was warmed to room temperature for about 2 h, quenched with H_2O, and extracted with CH_2Cl_2. The organic phase was dried over anhydrous sodium sulfate and evaporated in vacuo to afford **19** (5.37 g, yield: 87%) as a beige oil. IR (KBr) *v*: 1724 (C═O); 1265 (C–N) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.16–1.20 (m, 2H); 1.58 (d, 2H); 1.78 (br s, 1H); 1.89 (t, 2H); 2.27 (s, 3H); 2.32–2.34 (m, 2H); 2.74 (d, 2H); 3.42 (s, 2H); 7.10 (d, 2H, J = 7.8 Hz); 7.15 (d, 2H, J = 8.2 Hz); 9.65 (s, 1H). MS (EI, 70 eV): *m/z* (%) = 231 ($[M]^+$, 5), 214 (15), 202 (20), 188 (56), 105 (100).

5.11. General procedure for the preparation of (4-biphenylmethyl)-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}amine derivatives (20–24)

Compound **19** (5.37 g, 23.25 mmol) and the appropriate 4-biphenylmethyl amine derivatives **8**–**12** (4.26 g, 23.25 mmol) were combined in MeOH (60 mL) and stirred in the presence of molecular sieves at room temperature, under N_2 atmosphere, overnight. Triacetoxysodiumborohydride (7.88 g, 37.19 mmol) was then added and stirred for 4–8 h. The reaction was followed by TLC (CH_2Cl_2/MeOH 95:5) and was found complete after 4–8 h (it depends on the 4-phenylbenzylamine derivative). The reaction was quenched with $NaHCO_3$, extracted with CH_2Cl_2, dried over anhydrous sodium sulfate, and evaporated. The residue was washed with diethyl ether and acetone in order to give the desired amines **20**–**24**.

5.11.1. Procedure for the preparation of (4′-fluoro-4-biphenylmethyl)-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}-amine (20). The title compound was synthesized from **19** and **8** according to the experimental procedure of Section 5.11 in order to provide **20** (0.73 g, yield: 44%) as a beige oil. IR (KBr) *v*: 3354 (N–H) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.05–1.13 (m, 2H); 1.35 (t, 3H); 1.56 (d, 2H); 1.83 (t, 2H); 2.27 (s, 3H); 2.72 (d, 2H); 3.47 (s, 4H); 3.67 (s, 2H); 7.08–7.15 (m, 4H); 7.27 (t, 2H); 7.39 (d, 2H, J = 7.9 Hz); 7.58 (t, 2H); 7.68 (t, 2H). MS (EI, 70 eV): *m/z* (%) = 416 ($[M^{\cdot}]^+$, 15), 397 (12), 245 (4), 231 (100), 213 (10).

5.11.2. Procedure for the preparation of (4′-methoxy-4-biphenylmethyl)-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}-amine (21). The title compound was synthesized from **19** and **9** according to the experimental procedure of Section 5.11 in order to provide **21** (0.80 g, yield: 40%) as a beige oil. IR (KBr) *v*: 3346 (N–H) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.09–1.15 (m, 4H); 1.32–1.36 (m, 1H); 1.54–1.60 (m, 2H); 1.91 (br s, 2H); 2.27 (s, 3H); 2.77–2.85 (m, 2H); 2.91–2.97 (m, 2H); 3.42–3.48 (m, 4H); 3.79 (s, 3H); 7.03 (d, 2H, J = 8.7 Hz); 7.11 (d, 2H, J = 7.6 Hz); 7.15 (d, 2H); 7.29 (t, 2H); 7.53–7.67 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 428 ($[M^{\cdot}]^+$, 5), 407 (4), 323 (5), 245 (5), 197 (100).

5.11.3. Procedure for the preparation of (2′-methoxy-4-biphenylmethyl)-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}-amine (22). The title compound was synthesized from **19** and **10** according to the experimental procedure of Section 5.11 in order to provide **22** (0.97 g, yield: 70%) as a beige oil. IR (KBr) *v*: 3345 (N–H) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.08–1.14 (m, 2H); 1.32–1.38 (m, 3H); 1.52–1.58 (m, 2H); 1.81–1.86 (m, 2H); 2.27 (s, 3H); 2.74 (br s, 2H); 2.91 (br s, 2H); 3.31–3.45 (m, 4H); 3.77 (s, 3H); 7.02 (t, 1H); 7.08–7.15 (m, 3H); 7.26 (d, 1H); 7.34 (d, 1H); 7.38–7.60 (m, 6H). MS (EI, 70 eV): *m/z* (%) = 428 ($[M^{\cdot}]^+$, 3), 323 (8), 231 (100), 212 (5), 197 (66).

5.11.4. Procedure for the preparation of (3′-cyano-4-biphenylmethyl)-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}-amine (23). The title compound was synthesized from **19** and **11** according to the experimental procedure of Section 5.11 in order to provide **23** (1.50 g, yield: 34%) as a beige oil. IR (KBr) *v*: 3354 (N–H) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.08 (br s, 2H); 1.32–1.37 (m, 3H); 1.56 (br s, 2H); 1.84 (t, 2H); 2.27 (s, 3H); 2.72–2.75 (m, 2H); 3.42 (br s, 4H); 3.63–3.78 (m, 2H); 7.08–7.15 (m, 4H); 7.28 (t, 2H); 7.42–7.48 (m, 2H); 7.65–7.70 (m, 2H); 7.79 (d, 1H); 8.00 (d, 1H); 8.12 (s, 1H). MS (EI, 70 eV): *m/z* (%) = 423 ($[M^{\cdot}]^+$, 9), 397 (6), 321 (9), 231 (100), 216 (32).

5.11.5. Procedure for the preparation of (4-biphenylmethyl)-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}amine (24). The title compound was synthesized from **19** and *p*-phenylbenzylamine **12** commercially available according to the experimental procedure of Section 5.11 in order to provide **24** (0.5 g, yield: 39%) as a white solid. Mp 187–189 °C. IR (KBr) *v*: 3430 (N–H) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.10–1.18 (m, 2H); 1.33 (br s, 1H); 1.53–1.60 (m, 4H); 1.90 (t, 2H); 2.27 (s, 3H); 2.76–2.82 (m, 4H); 3.47 (s, 2H); 4.03 (s, 2H); 7.11 (d, 2H, J = 7.8 Hz); 7.17 (d, 2H, J = 7.9 Hz); 7.38 (t, 1H, J = 7.3 Hz); 7.47 (t, 2 H, J = 7.6 Hz); 7.60 (d, 2H, J = 8.1 Hz); 7.67–7.40 (m, 2H). Anal. Calcd for $C_{28}H_{34}N_2$: C, 84.42%; H, 8.54%; N, 7.03%. Found: C, 84.40%; H, 8.48%; N, 6.73%.

5.12. General Procedure for the preparation of 1-(4-biphenylmethyl)-3-isopropyl-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]-ethyl}urea derivatives. Method A (2a–e)

A solution of **20**–**24** (1.00 equiv) in 20 mL of anhydrous dichloromethane was stirred at room temperature under N_2 atmosphere. Isopropylisocyanate (1.2 equiv) was then added at 0 °C and stirred at this temperature for about 2–3 h. The reaction was found complete by TLC (CH_2Cl_2/MeOH 95:5). The reaction was quenched with H_2O, extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH) in order to obtain the urea analogs **2a**–**e**.

5.12.1. Procedure for the preparation of 1-(4′-fluoro-4-biphenylmethyl)-3-isopropyl-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2a). The title compound was synthesized from **20** and isopropylisocyanate according to the experimental procedure of Section 5.12 and the crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 97:3) and preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) to provide **2a** (0.02 g, yield: 4%) as a beige oil. IR (KBr) *v*: 3380 (N–H); 1739 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.01–1.05 (s, 9H); 1.33–1.35 (m, 2H); 1.58 (d, 2H); 1.82–1.85 (m, 2H); 2.27 (s, 3H); 2.74 (d, 2H); 3.18 (s, 2H); 3.42 (s, 2H); 3.64–3.71 (m, 1H); 4.23 (d, 2H); 5.75 (s, 1H); 7.09–7.16 (m, 4H); 7.25–7.33 (m, 4H); 7.58 (t, 2H, J = 4.1 Hz); 7.66–7.70 (m, 2H). MS (EI, 70 eV): *m/z* (%) = 501 ($[M^{\cdot}]^+$, 8), 478 (2), 396 (27), 316 (30), 105 (100).

5.12.2. Procedure for the preparation of 3-isopropyl-1-(4′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2b). The title compound was synthesized from **21** and isopropylisocyanate according to the experimental procedure of Section 5.12 and the crude product was purified by preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) to provide **2b** (0.04 g, yield: 4%) as a beige oil. IR (KBr) *v*: 3346 (N–H); 1617 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.02–1.07 (m, 7H); 1.12 (d, 2H); 1.35 (m, 2H); 1.57 (d, 2H); 1.91 (m, 2H); 2.25 (s, 3H); 2.77 (s, 2H); 3.18 (d, 2H); 3.34 (s, 2H); 3.84 (m, 1H); 4.42 (d, 2H); 5.96 (s, 1H); 7.00 (d, 2H); 7.11 (d, 2H); 7.14 (d, 2H); 7.25 (d, 2H, J = 8.2 Hz); 7.54–7.59 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 513 ($[M^{\cdot}]^+$, 4), 428 (3), 408 (7), 295 (4), 105 (100).

5.12.3. Procedure for the preparation of 3-isopropyl-1-(2′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2c). The title compound was synthesized from **22** and isopropylisocyanate according to the experimental procedure of Section 5.12 and the crude product was purified by preparative thin-layer

chromatography (CH_2Cl_2/MeOH 90:10) to provide **2c** (0.09 g, yield: 6%) as a beige oil. IR (KBr) *v*: 3338 (N–H); 1636 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.02–1.07 (m, 7H); 1.12 (d, 2H); 1.35 (m, 2H); 1.57 (d, 2H); 1.91 (m, 2H); 2.25 (s, 3H); 2.77 (s, 2H); 3.18 (d, 2H); 3.34 (s, 2H); 3.84 (m, 1H); 4.42 (d, 2H); 5.96 (s, 1H); 7.00 (d, 2H); 7.11 (d, 2H); 7.14 (d, 2H); 7.25 (d, 2H, J = 8.2 Hz); 7.54–7.59 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 428 (2), 412 (3), 385 (2), 337 (8), 298 (100).

5.12.4. Procedure for the preparation of 1-(3′-cyano-4-biphenylmethyl)-3-isopropyl-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2d). The title compound was synthesized from **23** and isopropylisocyanate according to the experimental procedure of Section 5.12 and the crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH 95:5) to afford **2d** (0.02 g, yield: 2%) as a beige oil. IR (KBr) *v*: 3353 (N–H); 1627 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.04–1.09 (m, 9H); 1.28–1.36 (m, 2H); 1.55 (d, 2H); 1.79 (t, 2H); 2.27 (s, 3H); 2.70 (d, 2H); 3.09–3.18 (m, 2H); 3.35 (m, 2H); 3.78–3.86 (m, 1H); 4.36–4.45 (d, 2H); 5.99 (t, 1H,); 7.08–7.16 (m, 4H); 7.30–7.52 (d, 2H); 7.67 (t, 1H); 7.72 (d, 2H, J = 8.3 Hz); 7.81 (m, 1H); 8.01 (t, 1H); 8.15 (d, 1H). MS (EI, 70 eV): *m/z* (%) = 508 ($[M]^+$, 4), 403 (10), 318 (14), 231 (62), 105 (100).

5.12.5. Procedure for the preparation of 1-(4-biphenylmethyl)-3-isopropyl-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2e). The title compound was synthesized from **24** and isopropylisocyanate according to the experimental procedure of Section 5.12 and the crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) to provide **2e** (0.14 g, yield: 9%) as a yellow oil. IR (KBr) *v*: 3362 (N–H); 1621 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.06 (s, 9H); 1.35 (d, 2H); 1.56 (d, 2H); 1.80 (s, 2H); 2.27 (s, 3H); 2.70 (d, 2H); 3.15 (d, 2H); 3.42 (s, 2H); 3.80–3.85 (m, 1H); 4.44 (s, 2H); 6.00 (d, 1H); 7.09 (d, 2H, J = 7.9 Hz); 7.13 (d, 2H, J = 8.0 Hz); 7.28 (d, 2H, J = 8.0 Hz); 7.35 (t, 1H, J = 7.3 Hz); 7.45 (t, 2H, J = 7.6 Hz); 7.61–7.66 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 483 ($[M]^+$, 10), 468 (3), 378 (43), 316 (44), 167 (100).

5.13. Procedure for the preparation of urea derivatives. Method B (2f–z)

5.13.1. Procedure for the synthesis of 1-(acetyloxymethyl)-1-methyl-ethylisocyanate (25)

5.13.1.1. Acylation. First, the hydroxy group of 2,2-dimethyl-3-hydroxypropionic acid (5 g, 42.37 mmol) was acetylated by heating it in neat AcCl (15.12 mL, 211.86 mmol) until its dissolution. The reaction mixture was then cooled to room temperature and evaporated in order to obtain a colorless oil (7.92 g, yield: 97%). IR (KBr) *v*: 3324 (O–H); 1747 (C=O)cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.10 (s, 6H); 1.97 (s, 3H); 3.87 (s, 2H); 12.63 (br s, 1H).

5.13.1.2. Isocyanate formation. The compound obtained in the acylation (7.92 g, 54.25 mmol) by means of a Curtius rearrangement and using DPPA (12.50 g, 45.42 mmol) in the presence of NEt_3 (4.59 g, 45.42 mmol) in 100 mL of dry toluene was stirred under reflux for 12–15 h under N_2 atmosphere. The reaction mixture was then evaporated in order to obtain **25** (6.8 g, yield: 87%) as an orange-beige oil. IR (KBr) *v*: 2256 (N=C=O); 1746 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.22 (s, 6H); 1.99 (s, 3H); 4.11 (s, 2H). MS (EI, 70 eV): *m/z* (%) = 157 ($[M]^+$, 5), 141 (10), 125 (3), 113 (5), 94 (100).

5.13.2. Procedure for the synthesis of 1,1-di(acetyloxymethyl)propyl isocyanate (26)

5.13.2.1. Acylation. First, the hydroxy group of 2,2′-Bis(hydroxymethyl)butyric acid (5 g, 43.87 mmol) was acetylated by heating it in neat AcCl (15.65 mL, 219.36 mmol) until its dissolution. The reaction mixture was then cooled to room temperature and then evaporated in order to obtain a colorless oil (9.87 g, 97%). IR (KBr) *v*: 1752 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.98 (t, 3H); 1.59 (q, 3H); 2.14 (s, 6H); 4.27 (s, 4H); 12.68 (br s, 1H).

5.13.2.2. Isocyanate formation. The compound obtained in the acylation (9.87 g, 42.54 mmol) by means of a Curtius rearrangement and using DPPA (9.17 g, 42.54 mmol) in the presence of NEt_3 (4.30 g, 42.54 mmol) in 60 mL of dry toluene was stirred under reflux for 4 h under N_2 atmosphere. The reaction mixture was then evaporated in order to obtain 26 (7.36 g, 76%) as a beige oil. IR (KBr) *v*: 2255 (N=C=O); 1750 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (t, 3H, J = 7.5 Hz); 1.62–1.69 (m, 2H); 2.07 (s, 6H); 4.12 (s, 4H). MS (EI, 70 eV): *m/z* (%) = 228 ($[M]^+$, 2), 215 (3), 188 (15), 169 (5), 114 (100).

5.13.3. General procedure for the preparation of urea derivatives (2f–o).

A solution of corresponding amines **20**–**24** (1.00 equiv) in anhydrous dichloromethane was stirred at 0 °C under N_2 atmosphere. The appropriate isocyanate **25** or **26** was then added dropwise at 0 °C, and the reaction mixture was again stirred at this temperature for 5 h. Upon completion, the reaction mixture was filtered and evaporated in order to obtain the desired protected ureas **2f**–**o**.

5.13.3.1. Procedure for the synthesis of 3-[1-(acetyloxymethyl)-1-methylethyl]-1-(4′-fluoro-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2f). The title compound was synthesized from **20** and **25** according to the same procedure of Section 5.13.3 in order to afford **2f** (1.15 g, yield: 84%) as a beige oil. IR (KBr) *v*: 3411 (N–H); 1737 (ester C=O); 1654 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.19 (m, 3H); 1.22 (s, 6H); 1.36 (br s, 2H); 1.65 (d, 2H); 2.05 (m, 3H); 2.28 (s, 3H); 2.88 (d, 2H); 3.17 (d, 2H); 3.34 (m, 2H); 3.79 (s, 2H); 4.11 (d, 2H); 4.44 (s, 2H); 5.76 (s, 1H); 7.11–7.15 (m, 4H); 7.19-7.31 (m, 4H); 7.61 (m, 2H); 7.69–7.71 (m, 2H). MS (EI, 70 eV): *m/z* (%) = 573 ($[M]^+$, 3), 468 (15), 388 (17), 337 (4), 231 (100).

5.13.3.2. Procedure for the synthesis of 3-[1-(acetyloxymethyl)-1-methylethyl]-1-(4′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2g). The title compound was synthesized from **21** and **25** according to the same procedure of Section 5.13.3 in order to afford **2g** (1.26 g, yield: 96%) as a beige oil. IR (KBr) *v*: 3330 (N–H), 1651 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.04–1.10 (m, 3H); 1.21 (s, 6H); 1.33–1.38 (m, 2H); 1.53–1.65 (m, 2H); 1.86–1.88 (m, 2H); 2.07 (s, 3H); 2.25 (s, 3H); 2.74 (d, 2H); 3.39 (t, 2H); 3.64 (t, 2H); 4.12 (s, 2H); 4.43 (s, 2H); 6.73–6.99 (m, 4H); 7.10–7.17 (m, 4H); 7.24–7.30 (m, 2H); 7.53–7.68 (m, 2H). MS (EI, 70 eV): *m/z* (%) = 585 ($[M]^+$, 3), 452 (30), 388 (45), 368 (5), 105 (100).

5.13.3.3. Procedure for the synthesis of 3-[1-(acetyloxymethyl)-1-methylethyl]-1-(2′-methoxy-4-biphenyl methyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2h). The title compound was synthesized from **22** and **25** according to the same procedure of Section 5.13.3 in order to afford **2h** (1.05 g, yield: 70%) as a beige oil. IR (KBr) *v*: 3324 (N–H), 1735 (ester C=O); 1658 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.17 (s, 1H); 1.23 (s, 6H); 1.26 (m, 2H); 1.34 (m, 2H); 1.61 (d, 2H); 2.03 (s, 3H); 2.27 (s, 3H); 2.88 (d, 2H); 3.17 (d, 2H); 3.34 (m, 2H); 3.45 (m, 2H); 3.75 (s, 3H); 4.12 (s, 2H); 4.34 (s, 2H); 5.76 (s, 1H); 6.96 (m, 1H); 7.11 (m, 4H); 7.22 (m, 1H); 7.33 (m, 1H); 7.50 (m, 1H); 7.66-7.83 (m, 2H); 8.04 (t, 1H); 8.17 (d, 1H). MS (EI, 70 eV): *m/z* (%) = 452 (3), 388 (10), 368 (7), 231 (45), 105 (100).

5.13.3.4. Procedure for the synthesis of 3-[1-(acetyloxymethyl)-1-methylethyl]-1-(3′-cyano-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2i). The title compound was synthesized from **23** and **25** according to the same procedure of Section 5.13.3 in order to afford **2i** (0.85 g, yield: 89%) as a brown oil. IR (KBr) *v*: 3294 (N–H), 2229 (CN); 1738 (ester C=O); 1651 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.15 (s, 1H); 1.17 (s, 6H); 1.22 (m, 2H); 1.43 (br s, 2H); 1.80 (m, 2H); 2.07 (s, 3H); 2.27 (s, 3H); 2.73 (br s, 2H); 3.17 (m, 2H); 3.36 (m, 2H); 3.50 (m, 2H); 3.90 (s, 2H); 4.10 (s, 2H); 5.76 (s, 1H); 7.09–7.13 (m, 4H); 7.20–7.24 (m, 2H); 7.50 (m, 1H); 7.67–7.72 (m, 2H); 7.78–7.83 (m, 1H); 8.03 (m, 1H); 8.16 (d, 1H). MS (EI, 70 eV): *m/z* (%) = 475 (4), 454 (4), 388 (8), 295 (9), 231 (100).

5.13.3.5. Procedure for the synthesis of 3-[1-(acetyloxymethyl)-1-methylethyl]-1-(4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2j). The title compound was synthesized from **24** and **25** according to the same procedure of Section 5.13.3 in order to afford **2j** (0.50 g, yield: 64%) as a beige oil. IR (KBr) *v*: 3420 (N–H), 1737 (ester C=O); 1647 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.18 (t, 3H); 1.24 (s, 6H); 1.36 (br s, 2H); 1.69 (d, 2H); 2.03 (s, 3H); 2.30 (s, 3H); 3.00–3.05 (m, 4H); 3.17 (d, 2H); 3.93 (s, 2H); 4.15 (s, 2H); 4.45 (s, 2H); 5.76 (s, 1H); 7.09 (d, 2H, J = 7.9 Hz); 7.13 (d, 2H, J = 8.0 Hz); 7.28 (d, 2 H, J = 8.0 Hz); 7.35 (t, 1H, J = 7.3 Hz); 7.45 (t, 2H, J = 7.6 Hz); 7.61–7.66 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 555 ($[M]^+$, 9), 450 (32), 388 (23), 231 (97), 167 (100).

5.13.3.6. Procedure for the synthesis of 3-[1,1-di(acetyloxymethyl)propyl]-1-(4′-fluoro-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2k). The title compound was synthesized from **20** and **26** according to the same procedure of Section 5.13.3 in order to afford **2k** (0.96 g, yield: 95%) as a beige oil. IR (KBr) *v*: 3342 (N–H), 1639 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.90 (t, 3H, J = 7.5 Hz); 1.12 (m, 2H); 1.40 (br s, 2H); 1.60–1.67 (m, 2H); 1.75 (t, 2H, J = 7.6 Hz); 1.99 (s, 6H); 2.01–2.07 (m, 1H); 2.27 (s, 3H); 2.77 (d, 2H); 3.20 (t, 2H); 4.10–4.18 (m, 8H); 4.46 (s, 2H); 5.76 (s, 1H); 7.09–7.21 (m, 4H); 7.28–7.33 (m, 4H); 7.60 (t, 2H); 7.67–7.70 (m, 2H). MS (EI, 70 eV): *m/z* (%) = 645 ($[M]^+$, 4), 585 (7), 540 (15), 480 (56), 231 (100).

5.13.3.7. Procedure for the synthesis of 3-[1,1-di(acetyloxymethyl)propyl]-1-(4′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2l). The title compound was synthesized from **21** and **26** according to the same procedure of Section 5.13.3 in order to afford **2l** (2.34 g, yield: 79.9%) as a beige oil. This product was purified with SPE (solid phase extraction) using a C-18 E cartridge and water–acetonitrile as a mobile phase. IR (KBr) *v*: 3420 (N–H), 1740 (ester C=O); 1654 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.77 (t, 3H); 1.07 (t, 1H); 1.13 (d, 2H); 1.36 (d, 2H); 1.56 (d, 2H); 1.74 (m, 2H); 1.98 (s, 6H); 2.27 (s, 3H); 2.75 (d, 2H); 3.16–3.21 (m, 4H); 3.39 (s, 2H); 3.79 (s, 3H); 4.13–4.27 (dd, 4H); 4.44 (s, 2H); 5.52 (s, 1H); 7.02 (d, 2H); 7.11 (d, 2H, J = 8.0 Hz); 7.15 (d, 2H,J = 8.0 Hz); 7.27 (d, 2H,J = 8.3 Hz); 7.56–7.59 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 642 (2), 597 (4), 552 (3), 492 (16), 231 (100).

5.13.3.8. Procedure for the synthesis 3-[1,1-di(acetyloxymethyl)propyl]-1-(2′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2m). The title compound was synthesized from **22** and **26** according to the same procedure of Section 5.13.3 in order to afford **2m** (0.97 g, yield: 78.9%) as a beige oil. IR (KBr) *v*: 3358 (N–H), 1658 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.76–0.85 (m, 4H); 1.11 (m, 2H); 1.40 (d, 2H); 1.48 (m, 1H); 1.59 (d, 2H); 1.64–1.67 (m, 2H); 1.85 (s, 2H); 2.01 (s, 6H); 2.27 (s, 3H); 2.76 (d, 2H, J = 10.0 Hz); 3.20 (m, 2H); 3.38 (d, 2H, J = 6.7 Hz); 3.75 (s, 3H); 4.12 (d, 4H); 4.13–4.25 (m, 2H); 5.93 (s, 1H); 7.01 (t, 1H, J = 7.4 Hz); 7.09 (m, 3H); 7.14 (d, 2H); 7.26 (d, 2H); 7.33 (t, 1H); 7.40 (d, 2H); 7.50 (m, 1H). MS (EI, 70 eV): *m/z* (%) = 657 ($[M]^+$, 2), 597 (2), 552 (3), 492 (5), 114 (100).

5.13.3.9. Procedure for the synthesis of 3-[1,1-di(acetyloxymethyl)propyl]-1-(3′-cyano-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2n). The title compound was synthesized from **23** and **26** according to the same procedure of Section 5.13.3 in order to afford **2n** (1.00 g, yield: 93%) as a brown oil. IR (KBr) *v*: 3338 (N–H), 1739 (ester C=O); 1642 (urea

C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.75–0.83 (m, 3H); 1.04–1.06 (m, 2H); 1.42 (br s, 2H); 1.65 (br s, 2H); 1.72–1.81 (m, 2H); 1.97 (t, 1H); 2.01 (s, 6H); 2.26 (s, 3H); 2.72 (t, 2H); 3.17 (d, 2H); 3.37 (s, 2H); 4.10–4.27 (m, 6H); 7.08–7.15 (m, 4H); 7.32 (t, 2H, J = 8.4 Hz); 7.47 (d, 1H); 7.64 (t, 2H); 7.77 (d, 1H, J = 7.2 Hz); 7.97 (d, 1H, J = 7.0 Hz); 8.08 (s, 1H). MS (EI, 70 eV): m/z (%) = 460 (2), 337 (2), 256 (4), 186 (15), 114 (100).

5.13.3.10. Procedure for the synthesis of 3-[1,1-di(acetyloxymethyl)propyl]-1-(4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2o). The title compound was synthesized from **24** and **26** according to the same procedure of Section 5.13.3 in order to afford **2o** (0.80 g, 86%) as a yellow oil. IR (KBr) v: 3414 (N–H), 1740 (ester C=O); 1652 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.91 (t, 3H, J = 7.5 Hz); 1.17–1.21 (m, 2H); 1.39 (br s, 2H); 1.61–1.66 (m, 2H); 1.77 (t, 2H, J = 7.6 Hz); 1.98 (s, 6H); 2.02 (s, 1H); 2.07 (s, 2H); 2.28 (s, 3H); 2.84 (d, 2H); 3.22 (d, 2H, J = 7.1 Hz); 3.54 (s, 2H); 4.12 (d, 4H); 4.27 (d, 2H); 4.48 (s, 2H); 7.12 (d, 2H, J = 7.8 Hz); 7.20–7.25 (m, 2H); 7.30–7.37 (m, 3H); 7.43–7.47 (m, 2H); 7.63 (t, 4H). MS (EI, 70 eV): m/z (%) = 627 ($[M^-]^+$, 3), 567 (5), 522 (12), 462 (32), 130 (100).

5.13.4. General procedure for the preparation of urea derivatives (2p–z). A solution of the appropriate urea derivatives **2f–o** (1.0 g, 1.88 mmol) in methanol (80 mL) and 1 g K_2CO_3 (1.00 g, 7.25 mmol) was stirred at room temperature under N_2 atmosphere. The reaction was completed after 3 h of stirring, and then filtered and evaporated in vacuo. The residue was washed with water and quenched with dichloromethane. The organic layer was dried over $NaSO_4$, filtered, concentrated, and purified with flash column chromatography (CH_2Cl_2/MeOH 95:5) and then with silica gel thin layer preparative (CH_2Cl_2/MeOH 90:10) to afford the desired urea derivatives **2p–z**.

5.13.4.1. Procedure for the synthesis of 1-(4′-fluoro-4-biphenylmethyl)-3-(2-hydroxy-1,1-dimethylethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2p). The title compound was synthesized from **2f** according to the same procedure as of Section 5.13.4 in order to afford a beige oil, which was purified with flash column chromatography (CH_2Cl_2/MeOH 95:5) and then with silica gel thin layer preparative (CH_2Cl_2/MeOH 90:10) to give **2p** (12 mg, yield: 12%) as a beige oil. IR (KBr) v: 3411 (N–H), 1623 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.85–0.87 (m, 1H); 0.99–1.03 (m, 2H); 1.23 (s, 6H); 1.34 (m, 2H); 1.57 (d, 2H); 1.82–1.91 (d, 2H); 2.27 (s, 3H); 2.73 (br s, 2H); 3.17 (s, 2H); 3.35 (br s, 2H); 4.10 (d, 2H); 4.43 (s, 2H); 5.11 (br s, 1H); 5.38 (s, 1H); 7.09–7.18 (m, 4H); 7.23–7.30 (m, 4H); 7.59–7.61 (d, 2H, J = 4.0 Hz); 7.67–7.71 (m, 2H). MS (EI, 70 eV): m/z (%) = 531 ($[M^-]^+$, 4), 500 (3), 416 (13), 346 (7), 231 (100).

5.13.4.2. Procedure for the synthesis of 3-(2-hydroxy-1,1-dimethylethyl)-1-(4′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2r). The title compound was synthesized from **2g** according to the same procedure as of Section 5.13.4 in order to afford a beige oil, which was purified twice by preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) to give **2r** (0.02 g, yield: 2%) as a beige oil. IR (KBr) v: 3342 (N–H), 1639 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.86–0.90 (m, 2H); 1.05–1.36 (m, 9H); 1.57 (br s, 2H); 1.86 (br s, 2H); 2.27 (s, 3H); 2.76 (br s, 2H); 3.12 (br s, 2H); 3.35 (d, 2H); 4.12 (br s, 2H); 4.42 (br s, 2H); 6.73–6.76 (m, 4H); 7.10–7.16 (m, 4H); 7.26–7.30 (m, 2H); 7.58–7.69 (m, 2H). MS (EI, 70 eV): m/z (%) = 428 (12), 346 (5), 323 (10), 295 (8), 231 (100).

5.13.4.3. Procedure for the synthesis of 3-(2-hydroxy-1,1-dimethylethyl)-1-(2′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2s). The title compound was synthesized from **2h** according to the same procedure as of Section 5.13.4 in order to afford a beige oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) and then with silica gel thin layer preparative (CH_2Cl_2/MeOH 90:10) to afford **2s** (8.5 mg, yield: 1%) as a beige oil. IR (KBr) v: 3413 (N–H), 1628 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.17 (s, 6H); 1.20 (s, 1H); 1.22 (m, 2H); 1.33 (br s, 2H); 1.60 (br s, 2H); 2.27 (s, 3H); 2.83 (d, 2H); 3.10 (d, 2H); 3.29 (m, 2H); 3.45 (m, 2H); 3.75 (s, 3H); 4.34 (s, 2H); 5.07 (br s, 1H); 5.36 (s, 2H); 5.76 (s, 1H); 7.08–7.20 (m, 5H); 7.34 (m, 1H); 7.50 (m, 1H); 7.64–7.73 (m, 2H); 7.81 (d, 1H); 8.02 (d, 1H); 8.15 (s, 1H). MS (EI, 70 eV): m/z (%) = 542 ($[M^-]^+$, 2), 427 (3), 346 (5), 323 (5), 231 (100).

5.13.4.4. Procedure for the synthesis of 1-(3′-cyano-4-biphenylmethyl)-3-(2-hydroxy-1,1-dimethylethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2t). The title compound was synthesized from **2i** according to the same procedure as of Section 5.13.4 in order to afford a brown oil which was purified with silica gel column chromatography (CH_2Cl_2/MeOH 95:5) and then with silica gel thin layer preparative (CH_2Cl_2/MeOH 90:10) to afford **2t** (4.4 mg, yield: 0.6%) as a yellow oil. IR (KBr) v: 3355 (N–H), 1624 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.83 (m, 3H); 1.19 (s, 6H); 1.56 (d, 2H); 1.80 (m, 2H); 2.27 (s, 3H); 2.71 (d, 2H); 3.17 (m, 2H); 3.32 (br s, 2H); 3.50 (s, 2H); 4.14 (s, 2H); 4.45 (s, 2H); 5.15 (br s, 1H); 5.76 (s, 1H); 7.08–7.16 (m, 4H); 7.32–7.36 (m, 2H); 7.50 (d, 1H); 7.64–7.73 (m, 2H); 7.81 (d, 1H); 8.02 (d, 1H); 8.15 (s, 1H). MS (EI, 70 eV): m/z (%) = 507 (2), 477 (2), 423 (4), .394 (2), 105 (100).

5.13.4.5. Procedure for the synthesis of 1-(4-biphenylmethyl)-3-(2-hydroxy-1,1-dimethylethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2u). The title compound was synthesized from **2j** according to the same procedure as of Section 5.13.4 in order to afford a brown oil which was purified with silica gel column chromatography (CH_2Cl_2/MeOH 95:5) and then with silica gel thin layer preparative (CH_2Cl_2/MeOH 90:10) to afford **2u** (0.24 g, yield: 52%) as a yellow oil. IR (KBr) v: 3364 (N–H), 1635 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.87 (t, 3H); 1.20 (s,

6H); 1.39 (br s, 2H); 1.60 (d, 2H); 1.94 (d, 2H); 2.27 (s, 3H); 2.79 (br s, 2H); 3.17 (t, 2H); 3.35 (br s, 4H); 4.14 (s, 2H); 5.13 (t, 1H); 5.40 (s, 1H); 7.11 (d, 2H); 7.16 (d, 2H); 7.30 (d, 2H); 7.35 (t, 1H); 7.46 (t, 2H); 7.61-7.66 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 513 ($[M]^+$, 4), 440 (5), 398 (7), 335 (20), 167 (100).

5.13.4.6. Procedure for the synthesis of 1-(4′-fluoro-4-biphenylmethyl)-3-(1,1-di(hydroxymethyl)propyl)-1-{2-[1-(4-methylbenzyl)-4-piperidin]ethyl}urea (2v). The title compound was synthesized from **2k** according to the same procedure as of Section 5.13.4 in order to afford a beige oil. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 96:4) and preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) in order to obtain **2v** (0.05 g, yield: 6%) as a beige oil. IR (KBr) *v*: 3401 (N–H), 1623 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.74 (t, 3H, J = 7.3 Hz); 1.21 (t, 4H); 1.42 (t, 2H); 1.65 (t, 4H); 1.78 (t, 2H); 2.27 (s, 3H); 2.70 (br s, 1H); 3.19 (t, 2H); 3.40–3.46 (m, 4H); .46 (s, 2H); 5.06 (t, 2H); 5.60 (s, 2H); 7.15-7.19 (m, 4H); 7.26–7.32 (m, 4H); 7.61 (d, 2H, J = 8.1 Hz); 7.68-7.71 (m, 2H). MS (EI, 70 eV): *m/z* (%) = 562 ($[M]^+$, 8), 546 (4), 530 (5), 498 (7), 231 (100).

5.13.4.7. Procedure for the synthesis of 3-[1,1-di(hydroxymethyl)propyl]-1-(4′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2w). The title compound was synthesized from **2l** according to the same procedure as of Section 5.13.4 in order to afford a beige oil which was purified by silica gel column chromatography (CH_2Cl_2/MeOH 96:4) and preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) in order to obtain **2w** (0.07 g, yield: 4%) as a beige oil. IR (KBr) *v*: 3404 (N–H), 1728 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.73–0.78 (m, 3H); 1.03–1.21 (m, 3H); 1.41 (br s, 2H); 1.66 (t, 2H); 1.81–1.86 (m, 2H); 2.27 (s, 3H); 2.71 (d, 2H); 3.18 (t, 2H); 3.33–3.49 (m, 2H); 3.79 (s, 4H); 4.43 (s, 2H); 5.07 (t, 2H); 5.32 (s, 1H); 7.01 (d, 2H); 7.09–7.15 (m, 4H); 7.27 (d, 2H, J = 8.2 Hz); 7.58 (t, 1H). MS (EI, 70 eV): *m/z* (%) = 428 (15), 393 (2), 358 (8), 323 (11), 231 (100), 197 (96).

5.13.4.8. Procedure for the synthesis of 3-[1,1-di(hydroxymethyl)propyl]-1-(2′-methoxy-4-biphenylmethyl)-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2x). The title compound was synthesized from **2m** according to the same procedure as of Section 5.13.4 in order to afford a beige oil which was purified twice by preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) in order to obtain **2x** (0.01 g, yield: 1.15%) as a beige oil. IR (KBr) *v*: 3400 (N–H), 1644 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.71–0.81 (t, 3H); 1.06–1.11 (m, 3H); 1.32 (m, 2H); 1.48 (m, 1H); 1.56 (m, 2H); 1.60–1.68 (m, 2H); 1.82 (d, 2H); 2.27 (s, 3H); 2.73 (s, 2H); 3.37–3.41 (m, 4H); 3.77 (s, 3H); 4.21 (d, 2H); 5.75 (s, 1H); 7.02 (t, 1H); 7.09–7.14 (m, 5H); 7.25 (d, 2H, J = 7.1 Hz); 7.33 (t, 1H); 7.41 (t, 2H); 7.51 (d, 1H). MS (EI, 70 eV): *m/z* (%) = 428 (10), 368 (13), 323 (17), 231 (100), 197 (60).

5.13.4.9. Procedure for the synthesis of 1-(3′-cyano-4-biphenylmethyl)-3-[1,1-di(hydroxymethyl)propyl]-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2y). The title compound was synthesized from **2n** according to the same procedure as of Section 5.13.4 in order to afford a beige oil which was purified twice by preparative thin-layer chromatography (CH_2Cl_2/MeOH 90:10) in order to obtain **2y** (0.03 g, yield: 3%) as a yellow oil. IR (KBr) *v*: 3355 (N–H), 1624 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.75 (t, 3H); 1.24 (br s, 3H); 1.42 (br s, 2H,); 1.64–1.68 (m, 4H); 2.28 (s, 3H); 2.78 (br s, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.40–3.46 (m, 6H,); 4.47 (s, 2H); 5.05 (t, 2H); 5.33 (s, 1H); 7.14–7.18 (m, 4H); 7.34 (d, 2H, J = 8.0 Hz); 7.52 (t, 1H); 7.73 (d, 2H); 7.82 (d, 1H, J = 7.7 Hz); 8.02 (d, 1H, J = 8.1 Hz); 8.16 (s, 1H). MS (EI, 70 eV): *m/z* (%) = 549 (2), 441 (2), 391 (3), 318 (15), 231 (100).

5.13.4.10. Procedure for the synthesis of 1-(4-biphenylmethyl)-3-[1,1-di(hydroxymethyl)propyl]-1-{2-[1-(4-methylbenzyl)-4-piperidinyl]ethyl}urea (2z). The title compound was synthesized from **2o** according to the same procedure as of Section 5.13.4 in order to afford a yellow oil which was purified twice by flash column chromatography (CH_2Cl_2 (100) to CH_2Cl_2/MeOH 96:4) and preparative column in order to obtain **2z** (0.30 g, yield: 52%) as a beige oil. IR (KBr) *v*: 3364 (N–H), 1635 (urea C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.73 (t, 3H, J = 7.4 Hz); 1.05–1.17 (m, 3H); 1.39 (br s, 2H); 1.54 (d, 2H); 1.61 (t, 2H, J = 7.4 Hz); 1.78 (t, 2H); 2.26 (s, 3H); 2.68 (d, 2H); 3.15 (d, 2H); 3.37 (s, 2H); 3.42–3.48 (m, 2H); 3.63-3.68 (m, 2H); 4.43 (s, 2H); 7.07–7.13 (m, 4H); 7.30–7.36 (m, 3H); 7.44 (t, 2H, J = 7.6 Hz); 7.59–7.64 (m, 4H). MS (EI, 70 eV): *m/z* (%) = 542 ($[M]^+$, 2), 525 (2), 453 (3), 293 (15), 231 (100).

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