



Synthesis and pharmacological evaluation of (2-oxaadmant-1-yl)amines

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ABSTRACT

The synthesis of several (2-oxaadmant-1-yl)amines is reported. They were evaluated as NMDA receptor antagonists and several of them were more active than amantadine, but none was more potent than memantine. None of the tested compounds displayed antiviral activity. Two of the derivatives showed a significant level of trypanocidal activity.

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1. Introduction

1-Adamantylamine (amantadine) and its 3,5-dimethyl analogue, memantine, are NMDA receptor antagonists approved for the treatment of Parkinson's and Alzheimer's disease, respectively.¹ Amantadine also has prophylactic and therapeutic activities in influenza A virus infections², and related adamantane derivatives show antiviral activity.³ Moreover, amantadine, memantine, and related polycyclic amines possess trypanocidal properties.⁴

It is well known in medicinal chemistry that substitution of a methylene unit in a bioactive compound for an oxygen atom usually leads to analogues showing similar activity to the parent compound.⁵ Indeed, NGP1-01, a brain-permeable, oxa-polycyclic cage amine, is a dual action uncompetitive NMDA receptor antagonist and blocker of L-type calcium-channels. In addition, several experiments have shown that NGP1-01 has neuroprotective activity (Fig. 1).⁶

Based on the interesting and widely observed biological activity of amantadine, memantine, and NGP1-01, we therefore sought to

explore the biological profile of (2-oxaadmant-1-yl)amine derivatives.

In this paper, we report the synthesis of several (2-oxaadmant-1-yl)amines and related compounds and their pharmacological evaluation as NMDA receptor antagonists, and antivirals and trypanocidal agents.

2. Results and discussion

2.1. Chemistry

Starting from the known diketone **1**,⁷ we have prepared amines **2–4**, **7**, **8**, and **10–15** using classical methods in amine chemistry (see Scheme 1).

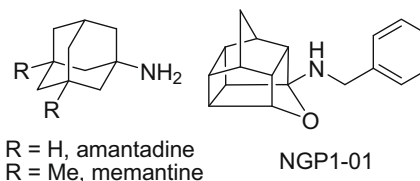


Figure 1. Amantadine, memantine, and NGP1-01 structures.

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Secondary amines **2a** and **2b** were obtained in high yields following a known general procedure that involves reductive amination of diketone **1**.⁸ Thus, reaction of **1** with benzylamine followed by reduction with LiAlH₄ led to amine **2a** in 58% yield. Similarly, reductive amination of **1** with phenethylamine furnished amine **2b** in 51% yield. Reductive alkylation of amines **2a,b** with formaldehyde and sodium cyanoborohydride afforded tertiary amines **3a,b** in high yields. Hydrogenolysis of the benzyl group of amines **2a** and **3a** led to **7** and **4**, respectively. Finally, alkylation of **2a** with benzyl chloride led to **8** in 85% yield.

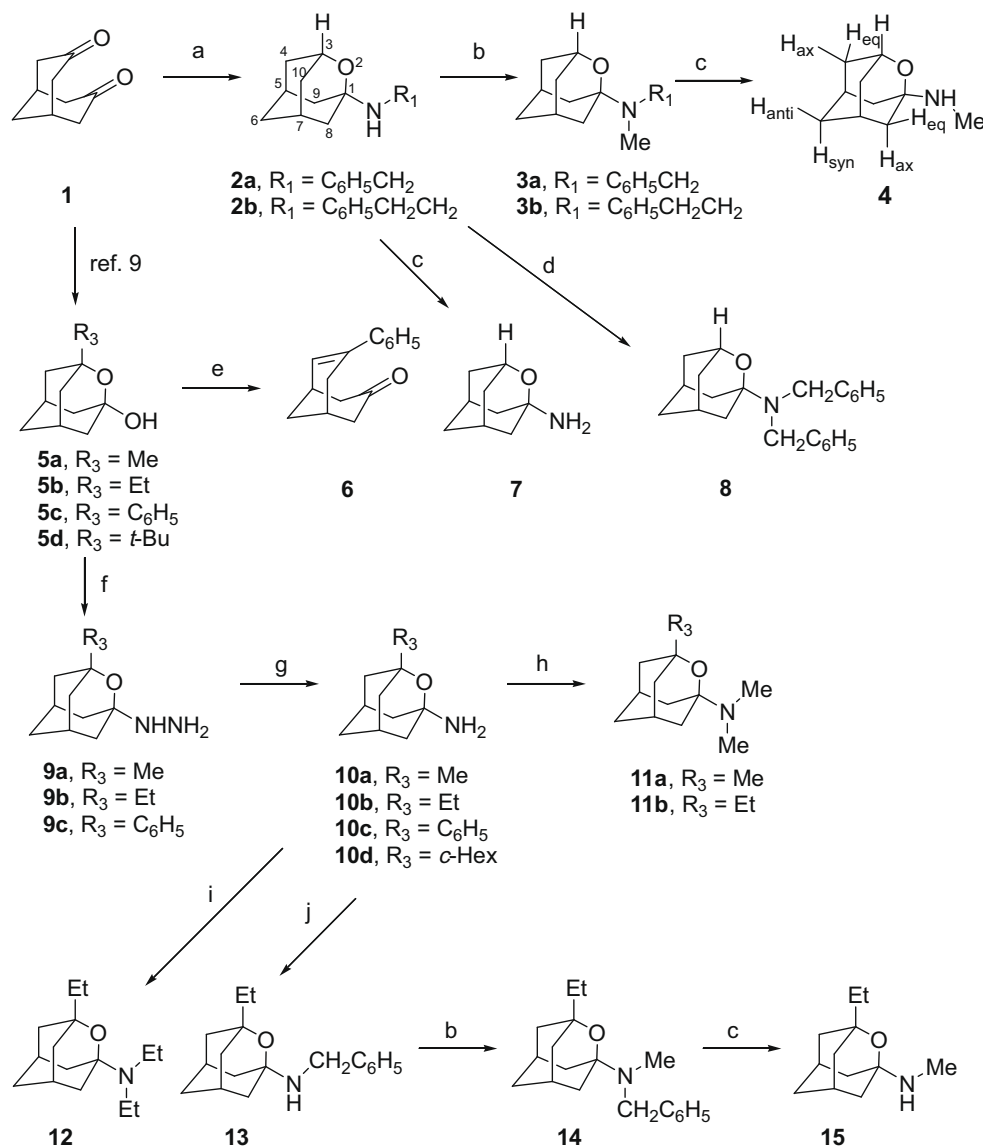
Alcohols of general structure **5** were prepared using a general method developed some time ago by our group.⁹ Several attempts to carry out the substitution of the hydroxyl group of **5** by a wide range of amines led to the recovery of the starting material. Moreover, the attempted Ritter reaction of **5c** with acetonitrile in acidic medium led to the known enone **6** in high yield.^{9c} However, reaction of **5a–c** with aqueous hydrazine led to hydrazines **9a–c** in high yields, probably due to the α -effect ensuring a higher nucleophilicity of hydrazine. Even though the reaction failed in the case of **5d**.

Catalytic hydrogenation of **9a,b** furnished amines **10a,b** in high yields. Surprisingly, **9c** led to a mixture of the expected amine **10c** and the cyclohexyl derivative **10d** in the ratio of 3:4. Both products were separated by column chromatography. Reductive methylation of amines **10a** and **10b** with formaldehyde and sodium cyanoborohydride afforded tertiary amines **11a** and **11b**, respectively. In a similar way, reductive alkylation of **10b** with acetaldehyde or benzaldehyde led to amines **12** and **13**, respectively. Finally, secondary amine **15** was synthesized from benzylamine **13** by reductive alkylation followed by catalytic debenzylation in good overall yield.

The structure of all new compounds was confirmed by elemental analysis or by accurate mass measurement, IR, ¹H NMR, ¹³C NMR, and mass spectral data.

2.2. NMDA receptor antagonist activity

In the last years there has been an intensive research on the development of new NMDA receptor antagonists, since this sub-



Scheme 1. Reagents and conditions: (a) Benzylamine or phenethylamine, anhyd THF, reflux, 30 min; then, LiAlH₄, anhyd Et₂O, reflux, 6 h; 58% for **2a**, 51% for **2b**; (b) formaldehyde, NaBH₃CN, AcOH, acetonitrile, 4 h; 99% for **3a**, 88% for **3b**, 86% for **14**; (c) H₂ (38 atm), 100 °C, Pd/C, EtOH, 24 h; 59% for **4**, 70% for **7**, 85% for **15**; (d) benzyl chloride, K₂CO₃, NaI, acetonitrile, reflux, 18 h, 85%; (e) acetonitrile, H₂SO₄, reflux, 18 h; 90%; (f) hydrazine hydrate, concd HCl, reflux, 18 h; 84% for **9a**, 45% for **9b**, 62% for **9c**; (g) H₂ (1 atm), PtO₂, EtOH, 4 days; 58% for **10a**, 48% for **10b**, 29% for **10c** and 42% for **10d**; (h) HCO₂H, CH₂O 37% aq, 80 °C, 10 h; 51% for **11a**, 27% for **11b**; (i) acetaldehyde, NaBH₃CN, acetic acid, MeOH, 18 h, 73%; (j) benzaldehyde, NaBH₃CN, AcOH, acetonitrile, 4 h, 79%.

Table 1
IC₅₀ (μM) values for (2-oxadamant-1-yl)amines as NMDA antagonists^{a,b}

| Compound | Glutamate (100 μM) | NMDA (100 μM) |
|------------|--------------------|---------------|
| 10b | 223 ± 52 | 83 ± 6 |
| 10c | 350 ± 108 | 226 ± 37 |
| 10d | >500 | 94 ± 13 |
| 11b | 106 ± 10 | 55 ± 12 |
| 12 | 22 ± 7 | 14 ± 3 |
| 15 | 108 ± 17 | 32 ± 9 |
| Amantadine | 358 ± 130 | 92 ± 29 |
| Memantine | 55 ± 12 | 1.5 ± 0.1 |

^a Functional data were obtained from primary cultures of cerebellar granule neurons using the method described in the experimental section by measuring the intracellular calcium concentration. Cells were challenged with glutamate (2nd column) or NMDA (3rd column) as indicated. Data shown are means ± SEM of at least three separate experiments carried out on three different batches of cultured cells.

^b Compounds **2a**, **2b**, **3a**, **3b**, **4**, **7**, **8**, **9a**, **10a**, **11a**, **13**, and **14** were found to have low potency as glutamate (IC₅₀ > 500 μM) and NMDA receptor antagonists (IC₅₀ > 200 μM). Hydrazines **9b** and **9c** were not evaluated.

type of receptors has been involved in the apoptotic process that develops during neurodegenerative diseases. Memantine is a non-competitive and low affinity blocker that acts selectively on NMDA receptors that is being used in Alzheimer's disease to slow down its progression.¹⁰

The activity of the different (2-oxadamant-1-yl)amines was assayed on cerebellar granule neurons loaded with the calcium-sensitive probe Fura-2.¹¹ Addition of glutamate or NMDA (100 μM) in the presence of glycine (10 μM) produced a robust and stable increase in intracellular calcium that was challenged with cumulative additions of the compounds to be tested. The data presented in Table 1 indicate that the presence of a substituent in C-3 in the 2-oxadamantane nucleus is essential for NMDA receptor antagonism. Thus, primary amine **7** and all its N-alkylated and N-dialkylated derivatives (**2a,b**, **3a,b**, **4**, and **8**) are inactive as it is the case of the methyl derivatives **10a** and **11a**. Phenyl derivative **10c** is only a weak NMDA receptor antagonist while more lipophilic amines **10b** and **10d** show a similar potency than amantadine. Further enhancement in potency was achieved by alkylation of **10b**, the most active derivative being **12**, a tertiary amine that is seven times more potent than amantadine, but still ten times less potent than memantine. Contrary to our expectations, all the benzyl derivatives were found to be inactive. This is in striking contrast with NGP1-01 that features a benzyl group essential for NMDA receptor antagonism, and with previous work by our groups that found that benzylated ring-contracted analogues of amantadine showed NMDA receptor antagonism.¹²

2.3. Antiviral activity

Primary amines **7**, **10c**, and **10d** and secondary amines **2a**, **4**, and **15** were tested for antiviral activity. None of the tested compounds displayed activity against the enveloped DNA viruses herpes simplex virus (type 1 or type 2) or vaccinia virus; the enveloped RNA viruses feline coronavirus, parainfluenza-3 virus, respiratory syncytial virus, vesicular stomatitis virus, sindbis virus, or Punta Toro virus; or the non-enveloped RNA viruses Coxsackievirus B4 and Reovirus-1. Also none of the compounds was found to be active against influenza virus A/H1N1, A/H3N2, or B.

2.4. Trypanocidal activity

Protozoan parasites of the *Trypanosoma brucei* species complex are the causative agents of African trypanosomiasis, a disease that is invariably fatal unless treated. However, current drugs are characterized by toxicity, the need for administration under medical

supervision, and in many cases, a lack of efficacy. New drugs to combat this important disease are urgently needed. A range of adamantylamine compounds have trypanocidal activity.⁴ We therefore investigated whether this property also extended to (2-oxadamant-1-yl)amine derivatives.

All the new derivatives described in this paper were tested for potency against cultured bloodstream form *T. brucei*. As was the case with the NMDA receptor antagonism, the presence of a substitution at the C-3 position in the 2-oxadamantane nucleus was found to be essential for trypanocidal activity. Of these compounds, the tertiary amines **11a,b** were found to be the most active. Amine **11b** had an IC₅₀ = 10.92 ± 0.21 μM and an IC₉₀ = 15.54 ± 1.14 μM, while the trimethyl derivative **11a** had an IC₅₀ = 3.97 ± 0.75 μM and an IC₉₀ = 6.82 ± 0.84 μM. Amine **11a** was the most potent compound tested, being approximately twice as active as rimantadine (IC₅₀ = 7.04 ± 0.12 μM; IC₉₀ = 13.97 ± 1.68 μM), and at least 30 times more active than amantadine (IC₅₀ > 130 μM). Amines **2a,b**, **3a,b**, **4**, **7**, and **8**, which lack the C3 substitution, had no activity at concentrations up to 5 mg mL⁻¹. The primary and secondary amines **10a–d**, **13**, and **15** also displayed no significant trypanocidal properties, even though they do carry a substitution at this position.

Several adamantane derivatives have previously been shown to have trypanocidal properties; however the oxanalogues reported here are the first heteroadamantanes to show significant activity against bloodstream form *T. brucei*.⁴

3. Conclusions

In summary, we have synthesized and fully characterized several (2-oxadamant-1-yl)amines. The presence of a substitution at the C-3 position is essential for NMDA receptor antagonism. Although **11b**, **12**, and **15** were more potent than amantadine against NMDA-induced calcium increase in cerebellar granule neurons, they were less potent than memantine. In contrast with the model compound NGP1-01, all our benzyl derivatives were devoid of NMDA receptor antagonism activity. None of the tested compounds showed antiviral activity. Two tertiary amines, **11a** and **11b**, displayed a significant level of trypanocidal activity; **11a** was twice as active as rimantadine. The mechanism by which adamantylamine derivatives kill trypanosomes is unknown, but it has been hypothesized by analogy with the known properties of this class of compound that it may involve channel blocking activity.⁴ The data obtained with the trimethyl amine **11a** now provides a basis for exploring if related derivatives have enhanced activity.

The synthesis and pharmacological evaluation of more polycyclic cage amines are in progress.

4. Experimental

4.1. Chemistry

4.1.1. General

Melting points were determined in open capillary tubes. Unless otherwise stated, NMR spectra were recorded in CD₃OD in the following spectrometers: ¹H NMR (500 MHz), ¹³C NMR (75.4 MHz). Chemical shifts (δ) are reported in ppm are related to internal tetramethylsilane (TMS). Assignments given for the NMR spectra are based on DEPT, COSY ¹H/¹H, HETCOR ¹H/¹³C (HSQC and HMBC sequences for one bond and long range ¹H/¹³C heterocorrelations, respectively), and NOESY experiments for selected compounds. For the MS and GC/MS analyses the sample was introduced directly or through a gas chromatograph. For GC/MS analyses, a 30-meter column [5% diphenyl-95% dimethylpolysiloxane, conditions: 10

psi, initial temperature: 35 °C (2 min), then heating at a range of 8 °C/min till 300 °C, then isothermic at 300 °C] was used. The electron impact (70 eV) or chemical ionization (CH₄) techniques were used. Only significant ions are given: those with higher relative abundance, except for the ions with higher *m/z* values. Accurate mass measurements were obtained using ESI technic. Absorption values in the IR spectra (KBr) are given as wave-numbers (cm⁻¹). Only the more intense bands are given. Column chromatography was performed on silica gel 60 Å (35–70 mesh). For the thin layer chromatography (TLC), aluminum-backed sheets with silica gel 60 F₂₅₄ were used and spots were visualized with UV light and/or 1% aqueous solutions of KMnO₄.

4.1.2. *N*-Benzyl(2-oxaadmant-1-yl)amine hydrochloride, **2a**·HCl

To a solution of diketone **1** (6.00 g, 39.4 mmol) in anhyd THF (200 mL), benzylamine (4.29 g, 40.0 mmol) was added and the solution was refluxed for 30 min. After cooling (ice-bath), this solution was added dropwise while stirring vigorously to a suspension of LiAlH₄ (3.00 g, 79.0 mmol) in anhyd diethyl ether (80 mL). The mixture was stirred for 6 h at 40 °C and then, while cooling with an ice-bath, 1 N NaOH (19 mL) was added dropwise. The precipitate formed was filtered through Celite®, the clear filtrate was dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo to give an oily residue (9.29 g). The residue was dissolved in acetone (120 mL), concd HCl (6 mL) was added and the solution was cooled at 4 °C, whereupon **2a** precipitated as its hydrochloride. Crystallization from 2-propanol gave pure **2a**·HCl (6.39 g, 58% yield), mp 257–259 °C (lit.^{8b} 253–255 °C). IR 2927, 2852, 2712, 2606, 2457, 2408, 2377, 1569, 1456, 1323, 1206, 1194, 1126, 1093, 1008, 994, 754, 739, 695 cm⁻¹. ¹H NMR 1.78 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.90 (dqint, *J* = 14.0 Hz, *J'* = 2.5 Hz, 1H, 6-H_{syn}), 1.97 (dtt, *J* = 14.0 Hz, *J'* = 2.5 Hz, *J''* = 1.5 Hz, 1H, 6-H_{anti}), 2.01–2.06 [complex signal, 4H, 4(10)-H_{eq} and 8(9)-H_{ax}], 2.14 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{eq}], 2.40 [broad s, 2H, 5(7)-H], 4.26 (s, 2H, CH₂-C₆H₅), 4.39 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H), 7.42–7.49 (complex signal, 3H, Ar-H_{meta} and Ar-H_{para}) 7.50 (m, 2 H, Ar-H_{ortho}). ¹³C NMR 29.4 [CH, C5(7)], 35.0 (CH₂, C6), 35.1 [CH₂, C4(10)], 37.8 [CH₂, C8(9)], 45.1 (CH₂, CH₂-C₆H₅), 73.6 (CH, C3), 86.6 (C, C1), 130.2 (CH, C_{meta}), 130.4 (CH, C_{para}), 131.1 (CH, C_{ortho}), 132.9 (C, C_{ipso}). MS (EI), *m/z* (%): 243 (M⁺, 26), 200 (9), 186 (36), 149 (26), 106 (16), 91 (100). Anal. Calcd for C₁₆H₂₁NO·HCl (279.81): C, 68.68; H, 7.92; N, 5.01; Cl, 12.67. Found: C, 68.51; H, 8.10; N, 5.00; Cl, 12.70.

4.1.3. *N*-(2-Phenylethyl)(2-oxaadmant-1-yl)amine hydrochloride, **2b**·HCl

From **1** (3.00 g, 19.7 mmol), phenethylamine (2.55 g, 21.1 mmol) in anhyd THF (100 mL) and following the above procedure, the amine **2b** was obtained as its hydrochloride (2.94 g, 51% yield), mp 256–259 °C (2-propanol). IR 2934, 2855, 2721, 2674, 2617, 2419, 1604, 1467, 1455, 1324, 1209, 1192, 1093, 1018, 1001, 784, 725, 698 cm⁻¹. ¹H NMR 1.74 [dm, *J* = 14.0 Hz, 2H, 4(10)-H_{ax}], 1.87 (dqint, *J* = 13.0 Hz, *J'* = 2.5 Hz, 1H, 6-H_{syn}), 1.95 (overlapped dm, 1H, 6-H_{anti}), 1.96–2.03 [complex signal, 4H, 4(10)-H_{eq} and 8(9)-H_{ax}], 2.06 [dm, *J* = 11.0 Hz, 2H, 8(9)-H_{eq}], 2.38 [broad s, 2H, 5(7)-H], 2.99 (m, 2H, CH₂-C₆H₅), 3.28 (m, 2H, CH₂N), 4.33 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H), 7.27 (tm, *J* = 7.5 Hz, 1H, Ar-H_{para}), 7.29 (dm, *J* = 7.5 Hz, 2H, Ar-H_{ortho}), 7.35 (tm, *J* = 7.5 Hz, 2H, Ar-H_{meta}). ¹³C NMR (50.3 MHz) 29.3 [CH, C5(7)], 33.6 (CH₂, CH₂-C₆H₅), 34.9 (CH₂, C6), 35.0 [CH₂, C4(10)], 37.7 [CH₂, C8(9)], 42.4 (CH₂, CH₂NH), 73.5 (CH, C3), 86.3 (C, C1), 128.2 (CH, C_{para}), 129.7 (CH, C_{ortho}), 130.0 (CH, C_{meta}), 137.8 (C, C_{ipso}). MS (EI), *m/z* (%): 257 (M⁺, 1), 200 (10), 167 (12), 166 (100), 137 (54), 105 (22), 104 (27). Anal. Calcd for C₁₇H₂₃NO·HCl (293.84): C, 69.49; H, 8.23; N, 4.77; Cl, 12.07. Found: C, 69.21; H, 8.31; N, 4.71; Cl, 11.98.

4.1.4. *N*-Benzyl-*N*-methyl(2-oxaadmant-1-yl)amine, **3a**

To a solution of **2a**·HCl (838 mg, 3.00 mmol) in acetonitrile (20 mL), formaldehyde (2.36 mL, 37 wt % in water solution, 30 mmol) and NaBH₃CN (595 mg, 9.00 mmol) were added. The mixture was stirred for 30 min at room temperature, acetic acid (0.6 mL) was added and the mixture was stirred at room temperature for 2 h. An additional portion of NaBH₃CN (595 mg, 9.00 mmol) was added and the mixture was further stirred at room temperature for 2 h. The mixture was concentrated to dryness, 2 N NaOH (30 mL) was added and the suspension was extracted with CH₂Cl₂ (3 × 45 mL). The combined organic phases were washed with H₂O (2 × 30 mL), dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo to give **3a** (765 mg, 99% yield) as a white solid. The analytical sample was obtained by crystallization from CH₂Cl₂, mp 60–61 °C (dec.). IR 2929, 2897, 2838, 1456, 1442, 1381, 1323, 1190, 994, 972, 957, 856, 747 cm⁻¹. ¹H NMR 1.55 [dm, *J* = 13.5 Hz, 2H, 4(10)-H_{ax}], 1.67 [broad d, *J* = 12.0 Hz, 2H, 8(9)-H_{ax}], 1.78 (dm, *J* = 13.5 Hz, 1H, 6-H_{syn}), 1.82 (dm, *J* = 13.5 Hz, 1H, 6-H_{anti}), 1.90 [dm, *J* = 13.5 Hz, 2H, 4(10)-H_{eq}], 2.16 [dm, *J* = 12.0 Hz, 2H, 8(9)-H_{eq}], 2.26 [broad s, 2H, 5(7)-H], 2.29 (s, 3H, CH₃-N), 3.81 (s, 2H, CH₂-C₆H₅), 4.17 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H), 7.19 (tm, *J* = 7.5 Hz, 1H, Ar-H_{para}), 7.28 (tm, *J* = 7.5 Hz, 2H, Ar-H_{meta}), 7.32 (dm, *J* = 7.5 Hz, 2H, Ar-H_{ortho}). ¹³C NMR (50.3 MHz) 28.5 [CH, C5(7)], 33.8 (CH₃, CH₃-N), 35.3 (CH₂, C6), 35.4 [CH₂, C4(10)], 38.4 [CH₂, C8(9)], 53.0 (CH₂, CH₂-C₆H₅), 70.2 (CH, C3), 85.4 (C, C1), 126.3 (CH, C_{para}), 128.07 (CH) and 128.12 (CH) (C_{meta} and C_{ortho}), 141.5 (C, C_{ipso}). MS (EI), *m/z* (%): 257 (M⁺, 27), 214 (15), 200 (42), 163 (41), 120 (19), 91 (100). Anal. Calcd for C₁₇H₂₃NO (257.37): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.25; H, 9.11; N, 5.38.

4.1.5. *N*-Methyl-*N*-(2-phenylethyl)(2-oxaadmant-1-yl)amine hydrochloride, **3b**

To a solution of **2b**·HCl (257 mg, 1.00 mmol) in acetonitrile (10 mL), formaldehyde (0.78 mL, 37 wt % in water solution, 10 mmol) and NaBH₃CN (188 mg, 3.00 mmol) were added. The mixture was stirred for 30 min at room temperature, acetic acid (0.3 mL) was added and the mixture was stirred at room temperature for 2 h. An additional portion of NaBH₃CN (188 mg, 3.00 mmol) was added and the mixture was further stirred at room temperature for 2 h. The mixture was concentrated to dryness, 2 N NaOH (10 mL) was added and the suspension was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phases were washed with H₂O (2 × 10 mL), dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo to give **3b** (239 mg, 88% yield) as a white solid. Its hydrochloride was obtained by adding an excess of Et₂O·HCl to a solution of the amine in EtOAc. The analytical sample of **16**·HCl was obtained by crystallization from EtOAc, mp 211–212 °C. IR 2956, 2915, 2855, 2596, 2417, 1481, 1467, 1454, 1411, 1376, 1210, 1086, 1027, 996, 749, 699 cm⁻¹. ¹H NMR (**3b** free base) 1.54 [dm, *J* = 13.0 Hz, 2H, 4(10)-H_{ax}], 1.59 [dm, *J* = 12.0 Hz, 2H, 8(9)-H_{ax}], 1.74 (dqint, *J* = 13.0 Hz, *J'* = 2.0 Hz, 2H, 6-H_{syn}), 1.80 (dqint, *J* = 13.0 Hz, *J'* = 2.0 Hz, 2H, 6-H_{anti}), 1.88 [dm, *J* = 13.0 Hz, 2H, 4(10)-H_{eq}], 2.07 [dm, *J* = 12.0 Hz, 2H, 8(9)-H_{eq}], 2.23 [broad s, 2H, 5(7)-H], 2.47 (s, 3H, CH₃-N), 2.79 (m, 2H, CH₂-C₆H₅), 2.89 (m, 2H, CH₂-N), 4.14 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H), 7.18 (tm, *J* = 7.5 Hz, 1H, Ar-H_{para}), 7.20 (dm, *J* = 7.5 Hz, 2H, Ar-H_{ortho}), 7.27 (tm, *J* = 7.5 Hz, 2H, Ar-H_{meta}). ¹³C NMR (50.3 MHz) (**3b** free base) 28.4 [CH, C5(7)], 34.0 (CH₃, CH₃-N), 35.3 (CH₂, C6), 35.4 [CH₂, C4(10)], 36.1 (CH₂, CH₂-C₆H₅), 38.0 [CH₂, C8(9)], 51.6 (CH₂, CH₂N), 69.9 (CH, C3), 85.4 (C, C1), 125.7 (CH, Ar-C_{para}), 128.2 (CH) and 128.7 (CH) (Ar-C_{ortho} and Ar-C_{meta}), 140.9 (C, Ar-C_{ipso}). MS (EI), *m/z* (%): 228 (2), 214 (2), 181 (13), 180 ([M-CH₂-C₆H₅]⁺, 100), 137 (49). Anal. Calcd for C₁₈H₂₅NO·HCl (307.86): C, 70.23; H, 8.51; N, 4.55; Cl, 11.52. Found: C, 70.19; H, 8.59; N, 4.54; Cl, 11.80.

4.1.6. *N*-Methyl(2-oxadamant-1-yl)amine hydrochloride, 4·HCl

A mixture of **3a** (765 mg, 2.97 mmol) and 10% Pd/C (50% in water, 200 mg) in absolute EtOH (80 mL) was hydrogenated at 38 atm and 100 °C for 24 h. The suspension was filtered, the residue was washed with EtOH, and to the combined organic filtrates an excess of Et₂O·HCl was added. Evaporation of the solvents from the filtrate in vacuo followed by crystallization from MeOH/Et₂O gave **4·HCl** (357 mg, 59% yield), mp 226–230 °C. IR 2928, 2856, 2750, 2694, 2416, 2372, 1467, 1209, 1157, 1097, 1078, 1023, 998 cm⁻¹. ¹H NMR 1.75 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.88 (dq, *J* = 13.0 Hz, *J'* = 2.5 Hz, 1H, 6-H_{syn}), 1.95 (overlapped dm, 1H, 6-H_{anti}), 1.97 [overlapped dm, 4H, 8(9)-H_{eq} and 8(9)-H_{ax}], 1.99 [overlapped dm, 2H, 4(10)-H_{eq}], 2.39 [broad s, 2H, 5(7)-H], 2.64 (s, 3H, CH₃-N), 4.33 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H). ¹³C NMR (50.3 MHz) 25.5 (CH₃, CH₃-N), 29.2 [CH, C5(7)], 34.9 (CH₂, C6), 35.0 [CH₂, C4(10)], 37.4 [CH₂, C8(9)], 73.4 (CH, C3), 85.6 (C, C1). MS (EI), *m/z* (%): 169 (18), 168 ([M+H]⁺, 51), 167 (20), 125 (30), 112 (21), 111 (100), 110 (44), 75 (23), 74 (79), 73 (44), 72 (48), 59 (32). Anal. Calcd for C₁₀H₁₇NO·1.05HCl·0.25H₂O (210.04): C, 57.18; H, 8.90; N, 6.67; Cl, 17.72. Found: C, 57.36; H, 8.77; N, 6.76; Cl, 17.65.

4.1.7. (2-Oxadmant-1-yl)amine hydrochloride, 7·HCl

A mixture of **2a·HCl** (2.20 g, 7.87 mmol) and 10% Pd/C (50% in water, 100 mg) in absolute EtOH (300 mL) was hydrogenated at 38 atm and 100 °C for 24 h. The suspension was filtered, the residue was washed with EtOH, and the combined organic filtrates were concentrated in vacuo to give a solid. 2 N NaOH (25 mL) was added to the residue which was then extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo to give a residue that was sublimed at 60 °C/2 Torr to give amine **7**. Its hydrochloride (1.05 g, 70% yield) was obtained by adding an excess of a solution of HCl in MeOH to the amine, followed by concentration in vacuo. The analytical sample of **7·HCl** was obtained by crystallization from MeOH, mp > 218 °C (dec.). IR 3034, 2945, 2851, 2789, 2744, 2697, 2631, 2563, 1578, 1502, 1384, 1359, 1329, 1304, 1211, 1156, 1016, 996 cm⁻¹. ¹H NMR 1.74 [d, *J* = 13.0 Hz, 2H, 4(10)-H_{ax}], 1.86 (dq, *J* = 13.5 Hz, *J'* = 2.5 Hz, 1H, 6-H_{syn}), 1.95 (overlapped dm, 1H, 6-H_{anti}), 1.96 [s, 4H, 8(9)-H_{ax} and 8(9)-H_{eq}], 1.98 [overlapped dm, 2H, 4(10)-H_{eq}], 2.35 [broad s, 2H, 5(7)-H], 4.28 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H). ¹³C NMR 29.2 [CH, C5(7)], 34.7 (CH₂, C6), 35.0 [CH₂, C4(10)], 39.5 [CH₂, C8(9)], 73.0 (CH, C3), 82.3 (C, C1). MS (EI), *m/z* (%): 153 (M⁺, 30), 136 (10), 110 (25), 96 (100), 95 (17), 94 (29), 85 (29), 67 (29), 60 (37), 59 (68), 57 (76). Anal. Calcd for C₉H₁₅NO·HCl (189.68): C, 56.99; H, 8.50; N, 7.38; Cl, 18.69. Found: C, 57.08; H, 8.61; N, 7.22; Cl, 18.54.

4.1.8. *N,N*-Dibenzyl(2-oxadamant-1-yl)amine, 8

A suspension of **2a·HCl** (280 mg, 1.00 mmol), K₂CO₃ (690 mg, 5.00 mmol), benzyl chloride (0.14 mL, 1.25 mmol), and NaI (50 mg, 0.33 mmol) in acetonitrile (10 mL) was heated under reflux for 18 h. To the cold mixture, CH₂Cl₂ (20 mL) was added and the solution was washed with water (2 × 20 mL). The organic layer was dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo. The residue was crystallized from EtOAc to give amine **8** (283 mg, 85% yield), mp 155–157 °C. IR 2932, 2922, 2851, 1600, 1493, 1449, 1382, 1321, 1198, 1158, 1122, 986, 959, 864, 746, 736, 699 cm⁻¹. ¹H NMR 1.54 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.59 [dm, *J* = 12.0 Hz, 2H, 8(9)-H_{ax}], 1.72 (broad d, *J* = 12.5 Hz, 1H, 6-H_{syn}), 1.76 (broad d, *J* = 12.5 Hz, 1H, 6-H_{anti}), 1.90 (dm, *J* = 12.5 Hz, 2H, 4(10)-H_{eq}), 2.14 [dm, *J* = 12.0 Hz, 2H, 8(9)-H_{eq}], 2.18 [broad s, 2H, 5(7)-H], 4.01 (s, 4H, CH₂-C₆H₅), 4.21 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H), 7.12 (t, *J* = 7.5 Hz, 2H, Ar-H_{para}), 7.20 (t, *J* = 7.5 Hz, 4H, H_{meta}), 7.30 (d, *J* = 7.5 Hz, 4H, H_{ortho}). ¹³C NMR 28.5 [CH, C5(7)],

35.2 (CH₂, C6), 35.3 [CH₂, C4(10)], 40.2 [CH₂, C8(9)], 51.9 (CH₂, CH₂-C₆H₅), 70.2 (CH, C3), 86.4 (C, C1), 126.1 (CH, C_{para}), 127.84 (CH) and 127.88 (CH) (C_{meta} and C_{ortho}), 142.2 (C, C_{ipso}). MS (EI), *m/z* (%): 333 (M⁺, 11), 276 (11), 242 (20), 148 (15), 106 (36), 91 (100). Anal. Calcd for C₂₃H₂₇NO (333.47): C, 82.84; H, 8.16; N, 4.20. Found: C, 82.59; H, 8.19; N, 4.12.

4.1.9. (3-Methyl-2-oxadamant-1-yl)hydrazine hydrochloride, 9a·HCl

A mixture of alcohol **5a** (10.5 g, 62.5 mmol), hydrazine hydrate (68.5 mL, 98% aq solution, 1.38 mol), and concd HCl (2.2 mL) was refluxed for 18 h. The suspension was cooled (ice-bath) and the solid hydrazine was filtered off and dried under reduced pressure. Its hydrochloride (11.5 g, 84% yield) was obtained by adding an excess of Et₂O·HCl to a solution of the hydrazine in EtOAc (10 mL). The analytical sample of **9a·HCl** was obtained by crystallization from MeOH/Et₂O, mp 181–183 °C. IR 3180, 2923, 2681, 1690, 1611, 1528, 1509, 1497, 1383, 1106, 1077, 943, 839 cm⁻¹. ¹H NMR 1.16 (s, 3H, CH₃-C3), 1.60 [dm, *J* = 13.5 Hz, 2H, 4(10)-H_{ax}], 1.63 [overlapped dm, 2H, 4(10)-H_{eq}], 1.66 [overlapped dm, *J* = 12.5 Hz, 2H, 8(9)-H_{ax}], 1.74 [dm, *J* = 12.5 Hz, 2H, 8(9)-H_{eq}], 1.79 [complex signal, 2H, 6-H_{anti} and 6-H_{syn}], 2.31 [m, 2H, 5(7)-H], 4.86 (s, mobile H). ¹³C NMR 29.0 (CH₃, C3-CH₃), 29.7 [CH, C5(7)], 34.9 (CH₂, C6), 37.5 [CH₂, C8(9)], 41.4 [CH₂, C4(10)], 74.8 (C, C3), 84.3 (C, C1). MS (EI), *m/z* (%): 183 (12), 182 (M⁺, 100), 167 (16), 164 (22), 151 (47), 125 (43), 109 (38), 107 (31), 100 (22), 96 (20), 95 (34), 93 (94), 91 (26), 81 (35), 79 (25), 77 (22), 74 (30), 72 (47), 67 (31), 55 (31). Accurate mass measurement (ESI⁺) calcd for [C₁₀H₁₈N₂O+H]⁺: 183.1491. Found: 183.1493.

4.1.10. (3-Ethyl-2-oxadamant-1-yl)hydrazine hydrochloride, 9b·HCl

From **5b** (5.60 g, 30.7 mmol), hydrazine hydrate (33.5 mL, 98% aq solution, 0.68 mol), and concentrated HCl (1.1 mL) and following the procedure described for **9a**, the hydrazine **9b** was obtained as its hydrochloride (3.20 g, 45% yield). The analytical sample of **9b·HCl** was obtained by crystallization from 2-propanol/hexane, mp 199–200 °C. IR 3176, 2914, 2852, 2682, 1609, 1529, 1515, 1442, 1383, 1206, 1138, 1079, 978, 956, 942, 839 cm⁻¹. ¹H NMR 0.91 (t, *J* = 7.5 Hz, 3H, CH₃-CH₂), 1.50 (q, *J* = 7.5 Hz, 2H, CH₃-CH₂), 1.58 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.62 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{eq}], 1.67 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{ax}], 1.74 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{eq}], 1.81 [complex signal, 2H, 6-H_{anti} and 6-H_{syn}], 2.33 [m, 2H, 5(7)-H], 4.86 (s, mobile H). ¹³C NMR 7.4 (CH₃, CH₂CH₃), 29.6 [CH, C5(7)], 35.3 (CH₂, C6), 35.4 (CH₂, CH₂CH₃), 37.8 [CH₂, C8(9)], 38.9 [CH₂, C4(10)], 77.0 (C, C3), 84.2 (C, C1). MS (EI), *m/z* (%): 196 (M⁺, 100), 178 (16), 167 (55), 165 (50), 125 (42), 107 (61), 95 (60), 93 (28), 91 (25), 81 (34), 79 (71), 74 (38), 72 (48), 67 (30), 57 (27), 55 (33). Accurate mass measurement (ESI⁺) calcd for [C₁₁H₂₀N₂O+H]⁺: 197.1648. Found: 197.1644.

4.1.11. (3-Phenyl-2-oxadamant-1-yl)hydrazine hydrochloride, 9c·HCl

From **5c** (1.85 g, 8.04 mmol), hydrazine hydrate (8.8 mL, 98% aq solution, 0.18 mol), and concentrated HCl (0.3 mL) and following the procedure described for **9a**, the hydrazine **9c** was obtained as its hydrochloride (1.39 g, 62% yield). The analytical sample of **9b·HCl** was obtained by crystallization from methanol, mp 203–204 °C. IR 3219, 2948, 2851, 2669, 1573, 1514, 1209, 996, 865, 754, 702 cm⁻¹. ¹H NMR 1.78 [dm, *J* = 12.5 Hz, 2H, 8(9)-H_{ax}], 1.85 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.86–1.92 [complex signal, 3H, 8(9)-H_{eq} and 6-H_{anti}], 1.98 (dm, *J* = 13.5 Hz, 1H, 6-H_{syn}), 2.07 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{eq}], 2.45 [m, 2H, 5(7)-H], 4.86 (s, mobile H), 7.22 (tm, 1H, *J* = 7.5 Hz, Ar-H_{para}), 7.32 (tm, *J* = 7.5 Hz, 2H, Ar-H_{meta}), 7.52 (dm, *J* = 7.5 Hz, 2H, Ar-H_{ortho}). ¹³C NMR (100.6 MHz) 30.0 [CH, C5(7)], 34.8 (CH₂, C6), 37.6 [CH₂, C8(9)],

41.7 [CH₂, C4(10)], 78.1 (C, C3), 85.1 (C, C1), 125.3 (CH, Ar-C_{ortho}), 127.9 (CH, Ar-C_{para}), 129.1 (CH, Ar-C_{meta}), 147.9 (C, Ar-C_{ipso}). MS (EI), *m/z* (%): 245 (14), 244 (M⁺, 76), 213 (32), 171 (13), 169 (15), 156 (17), 155 (100), 129 (20), 125 (31), 105 (23), 95 (29), 91 (34), 77 (37), 72 (29). Anal. Calcd for C₁₅H₂₀N₂O·HCl (280.80): C, 64.16; H, 7.54; N, 9.98; Cl, 12.63. Found: C, 64.03; H, 7.42; N, 9.86; Cl, 12.51.

4.1.12. (3-Methyl-2-oxadamant-1-yl)amine hydrochloride, **10a**·HCl

A mixture of **9a**·HCl (6.70 g, 30.6 mmol) and PtO₂ (20 mg) in absolute EtOH (200 mL) was hydrogenated at 1 atm and room temperature for 4 days. The suspension was filtered, the residue was washed with absolute EtOH, and the combined organic filtrates were concentrated in vacuo to dryness. The obtained white residue was taken in water (100 mL), the solution was basified with 2 N NaOH, and was extracted with EtOAc (5 × 80 mL). The combined organic extracts were dried with anhyd Na₂SO₄, and concentrated in vacuo to dryness. The residue was taken in the minimum amount of AcOEt and the solution was treated with an excess of a solution of HCl in Et₂O. The precipitate was filtered and washed with Et₂O to give **10a**·HCl (3.60 g, 58% yield). The analytical sample of **10a**·HCl was obtained by crystallization from MeOH, mp 268–269 °C. IR 2966, 2924, 2852, 1582, 1516, 1379, 1235, 1060, 1038, 1005 cm⁻¹. ¹H NMR 1.18 (s, 3H, CH₃-C3), 1.66 [dm, *J* = 14.0 Hz, 2H, 4(10)-H_{ax}], 1.70 [dm, *J* = 14.0 Hz, 2H, 4(10)-H_{eq}], 1.81 [complex signal, 2H, 6-H_{anti} and 6-H_{syn}], 1.85 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{eq}], 1.90 [dd, *J* = 11.5 Hz, *J'* = 2.5 Hz, 2H, 8(9)-H_{ax}], 2.38 [broad s, 2H, 5(7)-H], 4.86 (s, mobile H). ¹³C NMR 28.9 (CH₃, C3-CH₃), 29.8 [CH, C5(7)], 34.0 (CH₂, C6), 38.9 [CH₂, C8(9)], 40.9 [CH₂, C4(10)], 75.8 (C, C3), 83.2 (C, C1). MS (EI), *m/z* (%): 168 (9), 167 (M⁺, 73), 152 (33), 150 (27), 124 (27), 110 (100), 109 (37), 108 (68), 106 (21), 94 (28), 93 (49), 85 (72), 81 (37), 67 (22), 60 (21), 59 (47), 57 (66). Anal. Calcd for C₁₀H₁₇NO·HCl·0.25H₂O (208.22): C, 57.69; H, 8.96; N, 6.73; Cl, 17.03. Found: C, 57.78; H, 8.92; N, 7.01; Cl, 17.34.

4.1.13. (3-Ethyl-2-oxadamant-1-yl)amine hydrochloride, **10b**·HCl

From **9b**·HCl (2.00 g, 8.60 mmol) and PtO₂ (5 mg) in absolute EtOH (200 mL) and following the procedure described for **10a**, the amine **10b** was obtained as its hydrochloride (900 mg, 48% yield). The analytical sample of **10b**·HCl was obtained by crystallization from MeOH, mp 218–219 °C. IR 2934, 2854, 1588, 1507, 1461, 1377, 1345, 1302, 1279, 1057, 1015, 988 cm⁻¹. ¹H NMR 0.91 (t, *J* = 7.8 Hz, 3H, CH₃CH₂), 1.48 (q, *J* = 7.8 Hz, 2H, CH₃CH₂), 1.62 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.70 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{eq}], 1.82 [complex signal, 2H, 6-H_{anti} and 6-H_{syn}], 1.85 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{eq}], 1.91 [dd, *J* = 11.5 Hz, *J'* = 2.5 Hz, 2H, 8(9)-H_{ax}], 2.39 [broad s, 2H, 5(7)-H], 4.86 (s, mobile H). ¹³C NMR 7.2 (CH₃, CH₃CH₂), 29.7 [CH, C5(7)], 34.4 (CH₂, C6), 35.3 (CH₂, CH₃CH₂), 38.5 [CH₂, C4(10)], 39.1 [CH₂, C8(9)], 77.9 (C, C3), 83.2 (C, C1). MS (EI), *m/z* (%): 182 (15), 181 (M⁺, 76), 166 (11), 164 (31), 152 (79), 124 (39), 123 (37), 122 (69), 120 (20), 110 (100), 95 (35), 94 (55), 93 (63), 85 (81), 81 (33), 59 (43), 57 (82). Anal. Calcd for C₁₁H₁₉NO·HCl (217.74): C, 60.68; H, 9.26; N, 6.43; Cl, 16.28. Found: C, 60.78; H, 9.43; N, 6.44; Cl, 16.26.

4.1.14. (3-Phenyl-2-oxadamant-1-yl)amine hydrochloride, **10c**·HCl and (3-cyclohexyl-2-oxadamant-1-yl)amine hydrochloride, **10d**·HCl

From **9c**·HCl (1.30 g, 4.63 mmol) and PtO₂ (5 mg) in absolute EtOH (60 mL) and following the procedure described for **10a**, a mixture of amines **10c** and **10d** was obtained as their hydrochlorides. The mixture was diluted with water (25 mL) and then 2 N

NaOH was added till basic pH. The suspension was extracted with EtOAc (5 × 10 mL). The combined organic phases were dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo to give a mixture of **10c** and **10d**. Column chromatography of this mixture (silica gel, hexane/EtOAc mixtures) gave amine **10d** (hexane/EtOAc, 8/2, 454 mg, 43% yield) and amine **10c** (hexane/EtOAc, 6/4, 311 mg, 29% yield). Their hydrochlorides were obtained by adding excess of a solution of HCl in Et₂O to a solution of the corresponding amine in EtOAc. **10c**·HCl, mp 254–260 °C (dec.). IR 2920, 2859, 1502, 1232, 1028, 758, 699 cm⁻¹. ¹H NMR 1.86–1.92 [complex signal, 3H, 4(10)-H_{ax} and 6-H_{anti}], 1.98–2.05 [complex signal, 5H, 8(9)-H_{ax}, 8(9)-H_{eq} and 6-H_{syn}], 2.14 [dd, *J* = 12.7 Hz, *J'* = 2.5 Hz, 2H, 4(10)-H_{eq}], 2.51 [m, 2H, 5(7)-H], 4.86 (s, mobile H), 7.24 (tt, *J* = 7.5 Hz, *J'* = 1.5 Hz, 1H, Ar-H_{para}), 7.33 (tm, *J* = 7.5 Hz, 2H, Ar-H_{meta}), 7.46 (dm, *J* = 7.5 Hz, 2H, Ar-H_{ortho}). ¹³C NMR (100.6 MHz) 30.1 [CH, C5(7)], 33.9 (CH₂, C6), 39.0 [CH₂, C8(9)], 41.3 [CH₂, C4(10)], 79.0 (C, C3), 83.9 (C, C1), 125.0 (CH, Ar-C_{ortho}), 128.1 (CH, Ar-C_{para}), 129.2 (CH, Ar-C_{meta}), 147.2 (C, Ar-C_{ipso}). MS (EI), *m/z* (%): 230 (18), 229 (M⁺, 100), 212 (26), 170 (36), 155 (24), 129 (41), 110 (78), 105 (28), 91 (23), 77 (38), 57 (40). Anal. Calcd for C₁₅H₁₉NO·HCl (265.78): C, 67.79; H, 7.58; N, 5.27; Cl, 13.34. Found: C, 67.60; H, 7.70; N, 5.14; Cl, 13.37; **10d**·HCl, mp 255–256 °C. IR 2930, 2914, 2852, 1495, 1227, 1060, 1019 cm⁻¹. ¹H NMR 1.04 [dq, *J* = 2.5 Hz, *J'* = 12.5 Hz, 2H, 2'(6')-H_{ax}], 1.15 [overlapped tq, *J* = 3.5 Hz, *J'* = 13.0 Hz, 1H, 4'-H_{ax}], 1.15–1.25 [overlapped m, 2H, 3'(5')-H_{ax}], 1.30 [overlapped tt, *J* = 12.5 Hz, *J'* = 3.0 Hz, 1H, 1'-H], 1.65–1.70 [complex signal, 5H, 4'-H_{eq}, 4(10)-H_{ax} and 4(10)-H_{eq}], 1.77–1.92 [complex signal, 10H, 2'(6')-H_{eq}, 3'(5')-H_{eq}, 6-H_{anti}, 6-H_{syn}, 8(9)-H_{ax} and 8(9)-H_{eq}], 2.39 [broad s, 2H, 5(7)-H], 4.86 (s, mobile H). ¹³C NMR (100.6 MHz) 27.3 [CH₂, C2'(6')], 27.7 [CH₂, C4' and C3'(5')], 29.8 [CH, C5(7)], 34.7 (CH₂, C6), 36.5 [CH₂, C4(10)], 39.3 [CH₂, C8(9)], 49.3 (CH, C1'), 80.0 (C, C3), 83.2 (C, C1). MS (EI), *m/z* (%): 235 (M⁺, 28), 218 (11), 177 (12), 176 (60), 153 (18), 152 (100), 110 (56), 94 (38). Anal. Calcd for C₁₅H₂₅NO·HCl (271.83): C, 66.28; H, 9.64; N, 5.15; Cl, 13.04. Found: C, 66.67; H, 9.95; N, 5.01; Cl, 12.63.

4.1.15. *N,N*-Dimethyl(3-methyl-2-oxadamant-1-yl)amine hydrochloride, **11a**·HCl

To a cold (0 °C) solution of **10a** (410 mg, 2.45 mmol) in Et₂O (8 mL), formaldehyde (4.85 mL, 37 wt % in water solution, 61 mmol) and formic acid (3.8 mL, 98 mmol) were added dropwise, and the mixture was stirred at 80 °C for 10 h. The mixture was allowed to cool to room temperature, it was diluted with Et₂O (15 mL), 5 N NaOH (5 mL) was added dropwise, and the suspension was stirred at room temperature for 15 min. The organic layer was separated and the aqueous phase was extracted with Et₂O (4 × 25 mL). The combined organic phases were dried with anhyd Na₂SO₄, filtered, and an excess of a solution of HCl in Et₂O was added. Concentration in vacuo of this solution gave **11a**·HCl. The analytical sample of **11a**·HCl (300 mg, 51% yield) was obtained by crystallization from MeOH/Et₂O, mp 174–175 °C. IR 2963, 2912, 2856, 2654, 2556, 2519, 2458, 1488, 1471, 1450, 1438, 1410, 1378, 1240, 1155, 1033, 1021, 916 cm⁻¹. ¹H NMR 1.22 (s, 3H, CH₃-C3), 1.69 [overlapped dm, 2H, 4(10)-H_{ax}], 1.71 [overlapped dm, 2H, 4(10)-H_{eq}], 1.82 [complex signal, 2H, 6-H_{anti} and 6-H_{syn}], 1.85 [dm, *J* = 11.0 Hz, 2H, 8(9)-H_{eq}], 2.05 [dd, *J* = 11.0 Hz, *J'* = 2.0 Hz, 2H, 8(9)-H_{ax}], 2.46 [m, 2H, 5(7)-H], 2.83 [s, 6H, (CH₃)₂N]. ¹³C NMR 28.7 (CH₃, C3-CH₃), 30.2 [CH, C5(7)], 34.1 (CH₂, C6), 34.4 [CH₂, C8(9)], 36.9 [CH₃, (CH₃)₂N], 40.7 [CH₂, C4(10)], 77.2 (C, C3), 91.8 (C, C1). MS (EI), *m/z* (%): 196 (10), 195 (M⁺, 76), 180 (24), 152 (17), 138 (81), 122 (18), 113 (35), 109 (17), 98 (21), 88 (17), 87 (100), 85 (32), 72 (34). Anal. Calcd for C₁₂H₂₁NO·HCl·0.5H₂O (240.77): C, 59.86; H, 9.63; N, 5.82; Cl, 14.72. Found: C, 60.04; H, 9.32; N, 5.88; Cl, 14.73.

4.1.16. *N,N*-Dimethyl(3-ethyl-2-oxadamant-1-yl)amine hydrochloride, **11b**·HCl

To a cold (0 °C) solution of **10b** (300 mg, 1.65 mmol) in Et₂O (5 mL), formaldehyde (3.5 mL, 37 wt % in water solution, 42.7 mmol) and formic acid (2.85 mL, 74 mmol) were added dropwise, and the mixture was stirred at 80 °C for 10 h. The cold mixture was diluted with Et₂O (15 mL), 5 N NaOH (5 mL) was added dropwise, and the suspension was stirred at room temperature for 15 min. The organic layer was separated and the aqueous phase was extracted with Et₂O (4 × 15 mL). The combined organic phases were dried with anhyd Na₂SO₄, filtered, and treated with an excess of Et₂O·HCl. Concentration of the above mixture in vacuo gave **11b**·HCl. The analytical sample of **11b**·HCl (110 mg, 27% yield) was obtained by crystallization from MeOH/Et₂O, mp 129–130 °C. IR 2963, 2934, 2859, 2572, 2376, 1467, 1438, 1378, 1297, 1150, 1040, 1022, 972, 938 cm⁻¹. ¹H NMR 0.93 (t, *J* = 7.5 Hz, 3H, CH₃CH₂), 1.53 (q, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.64 [ddm, *J* = 13.0 Hz, *J'* = 2.0 Hz, 2H, 4(10)-H_{ax}], 1.73 [broad d, *J* = 13.0 Hz, 2H, 4(10)-H_{eq}], 1.84 [overlapped signal, 2H, 6-H_{anti} and 6-H_{syn}], 1.85 [overlapped broad d, 2H, 8(9)-H_{eq}], 2.05 [broad dd, *J* = 11.5 Hz, *J'* = 2.5 Hz, 2H, 8(9)-H_{ax}], 2.48 [broad s, 2H, 5(7)-H], 2.83 [s, 6H, (CH₃)₂N], 4.85 (s, mobile H). ¹³C NMR 7.2 (CH₃, CH₃CH₂), 30.1 [CH, C5(7)], 34.6 [CH₂, C6 and C8(9)], 35.1 (CH₂, CH₃CH₂), 36.8 [CH₃, (CH₃)₂N], 38.4 [CH₂, C4(10)], 79.3 (C, C3), 91.8 (C, C1). MS (EI), *m/z* (%): 209 (M⁺, 60), 180 (59), 152 (25), 138 (39), 122 (27), 113 (33), 88 (16), 87 (100), 72 (25). Accurate mass measurement (ESI+) calcd for [C₁₃H₂₃NO+H]⁺: 210.1852. Found: 210.1859.

4.1.17. *N,N*-Diethyl(3-ethyl-2-oxadamant-1-yl)amine hydrochloride, **12**·HCl

To a solution of **10b**·HCl (350 mg, 1.60 mmol) in methanol (20 mL), NaBH₃CN (95%, 200 mg, 3.20 mmol), AcOH (0.6 mL), and acetaldehyde (0.56 mL, 9.6 mmol) were added and the mixture was stirred at room temperature for 2 h. An additional portion of NaBH₃CN (95%, 100 mg, 1.60 mmol) and acetaldehyde (0.26 mL, 4.8 mmol) was added, the mixture was stirred at room temperature for 16 h, and then it was concentrated in vacuo to dryness. Water (30 mL) was added to the residue, the suspension was basified with NaHCO₃ (saturated aqueous solution), and was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo. The residue was taken in EtOAc and **12**·HCl (320 mg, 73% yield) was precipitated by adding an excess of a solution of HCl in Et₂O. The analytical sample of **12**·HCl was obtained by crystallization from MeOH/Et₂O, mp 195–196 °C. IR 2972, 2933, 2855, 2645, 2579, 2484, 1458, 1446, 1377, 1033, 1014, 975, 949 cm⁻¹. ¹H NMR 0.93 (t, *J* = 7.5 Hz, 3H, CH₃CH₂C3), 1.38 (t, *J* = 7.5 Hz, 6H, (CH₃CH₂)₂N), 1.53 (q, *J* = 7.5 Hz, 2H, CH₃CH₂C3), 1.64 [dm, *J* = 13.0 Hz, 2H, 4(10)-H_{ax}], 1.75 [dm, *J* = 13.0 Hz, 2H, 4(10)-H_{eq}], 1.82 (overlapped dm, 1H, 6-H_{anti}), 1.85 (overlapped dm, 1H, 6-H_{syn}), 1.94 [dm, *J* = 12.5 Hz, 2H, 8(9)-H_{eq}], 2.09 [dm, *J* = 12.5 Hz, 2H, 8(9)-H_{ax}], 2.47 [tm, *J* = 2.5 Hz, 2H, 5(7)-H], 3.06 (broad signal, 2H) and 3.59 (broad signal, 2H) [diastereotopic (CH₃CH₂)₂N]. ¹³C NMR (100.6 MHz) 7.2 (CH₃, CH₃CH₂C3), 12.1 [CH₃, (CH₃CH₂)₂N], 30.2 [CH, C5(7)], 34.6 (CH₂, C6), 35.2 (CH₂, CH₃CH₂C3), 35.4 [CH₂, C8(9)], 38.4 [CH₂, C4(10)], 45.4 [CH₂, (CH₃CH₂)₂N], 79.3 (C, C3), 93.9 (C, C1). MS (EI), *m/z* (%): 238 (16), 237 (M⁺, 59), 222 (14), 209 (19), 208 (74), 180 (30), 166 (48), 150 (23), 126 (31), 115 (100), 100 (54). Anal. Calcd for C₁₅H₂₇NO·HCl (273.85): C, 65.79; H, 10.31; N, 5.11; Cl, 12.95. Found: C, 65.64; H, 10.50; N, 5.13; Cl, 13.01.

4.1.18. *N*-Benzyl(3-ethyl-2-oxadamant-1-yl)amine hydrochloride, **13**·HCl

To a solution of **10b**·HCl (400 mg, 1.84 mmol) in MeOH (10 mL), NaBH₃CN (95%, 393 mg, 5.93 mmol), AcOH (0.3 mL),

and benzaldehyde (0.42 mL, 4.12 mmol) were added, and the mixture was stirred at room temperature for 2 h. An additional portion of NaBH₃CN (95%, 190 mg, 2.87 mmol) and benzaldehyde (0.21 mL, 2.06 mmol) was added, the mixture was stirred at room temperature for 16 h, and then it was concentrated in vacuo to dryness. Water (30 mL) was added to the residue, the suspension was basified with 1 N NaOH, and was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo. The residue was taken in EtOAc and **13**·HCl (451 mg, 79% yield) was precipitated by adding an excess of a solution of HCl in Et₂O. The analytical sample of **13**·HCl was obtained by crystallization from MeOH/Et₂O, mp 213–214 °C. IR 2922, 2851, 2725, 2656, 2619, 2414, 1566, 1463, 1056, 1042, 1007, 988, 749, 690 cm⁻¹. ¹H NMR 0.96 (t, *J* = 7.5 Hz, 3H, CH₃CH₂), 1.56 (q, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.67 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.77 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{eq}], 1.87 [broad signal, 2H, 6-H_{anti} and 6-H_{syn}], 1.98 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{ax}], 2.04 [dm, *J* = 11.5 Hz, 2H, 8(9)-H_{eq}], 2.46 [m, 2H, 5(7)-H], 4.25 [s, 2H, NCH₂], 4.86 (s, mobile H), 7.42–7.50 (complex signal, 5H, Ar-H). ¹³C NMR 7.2 (CH₃, CH₃CH₂), 29.9 [CH, C5(7)], 34.7 (CH₂, C6), 35.2 (CH₂, CH₃CH₂), 37.3 [CH₂, C8(9)], 38.6 [CH₂, C4(10)], 45.1 (CH₂, NCH₂), 78.7 (C, C3), 87.6 (C, C1), 130.2 (CH, Ar-C_{ortho}), 130.4 (CH, Ar-C_{para}), 131.1 (CH, Ar-C_{meta}), 133.0 (C, Ar-C_{ipso}). MS (EI), *m/z* (%): 272 (15), 271 (M⁺, 71), 242 (39), 200 (22), 160 (20), 149 (62), 91 (C₇H₇⁺, 100). Anal. Calcd for C₁₈H₂₅NO·1.1HCl (311.51): C, 69.40; H, 8.44; N, 4.50; Cl, 12.52. Found: C, 69.38; H, 8.38; N, 4.43; Cl, 12.29.

4.1.19. *N*-Benzyl-*N*-methyl(3-ethyl-2-oxadamant-1-yl)amine hydrochloride, **14**·HCl

To a solution of **13**·HCl (90 mg, 0.29 mmol) in acetonitrile (10 mL), formaldehyde (0.23 mL, 37 wt % in water solution, 0.29 mmol) and NaBH₃CN (95%, 55 mg, 0.83 mmol) were added. The mixture was stirred at room temperature for 30 min, AcOH (0.2 mL) was added and the mixture was stirred at room temperature for 2 h. An additional portion of NaBH₃CN (95%, 55 mg, 0.83 mmol) was added and the mixture was further stirred at room temperature for 16 h. The mixture was concentrated in vacuo to dryness, 1 N NaOH (15 mL) was added, and the suspension was extracted with CH₂Cl₂ (5 × 10 mL). The combined organic phases were washed with H₂O (2 × 10 mL), dried with anhyd Na₂SO₄, filtered, and concentrated in vacuo to give the amine **14**. The amine was taken in EtOAc and was precipitated as its hydrochloride (80 mg, 86% yield) by adding an excess of a solution of HCl in Et₂O. The analytical sample of **14**·HCl was obtained by crystallization from MeOH/Et₂O, mp 165–166 °C. IR 2969, 2921, 2853, 2472, 2353, 1458, 1033, 1024, 972, 938, 750, 702 cm⁻¹. ¹H NMR 0.99 (t, *J* = 7.5 Hz, 3H, CH₃CH₂), 1.60 (q, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.69 (dm, *J* = 12.5 Hz, 2H, 4-H_{ax} and 10-H_{ax}), 1.77–1.84 (broad signal, 2H, 4-H_{eq} and 10-H_{eq}), 1.87 (overlapped dm, 1H, 6-H_{anti}), 1.89 (overlapped dm, 1H, 6-H_{syn}), 1.94–2.08 [broad signal, 2H, 8-H_{ax} and 9-H_{ax}], 2.14–2.25 [broad signal, 2H, 8-H_{eq} and 9-H_{eq}], 2.53 [broad s, 2H, 5(7)-H], 2.71 (s, 3H, NCH₃), 3.93 (broad d, 1H, *J* = 8.0 Hz) and 4.85 (overlapped signal, 1H) (NCH₂Bn), 4.86 (s, mobile H), 7.50 (complex signal, 5H, Ar-H). ¹³C NMR 7.3 (CH₃, CH₃CH₂), 30.3 [CH, C5(7)], 33.5 (CH₃, CH₃N), 34.2 (CH₂) and 35.8 (CH₂) (diastereotopic C8 and C9), 34.7 (CH₂, C6), 35.2 (CH₂, CH₃CH₂), 38.3 (CH₂) and 38.5 (CH₂) (diastereotopic C4 and C10), 54.7 (CH₂, NCH₂), 79.8 (C, C3), 93.3 (C, C1), 130.3 (CH, Ar-C_{ortho}), 131.0 (CH, Ar-C_{para}), 131.5 (C, Ar-C_{ipso}), 132.4 (CH, Ar-C_{meta}). MS (EI), *m/z* (%): 286 (14), 285 (M⁺, 64), 256 (41), 228 (16), 214 (21), 174 (20), 163 (82), 91 (100). Anal. Calcd for C₁₉H₂₇NO·HCl·0.4H₂O (332.74): C, 69.34; H, 8.82; N, 4.26; Cl, 10.77. Found: C, 69.39; H, 8.73; N, 4.18; Cl, 11.05.

4.1.20. N-Methyl(3-ethyl-2-oxadamant-1-yl)amine hydrochloride, 15 HCl

A mixture of **14**·HCl (390 mg, 1.21 mmol) and 10% Pd/C (50% in water, 10 mg) in absolute EtOH (80 mL) was hydrogenated at 38 atm and 100 °C for 24 h. The suspension was filtered, the residue was washed with EtOH, and the combined organic filtrates were treated with an excess of a solution of HCl in Et₂O. The solution was concentrated in vacuo and the residue was crystallized from MeOH/Et₂O to give the analytical sample of **15**·HCl (240 mg, 85% yield), mp 155–156 °C. IR 2968, 2931, 2848, 2706, 2592, 1561, 1474, 1118, 1068, 1057, 1028, 991, 972 cm⁻¹. ¹H NMR 0.92 (t, *J* = 7.5 Hz, 3H, CH₃CH₂), 1.50 (q, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.63 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{ax}], 1.72 [dm, *J* = 12.5 Hz, 2H, 4(10)-H_{eq}], 1.84 [s, 2H, 6-H_{anti} and 6-H_{syn}], 1.87 [dm, *J* = 13.0 Hz, 2H, 8(9)-H_{ax}], 1.91 [dm, *J* = 13.0 Hz, 2H, 8(9)-H_{eq}], 2.43 [broad s, 2H, 5(7)-H], 2.63 (s, 3H, NCH₃). ¹³C NMR (100.6 MHz) 7.1 (CH₃, CH₃CH₂), 25.5 (CH₃, NCH₃), 29.8 [CH, C5(7)], 34.6 (CH₂, C6), 35.2 (CH₂, CH₃CH₂), 37.0 [CH₂, C8(9)], 38.6 [CH₂, C4(10)], 78.5 (C, C3), 86.5 (C, C1). MS (EI, CH₄), *m/z* (%): 196 (11), 195 (M⁺, 84), 180 (11), 166 (69), 138 (26), 124 (56), 108 (37), 99 (62), 95 (31), 74 (28), 73 (100), 71 (51). Anal. Calcd for C₁₂H₂₁NO·1.1HCl·0.5H₂O (242.60): C, 59.41; H, 9.58; N, 5.77; Cl, 15.34. Found: C, 59.41; H, 9.89; N, 6.11; Cl, 15.61.

4.2. NMDA receptor antagonist activity

The functional assay of antagonist activity at NMDA receptors was performed using primary cultures of cerebellar granule neurons, which were prepared according to established protocols.¹¹ Cells were grown on 10 mm poly-L-lysine-coated glass cover slips, and used for the experiments after 7–14 days in vitro. Cells were loaded with 6 μM Fura-2 AM (Invitrogen-Molecular Probes) for 45 min. Afterwards, the coverslip was mounted on a quartz cuvette containing a Locke-Hepes buffer using a special holder. Measurements were performed using a Perkin-Elmer LS-50B fluorometer equipped with a fast-filter accessory, under mild agitation and at 37 °C. Analysis from each sample was recorded real-time during 1200 s. After stimulation with NMDA or glutamate (100 μM, in the presence of 10 μM glycine), increasing cumulative concentrations of the compound to be tested were added. The percentages of inhibition at every tested concentration were analyzed using a nonlinear regression curve fitting (variable slope) by using the software GraphPad Prism 4.0.

4.3. Antiviral evaluation

The antiviral activity of the compounds was determined in established cell culture assays using a selection of DNA and RNA viruses, including three subtypes of influenza virus [A/Puerto Rico/8/34 (H1N1); A/Hong Kong/7/87 (H3N2); and B/Hong Kong/5/72].¹³ The compounds' inhibitory effect on virus replication as well as their cytotoxicity was monitored by microscopical examination, and confirmed by the colorimetric MTS cell viability assay.

4.4. *T. brucei* culturing and drug test

Cultures of bloodstream form *T. brucei* (strain 427) were maintained at 37 °C in modified Iscove's medium (pH 7.4).¹⁴ Trypanocidal activity was assessed by growing parasites for 48 h in the presence of various drug concentrations to determine the levels which inhibited growth by 50% (IC₅₀) and 90% (IC₉₀). In the case of untreated cultures (volume 4 mL), cell densities increased from 0.5 × 10⁴ to 1 × 10⁶ cells mL⁻¹ over this period. Experiments were performed in triplicate. Cell densities at each drug concentration

were determined using a hemocytometer (Weber Scientific International Ltd), and drug sensitivity was expressed as a percentage of growth of control cells.

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