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ORIGINAL PAPER

Synthesis and antinociception properties of phencyclidine derivatives with modified aromatic or cycloalkyl rings and amino group

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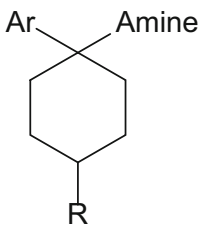
Abstract Phencyclidine is an arylcyclohexylamine compound which has received a lot of investigative attention due to the complex spectrum of behaviours and its complicated interactions with the central nervous system. Phencyclidine administration may act as stimulant, depressant, hallucinogen, and analgesic depending on dose and tested species. In this study, new phenyl and thienyl analogues with specific affinity for the phencyclidine sites in NMDA receptors, dopamine uptake blocking, or both of them were synthesized. The acute and chronic pain properties of these compounds were studied using the tail immersion and formalin tests on mice and the results were compared with control and phencyclidine groups at a dose of 10 mg/kg. The outcomes indicated that all synthesized compounds showed better activities to decrease acute thermal and chemical, but not chronic pains. Also, these effects were more significant for phenyl (group 1) compared to thiophene (group 2) analogues, which is probably due to the higher affinity of group 1 for inhibition of dopamine reuptake compared to binding to the phencyclidine sites in NMDA receptors in this family.

Graphical abstract



Keywords Phencyclidine · NMDA receptors · Dopamine reuptake blocking · Tail immersion test · Formalin test

Introduction

Phencyclidine (1-(1-phenylcyclohexyl)piperidine, **9a**) was originally considered for humans as an anaesthetic, but was soon striated due to its psychotomimetic properties, which include prolonged thought, visual disturbances, and agitation [1]. As a result, the scope of research on phencyclidine has shifted from its use as an anaesthetic compound to potential applications as a neuropharmaceutical [2]. It correlates with some neurotransmitter systems in the central nervous system. For instance, it is a noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, and it leads to the release and inhibits the reuptake of monoaminergic neurotransmitters, as well as dopamine, serotonin, and norepinephrine [3].

In addition to binding to the NMDA receptors, it also interferes with other brain functions. It blocks muscarinic and nicotinic acetylcholine receptors [4] as well as

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preventing neuronal depolarization at the aspartate-sensitive glutamate receptor [5]. It also binds to one of the several types of opiate receptors (sigma) on nerve cell membranes [6]. Up to now, many analogues of **9a** have been prepared and their pharmacological properties investigated [7–12].

Furthermore, the unique pharmacology of **9a** has already resulted in several structure–activity studies which have been researched in terms of its 3-cycle system; an aromatic cycle producing an area of negative charge, a basic heterocyclic nitrogen cycle bearing a localized positive charge, and a lipophilic cycloalkyl cycle. Alternations on these moieties could create many novel analogues with extensive biological activities [13].

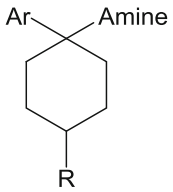
Therefore, as the first step a methyl group with high electron donating and dipole moment characters [9, 11, 12] were added on 4-position of the cyclohexyl ring to provide **9c** and **9h** of specifically binding to phencyclidine sites in the NMDA receptors [14].

Second, because of many pharmacological effects of 3,5-dimethyladamantan-1-amine (memantine), such as NMDA receptor antagonist [15], agonist of the dopamine D_2 receptor [16], local analgesic against cutaneous nociceptive stimuli [17], and treatment of moderate-to-severe Alzheimer's disease [18], it was used instead of the piperidine ring of **9a** to provide analogues **9b**, **9c**, **9g**, and **9h**. In addition, this amine moiety was replaced by cyclohexylamines (cyclohexylamine and *N*-methylcyclohexylamine) and pseudoephedrine with analgesic and many other pharmacological properties [19, 20] for synthesizing derivatives **9d**, **9e, 9f**, **9i**, **9j**, and **9k**.

Third, due to the reports on specific high binding affinity and selectivity for the phencyclidine sites in NMDA receptors, as well as neuroprotective potential properties of thienylcyclidine (1-[1-(2-thienyl)cyclohexyl]piperidine) [7] which was intended to replace the phenyl in **9a** by a bioisosteric 2-thienyl ring, this modification was also done for investigation on analgesic effects for all newly synthesized analogues with phenyl (group 1: compounds **9b**–**9f**) or thienyl (group 2: compounds **9g**–**9k**) rings (Scheme 1).

Finally, antinociception activities of these compounds were measured on mice using the tail immersion (acute thermal pain model) and the formalin (acute chemical and chronic pains model) tests and the outcomes are compared with the control and phencyclidine groups.

Scheme 1



Compound	Ar	Amine	R
9a	Phenyl	Piperidine	H
9b	Phenyl	Memantine	H
9c	Phenyl	Memantine	CH_3
9d	Phenyl	Pseudoephedrine	H
9e	Phenyl	Cyclohexylamine	H
9f	Phenyl	*N*-Methylcyclohexylamine	H
9g	2-Thienyl	Memantine	H
9h	2-Thienyl	Memantine	CH_3
9i	2-Thienyl	Pseudoephedrine	H
9j	2-Thienyl	Cyclohexylamine	H
9k	2-Thienyl	*N*-Methylcyclohexylamine	H

Results and discussion

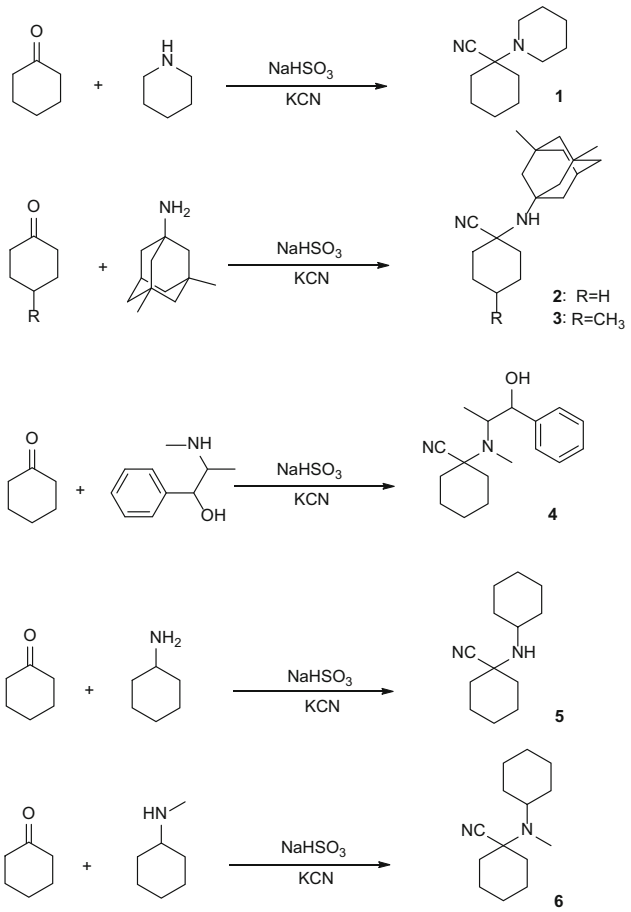
Chemistry

Phencyclidine (**9a**) and its analogues **9b**–**9k** were synthesized via Bruylants method [21], by the reaction between Grignard reagents **7**, **8** and substituted α-aminonitriles **1**–**6** (Schemes 2, 3). This method is easy to use when the final products are tertiary amines [22]. In the first step of this reaction, α-aminocarbonitrile intermediates **1**–**6** were prepared by the reaction of cyclohexanone or 4-methylcyclohexanone, amine (piperidine, memantine, pseudoephedrine, cyclohexylamine, or *N*-methylcyclohexylamine), KCN, and sodium bisulfite [23]. This compound ($NaHSO_3$) coordinates with the cyclohexanone (or 4-methylcyclohexanone), thus increasing its aqueous solubility and furthermore promoting nucleophilic attack [24].

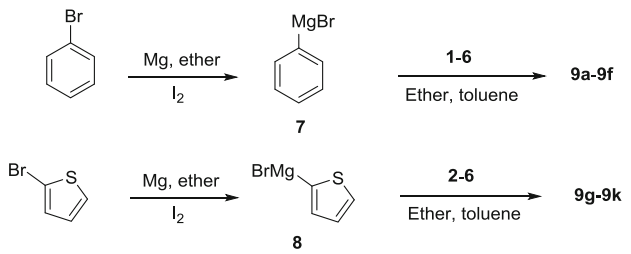
Then **9a**–**9k** were obtained by the reaction of these carbonitriles with Grignard reagents **7**, **8**. Nucleophilic attack of the Grignard reagent upon carbonitriles does not occur at the nitrile carbon, as in the classical sense [25] but does occur at the electron-deficient carbon alpha to the nitrile [26].

For increasing the rate of reaction in the final step, the molar ratio of Grignard reagents to carbonitriles were increased. This higher ratio could also increase the yield of reaction between these compounds to form the desired analogues **9a**–**9k**. Spectroscopic (IR, ^1H and ^{13}C NMR, mass) and elemental (CHN) data confirmed their structures.

Scheme 2



Scheme 3



The purity of each compound follows from the CHN analysis, also was checked by TLC using ethyl acetate/*n*-hexane as the eluent.

Anti-nociceptive activity of the compounds in tail immersion test

As indicated in Fig. 1 the pain threshold in the tail immersion test was markedly elevated by all compounds (except **9i**). However, compounds **9b**, **9c**, **9g**, and **9h** could exert prominent analgesic effects compared to the control and PCP animal groups ($p < 0.05$). Also, application of compounds **9d** and **9e**, **9f**, **9j**, and **9k** yielded a sensible anti-nociceptive activity which was higher than for the control mice ($p < 0.05$).

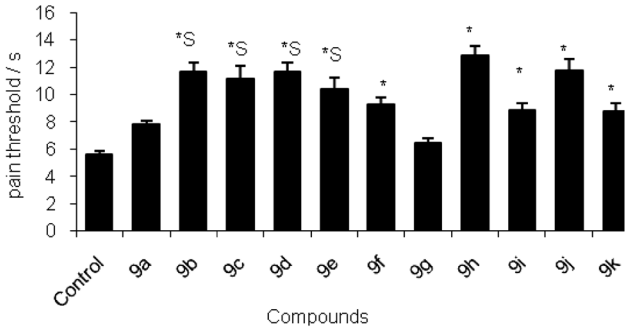


Fig. 1 Analgesic effect of **9a**–**9k** on pain threshold time produced by tail immersion test. *Bars* show the mean ± SEM pain thresholds in animal groups. *Asterisk* and *dollar* show $p < 0.05$ in comparison to the control and phencyclidine animal groups. $n = 12$

Pain assessment by formalin test

The licking frequency and duration time of the animal due to formalin injection are indicated in Figs. 2 and 3. As shown in Fig. 2 the compounds **9b**, **9d**, **9i**, and **9k** could significantly reduce the licking frequency at 10 min after formalin injection. Nevertheless, compounds **9b**, **9d**, and **9i** could respectively diminish the acute formalin pain to 72.2, 83.3, and 80 %, which was better than in the control group. On the other hand, **9k** has exerted a marked acute analgesic effect compared to the control (94.4 %) and PCP (92.5 %) animal groups ($p < 0.05$).

Licking duration time evaluation in concomitant to licking frequency show that the compounds **9b**, **9d**, **9i**, and especially **9k** could significantly reduce it. At 10 min after formalin injection (acute pain phase) compounds **9b**, **9d**, **9i**, and **9k,** respectively, reduced the duration time to 93.1, 95.3, 95.7, and 95.9 % ($p < 0.05$). However, the same analgesic activity was found for compounds **9b**, **9d**, and **9i** at 5 min after formalin injection, 54.9, 72.1, and 68.2 % ($p < 0.05$). Also, there was obtained a long-lasting acute analgesic effect for compound **9k** at 15 min after formalin application ($p < 0.05$).

Previous studies [14, 27] demonstrated that the two activities of arylcyclohexylamines (inhibition of dopamine reuptake and binding to PCP sites on NMDA receptors) are clearly separated. Modification of the aryl group of **9a** changes the selectivity of the compounds for the two sites: thus, BTCP (1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]piperidine, the famous analogue of phencyclidine with a unique high affinity for the dopamine transporter receptor with dopamine reuptake

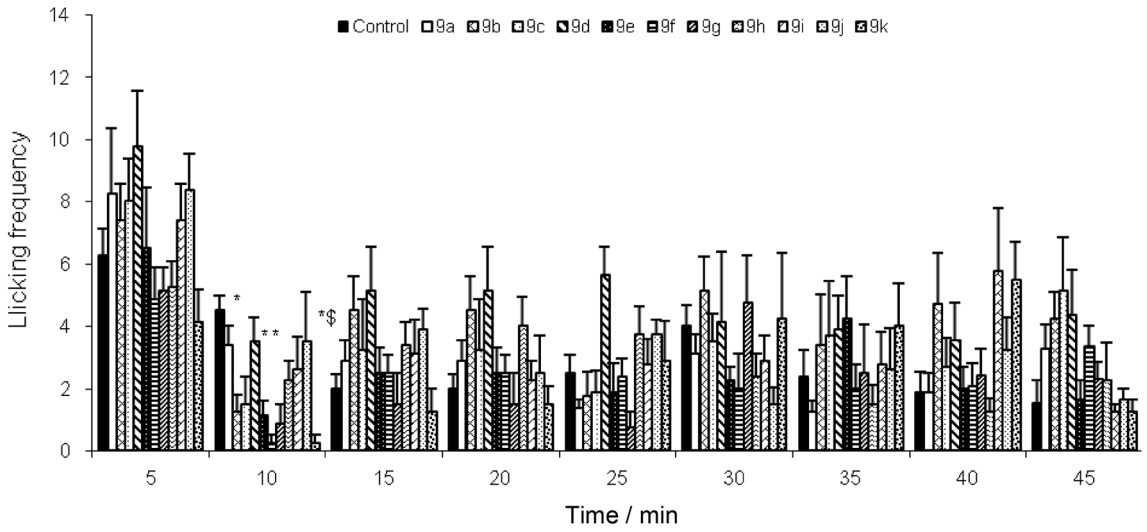


Fig. 2 The licking frequency of **9a–9k** in formalin test. *Bars* show mean ± SEM licking frequency. *Asterisk* and *dollar* show $p < 0.05$ in comparison to the control and phencyclidine animals. $n = 12$

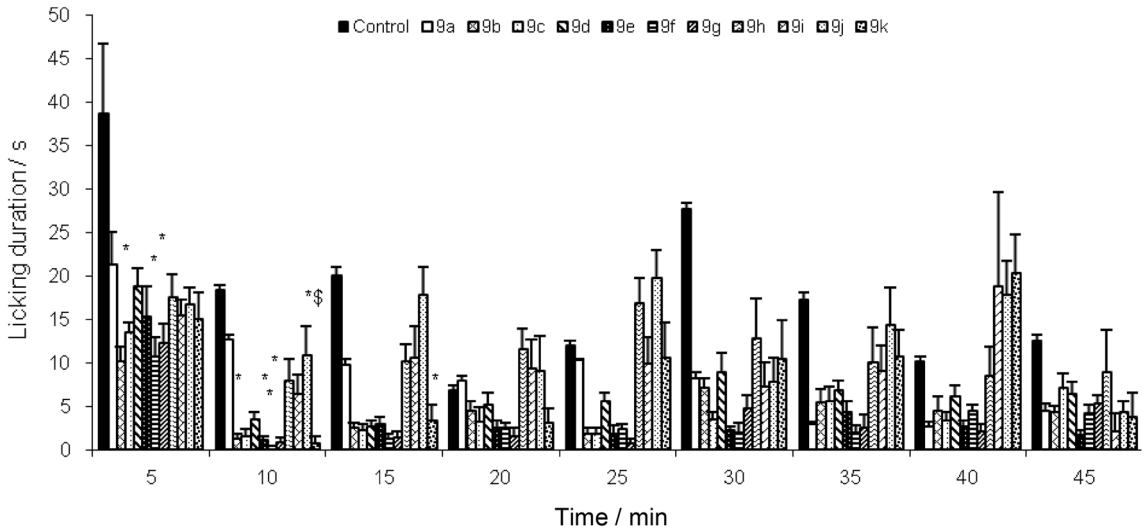


Fig. 3 The licking duration time of **9a–9k** in formalin test. *Bars* show mean ± SEM licking duration times. *Asterisk* and *dollar* show $p < 0.05$ in comparison to the control and phencyclidine animals. $n = 12$

blocking effects) is specific for the dopamine uptake and *N*-[1-(2-thienyl)cyclohexyl]pideridine is unique for PCP sites.

Phencyclidine (**9a**) and its analogues with an unmodified phenyl ring have close affinities for the two sites which are not selective. Therefore, it is expected that **9a** exerts its pharmacological activity through an action on the dopamine reuptake and on the PCP sites while the pharmacological activity of *N*-[1-(2-thienyl)cyclohexyl]pideridine is mediated mostly through correlation with the PCP sites [14]. Also, in such inhibitory processes, the role of cyclohexyl or piperidyl substitutions for modulating the affinities to these sites is very effective.

Therefore, in this study, modification on the three ring systems of **9a** was done. Initially, exchanging the aromatic moiety (an area with negative charge) with phenyl or thiophene rings could produce different affinity for inhibition of dopamine reuptake (benzothiophene analogues), PCP sites (thiophene analogues), or both of them (unmodified phenyl analogues), two groups of compounds were synthesized; group 1 contains compounds **9b–9f** with a phenyl ring and group 2 contains compounds **9g–9k** with a thiophene ring.

The results indicated that compounds in group 1 showed better activity to diminish acute thermal and chemical (except to compounds **9c** and **9h** that are contrary, 10 min after injection) but not chronic pains compared to group 2.

Secondly, because of addition of a methyl group with high electron donating and dipole moment activities [9–12] on the 4-position of the cyclohexyl ring of **9a** could produce

compounds with higher affinity for the PCP sites in NMDA receptors, compounds **9c** and **9h** were synthesized with this strategy. Comparison between substituted and unsubstituted cyclohexyl with phenyl (**9b** and **9c)** or thiophene (**9g** and **9h**) showed better analgesic effects for unsubstituted new analogues which may be due a higher affinity for both sites. These results also confirmed that dopamine uptake has a more effective role for antinociception in unsubstituted compounds whereas substituted ones are specific for PCP sites especially for compound **9h** with a thiophene ring.

Third, the piperidine ring (basic ring bearing a localized positive charge and with an affinity for both sites) of **9a** was changed pharmacologically potent amines (memantine, pseudoephedrine, and cyclohexylamines).

Memantine is a NMDA receptor antagonist which reduces certain types of brain activity by binding to the receptor on brain cells and blocking the activity of the neurotransmitter glutamate which plays a major role for treatment of Alzheimer's disease [15]. It also acts as an agonist at the dopamine D_2 receptor [16] and produces local analgesia against cutaneous nociceptive stimuli [17]. Also, cyclohexylamines affect the central nervous system and produce analgesic action as well as pseudoephedrine [19, 20].

Therefore, as shown in Figs. 1, 2 and 3, all of the analogues **9b–9f** with these pharmacological amines (especially memantine) were more effective than **9a** to reduce pains. Also, according to the previous studies, *N*-[1-(2-thienyl)cyclohexyl]pideridine analogues have less affinity for inhibition of dopamine reuptake compared to **9a** and BTCP but more specific for PCP sites [28].

However, unsubstituted *N*-[1-(2-thienyl)cyclohexyl]pideridine has better analgesic effects than unsubstituted **9a** [7, 29] analogues, but our results indicate less potent substituted *N*-[1-(2-thienyl)cyclohexyl]pideridine analogues **9g–9k** which proved that the affinity for dopamine uptake is a more effective factor than for PCP sites with respect to the analgesic activities in this family.

Conclusion

It can be concluded that unmodified phenyl analogues of phencyclidine (**9a**) with close affinity for DA uptake and PCP-binding sites on NMDA receptors are better candidates for reduction of acute and chemical pains compared to thiophene substituted ones with specific affinity for PCP sites.

Experimental

Cyclohexanone, 4-methylcyclohexanone, memantine, pseudoephedrine, cyclohexylamine, *N*-methylcyclohexylamine, piperidine, bromobenzene, 2-bromothiophene, magnesium turnings, diethyl ether, and all other chemicals were obtained from Merck Chemical Co. (Darmstadt, Germany). Melting points were determined with an Electrothermal digital apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX 300 MHz spectrometer (Karlsruhe, Germany) using TMS as internal reference. IR spectra were recorded on a Thermo Nicolet FT-IR (model Nexus-870, Nicolet Instrument Corp., Madison, Wisconsin, U.S.A.) 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 μm, Geel, Belgium). Elemental analysis was performed with a Perkin-Elmer CHN elemental analyzer model 2400; their results agreed favourably with the calculated values. Phencyclidine (PCP, **9a**) and carbonitrile intermediates were synthesized according to Refs. [22, 30].

Preparation of compounds 9a–9k

A solution of 0.0203 mol nitrile intermediates **1–6** in diethyl ether and toluene (1:1) were added to phenyl or 2-thiophene magnesium bromide reagents (**7** and **8**, prepared from refluxing of 0.0503 mol bromobenzene or 2-bromothiophene and 0.505 g of Mg in 100 cm^3 of dry ether). These mixtures were refluxed for additional hours (monitoring by TLC) and subsequently dipped into the solution of ice-NH_4Cl and NH_4OH. The organic layers were decanted and washed. The bases were acidified with 10 % H_2SO_4, basified with 10 % NaOH, neutralized by washing with water, extracted with ether, dried, and concentrated. The products were obtained as solids or viscous liquid compounds which for purification were passed through a silica gel column using ethyl acetate/*n*-hexane (95:5) as the eluent to yield **9a–9k**.

N-(1-Phenylcyclohexyl)-3,5-dimethyladamantan-1-amine (**9b**, $C_{24}H_{35}N$)
Yield 53 %; m.p.: 198 °C; IR (KBr): $\bar{\nu}$ = 3411, 3230, 2920, 1630, 1455, 1362, 698, 612 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.73–2.49 (29H, m), 4.27 (1H, s), 6.77–6.85 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 29.7, 32, 38.6, 38.9, 39.9, 40.0, 42.0, 42.8, 49.2, 50.0, 50.5, 126.3, 126.6, 128.8, 140.2 ppm; MS: *m/z* (%) = 337 (18), 286 (22), 259 (27), 229 (14), 202 (18), 179 (19), 163 (100), 122 (63), 107 (86), 93 (18), 71 (18).

N-(4-Methyl-1-phenylcyclohexyl)-3,5-dimethyladamantan-1-amine (**9c**, $C_{25}H_{37}N$)
Yield 65 %; m.p.: 208 °C; IR (KBr): $\bar{\nu}$ = 3404, 3031, 2906, 2842, 1593, 1482, 1454, 1356, 1250, 1071, 1008, 754, 738, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.73–2.48

(31H, m), 4.27 (1H, s), 7.04–7.44 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 25.9, 29.7, 29.9, 32.0, 38.6, 38.9, 39.2, 40.0, 42.0, 42.8, 49.2, 50.0, 50.5, 126.3, 126.6, 128.8, 140.2 ppm; MS: *m/z* (%) = 352 (12), 306 (12), 232 (23), 163 (100), 107 (76), 77 (29).

2-[N-Methyl-N-(1-phenylcyclohexyl)amino]-1-phenyl-propan-1-ol (**9d**, $C_{22}H_{29}NO$)
Yield 63 %; m.p.: 194 °C; IR (KBr): $\bar{\nu}$ = 3368, 3030, 2932, 2850, 1602, 1453, 1376, 1275, 1087, 1041, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.93–1.65 (13H, m), 2.13–2.54 (3H, m), 4.32–4.35 (1H, m), 4.57–4.59 (1H, m), 7.3–7.45 (10H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.4, 38.6, 39.2, 39.7, 40.0, 59.5, 68.2, 84.3, 125.3, 126.7, 127.6, 128.8, 129.3, 140.2 ppm; MS: *m/z* (%) = 323 (14), 273 (20), 248 (14), 202 (17), 160 (100), 111 (46), 77 (20).

N-Cyclohexyl-1-phenylcyclohexanamine (**9e**, $C_{18}H_{27}N$)
Yield 64 %; m.p.: 136 °C; IR (KBr): $\bar{\nu}$ = 3428, 2928, 1632, 1451, 1122, 1023, 875, 754, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.07–2.9 (20H, m), 4.26–4.28 (1H, m), 7.32–7.45 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 20.5, 24.2, 25.0, 30.6, 49.7, 67.4, 126.9, 127.8, 129.5, 140.8 ppm; MS: *m/z* (%) = 258 (15), 246 (18), 230 (100), 215 (20), 198 (18), 183 (35), 170 (45), 152 (20), 141 (18), 127 (15), 115 (18), 100 (40), 85 (35), 71 (45), 56 (78), 43 (80).

N-Cyclohexyl-N-methyl-1-phenylcyclohexanamine (**9f**, $C_{19}H_{29}N$)
Yield 76 %; m.p.: 139 °C; IR (KBr): $\bar{\nu}$ = 3425, 2939, 1637, 1499, 1457, 1391, 1125, 1023, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.07–1.94 (20H, m), 2.50 (3H, s), 2.87–2.93 (1H, m), 7.19–7.46 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.2, 25.0, 30.6, 49.7, 68.2, 80.02, 126.7, 127.9, 129.9, 140.6 ppm; MS: *m/z* (%) = 272 (12), 259 (14), 246 (21), 230 (32), 215 (33), 198 (30), 183 (59), 170 (47), 154 (67), 141 (18), 128 (14), 105 (35), 91 (18), 77 (35), 56 (100), 43 (59).

N-[1-(2-Thienyl)cyclohexyl]-3,5-dimethyladamantan-1-amine (**9 g**, $C_{22}H_{33}NS$)
Yellow viscous liquid; yield 50 %; IR (KBr): $\bar{\nu}$ = 3401, 2916, 1693, 1513, 1455, 1417, 1235, 1206, 1048, 828, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.78–2.48 (29H, m), 4.24 (1H, s), 7.04–7.44 (3H, m) ppm; ^{13}C NMR ($CDCl_3$):δ = 29.5, 30, 31.8, 38.6, 39.9, 40.0, 41.4, 45.8, 49.4, 50.5, 52.2, 123.8, 125.1, 126.2, 136.5, 144.3 ppm; MS: *m/z* (%) = 343 (70), 279 (18), 262 (10), 248 (90), 205 (18), 179 (54), 166 (68), 149 (41), 122 (100), 108 (90), 93 (14), 81 (10).

N-[4-Methyl-1-(2-thienyl)cyclohexyl]-3,5-dimethy-ladamantan-1-amine (**9 h**, $C_{23}H_{35}NS$)
Yellow viscous liquid; yield 58 %; IR (KBr): $\bar{\nu}$ = 3401, 2919, 2609, 1451, 1412, 1045, 827, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.74–2.47 (31H, m), 4.26 (1H, s), 7.04–7.45 (3H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 25.9, 29.5, 30.0, 31.8, 38.6, 39.7, 40.0, 41.4, 45.8, 49.3, 50.5, 52.2, 123.8, 125.1, 126.2, 136.5, 144.3 ppm; MS: *m/z* (%) = 358 (10), 315 (8), 287 (10), 220 (11), 179 (36), 122 (100), 107 (77), 80 (12).

2-[N-Methyl-N-[1-(2-thienyl)cyclohexyl]amino]-1-phenyl-propan-1-ol (**9i**, $C_{20}H_{27}NOS$)
Yellow viscous liquid; yield 57 %; IR (KBr): $\bar{\nu}$ = 3356, 3035, 2930, 2467, 1638, 1404, 1034, 761, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.82–1.57 (13H, m), 2.40–2.63 (3H, m), 3.2–3.25 (1H, m), 4.13–4.53 (1H, m), 6.94–7.86 (8H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.2, 29.7, 38.6, 39.2, 40.0, 59.2, 68.2, 86.7, 125.2, 126.6, 127.3, 128.2, 128.6, 140.2, 141.5 ppm; MS: *m/z* (%) = 329 (14), 287 (10), 248 (15), 195 (15), 179 (42), 166 (14), 149 (57), 127 (14), 111 (50), 91 (35), 77 (95), 58 (100).

N-Cyclohexyl-1-(2-thienyl)cyclohexanamine (**9j**, $C_{16}H_{25}NS$)
Yield 68 %; m.p.: 160 °C; IR (KBr): $\bar{\nu}$ = 3412, 2938, 2859,1638, 1456, 1281, 1125, 1022, 633 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.00–2.89 (20H, m), 4.26–4.28 (1H, m), 7.28–7.65 (3H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 20.4, 24.1, 25.1, 28.7, 30.5, 49.7, 67.8, 125.8, 128.7, 132.0, 144.8 ppm; MS: *m/z* (%) = 263 (17), 170 (83), 149 (100), 113 (18), 98 (15), 84 (15), 71 (40), 56 (72), 43 (55).

N-Cyclohexyl-N-methyl-1-(2-thienyl)cyclohexanamine (**9 k**, $C_{17}H_{27}NS$)
Yield 82 %; m.p.: 163 °C; IR (KBr): $\bar{\nu}$ = 3420, 2939, 2860, 1637, 1499, 1457, 1391, 1125, 1023, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.06–1.92 (20H, m), 2.50 (3H, s), 2.87–2.92 (1H, m), 7.19–7.9 (3H, m) ppm; ^{13}C NMR ($CDCl_3$): δ = 20.5, 24.2, 26.0, 28.7, 30.5, 49.7, 63.7, 125.5, 127.8, 128.8, 144.6 ppm; MS: *m/z* (%) = 278 (10), 264 (8), 236 (9), 202 (6), 171 (9), 149 (10), 138 (11), 125 (8), 111 (12), 99 (90), 82 (23), 70 (45), 56 (100), 43 (95).

Animals

Ninety-six laboratory male NMRI mice, weighing 25–31 g at the starting of the test were randomly housed, four per coop in a temperature-controlled colony room under 12 h light/dark period. Animals free access to feed or water and standard laboratory rat chow. All behavioural experiments were performed between 9 am and 4 pm under the enough room light and at 25 °C. This study was done according to the Guide for the Care and Use of Laboratory Animals and those of the Research Council of Shahed University of Medical Sciences (Tehran, Iran).

Mortality (number of death), morbidity (defined as any abnormal condition or behaviour due to a disorder),

irritability (a condition of aggressiveness or increased response on handling), and other related abnormal states were not observed in the experimental animals. In addition, the motor coordination index (measured by Rota-rod apparatus, Harvard, UK) did not indicate any significant difference among the treated rats.

Formalin test

In this test, formaldehyde solution (20 mm^3, 3 %) was subcutaneously injected into the plantar surface of control mice hind paw [31]. Then, the animals were placed in a Plexiglas chamber (30 × 30 × 30 cm^3) with a mirror at 45° angle underneath for accurate observation. In the treatment and control groups ($n = 8$ per group), the compounds **9a–9k** (10 mg/kg dosage) [32] and saline were administered intraperitoneally 30 min before formaldehyde injection. However, prior to the experiments, all animals were habituated to the observation chamber for 30 min prior to the experimental sessions 5 times at 5 min intervals to adapt them with the environment. The behavioral pain reactions i.e., the licking time and frequency were detected and recorded in each 5 min intervals during 45 min period after formalin injection. The first 10 min after formalin injection is known as the acute neurogenic pain and the period between 15 and 45 min is known as chronic inflammatory pain.

Tail immersion Test

The acute thermal pain was normally modelled by the tail immersion test [33]. Thirty minutes after an intraperitoneal injection of compounds **9a–9k** (10 mg/kg dosage) [31] and an equivalent volume of saline (control), the mice ($n = 8$ in each group) were housed in an animal restrainer. Then, the terminal 3 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 heated water was measured and recorded as pain threshold. The record of pain threshold was repeated in 5 min intervals until 45 min after initiation of the test. Cut-off latency in 15 s was employed to avoid damaging the tail.

Statistical analysis

Sigma stat 3.5 soft was used for statistical analysis. The measured data were presented as mean ± SEM. Comparisons were carried out as one-way analysis of variance (ANOVA) followed by post hoc Tukey test with a p value < 0.05 as the level of significance.

Experimental psychomotor coordination (PMC) index

This test was done by means of Rota-rod Treadmill with shock facility apparatus (Harvard model 865) after root or new drugs administration. First, animals were trained by their placing on the rolling bar where they had to walk on it. Then, for 5 times, they were placed in the 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 s, 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.

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