

Structure–activity relationships in platelet-activating factor. Part 13: Synthesis and biological evaluation of piperazine derivatives with dual anti-PAF and anti-HIV-1 or pure antiretroviral activity

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Abstract—HIV-1 infection of the brain and PAF neurotoxicity are implicated in AIDS dementia complex. We previously reported that a trisubstituted piperazine derivative is able to diminish both HIV-1 replication in monocyte-derived macrophages and PAF-induced platelet aggregation. We report in this work new compounds obtained by modifying its piperazine substituents. The structure–activity relationship study shows that a better dual activity or even pure antiretroviral compounds can be obtained in this series.

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1. Introduction

Human immunodeficiency virus type 1 (HIV-1) infection rapidly results in the invasion of the central nervous system (CNS) by the virus and in neurologic diseases in a large part of the infected population. HIV-associated dementia (HAD), including memory impairments and psychomotor slowing, occurs after HIV infection of the CNS and affected 15–20% of adults and 50% of children during the later stages of the disease.^{1,2} The introduction of the highly active antiretroviral therapy enables HAD incidence to decline to 8–10%.^{3,4} HIV-infected and activated brain-resident macrophages and

microglia, the main cellular targets of the virus in the CNS, seem to be the responsible cells for the inflammatory processes induced since the neurons do not appear to be infected by HIV-1 and neuronal death can occur soon after exposure to HIV-1-infected monocyte culture fluids.^{5–7} These data support the concept that the pathogenesis of HIV-associated dementia is likely due to indirect effects of HIV infection of the brain, possibly through the secretion of soluble factors by macrophages and microglia. Monocyte production of neurotoxic factors seems to require HIV-1 infection, monocyte activation and astroglia and/or neuronal monocyte interactions.^{6,8,9} The proinflammatory cytokine TNF- α and the phospholipid mediator platelet-activating factor (PAF) are such factors and their secretion has been shown to be enhanced in HIV-1-infected monocytes after a cell activation by antigenic stimuli in vitro or contact with

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neural cells in vivo.⁹ Moreover, high levels of PAF are detected in the cerebrospinal fluid (CSF) of HIV-1-infected patients with immunosuppression and signs of CNS dysfunctions.¹⁰ When applied to primary neuronal foetal cultures at concentrations close to those found in the CSF of HIV-infected patients, PAF induces a dose-dependent neurotoxicity which can be blocked by the PAF-antagonist WEB 2086, the *N*-methyl-D-aspartate receptor antagonist, MK-801, or by PAF-acetylhydrolase (PAF-AH), the catabolic enzyme of PAF.^{10,11} These results suggest that PAF is likely an HIV-1-induced neurotoxin which plays a critical role in the course of HIV-dementia and provide this mediator as a putative therapeutic target in this pathology.

We have previously shown that the compound **1a**¹² (PMS 601, Fig. 1), a piperazine derivative bearing a carbamate function on a carbon of the cycle and two 3,4,5-trimethoxybenzoyl substituents on the nitrogens, is able to inhibit HIV-1 replication in monocyte-derived macrophages (MDM) infected with the reference macrophage-tropic strain HIV-1/Ba-L with an IC₅₀ of 11 μ M. Moreover, this compound presents a PAF-antagonism with an 8 μ M IC₅₀ on PAF-induced platelet aggregation, that would enable it to diminish neurotoxic disorders generated by the important production of PAF from the infected cells in brain tissues.^{12,13}

In a previous study,¹⁴ we replaced the carbamate group of **1a** with other functions (ureate, thiocarbamate...) and evaluated the influence of this modification on both anti-PAF and anti-HIV-1 activities. The results obtained showed that compounds with a higher antiviral activity coupled or not with a PAF-antagonism can be obtained.

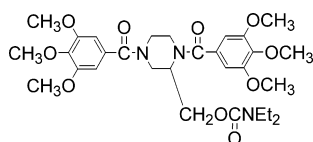
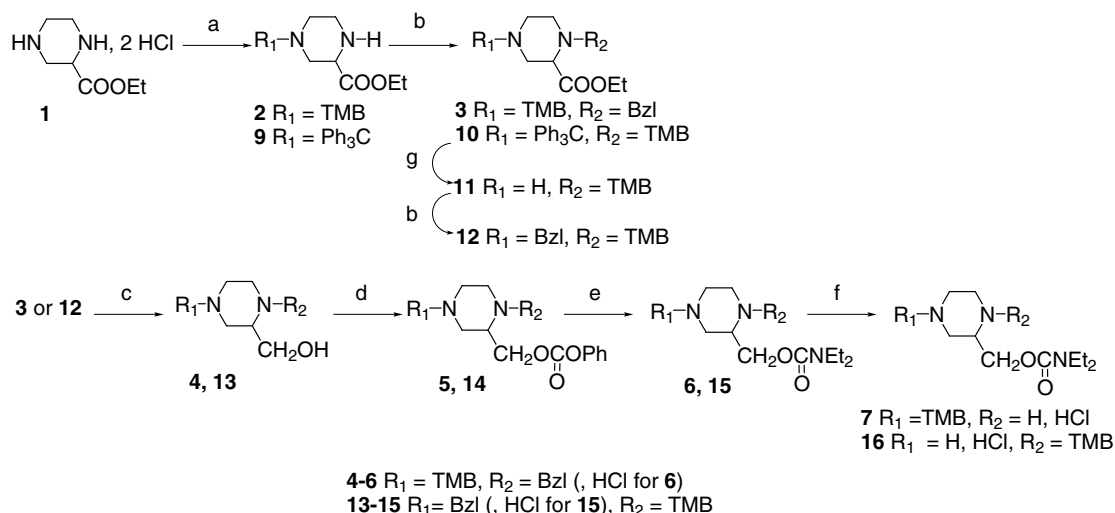


Figure 1. PMS 601.



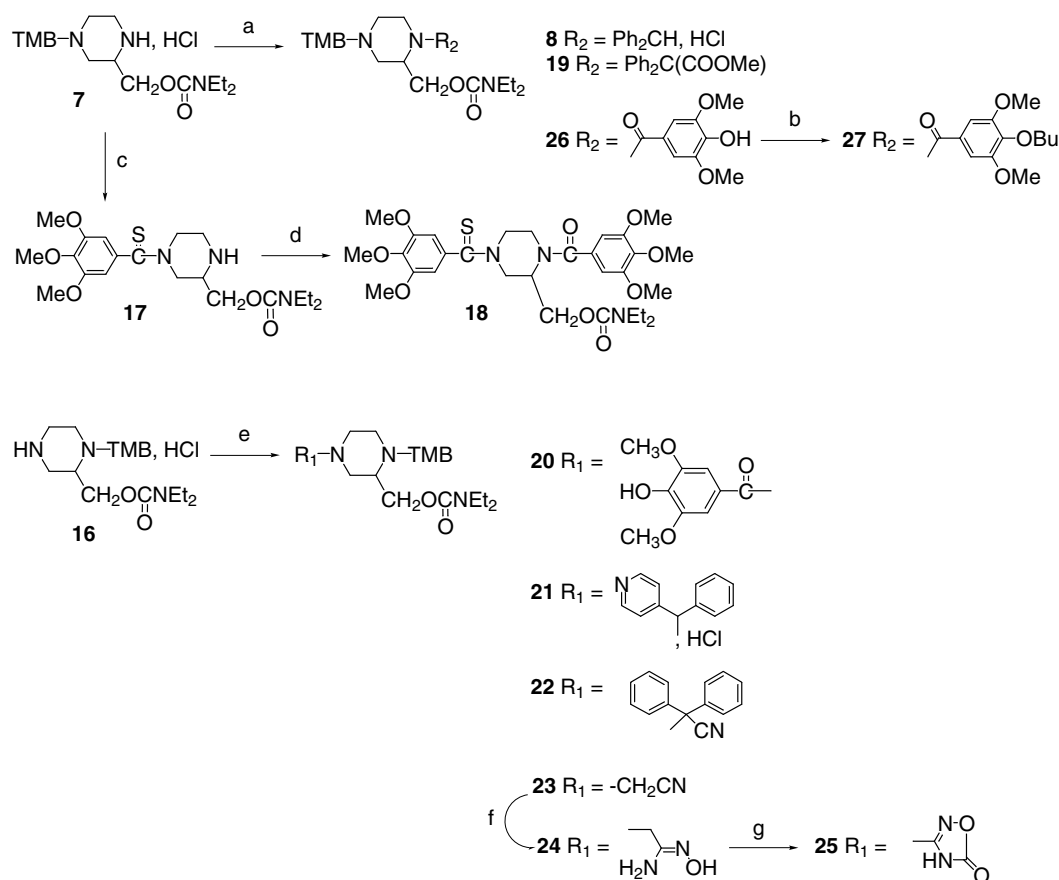
Scheme 1. Reagents and conditions: (a) TMBCl or Ph₃CCl, Et₃N, CH₂Cl₂, 0 °C; (b) BzlCl, K₂CO₃, KI, CH₃CN, reflux or TMBCl, Et₃N, CH₂Cl₂; (c) NaBH₄, MeOH, 0 °C; (d) PhOCOCl, pyr, CH₂Cl₂, 0 °C; (e) 1—HN(Et)₂, reflux; 2—HCl, EtOH; (f) H₂, Pd/C, EtOH, 40 °C; (g) i—HCl, MeOH, 0 °C.

In this work, the carbamate function of **1a** was maintained and new substituents were introduced on one or both nitrogens of the piperazine ring in order to modify either lipophilicity, electronic distribution or steric effect. These modifications included (i) the variation of the number and the position of the methoxy groups on the aromatic rings, (ii) the transformation of an amide to a thioamide function, (iii) the suppression of one or both substituents on the piperazine nitrogens and (iv) the replacement of one or both trimethoxyphenyl rings by one or two aryl groups or aromatic heterocycles. Their influence on both anti-PAF and anti-HIV-1 activities was investigated. Moreover, a molecular modelling analysis has been triggered to calculate 3D electrostatic potential maps of selected compounds and to study the conformational space of the sulfur-containing derivatives.

2. Results and discussion

2.1. Chemistry

In Scheme 1, the monosubstitution of **1**¹⁵ using 3,4,5-trimethoxybenzoyl chloride (TMBCl) or triphenylmethyl chloride led to **2** and **9**, respectively. Their free nitrogen was then substituted by either benzyl chloride for **2** leading to **3** or TMBCl for **9** providing **10**. The compound **11** was obtained after deprotection of **10** using HCl in MeOH and was benzylated into **12**. The carbamate function in **6** and **15** was obtained from the esters **3** and **12**, respectively, according to Serradji et al. and Lamouri et al.^{12,16} The catalytic hydrogenolysis of **6** and **15** led to **7** and **16**, respectively. In Scheme 2, the free base of **7** was (i) transformed into **8** and **19** using diphenylmethyl bromide and methyl 2-bromo-2,2-diphenylacetate, respectively; (ii) converted, using the Lawesson's reagent,^{17,18} into its thioamide analogue **17** which was acylated with TMBCl to give **18**; (iii) transformed, using syringic acid, DCC and HOBT, into **26** which was alkylated with 1-bromobutane into **27**. The reaction of the free base of **16** with (i) syringic acid, DCC and



Scheme 2. Reagents and conditions: (a) $(Ph)_2CHBr$, KI, K_2CO_3 , CH_3CN , reflux then HCl, EtOH or $Ph_2C(Br)COOMe$, KI, K_2CO_3 , CH_3CN , reflux or syringic acid, DCC, HOBT, CH_2Cl_2 , reflux; (b) *n*-BuBr, K_2CO_3 , acetone, reflux; (c) 1—NaHCO₃, 2—Lawesson's reagent, THF, 0 °C; (d) TMBCl, Et₃N, CH_2Cl_2 ; (e) 1—NaHCO₃; 2—syringic acid, DCC, HOBT, CH_2Cl_2 , reflux or PhPyrCHCl (for **21**) or $Ph_2C(Br)CN$ (for **22**) or $ClCH_2CN$ (for **23**), KI, K_2CO_3 , CH_3CN , reflux then HCl, EtOH (for **21**); (f) $NH_2OH \cdot HCl$, K_2CO_3 , EtOH, reflux; (g) $PhOCOCl$, pyr, C_6H_6 , reflux.

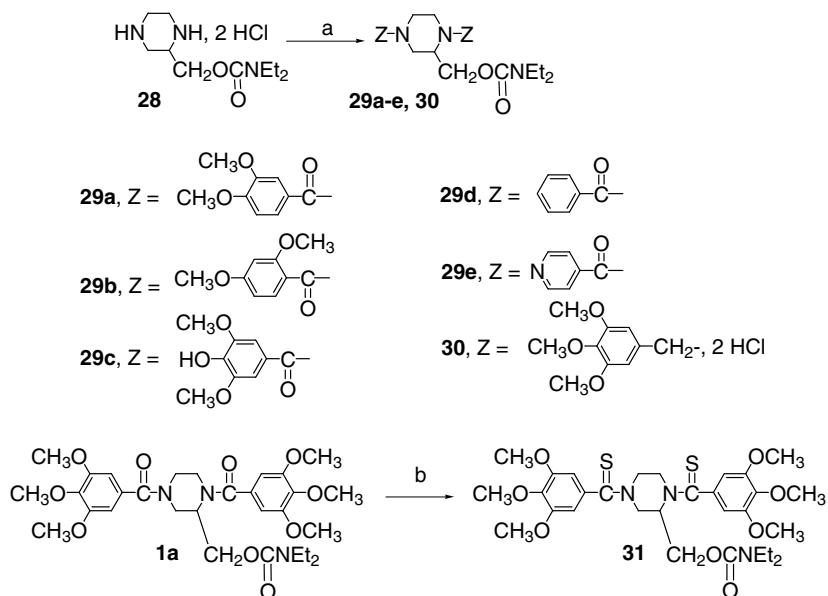
HOBT provided **20**; (ii) 4-[chloro(phenyl)methyl]pyridine or α -bromo- α -phenylbenzeneacetonitrile led to **21** and **22**, respectively; (iii) chloroacetonitrile gave **23**. The nitrile function of **23** was converted into the corresponding amidoxime **24**, using hydroxylamine, and the oxadiazolone **25** was obtained after reaction with phenyl chloroformate followed by an internal cyclization in refluxing benzene.¹⁹ The compounds **29a–e** and **30**, described in Scheme 3, were prepared from **28**¹⁶ and the corresponding acid, acyl or alkyl chloride. The compound **1a**¹⁶ was converted into the corresponding di-thioamide **31** using the Lawesson's reagent. In Scheme 4, the monosubstitution of **28** by either diphenylmethyl bromide or triphenylmethyl chloride led to **32** and **34**, respectively. The acylation of **34** by syringic acid resulted in **35** which was alkylated with *n*-butyl bromide into **36**. Compound **38** was obtained after removal of the trityl group of **36**, benzylation of **37** and treatment with the corresponding HCl salt. The compound **42** was obtained as previously described for **18**.

2.2. Results and discussion

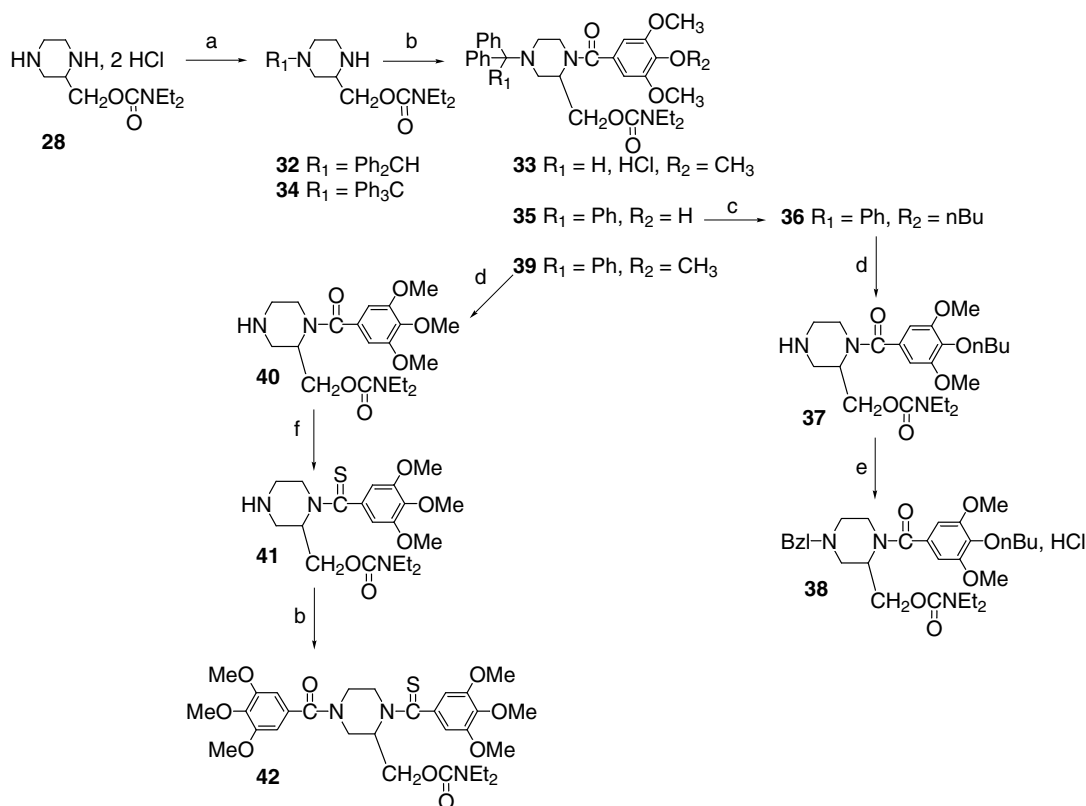
All the compounds were tested for their ability to inhibit PAF-induced platelet aggregation on the one hand and to block the viral replication in MDM infected with the reference macrophage-tropic HIV-1/Ba-L strain on the

other hand.^{12,13} In this new set of experiments, **1a** demonstrated identical effects as previously described with an anti-HIV-1 IC₅₀ and an anti-PAF IC₅₀ equal to 11 and 8 μ M, respectively.¹² It was then used as the reference compound to evaluate the impact of the various modifications performed in this study. The 1-octanol/water partition coefficient ($\log P$) of all the molecules was calculated using ALOGPS program^{20–22} to evaluate the influence of this parameter on both activities (Table 1).

2.2.1. Influence of the substituent on the piperazine ring (Table 1). The deletion of one of both methoxyl groups at the *meta*-position (**29a**) modifies neither the affinity to the PAF-receptor (PAF-R) nor the antiviral activity of the compound (42% at 10 μ M), while the displacement of the remaining *meta*-methoxyl to the *ortho*-position (**29b**) induces a complete loss of both activities. The modification of the electrostatic wells in the 'cache-oreilles' effect^{23,24} and/or an increase of steric hindrance at the *ortho*-position could explain this difference between **29a** and **29b**. The compound **29d**, which does not bear any methoxyl group, does not present a better activity than **1a**, supporting the importance of the electronic properties of these substituents towards, at least, the PAF-antagonism. Indeed, **29f**, which is the HCl salt of the previously described 1,4-dibenzyl-2-*N,N*-diethylami-



Scheme 3. Reagents and conditions: (a) ZCl, KI, K_2CO_3 , CH_3CN , reflux or Et_3N , CH_2Cl_2 or ZCOOH , DCC, HOBT, CH_2Cl_2 , reflux then HCl, EtOH for 30; (b) Lawesson's reagent, THF, 0°C .

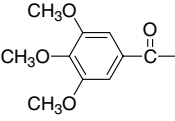
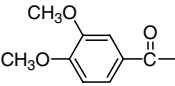
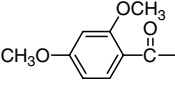
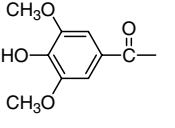
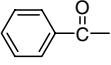
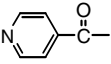
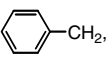
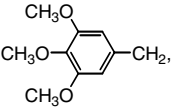


Scheme 4. Reagents and conditions: (a) Ph_3CCl , Et_3N , CH_2Cl_2 , 0°C or $(\text{Ph})_2\text{CHBr}$, KI, K_2CO_3 , CH_3CN , reflux; (b) syringic acid, DCC, HOBT, CH_2Cl_2 , reflux or TMBCl, Et_3N , CH_2Cl_2 then HCl, EtOH (for 33); (c) $\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{Br}$, K_2CO_3 , acetone, reflux; (d) HCl, MeOH, 0°C ; (e) 1-BzlCl, KI, K_2CO_3 , CH_3CN , reflux; 2-HCl, EtOH; (f) Lawesson's reagent, THF, 0°C .

nocarbonyloxymethylpiperazine,¹⁶ presents an anti-PAF activity higher than $100\ \mu\text{M}$. The absence of anti-PAF activity of **29c** can be explained by the orientation of the two hydroxyles on the aromatic rings to enable an intramolecular hydrogen bond with the neighbouring methoxyl as observed during its geometry optimization.

This is associated with a decrease of the electrostatic negative potentials generated by the methoxyle as shown in Figure 3 and suggests that this compound cannot interact properly with the PAF-R as its large 'cache-oreilles' system is not available.^{23,24} Lipophilicity of **29c** ($\log P = 2.21$) seems to be less implicated in the

Table 1. Influence of the substituent on the piperazine ring

$\text{Ar-X-N} \begin{array}{c} \diagup \diagdown \\ \text{CH}_2\text{OCNEt}_2 \\ \text{O} \end{array} \text{N-X-Ar}$						
Compound	Ar-X-	log P^a	Anti-PAF ^b IC ₅₀ (μM)	Anti-HIV-1 ^c IC ₅₀ (μM) or % inhibition	Toxicity ^d (μM)	SI ^e
1a^f		2.88	8	11	>1000	>90
29a		3.04	6.5	42% (10 μM)	>100	>10
29b		2.98	>100	>100	>100	—
29c		2.21	>100	35	>100	>2.85
29d		2.39	>10	43% (100 μM)	>100	>1
29e		0.26	>10	35% (100 μM)	>100	>1
29f^g	 -CH ₂ , HCl	1.98	>100	2	≥100 ^h	≥50
30	 -CH ₂ , HCl	3.02	2.5	75% (10 μM)	>10	>1

^a 1-Octanol/water partition coefficient calculated using ALOGPS2.1 program.^{20–22}^b Inhibition of PAF-induced platelet aggregation using platelet-rich plasma (PRP) of New Zealand rabbits calculated from dose–response curve as described in Section 4 ($n = 5$, mean $\pm 10\%$).^c Antiviral activity determined with HIV-1/Ba-L-infected monocyte-derived macrophages. All experiments were performed in triplicate in cells isolated from one blood donor (mean $\pm 10\%$).^d Cytotoxicity evaluated by neutral red staining on MDM.^e Antiviral selectivity index (toxicity/antiviral IC₅₀).^f See Ref. 12.^g HCl salt of the previously described compound.¹⁴^h Toxic at 100 μM.

variation of this activity as it is close to that of **1a** (log $P = 2.88$). The antiviral potency of this compound remains similar to that of **1a**. The replacement of the carbonyls of **1a** by methylenes in the compound **30** leads to an increase of both activities. When both 3,4,5-trimethoxybenzoyl groups are replaced simultaneously by two benzyls as in **29f**, the antiviral activity is surprisingly increased. Indeed, we saw that the deletion of the methoxyl groups in **29d** does not lead to an increase of the antiviral activity. Nevertheless, this observation should be associated with the presence of the benzoyls in **29d** whereas **29f** bears two benzyls. These compounds are devoid of anti-PAF activity probably because the negative electrostatic wells induced by the two benzyl or benzoyl groups are not sufficient enough to enable

a proper interaction of the compound with the PAF-R.²⁵ The introduction of a nitrogen in the aromatic ring in compound **29e** in order to modify the electronic distribution of the substituent does not improve both activities (Table 2).

2.2.2. Influence of sulfur towards antiviral and anti-PAF activities (Table 2). The transformation of one or both amide functions to thioamide ones leads, in all cases (compounds **18**, **31** and **42**), to an increase of the anti-PAF activity probably through the augmentation of the lipophilicity of the molecules as shown by thin-layer chromatography in MeOH/CH₂Cl₂ (5:95, v/v); $R_{f(1a)} = 0.33$ versus $R_{f(18)} = 0.42$ versus $R_{f(31)} = 0.55$. The position of the thioamide function seems to be

Table 2. Influence of sulfur towards antiviral and anti-PAF activities

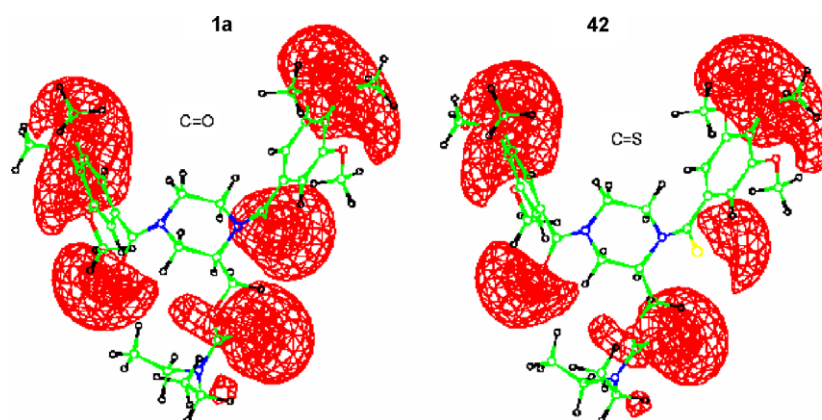
$$\text{Ar}_1\text{---N}\begin{array}{c} \diagup \diagdown \\ \text{CH}_2\text{OCN}(\text{Et})_2 \\ \text{O} \end{array}\text{N---Ar}_2$$

Compound	Ar ₁	Ar ₂	log <i>P</i> ^a	Anti-PAF ^b IC ₅₀ (μM)	Anti-HIV-1 ^c IC ₅₀ (μM) or % inhibition	Toxicity ^d (μM)	SI ^e
1a^f			2.88	8	11	>1000	>90
18			3.28	0.6	41% (10 μM)	>10	>1
31			3.96	0.35	76% (10 μM)	≥100 ^g	>10
42			3.30	0.44	>100	>100	—

^a 1-Octanol/water partition coefficient calculated using ALOGPS2.1 program.^{20–22}^b Inhibition of PAF-induced platelet aggregation using platelet-rich plasma (PRP) of New Zealand rabbits calculated from dose–response curve as described in Section 4 (*n* = 5, mean ± 10%).^c Antiviral activity determined with HIV-1/Ba-L infected monocytes derived macrophages. All experiments were performed in triplicate in cells isolated from one blood donor (mean ± 10%).^d Cytotoxicity evaluated by neutral red staining on MDM.^e Antiviral selectivity index (toxicity/antiviral IC₅₀).^f See Ref. 12.^g Toxic at 100 μM.

important for the anti-HIV-1 activity because no such activity was detected when it is at the N₁-position (**42**), whereas at the N₄-position, the corresponding compound **18** presents an antiviral activity close to that of the leader, **1a**. This difference of antiviral activity could be explained by the electronic effect induced by the presence of the sulfur at the N₁-position: it probably dis-

turbs the electronic environment of the carbamate function, known to be involved in the antiviral activity of the molecule.¹² Nevertheless, the presence of two thioamide functions in the compound **31** confers to it an antiviral activity which is even higher than that of **1a**. Thus, this compound presents a better dual activity than **1a** in spite of its toxicity at 100 μM.

**Figure 2.** 3D electrostatic maps of **1a** and **42** (isocontours drawn at –20 kcal/mol).

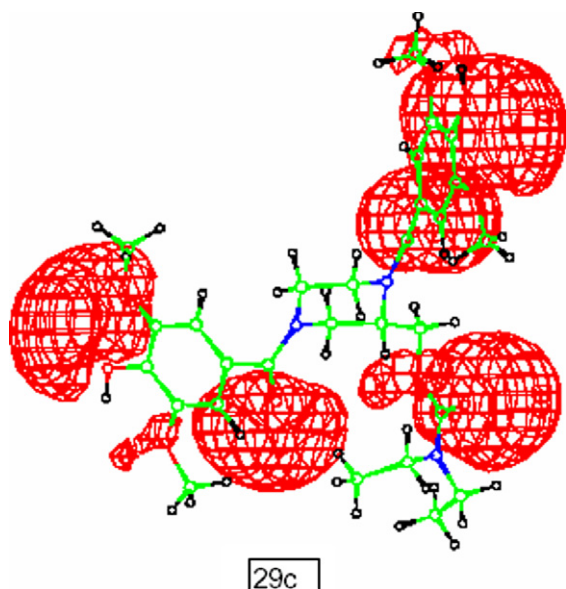


Figure 3. 3D electrostatic map of **29c** (isocontours drawn at -20 kcal/mol).

2.2.3. Molecular modelling. This study was initiated to assess the influence of the introduction of the sulfur atom in the compounds **18**, **31** and **42**. The 3D electrostatic potential maps of **1a** and **42** (isocontoured at -20 kcal/mol, Fig. 2) show that the introduction of a sulfur atom in the amide linkage in **42** does not clearly modify the electronic well observed in **1a**. This observation led us to perform a conformational analysis study of these compounds to determine their energetically accessible space. Their geometries were fully optimized using the double basis set 6-31g.²⁶ The geometry optimization carried out shows that four minima of relative energy can be found for each molecule: two boat and two chair conformations (Table 3).

For each conformer, the cisoid and transoid rotamers can be located.¹⁶ These four conformations are not equal in energy. For all the compounds, the chair conformations are the most stable (ΔE close to 0.0 kcal/mol) but an additional stable boat conformer appears for **18** as its relative energy is 0.639 kcal/mol. We can observe that the carbamate linkage takes place, in each conformer, to enable intramolecular interactions (hydrogen bonds). Moreover, the activation energy between the two chair conformers was calculated and the results are listed in Table 4. These values demonstrate that the interconversion between both conformers is easier for **1a** and **18** than for **31** and **42** and thus, the conformational flexibility of these compounds is different.

This study indicates that each molecule presents a specific conformational profile. Neither the mode of action of

the studied piperazine derivatives nor their biological target is identified in the antiviral assay. Nevertheless, we can assume that the population of the conformers at the active site will differ from one molecule to another, probably contributing to the difference of antiviral activity observed.

2.2.4. Modification of the N₁-substituent (Table 5). The non-substitution of this nitrogen in **7** leads to a total loss of both activities. This result shows that the presence of a substituent on both positions, 1 and 4, of the piperazine ring is essential. The replacement of one trimethoxybenzoyl group (**1a**) with a benzyl one as in **6** does not modify the anti-PAF activity. Indeed, we showed, in a previous work,²⁵ that the decrease of the electrostatic well due to the replacement of one trimethoxybenzoyl group by a benzyl moiety is balanced by its higher lipophilicity. The introduction of a diphenylmethyl moiety, more hydrophobic and sterically hindered, in the compounds **8** and **19** leads to an increase of the anti-PAF potency as expected but this amelioration is associated with an increased toxicity on macrophages and then seems baneful for the anti-HIV-1 activity. Indeed, **19** which presents a sub-micromolar anti-PAF potency is toxic on macrophages at 10 μ M and inactive at 1 μ M. To increase the lipophilic anchorage of the molecule in the PAF-R and thus, the anti-PAF activity, we prepared **27** with a butyl moiety on the aromatic ring. This modification conferred an important anti-PAF potency to the molecule but it is devoid of antiviral activity. Other factors such as the steric hindrance should be investigated to try to explain the variations of antiviral activity.

2.2.5. Modification of the N₄-substituent (Table 6). Compound **16**, as its position analogue **7** (Table 5), is totally inactive. The introduction of a benzyl group in **15** is without effect on the anti HIV-1 activity but leads to a decrease of the anti-PAF one, whereas its isomer **6** (Table 5) presents the same range of activities as **1a**. This suggests that both positions of the piperazine ring are not equivalent. Derivative **33**, which exhibits an anti-PAF activity as good as its analogue **8** (Table 5), could not be tested for its antiviral property because of the absence of a dose–effect relationship during the evaluation. The modification of the lipophilicity of the substituent

Table 4. Calculated activation energy

Compound	ΔE^a (kcal/mol)
1a	10.168
18	11.325
31	17.895
42	19.612

^a Activation energy.

Table 3. Calculated conformational energies and conformations of compounds **1a**, **18**, **31** and **42**

Compound	ΔE (kcal/mol), conformation			
1a	0.0 ($\phi = -26$), chair	0.159 ($\phi = 170$), chair	2.400 ($\phi = 21$), boat	4.959 ($\phi = 188$), boat
18	0.0 ($\phi = 14$), chair	0.639 ($\phi = 171$), boat	0.763 ($\phi = 173$), chair	2.595 ($\phi = 5$), boat
31	0.0 ($\phi = 14$), chair	0.829 ($\phi = 172$), chair	2.335 ($\phi = -19$), boat	2.547 ($\phi = 173$), boat
42	0.0 ($\phi = -30$), chair	1.966 ($\phi = 169$), chair	4.429 ($\phi = 20$), boat	4.823 ($\phi = 172$), boat

Table 5. Modification of the N₁-substituent

Compound	Z	log <i>P</i> ^a	Anti-PAF ^b IC ₅₀ (μM)	Anti-HIV-1 ^c IC ₅₀ (μM)	Toxicity ^d (μM)	SI ^e
1a^f		2.88	8	11	>1000	> 90
6		3.39	6	40	>100	> 2.5
7	–H, HCl	1.38	>100	>100	>100	—
8		3.66	0.75	3	≥ 100 ^g	≥ 33.3
19		4.57	0.25	ND ^h	≥ 10 ^h	—
27		3.96	0.001	>100	> 100	—

^a 1-Octanol/water partition coefficient calculated using ALOGPS2.1 program.^{20–22}^b Inhibition of PAF-induced platelet aggregation using platelet-rich plasma (PRP) of New Zealand rabbits calculated from dose response curve as described in Section 4 (*n* = 5, mean ± 10%).^c Antiviral activity determined with HIV-1/Ba-L infected monocytes derived macrophages. All experiments were performed in triplicate in cells isolated from one blood donor (mean ± 10%).^d Cytotoxicity evaluated by neutral red staining on MDM.^e Antiviral selectivity index (toxicity/antiviral IC₅₀).^f See Ref. 12.^g Toxic at 100 μM.^h Not determined as toxic at 10 μM and inactive at 1 μM.

and/or the introduction of an heterocyclic moiety able to generate an electrostatic potential well as in the compounds **20**, **21**, **22** and **25** modifies the anti-PAF activity without leading to an increase of the antiviral activity, suggesting that other factors than these are involved in this pharmacological activity.

2.2.6. Modification of the N₁- and N₄-substituents (Table 7). The compounds **15** (Table 6) and **29f** (Table 1) present an anti-HIV-1 activity equivalent to or higher than that of **1a** and are devoid of PAF-antagonism, whereas **27** (Table 5) presents the best anti-PAF activity of the series without any antiviral potency. To take advantage of these observations, we synthesized **38** which presents a benzyl at the N₄ position of the piperazine and a butyl moiety on the aromatic ring. The results show that the antiviral activity is not maintained with this structure, which inhibits only 40% of the viral replication at 5 μM and is toxic at 20 μM. The lack of anti-PAF activ-

ity of this molecule, and of compounds **15** and **29f**, seems to be linked to the presence of a benzyl group at the N₄-position of piperazine. We can note that in this case, the high lipophilicity of the molecule is not sufficient to confer to it a notable anti-PAF activity.

3. Conclusion

In summary, we have ameliorated the anti-PAF potency of our reference **1a** by modifying the substituents of the piperazine nitrogens. We can note that here again, both activities do not seem to be correlated as pure antiviral compounds with micromolar efficacy (**15** and **29f**) were obtained. We noticed that the parameters controlling the anti-PAF activity (i.e., hydrophobicity and ‘cache-oreilles’ effect) previously described do not seem to be clearly implicated in the variation of the antiviral activity in this set of compounds.

Table 6. Modification of the N₄-substituent

Compound	Y	log <i>P</i> ^a	Anti-PAF ^b IC ₅₀ (μM)	Anti-HIV-1 ^c IC ₅₀ μM or % inhibition	Toxicity ^d μM	SI ^e
1a^f		2.88	8	11	>1000	>90
15		3.39	>100	13	>100	>7.69
16	–H, HCl	1.38	>100	>100	>100	—
20		2.93	44% (10 μM)	66% (100 μM)	>100	>1
21		4.06	1.25	27% (10 μM)	≥100 ^g	≥10
22		4.29	3.1	44% (10 μM)	≥100 ^g	≥10
25		1.58	>10	13% (100 μM)	>100	<1
33		3.66	0.6	ND ^h	ND ^h	—

^a 1-Octanol/water partition coefficient calculated using ALOGPS2.1 program.^{20–22}^b Inhibition of PAF-induced platelet aggregation using platelet-rich plasma (PRP) of New Zealand rabbits calculated from dose–response curve as described in Section 4 (*n* = 5, mean ± 10%).^c Antiviral activity determined with HIV-1/Ba-L infected monocytes derived macrophages. All experiments were performed in triplicate in cells isolated from one blood donor (mean ± 10%).^d Cytotoxicity evaluated by neutral red staining on MDM.^e Antiviral selectivity index (toxicity/antiviral IC₅₀).^f See Ref. 12.^g Toxic at 100 μM.^h Not determined.

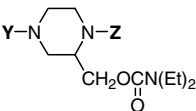
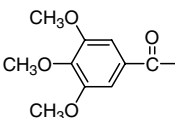
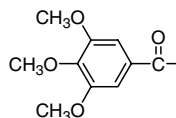
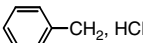
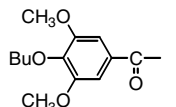
Otherwise, compound **1a** does not inhibit either the main targets of the highly active antiretroviral therapy (i.e., the reverse transcriptase, the viral protease and the entry of the virus in the cell) or the viral integrase.^{12,13} Additional studies are under consideration to clarify the mode of action of this compound. Indeed, the isolation and characterization of its biological target would enable us to ameliorate our structure-activity relationship.

4. Experimental

4.1. General

All materials were obtained from commercial suppliers (e.g., Acros, Aldrich, Fluka, Paris, France) and used without further purification. Thin-layer chromatography was performed on TLC plastic sheets of silica gel 60F₂₅₄ (layer thickness 0.2 mm) from Merck. Column

Table 7. Modification of the piperazine substituents

							
Compound	Y	Z	log <i>P</i> ^a	Anti-PAF ^b IC ₅₀ μM	Anti-HIV-1 ^c IC ₅₀ μM or % inhibition	Toxicity ^d μM	SI ^e
1a^f			2.88	8	11	>1000	>90
38	 ·HCl		3.95	>100	40% (5 μM)	≥20 ^g	< 5

^a 1-Octanol/water partition coefficient calculated using ALOGPS2.1 program.^{20–22}^b Inhibition of PAF-induced platelet aggregation using platelet-rich plasma (PRP) of New Zealand rabbits calculated from dose–response curve as described in Section 4 (*n* = 5, mean ± 10%).^c Antiviral activity determined with HIV-1/Ba-L infected monocytes derived macrophages. All experiments were performed in triplicate in cells isolated from one blood donor (mean ± 10%).^d Cytotoxicity evaluated by neutral red staining on MDM.^e Antiviral selectivity index (toxicity/antiviral IC₅₀).^f See Ref. 12.^g Toxic at 20 μM.

chromatography purification was carried out on silica gel 60 (70–230 mesh ASTM, Merck). All melting points were determined on a digital melting point apparatus (Electrothermal) and are uncorrected. The structures of all compounds were confirmed by IR and ¹H and ¹³C NMR spectra. IR spectra were obtained in paraffin oil with a ATI Mattson Genesis Series FTIR spectrometer, and ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ or in DMSO-*d*₆ on a BRUCKER AC 200 spectrometer using hexamethyldisiloxane (HMDS) as an internal standard. Chemical shifts are given in ppm and peak multiplicities are designated as follows: br s, broad singlet; s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; qt, quintuplet; sex, sextuplet. Elemental analyses were obtained from the ‘Service régional de microanalyse’ (Université Paris 6—Pierre et Marie Curie), Paris, France, and were within ±0.4% of theoretical values.

4.2. Chemistry

4.2.1. 3-Ethoxycarbonyl-1-(3,4,5-trimethoxybenzoyl)piperazine (2). To a cooled (ice bath) solution of **1**¹⁵ (20 g, 86 mmol) and Et₃N (42 mL, 301 mmol) in CH₂Cl₂ (400 mL) was added dropwise a solution of 3,4,5-trimethoxybenzoyl chloride (19.83 g, 86 mmol) in CH₂Cl₂ (200 mL). After the disappearance of the initial amine, as shown by TLC, the solution was washed with saturated NaHCO₃ solution and water until neutral pH. After drying (MgSO₄), filtration and evaporation, the residue was chromatographed on a silica gel column using MeOH/CH₂Cl₂ (1:99, v/v) as eluent to give the title compound (16.15 g, 53%) as a wax; *R*_f: 0.24 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 3333 (NH), 1736 (C=O ester), 1630 (C=O amide), 1584 (ArC=C); ¹H

NMR δ 6.59 (s, 2H, ArH), 4.16 (q, 2H, *J* = 7.05 Hz, CH₂O), 3.81 (s, 9H, CH₃O), 3.68–3.10 (m, 5H, piperazine), 3.04 (m, 1H, piperazine), 2.75 (m, 1H, piperazine), 2.28 (s, 1H, NH), 1.20 (t, 3H, *J* = 7.07 Hz, CH₃).

4.2.2. 1-Benzyl-2-ethoxycarbonyl-4-(3,4,5-trimethoxybenzoyl)piperazine (3). A mixture of **2** (18 g, 51 mmol), benzyl chloride (7.74 g, 61 mmol), K₂CO₃ (10 g, 72.46 mmol) and KI (cat.) in CH₃CN (200 mL) was refluxed for 3 h. After filtration of the salts and evaporation of the filtrate, the residue was taken in CH₂Cl₂, washed several times with water, dried (MgSO₄), filtered and evaporated. A purification on a silica gel column using CH₂Cl₂ as eluent yielded **3** (21.84 g, 97%) as a wax; *R*_f: 0.65 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 1727 (C=O ester), 1630 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.22 (m, 5H, ArH), 6.58 (s, H, ArH), 6.56 (s, H, ArH), 4.11 (m, 3H, CH₂O, piperazine), 3.83 (m, 1H, CH–Ph), 3.78 (s, 9H, CH₃O), 3.58 (m, 3H, CH–Ph, piperazine), 3.30 (m, 2H, piperazine), 3.09 (m, 1H, piperazine), 2.37 (m, 1H, piperazine), 1.19 (m, 3H, CH₃).

4.2.3. 1-Benzyl-2-hydroxymethyl-4-(3,4,5-trimethoxybenzoyl)piperazine (4). The same procedure as described in Tavet et al.²⁸ was used to prepare the compound **4**. Reduction of the ester **3** (21.8 g, 27.4 mmol) yielded, after a purification on a silica gel column using MeOH/CH₂Cl₂ (1:99, v/v) as eluent, **4** (4.31 g, 28%) as a wax; *R*_f: 0.28 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 3400 (OH), 1618 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.26 (m, 5H, ArH), 6.56 (s, 2H, ArH), 4.04 (d, 2H, *J* = 13.19 Hz, CH–Ph), 3.82 (m, 3H, piperazine), 3.78 (s, 9H, CH₃O), 3.73–3.36 (m, 5H, CH₂OH, piperazine), 3.50 (d, 2H, *J* = 13.34 Hz, CH–Ph), 2.77 (m, 2H, piperazine), 2.35 (m, 1H, piperazine).

4.2.4. 1-Benzyl-2-phenyloxycarbonyloxymethyl-4-(3,4,5-trimethoxybenzoyl)piperazine (5). Following the procedure described in Serradji et al.¹² but replacing Et₃N by pyridine, the compound **5** (4 g, 77%) was prepared from the alcohol **4** (4.31 g, 10 mmol) and phenyl chloroformate (3 g, 18 mmol) and obtained as a wax; *R*_f: 0.66 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 1761 (C=O carbonate), 1631 (C=O amide), 1584 (ArC=C); ¹H NMR (60 MHz) δ 7.33 (m, 10H, ArH), 6.66 (s, 2H, ArH), 4.43 (m, 3H, CH₂O, CH-Ph), 4.10 (m, 1H, piperazine), 3.81 (s, 9H, CH₃O), 3.70–3.26 (m, 4H, CH-Ph, piperazine), 3.16–1.90 (m, 3H, piperazine).

4.2.5. 1-Benzyl-2-*N,N*-diethylaminocarbonyloxymethyl-4-(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (6). The procedure described in Lamouri et al.¹⁶ led to 3.3 g (88%) of the title compound after a chloridration using bubbled HCl in EtOH and a crystallization in acetone/ether: *R*_f: 0.20 (MeOH/CH₂Cl₂, 5:95, v/v); mp 134 °C; IR (ν cm⁻¹) 3451 (NH⁺), 1720 (C=O carbamate), 1657 (C=O amide), 1584 (ArC=C); ¹H NMR δ 13.38 (br s, 1H, NH⁺), 7.58 (m, 2H, ArH), 7.39 (s, 3H, ArH), 6.55 (s, 2H, ArH), 5.15–3.85 (m, 7H, CH₂O, CH₂-Ph, piperazine), 3.78 (s, 9H, CH₃O), 3.55–2.10 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.05 (m, 6H, CH₃); ¹³C NMR δ 169.96 (C=O amide), 154.42 (C=O carbamate), 153.27, 139.62, 131.34, 130.20, 129.36, 128.73, 127.39, 104.27 (ArC=C), 61.09 (CH₂O), 60.71, 56.11 (CH₃O), 57.64 (CH piperazine), 42.07, 41.28 (N(CH₂CH₃)₂), 13.85, 13.13 (CH₃). Anal. (C₂₇H₃₈N₃ClO₆·0.75H₂O) C, H, N.

4.2.6. 3-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (7). The catalytic hydrogenation of **6** (2.3 g, mmol), as described in Serradji et al.,¹² led to **7** (460 mg, 24%) as crystals; *R*_f: 0.44 (MeOH/CH₂Cl₂, 10:90, v/v); mp 199.3 °C; IR (ν cm⁻¹) 3404 (NH⁺), 1703 (C=O carbamate), 1644 (C=O amide), 1585 (ArC=C); ¹H NMR δ 10.21 (br s, 2H, NH₂⁺), 6.55 (s, 2H, ArH), 5.20–4.00 (m, 4H, CH₂O, piperazine), 3.80 (s, 9H, CH₃O), 3.49 (m, 3H, piperazine), 3.16 (m, 4H, N(CH₂CH₃)₂), 2.55 (m, 2H, piperazine), 1.02 (m, 6H, CH₃); ¹³C NMR δ 170.41 (C=O amide), 154.66 (C=O carbamate), 153.45, 139.73, 129.02, 104.24 (ArC=C), 61.56 (CH₂O), 60.83, 56.28 (CH₃O), 54.41, 43.32 (piperazine), 42.18, 41.47 (N(CH₂CH₃)₂), 13.96, 13.25 (CH₃). Anal. (C₂₀H₃₂N₃ClO₆) C, H, N.

4.2.7. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-diphenylmethyl-4-(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (8). A mixture of **7** (free base, 300 mg, 0.67 mmole), diphenylmethyl bromide (320 mg, 1.34 mmol), K₂CO₃ (560 mg, 4 mmol) and KI (60 mg, 0.33 mmole) in CH₃CN (9.5 mL) was refluxed for 60 h. The salts were filtered, washed with CH₃CN and the filtrate concentrated in vacuum. The residue was taken in CH₂Cl₂, washed with a saturated NaHCO₃ solution and water, dried (MgSO₄), filtered and evaporated to provide a wax which was dissolved in EtOH and treated with HCl. A recrystallization from EtOH/Et₂O gave **8** (90 mg, 22%) as crystals; *R*_f: 0.57 (MeOH/CH₂Cl₂, 5:95, v/v); mp 189.5 °C; IR (ν cm⁻¹) 3349 (NH⁺), 1694 (C=O carba-

mate), 1623 (C=O amide), 1580 (ArC=C); ¹H NMR δ 13.48 (br s, 1H, NH⁺), 8.00 (d, 2H, *J* = 6.28 Hz, ArH), 7.88 (d, 2H, *J* = 5.90 Hz, ArH), 7.30 (m, 6H, ArH), 6.55 (s, 2H, ArH), 5.06 (s, 1H, CH-Ph), 4.61–3.86 (m, 5H, CH₂O, piperazine), 3.76 (s, 9H, CH₃O), 3.21–2.67 (m, 8H, CH₂CH₃, piperazine), 1.02–0.67 (m, 6H, CH₃). Anal. (C₃₃H₄₂N₃ClO₆) C, H, N.

4.2.8. 3-Ethoxycarbonyl-1-triphenylmethylpiperazine (9). Compound **9** was prepared as described for **34** but from **1**; ¹⁵ *R*_f: 0.21 (Et₂O); IR (ν cm⁻¹) 3349 (NH), 3059 (ArCH), 1723 (C=O ester), 1595 (ArC=C); ¹H NMR δ 7.39 (m, 6H, ArH), 7.11 (m, 9H, ArH), 4.05 (m, 2H, CH₂O), 3.85–2.00 (m, 7H, piperazine), 1.86 (s, 1H, NH), 1.17 (m, 3H, CH₃); ¹³C NMR δ 129.24, 127.42, 126.00 (ArC=C), 76.99 (CPh₃), 60.77 (CH₂O), 48.61 (piperazine), 14.08 (CH₃).

4.2.9. 2-Ethoxycarbonyl-1-(3,4,5-trimethoxybenzoyl)-4-triphenylmethylpiperazine (10). Compound **10** was prepared from **9** as described for **2** but at room temperature; *R*_f: 0.38 (Et₂O); mp 208.7 °C; IR (ν cm⁻¹) 1738 (C=O ester), 1634 (C=O amide), 1586 (ArC=C); ¹H NMR δ 7.34 (m, 6H, ArH), 7.17 (m, 9H, ArH), 6.53 (s, 2H, ArH), 4.52 (m, 1H, CHOCO), 4.25 (m, 1H, CHOCO), 3.88–3.62 (m, 13H, CH₃O, piperazine), 3.46 (m, 1H, piperazine), 3.00 (m, 2H, piperazine), 1.35 (m, 3H, CH₃); ¹³C NMR δ 171.11 (C=O), 170.93 (C=O), 153.27, 153.14, 139.00, 130.71, 129.20, 127.54, 126.35, 104.11 (ArC=C), 76.88 (CPh₃), 61.47 (CH₂O), 60.77, 56.14 (CH₃O), 52.80, 48.75, 48.36, 46.13 (piperazine), 14.16 (CH₃).

4.2.10. 2-Ethoxycarbonyl-1-(3,4,5-trimethoxybenzoyl)piperazine (11). Compound **11** was prepared as described for **40** but from **10** (10.8 g, 75%); *R*_f: 0.20 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 3559 (NH), 1738 (C=O ester), 1637 (C=O amide), 1584 (ArC=C); ¹H NMR δ 6.58 (s, 2H, ArH), 4.41 (q, 2H, *J* = 7.00 Hz, CH₂O), 3.79 (s, 9H, CH₃O), 3.65–2.55 (m, 7H, piperazine), 2.27 (s, 1H, NH), 1.18 (t, 3H, *J* = 7.09 Hz, CH₃).

4.2.11. 4-Benzyl-2-ethoxycarbonyl-1-(3,4,5-trimethoxybenzoyl)piperazine (12). This compound (9.5 g, 83%) was prepared as described for the compound **3**; *R*_f: 0.61 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 1742 (C=O ester), 1641 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.21 (m, 5H, ArH), 6.61 (s, 2H, ArH), 4.70–3.00 (m, 11H, piperazine, CH₂-Ph, CH₂O), 3.78 (s, 9H, CH₃O), 1.18 (m, 3H, CH₃).

4.2.12. 4-Benzyl-2-hydroxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine (13). This compound (1.44 g, 17%) was prepared following the same procedure as described in Tavet et al.²⁸ *R*_f: 0.24 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 3378 (OH), 1628 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.23 (m, 5H, ArH), 6.57 (s, 2H, ArH), 4.69–3.98 (m, 4H, piperazine, OH), 3.77 (s, 9H, CH₃O), 3.67 (br s, 2H, CH₂OH), 3.43 (s, 2H, CH₂-Ph), 2.86 (m, 2H, piperazine), 2.17 (m, 2H, piperazine); ¹³C NMR δ 171.11 (C=O), 153.32, 138.90, 136.92, 131.06, 128.74, 128.37, 127.39, 104.11 (ArC=C), 62.66 (CH₂-Ph), 60.72, 56.09 (CH₃O), 54.52 (CH₂OH), 52.72 (CH₂ piperazine).

4.2.13. 4-Benzyl-2-phenoxycarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine (14). This compound (1.8 g, 99%) was prepared following the same procedure as described in Serradji et al.¹² R_f : 0.71 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 1757 (C=O carbonate), 1650 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.49–7.00 (m, 10H, ArH), 6.59 (s, 2H, ArH), 5.26 (m, 2H, CH₂O), 4.80–3.80 (m, 4H, CH-Ph, piperazine), 3.79 (s, 3H, CH₃O), 3.69 (s, 6H, CH₃O), 3.60–2.15 (m, 5H, CH-Ph, piperazine).

4.2.14. 4-Benzyl-2-*N,N*-diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (15). This compound (1.41 g, 93%) was prepared as described for the compound **6**; R_f : 0.20 (MeOH/CH₂Cl₂, 5:95, v/v); mp 180.6 °C; IR (ν cm⁻¹) 3451 (NH⁺), 1720 (C=O carbamate), 1657 (C=O amide), 1584 (ArC=C); ¹H NMR δ 12.53 (br s, 1H, NH⁺), 7.61 (s, 2H, ArH), 7.36 (s, 3H, ArH), 6.62 (s, 2H, ArH), 5.06 (br s, 2H, piperazine), 4.39 (br s, 2H, piperazine), 4.13 (br s, 2H, CH₂O), 3.77 (s, 9H, CH₃O), 3.53–2.69 (m, 9H, CH₂-Ph, N(CH₂CH₃)₂, piperazine), 1.1 (m, 6H, CH₃). Anal. (C₂₇H₃₈N₃O₆·2H₂O) C, H, N.

4.2.15. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (16). This compound (1.2 g, 85%) was prepared as described for **7**; R_f : 0.22 (MeOH/CH₂Cl₂, 5:95, v/v); mp 194.9 °C; IR (ν cm⁻¹) 3423 (NH₂⁺), 1690 (C=O carbamate), 1640 (C=O amide), 1585 (ArC=C); ¹H NMR δ 9.75 (br s, 2H, NH₂⁺), 6.58 (s, 2H, ArH), 5.35–3.90 (m, 5H, CH₂O, piperazine), 3.80 (s, 9H, CH₃O), 3.70–2.70 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.00 (t, J = 6.66 Hz, 6H, CH₃); ¹³C NMR δ 170.46 (C=O amide), 155.35 (C=O carbamate), 153.40, 139.75, 129.27, 104.40 (ArC=C), 61.43 (CH₂O), 60.83, 56.27 (CH₃O), 43.42, 42.78, 41.92, 41.32 (NCH₂CH₃ carbamate, piperazine), 13.99, 13.34 (NCH₂CH₃). Anal. (C₂₀H₃₂N₃O₆·0.5H₂O) C, H, N.

4.2.16. 3-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxythiobenzoyl)piperazine (17). The same procedure as for the preparation of the compound **41** was followed to give 1.1 g (62.4%) of the compound **17**; R_f : 0.18 (MeOH/CH₂Cl₂, 5:95, v/v).

4.2.17. 3-*N,N*-Diethylaminocarbonyloxymethyl-4-(3,4,5-trimethoxybenzoyl)-1-(3,4,5-trimethoxythiobenzoyl)piperazine (18). The same procedure as described for **2** but at room temperature was followed to lead to **18** (150 mg, 41%); R_f : 0.42 (MeOH/CH₂Cl₂, 5:95, v/v); mp 100.9 °C; IR (ν cm⁻¹) 1691 (C=O carbamate), 1631 (C=O amide), 1584 (ArC=C); ¹H NMR δ 6.58 (s, 2H, ArH), 6.45 (m, 2H, ArH), 5.30–4.70 (m, 2H, piperazine), 4.50–4.00 (m, 3H, CH₂O, piperazine), 3.80 and 3.77 (2s, 18H, CH₃O), 3.60–2.60 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.03 (m, 6H, CH₃); ¹³C NMR δ 202.23 (C=S), 170.54 (C=O amide), 155.00 (C=O carbamate), 153.24, 139.55, 138.43, 137.53, 129.83, 129.62, 104.31 (ArC=C), 61.15 (CH₂O), 60.70, 60.65, 56.12 (CH₃O), 51.65, 49.30, 48.77 (piperazine), 41.75, 41.00 (NCH₂CH₃), 13.93, 13.26 (NCH₂CH₃). Anal. (C₃₀H₄₁N₃O₉S) C, H, N.

4.2.18. 3-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)-4-(methoxycarbonyldiphenylmethyl)piperazine (19). Compound **19** was prepared following the same process as for the compound **3**, but from methyl 2-bromo-2,2-diphenylacetate and **7**. A recrystallization from CH₂Cl₂/hexane yielded 400 mg (14%) of the title compound; R_f : 0.1 (MeOH/CH₂Cl₂, 2:98, v/v); mp 149.9 °C; IR (ν cm⁻¹) 1729 (C=O ester), 1694 (C=O carbamate), 1633 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.38 (m, 4H, ArH), 7.23 (m, 6H, ArH), 6.51 (s, 2H, ArH), 3.96 (m, 3H, CH₂OC=O, piperazine), 3.76 and 3.74 (2s, 9H, CH₃O), 3.72 (s, 3H, CH₃OC=O), 3.65–2.30 (m, 10H, N(CH₂CH₃)₂, piperazine), 0.97 (m, 6H, CH₃); ¹³C NMR δ 172.89 (C=O ester), 170.75 (C=O amide), 153.07, 140.20, 139.93, 131.05, 128.86, 128.59, 128.05, 127.95, 127.53, 127.39, 104.23 (ArC=C), 78.64 (CH₂ ester), 61.47 (CH₂O), 60.68, 56.12 (CH₃O), 53.25 (CH₃ ester), 52.27 (CH piperazine), 42.90, 41.43 (NCH₂CH₃), 13.50 (NCH₂CH₃). Anal. (C₃₅H₄₃N₃O₈·0.75H₂O) C, H, N.

4.2.19. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-(4-hydroxy-3,5-dimethoxybenzoyl)-1-(3,4,5-trimethoxybenzoyl)piperazine (20). A mixture of **16** (free base, 3 g, 7.33 mmol), syringic acid (1.5 g, 8.06 mmol), *N,N'*-dicyclohexylcarbodiimide (1.55 g, 8.06 mmol) and 1-hydroxybenzotriazole (1.2 g, 8.06 mmol) in CH₂Cl₂ was refluxed overnight. The mixture was then filtered and the filtrate washed with saturated NaHCO₃ solution and water, dried (MgSO₄), filtered and the solvent eliminated. The residue was chromatographed through a silica gel column using MeOH/CH₂Cl₂ (1:99, v/v) as eluent and recrystallized from MeOH/Et₂O. The titled compound was obtained (3.67 g, 84.5%) as white crystals; R_f : 0.21 (MeOH/CH₂Cl₂, 5:95, v/v); mp 129.3 °C; IR (ν cm⁻¹) 3373 (OH), 1686 (C=O carbamate), 1617 (C=O amide), 1586 (ArC=C); ¹H NMR δ 6.61 (s, 2H, ArH), 6.57 (s, 2H, ArH), 5.69 (s, 1H, OH), 5.30–3.90 (m, 5H, CH₂OC=O, piperazine), 3.80 (s, 15H, CH₃O), 3.60–2.40 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.01 (m, 6H, CH₃); ¹³C NMR δ 171.06, 170.62 (C=O amide), 155.05 (C=O carbamate), 153.26, 146.91, 139.46, 136.58, 130.21, 125.35, 104.42, 104.25 (ArC=C), 60.89 (CH₂O), 60.76, 56.38, 56.15 (CH₃O), 41.72, 41.01 (NCH₂CH₃), 13.80, 13.29 (NCH₂CH₃). Anal. (C₂₉H₃₉N₃O₁₀·1.5H₂O) C, H, N.

4.2.20. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-(phenyl(pyridin-4-yl)methyl)-1-(3,4,5-trimethoxybenzoyl)piperazine (21). The same procedure as for the preparation of compound **3** was used to prepare the compound **21** (890 mg, 53%) as white crystals from 4-[chloro(phenyl)methyl]pyridine and **16**; R_f : 0.44 (MeOH/CH₂Cl₂, 5:95, v/v); mp 79.1 °C; IR (ν cm⁻¹) 1692 (C=O carbamate), 1662 (C=O amide), 1583 and 1505 (ArC=C); ¹H NMR δ 8.40 (s, 1H, ArH), 7.54 (s, 2H, ArH), 7.39 (m, 2H, ArH), 7.12 (m, 4H, ArH), 6.54 (s, 2H, ArH), 5.20–3.85 (m, 4H, CH₂O, Pyr-CH-Ph, piperazine), 3.78 and 3.75 (2s, 9H, CH₃O), 3.75–2.50 (m, 8H, N(CH₂CH₃)₂, piperazine), 2.25–1.90 (m, 2H, piperazine), 1.06 (m, 3H, CH₃), 0.91 (m, 3H, CH₃); ¹³C NMR δ 170.27 (C=O amide), 161.69, 161.52, 153.16, 149.10, 140.43, 140.28, 139.10, 136.85, 131.02, 128.73, 128.02, 127.87, 127.54,

122.24, 121.73, 121.41, 104.27 (ArC=C and pyridine), 77.50 (CH-Pyr), 62.38 (CH₂O), 60.78, 56.14 (CH₃O), 51.85, 41.78, 41.21 (CH₂), 16.25, 13.97, 13.48 (CH₃). Anal. (C₃₂H₃₉N₄O₆·0.5H₂O) C, H, N.

4.2.21. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-(cyanodiphenylmethyl)-1-(3,4,5-trimethoxybenzoyl)piperazine (22). The same procedure as for the preparation of the compound **3**, but starting from α -bromo- α -phenyl-benzeneacetonitrile and **16** (free base), was used to prepare the compound **22** (100 mg, 4.5%) as white crystals; *R*_f: 0.37 (MeOH/CH₂Cl₂, 3:97, v/v); mp 176.4 °C; IR (ν cm⁻¹) 1701 (C=O carbamate), 1627 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.57 (m, 4H, ArH), 7.20 (m, 6H, ArH), 6.54 (s, 2H, ArH), 5.18–3.98 (m, 3H, CH₂O, piperazine), 3.77 and 3.73 (2s, 9H, CH₃O), 3.70–1.93 (m, 10H, N(CH₂CH₃)₂, piperazine), 1.33–0.78 (m, 6H, CH₃); ¹³C NMR δ 170.15 (C=O amide), 155.36 (C=O carbamate), 153.09, 139.07, 138.52, 138.39, 130.52, 129.49, 129.00, 128.46, 125.75 (ArC=C), 115.89 (CN), 104.11 (ArC=C), 75.39 (C–CN), 61.91 (CH₂O), 60.61, 56.03 (CH₃O), 49.10, 48.82, 41.69, 41.03 (CH₂), 13.80, 13.32 (NCH₂CH₃). Anal. (C₃₄H₄₀N₄O₆) C, H, N.

4.2.22. 4-Cyanomethyl-2-*N,N*-diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine (23). A mixture of **16** (free base, 3 g, 7.4 mmol), chloroacetonitrile (950 mg, 12.58 mmol), K₂CO₃ (6.2 g, 44.4 mmol) and KI (cat.) in CH₃CN (50 mL) was refluxed overnight. After filtration of the salts, the solvent was removed in vacuum. The residue was then taken in CH₂Cl₂, washed with saturated NaHCO₃ solution (2× 50 mL) and water. The organic layer was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The product was then recrystallized from MeOH/Et₂O to give **23** (1.8 g, 55%) as white crystals; *R*_f: 0.44 (MeOH/CH₂Cl₂, 5:95, v/v); mp 160.8 °C; IR (ν cm⁻¹) 2228 (CN), 1690 (C=O carbamate), 1624 (C=O amide), 1583 (ArC=C); ¹H NMR δ 6.56 (s, 2H, ArH), 5.40–4.20 (m, 2H, CHOC=O, piperazine), 4.18 (dd, 1H, *J* = 6.70 and 10.44 Hz, CHOC=O), 3.80 and 3.78 (2s, 9H, CH₃O), 3.70–3.35 (m, 2H, piperazine), 3.48 (s, 2H, CH₂CN), 3.19 (m, 4H, N(CH₂CH₃)₂), 2.90–2.45 (m, 3H, piperazine), 2.34 (m, 1H, piperazine), 1.03 (t, 6H, *J* = 7.05 Hz, CH₃); ¹³C NMR δ 170.36 (C=O amide), 155.29 (C=O carbamate), 153.18, 139.21, 130.51, 104.22 (ArC=C), 113.86 (CN), 62.06 (CH₂O), 60.71, 56.11 (CH₃O), 51.83, 51.51, 45.95, 41.73, 41.14 (NCH₂CH₃, piperazine), 13.95, 13.36 (NCH₂CH₃).

4.2.23. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-*N*-hydroxyamidinomethyl-1-(3,4,5-trimethoxybenzoyl)piperazine (24). A mixture of **23** (1.75 g, 3.90 mmol), hydroxylamine, hydrochloride (1.35 g, 19.5 mmol) and K₂CO₃ (2.7 g, 19.5 mmol) in absolute EtOH (50 mL) was refluxed for 7 h. After the filtration of the salts and the evaporation of the solvent, the residue was purified by silica gel column chromatography using MeOH/CH₂Cl₂ (3:97, v/v) as eluent to yield **24** (1.4 g, 74.6%) as a wax; *R*_f: 0.14 (MeOH/CH₂Cl₂, 5:95, v/v); IR (ν cm⁻¹) 3474 (OH), 3360 and 3182 (NH₂), 1699 (C=O carbamate), 1667 (C=N), 1627 (C=O amide), 1583 (ArC=C); ¹H NMR δ 6.54 (s, 2H, ArH), 4.93 (s, 2H, NH₂), 4.70–

3.93 (m, 4H, CH₂OC=O, N–OH, piperazine), 3.79 (s, 9H, CH₃O), 3.64–2.40 (m, 10H, N(CH₂CH₃)₂, CH₂–C=N, piperazine), 2.12 (m, 2H, piperazine), 1.05 (t, 6H, *J* = 6.35 Hz, CH₃); ¹³C NMR δ 170.45 (C=O amide), 155.52 (C=O carbamate), 153.16 (C=N–OH), 151.05, 139.20, 130.67, 104.28 (ArC=C), 61.85 (CH₂O), 60.74 (CH₃O), 57.40 (CH₂-amidoxime), 56.12 (CH₃O), 52.75, 41.78, 41.20 (NCH₂CH₃, piperazine), 13.97, 13.36 (NCH₂CH₃).

4.2.24. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-(4,5-dihydro-5-oxo-1,2,4-4*H*-oxadiazol-3-ylmethyl)-1-(3,4,5-trimethoxybenzoyl)piperazine (25). Phenyl chloroformate (440 μ L, 3.49 mmol) was added dropwise to a solution of **24** (1.4 g, 2.91 mmol) and pyridine (300 μ L, 3.49 mmol) in dry benzene. The solution was refluxed for 3 h and was then concentrated in vacuum. The residue was taken in CH₂Cl₂, washed with water, dried (MgSO₄), filtered and the solvent removed. A purification through a silica gel column using MeOH/CH₂Cl₂ (1:99, v/v) as eluent and a recrystallization from MeOH/Et₂O/hexane yielded **25** (500 mg, 34%) as white crystals; *R*_f: 0.27 (MeOH/CH₂Cl₂, 5:95, v/v); mp 173.4 °C; IR (ν cm⁻¹) 1779 (C=O oxadiazolone), 1673 (C=O carbamate), 1631 (C=O amide), 1584 (ArC=C); ¹H NMR δ 10.60 (br s, 1H, NH), 6.56 (s, 2H, ArH), 4.91 (br s, 2H, CH₂-cycle), 3.95 (m, 2H, CH₂OC=O), 3.79 (s, 9H, CH₃O), 3.66–3.00 (m, 7H, N(CH₂CH₃)₂, piperazine), 2.76 (m, 2H, piperazine), 2.37 (m, 2H, piperazine), 1.04 (t, 6H, *J* = 6.51 Hz, CH₃); ¹³C NMR δ 170.59 (C=O amide), 159.62 (C=O cycle), 157.28 (C=N), 155.85 (C=O carbamate), 153.36, 139.37, 130.43, 104.20 (ArC=C), 61.19 (CH₂O), 60.84, 56.24 (CH₃O), 52.47, 51.63, 42.10, 41.36 (NCH₂CH₃), 13.98, 13.36 (NCH₂CH₃). Anal. (C₂₃H₃₃N₅O₈) C, H, N.

4.2.25. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(4-hydroxy-3,5-dimethoxybenzoyl)-4-(3, 4,5-trimethoxybenzoyl)piperazine (26). A mixture of **7** (free base, 0.5 g, 1.22 mmol), syringic acid (242 mg, 1.22 mmol), DCC (252 mg, 1.22 mmol) and HOBT (198 mg, 4.68 mmol) was refluxed in CH₂Cl₂ (15 mL) for 24 h. The mixture was then filtered, washed twice with saturated NaHCO₃ solution and water, dried, filtered and evaporated under reduced pressure. A chromatography on a silica gel column using MeOH/CH₂Cl₂ (2:98, v/v) and a recrystallization from MeOH/Et₂O gave **26** (0.5 g, 70%) as white crystals; *R*_f: 0.37 (MeOH/CH₂Cl₂, 5:95, v/v); mp 152.6 °C; IR (ν cm⁻¹) 3175 (OH), 1693 (C=O carbamate), 1624 (C=O amide), 1574 (ArC=C); ¹H NMR δ 6.61 (s, 2H, ArH), 6.65 (s, 2H, ArH), 5.94 (br s, 1H, OH), 5.70–4.17 (m, 3H, piperazine), 4.03 (m, 2H, CH₃O), 3.78 (s, 15H, CH₃O), 3.77–3.03 (m, 8H, N(CH₂CH₃)₂, piperazine), 0.97 (m, 6H, CH₃); ¹³C NMR δ 170.81, 170.75 (C=O amide), 155.03 (C=O carbamate), 153.26, 146.84, 139.34, 136.65, 130.01, 125.47, 104.50, 104.23 (ArC=C), 60.86 (CH₂O), 60.76, 56.28, 56.15 (CH₃O), 41.73, 41.02 (NCH₂CH₃), 13.81, 13.27 (NCH₂CH₃).

4.2.26. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(4-butoxy-3,5-dimethoxybenzoyl)-4-(3,4,5-trimethoxybenzoyl)piperazine (27). A mixture of **26** (0.3 g, 0.51 mmol), 1-bromobutane (100 μ L, 1.02 mmol) and K₂CO₃

(140 mg, 1.02 mmol) was refluxed in acetone (10 mL) for 48 h. The solution was then evaporated and the residue taken in CH_2Cl_2 , washed with water, dried, filtered and the solvent eliminated under reduced pressure. A recrystallization from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane}$ led to **27** (240 mg, 73%) as white crystals; R_f : 0.34 (MeOH/ CH_2Cl_2 , 5:95, v/v); mp 99 °C; IR ($\nu \text{ cm}^{-1}$) 1692 (C=O carbamate), 1630 (C=O amide), 1584, 1505 (ArC=C); ^1H NMR δ 6.56 (s, 4H, ArH), 5.70–4.13 (m, 3H, piperazine), 4.04 (m, 2H, CH_2O), 3.91 (t, 2H, $J = 6.64$ Hz, CH_2OPh), 3.80 (s, 15H, CH_3O), 3.77–3.05 (m, 8H, NCH_2CH_3 , piperazine), 1.66 (m, 2H, CH_2), 1.39 (m, 2H, CH_2), 0.98 (m, 6H, NCH_2CH_3), 0.88 (t, 3H, $J = 7.16$ Hz, CH_3); ^{13}C NMR δ 170.84 (C=O amide), 155.09 (C=O carbamate), 153.58, 153.38, 139.46, 139.02, 130.11, 129.90, 104.56, 104.30 (ArC=C), 73.22 (PhOCH_2), 60.92 (CH_2O), 60.81, 56.24 (CH_3O), 41.82, 41.12 (NCH_2CH_3), 32.03, 18.94 (CH_2), 13.77, 13.38 (CH_3). Anal. ($\text{C}_{33}\text{H}_{47}\text{N}_3\text{O}_{10}$) C, H, N.

4.2.27. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-di(3,4-dimethoxybenzoyl)piperazine (29a). The same procedure as described in Serradji et al.¹² was followed to prepare **29a** but using 3,4-dimethoxybenzoyl chloride and led to 3.35 g (53.2%) of **29a** as white crystals; R_f : 0.49 (MeOH/ CH_2Cl_2 , 5:95, v/v); mp 103.9 °C; IR ($\nu \text{ cm}^{-1}$) 1693 (C=O carbamate), 1622 (C=O amide), 1583 (ArC=C); ^1H NMR δ 6.95 (s, 2H, ArH-2), 6.92 and 6.79 (2d, 4H, $J = 8.01$ Hz, ArH-5 and ArH-6), 5.10–4.10 (m, 3H, piperazine), 4.03 (m, 2H, CH_2O), 3.84 (br s, 12H, CH_3O), 3.75–2.70 (m, 8H, $\text{N}(\text{CH}_2\text{CH}_3)_2$, piperazine), 1.13 (br s, 6H, CH_3); ^{13}C NMR δ 170.87, 170.71 (C=O amide), 154.98 (C=O carbamate), 150.44, 150.37, 148.95, 148.83, 127.06, 126.89, 120.04, 119.84, 110.25 (ArC=C), 60.75 (CH_2O), 55.78 (CH_3O), 41.68, 40.98 (NCH_2CH_3), 13.75, 13.25 (NCH_2CH_3). Anal. ($\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_8$) C, H, N.

4.2.28. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-di(2,4-dimethoxybenzoyl)piperazine (29b). The same procedure as in Serradji et al.¹² was followed to prepare **29b** but using 2,4-dimethoxybenzoyl chloride and led to 960 mg (49%) of **29b** as white crystals; R_f : 0.27 (MeOH/ CH_2Cl_2 , 5:95, v/v); mp 85 °C; IR ($\nu \text{ cm}^{-1}$) 1708 (C=O carbamate), 1606 (C=O amide), 1600 (ArC=C); ^1H NMR δ 7.12 (m, 2H, ArH-3), 6.44 (m, 4H, ArH-5 and ArH-6), 5.10–4.10 (m, 3H, piperazine), 4.02 (m, 2H, CH_2O), 3.75 (br s, 12H, CH_3O), 3.60–2.50 (m, 8H, $\text{N}(\text{CH}_2\text{CH}_3)_2$, piperazine), 1.09 (br s, 6H, CH_3); ^{13}H NMR δ 168.39 (C=O amide), 161.78 (C=O carbamate), 156.46, 154.96, 129.63, 117.53, 104.94, 98.17 (ArC=C), 60.74 (CH_2O), 55.33 (CH_3O), 47.49, 43.10, 42.31 (piperazine), 41.68, 40.98 (NCH_2CH_3), 13.71, 13.35 (NCH_2CH_3). Anal. ($\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_8 \cdot \text{H}_2\text{O}$) C, H, N.

4.2.29. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-di(4-hydroxy-3,5-dimethoxybenzoyl)piperazine (29c). The same procedure as for the preparation of the compound **20** was followed to prepare **29c** and led to 1.46 g (37%) of this compound as white crystals; R_f : 0.21 (MeOH/ CH_2Cl_2 , 5:95, v/v); mp 140.1 °C; IR ($\nu \text{ cm}^{-1}$) 3470 and 3191 (OH), 1700 (C=O carbamate), 1630 (C=O amide), 1591 (ArC=C); ^1H NMR δ 6.61 (s, 4H, ArH), 5.96 (br s, 2H, OH), 5.20–3.99 (m, 5H, CH_2O , piperazine), 3.81

(s, 12H, CH_3O), 3.30–2.50 (m, 8H, $\text{N}(\text{CH}_2\text{CH}_3)_2$, piperazine), 1.00 (m, 6H, CH_3); ^{13}C NMR δ 171.03, 170.84 (C=O amide), 155.02 (C=O carbamate), 146.87, 136.64, 136.56, 125.45, 125.88, 104.52, 104.42 (ArC=C), 60.87 (CH_2O), 56.32, 56.28 (CH_3O), 41.66, 40.95 (NCH_2CH_3), 13.71, 12.25 (NCH_2CH_3). Anal. ($\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_{10} \cdot 0.75\text{H}_2\text{O}$) C, H, N.

4.2.30. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-dibenzoylpiperazine (29d). The same procedure as described in Serradji et al.¹² was followed to prepare **29d** but using benzoyl chloride and led to 600 mg (82%) of the title compound as white crystals; R_f : 0.19 (MeOH/ CH_2Cl_2 , 2:98, v/v); mp 120.9 °C; IR ($\nu \text{ cm}^{-1}$) 1692 (C=O carbamate), 1627 (C=O amide), 1577 (ArC=C); ^1H NMR δ 7.34 (br s, 10H, ArH), 5.10–4.10 (m, 3H, piperazine), 4.04 (m, 2H, CH_2O), 3.90–2.30 (m, 8H, $\text{N}(\text{CH}_2\text{CH}_3)_2$, piperazine), 1.01 (m, 6H, CH_3); ^{13}C NMR δ 171.06 (C=O amide), 155.12 (C=O carbamate), 135.08, 134.87, 130.02, 128.58, 128.53, 126.93 (ArC=C), 60.71 (CH_2O), 55.78 (OCH_3), 41.85, 41.16 (NCH_2CH_3), 13.88, 13.36 (NCH_2CH_3). Anal. ($\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_4$) C, H, N.

4.2.31. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-di(pyridin-4-ylcarbonyl)piperazine (29e). The same procedure as described in Serradji et al.¹² was followed to prepare **29e** but using isonicotinoyl chloride hydrochloride and led to 460 mg (62.6%) of the title compound as white crystals; R_f : 0.19 (MeOH/ CH_2Cl_2 , 5:95, v/v); mp 135.5 °C; IR ($\nu \text{ cm}^{-1}$) 1693 (C=O carbamate), 1628 (C=O amide), 1597 (ArC=C); ^1H NMR δ 8.64 (s, 4H, ArH), 7.22 (s, 4H, ArH), 5.50–4.15 (m, 3H, $\text{CHOC}=\text{O}$, piperazine), 4.02 (dd, 1H, $J = 6.03$ and 11.06 Hz, $\text{CHOC}=\text{O}$), 3.98–2.30 (9H, $\text{N}(\text{CH}_2\text{CH}_3)_2$, piperazine), 1.02 (m, 6H, CH_3); ^{13}C NMR δ 168.36 (C=O), 154.79 (C=O carbamate), 150.41, 142.41, 142.22, 120.99 (ArC=C), 60.38 (CH_2O), 48.19, 46.90 (piperazine), 41.95, 41.17 (NCH_2CH_3), 13.86, 13.34 (CH_3). Anal. ($\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_4$) C, H, N.

4.2.32. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-di(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (30). The same procedure as for the preparation of the compound **9** was followed to prepare **30** but using 3,4,5-trimethoxybenzyl chloride and **28** and led to 1.48 g (74%) of the corresponding free base, which (500 mg, 0.86 mmol) was bubbled with HCl in EtOH and recrystallized from EtOH/ Et_2O to provide **30** (430 mg, 77%) as a solid; R_f : (MeOH/ CH_2Cl_2 , 1:99, v/v); mp 163.2 °C; IR ($\nu \text{ cm}^{-1}$) 1700 (C=O), 1598 (ArC=C); ^1H NMR ($\text{DMSO}-d_6$) δ 11.80 (br s, 2H, NH^+), 7.09 (s, 4H, ArH), 4.71–3.92 (m, 7H, $\text{CH}_2\text{-Ph}$, $\text{CH}_2\text{OC}=\text{O}$, piperazine), 3.79 (s, 12H, CH_3O), 3.66 (s, 6H, CH_3O), 3.45 (m, 6H, CH_2N^+), 3.22 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.02 (m, 6H, CH_3); ^{13}C NMR ($\text{DMSO}-d_6$) δ 153.88 (C=O carbamate), 152.85, 138.03, 137.89, 125.14, 124.40, 108.78 (ArC=C), 60.65 (CH_2O), 59.93, 55.97 (CH_3O), 41.51, 40.74 (NCH_2CH_3), 14.03, 13.26 (CH_3). Anal. ($\text{C}_{30}\text{H}_{47}\text{N}_3\text{Cl}_2\text{O}_8 \cdot 1.5\text{H}_2\text{O}$) C, H, N.

4.2.33. 2-*N,N*-Diethylaminocarbonyloxymethyl-1,4-di(3,4,5-trimethoxythiobenzoyl)piperazine (31). This compound was prepared using the same procedure as for the compound **41** but from **1a**¹⁶ and **31** (460 mg, 87%) was obtained as yellow crystals; R_f : 0.55 (MeOH/ CH_2Cl_2 , 5:95, v/v); mp

95.1 °C; IR (ν cm⁻¹) 1700 (C=O), 1582 (ArC=C); ¹H NMR δ 6.48 (br s, 4H, ArH), 6.01 (m, 1H, piperazine), 5.65 (m, 1H, piperazine), 4.45 (m, 1H, piperazine), 4.09 (m, 2H, CH₂OC=O), 3.79 (s, 18H, CH₃O), 3.65–2.05 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.05 and 0.81 (2m, 6H, CH₃); ¹³C NMR δ 202.94, 202.64 (C=S), 154.93 (C=O), 153.28, 138.76, 137.71, 137.45, 103.33 (ArC=C), 61.07 (CH₂O), 60.82, 56.24 (OCH₃), 41.93, 41.29 (NCH₂CH₃), 14.08, 13.41 (CH₃). Anal. (C₃₀H₄₁N₃O₈S₂·0.5H₂O) C, H, N.

4.2.34. 3-*N,N*-Diethylaminocarbonyloxymethyl-1-diphenylmethylpiperazine (32). The process was the same as for the synthesis of **9** but using diphenylmethyl bromide and led to 900 mg (45.4%) of **32**; *R*_f: 0.15 (MeOH/CH₂Cl₂, 5:95, v/v); IR (ν cm⁻¹) 3251 (NH), 2965 (ArCH), 1704 (C=O), 1592 (ArC=C); ¹H NMR δ 7.31 (m, 4H, ArH), 7.13 (m, 6H, ArH), 4.14 (s, 1H, CHPh₂), 3.89 (m, 2H, CH₂O), 3.30–2.94 (m, 5H, NH, N(CH₂CH₃)₂), 2.88 (m, 2H, piperazine), 2.80–2.55 (m, 2H, piperazine), 1.96 (m, 1H, piperazine), 1.78 (m, 2H, piperazine), 0.96 (m, 6H, CH₃); ¹³C NMR δ 155.47 (C=O carbamate), 142.55, 142.41, 128.41, 127.82, 126.84 (ArC=C), 76.36 (CHPh₂) 66.71 (CH₂O), 54.93, 54.08, 52.56, 45.13 (piperazine), 41.68, 41.21 (NCH₂CH₃), 13.90, 13.51 (NCH₂CH₃).

4.2.35. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-diphenylmethyl-1-(3,4,5-trimethoxybenzoyl)piperazine, hydrochloride (33). This compound (700 mg, 48.5%) was prepared as described for the compound **2** and obtained as yellow crystals; *R*_f: 0.35 (MeOH/CH₂Cl₂, 3:97, v/v); mp 170.6 °C; IR (ν cm⁻¹) 1700 (C=O carbamate), 1648 (C=O amide), 1584 (ArC=C); ¹H NMR δ 7.91 (br s, 4H, ArH), 7.30 (m, 6H, ArH), 6.64 (br s, 2H, ArH), 5.50–3.90 (m, 5H, CH₂O, CHPh₂, piperazine), 3.76 (s, 9H, CH₃O), 3.60–1.90 (m, 9H, N(CH₂CH₃)₂, piperazine), 0.91 (m, 6H, CH₃); ¹³C NMR δ 170.28 (C=O amide), 154.73 (C=O carbamate), 153.19, 139.63, 134.27, 133.33, 129.58, 129.45, 129.20, 129.04, 128.44, 104.49 (ArC=C), 78.87 (CHPh₂), 62.17 (CH₂O), 60.63, 56.18 (CH₃O), 51.91, 51.32, 41.67, 41.00 (NCH₂CH₃, piperazine), 13.85, 13.19 (NCH₂CH₃). Anal. (C₃₃H₄₂N₃ClO₆) C, H, N.

4.2.36. 3-*N,N*-Diethylaminocarbonyloxymethyl-1-triphenylmethylpiperazine (34). To a solution of **28**¹⁶ (6.26 g, 21.73 mmol) and Et₃N (12 mL, 86.92 mmol) in CH₂Cl₂ (100 mL) was added dropwise a solution of triphenylmethyl chloride (6 g, 21.73 mmol) in CH₂Cl₂ (100 mL). The solution was stirred for 6 h and then washed with saturated NaHCO₃ solution and water to neutral pH, dried (MgSO₄) and the solvent evaporated. The residue (9.9 g, 99.7%) was used in the next step without any further purification; *R*_f: 0.093 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 3320 (NH), 3045 (ArCH), 1695 (C=O carbamate), 1595 (ArC=C); ¹H NMR δ 7.40 (m, 6H, ArH), 7.10 (m, 9H, ArH), 3.86 (m, 2H, CH₂O), 3.50–2.45 (m, 7H, CH₂CH₃, piperazine), 2.00–1.10 (m, 4H, piperazine), 0.97 (m, 6H, CH₃); ¹³C NMR δ 155.46 (C=O), 129.26, 127.40, 125.91 (ArC=C), 66.85 (CH₂O), 54.68, 51.50, 48.78, 45.75 (piperazine), 41.67, 41.21 (NCH₂CH₃), 13.93, 13.45 (NCH₂CH₃).

4.2.37. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(4-hydroxy-3,5-dimethoxybenzoyl)-4-triphenylmethylpiperazine (35). This compound was prepared from **34** using the same procedure as for the preparation of **20** and 2.2 g (52.4%) of **35** was obtained; *R*_f: 0.30 (MeOH/CH₂Cl₂, 5:95, v/v); IR (ν cm⁻¹) 3391 (OH), 1679 (C=O carbamate), 1620 (C=O amide), 1606 (ArC=C); ¹H NMR δ 7.38 (m, 6H, ArH), 7.16 (m, 9H, ArH), 6.53 (s, 2H, ArH), 5.61 (br s, 1H, OH), 5.22 (br s, 1H, CHOC=O), 4.98 (br s, 1H, CHOC=O), 4.40 (br s, 1H, piperazine), 3.78 (s, 6H, CH₃O), 3.46–2.81 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.78–1.73 (m, 2H, piperazine), 1.17–0.94 (m, 6H, CH₃).

4.2.38. 1-(4-Butoxy-3,5-dimethoxybenzoyl)-2-*N,N*-diethylaminocarbonyloxymethyl-4-triphenylmethylpiperazine (36). A mixture of **35** (950 mg, 1.49 mmol), 1-bromobutane (340 μ L, 2.98 mmol) and K₂CO₃ (411 mg, 2.98 mmol) in dry acetone (25 mL) was refluxed for 6 h. After filtration of the salts and evaporation of the solvent, the residue was taken in CH₂Cl₂, washed with water, dried (MgSO₄), filtered and the solvent eliminated in vacuum. A column chromatography through silica gel using MeOH/CH₂Cl₂ (0.5:99.5, v/v) as eluent yielded 850 mg (82.3%) of the title compound as a wax; *R*_f: 0.36 (MeOH/CH₂Cl₂, 2:98, v/v); IR (ν cm⁻¹) 1694 (C=O carbamate), 1638 (C=O amide), 1579 (ArC=C); ¹H NMR δ 7.34 (br s, 6H, ArH), 7.18–7.04 (m, 9H, ArH), 6.45 (s, 2H, ArH), 5.21 (br s, 1H, CHOC=O), 4.96 (br s, 1H, CHOC=O), 4.42 (br s, 1H, piperazine), 3.84 (t, 2H, *J* = 6.65 Hz, Ph–OCH₂), 3.68 (s, 6H, CH₃O), 3.60–2.70 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.74 (m, 2H, piperazine), 1.59 (qt, 2H, *J* = 6.99 Hz, Ph–OCH₂CH₂CH₂CH₃), 1.38 (sex, 2H, *J* = 7.46 Hz, Ph–OCH₂CH₂CH₂CH₃), 1.05 (t, 3H, *J* = 6.56 Hz, CH₃), 1.02 (m, 3H, CH₃), 0.82 (t, 3H, *J* = 7.30 Hz, CH₃); ¹³C NMR δ 169.96 (C=O amide), 155.62 (C=O carbamate), 153.08, 152.06, 138.27, 130.36, 129.03, 127.39, 126.06, 104.36 (ArC=C), 76.68 (CPh₃), 72.84 (CH₂OPh), 62.70 (CH₂O carbamate), 55.89 (CH₃O), 48.87, 47.90, 44.87 (CH₂ piperazine), 41.55, 40.99 (NCH₂CH₃), 31.77, 18.71 (OCH₂(CH₂)₂CH₃), 13.76, 13.54, 13.30 (NCH₂CH₃ and OCH₂(CH₂)₂CH₃).

4.2.39. 1-(4-Butoxy-3,5-dimethoxybenzoyl)-2-*N,N*-diethylaminocarbonyloxymethylpiperazine (37). This compound was prepared from **36** using the same procedure as for **40** and 340 mg (62%) of **37** was obtained; *R*_f: 0.13 (MeOH/CH₂Cl₂, 5:95, v/v); IR (ν cm⁻¹) 3325 (NH), 1676 (C=O carbamate), 1625 (C=O amide), 1577 (ArC=C); ¹H NMR δ 6.54 (s, 2H, ArH), 5.15–4.10 (m, 4H, CH₂OC=O, NH, piperazine), 3.89 (t, 2H, *J* = 6.71 Hz, Ph–OCH₂), 3.76 (s, 6H, CH₃O), 3.70–2.4 (m, 10H, N(CH₂CH₃)₂, piperazine), 1.65 (qt, 2H, *J* = 6.96 Hz, PhOCH₂CH₂CH₂CH₃), 1.39 (sex, 2H, *J* = 7.31 Hz, PhOCH₂CH₂CH₂CH₃), 1.01 (t, 6H, *J* = 7.03 Hz, CH₃), 0.87 (t, 3H, *J* = 7.25 Hz, CH₃).

4.2.40. 4-Benzyl-1-(4-butoxy-3,5-dimethoxybenzoyl)-2-*N,N*-diethylaminocarbonyloxymethylpiperazine, hydrochloride (38). This compound was prepared from **37** using the same procedure as for the preparation of **3**. A chlorhydrate using HCl and a recrystallization from MeOH/

Et₂O gave 200 mg (36.6%) of the title compound; *R*_f: (free base) 0.22 (MeOH/CH₂Cl₂, 2:98, v/v); mp 143.8 °C; IR (ν cm⁻¹) 1700 (C=O carbamate), 1647 (C=O amide), 1582 (ArC=C); ¹H NMR δ 11.10 (br s, 1H, NH⁺), 7.62 (m, 2H, ArH), 7.46 (m, 3H, ArH), 6.67 (s, 2H, ArH), 5.40–4.09 (m, 5H, CH₂OC=O, piperazine), 3.86 (t, 2H, *J* = 6.30 Hz, PhOCH₂), 3.78 (s, 6H, CH₃O), 3.30–2.90 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.59 (qt, 2H, *J* = 6.70 Hz, PhOCH₂CH₂CH₂CH₃), 1.42 (sex, 2H, *J* = 7.10 Hz, PhOCH₂CH₂CH₂CH₃), 0.90 (t, 9H, *J* = 7.17 Hz, CH₃); ¹³C NMR δ 169.90 (C=O amide), 155.10 (C=O carbamate), 153.45, 138.44, 131.92, 129.50, 128.70, 104.62 (ArC=C), 72.07 (CH₂OAr), 60.95 (CH₂O carbamate), 56.08 (CH₃O), 50.87 (CH₂Ph), 41.19, 40.74 (NCH₂CH₃), 31.66, 18.56 (–OCH₂(CH₂)₂ CH₃), 13.64, 13.34 (CH₃). Anal. (C₃₀H₄₄N₃ClO₆) C, H, N.

4.2.41. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)-4-triphenylmethylpiperazine (39).

Compound **39** was prepared from **34** as described for the compound **2** but at room temperature. A silica gel column using CH₂Cl₂ as eluent yielded **39** (9.52 g, 89%) as a wax; *R*_f: 0.33 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 1701 (C=O carbamate), 1616 (C=O amide), 1507 (ArC=C); ¹H NMR δ 7.38 and 7.19 (2m, 15H, ArH), 6.49 (s, 2H, ArCH), 4.99 and 4.41 (2m, 2H, piperazine), 3.83 (m, 2H, CH₂O), 3.74 and 3.73 (2s, 9H, CH₃O), 3.59 (q, 2H, *J* = 7.01 Hz, NCH₂CH₃), 3.60–2.60 (m, 6H, NCH₂CH₃, piperazine), 1.79 (m, 1H, piperazine), 1.09 (m, 6H, CH₃); ¹³C NMR 169.97 (C=O amide), 155.78 (C=O carbamate), 152.96, 138.96, 130.86, 129.13, 127.53, 126.20, 104.31 (ArC=C), 62.83 (CH₂O), 60.66, 56.02 (OCH₃), 49.25, 48.97, 48.00, 44.93 (piperazine), 41.69, 41.12 (NCH₂CH₃), 13.90, 13.43 (NCH₂CH₃).

4.2.42. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxybenzoyl)piperazine (40).

To a solution of **39** (6.5 g, 9.98 mmol) in MeOH (100 mL) was added dropwise HCl 12 N (6 mL). This solution was stirred for 10 min at room temperature and the solvent removed in vacuum. The residue was then taken up with CH₂Cl₂, washed with saturated NaHCO₃ solution and water, dried (MgSO₄), filtered and evaporated. A silica gel column using MeOH/CH₂Cl₂ as eluent (3:97, v/v) yielded **40** (3.8 g, 93%) as a wax; *R*_f: 0.11 (MeOH/CH₂Cl₂, 3:97, v/v); IR (ν cm⁻¹) 3330 (NH), 1693 (C=O carbamate), 1632 (C=O amide), 1584 (ArC=C); ¹H NMR δ 6.55 (s, 2H, ArH), 4.90–4.40 (m, 2H, piperazine), 4.29 (m, 2H, CH₂O), 3.79 and 3.77 (2s, 9H, CH₃O), 3.40–2.50 (m, 9H, N(CH₂CH₃)₂, piperazine), 1.37 (br s, 1H, NH), 1.02 (t, 6H, *J* = 7 Hz, CH₃); ¹³C NMR δ 170.44 (C=O amide), 155.36 (C=O carbamate), 153.07, 138.95, 130.94, 104.08 (ArC=C), 61.44 (CH₂O), 60.62, 56.10 (OCH₃), 45.86 (piperazine), 41.67, 41.07 (NCH₂CH₃), 13.88, 13.25 (NCH₂CH₃).

4.2.43. 2-*N,N*-Diethylaminocarbonyloxymethyl-1-(3,4,5-trimethoxythiobenzoyl)piperazine (41).

To a cooled (ice bath) solution of **40** (1.41 g, 3.44 mmol) in THF (30 mL) was added portionwise Lawesson's reagent (1.4 g, 3.44 mmol). The mixture was stirred for 30 min at 0 °C and then overnight at room temperature.

The solvent was removed in vacuum and a chromatography using MeOH/CH₂Cl₂ (1/99, v/v) as eluent yielded **41** (1.2 g, 82%) as a wax; *R*_f: 0.18 (MeOH/CH₂Cl₂, 5:95, v/v). The residue was then used without further purification.

4.2.44. 2-*N,N*-Diethylaminocarbonyloxymethyl-4-(3,4,5-trimethoxybenzoyl)-1-(3,4,5-trimethoxythiobenzoyl)piperazine (42).

Compound **42** was prepared from the compound **41**, as described for the compound **2**, and obtained as a pale yellow solid (405 mg, 23.2 %); *R*_f: 0.44 (MeOH/CH₂Cl₂, 5:95, v/v); mp 175 °C; IR (ν cm⁻¹) 1699 (C=O carbamate), 1642 (C=O amide), 1588 (ArC=C); ¹H NMR δ 6.58 (s, 2H, ArH), 6.47 (m, 2H, ArH), 5.10–4.00 (m, 5H, CH₂O, piperazine), 3.78 (s, 18H, CH₃O), 3.70–2.60 (m, 8H, N(CH₂CH₃)₂, piperazine), 1.04 (m, 6H, CH₃); ¹³C NMR δ 202.53 (C=S), 170.66 (C=O amide), 155.04 (C=O carbamate), 153.26, 153.07, 139.41, 138.41, 137.76, 129.60, 104.22 (ArC=C), 60.91 (CH₂O), 60.82, 56.12, 56.04 (OCH₃), 54.81, 47.65 (piperazine), 41.72, 41.10 (NCH₂CH₃), 13.90, 13.27 (NCH₂CH₃). Anal. (C₃₀H₄₁N₃O₉S) C, H, N.

4.2.45. Computational tools. All the calculations were performed with the Gaussian 98 program²⁶ on a SGI Origin 3800. All the selected conformations were fully optimized within RHF molecular orbital formalism, using the 6-31G basis set.²⁷ The 3D electrostatic potential has also been computed at that level with the same basis set.

4.3. Biological methods

4.3.1. Platelet aggregation. The inhibition of platelet aggregation was conducted according to the published procedures.¹² Briefly, it was determined using platelet-rich plasma (PRP) of New Zealand rabbits by the method of Cazenave et al.²⁹ Blood samples were collected from auricular artery into a citrate buffer (3.8%, pH 7.4), and PRP was obtained by centrifugation for 15 min at 1200 rpm. The antagonists were solubilized in DMSO at concentrations from 10⁻² to 10⁻⁷ M and added to the incubated and stirred PRP for 2 min before PAF (2.5 nM) challenge. Platelet aggregation induced by PAF in the presence of the antagonists was monitored by continuous recording of light transmission in a dual-channel recorder (Cronolog Coultronics Apparatus) and was compared to a control aggregation induced by PAF alone. The drug concentration required to produce 50% inhibition (IC₅₀) was calculated from dose-response curves (number of determinations: 5–6).

4.3.2. Antiviral assay. All experiments were performed in triplicate in cells isolated from one blood donor. Antiviral assays and data analysis were conducted according to the published procedures.^{12–14} HIV-1 replication was assessed in cell culture supernatants by quantifying reverse transcriptase (RT), using the RetroSys[®] kit (Innovagen).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.bmc.2006.07.031](https://doi.org/10.1016/j.bmc.2006.07.031).

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