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Brief Article

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Might Adrenergic α_{2C}-Agonists/α_{2A}-Antagonists Become Novel Therapeutic Tools for Pain Treatment with Morphine?[1]

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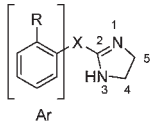
The imidazoline nucleus linked in position 2 via an oxyethylene bridge to a phenyl ring carrying an ortho substituent of moderate steric bulk provided α_2-adrenergic (AR) ligands endowed with significant α_{2C}-agonism/α_{2A}-antagonism. Similar behavior was displayed by cirazoline (**12**). For their positive morphine analgesia modulation (due to α_{2C}-AR stimulation) and sedation overcoming (due to α_{2A}-AR antagonism), **8** and **11** might be useful as adjuvant agents in the management of pain with morphine.

Introduction

α_2-Adrenoreceptors (α_2-ARs[a]) consist of three subtypes (α_{2A}, α_{2B}, and α_{2C})[2] and are considered attractive therapeutic targets. Studies of mice lacking or overexpressing α_2-AR subtypes[3] demonstrated that the α_{2A}-AR subtype mediates hypotension, sedation, analgesia, while the α_{2B} subtype mediates hypertension. The α_{2C}-AR subtype appears involved in many CNS processes and proves to contribute to adrenergic opioid synergy and spinal α_2-agonist-mediated analgesia.[4] It is known that imidazoline derivatives may interact with α-ARs and imidazoline binding sites (I_1-, I_2-IBS).[5] Our experience highlighted that the two groups, the bridge X and the aromatic area Ar forming the substituent in position 2 of the imidazoline nucleus (Chart 1), displayed different functions. Indeed, minor chemical modifications to the bridge determined the preferential recognition by a specific biological system,[6] whereas those in the aromatic region sometimes induced subtype-selective interaction but always caused decisive modulation of the ligand functional behavior.[7] In summary, the oxymethylene bridge (**1**) appeared favorable for α_2-ARs and I_2-IBS. Additionally, **1** demonstrated antagonist and agonist properties at α_2- and α_1-ARs, respectively. The methyl group in the bridge (**2**) improved the α_2-AR antagonist potency, slightly lowered α_1-AR intrinsic activity, and drastically reduced the I_2-IBS affinity.[6,8] The α_2-AR specificity of **2** was favored by the recognition of a lipophilic cavity, named "methyl pocket".[9] In a different manner, the wholly carbon nature of the bridge favored IBS selectivity: **3** (phenyzoline) and **4** proved effective for I_2- or I_1-IBS, respectively.[6] Moreover, in the case of α_2-AR ligands,[7] we demonstrated that chemical modifications in the Ar group, such as the introduction of an ortho phenyl substituent into the aromatic ring of the nonsubtype selective α_2-AR antagonist **2** caused an important modulation of receptor interactions. The antinociceptive α_{2A}- and α_{2C}-AR agonist biphenyline (**5**) was thus obtained.[8,10] Unambiguously, from comparative examination of several compounds some significant analogies between binding site cavity of α_2-ARs and IBS emerged. Indeed, the insertion of the ortho phenyl group turned the biological profile of **3** from positive to negative modulator (**6**, diphenyzoline) of morphine analgesia;[11] analogously, the antagonist **4** changed into the antihypertensive agonist **7**.[12] Interestingly, concerning α_2-AR ligands, we observed that the ortho allyl substituent of moderate steric bulk (MR = 14.49)[13] modulated the biological profile of the antagonist **2** only at α_{2C}-AR.[7] Indeed, at this subtype **8** showed good intrinsic activity and high potency, whereas it displayed the same antagonist character of its prototype **2** at the α_{2A}-subtype (Table 1). This observation highlighted the possibility of obtaining novel α_2-AR agonists, with the potential to evoke the physiological responses mediated by α_{2C}-AR subtype without having the side effects associated with α_{2A}-AR stimulation. To confirm this result, we prepared and studied some analogues of **8** (**9**−**11**). Similar to allyl, the methyl (MR = 5.65) (**9**), *n*-propyl (MR = 14.96) (**10**), and cyclopropyl (MR = 13.53) (**11**) pendent groups were endowed

Chart 1. Imidazoline Molecules Interacting with α_2-ARs and I_2-IBS (**1**), α_2-ARs (**2**, **5**, **8**−**14**), I_2-IBS (**3**, **6**), and I_1-IBS (**4**, **7**)



1, R = H, X = -O-CH_2-
2, R = H, X = -O-CH(CH_3)-
3, R = H, X = -CH_2-CH_2- (phenyzoline)
4, R = H, X = -CH_2-CH(CH_3)-
5, R = -C_6H_5, X = -O-CH(CH_3)- (biphenyline)
6, R = -C_6H_5, X = -CH_2-CH_2- (diphenyzoline)
7, R = -C_6H_5, X = -CH_2-CH(CH_3)-
8, R = -CH_2-CH=CH_2, X = -O-CH(CH_3)-
9, R = -CH_3, X = -O-CH(CH_3)-
10, R = -CH_2-CH_2-CH_3, X = -O-CH(CH_3)-
11, R =  , X = -O-CH(CH_3)-
12, R =  , X = -O-CH_2- (cirazoline)
13, R = -CH_3, X = -O-CH_2-
14, R = -CH_2-CH_2-CH_3, X = -O-CH_2-

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[a] Abbreviations: IBS, imidazoline binding sites; α_2-ARs, α_2-adrenoreceptors; (−)-NA, (−)-noradrenaline; MR, molar refraction; CHO, Chinese hamster ovary; DME, 1,2-dimethoxyethane; MPE, maximum possible effect.

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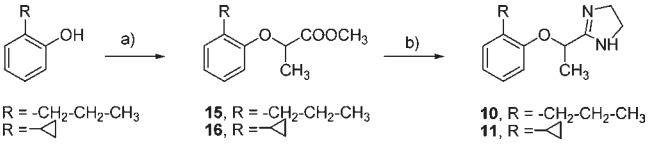
Table 1. Affinity (pK_i [a]), Antagonist Potency (pK_b [b]), Agonist Potency (pEC_{50} [b]), and Intrinsic Activity (ia[b]) on Human α_2-AR Subtypes

	α_{2A}			α_{2B}			α_{2C}		
compd	pK_i	pEC_{50} (pK_b)	ia	pK_i	pEC_{50} (pK_b)	ia	pK_i	pEC_{50} (pK_b)	ia
2	7.57 ± 0.09	(7.01 ± 0.10)		6.78 ± 0.13	(6.20 ± 0.18)		6.58 ± 0.12	(6.85 ± 0.15)	
8	7.24 ± 0.11	(7.40 ± 0.06)		6.47 ± 0.20	na		7.07 ± 0.14	7.30 ± 0.09	0.90
9	7.61 ± 0.14	(7.51 ± 0.08)		6.57 ± 0.20	6.00 ± 0.22	0.40	6.57 ± 0.12	7.20 ± 0.12	0.67
10	7.30 ± 0.11	(7.05 ± 0.20)		6.27 ± 0.15	5.30 ± 0.12	0.60	6.83 ± 0.21	7.60 ± 0.18	0.75
11	7.64 ± 0.20	(7.00 ± 0.09)		6.51 ± 0.13	5.50 ± 0.15	0.70	7.10 ± 0.16	7.40 ± 0.13	0.90
12	7.23 ± 0.10	(6.40 ± 0.12)		6.28 ± 0.14	6.00 ± 0.13	1.00	6.26 ± 0.15	6.40 ± 0.10	0.80
13	7.46 ± 0.10	(6.54 ± 0.16)		6.40 ± 0.09	6.00 ± 0.13	0.70	6.30 ± 0.13	5.54 ± 0.20	0.50
14	7.31 ± 0.11	(6.28 ± 0.06)		6.26 ± 0.20	5.60 ± 0.09	0.70	6.31 ± 0.14	6.81 ± 0.09	0.90
(−)-NA		6.43 ± 0.17	1.00		7.21 ± 0.25	1.00		6.10 ± 0.05	1.00

[a] pK_i values were calculated from [^{3}H]RX 821002 on membrane preparations from CHO cells expressing individually each human α_2-AR subtype (α_{2A}, α_{2B}, α_{2C}). [b] pK_b, pEC_{50}, and intrinsic activity (ia) values were determined by applying the Cytosensor microphysiometry system to the same cell models. Intrinsic activity of the tested compounds is expressed as the fraction of that of the full agonist (−)-NA taken as equal to 1. The data are expressed as the mean ± SEM of three to six separate experiments. Compounds exhibiting ia of < 0.3 were considered not active (na).

Scheme 1[a]



[a] Reagents and conditions: (a) methyl 2-bromopropionate, K_2CO_3; (b) $(CH_3)_3Al$, dry toluene, ethylenediamine, Δ.

with moderate steric bulk. The corresponding desmethyl analogues **12**−**14** were included in this study. The pharmacological profiles were evaluated by binding and functional studies on CHO cells expressing recombinant human α_2-AR and α_1-AR subtypes. **9**, **13**, and **14**, already known,[5] and **10**,[14] cited but not previously described, have never been studied from this point of view. Selected compounds were also evaluated on algesiometric and sedation tests.

Chemistry

9, **13**, and **14** were prepared as previously reported.[5] Condensation of the suitable phenols with methyl 2-bromopropionate afforded the esters **15** and **16**, which by treatment with ethylenediamine in the presence of $(CH_3)_3Al$ gave **10** and **11** (Scheme 1).

Results and Discussion

From the data reported in Table 1, it emerged that at the three different α_2-AR subtypes, **9**−**11** showed binding affinities comparable to those of their precursor **2**. However, as assessed by a Cytosensor microphysiometry,[7] analogous to lead **8**, they displayed good intrinsic activity and remarkable potency at α_{2C}-subtype (for **9**, pEC_{50} = 7.20, ia = 0.67; for **10**, pEC_{50} = 7.60, ia = 0.75; for **11**, pEC_{50} = 7.40, ia = 0.90). The α_{2B}-AR potencies were found to be significantly lower. The lack of α_{2A}-AR agonism and the good α_{2A}-AR affinity of **9**−**11** prompted us to evaluate their antagonist properties at this subtype. As expected, similar to the lead **8**,[7] **9**−**11** displayed the same antagonist character as **2** (pK_b α_{2A} of 7.51, 7.05, and 7.00, respectively). Since the recognition of the "methyl binding pocket" alone did not induce α_2-AR agonist activity,[8] the promising α_{2C}-AR agonism of **11**, which may be regarded as the methyl derivative of cirazoline (**12**), prompted us to re-examine the pharmacological profile of **12**, so far considered as an α_2-AR antagonist.[15] As expected, **12** behaved as antagonist at α_{2A}-subtype (pK_b = 6.40) and as agonist at α_{2C}- (pEC_{50} = 6.40, ia = 0.80) and α_{2B}-subtypes (pEC_{50} = 6.00, ia = 1.00) (Figure 1). **13** and **14**, the desmethyl analogues of **9** and **10**, respectively, showed similar profiles. The higher potency values of **8**−**11** at α_{2C}-subtype were probably favored by the presence of the methyl group in the bridge. To further delineate their functional behavior, **9**−**14** were tested for their capacity to cause receptor-mediated Erk phosphorylation. Compared to the positive control (−)-NA, **12** (Figure 1) and all the other compounds had only marginal incidence on Erk phosphorylation in cells expressing the α_{2A}-subtype but increased it in cells expressing α_{2B}- or α_{2C}-subtype. The α_{1A}-AR pK_i affinity values of **8**−**14** ranged between 6 and 6.9, but as expected,[8,9] from functional studies **8**−**11** showed low intrinsic activity (ia < 0.3), whereas **12** and the other desmethyl analogues **13** and **14** activated this receptor (for **12**, pEC_{50} = 7.00, ia = 0.6; for **13**, pEC_{50} = 6.49, ia = 0.7; for **14**, pEC_{50} = 6.80, ia = 0.9). Moreover, **8**−**14** displayed poor affinities (pK_i < 5) at α_{1B}- and α_{1D}-AR subtypes. As known, some nonsubtype selective α_2-agonists, such as clonidine, tizanidine, and brimonidine, are used as primary analgesics[16] and adjuvant analgesics in synergic combination with opioids.[17] Nevertheless, in systemic long-term use their side effects, associated with α_{2A}-activation, limit their therapeutic potential. Therefore, with the hope of exploring an alternative avenue to known opioids and non-opioids in combination management and obtaining the separation of the analgesic from side effects, we evaluated in vivo the behavior of some of our molecules. Morphine analgesia modulation and analgesia effects produced by **8**, **11**, and **12** and sedation effects produced by **8** and **11** were determined. Clonidine was included as reference compound. **8**, **11**, and **12** caused a significant increase in morphine analgesia (Figure 2), since augmented tail-flick latency was still observed 120 min after administration. Of note the lowest dose of **8** or **11** (0.05 mg/kg) caused an effect comparable to that obtained with a 0.5 mg/kg dose of **12** or clonidine. At lower doses (< 0.5 mg/kg) clonidine or **12** did not affect morphine analgesia; the higher doses required for these compounds might be due to their α_{1A}-AR activation, which can counterbalance their α_2-AR-induced effects.[16−18] Moreover, on the basis of the considerations reported in the Introduction, the I_2-IBS affinity (pK_i = 7.90)[5] due to the oxymethylene bridge[6] and the ortho substituent of the aromatic ring might confer on **12** some negative modulatory properties[11] and weaken its α_{2C}-AR-mediated morphine analgesia enhancement. Anyway, the potentiation of opioid-evoked analgesia displayed by **8** and **11** confirmed the previous results obtained from genetically engineered mice.[4]

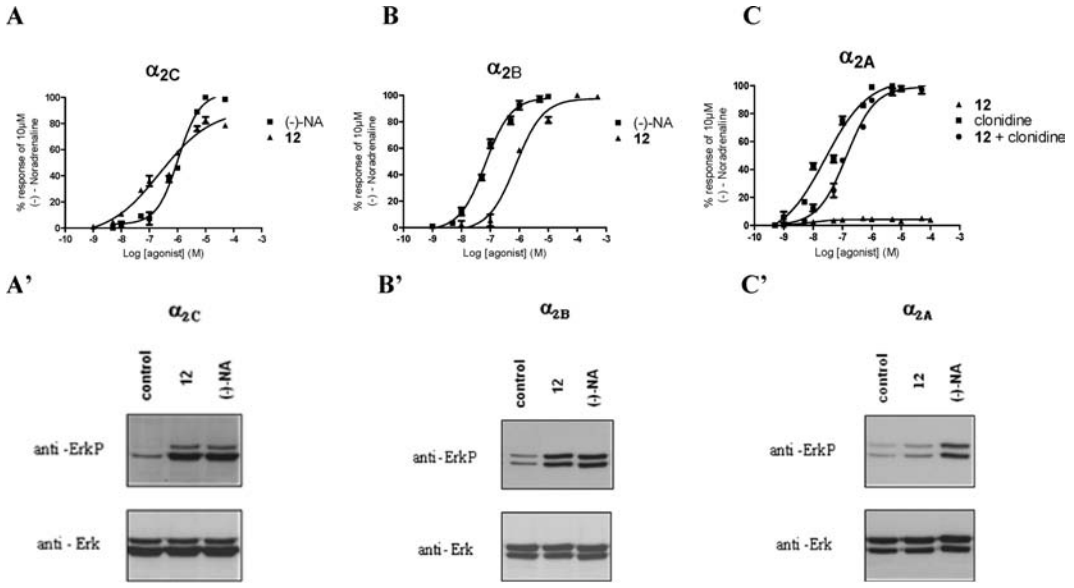


Figure 1. Stimulation of extracellular acidification in CHO cells stably expressing the human α_{2C}- (A) and α_{2B}-AR subtypes (B) by (−)-NA (■) and **12** (▲) and α_{2A}-AR subtype (C) by clonidine (■), **12** (▲), and **12** (1 μM) with clonidine (●). Data points with error bars represent the mean ± SEM of three to six separate experiments. Levels of Erk phosphorylation are produced by **12** and (−)-NA on CHO cells expressing α_{2C}- (A′), α_{2B}- (B′), and α_{2A}-AR subtypes (C′). Phosphorylated Erk (ErkP) and total Erk (Erk) were revealed by Western blotting with specific antibodies.

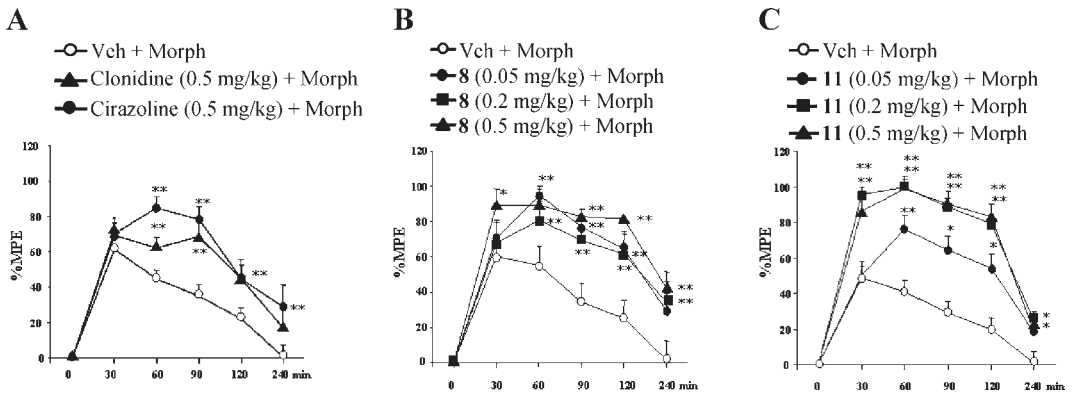


Figure 2. Effects of clonidine and cirazoline (A), **8** (B), and **11** (C) on morphine analgesia in the tail-flick test. The reaction latencies were expressed as a percent of the maximum possible effect (% MPE). Each point represents the mean ± SEM of six to eight animals. Significant differences are as follows: (*) $p < 0.05$, (**) $p < 0.01$ compared to morphine treated group. Where not indicated, the difference was not statistically significant.

In addition, the α_2-AR activation was unambiguously demonstrated by the observation that the effects of **8** and **11** were blocked by pretreatment with the α_2-AR antagonist yohimbine (Supporting Information Figure S1). **8** was devoid of antinociceptive properties, whereas **11** exhibited a weak and dose-dependent analgesic effect (Supporting Information Figure S2). Finally, in agreement with the expected lack of sedation, at doses producing significant potentiation of the analgesic effect of morphine, **8** and **11** did not increase the sleeping time induced by pentobarbital; in contrast, a 5- and 6.6-fold increase of sleeping time was caused by clonidine and diazepam administration, respectively (Figure 3). In conclusion, the present research (i) strengthened our convinction that α_2-AR specificity, functional behavior, and subtype selectivity of imidazoline molecules were determined by the peculiar nature of the X and Ar fractions of the substituent in position 2 of the imidazoline ring, (ii) demonstrated that the simultaneous presence of an oxyethylene bridge and ortho substituent of moderate steric size in the Ar fraction induced

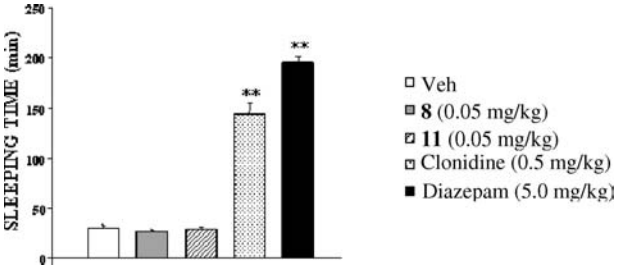


Figure 3. Effects of **8**, **11**, and clonidine on pentobarbital-induced sleeping time. The time between losing and regaining righting reflex was considered as the duration of sleep time (min): (**) $p < 0.01$ compared to vehicle.

preferential α_{2C}-activation, (iii) allowed us to further characterize the biological profile of cirazoline, and finally, (iv) suggested that given their ability to positively modulate morphine analgesia (due to α_{2C}-AR stimulation) and to overcome sedation (due to α_{2A}-AR antagonism), **8** and **11**

merit further investigation as novel and suitable adjuvants in the management of pain with opioids. The present results and the stereospecific requirements of α_2-ARs prompt us to prepare and study the enantiomers of **8** and **11**.

Experimental Section

The purity of the new compounds was determined by combustion analysis and was ≥95%.

2-(2-Propylphenoxy)propionic Acid Methyl Ester (15). A mixture of 2-propylphenol (0.26 g, 1.93 mmol), methyl 2-bromopropionate (0.22 mL, 1.93 mmol), and K_2CO_3 (0.27 g, 1.93 mmol) in DME was refluxed for 8 h. The mixture was filtered, and the solvent was removed. The residue was taken up in CH_2Cl_2 and washed with 2 N NaOH. Removal of the solvent afforded an oil which was purified by flash cromatography (cyclohexane/EtOAc, 9/1) (0.25 g, 59% yield). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3, CH_2CH_3), 1.62 (d, 3, $CHCH_3$), 1.64 (m, 2, CH_2), 2.67 (t, 2, CH_2), 3.73 (s, 3, OCH_3), 4.78 (q, 1, OC*H*), 6.65−7.18 (m, 4, Ar*H*).

2-(2-Cyclopropylphenoxy)propionic Acid Methyl Ester (16). Similarly, **16** was obtained from 2-cyclopropylphenol. Yield, 75%. ^{1}H NMR ($CDCl_3$) δ 0.57−1.02 (m, 4, CH_2CH_2), 1.67 (d, 3, $CHCH_3$), 2.26 (m, 1, C*H*), 3.78 (s, 3, OCH_3), 4.78 (m, 1, OC*H*), 6.62−7.12 (m, 4, Ar*H*).

2-[1-(2-Cyclopropylphenoxy)ethyl]-4,5-dihydro-1*H*-imidazole (11). A solution of ethylenediamine (0.42 mL, 6.28 mmol) in dry toluene (6 mL) was added dropwise to a mechanically stirred solution of 2 M $(CH_3)_3Al$ (3.2 mL, 6.28 mmol) in dry toluene (4 mL) at 0 °C under a nitrogen atmosphere. After the mixture was stirred at room temperature for 1 h, a solution of **16** (0.69 g, 3.14 mmol) in dry toluene (8 mL) was added dropwise. The mixture was heated to 110 °C for 3 h, cooled to 0 °C, and quenched with MeOH (0.8 mL) followed by H_2O (0.2 mL) and $CHCl_3$ (5 mL). The mixture was filtered and extracted with 2 N HCl. The aqueous layer was made basic with 10% NaOH and extracted with $CHCl_3$. The oil residue was purified by flash chromatography (cyclohexane/EtOAc/MeOH/33% NH_4OH, 6/4/1/0.1). The free base (63% yield) was transformed into the hydrogen oxalate salt and recrystallized from EtOH: mp 141−142 °C; ^{1}H NMR (DMSO) δ 0.51−0.98 (m, 4, CH_2CH_2), 1.58 (d, 3, $CHCH_3$), 2.24 (m, 1, C*H*), 3.91 (s, 4, NCH_2CH_2N), 5.37 (q, 1, OC*H*), 6.83−7.18 (m, 4, Ar*H*), 9.51 (br s, 1, N*H*, exchangeable with D_2O). Anal. ($C_{14}H_{18}N_2O\cdot H_2C_2O_4$) C, H, N.

2-[1-(2-Propylphenoxy)ethyl]-4,5-dihydro-1*H*-imidazole (10). Similarly, **10** was obtained from **15**. Yield, 65%. Recrystallization was from EtOH/Et_2O: mp 145.2−145.9 °C; ^{1}H NMR (DMSO) δ 0.95 (t, 3, CH_2CH_3), 1.68 (d, 3, $CHCH_3$), 1.60 (m, 2, CH_2), 2.67 (t, 2, CH_2), 3.85 (m, 4, NCH_2CH_2N), 5.38 (q, 1, OC*H*), δ 6.85−7.20 (m, 4, Ar*H*). Anal. ($C_{14}H_{20}N_2O\cdot H_2C_2O_4$) C, H, N.

Supporting Information Available: Chemical methodology, biological experiments, and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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