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N-3(9)-Arylpropenyl-*N*-9(3)-propionyl-3,9-diazabicyclo[3.3.1]nonanes as μ-Opioid Receptor Agonists. Effects on μ-Affinity of Arylalkenyl Chain Modifications

Gérard A. Pinna,[a,*] Giorgio Cignarella,[b] Giovanni Loriga,[a,c] Gabriele Murineddu,[a,c] Jean-Mario Mussinu,[a] Stefania Ruiu,[c] Paola Fadda[d] and Walter Fratta[d]

[a]*Dipartimento Farmaco Chimico Tossicologico, Università di Sassari, via F. Muroni 23/A, 07100 Sassari, Italy*
[b]*Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, viale Abruzzi 42, 20131 Milan, Italy*
[c]*Neuroscienze S.c.a.r.l., Zona Industriale Macchiareddu, 09010 Uta, Cagliari, Italy*
[d]*Dipartimento di Neuroscienze, Università di Cagliari, Cittadella Universitaria, 09042 Monserrato, Cagliari, Italy*

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Abstract—Two series of *N*-3-arylpropenyl-*N*-9-propionyl-3,9-diazabicyclo[3.3.1]nonanes (**1b–j**) and of the reverted *N*-3-propionyl-*N*-9-arylpropenyl isomers (**2b–j**) as analogues of the previously reported analgesic *N*-3(9)-cinnamyl-*N*-9(3)-propionyl-3,9-diazabicyclo[3.3.1]nonanes (DBN) (**1a**, **2a**) were synthesised and their affinity and selectivity towards opioid μ-, δ- and κ-receptors were evaluated. Several compounds (**1e**,**i**,**j**–**2d**,**e**,**f**,**g**,**j**) exhibited a μ-affinity in the low nanomolar range with moderate or negligible affinity towards δ- and κ-receptors. The representative term *N*-9-(3,3-diphenylprop-2-enyl)-*N*-3-propionyl-DBN (2d) displayed in vivo (mouse) a potent analgesic effect (ED_{50} 3.88 mg/kg ip) which favourably compared with that of morphine (ED_{50} 5 mg/kg ip). In addition, **2d** produced in mice tolerance after a period twice as long with morphine.

Introduction

Opioid analgesics are widely used clinically to relieve severe pain.[1] The μ-opioid receptor has commonly been suggested to be responsible for not only the therapeutic effects of opioid analgesic drugs but also for the numerous side effects. Currently, the major limitation in the medical utilization of opioids arises from two peculiar problems closely linked to their chronic use: tolerance and dependence.

Clinicians have observed that many patients showed wide-ranging sensitivity to the μ drugs, both with regard to analgesia and to side effects.

In this regard, the findings obtained both in animals and clinical studies indicate that genetic factors may influence the variable response of patients to μ-opioid analgesics and suggest that these drugs may not act through a single receptor mechanism. Accordingly, the cloning of the μ-opioid, MOR1 receptor gene, has demonstrated the presence of multiple μ-subtype receptors (splice variants differing at the intracellular carboxy terminus) and evidenced that more than one μ-receptor is responsible for opioid analgesia.

In conclusion, these observations suggest that μ-opioid analgesic drugs could bind with different affinity to multiple μ-opioid receptor sub-types providing an approach for the development of new compounds able to relieve acute and chronic pain, and which are lacking of the typical opioid side effects.[2]

Recently, we found that *N*-3(9)-cinnamyl-*N*-9(3)-propionyl-3,9-diazabicyclo[3.3.1]nonane (**1a**, **2a**) exhibited a significant affinity towards μ-opioid receptors with $K_i = 29$ nM for **1a** and 13 nM for **2a**.[3]

We also found that substitution of the phenyl moiety with Cl and/or NO_2 groups in various positions markedly reduced μ-affinity in series **1**. Interestingly, in the isomeric series **2**, this trend was reverted, the majority of the compounds derived from **2a** displaying μ-affinity higher (K_i 6–8 nM) than that of **2a**.[3]

Continuing our interest in this area, the cinnamyl chain of the lead compounds **1**,**2a** was modified as follows: (a) insertion at C-3′ of an additional group such as CH_3 (**1**,**2b**), C_6H_{11} (**1**,**2c**), C_6H_5 (**1**,**2d**), *o*,*m*-Cl–C_6H_4 (**1**,**2e**,**f**), (b) substitution at the *para* position of the phenyl groups of the chain with halogen (Cl, F) (**1**,**2 h**,**i**) or *m*-CF_3 (**1**,**2g**), and (c) reduction of the double bond of **1**,**2d** (**1**,**2j**) (Table 1).

*Corresponding author. Tel.: +39-079-228721; fax: +39-079-228720; e-mail: pinger@uniss.it

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Among this group, we found compound **2d** of particular interest. In fact, this compound binds to the μ-receptor with an affinity very close to that of morphine, but at the same time displays a higher selectively towards the μ-receptor.

For these reasons, aiming to better define the pharmacological profile of this compound, we have also investigated the effects of its in vivo administration.

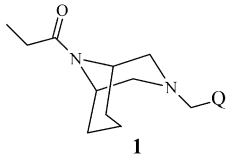
Chemistry

The synthetic pathway leading to the novel analogues of **1**,**2a** is outlined in Scheme 1. Precursors **3**[3] and **4**[3] were alkylated with the corresponding halides (**9b–i**) or methanesulfonate (**9j**) and potassium carbonate in refluxing acetone to give **1**,**2b–j**.

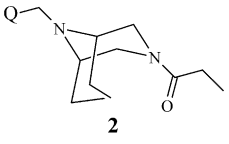
The required halides (**9b–i**) or methanesulfonate (**9j**) were prepared starting from the appropriate ketones (**5b–i**) by reaction with triethyl phosphonoacetate (Horner–Emmons condensation) to give the cinnamyl esters (**6b–i**), which were reduced with diisobutylaluminum hydride (DibAl-H) in toluene to the corresponding cinnamyl alcohols (**7b–i**) (Scheme 2). Finally, the alcohols **7b–i** were converted to bromides **9b**,**c** with Ph_3P and CBr_4 or, alternatively, to chlorides **9d–i** with methanesulfonyl chloride and Et_3N in CH_2Cl_2. This reagent was also employed to obtain the methanesulfonate **9j** from **8j** in turn prepared from **7d** by catalytic hydrogenation (Pd/C).

The Horner–Emmons condensation of **5** gave mixtures of geometrical isomers with the *E*-isomers, ***E*-6b**,**c**,**e**,**f**, as the primary products. The isomers were separated by flash chromatography and the *E*,*Z*-isomeric structures

Table 1. Binding affinities of **1**,**2a–j** for opioid receptors (K_i nM)[a]

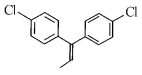
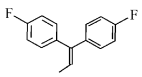


1



2

N_3-aralk(en)yl-3,9 DBN series — N_9-aralk(en)yl-3,9 DBN series

Compd	Q	Mp (°C)[b]	μ	δ	κ	K_i ratio δ/μ	K_i ratio κ/μ
1a		Oil	29±2.0	>5000	>5000	>172	>172
2a	(E)	Oil[3]	13±1.5	1750±144	2000±180	>134	>154
1b		187[c]	87±9.0	4361±38	>5000	50	>57.4
2b	(E)	195–200[c]	91±5.0	>5000	>5000	>55	>54.9
1c		218[c]	362.6±16.8	>5000	>5000	>14	>13.8
2c	(E)	225[c]	785±40	>5000	>5000	>6	>6.4
1d		97–100 dec	1167±33	>5000	>5000	>4	>4.3
2d		102–105 dec	5±0.6	630±70	2430±195	126	486
1e		135–136	14.3±2	331±3.46	>5000	23	>349.6
2e	(E)	125–127	7.2±0.7	3120±56	>5000	433	>694.4
1f		136	44.8±0.47	707±28	3474±53.3	15.8	77.54
2f	(E)	122–126	1.14±0.07	48.2±1.6	713±38	42.3	625.4
1g		128–135	257±9.6	620±17	>5000	2.4	>19.4
2g		91–92	1.36±0.07	9.46±0.7	>5000	6.9	>3676
1 h		112–115	62.3±2.4	2970±30	>5000	47.7	>80.2
2 h		126–127	156±7	1880±43	>5000	12.0	>32.0
1i		123	3.85±0.17	166±5.03	2422±84.4	43.1	629.1
2i		175[c]	46±4	388±11.5	>5000	8.4	>108.7
1j		141–145	10.6±0.7	189.3±9.5	2274±238	17.8	214.5
2j		158–160	2.45±0.05	70.7±2.7	649.6±31.7	28.8	265.1
Morphine			1.07±0.04	100.2±5.14	280.6±9.2	93.6	262.2

[a]The K_i values for the test ligands were determined with assays described in the experimental section. Results are mean±SEM for three independent experiments assayed in triplicate.
[b]As hydrochlorides.
[c]As fumarate.

were assigned by NMR spectra. In fact, fewer polar isomers of **6b**,**c** showed vinylic proton values deshielded, relative to those of the more polar *Z* isomers, due to the close proximity of the phenyl ring. In the case of **6e**,**f** the regiochemistry was determined by NOE experiments; interactions were observed between the *ortho*-hydrogens of the substituted phenyl rings of **6e**,**f** when the vinylic protons were irradiated.

Results and Discussion

The new compounds were submitted to binding studies on opioid receptors on mouse brain homogenates using [^{3}H]-DAMGO for μ-, [^{3}H]-DPDPE for δ- and [^{3}H]-Bremazocine for κ-receptor binding. Morphine was used as reference compound (see Table 1).

The evaluation of the affinity towards μ-, δ- and κ-opioid receptors demonstrated that in the series of analogues based on compound **1**, the μ-affinity of **1e**,**i**,**j** favourably compared with that of the lead **1a**,[3] the most potent **1i** exhibiting a K_i^{μ} 3.85 nM. In the reverted isomers **2**, a more favourable trend was observed. Five out of the nine derivatives tested displayed a μ-affinity higher than that of the lead **2a**[3] with K_i ranging from 1.36 to 7.2 nM. In addition, the abovementioned derivatives **1**,**2** exhibited a significant μ/δ and μ/κ selectivity (see Table 1).

As shown in Figure 1, **2d** produces a dose-related increase in response latency to the hot plate test with a ED_{50} value of 3.88 mg/kg (2.42–6.24; $n > 12$) (ED_{50} of morphine 5 mg/kg).

Furthermore, as shown in Figure 2, the analgesic activity of **2d** is completely reversed by pre-treatment with the opioid antagonist naloxone, thus confirming that analgesia is specifically mediated by the opioid receptors.

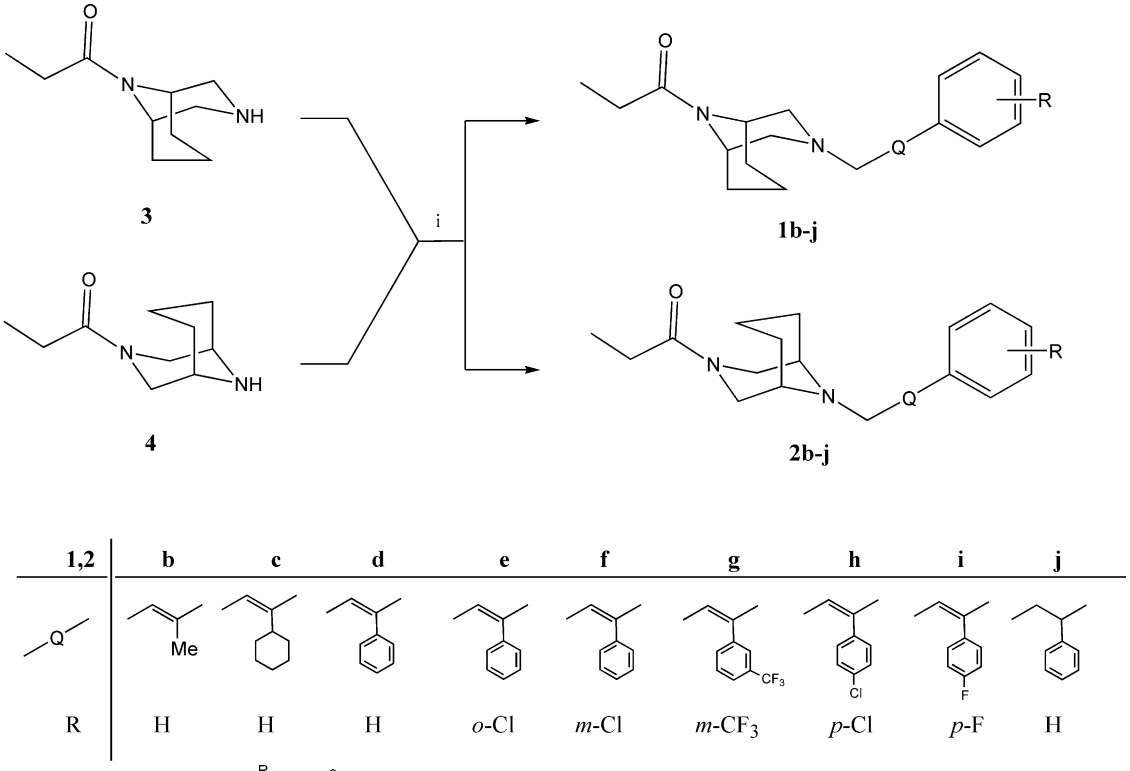
Finally, it was observed (Fig. 3) that tolerance to **2d** developed in mice after the 9th day of repeated administration (3.8 mg/kg ip per day). In comparison tolerance to morphine (Fig. 4) developed after 4 days of treatment (5 mg/kg ip per day). This difference in the time needed for the development of tolerance to the analgesic effect, much longer in **2d** than in morphine, is a very interesting point. In this regard, since 1984, studies by Pasternak and his collaborators have suggested the existence of at least two functionally distinct μ-receptor subtypes, namely μ_1 and μ_2. According to this hypothesis, both μ_1 and μ_2 are responsible for the opioid analgesia effects while only μ_2 would be responsible for tolerance and dependence.

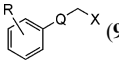
Should the latter be true, the different profile in inducing tolerance of **2d** compound could be linked to a different affinity of this compound for some μ-opioid receptor sub-types with respect to morphine.

Experimental

Chemistry

General information. Melting points were obtained on an Electrothermal IA 9100 digital melting point apparatus or on a Köfler melting point apparatus and are



Scheme 1. Reagents and conditions: (i)  (**9b–j**), K_2CO_3, acetone, Δ (X = Cl, Br or OSO_2CH_3).

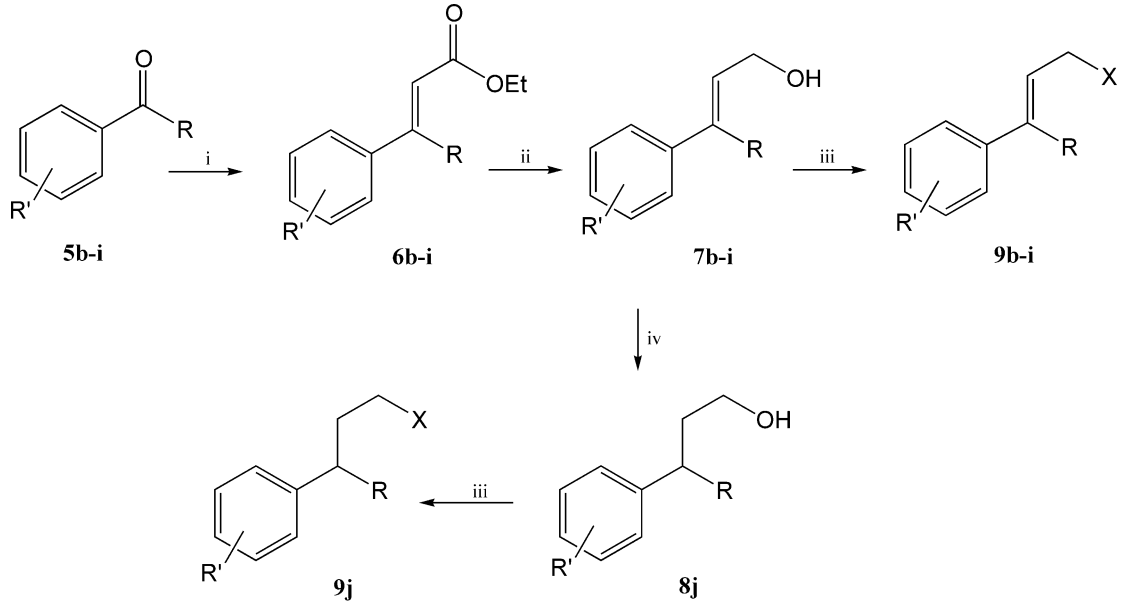
uncorrected. IR spectra were recorded as thin films (for oils) or Nujol mulls (for solids) on NaCl plates with a Perkin-Elmer 781 IR spectrophotometer and are expressed in ν (cm^{-1}). UV–vis spectra were recorded as ethanolic solution with a Perkin-Elmer lambda 5 spectrophotometer and are the absorption wavelength expressed as λ_{max} in nm followed by log ε in $dm^3\ mol^{-1}\ cm^{-1}$. All NMR spectra were taken on a Varian XL-200 NMR spectrometer with ^1H and ^{13}C being observed at 200 and 50 MHz, respectively. Chemical shifts for ^1H and ^{13}C NMR spectra were reported in δ or ppm downfield from TMS [$(CH_3)_4Si$]. Multiplicities are recorded as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), m (multiplet). Elemental analyses were performed by Laboratorio di Microanalisi, Dipartimento di Scienze Farmaceutiche, Università di Padova, Italy and are within ±0.4% of the calculated values. All reactions involving air or moisture-sensitive compounds were performed under argon atmosphere.

Unless otherwise specified, all materials, solvents, reagents and precursors **5b–i** were obtained from commercial suppliers.

Flash chromatography (FC) was performed using Merck silica gel 60 (230–400 mesh ASTM). Thin layer chromatography (TLC) was performed with Polygram® SIL N-HR/HV_{254} precoated plastic sheets (0.2 mm).

General arylpropenylation procedure for compounds 1 and 2. A mixture of the appropriate propionyl-3,9-diazabicyclo[3.3.1]nonane **3** or **4** (1.42 mmol), the required cinnamyl halide (**9b–i**) or methanesulfonate (**9j**) (1.42 mmol) and K_2CO_3 (3.55 mmol) in acetone (9 mL) was refluxed for 24 h under magnetic stirring. The inorganic salt was filtered off, the filtrate evaporated and the oily residue purified by flash chromatography to give the desired **1b–j** and **2b–j** as oils; the corresponding hydrochloride or fumarate was obtained as reported in Table 1.

3-[(2*E*)-3-Phenylbut-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1b. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 38%; R_f 0.46 (petroleum ether/EtOAc 5:5); mp 187 °C (as fumarate); IR 1650; UV: 205.0 (4.03), 225.0 (4.1); ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.8 Hz), 1.43–1.98 (m, 8H), 2.05 (s, 3H), 2.23–2.50 (m, 4H), 2.91–3.11 (m, 2H), 3.85–3.97 (m, 1H), 4.68–4.72 (m, 1H), 5.85 (t, 1H, J = 7.0 Hz), 7.20–7.63



5-9	b	c	d	e	f	g	h	i	j
R	CH_3	cC_6H_{11}	Ph	Ph	Ph	m-CF_3-Ph	p-Cl-Ph	p-F-Ph	Ph
R'	H	H	H	o-Cl	m-Cl	m-CF_3	p-Cl	p-F	H
X	Br	Br	Cl	Cl	Cl	Cl	Cl	Cl	OSO_2CH_3

Scheme 2. Reagents and conditions: (i) $(EtO)_2POCH_2COOEt$, NaH, toluene, room temperature; (ii) DibAl-H, toluene, room temperature; (iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0–10 °C or Ph_3P, CBr_4, CH_2Cl_2, room temperature; (iv) EtOH, Pd/C 10%, H_2.

(m, 5H). Anal. calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.57; H, 9.06; N, 8.95.

3-[(2*E*)-3-(2-Cyclohexyl)-3-phenylprop-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1c. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 8%; R_f 0.41 (petroleum ether/EtOAc 7:3); mp 218 °C (as fumarate); IR 1640; UV 225.0 (4.10); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.6 Hz), 1.57–1.96 (m, 12H), 1.96–2.40 (m, 7H), 2.80–3.04 (m, 5H), 3.80–3.90 (m, 2H), 3.95 (s, 1H), 4.60–4.70 (m, 1H), 7.12–7.60 (m, 5H). Anal. calcd for $C_{25}H_{36}N_2O$: C, 78.90; H, 9.53; N, 7.36. Found: C, 78.60; H, 9.49; N, 7.38.

3-(3,3-Diphenylprop-2-enyl)-9-propionyl-3,9-diazabicyclo[3.3.1] nonane 1d. Purified by FC (eluent: CH_2Cl_2 then CH_2Cl_2/CH_3COCH_3 9:1), yield 63%; R_f 0.60 (CH_2Cl_2/CH_3COCH_3 9:1); mp 97–100 °C (dec) (as hydrochloride); IR 1640; UV 216.0 (4.28), 250.0 (4.21); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.40–1.70 (m, 1H), 1.70–1.94 (m, 4H), 2.14–2.40 (m, 4H), 2.80–3.10 (m, 5H), 3.85–3.95 (m, 1H), 4.65–4.73 (m, 1H), 6.16 (t, 1H, J = 7.2 Hz), 7.12–7.60 (m, 10H). Anal. calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 80.45; H, 8.04; N, 7.45.

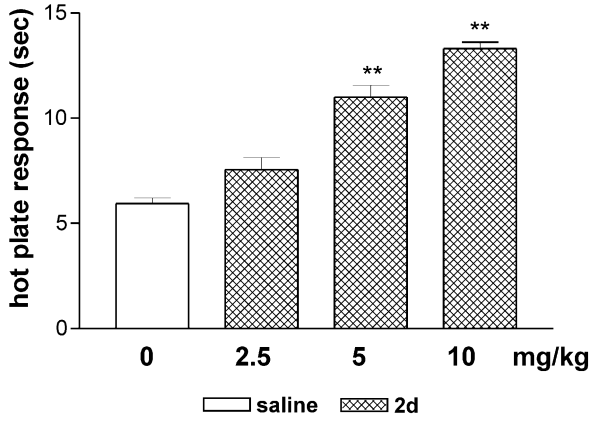


Figure 1. Bar graph showing effect of **2d** in the hot-plate test. Mice received **2d** at the indicated dose at time 0 and were tested on the hot-plate assay 15 min later. Each column represents the mean ± SEM of at least 12 mice per group. **$p < 0.01$ versus saline value.

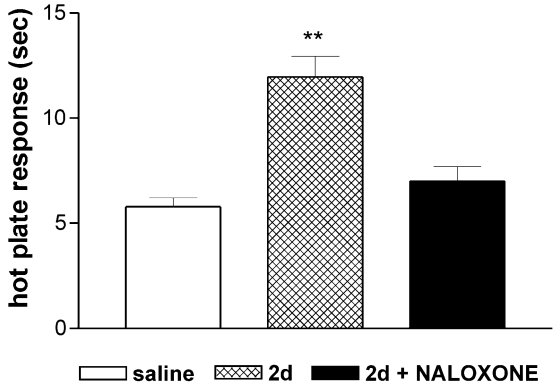


Figure 2. Antagonistic effect of naloxone on **2d**-induced antinociception. **2d** (5 mg/kg), naloxone (1 mg/kg) or vehicle were administered ip at time 0. Mice were tested on the hot plate 15 min post treatment. Each bar represents the mean ± SEM of at least six animals per group. **$p < 0.01$ versus saline value and **2d** + naloxone value.

3-[(2*E*)-3-(2-Chlorophenyl)-3-phenylprop-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1e. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 40%; R_f 0.31 (petroleum ether/EtOAc 7:3); mp 135–136 °C (as hydrochloride); IR 1630; UV 211.4 (4.19), 238.0 (3.11); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.47–1.64 (m, 1H), 1.64–2.10 (m, 4H), 2.12–2.50 (m, 4H), 2.70–3.10 (m, 5H), 3.85–3.95 (m, 1H), 4.65–4.75 (m, 1H), 6.17 (t, 1H, J = 7.0 Hz), 7.00–7.60 (m, 9H). Anal. calcd for $C_{25}H_{29}ClN_2O$: C, 73.42; H, 7.15; Cl, 8.67; N, 6.85. Found: C, 73.14; H, 7.12; Cl, 8.70; N, 6.83.

3-[(2*E*)-3-(3-Chlorophenyl)-3-phenylprop-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1f. Purified by FC (eluent: CH_2Cl_2 then CH_2Cl_2/CH_3COCH_3 9:1), yield 40%; R_f 0.32 (petroleum ether/EtOAc 7:3); mp 136 °C (as hydrochloride); IR 1640; UV 211.5 (3.80), 249.3

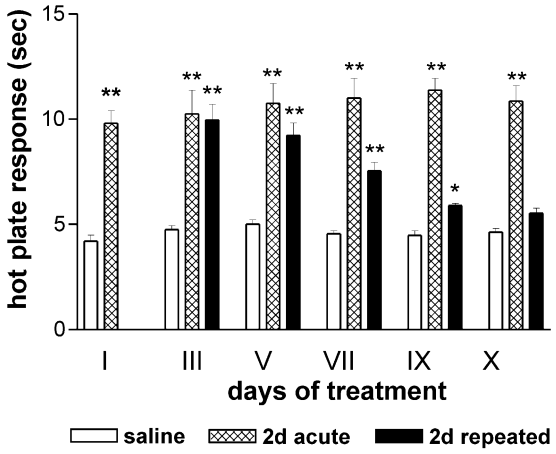


Figure 3. Tolerance to **2d**-induced antinociception in mice. Mice were acutely or repeatedly treated ip with **2d** (3.8 mg/kg ip) 15 min before the hot-plate test. Acute antinociceptive effect of **2d** was tested in mice repeatedly treated with vehicle from day 1 to the day of the acute test. Each column represents the mean ± SEM of at least 10 animals per group. * $p < 0.05$ versus saline value; ** $p < 0.01$ versus saline value.

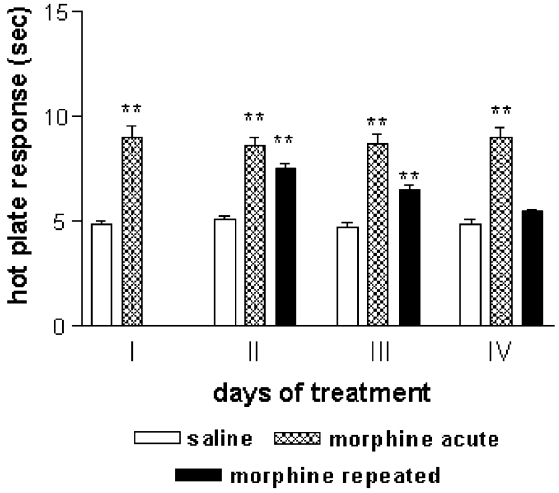


Figure 4. Tolerance to morphine-induced antinociception in mice. Mice were acutely or repeatedly treated ip with morphine (5 mg/kg ip) 15 min before the hot-plate test. Acute antinociceptive effect of morphine was tested in mice repeatedly treated with vehicle from day 1 to the day of the acute test. Each column represents the mean ± SEM of at least 10 animals per group. ** $p < 0.01$ versus saline value.

(3.43); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.4 Hz), 1.44–1.65 (m, 1H), 1.65–2.00 (m, 4H), 2.12–2.47 (m, 4H), 2.70–3.20 (m, 5H), 3.85–3.95 (m, 1H), 4.63–4.75 (m, 1H), 6.16 (t, 1H, J = 7.0 Hz), 7.00–7.60 (m, 9H). Anal. calcd for $C_{25}H_{29}ClN_2O$: C, 73.42; H, 7.15; Cl, 8.67; N, 6.85. Found: C, 73.22; H, 7.13; Cl, 8.49; N, 6.82.

3-{3,3-bis[3-(Trifluoromethyl)-phenyl]-prop-2-enyl}-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1g. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 38%; R_f 0.43 (petroleum ether/EtOAc 7:3); mp 128–135 °C (as hydrochloride); IR 1630; UV 205.0 (4.32), 224.0 (3.86); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7.4 Hz), 1.45–1.68 (m, 1H), 1.68–2.00 (m, 4H), 2.14–2.40 (m, 4H), 2.70–3.10 (m, 5H), 3.87–3.97 (m, 1H), 4.65–4.75 (m, 1H), 6.30 (t, 1H, J = 7.0 Hz), 7.23–7.70 (m, 8H). Anal. calcd for $C_{27}H_{28}F_6N_2O$: C, 63.52; H, 5.53; F, 22.33; N, 5.49. Found: C, 63.39; H, 5.51; F, 22.29; N, 5.47.

3-[3,3-bis(4-Chlorophenyl)-prop-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1h. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 43%; R_f 0.28 (petroleum ether/EtOAc 7:3); mp 112–115 °C (as hydrochloride); IR 1640; UV 208.6 (4.00), 253.4 (3.80); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.40–1.65 (m, 1H), 1.65–1.98 (m, 4H), 2.12–2.40 (m, 4H), 2.63–3.10 (m, 5H), 3.85–3.95 (m, 1H), 4.65–4.75 (m, 1H), 6.15 (t, 1H, J = 6.8 Hz), 7.00–7.50 (m, 8H). Anal. calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; Cl, 15.99; N, 6.32. Found: C, 67.48; H, 6.33; Cl, 15.96; N, 6.28.

3-[3,3-bis(4-Fluorophenyl)-prop-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 1i. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 54%; R_f 0.45 (petroleum ether/EtOAc 7:3); mp 123 °C (as hydrochloride); IR 1640; UV 205.6 (3.94), 249.0 (3.60); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.40–1.65 (m, 1H), 1.65–1.98 (m, 4H), 2.10–2.40 (m, 4H), 2.63–3.10 (m, 5H), 3.85–3.95 (m, 1H), 4.65–4.73 (m, 1H), 6.10 (t, 1H, J = 7.0 Hz), 6.85–7.50 (m, 8H). Anal. calcd for $C_{25}H_{28}F_2N_2O$: C, 73.15; H, 6.88; F, 9.26; N, 6.82. Found: C, 72.94; H, 6.85; F, 9.24; N, 6.80.

3-(3,3-Diphenylpropyl)-9-propionyl-3,9-diazabicyclo[3.3.1]-nonane 1j. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 27%; R_f 0.23 (petroleum ether/EtOAc 7:3); mp 141–145 °C (as hydrochloride); IR 1660; UV 197.1 (3.98), 245.0 (2.58); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, J = 7.6 Hz), 1.40–1.60 (m, 1H), 1.60–1.85 (m, 4H), 2.00–2.30 (m, 4H), 2.64–2.94 (m, 6H), 3.74–3.84 (m, 2H), 4.02 (t, 1H, J = 7.2 Hz), 4.55–4.65 (m, 1H), 7.04–7.30 (m, 10H). Anal. calcd for $C_{25}H_{32}N_2O$: C, 79.75; H, 8.57; N, 7.44. Found: C, 79.49; H, 8.54; N, 7.43.

9-[(2*E*)-3-Phenylbut-2-enyl]-3-propionyl-3,9-diazabicyclo[3.3.1]nonane 2b. Purified by FC (eluent: petroleum ether/EtOAc 6:4), yield 50%; R_f 0.10 (petroleum ether/EtOAc 7:3); mp 195–200 °C (as fumarate); IR 1650; UV 203.4 (3.91), 209.0 (3.83); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.4 Hz), 1.45–1.85 (m, 4H), 1.85–2.22 (m, 2H), 2.11 (s, 3H), 2.22–2.50 (m, 2H), 2.90–3.20 (m, 2H), 3.40–3.80 (m, 4H), 4.30–4.50 (m, 2H), 5.84 (t, 1H, J = 6.4 Hz), 7.00–7.70 (m, 5H). Anal. calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.65; H, 9.00; N, 8.94.

9-[(2*E*)-3-(2-Cyclohexyl)-3-phenylprop-2-enyl]-9-propionyl-3,9-diazabicyclo[3.3.1]nonane 2c. Purified by FC (eluent: petroleum ether/EtOAc 7:3), yield 14%; R_f 0.41 (petroleum ether/EtOAc 7:3); mp 225 °C (as fumarate); IR 1640; UV 220.4 (3.99); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7.4 Hz), 1.35–2.25 (m, 17H), 2.25–2.40 (m, 2H), 2.85–2.95 (m, 2H), 3.05–3.20 (m, 2H), 3.50–3.60 (m, 2H), 4.20–4.35 (m, 2H), 5.11 (s, 1H), 7.10–7.70 (m, 5H). Anal. calcd for $C_{25}H_{36}N_2O$: C, 78.90; H, 9.53; N, 7.36. Found: C, 78.69; H, 9.51; N, 7.33.

9-(3,3-Diphenylprop-2-enyl)-3-propionyl-3,9-diazabicyclo-[3.3.1]nonane 2d. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3 then CH_2Cl_2/CH_3COCH_3 6:4), yield 54%; R_f 0.60 (CH_2Cl_2/CH_3COCH_3 6:4); mp 102–105 °C (dec) (as hydrochloride); IR 1650; UV 213.2 (4.26), 249.8 (4.15); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.4 Hz), 1.35–1.70 (m, 2H), 1.70–1.98 (m, 2H), 2.20–2.35 (m, 2H), 2.70–2.90 (m, 2H), 2.90–3.14 (m, 1H), 3.30–3.52 (m, 5H), 4.29 (d, 2H, J = 13.2 Hz), 6.18 (t, 1H, J = 6.6 Hz), 7.10–7.50 (m, 10H). Anal. calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.95; H, 8.03; N, 7.46.

9-[(2*E*)-3-(2-Chlorophenyl)-3-phenylprop-2-enyl]-3-propionyl-3,9-diazabicyclo[3.3.1]nonane 2e. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 35%; R_f 0.33 (CH_2Cl_2/CH_3COCH_3 7:3); mp 125–127 °C (as hydrochloride); IR 1630; UV 221.0 (4.16), 254.1 (4.07); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.4 Hz), 1.34–1.63 (m, 4H), 1.63–2.00 (m, 2H), 2.20–2.30 (m, 2H), 2.76–2.91 (m, 2H), 2.96–3.10 (m, 1H), 3.20–3.60 (m, 4H), 4.25–4.36 (m, 1H), 6.18 (t, 1H, J = 6.6 Hz), 7.00–7.60 (m, 9H). Anal. calcd for $C_{25}H_{29}ClN_2O$: C, 73.42; H, 7.15; Cl, 8.67; N, 6.85. Found: C, 73.22; H, 7.11; Cl, 8.63; N, 6.82.

9-[(2*E*)-3-(3-Chlorophenyl)-3-phenylprop-2-enyl]-3-propionyl-3,9-diazabicyclo[3.3.1]nonane 2f. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 86%; R_f 0.63 (CH_2Cl_2/CH_3COCH_3 7:3); mp 122–126 °C (as hydrochloride); IR 1630; UV 214.0 (3.97), 235.0 (3.70); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.2 Hz), 1.37–1.70 (m, 5H), 1.70–2.10 (m, 2H), 2.20–2.50 (m, 2H), 2.80–3.10 (m, 3H), 3.20–3.60 (m, 3H), 4.20–4.42 (m, 1H), 6.35 (t, 1H, J = 6.4 Hz), 7.10–7.70 (m, 9H). Anal. calcd for $C_{25}H_{29}ClN_2O$: C, 73.42; H, 7.15; Cl, 8.67; N, 6.85. Found: C, 73.31; H, 7.12; Cl, 8.52; N, 6.83.

9-{3,3-bis[3-(Trifluoromethyl)-phenyl]-prop-2-enyl}-3-propionyl-3,9-diazabicyclo[3.3.1]nonane 2g. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 71%; R_f 0.65 (CH_2Cl_2/CH_3COCH_3 7:3); mp 91–92 °C (as hydrochloride); IR 1620; UV 205.0 (3.72), 244.0 (3.25); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.34–1.72 (m, 4H), 1.72–2.00 (m, 2H), 2.10–2.50 (m, 2H), 2.80–3.65 (m, 7H), 4.34 (d, 1H, J = 13.6 Hz), 6.29 (t, 1H, J = 6.8 Hz), 7.20–7.80 (m, 8H). Anal. calcd for $C_{27}H_{28}F_6N_2O$: C, 63.52; H, 5.53; F, 22.33; N, 5.49. Found: C, 63.41; H, 5.49; F, 22.30; N, 5.46.

9-[3,3-bis(4-Chlorophenyl)-prop-2-enyl]-3-propionyl-3,9-diazabicyclo[3.3.1]nonane 2h. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 82%; R_f 0.51 (CH_2Cl_2/CH_3COCH_3 7:3); mp 126–127 °C (as hydrochloride); IR 1620; UV 244.2 (4.21); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.4 Hz), 1.33–1.68 (m, 4H), 1.68–2.00 (m, 2H), 2.30–2.40 (m, 2H), 2.75–3.10 (m, 3H), 3.25–3.65 (m, 4H), 4.33 (d, 1H, J = 13.2 Hz), 6.16 (t, 1H, J = 6.8 Hz), 7.00–7.50 (m, 8H). Anal. calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; Cl, 15.99; N, 6.32. Found: C, 67.55; H, 6.35; Cl, 15.97; N, 6.30.

9-[3,3-bis(4-Fluorophenyl)-prop-2-enyl]-3-propionyl-3,9-diazabicyclo[3.3.1]nonane 2i. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 92%; R_f 0.47 (CH_2Cl_2/CH_3COCH_3 7:3); mp 175 °C (as fumarate); IR: 1630; UV: 224.7 (4.13), 248.2 (4.13); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.6 Hz), 1.34–1.76 (m, 4H), 1.76–2.00 (m, 2H), 2.10–2.50 (m, 2H), 2.80–3.10 (m, 3H), 3.36 (d, 2H, J = 6.8 Hz), 3.50–3.65 (m, 2H), 4.34 (d, 1H, J = 13.4 Hz), 6.29 (t, 1H, J = 6.8 Hz), 7.20–7.74 (m, 8H). Anal. calcd for $C_{25}H_{28}F_2N_2O$: C, 73.15; H, 6.88; F, 9.26; N, 6.82. Found: C, 73.00; H, 6.86; F, 9.23; N, 6.79.

9-(3,3-Diphenylpropyl)-3-propionyl-3,9-diazabicyclo[3.3.1]-nonane 2j. Purified by FC (eluent: CH_2Cl_2/CH_3COCH_3 7:3), yield 78%; R_f 0.51 (CH_2Cl_2/CH_3COCH_3 7:3); mp 158–160 °C (as hydrochloride); IR 1660; UV 209.3 (3.94), 269.6 (3.48); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7.4 Hz), 1.38–1.74 (m, 4H), 1.74–2.00 (m, 2H), 2.10–2.50 (m, 4H), 2.62 (t, 2H, J = 7.2 Hz), 2.70–2.90 (m, 2H), 3.00–3.14 (m, 2H), 4.12 (t, 1H, J = 7.2 Hz), 4.32 (d, 2H, J = 13.6 Hz), 7.30–7.40 (m, 10H). Anal. calcd for $C_{25}H_{32}N_2O$: C, 79.75; H, 8.57; N, 7.44. Found: C, 79.55; H, 8.55; N, 7.42.

General procedure for arylpropenyl esters 6. To a suspension of sodium hydride (60% dispersion in mineral oil, 4 mmol) in dry toluene (200 mL) was added dropwise triethyl phosphonoacetate (4 mmol) at 4 °C under argon atmosphere. After 30 min, the appropriate ketone **5** (2.7 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature and stirred for 2–5 days. The resulting mixture was washed with water and dried over sodium sulfate. Evaporation of the solvent gave the desired ester (**6d**,**g**,**h**,**i**) or a mixture of the isomers *E*/*Z* (**6b**,**c**,**e**,**f**), which were isolated by flash chromatography.

Ethyl (2*E*)-3-phenyl but-2-enoate (*E*)-6b and Ethyl (2*Z*)-3-phenyl but-2-enoate (*Z*)-6b. The mixture was purified by FC, eluting with: petrol ether/EtOAc (9.9:0.1). Fraction 1 contained (***E*)-6b**, yield 76%; R_f 0.35 (petrol ether/EtOAc = 9.9:0.1); bp 68–70 °C/0.01 mmHg (bp 115–116 °C/5 mmHg);[4] fraction 2 contained (***Z*)-6b**, yield 11%; R_f 0.18 (petrol ether/EtOAc = 9.9:0.1); bp 60–65 °C/0.01 mmHg (bp 80 °C/0.05 mmHg).[5]

Ethyl (2*E*)-3-cyclohexyl-3-phenyl prop-2-enoate (*E*)-6c and Ethyl (2*Z*)-3-cyclohexyl-3-phenyl prop-2-enoate (*Z*)-6c. The mixture was purified by FC, eluting with: petrol ether/EtOAc (9.75:0.25). Fraction 1 contained (***E*)-6c**, yield 62%; R_f 0.61 (petrol ether/EtOAc = 9.75:0.25); bp 90–100 °C/0.01 mmHg (bp 105–109 °C/0.1 mmHg);[6] fraction 2 contained (***Z*)-6c**, yield 26%; R_f 0.33 (petrol ether/EtOAc = 9.75:0.25); bp 90–92 °C/0.01 mmHg (bp 105–109 °C/0.06 mmHg).[6]

Ethyl 3,3-diphenylacrylate 6d. Purified by distillation at 130 °C/0.01 mmHg (yield 77%); R_f 0.27 (petrol ether/EtOAc 9.80:0.20) (bp 140 °C/0.05 mmHg).[7]

Ethyl (2*E*)-3-(2-chlorophenyl)-3-phenylprop-2-enoate (*E*)-6e. Purified by FC, eluting with: petrol ether/EtOAc (9.80:0.20), yield 65%; R_f 0.21 (petrol ether/EtOAc = 9.80:0.20); mp 55–60 °C (petrol ether); IR 1620, 1710; UV 218.5 (3.87), 275.5 (3.83); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.2 Hz), 4.04 (q, 2H, J = 7.2 Hz), 6.55 (s, 1H), 7.10–7.50 (m, 9H). Anal. calcd for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Cl, 12.36. Found: C, 70.93; H, 5.25; Cl, 12.33.

Ethyl (2*E*)-3-(3-chlorophenyl)-3-phenylprop-2-enoate (*E*)-6f. Purified by FC, eluting with: petrol ether/EtOAc (9.80:0.20), yield 20%; R_f 0.20 (petrol ether/EtOAc = 9.80:0.20); bp 160 °C/0.01 mmHg; IR 1620, 1720; UV 217.5 (3.88), 272.1 (3.66); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz), 4.05 (q, 2H, J = 7.4 Hz), 6.34 (s, 1H), 7.00–7.65 (m, 9H). Anal. calcd for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Cl, 12.36. Found: C, 70.97; H, 5.26; Cl, 12.32.

Ethyl 3,3-bis[3-(trifluoromethyl)phenyl]acrylate 6g. Purified by FC, eluting with: petrol ether/EtOAc (9:1), yield 91%; R_f 0.57 (petrol ether/EtOAc = 9:1); mp 42–45 °C (petrol ether); IR 1590 and 1610, 1720; UV 217.0 (4.01), 247.4 (4.02); ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.2 Hz), 4.07 (q, 2H, J = 7.2 Hz), 6.46 (s, 1H), 7.27–7.80 (m, 8H). Anal. calcd for $C_{19}H_{14}F_6O_2$: C, 58.77; H, 3.63; F, 29.36. Found: C, 58.65; H, 3.61; F, 29.29.

Ethyl 3,3-bis-(4-chlorophenyl)acrylate 6h. Purified by crystallisation from petrol ether, mp 49–50 °C (yield 84%); R_f 0.71 (petrol ether/EtOAc = 9:1) [mp 64.5 °C (ethanol)].[8]

Ethyl 3,3-bis-(4-fluorophenyl)acrylate 6i. Purified by crystallization from petrol ether, mp 54–56 °C (yield 69%); R_f 0.23 (petrol ether/EtOAc = 9.6:0.4) [mp 62–62.5 °C (ethanol)].[8]

General procedure for arylpropenyl alcohols 7. The required arylpropenyl ester **6** (30 mmol) in dry toluene (165 mL) was treated under argon with 1.5 M DibAl-H (50.8 mL, 75 mmol) in toluene at −5 °C. The mixture was stirred for 1 h, the temperature reaching 20 °C. The reaction was cooled at 0–5 °C, quenched by the dropwise addition of a saturated aqueous solution of potassium sodium tartrate (50 mL) and stirred overnight at room temperature. To the mixture Et_2O (150 mL) was added, the organic layers separated, washed (H_2O), dried (Na_2SO_4) and concentrated to afford pure **7** as an oil or a solid.

(2*E*)-3-phenylbut-2-en-1-ol (*E*)-7b. Yield 94%; R_f 0.14 (petrol ether/EtOAc = 9:1); bp 85 °C/0.01 mmHg (bp 78–80 °C/0.05 mmHg].[9]

(2*E*)-3-Cyclohexyl-3-phenylprop-2-en-1-ol (*E*)-7c. Yield 96%; R_f 0.27 (petrol ether/EtOAc = 9:1); mp 47–55 °C (bp 94–95 °C/0.1 mmHg).[10]

3,3-Diphenylprop-2-en-1-ol 7d. Yield 95%; R_f 0.63 (petrol ether/EtOAc = 7:3); mp 53–56 °C (hexane/Et_2O) [mp 55–57 °C (hexane/Et_2O)].[11]

(2*E*)-3-(2-Chlorophenyl)-3-phenylprop-2-en-1-ol (*E*)-7e. Yield 70%; R_f 0.56 (petrol ether/EtOAc = 9.75:0.25); bp 140–144 °C/0.01 mmHg; IR 3300; UV 215.5 (3.75), 250.1 (3.55); ^{1}H NMR ($CDCl_3$) δ 4.39 (d, 2H, J = 6.6 Hz), 6.43 (t, 1H, J = 6.8 Hz), 7.10–7.50 (m, 9H). Anal. calcd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.35; Cl, 14.49. Found: C, 73.39; H, 5.33; Cl, 14.47.

(2*E*)-3-(3-Chlorophenyl)-3-phenylprop-2-en-1-ol (*E*)-7f. Yield 98%; R_f 0.40 (petrol ether/EtOAc = 9:1); bp 150 °C/0.01 mmHg; IR 3300; UV 218.7 (3.79), 251.2 (3.58); ^{1}H NMR ($CDCl_3$) δ 4.21 (d, 2H, J = 6.8 Hz), 6.23 (t, 1H, J = 6.8 Hz), 7.00–7.60 (m, 9H). Anal. calcd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.35; Cl, 14.49. Found: C, 73.37; H, 5.32; Cl, 14.46.

3,3-bis[3-(trifluoromethyl)phenyl]prop-2-en-1-ol 7g. Yield 98%; R_f 0.54 (petrol ether/EtOAc = 7:3); bp 83 °C/0.01 mmHg; IR 3300; UV 239.7 (4.76); ^{1}H NMR ($CDCl_3$) δ 4.22 (d, 2H, J = 6.9 Hz), 6.35 (t, 1H, J = 6.8 Hz), 7.08–7.70 (m, 8H). Anal. calcd for $C_{17}H_{12}F_6O$: C, 58.97; H, 3.49; F, 32.92. Found: C, 58.69; H, 3.47; F, 32.88.

3,3-bis(4-Chlorophenyl)prop-2-en-1-ol 7h. Yield 99%; R_f 0.30 (petrol ether/EtOAc = 7:3); mp 67–72 °C (petrol ether); IR 3300; UV 242.0 (4.03); ^{1}H NMR ($CDCl_3$) δ 4.20 (d, 2H, J = 6.8 Hz), 6.22 (t, 1H, J = 6.8 Hz), 6.97–7.42 (m, 8H). Anal. calcd for $C_{15}H_{12}Cl_2O$: C, 64.54; H, 4.33; Cl, 25.40. Found: C, 64.36; H, 4.31; Cl, 25.37.

3,3-bis(4-Fluorophenyl)prop-2-en-1-ol 7i. Yield 98%; R_f 0.13 (petrol ether/EtOAc = 9:1); mp 71–72 °C (petrol ether); IR 3300; UV 244.6 (4.02); ^{1}H NMR ($CDCl_3$) δ 4.18 (d, 2H, J = 6.9 Hz), 6.16 (t, 1H, J = 6.8 Hz), 6.86–7.50 (m, 8H). Anal. calcd for $C_{15}H_{12}F_2O$: C, 73.16; H, 4.91; F, 15.43. Found: C, 72.88; H, 4.88; Cl, 15.40.

3,3-Diphenylpropanol 8j. To a solution of arylpropenyl alcohol **7d** (0.97 g, 4.61 mmol) in ethanol (9 mL) was added 10% Pd/C (0.092 g, 0.086 mmol). The mixture was hydrogenated at room temperature for 2.5 h, and the catalyst was filtered off and washed with ethanol. The filtrate was evaporated in vacuo to give **8j** pure as yellow oil. Yield 99%; R_f 0.5 (petrol ether/EtOAc = 7:3); bp 130 °C/0.01 mmHg (bp 132 °C/0.01 mmHg).[12]

General procedure for arylpropenyl bromides 9b,c. To a solution of appropriate arylpropenyl alcohol **7** (3.4 mmol) and carbon tetrabromide (5.1 mmol) in dry dichloromethane (12 mL) was added at room temperature a solution of Ph_3P (3.4 mmol) in dry dichloromethane (2.2 mL). The reaction mixture was stirred for 2 h, then *n*-hexane (22 mL) was added and the organic layers were washed with saturated aqueous solution of $NaHCO_3$, H_2O, dried (Na_2SO_4) and concentrated to afford **9b**,**c** as oils which were purified by flash chromatography or distillation.

[(1*E*)-3-Bromo-1-methylprop-1-enyl]benzene (*E*)-9b. Purified by distillation at 75–76 °C/0.01 mmHg (yield 98%); R_f 0.40 (petrol ether/EtOAc = 8:2) (bp 90–91 °C/0.8 mmHg].[13]

[(1*E*)-3-Bromo-1-cyclohexylprop-1-enyl]benzene (*E*)-9c. Purified by FC, eluting with: petrol ether/EtOAc (9.5:0.5), yield 80%; R_f 0.48 (petrol ether/EtOAc = 9.5:0.5); bp 146–148 °C/0.01 mmHg; IR 1249 (C-Br), 1440; UV 220.0 (3.95), 240.3 (4.00); ^{1}H NMR ($CDCl_3$) δ 0.72–1.84 (m, 11H), 3.80 (d, 2H, J = 8.6 Hz), 5.73 (t, 1H, J = 8.6 Hz), 7.07–7.58 (m, 5H). Anal. calcd for $C_{15}H_{19}Br$: C, 64.52; H, 6.86; Br, 28.62. Found: C, 64.26; H, 6.83; Br, 28.60.

General procedure for arylpropenyl chlorides 9d–i and methanesulfonate 9j. A solution of appropriate arylpropenyl alcohol **7** or **8j** (1.4 mmol) and Et_3N (4.3 mmol) in dry dichloromethane (6 mL) was stirred in an ice bath under argon. Mesyl chloride (4.3 mmol) was added and the reaction mixture was stirred for 7 h, at temperature below 10 °C. Additional mesyl chloride (2.9 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with dichloromethane and washed with 1 N HCl, saturated aqueous solution of $NaHCO_3$ and brine. The organic extracts were then dried (Na_2SO_4) and concentrated to afford the pure chlorides **9d**–**i** as oils or the methanesulfonate **9j** as a white solid.

3,3-Diphenylprop-2-enyl chloride 9d. Yield 99%; R_f 0.41 (petrol ether/EtOAc = 9.7:0.3); bp 65–66 °C/0.01 mmHg (bp 144–145 °C/1.5 mmHg).[14]

(*E*)-3-Phenyl-3-(2-chlorophenyl)prop-2-enyl chloride (*E*)-9e. Yield 81%; R_f 0.46 (petrol ether/EtOAc = 9.5:0.5); bp 120 °C/0.01 mmHg; IR 1620; UV 219.5 (4.03), 241.0 (4.04); ^{1}H NMR ($CDCl_3$) δ 4.65 (d, 2H, J = 6.8 Hz), 6.19 (t, 1H, J = 6.8 Hz), 7.10–7.60 (m, 9H). Anal. calcd for $C_{15}H_{12}Cl_2$: C, 68.46; H, 4.60; Cl, 26.94. Found: C, 68.29; H, 4.57; Cl, 26.91.

(*E*)-3-Phenyl-3-(3-Chlorophenyl)prop-2-enyl chloride (*E*)-9f. Yield 81%; R_f 0.49 (petrol ether/EtOAc = 9:1); bp 134 °C/0.01 mmHg; IR 1430; UV 211.1 (3.51), 256.4 (3.19); ^{1}H NMR ($CDCl_3$) δ 4.11 (d, 2H, J = 7.8 Hz), 6.23 (t, 1H, J = 7.8 Hz), 7.05–7.50 (m, 9H). Anal. calcd for $C_{15}H_{12}Cl_2$: C, 68.46; H, 4.60; Cl, 26.94. Found: C, 68.35; H, 4.57; Cl, 26.92.

3,3-bis[3-(trifluoromethyl)phenyl]prop-2-enyl chloride 9g. Yield 94%; R_f 0.39 (petrol ether/EtOAc = 9:1); bp 120 °C/0.01 mmHg; IR 1430; UV 217.7 (4.10), 254.5 (4.12); ^{1}H NMR ($CDCl_3$) δ 4.09 (d, 2H, J = 8 Hz), 6.36 (t, 1H, J = 8.4), 7.22–7.80 (m, 8H). Anal. calcd for $C_{17}H_{11}ClF_6$: C, 55.98; H, 3.04; Cl, 9.72; F, 31.25. Found: C, 55.74; H, 3.02; Cl, 9.69; F, 31.21.

3,3-bis(4-Chlorophenyl)prop-2-enyl chloride 9h. Yield 69.5%; R_f 0.46 (petrol ether/EtOAc = 9.5:0.5); bp 90–92 °C/0.01 mmHg; IR 1590 and 1620; UV 243.7 (4.04); ^{1}H NMR ($CDCl_3$) δ 4.09 (d, 2H, J = 8.2 Hz), 6.22 (t, 1H, J = 8.2), 7.00–7.50 (m, 8H). Anal. calcd for $C_{15}H_{11}Cl_3$: C, 60.54; H, 3.73; Cl, 35.74. Found: C, 60.35; H, 3.71; Cl, 35.71.

3,3-bis(4-Fluorophenyl)prop-2-enyl chloride 9i. Yield 57%; R_f 0.44 (petrol ether/EtOAc = 9:1); mp 48–54 °C (petrol ether); IR 1440; UV 243.4 (4.10); ^{1}H NMR ($CDCl_3$) δ 4.10 (d, 2H, J = 8.4 Hz), 6.18 (t, 1H, J = 8.2 Hz), 6.86–7.40 (m, 8H). Anal. calcd for $C_{15}H_{11}ClF_2$: C, 68.06; H, 4.19; Cl, 13.39; F, 14.35. Found: C, 67.88; H, 4.17; Cl, 13.36; F, 14.33.

3,3-Diphenylpropyl methanesulfonate 9j. Yield 86%; R_f 0.47 (petrol ether/EtOAc = 7:3); mp 78–82 °C (ethanol); IR 1450; UV 220.9 (3.98), 252.0 (3.20); ^{1}H NMR ($CDCl_3$) δ 2.40–2.56 (m, 2H), 2.89 (s, 3H), 4.10–4.20 (m, 3H), 7.20–7.38 (m, 10H). Anal. calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.04. Found: C, 65.99; H, 6.23; S, 11.01.

Biology

General information. Male albino Swiss mice weighing 20–25 g (Charles River, Italy) were used. Animals were kept on a 12 h artificial light/dark cycle (lights on at 7:00 am) at a costant temperature of 22 ± 2 °C and relative humidity of 60%. Food and water were available ad libitum. All testing was performed according to the recommendations and policies of the National Institutes of Health (USA) guidelines for the use of laboratory animals.

^{3}H-DAMGO ([D-Ala^2, N-Me-Phe^4,Gly-ol^5]-enkephalin), ^{3}H-DPDPE ([D-Pen^2,D-Pen^5]-enkephalin) and ^{3}H-Bremazocine were purchased from NEN (Life Science Products, Boston, M, USA).

Naloxone·HCl (Du Pont, USA), morphine·HCl (Salars, Como, Italy) and **2d** were administered ip at a volume of 0.250 mL/mouse of saline.

Opioid binding assay. Ligand binding assay were determined for compounds at μ-, δ- and κ-opioid receptors as described in detail elsewhere.[15] Binding affinities for μ, δ and κ receptors were determined by displacing, respectively, ^{3}H-DAMGO (1 nM), ^{3}H-DPDPE (1 nM) and ^{3}H-Bremazocine (1 nM) from mouse brain membrane binding sites. Brain membranes were incubated with the appropriate ^{3}H-ligand in 50 mM Tris–HCl buffer, pH 7.4 at 25 °C for 60 min in absence or presence of 10 μM naloxone. ^{3}H-Bremazocine binding was carried out in presence of unlabelled DAMGO (100 nM) and DADLE (100 nM) to prevent the binding at μ, δ sites. IC_{50} values were determined from log dose–displacement curves, and K_i values were calculated from the obtained IC_{50} values by means of the equation of Cheng and Prusoff,[16] using values of 1.03, 1.45, and 0.5 nM for the dissociation constants of ^{3}H-DAMGO, ^{3}H-DPDPE and ^{3}H-Bremazocine, respectively.

In vivo testing. Analgesia was estimated by means of the hot plate test described by Oden and Oden.[17] The effect of compounds on the reaction time of mice placed on a hot plate thermostically maintained at 56 °C was determined. The time at which mice displayed a nociceptive response, that is licking the front paws, fanning the hind paws, or jumping, was recordered. The 50% analgesic doses (ED_{50}) and 95% confidence intervals were determined by the methods of Litchfield and Wilcoxon.[18]

In the experiment designed to examine the ability of the opioid antagonist naloxone to reverse the analgesic effect of **2d**, naloxone HCl (1 mg/kg ip), **2d** (5 mg/kg ip) or vehicle were administered at the beginning of the hot-plate session. Mice were tested on the hot plate 15 min later.

To evaluate the development of tolerance to the analgesic effect, saline, morphine and **2d** were chronically administered to mice twice a day (8:00 am–8:00 pm). The hot-plate test was performed 15 min after the 8:00 am injections.

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