Design, Synthesis, and Structure–Activity Relationships of a New Series of α-Adrenergic Agonists: Spiro[(1,3-diazacyclopent-1-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)]

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The contractions induced by a partial α_1-adrenoceptor agonist in cutaneous veins, such as the saphenous vein, show a particular sensitivity to changes in local temperature: the contractility to a partial α_1-adrenoceptor agonist increases when the temperature is raised, a response that contrasts to that noted with full α_1- and α_2-adrenoceptor agonists. This observation may be of importance for the treatment of the symptoms of venous insuffiency, favored during warm summer days. A new series of full and partial α-adrenergic agonists was designed and synthesized, the spiro[(1,3-diazacyclopent-1-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)] **7a**–**kk** or spiro-imidazolines. Using *in vitro* (femoral artery and saphenous vein) and *in vivo* (pithed rat) biological evaluations, structure–activity relationships could be defined which allowed the discovery of a full α_2-agonist (**34b**), a full α_1-agonist (**7s**), and a nonselective partial α_1/α_2-agonist (**7aa**) endowed with an outstanding veinotonic selectivity as compared to its effect on mean arterial pressure. The latter compound is presently undergoing extensive pharmacological and toxicological evaluations, as a clinical candidate.

Introduction

α-Adrenoceptors play a key role in the control of the vascular tone. Thus, the neurotransmitter noradrenaline, by interacting with α-adrenoceptors present on the vasculature smooth muscle cells, contracts blood vessels thereby increasing pressure. Moreover, the release of noradrenaline from peripheral and cerebral nerve endings is subject to feedback regulation via α-adrenoceptors of the α_2-subtype. The importance of the α-adrenoceptors is emphasized[1] by the existence of two classes of antihypertensive drugs: the peripheral α_1-adrenoceptor antagonists and the centrally acting α_2-adrenoceptor agonists. The field has been recently reviewed,[2–4] and the number, as well as the diversity of the molecular entities which have been evaluated in this area, is breath taking.

Cutaneous veins are very sensitive to changes in environmental physical conditions such as temperature. Using the dog saphenous vein as a model, it was previously reported that contractions to α-adrenoceptor agonists were differentially altered by local temperature changes; thus contractions to full α_1 and α_2-adrenoceptor agonists increase, while those to partial α_1-adrenoceptor agonists decrease when the temperature is decreased.[5] The reverse is true when the temperature is raised. A deficit in venous blood return, leading to venous stasis, is particulary favored during the hot days of summer. Since these symptoms can be, at least in part, counteracted by venoconstrictor agents, we hypothesized that treatment with a partial adrenoceptor agonist, which will increase venous tone specifically as temperature rises, might be preferred.

Partial and full α_1 and α_2-adrenoceptor agonists belong to two well-defined classes of chemical structures: phenylethylamines and imidazolines with exclusive structure–activity relationships[3,4] (SAR). In our present design, the imidazoline moiety was used since this class of molecules can lead to very potent ligands endowed with good pharmacokinetic characteristics, good metabolic stability, and limited toxicological liabilities.[6]

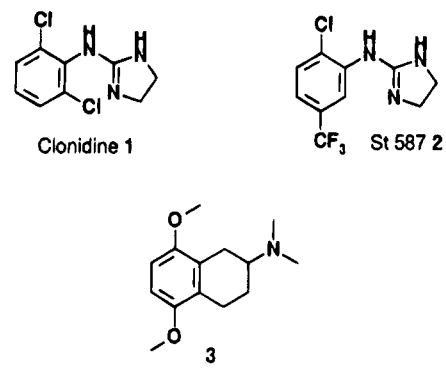

Figure 1.

A prototypical partial α_1-adrenoceptor agonist is St 587 (**2**) (Figure 1). This compound has been characterized in many different isolated organ preparations.[7] The close structural resemblance of this molecule with the partial α_2-adrenoceptor selective agonist clonidine (**1**) (Figure 1), a central antihypertensive drug,[8] indicates that the SARs dictating the α_1/α_2-adrenoceptor selectivity are very narrow.

A common feature of most of these drugs is the connectivity between the aromatic ring and one of the basic, potentially sp^2 nitrogens of the imidazoline: two atoms, a nitrogen and an sp^2 carbon. In addition, many authors[9–11] have speculated about the conformation the molecule has to adopt to interact with the receptor: the basic nitrogen must lie at a short distance above the plane of the aromatic ring with the plane of the imidazoline perpendicular to the plane of the aromatic ring, thus preventing resonance interaction between the aromatic portion and the imidazoline ring. From in-

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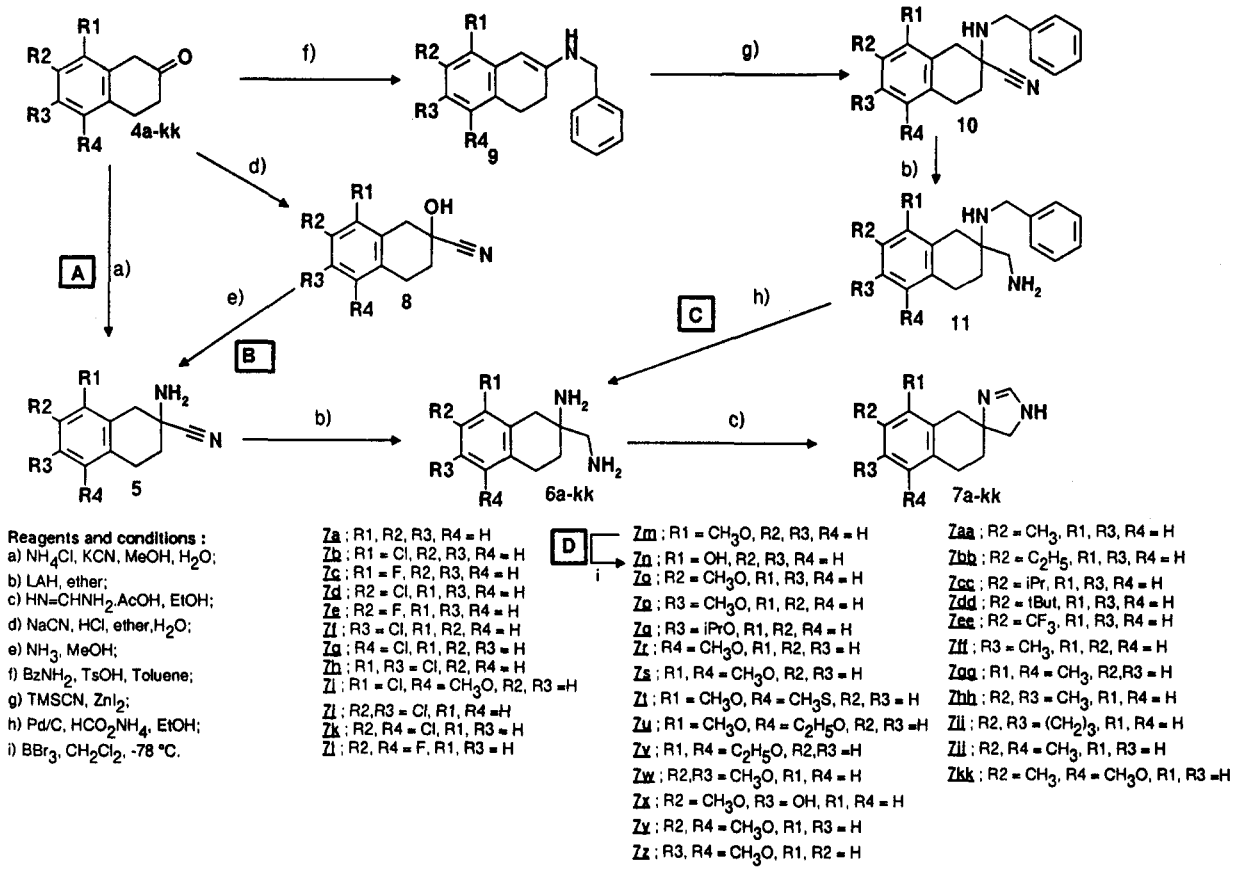
Scheme 1



vestigations related to the phenethylamines,[12] it was found that optimum activity resides in compounds where the basic nitrogen is exocyclic to a saturated six-membered ring such as in compound **3**. By combining all these elements, our design target could therefore be stipulated as an aromatic ring linked by two atoms of a saturated six-membered ring to a basic sp^2 nitrogen, the latter included in an imidazoline moiety in such a way that the imidazole plane lies perpendicular to the aromatic ring.

To fulfill these requirements, the idea of linking the imidazoline moiety to the tetraline nucleus through a spiranic carbon was investigated. Due to the tetrasubstituted nature of the carbon, it may no longer be sp^2 hybridized, and in order to keep the basic nitrogen atom sp^2 hybridized, the imidazoline ring has to be substituted in the 4(5) position instead of the classical 2 position. To our knowledge, the corresponding open form (4(5)-benzylimidazoline) has never been evaluated as a potential α-adrenergic ligand. In these structures, the two nitrogens are no longer equivalent, which in turn implies that the two tautomeric forms of the amidine are not equalized by symmetry which could potentialy lead to a decrease of affinity due to disfavored entropy change. Consideration of Dreiding models confirmed that some of the conformations of **3** could be shared by the rigid spiro-imidazoline **7**. Therefore, it was hoped that the rigidification of what was supposed to be the active conformation of agonist ligands at α-adrenoceptors would compensate for the unfavorable entropy contribution built in the 4(5)-substituted imidazolines.

The spiro-imidazolines **7a–kk** as well as the close analogues **25–28** and **32–34** were synthesized with the aim of exploring these hypotheses. The compounds were evaluated *in vitro* and *in vivo*, and the SARs were defined with the hope that an increase in venous tone could be achieved without much influence on the mean blood pressure. These efforts led to the selection of a potent partial adrenoceptor agonist which is presently in development as a potential human venotonic agent.

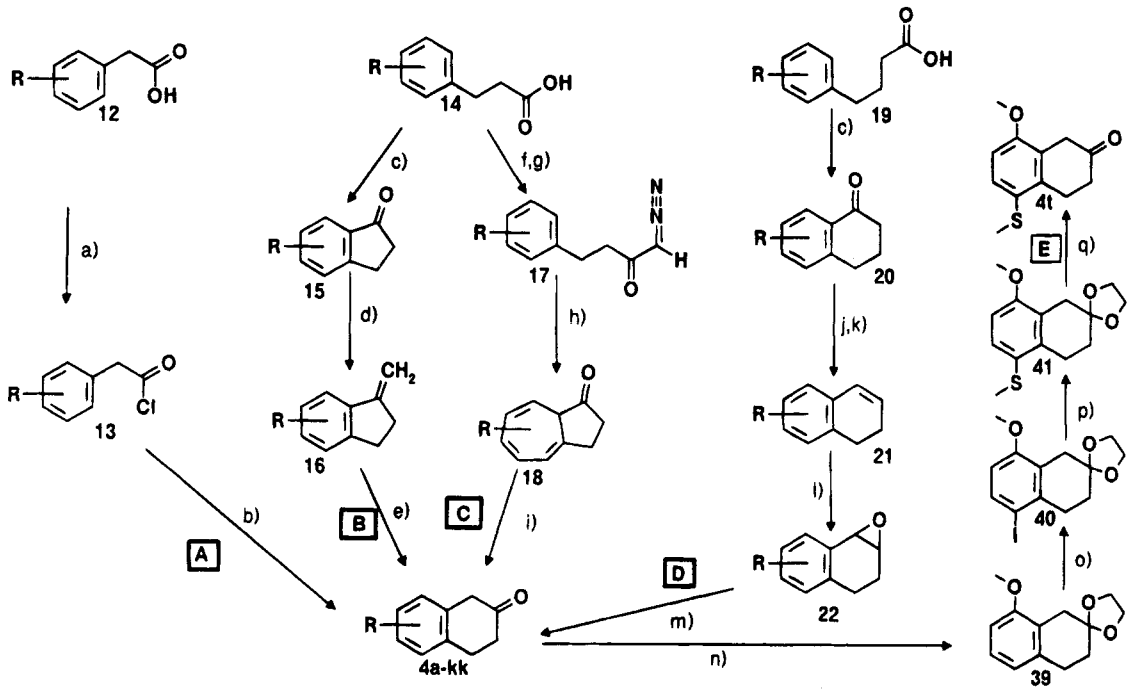
Synthesis

The spiro-imidazolines of interest, **7a–kk**, were synthesized initially through a three-step procedure starting from the tetralones **4a–kk** (Scheme 1, route A). The first step was the synthesis of the corresponding amino nitriles **5a–kk** by the Strecker reaction.[13–15] Reduction of the amino nitriles with lithium aluminum hydride in diethyl ether or tetrahydrofuran led to the ethylenediamine derivatives **6a–kk**, which in turn were cyclized by mild reaction with formamidine acetate in ethanol at room temperature to provide **7a–kk**.

In many cases, the Strecker reaction was sluggish, supposedly due to either the insolubility of the tetralones or their instability. Therefore, alternate routes were devised in order to improve the yield of this critical step. In a first variant (route B), the tetralones **4a–kk** were transformed into cyanohydrines **8a–kk** by the action of hydrocyanic acid in a two-phase (ether/water) system; treatment of these compounds with a methanolic solution of ammonia led to the corresponding amino nitriles **5a–kk** which were transformed into the spiro-imidazolines according to the procedure of method A.

In some cases, a more elaborated approach was used (method C) in which the tetralones were transformed into the enamines **9a–kk** by reaction with benzylamine

Scheme 2[a]



[a] Reagents and conditions: (a) $SOCl_2$, toluene or $SOCl_2$, DMF, $CHCl_3$; (b) $AlCl_3$, CH_2Cl_2, $CH_2{=}CH_2$; (c) PPA; (d) $Ph_3PCH_3{}^+Br^-$, KOtBu, ether; (e) $Tl(NO_3)_3$, MeOH, $CHCl_3$; (f) $(COCl)_2$, DMF, $CHCl_3$; (g) CH_2N_2; (h) $Rh(AcO)_2$, CH_2Cl_2; (i) CF_3CO_2H; (j) $NaBH_4$, EtOH; (k) TsOH, toluene; (l) mCPBA, CH_2Cl_2; (m) $BF_3{\cdot}Et_2O$, ether; (n) ethylene glycol, TsOH, Δ; (o) I_2, $Hg(OAc)_2$, AcOH; (p) CH_3SLi, Cu_2O, DMSO; (q) AcOH, H_2O.

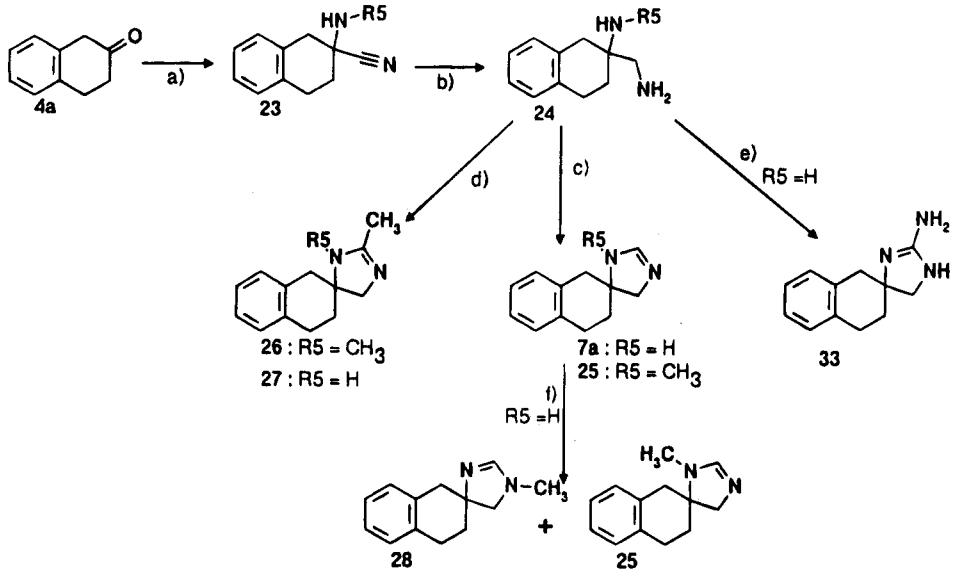
in the presence of a catalytic amount of *p*-toluenesulfonic acid and azeotropic removal of water by refluxing toluene. Unexpectedly, these enamines reacted with trimethylsilyl cyanide in the presence of zinc iodide to give the benzylamino nitriles **10a–kk**. Indeed, this route was inspired by the work of Ojima[16] who showed that the benzylimines reacted smoothly with trimethylsilyl cyanide to afford the benzylamino nitriles in the presence of zinc iodide. Therefore, we were surprised to realize that the condensation of the tetralones with benzylamine led, in all cases, to the enamines in place of the imines. Apparently the reaction of enamines with trimethylsilyl cyanide has not been reported in the litterature. The favorable course of reaction is perhaps linked to the presence of a very low concentration of the imine (undetectable in the NMR spectra) due to a putative equilibrium between the imine and the enamine allowing the reaction to go slowly to completion.

After reduction of the nitrile function with lithium aluminum hydride in diethyl ether or tetrahydrofuran, the benzyl-protected ethylenediamines **11a–kk** were produced and then transformed into **6a–kk** by debenzylation with amonium formate in the presence of palladium on carbon. The correct choice of synthetic method for a specific ethylenediamine was achieved through trial and error; today we are still unable to deduce rules pertaining to the choice of one method over another. However, experimenting with these three methods, we were always able to reach our target spiro-imidazolines.

Very few of the starting tetralones **4a–kk** were commercially available; some of them were not even described. Therefore we investigated the different known routes reported to lead to 2-tetralones (Scheme 2). From these experiences, we came up with the conclusion that depending on the substitution patterns, routes A and B are the more efficient and reliable ways to attain the different 2-tetralones **4a–kk**. Indeed, while trying to synthesize 2-tetralones with substituents in the 6 or 8 position, route A led unambiguously to the required compounds starting from the corresponding para- or ortho-substituted phenylacetic acids, respectively; whereas starting from para- or ortho-substituted phenylpropionic acids, 2-tetralones bearing substituents in the 7 or 5 position were obtained, respectively, following the procedure of route B. Route C which relied on the rhodium-catalyzed decomposition of diazo ketones led to conflicting results regarding the exact position of the substituents.[17] Finally, route D, which involves the transposition of 1-tetralones into 2-tetralones, is lengthy and limited by the availability of 4-phenylbutyric acid starting materials.

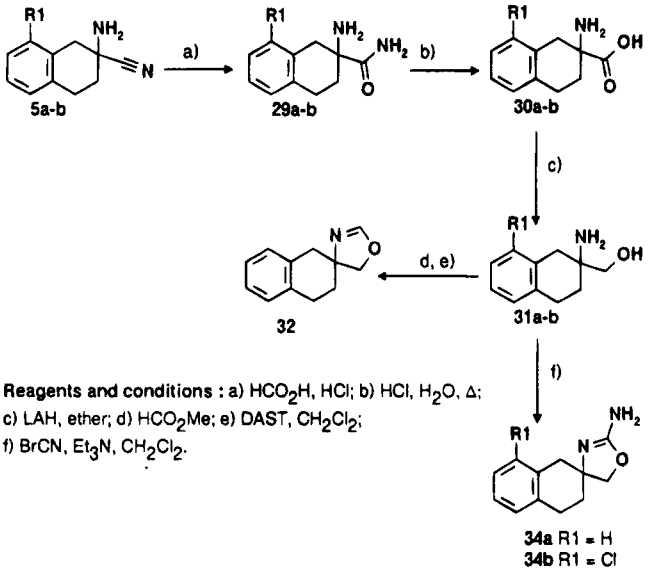
To reach the different methyl-substituted spiro-imidazolines **25**, **27**, and **28**, small variances of this synthetic scheme were elaborated. Indeed, when ammonium chloride was replaced with methylamine hydrochloride in the Strecker reaction (Scheme 3), the (methylamino)(aminomethylene)tetrahydronaphthalene derivatives **24** were obtained after the reduction step. Through condensation with formamidine acetate or acetamidine hydrochloride, the spiro-imidazolines **25** and **26** were produced, respectively. The reaction of the ethylenediamine **6a** with either acetamidine hydrochloride or cyanogen bromide (Scheme 3) led to the 2-substituted spiro-imidazolines **27** and **33**, respectively. Finally, the third methyl-substituted spiro-imidazoline isomer **28** was prepared through nonselective alkylation of the parent imidazoline **7a** with dimethyl sulfate in the presence of triethylamine followed by chromatographic separation of the two isomers (Scheme 3). The structure of **28** was unambiguously assigned by NMR spectroscopy through comparison with an authentic sample of **25** synthesized by the Strecker reaction with methylamine as described above. As expected[18] from

Scheme 3[a]

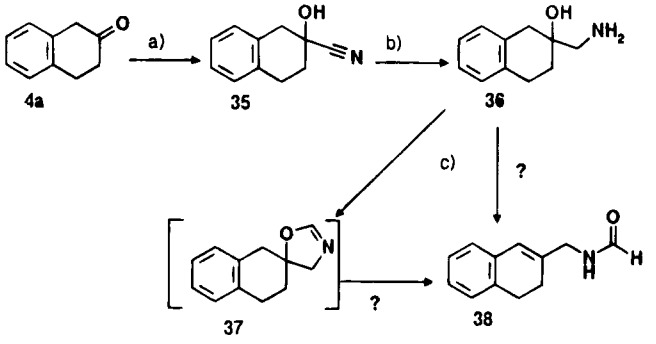


[a] Reagents and conditions: (a) CH_3NH_2·HCl, KCN, AcOH, MeOH; (b) LAH, ether; (c) HN=CHNH$_2$·AcOH, EtOH; (d) HN=C(CH_3)NH$_2$·HCl, EtOH; (e) BrCN, CH_2Cl_2, 0 °C; (f) $(CH_3O)_2SO_2$, Et_3N, CH_2Cl_2.

Scheme 4



Scheme 5[a]



[a] Reagents and conditions: (a) TMSCN, ZnI_2; (b) LAH, ether; (c) HCO_2Me.

the relative steric crowding of the two nitrogen reactive centers, the yield of **28** in the alkylation reaction was higher than the yield of **25**.

To reach spiro-oxazolines **32** and **34a,b**, a stepwise hydrolysis of the amino nitrile (Scheme 4) was necessary to prevent degradation of the amino nitrile, probably from a retro-Strecker reaction leading to the starting tetralone. Therefore, the amino amide was obtained by hydration of the nitriles **5a,b** in formic acid saturated with dry hydrochloric acid, and the amides **29a,b** were then safely hydrolyzed into the acids **30a,b**; the latter were reduced with lithium aluminum hydride into the amino alcohols **31a,b** which in turn were cyclized by either diethylaminosulfur trifluoride (DAST) or cyanogen bromide to give the spiro-oxazolines **32** and **34a,b**, respectively.

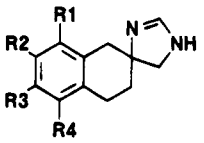
It is worth noting that attempts to synthesize the isomeric spiro-oxazoline **37** failed; this is due to the high reactivity of the quaternary hydroxyl group toward an elimination reaction leading to a compound bearing a conjugated trisubstituted double bond, **38** (Scheme 5).

Biology

The choice of the different tests used for screening was made after the evaluation in terms of reliability, time efficiency, and product throughput, of many biological assays relying to various organs from different animal species. Since the aim of our research was the discovery of new venotonic agents possessing α-adrenergic agonist properties, particular attention was paid to a possible hypertensive effect which could be a potential major side effect.

Therefore, the compounds described above were tested for their biological activity in the pithed rat (*in vivo*) and on segments of isolated canine saphenous vein and femoral artery (*in vitro*). The pithed rat assay allows the clean and quantitative determination of the impact of the tested compounds on the vascular tone defined by the dose (in μg/kg iv) which increases the arterial blood pressure by 20 mmHg (C_{20} in Tables 1 and 2). Additionally, the maximum pressure response caused by the agonist (max), expressed in mmHg, is an indication of the efficacy of the tested compounds. In the same assay, the use of selective α_1- and α_2-adrenoceptor antagonists (prazosin and yohimbine) in the presence of the tested compounds allows the definition of a C_{20} ratio (praz and yohim, respectively) which is indicative of the contribution of α_1- and α_2-adrenergic mechanisms

Table 1. *In Vitro* and *in Vivo* α-Adrenergic Activity of Compounds **7a–kk**



	structure				pithed rat				isolated blood vessel			
					control		C_{20}(antag)[c]/C_{20}(control)		femoral artery		saphenous vein	
compd	R1	R2	R3	R4	C_{20}[a]	max[b]	praz	yohim	EC_{50}[d] (μM)	E_{max}[e]	EC_{50}[d] (μM)	E_{max}[e]
2		ST 587			10 ± 3	73 ± 6	33	2.2	4.7 ± 0.7	22 ± 3	5.1 ± 1.1	81 ± 3
42		SDV NVI 085			23 ± 7	123 ± 3	5.1	2.4	38 ± 53	28 ± 11	0.023 ± 0.07	38 ± 2
7a	H	H	H	H	4 ± 0.4	120 ± 1	2	5.3	7.5 ± 2	19 ± 4	1.3 ± 0.2	99 ± 3
7b	Cl	H	H	H	0.3 ± 0.06	133 ± 3	1.9	4.7	1.6 ± 0.4	83 ± 7	0.24 ± 0.07	95 ± 2
7c	F	H	H	H	4.6 ± 1.7	131 ± 14	0.6	1	57 ± 21	75 ± 7	2.3 ± 0.9	99 ± 9
7d	H	Cl	H	H	6.3 ± 0.8	116 ± 5	2.6	5.8	ND	0	5.5 ± 1.1	72 ± 1
7e	H	F	H	H	7.8 ± 3	108 ± 6	5	7.7	ND	8 ± 0.7	11 ± 1	67 ± 7
7f	H	H	Cl	H	6.3 ± 0.8	120 ± 7	2.8	12.8	ND	0	6 ± 1	66 ± 6
7g	H	H	H	Cl	7 ± 1.4	125 ± 8	1.3	2.8	NT		NT	
7h	Cl	H	Cl	H	4.2 ± 0.5	137 ± 7	NT	NT	8 ± 2	75 ± 1	6 ± 0.7	100 ± 2
7i	Cl	H	H	CH_3O	NT		NT	NT	0.27 ± 0.16	102 ± 7	0.027 ± 0.008	106 ± 3
7j	H	Cl	Cl	H	33 ± 5	101 ± 5	7	3.1	ND	0	44 ± 36	36 ± 3
7k	H	Cl	H	Cl	19 ± 5	91 ± 10	9.5	3.1	21 ± 19	10 ± 3	2 ± 0.5	45 ± 3
7l	H	F	H	F	31 ± 10	84 ± 7	2.4	5.7	ND	0	6.3 ± 2.9	35 ± 8
7m	CH_3O	H	H	H	0.64 ± 0.2	139 ± 3	2	4.6	7.2 ± 5	97 ± 3	0.5 ± 0.1	100 ± 3
7n	OH	H	H	H	4.3 ± 0.4	119 ± 3	0.9	12	39 ± 3	22 ± 1	10 ± 4	66 ± 2
7o	H	CH_3O	H	H	1.5 ± 0.4	106 ± 6	3.9	6.9	ND	0	7.1 ± 0.3	49 ± 5
7p	H	H	CH_3O	H	42 ± 6	105 ± 7	2.6	1.5	ND	3	8.8 ± 2	60 ± 4
7q	H	H	iPrO	H	74 ± 27	62 ± 8	11	66	ND	0	3.9 ± 4	15 ± 3
7r	H	H	H	CH_3O	0.85 ± 0.2	139 ± 4	5.4	4.7	2 ± 0.7	93 ± 4	0.8 ± 0.2	101 ± 2
7s	CH_3O	H	H	CH_3O	0.05 ± 0.02	128 ± 7	21	2	0.12 ± 0.04	77 ± 4	0.3 ± 0.07	106 ± 2
7t	CH_3O	H	H	CH_3S	0.003 ± 0.01	136 ± 3	75	45	0.29 ± 0.2	96 ± 2	0.18 ± 0.13	98 ± 1
7u	CH_3O	H	H	C_2H_5O	0.06 ± 0.004	147 ± 15	21.5	4.8	0.08 ± 0.05	85 ± 5	0.8 ± 0.2	98 ± 0.5
7v	C_2H_5O	H	H	C_2H_5O	0.6 ± 0.1	157 ± 10	24	7.7	0.85 ± 0.5	55 ± 3	2.7 ± 1.3	68 ± 14
7w	H	CH_3O	CH_3O	H	98 ± 18	129 ± 10	1.8	NT	NT		NT	
7x	H	CH_3O	OH	H	1.2 ± 0.3	134 ± 7	9.2	2.8	1.4 ± 0.5	69 ± 8	19 ± 11	97 ± 1
7y	H	CH_3O	H	CH_3O	7.9 ± 1.9	109 ± 9	2.9	2.6	0.7 ± 0.7	25 ± 10	7.3 ± 3	44 ± 8
7z	H	H	CH_3O	CH_3O	142 ± 26	107 ± 4	2.9	2.4	50 ± 20	21 ± 5	52 ± 21	67 ± 13
7aa	H	CH_3	H	H	8 ± 1.5	111 ± 2	6.1	7.9	74 ± 56	5 ± 0.5	0.26 ± 0.01	64 ± 5
7bb	H	Et	H	H	209 ± 119	61 ± 13	2.5	2.6	ND	0	75 ± 57	50 ± 8
7cc	H	iPr	H	H	245 ± 44	66 ± 13	2.9	2.9	ND	0	4.3 ± 3	53 ± 20
7dd	H	tBut	H	H	465 ± 54	45 ± 1	1.7	1.6	ND	0	40 ± 2	35 ± 3
7ee	H	CF_3	H	H	320 ± 55	55 ± 8	10	2.7	ND		ND	7
7ff	H	H	CH_3	H	5.4 ± 1.3	114 ± 1	1.3	6.1	14 ± 10	12 ± 3	2.1 ± 1.1	44 ± 10
7gg	CH_3	H	H	CH_3	0.5 ± 0.09	140 ± 5	2.1	4.8	3 ± 1.7	67 ± 3	2.4 ± 1.8	84 ± 7
7hh	H	CH_3	CH_3	H	37 ± 4	72 ± 8	0.5	2.5	ND	0	2.7 ± 3.1	64 ± 13
7ii	H	$-CH_2-CH_2-CH_2-$		H	74 ± 11	68 ± 10	1.1	5	ND	0	0.07 ± 0.01	17 ± 2
7jj	H	CH_3	H	CH_3	20 ± 3.5	91 ± 10	2.9	2.8	0.8 ± 0.2	5 ± 0.5	2.9 ± 0.8	66 ± 9
7kk	H	CH_3	H	CH_3O	10 ± 6	136 ± 3	1.6	1	0.8 ± 0.5	60 ± 9	3.9 ± 1.9	81 ± 1

[a] Concentration which increases the arterial pressure by 20 mmHg in the pithed rat, expressed in μg/kg iv (mean ± SD). NT, not tested; ND, not determined due to the very low activity of the compound. [b] Maximal pressure response (mean ± SD) caused by the agonist, expressed in mmHg (the maximum obtained with phenylephrine is 150 mmHg). [c] Ratio of C_{20} obtained in the absence or presence of 0.1 mg of prazosin or 1 mg of yohimbine. [d] EC_{50} value for the agonist in the isolated blood vessel shown in μM (mean ± SD). [e] E_{max} = maximal contractile response obtained with the agonist expressed as the percentage (mean ± SD) of the maximal contraction to phenylephrine in the blood vessel indicated.

to the pressure response. The *in vitro* evaluation allows the comparison in terms of affinity (EC_{50}) and efficacy (E_{max}) on two types of vascular beds which might be responsible for either the expected therapeutic efficacy (saphenous vein) or the potential side effect (femoral artery).

Results and Discussion

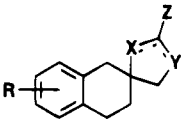
The results of the biological evaluation of the spiro-imidazolines are presented in Tables 1 and 2. A first conclusion to be drawn from these data is that a large number of active compounds was detected in this series. Moreover, the unsubstituted spiro-imidazoline **7a** is a very potent compound as compared to the 2-(phenylamino)imidazoline series (e.g., ST 587 and clonidine) where a 2,6 or 2,5 substitution pattern is requisite for high activity. A possible explanation is that the relative geometry of the nitrogen and the aromatic ring in the spiro-imidazolines fits particularly well the pharmacophore geometry of the adrenergic receptor agonist conformation.

A further interpretation of these tables in terms of SAR illustrated that the set of compounds emcompasses the whole spectra of α-adrenergic activities; indeed, the substances cover the whole range from full to partial α_1/α_2-adrenoceptor agonists.

From the hypothesis stated above, it is suspected that the nitrogen which mimicks the basic function of noradrenaline is N1 of the spiro-imidazoline. In addition, it might be that this nitrogen needs to be sp^2 hybridized.

In the spiro-imidazolines, there are two tautomeric forms: one with N1 sp^2 hybridized and the other with

Table 2. *In Vitro* and *in Vivo* α-Adrenergic Activity of Compounds **25–34b**



					pithed rat				isolated blood vessel			
	structure				control		C_{20}(antag)[c]/C_{20}(control)		femoral artery		saphenous vein	
compd	R	X	Y	Z	C_{20}[a]	max[b]	praz	yohim	EC_{50}[d] (μM)	E_{max}[e]	EC_{50}[d] (μM)	E_{max}[e]
7a	H	N	NH	H	4 ± 0.4	120 ± 3	2	5.3	7.5 ± 2	19 ± 4	1.3 ± 0.2	99 ± 3
25	H	NCH_3	N	H	675 ± 138	73 ± 28	1.55	1.9	ND	0	ND	0
26	H	NCH_3	N	CH_3	1059 ± 237	73 ± 27	1	1.1	ND	0	ND	0
27	H	N	NH	CH_3	166 ± 32	113 ± 7	1.8	5.3	ND	0	400 ± 27	23 ± 6
28	H	N	NCH_3	H	150 ± 27	77 ± 8	2.1	2.5	ND	0	25 ± 10	31 ± 6
32	H	N	O	H	>10,000	38	ND	ND	ND	0	ND	0
33	H	N	NH	NH_2	57 ± 4	53 ± 6	2.5	26	50 (2)	2	52 ± 3	36 ± 9
34a	H	N	O	NH_2	5.2 ± 0.9	95 ± 11	3.5	19.6	26 ± 23	18 ± 7	2.3 ± 0.3	76 ± 6
34b	8-Cl	N	O	NH_2	0.2 ± 0.02	140 ± 5	2	3	0.36 ± 0.09	68 ± 1	0.014 ± 0.04	117 ± 7

[a] Concentration which increases the arterial pressure by 20 mmHg in the pithed rat, expressed in μg/kg iv (mean ± SD). NT, not tested; ND, not determined due to the very low activity of the compound. [b] Maximal pressure response (mean ± SD) caused by the agonist, expressed in mmHg (the maximum obtained with phenylephrine is 150 mmHg). [c] Ratio of C_{20} obtained in the absence or presence of 0.1 mg of prazosin or 1 mg of yohimbine. [d] EC_{50} value for the agonist in the isolated blood vessel shown in μM (mean ± SD). [e] E_{max} = maximal contractile response obtained with the agonist expressed as the percentage (mean ± SD) of the maximal contraction to phenylephrine in the blood vessel indicated.

N3 sp^2 hybridized. To check which one of the two tautomers is actually present as the active ligand, the methyl-substituted spiro-imidazolines **25** and **28** were synthesized. It is clear from the activity of compound **27** that the steric crowding caused by a methyl in this area of the molecule has a dramatic negative influence. In terms of basicity, the influence of the methyl group on the delocalized amidine system must be the same for the two compounds. Therefore, the small difference in activity between the two compounds might correspond to a relatively better fit of the 3-substituted imidazoline (N1 being sp^2 hybridized) **28** than the 1-substituted imidazoline (N3 being sp^2 hybridized) **25**, which is in agreement with the hypothesis. Due to the lack of a strong discriminative activity with these compounds, the isomeric spiro-oxazolines **32** and **37** were synthesized with the aim of corroborating the hypothesis. As mentioned earlier, **37** is not stable and isomerized into **38**; in contrast, **32** was stable enough to be evaluated but was almost completely inactive. This might be the consequence of the very low basicity of oxazolines as compared to imidazolines. To increase the basicity of the nitrogen atom, the 2-aminoimidazoline **33** and 2-aminooxazoline **34a** were synthesized and provided much more active compounds. A delocalized basic function was restored which, when protonated, bears only one sp^2-hybridized atom: the C2.

Full adrenoceptor agonists in Table 1 and 2 are identified through the comparison of the E_{max} values in the femoral artery and saphenous vein preparations. When the values of the E_{max} are high and almost identical to each other whether the receptor reserve is small (femoral artery) or large (saphenous vein),[19,20] the compounds behave as full agonists as in cases **7b,c,h,i,m,r–u**. This is further emphasized by the observation that these compounds produce maximal pressor responses in the pithed rat comparable to those produced by the full α_1-adrenoceptor agonist phenylephrine.[21] The use of the latter criterion alone would have led to the selection of many misleading compounds such as **7a,d,f,g,n,v,w,x,gg,kk**. All the structures mentioned above but one, **7r**, share a common structural feature, that is, a substituent in the 8 position (R1 ≠ H) of the tetrahydronaphthalene portion of the molecule.

The α_1/α_2-adrenoceptor selectivity of the compounds was tested by comparing of the C_{20} values in the presence of prazosin, a selective α_1-adrenoceptor antagonist,[22] or yohimbine, a selective α_2-adrenoceptor antagonist.[23] The sensitivity to the antagonists is expressed by the ratio of the C_{20} in their presence or absence: *r*(praz) and *r*(yohim) in Tables 1 and 2. This analysis indicates that selective α_2-adrenoceptor agonists bear a substituent only in position 8 (R1 ≠ H) such as **7b,m**, while selective α_1-adrenoceptor agonists possess substituents in positions 5 and 8 (R1 and R4 ≠ H) such as **7s–u**. Similar relationships existed for the partial agonists such as **7n** and **34b** for the selective α_2 compounds and **7v** for the selective α_1 compounds, **7gg** being an exception to this rule.

In addition, it appears from Table 2 that successful modifications of the heterocycle spiro-imidazolines always lead to selective α_2 compounds, for example, compare **7a** with 2-amino-spiro-imidazoline **33** and 2-amino-spiro-oxazoline **34a**. However, the effect of substitution of the tetrahydronaphthalene and the effect of the modification of the heterocycle is not cummulative as **34b** shows only limited selectivity for the α_2-adrenoceptor.

Graphically, the conclusions could be represented by the three Markus formulae of Figure 2, where structure I represents mainly the selective α_2-adrenoceptor agonists, structure II the selective α_1-adrenoceptor agonists, and structure III the nonselective partial α-adrenoceptor agonists of various efficacy. It is clear from this picture that the SARs so far described are in agreement with previous data from the literature since structure I can mimic the substitution pattern of clonidine (**1**), a partial α_2-adrenoceptor agonist, and structure II represents the kind of substitution prevailing in ST 587 (**2**) and SDV NVI 085 (**42**),[24] two partial α_1-adrenoceptor agonists.[25]

A major goal of the present project was to detect compounds acting specifically on the veins while minimally affecting mean blood pressure. From the results of the biological evaluations presented in Tables 1 and

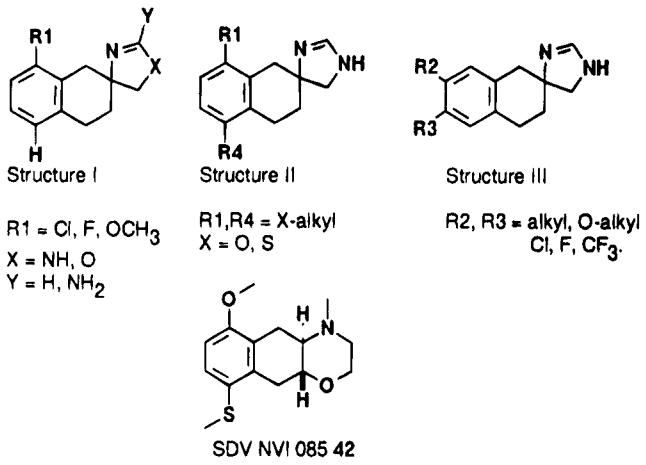


Figure 2.

Table 3. Ratio C_{20}/EC_{50} of Selected Compounds **7**

compd	C_{20} (μg/kg) pithed rat[a]	EC_{50} (μM) saphenous vein[b]	ratio C_{20}/EC_{50}
7d	6.3 ± 0.8	5.5 ± 1.1	1.15
7e	7.8 ± 3	11 ± 1	0.71
7f	6.3 ± 0.8	6 ± 1	1.05
7o	1.5 ± 0.4	7.1 ± 0.3	0.21
7p	42 ± 6	8.8 ± 2	4.77
7aa	8 ± 1.5	0.26 ± 0.01	31
7cc	245 ± 44	4.3 ± 3	57
7hh	37 ± 4	2.7 ± 3	14
7ii	74 ± 11	0.07 ± 0.01	1,057
7jj	20 ± 3.5	0.8 ± 0.5	25

[a] Concentration which increases the arterial pressure by 20 mmHg in the pithed rat, expressed in μg/kg iv (mean ± SD). [b] EC_{50} value for the agonist in the isolated blood vessel shown in μM (mean ± SD).

2, it is obvious that such compounds have been detected. For instance, by comparing the EC_{50} and E_{max} values on veins and arteries for compounds **7d–f,o,p,aa,cc,hh–jj**, a high level of selectivity for venous tissues could be detected since all these compounds powerfully contracted the veins but possessed very limited activity on arteries with EC_{50} values too low to be defined. Another way of specifying the venous selectivity was by calculating the empirical ratio between the C_{20} value in the pithed rat and the EC_{50} value obtained in the vein. The use of this ratio proved to be more discriminating than the use of the ratio of EC_{50} arteries versus veins since many compounds were only poorly active on the arteries *in vitro*.

Using the ratio reported in Table 3, it is possible to rank the molecules starting from the most selective compound to the least selective one: **7ii** > **7cc** > **7aa** > **7ii** > **7hh** > **7p** ≅ **7o** ≅ **7d** ≅ **7f** ≅ **7e**. The compounds of Table 3 present a very high structural homogeneity, in the sense that they all bear a substituent in the 6 and/or 7 position of the tetrahydronaphthalene (R2 and/or R3 ≠ H) and only in these positions. In addition, regarding the best profile, one can deduce that the better substituent is an alkyl (methylene, methyl, or isopropyl) in position 7; indeed, the first five of the eight compounds which have been ranked contain such a substituent. In terms of pharmacological characterization, the results of Table 1 indicate that these compounds obviously behave as partial adrenergic agonists with a low selectivity for the α-adrenoceptor subtypes. Despite this lack of selectivity, compound **7aa** proved to be the most interesting venotonic agent detected in this series. The design of the molecule was built from known compounds having known pharmacology, but the desired compound was a molecule endowed with a unique pharmacological profile. Therefore, the spiro-imidazolines were investigated in the search for the optimum compound, not knowing if this goal was realistic or not. At the start of the program, neither the exact selectivity between the α_1- and α_2-adrenoceptors nor the efficacy at each adrenoceptor site, necessary to fulfill our target, could be anticipated. Today, it is our goal to defined the exact pharmacology of our lead compound and the mechanism of the physiological effects measured.

Table 4. Binding Affinities (K_i, μM) of Selected Spiro-imidazolines for the α_1-, α_{2a}-, and α_{2b}-Adrenergic Sites

compd	α_1 rat cortex[a]	α_{2a} human platelets[a]	α_{2b} neonatal rat lung[a]
2	65.8	1.56	0.179
7a	14.4	0.034	0.275
7c	2.5	0.012	0.152
7k	0.7	0.003	0.095
7m	16	0.051	0.099
7o	16	0.018	0.193
7p	29.4	0.087	1.2
7r	3.4	0.012	0.159
7s	2		
7t	0.6		
7aa	1	0.007	0.05
7kk	0.6		
34b	0.8	0.0016	0.02

[a] Mean of at least three independent determinations made in duplicate. The standard deviations were always less than 45% of the geometric mean.

Extensive binding evaluation of the compounds described has not been performed because the pharmacological results obtained with several of the initial molecules synthesized were disappointing. Table 4 shows the results of this evaluation regarding the α_1-site and two subtypes of the α_2-adrenergic receptor, the α_{2a} and the α_{2b}. The affinities detected in the α_2 binding tests are well in line with the data collected in the isolated organs and the *in vivo* assays; the affinities detected for the α_1 binding site are much weaker than could be expected from the result of the saphenous vein assays for instance. Indeed, for a full agonist, the EC_{50} values should be in the same range as the K_i, and for a partial agonist, the EC_{50} values should be larger than the K_i.[26] Comparing the results of Table 4 with the results of Tables 1 and 2, it is illustrated that in most cases the K_i is larger than the EC_{50}, even when the compound clearly behaves as a partial agonist (**7aa**). We suspect that α_1-agonist binding is not correctly measured by the displacement of a tritiated antagonist such as prazosin.[27] Indeed, for some receptors, agonist binding needs to be defined by the displacement of a labeled agonist, while affinities of antagonists can only be correctly measured by the displacement of labeled antagonists.[28]

In conclusion, by developing a new family of adrenoceptor ligands derived from a spiro-imidazoline skeleton, we were able to define SARs leading to the discovery of a full α_2-adrenoceptor agonist (**34b**, S 17824-1), a full α_1-adrenoceptor agonist (**7s**, S 17265-1), and a nonselective partial α_1/α_2-adrenoceptor agonist (**7aa**, S 17089-1) endowed with an outstanding venous selectivity. The latter compound is presently undergoing extensive pharmacological and toxicological evaluation as a clini-

cal candidate. Reports dealing with the resolution of the two enantiomers of **7aa** as well as with its complete pharmacological characterization are currently in preparation.

Experimental Section

Biology. Pithed Rat. Male Sprague–Dawley rats (300–400 g) were anesthetized with ether. After cannulation of the trachea, the animals were pithed (to destroy the spinal cord) and immediately placed under artificial ventilation. The vagus nerves were sectioned, and the carotid arteries were ligated. One of the carotid arteries was cannulated for monitoring of the arterial blood pressure. Three more catheters were inserted into both jugular veins and the penile vein; these catheters were used for injection of compounds. The body temperature of the animals was maintained at 36 °C. The animals were pretreated with a dose of the β-adrenoceptor blocker tertatolol (100 mg/kg) and, in some cases, 10 min later with either the α_1-adrenoceptor antagonist prazosin (100 μg/kg) or the α_2-adrenoceptor antagonist yohimbine (1 mg/kg). Another 10 min later, cumulative doses of the compounds to be tested were injected at 20 s intervals. The changes in arterial pressure were recorded with a pressure transducer (Statham P23XL) and expressed in mmHg. The experimental setup allows the calculation of the dose which augments the arterial pressure with 20 mmHg (C_{20}) as well as the maximal effect of the compound which is expressed in mmHg. The reference α_1-adrenoceptor agonist phenylephrine augments arterial pressure maximally by 150 mmHg. The results are expressed as the mean (±SD) of three to six independent determinations. The α_1- or α_2-adrenergic properties of the compounds are evaluated by comparing the C_{20} values in the presence and absence of either prazosin or yohimbine by calculating the ratio C_{20}(antagonist)/C_{20}(control).

Isolated Blood Vessels. These experiments were performed on blood vessels obtained from mongrel dogs (weight 15–25 kg) anesthetized with sodium pentobarbital (30 mg/kg iv) using a technique previously described.[19] After anesthesia, saphenous vein and femoral artery segments were prepared and immediately placed in physiological saline solution (composition in mM: NaCl, 118; KCl, 4.7; $NaHCO_3$, 25; $CaCl_2$, 1.25; $MgSO_4$, 1.2; KH_2PO_4, 1.1; and glucose, 10). Rings were prepared from the blood vessels, and they were mounted under a tension of 4 g (femoral artery) or 1 g (saphenous vein) in organ chambers filled with the salt solution at 37 °C and oxygenated with 95% O_2/5% CO_2. The isometric tension development was continuously monitored via a force transducer (Statham) coupled to a computerized measuring system. After mounting, the tissues were allowed to equilibrate for 90 min prior to experimentation; the organ bath solution was replaced every 30 min. The blood vessels were then incubated, throughout the duration of the experiments, in physiological saline solution containing rauwolscine (10^{-7} M) in order to block the α_2-adrenoceptors. After readjustment of the basal tension, a contraction was evoked in each tissue with KCl (100 mM). After rinsing and return to base line conditions, a contraction was induced with a submaximal concentration of phenylephrine (1 μM). After rinsing and return to basal conditions, a concentration–response curve was performed with one of the putative α-adrenoceptor agonists using increasing concentrations separated by ½ log. This allowed determination of the maximal contraction to the agonist and calculation of the EC_{50} value (concentration that caused half-maximal contraction) using standard regression analysis techniques. Those values are the mean (±SD) of three to six independent determinations, unless otherwise indicated (2), and are used to compare the activities of the different substances in arterial and venous tissues.

Radioligand-Binding Assays. Binding to rat (α_1[29] and α_{2b}[30]) and human (α_{2a}[31]) adrenergic receptors was measured using [^{3}H]prazosin (0.3 nM) in rat cortex and [^{3}H]RX821002 (0.5 and 1.5 nM) in neonatal rat lung and human platelets, respectively. For each receptor, data were collected for a key reference ligand, prazosin (K_i = 0.14 nM) or phentolamine (K_i = 11 and 14 nM), respectively. Nonspecific binding was defined in the presence of cold prazosin (10 μM) and phentolamine (10 μM); the percentage of specific binding was 87%, 90%, and 95%, respectively. Drugs were tested on the specific binding for the three receptors. IC_{50} values for the displacement of the [^{3}H]radioligands were determinated by log-probit analysis of data from inhibition experiments in which nine concentrations of drugs spanning 3 orders of magnitude were used. K_i values were calculated according to the equation:[32] $K_i = IC_{50}/(1 + L/K_d)$ with L the concentration and K_d the apparent dissociation constant of the [^{3}H]ligand obtained from Scatchard analysis of saturation experiment data. Each K_i value was determined in at least three independent experiments made in duplicate.

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 agree with the calculated values within the ±0.4% range. 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 was performed on precoated 5 × 10 cm, Merck silica gel 60 F254 plates (layer thickness 0.25 mm).

Synthesis of Tetralones. Route B. Synthesis of Precursors (Substituted Phenylpropionic Acids). Ethyl 3-(2-Ethoxy-5-methoxyphenyl)prop-2-enoate. Maintaining a reaction temperature of 5–10 °C, a solution of ethyl diethylphosphonoacetate (6.30 g, 280 mmol) in toluene (230 mL) was added dropwise, under N_2, to a cooled (5 °C), stirred suspension of NaH (6.70 g, 280 mmol) in toluene (200 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. A solution of 2-ethoxy-5-methoxybenzaldehyde[33] (50.5 g, 280 mmol) in toluene (200 mL) was added dropwise and the medium stirred at 20 °C overnight. The mixture was poured onto ice/water (2 L) and extracted with Et_2O (2 × 500 mL). The organic layers were dried and concentrated under vacuum to give the crude cinnamate as an oil (52.5 g, 75%), used without further purification for the next step. ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 1H), 6.50 (d, 1H), 7.05 (d, 1H), 6.90–6.75 (m, 2H), 4.25 (q, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 1.40 (t, 3H), 1.30 (t, 3H).

Ethyl 3-(2,5-Diethoxyphenyl)prop-2-enoate. Using the above procedure, but starting from 2,5-diethoxybenzaldehyde,[34] ethyl (2,5-diethoxyphenyl)propenoate was obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 1H), 7.05 (d, 1H), 6.90 (dd, 1H), 6.85 (d, 1H), 6.85 (d, 1H), 6.50 (d, 1H), 4.25 (q, 2H), 4.15–3.90 (2q, 4H), 1.50–1.20 (3t, 9H).

Ethyl 3-(2-Ethoxy-5-methoxyphenyl)propanoate. Reduction of the above cinnamate (50 g, 200 mmol) under 1 atm of H_2 and in the presence of a catalytic amount of 10% Pd/C in EtOH (700 mL), followed by filtration and evaporation of the solvent, yielded the propanoate as a white solid (49.5 g, 98%). ^{1}H NMR ($CDCl_3$): δ (m, 3H), 4.15 (q, 2H), 4.00 (q, 2H), 3.75 (s, 3H), 2.90 (m, 2H), 2.60 (m, 2H), 1.35 (t, 3H).

Ethyl 3-(2,5-Diethoxyphenyl)propanoate. The above procedure applied to ethyl 3-(2,5-diethoxyphenyl)prop-2-enoate provided a solid, mp 125–126 °C. ^{1}H NMR ($CDCl_3$): δ 6.80–6.60 (m, 3H), 4.10 (q, 2H), 4.00 (m, 4H), 2.90 (m, 2H), 2.60 (m, 2H), 1.35 (2t, 6H), 1.25 (t, 3H).

3-(2-Ethoxy-5-methoxyphenyl)propanoic Acid (14u). Saponification of the corresponding ethyl ester (48 g, 190 mmol) with NaOH (2 N, 200 mL) in EtOH (350 mL) and acid workup gave the desired acid (41.50 g, 97%), mp 160–162 °C. ^{1}H NMR (DMSO-d_6): δ 12.10 (br d, 1H), 6.85 (d, 1H), 6.70 (dd, 1H), 4.00 (q, 2H), 3.65 (s, 3H), 2.75 (m, 2H), 2.50 (m, 2H), 1.30 (t, 3H).

3-(2,5-Diethoxyphenyl)propanoic Acid (14v). 14v was prepared in a similar fashion from the corresponding ester, mp 173–174 °C. ^{1}H NMR (DMSO-d_6): δ 12.00 (br d, 1H), 6.80 (d, 1H), 6.70 (d, 1H), 6.65 (dd, 1H), 4.00–3.80 (2q, 4H), 2.75 (m, 2H), 2.45 (m, 2H), 1.45–1.20 (2t, 6H).

Step a: 6-Ethyl-1-indanone (15bb). 3-(4-Ethylphenyl)-propanoic acid[35] (30 g, 168 mmol) was added portionwise to 500 g of polyphosphoric acid (PPA), warmed up to 60 °C. The mixture was stirred at 80 °C for 1 h, the reaction quenched with an ice/water mixture, and then the mixture extracted with CH_2Cl_2. Combined extracts were washed with water, dried ($MgSO_4$), and concentrated under vacuum to yield the indanone **15bb** (26 g, 97%) as a yellow solid. A sample was recrystallized to analytical purity from hexane, mp 55–56 °C. ^1H NMR ($CDCl_3$): δ 7.60 (d, 1H), 7.45 (dd, 1H), 7.40 (d, 1H), 3.10 (m, 2H), 2.70 (q, 2H), 2.65 (m, 2H), 1.25 (t, 3H).

The following compounds were obtained in the same manner.

6-Isopropyl-1-indanone (15cc): mp 73–74 °C. ^1H NMR ($CDCl_3$): δ 7.65 (m, 1H), 7.50 (dd, 1H), 7.45 (d, 1H), 3.10 (m, 2H), 3.00 (m, 1H), 2.70 (m, 2H), 1.25 (d, 6H).

6-*tert*-Butyl-1-indanone (15dd): mp 94–95 °C. ^1H NMR ($CDCl_3$): δ 7.80 (d, 1H), 7.70 (dd, 1H), 7.45 (d, 1H), 3.10 (m, 2H), 2.70 (m, 2H), 1.35 (s, 9H).

4-Ethoxy-7-methoxy-1-indanone (15u): oil. ^1H NMR ($CDCl_3$): δ 7.00 (d, 1H), 6.70 (d, 1H), 4.05 (q, 2H), 3.90 (s, 3H), 3.10–2.60 (m, 4H), 1.40 (t, 3H).

4,7-Diethoxy-1-indanone (15v): oil. ^1H NMR ($CDCl_3$): δ 6.65 (AB system, 2H), 4.05 (q, 4H), 3.10–2.60 (m, 4H), 1.40 (2t, 6H).

Step b: 6-Ethyl-1-methyleneindan (16bb). Following the procedure of Cannon et al.,[36] methyltriphenylphosphonium bromide (103 g, 284 mmol) and KOtBu (31.90 g, 284 mmol) were added successively to a solution of **15bb** (23 g, 143 mmol) in Et_2O (500 mL) and CH_2Cl_2 (160 mL). After stirring at 20 °C under N_2 for 1 h, the mixture was diluted with water (800 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The oily brown residue was purified by chromatography (SiO_2, cyclohexane as eluent) to give a pale yellow solid (12.40 g, 55%), mp 72–73 °C. ^1H NMR ($CDCl_3$): δ 7.30 (d, 1H), 7.20 (d, 1H), 7.05 (dd, 1H), 5.45 (m, 1H), 5.00 (m, 1H), 3.00–2.70 (m, 4H), 2.60 (q, 2H), 1.25 (t, 3H).

The following compounds were prepared by the above procedure.

6-Isopropyl-1-methyleneindan (16cc): mp 78–79 °C. ^1H NMR ($CDCl_3$): δ 7.35 (m, 1H), 7.25–7.05 (m, 2H), 5.45 (m, 1H), 5.00 (m, 1H), 5.00 (m, 1H), 3.00–2.70 (m, 5H), 1.35 (d, 6H).

6-*tert*-Butyl-1-methyleneindan (16dd): mp 87–88 °C. ^1H NMR ($CDCl_3$): δ 7.55 (d, 1H), 7.30 (dd, 1H), 7.20 (d, 1H), 5.45 (m, 1H), 5.00 (m, 1H), 2.95 (m, 2H), 2.80 (m, 2H), 1.35 (s, 9H).

5,6-Dimethyl-1-methyleneindan (16hh): starting from the known 5,6-dimethyl-1-indanone,[37] oil. ^1H NMR ($CDCl_3$): δ 7.25 (s, 1H), 7.00 (s, 1H), 5.35 (m, 1H), 4.95 (m, 1H), 3.00–2.70 (m, 4H), 2.25 (s, 6H).

3,5,6,7-Tetrahydro-1-methylene-1*H*-*s*-indacene (16ii): starting from the corresponding known indanone,[35] mp 104–105 °C. ^1H NMR ($CDCl_3$): δ 7.35 (s, 1H), 7.10 (s, 1H), 5.40 (m, 1H), 4.95 (br s, 1H), 3.05–2.75 (m, 8H), 2.25–2.00 (m, 2H).

4-Ethoxy-7-methoxy-1-methyleneindan (16u): oil. ^1H NMR ($CDCl_3$): δ 6.90 (d, 1H), 6.70 (d, 1H), 5.90 (m, 1H), 5.15 (m, 1H), 4.05 (q, 2H), 3.90 (s, 3H), 3.00–2.70 (m, 4H), 1.40 (t, 3H).

4,7-Diethoxy-1-methyleneindan (16v): mp 90–91 °C. ^1H NMR ($CDCl_3$): δ 6.60 (s, 2H), 5.90 (m, 1H), 5.15 (m, 1H), 4.15–3.90 (m, 4H), 3.00–2.70 (m, 4H), 1.55–1.30 (2t, 6H).

Step c: 1,2,3,4-Tetrahydro-7-ethyl-2(1*H*)-naphthalenone (4bb). Using the procedure of Cannon et al.,[34] a freshly prepared solution of $Tl(NO_3)_3$ (25.30 g, 57 mmol) in MeOH (75 mL) was added in one portion to a solution of **16bb** (9.0 g, 57 mmol) in MeOH (180 mL). The mixture was stirred for 10 min and then diluted with CH_2Cl_2 (300 mL). The resulting precipitate was removed by filtration and the filtrate washed with saturated aqueous $NaHCO_3$ and water before drying ($MgSO_4$) and concentrating under reduced pressure. The residue was purified by chromatography (SiO_2, CH_2Cl_2) to afford the tetralone **4bb** as a pale yellow solid (6.50 g, 66%), mp 85–86 °C. ^1H NMR ($CDCl_3$): δ 7.15 (d, 1H), 7.05 (dd, 1H), 6.95 (d, 1H), 3.60 (s, 2H), 3.00 (t, 2H), 2.65 (q, 2H), 2.55 (t, 2H), 1.25 (t, 3H).

The following compounds were prepared by the above procedure.

1,2,3,4-Tetrahydro-7-isopropyl-2(1*H*)-naphthalenone (4cc): mp 67–68 °C. ^1H NMR ($CDCl_3$): δ 7.20–6.90 (m, 3H), 3.55 (s, 2H), 3.05 (m, 2H), 3.20–2.75 (m, 1H), 2.55 (m, 2H), 1.25 (d, 6H).

1,2,3,4-Tetrahydro-7-*tert*-butyl-2(1*H*)-naphthalenone (4dd): mp 79–80 °C. ^1H NMR ($CDCl_3$): δ 7.30–7.10 (m, 3H), 3.60 (s, 2H), 3.05 (m, 2H), 2.55 (m, 2H), 1.30 (s, 9H).

1,2,3,4-Tetrahydro-5-ethoxy-8-methoxy-2(1*H*)-naphthalenone (4u): oil. ^1H NMR ($CDCl_3$): δ 6.70 (AB system, 2H), 4.00 (q, 2H), 3.80 (s, 3H), 3.50 (s, 2H), 3.10 (m, 2H), 2.55 (m, 2H), 1.45 (t, 3H).

1,2,3,4-Tetrahydro-5,8-diethoxy-2(1*H*)-naphthalenone (4v): mp 88–89 °C. ^1H NMR ($CDCl_3$): δ 6.70 (AB system, 2H), 4.00 (m, 4H), 3.50 (s, 2H), 3.10 (m, 2H), 2.55 (m, 2H), 1.40 (m, 6H).

Route C. Step a: 3-[4-(Trifluoromethyl)phenyl]propanoyl Chloride. A mixture of 3-[4-(trifluoromethyl)phenyl]-propanoic acid[38] (5.50 g, 25 mmol) and thionyl chloride (10 mL) in toluene (100 mL) was refluxed for 2 h. After cooling followed by evaporation under reduced pressure, the acid chloride was obtained as an oil. ^1H NMR ($CDCl_3$): δ 7.50 (m, 2H), 7.30 (m, 2H), 3.20 (m, 2H), 3.00 (m, 2H).

Step b: 1-Diazo-4-[4-(trifluoromethyl)phenyl]butan-2-one (17ee). A solution of the above acid chloride (5.20 g, 22 mmol) in ether (50 mL) was added to a cooled (−10 °C) solution of diazomethane (72 mmol) in ether (180 mL) at such a rate that the reaction temperature did not exceed 0 °C. After total addition, the temperature was allowed to rise to 20 °C and stirring was continued overnight. After evaporation of the solvent, **17ee** was obtained as a crystalline solid (5.20 g, 98%), mp 45–46 °C.

Step c: 6-(Trifluoromethyl)-3,4-dihydroazulen-1(2*H*)-one (18ee). A solution of crude **17ee** (4.90 g, 20 mmol) in CH_2Cl_2 (150 mL) was added dropwise to a boiling solution of rhodium acetate (4 mg, 0.4 mmol) in CH_2Cl_2 (200 mL). After evolution of gas had ceased, the solution was cooled and washed with water (2 × 150 mL) and saturated aqueous $NaHCO_3$ (150 mL), dried ($MgSO_4$), and concentrated. The brownish oily residue (4 g, 94%) was used for the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, 1H), 6.62 (d, 1H), 6.02 (d, 1H), 6.02 (t, 1H), 2.95 (d, 2H), 2.70 (dd, 2H), 2.66 (dd, 2H).

Step d: 1,2,3,4-Tetrahydro-7-(trifluoromethyl)-2(1*H*)-naphthalenone (4ee). A stirred solution of crude **18ee** (3.86 g, 18 mmol) in CH_2Cl_2 (80 mL) was acidified by addition of trifluoroacetic acid (TFA) (1.50 mL). After stirring at ambient temperature for 30 min, the mixture was washed with saturated aqueous $NaHCO_3$ (2 × 70 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (SiO_2) eluting with hexane/EtOAc (9/1) to afford the desired tetralone **4ee** (2.5 g, 65%) as an oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H), 7.42 (s, 1H), 7.40 (d, 1H), 3.70 (s, 2H), 3.10 (t, 2H), 2.45 (t, 2H).

1,2,3,4-Tetrahydro-5,7-dimethyl-2(1*H*)-naphthalenone (4jj). 4jj was prepared as described above for **4ee** but using 3-(3,5-dimethylphenyl)propanoic acid[39] as starting material, mp 52–53 °C. ^1H NMR ($CDCl_3$): δ 6.90 (s, 1H), 6.80 (s, 1H), 3.55 (s, 2H), 3.00 (m, 2H), 2.55 (m, 2H), 2.30 (2s, 6H).

1,2,3,4-Tetrahydro-5-methoxy-7-methyl-2(1*H*)-naphthalenone (4kk). 4kk was prepared as described for **4ee**, starting from 3-(3-methoxy-5-methylphenyl)propanoic acid.[40] ^1H NMR ($CDCl_3$): δ 6.60–6.50 (d, 2H), 3.80 (s, 3H), 3.55 (s, 2H), 3.05 (m, 2H), 2.50 (m, 2H), 2.30 (s, 3H).

1,2,3,4-Tetrahydro-5-methoxy-8-chloro-2(1*H*)-naphthalenone (4i). The procedure described for **4ee** was employed. Starting from 3-(2-chloro-5-methoxyphenyl) propanoic acid,[41] **4i** was obtained as a pale yellow solid, mp 74–75 °C. ^1H NMR ($CDCl_3$): δ 7.15 (d, 1H), 6.65 (d, 1H), 6.15 (s, br d, 1H), 5.25 (s, br d, 1H), 3.80 (s, 3H), 3.00–2.70 (m, 4H).

Route E. Step a: Spiro[(1,3-dioxocyclopentane)-2,2′-(8′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (39). A mixture of 1,2,3,4-tetrahydro-8-methoxy-2(1*H*)-naphthale-

none[42] (**4m**) (10 g, 56 mmol), ethylene glycol (3.47 g, 56 mmol), and a catalytic amount of *p*-toluenesulfonic acid in toluene (500 mL) was heated under reflux in a Dean–Stark apparatus. After 3 h of heating, another batch of ethylene glycol (3.40 g) was added and azeotropic distillation continued for a further 3 h. After cooling, the mixture was filtered, washed with water, dried ($MgSO_4$), and concentrated under vacuum to give a solid (10 g, 81%), mp 124–125 °C. ^1H NMR ($CDCl_3$): δ 7.10 (t, 1H), 6.75 (d, 1H), 6.65 (q, 1H), 4.05 (m, 4H), 3.80 (s, 3H), 3.00 (t, 2H), 2.90 (s, 2H), 1.90 (t, 2H).

Step b: Spiro[(1,3-dioxocyclopentane)-2,2′-(5′-iodo-8′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (40). To a warm (50 °C) solution of the above product (4.40 g, 20 mmol) in acetic acid (100 mL), solutions of I_2 (15.80 g, 62 mmol) in acetic acid (620 mL) and $Hg(OAc)_2$ (10.20 g, 32 mmol) in acetic acid (500 mL) were added dropwise, separately and simultaneously, while maintaining the reaction temperature between 45 and 55 °C. The mixture was stirred for 15 min at 50 °C, cooled to room temperature, and stirred for an additional 2 h. The acetic acid was evaporated off, and the crystalline residue was dissolved in concentrated NH_3 and extracted with CH_2Cl_2/H_2O. The organic fraction was dried ($MgSO_4$) and concentrated to leave a solid (6.0 g, 86%), mp 145–147 °C. ^1H NMR ($CDCl_3$): δ 7.55 (d, 1H), 6.40 (d, 1H), 4.00 (m, 4H), 3.70 (s, 3H), 2.85 (m, 2H), 2.80 (s, 2H), 1.85 (m, 2H).

Step c: Spiro[(1,3-dioxocyclopentane)-2,2′-(5′-(thiomethyl)-8′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (41). To a suspension of CH_3SLi (8.10 g, 150 mmol) in DMSO (120 mL) were added a solution of the above iodo derivative (6.0 g, 17 mmol) in DMSO (70 mL) and Cu_2O (33.50 g, 230 mmol). After stirring for 5 h at 80 °C under an Ar atmosphere, the mixture was filtered through Celite and washed with CH_2Cl_2; the filtrate was concentrated under vacuum. The residue was taken up in CH_2Cl_2/ice, the organic layer was separated, and the aqueous fraction was extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (SiO_2, cyclohexane/Et_2O = 80/20) to yield the thio ether as a yellow solid (3.40 g, 75%), mp 125–127 °C. ^1H NMR ($CDCl_3$): δ 7.05 (d, 1H), 6.60 (d, 1H), 4.00 (m, 4H), 3.70 (s, 3H), 2.95 (t, 2H), 2.30 (s, 3H), 1.90 (t, 2H).

Step d: 1,2,3,4-Tetrahydro-5-(thiomethyl)-8-methoxy-2(1*H*)-naphthalenone (4t). A suspension of the above dioxolane (3 g, 11 mmol) in aqueous acetic acid (50 mL, v/v = 30%) was heated overnight at 90 °C. The mixture was diluted with water and extracted with CH_2Cl_2; the organic phase was washed with water (until neutral pH), dried, and concentrated under vacuum to afford the tetralone **4t** as a yellow solid (2.32 g, 95%), mp 110–112 °C. ^1H NMR ($CDCl_3$): δ 7.20 (d, 1H), 6.70 (d, 1H), 3.75 (s, 3H), 3.50 (s, 2H), 3.20 (m, 2H), 2.50 (m, 2H), 2.30 (s, 3H).

Typical Procedures for the Synthesis of Spiro-imidazolines. Method A. Step a: 2-Amino-2-cyano-8-chloro-1,2,3,4-tetrahydronaphthalene (5b). To a vigorously stirred solution, maintained under N_2 atmosphere and containing 8-chloro-1,2,3,4-tetrahydronaphthalenone[43] (**4b**) (7.77 g, 43 mmol), EtOH (60 mL), and water (30 mL) were added KCN (2.87 g, 44 mmol) and NH_4Cl (2.35 g, 44 mmol) successively. After stirring for 20 h at 20 °C, the mixture was concentrated under vacuum and the residue was taken up in EtOAc. The organic phase was washed with water and then extracted with 1 N HCl. Rendering of the aqueous phase alkaline with 35% aqueous NaOH followed by extraction with EtOAc, drying, and evaporation under reduced pressure provided the desired amino nitrile **5b** (5.25 g, 58%) as a solid, mp 67–69 °C. ^1H NMR ($CDCl_3$): δ 7.30–7.00 (m, 3H), 3.40 (d, 1H), 3.05 (m, 2H), 2.90 (d, 1H), 2.15 (m, 1H), 2.00 (m, 1H).

Step b: 2-Amino-2-(aminomethyl)-8-chloro-1,2,3,4-tetrahydronaphthalene (6b). A solution of **5b** (5.25 g, 25 mmol) in anhydrous THF (40 mL) was added dropwise to a suspension of $LiAlH_4$ (1.63 g, 43 mmol) in anhydrous THF (50 mL) while maintaining the reaction temperature below 20 °C. The mixture was stirred for 20 min, cooled to 0 °C, and then hydrolyzed by addition of H_2O (1.6 mL), 2 N NaOH (1.6 mL), and H_2O (3.5 mL); the resulting suspension was filtered and the filtrate evaporated to give an oily residue. The diamine **6b** was obtained, after purification by column chromatography (SiO_2, $CH_2Cl_2/CH_3OH/NH_4OH$ = 90/10/1), as an oil (4.05 g, 77%). ^1H NMR ($CDCl_3$): δ 7.20–6.90 (m, 3H), 3.20–2.60 (m, 6H), 1.70 (m, 2H), 1.70–1.20 (m, br d, 4H).

Step c: Spiro[(1,3-diazacyclopent-1-ene)-5,2′-(8′-chloro-1′,2′,3′,4′-tetrahydronaphthalene)], Fumarate (7b). A mixture of the above diamine **6b** (2.10 g, 10 mmol) and formamidine acetate (1.18 g, 11.5 mmol) in EtOH (60 mL) was stirred at 20 °C under an N_2 atmosphere for 10 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with EtOAc and rendered basic with 35% aqueous NaOH; the mixture was extracted with EtOAc and the organic layer washed with saturated aqueous NaCl and evaporated. The solid residue was dissolved in EtOH (20 mL) and treated with a solution of fumaric acid (0.81 g, 7 mmol) in EtOH (20 mL). After evaporation of the solvent and recrystallization of the residue in EtOH, **7b** was isolated as a white solid (2.28 g, 68%), mp 213–214 °C. ^1H NMR (DMSO-d_6): δ 8.15 (s, 1H), 7.30 (dd, 1H), 7.15 (m, 2H), 6.45 (s, 2H), 4.70 (br d, 2H), 3.65 (AB system, 2H), 2.95 (m, 4H), 1.95 (m, 2H). Anal. ($C_{12}H_{13}ClN_2 \cdot C_4H_4O_4$) C, H, N, Cl.

Method B. Step a: 2-Amino-2-cyano-5-(methylthio)-8-methoxy-1,2,3,4-tetrahydronaphthalene (5t). A stirred mixture of tetralone **4t** (2 g, 9 mmol) and NaCN (1.42 g, 29 mmol) in water (50 mL) and Et_2O (40 mL) was cautiously treated with concentrated HCl (1 mL). After stirring for 1 h at 20 °C, the organic phase was separated, washed with water, dried, and concentrated. The oily residue was then treated with 3.5 N methanolic NH_3 solution (10 mL) and stirred in a closed vessel for 6 h at 20 °C. After evaporation of the solvent, the oil was taken up in Et_2O and extracted with 1 N HCl. The aqueous phases were rendered alkaline with 35% aqueous NaOH and then extracted with Et_2O. The amino nitrile **5t** was obtained as a solid after drying and evaporation of the organic phase (1.61 g, 72%), mp 128–130 °C. ^1H NMR ($CDCl_3$): δ 7.05 (d, 1H), 6.65 (d, 1H), 3.70 (s, 3H), 3.20 (d, 1H), 3.00–2.80 (m, 2H), 2.65 (d, 1H), 2.30 (s, 3H), 2.20–1.70 (m, 2H), 2.00–1.80 (br d, 2H).

Step b: 2-Amino-2-(aminomethyl)-5-(methylthio)-8-methoxy-1,2,3,4-tetrahydronaphthalene (6t). 6t was prepared according to the procedure described for **6b**, method A, step b, and obtained as an oil. ^1H NMR ($CDCl_3$): δ 7.10 (d, 1H), 6.70 (d, 1H), 3.80 (s, 3H), 3.10–2.50 (m, 6H), 2.40 (s, 3H), 2.00–1.50 (m, 2H), 1.80–1.50 (br d, 4H).

Step c: Spiro[(1,3-diazacyclopent-1-ene)-5,2′-(5′-(methylthio)-8′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)], Fumarate (7t). The compound was obtained as described for **13b** in method A, step c, as a white powder (60% yield), mp 188–190 °C. ^1H NMR (DMSO-d_6): δ 8.15 (s, 1H), 7.15 (d, 1H), 6.85 (d, 1H), 6.45 (s, 2H), 3.55 (AB system, 2H), 2.90–2.70 (m, 4H), 2.40 (s, 3H), 2.15–1.75 (m, 2H). Anal. ($C_{14}H_{18}N_2OS \cdot C_4H_4O_4$) C, H, N, S.

Method C. Step a: 2-(Benzylamino)-3,4-dihydronaphthalene (9a). A solution of 2-tetralone (25 g, 171 mmol), benzylamine (19.40, 181 mmol), and *p*-toluenesulfonic acid (100 mg) in toluene (500 mL) was brought to reflux with azeotropic distillation of the water/toluene mixture. After 2 h of reflux, the reaction mixture was cooled and filtered. The enamine **9a** was obtained as an oil (39.50 g, 99%) by evaporation of the solvent; it was used without purification for the next step. ^1H NMR ($CDCl_3$): δ 7.50–6.80 (m, 9H), 5.30 (s, 1H), 4.30 (br s, 2H), 3.50 (m, 1H), 2.80 (m, 2H), 2.30 (m, 2H).

Step b: 2-(Benzylamino)-2-cyano-1,2,3,4-tetrahydronaphthalene (10a). Trimethylsilyl cyanide (16.67 g, 168 mmol) and ZnI_2 (27.15 g, 85 mmol) were added successively to a solution of **9a** (39.50 g, 168 mmol) in CH_2Cl_2 (600 mL) maintained under an N_2 atmosphere. The mixture was stirred at 20 °C overnight and then washed with water; the organic phase was dried ($MgSO_4$) and concentrated under vacuum to afford **10a** as an oil (37.85 g, 86%). ^1H NMR ($CDCl_3$): δ 7.50–6.75 (m, 9H), 4.00 (s, br d, 2H), 3.10 (AB system, 2H), 3.00 (m, 2H), 2.20–2.00 (2m, 2H), 1.60 (m, 1H).

Step c: 2-(Benzylamino)-2-(aminomethyl)-1,2,3,4-tetrahydronaphthalene (11a). A solution of **10a** (37.70 g, 144 mmol) in anhydrous THF (200 mL) was added dropwise to a suspension of $LiAlH_4$ (10.60 g, 280 mmol) in anhydrous THF

Table 5. Preparation Methods of the Spiro-imidazolines **7a–kk**

compd	starting tetralone[a]	method	last step yield (%)	formula	elemental anal.	mp (°C)
7c	**4c**[44]	A	59	$C_{12}H_{13}FN_2 \cdot C_4H_4O_4$	C,H,N	188–190
7d	**4d**[45]	A	63	$C_{12}H_{13}ClN_2 \cdot C_4H_4O_4$	C,H,N,Cl	138–139
7e	**4e**[46]	A	55	$C_{12}H_{13}FN_2 \cdot 0.6C_4H_4O_4$	C,H,N	197–200
7f	**4f**[45]	A	62	$C_{12}H_{13}ClN_2 \cdot C_4H_4O_4$	C,H,N,Cl	201–203
7g	**4g**[45]	A	56	$C_{12}H_{13}ClN_2 \cdot C_4H_4O_4$	C,H,N,Cl	204–206
7h	**4h**[43]	A	61	$C_{12}H_{12}Cl_2N_2 \cdot C_4H_4O_4$	C,H,N; Cl: calcd, 19.10; found, 18.54	194–195
7i	**4i**	C	54	$C_{13}H_{15}ClN_2O \cdot C_4H_4O_4$	C,H,N,Cl	204–207
7j	**4j**[45]	A	57	$C_{12}H_{12}Cl_2N_2 \cdot C_4H_4O_4$	C,H,N,Cl	138–140
7k	**4k**[45]	A	56	$C_{12}H_{12}Cl_2N_2 \cdot C_4H_4O_4$	C,H,N,Cl	204–205
7l	**4l**[46]	A	61	$C_{12}H_{12}F_2N_2 \cdot 0.5C_4H_4O_4$	C,H,N	118–120
7m	**4m**[47]	A	64	$C_{13}H_{16}N_2O \cdot C_4H_4O_4$	C,H,N	186–188
7o	**4o**	A	70	$C_{13}H_{16}N_2O \cdot C_4H_4O_4$	C,H,N	188–190
7p	**4p**[48]	A	66	$C_{13}H_{16}N_2O \cdot C_4H_4O_4$	C,H,N	172–174
7q	**4q**[48]	C	63	$C_{15}H_{20}N_2O \cdot C_4H_4O_4$	C,H,N	175–177
7r	**4r**[48]	A	58	$C_{13}H_{16}N_2O \cdot C_4H_4O_4$	C,H,N	188–190
7s	**4s**[43]	C	61	$C_{14}H_{18}N_2O_2 \cdot C_4H_4O_4$	C,H,N	185–188
7u	**4u**	C	68	$C_{15}H_{20}N_2O_2 \cdot C_4H_4O_4$	C,H,N	174–176
7v	**4v**	C	66	$C_{16}H_{22}N_2O_2 \cdot C_4H_4O_4$	C,H,N	196–198
7w	**4w**[41]	A	42	$C_{14}H_{18}N_2O_2 \cdot C_4H_4O_4$	H,N; C: calcd, 59.66; found, 59.20	138–140
7x	**4x**[49]	C	52	$C_{13}H_{16}N_2O_2 \cdot C_4H_4O_4$	C,H,N	219–221
7y	**4y**[50]	C	66	$C_{14}H_{18}N_2O_2 \cdot C_4H_4O_4$	C,H,N	151–154
7z	**4z**[51]	C	63	$C_{14}H_{18}N_2O_2 \cdot C_4H_4O_4$	C,H,N	176–178
7aa	**4aa**[52]	A	71	$C_{13}H_{16}N_2 \cdot 0.5C_4H_4O_4$	C,H,N	211–214
7bb	**4bb**	C	69	$C_{14}H_{18}N_2 \cdot C_4H_4O_4$	C,H,N	148–151
7cc	**4cc**	C	65	$C_{15}H_{20}N_2 \cdot 1.5C_4H_4O_4$	C,H,N	192–194
7dd	**4dd**	C	67	$C_{16}H_{22}N_2 \cdot C_4H_4O_4$	C,H,N	188–190
7ee	**4ee**	C	62	$C_{13}H_{13}F_3N_2 \cdot C_4H_4O_4$	C,H,N	168–170
7ff	**4ff**[52]	C	59	$C_{13}H_{16}N_2 \cdot C_4H_4O_4$	C,H,N	170–173
7gg	**4gg**[12]	C	62	$C_{14}H_{18}N_2 \cdot C_4H_4O_4$	C,H,N	192–194
7hh	**4hh**	C	64	$C_{14}H_{18}N_2 \cdot C_4H_4O_4$	H,N; C: calcd, 65.44; found, 64.80	189–191
7ii	**4ii**	C	57	$C_{15}H_{18}N_2 \cdot 0.5C_4H_4O_4$	C,H,N	206–209
7jj	**4jj**	C	62	$C_{14}H_{18}N_2 \cdot 0.6C_4H_4O_4$	C,H,N	209–212
7kk	**4kk**	C	56	$C_{14}H_{18}N_2O \cdot C_4H_4O_4$	C,H,N	178–181

[a] Literature reference.

(700 mL) while maintaining a reaction temperature of less than 30 °C. After stirring for 24 h, the mixture was cooled to 0 °C and hydrolyzed by adding successively H_2O (11 mL), 2 N NaOH (11 mL), and H_2O (25 mL). The suspension was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in EtOAc (400 mL) and washed with water and 1 N HCl. The combined acidic aqueous phases were rendered alkaline with 35% aqueous NaOH and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated yielding the amine **11a** as an oil (26 g, 68%). ^{1}H NMR ($CDCl_3$): δ 7.50–6.80 (m, 9H), 3.70 (AB system, 2H), 3.00–2.50 (m, 6H), 2.10–1.60 (m, 2H), 1.60–1.30 (2m, 2H).

Step d: 2-Amino-2-(aminomethyl)-1,2,3,4-tetrahydronaphthalene (6a). A vigorously stirred suspension of **11a** (7.98 g, 30 mmol), ammonium formate (7.88 g, 125 mmol), and 10% Pd/C (6 g) in CH_3OH (250 mL) was heated under reflux for 30 min. After cooling, filtration of the catalyst, and evaporation of the solvent, the crude residue was purified by chromatography (SiO_2, $CH_2Cl_2/CH_3OH/NH_4OH$ = 90/10/1) to give the diamine **6a** as an oil (4.65 g, 88%). ^{1}H NMR ($CDCl_3$): δ 7.15–6.80 (m, 4H), 3.00–2.50 (m, 6H), 1.70 (m, 2H), 1.60–1.30 (2m, 4H).

Step e: Spiro[(1,3-diazacyclopent-1-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Benzenesulfonate (7a). A mixture of diamine **6a** (3.52 g, 20 mmol) and formamidine acetate (2.08 g, 20 mmol) in EtOH (60 mL) was stirred at 20 °C under an N_2 atmosphere for 12 h. The solvent was evaporated and the residue taken up with 1 N HCl (50 mL); the acidic phase was washed with EtOAc and rendered alkaline with 35% aqueous NaOH. The mixture was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous NaCl and concentrated under vacuum. The solid residue was dissolved in EtOH (50 mL) and treated with 1 equiv of benzenesulfonic acid dissolved in EtOH (20 mL). After evaporation of the solvent and crystallization from an EtOH/Et_2O mixture, the spiranic compound **7a** was isolated as a colorless solid (5.15 g, 74%), mp 124–125 °C. ^{1}H NMR (DMSO-d_6): δ 10.60 (br d, 1H), 10.20 (br d, 1H), 8.50 (s, br d, 1H), 7.60 (m, 2H), 7.30 (m, 3H), 7.10 (m, 4H), 3.65 (AB system, 2H), 3.00 (s, 2H), 2.90 (m, 2H). Anal. ($C_{12}H_{14}N_2 \cdot C_6H_6O_3S$) C, H, N, S.

Method D. Spiro[(1,3-diazacyclopent-1-ene)-5,2′-(8′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalene)], Fumarate (7n). A 1 M solution of BBr_3 in CH_2Cl_2 (16.5 mmol) was added dropwise to a cold (−78 °C) solution of **7m** (0.97 g, 4.5 mmol) (method A, step c) in CH_2Cl_2 (30 mL). The temperature of the reaction mixture was brought to 20 °C, and the mixture was then poured into a chilled $NaHCO_3$ solution. After evaporation of the aqueous phase, the residue was taken up in iPrOH. The resulting suspension was filtered and the filtrate concentrated under vacuum to leave an oily residue which was purified by chromatography (SiO_2, H_2O/dioxane/NH_4OH = 90/10/1 as eluent). The isolated solid was dissolved in EtOH (10 mL) and treated with a solution of fumaric acid (0.46 g, 4 mmol) in EtOH (10 mL). After evaporation and recrystallization of the residue from EtOH, the phenol **7n** was obtained as a white solid (0.56 g, 48%), mp 240–242 °C. ^{1}H NMR (DMSO-d_6): δ 7.70 (s, 1H), 6.90 (t, 1H), 6.65 (d, 1H), 6.55 (d, 1H), 6.40 (s, 1H), 4.10–3.00 (br d, 3H), 3.40 (AB system, 2H), 2.80 (m, 2H), 2.70 (s, 2H), 1.80 (m, 2H). Anal. ($C_{12}H_{14}N_2O \cdot C_4H_4O_4$) C, H, N.

Following the typical procedures described above (methods A–C), the spiro-imidazolines listed in Table 5 were prepared, starting from the appropriate tetralones.

Spiro[(1-methyl-1,3-diazacyclopent-2-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Hydrochloride (25). Step a: 2-(Methylamino)-2-cyano-1,2,3,4-tetrahydronaphthalene (23). A solution of 2-tetralone (**4a**) (1.46 g, 10 mmol) in MeOH (20 mL) was stirred for 18 h at room temperature in the presence of KCN (66 mg, 10.2 mmol), methylamine hydrochloride (776.5 mg, 11.5 mmol), and AcOH (1 mL). The solvents were evaporated under reduced pressure, and the residue was taken up in 1 N HCl (10 mL) and ether (100 mL). The aqueous phase was separated, and the organic phase was washed with H_2O (10 mL). The combined aqueous phases were rendered alkaline with 1 N NaOH. Extraction with CH_2-

Cl_2 (3 × 20 mL), drying over K_2CO_3, and evaporation under reduced pressure gave the desired compound as an oil (1.49 g, 80% yield). ^1H NMR ($CDCl_3$): δ 7.20–7.00 (m, 4H), 3.24 (d, 1H), 3.05–2.80 (m, 3H), 2.60 (s, 3H), 2.20 (m, 1H), 2.00 (m, 1H).

Step b: 2-(Methylamino)-2-(aminomethyl)-1,2,3,4-tetrahydronaphthalene (24). A solution of **23** (7.4 g, 39.2 mmol) in anhydrous ether (50 mL) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (4.5 g, 64.2 mmol) in anhydrous ether (500 mL). After addition, the suspension was heated to reflux for 1 h and then cooled (0 °C) and the excess hydride destroyed by careful addition of H_2O (4.5 mL), 2 N NaOH (4.5 mL), and H_2O (9 mL). The solid was filtered and washed extensively with ether (4 × 100 mL), and the combined ether solutions were evaporated under reduced pressure to provide the black oil **24** (5.5 g, 74% yield). ^1H NMR ($CDCl_3$): δ 7.10 (m, 4H), 3.00–2.40 (m, 6H), 2.30 (s, 3H), 1.60–2.00 (m, 2H).

Step c: Spiro[(1-methyl-1,3-diazacyclopent-2-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Hydrochloride (25). A solution of **24** (2 g, 10.5 mmol) and formamidine acetate (1.2 g, 11 mmol) in EtOH (50 mL) was stirred for 20 h at room temperature. The EtOH was evaporated off, and the residue was taken up in a mixture of 1 N HCl (15 mL) and ether (100 mL). The aqueous phase was separated; the organic phase was washed with H_2O (10 mL). Combined aqueous phases were made basic with 1 N NaOH. Extraction with CH_2Cl_2 (3 × 20 mL), drying over K_2CO_3, and evaporation under reduced pressure gave a complex mixture, separated by chromatography on silica gel using a gradient of EtOH/NH_4OH (9/1) in CH_2Cl_2. The desired compound **25** was eluted as an oil by a mixture of CH_2Cl_2/EtOH/NH_4OH (90/9/1). The oil was dissolved in EtOH, and a solution of HCl in ether was added; by dilution with ether, a solid precipitated which was filtered, crystallized from acetonitrile, and dried under vacuum at 50 °C (300 mg, 12% yield), mp 197 °C. ^1H NMR ($CDCl_3$): δ 10.55 (m, 1H), 8.65 (br s, 1H), 7.15 (m, 4H), 3.85 (d, 1H), 3.50 (d, 1H), 3.25 (d, 1H), 3.15 (s, 3H), 3.00 (m, 2H), 2.85 (dd, 1H), 2.20 (m, 1H), 1.95 (m, 1H). Anal. ($C_{13}H_{16}N_2$·HCl) C, H, N, Cl.

Spiro[(1,2-dimethyl-1,3-diazacyclopent-2-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Fumarate (26). A solution of **24** (2 g, 10.5 mmol) and acetamidine hydrochloride (1.04 g, 11 mmol) in EtOH (50 mL) was stirred for 20 h at room temperature. The EtOH was evaporated off, and the residue was taken up in a mixture of 1 N HCl (15 mL) and EtOAc (100 mL). The aqueous phase was separated off and washed with more EtOAc (50 mL) and CH_2Cl_2 (30 mL). The aqueous solution was made basic with 1 N NaOH and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried over K_2CO_3 and evaporated under reduced pressure. The residual oil was dissolved in EtOH, and 1 equiv of fumaric acid was added; by dilution with ether, a solid precipitated which was filtered and dried under vacuum (800 mg, 23% yield), mp 168 °C. ^1H NMR ($CDCl_3$): δ 7.15 (m, 4H), 6.45 (s, 2H), 3.55 (dd, 2H), 3.20 (d, 1H), 3.00 (s, 3H), 3.00–2.70 (2dd, d, 3H), 2.25 (s, 3H), 2.15 (m, 1H), 1.90 (m, 1H). Anal. ($C_{14}H_{18}N_2$·$C_4H_4O_4$) C, H, N.

Spiro[(2-methyl-1,3-diazacyclopent-1-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Fumarate (27). A solution of **6a** (1.65 g, 9.36 mmol) and acetamidine hydrochloride (0.898 g, 9.5 mmol) in EtOH (50 mL) was stirred for 20 h at room temperature. The EtOH was evaporated off, the residue was taken up in a mixture of 1 N HCl (15 mL) and ether (100 mL), and the aqueous phase was separated and washed with more ether (50 mL). The aqueous phase was rendered basic with 1 N NaOH and extracted with CH_2Cl_2 (3 × 20 mL) and the organic phase dried over K_2CO_3 and evaporated to dryness. The residual solid was crystallized from acetonitrile and dissolved in EtOH and 1 equiv of fumaric acid added; by dilution with diisopropyl ether, a solid precipitated which was filtered and dried under vacuum (1.5 g, 51% yield), mp 137 °C. ^1H NMR ($CDCl_3$): δ 7.15 (m, 4H), 6.40 (s, 2H), 3.60 (dd, 2H), 3.00 (s, 2H), 2.40 (m, 2H), 2.15 (s, 3H), 2.00 (m, 2H), 1.90 (m, 1H). Anal. ($C_{13}H_{16}N_2$·$C_4H_4O_4$) C, H, N.

Spiro[(3-methyl-1,3-diazacyclopent-1-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Fumarate (28). A solution of **7a** (700 mg, 3.76 mmol) and triethylamine (522 μL, 3.76 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C, and dimethyl sulfate (357 μL, 3.76 mmol) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature. The solution was washed with 0.1 N NaOH (50 mL), dried over K_2CO_3, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel by elution with a mixture of CH_2Cl_2/EtOH/NH_4OH (95/4.5/0.5). The first fractions contained the desired compound **28** (150 mg, 20% yield) followed by the 1-methyl isomer **25** (75 mg, 10% yield) and starting material **7a** (350 mg, 50% yield). The compound **28** was dissolved in MeOH, and 1 equiv of fumaric acid was added; by dilution with ether, a solid precipitated which was filtered and dried under vacuum, mp 197 °C. ^1H NMR ($CDCl_3$): δ 10.55 (m, 1H), 8.05 (s, 1H), 7.1 (m, 4H), 6.45 (s, 2H), 3.55 (d, 1H), 3.38 (d, 1H), 3.05 (s, 3H), 3.10–2.65 (m, 4H), 1.95 (m, 2H). Anal. ($C_{13}H_{16}N_2$·$C_4H_4O_4$) C, H, N.

Spiro[(1-oxa-3-azacyclopent-2-ene)-4,2′-(1′,2′,3′,4′-tetrahydronaphthalene)] (32). Step a: 2-Amino-2-(aminocarbonyl)-1,2,3,4-tetrahydronaphtalene (29a). A solution of amino nitrile **5a** (prepared as described for **7b**, method A, step a) (4.30 g, 25 mmol) in HCO_2H (80 mL) was cooled to 0 °C and saturated with anhydrous HCl. After evolution of gas had ceased, the solvent was evaporated and the residue taken up in acetone (50 mL). Filtration of the white crystalline solid afforded compound **29a** (4.04 g, 85%), mp 185–187 °C. ^1H NMR (DMSO-d_6): δ 8.70–7.70 (m, 5H), 7.25–7.05 (m, 4H), 3.20 (AB system, 2H), 2.85 (m, 2H), 2.50–2.20 (m, 1H), 2.20–2.00 (m, 1H).

Step b: 2-Amino-1,2,3,4-tetrahydro-2-naphthalenecarboxylic Acid (30a). A suspension of **29a** (4 g, 21 mmol) in 6 N aqueous HCl (25 mL) was refluxed until homogeneous. The solvent was evaporated off, and the residue was taken up with iPrOH and reconcentrated. The solid residue was dissolved in water and the mixture neutralized by addition of 1 N NaOH. The desired acid **30a** was obtained after filtration and drying (3.85 g, 96%), mp 205–206 °C. ^1H NMR (DMSO-d_6): δ 7.20–6.90 (m, 4H), 3.00 (AB system, 2H), 2.80–2.60 (m, 2H), 2.20–2.00 (m, 2H), 2.00–1.70 (m, 1H).

Step c: 2-Amino-2-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (31a). A suspension of $LiAlH_4$ (1.44 g, 38 mmol) in anhydrous THF (100 mL) was added dropwise under an N_2 atmosphere and at room temperature to a solution of acid **30a** (3.63 g, 19 mmol) in anhydrous THF (50 mL). The mixture was brought to reflux for 1 h, and after cooling to 0 °C, H_2O (1.5 mL), 2.5 N NaOH (1.5 mL), and H_2O (3 mL) were added successively. The resulting suspension was filtered and washed with THF. The combined filtrates were concentrated under vacuum to yield the amino alcohol **31a** as an oil (2.53 g, 75%). ^1H NMR ($CDCl_3$): δ 7.15–6.90 (m, 5H), 3.45 (s, 2H), 3.00–2.50 (br d, 2H), 2.90 (m, 2H), 2.75 (AB system, 2H), 1.75 (m, 2H).

Step d: Spiro[(1-oxa-3-azacyclopent-2-ene)-4,2′-(1′,2′,3′,4′tetrahydronaphthalene)] (32). A solution of **31a** (0.62 g, 3.5 mmol) in methyl formate (5 mL) is brought to reflux for 1 h. The excess formate is then evaporated and the residue dissolved in CH_2Cl_2 (40 mL). To this new solution, diethylaminosulfur trifluoride (DAST) (1.21 g, 7.5 mmol) in CH_2Cl_2 (3 mL) was added dropwise, at −10 °C, under an N_2 atmosphere. After stirring for 2 h at −10 °C, 25% NH_4OH solution (25 mL) was added. The organic layer was separated, dried ($MgSO_4$), and concentrated. The solid residue was purified by chromatography (SiO_2, CH_2Cl_2/EtOH = 99/1 as eluent) and, after crystallization from hexane at −30 °C, afforded the spiro derivative **32a** as a colorless solid (0.25 g, 38%), mp 45–46 °C. ^1H NMR ($CDCl_3$): δ 7.20–7.00 (m, 4H), 6.85 (s, 1H), 4.00 (AB system, 2H), 3.05 (m, 1H), 2.95 (AB system, 2H), 2.10 (m, 1H), 1.85 (m, 1H). Anal. ($C_{12}H_{13}NO$) C, N; H: calcd, 7.00; found, 7.42.

Spiro[(2-amino-1,3-diazacyclopent-1-ene)-5,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Hydrobromide (33). A solution of **6a** (1 g, 5.7 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and a solution of cyanogen bromide (690 mg, 5.7 mmol) in CH_2Cl_2 (5 mL) added in dropwise fashion. The reaction mixture was stirred overnight at room temperature. The white precipitate was collected by filtration and crystallized from 2-propanol (500 mg, 31% yield), mp 209 °C. ^1H NMR

($CDCl_3$): δ 7.3–7.0 (m, 4H), 3.45 (dd, 2H), 2.95 (s, 2H), 2.90 (m, 2H), 1.95 (m, 2H). Anal. ($C_{12}H_{15}N_3$·HBr) C, H, N, Br.

Spiro[(1-oxa-2-amino-3-azacyclopent-2-ene)-4,2′-(1′,2′,3′,4′-tetrahydronaphthalene)], Hydrochloride (34a). A solution of BrCN (1.27 g, 12 mmol) in CH_2Cl_2 (5 mL) was added rapidly at 0 °C to a solution of amino alcohol **31a** (1.76, 10 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred overnight at room temperature and the precipitated solid filtered off and washed with CH_2Cl_2. The filtrate was washed with $KHCO_3$ solution, dried, and evaporated under vacuum; the residue was purified by chromatography (SiO_2, CH_2Cl_2/CH_3OH/NH_4OH = 95/4.5/0.5 as eluent). The oil obtained was dissolved in Et_2O and treated with ethereal HCl. The precipitate was then filtered off and recrystallized from an iPrOH/Et_2O mixture to give **34a** as a white powder (1.55 g, 65%), mp 205–206 °C. ^1H NMR (DMSO-d_6): δ 11.00–8.50 (br d, 2H), 7.25–7.00 (m, 4H), 4.55 (AB system, 2H), 3.10 (s, 2H), 3.00–2.80 (m, 2H), 2.10–1.90 (m, 2H). Anal. ($C_{12}H_{14}N_2O$·HCl) C, H, Cl; N: calcd, 11.73; found, 10.96.

Spiro[(1-oxa-2-amino-3-azacyclopent-2-ene)-4,2′-(8′-chloro-1′,2′,3′,4′-tetrahydronaphthalene)], Hydrochloride (34b). Following the procedure described for **34a** but starting from **5b**, the spiro derivative **34b** was obtained as a white powder, mp 210–214 °C. ^1H NMR (DMSO-d_6): δ 10.80–9.10 (br d, 3H), 7.35–7.05 (m, 3H), 4.60 (AB system, 2H), 3.10 (m, 2H), 3.10–2.70 (m, 2H), 2.20–1.90 (m, 2H). Anal. ($C_{12}H_{13}ClN_2O$·HCl) C, H, N, Cl.

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