Original Research Article

Trials of phenanthrene opioids functionalization with hindered polycyclic carboxylic acids

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ABSTRACT

In the last decades, the number of patients undergoing pain relief for chronic or degenerative diseases has observed a significant increase, also due to an increase in the average age of the population. Morphine, the widely used opioid in pain therapy, is known to produce over time tolerance with the appearance of hyperalgesia and allodynia, conditions which may affect patient compliance. These phenomena have been re-conducted to one of its metabolite, the 3-*O*-glucuronide (accounting in humans for 80% of the dose administered), which was found to be an effective neuro-excitatory and a potent activator of microglia, so resulting to be responsible of the development of both hyperalgesia and allodynia. Therefore, the inhibition of glucuronidation represents an interesting pharmacological target to achieve greater therapeutic efficacy by morphine and the synthesis of new active compounds useful in the pain control therapy is still in the limelight. In this context, we observed that codeine and some codeine derivatives (in particular the acetyl and pivaloyl esters) are able to inhibit the formation of morphine-3-*O*-glucuronide so, in continuation of the previous work, we projected new codeine derivatives as potential useful compounds in the modulation of morphine glucuronidation. In this paper, we report the optimization of the synthetic procedure to obtain codeine esters with hindered polycyclic carboxylic acids by using a suitable alcohol (allyl alcohol) with the same configuration of 6-OH function of the codeine skeleton. Together with the allyl ester derivatives of these acids also the 1-adamantaneacetic acid ester derivative of codeine (4), a new codeine derivative, was finally synthesized following the reported synthetic approach.

1. Introduction

Problems related to the use of opioids for pain therapy have recently been the subject of extensive research regarding both the optimization of the current therapeutic regimens and the development of new therapeutic strategies. Such research is needed as the percentages of patients requiring this kind of therapy are increasing and this represents one of the major health problems worldwide (Graziottin et al., 2011). Morphine is the widely used opioid in pain therapy associated with chronic and degenerative diseases. During therapy with opioids, and in particular with prolonged exposure to morphine, tolerance is observed over time with the appearance of hyperalgesia and allodynia phenomena, that are feelings of pain due to stimuli which in themselves should not be painful. Such manifestations, of course, reduce the effectiveness of the treatments and may affect patient compliance. Recent studies have shown that a morphine metabolite with a neuro-excitatory activity is thought to be responsible for the onset of these problems. Liver glucuronidation is the main metabolic process of Phase II which transforms morphine in two metabolites: morphine-3-*O*-glucuronide (M3G) and morphine-6-*O*-glucuronide (M6G), both of which are more polar than the parent compound and so could be easily excreted (Smith, 2009). These metabolites are still active and

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if the M6G is a potent μ opioid receptor agonist, so maintaining the analgesic action proper to morphine, the second one (M3G) has an opposed effect and resulted to be an effective neuro-excitatory compound. The latter, being a potent activator of microglia, resulted to be responsible of the development of both hyperalgesia and allodynia (Milne et al., 1996; Watkins et al., 2005; Komatsu et al., 2009; Lewis et al., 2010). In humans, M3G is the main product derived from the liver metabolism of administered morphine, representing 80% of the dose, while the M6G is produced for the remaining 20% (Antonilli et al., 2013a). Therefore, inhibition of glucuronidation represents an interesting pharmacological target to achieve greater therapeutic efficacy by morphine and, in this context, we observed that codeine and some codeine derivatives are able to inhibit the formation of M3G. The inhibitory action seems to be related to its phenanthrenic structure (Elovaara et al., 2007; Antonilli et al., 2013a), which appears to be the fundamental requirement for a structure capable of interacting with the mechanism of glucuronidation. Other important structural features appear to be the presence of a double bond between the C-7 and C-8 on the phenanthrenic nucleus, as its saturation in derivatives such as dihydrocodeine causes almost no effect on the inhibition of morphine glucuronidation. Conversely, the acylation of the C-6(OH) group with an acetyl or pivaloyl residue (Antonilli et al., 2013a) gave derivatives more active as inhibitors than the parent compound while the esters with longer acyl chains, i.e. lauroyl resulted to be inactive. Compared to unmodified codeine, the acetyl and pivaloyl ester derivatives showed an increase in inhibition of M3G formation. Since the inhibition of M3G formation may have a crucial role in the control of the development of hyperlagesia and allodynia, these two derivatives are recently being the subjects of a patent (Antonilli et al., 2013b). In continuation of our ongoing project about the semisynthesis and functionalizaton of natural products to obtain new compounds with enhanced bioactivity (Venditti et al., 2013; Franceschin et al., 2014; Salemme et al., 2016; Venditti et al., 2017; Ornano et al., 2018) and considering that the synthesis of new active compounds useful in the pain control therapy is still in the limelight, we projected the synthesis of new codeine derivatives as potentially effective compounds in the modulation of morphine glucuronidation. Since it has been observed that the presence of an ester functionalization at the 6-OH position of codeine resulted in more active compounds, we continued with this approach. Moreover, considering that between the acetyl and the pivaloyl derivatives, the latter resulted more active suggesting also the presence of a contribution to the observed activity due to the bulk of the substituent. Following these hypothesis, we projected the synthesis of codeine esters with hindered acidic derivatives. In this paper, we reported the optimization of the synthetic procedure to obtain codeine ester with hindered polycyclic carboxylic acids by several trials using camphanic, 1-adamantanecarboxylic and 1-adamantaneacetic acids and a suitable alcohol (allyl alcohol) with the same configuration of 6-OH function of the codeine skeleton. Together with the allyl ester derivatives with these acids (**1-3**) also the 1-adamantaneacetic acid ester derivative of codeine (**4**) was finally prepared.

2. Experimental

2.1. Chemicals

All the solvents were at RPE purity grade if not diversely specified and were purchased from Sigma Aldrich (Milan, Italy) as well as the deuterated solvents $CDCl_3$ (deuterochloroform), CD_3OD (deuteromethanol); methanol having RS purity grade was used for the identification of the compounds by Mass Spectrometry; silica gel TLCs (60 F_{254}) were from Merck (Darmstadt, Germany) while silica gel 60 (70-230 mesh ASTM) was bought from Fluka Analytical (St. Louis, MO, USA). (1R)-(+)-camphanic acid 98% [(1R)-3-oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid], 1-adamantanecarboxylic acid 99% and 1-adamantaneacetic acid 98% were from Sigma Aldrich.

2.2. Instruments

NMR spectra were recorded on a Varian Mercury 300 MHz instrument and/or on a Bruker AVANCE III 400 MHz instrument. The chemical shifts were expressed from TMS signal at 0 ppm.
MS spectra were conducted on a Q-TOF MICRO spectrometer (Waters, Manchester, UK) equipped with an ESI source operating in the negative and/or positive ion mode. The flow rate of the sample infusion was 10 μL/min with 100 acquisitions per spectrum. Data were analyzed using the MassLynx software developed by Waters.

2.3. Synthesis procedures

Test 1: Camphanic acid allyl ester (1) (Scheme 1): Camphanic acid (251.0 mg, 1.26×10^{-3} mol), allyl alcohol (0.089 mL) and DCC (262.0 mg) (in ratio 1:1:1) were poured in a two neck flask (previously dried in an oven) and provided with a $CaCl_2$ trap and one loading funnel with 5 mL of dry THF. After adding the THF the mixture was kept under magnetic stirring for 24 h at room temperature to avoid DCC decomposition (Hassner et al., 1978). TLCs (eluent $CHCl_3$) were used to monitor the undergoing of reaction process. To the crude reaction mixture, 2 mL of distilled water was added to quench the reaction and then the mixture was filtered. The flask was washed with diethyl ether (3 x 4 mL) and the solutions were gathered to the filtrate and poured in a separating funnel. 2 mL of H_2SO_4 (2.0 N) was added and after the separation of the two phases, the organic layer was collected. The extraction procedure was repeated three times using diethyl ether as organic solvent (20 mL, each). The ethereal solution was washed with a dilute aqueous solution of $NaHCO_3$ and then with Brine until neutrality to litmus paper. The organic phase, now containing also dicycloesylurea was filtered (under gravity) and the solution was dried on anhydrous

sodium sulfate. After filtration, the organic solvent was removed under vacuum (at 35 °C) obtaining 168.0 mg of a mixture of ester and free acid. The purification was conducted by column chromatography with silica gel (7.0 g) as stationary phase and chloroform as eluent. The assembly of fractions 6-7 contained camphanic acid allyl ester (1) (47.0 mg), yield 12.3%.
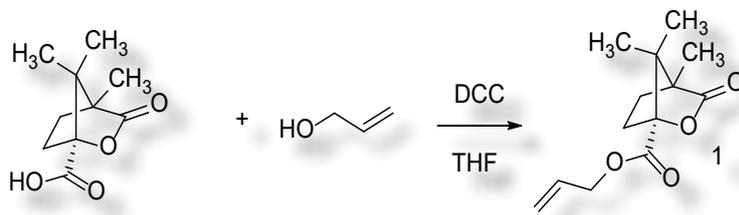
Scheme 1.

Camphanic acid allyl ester (1): ^{1}H-NMR (300 MHz, CDCl$_3$): δ: 5.91 (1H, ddd, J = 16.4, 11.0, 5.8 Hz, H-2'), 5.34 (1H, d, J = 17.2 Hz, Ha-3'), 5.25 (1H, d, J = 10.4 Hz, Hb-3'), 4.69 (2H, d, J = 5.8 Hz, H-1'), 2.41 (1H, ddd, J = 13.5, 10.7, 4.3 Hz, Ha-3), 2.07-1.83 (2H, m, Hb-3, Ha-4), 1.65 (1H, ddd, J = 13.4, 9.3, 4.2 Hz, Hb-4), 1.08 (3H, s, H-6), 1.03 (3H, s, H-7), 0.93 (3H, s, H-8). (Fig. 1) ^{13}C-NMR (75 MHz, CDCl$_3$): δ: 178.1 (C-1), 167.2 (C-9), 131.3 (C-2'), 119.4 (C-3'), 91.1 (C-2), 66.1 (C-1'), 54.8 (C-5), 54.2 (C-10), 30.7 (C-3), 29.0 (C-4), 16.74 (C-6), 16.69 (C-7), 9.7 (C-8) (Fig. 2). ESI-MS: m/z 261.12 [M+Na]$^+$; m/z 277.09 [M+K]$^+$.
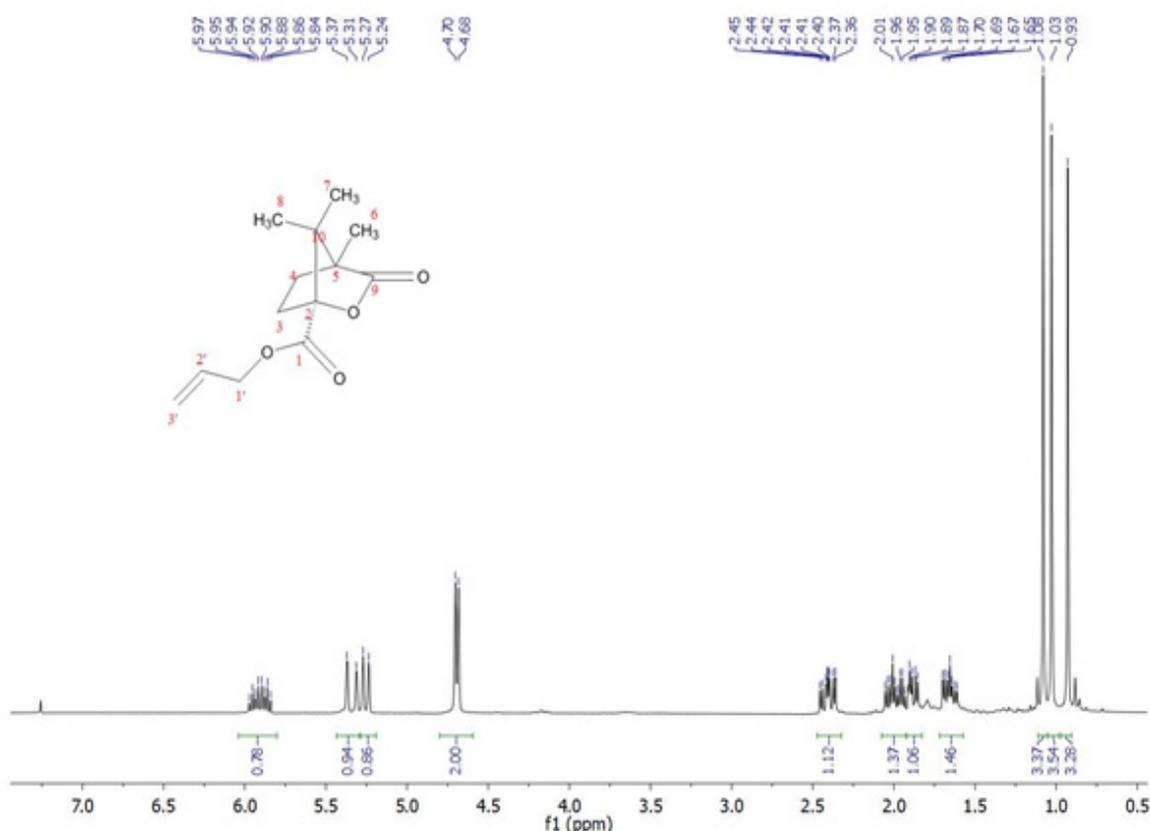
Fig. 1. ^{1}H-NMR of Camphanic acid allyl ester (1).

Test 2: 1-Adamantanecarboxylic acid allyl ester (2), (Scheme 2): the reaction between 1-adamantanecarboxylic acid (302.0 mg) and allyl alcohol (0.12 mL) was conducted in the presence of DCC (348.0 mg) (1:1:1) and THF (5 mL) as previously reported for camphanic acid with little modification. After 24 hours of reaction, the presence of free unreacted acid was conspicuous so an additional quantity of DCC (250.0 mg) was added to the mixture and the reaction was prolonged for 6 h, at r.t. (room temperature) and under continuous magnetic stirring. After the work-up of the crude reaction mixture, a mixture (124.5 mg) was collected, but by preliminary NMR analysis, the ester resulted in little amount (1:5 w/w in respect to unmodified acid).
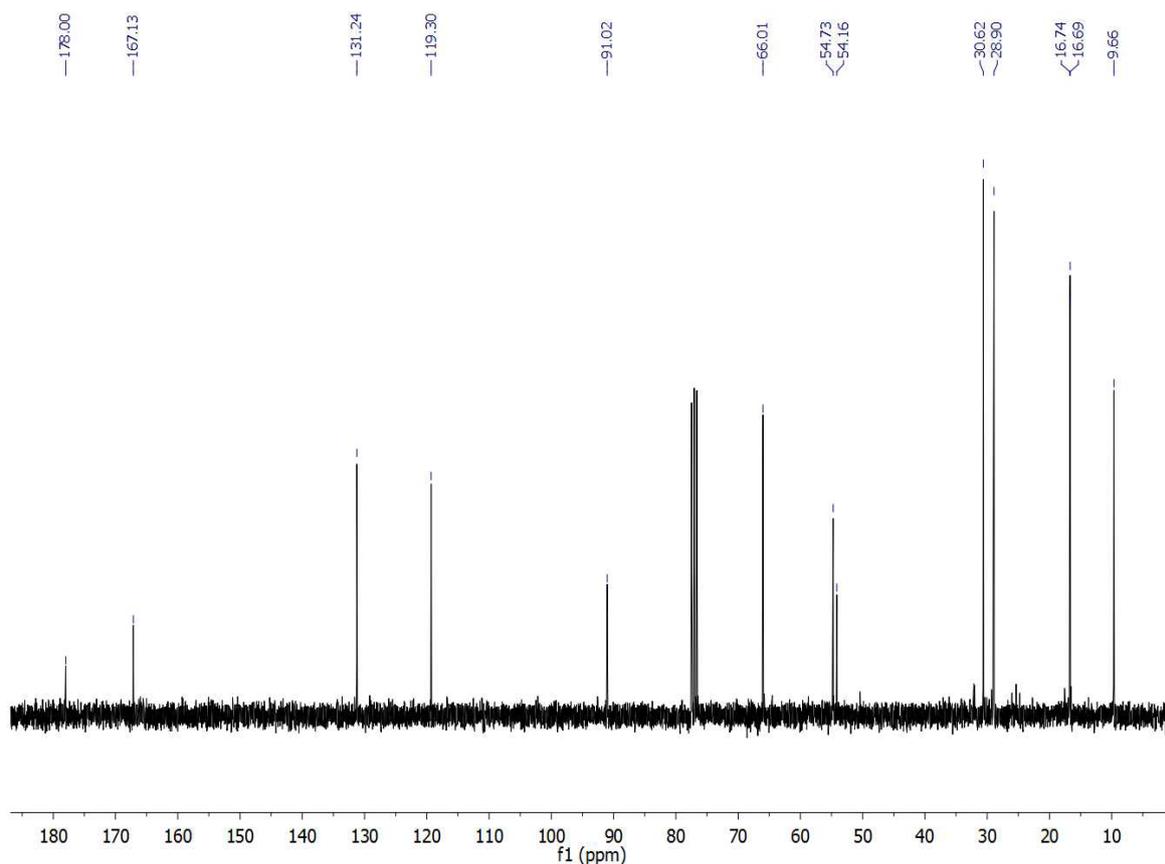
Fig. 2. ^{13}C-NMR of Camphanic acid allyl ester (**1**).

The reaction was modified by the use of a different coupling agent (EDC) and different ratios among 1-adamantanecarboxylic acid, ally alcohol and coupling agent.

Test 3: 1-Adamantanecarboxylic acid (300.0 mg), allyl alcohol (0.173 mL) and EDC (958.0 mg) in the presence of dry THF were reacted as previously reported for 24 h and obtaining 142.0 mg of a mixture, also in this case mainly composed of free unreacted acid.

Test 4: The synthesis conditions were further modified as reported in the Scheme 3. 1-Adamantanecarboxylic acid (307.0 mg), EDC (1.0870 g), DMAP (119.0 mg), allyl alcohol (0.175 mL) and dry CH_2Cl_2 (4.50 mL) were poured under magnetic stirring at r.t. in a flask provided with a moisture trap. After 5 h, the reaction was quenched with distilled water and treated with 2 mL of H_2SO_4 (2.0 N), neutralized with $NaHCO_3$ and transferred to a separating funnel. Dichloromethane (3 x 10 mL) was used as extracting solvent. The organic layers were collected, washed with brine and dried over anhydrous sodium sulfate. After removing the organic solvent under vacuum, 543.0 mg of crude materials were obtained and purified on silica gel (11.0 g) CC (ratio 1:25) using a gradient of *n*-hexane/ethyl acetate as eluting mixture, starting with 98:2 v/v (100 mL) to 95:5 v/v (100 mL). The product of interest (2) eluted with 95:5 mixture in fraction 31 (132.0 mg), yield 36%.
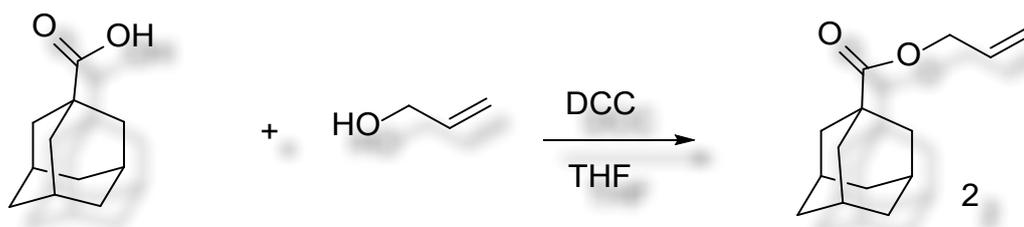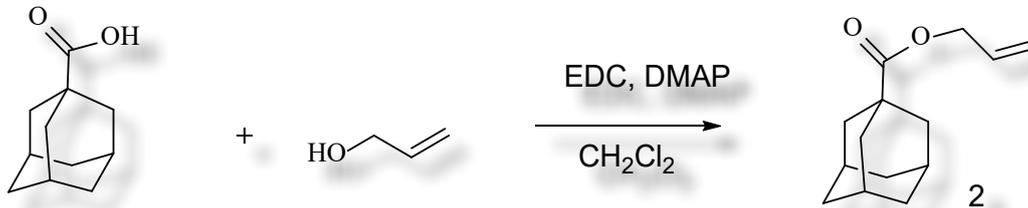

Scheme 2.

1-Adamantanecarboxylic acid allyl ester (2): ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.90 (1H, m, H-2'), 5.29 (1H, dd, J = 17.2, 1.6 Hz, Ha-3'), 5.20 (1H, dd, J = 10.5, 1.4 Hz, Hb-3'), 4.55 (2H, d, J = 5.4 Hz, H-1'), 2.01 (3H, br s, H-4; H-6; H-11), 1.90 (6H, br s, H-3; H-7; H-8), 1.71 (6H, br s, H-5; H-9; H-10) (Fig. 3).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 177.3 (C-1), 132.5 (C-2'), 117.3 (C-3'), 64.6 (C-1'), 40.7 (C-2), 38.8 (C-3; C-7; C-8), 36.5 (C-5; C-9; C-10), 27.9 (C-4; C-6; C11) (Fig. 4). ESI-MS: m/z 221.3 [M+H]$^+$; m/z 243.3 [M+Na]$^+$.
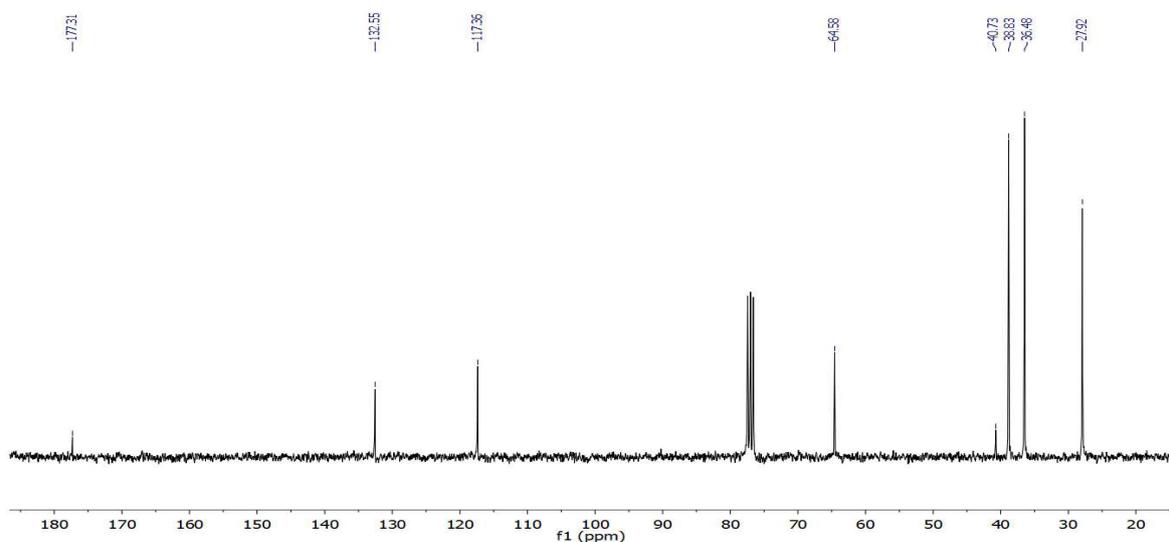

Scheme 3.

Test 5: 1-Adamantaneacetic acid allyl ester (3): 1-Adamantaneacetic acid (301.0 mg), EDC (1.015 g), DMAP (99.0 mg), allyl alcohol (160 μL), CH$_2$Cl$_2$ (4.50 mL) (Scheme 4) were reacted as previously reported and after work-up and chromatographic purification was recovered 15.0 mg of the pure compound (3).
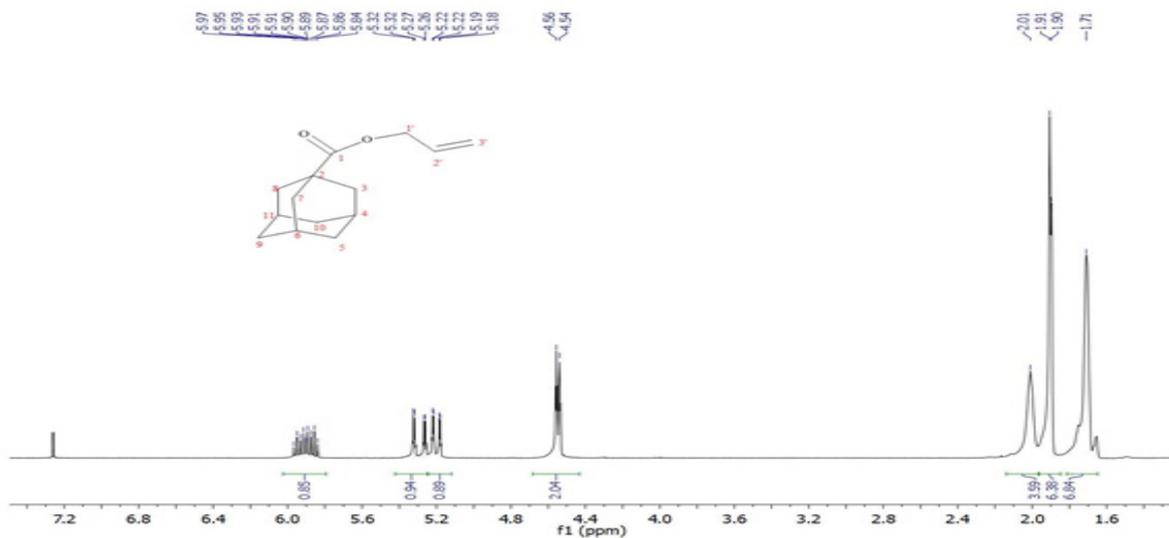

Fig. 3. ^{1}H-NMR of 1-adamantanecarboxylic acid allyl ester (2).

Fig. 4. ^{13}C-NMR of 1-adamantanecarboxylic acid allyl ester (2).

1-Adamantaneacetic acid allyl ester (3): ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 5.92 (1H, m, H-2'), 5.32 (1H, d, J = 17.2 Hz, Ha-3'), 5.23 (1H, d, J = 10.4 Hz, Hb-3'), 4.56 (2H, d, J = 5.7 Hz, H-1'), 2.10 (2H, br s, H-2), 1.97 (3H, br s, H-5; H-7; H-9), 1.66 (12H, m, H-4; H-6; H-8; H-10; H-11; H-12) (Fig. 5).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 171.4 (C-1), 132.4 (C-2'), 118.1 (C-3'), 64.7 (C-1'), 48.8 (C-2), 42.3 (C-4; C-11; C-12), 36.7 (C-6; C-8; C-10), 32.7 (C-5; C-7; C-9), 28.58 (C-3). ESI-MS: m/z 235.3 [M+H]$^+$; m/z 257.3 [M+Na]$^+$; m/z 491.5 [2M+Na]$^+$.
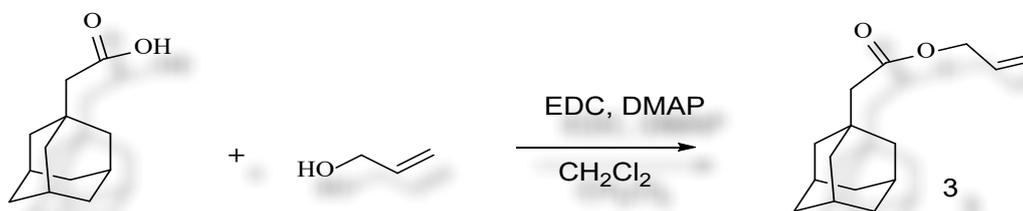
Scheme 4.

Synthesis of 6-O-[1-adamantaneacetoyl]-codeine (4), (Scheme 5): Codeine (20.0 mg), 1-adamantaneacetic acid (19.0 mg), EDC (48.0 mg), DMAP (46.0 mg), CH$_2$Cl$_2$ (1.0 mL), THF (2.0 mL) and dioxane (2.0 mL), all dry solvents, were stirred at r.t. in a 25 mL two neck flask provided with moisture trap (CaCl$_2$) for 5 h

(Scheme 5). After the work-up of the crude reaction mixture (220.1 mg) as previously reported and the chromatographic purification on silica gel (6.6 g) (column eluted with a mixture of chloroform/methanol 95:5 v/v), the pure codeine ester with adamantaneacetic acid (4) was obtained (4.0 mg), yield 12.6%.
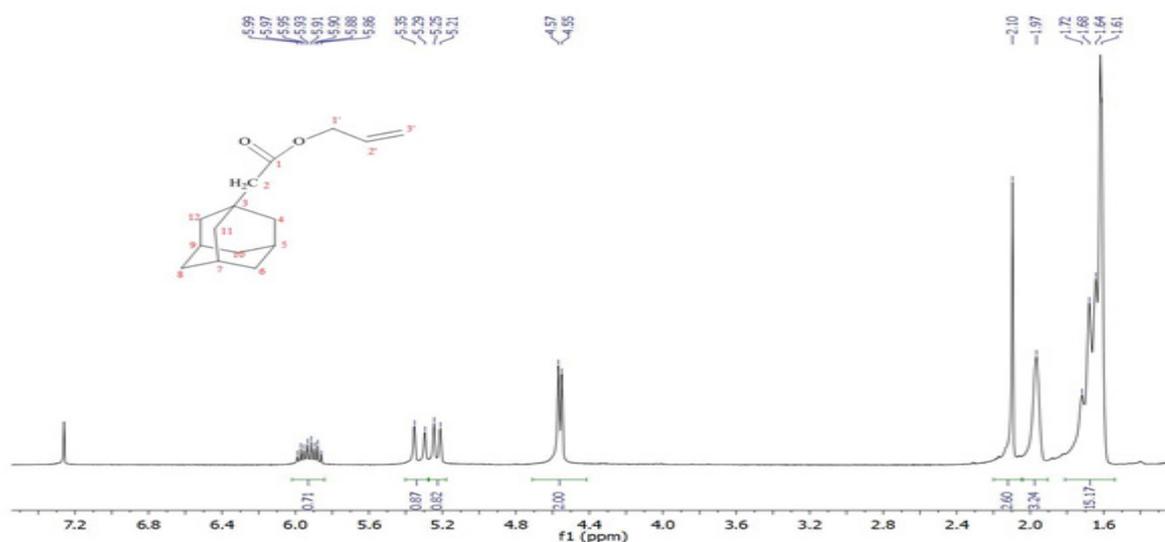
Fig. 5. ^{1}H NMR of 1-adamantaneacetic acid allyl ester (3).
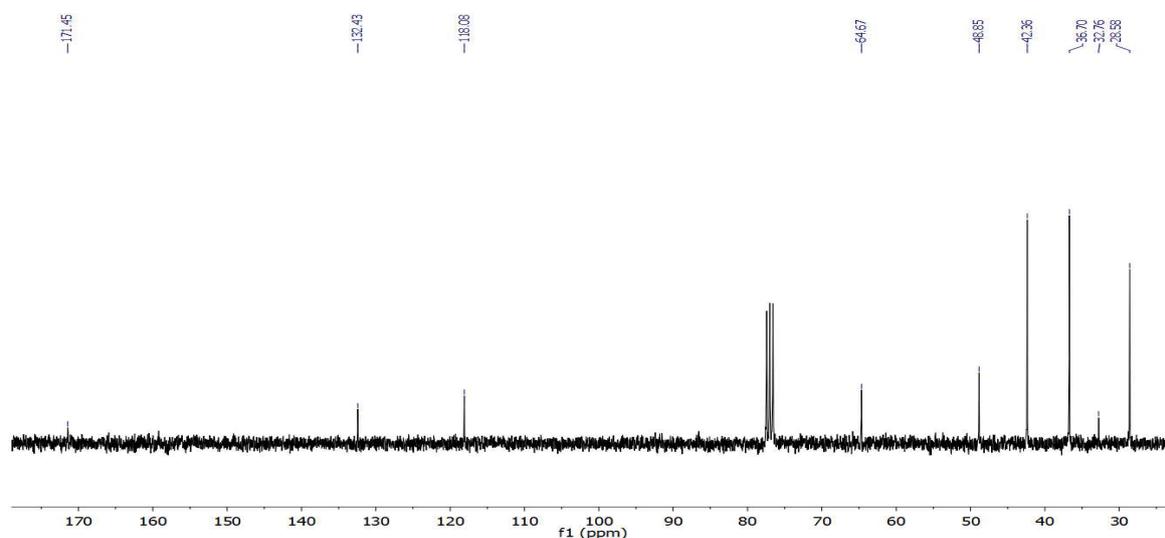
Fig. 6. ^{13}C NMR of 1-adamantaneacetic acid allyl ester (3).

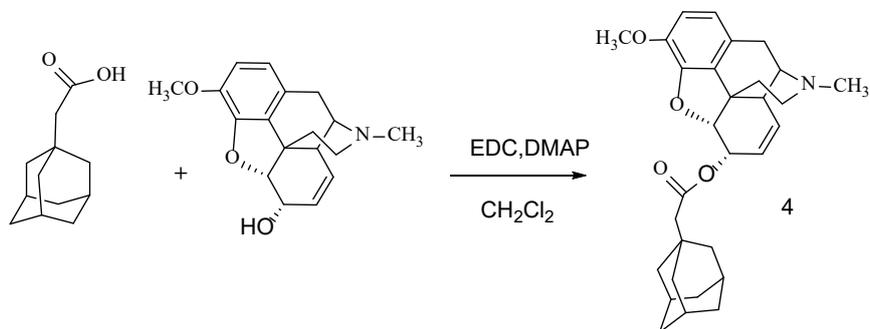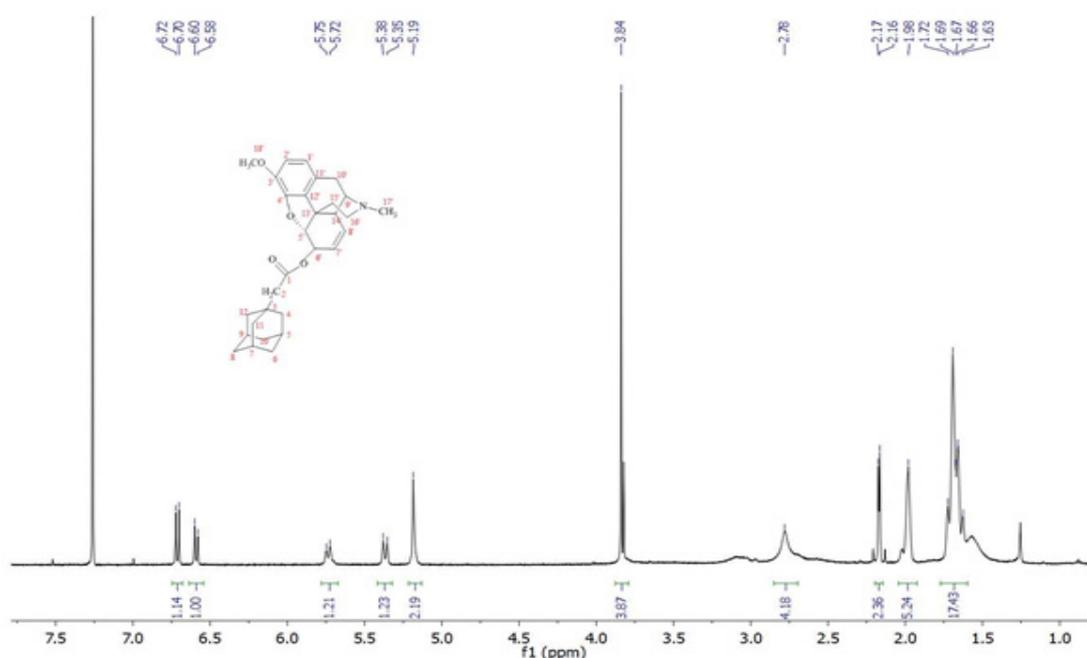6-*O*-[1-adamantaneacetoyl]-codeine (4): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.71 (1H, d, *J* = 8.4 Hz, H-1'), 6.59 (1H, d, *J* = 8.4 Hz, H-2'), 5.74 (1H, d, *J* = 9.8 Hz, H-7'), 5.37 (1H, d, *J* = 9.8 Hz, H-8'), 5.19 (2H, br s (overlapped), H-5'; H-6'), 3.84 (3H, s, CH$_3$O), 2.78 (2H, br signal, H-2), 2.17 (3H, s, H-17'), 1.98 (6H, br s (overlapped), H-4, H-11, H-12), 1.72-1.63 (9H, m overlapped signals, H-5, H-6, H-7, H-8, H-9, H-10) (Fig. 7). HRESI-MS: *m/z* 476.2789 [M+H]$^+$, for C$_{30}$H$_{37}$NO$_4$$^+$ (calc. 476.2795; Δm 1.2 ppm).

Scheme 5.

Fig. 7. ^{1}H NMR of 6-O-[1-adamantaneacetoyl]-codeine (4).

3. Results and Discussion

Codeine is included among the narcotic substances and is subjected to rigid legislation which provides for the use of a register on which all movements are reported. Therefore, it is necessary to verify and optimize the synthetic procedures of the ester before executing it directly on codeine.

The preliminary tests to optimize the reaction conditions were conducted using a simple alcohol (allyl alcohol) which reproduces the structural characteristics of the alcoholic function of codeine and with three polycyclic carboxylic acids with different steric hinderance, (1*R*)-(+)-camphanic acid, 1-adamantanecarboxylic acid and 1-adamantaneacetic acid.

All tests were carried out at room temperature to avoid the decomposition of the used coupling agent (Hassner et al., 1978). To perform the first three preliminary tests, the method of Angelova and co-workers (2005) was used, which employed dicyclohexylcarbodiimide (DCC) as coupling agent. Even if the formation of the ester product was observed, the yield was not equally satisfactory. For this reason, the DCC as coupling agent was replaced by EDC, also considering that EDC may form by-products which are easily eliminated by washing with acidic solutions (Gibson et al., 1994), but no significant improvements in terms of yields have been observed. Using DCC, the allyl ester of camphanic acid (**1**) was obtained. The proton spectrum of (**1**) is charaterized by a complex signal (ddd) at δ 5.91 due to the olefinic proton in C-2' and two sets of doubles at 5.34 and 5.25 ppm, signals assignable to the terminal olefine protons in C-3'; a doublet at 4.69 ppm due to the methylene protons in C1' was also observable and this signal coupled with the proton in C-2'; a complex signal at δ 2.41 (triple doublet like) is assignable to proton in

3*a*-position of camphanic acid; a multiplet was observed in the range δ 2.07-1.83 due to the overlapping of protons in 3*b* and 4*a* positions of camphane moiety; the second signal of the AB system relative to the proton in 4*b*-position resulted placed at δ 1.65; lastly, three singlets each integrating for three protons were present at 1.08, 1.03 and 0.93 ppm and assigned to the three methyl groups linked in C-6, C-7 and C-8 positions, respectively. In the carbon spectrum, 13 resonances were present. These were assigned to the ester carboxyl (178.1 ppm) (C-1), the lactone carboxyl in C-9 (167.2 ppm), the olefinic methyne of allyll alcohol (131.3 ppm) (C-2'), the olefinic methylene of allyl alcohol (119.4 ppm) in C-3', an oxygenated quaternary carbon in α-position to the ester function (C-2) (91.1 ppm); one oxygenated methylene (66.1) assigned to C-1'; a quaternary carbon (54.8 ppm) (C-5) in α-position in respect to the lactone function, another quaternary carbon (54.2 ppm) assigned to C-10; two methylene belonging to the ring system at (30.7 ppm and 29.0 ppm) assigned to C-3 and C-4, respectively; an lastly the three signals of methyls at 16.7, 16.6 and 9.7 ppm for C-6, C-7 and C-8, respectively. To increase the yield of the reaction, it was decided to follow the method developed by Leonelli and collaborators (2005) which envisages the use of EDC and 4-dimethylaminopyridine (DMAP), a nucleophilic catalyst that makes the reaction significantly faster especially in the case of acylation reactions (Höfle et al., 1978). With this modification to the synthetic procedure, the yields were higher than those obtained in the previous tests. The two allyl esters of 1-adamantanecarboxylic acid (**2**) and of 1-adamantaneacetic acid (**3**) were obtained applying this modified procedure.

The proton spectrum of (**2**) showed the complete set of signals due to the allyl substituents at 5.90, 5.29, 5.20 and 4.55 ppm; the resonance at 2.01 ppm was due to equivalent protons in C-4, C-6, C-11; at 1.90 ppm resonate the protons in C-3, C-7 and C-8 positions; while the remaining protons in C-5, C-9, C-10 resonate at 1.71 ppm. The carbon spectrum showed only seven resonances due to the symmetry of the adamantane skeleton. In particular, one quaternary carbon was present related to the carboxyl function at δ 177.3 (C-1); the complete set of signals of the allyl group at 132.5 (C-2'), 117.3 (C-3') and 64.6 (C-1'); the signal at 40.7 ppm is related to the methylene in α-position to the carboxyl (C-2); the signal at 38.8 ppm is due to the resonances of the symmetric carbons C-3, C-7, C-8; the signal at 36.5 ppm to carbons at C-5, C-9, C-10; and lastly 27.9 ppm belongs to methylenes in C-4, C-6, C-11. The proton spectrum of (**3**) showed the olefinic signals of the allylic moiety at 5.92, 5.32, 5.23 and 4.56 ppm, while at δ 2.10 a broad singlet is due to the methylene in C-2 position and at 1.97 ppm an overlapped signal the methylenes in C-5, C-7, C-9 positions of the adamantane skeleton. At 1.66 ppm, the signals of the remaining protons were present in C-4, C-6, C-8, C-10, C-11 and C-12 positions of the adamantane moiety. In the carbon spectrum, only nine resonances were observable because several nuclei of the adamantane skeleton gave one only signal due to the symmetry

of the structure. Among these, the carboxyl of ester function resonates at 171.4 ppm (C-1); the signals at 132.4, 118.1 and 64.7 belong to C-2', C-3' and C-1' of the allyl substituent, respectively; the quaternary carbon in α-position to the carboxyl in C-2 resonates at 48.8 ppm; the signal at 42.3 was assigned to the methylenes in C-4, and C-11; the signal at 36.7 ppm was assigned to the other methylenes in C-6, C-8 and C10; lastly, at 32.7 ppm was recognized the signal due to C-5, C-7 and C-9, while at 28.58 ppm was present the resonance of the quaternary carbon in C-3 position. Since the contemporaneous use of EDC and DMAP give the better results in term of yields, these conditions have been chosen to perform the esterification reaction with codeine. The codeine ester with 1-adamantaneacetic acid (**4**) obtained by applying the reported scheme is a new codeine derivative, not previously synthesized and described before the present study. The proton spectrum of compound (**4**) showed the characteristic signals of the codeine nucleus: two aromatic protons at 6.71 and 6.59 ppm, coupled one with the other, resulted splitted in two doublets characterized with a coupling constant (8.4 Hz) in agreement with those of two *ortho*-oriented protons (H-1', H-2'); two olefinic protons at 5.70 and 5.37 splitted in two doublets (*J* 9.8 Hz) and consistent with a *cis*-configuration of the 7',8'-double bond; one broad singlet at 5.19 ppm due to the overlapping of protons in C-5' and C-6' positions; one singlet integrating for three protons at 3.84 ppm is due to the methoxy function in C-18'; the broad signal at 2.78 ppm may be assigned to H-2; the singlet at 2.17 ppm is relative to protons of the methyl linked to nitrogen and lastly the broad signal at 1.98 is relative to the symmetric H-4, H-11, H-12 and those partially overlapped in the range 1.72-1.63 ppm are due to the remaining protons in (H-5,H-10) of the adamantane moiety. All the structures of the synthesized compounds were confirmed by means of HR-ESI-MS analysis.

4. Concluding remarks

A synthetic procedure to obtain allylic esters with sterically hindered acids has been developed and optimized with the ultimate purpose of functionalizing the codeine nucleus. Preliminary tests, conducted on a model alcohol, such as allyl alcohol, have allowed to identify the best procedure to be used for condensation with sterically hindered polycyclic carboxylic acids. The correct choice of the most suitable coupling agent allowed to obtain the desired products under mild reactions conditions which also allowed easily removal of the secondary products. In this regard, the coupling agent originally used (DCC) was replaced with a more water-soluble compound (EDC) with the contemporary use of a catalyzer such as DMAP. This permitted to optimize the synthetic procedure before working on codeine, and finally achieving the target results. Further developments of this method can lead to increased reaction yield, for example by improving reaction conditions or by operating on reaction times, so to obtain sufficient

materials to perform the biological activity tests. On the basis of the previous results in bioactivity tests conducted on acylated codeine derivatives, the highest inhibitory action was observed for the 6-*O*-pivaloyl derivative, therefore the presence of a short and sterically hindered chain resulted an important structural feature for activity. This structural motif has been retained in the adamantane derivatives which, from their side, offer also the rigidity to the structure together with the steric hindrance. The availability of morphine glucuronidation inhibitors as common drugs could be of primary importance for a major effectiveness of pain therapy in the future, since it has been demonstrated that the 3-*O*-morphine glucuronide (M3G) is the major metabolite formed from morphine in humans. This metabolite has neuroeccitatory properties, being a potent microglial activator, and has no sedative/analgesic properties because showed no affinity toward the μ opioid receptors. Therefore, the availability of compounds that are effective in modulating the morphine metabolism, such as could be the derivative (**4**), may have a primary role in the treatment of neuropathic pain and in all the clinical cases in which the pharmacological pain control is necessary. By the co-administration of glucuronidation inhibitors, it could be also possible to reduce the dosages of morphine. In fact, its clearance could be reduced by the inhibition of a key step of its metabolism which finally led to the excretion of the modified drug, thus obtaining the elimination of the pharmacological effect. The possibility of lowering the administered dosed of morphine in the co-treatment with glucuronidation inhibitors could be possible also because only the M3G formation seems to be strongly inhibited, while is not so for the M6G derivative (Antonilli et al., 2013a, 2013b). The latter is a potent μ opioid receptor agonist (6 times stronger than morphine), thus retaining the analgesic properties of the parent compound morphine and still resulting an effective analgesic.

Conflict of Interest

The authors declare that there is no conflict of interest.

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