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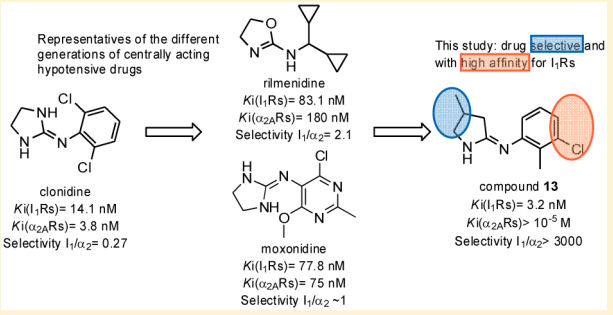
# Synthesis and Biological Evaluation of 2-Aryliminopyrrolidines as Selective Ligands for $I_1$ Imidazoline Receptors: Discovery of New Sympatho-Inhibitory Hypotensive Agents with Potential Beneficial Effects in Metabolic Syndrome

Vincent Gasparik,[‡] Hugues Greney,[‡] Stephan Schann,[†] Josiane Feldman, Lyne Fellmann, Jean-Daniel Ehrhardt, and Pascal Bousquet*

Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, Faculté de Médecine, EA 7296, Fédération de Médecine Translationnelle, Université de Strasbourg, 11 rue Humann, 67000 Strasbourg, France

Supporting Information

**ABSTRACT:** New 2-aryliminopyrrolidines (**1**−**18**) were synthesized and tested for their binding properties on $I_1$ imidazoline receptors vs $\alpha_2$-adrenergic receptors and their blood pressure effects after both systemic and intracerebral administrations. The purposes of this study were: (i) to analyze structure−activity and affinity relationships on $I_1$ imdazoline receptors and (ii) to propose some leader compounds for the development of new sympatho-inhibitory drugs with potential applications in hypertension and/or metabolic syndrome, i.e., a cluster of cardiovascular (hypertension) and metabolic disorders. Our study highlights decisive arguments of SAR concerning both the affinity for $I_1$Rs and the hypotensive activity of 2-aryliminopyrrolidines. Binding assays showed high affinity and selectivity of some compounds for $I_1$ imidazoline receptors over $\alpha_2$-adreergic receptors. Compound **13** (laboratory reference LNP599; $K_i$ = 3.2 nM on $I_1$imidazoline receptors) is the prototype for the development of new centrally acting agents targeting specifically $I_1$imidazoline receptors to be used in the management of hypertension and/or metabolic syndrome.




## INTRODUCTION

imidazoline receptors (IRs) are involved in several biological regulatory systems. The major one is the central regulation of blood pressure (BP).[1−3] They are also involved in other physiological functions such as insulin release,[4,5] intraocular pressure regulation,[6] and cardiac rhythm control.[7,8] IRs are classified in three different subtypes. The first subtype of imidazoline receptors, $I_1$Rs, is located in the rostro-ventrolateral medulla of the brainstem and was shown to be involved in the central regulation of the cardiovascular function.[9] The hypothesis of their existence and their role was first proposed by Bousquet and co-workers in the mid 1980s.[10,11] $I_1$Rs are sensitive to clonidine and other imidazoline-like drugs but not to catecholamines. Therefore, they are different from $\alpha_{2A}$ARs, which is the subtype of adrenoceptors involved in the central regulation of BP.[12] Recently, we demonstrated that $I_1$Rs are present in adipose tissue and that selective activation of $I_1$Rs not only reduces BP but also improves metabolic disorders which are associated with hypertension in the so-called MetS.[13]

Clonidine (Figure 1) was the leader compound of the first generation of centrally acting antihypertensive drugs. It was shown to bind to both $I_1$Rs and $\alpha_2$ARs. Its side effects, sedation in particular, were clearly attributed to the activation of $\alpha_2$ARs.[14] Drugs such as moxonidine and rilmenidine display some selectivity for $I_1$Rs over $\alpha_2$ARs, as compared to clonidine, they have a lower affinity for $\alpha_2$ARs.[15] Consequently, they also have fewer side effects in hypertensive patients.[16,17]

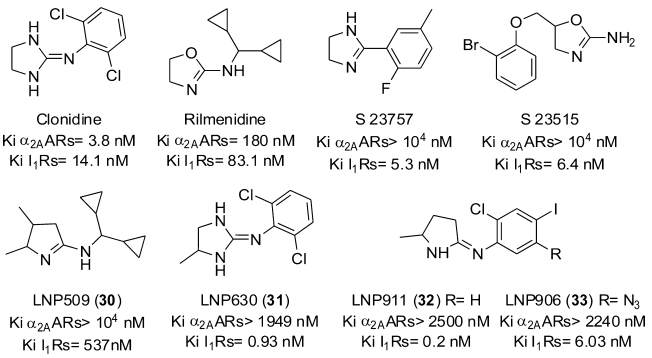



**Figure 1.** Structures of imidazolines and related compounds.

Over the last two decades, very active research on imidazoline derivatives and IRs led to the discovery of compounds either selective for $\alpha_2$ARs or new hybrid drugs

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partially selective for $\alpha_2$ARs over $I_1$Rs.[18−20] Interesting hypotheses were suggested to explain the selectivity of some drugs for $I_1$Rs by physicochemical and biophysical parameters.[21,22]

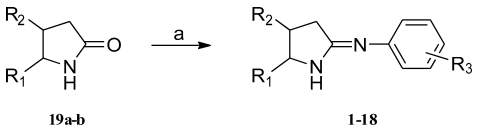
Our group is particularly interested in the cardiovascular effects of potential therapeutical interest of drugs selective for $I_1$Rs. Bruban et al. showed that drugs binding and acting exclusively on $I_1$Rs are able to decrease BP. Thus, S23515 (Figure 1) has a significant selectivity for $I_1$Rs over $\alpha_2$ARs,[23] whereas **30** (LNP509, Figure 1) was the first compound binding to $I_1$Rs, but devoid of any adrenergic property, able to lower the BP after ic injection.[24−26] **30** even lowered the BP of genetically engineered animals as D79N mice,[27] whose $\alpha_{2A}$ARs were no longer functional. IRC with nanomolar affinities for $I_1$Rs and great selectivities over $\alpha_2$ARs were synthesized. One of these IRC, **31** (LNP630, Figure 1), decreases BP efficiently.[28] Other compounds selective for $I_1$Rs, **32** and **33** (LNP911 and LNP906, Figure 1) which exhibited a subnanomolar affinity, were developed as a radioligand[29] and a photoaffinity−radioligand,[30] respectively, but they had no hypotensive activity. **32** behaves rather as an antagonist (personal observation), whereas **33**, as a photoactivable ligand, is unusable in in vivo experiments. These two molecules were used as tools to study and characterize $I_1$Rs. They are iminopyrrolidines by contrast with the historical leader compounds that are either imidazolines (S23757)[23] or amino-imidazolines (clonidine, **31**) or amino-oxazolines (rilmenidine).

Because of the high affinity of **32** for $I_1$Rs,[29] the aim of the present work was to further analyze structure−activity relationships of 2-aryliminopyrrolidines. Requirements for their selectivity and affinity for $I_1$Rs and their sympatho-inhibitory properties, mainly their BP effects, were studied. As a matter of fact, drugs suitable for use in MetS need to reduce BP as hypertension takes part of MetS. That is the reason why we screened our compounds for their BP effects first. In addition, according to our previous studies,[13] we can assume that drugs highly selective for $I_1$Rs, which reduce BP through a centrally mediated sympathetic inhibition, will most likely also improve the metabolic abnormalities of MetS.[31] We have especially focused our work on compounds that are substituted on the position-2 of the phenyl ring, since previous studies have shown that this kind of substitution was required for their biological activity.[32−35] The choice of the substituents on the aromatic ring is based on a classical rational strategy: starting from a substitution on the ortho position, we have made variations on the other positions to state about the influence of the region that is substituted on the biological activity. Cycles were introduced to determine the limits of the steric hindrance on the considered positions. We have also carried out some variations on the pyrrolidinyl ring to determine the influence of such substitutions on both the selectivity and the hypotensive activity of 2-aryliminopyrrolidines derivatives.

## CHEMISTRY

Compounds **1−18** were synthesized by coupling the appropriate lactam with a chosen aniline derivative and using a dehydrating agent, i.e., phosphorus oxychloride, in 1,2-dichloroethane at 60 °C under inert atmosphere (Scheme 1).[32] To determine the influence of the substitutions on the pyrrolidinyl ring, we chose two starting lactams differently methylated. The lactam **19a** was commercially available. The lactam **19b** was prepared according to standard procedures. First, nitromethane is reacted with methyl crotonate in the presence of catalytic amount of tetramethylguanidine.[36] The nitroester **20** was then hydrogenated and cyclized, affording the lactam in good yield (Scheme 2).[37] The choice of only alkyl and halogen as substituents is based on the physicochemical properties of such groups that serve the lipophilicity of central acting drugs.[38] Most of the anilines used in the study were obtained from commercial sources, but anilines **21−29** were synthesized. The starting point for the synthesis is the commercial mixture of 4- and 5-nitroindan as described in Scheme 3. After catalytic hydrogenation of the former mixture, the two anilines **21** and **22** were separated by column chromatography. Aniline **25** was prepared from **21**,[39] which was acylated with $Ac_2O$ to give **23** in 90% yield and treated in acetic acid with chlorine to give compound **24** in a nearly quantitative yield. The latter was then hydrolyzed in 4 M HCl to afford **25** in quantitative yield. The way to **28** was somewhat different. Aniline **21** was acylated as described above, but the product **23** was halogenated with bromine to afford **26** in 92% yield. Treatment of **26** with trimethylboroxine using the standard Suzuki coupling conditions, in dioxan, gave the methylated derivative **27** in 80% yield.[40] Aniline **28** was obtained quantitatively after the hydrolysis of the acetamido group in acidic condition. Aniline **29** was obtained from **22** following the procedure described for the preparation of **25**.

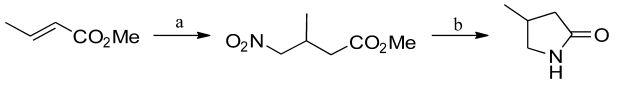
**Scheme 1. Synthesis of the 2-Aryliminopyrrolidines 1−18**[a]




19a-b 1-18

[a]Reaction conditions: (a) lactam **19a−b**, $R_3$-Ph-$NH_2$, $POCl_3$, 1,2-dichloroethane, 60 °C, 6 h. For R groups definitions, see Table 1.

**Scheme 2. Preparation of Lactams 19b**[a]




20 19b

[a]Reaction conditions: (a) nitromethane, TMG, rt, 12 h; (b) (i) $H_2$, 10% Pd/C, AcOH, rt, 12 h, (ii) TEA, EtOH, reflux, 20 h.

## PHARMACOLOGY

**Hemodynamic Effects.** The 18 compounds **1−18** were evaluated in vivo for their effects on mean arterial blood pressure (MBP) and heart rate (HR). On the basis of our experience in this field, results were defined as functionally significant for variations greater than 15% of the basal values. Cardiovascular parameters were recorded after intravenous injections (iv, 3 and 10 mg/kg when the 3 mg/kg dose was inactive) and ic injections (0.3 mg/kg) in normotensive anaesthetized Wistar rats (Table 1). The ic route of administration allowed us to confirm the central origin of the observed effects. These two routes of administration are commonly used by all the groups studying centrally acting drugs in different mammal species.[27,41−43] The first series of compounds tested included those bearing a methyl group on position-5 of the pyrrolidinyl ring (**1−11**). Compounds whose phenyl ring is disubstituted on positions-2 and -6 (**1**), on positions-2 and -5 (**2**, **3**), and on positions-2 and -4 (**4**) never decreased BP after the iv injection more than 10% of the initial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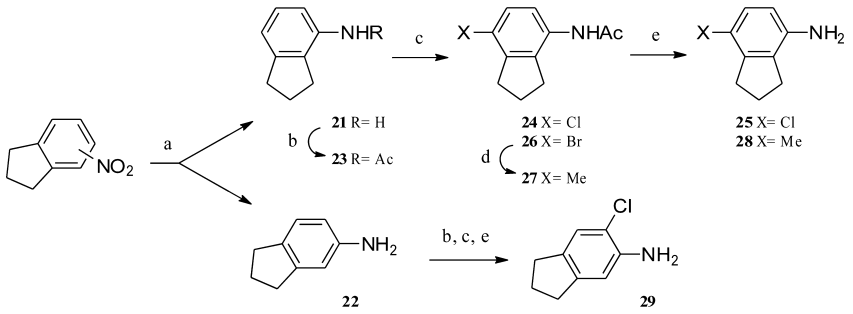
**Scheme 3. Synthesis of Indanamine Derivatives 21−29**[a]




[a]Reaction conditions: (a) $H_2$, 10% Pd/C, MeOH, rt, 12 h, separation of isomers; (b) $Ac_2O$, 0 °C to rt; (c) $X_2$, AcOH, 0 °C to rt, 1 h; (d) trimethylboroxine, 10%mol $Pd(PPh_3)_4$, 2 N $Na_2CO_3$, dioxan, reflux, 5 h; (e) 4 N HCl, reflux, 2 h.

**Table 1. Pharmacological Data of Compounds 1−18**

| | | | | cardiovascular effects[a] | | | | binding affinities $K_i$ (nM) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | intravenous injection | | intracisternal injection (0.3 mg/kg) | | | |
| compd | $R_1$ | $R_2$ | $R_3$ | max ΔMBP (% var) | max ΔHR (% var) | max ΔMBP (% var) | max ΔHR (% var) | $I_1R$ | $\alpha_{2A}R$ |
| **1** | Me | H | 2,6-$Me_2$ | −5* | −4* | na | na | nd | nd |
| **2** | Me | H | 2-F, 5-Me | −9* | −6* | na | na | nd | nd |
| **3** | Me | H | 2-Cl, 5-Me | −7* | −7* | na | na | nd | nd |
| **4** | Me | H | 2-Me, 4-F | −6* | −8* | na | na | nd | nd |
| **5** | Me | H | 2,3-$Me_2$ | −25* | −18* | −20 | −25 | 70 ± 5 | $>10^4$ |
| **6** | Me | H | 2-Me, 3-Cl | −28* | −20* | −25 | −30 | 27 ± 6 | $>10^4$ |
| **7** | Me | H | 2,3-$(CH_2)_3$ | −37* | −20* | −32 | −29 | 19 ± 8 | $>10^4$ |
| **8** | Me | H | 2,3-$(CH_2)_4$ | −37* | −26* | −29 | −10 | 73 ± 6 | $>10^4$ |
| **9** | Me | H | 3,4-$(CH_2)_3$ | −8* | −4* | na | na | nd | nd |
| **10** | Me | H | 2-Cl, 4,5-$(CH_2)_3$ | −9* | −3* | na | na | nd | nd |
| **11** | Me | H | 2,3-$(CH_2)_3$, 4-Cl | −6* | −7* | na | na | 2.8 ± 0.3 | $>10^4$ |
| **12** | H | Me | 2,3-$Me_2$ | −26# | −20# | −25 | −31 | 42 ± 5 | $= 10^4$ |
| **13** | H | Me | 2-Me, 3-Cl | −30# | −18# | −30 | −33 | 3.2 ± 0.5 | $>10^4$ |
| **14** | H | Me | 2,3-$(CH_2)_3$ | −35# | −22# | −30 | −30 | 19 ± 6 | $>10^4$ |
| **15** | H | Me | 2,3-$(CH_2)_3$, 4-Cl | −10* | −6* | na | na | 0.22 ± 0.02 | $>10^4$ |
| **16** | H | Me | 2,3-$(CH_2)_3$, 4-Me | −26* | −22* | −32 | −15 | 2.8 ± 0.2 | $>10^4$ |
| **17** | H | Me | 3,4-$(CH_2)_3$ | −8* | −4* | na | na | nd | nd |
| **18** | H | Me | 2,3-$(CH_2)_4$ | −5* | −3* | na | na | nd | nd |

[a]Effects on mean arterial blood pressure (MBP) and heart rate (HR) in normotensive anesthetized rats. Results presented are means of at least three independent experiments: for iv injections, # = 3 mg/kg and * = 10 mg/kg. Results were defined as functionally significant for variations greater than 15% of the basal value. Affinities for $I_1$Rs were measured with [$^{125}$I] PIC on PC12 cells; affinities for $\alpha_{2A}$Rs were measured with [$^3$H] RX 821002 on CHO transfected cells. Data are presented as mean ± SEM. na, non active; nd, not determined.

MBP value, even at the high dose of 10 mg/kg. The same compounds, administered via the ic route did not significantly modify MBP. On the opposite, compound **5**, which is 2,3-dimethylated, lowered MBP by 25% and HR by 18% at 10 mg/kg iv. Compound **6**, which has a methyl on position-2 and a chlorine on position-3, also decreased MBP but its hypotensive effect lasted much longer than that of **5**. For both compounds, hypotensive effect after ic administration and effects on HR were similar. Compound **7**, which is constituted of an indan-4-yl moiety, was more potent than **5** and **6** because MBP and HR were decreased by 37% and 20%, respectively, after iv at the same dose. After ic injection, it produced marked effects on these parameters, which decreased by 32% and 29%, respectively. Changing from an indan-4-yl to a tetrahydronaphth-5-yl scaffold, compound **8**, did not change the efficiency on both MBP and HR, which was quite as important as for **7**, either after iv or ic administrations. On the opposite, compound **9**, which is an isomer of position of compound **7** having an indan-5-yl moiety, was unable to affect MBP nor HR, after iv and ic administrations. Compound **10**, with a chlorine atom on position-7 of the indan-5-yl moiety reduced neither arterial pressure nor HR after both administration ways. Compound **11**, which is a derivative of **7** with a chlorine atom in position-4 of the indan-4-yl moiety, was inactive after both iv and ic administrations.

The compounds of the second series bear a methyl group on position-4 of the pyrrolidinyl ring (Table 1, entry **12**−**18**). Compounds **12** and **13**, which are position isomers of compounds **5** and **6**, respectively, displayed interesting activities because MBP was decreased by 26% and 30%, respectively, at the dose of 3 mg/kg iv, whereas HR was decreased by 20%. This was also the case for compound **14**, which lowered MBP by 35% at the same dose. Hypotensive and bradycardic activities of these three compounds were marked after ic injections, ranging from −25 to −30%. Compound **15**, which bears a chlorine atom on position-4 of the indan-4-yl moiety, did not significantly modify MBP and HR, after iv and ic administrations. Compound **16**, which is substituted by a



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J. Med. Chem. XXXX, XXX, XXX−XXX

methyl group instead of a chlorine atom on position-4 of the indan-4-yl moiety, had a marked activity on both MBP and HR at the dose of 10 mg/kg iv and was also active after ic injection. Compound **17**, a position isomer of compound **14** having an indan-5-yl moiety was inactive, after both administration ways. The tetrahydronapht-5-yl analogue **18** was also unable to decrease both MBP and HR.

**Binding Assays.** Compounds that were active on MBP and HR were evaluated for their binding properties on $I_1$Rs and $\alpha_{2A}$Rs (Table 1). The first important statement is that none of the compounds evaluated exhibited significant affinity on $\alpha_{2A}$Rs ($K_i > 10^{-5}$ M).

Compounds **5** and **8** had good affinity for $I_1$Rs, with $K_i$ values of 70 and 73 nM, respectively. Compounds **6**, **7**, **12**, and **14** showed even better affinities, with $K_i$ values ranging from 19 to 42 nM. Finally, compounds **13** and **16** had the highest affinities among the active compounds, with $K_i$ values of 3.2 and 2.8 nM, respectively. We also evaluated two inactive compounds, **11** and **15**, with $K_i$ values of 2.8 and 0.22 nM, respectively.

**Discussion.** One of the goals of the present work was to obtain compounds selective for $I_1$Rs over $\alpha_2$ARs with hypotensive activity. None of the tested compounds caused initial vasoconstriction after systemic injection, opposite to what happens with hybrid drugs, such as clonidine.[44] This fact indicates that our pyrrolidine ligands are devoid of adrenergic properties because the vasoconstrictive effect of clonidine-like compounds is known to be caused by the stimulation of vascular $\alpha$ARs.[45] This was confirmed by the binding assays performed on hypotensive compounds, because no significant affinities for $\alpha_{2A}$ARs were measured ($K_i$ values $\geq 10^4$ nM) (Table 1). Our experiments also showed that all hypotensive compounds bound specifically to $I_1$Rs (Table 1); they can therefore be considered as compounds selective for $I_1$Rs over $\alpha_2$ARs.

It has repeatedly been reported that many ligands selective for $I_1$Rs exhibited a biphasic binding to the receptors, suggesting that $I_1$Rs is a G protein-coupled receptor as assessed by the effect of nonhydrolyzable GTP on the binding curves.[29,46,47] The high affinity sites are the ones involved in the biological activities of the $I_1$Rs.[24,28,48,49] These are the reasons why only the high affinity sites are taken into account here. However, no direct correlation between the hypotensive effect of the 2-aryliminopyrrolidines and their affinities for $I_1$Rs has been sought because the hypotensive potential of $I_1$ selective drugs depends not only on their affinity for $I_1$Rs but also on a combination of many different parameters such as the capability of crossing the BBB after systemic delivery, their potential metabolism even after central administration, and their lipophilicity. Besides several arguments suggest that the signaling pathways which have been associated with $I_1$Rs so far, such as cAMP[48] and DAG,[50] are probably not the only ones to be involved. Thus, so far, our knowledge in this matter is not sufficient to correlate the hypotensive effects of $I_1$ selective drugs to their effects on second messengers. In all these domains, our series of 2-aryliminopyrrolidines is not distinguishable from amino-imidazolines or amino-oxazolines.

Some active 2-aryliminopyrrolidines described in the present study can decrease BP by about 30%; as the tested animals were initially normotensive, a 30% reduction of BP is important, close to the maximal possible effect (maximal efficacy). Nonetheless, the doses which produce these effects are quite large compared to the ones of amino-imidazolines, such as clonidine, which cause similar effects. Thus, hybrid drugs targeting both $I_1$Rs and $\alpha_2$ARs[23,27] or even drugs selective for $\alpha_2$ARs such as dexmedetomidine and marsanidine,[20,51,52] have greater potencies than $I_1$ selective drugs as they act at lower doses. $\alpha_2$ARs and $I_1$Rs are differently involved in BP blood pressure regulation. We showed previously that both types of receptors can synergistically interact to cause hypotensive effects at very low doses.[27] Therefore, $I_1$Rs selective drugs which cannot trigger such a synergism act at higher doses.

Nevertheless, $I_1$Rs selectivity has important advantages, such as the lack of the side effects clearly associated with $\alpha_2$ARs, i.e., sedation and mucosal dryness in particular. In addition, the more selective the drugs are for $I_1$Rs, the more they have beneficial metabolic effects (cholesterol reduction and improvement of glucose tolerance). Thus, as far as metabolic effects and MetS management are concerned, activation of $\alpha_2$ARs goes rather in the unfavorable direction.[53,54]

Concerning the structure−activity relationships, the binding selectivity seems to be due to the presence of the methyl group on the pyrrolidinyl ring, wherever it is located in position-4 or -5; position-3 was not considered since we demonstrated in a previous work that it was not favorable for the biological activity.[24] This steric hindrance may disfavor the linking interactions between ligands and $\alpha_2$ARs because nonmethylated 2-aryliminopyrrolidines still bind to $\alpha_2$ARs, but to a lesser extent than imidazoline compounds.[55] The same observation was supported by a study dealing with derivatives of brimonidine, an amino-imidazoline compound: the one which was methylated on the imidazolinyl ring had lost its adrenergic properties.[56] This assumption is also supported by our recent work on IRC demonstrating that methylated rilmenidine and methylated clonidine (**31**) are devoid of adrenergic properties, the later still being able to induce hypotensive response.[28] However, it is noticeable that, in the case of aliphatic aminopyrrolines, to which belongs **30**, the methylation on the pyrrolinyl ring is not necessary for $I_1/\alpha_2$ selectivity.

Furthermore, the substitution on the pyrrolidinyl ring appears to influence the affinity of the ligands. While compounds **7** and **14** had the same $K_i$ values for $I_1$Rs, the $K_i$ value of **12** is lower than that of **5**. Also, the $K_i$ values of **13** and **15** are lower than those of **6** and **11**, respectively. This suggests that methylation on position-4 of the pyrrolidinyl ring is more appropriate than in position-5 to improve the affinity of ligands toward $I_1$Rs.

How the aromatic ring is substituted leads to some interesting observations. As shown previously, a sole substituent on position-2 did not lead to hypotensive compounds, whatever its nature, alkyl group, or halogen atom,[28,57] opposite to what was observed with imidazoline compounds and nonselective pyrrolidines.[32,33,35] In the first series, in which compounds **1**−**11** bear a methyl group on position-5 of the pyrrolidinyl ring, addition of a second substituent on the phenyl ring had different influences on the hypotensive activity, according to its position. When it was placed in position-6, in position-5, or in position-4 of the phenyl ring (compounds **1**−**4**), compounds were unable to decrease MBP, even after ic injection. But when the additional substituent was placed on position-3 (**5**), the compound was very active. We synthesized other compounds with this kind of substitutions, and all of them were able to decrease MBP, whatever the route of administration (**6**−**8**). In the second series of compounds, the methyl group is on position-4 of the pyrrolidinyl ring (**12**−**18**). Compounds **12**−**14**, substituted on positions-2 and -3 of the phenyl, were very efficient hypotensive agents. Other combinations of substitu-



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tions in both series, either on positions-3 and -4 (**9**, **17**), or positions-2, -4, and -5 (**10**) of the phenyl, did not lead to active compounds. On the basis of these observations, we can conclude that the cardiovascular effects of such selective 2-aryliminopyrrolidines compounds were strongly dependent on the nature of the aniline moiety. The presence of substituents on both positions-2 and -3 of the aromatic ring was required for the hypotensive activity. These 2-aryliminopyrrolidines are the first to be selective for $I_1$Rs and to be hypotensive after systemic administration.

The influence of the nature of the substituent on position-3 on the pharmacological activity was not clear because changing from a methyl group to a chlorine atom did not modify the hypotensive activity (see **5** vs **6** and **12** vs **13**). Nevertheless, it seems to influence, in some extent, the binding properties. Affinity of compound **6** was higher than that of **5** (3-fold). This influence is noteworthy in the second series, as the chlorinated compound **13** had a rather higher affinity for $I_1$Rs than its alkyl analogues **12** and **14**, with a significant gain on the $K_i$ value (13- and 6-fold, respectively).

Addition of a third substituent on position-4 of a phenyl ring already substituted on positions-2 and -3 clearly increased the affinity of the ligands for $I_1$Rs. This is the case for **11** vs **7** (7-fold in $K_i$ gain) and for compounds **15** and **16** vs **14** (90- and 7-fold in $K_i$ gain, respectively). Such an observation is in agreement with previous observations when we compare the affinities of clonidine and its para-substituted analogues[58,59] and also when **32** was compared with its non-iodinated analogues.[28,29] This increase in affinity seems also to be dependent on the nature of this substituent. The chlorine atom was more efficient than the methyl group to improve the binding properties (see **15** vs **16** with 12-fold in $K_i$ gain). The 2-aryliminopyrrolidines we have synthesized display higher affinities for $I_1$Rs than **30**, whose $K_i$ = 537 nM. Some of them have affinities as high as our reference $I_1$Rs selective ligand **32** ($K_i$ = 0.22 nM) or clonidine and its methylated analogue **31** ($K_i$ = 14.1 and 0.93 nM, respectively) and even higher than that of rilmenidine and its methylated analogue ($K_i$ = 83.1 and 363 nM, respectively).[28] But although such additional substitutions increased the affinity of the ligands for $I_1$Rs, they did not necessarily increase their hypotensive activity (see **11** vs **7** and **15** vs **14**). Indeed, compound **16** is the sole of the series substituted in position-4 of the phenyl exhibiting a marked hypotensive activity. This difference of behavior between **16** and the chlorinated analogues **11** and **15** might not be due to differences of steric hindrance, because the van der Waals volumes of chlorine atom and methyl group are very close, with values of 22.4 and 21.6 Å$^3$, respectively.[60,61] The cause may be the differences of their intrinsic electronic natures. The chlorinated compounds may interact via halogen bonding[62,63] with residues of the active site of the receptor protein in a manner that favor the binding interactions but that does not allow the shaping of the active conformation of the protein. As a consequence, there will be no functional response. Another possible reason for the discrepancy of activity could be the lack of stability of this chlorinated molecule in vivo. The para position of the chlorine atom toward the amidine function may favor the rapid metabolism of the molecule.[64] This kind of electronic activation might not occur with the methyl analogue. Of course, this assumption deserves experimental confirmation. Investigations are in progress to define the nature of the interactions involved in the binding of the ligands, their metabolic pathway, and even to look at the possible antagonist activity of such nonhypotensive ligands.

One can notice that all the compounds that decreased BP after systemic administration also reduced BP after ic injection. It strongly suggests that the hypotensive activity of such compounds is due to their central sympatho-inhibitory action. This assumption is strengthened by the fact that all hypotensive compounds were able to decrease HR, which is centrally triggered. As a matter of fact, a drug which simultaneously reduces BP and HR after both systemic and central administration necessarily inhibits the sympathetic nervous system activity. This claim was recently confirmed when we showed that compound **13** decreased the sympathetic activity directly measured on the renal nerve.[13]

Compounds **1**−**4**, **9**−**11**, **15**, **17**, and **18**, which were inactive after iv injection, were also inactive after direct central administration. Indeed, their lack of activity on BP was not due to their inability to cross the blood−brain barrier (BBB). We calculated p$K_a$ and Log *P* of each molecule of the set (see Supporting Information).[65] These parameters (p$K_a$ ranging 7.9−9.3 units, Log *P* ranging 2.3−3.5 units) are in accordance with those required for a central action,[66] which are to be compared with those of rilmenidine (p$K_a$ = 9.22; Log *P* = 1.63) and clonidine (p$K_a$ = 8.11; Log *P* = 1.59).[67] These assumptions were completed by in silico estimations of the BBB crossing capacity of compounds **1**−**18** and reference compounds clonidine and rilmenidine (see Supporting Information). BBB transport parameters were calculated with ACD-iLab software and a correlation was established between LogBB, which is the logarithm of the distribution ratio of a compound between brain tissue and plasma, and Log(PS·$f_u$, brain), which is the logarithm of the brain/plasma equilibration rate, in order to predict if a compound is able to reach the CNS.[68] As a result, all compounds were estimated able to cross the BBB.

Our new active 2-aryliminopyrrolidines selective for $I_1$Rs are more promising hypotensive agents than any other pyrrolidine derivatives tested so far because they are active after systemic administration. This statement is even strengthened by our recent work dealing with the treatment of experimental MetS by a sympatho-inhibitory drug. Our leader compound (**13**) was fully tested in a rodent model of MetS. Compound **13**, which is orally bioavailable, not only reduces BP but also weight gain and total cholesterol; moreover, it improves glucose tolerance and insulin resistance, all relevant biological parameters related to MetS.[13,69] Other compounds belonging to our series of 2-aryliminopyrrolidines, highly selective for $I_1$Rs and shown to reduce BP, are currently tested for their metabolic effects.

## CONCLUSION

As a logical continuation of our previous structure−activity relationship studies on 2-aryliminopyrrolidines, additional compounds (**1**−**18**) were prepared and tested for their binding properties on $I_1$Rs and their cardiovascular in vivo effects after both systemic and direct intracerebral administrations. Some compounds have high affinity for $I_1$Rs and are selective for $I_1$Rs vs $\alpha_{2A}$Rs. They were totally devoid of any $\alpha_2$-adrenergic property. The selectivity of such ligands for $I_1$Rs over $\alpha_2$ARs was the consequence of the presence of the methyl group on position-4 or -5 of the pyrrolidinyl ring. The position-4 isomere seems more relevant, because the affinity to $I_1$Rs of 4-substituted compounds is higher. These 2-aryliminopyrrolidines must be substituted on positions-2 and -3 of the aromatic ring to cause hypotension and bradycardia, whatever the way of


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administration. The affinity is also strongly governed by the presence of a substituent on position-4 of the aromatic ring, a halogen atom being very efficient in improving the affinity for $I_1$Rs; the lack of hypotensive effect of some of such 4-substituted compounds might be due to unexpected additional pharmacological properties. It is interesting to note that the methylated derivative in position-4 causes hypotension.

The compounds tested in this study which decreased BP after iv administration as well as after ic injection, i.e., those which were able to cross the BBB, had variables potencies but had efficacies similar to those of reference drugs, such as clonidine, moxonidine, and rilmenidine.[27,41−43]

Although affinity for $I_1$Rs is a necessary but not a sufficient condition to cause hypotension, the present study shows further structure−activity relationship information on 2-aryliminopyrrolidines and provides the first examples of pyrrolidine ligands highly selective and with high affinity for $I_1$Rs, which are hypotensive after systemic injection. Their lack of adrenergic properties is expected to avoid the adverse effects usually caused by centrally active antihypertensive drugs of the first generation, such as sedation. Selective ligands such as **13** are valuable tools to further study the pharmacology of $I_1$Rs and to further explore the field of central regulation of the cardiovascular and metabolic functions. The results of this study, strengthened by those we recently obtained in the treatment of the MetS by **13** (LNP599),[13,69] support the therapeutic potential of such 2-aryliminopyrrolidines.

## EXPERIMENTAL SECTION

**Pharmacology.** *In Vivo Studies.* All animal care and experimental procedures complied with the rules of the European communities Council Directive of 24 November 1986 (86/609/EEC) and the French Department of Agriculture (license no. 67-337 to P. Bousquet).

**Arterial Blood Pressure and Heart Rate Measurements in Anaesthetized Wistar Rats.** Adult male Wistar rats were anesthetized (sodium pentobarbital 50 mg/kg, ip), and physiological temperature was maintained. The animals were then tracheotomized, and the left carotid vein was catheterized to allow iv injections. The animals were immobilized with pancuronium bromide (Pavulon, Organon) (1 mg/kg, (iv) and artificially ventilated with room air (Hugo Sachs electronic model 7025). A catheter was introduced into the left femoral artery and connected to a pressure processor and recorder (Gould Electronics model BS-272). Heart rate (HR), systolic (SBP), diastolic (DBP), and mean (MBP) arterial pressures (MBP = DBP + $^1/_3$(SBP − DBP)) were continuously monitored from the pressure signal (Gould Biotach amplifier model 13-4615-66). BP and HR were measured over a 90 min experimental period. Results were expressed as the maximal variation of mean arterial pressure (mmHg) and heart rate (bpm) compared to the basal values before treatment. The corresponding percentages of variation were also determined. Results were defined as significant for variation greater than 15% of the basal value. In experiments during which the drug was injected intracisternally, a volume of 0.2 mL of drug solution was injected after removal of the same volume of cerebrospinal fluid.

**Radioligand Binding Assays. $I_1$−Receptors Binding Assays.** *Cell Culture.* PC-12 cells obtained from Dr. G. Rebel (IRCAD, Strasbourg, France) were cultured in 75 $cm^2$ flasks in DMEM (1 g/L glucose) supplemented with 10% heat-inactivated fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin. When the cells reached confluence (3−4 days after plating), they were harvested by a 2 min exposure to 0.25% trypsin at 37 °C. For binding assays, after removing the medium, cells at confluence were frozen in the flasks at −20 °C until used to prepare membranes.

*Cell Extracts.* Frozen PC-12 cells were scraped into cold Tris-HEPES buffer (5 mM Tris-HEPES, pH 7.7, 0.5 mM EDTA, 0.5 mM EGTA, and 0.5 mM $MgCl_2$) and homogenized and lyzed with a Potter homogenizer. After centrifugation at 75000*g* for 20 min, the pellet was washed twice in cold Tris-HEPES buffer and centrifuged. Pellets were resuspended in the same buffer at a concentration of 1−2 mg of protein/mL. Membrane preparations were stored at −80 °C until use.

*Binding Experiments.* Competition binding assays were performed using 0.5 nM [$^{125}$I]PIC (2200 Ci/mmol (PerkinElmer, USA)) and seven different concentrations of the unlabeled ligand under investigation, ranging from $10^{-10}$ to $10^{-4}$ M. Nonspecific binding was defined as [$^{125}$I]PIC binding in the presence of 10 μM PIC. Each point is the mean of 3−5 experiments performed in triplicate using different membrane preparations.

Incubation was initiated by the addition of PC12 cell membranes (10−30 μg of protein) in a final volume of 250 μL of Tris−HEPES buffer (5 mM Tris−HEPES, pH 7.7, 0.5 mM EDTA, 0.5 mM EGTA, and 0.5 mM $MgCl_2$) and was carried out at 25 °C for 45 min. The reaction was stopped by rapid vacuum filtration through GF/B glass fiber filters treated with 0.3% PEI with a Brandel harvester, followed by three rapid washes of the filters with 3 mL of ice-cold 50 mM Tris−HCl buffer, pH 7.4. Radioactivity retained on the dried filters was determined in a Minaxi gamma counter (Packard, Meriden, CT, USA).

**$\alpha_2$-Adrenoreceptors Binding Assays.** Membranes were prepared as described by Newman-Tancredi et al.[70] These membranes (30 μg protein/mL for CHO-h$\alpha_{2A}$) were incubated for 60 min at room temperature in binding buffer (33 mM Tris HCl, 1 mM EDTA, pH 7.5) in a final volume of 500 μL containing 1 nM [$^3$H]RX821002. The incubation was stopped by rapid filtration under vacuum through GF/B glass fiber filters followed by three successive washes with ice-cold binding buffer. Nonspecific binding was defined with 100 μM (−)epinephrine.

**Data Analysis.** Competition experiments were analyzed using the iterative nonlinear least-squares curve-fitting program GraphPad. $K_i$ were determined using the method of Cheng and Prussof.[71] Data are presented as mean ± SEM.

**Chemistry.** All solvents were purified according to standard procedures before use. Thin-layer chromatography was performed on precoated plate of silica gel 60F254 (Merk). Flash chromatography was conducted with silica gel Supporting Information 60 (40−63 μm) as a stationary phase. Melting points were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or $D_2O$ on a Bruker AV300 spectrometer. Chemical shifts ($\delta$) are expressed in parts per million (ppm), and coupling constants ($J$) are expressed in hertz (Hz). The abbreviations used for the multiplicities are as follow: m, unspecified multiplet, s, singlet, d, doublet, t, triplet, q, quartet. All target compounds were tested as their hydrochloride salts. Elemental analyses were performed at the Service de Microanalyses, University of Strasbourg, Strasbourg, France. Analytical results obtained for C, H, and N were within ±0.4% of the calculated theoretical values (see Supporting Information). Lactam **19a** and anilines used to prepare compounds **1**−**6**, **8**, **12**, **13**, and **18** were obtained from commercial sources. Procedure and data concerning compounds **19b** and **21**−**29** are described in Supporting Information. Calculations of the physical properties of compounds and estimations of their BBB crossing ability are reported in Supporting Information. The 2-aryliminopyrrolidines **1**−**18** described here were patented recently by the University of Strasbourg.[69]

**General Procedure for the Preparation of 2-Aryliminopyrrolidines 1−18.**[32] A solution of the appropriate lactam **19a/b** (5 mmol) and the chosen aniline derivative (1 equiv) was prepared in dichloroethane (10 mL), under an argon atmosphere. $POCl_3$ (1 equiv) was added dropwise to the vigorously stirred mixture, which was then heated at 60 °C for 6 h. The cooled mixture was hydrolyzed with 5 mL of a saturated aqueous solution of $Na_2CO_3$. The aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried over anhydrous $Na_2SO_4$, and the solvent was distilled under reduced pressure. The product was purified by flash chromatography (3% TEA in AcOEt) to give the 2-aryliminopyrrolidines **1**−**18**. The hydrochloride salts were prepared by the addition of an anhydrous ethanolic HCl solution of known concentration to an anhydrous


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J. Med. Chem. XXXX, XXX, XXX−XXX

ethanolic solution of the base (1 equiv). The salts were recrystallized in iPrOH−$Et_2O$. All of them decompose over 200 °C.

*N-(2,6-Dimethylphenyl)-5-methylpyrrolidin-2-imine Hydrochloride (**1**).* Yield 32%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.24 (d, 1H, Har, $J$ = 7.6), 7.17 (t, 1H, Har, $J$ = 7.7), 7.06 (d, 1H, Har, $J$ = 7.6), 4.02 (h, 1H, CH, $J$ = 6.4), 3.05 (m, 2H, $CH_2$), 2.34 (m, 1H, 1/2 $CH_2$), 2.24 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 1.81 (m, 1H, 1/2 $CH_2$), 1.13 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.2, 139.2, 133.5, 133.1, 131.2, 126.6, 124.0, 56.2, 43.8, 37.0, 28.6, 24.9, 17.2. Anal. ($C_{13}H_{18}N_2$·HCl) C, H, N.

*N-(2-Fluoro-5-methylphenyl)-5-methylpyrrolidin-2-imine Hydrochloride (**2**).* Yield 4, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.20−7.09 (m, 3H, Har), 4.11 (hex, 1H, CH, $J$ = 6.8), 3.05 (m, 2H, $CH_2$), 2.39 (m, 1H, 1/2 $CH_2$), 2.25 (s, 3H, $CH_3$), 1.80 (m, 1H, 1/2 $CH_2$), 1.08 (d, 3H, $CH_3$, $J$ = 6.5). $^{13}$C NMR ($D_2O$) $\delta$ 168.4, 154.3 (d, $J^1_{C-F}$ = 244.5), 135.7, 130.9, 126.9, 121.6 (d, $J^2_{C-F}$ = 13.2), 116.4 (d, $J^2_{C-F}$= 19.5), 57.2, 30.5, 28.1, 21.3, 19.7. $^{19}$F NMR ($D_2O$) $\delta$ −128.3. Anal. ($C_{12}H_{15}FN_2$·HCl) C, H, N.

*N-(2-Chloro-5-methylphenyl)-5-methylpyrrolidin-2-imine Hydrochloride (**3**).* Yield 47%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.38 (dd, 1H, Har, $J$ = 3.1, $J$ = 7.8), 7.18 (d, 1H, Har, $J$ = 2.9), 7.16 (dd, 1H, Har, $J$ = 3.0, $J$ = 7.7), 4.05 (m, 1H, CH), 2.99 (m, 2H, $CH_2$), 2.37 (m, 1H, 1/2 $CH_2$), 2.24 (s, 3H, $CH_3$), 1.77 (m, 1H, 1/2 $CH_2$), 1.16 (d, 3H, $CH_3$, $J$ = 6.3). $^{13}$C NMR ($D_2O$) $\delta$ 168.5, 139.4, 131.2, 130.2, 128.0, 126.8, 124.4, 57.1, 30.2, 28.1, 19.8, 19.7. Anal. ($C_{12}H_{15}ClN_2$·HCl) C, H, N

*N-(4-Fluoro-2-methylphenyl)-5-methylpyrrolidin-2-imine Hydrochloride (**4**).* Yield 35%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.22 (dd, 1H, Har, $J$ = 5.4, $J$ = 8.7), 7.09 (dd, 1H, Har, $J$ = 2.9, $J$ = 8.7), 7.0 (dt, 1H, Har, $J$ = 2.9, $J$ = 8.8), 4.14 (hex, 1H, CH, $J$ = 6.7), 3.07 (m, 2H, $CH_2$), 2.41 (m, 1H, 1/2 $CH_2$), 2.17 (s, 3H, $CH_3$), 1.77 (m, 1H, 1/2 $CH_2$), 1.11 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 169.8, 161.9 (d, $J^1_{C-F}$ = 248.8), 137.8 (d, $J^3_{C-F}$ = 9.2), 129.3 (d, $J^4_{C-F}$ = 2.8), 128.3 (d, $J^3_{C-F}$ = 9.6), 117.5 (d, $J^2_{C-F}$ = 22.7), 114.2 (d, $J^2_{C-F}$ = 23.0), 55.6, 31.5, 28.8, 19.7, 19.5. $^{19}$F NMR ($D_2O$) $\delta$ −113.4. Anal. ($C_{12}H_{15}FN_2$·HCl) C, H, N.

*N-(2,3-Dimethylphenyl)-5-methylpyrrolidin-2-imine Hydrochloride (**5**).* Yield 43%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.24 (d, 1H, Har, $J$ = 7.6), 7.17 (t, 1H, Har, $J$ = 7.7), 7.06 (d, 1H, Har, $J$ = 7.6), 4.02 (h, 1H, CH, $J$ = 6.4), 3.05 (m, 2H, $CH_2$), 2.34 (m, 1H, 1/2 $CH_2$), 2.24 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 1.81 (m, 1H, 1/2 $CH_2$), 1.13 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.2, 139.2, 133.5, 133.1, 131.2, 126.6, 124.0, 56.2, 43.8, 37.0, 28.6, 24.9, 17.2. Anal. ($C_{13}H_{18}N_2$·HCl) C, H, N.

*N-(3-Chloro-2-methylphenyl)-5-methylpyrrolidin-2-imine Hydrochloride (**6**).* Yield 44%, white solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.41 (d, 1H, Har, $J$ = 7.8), 7.23 (d, 1H, Har, $J$ = 7.9), 7.18 (t, 1H, Har, $J$ = 7.8), 4.02 (h, 1H, CH, $J$ = 6.4), 3.08 (m, 2H, $CH_2$), 2.34 (m, 1H, 1/2 $CH_2$), 2.25 (s, 3H, $CH_3$), 2.11 (s, 3H, $CH_3$), 1.83 (m, 1H, 1/2 $CH_2$), 1.13 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.7, 139.5, 133.4, 132.8, 130.5, 126.8, 123.7, 56.2, 32.3, 30.5, 29.7, 24.9, 20.2. Anal. ($C_{12}H_{15}ClN_2$·HCl) C, H, N.

*N-(2,3-Dihydro-1H-inden-4-yl)-5-methylpyrrolidin-2-imine Hydrochloride (**7**).* Yield 42%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.28 (d, 1H, Har, $J$ = 7.5), 7.21 (t, 1H, Har, $J$ = 7.6), 7.02 (d, 1H, Har, $J$ = 7.6), 4.07 (h, 1H, CH, $J$ = 6.4), 3.03 (m, 2H, $CH_2$), 2.88 (t, 2H, $CH_2$, $J$ = 7.5), 2.74 (t, 2H, $CH_2$, $J$ = 7.4), 2.37 (m, 1H, 1/2 $CH_2$), 2.00 (qn, 2H, $CH_2$, $J$ = 7.3), 1.79 (m, 1H, 1/2 $CH_2$), 1.17 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.0, 147.6, 140.3, 130.7, 127.9, 125.0, 122.6, 56.8, 32.6, 30.1, 29.9, 28.2, 24.8, 19.9. Anal. ($C_{14}H_{18}N_2$·HCl) C, H, N.

*N-(5,6,7,8-Tetrahydronaphthalen-1-yl)-5-methylpyrrolidin-2-imine Hydrochloride (**8**).* Yield 85%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.17 (d, 2H, Har, $J$ = 7), 7.03 (t, 1H, Har, $J$ = 7.1), 4.03 (m, 1H, CH), 3.00 (m, 2H, $CH_2$), 2.72 (t, 2H, $CH_2$, $J$ = 5.7), 2.51 (t, 2H, $CH_2$, $J$ = 5.9), 2.36 (m, 1H, 1/2 $CH_2$), 1.81−1.61 (m, 5H, 1/2 $CH_2$ + 2 × $CH_2$), 1.15 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.6, 140.1, 133.9, 133.0, 130.2, 126.6, 123.6, 56.6, 29.9, 28.9, 28.2, 24.1, 22.1, 22.0, 19.8. Anal. ($C_{15}H_{20}N_2$·HCl) C, H, N.

*N-(2,3-Dihydro-1H-inden-5-yl)-5-methylpyrrolidin-2-imine Hydrochloride (**9**).* Yield 31%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.26 (d, 1H, Har, $J$ = 8.0), 7.08 (d, 1H, Har, $J$ = 1.5), 6.96 (dd, 1H, Har, $J$ = 1.9, $J$ = 7.9), 4.03 (h, 1H, CH, $J$ = 6.6), 2.95 (m, 2H, $CH_2$), 2.80 (t, 4H, 2 × $CH_2$, $J$ = 7.5), 2.32 (m, 1H, 1/2 $CH_2$), 1.97 (qn, 2H, $CH_2$, $J$ = 7.5), 1.75 (m, 1H, 1/2 $CH_2$), 1.16 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 167.7, 145.7, 145.1, 132.7, 125.5, 121.9, 120.1, 56.9, 32.3, 32.0, 30.4, 28.0, 25.3, 19.8. Anal. ($C_{14}H_{18}N_2$·HCl) C, H, N.

*N-(6-Chloro-2,3-dihydro-1H-inden-5-yl)-5-methylpyrrolidin-2-imine Hydrochloride (**10**).* Yield 50%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.18 (s, 1H, Har), 6.91 (s, 1H, Har), 4.07 (h, 1H, CH, $J$ = 6.6), 2.93 (m, 2H, $CH_2$), 2.81 (t, 4H, 2 × $CH_2$, $J$ = 7.5), 2.32 (m, 1H, 1/2 $CH_2$), 1.97 (qn, 2H, $CH_2$, $J$ = 7.5), 1.75 (m, 1H, 1/2 $CH_2$), 1.63 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.5, 145.3, 145.9, 133.4, 127.5, 122.7, 121.6, 57.2, 32.2, 31.8, 30.6, 27.9, 25.5, 21.1. Anal. ($C_{14}H_{17}ClN_2$·HCl) C, H, N.

*N-(7-Chloro-2,3-dihydro-1H-inden-4-yl)-5-methylpyrrolidin-2-imine Hydrochloride (**11**).* Yield 69%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.22 (d, 1H, Har, $J$ = 8.3), 7.01 (d, 1H, Har, $J$ = 8.4), 4.05 (h, 1H, CH, $J$ = 6.4), 3.02 (m, 2H, $CH_2$), 2.93 (t, 2H, $CH_2$, $J$ = 7.6), 2.81 (t, 2H, $CH_2$, $J$ = 7.5), 2.36 (m, 1H, 1/2 $CH_2$), 2.03 (qn, 2H, $CH_2$, $J$ = 7.6), 1.79 (m, 1H, 1/2 $CH_2$), 1.17 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.4, 145.1, 142.5, 130.5, 129.2, 127.8, 124.4, 56.8, 32.6, 30.1, 29.9, 28.2, 24.8, 19.9. Anal. ($C_{14}H_{18}ClN_2$·HCl) C, H, N.

*N-(2,3-Dimethylphenyl)-4-methylpyrrolidin-2-imine Hydrochloride (**12**).* Yield 40%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.21 (d, 1H, Har, $J$ = 7.7), 7.16 (t, 1H, Har, $J$ = 7.7), 7.03 (d, 1H, Har, $J$ = 7.6), 3.68 (m, 1H, 1/2 $CH_2$), 3.20 (m, 2H, 1/2 $CH_2$ + CH), 2.72 (m, 2H, $CH_2$), 2.30 (s, 3H, $CH_3$), 2.11 (s, 3H, $CH_3$), 1.12 (s, 6H, 2 × $CH_3$). $^{13}$C NMR ($D_2O$) $\delta$ 168.7, 139.5, 133.4, 132.8, 130.5, 126.8, 123.7, 54.5, 43.7, 37.0, 25.6, 19.4, 12.3. Anal. ($C_{13}H_{18}N_2$·HCl) C, H, N.

*N-(3-Chloro-2-methylphenyl)-4-methylpyrrolidin-2-imine Hydrochloride (**13**).* Yield 51%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.45 (d, 1H, Har, $J$ = 7.9), 7.25 (d, 1H, Har, $J$ = 7.9), 7.20 (t, 1H, Har, $J$ = 7.8), 3.70 (m, 1H, 1/2 $CH_2$), 3.19 (m, 2H, 1/2 $CH_2$ + CH), 2.74 (m, 2H, $CH_2$), 2.22 (s, 3H, $CH_3$), 1.10 (d, 3H, $CH_3$, $J$ = 6.5). $^{13}$C NMR ($D_2O$) $\delta$ 169.1, 135.5, 133.4, 132.3, 130.1, 128.1, 125.3, 54.2, 37.9, 29.5, 18.1, 14.2. Anal. ($C_{12}H_{15}ClN_2$·HCl) C, H, N.

*N-(2,3-Dihydro-1H-inden-4-yl)-4-methylpyrrolidin-2-imine Hydrochloride (**14**).* Yield 33%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.28 (d, 1H, Har, $J$ = 7.5), 7.21 (t, 1H, Har, $J$ = 7.6), 7.03 (d, 1H, Har, $J$ = 7.5), 3.70 (dd, 1H, 1/2 $CH_2$, $J$ = 10.8, $J$ = 7.8), 3.19 (dd, 1H, 1/2 $CH_2$, $J$ = 11, $J$ = 6), 3.14 (m, 1H, 1/2 $CH_2$), 2.89 (t, 2H, $CH_2$, $J$ = 7.4), 2.74 (t, 2H, $CH_2$, $J$ = 7.4), 2.65 (m, 2H, CH + 1/2 $CH_2$), 2.01 (qn, 2H, $CH_2$, $J$ = 7.5), 1.10 (d, 3H, $CH_3$, $J$ = 7). $^{13}$C NMR ($D_2O$) $\delta$ 168.3, 147.6, 140.2, 130.5, 127.9, 124.9, 122.5, 54.1, 37.8, 32.6, 29.9, 29.5, 24.7, 17.6. Anal. ($C_{14}H_{18}N_2$·HCl) C, H, N.

*N-(7-Chloro-2,3-dihydro-1H-inden-4-yl)-4-methylpyrrolidin-2-imine Hydrochloride (**15**).* Yield 43%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.22 (d, 1H, Har, $J$ = 8.3), 7.01 (d, 1H, Har, $J$ = 8.4), 3.70 (dd, 1H, 1/2 $CH_2$, $J$ = 10.9, $J$ = 7.7), 3.20 (dd, 1H, 1/2 $CH_2$, $J$ = 10.9, $J$ = 7.2), 3.12 (m, 1H, 1/2 $CH_2$), 2.93 (t, 2H, $CH_2$, $J$ = 7.6), 2.82 (t, 2H, $CH_2$, $J$ = 7.5), 2.65 (m, 2H, CH + 1/2 $CH_2$), 2.04 (qn, 2H, $CH_2$, $J$ = 7.6), 1.08 (d, 3H, $CH_3$, $J$ = 6.8). $^{13}$C NMR ($D_2O$) $\delta$ 168.5, 145.2, 142.4, 130.4, 129.1, 127.8, 124.5, 54.2, 37.9, 32.2, 30.9, 29.5, 23.8, 17.7. Anal. ($C_{14}H_{17}ClN_2$·HCl) C, H, N.

*N-(7-Methyl-2,3-dihydro-1H-inden-4-yl)-4-methylpyrrolidin-2-imine Hydrochloride (**16**).* Yield 51%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.06 (d, 1H, Har, $J$ = 8), 6.95 (d,1H, Har, $J$ = 8), 3.7 (dd, 1H, 1/2 $CH_2$, $J$ = 10.8, $J$ = 7.7), 3.21−3.09 (m, 2H, 1/2 $CH_2$ + CH), 2.82 (t, 2H, CH2, $J$ = 7.5), 2.75 (t, 2H, $CH_2$, $J$ = 7.5), 2.67 (m, 2H, $CH_2$), 2.19 (s, 3H, $CH_3$), 2.01 (qn, 2H, $CH_2$, $J$ = 7.5), 1.09 (d, 3H, $CH_3$, $J$ = 6.7). $^{13}$C NMR ($D_2O$) $\delta$ 168.4, 145.9, 139.8, 135.2, 132.4, 128.5, 128.1, 122.8, 54.0, 37.8, 31.3, 30.1, 29.6, 24.2, 18.1, 17.7. Anal. ($C_{15}H_{20}N_2$·HCl) C, H, N.

*N-(2,3-Dihydro-1H-inden-5-yl)-4-methylpyrrolidin-2-imine Hydrochloride (**17**).* Yield 55%, white solid. $^1$H NMR ($D_2O$) $\delta$ 7.26 (d, 1H, Har, $J$ = 8.0), 7.08 (d, 1H, Har, $J$ = 1.5), 6.96 (dd, 1H, Har, $J$ = 1.9, $J$ = 7.9), 4.03 (h, 1H, CH, $J$ = 6.6), 2.95 (m, 2H, $CH_2$), 2.80 (t, 4H, 2 × $CH_2$, $J$ = 7.5), 2.32 (m, 1H, 1/2 $CH_2$), 1.97 (qn, 2H, $CH_2$, $J$ = 7.5), 1.75 (m, 1H, 1/2 $CH_2$), 1.16 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 167.7, 145.7, 145.1, 132.7, 125.5, 121.9, 120.1, 56.9, 32.3, 32.0, 30.4, 28.0, 25.3, 19.8. Anal. ($C_{14}H_{18}N_2$·HCl) C, H, N.

*N-(5,6,7,8-Tetrahydronaphthalen-1-yl)-4-methylpyrrolidin-2-imine Hydrochloride (**18**).* Yield 60%, white solid. $^1$H NMR ($D_2O$) $\delta$


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J. Med. Chem. XXXX, XXX, XXX−XXX

7.17 (d, 2H, Har, $J$ = 7), 7.03 (t, 1H, Har, $J$ = 7.1), 4.03 (m, 1H, CH), 3.00 (m, 2H, $CH_2$), 2.72 (t, 2H, $CH_2$, $J$ = 5.7), 2.51 (t, 2H, $CH_2$, $J$ = 5.9), 2.36 (m, 1H, 1/2 $CH_2$), 1.81−1.61 (m, 5H, 1/2 $CH_2$ + 2 × $CH_2$), 1.15 (d, 3H, $CH_3$, $J$ = 6.4). $^{13}$C NMR ($D_2O$) $\delta$ 168.6, 140.1, 133.9, 133.0, 130.2, 126.6, 123.6, 56.6, 29.9, 28.9, 28.2, 24.1, 22.1, 22.0, 19.8. Anal. ($C_{15}H_{20}N_2$·HCl) C, H, N.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental part for the syntheses and characterizations of compounds **19b−29**, data of elemental analysis of compounds **1−18**, and calculations of their physical properties. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*Phone: +33 (0) 3 68 85 33 90. Fax: +33 (0)3 68 85 33 88. E-mail: pascal.bousquet@unistra.fr.

### Present Address

†For S.S.: Domain Therapeutics, Quai Sébastien Brandt, 67400 Illkirch, France.

### Author Contributions

‡V.G. and H.G. contributed equally to this study.


### Notes

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## ■ ABBREVIATIONS USED

$\alpha$ARs, alpha-adrenergic receptors; BP, blood pressure; bpm, beats per minute; DAG, diacylglycerol; DMEM, Dulbecco's Modified Eagle Medium; EGTA, ethylene glycol-bis(2-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid; HEPES, 2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; IRs, imidazoline receptors; ic, intracisternal; IRC, imidazoline related compounds; MetS, metabolic syndrome; PEI, polyethylenimine; PIC, para-iodoclonidine; RX821002, 2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline

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*J. Med. Chem.* XXXX, XXX, XXX−XXX