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New morpholine and piperazine derivatives of ketamine: synthesis and anti-nociceptive effects

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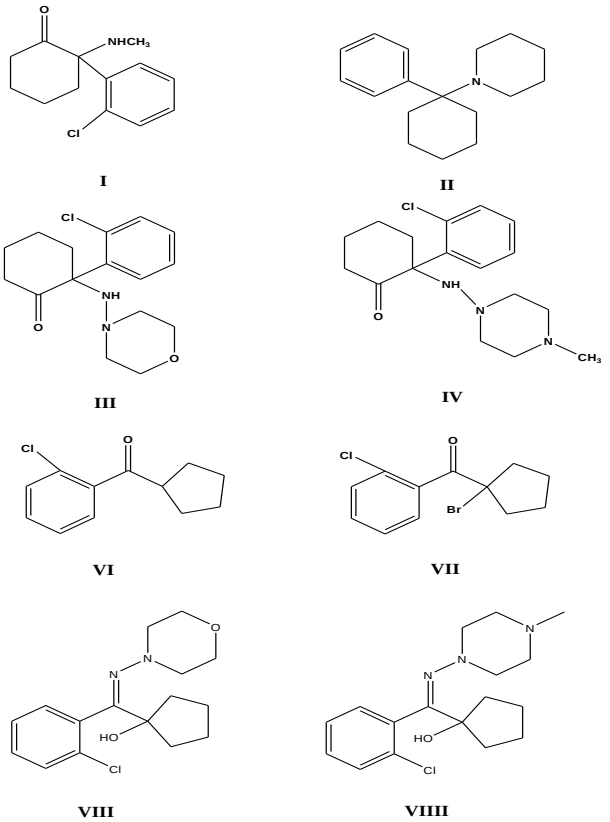
Ketamine has widely been used as ananesthetic and analgesic in human and veterinary medicine. Although it interacts with multiple binding sites in receptors, NMDA receptor antagonism is believed to account for most of its anesthetic and analgesic effects. In this work, two new derivatives of ketamine with a substitution in methylamine group for N-amino-morpholine and N-amino-4-methyl piperazine were synthesized. Their analgesic effects were evaluated in tail immersion and formalin tests with rats and the results were compared to ketamine effects on control groups. Results indicated that the new derivatives could effectively decrease pain in tail immersion and formalin tests and their analgesic effects were more significant in the acute thermal period and in late phase II of chronic chemical pains on rats at 6 mg/kg dosage.

Keywords: Ketamine, Morpholine derivative, Piperazine derivative, Anti-nociceptive effect, Tail immersion test, Formalin test.

INTRODUCTION

Ketamine (2-o-chlorophenyl-2-methylamino-cyclohexane, **I**, Scheme 1) has widely been used as anaesthetic and analgesic in human and veterinary medicine [1]. Its chemical structure, action mechanism, and pharmacological effects are similar to those of phencyclidine (1-[1-phenylcyclohexyl] piperidine, **II**, Scheme 1), but KT is much less potent than PCP [2]. Although ketamine interacts with multiple binding sites (N-methyl-d-aspartate [NMDA], non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, adrenergic and opioid receptors), it is mostly believed that NMDA receptor antagonism accounts for its anesthetic and analgesic effects. Some of ketamine analgesic effects, however, are mediated through its agonistic effects on opioid receptors within the central nervous system (CNS) and non-opioid mechanisms [3-7]. Ketamine shows anti-nociceptive effects in many analgesic standard tests, such as tail-flick test in rats, acetic acid and phenyl quinone writhing test in mice, latency increase of tail withdrawal from heat stimulus in Rhesus monkeys, formalin test in rats [8] and curing patients with neuropathic pain of various origins, such as postherpetic neuralgia, complex regional pain syndrome (CRPS), cancer pain, orofacial pain, and phantom limb pain [9, 10].



Scheme 1. Structure formulas of ketamine (**i**), phencyclidine (**ii**), ketamino-morpholine (**iii**),ketamino-piperazine (**iv**), (2-chlorophenyl)-cyclopentyl-methanone (**vi**), (1-bromocyclopentyl)-(2-chlorophenyl)-methanone **(vii),** 1-[(2-chloro-phenyl)-(morpholin-4-ylimino)-methyl]-cyclopentanol (**viii**) and 1-[(2-chloro-phenyl)-(4-methyl-piperazin-1-ylimino)-methyl]-cyclopentanol **(ix)**.

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So far, many ketamine derivatives have been synthesized [11-16] and their pharmacological activities, such as anti-nociceptive activity [11, 17-22] have been studied. It may be concluded, therefore, that the potency of this family is directly influenced by substitutions of amine group in the ketamine molecule [11]. In this study, therefore, two new derivatives (**III** and **IV**) of **I** were synthesized with a substitution for amine group (N-amino-4-methylpiperazine and N-amino morphine instead of methylamine) in the ketamine molecule. The analgesic effects of these new compounds were evaluated in tail immersion (as a model of acute thermal pain) and formalin (as a model of acute chemical and chronic pain) tests [23-25] with experimental animals and the results were compared to ketamine (**I**) effects on control (saline) groups.

EXPERIMENTAL

General

All chemicals and reagents were purchased from Merck Chemicals Co. (Darmstadt, Germany). Melting points (uncorrected) were determined with a digital electro thermal melting point apparatus (Model 9100, Electrothermal Engineering Ltd., Essex, UK). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300MHz (AMX model, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded with a Thermo Nicolet FT-IR (Nexus-870 model, Nicolet Instrument Corp, Madison, Wisconsin, U.S.A.) spectrophotometer. Mass spectra were recorded with an Agilent Technologies spectrometer (Wilmington, USA) with 5973 mass selective detector (MSD). Elemental analyses were carried out using a Perkin-Elmer, CHN element analyzer model 2400 and were within ± 0.4% of the theoretical values. Column chromatographic separations were performed over Acros silica gel (No.7631-86-9 particle size 35-70 micrometer, Geel, Belgium).

Preparations (Scheme 2)

*Cyclopentyl magnesium bromide, **V***

This compound was prepared from cyclopentyl bromide and magnesium in diethyl ether as a pale green solution following a published method [26].

*(2-Chlorophenyl)-cyclopentyl-methanone, **VI***

This compound was prepared from cyclopentyl magnesium bromide (**V**) and 2-chloro-benzonitrile as pale brown oil according to a known procedure [16].

*(1-Bromocyclopentyl) - (2-chlorophenyl)-methanone, **VII***

This compound was prepared from **VI** and bromine in carbon tetrachloride at 0 °C as brown oil following a published method [16].

*2-(2-Chlorophenyl)-2-(morpholin-4-ylamino)-cyclohexanone, **III***

A benzene (20 ml) solution of bromoketone (**VII**, 5.4 g, 0.019 mol) was added to a benzene (10 ml) solution of N-aminomorpholine (2 g, 0.019 mol) and the mixture was stirred in room temperature for 7 days. Next, N-pentane was added and the mixture was filtered, evaporated and concentrated under reduced pressure to obtain a brown oily hydroxyimine compound (1-[(2-chlorophenyl)-(morpholin-4-ylimino)-methyl]-cyclopentanol, **VIII**) that was used in the next step without further purification. A decaline (15 ml) solution of this compound was refluxed for 4.5 hours at 190 °C. The solvent was evaporated under reduced pressure. The mixture was extracted with diethyl ether, re-extracted with 10% HCl, neutralized with 10% NaOH and n-hexane, dried over $MgSO_4$, and evaporated under vacuum to obtain the desired oily residue which was passed through a silica gel column with ethyl acetate-hexane as the eluent to afford 1.18 g of **III** as brown oil (49 % yield). The hydrochloride salt of **III** (m.p.127˚C, red-brownish solid) was prepared with 2-propanol and HCl, and re-crystallized from 2-propanol.

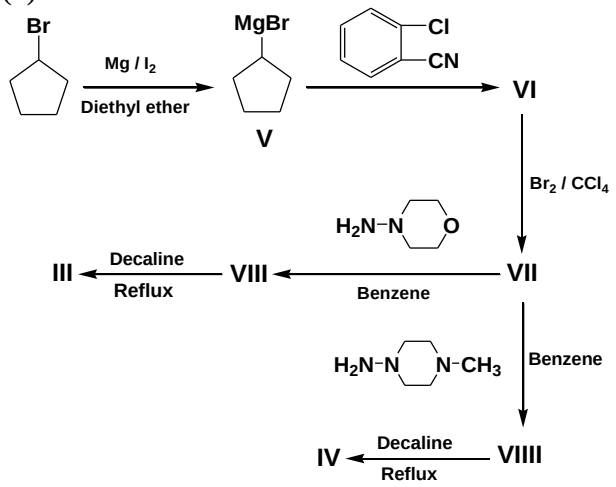
IR (KBr): 3367, 2956, 2869, 1614, 1502, 1434, 1305, 1267, 1108, 761 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (ppm):1.49-4.67 (16H, m), 7.07-7.74 (4H, m). $^{13}C\{^{1}H\}$-NMR ($CDCl_3$) (ppm): 24.4, 25.4, 32.2, 38.1, 57.5, 63.3, 69.3, 128.1, 129.6, 130.9, 133.5, 135.6, 137.4, 212.3. Anal. Calcd. for $C_{16}H_{21}ClN_2O_2$: C, 62.23%; H, 6.85%; N, 9.07%. Found: C, 62.33%; H, 6.91%; N, 9.01%. MS: m/z (Regulatory Intensity):86 (37), 100 (100), 113 (61), 197 (19), 207 (42), 211(31), 222 (20), 257 (13), 273 (26), 292 (18), 309 (14).

*2-(2-Chlorophenyl)-2-(4-methylpiperazin-1-ylamino)-cyclohexanone, **IV***

To a benzene (20 ml) solution of bromoketone (**VII**, 5.4 g, 0.019 mol), a benzene (10 ml) solution of N-amino-4-methylpiperazine (2.2 g, 0.019 mol) was added, then the mixture was stirred at room temperature for 7 days. n-Pentane was added to the mixture which was filtered, evaporated and concentrated under reduced pressure to obtain a brown oily hydroxyimine compound (1-[(2-chlorophenyl)-(4-methylpiperazin-1-ylimino)-methyl]-cyclopentanol, **IX**) that was used in the next step without further purification. A decaline (20 ml)

solution of the compound was refluxed for 3.5 hours at 190 °C. The solvent was evaporated under reduced pressure and the mixture was extracted with diethyl ether, re-extracted with 10% HCl, neutralized with 10% NaOH and n-hexane, dried over $MgSO_4$ and evaporated under vacuum to obtain the desired oily residue which was passed through a silica gel column using ethylacetate-hexane as the eluent to afford 1.56 g of **IV** as a brown oil (52% yield). The hydrochloride salt of **IV** (m.p.141°C, red-brownish solid) was prepared using 2-propanol and HCl, and re-crystallized from 2-propanol.

IR (KBr): 3411, 2952, 1613, 1503, 1454, 1313, 1041, 763, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (ppm): 1.52-4.67 (19H, m), 7.01-7.95 (4H, m).^{13}C{^{1}H}-NMR ($CDCl_3$) (ppm):21.1, 25.2, 32.1, 37.8, 40.8, 49.1, 52.4, 67.6, 121.7, 124.5, 127.2, 129.8, 133.4, 140.6, 212.4. Anal. Calcd. for $C_{17}H_{24}ClN_3O$: C, 63.44%; H, 7.52%; N, 13.06%. Found: C, 63.39%; H, 7.55%; N, 13.09%. MS: m/z (Regulatory Intensity): 81 (45), 84 (28), 96 (56), 98 (100), 111 (27), 115 (25), 206 (23), 210 (18), 306 (14), 321 (8).



Scheme 2. Synthesis of intermediates (**V**-IX) and final compounds (**III** and **IV**).

Pharmacological Methods

Animals

Sixteen adult female wistar rats (Pasteur's Institute, Tehran, Iran), weighing 100-220 g, were randomly housed in four groups of four per cage in a temperature controlled colony room under light/dark cycles. Rats were given free access to water and standard laboratory rat chow (supplied by Pars Company, Tehran, Iran). All behavioral experiments were carried out from 11 a.m. to 4 p.m. under normal room light and at 25^{o}C temperature. All animals were injected by a researcher, and evaluated by another. This study was carried out according to the Guides for the "Care and Use of Laboratory Animals" (NIH) and those at the "Research Council of Shahed University of Medical Sciences, Tehran, Iran".

Tail Immersion Test

The acute thermal pain was modeled in the tail immersion test [23, 24].Twenty minutes after intra peritoneal injection of drugs in the treatment group (ketamine and its analogues, 6 mg/kg), and an equivalent volume of saline (in the control group), the rats were housed in an animal restrainer. Then, the terminal 5 cm of their tails was first submerged into room temperature water (22~24 °C) to check their aversion to water and then immersed in 52 °C water. The reaction time between immersing the tail and its removal from the heated water was measured and recorded as the pain threshold. Cut-off latency in 15 sec was employed to avoid damaging the tail.

Formalin Test

The formalin test was introduced by Dubuisson and Dennis (1977). In this test, the formaldehyde solution (50 µl, 2.5%) was subcutaneously injected into the plantar surface of the hind paw. Then, the animals were placed in a Plexiglas chamber (30×30×30 cm^3) mirrored at 45^o angle underneath for accurate observations. In treatment groups, the drugs (ketamine and its analogues) and in control ones an equivalent volume of saline was intraperitoneally injected 30 min prior to the formaldehyde injection. Before the experiments, all animals were brought to the test chamber five times at five-minute-intervals in order to adapt them to the environment. The behavioral pain reactions after formalin injection were detected and recorded for 1 hour. The scores for pain reaction were as follows: 0, normal weight bearing on the injected paw; 1, limping during locomotion or resting the paw lightly on the floor; 2, elevation of the injected paw; 3, licking or biting of the injected paw, or grooming [25]. Behavioral responses have been observed every 15 seconds. The average pain scores from every 3 minutes block were compared with each other in different groups. The rats were not tested more than once and experiments were carried out between 09:00 and 15:00. The first 15 minutes after formalin injection were labeled as the early (I) or Acute Phase, and the period between 15-60 minutes as the second (II) or Chronic Phase. Chronic Phase was divided into initial (15-40 min) and late (40-60 min) periods.

Experimental psychomotor coordination (PMC) index

This test was done by Rota-rod Treadmill with a shock facility apparatus (Harvard model 865) after

root or new drugs administration. First, animals were trained by their placing on the rolling bar and had been led to walk on it. Then, for 5 times, they were placed in a case with these characteristics: initial speed = 4 rpm, final speed = 30 rpm, initial to final speed time = 4 min, shock intensity = 1.1 mA, shock duration = 0.2-0.8 sec, experimental length time = 5 min, interval between experiments = 2 min. The mean stay time on the rod per trial was taken as a PMC index.

Statistical analysis

Sigmastat 3.5 software was used for statistical analysis. The measured data were presented as means ± S.E.M. Comparisons were carried out as one way analysis of variance (ANOVA) followed by post-hoc Tukey test with a p-value < 0.05 level of significance.

RESULTS

Chemistry

Ketamine **(I)** and its newly synthesized derivatives (**III** and **IV)** were synthesized by reaction of bromoketone (**VII**) with pharmacological amines (methyl amine, N-amino-4-methylpiperazine and N-amino-morpholine).These amines are widely used as intermediates in the synthesis of many drugs [27-30]. The process of this synthesis method involves a thermal rearrangement of the carbon skeleton of cyclopentyl α-hydroxyimines (**VIII** and **IX**) to cyclohexanone amines (**III** and **IV**) in a hydrocarbon solvent (decalin). As it can be seen, this skeletal rearrangement can result in ring expansion of α-hydroxyimines producing larger size of the rings [16].

The known procedures were applied to synthesize the compounds **V**-**VII** [16, 26]. The structures of the newly synthesized compounds (**III** and **IV**) were confirmed on the basis of spectroscopic data IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analysis. The purity of each compound was checked by TLC using ethyl acetate-hexane as the eluent.

Pharmacology

General Considerations

Mortality (number of deaths), morbidity (abnormal condition or behavior due to a disorder), irritability (condition of aggressiveness or increased response on handling) and other related abnormal states were observed in the treated animals. The motor coordination index (measured on a Rota-rod apparatus, Harvard, UK) did not indicate any significant differences between control and treated rats.

Anti-nociceptive activity of the compounds in tail immersion test

Intraperitoneal injection of ketamine (**I**) in a dosage of 6 mg/kg generated analgesic affects in the tail immersion test (as a model of acute thermal pain) (Figure 1). However, application of its two newly synthesized derivatives (**III** and **IV**) hydrochlorides at a 6 mg/kg dosage could produce no identical analgesic effects in the tail immersion test. Although, mild prominent analgesia was observed at 30-40 min after new drugs (especially piperazine derivative) administration.

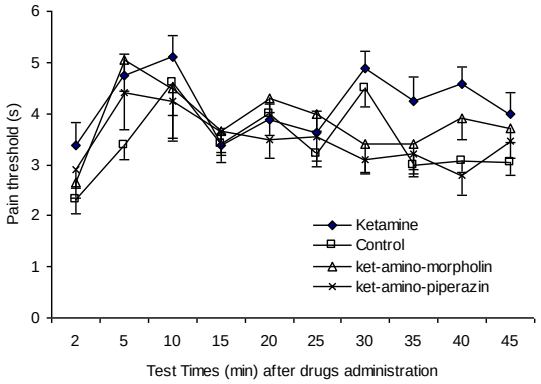


Fig.1. Mean tail immersion latency (s) in animals receiving ketamine (**I**), ketamino-morpholine (**III**) and ketamino-piperazine (**IV**) hydrochloride or saline (control) in doses of 6 mg/kg. The tail immersion test was conducted 20 minutes after the drug injection. Each point represents the mean ± S.E.M. of tail immersion latency (s) in 8 animals. Statistical analysis was done by analysis of variance (ANOVA) test followed by Tukey post-hoc test. p-value < 0.05 was considered as the level of significance.

Anti-nociceptive activity of the compounds in formalin test

The drugs (**I, III** and **IV**) were intraperitoneally injected in a dosage of 6 mg/kg, 30 minutes before formaldehyde injection. Results showed that all compounds significantly decreased the acute and chronic formalin chemical pains (Figure 2) comparing to the control group. However, chronic formalin pain (phase I and II) could significantly attenuate with compounds **III** and **IV** comparing to other groups (**I** and control) in the late second phase.

PMC index in control and treated animals

Figure 3 shows the results of the psychomotor coordination test by Rota-rod treadmill apparatus. The mean PMC indices of experiments for control, ketamine, ketamino-morpholine and ketamino-piperazine animal groups were obtained, 148 ± 20.57, 144 ± 19.29, 163 ± 21.71 and 118 ± 17.56, respectively. However, statistical analysis

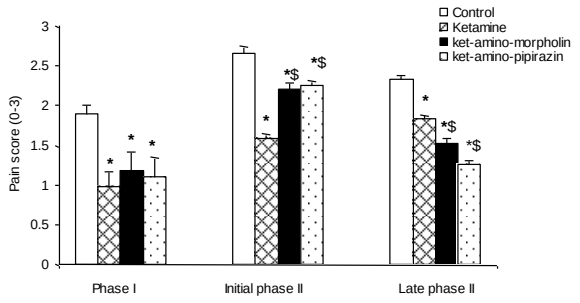


Fig. 2. Comparison between the acute and chronic formalin pains in ketamine (**I**), ketamino-morpholine (**III**), ketamino-piperazine (**IV**) hydrochloride or saline (control) in doses of 6 mg/kg. Data show the mean ± S.E.M of pain score. *n* = 8, * p<0.05, when compared with control and $, p < 0.05 when compared with ketamine group. Analysis of variance (ANOVA) test followed by Tukey post-hoc test and p-value < 0.05 was considered for data analysis.

shows no significant difference between mean of PMC in control and treated animals. Regarding the inflammatory origins for phase II of formalin pain, through release of the local mediators like prostaglandins, kinnins, interleukins, substance p and potassium [31], it can be concluded that these new drugs may have a modulatory effect on the mentioned inflammatory mediators.

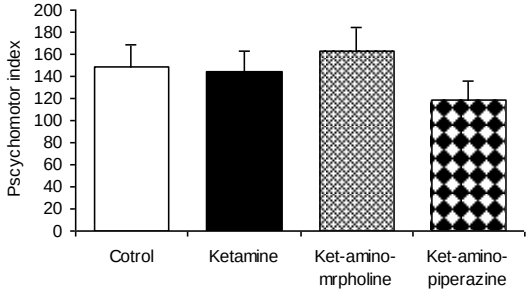


Fig. 3. Comparison effect of motor coordination system between control and treated animals. Bars show the mean ± SEM psychomotor index in the experimental animals. n = 8, each group. Analysis of variance (ANOVA) test followed by post-hoc Tukey test was considered for data analysis. p-value < 0.05 was used for significant comparison.

4. DISCUSSION

Ketamine as an NMDA receptor antagonist in high and low doses, respectively, could yield anesthetic and analgesic properties [32]. The use of ketamine as an analgesic is now generally accepted, however, the evidence base remains poor. Little formal research has been done on the efficacy and safety of ketamine in chronic pain management, especially in long-term oral administration [32]. Because the potency of this family was influenced by substitution on the amine group in the KT molecule [11], two amines with many pharmacological properties (N-amino-4-methylpiperazine and N-amino-morpholine) and intermediates for the synthesis of many drugs [27-30] were substituted on this site of the molecule for obtaining the new ketamine derivatives (**III** and **IV)**. Results indicated that these new derivatives (**III** and **IV**) of KT (**I**) could be more effective in decreasing pain, comparing to the control group in formalin chemical pain and especially in the late chronic phase. However, these analgesic effects were not always significant in acute thermal pain (tail immersion test). Nevertheless, the neurological origins especially through the central nervous system were introduced as the main mechanism(s) for acute (thermal or chemical) pain conducting [33]. With respect to the non-significant differences between ketamine and the two new derivatives on acute analgesic potency, it can be concluded that adding morpholine and piperazine to ketamine drug does not change the efficiency of ketamine neurological pain modulation reactions. Unlikely, new drugs' significant chronic anti-nociceptive effects could be resulting from more antagonizing production of inflammatory mediators like kinnins, interleukins, substance p and potassium. Therefore, peripheral inflammatory mediator enhancement following the acute phase is the main mechanism for chronic chemical pain [34]. Although it seems that replacing methylamine (in KT) by N-amino-morpholine (in **III**) and N-amino-4-methylpiperazine (in **IV**) could be as effective as ketamine in producing new analgesic drugs, they could not be more effective than **I** in most cases. However, stronger analgesic effects in acute thermal (in a shorter time) and chronic chemical pains of the morpholine derivative (ketamino-morpholine, **III**) comparing to the piperazine one (ketamino-piperazine, **IV**) were observed due to the stronger pharmacological properties of morpholine [35-37]. These effects were weaker than the ketamine analgesic effects mostly in acute thermal (in tail immersion test) and in acute chemical and initial phase of chronic (in formalin test) pains. From pharmacokinetic point of view, more antagonizing functions displayed by these new drugs (**III** and **IV**) on the NMDA receptor might underlie their more anti-nociceptive activities compared to the control group. Also, a methyl group on the amine moiety of KT had a more effective role in decreasing pain comparing to morpholine and piperazine groups, which might account for a high electron distribution and dipole moments by this group [38]. Moreover, it indicated stronger anti-nociceptive effects produced by some analgesic drugs [39-41] compared to other new amine groups.

5. CONCLUSION

It was concluded that swapping methylamine (in ketamine, **I**) with N-aminomorpholine (in ketamino-morpholine, **III**) and N-amino-4-methylpiperazine (in ketamino-piperazine, **IV**) could generate analgesic effects in tail immersion and formalin tests comparing to the control group (in most of cases) where ketamine was injected in rats at a 6 mg/kg dosage.

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НОВИ ПРОИЗВОДНИ НА КЕТАМИНА С МОРФОЛИН И ПИПЕРАЗИН: СИНТЕЗИ И АНТИ-НОЦИСЕПТИВЕН ЕФЕКТ

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Кетаминът е широко използван като упойка или аналгетик в хуманната и ветеринарна медицина. Въпреки че взаимодейства с множествените свързващи центрове на рецепторите се смята, че NMDA- рецепторен антагонизъм е отговорен за повечето анестетични и аналгетични ефекти. В настоящата работа са синтезирани две нови производни на кетамина чрез заместване в метиламиновата група с N-амино-морфолин или N-амино-4-метил-пиперазин. Оценен е тяхният аналгетичен ефект Their analgesic effects were evaluated върху плъхове и резултатите са сравнени с ефекта на кетамина при контролна група. Резултатите показват, че новите производни могат ефикасно да намалят болката, а тяхният аналгетичен ефект в доза 6 mg/kg е по-значим в акутния термичен период и в късната фаза II на хронични болки при плъхове.