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Synthesis and pharmacological evaluation of several ring-contracted amantadine analogs

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ABSTRACT

The synthesis of several (3-noradamantyl)amines, [(3-noradamantyl)methyl]amines, (3,7-dimethyl-1-bisnoradamantyl)amines, and [(3,7-dimethyl-1-bisnoradamantyl)methyl]amines is reported. They were evaluated against a wide range of viruses and one of them inhibited the cytopathicity of influenza A virus at a concentration similar to that of amantadine. Several of the new polycyclic amines show an interesting activity as NMDA receptor antagonists. A rimantadine analogue displayed significant trypanocidal activity. Moreover, to further characterize the pharmacology of these compounds, their effects on dopamine uptake were also assessed.

1. Introduction

1-Adamantylamine (amantadine) and (α-methyl-1-adamantyl)methylamine (rimantadine) have prophylactic and therapeutic activity in influenza A virus infections.[1] Related adamantane derivatives also show antiviral activity.[2] Adamantane derivatives are inexpensive, but resistance against the drugs develops readily and treatment is frequently complicated by central nervous system (CNS) side-effects. In fact, amantadine and its 3,5-dimethyl analogue memantine are NMDA receptor antagonists and are approved for the treatment of Parkinson's and Alzheimer's disease, respectively.[3] Thus, the design of new amantadine-related anti-influenza agents without CNS side-effects is a highly desirable goal. Amantadine, rimantadine, memantine, and related polycyclic amines also possess trypanocidal activity (Fig. 1).[4]

Biological activity has also been found in other polycyclic cage amines. For example, compounds **1**–**4** have anti-influenza activity,[5] **5** is a MAO-B inhibitor,[6] and **6** is a NMDA receptor antagonist (Fig. 2).[7]

For more than 20 years two of us (P.C. and S.V.) have worked on a project aimed at exploring the structure and the reactivity of noradamantane[8] and bisnoradamantane derivatives.[9] Up to now, our work on this topic has been done from a purely synthetic point of view. For example, we have developed several general entries to these skeletons. However, systematic studies directed towards the synthesis of biologically active noradamantane and bisnoradamantane derivatives have not yet been carried out (Fig. 3).[10]

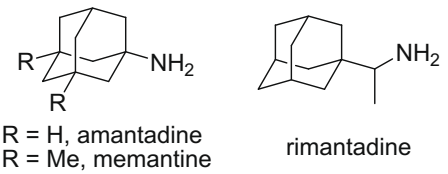

Figure 1. Amantadine, memantine, and rimantadine.

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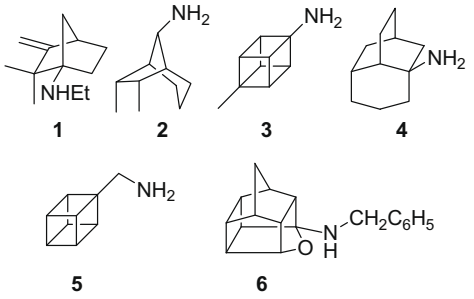


Figure 2. Polycyclic cage amines with biological activity.

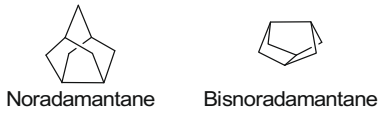
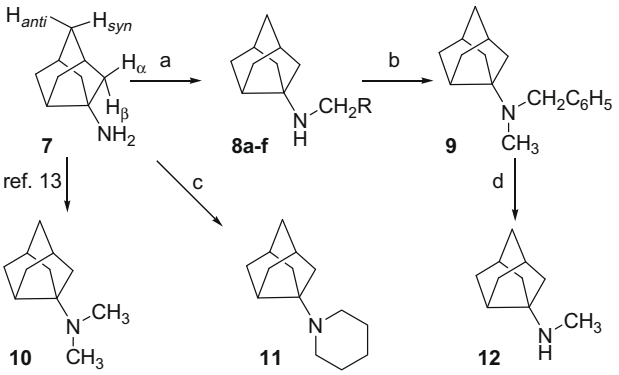


Figure 3. Noradamantane and bisnoradamantane.



Scheme 1. Reageants and conditions: (a) aldehyde, $NaBH_3CN$, acetic acid, methanol, 18 h; 92% for **8a**, R = phenyl; 79% for **8b**, R = 4-methoxyphenyl; 44% for **8c**, R = 2-methoxyphenyl; 78% for **8d**, R = 3-methoxyphenyl; 77% for **8e**, R = 4-fluorophenyl; 63% for **8f**, R = 2-thienyl; (b) formaldehyde, $NaBH_3CN$, acetic acid, acetonitrile, 4 h; 91%; (c) anhyd Et_3N, 1,5-dibromopentane, DMF, 60 °C, 26 h, 48%. (d) H_2 (1 atm), Pd/C, ethanol, 89%.

It is well known in medicinal chemistry that when drugs contain cyclic systems, it is generally worth synthesizing analogues where the ring is opened, expanded or contracted by one unit, because these analogues show similar activity to the parent compound.[11] Tricyclo[3.3.1.0^{3,7}]non-3-ylamine [(3-noradamantyl)amine] and tricyclo[3.3.0.0^{3,7}]oct-1-ylamine [(1-bisnoradamantyl)amine] may be viewed as ring contracted analogs of amantadine, featuring a skeleton with one and two carbon less than the model, respectively. For this reason, in this paper, we describe the preparation of a series of (3-noradamantyl)amines, (1-bisnoradamantyl)amines and related compounds as well as the results of their antiviral, trypanocidal, NMDA receptor antagonist, and dopamine reuptake inhibitory activities.

2. Results and discussion

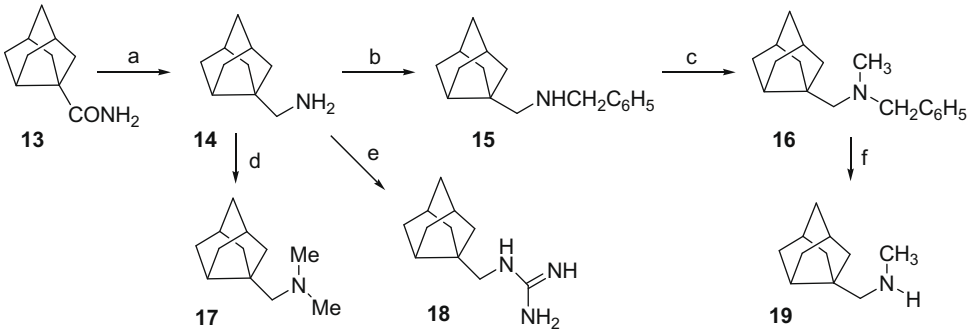
2.1. Chemistry

Starting from the known amine **7**,[10,12] we have prepared noradamantane amines **8**–**12** using classical methods in amine chemistry. Thus, reductive alkylation of **7** with several aromatic aldehydes afforded secondary amines **8a–f** in moderate to high yields. Dimethylated derivative **10** was prepared as previously described in the literature.[13] Monomethyl derivative **12** was synthesized from **8a** by reductive alkylation followed by catalytic debenzylation in good overall yield. Finally, piperidine derivative **11** was prepared by alkylation of primary amine **7** with 1,5-dibromopentane in 51% yield (Scheme 1).

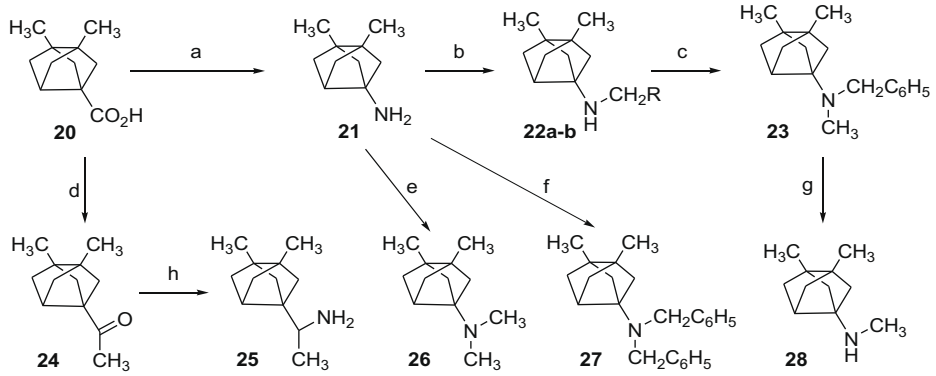
Starting from the known amide **13**,[14] a series of 3-(noradamantyl)methylamines were synthesized. Thus, reduction of amide **13** with $LiAlH_4$ followed by acidic work-up led to the hydrochloride of amine **14** in 90% yield. Reductive alkylation of **14** with benzaldehyde and $NaCNBH_3$ in methanol gave **15** in 77% yield. Reductive methylation of **15** followed by catalytic hydrogenation led to **19** in high yield. Reductive methylation of **14** with formic acid and formaldehyde furnished dimethyl derivative **17** in 68% yield. Finally, reaction of **14** with 1*H*-pyrazol-1-carboxamidine led to guanidine **18** in 84% yield (Scheme 2).

On the other hand, starting from the known acid **20**,[9g] we have prepared amines **21**–**23**, **25**–**28**, and **30**–**36** using classical methods in amine chemistry. Although the synthesis of amine **21** from acid **20** was very low yielding using the classical Schmid's or Curtius' reactions (14% and 24% yield, respectively), application of the Yamada's modification of the Curtius reaction allowed us to obtain and fully characterize the hydrochloride of amine **21** in 73% yield.

From this amine, reductive alkylation with benzaldehyde led to **22a** in 60% yield. Similarly, reductive alkylation with 2-thiophenecarbaldehyde led to **22b** in 69% yield. Reductive methylation of **22a** followed by catalytic debenzylation furnished secondary amine **28** in high yield. Dimethylated derivative **26** was obtained in 83% yield by treating amine **21** with excess of formic acid and formaldehyde. Finally, dibenzylated compound **27** was prepared by double alkylation of **21** with benzyl chloride in 73% yield (Scheme 3).



Scheme 2. Reageants and conditions: (a) $LiAlH_4$, THF, reflux, 15 h, 90%; (b) benzaldehyde, $NaBH_3CN$, acetic acid, methanol, 18 h; 77%; (c) formaldehyde, $NaBH_3CN$, acetic acid, acetonitrile, 4 h; 96%; (d) formaldehyde, formic acid, diethyl ether, 80 °C, 10 h, 68%; (e) anhyd Et_3N, 1*H*-pyrazol-1-carboxamidine hydrochloride, acetonitrile, reflux, 6 h, 70%; (f) H_2 (1 atm), Pd/C, ethanol, 78%.



Scheme 3. Reageants and conditions: (a) Diphenylphosphorylazide, Et_3N, toluene, reflux, 3 h; then 6 N HCl, reflux, 24 h, 73%; (b) aldehyde, $NaBH_3CN$, AcOH, MeOH, 18 h; 60% for **22a**, R = phenyl; 69% for **22b**, R = 2-thienyl; (c) 37% aqueous formaldehyde, $NaBH_3CN$, AcOH, CH_3CN, 4 h, 88%; (d) MeLi, anhyd Et_2O, 0 °C to reflux, 16 h, 19%; (e) 37% aqueous formaldehyde, formic acid, Et_2O, 80 °C, 10 h, 83%; (f) benzyl chloride, NaI, K_2CO_3, CH_3CN, reflux, 24 h, 41%; (g) H_2, Pd/C, EtOH, 89%; (h) NH_2OH, NaOH, EtOH; then, $LiAlH_4$, Et_2O, reflux, 16 h, 43%.

Moreover, reaction of **20** with methyllithium gave ketone **24** in low yield. Reaction of **24** with hydroxylamine followed by reduction of the obtained oxime with $LiAlH_4$ gave amine **25**, a compound that can be viewed as a ring contracted analog of the antiviral rimantadine (Scheme 3).

Finally, reduction of the amide **29**, easily available from acid **20**, with $LiAlH_4$ followed by acidic work-up gave the hydrochloride of amine **30** in 70% overall yield. Following a similar sequence of the previously used with amine **21**, amines **31**, **32**, **33**, and **36** were obtained in high yields. Piperidine derivative **34** was obtained by alkylation of amine **30** with 1,5-dibromopentane in 53% yield. Finally, reaction of **30** with 1*H*-pyrazol-1-carboxamidine led to guanidine **35** in 90% yield (Scheme 4).

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

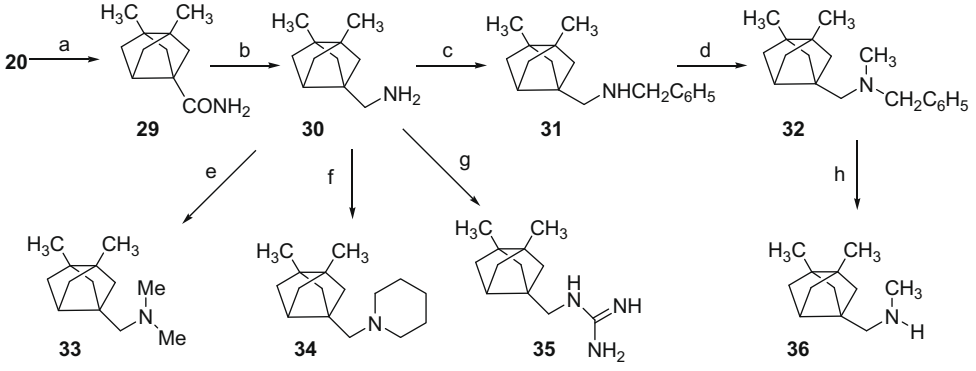
2.2. Trypanocidal activity

The tsetse fly-transmitted protozoan parasite *Trypanosoma brucei* is the causative agent of Human African Trypanosomiasis (HAT). After a major upsurge of the disease in the late 1990s throughout many parts of sub-Saharan Africa, annual infections have now fallen to 70,000 as a result of major surveillance and treatment programmes.[15] However, over 60 million people remain at risk, and in some areas death rates exceed those from HIV/AIDS and malaria. The drugs currently available to treat HAT require administration under medical supervision and are characterized by limited efficacy, toxicity, and resistance. For example, the arsenical drug melarsoprol, which is used to treat late stage disease, can result in a reactive encephalopathy which kills up to 10% of patients. In the absence of treatment, HAT is invariably fatal and new drugs are therefore urgently required. Recently, it was reported that the anti-influenza virus drug rimantadine was active in vitro against bloodstream form *T. brucei,* and that other aminoadamantane derivatives had enhanced activity.[4,16] To extend these observations, we have tested several new bisnoradamantanes and related compounds for activity against bloodstream form *T. brucei.*

The noradamantylamines and [(3-noradamantyl)methyl]amines described in this paper and the birnoradamantyl derivatives **21**, **22a**, **23**, **27**, **28**, **32**, **34**, and **36** were found to have no significant activity against cultured bloodstream from *T. brucei* at concentrations up to 5 μg mL^{-1}. Compounds **26**, **30**, and **31** showed transient effect on growth at 5 μg mL^{-1}, but cells grew to normal density. Rimantadine analog **25** was the most active of the compounds tested and we established its IC_{50} (6.02 ± 0.36 μM) and IC_{90} (9.48 ± 2.64 μM) values. Amine **25** was found to be slightly more active than rimantadine (IC_{50} = 7.04 ± 0.12 μM; IC_{90} = 13.97 ± 1.68 μM) and at least 20 times more active than amantadine (IC_{50} > 130 μM).

2.3. NMDA receptor antagonist activity

NMDA receptor antagonists are highly interesting compounds since these receptors have been involved in several neurodegenerative disorders. In fact, memantine is widely used in therapeutics to slow down the progression of Alzheimer's disease.[17]



Scheme 4. Reageants and conditions: (a) $SOCl_2$, reflux, 2 h; then NH_4OH, $CHCl_3$, rt, 15 h, 84%; (b) $LiAlH_4$, THF, reflux, 15 h, 83%; (c) benzaldehyde, $NaBH_3CN$, AcOH, MeOH, rt, 18 h, 68% (d) 37% aqueous formaldehyde, $NaBH_3CN$, AcOH, CH_3CN, reflux, 4 h, 70%; (e) 37% aqueous formaldehyde, formic acid, Et_2O, 80 °C, 10 h, 61%; (f) Et_3N, 1,5-dibromopentane, DMF, 60 °C, 26 h, 53%; (g) Et_3N, 1*H*-pyrazol-1-carboxamidine, CH_3CN, reflux, 6 h, 90%; (h) H_2, Pd/C, EtOH, 38 atm, 85%.

The activity of the different new polycyclic compounds was assayed on cerebellar granule neurons loaded with the calcium-sensitive probe Fura-2.[18] 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. Although all the noradamantyl derivatives and several of the bisnoradamantyl compounds were able to inhibit calcium entry through NMDA receptors, none of the compounds was more potent than memantine against glutamate- or NMDA-induced calcium increase in cerebellar granule neurons (Table 1).

In general, the bisnoradamantane derivatives are more potent as NMDA receptor antagonists than the noradamantane amines. For example, amine **21** is 4 times more potent as NMDA receptor antagonist than 3-noradamantylamine, **7**, and the guanidine derivative **35** is 3.5 times more potent than its corresponding noradamantyl analog, **18**.

Bisnoradamantylamines were usually more active than their corresponding (bisnoradamantyl)methylamine analogs as exemplified by the pairs **21**/**30**, **26**/**33**, and **28**/**36**, and alkyl substitution causes a reduction in the potency (e.g., series **21**/**28**/**26** or **30**/**36**/**33**). The guanidine derivative **35** was the more potent compound, being 10 times more potent than amantadine and 5 times less potent than memantine. Attempts to synthesize a guanidine derivative from **21** were not successful.

2.4. Antiviral activity

None of the synthesized compounds was found to have antiviral 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. In the influenza virus assays, only compounds **7** and **14**, two primary amines, displayed reasonable activity against the influenza A/H1N1 and A/H3N2 subtypes, secondary and tertiary amines were not active (Table 2). The antiviral data obtained by microscopy were confirmed by a colorimetric cell viability assay (data not shown). The highest selectivity was noted with compound **7** tested against the A/H3N2 subtype. As anticipated, all compounds proved to be inactive against influenza B virus, which is known to be insensitive to amantadine and rimantadine.

Table 1
IC_{50} (μM) values for selected polycyclic amines as NMDA antagonists.[a,b]

Compound	Glutamate (100 μM)	NMDA (100 μM)
7	>500	92 ± 19
8c	>500	92 ± 30
8d	>500	87 ± 46
8f	384 ± 130	17 ± 4
9	>500	36 ± 2
10	>500	173 ± 4
11	>500	45 ± 4
12	205 ± 25	65 ± 15
15	>500	138 ± 16
16	>500	178 ± 25
18	453 ± 113	25 ± 8
19	>500	71 ± 6
21	274 ± 68	23 ± 2.2
22a	143 ± 62	70 ± 9.3[c]
22b	204 ± 13	80 ± 15
25	94 ± 29	37 ± 10
26	185 ± 69	153 ± 18
28	NE[d]	35 ± 3
30	>500	128 ± 39
31	NA[e]	47 ± 15[c]
32	NA	160 ± 24[c]
35	104 ± 31	7.1 ± 0.4
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 Section 4 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 diferent batches of cultured cells.

[b] Compounds **8a**, **8b**, **8e**, **14**, **17**, **23**, **33**, **34**, and **36** were found to have low potency as NMDA receptor antagonists (IC_{50} > 200 mM), while compound **27** was found not active at the highest concentration tested.

[c] Only 60% maximal inhibition due to insolubility in the assay buffer.

[d] NE, not evaluated.

[e] NA, not active at the highest concentration tested.

Table 2
Antiviral activity against influenza virus in MDCK cells.

Compound	Antiviral EC_{50}[a] in μM			Cytotoxicity (MCC[b] in MDCK)
	A/H1N1	A/H3N2	B	
7	196 ± 109	26.5 ± 22.5	NA[c]	>575
14	36 ± 11	52 ± 16	NA	>530
Amantadine	77 ± 21	2.7 ± 1.1	NA	>100
Rimantadine	29 ± 18	0.85 ± 1.1	NA	>100

[a] EC_{50}: compound concentration producing 50% antiviral effect, as determined by microscopic scoring of the virus-induced cytopathic effect.

[b] MCC, minimum cytotoxic concentration, or compound concentration causing minimal changes in cell morphology.

[c] NA, not active at subtoxic concentrations, or at the highest concentration tested.

2.5. Dopamine

It is known that amantadine increases extracellular dopamine levels by antagonism of the NMDA receptor,[19] although the exact mechanism has not been fully elucidated. As several of our new amines showed NMDA receptor antagonist activity with IC_{50} similar or even lower than amantadine, we have determined their effect on [^{3}H]dopamine uptake in rat striatal synaptosomes (Table 3). At the concentration tested (100 μM), several of the compounds were able to inhibit [^{3}H]dopamine uptake in some manner, show-

Table 3
Effect of compounds on dopamine uptake (at 100 μM).

Compound	[^{3}H]Dopamine uptake, % control ± SEM (n = 3)
7	84.9 ± 1.6
8a	31.7 ± 6.1
8b	63.9 ± 4.2
8c	58.3 ± 2.9
8d	45.8 ± 0.5
8e	81.1 ± 8.5
8f	47.7 ± 4.2
9	47.2 ± 3.4
10	71.3 ± 2.6
11	68.5 ± 2.3
12	65.2 ± 4.8
14	50.1 ± 3.5
15	57.9 ± 4.6
16	45.0 ± 2.5
17	62.5 ± 1.2
18	118.7 ± 7.3
19	76.3 ± 3.1
21	54.8 ± 14.3
25	72.2 ± 10.9
26	75.2 ± 6.9
27	74.3 ± 5.3
28	74.6 ± 6.6
30	39.1 ± 2.1
34	39.8 ± 7.4
36	57.3 ± 6.7
Amantadine	47.4 ± 2.0
Memantine	53.7 ± 2.6

ing similar values of inhibition than amantadine or memantine. However, it seems that no correlation exists with their potency as antagonists at the NMDA receptor. Probably, other mechanisms are being involved in the regulation of dopamine release, like different activities at D_2 receptors or through inhibition at the dopamine transporter.

3. Conclusions

In summary, we have synthesized and fully characterized several (3-noradamantyl)amines, (3-noradamantyl)methylamines, (3-bisnoradamantyl)amines, and (3-bisnoradamantyl)methylamines. Although these compounds were less potent than memantine against NMDA-induced calcium increase in cerebellar granule neurons, several compounds were more potent than amantadine, the bisnoradamantane amines being more potent than the corresponding noradamantane amines. Interestingly, none of those compounds showed antiviral activity, while compound **14**, that displayed reasonable activity against the influenza A/H1N1 and A/H3N2 subtypes, showed no NMDA receptor antagonist activity. Moreover, none of the compounds were significantly more potent, at the tested concentration, than amantadine or memantine as inhibitors of the dopamine uptake.

Amantadine displays both anti-influenza activity and NMDA receptor antagonism. As selectivity is usually highly desirable in drugs, the amines herein reported open the way for the design of new aminopolycyclic compounds with selective anti-influenza or NMDA receptor antagonist activity.

Interestingly, amine **25**, that is 2.5 times more potent than amantadine as NMDA receptor antagonist, also displayed trypanocidal activity, being slightly more active than rimantadine and at least 21 times more active than amantadine.

Guanidine **35** is a polycyclic cage compound with selective NMDA receptor antagonist activity (IC_{50} = 7.1 μM) without antiviral and trypanocidal activities.

The synthesis and pharmacological evaluation of more polycyclic cage amines is in progress to reach more potent and selective derivatives.

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 (100.6 MHz). Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane (TMS). Assignments given for the NMR spectra are based on DEPT, COSY $^1H/^1H$, and 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-m 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}). 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(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (8a·HCl)

To a solution of **7**·HCl (600 mg, 3.46 mmol) in MeOH (10 mL), $NaBH_3CN$ (95%, 445 mg, 6.72 mmol), AcOH (0.3 mL), and benzaldehyde (0.5 mL, 4.92 mmol) were added and the mixture was stirred at room temperature for 2 h. An additional portion of $NaBH_3CN$ (95%, 220 mg, 3.33 mmol) and benzaldehyde (0.25 mL, 2.46 mmol) were added, the mixture was stirred at room temperature overnight and concentrated 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. The residue was taken in EtOAc and the amine **8a** was precipitated as its hydrochloride (839 mg, 92% yield) by adding an excess of Et_2O·HCl. The analytical sample of **8a**·HCl was obtained by crystallization from MeOH, mp >300 °C (dec). IR: 2942, 2757, 2656, 2600, 2428, 2363, 2340, 1458, 1425, 1331, 728, 694 cm^{-1}. ^1H NMR 1.64 (dquint, J = 13.2 Hz, J' = 2.5 Hz, 1H, 9-H_{syn}), 1.73 (dd, J = 11.0 Hz, J' = 2.5 Hz, 2H, 6(8)-H_α], 1.75 (overlapped dm, 1H, 9-H_{anti}), 2.04 [m, 2H, 6(8)-H_β], 2.10 [m, 2H, 2(4)-H_β], 2.14 [dd, J = 10.5 Hz, J' = 2.0 Hz, 2H, 2(4)-H_α], 2.45 [broad s, 2H, 1(5)-H], 2.48 [tt, J = 7.0 Hz, J' = 1.5 Hz, 1H, 7-H], 4.21 (s, 2H, CH_2C$_6$H$_5$), 7.44–7.50 [complex signal, 3H, Ar-3(5)-H, and Ar-4-H], 7.55 [m, 2H, Ar-2(6)-H]. ^{13}C NMR 35.0 (CH_2, C9), 38.8 [CH, C1(5)], 43.66 (CH, C7), 43.73 [CH_2, C6(8)], 46.3 [CH_2, C2(4)], 48.8 (CH_2, CH_2–C$_6$H$_5$), 71.9 (C, C3), 130.3 [CH, Ar-C3(5)], 130.6 (CH, Ar-C4), 130.9 [CH, Ar-C2(4)], 133.2 (C, Ar-C1). MS (EI), *m*/*z* (%): 228 ([M+H]$^+$, 30), 227 (20), 185 ([M−C$_3$H$_6$]$^{\cdot+}$, 83), 184 (52), 91 (C$_7$H$_7^+$, 100). Anal. Calcd for C$_{16}$H$_{21}$N·HCl (263.81): C, 72.85; H, 8.41; N, 5.31; Cl, 13.44. Found: C, 72.90; H, 8.31; N, 5.18; Cl, 13.96.

4.1.3. *N*-(4-Methoxybenzyl)(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (8b·HCl)

From **7**·HCl (173 mg, 1.00 mmol), $NaBH_3CN$ (95%, 142 mg, 2.15 mmol), AcOH (0.3 mL), and 4-methoxybenzaldehyde (0.18 mL, 1.48 mmol) in MeOH (7 mL) and following the above procedure, **8b**·HCl was obtained (233 mg, 79% yield). The analytical sample of **8b**·HCl was obtained by crystallization from 2-propanol, mp >300 °C (dec). IR: 2926, 2794, 2751, 2716, 2678, 2592, 2578, 2443, 1613, 1588, 1514, 1460, 1440, 1333, 1306, 1272, 1248, 1178, 1040, 993, 826, 814, 767 cm^{-1}. ^1H NMR 1.63 (dquint, J = 13.1 Hz, J' = 2.5 Hz, 1H, 9-H_{syn}), 1.72 [dd, J = 11.5 Hz, J' = 2.2 Hz, 2H, 6(8)-H_α], 1.74 (overlapped dm, 1H, 9-H_{anti}), 2.00–2.09 [complex signal, 4H, 2(4)-H_β, and 6(8)-H_β], 2.12 [dd, J = 10.5 Hz, J' = 2.2 Hz, 2H, 2(4)-H_α], 2.43–2.46 [complex signal, 3H, 1(5)-H, and 7-H], 3.82 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2–C$_6$H$_5$), 7.01 [m, 2H, Ar-3(5)-H], 7.45 [m, 2H, Ar-2(6)-H]. ^{13}C NMR (75.4 MHz) 35.0 (CH_2, C9), 38.8 [CH, C1(5)], 43.7 (CH, C7), 43.7 [CH_2, C6(8)], 46.4 [CH_2, C2(4)], 48.1 (CH_2, CH_2–C$_6$H$_5$), 55.9 (CH_3, OCH_3), 71.6 (C, C3), 115.6 [CH, Ar-C3(5)], 124.9 (C, Ar-C1), 132.4 [CH, Ar-C2(6)], 162.1 (C, Ar-C4). MS (EI), *m*/*z* (%): 257 (M$^{\cdot+}$, 38), 214 ([M−C$_3$H$_7$]$^+$, 48), 121 [(CH$_3$OC$_6$H$_4$CH$_2$)$^+$, 100]. Anal. Calcd for C$_{17}$H$_{23}$NO·1.05 HCl (295.7): C, 69.06; H, 8.20; N, 4.74; Cl, 12.59. Found: C, 68.69; H, 8.19; N, 4.70; Cl, 12.73.

4.1.4. *N*-(2-Methoxybenzyl)(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (8c·HCl)

From **7**·HCl (173 mg, 1.00 mmol), $NaBH_3CN$ (95%, 142 mg, 2.15 mmol), AcOH (0.3 mL), and 2-methoxybenzaldehyde (0.18 mL, 1.46 mmol) in MeOH (7 mL) and following the procedure described for **8a**, **8c**·HCl was obtained (128 mg, 44% yield). The analytical sample of **8c**·HCl was obtained by crystallization from 2-propanol, mp 262–263 °C. IR: 2956, 2921, 2717, 2678, 2582, 2433,

1605, 1584, 1496, 1466, 1456, 1446, 1435, 1332, 1292, 1253, 1121, 1050, 1031, 771, 752 cm^{-1}. ^1H NMR 1.63 (dquint, J = 13.4 Hz, J' = 2.5 Hz, 1H, 9-H_{syn}), 1.73 [dd, J = 11.0 Hz, J' = 2.5 Hz, 2H, 6(8)-H_α], 1.76 (overlapped dm, 1H, 9-H_{anti}), 1.99–2.05 [complex signal, 2H, 6(8)-H_β], 2.07 [dm, J = 10.5 Hz, 2H, 2(4)-H_β], 2.14 [dd, J = 10.5 Hz, J' = 2.5 Hz, 2H, 2(4)-H_α], 2.44 [broad s, 2H, 1(5)-H], 2.49 (tt, J = 6.7 Hz, J' = 1.7 Hz, 1H, 7-H), 3.94 (s, 3H, OCH_3), 4.19 (s, 2H, $CH_2C_6H_5$), 7.03 (td, J = 7.7 Hz, J' = 1.0 Hz, 1H, Ar-5-H), 7.11 (d, J = 8.5 Hz, 1H, Ar-3-H), 7.42 (dd, J = 7.2 Hz, J' = 1.7 Hz, 1H, Ar-6-H), 7.46 (ddd, J = 8.4 Hz, J' = 7.4 Hz, J'' = 1.6 Hz, 1H, Ar-4-H). ^{13}C NMR 35.0 (CH_2, C9), 38.7 [CH, C1(5)], 43.5 (CH, C7), 43.8 [CH_2, C6(8)], 44.4 (CH_2, $CH_2C_6H_5$), 46.3 [CH_2, C2(4)], 56.1 (CH_3, OCH_3), 71.9 (C, C3), 112.1 (CH, Ar-C3), 121.1 (C, Ar-C1), 122.0 (CH, Ar-C5), 132.6 (CH, Ar-C6), 132.7 (CH, Ar-C4), 159.4 (C, Ar-C2). MS (EI), m/z (%): 257 ($M^{\cdot+}$, 35), 214 ([$M-C_3H_7$]$^+$, 57), 121 ([$CH_3OC_6H_4CH_2$]$^+$, 100), 91 (55). Anal. Calcd for $C_{17}H_{23}NO{\cdot}HCl$ (293.83): C, 69.49; H, 8.23; N, 4.77; Cl, 12.07. Found: C, 69.21; H, 8.29; N, 4.80; Cl, 12.32.

4.1.5. *N*-(3-Methoxybenzyl)(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (8d·HCl)

From **7**·HCl (173 mg, 1.00 mmol), $NaBH_3CN$ (95%, 142 mg, 2.15 mmol), AcOH (0.3 mL), and 3-methoxybenzaldehyde (0.18 mL, 1.45 mmol) in MeOH (7 mL) and following the procedure described for **8a**, **8d**·HCl was obtained (228 mg, 78% yield). The analytical sample of **8d**·HCl was obtained by crystallization from 2-propanol, mp >257 °C (dec). IR: 3002, 2923, 2873, 2792, 2734, 2708, 2678, 2585, 2446, 1606, 1599, 1588, 1494, 1460, 1437, 1331, 1306, 1272, 1256, 1174, 1035, 851, 794 cm^{-1}. ^1H NMR 1.63 (dquint, J = 13.3 Hz, J' = 2.6 Hz, 1H, 9-H_{syn}), 1.72 (broad d, J = 11.0 Hz, 2H, 6(8)-H_α), 1.74 (overlapped dm, 1H, 9-H_{anti}), 2.05 [m, 2H, 6(8)-H_β], 2.09–2.14 [complex signal, 4H, 2(4)-H_α, and 2(4)-H_β], 2.44 [broad s, 2H, 1(5)-H], 2.50 (tt, J = 1.6 Hz, J' = 6.7 Hz, 1H, 7-H), 3.84 (s, 3H, OCH_3), 4.18 (s, 2H, $CH_2C_6H_5$), 7.00 (ddd, J = 8.5 Hz, J' = 2.5 Hz, J'' = 1.0 Hz, 1H, Ar-4-H), 7.12 (dt, J = 7.5 Hz, J' = 1.0 Hz, 1H, Ar-6-H), 7.17 (t, J = 2.5 Hz, 1H, Ar-2-H), 7.38 (pseudo t, J = 8.0 Hz, 1H, Ar-5-H). ^{13}C NMR 35.0 (CH_2, C9), 38.8 [CH, C1(5)], 43.66 (CH, C7), 43.72 [CH_2, C6(8)], 46.3 [CH_2, C2(4)], 48.7 (CH_2, $CH_2C_6H_5$), 55.9 (CH_3, OCH_3), 71.9 (C, C3), 116.0 (CH, Ar-C4), 116.4 (CH, Ar-C2), 122.8 (CH, Ar-C6), 131.5 (CH, Ar-C5), 134.5 (C, Ar-C1), 161.8 (C, Ar-3). MS (EI), m/z (%): 258 ([M+H]$^+$, 31), 257 ($M^{\cdot+}$, 25], 215 ([$M-C_3H_6$]$^{\cdot+}$, 55), 214 ([$M-C_3H_7$]$^+$, 41), 121 ([$CH_3OC_6H_4CH_2$]$^+$, 100], 91 (17). Anal. Calcd for $C_{17}H_{23}NO{\cdot}1.1HCl{\cdot}0.1H_2O$ (299.28): C, 68.23; H, 8.18; N, 4.68; Cl, 13.03. Found: C, 68.13; H, 8.34; N, 4.69; Cl, 12.91.

4.1.6. *N*-(4-Fluorobenzyl)(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (8e·HCl)

From **7**·HCl (150 mg, 0.86 mmol), $NaBH_3CN$ (95%, 125 mg, 1.89 mmol), AcOH (0.3 mL), and 4-fluorobenzaldehyde (0.14 mL, 1.31 mmol) in MeOH (8 mL) and following the procedure described for **8a**, **8e**·HCl was obtained (186 mg, 77% yield). The analytical sample of **8e**·HCl was obtained by crystallization from ethyl acetate, mp >300 °C (dec). IR: 2947, 2920, 2797, 2754, 2580, 2446, 1604, 1590, 1514, 1457, 1440, 1429, 1334, 1232, 1163, 1127, 830, 778 cm^{-1}. ^1H NMR 1.64 (dquint, J = 13.2 Hz, J' = 2.5 Hz, 1H, 9-H_{syn}), 1.73 (dd, J = 11.0 Hz, J' = 2.5 Hz, 2H, 6(8)-H_α), 1.76 (overlapped dm, 1H, 9-H_{anti}), 2.00-2.06 [m, 2H, 6(8)-H_β], 2.08 [dm, J = 10.5 Hz, 2H, 2(4)-H_β], 2.13 [dd, J = 10.2 Hz, J' = 1.7 Hz, 2H, 2(4)-H_α], 2.45 [broad s, 2H, 1(5)-H], 2.47 [overlapped tt, J = 6.7 Hz, J' = 1.7 Hz, 1H, 7-H], 4.21 (s, 2H, CH_2–C_6H_5), 7.22 (tt, J = 8.7 Hz, J' = 2.2 Hz, 2H, Ar-3(5)-H), 7.58 (m, 2H, Ar-2(6)-H). ^{13}C NMR 35.0 (CH_2, C9), 38.8 [CH, C1(5)], 43.67 (CH, C7), 43.72 [CH_2, C6(8)], 46.3 [CH_2, C2(4)], 48.0 (CH_2, CH_2–C_6H_5), 71.8 (C, C3), 117.1 [CH, d, $^2J_{CF}$ = 22.4 Hz, Ar-C3(5)], 129.3 (C, Ar-C1), 133.3 [CH, d, $^3J_{CF}$ = 9.0 Hz, Ar-C2(6)], 164.8 (C, d, $^1J_{CF}$ = 247.7 Hz, Ar-C4). MS (EI), m/z (%): 245 ($M^{\cdot+}$, 32), 203 (16), 202 ([$M-C_3H_7$]$^+$, 100), 109 ([$FC_6H_4CH_2$]$^+$, 100), 106 (20). Anal. Calcd for $C_{16}H_{20}NF{\cdot}1.1HCl{\cdot}0.33H_2O$ (291.45): C, 65.94; H, 7.53; N, 4.81; Cl, 13.38; F, 6.52. Found: C, 66.01; H, 7.67; N, 4.83; Cl, 13.31; F, 6.34.

4.1.7. *N*-(2-Thenyl)(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (8f·HCl)

From **7**·HCl (150 mg, 0.86 mmol), $NaBH_3CN$ (95%, 125 mg, 1.89 mmol), AcOH (0.3 mL), and 2-thiophenecarbaldehyde (0.12 mL, 1.37 mmol) in MeOH (8 mL) and following the procedure described for **8a**, **8f**·HCl was obtained (145 mg, 66% yield). The analytical sample of **8f**·HCl was obtained by crystallization from EtOAc, mp 278 °C (dec). IR: 2939 2917, 2790, 2747, 2442, 1589, 1457, 1440, 1429, 1334, 1256, 1194, 1126, 984, 854, 695 cm^{-1}. ^1H NMR 1.64 (dquint, J = 13.0 Hz, J' = 2.5 Hz, 1H, 9-H_{syn}), 1.73 (dd, J = 11.0 Hz, J' = 2.5 Hz, 2 H, 6(8)-H_α), 1.75 (overlapped dm, 1H, 9-H_{anti}), 2.00–2.05 [m, 2H, 6(8)-H_β], 2.07 [dm, J = 10.0 Hz, 2H, 2(4)-H_β], 2.12 [dd, J = 10.0 Hz, J' = 2.5 Hz, 2H, 2(4)-H_α], 2.44 [broad s, 2H, 1(5)-H], 2.46 (overlapped tt, J = 8.5 Hz, J' = 2.0 Hz, 1H, 7-H), 4.46 (s, 2H, $CH_2C_4H_3S$), 7.12 (dd, J = 5.0 Hz, J' = 4.0 Hz, 1H, Ar-4-H), 7.34 (dm, J = 3.5 Hz, 1H, Ar-3-H), 7.57 (dd, J = 5.0 Hz, J' = 1.0 Hz, 1H, Ar-5-H). ^{13}C NMR 35.0 (CH_2, C9), 38.8 [CH, C1(5)], 42.6 (CH_2, $CH_2C_4H_3S$), 43.7 (CH, C7), 43.7 [CH_2, C6(8)], 46.2 [CH_2, C2(4)], 71.8 (C, C3), 128.7 (CH, Ar-C4), 129.2 (CH, Ar-C5), 131.5 (CH, Ar-C3), 134.0 (C, Ar-C1). MS (EI), m/z (%): 233 ($M^{\cdot+}$, 56), 190 ([$M-C_3H_7$]$^+$, 78), 106 (45), 97 [($C_4H_3SCH_2$)$^+$, 100]. Anal. Calcd for $C_{14}H_{19}NS{\cdot}1.05HCl{\cdot}0.25H_2O$ (276.17): C, 60.89; H, 7.50; N, 5.07; S, 11.61; Cl, 13.48. Found: C, 60.99; H, 7.59; N, 5.09; S, 11.28; Cl, 13.49.

4.1.8. *N*-Benzyl-*N*-methyl(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (9·HCl)

To a solution of **8a**·HCl (395 mg, 1.5 mmol) in acetonitrile (10 mL), formaldehyde (1.18 mL, 37% wt. in water solution, 15 mmol), and $NaBH_3CN$ (95%, 238 mg, 4.28 mmol) were added. The mixture was stirred for 30 min at room temperature, AcOH (0.3 mL) was added and the mixture was stirred at room temperature for 2 h. An additional portion of $NaBH_3CN$ (95%, 283 mg, 4.28 mmol) was added and the mixture was further stirred at room temperature for 2 h. The mixture was concentrated to dryness, 2 N NaOH (20 mL) was added and the suspension was extracted with CH_2Cl_2 (3× 20 mL). The combined organic phases were washed with H_2O (2× 20 mL), dried with anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was taken in EtOAc and the amine **9** was precipitated as its hydrochloride (327 mg, 91% yield) by adding an excess of Et_2O·HCl. The analytical sample of **9**·HCl was obtained by crystallization from 2-propanol, mp 258–259 °C (dec). IR: 3042, 2927, 2872, 2850, 2608, 2553, 2520, 2487, 2472, 2391, 1498, 1458, 1405, 1332, 994, 748, 696 cm^{-1}. ^1H NMR 1.64 (dquint, J = 13.5 Hz, J' = 2.6 Hz, 1H, 9-H_{syn}), 1.78 (dd, J = 11.5 Hz, J' = 3.0 Hz, 2 H, 6(8)-H_α), 1.79 (dm, J = 13.5 Hz, 1H, 9-H_{anti}), 2.09–2.29 [complex signal, 6 H, 6(8)-H_β, 2(4)-H_α, and 2(4)-H_β], 2.50 [broad s, 2 H, 1(5)-H], 2.73 (s, 3 H, N-CH_3), 2.75 (tt, J = 7.0 Hz, J' = 2.0 Hz, 1H, 7-H), 4.09 (d, J = 11.7 Hz, 1H) and 4.60 (d, J = 11.7 Hz, 1H) (CH_2–C_6H_5), 7.49–7.53 [complex signal, 3 H, Ar-3(5)-H and Ar-4-H], 7.59 [m, 2 H, Ar-2(6)H]. ^{13}C NMR 35.2 (CH_2, C9), 36.5 (CH_3, NCH_3), 38.8 [CH, C1(5)], 42.8 (CH, C7), 43.8 [CH_2, C6(8)], 44.4 (broad signal, CH_2) and 45.4 (broad signal, CH_2) (C2 and C4), 58.1 (CH_2, $CH_2C_6H_5$), 79.9 [C, C3), 130.3 (CH, Ar-C3(5)], 131.1 (CH, Ar-C4), 131.3 (C, Ar-C1), 132.4 [C, Ar-C2(6)]. MS (EI), m/z (%): 241 ($M^{\cdot+}$, 70), 199 (25), 198 ([$M-C_3H_7$]$^+$, 100), 185 (40), 120 (17), 91 (96). Anal. Calcd for $C_{17}H_{23}N{\cdot}HCl$ (277.84): C, 73.49; H, 8.71; N, 5.04; Cl, 12.76. Found: C, 73.61; H, 8.74; N, 5.04; Cl, 12.99.

4.1.9. *N*-(Tricyclo[3.3.1.0^{3,7}]non-3-yl)piperidine hydrochloride (11·HCl)

To a solution of **7**·HCl (173 mg, 1.00 mmol) in DMF (2.5 mL), anhyd Et_3N (0.4 mL, 2.9 mmol) was added and the suspension was

stirred at room temperature for 2 h. 1,5-Dibromopentane (0.17 mL, 1.2 mmol) was added and the mixture was heated at 60 °C for 26 h. To the cold mixture, water (15 mL) was added and the solution was washed with EtOAc (3× 10 mL). The aqueous phase was basified with 2 N NaOH (5 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with water (3× 10 mL), dried with anhyd Na_2SO_4, filtered and excess of Et_2O·HCl was added. The solution was concentrated in vacuo to dryness to give **11**·HCl (117 mg, 48% yield). The analytical sample of **11**·HCl was obtained by crystallization from MeOH/Et_2O, mp >264 °C (dec). IR: 2941, 2930, 2871, 2851, 2634, 2530, 2451, 2401, 1471, 1455, 1351, 1333, 1187, 1124, 1016, 992, 858, 708 cm^{-1}. ^1H NMR 1.54 (dm, J = 13.0 Hz, 1H, 4′-H_{ax}), 1.62 (dquint, J = 13.3 Hz, 1H, 9-H_{syn}), 1.72 [dd, J = 11.5 Hz, J' = 3.0 Hz, 2H, 6(8)-H_α], 1.74 (dm, J = 13.0 Hz, 1H, 9-H_{anti}), 1.84-2.02 [complex signal, 9 H, 6(8)-H_β, 2(4)-H_β, 4′-H_{eq}, 3′(5′)-H_{ax}, and 3′(5′)-H_{eq}], 2.15 [dm, J = 10.0 Hz, 2H, 2(4)-H_α], 2.44 [broad signal, 2H, 1(5)-H], 2.65 [tt, J = 6.7 Hz, J' = 1.8 Hz, 1H, 7-H], 3.05 [broad t, J = 12.0 Hz, 2H, 2′(6′)-H_{ax}], 3.51 [d, J = 12.0 Hz, 2H, 2′(6′)-H_{eq}]. ^{13}C NMR 23.1 (CH_2, C4′), 24.6 [CH_2, C3′(5′)], 35.2 (CH_2, C9), 38.7 [CH, C1(5)], 42.0 (CH, C7), 43.7 [CH_2, C6(8)], 44.8 [CH_2, C2(4)], 51.0 [CH_2, C2′(6′)], 78.8 (C, C3). MS (EI), m/z (%): 205 ($M^{\cdot+}$, 15), 163 (14), 162 ([M−C_3H_7]$^+$, 100), 149 (26). Anal. Calcd for $C_{14}H_{23}N$·HCl (241.80): C, 69.54; H, 10.00; N, 5.79. Found: C, 69.60; H, 10.0; N, 5.78.

4.1.10. *N*-Methyl(tricyclo[3.3.1.0^{3,7}]non-3-yl)amine hydrochloride (12·HCl)

A solution of **9**·HCl (275 mg, 0.99 mmol) and 5% Pd/C (50% in water, 10 mg) in absolute EtOH (25 mL) was hydrogenated at 1 atm for 24 h. The suspension was filtered, the residue was washed with EtOH, and the organic layer was concentrated in vacuo to give a solid. Crystallization from MeOH/Et_2O gave **12**·HCl (165 mg, 89% yield), mp 165−166 °C. IR: 2947, 2922, 2870, 2856, 2763, 2728, 2692, 2587, 2516, 2458, 1466, 1420, 1348, 1332, 1311, 1258, 1160, 1111, 1094, 1060, 1018, 996, 630 cm^{-1}. ^1H NMR 1.61 (dquint, J = 13.0 Hz, J' = 2.5 Hz, 1H, 9-H_{syn}), 1.71 (dd, J = 12.0 Hz, J' = 2.5 Hz, 2H, 6(8)-H_α), 1.74 (overlapped m, 1H, 9-H_{anti}), 1.96–2.03 [complex signal, 6H, 6(8)-H_β, 2(4)-H_α, and 2(4)-H_β], 2.42 [complex signal, 3H, 1(5)-H, and 7-H], 2.68 (s, 3H, N-CH_3). ^{13}C NMR 29.1 (CH_3, N-CH_3), 34.9 (CH_2, C9), 38.7 [CH, C1(5)], 43.1 (CH, C7), 43.8 [CH_2, C6(8)], 45.8 [CH_2, C2(4)], 71.5 (C, C3). MS (EI), m/z (%): 151 (M^+, 15), 108 ([M−C_3H_7]$^+$, 100). Anal. Calcd for $C_{10}H_{17}N$·HCl·0.33H_2O (193.66): C, 62.02; H, 9.71; N, 7.23. Found: C, 62.13; H, 9.63; N, 7.20.

4.1.11. [(Tricyclo[3.3.1.0^{3,7}]non-3-yl)methyl]amine hydrochloride (14·HCl)

To a cold (0 °C) solution of **13** (600 mg, 3.64 mmol) in anhyd THF (50 mL), $LiAlH_4$ (443 mg, 11.1 mmol) was added and the suspension was heated under reflux for 15 h. The suspension was cooled (ice bath), carefully basified with 10 N NaOH (10 mL), and stirred for 1 h at room temperature. The precipitate was filtered and washed with CH_2Cl_2 (3× 25 mL). The combined filtrate and washings were dried with anhyd Na_2SO_4, filtered, and excess of Et_2O·HCl was added. The solution was concentrated in vacuo to give a solid that was crystallized from MeOH/Et_2O to give **14**·HCl (613 mg, 90% yield), mp >300 °C (dec). IR: 3019, 2926, 2867, 1597, 1499, 1384, 1337, 1116, 981, 864 cm^{-1}. ^1H NMR 1.61−1.72 (complex signal, 6H, 9-H_{syn}, 9-H_{anti}, 6(8)-H_α, and 2(4)-H_β], 1.75 [dd, J = 10.5 Hz, J' = 3.0 Hz, 2H, 2(4)-H_α], 1.81 [m, 2H, 6(8)-H_β], 2.18 [t, J = 6.7 Hz, 1H, 7-H], 2.29 [broad signal, 2H, 1(5)-H], 3.08 (s, 2H, CH_2N). ^{13}C NMR 35.8 (CH_2, C9), 38.9 [CH, C1(5)], 43.2 (CH, C7), 44.6 [CH_2, C6(8)], 47.4 [CH_2, C2(4)], 48.2 (CH_2, CH_2N), 48.8 (C, C3). MS (EI), m/z (%): 153 (24), 152 ([M+H]$^+$, 36], 151 (20), 135 [($C_{10}H_{15}$)$^+$, 53], 134 (70), 119 (29), 96 (45), 95 (59), 94 (33), 93 (57), 92 (100), 91 (58), 79 (74), 77 (40). Anal. Calcd for $C_{10}H_{17}N$·HCl (187.71): C, 63.99; H, 9.66; N, 7.46; Cl, 18.89. Found: C, 64.07; H, 9.66; N, 7.43; Cl, 18.97.

4.1.12. *N*-Benzyl[(tricyclo[3.3.1.0^{3,7}]non-3-yl)methyl]amine hydrochloride (15·HCl)

From **14**·HCl (500 mg, 2.67 mmol), MeOH (10 mL), $NaBH_3CN$ (95%, 380 mg, 5.74 mmol), AcOH (0.3 mL), benzaldehyde (0.4 mL, 3.92 mmol), an additional portion of $NaBH_3CN$ (95%, 190 mg, 2.87 mmol), and benzaldehyde (0.2 mL, 1.96 mmol) and following the procedure described for **8a**, **15**·HCl was obtained (567 mg, 77% yield). The analytical sample of **15**·HCl was obtained by crystallization from EtOAc, mp >277 °C (dec). IR: 2931, 2865, 2781, 1588, 1446, 750, 700 cm^{-1}. ^1H NMR 1.58–1.70 [complex signal, 6H, 2(4)-H_β, 6(8)-H_α, and 9-H_{syn} and 9-H_{anti}], 1.76–1.81 [complex signal, 4H, 2(4)-H_α and 6(8)-H_β], 2.15 [t, J = 7.0 Hz, 1H, 7-H], 2.27 [broad s, 2H, 1(5)-H], 3.11 (s, 2H, CH_2–N), 4.28 (s, 2H, C$H_2C_6H_5$), 7.45–7.50 [complex signal, 3H, Ar-4-H and Ar-3(5)-H], 7.55–7.57 [m, 2H, Ar-2(6)-H]. ^{13}C NMR 35.7 (CH_2, C9), 39.0 [CH, C1(5)], 44.0 (CH, C7), 44.4 [CH_2, C6(8)], 47.8 [CH_2, C2(4)], 48.4 (C, C3), 53.1 (CH_2, C$H_2C_6H_5$), 55.9 (CH_2, CH_2N), 130.3 [CH, Ar-C3(5)], 130.8 (CH, Ar-C4), 131.5 [CH, Ar-C2(6)], 132.0 (C, Ar-C1). MS (EI), m/z (%): 241 ($M^{\cdot+}$, 6), 240 ([M−H]$^+$, 8), 150 [($C_{10}H_{16}N$)$^+$, 10], 120 (54), 106 [(C_7H_8N)$^+$, 58), 91 [(C_7H_7)$^+$, 100]. Anal. Calcd for $C_{17}H_{23}N$·1.1HCl·0.1H_2O (283.3): C, 72.08; H, 8.65; N, 4.94; Cl, 13.77. Found: C, 72.03; H, 8.56; N, 4.85, Cl, 13.94.

4.1.13. *N*-Benzyl-*N*-methyl[(tricyclo[3.3.1.0^{3,7}]non-3-yl)methyl]amine hydrochloride (16·HCl)

From **15**·HCl (465 mg, 1.67 mmol), acetonitrile (10 mL), formaldehyde (1.31 mL, 37% wt. in water solution, 16.7 mmol), and two portions of $NaBH_3CN$ (95%, 314 mg, 4.75 mmol) and following the procedure described for **9**, the amine **16** was obtained (411 mg, 96% yield). Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in EtOAc, followed by concentration in vacuo to dryness. The analytical sample of **16**·HCl was obtained by crystallization from EtOAc, mp 251−252 °C. IR: 3042, 2924, 2865, 2698, 2641, 2550, 2530, 1458, 1423, 1337, 1085, 906, 745, 701 cm^{-1}. ^1H NMR 1.46 [d, J = 9.0 Hz, 1H, 2-H_α or 4-H_α], 1.59−1.70 [complex signal, 4H, 6-H_α, 8-H_α, 9-H_{syn}, and 9-H_{anti}], 1.71−1.78 [complex signal, 3H, 4-H_α or 2-H_α, 6-H_β, and 8-H_β], 1.87 [m, 2 H, 2-H_β and 4-H_β], 2.10 [t, J = 6.7 Hz, 1H, 7-H], 2.27 (broad s, 1H) and 2.30 (broad s, 1H) (1-H and 5-H), 2.94 (s, 3 H, CH_3–N), 3.32 (d, J = 13.5 Hz, 1H, CH_aN), 3.46 (d, J = 13.5 Hz, 1H, CH_bN), 4.37 (d, J = 12.2 Hz, 1H, $CH_aC_6H_5$), 4.43 (d, J = 12.2 Hz, 1H, $CH_bC_6H_5$), 7.50–7.52 [complex signal, 3H, Ar-4-H and Ar-3(5)-H], 7.59 [m, 2H, Ar-2(6)H]. ^{13}C NMR 35.5 (CH_2, C9), 39.1 (CH) and 39.4 [CH, C1 and C5], 43.0 (CH_3, CH_3–N), 44.0 (CH_2, C6, and C8), 46.0 (CH, C7), 48.6 (C, C3), 48.8 (CH_2, C2, and C4), 62.8 (CH_2, CH_2–C_6H_5), 65.1 (CH_2, CH_2–N), 130.4 [CH, Ar-C3(5)], 130.9 (C, Ar-C1), 131.4 (CH, Ar-C4), 132.6 [CH, Ar-C2(6)]. MS (EI), m/z (%): 255 ($M^{\cdot+}$, 10), 135 (17), 134 ([$C_6H_5CH_2N(CH_3)$=CH_2]$^+$, 100), 120 ([C_6H_5CH=$NHCH_3$]$^+$, 34), 91 [(C_7H_7)$^+$, 89]. Anal. Calcd for $C_{18}H_{25}N$·HCl (291.86): C, 74.07; H, 8.98; N, 4.80; Cl, 12.15. Found: C, 74.15; H, 8.96; N, 4.81; Cl, 12.43.

4.1.14. *N,N*-Dimethyl[(tricyclo[3.3.1.0^{3,7}]non-3-yl)methyl]amine hydrochloride (17·HCl)

To a cold (0 °C) solution of **14** (128 mg, 0.68 mmol) in Et_2O (5 mL), formaldehyde (1.38 mL, 37% wt. in water solution, 17.6 mmol) and, dropwise, formic acid (1.17 mL, 30.5 mmol) were added and the mixture was stirred at 80 °C for 10 h. To the cold mixture Et_2O (15 mL) was added, 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× 10 mL). The combined organic phases were dried with anhyd Na_2SO_4, filtered, and an excess of Et_2O·HCl

was added. Concentration in vacuo gave **17**·HCl (100 mg, 68% yield). The analytical sample of **17**·HCl was obtained by crystallization from MeOH/Et_2O, mp >260 °C (dec). IR (KBr): 2930, 2915, 2868, 2847, 2681, 2570, 2468, 2360, 1471, 1413, 1338, 1306, 1225, 1062, 971, 946 cm^{-1}. ^1H NMR 1.62–1.71 [complex signal, 4H, 9-H_{syn}, 9-H_{anti}, and 6(8)-H_α], 1.71–1.76 [dm, J = 10.5 Hz, 2H, 2(4)-H_β], 1.83 [m, 2H, 6(8)-H_β], 1.87 [dd, J = 10.5 Hz, J' = 3.0 Hz, 2H, 2(4)-H_α], 2.19 [t, J = 6.7 Hz, 1H, 7-H], 2.32 [broad signal, 2H, 1(5)-H], 2.95 [s, 6H, $N(CH_3)_2$], 3.38 (s, 2H, CH_2N). ^{13}C NMR 35.7 (CH_2, C9), 39.2 [CH, C1(5)], 44.1 [CH_2, C6(8)], 45.5 (CH_3, CH_3N), 46.0 (CH, C7), 48.3 [CH_2, C2(4)], 48.6 (C, C3), 67.4 (CH_2, CH_2N). MS (EI), m/z (%): 179 ($M^{\cdot+}$, 16), 91 (7), 79 (8), 77 (7), 58 ([CH_2=$N(CH_3)_2$]$^+$, 100). Anal. Calcd for $C_{12}H_{21}N$·1.05HCl·0.25H_2O (222.09): C, 64.90; H, 10.23; N, 6.31; Cl, 16.76. Found: C, 64.77; H, 10.42; N, 6.32; Cl, 16.70.

4.1.15. *N*-[(Tricyclo[3.3.1.0^{3,7}]non-3-yl)methyl]guanidine hydrochloride (18·HCl)

To a cold (0 °C) solution of **14**·HCl (150 mg, 0.8 mmol) in acetonitrile (2.5 mL), anhyd Et_3N (0.2 mL, 1.45 mmol), and 1H-pyrazol-1-carboxamide hydrochloride (140 mg, 0.94 mmol) were added. The suspension was heated at 70 °C for 6 h and cooled at 0 °C for 24 h. The precipitate was filtered and washed with cold acetonitrile (2× 5 mL) to give **18**·HCl (129 mg, 70% yield). The above product was taken in EtOAc, excess Et_2O·HCl was added, and the solvent was eliminated in vacuo. The analytical sample of **18**·HCl was obtained by crystallization from MeOH/Et_2O, mp 298–299 °C. IR (KBr): 3357, 3262, 3169, 2926, 2861, 1664, 1623, 1578, 1458, 1356, 1094, 690 cm^{-1}. ^1H NMR 1.61–1.68 [complex signal, 6H, 6(8)-H_α, 2(4)-H_β, 9-H_{syn}, and 9-H_{anti}], 1.72 [dd, J = 10.7 Hz, J' = 2.7 Hz, 2H, 2(4)-H_α], 1.81 [m, 2H, 6(8)-H_β], 2.12 [t, J = 6.7 Hz, 1H, 7-H], 2.26 [broad s, 2H, 1(5)-H], 3.30 (s, 2H, CH_2N). ^{13}C NMR (75.4 MHz) 36.1 (CH_2, C9), 38.8 [CH, C1(5)], 42.8 (CH, C7), 44.8 [CH_2, C6(8)], 47.7 [CH_2, C2(4)], 49.9 (CH_2, CH_2N), 50.2 (C, C3), 159.1 (C, C guanidine). MS (EI), m/z (%): 194 (12), 193 ($M^{\cdot+}$, 60), 150 ([$M-C_3H_7$]$^+$, 24), 93 (21), 92 (30), 91 (44), 79 (36), 77 (29), 72 [($C_2H_6N_3$)$^+$, 49], 60 ([CH_6N_3]$^{\cdot+}$, 100). Anal. Calcd for $C_{11}H_{19}N_3$·HCl (229.75): C, 57.51; H, 8.77; N, 18.29; Cl, 15.43. Found: C, 57.65; H, 8.88; N, 18.23; Cl, 15.68.

4.1.16. *N*-Methyl[(tricyclo[3.3.1.0^{3,7}]non-3-yl)methyl]amine hydrochloride (19·HCl)

From **16**·HCl (267 mg, 0.91 mmol), 5% Pd/C (50% in water, 10 mg), and absolute EtOH (30 mL) and following the procedure described for **12**, **19**·HCl (143 mg, 78% yield) was obtained after crystallization from MeOH/Et_2O, mp >224 °C (dec). IR: 2931, 2866, 2770, 2435, 1668, 1611, 1460, 1430, 1398, 1338, 1302, 1154, 1028, 732 cm^{-1}. ^1H NMR 1.61–1.73 [complex signal, 6H, 2(4)-H_β, 6(8)-H_α, 9-H_{syn}, and 9-H_{anti}], 1.75 [dd, J = 10.5 Hz, J' = 3.0 Hz, 2H, 2(4)-H_α], 1.81 [m, 2H, 6(8)-H_β], 2.19 [t, J = 6.7 Hz, 1H, 7-H], 2.30 [broad s, 2H, 1(5)-H], 2.75 (s, 3H, CH_3N), 3.16 (s, 2H, CH_2–N). ^{13}C NMR 35.0 (CH_3, CH_3N), 35.7 (CH_2, C9), 39.0 [CH, C1(5)], 43.7 (CH, C7), 44.5 [CH_2, C6(8)], 47.7 [CH_2, C2(4)], 48.5 (C, C3), 58.6 (CH_2, CH_2–N). MS (EI), m/z (%): 166 (13), 165 ($M^{\cdot+}$, 100), 164 ([$M-H$]$^+$, 48), 135 (20), 134 (87), 108 (54), 93 (46), 92 (86), 91 (55), 79 (60), 77 (39). Anal. Calcd for $C_{11}H_{19}N$·HCl·0.25H_2O (206.24): C, 64.06; H, 10.02; N, 6.79. Found: C, 64.02; H, 10.23; N, 6.86.

4.1.17. 3,7-Dimethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine·HCl (21·HCl)

To a solution of acid **20** (389 mg, 2.16 mmol) in toluene (6.5 mL), Et_3N (0.4 mL, 2.9 mmol), and diphenylphosphorylazide (875 mg, 3.18 mmol) were added and the mixture was heated under reflux for 3 h. The cold (ice-bath) solution was washed with cold 1 N HCl (10× 5 mL). Then, 6 N HCl (9 mL) was added to the organic solution and the mixture was heated under reflux for 24 h. The organic layer was separated, the aqueous layer was washed with Et_2O (3× 5 mL) and the water was removed in a freeze–dryer giving **21**·HCl as a white solid (296 mg, 73% yield). The analytical sample was obtained by crystallization from water, mp 210–211 °C. IR: 2959, 2945, 2891, 2863, 2765, 2685, 2579, 1602, 1493, 1480, 1460, 1308, 1285, 1163, 984 cm^{-1}. ^1H NMR 1.20 (s, 6H, C3(7)-CH_3), 1.44 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_α], 1.70–1.73 [complex signal, 4H, 2(8)-H_α, and 2(8)-H_β], 1.75 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.34 [t, J = 3.0 Hz, 1H, 5-H], 4.85 (s, mobile H). ^{13}C NMR 16.4 [CH_3, C3(7)-CH_3], 44.1 (CH, C5), 48.1 [C, C3(7)], 53.8 [CH_2, C4(6)], 56.7 [CH_2, C2(8)], 61.4 (C, C1). MS (EI), m/z (%): 152 ([M+H]$^+$, 3), 151 ($M^{\cdot+}$, 2), 138 (14), 137 (12), 124 (27), 123 (25), 111 (57), 110 (88), 109 (53), 97 (81), 96 (100), 95 (70), 94 (29), 91 ([C_7H_7]$^+$, 23), 82 (36), 81 (30), 79 (26), 77 (36), 67 (24), 55 (44), 53 (35). Anal. Calcd for $C_{10}H_{17}N$·HCl (187.71): C, 63.99; H, 9.67; N, 7.46; Cl, 18.89. Found: C, 63.71; H, 9.70; N, 7.48; Cl, 18.88.

4.1.18. *N*-Benzyl-3,7-dimethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine hydrochloride (22a·HCl)

To a solution of **21**·HCl (770 mg, 4.11 mmol) in MeOH (15 mL), $NaBH_3CN$ (95%, 585 mg, 8.86 mmol), AcOH (0.3 mL), and benzaldehyde (653 mg, 6.16 mmol) were added, and the mixture was stirred at room temperature for 18 h. The solution was concentrated to dryness, water (30 mL) was added to the residue and the mixture was extracted with Et_2O (3× 25 mL). The combined organic extracts were washed with 2 N NaOH (3× 25 mL) and brine (2× 25 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The residue was subjected to column chromatography (silica gel; hexane/EtOAc, 97/3) to give amine **22a** (594 mg, 60% yield). An analytical sample of **22a**·HCl was obtained by adding an excess of Et_2O·HCl to a solution of **22a** in EtOAc and filtration of the formed precipitate, mp >258 °C (dec). IR: 2957, 2934, 2917, 2911, 2759, 2739, 2732, 2725, 2626, 2619, 2578, 2423, 1459, 1452, 1308, 1160, 1028, 731, 693 cm^{-1}. ^1H NMR 1.23 (s, 6H, C3(7)-CH_3), 1.50 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2 H, 4(6)-H_α], 1.79 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 1.82–1.86 [complex signal, 4H, 2(8)-H_α, and 2(8)-H_β], 2.51 [t, J = 3.0 Hz, 1H, 5-H], 4.21 (s, 2H, C$H_2C_6H_5$), 4.85 (s, mobile H), 7.42–7.48 [complex signal, 3H, Ar-3(5)-H, and Ar-4-H], 7.52 [dd, J = 8.0 Hz, J' = 2.0 Hz, 2H, Ar-2(6)-H]. ^{13}C NMR 16.4 [CH_3, C3(7)-CH_3], 43.6 (CH, C5), 47.8 [C, C3(7)], 49.6 (CH_2, CH_2–C6H_5), 53.6 [CH_2, C4(6)], 54.9 [CH_2, C2(8)], 68.2 (C, C1), 130.3 [CH, Ar-C3(5)], 130.6 (CH, Ar-C4), 130.8 (CH, Ar-C2(6)], 133.1 (C, Ar-C1). MS (EI), m/z (%): 241 ($M^{\cdot+}$, 2), 227 (3), 226 (3), 213 (6), 200 (34), 199 (35), 91 ([$C_6H_5CH_2$]$^+$, 100). Anal. Calcd for $C_{17}H_{23}N$·HCl (277.83): C, 73.49; H, 8.71; N, 5.04; Cl, 12.76. Found: C, 73.83; H, 8.78; N, 5.02; Cl, 12.92.

4.1.19. *N*-(2-Thenyl)-3,7-dimethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine hydrochloride (22b·HCl)

From **21**·HCl (187.7 mg, 1.00 mmol), $NaBH_3CN$ (95%, 198 mg, 3 mmol), acetic acid (0.3 mL), and 2-thiophenecarbaldehyde (0.15 mL, 1.65 mmol) in methanol (10 mL) and following the above procedure, **22b**·HCl (196 mg, 69% yield) was obtained. The analytical sample of **22b**·HCl was obtained by crystallization from MeOH/Et_2O, mp >255 °C (dec). IR: 3062, 2952, 2919, 2887, 2727, 2689, 2549, 2451, 1583, 1477, 1440, 1375, 1307, 1280, 1247, 1159, 1068, 1007, 937, 855, 837, 731, 712, 701 cm^{-1}. ^1H NMR 1.23 (s, 6 H, C3(7)-CH_3), 1.49 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_α], 1.79 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 1.84 [complex signal, 4H, 2(8)-H_α, and 2(8)-H_β], 2.51 [t, J = 3.0 Hz, 1H, 5-H], 4.46 (s, 2H, CH_2N), 4.86 (s, mobile H), 7.11 (dd, J = 5.0 Hz, J' = 4.0 Hz, 1H, Ar-4-H), 7.33 (dm, J = 3.5 Hz, 1H, Ar-3-H), 7.56 (dd, J = 5.0 Hz, J' = 1.0 Hz, 1H, Ar-5-H). ^{13}C NMR 16.4 [CH_3, C3(7)-CH_3], 43.5 (CH_2, CH_2N), 43.6 (CH, C5), 47.8 [C, C3(7)], 53.6 [CH_2, C4(6)], 54.9 [CH_2, C2(8)], 68.0 (C, C1), 128.7 (CH, Ar-C4), 129.2 (CH, Ar-C5),

131.4 (CH, Ar-C3), 134.0 (C, Ar-C1). MS (EI), *m*/*z* (%): 247 ($M^{\cdot+}$, 2), 233 (3), 219 (7), 206 (50), 205 (30), 192 (11), 97 ($[C_4H_3SCH_2]^+$, 100). Anal. Calcd for $C_{15}H_{21}NS{\cdot}1.1HCl{\cdot}0.1H_2O$ (289.30): C, 62.27; H, 7.77; N, 4.84; S, 11.08; Cl, 13.48. Found: C, 62.25; H, 7.69; N, 4.85; S, 10.95; Cl, 13.07.

4.1.20. *N*-Benzyl-*N*,3,7-trimethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine hydrochloride (23·HCl)

From a solution of **22a**·HCl (635 mg, 2.29 mmol), acetonitrile (15 mL), formaldehyde (1.81 mL, 37% wt. in water solution, 23 mmol), two portions of $NaBH_3CN$ (95%, 455 mg, 6.88 mmol) and following the procedure described for **9**, the amine **23** (516 mg, 88.5% yield) was obtained. An analytical sample of **23**·HCl was obtained by adding an excess of Et_2O·HCl to a solution of **23** in EtOAc followed by filtration of the obtained precipitate, mp >228 °C (dec). IR: 2952, 2886, 2680, 2439, 2372, 1456, 1310, 749, 705, 695 cm^{-1}. ^1H NMR 1.25 [s, 6H, C3(7)-CH_3], 1.56 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2H, 4(6)-H_α], 1.83 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 1.92–1.95 [complex signal, 4H, 2(8)-H_α, and 2(8)-H_β], 2.71 (s, 3H, CH_3N), 2.74 [t, J = 3.0 Hz, 1H, 5-H], 4.09 (broad signal, 1H) and 4.61 (broad signal, 1H) ($CH_2C_6H_5$), 4.84 (s, mobile H), 7.49–7.51 [complex signal, 3H, Ar-3(5)-H and Ar-4-H], 7.53–7.56 [m, 2H, Ar-2(6)-H]. ^{13}C NMR 16.5 [CH_3, C3(7)-CH_3], 37.2 (CH_3, CH_3N), 43.3 (CH, C5), 47.6 (CH_2, $CH_2C_6H_5$), 53.5 [CH_2, C4(6)], 53.7 [CH_2, C2(8)], 58.7 [C, C3(7)], 76.2 (C, C1), 130.3 [CH, Ar-C3(5)], 131.1 (CH, Ar-C4), 131.2 (C, Ar-C1), 132.1 [CH, Ar-C2(6)]. MS (EI), *m*/*z* (%): 255 ($M^{\cdot+}$, 3), 254 ($[M-H]^+$, 3), 240 (7), 226 (7), 213 (82), 212 (28), 91 ($[C_6H_5CH_2]^+$, 100). Anal. Calcd for $C_{18}H_{25}N{\cdot}0.95HCl$ (290.04): C, 74.54; H, 9.02; N, 4.83; Cl, 11.61. Found: C, 74.63; H, 9.13; N, 4.84; Cl, 11.60.

4.1.21. 1-(3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)ethylamine hydrochloride (25·HCl)

4.1.21.1. 1-(3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)-1-ethanone (24). To a suspension of Li_2CO_3 (189 mg, 2.55 mmol) in H_2O (40 mL) solid **20** (900 mg, 5.00 mmol) was added and the resulting suspension was stirred for 48 h at room temperature. The water of the resulting solution was removed in a freeze–dryer giving the lithium salt of **20** as a white solid. This salt was added to anhyd Et_2O (20 mL) and the resulting suspension was cooled to 0 °C. Methyllithium (18.8 mL, 1.6 M in Et_2O, 30 mmol) was added dropwise and the suspension was heated under reflux for 18 h. To the cold (ice-bath) mixture, water (15 mL) was added dropwise, and the mixture was further stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with Et_2O (3× 15 mL). The combined organic phases were dried (anhyd Na_2SO_4) and concentrated in vacuo at room temperature to give ketone **24** (382 mg, 43% yield; 57% yield based on unrecovered starting material). The aqueous layer was made acidic and extracted with CH_2Cl_2 (4× 10 mL). The combined organic phases were dried (anhyd Na_2SO_4), and concentrated in vacuo to give starting acid **20** (223 mg). IR: 2956, 2885, 1716, 1699, 1438, 1360, 1302, 1220 cm^{-1}. ^1H NMR (300 MHz) 1.18 (s, 6H, C3(7)-CH_3), 1.37 [dd, J = 8.5 Hz, J' = 3.6 Hz, 2H, 4(6)-H_α], 1.56–1.62 [complex signal, 4H, 2(8)-H_α and 4(6)-H_β], 1.70 [dm, J = 7.8 Hz, 2(8)-H_β], 2.16 (d, J = 0.6 Hz, 3H, CH_3CO), 2.60 [t, J = 3.0 Hz, 1H, 5-H]. MS (EI), *m*/*z* (%): 178 ($M^{\cdot+}$, 3), 163 ($[M-CH_3]^+$, 7), 136 (11), 135 ($[C_{10}H_{15}]^+$, 23), 123 (20), 122 (31), 107 (21), 95 (41), 93 (27), 43 ($[CH_3CO]^+$, 100). Accurate mass measurement (ESI^+) calcd for $[C_{12}H_{18}O+H]^+$: 179.1430. Found: 179.1431.

4.1.21.2. 1-(3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)-1-ethanone oxime. To a solution of ketone **24** (168 mg, 0.94 mmol) in ethanol (1 mL), hydroxylamine hydrochloride (103 mg, 1.49 mmol), water (0.1 mL), and powdered NaOH (190 mg, 4.75 mmol) were added and the mixture was heated under reflux for 5 min. The cold solution (ice-bath) was added to a cold solution (ice bath) of concd HCl (0.64 mmol, 7.72 mmol) and water (3.5 mL). The obtained precipitate was filtered, washed with cold water (2× 2 mL) and dried in vacuo over P_4O_{10} to give the title oxime (135 mg, 74% yield) that was used without further purification in the next step. IR: 3234, 2949, 2881, 1667, 1446, 1371, 1018, 918, 893, 775 cm^{-1}.

4.1.21.3. 1-(3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)ethylamine hydrochloride (25·HCl). To a suspension of $LiAlH_4$ (110 mg, 2.90 mmol) in anhyd Et_2O (3 mL) a solution of the above oxime (135 mg, 0.70 mmol) in anhyd THF (2 mL) was added dropwise and the mixture was heated under reflux for 16 h. To the cold mixture, water (0.1 mL, 5.55 mmol) was added dropwise and the suspension was stirred at room temperature for 1 h. The formed precipitate was filtered through Celite® and washed with Et_2O (3× 10 mL). The filtrate was dried (anhyd Na_2SO_4), an excess of Et_2O·HCl was added and the precipitate was filtered to give **25**·HCl (66 mg, 44% global yield from **24**), mp >278 °C (dec). IR: 2952, 2932, 2881, 2567, 1601, 1511, 1479, 1458, 1386, 1320, 1292, 1202, 1162, 1062 cm^{-1}. ^1H NMR 1.192 (s, 3H) and 1.195 (s, 3H) [C3-CH_3 and C7-CH_3], 1.32 [d, J = 7.0 Hz, 3H, CH_3CH], 1.38–1.60 (complex signal, 8H, methylene protons), 2.26 [t, J = 3.0 Hz, 1H, 5-H], 3.54 (q, J = 7.0 Hz, 1H, C*H*N), 4.86 (s, mobile H). ^{13}C NMR 16.4 (CH_3, CH_3CH), 16.8 (CH_3) and 16.9 (CH_3) (C3-CH_3 and C7-CH_3), 42.1 (CH, C5), 48.4 (C) and 48.5 (C) (C3 and C7), 51.3 (CH, CHN), 54.5 (CH_2) and 54.6 (CH_2) (C4 and C6), 54.7 (C, C1), 55.2 (CH_2) and 55.4 (CH_2) (C2 and C8). MS (EI), *m*/*z* (%): 179 ($M^{\cdot+}$, 2), 178 ($[M-H]^+$, 3), 164 (36), 147 (50), 122 (36), 121 (77), 119 (37), 109 (45), 108 (32), 107 (100), 106 (63), 105 (73), 93 (34), 91 (76), 83 (69), 80 (30), 79 (46), 77 (36), 70 (51). Anal. Calcd for $C_{12}H_{21}N{\cdot}1.05HCl{\cdot}0.1H_2O$ (219.39): C, 65.70; H, 10.22; N, 6.38; Cl, 16.97. Found: C, 65.53; H, 10.49; N, 6.36; Cl, 16.86.

4.1.22. *N*,*N*-3,7-Tetramethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine hydrochloride (26·HCl)

From amine **21** (151 mg, 1.0 mmol) in Et_2O (5 mL), formaldehyde (1.8 mL, 37% wt. in water solution, 22.8 mmol), and formic acid (1.5 mL, 39 mmol) and following the procedure described for **17**, the amine **26** was obtained as its hydrochloride. The analytical sample of **26**·HCl (180 mg, 83.5% yield) was obtained by crystallization from MeOH/Et_2O, mp 173–174 °C. IR 2999, 2955, 2933, 2886, 2628, 2569, 2540, 2518, 2468, 1472, 1455, 1439, 1312, 1054 cm^{-1}. ^1H NMR 1.22 [s, 6 H, C3(7)-CH_3], 1.51 [dm, J = 9.0 Hz, 2H, 4(6)-H_α], 1.75 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 1.81 [m, 4H, 2(8)-H_2], 2.59 [t, J = 3.0 Hz, 1H, 5-H], 2.88 (s, 6H, $(CH_3)_2N$). ^{13}C NMR 16.5 [CH_3, C3(7)-CH_3], 40.8 (CH_3, $(CH_3)_2N$), 42.5 (CH, C5), 47.7 [C, C3(7)], 53.2 [CH_2, C2(8)], 53.5 [CH_2, C4(6)], 75.4 (C, C1). MS (EI), *m*/*z* (%): 179 ($M^{\cdot+}$, 2), 178 ($[M-H]^+$, 4), 164 (14), 150 (18), 138 (22), 137 (100), 136 (79), 123 (46), 122 (45), 108 (35), 77 (24), 55 (35). Anal. Calcd for $C_{12}H_{21}N{\cdot}HCl$ (215.77): C, 66.80; H, 10.28; N, 6.49; Cl, 16.43. Found: C, 66.81; H, 10.30; N, 6.41; Cl, 16.65.

4.1.23. *N*,*N*-Dibenzyl-3,7-dimethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine hydrochloride (27·HCl)

A mixture of **21**·HCl (178 mg, 0.95 mmol), K_2CO_3 (1.03 g, 7.5 mmol), benzyl chloride (0.29 mL, 2.5 mmol) and NaI (100 mg, 0.67 mmol) in acetonitrile (10 mL) was heated under reflux for 24 h. The mixture was concentrated in vacuo and EtOAc (30 mL) was added to the residue. The organic solution was washed with water (2× 20 mL), dried (anhy Na_2SO_4) and concentrated in vacuo. The residue was subjected to column chromatography (silica gel; hexane/EtOAc, 99:1) to give amine **27** (130 mg, 41% yield). An analytical sample of **27**·HCl was obtained by adding an excess of Et_2O·HCl to a solution of **27** in EtOAc and filtration of the formed precipitate, mp 191–192 °C. IR: 3034, 2959, 2920, 2887, 2864,

2806, 2674, 2590, 2546, 1526, 1482, 1457, 1420, 1400, 1312, 1162, 1014, 921, 859, 742, 692 cm^{-1}. ^1H NMR 1.25 (s, 6H, C3(7)-CH_3), 1.55 [broad d, J = 9.0 Hz, 2H, 4(6)-H_α], 1.86 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.05 [s, 4H, 2(8)-H_2], 2.73 [t, J = 3.0 Hz, 1H, 5-H], 4.38 [d, J = 13.5 Hz, 2H) and 4.60 [d, J = 13.5 Hz, 2H) ($CH_2C_6H_5$)], 4.86 (s, mobile H), 7.23 [dm, J = 8.0 Hz, 4H, Ar-2(6)-H], 7.34 [tm, J = 7.5 Hz, 4H, Ar-3(5)-H], 7.39 (tt, J = 7.5 Hz, J' = 2.0 Hz, 2H, Ar-4-H). ^{13}C NMR 16.5 [CH_3, C3(7)-CH_3], 44.2 (CH, C5), 47.3 [C, C3(7)], 53.6 [CH_2, C4(6)], 54.5 [CH_2, C2(8)], 58.4 (CH_2, $CH_2C_6H_5$), 78.0 (C, C1), 130.2 [CH, Ar-C3(5)], 130.9 (CH, Ar-C4), 131.9 [CH, Ar-C2(6)], 132.0 (C, Ar-C1). MS (EI), m/z (%): 331 [$M^{\cdot+}$, 1], 316 (2), 289 (43), 198 ([$(C_6H_5CH_2)_2NH_2]^+$, 10), 91 ([$C_6H_5CH_2]^+$, 100). Anal. Calcd for $C_{24}H_{29}N{\cdot}1.4HCl$ (382.55): C, 75.34; H, 8.01; N, 3.66; Cl, 12.99. Found: C, 75.34; H, 8.10; N, 3.60; Cl, 13.09. Accurate mass measurement (ESI^+) calcd for [$C_{24}H_{29}N+H]^+$: 332.2372. Found: 332.2382.

4.1.24. *N*-3,7-Trimethyl(tricyclo[3.3.0.0^{3,7}]oct-1-yl)amine hydrochloride (28·HCl)

A mixture of **23**·HCl (390 mg, 1.33 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 organic layer was concentrated in vacuo to give a solid. Crystallization from MeOH/Et_2O gave **28**·HCl (240 mg, 89% yield). An analytical sample of **28**·HCl was obtained by crystallization from THF, mp 167–168 °C. IR (KBr) 2961, 2939, 2807, 2739, 2521, 2431, 2392, 2370, 1458, 1310, 1161, 1099, 1077, 878 cm^{-1}. ^1H NMR 1.22 [s, 6H, C3(7)-CH_3], 1.47 [dd, J = 8.5 Hz, J' = 2.0 Hz, 2H, 4(6)-H_α], 1.75-1.79 [complex signal, 6 H, 4(6)-H_β, 2(8)-$H_\alpha$and 2(8)-H_β], 2.47 [t, J = 2.5 Hz, 1H, 5-H], 2.69 (s, 3H, CH_3–N), 4.85 (s, mobile H). ^{13}C NMR (75.4 MHz) 16.5 [CH_3, C3(7)-CH_3], 30.1 (CH_3, CH_3–N), 43.0 (CH, C5), 47.7 [C, C3(7)], 53.6 [CH_2, C4(6)], 54.4 [CH_2, C2(8)], 68.1 (C, C1). MS (EI), m/z (%): 165 ($M^{\cdot+}$, 1), 164 ([M−H]$^+$, 8), 150 ([M−CH_3]$^+$, 24), 136 (33), 124 (23), 123 (100), 122 (76), 109 (56), 108 (44), 94 (27). Anal. Calcd for $C_{11}H_{19}N{\cdot}HCl{\cdot}0.15H_2O$ (204.44): C, 64.63; H, 10.01; N, 6.85. Found: C, 64.71; H, 9.92; N, 6.86.

4.1.25. (3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)carboxamide (29)

A solution of acid **20** (1.12 g, 6.22 mmol) in thionyl chloride (18 mL, 0.24 mmol) was heated under reflux for 2 h. The excess thionyl chloride was removed under vacuum, the residue was taken in toluene (5 mL) and evaporated to dryness (twice). The oily yellow residue (1.16 g) was dissolved in $CHCl_3$, the solution was cooled to 0 °C and NH_4OH (60 mL, 25% aqueous solution) was added dropwise. After stirring for 15 h at room temperature, the suspension was extracted with CH_2Cl_2 (4× 30 mL). The aqueous layer was made acidic with concd HCl and extracted with EtOAc (3× 30 mL). The combined EtOAc extracts were dried (anhyd Na_2SO_4) and concentrated in vacuo to give the starting acid **20** (438 mg). The combined CH_2Cl_2 extracts were washed with brine (2× 30 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo to give amide **29** (572 mg, 51% yield, 84% yield taking into account the recovered starting acid). An analytical sample of **29** was obtained by crystallization from EtOAc, mp 105–106 °C. IR, 3458, 3410, 3348, 3298, 3199, 3000, 2950, 2883, 1655, 1613, 1478, 1397, 1304, 1160, 790 cm^{-1}. ^1H NMR ($CDCl_3$) 1.17 (s, 6H, C3(7)-CH_3), 1.37 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.61 [dd, J = 7.5 Hz, J' = 3.5 Hz, 2H, 2(8)-H_α], 1.62 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_β], 1.70 [dm, J = 11.5 Hz, 2H, 2(8)-H_β], 2.56 [t, J = 3.0 Hz, 1H, 5-H], 5.50 (broad signal, 1H), 5.72 (broad signal, 1H) ($CONH_2$). ^{13}C NMR ($CDCl_3$) 16.3 [CH_3, C3(7)-CH_3], 43.5 (CH, C5), 47.9 [C, C3(7)], 53.5 [CH_2, C4(6)], 54.5 (C, C1), 57.1 [CH_2, C2(8)], 177.9 (C, CO). MS (EI), m/z (%): 179 ($M^{\cdot+}$, 4), 164 (5), 138 (24), 135 ([$C_{10}H_{15}]^+$, 21), 124 (39), 123 (42), 95 (100), 93 (38), 91 (34), 81 (72), 80 (33), 79 (60), 77 (40). Anal. Calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.64; H, 9.55; N, 7.74.

4.1.26. [(3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]amine hydrochloride (30·HCl)

To a cold (0 °C) solution of **29** (570 mg, 3.18 mmol) in anhyd THF (70 mL), $LiAlH_4$ (388 mg, 9.72 mmol) was added and the suspension was heated under reflux for 15 h. The suspension was cooled (ice bath), carefully basified with 10 N NaOH (5 mL) and stirred for 1 h at room temperature. The precipitate was filtered and washed with CH_2Cl_2 (3× 25 mL). The combined filtrate and washings were dried (anhyd Na_2SO_4) and excess of Et_2O·HCl was added. The solution was concentrated in vacuo to give a solid that was crystallized from MeOH/Et_2O to give **30**·HCl (534 mg, 83% yield), mp >270 °C (dec). IR 2952, 2881, 1600, 1505, 1480, 1457, 1389, 1322, 1292 cm^{-1}. ^1H NMR 1.19 (s, 6 H, C3(7)-CH_3), 1.39 [dd, J = 8.0 Hz, J' = 4.0 Hz, 2 H, 4(6)-H_α], 1.43 [dd, J = 8.0 Hz, J' = 4.0 Hz, 2H, 2(8)-H_α], 1.49 [dm, J = 7.5 Hz, 2H, 2(8)-H_β], 1.62 [dd, J = 8.0 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.20 [t, J = 3.0 Hz, 1H, 5-H], 3.19 (s, 2 H, CH_2N), 4.85 (s, mobile H). ^{13}C NMR (75.4 MHz) 16.8 [CH_3, C3(7)-CH_3], 42.8 (CH, C5), 43.8 (CH_2, CH_2N), 48.6 [C, C3(7)], 49.7 (C, C1), 54.6 [CH_2, C4(6)], 56.7 [CH_2, C2(8)]. MS (EI), m/z (%): 166 (1), 165 ($M^{\cdot+}$, 1), 152 (3), 151 (3), 148 (8), 136 (26), 135 ([$C_{10}H_{15}]^+$, 46), 133 (30), 107 (82), 106 (41), 105 (43), 93 (100), 92 (38), 91 (91), 79 (49), 77 (51), 71 (41). Anal. Calcd for $C_{11}H_{19}N{\cdot}HCl{\cdot}0.5H_2O$ (210.75): C, 62.69; H, 10.04; N, 6.65; Cl, 16.82. Found: C, 62.38; H, 9.71; N, 6.58, Cl, 16.55.

4.1.27. *N*-Benzyl[(3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]amine hydrochloride (31·HCl)

From **30**·HCl·0.5H_2O (500 mg, 2.37 mmol), MeOH (10 mL), $NaBH_3CN$ (95%, 335 mg, 5.3 mmol), AcOH (0.3 mL), and benzaldehyde (395 mg, 3.68 mmol) and following the procedure described for **22a**, **31**·HCl (489 mg, 68% yield) was obtained, mp >270 °C (dec). IR: 2948, 2880, 2781, 2371, 1586, 1478, 1447, 1420, 1382, 1355, 1321, 1289, 1237, 1084, 1025, 748, 698 cm^{-1}. ^1H NMR 1.18 (s, 6H, 3(7)-CH_3), 1.37 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.44 [dd, J = 8.0 Hz, J' = 3.5 Hz, 2H, 2(8)-H_α], 1.49 [dm, J = 8.0 Hz, 2H, 2(8)-H_β], 1.61 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.18 [t, J = 3.0 Hz, 1H, 5-H], 3.25 (s, 2H, CH_2N), 4.26 (s, 2H, $CH_2C_6H_5$), 4.86 (s, mobile H), 7.46–7.50 [complex signal, 3H, Ar-3(5)-H and Ar-4-H], 7.55 [m, 2H, Ar-2(6)-H]. ^{13}C NMR 16.7 [CH_3, C3(7)-CH_3], 43.5 (CH, C5), 48.6 [C, C3(7)], 48.9 (C, C1), 51.4 (CH_2, CH_2N), 53.1 (CH_2, $C_6H_5CH_2$), 54.6 [CH_2, C4(6)], 57.1 [CH_2, C2(8)], 130.3 [CH, Ar-C3(5)], 130.8 (CH, Ar-C4), 131.4 [CH, Ar-C2(6)], 132.1 (C, Ar-C1). MS (EI), m/z (%): 255 ($M^{\cdot+}$, 3), 254 ([M−H]$^+$, 2), 199 (10), 120 ([$C_6H_5CH_2{}^+NH{=}CH_2$], 67), 93 (18), 91 ([$C_6H_5CH_2]^+$, 100). Anal. Calcd for $C_{18}H_{25}N{\cdot}HCl{\cdot}0.05\ H_2O$ (292.76): C, 73.85; H, 8.99; N, 4.78; Cl, 12.11. Found: C, 73.58; H, 8.91; N, 4.70; Cl, 12.47.

4.1.28. *N*-Benzyl-*N*-methyl[(3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]amine hydrochloride (32·HCl)

From a solution of **31**·HCl (400 mg, 1.37 mmol), acetonitrile (10 mL), formaldehyde (1.08 mL, 37% wt. in water solution, 13.7 mmol) and two portions of $NaBH_3CN$ (95%, 272 mg, 4.11 mmol) and following the procedure described for **9**, the amine **32** (260 mg, 70.5% yield) was obtained. Its hydrochloride was obtained by adding an excess of Et_2O·HCl to a solution of the amine in EtOAc followed by concentration to dryness in vacuo. The analytical sample of **32**·HCl was obtained by crystallization from EtOAc, mp 215–216 °C. IR: 3030, 3011, 2946, 2879, 2862, 2695, 2635, 2512, 1478, 1455, 1070, 917, 906, 746, 697 cm^{-1}. ^1H NMR 1.18 [s, 6H, C3(7)-CH_3], 1.40 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.45-1.60 [complex signal, 4H, 2(8)-H_α, and 2(8)-H_β], 1.62 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.16 [t, J = 3.0 Hz, 1H, 5-H], 2.89 (s, 3H, CH_3N), 3.43 (d, J = 13.5 Hz, 1H) and 3.54 (d, J = 13.5 Hz, 1H) (CH_2N), 4.33 (d, J = 12.5 Hz, 1H)

and 4.43 (d, J = 12.5 Hz, 1H) ($CH_2C_6H_5$), 7.49–7.52 [complex signal, 3H, Ar-3(5)-H and Ar-4-H], 7.57 [m, 2H, Ar-2(6)-H]. ^{13}C NMR 16.6 [CH_3, C3(7)-CH_3], 42.4 (CH_3, CH_3–N), 44.8 (CH, C5), 48.5 [C, C3(7)], 48.7 (C, C1), 54.4 [CH_2, C4(6)], 57.8 [CH_2, C2(8)], 60.3 (CH_2, CH_2N), 62.3 (CH_2, $CH_2C_6H_5$), 130.4 [CH, Ar-C3(5)], 130.8 (C, Ar-C1), 131.3 (CH, Ar-C4), 132.5 [CH, Ar-C2(6)]. MS (EI), m/z (%): 269 ($M^{\cdot+}$, 7), 213 (15), 134 (87), 120 (13), 107 (10), 93 (15), 92 (13), 91 ($[C_6H_5CH_2]^+$, 100). Anal. Calcd for $C_{19}H_{27}N{\cdot}HCl$ (305.89): C, 74.60; H, 9.23; N, 4.58; Cl, 11.59. Found: C, 74.51; H, 9.26; N, 4.55; Cl, 11.74.

4.1.29. N,N-Dimethyl[(3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]amine hydrochloride (33·HCl)

From a cold (0 °C) solution of **30**·HCl (80 mg, 0.48 mmol) in Et_2O (5 mL), formaldehyde (1.0 mL, 37% wt. in water solution, 12.7 mmol) and formic acid (0.85 mL, 22 mmol) and following the procedure described for **17**, **33**·HCl was obtained. The analytical sample of **33**·HCl (68 mg, 61% yield) was obtained by crystallization from THF, mp >250 °C. IR (KBr): 2952, 2884, 2691, 1479, 1412, 1316, 1211, 1136, 973, 948 cm^{-1}. ^{1}H NMR 1.20 [s, 6H, C3(7)-CH_3], 1.43 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.52 [dd, J = 7.5 Hz, J' = 3.5 Hz, 2H, 2(8)-H_α], 1.57 [dm, J = 7.5 Hz, 2H, 2(8)-H_β], 1.65 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.25 [t, J = 3.0 Hz, 1H, 5-H], 2.93 (s, 6H, $(CH_3)_2$N), 3.47 (s, 2H, CH_2N), 4.85 (s, mobile H). ^{13}C NMR 16.6 [CH_3, C3(7)-CH_3], 44.7 (CH, C5), 45.1 (CH_3, CH_3N), 48.5 [C, C3(7)], 54.5 [CH_2, C4(6)], 57.7 [CH_2, C2(8)], 62.5 (CH_2, CH_2N). The signal corresponding to C1 was not observed. MS (EI), m/z (%): 193 ($M^{\cdot+}$, 3), 137 (5), 107 (7), 93 (12), 91 (11), 58 ($[Me_2NCH_2]^+$, 100). Anal. Calcd for $C_{13}H_{23}N{\cdot}1.6HCl$ (251.67): C, 62.04; H, 9.85; N, 5.57. Found: C, 62.23; H, 10.16; N, 5.76. Accurate mass measurement (ESI$^+$) calcd for $[C_{13}H_{23}N{+}H]^+$: 194.1903. Found: 194.1909.

4.1.30. *N*-[(3,7-Dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]piperidine hydrochloride (34·HCl)

From **30**·HCl (201 mg, 1.00 mmol), DMF (2.5 mL), anhyd Et_3N (0.4 mL, 2.9 mmol), 1,5-dibromopentane (0.17 mL, 1.2 mmol) and following the procedure described for **11**, **34**·HCl (111 mg, 41% yield) was obtained. The analytical sample of **34**·HCl was obtained by crystallization from 2-propanol, mp >265 °C (dec). IR: 2948, 2879, 2857, 2644, 2580, 2534, 1477, 1455, 1438, 1376, 1318, 950 cm^{-1}. ^{1}H NMR 1.20 [s, 6H, C3(7)-CH_3], 1.43 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.52 [dd, J = 7.5 Hz, J' = 3.5 Hz, 3 H, 2(8)-H_α], 1.50–1.55 (overlapped m, 1H, 4′-H_{ax}], 1.57 [dm, J = 7.5 Hz, 2H, 2(8)-H_β], 1.65 [dd, J = 9.0 Hz, J' = 3.0 Hz, 2 H, 4(6)-H_β], 1.75–1.97 [broad signal, 5 H, 4′-H_{eq}, 3′(5′)-H_{ax}, and 3′(5′)-H_{eq}], 2.24 [t, J = 2.5 Hz, 1H, 5-H], 3.02 [broad signal, 2 H, 2′(6′)-H_{ax}], 3.42 (s, 2 H, CH_2N), 3.53 [broad signal, 2 H, 2′(6′)-H_{eq}], 4.85 (s, mobile H). ^{13}C NMR 16.6 [CH_3, C3(7)-CH_3], 22.5 (CH_2, C4′), 23.8 [CH_2, C3′(5′)], 45.1 (CH, C5), 48.4 [C, C3(7)], 49.4 (C, C1), 54.5 [CH_2, C4(6)], 55.3 [CH_2, C2′(6′)], 58.1 [CH_2, C2(8)], 61.5 (CH_2, CH_2N). MS (EI), m/z (%):233 ($M^{\cdot+}$, 9), 177 (14), 98 ($[C_5H_{10}NCH_2]^+$, 100), 93 (13), 91 (13), 84 ($[C_5H_{10}N]^+$, 17). Anal. Calcd for $C_{16}H_{27}N{\cdot}HCl$ (269.86): C, 71.21; H, 10.46; N, 5.19; Cl, 13.14. Found: C, 71.19; H, 10.45; N, 5.17; Cl, 13.12.

4.1.31. *N*-[(3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]guanidine hydrochloride (35·HCl)

From a solution of **30**·HCl (150 mg, 0.74 mmol), acetonitrile (2.5 mL), anhyd Et_3N (0.2 mL, 1.45 mmol) and 1*H*-pyrazol-1-carboxamidine hydrochloride (130 mg, 0.89 mmol) and following the procedure described for **18**, **35**·HCl (139 mg, 77% yield) was obtained. The analytical sample of **35**·HCl was obtained by crystallization from MeOH/Et_2O, mp 214–215 °C. IR: 3600–3000 (max at 3376, 3247, 3170), 2948, 2879, 1646, 1456, 1354, 1319, 1291, 1160 cm^{-1}. ^{1}H NMR 1.18 [s, 6H, C3(7)-CH_3], 1.37 [dd, J = 7.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.39-1.46 [complex signal, 4H, 2(8)-H_α and 2(8)-H_β], 1.61 [dd, J = 7.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.12 [t, J = 2.5 Hz, 1H, 5-H], 3.41 (s, 2H, CH_2N), 4.86 (s, mobile H). ^{13}C NMR 16.9 [CH_3, C3(7)-CH_3], 42.7 (CH, C5), 45.6 (CH_2, CH_2N), 48.5 [C, C3(7)], 51.5 (C, C1), 54.8 [CH_2, C4(6)], 56.9 [CH_2, C2(8)], 158.9 (C, C guanidine). MS (EI), m/z (%): 209 (9), 208 ([M+H]$^+$, 9), 195 (5), 194 (5), 167 (14), 166 (15), 154 (12), 153 (12), 148 (17), 133 (31), 119 (22), 107 (81), 106 (42), 105 (48), 93 (83), 92 (38), 91 (100), 79 (46), 77 (66), 75 (39), 74 (38), 63 (47), 62 (68), 61 (48). Anal. Calcd for $C_{12}H_{21}N_3{\cdot}HCl{\cdot}1.5H_2O$ (270.80): C, 53.22; H, 9.30; N, 15.52. Found: C, 53.37; H, 9.03; N, 15.52.

4.1.32. *N*-Methyl[(3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1-yl)methyl]amine hydrochloride (36·HCl)

From **32**·HCl (200 mg, 0.65 mmol), 10% Pd/C (50% in water, 10 mg) and absolute ethanol (25 mL) and following the procedure described for **28**, **36**·HCl (120 mg, 85% yield) was obtained after crystallization from MeOH/Et_2O, mp >255 °C. IR: 2952, 2880, 2764, 1588, 1458, 1427, 1385, 1325, 1292, 1088, 1022, 806 cm^{-1}. ^{1}H NMR 1.19 [s, 6H, C3(7)-CH_3], 1.40 [dd, J = 8.5 Hz, J' = 3.5 Hz, 2H, 4(6)-H_α], 1.43-1.46 [dd, J = 7.5 Hz, J' = 3.5 Hz, 2H, 2(8)-H_α], 1.50 [dm, J = 7.5 Hz, 2H, 2(8)-H_β], 1.61 [dd, J = 8.5 Hz, J' = 3.0 Hz, 2H, 4(6)-H_β], 2.22 [t, J = 3.0 Hz, 1H, 5-H], 2.74 (s, 3H, CH_3N), 3.27 (s, 2H, CH_2N), 4.86 (s, mobile H). ^{13}C NMR 16.7 [CH_3, C3(7)-CH_3], 34.8 (CH_3, CH_3N), 43.2 (CH, C5), 48.6 [C, C3(7)], 54.0 (CH_2, CH_2N), 54.6 [CH_2, C4(6)], 57.0 [CH_2, C2(8)]. The signal corresponding to C1 was not observed. MS (EI), m/z (%): 179 ($M^{\cdot+}$, 4), 165 (5), 164 (4), 148 (6), 147 (6), 136 (15), 135 ($[C_{10}H_{15}]^+$, 34), 134 (32), 133 (27), 124 (26), 123 (29), 107 (71), 106 (35), 105 (44), 93 (100), 92 (38), 91 (97), 79 (42), 77 (56). Anal. Calcd for $C_{12}H_{21}N{\cdot}HCl{\cdot}0.5H_2O$ (224.77): C, 64.12; H, 10.31; N, 6.23. Found: C, 64.22; H, 10.24; N, 6.35.

4.2. *Trypanosoma* 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).[20] Trypanocidal activity was assessed by growing parasites for 48 h in the presence of various drug concentrations and determining 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 0.25×10^5 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.

4.3. 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.[18] 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 PerkinElmer 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.

4.4. 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].[21] The compounds' inhibitory effect on virus replication as well as their cytotoxicity were monitored by microscopical examination, and confirmed by the colorimetric MTS cell viability assay.

4.5. Dopaminergic evaluation

4.5.1. Synaptosomal preparation

Female Wistar rats (200–250 g) were used throughout. Briefly, rats were killed by decapitation and the striatum was dissected and homogenized in 10 volumes (w/v) of 0.32 M sucrose using a Potter–Elvejhem. The resulting crude synaptosomal preparation was centrifuged at 1000*g* for 10 min. The supernatant was stored and the pellet was resuspended in 10 volumes of 0.32 M sucrose and recentrifuged. The two supernatants were combined and the mixture centrifuged at 16,000g for 30 min. The resultant pellet was suspended in 10 volumes of ice-cold Krebs medium. Protein concentrations were determined using the Bradford protein assay.

4.5.2. [^{3}H]DA uptake assay

[^{3}H]Dopamine uptake was evaluated on aliquots of the synaptosomal preparation. After a 10 min preincubation at 37 °C in Krebs buffer containing 10 μM pargyline (to block metabolism of dopamine by monoamine oxidase), [^{3}H]dopamine (47 Ci/mmole, Amersham) was added to a final 0.5 nM concentration. Ten minute incubations were stopped by dilution into ice-cold Krebs medium. Samples were filtered rapidly through Grade 30 fiberglass filters (Schleicher & Schuell) using a Brandel cell harvester (model M-24, Biochemical Research and Development Laboratories, Inc.). Filters were washed twice with 3 mL cold Krebs medium and dried. Non-specific [^{3}H]DA uptake was determined in duplicate samples in the presence of 10 μM nomifensine (dopamine uptake inhibitor). Filters were placed into scintillation mixture (Optiphase 'Hisafe' 2, Perkin-Elmer) and radioactivity was determined by scintillation spectrometry.

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