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Synthesis of New Trisubstituted 4-Aminopiperidines as PAF-Receptor Antagonists

Houcine Benmehdi,[a,b] Aazdine Lamouri,[a] Nawal Serradji,[a] Frédérique Pallois,[a] and Françoise Heymans*[a]

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Two novel classes of 4-aminopiperidines substituted in the 3-position by groups bearing either a carbamate or a ureido function have been synthesized from ethyl 4-oxo-3-piperidinecarboxylate and 3,3′-iminobis(propanenitrile), respectively. The key step in this synthesis, the reduction of the piperidinic β-enamino ester or nitrile, occurred readily. In contrast to published works, the free primary amines could be isolated from the corresponding β-amino ester or nitrile. Regioselective amidification of the amino group offered two pairs of diastereoisomers which were successfully separated and identified. Measurement of PAF-receptor antagonist activity gave interesting results with an IC_{50} close to the micromolar.

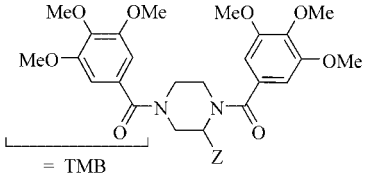
Introduction

After characterization[1–3] of the platelet activating factor (PAF), elucidation of its structure by three independent research groups[4–6] and its stereospecific synthesis,[7–11] sufficient material was available to allow evaluation of the pharmacology and physiopathology of this agent. PAF is recognized as a potent phospholipidic inflammatory mediator and plays a physiopathological role in a variety of clinical conditions such as asthma[12] and pulmonary dysfunction, acute inflammation, cardiac anaphylaxis, thrombosis, gastrointestinal ulceration, endotoxic shock, allergic skin diseases, transplanted organ rejection, ovoimplantation in pregnancy and retinal and corneal diseases.[13–20] Moreover, in the central nervous system, high PAF concentrations are reported in the cerebrospinal fluid of patients suffering from dementia and an altered immune system.[21] Since direct infection of neurons by HIV is unlikely and because TNF-α and PAF are both neurotoxic, there is a consensus that neuronal dysfunction and apoptosis are mediated by these soluble factors released by macrophages and microglia in the CNS.[22] PAF is probably the key element in this phenomenon since TNF-α mediated neuronal apoptosis can also be blocked by co-incubation with PAF acetylhydrolase,[21] the main catabolic enzyme for PAF, or by a PAF-receptor antagonist.[21] Blocking pathologic effects of PAF may therefore be favourable in the treatment of HIV-associated dementia and inflammatory syndrome.[23]

The search for molecules able to antagonize the effects of PAF has been a part of our work for a while. A study of natural and synthetic inhibitors through their 3D electrostatic potential maps, which take into account volume, conformation and electronic distribution, led us to propose first a simple model for a PAF-receptor comprising a bipolarized cylinder[24,25] and then a tetrapolarized one.[26] From these findings we chose piperazine as a support for functionalized moieties, in accordance with the hypotheses, and designed and synthesized potent antagonists.[27,28] Besides this activity, some of these compounds showed inhibition of HIV-1 replication in monocyte-derived macrophages (MDMs).[29–31] Following our interest in this field, we undertook to replace the piperazine ring of compounds **1** and **2** (Figure 1), previously synthesized, by an aminopiperidine moiety to evaluate the influence of this ring on both biological activities. These modifications aimed to reinforce the dual anti-PAF and anti-HIV-1 activity of **1** and to increase the anti-PAF potency of **2** (Table 1). Indeed, the aminopiperidine moiety is beneficial in compounds showing various biological activities such as narcotic analgesics,[32] neurokin-1 receptor ligands,[33] 5-HT_{2A} serotonin receptor antagonists,[34] CCR5 chemokine receptor ligands,[35] human β_3-adrenergic receptor antagonists,[36] potent cognition enhancing drugs,[37] ORL 1 antagonists[38] and human-cloned dopamine D_4 receptor antagonists[39] and has been used as a supporting structure for nitrogen-type antago-

[a] Unité de Pharmacochimie Moléculaire et Systèmes Membranaires (EA 2381), Université Paris 7 – Denis Diderot, case 7066, 2 Place Jussieu, 75251 Paris Cedex 05, France
Fax: +33-144275641
E-mail: heymans@ccr.jussieu.fr
[b] Laboratoire de Chimie Organique, Substances Naturelles et Analyse (COSNA), Faculté des Sciences, Université Aboubakr Belkaid,
B. P. 119, Tlemcen, Algeria

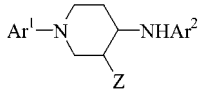
nists.[40] By using substituted 4-aminopiperidines instead of their piperazine analogues, three important parameters are modified: (i) the flexibility, (ii) the distance between the two nitrogen atoms and, therefore, (iii) the substituent-induced electronic distribution. To the best of our knowledge, the properties of trisubstituted aminopiperidines have been poorly investigated so far; only a few papers have dealt with this topic.[41–49] This prompted us to develop a new and convenient synthesis of trisubstituted aminopiperidine derivatives and to study their biological activity. We have succeeded in synthesizing new 4-aminopiperidine derivatives substituted in position 3 by groups bearing a carbamate (see Scheme 3) or a ureido (see Scheme 4) function. In these two classes of compounds, we reduced conjugated double bonds by using $NaBH_3CN$/HCl or CH_3COOH as the reducing agent. The interesting point was that we were able to separate diastereoisomers in a later step.



1: Z = $CH_2OCONEt_2$: anti-PAF IC_{50} = 8 μM, anti-HIV IC_{50} = 11 μM.
2: Z = $CH_2NHCONHC_6H_{13}$: anti-PAF IC_{50} > 100 μM, anti-HIV IC_{50} = 1 μM.

Figure 1. Piperazine derivatives **1** and **2** and their biological data.

Table 1. In vitro anti-PAF activity of 4-aminopiperidine derivatives.



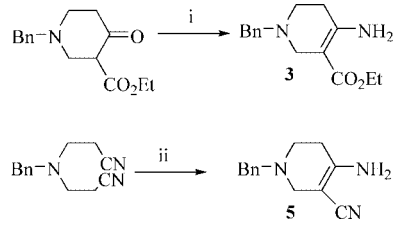
Compound	Ar^1	Ar^2	Z	Anti-PAF IC_{50} [μM]
1	TMB	TMB	$–CH_2OCON(Et)_2$	8
2	TMB	TMB	$–CH_2NHCONHC_6H_{12}$	>100
trans-**10**	$PhCH_2$	TMB	$–CH_2OCON(Et)_2$	0.28
cis-**10**	$PhCH_2$	TMB	$–CH_2OCON(Et)_2$	2.63
cis-**12**	TMB	TMB	$–CH_2OCON(Et)_2$	2.28
cis-**14**	$PhCH_2$	TMB	$–CH_2NHCONHC_5H_{11}$	0.63

Results and Discussion

Chemistry

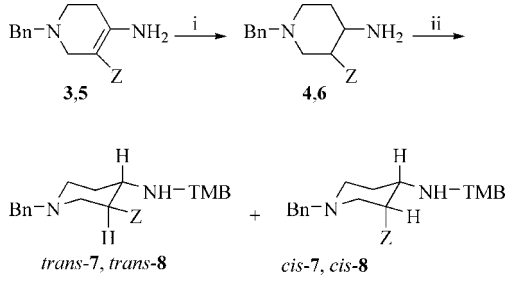
Carbamate Series

As described in Scheme 1, ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate was treated with a large excess of ammonium acetate in MeOH at room temperature to give the corresponding enamine **3**.[38]



Scheme 1. Reagents and conditions: (i) $AcONH_4$, MeOH, room temp., 1 h, 99%; (ii) $NaNH_2$, THF, reflux, 2 h, 81%.

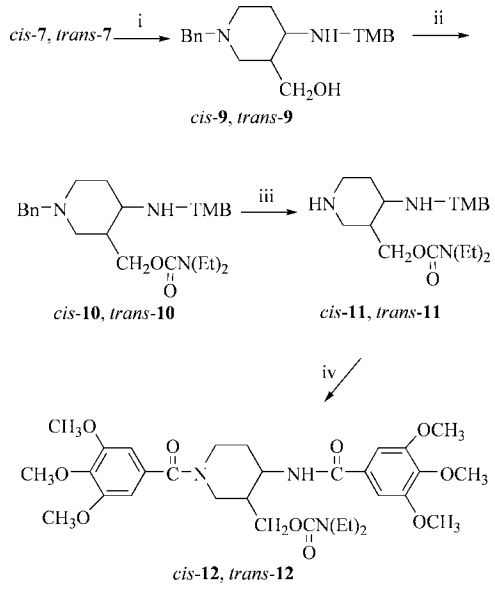
Several attempts were made to perform the *N*-alkylation or *N*-acylation of this enamine **3** by using either benzyl chloride or 3,4,5-trimethoxybenzoyl chloride (TMB-Cl) in refluxing toluene (2 weeks) but none was satisfactory as only traces of the final products were obtained. Three hypotheses could explain these results: (i) a strong conjugated system between the amine function, the double bond and the carbonyl of the ester group, (ii) the formation of a six-membered ring stabilized by hydrogen bonding between the amine and ester functions and finally (iii) an equilibrium displaced more towards the imine than the enamine group under basic conditions. The high stability of the enamine **3** did not allow its reduction into the desired amine under common conditions: $NaBH_3CN$ in MeOH, $NaBH_4$ in EtOH or $NaBH_3CN$ in *n*BuOH. Published work has revealed that β-enamino esters can easily be reduced into the corresponding β-amino esters.[50–53] A few methods for the reduction of piperidinic β-enamino esters have been described,[38,47–49] but the free primary amines could not be isolated from the corresponding piperidinic β-amino esters or nitriles in any of the cases. As shown in Scheme 2, the intermediate **3** was successfully reduced to the key compound **4** after treatment with $NaBH_3CN$ in acidic conditions (HCl or acetic acid) and EtOH at 50 °C, affording in good yield a crude mixture of inseparable diastereoisomers. However, the addition of 3,4,5-trimethoxybenzoyl chloride led to the desired amides **7** as two pairs of diastereoisomers which could be easily separated by silica gel column chromatography. In accord with the results of Kawamoto et al., we chose to use the stereodescriptor *trans* to characterize the stereoisomers presenting the higher R_f on TLC



Scheme 2. Reagents and conditions: **3**,**4**,**7**: Z = CO_2Et, **5**,**6**,**8**: Z = CN. (i) for **4**: $NaBH_3CN$, EtOH, HCl, 50 °C, 3 h, 65%; for **6**: $NaBH_3CN$, EtOH, HCl, 50 °C, 12 h, 81%; (ii) for *cis*- and *trans*-**7**: TMB-Cl, NEt_3, CH_2Cl_2, room temp., 4 h, 56.3 and 30.4%, respectively; for *cis*- and *trans*-**8**: TMB-Cl, NEt_3,THF, room temp., 1 h, 50 and 36%, respectively.

and *cis*, the ones with the smaller R_f (Scheme 2).[38] The ^1H NMR spectra revealed that each diastereoisomer exists as a pair of enantiomers.

The reduction of *cis*- and *trans*-**7** with $NaBH_4$/LiCl according to the published procedure provided alcohols *cis*- and *trans*-**9** (Scheme 3), respectively,.[54] Treatment of alcohols **9** with first NaH and then by diethylcarbamoyl chloride afforded carbamates *cis*- and *trans*-**10** respectively, in quantitative yields.[55] Subsequent removal of the *N*-benzyl protecting group using ammonium formate and the Pd/C catalyst generated the derivatives *cis*- and *trans*-**11**.[56] Our synthesis was completed by a final treatment with 3,4,5-trimethoxybenzoyl chloride to provide compounds *cis*- and *trans*-**12** in 88 and 71% yields, respectively.



Scheme 3. Reagents and conditions: (i) $NaBH_4$, LiCl, THF, EtOH, room temp., 36 h, 57 and 83%, respectively; (ii) NaH, THF, $ClCON(Et)_2$, reflux, 90 min, 81 and 93%, respectively; (iii) Pd/C, HCO_2NH_4, MeOH, reflux, 1 h, 81 and 43%, respectively; (iv) 3,4,5-$(CH_3O)_3C_6H_2COCl$, NEt_3, THF, room temp., 90 min, 88 and 71%, respectively.

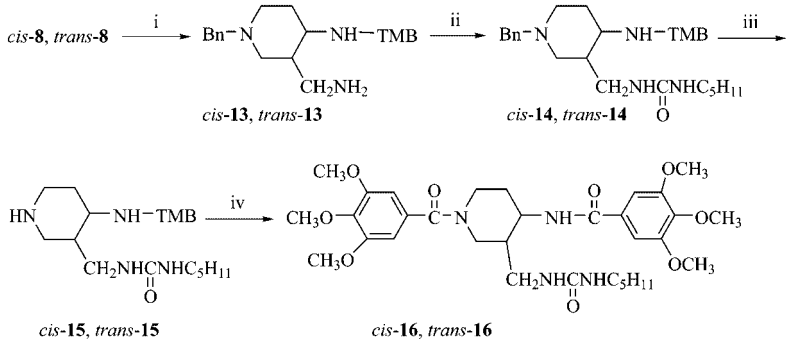
Ureido Series

As outlined in Scheme 1, compound **5** was obtained in good yield from 3,3′-[(phenylmethyl)imino]bis(propanenitrile)[57,58] after Thorpe intramolecular cyclization using sodium amide in refluxing THF.[59] As for the corresponding ester **3**, several strategies to prepare *N*-acylated or *N*-alkylated compounds were investigated but all failed, probably for the reasons we evoked in the ester **3** case. Compound **5** was then reduced by using $NaBH_3CN$ in the presence of concentrated HCl in EtOH to give the corresponding β-aminonitrile **6** as a mixture of inseparable diastereoisomers (Scheme 2). Treatment of its amine function with TMB-Cl gave two pairs of diastereoisomers *cis*- and *trans*-**8** which were separated by silica gel column chromatography in 50 and 36% yields, respectively.

In the next step (Scheme 4) the hydrogenation of the nitrile function of compounds **8** was carried out in acidic ethanol in the presence of the Raney nickel catalyst[60] and provided the corresponding amines *cis*- and *trans*-**13** which reacted with pentyl isocyanate to give the ureido compounds *cis*- and *trans*-**14** in moderate yields. Debenzylation occurred with HCO_2NH_4 and Pd/C in refluxing methanol and gave *cis*- and *trans*-**15** in 79 and 60% yields, respectively. These compounds were then acylated with TMB-Cl to the desired final products *cis*- and *trans*-**16** in 61 and 74% yields, respectively.

Biological Results

The inhibition of platelet aggregation was evaluated by the method of Cazenave et al. by using platelet-rich plasma (PRP) of New Zealand rabbits.[61] The intermediates were tested for their ability to antagonize PAF-induced platelet aggregation. All the results obtained are listed in Table 1. In the case of the carbamate series, *cis*-**12** and the reference compound **1** present similar anti-PAF activities showing that the piperazine ring of **1** can be replaced by an aminopiperidine moiety (*cis*-**12**) without any alteration of the biological activity. Replacement of one of the 3,4,5-trimethoxybenzoyl groups of **1** by a benzyl substituent (*trans*- and



Scheme 4. Reagents and conditions: (i) H_2, Ni, EtOH, concd. HCl (cat.), 60 °C, 12 h, 75 and 37%, respectively; (ii) $C_5H_{11}N{=}C{=}O$, CH_2Cl_2, room temp., 2 h, 65%; (iii) Pd/C, HCO_2NH_4, MeOH, reflux, 1 h, 79 and 60%, respectively; (iv) 3,4,5-$(CH_3O)_3C_6H_2COCl$, NEt_3, THF, room temp., overnight, 61 and 74%, respectively.

cis-**10**) leads to potent compounds and diastereoisomers: *trans*-**10** (IC_{50} = 0.28 μM) is nearly 10 times more active than its analogue *cis*-**10** (IC_{50} = 2.63 μM). In the ureido series, *cis*-**14** presents a good antagonism (IC_{50} = 0.63 μM) towards the PAF-receptor in contrast to the piperazine analogue **2** which is inactive. Evaluation of the HIV-1 activity of our synthesized trisubstituted 4-aminopiperidine derivatives is currently underway.

Conclusions

In summary, an efficient synthesis of trisubstituted aminopiperidine with ureido and carbamate functions has been developed. Contrary to the previously published papers, we succeeded in isolating the β-amino ester **4** and β-aminonitrile **6** which are the key intermediates in the preparation of other compounds. Two pairs of diastereoisomers in each series were isolated and characterized by ^{1}H NMR spectroscopy. Preliminary biological results are interesting as all the compounds present anti-PAF activity in the micromolar range. Anti-retroviral evaluation of the racemic mixtures of *cis*-/*trans*-**12** and *cis*-/*trans*-**16** is currently under investigation and chiral resolution of these mixtures could be attempted if interesting results are obtained in order to test the two enantiomeric forms separately.

Experimental Section

Materials and Methods: All reactions were monitored by thin-layer chromatography on TLC plastic sheets (silica gel 60F254, layer thickness 0.2 mm) from Merck. Column chromatography purification was carried out on silica gel 60 (particle size 0.063–0.200 mm) from Merck without any special treatment. All melting points were determined with a digital melting point apparatus (Electrothermal) and are uncorrected. The structures of all compounds were confirmed by IR, ^{1}H and ^{13}C NMR spectra. IR spectra were recorded with an ATI Mattson Genesis Series FTIR infrared spectrometer (4000–600 cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker AC 200 spectrometer. Chemical shifts (δ) were measured in ppm and are reported relative to the solvent peak of TMS. All elemental analyses were within ±0.4% of theoretical values.

Ethyl 4-Amino-1-benzyl-1,2,5,6-tetrahydro-3-pyridinecarboxylate (3): $AcONH_4$ (51 g, 662 mmol) was added to a solution of 1-benzyl-3-ethoxycarbonyl-4-piperidone (20 g, 67 mmol) in methanol (400 mL) at room temperature and the reaction mixture was stirred for 1 h and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed successively with a solution of $NaHCO_3$ and water. The organic layer was dried with $MgSO_4$, filtered and concentrated to dryness to give compound **3** as a colourless oil (16 g, yield 99%). R_f = 0.25 (CH_2Cl_2/MeOH, 95:5 v/v). IR (film): $\tilde{\nu}$ = 3440–3331 (NH_2), 2903–2803 (CH_2 and CH_3), 1671 (CO_2Et), 1621 (C=C), 1548 (ArC=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.21–7.37 (m, 5 H, ArH), 6.00 (br. s, 2 H, NH_2), 4.07–4.17 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.61 (s, 2 H, $ArCH_2$), 3.24 (s, 2 H, N-CH_2 piperidine), 2.47–2.53 (t, J = 5.6 Hz, 2 H, N-CH_2 piperidine), 2.26–2.31 (t, J = 5.6 Hz, 2 H, N-CH_2CH_2-), 1.20–1.27 (t, J = 7 Hz, 3 H, OCH_2CH_3) ppm.

4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydropyridine (5): A suspension of sodium amide (7.25 g, 18 mmol) was added to a solution of 3,3′-[(phenylmethyl)imino]bis(propanenitrile)[58,59] (33 g, 0.15 mol) in THF (400 mL) . The solution was then stirred and refluxed for 2 h. The sodium amide excess was destroyed with water at 0 °C and the solvents were removed to dryness. The residue was dissolved in CH_2Cl_2, washed with water and dried with $MgSO_4$. The organic layer was then concentrated in vacuo. Compound **5** was obtained as a yellow solid (27 g, yield 81%). M.p. 152 °C, R_f = 0.51 (CH_2Cl_2/MeOH, 90:10, v/v). IR (KBr): $\tilde{\nu}$ = 3427 (NH_2), 2928, 2823 (CH_2), 1642 (C=C), 1615 (ArC=C), 2181 (CN) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.25–7.32 (m, 5 H, ArH), 4.39 (s, 2 H, NH_2), 3.58 (s, 2 H, $ArCH_2$), 3.07 (s, 2 H, CH_2 piperidine), 2.58–2.64 (t, J = 5.73 Hz, 2 H, CH_2 piperidine), 2.2–2.3 (t, J = 5.71 Hz, 2 H, CH_2 piperidine) ppm. ^{13}C NMR ($CDCl_3$): δ = 154.7 (C=C-NH_2), 137.5, 128.4, 127.4 (ArC=C), 119.1 (CN), 72.6 (C=C-CN), 61.5, 50.7, 48.2, 28.0 ($ArCH_2$ and CH_2 piperidine) ppm.

General Procedure for the Synthesis of Compounds 4 and 6: $NaBH_3CN$ (2 equiv.) and acetic acid or hydrochloric acid (3 equiv.) were added to a solution of the enamine **3** or **5** in ethanol at room temperature and the mixture was heated at 50 °C until the reaction was complete (TLC monitoring). After cooling, the excess $NaBH_3CN$ was destroyed with water. After evaporation of the solvents, the residue was dissolved in CH_2Cl_2 and washed with a solution of $NaHCO_3$ and water. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo.

Ethyl 4-Amino-1-benzyl-3-piperidinecarboxylate (4): Compound **4** was prepared according to the general procedure using **3** (34 g, 130 mmol) in ethanol (500 mL), $NaBH_3CN$ (16.5 g, 262 mmol) and acetic acid (18.5 mL, 323 mmol). Further purification by silica gel column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH, 97:3, v/v) gave the title compound as a green oil (18 g, yield 65%). R_f = 0.34 (CH_2Cl_2/MeOH, 93:7, v/v). IR (film): $\tilde{\nu}$ = 3378 (NH_2), 2925–2808 (CH_2 and CH_3), 1726 (CO_2Et), 1601 (ArC=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.22–7.30 (m, 5 H, ArH), 4.07–4.18 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.06–3.44 (m, 2 H, Ar-CH_2), 2.36–3.08 (2m, 4 H, CH_2 and CH piperidine), 2.28 (s, 2 H, NH_2), 1.41–2.14 (3 m, 4 H, NCH_2CH_2), 1.19–1.26 (t, J = 7 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.9 (C=O ester), 137.8 (ArC=C), 129.0, 128.7, 128.0, 126.9 (ArCH=CH), 62.2 (OCH_2CH_3), 60.3 ($ArCH_2$), 53.8, 51.9, 33.4 (CH_2 piperidine), 51.0, 50.2 (CH piperidine), 14.0 (OCH_2CH_3) ppm.

4-Amino-1-benzyl-3-cyanopiperidine (6): Concentrated hydrochloric acid (12 N, 4.5 mL, 140 mmol) was added to a mixture of **5** (10.6 g, 50 mmol) in ethanol (100 mL) and $NaBH_3CN$ (6.25 g, 100 mmol) was added. The solution was heated at 50 °C for 12 h. Purification by silica gel column chromatography eluted with CH_2Cl_2 and CH_2Cl_2/MeOH (97:3, v/v) gave the title compound as a green oil (8.6 g, yield 80%). R_f = 0.23 (CH_2Cl_2/MeOH, 97:3, v/v). IR (film): $\tilde{\nu}$ = 3371–3303 (NH_2), 2941–2807 (CH_2), 1599 (ArC=C), 2239 (CN) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.16–7.27 (m, 5 H, ArH), 3.53 (d, J = 13.4 Hz, ArC*H*), 3.4 (d, J = 13.4 Hz, ArC*H*), 2.73–2.87 (m, 4 H, CH and CH_2 piperidine), 2.13–2.06 (m, 2 H, CH_2 piperidine), 1.71–1.64 (q, J = 3.9 Hz, 2 H, CH_2 piperidine) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.4, 137.1 (ArC=C), 128.4, 128.2, 127.9, 126.9, 126.7 (ArCH=CH), 119.7, 119.2 (CN), 61.5, 61.3 ($ArCH_2$), 53.1, 52.2, 51.3, 33.3, 31.8 (CH_2 piperidine), 50.9, 48.7, 37.9, 37.2 (CH piperidine) ppm.

General Procedure for the Synthesis of Compounds *cis*-7, *trans*-7, *cis*-8, *trans*-8, *cis*-12, *trans*-12, *cis*-16 and *trans*-16: A solution of 3,4,5-trimethoxybenzoyl chloride (1.1 equiv.) in dichloromethane or THF was added dropwise to a solution of **4**, **6**, *cis*-**11**, *trans*-**11**, *cis*-**15** or *trans*-**15** in dichloromethane or THF and triethylamine (3 equiv.). The solution was stirred at room temperature until the

reaction was complete (TLC monitoring). After washing with a $NaHCO_3$ solution and water, the organic layer was dried with $MgSO_4$, filtered and concentrated to dryness. The residue was purified by chromatography on a silica gel column as indicated.

Ethyl 1-Benzyl-4-(3,4,5-trimethoxybenzoylamino)-3-piperidinecarboxylate (*trans*- and *cis*-7): Compounds *trans*- and *cis*-**7** were prepared by using **4** (11.8 g, 45 mmol) in dichloromethane (150 mL), triethylamine (19 mL, 135 mmol) and a solution of 3,4,5-trimethoxybenzoyl chloride (11.43 g, 49.58 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at room temperature for 4 h and after usual treatment a mixture of the two pairs of diastereoisomers was obtained as a white solid. Separation by silica gel column chromatography using (CH_2Cl_2 then CH_2Cl_2/MeOH, 9:1, v/v) as eluent afforded *trans*-**7** (6.7 g, 30.4% yield), m.p. 163 °C, R_f = 0.34 (CH_2Cl_2/MeOH, 97:3, v/v), and *cis*-**7** (12.4 g, 56.3% yield), m.p. 146 °C, R_f = 0.26 (CH_2Cl_2/MeOH, 97:3, v/v), as white solids. IR (KBr) (*trans*-**7** diastereoisomer): $\tilde{\nu}$ = 3341 (NH amide), 2903 (CH_2 and CH_3), 1725 (CO_2Et), 1630 (C=O amide), 1581 (ArC=C) cm^{-1}; (*cis*-**7** diastereoisomer) : $\tilde{\nu}$ = 3240 (NH amide), 2929–2802 (CH_2 and CH_3), 1733 (CO_2Et), 1628 (C=O amide), 1582 (ArC=C) cm^{-1}. ^1H NMR ($CDCl_3$) (*trans*-**7** diastereoisomer): δ = 7.38–7.43 (d, J = 10 Hz, 1 H, NHCO), 7.23–7.28 (m, 5 H, ArH), 6.98 (s, 2 H, ArH), 4.2–4.4 (m, 1 H, CH piperidine), 4.07–4.17 (q, J = 7.14 Hz, 2 H, OCH_2CH_3), 3.85–3.88 [2 s, 9 H, $(OCH_3)_3$], 3.32–3.62 (dd, J = 13.3 Hz, 2 H, $ArCH_2$), 2.20–3.32 (m, 7 H, CH and CH_2 piperidine), 1.13–1.20 (t, J = 7.14 Hz, 3 H, OCH_2CH_3); (*cis*-**7** diastereoisomer): δ = 7.26–7.32 (m, 5 H, ArH), 6.96 (s, 2 H, ArH), 6.17–6.21 (d, J = 8 Hz, 1 H, NHCO), 4.03–4.10 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.10–4.14 (m, 1 H, CH piperidine), 3.86–3.88 [2 s, 9 H, $(OCH_3)_3$], 3.55 (s, 2 H, $ArCH_2$), 1.5–3.1 (m, 7 H, CH and CH_2 piperidine), 1.12–1.19 (t, J = 7.14 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$) (*trans*-**7** diastereoisomer): δ = 173.5 (C=O ester), 166.0 (C=O amide), 153.0, 140.7, 138.3, 130.0 (ArC=C), 128.7, 128.0, 126.9, 104.2 (ArCH=CH), 62.4 ($ArCH_2$), 60.8, 56.2 (OCH_3), 60.5 (OCH_2CH_3), 54.4, 53.0, 29.0 (CH_2 piperidine), 47.1, 44.3 (CH piperidine), 13.9 (OCH_2CH_3); (*cis*-**7** diastereoisomer): δ = 173.5 (C=O ester), 166.0 (C=O amide), 153.1, 140.0, 138.3, 130.0 (ArC=C), 128.7, 128.0, 126.9, 104.2 (ArCH=CH), 62.4 ($ArCH_2$), 56.2, 60.8 (OCH_3), 60.5 (OCH_2CH_3), 54.4, 53.0, 29.0 (CH_2 piperidine), 47.2, 44.3 (CH piperidine), 14.0 (OCH_2CH_3) ppm.

1-Benzyl-3-hydroxymethyl-4-(3,4,5-trimethoxybenzoylamino)piperidine (*trans*-9): Dry LiCl (1.48 g, 34.84 mmol), $NaBH_4$ (0.66 g, 17.36 mmol) and absolute EtOH (25 mL) were added successively to a solution of *trans*-**7** (2 g, 438 mmol) in anhydrous THF (50 mL). The reaction mixture was stirred at room temperature for 36 h under argon. The excess $NaBH_4$ and LiCl were destroyed with water and the solvents were evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with water and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. Further purification by silica gel column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH) gave *trans*-**9** as a white solid (1.5 g, yield 83%). M.p. 143 °C, R_f = 0.20 (CH_2Cl_2/1% MeOH, 5:5, v/v). IR (KBr): $\tilde{\nu}$ = 3409 (OH), 3308 (NH amide), 2921–2856 (CH_2 and CH_3), 1626 (C=O amide), 1580 (ArC=C), 1128 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.27–7.33 (m, 5 H, ArH), 7.01 (s, 2 H, ArH), 6.80–6.85 (br. d, 1 H, NHCO), 4.22–4.42 (m, 1 H, CH piperidine), 3.87–3.91 [2 s, 9 H, $(OCH_3)_3$], 3.79–3.82 (m, 3 H, CH_2OH), 3.53 (s, 2 H, $ArCH_2$), 1.98–2.7 (m, 7 H, CH and CH_2 piperidine) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.0 (C=O amide), 153.1, 141.1, 137.9 (ArC=C), 129.1, 128.1, 127.0, 104.4 (ArCH=CH), 62.9 ($ArCH_2$), 61.7 (CH_2OH), 60.7, 56.2 (OCH_3), 55.6, 52.5, 31.7 (CH_2 piperidine), 48.2, 44.9 (CH piperidine) ppm.

[1-Benzyl-4-(3,4,5-trimethoxybenzoylamino)piperidin-3-yl]methyl *N*,*N*-Diethylcarbamate (*trans*-10): NaH (0.12 g, 5 mmol) was added to a solution of *trans*-**9** (1 g, 2.4 mmol) in dry THF (60 mL). The mixture was stirred at 60 °C for 0.5 h, then a solution of diethylcarbamoyl chloride (0.36 g, 2.65 mmol) was added dropwise. The reaction mixture was stirred at 60 °C for 1 h. The excess NaH was destroyed with water and the solvents were removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel column chromatography, eluting with CH_2Cl_2 and CH_2Cl_2/1% MeOH, gave the title compound as a white solid (1 g, yield 81%). M.p. 133 °C, R_f = 0.43 (CH_2Cl_2/MeOH, 93:7, v/v). $C_{28}H_{39}N_3O_6 \cdot ¾H_2O$ (526.5): C 63.75, H 7.96, N 7.96; found C 63.91, H 7.65, N 7.95. IR (KBr): $\tilde{\nu}$ = 3307 (NH amide), 2922 (CH_2 and CH_3), 1703 (C=O carbamate), 1626 (C=O amide), 1583 (ArC=C), 1128 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.6–7.7 (br. d, 1 H, NHCO), 7.26–7.33 (m, 5 H, ArH), 7.20 (s, 2 H, ArH), 4.2–4.51 (m, 2 H, CH_2OH), 4.0–4.18 (m, 1 H, CH piperidine), 3.87–3.93 [2 s, 9 H, $(OCH_3)_3$], 3.47–3.6 (dd, J = 10 Hz, 2 H, $ArCH_2$), 3.0–3.4 [br. q, 4 H, $N(CH_2CH_3)_2$], 1.50–2.83 (m, 7 H, CH and CH_2 piperidine), 0.9–1.2 [br. t, 6 H, $N(CH_2CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 166.7 (C=O amide), 156.0 (C=O ureido), 152.9, 140.5, 138.1 (ArC=C), 129.7, 128.8, 128.1, 127.0, 104.3 (ArCH=CH), 64.9 [$CH_2OCON(Et)_2$], 62.7 ($ArCH_2$), 60.7, 56.1 (OCH_3), 57.0, 52.2, 32.1 (CH_2 piperidine), 49.1, 42.4 (CH piperidine), 41.7, 41.2 (NCH_2CH_3), 13.8, 13.3 (NCH_2CH_3) ppm.

General Procedure for the Synthesis of Compounds *cis*-11, *trans*-11, *cis*-15 and *trans*-15: Ammonium formate, triethylamine (3 equiv.) and palladium on activated carbon were added to a solution of *cis*-**10**, *trans*-**10**, *cis*-**14** or *trans*-**14** in methanol. The mixture was refluxed until the reaction was complete (TLC monitoring). After cooling at room temperature, filtration of Pd/C and evaporation of the solvent to dryness, the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography as indicated.

[4-(3,4,5-Trimethoxybenzoylamino)piperidin-3-yl]methyl *N*,*N*-Diethylcarbamate (*trans*-11): This compound was prepared using a solution of *trans*-**10** (1 g, 1.94 mmol) in methanol (80 mL), ammonium formate (1.5 g, 23.8 mmol) and Pd/C (0.3 g). The reaction mixture was refluxed for 1 h. After concentrating in vacuo, purification on a silica gel column chromatography, eluting with (CH_2Cl_2/MeOH, 97:3 and 90:10, v/v), gave the title compound as a viscous solid (0.35 g, yield 43%). R_f = 0.38 (CH_2Cl_2/MeOH, 80:20, v/v). IR (film): $\tilde{\nu}$ = 3346 (NH, piperidine and NH amide), 2924–2855 (CH_2 and CH_3), 1676 (C=O carbamate), 1636 (C=O amide), 1583 (ArC=C), 1125 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.6–7.8 (br. d, 1 H, NHCO), 7.1–7.25 (s, 2 H, ArH), 4.35–4.45 (d, J = 6 Hz, 1 H, HN piperidine), 4.15–4.3 (m, 1 H, CH piperidine), 3.75–4.00 [2 s, 9 H, $(OCH_3)_3$], 3.0–3.4 [br. q, 4 H, $N(CH_2CH_3)_2$], 2.6–3.0 (m, 2 H, CH_2OCO), 1.2–3.0 (m, 7 H, CH and CH_2 piperidine), 1.01–1.08 [t, J = 7 Hz, 6 H, $N(CH_2CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 166.5 (C=O amide), 155.9 (C=O ureido), 152.9, 140.4, 129.6, 104.3 (ArC=C), 64.8 [$CH_2OCON(Et)_2$], 60.6, 56.0 (OCH_3), 50.0, 45.2, 33.1 (CH_2 piperidine), 49.2, 43.1 (CH piperidine), 41.7, 41.1 (NCH_2CH_3), 13.9, 13.2 [$N(CH_2CH_3)$] ppm.

[1-(3,4,5-Trimethoxybenzoyl)-4-(3,4,5-trimethoxybenzoylamino)-piperidin-3-yl]methyl *N*,*N*-Diethylcarbamate (*trans*-12): Compound *trans*-**12** was prepared using *trans*-**11** (0.34 g, 0.8 mmol), triethylamine (0.3 mL, 2.1 mmol) in THF (60 mL) and a solution of 3,4,5-trimethoxybenzoyl chloride (0.20 g, 0.86 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 1.5 h.

Evaporation of THF to dryness and crystallization of the crude product in methanol gave *trans*-**12** as a white solid (0.35 g, yield 71%). M.p. 240 °C, R_f = 0.33 (CH_2Cl_2/MeOH, 95:5, v/v). $C_{31}H_{43}N_3O_{10}$ (617): C 60.27, H 7.01, N 6.80; found C 60.36, H 7.04, N 6.75. IR (KBr): $\tilde{\nu}$ = 3368 (NH amide), 2925–2856 (CH_2 and CH_3), 1695 (C=O carbamate), 1656 (C=O amide), 1585 (ArC=C), 1123 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.22 (s, 2 H, ArH), 6.63 (s, 2 H, ArH), 4.25–4.5 (m, 2 H, NHCO and CH piperidine), 4.1–4.25 (m, 2 H, CH_2OCO), 3.86–3.89 [2 s, 18 H, $(OCH_3)_6$], 3.0–3.4 [br. q, 4 H, $N(CH_2CH_3)_2$], 1.5–3.4 (m, 7 H, CH and CH_2 piperidine), 0.9–1.2 [br. t, 6 H, $N(CH_2CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 170.8 (C=O amide), 166.5 (C=O amide), 153.3 (C=O ureido), 153.0, 130.8, 129.1, 148.4, 148.7, 104.5, 104.2 (ArC=C), 60.8, 56.2, 56.1 (OCH_3 and CH piperidine), 41.9, 41.2, 28.1 (CH_2 piperidine), 13.9, 13.3 [$N(CH_2CH_3)$] ppm.

1-Benzyl-3-hydroxymethyl-4-(3,4,5-trimethoxybenzoylamino)piperidine (*cis*-9): Compound *cis*-**9** was prepared from *cis*-**7** (3.17 g, 6.95 mmol), LiCl (1.18 g, 27.78 mmol) and $NaBH_4$ (0.53 g, 13.94 mmol) using the procedure described for *trans*-**9** and was obtained as a white solid (1.5 g, yield 57%). M.p. 164 °C, R_f = 0.23 (CH_2Cl_2/MeOH, 93:07, v/v). IR (KBr): $\tilde{\nu}$ = 3422 (OH), 3330 (NH amide), 2941–2836 (CH_2 and CH_3), 1633 (C=O amide), 1582 (ArC=C), 1128 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.25–7.30 (m, 5 H, ArH), 6.9 (s, 2 H, ArH), 6.20–6.24 (d, J = 8.48 Hz, 1 H, NHCO), 3.90–3.98 (m, 2 H, CH piperidine and OH), 3.87 [2 s, 9 H, $(OCH_3)_3$], 3.60 (s, 2 H, $ArCH_2$), 1.5–3.61 (m, 9 H, CH and CH_2 piperidine and CH_2OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.0 (C=O amide), 153.1, 137.2, 141.0 (ArC=C), 129.7, 128.9, 128.4, 127.4, 104.4 (ArCH=CH), 63.7 ($ArCH_2$), 62.9 (CH_2OH), 60.8, 56.3 (OCH_3), 55.3, 51.6, 29.4 (CH_2 piperidine), 47.6, 38.9 (CH piperidine) ppm.

[1-Benzyl-4-(3,4,5-trimethoxybenzoylamino)piperidin-3-yl]methyl *N*,*N*-Diethylcarbamate (*cis*-10): Compound *cis*-**10** was prepared from *cis*-**9** (1.52 g, 3.48 mmol), NaH (0.17 g, 7.4 mmol) and diethylcarbamoyl chloride (0.52 g, 3.83 mmol) using the same procedure as for *trans*-**10** and was obtained as a white solid (1.65 g, yield 93%). M.p. 186 °C, R_f = 0.33 (CH_2Cl_2/MeOH, 93:07, v/v). $C_{28}H_{39}N_3O_6$ (513): C 65.47, H 7.65, N 8.18; found C 65.81, H 7.44, N 7.79. IR (KBr): $\tilde{\nu}$ = 3317 (NH amide), 2936–2836 (CH_2 and CH_3), 1696 (C=O carbamate), 1626 (C=O amide), 1583 (ArC=C), 1127 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.27–7.32 (m, 5 H, ArH), 7.26 (s, 2 H, ArH), 7.00–7.11 (br. d, 1 H, NHCO), 4.40–4.45 (2 dd, 1 H, CH piperidine), 3.86–3.91 [2 s, 9 H, $(OCH_3)_3$], 3.62–3.66 (m, 2 H, CH_2O), 3.54 (s, 2 H, $ArCH_2$), 3.00–3.35 [br. q, 4 H, $N(CH_2CH_3)_2$], 1.5–3.00 (m, 7 H, CH and CH_2 piperidine), 0.90–1.20 [br. t, 6 H, $N(CH_2CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 166.7 (C=O amide), 155.9 (C=O carbamate), 152.9, 140.4, 138.0 (ArC=C), 129.7, 128.8, 128.1, 126.9, 104.3 (ArCH=CH), 64.9 [$CH_2OCON(Et)_2$], 62.7 ($ArCH_2$), 60.7, 56.0 (OCH_3), 57.0, 52.2, 32.1 (CH_2 piperidine), 49.1, 42.3 (CH piperidine), 41.7, 41.1 [$N(CH_2CH_3)$], 13.8, 13.3 [$N(CH_2CH_3)$] ppm.

[4-(3,4,5-Trimethoxybenzoylamino)piperidin-3-yl]methyl *N*,*N*-Diethylcarbamate (*cis*-11): Compound *cis*-**11** was prepared from *cis*-**10** (1.35 g, 2.63 mmol), ammonium formate (1.66g, 26.32 mmol) and Pd/C (0.5 g) using the procedure described for *trans*-**11**. Compound *cis*-**11** was obtained as a white solid (0.90 g, yield 81%). M.p. 149 °C, R_f = 0.21 (CH_2Cl_2/MeOH, 80:20, v/v). IR (KBr): $\tilde{\nu}$ = 3328–3269 (NH of piperidine and NH amide), 2940 (CH_2 and CH_3), 1691 (C=O carbamate), 1625 (C=O amide), 1582 (ArC=C), 1127 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.12–7.18 (m, 3 H, ArH and NHCO), 4.40–4.45 (2 dd, 1 H, CH piperidine), 3.85–3.91 [2 s, 9 H, $(OCH_3)_3$], 3.60–3.69 (m, 2 H, CH_2O), 3.17–3.28 [q, J = 7 Hz, 4 H, $N(CH_2CH_3)_2$], 1.4–3.28 (m, 7 H, CH and CH_2 piperidine), 2.38 (s, 1 H, HN piperidine), 1.05–1.12 [t, J = 7 Hz, 6 H, $N(CH_2CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 166.5 (C=O amide), 155.9 (C=O carbamate), 152.9, 140.4, 129.6, 104.4 (ArC=C), 64.8 [$CH_2OCON(Et)_2$], 60.6, 56.0 (OCH_3), 50.0, 45.2, 33.1 (CH_2 piperidine), 49.2, 43.1 (CH piperidine), 41.7, 41.1 [$N(CH_2CH_3)$], 13.9, 13.2 [$N(CH_2CH_3)$] ppm.

[1-(3,4,5-Trimethoxybenzoyl)-4-(3,4,5-trimethoxybenzoylamino)-piperidin-3-yl]methyl *N*,*N*-Diethylcarbamate (*cis*-12): Compound *cis*-**12** was prepared from *cis*-**11** (0.35 g, 86 mmol), triethylamine (0.36 mL, 2.56 mmol) and a solution of 3,4,5-trimethoxybenzoyl chloride (0.25 g, 1 mmol) using the same process as for *trans*-**12**. Compound *cis*-**12** was obtained as a white solid (0.45 g, yield 88%). M.p. 112 °C, R_f = 0.20 (CH_2Cl_2/MeOH, 95:05, v/v). $C_{31}H_{43}N_3O_{10}\cdot H_2O$ (635): C 57.76, H 7.14, N 6.52; found C 57.86, H 7.28, N 6.20. IR (KBr): $\tilde{\nu}$ = 3345 (NH amide), 3055 (ArCH=CH), 2974–2836 (CH_2 and CH_3), 1695 (C=O carbamate), 1624 (C=O amide), 1585 (ArC=C), 1127 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.18 (s, 2 H, ArH), 6.61 (s, 2 H, ArH), 4.47–4.54 (br. d, J = 12.2 Hz, 1 H, NHCO), 3.85–3.92 [2 s, 18 H, $(OCH_3)_6$], 3.5–3.92 (m, 3 H, CH_2O and CH piperidine), 3.0–3.4 [br. q, 4 H, $N(CH_2CH_3)_2$], 1.0–3.1 (m, 7 H, CH and CH_2 piperidine), 1.0–1.12 [br. t, 6 H, $N(CH_2CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 170.1 (C=O amide), 166.8 (C=O amide), 153.2 (C=O ureido), 153.0, 140.8, 139.2, 130.8, 129.2, 104.4, 104.0 (ArC=C), 64.2 [$CH_2OCON(Et)_2$], 60.8, 56.1, 49.3 (OCH_3), 41.9, 41.3, 21.1 (CH_2 piperidine), 13.8, 13.3 N (CH_2CH_3) ppm.

1-Benzyl-3-cyano-4-(3,4,5-trimethoxybenzoylamino)piperidine (*cis*-8 and *trans*-8): Compounds *cis*- and *trans*-**8** were prepared using **6** (13.3 g, 61.86 mmol), triethylamine (21.7 mL, 154.4 mmol) in THF (150 mL) and a solution of 3,4,5-trimethoxybenzoyl chloride (15 g, 65 mmol) in THF (50 mL). The reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and crystallized by adding methanol to give 19.4 g (yield 78%) of a mixture of *cis*-**8** and *trans*-**8** diastereoisomers as a white powder. They were separated by silica gel column chromatography using CH_2Cl_2 then CH_2Cl_2/MeOH (98:2, v/v) as eluent to give 7 g of *trans*-**8** (yield 36%), m.p. 200 °C, R_f = 0.54 (CH_2Cl_2/MeOH, 95:5, v/v), and 9.7 g of *cis*-**8** (yield 50%), m.p. 195 °C, R_f = 0.29 (CH_2Cl_2/MeOH, 95:5, v/v)]. IR (KBr) (*trans*-**8** diastereoisomer): $\tilde{\nu}$ = 3308 (NH amide), 3054 (ArC-H), 2943–2810 (CH_2), 2305–2241 (CN), 1632 (C=O amide), 1582 (ArC=C) cm^{-1}; (*cis*-**8** diastereoisomer): $\tilde{\nu}$ = 3334 (NH amide), 2956–2815 (CH_2 of piperidine), 2244 (CN), 1642 (C=O amide), 1585 (ArC=C) cm^{-1}. ^1H NMR ($CDCl_3$) (*trans*-**8** diastereoisomer): δ = 7.23–7.35 (m, 5 H, ArH), 7.03 (s, 2 H, ArH), 6.71–6.75 (d, J = 7.62 Hz, 1 H, NHCO), 4.10–4.12 (m, 1 H, CH piperidine), 3.83–3.88 [s, 9 H, $(OCH_3)_3$], 3.48–3.63 (dd, J = 3.56 Hz, 2 H, $ArCH_2$), 3.40–3.41 (br. d, 1 H, CH piperidine), 2.90–3.14 (2 br. d, 1 H, CH piperidine), 1.90–2.33 (m, 4 H, CH_2 piperidine); (*cis*-**8** diastereoisomer): δ = 7.25–7.36 (m, 5 H, ArH), 6.99 (s, 2 H, ArH), 6.39–6.43 (d, J = 8.13 Hz, 1 H, NHCO), 4.17–4.22 (m, 1 H, CH piperidine), 3.86 [s, 9 H, $(OCH_3)_3$], 3.56 (s, 2 H, ArH), 2.81–3.10 (m, 3 H, CH and CH_2 piperidine), 1.72–2.45 (m, 4 H, CH_2 piperidine) ppm. ^{13}C NMR ($CDCl_3$) (*trans*-**8** diastereoisomer): δ = 167.0 (C=O amide), 153.0, 141.1, 137.5, 128.8 (ArC=C), 128.5, 128.3, 127.2, 104.5 (ArCH=CH), 119.6 (CN), 61.8 ($ArCH_2$), 60.8, 56.2 (OCH_3), 52.9, 51.9, 28.3 (CH_2 piperidine), 48.0, 34.2 (CH piperidine); (*cis*-**8** diastereoisomer): δ = 166.9 (C=O amide), 153.0, 141.1, 137.5, 128.8 (ArC=C), 128.5, 128.3, 127.2, 104.5 (ArCH=CH), 119.6 (CN), 61.7 ($ArCH_2$), 60.7, 56.2 (OCH_3), 52.9, 51.9, 28.3 (CH_2 piperidine), 48.0, 34.2 (CH piperidine) ppm.

3-Aminomethyl-1-benzyl-4-(3,4,5-trimethoxybenzoylamino)piperidine (*trans*-13): HCl (12 N, 0.5 mL, 16.16 mmol) and an activated Raney nickel suspension (5 mL) were added to a solution of compound *trans*-**8** (4.62 g, 11.29 mmol) in absolute EtOH (80 mL). The resulting mixture was hydrogenated under pressure (40 psi) with shaking at 60 °C for 12 h. The catalyst was removed by filtration and the ethanol was evaporated to dryness. The crude residue was dissolved in dichloromethane and washed with a $NaHCO_3$ solution and water. The organic layer was then dried with $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography in CH_2Cl_2 then 97:3 and 93:7 (v/v) CH_2Cl_2/MeOH solutions afforded the pure product *trans*-**13** as a white solid (1.68 g, yield 37%). M.p. 70 °C, R_f = 0.28 (CH_2Cl_2/MeOH, 80:20, v/v). IR (KBr): $\tilde{\nu}$ = 3368 (NH_2), 3277 (NH amide), 3054 (ArC–H), 2939–2836 (CH_2 of piperidine), 1643 (C=O amide), 1583 (ArC=C), 1126 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.24–7.35 (m, 5 H, ArH), 7.15 (2 s, 2 H, ArH), 6.97–7.00 (d, J = 4.7 Hz, 1 H, NHCO), 4.22–4.24 (m, 1 H, CH piperidine), 3.83–3.93 [s, 9 H, $(OCH_3)_3$], 3.48–3.63 (m, 4 H, $ArCH_2$ and NH_2), 3.08–3.25 (2 br. d, 1 H, CH_2 piperidine), 2.64–3.02 (2 br. d, 2 H, C$H_2$$NH_2$), 1.98–2.33 (m, 5 H, CH and CH_2 piperidine) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.3 (C=O amide), 153.0, 137.4, 136.8 (ArC=C), 129.3, 129.1, 128.3, 128.2, 127.4, 127.2, 104.8, 104.6 (ArCH=CH), 62.6 ($ArCH_2$), 60.8, 56.2 (OCH_3), 52.4, 50.2 (CH piperidine), 41.8, 34.1, 31.6 (CH_2 piperidine) ppm.

3-[1-Benzyl-4-(3,4,5-trimethoxybenzoylamino)piperidin-3-ylmethyl]-1-pentylurea (*trans*-14): A solution of pentyl isocyanate (0.42 g, 3.71 mmol) in dry dichloromethane (10 mL) was added dropwise to a solution of *trans*-**13** (1.55 g, 3.7 mmol) in dry dichloromethane (60 mL). The reaction mixture was then stirred at room temperature for 2 h and washed successively with water and brine. The organic layer was dried with $MgSO_4$ and the solvent was evaporated to dryness. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 97:3 and 93:7, v/v) to give *trans*-**14** as a white solid (1.3 g, yield 65%). M.p. 133 °C, R_f = 0.38 (CH_2Cl_2/MeOH, 93:7, v/v). $C_{28}H_{39}N_3O_6 \cdot ½H_2O$ (522): C 65.01, H 7.84, N 10.46; found C 65.05, H 8.10, N 10.81. IR (KBr): $\tilde{\nu}$ = 3283 (NH amide and ureido), 3053 (ArC–H), 2936 (CH_2 and CH_3 of piperidine and alkyl chain), 1648 (C=O of amide and ureido), 1583 (ArC=C), 1127 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.90 (br. s, 1 H, NHCO), 7.25–7.45 (m, 7 H, ArH), 5.1–5.4 (br. t, 1 H, CH_2NHCO), 4.60 (br. t, 1 H, CONHCH_2), 4.08–4.29 (m, 1 H, CH piperidine), 3.86–3.93 [s, 9 H, $(OCH_3)_3$], 3.67–3.80 (m, 1 H, CH_2 piperidine), 3.40–3.57 (dd, J = 12.7 Hz, 2 H, $ArCH_2$), 1.72–3.13 (m, 10 H, CH_2NH, NHCH_2, CH_2 piperidine), 1.36–1.47 [m, 2 H, C$H_2$$(CH_2)_2CH_3$], 1.22–1.28 [m, 4 H, $(CH_2)_2CH_3$], 0.82–0.89 (t, J = 6.7 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.5 (C=O amide), 158.0 (C=O ureido), 153.0, 140.5, 129.6 (ArC=C), 128.9, 128.3, 127.3, 104.6 (ArCH=CH), 63.1 ($ArCH_2$), 60.8, 56.2 (OCH_3), 52.3, 47.1 (CH_2 piperidine), 41.0, 40.7 (CH piperidine), 39.0 (CH_2NHCO), 29.8 ($NHCH_2$), 28.9 ($NHCH_2CH_2$), 29.1 ($CH_2$$CH_3$), 22.3 ($CH_2CH_3$), 13.9 ($CH_3$) ppm.

1-Pentyl-3-[4-(3,4,5-trimethoxybenzoylamino)piperidin-3-ylmethyl]-urea (*trans*-15): Compound *trans*-**15** was prepared using a solution of *trans*-**14** (1 g, 1.85 mmol) in methanol (60 mL), ammonium formate (1.16 g, 184 mmol) and Pd/C (0.4 g) as the catalyst. The reaction mixture was stirred at reflux for 1 h. After filtration and evaporation of the solvent a white solid was obtained (0.5 g, yield 60%). M.p. 175 °C, R_f = 0.27 (CH_2Cl_2/MeOH/NH_4OH, 80:20:2, v/v/v). IR (KBr): $\tilde{\nu}$ = 3311–3306 (NH), 2935–2864 (CH_2 and CH_3), 1634 (C=O), 1581 (ArC=C), 1123 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.77 (br. s, 1 H, NHCO), 7.26–7.36 (s, 2 H, ArH), 5.81 (br. s, 1 H, CH_2NHCO), 4.56 (br. t, 1 H, CONHCH_2), 4.38–4.5 (m, 1 H, CH piperidine), 3.89–3.99 [2 s, 9 H, $(OCH_3)_3$], 2.85–3.18 (m, 5 H, CH piperidine, NHC$H_2$$CH_2$-), 1.26–1.88 [m, 13 H, HN piperidine, $(CH_2)_3$, CH and CH_2 piperidine], 0.85–0.91 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.7 (C=O amide), 158.8 (C=O ureido), 153.0, 129.6, 104.7 (ArC=C), 60.8, 56.3 (OCH_3), 47.0, 42.0 (CH_2 piperidine), 44.7, 38.9 (CH piperidine), 40.6 (CH_2NHCO), 29.8 (CONHCH_2), 29.5 ($CONHCH_2CH_2$), 28.9 (NH $(CH_2)_2CH_2$), 22.3 (CH_2CH_3), 13.9 (CH_3) ppm.

1-Pentyl-3-[1-(3,4,5-trimethoxybenzoyl)-4-(3,4,5-trimethoxybenzoylamino)piperidin-3-ylmethyl]urea (*trans*-16): Compound *trans*-**16** was prepared using *trans*-**15** (0.47 g, 1.04 mmol), triethylamine (0.41 mL, 2.96 mmol) in dichloromethane (60 mL) and a solution of 3,4,5-trimethoxybenzoyl chloride (0.26 g, 1.13 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight. Purification by silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/MeOH, 97:3 and 95:5, v/v) gave the title compound as a white solid (0.43 g, yield 74%). M.p. 179 °C, R_f = 0.50 (CH_2Cl_2/MeOH, 93:7, v/v). $C_{32}H_{46}N_4O_9 \cdot ¼H_2O$ (634.5): C 60.48, H 7.24, N 8.82; found C 60.13, H 7.30, N 8.47. IR (KBr): $\tilde{\nu}$ = 3343–3260 (NH), 2924–2858 (CH_2 and CH_3), 1634 (C=O), 1581 (ArC=C), 1123 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.17–8.23 (br. s, 1 H, NHCO), 7.29 (s, 2 H, ArH), 6.57 (s, 2 H, ArH), 5.90 (br. s, 1 H, CH_2N*H*CO), 4.78–5.00 (m, 2 H, CH piperidine and CON*H*CH_2), 3.80–3.89 [2 s, 18 H, $(OCH_3)_6$], 2.90–3.78 (m, 4 H, CH_2NHCO and CONHCH_2), 2.15–2.65 (m, 5 H, CH and CH_2 piperidine), 1.23–1.38 [m, 8 H, CH_2 piperidine and -$(CH_2)_3CH_3$], 0.81–0.87 (t, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.9, 166.2 (C=O amide), 159.4 (ureido), 153.4, 153.0, 130.5, 129.4, 104.7, 104.0 (ArC=C), 60.8, 56.2, 56.1 (OCH_3), 47.9 (CH piperidine), 40.4 (CH_2NHCO), 30.0 (CONHCH_2), 29.0 ($CONHCH_2CH_2$), 22.3 (CH_2CH_3), 13.9 (CH_3) ppm.

1-Benzyl-3-methylamino-4-(3,4,5-trimethoxybenzoylamino)piperidine (*cis*-13): This compound was prepared from *cis*-**8** (1.75g, 4.3 mmol), HCl (12 N, 0.5 mL, 16.16 mmol) and an activated Raney nickel solution (5 mL) using the same procedure as described for *trans*-**13**. The crude product was purified by silica gel column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH, 97:3 and 93:7, v/v) to give pure *cis*-**13** as a white solid (1.45 g, yield 75%). M.p. 115 °C, R_f = 0.22 (CH_2Cl_2/MeOH, 80:20, v/v). IR (KBr): $\tilde{\nu}$ = 3313 (NH_2), 3309 (NH amide), 3053 (ArC-H), 2942 (CH_2), 1640 (C=O amide), 1584 (ArC=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.58–7.62 (d, J = 7.69 Hz, 1 H, NHCO), 7.10–7.27 (m, 7 H, ArH), 4.69 (br. s, 3 H, CH_2NH_2 and CH piperidine), 3.84–3.85 [s, 9 H, $(OCH_3)_3$], 3.40–3.57 (m, 2 H, $ArCH_2$), 2.66–3.02 (m, 4 H, C$H_2$$NH_2$ and CH_2 piperidne), 1.61–2.07 (m, 5 H, CH and CH_2 piperidine) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.2 (C=O amide), 153.0, 137.4, 136.8 (ArC=C), 129.3, 129.1, 128.3, 128.2, 127.4, 127.2, 104.8, 104.6 (ArCH=CH), 62.6 ($ArCH_2$), 60.8, 56.4, 56.3 (OCH_3), 52.4, 51.7, 50.2 (CH piperidine), 42.0, 41.8, 34.2, 31.6 (CH_2 piperidine) ppm.

3-[1-Benzyl-4-(3,4,5-trimethoxybenzoylamino)piperidin-3-ylmethyl]-1-pentylurea (*cis*-14): Compound *cis*-**14** was prepared from *cis*-**13** (0.6 g, 1.47 mmol) and pentyl isocyanate (0.17 g, 1.5 mmol) using the same procedure as for compound *trans*-**14** and obtained in the form of a white solid (0.5 g, yield 65%). M.p. 193 °C, R_f = 0.29 (CH_2Cl_2/MeOH, 93:7, v/v). $C_{29}H_{42}N_4O_5 \cdot {}^1/_3H_2O$ (532): C 65.37, H 7.89, N 10.51; found C 65.20, H 8.30, N 10.36. IR (KBr): $\tilde{\nu}$ = 3356–3292 (NH), 2932 (CH_2), 1630 (C=O), 1584 (ArC=C), 1127 (CH_3O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.24–7.31 (m, 5 H, ArH), 7.14 (s, 2 H, ArH), 6.93–6.97 (d, J = 8 Hz, 1 H, NHCO), 5.28–5.30 (br. t, 1 H, CH_2N*H*CO), 4.30–4.36 (br. t, 1 H, CON*H*CH_2), 3.88–3.93 [2 s, 9 H, $(OCH_3)_3$], 3.67–3.76 (m, 1 H, CH piperidine), 3.40–3.62 (dd, J = 30.2 Hz, 2 H, $ArCH_2$), 2.85–3.18 (m, 4 H, CH_2NHCO and CONHCH_2), 2.64–2.74 (m, 1 H, CH piperidine), 1.82–2.17 (m,

6 H, CH and CH_2 piperidine), 1.45–1.63 (m, 2 H, $NHCH_2CH_2$), 1.26–1.34 [m, 4 H, $(CH_2)_2CH_3$], 0.87–0.94 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.4 (C=O amide), 158.6 (C=O ureido), 153.0, 140.7, 137.5, 129.4, 129.1 (ArC=C), 128.2, 127.2, 104.5 (ArCH=CH), 62.6 ($ArCH_2$), 60.8, 57.2 (OCH_3), 56.2, 52.0, 40.2 (CH_2 piperidine), 49.7, 43.2 (CH piperidine), 40.5 (CH_2NHCO), 31.7 ($CONHCH_2$), 29.8 ($CONHCH_2CH_2$), 29.0 ($CONHCH_2CH_2CH_2$), 22.3 (CH_2CH_3), 13.9 (CH_3) ppm.

1-Pentyl-3-[4-(3,4,5-trimethoxybenzoylamino)piperidin-3-ylmethyl]-urea (*cis*-15): Compound *cis*-**15** was prepared from *cis*-**14** (0.4 g, 0.76 mmol), ammonium formate (0.8 g, 1.27 mmol) and Pd/C (0.1 g) as the catalyst using the same procedure as for *trans*-**15** and gave the title compound in the form of a white solid (0.26 g, yield 79%). M.p. 184 °C, R_f = 0.24 (CH_2Cl_2/MeOH/NH_4OH, 80:20:2, v/v/v). IR (KBr): $\tilde{\nu}$ = 3317–3286 (NH), 2905 (CH_2), 1629 (C=O), 1583 (ArC=C), 1126 (CH_3O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.08–7.19 (m, 3 H, ArH and NHCO), 5.52 (br. t, 1 H, CH_2NHCO), 4.50–4.53 (br. t, 1 H,$CONHCH_2$), 3.88–3.93 [2 s, 9 H,$(OCH_3)_3$], 3.56–3.66 (m, 1 H, CH piperidine), 2.11–3.24 (m, 9 H, CH_2NHCO, CH_2 and HN piperidine, $CONHCH_2$), 1.26–1.68 [m, 8 H, CH_2 piperidine, $NHCH_2CH_2$, $(CH_2)_2CH_3$], 0.85–0.92 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.7 (C=O amide), 158.8 (C=O ureido), 153.0, 129.6, 104.6 (ArC=C), 60.8, 56.2 (OCH_3), 47.0, 42.0 (CH_2 piperidine), 44.6, 38.9 (CH piperidine), 40.5 (CH_2NHCO), 29.8 ($CONHCH_2$), 29.5 ($NHCH_2CH_2$), 28.9 ($CH_2CH_2CH_3$), 22.3 (CH_2CH_3),13.9 (CH_3) ppm.

1-Pentyl-3-[1-(3,4,5-trimethoxybenzoyl)-4-(3,4,5-trimethoxybenzoyl-amino)piperidin-3-ylmethyl]urea (*cis*-16): Compound *cis*-**16** was prepared from *cis*-**15** (0.14 g, 0.32 mmol), triethylamine (0.14 g, 1.38 mmol) and 3,4,5-trimethoxybenzoyl chloride (76 mg, 0.33 mmol) using the same procedure as for *trans*-**16** and gave the title compound in the form of a white solid (0.11 g, yield 61%). M.p. 110 °C, R_f = 0.37 (CH_2Cl_2/MeOH, 93:7, v/v). $C_{32}H_{46}N_4O_9 \cdot {}^2/_3H_2O$ (642): C 59.78, H 7.16, N 8.72; found C 59.50, H 7.44, N 9.14. IR (KBr): $\tilde{\nu}$ = 3393–3331 (NH), 3053 (ArCH), 2935–2867 (CH_2 and CH_3), 1631 (C=O), 1583 (ArC=C), 1128 (CH_3O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.92 (br. s, 1 H, NHCO), 7.38 (s, 2 H, ArH), 6.64 (s, 2 H, ArH), 5.63 (br. s, 1 H, CH_2NHCO), 5.3 (br. s, 1 H, $CONHCH_2$), 4.53 (m, 1 H, CH piperidine), 3.86–3.95 [s, 9 H, $(OCH_3)_3$], 3.58–3.86 (m, 1 H, CH piperidine), 3.02–3.17 (m, 4 H, $CONHCH_2$, CH_2NHCO), 1.27–1.99 [m, 12 H, CH_2 piperidine, $NHCH_2CH_2$, $(CH_2)_2CH_3$], 0.84–0.91 (t, J = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.9, 166.2 (C=O amide), 159.4 (C=O ureido), 153.4, 152.9, 130.5, 129.4, 104.7, 104.0 (ArC=C), 60.9, 60.8, 56.2, 56.1 (OCH_3), 47.9 (CH piperidine), 40.4 (CH_2NHCO), 30.0 ($CONHCH_2$), 29.0 ($CONHCH_2CH_2$), 22.3 (CH_2CH_3), 13.9 (CH_3) ppm.

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