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Synthesis of Novel Diazatricyclodecanes (DTDs). Effects of Structural Variation at the C3′ Allyl End and at the Phenyl Ring of the Cinnamyl Chain on μ-Receptor Affinity and Opioid Antinociception

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Abstract—Two series of analogues of 9-propionyl-10-cinnamyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (**1a**) and 2-propionyl-7-cinnamyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (**2a**), in which the cinnamyl moiety was replaced by various aralkenyl chains, **1b–l** and **2b–l**, respectively, have been synthesized and evaluated for their ability to bind to the opioid μ-, δ- and κ-receptors. The binding data indicated that compounds **1b**,**d**,**e**,**h** and **2b**,**d**,**e**,**f**,**h**,**i** showed a μ-affinity in the low nanomolar range with moderate or negligible affinity towards δ- and κ-receptors. Selected DTDs, the pairs **1**,**2b**, **1**,**2e** and **1**,**2h**, were also evaluated for analgesic effect. In the hot plate test, only **1b** given ip was found to have similar opioid antinociception and chronic tolerance as morphine.

Introduction

Opioid analgesics are widely used clinically to relieve severe pain.[1] The μ-opioid receptor has commonly been suggested to be responsible not only for 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.[2]

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 sub-type receptors providing an approach for the development of new compounds able to releive acute and chronic pain, and which are lacking of the typical opioid side effects.[2]

We recently reported that 9-propionyl-10-cinnamyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (**1a**) (Table 1) and 2-propionyl-7-cinnamyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (**2a**) (Table 1) exhibited a significant affinity towards

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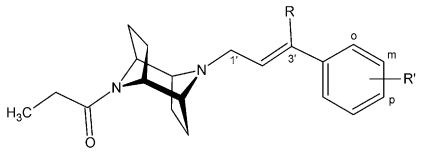
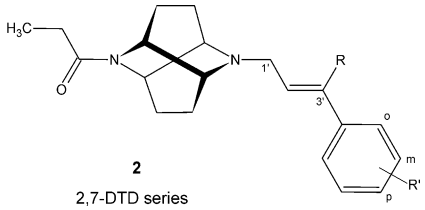
Table 1. Binding affinity of **1**,**2a–l** for opioid receptors K_i (nM)[a]



1
9,10-DTD series



2
2,7-DTD series

Compd[b]	R	R′	μ	δ	κ	K_i ratio δ/μ	K_i ratio κ/μ
1a	H	H	6.7±0.28	159±17	2015±164	23.7	300.7
1b	CH_3	H	4.3±0.25	105±5.9	922±75	24.4	214.4
1c	CF_3	H	545±30	>5000	>5000	>9.2	>9.2
1d	cC_6H_{11}	H	4.18±0.6	199±8.8	732±29	47.6	175.2
1e	C_6H_5	H	5.1±0.1	57±0.5	2969±46	11.1	582.2
1f	CH_3	*o*-Cl	11.3±0.31	212±4	4583±171	18.7	405.6
1g	CH_3	*m*-Cl	45.2±2	1634±10	2633±33	36.1	58.2
1h	CH_3	*p*-Cl	2.62±0.09	156±10	649±25	59.4	247.7
1i	CH_3	*m*,*p*-Cl_2	18±7.5	3860±27	1926±25	214.4	107.0
1j	CH_3	*o*,*p*-Cl_2	264±8.9	>5000	>5000	>18.9	>18.9
1k	*p*-F-C_6H_4	*p*-F	27.4±0.4	598±13	>5000	21.8	>182.5
1l	*p*-Cl-C_6H_4	*p*-Cl	414±1.5	5558±29	>5000	13.4	>12.1
2a	H	H	5.0±0.5	118±4	1510±46	23.6	302
2b	CH_3	H	4.07±0.2	65.4±1.6	980±71	16.1	240.8
2c	CF_3	H	258±11	>5000	>5000	>19	>19
2d	cC_6H_{11}	H	4.67±0.02	156±6.7	590±15	33.4	126.4
2e	C_6H_5	H	6.3±0.53	183±15.1	2918±40	29.0	463.2
2f	CH_3	*o*-Cl	4.1±0.44	136±0.57	1652±32	33.2	402.9
2g	CH_3	*m*-Cl	12.65±0.6	1186±100	3666±166	93.7	289.8
2h	CH_3	*p*-Cl	1.29±0.04	33±0.9	722±11	25.5	559.6
2i	CH_3	*m*,*p*-Cl_2	2.9±0.38	363±16	1277±55	125.2	440.3
2j	CH_3	*o*,*p*-Cl_2	38.2±1.7	2787±86	4171±62	72.9	109.2
2k	*p*-F-C_6H_4	*p*-F	10±05	451±20	1097±50	45.1	109.7
2l	*p*-Cl-C_6H_4	*p*-Cl	30.4±0.65	1101±8.7	>5000	36.2	164.5
Morphine			1.07±0.04	100.2±5.14	280.8±9.2	93.4	262.4

[a]The K_i values for the test ligands were determined with assays described in the Experimental. Results are mean±SEM for three independent experiments assayed in triplicate.
[b]The receptor binding affinities of all compounds were carried on their hydrochlorides.

μ-opioid receptors with $K_i = 10$ nM (rat) and 6.7 nM (mouse) for **1a** and 7 nM (rat) and 5 nM (mouse) for **2a**.[3]

We also found that substitution of the phenyl moiety with Cl or NO_2 groups in various positions reduced μ-affinity in both series **1** and **2**.[3]

Remarkably, in the mouse hot plate test, **2a** given ip, produced a potent analgesic effect ($ED_{50} = 0.84$ mg/kg), being about 6 times more potent than morphine ($ED_{50} = 5$ mg/kg).[3]

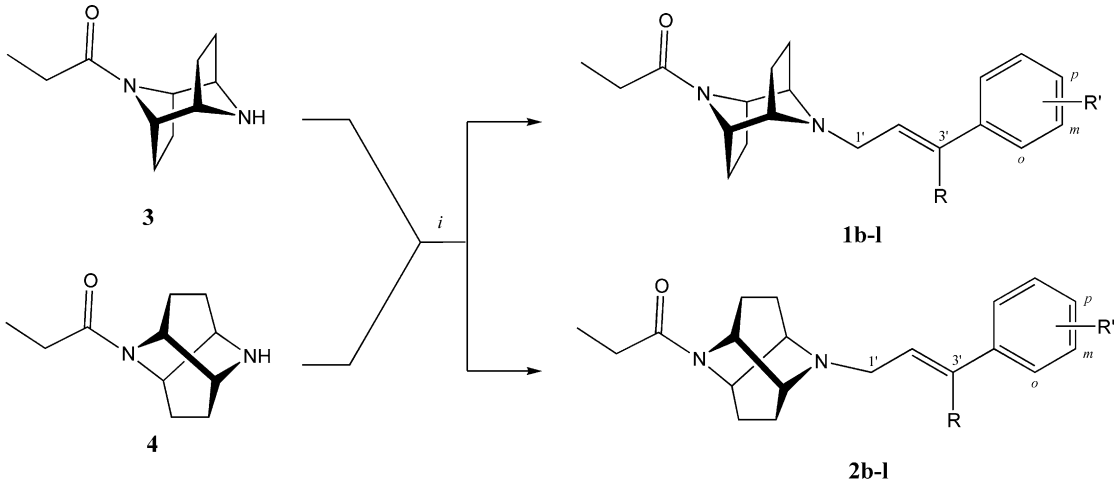
Continuing our interest in this area, we report the synthesis and binding data against μ-, δ- and κ-receptors of two series of diazatricyclodecanes (DTDs), related to **1a** and **2a**, in which additional substituents were introduced in the cinnamyl chain, in particular at the 3′ position of the allylic chain (Table 1). Representative terms **1**,**2b**, **1**,**2e** and **1**,**2h** were also evaluated for their in vivo activity.

Chemistry

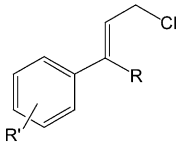
The synthetic pathway leading to the novel analogues of **1**,**2a** is outlined in Scheme 1. Precursors **3**[3] and **4**[3] were alkylated with the appropriate chlorides (**5b–l**) in refluxing acetone and in the presence of potassium carbonate to give **1**,**2b–l**.

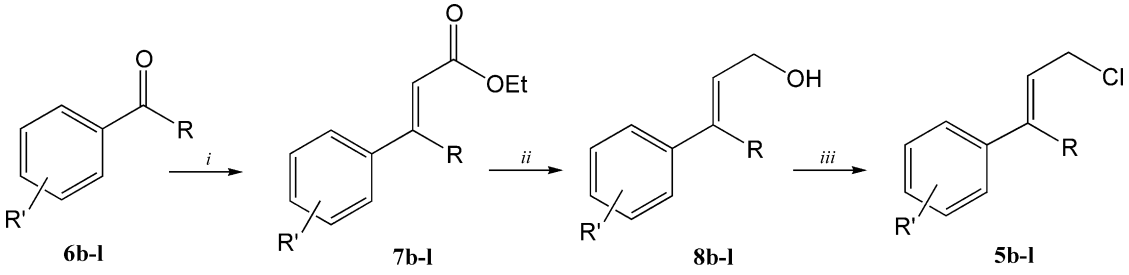
The required chlorides (**5b–l**) were prepared starting from the appropriate ketones (**6b–l**) (Scheme 2) by reaction with triethyl phosphonoacetate (Horner–Emmons condensation) to give the cinnamyl esters (**7b–l**), which were reduced with diisobutylaluminum hydride (DibAl-H) in toluene to give the corresponding cinnamyl alcohols (**8b–l**) which were converted to chlorides **5b–l** with methanesulfonyl chloride and Et_3N in CH_2Cl_2.

It is to note that the Horner–Emmons condensation of **8** gave mixtures of *E* and *Z* isomers with the *E* isomers of **7b–d**,**f–j** being the most abundant. The isomers were separated by flash-chromatography and identified by NMR spectra. In particular, less polar *E* isomers of **7g**,**i** 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 **7f**,**j** the regiochemistry was determined by nOe experiments by observing interactions, for the isomers *E*, between the *ortho*-hydrogens of the substituted phenyl rings of **7f**,**j** when the vinylic protons were irradiated.



1,2	b	c	d	e	f	g	h	i	j	k	l
R	CH_3	CF_3	cC_6H_{11}	C_6H_5	CH_3	CH_3	CH_3	CH_3	CH_3	*p*-F-C_6H_4	*p*-Cl-C_6H_4
R'	H	H	H	H	*o*-Cl	*m*-Cl	*p*-Cl	*m,p*-Cl_2	*o,p*-Cl_2	*p*-F	*p*-Cl

Scheme 1. Reagents and conditions: (i)  (**5b–l**), K_2CO_3, acetone, Δ.



5-8	b	c	d	e	f	g	h	i	j	k	l
R	CH_3	CF_3	cC_6H_{11}	C_6H_5	CH_3	CH_3	CH_3	CH_3	CH_3	*p*-F-C_6H_4	*p*-Cl-C_6H_4
R'	H	H	H	H	*o*-Cl	*m*-Cl	*p*-Cl	*m,p*-Cl_2	*o,p*-Cl_2	*p*-F	*p*-Cl

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.

Biological Results and Discussion

The new DTDs were submitted to binding studies on opioid receptors of 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 the reference compound (Table 1).

The present two series of DTDs were designed in order to better define the structure–activity relationship in two specific regions of the DTD templates. Several analogues incorporate a variety of alkyl and aryl groups at the terminus of the allyl side chain (**1**,**2b–e**) and/or halogens in the aromatic region (**1**,**2f–l**) of the arylalkenyl chain. As seen from the results listed in Table 1, these structural variations have resulted in a wide range of biological activity.

Considering first the effect of changing the C-3′ hydrogen of **1a**[3] and **2a**[3] at the end of the alkenyl chain, the methyl (**1**,**2b**), cyclohexyl (**1**,**2d**) and phenyl (**1**,**2e**) showed high affinity for the μ-opioid receptors while analogues with a CF_3 group (**1**,**2c**) had considerably less

affinity for all of the opioid receptors. These results revealed that the strong electronegative effect of the CF_3 moiety may modify the electronic C-3′ environment to induce the decrease in μ affinity.

In contrast, this region tolerated various types of alkyl or aryl moieties supporting the presence in the μ-receptor of an area of preferred lipophylicity and of steric tolerance. Looking at biological effects of the substitution at the phenyl ring with halogens, compounds **1**,**2f–h** containing a *o*-, *m*-, and *p*-chloro substituent, were firstly examined taking the unsubstituted **1b**, **2b** as reference. Their μ-receptor affinities were either decreased with *ortho* (**1f**) and *meta* (**1**,**2g**) substitution or increased with *para* substitution (**1**,**2h**) when compared to that of **1**,**2b**. The *o*-chloro analogue, **2f**, showed μ-receptor affinity similar to that of **2b**, whereas the *p*-chloro analogue **2h** exhibited a μ-receptor affinity ($K_i^{\mu} = 1.29$ nM) comparable to that of morphine ($K_i^{\mu} = 1.07$ nM). The dichloro substituted compounds (**1**,**2i**,**j**) displayed a different pattern of binding to μ receptors. The *o*,*p*-dichloro substituted derivative **1j**, had a low affinity for μ receptors, whereas both the *m*,*p*-dichloro (**1i**) and the *o*,*p*-dichloro-disubstituted (**2j**) analogues, displayed a moderate receptor affinity. The *m*,*p*-dichloro substituted compound **2i**, had the highest μ-receptor affinity among the

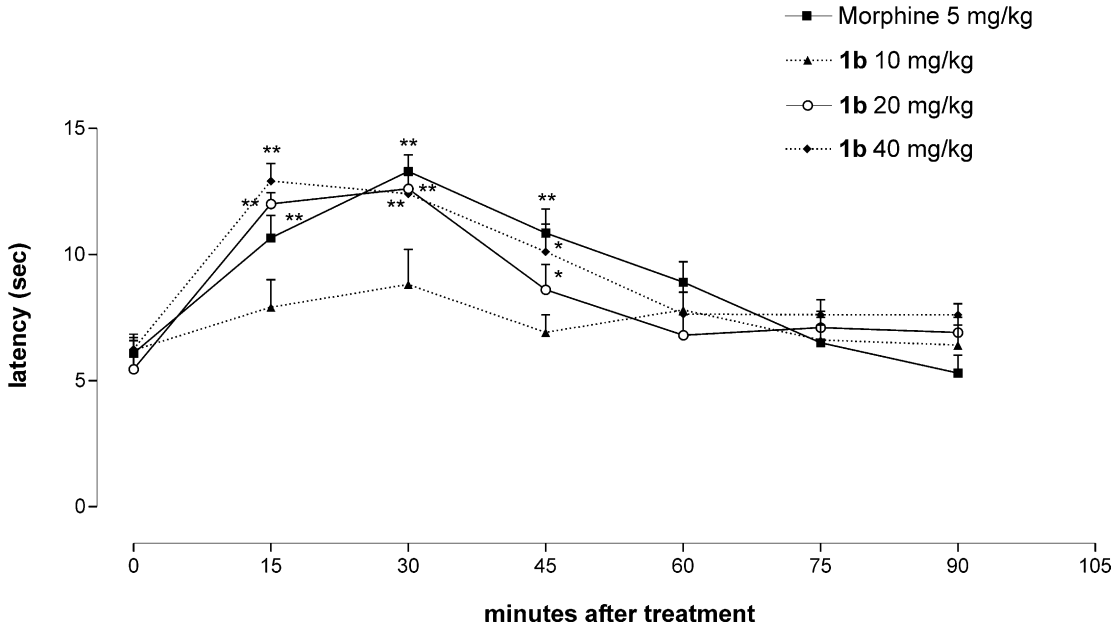


Figure 1. Antinociceptive effect of **1b** on mice hot-plate test. Each point represents the mean ± SEM of at least eight mice for group ($n = 8$, morphine. $n = 10$, **1b** 10, 20 and 40 mg/kg). ANOVA followed by Newman–Keuls test. ** $p < 0.01$, * $p < 0.05$; versus basal value.

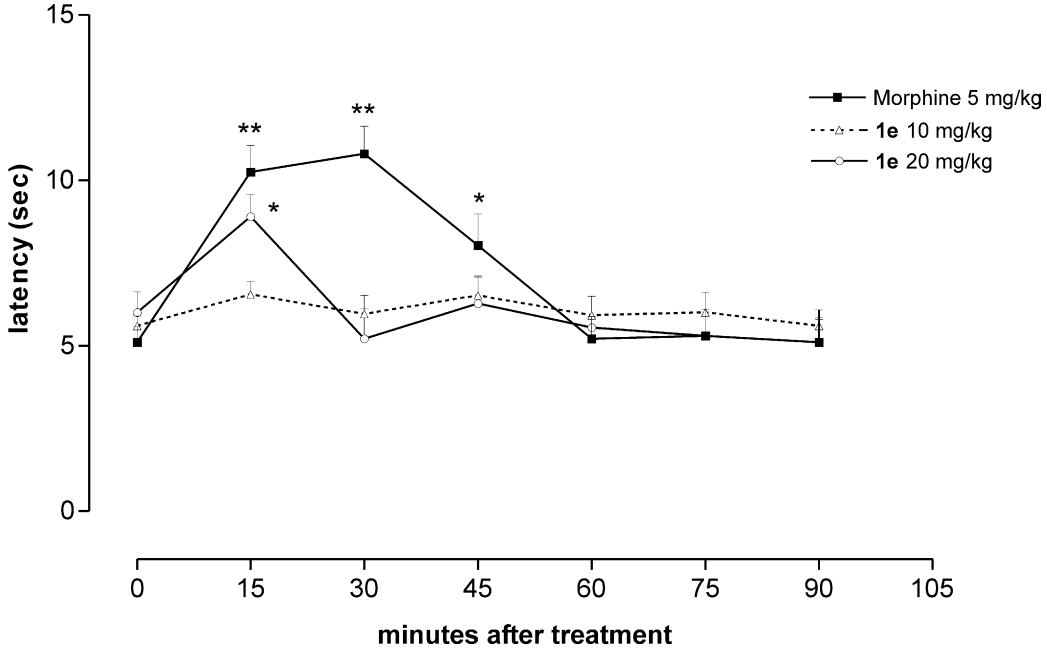


Figure 2. Antinociceptive effect of **1e** on mice hot-plate test. Each point represents the mean ± SEM of at least eight mice for group ($n = 8$, morphine. $n = 10$, **1e** 10 and 20 mg/kg). ANOVA followed by Newman–Keuls test; ** $p < 0.01$, * $p < 0.05$; versus basal value.

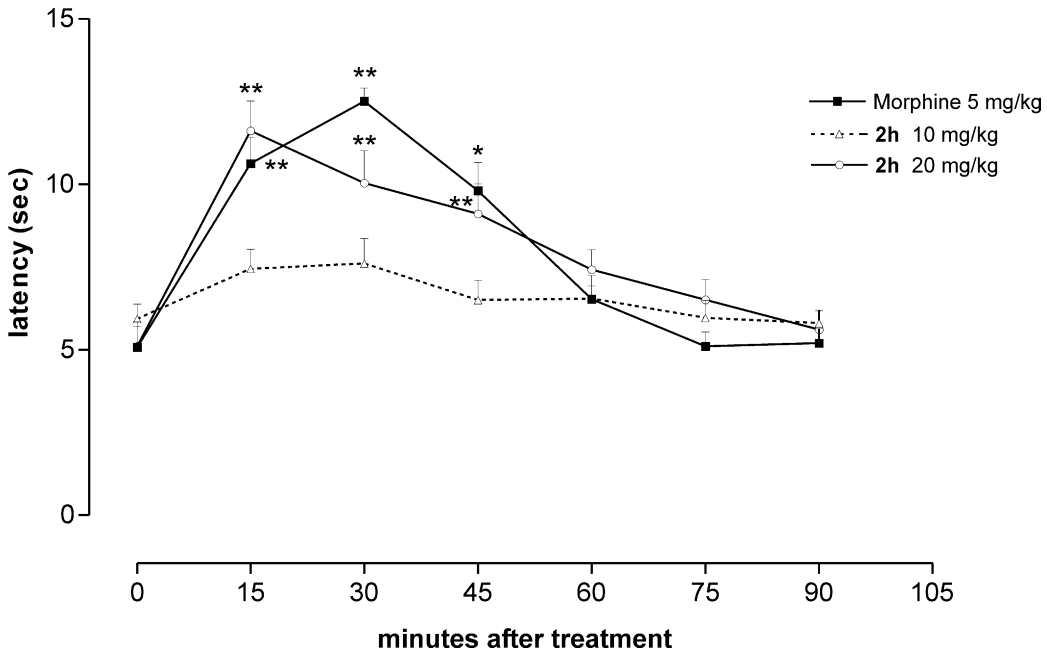


Figure 3. Antinociceptive effect of **2h** on mice hot-plate test. Each point represents the mean ± SEM of at least eight mice for group. ($n = 8$, morphine. n = 10, **2h** 10 and 20 mg/kg). ANOVA followed by Newman–Keuls test, ** $p < 0.01$, * $p < 0.05$; versus basal value.

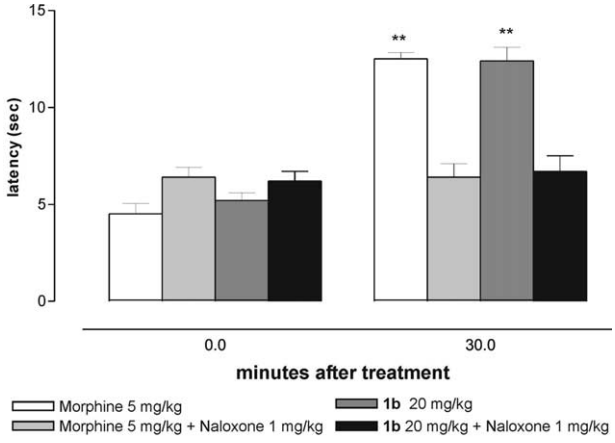


Figure 4. Antagonism of naloxone on antinociceptive effect of morphine and **1b**. Each column represents the mean ± SEM of at least eight mice for group. ANOVA followed by Newman–Keuls test. ** $p < 0.01$; versus correspondent basal ($n = 8$, for all groups).

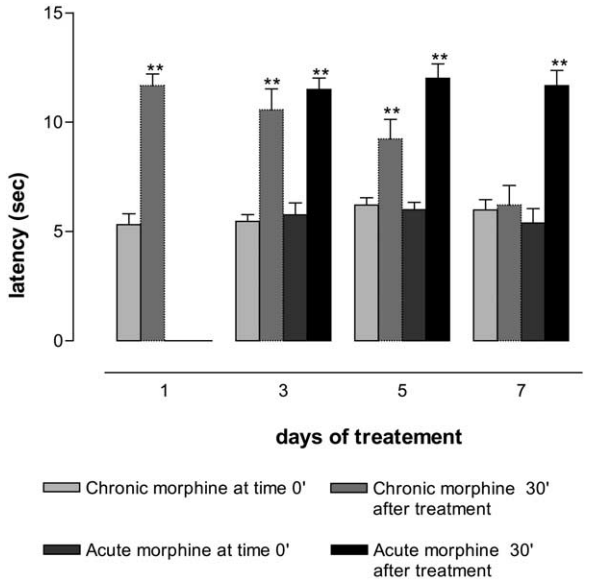


Figure 5. Tolerance to morphine (5 mg/kg). Each column represents the mean ± SEM of at least eight mice for group. ANOVA followed by Newman–Keuls test. ** $p < 0.01$; versus respective basal ($n = 10$, for all groups).

four disubstituted analogues, with a $K_i^{\mu} = 2.9$ nM which favourably compared with compound **2b** ($K_i^{\mu} = 4.07$ nM). Finally, the compounds containing *p*-F-diphenylpropenyl and *p*-Cl-diphenylpropenyl chains, namely, **1**,**2k** and **1**,**2l** displayed a decrease in μ receptor affinity, particularly relevant in **1l** ($K_i^{\mu} = > 400$ nM).

In conclusion, the results of the in vitro binding studies showed that compounds **1b**,**d**,**e**,**h** and **2b**,**d**–**f**,**h**,**i** exhibited an μ affinity similar or better than that of the prototypes **1**,**2a**, with a significant μ/δ and μ/κ selectivity (Table 1).

The analgesic activity of the pairs **1**,**2b**, **1**,**2e** and **1**,**2h** was evaluated in the hot plate test in mice.

As shown in Figure 1, administration of **1b** induced a significant analgesic effect at the dose of 20 and 40 mg/kg from 15 to 45 min after treatment. This effect was similar to the morphine effect. **1b** at the dose of 10 mg/kg did not induce any significant effect.

Figure 2 shows the analgesic effect of morphine and of **1e**. While morphine (5 mg/kg) induced a time-dependent analgesic effect (15–30–45 min), **1e** induced a significant effect after 15 min, only at the dose of 20 mg/kg.

Figure 3 shows that both administration of morphine (5 mg/kg) and **2h** (20 mg/kg) induced a significant time-dependent analgesic effect (15–30–45 min). No significant

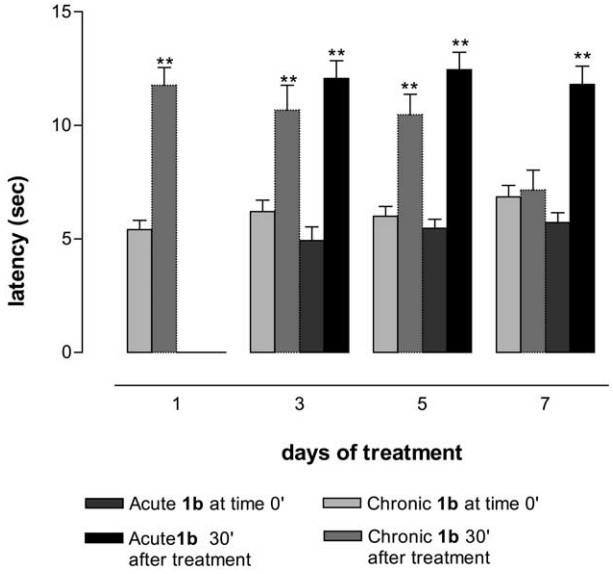


Figure 6. Tolerance to **1b** (20 mg/kg). Each column represents the mean±SEM of at least eight mice for group. ANOVA followed by Newman–Keuls test. ** $p<0.01$; versus respective basal ($n=10$, for all groups).

effect was present after administration of **2h** at the dose of 10 mg/kg.

Figure 4 shows that the opioid receptor antagonist Naloxone (1 mg/kg) prevents both morphine (5 mg/kg) and **1b** (20 mg/kg) analgesic effect. The same results were obtained with the compound **2h** (data not shown).

Figures 5 and 6 show that mice treated with morphine or **1b** developed tolerance to the analgesic effect. Both morphine and **1b** induced a significant analgesic effect up to 5 days of treatment but failed to show significant effects at the seventh day.

Administration of **2b**, **2e** and **1h** at the doses of 10 mg/kg did not induce any significant effect. However, higher dose (20 mg/kg) induced relevant signs of motor impairment and convulsions which did not allowed an evaluation of analgesic effect in the hot plate (data not shown).

In this study, we have tested for their analgesic activity six compounds (**1b**, **2b**, **1e**, **2e**, **1h**, **2h**) which have been selected on the basis of their good affinity and selectivity for the μ-opioid receptor. Our results indicate that only **1b** and **2h** show a good analgesic activity similar to that of morphine although at higher doses. Compound **1e** also shows a significant analgesic activity which lasts only 15 min. On the contrary, compounds **1h**, **2b** and **2e** did not show any analgesic activity. A possible explanation is, from the behavioural signs observed in these animals, that analgesic activity could be hindered by unspecific side effects (convulsions, motor impairment) due to interactions with other receptors. On the other hand, analgesic effect of **1b** as well as of **2h** are specifically mediated by μ receptor since this effect is completely antagonised by Naloxone. As far as tolerance to the analgesic effect is concerned, no difference was observed between morphine and **1b**. In conclusion, results of this study indicate that among DTD compounds some of them might have an analgesic profile very similar to morphine. However, the low number of compounds tested so far does not allow to evidentiate particular differences between 9,10-DTD and 2,7-DTD series.

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 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 spectra were recorded as ethanolic solution with a Perkin-Elmer lambda 5 spectrophotometer and the absorption wavelength are expressed as λ_{max} in nm followed by log ε. All NMR spectra were taken on a Varian XL-200 NMR spectrometer with ^{1}H and ^{13}C being observed at 200 and 50 MHz, respectively. Chemical shifts for ^{1}H and 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), m (multiplet). Elemental analyses were performed by Laboratorio di Microanalisi, Dipartimento di Chimica, Università di Sassari, Italy and are within ±0.4% of the calculated values. All reactions involving air or moisture-sensitive compounds were performed under argon atmosphere.

The general procedure for conversion to an HCl salt was the addition of excess ethereal HCl solution to a solution of the compound in ethanol or diethyl ether. The solvent was evaporated and the resulting salt was triturated with anhydrous ether and dried on vacuum.

The general procedure for conversion to a fumarate salt was the addition of a stoichiometric amount of a solution of fumaric acid in dry methanol to a solution of the compound in dry methanol. The solvent was evaporated and the resulting salt was triturated with anhydrous ether and dried on vacuum.

Unless otherwise specified, all materials, solvents, reagents and precursors **6b–l** 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 1b–l and 2b–l

A mixture of the appropriate propionyl-diazatricyclodecane **3** or **4** (1.42 mmol), the required cinnamyl chloride

(**5b–l**) (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–l** and **2b–l** as oils. All final compounds were converted into the HCl salts.

9-Propionyl-10-(3′-phenyl-3′-methylprop-2′-en-1′-yl)-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (1b). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 52%; R_f 0.40 (petroleum ether/EtOAc 1:1); mp 158–160 °C (as hydrochloride); IR: 1630; UV: 244.2 (3.89); ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, 3H, J = 7.8 Hz), 1.40–2.20 (m, 11H), 2.29 (q, 2H, J = 7.6 Hz), 3.00–3.10 (m, 2H), 3.80–3.90 (m, 2H), 4.43–4.53 (m, 2H), 5.85 (t, 1H, J = 6.6 Hz), 7.20–7.43 (m, 5H). Anal. calcd for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.64. Found: C, 78.00; H, 8.73; N, 8.67.

9-Propionyl-10-(3′-trifluoromethyl-3′-phenylprop-2′-en-1′-yl)-9,10-diazatricyclo[4.2.1.1^{2,5}] decane (1c). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 93%; R_f 0.37 (petroleum ether/EtOAc 1:1); mp 128–130 °C (as hydrochloride); IR: 1635; UV: 236.2 (4.17); ^{1}H NMR ($CDCl_3$) δ: 1.13 (t, 3H, J = 7.8 Hz), 1.20–2.10 (m, 8H), 2.26 (q, 2H, J = 7.8 Hz), 2.65–3.00 (m, 2H), 3.80–4.00 (m, 2H), 4.45–4.58 (m, 2H), 6.48–6.60 (m, 1H), 7.20–7.51 (m, 5H). Anal. calcd for $C_{21}H_{25}F_3N_2O$: C, 66.65; H, 6.66; F, 15.06; N, 7.40. Found: C, 66.38; H, 6.64; F, 15.03; N, 7.38.

9-Propionyl-10-(3′-cyclohexyl-3′-phenylprop-2′-en-1′-yl)-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (1d). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 98%; R_f 0.37 (petroleum ether/EtOAc 1:1); mp 135–136 °C (as hydrochloride); IR: 1680; UV: 240.1 (4.00); ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 3H, J = 7.6 Hz), 1.21–2.10 (m, 21H), 2.24 (q, 2H, J = 7.4 Hz), 2.57–2.65 (m, 1H), 2.85–2.95 (m, 1H), 3.75–3.85 (m, 1H), 4.40–4.50 (m, 1H), 5.46 (t, 1H, J = 6.8 Hz), 7.00 (d, 1H, J = 7.4 Hz), 7.14–7.32 (m, 3H), 7.52 (d, 1H, J = 7.0 Hz). Anal. calcd for $C_{26}H_{36}N_2O$: C, 79.54; H, 9.24; N, 7.14. Found: C, 79.22; H, 9.20; N, 7.17.

9-Propionyl-10-(3′,3′-diphenylprop-2′-en-1′-yl)-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (1e). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 93%; R_f 0.37 (petroleum ether/EtOAc 1:1); mp 112–113 °C (as hydrochloride); IR: 1630; UV: 245.1 (4.19); ^{1}H NMR ($CDCl_3$) δ: 1.13 (t, 3H, J = 7.6 Hz), 1.35–2.18 (m, 8H), 2.26 (q, 2H, J = 7.4 Hz), 2.86 (d, 2H, J = 6.8 Hz), 2.92–3.08 (m, 2H), 3.80–3.89 (m, 1H), 4.44–4.50 (m, 1H), 6.17 (t, 1H, J = 6.8 Hz), 7.11–7.32 (m, 10H). Anal. calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.83; N, 7.25. Found: C, 80.62; H, 7.83; N, 7.23.

9-Propionyl-10-[3′-methyl-3′-(*o*-chlorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo[4.2.1.1^{2,5}] decane (1f). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 88%; R_f 0.37 (petroleum ether/EtOAc 1:1); mp 141–143 °C (as hydrochloride); IR: 1630; UV: 230.0 (3.81); ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, J = 7.6 Hz), 1.50–2.15 (m, 12H), 2.30 (q, 2H, J = 7.6 Hz), 2.99 (d, 2H, J = 6.6 Hz), 3.04–3.18 (m, 1H), 3.85–3.92 (m, 1H), 4.47–4.55 (m, 1H), 5.49 (t, 1H, J = 6.5 Hz), 7.08–7.42 (m, 4H). Anal. calcd for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 70.05; H, 7.56; Cl, 9.85; N, 7.79.

9-Propionyl-10-[3′-methyl-3′-(*m*-chlorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo[4.2.1.1^{2,5}] decane (1g). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 97%; R_f 0.40 (petroleum ether/EtOAc 1:1); mp 110–112 °C (as hydrochloride); IR: 1630; UV: 250.2 (4.10); ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, J = 7.2 Hz), 1.40–2.15 (m, 12H), 2.26 (q, 2H, J = 7.2 Hz), 2.95–3.10 (m, 3H), 3.80–3.95 (m, 1H), 4.40–4.60 (m, 1H), 5.83 (t, 1H, J = 6.8 Hz), 7.22–7.40 (m, 4H). Anal. calcd for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 70.09; H, 7.55; Cl, 9.87; N, 7.78.

9-Propionyl-10-[3′-methyl-3′-(*p*-chlorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo[4.2.1.1^{2,5}] decane (1h). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 87%; R_f 0.40 (petroleum ether/EtOAc 1:1); mp 145–147 °C (as hydrochloride); IR: 1630; UV: 250.2 (3.92); ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, J = 7.4 Hz), 1.45–2.20 (m, 12H), 2.28 (q, 2H, J = 7.4 Hz), 2.95–3.10 (m, 3H), 3.80–3.95 (m, 1H), 4.45–4.60 (m, 1H), 5.85 (t, 1H, J = 7.0 Hz), 7.15–7.45 (m, 4H). Anal. calcd for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 70.12; H, 7.56; Cl, 9.87; N, 7.80.

9-Propionyl-10-[3′-methyl-3′-(*m*,*p*-dichlorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo [4.2.1.1^{2,5}]decane (1i). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 95%; R_f 0.40 (petroleum ether/EtOAc 1:1); mp 162–164 °C (as hydrochloride); IR: 1630; UV: 236.2 (4.08); ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, J = 7.6 Hz), 1.44–2.12 (m, 12H), 2.29 (q, 2H, J = 7.6 Hz), 2.98 (d, 2H, J = 6.4 Hz), 3.05–3.12 (m, 1H), 3.82–3.98 (m, 1H), 4.48–4.55 (m, 1H), 5.48 (t, 1H, J = 6.4 Hz), 7.08–7.40 (m, 3H). Anal. calcd for $C_{21}H_{26}Cl_2N_2O$: C, 64.12; H, 6.66; Cl, 18.03; N, 7.12. Found: C, 64.01; H, 6.64; Cl, 17.99; N, 7.09.

9-Propionyl-10-[3′-methyl-3′-(*o*,*p*-dichlorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo [4.2.1.1^{2,5}]decane (1j). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 98%; R_f 0.37 (petroleum ether/EtOAc 1:1); mp 128–130 °C (as hydrochloride); IR: 1630; UV: 236.2 (4.17); ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, 3H, J = 7.4 Hz), 1.45–2.17 (m, 12H), 2.29 (q, 2H, J = 7.4 Hz), 2.92–3.10 (m, 3H), 3.80–3.98 (m, 1H), 4.45–4.54 (m, 1H), 5.83–5.90 (m, 1H), 7.23–7.50 (m, 3H). Anal. calcd for $C_{21}H_{26}Cl_2N_2O$: C, 64.12; H, 6.66; Cl, 18.03; N, 7.12. Found: C, 64.05; H, 6.63; Cl, 17.98; N, 7.10.

9-Propionyl-10-[(3′,3′-di-*p*-fluorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo[4.2.1.1^{2,5}] decane (1k). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 94%; R_f 0.40 (petroleum ether/EtOAc 1:1); mp 126–128 °C (as hydrochloride); IR: 1680; UV: 249.4 (4.26); ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 3H, J = 7.4 Hz), 1.40–2.32 (m, 10H), 2.85 (d, 2H, J = 6.8 Hz), 2.95–3.05 (m, 2H), 3.80–3.92 (m, 1H), 4.40–4.51 (m, 1H), 6.11 (t, 1H, J = 6.8 Hz), 6.90–7.28 (m, 8H). Anal. calcd for $C_{26}H_{28}F_2N_2O$: C,

73.91; H, 6.68; F, 8.99; N, 6.63. Found: C, 73.85; H, 6.66; F, 8.96; N, 6.61.

9-Propionyl-10-[(3′,3′-di-*p*-chlorophenyl)-prop-2′-en-1′-yl]-9,10-diazatricyclo[4.2.1.1^{2,5}] decane (1l). Purified by FC (eluent: petroleum ether/EtOAc 1:1), yield 94%; R_f 0.44 (petroleum ether/EtOAc 1:1); mp 118–120 °C (as hydrochloride); IR: 1680; UV: 250.8 (3.36); ^{1}H NMR ($CDCl_3$) δ: 1.13 (t, 3H, J = 7.6 Hz), 1.40–2.10 (m, 8H), 2.24 (q, 2H, J = 7.6 Hz), 2.83 (d, 2H, J = 7.0 Hz), 2.91–3.10 (m, 2H), 3.80–3.90 (m, 1H), 4.40–4.52 (m, 1H), 6.15 (t, 1H, J = 7.0 Hz), 7.00–7.40 (m, 8H). Anal. calcd for $C_{26}H_{28}Cl_2N_2O$: C, 68.57; H, 6.20; Cl, 15.57; N, 6.15. Found: C, 68.49; H, 6.18; Cl, 15.54; N, 6.13.

2-Propionyl-7-(3′-phenyl-3′-methylprop-2′-en-1′-yl)-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (2b). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 66%; R_f 0.40 (CH_2Cl_2/acetone 6:4); mp 217–220 °C (as hydrochloride); IR: 1630; UV: 240.8 (3.96); ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, 3H, J = 7.4 Hz), 1.30–2.10 (m, 8H), 2.09 (s, 3H), 2.17–2.35 (m, 2H), 3.00–3.10 (m, 2H), 3.50–3.60 (m, 2H), 3.75–3.85 (m, 1H), 4.28–4.35 (m, 1H), 5.80–5.88 (m, 1H), 7.20–7.42 (m, 5H). Anal. calcd for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.64. Found: C, 77.42; H, 8.73; N, 8.61.

2-Propionyl-7-(3′-trifluoromethyl-3′-phenylprop-2′-en-1′-yl)-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2c). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 80%; R_f 0.36 (CH_2Cl_2/acetone 6:4); mp 141–143 °C (as hydrochloride); IR: 1630; UV: 221.4 (4.02), 258.5 (3.52); ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 3H, J = 7.4 Hz), 1.20–2.30 (m, 10H), 2.89–2.95 (m, 2H), 3.23–3.35 (m, 2H), 3.69–3.75 (m, 1H), 4.20–4.32 (m, 1H), 6.40 (t, 1H, J = 6.6 Hz), 7.20–7.48 (m, 5H). Anal. calcd for $C_{21}H_{25}F_3N_2O$: C, 66.65; H, 6.66; F, 15.06; N, 7.40. Found: C, 66.51; H, 6.67; F, 15.07; N, 7.39.

2-Propionyl-7-(3′-cyclohexyl-3′-phenylprop-2′-en-1′-yl)-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2d). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 24%; R_f 0.50 (CH_2Cl_2/acetone 6:4); mp 185–187 °C (as fumarate); IR: 1630; UV: 231.3 (3.97); ^{1}H NMR ($CDCl_3$) δ: 1.15–2.35 (m, 24H), 3.01 (d, 2H, J = 4.8 Hz), 3.50–3.54 (m, 2H), 3.60–3.80 (m, 1H), 4.25–4.34 (m, 1H), 5.60–5.80 (m, 1H), 7.20–7.40 (m, 5H). Anal. calcd for $C_{26}H_{36}N_2O$: C, 79.54; H, 9.24; N, 7.14. Found: C, 79.25; H, 9.22; N, 7.11.

2-Propionyl-7-(3′, 3′-diphenylprop-2′-en-1′-yl)-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (2e). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 98%; R_f 0.36 (CH_2Cl_2/acetone 6:4); mp 54–55 °C (as hydrochloride); IR: 1630; UV: 221.2 (4.09), 249.5 (3.60); ^{1}H NMR ($CDCl_3$) δ: 1.10–2.35 (m, 13H), 2.97–3.05 (m, 1H), 3.17–3.28 (m, 1H), 3.36–3.43 (m, 2H), 3.70–3.80 (m, 1H), 4.21–4.32 (m, 1H), 6.14 (t, 1H, J = 7.3 Hz), 7.20–7.45 (m, 10H). Anal. calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.83; N, 7.25. Found: C, 80.65; H, 7.85; N, 7.23.

2-Propionyl-7-[3′-methyl-3′-(*o*-chlorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2f). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 70%; R_f 0.36 (CH_2Cl_2/acetone 6:4); mp 152–154 °C (as hydrochloride); IR: 1630; UV: 233.2 (4.12); ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, 3H, J = 7.6 Hz), 1.35–2.42 (m, 13H), 3.05–3.21 (m, 2H), 3.46–3.67 (m, 2H), 3.80–3.92 (m, 1H), 4.30–4.40 (m, 1H), 5.48–5.55 (m, 1H), 7.08–7.42 (m, 4H). Anal. calcd for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 69.88; H, 7.61; Cl, 9.90; N, 7.82.

2-Propionyl-7-[3′-methyl-3′-(*m*-chlorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2g). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 87%; R_f 0.40 (CH_2Cl_2/acetone 6:4); mp 98–100 °C (as hydrochloride); IR: 1630; UV: 251.8 (4.02); ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, 3H, J = 7.8 Hz), 1.30–2.35 (m, 13H), 3.00–3.15 (m, 2H), 3.50–3.65 (m, 2H), 3.85–4.00 (m, 1H), 4.40–4.50 (m, 1H), 5.75–5.90 (m, 1H), 7.20–7.40 (m, 4H). Anal. calcd for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 70.16; H, 7.60; Cl, 9.91; N, 7.77.

2-Propionyl-7-[3′-methyl-3′-(*p*-chlorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2h). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 97%; R_f 0.40 (CH_2Cl_2/acetone 6:4); mp 140–142 °C (as hydrochloride); IR: 1630; UV: 240.6 (3.50); ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, 3H, J = 7.2 Hz), 1.33–2.42 (m, 13H), 3.00–3.20 (m, 2H), 3.50–3.68 (m, 2H), 3.79–3.92 (m, 1H), 4.30–4.40 (m, 1H), 5.80–5.95 (m, 1H), 7.25–7.48 (m, 4H). Anal. calcd for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 70.14; H, 7.59; Cl, 9.85; N, 7.83.

2-Propionyl-7-[3′-methyl-3′-(*m*,*p*-dichlorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2i). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 96%; R_f 0.37 (CH_2Cl_2/acetone 6:4); mp 136–138 °C (as hydrochloride); IR: 1630; UV: 237.6 (3.88); ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, 3H, J = 7.8 Hz), 1.30–2.40 (m, 13H), 2.95–3.12 (m, 1H), 3.35–3.70 (m, 2H), 3.78–3.90 (m, 2H), 4.28–4.37 (m, 1H), 5.82–5.88 (m, 1H), 7.20–7.50 (m, 3H). Anal. calcd for $C_{21}H_{26}Cl_2N_2O$: C, 64.12; H, 6.66; Cl, 18.03; N, 7.12. Found: C, 63.99; H, 6.63; Cl, 18.00; N, 7.10.

2-Propionyl-7-[3′-methyl-3′-(*o*,*p*-dichlorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}] decane (2j). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 95%; R_f 0.40 (CH_2Cl_2/acetone 6:4); mp 100–102 °C (as hydrochloride); IR: 1630; UV: 247.8 (3.88); ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, 3H, J = 7.6 Hz), 1.30–2.41 (m, 13H), 2.90–3.18 (m, 1H), 3.35–3.70 (m, 2H), 3.78–3.90 (m, 2H), 4.30–4.36 (m, 1H), 5.42–5.46 (m, 1H), 7.08–7.37 (m, 3H). Anal. calcd for $C_{21}H_{26}Cl_2N_2O$: C, 64.12; H, 6.66; Cl, 18.03; N, 7.12. Found: C, 63.99; H, 6.70; Cl, 17.99; N, 7.09.

2-Propionyl-7-[(3′,3′-di-*p*-fluorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (2k). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 70%; R_f 0.36 (CH_2Cl_2/acetone 6:4); mp 163–165 °C (as hydrochloride); IR: 1630; UV: 249.9 (3.79); ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 3H, J = 6.00 Hz), 1.21–2.40 (m, 10H), 2.95–3.15

(m, 1H), 3.35–3.50 (m, 2H), 3.72–3.95 (m, 2H), 4.25–4.50 (m, 1H), 6.05–6.20 (m, 1H), 6.93–7.22 (m, 8H). Anal. calcd for $C_{26}H_{28}F_2N_2O$: C, 73.91; H, 6.68; F, 8.99; N, 6.63. Found: C, 73.99; H, 6.65; F, 9.02; N, 6.62.

2-Propionyl-7-[(3′,3′-di-*p*-chlorophenyl)-prop-2′-en-1′-yl]-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (2l). Purified by FC (eluent: CH_2Cl_2/acetone 6:4), yield 70%; R_f 0.36 (CH_2Cl_2/acetone 6:4); mp 156–158 °C (as hydrochloride); IR: 1630; UV: 231.6 (3.46); ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, J = 6.00 Hz), 1.21–2.35 (m, 10H), 2.95–3.05 (m, 1H), 3.38 (d, 2H, J = 6.6 Hz), 3.50–3.61 (m, 1H), 3.71–3.87 (m, 1H), 4.20–4.43 (m, 1H), 6.12 (t, 1H, J = 6.8 Hz), 7.09–7.85 (m, 8H). Anal. calcd for $C_{26}H_{28}Cl_2N_2O$: C, 68.57; H, 6.20; Cl, 15.57; N, 6.15. Found: C, 68.60; H, 6.17; Cl, 15.55; N, 6.12.

General procedure for arylpropenyl esters 7

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 **6** (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 (**7e**,**f**,**k**,**l**) or a mixture of the isomers *E*/*Z* (**7b–d**,**g–j**), which were isolated by flash chromatography.

Ethyl (2*E*)-3-phenyl but-2-enoate (*E*)-7b and ethyl (2*Z*)-3-phenyl but-2-enoate (*Z*)-7b. (*E*)-7b. Yield 76%; bp 68–70 °C/0.01 mmHg (bp 115-116 °C/5 mmHg);[4] **(*Z*)-7b**. Yield 11%; bp 60–65 °C/0.01 mmHg (bp 80 °C/0.05 mmHg).[4]

Ethyl (2*E*)-3-trifluoromethyl-3-phenyl prop-2-enoate (*E*)-7c and ethyl (2*Z*)-3-trifluoromethyl-3-phenyl prop-2-enoate (*Z*)-7c. The mixture was purified by FC, eluting with: petroleum ether/ethyl ether (9.9:0.1). Fraction 1 contained **(*E*)-7c**, yield 65%; bp 41 °C/0.01 mmHg (bp 75-82 °C/1,5 mmHg).[5] Fraction 2 contained **(*Z*)-7c**, yield 21%; bp 45 °C/0,01 mmHg (bp 243.5 °C/740 mmHg).[6]

Ethyl (2*E*)-3-cyclohexyl-3-phenyl prop-2-enoate (*E*)-7d and ethyl (2*Z*)-3-cyclohexyl-3-phenyl prop-2-enoate (*Z*)-7d. (*E*)-7d Yield 62%; bp 90–100 °C/0.01 mmHg (bp 105–109 °C/0.1 mmHg);[4] **(*Z*)-7d** yield 26%; bp 90–92 °C/0.01 mmHg (bp 105–109 °C/0.06 mmHg).[4]

Ethyl 3,3-diphenylacrylate (7e). Yield 77%; bp 130 °C/0.01 mmHg (bp 140 °C/0.05 mmHg).[4]

Ethyl (2*E*)-3-(2′-chlorophenyl)-but-2-enoate (*E*)-7f. Yield 65%; R_f 0.52 (petroleum ether/EtOAc = 9.9:0.1); bp 80 °C/0.01 mm Hg; IR: 1720; UV: 236.5 (3.92); ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, J = 7.2 Hz), 2.49 (s, 3H), 4.22 (q, 2H, J = 7.2 Hz), 5.83 (s, 1H), 7.20–7.31 (m, 4H). Anal. calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.24; H, 5.81; Cl, 15.81.

Ethyl (2*E*)-3-(3′-chlorophenyl)-but-2-enoate (*E*)-7g and ethyl (2*Z*)-3-(3′-chlorophenyl)-but-2-enoate (*Z*)-7g. The mixture was purified by FC, eluting with: petroleum ether/ethyl ether (9.9:0.1). Fraction 1 contained **(*E*)-7g**, yield 77%; R_f 0.65 (petroleum ether/ethyl ether 9.9:0.1); bp 112–115 °C/0.01 mmHg; IR: 1720; UV: 249.6 (3.94); ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, J = 7.2 Hz), 2.52 (s, 3H), 4.21 (q, 2H, J = 7.2 Hz), 6.11 (s, 1H), 7.30–7.40 (m, 4H). Anal. calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.08; H, 5.82; Cl, 15.72. Fraction 2 contained **(*Z*)-7g**, yield 5%; R_f 0.46 (petroleum ether: ethyl ether 9.9:0.1); bp 90 °C/0.01 mmHg. IR: 1720; UV: 244.9 (3.86); ^{1}H NMR ($CDCl_3$) δ: 1.09 (t, 3H, J = 7.0 Hz), 2.16 (s, 3H), 4.03 (q, 2H, J = 7.0 Hz), 5.91 (s, 1H), 7.20–7.40 (m, 4H). Anal. calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.20; H, 5.80; Cl, 15.82.

Ethyl (2*E*)-3-(4′-chlorophenyl)-but-2-enoate (*E*)-7h and ethyl (2*Z*)-3-(4′-chlorophenyl)-but-2-enoate (*Z*)-7h. The mixture was purified by FC, eluting with: petroleum ether/ethyl ether (9.9:0.1). Fraction 1 contained **(*E*)-7h**, yield 74%; R_f 0.52 (petroleum ether/ethyl ether 9.9:0.1); bp 75 °C/0.01 mmHg (bp 150 °C/3 mmHg).[7] Fraction 2 contained **(*Z*)-7h**, yield 14%; R_f 0.32 (petroleum ether/ethyl ether 9.9:0.1); bp 92 °C/0.01 mmHg. IR: 1720; UV: 249.3 (3.77); ^{1}H NMR ($CDCl_3$) δ: 1.11 (t, 3H, J = 7.2 Hz), 2.15 (s, 3H), 4.01 (q, 2H, J = 7.2 Hz), 5.93 (s, 1H), 7.14 (d, 2H, J = 8.8 Hz), 7.32 (d, 2H, J = 8.8 Hz). Anal. calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.08; H, 5.81; Cl, 15.75.

Ethyl (2*E*)-3-(3′,4′-dichlorophenyl)-but-2-enoate (*E*)-7i and ethyl (2*Z*)-3-(3′,4′-dichlorophenyl)-but-2-enoate (*Z*)-7i. The mixture was purified by FC, eluting with: petroleum ether/ethyl ether (9.9:0.1). Fraction 1 contained **(*E*)-7i**, yield 77%; R_f 0.45 (petroleum ether/ethyl ether 9.9:0.1); bp 90 °C/0.01 mmHg. IR: 1720; UV: 235.8 (3.99); ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, J = 6.8 Hz), 2.52 (s, 3H), 4.21 (q, 2H, J = 6.8 Hz), 6.12 (s, 1H), 7.27–7.33 (m, 1H), 7.42–7.46 (m, 1H), 7.55 (s, 1H). Anal. calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.62; H, 4.67; Cl, 27.36. Found: C, 55.73; H, 4.65; Cl, 27.39. Fraction 2 contained **(*Z*)-7i**, yield 18%; R_f 0.35 (petroleum ether/ethyl ether 9.9:0.1); bp 100 °C/0.01 mmHg. IR: 1720; UV: 233.4 (3.94); ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 3H, J = 7.2 Hz), 2.15 (s, 3H), 4.03 (q, 2H, J = 7.2 Hz), 5.94 (s, 1H), 7.03–7.08 (m, 1H), 7.29 (s,1H), 7.33–7.44 (m, 1H). Anal. calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.62; H, 4.67; Cl, 27.36. Found: C, 55.32; H, 4.48; Cl, 27.02.

Ethyl (2*E*)-3-(2′,4′-dichlorophenyl)-but-2-enoate (*E*)-7j and ethyl (2*Z*)-3-(2′,4′-dichlorophenyl)-but-2-enoate (*Z*)-7j. The mixture was purified by FC, eluting with: petroleum ether/ethyl ether (9.9:0.1). Fraction 1 contained **(*E*)-7j**, yield 54%; R_f 0.53 (petroleum ether/ethyl ether 9.9:0.1); bp 110 °C/0.01 mmHg. IR: 1720; UV: 229.2 (3.98); ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, J = 6.8 Hz), 2.46 (s, 3H), 4.22 (q, 2H, J = 6.8 Hz), 5.81 (s, 1H), 7.10 (d, 1H, J = 7.8 Hz), 7.24 (d, 1H, J = 9.8 Hz), 7.41 (s, 1H). Anal. calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.62; H, 4.67; Cl, 27.36. Found: C, 55.84; H, 4.68; Cl, 27.27. Fraction 2 contained **(*Z*)-7j**, yield 18%; R_f 0.35 (petroleum ether: ethyl ether 9.9:0.1); bp 100 °C/0.01 mmHg. IR: 1720;

UV: 233.4 (3.94); ^{1}H NMR ($CDCl_3$) δ: 1.10 (t, 3H, J = 7.2 Hz), 2.15 (s, 3H), 4.03 (q, 2H, J = 7.2 Hz), 6.02 (s, 1H), 7.03–7.08 (m, 1H), 7.29 (s,1H), 7.33–7.44 (m, 1H). Anal. calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.62; H, 4.67; Cl, 27.36. Found: C, 55.78; H, 4.69; Cl, 27.32.

Ethyl 3,3-bis-(4′-fluorophenyl)acrylate (7k). Yield 69%; mp 54–56 °C (petroleum ether) [mp 62–62.5 °C (ethanol)].[4]

Ethyl 3,3-bis-(4′-chlorophenyl)acrylate (7l). Yield 84%; mp 49–50 °C (petroleum ether) [mp 64.5 °C (ethanol)].[4]

General procedure for arylpropenyl alcohols 8

The required arylpropenyl ester **7** (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 **8** as an oil or a solid.

(2*E*)-3-Phenylbut-2-en-1-ol (*E*)-8b. Yield 94%; bp 85 °C/0.01 mmHg (bp 78–80 °C/0.05 mmHg).[4]

(2*E*)-3-Trifluoromethyl-3-phenyl prop-2-en-1-ol (*E*)-8c. Yield 67%; bp 90 °C/0.01 mmHg (bp 78–80 °C/0.05 mmHg).[8]

(2*E*)-3-Cyclohexyl-3-phenylprop-2-en-1-ol (*E*)-8d. Yield 96%; mp 47–55 °C [bp 94–95 °C/0.1 mmHg].[4]

3,3-Diphenylprop-2-en-1-ol (8e). Yield 95%; mp 53–56 °C (hexane/Et_2O) [mp 55–57 °C (hexane/Et_2O)].[4]

(2*E*)-3-(2′-Chlorophenyl)-but-2-en-1-ol (*E*)-8f. Yield 87%; R_f 0.23 (petroleum ether/EtOAc = 9:1); bp 74 °C/0.01 mmHg; IR: 3300; UV: 230.2 (3.75); ^{1}H NMR ($CDCl_3$) δ: 1.78 (br s, 1H, OH exch. with D_2O), 2.03 (s, 3H), 4.34 (d, 2H, J = 6.8 Hz), 5.63 (t, 1H, J = 6.5 Hz), 7.10–7.40 (m, 4H). Anal. calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 65.65; H, 6.08; Cl, 19.35.

(2*E*)-3-(3′-Chlorophenyl)-but-2-en-1-ol (*E*)-8g. Yield 92%; R_f 0.24 (petroleum ether/EtOAc = 9:1); bp 142 °C/0.01 mmHg; IR: 3300; UV: 242.4 (3.82); ^{1}H NMR ($CDCl_3$) δ: 1.59 (br s, 1H, OH exch. with D_2O), 2.05 (s, 3H), 4.36 (d, 2H, J = 6.6 Hz), 5.98 (t, 1H, J = 6.6 Hz), 7.20–7.33 (m, 3H), 7.38 (s, 1H). Anal. calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 65.56; H, 6.04; Cl, 19.33.

(2*E*)-3-(4′-Chlorophenyl)-but-2-en-1-ol (*E*)-8 h. Yield 89%; R_f 0.30 (petroleum ether/EtOAc = 9:1); bp 139–140 °C/0.01 mmHg; IR: 3300; UV: 246.4 (3.80); ^{1}H NMR ($CDCl_3$) δ: 1.58 (br s, 1H, OH exch. with D_2O), 2.05 (s, 3H), 4.36 (d, 2H, J = 6.6 Hz), 5.96 (t, 1H, J = 6.6 Hz), 7.20–7.40 (m, 4H). Anal. calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 66.02; H, 6.05; Cl, 19.37.

(2*E*)-3-(3′,4′-Dichlorophenyl)-but-2-en-1-ol (*E*)-8i. Yield 98%; R_f 0.30 (petroleum ether/EtOAc = 9:1); bp 96 °C/0.01 mmHg; IR: 3300; UV: 230.1 (3.91); ^{1}H NMR ($CDCl_3$) δ: 1.73 (br s, 1H, OH exch. with D_2O), 2.03 (s, 3H), 4.30 (d, 2H, J = 6.6 Hz), 5.64 (t, 1H, J = 6.6 Hz), 7.20 (d, 1H, J = 7.8 Hz), 7.37 (d, 1H, J = 7.8 Hz), 7.45 (s, 1H). Anal. calcd for $C_{10}H_{10}Cl_2O$: C, 55.33; H, 4.64; Cl, 32.66. Found: C, 55.38; H, 4.63; Cl, 32.79.

(2*E*)-3-(2′,4′-Dichlorophenyl)-but-2-en-1-ol (*E*)-8j. Yield 98%; R_f 0.30 (petroleum ether/EtOAc = 9:1); bp 140 °C/0.01 mmHg; IR: 3300; UV: 233.2 (3.85); ^{1}H NMR ($CDCl_3$) δ: 1.66 (br s, 1H, OH exch. with D_2O), 1.99 (s, 3H), 4.34 (d, 2H, J = 6.6 Hz), 5.62 (t, 1H, J = 6.6 Hz), 7.10–7.30 (m, 2H), 7.36 (s, 1H). Anal. calcd for $C_{10}H_{10}Cl_2O$: C, 55.33; H, 4.64; Cl, 32.66. Found: C, 55.47; H, 4.62; Cl, 32.62.

3,3-bis(4′-Fluorophenyl)prop-2-en-1-ol (8k). Yield 97%; mp 66–68 °C [mp 71–72 °C (petroleum ether)].[4]

3,3-bis(4′-Chlorophenyl)prop-2-en-1-ol (8l). Yield 98%; mp 64-66 °C [mp 67–69 °C (petroleum ether)].[4]

General procedure for arylpropenyl chlorides 5b–l

A solution of appropriate arylpropenyl alcohol **8** (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 **5b–l** as oils.

(2*E*)-3-Phenylbut-2-en-1-yl chloride (*E*)-5b. Yield 95%; R_f 0.45 (petroleum ether/EtOAc = 9.8:0.2); bp 75 °C/0.01 mmHg; IR: 1590, 1620; UV: 245.6 (3.80); ^{1}H NMR ($CDCl_3$) δ: 2.14 (s, 3H), 4.28 (d, 2H, J = 8.0 Hz), 6.00 (t, 1H, J = 8.0 Hz), 7.20–7.48 (m, 5H). Anal. calcd for $C_{10}H_{11}Cl$: C, 72.07; H, 6.65; Cl, 21.27. Found: C, 71.99; H, 6.67; Cl, 21.45.

(2*E*)-3-Trifluoromethyl-3-phenyl prop-2-en-1-yl chloride (*E*)-5c. Yield 79%; R_f 0.43 (petroleum ether/EtOAc = 9.8:0.2); bp 135 °C/0.01 mmHg; IR: 1600, 1620; UV: 228.9 (3.45); ^{1}H NMR ($CDCl_3$) δ: 3.94 (d, 2H, J = 7.8 Hz), 6.56 (t, 1H, J = 7.8 Hz), 7.20–7.50 (m, 5H). Anal. calcd for $C_{10}H_8ClF_3$: C, 54.44; H, 3.65; Cl, 16.07; F, 25.83. Found: C, 54.33; H, 3.63; Cl, 16.13; F, 25.66.

(2*E*)-3-Cyclohexyl-3-phenyl prop-2-en-1-yl chloride (*E*)-5d. Yield 98%; R_f 0.37 (petroleum ether/EtOAc = 9.8:0.2); bp 125 °C/0.01 mmHg; IR: 1600, 1620; UV: 221.9 (3.93); ^{1}H NMR ($CDCl_3$) δ: 1.00–2.30 (m, 11H), 3.80 (d, 2H, J = 8.6 Hz), 5.63 (t, 1H, J = 8.6 Hz),

7.00–7.50 (m, 5H). Anal. calcd for $C_{15}H_{19}Cl$: C, 76.74; H, 8.16; Cl, 15.10. Found: C, 76.43; H, 8.13; Cl, 15.05.

3,3-Diphenylprop-2-en-1-yl chloride (5e). Yield 98%; bp 65–66 °C/0.01 mmHg (bp 144–145 °C/1.5 mmHg).[4]

(2*E*)-3-(2′-Chlorophenyl)but-2-en-1-yl chloride (*E*)-5f. Yield 98%; R_f 0.39 (petroleum ether/EtOAc = 9:1); bp 77 °C/0.01 mmHg; IR: 1590, 1650; UV: 235.6 (3.83); ^{1}H NMR ($CDCl_3$) δ: 2.10 (s, 3H), 4.24 (d, 2H, J = 8.0 Hz), 5.66 (t, 1H, J = 8.0 Hz), 7.10–7.40 (m, 4H). Anal. calcd for $C_{10}H_{10}Cl_2$: C, 59.73; H, 5.01; Cl, 35.26. Found: C, 59.67; H, 5.03; Cl, 35.12.

(2*E*)-3-(3′-Chlorophenyl)but-2-en-1-yl chloride (*E*)-5g. Yield 76%; R_f 0.41 (petroleum ether/EtOAc = 9:1); bp 80 °C/0.01 mmHg; IR: 1600, 1640; UV: 248.0 (4.80); ^{1}H NMR ($CDCl_3$) δ: 2.11 (s, 3H), 4.25 (d, 2H, J = 7.4 Hz), 5.99 (t, 1H, J = 7.4 Hz), 7.11–7.38 (m, 4H). Anal. calcd for $C_{10}H_{10}Cl_2$: C, 59.73; H, 5.01; Cl, 35.26. Found: C, 59.63; H, 5.03; Cl, 35.17.

(2*E*)-3-(4′-Chlorophenyl)but-2-en-1-yl chloride (*E*)-5 h. Yield 90%; R_f 0.40 (petroleum ether/EtOAc = 9:1); bp 82 °C/0.01 mmHg; IR: 1600, 1640; UV: 225.4 (3.87), 243.3 (3.87); ^{1}H NMR ($CDCl_3$) δ: 2.11 (s, 3H), 4.26 (d, 2H, J = 7.6 Hz), 5.97 (t, 1H, J = 7.6 Hz), 7.15–7.42 (m, 4H). Anal. calcd for $C_{10}H_{10}Cl_2$: C, 59.73; H, 5.01; Cl, 35.26. Found: C, 59.60; H, 4.99; Cl, 35.33.

(2*E*)-3-(3′,4′-Dichlorophenyl)but-2-en-1-yl chloride (*E*)-5i. Yield 98%; R_f 0.38 (petroleum ether/EtOAc = 9:1); bp 100 °C/0.01 mmHg; IR: 1590, 1640; UV: 232.4 (3.90); ^{1}H NMR ($CDCl_3$) δ: 2.10 (s, 3H), 4.24 (d, 2H, J = 6.6 Hz), 5.99 (t, 1H, J = 6.6), 7.20–7.50 (m, 3H). Anal. calcd for $C_{10}H_9Cl_3$: C, 50.99; H, 3.85; Cl, 45.16. Found: C, 51.06; H, 3.90; Cl, 45.07.

(2*E*)-3-(2′,4′-Dichlorophenyl)but-2-en-1-yl chloride (*E*)-5j. Yield 61%; R_f 0.39 (petroleum ether/EtOAc = 9:1); bp 110 °C/0.01 mmHg; IR: 1590, 1620; UV: 224.3 (3.92); ^{1}H NMR ($CDCl_3$) δ: 2.06 (s, 3H), 4.21 (d, 2H, J = 7.8 Hz), 5.65 (t, 1H, J = 7.8 Hz), 7.11–7.40 (m, 3H). Anal. calcd for $C_{10}H_9Cl_3$: C, 50.99; H, 3.85; Cl, 45.16. Found: C, 50.90; H, 3.86; Cl, 45.00.

3,3-bis(4′-Fluorophenyl)prop-2-en-1-yl chloride (5k). Yield 57%; mp 48–50 °C (petroleum ether) [mp 48–54 °C (petrol ether)].[4]

3,3-bis(4′-Chlorophenyl)prop-2-en-1-yl chloride (5l). Yield 70%; bp 89 °C/0.01 mmHg [bp 90–92 °C/0.01 mmHg].[4]

Biology

General information. Male Albino CD1 mice weighing 26–30 g (Charles River, Italy) were used. Animals were kept on a 12 h artificial light/dark cycle (lights on at 7:00 a.m.) at a constant 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, MD, USA).

Naloxone·HCl (Du Pont, USA), morphine·HCl (S.A.L.A.R.S., Como, Italy), **1b**, **1**,**2e** and **1**,**2h** were administered sc at a volume of 0.200 mL/mouse of saline.

Opioid binding assay. Ligand binding assay were determined for compounds at μ-, δ- and κ-opioid receptors as previously described.[9] 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,[10] 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.[11] The effect of compounds on the reaction time of mice placed on a hot plate thermostatically maintained at 55 °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 recorded; 14 s was set as the cut off time to avoid damage to the paws.

In the experiment designed to examine the ability of the opioid antagonist naloxone to reverse the analgesic effect of **1b**, naloxone HCl (1 mg/kg ip), **1b** (20 mg/kg sc), morphineHCl (5 mg/kg sc) or vehicle were administered at 0 and 30 min after treatment.

To evaluate the development of tolerance to the analgesic effect, saline, morphine and **1b** were chronically administered to mice twice a day (8:00 a.m.–8:00 p.m.). The hot plate test was performed 30 min after the 8:00 am injections.

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