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Letter

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# Exploring Multitarget Interactions to Reduce Opiate Withdrawal Syndrome and Psychiatric Comorbidity

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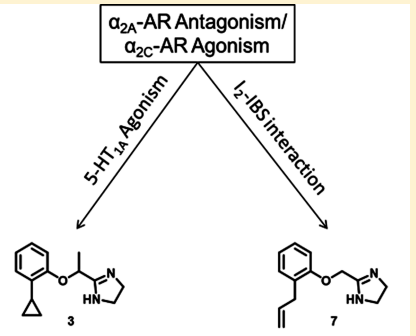
Supporting Information

**ABSTRACT:** Opioid addiction is often characterized as a chronic relapsing condition due to the severe somatic and behavioral signs, associated with depressive disorders, triggered by opiate withdrawal. Since prolonged abstinence remains a major challenge, our interest has been addressed to such objective. Exploring multitarget interactions, the present investigation suggests that **3** or its (*S*)-enantiomer and **4**, endowed with effective $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism/5-HT$_{1A}$-R agonism, or **7** and **9**−**11** producing efficacious $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism/$I_2$−IBS interaction might represent novel multifunctional tools potentially useful for reducing withdrawal syndrome and associated depression. Such agents, lacking in sedative side effects due to their $\alpha_{2A}$-AR antagonism, might afford an improvement over current therapies with clonidine-like drugs.




Favorable synergisms in managing opioid addiction

**KEYWORDS:** *$\alpha_2$-Adrenergic ligands, 5-HT$_{1A}$ agonists, $I_2$−IBS ligands, morphine withdrawal symptoms reduction, antidepressant-like effect*

Opioid exposure is known to induce potent analgesic effect as well as relaxation and euphoria. The repeated use of opiate drugs, both for the relief of chronic or cancer-related pain and for recreational drug-taking behavior, can lead to the development of dependence. Addiction to opioids is a complex syndrome involving tolerance, drug-seeking, and physical dependence with withdrawal avoidance behaviors. It is often characterized as a chronic relapsing condition and is a major health and social issue in most societies.[1] Detoxification, a necessary step for many forms of long-term abstinence-based treatments, makes use of two approaches: tapering using methadone or buprenorphine, or abrupt termination of opioid use, potentially precipitated by an opioid antagonist (i.e., naltrexone) with administration of $\alpha_2$-adrenoreceptor ($\alpha_2$-AR) agonists to reduce withdrawal symptoms.[1] $\alpha_2$-ARs have been demonstrated to be extremely sensitive to opioid exposure.[2] Subdivided into $\alpha_{2A}$-, $\alpha_{2B}$-, and $\alpha_{2C}$-subtypes, $\alpha_2$-ARs belong to the superfamily of G-protein-coupled receptors and are widely distributed in the central nervous system (CNS) and in peripheral tissues.[3] The $\alpha_{2A}$ subtype mediates hypotension, sedation and analgesia, as well as inhibition of monoamine release and metabolism in the brain. The $\alpha_{2B}$-subtype mediates vasoconstriction. The $\alpha_{2C}$-subtype appears to be involved in feedback inhibition of adrenal cathecolamine release and can contribute to adrenergic-opioid synergy. In the brain, $\alpha_{2A}$- and $\alpha_{2C}$-ARs, as "heteroreceptors", inhibit dopamine and serotonin release.[3−5] The nonsubtype selective $\alpha_2$-AR agonist clonidine has been clinically used alone or in combination with traditional treatments for relief of withdrawal symptoms during detoxification, thus increasing treatment duration. Nevertheless, clonidine, due to its $\alpha_{2A}$-AR subtype activation, is responsible for side effects of sedation and hypotension,[1] that limit the use of high doses. Strong association between protracted abstinence and depressive disorders, contributing to relapse, emerges from epidemiologic retrospective studies, and adjunct antidepressants are often included in the traditional treatments.[1,6,7] Therefore, since prolonged abstinence remains a major challenge, strategies addressed to discover multifunctional agents that ameliorate withdrawal symptoms and relieve depressive disorders should be explored. Recently,[8,9] we reported that allyphenyline (**1**) and cyclomethyline (**2**) (Chart 1), devoid of sedative side effects, were able at the same low dose (0.05 mg/kg) to significantly decrease the naloxone-precipitated withdrawal syndrome and to exert a

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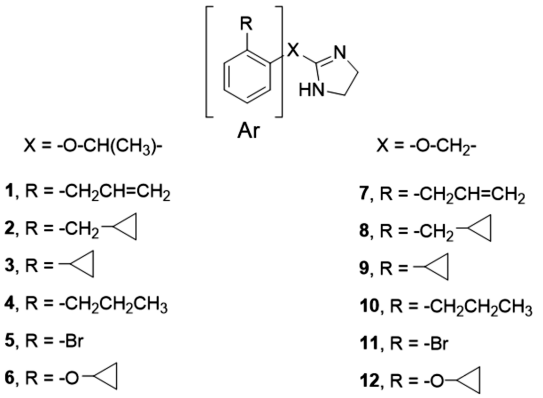
**Chart 1. Chemical Structures of Imidazoline Derivatives**



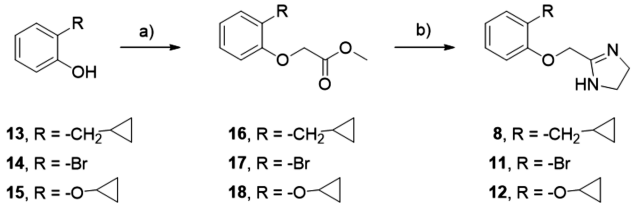

potent antidepressant-like effect. It appeared that the $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism displayed by these compounds and their enantiomers, represented a suitable condition to induce positive effects on morphine dependence, while additional 5-$HT_{1A}$-receptor (5-$HT_{1A}$-R) activation, as triggered by **1** or its (*S*)-(+) enantiomer and **2** or both its enantiomers, favored the antidepressant-like effect, recorded in the mouse forced swimming test (FST).[10] Experiments carried out in the presence of the $\alpha_2$-AR antagonist yohimbine and the 5-$HT_{1A}$-R antagonist WAY100135 suggested that dual $\alpha_{2C}$-AR/5-$HT_{1A}$-R activation was required for the antidepressant-like effect induced by low doses of the aforementioned compounds.[9] On the other hand, the participation of 5-$HT_{1A}$-R in the antidepressant effect was supported by preclinical results suggesting that postsynaptic 5-$HT_{1A}$-Rs are particularly important in the antidepressant response. Moreover, behavioral models of stress and antidepressant drug effects in animals, such as the FST, indicated that the activation of postsynaptic 5-$HT_{1A}$-Rs induced changes similar to those of conventional antidepressants.[11]

Biologically active ligands bearing the imidazoline nucleus have been the focus of our studies over the years.[12−15] The present research is a development of our previous observations. We demonstrated that, in molecular structures sharing the common pharmacophore reported in Chart 1, the bridge (X) and the aromatic area (Ar) forming the substituent in position 2 of the imidazoline nucleus displayed different functions. Indeed, minor chemical modifications of the bridge determined the preferential recognition of a specific biological system, whereas those in the Ar region (i.e., introduction of ortho substituents of different nature) affected ligand affinity and functional behavior.

In particular, the −OCH($CH_3$)− bridge, as in **1**−**6**, was suitable for the $\alpha_2$-AR interaction favored by the recognition of a lipophilic cavity promoted by the methyl group. In contrast, this group drastically reduced the $I_2$−imidazoline binding site ($I_2$−IBS) affinity. Interestingly, the −$OCH_2$− bridge proved to be compatible with both systems. In the present investigation, our interest for the $I_2$−IBS was stimulated by the observation that also these binding proteins are involved in depression and modulation of morphine analgesia as well as tolerance and opioid addiction.[13,16] The IBS recognize with high affinity compounds containing the imidazoline moiety. They also include $I_1$−IBS, which participate in the regulation of cardiovascular function,[17] and $I_3$−IBS, which regulate insulin secretion.[18] Biochemical and pharmacological studies suggest that the $I_2$−IBS are allosteric sites located on monoamine oxidase (MAO).[19] On the basis of the interesting results obtained with **1** and **2**, the aim of the present study was to widen the availability of tools potentially useful in managing opioid addiction and associated disorders. To this end, we first determined the 5-$HT_{1A}$-R profiles of **3** and its enantiomers,[8] and **4**−**6**.[15] The choice of such compounds was suggested by the observation that, analogously to **1** and **2**, they were endowed with efficacious $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism due to their preferred extended conformation.[15] In addition, the antidepressant-like effects of **3** and its enantiomers at the low doses of 0.05 and 0.025 mg/kg, respectively, have been evaluated in FST. Subsequently, our strategy was directed to explore another multitarget combination. Therefore, compounds **7**−**12** were prepared. Such compounds bear the same Ar region of their corresponding leads **1**−**6** and the −$OCH_2$− bridge, which, as mentioned above, is compatible with $\alpha_2$-ARs and $I_2$−IBS. This compatibility was supported by the results of our previous studies, which indicated good $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism of **9** (cirazoline) and **10**[14] and the high $I_2$−IBS affinity of **7**, **9**, and **10**.[20,21] However, the human $\alpha_2$-AR subtype and 5-$HT_{1A}$-R profiles as well as the $I_2$−IBS affinities of **7**−**12** were assessed. For useful comparison, the $I_2$−IBS affinities of **1**−**6** were also determined. Finally, the effects of **7**, **8**, and **10** were evaluated on depression and those of **7** on acquisition and expression of morphine dependence. The in vitro and in vivo tests were performed according to previously reported procedures.[8,9,13,22]

Imidazolines **8**, **11**, and **12** were prepared according to Scheme 1. Condensation of the suitable phenols **13**−**15** with

**Scheme 1. Preparation of Novel Imidazoline Derivatives**[a]




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

methyl bromoacetate afforded the esters **16**−**18**, respectively, which, by treatment with ethylenediamine in the presence of $(CH_3)_3Al$, gave the desired compounds.

The data shown in Table 1 indicate that **3** was endowed with high 5-$HT_{1A}$-R affinity ($pK_i$ = 8.14) and effective agonism ($pD_2$ = 7.24; $\%E_{max}$ = 92), comparable to those of the known 5-$HT_{1A}$-R agonist 8-OH-DPAT.[22] These properties were maintained and even enhanced only by the (*S*)-(+)-**3** enantiomer, whereas (*R*)-(−)-**3** was endowed with negligible affinity ($pK_i$ < 5). Such behavior was analogous to that observed for **1** and its enantiomers,[9] and this similarity was also confirmed by the FST test.

Indeed, as observed with **1**, the same low dose of 0.05 mg/kg of **3** induced significant reduction of immobility time, and this effect was comparable to that obtained with the dose of 20 mg/kg of the selective 5-HT reuptake inhibitor fluoxetine, included as the reference compound.[9] This effect was associated only with the (*S*)-(+)-enantiomer, whereas (*R*)-(−)-**3**, lacking in significant 5-$HT_{1A}$-R affinity, was inactive (Figure 1A). This observation strengthened the previous result and unequivocally


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Table 1. [a] Affinity ($pK_i$), Antagonist Potency ($pK_b$), Agonist Potency ($pEC_{50}$), and Intrinsic Activity (i.a.) on Human $\alpha_2$-AR Subtypes[b]; Affinity ($pK_i$), Agonist Potency ($pD_2$), and Relative Efficacy ($\%E_{max}$) on Human 5-$HT_{1A}$-R[c]; Affinity ($pK_i$) on $I_2$–IBS on Rat Brain Membranes[d]

| | $\alpha_{2A}$ | $\alpha_{2B}$ | | $\alpha_{2C}$ | | 5-$HT_{1A}$ | | $I_2$–IBS |
|---|---|---|---|---|---|---|---|---|
| compd | $pK_b$ ($pK_i$) | $pEC_{50}$ ($pK_i$) | i.a. | $pEC_{50}$ ($pK_i$) | i.a. | $pD_2$ ($pK_i$) | $\%E_{max}$ | $pK_i$ |
| **1** | 7.40 ± 0.06 (7.24 ± 0.11) | NA[e] (6.47 ± 0.20) | | 7.30 ± 0.09 (7.07 ± 0.14) | 0.90 | 6.86 ± 0.09 (7.55 ± 0.16) | 67 | <6 |
| (*R*)-(−)-**1** | 7.40 ± 0.09 (7.00 ± 0.08) | NA[e] (6.25 ± 0.12) | | 6.73 ± 0.11 (6.75 ± 0.11) | 0.50 | (<5) | | |
| (*S*)-(+)-**1** | 7.80 ± 0.13 (7.28 ± 0.05) | 6.00 ± 0.09 (6.40 ± 0.09) | 0.65 | 7.60 ± 0.14 (7.15 ± 0.09) | 0.90 | 7.19 ± 0.10 (7.45 ± 0.15) | 96 | |
| **2** | 7.70 ± 0.12 (7.44 ± 0.09) | 5.48 ± 0.15 (6.39 ± 0.05) | 0.70 | 8.70 ± 0.08 (6.56 ± 0.21) | 0.80 | 7.20 ± 0.13 (7.98 ± 0.07) | 75 | <6 |
| (*R*)-(−)-**2** | 7.20 ± 0.11 (7.35 ± 0.10) | 5.40 ± 0.11 (6.47 ± 0.07) | 0.65 | 6.50 ± 0.07 (6.63 ± 0.05) | 0.75 | 6.80 ± 0.10 (7.40 ± 0.08) | 68 | |
| (*S*)-(+)-**2** | 7.70 ± 0.09 (7.38 ± 0.07) | 5.80 ± 0.06 (6.39 ± 0.10) | 0.70 | 8.70 ± 0.11 (6.56 ± 0.13) | 0.85 | 7.40 ± 0.02 (8.24 ± 0.16) | 97 | |
| **3** | 7.00 ± 0.09 (7.64 ± 0.20) | 5.50 ± 0.15 (6.51 ± 0.13) | 0.70 | 7.40 ± 0.13(7.10 ± 0.16) | 0.90 | 7.24 ± 0.10 (8.14 ± 0.08) | 92 | <6 |
| (*R*)-(−)-**3** | 6.90 ± 0.07 (7.35 ± 0.10) | NA[e] (6.25 ± 0.10) | | 6.90 ± 0.12 (6.90 ± 0.13) | 0.50 | (<5) | | |
| (*S*)-(+)-**3** | 7.70 ± 0.11 (7.68 ± 0.12) | 5.50 ± 0.13 (6.58 ± 0.08) | 0.65 | 7.45 ± 0.16 (7.20 ± 0.10) | 0.90 | 7.86 ± 0.06 (8.22 ± 0.09) | 102 | |
| **4** | 7.05 ± 0.20 (7.30 ± 0.11) | 5.30 ± 0.12 (6.27 ± 0.15) | 0.60 | 7.60 ± 0.18 (6.83 ± 0.21) | 0.75 | 7.08 ± 0.11 (7.86 ± 0.05) | 118 | <6 |
| **5** | 7.04 ± 0.08 (7.64 ± 0.09) | 6.50 ± 0.07 (6.45 ± 0.16) | 0.40 | 8.00 ± 0.11 (6.55 ± 0.09) | 0.87 | (6.83 ± 0.14) | | <6 |
| **6** | 6.90 ± 0.12 (7.08 ± 0.09) | 4.89 ± 0.10 (5.98 ± 0.11) | 0.60 | 7.32 ± 0.13 (6.17 ± 0.14) | 0.70 | (7.83 ± 0.04) | | <6 |
| 8-OH DPAT | | | | | | 7.60 ± 0.06 (8.47 ± 0.13) | 100 | |

[a]The data were expressed as means ± SEM of 3−6 separate experiments. [b]According to ref 8. [c]According to ref 22. [d]According to ref 13. [e]Compounds exhibiting i.a. of <0.3 were considered not active (NA).

indicated the crucial role played by the 5-$HT_{1A}$-R activation in the observed antidepressant-like effect.

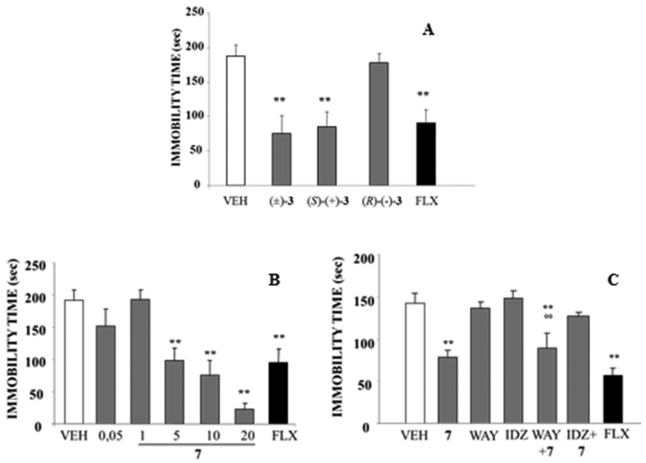


**Figure 1.** Immobility time in the FST in mice following i.p. administration of (±)-**3** at 0.05 mg/kg, (*S*)-(+)-**3** and (*R*)-(-)-**3** at 0.025 mg/kg (A), and of **7** at 0.05, 1, 5, 10, and 20 mg/kg (B). Influence of the 5-$HT_{1A}$-R antagonist WAY 100635 (0.1 mg/kg, s.c.) and the $I_2$–IBS/$\alpha_2$-AR antagonist idazoxan (2 mg/kg, i.p.) on the antidepressant-like effect of **7** (5 mg/kg, i.p.) (C). Fluoxetine (FLX; 20 mg/kg) has been included as a reference drug. Data represent mean (±SEM) of 8 animals. Significant differences: $^{**}p < 0.01$, compared with vehicle group; $^{\circ\circ}p < 0.01$, compared with antagonist-treated mice; where not indicated, the differences are not statistically significant.

In addition, the low dose required also for **3** and its (*S*)-(+)-enantiomer, both endowed with efficacious dual $\alpha_{2C}$-AR/5-$HT_{1A}$-R agonism, confirmed the already reported peculiar relationship between $\alpha_{2C}$-AR activation and 5-HT function.[9] From the present study, it also emerged that the racemate **4** displayed high 5-$HT_{1A}$-R affinity and agonist potency ($pK_i$ = 7.86; $pD_2$ = 7.08; $\%E_{max}$ = 118). Therefore, **3** or its (*S*)-enantiomer and **4** might, analogously to **1** and **2**, represent novel and advantageous potential tools in managing opioid addiction and psychiatric comorbidity. Moreover, while **5**, bearing an ortho-phenyl substituent of reduced steric bulk and moderate lipophilic character,[15] appeared less interesting, **6** proved to be endowed with an important 5-$HT_{1A}$-R affinity ($pK_i$ = 7.83), probably due to the re-established favorable combination of the physicochemical parameters of its *ortho*-phenyl substituent. Compounds **7**−**12** (Table 2), devoid of the methyl group on the bridge, produced $\alpha_{2C}$-AR agonism, $\alpha_{2A}$-AR antagonism, and 5-$HT_{1A}$-R recognition similar to those of their corresponding homologues **1**−**6**.

The 5-$HT_{1A}$-R affinity values at least of **7** and **9** were unexpected. Indeed, the study of their methyl homologues **1** and **3**, which indicated that only the (*S*) enantiomers interacted with 5-$HT_{1A}$-R, suggested that the methyl group on the bridge played a critical role in the 5-$HT_{1A}$-R interaction. Moreover, the 5-$HT_{1A}$-R profile of (*R*)-(−)-**2** compared with those of (*R*)-(−)-**1** and (*R*)-(−)-**3** and, as mentioned above, the low affinity of **5** and similarly of **11**, demonstrated that this interaction was also affected by the nature of the *ortho*-phenyl substituent. Therefore, modeling studies of the 5-$HT_{1A}$-R and ligand docking simulations have been planned. Indeed, they cast upon possible interactions into the putative 5-$HT_{1A}$-R binding site maybe justifying our observations and suggesting useful *ortho*-phenyl decorations to enhance the ligand 5-$HT_{1A}$-R recognition.

Compounds **7** and **9**−**11** showed interesting $I_2$–IBS affinities. The $I_2$–IBS $pK_i$ values between 8.88 and 7.9 proved significantly higher than those of the analogues **1** and **3**−**5** ($5 < pK_i < 6$). In contrast, reduced and even negligible $I_2$–IBS affinity was observed for **8** and **12**, respectively. Our data suggest that suitable *ortho*-phenyl substituents might be accepted by 5-$HT_{1A}$ and $I_2$–IBS systems. Because of its interesting in vitro profile, **7** was tested in vivo. From the FST (Figure 1B), it emerged that **7** induced significant reduction of immobility time. This effect amounted to 50% at the dose of 5 mg/kg and was comparable to that evoked by 20 mg/kg of fluoxetine. It increased at higher doses. In contrast to what was verified for **1**−**3**, no activity was induced at the dose of 0.05 mg/kg. The observation that the anti-immobility effect of **7** was induced at a dose higher than that requested by **1** and **2**[9] and that it did not exhibit the dose-dependent U-shaped trend as shown by both of them suggests that not the 5-$HT_{1A}$-R


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Table 2. [a] Affinity ($pK_i$), Antagonist Potency ($pK_b$), Agonist Potency ($pEC_{50}$), and Intrinsic Activity (i.a.) on Human $\alpha_2$-AR Subtypes[b]; Affinity ($pK_i$) on Human 5-$HT_{1A}$-R[c]; Affinity ($pK_i$) on $I_2$−IBS on Rat Brain Membranes[d]

| | $\alpha_{2A}$ | $\alpha_{2B}$ | | $\alpha_{2C}$ | | 5-$HT_{1A}$ | $I_2$−IBS |
|---|---|---|---|---|---|---|---|
| compd | $pK_b$ ($pK_i$) | $pEC_{50}$ ($pK_i$) | i.a. | $pEC_{50}$ ($pK_i$) | i.a. | $pK_i$ | $pK_i$ |
| **7** | 6.50 ± 0.06 (6.90 ± 0.11) | 6.01 ± 0.10 (6.15 ± 0.14) | 0.60 | 7.21 ± 0.08 (7.15 ± 0.12) | 0.73 | 7.15 ± 0.03 | 8.88 ± 0.07 |
| **8** | 6.35 ± 0.11 (7.11 ± 0.09) | 5.77 ± 0.15 (6.30 ± 0.10) | 0.55 | 6.63 ± 0.08 (6.20 ± 0.16) | 0.80 | 7.08 ± 0.07 | 6.90 ± 0.12 |
| **9** | 6.40 ± 0.12 (7.23 ± 0.10) | 6.00 ± 0.13 (6.28 ± 0.14) | 1.0 | 6.40 ± 0.10 (6.26 ± 0.15) | 0.80 | 7.46 ± 0.16 | 8.35 ± 0.11 |
| **10** | 6.28 ± 0.06 (7.31 ± 0.11) | 5.60 ± 0.09 (6.26 ± 0.20) | 0.70 | 6.81 ± 0.09 (6.31 ± 0.14) | 0.90 | 7.10 ± 0.15 | 8.25 ± 0.09 |
| **11** | 6.72 ± 0.09 (7.02 ± 0.09) | 5.90 ± 0.12 (6.21 ± 0.08) | 0.40 | 7.01 ± 0.04 (6.40 ± 0.14) | 0.88 | 6.25 ± 0.11 | 7.90 ± 0.09 |
| **12** | 6.22 ± 0.13 (6.50 ± 0.07) | 5.50 ± 0.11 (6.10 ± 0.10) | 0.50 | 6.00 ± 0.08 (6.10 ± 0.11) | 1.0 | 7.10 ± 0.09 | <6 |
| 2-BFI | $\alpha_2$-ARs: (4.57)[e] | | | | | | 8.89[e] |

[a]The data were expressed as means ± SEM of 3−6 separate experiments. [b]According to ref 8. [c]According to ref 22. [d]According to ref 13. [e]Reference 18.

activation but probably the $I_2$−IBS interaction was involved in this effect.

This involvement was also justified by the observation that, while **10** endowed with high $I_2$−IBS affinity ($pK_i$ = 8.25) behaved similarly to **7**, **8** displaying smaller affinity ($pK_i$ = 6.9), required the dose of 10 mg/kg for a significant antidepressant-like effect (Supporting Information, Figures 3 and 4). To support our observations, **7** was tested in the presence of the 5-$HT_{1A}$-R antagonist WAY100135 and the $I_2$−IBS/$\alpha_2$-AR antagonist idazoxan (Figure 1C). As expected, the pretreatment with WAY100135 did not affect the antidepressant effect, which, on the contrary, was significantly contrasted by idazoxan. This result supported the lack of 5-$HT_{1A}$-R participation and confirmed the $I_2$−IBS involvement. The fact that **7** kept the 5-$HT_{1A}$-R affinity but not the agonist potency of its methyl homologue **1** did not contrast with previous results showing that minor modifications of the chemical structure of 5-$HT_{1A}$-R agonists were compatible with the maintenance of the affinity, but drastically reduced their 5-$HT_{1A}$-R agonism.[23]

At the dose of 5 mg/kg, **7** was effective both in preventing acquisition of morphine dependence and countering its expression (Figure 2).

In particular, on the expression of morphine dependence, the reduction of the frequencies of naloxone-precipitated jumping and other somatic signs was >50%. The favorable synergism induced by effective $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism and $I_2$−IBS interaction might also be underlined by the fact that 2-BFI, known as a selective $I_2$−IBS ligand ($I_2$−IBS/$\alpha_2$-AR = 2874),[18] required higher doses to attenuate morphine withdrawal[24] and to produce an antidepressant effect[19] comparable to that of **7** (10 mg/kg and 19 mg/kg, respectively). However, higher doses were required by the selective $I_2$−IBS ligands such as *ortho*-methylphenyzoline ($I_2$−IBS/$\alpha_2$-AR = 332)[13] or LSL60101[25] to attenuate the severity of the withdrawal syndrome (10 or 20 mg/kg, respectively).

In conclusion, the present study (i) confirms the advantage of having ligands that display effective $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism/5-$HT_{1A}$-R agonism. Indeed, **3** or its (*S*)-enantiomer and **4** might represent novel multifunctional tools potentially useful in the reduction of withdrawal syndrome and associated depression at very low dose. (ii) Moreover, it indicates that also ligands producing significant $\alpha_{2C}$-AR agonism/$\alpha_{2A}$-AR antagonism/$I_2$−IBS interaction, such as **7** and **9**−**11**, might similarly be beneficial to both disorders, as demonstrated by **7** at the dose of 5 mg/kg. Since $I_2$−IBS are involved in several psychiatric disorders,[16,18] **7** and **9**−**11** might also relieve further withdrawal comorbid neurobiologic conditions. Anyway, all the aforementioned multifunctional

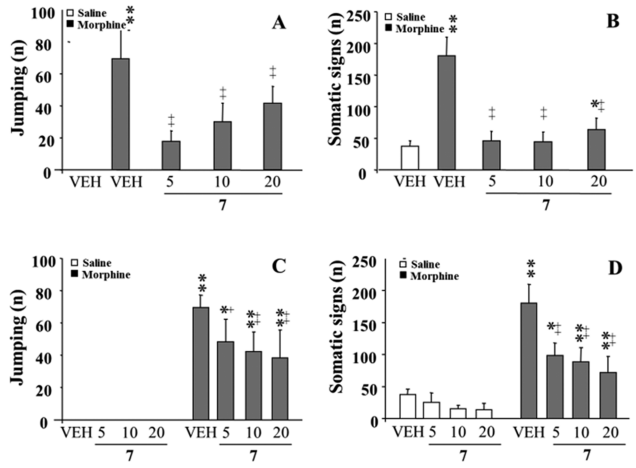


**Figure 2.** Effects of acute (A,B) or repeated (C,D) i.p. administration of **7** (5, 10, 20 mg/kg) on expression and acquisition of morphine dependence, respectively. Naloxone-precipitated withdrawal symptoms, both in control and morphine treated mice, are given as a measure of the frequency of jumping (A,C) and somatic signs (B,D) expressed as summary of rearing, forepaw tremors, and teeth chatter. Data represent mean (±SEM) of 8 animals. Significant differences: $^{*}p < 0.05$, $^{**}p < 0.01$, compared to vehicle; $^{+}p < 0.05$, $^{++}p < 0.01$, compared to morphine group.

compounds, lacking in sedative side effects and potentially endowed with favorable ADME profiles and limited activity on the hERG channel, as demonstrated for **1** and **2**,[8,9] might afford an improvement over current therapies with clonidine-like drugs.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic procedure, Figures 3 and 4, and elemental analysis of the final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS

$\alpha_2$-ARs, $\alpha_2$-adrenoreceptors; 5-HT, 5-hydroxytryptamine; 5-$HT_{1A}$-R, 5-$HT_{1A}$ receptor; i.p, intraperitoneally; s.c, subcutaneously; $I_2$−IBS, $I_2$−imidazoline binding sites; FST, forced swimming test; ADME, absorption, distribution, metabolism, excretion; hERG, human ether-à-go-go-related gene

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