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# Antidepressant-like profile of action of two 4-amine derivatives of 10,11-dihydro-5*H*-dibenzo [*a*,*d*] cycloheptane in mice evaluated in the forced swimming test

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**Abstract**—This study investigated the antidepressant-like effect of 4-amine derivatives of 10,11-dihydro-5*H*-dibenzo-alkylamine-cycloheptane, 4-amine (3-*N*,*N*-dimethylpropylamine)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane-5-one (ADDCH1) and 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2), in a validated experimental model of depression, the forced swimming test (FST) in mice. Female adult mice were sub-chronically (three doses in 24 h) or repeatedly (once a day for 10 days) treated with either of the compounds and evaluated in the FST. The sub-chronic treatment promoted a dose-dependent reduction in the immobility time in the FST with the doses of 50 mg/kg (ADDCH1) and 30 mg/kg (ADDCH2) ip being the most effective (33% and 37% of reduction, respectively). A similar profile of action was observed in the animals repeatedly treated with ADDCH1 50 mg/kg or ADDCH2 30 mg/kg ip (for 10 days) and there was no sign of motor impairment or locomotor activation as evaluated in the rota-rod and open-field tests, respectively. These findings suggest that these amine derivatives of the system dibenzo-cycloheptane have an antidepressant-like action which could be of clinical interest and, therefore, deserves further investigation. In addition, putative underlying mechanisms of action are discussed.


## 1. Introduction

Depression is one of the most prevalent psychopathologies in the Western world with prevalence number between 9% and 18%[1] affecting 1 in 10 men and 1 in 5 women in adulthood.[2] Its clinical therapy is based on classical antidepressant drugs such as monoamine oxidase inhibitors (e.g., tranylcypromine) and drugs that prevent the reuptake of catecholamines (e.g., imipramine). Second generation drugs include compounds such as the selective inhibitors of serotonin reuptake (e.g., fluoxetine) and drugs with non-conventional mechanisms of action (e.g., trazodone, nefazodone and mirtazapine). These therapeutic tools are clinically effective but all of them also present numerous side-effects besides a delay to the onset of beneficial clinical effects.[3,4] For these reasons, at least, new therapeutic agents, perhaps with fewer collateral effects and/or with innovative mechanisms of action, which could reduce the delay in the onset of antidepressant therapy, are highly desirable.

Previously, Jansen (1964)[5] proposed that the compound 5-alkylamine 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane should possess antidepressant activity due to its structural similarity to other antidepressants such as imipramine, although so far no studies were performed to confirm this effect for this class of compounds. Therefore, the present study examined the putative antidepressant-like activity of two 4-amine derivatives of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane, 4-amine(3-*N*,*N*-dimethylpropylamine)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane-5-one (ADDCH1) and 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2), in a well-validated experimental model of depression, the forced swimming test (FST).[6]

*Keywords*: Depression; Forced swimming test; Amine derivatives; Dibenzocyclo heptane; Heterocyclic compounds.
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## 2. Results

### 2.1. Evaluation of the antidepressant-like effect of the 4-amine-dibenzocycloheptane derivatives after sub-chronic treatment

Sub-chronic treatment with the compound ADDCH1 or ADDCH2 promoted a dose-related decrease in the immobility time in the FST, as depicted in Figure 1 (control = 210.65 ±4.37 s; $ADDCH1_{(5mg/kg)}$ = 220.22 ± 5.19 s; ADD $CH1_{(15mg/kg)}$ = 187.10 ± 4.39 s; $ADDCH1_{(30mg/kg)}$ = 169.31 ± 13.72 s; $ADDCH1_{(50mg/kg)}$ = 132.00 ± 21.03 s; $ADDCH1_{(100mg/kg)}$ = 206.38 ± 12.38 s; $IMI_{(15mg/kg)}$ = 138.33 ± 12.76 s) ($F_{(6,81)}$ = 7.37; $P < 0.0001$) and Figure 2 (control = 215.67 ± 2.82 s; ADD $CH2_{(1mg/kg)}$ = 215.00 ±9.48 s; $ADDCH2_{(5mg/kg)}$ = 197.00 ± 7.35 s; ADD $CH2_{(15mg/kg)}$ = 186.57 ± 13.66 s; $ADDCH2_{(30mg/kg)}$ = 169.92 ± 6.67 s; $ADDCH2_{(50mg/kg)}$ = 199.25 ± 14.51 s; $IMI_{(15mg/kg)}$ = 137.33 ± 23.43 s) ($F_{(6,66)}$ = 6.21; $P < 0.0001$). The most effective antidepressant-like doses for ADDCH1 and ADDCH2 were 50 mg/kg and 30 mg/kg, respectively, while the immobility time of animals treated with the highest doses did not differ from control values.

### 2.2. Evaluation of the antidepressant-like effect of the 4-amine-dibenzocycloheptane derivatives after repeated treatment (once a day for 10 days)

As shown in Figure 3, systemic repeated treatment with ADDCH1 (50 mg/kg) or ADDCH2 (30 mg/kg) for 10 days reduced (13% and 15%, respectively) the immobility time of mice in a similar way to that observed after the acute treatment and imipramine treatment when compared to control values (control = 218.25 ± 6.62 s; $ADDCH1_{(50mg/kg)}$ = 190.33 ± 7.91 s; $ADDCH2_{(30mg/kg)}$ = 186.40 ± 11.12; $IMI_{(15mg/kg)}$ = 177.50 ± 6.06 s) ($F_{(3,21)}$ = 5.90; $P < 0.01$).

### 2.3. Evaluation of the effect of the 4-amine-dibenzocycloheptane derivatives on the locomotor activity and motor co-ordination after repeated treatment

The spontaneous locomotor activity and the motor co-ordination of the animals, as evaluated in the open-field

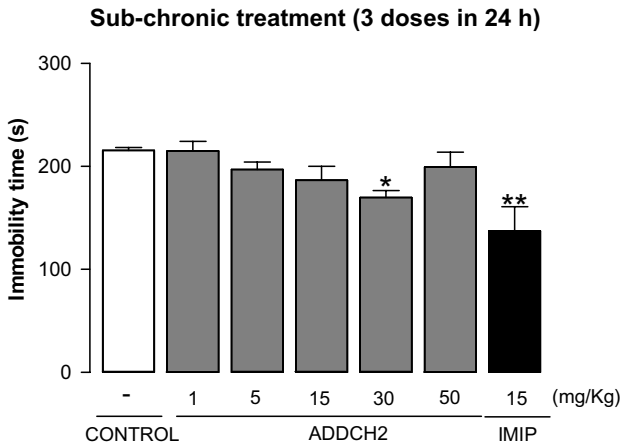



**Figure 2.** Effects of the sub-chronic treatment with 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2) and imipramine (three doses in 24 h) on the immobility time in a 5-min swim test. Each column represents the mean ± SEM of 7–15 animals. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus control group (all comparisons were made by ANOVA followed by Newman–Keuls' test).

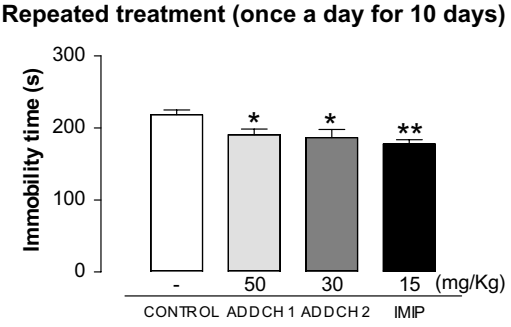



**Figure 3.** Effects of the repeated treatment (10 days) with 4-amine-(3-*N*,*N*-dimethyl propylamine)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]-cycloheptane-5-one (ADDCH1) or 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2) and imipramine on the immobility time in a 5-min test. Each column represents the mean ± SEM of 5–8 animals. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus control group (all comparisons were made by ANOVA followed by Newman–Keuls' test).

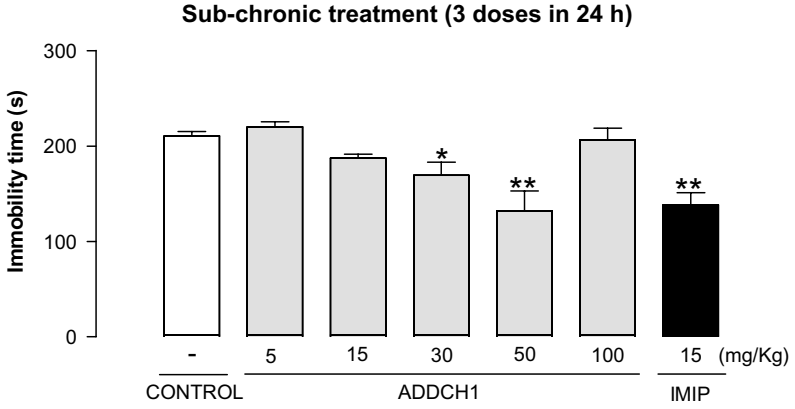



**Figure 1.** Effects of the sub-chronic treatment with 4-amine-(3-*N*,*N*-dimethyl propylamine)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]-cycloheptane-5-one (ADDCH1) and imipramine (three doses in 24 h) on the immobility time in a 5-min swim test. Each column represents the mean ± SEM of 6–19 animals. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus control group (all comparisons were made by ANOVA followed by Newman–Keuls' test).

**Table 1.** Effects of the repeated treatment (10 days) with 4-amine-(3-*N*,*N*-dimethyl propylamine)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]-cycloheptane-5-one (ADDCH1) or 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2) and imipramine on the locomotor activity and motor performance evaluated in the open-field and rota-rod tests, respectively

| Drug | Dose (mg/kg) | Open-field locomotor activity | Rota-rod | | Number of animals |
|---|---|---|---|---|---|
| | | | Number of falls | Time on the rotating bar (s) | |
| Control | — | 84.12 ± 4.98 | 0.75 ± 0.31 | 57.85 ± 0.82 | 8 |
| ADDCH1 | 50 | 91.33 ± 4.59 | 0.50 ± 0.34 | 59.50 ± 0.50 | 6 |
| ADDCH2 | 30 | 81.20 ± 13.10 | 0.40 ± 0.24 | 58.60 ± 0.98 | 5 |
| IMIP | 15 | 82.83 ± 9.25 | 0.83 ± 0.40 | 58.11 ± 0.87 | 6 |

Data are expressed as means ± SEM of 5–8 animals (all comparisons were made by ANOVA followed by Newman–Keuls' test).

and rota-rod tests, respectively, were not affected by the repeated treatment with both compounds ADDCH1 and ADDCH2, as shown in Table 1 ($P > 0.05$).

## 3. Discussion

The compounds 4-amine(3-*N*,*N*-dimethylpropylamine)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane-5-one (ADDCH1) and 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2) clearly present antidepressant-like profiles of action after sub-chronic and repeated treatment, as shown by the significant reduction in the immobility time recorded in the forced swimming test (FST). A reduction in the immobility time in the FST is exhibited by therapeutically useful antidepressant drugs[7,8] and is very well accepted as a reliable indicator of this kind of pharmacological activity.[9–11] However, a demonstration of effect under an acute schedule of administration is not sufficient to postulate an antidepressant activity since there have been some false positive results for drugs such as caffeine, anticholinergic and antihistaminergic drugs.[12] Nevertheless, the results obtained after the repeated treatment with these 4-amine-dibenzocycloheptane derivatives confirm their antidepressant-like profiles of action since the effect is still present at the end of a 10-day treatment.

Due to the fact that the FST is based on a motor response of animals, it could be affected by changes in their motor activity and/or performance. For this reason, animals were evaluated in the rota-rod and open-field tests. Sub-chronic and repeated treatment with ADDCH1 or ADDCH2 did not alter the behavioral performance of the animals which essentially depends on their motor function. This observation strongly indicates that the reduction in the immobility time is due to a selective antidepressant-like effect of these 4-amino-dibenzocycloheptane compounds, and not merely the result of a general stimulation of the animal's motor activity.

Several drugs with central nervous system (CNS) activity possess two benzenoid rings fused to a six- or seven-membered ring, in some cases aromatic, and to an alkyl chain with terminal substituted nitrogens.[13,14] The 10,11-dihydro-5*H*-dibenzo-alkylamine cycloheptane system could exhibit several pharmacological effects including antidepressant[5] and antipsychotic activity.[15–17] The main differences between 4 -amine (3-*N*,*N*-dimethylpropylamine)-10,11-dihydro-5*H*-dibenzo[*a*,*d*] cycloheptane-5-one and other drugs known to be centrally active are the terminal groups which present different electron density and the positions of their nucleophilic moiety. These changes could endow the molecule with different pharmacological properties such as antidepressant-like (ADDCH1 and ADDCH2), or antipsychotic-like (chlorpromazine) activity which is not investigated in the present study.

The mechanisms of action to support this antidepressant-like activity, an effect on the NA and/or 5-HT systems, function in a similar way to some commercially clearly structurally similar to typical tricyclic antidepressants, besides also sharing similarities with CNS-acting phenothiazines and histaminergics such as clozapine and cyproheptadine.[14] Therefore, based on the chemical structures of ADDCH1 and ADDCH2, their putative underlying mechanisms of action involving the catecholaminergic system are presently under investigation in our laboratory.[18]

## 4. Conclusion

In conclusion, the present results showed a clear antidepressant-like effect of 4-amine(3-*N*,*N*-dimethylpropylamine)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]-cycloheptane-5-one (ADDCH1) and 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2). The underlying molecular mechanism of action is presently under investigation but the findings shown here are very significant because they reveal a new potential tool for the treatment of depression, an important medical field, since this psychopathology is one of the most prevalent throughout the world and is still in need of new and perhaps better therapeutic approaches.[19]

## 5. Materials and methods

### 5.1. Drugs and solvents

The drugs and solvents used were: imipramine chlorhydrate, from Sigma Chemical Company (St. Louis, USA) which and two 4-amine derivatives of dibenzocycloheptane (ADDCH1 and ADDCH2), were synthesized in-house according to the method described by Romeiro and Martins (2001).[13]

### 5.2. Animals

Female adult Swiss mice (25–35 g) were used in all experiments. They were housed in groups of 20 animals per plastic cage under controlled conditions of light (from 07:00 to 19:00 h) and temperature (23 ± 2 °C). The animals were allowed free access to standard laboratory food and tap water, and to adapt to the laboratory environment for at least one week before the behavioural assessment. For each treatment, a different group of experimental and control animals was used. All animal testing was carried out according to international standards of animal welfare recommended by the Brazilian Society of Neuroscience and Behaviour (Act 1992) and approved by the local Committee for Animal Care in Research (# 081/CEUA and 23080.001156// 2001-50/UFSC). The minimum number of animals and duration of observation required to obtain consistent data were employed.

### 5.3. Measurement of immobility

To measure immobility, we essentially followed the method proposed by Porsolt and colleagues (1977,1978).[7,8] Briefly, animals were submitted to a swimming stress session for 15 min (pre-test), 24 h before being individually returned to the same plastic cylinders (height 18.5 cm, diameter 12.5 cm) containing 13.5 cm of water at 25 °C, for 5 min (test). In the test session, animals were placed in the plastic cylinders for just 5 min, 1 h after the last injection (sub-chronic or repeated treatment). In both treatments, the behavioural observation was performed for up to 5 min by an experienced observer, who was blind to the treatment conditions. Animals were judged to be immobile when they ceased struggling and remained floating motionless in the water, making only those movements necessary to keep their head above water.

### 5.4. Measurement of locomotor activity

Animals were tested for their spontaneous locomotor activity on the tenth day of treatment. The test was carried out in a transparent Plexiglas arena (30 × 30 × 15 cm). The apparatus floor, made from black Plexiglas, was divided into nine equal squares and the number of squares crossed in 5 min was counted. The behaviour of each animal was assessed under red light illumination (15 W). The field was thoroughly cleaned with 10% ethanol solution between tests. All sessions were videotaped using an infra-red video camera (Philco, model PVC-4H10, Manaus, Brazil), to enable playback when necessary.

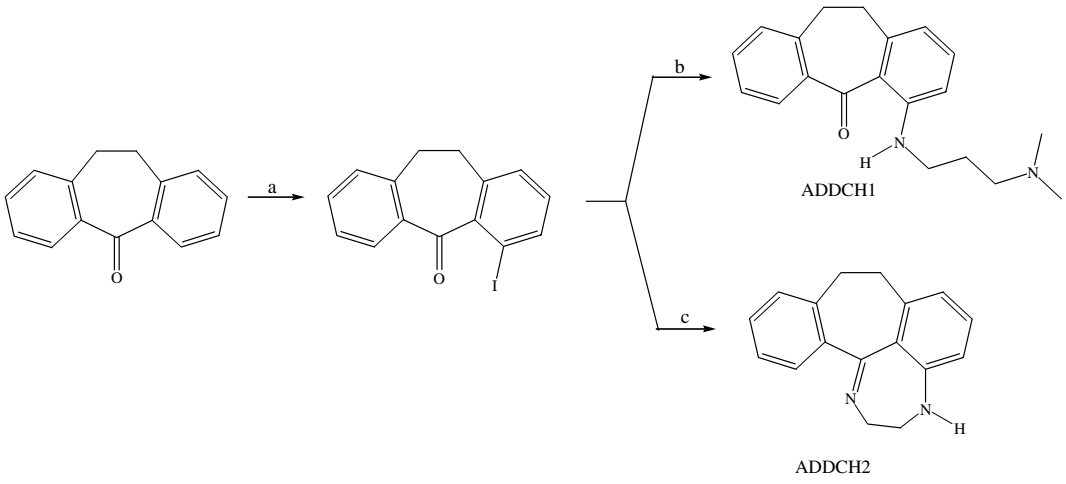
### 5.5. Measurement of motor performance

Mice were placed on the horizontal rotating bar (diameter 2.5 cm, 12 rpm) of the rota-rod apparatus on the tenth day of treatment, immediately after the open-field test. Total time spent on the bar during a 1-min session was registered using a stopwatch, and the number of falls during the session was also recorded.[20]

### 5.6. Experimental procedures

**5.6.1. Compound synthesis and features.** Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1420 spectrometer in potassium bromide pellets. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a 300 MHz Varian Unity spectrometer, with TMS as an internal standard, coupling constants are given in Hz. Low-resolution EI mass spectra were recorded on a MAT 711A Finnigan instrument, at 70 eV with the source at 200 °C and an accelerating voltage of 8 KV. The samples were heated and introduced directly into the source area. Analytical thin-layer chromatography (TLC) was performed on silica gel plates, 60F-254 (0.25 mm, Merck).

**5.6.2. General procedure for ADDCH1 and ADDCH2.** The first step in the synthesis of dibenzocycloheptane derivatives is the introduction of the iodine atom in position 4 of the dibenzosuberone to give a iodinated compound. A solution of the iodinated ketone and appropriated amine was stirred under reflux for several



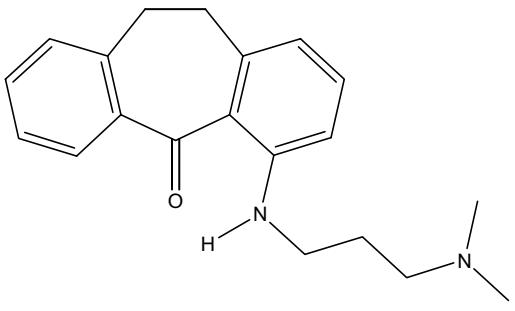

**Scheme 1.** Reagents and conditions: (a) Thalium trifluoroacetate (TTFA)/trifluoroacetic acid (TFA)/KI/48 h; (b) *N*,*N*-dimethylpropylamine/reflux; (c) ethilinediamine/reflux.

hours. The solution was cooled and chloroform was added before washing three times with water. The organic phase was dried with $Na_2SO_4$ and concentrated. Column chromatography of the residue on silica gel afforded the product as yellow oil (Scheme 1), which was characterized by infrared, NMR and mass spectrometry.[13]

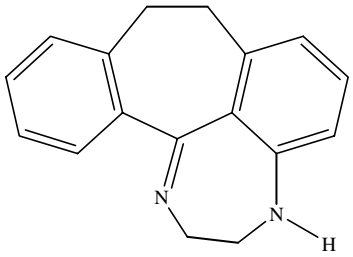
Compound 1, 4-amine(3-*N*,*N*-dimethylpropylamine)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane-5-one (ADDCH1), was isolated with 55% yield. IR (film $cm^{-1}$) 3391, 2941, 2815, 1596, 1573, 1505, 1462, 1277, 1242, 1158, 1101, 1080, 926, 781, 719, 665. EIMS (70 eV) *m*/*z* (%), $[M]^+$ 308.18881 (12), 237.11060 (20), 220.10434 (52), 149.01597 (10), 81.05897 (19). $C_{20}H_{24}N_2O$ HR. Calcd 308.18886; found: 308.18881. $^1H$ NMR d ($CDCl_3$, ppm) 1.83 (tt, $J = 7.2$ and 7.2 Hz, 2H), 2.25 (s, 6H), 2.39 (t, $J = 7.2$ Hz, 2H), 3.07–3.25 (m, 6), 6.44 (d, $J = 7.2$ Hz, 1H), 6.61 (d, $J = 7.8$ Hz, 1H), 7.17–7.39 (m, 4H), 7.73 (br s, 1H), 7.98 (dd, $J = 8.1$ and 1.5 Hz, 1H). $^{13}C$ NMR ($CDCl_3$) 26.93, 34.76, 35.65, 41.60, 45.30, 57.37, 109.78, 115.77, 121.57, 126.09, 128.81, 130.84, 131.52, 132.90, 139.92, 140.49, 143.11, 149.78, 197.52 (Scheme 2).

Compound 2, 1,2,3,4,8,9-hexahydro-dibenzocyclohepta[4,4*a*,5-*ef*]1,4-diazepin (ADDCH2), was isolated with 60% yield. IR (film $cm^{-1}$) 3365, 3281, 3053, 2920, 2858, 1614, 1596, 1478, 1459, 1330, 1314, 1295, 1262, 1215, 1160, 1101, 1063, 1033, 994, 961, 894, 849, 804, 776, 759, 735, 700, 688, 642. EIMS (70 eV) $C_{17}H_{16}N_2$. *m*/*z* (%), $[M]^+$ 248 (35), 247 (100), 220 (20), 204 (20), 189 (15), 178 (10), 165 (12), 115 (10), $^1H$ NMR d ($CDCl_3$, ppm) 3.17–3.02 (m, 5H), 3,84–3.74 (m, 4H), 6,56 (dd, $J = 7.5$ and 0.9 Hz, 1H), 6,80 (dd, $J = 8.1$ and 0.9 Hz, 1H), 7,09 (dd, 7.5 and 1.5 Hz, 1H) 7,12 (t, $J = 7,8$ Hz, 1H), 7.29–718 (m, 2H), 7,85 (dd, 7.2 and 2.1 Hz, 1H). $^{13}C$ NMR ($CDCl_3$) 32.60, 33.82, 49.24, 53.73, 118.01, 121.13, 125.99, 127.34, 129.09, 129.51, 129.62, 130.19, 137.88, 139.09, 140.14, 145.05. 172.51 (Scheme 3).

**5.6.3. Evaluation of the antidepressant-like effect of the 4-amine-dibenzocycloheptane derivatives after sub-chronic treatment (three doses in 24 h).** The compound ADDCH1 (5–100 mg/kg, ip) or ADDCH2 (1–50 mg/kg, ip) was administered 1 and 18 h after the swimming stress session and a third dose was administered 1 h before the mice were tested in the forced swimming test for




Scheme 2.




Scheme 3.

5 min, as previously described. Imipramine (IMI, 15 mg/kg ip) was employed as the antidepressant standard drug using the same administration schedule. The control group received 0.9% NaCl in a constant volume by the same route and under a similar schedule of administration.

**5.6.4. Evaluation of the antidepressant-like effect of the 4-amine-dibenzocycloheptane derivatives after repeated treatment (once a day for 10 days).** Another group of animals was treated for 10 days with ADDCH1 (50 mg/kg ip) or ADDCH2 (30 mg/kg ip) and tested in the forced swimming test 1 h after the last drug administration. The control group received vehicle (0.9% NaCl) in a constant volume by the same route and under a similar schedule of administration.

**5.6.5. Evaluation of the effect of the 4-amine-dibenzocycloheptane derivative on the locomotor activity and motor co-ordination after repeated treatment.** The locomotor activity and motor co-ordination were assessed immediately before the forced swimming test. Imipramine (15 mg/kg ip) was used as the antidepressant standard drug following the same administration protocol.

### 5.7. Statistical analysis

Values are presented as group means and SEM. The data were analysed by one-way analysis of variance (ANOVA), and post hoc comparison of means was carried out with Newman–Keuls' test (sub-chronic and repeated treatments), using GraphPad Prism® version 3.0, with $P < 0.05$ being considered statistically significant.

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