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

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ABSTRACT

The synthesis of several (2-oxaadamant-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.

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 infections[2], 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]

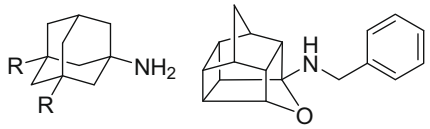
Based on the interesting and widely observed biological activity of amantadine, memantine, and NGP1-01, we therefore sought to explore the biological profile of (2-oxaadamant-1-yl)amine derivatives.

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



R = H, amantadine
R = Me, memantine

NGP1-01

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 $LiAlH_4$ 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.

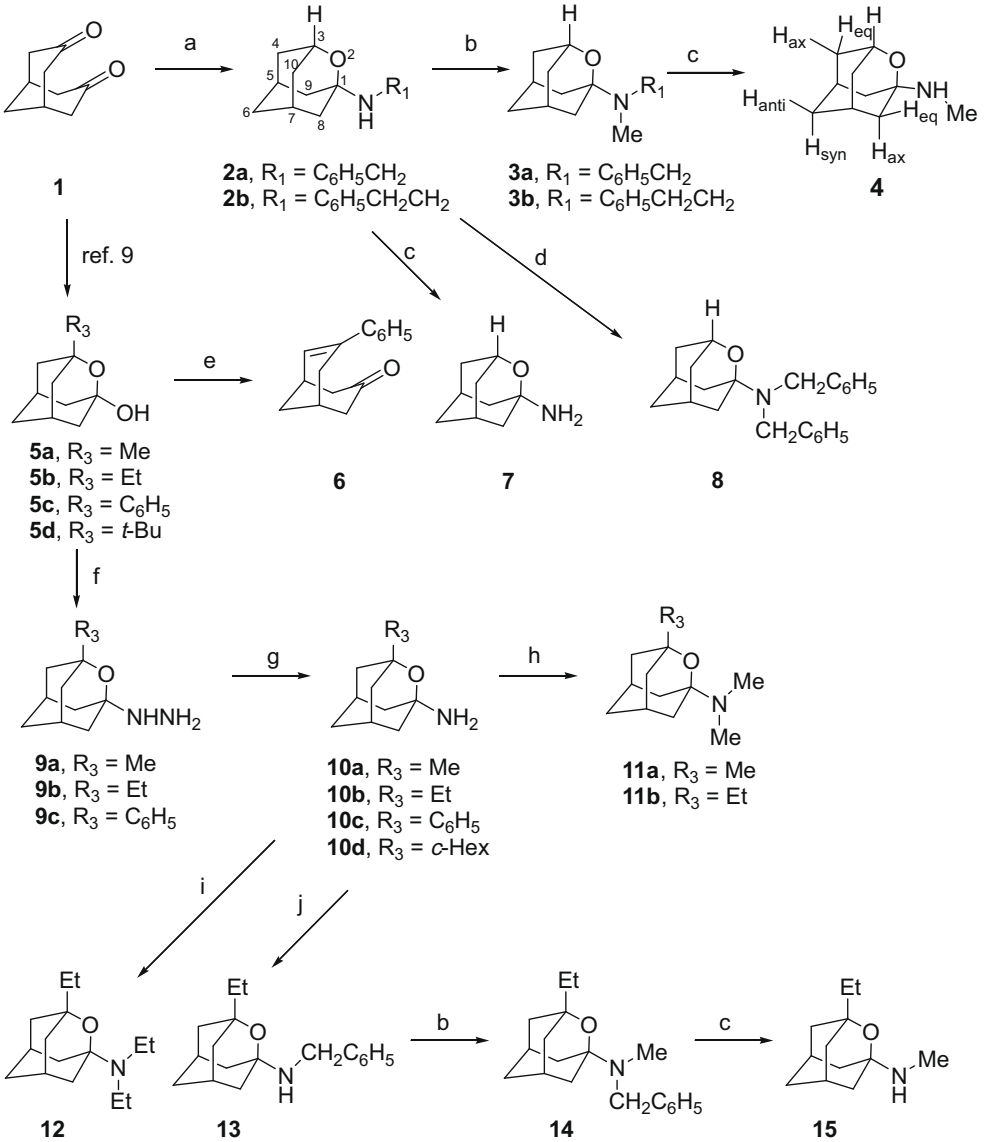
Alcohols of general structure **5** were prepared using a general method developed some time ago by our group.[9] Several attempts to carry out the substitution of the hydroxyl group of **5** by a wide range of amines led to the recovery of the starting material. Moreover, the attempted Ritter reaction 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, ^{13}C 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, $LiAlH_4$, anhyd Et_2O, reflux, 6 h; 58% for **2a**, 51% for **2b**; (b) formaldehyde, $NaBH_3CN$, AcOH, acetonitrile, 4 h; 99% for **3a**, 88% for **3b**, 86% for **14**; (c) H_2 (38 atm), 100 °C, Pd/C, EtOH, 24 h; 59% for **4**, 70% for **7**, 85% for **15**; (d) benzyl chloride, K_2CO_3, NaI, acetonitrile, reflux; 18 h, 85%; (e) acetonitrile, H_2SO_4, reflux, 18 h; 90%; (f) hydrazine hydrate, concd HCl, reflux, 18 h; 84% for **9a**, 45% for **9b**, 62% for **9c**; (g) H_2 (1 atm), PtO_2, EtOH, 4 days; 58% for **10a**, 48% for **10b**, 29% for **10c** and 42% for **10d**; (h) HCO_2H, CH_2O 37% aq, 80 °C, 10 h; 51% for **11a**, 27% for **11b**; (i) acetaldehyde, $NaBH_3CN$, acetic acid, MeOH, 18 h, 73%; (j) benzaldehyde, $NaBH_3CN$, AcOH, acetonitrile, 4 h, 79%.

Table 1
IC_{50} (μM) values for (2-oxaadamant-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 (IC_{50} > 500 μM) and NMDA receptor antagonists (IC_{50} > 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-oxaadamant-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-oxaadamantane 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-oxaadamant-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 IC_{50} = 10.92 ± 0.21 μM and an IC_{90} = 15.54 ± 1.14 μM, while the trimethyl derivative **11a** had an IC_{50} = 3.97 ± 0.75 μM and an IC_{90} = 6.82 ± 0.84 μM. Amine **11a** was the most potent compound tested, being approximately twice as active as rimantadine (IC_{50} = 7.04 ± 0.12 μM; IC_{90} = 13.97 ± 1.68 μM), and at least 30 times more active than amantadine (IC_{50} > 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-oxaadamant-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 CD_3OD in the following spectrometers: ^1H NMR (500 MHz), ^{13}C 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 $^1H/^{13}C$ (HSQC and HMBC sequences for one bond and long range $^1H/^{13}C$ 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 (CH_4) 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 F_{254} were used and spots were visualized with UV light and/or 1% aqueous solutions of $KMnO_4$.

4.1.2. *N*-Benzyl(2-oxaadamant-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 $LiAlH_4$ (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 Na_2SO_4, 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 (dquint, 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, CH_2–C_6H_5), 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}). ^{13}C NMR 29.4 [CH, C5(7)], 35.0 (CH_2, C6), 35.1 [CH_2, C4(10)], 37.8 [CH_2, C8(9)], 45.1 (CH_2, CH_2–C_6H_5), 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 ($M^{\cdot+}$, 26), 200 (9), 186 (36), 149 (26), 106 (16), 91 (100). Anal. Calcd for $C_{16}H_{21}NO$·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-oxaadamant-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 (dquint, 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, CH_2–C_6H_5), 3.28 (m, 2H, CH_2N), 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}). ^{13}C NMR (50.3 MHz) 29.3 [CH, C5(7)], 33.6 (CH_2, C$H_2C_6H_5$), 34.9 (CH_2, C6), 35.0 [CH_2, C4(10)], 37.7 [CH_2, C8(9)], 42.4 (CH_2, CH_2NH), 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 ($M^{\cdot+}$, 1), 200 (10), 167 (12), 166 (100), 137 (54), 105 (22), 104 (27). Anal. Calcd for $C_{17}H_{23}NO$·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-oxaadamant-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 $NaBH_3CN$ (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 $NaBH_3CN$ (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 CH_2Cl_2 (3 × 45 mL). The combined organic phases were washed with H_2O (2 × 30 mL), dried with anhyd Na_2SO_4, filtered, and concentrated in vacuo to give **3a** (765 mg, 99% yield) as a white solid. The analytical sample was obtained by crystallization from CH_2Cl_2, 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, CH_3–N), 3.81 (s, 2H, CH_2–C_6H_5), 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}). ^{13}C NMR (50.3 MHz) 28.5 [CH, C5(7)], 33.8 (CH_3, CH_3–N), 35.3 (CH_2, C6), 35.4 [CH_2, C4(10)], 38.4 [CH_2, C8(9)], 53.0 (CH_2, CH_2–C_6H_5), 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 ($M^{\cdot+}$, 27), 214 (15), 200 (42), 163 (41), 120 (19), 91 (100). Anal. Calcd for $C_{17}H_{23}NO$ (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-oxaadamant-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 $NaBH_3CN$ (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 $NaBH_3CN$ (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 CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried with anhyd Na_2SO_4, 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 Et_2O·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 (dquint, J = 13.0 Hz, J' = 2.0 Hz, 2H, 6-H_{syn}), 1.80 (dquint, 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, CH_3–N), 2.79 (m, 2H, CH_2–C_6H_5), 2.89 (m, 2H, CH_2–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}). ^{13}C NMR (50.3 MHz) (**3b** free base) 28.4 [CH, C5(7)], 34.0 (CH_3, CH_3–N), 35.3 (CH_2, C6), 35.4 [CH_2, C4(10)], 36.1 (CH_2, C$H_2C_6H_5$), 38.0 [CH_2, C8(9)], 51.6 (CH_2, CH_2N), 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 ($[M-CH_2C_6H_5]^+$, 100), 137 (49). Anal. Calcd for $C_{18}H_{25}NO$·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-oxaadamant-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 Et_2O·HCl was added. Evaporation of the solvents from the filtrate in vacuo followed by crystallization from MeOH/Et_2O 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 (dquint, 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, CH_3–N). 4.33 (broad s, 1H, 3-H), 4.86 (broad signal, mobile H). ^{13}C NMR (50.3 MHz) 25.5 (CH_3, CH_3–N), 29.2 [CH, C5(7)], 34.9 (CH_2, C6), 35.0 [CH_2, C4(10)], 37.4 [CH_2, C8(9)], 73.4 (CH, C3), 85.6 (C, C1). MS (CI, CH_4), *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 $C_{10}H_{17}NO{\cdot}1.05HCl{\cdot}0.25H_20$ (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-Oxaadamant-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 Na_2SO_4, 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 (dquint, 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). ^{13}C NMR 29.2 [CH, C5(7)], 34.7 (CH_2, C6), 35.0 [CH_2, C4(10)], 39.5 [CH_2, C8(9)], 73.0 (CH, C3), 82.3 (C, C1). MS (EI), *m/z* (%): 153 (M$^{\cdot+}$, 30), 136 (10), 110 (25), 96 (100), 95 (17), 94 (29), 85 (29), 67 (29), 60 (37), 59 (68), 57 (76). Anal. Calcd for $C_9H_{15}NO{\cdot}HCl$ (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-oxaadamant-1-yl)amine, 8

A suspension of **2a**·HCl (280 mg, 1.00 mmol), K_2CO_3 (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, CH_2Cl_2 (20 mL) was added and the solution was washed with water (2 × 20 mL). The organic layer was dried with anhyd Na_2SO_4, 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, CH_2–C_6H_5), 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}). ^{13}C NMR 28.5 [CH, C5(7)], 35.2 (CH_2, C6), 35.3 [CH_2, C4(10)], 40.2 [CH2, C8(9)], 51.9 (CH_2, CH_2–C_6H_5), 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$^{\cdot+}$, 11), 276 (11), 242 (20), 148 (15), 106 (36), 91 (100). Anal. Calcd for $C_{23}H_{27}NO$ (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-oxaadamant-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 Et_2O·HCl to a solution of the hydrazine in EtOAc (10 mL). The analytical sample of **9a**·HCl was obtained by crystallization from MeOH/Et_2O, 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, CH_3–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). ^{13}C NMR 29.0 (CH_3, C3-CH_3), 29.7 [CH, C5(7)], 34.9 (CH_2, C6), 37.5 [CH_2, C8(9)], 41.4 [CH_2, C4(10)], 74.8 (C, C3), 84.3 (C, C1). MS (EI), *m/z* (%): 183 (12), 182 (M$^{\cdot+}$, 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 $[C_{10}H_{18}N_2O+H]^+$: 183.1491. Found: 183.1493.

4.1.10. (3-Ethyl-2-oxaadamant-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, CH_3–CH_2), 1.50 (q, J = 7.5 Hz, 2H, CH_3–CH_2), 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). ^{13}C NMR 7.4 (CH_3, CH_2CH_3), 29.6 [CH, C5(7)], 35.3 (CH_2, C6), 35.4 (CH_2, CH_2CH_3), 37.8 [CH_2, C8(9)], 38.9 [CH_2, C4(10)], 77.0 (C, C3), 84.2 (C, C1). MS (EI), *m/z* (%): 196 (M$^{\cdot+}$, 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 $[C_{11}H_{20}N_2O+H]^+$: 197.1648. Found: 197.1644.

4.1.11. (3-Phenyl-2-oxaadamant-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}). ^{13}C NMR (100.6 MHz) 30.0 [CH, C5(7)], 34.8 (CH_2, C6), 37.6 [CH_2, C8(9)],

41.7 [CH_2, 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 $C_{15}H_{20}N_2O{\cdot}HCl$ (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-oxaadamant-1-yl)amine hydrochloride, 10a·HCl

A mixture of **9a**·HCl (6.70 g, 30.6 mmol) and PtO_2 (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 Na_2SO_4, 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 Et_2O. The precipitate was filtered and washed with Et_2O 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, CH_3–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). ^{13}C NMR 28.9 (CH_3, C3–CH_3), 29.8 [CH, C5(7)], 34.0 (CH_2, C6), 38.9 [CH_2, C8(9)], 40.9 [CH_2, C4(10)], 75.8 (C, C3), 83.2 (C, C1). MS (EI), *m/z* (%): 168 (9), 167 ($M^{\cdot+}$, 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 $C_{10}H_{17}NO{\cdot}HCl{\cdot}0.25H_2O$ (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-oxaadamant-1-yl)amine hydrochloride, 10b·HCl

From **9b**·HCl (2.00 g, 8.60 mmol) and PtO_2 (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, CH_3CH$_2$), 1.48 (q, J = 7.8 Hz, 2H, CH_3CH_2), 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). ^{13}C NMR 7.2 (CH_3, CH_3CH_2), 29.7 [CH, C5(7)], 34.4 (CH_2, C6), 35.3 (CH_2, CH_3CH_2), 38.5 [CH_2, C4(10)], 39.1 [CH_2, C8(9)], 77.9 (C, C3), 83.2 (C, C1). MS (EI), *m/z* (%): 182 (15), 181 ($M^{\cdot+}$, 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 $C_{11}H_{19}NO{\cdot}HCl$ (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-oxaadamant-1-yl)amine hydrochloride, 10c·HCl and (3-cyclohexyl-2-oxaadamant-1-yl)amine hydrochloride, 10d·HCl

From **9c**·HCl (1.30 g, 4.63 mmol) and PtO_2 (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 Na_2SO_4, 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 Et_2O 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_{ec}], 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}). ^{13}C NMR (100.6 MHz) 30.1 [CH, C5(7)], 33.9 (CH_2, C6), 39.0 [CH_2, C8(9)], 41.3 [CH_2, 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 ($M^{\cdot+}$,100), 212 (26), 170 (36), 155 (24), 129 (41), 110 (78), 105 (28), 91 (23), 77 (38), 57 (40). Anal. Calcd for $C_{15}H_{19}NO{\cdot}HCl$ (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). ^{13}C NMR (100.6 MHz) 27.3 [CH_2, C2′(6′)], 27.7 [CH_2, C4′ and C3′(5′)], 29.8 [CH, C5(7)], 34.7 (CH_2, C6), 36.5 [CH_2, C4(10)], 39.3 [CH_2, C8(9)], 49.3 (CH, C1′), 80.0 (C, C3), 83.2 (C, C1). MS (EI), *m/z* (%): 235 ($M^{\cdot+}$,28), 218 (11), 177 (12), 176 (60), 153 (18), 152 (100), 110 (56), 94 (38). Anal. Calcd for $C_{15}H_{25}NO{\cdot}HCl$ (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-oxaadamant-1-yl)amine hydrochloride, 11a·HCl

To a cold (0 °C) solution of **10a** (410 mg, 2.45 mmol) in Et_2O (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 Et_2O (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 Et_2O (4 × 25 mL). The combined organic phases were dried with anhyd Na_2SO_4, filtered, and an excess of a solution of HCl in Et_2O 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/Et_2O, 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, CH_3–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, $(CH_3)_2N$]. ^{13}C NMR 28.7 (CH_3, C3–CH_3), 30.2 [CH, C5(7)], 34.1 (CH_2, C6), 34.4 [CH_2, C8(9)], 36.9 [CH_3, $(CH_3)_2N$], 40.7 [CH_2, C4(10)], 77.2 (C, C3), 91.8 (C, C1). MS (EI), *m/z* (%): 196 (10), 195 ($M^{\cdot+}$, 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 $C_{12}H_{21}NO{\cdot}HCl{\cdot}0.5H_2O$ (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-oxaadamant-1-yl)amine hydrochloride, 11b·HCl

To a cold (0 °C) solution of **10b** (300 mg, 1.65 mmol) in Et_2O (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 Et_2O (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 Et_2O (4 × 15 mL). The combined organic phases were dried with anhyd Na_2SO_4, filtered, and treated with an excess of Et_2O·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/Et_2O, 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, CH_3CH_2), 1.53 (q, J = 7.5 Hz, 2H, CH_3CH_2), 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, $(CH_3)_2N$], 4.85 (s, mobile H). ^{13}C NMR 7.2 (CH_3, CH_3CH_2), 30.1 [CH, C5(7)], 34.6 [CH_2, C6 and C8(9)], 35.1 (CH_2, CH_3CH_2), 36.8 [CH_3, $(CH_3)_2N$], 38.4 [CH_2, C4(10)], 79.3 (C, C3), 91.8 (C, C1). MS (EI), *m/z* (%): 209 ($M^{\cdot+}$, 60), 180 (59), 152 (25), 138 (39), 122 (27), 113 (33), 88 (16), 87 (100), 72 (25). Accurate mass measurement (ESI+) calcd for $[C_{13}H_{23}NO+H]^+$: 210.1852. Found: 210.1859.

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

To a solution of **10b**·HCl (350 mg, 1.60 mmol) in methanol (20 mL), $NaBH_3CN$ (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 $NaBH_3CN$ (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 $NaHCO_3$ (saturated aqueous solution), and was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried with anhyd Na_2SO_4, 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 Et_2O. The analytical sample of **12**·HCl was obtained by crystallization from MeOH/Et_2O, 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, CH_3CH_2C3), 1.38 (t, J = 7.5 Hz, 6H, $(CH_3CH_2)_2N$), 1.53 (q, J = 7.5 Hz, 2H, CH_3CH_2C3), 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 $(CH_3CH_2)_2N$]. ^{13}C NMR (100.6 MHz) 7.2 (CH_3, CH_3CH_2C3), 12.1 [CH_3, $(CH_3CH_2)_2N$], 30.2 [CH, C5(7)], 34.6 (CH_2, C6), 35.2 (CH_2, CH_3CH_2C3), 35.4 [CH_2, C8(9)], 38.4 [CH_2, C4(10)], 45.4 [CH_2, $(CH_3CH_2)_2N$], 79.3 (C, C3), 93.9 (C, C1). MS (EI), *m/z* (%): 238 (16), 237 ($M^{\cdot+}$, 59), 222 (14), 209 (19), 208 (74), 180 (30), 166 (48), 150 (23), 126 (31), 115 (100), 100 (54). Anal. Calcd for $C_{15}H_{27}NO$·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-oxaadamant-1-yl)amine hydrochloride, 13·HCl

To a solution of **10b**·HCl (400 mg, 1.84 mmol) in MeOH (10 mL), $NaBH_3CN$ (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 $NaBH_3CN$ (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 Na_2SO_4, 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 Et_2O. The analytical sample of **13**·HCl was obtained by crystallization from MeOH/Et_2O, 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, CH_3CH_2), 1.56 (q, J = 7.5 Hz, 2H, CH_3CH_2), 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, NCH_2], 4.86 (s, mobile H), 7.42-7.50 (complex signal, 5H, Ar-H). ^{13}C NMR 7.2 (CH_3, CH_3CH_2), 29.9 [CH, C5(7)], 34.7 (CH_2, C6), 35.2 (CH_2, CH_3CH_2), 37.3 [CH_2, C8(9)], 38.6 [CH_2, C4(10)], 45.1 (CH_2, NCH_2), 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 ($M^{\cdot+}$, 71), 242 (39), 200 (22), 160 (20), 149 (62), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{18}H_{25}NO$·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-oxaadamant-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 $NaBH_3CN$ (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 $NaBH_3CN$ (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 CH_2Cl_2 (5 × 10 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried with anhyd Na_2SO_4, 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 Et_2O. The analytical sample of **14**·HCl was obtained by crystallization from MeOH/Et_2O, 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, CH_3CH_2), 1.60 (q, J = 7.5 Hz, 2H, CH_3CH_2), 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, NCH_3), 3.93 (broad d, 1H, J = 8.0 Hz) and 4.85 (overlapped signal, 1H) (NCH_2Bn), 4.86 (s, mobile H), 7.50 (complex signal, 5H, Ar-H). ^{13}C NMR 7.3 (CH_3, CH_3CH_2), 30.3 [CH, C5(7)], 33.5 (CH_3, CH_3N), 34.2 (CH_2) and 35.8 (CH_2) (diastereotopic C8 and C9), 34.7 (CH_2, C6), 35.2 (CH_2, CH_3CH_2), 38.3 (CH_2) and 38.5 (CH_2) (diastereotopic C4 and C10), 54.7 (CH_2, NCH_2), 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 ($M^{\cdot+}$, 64), 256 (41), 228 (16), 214 (21), 174 (20), 163 (82), 91 (100). Anal. Calcd for $C_{19}H_{27}NO$·HCl·0.4H_2O (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-oxaadamant-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 Et_2O. The solution was concentrated in vacuo and the residue was crystallized from MeOH/Et_2O 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, CH_3CH_2), 1.50 (q, J = 7.5 Hz, 2H, CH_3CH_2), 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, NCH_3). ^{13}C NMR (100.6 MHz) 7.1 (CH_3, CH_3CH_2), 25.5 (CH_3, NCH_3), 29.8 [CH, C5(7)], 34.6 (CH_2, C6), 35.2 (CH_2, CH_3CH_2), 37.0 [CH_2, C8(9)], 38.6 [CH_2, C4(10)], 78.5 (C, C3), 86.5 (C, C1). MS (EI, CH_4), m/z (%): 196 (11), 195 ($M^{\cdot+}$, 84), 180 (11), 166 (69), 138 (26), 124 (56), 108 (37), 99 (62), 95 (31), 74 (28), 73 (100), 71 (51). Anal. Calcd for $C_{12}H_{21}NO{\cdot}1.1HCl{\cdot}0.5H_2O$ (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% (IC_{50}) and 90% (IC_{90}). In the case of untreated cultures (volume 4 mL), cell densities increased from 0.5×10^4 to 1×10^6 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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