Design and Synthesis of Imidazoline Derivatives Active on Glucose Homeostasis in a Rat Model of Type II Diabetes. 2. Syntheses and Biological Activities of 1,4-Dialkyl-, 1,4-Dibenzyl, and 1-Benzyl-4-alkyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazines and Isosteric Analogues of Imidazoline

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Received October 5, 1998

Piperazine derivatives have been identified as new antidiabetic compounds. Structure−activity relationship studies in a series of 1-benzyl-4-alkyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazines resulted in the identification of 1-methyl-4-(2′,4′-dichlorobenzyl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine, PMS 812 (S-21663), as a highly potent antidiabetic agent on a rat model of diabetes, mediated by an important increase of insulin secretion independently of α_2 adrenoceptor blockage. These studies were extended to find additional compounds in these series with improved properties. In such a way, substitution of both piperazine N atoms was first optimized by using various alkyl, branched or not, and benzyl groups. Second, some modifications of the imidazoline ring and its replacement by isosteric heterocycles were carried out, proceeding from PMS 812, to evaluate their influence on the antidiabetic activity. The importance of the distance between the imidazoline ring and the piperazine skeleton was studied third. Finally, the influence of the *N*-benzyl moiety was also analyzed compared to a direct *N*-phenyl substitution. The pharmacological evaluation was performed in vivo using glucose tolerance tests on a rat model of type II diabetes. The most active compounds were 1,4-diisopropyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (**41a**), PMS 847 (S-22068), and 1,4-diisobutyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (**41b**), PMS 889 (S-22575), which strongly improved glucose tolerance without any side event or hypoglycemic effect. More particularly, PMS 847 proved to be as potent after po (100 μmol/kg) as after ip administration and appears as a good candidate for clinical investigations.

Introduction

Non-insulin-dependent diabetes mellitus (NIDDM) is one of the most common chronic and dangerous diseases with a prevalence of 4% in the Western world's population. Despite large efforts to discover new antidiabetic drugs, only two classes of oral hypoglycemic agents (sulfonylureas and biguanides) are available for the treatment of NIDDM, and for both of them, a residual insulin secretion is necessary for activity. Sulfonylureas, such as tolbutamide and gliclazide, are hypoglycemic compounds which stimulate insulin secretion via a well-known mechanism.[1] But a major drawback of sulfonylurea-based therapies is the occurrence of severe hypoglycemia. Biguanides (particularly metformine) act mainly by decreasing gluconeogenesis and increasing peripheral utilization of glucose.[2−5] Among the most promising therapeutic approaches, imidazoline derivatives such as midaglizole,[6,7] deriglidole,[8,10] and efaroxan[11] were reported to be antihyperglycemic agents.

In the past few years evidence occurred that the insulin-secreting potency of imidazoline derivatives was not correlated with their α_2 antagonistic properties,[12,13] and it has been proposed that some of these compounds could interact with imidazoline preferring binding sites (I-PBS).[14,15]

In a previous paper,[16] we described the syntheses and pharmaceutical evaluation of new antihyperglycemic 1,4-disubstituted-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)-

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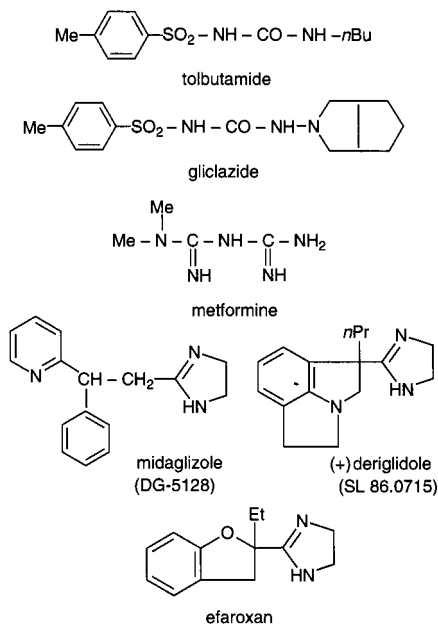‡ Université of Paris 7-Denis Diderot−CNRS ESA 7059.
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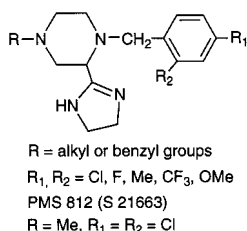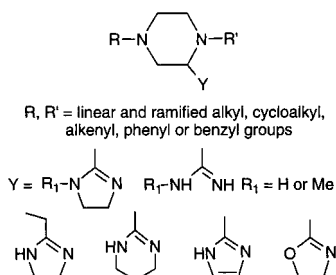⊥ Université of Liège.
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tolbutamide

gliclazide

metformine

midaglizole
(DG-5128)

(+)deriglidole
(SL 86.0715)

efaroxan

piperazines having the following general formula:

R = alkyl or benzyl groups
R1, R2 = Cl, F, Me, CF3, OMe
PMS 812 (S 21663)
R = Me, R1 = R2 = Cl

These compounds proved to be potent antihyperglycemic agents in glucose tolerance tests using a rat model of type II diabetes obtained by iv single injection of a low dose (35 mg/kg) of streptozotocin (STZ rats). The structure−activity relationships obtained within this first series showed that good potency was reached when R is a short linear or branched alkyl chain and the phenyl ring is substituted with halogens (more particularly chlorine atoms). One of the most active compounds was 1-(2′,4′-dichlorobenzyl)-4-methyl-2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)piperazine, PMS 812 (S-21663). Diabetic rats treated with such compounds, especially PMS 812, exhibited similar glycemia as nondiabetic control rats.[16,17] None of the compounds of this series presented a potent affinity for adrenoreceptors and I-PBS.[16] Moreover PMS 812 was considered as a very efficient glucose-independent insulin secretagogue acting through a novel imidazoline site, linked to K^+ channels, and distinct from I_1- and I_2-PBS.[18]

R, R' = linear and ramified alkyl, cycloalkyl,
alkenyl, phenyl or benzyl groups

Y = R1 in imidazoline, R1−NH NH R1 = H or Me

In the continuation of this previous work,[16] we report here the synthesis and the biological evaluation of 1,4-

dialkyl-, 1,4-dibenzyl-, and 1-alkyl-4-benzyl(or phenyl)-2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)piperazine derivatives. Pharmacomodulation was also performed on the imidazoline moiety itself which was substituted by a methyl or replaced by isosteric groups such as oxazoline, tetrahydropyrimidine, or amidine. All these compounds were evaluated in vivo for their antidiabetic activity using glucose tolerance tests. In vitro binding experiments were performed on selected compounds and showed the same negative results as observed in the previous study.[16]

Chemistry

The 2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)- (**41a−q**, **42**, and **60−63**), 2-(4′,5′-dihydro-1′,3′-oxaxazol-2′-yl)- (**50**), and 2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)- (**59**) piperazines were prepared from the corresponding esters synthesized according to pathways described in Schemes 1−4.

Scheme 1 describes the synthesis of the major part of the 1,4-alkylated and 1,4-benzylated ester derivatives. Alkylation of ethyl piperazine-2-carboxylate (**1**)[16] with 2 equiv of alkyl or allyl halides in refluxing acetone or acetonitrile afforded the disubstituted compounds **2a−g**. In the case of chloro or bromo derivatives, the yields of **2** were improved by addition of catalytic amounts of KI.[19] Selective alkylation in position 1 needed the use of a protective group in position 4, i.e., triphenylmethyl which was introduced by treating **1** at −10 °C with 1 equiv of trityl chloride. Ethyl 4-tritylpiperazine-2-carboxylate (**3**)[16] was then alkylated into **5** and the trityl group removed under acidic conditions leading to **6**. Reductive alkylation[20] of **6** afforded the ethyl 1-alkyl-4-methylpiperazine-2-carboxylate (**7**). Monosubstitution of **1** in position 4 was performed in conditions depending on the halide derivative. Ethyl 4-alkylpiperazine-2-carboxylates **4** were achieved in refluxing acetone with alkyl halides and at room temperature with allyl and benzyl chlorides. In all cases a mixture of 4-monosubstituted and 1,4-disubstituted piperazine derivatives was obtained, but the components were easily separated by column chromatography on silica gel. No 1-N-monosubstituted compound was detected, and this can be explained by the steric hindrance due to the substituent in position 2. This effect disappears probably by change of piperazine conformation after 4-N-alkylation.

When R is a phenyl or a dicyclopropylmethyl group and R′ a methyl or a dicyclopropylmethyl moiety, the corresponding N,N′-disubstituted ethylenediamine was prepared before cyclization into the piperazine ring as seen in Schemes 2 and 3. In Scheme 2, reductive alkylation of commercial *N*-benzylaminoethanol afforded **9** which was converted to chloride **10** by treatment with thionyl chloride. The amine **11**, easily purified by distillation, was then obtained in good yield using an excess of ammonia (30 times more). Prolonged heating (14 days) at 80 °C of **11** or ethylenediamine with dicyclopropyl ketone was required to produce the imine **13** or diimine **14**. After sodium borohydride reduction (and catalytic debenzylation of compound **15**), the resulting amines **16** and **17** reacted with ethyl 2,3-dibromopropionate to give 1-dicyclopropylmethyl-4-methyl (**18**) and 1,4-bis(dicyclopropylmethyl) (**19**) ester intermediates. Two isomers could be expected from the

Scheme 1. Synthesis of Alkyl and Benzyl Ester Intermediates **2a**−**g**, **7a**−**d**, and **8a**−**c**[a]
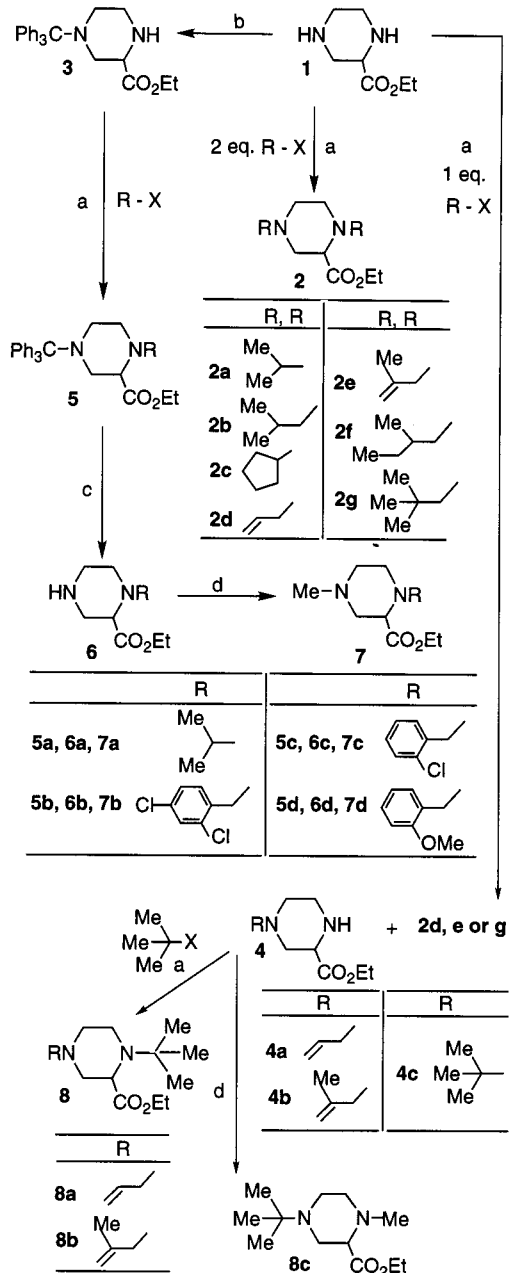
[a] (a) MeCN or Me$_2$CO, K$_2$CO$_3$, KI; (b) Ph$_3$C-Cl, NEt$_3$, CH$_2$Cl$_2$, −10 °C; (c) HCl, Me$_2$CO then Na$_2$CO$_3$; (d) HCO$_2$H, HCHO, MeOH.

Scheme 2. Synthesis of Dicyclopropylmethyl Ester Intermediates **18** and **19**[a]
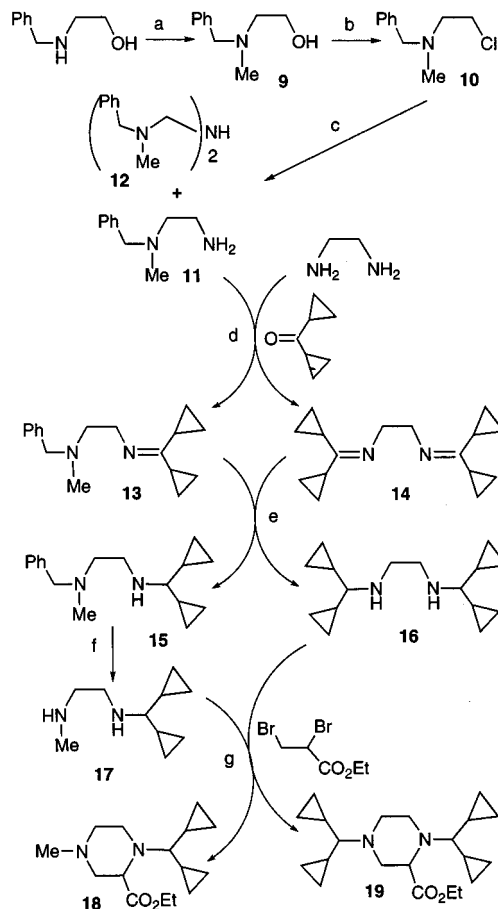
[a] (a) HCO$_2$H, HCHO, MeOH then Na$_2$CO$_3$; (b) SOCl$_2$; (c) NH$_3$, H$_2$O; (d) C$_6$H$_6$; (e) NaBH$_4$, MeOH; (f) H$_2$, Pd/C, EtOH; (g) C$_6$H$_6$, NEt$_3$, 80 °C.

condensation of amine **17**. Only the isomer **18** was isolated. The reaction is a type II NS. The first attack comes from the nonbulky nitrogen on C3 bromide of ethyl 2,3-dibromopropionate. If the methyl group is replaced by a more bulky substituent such as an isopropyl group, the cyclization provided two regioiso-mers,[21] suggesting that steric control plays a major role in determining the high selectivity.

N-Phenyl-substituted esters **24**, **29**, and **35** were prepared using the corresponding 1-phenyl-4-alkyleth-ylenediamines **23**, **28**, and **34**. These diamines were synthesized by three different pathways described in Scheme 3. In method A, reaction of aniline with 0.5 equiv of benzoyl chloride followed by alkylation of the resulting amide **20** with 2-chloro-1-*N*-methyl-*N*-benzyl-aminoethane gave compound **21**. Both protecting groups

were successively removed (i) by heating in acidic medium to give **22** and (ii) then by catalytic hydro-genolysis at room temperature leading to **23**. If the mixture was warmed at 50 °C or treated under pressure (40 psi), the phenyl group was cleaved too. The diamine **28** could not be prepared by this method, because of the cleavage of the *N*-isopropyl bond in strong acidic condi-tions, but according to method B. The N-protection of *N*-phenylethanolamine was selectively performed in good yield using 0.5 equiv of benzyl chloride to afford **25**. This alcohol was converted into the corresponding tosylate **26** which reacted with isopropylamine to pro-vide compound **27**. Benzyl protecting group was then removed by catalytic hydrogenolysis at room tempera-ture affording **28**. Because of the sensibility to hydro-genolysis of the chloro substituent (Scheme 3, methods A and B, step d), another protocol was used (method C) for preparing diamine **34**. 2-Chloroaniline was acylated by benzoyl chloride and the resulting amide **30** alkylated with chloroacetonitrile to give **31**. Catalytic hydrogena-tion of the nitrile in the presence of Raney nickel in acetic anhydride afforded the diamide **32** which was alkylated. Acidic hydrolysis of compound **33** provided the diamine **34**. Cyclization of the diamines **23**, **28**, and **34** with ethyl 2,3-dibromopropionate was difficult be-cause of the low nucleophilicity of the nitrogen substi-tuted with the aromatic ring. Anyway, the two possible regioisomers were obtained. The ratio of the esters, **24a**:

Scheme 3. Synthesis of 1-Aryl-4-alkyl Ester Intermediates **24a**,**b**, **29a**,**b**, and **35a**,**b**[a]

Method A

Method B

Method C
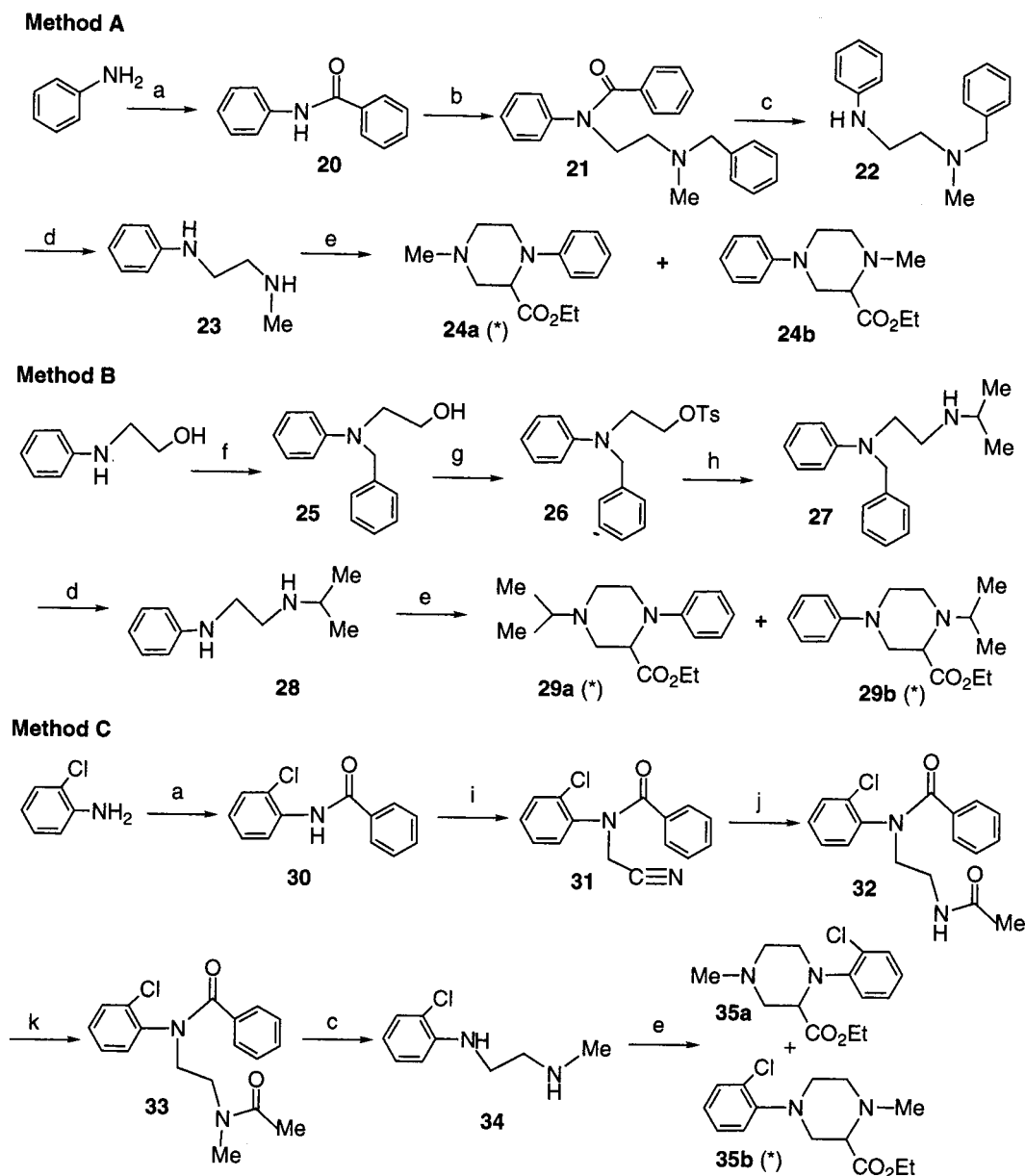
[a] (a) 0.5 equiv of Ph-COCl, CH₂Cl₂; (b) (1) NaH, DMF, 60 °C, (2) Bzl-N(Me)CH₂-CH₂-Cl; (c) 6 N HCl, EtOH/H₂O; (d) H₂, Pd/C, EtOH; (e) Br-CH₂CHBr-CO₂-Et; (f) 0.5 equiv of Bzl-Cl, rt, C₆H₆; (g) Ts-Cl, NEt₃, CHCl₃, 0 °C; (h) Me₂CHNH₂, CH₂Cl₂; (i) (1) NaH, DMF, rt, (2) Cl-CH₂-CN; (j) Raney Ni, (MeCO)₂O, H₂ 40 psi; (k) (1) NaH, DMF, rt, (2) MeI. *Isolated and purified for further syntheses.

24b (4:1), **29a:29b** (7:3), and **35a:35b** (1:9), depended on the structure of the starting diamine. Only compounds **24a**, **29a**, **29b**, and **35b** were isolated pure, the percentage of minor isomer being determined by ¹H NMR.
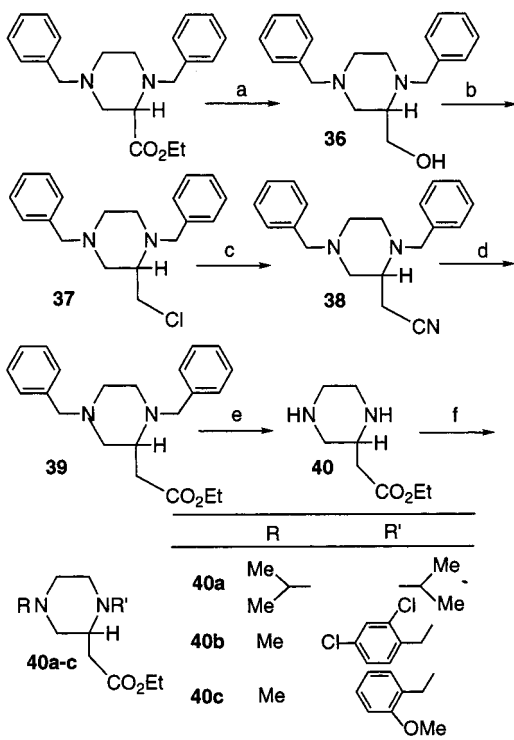
The preparation of ethyl piperazin-2-ylacetate (**40**) is described in Scheme 4. Ethyl 1,4-dibenzylpiperazine-2-carboxylate[16] was first reduced by AlLiH₄ to afford the intermediate **36**. This alcohol was treated with thionyl chloride to give chloride **37** which was then substituted by CN⁻. Hydrolysis of the nitrile function of **38** by H₂-SO₄ in EtOH afforded the corresponding ethyl 1,4-dibenzylpiperazin-2-ylacetate (**39**). Its debenzylation led to the key intermediate **40** which could be treated as described in Scheme 1 to provide compounds **40a**−**c**.

Imidazoline analogues were prepared according to Neef general procedure[22] with a minor modification[16] (Scheme 5). Reaction of esters with ethylenediamine in the presence of an excess of Al(CH₃)₃ provided the imidazoline ring (**41a**−**q**, **60**−**63**). *N*-Methylethylenediamine afforded the corresponding derivative **42**. The tetrahydropyrimidine **43** was prepared from 1,3-diaminopropane.

Both enantiomers of imidazoline derivative **41a** were tentatively prepared from (2*R*)- and (2*S*)-(1′*R*, 2′*S*, 5′*R*-menthoxycarbonyl)piperazines obtained according to Aebischer et al.[23] These diastereoisomers were alkylated with isopropyl iodide and the resulting esters converted into the optically active imidazolines as described in Scheme 5. Unfortunately these enantiomers were slowly racemized in solution.[21] For this reason, no further investigation was performed on separation of enantiomers in these series (see Conclusion).

The synthetic strategy for preparing the oxazoline **50** is illustrated in Scheme 6. Compound **46** was prepared first by N-benzylation of ethanolamine, then protection

Scheme 4. Synthesis of Key Ester Intermediates **39** and **40a–c**[a]

	R	R'
40a	Me, Me (isopropyl)	Me, Me, Cl (substituted)
40b	Me	Cl, Cl, ethyl (substituted)
40c	Me	ethyl, OMe (substituted)

[a] (a) AlLiH₄, THF; (b) SOCl₂, CHCl₃; (c) KCN, EtOH, H₂O; (d) H₂SO₄, EtOH, H₂O; (e) H₂, Pd/C, EtOH, HCl; (f) **40a–c** were prepared as for **2a**, **7b**, and **7d**, respectively (Scheme 1).

Scheme 5. Syntheses of Final Imidazolines **41a–q**, **42**, and **60–63** and Tetrahydropyrimidine **43**
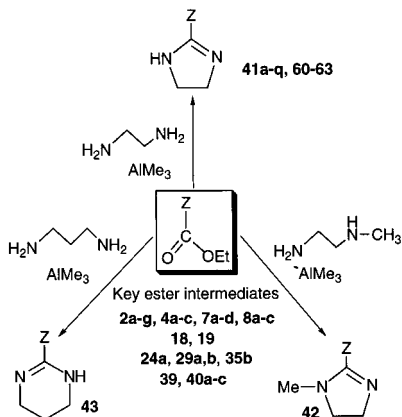
of the alcohol **44** using dihydropyran, and finally removal of both benzyl protecting groups of the substituted ethanolamine **45**. Condensation of the amine **46** with ester **7c** in the presence of Al(CH₃)₃ afforded the amide **47**. After removal of the THP protecting group, the resulting alcohol **48** was converted into the corresponding chloride **49**. Its cyclization in the presence of NaOH gave the oxazoline analogue **50**.

The synthesis of the amidines **52a**, **52b**, and **56** (Scheme 7) started from the cyanopiperazines **51** or **55** prepared by cyclization of N,N′-disubstituted ethylenediamine and 2,3-dibromopropionitrile in refluxing benzene. According to Garigipati's method,[24] the amidines **52a**, **52b** and **56** were obtained from nitriles by addition of methylchloroaluminum amides[25] generated from tri-

**Scheme 6.** Synthesis of Oxazoline Analogue **50**[a]
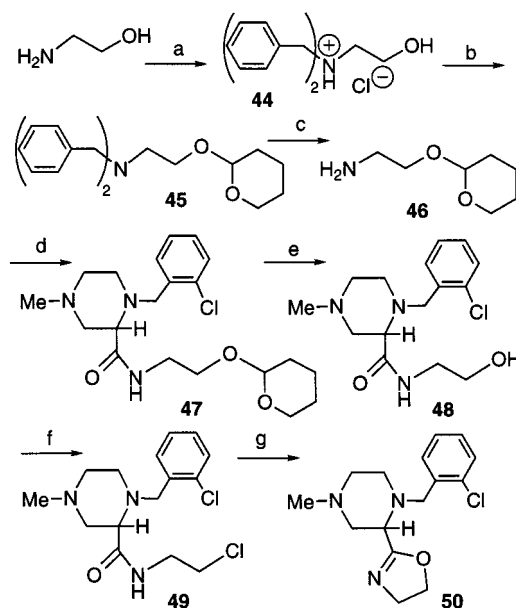
[a] (a) (1) 2 equiv of C₆H₅CH₂Cl, NEt₃, (2) HCl; (b) DHP, CH₂Cl₂ then Na₂CO₃; (c) H₂, Pd/C, EtOH; (d) **7c**, AlMe₃, toluene; (e) HCl, MeOH then Na₂CO₃; (f) SOCl₂, CHCl₃ then Na₂CO₃; (g) NaOH.

Scheme 7. Syntheses of Amidine **52a** and Methylamidines **52b** and **56**[a]
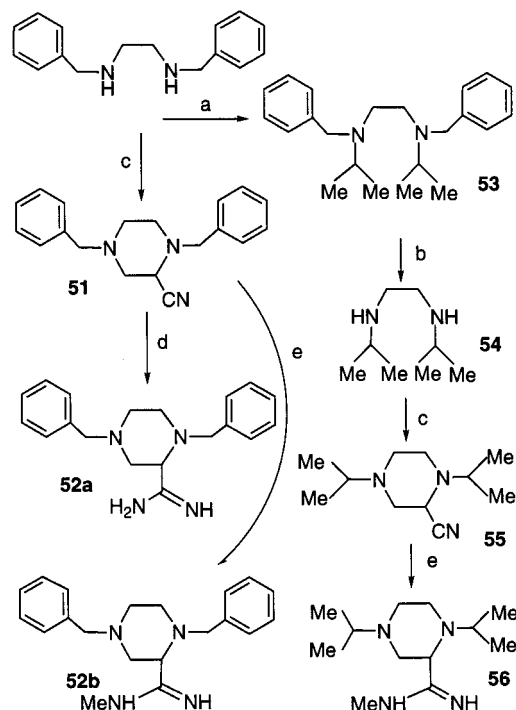
[a] (a) Me₂CH-I, K₂CO₃, KI; (b) H₂, Pd/C, EtOH; (c) Br-CH₂CH(Br)-CN, C₆H₆, NEt₃; (d) AlMe₃, NH₄Cl, C₆H₅Me; (e) AlMe₃, CH₃-NH₂, HCl, toluene.

methylaluminum and ammonium chloride or methylamine hydrochloride.

The first step of the imidazole analogue **59** synthesis (Scheme 8) was the reduction of ethyl 1-(2′,4′-dichlorobenzyl)-4-methylpiperazine-2-carboxylate into the alcohol **57**.[16] Subsequent oxidation into aldehyde **58** under Swern's conditions[26] and then reaction with ammonia and glyoxal[27] gave the final product.

Scheme 8. Preparation of Imidazole Analogue **59**[a]
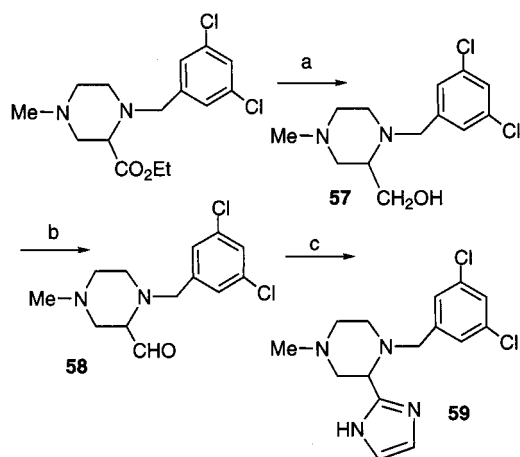
[a] (a) LiAlH$_4$, THF; (b) trifluoroacetic anhydride, DMSO, Et$_3$N, CH$_2$Cl$_2$, N$_2$ atm; (c) glyoxal, NH$_3$, MeOH.

Significance and Validity of Pharmacological Parameters. As previously described,[16] antidiabetic properties of all the synthesized compounds were evaluated in vivo by their ability to improve the glucose tolerance during intravenous glucose tests (IVGTT) performed on a rat model of mild diabetes.[28] This model presents moderate basal hyperglycemia, glucose intolerance, and impairment of the glucose-induced insulin secretion which are the main features in patients with NIDDM. IVGTT were carried out after a single ip administration of 100 μmol/kg of each synthesized molecule, and glucose tolerance was evaluated according to three parameters: (i) G_{30}, which is the glycemic value at 30 min after glucose administration, (ii) ΔG, which represents the increase of glycemia over the baseline integrated over a period of 30 min following the glucose load, and (iii) K, which is the rate of glucose disappearance between 5 and 30 min after glucose administration.

To correct for the slight variations that appeared when glucose tolerance tests were performed with different control diabetic rats, we expressed the results as a percentage (ΔG^*) of variation of ΔG between treated and untreated diabetic rats:

$$\Delta G^* = \left| \frac{\Delta G_{\text{treated STZ rats}} - \Delta G_{\text{untreated STZ rats}}}{\Delta G_{\text{untreated STZ rats}} - \Delta G_{\text{control rats}}} \right| \times 100$$

In the same way, we defined G_{30}^* and K^*. To be considered as effective antidiabetics, compounds must induce high percentages of variation for ΔG^*, K^*, and G_{30}^*. Results around 100% or more indicate that the parameters for the treated diabetic animals are close to those obtained with nondiabetic control animals. Among these three parameters, G_{30} which is obtained via a direct measurement, is considered as the most relevant when the compounds are tested po.

Results and Discussion

Within this new series, the first synthesized and evaluated compounds were symmetrically substituted on both piperazine nitrogen atoms by branched alkyl or cycloalkyl chains.
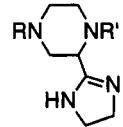
The compounds **41a**, **41b**, and **41f**, respectively substituted by two isopropyl, isobutyl, or 2-methylbutyl groups, show potent effects on glycemia with values similar to those of nondiabetic control rats. As in our first paper,[16] this correlates very well with their effects on ΔG^* and G_{30}^* with values around 100% (Table 1). Their effect on the K parameter is also very significant but less potent, since K^* values remain between 47% for compound **41a** and 82% for compound **41f**. The derivatives **41c** and **41g**, substituted by two cyclopentyl and neopentyl groups, are clearly less active on ΔG ($\Delta G^* = 58\%$ and 54%, respectively) than their isobutyl (compound **41b**, $\Delta G^* = 141\%$) and 2-methylbutyl (compound **41f**, $\Delta G^* = 104\%$) analogues, probably due to problems of steric hindrance. Concerning the compound **41c**, there is a slight discrepancy between the effects on ΔG and K which is rather moderate and the effect on G_{30} which is very high ($G_{30}^* = 103\%$). Compound **41h**, substituted by two dicyclopropylmethyl groups, was slightly less active on ΔG ($\Delta G^* = 24\%$). This is not surprising if cyclopropyl molecular orbitals are considered to have a partial π character so that compound **41h** is comparable in some respects with the dibenzyl-substituted imidazolinylpiperazines which were found inactive in our first paper.[16] Replacement of the two isobutyl moieties (compound **41b**) by two 2-methyl-2-propenyl substituents (compound **41e**) has no deleterious effect on the three parameters which are all around 100%. This is not the case for the diallyl-substituted compound **41d** which is almost inactive ($\Delta G^* = 19\%$, $G_{30}^* = 30\%$, $K^* = 35\%$).

Unsymmetrically substituted compounds (Table 1) were then prepared and evaluated. The compounds **41l** and **41m**, 4-methyl and respectively 1-isobutyl and 1-dicyclopropylmethyl substituted, are equipotent with values around 100% for ΔG^* and around 50% for G_{30}^* and K^*. It is noteworthy that compound **41m** is much more potent than its inactive symmetrically substituted analogue **41h**, while compound **41l** is only slightly less active than its analogue **41b** but much more potent than compound **41k** ($\Delta G^* = 40\%$, $G_{30}^* = 21\%$, $K^* = 42\%$), for which the methyl and isobutyl substituents have been inverted. Surprisingly, while compound **41i**, 1-isobutyl, 4-allyl remains very potent ($\Delta G^* = 115\%$), its 4-propenyl analogue **41j** is clearly less active ($\Delta G^* = 53\%$). When compared to symmetrically substituted compounds **41d** and **41e**, the results are inverted. Compounds bearing a phenyl or a 2-chlorophenyl group were finally synthesized and evaluated (compounds **41n**, **41o**, **41p**, **41q**). All of them proved to be inactive on ΔG so that a phenyl substitution seems to be unfavorable. An expected pK_a variation cannot be taken into account. In our first paper,[16] we clearly demonstrated that the protonation center at physiological pH in such series was the imidazoline ring (p$K_a \sim 9.5$) and not the piperazine one (p$K_a \sim 5.5$). Consequently this negative effect should be due to a decrease of flexibility of these molecules. Moreover, concerning compound **41o**, significant unexplainable discrepancies can be noticed concerning the effects on ΔG and those on K and G_{30}. It is noteworthy that the 2-chlorobenzyl analogue of compound **41p**, PMS 774, is very potent ($\Delta G^* = 81\%$, $K^* = 98\%$, $G_{30}^* = 103\%$).[16]

In a second step, chemical modulations on the imidazoline pharmacophore itself were performed (Table 2). Insertion of a methylene spacer between the piperazine and imidazoline rings results in a very clear

Table 1. Variation of the Glycemia Parameters after ip Administration of 100 μmol/kg of 1,4-Disubstituted-2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)piperazines to STZ Rats[a]

| Compd	R	R'	ΔG^{*b}	G_{30}^*	K^{*d}
41a PMS 847	(isopropyl)	(isopropyl)	138 (±7)	89 (±6)	47 (±3)
41b PMS 889	(sec-butyl)	(sec-butyl)	141 (±11)	89 (±5)	79 (±6)
41c	(cyclopentyl)	(cyclopentyl)	58 (±4)	103 (±11)	23 (±2)
41d	(allyl)	(allyl)	19 (±1)	30 (±4)	35 (±1)
41e	(structure)	(structure)	116 (±9)	96 (±3)	117 (±7)
41f	(structure)	(structure)	104 (±5)	83 (±4)	82 (±5)
41g	(structure)	(structure)	54 (±3)	81 (±7)	67 (±5)
41h	(structure)	(structure)	24 (±2)	89 (±5)	41 (±2)
41i	(structure)	(structure)	115 (±7)	55 (±4)	61 (±3)
41j	(structure)	(structure)	53 (±4)	41 (±6)	76 (±4)
41k	(structure)	−Me	40 (±2)	21 (±3)	42 (±3)
41l	Me−	(structure)	113 (±8)	48 (±5)	55 (±3)
41m	Me−	(structure)	101 (±6)	55 (±3)	47 (±4)
41n	Me−	(phenyl)	6.0 (±0.4)	28 (±2)	39 (±1)
41o	(benzyl)	(isopropyl)	0	15 (±1)	60 (±3)
41p	(chlorobenzyl)	−Me	10 (±1)	17 (±1)	60 (±4)
41q	(structure)	(phenyl)	11 (±1)	91 (±4)	102 (±9)
idazoxan			8.0 (±0.5)	48 (±5)	79 (±6)
midaglizole			32 (±3)	121 (±10)	98 (±7)

[a] Three-month-old male Wistar rats (250 g) treated with 35 mg/kg iv of streptozotocin. [b] ΔG, incremental glycemia values over baseline integrated over 30 min after glucose (0.5 g/kg iv) administration. [c] G_{30}, glycemia value 30 min after glucose administration. [d] K, rate of glucose disappearance between 5 and 30 min after glucose administration. All results (asterisk) are expressed as the percent of variation of the parameters between treated rats (with an ip administration of 100 μmol/kg of the tested compound) and untreated rats. Number of treated rats for each compound included between 4 and 8 (±SEM).

Table 2. Variation of the Glycemia Parameters after ip Administration of 100 μmol/kg of Substituted Imidazolines, Tetrahydropyrimidine, Oxazoline, Amidines, Imidazole, and 2-Methylimidazoline to STZ Rats[a]

Compd	R	R'	Y	ΔG^*	$G_{30}^*($	K^*
42	Me−	(dichlorobenzyl)	(Me-N imidazoline)	24 (±1)	75 (±4)	64 (±4)
43	Me−	(dichlorobenzyl)	(HN tetrahydropyrimidine)	47 (±3)	30 (±3)	38 (±3)
50	Me−	(chlorobenzyl)	(oxazoline)	8.0 (±0.6)	0	0
52a	(benzyl)	(benzyl)	(H_2N amidine)	55 (±4)	65 (±6)	65 (±5)
52b	(benzyl)	(benzyl)	(Me-N amidine)	50 (±3)	62 (±5)	60 (±5)
56	(isopropyl)	(isopropyl)	(Me-N amidine)	43 (±3)	77 (±5)	62 (±5)
59	Me−	(chlorobenzyl)	(imidazole)	0	14.0 (±0.3)	37 (±3)
60	(isopropyl)	(isopropyl)	(imidazoline)	27 (±1)	0	79 (±4)
61	(benzyl)	(benzyl)	(imidazoline)	0	0	49 (±3)
62	Me−	(methoxybenzyl)	(imidazoline)	31 (±2)	36 (±2)	53 (±4)
63	Me−	(dichlorobenzyl)	(imidazoline)	19 (±2)	42 (±3)	91 (±6)
PMS 812[b]				105 (±10)	112 (±9)	143 (±12)

[a] See footnotes of Table 1. [b] See formula in Introduction, PMS 812 or S-21663.

decrease of hypoglycemic properties for three of the four synthesized derivatives (**60**, **62**, and **63**). Concerning the fourth compound, the dibenzyl derivative **61**, a moderate but clear effect on ΔG^* is observed, while its analogue without the methylene spacer was totally inactive.[16] It can be postulated that introduction of a spacer gives more flexibility to this bulky molecule and consequently allows a better access to a hypothetic imidazoline binding site. Substitution of the imidazoline ring by a methyl in position 1 (compound **42**) leads to a poorly active compound ($\Delta G^* = 24\%$) as compared to its very potent nonmethylated analogue PMS 812 (S-21663) ($\Delta G^* = 105\%$). Replacement of the imidazoline by an imidazole (compound **59**) or an oxazoline (compound **50**) induces a total loss of activity. However only a partial decrease in activity is observed for the tetrahydropyrimidine analogue **43** ($\Delta G^* = 47\%$) as compared to PMS 812 ($\Delta G^* = 105\%$). The results obtained with amidine and *N*-methylamidine are more contrasted. The *N*-methylamidino diisopropyl compound **56** is clearly less potent ($\Delta G^* = 43\%$) than its imidazoline counterpart **41a** ($\Delta G^* = 138\%$), and the amidino **52a** ($\Delta G^* = 55\%$) and *N*-methylamidino **52b** ($\Delta G^* = 50\%$) dibenzyl derivatives are moderately active, while their imidazoline analogue is totally inactive.[16]

Due to their good activity via ip administration, compounds **41a**, **41b**, **41e**, **41f**, and **41i** were selected to be tested via po administration at 100 μmol/kg (Table 3). Among these five derivatives, only compounds **41a** and **41b** proved to be active via po administration with significant effects on G_{30}* (respectively 73% and 66%). This could be explained by the poor bioavailability of the other compounds with (i) perhaps problems of metabolism for the unsaturated compounds **41e** and **41i**, despite their isolipophilicity (log P = 1.45 and 1.30, respectively) with the congener **41a**, or (ii) a too high hydrophobicity for compound **41f** (log P = 3.22) as compared to 1.15 and 2.18 for compounds **41a** and **41b**, respectively (cf. Table 3 and Experimental Section for calculations). It seems that the range of lipophilicity required for a good bioavailability of these compounds is included between 2.2 and 1.1 units of log P approximately. Moreover, the log P value of PMS 812, a very potent in vivo antihyperglycemic compound,[16,17] was equal to 2.21.

Compound **41a** was then selected for further pharmacological studies and first evaluated for its capacity to stimulate the secretion of insulin during IVGTT. Surprisingly and unlike the substituted benzylpiperazine derivative PMS 812,[16-18] compound **41a**, PMS 847 (S-22068), has a poor stimulating effect on insulin secretion.[30]

The in vitro binding experiments performed with these compounds demonstrated that they were clearly devoid of any affinity for the I_1 and I_2 binding sites as well as for the α_2 adrenoreceptor ($K_I \geq 10^{-5}$ M). This is in agreement with an increasing number of studies showing that α_2 adrenergic antagonists are able to stimulate insulin secretion independently of α_2 and I_1, I_2 blockage.[16,17,28,29,31-38]

Conclusion

In conclusion, 29 new imidazoline derivatives were synthesized and evaluated (100 μmol/kg via ip administration) for their antidiabetic properties in glucose tolerance tests. Seven of them (compounds **41a**, **41b**, **41e**, **41f**, **41i**, **41l**, and **41m**) have a potent effect on the glucose tolerance via ip administration, and 2 of them (compounds **41a** and **41b**) were also found active after po administration (100 μmol/kg). Surprisingly, compound **41a** (PMS 847, S-22068)[30] has no effect on insulin secretion and is devoid of any affinity either for the I_1 and I_2 imidazoline binding sites or for the α_2 adrenoreceptors. This compound undergoes current complementary studies in order to investigate its possible mechanism of action. Concurrently, the structure−activity relationships that have been established with this present work and the previous one[16] show unambiguously that an unsubstituted imidazoline ring is a required pharmacophore for potent antihyperglycemic properties. All attempts to substitute it or to replace it by imidazole, tetrahydropyrimidine, oxazoline, or amidine result in a clear decrease or a total loss of activity. This could be an argument for the involvement of specific and still unknown imidazoline binding sites in the regulation of glucose homeostasis.

Finally it is noteworthy that a spontaneous slow racemization at the chiral carbon 2 is observed in such molecules (cf. compound **41a**, see Chemistry). This is a consequence of a hydrogen transfer to the imidazoline ring inducing an intermediate tautomeric form. It is reasonable to suspect that such a phenomenon takes place in vivo. If their exceptional conformational flexibility is taken into account,[16] such derivatives should present great adaptability to special binding sites and probably interact via dynamic processes.[39]

Table 3. Variation of the Glycemia Parameters after po Administration of 100 μmol/kg of 1,4-Disubstituted-2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)piperazines to STZ Rats and Partition Coefficient[a]

Compd	R	R'	G_{30}*	log P
41a	Me, Me (isopropyl)	Me, Me (isopropyl)	73-±4	1.15
41b	Me, Me	Me, Me	66 ±4	2.18
41e	Me (allyl)	Me	0	1.45
41f	Me, Me	Me, Me	4.3 ±2	3.22
41i	(allyl)	Me, Me	23 ±1	1.30
PMS 812			64 ±3	2.21

[a] See footnotes of Table 1 and Experimental Section for calculation of log P.

Experimental Section

Chemistry. General Methods. The purity of each compound was checked by thin-layer chromatography on TLC plastic sheets (silica gel 60F254, layer thickness 0.2 mm) from Merck. Column chromatography purification was carried out on silica gel 60 (particle size 0.063−0.200 mm) from Merck, without any special treatment. All melting points were determined in a digital melting point apparatus (Electrothermal) and are uncorrected. The structures of all compounds were confirmed by IR and ^{1}H NMR spectra. IR spectra were obtained with an ATI Mattson Genesis Series FTIR infrared spectrometer, and ^{1}H NMR spectra were recorded in CDCl$_3$ on a Brucker AC 200 spectrometer or a JEOL PMX60SI NMR spectrometer using hexamethyldisiloxane (HMDS) as an internal standard. All elemental analyses were within ±0.4% of theoretical values.

Preparation of Alkyl and Benzyl Ester Intermediates 2a−g, 7a−d, and 8a−c (Scheme 1). Ethyl 1,4-Diisopropylpiperazine-2-carboxylate Dihydrochloride (2a). A suspension of **1**·2HCl (23.1 g, 0.1 mol) and dry K$_2$CO$_3$ (40 g) in 200 mL of acetonitrile was stirred for 1 h at room temperature to regenerate the free amine; 51 g (0.3 mol) of isopropyl iodide was added, and the mixture refluxed for 24 h. The reaction mixture was cooled and filtered and the filtrate diluted with ether. The organic layer was washed with water and dried over MgSO$_4$, and the solvents were removed in vacuo. The crude product was dissolved in CH$_2$Cl$_2$, and after the product was cooled in an ice bath, EtOH saturated with HCl gas was added until acidic pH. The solvents were evaporated and the dihydrochloride salt recrystallized from CH$_2$Cl$_2$−acetone−ether to afford 22 g (72%) of **2a**·2HCl: mp 94−95 °C. Usual treatment of this salt gave free amine **2a** as a colorless oil: IR (film, cm^{-1}) ν 1755 (C=O); ^{1}H NMR δ 4.16

(2H, q, $J = 6.5$ Hz, H_2C-O), 3.40 (1H, dd, $J = 4.3$ and 5.2 Hz, HC$-$N), 2.95$-$2.38 (8H, ma, three H_2C-N and two HC(CH$_3$)$_2$), 1.21 (3H, t, $J = 6.5$ Hz, H_3C-CH_2O), 1.09, 0.96, 0.95, 0.90 (12H, 4d, $J = 6.5$ Hz, two $(H_3C)_2$CH).

Compounds **2b**$-$**g** (free amines as oils) were prepared by the same procedure using acetone as solvent instead of acetonitrile, catalytic amount of KI, and the corresponding chloro or bromo derivative.

Ethyl 1,4-diisobutylpiperazine-2-carboxylate (2b): ^{1}H NMR δ 4.17$-$4.01 (2H, m, H_2C-O), 3.16 (1H, dd, $J = 3.42$ and 5.72 Hz, HC$-$N), 3.08$-$3.0, 2.73$-$2.64, 2.43$-$2.22 (7H, 3m, three H_2C-N and H-CH$-N_1$), 2.12 (1H, dd, $J = 6.42$ and 12.46 Hz, H-CH$-N_1$), 1.97 (2H, d, $J = 7.66$ Hz, H_2C-N_4), 1.73$-$1.56 (2H, m, two HC(CH$_3$)$_2$), 1.19 (3H, t, $J = 7.12$ Hz, H_3C-CH_2O), 0.82 and 0.80 (12H, 2d in 1:3 ratio, two $(H_3C)_2$CH).

Ethyl 1,4-dicyclopentylpiperazine-2-carboxylate (2c): ^{1}H NMR δ 4.19$-$4.05 (2H, m, H_2C-O), 3.42 (1H, dd, $J = 3.56$ and 5.8 Hz, HC$-$N), 3.18$-$3.01, 2.81$-$2.73, 2.55$-$2.36, 1.78$-$1.27 (24H, 4m, in ratio 2:1:5:16, three H_2C-N and H cyclopentyl), 1.21 (3H, t, $J = 7.1$ Hz, H_3C-CH_2O).

Ethyl 1,4-di(2′-propen-1′-yl)piperazine-2-carboxylate (2d): ^{1}H NMR δ 5.90$-$5.55 (2H, m, two HC=), 5.3$-$5.0 (4H, m, H_2C=), 4.17 (2H, q, $J = 7.2$ Hz, H_2C-O), 3.62$-$2.0 (11H, m, H piperazine and two H_2C-CH=), 1.23 (3H, t, $J = 7.2$ Hz, H_3C-CH_2O).

Ethyl 1,4-di(2′-methyl-2′-propen-1′-yl)piperazine-2-carboxylate (2e): ^{1}H NMR δ 4.85$-$4.46 (4H, m, two H_2C=), 4.15$-$4.02 (2H, m, H_2C-O), 3.22$-$2.22 (11H, m, H piperazine and two H_2C-C=C), 1.66 and 1.63 (6H, 2s, two H_3C-C=), 1.20 (3H, t, $J = 7.1$ Hz, H_3C-CH_2O).

Ethyl 1,4-di(2′-methylbutyl)piperazine-2-carboxylate (2f): ^{1}H NMR δ 4.15$-$4.02 (2H, m, H_2C-O), 3.18$-$1.91 (9H, m, H piperazine and two HC$-$N), 1.48$-$1.29 (4H, m, H_2C-CH$_3$), 1.20 (3H, t, $J = 7.15$ Hz, H_3C-CH_2O), 0.80 (6H, t, $J = 6.87$ Hz, two H_3C-CH$_2$), 0.81 and 0.79 (6H, 2d, $J = 6.87$ Hz, two H_3C-CH).

Ethyl 1,4-dineopentylpiperazine-2-carboxylate (2g): ^{1}H NMR δ 4.15$-$4.05 (2H, m, H_2C-O), 3.22$-$2.5 (7H, m, H piperazine), 1.9 (4H, s, two H_2C-C(CH$_3$)$_3$), 1.2 (3H, t, $J = 7.17$ Hz, H_3C-CH_2O), 0.75 (18H, s, $(H_3C)_3-$C).

Ethyl 4-(2′-Propen-1′-yl)piperazine-2-carboxylate (4a). A suspension of **1** (23.1 g, 0.1 mol), dry K_2CO_3 (40 g), and KI (4 g) in DMF (200 mL) was stirred vigorously and heated at 40 °C. After the mixture cooled, 1-bromo-2-propene (12.1 g, 0.1 mol) in DMF (80 mL) was added dropwise and the mixture stirred at room temperature for 24 h. The solid material was filtered and the filtrate diluted with ether and water. The aqueous layer was extracted with ether. The organic layer was dried over MgSO$_4$ and concentrated. The crude product was purified by column chromatography using petroleum ether/ether (first 60:40 then 50:50, v/v) as eluent to give 6.1 g (31%) of **4a** as a yellow oil: IR (film, cm^{-1}) ν 3320 (N$-$H), 1740 (C=O); ^{1}H NMR δ 5.85$-$5.68 (1H, m, HC=), 5.18$-$5.09 (2H, m, H_2C=), 4.13 (2H, q, $J = 7.1$ Hz, H_2C-O), 3.66$-$2.10 (9H, m, H piperazine and H_2C-C=), 1.97 (1H, s, D$_2$O exchange, H$-$N), 1.20 (3H, t, $J = 7.1$ Hz, H_3C-CH_2O).

Compounds **4b** and **4c** were prepared by the same procedure using the corresponding bromo derivative.

Ethyl 1-Isobutyl-4-(triphenylmethyl)piperazine-2-carboxylate (5a). A mixture of **3**[16] (40 g, 0.1 mol), dry K_2CO_3 (40 g), KI (4 g), and isobutyl bromide (16.4 g, 0.12 mol) in acetonitrile (400 mL) was heated at 80 °C with stirring for 15 h. After filtration of solid material, the filtrate was diluted with ether and washed with water. The aqueous layer was extracted with ether, and the combined organic layers were dried over MgSO$_4$. Solvents were removed in vacuo, and this crude **5a** was used in the next step without purification.

Compounds **5b**$-$**d** were prepared using the corresponding chloro derivatives.

Ethyl 1-Isobutylpiperazine-2-carboxylate (6a). Crude **5a** was dissolved in acetone (600 mL) containing 12 M HCl (25 mL). After 3 h stirring at room temperature, the solvent was removed in vacuo and the residue was partitioned between ether and water. The aqueous layer was treated with a saturated NaHCO$_3$ solution until basic pH and extracted with ether. The organic phase was dried over MgSO$_4$ and the solvent evaporated under vacuo. The crude product was purified by column chromatography using first petroleum ether/ether (30:70, v/v) and then ether to afford 17 g (80%) of **6a** as a colorless oil: IR (film, cm^{-1}) ν 3340 (N$-$H), 1740 (C=O); ^{1}H NMR δ 4.15 (2H, q, $J = 7.1$ Hz, H_2C-O), 3.19$-$1.99 (7H, m, H piperazine), 1.96 (2H, d, $J = 7.68$ Hz, H_2C-CH), 1.73$-$1.56 (1H, m, HC(CH$_3$)$_2$), 1.5 (1H, br s, D$_2$O exchange, H$-$N), 1.23 (3H, t, $J = 7.1$ Hz, H_3C-CH_2O), 0.82 (6H, d, $J = 6.4$ Hz, $(H_3C)_2$CH).

Compounds **6b**$-$**d** were prepared using the same procedure.

Ethyl 1-Isobutyl-4-methylpiperazine-2-carboxylate (7a). A mixture of **6a** (17 g, 0.08 mol), 37% formaldehyde (10 mL, 0.13 mol), and formic acid (10 mL, 0.25 mol) in MeOH (110 mL) was refluxed for 20 h. After evaporation of the solvent, the residue was taken up in ether and washed with saturated NaHCO$_3$ solution until basic pH. The organic layer was washed with water and dried over MgSO$_4$, and the solvent was removed in vacuo. The crude product was purified by crystallization of the hydrochloride salt from ethanol$-$ether. Usual treatment of this salt afforded 15.5 g (85%) of **7a** as a colorless oil: IR (film, cm^{-1}) ν 1745 (C=O); ^{1}H NMR δ 4.15 (2H, q, $J = 7.10$ Hz, H_2C-O), 3.07$-$2.20 (7H, m, H piperazine), 2.27 (3H, s, H_3C-N), 2.02 (2H, d, $J = 7.29$ Hz, H_2C-CH), 1.79$-$1.59 (1H, m, HC(CH$_3$)$_2$), 1.22 (3H, t, $J = 7.10$ Hz, H_3C-CH_2O), 0.81 (6H, d, $J = 6.33$ Hz, $(H_3C)_2$CH).

Compounds **7b**$-$**d** were prepared using the same procedure.

Ethyl 1-(2′,4′-dichlorobenzyl)-4-methylpiperazine-2-carboxylate (7b): ^{1}H NMR δ 7.38$-$7.11 (3H, m, Ar$-$H), 4.06 (2H, q, $J = 7.09$ Hz, H_2C-O), 3.75 and 3.44 (2H, AB spectrum, $J = 14.76$ Hz, H_2C-Ar), 3.6$-$2.24 (7H, m, H piperazine), 2.19 (3H, s, H_3C-N), 1.16 (3H, t, $J = 7.09$ Hz, H_3C-CH_2O).

Ethyl 1-(2′-chlorobenzyl)-4-methylpiperazine-2-carboxylate (7c) and ethyl 1-(2′-methoxybenzyl)-4-methylpiperazine-2-carboxylate (7d): ^{1}H NMR spectra were the same as for **7b**; particular signal for **7d** δ 6.69 (3H, s, H_3C-O).

Ethyl 1-Isobutyl-4-(2′-propen-1′-yl)piperazine-2-carboxylate (8a). This compound was prepared following the procedure described for **5a**, starting from **4a** (19.8 g, 0.1 mol) and isobutyl bromide (16.4 g, 0.12 mol). After treatment the crude product was purified by column chromatography using petroleum ether/ether (first 70:30 then 50:50, v/v) as eluent to afford 18 g (71%) of **8a** as a colorless oil: IR (film, cm^{-1}) ν 1745 (C=O); ^{1}H NMR δ 5.79$-$5.75 (1H, m, HC=), 5.24$-$5.14 (2H, m, H_2C=), 4.12 (2H, q, $J = 7.2$ Hz, H_2C-O), 3.10$-$2.24 (11H, m, H piperazine, H_2C-C= and H_2C-CH(CH$_3$)$_2$), 1.72$-$1.62 (1H, m, H-C(CH$_3$)$_2$, 1.19 (3H, t, $J = 7.2$ Hz, H_3C-CH_2O), 0.82 and 0.79 (6H, 2d, $J = 6.2$ Hz, $(H_3C)_2$CH).

Ethyl 1-isobutyl-4-(2′-methyl-2′-propen-1′-yl)piperazine-2-carboxylate (8b): prepared like compound **8a** starting from **4b**; ^{1}H NMR δ 4.77 (2H, br s, H_2C=), 4.45$-$4.15 (2H, m, H_2C-O), 3.20$-$2.08 (11H, H piperazine, H_2C-N_1 and H_2C-N_4), 1.63 (3H, s, H_3C-C=), 1.20 (3H, t, $J = 7.13$ Hz, H_3C-CH_2O), 0.82 and 0.79 (6H, 2d, $J = 6.35$ Hz, $(H_3C)_2$CH).

Ethyl 1-methyl-4-isobutylpiperazine-2-carboxylate (8c): obtained as described for **7a** starting from **4c**; ^{1}H NMR δ 4.14 (2H, q, $J = 7.1$ Hz, H_2C-O), 3.71$-$2.12 (7H, m, H piperazine), 2.27 (3H, s, H_3C-N), 2.02 (2H, d, $J = 7.37$ Hz, H_2C-N), 1.79$-$1.59 (1H, m, HC(CH$_3$)$_2$), 1.22 (3H, t, $J = 7.10$ Hz, H_3C-CH_2O), 0.81 (6H, d, $J = 7.37$ Hz, $(H_3C)_2$CH).

Preparation of Dicyclopropylmethyl Ester Intermediates 18 and 19 (Scheme 2). *N*-Benzyl-*N*-methylethanolamine (9). This compound was prepared following the same procedure as for **7a**. The crude product was purified by distillation ($E_{15} = 140-142$ °C); 151 g (1 mol) of *N*-benzylethanolamine afforded 138 g (84%) of **9**: IR (film, cm^{-1}) ν 3500 (OH), 1590 (C=C); ^{1}H NMR δ 7.20 (5H, s, Ar$-$H), 3.80 (1H, br s, D$_2$O exchange, H$-$O), 3.54 (2H, t, $J = 5.6$ Hz, H_2C-O), 3.49 (2H, s, H_2C-Ar), 2.47 (2H, t, $J = 5.6$ Hz, H_2C-N), 2.13 (3H, s, $J = 7.2$ Hz, H_3C-N).

2-Chloro-*N*-benzyl-*N*-methylethylamine Hydrochloride (10). To 130 g (0.79 mole) of **9** in CHCl$_3$ (400 mL) was added dropwise 70 mL of SOCl$_2$ in CHCl$_3$ (70 mL). After 15 h stirring at room temperature, the solvent was removed in vacuo. The residue was crystallized from acetone/MeOH (80: 20, v/v) to give 146 g (84%) of **10** as a white powder: mp 140−141 °C; IR (free base, film, cm^{-1}) 1595 ν (C=C); ^{1}H NMR (free base) δ 7.24 (5H, m, Ar−H), 3.54 (2H, s, H$_2$C−Ar), 3.53 (2H, t, J = 6.8 Hz, H$_2$C−Cl), 2.69 (2H, t, J = 6.8 Hz, H$_2$C−N), 2.21 (3H, s, H$_3$C−N).

***N*-Benzyl-*N*-methylethylenediamine (11)**. **10** (110 g, 0.5 mol) was solubilized in a 28% aqueous ammonia solution (1 L) and stirred for 3 days at room temperature. The water was partially removed in vacuo, and 28 g of KOH pellets was added. The aqueous layer was extracted with CH$_2$Cl$_2$, and the organic layer was dried over MgSO$_4$ and concentrated. The crude product was purified by distillation (E_{15} = 152−154 °C) to give 49 g (60%) of **11**: IR (film, cm^{-1}) ν 3410 and 3405 (NH$_2$), 1590 (C=C); ^{1}H NMR (60 MHz) δ 7.18 (5H, s, Ar−H), 3.41 (2H, s, H$_2$C−Ar), 2.80−2.20 (4H, m, two H$_2$C−N), 2.10 (3H, s, H$_3$C−N), 1.12 (2H, br s, D$_2$O exchange, H$_2$N).

***N*-Benzyl-*N*-methyl-*N*-(dicyclopropylmethyl)ethylenediamine (15)**. A mixture of 8.2 g (0.05 mol) of **11** and 5.5 g (0.05 mol) of dicyclopropyl ketone in benzene (50 mL) was refluxed for 15 days using a Dean−Stark apparatus. Advancement of the reaction was followed by IR. The solvent was evaporated, and the residue was diluted in dry and cold MeOH (50 mL); then 1.9 g (0.05 mol) of NaBH$_4$ was added portionwise. After 15 h stirring at room temperature, the mixture was poured into water containing 2 g of NaOH, saturated with NaCl, and extracted with hexane. The organic layer was dried over MgSO$_4$ and concentrated. The crude product was purified by column chromatography using CH$_2$Cl$_2$ and then CH$_2$Cl$_2$/MeOH (97:3, v/v) as eluents to give 5.2 g (40%) of **15**: IR (film, cm^{-1}) ν 3380 (NH), 3100, 3080 (cyclopropyl), 1580 (C=C); ^{1}H NMR (60 MHz) δ 7.19 (5H, s, Ar−H), 3.45 (2H, s, H$_2$C−Ar), 2.95−2.67 (4H, m, two H$_2$C−N), 1.90 (1H, s, D$_2$O exchange, H−N), 1.35−0.48 (11H, m, HC−dicyclopropyl and H cyclopropyl).

***N*-Methyl-*N*-(dicyclopropylmethyl)ethylenediamine (17)**. A shaken suspension of **15** (23 g, 0.09 mol) and 10% Pd/C (300 mg) in anhydrous ethanol (120 mL) was heated at 40 °C under H$_2$ atmosphere for 3 h. The reaction mixture was filtered through Celite and concentrated. The crude product was purified by distillation ($E_{0.05}$ = 48−52 °C) to give 12.8 g (85%) of **17** as a colorless oil: IR (film, cm^{-1}) ν 3400 (NH), 3100, 3080 (cyclopropyl); ^{1}H NMR (60 MHz) δ 2.95−2.50 (4H, m, two H$_2$C−N), 1.75 (2H, s, D$_2$O exchange, two H−N), 1.35−0.45 (11H, m, HC-dicyclopropyl and H cyclopropyl).

Ethyl 1-(Dicyclopropylmethyl)-4-methylpiperazine-2-carboxylate (18). To a hot (80 °C) stirred solution of **17** (12 g, 0.07 mol) and triethylamine (24 mL, 0.17 mol) in toluene (100 mL) was added dropwise, but rapidly, ethyl 2,3-dibromomopropionate (18.3 g, 0.071 mol) in toluene (100 mL). After the addition, the reaction mixture was stirred at 80 °C for 3 h, then cooled, and filtered. The filtrate was washed with saturated aqueous NaHCO$_3$ (100 mL). The organic layer was dried over MgSO$_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography using petroleum ether/ether (80:20, v/v) as eluent to afford 9.5 g (54%) of **18** as a pale-yellow oil: IR (film, cm^{-1}) ν 3100, 3080 (cyclopropyl), 1745 (C=O); ^{1}H NMR δ 4.08 (2H, q, J = 7.2 Hz, H$_2$C−O), 4.03 (1H, t, J = 6.3 Hz, HC−N), 3.23−3.04, 2.74−2.70, 2.60−2.38 (6H, 3m, three H$_2$C−N), 2.25 (3H, s, J = 7.2 Hz, H$_3$C−N), 1.49 (1H, t, J = 9 Hz, HC-dicyclopropyl), 1.26 (3H, t, J = 7.2 Hz, H$_3$C−CH$_2$O), 0.9−0.76, 0.56−0.1 (10H, 2m, H cyclopropyl).

Ethyl 1,4-Bis(dicyclopropylmethyl)piperazine-2-carboxylate (19). Compound **19** was obtained similarly, starting with disubstituted ethylenediamine **16**: ^{1}H NMR δ 4.15−3.95 (3H, m, H$_2$C−O and HC−N), 3.15−2.73 (6H, m, three H$_2$C−N), 1.45 (1H, t, J = 9 Hz, HC-dicyclopropyl), 1.06 (1H, t, J = 8.5 Hz, HC-dicyclopropyl), 1.18 (3H, t, J = 7.1 Hz, H$_3$C−CH$_2$O), 0.8−0.69, 0.47−0.08 (20H, 2m, H cyclopropyl).

Preparation of 1-Phenyl-4-alkyl Ester Intermediates 24a, 29a,b, and 35b (Scheme 3). *N*-Benzoylaniline (20). To a cold solution of 150 mL (1.65 mol) of aniline in CH$_2$Cl$_2$ (400 mL) was added dropwise 90 mL (0.776 mol) of benzoyl chloride in CH$_2$Cl$_2$ (200 mL). After 2 h stirring at room temperature, water (300 mL) and concentrated HCl (20 mL at 37%) were added. The mixture was filtered and the solid product washed with water and then with acetone to afford 120 g of **20**. The filtrate was concentrated to provide another 28 g of **20** (global yield 97%): mp 162−164 °C; IR (film, cm^{-1}) ν 3399 (NH), 1642 (C=O); ^{1}H NMR δ 7.82 (1H, br s, D$_2$O exchange, H−N), 7.80−7.04 (10H, m, Ar−H).

***N*-Benzoyl-*N*-phenyl-*N*-benzyl-*N*-methylethylenediamine (21)**. To a stirred cold suspension of NaH (25 g, 0.625 mol) in DMF (100 mL) was added dropwise the amide **20** (118 g, 0.6 mol) in DMF (500 mL). The mixture was stirred for 1 h at room temperature, and then 105 g (0.57 mol) of 2-chloro-*N*-benzyl-*N*-methylethylamine dissolved in DMF (100 mL) was added. The solution was stirred and heated for 3 h at 60 °C, and after the solution had cooled in an ice bath, water (500 mL) was added. The aqueous layer was extracted several times with ether and the etheral layer washed with aqueous HCl until acidic pH. The aqueous layer was extracted with CH$_2$Cl$_2$ (the hydrochloride salt of compound **21** is very soluble in CH$_2$Cl$_2$) and the organic layer washed with aqueous Na$_2$CO$_3$ until basic pH. The dichloromethane phase was dried over MgSO$_4$ and concentrated. The crude product was crystallized from pentane/ether (90:10, v/v) to give 120 g (58%) of **21** as a white powder: mp 52.5−53 °C; IR (KBr, cm^{-1}) ν 1634 (C=O), 1594 (C=C); ^{1}H NMR δ 7.22−6.92 (15H, ma, Ar−H), 4.00 (2H, t, J = 6.8 Hz, H$_2$C−N), 3.46 (2H, s, H$_2$C−Ar), 2.62 (2H, t, J = 6.8 Hz, H$_2$C−N′), 2.14 (3H, s, H$_3$C−N′).

***N*-Phenyl-*N*-benzyl-*N*-methylethylenediamine (22)**. **21** (120 g, 0.35 mol) was solubilized in 1 L of HCl (6 M) and refluxed for 24 h. After cooling in an ice bath and filtration of benzoic acid, the water was partially evaporated. The aqueous solution was extracted twice with CH$_2$Cl$_2$, treated with Na$_2$CO$_3$ until basic pH, and then re-extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and concentrated to afford 81 g (96%) of **22** as a colorless oil: IR (film, cm^{-1}) ν 3389 (NH), 1603 (C=C); ^{1}H NMR δ 7.23−6.52 (10H, m, Ar−H), 4.18 (1H, br s, D$_2$O exchange, H−N), 3.45 (2H, s, H$_2$C−Ar), 3.09 (2H, t, J = 5.6 Hz, H$_2$C−N), 2.58 (2H, t, J = 5.6 Hz, H$_2$C−N′), 2.13 (3H, s, H$_3$C−N′).

***N*-Phenyl-*N*-methylethylenediamine Dihydrochloride (23)**. A shaken suspension of **22** (80 g, 0.33 mol) and 10% Pd/C (600 mg) in anhydrous ethanol (300 mL) was kept under an H$_2$ atmosphere for 24 h at room temperature. The solution was filtered; the filtrate was diluted with EtOH/HCl and then concentrated; 65.5 g (89%) of **23** was obtained as a white powder: mp 153−168 °C dec; IR (free base, film, cm^{-1}) ν 3391 (NH), 1603 (C=C); ^{1}H NMR (free base) δ 7.15−7.05, 6.65−6.52 (5H, 2m, Ar−H), 4.16 (1H, br s, D$_2$O exchange H−N), 3.11 (2H, t, J = 6.1 Hz, H$_2$C−N), 2.73 (2H, t, J = 6.1 Hz, H$_2$C−N′), 2.34 (3H, s, H$_3$C−N′), 1.55 (1H, br s, D$_2$O exchange, H−N′).

Ethyl 1-Phenyl-4-methylpiperazine-2-carboxylate (24a). The title compound was prepared according to the procedure used for **18**, starting from 65 g (0.29 mol) of **23** dihydrochloride salt (the free base was regenerated in situ). The crude product was purified by column chromatography using petroleum ether/ether (first 80:20 then 70:30, v/v) as eluent, to afford 27 g (39%) of the two isomers **24a** and **24b**. The pure isomer **24a** was obtained by crystallization of the dihydrochloride salt from acetone−ether and then recrystallized from acetone/ethanol (90:10, v/v): mp 159 °C. The mother liquor was concentrated, and the residue, after alkalization, gave a pale-yellow oil, mixture of the two isomers **24a** and **24b** in the ratio 1:1; IR (free base, film, cm^{-1}) of **24a**: ν 1743 (C=O), 1599 (C=C); ^{1}H NMR δ 7.18−7.10, 6.77−6.67 (5H, 2m, Ar−H), 4.36 (1H, t, J = 3.3 Hz, H−N)*, 4.00 (2H, dq, J = 6.5 and 1.8 Hz, H$_2$C−O), 3.46−2.04 (6H, 3m, three H$_2$C−N), 2.20 (3H, s, H$_3$C−N), 1.05 (3H, t, J = 6.5 Hz, H$_3$C−CH$_2$O). *This signal allowed to determine the ratio of the isomers. It presents 0.5H in the mixture obtained from the mother liquor.

N-Benzyl-2-anilinoethanol (25). To 175.5 g (1.28 mol) of 2-anilinoethanol in benzene (200 mL) was added 79 g (0.625 mol) of benzyl chloride. The solution was stirred for 48 h at room temperature, then water (200 mL) was added, and the aqueous layer was extracted with ether. The organic phase was dried over MgSO$_4$ and concentrated. The residue was taken up in aqueous HCl and extracted with CH$_2$Cl$_2$ (the hydrochloride salt of **25** is very soluble in CH$_2$Cl$_2$). The organic layer was neutralized and dried over MgSO$_4$ and the solvent evaporated. The crude product was purified by distillation ($E_{0.05}$ = 145−147 °C) to give 80 g (56%) of **25**: IR (KBr, cm^{-1}) ν 3568−3531 (OH), 1598 (C=C); ^{1}H NMR δ 7.20−7.05, 6.70−6.60 (10H, 2m, Ar−H), 4.50 (2H, s, H$_2$C−Ar), 3.68 (2H, dt, J = 5.66 and 5.60 Hz, H$_2$C−O), 3.49 (2H, t, J = 5.66 Hz, H$_2$C−N), 1.83 (1H, t, J = 5.60 Hz, D$_2$O exchange, H−O).

N-Benzyl-N-phenyl-2-(p-tolylsulfonyloxy)ethylamine (26). **25** (113.5 g, 0.5 mol) was dissolved in chloroform (500 mL) and cooled in a salted ice bath. Et$_3$N (83 mL, 0.6 mol) was then added, followed by the addition of 95.2 g (0.5 mol) of p-toluenesulfonyl chloride in one portion with constant stirring. The reaction was complete in 24 h at 0 °C. Ether (200 mL) was added, and the precipitate of triethylamine hydrochloride was filtered. The filtrate was concentrated in vacuo and the residue dissolved in ether. The etheral phase was washed successively with diluted HCl and water. The organic layer was dried over MgSO$_4$, and the solvent was removed under reduced pressure. The crude tosylate was purified by crystallization from hexane/CH$_2$Cl$_2$ to give **26** (127 g, 67%) as white crystals: mp 82−84 °C; IR (KBr, cm^{-1}) ν 1598 (C=C); ^{1}H NMR δ 7.64 (2H, d, J = 8.30 Hz, 2H in *ortho* of Ar−SO$_2$), 7.25−6.52 (12H, m, Ar−H), 4.41 (2H, s, H$_2$C−Ar), 4.11 (2H, t, J = 6.40 Hz, H$_2$C−O), 3.61 (2H, t, J = 6.40 Hz, H$_2$C−N), 2.34 (3H, s, H$_3$C−Ar).

N-Benzyl-N-phenyl-N-isopropylethylenediamine (27). An amount of 150 mL (1.74 mol) of isopropylamine was added to 114 g (0.3 mol) of tosylate **26** in CH$_2$Cl$_2$ (200 mL). After 8 days stirring at room temperature, the solvent and excess of isopropylamine were evaporated under reduced pressure. The residue was treated with ether and 2 M NaOH until basic pH. The aqueous layer was extracted with ether, the extracts were dried over MgSO$_4$, and the solvent was removed in vacuo. The diamine **27** was purified by crystallization of its hydrochloride salt from ether/ethanol. After alkylization, 57 g (71%) of **27** was obtained as a pale-yellow oil: IR (KBr, cm^{-1}) ν 3316 (NH), 1598 (C=C); ^{1}H NMR δ 7.25−7.07, 6.70−6.57 (10H, 2m, Ar−H), 4.50 (2H, s, H$_2$C−Ar), 3.48 (2H, t, J = 6.80 Hz, H$_2$C−N), 2.82 (2H, t, J = 6.80 Hz, H$_2$C−N′), 2.67 (1H, hp, J = 6.20 Hz, HC(CH$_3$)$_2$), 1.31 (1H, br s, D$_2$O exchange, H−N), 0.94 (6H, d, J = 6.20 Hz, (H$_3$C)$_2$CH).

N-Phenyl-N-isopropylethylenediamine Dihydrochloride (28). This compound was prepared in a similar way as **17**, starting from **27** (53 g, 0.20 mol). The crude product was dissolved in CH$_2$Cl$_2$, and after it had cooled in an ice bath, C$_2$H$_5$OH saturated with HCl gas was added until acidic pH. The solvent was evaporated and the dihydrochloride salt recrystallized from acetone/ethanol (90:10, v/v) to afford 35 g (70%) of **28** as a white powder: mp 154 °C; IR (KBr, cm^{-1}) ν 3371 (NH), 1599 (C=C); ^{1}H NMR (free base)δ 7.19−7.05, 6.67−6.55 (4H, 2m, Ar−H), 4.19 (1H, t, D$_2$O exchange, H−N−Ar), 3.19 (2H, t, J = 5.50 Hz, H$_2$C−N), 2.84−2.69 (3H, m, H$_2$C−N′ and HC(CH$_3$)$_2$), 2.09 (1H, br s, D$_2$O exchange, H−N′), 1.03 (6H, d, J = 6.30 Hz, (H$_3$C)$_2$CH).

Ethyl 1-Phenyl-4-isopropylpiperazine-2-carboxylate (29a) and Ethyl 1-Isopropyl-4-phenylpiperazine-2-carboxylate (29b). The title compounds were prepared according to the procedure used to dispose **18**, starting from 32 g (0.127 mol) of **28** dihydrochloride salt (the free base was regenerated in situ). Compounds **29a** and **29b** were separated by column chromatography using petroleum ether/ether (90:10, 85:15, 80:20, v/v) as eluent. **29a**: 15 g (43%); mp 70−72 °C (hexane); ^{1}H NMR spectrum of this ester was similar to that of **24a**; particular signal δ 0.97 and 0.93 (6H, 2d, J = 6.6 Hz, (H$_3$C)$_2$CH). **29b**: 6 g (17%), pale-yellow oil (after crystallization of the dihydrochloride salt from acetone/hexane/CH$_2$Cl$_2$ and

regeneration of the free base); ^{1}H NMR δ 7.23−7.14, 6.86−6.75 (5H, 2m, Ar−H), 4.15 (2H, q, J = 7.1 Hz, H$_2$C−O), 3.58 (1H, t, J = 5.9 Hz, HC−N), 3.35−2.94 (6H, m, three H$_2$C−N), 2.68−2.57 (1H, m, HC(CH$_3$)$_2$), 1.22 (3H, t, J = 1 Hz, H$_3$C−CH$_2$O), 1.10 and 0.94 (6H, 2d, J = 6.5 Hz, (H$_3$C)$_2$CH).

N-Benzoyl-o-chloroaniline (30). To a cold solution of 132 g (1.035 mol) of o-chloroaniline in CH$_2$Cl$_2$ (300 mL) was added dropwise 60 mL (0.517 mol) of benzoyl chloride in CH$_2$Cl$_2$ (200 mL). After 2 h stirring at room temperature, the hydrochloride salt of o-chloroaniline was filtered and the filtrate washed first with diluted HCl and then with water. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The product crystallized from hexane to afford 108 g (90%) of **30** as a white powder: mp 163 °C; IR (KBr, cm^{-1}) ν 1642 (C=O), 1596 (C=C); ^{1}H NMR δ 8.50 (1H, d, J = 7.96 Hz, Ar−H), 8.39 (1H, s, D$_2$O very slow exchange, H−N), 7.88−6.98 (8H, m, Ar−H).

N-Benzoyl-N-(o-chlorophenylamino)acetonitrile (31). To a cold suspension of NaH (14 g, 0.35 mol) in DMF (100 mL) was added dropwise the amide **30** (75 g, 0.324 mol) in DMF (300 mL). The mixture was stirred for 2 h at room temperature; then 25 g (0.33 mol) of 2-chloroacetonitrile dissolved in DMF (100 mL) was added dropwise. The solution was stirred for 15 h and then poured into iced water (500 mL). The aqueous layer was extracted several times with ether and the extract dried over MgSO$_4$ and concentrated. The crude product crystallized from hexane/CH$_2$Cl$_2$ to give 46 g of **31** as a white powder: mp 93 °C. The mother liquor was concentrated and purified by column chromatography using petroleum ether/ether/CH$_2$Cl$_2$ (70:20:10, v/v/v) as eluent, to give 17 g of **31** (total yield 72%): IR (KBr, cm^{-1}) ν 2242 (CN), 1642 (C=O), 1596 (C=C); ^{1}H NMR δ 7.38−7.08 (9H, m, Ar−H), 5.05 and 4.21 (2H, 2d, J = 17.1 Hz, H$_2$C−CN).

N-Benzoyl-N-(o-chlorophenyl)-N′-acetylethylenediamine (32). A mixture of **31** (27 g, 0.1 mol), dry CH$_3$CO$_2$Na (12 g), and Raney nickel in 200 mL of acetic anhydride was heated at 50 °C and hydrogenated on a Parr hydrogenator apparatus under a 40−50 psi pressure for 18 h. The catalyst was separated by decantation and the solvent removed under vacuo. The crude product was dissolved in CH$_2$Cl$_2$, the solution washed with water and then dried over MgSO$_4$, and the solvent removed. Addition of ether to the residue gave 22 g of **32**. The mother liquor was concentrated and then chromatographed using CH$_2$Cl$_2$/MeOH (99:1, v/v) as eluent to afford 5 g of **32** (total yield 27 g, 85%): mp 138.5−139 °C; IR (KBr, cm^{-1}) ν 3257 (NH), 1650 (C=O), 1595 (C=C); ^{1}H NMR δ 7.27−7.03 (9H, m, Ar−H), 6.86 (1H, br s, D$_2$O exchange, H−N), 4.29, 3.56 and 3.30 (4H, 3m in 1:2:1 ratio, H$_2$C−N and H$_2$C−N′), 1.89 (3H, s, H$_3$C−C=O).

N-(o-Chlorophenyl)-N-benzoyl-N′-acetyl-N′-methylethylenediamine (33). To a cooled (0 °C) suspension of NaH (3.6 g, 0.09 mol) in DMF (50 mL) was added dropwise the diamide **32** (25.9 g, 0.082 mol) in DMF (100 mL). The mixture was then stirred for 3 h at room temperature, and 13 g (0.09 mole) of methyl iodide dissolved in DMF (30 mL) was added dropwise. The solution was stirred overnight, then poured into cold water (500 mL), and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, and the solvents were evaporated in vacuo to dryness. The crude product **33** was used in the next step without purification.

N-(o-Chlorophenyl)-N-methylethylenediamine Dihydrochloride (34). This compound was prepared using the procedure described to prepare compound **22** except the time of the reaction (48 h). The hydrochloride salt was crystallized from acetone/ethanol (90:10, v/v) to afford 10 g (47% for the two steps) of **34**: mp 116 °C; IR (KBr, cm^{-1}) ν 3337 (NH), 1599 (C=C); ^{1}H NMR δ 7.20−7.02, 6.63−6.51 (4H, 2m, Ar−H), 4.62 (1H, br s, D$_2$O exchange, H−N), 3.21 (2H, t, J = 6.1 Hz, H$_2$C−N), 2.82 (2H, t, J = 6.1 Hz, H$_2$C−N′), 2.41 (3H, s, H$_3$C−N′), 2.35 (1H, s, D$_2$O exchange, H−N′).

Ethyl 1-Methyl-4-(2′-chlorophenyl)piperazine-2-carboxylate (35b). The title compound was prepared according to the procedure used to prepare **18** starting from 16 g (0.062 mol) of **34** dihydrochloride salt (the free base was regenerated in situ). Two successive purifications by column chromatog-

raphy using petroleum ether/ether (85:15, v/v) as eluent afforded 3.8 g (22%) of pure **35b** as a pale-yellow oil and 0.8 g of a mixture of the two isomers **35a** and **35b** in a 1:1 ratio. The ^{1}H NMR spectrum of **35b** was similar to that of **29b**, particular signal δ 2.35 (3H, s, H$_3$C-N).

Preparation of the Ester Intermediates 39 and 40a-c (Scheme 4). 1,4-Dibenzyl-2-(hydroxymethyl)piperazine (36). A stirred suspension of LiAlH$_4$ (5 g, 0.13 mol) in dry tetrahydrofuran (200 mL) was cooled at 0 °C, and 57 g (0.17 mol) of ethyl 1,4-dibenzylpiperazine-2-carboxylate in tetrahydrofuran (200 mL) was added. The mixture was stirred for 20 h at room temperature, then cooled, and treated carefully with aqueous NaOH (20%). The aqueous layer was extracted with CH$_2$Cl$_2$, and the extracts were dried over MgSO$_4$. After the solvents were removed, crystallization of the crude product afforded 47 g (93%) of **36** as a white powder: mp 70-72 °C; IR (KBr, cm^{-1}) ν 3400 (OH), 1600 (C=C); ^{1}H NMR (500 MHz) δ 7.22 (10H, m, Ar-H), 4.05 and 3.58 (2H, two dd, J = 11.14 and 2.86 Hz, H$_2$C-O), 3.98 and 3.47 (2H, 2d, J = 13.2 Hz, H$_2$C-Ar), 3.49 (2H, s, H$_2$C-Ar), 2.56 (1H, s, D$_2$O exchange, H-O), 2.98-2.94 (1H, m, HC-N), 2.69-2.60, 2.52-2.44 and 2.40-2.37 (6H, 3m, H$_2$C-N).

1,4-Dibenzyl-2-(chloromethyl)piperazine (37). Compound **37** was prepared according to the procedure used to dispose **10**. The crude product obtained from 20 g (0.068 mol) of **36** was partitioned between ether and water. The aqueous layer was treated with Na$_2$CO$_3$ and extracted with CHCl$_3$. The organic layer was dried over MgSO$_4$ and the solvent removed in vacuo. The residue was purified by column chromatography using petroleum ether/ether (90:10, v/v) as eluent, to afford 17 g (79%) of **37** as a yellow oil: IR (film, cm^{-1}) ν 1600 (C=C); ^{1}H NMR δ 7.23 (10H, br s, Ar-H), 3.97 and 3.54 (2H, AB spectrum, J = 12 Hz, H$_2$C-Ar), 3.50 and 3.35 (2H, AB spectrum, J = 11.8 Hz, H$_2$C-Ar), 3.30-2.30 (9H, m, H piperazine and H$_2$C-Cl).

1,4-Dibenzyl-2-(cyanomethyl)piperazine (38). To a refluxing solution of KCN (4.57 g, 0.07 mol) in water (20 mL) was added dropwise the halide **37** (17 g, 0.054 mol) in ethanol (20 mL). The mixture was stirred and refluxed for 3 h. Ethanol was evaporated, the residue was taken up in chloroform, washed with water, and dried over MgSO$_4$, and the solvent was removed in vacuo. Crystallization from hexane/ether gave 13.2 g (80%) of **38** as a white powder: mp 80-89 °C; IR (film, cm^{-1}) ν 2215 (CN), 1600 (C=C); ^{1}H NMR δ 7.21 (10H, br s, Ar-H), 3.72 and 3.40 (2H, AB spectrum, J = 13.5 Hz, H$_2$C-Ar), 3.45 (2H, s, H$_2$C-Ar), 3.00-2.10 (9H, m, H piperazine and H$_2$C-CN).

Ethyl 1,4-Dibenzylpiperazin-2-ylacetate (39). A mixture of 13.2 g (0.043 mol) of **38**, H$_2$SO$_4$ (10 mL at 95%), and ethanol (30 mL) was stirred and refluxed for 3 h. Then ethanol was evaporated, and the residue was taken up in chloroform, washed with water, and dried over MgSO$_4$. Evaporation of the organic layer gave a crude product which was purified by column chromatography using petroleum ether/ether (90:10, v/v) as eluent to give 11.4 g (75%) of **38** as a yellow oil: IR (film, cm^{-1}) ν 1720 (C=O), 1600 (C=C); ^{1}H NMR δ 7.23-7.14 (10H, m, Ar-H), 4.07 (2H, dq, J = 6.95 and 3.25 Hz, H$_2$C-O), 3.72 and 3.34 (2H, AB spectrum, J = 13.3 Hz, H$_2$C-Ar), 3.47 and 3.38 (2H, AB spectrum, J = 13.1 Hz, H$_2$C-Ar), 3.07-3.02 (1H, m, HC-N), 2.60 and 2.22 (8H, m, three H$_2$C-N and H$_2$C-C=O), 1.15 (3H, t, J = 7.10 Hz, H$_3$C-CH$_2$O).

Ethyl Piperazin-2-ylacetate Dihydrochloride (40). To a solution of **39** (20 g, 0.057 mol) in ethanol (200 mL) were added concentrated HCl (9 mL) and 10% palladium on charcoal. The mixture was kept under H$_2$ atmosphere for 5 h at 50 °C. The catalyst was filtered and the solvent removed in vacuo. The crude product **40** was used in the next step without purification.

Ethyl 1,4-diisopropylpiperazin-2-ylacetate (40a): prepared like **2a** starting from **40**; ^{1}H NMR δ 4.07 (2H, q, J = 7.13 Hz, H$_2$C-O), 3.16-2.28 (11H, m, H piperazine, H$_2$C-CO$_2$, two HC(CH$_3$)$_2$), 1.22-0.90 (15H, m, H_3C-CH$_2$O, two (H$_3$C)$_2$-CH, H$_3$C signals overlapping).

Ethyl 1-(2′,4′-dichlorobenzyl)-4-methylpiperazin-2-ylacetate (40b) and ethyl 1-(2′-methoxybenzyl)-4-methylpiperazin-2-ylacetate (40c): prepared like **7b**; ^{1}H NMR δ 7.38-7.11 (3H, m, H-Ar), 4.06 (2H, q, J = 7.09 Hz, H$_2$C-O), 3.75 and 3.44 (2H, AB spectrum, J = 14.76 Hz, H$_2$C-Ar), 3.6-2.19 (9H, m, H piperazine and H$_2$C-CO$_2$), 2.24 (3H, s, H$_3$C-N), 1.16 (3H, t, J = 7.09 Hz, H_3C-CH$_2$O). ^{1}H NMR spectrum of **40c** was similar to the one of compound **40b**; particular signal δ 3.69 (3H, s, H$_3$C-O).

Preparation of Final Imidazoline (41a-q, 42, 60-63) and Tetrahydropyrimidine (43) Analogues (Scheme 5). The compounds **41a-q, 42**, and **60-63** were prepared as described in our previous publication[16] using the corresponding esters. All the ^{1}H NMR spectra were recorded from the free bases. The hydrogens of the imidazoline ring of compounds **41a, 41b, 41d, 41e, 41g, 41n, 41j, 41l**, and **41m** gave unresolved peaks. The corresponding signal is very broad, and the summit of this signal was a coalescence point.

1,4-Diisopropyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41a): ^{1}H NMR δ 5.3 (1H, br s, D$_2$O exchange, H-N), 3.52 (1H, dd, J = 3.37 and 7.91 Hz, HC-N), 3.65 and 3.49 (4H, 2 coalescence points, H imidazoline), 2.83-2.26 (8H, m, three H$_2$C-N and two HC(CH$_3$)$_2$), 1.00, 0.96, 0.95 and 0.93 (12H, 4d, J = 6.35 and 6 Hz, two (H$_3$C)$_2$CH). **41a·1.5HCl:** 35% yield; mp 145-147 °C (acetone/ether). Anal. (C$_{13}$H$_{26}$N$_4$·3HCl·1.5H$_2$O) C, H, N.

1,4-Diisobutyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41b): ^{1}H NMR δ 5.45 (1H, br s, D$_2$O exchange, H-N), 3.53-3.47 (4H, m, H imidazoline), 3.20 (1H, dd, J = 3.32 and 7.01 Hz, HC-N), 2.82-1.93 (10 H, m, three H$_2$C-N and two H$_2$C-CH), 1.81-1.62 (2H, m, two HC(CH$_3$)$_2$), 0.61, 0.79 and 0.77 (12H, 3d in 2:1:1 ratio, J = 6.29 Hz, two (H$_3$C)$_2$CH). **41b·3HCl:** 33% yield; mp 152-154 °C (acetone/CH$_2$Cl$_2$). Anal. (C$_{15}$H$_{30}$N$_4$·3HCl·0.75H$_2$O) C, H, N.

1,4-Dicyclopentyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41c): ^{1}H NMR δ 5.1 (1H, br s, D$_2$O exchange, H-N), 3.61-3.49, 2.77-2.35 and 2.00-1.19 (29H, 3m in 5:8:16 ratio). **41c·3HCl:** 29% yield; mp 159-161 °C. Anal. (C$_{17}$H$_{30}$N$_4$·3HCl·0.5H$_2$O) C, H, N.

1,4-Di(2′-propen-1′-yl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41d): 20% yield; mp 102-104 °C (hexane); ^{1}H NMR δ 5.85-5.64 (2H, m, two HC=), 5.17-5.06 (5H, m, two H$_2$C= and H-N′), 3.50 (4H, coalescence point, H imidazoline), 3.27 (1H, dd, J = 3.20 and 8.45 Hz, HC-N), 3.15-2.17 (10H, m, three H$_2$C-N and two H$_2$C-C=). Anal. (C$_{13}$H$_{22}$N$_4$) C, H, N.

1,4-Di(2′-methyl-2′-propen-1′-yl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41e): 30% yield; mp 83-84 °C (hexane); ^{1}H NMR δ 5.2 (1H, br s, D$_2$O exchange, H-N), 4.84-4.78 (4H, m, two H$_2$C=), 3.50 (4H, coalescence point, H imidazoline), 3.24 (1H, dd, J = 3.2 and 7.96 Hz, HC-N), 2.91-1.64 (10H, m, three H$_2$C-N and two H$_2$C-C=), 1.65 and 1.64 (6H, 2s, two H$_3$C-C=). Anal. (C$_{15}$H$_{26}$N$_4$) C, H, N.

1,4-Di(2′-methylbutyl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41f): ^{1}H NMR δ 5.20 (1H, br s, H-N), 3.50-3.46 and 3.26-3.19 (4H, 2m, H imdazoline), 2.91-2.90 (11H, m, H piperazine and two H$_2$C-CH), 1.56-0.94 (6H, m, two H$_2$C-CH$_3$ and two HC(CH$_3$)), 0.85-0.74 (12H, m, two H$_3$C-CH$_2$ and two H$_3$C-CH, H$_3$C signals overlapping). **41f·3HCl:** 30% yield; mp 160 °C dec (MeOH/acetone). Anal. (C$_{17}$H$_{34}$N$_4$·3HCl·0.25H$_2$O) C, H, N.

1,4-Dineopentyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41g): ^{1}H NMR δ 5.3 (1H, br s, D$_2$O exchange, H-N), 3.60 and 3.35 (4H, coalescence point, H imidazoline), 3.3 (1H, dd, J_1 = J_2 = 3.88 Hz, HC-N), 3.08-3.10 and 2.75-2.30 (7H, 2m, three H$_2$C-N and H-CH-C(CH$_3$)$_3$), 2.05 (2H, s, H$_2$C-C(CH$_3$)$_3$), 1.93 (1H, d, part B of AB spectrum, J = 14.93 Hz, H-CH-C(CH$_3$)$_3$), 0.85 (18H, br s, two (H$_3$C)$_3$-C). **41g·2HCl:** 25% yield; mp 178 °C dec (CH$_2$Cl$_2$/MeOH/hexane). Anal. (C$_{17}$H$_{34}$N$_4$·2HCl·2H$_2$O) C, H, N.

1,4-Bis(dicyclopropylmethyl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41h): 58% yield; mp 156 °C (CH$_2$Cl$_2$/ether); ^{1}H NMR δ 5.6 (1H, br s, D$_2$O exchange, H-N), 3.90 (1H, dd, J = 3.37 and 7.0 Hz, HC-N), 3.50 (4H, coalescence

point, H imidazoline), 3.16−2.52 (6H, m, three H_2C-N), 1.39 and 1.05 (2H, 2t, $J = 8.3$ and 8.5 Hz, two HC-dicyclopropyl), 0.97−0.10 (10H, m, H cyclopropyl). Anal. ($C_{21}H_{34}N_4$) C, H, N.

1-Isobutyl-4-(2′-propen-1′-yl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41i): 29% yield; mp 96−98 °C (hexane); ^{1}H NMR δ 5.86−5.66 (1H, m, HC=), 5.3 (1H, br s, D_2O exchange, H−N), 5.15−5.06 (2H, m, H_2C=), 3.49 (4H, coalescence point, H imidazoline), 3.16 (1H, dd, $J = 3.24$ and 8.80 Hz, HC−N), 3.00−2.61 and 2.26−1.93 (10H, 2m, three H_2C−N, H_2C−CH and H_2C−C=), 1.82−1.68 (1H, m, HC(CH$_3$)$_2$), 0.81 and 0.78 (6H, 2d, $J = 6.5$ Hz, $(H_3C)_2$CH). Anal. ($C_{14}H_{26}N_4$·0.25 H_2O) C, H, N.

1-Isobutyl-4-(2′-methyl-2′-propen-1′-yl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41j): 30% yield; mp 104−106 °C (hexane); ^{1}H NMR δ 5.2 (1H, br s, D_2O exchange, H−N), 4.78 (2H, s, H_2C=), 3.50 (4H, coalescence point, H imidazoline), 3.20 (1H, dd, $J = 3.30$ and 7.82 Hz, HC−N), 2.84−1.65 (11H, m, three H_2C−N, H_2C−CH, H_2C−C= and HC(CH$_3$)$_2$), 0.81 and 0.78 (6H, 2d, $J = 6.2$ Hz, $(H_3C)_2$CH). Anal. ($C_{15}H_{28}N_4$) C, H, N.

1-Methyl-4-isobutyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)-piperazine (41k): ^{1}H NMR δ 4.55 (1H, br s, D_2O exchange, H−N), 3.60 (4H, br s, H imidazoline), 3.50−2.00 (10H, m, H piperazine, H_2C−CH, HC(CH$_3$)$_2$), 2.25 (3H, s, H_3C−N). **41k·**3HCl: 40% yield; mp 142 °C dec (acetone). Anal. ($C_{12}H_{24}N_4$·3HCl·H_2O) C, H, N.

1-Isobutyl-4-methyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41l): ^{1}H NMR δ 5.0 (1H, br s, D_2O exchange, H−N), 3.50 (4H, coalescence point, H imidazoline), 3.25 (1H, dd, $J = 3.25$ and 7.80 Hz, HC−N), 2.80−2.0 (8H, three H_2C−N and H_2C−CH), 1.80−1.65 (1H, m, HC(CH$_3$)$_2$), 0.80 and 0.78 (6H, 2d, $J = 6.3$ Hz, $(H_3C)_2$CH). **41l·**2HCl: 38% yield; mp 137.5−139 °C. Anal. ($C_{12}H_{24}N_4$·2HCl·H_2O) C, H, N.

1-(Dicyclopropylmethyl)-4-methyl-2-(4′,5′-dihydro-1′H-imidazol-2′yl)piperazine (41m): 50% yield; mp 96−98 °C (ethanol/acetone); ^{1}H NMR δ 5.0 (1H, br s, D_2O exchange, H−N), 3.88 (1H, dd, $J = 3.31$ and 9.1 Hz, HC−N), 3.46 (4H, coalescence point, H imidazoline), 3.06−2.97, 2.87−2.59 and 2.2−2.05 (6H, 3m, H_2C−N), 2.2 (3H, s, H_3C−N), 1.32 (1H, t, $J = 8.36$ Hz, HC-dicyclopropyl), 0.88−0.05 (10H, m, H cyclopropyl). Anal. $(C_{15}H_{26}N_4)$ C, H, N.

1-Phenyl-4-methyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41n): 10% yield; mp 106−108 °C (hexane); ^{1}H NMR δ 7.23−7.16, 6.97−6.93 and 6.83−6.76 (5H, 3m, Ar−H), 4.41 (1H, dd, $J_1 = J_2 = 4.0$ Hz, HC−N), 3.40 (4H, br s, H imidazoline), 3.33−3.27, 2.87−2.79, 2.71−2.64, 2.57−2.49 and 2.37−2.31 (6H, 5m, three H_2C−N), 2.23 (3H, s, H_3C−N). Anal. ($C_{14}H_{20}N_4$) C, H, N.

1-Isopropyl-4-phenyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41o): 25% yield; mp 98−100 °C (ether/hexane); ^{1}H NMR δ 7.22−7.06 and 6.87−6.75 (5H, 2m, Ar−H), 4.25 (1H, br s, D_2O exchange, H−N), 3.66−3.35, 2.93−2.76 and 2.59−2.47 (12H, 3m, H imidazoline, H piperazine and HC-(CH$_3$)$_2$), 1.05 and 0.93 (6H, 2d, $J = 6.53$ Hz, $(H_3C)_2$CH). Anal. ($C_{14}H_{24}N_4$) C, H, N.

1-Methyl-4-(2′-chlorophenyl)-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41p): 12% yield; mp (free base) 115−117 °C (acetone/ether); ^{1}H NMR δ 7.32−6.90 (4H, m, Ar−H), 4.25 (1H, br s, D_2O exchange, H−N), 3.54 (4H, br s, H imidazoline), 3.36−3.26, 3.06−2.88 and 2.60−2.51 (7H, 3m, H piperazine), 2.27 (3H, s, H_3C−N). Anal. ($C_{14}H_{19}ClN_4$) C, H, N.

1-Phenyl-4-isopropyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)piperazine (41q): 15% yield; mp 120−122 °C (acetone/ether); ^{1}H NMR δ 7.22−7.14, 7.0−6.96 and 6.82−6.74 (5H, 3m, Ar−H), 4.99 (1H, br s, D_2O exchange, H−N), 4.41 (1H, dd, $J_1 = J_2 = 4.02$ Hz, HC−N), 3.36 (4H, s, H imidazoline), 3.31−3.26 and 2.84−2.67 (6H, 2m, three H_2C−N), 2.63−2.47 (1H, m, HC(CH$_3$)$_2$), 1.02 and 1.01 (6H, 2d, $J = 6.5$ Hz, $(H_3C)_2$CH). Anal. ($C_{16}H_{24}N_4$) C, H, N.

1-(2′,4′-Dichlorobenzyl)-4-methyl-2-(4′,5′-dihydro-1′-methylimidazol-2′-yl)piperazine (42): ^{1}H NMR δ 7.52−7.0 (3H, m, Ar−H), 3.9−2.0 (13H, m, H_2C−Ar, H piperazine and H imidazoline), 2.95 (3H, s, H_3C−N−C=), 2.27 (3H, s, H_3C−

N). **42·**3HCl: 40% yield; mp 160−162 °C (acetone/ethanol). Anal. ($C_{16}H_{22}Cl_2N_4$·3HCl·2.5H_2O) C, H, N.

1-(2′,4′-Dichlorobenzyl)-4-methyl-2-(1′,4′,5′,6′-tetrahydro-1′H-pyrimidin-2′-yl)piperazine (43): ^{1}H NMR δ 7.29−7.19 (3H, m, Ar−H), 5.52 (1H, br s, H−N), 3.68−3.40, 2.80−2.10 and 1.89−1.68 (15H, 3m, H_2C−Ar, H piperazine and H tetrahydropyrimidine), 2.25 (3H, s, H_3C−N). **43·**3HCl: 39% yield; mp 175−177 °C (methanol/acetone). Anal. ($C_{16}H_{22}Cl_2N_4$·3HCl·H_2O) C, H, N.

1,4-Diisopropyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)-methylpiperazine (60): 32% yield; mp 197 °C (hexane/ether); ^{1}H NMR δ 4.45 (2H, br s, D_2O exchange, H−N and 0.5 H_2O), 3.53−2.03 (15H, m, H imidazoline, H piperazine, two HC(CH$_3$)$_2$ and H_2C−C=N), 1.06, 0.96 and 0.88 (12H, 3d in 1:2:1 ratio, $J = 6.50$ Hz, two $(H_3C)_2$CH). Anal. ($C_{14}H_{28}N_4$·3HCl·3H_2O) C, H, N.

1,4-Dibenzyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)-methylpiperazine (61): ^{1}H NMR δ 7.35−7.15 (10H, m, Ar−H), 3.95 (1H, part A of AB spectrum, $J = 12.7$ Hz, HCH−Ar), 3.55−3.20 (7H, m, H imidazoline, H_2C−Ar and HCH−Ar), 2.85−2.10 (9H, m, H piperazine, H_2C−C=N). **61·**3HCl: 70% yield; mp 176−178 °C (ether/hexane). Anal. ($C_{22}H_{28}N_4$·3HCl·2H_2O) C, H, N.

1-(2′-Methoxybenzyl)-4-methyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)methylpiperazine (62): ^{1}H NMR spectrum similar to compound **61**, particular signal δ 3.88 (3H, s, H_3C−O). **62·**3HCl: 40% yield; mp 160−162 °C (ethanol/acetone). Anal. ($C_{17}H_{26}N_4O$·3HCl·2H_2O) C, H, N.

1-(2′,4′-Dichlorobenzyl)-4-methyl-2-(4′,5′-dihydro-1′H-imidazol-2′-yl)methylpiperazine (63): ^{1}H NMR δ 7.35−7.13 (3H, m, Ar−H), 3.88 and 3.48 (2H, AB spectrum, $J = 14.2$ Hz, H_2C−Ar), 3.47 (4H, br s, H imdazoline), 2.86−2.2 (9H, m, H piperazine, H_2C−C=N), 2.17 (3H, s, H_3C−N). **63·**2HCl: 70% yield; mp 160−162 °C (ether/hexane). Anal. ($C_{16}H_{22}Cl_2N_4$·2HCl·H_2O) C, H, N.

Preparation of Oxazoline Analogue 50 (Scheme 6). N,N-Dibenzylethanolamine Hydrochloride (44). To 18 mL (0.3 mol) of ethanolamine in absolute EtOH (400 mL) and Et_3N (100 mL) was added 69 mL (0.6 mol) of benzyl chloride in absolute EtOH (70 mL). The solution was refluxed overnight; then the ethanol was evaporated and the residue taken up in a saturated Na_2CO_3 solution and ether. The organic layer was washed with diluted HCl; the aqueous layer was neutralized with Na_2CO_3 and extracted with ether. After drying over $MgSO_4$ the solvent was evaporated and the residue purified by crystallization of the hydrochloride salt from ethanol/ether to afford 46 g (55%) of **44** as a white powder: mp 149.5 °C; IR (film, cm^{-1}) ν 3550−3525 (OH), 1599 (C=C); ^{1}H NMR δ 7.30−7.01 (10H, m, Ar−H), 3.68 (4H, s, two H_2C−Ar), 3.50 (1H, s, D_2O exchange, H−O), 3.45 (2H, t, $J = 6.8$ Hz, H_2C−O), 2.54 (2H, t, $J = 6.8$ Hz, H_2C−N).

Tetrahydropyran-2-yloxyethylamine (46). A total of 50 mL (0.56 mol) of dihydropyran was added dropwise to 78 g (0.28 mol) of **44** in CH_2Cl_2 (500 mL). The solution was stirred at room temperature for 2 days and then poured into a molar solution of Na_2CO_3 (300 mL). The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to give **45** which was used in the next step without purification. A shaken suspension of 10% Pd/C (300 mg) and **45** (50 g, 0.21 mol) in anhydrous ethanol (300 mL) was kept under an H_2 atmosphere for 12 h at room temperature. The solution was filtered through Celite, and the filtrate was concentrated. The crude **46** was purified by distillation ($E_{15} = 102−104$ °C) to give 32 g (79%) of the title compound: IR (KBr, cm^{-1}) ν 3380−3369 (NH); ^{1}H NMR δ 4.53 (1H, t, $J = 3.19$ Hz, HC−HO), 3.84−3.63 and 3.47−3.30 (4H, 2m, two H_2C−O), 2.79 (2H, t, $J = 5.32$ Hz, H_2C−O), 2.02 (2H, br s, D_2O exchange, H_2N), 1.78−1.46 (6H, m, H_2C−C).

1-(2′-Chlorobenzyl)-4-methyl-2-[((tetrahydropyran-2-yloxy)ethylamino)carbonyl]piperazine (47). **46** (7.3 g, 0.05 mol) in toluene (25 mL) was added dropwise to a stirred and cooled solution of 25 mL of $Al(CH_3)_2$ (0.05 mol) in toluene at 0 °C, so that the temperature did not exceed 10 °C. After 1 h, 10 g (0.038 mol) of **7c** dissolved in toluene (20 mL) was added

gradually at room temperature. The reaction mixture was refluxed for 4 h (argon atmosphere) and stirred one night at room temperature. The mixture was then cooled again and treated dropwise with 100 mL of water/MeOH (20:80, v/v). After filtration and solvent evaporation, the residue was suspended in methylene chloride (200 mL). The organic layer was washed with water and dried over MgSO$_4$ and the solvent removed in vacuo. The crude product **47** was used in the next step without purification.

1-(2′-Chlorobenzyl)-4-methyl-2-[(hydroxyethylamino)-carbonyl]piperazine (48). **47** (11 g) was solubilized in MeOH saturated with HCl (75 mL) and stirred for 2 h. The solvent was removed in vacuo, and the residue was taken up in water. The aqueous solution was extracted with CH$_2$Cl$_2$ and then neutralized with Na$_2$CO$_3$. The organic layer was dried over MgSO$_4$ and concentrated to afford 7.3 g (62%) of **48**: IR (film, cm^{-1}) ν 3400 (NH and OH), 1660 (C=O); ^{1}H NMR δ 7.66 (1H, br s, D$_2$O exchange, H—N), 7.38–7.11 (4H, ma, Ar—H), 3.80 and 3.48 (2H, AB spectrum, J = 13.9 Hz, H$_2$C—Ar), 3.70–3.55 (2H, m, H$_2$C—O), 3.38–3.33 (2H, m, H$_2$C—N—C=O), 3.15 (1H, dd, J = 3.6 and 8 Hz, HC—N), 2.89–2.70 and 2.51–2.11 (6H, 2m, three H$_2$C—N), 2.21 (3H, s, H$_3$C—N), 1.87 (1H, br s, D$_2$O exchange, H—O).

1-(2′-Chlorobenzyl)-4-methyl-2-[(chloroethylamino)-carbonyl]piperazine (49). To **48** (7 g, 0.022 mol) in ice bath-cooled chloroform (50 mL) was added dropwise 2.7 mL (0.037 mol) of freshly distilled thionyl chloride in CHCl$_3$ (10 mL). The mixture was stirred 12 h in ice bath and then poured in a molar solution of Na$_2$CO$_3$ (60 mL). The organic layer was dried over MgSO$_4$ and concentrated. The crude product was purified by column chromatography using ether/petroleum ether (50: 50, v/v) as eluent to give 4.5 g (61%) of **49** as white crystals: mp 74–75 °C; IR (KBr, cm^{-1}) ν 3300 (NH, OH), 1670 (C=O), 1600 (C=C); ^{1}H NMR δ 7.80 (1H, s, HN—C=O), 7.38–7.10 (4H, m, Ar—H), 3.70 and 3.55 (2H, AB spectrum, J = 14.5 Hz, H$_2$C—Ar), 3.54 (4H, s, H$_2$C—N—C=O and H$_2$C—Cl), 3.18–3.10, 2.82–2.69 and 2.50–2.20 (7H, 3m, H piperazine), 2.23 (3H, s, H$_3$C—N).

1-(2′-Chlorobenzyl)-4-methyl-2-(4′,5′-dihydro-1′,3′-oxazol-2′-yl)piperazine (50). To 2.2 g (6.7 mmol) of **49** in EtOH (15 mL) was added rapidly 0.26 g (6.5 mmol) of NaOH in hot EtOH at 80% (6 mL). The mixture was stirred overnight at room temperature, then filtered, and concentrated. The residue was taken up in ether and washed with water. The organic layer was dried over MgSO$_4$ and the ether removed in vacuo; 1.7 g (85%) of **51** as white crystals was obtained after addition of hexane: mp 97 °C; IR (KBr, cm^{-1}) ν 1680 (C=N), 1590 (C=C) cm^{-1}; ^{1}H NMR δ 7.41–7.46 and 7.35–7.05 (4H, 2m, Ar—H), 4.25–4.03 and 3.88–3.72 (4H, 2m, H oxazoline), 3.76 and 3.64 (2H, AB spectrum, J = 17 Hz, H$_2$C—Ar), 3.43 (1H, dd, J = 3.5 and 8.5 Hz, HC—N), 2.93–2.82, 2.72–2.65 and 2.54–2.21 (6H, 3m, three H$_2$C—N), 2.21 (3H, s, H$_3$C—N). Anal. (C$_{15}$ H$_{20}$ClN$_3$O) C, H, N.

Preparation of Amidine Analogues 52a, 52b, and 56 (Scheme 7). 1,4-Dibenzyl-2-cyanopiperazine Dihydrochloride (51). To a hot (80 °C) stirred solution of *N,N*-dibenzylethylenediamine (72 g, 0.3 mol) and triethylamine (100 mL, 0.72 mol) in toluene (300 mL) was added dropwise, but rapidly, freshly distilled 2,3-dibromopropionitrile (70 g, 0.3 mol) in toluene (300 mL). After the addition, the reaction mixture was stirred at 80 °C for 3 h, then cooled, and filtered. The filtrate was washed with saturated aqueous NaHCO$_3$ (200 mL). The organic layer was dried over MgSO$_4$ and the solvent removed in vacuo. The crude product was dissolved in anhydrous EtOH (400 mL) and saturated with HCl gas. The addition of ether gave a precipitate of **51** (65.5 g, 60%) as a white powder: mp 152–154 °C; IR (free base, film, cm^{-1}) ν 2200 (CN), 1600 (C=C); ^{1}H NMR δ 7.40–7.10 (10H, m, Ar—H), 3.38–3.88 (4H, m, H$_2$C—Ar), 3.32–3.21, 3.05–2.95 and 2.69–2.27 (7H, 3m, H piperazine).

1,4-Dibenzyl-2-amidinopiperazine Hydrochloride (52a). A total of 50 mL of a solution of Al(CH$_3$)$_3$ (2 M) in toluene was added dropwise to a cold and stirred suspension of NH$_4$Cl (5.35 g, 0.1 mol) in 50 mL of toluene according to Levin et al.

procedure.[25] The mixture was stirred 1 h at room temperature; then 10 g (0.034 mol) of **51** dissolved in toluene (50 mL) was added dropwise. The solution was heated at 80–90 °C overnight. After cooling in an ice bath, MeOH/H$_2$O (80:20, v/v) was added carefully and the mixture filtered. The salts were washed with CHCl$_3$, and the filtrate was acidified. The solvents were evaporated to dryness; the residue was taken up in CHCl$_3$ and filtered again. After evaporation of CHCl$_3$, the crude product was purified by column chromatography using CHCl$_3$/MeOH (95: 5, v/v) as eluent to give 4.2 g (36%) of **52a** as a white powder: mp 175–177 °C (CH$_2$Cl$_2$/ether); IR (film, cm^{-1}) ν 3420–3390 (NH), 1615 (C=N), 1595 (C=C); ^{1}H NMR (free base) δ 7.28–7.13 (10H, m, Ar—H), 4.56 (5H, br s, D$_2$O exchange, H$_2$N, HN= and 1H$_2$O), 3.77 and 3.18 (2H, AB spectrum, J = 13.37 Hz, H$_2$C—Ar), 3.39 (2H, s, H$_2$C—Ar), 3.05 (1H, dd, J = 3.3 and 8.7 Hz, HC—N), 2.85–2.51 and 2.32–2.10 (6H, 2m, three H$_2$C—N). Anal. (C$_{19}$H$_{24}$N$_4$·0.75HCl) C, H, N.

1,4-Dibenzyl-2-(*N*-methylamidino)piperazine Hydrochloride (52b). It was prepared by the same procedure as above using the corresponding nitrile **51** derivative and methylamine hydrochloride salt: 52%; mp 221–223 °C dec (CH$_2$Cl$_2$/acetone); this compound gave ^{1}H NMR spectrum similar to that of **52a**, particular signal δ ppm 2.31 (3H, s, H$_3$C—N=). Anal. (C$_{20}$H$_{26}$N$_4$·1HCl) C, H, N.

***N,N*-Dibenzyl-*N,N*-diisopropylethylenediamine (53).** A total of 38 g (0.223 mol) of isopropyl iodide was added to a suspension of 24 g (0.1 mol) of *N,N*-dibenzylethylenediamine and 35 g of dry K$_2$CO$_3$ in 100 mL of acetonitrile. The reaction mixture was refluxed for 48 h. After cooling and filtration, the solvent was removed in vacuo. The residue was dissolved in CH$_2$Cl$_2$, the solution washed with water and then dried over MgSO$_4$, and the solvent evaporated. The crude product was purified by column chromatography using petroleum ether/ether (80:20, 70:30 then 50:50, v/v) as eluent to give 29 g (89%) of **53** as a colorless oil: IR (film, cm^{-1}) ν 1590 (C=C); ^{1}H NMR δ 7.25–7.09 (10H, m, Ar—H), 3.44 (4H, s, two H$_2$C—Ar), 2.88–2.70 (2H, m, two *H*C(CH$_3$)$_2$), 2.33 (4H, s, two H$_2$C—N), 0.87 (12H, d, J = 6.6 Hz, two (*H$_3$C*)$_2$CH).

***N,N*-Diisopropylethylenediamine (54).** The procedure was the same as the one used for the preparation of **17** starting from 28 g (0.086 mol) of **53**. The crude product was purified by distillation (E_{15} = 60 °C) yielding 9 g (70%) of **54** as a colorless oil: IR (film, cm^{-1}) ν 3300 (NH), 1590 (C=C); ^{1}H NMR δ 2.89 (1H, br s, D$_2$O exchange, two HN), 2.80 (2H, sept, J = 6.3 Hz, two *H*C—(CH$_3$)$_2$), 2.73 (4H, s, two H$_2$C—N), 1.05 (12H, d, J = 6.4 Hz, two (*H$_3$C*)$_2$CH).

1,4-Diisopropyl-2-cyanopiperazine (55). The procedure was the same as for the preparation of **51** using 7 g (0.05 mol) of **54**. The crude product was purified by distillation ($E_{0.05}$ = 76–82 °C) yielding 5 g (51%) of **55** as a yellow oil: IR (film, cm^{-1}) ν 2200 (C=N); ^{1}H NMR δ 3.90 (1H, br s, HC—N), 2.91–2.25 (8H, m, three H$_2$C—N and two *H*C(CH$_3$)$_2$), 1.09–0.92 (12H, m, (*H$_3$C*)$_2$CH, the CH$_3$ groups were nonequivalents and the doublets overlapped).

1,4-Diisopropyl-2-(*N*-methylamidino)piperazine hydrochloride (56): 55%; mp 208–210 °C (acetone); ^{1}H NMR δ 5.65 (4H, br s, D$_2$O exchange, H—N, HN= and 1H$_2$O), 3.54 (1H, dd, J = 3.30 and 7.44 Hz, HC—N), 2.92 (3H, s, H$_3$C—N), 2.97–2.27 (8H, m, three H$_2$C—N and two *H*C(CH$_3$)$_2$), 0.99, 0.95 and 0.86 (2H, 3d in 1:2:1 ratio, J = 7.0 and 6.54 Hz, two (*H$_3$C*)$_2$—CH). Anal. (C$_{12}$H$_{26}$N$_4$·2HCl) C, H, N.

Preparation of Imidazole Analogue 56 (Scheme 8). 1-(2′,4′-Dichlorobenzyl)-4-methyl-2-(hydroxymethyl)piperazine (57). This compound was prepared from ethyl 1-(2′,4′-dichlorobenzyl)-4-methylpiperazine-2-carboxylate[16] using the same procedure as for derivative **36**: IR (film, cm^{-1}) ν 3400 (OH), 1600 (C=C); ^{1}H NMR δ 7.50–7.05 (3H, m, Ar—H), 5.20 (1H, br s, D$_2$O exchange, H—O), 4.20–3.40 (5H, m, H$_2$C—Ar, H$_2$C—O and HC—N), 3.05–2.30 (6H, m, three H$_2$C—N), 2.20 (3H, s, H$_3$C—N).

1-(2′,4′-Dichlorobenzyl)-4-methyl-2-formylpiperazine (58). To a solution of DMSO (20 mL) in dry CH$_2$Cl$_2$ (140 mL) was added dropwise for 10 min at −60 °C freshly distilled

oxalyl chloride (30 mL) in dry CH_2Cl_2 (60 mL) with stirring under nitrogen atmosphere. After 15 min, 15 g of **57** in dry CH_2Cl_2 (250 mL) was added dropwise to the solution mixture while the temperature was maintained at -60 °C. After stirring 90 min, triethylamine (56 mL) was added quickly and the reaction mixture was allowed to warm to -30 °C. After stirring for 2 h, the solution mixture was allowed to warm to room temperature and concentrated. The residue was taken up in chloroform; the organic layer was washed with water and dried over $MgSO_4$. After evaporation the residue was purified by column chromatography using ether as eluent to afford **58** as a viscous oil (6.76 g, 35%): IR (film, cm^{-1}) ν 1740 (C=O), 1600 (C=C); ^{1}H NMR δ 9.70 (1H, d, $J = 2.4$ Hz, HC=O), 7.45−7.10 (3H, m, Ar−H), 3.90 and 3.82 (2H, AB spectrum, $J = 14$ Hz, H_2C−Ar), 3.55−2.12 (7H, m, H piperazine), 2.20 (3H, s, H_3C−N).

1-(2′,4′-Dichlorobenzyl)-4-methyl-2-(imidazol-2′-yl)piperazine (59). To a stirred solution of **58** (5.5 g, 0.019 mol) and glyoxal (2 g) in MeOH (100 mL) was added dropwise anhydrous ammonia at -10 °C. This temperature was maintained for 2 h; then the solution was allowed to warm to room temperature. The addition of water (200 mL) gave a precipitate of **59** as a white powder (3.41 g, 55%): mp (free base)152−154 °C; ^{1}H NMR δ 10.95 (1H, br s, D_2O exchange, H−N), 7.45−7.02 (3H, m, Ar−H), 6.95 (2H, s, two HC=), 3.98 (1H, t, $J = 3.7$ Hz, HC−N), 3.63 and 3.16 (2H, AB spectrum, $J = 13.7$ Hz, H_2C−Ar), 2.71−2.30 (6H, m, three H_2C−N), 2.24 (3H, s, H_3C−N). Anal. ($C_{15}H_{18}Cl_2N_4 \cdot 2HCl$) C, H, N.

Pharmacology. Animals and Treatments. Three month-old male Wistar rats (Iffa-Credo, France) weighing about 250 g were used in all the experiments. The animals were housed in wire-bottomed cages and maintained at 21 ± 2 °C in a room with a 12-h fixed light−dark schedule. Water and standard laboratory chow (UAR, Villemoison-sur-Orge, France) were freely available.

Moderate diabetes were obtained by a single iv injection of a low dose (35 mg/kg) of streptozotocin (STZ) dissolved in a citrate buffer[28] under ketamine hydrochloride anesthesia (75 mg/kg ip; Imalgene, Mérieux, France). These rats were called STZ rats. Control rats received an injection of the vehicle under the same conditions.

Glucose homeostasis and insulin secretion were assessed by glucose tolerance tests performed 2 weeks after STZ injection.

Intravenous Glucose Tolerance Tests (IVGTT). Glucose was dissolved in 0.9% saline and given by the saphenous vein route (0.5 g/kg) in rats under pentobarbital anesthesia (60 mg/kg ip; Clin-Midy, France). Blood samples were collected sequentially from the tail vessels before and 5, 10, 15, 20, and 30 min after the injection of glucose. They were then centrifuged, and the plasma was separated. Plasma glucose concentration was immediately determined in a 10-μL aliquot, and the plasma left was kept at -20 °C until radioimmunoassay of insulin.

Drug Administration and Antidiabetic Activity. The 2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)piperazine derivatives were tested by a single ip injection of 100 μmol/kg in the STZ rat 20 min before the IVGTT. All the compounds were used in the form of hydrochloride salts and were water-soluble. Antidiabetic activity of the compounds was evaluated using two parameters: ΔG, which represents the increase in glycemia over baseline integrated over a period of 30 min (IVGTT) following the glucose load, and K, which is the rate of glucose disappearance between 5 and 30 min (in the case of IVGTT), after glucose administration. The K coefficient was calculated only during IVGTT.

Tissue and Membrane Preparation. Cerebral cortex was obtained from whole bovine brains and homogenized in 20 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4). The homogenate was centrifuged twice at $48000g$ for 25 min at 4 °C. The pellet (used for α_2 binding assays) was resuspended in a phosphate buffer (pH 7.4), flash-frozen, and stored at -80 °C until α_2 binding assays.

Reticular nucleus from calf's bulbis was homogenized in ice-cold 50 mM Tris-HCl buffer (pH 7.7) containing 5 mM EDTA.

The homogenate was centrifuged at $500g$ for 10 min at 4 °C. The pellet (P1) was resuspended in the same buffer and centrifuged again. The combined supernatants were centrifuged at $50000g$ for 25 min at 4 °C. The resulting pellet (P2) was resuspended in 50 mM Tris-HCl buffer (pH 7.7) containing 0.1 mM p-methanesulfonyl fluoride, incubated for 30 min at 25 °C, then centrifuged again in the same conditions, resuspended in 50 mM Tris-HCl (pH 7.7), flash-frozen, and stored at -80 °C until I_1-imidazoline binding assays.

Renal cortex was obtained from male New Zealand white rabbits and homogenized in ice-cold preparation buffer (20 mM $NaHCO_3$).[42] The homogenate was centrifuged at $40000g$ for 30 min at 4 °C. The pellet was resuspended in 50 mM Tris-HCl buffer containing 0.5 mM EDTA (pH 7.4), centrifuged again, resuspended in the same buffer, flash-frozen, and stored at -80 °C until I_2-imidazoline binding assays.

Binding Assays. [^{3}H]RX 821002 (48 Ci/mmol), [^{3}H]-*p*-aminoclonidine (50 Ci/mmol), and [^{3}H]idazoxan (42 Ci/mmol) were obtained from Amersham (Buckinghamshire, U.K.), and phentolamine, guanabenz, tolazoline, idazoxan, yohimbine, clonidine, naphazoline, and amiloride were from Sigma (St Louis, MO). Radioligand binding assays with [^{3}H]RX 821002, [^{3}H]-*p*-aminoclonidine, or [^{3}H]idazoxan for determination of specific binding to α_2 adrenoceptors, I_1-PBS, and I_2-PBS, respectively, were performed by a modification of methods previously described.[43,44] Membranes were slowly thawed and diluted to a concentration of 0.4 mg of protein/mL for renal and cerebral cortex and 0.7 mg of protein/mL for calf's bulbis. Assays were conducted in a total volume of 525 μL in polypropylene tubes, and each tube contained 500 μL of membrane suspension, 20 μL of radioligand, and 5 μL of drug. Incubation was initiated by the addition of membrane and was carried out for 45 min at 25 °C. Nonspecific binding was defined in the presence of yohimbine (10 μM) in [^{3}H]RX 821002 binding assays, either phentolamine (10 μM) or guanabenz (5 μM) in [^{3}H]-*p*-aminoclonidine binding assays, and either tolazoline (10 μM) or amiloride (10 μM) in [^{3}H]idazoxan binding assays. For each drug, six concentrations from 10^{-4} to 10^{-11} M were used in triplicate. Incubations were terminated by vacuum filtration over Whatman GF/B glass fiber filters using a cell harvester. The filters were washed three times with the buffer, placed in scintillation vials, covered with 2 mL of scintillation cocktail (Pico-Fluor, Packard Instrument), and counted (Packard 2000 CA). Protein was assayed by a Bradford method.

Binding results were analyzed by linear regression, and the curves were obtained with Graph PAD program (Institute for Scientific Information, Philadelphia, PA). K_i was calculated with the Cheng−Prusoff equation.

Analytical Methods. Plasma glucose was determined using a glucose analyzer (Beckman Inc., Fullerton, CA). Plasma immunoreactive insulin (IRI) concentration was determined with a radioimmunoassay kit (CEA, Gif-sur-Yvette, France). The lower limit of the assay was 19.5 pmol/L with a coefficient of variation within and between assays of 6%.

Statistics. Results of Tables 1−3 are expressed as a mean $\pm$ SEM. The significance of differences between means was evaluated by one-way analysis of variance (ANOVA), and differences were considered significant at $p < 0.05$.

Partition Coefficients. Log P of bases was calculated according to Rekker's method[40] and from Hansch's data bank.[41] f(1,2,4-trisubstituted-piperazinyl) = log P(piperazine) − ($2f$(H neg) + f(H)) = $-1.50 - 1.124 = -2.624$. f(2-substituted-imidazolinyl) = log P(tolazoline or 2-benzylimidazoline) − f(benzyl) = $2.65 - 2.359 = +0.291$. Controlled via another way: f(2-imidazolinyl) = f(2-imidazolyl) + $2f$(H) = $-0.080 + 0.364 = +0.284$ ($|\Delta| = 0.007$). f(1,4-disubstituted-2-(4′,5′-dihydro-1′*H*-imidazolyl-2′-yl)piperazine) = -2.333.

The hydrophobic fragmental constants of the 1,4-substituents of piperazine were added to this last value.

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