New Substituted 1,4-Benzoxazine Derivatives with Potential Intracellular Calcium Activity

Anne-Sophie Bourlot,[†] Isabel Sánchez,[‡] Georges Dureng,[§] Gérald Guillaumet,[†] Roy Massingham,[§,||] André Monteil,[§] Eileen Winslow,[§] M. Dolors Pujol,*[,‡] and Jean-Yves Mérour*[,†]

Institut de Chimie Organique et Analytique associé au CNRS, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France, Facultat de Farmàcia, Química Farmacèutica, Universitat de Barcelona, Avda Diagonal 643, 08028 Barcelona, Spain, and RL-CERM, ZI La Varenne, rue H. Goudier, 63203 Riom Cedex, France

Received November 21, 1997

Substituted 1,4-benzoxazines bearing an amino side chain at the 2-position were prepared and were found to have a moderate activity on intracellular calcium. Of the compounds studied it was found that those which possess a homoveratrylamino moiety exhibited superior potency. The chain length and the nature of the amine (4-fluorophenylpiperazine, 4-fluorobenzhydryloxyethylamine, *N*-substituted homoveratrylamine) is discussed. The 4-benzyl-3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-2*H*-1,4-benzoxazine (**3c**) is the most potent derivative of the series with a ratio of IC_{50} values against PE (phenylephrine) and K^+ of 2.1. Under these test conditions a ratio near 1 indicates potential intracellular calcium activity while a ratio greater than 100 an action on extracellular calcium influx.

Introduction

The targets of many cardiovascular drugs are either G-protein-coupled or ion channel receptors. Receptors recognize and bind ligands to provoke cellular responses through specific signal transduction pathways. Receptors may act directly upon their cellular targets or indirectly via intermediary molecules known as second messengers.[1] Relatively few second messengers have been identified; the first was cyclic AMP and another, ubiquitous second messenger is Ca^{2+}.[2] Given its role as a second messenger, modulation of intracellular Ca^{2+} can be expected to exert several important effects upon cell function[3] including myocyte contraction, cell secretion, and platelet aggregation.

Cytoplasmic levels of Ca^{2+} are controlled by the regulation of calcium entry via several different Ca^{2+}-selective channels in the cell membrane and by uptake and release from intracellular stores.[4,5] At least three different types of voltage-operated calcium channels (VOCs) have been identified which may be involved in mediating different cell/tissue events. For example, L-type channels predominate in vascular smooth muscle (VSM), T-type channels are linked to cardiac pacemaker activity and N-type channels mediate neurotransmitter release.[6,7] Activation of receptor-operated channels (ROCs) leads to influx of Ca^{2+} from the extracellular space and also, in some instances, to its release from intracellular stores by the intermediary of inositol 1,4,5-triphosphate (IP_3), liberated from a membrane phospholipid by phospholipase C.[8,9] This reaction also produces diacylglycerol, which potentiates the effects of protein kinase C. Ca^{2+} regulate cellular activity of smooth muscle by interacting especially with protein kinase C and calmodulin (Chart 1).[1]

In this work we have attempted to enhance the pharmacological effects of the antianginal calcium antagonist bepridil[10] (Chart 1) and in particular its intracellular activity.[11,12] The biological target for this drug was initially described as the slow L-type Ca^{2+} channel.[13,14] However, unlike other L-type Ca^{2+} channel blockers, it markedly increases oxygen content in coronary sinus blood at doses having only small, relatively short-lived effects on blood pressure and cardiac contractility. In addition, persistent bradycardia and lack of blood pressure-lowering activity are characteristic findings clearly differentiating bepridil from other known agents in this class.[15] The interesting profile of bepridil in animal models may be linked to the broader range of inhibitory activities observed with the compound in isolated tissues. In the low micromolar concentration range, bepridil has effects not only at L-type VOCs but ROCs[16] and upon calmodulin (IC_{50} = 8 μM).[11,17] Bepridil also possesses additional intracellular effects at slightly higher concentrations and inhibits caffeine-induced Ca^{2+} release from intracellular stores. Interestingly this property is not shared by other calmodulin antagonists.[18]

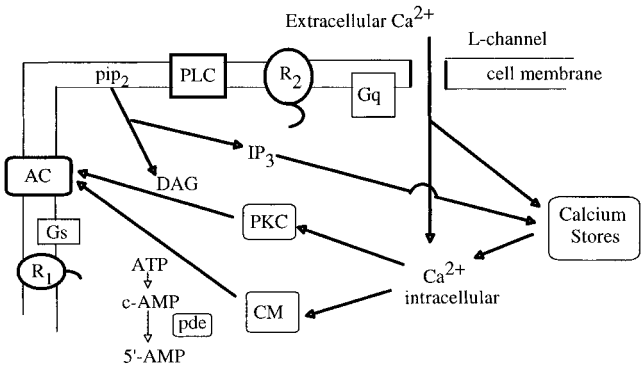
Since platelets accumulating at sites of endothelial damage or dysfunction are thought to be involved in the process of atherosclerotic plaque formation and progression,[19−21] future antianginal agents combining beneficial haemodynamic, anti-ischaemic activity with antiplatelet effects represent an interesting therapeutic goal.[22,23] Platelet membranes do not contain L-type VOCs,[24] and compounds belonging to the various classes of currently described calcium antagonists[5,25,26] do not possess antiaggregant properties. Nevertheless, as in contractile tissues, Ca^{2+} is still an important second messenger in platelets and the cytosolic Ca^{2+} concentration mediates shape change, adhesion, and aggregation.[3,24]

Future strategies for the treatment of cardiovascular diseases should be directed toward the underlying

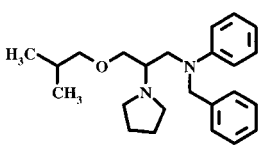
* To whom correspondence should be addressed.
[†] Université d'Orléans.
[‡] Universitat de Barcelona.
[§] RL-CERM.
[||] Present address: UCB Pharma, Pharmaceutical Sector, Chemin du Foriest, B-1420 Braine-L'Alleud (Belgique).

S0022-2623(97)00795-4 CCC: $15.00
Published on Web 07/17/1998

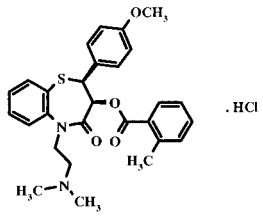
Chart 1. Second Messengers Involved in the Intracellular Signaling of Vascular Smooth Muscle



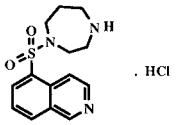
R_1: receptor (e.g. β-adrenoceptor); **R_2**: (e.g. α_1-adrenoceptor); **AC**: adenyl cyclase; **Gq, Gs**: G proteins; **pde**: phosphodiesterase; **PLC**: phospholipase C; **IP_3**: 1,4,5-inositol triphosphate; **pip_2**: phosphotidyl inositol-4,5-biphosphate; **PKC**: protein kinase C; **CM**: calmodulin; **DAG**: diacylglycerol; **L-channel**: L-type calcium channel.



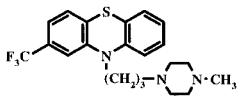
Bepridil



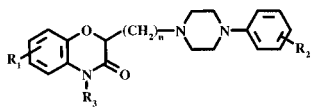
TA-3



HA-1077



Trifluoperazine

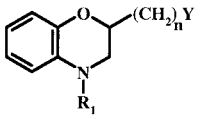


I

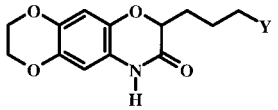
causes of the disease rather than its symptomatic treatment since only by correcting the structural abnormalities in the heart and blood vessels can optimum pharmacotherapy of diseases such as heart failure and hypertension be expected.[27] A potential way, therefore, to improve and extend efficacy in a new generation of antianginal drugs would be via enhanced intracellular effects, for example, upon calmodulin or protein kinase C (Chart 1). Such compounds would be expected to elicit effects in both vascular smooth muscle (VSM) and platelets and perhaps also, given the ubiquitous nature of the second messenger actions of Ca^{2+}, intervene at the level of the underlying cause of the disease, that is on the atherosclerotic process in the larger coronary arteries.[28−31]

Despite the large amount of work that has been done on calcium antagonists[32−36] to date, only few representatives of intracellular calcium antagonists have been described; in this respect we can mention the *cis*-(2-(4-methoxyphenyl)-3-((2-methylbenzoyl)oxy)-2,3-dihydro-5-(2-(dimethylamino)ethyl)-1,5-benzothiazepin-4(5*H*)-

Chart 2

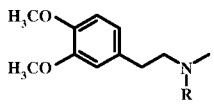


1-4

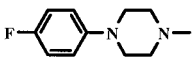


5

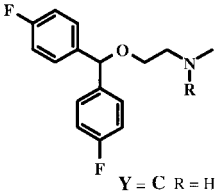
Y groups used



Y = A R = H
Y = E R = CH_3
Y = F R = Bn



Y = B



Y = C R = H
Y = D R = CH_3

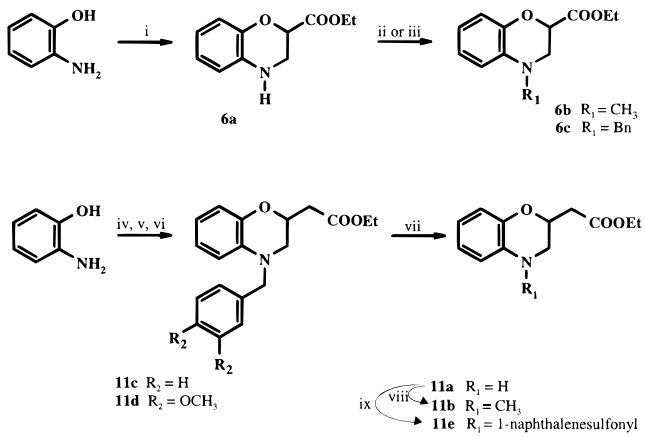
one hydrochloride (TA-3),[37] the 1-(5-isoquinolinesulfonyl)homopiperazine hydrochloride (HA 1077),[38] and trifluoperazine[39] (Chart 1). HA 1077 has been just launched on the market.

Recently a new series of 1,4-benzoxazine derivatives (**I**) (Chart 1) possessing (4-phenyl-1-piperazinyl)alkyl moieties at the C-2 position of the oxazine ring[40] was synthesized and tested for calcium antagonistic, calmodulin antagonistic, and antihypertensive activities; for example compound **I** (R_1 = 6,7-$(CH_2)_4$-, R_2 = 4-F, R_3 = H, *n* = 3) has shown calmodulin antagonist activity (IC_{50} = 0.52 μM) (racemic or enantiomeric compounds have a similar activity). In connection with our interest in benzodioxine[41−43] and benzoxazine[44−46] chemistry, we have conceived a new set of 1,4-benzoxazine derivatives, divided in two structural models. The first (derivatives **1**−**4**), in which the 1,4-benzoxazin-3-one skeleton has been replaced by a benzoxazine framework, has allowed us to explore, among others things, the influence of amine Y and the chain length (*n*) (Chart 2). The second model (derivatives **5**) was based on the introduction of a benzodioxane entity, which has already showed promising activities in our laboratory[41−43] (Chart 2). Herein we report the synthesis of these series of compounds and their pharmacological evaluation as potential intracellular calcium antagonists. To this end effects upon K^+-induced contractions were taken as an indicator of potential activity of L-type Ca^{2+} channels and effects upon phenylephrine (PE)-induced contractions as an index of intracellular effects. To discount a potential α-adrenoceptor mediated effect of these new compounds, all structures found active on PE responses were reexamined upon caffeine-induced contractions to confirm the presence of intracellular activity.

Chemistry

The synthesis of the amines **1a**−**f** (*n* = 1, *m* = 0), is presented in Scheme 2. Two methods were employed for the preparation of the carboxamides derivatives **8a**−**f**. The method planned the first isolation of the car-

Scheme 1[a]



[a] (i) Ethyl 2,3-dibromopropanoate, K_2CO_3, acetone, reflux, 75%; (ii) ICH_3, K_2CO_3, acetone 86%; (iii) BnCl, K_2CO_3, NaI, DMF, 60 °C, 76%; (iv) C_6H_5CHO or 3,4-$(CH_3O)_2C_6H_3CHO$; (v) $NaBH_4$, EtOH (75%, 91%); (vi) $BrCH_2CH{=}CHCOOEt$, $NaHCO_3$, EtOH then K_2CO_3, EtOH (**11c**, 95%, **11d**, 85%); (vii) **11c**/H_2/Pd/AcOH, 77%; (viii) CH_3I/K_2CO_3, acetone, 70%; (ix) 1-naphthalenesulfonyl chloride, Et_3N, toluene, 66%.

boxylic acids **7a**−**c** (83−88% yield), obtained by basic hydrolysis of the corresponding esters **6a**−**c**. The use of iodomethane in the presence of potassium carbonate in acetone converted the ester **6a**[47] into its *N*-methyl analogue **6b** in 67% yield (Scheme 1). The preparation of *N*-benzyl ester **6c** was carried out according to standard procedure (benzyl chloride, potassium carbonate, *N*,*N*-dimethylformamide) in 70% yield (Scheme 1). The reaction of the acids **7a**−**c** with ethyl chloroformate led to the formation of the mixed anhydride, which quickly reacted on contact with the appropriate amine to provide the carboxamides **8b**,**c** in the case of the use of homoveratrylamine (A) and **8d**−**f** in the case of *p*-fluorophenylpiperazine (B). A direct conversion of the ester **6a** into the amide **8a** (80% yield), by reaction with homoveratrylamine (A) in the presence of dicyclohexylcarbodiimide and potassium carbonate in toluene, represented the second way of preparation of carboxamides **8**. Reduction of derivatives **8a**−**f** by lithium aluminum hydride in tetrahydrofuran provided the expected amines **1a**−**f**.

Scheme 2 also depicts the synthesis of the amines **1g**−**i** which possess the benzhydryloxyethyl moiety. Treatment of the esters **6a** or **6c** with an aqueous ammonia hydroxide solution gave the corresponding amides **8g** and **8i**, respectively. In the same way, ester **6a** was converted into the amide **8h** by reacting with methylamine in toluene. Reduction of the amides **8g**−**i** by lithium aluminum hydride afforded the amines **9g**−**i**, which were condensed on 2-bromo[[bis(4-fluorophenyl)methyl]oxy]ethane, in the presence of potassium carbonate in *N*,*N*-dimethylformamide, to give the expected amines **1g**−**i**.

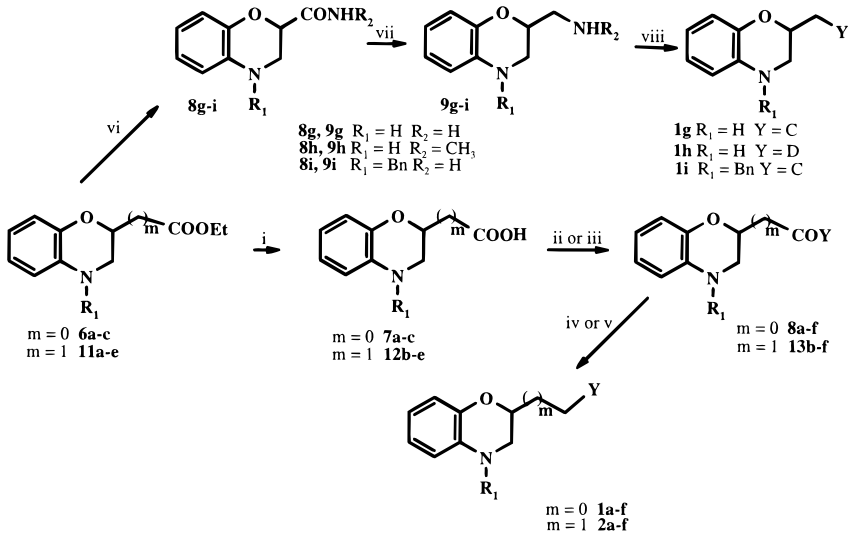
To explore the influence of chain length at the C-2 position of the oxazine ring, the synthesis of derivatives **2** ($n = 2$, $m = 1$) was targeted (Scheme 2) from the corresponding 1,4-benzoxazines derivatives **11** (Scheme 1). Reductive amination of benzaldehyde or 3,4-dimethoxybenzaldehyde by 2-aminophenol, in the presence of sodium borohydride in ethanol, furnished the *N*-benzyl intermediate phenols. In contact with ethyl 4-bromocrotonate and sodium bicarbonate in ethanol, their cyclization provided the esters **11c**[48] and **11d** in 95% and 85% yield, respectively (Scheme 1). Unfortunately, attempts to prepare the ester **11a**, in good yield, by direct condensation of 2-aminophenol onto ethyl 4-bromocrotonate, as previously described,[48] failed due to the formation of the di-N-alkylated byproduct. Hydrogenolysis of the ester **11c** in acetic acid led to the obtention of **11a** (77% yield), which was the necessary intermediate for the access of N-substituted derivatives **11b** and **11e**. N-Methylation of **11a**, following the standard procedure (iodomethane, potassium carbonate, acetone), gave the ester **11b** in 70% yield. Treatment of **11a** with 1-naphthalenesulfonyl chloride in the presence of triethylamine in toluene provided the ester **11e** in 66% yield.

Amidification of the carboxylic acids **12b**−**e**, easily obtained by basic hydrolysis of the esters **11b**−**e** (48−85% yield), by homoveratrylamine or *N*-methylhomoveratrylamine, in the presence of EDCI, resulted respectively in the isolation of amides **13b**−**e** and **13f** (68−86%). In some cases, the hydrolysis of the esters **11** with the hydroxide anion, generated a byproduct, formed by a retrograde reaction. This resulting ring opening explained the modest yield of 48%, observed in the obtention of the acid **12e**. The amides **13b**−**f** were finally converted by reduction with borane−methyl sulfide complex in tetrahydrofuran into the amines **2b**−**f** in good yields (70−84%) (opening of the oxazine ring, with formation of degradation products, resulted from reduction with lithium aluminum hydride). Hydrogenolysis of **2c** in acetic acid furnished the amine **2a** in 77% yield.

For the preparation of the amine **2g**, another synthetic route was selected, due to the incompatibility of use of borane−methyl sulfide complex in the last stage on account of the presence of the isoquinoline moiety (Scheme 3). The initial step was the protection of the secondary amine function of **2c** by the Boc group under standard conditions. Compound **14** was generated in 97% yield. Then, hydrogenolysis of **14** in acetic acid gave the intermediate **15** in 95% yield. The introduction of isoquinoline moiety by reaction of **15** with 5-isoquinolinesulfonyl chloride,[49] followed by the removal of Boc group with trifluoroacetic acid, provided the expected amine **2g** in 62% yield.

On further investigation, the synthesis of analogues **3** ($n = 3$, $m = 0$) was tackled in Scheme 4. The previously described ester **6c** was subjected to a reduction−oxidation stage to generate the aldehyde **16** in 75% global yield. In fact, direct use of diisobutylaluminum hydride with **6c** gave a mixture of expected aldehyde **16** and its reduced form (alcohol), whatever the experimental conditions; so we have preferred, for practical reasons, to reduce, in high yield, the ester group with lithium aluminum hydride into the corresponding alcohol, followed by a Swern oxidation to give the aldehyde **16**; this procedure gave a better overall yield. A Wittig reaction between aldehyde **16** and (carbethoxymethylene)triphenylphosphorane furnished the α,β-unsaturated ester as a mixture of *(E)* and *(Z)* isomers, which was converted into its saturated form by hydrogenation in the presence of Raney nickel in 71% global yield. Finally, basic hydrolysis of this intermediate with potassium hydroxide in ethanol provided the acid **17** in

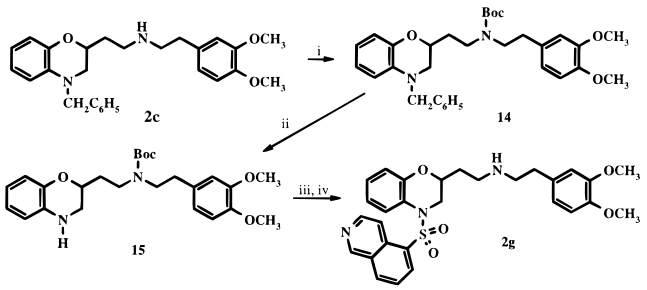
Scheme 2[a]



1a, 2a, 6a-8a, 11a $R_1 = H$ Y = A
1b, 2b, 6b-8b, 11b-13b $R_1 = CH_3$ Y = A
1c, 2c, 6c-8c, 11c-13c $R_1 = Bn$ Y = A
1d, 8d $R_1 = H$ Y = B
2d, 11d-13d $R_1 = 3,4\text{-}(CH_3O)_2C_6H_3CH_2$ Y = A
1e, 8e $R_1 = CH_3$ Y = B
2e, 11e-13e R_1 = 1-naphthalenesulfonyl Y = A
1f, 8f $R_1 = Bn$ Y = B
2f, 13f $R_1 = Bn$ Y = E

[a] (i) KOH/EtOH/H_2O (**7a**, **7b**, **12b**−**e**, 48−85%) except for **6c**, NaOH/H_2O (**7c**, 88%); (ii) $m = 0$, ClCOOEt, Et_3N, $CHCl_3$, homoveratrylamine (**8b**, 54%, **8c**, 41%) or (4-fluorophenyl)piperazine (**8d**−**f**, 75−96%); (iii) $m = 1$, EDCI, homoveratrylamine, CH_2Cl_2, (**13b**−**e**, 57−84%) or 3,4-$(CH_3O)_2C_6H_3CH_2CH_2NHCH_3$ (**13f**, 86%); (iv) $m = 0$, $LiAlH_4$, THF, (**1a**−**f**, 15−71%); (v) $m = 1$, $BH_3{\cdot}(CH_3)_2S$, THF, (**2b**−**f**, 70−84%); **2c**/H_2/Pd/AcOH (**2a**, 77%); (vi) NH_4OH, **8g**, **8i** or CH_3NH_2, toluene, **8h**; (vii) $LiAlH_4$, THF; (viii) (4-$FC_6H_4)_2CHOCH_2CH_2Br$, K_2CO_3, KI, DMF (**1g**, vi + vii + viii, 28%; **1h**, vi + vii + viii, 36%; **1i**, vi + vii + viii, 5%).

Scheme 3[a]



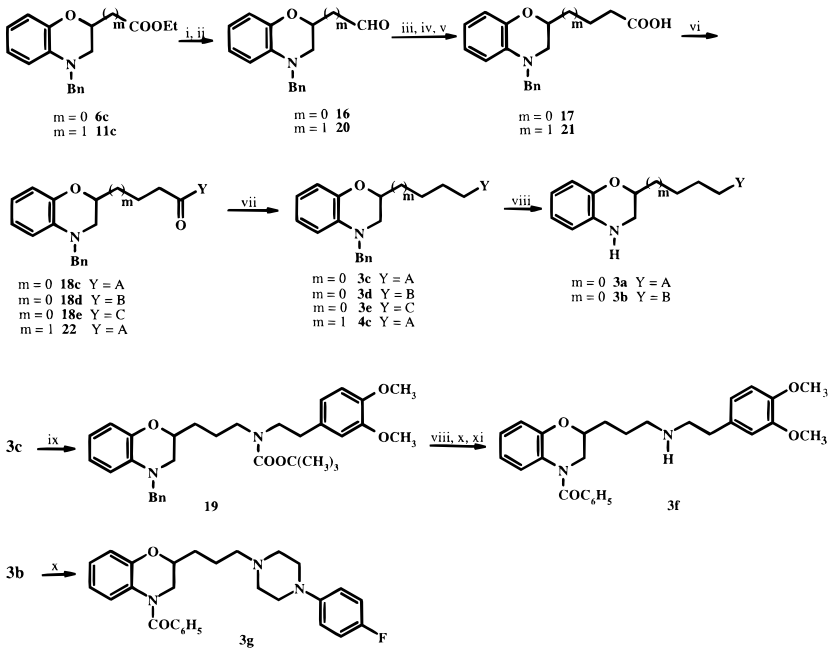
[a] (i) $(Boc)_2O$, CH_2Cl_2 (97%); (ii) H_2, Pd/C, AcOH (95%); (iii) 5-isoquinolinesulfonyl chloride, Et_3N, $PhCH_3$ (63%); (iv) CF_3CO_2H, CH_2Cl_2 (98%).

98% yield. The obtention of the amines **3c**−**e** followed sequences identical to the ones previously described (Scheme 2). So amides **18c**−**e** were prepared in a similar manner by amidification with the appropriate amine, i.e. homoveratrylamine (A), (4-fluorophenyl)-piperazine (B), or 2-[[bis(4-fluorophenyl)methyl]oxy]-ethylamine (C), of the acid **17**. Reduction of the amides **18c**−**e**, applying the previously mentioned protocol with borane-methyl sulfide complex, furnished the amines **3c**−**e** in 81%, 84%, and 82% yield, respectively. Hydrogenolysis in acetic acid of the amines **3c** and **3d** generated the amines **3a** (97% yield) and **3b** (93% yield), respectively. The preparation of **3f** from the amine **3c** required a secondary amine function protection stage before the introduction of the benzoyl group (Scheme 4). Boc derivative **19** was so isolated, in 98% yield, in previously described standard conditions (Scheme 3). Hydrogenolysis of compound **19**, benzoylation with benzoyl chloride in the presence of triethylamine in dichloromethane, and removal of the Boc group with trifluoroacetic acid finally provided the amine **3f** in 55% global yield. In contrast, direct benzoylation of amine **3b**, following the standard procedure, furnished **3g** in 66% yield.

Scheme 4 depicts the synthesis of **4c**, which has one more methylene group ($n = 4$, $m = 1$) between the oxazine ring C-2 position and the amine than compound **3c**. The ester **11c** was first converted into the aldehyde **20** in two steps (68% global yield). Wittig reaction, hydrogenation, and basic hydrolysis, following a previously mentioned protocol for **6c**, led to the formation of the acid **21** in 51% global yield. Amidification of **21** by homoveratrylamine (79% yield) and reduction of the obtained amide **22** with borane−methyl sulfide complex provided the expected amine **4c** in 79% yield.

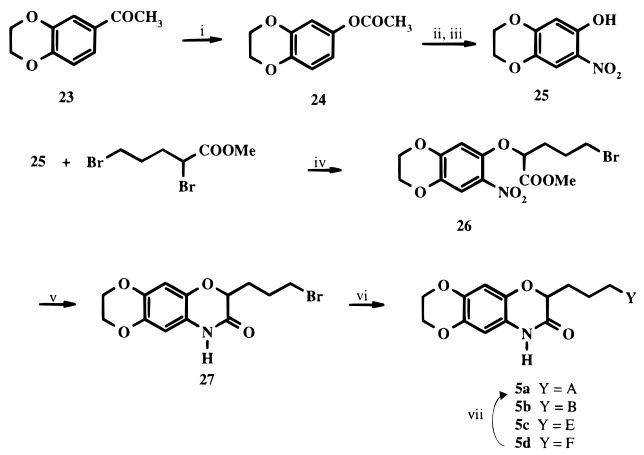
The introduction of a benzodioxane moiety was considered in Scheme 5. The commercially available ketone **23** was oxidized with *m*-chloroperbenzoic acid into the acetate **24** in 78% yield.[41] By applying the general protocol outlined by Kajino,[40] **24** was then treated with nitric acid in acetic acid, followed by a basic hydrolysis to give the nitrophenol **25** in 94% global yield. Alkylation of **25** by 2,5-dibromovaleric acid methyl ester,[50,51] in the presence of potassium carbonate in *N*,*N*-dimethylformamide, gave the intermediate **26** in 84% yield. Cyclization of **26**, under hydrogenation conditions, generated the bromo derivative **27** in 77% yield. Condensation of the appropriate amine, i.e. (4-fluorophenyl)piperazine (B), *N*-methylhomoveratrylamine (E), or *N*-benzylhomoveratrylamine (F), on **27** provided the expected derivatives **5b**, **5c**, and **5d** in 86%, 74%, and 56% yield, respectively. Surprisingly, direct condensation of homoveratrylamine (A) on **27** did not afford **5a**. Nevertheless, **5a** was isolated by hydrogenolysis of **5d** in acetic acid, in 56% yield. All compounds prepared were obtained as racemic mixtures. The modest thera-

Scheme 4[a]



[a] (i) $LiAlH_4$, THF, (97%, 80%); (ii) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N, (**16**, 77%; **20**, 85%); (iii) $Ph_3P{=}CHCOOEt$, toluene (77%, 88%); (iv) H_2, Ni Ra, EtOH (92%, 65%); (v) KOH, EtOH (**17** 98%), (**21**, 90%); (vi) EDCI, CH_2Cl_2, homoveratrylamine, (**18c**, 83%), (4-fluorophenyl)piperazine (**18d**, 97%), $(4\text{-}FC_6H_4)_2CHOCH_2CH_2NH_2$ (**18e**, 94%); for $m = 1$ homoveratrylamine (**22**, 79%); (vii) $BH_3{\cdot}(CH_3)_2S$, THF (79−84%); (viii) H_2/Pd, AcOH (93−97%); (ix) $(Boc)_2O$, CH_2Cl_2 (98%); (x) benzoyl chloride, Et_3N, CH_2Cl_2 (**3f**, 70%; **3g**, 66%); (xi) CF_3COOH, CH_2Cl_2 (84%).

Scheme 5[a]



[a] (i) *m*-CPBA, CH_2Cl_2 (78%); (ii) HNO_3, AcOH (96%); (iii) KOH, EtOH (98%); (iv) K_2CO_3, DMF (84%); (v) H_2, Pd/C, EtOH, THF (77%); (vi) *i*-Pr_2NEt, CH_3CN, 4-(fluorophenyl)piperazine (**5b**, 86%), *N*-methylhomoveratrylamine (**5c**, 74%), *N*-benzylhomoveratrylamine (**5d**, 56%); (vii) H_2,Pd/C, AcOH (74%).

peutic activities manifested by the compounds did not prompt us to invest time in an enantioselective synthesis; elsewhere compound **I**, as pure enantiomers or as racemic mixture has shown a similar activity.[48]

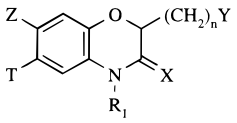
Results and Discussion

The potential therapeutic activity of these novel calcium antagonists was assessed in term of their ability to inhibit contractions of vascular smooth muscle. The agonists chosen to provoke contractions in these studies have been well described to utilize different pools of calcium in their responses. Thus responses to high concentrations of extracellular K^+ are mediated by an influx of calcium into the cell, via L-type slow calcium channels, from the extracellular space.[32−36] Since part of the contraction to PE is due to the mobilization of calcium from intracellular storages sites, any compound capable of inhibiting PE responses may have an intracellular locus of actions, for example, on calmodulin.[37−39]

However, since α_1-adrenoceptor antagonists would also be active against PE responses and give false positive results in this test, caffeine contractions were included in the screening battery. Caffeine is well-known for its ability to mobilize calcium from the intracellular storage sites of the sarcoplasmic reticulum.[18] Therefore, as previously suggested by Winslow et al.,[52] the ratio of IC_{50} values for compounds against PE and K^+ (PE/K^+ ratio = R) can be used to assess potential intracellular activity. PE/K^+ ratios where R is greater than 100 would indicate an effect of the compound at the slow calcium channel to prevent extracellular calcium influx, like nifedipine and Diltiazem.[15] Ratios where R was around unity ($R = 1$) would indicate a potential intracellular effect, while R ratios much less than unity ($R < 0.001$) would suggest an action of the compound at the α_1-adrenoceptor. In such cases caffeine was used as the discriminating stimulus for intracellular effects.

Results are given in Table 2 for the newly synthesized compounds **1**−**5**. For analyzing structure−activity relationships, three structural components are considered, the nature of the heterocyclic nitrogen substituent, the nature of the amine function of the side chain, and the length of the side chain (the distance between the heterocyclic nucleus and the amine of the side chain). First with respect to the side chain length, in general, for compounds for which $n = 3$, the percentages of inhibition of contractions induced by caffeine range from 0 to 50% for a dose of 30 μM, which indicates a very

Table 1. Chemical Properties of Compounds **1**−**5**



Nature of Y

A = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2NH$ B = 4-fluorophenylpiperazinyl
C = $(4\text{-}FC_6H_4)_2CHOCH_2CH_2NH$ D = $(4\text{-}FC_6H_4)_2CHOCH_2CH_2NCH_3$
E = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$ F = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_2C_6H_5$

compd	Z	T	X	R_1	Y	*n*	yield (%)	mp (°C)	crystn solvent[f]	formula	anal	scheme
1a	H	H	H,H	H	A	1	71	oil		$C_{19}H_{24}N_2O_3$	C,H,N	2
1b	H	H	H,H	CH_3	A	1	65	oil		$C_{20}H_{26}N_2O_3$	C,H,N	2
1c	H	H	H,H	Bn[d]	A	1	15	oil		$C_{26}H_{30}N_2O_3$	C,H,N	2
1d	H	H	H,H	H	B	1	62	oil		$C_{19}H_{22}FN_3O$	C,H,N	2
1e	H	H	H,H	CH_3	B	1	35	oil		$C_{20}H_{24}FN_3O$	C,H,N	2
1f	H	H	H,H	Bn[d]	B	1	65	oil		$C_{26}H_{28}FN_3O$	C,H,N	2
1g	H	H	H,H	H	C	1	50	oil		$C_{24}H_{24}F_2N_2O_2$	C,H,N	2
1h	H	H	H,H	H	D	1	52	oil		$C_{25}H_{26}F_2N_2O_2$	C,H,N	2
1i	H	H	H,H	Bn[d]	C	1	12	oil		$C_{31}H_{30}F_2N_2O_2$	C,H,N	2
2a	H	H	H,H	H	A	2	77	166−168	A	$C_{20}H_{26}N_2O_3 \cdot C_2H_2O_4$	C,H,N	2
2b	H	H	H,H	CH_3	A	2	70	200−202	A	$C_{21}H_{28}N_2O_3 \cdot C_2H_2O_4$	C,H,N	2
2c	H	H	H,H	Bn[d]	A	2	84	204−206	A	$C_{27}H_{32}N_2O_3 \cdot C_2H_2O_4$	C,H,N	2
2d	H	H	H,H	*a*	A	2	83	188−190	A	$C_{29}H_{36}N_2O_5 \cdot C_2H_2O_4$	C,H,N	2
2e	H	H	H,H	*b*	A	2	76	198−200	A	$C_{30}H_{32}N_2O_5S \cdot C_2H_2O_4$	C,H,N	2
2f	H	H	H,H	Bn[d]	E	2	74	152−154	A	$C_{28}H_{34}N_2O_3 \cdot C_2H_2O_4$	C,H,N	2
2g	H	H	H,H	*c*	A	2	98	166−168	A	$C_{29}H_{31}N_3O_5S \cdot 0.75C_2H_2O_4$	C,H,N	3
3a	H	H	H,H	H	A	3	97	170−172	A	$C_{21}H_{28}N_2O_3 \cdot 0.5C_4H_4O_4$	C,H,N	4
3b	H	H	H,H	H	B	3	93	108−110	Et	$C_{21}H_{26}FN_3O$	C,H,N	4
3c	H	H	H,H	Bn[d]	A	3	81	168−170	A	$C_{28}H_{34}N_2O_3 \cdot 0.5C_4H_4O_4$	C,H,N	4
3d	H	H	H,H	Bn[d]	B	3	84	106−108	Et	$C_{28}H_{32}FN_3O$	C,H,N	4
3e	H	H	H,H	Bn[d]	C	3	82	170−172	A	$C_{33}H_{34}F_2N_2O_2 \cdot C_2H_2O_4$	C,H,N	4
3f	H	H	H,H	Bz[e]	A	3	84	180−182	A	$C_{28}H_{32}N_2O_4 \cdot C_2H_2O_4$	C,H,N	4
3g	H	H	H,H	Bz[e]	B	3	66	136−138	Et	$C_{28}H_{30}FN_3O_2$	C,H,N	4
4c	H	H	H,H	Bn[d]	A	4	79	172−174	A	$C_{29}H_{36}N_2O_3 \cdot C_2H_2O_4$	C,H,N	4
5a	$-O(CH_2)_2O-$		O	H	A	3	74	202−204	A	$C_{23}H_{28}N_2O_6 \cdot C_2H_2O_4$	C,H,N	5
5b	$-O(CH_2)_2O-$		O	H	B	3	86	176−178	Et	$C_{23}H_{26}FN_3O_4$	C,H,N	5
5c	$-O(CH_2)_2O-$		O	H	E	3	74	150−152	A	$C_{24}H_{30}N_2O_6 \cdot C_2H_2O_4$	C,H,N	5
5d	$-O(CH_2)_2O-$		O	H	F	3	56	120−122	A	$C_{30}H_{34}N_2O_6 \cdot C_2H_2O_4$	C,H,N	5

[a] 3,4-$(CH_3O)_2C_6H_3CH_2$. [b] 1-Naphthalenesulfonyl. [c] 5-Isoquinolinesulfonyl. [d] Bn = $C_6H_5CH_2$. [e] Bz = C_6H_5CO. [f] A, acetone; Et, ethanol.

low intracellular activity. The most conspicuous compound is compound **3c** (IC_{50}(CAF) = 11.8 μM); the ratio IC_{50}(PE)/IC_{50}(K^+) = 2.1 indicates intracellular anticalcium activity.

Results[18] obtained with three references calcium antagonists compounds nifedipine, diltiazem, and bepridil are reported below.

	K^+ (IC_{50}, μM)	NA (IC_{50}, μM)	ratio NA/K^+	caffeine (IC_{50}, μM)
nifedipine	$8.6 \pm 2.3\ 10^{-3}$	>10	1000	≫10
diltiazem	0.64 ± 0.24	64 ± 2	100	>100
bepridil	1.3 ± 0.2	17 ± 3	13	37

As to the type of substituent of the heterocyclic nitrogen atom, preliminary observations of compounds **3b, 3d**, and **3g**, which have a (4-fluorophenyl)piperazine-type amine in the side chain, show that the unsubstituted compound **3b** shows greater activity than the benzyl or benzoyl analogues in CAF and K^+ tests, but almost the same in the PE test (see IC_{50}).

A parallel examination of compounds **3a, 3c**, and **3f**, which have homoveratrylamine as the substituent in the side chain, shows that **3a** (−NH), in contrast to **3b**, is the least active of the series. Apart from **3c** (−*N*Bn), which is the compound with the highest activity, **3f**, a benzoyl derivative on the heterocyclic nitrogen atom, is interesting due to the (PE)/(K^+) ratio = 1.5, indicating intracellular anticalcium activity.

Three distinct amines have been studied on the side chain: 1-(4-fluorophenyl)piperazine, homoveratrylamine, and 2-[bis(4-fluorophenyl)methoxy]ethylamine. For the *N*-benzyl derivatives, homoveratrylamine confers greater activity for the inhibition of contractions induced by caffeine (**3c**, IC_{50} = 11.8 μM). We should also highlight here the low activity of the derivatives with the benzhydryl moiety.

It is important to point out that there is an inversion of activities in the tests of PE and K^+ depending on the amine considered. While homoveratrylamine shows a slightly higher response for the contractions caused by a high concentration of K^+ compared with those induced by PE, 1-(4-fluorophenyl)piperazine shows the opposite.

The influence of the amine on the unsubstituted derivatives, such as compounds **3a** and **3b**, is not marked and no important differences between these compounds was observed in the caffeine test. **3b** shows greater activity according to the results of the PE test and the K^+ test; this is the only case in which the piperazinyl substituent appears more active than the homoveratryl derivative.

As for those compounds that have two methylene units, compound **2c** with a homoveratrylamine-type substituent and *N*-benzyl were found to have the highest activity in the caffeine test (IC_{50} = 12.3 μM).

Table 2. Pharmacological Activity of Derivatives **1**−**5**

compd	IC_{50} (CAF)[a] (μM)	95% conf limits	IC_{50} (PE)[a] (μM)	95% conf limits	IC_{50} (K^+)[a] (μM)	95% conf limits	IC_{50} (PE)[b]/IC_{50} (K^+)
1a	>30 (26%)						
1b	≥30 (46%)		20.9	17−25	57.4	3.1−107	0.36
1c	≥30 (48%)		11.4	8.3−15.8	9.4	7.4−11.9	1.2
1d	>30 (9%)		1.6	1.3−2.0	24.7	18−33	0.07
1e	>30 (32%)		1.4	0.9−2.1	23.1	16−32	0.06
1f	>30 (2%)		10.9	6.7−17.9	52.4	24−114	0.21
1g	26.3	20.4−32.1			74.8	38−115	
1h	>30 (23%)				5.1	4.2−6.1	
1i	>30 (5%)		93.3	76−114	17.6	15−21	−5.3
2a	>30 (26%)		42	25−70	>100 (25%)		
2b	21.8	11.9−30.6	11.8	8.1−17.2	44.7	30−67	0.26
2c	12.3	10.1−14.5	10.1	6.7−15.3	4.4	2.1−9.2	2.3
2d	30 (57%)		33.7	13−87	15.1	12.8−17.8	2.2
2e	≥30 (46%)		83.7	46−154	8.3	6.3−10.8	10.1
2f	≥30 (37%)		32.6	18−59	7.9	4.7−13.3	4.1
2g	>30 (23%)		13.3	9.7−18.3	7.3	6.2−8.7	1.8
3a	>30 (16%)		100 (49%)		>100 (30%)		
3b	>30 (22%)		3.2	2.0−5.3	11	8.1−15.0	0.29
3c	11.8	10.0−13.6	21.6	18.7−25	10.2	8.2−12.6	2.1
3d	>30 (0%)		4.3	3.1−6.6	76.5	54−110	0.06
3e	>30 (5%)		>100 (12%)		>100 (26%)		
3f	30	(50%)	12.6	9.6−16.6	8.4	6.7−10.4	1.5
3g	>30 (8%)		2.8	1.6−4.2	19	16−24	0.15
4c	13.9	11.8−16.1	43.1	14−128	8.6	6.1−12.0	5
5a	>30 (0%)		14.2	10.7−18.9	>100 (38%)		
5b	>30 (22%)		0.43	0.25−0.74	45.3	32−63	0.009
5c	>30 (0%)		14.6	10.1−21.2	2.2	1.3−3.3	7.3
5d	>30 (0%)		100 (47%)		≥100 (41%)		≥1

[a] IC_{50} is defined as the concentration (M) of the tested compounds (oxalate salt or base, see Table 2) that inhibited 50% of contraction induced by caffeine, PE or K^+. [b] The ratio IC_{50} PE/IC_{50} K^+ gives an indication of the intracellular calcium antagonistic activity of the compound. Each result was obtained from five to nine preparations.

2b, which has the heterocyclic nitrogen substituted by a methyl group, shows interesting activity also in this test with $IC_{50} = 21.8$ μM (CAF test).

The substitution of the aromatic nucleus of the heterocyclic nitrogen **2d** reduces the activity in comparison with **2c** (without substitution on the benzyl substituent) in the caffeine test indicative of reduced intracellular activity. Compounds **2e** and **2g**, derivatives with *N*-naphthalenesulfonyl and *N*-isoquinolinesulfonyl respectively, present activity of the same order as **2a** (unsubstituted) (CAF test). As for the other two tests used, the influence of the substituent of the heterocyclic nitrogen atom seems slight. It should be emphasized that the isoquinolinesulfonyl radical **2g** is that which shows the greatest intracellular potential (PE/$K^+ = 1.8$), while the *N*-methyl derivative **2b** despite the low PE/K^+ ratio (PE/$K^+ = 0.26$) probably possesses an element of α-blockade since it was only weakly active agonist K^+ and caffeine contractions.

By comparison of the secondary and the tertiary amines (**2c** and **2f**) ($n = 2$), the secondary amine is preferable to the tertiary amine just as far as intracellular effects are concerned. Bearing in mind just the nature of the amine, the most active compounds are those that have homoveratrylamine, as shown by the following results:

2c: $n = 2$ IC_{50} (CAF) $= 12.3 \pm 1.6$ μM

3c: $n = 3$ IC_{50} (CAF) $= 11.8 \pm 0.9$ μM

4c: $n = 4$ IC_{50} (CAF) $= 13.9 \pm 1.0$ μM

First with respect to the side chain length, there appears no great difference in the inhibition of PE- and K^+-induced contractions. For example within the series **1c**−**4c**, the greatest difference was only 2.4-fold. However with the chain length too short (e.g., **1c**: $n = 1$) the compounds became inactive toward caffeine-induced contraction.

Whatever the chain length, these derivatives are the most active in each of the series studied, and they have very similar values for IC_{50} (CAF). In general, increasing chain length from $n = 2$ to $n = 3$ has very little influence on calcium antagonist activity. However, it should be emphasized that the activity decreases slightly when $n = 4$.

In the subseries where $n = 1$, the effect of the substituent of the heterocyclic nitrogen atom for compounds **1d** (R = H) and **1f** (R = Bn) appears to be slight: both show little inhibition in the caffeine test. In the K^+ test the unsubstituted derivative **1d** shows activity greater than that of the corresponding *N*-benzyl (**1f**), analogously to the series where $n = 3$, and upon PE responses **1d** is also more potent, indicating some activity as an α_1-adrenoceptor blocking agent.

When the derivatives of *N*-homoveratrylamine for which $n = 2$ were compared with those for which $n = 1$, in both cases the *N*-benzyl derivative is more promising than the corresponding *N*-methyl. For $n = 1$ compare **1b** and **1c**; for $n = 2$ compare **2b** and **2c**.

The influence of the amine is apparent when we compare the compounds with *N*-(4-fluorophenyl)piperazine to those with *N*-homoveratryl and the derivatives of *p*-fluorobenzhydryl ether. Homoveratrylamine clearly confers to the molecule ability to inhibit contractions induced by caffeine (**1c**, 48% inhibition; **1f**, 2%; **1i**, 5%). The conclusions agree with those of the other tests performed, in which the benzhydryl entity showed unpromising results.

For compounds **5**, the percentage of inhibition of contractions induced by caffeine range from 0 to 22% for a dose of 30 μM which indicates a very low intracellular activity. Compound **5c** has been evaluated on PE and K^+ tests (IC_{50} =14.6 and 2.2 μM, respectively) and shows a similar activity than flunarizine (IC_{50} =18 and 1.5 μM, respectively).

Conclusions. We have synthesized and evaluated a series of 1,4-benzoxazines as potential intracellular calcium antagonists. On the basis of the structure of the benzoxazines, we can conclude that the best substituent for intracellular calcium antagonist activity of the heterocyclic nitrogen atom is the benzyl radical. Furthermore homoveratrylamine shows better calcium antagonist activity than the other amines studied; the activity is maximal when the homoveratrylamine is present on a 1,4-benzoxazine moiety without substituents on the nitrogen atom. The most suitable chain would appear to be of three carbon atoms between the heterocyclic nucleus and the amine function of the side chain as in compound (**3c**). Compounds with the dioxino[2,3-*g*][1,4]benzoxazin-3-one moiety (**5**) are less active than their 1,4-benzoxazines analogues (**3**).

Experimental Section

Chemistry. Melting points (uncorrected) were determined in capillary tubes on a Gallenkamp apparatus or on a Kofler hot-stage apparatus. IR spectra were recorded in a FTIR Perkin-Elmer 1600 spectrometer or were determined with a Perkin-Elmer 1310 spectrometer. NMR spectra were registered with a Varian Gemini-200 or/and Varian XL-300 spectrometer or were obtained on a Bruker AM 300 spectrometer, using tetramethylsilane as an internal standard in all cases. Chemical shifts are in parts per million (ppm). Chemical ionization mass spectral data (MS) were reported on R10-10C Nermag (70 eV) apparatus using chemical ionization (CI/NH_3). All compounds were analyzed for C, H, and N. Analytical results obtained for these elements were within ±0.4% of the calculated values for the formula shown. Merck 60 (40−60 μm) and Merck 60 F_{254} silica gel were used for column chromatography and thin-layer chromatography, respectively. All reagents were of commercial quality or were purified before use. Organic solvents were purified by standard procedures.

General Method for the Preparation of the Amines 1a−f. A solution containing the corresponding carboxamide (1.0 mmol) in anhydrous THF (10 mL) was slowly added to a suspension of $LiAlH_4$ (2.0 mmol) in 50 mL of anhydrous THF and stirred at room temperature for 12 h. After hydrolysis of $LiAlH_4$, the suspension was filtered and the solvent was removed under vacuum. The residue obtained was diluted with water and extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the reduced compound which was purified by silica gel column chromatography (eluent: EtOAc/MeOH 95/15).

2-[[*N*-[(3,4-Dimethoxyphenyl)ethyl]amino]methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1a). The preparation of alkylated compound **1a** (3.50 g, 71%, oil) was carried out via the general procedure for reduction of carboxamides, taking as starting material the amide **8a** (5.30 g, 15.0 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.96 (s, 1H, N**H**), 2.61 (m, 6H, C**H**$_2$-NC**H**$_2$C**H**$_2$Ar), 2.95 (dd, J = 7.0, 12.0 Hz, 1H, NC**H**), 3.12 (dd, J = 2.0, 12.0 Hz, 1H, NC**H**), 3.62 (s, 6H, C**H**$_3$O), 4.00 (m, 1H, OC**H**), 6.38 (m, 2H, Ar**H**), 6.51 (m, 5H, Ar**H**). Anal. ($C_{19}H_{24}N_2O_3$) C, H, N.

2-[[*N*-[(3,4-Dimethoxyphenyl)ethyl]amino]methyl]-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (1b). Amine **1b** (0.100 g, 65%, oil) was obtained from compound **8b** (0.159 g, 0.45 mmol) via the general procedure for reduction of carboxamides: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.81 (br s, 1H, N**H**), 2.81 (m, 4H, C**H**$_2$Ar, C**H**$_2$N), 2.85 (s, 5H, C**H**$_3$N, C**H**$_2$N), 3.13 (dd, J = 7.0, 11.0 Hz, 1H, C_3**H**), 3.20 (dd, J = 2.0, 11.0 Hz, 1H, C_3**H**), 3.86 (s, 6H, C**H**$_3$O), 4.32 (m, 1H, C_2**H**), 6.62 (d, J = 7.0 Hz, 1H, C_5**H**), 6.78 (m, 6H, Ar**H**); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 35.8 (CH_2), 38.6 (CH_3), 51.3, 51.6 and 51.9 (CH_2, C_3), 55.7 (2xCH_3), 72.8 (C_2H), 111.2 and 111.8 ($C_{2'}$H, $C_{5'}$H), 112.2 (C_5H), 115.8 (C_8H), 118.1 (C_7H), 120.5 ($C_{6'}$H), 121.2 (C_6H), 132.3 (C_{4a}), 138.0 ($C_{1'}$), 143.7 (C_{8a}), 147.3 and 148.8 ($C_{3'}$, $C_{4'}$). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

4-Benzyl-2-[[*N*-[(3,4-dimethoxyphenyl)ethyl]amino]-methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1c). The synthesis of compound **1c** (0.147 g, 15% yield, oil) was carried out following the general procedure for reduction of carboxamides, taking as starting material the compound **8c** (1.0 g, 2.3 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.91 (m, 6H, C**H**$_2$-NC**H**$_2$C**H**$_2$Ar), 3.16 (m, 1H, C_3**H**), 3.24 (m, 1H, C_3**H**), 3.82 (s, 6H, C**H**$_3$O), 4.11 (m, 1H, C_2**H**), 4.39 (s, 2H, NC**H**$_2$Ar), 4.89 (br s, 1H, N**H**), 6.70 (m, 7H, Ar**H**), 7.29 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 34.9 (CH_2), 49.8 (CH_2), 50.9 (CH_2), 54.8 (CH_2), 55.9 (CH_3), 71.9 (C_2H), 111.4 (C_5H)*, 112.0 ($C_{5'}$H)*, 112.5 ($C_{2'}$H)*, 116.5 (C_8H), 118.0 (C_6H), 120.7 ($C_{6'}$H)**, 121.8 (C_7H)-**, 127.1 ($C_{2''}$H, $C_{6''}$H), 127.2 ($C_{4''}$H), 128.7 ($C_{3''}$H, $C_{5''}$H), 131.6 ($C_{1''}$), 135.1 (C_{4a}), 137.9 ($C_{1'}$), 143.0 (C_{8a}), 147.6 ($C_{4'}$), 149.0 ($C_{3'}$) (*, ** interchangeable). Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

2-[[4-(*p*-Fluorophenyl)-1-piperazinyl]methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1d). The preparation of amine **1d** (0.520 g, 62% yield, oil) was carried out from compound **8d** (0.870 g, 2.55 mmol) following the general procedure for reduction of carboxamides: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (m, 6H, C**H**$_2$N), 3.06 (m, 4H, C**H**$_2$N), 3.39 (m, 1H, C_3**H**), 3.68 (m, 2H, C_3**H**, N**H**), 4.25 (m, 1H, C_2**H**), 6.55 (m, 2H, Ar**H**), 6.81 (m, 6H, Ar**H**); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 42.8 (CH_2), 47.8

(CH_2), 58.1 (CH_2), 68.7 (C_2H), 115.7 and 116.1 (J = 22.0 Hz, $C_{3''}H$, $C_{5''}H$), 117.5 (C_5H), 118.9 (C_8H), 119.3 and 119.4 (J = 8.0 Hz, $C_{2''}H$, $C_{6''}H$), 122.4 (C_7H), 123.1 (C_6H), 126.9 (C_{4a}), 143.5 ($C_{1''}$), 145.6 (C_{8a}), 157.3 and 160.6 (J = 247.0 Hz, $C_{4''}$). Anal. ($C_{19}H_{22}N_3FO$) C, H, N.

2-[[4-(*p*-Fluorophenyl)-1-piperazinyl]methyl]-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (1e). Starting from compound **8e** (1.60 g, 4.5 mmol) and operating via general procedure for reduction of carboxamides, we obtained the piperazine **1e** (0.540 g, 35% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (m, 6H, C**H$_2$**N), 2.84 (s, 3H, C**H$_3$**N), 3.09 (m, 5H, C_3**H, CH$_2$**), 3.27 (dd, J = 3.0, 11.0 Hz, 1H, C_3**H**), 4.39 (m, 1H, C_2**H**), 6.65 (m, 2H, Ar**H**), 6.83 (m, 4H, Ar**H**), 6.90 (m, 2H, Ar**H**); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 38.5 (CH_3, CH_3N), 49.9 (CH_2), 52.4 (CH_2), 53.7 (CH_2), 60.2 (CH_2), 71.6 (C_2H), 112.1 (C_5H), 115.1 and 115.4 (J = 21.0 Hz, $C_{3''}H$, $C_{5''}H$), 115.9 (C_8H), 117.4 and 117.5 (J = 7.0 Hz, $C_{2''}H$, $C_{6''}H$), 118.0 (C_7H), 121.2 (C_6H), 136.0 (C_{4a}), 143.6 ($C_{1''}$), 147.8 (C_{8a}), 155.3 and 158.5 (J = 239.0 Hz, $C_{4''}$). Anal. ($C_{20}H_{24}N_3FO$) C, H, N.

4-Benzyl-2-[[4-(*p*-fluorophenyl)-1-piperazinyl]methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1f). Starting from compound **8f** (1.25 g, 2.99 mmol) and following the general procedure for reduction of carboxamides, we obtained the amine **1f** (0.820 g, 65% yield, oil): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.69 (m, 6H, C**H$_2$**N), 3.15 (m, 5H, C**H$_2$**N, C_3**H**), 3.39 (dd, J = 3.0, 11.0 Hz, C_3**H**), 4.38 (m, 1H, C_2**H**), 4.44 (fd, 2H, C**H$_2$**Ar), 6.68 (m, 2H, $C_{3''}$**H**, $C_{5''}$**H**), 6.86 (m, 4H, Ar**H**), 6.94 (m, 2H, Ar**H**), 7.30 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 50.1 (CH_2), 50.4 (CH_2), 53.8 (CH_2), 54.8 (CH_2), 60.1 (CH_2), 71.5 (C_2H), 112.3 (C_5H), 115.3 and 115.4 (J = 22.0 Hz, $C_{3''}H$, $C_{5''}H$), 116.5 (C_8H), 117.7 and 117.8 (J = 8.0 Hz, $C_{2''}H$, $C_{6''}H$, C_7H), 121.6 (C_6H), 127.1 ($C_{2''}H$, $C_{6''}H$), 128.5 ($C_{4''}H$), 128.6 ($C_{3''}H$, $C_{5''}H$), 129.1 ($C_{1''}$), 135.2 ($C_{1''}$), 138.1 (C_{4a}), 143.3 (C_{8a}), 155.2 and 158.5 (J = 249.0 Hz, $C_{4''}$). Anal. ($C_{26}H_{28}N_3FO$) C, H, N.

2-[[*N*-[[Bis(*p*-fluorophenyl)methoxy]ethyl]amino]methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1g). Anhydrous K_2CO_3 (0.363 g, 9.69 mmol) and a catalytic amount of KI were added to a solution of the amine **9g** (0.530 g, 3.23 mmol) and 2-bromo[[bis(4-fluorophenyl)methyl]oxy]ethane (2.10 g, 6.46 mmol) in dry DMF (15 mL). The mixture was stirred, under argon atmosphere, at room temperature for 3 days. After the solvent was removed, the residue was diluted with water and extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography, using hexane/EtOAc (7/3) as eluent, allowed us to obtain the corresponding alkylated compound **1g** as a colorless oil (0.660 g, 50%): IR ν 3649, 2900, 2800, 1506, 1250, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 200 MHz) δ 2.89 (m, 4H, C**H$_2$**N), 3.12 (dd, J = 7.0, 12.0 Hz, 1H, C_3**H**), 3.31 (dd, J = 3.0, 12.0 Hz, 1H, C_3**H**), 3.53 (t, J = 4.0 Hz, 2H, C**H$_2$**O), 4.30 (m, 1H, C_2**H**), 5.28 (s, 1H, OC**H**), 6.18 (m, 4H, Ar**H**), 6.92 (m, 4H, Ar**H**), 7.18 (m, 4H, Ar**H**). Anal. ($C_{24}H_{24}N_2F_2O_2$) C, H, N.

2-[[*N*-[[Bis(*p*-fluorophenyl)methoxy]ethyl]-*N*-methylamino]methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1h). Anhydrous K_2CO_3 (2.09 g, 15.0 mmol) and a catalytic amount of KI were added to a solution of the amine **9h** (0.900 g, 5.0 mmol) and 2-bromo[[bis(4-fluorophenyl)methyl]oxy]ethane (1.70 g, 10.0 mmol) in dry DMF (10 mL). The reaction mixture was stirred at room temperature for 5 days. After the solvent was removed, the suspension obtained was diluted with water and extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the crude product was subjected to silica gel column chromatography using hexane/EtOAc (7/3) as an eluent. The corresponding alkylated compound **1h** (1.10 g, 52%) was obtained as an orange oil: IR ν 3400, 2952, 2856, 1506, 1200, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 200 MHz) δ 2.40 (s, 3H, C**H$_3$**N), 2.70 (m, 4H, C**H$_2$**N), 3.15 (dd, J = 7.0, 12.0 Hz, 1H, OC**H**), 3.40 (dd, J = 2.0, 12.0 Hz, 1H, C_3**H**), 3.52 (t, J = 6.0 Hz, 2H, C**H$_2$**O), 4.30 (m, 1H, C_2**H**), 5.31 (s, 1H, OC**H**), 6.70 (m, 4H, Ar**H**), 7.03 (m, 4H, Ar**H**), 7.25 (m, 4H, Ar**H**); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 43.9 (CH_3), 57.5 (CH_2), 59.6 (CH_2), 67.1 (CH_2), 72.2 (C_2H), 82.6 (CHAr), 115.1 and 115.4 (J = 21.0 Hz, $C_{3'}H$, $C_{5'}H$, C_5H), 116.9 (C_8H), 118.8 (C_6H), 121.2 (C_7H), 128.5 and 128.6 (J = 8.0 Hz, $C_{2'}H$, $C_{6'}H$), 133.2 (C_{4a}), 137.8 ($C_{1'}$), 143.4 (C_{8a}), 159.7 and 164.6 (J = 246.0 Hz, $C_{4'}$). Anal. ($C_{25}H_{26}N_2F_2O_2$) C, H, N.

4-Benzyl-2-[[*N*-[[bis(*p*-fluorophenyl)methoxy]ethyl]amino]methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (1i). Anhydrous K_2CO_3 (0.741 g, 5.4 mmol) and a small amount of KI were added to a solution of 2-bromo[[bis(4-fluorophenyl)-methyl]oxy]ethane (1.76 g, 5.4 mmol) and of the oily amine **9i**, in dry DMF (25 mL). The reaction mixture was stirred under inert atmosphere at room temperature for 3 days. Then, the DMF was removed and the residue was diluted with water. The suspension obtained was extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum, and the crude product was purified by silica gel column chromatography. Using a mixture of hexane/EtOAc (1/1) as eluent, the alkylated compound **1i** (0.108 g, 12% global yield) was obtained as a colorless oil: IR ν 3603, 2928, 2890, 1507, 1247, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 (br s, 1H, N**H**), 3.27 (t, J = 3.0 Hz, 2H, C**H$_2$**N), 3.55 (t, J = 6.0 Hz, 2H, C**H$_2$**N), 3.78 (m, 4H, C**H$_2$**O, C_3**H**), 4.25 (m, 1H, C_2**H**), 4.43 (s, 2H, NC**H$_2$**Ar), 5.36 (s, 1H, OC**H**), 6.68 (m, 2H, Ar**H**), 6.84 (m, 2H, Ar**H**), 7.02 (m, 4H, Ar**H**), 7.27 (m, 9H,-Ar**H**); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 43.2 (CH_2), 54.9 (CH_2), 62.0 (CH_2), 63.4 (CH_2), 70.3 (CH_2), 73.8 (C_2H), 82.7 (CHAr), 112.5 (C_5H), 115.2 and 115.7 (J = 21.0 Hz, $C_{3'}H$, $C_{5'}H$), 116.4 (C_8H), 118.0 (C_6H), 121.8 (C_7H), 127.1 ($C_{2''}H$, $C_{6''}H$), 127.2 ($C_{4''}H$), 128.5 and 128.6 (J = 8.0 Hz, $C_{2'}H$, $C_{6'}H$), 128.7 ($C_{3''}H$, $C_{5''}H$), 135.1 (C_{4a}), 137.4 and 137.8 ($C_{1'}$, $C_{1''}$), 143.4 (C_{8a}), 160.6 and 163.8 (J = 246.0 Hz, $C_{4'}$). Anal. ($C_{31}H_{30}N_2F_2O_2$) C, H, N.

3,4-Dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]ethyl]-2*H*-1,4-benzoxazine (2a). 2a was prepared in a manner similar to that of **11a**, using palladium on carbon (10%) in glacial acetic acid, from **2c**. The residue was then purified by filtration on silica gel (eluent: CH_2Cl_2/MeOH, 96/4) to give **2a** as an oil in 77% yield: IR (film) ν 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80−1.98 (m, 2H, OCHC**H$_2$**), 2.82−2.88 (m, 2H, NC**H$_2$**), 2.91−3.04 (m, 4H, NC**H$_2$**, C**H$_2$**Ph), 3.14 (dd, J = 7.3, 11.8 Hz, 1H, C_3**H**), 3.32 (dd, J = 2.2, 11.8 Hz, 1H, C_3**H**), 3.84 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 4.10−4.22 (m, 1H, OC**H**), 4.69 (s, 2H, N**H**), 6.54−6.83 (m, 7H, Ar**H**); MS (CI/NH_3) m/z 343 (M^+ + 1). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

General Procedure for the Preparation of the Amines 2b−f, 3c−e, and 4c. To a stirring and refluxing solution of the appropriate amide (4.1 mmol) in dry THF (20 mL) was added dropwise borane−methyl sulfide complex (2 M in THF) (9.43 mmol). The solution was heated under reflux for 4 h, and then the solvent was evaporated to dryness. The residue was heated on a steam bath for 1.5 h with 2 M HCl (10 mL) and MeOH (10 mL). The solution was cooled and basified with 2 M NaOH, and the product was extracted with EtOAc. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography to give the desired amine.

3,4-Dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]ethyl]-4-methyl-2*H*-1,4-benzoxazine (2b). Following the general procedure applied to the amide **13b** (1.50 g, 4.1 mmol), the crude was purified on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1) to furnish the amine **2b** (1.0 g, 70%) as an oil: IR (film) ν 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.66−1.91 (m, 2H, OCHC**H$_2$**), 2.70−2.78 (m, 2H, C**H$_2$**Ph), 2.79 (s, 3H, NC**H$_3$**), 2.80−2.89 (m, 4H, NC**H$_2$**), 2.93 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.10 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.83 (s, 3H, OC**H$_3$**), 3.85 (s, 3H, OC**H$_3$**), 4.15−4.25 (m, 1H, OC**H**), 6.50−6.81 (m, 7H, Ar**H**); MS (CI/NH_3) m/z 357 (M^+ + 1). Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

4-Benzyl-3,4-dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]amino]ethyl]-2*H*-1,4-benzoxazine (2c). The general procedure applied to the amide **13c** (2.35 g, 5.26 mmol) gave the desired amine, which was purified on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1) to furnish **2c** (1.90 g, 84%) as an oil: IR (film) ν 3360 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.62−1.95 (m, 2H, OCHC**H$_2$**), 2.72−2.78 (m, 2H, NC**H$_2$**), 2.81−2.91 (m, 4H, NC**H$_2$**, C**H$_2$**Ph), 3.12 (dd, J = 7.3, 11.8 Hz,

1H, NC**H**), 3.24 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**$_3$), 3.83 (s, 3H, OC**H**$_3$), 3.85 (s, 3H, OC**H**$_3$), 4.15−4.25 (m, 1H, OC**H**), 4.41 (s, 2H, NC**H**$_2$Ph), 6.56−6.82 (m, 8H, Ar**H**), 7.18−7.36 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 433 ($M^+ + 1$). Anal. ($C_{27}H_{32}N_2O_3$) C, H, N.

3,4-Dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]ethyl]-4-[(3,4-dimethoxyphenyl)methyl]-2*H*-1,4-benzoxazine (2d). Following the general procedure, the amide **13d** (2.20 g, 4.34 mmol) was reduced into the amine **2d**, which was purified on silica gel column (eluent: CH_2Cl_2/MeOH, 98/2) to give an oil in 83% yield: IR (film) ν 3340 cm^{-1}; ^{1}H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 1.59−1.88 (m, 2H, OCHC**H**$_2$), 2.65−2.74 (m, 2H, NC**H**$_2$), 2.75−2.85 (m, 4H, NC**H**$_2$, C**H**$_2$Ph), 3.00 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.15 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.77 (s, 3H, OC**H**$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.80 (s, 6H, 2 × OC**H**$_3$), 4.08−4.19 (m, 1H, OC**H**), 4.29 (s, 2H, NC**H**$_2$-Ph), 6.53−6.76 (m, 10H, Ar**H**); MS (CI/NH_3) m/z 493 ($M^+ + 1$). Anal. ($C_{29}H_{36}N_2O_5$) C, H, N.

3,4-Dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]ethyl]-4-(1-naphthalenesulfonyl)-2*H*-1,4-benzoxazine (2e). The general procedure, applied to the amide **13e** (0.564 g. 1.03 mmol), furnished the amine **2e** (0.416 g, 76%) as an oil, after purification by silica gel column chromatography, eluting with CH_2Cl_2/MeOH (98/2): IR (film) ν 3420, 1330, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 1.46−1.68 (m, 2H, OCHC**H**$_2$), 2.45−2.60 (m, 2H, C**H**$_2$Ph), 2.61−2.76 (m, 4H, NC**H**$_2$), 3.15 (dd, J = 9.5, 14.7 Hz, 1H, NC**H**), 3,27−3.37 (m, 1H, OC**H**), 3.80 (s, 6H, OC**H**$_3$), 4.23 (dd, J = 2.2, 14.7 Hz, 1H, NC**H**), 6.58−6.76 (m, 4H, Ar**H**), 6.79−6.86 (m, 1H, Ar**H**), 6.93−7.01 (m, 1H, Ar**H**), 7.34−7.51 (m, 3H, Ar**H**), 7.57 (dd, J = 1.5, 8.1 Hz, 1H, Ar**H**), 7.82 (d, J = 8.8 Hz, 1H, Ar**H**), 7.99 (d, J = 8.1 Hz, 1H, Ar**H**), 8.13 (d, J = 7.3 Hz, 1H, Ar**H**), 8.34 (d, J = 8.1 Hz, 1H, Ar**H**); MS (CI/NH_3) m/z 533 ($M^+ + 1$). Anal. ($C_{30}H_{32}N_2O_5S$) C, H, N.

4-Benzyl-3,4-dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-methylamino]ethyl]-2*H*-1,4-benzoxazine (2f). Following the general procedure, the amide **13f** (2.20 g, 4.78 mmol) was reduced into the desired amine. The crude product was purified on silica gel column, eluting with CH_2Cl_2/MeOH (97/3), to furnish **2f** (1.57 g, 74%) as an oil: IR (film) ν 1600, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61−1.88 (m, 2H, OCHC**H**$_2$), 2.25 (s, 3H, NC**H**$_3$), 2.52−2.60 (m, 4H, NC**H**$_2$, C**H**$_2$-Ph), 2.63−2.70 (m, 2H, NC**H**$_2$), 3.07 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.21 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.78 (s, 3H, OC**H**$_3$), 3.79 (s, 3H, OC**H**$_3$), 4.11−4.20 (m, 1H, OC**H**), 4.33 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.40 (d, J = 16.2 Hz, 1H, NC**H**Ph), 6.53−6.78 (m, 8H, Ar**H**), 7.16−7.30 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 447 ($M^+ + 1$). Anal. ($C_{28}H_{34}N_2O_3$) C, H, N.

3,4-Dihydro-2-[2-(3,4-dimethoxyphenyl)ethyl]-4-(5-isoquinolinesulfonyl)-2*H*-1,4-benzoxazine (2g). To a solution of **15** (0.662 g, 1.5 mmol) in dry toluene (15 mL) were added Et_3N (0.46 mL, 3.3 mmol) and 5-isoquinolinesulfonyl chloride hydrochloride (0.495 g, 1.8 mmol).[49] The mixture was stirred at room temperature for 18 h and then heated to 90 °C for 4 h. The crude reaction mixture was allowed to cool, concentrated in vacuo and partitioned between CH_2Cl_2 and H_2O. The organic layers were washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. A purification on silica gel (eluent: cyclohexane/EtOAc, 1/1) led to 3,4-dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(*tert*-butoxycarbonyl)amino]ethyl]-4-(5-isoquinolinesulfonyl)-2*H*-1,4-benzoxazine (0.600 g, 63%) as an oil: IR (film) ν 1670, 1360, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.37 (s, 9H, C**H**$_3$), 1.47−1.77 (m, 2H, OCHC**H**$_2$), 2.55−2.68 (m, 2H, C**H**$_2$Ph), 2.90−3.37 (m, 6H, NC**H**$_2$), 3.80 (s, 6H, OC**H**$_3$), 4.07−4.19 (m, 1H, OC**H**), 6.52−6.78 (m, 5H, Ar**H**), 6.86 (dd, J = 7.3, 8.1 Hz, 1H, Ar**H**), 7.01 (dd, J = 7.3, 8.1 Hz, 1H, Ar**H**, 7.59 (dd, J = 7.3, 8.1 Hz, 1H, Ar**H**), 7.98 (d, J = 7.3 Hz, 1H, Ar**H**), 8.13 (d, J = 8.1 Hz, 1H, Ar**H**), 8.30 (d, J = 7.3 Hz, 1H, Ar**H**), 8.38 (d, J = 7.3 Hz, 1H, Ar**H**), 9.22 (s, 1H, Ar**H**).

To a solution of the above intermediate (0.500 g, 0.79 mmol) in CH_2Cl_2 (10 mL) was added dropwise trifluoroacetic acid (1.82 mL, 23.7 mmol). The solution was then stirred at room temperature for 6 h. After hydrolysis with 2 M NaOH, the expected amine was extracted with EtOAc. The organic phase was washed, dried ($MgSO_4$), and concentrated in vacuo. A purification on silica gel column (eluent: CH_2Cl_2/MeOH, 96/4) gave **2g** (0.412 g, 98%) as an oil: IR (film) ν 3320, 1340, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 1.48−1.72 (m, 2H, OCHC**H**$_2$), 2.48−2.65 (m, 2H, C**H**$_2$Ph), 2.66−2.72 (m, 2H, NC**H**$_2$), 2.73−2.80 (m, 2H, NC**H**$_2$), 3.19 (dd, J = 9.5, 14.0 Hz, 1H, NC**H**), 3.24−3.35 (m, 1H, OC**H**), 3.81 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 4.28 (dd, J = 2.2, 14.0 Hz, 1H, NC**H**), 6.61−6.78 (m, 5H, Ar**H**), 6.84−6.91 (m, 1H, Ar**H**), 6.99−7.05 (m, 1H, Ar**H**), 7.62 (dd, J = 7.3, 8.1 Hz, 1H, Ar**H**), 8.07 (d, J = 7.3 Hz, 1H, Ar**H**), 8.15 (d, J = 8.1 Hz, 1H, Ar**H**), 8.33 (d, J = 7.3 Hz, 1H, Ar**H**), 8.43 (d, J = 7.3 Hz, 1H, Ar**H**), 9.26 (s, 1H, Ar**H**); MS (CI/NH_3) m/z 534 ($M^+ + 1$). Anal. ($C_{29}H_{31}N_3O_5S$) C, H, N.

3,4-Dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-2*H*-1,4-benzoxazine (3a). The debenzylation of the amine **3c** (1.94 g, 4.35 mmol) was realized according to the procedure describing for **11a**. After purification by column chromatography (eluent: CH_2Cl_2/MeOH, 96/4), the compound **3a** (1.50 g, 97%) was isolated as an oil: IR (film) ν 3320 cm^{-1}; ^{1}H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 1.58−1.88 (m, 4H, OCHC**H**$_2$C**H**$_2$), 2.73 (t, J = 6.6 Hz, 2H, C**H**$_2$Ph), 2.78−2.84 (m, 2H, NC**H**$_2$), 2.87−2.94 (m, 2H, NC**H**$_2$), 3.11 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.34 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.67 (s, 3H, OC**H**$_3$), 3.86 (s, 3H, OC**H**$_3$), 4.03−4.11 (m, 1H, OC**H**), 6.56−6.83 (m, 7H, Ar**H**); MS (CI/NH_3) m/z 357 ($M^+ + 1$). Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

3,4-Dihydro-2-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzoxazine (3b). The compound **3b** was obtained applying the procedure used for the preparation of **11a** to the amine **3d** (1.30 g, 2.9 mmol). A purification of the residue on silica gel column (eluent: CH_2Cl_2/MeOH, 98/2) provided **3b** (0.958 g, 93%) as a solid: mp 109−110 °C; IR (KBr) ν 3280 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54−1.85 (m, 4H, C**H**$_2$), 2.43 (t, J = 7.3 Hz, 2H, NC**H**$_2$), 2.56−2.62 (m, 4H, NC**H**$_2$), 3.06−3.15 (m, 6H, NC**H**$_2$, NC**H**), 3.34 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.02−4.12 (m, 1H, OC**H**), 6.54−6.76 (m, 5H, Ar**H**), 6.81−6.95 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 356 ($M^+ + 1$). Anal. ($C_{21}H_{26}N_3FO$) C, H, N.

4-Benzyl-3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]amino]propyl]-2*H*-1,4-benzoxazine (3c). Reduction of the amide **18c** (2.02 g, 4.39 mmol) according to the general procedure reported above followed by purification on silica gel column (eluent: CH_2Cl_2/MeOH, 98/2) gave the pure amine **3c** (1.59 g, 81%) as an oil: IR (film) ν 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49−1.79 (m, 4H, OCHC**H**$_2$C**H**$_2$), 2.50 (s, 1H, N**H**), 2.66 (t, J = 6.6 Hz, 2H, C**H**$_2$Ph), 2.72−2.79 (m, 2H, NC**H**$_2$), 2.81−2.90 (m, 2H, NC**H**$_2$), 3.07 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.21 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.81 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 4.04−4.12 (m, 1H, OC**H**), 4.38 (s, 2H, NC**H**$_2$Ph), 6.55−6.64 (m, 3H, Ar**H**), 6.68−6.78 (m, 5H, Ar**H**), 7.20−7.30 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 447 ($M^+ + 1$). Anal. ($C_{28}H_{34}N_2O_3$) C, H, N.

4-Benzyl-3,4-dihydro-2-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzoxazine (3d). Reduction of the amide **18d** (1.85 g, 4.03 mmol) according to the general procedure followed by purification on silica gel column of the residue (eluent: CH_2Cl_2/MeOH, 98/2) provided the amine **3d** (1.51 g, 84%) as a solid: mp 107−108 °C; IR (KBr) ν 1600, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54−1.86 (m, 4H, C**H**$_2$), 2.44 (t, J = 7.3 Hz, 2H, NC**H**$_2$), 2.57−2.63 (m, 4H, NC**H**$_2$), 3.09−3.17 (m, 5H, NC**H**$_2$, NC**H**), 3.27 (dd, J = 2.2, 11.4 Hz, 1H, NC**H**), 4.11−4.21 (m, 1H, OC**H**), 4.43 (s, 2H, NC**H**$_2$Ph), 6.59−6.69 (m, 3H, Ar**H**), 6.74−7.00 (m, 6H, Ar**H**), 7.24−7.36 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 446 ($M^+ + 1$). Anal. ($C_{28}H_{32}N_3FO$) C, H, N.

4-Benzyl-3,4-dihydro-2-[3-[[2-[[bis(4-fluorophenyl)-methyl]oxy]ethyl]amino]propyl]-2*H*-1,4-benzoxazine (3e). The amine **3e** was obtained from the amide **18e** (1.13 g, 2.08 mmol) following the general procedure. Purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1) led to the pure amine **3e** (0.900 g, 82%) as an oil: IR (film) ν 3360 cm^{-1}; ^{1}H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 1.48−1.77 (m, 4H, OC**H**$_2$C**H**$_2$), 2.59−2.66 (m, 2H, NC**H**$_2$), 2.76−2.83 (m, 2H, NC**H**$_2$), 3.07 (dd,

J = 7.9, 11.6 Hz, 1H, NC**H**), 3.21 (dd, J = 3.0, 11.6 Hz, 1H, NC**H**), 3.51 (t, J = 5.5 Hz, 2H, OC**H$_2$**), 4.04−4.13 (m, 1H, OC**H**), 4.38 (s, 2H, NC**H$_2$**Ph), 5.28 (s, 1H, OC**H**), 6.55−6.65 (m, 5H, **ArH**), 6.70−6.80 (m, 4H, **ArH**), 6.91−7.00 (m, 4H, **ArH**), 7.17−7.31 (m, 4H, **ArH**); MS (CI/NH_3) m/z 529 (M^+ + 1). Anal. ($C_{33}H_{34}N_2F_2O_2$) C, H, N.

4-Benzoyl-3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]amino]propyl]-2*H*-1,4-benzoxazine (3f). The debenzylation of the compound **19** (0.319 g, 0.58 mmol) was performed according to the procedure describing for **11a**. After purification by column chromatography (eluent: CH_2Cl_2/MeOH, 99/1), 3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(*tert*-butoxycarbonyl)amino]propyl]-2*H*-1,4-benzoxazine (0.250 g, 94%) was isolated as an oil: IR (film) ν 3300, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.42 (s, 9H, C**H$_3$**), 1.45−1.87 (m, 4H, OCHC**H$_2$**C**H$_2$**), 2.65−2.81 (m, 2H, C**H$_2$**Ph), 3.07 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.08−3.22 (m, 2H, NC**H$_2$**), 3.30 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.31−3.40 (m, 2H, NC**H$_2$**), 3.81 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.98−4.08 (m, 1H, OC**H**), 6.52−6.78 (m, 7H, Ar**H**).

A solution of the above intermediate (0.280 g, 0.61 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. After addition of Et_3N (0.08 mL, 0.61 mmol) and benzoyl chloride (0.07 mL, 0.64 mmol), the reaction mixture was stirred at 0 °C for 1 h and then at room temperature for the same time. The solution was then hydrolyzed and the compound extracted with CH_2Cl_2. The organic phase was washed, dried ($MgSO_4$), and evaporated to dryness. The purification on silica gel column (eluent: petroleum ether/ether, 1/1) furnished 4-benzoyl-3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(*tert*-butoxycarbonyl)amino]propyl]-2*H*-1,4-benzoxazine (0.242 g, 70%) as an oil: IR (film) ν 1670, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H, C**H$_3$**), 1.46−1.80 (m, 4H, OCHC**H$_2$**C**H$_2$**), 2.64−2.80 (m, 2H, C**H$_2$**Ph), 3.05−3.23 (m, 2H, NC**H$_2$**), 3.25−3.40 (m, 2H, NC**H$_2$**), 3.40 (dd, J = 8.1, 13.2 Hz, 1H, NC**H**), 3.81 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 4.15−4.30 (m, 2H, OC**H**, NC**H**), 6.57−6.97 (m, 8H, Ar**H**), 7.28−7.50 (m, 4H, Ar**H**).

The removal of the BOC group of the above intermediate (0.319 g, 0.58 mmol) was performed according to the procedure describing for the preparation of **2g**. After purification by column chromatography (eluent: CH_2Cl_2/MeOH, 97/3), **3f** (0.690 g, 84%) was obtained as an oil: IR (film) ν 3400, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.55−1.78 (m, 4H, OCHC**H$_2$**C**H$_2$**), 2.66 (t, J = 6.6 Hz, 2H, C**H$_2$**Ph), 2.69−2.76 (m, 2H, NC**H$_2$**), 2.80−2.88 (m, 2H, NC**H$_2$**), 3.41 (dd, J = 8.1, 13.2 Hz, 1H, NC**H**), 3.81 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 4.17−4.30 (m, 2H, OC**H**, NC**H**), 6.55−6.62 (m, 1H, Ar**H**), 6.68−6.97 (m, 7H, Ar**H**), 7.28−7.48 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 461 (M^+ + 1). Anal. ($C_{28}H_{32}N_2O_4$) C, H, N.

4-Benzoyl-3,4-dihydro-2-[3-[(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzoxazine (3g). The benzoylation of **3b** (0.875 g, 2.45 mmol) was executed, applying the same procedure as the one reported in the preparation of **3f**. Purification on silica gel column (eluent: CH_2Cl_2/MeOH, 98/2) provided **3g** (0.740 g, 66%) as a solid: mp 136−137 °C; IR (KBr) ν 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60−1.84 (m, 4H, C**H$_2$**), 2.42 (t, J = 7.3 Hz, 2H, NC**H$_2$**), 2.53−2.60 (m, 4H, NC**H$_2$**), 3.04−3.12 (m, 4H, NC**H$_2$**), 3.48 (dd, J = 7.3, 12.5 Hz, 1H, NC**H**), 4.19−4.23 (m, 1H, NC**H**), 4.24−4.36 (m, 1H, OC**H**), 6.57−6.62 (m, 1H, Ar**H**), 6.79−6.96 (m, 8H, Ar**H**), 7.29−7.47 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 460 (M^+ + 1). Anal. ($C_{28}H_{30}N_3FO_2$) C, H, N.

4-Benzyl-3,4-dihydro-2-[4-[[2-(3,4-dimethoxyphenyl)-ethyl]amino]butyl]-2*H*-1,4-benzoxazine (4c). Reduction of the amide **22** (2.14 g, 4.51 mmol) according to the general procedure, followed by purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1), gave the pure amine **4c** (1.63 g, 79%) as an oil: IR (film) ν 3340 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.27−1.75 (m, 6H, C**H$_2$**), 2.58 (t, J = 6.6 Hz, 2H, C**H$_2$**Ph), 2.66−2.73 (m, 2H, NC**H$_2$**), 2.77−2.84 (m, 2H, NC**H$_2$**), 3.06 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.19 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.79 (s, 3H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 4.00−4.11 (m, 1H, OC**H**), 4.37 (s, 2H, NC**H$_2$**Ph), 6.51−6.80 (m, 8H, Ar**H**), 7.15−7.31 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 461 (M^+ + 1). Anal. ($C_{29}H_{36}N_2O_3$) C, H, N.

2,3,8,9-Tetrahydro-7-[3-[2-(3,4-dimethoxyphenyl)ethyl]-amino]propyl]-7*H*-[1,4]dioxino[2′,3′:4,5]benzo[*b*][1,4]-oxazin-8-one (5a). The debenzylation of the compound **5d** (0.589 g, 1.14 mmol) was performed according to the procedure describing for **11a**. After purification by column flash chromatography (eluent: CH_2Cl_2/MeOH, 85/15), the expected compound **5a** (0.363 g, 74%) was isolated as an oil: IR (film) ν 3420, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.68−2.05 (m, 4H, C**H$_2$**), 2.85−3.01 (m, 4H, NC**H$_2$**, C**H$_2$**Ph), 3.05−3.17 (m, 2H, NC**H$_2$**), 3.75 (s, 3H, OC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 4.13 (s, 4H, OC**H$_2$**), 4.23−4.39 (m, 1H, OC**H**), 6.40 (s, 1H, Ar**H**), 6.47 (s, 1H, Ar**H**), 6.61−6.80 (m, 3H, Ar**H**), 8.24 (s, 1H, N**H**); MS (CI/NH_3) m/z 429 (M^+ + 1). Anal. ($C_{23}H_{28}N_2O_6$) C, H, N.

General Procedure for the Preparation of Compounds 5b−d. To a solution of the derivative **27** (0.46 mmol) in CH_3CN (10 mL) were added diisopropylethylamine (0.69 mmol) and the appropriate amine (0.69 mmol). The reaction mixture was then heated to reflux overnight. The solvent was concentrated under reduced pressure and the residue quenched by a 10% $NaHCO_3$ solution. The compound was extracted with EtOAc, washed, dried ($MgSO_4$), and evaporated to dryness. The crude was then purified on silica gel column.

2,3,8,9-Tetrahydro-7-[3-[4-(*p*-fluorophenyl)-1-piperazinyl]propyl]-7*H*-[1,4]dioxino[2′,3′:4,5]benzo[*b*][1,4]oxazin-8-one (5b). The compound **5b** was synthesized according to the above general procedure using (4-fluorophenyl)piperazine (0.123 g, 0.69 mmol). Purification by column chromatography (eluent: ether) provided the desired compound **5b** (0.168 g, 86%) as a solid: mp 176−177 °C; IR (KBr) ν 3260, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63−1.95 (m, 4H, C**H$_2$**), 2.41 (t, J = 7.3 Hz, 2H, NC**H$_2$**), 2.53−2.59 (m, 4H, NC**H$_2$**), 3.04−3.10 (m, 4H, NC**H$_2$**), 4.17 (s, 4H, OC**H$_2$**), 4.44−4.50 (m, 1H, OC**H**), 6.29 (s, 1H, Ar**H**), 6.50 (s, 1H, Ar**H**), 6.79−6.95 (m, 4H, Ar**H**), 7.80 (s, 1H, N**H**); MS (CI/NH_3) m/z 428 (M^+ + 1). Anal. ($C_{23}H_{26}N_3FO_4$) C, H, N.

2,3,8,9-Tetrahydro-7-[3-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylamino]propyl]-7*H*-[1,4]dioxino[2′,3′:4,5]benzo-[*b*][1,4]oxazin-8-one (5c). Following the general procedure described above, the compound **5c** was prepared using *N*-methylhomoveratrylamine (0.730 g, 3.75 mmol). The residue was purified on silica gel column (eluent: CH_2Cl_2/MeOH, 97/3) and gave **5c** (0.933 g, 74%) as an oil: IR (film) ν 3280, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58−1.91 (m, 4H, C**H$_2$**), 2.27 (s, 3H, NC**H$_3$**), 2.44 (t, J = 7.3 Hz, 2H, **CH$_2$**Ph), 2.53−2.61 (m, 2H, NC**H$_2$**), 2.64−2.72 (m, 2H, NC**H$_2$**), 3.80 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 4.16 (s, 4H, OC**H$_2$**), 4.40−4.48 (m, 1H, OC**H**), 6.28 (s, 1H, Ar**H**), 6.48 (s, 1H, **H**), 6.64−6.77 (m, 3H, Ar**H**), 8.03 (s, 1H, N**H**); MS (CI/NH_3) m/z 443 (M^+ + 1). Anal. ($C_{24}H_{30}N_2O_6$) C, H, N.

2,3,8,9-Tetrahydro-7-[3-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-benzylamino]propyl]-7*H*-[1,4]dioxino[2′,3′:4,5]benzo-[*b*][1,4]oxazin-8-one (5d). The compound **5d** was synthesized according to the above general procedure using *N*-benzylhomoveratrylamine (0.186 g, 0.69 mmol). Purification by column chromatography (eluent: petroleum ether/EtOAc, 1/1) provided the desired compound **5d** (0.132 g, 56%) as an oil: IR (film) ν 3400, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52−1.86 (m, 4H, C**H$_2$**), 2.49 (t, J = 7.3 Hz, 2H, C**H$_2$**Ph), 2.58−2.67 (m, 4H, NC**H$_2$**), 3.53 (d, J = 14.0 Hz, 1H, NC**H**Ph), 3.59 (d, J = 14.0 Hz, 1H, NC**H**Ph), 3.76 (s, 3H, OC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 4.13 (s, 4H, OC**H$_2$**), 4.33−4.42 (m, 1H, OC**H**), 6.28 (s, 1H, Ar**H**), 6.44 (s, 1H, Ar**H**), 6.54−6.62 (m, 2H, Ar**H**), 6.67−6.73 (m, 2H, Ar**H**), 7.08−7.27 (m, 4H, Ar**H**), 8.31 (s, 1H, N**H**); MS (CI/NH_3) m/z 519 (M^+ + 1). Anal. ($C_{30}H_{34}N_2O_6$) C, H, N.

2-(Ethoxycarbonyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (6b). The ester **6a** (2.0 g, 9.6 mmol), anhydrous K_2CO_3 (2.60 g, 18.8 mmol), and dimethyl sulfate (1.2 mL) were added to distilled acetone (100 mL), and the mixture was refluxed for 48 h. Then, the suspension obtained was filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc, 7/3) to give **6b** (1.0 g, 47%, oil): IR (film) ν 1750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (m, 3H, CH_2CH_3), 2.86 (s, 3H, CH_3N), 3.41 (m, 2H, NCH_2), 4.24 (m, 2H, CH_2), 4.85 (m, 1H, OCH), 6.66 (m, 2H, ArH), 6.91 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 14.1 (CH_3), 38.5 (CH_3), 50.3 (CH_2), 61.4 (CH_2), 72.7 (C_2), 112.6 (C_5H), 115.9 (C_8H), 118.8 (C_7H), 121.7 (C_6H), 135.8 (C_{4a}), 143.2 (C_{8a}), 169.3 (CO). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

4-Benzyl-2-(ethoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine (6c). Anhydrous K_2CO_3 (11.0 g, 76.0 mmol) and benzyl bromide (4.5 mL, 38.0 mmol) were added to a solution of ester **6a** (4.0 g, 19.0 mmol) in distilled acetone (100 mL), and the mixture obtained was refluxed for 12 h; the suspension was filtered at room temperature and the solvent removed under vacuum. The crude product was subjected to silica gel column chromatography (eluent: hexane/EtOAc, 1/1) to give the compound **6c** as a colorless oil (4.0 g, 70%): IR (film) ν 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.52 (m, 2H, CH_2Ar), 4.14 (q, J = 7.0 Hz, 2H, CH_2-CH_3), 4.42 (m, 2H, NCH_2), 4.82 (t, J = 5.0 Hz, 1H, OCH), 6.76 (m, 4H, ArH), 7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 14.1 (CH_3), 48.5 (CH_2), 54.8 (CH_2), 61.6 (CH_2), 72.5 (C_2H), 112.8 (C_5H), 116.5 (C_8H), 118.7 (C_6H), 121.8 (C_7H), 127.1 ($C_{2'}H$, $C_{6'}H$), 127.2 ($C_{4'}H$), 128.6 ($C_{3'}H$, $C_{5'}H$), 134.7 (C_{4a}), 137.6 ($C_{1'}$), 142.9 (C_{8a}), 169.3 (COOEt). Anal. ($C_{18}H_{19}NO_3$) C, H, N.

4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic Acid (7b). The mixture of ester **6b** (1.0 g, 4.5 mmol) and KOH (5.60 g, 72.0 mmol), in a solution of ethanol/water (8/2) (100 mL), was stirred under reflux for 10 h.The mixture was acidified at room temperature with an aqueous solution of 3 N HCl and extracted with ether. The organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue obtained was recrystallized from hexane/EtOAc (1/1) to give a white amorphous solid identified as compound **7b** (0.750 g, 87%): ^{1}H NMR ($CDCl_3$ + D_2O, 200 MHz) δ 2.72 (s, 3H, CH_3N), 3.31 (d, J = 5.0 Hz, 2H, NCH_2), 4.81 (t, J = 5.0 Hz, 1H, OCH), 6.57 (t, J = 6.0 Hz, 2H, ArH), 6.75 (m, 2H, ArH). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic Acid (7c). A mixture of ester **6c** (1.0 g, 3.4 mmol) and an aqueous solution of 2 N NaOH (100 mL) was stirred under reflux for 2h. After the room temperature was recovered, the mixture was acidified with an aqueous solution of 2 N HCl and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the carboxylic acid **7c** as a amorphous solid (0.800 g, 88%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H, NCH_2Ar), 4.51 (m, 2H, C_3H), 4.96 (m, 1H, OCH), 6.80 (m, 3H, ArH), 7.01 (d, J = 8 Hz, 1H, ArH), 7.29 (m, 5H, ArH), 11.20 (br s, 1H, COOH). Anal. ($C_{16}H_{15}NO_3$) C, H, N.

2-[*N*-[2-(3,4-Dimethoxyphenyl)ethyl]carbamoyl]-3,4-dihydro-2*H*-1,4-benzoxazine (8a). The ester **6a** (4.0 g, 19.0 mmol) was added to a suspension of anhydrous K_2CO_3 (13.11 g, 95.0 mmol) in distilled toluene (100 mL), and the mixture was softly heated. Then, homoveratrylamine and a small amount of DCCI were added, and the suspension obtained was stirred at reflux temperature for 12 h. After the solvent was removed under vacuum, the residue was diluted with water and extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated to give the corresponding carboxamide **8a** (5.30 g, 80%) which was purified by silica gel column chromatography (eluent: hexane/EtOAc, 1/1). Anal. ($C_{19}H_{22}N_2O_4$) C, H, N.

General Procedure for the Preparation of the Carboxamides 8b−f. A solution of the corresponding carboxylic acid (1.0 mmol) and distilled triethylamine (1.0 mmol) in chloroform (20 mL) was cooled to 0 °C, and ethyl chloroformate (1.0 mmol) was slowly added. The solution was stirred for 5 min at 0 °C, and then the appropriate amine (1.0 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The chloroformic solution obtained was washed with an aqueous solution of 2 N HCl, then with an aqueous solution of 2 N NaOH, and finally with water. The organic layer was dried (Na_2SO_4) and filtered and the solvent removed under vacuum to give the corresponding carboxamides **8b−f**, which were purified by silica gel column chromatography (eluent: hexane/EtOAc, 1/1).

2-[*N*-[2-(3,4-Dimethoxyphenyl)ethyl]carbamoyl]-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (8b). Compound **8b** (0.300 g, 54%, oil) was synthesized following the general procedure for preparation of amides, taking as starting material the carboxylic acid **7b** (0.300 g, 1.6 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.72 (t, J = 6.0 Hz, 2H, CH_2Ar), 2.85 (s, 3H, CH_3N), 3.28 (dd, J = 7.0, 12.0 Hz, 1H, NCH), 3.48 (m, 3H, CH_2N, NCH), 3.83 (s, 6H, CH_3O), 4.70 (m, 1H, OCH), 6.68 (m, 6H, ArH), 6.89 (m, 1H, ArH). Anal. ($C_{20}H_{24}N_2O_4$) C, H, N.

3,4-Dihydro-2*H*-1,4-benzoxazine-2-carboxamide (8g). The ester **6a** (0.993 g, 4.8 mmol) was added to an aqueous solution of NH_3 (30 mL, 25% weight) and heated under reflux for 12 h. After the room temperature was recovered, the mixture was extracted with ether, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The high polarity of the residue obtained did not allow us to obtain the carboxamide pure: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.45 (dd, J = 7.0, 12.0 Hz, 1H, C_3H), 3.66 (dd, J = 3.0, 12.0 Hz, 1H, C_3H), 4.62 (m, 1H, C_2H), 6.33 (br s, 2H, NH_2), 6.72 (m, 4H, ArH). Anal. ($C_9H_{10}N_2O_2$) C, H, N.

2-(*N*-Methylcarbamoyl)-3,4-dihydro-2*H*-1,4-benzoxazine (8h). Aqueous methylamine (11 mL, 144.0 mmol, 40% weight) was added to a solution of ester **6a** (2.0 g, 9.6 mmol) in 20 mL of toluene. After the reaction mixture was stirred at 40 °C for 18 h, the solvent and the excess of methylamine were removed under vacuum. The complexity of the crude mixture did not allow us to obtain the pure carboxamide: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.72 (br s, 1H, NH), 2.87 and 2.90 (s, 3H, CH_3), 3.44 (dd, J = 6.0, 13.0 Hz, 1H, C_3H), 3.69 (m, 1H, C_3H), 3.85 (br s, 1H, NH), 4.63 (m, 1H, C_2H), 6.73 (m, 4H, ArH). Anal. ($C_{10}H_{12}N_2O_2$) C, H, N.

4-Benzyl-2-carbamoyl-3,4-dihydro-2*H*-1,4-benzoxazine (8i). Compound **6c** (1.23 g, 4.1 mmol) was slowly added to an aqueous solution of NH_4OH (100 mL, 28% weight), and the mixture obtained was stirred under reflux for 10 h. Next, the residue was extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: hexane/EtOAc, 1/1) to give the carboxamide **8i** (0.480 g, 46%) as white crystals: mp 132−133 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.48 (dd, J = 7.0, 12.0 Hz, 1H, NCH_2), 3.60 (dd, J = 3.0, 12.0 Hz, 1H, NCH_2), 4.50 (s, 2H, CH_2Ar), 4.70 (m, 1H, OCH), 5.98 (br s, 1H, NH), 6.53 (br s, 1H, NH), 6.69 (m, 2H, ArH), 6.88 (m, 2H, ArH), 7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 48.6 (CH_2), 55.2 (CH_2), 73.7 (C_2H), 113.2 (C_5H), 116.3 (C_8H), 118.3 (C_6H), 122.5 (C_7H), 127.1 ($C_{2'}H$, $C_{6'}H$), 127.2 ($C_{4'}H$), 128.7 ($C_{3'}H$, $C_{5'}H$), 135.0 (C_{4a}), 137.5 ($C_{1'}$), 142.1 (C_{8a}), 171.8 (CON). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

2-(Aminomethyl)-3,4-dihydro-2*H*-1,4-benzoxazine (9g). A solution of the compound **8g** in anhydrous THF was added to a suspension of $LiAlH_4$ (0.364 g, 9.6 mmol) in anhydrous THF and stirred at 45 °C for 36 h. Next, the solvent was removed and the residue diluted with water and extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude obtained was purified by silica gel column chromatography using EtOAc/MeOH (9/1) as an eluent to give **9g** (0.534 g, 68% global yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 (br s, 2H, NH_2), 2.86 (m, 2H, CH_2N), 3.09 (dd, J = 7.0, 12.0 Hz, 1H, NCH), 3.25 (dd, J = 2.0, 12.0 Hz, 1H, NCH), 4.02 (m, 1H, OCH), 6.62 (m, 4H, ArH). Anal. ($C_9H_{12}N_2O$) C, H, N.

2-[(*N*-Methylamino)methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (9h). The residue obtained in the previous reaction, containing the carboxamide **8h**, was added to a suspension of $LiAlH_4$ (1.82 g, 48.0 mmol) in 50 mL of anhydrous THF and stirred under reflux for 36 h. After hydrolysis of $LiAlH_4$ by adding small amounts of water, the suspension was filtered and the THF removed. The residue was diluted with water and extracted with ether. The organic layers were dried (Na_2-

SO_4), filtered, and concentrated. The product obtained was purified by silica gel column chromatography (eluent: EtOAc/MeOH, 9/1) to give **9h** (0.950 g, 56% global yield) as a yellow oil: ^{1}H NMR ($CDCl_3$ + D_2O, 200 MHz) δ 2.45 (s, 3H, C**H$_3$**N), 2.76 (dd, J = 4.0, 12.0 Hz, 1H, C**H$_2$**N), 2.82 (dd, J = 7.0, 12.0 Hz, C**H$_2$**N), 3.11 (dd, J = 7.0, 12.0 Hz, 1H, C**H$_2$N**), 3.5 (dd, J = 2.0, 12.0 Hz, C**H$_2$N**), 4.21 (m, 1H, OC**H**), 6.64 (m, 4H, Ar**H**); ^{13}C NMR ($CDCl_3$, 50.4 MHz) δ 36.5 (CH_3), 43.6 (CH_2), 53.8 (CH_2), 73.0 (C_2H), 115.3 (C_5H), 116.7 (C_8H), 118.5 (C_7H), 121.2 (C_6H), 133.2 (C_{4a}), 143.2 (C_{8a}). Anal. ($C_{10}H_{14}N_2O$) C, H, N.

4-Benzyl-2-(aminomethyl)-3,4-dihydro-2*H*-1,4-benzoxazine (9i). The carboxamide **8i** (0.480 g, 1.8 mmol) was slowly added to a suspension of $LiAlH_4$ (0.068 g, 1.8 mmol) in anhydrous THF (25 mL), and the reaction mixture was stirred at 45 °C for 24 h. After hydrolysis of $LiAlH_4$ with small amounts of water, the suspension was filtered and the THF removed. The residue was diluted with water and extracted with ether. The organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product obtained was subjected to silica gel column chromatography (eluent: hexane/EtOAc, 1/1) to give an unstable oil containing the primary amine **9i** and other byproducts that did not allow us to calculate the yield of this reaction: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.80 (br s, 2H, N**H$_2$**), 2.93 (m, 2H, C**H$_2$**N), 3.24 (m, 2H, C_3**H**), 4.15 (m, 1H, C_2**H**), 4.43 (s, 2H, NC**H$_2$**Ar), 6.75 (m, 4H, Ar**H**), 7.30 (m, 5H, Ar**H**). Anal. ($C_{16}H_{18}N_2O$) C, H, N.

3,4-Dihydro-2*H*-1,4-benzoxazine-2-acetic Acid, Ethyl Ester (11a).[48] Compound **11c** (0.250 g, 0.8 mmol) was dissolved in glacial acetic acid (5 mL). Palladium on carbon (10%) (0.037 g, 15% weight) was added, and the mixture was hydrogenated at balloon pressure at 40 °C for 8 h. The catalyst was removed and the acetic acid evaporated under reduced pressure. The remaining residue was hydrolyzed with 10% NaOH and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The compound **11a** was purified by filtration on silica gel (eluent: CH_2Cl_2) and obtained as an oil (0.136 g, 77%): IR (film) ν 3420, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.3 Hz, 3H, C**H$_3$**), 2.60 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 2.76 (dd, J = 5.9, 15.4 Hz, 1H, C**H**CO), 3.18 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.46 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.71 (s, 1H, N**H**), 4.18 (q, J = 7.3 Hz, 2H, OC**H$_2$**), 4.51−4.61 (m, 1H, OC**H**), 6.54−6.79 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 222 (M^+ + 1). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

3,4-Dihydro-4-methyl-2*H*-1,4-benzoxazine-2-acetic Acid, Ethyl Ester (11b).[48] Compound **11a** (2.40 g, 10.9 mmol) was dissolved in dry acetone (30 mL). K_2CO_3 (4.50 g, 32.6 mmol) and iodomethane (4.10 mL, 65.0 mmol) were then added. The reaction mixture was warmed to reflux and stirred at this temperature overnight. The solvent was evaporated, the residue hydrolyzed, and the product extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude residue was purified by silica gel column flash chromatography (eluent: CH_2Cl_2) to give the product **11b** (1.78 g, 70%) as an oil: IR (film) ν 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.3 Hz, 3H, C**H$_3$**), 2.56 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 2.72 (dd, J = 6.1, 15.4 Hz, 1H, C**H**CO), 2.80 (s, 3H, NC**H$_3$**), 3.00 (dd, J = 6.6, 11.8 Hz, 1H, NC**H**), 3.27 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.14 (q, J = 7.3 Hz, 2H, OC**H$_2$**), 4.57−4.67 (m, 1H, OC**H**), 6.56−6.64 (m, 2H, Ar**H**), 6.69−6.84 (m, 2H, Ar**H**). Anal. ($C_{13}H_{17}NO_3$) C, H, N.

General Procedure for the Preparation of the Esters 11c,d. To a solution of the appropriate aminophenol (9.0 mmol) in absolute EtOH (20 mL) were added $NaHCO_3$ (11.0 mmol) and ethyl 4-bromocrotonate (10.0 mmol), and the mixture was stirred at room temperature for 8 h. It was then evaporated to dryness, and the residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was then dissolved in absolute EtOH (25 mL) and stirred at room temperature for 1 h with K_2CO_3 (9.0 mmol). The same treatment was realized once more, and the residue was then purified on silica gel column.

4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-acetic Acid, Ethyl Ester (11c).[48] The ester **11c** was prepared from 2-(benzylamino)phenol (1.79 g, 9.0 mmol) (resulting from reductive amination of benzaldehyde by 2-aminophenol in the presence of $NaBH_4$) according to the general procedure described above. The pure product **11c** was obtained after purification on silica gel column (eluent: petroleum ether/CH_2Cl_2, 3/7) as an oil (2.66 g, 95%): IR (film) ν 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.3 Hz, 3H, C**H$_3$**), 2.58 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 2.78 (dd, J = 6.3, 15.4 Hz, 1H, C**H**CO), 3.16 (dd, J = 6.6, 11.8 Hz, 1H, NC**H**), 3.37 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 4.15 (q, J = 7.3 Hz, 2H, OC**H$_2$**), 4.38 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.47 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.58−4.68 (m, 1H, OC**H**), 6.58−6.84 (m, 4H, Ar**H**), 7.20−7.39 (m, 5H, Ar**H**). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

3,4-Dihydro-4-[(3,4-dimethoxyphenyl)methyl]-2*H*-1,4-benzoxazine-2-acetic Acid, Ethyl Ester (11d). The compound **11d** was obtained from 2-[(3,4-dimethoxyphenyl)methyl]-aminophenol (3.0 g, 11.0 mmol) (resulting from reductive amination of 3,4-dimethoxybenzaldehyde by 2-aminophenol in the presence of $NaBH_4$) via the general procedure described above. Purification on silica gel column (eluent: CH_2Cl_2) gave the desired ester **11d** (3.46 g, 85%) as an oil: IR (film) ν 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, J = 7.3 Hz, 3H, C**H$_3$**), 2.53 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 2.71 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 3.04 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.29 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.78 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 4.09 (q, J = 7.3 Hz, 2H, OC**H$_2$**), 4.26 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.33 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.52−4.60 (m, 1H, OC**H**), 6.55−6.83 (m, 7H, Ar**H**). Anal. ($C_{21}H_{25}NO_5$) C, H, N.

3,4-Dihydro-4-(1-naphthalenesulfonyl)-2*H*-1,4-benzoxazine-2-acetic Acid, Ethyl Ester (11e). A mixture of **11a** (2.0 g, 9.05 mmol), Et_3N (1.50 mL, 10.86 mmol), and 1-naphthalenesulfonyl chloride (2.87 g, 12.67 mmol) in dry toluene (25 mL) was warmed to reflux and stirred for 4 h. After removal of the solvent, the residue was hydrolyzed, and the *N*-sulfonylated product was extracted with CH_2Cl_2. The organic phase was then dried ($MgSO_4$) and concentrated in vacuo. A purification on silica gel column (eluent: petroleum ether/CH_2Cl_2, 3/7) provided the desired compound **11e** (2.45 g, 66%) as a yellow solid: mp 82−84 °C; IR (KBr) ν 1720, 1350, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, J = 7.3 Hz, 3H, C**H$_3$**), 2.39 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.53 (dd, J = 5.9, 15.4 Hz, 1H, C**H**CO), 3.26 (dd, J = 9.5, 14.0 Hz, 1H, NC**H**), 3.69−3.79 (m, 1H, OC**H**), 4.08 (q, J = 7.3 Hz, 2H, OC**H$_2$**), 4.34 (dd, J = 2.9, 14.0 Hz, 1H, NC**H**), 6.67 (dd, J = 1.5, 8.1 Hz, 1H, Ar**H**), 6.80−6.87 (m, 1H, Ar**H**), 6.94−7.00 (m, 1H, Ar**H**), 7.34−7.51 (m, 3H, Ar**H**), 7.59 (d, J = 8.1 Hz, 1H, Ar**H**), 7.83 (d, J = 8.1 Hz, 1H, Ar**H**), 8.01 (d, J = 8.1 Hz, 1H, Ar**H**), 8.21 (d, J = 7.3 Hz, 1H, Ar**H**), 8.28 (d, J = 8.8 Hz, 1H, Ar**H**). Anal. ($C_{22}H_{21}NO_5S$) C, H, N.

General Procedure for the Preparation of the Carboxylic Acids 12b−e. A solution of the appropriate ester (3.2 mmol) in EtOH (20 mL) was treated with KOH (4.2 mmol) and stirred at room temperature overnight. Ethanol was then evaporated, and the crude product was hydrolyzed and extracted with EtOAc. The aqueous phase was then acidified (pH 3) with 2 M HCl, and the acid was also extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The desired acid was used without further purification.

2-(3,4-Dihydro-4-methyl-2*H*-1,4-benzoxazin-2-yl)acetic Acid (12b). Following the general procedure described above the ester **11b** (0.130 g, 0.6 mmol) was saponified into the acid **12b** (0.080 g, 70%) as a solid: mp 114−115 °C; IR (KBr) ν 3400−3100, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 2.64 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 2.78 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 2.83 (s, 3H, NC**H$_3$**), 3.02 (dd, J = 6.6, 11.8 Hz, 1H, NC**H**), 3.20 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.58−4.67 (m, 1H, OC**H**), 6.57−6.83 (m, 4H, Ar**H**). Anal. ($C_{11}H_{13}NO_3$) C, H, N.

2-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetic Acid (12c). By applying the general procedure, acid **12c**

(0.771 g, 85%) was obtained from ester **11c** (1.0 g, 3.21 mmol) as a solid: mp 158−159 °C; IR (KBr) ν 3200 (large), 1700 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 2.66 (dd, J = 5.9, 16.2 Hz, 1H, C**H**CO), 2.84 (dd, J = 7.3, 16.2 Hz, 1H, C**H**CO), 3.19 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.39 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.41 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.47 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.60−4.71 (m, 1H, OC**H**), 6.61−6.87 (m, 4H, Ar**H**), 7.24−7.38 (m, 5H, Ar**H**). Anal. ($C_{17}H_{17}NO_3$) C, H, N.

2-[3,4-Dihydro-4-[(3,4-dimethoxyphenyl)methyl]-2*H*-1,4-benzoxazin-2-yl]acetic Acid (12d). In a manner similar to the general procedure described above, the ester **11d** (3.46 g, 9.3 mmol) was converted into the acid **12d** (2.16 g, 68%), obtained as a solid: mp 150−151 °C; IR (KBr) ν 3200 (large), 1690 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 2.61 (dd, J = 6.6, 16.2 Hz, 1H, C**H**CO), 2.77 (dd, J = 6.6, 16.2 Hz, 1H, C**H**CO), 3.06 (dd, J = 6.6, 11.8 Hz, 1H, NC**H**), 3.29 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.78 (s, 3H, OC**H$_3$**), 3.79 (s, 3H, OC**H$_3$**), 4.28 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.35 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.53−4.62 (m, 1H, OC**H**), 6.57−6.80 (m, 7H, Ar**H**). Anal. ($C_{19}H_{21}NO_5$) C, H, N.

2-[3,4-Dihydro-4-(1-naphthalenesulfonyl)-2*H*-1,4-benzoxazin-2-yl]acetic Acid (12e). Following the general procedure applied to the ester **11e** (0.500 g, 1.2 mmol), the acid **12e** was formed, but contaminated with the product resulting from the heterocycle opening. Flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH, 93/7) led to the pure acid (0.221 g, 48%) as a solid: mp 78−79 °C; IR (KBr) ν 3380, 1700, 1330, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (dd, J = 7.3, 16.9 Hz, 1H, C**H**CO), 2.60 (dd, J = 5.1, 16.9 Hz, 1H, C**H**CO), 3.26 (dd, J = 9.5, 14.0 Hz, 1H, NC**H**), 3.63−3.75 (m, 1H, OC**H**), 4.33 (dd, J = 2.9, 14.0 Hz, 1H, NC**H**), 6.69 (d, J = 8.1 Hz, 1H, Ar**H**), 6.84−7.02 (m, 2H, Ar**H**), 7.32−7.49 (m, 3H, Ar**H**), 7.63 (d, J = 8.1 Hz, 1H, Ar**H**), 7.83 (d, J = 8.1 Hz, 1H, Ar**H**), 7.97−8.03 (m, 1H, Ar**H**), 8.20 (d, J = 7.3 Hz, 1H, Ar**H**), 8.27 (d, J = 8.8 Hz, 1H, Ar**H**). Anal. ($C_{20}H_{17}NO_5S$) C, H, N.

General Procedure for the Preparation of the Amides 13b−f, 18c−e, and 22. The appropriate acid (7.38 mmol) was dissolved in CH_2Cl_2 (25 mL). EDCI (7.38 mmol) and the appropriate amine (8.11 mmol) were added, and the reaction mixture was then stirred at room temperature for 5 h. After hydrolysis, the amide was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography on silica gel to obtain the pure amides.

2-(3,4-Dihydro-4-methyl-2*H*-1,4-benzoxazin-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (13b). Following the general procedure described above, the amide **13b** (0.088 g, 70%) was obtained from the acid **12b** (0.071 g, 0.3 mmol) and homoveratrylamine (0.1 mL, 0.6 mmol) as a solid, after purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1): mp 90−91 °C; IR (KBr) ν 3310, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.48 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.70 (t, J = 6.6 Hz, 2H, C**H$_2$**Ph), 2.75 (s, 3H, NC**H$_3$**), 2.91 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.15 (dd. J = 2.2, 11.8 Hz, 1H, NC**H**), 3.42−3.47 (m, 2H, NC**H$_2$**), 3.75 (s, 6H, OC**H$_3$**), 4.42−4.52 (m, 1H, OC**H**), 6.10 (s, 1H, N**H**), 6.54−6.82 (m, 7H, Ar**H**). Anal. ($C_{21}H_{26}N_2O_4$) C, H, N.

2-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (13c). By applying the general procedure to the acid **12c** (2.09 g, 7.38 mmol) and homoveratrylamine (1.37 mL, 8.11 mmol), the amide **13c** (2.25 g, 68%) was isolated as an oil, after purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1): IR (film) ν 3220, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (dd, J = 4.4, 15.4 Hz, 1H, C**H**CO), 2.53 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.73 (t, J = 7.3 Hz, 2H, C**H$_2$**Ph), 3.08 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.28 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.47−3.52 (m, 2H, NC**H$_2$**), 3.79 (s, 3H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 4.34 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.41 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.45−4.53 (m, 1H, OC**H**), 5.99 (s, 1H, N**H**), 6.55−6.80 (m, 8H, Ar**H**), 7.16−7.32 (m, 4H, Ar**H**). Anal. ($C_{27}H_{30}N_2O_4$) C, H, N.

2-[3,4-Dihydro-4-[(3,4-dimethoxyphenyl)methyl]-2*H*-1,4-benzoxazin-2-yl]-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (13d). Following the general procedure described above, the amide **13d** (0.115 g, 78%) was obtained from the acid **12d** (0.100 g, 0.29 mmol) and homoveratrylamine (0.05 mL, 0.32 mmol) as an oil, after purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1): IR (film) ν 3380, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (dd, J = 4.4, 15.4 Hz, 1H, C**H**CO), 2.47 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.69 (t, J = 7.3 Hz, 2H, C**H$_2$**Ph), 3.00 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.22 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.41−3.51 (m, 2H, NC**H$_2$**), 3.76 (s, 3H, OC**H$_3$**), 3.77 (s, 6H, OC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 4.27 (s, 2H, NC**H$_2$**Ph), 4.38−4.49 (m, 1H, OC**H**), 5.99 (s, 1H, N**H**), 6.54−6.78 (m, 10H, Ar**H**). Anal. ($C_{29}H_{34}N_2O_6$) C, H, N.

2-[3,4-Dihydro-4-(1-naphthalenesulfonyl)-2*H*-1,4-benzoxazin-2-yl]-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (13e). By applying the general procedure to the acid **12e** (1.20 g, 1.56 mmol) with homoveratrylamine (0.58 mL, 1.72 mmol), the amide **13e** (0.975 g, 57%) was isolated as an oil, after purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1): IR (film) ν 3320, 1640, 1350, 1160 cm^{-1}; H NMR ($CDCl_3$, 300 MHz) δ 2.34 (d, J = 6.6 Hz, 2H, C**H$_2$**CO), 2.66 (td, J = 2.9, 7.3 Hz, 2H, C**H$_2$**Ph), 3.36 (dd, J = 8.8, 14.0 Hz, 1H, NC**H**), 3.40−3.46 (m, 2H, NC**H$_2$**), 3.76 (s, 6H, OC**H$_3$**), 3.83−3.95 (m, 1H, OC**H**), 4.20 (dd, J = 2.9, 14.0 Hz, 1H, NC**H**), 5.62 (s, 1H, N**H**), 6.53−6.66 (m, 3H, Ar**H**), 6.79−6.86 (m, 1H, Ar**H**), 6.92−6.99 (m, 1H, Ar**H**), 7.40−7.52 (m, 5H, Ar**H**), 7.84 (d, J = 7.3 Hz, 1H, Ar**H**), 8.02 (d, J = 8.1 Hz, 1H, Ar**H**), 8.17 (d, J = 7.3 Hz, 1H, Ar**H**), 8.34 (d, J = 8.1 Hz, 1H. Ar**H**). Anal. ($C_{30}H_{30}N_2O_6S$) C, H, N.

2-(4-Benzyl-3.4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylacetamide (13f). Following the general procedure applied to the acid **12c** (1.60 g, 5.65 mmol) and *N*-methylhomoveratrylamine (1.20 g, 6.21 mmol), the amide **13f** (2.22 g, 86%) was obtained as an oil, after purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1): IR (film) ν 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.61 (dd, J = 5.1, 15.4 Hz, 1H, C**H**CO), 2.72 (t, J = 7.3 Hz, 2H, C**H$_2$**Ph), 2.90 (s, 3H, NC**H$_3$**), 3.13 (dd, J = 6.6, 11.8 Hz, 1H, NC**H**), 3.38 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.40−3.49 (m, 2H, NC**H$_2$**), 3.77 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 4.33 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.44 (d, J = 16.2 Hz, 1H, NC**H**Ph), 4.52−4.61 (m, 1H, OC**H**), 6.51−6.77 (m, 8H, Ar**H**), 7.14−7.29 (m, 4H, Ar**H**); MS (CI/NH_3) m/z 461 ($M^+ + 1$). Anal. ($C_{28}H_{32}N_2O_4$) C, H, N.

4-Benzyl-3,4-dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-(*tert*-butoxycarbonyl)amino]ethyl]-2*H*-1,4-benzoxazine (14). To an ice-cooled solution of di-*tert*-butyl dicarbonate (3.65 g, 16.7 mmol) in CH_2Cl_2 (20 mL) was added a solution of **2c** (4.82 g, 11.1 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at 0 °C for 3 h and then concentrated in vacuo. The residue was purified on silica gel column (eluent: CH_2Cl_2) to give **14** (5.54 g, 97%) as an oil: IR (film) ν 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 9H, C**H$_3$**), 1.63−1.84 (m, 2H, OCHC**H$_2$**), 2.65−2.78 (m, 2H, C**H$_2$**Ph), 3.00−3.13 (m, 1H, NC**H**), 3.14−3.46 (m, 5H, NC**H$_2$**, NC**H**), 3.79 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 4.02−4.13 (m, 1H, OC**H**), 4.37 (s, 2H, NC**H$_2$**Ph), 6.52−6.77 (m, 8H, Ar**H**), 7.17−7.29 (m, 4H, Ar**H**). Anal. ($C_{32}H_{40}N_2O_5$) C, H, N.

3,4-Dihydro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(*tert*-butoxycarbonyl)amino]ethyl]-2*H*-1,4-benzoxazine (15). 15 was prepared from **14**, in a manner similar to that of **11a**, using palladium on carbon in glacial acetic acid. The residue was then purified by filtration on silica gel (eluent: CH_2Cl_2/MeOH, 99/1) and obtained as an oil in 95% yield: IR (film) ν 3360, 1670 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$, 300 MHz) δ 1.39 (s, 9H, C**H$_3$**), 1.69−1.90 (m, 2H, OCHC**H$_2$**), 2.66−2.79 (m, 2H, C**H$_2$**Ph), 3.06 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.17−3.47 (m, 5H, NC**H$_2$**, NC**H**), 3.79 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 3.96−4.06 (m, 1H, OC**H**), 6.50−6.77 (m, 7H, Ar**H**). Anal. ($C_{25}H_{34}N_2O_5$) C, H, N.

4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carbaldehyde (16). 16 was prepared from **6c** according our described procedure.[45]

3-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)propanoic Acid (17). To a solution of **16** (4.0 g, 20.0 mmol) in dry toluene (50 mL) was added (carbethoxymethylene)triphenylphosphorane (8.25 g, 20.0 mmol), and the reaction mixture was heated to reflux for 2 h. After removal of the toluene in vacuo, the residue was purified on silica gel column (eluent: CH_2Cl_2) to give 4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-acrylic acid, ethyl ester (4.0 g, 77%) as an oil (mixture of *(E)* and *(Z)* isomers 1/2): *(Z) isomer:* IR (film) ν 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.2 Hz, 3H, C**H**$_3$), 3.25 (dd, J = 6.2, 11.9 Hz, 1H, NC**H**), 3.51 (dd, J = 3.1, 11.9 Hz, 1H, NC**H**), 4.15 (q, J = 7.2 Hz, 2H, OC**H**$_2$), 4.38 (d, J = 16.5 Hz, 1H, NC**H**Ph), 4.50 (d, J = 16.5 Hz, 1H, NC**H**Ph), 5.53−5.55 (m, 1H, OC**H**), 5.89 (dd, J = 1.5, 11.9 Hz, 1H, =C**H**), 6.34 (dd, J = 7.2, 11.9 Hz, 1H, =C**H**), 6.62−6.70 (m, 3H, Ar**H**), 6.76−6.87 (m, 2H, Ar**H**), 7.20−7.33 (m, 4H, Ar**H**). *(E) isomer*: IR (film) ν 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 3H, C**H**$_3$), 3.13 (dd, J = 7.2, 11.9 Hz, 1H, NC**H**), 3.35 (dd, J = 2.6, 11.9 Hz, 1H, NC**H**), 4.19 (q, J = 7.2 Hz, 2H, OC**H**$_2$), 4.42 (s, 2H, NC**H**$_2$Ph), 4.77−4.83 (m, 1H, OC**H**), 6.17 (dd, J = 1.5, 15.5 Hz, 1H, =C**H**), 6.62−6.72 (m, 3H, Ar**H**), 6.78−6.86 (m, 2H, Ar**H**), 6.92 (dd, J = 4.7, 15.5 Hz, 1H, =C**H**), 7.26−7.35 (m, 4H, Ar**H**). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

This mixture of *(E)* and *(Z)* isomers (0.250 g, 0.77 mmol) was hydrogenated in the presence of Raney nickel (0.135 g, suspension in water) in absolute EtOH (10 mL), under hydrogen pressure (50 psi) at 20 °C. After 4 h, catalyst nickel was removed by filtration and washed with EtOH and EtOAc. The solvents were evaporated to dryness, and the residue was purified on silica gel (eluent: CH_2Cl_2) to give 3-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)propionoic acid, ethyl ester (0.230 g, 92%) as an oil: IR (film) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.85−1.95 (m, 2H, C**H**$_2$), 2.43 (dd, J = 7.3, 15.4 Hz, 1H, C**H**CO), 2.53 (dd, J = 6.6, 15.4 Hz, 1H, C**H**CO), 3.08 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.22 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 4.08 (q, J = 7.3 Hz, 2H, OC**H**$_2$), 4.11−4.17 (m, 1H, OC**H**), 4.37 (s, 2H, NC**H**$_2$Ph), 6.55−6.62 (m, 3H, Ar**H**), 6.69−6.77 (m, 2H, Ar**H**), 7.17−7.29 (m, 4H, Ar**H**). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

The 3-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)propanoic acid, ethyl ester (2.80 g, 8.64 mmol) was dissolved in EtOH (30 mL). After addition of KOH (0.532 g, 9.5 mmol), the mixture was heated to reflux overnight. The alcohol was evaporated to dryness and the residue hydrolyzed. After extraction with EtOAc, the aqueous phase was acidified (pH 3) with 2 M HCl. The acid was then extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo. **17** was obtained as a solid (2.52 g, 98%) and used in next step without further purification: mp 102−103 °C; IR (KBr) ν 3100 (large), 1700 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.87−2.00 (m, 2H, C**H**$_2$), 2.49−2.69 (m, 2H, C**H**$_2$CO), 3.10 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.25 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.12−4.22 (m, 1H, OC**H**), 4.40 (s, 2H, NC**H**$_2$Ph), 6.58−6.68 (m, 3H, Ar**H**), 6.71−6.80 (m, 2H, Ar**H**), 7.22−7.31 (m, 4H, Ar**H**). Anal. ($C_{18}H_{19}NO_3$) C, H, N.

3-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (18c). By applying the general procedure to acid **17** (0.945 g, 3.18 mmol) with homoveratrylamine (0.91 mL, 5.4 mmol), the amide **18c** (1.22 g, 83%) was obtained as a solid, after purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1): mp 134−135 °C; IR (KBr) ν 3230, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.79−2.03 (m, 2H, C**H**$_2$CH$_2$CO), 2.24−2.42 (m, 2H, C**H**$_2$CO), 2.72 (t, J = 7.0 Hz, 2H, C**H**$_2$Ph), 3.08 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.24 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.42−3.51 (m, 2H, NC**H**$_2$), 3.79 (s, 3H, OC**H**$_3$), 3.83 (s, 3H, OC**H**$_3$), 4.04−4.15 (m, 1H, OC**H**), 4.39 (s, 2H, NC**H**$_2$Ph), 5.55 (s, 1H, N**H**), 6.55−6.68 (m, 8H, Ar**H**), 7.18−7.32 (m, 4H, Ar**H**). Anal. ($C_{28}H_{32}N_2O_4$) C, H, N.

3-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[4-(4-fluorophenyl)-1-piperazinyl]propanamide (18d). The amide **18d** was obtained using (4-fluorophenyl)piperazine (2.50 g, 12.0 mmol) with the acid **17** (3.70 g, 12.0 mmol), as reported in general procedure. Purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1) led to **18d** (5.37 g, 97%) as an oil: IR (film) ν 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.88−2.11 (m, 2H, C**H**$_2$), 2.58 (t, J = 7.3 Hz, 2H, C**H**$_2$CO), 3.00−3.06 (m, 4H, NC**H**$_2$), 3.16 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.28 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.61−3.65 (m, 2H, NC**H**$_2$), 3.71−3.78 (m, 2H, NC**H**$_2$), 4.13−4.22 (m, 1H, OC**H**), 4.40 (s, 2H, NC**H**$_2$-Ph), 6.55−6.65 (m, 3H, Ar**H**), 6.71−6.85 (m, 4H, Ar**H**), 6.90−6.97 (m, 2H, Ar**H**), 7.21−7.30 (m, 4H, Ar**H**); MS (CI/NH_3) *m/z* 460 (M^+ + 1). Anal. ($C_{28}H_{30}N_3FO_2$) C, H, N.

3-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[2-[[bis(4-fluorophenyl)methyl]oxy]ethyl]propanamide (18e). The amide **18e** was prepared from acid **17** (0.915 g, 3.08 mmol) and 2-[[bis(4-fluorophenyl)methyl]oxy]ethylamine (0.910 g, 3.08 mmol). Purification on silica gel column (eluent: CH_2Cl_2) gave the amide **18e** (1.41 g, 84%) as a solid: mp 108−109 °C; IR (KBr) ν 3300, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.77−2.01 (m, 2H, C**H**$_2$CH$_2$CO), 2.29−2.41 (m, 2H, C**H**$_2$CO), 3.06 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.22 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 3.42−3.49 (m, 4H, NC**H**$_2$, OC**H**$_2$), 4.06−4.16 (m, 1H, OC**H**), 4.37 (s, 2H, NC**H**$_2$Ph), 5.26 (s, 1H, OC**H**), 5.86 (s, 1H, N**H**), 6.54−6.65 (m, 5H, Ar**H**), 6.70−6.78 (m, 4H, Ar**H**), 6.91−7.00 (m, 4H, Ar**H**), 7.16−7.31 (m, 4H, Ar**H**). Anal. ($C_{33}H_{32}N_2F_2O_3$) C, H, N.

4-Benzyl-3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-(*tert*-butoxycarbonyl)amino]propyl]-2*H*-1,4-benzoxazine (19). Compound **19** was isolated following the procedure described for **14** applied to the compound **3c** (1.60 g, 3.58 mmol). Purification of the residue on silica gel column (eluent: CH_2Cl_2) led to **19** (1.94 g, 98%) as an oil: IR (film) ν 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H, C**H**$_3$), 1.42−1.80 (m, 4H, C**H**$_2$), 2.68−2.80 (m, 2H, C**H**$_2$Ph), 3.06 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.09−3.19 (m, 2H, NC**H**$_2$), 3.20 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.26−3.39 (m, 2H, NC**H**$_2$), 3.81 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 4.04−4.13 (m, 1H, OC**H**), 4.39 (s, 2H, NC**H**$_2$Ph), 6.55−6.80 (m, 8H, Ar**H**), 7.18−7.32 (m, 4H, Ar**H**). Anal. ($C_{33}H_{42}N_2O_5$) C, H, N.

2-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetaldehyde (20). The ester **11c** (5.30 g, 17.0 mmol) was first reduced into its corresponding alcohol following the procedure described in the preparation of **16**. A purification on silica gel column (eluent CH_2Cl_2/MeOH, 99/1) furnished 2-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-ethanol (3.70 g, 80%) as an oil: IR (film) ν 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.71−1.96 (m, 2H, C**H**$_2$), 3.14 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.24 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.79−3.87 (m, 2H, OC**H**$_2$), 4.27−4.37 (m, 1H, OC**H**), 4.38 (s, 2H, NC**H**$_2$Ph), 6.53−6.65 (m, 2H, Ar**H**), 6.69−6.79 (m, 3H, Ar**H**), 7.15−7.32 (m, 4H, Ar**H**). Anal. ($C_{17}H_{19}NO_2$) C, H, N.

This intermediate alcohol (3.60 g, 13.0 mmol) was then oxidized into the expected aldehyde, applying the same methodology used in the preparation of **16**. The residue was then purified by flash chromatography (eluent CH_2Cl_2/MeOH, 99/1), providing **20** (2.97 g, 85%) as an oil, which was relatively unstable: IR (film) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.61 (dd, J = 5.1, 16.9 Hz, 1H, C**H**CO), 2.82 (dd, J = 7.3, 16.9 Hz, 1H, C**H**CO), 3.11 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.31 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.36 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.42 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.62−4.72 (m, 1H, OC**H**), 6.57−6.81 (m, 5H, Ar**H**), 7.17−7.33 (m, 4H, Ar**H**), 9.83 (s, 1H, C**H**O). Anal. ($C_{17}H_{17}NO_2$) C, H, N.

4-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)butanoic Acid (21). The procedure used for the preparation of the acid **17** was repeated from the aldehyde **20** (2.95 g, 11.0 mmol). This allowed (*E*)-4-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-2-butenoic acid, ethyl ester (3.37 g, 88%) to be isolated after purification on silica gel column (eluent: petroleum ether/CH_2Cl_2, 3/7) as an oil: IR (film) ν 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.3 Hz, 3H, C**H**$_3$), 2.39−2.50 (m, 1H, OCHC**H**), 2.53−2.64 (m, 1H, OCHC**H**), 3.09 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.21 (dd, J = 2.9, 11.8 Hz, 1H, NC**H**), 4.14 (q, J = 7.3 Hz, 2H, OC**H**$_2$), 4.19−4.28 (m, 1H, OC**H**), 4.34 (d, J = 15.4 Hz, 1H, NC**H**Ph), 4.41 (d, J = 15.4 Hz, 1H, NC**H**Ph), 5.86 (d, J = 16.2 Hz, 1H, =C**H**), 6.55−6.66 (m, 3H,

ArH), 6.70−6.82 (m, 2H, **ArH**), 6.93 (td, J = 7.3, 16.2 Hz, 1H, =C**H**), 7.19−7.31 (m, 4H, **ArH**). Anal. ($C_{21}H_{23}NO_3$) C, H, N.

This intermediate (0.350 g, 1.03 mmol), after hydrogenation (Raney nickel), gave access to 4-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)butanoic acid ethyl ester (0.229 g, 65%) as an oil, after purification on silica gel column (eluent: CH_2Cl_2): IR (film) ν 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J = 7.3 Hz, 3H, C**H$_3$**), 1.43−1.92 (m, 4H, C**H$_2$**), 2.30 (t, J = 7.3 Hz, 2H, C**H$_2$**CO), 3.07 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.21 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.00−4.13 (m, 1H, OC**H**), 4.07 (q, J = 7.3 Hz, 2H, OC**H$_2$**), 4.37 (s, 2H, NC**H$_2$**Ph), 6.53−6.62 (m, 3H, Ar**H**), 6.67−6.78 (m, 2H, Ar**H**), 7.18−7.30 (m, 4H, Ar**H**). Anal. ($C_{21}H_{25}NO_3$) C, H, N.

Finally, the expected acid **21** was obtained by alkaline hydrolysis of the ethyl ester (0.210 g, 0.62 mmol). The acid **21** (0.173 g, 90%) was obtained as an oil and involved in the next step without further purification: IR (film) ν 3500 (large) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.51−1.95 (m, 4H, C**H$_2$**), 2.38 (t, J = 7.3 Hz, 2H, C**H$_2$**CO), 3.07 (dd, J = 7.3, 11.8 Hz, 1H, NC**H**), 3.20 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 4.03−4.13 (m, 1H, OC**H**), 4.37 (s, 2H, NC**H$_2$**Ph), 6.53−6.64 (m, 3H, Ar**H**), 6.68−6.79 (m, 2H, Ar**H**), 7.18−7.32 (m, 4H, **ArH**). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

4-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]butanamide (22). The acid **21** (2.07 g, 6.65 mmol) was dissolved in dichloromethane (25 mL), and homoveratrylamine (1.23 mL, 7.31 mmol) and EDCI (1.53 g, 7.98 mmol) were added. The mixture was stirred at room temperature for 2 h. After workup and purification on silica gel column (eluent: CH_2Cl_2/MeOH, 99/1), the amide **22** (2.49 g, 79%) was obtained as an oil: IR (film) ν 3320, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46−1.89 (m, 4H, C**H$_2$**), 2.14 (t, J = 6.6 Hz, 2H, C**H$_2$**CO), 2.69 (t, J = 6.6 Hz, 2H, C**H$_2$**-Ph), 3.05 (dd, J = 8.1, 11.8 Hz, 1H, NC**H**), 3.19 (dd, J = 2.2, 11.8 Hz, 1H, NC**H**), 3.44 (q, J = 6.6 Hz, 2H, NC**H$_2$**), 3.78 (s, 3H, OC**H$_3$**), 3.79 (s, 3H, OC**H$_3$**), 4.00−4.12 (m, 1H, OC**H**), 4.37 (s, 2H, NC**H$_2$**Ph), 5.41 (s, 1H, N**H**), 6.52−6.76 (m, 8H, Ar**H**), 7.16−7.30 (m, 4H, Ar**H**). Anal. ($C_{29}H_{34}N_2O_4$) C, H, N.

2,3-Dihydro-1,4-benzodioxin-6-ylacetate (24). This compound was prepared from **23** (2.0 g, 11.0 mmol) using our described method.[41]

2,3-Dihydro-7-nitro-1,4-benzodioxin-6-ol (25). To an ice-cooled solution of **24** (3.50 g, 15.0 mmol) in glacial acetic acid (10 mL) was added dropwise fuming nitric acid (0.88 mL, 0.02 mmol). The solution was then allowed to warm to room temperature and stirred for 3 h. The mixture was quenched by 2 M NaOH (pH 7). The nitro compound was then extracted with CH_2Cl_2, washed, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by filtration on silica gel (eluent: CH_2Cl_2) to provide (2,3-dihydro-7-nitro-1,4-benzodioxin-6-yl)acetate (4.60 g, 96%) as a solid: mp 110−111 °C; IR (KBr) ν 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H, C**H$_3$**), 4.22−4.35 (m, 4H, OC**H$_2$**), 6.65 (s, 1H, Ar**H**), 7.69 (s, 1H, Ar**H**).

To a solution of the above intermediate (3.50 g, 15.0 mmol) in EtOH (35 mL) was added KOH (1.07 g, 19.5 mmol), and the reaction mixture was then stirred for 0.5 h. The solvent was evaporated to dryness and the residue hydrolyzed by 2 M HCl (pH 7). The expected phenol was extracted with CH_2Cl_2, washed, dried ($MgSO_4$), and concentrated in vacuo. Pure compound **25** (2.89 g, 98%) was isolated as a solid and used in the next step without further purification: mp 170−171 °C; IR (KBr) ν 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.19−4.25 (m, 2H, OC**H$_2$**), 4.28−4.35 (m, 2H, OC**H$_2$**), 6.54 (s, 1H, Ar**H**), 7.59 (s, 1H, Ar**H**), 10.51 (s, 1H, O**H**). Anal. ($C_8H_7NO_5$) C, H, N.

5-Bromo-2-[(2,3-dihydro-7-nitro-1,4-benzodioxin-6-yl)-oxy]valeric Acid, Methyl Ester (26). Compound **26** was synthesized following the procedure of Kajino[40] starting from the nitrophenol **25** (2.0 g, 10.0 mmol) and 2,5-dibromovaleric acid methyl ester (2.92 g, 10.0 mmol). Purification on silica gel column (eluent: CH_2Cl_2) provided **26** (3.28 g, 84%) as a solid: mp 86−87 °C; IR (KBr) ν 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.10−2.26 (m, 4H, C**H$_2$**), 3.44 (t, J = 5.9 Hz, 2H, C**H$_2$**), 3.75 (s, 3H, OC**H$_3$**), 4.21 (dd, J = 2.9, 5.9 Hz, 2H, OC**H$_2$**), 4.28 (dd, J = 2.9, 5.9 Hz, 2H, OC**H$_2$**), 4.62 (dd, J = 4.4, 6.6 Hz, 1H, OC**H**), 6.37 (s, 1H, Ar**H**), 7.53 (s, 1H, Ar**H**). Anal. ($C_{14}H_{16}BrNO_7$) C, H, N.

7-(3-Bromopropyl)-2,3,8,9-tetrahydro-7*H*-[1,4]dioxino[2′,3′:4,5]benzo[*b*][1,4]oxazin-8-one (27). Compound **27** was isolated following the procedure of Kajino[40] by reductive cyclization of **26** (0.410 g, 1.14 mmol) in the presence of 10% Pd−C under hydrogen pressure (45 psi). Column chromatography (eluent: CH_2Cl_2/MeOH, 99/1) led to the desired compound **27** (0.289 g, 77%) as a solid: mp 108−109 °C; IR (KBr) ν 3180, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88−2.15 (m, 4H, C**H$_2$**), 3.39−3.45 (m, 2H, C**H$_2$**), 4.17 (s, 4H, OC**H$_2$**), 4.41−4.47 (m, 1H, OC**H**), 6.32 (s, 1H, Ar**H**), 6.50 (s, 1H, Ar**H**), 8.61 (s, 1H, N**H**). Anal. ($C_{13}H_{14}BrNO_4$) C, H, N.

Pharmacology. Contractility of Rabbit Aortic Tissue. Aortic rings (3−5 mm long) were obtained from male, New Zealand White rabbits (weighting 2.2−3.5 kg), denuded of endothelium by gentle rubbing with a metal rod, and mounted between stainless steel hooks in 10 mL organ baths containing Krebs' solution of composition (mmol/L) NaCl, 118.1; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 0.6; KH_2PO_4, 1.2; $NaHCO_3$, 25; $CaCl_2 \cdot 2H_2O$, 2.5; D-glucose, 11.1, according to the method of Winslow *et al.*[52] The salt solution was gassed with 95% oxygen and 5% carbon dioxide and maintained at a temperature of 37 °C. A tension of 10g was applied and the tissue allowed to equilibrate for 1 h.

Endothelial denudation was verified by failure of the phenylephrine (0.1 μM) contracted tissue to relax in response to acetylcholine (1 μM). Reproducible responses to 40 mM potassium were obtained and then sustained tonic responses obtained to either potassium 40 mM or phenylephrine (5 μM). Test compounds were added cumulatively until maximum relation in response to the antagonist was obtained.

Contractility of Rabbit Renal Artery. Left renal artery rings (2.5−3 mm long) were obtained from male, New Zealand White rabbits (weighting 2.2−3.5 kg) and mounted between stainless steel hooks in a 10 mL organ bath filled with Krebs' solution at 37 °C and gassed with 95% O_2/5% CO_2. Each ring was set at an optimal preload of 3g. A 90 min equilibration period was allowed during which the tension generated was monitored by means of an isometric tension transducer. Tissues were contracted with caffeine (10 mM) to obtain three comparable consecutive control contractions. Test substances, at the lowest concentration, were added and the caffeine-induced contractions repeated 20 min until the maximum inhibitory response was obtained. The same procedure was repeated with increasing concentrations of the test products.

IC_{50} Determination. IC_{50} values defined as the concentration (μM) of the test compounds that inhibited 50% of contraction induced by potassium, phenylephrine or caffeine were obtained using linear regression analysis.

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JM970795T