Potential Antidepressants Displayed Combined α_2-Adrenoceptor Antagonist and Monoamine Uptake Inhibitor Properties

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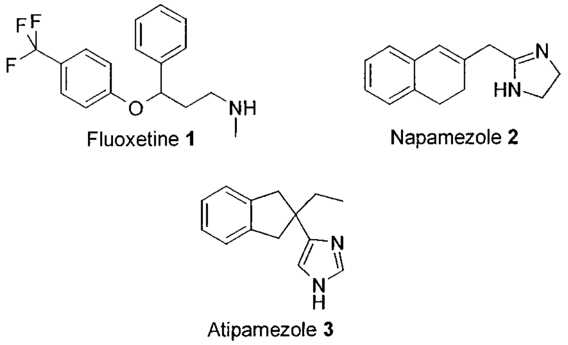
Classical antidepressants are thought to act by raising monoamine (serotonin and noradrenaline) levels in the brain. This action is generally accomplished either by inhibition of monoamine metabolism (MAO inhibitors) or by blockade of monoamine uptake (tricyclic antidepressants and selective serotonin or noradrenaline reuptake inhibitors). However, all such agents suffer from a time lag (3−6 weeks) before robust clinical efficacy can be demonstrated. This delay may reflect inhibitory actions of noradrenaline at presynaptic α_{2A}-adrenergic auto- or heteroreceptors which gradually down-regulate upon prolonged exposure. Blockade of presynaptic α_{2A}-adrenoceptors by an antagonist endowed with monoamine uptake inhibition properties could lead to new antidepressants with greater efficacy and a shorter time lag. In the literature, only two molecules have been described with such a pharmacological profile. Of these, napamezole (**2**) was chosen as a point of departure for the design of 4(5)-[(3,4-dihydro-2-naphthalenyl)methyl]-4,5-dihydroimidazole (**4a**), which displayed the desired profile: α_{2A}-adrenoceptor antagonist properties and serotonin/noradrenaline uptake inhibition. From this original molecule, a series of derivatives was designed and synthesized, encompassing substituted as well as rigid analogues. Structure−activity relationships permitted the selection of **14c** (4(5)-[(5-fluoroindan-2-yl)methyl]-4,5-dihydroimidazole) as a development candidate.

Introduction

The monoaminergic hypothesis of depression assumes that the principle symptoms of depression reflect an insufficient concentration of noradrenaline (NA) and serotonin (SER) in corticolimbic synaptic clefts. Classical antidepressants are thought to act by raising monoamine levels in the brain. This is accomplished either by inhibition of monoamine metabolism (MAO inhibitors) or by blockade of monoamine uptake (tricyclic antidepressants: TCAs; selective SER reuptake inhibitors: SSRIs; and selective NA reuptake inhibitors: SNRIs). Historically, the monoaminergic hypothesis initially emphasized the role of NA,[1] but over the past decade, following the demonstration of the efficacy and safety of SSRIs,[2] as exemplified by the success of fluoxetine (**1**; Figure 1), the importance of serotoninergic mechanism has been underlined.

Currently, the major handicap of used antidepressant agents, irrespective of their mechanism of action, is the 4−6 week delay required to establish therapeutic efficacy.[3] This time lag may reflect monoaminergic mechanisms. Thus inhibition of NA uptake by antidepressants increases levels of NA in the synaptic cleft, which reinforces postsynaptically transmission, and also activates presynaptic α_{2A}-adrenergic autoreceptors,[4] which decreases the release of NA as well as the release of SER through α_{2A}-adrenergic heteroreceptors located on serotoninergic terminals. The immediate consequence of these two opposite processes, inhibition of uptake and release, could be a status quo or even an overall decrease in the neurotransmission. The same consideration may be applied to the action of SSRIs which activate presynaptic 5-HT_{1A} and 5-HT_{1B} serotoninergic autoreceptors. These presynaptic receptors also slowly desensitize leading to a gradual increase of therapeutically effective monoamine concentration in the presence of antidepressant agents. This hypothesis may be tested either by coadministration of a TCA, a SSRI, or a SNRI with an antagonist of these auto- or heteroreceptors or by administration of a drug endowed with both properties.[5−10]



Fluoxetine **1**
Napamezole **2**
Atipamezole **3**

Figure 1. Reference compound structures.

A second strategy implying the discovery of molecules acting both as NA[11,12] and/or SER[13] uptake inhibitors and as antagonists at presynaptic auto- or heteroreceptors has been little exploited. Our research effort aimed to identify a molecule endowed with NA and/or SER uptake inhibitor properties and antagonist activity at presynaptic α_2-adrenergic autoreceptors. We considered napamezole from Sterling Laboratories (**2**; Figure 1)[14]

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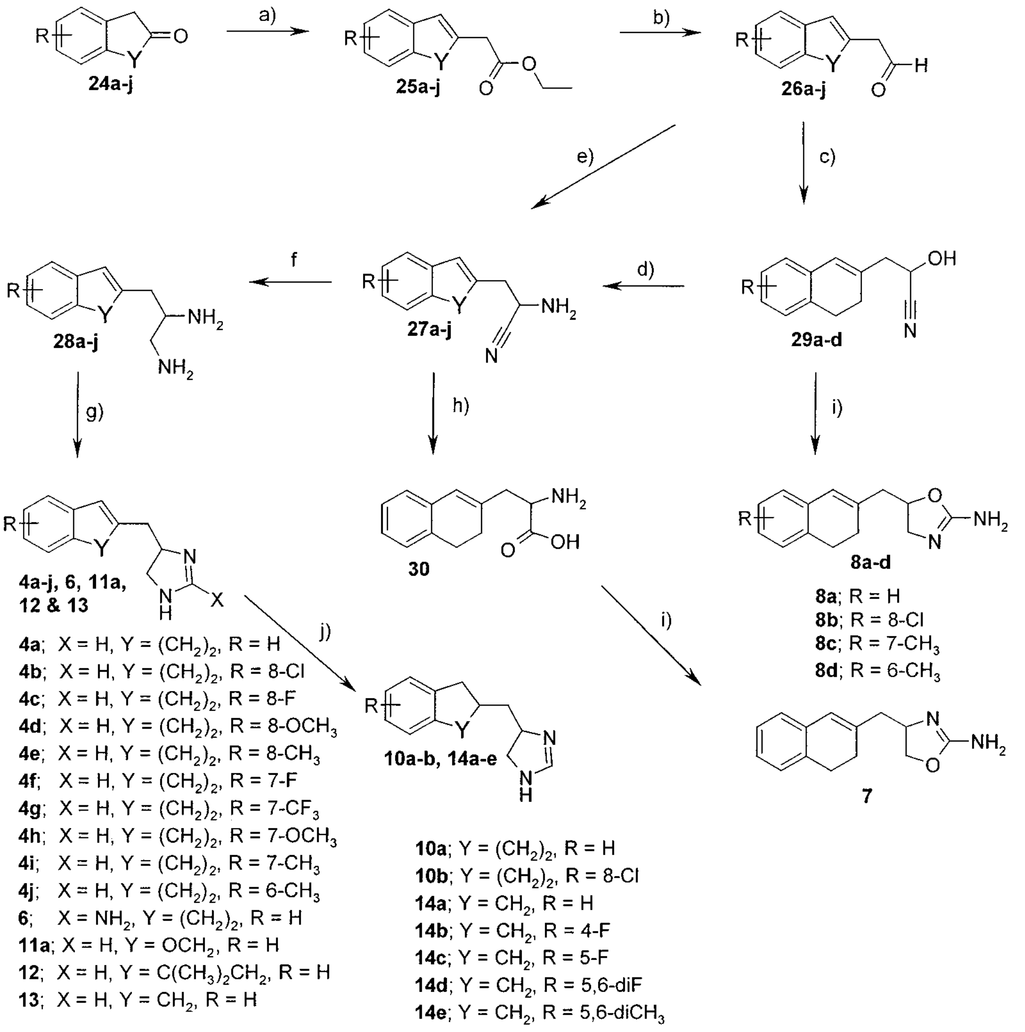
Scheme 1. Method A[a]



[a] Reagents: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) DIBAL-H, CH_2Cl_2 or (1) $LiAlH_4$, THF, (2) IBX, THF; (c) TMSCN, ZnI_2; (d) NH_3, MeOH; (e) NaCN, NH_4Cl, MeOH, H_2O; (f) Raney Ni, NH_3, MeOH or $LiAlH_4$, THF or AlH_3, ether; (g) $HC(=NH)NH_2 \cdot AcOH$, EtOH or BrCN, CH_2Cl_2; (h) (1) HCO_2H, HCl, (2) HCl, H_2O; (i) (1) $LiAlH_4$, THF, (2) BrCN, CH_3CN, K_2CO_3; (j) H_2/Pd/C, EtOH.

to be a prototype for this novel class of compounds and a source of inspiration for our design. Although claimed as a SER uptake blocker displaying α_2-adrenoceptor antagonist properties, this compound manifests far higher affinity for the latter site than for the former site (see Table 1). Atipamezole (**3**; Figure 1),[15] a potent α_2-adrenoceptor antagonist, displays an imidazole moiety substituted in the 4(5)-position, encouraging exploration of various substitutions of the imidazoline in the napamezole skeleton (**4**). This change permitted a differentiation of the two nitrogen atoms and revealed their potential ability to afford contrasting pharmacological profiles. In addition, we have evaluated the importance of the imidazole nucleus by replacing it with different heterocycles (**5**−**8**), examined the importance of the dihydronaphthalene skeleton by undertaking diverse modifications (**9**−**15**), and, finally, rigidified the molecule (**16**−**24**) in order to define the active conformation required for pharmacological efficacy.

Chemistry

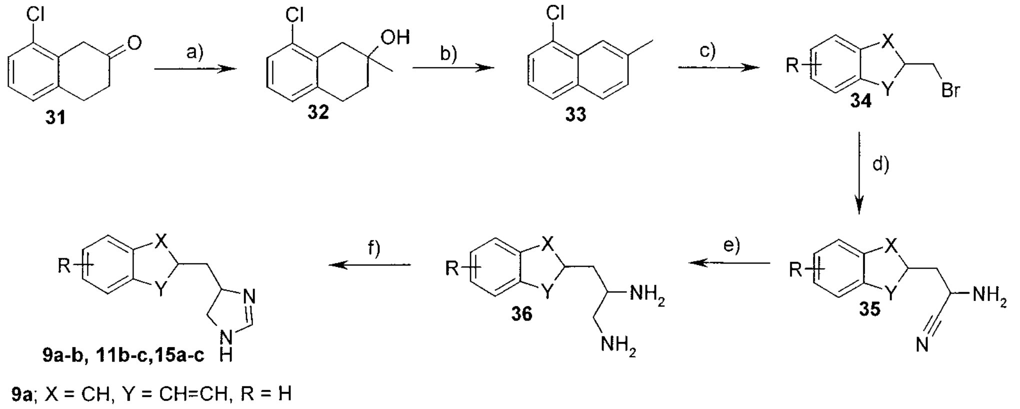
Most of the compounds were obtained following general synthetic routes described in Scheme 1 (method A). The key intermediates were ethylenediamines **28a**−**j** which cyclized to imidazolines by reaction with formamidine acetate in EtOH. The imidazolines were usually isolated as fumarate salts affording highly crystalline salts from mixtures of *i*-PrOH and acetone.

Various ethylenediamines were obtained by reduction of aminonitriles produced by Strecker reaction or one of its variations, as observed in our previous work on spiroimidazolines.[16] Another method that allowed access to some aminonitriles was the substitution of a halide or any other leaving group by the anion of the synthon *N*-(diphenylmethylene)aminoacetonitrile developed by O'Donnell (method B, Scheme 2).[17]

Substrates of the Strecker reaction were aldehydes **26a**−**j**, **69** and ketone **67** obtained mainly through Wadsworth−Emmons reaction of triethyl phosphonoacetate on various 2-indanones and 2- tetralones. Esters were either reduced directly in aldehydes using DIBAL-H or reduced first to alcohol by $LiAlH_4$ and further oxidized using pyridinium chromate or iodoxybenzoic acid (IBX)[18] to aldehydes.

Synthesis of aminoimidazolines and oxazolines was accomplished via reaction of cyanogen bromide with the corresponding ethylenediamines or 2-aminoethanols (Scheme 1). These last intermediates were prepared

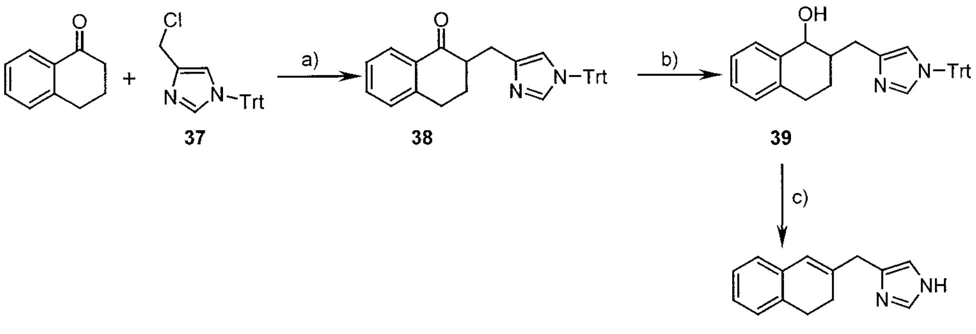
Scheme 2. Method B[a]



9a; X = CH, Y = CH=CH, R = H
9b; X = CH, Y = CH=CH, R = 8-Cl
11b; X = O, Y = OCH_2, R = H
11c; X = O, Y = $(CH_2)_2$, R = H
15a; X = CH, Y = O, R = H
15b; X = CH, Y = O, R = 5-F
15c; X = CH, Y = O, R = 5-C_6H_5

[a] Reagents: (a) MeMgCl, $TiCl_4$; (b) CF_3CO_2H, trityl-OH; (c) NBS, AlBN; (d) (i) $(C_6H_5)_2C{=}NCH_2CN$, KOH, TBAB, (ii) 1 N HCl, ether; (e) $LiAlH_4$, THF; (f) $HC({=}NH)NH_2{\cdot}AcOH$, EtOH.

Scheme 3[a]



[a] Reagents: (a) KO-*t*-Bu, toluene; (b) $NaBH_4$, MeOH; (c) CF_3CO_2H, CH_2Cl_2.

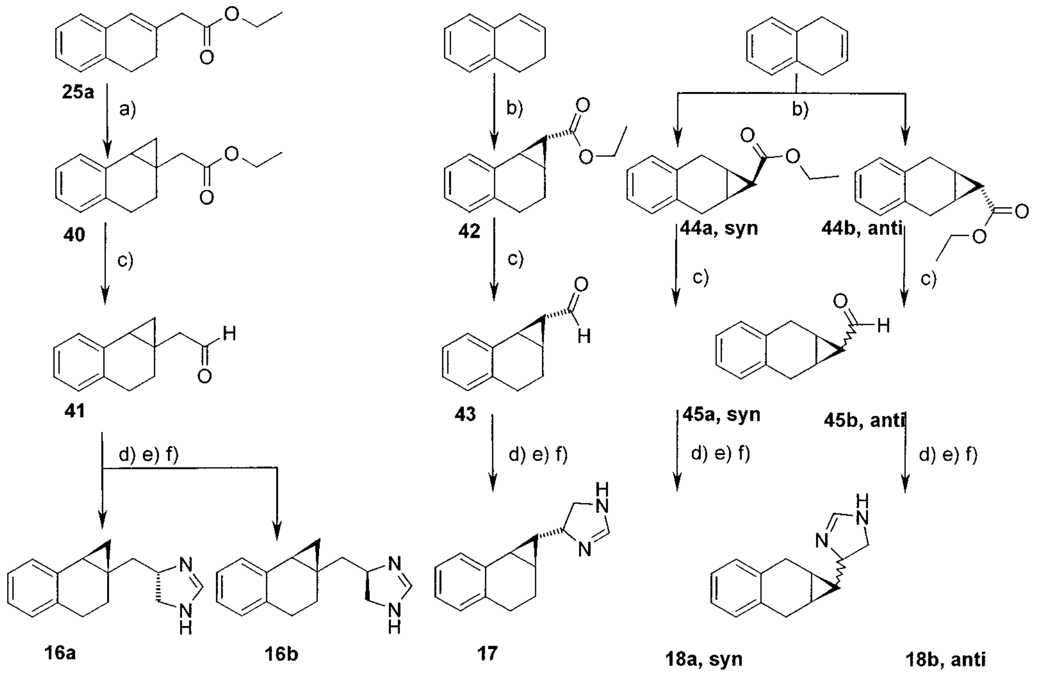
either by hydrolysis followed by reduction of the aminonitrile **27a** or by reduction of the cyanohydrin **29a**, respectively.

In the synthesis of the imidazole derivative **5**, another method (Scheme 3) was used. Alkylation of the 1-tetralone with 1-trityl-4-chloromethylimidazole[11] led to **39** which was submitted to the reduction of the keto group affording the alcohol which was deprotected and dehydrated at the same time, by trifluoroacetic acid.

In the case of rigid molecules, synthesis of corresponding aldehydes **41, 43, 45a,b, 53a,b** and ketone **59** required additional steps. For instance, the different tetrahydrocyclopropanaphthalenyl aldehydes **41, 43,** and **45a,b** were prepared by carbene addition to the corresponding olefins (Scheme 4) and transformation of the esters into the aldehydes by reduction followed by oxidation. As described (Scheme 5) for molecules **20a,b,** analogues of **19a,b,**[19,20] the spiro cyclopropylic ester was formed from interaction of 1-indanone **47** with ethyl 2-methylenephosphonoacetate in alkaline conditions.[21] The ketone functionality of the indanone was reduced using $NaBH_3CN$ in the presence of ZnI_2,[22] and the ester group was reduced by $LiAlH_4$ into the corresponding alcohol, which was further oxidized to the aldehyde **53b** using pyridinium chromate. The Strecker reaction was accomplished via a two-step procedure, where the aldehyde was first condensed with di(*p*-methoxyphenyl)methylamine[23] in the presence of 4 Å molecular sieves and then reacted with TMSCN. High-yield reduction of the aminonitrile with $LiAlH_4$ afforded two diastereoisomeric ethylenediamines which were easily separated by column chromatography on silica gel eluting with a gradient (0−5%) of MeOH/NH_4OH (9/1) in CH_2Cl_2. The ethylenediamines were deprotected in a mixture of AcOH/H_2O (9/1), and the resulting diamines were cyclized classically by reaction with formamidine acetate. The use of di(*p*-methoxyphenyl)methylamine in the Strecker reaction brought two advantages to the synthetic practice: (1) there was no hydride substitution during the $LiAlH_4$ reduction of the aminonitrile and (2) the chromatographic separation of the diastereoisomers was made easier, the introduction of bulky groups close to the stereogenic position amplifying the difference between the two isomers.

On the basis of the work of Ghatak,[24] the ketone intermediate **59** in the synthesis of **21a,b** was obtained by 6-*endo*-aryl cyclization leading to the desired *trans* ring junction (Scheme 6). The precursor of this cyclization was prepared by successive condensation of (2-bromophenyl)methyl bromide with the monoacetal of 1,4-cyclohexanedione and tranformation of the keto group in an *exo*-methylene group by Wittig reaction.[25]

Scheme 4[a]



[a] Reagents: (a) $ZnEt_2$, ICH_2Cl, $C_2H_4Cl_2$; (b) $Rh_2(Acac)_4$, N_2CHCO_2Et, ether; (c) (i) $LiAlH_4$, THF, (ii) CrO_3·pyridine; (d) NaCN, NH_4Cl, MeOH, H_2O; (e) $LiAlH_4$, THF; (f) $HC(=NH)NH_2$·AcOH, EtOH, SiO_2 chromatography: CH_2Cl_2/MeOH/NH_4OH.

The dioxolane moiety was mildly cleaved using pyridinium tosylate.[26]

The synthesis of **22** (Scheme 7) took advantage of the symmetry of the molecule which exists as a single stereoisomer. Starting from 1,2-di(bromomethyl)benzene, a double alkylation of dimethyl malonate led to the five-membered ring **63**. Transformation of the ester groups into dibromide derivative **64** through reduction and formation of the ditosylate derivative[27] allowed the formation of the four-membered ring **65** through dialkylation of the synthon *N*-(diphenylmethylene)aminoacetonitrile. Straightforward reduction and cyclization afforded the desired product **22**.

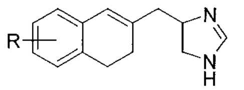
The synthesis of compound **23** (Scheme 8) started with preparation of the corresponding ketone **67** through a modified Wittig–Horner reaction.[28] Application of classical conditions for the Strecker reaction, followed by reduction and cyclization, led to **23** in moderate yields.

Finally, the diastereoisomers **24a,b** (Scheme 9) are further examples of successful use of the di(*p*-methoxyphenyl)methylamine as an ammonia substitute in the Strecker reaction leading to easier separation of the diastereoisomers at the diamine level and more efficient reduction of the nitrile group, avoiding nucleophilic hydride substitution. The key aldehyde **69** was obtained by alkylation of 2-methyl-1-tetralone by ethyl 2-bromoacetate, followed by reduction and oxidation.

Biology

Molecules were evaluated in in vitro assays to define their affinity at α_1- and α_2-adrenoceptors and SER and NA reuptake sites. The results of this primary evaluation allowed elaboration of structure–activity relationships (SARs) discussed in this paper. In addition, certain compounds were further evaluated in vivo to define their bioavailability (ip and po) and antidepressant properties. Detailed reports of the pharmacological profiles of selected compounds will appear elsewhere.

Table 1. Binding Affinities (pK_i) at Native Rat Receptors and Uptake Sites for Compounds with Substitution of the Aromatic Moiety

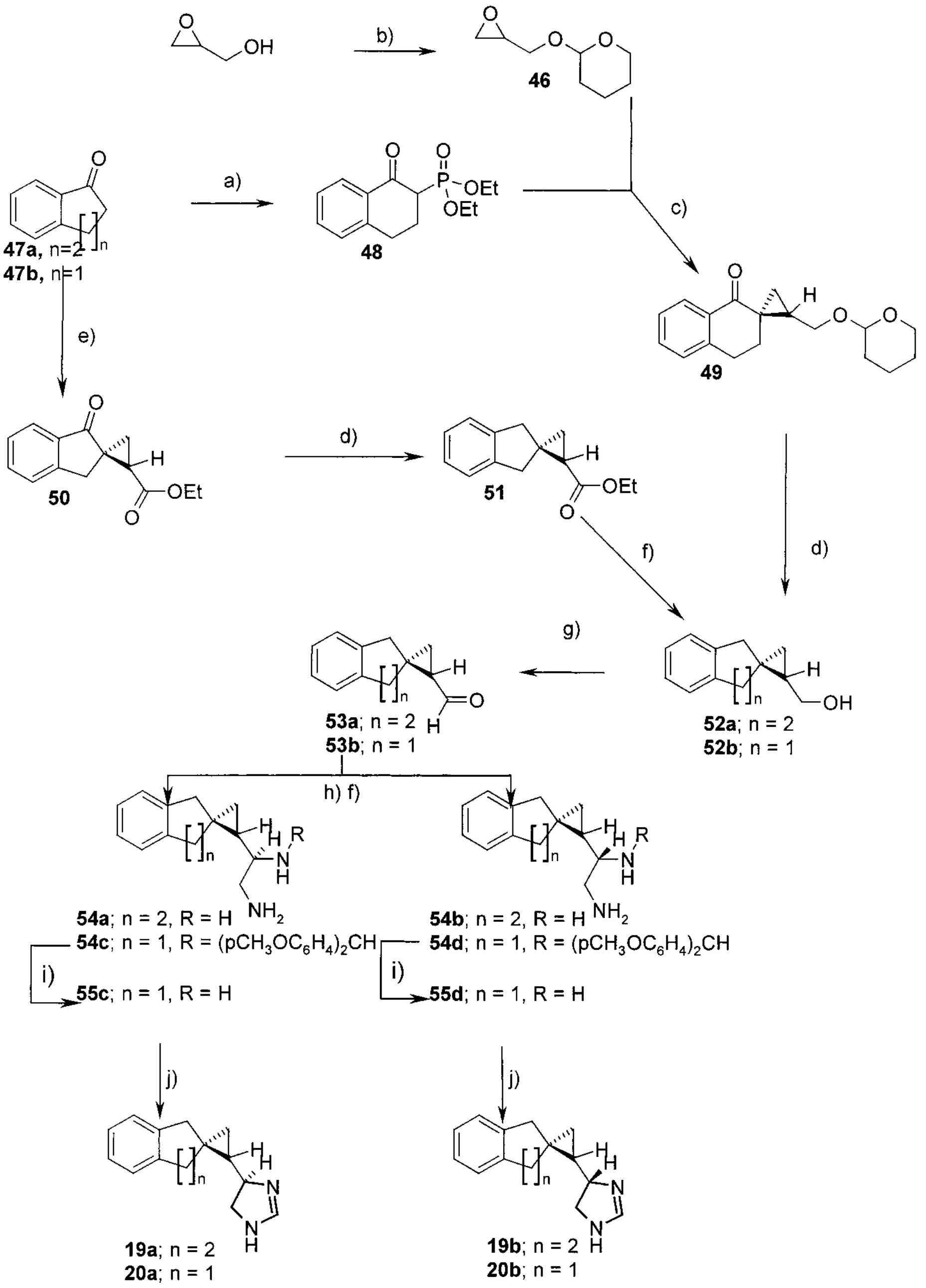


Compd #	R	Adrenoceptor		Uptake	
		α_1[a]	α_2[a]	SER[a]	NA[a]
1	Fluoxetine	5.4	5.3	8.0	6.1
2	Napamezole	7.0	8.5	6.7	<6
3	Atipamezole	5.7	9.9	< 5.5	< 5
4a	H	6.4	7.1	7.4	7.3
4b	8-Cl	6.4	7.6	7.7	7.3
4c	8-F	6.3	7.4	7.1	6.9
4d	8-OCH_3	6.8	7.6	7.8	6.0
4e	8-CH_3	6.2	6.8	7.9	6.0
4f	7-F	6.6	6.7	8.8	7.3
4g	7-CF_3	5.9	6.4	6.8	< 5
4h	7-OCH_3	5.6	6.3	6.7	< 6
4i	7-CH_3	6.4	6.8	7.2	6.0
4j	6-CH_3	nt	6.4	7.8	< 6

[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit. nt: not tested.

The primary evaluation consisted in determination of affinity at rat α_1- and α_2-adrenoceptors by competition with [^{3}H]prazosin and [^{3}H]RX 821,002, respectively, on membranes prepared from rat cerebral cortex. In addition, affinities at SER and NA reuptake sites were determined by competition experiments employing [^{3}H]-paroxetine and [^{3}H]nisoxetine, respectively, and membranes prepared from rat frontal cortex (Tables 1–6).

Scheme 5[a]



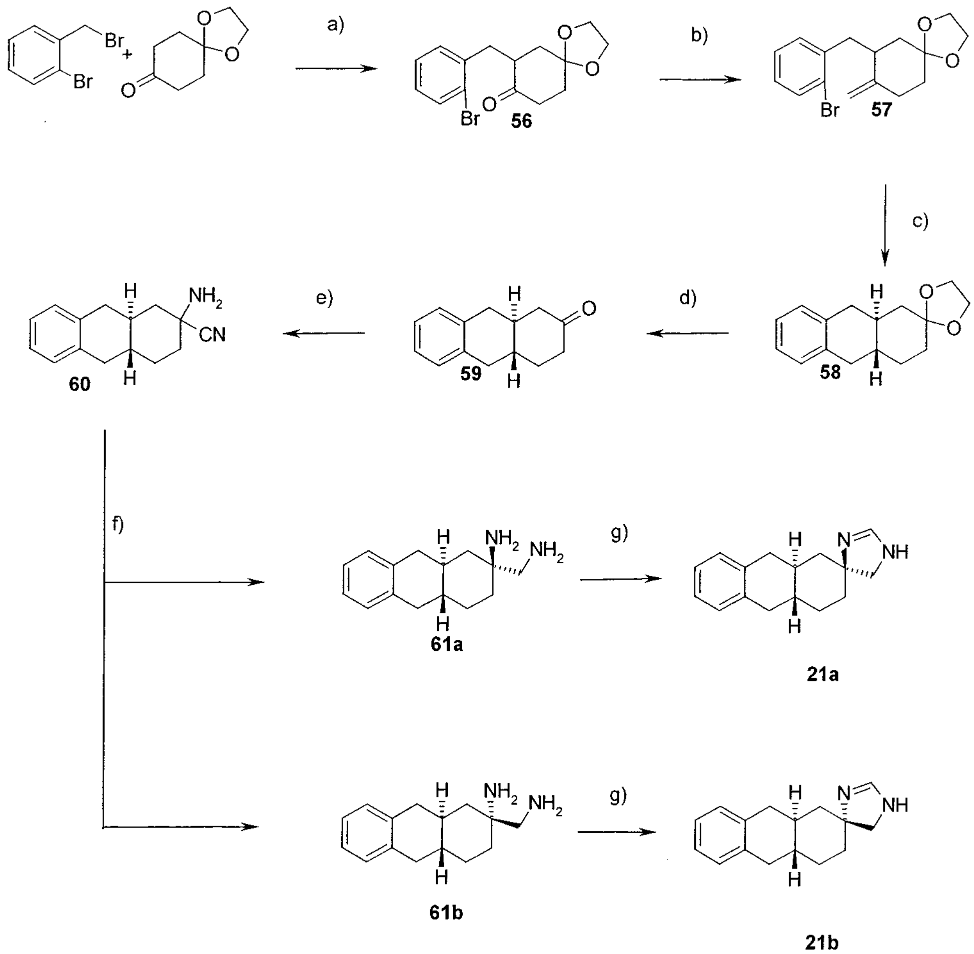
[a] Reagents: (a) LDA, $ClP(O)(OEt)_2$, THF; (b) DHP, PPTS, CH_2Cl_2; (c) NaH, toluene; (d) $NaBH_3CN$, ZnI_2, DCE; (e) KOtBu, $CH_2{=}C(OPO_3Et_2)CO_2Et$, DMSO; (f) $LiAlH_4$, THF; (g) CrO_3, pyridine, CH_2Cl_2; (h) KCN, NH_4Cl, $MeOH/H_2O$ and $MeOH/NH_3$, or $(p\text{-}CH_3OC_6H_4)_2CHNH_2$, CH_2Cl_2 and TMSCN; (i) $AcOH/H_2O$; (j) $HC({=}NH)NH_2{\cdot}AcOH$, EtOH.

Antagonist actions at α_2-adrenoceptors were demonstrated for selected compounds by modulation of [^{35}S]-GTPγS binding at hα_{2A}-adrenoceptors expressed in CHO cells, as previously reported[29] (Table 7).

Discussion

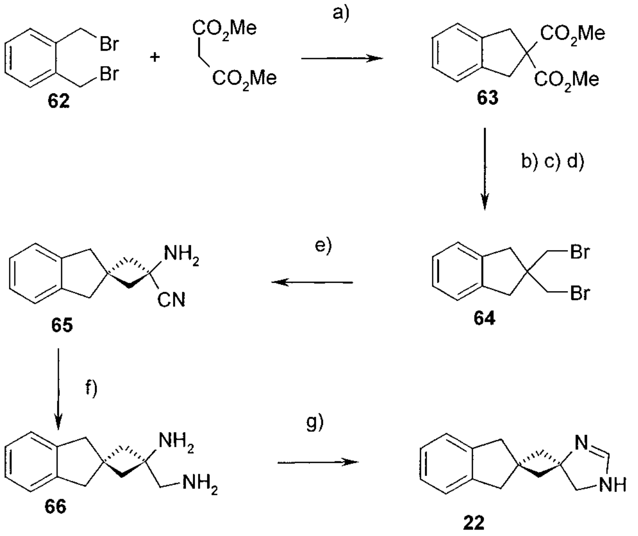
Compound **4a** demonstrates how a small displacement of one atom (nitrogen) can profoundly affect the pharmacological profile of a molecule. Comparing napamezole (**2**) with its isomer **4a** (Table 1), affinity at α_2-adrenoceptors is lowered by 1.4 log units, while affinities at SER and NA uptake sites are increased by 0.7 and >1.3 log units, respectively, leading to a molecule with an equilibrated receptorial profile. In this new series of molecules, regarding substitution of the aromatic moiety, the most striking effect lies with the chloro substitution at position 8, which increases affinity at α_2-adrenoceptors (0.5 log unit), whereas affinities at SER and NA uptake sites are only marginally affected (0.3 and 0 log unit, respectively). The other substituents at position 8 show less favorable profiles with the fluorine being less potent, the methoxy group being selective for the α_2-adrenoceptor and SER uptake sites but losing efficacy at NA uptake sites, and the methyl substitution leading to a specific SER uptake effect. Among substituents at position 7, only fluorine manifests an interesting profile with a substantial increase in affinity at SER uptake sites (1.4 log units), accompanied, however, with a loss of affinity at α_2-adrenoceptors (0.4 log unit). All other substituents in

Scheme 6[a]



[a] Reagents: (a) LDA, THF; (b) $Ph_3P^+MeI^-$, t-$C_5H_{11}O^-Na^+$, toluene; (c) Bu_3SnH, AIBN, toluene; (d) PPTS, CH_2Cl_2; (e) KCN, NH_4Cl, $MeOH/H_2O$, $MeOH/NH_3$; (f) $LiAlH_4$, THF; (g) $HC(=NH)NH_2 \cdot AcOH$, MeOH.

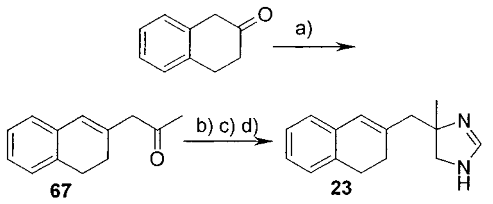
Scheme 7[a]



[a] Reagents: (a) K_2CO_3, butanone; (b) $LiAlH_4$, THF/Et_2O; (c) TsCl, pyridine; (d) LiBr, DMF; (e) NaH, $(C_6H_5)_2C=NCH_2CN$, THF, HCl/Et_2O; (f) H_2, Ni, $MeOH/NH_3$; (g) $HC(=NH)NH_2 \cdot AcOH$, MeOH.

this position induce a modest selectivity for SER uptake sites compared to affinity at NA uptake sites and α_2-adrenoceptors, with a lower overall level of activity. The same trend can be found in the only example of substitution at position 6.

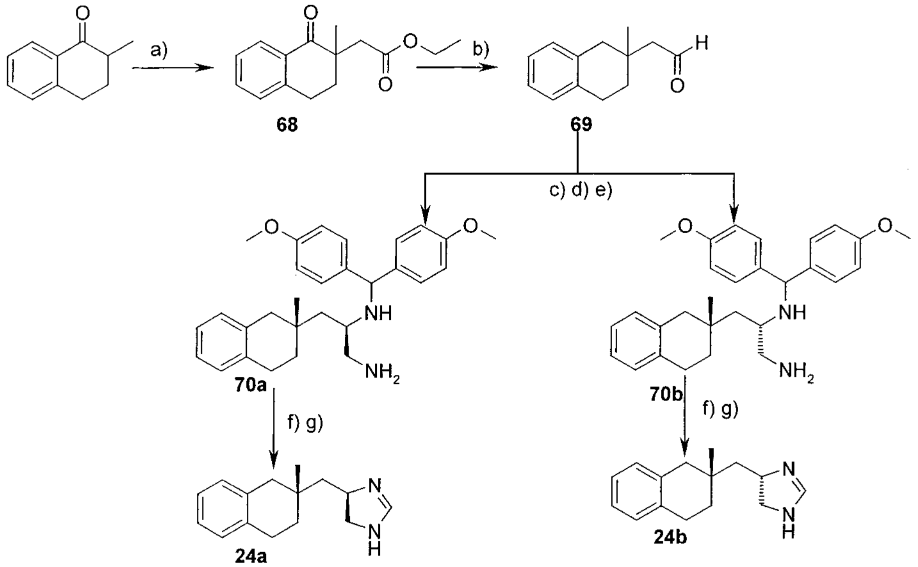
Scheme 8[a]



[a] Reagents: (a) $(EtO)_2P(O)CH_2COCH_3$, K_2CO_3, H_2O; (b) KCN, NH_4Cl, MeOH, H_2O; (c) $LiAlH_4$, THF; (d) $HC(=NH)NH_2 \cdot AcOH$, EtOH.

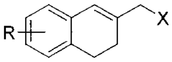
Replacement of 4(5)-imidazoline by 4(5)-imidazole, as in **5** (Table 2), significantly abolishes affinities at uptake sites (−1.2 log units for both SER and NA uptake) but enhances affinity at α_2-adrenoceptors by 1.9 log units. This result supports the selectivity of the imidazole moiety for α_2-adrenoceptors as exemplified by the structures of atipamezole (**3**)[15] and MPV 1743[30] which are potent and selective α_2-adrenoceptors antagonists. It implies that affinity at α_2-adrenoceptors is more tolerant than affinities at bioamine uptake sites to the pK_a of the critical nitrogen. Addition of an amino group at position 2 of the 4(5)-imidazoline, as in **6**, induces a loss of affinity at α_2-adrenoceptors (−0.5 log unit) accompanied by an increase of affinity at α_1-adrenoceptors (0.8 log unit) leading to a α_1-adrenergic selective molecule, whereas affinities at SER and NA uptake sites are not modified. Replacement of one nitrogen by

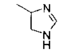
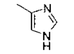
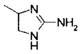
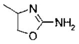
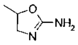
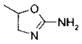
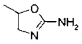
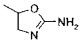
Scheme 9[a]



[a] Reagents: (a) ICH_2CO_2Et, KO-*t*-Bu, THF; (b) (i) $NaBH_3CN$, ZnI_2, $C_2H_4Cl_2$, (ii) $LiAlH_4$, THF, (iii) IBX, THF; (c) (i) $(4\text{-}MeOC_6H_4)_2CHNH_2$, molecular sieves, CH_2Cl_2, (ii) TMSCN; (d) $LiAlH_4$, THF; (e) SiO_2 chromatography: $CH_2Cl_2/EtOH/NH_4OH$; (f) AcOH, H_2O; (g) $HC(=NH)NH_2 \cdot AcOH$, EtOH.

Table 2. Binding Affinities (pK_i) at Native Rat Receptors and Uptake Sites for Compounds with Replacement of the 4(5)-Imidazoline Residue by Other Heterocycles



Compd #	R	X	Adrenoceptor		Uptake	
			α_1[a]	α_2[a]	SER[a]	NA[a]
4a	H		6.4	7.0	7.4	7.3
5	H		7.3	8.9	6.2	6.1
6	H		7.2	6.5	7.4	7.1
7	H		nt	7.3	6.8	6.3
8a	H		nt	6.0	7.2	6.0
8b	8-Cl		6.5	6.2	nt	< 6
8c	7-CH_3		6.6	5.8	6.6	< 6
8d	6-CH_3		nt	5.8	7.1	< 6.0

[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit. nt: not tested.

oxygen, in this specific heterocycle, leads either to the 5-(2-aminooxazoline) or to the 4-(2-aminooxazoline) derivative, **7** and **8** respectively. In the former case, affinity at α_2-adrenoceptors is preserved, and in the latter case, affinity at SER uptake sites is maintained, indicating that the two intracyclic nitrogen atoms might contribute differently to affinities at α_2-adrenoceptors and SER uptake sites, respectively. An additional element supporting this analysis lies in the observation that, in **2**, both nitrogens are equivalent and lie in the optimal position for high affinity at α_2-adrenoceptors, while there is no nitrogen in the position responsible for affinity at SER uptake sites, resulting in a pharmacological profile favoring affinity at α_2-adrenoceptors.

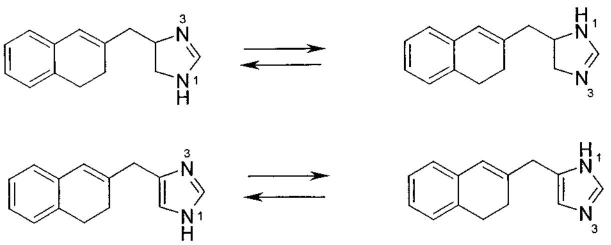
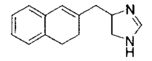
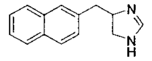
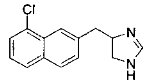
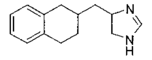
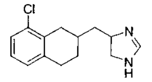
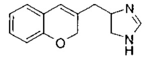
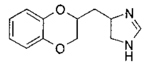
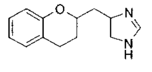
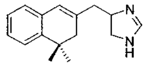
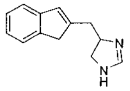
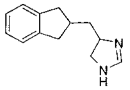
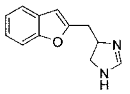
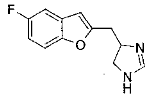
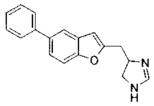


Figure 2. Imidazoline and imidazole tautomerism.

This mode of analysis is complicated, however, by the tautomerism exhibited by imidazoline and imidazole residues (Figure 2), each nitrogen in both heterocycles being alternatively a basic sp^2 nitrogen with its lone pair of electrons lying in the plane of the five-membered ring (N^3) or a less basic more sp^3 nitrogen with its lone pair of electrons either conjugated with a π-system or involved in an aromatic ring current (N^1). In addition, at physiological pH, imidazoline residues are protonated inducing a degeneracy of the electronic properties of the two nitrogens but not of their spatial attributes.

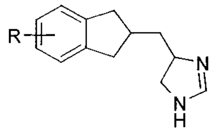
Modification of the 3,4-dihydronaphthalene skeleton, initially by oxidation, leading to the aromatic naphthalenyl derivative **9** (Table 3), results in an increase of the affinity at NA uptake sites only, with no sensible change of affinity at either α_2-adrenoceptors or SER uptake sites. Reduction of the 3,4-dihydronaphthalenyl group affords **10a** as a mixture of diastereoisomers (≈50/50) which exhibits enhanced affinities at α_2-adrenoceptors and SER uptake sites without any influence on affinity at NA uptake sites. As previously demonstrated for the parent molecule **4a**, addition of a 8-chloro substitution to this structure (**10b**) further increases this effect. In contrast, replacement of the CH_2 group in position 4 by an oxygen atom (**11a**) or a *gem*-dimethyl moiety (**12**) reduces affinities at α_2-adrenoceptors and SER uptake sites while keeping affinity at NA uptake sites constant. Replacement of 3,4-dihydronaphthalenyl skeleton by an indene ring (**13**) increases affinity at α_2-adrenoceptors. In this structure, reduction of the double

Table 3. Binding Affinities (pK_i) at Native Rat Receptors and Uptake Sites for Compounds with Modification of the 3,4-Dihydronaphthalene Moiety

Compd #	Structure	Adrenoceptor		Uptake	
		α_1[a]	α_2[a]	SER[a]	NA[a]
4a		6.4	7.0	7.4	7.3
9a		6.0	6.9	7.3	7.8
9b		6.4	7.5	7.5	7.7
10a		6.1	7.8	8.0	7.0
10b		6.5	8.8	8.3	7.0
11a		5.8	6.9	6.6	7.2
11b		6.2	7.5	5.9	6.0
11c		6.5	7.3	6.3	6.1
12		6.1	6.0	< 5	7.4
13		5.9	7.8	7.1	7.5
14a		6.3	8.7	7.2	7.4
15a		5.6	7.9	6.0	7.2
15b		nt	7.0	6.8	6.1
15c		< 5.5	< 5	< 5	6.8

[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit. nt: not tested.

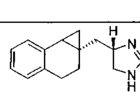
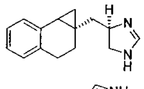
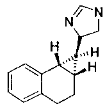
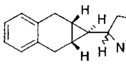
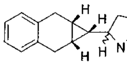
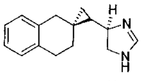
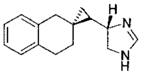
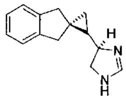
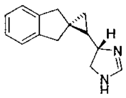
Table 4. Binding Affinities (pK_i) at Native Rat Receptors and Uptake Sites for Derivatives of Dihydroindans



Compd #	R	Adrenoceptor		Uptake	
		α_1[a]	α_2[a]	SER[a]	NA[a]
14a	H	6.3	8.7	7.2	7.4
14b	4-F	6.8	8.9	7.0	7.0
14c	5-F	6.2	8.1	7.6	6.5
14d	5,6-diF	6.1	7.3	7.9	7.0
14e	5,6-diMe	6.7	7.6	7.7	7.6

[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit.

Table 5. Binding Affinities (pK_i) at Native Rat Receptors and Uptake Sites for Compounds with Partial Rigidification of the Skeleton

Compd #	Structure	Adrenoceptor		Uptake	
		α_1[a]	α_2[a]	SER[a]	NA[a]
16a		5.9	7.3	7.3	6.1
16b		5.9	7.2	7.7	6.5
17		nt	6.4	< 5.5	6.6
18a		6.3	6.3	6.2	nt
18b		6.1	5.5	< 6	7.3
19a		6.3	8.2	8.7	7.0
19b		6.0	6.6	7.6	6.4
20a		5.2	7.1	6.4	6.5
20b		6.9	9.1	7.3	7.5

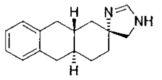
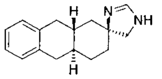
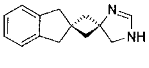
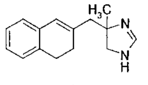
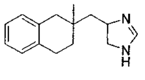
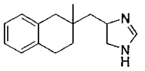
[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit. nt: not tested.

bond (**14a**) leads to a selective α_2-adrenergic ligand by increasing affinity at α_2-adrenoceptors (1.7 log units compared to **4a**) without changing the other interactions. Replacement of the 3-methylene group by oxygen (**15a**) decreases affinity at SER uptake sites by 1.1 log units compared to **13**.

Aromatic substitution of the indan derivatives **14a**–**e** (Table 4) reinforces the SARs discovered in the dihydronaphthalene skeleton (**4a**–**j**). Substitution by a fluorine at position 4 (**14b** equivalent to position 8 in **4c**) increases slightly affinity at α_2-adrenoceptors while depressing slightly affinity at uptake sites and confers overall a selective α_2-adrenoceptor antagonist profile to the molecule. The same substitution at position 5 (**14c** equivalent to position 7 in **4f**) increases slightly affinity at SER uptake sites while depressing slightly affinity at α_2-adrenoceptors and significantly at NA uptake sites, conferring an equilibrated α_2-adrenoceptor antagonist and SER uptake inhibitor profile to the molecule. In an attempt to avoid the new chiral center in position 2 of the indan moiety created by these substitution patterns, symmetrical disubstitution in position 5,6 was investigated. Molecule **14d** demonstrates a profound decreased affinity at α_2-adrenoceptors and a slight decreased affinity at NA uptake sites, with a significant increased affinity for the SER uptake sites.

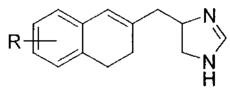
In an attempt to clarify the active conformation of these compounds at their different sites of action, the

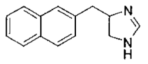
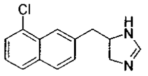
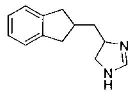
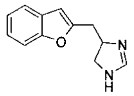
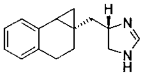
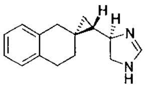
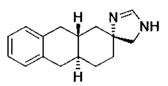
Table 6. Binding Affinities (pK_i) at Native Rat Receptors and Uptake Sites for Compounds with Complete Rigidification and Methyl Substitution of the Skeleton

Compd #	Structure	Adrenoceptor		Uptake	
		α_1[a]	α_2[a]	SER[a]	NA[a]
21a		6.1	8.0	7.8	6.7
21b		6.2	6.1	7.6	< 6
22		5.3	6.2	5.2	< 5
23		5.9	6.1	7.2	6.5
24a		6.0	7.1	8.0	6.7
24b		5.7	6.6	7.5	7.2

[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit.

Table 7. Binding Affinities (pK_i) and Antagonist Potency (pK_B) at hα_{2A}-Receptors Expressed in CHO Cells



S #	R	hα_{2a} Adrenoceptor	
		Binding[a]	GTPγS[a]
1	Napamezole	8.2	7.4
3	Atipamezole	8.5	8.9
4a	H	7.0	6.6
4b	8-Cl	7.5	7.6
4c	8-F	7.4	6.8
4f	7-F	6.8	6.7
9a		7.3	6.7
9b		7.6	7.5
14a		8.4	8.1
15a		7.7	6.9
16a		7.2	6.8
19a		8.5	8.2
21a		8.9	8.2

[a] Mean of at least two independent determinations made in triplicate; the dispersion on pK_i values is only about 0.2 log unit.

skeleton was rigidified by means of cyclopropyl rings (Figure 3). New bonds (1−4) bridging unbonded carbons can be added to structure **10**, thereby reducing the number of freely rotating bonds to one. These transformations also confine the imidazoline ring to a specific part of the configurational space available to the parent molecule. The 1,2-methano compounds **16a,b** demonstrate a decreased affinity at NA uptake sites while affinities at α_2 adrenergic and SER uptake sites are modulated by specific configuration of the diastereoisomer (Table 5). The cyclopropyl derivative obtained when bonds 1 and 3 were reduced to a unique bond (**17**) loses affinity at all three sites. In contrast, one of the diastereoisomers of the 4-cyclopropyl derivative (**18b**) retains affinity at NA uptake sites. The most interesting pair of diastereoisomers is obtained when 2 and 3 become the bonds of a cyclopropyl ring leading to **19a,b**. Potentiation occurs at α_2-adrenergic sites (1.1 log units) and SER uptake sites (1.3 log units) without affecting NA uptake sites in one diastereoisomer (**19a**), while decreased affinity for α_2-adrenergic sites and NA uptake sites accompanied with a slight increase in affinity at SER uptake sites is obtained in the other diastereoisomer (**19b**). This trend is not observed when the identical cyclopropyl rigidification is carried out on the indan skeleton. The more potent diastereoisomer (**20b**) is a selective α_2-adrenoceptor antagonist.

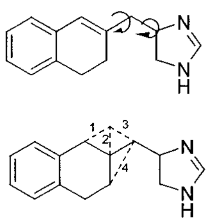
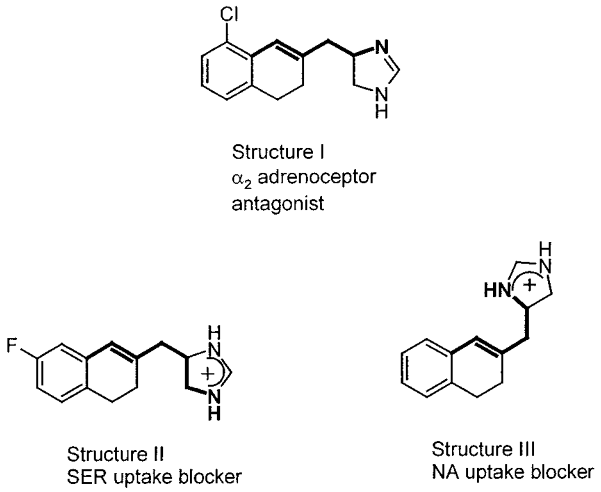


Figure 3. Cyclopropyl rigidifications of molecule **4a**.

Total rigidification of the parent molecule (**4a**) was accomplished in compounds **21a,b** where the two diastereoisomers differ only by the spatial position of one of the nitrogen atoms (N^3 in the tautomer drawn, Table 6). In **21a**, this nitrogen is equatorial with its lone pair of electrons projecting perpendicularly to the main plane of the molecule, and in **21b**, this nitrogen is axial with its lone pair of electrons oriented toward the aromatic ring. The other nitrogen atom (N^1 in the tautomer drawn) occupies more or less the same position in the two diastereoisomers. This difference has a profound effect on affinity at α_2-adrenoceptors (Table 6), **21a** being more potent than **21b** by nearly 2 orders of magnitude. On the other hand, it has a minimal effect regarding affinity at SER uptake sites, **21a** being more potent than **21b** by only 0.2 log unit. This result confirms our previous analysis that N^3 is the critical nitrogen atom for α_2-adrenergic affinity while N^1 controls affinity at SER uptake sites. Recent work by Kozikowski's group on tropane analogues[31] also emphasizes the importance of geometry between aromatic moieties and the basic nitrogen, as *Z* and *E* isomers of the phenylmethylene-7-azatricyclo[4.3.1.0^{3,7}]decane derivative displayed contrasting activities at NA, SER, and DA uptake sites.

Since neither of our totally rigid compounds is particularly potent at NA uptake sites, we synthesized **21** as an alternative strategy to rigidify the parent molecule **4a** with, in this case, the lone pair of the nitrogen lying in the plane of the aromatic ring. Results from the



Structure I
α_2 adrenoceptor
antagonist

Structure II
SER uptake blocker

Structure III
NA uptake blocker

Figure 4. Critical structural and conformational features for interaction with the α_2 adrenoceptor site and the SER and NA uptake sites.

biological evaluation (Table 6) demonstrate that this orientation is inappropriate as the molecule loses all activity.

The last change envisaged was the introduction of a methyl substituent on the parent molecule (**4a**) either at position 4(5) of the imidazoline (**23**) or at position 2 of the naphthalene moiety (**24a**,**b**). In the former case, this modification has a deleterious effect on affinities at α_2-adrenoceptors and NA uptake sites whereas affinity at SER uptake sites remained unchanged. In the latter case, one diastereoisomer (**24a**) displays enhancement affinity at SER uptake sites while the other (**24b**) exhibits decreased affinity at α_2-adrenoceptors.

To sum up, analysis of this series of napamezole (**2**) analogues reveals several critical features modulating affinities at α_2-adrenoceptors and SER and NA uptake sites. Notably, α_2-adrenergic affinity is favored by the presence of a sp^2 nitrogen atom, at a distance from an aromatic ring which is best accommodated by a four-atom chain in extended conformation. This nitrogen must be able to attain a conformation in which its lone pair of electrons points perpendicularly to the plane of the aromatic ring and it is intolerant to steric crowding in its close vicinity. Further, a broad range of pK_as encompassing imidazole (p$K_a \approx 7$) and 2-aminoimidazoline (p$K_a > 10$) is acceptable for this nitrogen atom. In addition, substituents in position 8 of the dihydronaphthalene, in particular chlorine, selectively enhance this property (structure I, Figure 4).

In contrast, affinity at SER uptake sites is dependent on the presence of a protonated nitrogen atom located at a slightly higher distance from an aromatic ring with a much broader tolerance in terms of the precise orientation of the lone pair of electrons. Potentiation occurs selectively when the aromatic ring is substituted by a fluorine at position 7. On the other hand, systematic replacement of a CH_2 group by an oxygen atom at position 4 of dihydronaphthalene or at position 3 of indene leads to a decreased potency. Both affinities at α_2-adrenoceptors and SER uptake sites are incompatible with the presence of additional bulky substituents at position 4 of the dihydronaphthalene (structure II, Figure 4).

Finally, affinity at NA uptake sites is more difficult to improve. The only change achieving a significant increase was aromatization of the dihydronaphthalene. This can be understood as a shortening of the distance between a protonated nitrogen atom and an aromatic ring (2 or 3 atoms apart versus 4 or 5 atoms). The most striking effect emerged from the analysis of different means for rigidification of the molecule. Indeed, each rigidification which improved affinities at α_2-adrenoceptors and SER uptake sites decreased affinity at NA uptake sites and vice versa. This observation reinforces the conviction that a fundamental difference, such as the distance between a critical nitrogen atom and an aromatic ring, exists between these two sets of properties: on the one hand, affinities at α_2-adrenoceptors and SER uptake sites and, on the other hand, affinity at NA uptake sites. As long as enough flexibility is preserved in the molecule the two conditions are compatible, but as rigidity increases to improve affinities at α_2-adrenoceptors and SER uptake sites, a conformation necessary to accommodate the NA uptake site becomes inaccessible and, in parallel, potency at this site diminishes. In addition, affinity at NA uptake sites is very sensitive to steric crowding as potency decreases when substitution is implemented at position 4(5) of the imidazoline or position 1 of the tetrahydronaphthalenyl skeleton.

In addition to the results discussed above, we also determined the affinities of specific compounds at α_1-adrenoceptors. In most of cases, these affinities were lower than for α_2-adrenoceptors with a difference close to 2 log units for the most interesting compounds. Finally, according to the hypothesis stated in the Introduction, these SARs are based on the principle that the interaction at α_2-adrenoceptors is antagonistic in nature. We verified this by [^{35}S]GTPγS binding (Table 7). In the absence of the NA, no compound manifested intrinsic activity, whereas the increase of [^{35}S]GTPγS binding elicited by NA was dose-dependently inhibited by all compounds tested. The pK_bs were, generally, in good agreement with the pK_is determined in the same cell line (Table 7) as the regression curve appears as a straight line with a correlation coefficient and slope close to unity: 0.916 and 0.986, respectively.

On the basis of this analysis, compound **14c** (S 34324) was chosen for further pharmacological characterization of the functionnal properties of α_2-adrenoceptor antagonist and SER uptake inhibitor endowed with NE uptake inhibition potency. The separation and stereospecific synthesis of the four isomers of **14c** will be reported later. Today, in vivo experiments indicate that compound **14c** is active in behavioral and neurochemical models predictive of antidepressant activity (data not shown).

Experimental Section

Biology. 1. Determination of Affinity for rα_1-Adrenoceptors. Binding affinity was determined as described[32] by competition with [^{3}H]prazosin (Amersham, Les Ulis, France). Rat cerebral cortex was homogenized using a polytron in 20 volumes (w/v) of buffer (50 mM Tris-HCl pH 7.4, 4 mM $CaCl_2$, 0.1% w/v ascorbic acid and 10 μM). The homogenate was centrifuged (35000*g*, 20 min, 4 °C) and the pellet was resuspended in the same volume of buffer for a second centrifugation. The final pellet was resuspended in 80 volumes of buffer and used for binding (final concentration 1/100 w/v). Membranes were incubated in triplicate with 0.2 nM [^{3}H]prazosin

Table 8. Preparation Methods for the Imidazolines **4a**−**j**, **9a**, **11a**−**c**, **12**, **13**, **14a**−**e**, and **15a**−**c**

compd	method	last step yield (%)	formula	elemental analysis	mp (°C)
4b	A	83	$C_{14}H_{15}ClN_2{\cdot}C_4H_4O_4$	C, H, N, Cl	191−195
4c	A	55	$C_{14}H_{15}FN_2{\cdot}C_4H_4O_4$	C, H, N	183−185
4d	A	88	$C_{15}H_{16}N_2O{\cdot}C_4H_4O_4$	H, N; C: calcd, 63.68; found, 63.00	206−208
4e	A	90	$C_{15}H_{16}N_2{\cdot}C_4H_4O_4$	H, N; C: calcd, 66.65; found, 66.08	182−184
4f	A	62	$C_{14}H_{15}FN_2{\cdot}C_4H_4O_4$	C, N; H: calcd, 4.83; found, 5.25	155−157
4g	A	75	$C_{15}H_{15}F_3N_2{\cdot}C_4H_4O_4$	C, H, N	169−171
4h	A	57	$C_{15}H_{18}N_2O{\cdot}C_4H_4O_4$	C, H, N	136−138
4i	A	45	$C_{15}H_{18}N_2{\cdot}C_4H_4O_4$	C, H, N	137−139
4j	A	48	$C_{15}H_{18}N_2{\cdot}C_4H_4O_4$	C, H, N	177−178
9a	B	77	$C_{14}H_{14}N_2{\cdot}C_4H_4O_4$	C, H, N	149−150
11a	A	52	$C_{13}H_{14}N_2O{\cdot}C_4H_4O_4$	C, H, N	148−150
11b	B	73	$C_{12}H_{14}N_2O_2{\cdot}C_4H_4O_4$	C, H, N	145−146
11c	B	60	$C_{13}H_{16}N_2O{\cdot}C_4H_4O_4$	C, H, N	137−139
12	A	58	$C_{16}H_{20}N_2{\cdot}0.5C_4H_4O_4$	C, H, N	178−179
13	A	28	$C_{13}H_{14}N_2{\cdot}C_4H_4O_4$	C, H, N	161−162
14a	B	64	$C_{13}H_{16}N_2{\cdot}0.5C_4H_4O_4$	C, H, N	208−210
14b	B	71	$C_{13}H_{15}FN_2{\cdot}0.5C_4H_4O_4$	H, N; C: calcd, 65.20; found, 64.34	212−215
14c	B	59	$C_{13}H_{15}FN_2{\cdot}0.5C_4H_4O_4$	C, H, N	187−190
14d	B	78	$C_{13}H_{14}F_2N_2{\cdot}0.5C_4H_4O_4$	C, H, N	201−202
14e	B	73	$C_{15}H_{20}N_2{\cdot}C_4H_4O_4$	C, H, N	198−200
15a	B	66	$C_{12}H_{12}N_2O{\cdot}C_4H_4O_4$	C, H, N	154−156
15b	B	61	$C_{12}H_{11}FN_2O{\cdot}C_4H_4O_4$	C, H, N	148−151
15c	B	57	$C_{18}H_{16}N_2O{\cdot}C_4H_4O_4$	C, H, N	152−153

and competing ligand in a final volume of 0.5 mL, for 1 h at 22 °C. Nonspecific binding was defined with 10 μM phentolamine.

2. Determination of Affinity for rα_2-Adrenoceptors. Binding affinity was determined as described[33] by competition with [^{3}H]RX 821002 (Amersham, Les Ulis, France). Rat cerebral cortex was homogenized using a polytron in 20 volumes (w/v) of buffer (Tris-HCl 50 mM, pH 7.5 at 25 °C, EDTA 1 mM and guanylyl imidodiphosphate, GppNHp, 100 μM). The homogenate was centrifuged (35000*g*, 20 min, 4 °C) and the pellet was resuspended in the same volume of buffer for a second centrifugation. The final pellet was resuspended in 300 volumes of buffer and used for binding (final concentration 1/400 w/v). For binding experiments membranes were incubated with [^{3}H]RX 821002 (0.4 nM final) and competing ligand for 1 h at 22 °C. Nonspecific binding was defined with phentolamine (10 μM).

3. Determination of Affinity for CHO-hα_{2A}-Adrenoceptors. Binding affinity was determined as described[32] by competition with [^{3}H]RX 821002 (Amersham, Les Ulis, France). Membranes were prepared from CHO-hα_{2A} cells stably expressing the human adrenergic α_{2A}-receptor (provided by Prof. A. D. Strosberg, Inst. Cochin, Paris, France). Cells grown in adherent culture were harvested by centrifugation and homogenized using a polytron. The homogenate was centrifuged (43000*g*, 30 min, 4 °C) and the membrane pellet resuspended in buffer (Tris-HCl 33 mM, pH 7.5, EDTA 1 mM) with 10 strokes in a Potter homogenizer sonicated for 15 s and stored at −80 °C until use. For binding experiments, ~10 μg membranes were incubated with [^{3}H]RX 821002 (0.8 nM final) and competing ligand, for 1 h at 22 °C. Nonspecific binding was defined with phentolamine (10 μM).

4. [^{35}S]GTPγS Binding Assay. Efficacy at CHO-hα_{2A} receptors was determined by the binding of [^{35}S]GTPγS (Amersham, Les Ulis, France) as described.[29] Membranes (40 μg/mL) were preincubated 30 min at room temperature in the presence of drugs or GTPγS diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 μM GDP and 3mM $MgCl_2$). Incubation was started by the addition of 0.2 nM [^{35}S]GTPγS and further followed 60 min at room temperature. Nonspecific binding was defined using nonradiolabeled GTPγS (10 μM).

5. Ligand Binding at Native Rat SER Reuptake Sites. Binding affinity was determined as described[34] by competition with [^{3}H]paroxetine (NEN, Les Ulis, France). Membranes were prepared from rat frontal cortex by homogenization with a polytron followed by two centrifugations at 20000*g*. The pellet was resuspended each time in incubation buffer. The final resuspension was made in 40 volumes of buffer. For binding experiments, freshly prepared membranes (final concentration 1/80 w/v) were incubated in triplicate with 2nM [^{3}H]paroxetine and competing ligand in a final volume of 0.4 mL for 2 h at 25 °C. The high concentration of [^{3}H]paroxetine was necessary due to its low specific activity (<20 Ci/mmol). The incubation buffer contained 50 nM Tris-HCl (pH 7.4), 120 nM NaCl and 5 mM KCl. Nonspecific binding was defined with 10 μM citalopram.

6. Ligand Binding at Native Rat NA Reuptake Sites. Binding affinity was determined as described[35] by competition with [^{3}H]nisoxetine (Amersham, Les Ulis, France). Membranes were prepared from rat frontal cortex by homogenization with a polytron followed by two centrifugations at 20000*g*. The pellet was resuspended each time in 60 volumes of incubation buffer. For binding experiments, freshly prepared membranes (final concentration 1/100 w/v) were incubated in triplicate with 2 nM [^{3}H]nisoxetine and competing ligand in a final volume of 0.5 mL for 4 h at 4 °C. The incubation buffer contained 50 mM Tris-HCl (pH 7.4), 120 mM NaCl and 5 mM KCl. Nonspecific binding was defined with 10 μM desipramine.

In all the experiments, at the end of the incubation period, membranes were filtered through Whatman GF/B filters pretreated with 0.1% de polyethylenimine followed by three successive washes with ice-cold buffer. Radioactivity retained on the filters was determined by scintillation counting.

7. Data Analysis. Binding isotherms were analyzed by nonlinear regression using the program Prism (GraphPad Software Inc., San Diego, CA) to determine IC_{50} values. These were converted to inhibition constants (K_i) via the Cheng−Prusoff equation:[36] $K_i = IC_{50}/\{(L/K_D) - 1\}$, where L is the concentration of [^{3}H]ligand and K_D is its disscociation constant. In practice, the amount of free [^{3}H]ligand varies minimally (<10%) from the total [^{3}H]ligand added, so L was routinely taken as equal to total [^{3}H]ligand. The K_D values were: 0.4 nM for [^{3}H]RX 821002 at rat α_2-receptors and 0.4 nM at hα_{2A}-receptors, 0.1 nM for [^{3}H]prazosin, 1.2 nM for [^{3}H]nisoxetine, and 0.13 nM for [^{3}H]paroxetine.

In the GTPγS binding experiment, antagonist potencies are expressed as $pK_B = -\log K_B$, with $K_B = IC_{50}/1 + ([ago]/EC_{50}ago)$, where IC_{50} is the inhibitory concentration of antagonist that gives 50% inhibition of [^{35}S]GTPγS binding in the presence of a fixed concentration of agonist ([ago], NA 10 μM) and EC_{50}ago is the EC_{50} of the agonist when tested alone.

Chemistry. Reagents were commercially available and of synthetic grade. ^{1}H NMR spectra relative to TMS were recorded on Bruker 200 or 400 MHz spectrometers. Infrared spectra were obtained as Nujol emulsion, on a Bruker Fourier transform spectrometer. All new substances were homogeneous in TLC and exhibited spectroscopic data consistent with the assigned structures. Elemental analyses (C, H, N) were performed on a Carlo Erba 1108 instrument and are in agreement with the calculated values within the ±0.4% range unless otherwise stated. Melting points were obtained on a Reichert hot stage microscope and are uncorrected. Silica gel 60, Merck 230−400 mesh, was used for both flash and medium-pressure chromatography. TLC were performed on precoated 5- × 10-cm, Merck silica gel 60 F254 plates (layer thickness 0.25 mm).

Method A: 4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (4a). Ethyl (3,4-Dihydronaphthalen-2-yl)acetate (25a). A solution of triethyl phosphonoacetate (56 g, 0.25 mol) in anhydrous THF (70 mL) was added dropwise to a suspension of NaH (6 g, 0.25 mol) in anhydrous THF maintained at 0 °C under an N_2 atmosphere. The reaction mixture was stirred at 10 °C for 30 min, cooled at 0 °C and a solution of β-tetralone **24a** (36.5 g, 0.25 mol) in anhydrous THF (50 mL) was added dropwise. The solution was stirred for 3 h at 20 °C, hydrolyzed at 0 °C by the addition of water (200 mL). The organic solvents were evaporated under reduced pressure and the residue extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated to afford **25a** as a brown oil which was purified through vacuum distillation as a colorless oil (46.5 g, 86%), bp 88−91 °C/0.03 mmHg. ^1H NMR ($CDCl_3$): δ 7.20−6.95 (m, 4H), 6.35 (s, 1H), 4.20 (q, 2H), 3.20 (s, 2H), 2.85 (t, 2H), 2.35 (t, 2H), 1.25 (t, 3H).

(3,4-Dihydronaphthalen-2-yl)acetaldehyde (26a). A solution of DIBAL-H in CH_2Cl_2 (1 M, 170 mL) was added dropwise to a solution, cooled at −60 °C, of **25a** (18.6 g, 0.086 mol) in CH_2Cl_2 (360 mL). After 2 h stirring at −60 °C, the reaction mixture was hydrolyzed by successive additions of NH_4Cl (10%, 35 mL) and HCl (1 N, 42 mL). The temperature was brought to 20 °C in 1 h and the solid was filtered and washed with CH_2Cl_2 (2 × 50 mL). The pooled filtrates were washed with water (100 mL) and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (SiO_2, cyclohexane/AcOEt = 95/5) to yield **26a** as a colorless oil (9.2 g, 62%). ^1H NMR ($CDCl_3$): δ 9.75 (t, 1H), 7.15−6.95 (m, 4H), 6.40 (s, 1H), 3.30 (s, 2H), 2.85 (t, 2H), 2.30 (t, 2H).

2-Amino-3-(3,4-dihydronaphthalen-2-yl)propionitrile (27a). A solution of **26a** (3.44 g, 20 mmol) and ZnI_2 (0.25 g, 0.8 mmol) in CH_2Cl_2 (100 mL) was treated dropwise with TMSCN (2.18 g, 22 mmol). After 20 h stirring, the solution was evaporated under reduced pressure and the residue poured into a solution of NH_3 in MeOH (7 N, 200 mL). The reaction mixture was kept in a sealed vessel for 4 h and concentrated. The residue was taken up in HCl (1 N, 100 mL), washed with ether (50 mL), the aqueous phase was basified by addition of NaOH (6 N) and extracted with CH_2Cl_2 (3 × 50 mL). The pooled organic phases were washed with brine, dried ($MgSO_4$) and concentrated to afford **27a** as an oil (2.8 g, 71%) used without purification.

3-(3,4-Dihydronaphthalen-2-yl)propane-1,2-diamine (28a). A mixture of **27a** (2.57 g, 13 mmol), Raney Ni (2 g) in MeOH (120 mL) and a solution of NH_3 in MeOH (7 N, 50 mL) was hydrogenated under 1 atm for 16 h. The reaction mixture was filtered over Celite, concentrated and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH = 90/9/1) to yield **28a** as a colorless oil (1.45 g, 55%). ^1H NMR (DMSO-d_6): δ 7.10 (m, 3H), 6.95 (d, 1H), 6.25 (s, 1H), 3.20 (m, 1H), 2.85 (dd, 1H), 2.70 (m, 3H), 2.25 (d, 2H), 2.10 (t, 2H).

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (4a). A mixture of **28a** (0.50 g, 2.5 mmol) and formamidine acetate (0.29 g, 2.75 mmol) in EtOH (20 mL) was stirred for 20 h. The solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2 (10 mL). After treatment with NaOH (2 N, 5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The pooled organic phases were dried ($MgSO_4$) and concentrated. The remaining oil was dissolved in EtOH (10 mL) and treated with a solution of fumaric acid (290 mg, 2.5 mmol) in EtOH (5 mL); **4a** was obtained as a white powder (0.53 g, 65%), mp 165−166 °C. ^1H NMR (DMSO-d_6): δ 8.20 (m, 1H), 7.05 (m, 4H), 6.45 (s, 2H), 6.30 (s, 1H), 4.40 (m, 1H), 3.85 (t, 1H), 3.45 (dd, 1H), 2.75 (t, 2H). Anal. ($C_{14}H_{16}N_2$·$C_4H_4O_4$) C, H, N.

Following the typical procedure described above, part of the imidazolines listed in Table 8 were prepared, starting from the appropriate tetralones.

2-Amino-4(5)-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Bromhydrate (6). A solution of BrCN (0.12 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **28a** (0.21 g, 1 mmol) in CH_2Cl_2 (5 mL), cooled at 0 °C. After 2 h stirring, the solid was collected by filtration and dried to afford **6** as a white powder (0.23 g, 75%), mp 143 °C. ^1H NMR (DMSO-d_6): δ 7.10 (m, 3H), 7.05 (d, 1H), 6.30 (d, 1H), 4.20 (m, 1H), 3.70 (t, 1H), 3.30 (dd, 1H), 2.75 (t, 2H), 2.40 (m, 2H), 2.20 (t, 2H). Anal. ($C_{14}H_{17}N_3$·HBr) C, H, N, Br.

2-Amino-4-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Hydrochloride (7). 2-Amino-3-(3,4-dihydronaphthalen-2-yl)propionic Acid, Hydrochloride (30). A solution of **27a** (4.14 g, 21 mmol) in formic acid (20 mL) was saturated at 0 °C with anhydrous HCl. When the gas evolution subsided, the acid was evaporated under reduced pressure and the waxy residue was dissolved in HCl (6 N, 30 mL) and brought to reflux overnight. The solvent was evaporated under reduced pressure and the residue crystallized from EtOH to afford **30**·HCl as a white powder (4.88 g, 92%). ^1H NMR (DMSO-d_6): δ 9.50−8.20 (bd, 4H), 7.20−7.00 (m, 4H), 6.35 (s, 1H), 4.05 (m, 2H), 3.00−2.70 (m, 4H), 2.40−2.00 (m, 2H).

2-Amino-4-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Hydrochloride (7). A suspension of **30**·HCl (5.32 g, 21 mmol) in anhydrous THF (125 mL) was added dropwise to a suspension of $LiAlH_4$ (3.3 g, 87 mmol) in anhydrous THF (500 mL) cooled at −10 °C. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive careful addition of water (3.3 mL), NaOH (3.3 mL) and water (6.6 mL). Ether (300 mL) was added and the suspension was stirred for 45 min, filtered and the filtrate concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH = 90/9/1) to afford 2-amino-3-(3,4-dihydronaphthalen-2-yl)propanol as a colorless oil (1.49 g, 35%). A solution of BrCN (0.90 g, 8.6 mmol) in THF (20 mL) was added dropwise at 0 °C, to a solution of the amino alcohol in THF (12 mL) in the presence of K_2CO_3 (1.20 g, 8.6 mmol). After 1 h stirring at room temperature, the solid was filtered and the THF was evaporated under reduced pressure. The residue was taken up in EtOH (25 mL) and treated with ethereal HCl. The precipitate was then filtered and recrystallized from a *i*-PrOH (10 mL)/diethyl ether (30 mL) mixture to give **7** as a white powder (0.45 g, 16%), mp 168−170 °C. ^1H NMR (DMSO-d_6): δ 9.50−8.50 (bd, 3H), 7.20−6.95 (m, 4H), 6.35 (s, 1H), 4.85 (m, 1H), 4.60−4.35 (m, 2H), 2.90−2.65 (m, 3H), 2.60 (m, 1H), 2.25 (m, 2H). Anal. ($C_{14}H_{16}N_2O$·HCl) C, H, N.

2-Amino-5-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Fumarate (8a). 2-Hydroxy-3-(3,4-dihydronaphthalen-2-yl)propionitrile (29a). A solution of **26a** (3.44 g, 20 mmol) and ZnI_2 (0.25 g, 0.8 mmol) in CH_2Cl_2 (100 mL) was treated dropwise with TMSCN (2.18 g, 22 mmol). After 20 h stirring, the solution was evaporated under reduced pressure and the residue was used without further purification.

2-Amino-5-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Fumarate (8a). A solution of **29a** (15.6 g, 79 mmol) in anhydrous THF (125 mL) was added dropwise to a suspension of $LiAlH_4$ (3.3 g, 87 mmol) in anhydrous THF (500 mL) cooled at −10 °C. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive careful addition of water (3.3 mL), NaOH (3.3 mL) and water (6.6 mL). Ether (300 mL) was added and the suspension was stirred for 45 min, filtered and the filtrate concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH = 90/9/1) to afford 2-amino-3-(3,4-dihydronaphthalen-2-yl)propanol as a colorless oil (5.90

g, 37%). To a solution of the amino alcohol (1 g, 5 mmol) in THF (30 mL) in the presence of K_2CO_3 (0.75 g, 5.4 mmol), a solution of BrCN (0.57 g, 5.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. After 1 h stirring at room temperature, the solid was filtered and the THF was evaporated under reduced pressure. The oily residue was dissolved in EtOH (25 mL) and treated with fumaric acid (0.25 g, 2.15 mmol). The mixture was refluxed for 30 min and stirred at 20 °C for 3 h. The solid **8a** was collected by filtration and dried under vacuum as a white powder (0.43 g, 30%), mp 213 °C. ^1H NMR (DMSO-d_6): δ 7.20−7.00 (m, 4H), 7.75 (d, 1H), 6.45 (s, 1H), 6.35 (s, 1H), 5.00 (m, 1H), 3.80 (dd, 1H), 3.40 (dd, 1H), 2.80 (t, 2H), 2.60 (m, 2H), 2.25 (t, 2H). Anal. ($C_{14}H_{16}N_2O{\cdot}C_4H_4O_4$) C, H, N.

2-Amino-5-[(8-chloro-3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Fumarate (8b). The compound was obtained as described for **8a**, as a white powder (32%), mp 186−188 °C. ^1H NMR (DMSO-d_6): δ 7.25 (m, 1H), 7.15 (m, 2H), 6.70 (s, 1H), 6.45 (s, 2H), 5.25 (m, 1H), 3.90 (t, 1H), 3.50 (dd, 1H), 2.80 (t, 2H), 2.75 (m, 2H), 2.30 (t, 2H). Anal. ($C_{14}H_{15}ClN_2O{\cdot}C_4H_4O_4$) C, H, N.

2-Amino-5-[(7-methyl-3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Fumarate (8c). The compound was obtained as described for **8a**, as a white powder (24%), mp 190−192 °C. ^1H NMR (DMSO-d_6): δ 7.00 (m, 1H), 6.90 (d, 1H), 6.85 (s, 1H), 6.45 (s, 2H), 6.30 (s, 1H), 5.20 (m, 1H), 3.85 (t, 1H), 3.45 (m, 1H), 2.65 (m, 4H), 2.20 (m, 5H). Anal. ($C_{15}H_{18}N_2O{\cdot}C_4H_4O_4$) C, H, N.

2-Amino-5-[(6-methyl-3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Hemifumarate (8d). The compound was obtained as described for **8a**, as a white powder (31%), mp 214−215 °C. ^1H NMR (DMSO-d_6): δ 6.95 (d, 3H), 6.40 (s, 2H), 6.30 (s, 1H), 5.05 (m, 1H), 3.80 (t, 1H), 3.35 (dd, 1H), 2.70 (t, 2H), 2.55 (t, 2H), 2.25 (m, 5H). Anal. ($C_{15}H_{18}ClN_2O{\cdot}0.5C_4H_4O_4$) C, H, N.

4(5)-[(1,2,3,4-Tetrahydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Succinate (10a). A solution of **4a** (1 g, 3 mmol) in EtOH (20 mL) was hydrogenated in the presence of Pd/C (10%, 100 mg) under 1 atm. After 2 h, the catalyst was filtered through glass fibers and the solvent evaporated under reduced pressure. The waxy residue was concentrated through scratching in acetone (10 mL); compound **10a** was obtained as a white powder (0.99 mg, 98%), mixture (45/55) of the two diastereoisomers, mp 158−159 °C. ^1H NMR (DMSO-d_6): δ 8.15 (s, 1H), 7.05 (m, 4H), 4.30 (m, 1H), 3.90−3.40 (m, 2H), 2.80 (dd, 3H), 2.40 (dd, 1H), 2.25 (s, 4H), 1.85 (m, 2H), 1.70−1.40 (m, 3H). Anal. ($C_{14}H_{18}N_2{\cdot}C_4H_6O_4$) C, H, N.

Method B: 4(5)-(8-Chloro-2-naphthylmethyl)-4,5-dihydroimidazole, Fumarate (9b). 8-Chloro-2-methyl-1,2,3,4-tetrahydronaphthalen-2-ol (32). To a cooled (−40 °C) solution of $TiCl_4$ (1 M, 90 mL) in CH_2Cl_2, MeMgBr (3 M, 30 mL) in THF was added over 30 min. To the resulting mixture, 8-chloro-2-tetralone (**31**; 13.5 g, 74.8 mmol) dissolved in CH_2Cl_2 (60 mL) was added over 30 min. The resulting mixture was then warmed to 0 °C. After 3 h, the suspension was poured over ice (300 g), the layers were separated, the organic phase was washed with HCl (2 N, 100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to afford **32** as a brown solid (14.1 g, 96%) used without further purification. ^1H NMR ($CDCl_3$): δ 7.30−7.00 (m, 3H), 3.15−2.70 (m, 4H), 2.00−1.65 (m, 2H), 1.60 (m, 1H), 1.40 (s, 3H).

1-Chloro-7-methylnaphthalene (33). A mixture of **32** (14.2 g, 72 mmol), trityl-OH (21.9 g, 84 mmol) and CF_3CO_2H (54 mL) was stirred at room temperature for 2 days. The mixture was then extracted with cyclohexane (3 × 100 mL), the pooled organic phases were washed with H_2O (100 mL), $NaHCO_3$ (5%, 100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to give a brown oil which was purified by flash column chromatography (SiO_2, cyclohexane/AcOEt = 95/5) to afford **33** as a colorless oil (10.5 g, 85%). ^1H NMR ($CDCl_3$): δ 8.05 (d, 1H), 7.75 (d, 1H), 7.70 (dd, 1H), 7.55 (m, 1H), 7.35 (dd, 1H), 7.25 (m, 1H), 2.55 (s, 3H).

1-Chloro-7-bromomethylnaphthalene (34). A solution of **33** (10.8 g, 61.2 mmol), NBS (11.4 g, 64 mmol) and AIBN (0.8 g, 5.1 mmol) in CCl_4 (175 mL) was heated under reflux for 1 h. The suspension was then cooled to 10 °C, filtered and the filtrate concentrated to afford **34** (10.5 g, 76%) as a white solid, mp 123−124 °C. ^1H NMR ($CDCl_3$): δ 8.15 (d, 1H), 7.95 (d, 1H), 7.70 (d + dd, 2H), 7.85 (d, 1H), 7.75 (d, 1H), 7.35 (t, 1H), 4.70 (s, 2H).

2-Amino-3-(8-chloro-2-naphthyl)propionitrile (35). A solution of **34** (5 g, 19 mmol) in CH_2Cl_2 (75 mL) was added dropwise under an N_2 atmosphere, to a cooled (0 °C) suspension of *N*-(diphenylmethylene)aminoacetonitrile (4.5 g, 20.4 mmol), tetrabutylamonium bromide (0.6 g, 1.86 mmol) and powdered KOH (85%, 1.3 g, 19.7 mmol) in CH_2Cl_2 (75 mL). After stirring for 1 night at room temperature, the suspension was filtered and the filtrate concentrated. The resulting oily residue was taken up in ether (200 mL) and HCl (1 N, 200 mL) and stirred vigorously overnight. The aqueous phase was separated, basified with NaOH (6 N), extracted with CH_2Cl_2 (3 × 80 mL), dried ($MgSO_4$) and concentrated to afford compound **35** as a brown oil (3.3 g, 73%) which was used without further purification.

4(5)-(8-Chloro-2-naphthylmethyl)-4,5-dihydroimidazole, Fumarate (9b). Starting from **35**, the compound **9b** was obtained as described for **4a**, as a white powder (86%), mp 172−175 °C. ^1H NMR (DMSO-d_6): δ 8.05 (s, 1H), 8.00 (d, 1H), 7.95 (d, 1H), 7.90 (dd, 1H), 7.65 (dd, 1H), 7.45 (t, 1H), 6.45 (s, 2H), 4.50 (m, 1H), 3.75 (m, 1H), 3.50 (m, 1H), 3.10 (m, 2H). Anal. ($C_{14}H_{13}ClN_2{\cdot}C_4H_4O_4$) C, H, N, Cl.

Following the typical procedures described above, some of the imidazolines listed in Table 8 were prepared, starting from the appropriate bromides.

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]imidazole, Fumarate (5). 4-[(1,2,3,4-Tetrahydronaphthalen-1-on-2-yl)methyl]-1-tritylimidazole (38). A mixture of 1-tetralone (0.73 g, 5 mmol), potassium *tert*-butylate (0.56 g, 5 mmol) and 4-chloromethyl-1-tritylimidazole (**37**; 1.8 g, 5 mmol) in toluene (30 mL), was brought to reflux for 5 h. The solvents were then evaporated, the residue taken up in a mixture of CH_2Cl_2/H_2O (50 mL/50 mL), the organic phase separated, dried ($MgSO_4$) and concentrated. The residual solid was purified by column chromatography (SiO_2, cyclohexane/AcOEt = 3/1) to afford **38** as a white solid (0.59 g, 25%). ^1H NMR ($CDCl_3$): δ 7.90 (d, 1H), 7.50 (t, 1H), 7.40−7.10 (m, 11H), 7.05 (m, 6H), 6.50 (s, 2H), 3.00 (t, 2H), 2.90 (AB system, 4H), 2.15 (t, 2H).

4-[(1,2,3,4-Tetrahydronaphthalen-1-ol-2-yl)methyl]-1-tritylimidazole (39). A mixture of **38** (0.12 g, 0.25 mmol) and $NaBH_4$ (0.04 g, 1 mmol) in MeOH (12 mL) was stirred overnight. Solvent was then evaporated, the residue taken up in a mixture of Ether/H_2O (20 mL/20 mL), the organic phase separated, dried ($MgSO_4$) and concentrated to afford **39** as a mixture of two diastereoisomers (0.10 g, 93%). ^1H NMR ($CDCl_3$): δ 7.65 (d, 1H), 7.35 (m, 11H), 7.15 (m, 8H), 6.60 (2s, 1H), 4.60 (2d, 1H), 2.90−2.70 (m, 4H), 2.05 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H).

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]imidazole, Fumarate (5). To a solution of **39** (0.61 g, 1.3 mmol) in CH_2Cl_2 (30 mL), CF_3CO_2H (1 mL) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. The solution was stirred overnight, solvent was then evaporated, the residue taken up in HCl (0.5 N, 100 mL), the aqueous phase washed with ether (2 × 100 mL), basified with NaOH (38%) up to pH 14, extracted with CH_2Cl_2 (2 × 100 mL), dried ($MgSO_4$) and concentrated. The residual solid was purified by column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH = 95/4.5/0.5), dissolved in acetone (15 mL) and fumaric acid (0.12 g) in *i*-PrOH (2.5 mL) was added and **5** was obtained by filtration as an off-white solid (0.24 g, 56%), mp 138.5−140.5 °C. ^1H NMR (DMSO-d_6): δ 7.70 (s, 1H), 7.10 (m, 3H), 6.95 (d, 1H), 6.85 (s, 1H), 6.60 (s, 2H), 6.25 (s, 1H), 4.00−3.00 (m, 2H), 3.40 (s, 2H), 2.70 (t, 2H), 2.20 (t, 2H). Anal. ($C_{14}H_{14}N_2{\cdot}C_4H_4O_4$) H, N; C: calcd, 66.25; found, 65.73.

4(5)-(1,2,3,7b-Tetrahydrocyclopropa[*a*]naphthalen-1a-ylmethyl)-4,5-dihydroimidazole, Fumarate (16a). Ethyl 1-(1,2,3,7b-Tetrahydrocyclopropa[*a*]naphthalen-1a-yl)acetate (40). A solution of Et_2Zn in hexane (1 M, 200 mL) and a solution of ICH_2Cl (71 g, 400 mmol) in 1,2-dichloroethane

(125 mL) were added successively dropwise to a solution of **25a** (7.2 g, 33 mmol) in 1,2-dichloroethane (75 mL) cooled at −25 °C. The temperature of the reaction mixture was brought to 10 °C and maintained at that temperature under stirring for 4 h. After cooling to 0 °C, the mixture was treated with saturated NH_4Cl (50 mL) then water (100 mL) and extracted with ether (3 × 200 mL). The pooled organic phases were washed with brine, dried ($MgSO_4$) and concentrated to afford **40** as an oil (7.4 g, 98%) which was used without further purification. ^1H NMR ($CDCl_3$): δ 7.20 (m, 1H), 7.15 (m, 1H), 7.10 (m, 1H), 7.00 (m, 1H), 4.45 (q, 2H), 2.75−2.45 (m, 2H), 2.60 (d, 1H), 2.35 (d, 1H), 2.20 (m, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.25 (t, 3H), 1.15 (m, 1H), 0.90 (m, 1H).

1-(1,2,3,7b-Tetrahydrocyclopropa[*a*]naphthalen-1a-yl)acetaldehyde (41). A solution of compound **40** (5 g, 21.5 mmol) in anhydrous THF (75 mL) was added dropwise to a suspension of $LiAlH_4$ (0.97 g, 25 mmol) in anhydrous THF (75 mL) cooled at 0 °C. After 2 h stirring at room temperature, the reaction mixture was hydrolyzed by the cautious addition of NaOH (1 N, 7 mL), followed by ether (250 mL). The suspension was stirred for 2 h, filtered and the filtrate concentrated. To a solution of pyridine (18.5 mL, 226.5 mmol) in CH_2Cl_2 (360 mL) at 0 °C under a N_2 atmosphere, was added CrO_3 (11.60 g, 116.2 mmol). After stirring for 1 h at room temperature, alcohol obtained from **40** (3.64 g, 19.4 mmol) in solution in CH_2Cl_2 (80 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered and the filtrate evaporated The residue was diluted with Et_2O, washed with 1 N NaOH, 1 N HCl and brine, dried ($MgSO_4$) and concentrated to give the pure aldehyde **41** (3.05 g, 79%) as an oil. ^1H NMR ($CDCl_3$): δ 9.85 (s, 1H), 7.30−6.95 (m, 4H), 2.80−2.35 (m, 4H), 2.15 (m, 1H), 1.85 (dd, 1H), 1.65 (m, 1H), 1.25 (m, 1H), 0.90 (m, 1H).

4(5)-(1,2,3,7b-Tetrahydrocyclopropa[*a*]naphthalen-1a-ylmethyl)-4,5-dihydroimidazole, Fumarate (16a,b). Starting from the aldehyde **41**, the compound was obtained as described for **4a**, as a mixture of diastereoisomers (50/50) which were separated by column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH = 95/4.5/0.5). Each diastereoisomer was salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder. Diastereoisomer 1, **16a** (12%), mp 192 °C. ^1H NMR (DMSO-d_6): δ 8.20 (s, 1H), 7.20 (dd, 1H), 7.15−7.00 (m, 3H), 6.45 (s, 2H), 4.35 (m, 1H), 2.60 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.80−1.65 (m, 2H), 1.50 (m, 1H), 1.05 (m, 1H), 0.80 (m, 1H). Anal. ($C_{15}H_{18}N_2{\cdot}C_4H_4O_4$) C, H, N. Diastereoisomer 2, **16b** (10%), mp 204 °C. ^1H NMR (DMSO-d_6): δ 7.95 (s, 1H), 7.20 (m, 1H), 7.15−6.95 (m, 3H), 6.40 (s, 2H), 4.25 (m, 1H), 3.85 (m, 1H), 3.40 (m, 1H), 2.70−2.35 (m, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.05 (m, 1H), 0.85 (m, 1H). Anal. ($C_{15}H_{18}N_2{\cdot}C_4H_4O_4$) C, H, N.

4(5)-(1a,2,3,7b-Tetrahydro-1*H*-cyclopropa[*a*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (17). 1a,2,3,7b-Tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylic Acid, Ethyl Ester (42). To a solution of 1,2-dihydronaphthalene (6.5 g, 50 mmol) and $Rh_2(AcO)_4$ (51 mg, 0.11 mmol) in ether (30 mL), N_2CHCO_2Et (5.7 g, 50 mmol) dissolved in ether (15 mL) was added, at room temperature, at the rate of 2.5 mL/h. The reaction mixture was filtered over Al_2O_3 (10 g), the solids rinsed with ether (100 mL) and the pooled filtrates concentrated. The oily residue was purified by column chromatography (SiO_2, cyclohexane/AcOEt = 1.25%) to afford the isomers *syn* (2.7 g, 25%) and *anti* (**42**; 3.68 g, 34%). ^1H NMR ($CDCl_3$): 7.35−6.90 (m, 4H), 6.15 (q, 2H), 2.80−2.30 (m, 3H), 2.30−2.10 (m, 2H), 2.05 (m, 1H), 1.90−1.60 (m, 1H), 1.25 (t, 3H).

1a,2,3,7b-Tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxaldehyde (43). A solution of compound **42** (2.6 g, 12 mmol) in anhydrous THF (75 mL) was added dropwise to a suspension of $LiAlH_4$ (0.7 g, 18 mmol) in anhydrous THF (75 mL) cooled at 0 °C. After 2 h stirring at room temperature, the reaction mixture was hydrolyzed by the cautious addition of NaOH (1 N, 7 mL), followed by ether (250 mL). The suspension was stirred for 2 h, filtered and the filtrate concentrated. To a solution of pyridine (11.4 mL, 140 mmol) in CH_2Cl_2 (150 mL) at 0 °C under a N_2 atmosphere was added CrO_3 (7.25 g, 72.7 mmol). After stirring for 1 h at room temperature, alcohol prepared from **42** dissolved in CH_2Cl_2 (100 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered and the filtrate evaporated. The residue was diluted with Et_2O, washed with 1 N NaOH, 1 N HCl and brine, dried ($MgSO_4$) and concentrated to give the pure aldehyde **43** (1.63 g, 79%) as an oil. ^1H NMR ($CDCl_3$): δ 9.35 (d, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 7.00 (m, 1H), 2.75−2.60 (m, 2H), 2.50 (m, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 1.90 (m, 1H).

4(5)-(1a,2,3,7b-Tetrahydro-1*H*-cyclopropa[*a*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (17). Starting from the aldehyde **43**, the compound was obtained as described for **4a**, as a mixture of diastereoisomers (55/45) which was salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder (61%), mp 95 °C. ^1H NMR (DMSO-d_6): δ 8.30 (s, 1H), 7.30−7.25 (2d, 1H), 7.15−6.95 (m, 3H), 6.45 (s, 2H), 3.90 (m, 2H), 3.55−3.45 (2m, 1H), 2.65−2.35 (m, 2H), 2.10−2.00 (2m, 2H), 1.65−1.55 (m, 3H). Anal. ($C_{14}H_{16}N_2{\cdot}C_4H_4O_4$) C, H, N.

4(5)-(1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (18a,b). 1a,2,7,-7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-carboxylic Acid, Ethyl Ester (44a,b). To a solution of 1,4-dihydronaphthalene (4.32 g, 33 mmol) and $Rh(AcO)_4$ (73 mg, 0.17 mmol) in ether (100 mL), N_2CHCO_2Et (3.8 g, 33 mmol) dissolved in ether (21.5 mL) was added, at room temperature, at the rate of 4 mL/h. The reaction mixture was filtered over Al_2O_3 (10 g), the solids rinsed with ether (100 mL) and the pooled filtrates concentrated. The oily residue was purified by column chromatography (SiO_2, cyclohexane/AcOEt: 1%) to afford the isomers *anti* (**44a**; 1.4 g, 20%). ^1H NMR ($CDCl_3$): δ 7.10 (m, 2H), 7.00 (m, 2H), 4.10 (q, 2H), 3.20−3.00 (m, 4H), 2.00 (m, 2H), 1.50 (m, 1H), 1.25 (m, 3H). And *syn* (**44b**; 1.97 g, 28%). ^1H NMR ($CDCl_3$): δ 7.05 (m, 4H), 3.75 (q, 4H), 3.20−3.00 (m, 4H), 1.85−1.65 (m, 3H), 1.10 (t, 3H).

1a,2,3,7b-Tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (45a). A solution of compound **44a** (1.4 g, 6.5 mmol) in anhydrous THF (50 mL) was added dropwise to a suspension of $LiAlH_4$ (0.37 g, 9.8 mmol) in anhydrous THF (50 mL) cooled at 0 °C. After 2 h stirring at room temperature, the reaction mixture was hydrolyzed by the cautious addition of NaOH (1 N, 0.4 mL), followed by ether (100 mL). The suspension was stirred for 2 h, filtered and the filtrate concentrated. To a solution of pyridine (6.15 mL, 75 mmol) in CH_2Cl_2 (100 mL) at 0 °C under a N_2 atmosphere was added CrO_3 (3.92 g, 39 mmol). After stirring for 1 h at room temperature, alcohol prepared from **44a** dissolved in CH_2Cl_2 (25 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered and the filtrate evaporated The residue was diluted with Et_2O, washed with 1 N NaOH, 1 N HCl and brine, dried ($MgSO_4$) and concentrated to give the pure aldehyde **45a** (0.62 g, 55%) as an oil. ^1H NMR ($CDCl_3$): δ 7.15−7.00 (m, 4H), 3.50 (d, 2H), 3.05 (m, 4H), 1.25 (bd, 1H), 1.20 (m, 2H), 0.90 (m, 1H).

4(5)-(1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (18a). Starting from the aldehyde **45a**, the compound was obtained as described for **4a**, salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder (61%), mp 194 °C. ^1H NMR (DMSO-d_6): δ 7.70 (s, 1H), 7.15−7.00 (m, 4H), 6.35 (s, 2H), 3.80−3.60 (m, 2H), 3.30 (m, 1H), 3.10−2.85 (m, 4H), 1.30 (m, 2H), 0.60 (m, 1H). Anal. ($C_{14}H_{16}N_2{\cdot}C_4H_4O_4$) H, N; C: calcd 69.86; found 69.41.

4(5)-(1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (18b). Starting from the ester **44b**, the compound was obtained as described for **18a**, salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder (41%), mp 185−187 °C. ^1H NMR (DMSO-d_6): δ 8.10 (s, 1H), 7.05 (m, 4H), 6.45 (s, 1H), 3.70 (m, 1H), 3.55−3.30 (m, 2H), 3.25−2.65 (m, 4H), 1.45 (m, 2H), 1.15 (m, 1H). Anal. ($C_{14}H_{16}N_2{\cdot}C_4H_4O_4$) C, H, N.

4(5)-{Spiro[cyclopropane-2′:2″-(1″,2″,3″,4″-tetrahydronaphthalene)]-1′-yl}-4,5-dihydroimidazole, Fumarate (19a). (1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)phosphonic Acid, Diethyl Ester (48). A solution of 1-tetralone (10 g, 68 mmol) in anhydrous THF (120 mL) was added dropwise to a stirred 1 M solution of lithium diisopropylamide (75 mmol, 75 mL) at −65 °C under N_2. After stirring for 45 min, the resulting enolate was treated with diethyl chlorophosphate (12.90 g, 75 mmol) and the mixture was allowed to warm to 0 °C over the course of 50 min. After this mixture was cooled to −70 °C, it was transferred to a 2 M solution of lithium diisopropylamide (150 mmol, 75 mL). The resulting solution was allowed to warm to 10 °C over 2 h and was treated with a solution of acetic acid (272 mmol, 15.5 mL) in Et_2O (250 mL). The resulting mixture was filtered and the filtrate concentrated. The oily residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 60/40) to give the phosphonate **48** (13.5 g, 70%) as a brown oil. ^1H NMR ($CDCl_3$): δ 8.05 (d, 1H), 7.50 (td, 1H), 7.40−7.20 (m, 2H), 4.30−4.00 (m, 4H), 3.40−3.10 (m, 2H), 3.00−2.60 (m, 1H), 2.60−2.30 (m, 2H), 1.40−1.10 (2t, 6H).

2-Oxiranylmethoxytetrahydropyran (46). A solution of glycidol (5 g, 67.5 mmol), dihydropyran (28.4 g, 337.5 mmol) and pyridinium tosylate (1.70 g, 6.7 mmol) in CH_2Cl_2 (300 mL) was stirred for 4 h at 20 °C. The solution was then washed once with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 50/50) to give the epoxyde **46** (3.78 g, 35%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 4.65 (m, 1H), 3.85 and 3.50 (2m, 2H), 3.95, 3.70 and 3.40 (3m, 2H), 3.20 (m, 1H), 2.80, 2.70 and 2.60 (3m, 2H), 2.00−1.40 (m, 6H).

2′-(Tetrahydropyran-2-yloxymethyl)spiro[1′.2]cyclopropane-3,4-dihydro-1-oxonaphthalene (49). A solution of phosphonate **48** (27 g, 95 mmol) in toluene (60 mL) was added to a suspension of NaH (4.40 g, 109.2 mmol) in toluene (160 mL) at 20 °C under N_2. The reaction mixture was stirred at ambient temperature for 1 h and epoxyde **46** (30 g, 190 mmol) was added. After refluxing for 4 days, the solution was cooled, hydrolyzed with water and extracted with Et_2O (3 × 100 mL). The organic layer was then washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 80/20) to give the compound **49** (19 g, 70%) as a pale red oil. ^1H NMR ($CDCl_3$): δ 8.00 (d, 1H), 7.50 (t, 1H), 7.40−7.20 (m, 2H), 4.65 (2m, 1H), 4.05, 3.75, 3.65 and 3.40 (4m, 2H), 3.85 and 3.55 (2m, 2H), 3.30−2.90 (m, 2H), 2.20−2.00 (m, 3H), 1.70−1.40 (m, 7H), 0.70 (m, 1H).

{Spiro[cyclopropane-2:2′-(1′,2′,3′,4′-tetrahydronaphthalene)]-1-yl}methanol (52a). To a solution of compound **49** (2.50 g, 8.7 mmol) in 1,2-dichloroethane (45 mL) at room temperature under N_2 were added solid ZnI_2 (4.16 g, 13 mmol) and $NaBH_3CN$ (4.10 g, 62.2 mmol). The reaction mixture was heated at 80−85 °C for 3 h. It was then cooled and poured into an ice cold mixture of saturated aqueous NH_4Cl containing 10 vol % of 5 N HCl (180 mL). The mixture was extracted with EtOAc (3 × 80 mL) and the combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 70/30) to give the alcohol **52a** (760 mg, 46%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 7.05 (m, 4H), 3.70 (t, 2H), 2.90 (t, 2H), 2.80 and 2.55 (2d, 2H), 1.80 (m, 2H), 1.20 (m, 2H), 0.65 and 0.30 (2dd, 2H).

{Spiro[cyclopropane-2:2′-(1′,2′,3′,4′-tetrahydronaphthalene)]-1-yl}carboxaldehyde (53a). To a solution of pyridine (18.5 mL, 226.5 mmol) in CH_2Cl_2 (360 mL) at 0 °C under N_2 was added CrO_3 (11.60 g, 116.2 mmol). After stirring for 1 h at room temperature, alcohol **52** (3.64 g, 19.4 mmol) in solution in CH_2Cl_2 (80 mL) was added and the mixture was stirred at room temperature for 2 h. The reaction was then filtered and the filtrate evaporated in vacuo. The residue was diluted with Et_2O, washed with 1 N NaOH, 1 N HCl and saturated aqueous NaCl, dried ($MgSO_4$) and evaporated under reduced pressure to give the pure aldehyde **53a** (3.05 g, 85%) as an oil. ^1H NMR ($CDCl_3$): δ 9.50 (d, 1H), 7.05 and 6.95 (2m, 4H), 3.00−2.60 (m, 4H), 2.10−1.80 (m, 3H), 1.20 and 1.50 (2m, 2H).

1-{Spiro[cyclopropane-2′:2″-(1″,2″,3″,4″-tetrahydronaphthalene)]-1′-yl}ethane-1,2-diamine (54a,b). Starting from the aldehyde **53a**, the compounds were obtained as described for **4a**, as a mixture of two diastereoisomers (50/50) **54a**/**54b** (0.905 g, 36%) as a brown oil. The two diastereoisomers were separated by HPLC (Kromasil 100.5 C18, 265 nm, $CH_3OH/H_2O/CF_3COOH$ = 350/650/5). **54a:** ^1H NMR ($CDCl_3$): δ 7.20−7.00 (2m, 4H), 3.05 and 2.80 (m, 2H), 2.90 (m, 3H), 2.70 (m, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.65 (m, 1H), 1.60 (m, 4H), 0.75 (m, 1H), 0.60 (m, 1H), 0.25 (m, 1H). **54b:** ^1H NMR ($CDCl_3$): δ 7.20−7.00 (2m, 4H), 3.00 and 2.20 (m, 2H), 2.90 (m, 3H), 2.65 (m, 1H), 2.45 (m, 1H), 1.90 (m, 1H), 1.60 (m, 1H), 1.60 (m, 4H), 0.75 (m, 1H), 0.65 (m, 1H), 0.30 (m, 1H).

4(5)-{Spiro[cyclopropane-2′:2″-(1″,2″,3″,4″-tetrahydronaphthalene)]-1′-yl}-4,5-dihydroimidazole, Fumarate (19a). A mixture of the above diamine **54a** (0.17 g, 0.8 mmol) and formamidine acetate (0.094 g, 0.9 mmol) in EtOH (5 mL) was stirred at 20 °C under N_2 for 12 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with Et_2O and rendered basic with aqueous NaOH (35%); the mixture was extracted with CH_2Cl_2 and the organic layer washed with brine, dried ($MgSO_4$) and evaporated. The solid residue was dissolved in acetone (10 mL) and treated with a solution of fumaric acid (0.082 g, 0.7 mmol) in *i*-PrOH (4 mL). After evaporation and crystallization of the residue from acetone/*i*-PrOH, the derivative **19a** was obtained as a white powder (0.068 g, 65%), mp 149 °C. ^1H NMR (DMSO-d_6): δ 8.20 (s, 1H), 7.10 (m, 3H), 7.00 (d, 1H), 3.90 (m, 1H), 3.90 and 3.55 (m, 2H), 2.95 and 2.80 (m, 2H), 2.90 and 2.25 (m, 2H), 2.00 and 1.55 (m, 2H), 1.05 (m, 1H), 0.55 (m, 1H), 0.30 (m, 1H). Anal. ($C_{15}H_{18}N_2{\cdot}C_4H_4O_4$) C, H, N.

4(5)-{Spiro[cyclopropane-2′:2″-(1″,2″,3″,4″-tetrahydronaphthalene)]-1′-yl}-4,5-dihydroimidazole, Fumarate (19b). Compound **19b** was prepared according to the procedure described for **19a** and obtained as a white solid, mp 164 °C. ^1H NMR (DMSO-d_6): δ 8.25 (s, 1H), 7.10 (m, 3H), 7.05 (d, 1H), 3.95 (m, 1H), 3.95 and 3.35 (m, 2H), 2.80 and 2.45 (m, 2H), 2.80 (m, 2H), 1.75 and 1.65 (m, 2H), 0.97 (m, 1H), 0.65 (m, 1H), 0.55 (m, 1H). Anal. ($C_{15}H_{18}N_2{\cdot}C_4H_4O_4$) C, H; N: calcd, 8.18; found, 7.65.

4(5)-[Spiro(cyclopropane-2′:2″-indan)-1′-yl]-4,5-dihydroimidazole, Fumarate (20a). {Spiro[cyclopropane-2:2′-(1′-indanone)]-1-yl}carboxylic Acid, Ethyl Ester (50). Solid NaH (3.43 g, 140 mmol) was added portionwise to a solution of 1-indanone (20 g, 120 mmol) and ethyl 2-[(diethoxyphosphoryl)oxy]acrylate (36 g, 140 mmol) in anhydrous THF (260 mL) in such a way that the temperature did not exceed 35 °C. At the end of the addition the reaction vessel was plunged into an oil bath at 50 °C, the reaction mixture temperature climbed to 60 °C, afterward it was kept stirring at 45 °C for 1 h. The reaction mixture was poured on a mixture of ice (1 L) and HCl (1 N, 1 L), extracted with AcOEt (3 × 600 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (SiO_2, cyclohexane/AcOEt = 93/7) to yield **50** as a colorless oil (3.8 g, 26%). ^1H NMR ($CDCl_3$): δ 7.80 (m, 1H), 7.65 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 4.20 (m, 2H), 3.30 (s, 1H), 2.50 (m, 1H), 1.75 (m, 2H)1.25 (t, 3H).

[Spiro(cyclopropane-2:2′-indan)-1-yl]carboxylic Acid, Ethyl Ester (51). Compound **50** (24.2 g, 90 mmol) was added dropwise under mechanical stirring, to a suspension of $NaBH_3CN$ (42.7 g, 680 mmol) and ZnI_2 (41.5 g, 130 mmol) in 1,2-dichloroethane (500 mL). The suspension was brought to reflux under stirring for 14 h. The inorganic salts were filtered and the filtrate was hydrolyzed by NH_4Cl (10%, 1 L) and HCl (6 N, 180 mL). The aqueous phase was extracted with AcOEt (2 × 500 mL), the salts were hydrolyzed in the same aqueous phase which was extracted one more time with AcOEt (2 × 300 mL). The pooled organic phases were washed with Na_2CO_3 (10%, 500 mL) and brine (500 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, cyclohexane/AcOEt = 95/5) to yield **51** as a colorless oil (3.8 g, 26%). ^1H NMR ($CDCl_3$): δ 7.25−7.10 (m, 4H), 4.15 (m, 2H), 3.25−2.80 (m, 4H), 1.85 (m, 1H), 1.35 (m, 1H), 1.25 (m, 3H), 1.20 (m, 1H).

[Spiro(cyclopropane-2:2′-indan)-1-yl]carbinol (52b). A solution of compound **51** (13.9 g, 53 mmol) in anhydrous THF (250 mL)was added dropwise to a suspension of $LiAlH_4$ (3.1 g, 82 mmol) in anhydrous THF (250 mL) cooled at −18 °C. After 3 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive cautious additions of water (3.1 mL), NaOH (3.1 mL) and water (6.2 mL). The resulting suspension was stirred overnight, filtered and the filtrate concentrated. Compound **52b** was used without further purification. ^1H NMR ($CDCl_3$): δ 7.20 (m, 4H), 3.80−3.50 (m, 2H), 3.20−2.75 (m, 4H), 1.30 (m, 2H), 0.85 (m, 1H), 0.50 (m, 1H).

[Spiro(cyclopropane-2:2′-indan)-1-yl]carboxaldehyde (53b). A solution of compound **52b** (14.3 g, 68 mmol) in CH_2Cl_2 (140 mL)was added dropwise to a suspension of pyridinium chromate prepared at 0 °C from pyridine (68 mL, 670 mmol) and CrO_3 (42 g, 420 mmol) in CH_2Cl_2 (1 L). After 5 h stirring, the solids were filtered, washed with ether (100 mL) and the filtrates concentrated. The residue was taken up in ether (1 L), the insoluble material filtered, the filtrate washed successively with NaOH (1 N, 1 L), HCl (1 N, 2 × 750 mL), $NaHCO_3$ (10%, 2 × 500 mL), brine (500 mL), dried ($MgSO_4$) and concentrated to afford compound **53b** which was used without further purification. ^1H NMR ($CDCl_3$): δ 9.40 (d, 1H), 7.20 (m, 4H), 3.30−2.85 (m, 4H), 2.10 (m, 1H), 1.40 (m, 1H), 0.60 (m, 1H).

2-Di(4-methoxyphenyl)methylamino-2-[spiro(cyclopropane-2′:2″-indan)-1′-yl]ethylamine (54c,d). A solution of compound **53b** (12 g, 58 mmol) in CH_2Cl_2 (250 mL) was stirred for 2 h in the presence of di(4-methoxyphenyl)methylamine (14 g, 58 mmol) and molecular sieves (4 Å, 18 g). Then, TMSCN (6.3 g, 64 mmol) was added and the suspension stirred for 14 h. The solids were filtered, the filtrate washed with NaOH (0.1 N, 500 mL) and brine (250 mL), dried ($MgSO_4$) and concentrated to afford the aminonitrile which was used without further purification. A solution of the aminonitrile (26.7 g, 68 mmol) in anhydrous THF (125 mL) was added dropwise to a suspension of $LiAlH_4$ (3.3 g, 87 mmol) in anhydrous THF (500 mL) cooled at −10 °C. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive cautious addition of water (3.3 mL), NaOH (3.3 mL) and water (6.6 mL). Ether (300 mL) was added and the suspension was stirred 45 min, filtered and the filtrate concentrated. The two diastereoisomers were separated by column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH = 90/9/1).

2-Amino-2-[spiro(cyclopropane-2′:2″-indan)-1′-yl]ethylamine (diastereomer 1, 55c). A solution of **54c** (3.12 g, 6.7 mmol) in a mixture AcOH/H_2O (80/20, 200 mL) was plunged for 45 min in an oil bath at 90 °C. The acetic acid was then evaporated and the residue was dissolved in HCl (1 N, 100 mL), washed with ether (3 × 75 mL), basified with NaOH (9 N, 20 mL), extracted with CH_2Cl_2 (3 × 75 mL), dried (K_2CO_3) and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH = 90/9/1) to afford the product **55c** as an oil. ^1H NMR ($CDCl_3$): δ 7.25−7.10 (m, 4H), 3.20−2.80 (m, 4H), 2.90 (dd, 1H), 2.70 (dd, 1H), 2.30 (m, 1H), 1.70−1.30 (m, 2H), 1.00−0.70 (m, 2H), 0.50 (m, 1H).

4(5)-[Spiro(cyclopropane-2′:2″-indan)-1′-yl]-4,5-dihydroimidazole, Hemifumarate (diastereomer 1, 20a). A solution of compound **55c** (1.5 g, 6.3 mmol) and formamidine acetate (654 mg, 6.3 mmol) in EtOH (100 mL) was stirred for 14 h at room temperature. EtOH was then evaporated under reduced pressure and the white solid was taken up in acetone (75 mL) and *i*-PrOH (10 mL). The solution was filtered and fumaric acid (694 mg, 6.3 mmol), dissolved by gentle warming in acetone (25 mL) and *i*-PrOH (10 mL), was added. The solid **20a** was collected by filtration and dried under vacuum as a white powder (66%), mp 212 °C. ^1H NMR (DMSO-d_6): δ 8.20 (s, 1H), 7.25−7.10 (m, 4H), 6.65 (s, 1H), 4.10 (m, 1H), 3.95−3.75 (m, 2H), 3.45−3.15 (m, 2H), 2.80 (m, 2H), 1.35 (m, 1H), 0.95 (m, 1H), 0.60 (m, 1H). Anal. ($C_{14}H_{16}N_2$·$0.5C_4H_4O_4$) C, H, N.

4(5)-[Spiro(cyclopropane-2′:2″-indan)-1′-yl]-4,5-dihydroimidazole, Fumarate (diastereomer 2, 20b). Starting from the diamine **55d** (diastereomer 2), the compound was obtained as described for **20a**, **20b** (68%), mp 178 °C. ^1H NMR (DMSO-d_6): δ 8.25 (s, 1H), 7.30−7.10 (m, 4H), 6.45 (s, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.50 (m, 1H), 3.15−2.65 (m, 4H), 1.20 (m, 1H), 0.90 (m, 1H), 0.70 (m, 1H). Anal. ($C_{14}H_{16}N_2$·$C_4H_4O_4$) C, H, N.

Spiro[(1,3-diazacyclopent-1-ene)-5:2′-(*trans*-1′,2′,3′,4′,4′a,9′,9′a,10′-octahydroanthracene)], Fumarate (21a). 7-(2-Bromobenzyl)-1,4-dioxaspiro[4.5]decan-8-one (56). To a THF solution of lithium diisopropylamide (1 M, 150 mL) cooled to −78 °C under N_2 was added dropwise a solution of 1,4-cyclohexanedione monoethylene ketal (20 g, 128 mmol) in THF (360 mL) and the cooling bath was removed. Stirring was continued for 1 h to give a cream colored solution. This solution was then cooled to −78 °C and 2-bromobenzyl bromide (35.2 g, 141 mmol) was added dropwise. After stirring for 30 min at −78 °C, the reaction was then allowed to warm to 0 °C and stirred 3 h at 0 °C before being partitioned between Et_2O and H_2O. The solution was extracted with Et_2O (3 × 100 mL) and the organic layer was washed with aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuo. The crude compound was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 80/20) to yield the compound **56** (20 g, 50%) as a white solid, mp 123 °C. ^1H NMR ($CDCl_3$): δ 7.50 (m, 1H), 7.20 (m, 2H), 7.05 (m, 1H), 3.95 (m, 4H), 3.35 (dd, 1H), 3.05 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.10−1.85 (m, 3H), 1.80 (m, 1H).

7-(2-Bromobenzyl)-8-methylene-1,4-dioxaspiro[4.5]decane (57). To a suspension of methyl(triphenyl)phosphonium iodide (25 g, 61.8 mmol) in toluene (50 mL) was added a toluene solution of freshly prepared sodium *t*-pentoxide (70 mL of 1 M solution) and the mixture was stirred at room temperature under N_2 for 20 min. The ketone **56** (6.70 g, 20.6 mmol) in toluene (50 mL) was then added dropwise and the mixture was refluxed for 3 h. After cooling, the reaction was hydrolyzed with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 50 mL). The extract was washed with saturated aqueous NaCl, water and dried ($MgSO_4$). Evaporation provided an oil which was purified by flash chromatography (SiO_2, toluene/cyclohexane = 60/40) to give the pure alkene **57** (6 g, 90%) as a white powder, mp 68 °C. ^1H NMR ($CDCl_3$): δ 7.55 (dd, 1H), 7.30−7.10 (m, 2H), 7.05 (m, 1H), 4.80 and 4.70 (2s, 2H), 4.00−3.80 (m, 4H), 3.20 (m, 1H), 2.85−2.60 (m, 2H), 2.50−2.25 (m, 2H), 1.85−1.60 (m, 3H), 1.60−1.40 (m, 1H).

2-Dioxolanyl-*trans*-1,2,3,4,4a,9,9a,10-octahydroanthracene (58). A solution of bromide **57** (5 g, 15.5 mmol), AIBN (510 mg, 0.02 mmol) and Bu_3SnH (6.75 g, 23.2 mmol) in toluene (750 mL) under N_2 was refluxed for 5 h 30 min. The solvent was removed under reduced pressure and the residue was stirred rapidly for 3 h with a mixture of Et_2O (120 mL) and saturated aqueous KF solution (120 mL). Filtration of the precipitate, extraction with Et_2O (3 × 40 mL), drying ($MgSO_4$) and concentration in vacuo gave an oily residue which was purified by flash chromatography (SiO_2, cyclohexane/Et_2O = 80/20) to yield the *trans*-octahydroanthracenic compound **58** (2 g, 50%), as a white solid, mp 71 °C. ^1H NMR ($CDCl_3$): δ 7.10 (m, 4H), 3.95 (m, 4H), 2.85 (m, 2H), 2.00−1.30 (m, 8H), 2.50 (m, 2H).

***trans*-3,4,4a,9,9a,10-Hexahydro-1*H*-anthracen-2-one (59).** A solution of the acetal **58** (6 g, 24.6 mmol) in acetone (100 mL) and water (25 mL) containing pyridinium tosylate (1.85 g, 7.4 mmol) was refluxed for 4 h. Excess solvent was then removed in vacuo, Et_2O (500 mL) was added and the mixture was washed with saturated aqueous Na_2CO_3 and saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 80/20) to give the ketone **59** (3.90 g, 80%) as a white solid, mp 99 °C. ^1H NMR ($CDCl_3$): δ 7.10 (m, 4H), 2.95−2.65 (m, 2H), 3.05−2.55 (m, 2H), 2.60 (m, 2H), 2.60 and 2.20 (m, 2H), 1.70 (m, 2H), 2.25 and 1.56 (m, 2H).

2-Amino-*trans*-1,2,3,4,4a,9,9a,10-octahydroanthracene-2-carbonitrile (60). To a vigorously stirred solution, maintained under N_2 and containing the above ketone **59** (1.25 g, 6.2 mmol), MeOH (30 mL) and water (15 mL) were added KCN (410 mg, 6.3 mmol) and NH_4Cl (340 mg, 6.3 mmol) successively. After stirring for 12 h at 20 °C, the solution was diluted in CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated. The residue was then treated with 7 N methanolic NH_3 solution (25 mL) and stirred in a closed vessel for 12 h at 20 °C. Evaporation under reduced pressure provided the desired aminonitrile **60** (1.39 g, 100%) as a white solid, mp 128 °C. ^1H NMR ($CDCl_3$): δ 7.10 (m, 4H), 2.90−2.85 (2t, 2H), 2.60−2.45 (m, 2H), 2.20−1.25 (m, 8H), 1.90 (m, 2H).

2-Aminomethyl-*trans*-1,2,3,4,4a,9,9a,10-octahydroanthracen-2-ylamine (61). A solution of the above aminonitrile **60** (1.39 g, 6.1 mmol) in anhydrous THF (35 mL) was added dropwise to a suspension of $LiAlH_4$ (350 mg, 9.2 mmol) in anhydrous THF (35 mL) at −20 °C under N_2. The mixture was stirred for 1 h 30 min before hydrolysis by addition of H_2O (2.3 mL), 35% aqueous NaOH (4.6 mL) and H_2O (4.9 mL). The resulting suspension was filtered and the filtrate evaporated to afford an oily residue which, after purification by flash chromatography (SiO_2, $CH_2Cl_2/CH_3OH/NH_4OH = 90/10/1$) gave a mixture of two diastereoisomers (85/15) **61a/61b** (0.505 g, 36%) as a white solid. The two diastereoisomers were separated by HPLC (Kromasil 100.10 C18, 210 nm, $CH_3CN/H_2O/CF_3CO_2H = 170/830/5$). **61a:** mp 123 °C. ^1H NMR ($CDCl_3$): δ 8.50−7.00 (m, 4H), 7.05 (m, 4H), 3.00 (s, 2H), 2.75 (m, 2H), 2.70−2.30 (m, 2H), 2.00−1.30 (m, 8H). **61b:** mp 183 °C. ^1H NMR ($CDCl_3$): δ 7.05 (m, 4H), 2.80 (m, 2H), 2.55 (s, 2H), 2.50 (m, 2H), 1.90−1.00 (m, 8H), 1.40 (m, 4H).

Spiro[(1,3-diazacyclopent-1-ene)-5:2′-(*trans*-1′,2′,3′,4′,-4′a,9′,9′a,10′-octahydroanthracene)], Fumarate (21a). A mixture of the above diamine **61a** (0.495 g, 2.2 mmol) and formamidine acetate (258 mg, 2.5 mmol) in EtOH (10 mL) was stirred at 20 °C under N_2 for 12 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with Et_2O and basified with 35% aqueous NaOH; the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the organic layer washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated. The solid residue was dissolved in EtOH (10 mL) and treated with a solution of fumaric acid (0.225 g, 1.9 mmol) in EtOH (10 mL). After evaporation and recrystallization of the residue from EtOH, compound **21a** was obtained as a white powder (0.50 g, 65%), mp 233−237 °C. ^1H NMR (TFA-d_1): δ 7.75 (s, 1H), 6.75 (s, 1H), 6.70 (m, 4H), 3.10 (s, 2H), 2.55 (m, 2H), 2.20 and 2.10 (m, 2H), 1.80 (m, 3H), 1.60 (m, 1H), 1.30 (m, 1H), 1.20 (m, 2H), 0.96 (m, 1H). Anal. ($C_{16}H_{20}N_2 \cdot C_4H_4O_4$) C, H, N.

Spiro[(1,3-diazacyclopent-1-ene)-5:2′-(*trans*-1′,2′,3′,4′,-4′a,9′,9′a,10′-octahydroanthracene)], Fumarate (21b). The derivate **21b** was prepared according to the procedure described for **21a** and obtained as a white solid, mp 215 °C. ^1H NMR (DMSO-d_6): δ 8.35 (s, 1H), 7.05 (m, 4H), 6.45 (s, 2H), 3.55 (s, 2H), 2.85−2.70 (m, 2H), 2.50−2.35 (m, 2H), 2.00−1.35 (m, 8H). Anal. ($C_{16}H_{20}N_2 \cdot C_4H_4O_4$) C, H, N.

Spiro{(1,3-diazacyclopent-1-ene)-5:3′-[spiro(cyclobutane-1′:2″-indan)]}, Fumarate (22). Indan-2,2-dicarboxylic Acid, Dimethyl Ester (63). A solution of 1,2-di(bromomethyl)benzene (**62;** 30 g, 115 mmol), dimethyl malonate (15.20 g, 115 mmol) and K_2CO_3 (31.50 g, 230 mmol) in ethylmethylacetone (600 mL) under N_2 was refluxed for 14 h. After cooling, the reaction was filtered and the filtrate evaporated. The oily residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 80/20) to give the diester **63** (16 g, 60%) as a white solid. ^1H NMR ($CDCl_3$): δ 7.15 (m, 4H), 3.75 (s, 6H), 3.65 (s, 4H).

2,2-Bis(bromomethyl)indan (64). A solution of the diester **63** (8 g, 34.2 mmol) in anhydrous THF (25 mL) and Et_2O (50 mL) was added dropwise to a suspension of $LiAlH_4$ (3.25 g, 85.5 mmol) in anhydrous THF (10 mL) and Et_2O (20 mL) at 20 °C under N_2. The mixture was stirred for 1 h 30 min before being hydrolyzed by addition of H_2O (21 mL), 35% aqueous NaOH (43 mL) and H_2O (45 mL). The resulting suspension was filtered and the filtrate evaporated to give the diol (5.79 g, 85%) as a white solid, used without further purification, mp 109 °C. ^1H NMR ($CDCl_3$): δ 7.15 (m, 4H), 3.75 (d, 4H), 2.85 (s, 4H), 2.35 (s, 2H). To a solution of diol (5.53 g, 27.4 mmol) in pyridine (20 mL) under N_2 at 0 °C was added *p*-toluenesulfonyl chloride (13 g, 68.5 mmol). After stirring for 4 h at 20 °C, the mixture was filtered and the precipitate washed with 1 N HCl and Et_2O to give the ditosylate (14 g, 100%) as a white solid, mp 135 °C. ^1H NMR ($CDCl_3$): δ 7.75 (d, 4H), 7.40 (d, 4H), 7.10 (m, 4H), 3.95 (s, 4H), 2.75 (s, 4H), 2.50 (s, 6H). A mixture of the ditosylate (14 g, 27.3 mmol) and LiBr (9.30 g, 109 mmol) in DMF (22 mL) under N_2 was refluxed for 5 h and added to approximately 40 mL of crushed ice. The reaction was extracted with Et_2O (3 × 20 mL) and the organic layer was washed with water and saturated aqueous NaCl, dried ($MgSO_4$) and evaporated under reduced pressure to give the pure compound **64** (7.20 g, 86%) as a white solid, mp 48.5 °C. ^1H NMR ($CDCl_3$): δ 7.15 (s, 4H), 3.70 (s, 4H), 3.05 (s, 4H).

Spiro[(1-amino-1-cyanocyclobutane)-3:2′-indan] (65). To a refluxing solution of NaH (2.30 g, 56 mmol), in anhydrous THF (22 mL) was added dropwise a mixture of *N*-(diphenylmethylene)aminoacetonitrile (2.46 g, 11.2 mmol) and compound **64** (3.4 g, 11.2 mmol) in anhydrous THF (22 mL). The solution was refluxed for 24 h before being cooled and hydrolyzed by addition of water. The mixture was extracted with EtOAc (3 × 60 mL) and the organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated in vacuo. The residue was then treated with 1 N HCl (30 mL) and Et_2O (30 mL) and vigorously stirred for 12 h at 20 °C. The two layers were separated and the acidic phase was washed with Et_2O, basified with 35% aqueous NaOH and extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated to give the desired aminonitrile **65** as a brown oil. ^1H NMR ($CDCl_3$): δ 7.15 (m, 4H), 3.20 (s, 2H), 3.10 (s, 2H), 2.45 (m, 4H), 1.85 (m, 2H).

Spiro[(1-aminocyclobutane)-3:2′-indan]-1-methylamine (66). A solution of the above aminonitrile **65** (1.49 g, 7.1 mmol) in 2 N methanolic NH_3 solution (140 mL) was hydrogenated over 50% aqueous Raney Nil at room temperature for 5 h. The reaction was filtered to remove the catalyst and concentrated to give an oil which was purified by flash chromatography (SiO_2, $CH_2Cl_2/CH_3OH/NH_4OH = 90/10/1$), providing the corresponding diamine **66** (1.04 g, 70%) as a pale yellow oil. ^1H NMR ($CDCl_3$): δ 7.15 (m, 5H), 3.10 and 3.00 (2s, 4H), 2.80 (s, 2H), 2.15 and 1.95 (m, 4H).

Spiro{(1,3-diazacyclopent-1-ene)-5:3′-[spiro(cyclobutane-1′:2″-indan)]}, Fumarate (22). A mixture of the above diamine **66** (1.03 g, 4.8 mmol) and formamidine acetate (0.576 g, 5.5 mmol) in EtOH (20 mL) was stirred at 20 °C under N_2 for 12 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with Et_2O and basified with 35% aqueous NaOH; the mixture was extracted with CH_2Cl_2 and the organic layer washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated. The solid residue was dissolved in EtOH (20 mL) and treated with a solution of fumaric acid (557 mg, 4.8 mmol) in EtOH (20 mL). After evaporation and recrystallization of the residue from EtOH, the derivate **22** was obtained as a white powder (1.26 g, 80%), mp 189 °C. ^1H NMR (DMSO-d_6): δ 8.05 (s, 1H), 7.20−7.00 (m, 4H), 6.45 (s, 2H), 3.95 (s, 2H), 3.00 (s, 4H), 2.35 (m, 4H). Anal. ($C_{14}H_{16}N_2 \cdot C_4H_4O_4$) C, H, N.

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4(5)-methyl-4,5-dihydroimidazole, Fumarate (23). 1-(3,4-Dihydronaphthalen-2-yl)propan-2-one (67). A vigorously stirred suspension of 2-tetralone (13.15 g, 90 mmol), (2-oxopropyl)-phosphonic acid diethyl ester (20.16 g, 104 mmol) and K_2CO_3 (24.9 g, 180 mmol) in H_2O (30 mL) was heated under reflux for 3 h. After cooling (0 °C), the mixture was diluted with water (30 mL) and extracted with ether (4 × 100 mL). The combined extracts were dried and concentrated. The resulting oily residue was purified by column chromatography (SiO_2, cyclohexane/AcOEt: 95/5) to afford **67** as a colorless oil (9 g, 54%). ^{1}H NMR ($CDCl_3$): δ 7.20−6.95 (m, 4H), 6.35 (s, 1H), 3.30 (s, 1H), 2.55 (t, 2H), 2.30 (t, 2H), 2.20 (s, 3H).

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4(5)-methyl-4,5-dihydroimidazole, Fumarate (23). Starting from the ketone **67,** the compound was obtained as described for **4a**, as a white powder (75%), mp 146−148 °C. ^{1}H NMR (DMSO-d_6): δ 8.10 (s, 1H), 7.20−6.95 (m, 4H), 6.40 (s, 2H), 6.35 (s, 1H), 3.55 (AB system, 2H), 2.70 (m, 2H), 2.50 (m, 2H), 2.20 (s, 3H), 2.30 (m, 2H), 1.35 (s, 3H). Anal. ($C_{15}H_{18}N_2{\cdot}C_4H_4O_4$) C, H, N.

4(5)-[(2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (24a,b). Ethyl (2-Methyl-1,2,3,4-tetrahydronaphthalen-1-on-2-yl)acetate (68). To a solution of 2-methyl-1-tetralone (1 g, 6.25 mmol) in anhydrous THF (50 mL), KO-*t*-Bu (0.77 g, 6.9 mmol) was added portionwise at −60 °C under a N_2 atmosphere. The reaction mixture was brought to 0 °C, stirred 1 h at that temperature and cooled again to −60 °C, when a solution of ethyl iodoacetate (1.47 g, 6.9 mmol) in anhydrous THF (2 mL) was added dropwise. The solution was maintained at −60 °C under stirring and brought to room temperature overnight. The reaction mixture was quenched by dropwise addition of water (50 mL), extracted with ether (2 × 100 mL), the pooled organic phases were washed with brine, dried ($MgSO_4$) and concentrated to afford **68** as a brown oil which was purified through column chromatography (SiO_2, cyclohexane/AcOEt = 90/10) and used without further purification. ^{1}H NMR ($CDCl_3$): δ 8.05 (m, 1H), 7.45 (m, 1H), 7.30 (m, 1H), 7.25 (m, 1H), 4.15 (q, 2H), 3.20−2.85 (d + m, 2H), 2.55−2.35 (m, 1H), 1.95 (m, 1H), 1.25 (s, 3H), 1.20 (t, 3H).

(2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetaldehyde (69). A suspension of **68** (15.3 g, 62 mmol), $NaBH_3CN$ (29.5 g, 470 mmol) and ZnI_2 (29.7 g, 93 mmol) in $(CH_2Cl)_2$ (375 mL) was heated to reflux overnight under a N_2 atmosphere. Insoluble materials were dissolved by addition of a mixture of NH_4Cl (10%, 1 L) and HCl (0.5 N, 100 mL), the aqueous phase was extracted with AcOEt (3 × 250 mL), the pooled organic phases were washed with Na_2CO_3 (10%), dried ($MgSO_4$) and concentrated to afford a mixture of ethyl (2-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetate and the corresponding alcohol (1/1) which was dissolved in anhydrous THF (100 mL) and added dropwise to a suspension of $LiAlH_4$ (1.5 g, 41 mmol) in THF (400 mL) kept at −10 °C. At the end of the addition, the temperature was raised to room temperature and the mixture stirred for 1 h. The reaction mixture was then quenched by the successive cautious additions of water (1.5 mL), NaOH (1 N, 1.5 mL) and water (3 mL). Ether (250 mL) was added and the suspension was stirred for 1.5 h, filtered and the filtrate concentrated to give 2-(2-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)ethanol (9.2 g, 75%). To a solution of this alcohol (8.6 g, 45 mmol) in THF (175 mL), IBX (13.95 g, 49 mmol) was added portionwise. The suspension was heated under reflux for 2 h, cooled and filtered. The solid was washed with THF (100 mL), the filtrates concentrated, the residue dissolved in ether (350 mL), the organic solution washed with Na_2CO_3 (10%, 100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to afford **69** as colorless oil (8.41 g, 99%) used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.20−7.00 (m, 4H), 4.15 (q, 2H), 2.85 (m, 2H), 2.65 (AB system, 2H), 2.30 (AB system, 2H), 1.85−1.55 (m, 2H), 1.25 (t, 3H), 1.10 (s, 3H).

4(5)-[(2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (24a,b). Starting from the aldehyde **69**, the compounds were obtained as described for **20a**. Diastereomer 1, **24a** (83%), mp 154 °C. ^{1}H NMR (DMSO-d_6): δ 8.10 (s, 1H), 7.05 (m, 4H), 6.40 (s, 2H), 4.25 (m, 1H), 3.95 (m, 1H), 3.30 (m, 1H), 2.75 (m, 2H), 2.50 (AB system, 2H), 1.75−1.50 (m, 4H), 0.95 (s, 3H). Anal. ($C_{15}H_{20}N_2{\cdot}C_4H_4O_4$) C, H, N. Diastereomer 2, **24b** (88%), mp 152 °C. ^{1}H NMR (DMSO-d_6): δ 8.15 (s, 1H), 7.05 (m, 4H), 6.45 (s, 2H), 4.25 (m, 1H), 4.00 (m, 1H), 3.35 (m, 1H), 2.75 (m, 2H), 2.55 (AB system, 2H), 1.75−1.45 (m, 4H), 0.95 (s, 3H). Anal. ($C_{15}H_{20}N_2{\cdot}C_4H_4O_4$) H, N; C: calcd, 66.36; found, 65.72.

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