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# New morpholine analogues of phencyclidine: Chemical synthesis and pain perception in rats

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ABSTRACT

Phencyclidine (PCP, I) and most its derivatives have demonstrated some pharmacological effects. Accordingly, in this study, the new methoxy (III) and hydroxy-methyl (IV) morpholine PCP derivatives were synthesized. The acute and chronic pain activities of these drugs (III, IV) were investigated by tail immersion and formalin tests on rats and the results were compared with those in PCP, PCM (PCP-morpholine, II), and methyl-PCM (V). Findings indicated that **III** (6 mg/kg, i.p.) generates more analgesic effects in tail immersion test in comparison with **I** and **II** in 20, 40, 45 and 55 min post-injection. These effects were observed in 10, 20, 40, 45 and 50 min after the application of **IV** (at the same dosage). This analgesic effect was markedly seen in 20, 40, 45 and 50 min after compound **IV**'s application in comparison with the drugs (**I–V**). In formalin test analysis, the acute chemical pain (Phase I) could not be affected by any drugs (**I–V**) while chronic formalin pain would be diminished by these new synthesized drugs (**III** and **IV**), especially in late Phase II, compared to **I** and **II** at the dosage of 6 mg/kg. It is, therefore, concluded that these new synthesized PCP derivates including methoxy-PCM (**III**) and hydroxy-methyl-PCM (**IV**) could substantially and respectively diminish acute thermal and chronic chemical pains.

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## 1. Introduction

1-(1-phenylcyclohexyl) piperidine (Phencyclidine, CAS 77-10-1, PCP, **I**) is a synthetic drug with outstanding physiological properties. It is initially synthesized in the early 1950 s as a potential surgical anesthetic. PCP allows patients to enter into a trance-like state in which the 'perception' of pain could be separated from the 'sensation' of pain, a state that has been termed 'dissociative anesthesia' (Erard et al., 1980). It is also a non-competitive *N*-methyl-D-asparate (NMDA) receptor antagonist, which has been demonstrated to produce psychotomimetic effects on humans, but it is a widely abused drug (Mori et al., 2001). Phencyclidine and its derivatives influence the central nervous system and display analgesic, stimulant, depressant, and hallucinogenic effects due to the existence of specific binding sites in the brain (Al-deeb, 1994; Ahmadi and Mahmoudi, 2006).

PCP binds into the *N*-methyl-D-asparate (NMDA) receptor complex and blocks NMDA-mediated gating of the calcium channel conductance (Kapur and Seeman, 2002; Olney et al., 1991). They are classified with many behavioral effects in common with other phencyclidine-like drugs including anaesthetics, antinociceptives, psychotomimetics, anticonvulsants, neuroprotectives and amnesic drugs concern to non-competitive, 'open channel blockers' of the NMDA receptor (Honey et al., 1985). However, different receptors in the central nervous system are involved in the modulation of behavioral effect of PCP and its analogues.

Many PCP derivatives (with changes in substitution on the molecule) have been synthesized and their pharmacological activities have been tested in recent years (Al-deeb, 1996; Ogunbadeniyi and Adejare, 2002; Ahmadi and Mahmoudi, 2005). 1-[1-[2-methoxyphenyl][cyclohexyl] morpholine (methoxy-PCM, **III**) and 1-[1-[4-hydroxy-2-methylphenyl] [cyclohexyl] morpholine, (hydroxy-methyl-PCM, **IV**) as new analogues of **I**, have been synthesized in this study. Methoxy and hydroxyl-methyl groups were added to the aromatic ring and morpholine group instead of the piperidine ring of the molecule to examine analgesic effects on rats using the tail immersion (as a model of acute thermal pain) and the formalin (as a model of acute chemical and chronic pain) tests. The results were compared with PCP and PCM (1-[1-phenylcyclohexyl] morpholine, CAS 2201-40-3, PCP-morpholine, **II**) and methyl-PCM (1-[1-[4-methylphenyl][cyclohexyl] morpholine, **V**) (Ahmadi et al., 2010; Ahmadi et al., 2011).

As it was revealed in previous works (Ahmadi et al., 2009; Ahmadi et al., 2010) with this family of compounds, the incorporation of methyl and methoxy groups to the aromatic ring of the molecule would generate pronounced effects on electron distribution and dipole moments because of their high electron donating characters (Johnson et al., 1981). The same have been applied to the incorporation of

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morpholine, with many pharmacological behaviors (Beckett and Kourounakis, 1976; Chen et al., 2003), and analgesic properties (Beckett and Kourounakis, 1976). In addition, the hydroxyl group with high hydrophilic, polarity, and solubility properties (Shebley et al., 2006) may produce more analgesic effects in this family. Also, to increase the low potency (Soine, 1986; Budd, 1981) of PCM, compared to PCP, these changes are applied to the PCM molecule in anticipation of producing the pronounced effects on the activity of the new synthesized drugs (**III** and **IV**) in the current study.

## 2. Materials and method

### 2.1. General

Cyclohexanone, piperidine, bromo benzene, magnesium turning, diethyl ether, 4-bromo toluene, morpholine, 2-bromo anisole, 4-chloro-3-methyl phenol and all other chemicals were purchased from Merck Chemical Co. (Darmstadt, Germany). Later, the melting points (uncorrected) were determined using a digital Electrothermal melting point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded on a Thermo Nicolet FT-IR (model Nexus-870, Nicolet Instrument Corp., Madison, Wisconsin, USA) spectrometer. Mass spectra were recorded on an Agilent Technology-5973 Mass Selective Detector (MSD) spectrometer (Wilmington, USA). Column chromatographic separations were performed over Acros silica gel (No. 7631-86-9 particle size 35–70 micrometer, Geel, Belgium). Adult female rats (at Pasteur's Institute, Tehran, Iran), weighing 250–300 g were used for the pharmacological testing.

### 2.2. Preparations (Schemes 1–3)

#### 2.2.1. 1-Piperidinocyclohexanecarbonitrile, PCC (1)

This compound was prepared in an organic solvent based on a published method (Geneste et al., 1980) from 4-piperidinol, cyclohexanone and KCN with a yield of 77% (m.p: 113–114 °C), IR: 2222 $cm^{1-}$, $^{C\equiv N}$, str.

#### 2.2.2. 1-Morpholinocyclohexanecarbonitrile, MCC (2)

This compound was prepared according to a published method (Abdol-Rahman et al., 1975; Geneste et al., 1980) from morpholine, cyclohexanone and KCN with a yield of 81.5% (m.p: 41–43 °C), IR: 2220 $cm^{1-}$, $^{C\equiv N}$, str.

#### 2.2.3. 1-[1-phenylcyclohexyl] piperidine (PCP) (I)

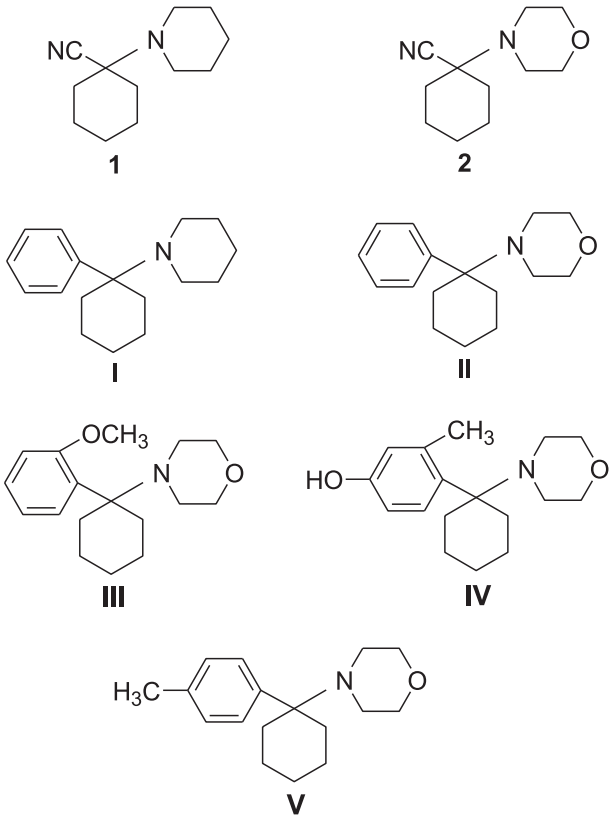
This compound was prepared in a 58% yield based on a published method (Maddox et al., 1965) from adding a solution of 1-piperidinocyclohexanecarbonitrile (**1**) in an organic solvent to a refluxing solution of phenyl magnesium bromide (prepared from 79 g bromobenzene and 12.3 g of Mg in 200 ml of dry ether). The hydrochloride salt of **I** (m.p. 233–234 °C) was prepared using 2-propanol and HCl, and it was recrystallized from 2-propanol.

#### 2.2.4. 1-[1-phenylcyclohexyl] morpholine (PCM) (II)

This compound was prepared in a 70.6% yield based on a published method (Maddox et al., 1965) from adding a solution of 1-morpholinocyclohexanecarbonitrile (**2**) in an organic solvent to a refluxing solution of phenyl magnesium bromide (prepared from 7.85 bromobenzene and 1.22 g of Mg in 20 ml of dry ether). The hydrochloride salt of **II** (m.p. 187–188 °C) was prepared using diethyl ether and HCl, and it was recrystallized from 2-propanol.

#### 2.2.5. 1-[1-[4-methylphenyl][cyclohexyl] Morpholine (V)

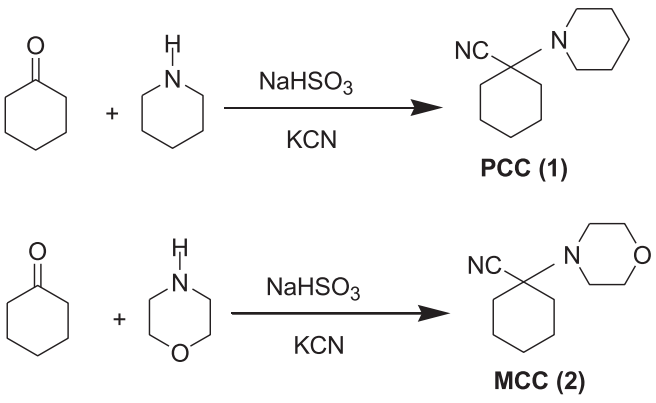
This compound was prepared in a 68.7% yield based on a published method (Ahmadi et al., 2010) from adding a solution of 1-morpholinocyclohexanecarbonitrile (**2**) in an organic solvent to a refluxing solution of 4-tolyl magnesium bromide (prepared from 8.55 g 4-bromotoluene and 1.22 g of Mg in 20 ml of dry ether). The hydrochloride salt of **I** (m.p. 183–184 °C) was prepared using diethyl ether and HCl, and it was recrystallized from 2-propanol.



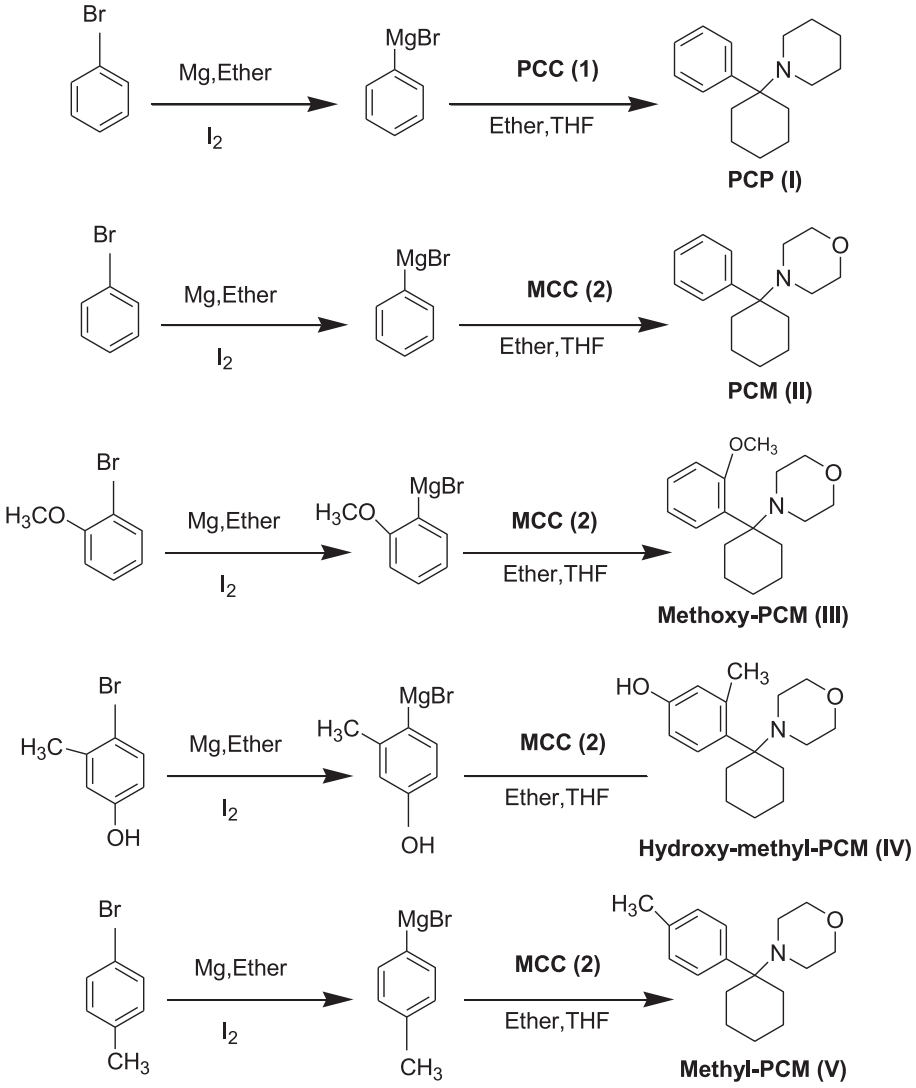

**Scheme 1.** Structure formulas of PCP (**I**), PCM (**II**), methoxy-PCM (**III**), hydroxy-methyl-PCM (**IV**), methyl-PCM (**V**) and carbonitrile intermediates **1** and **2**.

#### 2.2.6. 1-[1-[2-methoxylphenyl][cyclohexyl] morpholine (methoxy-PCM) (III)

A solution, containing 3.84 g (0.02 mol) of nitrile compound (**MCC**, **2**) in the mixture of dry diethyl ether and THF (1:1), was added to a refluxing solution of 2-anisol magnesium bromide (Grignard reagent), which was prepared from 9.35 g of 2-bromo anisole and 1.22 g of Mg in 20 ml of dry ether. It was refluxed for 10 additional hours and was left overnight at ambient temperature (25 °C) and was subsequently poured into ice-$NH_4Cl$. The organic layer was separated and washed with water and the base was neutralized with 10% of




**Scheme 2.** Synthesis of intermediates **1** and **2**.




**Scheme 3.** Synthesis of target compounds **I–V**.

$H_2SO_4$, washed with 20% of NaOH, reextracted with *n*-hexane, and it was dried and concentrated. The pale solid compound was obtained, which was passed through a silica gel column using ethyl acetate-hexane (95:5) as the eluent to afford 3.9 g of **III** (41% yield).

The hydrochloride salt of **III** (m.p. 167–169 °C) was prepared using diethyl ether and HCl, and it was recrystallized from 2-propanol.

IR (KBr): *2932, 2852, 1596, 1491, 1455, 1263, 1240, 1118, 804 cm$^{-1}$.*

$^1$H N.M.R. ($CDCl_3$) (p.p.m.): *1.2–1.92 (10 H, m), 2.33–2.6 (4 H, m), 3.62–3.65 (4 H, m),3.79 (3 H, s), 6.8–7.4 (4 H, m).*

$^{13}$C N.M.R. (CDCl3) (p.p.m.): *25.7, 26, 32.6, 51.3, 56.1, 67.3, 75.4, 112, 120.7, 126.9, 127.5, 134.5, 161.2.*

MS: *m/z* (regulatory intensity): 275 (80).

*2.2.7. 1-[1-[4-Hydroxy-2-methylphenyl][cyclohexyl] morpholine (hydroxy-methyl –PCM) (IV)*

A solution, containing 3.84 g (0.02 mol) of nitrile compound (**MCC**, **2**) in the mixture of dry diethyl ether and THF (1:1), was added to a refluxing solution of 4-hydroxy-2-methylphenyl magnesium chloride (Grignard reagent) which was prepared from 10.70 g of 4-chloro-3-methyl phenol and 1.22 g of Mg in 20 ml of dry ether and it was refluxed for 15 additional hours. It was left overnight at ambient temperature (25 °C) and was then poured into ice-$NH_4Cl$. The organic layer was separated and washed with water and the base was neutralized with 10% of $H_2SO_4$, washed with 20% of NaOH, reextracted with *n*-hexane, and it was dried and concentrated. The pale solid compound was obtained, which was passed through a silica gel column using ethyl acetate-hexane (95:5) as the eluent to afford 1.3 g (38% yield) of **IV** (m.p. 38-39.3).

The hydrochloride salt of **IV** (m.p. 181–182 °C) was prepared using diethyl ether and HCl, and it was recrystallized from 2-propanol.

IR (KBr): *3377, 2937, 2861,2823, 1580, 1455, 1276, 1119, 1034, 802 cm$^{-1}$.*

$^1$H N.M.R. ($CDCl_3$) (p.p.m.): *1.2–1.98 (10 H, m), 2.1–2.5 (4 H, m), 2.6 (3 H, s), 3.70–3.73 (4 H, m), 5.78 (1 H, s), 6.9–7.66 (4 H, m).*

$^{13}$C N.M.R. (CDCl3) (p.p.m.): *19.7, 25.7, 26, 32.6, 51.3, 67.3, 78.8, 112.6, 117.2, 127.8, 131.7, 135.7, 154.1.*

MS: *m/z* (regulatory intensity): 275 (11).

*2.3. Pharmacological methods*

Adult female rats (at Pasteur's Institute, Tehran), weighing 250–300 g at the beginning of the experiment were randomly housed. There were three to four of them per cage in a temperature-controlled colony room under light/dark cycles. The animals were given free

access to water and standard laboratory rat chow (supplied by Pars Company, Tehran, Iran). All behavioral experiments were carried out between 11 a.m. and 4 p.m. under normal room light and at the 25 °C temperature. All animals were injected by an investigator and were evaluated by another. The study was carried out in accordance with the guidelines set forth in the Guide for the 'Care and Use of Laboratory Animals' (NIH) and those of the 'Research Council of Shahed University of Medical Sciences' (Tehran, Iran).

*2.3.1. Tail immersion test*

The acute thermal pain was modeled by the tail immersion test (Ramabadran et al., 1989; Molina et al., 1994). Thirty minutes after an i.p. injection of drugs, (PCP, PCM, methyl-PCM, methoxy-PCM and hydroxy-methy-PCM, 6 mg/kg; dissolved in saline), the rats ($n=12$ in each group) were housed in an animal restrainer (in control group saline as vehicle were applied). Then, the terminal 5 cm of their tails were first submerged into the water temperature room (22~24 °C) to check the aversion to water and were then immersed into the 54 °C water. The reaction time between immersing the tail and its removal from heated water was measured. Cut-off latency in 15 s was employed to avoid damaging the tail (Hamura et al., 2000).

*2.3.2. Formalin test*

The formalin test has been introduced by (Dubuisson and Dennis (1977). In this test, the formaldehyde solution (50 μl, 2.5%) was injected subcutaneously into the plantar surface of the hind paw. Then, the animal was placed in a Plexiglas chamber ($30\times30\times30$ cm$^3$), with a mirror placed at the 45° angle underneath for accurate observation. In the treatment groups, the drugs (PCP, PCM, methyl-PCM, methoxy-PCM and hydroxy-methy-PCM, 6 mg/kg; dissolved in saline) were administered intraperitoneally 30 min prior to the formaldehyde injection (in control group saline as vehicle were applied). Before the experiment, all animals were brought to the test chamber five times at 5-min intervals in order for them to be adapted to the environment. The behavioral pain reactions, due to formalin injection, were detected and recorded for 1 h. The first 15 min after formalin injection is known as the early (I) or acute chemical phase, and the period between 15 and 60 min is known as the second (II) or the chronic phase. However, the chronic phase can be divided into the initial (15–40 min) and the late (40–60 min) periods.

## 3. Results

### 3.1. Chemistry

Phencyclidine, 1-[1-phenylcyclohexyl] morpholine, 1-[1-[2-methoxylphenyl] [cyclohexyl] morpholine, 1-[1-[4-hydroxy-2-methylphenyl][cyclohexyl] morpholine, and 1-[1-[4-methylphenyl] [cyclohexyl] morpholine (**I–V)** were synthesized by the reaction of substituted Grignard reagent and carbonitrile compounds. The addition of methyl and methoxy groups to the aromatic ring (having high electron donating, electron distribution, and dipole moments characters) and hydroxyl group (with strong hydrophilic, polarity, and solubility properties) introduced more analgesic effects to this family (Johnson et al., 1981; Al-deeb, 1994; Ahmadi et al., 2009). In addition, the incorporation of morpholine group, with substantial pharmacological and analgesic properties (Rekka et al., 1990; Chen et al., 2003) of its derivatives, is induced to have pronounced effects on our new synthesized [**III** and **IV**] drugs' activity. The known procedures with appropriate modifications were applied in the synthesis of compounds **I**, **II**, **V**, **1**, and **2 (**Maddox et al., 1965; Abdol-Rahman et al., 1975; Geneste et al., 1980).

Bromobenzene and its methoxy (**III**), hydroxyl-methyl (**IV**), and methyl (**V**) derivatives were reacted with magnesium to form Grignard reagents which were then reacted with piperinocyclohexanecarbonitrile (**PCC, 1**) and morpholinocyclohexanecarbonitrile (**MCC, 2**) to form the desired compounds. The reaction between Grignard reagents and carbonitriles was slow and incomplete. Therefore, to overcome this limitation, molar ratio of Grignard reagents to carbonitriles was increased. This higher ratio could also help the reaction between Mg and hydroxyl substituted phenyl (**IV**) to form the Grignard reagent, without protecting hydroxyl group by trimethylchlorosilane, which has been applied previously (Itzhak et al., 1981). Even then, still significant quantities of unreacted carbonitrile were present in the reaction products and the yield was low. Long reaction times were then resorted, but these alternatives caused problems such as the formation of side products. The mechanism of the reaction seems to explain the formation copious amounts of side products. Nitrile, which is an efficient leaving group, could be easily removed from the quaternary carbon of the carbonitrile, particularly given the effects of neighboring nitrogen on stabilizing resulting tertiary carbocation. The $S_N1$ attack of the Grignard reagent on the carbocation is complicated by the neighboring piperidine and morpholine, which can form an enamine or imine. The reactivity of these groups could contribute significantly to the formation of side products observed (Ahmadi et al., 2009).

Spectroscopic data (IR, $^1$H and $^{13}$C NMR, mass) confirmed the structure of the compound **III** and **IV**. The melting points of the known compounds also confirmed their identity. The purity of each compound was checked by TLC using ethyl acetate-hexane as the eluent.

### 3.2. Pharmacology

*3.2.1. General consideration*

Mortality (number of death), morbidity (defined as any abnormal condition or behavior due to a disorder), irritability (a condition of aggressiveness or increased response on handling) and other related abnormal states have not been observed in the experimental animals. However, the motor coordination index (measured by Rota-rod apparatus, Harvard, UK) did not indicate any significant difference among the treated rats.

*3.2.2. The analgesic activity of PCP (I), PCM (II), methoxy-pcm (III), hydroxy-methyl-PCM (IV) and methyl-PCM (V) hydrochloride with tail immersion test*

The intraperitoneal injection of PCP (**I**), PCM (**II**), methoxy-PCM (**III**), hydroxy-methyl-PCM (**IV**) and methyl-PCM (**V**) with the dosage of 6 mg/kg generated analgesic effects in the tail immersion test. The results indicated that **III** can generate more analgesic effects in the tail immersion test (as a model of acute thermal pain) in comparison with PCP and PCM, especially in 20, 40, 45 and 55 min after the drug injection (Fig. 1). These effects were seen 10, 20, 40, 45 and 50 min after the application of hydroxy-methyl-PCM (**IV**, with the

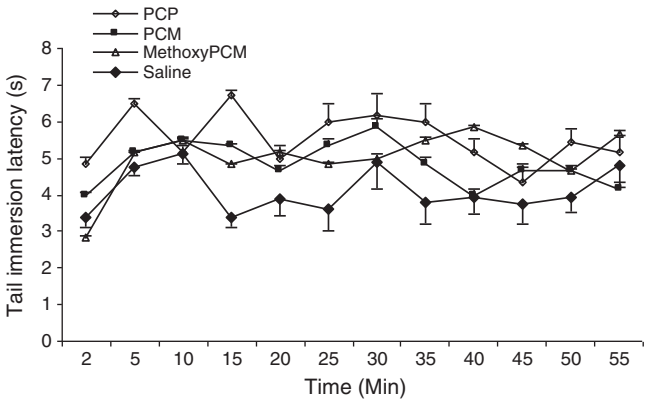



**Fig. 1.** Mean tail immersion test (s) in animals receiving PCP (**I**), PCM (**II**) and Methoxy-PCM (**III**) hydrochloride. The bars in each line represent mean ± SEM of tail withdrawal latency (s) in 12 animals.

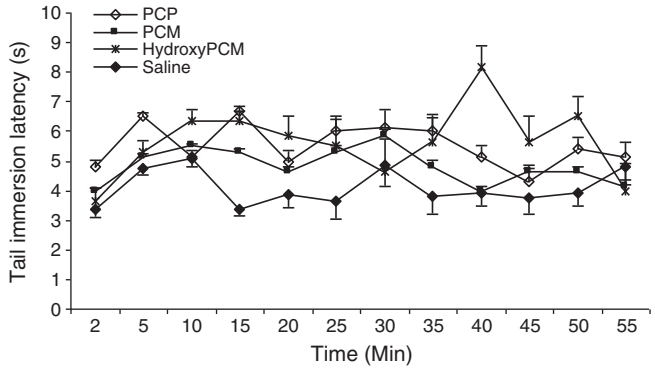



**Fig. 2.** Mean tail immersion test (s) in animals receiving PCP (**I**), PCM (**II**) and hydroxy-methyl-pCM (**IV**) hydrochloride. The bars in each line represent mean ± SEM of tail withdrawal latency (s) in 12 animals.

same dosage**)** (Fig. 2). Meanwhile, this analgesic effect was markedly observed in 20, 40, 45 and 50 min after the compound **IV** application in comparison with drugs (**I–V**) (Fig. 3). Therefore, it seems that the strong electron donating property of the methoxy and methyl groups; the hydrophilic, polarity, and solubility properties of hydroxyl group on phenyl ring; and also morpholine instead of piperidine rings (Beckett and Kourounakis, 1976; Shebley et al., 2006), facilitated more binding to the NMDA receptor complex and could increase the tail immersion latencies in comparison with other drugs, as anticipated. The difference between the tail immersion latencies was evaluated utilizing the analysis of variance method (ANOVA).

*3.2.3. The analgesic activity of PCP (I), PCM (II), methoxy-PCM (III), hydroxy-methyl-PCM (IV) and methyl-PCM (V) hydrochloride with formalin test*

The drugs (**I–V**) were administered intraperitoneally with the dosage of 6 mg/kg, 30 min before the formaldehyde injection. The results showed that **III** and **IV** were not effective for acute formalin chemical pain similar to other drugs (Figs. 4 and 5). However, the chronic formalin pain (phase II) could significantly be attenuated using **IV** and **III** compared to PCP and PCM, and the later derivative (**III**) was more effective in the late phase of the chronic pain compared to other drugs (Fig. 6). The difference in the pain scores was evaluated using the analysis of variance method (ANOVA).

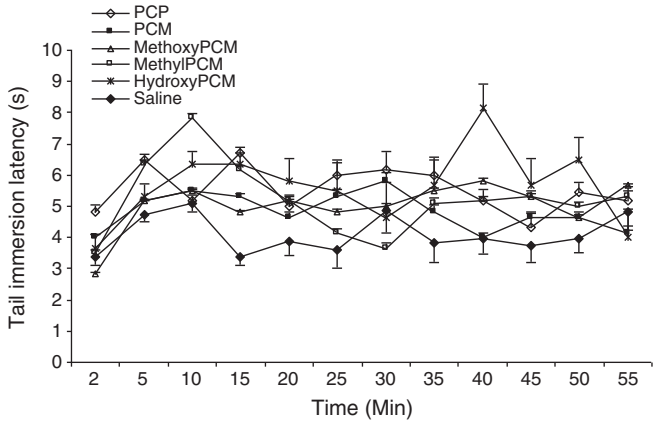



**Fig. 3.** Mean tail immersion test (s) in animals receiving PCP (**I**), PCM (**II**), methoxy-PCM (**III**), hydroxy-methyl-PCM (**IV**) and methyl-PCM (**V**) hydrochloride. The bars in each line represent mean ± SEM of tail withdrawal latency (s) in 12 animals.

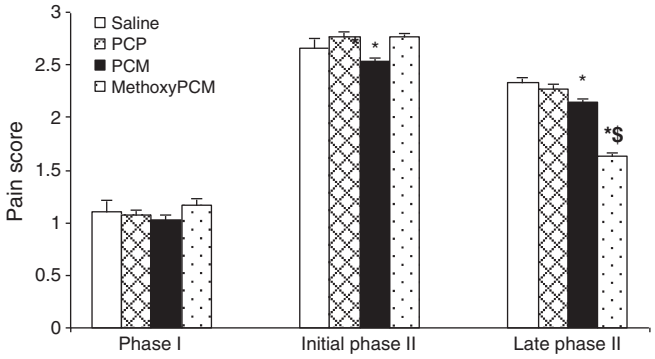



**Fig. 4.** Comparison of the acute chemical and chronic formalin pain in PCP (**I**), PCM (**II**) and methoxy-PCM (**III**) hydrochloride animal groups. Bars show the mean ± SEM of pain score. As indicated, administration of the **III** had no effect in acute chemical pain (phase I) in comparison with **I** and **II**, but the initial and late phases of chronic pain could be significantly reduced by following the administration of PCM and especially compound **III** in late phase. $n = 12$ in each experimental group. * and $ ($p<0.05$) show the difference between control (saline) and PCM groups, respectively.

## 4. Discussion

Phencyclidine is well absorbed by all routes of administration. The intravenous administration results, in a very rapid (in seconds) onset of action with peak effect, were reached after 10 min (Mozayani, 2003).Interestingly; studies on a single bolus of PCP in rats have shown that the peak PCP concentration in the brain occurs in 30 s. This apparent contradiction with the onset of peak effects is probably due to the fact that the serum level decreases 30 times faster than the brain concentration. Thus, the drug reaches a peak at 30 s, but it tends to remain in the brain for a longer duration of time than the blood levels would indicate.

Various animal models of nociception have been used to characterize the specific pain conditions in human beings. For example, tail immersion, tail flick, and hot plate experiments evaluated analgesic effects on acute coetaneous thermal pain; and intraplantar injections of formalin, Zymosan, and carrageenan are also the models of chemical acute and chronic pain (Dougherty and Staats, 1999).

The analgesic activities of new synthesized analogues of PCP (**III**, **IV**) with the changes in substitution on its phenyl (with methoxy and hydroxyl-methyl groups) and replacing of piperidine with morpholine rings were evaluated by tail immersion and formalin tests in this paper.

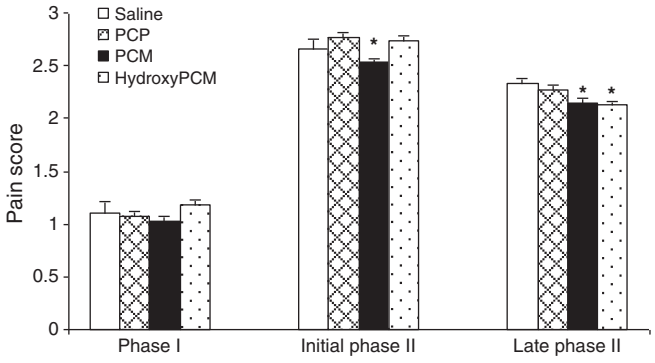



**Fig. 5.** Comparison of the acute chemical and chronic formalin pain in PCP (**I**), PCM (**II**) and hydroxy-methyl-PCM (**IV**) hydrochloride animal groups. Bars show the mean ± SEM of pain score. As indicated, administration of the **IV** had no effect in acute chemical pain (phase I) in comparison with **I** and **II**, but the initial and late phases of chronic pain could be significantly reduced by following the administration of PCM and especially compound **IV** in late phase. $n = 12$ in each experimental group. * and $ ($p<0.05$) show the difference between control (saline) and PCM groups, respectively.

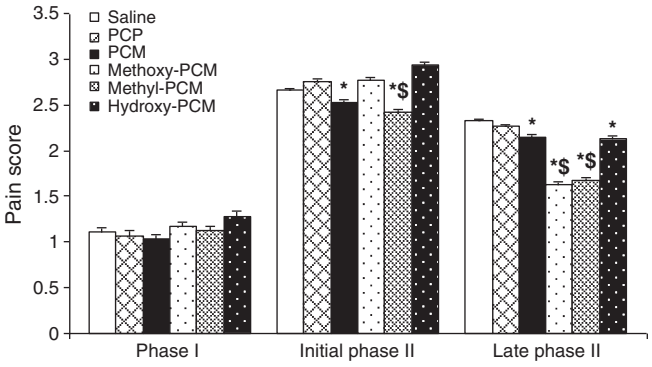



**Fig. 6.** Comparison of the acute chemical and chronic formalin pain in PCP (**I**), PCM (**II**), methoxy-PCM (**III**) and hydroxy-methyl-PCM (**IV**) hydrochloride animal groups. Bars show the mean ± SEM of pain score. As indicated, the administration of the new drugs (**III** and **IV**) had no effects in acute chemical pain (phase I), but the initial and late phases of the chronic pain could be significantly reduced by following the administration of PCM and especially compound **III** in late phase. $n = 12$ in each experimental group. * and $ ($p < 0.05$) show the difference between control (saline) and PCM groups, respectively.

The results indicated that **III** and **IV** produce more analgesic effects in the tail immersion test compared with PCP and PCM. In addition, this analgesic effect was remarkably seen after the compound **IV**'s application in comparison with all drugs (**I–V**). It was reported that NMDA receptors, especially NR2B-containing receptor subtypes, have a key role as a pain killer (Chizh et al., 2001; Jacquet, 1988) and it has shown the central mechanism(s) for the mentioned effects via antagonizing the NMDA receptors on pain modulatory center periaqueductal gray. As a result, the new synthetic drugs (compound **III** and **IV**) in this study would release more anti-nociception than other drugs. In the formalin test analysis, the acute chemical pain (phase I) could not be affected by any drugs (**I–V**) and chronic formalin pain could be diminished by these newly synthesized drugs (**III** and **IV**), especially in late phase II compared to PCP and PCM. However, biphasic analgesic effects of these new drugs in acute thermal pain could be justified by their potent pharmacokinetic/pharmacodynamic ratio (i.e., rapid and high serum level concentration of drugs due to i.p. injection) in rats (Proksch et al., 2000). In addition, high tissue storage of the drugs, their redistribution to the serum, and the production of potent drugs which are active metabolites in the liver or other organs, could explain the analgesic effects of these drugs in late chronic formalin and second acute (40–45 min) thermal pain (Deleuze-Masquefa et al., 1997; Proksch et al., 2000).

Finally, with respect to marked acute analgesic effects of III and IV and chronic anti-nociceptive effects of IV, it could be concluded that III and IV act through central and peripheral analgesic mechanism(s), respectively. Because it was revealed that formalin acute pain was mediated through central mechanism(s) and peripheral modulatory substances like inflammatory mediators (prostaglandins, interlukins, potassium and substance p) were considered as responsible for chronic formalin pain (Hunskaar and Hole, 1987; Shibata et al., 1989).

## 5. Conclusion

It is concluded that these new synthesized derivates of PCP including methoxy-PCM (**III**) and hydroxy-methyl-PCM (**IV**) could substantially and respectively diminish acute thermal and chronic chemical pains.

## 6. Conflict of interest

This research is not a part of our normal lecturing, employment, consultation, and involvement; and no institution will require any rights from this work.

In addition, no patent has been applied nor any commercial right has been given to any company and/or institution, and it will not be done later either.

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