Synthesis and Biological Evaluation of New 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine Derivatives

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2-(4,5-Dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine derivatives and tricyclic analogues with a fused additional ring on the nitrogen atom of the benzoxazine moiety have been prepared and evaluated for their cardiovascular effects as potential antihypertensive agents. The imidazoline ring was generated by reaction of the corresponding ethyl ester with ethylenediamine. Affinities for imidazoline binding sites (IBS) I_1 and I_2 and α_1 and α_2 adrenergic receptors were evaluated as well as the effects on mean arterial blood pressure (MAP) and heart rate (HR) of spontaneously hypertensive rats. With few exceptions the most active compounds on MAP were those with high affinities for IBS and α_2 receptor. Among these, compound **4h** was the most interesting and is now, together with its enantiomers, under complementary pharmacological evaluation.

Introduction

The hypotensive/antihypertensive effects of imidazoline-like drugs such as clonidine, rilmenidine, and moxonidine (Figure 1) are believed to be mediated by inhibition of the sympathetic outflow at the central level.[1] These effects were first attributed to the exclusive stimulation of central α_2 adrenoceptors ($a\alpha_2AR$) since several studies had established that selective α_2AR antagonists could suppress this hypotensive response.[2,3] Using α_2AR genetically engineered mice it was then demonstrated that the $\alpha_{2A}AR$ was the α_2AR subtype involved.[4,5]

Things became more complicated after the publication of experimental data, suggesting that this exclusive involvement of α_2AR in the hypotensive effects of imidazoline-like drug was unlikely, since direct administration of α_2AR agonists with phenylethylamine structures in the rostroventrolateral medulla (RVLM located in the brainstem) did not mimic the hypotensive effects of imidazoline drugs injected in the same region.[6−8] In addition, α_2AR antagonists failed to prevent imidazoline-induced hypotension when administered directly into the RVLM while microinjection of antagonists with imidazoline structures, such as idazoxan and efaroxan, prevented the action of clonidine analogues.[9,10] These data led to the assumption that there exist nonadrenergic receptors sensitive to imidazoline derivatives.[11] Since then, binding studies suggested the existence of two specific binding sites for imidazoline compounds, namely imidazoline I_1 and I_2 binding sites (IBS) which are insensitive to catecholamines.[12−14] The I_1 binding site which is sensitive to clonidine and idazoxan is the subtype involved in the hypotensive properties of the imidazoline like drugs.[15] The I_2 binding site is insensitive to clonidine but sensitive to idazoxan has been postulated to be an allosteric site on monoamine oxidase.[16,17] Agmatine and Harmane[18−20] have been postulated as endogenous ligands of these binding sites that are distributed in the peripheral as well as in the central nervous systems. Both compounds have been reported to affect blood pressure (either increase or decrease following a central administration in rats).[19,20]

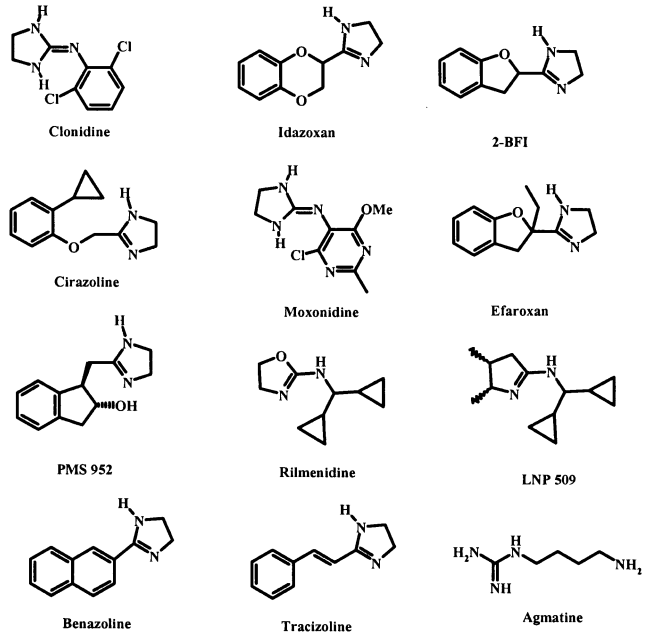

Figure 1. Different families of compounds that interact with the imidazoline binding sites.

In addition to their cardiovascular implications, IBS could play a role in the control of glucose homeostasis[21,22] as well as in other physiological functions[23−27] (imidazolines derivatives can be serotonergic ligands).[28]

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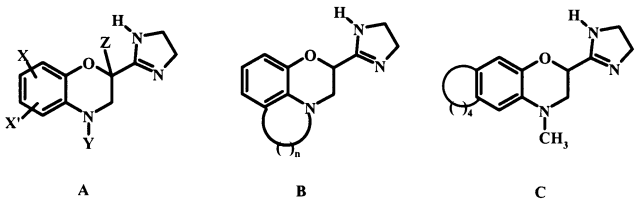


Figure 2. General structures (A, B, C) of synthesized imidazoline derivatives.

A third imidazolinic binding site (putative designated I_3) in pancreatic β-cells is associated with control of insulin.[29,30] Analogues of cirazoline, a selective α_1 adrenoreceptor agonist, have been synthesized.[31] Substituted aryl and heteroaryl imidazolines have been evaluated in order to obtain I_1 or I_2 selective ligands.[32−34] Antiaggregatory effects of some *N*-(4,5-dihydro-1*H*-imidazol-2-yl)indoles have been described.[35]

Recently I_1 imidazoline binding site (I_1BS) selective ligands PMS 952[36] and LNP 509[37] with hypotensive have been reported (Figure 1). Pigini also reported the synthesis of benazoline and tracizoline with high selectivity for I_1BS over α_2AR, but these ligands are devoid of hypotensive activity.[38]

The literature describes numerous imidazoline binding sites (IBS) ligands where the imidazoline ring is combined with the benzofuran or benzodioxane skeleton; this is illustrated by idazoxan,[39] 2-BFI,[40] and efaroxan.[41] Dihydro[1,4]benzoxazine in some extent can be considered as bioisostere of dihydro[1,4]benzodioxine. Numerous benzoxazinic derivatives possess pharmacological properties[42−57] in many areas. These facts encourage us to combine in the same structure the imidazoline and the benzoxazine moieties.

In this paper we describe the synthesis, the binding affinities (α adrenoceptors and IBS), and the in vivo cardiovascular evaluation (mean arterial blood pressure MAP and heart rate HR) of new 2-(4,5-dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine derivatives of type **A** and some of tricyclic analogues of type **B** and **C** (Figure 2).

Chemistry

The synthesis of the imidazolinic derivatives **(4a−k**, **4m−o)** was accomplished via the route illustrated in Scheme 1. The methods used in this scheme were described previously. Thus, appropriate 2-aminophenols **1a−k** were treated with ethyl 2,3-dibromopropanoate in refluxing acetone[58−66] in the presence of potassium carbonate to provide the corresponding dihydro[1,4]-benzoxazines **2a−k** which were then *N*-methylated with iodomethane. Generation of the imidazolinic[67−71] group was performed by using trimethyl aluminum[72] and ethylenediamine in refluxing toluene to give the imidazoline derivatives **4a−k**. The substitution of the nitrogen atom of compound **2a** was accomplished with benzyl chloride or 1-iodopropane to afford the benzoxazines **3n** and **3o** in 98% and 62% yield, respectively. The imidazolines **4n**,**o** were obtained in a similar manner as for **4a−k.** The unsubstituted imidazoline on the nitrogen atom **4m** was obtained directly from **2a** in 66% yield. Compounds **4a** and **4m**,**n** have been previously prepared by Chapleo.[60] Racemic compound (±)-**4h** has been resolved using dibenzoyl-D(+)- or L(−)-tartaric acid, respectively into (+)-**4h** and (−)-**4h** by precipitation in ethanol of the corresponding diastereomeric salt followed by liberation in basic medium of the imidazolinic enantiomers. These enantiomers quickly racemized as free bases but were stable as oxalate salts.

Synthesis of Substituted 2-Aminophenols. The synthesis of the 2 aminophenol **1j** was performed from the 4-hydroxy-3-nitrobenzaldehyde by first, reducing the formyl group by $NaBH_4$[73] (68% yield) and then reaction with stannous chloride[74] in ethanol affording 2-amino-(4-ethoxymethyl)phenol **1j** (42% yield) which corresponds to an additional etherification with ethanol of the substituted benzyl alcohol. This 2-aminophenol was used to prepare the benzoxazinic derivative **2j** (60% yield) which was treated with iodomethane to afford **3j** (63% yield) and finally the imidazoline derivative **4j** in 66% yield according to conditions reported in Scheme 1. The 6-hydroxymethyl-2-aminophenol **1k** was obtained by $LiAlH_4$ reduction[75] of 2-aminophenol **1l**. For the imidazoline derivative **4l** which possesses a methoxycarbonyl group as substituent in the 6-position, another approach was used. The substituted 2-aminophenol **1l** was treated with 2-chloroacrylonitrile[61] to afford the dihydro[1,4]benzoxazine derivative **5** substituted in the 2-position by a nitrile group (Scheme 2). It was possible to generate regioselectively the imidazoline group from **6** by using ethylenediamine in the presence of P_2S_5 as catalyst.[76−78] Imidazoline **4l** was thus obtained in 61% yield.

Imidazoline **8**, disubstituted in the 6- and 7-positions with a methyl group, was obtained from the corresponding disubstituted [1,4]benzoxazine **7** in 68% yield (Scheme 3). Thus bromination of the dihydro[1,4]benzoxazine **4c** using NBS/DMF gave exclusively the bromo derivative **6** in 90% yield and not the bromomethyl derivative. Compound **6** was submitted to a Stille reaction with tetramethyltin in the presence of tetrakis(triphenylphosphine)palladium as catalyst (20%) using HMPA as solvent to afford **7** in 66% yield (DMF gave lower yield, and $PdCl_2[P(C_6H_5)_3]_2$ in toluene was not effective).

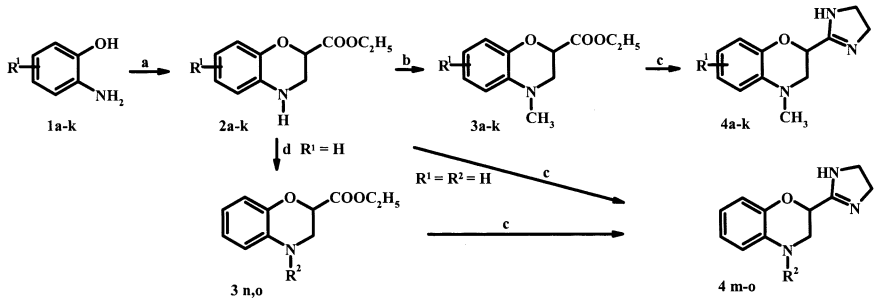
The anologous imidazoline **9** dimethylated in 6- and 8-positions was obtained from commercially available 2-amino-4,6-dimethylphenol in a global 15% yield.

Linear Tricyclic Imidazoline Derivatives. After preparing various substituted dihydro[1,4]benzoxazines, we have considered the synthesis of imidazolinic derivatives possessing an additional ring fused to the phenyl ring.

Synthesis of 3-amino-5,6,7,8-tetrahydro-2-naphthol **11** was performed from **10** by a slight modification of literature report.[46,79] **10** was first brominated in the 1-position and then nitrated in the 3-position and hydrogenated with loss of a bromine atom to afford **11**. The imidazoline **13** was then obtained from benzoxazine **12** in 90% yield (Scheme 4).

If the synthesis of the imidazoline derivative **15** from 2-amino-1-naphthol **14** did not meet any difficulty, the generation of the isomeric benzoxazine derivative **18** appeared to be more problematic. Thus the standard treatment of 3-amino-2-naphthol **16** with ethyl 2,3-dibromopropanoate/K_2CO_3/acetone afforded exclusively the naphtho[2,1-*b*]furan derivative **17** in good yield; we have recently described this behavior of 3-substituted 2-naphthols.[80] Nevertheless we were able to ob-

Scheme 1. Preparation of Imidazolines Derivatives of Type A[a]

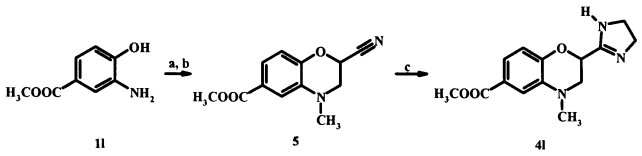


2, 3, 4	a	b	c	d	e	f	g	h	i	j	k
R^1	H	5-CH_3	6-CH_3	7-CH_3	8-CH_3	6-Cl	6-CH_3O	6-F	6-CF_3	6-$CH_2OC_2H_5$	6-CH_2OH
4	m	n	o								
R^2	H	Bn	*n*Pr								

Compounds	a	b	c	d	e	f	g	h	i	j	k	m	n	o
2 (yield %)	68	90	77	72	68	62	42	53	75	60	39	-	-	-
3 (yield %)	67	80	63	61	55	60	55	80	75	63	55	-	98	62
4 (yield %)	68	90	49	91	86	71	86	68	76	66	62	66	85	78

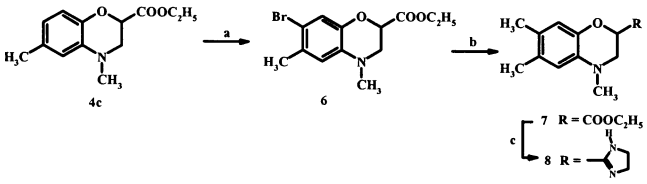
[a] (a) Ethyl 2,3-dibromopropanoate, K_2CO_3, acetone, reflux; 42−90% yield; (b) CH_3I, K_2CO_3, acetone, 55−80% yield; (c) $Al(CH_3)_3$, ethylenediamine, toluene, reflux, 40−90% yield; (d) Benzyl chloride, NaI, K_2CO_3, DMF, **3n** R^2= Bn, 98% yield, 1-iodopropane, K_2CO_3, acetone, HMPA, **3o** $R^2 = n\text{-}C_3H_7$, 62% yield.

Scheme 2. Synthesis of Functionalized Imidazoline[a]



[a] (a) 2-chloroacrylonitrile, K_2CO_3, acetonitrile 77% yield; (b) NaH, CH_3I, HMPA, 45% yield; (c) P_2S_5, toluene, ethylenediamine, reflux, 61% yield.

Scheme 3. Synthesis of Disubstituted Imidazoline[a]

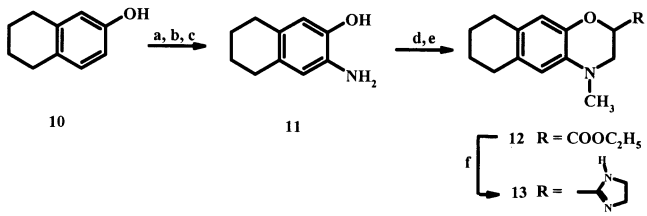


[a] (a) NBS, AIBN, acetonitrile, 90% yield; (b) $(CH_3)_4Sn$, Pd[P-$(C_6H_5)_3]_4$, HMPA, 66% yield; (c) $Al(CH_3)_3$, ethylenediamine, toluene, reflux, 68% yield.

tain in low yield the 2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate **18** by changing the nature of the base ($KHCO_3$ or $NaHCO_3$ instead of K_2CO_3). Compound **18** (21% yield) was always accompanied with **17** (42% yield) and unreacted 3-amino-2-naphthol **16** (24% yield) using $KHCO_3$ as a base. Similarly **18** was obtained in only 15% yield with $NaHCO_3$ as a base. Transformation of **18** into imidazoline **19** was then routinely done (Scheme 5).

2,2-Disubstituted Benzoxazinic Derivatives. To investigate the role of a substituent in α position of the imidazoline ring the synthesis of **21a**,**b** was attempted. The benzoxazine derivative **3a** was treated with alcoholic potassium hydroxide to generate the acid function and then with LDA/THF/−50 °C followed by quenching the dianion[81] with iodomethane or 1-iodopropane. Heating in methanol in the presence of PTSA afforded **20a** and **20b** in 69% and 72% yield, respectively. The imidazolines **21a**,**b** were obtained from **20a**,**b** in 81% and 44% yield, respectively (Scheme 6).

Scheme 4. Preparation of 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4,6,7,8,9-hexahydro-2*H*-naphtho[2,3-*b*][1,4] Oxazine[a]

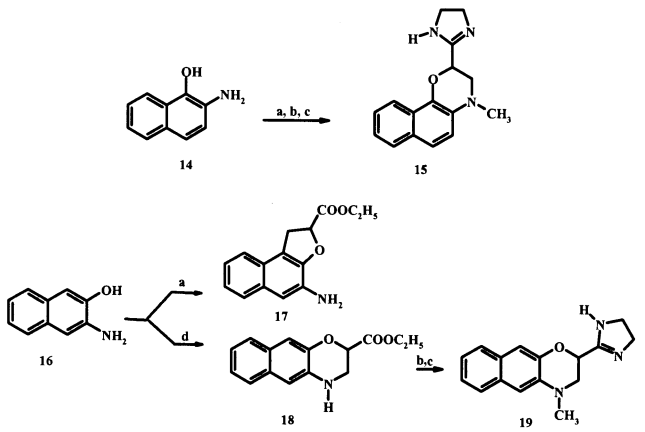


[a] (a) NBS, DMF, 94% yield; (b) $HNO_3/CH_3COOH/H_2O$, 59% yield; (c) H_2/Pd/C 10%, methanol, 95% yield; (d) ethyl 2,3-dibromopropanoate, K_2CO_3, acetone, reflux, 59% yield; (e) CH_3I, K_2CO_3, acetone 66% yield; (f) $Al(CH_3)_3$, ethylenediamine, toluene, reflux, 90% yield.

Tricyclic Derivatives. The nitrogen atom of the benzoxazine scaffold of the previous derivatives was substituted with a methyl group. We then planned to incorporate the nitrogen atom in an additional ring.

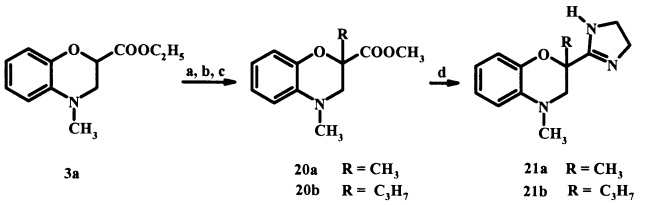
Benzoxazines **2a**,**c** were *N*-alkylated with benzyl 3-bromopropanoate to afford **22a**,**c** in only 20% yield. To improve the yield of **22**, we used a Michael-type addition of compounds **2a**,**c** on benzyl acrylate[82] in the presence of Triton B. Compounds **22a**,**c** were thus obtained in 91% and 90% yield, respectively (Scheme 7). Debenzylation to furnish compounds **23a**,**c** was accomplished by catalytic hydrogenolysis over palladium in good yield. Cyclization in order to obtain **24a**,**c** was performed using trifluoacetic anhydride in dichloromethane at room temperature. Compounds **24a**,**c** obtained in 41% and 37% yield, were accompanied with **25a**,**c** respectively in 11% and 16% yield. Attempted hydrogenation of **25c** did not give **24c**. The formation of unsaturated ring during Friedel−Crafts cyclization has been previously mentioned in the literature.[83]

Scheme 5. Synthesis of Benzo-fused Imidazolines of Type C[a]



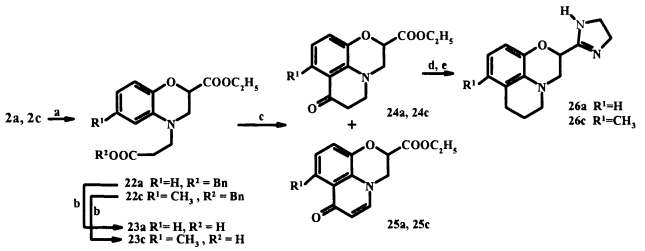
[a] (a) Ethyl 2,3-dibromopropanoate, K_2CO_3, acetone, reflux, 29% yield; (**17** 80% yield); (b) CH_3I, K_2CO_3, acetone, 77−80% yield; (c) $Al(CH_3)_3$, ethylenediamine, toluene, reflux **15**, 57% yield, **19**, 68% yield; (d) ethyl 2,3-dibromopropanoate, $KHCO_3$, acetone, reflux, 21% yield.

Scheme 6. Preparation of 2-Substituted Imidazolines of Type A[a]



[a] (a) KOH, ethanol, 93% yield; (b) LDA, −50 °C, CH_3I or C_3H_7; (c) methanol, APTS, **20a**, 69% yield, **20b**, 72% yield (two steps); (d) $Al(CH_3)_3$, ethylenediamine, toluene, reflux, **21a**, 81% yield, **21b**, 44% yield.

Scheme 7. Synthesis of Tricyclic Imidazolines of Type B[a]

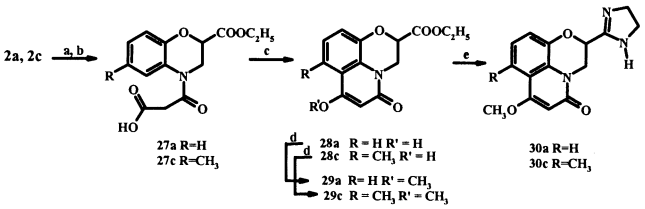


[a] (a) Triton B, benzyl acrylate, toluene, **22a**, 91% yield, **22c**, 90% yield; (b) H_2, Pd/C 10%, ethanol, **23a**, 97% yield, **23c**, 86% yield; (c) trifluoroacetic anhydride, CH_2Cl_2, **24a**, 41%yield, **24c**, 37% yield, **25a**, 11% yield, **25c**, 16% yield; (d) H_2,Pd/C 10%, 3 atm, ethanol; (e) $Al(CH_3)_3$, ethylenediamine, toluene, reflux, **26a**, 43% yield (two steps), **26c**, 24% yield (two steps).

Hydrogenation of the keto group and hydrogenolysis of **24a**,**c** was performed by hydrogenation (3 atm) over palladium on carbon, to afford the tetrahydro[1,4]-oxazino[2,3,4-*ij*]quinoline. Then standard generation of the imidazolinic function gave **26a**,**c** in 43% yield and 24% yield, respectively, for the two steps.

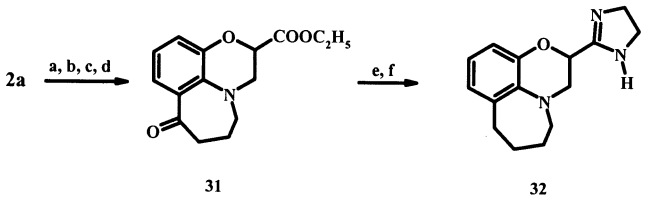
Reaction of benzyl 3-chloro-3-oxopropanoate[84] ($ClCOCH_2COOBn$) with benzoxazines **2a**,**c** afforded first the isolated corresponding amides and second, after hydrogenolysis, acids **27a**,**c** (Scheme 8). They were cyclized into **28a**,**c** (obtained as enols) using the conditions developed to obtain **24a**,**c**. The enol form of the ketone

Scheme 8. Synthesis of Tricyclic Imidazolines[a]



[a] (a) $ClOCCH_2COOBn$, $(C_2H_5)_3N$, CH_2Cl_2; (b) H_2, Pd/C 10%, ethanol **27a**, 51% yield, **27c**, 55% yield (two steps); (c) trifluoroacetic anhydride, CH_2Cl_2 **28a**, 51% yield, **28c**, 70% yield; (d) $TsCH_3$, DMF **29a**, 85% yield, **29c**, 67% yield; (e) $Al(CH_3)_3$, ethylenediamine, toluene, reflux **30a**, 67% yield, **30c**, 49% yield.

Scheme 9. Seven-Membered Imidazolines[a]



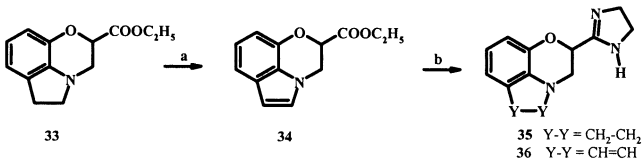
[a] (a) $ClOCCH_2CH_2COOBn$, $(C_2H_5)_3N$, CH_2Cl_2, 98% yield; (b) BH_3, THF, 79% yield; (c) H_2, Pd/C 10%, ethanol, 97% yield; (d) trifluoroacetic acid anhydride, CH_2Cl_2, **31**, 62% yield; (e) H_2, Pd/C, 10%, 3 atm, ethanol, 49% yield; (f) $Al(CH_3)_3$, ethylenediamine, toluene, reflux, **32**, 89% yield.

was *O*-methylated using methyl tosylate[85] to afford **29a**,**c**, respectively, in 85% and 67% yields. The regioselectivity of the methylation was confirmed by 2D NMR experiments. The imidazolines **30a**,**c** were obtained in 67% and 49% yields from **29a**,**c**.

Direct reaction of benzoxazine **2a** with benzyl 4-bromobutanoate did not afford the expected *N*-alkylated derivative. So we investigated the formation of an amide bond with a functionalized acid chloride, as for compound **27a**, to introduce the chain which would generate the seven-membered ring (Scheme 9). Thus compound **31** with a seven-membered ring was obtained from **2a** in a four-step procedure. Amidification of **2a** with benzyl 4-chloro-4-oxobutanoate[86] ($ClCO(CH_2)_2COOBn$) followed by selective reduction of the amide function with BH_3·THF and hydrogenolysis of the benzyl ester afforded the 4-substituted butanoic acid. Cyclization of the acid using the cyclization conditions reported for acids **22** afforded the saturated cyclic ketone **31** in a 46% global yield. Imidazoline **32** was obtained from compound **31** in 43% yield for the two-step procedure.

After having prepared the six- and seven-membered imidazolines **26a**,**b** and **32**, we started with the synthesis of the five-membered ring imidazoline **35**. A different approach was used to synthesize the five-membered ring derivative **33**, as we were unable to cyclize the 2-(3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)acetic acid **37** under Friedel−Crafts conditions (**37** resulted from the alkylation of benzoxazine **2a** with benzyl bromoacetate followed by debenzylation). So we decided to generate the 1,4-oxazine ring after the synthesis of the five-membered ring. The five-membered ring was present in 7-hydroxyindoline which was reacted with ethyl 2,3-dibromopropanoate to generate the 1,4-oxazino compound **33**[87] in an 83% yield (Scheme 10). Compound **33** was easily oxidized with DDQ into the indolic compound **34** in a moderate 50% yield. Finally, **33** and **34** gave

Scheme 10. Preparation of Five-Membered Imidazolines[a]



[a] (a) DDQ, toluene, 0 °C, 50% yield; (b) $Al(CH_3)_3$, ethylenediamine, toluene, reflux.

access to imidazolines **35** and **36**, respectively, in 72 and 85% yields.

Pharmacology

Nineteen compounds of type **A**, seven tricyclic analogues of type **B**, and three of type **C** have been prepared and evaluated for their biological properties. All of them were first investigated for their affinities toward the α_1 and α_2 receptors as well for the I_1 and I_2 binding sites (IBS) which were determined from radioligand binding assay. Most of them were then evaluated in vivo for their cardiovascular effects on mean arterial blood pressure (MAP) and heart rate (HR) via ip administration in spontaneously hypertensive anesthetized rats (SHR). The most active compounds were then evaluated by po administration in conscious SHR.

In the first step, we investigated the effect of substitution of the basic nitrogen atom of the benzoxazine ring (R^2). We first validated our concept with compounds **4a** and **4m** which can be considered as the structural bioisosteres of idazoxan. Both compounds appeared to be potent ligands for the I_2 binding sites (BS) with K_i values of respectively of 8×10^{-9} M and 5.1×10^{-8} M. Compound **4a** proved also to be a good ligand for the I_1 BS ($K_i = 5.6 \times 10^{-8}$ M) and α_2 adrenoceptors ($K_i = 7.4 \times 10^{-8}$ M); in contrast, compound **4m** was devoid of affinity for α_2 adrenoceptors. Neither **4a** nor **4m** exhibit clear affinity for the α_1 receptors, with K_i values of, respectively, 1.1×10^{-6} M and $>10^{-5}$ M. Replacement of the methyl substituent of **4a** by a benzyl (compound **4n**) or an *n*-propyl (compound **4o**) clearly decreased the affinity toward IBS and α_2 adrenoceptors. On the basis of these results, we decided to retain the methyl group on all the compounds prepared on the **A** family. Further evaluations were performed with introduction of angular alkyl groups on the carbon-2 bearing the imidazoline moiety. Introduction of a methyl substituent (compound **21a**) or an *n*-propyl substituent (compound **21b**) results in a very significant decrease in affinity for IBS and α_2 adrenoceptors. We then focused our pharmacomodulations on benzoxazine derivatives bearing substituents on the aromatic ring (e.g., methyl, methoxy, halogen). To determine the optimal position for enhanced affinity, a methyl substituent was introduced on the 5,6,7,8-positions of the aromatic ring (compounds **4b**−**e**). It appeared that compound **4c** can be considered as the most potent on the panel of I_1, I_2 (IBS) and α_2 adrenoceptors with K_i values of, respectively, 2.17×10^{-8} M (I_1), 1.99×10^{-9} M (I_2) and 7×10^{-8} M (α_2). Dimethyl-substituted analogues were also prepared in the 6,7-positions (compound **8**) and the 6,8-positions (compound **9**). Only compound **8** remains potent on IBS and α_2 adrenoceptors with a K_i in the range of 10^{-8} M, slightly less potent than compound **4c**.

Analogues of compound **4c** with other substituents than methyl in the 6-position were preparated and evaluated. Compound **4i** (CF_3) was clearly less potent than **4c** on all the receptors. Replacement of the methyl group by a methoxy (**4g**) results in a slight decrease in affinity which is even more important for **4k** (CH_2OH). Surprisingly the methoxycarbonyl group (**4l**) has a deleterious effect on the α_2 adrenoceptor affinity but not on the IBS affinities. To a lesser extent this is also the case for **4h** (fluoro) but not for **4f** where the chloro atom has no effect on α_2 affinity but decreases the IBS affinities. Compound **4j** ($CH_2OC_2H_5$) retains affinity only for the I_2BS $K_i = 1.7 \times 10^{-8}$ M ($>10^{-6}$ M for other receptors).

Seven tricyclic analogues of type **B** (e.g., oxazinoindole, oxazinoquinoline) were then prepared. Compound **35** (five-membered additional ring) was the only one to retain potent affinities for IBS and α_2 adrenoceptor (K_i between 2 and 5×10^{-8} M). These affinities are higher than those of the *N*-propyl-substituted benzoxazine **4o** previously mentioned. Increase of the size of the additional ring (**26c** and **32**) results in a clear decrease in the affinity. Deletion of the basic character of the nitrogen atom of the oxazino ring (**30a**, **30c**) led to almost inactive compounds. Modification of **35** by introduction of a double bond ("indole like" moiety) results in the compound **36** with a clearly improved affinity for the I_2BS but a decrease affinity for the α_2 adrenoceptors.

Because of the good results obtained with the disubstituted compound **8**, we prepared a tricyclic analogue **13** possessing an additional fused cyclohexyl ring in the 6,7-positions. This compound appeared to be less potent on all the receptors; this is also the case for its aromatic analogues **19** and **15**.

In a second step, compounds were evaluated at 25 mg/kg ip for their cardiovascular effects in the spontaneously hypertensive anesthetized rat (Table 1). With few exceptions such as compound **8**, the most active compounds on mean arterial blood pressure were those with high affinities for IBS and α_2 receptor. The most potent of them were compounds **4h** (−36% on mean arterial blood pressure (MAP) and −44% on heart rate (HR), **4f** (−28% MAP and −32% HR), **35** (−30% MAP and −25% HR), and to a lesser extent compounds **4a** (−21% MAP, − 44% HR), **4d** (- 20% MAP, −19% HR), and **4c** (−17.5% MAP and −37% HR).

Compounds found the most active in vivo were not always the most potent in terms of affinities, probably due to differences in metabolism and/or bioavailability. This could be the case for **4c** which is a better ligand than **4f** and **4h** but is less active on MAP. Because of the good activity of **4h**, which is a racemic mixture, its two enantiomers (+)-**4h** and (−)-**4h** were prepared by resolution with, respectively, D(+)- and L(−)-dibenzoyl tartaric acids and evaluated. Both enantiomers appeared active in the SHR with no clear difference on MAP, but compound (+)-**4h** seems to induce less bradycardia (−25%) than (−)-**4h** (−45%). This could perhaps be explained by the affinity profile which are slightly different. The results obtained are summarized in Table 1.

In the last step some of the most active compounds were administered per os to conscious SHR, and the effects on mean arterial blood pressure and heart rate

Table 1. Binding Affinities and Effects of the Compounds (oxalate salts) at 25 mg/kg ip on Mean Arterial Blood Pressure and Heart Rate in Spontaneously Hypertensive Anesthetized Rats

					effects at 25 mg/kp ip			
					blood pressure		heart rate	
	I_1 K_i M	I_2 K_i M	α_1 K_i M	α_2 K_i M	max Δ MAP (mmHg)[a]	max Δ MAP (% variation)	max Δ HR (bpm)[b]	max Δ HR (% variation)
4a	5.6×10^{-8}	8×10^{-9}	1.1×10^{-6}	7.4×10^{-8}	−36**	−21	−148***	−44
4b	7.6×10^{-7}	4.7×10^{-7}	4.74×10^{-6}	1.45×10^{-7}	+47***	+23	−52**	−16
4c	2.17×10^{-8}	1.99×10^{-9}	$>10^{-6}$	7.0×10^{-8}	−32***	−17,5	−127***	−37
4d	2.6×10^{-7}	4.7×10^{-8}	1.0×10^{-6}	3.0×10^{-8}	−34***	−20	−60***	−19
4e	2.27×10^{-8}	5.38×10^{-8}	$>10^{-6}$	7.3×10^{-9}	−24	−13	−79*	−25
4f	1.4×10^{-7}	1.73×10^{-7}	$1.46 \times 10^{-6} \pm 5.8 \times 10^{-7}$	5.25×10^{-8}	−53***	−28	−96***	−32
4g	7.86×10^{-8}	6.65×10^{-8}	$>10^{-5}$	2.87×10^{-7}	−14*	−8	−54**	−18
4h	3.1×10^{-8}	6×10^{-8}	$5.91 \times 10^{-6} \pm 4.09 \times 10^{-6}$	1.04×10^{-7}	−6 ***	−36	−139***	−44
(−)-**4h**	24% at 10^{-7} M	1.7×10^{-8} M	$>10^{-6}$	$3.29 \times 10^{-8} \pm 1.33 \times 10^{-8}$	−55***	−31	−143***	−45
(+)-**4h**	5.7×10^{-8}	4.7×10^{-9}	$2.54 \times 10^{-6} \pm 2.2 \times 10^{-7}$	$6.82 \times 10^{-8} \pm 2.2 \times 10^{-9}$	−50***	−28	−85 NS	−25
4i	$>10^{-6}$	$>10^{-6}$	$>10^{-5}$	2.63×10^{-7}	−32**	−18	−134***	−43
4j	$>10^{-5}$	1.7×10^{-8}	$>10^{-5}$	$>10^{-6}$	NT	NT	NT	NT
4k	2.04×10^{-7}	$\#10^{-7}$	$>10^{-5}$	$1.04 \times 10^{-8} \pm 6.52 \times 10^{-9}$	NT	NT	NT	NT
4l	8.8×10^{-8}	7.0×10^{-9}	$>10^{-5}$	$7.5 \times 10^{-6} \pm 6.4 \times 10^{-6}$	NT	NT	NT	NT
4m	8.4×10^{-7}	5.1×10^{-8}	$>10^{-5}$	$>10^{-5}$	−17 NS	−9	−8 NS	−3
4n	3.8×10^{-6}	1.,6×10^{-6}	3.5×10^{-6}	1.3×10^{-6}	−4 NS	−2	−21 NS	−7
4o	4.5×10^{-7}	1.6×10^{-7}	$>10^{-5}$	1.32×10^{-7}	−26*	−14	−90***	−27
8	4.4×10^{-8}	4.3×10^{-8}	$5.66 \times 10^{-6} \pm 3.6 \times 10^{-7}$	$2.6 \times 10^{-8} \pm 7 \times 10^{-9}$	−8 NS	−5	−100***	−33
9	$>10^{-6}$	$>10^{-6}$	$>10^{-6}$	$1.24 \times 10^{-8} \pm 1.01 \times 10^{-9}$	lethal at 12.5 mg; toxic at 5 mg; inactive at 0.5 mg			
13	6.9×10^{-7}	8.0×10^{-7}	$>10^{-5}$	9.8×10^{-8}	−15**	−9	−53*	−17
15	1.43×10^{-6}	6.21×10^{-7}	$>10^{-5}$	1.43×10^{-7}	−14**	−8	−80**	−24
19	9.3×10^{-8}	$2.78 \times 10^{-7} \pm 2.41 \times 10^{-7}$	$>10^{-5}$	$4.02 \times 10^{-7} \pm 1.18 \times 10^{-7}$	−17 NS	−9%	−47 NS	−16
21a	$>10^{-5}$	$>10^{-5}$	$>10^{-6}$	$>10^{-6}$	−17 NS	−9	−37 NS	−11
21b	5.59×10^{-6}	8.53×10^{-6}	$>10^{-6}$	$>10^{-6}$	+22**	+11	−56*	−17
26a	1.5×10^{-7}	1.0×10^{-8}	7.1×10^{-7}	3.4×10^{-7}	−34**	−20	−77***	−24
26c	$>10^{-6}$	$>10^{-6}$	$>10^{-5}$	2.3×10^{-7}	−17 NS	−9	−79***	−25
30a	5.6×10^{-7}	7.5×10^{-7}	$>10^{-5}$	1.3×10^{-5}	−9	−5	+13	+4
30c	5.3×10^{-6}	1.8×10^{-5}	9.4×10^{-6}	6.8×10^{-6}	−1 NS	0	−17 NS	−6
32	2.44×10^{-6}	6.43×10^{-7}	4.6×10^{-6}	2.15×10^{-6}	+21*	+11	−65**	−22
35	4.8×10^{-8}	3.3×10^{-8}	$>10^{-5}$	2.86×10^{-8}	−56***	−30	−103***	−25
36	1.3×10^{-8}	3.5×10^{-9}	$>10^{-6}$	3.6×10^{-7}	−24 *	−14	−45*	−14

[a] Maximum variation of mean arterial pressure (mmHg). [b]Maximum variation of heart rate (bpm) NS: nonsignificant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, $n = 6$/group. NT not tested.

Table 2. Effects after po Administration in Conscious Spontaneously Hypertensive Rats

		blood pressure		heart rate	
	dose (mg/kg po)	max Δ MAP (mmHg)[a]	max Δ MAP (% variation)	max Δ HR (bpm)[b]	max Δ HR (% variation)
4a	25	−65***	−36	−97***	−26
4f	30	−47**	−24	−40 NS	+11
4h	10	−34 NS	−18	+25 NS	+7
	30	−56**	−29	−43**	−12
	100	−81**	−44	−61**	−18
35	10	−19 NS	−10	−50*	−14
	30	−48**	−25	−94***	−27
4c	10	−18 NS	−10	−11 NS	−3
	30	−43*	−23	−32**	−10
	100	−53***	−28	−77***	−23

[a] Maximum variation of mean arterial pressure (mmHg). [b] Maximum variation of heart rate (bpm) NS: nonsignificant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

were evaluated (Table 2). Compound **4c** was statistically active at 30 mg/kg with clear decreases of MAP and HR (−23% and −10%, respectively) but was inactive at 10 mg/kg po. We obtained the same results for compound **35**. Compound **4h** was the most interesting of the series with a pronounced effect on MAP and HR (−29% and −12%, respectively) at 30 mg/kg.

A good correlation was observed between the dose and the maximum effects on both mean arterial blood pressure and heart rate. As reported in Figures 3 and 4, the duration of action of compound **4h** was dose-related (statistically significant decrease of the MAP for 3 h at 30 mg/kg po and at least for 8 h at 100 mg/kg po).

Oral general acute toxicity of compound **4h** as well as its behavioral effects were then investigated using an Irwin test performed in normotensive rats via per os administration. The first behavioral changes were sedation and ptosis that appeared at 30 mg/kg po while the mortality threshold dose was around 600 mg/kg (1/3).

Conclusion

We have prepared and evaluated 29 imidazolinic derivatives with a benzoxazine framework. Compounds with high affinities for IBS and α_2 adrenoceptors showed pronounced cardiovascular effects on both blood pres-

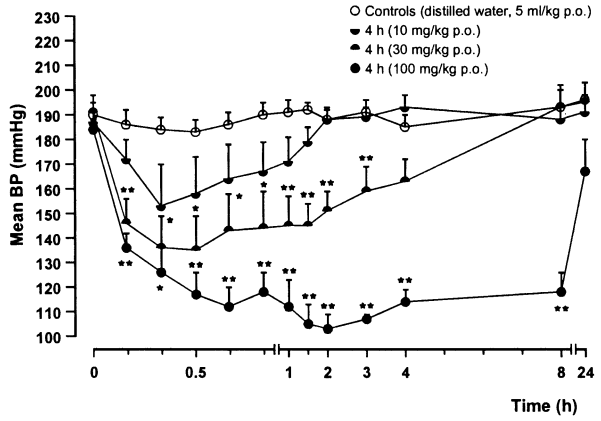


Figure 3. Effects of **4h** on mean arterial blood pressure in spontaneously hypertensive conscious rats. Means ± SEM (n = 6 except n = 4 treated at 100 mg/kg). Intergroup comparison (treated versus controls): no indication = NS; *p < 0.05; **p < 0.01; ***p < 0.001.

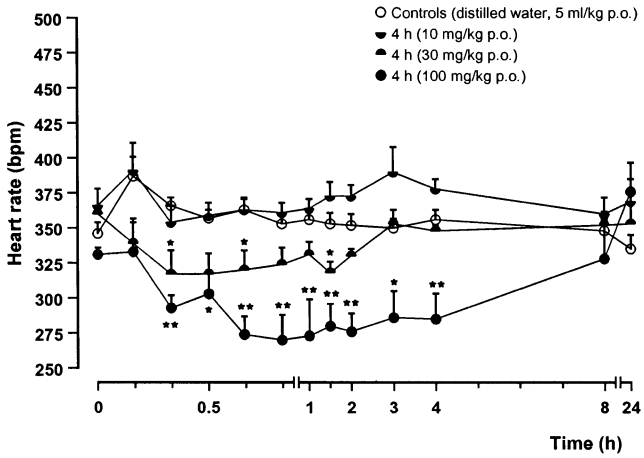


Figure 4. Effects of **4h** on heart rate in spontaneously hypertensive conscious rats. Means ± SEM (n = 6 except n = 4 treated at 100 mg/kg). Intergroup comparison (treated versus controls): no indication = NS; *p < 0.05; **p < 0.01; ***p < 0.001.

sure and heart rate either after ip or po administration. Among them, compound **4h**, was the most interesting as a potent antihypertensive agent and is now, together with its enantiomers, under extended phamacological evaluation.

Experimental Section

Chemistry. Melting points were determined using a Büchi SMP-20 melting point apparatus and were uncorrected. The IR spectra of compounds were recorded on a Perkin-Elmer FTIR paragon 1000 spectrophotometer. NMR spectra were recorded at 300 K in $CDCl_3$ or DMSO on a Bruker Avance DPX 250. Chemical shifts were expressed in parts per million and referenced to TMS. MS spectra were recorded on Perkin-Elmer SCIEX API 300 using ionspray methodology. 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. Thin-layer chromatography was performed on precoated plate of silica gel $60F_{254}$ (Merck) and the spots visualized using an ultraviolet lamp. Flash chromatography was conducted with Merck silica gel 60 (0.040−0.063 mm) as the stationary phase. All air- and moisture-sensitive reactions were conducted under a prepurified argon atmosphere. Organic solvents were purified by standard procedures anhydrous solvents or reagents were transferred via syringe. Compounds **2a**−**g** have been described in the literature,[42,58−61,65] and compounds **4a**, **4m**, **4n**[60] have been reported. Compounds **20a**,**b** have been prepared according to the procedure of Kozikowski.[81] All compounds **4** were tested as oxalate salts.

2-Amino-4-(ethoxymethyl)phenol (1j). 4-Hydroxymethyl-2-nitrophenol. To a solution of 4-hydroxy-3-nitrobenzaldehyde (250 mg, 1.5 mmol) in methanol (15 mL) at 0 °C was added $NaBH_4$ (57 mg, 1.5 mmol). After the mixture was stirred at 0 °C for 1 h, dichloromethane (25 mL) was added and the mixture was extracted. The organic layers were dried over $MgSO_4$ and evaporated, and the red residue was chromatographed on a silica gel column (eluent CH_2Cl_2/MeOH 85:15) to give an oil (172 mg, 68%). IR (film) υ(cm^{-1}) 3380, 3305 (NH, OH). ^1H NMR (DMSO-d_6) δ 2.20 (br s, 1H, OH); 4.67 (s, 2H, CH_2); 7.14 (d, 1H, J = 8.5 Hz, H_6); 7.59 (dd, 1H, J = 1.4 Hz, 8.5 Hz, H_5); 8.08 (d, 1H, J = 1.4 Hz, H_3); 10.53 (br s, 1H, OH). MS m/z 170 $(M + H)^+$. Anal. ($C_7H_7NO_4$) C, H, N.

2-Amino-(4-ethoxymethyl)phenol (1j). To a solution of 4-hydroxymethyl-2-nitrophenol (665 mg, 3.93 mmol) in ethanol (25 mL) was added $SnCl_2{\cdot}2H_2O$ (5.42 g, 23.88 mmol). The mixture was stirred for 2 h at reflux. After cooling, ice was added and the pH was made basic with 30% NaOH. The mixture was extracted with ethyl acetate (4 × 25 mL), and the organic layers were washed with brine and dried over $MgSO_4$. After evaporation an oil was obtained (279 mg, 42%). IR (film) υ(cm^{-1}) 3500−3110 (NH, OH). ^1H NMR ($CDCl_3/D_2O$) δ 1.21 (t, 3H, J = 6.9 Hz, CH_3); 3.50 (q, 2H, J = 6.9 Hz, OCH_2); 4.34 (s, 2H, OCH_2); 6.57 (s, 2H, H_{ar}); 6.71 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 15.3 (CH_3); 65.6 (CH_2); 72.8 (CH_2); 115.3 (CH); 117.0 (CH); 119.7 (CH); 130.8 (C); 134.5 (C); 144.2 (C). MS m/z 168 $(M + H)^+$. Anal. ($C_9H_{13}NO_2$) C, H, N.

Synthesis of Imidazolines 2a−j: General Procedure. Ethyl 3,4-Dihydro-2*H*-1,4-benzoxazine-2-carboxylate 2. General Procedure. Ethyl 2,3-dibromopropanoate (11 mmol) was added to a suspension of the 2-aminophenol **1** (10 mmol) and potassium carbonate (28 mmol) in acetone (20 mL). The mixture was refluxed for 20 h. After cooling and evaporation of the solvent, the residue was treated with water and extracted with dichloromethane or ethyl acetate. The organic layers were washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue which was chromatographed on a silica gel column using CH_2Cl_2/PE or EtOAc/PE as eluent.

Ethyl 6-Fluoro-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2h). Yield 53%; oil. IR (film) υ(cm^{-1}) 3381 (NH), 1743 (CO); ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.0 Hz, CH_3); 3.53−3.57 (m, 2H, H_{3a}, H_{3b}); 3.95 (br s, 1H, NH); 4.23 (q, 2H, J = 7.0 Hz, OCH_2.); 4.75 (dd, 1H, J = 3.5 Hz, 4.7 Hz, H_2); 6.28−6.41 (m, 2H, H_{ar}); 6.83 (dd, 1H, J = 3.5 Hz, 9.0 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 42.7 (NCH_2); 62.1 (OCH_2), 72.8 (CH); 102.5 (CH, J = 27 Hz); 105.6 (CH, J = 23 Hz); 117.7 (CH, J = 9.7 Hz); 133.8 (C, J = 10.7 Hz); 139.1 (C, J = 2.7 Hz); 158.0 (C_6F, J = 237 Hz); 169.7 (CO). MS m/z 226 $(M + H)^+$. Anal. ($C_{11}H_{12}FNO_3$) C, H, N.

Ethyl 6-Trifluoromethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2i). Yield 75%; mp: 106−107 °C. IR (KBr) υ(cm^{-1}): 3375 (NH), 1752 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz, CH_3); 3.60 (d, 2H, J = 3.8 Hz, H_{3a}, H_{3b}); 3.95 (br s, 1H, NH); 4.24 (q, 2H, J = 7.1 Hz, OCH_2); 4.83 (t, 1H, J = 3.8 Hz, H_2); 6.82 (s, 1H, H_{ar}); 6.97 (s, 2H, H_{ar}). ^{13}CNMR ($CDCl_3$) δ 14.5 (CH_3); 42.5 (CH_2); 62.2 (NCH_2), 73.2 (CH); 112.8 (CH); 116.8 (CH); 116.9 (CH); 123.3 (C−CF_3, J = 35 Hz); 126.3 (CF_3, J = 263 Hz); 133.2 (C); 145.6 (C); 169.3 (CO). MS m/z 276 $(M + H)^+$. Anal. ($C_{12}H_{12}F_3NO_3$) C, H, N.

Ethyl 4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3). General Procedure. Benzoxazine **2** (10 mmol) was dissolved in acetone (20 mL) containing K_2CO_3 (30 mmol) and iodomethane (30 mmol). The mixture was heated for 18 h at reflux. After cooling and evaporation of the solvent, the semisolid residue was treated with water and extracted (ethyl acetate). The organic layers were washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate/PE as eluent.

Ethyl 4,6-Dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3c). Yield 63%; oil. IR (film) $\upsilon(cm^{-1})$ 1756 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7$ Hz, CH_3); 2.07 (s, 3H, CH_3); 2.88 (s, 3H, NCH_3); 3.43 (d, 2H, $J = 4.0$ Hz, $H_{3a,}$ H_{3b}); 4.25 (q, 2H, $J = 7$ Hz, OCH_2); 4.85 (t, 1H, $J = 4$ Hz, H_2); 6.53 (d, 2H, $J = 8.5$ Hz, H_8, H_7); 6.83 (d, 1H, $J = 2.0$ Hz, H_5). ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3); 23.3 (CH_3); 40.9 (CH_3); 52.7 (NCH_2); 65.6 (OCH_2); 74.9 (CH); 114.5 (CH); 118.0 (CH); 121.5 (CH); 113.3 (C); 137.6 (C); 143.4 (C); 171.7 (CO). MS *m/z* 236 $(M + H)^+$Anal. ($C_{13}H_{17}NO_3$) C, H, N.

Ethyl 6-Fluoro-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3h). Yield 80%; oil. IR (film) $\upsilon(cm^{-1})$ 1757 (CO); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J = 7.1$ Hz, CH_3); 2.83 (s, 3H, NCH_3); 3.41 (d, 2H, $J = 4.2$ Hz, H_{3a}, H_{3b}); 4.20 (q, 2H, $J = 7.1$ Hz, OCH_2); 4,77 (ft, 1H, $J = 4.2$ Hz, H_2); 6.30−6.37 (m, 2H, H_{ar}); 6.76−6.82 (m, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 43.1 (NCH_3); 50.3 (NCH_2); 62.0 (OCH_2); 72.7 (CHO), 99.8 (CH, $J = 28.1$ Hz); 103.7 (CH, $J = 23.3$ Hz); 116.6 (CH, $J = 9.7$ Hz); 136.9 (C, $J = 10.5$ Hz); 139.4 (C, $J = 2.1$ Hz); 158.5 (C_6F, $J = 237$ Hz); 169.5 (CO). MS *m/z* 240 $(M + H)^+$. Anal. ($C_{12}H_{14}FNO_3$) C, H, N.

Ethyl 6-Trifluoromethyl-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3i). Yield 75%; oil. IR (film) $\upsilon(cm^{-1})$ 1746 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz, CH_3); 2.91 (s, 3H, NCH_3); 3.47 (d, 2H, $J = 4.2$ Hz, H_{3a}, H_{3b}); 4.25 (q, 2H, $J = 7.1$ Hz, OCH_2); 4.89 (t, 1H, $J = 4.2$ Hz; H_2); 6.85 (s, 1H, H_{ar}); 6.94−6.96 (br s, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3); 38.0 (NCH_3); 49.3 (NCH_2); 61.3 (OCH_2); 72.2 (CH), 108.6 (CH); 115.4 (CH); 115.5 (CH); 123.4 (C, $J = 32$ Hz); 125.1 (CF_3, $J = 273$ Hz); 135.3 (C); 145.0 (C); 168.4 (CO). MS *m/z* 290 $(M + H)^+$. Anal. ($C_{13}H_{14}F_3NO_3$) C, H, N.

Ethyl 4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3n). Benzoxazine **2a** (10.3 g, 49.7 mmol) was dissolved in DMF (50 mL) containing K_2CO_3 (20.6 g, 149.1 mmol), sodium iodide (1 g, 6.7 mmol), and benzyl chloride (8.6 mL, 74.7 mmol). The mixture was heated at 60 °C for 6 h. After evaporation of the solvent, the residue was treated with water and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed over a silica gel column using CH_2Cl_2/PE 1:1 as eluent to give a solid (14.46 g, 98%); mp 80 °C (lit. 80 °C).[60] IR (KBr) $\upsilon(cm^{-1})$ 1725 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7$ Hz, CH_3); 3.51 (d, 2H, $J = 4.0$ Hz, $H_{3a,}$ H_{3b}); 4.19−4.27 (m, 2H, OCH_2); 4.34 (d, 1H, $J = 16$ Hz, NCH_2Ph); 4.49 (d, 1H, $J = 16$ Hz, NCH_2Ph); 4.82 (t, 1H, $J = 4.0$ Hz, H_2); 6.67−6.98 (m, 4H, H_{ar}); 7.26−7.33 (m, 5H, H_{ar}). Anal. ($C_{18}H_{19}NO_3$) C, H, N.

Ethyl 4-Propyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3o). Benzoxazine **2a** (1.92 g, 9.27 mmol) was dissolved in a mixture of CH_3CN (20 mL) and HMPA (2 mL) containing K_2CO_3 (3.84 g, 27.8 mmol) and 1-iodopropane (1.8 mL, 18.5 mmol). The mixture was heated at reflux for 18 h. After workup (see **3n**), the residue was chromatographed on a silica gel column using EtOAc/PE as eluent to give an oil (1.42 g, 62%). IR (film) $\upsilon(cm^{-1})$ 1759 (CO); ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, $J = 7$ Hz, CH_3); 1.28 (t, 3H, $J = 7$ Hz, CH_3); 1.55−1.70 (m, 2H, CH_2CH_3); 3,13−3.27 (m, 2H, NCH_2); 3.51 (d, 2H, $J = 4.0$ Hz, $H_{3a,}$ H_{3b}); 4.25 (q, 2H, $J = 7.0$ Hz, OCH_2); 4.80 (t, 1H, $J = 4.0$ Hz, H_2); 6.65−6.96 (m, 4H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 11.5 (CH_3); 14.2 (CH_3); 19.5 (CH_2); 48.3 (CH_2); 52.3 (CH_2); 61.5 (CH_2); 72.4 (CH); 112.1 (CH); 116.5 (CH); 117.8 (CH); 121.8 (CH); 134.6 (C); 142.8 (C); 169.4 (CO). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-2*H*-1,4-benzoxazine (4). General Procedure. To a solution of ethylenediamine (8.7 mmol) in toluene (10 mL) cooled with an ice-bath was dropwise added a 2 M solution of trimethylaluminum in toluene (8.7 mmol). Compound **3** (5 mmol) was added at 0 °C, and then the mixture was heated at reflux for 5−15 h. After cooling and filtration over the filter aid, the mixture was evaporated in vacuo to leave a residue. Water was added, and the residue was extracted with dichloromethane. The organic layers were dried over $MgSO_4$ and evaporated. Column chromatography over pretreated silica gel with triethylamine, using dichloromethane/MeOH 95:5 as eluent, afforded compounds **4**.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,5-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (4b). Yield 90%; white solid; mp 134 °C. IR (KBr) $\upsilon(cm^{-1})$ 3404 (NH), 1631 (C═N); ^1H NMR ($CDCl_3/D_2O$) δ 2.32 (s, 3H, CH_3); 2.76 (s, 3H, NCH_3); 3.04 (dd, 1H, $J = 9.8$ Hz, 14.0 Hz, H_{3a}); 3.38 (dd, 1H, $J = 2.0$ Hz, 14.0 Hz, H_{3b}); 3.68 (s, 4H, NCH_2); 4.80 (dd, 1H, $J = 2.0$ Hz, 9.8 Hz, H_2); 5.03 (s, 1H, NH); 6.77−6.92 (m, 3H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 17.9 (CH_3); 43.6 (CH_3); 49.7 (2 CH_2); 53.4 (CH_2); 65.3 (CH), 114.7 (CH); 123.1 (CH); 123.6 (CH); 133.1 (C); 134.0 (C); 146.7 (C); 165.8 (CN). MS *m/z* 231 $(M)^+$. Anal. ($C_{13}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (4c). Yield 49%; oil. IR (film) $\upsilon(cm^{-1})$ 3408 (NH), 1613 (C═N); ^1H NMR ($CDCl_3/D_2O$) δ 2.29 (s, 3H, $ArCH_3$); 2.90 (s, 3H, NCH_3); 3.34 (dd, 1H, $J = 8.0$ Hz, 11.5 Hz, H_{3a}); 3.52 (dd, 1H, $J = 2.5$ Hz, 11.5 Hz, H_{3b}); 3.68 (s, 4H, NCH_2); 4.96 (dd, 1H, $J = 2.5$ Hz, 8.0 Hz, H_2); 6.51 (d, 1H, $J = 9.0$ Hz, H_{ar}); 6.53 (s, 1H, H_5); 6.74 (d, 1H, $J = 9.0$ Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) 21.5 (CH_3); 39.1 (CH_3); 50.1 (2 CH_2); 52.0 (CH_2); 71.4 (CH); 113.8 (CH); 116.1 (CH); 119.1 (CH); 131.9 (C); 136.0 (C); 141.3 (C); 166.3 (C═N). MS *m/z* 231 $(M)^+$. Anal. ($C_{13}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,7-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (4d). Yield 91%; yellow solid; mp 108 °C. IR (KBr) $\upsilon(cm^{-1})$ 3207 (NH), 1618 (CN); ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3); 2.78 (s, 3H, NCH_3); 3.20 (dd, 1H, $J = 7.5$ Hz, 11.8 Hz, H_{3a}); 3.40 (dd, 1H, $J = 2.8$ Hz, 11.8 Hz, H_{3b}); 3.58 (s, 4H, NCH_2); 4.80 (br s, 1H, NH); 4.84 (dd, 1H, $J = 2.8$ Hz, 7.5 Hz, H_2); 6.52−6.61 (m, 3H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3); 39.0 (CH_3); 49.8 (2 CH_2); 51.9 (CH_2); 71.3 (CH); 113.0 (CH); 116.6 (CH); 122.4 (CH); 128.3 (C); 133.7 (C); 143.2 (C); 165.8 (C═N). MS *m/z* 232 = $(M + H)^+$. Anal. ($C_{13}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,8-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (4e). Yield 86%; yellow solid; mp 142 °C. IR (KBr) $\upsilon(cm^{-1})$ 3212 (NH), 1624 (C═N); ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H, CH_3); 2.87 (s, 3H, NCH_3); 3.30 (dd, 1H, $J = 7.9$ Hz, 11.8 Hz, H_{3a}); 3.51 (dd, 1H, $J = 2.8$ Hz, 11.8 Hz, H_{3a}); 3.66 (s, 4H, NCH_2); 4.58 (br s, 1H, NH); 4.97 (dd, 1H, $J = 2.8$ Hz, 7.9 Hz, H_2); 6.55 (d, 1H, $J = 8$ Hz, H_{ar}); 6.75 (d, 1H, $J = 8$ Hz, H_{ar}); 6.79 (t, 1H, $J = 8$ Hz, H_6). ^{13}C NMR ($CDCl_3$) δ 16.0 (CH_3); 39.0 (CH_3); 49.9 (2 CH_2); 51.7 (CH_2); 71.1 (CH); 110.7 (CH); 121.0 (CH); 121.2 (CH); 125.1 (C); 135.7 (C); 141.1 (C); 165.9 (C═N). MS *m/z* 232 $(M + H)^+$. Anal. ($C_{13}H_{17}N_3O$. $C_2H_2O_4$) C, H, N.

6-Chloro-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4f). Yield 71%; white solid; mp 172 °C. IR (KBr) $\upsilon(cm^{-1})$ 3192 (NH), 1616 (C═N); ^1H NMR $CDCl_3/D_2O$) δ 2.87 (s, 3H, NCH_3); 3.33 (dd, 1H, $J = 7.7$ Hz, 12.0 Hz, H_{3a}); 3.51 (dd, 1H, $J = 3.0$ Hz, 12.0 Hz, H_{3b}); 3.64 (s, 4H, NCH_2); 4.40−4.80 (br s, 1H, NH); 4.89 (dd, 1H, $J = 3.0$ Hz, 7.7 Hz, H_2); 6.65−6.83 (m, 3H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 38.3 (CH_3); 49.7 (2 CH_2); 51.2 (CH_2); 70.8 (CH), 112.0 (CH); 116.5 (CH); 117.3 (CH); 126.9 (C); 136.7 (C); 141.4 (C); 164.9 (CN). Anal. ($C_{12}H_{14}ClN_3O$. $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-6-methoxy-3,4-dihydro-2*H*-1,4-benzoxazine (4g). Yield 86%; white solid; mp 122 °C. IR (KBr) $\upsilon(cm^{-1})$ 3204 (NH), 1620 (C═N); ^1H NMR ($CDCl_3$) δ 2.81 (s, 3H, NCH_3); 3.27 (dd, 1H, $J = 7.8$ Hz, 11.8 Hz, H_{3a}); 3.43 (dd, 1H, $J = 2.8$ Hz, 11.8 Hz, H_{3b}); 3.57 (s, 4H, NCH_2); 3.68 (s, 3H, OCH_3); 4.81 (dd, 1H, $J = 2.8$ Hz, 7.8 Hz, H_2); 4.94 (br s, 1H, NH); 6.13 (dd, 1H, $J = 2.8$ Hz, 8.6 Hz, H_7); 6.19 (d, 1H, $J = 2.9$ Hz, H_5); 6.66 (d, 1H, $J = 8.6$ Hz, H_8). ^{13}C NMR ($CDCl_3$) δ 38.8 (CH_3); 50.0 (2 CH_2); 51.8 (CH_2); 55.8 (CH_3); 71.1 (CH); 100.0 (CH); 102.0 (CH); 116.2 (CH); 136.9 (C); 137.6 (C); 155.3 (C); 166.0 (C═N). MS *m/z* 247 $(M)^+$. Anal. $C_{13}H_{17}N_3O_2$, $C_2H_2O_4$) C, H, N.

6-Fluoro-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4h). Yield 68%; solid; mp 142 °C. IR (KBr) $\upsilon(cm^{-1})$ 3201 (NH), 1617 (C═N); ^1H NMR ($CDCl_3/D_2O$) δ 2.81 (s, 3H, NCH_3); 3.31 (dd, 1H, $J = 9.0$ Hz,

14.0 Hz, H_{3a}); 3.46 (dd, 1H, J = 3.1 Hz, 14.0 Hz, H_{3b}); 3.59 (s, 4H, NCH_2); 4.82 (dd, 1H, J = 3.1 Hz, 9.0 Hz; H_2); 6.22−6.35 (m, 2H, H_{ar}); 6.63−6.70 (m, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 38.8 (NCH_3); 49.6 (2 CH_2); 51.5 (NCH_2); 71.2 (CH); 99.8 (CH, J = 28 Hz); 103.7 (CH, J = 23 Hz); 116.4 (CH, J = 10 Hz); 137.2 (C, J = 2 Hz); 139.3 (C, J = 10 Hz); 159.1 (C_6F, J = 231 Hz); 165.7 (CN). MS m/z 236 $(M + H)^+$. Anal. ($C_{12}H_{14}FN_3O$. $C_2H_2O_4$) C, H, N. The racemic mixture was dissolved in the minimum amount of ethanol, and D(+)-dibenzoyl tartaric acid (0.5 equiv) in the minimum amount of ethanol was slowly added. After stirring for 2 h at room temperature, the mixture was chilled with an ice-bath. The solid was filtered and washed with ice-cold ethanol, and the diastereomic purity was checked by capillary electrophoresis. The solid was dissolved in dichloromethane and treated with an aqueous solution of sodium hydrogenocarbonate to afford the enantiomer (+)-**4h** which was immediately treated, to prevent the quick racemization, with an ethanolic solution of oxalic acid to afford the oxalate salt; mp 199 °C α_D = +57° DMSO c = 1.0. The enantiomeric purity of (+)-**4h** was of 97% determined by capillary electrophoresis on the free base. Similarly (−)-**4h** is obtained from L(−)-dibenzoyl tartaric acid; enantiomeric purity 98%; mp 199 °C; α_D = −54.2° DMSO, c = 0.8.

6-Trifluoromethyl-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4i). Yield 76%; solid; mp 151−152 °C. IR (KBr) υ(cm^{-1}) 3208 (NH), 1617 (C═N); ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3H, NCH_3); 3.35 (dd, 1H, J = 7.5 Hz, 12.0 Hz, H_{3a}); 3.53 (dd, 1H, J = 2.7 Hz, 12.0 Hz, H_{3b}); 3.64 (s, 4H, NCH_2); 4.95 (dd, 1H, J = 2.7 Hz, 7.5 Hz, H_2); 6.83−6.93 (m, 3H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 38.5 (NCH_3); 50.0 ($2CH_2$); 51.1 (CH_2); 71.4 (CH); 109.5 (CH); 115.4 (CH); 116.2 (CH); 124.1 (C−CF_3, J = 32 Hz); 126.0 (CF_3, J = 271 Hz); 136.4 (C); 145.8 (C); 165.0 (CN). MS m/z 286 $(M + H)^+$. Anal. ($C_{13}H_{14}F_3N_3O$. $C_2H_2O_4$) C, H, N.

6-Ethoxymethyl-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4j). Ethyl 6-(ethoxymethyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2j). Obtained from **1j** using the general procedure; yield 60%; oil. IR (film) υ(cm^{-1}) 3378 (NH), 1755 (CO); ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 6.9 Hz, CH_3); 1.27 (t, 3H, J = 6.9 Hz, CH_3); 3.50 (q, 2H, J = 6.9 Hz, OCH_2); 3.55 (d, 2H, J = 4.1 Hz, H_{3a}, H_{3b}); 3.78 (br s, 1H, NH); 4.23 (q, 2H, J = 6.9 Hz, OCH_2); 4.35 (s, 2H, OCH_2); 4.77 (t, 1H, J = 4.1 Hz, H_2); 6.61 (d, 1H, J = 1.9 Hz, H_5); 6.67 (dd, 1H, J = 1.9 Hz, 8.2 Hz, H_7); 6.88 (d, 1H, J = 8.2 Hz, H_8). ^{13}C NMR ($CDCl_3$) δ 14.53 (CH_3); 15.6 (CH_3); 43.0 (NCH_2); 62.0 (OCH_2), 65.9 (CH_2); 72.9 (CH_2); 73.2 (CH); 115.7 (CH); 117.1 (CH); 119.6 (CH); 132.3 (C); 133.0 (C); 142.86 (C); 169.8 (CO). MS m/z 266 $(M + H)^+$. Anal. ($C_{14}H_{19}NO_4$) C, H, N.

Ethyl 6-Ethoxymethyl-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3j). Obtained from **2j** using the general procedure. Yield 63%; oil. IR (film) υ(cm^{-1}) 1759 (CO); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 6.9 Hz, CH_3); 1.27 (t, 3H, J = 6.9 Hz, CH_3); 2.88 (s, 3H, NCH_3); 3.43 (d, 2H, J = 4.1 Hz, H_{3a}, H_{3b}); 3.51 (q, 2H, J = 6.9 Hz, OCH_2); 4.24 (q, 2H, J = 6.9 Hz, OCH_2); 4.39 (s, 2H, OCH_2); 4.85 (t, 1H, J = 4.1 Hz, H_2); 6.61−6.65 (m, 2H, H_{ar}); 6.87 (d, 1H, J = 8.4 Hz, H_8). ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3); 15.2 (CH_3); 38.6 (NCH_3); 50.2 (NCH_2); 61.5 (OCH_2); 65.4 (CH_2); 72.7 (CH_2O); 72.8 (CH), 112.2 (CH); 115.7 (CH); 118.6 (CH); 131.8 (C); 135.7 (C); 142.6 (C); 169.3 (CO). MS m/z 280 $(M + H)^+$. Anal. ($C_{15}H_{21}NO_4$) C, H, N.

6-Ethoxymethyl-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4j). Obtained from **3j** using the general procedure. Yield 66%; gum. IR (KBr) υ(cm^{-1}) 3088 (NH), 1607 (C═N); ^{1}H NMR ($CDCl_3$/D_2O) δ 1.24 (t, 3H, J = 6.9 Hz, CH_3); 2.90 (s, 3H, NCH_3); 3.35 (dd, 1H, J = 4.4 Hz, 7.5 Hz, H_{3a}); 3.52 (q, 2H, J = 6.9 Hz, OCH_2); 3.53 (dd, 1H, J = 2.8 Hz, 7.5 Hz, H_{3b}); 3.65 (s, 4H, NCH_2); 4.40 (s, 2H, OCH_2); 4.94 (dd, 1H, J = 2.8 Hz, 4.4 Hz, H_2); 6.62−6.68 (m, 2H, H_{ar}); 6.78 (d, 1H, J = 8.2 Hz, H_8). ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3); 39.0 (NCH_3); 50.1 ($2CH_2$); 51.9 (CH_2); 65.9 (CH_2); 71.5 (CH); 73.9 (CH_2); 112.7 (CH); 116.0 (CH); 118.4 (CH); 132.6 (C); 136.3 (C); 143.0 (C); 166.1 (CN). MS m/z 276 $(M + H)^+$. Anal. ($C_{15}H_{21}N_3O_2$. $C_2H_2O_4$) C, H, N.

6-Hydroxymethyl-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4k). 4-Hydroxymethyl-2-aminophenol (1k). To a suspension of $LiAlH_4$ (270 mg, 7.11 mmol) in THF (5 mL) cooled at 10 °C was added dropwise 3-nitro-4-hydroxybenzaldehyde (300 mg, 1.79 mmol) in THF (5 mL). After the mixture was stirred for 1 h at 40 °C, THF (15 mL) was added and then water. Diluted HCl was added till pH 7, and the mixture was filtered. The residue was evaporated in the presence of methanol and then chromatographed on a silica gel column using as eluent CH_2Cl_2/MeOH 19:1 to give an orange solid (92 mg, 37%); mp 143−144 °C. IR (KBr) υ(cm^{-1}) 3250−3390 (NH, OH). ^{1}H NMR (MeOD) δ 4.41 (s, 2H, CH_2); 4.80−4.95 (br s, 3H, OH, NH_2); 6.58 (dd, 1H, J = 1.9 Hz, 8.2 Hz, H_5); 6.67 (d, 1H, J = 8.2 Hz, H_6); 6.75 (d, 1H, J = 1.9 Hz, H_3); 8.91 (br s, 1H, OH). ^{13}C NMR (MeOD) δ 65.3 (CH_2); 113.2 (CH); 115.2 (CH); 119.2 (CH); 134.0 (C); 135.9 (C); 145.8 (C). MS m/z 140 $(M + H)^+$. Anal. ($C_7H_9NO_2$) C, H, N.

Ethyl 6-Hydroxymethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (2k). Obtained from **1k** using the general procedure. Yield 39%; brown oil. IR (film) υ(cm^{-1}) 3378 (NH, OH), 1755 (CO); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz, CH_3); 3.54 (dd, 2H, J = 3.4 Hz, 4.7 Hz, H_{3a}, H_{3b}); 4.23 (q, 2H, J = 7.2 Hz, OCH_2); 4.50 (s, 2H, OCH_2); 4.77 (dd, 1H, J = 3.4 Hz, 4.7 Hz, H_2); 6.59 (d, 1H, J = 1.9 Hz, H_5); 6.67 (dd, 1H, J = 1.9 Hz, 8.2 Hz, H_7); 6.88 (d, 1H, J = 8.2 Hz, H_8). ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3); 42.5 (CH_2); 61.6 (OCH_2), 65.1 (OCH_2); 72.8 (CH); 114.6 (CH); 116.8 (CH); 118.4 (CH); 132.7 (C); 134.4 (C); 142.4 (C); 169.4 (CO). MS m/z 238 $(M + H)^+$. Anal. ($C_{12}H_{15}NO_4$) C, H, N.

Ethyl 6-Hydroxymethyl-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (3k). Obtained from **2k** using the general procedure. Yield 55%; oil. IR (film) υ(cm^{-1}): 1759 (CO); ^{1}H NMR ($CDCl_3$/D_2O) δ 1.27 (t, 3H, J = 7.1 Hz, CH_3); 2.89 (s, 3H, NCH_3); 3.43 (d, 2H, J = 4.2 Hz, H_{3a}, H_{3b}); 4.25 (q, 2H, J = 7.1 Hz, OCH_2); 4.57 (s, 2H, OCH_2); 4.85 (t, 1H, J = 4.2 Hz, H_2); 6.68 (d, 1H, J = 7.0 Hz, H_8); 6.70 (d, 1H, J = 1.5 Hz, H_5); 6.89 (dd, 1H, J = 1.5 Hz, 7.0 Hz, H_7). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 38.8 (NCH_3); 50.4 (NCH_2); 61.7 (OCH_2); 65.7 (CH_2); 72.8 (CH), 111.8 (CH); 116.2 (CH); 117.9 (CH); 134.5 (C); 136.0 (C); 142.9 (C); 169.5 (CO). MS m/z 252 $(M + H)^+$. Anal. ($C_{13}H_{17}NO_4$) C, H, N.

6-Hydroxymethyl-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (4k). Obtained from **3k** using the general procedure. Yield 62%; white solid; mp 141−142 °C. IR (KBr) υ(cm^{-1}): 3420−3240 (OH, NH), 1617 (C═N); ^{1}H NMR ($CDCl_3$/D_2O) δ 2.86 (s, 3H, NCH_3); 3.25 (dd, 1H, J = 2.8 Hz, 11.9 Hz, H_{3a}); 3.43 (dd, 1H, J = 7.8 Hz, 11.9 Hz, H_{3b}); 3.64 (s, 4H, NCH_2); 4.55 (s, 2H, OCH_2); 4.66 (dd, 1H, J = 2.8 Hz, 7.8 Hz, H_2); 6.62 (dd, 1H, J = 1.6 Hz, 7.9 Hz, H_7); 6.70 (d, 1H, J = 1.6 Hz, H_5); 6.77 (d, 1H, J = 7.9 Hz, H_8). ^{13}C NMR ($CDCl_3$) δ 38.5 (NCH_3); 49.9 ($2CH_2$); 51.5 (CH_2); 64.8 (CH_2OH); 70.7 (CH); 111.5 (CH); 115.6 (CH); 116.8 (CH); 135.5 (C); 135.7 (C); 142.2 (C); 165.7 (CN). MS m/z 248 $(M + H)^+$. Anal. ($C_{13}H_{17}N_3O_2$, $C_2H_2O_4$) C, H, N.

Methyl 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate (4l). To a solution of **5** (464 mg, 2 mmol) in toluene (5 mL) were added ethylenediamine (1.81 g, 30 mmol, 15 equiv) and a catalytic amount of phosphorus pentasulfide. The mixture was heated at reflux for 4 h. Evaporation of the solvent and addition of water was followed by extraction with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatagraphed on a silica gel column (eluent CH_2Cl_2/MeOH 90:10) to give a white solid (335 mg, 61%); mp 127−129 °C. IR (KBr) υ(cm^{-1}) 3101 (NH), 1749 (CO), 1617 (C═N); ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3H, NCH_3); 3.34 (dd, 1H, J = 7.8 Hz, 12.9 Hz, H_{3a}); 3.54 (dd, 1H, J = 2.9 Hz, 12.9 Hz, H_{3b}); 3.65 (s, 4H, NCH_2); 4.99 (dd, 1H, J = 2.9 Hz, 7.8 Hz, H_2); 6.82 (d, 1H, J = 8.3 Hz, H_8); 7.37 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 39.4 (NCH_3); 46.1 ($2CH_2$); 50.0 (CH_2); 53.2 (CH_3); 70.3 (CH); 114.6 (CH); 117.5 (CH); 121.5 (CH); 124.8 (C); 137.1 (C); 147.2 (C); 165.8 (C═N or C═O); 168.7 (C═N or C═O). MS m/z $(M + H)^+$= 276. Anal. ($C_{14}H_{17}N_3O_3$, $C_2H_2O_4$) C, H, N.

4-Propyl-2(4,5-dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine (4o). Obtained from **3o** using the general procedure described for **4** in 78% yield; white solid; mp 140 °C. IR (KBr) $\upsilon(cm^{-1})$ 3188 (NH), 1616 (C═N); ^1H NMR ($CDCl_3/D_2O$) δ 0.94 (t, 3H, J = 7.0 Hz, CH_3); 1.55−1.70 (m, 2H, CH_2); 3.10−3.34 (m, 2H, CH_2); 3.38 (dd, 1H, J = 8.0 Hz, 12.0 Hz, H_{3a}); 3.59 (dd, 1H, J = 3.0 Hz, 12.0 Hz, H_{3b}); 3.66 (s, 4H, NCH_2); 4.85 (dd, 1H, J = 3.0 Hz, 8.0 Hz, H_2); 6.62−6.87 (m, 4H, H_{ar}). ^{13}C NMR ($CDCl_3/D_2O$) δ 11.5 (CH_3); 19.5 (CH_2); 49.7 (CH_2); 49.8 (2 CH_2), 52.9 (CH_2); 70.7 (CH); 112.3 (CH); 116.4 (CH); 117.2 (CH); 122.2 (CH); 134.9 (C); 142.8 (C); 175.3 (C═N). MS m/z 245 $(M)^+$. Anal. ($C_{14}H_{19}N_3O$, $C_2H_2O_4$) C, H, N.

Methyl 2-Cyano-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate (5). Methyl 2-Cyano-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate. Methyl 3-amino-4-hydroxybenzoate (1.34 g, 8 mmol), K_2CO_3 (2.99 g, 21.6 mmol), and 2-chloroacrylonitrile (0.75 mL, 8.8 mmol) in acetonitrile (30 mL) were heated at reflux for 18 h. After cooling, the solvent was evaporated, water was added, and the mixture was extracted with CH_2Cl_2. Drying over $MgSO_4$ and evaporation a residue which was chromatagraphed on a silica gel column (eluent EtOAc/PE 8:2) to give a brown oil (1.44 mg, 77%). IR (film) $\upsilon(cm^{-1})$ 3378 (NH), 2210 (C≡N); 1745 (CO); ^1H NMR ($CDCl_3$) δ 3.64 (t, 2H, J = 3.2 Hz, H_{3a}, H_{3b}); 3.87 (s, 3H, CH_3); 4.28 (br s, 1H, NH); 5.15 (t, 1H, J = 3.2 Hz, H_2); 6.90 (d, 1H, J = 8.2 Hz, H_8); 7.42 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) 43.5 (CH_2); 52.5 (CH_3); 62.9 (CH); 116.1 (C); 117.7 (CH); 118.0 (CH); 122.0 (CH); 125.4 (C); 131.9 (C); 145.0 (C); 167.1 (CO). MS m/z 219 $(M + H)^+$. Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.

Methyl 2-Cyano-4-methyl-3−4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate (5). Same procedure as for **3** using HMPA instead of acetone as solvent; yellow solid; yield 45%. Mp 119−120 °C. IR (KBr) $\upsilon(cm^{-1})$ 2211 (C≡N), 1755 (CO); ^1H NMR ($CDCl_3$) δ 3.02 (s, 3H, CH_3); 3.42−3.57 (m, 2H, H_{3a}, H_{3b}); 3.89 (s, 3H, CH_3); 5.20 (t, 1H, J = 3.4 Hz, H_2); 6.89 (d, 1H, J = 8.3 Hz, H_8); 7.41−7.45 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 39.0 (NCH_3); 50.7 (CH_2); 52.4 (OCH_3); 63.0 (CH); 117.7 (CH); 114.6 (CH); 116.2 (CN); 121.5 (CH); 125.4 (C); 135.2 (C); 145.3 (C); 167.2 (CO). MS m/z 233 $(M + H)^+$. Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

Ethyl 7-Bromo-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (6). Benzoxazine **4c** (705 mg, 3 mmol), NBS (561 mg, 3.15 mmol), and AIBN (10 mg) in CCl_4 (20 mL) were heated at reflux for 2 h. After cooling and filtration, water was added and the mixture extracted with ethyl acetate. The organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column using EtOAc/PE 3:7 as eluent to yield an oil (848 mg, 90%). IR (film) $\upsilon(cm^{-1})$ 1731 (CO); ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.0 Hz, CH_3); 2.26 (s, 3H, CH_3); 2.81 (s, 3H, NCH_3); 3.37 (d, 2H, J = 4.3 Hz, H_{3a}, H_{3b}); 4.25 (q, 2H, J = 7.0 Hz, CH_2); 4.80 (t, 1H, J = 4.3 Hz, H_2); 6.50 (s, 1H, H_{ar}); 7.07 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3); 22.7 (NCH_3); 39.0 (CH_3); 50.5 (NCH_2); 62.1 (OCH_2); 73.1 (CH); 112.6 (C); 114.7 (CH); 119.7 (CH); 130.7 (C); 135.4 (C); 142.1 (C); 169.6 (CO). MS m/z 314 and 316 $(M + H)^+$. Anal. ($C_{13}H_{16}BrNO_3$) C, H, N.

Ethyl 4,6,7-Trimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (7). Benzoxazine **6** (471 mg, 1.5 mmol), tetramethyltin (1 mL, 7.2 mmol), and $Pd(PPh_3)_4$ (333 mg, 0.29 mmol) in HMPA (10 mL) were heated at reflux for 3 h. After cooling, water was added and the mixture twice extracted with dichloromethane (2 × 25 mL). The organic layers were washed six times with water and dried over $MgSO_4$. Evaporation in vacuo left a residue which was chromatographed on a silica gel column using AcOEt/PE 3:7 as eluent to give an oil (246 mg, 66%). IR (film) $\upsilon(cm^{-1})$ 1732 (CO);^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz, CH_3); 2,14 (s, 3H, CH_3); 2.17 (s, 3H, CH_3); 2.82 (s, 3H, NCH_3); 3.40 (dd, 2H, J = 4.2 Hz, 11.7 Hz, H_{3a}, H_{3b}); 4.28 (q, 2H, J = 7.2 Hz, OCH_2.); 4.83 (t, 1H, J = 4.2 Hz, H_2); 6.17 (s, 1H, H_{ar}); 6.72 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 18.8 (CH_3); 19.3 (CH_3); 39.0 (NCH_3); 50.8 (CH_2); 61.5 (CH_2); 72.8 (CH); 114.0 (CH); 117.3 (CH); 127.0 (C); 129.2 (C); 133.4 (C); 141.2 (C); 169.6 (CO). MS m/z 250 $(M + H)^+$. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

2(4,5-Dihydro-1*H*-imidazol-2-yl)-4,6,7-trimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (8). This compound was obtained in 68% yield from **7** according to the general procedure; white solid; mp 151 °C. IR (KBr) $\upsilon(cm^{-1})$ 3181 (NH), 1614 (C═N); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3); 2.16 (s, 3H, CH_3); 2.87 (s, 3H, NCH_3); 3.24 (dd, 1H, J = 7.5 Hz, 11.7 Hz, H_{3a}); 3.43 (dd, 1H, J = 2.6 Hz, 11.7 Hz, H_{3b}); 3.63 (s, 4H, NCH_2); 4.60 (br s, 1H, NH); 4.92 (dd, 1H, J = 2.6 Hz, 7.5 Hz, H_2); 6.49 (s, 1H, H_{ar}); 6.61 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 19.2 (CH_3); 19.7 (CH_3); 39.4 (CH_3); 50.1 ($2CH_2$); 52.4 (CH_2); 71.5 (CH); 114.9 (CH); 117.5 (CH); 126.9 (C); 130.0 (C); 134.0 (C); 141.5 (C); 166.5 (C═N). MS m/z 246 $(M + H)^+$. Anal. ($C_{14}H_{19}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,6,8-trimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (9). Ethyl 6,8-Dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. Obtained from 2,4-dimethyl-6-aminophenol according to the general procedure, as an oil; yield 32%. IR (film) $\upsilon(cm^{-1})$ 3382 (NH), 1759 (CO). ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3); 2.16 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 3.54 (d, 2H, J = 3.8 Hz, H_{3a}, H_{3b}); 3.60 (s, 1H, NH); 4.25 (q, 2H, J = 7.2 Hz, OCH_2); 4.77 (t, 1H, J = 3.8 Hz, H_2); 6.26 (s, 1H, H_{ar}); 6.38 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 15.7 (CH_3); 20.8 (CH_3); 42.8 (CH_2); 61.5 (CH_2); 72.9 (CH); 114.1 (CH); 122.0 (CH); 126.1 (C); 130.3 (C); 132.0 (C); 139.0 (C); 169.8 (CO). MS m/z 236 $(M + H)^+$. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

Ethyl 4,6,8-Trimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. Obtained from ethyl 6,8-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate using the general procedure. Yield 65%; oil. IR (film) $\upsilon(cm^{-1})$ 1759 (CO); ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz, CH_3); 2.19 (s, 3H, CH_3); 2.21 (s, 3H, CH_3); 2.83 (s, 3H, NCH_3); 3.39 (d, 2H, J = 4.0 Hz, H_{3a}, H_{3b}); 4.23 (q, 2H, J = 7.1 Hz, OCH_2); 4.84 (t, 1H, J = 4.0 Hz, H_2); 6.34 (s, 1H, H_{ar}); 6.40 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 16.2 (CH_3); 21.4 (CH_3); 39.3 (NCH_3); 51.0 (CH_2); 60.8 (CH_2); 73.0 (CH); 111.5 (CH); 121.8 (CH); 125.5 (C); 130.4 (C); 135.6 (C); 139.5 (C); 171.1 (CO). MS m/z 250 $(M + H)^+$. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,6,8-trimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (9). Obtained from ethyl 4,6,8-trimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. Yield 70%; white solid; mp 159 °C; IR (KBr) $\upsilon(cm^{-1})$ 3127 (NH), 1626 (C═N); ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 2.86 (s, 3H, NCH_3); 3.30 (dd, 1H, J = 7.5 Hz, 11.6 Hz, H_{3a}); 3.46 (dd, 1H, J = 2.8 Hz, 11.6 Hz, H_{3b}); 3.66 (s, 4H, NCH_2); 3.93 (br s, 1H, NH); 4.95 (dd, 1H, J = 2.8 Hz, 7.5 Hz, H_2); 6.37 (s, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 15.9 (CH_3); 21.0 (CH_3); 38.9 (NCH_3); 49.6 ($2CH_2$); 51.7 (CH_2); 70.9 (CH); 111.2 (CH); 120.9 (CH); 124.6 (C); 130.5 (C); 135.4 (C); 138.9 (C); 166.2 (C═N). MS m/z 246 $(M + H)^+$. Anal. ($C_{14}H_{19}N_3O$. $C_2H_2O_4$) C, H, N.

3-Amino-5,6,7,8-tetrahydro-2-naphthol Bromhydrate (11). 1-Bromo-5,6,7,8-tetrahydro-2-naphthol.[46,79] To a solution of compound **10** (2.50 g, 16.9 mmol) in DMF (5 mL) was added NBS (3 g, 16.9 mmol) dissolved in DMF (5 mL). The mixture was stirred at room temperature for 24 h. Water was added, and the mixture was extracted with CH_2Cl_2. Drying of the organic layers over $MgSO_4$ and evaporation in vacuo left a residue which was chromatographed on a silica gel column using CH_2Cl_2/PE 75:25 as eluent. A white solid was obtained (3.62 g, 94%); mp 67−68 °C; (Lit 74 °C).[46] IR (KBr) $\upsilon(cm^{-1})$ 3313 (OH); ^1H NMR ($CDCl_3$): δ 1.74−1.83 (m, 4H, CH_2); 2.69−2.74 (m, 4H, CH_2); 5.44 (s, 1H, OH); 6.80−6.83(d, 1H, J = 8.3 Hz, H_{ar}); 6.95 (d, 1H, J = 8.3 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.7 (CH_2); 23.1 (CH_2); 29.3 (CH_2); 30.5 (CH_2); 112.8 (CH); 113.5 (C); 129.1 (CH); 131.0 (C); 136.6 (C); 150.0 (C). Anal. ($C_{10}H_{11}BrO$) C, H, N.

1-Bromo-3-nitro-5,6,7,8-tetrahydro-2-naphthol. 1-Bromo-5,6,7,8-tetrahydro-2-naphthol (2.30 g, 10.1 mmol) was dissolved in acetic acid (23 mL) and water (2.3 mL). After cooling at 5 °C, fuming HNO_3 (0.5 mL) in acetic acid (4.5 mL) was dropwise added. The mixture was stirred 15 min at 5 °C, and water was added. Extraction with CH_2Cl_2, washing the organic layers with water, drying over $MgSO_4$, and evaporation left a residue which was chromatographed on a silica gel column

using EtOAc/PE 1:9 as eluent. A yellow solid was obtained (1.62 g, 59%); mp 133−134 °C; (lit. 133 °C)[46] IR (KBr) υ(cm^{-1}) 3160 (OH); ^{1}H NMR ($CDCl_3$): δ 1.76−1.83 (m, 4H, CH_2); 2.75−2.84 (m, 4H, CH_2); 7.82 (s, 1H, H_4); 11.05 (s, 1H, OH). ^{13}C NMR; ($CDCl_3$) δ 22.4 (CH_2); 22.8 (CH_2); 29.6 (CH_2); 31.9 (CH_2); 115.7 (C); 123.6 (CH); 131.1 (C); 131.9 (C); 148.8 (C); 150.0 (C). Anal. ($C_{10}H_{10}BrNO_3$) C, H, N.

3-Amino-5,6,7,8-tetrahydro-2-naphthol Bromhydrate (11). 1-Bromo-3-nitro-5,6,7,8-tetrahydro-2-naphthol (1.70 g, 6.25 mmol) was dissolved in a mixture of methanol (17 mL) and THF (17 mL), Pd/C 10% (425 mg) was added, hydrogen was admitted (3 atm), and the mixture was stirred at room temperature for 24 h. After filtration and evaporation in vacuo, a solid was obtained which was recrystallized in ether to afford a gray solid (960 mg, 63%); mp 123−124 °C (lit. 130 °C).[44] IR (KBr): υ(cm^{-1}) 3424, 3238 (NH, OH); ^{1}H NMR (DMSO-d_6) δ 1.60−1.72 (m, 4H, CH_2); 2.53−2.67 (m, 4H, CH_2); 6.69 (s, 1H, H_{ar}); 6.96 (s, 1H, H_{ar}); 9.67 (br s, 2H, NH_2); 10.21 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_2); 21.1 (CH_2); 26.3 (CH_2); 27.0 (CH_2); 114.4 (C); 114.9 (CH); 122.3 (C); 126.0 (CH); 136.1 (C); 146.6 (C). Anal. ($C_{10}H_{13}NO$, HBr) C, H, N.

Ethyl 4-Methyl-3,4,6,7,8,9-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate (12). Ethyl 3,4,6,7,8,9-Hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate. Obtained in a manner similar to **2a**, starting from compound **11**. Yield 59%; oil. IR (film) υ(cm^{-1}) 3380 (NH), 1731 (CO); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz, CH_3); 1.68−1.70 (m, 4H, CH_2); 2.55−2.63 (m, 4H, CH_2); 3.45−3.55 (m, 2H, H_{3a}, H_{3b}); 3.57 (br s, 1H, NH); 4.21 (q, 2H, J = 7.1 Hz, OCH_2); 4.71 (t, 1H, J = 3.5 Hz, H_2); 6.28 (s, 1H, H_{ar}); 6.60 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 23.4 (CH_2); 23.4 (CH_2); 28.7 (CH_2); 28.7 (CH_2); 42.9 (CH_2); 61.5 (CH_2); 73.0 (CH); 115.9 (CH); 116.7 (CH); 128.4 (C); 130.0 (C); 130.2 (C); 141.1 (C); 169.6 (CO). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

Ethyl 4-Methyl-3,4,6,7,8,9-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate 12. Similarly obtained as for **3a** starting from ethyl 3,4,6,7,8,9-hexahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate; yield 66%; oil. IR (film) υ(cm^{-1}) 1756 (CO);^{1}H NMR ($CDCl_3$/D_2O) δ 1.29 (t, 3H, J = 7.0 Hz, CH_3); 1.62−1.78 (m, 4H, CH_2); 2.60−2.75 (m, 4H, CH_2); 2.84 (s, 3H, NCH_3); 3.37 (d, 2H, J = 4.1 Hz, H_{3a}, H_{3b}); 4.26 (q, 2H, J = 7.0 Hz, OCH_2); 4.83 (t, 1H, J = 4.1 Hz, H_2); 6.38 (s, 1H, H_{ar}); 6.65 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3); 24.9 (CH_2); 25.0 (CH_2); 30.1 (CH_2); 30. 6 (CH_2); 40.4 (CH_3); 52.2 (CH_2); 63.0 (CH_2); 74.4 (CH); 117.5 (CH); 117.5 (CH); 129.2 (C); 131.3 (C); 135.2 (C); 142.8 (C); 171.1 (CO). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4,6,7,8,9-hexahydro-2*H*-naphtho[2,3-*b*][1,4] oxazine (13). Obtained from **12** using the general procedure described for **4a**; yield 90%; white solid; mp 121−122 °C. IR (KBr): υ(cm^{-1}) 3159 (NH), 1612 (C═N); ^{1}H NMR ($CDCl_3$/D_2O) δ 1.70−1.77 (m, 4H, CH_2); 2.60−2.75 (m, 4H, CH_2); 2.83 (s, 3H, NCH_3); 3.25 (dd, 1H, J = 7.6 Hz, 11.7 Hz, H_{3a}); 3.45 (dd, 1H, J = 2.9 Hz, 11.7 Hz, H_{3b}); 3.63 (s, 4H, NCH_2); 4.92 (dd, 1H, J = 2.9 Hz, 7.6 Hz, H_2); 6.38 (s, 1H, H_{ar}); 6.53 (s, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.6 (CH_2); 22.7 (CH_2); 27.7 (CH_2); 28.2 (CH_2); 38.1 (CH_3); 48.9 (2 CH_2); 51.1 (CH_2); 70.4 (CH); 112.2 (CH); 115.0 (CH); 126.3 (C); 129.4 (C); 133.1 (C); 140.8 (C); 165.1 (CN). MS m/z 272 (M + H)$^+$. Anal. ($C_{16}H_{21}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine (15). Ethyl 3,4-Dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-2-carboxylate. Obtained from **14** as for **2a**; yield 29%; oil. IR (film) υ(cm^{-1}) 3402 (NH), 1746 (CO); ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 7.1 Hz, CH_3); 3.71−3.80 (m, 2H, H_{3a}, H_{3b}); 4.02 (br s, 1H, NH); 4.23 (q, 2H, J = 7.1 Hz, OCH_2); 4.81 (t, 1H, J = 4.0 Hz, H_2); 7.18−7.45 (m, 4H, H_{ar}); 7.65−7.79 (m, 2H, H_{ar}). ^{13}C NMR: ($CDCl_3$) δ 12.8 (CH_3); 41.8 (CH_2); 60.2 (CH_2); 70.9 (CH); 117.0 (CH); 118.0 (CH); 118.3 (CH); 122.4 (CH); 123.4 (C); 123.6 (C); 124.0 (CH); 127.1(CH); 128.3 (C); 137.8 (C); 168.1 (CO). Anal. ($C_{15}H_{15}NO_3$) C, H, N.

Ethyl 4-Methyl-3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-2-carboxylate. Obtained in 77% yield from ethyl 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-2-carboxylate as for **3**; oil; IR (film) υ(cm^{-1}) 1760 (CO); ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3H, J = 7.0 Hz, CH_3); 2.99 (s, 3H, NCH_3); 3.25 (dd, 1H, J = 9.0 Hz, 14.0 Hz, H_{3a}); 3.52 (dd, 1H, J = 2.7 Hz, 14.0 Hz, H_{3b}); 4.32 (q, 2H, J = 7.0 Hz, OCH_2); 4.74 (dd, 1H, J = 2.7 Hz, 9.0 Hz, H_2); 7.23 (d, 1H, J = 8.2 Hz, H_{ar}); 7.30−7.50 (m, 3H, H_{ar}); 7.75 (d, 1H, J = 8.2 Hz H_{ar}); 8.03 (d, 1H, J = 8.2 Hz, H_{ar}). ^{13}C NMR; ($CDCl_3$) δ 13.7 (CH_3); 44.5 (CH_3); 51.5 (CH_2); 61.1 (CH_2); 66.1 (CH); 118.2 (CH); 121.5 (CH); 123.2 (CH); 123.9 (CH); 125.3 (CH); 127.0 (C); 127.9 (CH); 128.7 (C); 129.5 (C); 143.1 (C); 168.9 (CO). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine (15). Obtained in 57% yield from ethyl 4-methyl-3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-2-carboxylate as for **4**; oil. IR (film) υ(cm^{-1}) 3420 (NH), 1630 (C═N); ^{1}H NMR ($CDCl_3$/D_2O) δ 2.97 (s, 3H, NCH_3); 3.17 (dd, 1H, J = 9.8 Hz, 14.0 Hz, H_{3a}); 3.53 (dd, 1H, J = 2.6 Hz, 14.0 Hz, H_{3b}); 3.66 (s, 4H, NCH_2); 4.87 (dd, 1H, J = 2.6 Hz, 9.8 Hz, H_2); 7.07 (d, 1H, J = 8.2 Hz, H_{ar}); 7.25−7.50 (m, 3H, H_{ar}); 7.72 (d, 1H, J = 8.2 Hz, H_{ar}); 8.04 (d, 1H, J = 8.2 Hz, H_{ar}). ^{13}C NMR: ($CDCl_3$) δ 45.8 (CH_3); 50.5 (2CH_2); 53.7 (CH_2); 65.9 (CH); 117.9 (CH); 122.9 (CH); 124.4 (CH); 124.9 (CH); 126.6 (CH); 128.8 (C); 129.0 (CH); 130.0 (C); 130.6 (C); 144.2 (C); 166.3 (C═N). MS m/z 268 (M + H)$^+$. Anal. ($C_{16}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

Ethyl 3,4-Dihydro-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate (18). Compound **16** (636 mg, 4 mmol), $KHCO_3$ (1.62 g, 16 mmol), and ethyl 2,3-dibromopropanoate (0.86 mL, 6 mmol) in acetone (20 mL) were heated at reflux for 18 h. After cooling and evaporation, water was added, the mixture was extracted with CH_2Cl_2, and the organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column using EtOAc/PE 8:2 as eluent to give a yellow gum (224 mg, 21%). IR (film) υ(cm^{-1}) 3383 (NH), 1767 (CO); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.0 Hz, CH_3); 3.66 (d, 2H, J = 4.0 Hz, H_{3a}, H_{3b}); 4.11 (br s, 1H, NH); 4.25 (q, 2H, J = 7.0 Hz, OCH_2); 4.89 (t, 1H, J = 4.0 Hz, H_2); 6.89 (s, 1H, H_{ar}); 7.17−7.28 (m, 2H, H_{ar}), 7.31 (s, 1H, H_{ar}); 7.51−7.63 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 42.8 (CH_2); 62.1 (CH_2), 73.1 (CH); 109.8 (CH); 112.6 (CH); 123.4 (CH); 124.6 (CH); 125.7 (CH); 127.0 (CH); 129.0 (C); 130.5 (C); 134.1 (C); 145.0 (C); 169.8 (CO). MS m/z 258 (M + H)$^+$. Anal. ($C_{15}H_{15}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-naphtho[2,3-*b*][1,4]oxazine (19). Ethyl 3,4-Dihydro-4-methyl-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate. Obtained from **18** using the general procedure; yield 53%; oil. IR (film) υ(cm^{-1}) 1745 (CO); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz, CH_3); 2.98 (s, 3H, NCH_3); 3.52 (d, 2H, J = 4.1 Hz, H_{3a}, H_{3b}); 4.25 (q, 2H, J = 7.1 Hz, OCH_2); 4.93 (t, 1H, J = 4.1 Hz, H_2); 6.88 (s, 1H, H_{ar}); 7.17−7.27 (m, 2H, H_{ar}); 7.29 (s, 1H, H_{ar}), 7.56−7.63 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3); 39.2 (NCH_3); 50.5 (CH_2); 62.1 (CH_2); 73.3 (CH), 107.3 (CH); 111.9 (CH); 123.4 (CH); 124.6 (CH); 126.2 (CH); 126.7 (CH); 128.6 (C); 130.7 (C); 136.9 (C); 144.2 (C); 169.8 (CO). MS m/z 272 (M + H)$^+$. Anal. ($C_{16}H_{17}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-naphtho[2,3-*b*][1,4]oxazine (19). Obtained from ethyl 3,4-dihydro-4-methyl-2*H*-naphtho[2,3-*b*][1,4]oxazine-2-carboxylate using the general procedure. Yield 68%; white solid; mp 66 °C. IR (KBr) υ(cm^{-1}) 3061 (NH), 1604 (C═N); ^{1}H NMR ($CDCl_3$/D_2O) δ 2.95 (s, 3H, NCH_3); 3.50−3.70 (m, 2H, H_{3a}, H_{3b}); 3.74 (s, 4H, NCH_2); 5.12 (dd, 1H, J = 2.9 Hz, 7.8 Hz, H_2); 6.96 (s, 1H, H_{ar}); 7.29 (s, 1H, H_{ar}); 7.26−7.40 (m, 2H, H_{ar}); 7.66−7.72 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 38.6 (NCH_3); 50.0 (2CH_2); 51.1 (CH_2); 71.2 (CH); 106.4 (CH); 111.2 (CH); 122.8 (CH); 124.2 (CH); 125.7 (CH); 126.1 (CH); 127.6 (C); 130.5 (C); 136.4 (C); 143.8 (C); 165.2 (C═N). MS m/z 268 (M + H)$^+$. Anal. ($C_{16}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

Methyl 2,4-Dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (20a).[81] Compound **3a** (2.5 g, 11.3 mmol) was dissolved in methanol (10 mL) and THF (10 mL), 5% aqueous KOH (20 mL) was added, and the mixture was stirred for 1 h at room temperature. Evaporation of the solvent and addition

of water left a residue which was extracted with ethyl acetate. The aqueous layer was acidified to pH 1 with 10% HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to leave a brown solid (2.03 g, 93%) which was engaged in the next step; mp 130 °C. IR (KBr) $\upsilon(cm^{-1})$ 3500−3000 (OH), 1730 (CO); ^1H NMR ($CDCl_3$) δ 2.87 (s, 3H, NCH_3); 3.45 (d, 2H, $J = 4.0$ Hz, H_{3a}, H_{3b}); 4.90 (t, 1H, $J = 4.0$ Hz, H_2); 6.68−6.75 (m, 2H, H_{ar}); 6.86−6.94 (m, 2H, H_{ar}); 7.60 (br s, 1H, OH).^{13}C NMR ($CDCl_3$) δ 37.1 (CH_3); 48.6 (CH_2); 71.1 (CH); 111.3 (CH); 114.5 (CH); 117.5 (CH); 120.2 (CH); 134.3 (C); 141.5 (C); 172.4 (CO).

To a solution of the acid (800 mg, 4.14 mmol) in THF (30 mL), under argon and cooled at −50 °C, was dropwise added a solution of 2 M LDA (8.3 mL, 16.6 mmol) in THF. The mixture was stirred for 2 h at −50 °C, iodomethane (16.6 mmol, 2.35 g) was added, and the mixture was allowed to reach room temperature in 2 h. Water was added and then 5% HCl to adjust the pH to 4. The mixture was then extracted with ethyl acetate, dried over $MgSO_4$, and evaporated in vacuo to leave a residue which was dissolved in methanol (50 mL). Addition of a catalytic amount of PTSA was followed by heating to reflux for 18 h. Evaporation of methanol, addition of water, extraction with ethyl acetate, drying over $MgSO_4$, and finally evaporation left a residue which was chromatographed over silica gel column using EtOAc/PE 3:7 as eluent. Compound **20a** was obtained as an oil (637 mg, 69%). IR (film) $\upsilon(cm^{-1})$ 1756 (CO); ^1H NMR ($CDCl_3$) δ 1.64 (s, 3H, CH_3); 2.91 (s, 3H, NCH_3); 3.10 (d, 1H, $J = 11.5$ Hz, H_{3a}); 3.63 (d, 1H, $J = 11.5$ Hz, H_{3b}); 3.77 (s, 3H, OCH_3); 6.70−6.98 (m, 4H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 23.1 (CH_3); 38.9 (CH_3); 53.1 (CH_3); 56.4 (CH_2); 78.1 (C); 112.7 (CH); 116.3 (CH); 119.4 (CH); 121.9 (CH); 135.7 (C); 143.7 (C); 173.3 (CO). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

Methyl 4-Methyl-2-propyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (20b). Similarly obtained as for **20a** from **3a** using 1-iodopropane instead of iodomethane; yield 72%; oil; IR (film) $\upsilon(cm^{-1})$ 1737 (CO); ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, $J = 7.5$ Hz, CH_3); 1.33−1.38 (m, 2H, CH_2); 1.76−1.92 (m, 2H, CH_2); 2.86 (s, 3H, NCH_3); 3.09 (d, 1H, $J = 11.2$ Hz, H_{3a}); 3.52 (d, 1H, $J = 11.2$ Hz, H_{3b}); 3.73 (s, 3H, OCH_3); 6.65−6.96 (m, 4H, H_{ar}). ^{13}C NMR; ($CDCl_3$) δ 14.3 (CH_3); 16.6 (CH_2); 38.4 (CH_2); 38.5 (CH_3); 52.5 (CH_3); 55.2 (CH_2); 80.7 (C); 112.3 (CH); 115.9 (CH); 119.0 (CH); 122.3 (CH); 135.6 (C); 143.5 (C); 172.5 (CO). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,4-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (21a). Obtained from **20a** using the general procedure; yield 81%; oil; IR (film): $\upsilon(cm^{-1})$ 3500 (NH), 1605 (C=N); ^1H NMR ($CDCl_3/D_2O$) δ 1.65 (s, 3H, CH_3); 2.96 (s, 3H, NCH_3); 3.22 (d, 1H, $J = 11.5$ Hz, H_{3a}); 3.55 (d, 1H, $J = 11.5$ Hz, H_{3b}); 3.68−3.71 (br s, 4H, NCH_2); 6.71−6.95 (m, 4H, H_{ar}). ^{13}C NMR; ($CDCl_3$) δ 22.8 (CH_3); 38.5 (CH_3); 49.6 ($2CH_2$); 56.0 (CH_2); 75.1 (C); 112.3 (CH); 115.9 (CH); 118.3 (CH); 121.7 (CH); 135.4 (C); 142.2(C); 170.0 (CN). MS *m/z* 232 $(M + H)^+$. Anal. ($C_{13}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-2-propyl-3,4-dihydro-2*H*-1,4-benzoxazine (21b). Obtained from **20b** using the general procedure; yield 44%; oil. IR (film) $\upsilon(cm^{-1})$ 3400 (NH), 1609 (C=N); ^1H NMR ($CDCl_3$) δ 0.91 (t. 3H, $J = 7.3$ Hz, CH_3); 1.34−1.57 (m, 2H, CH_2); 1.71 (t, 2H, $J = 7.3$ Hz, CH_2); 2.85 (s, 3H, NCH_3); 3.22 (d, 1H, $J = 11.6$ Hz, H_{3a}); 3.47 (d, 1H, $J = 11.6$ Hz, H_{3b}); 3.65 (s, 4H, CH_2N); 4.30 (br s, 1H, NH); 6.61−6.70 (m, 2H, H_{ar}), 6.77−6.89 (m, 2H, Har). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3); 16.2 (CH_2); 38.2 (CH_3); 38.9 (CH_2); 50.0 (2 CH_2); 55.0 (CH_2); 77.6 (C); 112.0 (CH); 116.2 (CH); 118.0 (CH); 121.5 (CH); 135.6 (C); 142.0 (C); 169.1 (CN). MS *m/z* 260 $(M + 1)^+$. Anal. ($C_{15}H_{21}N_3O$, $C_2H_2O_4$) C, H, N.

Ethyl 4-[3-(Benzyloxy)-3-oxopropyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (22a). Compound **2a** (5.0 g, 24.1 mmol) was dissolved in toluene (17 mL) containing benzyl acrylate (12.8 g, 79.0 mmol). Triton B (40% in water) (2.26 mmol) was added and the mixture heated at reflux for 24 h. The solvent was evaporated, and the mixture was heated again at 110 °C for 24 h. After cooling and addition of water, the mixture was extracted with ethyl acetate. The organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column using EtOAc/PE 3:7 as eluent to afford **22a** as an oil (8.12 g, 91%). IR (film) $\upsilon(cm^{-1})$ 1750 (CO), 1740 (CO); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, $J = 7.2$ Hz, CH_3); 2.63 (t, 2H, $J = 6.9$ Hz, CH_2CO); 3.43−3.48 (m, 2H, H_{3a}, H_{3b}); 3.58 (t, 2H, $J = 6.9$ Hz, NCH_2); 4.18−4.26 (m, 2H, OCH_2); 4.70 (dd, 1H, $J = 3.5$ Hz, 4.8 Hz, H_2); 5.09 (s, 2H, CH_2); 6.65−6.73 (m, 2H, H_{ar}); 6.81−6.95 (m, 2H, H_{ar}); 7.30−7.33 (m, 5H, H_{ar}). Anal. ($C_{21}H_{23}NO_5$) C, H, N.

Ethyl 4-[3-Benzyloxy)-3-oxopropyl]-6-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (22c). Obtained similarly from **2c** in 90% yield as an oil. IR (film) $\upsilon(cm^{-1})$ 1756 (CO), 1731 (CO); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, $J = 7.0$ Hz, CH_3); 2.31 (s, 3H, CH_3); 2.72 (t, 2H, $J = 6.9$ Hz, CH_2CO); 3.48−3.55 (m, 2H, H_{3a}, H_{3b}); 3.68 (t, 2H, $J = 6.9$ Hz, NCH_2); 4.29 (q, 2H, $J = 7.0$ Hz, OCH_2); 4.77 (t, 1H, $J = 3.8$ Hz, H_2); 5.20 (s, 2H, CH_2); 6.55−6.57 (m, 2H, H_{ar}); 6.88−6.91 (m, 1H, H_{ar}); 7.42 (br s, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3); 21.3 (CH_3); 31.7 (CH_2); 46.7 (CH_2); 48.7 (CH_2); 61.7 (CH_2); 66.8 (CH_2); 72.4 (CH); 113.0 (CH); 116.7 (CH); 119.6 (CH); 128.6 (3 CH); 128.7 (2 CH); 131.5 (C); 133.3 (C); 135.8 (C); 141.1 (C); 171.4 (CO); 174.0 (CO). Anal. ($C_{22}H_{25}NO_5$) C, H, N.

3-[2-(Ethoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl]propanoic Acid (23a). Compound **22a** (1.50 g, 4 mmol) was dissolved in ethanol (20 mL) containing Pd/C 10% (150 mg). Stirring the mixture under 1 atm of H_2 for 4 h followed by filtration under filter aid and evaporation left an oil (1.08 g, 97%). IR (film) $\upsilon(cm^{-1})$ 3600−3100 (OH), 1730 (CO), 1720 (CO); ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, $J = 7.0$ Hz, CH_3); 2.57 (t, 2H, $J = 7.0$ Hz, CH_2CO); 3.45 (d, 2H, $J = 4.4$ Hz, H_{3a}, H_{3b}); 3.51−3.56 (m, 2H, NCH_2); 4.16 (q, 2H, $J = 7.0$ Hz, OCH_2); 4.71 (t, 1H, $J = 4.4$ Hz, H_2); 6.61−6.87 (m, 4H, H_{ar}); 9.70 (br s, 1H, OH). Anal. ($C_{14}H_{17}NO_5$) C, H, N.

3-[2-(Ethoxycarbonyl)-6-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl]propanoic Acid (23c). Same procedure as for **23a**, starting from **22c**. Yield 86%; oil. IR (film) $\upsilon(cm^{-1})$ 3700−3000 (OH), 1736 (CO); ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, $J = 7$ Hz, CH_3); 2.26 (s, 3H, CH_3); 2.64 (t, 2H, $J = 7$ Hz, CH_2CO); 3.51−3.62 (m, 4H, H_{3a}, H_{3b}, NCH_2); 4.20−4.28 (m, 2H, OCH_2); 4.74−4.80 (m, 1H, H_2); 6.52 (br s, 1H, H_5); 6.54 (d, 1H, $J = 8.4$ Hz, H_8); 6.85 (dd, 1H, $J = 2.5$ Hz, 8.4 Hz, H_7); 7.49 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 16.3 (CH_3); 23.0 (CH_3); 33.5 (CH_2); 48.6 (CH_2); 50.7 (CH_2); 63.8 (CH_2); 74.5 (CH); 115.0 (CH); 118.7 (CH); 122.1 (CH); 133.3 (C); 135.3 (C); 143.1 (C); 171.6 (CO); 179.6 (CO). Anal. ($C_{15}H_{19}NO_5$) C, H, N.

Ethyl 7-Oxo-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-2-carboxylate (24a). Trifluoroacetic anhydride (1.11 mL, 7.9 mmol) was added at 0 °C to a solution of acid **23a** (1.01 g, 3.61 mmol) in dichloroethane, and the mixture was stirred for 5 h at room temperature. Water and 5 N NaOH were added to adjust the pH to 9. Extraction with ethyl acetate, washing of the organic layers with water, drying over $MgSO_4$, and evaporation left a residue. The residue was purified by chromatography on a silica gel column using CH_2Cl_2 as eluent to afford **24a** as an amorphous yellow solid (388 mg, 41%) and **25a** as a red solid (103 mg, 11%); **24a**: mp 152 °C. IR (KBr) $\upsilon(cm^{-1})$ 1750 (CO), 1740 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7.0$ Hz, CH_3); 2.74 (t, 2H, $J = 6.5$ Hz, CH_2CO); 3.37 (t, 2H, $J = 6.5$ Hz, NCH_2); 3.45 (d, 2H, $J = 3.9$ Hz, H_{3a}, H_{3b}); 4.27 (q, 2H, $J = 7.0$ Hz, OCH_2); 4.95 (t, 1H, $J = 3.9$ Hz, H_2); 6.74 (t, 1H, $J = 8.0$ Hz, H_9); 7.06 (d, 1H, $J = 1.5$ Hz, 8.0 Hz, H_{ar}); 7.50 (dd, 1H, $J = 1.5$ Hz, 8.0 Hz, H_{ar}). Anal. ($C_{14}H_{15}NO_4$) C, H, N.

Ethyl 8-Methyl-7-oxo-2,3,6,7-tetrahydro-5*H*-[1,4]-oxazino[2,3,4-*ij*]quinoline-2-carboxylate (24c). Similarly obtained as for **24a**, starting from **23c**; yield 37%. Oil. IR (film) $\upsilon(cm^{-1})$ 1738 (CO), 1718 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7.0$ Hz, CH_3); 2.52 (s, 3H, CH_3); 2.72 (t, 2H, $J = 7.0$ Hz, CH_2CO); 3.33 (t, 2H, $J = 7.0$ Hz, NCH_2); 3.45 (d, 2H, $J = 4.0$ Hz, H_{3a}, H_{3b}); 4.27 (q, 2H, $J = 7.0$ Hz, OCH_2); 4.90 (t, 1H, $J = 4.0$ Hz, H_2); 6.51 (d, 1H, $J = 8.2$ Hz, H_{ar}); 7.00 (d, 1H, $J = 8.2$ Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 22.9 (CH_3); 39.4 (CH_2); 49.3 (CH_2); 49.8 (CH_2); 61.8 (CH_2); 72.0 (CH); 119.1 (C); 120.4 (CH); 122.0 (CH); 134.9 (C); 139.5 (C); 141.3 (C); 168.9 (CO); 194.4 (CO). Anal. ($C_{15}H_{17}NO_4$) C, H, N.

Ethyl 7-Oxo-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-2-carboxylate (25a). Obtained in 11% yield during the cyclization of **23a**. Mp 149−150 °C. IR (KBr) $\upsilon(cm^{-1})$ 1756 (CO), 1636 (CO); ^1H ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3); 4.24 (q, 2H, J = 7.2 Hz, OCH_2); 4.30−4.40 (m, 2H, H_{3a}, H_{3b}); 5.04 (dd, 1H, J = 3.8 Hz, 5.6.Hz, H_2); 6.21 (d, 1H, J = 7.5 Hz, =CH); 7.25−7.33 (m, 2H, H_{ar}); 7.39 (d, 1H, J = 7.5 Hz, =CH); 7.93 (dd, 1H, J = 2.6 Hz, 6.9 Hz, H_{ar}). Ms m/z 260 $(M + H)^+$. Anal. ($C_{14}H_{13}NO_4$) C, H, N.

Ethyl 8-Methyl-7-oxo-2,3-dihydro-7*H*-[1,4]-oxazino-[2,3,4-*ij*]quinoline-2-carboxylate (25c). Obtained during the cyclization of **23c** as an oil; yield 16%. IR: (film) $\upsilon(cm^{-1})$ 1756 (CO), 1626 (CO); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz, CH_3); 2.91 (s, 3H, CH_3); 4.33 (q, 2H, J = 7.0 Hz, OCH_2); 4.34 (m, 2H, H_{3a}, H_{3b}); 5.00 (dd, 1H, J = 4.0 Hz, 5.4 Hz, H_2); 6.22 (d, 1H, J = 7.8 Hz, =CH); 7.00 (d, 1H, J = 8.0 Hz, H_{9ar}); 7.18 (d, 1H, J = 8.0 Hz, H_{10ar}); 7.30 (d, 1H, J = 7.8 Hz, =CH). ^{13}C NMR ($CDCl_3$) δ 14,1 (CH_3); 23.2 (CH_3); 50.1 (CH_2); 62.0 (CH_2); 70.7 (CH); 112.3 (CH); 117.8 (CH); 125.4 (C); 126.3 (CH); 129.0 (C); 134.2 (C); 139.5 (CH); 141.7 (C); 167.4 (CO); 180.4 (CO). MS m/z 274 $(M + H)^+$. Anal. ($C_{15}H_{15}NO_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline (26a). Ethyl 2,3,6,7-Tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-2-carboxylate. Compound **24a** (200 mg, 0.76 mmol) in ethanol (20 mL) was stirred with Pd/C 10% (50 mg) under hydrogen (3 atm) for 48 h. After filtration over a filter aid, the solvent was evaporated and the residue was purified by column chromatography using CH_2Cl_2 as eluent. An oil was obtained (131 mg, 70%). IR (film) $\upsilon(cm^{-1})$ 1742 (CO); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz, CH_3); 1.99−2.06 (m, 2H, CH_2); 2.76 (t, 2H, J = 6.5 Hz, CH_2); 3.08 (t, 2H, J = 6.5 Hz, CH_2N); 3.33−3.35 (m, 2H, H_{3a}, H_{3b}); 4.27 (q, 2H, J = 7.1 Hz, OCH_2); 4.86 (dd, 1H, J = 3.7 Hz, 4.7 Hz, H_2); 6.58−6.61 (m, 2H, H_{ar}); 6.74 (t, 1H, J = 6.0 Hz, H_9). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline (26a). Obtained from ethyl 2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-2-carboxylate as for **4**. Yield 61%; oil. IR (film) $\upsilon(cm^{-1})$ 3395 (NH), 1667, 1633(C=N); ^1H ($CDCl_3$) δ 1.98 (m, 2H, CH_2); 2.76 (t, 2H, J = 7.0 Hz, CH_2); 3.08−3.12 (m, 2H, CH_2N); 3.31 (dd, 1H, J = 7.5 Hz, 11.8 Hz, H_{3a},); 3.49 (dd, 1H, J = 2.6 Hz, 11.8 Hz, H_{3b}); 3.70 (s, 4H, NCH_2); 4.70 (br s, 1H, NH); 5.02 (dd, 1H, J = 2.6 Hz, 7.5 Hz, H_2); 6.51−6.58 (m, 3H, H_{ar}). MS m/z 244 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-8-methyl-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline (26c). Same procedure as for **26a**, starting from **24c**. **Ethyl 8-Methyl-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-2-carboxylate**. This compound was obtained from **24c** by hydrogenation under 3 atm of hydrogen; yield 31%; oil. IR (film) $\upsilon(cm^{-1})$ 1759 (CO); ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz, CH_3); 2.00−2.10 (t, 2H, m, CH_2); 2.10 (s, 3H, CH_3); 2.62 (t, 2H, J = 6.5 Hz, CH_2); 3.03 (t, 2H, J = 6.5 Hz, NCH_2); 3.32 (d, 2H, J = 4.5 Hz, H_{3a}, H_{3b}); 4.26 (q, 2H, J = 7.0 Hz, OCH_2); 4.84 (t, 1H, J = 4.5 Hz, H_2); 6.49 (d, 1H, J = 8.5 Hz, H_{ar}); 6.69 (d, 1H, J = 8.5 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3); 19.5 (CH_3); 22.3 (CH_2); 24.8 (CH_2); 49.1 (CH_2); 49.7 (CH_2); 68.8 (CH_2); 73.3 (CH); 113.7 (CH); 120.1 (CH); 122. 7 (C); 126.3 (C); 132.5 (C); 141.2 (C); 170.0 (CO). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-8-methyl-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinoline (26c). Obtained from ethyl 8-methyl-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino-[2,3,4-*ij*]quinoline-2-carboxylate as for **4** as an oil; yield 77%. IR (film) $\upsilon(cm^{-1})$ 3310 (NH), 1667, 1633 (C=N); ^1H NMR ($CDCl_3$) δ 2.00−2.10 (m, 2H, CH_2); 2.10 (s, 3H, CH_3); 2.60−2.67 (m, 2H, CH_2); 2.95−3.15 (m, 2H, NCH_2); 3.17 (dd, 1H, J = 8.0 Hz, 11.5 Hz, H_{3a}); 3.40 (dd, 1H, J = 2.5 Hz, 11.5 Hz, H_{3b}); 3.65 (s, 4H, NCH_2); 4.96 (dd, 1H, J = 2.5 Hz, 8.0 Hz, H_2); 5.38 (br s, 1H, NH); 6.44 (d, 1H, J = 8.0 Hz, H_{ar}); 6.58 (d, 1H, J = 8.0 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 19.1 (CH_3); 21.5 (CH_2); 24.5 (CH_2); 48.6 (CH_2); 49.2 ($2CH_2$); 49.7 (CH_2); 71.2 (CH); 113.1 (CH); 119.1 (CH); 122.0 (C); 129.0 (C); 132.2 (C); 140.1 (C); 167.4 (C=N). MS m/z 257 $(M)^+$. Anal. ($C_{15}H_{19}N_3O$, $C_2H_2O_4$) C, H, N.

3-[2-(Ethoxycarbonyl)-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoic acid (27a). Benzyl 3-[2-(Ethoxycarbonyl)-3,4-dihydro-1,4-benzoxazine-4-yl]-3-oxopropanoate. To a solution of compound **2a** (3.53 g, 17.1 mmol) in CH_2Cl_2 (35 mL) was dropwise added at 0 °C a solution of triethylamine (7.6 mL, 54.6 mmol) and benzyl 3-chloro-3-oxopropanoate (7.64 g, 35.9 mmol) in CH_2Cl_2 (35 mL), and the mixture was stirred for 1 h at room temperature. Water was added, and the organic layer was decanted and washed with water. Drying over $MgSO_4$ and evaporation left a residue which was chromatographed on a silica gel column using EtOAc/PE 2:8 as eluent to give an oil (3.50 g, 53%). IR (film) $\upsilon(cm^{-1})$ 1750 (CO), 1672 (CO); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz, CH_3); 3.60−3.65 (m, 1H, CH_2CO); 3.85−3.97 (m, 2H, CH_2CO, H_{3a}); 4.50−4.55 (m, 1H, H_{3b}); 4.25 (q, 2H, J = 7.0 Hz, OCH_2); 4.94 (t, 1H, J = 4.0 Hz, H_2); 5.22 (s, 2H, CH_2); 6.90−7.23 (m, 4H, H_{ar}); 7.40 (s, 5H, H_{ar}). Anal. ($C_{21}H_{21}NO_6$) C, H, N.

3-[2-(Ethoxycarbonyl)-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoic Acid (27a). Benzyl 3-[2-(ethoxycarbonyl)-3,4-dihydro-1,4-benzoxazine-4-yl]-3-oxopropanoate was hydrogenolyzed as for **22a** to afford the acid **27a** in 97% yield; oil. IR: (film) $\upsilon(cm^{-1})$ 3500−2700 (OH), 1760 (CO), 1670 (CO); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.0 Hz, CH_3); 3.55−3.94 (m, 3H, CH_2CO, H_{3a}); 4.20 (q, 2H, J = 7.0 Hz, OCH_2); 4.62−4.81 (m, 1H, H_{3b}); 5.01 (s large, 1H, H_2); 6.85−7.19 (m, 4H, H_{ar}); 9.64 (br s, 1H, OH). Anal. ($C_{14}H_{15}NO_6$) C, H, N.

3-[2-(Ethoxycarbonyl)-6-methyl-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoic Acid (27c). Benzyl 3-[2-(Ethoxycarbonyl)-6-methyl-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoate. This ester was similarly obtained in 61% yield as for benzyl 3-[2-(ethoxycarbonyl)-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoate, starting from compound **2c**. Oil. IR (film) $\upsilon(cm^{-1})$ 1744 (CO), 1668 (CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz, CH_3); 2.26 (s, 3H, CH_3); 3.59−3.65 (m, 1H, CH_2CO); 3.81−3.90 (mas, 2H, CH_2CO, H_{3a}); 4.20 (q, 2H, J = 7.0 Hz, OCH_2); 4.43−4.55 (m, 1H, H_{3b}); 4.90 (t, 1H, J = 4.0 Hz, H_2); 5.22 (s, 2H, CH_2); 6.94−6.98 (m, 3H, H_{ar});. 7.39 (s, 5H, H_{ar}). Anal. ($C_{22}H_{23}NO_6$) C, H, N.

3-[2-(Ethoxycarbonyl)-6-methyl-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoic Acid (27c). Obtained by hydrogenolysis, as for **22a**, of benzyl 3-[2-(ethoxycarbonyl)-6-methyl-3,4-dihydro-1,4-benzoxazin-4-yl]-3-oxopropanoate. Yield 90%; oil. IR (film) $\upsilon(cm^{-1})$ 3400−2700 (OH), 1738 (CO), 1670 (CO); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.0 Hz, CH_3); 2.35 (s, 3H, CH_3); 3.65−3.85 (m, 3H, CH_2CO, H_{3a}); 4.24 (q, 2H, J = 7.0 Hz, OCH_2); 4.67−4.93 (m, 1H, H_{3b}); 4.98 (br s, 1H, H_2); 6.94−7.01 (m, 3H, H_{ar}); 7.52 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3); 20.8 (CH_3); 38.7 (CH_2); 41.7 (CH_2); 62.3 (CH_2); 73.5 (CH); 117.8 (CH); 123.9 (CH); 124.2 (C); 129.1 (C); 130.8 (CH); 144.6 (C); 168.2 (CO); 168.9 (2CO). Anal. ($C_{15}H_{17}NO_6$) C, H, N.

Ethyl 7-Hydroxy-5-oxo-2,3-dihydro-5*H*-[1,4]-oxazino-[2,3,4-*ij*]quinoline-2-carboxylate (28a). To a solution of compound **27a** (2.34 g 8 mmol) in CH_2Cl_2 (40 mL) was dropwise added trifluoroacetic anhydride (5 mL, 35 mmol) at 0 °C, and the mixture was stirred for 18 h at room temperature. Water was added, and the pH of the aqueous layer was adjusted to pH 4−5. The obtained solid from the mixture was filtered (1.12 g, 51%); mp 242 °C. IR (KBr) $\upsilon(cm^{-1})$ 3086 (OH), 1752 (CO), 1646 (CO); ^1H (DMSO-d_6) δ 1.13 (t, 3H, J = 7.0 Hz, CH_3); 4.10 (q, 2H, OCH_2); 4.18 (dd, 1H, J = 3.8 Hz, 13.6 Hz, H_{3a}); 4.35 (dd, 1H, J = 5.2 Hz, 13.6 Hz, H_{3b}); 5.30 (dd, 1H, J = 3.8 Hz, 5.2 Hz, H_2); 5.85 (s, 1H, =CH); 7.12−7.25 (m, 2H, H_{ar}); 7.47 (dd, 1H, J = 1.5 Hz, 7.8 Hz); 11.52 (s, 1H, OH). MS m/z 276 $(M + H)^+$. Anal. ($C_{14}H_{13}NO_5$) C, H, N.

Ethyl 7-Hydroxy-8-methyl-5-oxo-2,3-dihydro-5*H*-[1,4]-oxazino[2,3,4-*ij*]quinoline-2-carboxylate (28c). Same procedure as for **28a**, starting from **27c**; yield 70%, mp 167−168 °C. IR (KBr) $\upsilon(cm^{-1})$ 3086 (OH), 1732 (CO), 1648 (CO); ^1H NMR (DMSO-d_6) δ 1.14 (t, 3H, J = 7.0 Hz, CH_3); 2.64 (s, 3H,

CH_3); 4.14 (q, 2H, J = 7.0 Hz, OCH_2); 4.16 (dd, 1H, J = 4.0 Hz, 14.0 Hz, H_{3a}); 4.37 (dd, 1H, J = 5.0 Hz, 14.0 Hz, H_{3b}); 5.21 (dd, 1H, J = 4.0 Hz, 5.0 Hz, H_2); 5.83 (s, 1H, =CH); 6.90 (d, 1H, J = 8.0 Hz, H_{ar}); 7.10 (d, 1H, J = 8.0 Hz, H_{ar}); 11.33 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 13.1 (CH_3); 22.3 (CH_3); 41.0 (CH_2); 60.5 (CH_2); 69.5 (CH); 97.3 (CH); 114.2 (C); 116.1 (CH); 124.1 (CH); 126.8 (C); 128.3 (C); 139.0 (C); 159.4 (C); 163.7 (CO); 167.1 (CO). MS m/z 289 $(M)^+$. Anal. ($C_{15}H_{15}NO_5$) C, H, N.

Ethyl 7-Methoxy-5-oxo-2,3-dihydro-5*H*-[1,4]oxazino-[2,3,4-*ij*]quinoline-2-carboxylate (29a). To compound **28a** (1 g, 3.63 mmol) dissolved in DMF (10 mL) were added K_2CO_3 (1 g, 7.25 mmol) and methyl tosylate (1.01 g, 5.43 mmol). The mixture was heated at 50 °C for 1 h and then treated with water. Extraction with ethyl acetate, washings with water, drying over $MgSO_4$, and evaporation left a residue. The residue was chromatographed on a silica gel column using CH_2Cl_2 as eluent to give **29a** as white solid (891 mg, 85%); mp 144 °C. IR (KBr) υ(cm^{-1}) 1748 (CO), 1653 (CO); ^{1}H NMR (DMSO-d_6) δ 1.29 (t, 3H, J = 7.2 Hz, CH_3); 3.95 (s, 3H, OCH_3); 4.16−4.33 (m, 3H, H_{3a}, OCH_2); 4.63 (dd, 1H, J = 3.5 Hz, 14.0 Hz, H_{3b}); 4.85 (dd, 1H, J = 3.5 Hz, 7.5 Hz, H_2); 6.01 (s, 1H, =CH); 7.12 (t, 1H, J = 8.0 Hz, H_8); 7.25 (dd, 1H, J = 1.5 Hz, 8.0 Hz, H_{ar}); 7.58 (dd, 1H, J = 1.5 Hz, 8.0 Hz, H_{ar}). ^{13}C NMR (DMSO-) δ 12.7 (CH_3); 39.6 (CH_2); 54.5 (CH_3); 60.7 (CH_2); 70.0 (CH); 94.7 (CH); 114.9 (CH); 116.5 (CH); 121.0 (CH); 115.4 (C); 124.4 (C); 140.4 (C); 160.3(C); 161.9 (CO); 166.2 (CO). MS m/z 289 $(M)^+$. Anal. ($C_{15}H_{15}NO_5$) C, H, N.

Ethyl 7-Methoxy-8-methyl-5-oxo-2,3-dihydro-5*H*-[1,4]-oxazino[2,3,4-*ij*]quinoline-2-carboxylate (29c). Obtained as for **29a**; yield 67%; white solid; mp 167 °C. IR (KBr) υ(cm^{-1}) 1754 (CO), 1656 (CO); ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz, CH_3); 2.64 (s, 3H, CH_3); 3.90 (s, 3H, OCH_3); 4.16−4.33 (m, 3H, OCH_2, H_{3a}); 4.62 (dd, 1H, J = 3.5 Hz, 14.0 Hz, H_{3b}); 4.80 (dd, 1H, J = 3.5 Hz, 7.2 Hz, H_2); 5.97 (s, 1H, CH); 6.90 (d, 1H, J = 8.2 Hz, H_{ar}); 7.12 (d, 1H, J = 8.2 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.11 (CH_3); 28.8 (CH_3); 41.2 (CH_2); 55.6 (CH_3); 62.1 (CH_2); 71.0 (CH); 96.2 (CH); 115.6 (C); 117.5 (CH); 126.0 (CH); 127.1 (C); 120.0(C); 140.2 (C); 161.5 (C); 166.1 (CO); 167.8 (CO). Anal. ($C_{16}H_{17}NO_5$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-7-methoxy-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-5-one (30a). Similarly obtained from **29a** using the general procedure; white solid; mp 229 °C; yield 67%. IR (KBr) υ(cm^{-1}) 3440 (NH), 1643 (C=O, C=N); ^{1}H NMR ($CDCl_3$) δ 3.50 (br s, 1H, NH); 3.71 (s, 4H, CH_2N); 3.79 (dd, 1H, J = 9.0 Hz, 14.0 Hz, H_{3a}); 3.96 (s, 3H, OCH_3); 4.86 (dd, 1H, J = 3.0 Hz, 9.0 Hz, H_2); 4.99 (dd, 1H, J = 3.0 Hz, 14.0 Hz, H_{3b}); 6.00 (s, 1H, =CH); 7.07−7.17 (m, 2H, Har); 7.55 (dd, 1H, J = 2.2 Hz, 7.3 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 41.4 (CH_2); 48.9 (2 CH_2); 55.0 (CH_3); 69.5 (CH); 95.4 (CH); 115.5 (CH); 115.9 (C); 116.6 (CH); 121.2 (CH); 125.9 (C); 140.5 (C); 160.7 (C); 162.1 (C); 162.6 (CO). MS m/z 286 $(M + H)^+$. Anal. ($C_{15}H_{15}N_3O_3$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-7-methoxy-8-methyl-2,3-dihydro-5*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-5-one (30c). Similarly obtained as for **30a**; oil; yield 49%. IR (film): υ(cm^{-1}) 3440 (NH), 1665 (C=O, C=N); ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H, CH_3); 3.72 (s, 4H, CH_2N); 3.75 (dd, 1H, J = 9.2 Hz, 14.1 Hz, H_{3a}); 3.90 (s, 3H, OCH_3); 4.84 (dd, 1H, J = 2.7 Hz, 9.2 Hz, H_2); 5.01 (dd, 1H, J = 2.7 Hz, 14.1 Hz, H_{3b}); 6.00 (s, 1H, =CH); 6.90 (d, 1H, J = 8.1 Hz, H_{ar}); 7.05 (d, 1H, J = 8.1 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_3); 42.9 (CH_2); 50.3 (2 CH_2); 55.9 (CH_3); 70.3 (CH); 96.7 (CH); 116.0 (C); 117.5 (CH); 126.0 (CH); 127.7 (C); 130.5 (C); 140.8 (C); 161.8 (C); 164.0 (C); 166.3 (CO). MS m/z 300 $(M + H)^+$. Anal. ($C_{16}H_{17}N_3O_3$) C, H, N.

Ethyl 7-Oxo-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[*de*]naphthalene-2-carboxylate (31). Ethyl 4-[3-(Benzyloxycarbonyl) propanoyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. To a solution of **2a** (4.0 g, 19.32 mmol) in CH_2Cl_2 (40 mL) were dropwise added triethylamine (8.6 mL, 61.83 mmol) and benzyl 3-chlorocarbonylpropanoate (9.63 g, 42.5 mmol). The mixture was stirred for 30 min at room temperature, water was added, and the organic layer was washed three times with water, dried over $MgSO_4$, evaporated, and purified by column chromatography on silica gel using EtOAc/PE 3:7 as eluent to afford an oil (7.54 g, 98%). IR (film) υ(cm^{-1}) 1740−1736 (CO), 1672 (CO); ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 3H, J = 7.0 Hz, CH_3); 2.68−3.12 (m, 4H, CH_2); 3.87 (dd, 1H, J = 4.0 Hz, 13.5 Hz, H_{3a}); 4.40−4.60 (m, 1H, H_{3b}); 4.19 (q, 2H, J = 7.0 Hz, OCH_2); 4.91 (t, 1H, J = 4.0 Hz, H_2); 5.17 (s, 2H, CH_2); 6.98 (t, 1H, J = 2.0 Hz, 8.0 Hz, Har); 7.07−7.17 (m, 2H, H_{ar}); 7.30−7.39 (m, 6H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 29.4 (CH_2); 30.0 (CH_2); 62.3 (CH_2); 66.8 (2 CH_2); 74.0 (CH); 117.8 (CH); 121.0 (CH); 124.8 (C); 126.3 (CH); 128.1 (CH); 128.6 (3 CH); 128.7 (2 CH); 136.3 (C); 146.5 (C); 169.1 (CO); 171.4 (CO); 172.9 (CO). Anal. ($C_{22}H_{23}NO_6$) C, H, N.

Ethyl 4-[3-(Benzyloxycarbonyl)propyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. To ethyl 4-[3-(benzyloxycarbonyl)propanoyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (4.3 g, 10.8 mmol) dissolved in THF (20 mL) was addded 1 M BH_3·THF (21.7 mL, 21.7 mmol). The mixture was heated for 24 h at reflux, BH_3·THF (10.8 mL, 10.8 mmol) was added again, and the mixture was heated for 2 h. After cooling, the mixture was evaporated and water added, and extraction with ethyl acetate, drying over $MgSO_4$, and evaporation afforded a residue which was chromatographed on a silica gel column using EtOAc/PE 3/7 as eluent. An oil was obtained (3.28 g, 79%). IR (film) υ(cm^{-1}) 1756 (CO), 1732 (CO); ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz, CH_3); 1.94−2.08 (m, 2H, CH_2); 2.46 (t, 2H, J = 7.0 Hz, CH_2CO); 3.25−3.38 (m, 2H, NCH_2); 3.50 (d, 2H, J = 4.0 Hz, H_{3a}, H_{3b}); 4.21−4.31 (m, 2H, OCH_2); 4.81 (t, 1H, J = 4.0 Hz, H_2); 5.17 (s, 2H, CH_2Ph); 6.69−6.75 (m, 2H, H_{ar}); 6.87 (td, 1H, J = 2.0 Hz, 7.5 Hz, Har); 6.98 (dd, 1H, J = 2.0 Hz, 7.5 Hz, Har); 7.40 (s, 5H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3); 22.6 (CH_2); 33.0 (CH_2); 49.3 (CH_2); 51.1 (CH_2); 62.6 (CH_2); 67.4 (CH_2); 73.3 (CH); 113.3 (CH); 117.7 (CH); 119.3 (CH); 123.0 (CH); 129.2 (2CH); 129.3 (3CH); 135.3 (C); 136.8 (C); 143.9 (C); 170.3 (CO); 174.0 (CO). Anal. ($C_{22}H_{25}NO_5$) C, H, N.

4-[2-(Ethoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl]butanoic Acid. Obtained by hydrogenolysis of ethyl 4-[3-(benzyloxycarbonyl)propyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate as for **23a**; yield 97%. Oil; IR (film) υ(cm^{-1}) 3500−3000 (OH), 1731 (CO), 1710 (CO); ^{1}H NMR ($CDCl_3$/D_2O) δ 1.28 (t, 3H, J = 7.0 Hz, CH_3); 1.93 (m, 2H, CH_2); 2.43 (t, 2H, J = 7.0 Hz, CH_2CO); 3.26−3.35 (m, 2H, NCH_2); 3.52 (d, 2H, J = 4.0 Hz, H_{3a}, H_{3b}); 4.21−4.31 (m, 2H, OCH_2); 4.77 (t, 1H, J = 4.0 Hz, H_2); 6.66−6.96 (m, 4H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3); 21.2 (CH_2); 31.0 (CH_2); 48.1 (CH_2); 49.9 (CH_2); 61. 6 (CH_2); 72.2 (CH); 112.1 (CH); 116.5 (CH); 118.2 (CH); 121.8 (CH); 134.1 (C); 142.7 (C); 169.3 (CO); 178.1 (CO). Anal. ($C_{15}H_{19}NO_5$) C, H, N.

Ethyl 7-Oxo-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[*de*]naphthalene-2-carboxylate 31. Cyclization of 5-[2-(ethoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl]butanoic acid according to **24a** afforded **31**; yield 62%; oil. IR (film) υ(cm^{-1}) 1755 (CO), 1673 (CO); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz, CH_3); 2.10−2.16 (m, 2H, CH_2); 2.71−2.83 (m, 2H, CH_2); 3.22 (t, 2H, J = 6.6 Hz, NCH_2); 3.64 (dd, 1H, J = 6.0 Hz, 12.5 Hz, H_{3a}); 3.73 (dd, 1H, J = 3.0 Hz, 12.5 Hz, H_{3a}); 4.28 (q, 2H, J = 7.0 Hz, OCH_2); 4.81 (dd, 1H, J = 3.0 Hz, 6 Hz, H_2); 6.78 (t, 1H, J = 8.0 Hz, H_5); 7.04 (dd, 1H, J = 1.6 Hz, 8.0 Hz, H_{ar}); 7.36 (dd, 1H, J = 1.6 Hz, 8.0 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3); 29.2 (CH_2); 40.7 (CH_2); 51.7 (CH_2); 53.3 (CH_2); 61.6 (CH_2); 71.3 (CH); 119.3 (CH); 119.7 (CH); 122.2 (CH); 128.2 (C); 138.8 (C); 144.2 (C); 168.5 (CO); 201.9 (CO). Anal. ($C_{15}H_{17}NO_4$) C, H, N.

Ethyl 2-[4,5-Dihydro-1*H*-2-imidazolinyl]-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[*de*]naphthalene-2-carboxylate (32). Ethyl 1,2,7,8,9,10-Hexahydro-3-oxa-10a-azacyclohepta[*de*]naphthalene-2-carboxylate. Obtained by hydrogenation of **31** according to the synthesis of **26a**; yield 44%; oil. IR (film) υ(cm^{-1}) 1755 (CO);^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.0 Hz, CH_3); 1.46−1.54 (m, 2H, CH_2); 1.70−1.90 (m, 2H, CH_2); 2.71−2.85 (m, 2H, CH_2); 2.99−3.03 (m, 2H, NCH_2); 3.36 (dd, 1H, J = 7.5 Hz, 13.6 Hz, H_{3a}); 3.53 (dd, 1H, J = 3.0 Hz, 13.6 Hz, H_{3a}); 4.30 (q, 2H, J = 7.0 Hz, OCH_2); 4.59

(dd, 1H, J = 3.0 Hz, 7.5 Hz, H_2); 6.74−6.94 (m, 3H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 17.1 (CH_3); 28.5 (CH_2); 33.7 (CH_2); 37.8 (CH_2); 56.2 (CH_2); 58.4 (CH_2); 65.2 (CH_2); 71.9 (CH); 118.3 (CH); 125.2 (CH); 125.3 (CH); 137.2 (C); 140.5 (C); 148.4 (C); 172.5 (CO).). MS m/z 261 (M^+). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

Ethyl 2-[4,5-Dihydro-1*H*-2-imidazolinyl]-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[*de*]naphthalene (32). Obtained from ethyl 1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[*de*]naphthalene-2-carboxylate as for **26a**. Yield 89%; oil. IR (film) υ(cm^{-1}) 3416 (NH), 1628 (C═N); ^1H NMR ($CDCl_3$) δ 1.26−1.34 (m, 2H, CH_2); 1.77−1.88 (m, 2H, CH_2); 2.64−3.18 (m, 4H, CH_2); 3.20 (dd, 1H, J = 9.2 Hz, 14.0 Hz, H_{3a}); 3.48 (dd, 1H, J = 2.5 Hz, 14.0 Hz, H_{3a}); 3.65 (s, 4H, NCH_2); 4.41 (br s, 1H, NH); 4.65 (dd, 1H, J = 2.5 Hz, 9.2 Hz, H_2); 6.74−6.87 (m, 3H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2); 29.4 (CH_2); 34.2 (CH_2); 49.2 (2 CH_2); 56.1 (CH_2); 58.3 (CH_2); 67.4 (CH); 115.1 (CH); 122.4 (2 CH); 134.9 (C); 138.2 (C); 145.7 (C); 166.0 (CN). MS m/z 257 $(M)^+$. Anal. ($C_{15}H_{19}N_3O$, $C_2H_2O_4$) C, H, N.

Ethyl 2,3,5,6-Tetrahydro[1,4]oxazino[2,3,4-*ij*]indole-2-carboxylate (33). Same procedure as for **2**, starting from 7-hydroxyindoline;[87,88] yield 83%; oil. IR (film) υ(cm^{-1}) 1753 (CO); ^1H NMR (pyridine-d_5, 400 MHz) δ 1.15 (t, 3H, J = 7.0 Hz, CH_3); 2.70−2.80 (m, 2H, CH_2); 2.89 (q, 1H, J = 8.9 Hz, NCH_2); 3.03 (dd, 1H, J = 2.8 Hz, 12.0 Hz H_{3a}); 3.20−3.28 (m, 1H, NCH_2); 3.49 (dd, 1H, J = 4.3 Hz, 12.0 Hz, H_{3b}); 4.29 (m, 2H, J = 7.0 Hz, OCH_2); 5.23 (dd, 1H, J = 2.8 Hz, 4.3 Hz, H_2); 6.67−6.75 (m, 2H, H_{ar}); 6.90−6.95 (m, 1H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3); 30.2 (CH_2); 49.5 (CH_2); 56.9 (CH_2); 62.5 (CH_2); 75.2 (CH); 113.7 (CH); 118.0 (CH); 121.6 (CH); 131.1 (C); 138.6 (C); 142.7 (C); 170.2 (CO). MS m/z 234 $(M + H)^+$. Anal. ($C_{13}H_{15}NO_3$) C, H, N.

Ethyl 2,3-Dihydro[1,4]oxazino[2,3,4-*hi*]indole-2-carboxylate (34). DDQ (204 mg, 0.90 mmol) was added to an ice-cooled solution of **33** (200 mg, 0.86 mmol) in toluene (6 mL). The mixture was stirred at 0 °C for 30 min. Water was added, and the mixture was neutralized with 5% aq NaOH. Extraction with ethyl acetate, drying of the organic later over $MgSO_4$, and evaporation in vacuo left a residue which was chromatographed on a silica gel column using EtOAc/PE 1:9 as eluent to yield **34** as an oil (100 mg, 50%). IR: (film): υ(cm^{-1}) 1760 (CO). ^1H NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 7 Hz, CH_3); 4.23 (q, 2H, J = 7 Hz, OCH_2); 4.42 (dd, 1H, J = 7 Hz and 12 Hz, NCH_2-CHO); 4.52 (d, 1H, J = 4 Hz, 12 Hz, NCH_2CHO); 5.03 (dd, 1H, J = 4 Hz, 7 Hz, NCH_2CHO); 6.48 (d, 1H, J = 3 Hz, ═CH); 6.80 (d, 1H, J = 8 Hz, H_{ar}); 7.01 (t, 1H, J = 8 Hz, H_{ar}); 7.05 (d, 1H, J = 3 Hz, ═CH); 7.23 (d, 1H, J = 8 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$): δ 15.6 (CH_3); 47.0 (CH_2); 63.7 (CH_2); 74.8 (CH); 104.1 (CH); 107.2 (CH); 115.6 (CH); 122.4 (CH); 126.5 (C); 126. 9 (CH); 129.2 (C); 143.2 (C); 169.7 (CO). MS m/z 232 $(M + 1)^+$. Anal. ($C_{13}H_{13}NO_3$) C, H, N.

2-[4,5-Dihydro-1*H*-imidazol-2-yl]-2,3,5,6-tetrahydro-[1,4]oxazino[2,3,4-*hi*]indole (35). Same procedure as for **4**, starting from **33**; yield 85%. Oil; IR (film) υ(cm^{-1}) 3409 (NH); 1664, 1631 (C═N); ^1H NMR ($CDCl_3$) δ 2.89−3.15 (m, 4H, CH_2); 3.35−3.45 (m, 2H, CH_2); 3.62 (s, 4H, NCH_2); 4.45 (s, 1H, NH); 5.09 (dd,1H, J = 2.8 Hz, 7.1 Hz, H_2); 6.59−6.74 (m, 3H, H_{ar}).^{13}C NMR ($CDCl_3$) δ 29.8 (CH_2); 50.0 (2 CH_2); 50.1 (CH_2); 56.4 (CH_2); 73.5 (CH); 113.1 (CH); 117.8 (CH); 120.9 (CH); 130.9 (C); 138.4 (C); 142.1(C); 166.2 (CN). MS m/z 230 $(M + H)^+$. Anal. ($C_{13}H_{15}N_3O$, $C_2H_2O_4$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,3-dihydro[1,4]-oxazino[2,3,4-*hi*]indole (36). Similarly obtained as for **35** from **34**; eluent CH_2Cl_2/Et_3N 100:1; oil; yield 72%. IR: (film): υ(cm^{-1}) 3406 (NH); 1630 (C═N). ^1H NMR ($CDCl_3$) δ 3.62 (s, 4H, NCH_2CH_2N); 4.29 (dd, 1H, J = 9 Hz, 13 Hz, NCH_2CHO); 4.56 (dd, 1H, J = 3 Hz, 13 Hz, NCH_2CHO); 5.04 (dd,1H, J = 3 Hz, 9 Hz, NCH_2CHO); 6.47 (d, 1H, J = 3 Hz, H_{ar}); 6.67 (d, 1H, J = 8 Hz, H_{ar}); 7.03 (d, 1H, J = 8 Hz, H_{ar}); 7.03 (d, 1H, J = 3 Hz, H_{ar}); 7.22 (d, 1H, J = 8 Hz, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 46.2 (CH_2); 49.6 ($2CH_2$); 71.9 (CH); 102.0 (CH); 104.8 (CH); 112.6 (CH); 120.4 (CH); 124.8 (C); 125.5 (CH); 127.6 (C); 141.66 (C); 164.1 (CN). MS m/z 228 $(M + 1)^+$. Anal. ($C_{13}H_{13}N_3O$, $C_2H_2O_4$) C, H, N.

Pharmacology. Radioligand Binding Assays. I_1-Binding Site Assays. Bovine adrenal medulla plasma membranes were prepared as described by Molderings et al.[89] These membranes (0.8 mg protein/mL) were incubated for 40 min with 7 nM [^3H]clonidine at 22 °C in binding buffer (PBS, 0.5 mM EGTA, 0.5 mM $MgCl_2$, 0.5%, ascorbic acid, pH 7.5) and increasing concentrations of competitors (10^{-9} to 10^{-4} M) in the presence of 1 μM of RX821002 to mask α_2-adrenoceptors. Nonspecific binding was defined as [^3H]clonidine binding in the presence of 1 μM of S22687−1 ([5-(2-methylphenoxymethyl)-1,3-oxazolin-2-yl]amine; high affinity I_1 competing drug, K_i = 4.98 10^{-9} M).[11]

I_2-Binding Site Assays. Rabbit kidney membrane preparation and determination of affinities of compounds were performed as described[38] except that 2-BFI (10 μM) was used to define nonspecific binding instead of cirazoline (10 μM).

α_1 and α_2 Adrenergic Binding Assays. Calf frontal cortex membranes were prepared according to Liefde et al.[90] for binding assays to α_1 and α_2AR. α_1-Adrenergic binding: membranes (0.5 mg protein/mL) were incubated for 40 min at 25 °C with 0.5 nM [^3H]prazosin in 50 mM phosphate buffer, 10 mM $MgCl_2$, and increasing concentrations of competitors (10^{-9} to 10^{-4} M) in a final volume of 525 μL. α_2-Adrenergic binding: membranes (0.5 mg protein/mL) were incubated for 60 min at 25 °C with 0.8 nM [^3H]RX821002 in the presence of 0.3 μM serotonin to mask $5HT_{1A}$ receptors in 50 mM sodium phosphate buffer, pH 7.4, with increasing concentrations of competitors (10^{-9} to 10^{-4} M). Nonspecific binding was defined with 10 μM phentolamine in both assays. In these assays, incubations were terminated by rapid filtration under vacuum through Whatman GF/C glass fiber filters followed by rapid washing of the tubes and filtering three times with ice-cold binding buffer. The remaining protocol was described elsewhere.[37,91]

In Vivo Studies: Arterial Blood Pressure and Heart Rate in the Spontaneously Hypertensive Anesthetized Rat. Adult male spontaneously hypertensive rats (SHR) were anaesthetized (sodium pentobarbital 50 mg/kg ip), and a catheter (0.86 mm internal diameter, 1.27 mm external diameter, filled with isotonic saline containing 150 IU/mL heparin) was introduced into the left carotid artery. The catheter was connected to a Gould P23XL transducer for recording mean, systolic and diastolic blood pressures (BP, mmHg), and heart rate (HR, bpm) which was derived from pulse blood pressure. Recordings were taken on a Gould TA 240 Easygraph. BP and HR were allowed to stabilize for a period of at least 40 min, and the test substance was administered at 25 mg/kg intraperitoneal single dose (six animals studied per group). BP and HR were measured over a 90 min experimental period. Control animals receiving vehicle (carboxymethylcellulose 0.5% in distilled water, 2.5 mL/kg) did not show any significant modification of BP and HR over the 90 min experimental period. Results were expressed as the maximal variation of mean arterial pressure (mmHg) and heart rate (bpm) compared to the basal values before treatment. The corresponding percentage of variation were also determined. Intragroup comparison was performed for each group using a one-way analysis of variance (time) with repeated measures at each time, followed by Dunnett's tests in case of significant time effect, to compare each time value with the basal value (i.e., before administration). Differences were considered statistically significant when p was $<$ or $=$ to 0.05.

Arterial Blood Pressure and Heart Rate in the Spontaneously Hypertensive Conscious Rat. Adult male spontaneously hypertensive rats were anesthetized using 300 mg/kg chloral hydrate ip. A catheter (0.86 mm internal diameter, 1.27 mm external diameter, filled with physiological saline containing 150 IU/mL heparin) was implanted into the left carotid artery. The free end of the catheter was advanced subcutaneously to emerge at the nape of the neck, using a stainless steel button, a tether assembly, and a cannula swivel (Instech Lab.) The animals were then given an im injection of 100 000 IU penicillin G and returned individually to their

cages. The catheter was connected to a Gould P23XL transducer for recording mean, diastolic and systolic blood pressure (BP, mmHg), and heart rate (HR, bpm) which was derived from pulse blood pressure.

The experiment was performed 24 h after surgery. Recordings were carried out using a Gould TA240 Easygraph. BP and HR were allowed to stabilize for a period of at least 40 min, and the test substance was administered orally by gavage (six animals studied per group). BP and HR were measured over a 24 h experimental period. Control animals receiving vehicle (carboxymethylcellulose 0.5% in distilled water, 5 mL/kg) did not show any significant modification of BP and HR over the 24 h experimental period. Results were expressed as the maximal variation of mean arterial pressure (mmHg) and heart rate (bpm) compared to the basal value before treatment. The corresponding percentage of variation were also determined.

Intragroup comparison was performed for each group using a one-way analysis of variance (time) with repeated measures at each time, followed by Dunnett's tests in case of significant time effect, to compare each time value with the basal value (i.e., before administration). Differences were considered statistically significant when p was $<$ or $=$ to 0.05.

Behavioral Effects in the Rat (Irwin test). Adult male Wistar rats (three rats per dose) were administered po the test substance dispersed in 0.5% carboxymethylcellulose in distilled water and were observed simultaneously to a control group given vehicle. Observations were carried out through a standardized observation grid at regular intervals for up to 24 h, and behavioral modifications, physiological and neurotoxicity symptoms, pupil diameter, and rectal temperature were recorded.[92]

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