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Antagonism/Agonism Modulation to Build Novel Antihypertensives Selectively Triggering I_1-Imidazoline Receptor Activation

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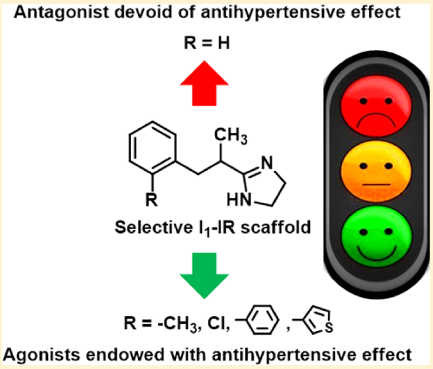
Supporting Information

ABSTRACT: Pharmacological studies have suggested that I_1-imidazoline receptors are involved in the regulation of cardiovascular function and that selective I_1-agonists, devoid of the side effects associated with the common hypotensive α_2-adrenoreceptor agonists, might be considered as a second generation of centrally acting antihypertensives. Therefore, in the present study, inspired by the antihypertensive behavior of our selective I_1-agonist **4**, we designed, prepared, and studied the novel analogues **5**−**9**. A selective I_1-profile, associated with significant hemodinamic effects, was displayed by **5**, **8**, and **9**. Interestingly, the highest potency and longest lasting activity displayed by **8** (carbomethyline) suggested that van der Waals interactions, promoted by the ortho methyl decoration of its aromatic moiety, are particularly advantageous. In addition, in analogy to what was noted for (*S*)-(+)-**4**, the observation that only (*S*)-(+)-**8** displayed significant hemodynamic effects unequivocally confirmed the stereospecific nature of the I_1 proteins.



KEYWORDS: *imidazoline compounds, I_1-agonists, antihypertensive agents, bradicardic agents, stereoselectivity, carbomethyline*

The existence of imidazoline binding sites (IBS) was hypothesized about 20 years ago, when Bousquet et al. discovered that the imidazoline compound clonidine and its analogues yielded their central therapeutic antihypertensive effects by interacting not only with α_2-adrenergic receptors (α_2-ARs), but also with imidazoline preferring binding sites (IBS).[1,2]

The α_2-ARs, subdivided into α_{2A}-, α_{2B}-, and α_{2C}-subtypes, belong to the superfamily of G-protein-coupled receptors. Briefly, the α_{2A}-subtype mediates hypotension, sedation and analgesia, the α_{2B}-subtype mediates vasoconstriction, whereas the α_{2C}-subtype contributes to the adrenergic-opioid synergy.[3−5]

The IBS, which are not activated by catecholamines, proved to be pharmacologically distinct from the α_2-ARs. The structures of these binding proteins, as well as their conclusive subclassification and some physiological roles, still remain to be assessed, mainly because the ligands used for their characterization often suffered from lack of selectivity within the same system and with respect to other receptor systems. Anyway, at present, the IBS appear to be divided into the I_1-IBS, I_2-IBS, and I_3-IBS subtypes, with the first two recognized preferentially by [^{3}H]-clonidine and [^{3}H]-idazoxan, respectively. Agmatine, a metabolite of arginine, has been reported as one of their possible endogenous ligands. The I_2-IBS are mainly involved in psychiatric disorders, analgesia, opiate withdrawal, and Parkinson's and Alzheimer's diseases. The I_3-IBS regulate insulin secretion.[6,7] The I_1-IBS (or I_1-IRs, for I_1-imidazoline receptors) have been identified in the human and bovine brainstem membranes, and a fairly high density is observed in the region of the medulla oblongata, that contains the sites of the hypotensive action for imidazoline-like and related drugs. The I_1-IRs display an important role in central cardiovascular regulation.[7] Several experimental studies suggest coupling of the I_1-IRs to G-proteins. Activation of phosphatidylcholine-sensitive phospholipase C (PC-PLC)[8] and inhibition of adenylcyclase[9] are two main signal transduction mechanisms associated with I_1-IR activation. I_1-IR agonists, such as rilmenidine or benazoline, activate both transduction pathways;

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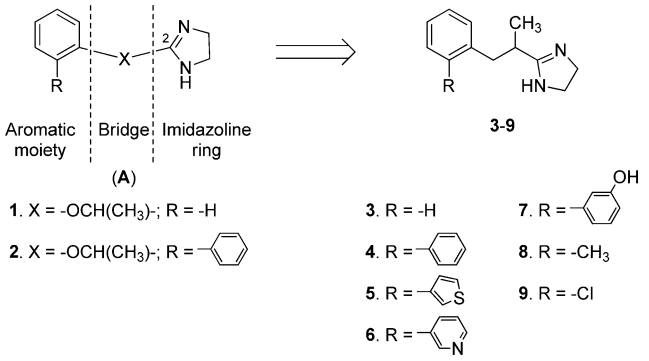
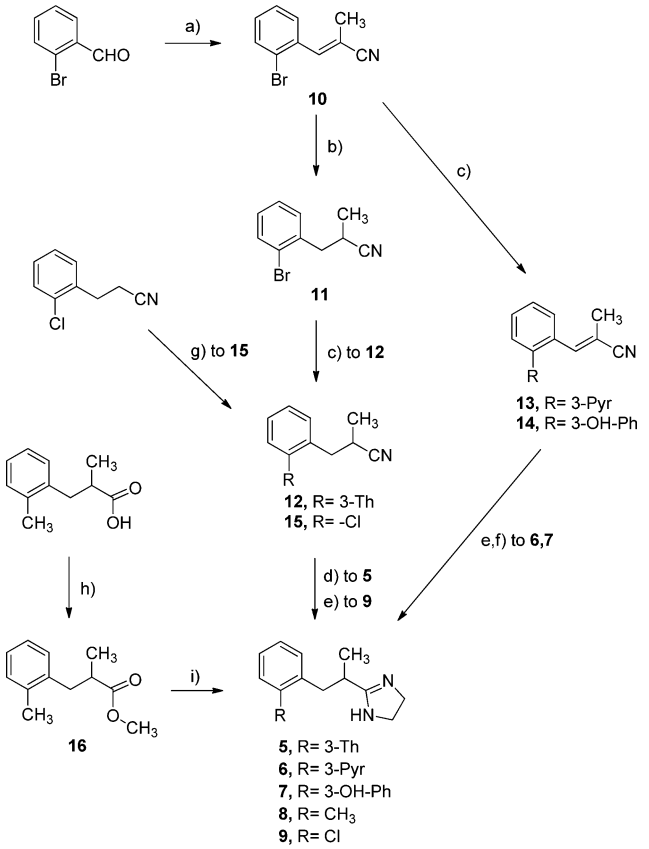
the partial agonist Efaroxan activates only the second transduction pathway, whereas the antagonist S23757 blocks both transduction pathways.[8,9] Activation triggered by I_1-IR agonists also induces an increase in phosphorylation of mitogen-activated protein kinases (MAPK1 and MAPK3) in Rostral Ventrolateral Medulla (RVLM) neurons, which reduces blood pressure.[10] The involvement of I_1-IRs proved to be particularly advantageous in the case of the antihypertensive drugs rilmenidine and moxonidine, which, although binding with good affinity to both α_2-ARs and I_1-IRs, are endowed with some selectivity for the latter.[6,11] Indeed, compared to clonidine, rilmenidine and moxonidine show a reduced incidence and a less pronounced severity of the side effects associated with α_2-AR activation (i.e., sedation, dry mouth, drowsiness). Therefore, on the basis of such observations, selective I_1-IR agonists might be considered a second generation of centrally acting anthypertensives.[12] Over the years our research has yielded several imidazoline molecules that interact with IBS and α_2-ARs and share the common scaffold (A) reported in Chart 1.

From our previous structure−activity relationship (SAR) studies, it emerged that the bridge (X) and the aromatic moiety, which taken together constitute the substituent at position 2 of the imidazoline nucleus, display different functions. Indeed, the chemical nature of the bridge was especially responsible for preferential or multitarget recognition,[13,14] whereas that of the aromatic moiety appeared to modulate the functional behavior of the ligand.[15,16] In particular, the $-OCH(CH_3)-$ bridge was suitable for ligands addressed to the α_2-ARs (e.g., compounds **1** and **2**), whereas the isosteric wolly carbon $-CH_2CH(CH_3)-$ chain yielded high I_1-IR affinity and significant selectivity over the α_2-ARs, as observed for compound **3** (pK_i = 8.30; selectivity ratio I_1/α_2 = 708). In both cases, the presence of the methyl group in the bridge strongly disadvantaged the I_2-IBS interaction.[13] Such observations suggested the existence of a "methyl pocket" in the α_2-AR[17] and I_1-IR, but not in the I_2-IBS binding cavity. Compound **1** behaved as an antagonist at the three α_2-AR subtypes. Nevertheless, the introduction of substituents in the ortho position of its phenyl ring significantly modulated its biological profile. Indeed, its ortho phenyl derivative **2** (biphenyline) behaved as an efficacious agonist. Its enantiomer (*S*)-(−)-**2** was also endowed with a significant and long-lasting antinociceptive effect.[18] Several novel α_2-AR agonists (also subtype selective) were obtained by insertion of different substituents at the ortho position of the phenyl ring of antagonist **1**.[19] Similarly, the unsubstituted I_1-IR selective ligand **3** behaved as an antagonist. Indeed, in in vivo studies, **3** displayed no cardiovascular effect and prevented the hypotensive and bradycardic action of clonidine.[13] The fact that several classes of substances, including those bearing an imidazoline ring, interact with α_2-ARs and I_1-IRs suggests that such systems might present analogies in the nature of some critical binding sites.[20] Based on this hypothesis, to modulate the biological profile of **3** from antagonism to agonism, recently, we prepared and studied its ortho phenyl derivative **4**. This derivative, though endowed with lower affinity, showed the same I_1-character (I_1/α_2 selectivity ratio =513) of the lead. Moreover, probably due to additional $\pi-\pi$ interactions between the ortho phenyl substituent and the corresponding I_1-IR aromatic cluster, **4** behaved as an agonist. Indeed, injected intracisternally (ic) in pentobarbital anaesthetized normotensive rats, it significantly decreased mean arterial blood pressure (MABP) and heart rate (HR). In addition, the very low α_2-AR affinity of **4** ruled out the possible α_2-AR involvement in its

Chart 1. Chemical Structures of Imidazolines 1−9



Scheme 1. Preparation of Imidazolines 5−9[a]



[a]Reagents: (a) $CH_3CH(CN)P(O)(OCH_2CH_3)_2$, NaH, DME; (b) $NaBH_4$, MeOH, DME; (c) $Pd[(C_6H_5)_3P]_4$; Na_2CO_3, 3-thienylboronic acid for **12**, diethyl(3-pyridil)borane for **13**, 3-hydroxyphenilboronic acid for **14**, DME; (d) $NH_2CH_2CH_2NH_2$, $NaOCH_3$; (e) $NH_2CH_2CH_2NH_2$, HCl, MeOH; (f) H_2, Pd/C, (g) MeI, LDA; (h) CH_3OH, H_2SO_4; (i) $NH_2CH_2CH_2NH_2$, $Al(CH_3)_3$.

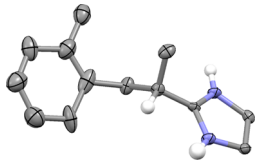


Figure 1. X-ray structure of (*S*)-(+)-**8**. Displacement ellipsoids are drawn at the 50% probability levels.

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Table 1. Binding Affinities (pK_i[a]) of Compounds 1−9 at I_1-R and α_2-AR and Cardiovascular Effects of Compounds 4, 5, 8 and its Enantiomers, and 9 in SHR

	I_1-R	α_2-AR	% MABP reduction[b]			% HR reduction[b]			
compound	pK_i	pK_i	30′	60′	120′	30′	60′	120′	ref
1	6.51 ± 0.17	7.01 ± 0.08							13
2, biphenyline	6.90 ± 0.18	7.91 ± 0.05							21
3	8.30 ± 0.09	5.45 ± 0.07							13
(*R*)-(+)-**3**	5.20 ± 0.08	5.40 ± 0.15							13
(*S*)-(−)-**3**	8.97 ± 0.16	5.30 ± 0.06							13
4	6.81 ± 0.05[c]	4.10 ± 0.15[c]	27.63	25.35	34.92	14.21	13.81	11.92	
(*R*)-(−)-**4**	5.65 ± 0.12								21
(*S*)-(+)-**4**	7.01 ± 0.10								21
5	7.20 ± 0.13	<6	24.77	35.10	10.80	26.36	19.66	11.19	
6	<6	<6							
7	<6	<6							
8	7.63 ± 0.10	<6	32.36	29.68	53.13	11.66	13.58	7.66	
(*R*)-(−)-**8**	5.98 ± 0.14	<6	8.67	12.67	3.01	9.17	4.18	0.00	
(*S*)-(+)-**8**	7.88 ± 0.12	<6	34.44	25.98	7.85	11.99	11.09	5.89	
9	6.71 ± 0.09	<6	37.75	31.41	32.41	11.11	11.56	8.02	

[a]According to ref 13. [b]% MABP and % HR reduction after ip administration (30 mg/kg). Measurements were repeated at 30, 60, 120 min. [c]Ref 21.

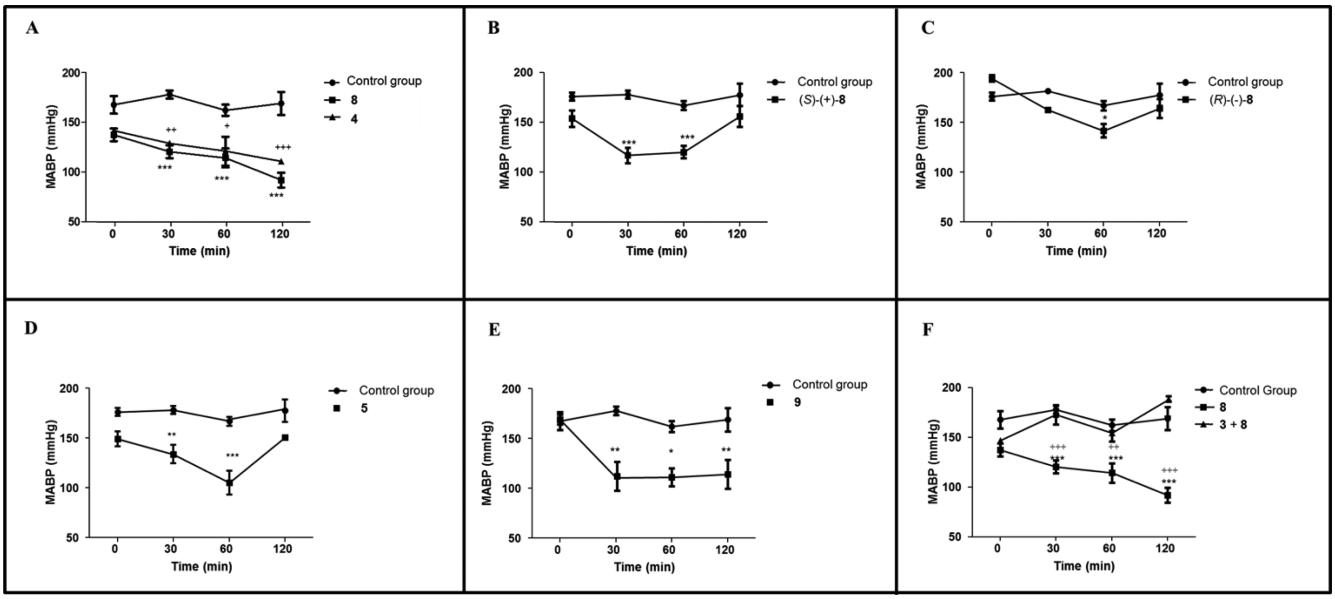

Figure 2. Effects of **8** and **4** (A), (*S*)-(+)-**8** (B), (*R*)-(−)-**8** (C), **5** (D), and **9** (E) on blood pressure measured in SHR after single ip administration (30 mg/kg). Effects of pretreatment with **3** (F) (30 mg/kg) on blood pressure measured in SHR after single ip administration of **8** (30 mg/kg). Measurements were repeated at 30, 60, and 120 min. Data are reported as MABP ± SEM (n = 5). *P < 0.05, **P < 0.01, ***P < 0.001, ^{+}P < 0.05, ^{++}P < 0.01, and ^{+++}P < 0.001 compared to the value of control rats (0 mg/kg). ^{+++}P < 0.001 and ^{++}P < 0.01 compared to the value of **3** + **8** treated rats (30 mg/kg).

cardiovascular effects. This consideration was also supported by the observation that antagonist **3** prevented the hypotensive and bradycardic activity of **4**.[21]

In the present study, to investigate the influence of the specific chemical nature of the ortho substituent on I_1-IR activation and to discover more potent antihypertensive agents, we designed, prepared and studied the novel compounds **5**−**9**, inspired by **4**. Therefore, the role played by the $\pi-\pi$ interactions, hypothesized for the ortho phenyl substituent of **4**, was tested through the design of compounds **5**−**7**, which bear substituents of comparable (**5**) or reduced (**6** and **7**) aromaticity. In addition, van der Waals and polar interactions were probed with methyl and clorine substituents (compounds **8** and **9**, respectively). Such decorations were suggested by our studies with α_2-AR ligands.[15,19,22]

Moreover, both enantiomers of **8** were prepared and included in the present study to support our statement on the stereospecific nature of the I_1 proteins. As we already reported, a high eudismic ratio was observed for **3** [(*S*)/(*R*) = 5888],[13] and, in the case of **4**, only the (*S*)-(+) enantiomer displayed hypotensive and bradicardic effects.[21]

The imidazolines **5**−**9** were prepared according to the synthetic procedure reported in Scheme 1. The reaction of 2-bromobenzaldehyde with diethyl-(1-cyanoethyl)-phosphonate in the presence of NaH led to the nitrile **10**. Its reduction with $NaBH_4$ afforded compound **11** and, followed by treatment with 3-thienylboronic acid in the presence of tetrakis-

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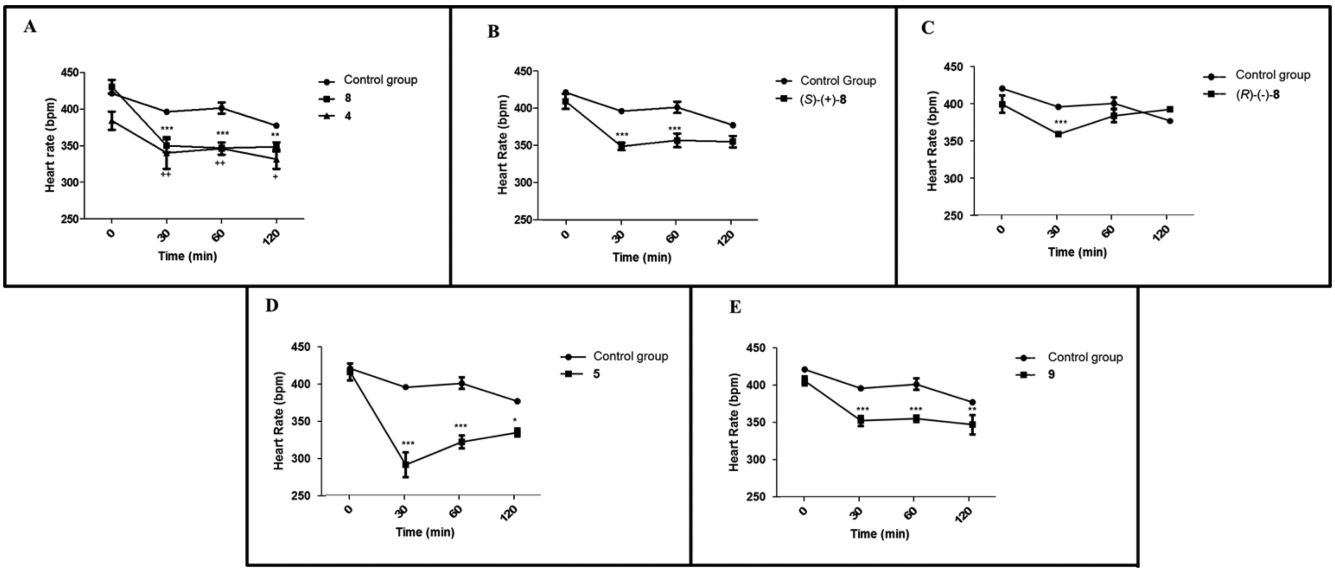

Figure 3. Effects of **8** and **4** (A), (*S*)-(+)-**8** (B), (*R*)-(−)-**8** (C), **5** (D), and **9** (E) on HR measured in SHR after single ip administration (30 mg/kg). Measurements were repeated at 30, 60, 120 min. Data are reported as bpm ± SEM (n = 5). *P < 0.05, **P < 0.01, ***P < 0.001, ^{+}P < 0.05, and ^{++}P < 0.01 compared to the value of control rats (0 mg/kg).

(triphenylphosphine)palladium(0), led to **12**. This intermediate was transformed into the desired imidazoline **5** by condensation with ethylenediamine under basic conditions. The reaction of **10** with diethyl(3-pyridil)borane or 3-hydroxyphenylboronic acid in the presence of tetrakis-(triphenylphosphine)palladium(0) led to **13** and **14**, respectively. Their condensation with ethylenediamine under acidic conditions, followed by catalitic hydrogenation using Pd/C as the catalyst, yielded the desired compounds **6** and **7**, respectively. The methylation of 2-chlorohydrocinnamonitrile (Aldrich) with methyl iodide in the presence of LDA afforded the intermediate **15**, which was transformed in the desired imidazoline **9** by condensation with ethylenediamine under acidic conditions. Finally, the reaction of 2-methyl-3-(*o*-tolyl)propanoic acid[23] with methanol in the presence of H_2SO_4 yielded the methyl ester **16**, which was transformed into the imidazoline **8** by condensation with ethylenediamine in the presence of $Al(CH_3)_3$.

The enantiomers (+)-**8** and (−)-**8** were obtained by fractional crystallization of the salts of (±)-**8** with hydrogen dibenzoyl-D- and hydrogen dibenzoyl-L-tartaric acid, respectively. The enantiomeric purity, determined by ^{1}H NMR spectroscopy in the presence of the chiral solvating reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol, was found to be >98% (detection limit) for both enantiomers. Indeed, the ^{1}H NMR spectrum of racemic compound (±)-**8** showed two doublets at δ 1.20 for the protons of the methyl group of the bridge, whereas only one doublet was observed for (+)-**8** and (−)-**8** at δ 1.21 and δ 1.19, respectively. The absolute configuration *S* was assigned to the dextrorotatory enantiomer (+)-**8** through X-ray diffraction analysis of its dibenzoyl-D-tartrate salt (Figure 1).

I_1-IR affinity values for **5**−**9**, obtained following previously described procedures,[13] are reported in Table 1 along with those of **3**, **4**, and their enantiomers, which were included for useful comparison. The data suggest that in the case of aromatic substituents, only a strong aromaticity, as that associated with the phenyl of **4** (pK_i = 6.81) or the thiophenyl of **5** (pK_i = 7.20) moieties, is favorable. Indeed, negligible affinity (pK_i < 6) was displayed by **6** and **7**, in which the aromaticity of the substituent is weakened by the presence of polar functions inducing an electron-withdrawing effect as the 3-nitrogen atom in **6** or the meta OH group in **7**.[24]

The CH_3 or Cl decorations, characterized by similar moderate steric bulk and positive lipophilic contributions[24] [MR = 6.88, π = +0,56 (**8**) and MR = 6.73, π = +0,71 (**9**)], are compatible with I_1-IR interaction. Nevertheless, the higher I_1-IR affinity value of **8** (pK_i = 7.63) with respect to that of **9** (pK_i = 6.71) suggests that the van der Waals interactions played by the methyl group are more advantageous than the polar interactions induced by the chlorine atom. Analogously to what observed for **3** and **4**, also in the case of **8** the higher I_1-IR affinity was associated with its (*S*)-(+) enantiomer [(*S*)/(*R*) about 80]. This suggests that the three compounds interact with I_1-IRs in a similar manner. Finally, according to the considerations reported in the introduction, all novel compounds displayed negligible α_2-AR affinity (pK_i < 6) (Table 1).

In in vivo studies the effects of **5**, **8** and its enantiomers, and **9** on MABP and HR after single intraperitoneal (ip) administration (30 mg/kg) were measured on adult male spontaneously hypertensive rats (SHR). Measurements were repeated at 30, 60, and 120 min after drug administration. Using the same experimental protocol, **4** was also included in the study. As shown in Table 1 and Figure 2, the tested compounds displayed efficacious hypotensive effects, with the exception of (*R*)-(−)-**8**. Interestingly, **8** showed the highest potency and longest lasting activity (% MABP reduction from 32.36 at 30′ to 53.13 at 120′).

Moreover, analogously to what was observed for its I_1-IR affinity, also its hypotensive effect was significantly higher than that of **4** (Figure 2A). (*S*)-(+)-**8** and **5** showed the highest % MABP reduction at 30′ or 60′, respectively. The MABP reduction induced by **9** had the same value (about % 33) at all the considered times. The observed hypotensive effects were not preceded by any vasoconstrictive action, indicating the lack of the α_2-AR involvement. On the other hand, pretreatment with the I_1 antagonist **3** prevented the hypotensive activity of **8**

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(Figure 2F), confirming the important role of I_1-IRs in the cardiovascular properties of the novel compounds.

As expected, all compounds, and to a lower extent (*R*)-(−)-**8**, displayed also bradicardic action (Figure 3), that was comparable for **8** and **4** (Figure 3A).

In conclusion, according to what was previously seen for compound **4**, the efficacious hypotensive effects of the novel selective I_1-IR agonists **5**, **8**, and **9** confirmed that the introduction of suitable substituents in the ortho position of the phenyl ring of the selective I_1-IR antagonist **3** was able to induce antagonism/agonism modulation. Obviously, such modulation was affected by the physicochemical characteristics of the decorations at the ortho position. In particular, in the case of aromatic substituents, only a strong aromaticity (**4** and **5**) triggered efficacious I_1-IR interactions. Productive I_1-IR interactions were also provided by aliphatic or halogen substituents endowed with moderate steric hindrance and positive lipophilic contributions (**8** and **9**). Nevertheless, the fact that **8** (named carbomethyline) proved to have the highest potency and longest lasting activity suggests that the van der Waals interactions associated with the methyl group are particularly advantageous. The aforementioned observations will be useful in the design of novel I_1-IR agonists inspired by our scaffold. Finally, similarly to what was verified for (*S*)-(+)-**4**, the observation that only (*S*)-(+)-**8** displayed significant hemodynamic effects unequivocally confirmed the stereospecific nature of the I_1 proteins. It has also been reported that I_1-IR agonists display positive effects on metabolic abnormalities, such as insulin resistance, impaired glucose tolerance, and dyslipidemia. This cluster of dysfunctions, together with hypertension, constitute the "syndrome X", which causes an elevated risk for cardiovascular disease and premature death.[25−28] Therefore, the discovery of ligands devoid of the side effects induced by α_2-AR stimulation and that selectively activate I_1-IRs can be regarded as a promising goal.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedure, X-ray crystallographic data for (*S*)-(+)-**8**, experimental details of in vivo assays, and elemental analysis of the final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

The X-ray coordinates of compound (*S*)-(+)-**8** have been deposited with Cambridge Crystallographic Data Centre with accession number CCDC1025169.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

α_2-ARs, α_2-adrenoreceptors; HR, heart rate; IBS, imidazoline binding site; I_1-IR, I_1-imidazoline receptor; MABP, mean arterial blood pressure; PC-PLC, phosphatidylcholine-sensitive phospholipase C; SHR, spontaneously hypertensive rats; RVLM, rostral ventrolateral medulla; SAR, structure−activity relationship; ip, intraperitoneal; ic, intracisternal

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