

New Derivatives from Phencyclidine Increase Food and Water Intake in Wistar Rats

A. AHMADI, J. SOLATI and M. KHALILI

For author affiliations, see end of text.

Received October 10, 2009; Revised April 3, 2010; Accepted June 22, 2010

This paper is available online at <http://ijpt.iuums.ac.ir>

ABSTRACT

Phencyclidine (1-(1-phenylcyclohexyl) piperidine, CAS 956-90-1, PCP, I) and its derivatives have shown many pharmacological and behavioral effects. Also, food and water intake of many drugs such as PCP and its analogues have been studied in laboratory animals. In this work, two derivatives (II, III) of phencyclidine were tested for feeding behaviors effects on rats and compared to PCP and vehicle (saline). The results showed that, both derivatives can increase food and water intake in comparison to the PCP and vehicle (control) groups that have measured 1-12 h for food and 30–180 min for water intake after injection.

Keywords: *Phencyclidine derivatives, Pharmacological effects, Food and water intake*

Phencyclidine (1-(1-phenylcyclohexyl) piperidine, CAS 956-90-1, PCP, I) (Scheme 1) and its derivatives display analgesic [1-8], stimulant [9,10], anticonvulsant [11,12] and behavioral effects [13-15] because of specific binding sites in the brain [14]. PCP binds to the N-methyl-D-aspartate (NMDA) receptor complex and blocks NMDA-mediated gating of the calcium channel conductance [15,16]. These have many common behavioral effects with other phencyclidine-like drugs, including anaesthetics, antinociceptives, psychotomimetics, anticonvulsants, neuroprotectives and amnesic drugs due to non-competitive "open channel blocking" of the NMDA receptor [17].

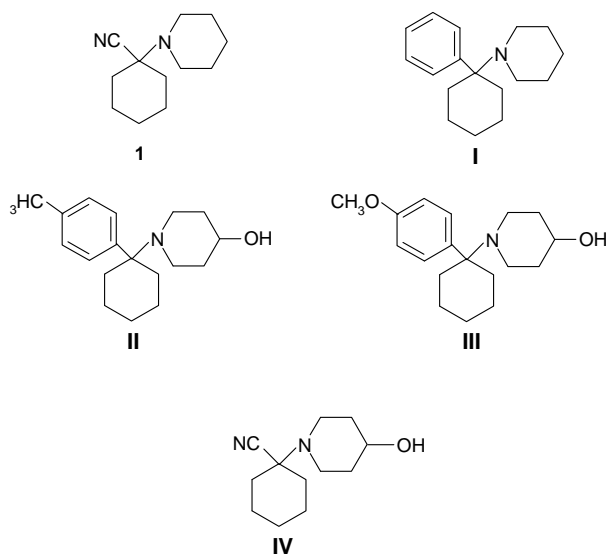
Food and water intake as a model of behavioral effects of many drugs such as PCP and its analogues, morphine, amphetamine, dexfenfluramine and diazepam, have been studied in laboratory animals [18-35]. Various brain systems are involved in behavioral effects of them [15,16]. Previous studies showed the important role of nicotine and nicotinic acetylcholine receptors on feeding behaviors of animals. PCP analogues have been shown the inhibition of nicotinic acetylcholine receptor channels (nAChR) in rats [36-42]. The recent studies also showed that NMDA receptor antagonists like PCP have direct effects on serotonin (5-HT) receptors and that systemic PCP treatment elevates brain extracellular 5-HT level by interaction with 5-HT reuptake site [16,18]. Serotonin has been extensively implicated in an array of

behavioral and physiological functions including the control of ingestive behaviors [43,44].

Therefore; it seems that all of the NMDA glutamatergic system, nicotinic acetylcholine receptors and serotonin (5-HT) receptors have very important role on modulation of feeding behavior [16,18,36-43]. In this work, two methyl and methoxy hydroxyl derivatives of Phencyclidine [45] [(1-[1-(4-methylphenyl) (cyclohexyl)] 4-piperidinol, II), (1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol, III)] were tested for food and water intake in rats and were compared with PCP and vehicle.

MATERIALS AND METHODS

Cyclohexanone, Piperidine, Bromobenzene, magnesium turning, diethyl ether, 4-bromo toluene, 4-bromo anisole, 4-piperidinol and all other chemicals were purchased from Merck Chemical Co (Darmstadt, Germany). Melting points (uncorrected) were determined using a digital Electrothermal melting point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). ¹H and ¹³C NMR spectra were recorded on a 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 Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmington,



Scheme 1. Structure formulas of PCP (**I**), PCP-CH₃-OH (**II**), PCP-OCH₃-OH (**III**) and Carbonitrile intermediates **I** and **IV**.

USA). Column chromatographic separations were performed over Acros silica gel (No. 7631-86-9 particle size 35-70 micrometer, Geel, Belgium). Adult male Wistar rats (Pasteur's Institute, Tehran, Iran), weighing 220 -260 g were used for pharmacological testing.

Preparations (Scheme 1)

4-hydroxypiperidinocyclohexylcarbonitrile IV: This compound was prepared in an organic solvent from 4-piperidinol, cyclohexanone and KCN [46].

(1-(1-phenylcyclohexyl) piperidine (PCP) I: This compound was prepared from 1-piperidinocyclohexanecarbonitrile (**I**) and phenyl magnesium bromide. The hydrochloride salt of **I** was prepared using 2-propanol and HCl and was recrystallized from 2-propanol [47].

1-(4-methylphenyl) (cyclohexyl) 4-piperidinol II: This compound was prepared from nitrile compound (**IV**) and *p*-tolyl magnesium bromide (Grignard reagent) according to a published method [45]. The hydrochloride salt of **II** was prepared using 2-propanol and HCl and was recrystallized from 2-propanol [45].

1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol III: This compound was prepared from nitrile compound (**IV**) and *p*-anisol magnesium bromide (Grignard reagent) according to a published method [45]. The hydrochloride salt of **III** was prepared using 2-propanol and HCl and was re-crystallized from 2-propanol [45].

Pharmacological methods

Adult male Wistar rats (Pasteur's Institute, Tehran), weighing 220 -270 g were housed in individual polypropylene cages under controlled temperature (25°C) and light (12 h: 7 am to 7 pm)/dark (12 h) cycle with ad libitum access to food (standard laboratory rat chow, Pars company, Tehran, Iran) and water. The experimental procedures adhered to the National

Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH) and those of the Research Council of Biology Department of Karaj Islamic Azad University (Karaj, Iran).

Food intake study

In this experiment, the four groups of animals after 1 week of habituation to their new housing conditions were deprived of food for 24 h (rats were fasted in separate cages with free access to water), three groups were IP-injected with drugs (**I**, **II**, **III**) hydrochloride (5 mg/kg, that is under LD₅₀ limit dosage of PCP and its analogues [5], solved in 0.2 ml saline) and another group received equivalent volume of saline. The number of rats was six in each group. Immediately after injection, each rat was returned to its cage and a weighed hopper of food was placed in the cage. The quantities of cumulative food (standard laboratory rat chow) consumed were measured 1-12 h after injection of the solutions.

Water intake study

Rats had free access to water and food and were put in the separate metabolic cages at least 7 days before the experiments. The amount of water ingested in the various experiments was measured with 0.1 ml graduated glass burettes adapted with a metal drinking spout. Intake was induced by water deprivation during the 24 h that preceded the experiment. Four groups of animals were deprived of water, three groups were IP-injected with drugs (**I**, **II**, **III**) hydrochloride (5 mg/kg, that is under LD₅₀ limit dosage of PCP and its analogues [5], solved in 0.2 ml saline and another group received equivalent volume of saline. The number of rats was six in each group. Immediately after injection, each rat was returned to its cage and cumulative water intake was measured 30–180 min after injection of the solutions.

Intraperitoneal (IP) injection of saline and drugs

At the beginning of the experiment, the animals were injected (5 mg/kg, ip) with saline (vehicle), and PCP (**I**), PCP-CH₃-OH (**II**), PCP-OCH₃-OH (**III**) hydrochloride that were dissolved in saline.

Statistical analysis

The differences between vehicle, PCP and derivatives were evaluated using analysis of variance method (ANOVA). The *p* value < 0.05 was considered to represent significant difference. The cumulative food and water intake were measured (1-12 h for food and 30–180 min for water) after injection of the solutions.

RESULTS

Chemistry

Phencyclidine (**I**), 1-[1-(4-methylphenyl) (cyclohexyl) 4-piperidinol (**II**) and 1-[1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol (**III**) were synthesized by reaction of substituted Grignard reagents and carbonitrile compounds [45]. This compounds (**II**,

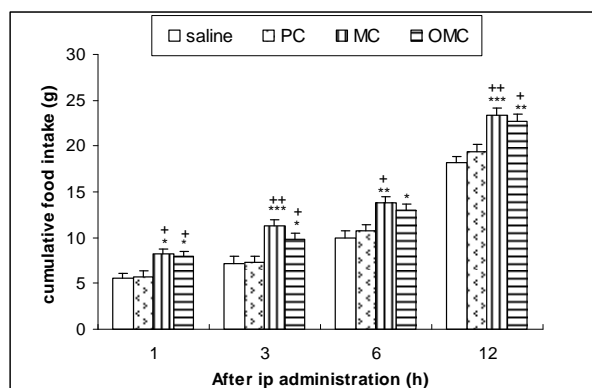


Fig 1. Effects of i.p. injection of PC (I), MC (II), and OMC (III) hydrochloride or saline (vehicle) (5 mg/kg) on cumulative food intake in food deprived rats (24 h), 1–12 h after injection of solutions. Data for food intake are expressed as the mean \pm SEM (n = 6). * p < 0.05, ** p < 0.01 and *** p < 0.001 compared with saline-injected rats; + p < 0.05 and ++ p < 0.01 compared with PC.

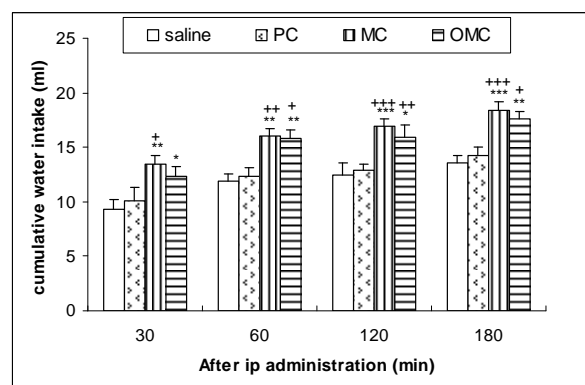


Fig 2. Effects of i.p. injection of PC (I), MC (II), and OMC (III) hydrochloride or saline (vehicle) (5 mg/kg) on cumulative water intake in water deprived rats (24 h), 30–180 min after injection of solutions. Data for water intake are expressed as the mean \pm SEM (n = 6–9). * p < 0.05, ** p < 0.01 and *** p < 0.001 compared with saline-injected rats; + p < 0.05, ++ p < 0.01 and +++ p < 0.001 compared with PC.

III) have stronger hydrophilic and polarity (a hydroxyl group on the piperidine ring) and the high electron donating, distribution and dipole moments (a methyl (II) or methoxy (III) group on the aromatic ring) properties. Known procedures were applied for the synthesis of all compounds I-IV with the appropriate modifications described previously [46-48].

Pharmacology

General Consideration

Animal behavioral observation showed no mortality, morbidity, irritability and other side effects due to drugs administration. However, comparison of the motor coordination index (as measured by Rota-rod apparatus, Harvard, UK) indicated no significant differences between control and treatment rats.

The effect of PCP (I), 1-[1-(4-methylphenyl) (cyclohexyl) 4-piperidinol (II) and 1-[1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol (III) hydrochloride in food and water intake

The results showed that two derivatives of phencyclidine (II, III) can increase feeding consumption in comparison to the PCP and vehicle (control) groups in food- and water-deprived rats (24 h). In details, II increased food and water intake more than III with a marked significant increase in the intaking time (Figs 1-2). Also the most quantities were seen after 12 h for food and after 180 min. for water intake.

DISCUSSION

Results of present study showed that methyl and methoxy hydroxyl derivatives of Phencyclidine [45], [(1-[1-(4-methylphenyl) (cyclohexyl)] 4-piperidinol, II) and (1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol, III)], increase food and water intake in wistar rats. However, more studies are necessary for demonstration of mechanisms that under which this new derivatives can affect feeding behaviors.

As it mentioned before, PCP works primarily as an NMDA receptor antagonist, which blocks the activity of the NMDA receptor [15-17]. Some studies have shown that NMDA glutamatergic system has a role on modulation of feeding behaviors as systemic injection of the non-competitive NMDA antagonist, MK801, increased food intake in rats [49]. Cholinergic systems may also have a role in modulation behavioral effects of PCP derivatives and would be caused to increase food and water intake by inhibition of nicotinic acetylcholine receptor channels (nAChR). Other studies also demonstrated that nicotine administration and activation of nAChRs associated with decreased in food and water intake and lower body weight in rats [36-42].

PCP derivatives can also affect food and water intake by interaction with serotonergic system so that PCP administration increase brain serotonin level and affect different 5-HT receptors [16,18] and several studies have been shown the effects of serotonergic system and 5-HT receptors system in different brain regions on control of food and water intake [43, 44].

From above-mentioned studies, it can be concluded that various brain systems and receptors are involved in modulating behavioral effects of PCP and its analogues. As there was no report for PCP increasing food and water intake [13, 26], we applied two derivatives of this molecule with the changes in substitution on its phenyl and piperidine rings (II, III) that had more hydrophilic, polarity, electron distribution and dipole moments properties for increasing in feeding behavior [45, 48]. Therefore, it seems that strong electron donating properties of the methyl group on *para* position of phenyl ring and also hydrophilic and polarity properties of hydroxyl group on the piperidine ring of the molecule (II) facilitate increases affinity to receptors and it is anticipated that food and water intake could be increased in comparison with PCP and vehicle (control). Also, strong electron donating properties of the methoxy group on *para* position of phenyl ring and hydrophilic and polarity properties of hydroxyl group on the piperidine ring of the molecule (III) increased feeding

consuming in comparison to the PCP and vehicle (control). Because of undesired reactions with cationoid intermediates [50], little decrease in receptor binding could be anticipated. This increase is less than that in II but still it is higher than PCP and vehicle (control).

In conclusion, this study showed that both of two derivatives of phencyclidine (II, III) were more effective than PCP in modulation of feeding behavior in rats and appropriate substitution of the methyl, methoxy and hydroxyl groups may result in ligands with higher affinity for the PCP site on receptors.

ACKNOWLEDGMENTS

The authors would like to thank Karaj Islamic Azad University for its financial support of this project.

REFERENCES

- Greifenstein, FE, Yoshitake J, De Vault, M, Gajewski, JE. A study of 1-arylcylohexylamine for anesthesia. *Anesth Analg* 1958; 37:283-4.
- Ahmadi A, Shafieezadeh M, Fathollahi Y. Synthesis with improved yield and study on analgesic effect of 2-hydroxyphencyclidine. *Arzneim-Forsch/Drug Res* 2005; 55:172-6.
- Al-deeb OAA. Synthesis and analgesic activity of new phencyclidine derivatives. *Arzneim-Forsch/Drug Res* 1994; 44:1141-4.
- Ahmadi A, Mahmoudi A. Synthesis with improved yield and study on analgesic effect of 2-methoxyphencyclidine. *Arzneim-Forsch/Drug Res* 2006; 56:346-50.
- Al-deeb OAA. New analgesic derived from the phencyclidine analogue thiencyclidine. *Arzneim-Forsch/Drug Res* 1996; 46:505-8.
- Itzhak Y, Kalir A, Weissman BA, Cohen S. New analgesic drugs derived from phencyclidine. *J Med Chem* 1981; 24:496-9.
- Chen G, Weston JK. The analgesic and anesthetic effects of 1-(1-phenylcyclohexyl) piperidine.HCl on the monkey. *Anesth Analg* 1960; 39:132-7.
- Ahmadi A, Mahmoudi A. Synthesis and Biological Properties of 2-Hydroxy-1-(1-Phenyltetralin) Piperidine and some of its Intermediates as Derivatives of Phencyclidine. *Arzneim-Forsch/Drug Res* 2005; 55:528-32.
- Jackson A, Sanger DJ. Is the discriminative stimulus produced by phencyclidine due to an interaction with N-methyl-D-aspartate receptors? *Psychopharmacology* 1988; 96:87-92.
- Mori A, Noda Y, Mamiya T, Miamoto Y, Nakajima A, Furukawa H, Nabeshima T. Phencyclidine-induced discriminative stimulus is mediated via Phencyclidine binding sites on the N-methyl-D-aspartate receptor-ion channel complex, not via sigma receptors. *Behavioral Brain Research* 2001; 119:33-40.
- Thurkauf A, De Costa B, Yamaguchi S, Mattson M, Jacobson A, Rice K, Rogawski M. Synthesis and anticonvulsant activity of 1-phenylcyclohexylamine analogues. *J Med Chem* 1990; 33:1452-8.
- Geller EB, Adler LH, Wojno C, Adler MW. The Anticonvulsant Effect of Phencyclidine in Rats. *Psychopharmacology* 1981; 74:97-8.
- Balster RL, Chait LD. The behavioral pharmacology of Phencyclidine. *Clin Toxicol* 1976; 9:513-28.
- Chen G, Ensor CR, Russell D, Bohner B. The pharmacology of 1-(1-phenylcyclohexyl) piperidine.HCl. *J Pharmacol Exp Ther* 1959; 127:241-50.
- Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA. NMDA antagonist neurotoxicity: mechanism and prevention. *Science* 1991; 254:1515-8.
- Kapur S, Seeman P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D (2) and serotonin 5-HT (2) receptors-implications for models of schizophrenia. *Mol Psychiatry* 2002; 7:837-44.
- Honey CR, Miljkovic Z, McDonald JF. Ketamine and phencyclidine cause a voltage-dependent block of responses to L-aspartic acid. *Neurosci Lett* 1985; 61:135-9.
- Nabeshima T, Yamaguchi K, Hiramatsu M, Amano M, Furukawa H, Kameyama T. Serotonergic involvement in phencyclidine-induced behaviors. *Pharmacol Biochem Behav* 1984; 21:401-8.
- Woolverton WL, Balster RL. Tolerance to the behavioral effects of phencyclidine: the importance of behavioral and pharmacological variables. *Psychopharmacology* 1979; 64:19-24.
- Lukas SE, Griffiths RR, Brady JV, Wurster RM. Phencyclidine-analogue self-injection by the baboon. *Psychopharmacology* 1984; 83:316-20.
- Fico TA, Banks AN, Hutchings DE. Prenatal phencyclidine in rats: Effects on apomorphine-induced climbing. *Pharmacol Biochem Behav* 1990; 35:93-7.
- Merkel AD, Wayner MJ, Jolicoeur FB, Mintz R. Effects of caffeine administration on food and water consumption under various experimental. *Pharmacol Biochem Behav* 1981; 14:235-40.
- Sanger DJ, McCarthy PS. Differential effects of Morphine on food and water intake in food deprived and freely-feeding rats. *Psychopharmacology* 1980; 72:103-6.
- Brown DR, Holtzman SG. Suppression of deprivation-induced food and water intake in rats and mice by naloxone. *Pharmacol Biochem Behav* 1979; 11:567-73.
- King BM, Castellanos FX, Kastin AJ, Berzas MC, Mauk MD, Olson GA, Olson RD. Naloxone-induced suppression of food intake in normal and hypothalamic obese rats. *Pharmacol Biochem Behav* 1979; 11:729-32.
- Foltin RW. Effects of amphetamine, dexfenfluramine, diazepam and other pharmacological and dietary manipulations on food seeking and taking behavior in non-human primates. *Psychopharmacology* 2001; 158:28-38.
- Gardner JD, Rothwell NJ, Luheshi GN. Leptin affects food intake via CRF-receptor-mediated pathways. *Nat Neurosci* 1998; 1:103.
- Inoue K, Valdez GR, Reyes TM, Reinhardt LE, Tabarin A, Rivier J. Human urocortin II, a selective agonist for the type 2 corticotropin-releasing factor receptor, decreases feeding and drinking in the rat. *J Pharmacol Exp Ther* 2003; 305:385-93.
- Eidi M, Oryan S, Eidi A, Sepehrara L. Effect of morphine, naloxone and histamine system on water intake in adult male rats. *Eur J Pharmacol* 2003; 478:105-10.
- Ohata H, Shibasaki T. Effects of urocortin 2 and 3 on motor activity and food intake in rats. *Peptides* 2004; 25:1703-9.
- Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA, Patterson M, Ghatei MA, Bloom SR. Peripheral oxyntomodulin reduces food intake and body weight gain in rats. *Endocrinology* 2004; 145:2687-95.
- Zorrilla EP, Inoue K, Fekete EM, Tabarin A, Valdez GR, Koob GF. Measuring meals: structure of prandial food and water intake of rats. *Am J Physiol Regul Integr Comp Physiol* 2005; 288:1450-67.
- Fekete EM, Inoue K, Zhao Y, Rivier JE, Vale WW, Szu A, Koob GF, Zorrilla EP. Delayed Satiety-Like Actions and Altered Feeding Microstructure by a Selective Type 2 Corticotropin-Releasing Factor Agonist in Rats: Intra-Hypothalamic Urocortin 3 Administration Reduces Food Intake by Prolonging the Post-Meal Interval. *Neuropsychopharmacology* 2007; 32:1052-68.

34. Moon BH, Hong CG, Kim SY, Kim HJ, Shin SK, Kang S, Lee KJ, Kim YK, Lee MS, Shin KH. A single administration of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin that produces reduced food and water intake induces long-lasting expression of corticotropin-releasing factor, arginine vasopressin, and proopiomelanocortin in rat brain. *Toxicology and Applied Pharmacology* 2008; 233:314-22.
35. Taraschenko OD, Rubbinaccio HY, Maisonneuve IM, Glick SD. 18-methoxycoronaridine: a potential new treatment for obesity in rats? *Psychopharmacology* 2008; 201:339-50.
36. Guan G, Kramer SF, Bellinger LL, Wellman PJ, Kramer PR. Intermittent nicotine administration modulates food intake in rats by acting on nicotine receptors localized to the brainstem. *Life Sci* 2004; 74:2725-37.
37. Clarke PB, Kumar R. Some effects of nicotine on food and water intake in undrugged rats. *Br J Pharmacol* 1984; 82: 233-9.
38. Hucho F. The nicotinic acetylcholine receptor and its ion channel. *Eur J Biochem* 1986; 158:211-26.
39. Fryer JD, Lukas RJ. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. *J Pharmacol Exp Ther* 1999; 288:88-92.
40. Ochoa EL, Li L, McNamee MG. Desensitization of central cholinergic mechanisms and neuroadaptation to nicotine. *Mol Neurobiol* 1990; 4:251-87.
41. Aceto MD, Tucker SM, Hinson JR, Ferguson GS. Chronic nicotine exposure: studies on water intake, body weight, blood pressure and behavior. *NIDA Res Monogr* 1987; 76:327-33.
42. Wellman PJ, Bellinger LL, Cepeda-Benito A, Susabda A, Ho DH, Davis KW. Meal patterns and body weight after nicotine in male rats as a function of chow or high-fat diet. *Pharmacol Biochem Behav* 2005; 82:627-34.
43. Vickers SP, Benwell KR, Porter RH, Bickerdike MJ, Kennett GA, Dourish CT. Comparative effects of continuous infusion of mCPP, Ro 60-0175 and d-fenfluramine on food intake, water intake, body weight and locomotor activity in rats. *Br. J. Pharmacol* 2000; 130:1305-14.
44. Saadoun A, Cabrera MC. Effect of the 5-HT (1A) receptor agonist 8-OH-DPAT on food and water intake in chickens. *Physio Behav* 2002; 75:271-5.
45. Ahmadi A, Khalili M, Abbassi S, Javadi M, Mahmoudi A, Hajikhani R. Synthesis and Study on Analgesic Effects of 1-[1-(4-methylphenyl) (cyclohexyl)] 4-piperidinol and 1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol as Two new Phencyclidine Derivatives. *Arzneim-Forsch/Drug Res* 2009; 59:202-6.
46. Geneste P, Kamenka JM, Dessapt P. Method for Stereoselective Production of Substituted Cyclohexylcyanhydrines. *Bull Soc Chim Fr* 1980; 2:187-91.
47. Maddox VH, Godefroi EF, Parcell RF. The synthesis of phencyclidine and other 1-arylcyclohexylamines. *J Med Chem* 1965; 8:230-5.
48. Shebley M, Jushchysyn MI, Hollenberg F. Selective pathways for the metabolism of phencyclidine by cytochrome P450 2B enzymes: identification of electrophilic metabolites, glutathione and N-acetyl cysteine adducts. *Drug metabol Dispos* 2006; 34:375-83.
49. Burns GA, Ritter RC. The non-competitive NMDA antagonist MK-801 increases food intake in rats. *Pharmacol Biochem Behav* 1997, 56:145-9.
50. Ingold K. Structure and mechanism in organic chemistry. Cornell University Press, NY Ithaca, USA, 1953.

CURRENT AUTHOR ADDRESSES

- A. Ahmadi, Department of Chemistry, Faculty of Science, Islamic Azad University, Karaj, Iran. E-mail: abbas_ahmady_3957@yahoo.com (Corresponding author)
- J. Solati, 2Department of Physiology, Faculty of Science, Islamic Azad University, Karaj, Iran.
- M. Khalili, Department of Physiology, Faculty of Medicine, Shahed University, Tehran, Iran.