

# Low Doses of Allyphenylene and Cyclomethylene, Effective against Morphine Dependence, Elicit an Antidepressant-like Effect

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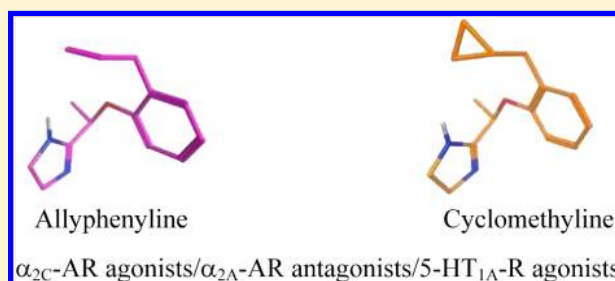
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## S Supporting Information

**ABSTRACT:** This study demonstrated that cyclomethylene (**2**) and the corresponding enantiomers (*R*)-(-)-**2** and (*S*)-(+)-**2**, displaying  $\alpha_{2C}$ -adrenoreceptor (AR) agonism/ $\alpha_{2A}$ -AR antagonism, similarly to allyphenylene (**1**) and its enantiomers, significantly decreased the naloxone-precipitated withdrawal symptoms in mice at very low doses. It also highlighted that such positive effects on morphine dependence can even be improved by additional serotonergic 5-HT<sub>1A</sub> receptor (5-HT<sub>1A</sub>-R) activation. Indeed, **1** or the single (*S*)-(+)-**1**, **2**, or both its enantiomers, all behaving as  $\alpha_{2C}$ -AR agonists/ $\alpha_{2A}$ -AR antagonists/5-HT<sub>1A</sub>-R agonists, alone and at the same low dose, improved morphine withdrawal syndrome and exerted a potent antidepressant-like effect. Therefore, considering the elevated comorbidity between opiate abuse and depressed mood and the benefit of these multifunctional compounds to both disorders, it is possible that they prove more efficacious and less toxic than a cocktail of drugs in managing opioid addiction.

**KEYWORDS:**  $\alpha_2$ -adrenergic ligands, 5-HT<sub>1A</sub>-R agonists, morphine withdrawal symptoms reduction, antidepressant-like effect



Morphine use is the classical approach in the treatment of chronic or cancer-related pain. Nevertheless, even when legally allowed and closely monitored, long-term opioid administration alters central pain-related systems, inducing tolerance and dependence. Opioid addiction, termed a “chronic relapsing disease”, is associated with a myriad of health and social problems; hence, its management is an extremely important area of research.<sup>1</sup>

$\alpha_2$ -Adrenoreceptors ( $\alpha_2$ -ARs), which have been demonstrated to be extremely sensitive to opioid exposure and to play a key role in opiate withdrawal symptoms,<sup>2</sup> belong to the superfamily of G-protein-coupled receptors. The three  $\alpha_{2A}$ -,  $\alpha_{2B}$ -, and  $\alpha_{2C}$ -AR subtypes are widely distributed in the central nervous system (CNS) and peripheral tissues.<sup>3</sup> Studies with genetically engineered mice have demonstrated that 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, while the  $\alpha_{2C}$  subtype appears to be involved in many CNS processes, such as the startle reflex, stress responses, and control of locomotion as well as feedback inhibition of adrenal catecholamine release. Moreover, in the brain,  $\alpha_{2A}$ - and  $\alpha_{2C}$ -ARs, as “heteroreceptors”, inhibit dopamine and serotonin release. Finally, the  $\alpha_{2C}$  subtype can contribute to adrenergic-opioid synergy and spinal  $\alpha_2$ -

agonist-mediated analgesia.<sup>3–5</sup> In detoxification,  $\alpha_2$ -AR agonists such as clonidine and lofexidine are often clinically used alone or in combination with traditional treatments to reduce the intensity of withdrawal symptoms, thus increasing treatment duration. However, the  $\alpha_{2A}$ -AR activation triggered by these compounds is responsible for side effects such as sedation and hypotension.<sup>1</sup> It has been reported that in comparison to clonidine, lofexidine showed decreased incidence and severity of adverse events.<sup>1,6</sup> The partial  $\alpha_{2A}$ -AR agonism of lofexidine, as recently assessed by us,<sup>7</sup> might justify its behavior (Table 1). Therefore, selective  $\alpha_{2C}$ -AR agonists, devoid of the side effects associated with  $\alpha_{2A}$ -AR stimulation, alone or in combination with opioids, might afford an improvement over current therapies with clonidine-like drugs. We reported the interesting behavior of allyphenylene (**1**), which displays a significant  $\alpha_{2C}$ -AR agonist/ $\alpha_{2A}$ -AR antagonist profile<sup>8</sup> ascribed to its preferred extended molecular conformation.<sup>7</sup> In *in vivo* studies, **1** enhanced morphine analgesia (due to its  $\alpha_{2C}$ -agonism), was devoid of a sedative effect (due to its  $\alpha_{2A}$ -antagonism),<sup>8,9</sup> and contrasted and prevented morphine tolerance and dependence

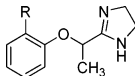
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**Table 1.** <sup>a</sup>Affinity (pK<sub>i</sub>), Antagonist Potency (pK<sub>b</sub>), Agonist Potency (pEC<sub>50</sub>), and Intrinsic Activity (ia) on Human  $\alpha_2$ -AR Subtypes<sup>b</sup> and Affinity (pK<sub>i</sub>), Agonist Potency (pD<sub>2</sub>), and Relative Efficacy (%E<sub>max</sub>) on Human 5-HT<sub>1A</sub>-R<sup>c</sup>



<sup>1</sup> R = -CH<sub>2</sub>CH=CH<sub>2</sub>  
<sup>2</sup> R = -CH<sub>2</sub>-

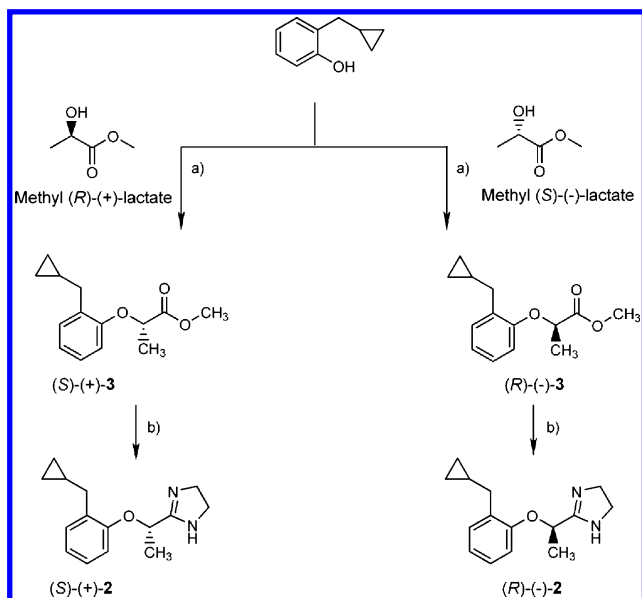
compd	$\alpha_{2A}$	$\alpha_{2B}$	ia	$\alpha_{2C}$	ia	5-HT <sub>1A</sub>	
	pK <sub>b</sub> (pK <sub>i</sub> )	pEC <sub>50</sub> (pK <sub>i</sub> )		pEC <sub>50</sub> (pK <sub>i</sub> )		pD <sub>2</sub> (pK <sub>i</sub> )	%E <sub>max</sub>
(±)-1	7.40 ± 0.06 (7.24 ± 0.11)	NA <sup>d</sup> (6.47 ± 0.20)		7.30 ± 0.09 (7.07 ± 0.14)	0.90	6.86 ± 0.09 (7.55 ± 0.16)	67
(R)-(-)-1	7.40 ± 0.09 (7.00 ± 0.08)	NA <sup>d</sup> (6.25 ± 0.12)		6.73 ± 0.11 (6.75 ± 0.11)	0.50	<5 (<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
(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
clonidine <sup>b</sup>	<sup>e</sup>	5.95 ± 0.27	0.45	7.24 ± 0.14	0.60	(5.49 ± 0.13)	
lofexidine <sup>f</sup>	<sup>g</sup> (8.36 ± 0.11)	6.90 ± 0.14 (7.17 ± 0.18)	0.80	8.86 ± 0.20 (7.16 ± 0.07)	0.80	(6.90 ± 0.11)	
8-OH-DPAT						7.60 ± 0.06 (8.47 ± 0.13)	100

<sup>a</sup>The data were expressed as means ± SEMs of 3–6 separate experiments. <sup>b</sup>According to ref 9. <sup>c</sup>pK<sub>i</sub> values were derived from displacement of [<sup>3</sup>H]-8-OH-DPAT binding on human cloned 5-HT<sub>1A</sub>-R. pD<sub>2</sub> values are the negative logarithm of the agonist concentration required to obtain 50% of the maximal stimulation of [<sup>35</sup>S]GTPγS binding. Maximal stimulation (%E<sub>max</sub>) is expressed as a percentage of the maximal 8-OH-DPAT response. <sup>d</sup>Compounds exhibiting ia of <0.3 were considered not active (NA). <sup>e</sup>pEC<sub>50</sub> = 8.08 ± 0.12; ia = 0.90. <sup>f</sup>Ref 7. <sup>g</sup>pEC<sub>50</sub> = 8.20 ± 0.10; ia = 0.60.

at a very low dose (0.05 mg/kg).<sup>9</sup> In contrast, clonidine attenuated the expression of morphine withdrawal symptoms at a higher dose (5 mg/kg) and was ineffective in preventing them.<sup>10</sup> Because  $\alpha_2$ -AR antagonists (i.e., yohimbine) also attenuated the intensity of withdrawal symptoms,<sup>11</sup> we attributed the unique profile of **1** to the synergistic combination of its effective dual  $\alpha_{2C}$ -AR agonism/ $\alpha_{2A}$ -AR antagonism.<sup>9</sup> The positive effects of **1** on dependence were also displayed by (S)-(+)-**1** (potent  $\alpha_{2C}$ -AR full agonist) and (R)-(-)-**1** ( $\alpha_{2C}$ -AR partial agonist); they both were endowed with similar  $\alpha_{2A}$ -AR antagonism.<sup>9</sup> To confirm the aforementioned results and discover novel tools for the management of opioid withdrawal symptoms that have a major role in relapse to drug-taking behavior after detoxification, we extended the study to the recently reported allylphenyl analogue **2**,<sup>7</sup> now named cyclomethyl, and its enantiomers, prepared in the present investigation. Compound **2** showed interesting  $\alpha_{2C}$ -AR agonism/ $\alpha_{2A}$ -AR antagonism (Table 1), and according to what reported for **1**,<sup>7</sup> this functional profile might be associated with a preferred extended molecular conformation. Therefore, the corresponding enantiomers were evaluated by binding and functional assays on Chinese hamster ovary (CHO) cells expressing recombinant human  $\alpha_2$ -AR subtypes according to previous procedures.<sup>9</sup> Moreover, the effects of the racemate **2** at the dose of 0.05 mg/kg and its enantiomers at the dose of 0.025 mg/kg (ip) on the expression and acquisition of morphine dependence were determined. To learn more about the pharmacological properties of this novel class of compounds, especially in light of the strong comorbidity between opioid addiction and depressive disorders seen in several clinical studies,<sup>12</sup> **1** and **2** and their enantiomers were evaluated in a behavioral model of depression in mice. It is known that the

serotonergic [5-hydroxytryptamine (5-HT)] system is involved in the neural regulation of mood, and abnormalities in 5-HT neurotransmission have been observed in the pathophysiology of depression. Moreover, 5-HT dysfunction is one of the main mechanisms contributing to mood disorders in opiate abstinence.<sup>13</sup> It has also been suggested that  $\alpha_{1A}$ -AR agonists might represent a novel treatment for depression.<sup>14</sup> Therefore, the biological profiles of the aforementioned compounds at 5-HT<sub>1A</sub> receptor (5-HT<sub>1A</sub>-R), particularly relevant to antidepressant responses in human beings,<sup>15</sup> and at  $\alpha_{1A}$ -AR were assessed according to procedures previously reported.<sup>16</sup> Finally, an assessment of the in vitro absorption, distribution, metabolism, excretion (ADME) properties<sup>9</sup> of **2** and of the activity of **1** and **2** on the human ether-à-go-go-related gene (hERG) channel<sup>17</sup> was performed.

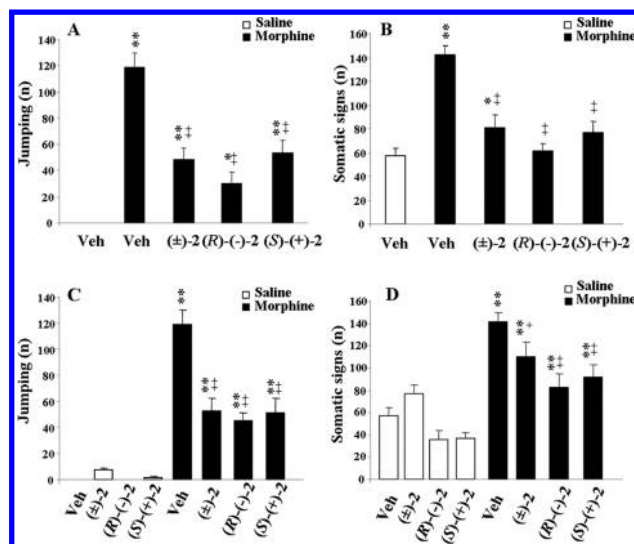
The enantiomers of **2** were prepared according to Scheme 1. (S)-(+)- and (R)-(-)-2-(2-cyclopropylmethyl)propionic acid methyl ester [(S)-(+)-**3** and (R)-(-)-**3**, respectively] were obtained by Mitsunobu reaction from 2-(cyclopropylmethyl)-phenol<sup>18</sup> and methyl (R)-(-)- or (S)-(+)-lactate, respectively, with inversion of configuration.<sup>19</sup> The reaction of (S)-(+)- or (R)-(-)-**3** with ethylenediamine in the presence of (CH<sub>3</sub>)<sub>3</sub>Al yielded the corresponding imidazolines (S)-(+)- and (R)-(-)-**2**, whose e.e. determined by <sup>1</sup>H NMR spectroscopy was about 85%, due to partial racemization occurring under the conditions used in the reactions. Indeed, their spectra, as well as that of the racemic (±)-**2** on addition of the chiral shift reagent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol, showed a doublet at  $\delta$  1.38 ppm for the methyl protons. The resolution of the racemic imidazoline (±)-**2** was performed by HPLC using Chiralcel OD-H (25 cm × 0.46 cm, 5  $\mu$ m particle size) as the chiral stationary phase and *n*-hexane/2-propanol 90/10 v/v

Scheme 1. Synthesis of (S)-(+)-2 and (R)-(-)-2<sup>a</sup>

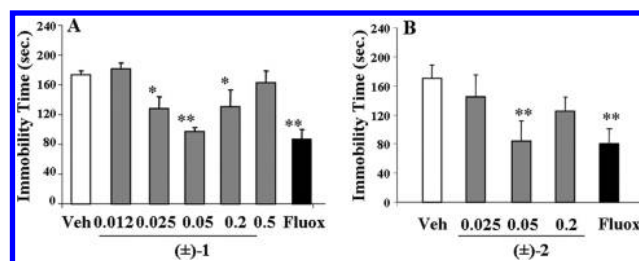
<sup>a</sup>Reagents and conditions: (a) DIAD, Ph<sub>3</sub>P, THF, rt. (b) Ethylenediamine, Al(CH<sub>3</sub>)<sub>3</sub>, toluene, 0–65 °C, 7 h.

as the mobile phase. Detection was monitored at a wavelength of 220 nm, and the retention times were 5.9 and 10.3 min for (+)-2 and (–)-2, respectively; (+)-2: [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +19.28, e.e. 100%; (–)-2: [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –19.59, e.e. 100%. In this case, the <sup>1</sup>H NMR spectra, similarly performed, showed for the methyl group of (+)-2 and (–)-2 only one doublet at  $\delta$  1.36 and  $\delta$  1.40 ppm, respectively. The absolute configuration of the stereocenter in the bridge of these enantiomers was determined by comparing the sign of their optical rotations with those of the enantiomers obtained by stereoselective synthesis. Consequently, the (S) absolute configuration was assigned to the dextrorotatory enantiomer (+)-2 and (R) to the levorotatory (–)-2.

The affinity values (pK<sub>i</sub>), antagonist properties (pK<sub>b</sub>), agonist potencies, and intrinsic activities (pEC<sub>50</sub> and i<sub>a</sub>, respectively) of the enantiomers of **2** on  $\alpha_2$ -AR subtypes are reported in Table 1. The biological profiles of **2**, **1**, and its enantiomers were also included for useful comparison. This study indicates that (i) both enantiomers of **2** displayed binding affinities for the three  $\alpha_2$ -AR subtypes comparable to those of the racemic compound; (ii) (S)-(+)-2 was endowed with the highest  $\alpha_{2C}$ -AR agonist activity; (iii) (R)-(-)-2 was characterized by lower but still significant  $\alpha_{2C}$ -AR agonism; and (iv) (R)-(-)-2 and (S)-(+)-2 showed weak  $\alpha_{2B}$ -AR activation but effective  $\alpha_{2A}$ -AR antagonist potencies. Interestingly, **2**, (R)-(-)-2 and (S)-(+)-2 affected expression and acquisition of morphine dependence (Figure 1) as observed previously for **1** and its enantiomers.<sup>9</sup> The frequencies of naloxone-precipitated jumping and other somatic signs (rearing, forepaw tremors, and teeth chatter) decreased significantly. To study possible antidepressant-like activity, the mouse forced swimming test (FST), a behavioral model with good reliability and predictive validity for screening antidepressants,<sup>20</sup> was used. Figure 2A shows that **1** induced significant reduction of immobility time. This effect was maximal at the dose of 0.05 mg/kg and comparable to that obtained with the dose of 20 mg/kg of the selective 5-HT reuptake inhibitor fluoxetine, included as reference compound.<sup>21</sup> Significant antidepressant activity was also observed



**Figure 1.** Effects of acute (A, B) or repeated (C, D) ip administration of (±)-2 (0.05 mg/kg), (R)-(-)-2, and (S)-(+)-2 (0.025 mg/kg) on expression and acquisition of morphine dependence, respectively. Naloxone-precipitated withdrawal symptoms, in both control and morphine-treated mice, are given as a measure of the frequency of jumping (A, C) and somatic signs (B, D) expressed as a summary of rearing, forepaw tremors, and teeth chatter. Significant differences: \**p* < 0.05, \*\**p* < 0.01, as compared to vehicle; +*p* < 0.01, as compared to the morphine group.

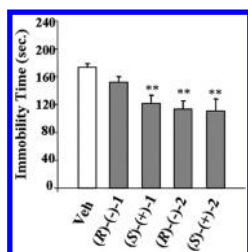


**Figure 2.** Immobility time in the FST in mice following ip administration of (±)-1 at 0.012, 0.025, 0.05, 0.2, and 0.5 mg/kg (A), (±)-2 at 0.025, 0.05, and 0.2 mg/kg (B), and fluoxetine (Fluox; 20 mg/kg) as a reference drug. Data represent means (±SEM) of 8–9 animals. Differences from vehicle-treated: \**p* < 0.05, \*\**p* < 0.01; where not indicated, the differences are not statistically significant.

at 0.025 and 0.2 mg/kg doses, whereas no activity was observed at lower and higher doses. Similarly, the maximal effect of **2** was displayed at the dose of 0.05 mg/kg (Figure 2B). Nevertheless, the antidepressant response of **1** was only associated with the (S)-(+)-1 enantiomer, whereas the effect of **2** was similarly induced by both its enantiomers (Figure 3). In Table 1, affinities and functional values of all compounds at 5-HT<sub>1A</sub>-R are also reported. The 5-HT<sub>1A</sub>-R agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) was included for useful comparison.<sup>16</sup> From the data, it emerged that **1** displayed good 5-HT<sub>1A</sub>-R affinity and behaved as an agonist. These properties were maintained and even enhanced only by the (S)-(+)-1 enantiomer, whereas (R)-(-)-1 showed negligible affinity (pK<sub>i</sub> < 5).

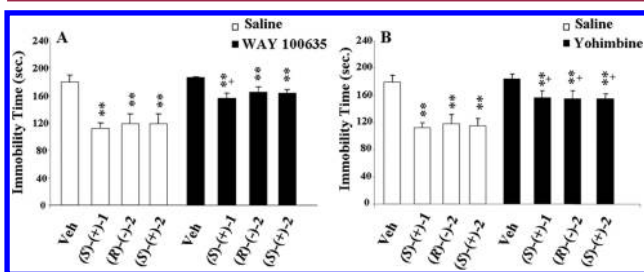
In contrast, **2**, (R)-(-)-2 and (S)-(+)-2 displayed similar and significant 5-HT<sub>1A</sub>-R affinities and agonist potencies. None of the compounds studied showed significant  $\alpha_{1A}$ -AR agonism (i<sub>a</sub> < 0.35). Altogether, the data indicated that dual  $\alpha_{2C}$ -AR/5-HT<sub>1A</sub>-R activation was requested for the antidepressant-like





**Figure 3.** Immobility time in the FST in mice following ip administration of (R)-(-)-1, (S)-(+)-1, (R)-(-)-2, and (S)-(+)-2 (0.025 mg/kg). Data represent means ( $\pm$ SEMs) of eight animals. Differences from vehicle-treated: \*\* $p < 0.01$ ; where not indicated, the differences are not statistically significant.

effect induced by low doses of **1** and the single (S)-(+)-1 enantiomer, **2**, and both its enantiomers. This consideration does not contrast with the results of previous studies.<sup>22,23</sup> Indeed, they indicated that low doses of clonidine (0.01–0.06 mg/kg) increased 5-HT neurotransmission by attenuating the release of endogenous noradrenaline via activation of  $\alpha_2$ -AR autoreceptors on adrenergic neurones<sup>22</sup> and, hence, induced anti-immobility effects with subactive doses of 5-HT<sub>1A</sub>-R agonists (i.e., 8-OH-DPAT) in mouse FST.<sup>23</sup> On the contrary, higher doses (0.1–0.4 mg/kg) decreased 5-HT neurotransmission through the direct activation of the  $\alpha_2$ -AR heteroreceptors on the 5-HT terminals.<sup>22</sup> The peculiar relationship between  $\alpha_2$ -AR activation and 5-HT function, highlighted by such studies, might justify the dose-dependent U-shaped trend exhibited by the anti-immobility effect of our  $\alpha_{2C}$ -AR/5-HT<sub>1A</sub>-R agonists. To support our observations, experiments in the presence of the 5-HT<sub>1A</sub>-R antagonist WAY 100635<sup>24</sup> and the  $\alpha_2$ -AR antagonist yohimbine<sup>25</sup> were carried out. Both antagonists, ineffective when given alone, significantly and similarly contrasted the actions evoked by 0.025 mg/kg dose of (S)-(+)-1, (R)-(-)-2, and (S)-(+)-2 (Figure 4). Therefore, these results confirmed that dual  $\alpha_{2C}$ -



**Figure 4.** Influence of the 5-HT<sub>1A</sub>-R antagonist WAY 100635 (0.1 mg/kg, sc) (A) and the  $\alpha_2$ -AR antagonist yohimbine (1.250 mg/kg, ip) (B) on the antidepressant-like effect of the enantiomers (S)-(+)-1, (R)-(-)-2, and (S)-(+)-2 (0.025 mg/kg, ip) on the FST. Data represent means ( $\pm$ SEMs) of 7–8 animals. Significant differences: \*\* $p < 0.01$ , as compared with vehicle group; ++ $p < 0.01$ , as compared with enantiomers related-treated mice; and ° $p < 0.05$ , as compared with antagonist-treated mice; where not indicated, the differences are not statistically significant.

AR/5-HT<sub>1A</sub>-R activation, favorably triggered by the same molecule, took part in the anti-immobility effect. It has been reported that selective  $\alpha_{2C}$ -AR antagonists, allowing  $\alpha_{2A}$ -AR stimulation, produced important antidepressant effects in the FST.<sup>26</sup> Because  $\alpha_{2A}$ - and  $\alpha_{2C}$ -AR subtypes complement each other to integrate CNS function and behavior,<sup>5</sup> it is possible that also the  $\alpha_{2C}$ -AR agonism/ $\alpha_{2A}$ -AR antagonism combination,

associated with 5-HT<sub>1A</sub> activation, as verified for the examined compounds, is equally compatible with an antidepressant-like effect. The advantage of this peculiar biological profile was also supported by the observation that yohimbine, a 5-HT<sub>1A</sub>-R agonist<sup>27</sup> and antagonist at all three  $\alpha_2$ -AR subtypes,<sup>25</sup> did not display antidepressant activity. The physicochemical and in vitro ADME<sup>9</sup> profile of **2** proved to be similar to that of **1**. Indeed, **2** was highly soluble in water at physiological pH. The permeation rate in a parallel artificial membrane permeability assay (PAMPA) assay and the percentage remaining after incubation for 1 h with recombinant hCYP3A4 were very high. From an automatic patch clamp assay on HEK293 cells overexpressing the hERG channel,<sup>17</sup> compounds **1** and **2** showed to be weak inhibitors, with IC<sub>50</sub> values of 16.9 and 8.9  $\mu$ M, respectively, suggesting a low cardiotoxicity risk associated with their potential therapeutic use.

In summary, the present study demonstrated that cyclo-methylene (**2**) and its enantiomers, characterized by  $\alpha_{2C}$ -AR agonist/ $\alpha_{2A}$ -AR antagonist profile, significantly decreased the naloxone-precipitated withdrawal symptoms in mice at very low doses. These properties are in agreement with those shown by the lead **1** and its enantiomers and confirm that dual  $\alpha_{2C}$ -AR agonism/ $\alpha_{2A}$ -AR antagonism represents a favorable condition for inducing positive effects on morphine dependence.<sup>9</sup> Interestingly, such effects can even be improved by additional 5-HT<sub>1A</sub>-R activation. Indeed, unlike clonidine, **1** or the single (S)-(+)-1 enantiomer, **2**, or both its enantiomers, all behaving as  $\alpha_{2C}$ -AR agonists/ $\alpha_{2A}$ -AR antagonists/5-HT<sub>1A</sub>-R agonists, alone and at the same low dose, improved morphine withdrawal syndrome and exerted a potent antidepressant-like effect. It has been suggested that opiate abuse may induce depressed mood, or conversely, depression can drive to drug abuse in a self-medication hypothesis. Therefore, such multifunctional compounds might be beneficial to both disorders.<sup>13</sup> In addition, their therapeutic potential is strongly enhanced by the lack of sedative side effects (due to their  $\alpha_{2A}$ -antagonism) and alteration of motor activity (data not shown), as well as by their favorable in vitro ADME profiles and limited activity on the hERG channel.

## ■ ASSOCIATED CONTENT

### ⑤ Supporting Information

Synthetic procedure, hERG activity assay, detail of biological assay, 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

AR, adrenoreceptor; CNS, central nervous system; CHO, Chinese hamster ovary; 5-HT, 5-hydroxytryptamine; 5-HT<sub>1A</sub>-R, 5-HT<sub>1A</sub> receptor; ee, enantiomeric excess; ip, intraperitoneally;

sc, subcutaneously; ADME, absorption, distribution, metabolism, excretion; PAMPA, parallel artificial membrane permeability assay; DIAD, diisopropyl azodicarboxylate; CYP, cytochrome P450; hERG, human ether-à-go-go-related gene

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