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New oxapolycyclic cage amines with NMDA receptor antagonist and trypanocidal activities

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ABSTRACT

The synthesis of several (1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amines and related compounds is reported. Several of them display very similar activity to memantine as NMDA receptor antagonists. Several derivatives showed a significant level of trypanocidal activity.

1. Introduction

Neurodegerative disorders like Parkinson's disease and Alzheimer's disease, which are caused by the degeneration of dopaminergic and cholinergic neurons, respectively, are becoming more and more problematic for the older population.[1] Unfortunately, current treatments neither prevent nor reduce the progression of neurodegeneration. Therefore, great efforts have been undertaken to develop drugs that meet this impairment.[2]

With regard to Alzheimer's disease, NMDA receptor antagonists act by protecting neurons from excessive pathological calcium influx, which leads to neuronal damage and finally to neuronal cell death.[3] Up to now, the polycyclic amine memantine is the only NMDA receptor antagonist with low NMDA receptor affinity that has been introduced for the treatment of Alzheimer's disease.[4] The particular advantage of memantine is the fast off-rate kinetics which prevents the drug from accumulating in the ion channel. Therefore, memantine enters the open channel preferentially when it is pathologically activated for long periods of time. The physiological neurotransmission is not disturbed by memantine resulting in minimal adverse effects.[5]

Another polycyclic amine, amantadine, displays moderate NMDA receptor affinity and is used for the treatment of Parkinson's disease.[6] Moreover, amantadine also has prophylactic and therapeutic activity in influenza A virus infections.[7] Interestingly, amantadine, memantine and related polycyclic amines also possess trypanocidal activity.[8]

Biological activity has also been found with other polycyclic cage amines.[9] For example, **1** displayed in vivo activity against herpex simplex-II and influenza A2 virus,[10] **2** was studied as an anti-Parkinsonian agent,[11] and cubylamine, **3**, was found to be a MAO-B inhibitor (Fig. 1).[12] Moreover, heteroatom substituted polycyclic cage amines are an interesting and highly promising group of compounds that are receiving intense scrutiny as potential scaffolds for the development of new drugs. For example, a series of oxapentacycloundecylamines, such as NGP1-01 and related compounds, has showed neuroprotective properties through NMDA receptor

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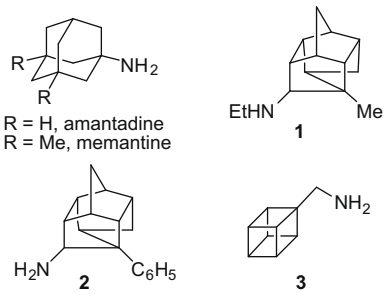


Figure 1. Polycyclic cage compounds with biological activity.

antagonist activity,[13] and several azapentacycloundecylalcohols such as TC1 and TC4, have high affinity for sigma receptors (Fig. 2).[14]

Recently, we have found that several (3-alkyl-2-oxaadamant-1-yl)amines, such as **4**, showed NMDA receptor antagonist activity. They were more potent than amantadine against NMDA-induced calcium increase in cerebellar granule neurons, although they were less potent than memantine. Moreover, two tertiary amine analogs of **4** displayed a significant level of trypanocidal activity. However, they were devoid of any antiviral activity (Fig. 2).[15]

Following our work on the synthesis of oxapolycyclic compounds as analogs of amantadine and memantine, we now describe the synthesis and biological evaluation of a series of (1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amines, and show that they contain structural features necessary for NMDA receptor antagonist activity and trypanocidal activity.

2. Results and discussion

2.1. Synthesis

For the synthesis of the new amines, known alcohol **5** was used as starting material.[16] Reaction of alcohol **5** with several primary amines led to the recovery of the starting material. However, reaction of **5** with aqueous hydrazine led to the known hydrazine **6** in 79% yield, probably due to the α-effect ensuring a higher nucleophilicity of hydrazine.[17] Catalytic hydrogenation of **6** furnished amine **7** in 82% yield (Scheme 1).

In order to explore an alternative route to amine **7** we carried out a Ritter reaction of **5** with acetonitrile in toluene in acidic medium that led, after column chromatography, to the expected amide, **8**, in 47% yield, along with the recovery of 20% of starting material and small quantities (2–3%) of compounds **9**–**11**. The origin of **9** can be rationalized as an electrophilic attack of the bridgehead carbocation involved in the Ritter reaction to toluene. Regarding esters **10** and **11**, their formation may involve nucleophilic attack of **5** and its corresponding keto-alcohol opened derivative, respectively, to protonated acetonitrile followed by hydrolysis of the corresponding imidate. Taking into account the medium yield of the Ritter reaction we did not carry out the hydrolysis of amide **8** (Scheme 1).

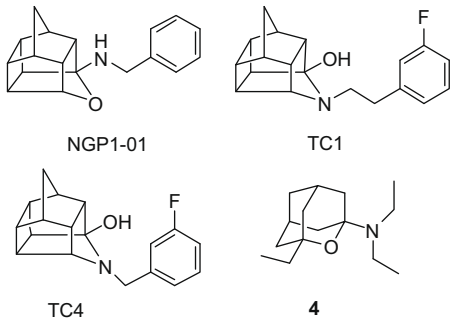
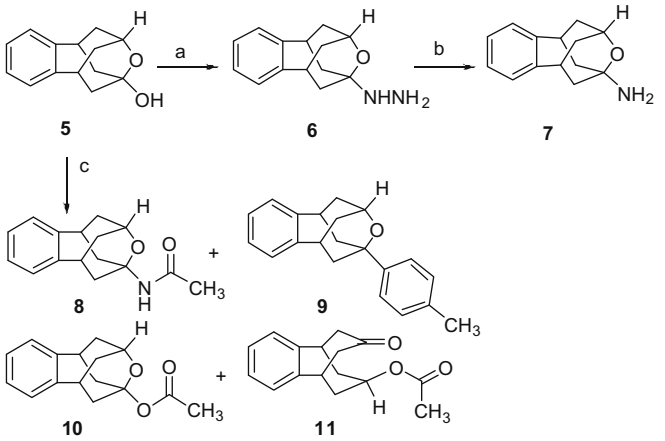


Figure 2. Heteropolycyclic cage compounds with biological activity.



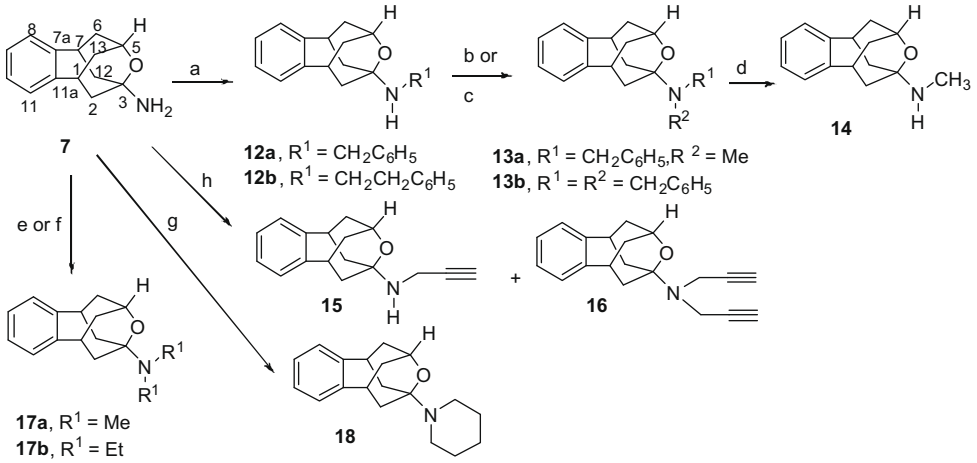
Scheme 1. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, concd HCl, reflux, 4 h, 79%; (b) H_2, PtO_2, 1 atm, rt, 3 days, 82% yield; (c) acetonitrile, toluene, concd H_2SO_4, reflux, 18 h, 47% of **8**, 3% of **9**, 2% of **10**, 3% of **11**, and 20% of recovered **5**.

Starting from amine **7**, we have prepared amines **12**–**18** using classical methods in amine chemistry. Reductive alkylation of amine **7** with benzaldehyde or phenylacetaldehyde and sodium cyanoborohydride in methanol afforded secondary amines **12a** and **12b**, respectively. Reductive alkylation of benzylamine **12a** with formaldehyde led to **13a** in 91% yield, while alkylation of **12a** with benzyl chloride led to the dibenzyl derivative **13b** in 74% yield. Hydrogenolysis of amine **13a** led to secondary amine **14** in 82% yield. Moreover, reductive alkylation of amine **7** with excess formaldehyde and formic acid led to the dimethyl derivative **17a**, while reaction of **7** with excess of acetaldehyde and sodium cyanoborohydride in methanol afforded the diethyl derivative **17b**. Alkylation of **7** with propargyl bromide led to a mixture of propargylamine **15** and dipropargylamine **16**. Column chromatography of this mixture gave pure **15** and **16** in 34 and 40% yield, respectively. Finally, alkylation of **7** with 1,5-dibromopentane led to the piperidine derivative **18** in 46% yield (Scheme 2).

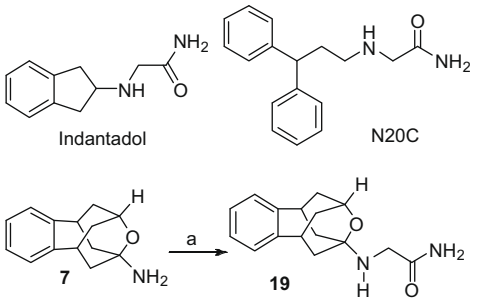
Recently, a new NMDA receptor antagonist, indantadol, has been introduced in clinical trials for the treatment of neuropathic pain. Worthy of note, indantadol also inhibits MAO-A and MAO-B with IC_{50} values of 7.2 and 60.3 μM, respectively.[18] This compound features an indane nucleus and an aminoacetamide chain in its structure. On the other hand, another non-competitive NMDA receptor antagonist with in vitro an in vivo neuroprotective properties, N20C, also features an aminoacetamide group in its structure.[19] After noticing the NMDA receptor antagonist activity of several of our new amines, we synthesized acetamide **19** that shares structural elements with both indantadol and N20C. Thus, reaction of amine **7** with chloroacetamide in the presence of sodium iodide and potassium carbonate led to acetamide **19** in 55% yield (based on recovered starting material) (Scheme 3).

Taking into account that in our previous work with 2-oxaadamant-1-ylamines we found that 3-alkyl derivatives were more potent than the corresponding 3-unsubstituted derivatives,[15] we also planned to carry out the synthesis and evaluation of 5-alkyl derivatives of amine **7**.

Reaction of the known[16] diketone **20** with methylmagnesium bromide and ethylmagnesium bromide led to alcohols **21a** and **21b**, respectively, in very high yields. While reaction of alcohol **21a** with refluxing acetonitrile in the presence of concd H_2SO_4 led to the expected amide **22a** in 81% yield, Ritter reaction of



Scheme 2. Reagents and conditions: (a) benzaldehyde or phenylacetaldehyde, $NaBH_3CN$, AcOH, MeOH, rt, 18 h, 66% for **12a**, 60% for **12b**; (b) CH_2O, $NaBH_3CN$, AcOH, acetonitrile, rt, 2 h, 91% for **13a**; (c) benzyl chloride, K_2CO_3, NaI, acetonitrile, reflux, 24 h, 74% for **13b**; (d) H_2, Pd/C, 38 atm, 100 °C, 24 h, 82% yield; (e) HCO_2H, 37% aq CH_2O, 80 °C, 24 h, 92% for **17a**; (f) acetaldehyde, $NaBH_3CN$, AcOH, acetonitrile, rt, 2 h, 91% for **17b**; (g) 1,5-dibromopentane, Et_3N, DMF, 60 °C, 26 h, 46%; (h) propargyl bromide, K_2CO_3, NaI, acetonitrile, reflux, 18 h, 34% of **15** and 40% of **16**.

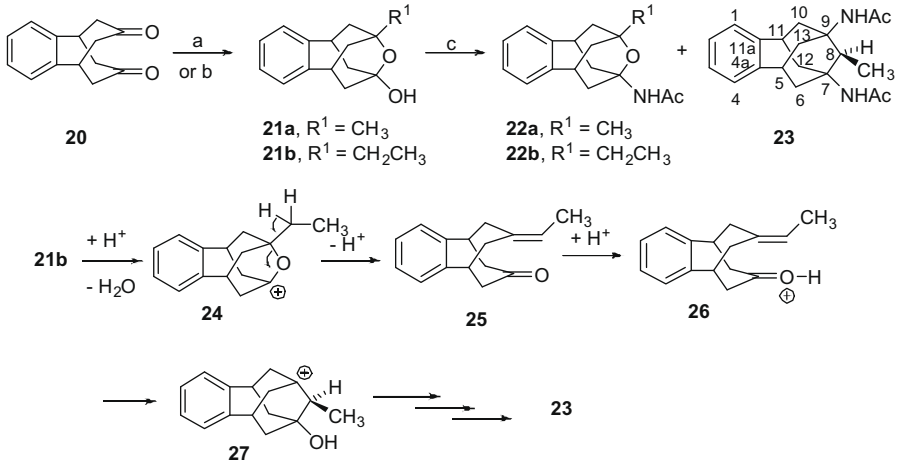


Scheme 3. Indantadol and N20C, NMDA receptor antagonists bearing an aminoacetamide group and synthesis of analog **19**. Reagents: (a) chloroacetamide, K_2CO_3, NaI, acetonitrile, reflux, 18 h, 55% (brsm).

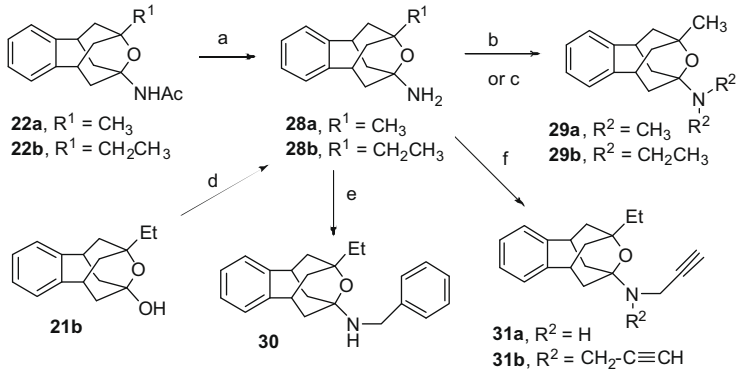
alcohol **21b** furnished a mixture of two products, the expected amide, **22b**, isolated after column chromatography in 22% yield, and the rearranged diamide **23**, isolated in 13% yield. The formation of diamide **23** can be explained taking into account the mechanism of the Ritter reaction that involves the formation of a carbocation at the bridgehead position. Thus, after protonation of the alcohol group in **21b** and loss of water the carbocation **24** may rearrange to a new carbocation, **27**, through enone **25**. Acetonitrile attack to **27** followed by Ritter reaction of the remaining alcohol may lead to the diamide **23** (Scheme 4).

Acidic hydrolysis of amides **22a** and **22b** led to amines **28a** and **28b** in 87% and 90% yield, respectively. In view of the aforementioned problems for obtaining acetamide **22b**, we developed an alternative procedure for the synthesis of amine **28b** from alcohol **21b**. Thus, reaction of **21b** with urea in trifluoroacetic acid led to **28b** in 70% yield (Scheme 5).[20]

Starting from amines **28a** and **28b**, we prepared amines **29a**, **29b**, **30**, **31a** and **31b** using similar procedures to those previously described starting from amine **7**. Thus, reductive alkylation of **28a** with formaldehyde and formic acid or with acetaldehyde and sodium cyanoborohydride led to **29a** and **29b**, respectively. On the other hand, reductive alkylation of amine **28b** with benzaldehyde and sodium cyanoborohydride in methanol afforded secondary amine **30** in 81% yield. Finally, alkylation of **28b** with propargyl bromide led to a mixture of propargylamine **31a** and dipropargylamine **31b**. Column chromatography of this mixture furnished pure **31a** and **31b** in 35% and 22% yield, respectively (Scheme 5).



Scheme 4. Reagents and conditions: (a) methylmagnesium bromide or ethylmagnesium bromide, anhyd toluene, 0 °C, overnight, 99% for **21a**; (b) ethylmagnesium bromide, anhyd toluene, 0 °C, overnight, 90% for **21b**; (c) acetonitrile, H_2SO_4, reflux, 18 h; 81% for **22a**; 22% for **22b** and 13% for **23**.



Scheme 5. Reagents and conditions: (a) HCl concd, reflux, 18 h, 87% for **28a**; 90% for **28b**; (b) HCO_2H, 37% aq CH_2O, 80 °C, 24 h, 72% of **29a**; (c) acetaldehyde, $NaBH_3CN$, AcOH, acetonitrile, rt, 18 h, 91% of **29b**; (d) urea, CF_3CO_2H, 115 °C, 18 h, 70%; (e) benzaldehyde, $NaBH_3CN$, AcOH, MeOH, rt, 18 h, 81%; (f) propargyl bromide, K_2CO_3, NaI, acetonitrile, reflux, 18 h, 35% of **31a** and 22% of **31b**.

The structures of all new compounds were confirmed by elemental analysis or accurate mass measurement, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

2.2. NMDA receptor antagonist activity

NMDA receptors mediate most of the important actions of glutamate as a neurotransmitter in the brain. The development of NMDA receptor antagonists has been intensive in the last decades due to its neuroprotective actions.[3a] However, drug development in this area has been hindered due to important side-effects in clinical trials. Nonetheless, memantine, a non-competitive and low-affinity NMDA receptor antagonist, is being used as a neuroprotective drug in Alzheimer's disease.[21] Memantine is an un-competitive antagonist with fast on-off kinetics. Another important feature is that glutamate has to be present to activate the NMDA receptor before memantine exerts its action as antagonist. Amantadine, a drug that is used in Parkinson's disease (PD) has also some NMDA antagonist activity and it has been proposed that part of its beneficial actions on PD are due to its effect on NMDA receptors.[22] To evaluate if the synthesized compounds were able to antagonize NMDA receptors, we have measured their effect on the increase in intracellular calcium evoked by glutamate or NMDA (both 100 μM, in the presence of 10 μM of glycine) on rat cultured cerebellar granule neurons.[23] Compounds **14**, **17a**, **29a** and **29b** had IC_{50} values (NMDA) that were in the micromolar order, similar to memantine (Table 1).

From the inspection of the results shown in Table 1 several trends are evident. First, all the benzyl derivatives, **12a**, **13a**, **13b** and **30**, and the phenethyl derivative **12b**, were devoid of activity, in striking contrast with NGP1-01, a low micromolar NMDA receptor antagonist that features a benzyl group in its structure. Also, propargyl derivatives were either inactive (compounds **16**, **31a** and **31b**) or had only a moderate activity (compound **15**, IC_{50} = 34 μM). On the other hand, in the active compounds, the potency increases on going from primary amines to N-alkylated and N-dialkylated derivatives (e.g., series **7**/**14**/**17a** or **28a**/**29a**/**29b**), the methyl or dimethyl substituted amines being optimum for NMDA receptor antagonism.

Worthy of note, amantadine is more than 60 times less active than its dimethyl derivative, memantine, as a NMDA receptor antagonist. The positive effect of having methyl groups directly attached to the polycyclic structure was also noticed in our previous work with (2-oxaadamant-1-yl)amines,[15] with the 3-methyl and 3-ethyl derivatives being much more active than the unsubstituted compounds. However, among the products reported here, the introduction of a 5-methyl or a 5-ethyl group did not increase the activity (e.g., series **7**/**28a**/ **28b** or **17a**/**29a** or **15**/**31a**).

Table 1
IC_{50} (μM) values for (2-oxaadamant-1-yl)amines as NMDA antagonists[a,b]

Compound	Glutamate (100 μM)	NMDA (100 μM)
7	408 ± 110	35 ± 6.8
14	28 ± 4.5	6.0 ± 1.3
15	115 ± 17	34 ± 2.3
16	>500	>200
17a	39 ± 1.5	3.8 ± 0.3
17b	96 ± 13	14 ± 1.1
18	168 ± 54	30 ± 1.0
28a	167 ± 36	98 ± 26
28b	>500	>200
29a	7.7 ± 1.1	3.9 ± 0.4
29b	22 ± 3.1	7.7 ± 1.0
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 (second column) or NMDA (third 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 **12a**, **12b**, **13a**, **13b**, **19**, **30**, **31a** and **31b** were found to have low potency as glutamate (IC_{50} >500 μM) and NMDA receptor antagonists (IC_{50} >200 μM).

2.3. MAO inhibitory activity

It is well known that rasagiline and selegiline, two clinically approved drugs for the treatment of Parkinson's disease, display monoaminooxidase (MAO) inhibitory activity.[24] Taking into account that both compounds feature a propargylamine unit and that structure–activity studies have shown that this moiety is associated with inhibition of MAO, we envisaged that our new derivatives **15**, **16**, **31a** and **31b**, which also include propargyl substituents, may also inhibit MAO. On the other hand, since indantadol also shows MAO inhibitory activity,[18] we tested our analog **19**. However, none of the tested compounds (tested at 10 and 50 μM) showed MAO inhibitory activity. Selegiline (10 μM) was used as a positive control, yielding a 85.5 ± 5.5% inhibition of MAO activity (n = 3, mean ± SEM).

2.4. Trypanocidal activity

Human African trypanosomiasis (HAT) is caused by infection with protozoan parasites of the *Trypanosoma brucei* species complex. The disease is endemic in many parts of sub-Saharan Africa, with upwards of 60 million people at risk. A process of antigenic variation prevents elimination of the parasite by the immune sys-

Table 2
IC_{50} and IC_{90} (μM) values for oxapolycyclic cage amines that display inhibitory activity against cultured bloodstream form *T. brucei*[a]

Compound	IC_{50} (μM)	IC_{90} (μM)
30	13.86 ± 0.4	19.95 ± 0.42
31a	15.23 ± 1.35	25.59 ± 0.94
31b	14.63 ± 1.18	24.08 ± 1.07
Rimantadine	7.04 ± 0.27	13.97 ± 1.68
Memantine	13.75 ± 1.26	21.43 ± 0.55

[a] Compounds were tested for in vitro activity against bloodstream form *T. brucei* at a range of concentrations and IC_{50} and IC_{90} values established (Section 4.3). Data are the mean of triplicate experiments ± SEM. Values for rimantadine and memantine are shown for comparison.

tem, and the prospects of developing a vaccine are thought to be remote. New drugs against HAT are therefore a major priority. Drugs currently available against HAT are characterized by problems including toxicity, limited efficacy, cost and the need to administer under medical supervision.

The anti-influenza virus drug rimantadine has been shown to be active in vitro against bloodstream form *T. brucei* and other aminoadamantane derivatives have even greater activity.[8] Moreover, very recently, we found that several (3-alkyl-2-oxadamant-1-yl)amines showed significant activity against bloodstream form *T. brucei*.[15] We therefore investigated if the newly synthesized oxapolycyclic cage amines reported here also displayed significant activity against this parasite.

A total of 17 compounds were tested. Of these the oxapolycyclic cage amines **7**, **12a**, **12b**, **13a**, **13b**, **14**, **15**, **16**, **17a**, **19**, **28a**, **28b**, **29a** and **29b** displayed little or no inhibitory activity against cultured bloodstream form *T. brucei* at 5 μg mL^{-1} (15–20 μM). However, compounds **30**, **31a** and **31b** significantly inhibited parasite growth, at levels comparable to rimantadine and memantine (Table 2), and at least 10-fold lower than amantadine.[8] As selectivity is a highly desired goal in pharmacology, it is noteworthy that the compounds with trypanocidal activity are devoid of NMDA receptor antagonist activity.

3. Conclusions

In summary, we have synthesized and fully characterized several oxapolycyclic amines. None of the tested compounds showed MAO inhibitory activity. Several derivatives were more potent than amantadine against NMDA-induced calcium increase in cerebellar granule neurons, and four compounds showed a very similar potency to memantine. All the benzyl derivatives were devoid of NMDA receptor antagonism activity, a trend previously observed in the (2-oxaadamant-1-yl)amines.[11] In contrast with our previous work with (2-oxaadamant-1-yl)amines, introduction of an alkyl group at C-5 does not increase the potency. However, the introduction of an ethyl group in C-5 increases the trypanocidal activity.

Work is in progress in order to evaluate the neuroprotective activity of compounds **14**, **17a**, **17b**, **29a** and **29b** in vitro. In addition, the synthesis and pharmacological evaluation of related polycyclic cage amines containing a methylene unit instead of the oxygen atom are currently 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 shits (δ) are reported in ppm 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 ratio, 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 solution of $KMnO_4$.

4.1.2. (1,2,3,5,6,7-Hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 7·HCl

A mixture of hydrazine **6** (9.19 g, 34.5 mmol)[17] and PtO_2 (10 mg) in absolute EtOH (400 mL) was hydrogenated at atmospheric pressure and room temperature for three days. The suspension was filtered, the residue was washed with EtOH and concentrated in vacuo. To the obtained white solid, water (225 mL) was added, the solution was made basic with 2 N NaOH and extracted with ethyl acetate (5 × 100 mL). The combined organic extracts were dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to about 25 mL. An excess of Et_2O·HCl was added and the solution was cooled at 4 °C whereupon **7** precipitated as its hydrochloride (7.17 g, 82% yield), mp 274–276 °C (EtOAc). IR 3407, 2941, 2924, 2848, 2725, 2642, 2546, 2365, 2064, 1606, 1508, 1223, 1149, 1043, 1007, 962, 770 cm^{-1}. ^1H NMR 1.73 [dd, J = 13.5 Hz, J' = 1.0 Hz, 2H, 6(13)-H_{exo}], 1.98 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 2.24 [dm, J = 12.5 Hz, 2H, 2(12)-H_{endo}], 2.30 (dt, J = 13.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 3.27 [t, J = 6.0 Hz, 2H, 1(7)-H], 4.53 (t, J = 5.5 Hz, 1H, 5-H), 4.86 (s, 3H, mobile H), 7.13–7.16 [m, 2H, 9(10)-H], 7.17–7.19 [m, 2H, 8(11)-H]. ^{13}C NMR 33.1 [CH_2, C6(13)], 38.0 [CH_2, C2(12)], 39.3 [CH, C1(7)], 73.6 (CH, C5), 82.5 (C, C3), 128.2 [CH, C9(10)], 129.7 [CH, C8(11)], 145.9 [C, C7a(C11a)]. MS (EI), *m/z* (%): 215 (M^+, 17), 157 (19), 156 ([M−C_3H_7O]$^+$, 100), 141 ($C_{11}H_9^+$, 51), 129 (23), 128 (20), 115 (22), 59 (28). Anal. Calcd for $C_{14}H_{17}NO$·HCl·0.25H20 (256.26): C, 65.62; H, 7.28; N, 5.47. Found: C, 65.67; H, 7.32; N, 5.67.

4.1.3. *N*-(1,2,3,5,6,7-Hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)acetamide hydrochloride, 8

A mixture of alcohol **5** (1.44 g, 6.67 mmol), toluene (2 mL), acetonitrile (0.68 mL, 13.4 mmol) and concentrated H_2SO_4 (1.20 mL, 22.5 mmol) was stirred under reflux for 18 h. The cold solution was concentrated in vacuo, water (40 mL) was added to the residue and extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with water (2 × 30 mL) and brine (30 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give an oily residue (1.34 g). Column chromatography (hexane/EtOAc mixtures) gave, in order of elution **9** (63 mg, 3% yield), **10** (29 mg, 2%), **11** (45 mg, 3%), **5** (282 mg, 20%) and the title acetamide, **8** (810 mg, 47%).

Compound **8**, mp 200–201 °C (CH_2Cl_2). IR 3289, 3057, 3021, 2929, 2912, 2876, 2836, 1669, 1663, 1655, 1541, 1534, 1522, 1492, 1450, 1435, 1390, 1369, 1352, 1335, 1300, 1276, 1248, 1215, 1196, 1169, 1112, 1072, 1036, 995, 865, 756, 699 cm^{-1}. ^1H NMR ($CDCl_3$) 1.69 [d, J = 13.0 Hz, 2H, 6(13)-H_{exo}], 1.93 (s, 3H,

$COCH_3$), 2.22 [dd, J = 12.5 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{endo}], 2.28 [dt, J = 13.0 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.48 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 3.12 [br s, 2H, 1(7)-H], 4.44 (t, J = 5.5 Hz, 1H, 5-H), 5.72 (s, 1H, NH), 7.11 [s, 4H, 9(10)-H and 8(11)-H]. ^{13}C NMR ($CDCl_3$) 24.4 (CH_3, $COCH_3$), 32.8 [CH_2, C6(13)], 37.8 [CH_2, C2(12)], 38.5 [CH, C1(7)], 71.4 (CH, C5), 82.3 (C, C3), 126.6 [CH, C9(10)], 128.4 [CH, C8(11)], 145.5 [C, C7a(C11a)], 168.3 (C, CO). MS (EI), m/z (%): 258 (13), 257 (M^+, 71), 198 (29), 180 (17), 157 (26), 156 (100), 155 (30), 142 (22), 141 (61), 129 (42), 128 (40), 115 (32), 43 (22). Anal. Calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 7.44; N, 5.44. Found: C, 74.51; H, 7.51; N, 5.43.

1,2,3,5,6,7-Hexahydro-3-(*p*-tolyl)-1,5:3,7-dimethano-3-4-benzoxonin, **9**, mp 173–174 °C (Et_2O). IR 3042, 3017, 2922, 2907, 2866, 2835, 1509, 1493, 1452, 1431, 1334, 1322, 1284, 1230, 1213, 1196, 1182, 1099, 1069, 1037, 1013, 968, 903, 810, 784, 767, 717 cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.80 [d, J = 13.0 Hz, 2H, 6(13)-H_{exo}], 2.14 [complex signal, 4H, 2(12)-H_{exo} and 2(12)-H_{endo}], 2.33 (s, 3H, CH_3), 2.37 [overlapped dt, J = 12.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 3.15 [m, 2H, 1(7)-H], 4.53 (t, J = 5.5 Hz, 1H, 5-H), 7.13–7.19 [complex signal, 6H, 9(10)-H, 8(11)-H and Ar-3(5)-H], 7.33 [dm, J = 8.0 Hz, 2H, Ar-2(6)-H]. ^{13}C NMR ($CDCl_3$) 21.0 (CH_3, Ar-CH_3), 33.2 [CH_2, C6(13)], 39.3 [CH, C1(7)], 40.1 [CH_2, C2(12)], 69.2 (CH, C5), 72.0 (C, C3), 123.5 [CH, Ar-C2(6)], 126.5 [CH, C9(10)], 128.5 [CH, C8(11)], 128.8 [CH, Ar-C3(5)], 135.9 (C, Ar-C4), 146.4 [C, C7a(C11a)], 146.9 (C, Ar-C1). MS (EI), m/z (%): 291 (6), 290 (M^+, 27), 156 (100), 141 (43), 119 (25), 91 (18). Anal. Calcd for $C_{21}H_{22}O$ (290.41): C, 86.85; H, 7.64. Found: C, 86.62; H, 7.76.

1,2,3,5,6,7-Hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl acetate, **10**, mp 99–100 °C (Et_2O). IR 3019, 2945, 2926, 2851, 1728, 1493, 1450, 1438, 1374, 1326, 1279, 1254, 1210, 1197, 1117, 1087, 1062, 1048, 1030, 1019, 977, 960, 937, 764, 741, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.67 [dd, J = 13.5 Hz, J' = 1.5 Hz, 2H, 6(13)-H_{exo}], 2.05 (s, 3H, $COCH_3$), 2.21–2.26 [m, 2H, 2(12)-H_{endo}], 2.32 [dt, J = 13.5 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.59 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 3.20 [t, J = 6.0 Hz, 2H, 1(7)-H], 4.61 (t, J = 5.5 Hz, 1H, 5-H), 7.13 [s, 4H, 9(10)-H and 8(11)-H]. ^{13}C NMR ($CDCl_3$) 22.3 (CH_3, $COCH_3$), 32.5 [CH_2, C6(13)], 37.1 [CH_2, C2(12)], 39.0 [CH, C1(7)], 73.6 (CH, C5), 102.1 (C, C3), 126.8 [CH, C9(10)], 128.5 [CH, C8(11)], 145.2 [C, C7a(C11a)], 168.5 (C, CO). MS (EI), m/z (%): 258 (M^+, 14), 216 (14), 198 (75), 157 (26), 156 (100), 141 (45), 129 (56), 128 (40), 115 (34), 43 (22). Anal. Calcd for $C_{16}H_{18}O_3$ (258.32): C, 74.40; H, 7.02. Found: C, 74.58; H, 7.12.

11-*endo*-Acetoxi-5,6,8,9-tetrahydro-5,9-propanobenzocyclohepten-7-one, **11**, mp 186–187 °C (Et_2O). IR 3021, 2931, 1726, 1691, 1493, 1455, 1428, 1403, 1374, 1247, 1216, 1202, 1180, 1092, 1068, 1036, 1023, 978, 933, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$) 2.01 (s, 3H, $COCH_3$), 2.09 [dt, J = 15.0 Hz, J' = 3.5 Hz, 2H, 10(12)-H_{endo}], 2.16 [dt, J = 15.0 Hz, J' = 4.5 Hz, 2H, 10(12)-H_{exo}], 2.66 [dd, J = 17.5 Hz, J' = 4.5 Hz, 2H, 6(8)-H_{exo}], 2.90 [ddm, J = 17.5 Hz, J' = 4.0 Hz, 2H, 6(8)-H_{endo}], 3.22 [pseudo quint, J = 4.5 Hz, 2H, 5(9)-H], 5.24 (quint, J = 4.5 Hz, 1H, 11-H), 7.18 [m, 2H, 1(4)-H], 7.21 [m, 2H, 2(3)-H]. ^{13}C NMR ($CDCl_3$) 21.5 (CH_3, $COCH_3$), 34.9 [CH_2, C10(12)], 39.6 [CH, C5(9)], 48.6 [CH_2, C6(8)], 72.1 (CH, C11), 127.6 [CH, C2(3)], 128.5 [CH, C1(4)], 143.8 [C, C4a(C9a)], 170.1 (C, $COCH_3$), 210.5 (C, C7). MS (EI), m/z (%): 258 ($M^{\cdot+}$, 0.2), 198 ([M–AcOH]$^{\cdot+}$, 21), 156 (17), 142 (16), 141 (100), 129 (28), 128 (28), 115 (21), 43 (16). Anal. Calcd for $C_{16}H_{18}O_3$ (258.32): C, 74.40; H, 7.02. Found: C, 74.10; H, 7.19.

4.1.4. *N*-Benzyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 12a·HCl

To a solution of amine **7**·HCl (251 mg, 1.00 mmol) in MeOH (10 mL), $NaBH_3CN$ (95%, 135 mg, 2.04 mmol), AcOH (0.3 mL) and benzaldehyde (106 mg, 1.00 mmol) were added and the mixture was stirred at room temperature for 18 h. After concentration to dryness, water (10 mL) was added to the residue and the mixture was extracted with Et_2O (4 × 15 mL). The combined organic extracts were washed with 2 N NaOH (3 × 25 mL), brine (2 × 25 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was taken in EtOAc and the amine **12a** was precipitated as its hydrochloride (225 mg, 66% yield) by adding an excess of Et_2O·HCl. The analytical sample was obtained by crystallization from EtOAc, mp 275–276 °C. IR 3100–2300 (max. at 2952, 2926, 2784, 2687, 2612, 2548, 2366), 1564, 1495, 1456, 1437, 1360, 1335, 1302, 1200, 1075, 1040, 1004, 966, 774, 761, 700 cm^{-1}. ^{1}H NMR 1.78 [d, J = 14.0 Hz, 2H, 6(13)-H_{exo}], 2.09 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 2.37 [dt, J = 13.5 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.41–2.45 (m, 2 H, 2(12)-H_{endo}], 3.34 [t, J = 5.5 Hz, 2H, 1(7)-H], 4.29 (s, 2H, CH_2–C_6H_5), 4.63 (t, J = 5.5 Hz, 1H, 5-H), 7.16 [m, 2H, 9(10)-H], 7.21 [m, 2H, 8(11)-H], 7.44–7.48 (complex signal, 3H, Ar-H_{meta} and Ar-H_{para}), 7.51 (dd, J = 7.5 Hz, J = 2.0 Hz, 2H, Ar-H_{ortho}). ^{13}C NMR 33.2 [CH_2, C6(13)], 36.1 [CH_2, C2(12)], 39.3 [CH, C1(7)], 45.3 (CH_2, CH_2–C_6H_5), 74.1 (CH, C5), 87.0 (C, C3), 128.3 [CH, C9(10)], 129.6 [CH, C8(11)], 130.2 (CH, Ar-C_{meta}), 130.5 (CH, Ar-C_{para}), 131.1 (CH, Ar-C_{ortho}), 132.7 (C, Ar-C_{ipso}), 145.9 [C, C7a(C11a)]. MS (EI), m/z (%): 306 ([M+H]$^+$, 6), 305 ($M^{\cdot+}$, 4), 150 (36), 149 (30), 129 (19), 128 (16), 115 (17), 91 (100), 65 (22). Anal. Calcd for $C_{21}H_{23}NO$·HCl (341.88): C, 73.78; H, 7.08; N, 4.10; Cl, 10.37. Found: C, 73.82; H, 7.29; N, 4.01; Cl, 9.89.

4.1.5. *N*-(2-Phenylethyl)-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 12b·HCl

To a solution of amine **7**·HCl (251 mg, 1.00 mmol) in MeOH (20 mL), $NaBH_3CN$ (95%, 135 mg, 2.04 mmol), AcOH (0.3 mL) and phenylacetaldehyde (120 mg, 1.00 mmol) were added and the mixture was stirred at room temperature for 18 h. After concentration to dryness, water (15 mL) was added to the residue and the mixture was extracted with Et_2O (4 × 20 mL). The combined organic extracts were washed with 2 N NaOH (3 × 20 mL), brine (2 × 20 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give a residue which was subjected to column chromatography (silica gel, hexane/EtOAc 9:1) furnishing amine **12b** (192 mg, 60% yield). From a solution of **12b** in EtOAc, its corresponding hydrochloride was precipitated by adding an excess of Et_2O·HCl. The analytical sample was obtained by crystallization from MeOH/Et_2O, mp 280–281 °C. IR 2951, 2921, 2900, 2786, 2753, 2720, 2439, 2362, 2340, 1579, 1484, 1456, 1361, 1332, 1218, 1100, 1065, 1041, 1004, 972, 763, 748, 702 cm^{-1}. ^{1}H NMR 1.74 [dd, J = 14.0 Hz, J' = 1.5 Hz, 2H, 6(13)-H_{exo}], 2.02 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.30–2.36 [complex signal, 4H, 6(13)-H_{endo} and 2(12)-H_{endo}], 3.00 (m, 2H, CH_2–C_6H_5), 3.32 [complex signal, 4H, CH_2–CH_2–C_6H_5 and 1(7)-H], 4.58 (t, J = 5.5 Hz, 1H, 5-H), 7.14 [m, 2H, 9(10)-H], 7.18 [m, 2H, 8(11)-H], 7.27 (tt, J = 7.5 Hz, J' = 1.5 Hz, 1H, Ar-H_{para}), 7.30 (dm, J = 7.5 Hz, 2H, Ar-H_{ortho}), 7.34 (tm, J = 7.5 Hz, 2H, Ar-H_{meta}). ^{13}C NMR 33.1 [CH_2, C6(13)], 33.6 (CH_2, CH_2–C_6H_5), 36.1 [CH_2, C2(12)], 39.2 [CH, C1(7)], 42.5 (CH_2, CH_2–CH_2–C_6H_5), 74.0 (CH, C5), 86.7 (C, C3), 128.3 [CH, C9(10) and Ar-C_{para}], 129.66 [CH, C8(11)], 129.72 (CH, Ar-C_{ortho}), 129.9 (CH, Ar-C_{meta}), 137.8 (C, Ar-C_{ipso}), 145.9 [C, C7a(C11a)]. MS (EI), m/z (%): 320 ([M+H]$^+$, 1), 319 ($M^{\cdot+}$, 1), 230 (20), 229 (100), 228 (27), 199 (73), 157 (39), 141 (22), 129 (49), 128 (19), 115 (25), 105 (23), 104 (33), 91 (28). Anal. Calcd for $C_{22}H_{25}NO$·HCl (355.91): C, 74.24; H, 7.36; N, 3.94; Cl, 9.96. Found: C, 73.88; H, 7.39; N, 3.95; Cl, 10.17.

4.1.6. *N*-Benzyl-*N*-methyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 13a·HCl

To a solution of **12a**·HCl (341 mg, 1.00 mmol) in acetonitrile (10 mL), formaldehyde (0.78 mL, 37 wt % in water solution, 10 mmol) and $NaBH_3CN$ (198 mg, 3.00 mmol) were added. The mixture was stirred for 30 min at room temperature, acetic acid (0.4 mL) was added and the mixture was stirred at room tempera-

ture for 2 h. An additional portion of $NaBH_3CN$ (198 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 **13a** (289 mg, 91% 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, followed by filtration of the formed precipitate. The analytical sample was obtained by crystallization from MeOH/CH_2Cl_2, mp 235−236 °C. IR 3500–2100 (max. at 3428, 3031, 2945, 2933, 2845, 2399, 2304), 1624, 1496, 1456, 1436, 1410, 1396, 1361, 1333, 1306, 1222, 1197, 1176, 1131, 1079, 1059, 1033, 973, 958, 910, 868, 788, 778, 759, 737, 706, 699 cm^{-1}. ^1H NMR 1.79 [dd, J = 14.0 Hz, J' = 1.0 Hz, 2H, 6(13)-H_{exo}], 2.18–2.48 [br signal, 6H, 2(12)-H_{exo}, 2(12)-H_{endo} and 6(13)-H_{endo}], 2.74 (s, 3H, CH_3–N), 3.40 [br s, 2H, 1(7)-H], 3.96 (br signal, 1H, CH_a–C_6H_5), 4.72 (t, J = 5.5 Hz, 1H, 5-H), 4.88 (br signal, 1H, CH_b–C_6H_5), 7.17 [m, 2H, 9(10)-H], 7.23 [m, 2H, 8(11)-H], 7.48–7.53 (complex signal, 5H, Ar-H benzyl). ^{13}C NMR 33.0 [CH_2, C6(13)], 33.4 (CH_3, CH_3–N), 33.8 [br CH_2, C2(12)], 39.2 [CH, C1(7)], 54.8 (CH_2, CH_2–C_6H_5), 75.0 (CH, C5), 92.3 (C, C3), 128.4 [CH, C9(10)], 129.7 [CH, C8(11)], 130.3 (CH, Ar-C_{meta}), 131.1 (CH, Ar-C_{para}), 131.3 (C, Ar-C_{ipso}), 132.6 (CH, Ar-C_{ortho}), 146.0 [C, C7a(C11a)]. MS (EI), m/z (%): 319 ($M^{\cdot+}$, 18), 164 (14), 163 (100), 162 (25), 91 (38). Anal. Calcd for $C_{22}H_{25}NO$·HCl·0.25H_2O (360.41): C, 73.32; H, 7.41; N, 3.89; Cl, 9.84. Found: C, 73.30; H, 7.44; N, 4.00; Cl, 9.69.

4.1.7. *N,N*-Dibenzyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 13b·HCl

A suspension of **12a**·HCl (200 mg, 0.59 mmol), K_2CO_3 (70 mg, 0.5 mmol), benzyl chloride (0.11 mL, 1.00 mmol) and NaI (65 mg, 0.43 mmol) in acetonitrile (10 mL) was heated under reflux for 24 h. To the cold mixture, AcOEt (30 mL) was added and the solution was washed with water (3 × 20 mL). The organic layer was dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give a residue which was subjected to column chromatography (hexane/EtOAc 99:1) gave **13b** (172 mg, 74% yield). Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in EtOAc, followed by filtration of the formed precipitate. The analytical sample was obtained by crystallization from MeOH/Et_2O, mp 268–270 °C. IR 3500–2300 (max. at 3356, 3041, 2936, 2916, 2843, 2471), 1625, 1492, 1458, 1333, 1225, 1198, 1078, 1064, 1041, 964, 853, 747, 696 cm^{-1}. ^1H NMR 1.81 [d, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 2.36–2.50 [complex signal, 4H, 2(12)-H_{exo} and 6(13)-H_{endo}], 2.60 (br s, 2H, 2(12)-H_{endo}], 3.43 [br s, 2H, 1(7)-H], 4.22 (d, J = 12.5 Hz, 2H, 2CH_a–C_6H_5), 4.80 (br s, 1H, 5-H), 4.89 (d, J = 12.5 Hz, 2H, 2CH_b–C_6H_5), 7.13–7.20 [complex signal, 6H, 9(10)-H and 2 Ar-H_{ortho}], 7.21–7.32 [complex signal, 6H, 8(11)-H and 2 Ar-H_{meta}], 7.33–7.40 (br signal, 2H, 2 Ar-H_{para}). ^{13}C NMR 33.0 [CH_2, C6(13)], 34.3 [CH_2, C2(12)], 39.3 [CH, C1(7)], 54.2 (CH_2, 2CH_2–C_6H_5), 75.0 (CH, C5), 94.8 (C, C3), 128.4 [CH, C9(10)], 129.7 [CH, C8(11)], 130.0 [CH, 2 Ar-C_{meta}], 130.6 (CH, 2 Ar-C_{para}), 132.4 (CH, 2 Ar-C_{ortho}), 132.0 (C, 2 Ar-C_{ipso}), 146.1 [C, C7a(C11a)]. MS (EI), m/z (%): 396 ([M+H]$^+$, 6), 395 ($M^{\cdot+}$, 13), 239 (28), 148 (42), 129 (20), 106 (28), 91 (100). Anal. Calcd for $C_{28}H_{29}NO$·HCl·0.5H_2O (441.01): C, 76.26; H, 7.09; N, 3.18; Cl, 8.04. Found: C, 76.36; H, 7.11; N, 3.23; Cl, 8.06.

4.1.8. *N*-Methyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 14·HCl

A suspension of **13a**·HCl·0.25H_2O (465 mg, 1.29 mmol) and 5% Pd/C (50% in water, 100 mg) in absolute EtOH (50 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 of the residue from MeOH/Et_2O gave **14**·HCl·0.25H_2O (287 mg, 82% yield), mp 265–266 °C. IR 3500–2400 (max. at 3429, 2945, 2918, 2840, 2798, 2754, 2682, 2485, 2412), 1624, 1481, 1453, 1336, 1227, 1198, 1163, 1089, 1072, 1042, 971, 758 cm^{-1}. ^1H NMR 1.74 [dd, J = 14.0 Hz, J' = 1.0 Hz, 2H, 6(13)-H_{exo}], 2.00 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.24–2.28 [m, 2H, 2(12)-H_{endo}], 2.32 (dt, J = 13.5 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.67 (s, 3H, CH_3–N), 3.30–3.33 [br t, J = 5.5 Hz, 2H, 1(7)-H], 4.57 (t, J = 5.5 Hz, 1H, 5-H), 7.14–7.17 [m, 2H, 9(10)-H], 7.18–7.20 [m, 2H, 8(11)-H]. ^{13}C NMR 25.7 (CH_3, CH_3–N), 33.1 [CH_2, C6(13)], 35.8 [CH_2, C2(12)], 39.1 [CH, C1(7)], 74.0 (CH, C5), 85.9 (C, C3), 128.3 [CH, C9(10)], 129.7 [CH, C8(11)], 145.9 [C, C7a(C11a)]. MS (EI), m/z (%): 230 ([M+H]$^+$, 21), 229 ($M^{\cdot+}$, 15), 156 (22), 141 (28), 129 (18), 115 (14), 75 (15), 74 (100), 73 (74). Anal. Calcd for $C_{15}H_{19}NO$·HCl·0.25H_2O (270.29): C, 66.66; H, 7.64; N, 5.18; Cl, 13.12. Found: C, 66.67; H, 7.66; N, 5.23; Cl, 13.48.

4.1.9. *N*-Propargyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 15·HCl and *N,N*-dipropargyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 16·HCl

A suspension of **7**·HCl (275 mg, 1.09 mmol), K_2CO_3 (180 mg, 1.28 mmol), propargyl bromide (0.16 mL, 80% solution in toluene, 1.44 mmol) and NaI (15 mg, 0.1 mmol) in acetonitrile (15 mL) was heated under reflux for 18 h. After concentration to dryness in vacuo, the residue was taken in CH_2Cl_2 (20 mL) and the solution was washed with water (3 × 10 mL). The organic layer was dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give a residue which was subjected to column chromatography (hexane/EtOAc mixtures) affording **16** (hexane/EtOAc 97:3, 129 mg, 40% yield) and **15** (hexane/EtOAc 95:5, 108 mg, 34% yield). The hydrochlorides of **15** and **16** were obtained by adding an excess of Et_2O·HCl to a solution of the amine in EtOAc, followed by filtration of the formed precipitate. **15**: mp 230–231 °C (EtOAc/Et_2O). IR 3500–2450 (max. at 3448, 3285, 3199, 2994, 2919, 2844, 2761, 2734, 2699, 2647, 2580, 2392), 2123, 1569, 1455, 1434, 1336, 1218, 1198, 1070, 1050, 1039, 1018, 1007, 964, 760, 740, 705 cm^{-1}. ^1H NMR 1.74 [d, J = 14.0 Hz, 2H, 6(13)-H_{exo}], 1.99 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.29–2.35 [complex signal, 4H, 2(12)-H_{endo} and 6(13)-H_{endo}], 3.20 (t, J = 2.5 Hz, 1H, $CH_2C{\equiv}CH$), 3.31 [t, J = 5.5 Hz, 2H, 1(7)-H], 4.03 (d, J = 2.5 Hz, 2H, C$H_2C{\equiv}$CH), 4.58 (t, J = 5.5 Hz, 1H, 5-H), 7.15 [m, 2H, 9(10)-H], 7.19 [m, 2H, 8(11)-H]. ^{13}C NMR 30.6 (CH_2, C$H_2C{\equiv}$CH), 33.0 [CH_2, C6(13)], 36.0 [CH_2, C2(12)], 39.1 [CH, C1(7)], 74.2 (CH, $CH_2C{\equiv}$CH), 75.3 (CH, C5), 78.6 (C, $CH_2C{\equiv}$CH), 86.8 (C, C3), 128.4 [CH, C9(10)], 129.7 [CH, C8(11)], 145.8 [C, C7a(C11a)]. MS (EI), m/z (%): 253 ($M^{\cdot+}$, 18), 252 (14), 238 (36), 210 (19), 157 (48), 156 (63), 155 (32), 143 (25), 142 (32), 141 (100), 129 (76), 128 (70), 115 (66), 97 (87), 96 (63). Anal. Calcd for $C_{17}H_{19}NO$·1.05HCl (291.63): C, 70.02; H, 6.93; N, 4.80; Cl, 12.76. Found: C, 69.84; H, 7.01; N, 4.72; Cl, 12.81. Compound **16**: mp 172–173 °C. IR 3276, 3227, 3167, 2930, 2911, 2429, 2221, 2117, 1731, 1491, 1452, 1433, 1358, 1335, 1260, 1218, 1135, 1122, 1075, 1065, 1034, 967, 905, 767, 729, 694 cm^{-1}. ^1H NMR 1.67 [dd, J = 13.5 Hz, J' = 1.5 Hz, 2H, 6(13)-H_{exo}], 2.06 [d, J = 13.5 Hz, 2H, 2(12)-H_{exo}], 2.22–2.27 [complex signal, 4H, 2(12)-H_{endo} and 6(13)-H_{endo}], 2.79 (s, 2H, 2$CH_2C{\equiv}CH$), 3.22 [t, J = 6.0 Hz, 2H, 1(7)-H], 3.97 (s, 4H, 2C$H_2C{\equiv}$CH), 4.48 (t, J = 5.5 Hz, 1H, 5-H), 7.11 [m, 2H, 9(10)-H], 7.15 [m, 2H, 8(11)-H]. ^{13}C NMR 33.5 [CH_2, C6(13)], 36.17 (CH_2, 2$CH_2C{\equiv}$CH), 36.21 [CH_2, C2(12)], 39.8 [CH, C1(7)], 73.7 (CH, C5), 76.5 (CH, 2$CH_2C{\equiv}$CH), 78.7 (C, 2$CH_2C{\equiv}$CH), 88.7 (C, C3), 128.0 [CH, C9(10)], 129.5 [CH, C8(11)], 146.6 [C, C7a(C11a)]. MS (EI), m/z (%): 291 ($M^{\cdot+}$, 12), 290 (20), 276 (50), 209 (24), 195 (18), 181 (16), 169 (28), 168 (18), 167 (18), 157 (60), 155 (39), 154 (20), 153 (23), 143 (34), 142 (39), 141 (90), 135 (33), 134 (38), 130 (20), 129 (100), 128 (76), 127 (24), 116 (20), 115 (77), 91 (24). Accurate mass measurement

(ESI+) calcd for $[C_{20}H_{22}NO+H]^+$: 292.1696. Found: 292.1689. Anal. Calcd for the free base $C_{20}H_{21}NO$ (291.39): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.12; H, 7.39; N, 4.58.

4.1.10. *N,N*-Dimethyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 17a·HCl

To a cold (0 °C) solution of **7** (503 mg, 2.00 mmol) in Et_2O (10 mL), formaldehyde (3.5 mL, 37 wt % in water solution, 44.4 mmol) and, dropwise, formic acid (3.0 mL, 80 mmol) were added and the mixture was stirred at 80 °C for 24 h. The mixture was allowed to cool to room temperature, was diluted with Et_2O (20 mL), 5 N NaOH (10 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 × 20 mL). The combined organic phases were washed with brine (30 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give **17a** (447 mg, 92% yield). Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in EtOAc, followed by filtration of the formed precipitate. The analytical sample was obtained by crystallization from MeOH/Et_2O, mp 263–264 °C. IR 3500–2300 (max. at 3370, 3320, 3016, 2961, 2946, 2915, 2844, 2612, 2583, 2507, 2401), 1616, 1479, 1452, 1433, 1390, 1361, 1335, 1222, 1196, 1166, 1154, 1122, 1074, 1051, 1030, 1003, 965, 956, 909, 790, 613 cm^{-1}. ^1H NMR 1.75 [dd, J = 14.0 Hz, J' = 1.0 Hz, 2H, 6(13)-H_{exo}], 2.14 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.23–2.27 [m, 2H, 2(12)-H_{endo}], 2.32 (dt, J = 13.5 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.85 (s, 6H, CH_3–N), 3.34–3.37 [br t, J = 5.5 Hz, 2H, 1(7)-H], 4.63 (t, J = 5.5 Hz, 1H, 5-H), 7.16 [m, 2H, 9(10)-H], 7.21 [m, 2H, 8(11)-H]. ^{13}C NMR 32.9 [CH_2, C6(13)], 33.4 [CH_2, C2(12)], 36.8 (CH_3, CH_3–N), 39.0 [CH, C1(7)], 74.6 (CH, C5), 90.8 (C, C3), 128.3 [CH, C9(10)], 129.7 [CH, C8(11)], 145.8 [C, C7a(C11a)]. MS (EI), *m/z* (%): 243 (M^{+}, 19), 141 (19), 129 (17), 128 (17), 115 (19), 87 (100), 72 (24). Anal. Calcd for $C_{16}H_{21}NO·HCl·0.5H_2O$ (288.82): C, 66.54; H, 8.03; N, 4.85; Cl, 12.28. Found: C, 66.74; H, 8.10; N, 4.93; Cl, 11.93.

4.1.11. *N,N*-Diethyl-(1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine (2*R*,3*R*)-tartrate, 17b·(2*R*,3*R*)-tartrate

To a solution of **7**·HCl (251 mg, 1.00 mmol) in methanol (13 mL), $NaBH_3CN$ (95%, 145 mg, 2.19 mmol), AcOH (0.4 mL) and acetaldehyde (0.33 mL, 5.9 mmol) were added and the mixture was stirred at room temperature for 8 h. An additional portion of $NaBH_3CN$ (95%, 77 mg, 1.16 mmol) and acetaldehyde (0.16 mL, 2.9 mmol) were added, the mixture was stirred at room temperature for 10 h and then it was concentrated in vacuo to dryness. Water (20 mL) was added to the residue, the suspension was basified with 1 N NaOH (8 mL) and was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give **17b** as an oil (246 mg, 91% yield). An analytical sample of the (2*R*,3*R*)-tartrate of **17b** was obtained by adding 1 equiv of (2*R*,3*R*)-(+)-tartaric acid in MeOH (15 mL) to a solution of **17b** in EtOAc (15 mL), evaporation to dryness and crystallization from 2-propanol, mp 167–168 °C. IR 3600–2500 (max. at 3321, 3277, 2926, 2857, 2666), 1733, 1579, 1417, 1335, 1306, 1264, 1216, 1135, 1076, 1067, 1034, 968, 901, 789, 772, 680 cm^{-1}. ^1H NMR 1.39 (t, J = 7.5 Hz, 6H, $2CH_2CH_3$), 1.74 [dd, J = 14.0 Hz, J' = 1.0 Hz, 2H, 6(13)-H_{exo}], 2.16 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 2.30–2.36 [complex signal, 4H, 6(13)-H_{endo} and 2(12)-H_{endo}], 3.30–3.38 [complex signal, 6H, $2CH_2$–CH_3 and 1(7)-H], 4.40 (s, 2 H, 2CHOH tartaric acid), 4.63 (t, J = 5.5 Hz, 1H, 5-H), 7.15 [m, 2H, 9(10)-H], 7.20 [m, 2H, 8(11)-H]. ^{13}C NMR 12.4 (CH_3, CH_2CH_3), 33.0 [CH_2, C6(13)], 34.0 [CH_2, C2(12)], 39.1 [CH, C1(7)], 45.9 (CH_2, $2CH_2$–CH_3), 74.0 (CH, 2CHOH tartaric acid), 74.5 (CH, C5), 93.0 (C, C3), 128.3 [CH, C9(10)], 129.7 [CH, C8(11)], 146.0 [C, C7a(C11a)], 176.5 (C, $2CO_2H$). MS (EI), *m/z* (%): 272 ([M+H]$^+$, 13), 271 (M^{+}, 6), 141 (19), 129 (30), 128 (19), 116 (38), 115 (100), 100 (46), 72 (19). Anal. Calcd for $C_{18}H_{25}NO·C_4H_6O_6·1.5H_2O$ (448.51): C, 58.92; H, 7.64; N, 3.12. Found: C, 58.68; H, 7.76; N, 2.79.

4.1.12. *N*-(1,2,3,5,6,7-Hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)piperidine hydrochloride, 18·HCl

To a solution of **7**·HCl (590 mg, 2.37 mmol) in DMF (8.0 mL), anhyd Et_3N (1.32 mL, 9.45 mmol) was added and the suspension was stirred at room temperature for 2 h. 1,5-Dibromopentane (0.53 mL, 3.88 mmol) was added and the mixture was heated at 60 °C for 26 h. To the cold mixture, water (30 mL) was added and the solution was extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with water (5 × 15 mL), dried with anhyd Na_2SO_4 and filtered. Excess of Et_2O·HCl was added and the solution was concentrated in vacuo to dryness to give **18**·HCl (348 mg, 46% yield). The analytical sample of **18**·HCl was obtained by crystallization from MeOH/Et_2O, mp 187–188 °C. IR 3016, 2946, 2914, 2856, 2643, 2599, 2543, 2480, 2459, 2375, 1492, 1452, 1440, 1426, 1331, 1220, 1198, 1113, 1098, 1077, 1048, 1029, 1014, 970, 896, 753, 674 cm^{-1}. ^1H NMR 1.54 (br s, 1H, piperidine 4-H_{ax}), 1.74 [dd, J = 14.0 Hz, J' = 1.0 Hz, 2H, 6(13)-H_{exo}], 1.76–1.99 [complex signal, 5H, piperidine 4-H_{eq}, 3(5)-H_{ax} and 3(5)-H_{eq}], 2.14 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 2.30–2.35 [complex signal, 4H, 2(12)-H_{endo} and 6(13)-H_{endo}], 2.96 [br s, 2H, piperidine 2(6)-H_{ax}], 3.34 [t, J = 5.5 Hz, 2H, 1(7)-H], 3.71 [br s, 2H, piperidine 2(6)-H_{eq}], 4.63 (t, J = 5.5 Hz, 1H, 5-H), 7.15 [m, 2H, 9(10)-H], 7.19 [m, 2H, 8(11)-H]. ^{13}C NMR 23.4 (CH_2, piperidine C4), 24.5 [CH_2, piperidine C3(5)], 33.1 [CH_2, C6(13)], 33.9 [CH_2, C2(12)], 39.1 [CH, C1(7)], 47.7 [CH_2, piperidine C2(6)], 74.6 (CH, C5), 91.4 (C, C3), 128.4 [CH, C9(10)], 129.7 [CH, C8(11)], 146.0 [C, C7a(C11a)]. MS (EI), *m/z* (%): 283 (M^{+}, 20), 141 (15), 129 (18), 128 (27), 127 (100), 115 (13), 112 (18). Anal. Calcd for $C_{19}H_{25}NO·HCl$ (319.87): C, 71.34; H, 8.19; N, 4.38; Cl, 11.08. Found: C, 70.91; H, 8.28; N, 4.27; Cl, 10.96.

4.1.13. 2-[(1,2,3,5,6,7-Hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amino]acetamide hydrochloride, 19·HCl

A suspension of **7**·HCl (190 mg, 0.75 mmol), K_2CO_3 (123 mg, 0.88 mmol), 2-chloroacetamide (93 mg, 0.94 mmol) and NaI (15 mg, 0.1 mmol) in acetonitrile (10 mL), was heated under reflux for 18 h and then it was concentrated in vacuo to dryness. CH_2Cl_2 (20 mL) was added to the residue, the organic solution was washed with water (3 × 10 mL), was dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give an oily residue. Column chromatography (silica gel) gave starting amine **7** (hexane/EtOAc 4:6, 31 mg) and acetamide **19** (EtOAc/MeOH 95/5, 91 mg, 55% yield based on unrecovered starting material). Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in Et_2O, followed by filtration of the precipitated solid, mp 254–255 °C. IR 3600–2400 (max. at 3563, 3322, 3176, 3057, 2934, 2722, 2613, 2402), 1683, 1622, 1558, 1493, 1453, 1435, 1418, 1400, 1361, 1335, 1304, 1219, 1197, 1075, 1039, 969, 759 cm^{-1}. ^1H NMR 1.74 [d, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 1.99 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.28–2.34 [complex signal, 4H, 2(12)-H_{endo} and 6(13)-H_{endo}], 3.30 [t, J = 5.5 Hz, 2H, 1(7)-H], 3.90 (s, 2H, CH_2CONH_2), 4.57 (t, J = 5.5 Hz, 1H, 5-H), 7.15 [m, 2H, 9(10)-H], 7.19 [m, 2H, 8(11)-H]. ^{13}C NMR 33.1 [CH_2, C6(13)], 36.1 [CH_2, C2(12)], 39.2 [CH, C1(7)], 42.0 (CH_2, CH_2CONH_2), 74.1 (CH, C5), 86.5 (C, C3), 128.3 [CH, C9(10)], 129.7 [CH, C8(11)], 145.9 [C, C7a(C11a)], 168.9 (C, CO). MS (EI), *m/z* (%): 274 (6), 273 ([M+H]$^+$, 10), 272 (M^{+}, 6), 256 (12), 231 (14), 230 (45), 229 (69), 228 (41), 201 (30), 200 (49), 199 (34), 158 (46), 157 (68), 156 (41), 155 (32), 143 (23), 142 (38), 141 (80), 130 (50), 129 (100), 128 (52), 117 (38), 116 (97), 115 (59), 99 (50). Anal. Calcd for $C_{16}H_{20}N_2O_2·HCl·0.75H_2O$ (322.32): C, 59.62; H, 7.04; N, 8.69; Cl, 11.00. Found: C, 59.94; H, 6.96; N, 8.61; Cl, 10.95.

4.1.14. 1,2,3,5,6,7-Hexahydro-5-methyl-1,5:3,7-dimethano-4-benzo-xonin-3-ol, 21a

To a flask containing anhyd toluene (100 mL) at 0 °C, methylmagnesium bromide (84 mL, 3 M in Et_2O, 0.25 mol) was added. Then, a solution of **20** (11.00 g, 51.4 mmol) in anhyd toluene (300 mL) was added dropwise, keeping the temperature between −10 and 0 °C. The mixture was allowed to reach room temperature with stirring overnight. An aqueous solution of NH_4Cl (10%) was added until the resulting precipitate was completely dissolved. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give a white solid (11.7 g, 99% yield), mp 169–170 (lit. 167–169).[16]

4.1.15. 5-Ethyl-1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-ol, 21b

To a flask containing anhyd toluene (50 mL) at 0 °C, ethylmagnesium bromide (40 mL, 3 M in Et_2O, 0.12 mol) was added. Then, a solution of **20** (5.00 g, 23.4 mmol) in anhyd toluene (150 mL) was added dropwise, keeping the temperature between −10 and 0 °C. The mixture was allowed to reach room temperature with stirring overnight. An aqueous solution of NH_4Cl (10%) was added until the resulting precipitate was completely dissolved. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give a white solid (5.14 g, 90% yield), mp 155 °C (methanol/Et_2O). IR 3321, 3071, 3026, 2973, 2958, 2934, 2912, 2874, 2837, 1495, 1458, 1439, 1426, 1357, 1347, 1279, 1246, 1164, 1140, 1125, 1112, 1007, 970, 945, 910, 760, 662 cm^{-1}. ^1H NMR ($CDCl_3$) 0.88 (t, J = 7.7 Hz, 3H, CH_2CH_3), 1.56 (q, J = 7.7 Hz, 2H, CH_2CH_3), 1.62 [unsolved dt, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 1.84 [ddm, J = 13.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 1.91 [dt, J = 13.0 Hz, J' = 1.5 Hz, 2H, 2(12)-H_{exo}], 1.99 [ddm, J = 13.0 Hz, J' = 6.0 Hz, 2H, 2(12)-H_{endo}], 3.1–3.5 (br signal, 1H, OH), 3.22 [tt, J = 6.0 Hz, J' = 1.5 Hz, 1H, 1(7)-H], 7.14 [pseudo s, 4H, 9(10)-H and 8(11)-H]. ^{13}C NMR (100.6 MHz, $CDCl_3$) 7.4 (CH_3, CH_2CH_3), 35.9 [CH_2, C6(13)], 37.0 (CH_2, CH_2CH_3), 39.4 [CH, C1(7)], 39.8 [CH_2, C2(12)], 78.3 (C, C5), 94.7 (C, C3), 126.7 [CH, C9(10)], 128.4 [CH, C8(11)], 145.3 [C, C7a(C11a)]. MS (EI), m/z (%): 245 (18), 244 (M^{+}, 100), 215 (18), 184 (38), 172 (26), 169 (29), 157 (35), 156 (28), 155 (33), 129 (85), 128 (42), 115 (47). Anal. Calcd for $C_{16}H_{20}O_2$ (244.33): C, 78.65; H, 8.25. Found: C, 78.59; H, 8.20.

4.1.16. *N*-(1,2,3,5,6,7-Hexahydro-5-methyl-1,5:3,7-dimethano-4-benzoxonin-3-yl)acetamide hydrochloride, 22a

A mixture of alcohol **21a** (500 mg, 2.17 mmol), acetonitrile (10 mL) and concentrated H_2SO_4 (0.1 mL, 1.87 mmol) was stirred under reflux for 18 h. The mixture was allowed to cool to room temperature, water (20 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give **22a** as a white solid (477 mg, 81% yield). The analytical sample of **22a** was obtained by crystallization from CH_2Cl_2, mp 172−177 °C. IR 3239, 3042, 2973, 2917, 1635, 1540, 1495, 1448, 1432, 1372, 1284, 1226, 1174, 1040, 982, 841, 762, 738, 603 cm^{-1}. ^1H NMR ($CDCl_3$) 1.22 (s, 3H, CH_3), 1.65 [dm, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 1.91 [overlapped dd, J = 13.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 1.93 (s, 3H, $COCH_3$), 2.01 [dd, J = 13.5 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{exo}], 2.56 [d, J = 13.5 Hz, 2H, 2(12)-H_{endo}], 3.12 (t, J = 6.0 Hz, 2H, 1(7)-H], 5.76 (s, 1H, NH), 7.08–7.12 [complex signal, 4H, 9(10)-H and 8(11)-H]. ^{13}C NMR ($CDCl_3$) 24.4 (CH_3, $COCH_3$), 31.4 (CH_3, C5–CH_3), 37.2 [CH_2, C2(12)], 38.68 [CH, C1(7)], 38.72 [CH_2, C6(13)], 73.7 (C, C5), 84.1 (C, C3), 126.6 [CH, C9(10)], 128.3 [CH, C8(11)], 145.1 [C, C7a(C11a)], 168.1 (C, $COCH_3$). MS (EI), m/z (%): 272 (20), 271 (M^{+}, 100), 253 (16), 212 (44), 198 (33), 197 (19), 194 (25), 170 (88), 169 (42), 157 (46), 156 (30), 155 (74), 142 (26), 129 (56), 128 (40), 115 (30). Anal. Calcd for $C_{17}H_{21}NO_2 \cdot 0.15CH_2Cl_2$ (284.10): C, 72.51; H, 7.56; N, 4.93. Found: C, 72.16; H, 7.54; N, 4.82.

4.1.17. *N*-(5-Ethyl-1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)acetamide, 22b

A mixture of alcohol **21b** (3.50 g, 14.3 mmol), acetonitrile (75 mL) and concentrated H_2SO_4 (0.6 mL, 11.3 mmol) was stirred under reflux for 18 h. The solution was allowed to cool to room temperature, water (150 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give a residue (1.62 g), which was subjected to column chromatography (hexane/EtOAc mixtures) to give, in order of elution, acetamide **22b** (860 mg, 22% yield) and **23** (630 mg, 13% yield) as white solids. The analytical samples of **22b** and **23** were obtained by crystallization from CH_2Cl_2.

Compound **22b**, mp 191−192 °C. IR 3219, 3029, 2919, 2841, 1639, 1537, 1493, 1451, 1435, 1369, 1347, 1279, 1220, 1199, 1166, 1145, 1056, 1045, 1028, 988, 944, 840, 833, 764, 736, 627, 609 cm^{-1}. ^1H NMR ($CDCl_3$) 0.87 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.50 [q, J = 7.5 Hz, 2H, CH_2CH_3], 1.64 [d, J = 13.0 Hz, 2H, 6(13)-H_{exo}], 1.86 [dd, J = 13.0 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 1.93 (s, 3H, $COCH_3$), 1.99 [dd, J = 13.0 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{exo}], 2.59 [d, J = 13.0 Hz, 2H, 2(12)-H_{endo}], 3.14 [t, J = 5.5 Hz, 1H, 1(7)-H], 5.78 (s, 1H, NH), 7.08–7.12 [complex signal, 4H, 9(10)-H and 8(11)-H]. ^{13}C NMR (100.6 MHz, $CDCl_3$) 7.1 (CH_3, CH_2CH_3), 24.3 (CH_3, $COCH_3$), 36.3 [CH_2, C6(13)], 37.1 (CH_2, CH_2CH_3), 37.6 [CH_2, C2(12)], 38.5 [CH, C1(7)], 75.7 (C, C5), 84.0 (C, C3), 126.6 [CH, C9(10)], 128.3 [CH, C8(11)], 145.3 [C, C7a(C11a)], 168.1 (C, CH_3CO). MS (EI), m/z (%): 286 (16), 285 (M^{+}, 81), 226 (44), 208 (22), 198 (59), 197 (35), 185 (27), 184 (74), 170 (34), 169 (92), 157 (60), 156 (50), 155 (100), 154 (32), 143 (26), 142 (25), 141 (35), 129 (80), 128 (59), 115 (44), 43 (42). Anal. Calcd for $C_{18}H_{23}NO_2$ (285.39): C, 75.76; H, 8.12; N, 4.91. Found: C, 75.88; H, 8.22; N, 4.84.

7,9-Bisacetamido-6,7,8,9,10,11-hexahydro-8-methyl-5,9:7,11-dimethano-5*H*-benzocyclononene, **23**, mp 261−262 °C. IR 3406, 3291, 3081, 2969, 2923, 2862, 1662, 1560, 1496, 1446, 1368, 1348, 1320, 1297, 1130, 1074, 1034, 970, 942, 759, 657, 601 cm^{-1}. ^1H NMR 1.01 (d, J = 7.5 Hz, 3H, C8–CH_3), 1.91 (s, 6H, $2COCH_3$), 1.95 [d, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 2.06 [dm, 4H, 10(12)-H_{exo} and 2(13)-H_{endo}], 2.58 [ddd, J = 13.5 Hz, J' = 6.5 Hz, J'' = 2.5 Hz, 2H, 10(12)-H_{endo}], 3.07 (overlapped t, J = 7.0 Hz, 1H, 5-H), 3.09 (overlapped t, J = 7.0 Hz, 1H, 11-H), 3.16 (q, J = 7.5 Hz, 1H, 8-H), 5.09 (s, 2H, 2 NH), 7.01–7.11 (complex signal, 4H, Ar-H). ^{13}C NMR 8.6 (CH_3, C8–CH_3), 24.6 (CH_3, $COCH_3$), 33.3 [CH_2, C6(13)], 39.0 [CH_2, C10(12)], 39.6 (CH) and 39.8 (CH) (C5 and C11), 40.9 (CH, C8), 57.7 [C, C7(9)], 126.5 (CH) and 126.7 (CH) (C2 and C3), 127.8 (CH) and 128.2 (CH) (C1 and C4), 145.3 (C) and 145.9 (C) (C4a and C11a), 169.1 (C, $2COCH_3$). MS (EI), m/z (%): 327 (23), 326 (M^{+}, 100), 283 (22), 267 (31), 224 (23), 209 (25), 208 (92), 198 (20), 193 (50), 186 (41), 179 (22), 169 (42), 168 (79), 167 (31), 156 (42), 141 (48), 129 (26), 128 (31), 115 (24). Anal. Calcd for $C_{20}H_{26}N_2O_2 \cdot 1.25H_2O$ (348.96): C, 68.84; H, 8.23; N, 8.03. Found: C, 68.98; H, 8.27; N, 8.01.

4.1.18. (1,2,3,5,6,7-Hexahydro-5-methyl-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 28a

A mixture of acetamide **22a** (4.00 g, 14.7 mmol), water (188 mL) and concentrated HCl (24 mL, 288 mmol) were heated under reflux for 24 h. The solution was cooled to 0 °C and the title compound precipitated as a white solid that was filtered and washed with cold water (2 × 20 mL) and EtOAc (1 × 20 mL) to give **28a**·HCl

(2.72 g, 87% yield, based on unrecovered starting compound). The aqueous layer was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give starting **22a** as a white solid (0.8 g). The analytical sample of **28a**·HCl was obtained by crystallization from MeOH/Et_2O, mp >285 °C (dec). IR 3500–2500 (max. at 3439, 3187, 3131, 3075, 3019, 2985, 2924, 2845, 2731, 2666, 2621, 2554, 2504), 2039, 1602, 1516, 1490, 1451, 1286, 1236, 1214, 1177, 1046, 1020, 993, 836, 755 cm^{-1}. ^1H NMR 1.29 (s, 3H, CH_3), 1.71 [d, J = 14.0 Hz, 2H, 6(13)-H_{exo}], 1.93 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 1.98 [dd, J = 13.0 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 2.15 [dd, J = 11.5 Hz, J' = 6.5 Hz, 2H, 2(12)-H_{endo}], 3.30 (t, J = 5.5 Hz, 2H, 1(7)-H], 4.87 (s, mobile H), 7.14–7.19 [complex signal, 4H, 9(10)-H and 8(11)-H]. ^{13}C NMR 31.3 (CH_3, C5–CH_3), 37.3 [CH_2, C2(12)], 39.0 [CH_2, C6(13)], 39.6 [CH, C1(7)], 76.5 (C, C5), 84.0 (C, C3), 129.3 [CH, C9(10)], 129.6 [CH, C8(11)], 145.7 [C, C7a(C11a)]. MS (EI), m/z (%): 230 ([M+H]$^+$, 26), 229 (M$^{\cdot+}$, 30), 171 (25), 170 (100), 155 (67), 143 (18), 129 (27), 128 (23), 115 (21). Anal. Calcd for $C_{15}H_{19}NO·1.1HCl·0.4H_2O$ (276.63): C, 65.13; H, 7.62; N, 5.06; Cl, 14.10. Found: C, 65.05; H, 7.66; N, 5.40; Cl, 13.84.

4.1.19. (5-Ethyl-1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 28b

(a) From **22b**: A mixture of acetamide **22b** (380 mg, 1.33 mmol), water (18 mL) and concentrated HCl (2.3 mL, 27.6 mmol) was heated under reflux for 24 h. The solution was cooled to 0 °C and the title compound precipitated as a white solid that was filtered and washed with cold water (5 mL) and EtOAc (2 × 5 mL) to give **28b**·HCl (300 mg, 81% yield, 90% based on unrecovered starting compound). The combined organic phase was dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give starting **22b** as a white solid (40 mg). The analytical sample of **28b**·HCl was obtained by crystallization from MeOH/Et_2O, mp >300 °C (dec). IR 3600–2500 (max. at 3501, 2967, 2879, 2676, 2623, 2535), 1592, 1508, 1494, 1465, 1453, 1436, 1354, 1335, 1286, 1237, 1218, 1174, 1057, 1033, 985, 897, 836, 754 cm^{-1}. ^1H NMR 0.93 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.58 [q, J = 7.5 Hz, 2H, CH_2CH_3], 1.67 [d, J = 13.5 Hz, 2 H, 6(13)-H_{exo}], 1.93 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 1.97 [overlapped dd, J = 13.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 2.14 [ddm, J = 13.5 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{endo}], 3.31 [t, J = 6.0 Hz, 2H, 1(7)-H], 4.86 (s, mobile H), 7.14 [m, 2H, 9(10)-H], 7.17 [m, 2H, 8(11)-H]. ^{13}C NMR 7.3 (CH_3, CH_2CH_3), 36.7 [CH_2, C6(13)], 37.5 (CH_2, CH_2CH_3), 37.6 [CH_2, C2(12)], 39.4 [CH, C1(7)], 78.5 (C, C5), 84.0 (C, C3), 128.3 [CH, C9(10)], 129.6 [CH, C8(11)], 145.8 [C, C7a(C11a)]. MS (EI), m/z (%): 243 (M$^{\cdot+}$, 49), 185 (21), 184 (100), 172 (26), 169 (51), 156 (42), 155 (91), 143 (26), 131 (28), 129 (42), 128 (35), 115 (32). Anal. Calcd for $C_{16}H_{21}NO·HCl·0.33H_2O$ (285.75): C, 67.25; H, 7.99; N, 4.90; Cl, 12.41. Found: C, 67.24; H, 7.87; N, 4.98; Cl, 12.41. (b) From **21b**: To a mixture of alcohol **21b** (300 mg, 1.23 mmol) and urea (148 mg, 2.46 mmol) trifluoroacetic acid (0.9 mL, 12.3 mmol) was added and the suspension was heated at 115 °C for 18 h. To the cold (0 °C) solution water (10 mL) and 1 N NaOH till basic pH were added. The solution was extracted with Et_2O (4 × 5 mL) and the combined organic extracts were washed with water (2 × 5 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give **28b** as a yellow solid (253 mg) that was crystallized from EtOAc. Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in Et_2O and filtration of the precipitated white solid (240 mg, 70% yield).

4.1.20. *N,N*-Dimethyl-(1,2,3,5,6,7-hexahydro-5-methyl-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 29a·HCl

To a cold (0 °C) solution of **28a** (343 mg, 1.50 mmol) in Et_2O (10 mL), formaldehyde (2.6 mL, 37 wt % in water solution, 33 mmol) and, dropwise, formic acid (2.3 mL, 61 mmol) were added and the mixture was stirred at 80 °C for 24 h. The mixture was allowed to cool to room temperature, was diluted with Et_2O (20 mL), 5 N NaOH (15 mL) was added dropwise and the mixture was stirred at room temperature for 15 min. The organic layer was separated and the aqueous phase was extracted with Et_2O (4 × 10 mL). The combined organic phases were washed with brine (1 × 30 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give **29a** (276 mg, 72% yield). Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in EtOAc, followed by filtration of the precipitated solid. The analytical sample was obtained by crystallization from MeOH/Et_2O, mp 208–209 °C. IR 3014, 2974, 2924, 2840, 2588, 2532, 2509, 2436, 2306, 1499, 1474, 1454, 1434, 1345, 1239, 1219, 1183, 1163, 1132, 1076, 1062, 1022, 914, 900, 783 cm^{-1}. ^1H NMR 1.32 (s, 3H, CH_3), 1.72 [d, J = 14.0 Hz, 2H, 6(13)-H_{exo}], 2.00 [ddm, J = 14.5 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.09 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.16 [ddm, J = 13.0 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{endo}], 2.85 [s, 6H, $N(CH_3)_2$], 3.38 [t, J = 6.0 Hz, 2H, 1(7)-H], 4.86 (s, mobile H), 7.16 [m, 2H, 9(10)-H], 7.20 [m, 2H, 8(11)-H]. ^{13}C NMR 31.1 (CH_3, C5–CH_3), 32.8 [CH_2, C2(12)], 36.8 [CH_3, $N(CH_3)_2$], 38.9 [CH_2, C6(13)], 39.4 [CH, C1(7)], 77.9 (C, C5), 92.6 (C, C3), 128.4 [CH, C9(10)], 129.6 [CH, C8(11)], 145.6 [C, C7a(C11a)]. MS (EI), m/z (%): 258 (11), 257 (M$^{\cdot+}$, 58), 155 (28), 129 (15), 128 (15), 87 (100). 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, 69.32; H, 8.28; N, 4.58; Cl, 11.98.

4.1.21. *N,N*-Diethyl-(1,2,3,5,6,7-hexahydro-5-methyl-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine (2*R*,3*R*)-tartrate, 29b·(2*R*,3*R*)-tartrate

To a solution of **28a**·HCl (265 mg, 0.9 mmol) in MeOH (15 mL), $NaBH_3CN$ (95%, 132 mg, 2.0 mmol), AcOH (0.3 mL) and acetaldehyde (0.34 mL, 6.0 mmol) were added and the mixture was stirred at room temperature for 8 h. An additional portion of $NaBH_3CN$ (95%, 66 mg, 1.0 mmol) and acetaldehyde (0.17 mL, 3.0 mmol) were added, the mixture was stirred at room temperature for 18 h and then it was concentrated in vacuo to dryness. Water (20 mL) was added to the residue, the suspension was basified with 1 N NaOH and was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo to give **29b** as an oil (258 mg, 91% yield). An analytical sample of the (2*R*,3*R*)-tartrate of **29b** was obtained by adding 1 equiv of (2*R*,3*R*)-(+)-tartaric acid in methanol (15 mL) to a solution of **29b** in EtOAc (15 mL), concentration to dryness and crystallization from 2-propanol, mp 111−112 °C. IR 3600–2400 (max. at 3321, 3271, 2974, 2935, 2649, 2476), 1871, 1734, 1580, 1409, 1337, 1305, 1261, 1213, 1132, 1068, 1003, 788, 763, 679, 618 cm^{-1}. ^1H NMR 1.32 (s, 3H, C5–CH_3), 1.38 (t, J = 7.5 Hz, 6H, $2CH_2CH_3$), 1.72 [d, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 2.01 [dd, J = 13.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 2.10 [d, J = 13.5 Hz, 2H, 2(12)-H_{exo}], 2.24 [ddm, J = 13.5 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{endo}], 3.36 [complex signal, 6H, $2CH_2CH_3$ and 1(7)-H], 4.39 (s, 2H, 2CHOH tartrate), 4.86 (s, mobile H), 7.16 [m, 2H, 9(10)-H], 7.19 [m, 2H, 8(11)-H]. ^{13}C NMR (100.6 MHz) 12.5 (CH_3, $2CH_2CH_3$), 31.1 (CH_3, C5–CH_3), 33.5 [CH_2, C2(12)], 38.9 [CH_2, C6(13)], 39.5 [CH, C1(7)], 45.9 (CH_2, $2CH_2CH_3$), 74.1 (CH, 2CHOH tartrate), 77.7 (C, C5), 94.7 (C, C3), 128.4 [CH, C9(10)], 129.6 [CH, C8(11)], 145.7 [C, C7a(C11a)], 176.8 (C, $2CO_2H$ tartrate). MS (EI), m/z (%): 285 (M$^{\cdot+}$, 23), 155 (17), 129 (15), 115 [$Et_2NCH(CH_3)_2^{\cdot+}$, 100], 100 ($Et_2N{=}CHCH_3^+$, 39), 72 (11). Anal. Calcd for $C_{23}H_{33}NO_7·0.5H_2O$ (444.53): C, 62.15; H, 7.71; N, 3.15. Found: C, 61.96; H, 7.94; N, 3.14.

4.1.22. *N*-Benzyl-(5-ethyl-1,2,3,5,6,7-hexahydro-1,5:3,7-dimeth-ano-4-benzoxonin-3-yl)amine hydrochloride, 30·HCl

To a solution of amine **28b**·HCl (320 mg, 1.14 mmol) in MeOH (10 mL), $NaBH_3CN$ (95%, 152 mg, 2.30 mmol), AcOH (0.3 mL) and

benzaldehyde (0.18 mL, 1.73 mmol) were added and the mixture was stirred at room temperature for 2 h. Then, an additional amount of $NaBH_3CN$ (95%, 76 mg, 1.15 mmol) and benzaldehyde (0.09 mL, 0.86 mmol) were added and the mixture was stirred at room temperature for 18 h and concentrated in vacuo to dryness. Water (15 mL) was added to the residue, and the mixture was extracted with Et_2O (4 × 15 mL). The combined organic extracts were washed with 1 N NaOH (1 × 25 mL), brine (2 × 25 mL), dried with anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was taken in EtOAc and the amine **30** was precipitated as its hydrochloride (341 mg, 81% yield) by adding an excess of Et_2O·HCl. The analytical sample was obtained by crystallization from EtOAc, mp 246–248 °C. IR 3500–2400 (max. at 3418, 3030, 2935, 2691, 2614, 2549, 2396), 1564, 1495, 1456, 1352, 1216, 1026, 999, 984, 758, 698 cm^{-1}. ^1H NMR 0.97 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.65 [q, J = 7.5 Hz, 2H, CH_2CH_3], 1.71 [d, J = 14.0 Hz, 2H, 6(13)-H_{exo}], 2.03 [overlapped dd, 2H, 6(13)-H_{endo}], 2.04 [d, J = 12.5 Hz, 2H, 2(12)-H_{exo}], 2.34 [ddm, J = 13.0 Hz, J' = 6.0 Hz, 2H, 2(12)-H_{endo}], 3.38 [t, J = 6.0 Hz, 2H, 1(7)-H], 4.28 (s, 2H, CH_2–C_6H_5), 4.86 (s, mobile H), 7.17 [m, 2H, 9(10)-H], 7.21 [m, 2H, 8(11)-H], 7.43–7.50 (complex signal, 5H, Ar-H benzyl). ^{13}C NMR 7.4 (CH_3, CH_2CH_3), 35.8 [CH_2, C2(12)], 36.8 [CH_2, C6(13)], 37.5 (CH_2, CH_2CH_3), 39.4 [CH, C1(7)], 45.3 (CH_2, CH_2–C_6H_5), 79.2 (C, C5), 88.6 (C, C3), 128.3 [CH, C9(10)], 129.6 [CH, C8(11)], 130.3 (CH, Ar-C_{meta}), 130.5 (CH, Ar-C_{para}), 131.1 (CH, Ar-C_{ortho}), 132.9 (C, Ar-C_{ipso}),145.8 [C, C7a(C11a)]. MS (EI), *m/z* (%): 334 (15), 333 (M^+, 49), 304 (15), 184 (14), 169 (18), 155 (23), 150 (21), 149 (100), 91 (73). Anal. Calcd for $C_{23}H_{27}NO$·HCl·0.4H_2O (377.14): C, 73.25; H, 7.70; N, 3.71; Cl, 9.40. Found: C, 73.23; H, 7.56; N, 3.56; Cl, 9.75.

4.1.23. *N*-Propargyl-(5-ethyl-1,2,3,5,6,7-hexahydro-1,5:3,7-dimethano-4-benzoxonin-3-yl)amine hydrochloride, 31a·HCl and *N,N*-dipropargyl-(5-ethyl-1,2,3,5,6,7-hexahydro-1,5:3,7-dimetha-no-4-benzoxonin-3-yl)amine hydrochloride, 31b·HCl

A suspension of **28b**·HCl (920 mg, 3.29 mmol), K_2CO_3 (459 mg, 3.29 mmol), propargyl bromide (0.32 mL, 80% solution in toluene, 2.88 mmol) and NaI (40 mg, 0.27 mmol) in acetonitrile (35 mL) was heated under reflux for 18 h and concentrated in vacuo to dryness. To the residue, CH_2Cl_2 (50 mL) was added and the solution was washed with water (3 × 20 mL). The organic layer was dried with anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc mixtures) to give **31b** (hexane/EtOAc 98:2, 202 mg, 22% yield) and **31a** (hexane/EtOAc 95:5, 321 mg, 35% yield). The hydrochlorides of **31a** and **31b** were obtained by adding an excess of Et_2O·HCl to a solution of the corresponding amine in EtOAc followed by filtration of the formed precipitates. The analytical samples of **31a** and **31b** were obtained by crystallization from Et_2O. **31a**: mp 186–187 °C. IR 3500–2400 (max. at 3458, 3306, 3245, 3179, 2965, 2939, 2919, 2728, 2629, 2406), 2125, 1557, 1493, 1451, 1350, 1217, 1031, 987, 764 cm^{-1}. ^1H NMR 0.94 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.61 (q, J = 7.5 Hz, 2H, CH_2CH_3), 1.68 [d, J = 13.5 Hz, 2H, 6(13)-H_{exo}], 1.94 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 1.99 [dd, J = 13.5 Hz, J' = 5.5 Hz, 2H, 6(13)-H_{endo}], 2.23 [ddm, J = 13.5 Hz, J' = 5.5 Hz, 2H, 2(12)-H_{endo}], 3.19 (t, J = 3.0 Hz, 1H, $CH_2C{\equiv}CH$), 3.35 [t, J = 5.5 Hz, 2H, 1(7)-H], 4.01 (d, J = 3.0 Hz, 2H, $CH_2C{\equiv}CH$), 7.15 [m, 2H, 9(10)-H], 7.18 [m, 2H, 8(11)-H]. ^{13}C NMR (100.6 MHz) 7.3 (CH_3, CH_2CH_3), 30.6 (CH_2, $CH_2C{\equiv}CH$), 35.7 [CH_2, C2(12)], 36.7 [CH_2, C6(13)], 37.4 (CH_2, CH_2CH_3), 39.2 [CH, C1(7)], 75.3 (CH, $CH_2C{\equiv}CH$), 78.5 (C, C5), 79.4 (C, $CH_2C{\equiv}CH$), 88.3 (C, C3), 128.4 [CH, C9(10)], 129.6 [CH, C8(11)], 145.6 [C, C7a(C11a)]. MS (EI), *m/z* (%): 281 (M^+, 29), 252 (28), 194 (25), 185 (35), 184 (82), 169 (63), 155 (100), 143 (30), 141 (35), 131 (27), 129 (62), 128 (57), 115 (47), 97 (61), 96 (34). Anal. Calcd for $C_{19}H_{23}NO$·HCl·0.4H_2O (325.06): C, 70.20; H, 7.69; N, 4.31; Cl, 10.91. Found: C, 70.17; H, 7.51; N, 4.21; Cl, 11.11. Compound **31b**: mp 177–178 °C. IR 3500–2150 (max. at 3428, 3180, 2967, 2948, 2925, 2880, 2418, 2385, 2355, 2203), 2119, 1494, 1463, 1454, 1435, 1350, 1222, 1202, 1028, 1006, 985, 962, 919, 837, 774, 723, 675 cm^{-1}. ^1H NMR 0.95 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.64 (q, J = 7.5 Hz, 2H, CH_2CH_3), 1.68 [d, J = 15.5 Hz, 2H, 6(13)-H_{exo}], 2.00 [dd, J = 12.5 Hz, J' = 6.0 Hz, 2H, 6(13)-H_{endo}], 2.18 [d, J = 13.0 Hz, 2H, 2(12)-H_{exo}], 2.30 [ddm, J = 13.5 Hz, J' = 6.0 Hz, 2H, 2(12)-H_{endo}], 3.25 (br s, 2H, $CH_2C{\equiv}CH$), 3.37 [t, J = 6.0 Hz, 2H, 1(7)-H], 4.32 (d, J = 2.5 Hz, 4H, $CH_2C{\equiv}CH$), 7.16 [m, 2H, 9(10)-H], 7.19 [m, 2H, 8(11)-H]. ^{13}C NMR 7.4 (CH_3, CH_2CH_3), 34.8 [CH_2, C2(12)], 36.6 [CH_2, C6(13)], 37.5 (CH_2, CH_2CH_3), 37.6 (CH_2, $2CH_2C{\equiv}CH$), 39.4 [CH, C1(7)], 74.6 (C, $2CH_2C{\equiv}CH$), 80.4 (C, $2CH_2C{\equiv}CH$ and C5), 94.8 (C, C3), 128.4 [CH, C9(10)], 129.5 [CH, C8(11)], 145.7 [C, C7a(C11a)]. MS (EI), *m/z* (%): 319 (M^+, 6), 318 (10), 290 (24), 248 (14), 237 (19), 222 (20), 185 (40), 169 (56), 155 (55), 143 (47), 141 (52), 135 (100), 134 (60), 129 (82), 128 (70), 115 (57). Anal. Calcd for $C_{22}H_{25}NO$·HCl·0.25H_2O (360.41): C, 73.32; H, 7.41; N, 3.89; Cl, 9.84. Found: C, 73.39; H, 7.37; N, 3.86; Cl, 9.85.

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.[23] 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 non-linear regression curve fitting (variable slope) by using the software GraphPad Prism 4.0.

4.3. MAO inhibitory activity

The ability of the compounds to inhibit MAO activity was measured using the MAO-Glo™ Assay (Promega). As a tissue homogenate, we used a crude mitochondrial preparation from mice cortex (NIH Swiss, Harlan).[25] Compounds were tested for non-specific MAO activity at a concentration of 10 and 50 μM. The assays were carried out according to manufacturer's protocol. Readings were performed using a tube luminometer (Berthold Lumat).

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).[26] 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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