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Synthesis, conformational characteristics and anti-influenza virus A activity of some 2-adamantylsubstituted azacycles

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Abstract

The broad-spectrum antiviral activity of 2-(2-adamantyl)piperidines **11**, **13a**,**b**, and **15**, 3-(2-adamantyl)pyrrolidines **27**, **21a**–**g** and 2-(2-adamantylmethyl)piperidines **30**, **32a**–**c**, and **35a**–**d** was examined. Several compounds in the new series were potent against influenza A H_3N_2 virus. When 1-aminoethyl pharmacophore group of 2-rimantadine **4** (2-isomer of rimantadine) is included into a saturated nitrogen heterocycle, see compound **11**, potency was retained. The diamine derivatives **21e**–**g** and particularly **35a**–**c** possessing three pharmocophoric groups, that is, the adamantyl and the two amine groups, exhibited high potency. The new compounds did not afford specific activity at non-toxic concentrations against any of the other viruses tested. According to NMR spectroscopy and molecular mechanics calculations it is striking that the parent structures **11** and **27** adopt a fixed *trans* conformation around C2—C2′ bond. In the parent amines, which proved to be active compounds, the distance between nitrogen and adamantyl pharmacophoric groups was different; N—C2′ distance is 3.7, 3.8 Å for **27**, **30** and 2.5 Å for **11** suggesting that M2 receptor site can accommodate different in size and orientation lipophilic cages.

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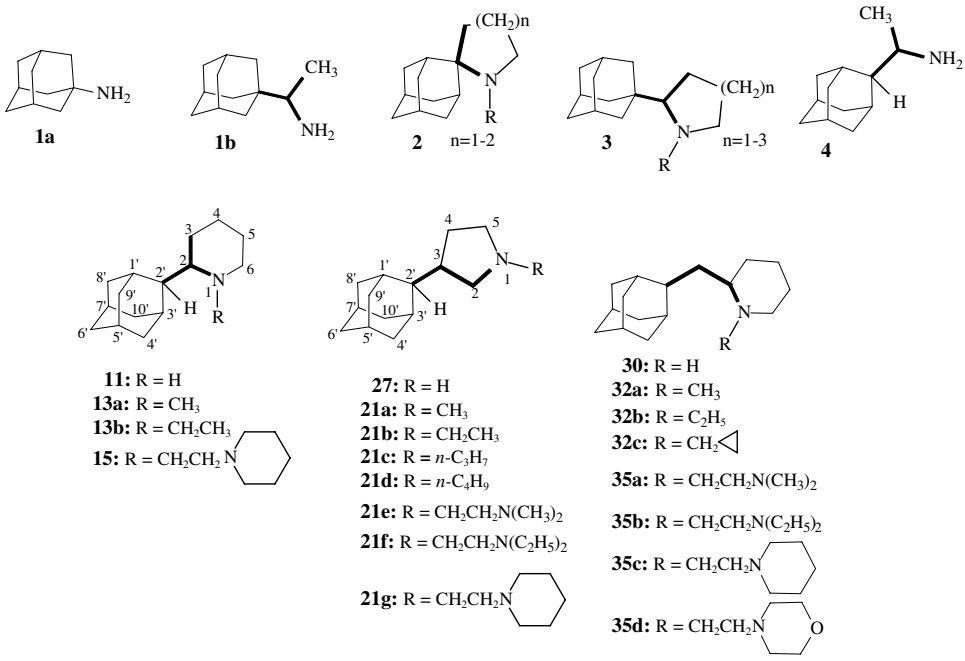
1. Introduction

In the 20th century in Europe influenza A inflicted more casualties than any other infectious disease. The Spanish flu pandemic of 1918 was the most lethal infectious epidemic in the history of mankind, more than doubling the casualty total of the previous infamous leader, the Black Death. Recent epidemics, while not as lethal, are still capable of infecting significant portions of the population (up to at least 10%), resulting in a tremendous amount of temporary debilitation, unsurpassed by any other human disease. In view of the lethal effects of 1997 and the 2003 Asia influenza types, the danger of another major pandemic, as occurred in 1957 and 1968, highlights the need to develop more effective therapies [1].

Amantadine **1a** and rimantadine **1b** (Scheme 1) are anti-influenza A drugs that inhibit virus replication at micromolar concentrations; their protonated form blocks the influenza A M2 ion channel protein [2]. Many aminoadamantanes, potent against influenza virus A, were synthesized in our laboratory during the past 10 years [3,4]. Some interesting results are summarised in the next paragraph.

When the amino group is attached at C-2 of the adamantane nucleus biological potency is retained (see structure **2**, Scheme 1) [4a,4b,4i]. The 2-isomer of rimantadine (2-rimantadine,



Scheme 1. Structures of some aminoadamantane compounds.

4) and some analogs proved to be more potent than rimantadine **1b** [4g]. Recently, we demonstrated that antiviral potency is increased if the 1-aminoethyl pharmacophoric group of rimantadine drug **1b** is included into a pyrrolidine or piperidine ring (compounds **3**: $n = 1$, 2) [4h].

After short reports, [4d,4e] in this paper the antiviral potency of some new azacycles is described. The 2-(2-adamantyl)piperidines **11**, **13a**,**b**, and **15**, the 3-(2-adamantyl)pyrrolidines **27**, **21a**–**g**, and the 2-(2-adamantylmethyl)piperidines **30**, **32a**–**c**, and **35a**–**d**, depicted in Scheme 1, were synthesized and their activity was tested against many viruses. The contribution of a second amine group to the anti-influenza A potency and the effect of including the aminoethyl pharmacophore group of 2-rimantadine **4** into a piperidine ring, as shown for the 2-(2-adamantyl)piperidine **11**, were investigated. In the parent 3-(2-adamantyl)pyrrolidine **27** and the 2-(2-adamantylmethyl)piperidine **30** nitrogen is one carbon further remote from adamantane ring in comparison with compound **11**.

2. Materials and methods

2.1. Chemical synthesis

2.1.1. Materials

Melting points were determined using a Buchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC 200 at 200 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra were recorded on a Brucker AC 200 spectrometer at 50 MHz, using $CDCl_3$ as solvent and TMS as internal standard. Carbon multiplicities were established by the DEPT experiments. The 2D NMR techniques (XHCORR and COSY) were used for the elucidation of the structures of some derivatives. All solvents were carefully dried before used. 1-Methyl-2-pyrrolidinone was commercially available. Microanalyses were carried out by the Service Central de Microanalyse (CNRS) France, and the results obtained had a maximum deviation of ±0.4% from the theoretical value.

*2.1.1.1. 2-(2-Pyridinyl)tricyclo[3.3.1.1 ^{3,7}]decan-2-ol (**6**).* To a stirred solution of 1.6 M *n*-BuLi in hexanes (13.2 mL, 21.1 mmol), a solution of 2-bromopyridine (3.16 g, 20.0 mol) in dry ether (25 mL) was added dropwise at −85 °C under argon atmosphere. The mixture was then warmed to −60 °C and a solution of 2-adamantanone **5** (2.0 g, 13.3 mmol) in dry THF (10 mL) was added dropwise over 30 min. The reaction mixture was allowed to reach slowly room temperature and poured into HCl 10%. The organic layer was separated and the aqueous layer was washed with ether and made alkaline with solid Na_2CO_3. The oily residue was extracted with ether and the combined organic extracts were washed several times with water, dried (Na_2SO_4), and evaporated *in vacuo* to give a dark coloured solid product. After filtration through neutral aluminum oxide using ether as eluent the solid base **6** was obtained (2.5 g, 82%); mp 105–107 °C (ether–*n*-pentane); IR (Nujol): ν(OH) 3360 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.45–1.95 (complex m, 10H, 4eq,5,6,7,8,9eq,10-adamantane H), 2.20–2.51 (d, 2H, $J \sim 12$ Hz, 2H, 4ax,9ax-adamantane H), 2.33 (br s, 1H, OH), 2.65 (s, 2H, 1,3-adamantane H), 7.11 (m, 1H, 5-pyridine H), 7.46 (d, 1H, $J \sim 8$ Hz, 3-pyridine H), 7.65 (td, 1H, $J = 2$, 8 Hz, 4-pyridine H), 8.51 (d, 1H, $J \sim 5$ Hz, 6-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 26.95, 27.28

(5,7-adamantane C), 32.79 (4,9-adamantane C), 34.74 (8,10-adamantane C), 34.90 (1,3-adamantane C), 37.64 (6-adamantane C), 76.99 (2-adamantane C), 120.14 (3-pyridine C), 122.02 (5-pyridine C), 136.58 (4-pyridine C), 149.05 (6-pyridine C), and 164.03 (2-pyridine C). Anal. ($C_{15}H_{19}NO$) C, H. Hydrochloride: mp 197–199 °C (EtOH–Et_2O).

*2.1.1.2. 2-(2-Piperidinyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol (**7**).* A solution of the hydrochloride of 2-(2-pyridinyl)-2-adamantanol **6** (1.0 g, 3.76 mmol) in absolute ethanol (20 mL) was hydrogenated over PtO_2 (60 mg) at 45 Ψ for 8 h. The suspension was filtered to remove the catalyst, and the filtrate was evaporated under reduced pressure. The crude solid hydrochloride was triturated with dry ether and filtered off. The solid material was dissolved in water and the solution was made alkaline with solid Na_2CO_3. The mixture was extracted with ether and the combined organic extracts were dried (Na_2SO_4) and evaporated to give the solid piperidine **7**: yield 860 mg (98%); mp 71–73 °C (*n*-pentane); IR (Nujol): ν(NH), ν(OH) 3480–3180 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.10–1.95 (complex m, 18H, 3,4,5-piperidine H, 1,3,4eq,5,6,7,8,9eq,10-adamantane H), 2.12–2.18 (m, 2H, 4ax,9ax-adamantane H), 2.67 (td, 1H, $J = 12$, 3 Hz, 6ax-piperidine H), 2.0 (br s, 2H, NH, OH), 2.98–3.15 (m, 2H, 2,6eq-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 23.84 (4-piperidine C), 24.59 (5-piperidine C), 25.95 (3-piperidine C), 26.92, 27.19 (5,7-adamantane C), 33.13 (4,9-adamantane C), 34.04 (1,3-adamantane C), 34.14 (8,10-adamantane C), 38.07 (6-adamantane C), 46.91 (6-piperidine C), 59.96 (2-piperidine C), and 74.26 (2- adamantane C). Anal. ($C_{15}H_{25}NO$) C, H. Hydrochloride: mp >250 °C (EtOH–Et_2O).

*2.1.1.3. 2-(Tricyclo[3.3.1.1 ^{3,7}]dec-2-yl)-3,4,5,6- tetrahydropyridine (**10**).* Thionyl chloride (5 mL) in dichloromethane (15 mL) was added dropwise at 0 °C to a stirred solution of 2-(2-piperidinyl)-2-adamantanol **7** (5.35 g, 24.6 mmol) in dichloromethane (60 mL). After stirring at room temperature for 2 h the reaction mixture was refluxed for 5 h. The solvent was evaporated under vacuum to give crude **8**. A solution of KOH (4.0 g, 71.3 mmol) in ethanol (50 mL) was added under ice cooling and the reaction mixture was stirred for 24 h at room temperature under argon, and then refluxed for 3 h. Solvent was evaporated, water was added to the residue and the mixture was extracted with ether. The organic phase was washed with water and extracted with HCl 5%. The acidic aqueous solution was washed with ether and made alkaline with solid Na_2CO_3. The oil formed was extracted with ether and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue obtained was chromatographed on neutral aluminum oxide with ether as eluent to give the oily imine **10**: yield 3.04 g (61%); IR (film): ν(C=N) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.35–1.93 (complex m, 16H, 4,5-piperidine H, 4,5,6,7,8,9eq,10-adamantane H), 2.04 (t, 2H, $J = 7$ Hz, 3-piperidine H), 2.25 (br s, 3H, 1,2,3-adamantane H), 3.49–3.68 (m, 2H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 19.67 (4-piperidine C), 22.16 (5-piperidine C), 27.31 (3-piperidine C), 27.81, 27.94 (5,7-adamantane C), 29.18 (1,3-adamantane C), 32.66, 37.69, 38.84 (4,6,8,9,10-adamantane C), 49.31 (6-piperidine C), 53.09 (2-adamantane C), and 171.21 (2-piperidine C). Picrate: mp 159–161 °C dec (MeOH). Anal. ($C_{21}H_{26}N_4O_7$) C, H.

*2.1.1.4. 2-(Tricyclo[3.3.1.1^{3,7}]dec-2-yl)piperidine (**11**).* $NaBH_4$ (1.10 g, 2.90 mmol) was added portionwise to a solution of tetrahydropyridine **10** (2.12 g, 9.80 mmol) in methanol

(45 mL) at 0 °C, and the reaction mixture was stirred for 5 h at this temperature. The solvent was evaporated and the residue was treated with HCl 10%. The acidic aqueous mixture was washed several times with ether and made alkaline with solid Na_2CO_3. The oil separated was extracted with ether and the combined organic phase was dried (Na_2SO_4) and evaporated under vacuum to afford the oily piperidine **11**: yield 2.02 g (94%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.80–1.0 (m, 1H, 3-piperidine H), 1.20–2.0 (complex m, 21H, 1,3,4,5-piperidine H, adamantane H), 2.48–2.73 (complex m, 2H, 2,6-piperidine H), 2.98–3.16 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 25.0 (4-piperidine C), 26.65 (5-piperidine C), 27.65, 27.75 (5,7-adamantane C), 27.94, 28.37 (1,3-adamantane C), 30.36 (3-piperidine C), 31.92, 32.16 (4,9-adamantane C), 38.13 (6-adamantane C), 38.82, 39.13 (8,10-adamantane C), 47.40 (6-piperidine C), 49.54 (2-adamantane C), and 55.72 (2-piperidine C). Hydrochloride: mp >300 °C dec (EtOH–Et_2O). Picrate: mp 210–212 °C dec (MeOH). Anal. ($C_{21}H_{28}N_4O_7$) C, H.

*2.1.1.5. 1-Methyl-2-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)piperidine (**13a**).* A solution of ethyl chloroformate (1.04 g, 9.30 mmol) in dry ether (15 mL) was added dropwise to a stirred solution of piperidine **11** (1.23 g, 5.62 mmol) and triethylamine (1.85 g, 18.3 mmol) in dry ether (20 mL) under ice cooling. The reaction mixture was stirred at room temperature for 24 h, and then treated with water. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with water, HCl 2%, water and dried (Na_2SO_4). After removal of the solvent the carbamate **12a** was obtained as an oil (1.37 g, 84%; IR film: ν(C=O) 1695 cm^{-1}) and was used without further purification for the preparation of derivative **13a** as follows.

To a stirred suspension of $LiAlH_4$ (1.60 g, 46.3 mmol) in THF (50 mL) was added dropwise to a solution of the carbamate **12a** (1.35 g, 4.63 mmol) in dry THF (20 mL). The reaction mixture was refluxed for 15 h and hydrolyzed with water and NaOH 10% under ice cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and extracted with HCl 5%. The acidic aqueous layer was made alkaline with solid Na_2CO_3 and extracted with ether. The combined ether extracts were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel with ether as eluent to afford the amine **13a**: yield 900 mg (83%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.20–1.97 (complex m, 20H, 3,4,5-piperidine H, 1,2,4,5,6,7,8,9,10-adamantane H), 2.03 (br s, 1H, 3-adamantane H), 2.30 (s, 3H, *N*—CH_3), 2.73–3.09 (complex m, 3H, 2,6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 19.07 (5-piperidine C), 20.19 (4-piperidine C), 24.89 (3-piperidine C), 27.77 (1,3-adamantane C), 28.13, 28.74 (5,7-adamantane C), 31.93 (4,9-adamantane C), 34.67 (*N*—CH_3), 38.33 (6-adamantane C), 39.03, 39.57 (8,10-adamantane C), 45.04 (2-adamantane C), 54.73 (6-piperidine C), and 59.05 (2-piperidine C). Fumarate: mp 195–197 °C dec (EtOH–Et_2O). Picrate: mp 180–182 °C dec (MeOH). Anal. ($C_{22}H_{30}N_4O_7$) C, H.

*2.1.1.6. 1-Ethyl-2-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)piperidine (**13b**).* Amide **12b** was prepared by the procedure used for **12a**, by the reaction of acetyl chloride with piperidine **11** in the presence of triethylamine. The oily residue thus obtained was chromatographed on alkaline aluminum oxide with ether–*n*-hexane 1:1 as eluent to afford the solid compound **12b**: yield 94%; mp 90–92 °C (ether–*n*-pentane); IR (Nujol): ν(C=O) 1655, 1625 cm^{-1}. Anal. ($C_{17}H_{27}NO$) C, H.

The oily *N*-ethylpiperidine **13b** was prepared by the $LiAlH_4$ reduction of acetamide **12b** in THF, using the procedure followed for the preparation of **13a**: yield 74%; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.98 (t, 3H, $J = 6$ Hz, $N{-}CH_2CH_3$), 1.08–1.95 (complex m, 20 H, 3,4,5-piperidine H, 1,2,4,5,6,7,8,9,10-H), 2.03 (br s, 1H, 3-adamantane H), 2.38–2.80 (complex m, 3H, 6-piperidine H, $N{-}CH_2CH_3$), 2.81–2.94 (m, 1H, 2-piperidine H), 2.96–3.12 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.17 ($N{-}CH_2CH_3$), 19.11 (5-piperidine C), 20.06 (4-piperidine C), 22.91 (3-piperidine C), 27.52, 27.80 (1,3-adamantane C), 28.19, 29.02 (5,7-adamantane C), 31.88 (4,9-adamantane C), 38.34 (6-adamantane C), 39.20, 39.64 (8,10-adamantane C), 41.92 ($N{-}CH_2CH_3$), 43.28 (2-adamantane C), 48.03 (6-piperidine C), and 57.12 (2-piperidine C). Fumarate: mp 169–171 °C dec (EtOH–Et_2O). Picrate: mp 164–166 °C dec (MeOH). Anal. ($C_{23}H_{32}N_4O_7$) C, H.

*2.1.1.7. 1-[2-(1-Piperidinyl)ethyl]-2-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)piperidine (**15**).* To a solution of the piperidine **11** (2.03 g, 9.25 mmol) in dichloromethane (40 mL) was added a solution of K_2CO_3 (1.42 g, 10.3 mmol) in water (10 mL). To the vigorously stirred mixture was added dropwise under ice cooling a solution of bromoacetyl chloride (1.61 g, 10.2 mmol) in dichloromethane (20 mL). After stirring for 3 h under ice cooling, the organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were evaporated under vacuum, and the oily residue was dissolved in ether. The ethereal solution was washed successively with Na_2CO_3 10%, water, HCl 3%, water and dried (Na_2SO_4). After solvent evaporation the solid 2-(2-adamantyl)-1-(brom0acetyl)piperidine **12c** was obtained: yield 2.71 g (86%); mp 113–115 °C (ether); IR (Nujol): ν(C=O) 1635 cm^{-1}; Anal. ($C_{17}H_{26}BrNO$) C, H.

To a stirred solution of bromoacetylpiperidine **12c** (3.23 mmol) in dry benzene (10 mL) was added dropwise under ice cooling a solution of piperidine (13.3 mmol) in dry benzene (10 mL). The mixture was stirred for 30 min at 0 °C, and 24 h at room temperature. The solvent was evaporated *in vacuo*, and water was added to the residue. The aqueous mixture was extracted with ether and the combined ether extracts were washed with water and extracted with HCl 3%. The acidic aqueous solution was washed with ether and made alkaline with solid Na_2CO_3. The mixture was extracted many times with ether and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel with ether–*n*-hexane as eluent to afford the solid amide **14**: yield 60%; mp 94–96 °C (ether–*n*-pentane); IR (Nujol): ν(C=O) 1632 cm^{-1}; Anal. ($C_{22}H_{36}N_2O$) C, H.

The oily *N*-piperidinoethyl derivative **15** was prepared by the $LiAlH_4$ reduction of amide **14** in THF, using the procedure followed for the preparation of **13a**: yield 78%; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.10–1.92 (complex m, 26H, $2 \times$ 3,4,5-piperidine H, 1,2,4,5,6,7,8,9,10-adamantane H), 2.10 (br s, 1H, 3-adamantane H), 2.15–2.48 (complex m, 6H, $NCH_2CH_2N(CH_2CH_2)_2C\ H_2$), 2.50–3.01 (complex m, 5H, 2,6-piperidine H, $NCH_2CH_2N(CH_2CH_2)_2CH_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 19.47 (5-piperidine C), 20.45 (4-piperidine C), 22.70 (3-piperidine C), 24.37 ($N(CH_2CH_2)_2CH_2$), 25.94 ($N(CH_2CH_2)_2C\ H_2$), 27.50, 27.738 (1,3-adamantane C), 28.15, 28.95 (5,7-adamantane C), 31.84, 31.90 (4,9-adamantane C), 38.36 (6-adamantane C), 39.14, 39.54 (8,10-adamantane C), 43.31 (2-adamantane C), 46.47 ($NCH_2CH_2N(CH_2CH_2)_2CH_2$), 49.03 (6-piperidine C), 55.12 ($N(CH_2CH_2)_2C\ H_2$), 58.31 (2-piperidine C), and 59.29 ($NCH_2CH_2N(CH_2CH_2)_2CH_2$). Monofumarate: 195–197 °C dec (EtOH–Et_2O). Anal. ($C_{26}H_{42}N_2O_4$) C, H.

*2.1.1.8. General procedure for the preparation of 2-(2-oxopyrrolidin-3-yl)tricyclo[3.3.1.1^{3,7}]decan-2-ols (**18a**)–(**18d**) and (**23**).* To a vigorously stirred solution of 2-pyrrolidinone **16** (10.0 g, 0.12 mol) in dry DMF (40 mL) or dry benzene (80 mL), NaH (3.10 g, 0.13 mol) was added in small portions, and the mixture was heated for 1 h at 60 °C under nitrogen atmosphere. A solution of the suitable alkyliodide (0.13 mol) in the same solvent (10 mL) was added dropwise and the resulting mixture was heated at 80 °C for 3 h (benzene) or 15 h (DMF). When DMF was used as a solvent, brine was added to the reaction mixture; when benzene was used, solvent was first evaporated at ambient temperature and then brine was added. The mixture was extracted many times with ether and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. Fractional distillation of the oily residue gave pure 1-ethyl-2-pyrrolidinone **17b**; yield 42%; bp 95–98 °C (20 mmHg), 1-propyl-2-pyrrolidinone **17c**; yield 36%; bp 102–104 °C (15 mmHg), 1-butyl-2-pyrrolidinone **17d**; yield 33%; bp 126–127 °C (20 mmHg).

1-Trimethylsilyl-2-pyrrolidinone **22** was prepared by refluxing for 4 h of a mixture of 2-pyrrolidinone **16** (26.5 g, 0.311 mol), triethylamine (37.7 g, 0.373 mol), and trimethylchlorosilane (40.5 g, 0.373 mol) in benzene (100 mL). After cooling at ambient temperature the mixture was filtered off and the filtrate was evaporated under vacuum. Fractional distillation of the residue gave pure product; yield 67%; bp 102–104 °C (25 mmHg).

To a stirred solution of dry diisopropylamine (5.05 g, 0.05 mol) in dry ether (30 mL) was added, under an argon atmosphere at −80 °C, a 1.6 M solution of *n*-BuLi in hexanes (23.5 mL, 37.5 mmol). The solution was stirred for 15 min, and then a solution of 1-substituted-2-pyrrolidinone **17a**–**d** or **22** (0.04 mol) in dry THF (10 mL) was added at −80 °C. After stirring for 20 min at the same temperature, a solution of 2-adamantanone **5** (3.76 g, 0.025 mol) in dry THF (45 mL) was added dropwise, and the mixture was allowed to slowly reach room temperature. Stirring was continued for 18 h under argon atmosphere, and the mixture was acidified with HCl 5% under ice cooling. In the case of trimethylsilyl adduct **23**, stirring for 1.5 h was needed in order to hydrolyze the *N*—Si bond. The organic phase was separated and the aqueous phase was extracted many times with ether. The combined organic extracts were dried (Na_2SO_4) and evaporated to give **18a**–**d**, **23**.

*2.1.1.9. 2-(1-Methyl-2-oxopyrrolidin-3-yl)tricyclo[3.3.1.1^{3,7}]decan-2-ol (**18a**).* Recrystallization from ether afforded 5.70 g of pure lactam **18a**: yield 91%; mp 134–135 °C (ether); IR (Nujol): ν(OH) 3401, *ν*(C=O) 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* (ppm) 1.43–2.21 (complex m, 16H, 3,4,5,6,7,8,9,10-adamantane H, 4-H, OH), 2.78 (br s, 4H, CH_3, 1-adamantane H), 3.08 (∼t, 1H, $J \approx 9.6$ Hz, 3-H), 3.20–3.27 (m, 2H, 5-H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ* (ppm) 19.95 (4-C), 26.74, 26.91 (5,7-adamantane C), 29.64 (*N*—CH_3), 32.48, 32.67, 33.97, 34.94 (4,8,9,10-adamantane C), 34.41 (1,3-adamantane C), 38.13 (6-adamantane C), 45.73 (3-C), 47.19 (5-C), 75.09 (2-adamantane C), and 175.20 (C=O). Anal. ($C_{15}H_{23}NO_2$) C, H.

*2.1.1.10. 2-(1-Ethyl-2-oxopyrrolidin-3-yl)tricyclo[3.3.1.1^{3,7}]decan-2-ol (**18b**).* Recrystallization from ether-*n*-pentane afforded 5.52 g of pure lactam **18b**: yield 84%; mp 117–119 °C (ether–*n*-pentane); IR (Nujol): *ν*(OH) 3488, *ν*(C=O) 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* (ppm) 1.04 (*t*, 3H, $J = 7.2$ Hz, CH_3) 1.44–2.20 (complex m, 16H, 3,4,5,6,7,8,9,10-adamantane H, 4-H, OH), 2.78 (br s, 4H, CH_3, 1-adamantane H), 3.07 (∼t, 1H, $J \approx 9.6$ Hz, 3-H), 3.20–3.27 (m, 4H, 5-H, CH_2CH_3); ^{13}C NMR ($CDCl_3$,

50 MHz) δ (ppm) 12.40 (N—CH_2CH_3), 20.0 (4-C), 26.70, 26.90 (5,7-adamantane C), 32.40, 32.60, 33.90, 34.90 (4,8,9,10-adamantane C), 34.30 (1-adamantane C), 34.40 (3-adamantane C), 37.0 (N—CH_2CH_3), 38.10 (6-adamantane C), 44.20 (5-C), 45.90 (3-C), 75.0 (2-adamantane C), and 174.70 (C=O). Anal. ($C_{16}H_{25}NO_2$) C, H.

*2.1.1.11. 2-(2-Oxo-1-propylpyrrolidin-3-yl)tricyclo[3.3.1.1^{3,7}]decan-2-ol (**18c**).* Recrystallization from *n*-pentane afforded 6.58 g of pure lactam: yield 95%; mp 80–81 °C (*n*-pentane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.84 (*t*, $J = 7.4$ Hz, 3H, CH_3), 1.43–2.21 (complex m, 18H, 3,4,5,6,7,8,9,10-adamantane H, 4-H, CH_2CH_3, OH), 2.79 (br s, 4H, CH_3, 1-adamantane H), 3.04–3.29 (m, 5H, 3,5-H, N—CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 11.30 (CH_3), 20.20 (4-C), 20.5 (N—$CH_2CH_2CH_3$), 26.70, 26.90 (5,7-adamantane C), 32.50, 32.70, 34.0, 35.0 (4,8,9,10-adamantane C), 34.40 (1-adamantane C), 34.60 (3-adamantane C), 38.10 (6-adamantane C), 44.0 (N—CH_2), 44.80 (5-C), 46.0 (3-C), 75.0 (2-adamantane C), 175.10 (C=O). Anal. ($C_{17}H_{27}NO_2$) C, H.

*2.1.1.12. 2-(1-Butyl-2-oxopyrrolidin-3-yl)tricyclo[3.3.1.1^{3,7}]decan-2-ol (**18d**).* Chromatography on silica gel afforded 5.53 g of pure lactam: yield 85%; mp 41 °C (*n*-pentane); IR (Nujol): ν(OH) 3459, ν(C=O) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.87 ($\sim t$, $J = 7.4$ Hz, 3H, CH_3), 1.16–1.34 (m, 2H, CH_2CH_3), 1.38–2.21 (complex m, 18H, 3,4,5,6,7,8,9,10-adamantane H, 4-H, N—CH_2CH_2, OH), 2.78 (br s, 1H, 1-adamantane H), 3.03–3.13 (m, 1H, 3-H), 3.18–3.28 (m, 4H, 5-H, N—CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 13.70 (CH_3), 20.0 (CH_2CH_3), 20.20 (4-C), 26.70, 26.90 (5,7-adamantane C), 29.20 (NCH_2CH_2), 32.50, 32.70, 33.90, 35.0 (4,8,9,10-adamantane C), 34.30 (1-adamantane C), 34.60 (3-adamantane C), 38.10 (6-adamantane C), 42.20 (N—CH_2), 44.80 (5-C), 45.90 (3-C), 75.0 (2-adamantane C), 175.0 (C=O). Anal. ($C_{18}H_{29}NO_2$) C, H.

*2.1.1.13. 2-(2-Oxopyrrolidin-3-yl)tricyclo[3.3.1.1^{3,7}] decan-2-ol (**23**).* Chromatography on silica gel with ether–ethyl acetate as an eluent afforded 5.60 g of pure lactam **23**: yield 95%; mp 169–171 °C (acetone); IR (Nujol): ν(NH), ν(OH) 3220–3100, ν(C=O) 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.20–2.31 (complex m, 16H, 3,4,5,6,7,8,9,10-adamantane H, 4-H, OH), 2.75 (br s, 1H, 1-adamantane H), 3.06 ($\sim$t, 1H, $J \approx 9.6$ Hz, 3-H), 3.27 (q, 2H, $J = 8.8$ Hz, 5-H), 6.11 (br s, 1H, *N*H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 22.73 (4-C), 26.75, 26.87 (5,7-adamantane C), 32.51, 32.68, 33.96, 34.95 (4,8,9,10-adamantane C), 34.48 (1,3-adamantane C), 38.12 (6-adamantane C), 40.03 (5-C), 44.73 (3-C), 75.06 (2-adamantane C), and 175.40 (C=O). Anal. ($C_{14}H_{21}NO_2$) C, H.

*2.1.1.14. General procedure for the preparation of 2-[1-(2-dialkylaminoethyl)-2-oxopyrrolidin-3-yl]tricyclo[3.3.1.1^{3,7}]decan-2-ols **18e–g**.* To a stirred solution of 2-pyrrolidinone **16** (10.0 g, 0.12 mol) in dry DMF (40 mL) were added successively NaH (9.40 g, 0.39 mol) and dialkylaminoethylchloride hydrochloride (18.7 g, 0.13 mol). The mixture was heated at 70 °C for 6 h under inert atmosphere, and then poured into an ice-water mixture and extracted many times with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness. Fractional distillation of the resulted oily residue gave pure 1-(2-dialkylaminoethyl)-2-pyrrolidinone **17e–g**.

To a stirred solution of dry diisopropylamine (3.80 g, 37.5 mmol) in dry THF (20 mL) was added, at −80 °C under argon atmosphere, a 2.5 M solution of *n*-BuLi in hexanes (11.2 mL). The solution was stirred for 10 min, and then a solution of 1-(2-dialkylamino-

ethyl)-2-pyrrolidinone **17e–g** (28.0 mmol) in dry THF (20 mL) was rapidly added at −80 °C. After stirring for 20 min at the same temperature a solution of 2-adamantanone **5** (2.85 g, 19.0 mmol) in dry THF (50 mL) was added dropwise, and the mixture was allowed to reach slowly room temperature. Stirring was continued for 12 h under an argon atmosphere and the solvent was removed under vacuum. Water was added and the resulting mixture was extracted many times with ether. The ether phase was washed with water and extracted with HCl 5%. The aqueous phase was made alkaline with solid Na_2CO_3 and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give solid **18e–g**.

*2.1.1.15. 2-[1-(2-Dimethylaminoethyl)-2-oxopyrrolidin-3-yl]tricyclo[3.3.1. $1^{3,7}$]decan-2-ol (**18e**).* Yield 91%; mp 110–112 °C (ether–*n*-pentane); IR (Nujol): ν(OH) 3216, ν(C=O) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.41–2.33 (complex m, 24H, adamantane H, 4-H, *H*CHN(CH_3)$_2$, OH), 2.52–2.66 (m, 1H, HC*H*N(CH_3)$_2$), 2.82–2.93 (m, 1H, HC*H*CH_2N(CH_3)$_2$), 3.04–3.14 (m, 2H, 5-H), 3.37–3.49 (m, 1H, 3-H), 3.86–4.01 (m, 1H, *H*CHCH_2N(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 19.72 (4-C), 27.14 (5,7-adamantane C), 32.76, 32.88, 34.14, 34.48 (4,8,9,10-adamantane C), 34.23 (1-adamantane C), 35.42 (3-adamantane C), 38.35 (6-adamantane C), 39.65 (*C*H_2CH_2N(CH_3)$_2$), 45.12 (CH_3), 45.68 (5-C), 45.99 (3-C), 55.38 (N(CH_3)$_2$), 75.83 (2-C), and 175.60 (C=O). Anal. ($C_{18}H_{30}N_2O_2$) C, H.

*2.1.1.16. 2-[1-(2-Diethylaminoethyl)-2-oxopyrrolidin-3-yl]tricyclo[3.3.1. $1^{3,7}$]decan-2-ol (**18f**).* Yield 91%; mp 79–81 °C (ether–*n*-pentane); IR (Nujol): ν(OH) 3490–3270, ν(C=O) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.97–1.01 (t, 6H, $J = 7$ Hz, CH_3), 1.50–2.67 (complex m, 23H, adamantane H, 4-H, *HCH*N(CH_2CH_3)$_2$, OH), 2.96–3.01 (m, 1H, HC*H*CH_2N(CH_2CH_3)$_2$), 3.11–3.21 (m, 2H, 5-H), 3.43–3.49 (m, 1H, 3-H), 3.82–3.89 (m, 1H, *H*CHCH_2N(CH_2CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 10.34 (CH_3), 19.84 (4-C), 27.06, 27.12 (5,7-adamantane C), 32.70, 32.83, 34.08, 34.64 (4,8,9,10-adamantane C), 34.30 (1-adamantane C), 35.13 (3-adamantane C), 38.30 (6-adamantane C), 39.79 (*C*H_2CH_2N(CH_3)$_2$), 45.63, 47.71 (5-C, *C*$H_2$$CH_3$), 46.0 (3-C), 46.0 (3-C), 49.41 (*C*H_2N(CH_2CH_3)$_2$), 75.79 (2-C), and 175.30 (C=O). Anal. ($C_{20}H_{34}N_2O_2$) C, H.

*2.1.1.17. 2-[2-Oxo-1-[2-(1-piperidinylethyl)pyrrolidin-3-yl]tricyclo[3.3.1. $1^{3,7}$]decan-2-ol (**18g**).* Yield 73%; mp 173–175 °C (dichloromethane–ether); IR (Nujol): ν(OH) 3293 ν(C=O) 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.34–2.79 (complex m, 24H, adamantane H, 4-H, CH_2N(CH_2)$_5$, 3,4,5-piperidine H, OH), 2.45–2.79 (m, 6H, 3-adamantane H,2,6-piperidine H, *H*CHCH_2N(CH_2)$_5$), 3.0–3.12 (m, 2H, 5-H), 3.42–3.54 (m, 1H, 3-H), 4.04–4.26 (m, 1H, *H*CHCH_2N(CH_2)$_5$; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 19.43 (4-C), 24.16 (4-piperidine C), 25.21 (3,5-piperidine C), 27.15, 27.23 (5,7-adamantane C), 32.82, 32.92, 34.03, 34.55 (4,8,9,10-adamantane C), 34.24 (1-adamantane C), 35.23 (3-adamantane C), 38.34 (6-adamantane C), 38.67 (*C*H_2CH_2N(CH_2)$_5$), 45.53 (5-C), 45.97 (3-C), 54.65 (2,6-piperidine C), 55.48 (*C*H_2N(CH_2)$_5$), 76.65 (2-C), and 175.34 (C=O). Anal. ($C_{21}H_{34}N_2O_2$) C, H.

*2.1.1.18. General procedure for the preparation of 1-alkyl- and 1-[2-(dialkylamino)ethyl]-3-(tricyclo[3.3.1.$1^{3,7}$]dec-2-yl)-2-pyrrolidinones **20a–g**.* A solution of *p*-toluenesul-

phonic acid monohydrate (20.5 mmol) in dry benzene (80 mL) was heated to reflux for 1 h using a Dean Stark receiver. To the refluxing solution adamantanol **18a–g** was added (8.2 mmol) and refluxing was continued for the appropriate time (12–26 h for the different derivatives; TLC monitoring). The organic solution was washed with water, NaOH 10%, dried (Na_2SO_4) and evaporated to dryness. The crude solid material was chromatographed on alkaline aluminum oxide using ether as an eluent, to afford pure lactam **19a–g**.

A solution of the adamantyliden lactam **19a–g** (9.90 mmol) in dry ethanol (35 mL) was hydrogenated in the presence of Adams catalyst (100 mg), at ambient temperature, for 15–24 h. The suspension was filtered off to remove the catalyst, and the filtrate was evaporated to dryness to afford lactam **20a–g**.

*2.1.1.19. 1-Methyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20a**).* 1-Methyl-3-(tricyclo [3.3.1.1^{3,7}]dec2-yliden)-2-pyrrolidinone **19a**: yield 92%; mp 116–117 °C (ether–*n*-pentane); IR (Nujol): ν(C=O), ν(C=C) 1669–1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.71–1.91 (complex m, 12H, 4,5,6,7,8,9,10-adamantane H) 2.50 (br s, 1H, 1-adamantane H), 2.59 (~t, 2H, $J \approx 7.0$ Hz, 4-H), 2.85 (s, 3H, CH_3), 3.31 (t, 2H, $J \approx 7.0$ Hz, 5-H), 4.55 (br s, 1H, 3-adamantane H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 22.70 (4-C), 27.80 (5,7-adamantane C), 29.90 (CH_3, 1-adamantane C), 35.90 (3-adamantane C), 36.90 (6-adamantane C), 39.0, 39.30 (4,8,9,10-adamantane C), 45.80 (5-C), 116.80, 157.10 (C=C), 169.60 (C=O). Anal. ($C_{15}H_{21}NO$) C, H.

(***20a***): yield 99%; mp 42–44 °C (ether–*n*-pentane); IR (Nujol): ν(C=O) 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.48–2.18 (complex m, 16H, 1,3,4,5,6,7,8,9,10-adamantane H, 4-H) 2.58–2.70 (m, 2H, 3-H, 2-adamantane H), 2.78 (s, 3H, CH_3), 3.13–3.32 (m, 2H, 5-H), 4.55 (br s, 1H, 3-adamantane H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 23.99 (4-C), 27.51, 27.86 (5,7-adamantane C), 28.80 (1-adamantane C), 29.59 (CH_3), 30.04 (3-adamantane C), 31.62, 31.73 (4,9-adamantane C), 38.21, 38.60 (8,10-adamantane C), 39.14 (6-adamantane C), 41.08 (3-C), 46.19 (2-adamantane C), 47.17 (5-C), and 176.90 (C=O). Anal. ($C_{15}H_{23}NO$) C, H.

*2.1.1.20. 1-Ethyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20b**).* 1-Ethyl-3-(tricyclo[3.3.1.1^{3,7}] dec-2-yliden)-2-pyrrolidinone, **19b**: yield 96%; mp 128–130 °C (ether–*n*-pentane); IR (Nujol): ν(C=O), ν(C=C)1667–1647 cm^{-1}; Anal. ($C_{16}H_{23}NO$) C, H.

(***20b***): yield 98%; mp 41–42 °C (ether–*n*-pentane); IR (Nujol): ν(C=O) 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.10 (~t, 3H, $J = 7.1$ Hz, CH_3), 1.53–1.91 (complex m, 14H, 1,3,4,5,6,7,8,9,10-adamantane H) 2.01–2.16 (m, 2H, 4-H), 2.64–2.71 (m, 2H, 3-H, 2-adamantane H), 3.21–3.34 (m, 4H, 5-H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 12.49 (CH_3), 24.14 (4-C), 27.56, 27.91 (5,7-adamantane C), 28.92 (1-adamantane C), 30.07 (3-adamantane C), 31.69 31.79 (4,9-adamantane C), 36.98 (CH_2CH_3), 38.26, 38.66 (8,10-adamantane C), 39.18 (6-adamantane C), 41.55 (3-C), 44.22 (5-C), 46.16 (2-C), and 176.53 (C=O). Anal. ($C_{16}H_{25}NO$) C, H.

*2.1.1.21. 1-Propyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20c**).* 1-Propyl-3-(tricyclo[3.3.1.1^{3,7}] dec-2-yliden)-2-pyrrolidinone, **19c**: yield 93%; mp 57–58 °C (ether–*n*-pentane); IR (Nujol): ν(C=O), ν(C=C) 1669–1646 cm^{-1}; Anal. ($C_{17}H_{25}NO$) C, H.

(***20c***): Yield 98%; mp 45–46 °C (ether–*n*-pentane); IR (Nujol): ν(C=O) 1689 cm^{-1}; Anal. ($C_{17}H_{27}NO$) C, H.

*2.1.1.22. 1-Butyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20d**).* 1-Butyl-3-(tricyclo[3.3.1.1^{3,7}] dec-2-yliden)-2-pyrrolidinone, **19d**: yield 80%; mp <25 °C; IR (Nujol): ν(C=O), ν(C=C) 1665–1640 cm^{-1}.

(***20d***): Yield 99% (oil); IR (film): ν(C=O) 1687 cm^{-1}.

*2.1.1.23. 1-[2-(Dimethylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20e**).* 1-[2-(Dimethylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yliden)-2-pyrrolidinone, **19e**: yield 83%; mp 91–92 °C (ether–*n*-pentane); IR (Nujol): ν(C=O), ν(C=C) 1668–1639 cm^{-1}; Anal. ($C_{18}H_{28}N_2O$) C, H.

(***20e***): yield quantitative (oil); IR (film): ν(C=O) 1691–1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.55–2.15 (complex m, 16H, 1,3,4,5,6,7,8,9,10-adamantane H), 4-H, 2.26 (s, 6H, $2\times CH_3$), 2.39–2.48 (m, 2H, 2-adamantane H, 3-H), 2.67–2.74 (m, 2H, 5-H), 3.28–3.45 (m, 4H, NCH_2CH_2N); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.27 (4-C), 27.57, 27.92 (5,7-adamantane C), 28.96 (1-adamantane C), 30.08 (3-adamantane C), 31.71 31.80 (4,9-adamantane C), 38.26, 38.67 (8,10-adamantane C), 39.20 (6-adamantane C), 40.57 ($NCH_2CH_2NMe_2$), 41.36 (3-C), 45.38 (5-C), 45.50 (CH_2NMe_2), 46.13 (2-adamantane C), 56.69 ($2\times CH_3$), and 179.30 (C=O). Picrate: mp 177–179 °C (MeOH–ether). Anal. ($C_{24}H_{33}N_5O_8$) C, H.

*2.1.1.24. 1-[2-(Diethylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20f**).* 1-[2-(Diethylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yliden)-2-pyrrolidinone, **19f**: yield 87%; mp 60–62 °C (ether–*n*-pentane); IR (Nujol): ν(C=O), ν(C=C) 1670–1640 cm^{-1}; Anal. ($C_{20}H_{32}N_2O$) C, H.

20f: yield quantitative (oil); IR (film): ν(C=O) 1686 cm^{-1}; Fumarate: mp 109–111 °C (EtOH–Et_2O). Anal. ($C_{24}H_{38}N_2O_5$) C, H.

*2.1.1.25. 1-[2-(Piperidino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**20g**).* 1-[2-(Piperidino) ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yliden)-2- pyrrolidinone **19g**: yield 79%; mp 108–110 °C (ether–*n*-pentane); IR (Nujol): ν(C=O), ν(C=C) 1666–1648 cm^{-1}; Picrate: mp 162–164 °C (MeOH–Et_2O). Anal. ($C_{27}H_{35}N_5O_8$) C, H.

(***20g***): yield quantitative; IR (Nujol): ν(C=O) 1675 cm^{-1}; mp 108–110 °C (ether–*n*-pentane). Anal. ($C_{21}H_{34}N_2O$) C, H.

*2.1.1.26. 3-(Tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidinone (**26**).* To a stirred solution of adamantanol **23** (2.50 g, 11.0 mmol) in chloroform (35 mL) was added dropwise $SOCl_2$ (6.30 g, 53.0 mmol), distilled over quinoline and $CaCO_3$ (300 mg, 3.0 mmol). The mixture was stirred at room temperature for 2 h, refluxed for 3 h and then cooled at 0 °C and filtered off. The filtrate was evaporated under vacuum, and water was added to the solid residue. The mixture was extracted with chloroform and the combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The resulted solid residue (1.47 g) was treated with MeONa/MeOH solution (1.26 g Na was added to 60 mL of dry methanol). After treatment, solvent was removed under reduced pressure, water was added and the mixture was extracted many times with chloroform. The organic extracts were washed with water, dried and evaporated to afford the solid unsaturated lactam **25** (1.26 g, 53%); mp 247–249 °C (CH_2Cl_2–Et_2O); IR (Nujol): ν(NH) 3200–3073, ν(C=O) 1681, ν(C=C)1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.73–1.90 (complex m, 12H, 4,5,6,7,8,9,10-adamantane

H), 2.52 (s, 1H, 1-adamantane H), 2.69 (t, 2H, $J = 7.0$ Hz, 4-H), 3.33 (t, 2H, $J = 7.0$ Hz, 5-H), 4.45 (s, 1H, 3-adamantane H), 6.61 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 25.34 (4-C), 27.69 (5,7-adamantane C), 30.04 (1-adamantane C), 36.06 (3-adamantane C), 36.82 (6-adamantane C), 38.63 (5-C), 38.96, 39.28 (4,8,9,10-adamantane C), 116.17, 158.28 (C=C), and 173.01 (C=O). Anal. ($C_{14}H_{19}NO$) C, H.

Compound **25** was hydrogenated in the presence of Adams catalyst—using the same procedure described for the preparation of lactams **20a**–**g**—to afford pyrrolidinone **26**: yield quantitative; mp 200–201 °C (CH_2Cl_2–Et_2O); IR (Nujol): ν(NH) 3190, ν(C=O) 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$,400 MHz) δ (ppm) 1.54–2.03 (complex m, 15H, 1,3,4,5,6,7,8,9,10-adamantane H, 4-H) 2.17–2.24 (m, 1H, 4-H), 2.59–2.66 (m, 2H, 3-H, 2-adamantane H), 3.24–3.35 (m, 2H, 5-H), 6.59 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 26.70 (4-C), 27.50, 27.80 (5,7-adamantane C), 28.92 (1-adamantane C), 30.07 (3-adamantane C), 31.58, 31.74 (4,9-adamantane C), 38.18, 38.63 (8,10-adamantane C), 39.11 (6-adamantane C), 40.03 (5-C), 40.47 (2-adamantane C), 45.58 (3-C), and 181.08 (C=O). Anal. ($C_{14}H_{21}NO$) C, H.

*2.1.1.27. General procedure for the preparation of 1-alkyl- and 1-[2-(dialkylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)pyrrolidines (**21a**–**g**) and (**27**).* To a stirred suspension of $LiAlH_4$ (0.59 g, 15.0 mmol) in dry THF (25 mL) was added dropwise to a solution of the lactam **20a**–**g** or **26** (3.9 mmol) in dry THF (30 mL). The reaction mixture was refluxed for 25 h, and then hydrolyzed with water and NaOH (10%) under ice cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was concentrated in *vacuo*. The residue was dissolved in ether and extracted with HCl 5%. The aqueous layer was made alkaline with solid Na_2CO_3 and extracted with ether. The combined ether extracts were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel with ether as an eluent to give the oily pyrrolidine **21a**–**g** or **27**.

*2.1.1.28. 1-Methyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)pyrrolidine (**21a**).* Yield 89% (oil); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.21–1.87 (complex m, 17H, adamantane H, 4-H), 1.91–2.01 (m, 1H, 2-H), 2.23–2.34 (m, 4H, 5-H, CH_3), 2.42–2.59 (m, 1H, 3-H), 2.65–2.85 (m, 2H, 2,5-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.72, 28.10 (5,7-adamantane C), 29.64 (4-C), 30.23, 31.03 (1,3-adamantane C), 31.60, 31.68 (4,9-adamantane C), 38.37 (6-adamantane C), 38.87 (3-C), 39.12 (8,10-adamantane C), 42.46 (CH_3), 50.03 (2-adamantane C), 56.04 (5-C), 61.25(2-C). Hydrochloride: mp 223–225 °C (EtOH–Et_2O); Picrate: mp 157–159 °C (MeOH). Anal. ($C_{21}H_{28}N_4O_7$) C, H.

*2.1.1.29. 1-Ethyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)pyrrolidine (**21b**).* Yield 86% (oil); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.06 (t, 3H, $J = 7.0$ Hz, CH_3), 1.34–1.97 (complex m, 18H, adamantane H, 2,4-H), 2.24–2.48 (m, 4H, 5-H, 3-H, CH_2CH$_3$), 2.75–2.91 (m, 2H, 2,5-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 13.58 (CH_3), 27.63, 28.0 (5,7-adamantane C), 28.80 (4-C), 30.23, 30.95 (1,3-adamantane C), 31.60 (4,9-adamantane C), 38.12 (3-C), 38.26 (6-adamantane C), 39.0 (8,10-adamantane C), 49.93 (2-adamantane C), 50.40 (CH_2CH_3), 53.47 (5-C), 58.72 (2-C). Hydrochloride: mp 210–211 °C (EtOH–Et_2O); Picrate: mp 163–165 °C (MeOH). Anal. ($C_{22}H_{30}N_4O_7$) C, H.

*2.1.1.30. 1-Propyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)pyrrolidine (**21c**).* Yield 75% (oil); Hydrochloride: mp 201–203 °C (EtOH–Et_2O); Picrate: mp 138–140 °C (MeOH). Anal. ($C_{23}H_{32}N_4O_7$) C, H.

*2.1.1.31. 1-Butyl-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)pyrrolidine (**21d**).* Yield 72% (oil); Hydrochloride: mp 218–220 °C (EtOH–Et_2O); Picrate: mp 106–108 °C (MeOH). Anal. ($C_{24}H_{34}N_4O_7$) C, H.

*2.1.1.32. 1-[2-(Dimethylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidine (**21e**).* Yield 83% (oil); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.36–1.99 (complex m, 18H, adamantane H, 2,4-H), 2.24 (br s, 6H, $2 \times CH_3$), 2.30–2.38 (m, 1H, 5-H), 2.42–2.55 (m, 4H, NCH_2CH_2N), 2.57–2.64 (m, 1H, 3-H), 2.85–2.94 (m, 2H, 2,5-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.72, 28.09 (5,7-adamantane C), 28.91 (4-C), 30.31 (1-adamantane C), 31.01 (3-adamantane C), 31.64 (4,9-adamantane C), 38.19 (3-C), 38.36 (6-adamantane C), 39.11 (8,10-adamantane C), 45.85 (CH_3), 50.05 (2-adamantane C), 54.24 (5-C), 54.87, 58.56 ($NCH_2CH_2NMe_2$), 59.62 (2-C). Difumarate: mp 218–220 °C (EtOH–Et_2O). Anal. ($C_{26}H_{40}N_2O_8$) C, H.

*2.1.1.33. 1-[2-(Diethylamino)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidine (**21f**).* Yield 80% (oil); Difumarate: mp 142–144 °C (EtOH–Et_2O). Anal. ($C_{28}H_{44}N_2O_8$) C, H.

*2.1.1.34. 1-[2-(1-Piperidinyl)ethyl]-3-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-pyrrolidine (**21g**).* Yield 86% (oil); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.32–1.99 (complex m, 24H, adamantane H, 2,4-H, 3,4,5-piperidine H), 2.31–2.93 (m, 12H, 2,5-H, 3-H, NCH_2CH_2N, 2,6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.30 (4-piperidine C), 25.89 (3,5-piperidine C), 27.73, 28.10 (5,7-adamantane C), 28.92 (4-C), 30.32 (1-adamantane C), 31.02 (3-adamantane C), 31.64, 31.70 (4,9-adamantane C), 38.21 (3-C), 38.37 (6-adamantane C), 39.11 (8,10-adamantane C), 50.05 (2-adamantane C), 54.14 (5-C), 54.31 ($NCH_2CH_2NC_5H_{10}$), 55.04 (2,6-piperidine C), 58.29 ($NCH_2CH_2NC_5H_{10}$), 59.61 (2-C). Difumarate: mp 212–214 °C (EtOH–Et_2O). Anal. ($C_{29}H_{44}N_2O_8$) C, H.

*2.1.1.35. 3-(Tricyclo[3.3.1.1^{3,7}]dec-2-yl)pyrrolidine (**27**).* Yield 68% (oil); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.16–1.97 (complex m, 17H, adamantane H, 4-H), 2.17–2.46 (m, 2H, 2,3-H), 2.82–3.26 (m, 3H, 2,5-H), 4.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.73, 28.05 (5,7-adamantane C), 30.67 (4-C), 31.03, 31.30 (1,3-adamantane C), 31.76 (4,9-adamantane C), 38.34 (6-adamantane C), 39.08, 39.13 (8,10-adamantane C), 40.47 (3-C), 46.19 (5-C), 49.54 (2-adamantane C), 50.98 (2-C). Fumarate: mp 145–146 °C (EtOH–Et_2O); Anal. ($C_{18}H_{27}NO_4$) C, H.

*2.1.1.36. 2-(2-Pyridinylmethyl)tricyclo[3.3.1.1^{3,7}]decane-2-ol (**28**).* To a stirred solution of 2-picoline (3.1 g, 33.3 mmol) in dry THF (25 mL) cooled at −20 °C was added dropwise under argon atmosphere, a 2.5 M solution of *n*-BuLi in hexanes (13.4 mL, 33.3 mmol) during a 45 min period. The reaction mixture was left to reach ambient temperature and a solution of 2-adamantanone **5** (5 g, 33.3 mmol) in dry THF (18 mL) was added under vigorous stirring in 15 min. The reaction mixture was stirred for 2 h, and hydrolysed with water. The organic layer was separated and the aqueous was extracted with ether. The combined organic extracts were evaporated in vacuo and the oily residue was dissolved

in ether. The ether solution was washed with water and extracted with HCl (5%). The acidic aqueous phase was made alkaline with solid Na_2CO_3 and extracted with ether. The combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated to give 5.5 g of **28** as a yellow solid: yield 93%; mp 84–85 °C (n-pentane); IR (Nujol): ν(OH) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.40–1.93 (complex m, 12H, 4,5,6,7,8,9,10-adamantane H), 2.30 (d, 2H, 1,3-adamantane H), 3.11 (s, 1H, C*H*$_2$), 6.04 (br s, 1H, OH), 7.10–7.14 (m, 2H, 3,5-pyridine H), 7.54–7.63 (m, 1H, 4-pyridine H), 8.5 (~t, 1H, 6-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.38, 27.42 (5,7-adamantane C), 32.77 (4,9-adamantane C), 34.66 (8,10-adamantane C), 37.23 (1,3-adamantane C), 38.44 (6-adamantane C), 43.63 (CH_2), 75.46 (2-adamantane C), 121.31, 124.43 (3,5-pyridine C), 136.70 (4-pyridine C), 148.41 (6-pyridine C), and 159.65 (2-pyridine C). Anal. ($C_{16}H_{21}NO$) C, H.

*2.1.1.37. 2-(Tricyclo[3.3.1.1^{3,7}]dec-2-ylidenmethyl)pyridine (**29**).* A mixture of alcohol **28** (1.78 g, 7.31 mmol) and *p*-TSA (3.36 g, 17.6 mmol) in dry benzene (50 mL) was refluxed using a Dean-Stark receiver for 15 h. The solution was poured to NaOH (10%), the organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were extracted with HCl (5%) and the aqueous solution was made alkaline with solid Na_2CO_3. The mixture was extracted with ether, the ether solution was dried (Na_2SO_4) and evaporated to dryness. The obtained residue was chromatographed on alkaline aluminum oxide with ether–hexane (1:2) as the eluent to give pure **29** (1.52 g, 93%): mp 43–44 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.85–1.96 (m, 12H, 4,5,6,7,8,9,10-adamantane H), 2.50 (br s, 1H, 1-adamantane H), 3.56 (br s, 1H, 3-adamantane H), 6.22 (br s, 1H, =CH), 7.0 (q, 1H, M region, AMXY, $J_{AM} = 4.8$ Hz, $J_{MX} = J_{XY} = 7.6$ Hz, 5-pyridine H), 7.10 (d, 1H, Y region, AMXY, $J_{MX} = J_{XY} = 7.6$ Hz, 3-pyridine H), 7.50 (t, 1H, X region, AMXY, $J_{MX} = J_{XY} = 7.6$ Hz, 4-pyridine H), 8.50 (d, 1H), 7.10–7.14 (m, 2H, 3,5-pyridine H), 7.54–7.63 (m, 1H, 4-pyridine H), 8.50 (d, 1H, A region, AMXY, $J_{AM} = 4.8$ Hz, 6-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 28.21 (5,7-adamantane C), 32.33 (3-adamantane H), 37.08 (4,9-adamantane C), 38.95 (8,10-adamantane C), 39.89 (6-adamantane C), 41.24 (1-adamantane C), 117.49 (=CH), 120.34 (5-pyridine C), 123.56 (3-pyridine C), 135.75 (4-pyridine C), 149.18 (6-pyridine C), 156.01 (2-adamantane C), 157.38 (2-pyridine C). Hydrochloride: mp 173–175 °C (EtOH–Et_2O). Anal. ($C_{16}H_{20}NCl$) C, H.

*2.1.1.38. 2-(Tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**30**).* A solution of 2-(2-adamantylidenemethyl)pyridine **29** hydrochloride (1.52 g, 5.8 mmol) in absolute ethanol (60 mL) was hydrogenated over PtO_2 (100 mg) under a pressure of 45 Ψ for 8 h. The suspension was filtered to remove the catalyst, and the filtrate was evaporated under reduced pressure. The solid crude hydrochloride was treated with dry ether and filtered off. The solid material was dissolved in water and the solution was made alkaline with solid Na_2CO_3. The mixture was extracted with ether and the combined organic extracts were dried (Na_2SO_4) and evaporated to give 1.53 g of piperidine **30**: yield 98%; IR (film): ν(NH) 3280 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.06–1.84 (complex m, 24H, C*H*$_2$, 1,3,4,5-piperidine H, adamantane H), 2.42–2.44 (m, 1H, 6-piperidine H), 2.58 (t, 1H, 2-piperidine H), 3.02 (d, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.97 (5-piperidine C), 26.68 (4-piperidine C), 28.03, 28.19 (1,3-adamantane C), 29.68 (7-adamantane C), 31.59 (5-adamantane C), 31.63 (3-piperidine C), 31.76 (CH_2), 32.49, 33.50 (4,9-adamantane C), 38.35 (6-adamantane C), 39.22, 40.50 (8,10-adamantane C),

40.32 (2-adamantane C), 47.27 (6-piperidine C), and 54.28 (2-piperidine C). Hydrochloride: mp >250 °C (EtOH–Et_2O). Picrate: 161–164 °C (MeOH–Et_2O). Anal. ($C_{22}H_{30}N_4O_7$) C, H.

*2.1.1.39. 1-Methyl-2-(tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**32a**).* To a stirred solution of piperidine **30** (750 mg, 3.21 mmol) and triethylamine (1.05 g, 10 mmol) in dry ether (20 mL) was added dropwise under ice cooling a solution of ethyl chloroformate (590 mg, 5.4 mmol) in dry ether (15 mL). The mixture was stirred at room temperature for 3 h and poured into water. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with water, HCl (5%), water and dried (Na_2SO_4). After removal of the solvent the carbamate **31a** [IR (film): ν(C=O) 1695 cm^{-1}] was obtained as an oil (900 mg, 92%) which was used without further purification for the preparation of derivative **32a** as follows.

To a stirred suspension of $LiAlH_4$ (0.60 g, 15.0 mmol) in dry THF (40 mL) was added dropwise a solution of the carbamate **31a** (3 mmol) in dry THF (10 mL). The reaction mixture was refluxed for 15 h and then hydrolyzed with water and NaOH (10%) under ice cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and extracted with HCl (5%). The aqueous layer was made alkaline with solid Na_2CO_3 and extracted with ether. The combined ether extracts were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silical gel with ether as an eluent to give amine **32a** as an oil: yield 75%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.04–2.15 (complex m, 25H, AdCH_2, 2,3,4,5,6-piperidine H, adamantane H), 2.25 (s, 3H, CH_3), 2.80 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.22 (5-piperidine C), 25.84 (4-piperidine C), 27.93, 28.15 (1,3-adamantane C), 30.95 (7-adamantane C), 31.39 (5-adamantane C), 31.44 (3-piperidine C), 31.85 (Ad*C*H_2), 33.46, 35.36 (4,9-adamantane C), 38.35 (6-adamantane C), 39.11, 39.31 (8,10-adamantane C), 41.04 (NCH_3), 43.11 (2-adamantane C), 57.02 (6-piperidine C), and 62.32 (2-piperidine C). Hydrochloride: 231–233 °C (EtOH–Et_2O). Anal. ($C_{17}H_{30}NCl$) C, H.

*2.1.1.40. 1-Ethyl-2-(tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**32b**).* To a stirred solution of piperidine **30** (730 mg, 3.13 mmol) and triethylamine (1.05 g, 10 mmol) in dry ether (30 mL) was added dropwise under ice cooling a solution of acetyl chloride (1.02 g, 18.0 mmol) in dry ether (20 mL). The mixture was stirred at room temperature for 8 h and poured into water. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with water, HCl (5%), water and dried (Na_2SO_4). The solvent was evaporated and the residue was filtered through alkaline alumina with ethyl acetate as an eluent. After removal of the solvent the amide **31b** (IR film: ν(C=O) 1640 cm^{-1}) was obtained as an oil (770 mg, 89%) which was used without further purification for the preparation of derivative **32b**.

Compound **32b** was prepared by the $LiAlH_4$ reduction of the corresponding amide **31b** using the same procedure followed for the preparation of **32a**: yield 80%;^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.98 (t, 3H, A_3X_2, $J_{AX} = 7$ Hz, NCH_2CH_3), 1.07–1.95 (complex m, 23 H, AdCH_2, 3,4,5-piperidine H, adamantane H), 2.13–2.27 (m, 3H, 6-piperidine H, NCH_2CH_3), 2.38–2.55 (m, 1H, 2-piperidine H), 2.62–2.80 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 10.84 (CH_3), 23.36 (5-piperidine C), 25.58 (4-piperidine C), 27.95, 28.15 (1,3-adamantane C), 30.73 (7-adamantane C), 30.98 (5-adamantane C),

31.61 (3-piperidine C), 31.88 (Ad*C*H_2), 33.17, 33.54 (4,9-adamantane C), 38.33 (6-adamantane C), 39.14, 39.36 (8,10-adamantane C), 41.26 (2-adamantane C), 47.12 (N*C*H_2CH$_3$), 51.03 (6-piperidine C), and 57.87 (2-piperidine C). Fumarate: 136–139 °C (EtOH–Et_2O). Anal. ($C_{22}H_{35}NO_4$) C, H.

*2.1.1.41. 1-Cyclopropylmethyl-2-(Tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**32c**).* To a stirred solution of piperidine **30** (850 mg, 3.64 mmol) and triethylamine (1.90 g, 18.8 mmol) in dry THF (20 mL) was added dropwise under ice cooling a solution of cyclopropanecarbonylchloride (1.26 g, 12.0 mmol) in dry THF (10 mL). The mixture was stirred at room temperature for 4 h and heated at 60 °C for 30 min. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated to dryness. The residue obtained was dissolved in ether and the organic solution was washed with HCl (5%), water, NaOH (5%), water and dried (Na_2SO_4). The solvent was evaporated and the residue was filtered through alkaline alumina with ether as an eluent. After removal of the solvent the amide **31c** [IR (film): ν(C=O) 1635 cm^{-1}] was obtained as an oil (900 mg, 82%) which was used without further purification for the preparation of derivative **32c**.

Compound **32c** was prepared by the $LiAlH_4$ reduction of the corresponding amide **31c** using the same procedure followed for the preparation of **32a**: yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.15–0.25 (m, 2H, 2,3-cyclopropane H), 0.55–0.65 (m, 2H, 2,3-cyclopropane H), 0.92–1.0 (m, 1H, 1-cyclopropane H), 1.30–2.0 (complex m, 23 H, Ad*C*H_2, 3,4,5-piperidine H, adamantane H), 2.33–2.50 (m, 3H, 6-piperidine H, $CH_2CH(CH_2)_2$), 2.65 (q, 1H, 2-piperidine H), 3.12–3.20 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 4.01, 4.12 (2,3-cyclopropane C), 8.24 (1-cyclopropane C), 23.51 (5-piperidine C), 25.28 (4-piperidine C), 27.95, 28.16 (1,3-adamantane C), 30.64 (7-adamantane C), 31.11 (5-adamantane C), 31.64 (3-piperidine C), 31.89 (Ad*C*H_2), 33.44, 34.02 (4,9-adamantane C), 38.35 (6-adamantane C), 39.14, 39.35 (8,10-adamantane C), 41.28 (*C*H_2CH(CH$_2$)$_2$), 52.14 (2-adamantane C), 58.49 (6-piperidine C), and 59.07 (2-piperidine C). Fumarate: 158–160 °C (EtOH–Et_2O). Anal. ($C_{24}H_{37}NO_4$) C, H.

*2.1.1.42. 1-(2-Dimethylaminoethyl)-2-(tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**35a**).* To a solution of piperidine **30** (3.2 g, 13.7 mmol) in dichloromethane (50 mL) was added a solution of K_2CO_3 (1.99, 14.4 mmol) in water (15 mL). To the vigorously stirred mixture was added dropwise under ice cooling a solution of bromoacetyl chloride (2.30 g, 14.4 mmol) in dichloromethane (20 mL). After stirring for 3 h under ice cooling, the organic phase was separated and the aqueous was extracted with dichloromethane. The combined organic extracts were evaporated under vacuum and the oil residue was dissolved in ether. The ether solution was washed with Na_2CO_3 (10%), water, HCl (5%), water, brine and dried (Na_2SO_4). After removal of the solvent the amide **33** [IR (film): ν(C=O) 1650, 1660 cm^{-1}] was obtained as an oil (4.5 g, 93%) which was used without further purification for the preparation of derivatives **34a**–**d**.

To a stirred solution of *N*-bromoacetylpiperidine **33** (1.50 mg, 4.2 mmol) in dry benzene (15 mL) was added dropwise under ice cooling a 15% solution of dimethylamine (16.9 mmol) in benzene. The mixture was stirred under ice cooling for 30 min and 24 h at room temperature. The solvent was evaporated *in vacuo* and water was added to the residue. The aqueous mixture was extracted with ether and the combined ether extracts were washed with water and extracted with HCl (5%). The resulted acidic aqueous solu-

tion was washed with ether and made alkaline with solid Na_2CO_3. The mixture was extracted many times with ether and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on alkaline alumina with ether as an eluent. After removal of the solvent amide **34a** was obtained as an oil (1.18 g, 89%), [IR (film): ν(C=O) 1640 cm^{-1}]. Picrate: 158–160 °C (MeOH–Et_2O). Anal. ($C_{26}H_{37}N_5O_8$) C, H.

To a stirred suspension of $LiAlH_4$ (0.59 g, 15.0 mmol) in dry THF (25 mL) was added dropwise a solution of the amide **34a** (3 mmol) in dry THF (30 mL). The reaction mixture was refluxed for 20 h and then hydrolyzed with water and NaOH (10%) under ice cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and extracted with HCl (5%). The aqueous layer was made alkaline with solid Na_2CO_3 and extracted with ether. The combined ether extracts were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silical gel with ether as an eluent to give dimethylaminoethylpiperidine **35a** as an oil: yield 80%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.12–1.90 (complex m, 23H, AdCH_2, 3,4,5-piperidine H, adamantane H), 2.22 (s, 6H, Me_2N), 2.24–2.52 (m, 5H, NCH_2CH_2N, 6-piperidine H), 2.70–2.87 (m, 2H, 2,6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 23.02 (5-piperidine C), 25.11 (4-piperidine C), 27.87, 28.10 (1,3-adamantane C), 30.30 (7-adamantane C), 30.98 (5-adamantane C), 31.58 (3-piperidine C), 31.81 (AdCH_2), 33.37, 33.42 (4,9-adamantane C), 38.27 (6-adamantane C), 39.07, 39.27 (8,10-adamantane C), 41.26 (2-adamantane C), 45.95 ($2\times CH_3$), 51.61 ($NCH_2CH_2NMe_2$), 52.04 (6-piperidine C), 57.12 ($NCH_2CH_2NMe_2$), 59.91 (2-piperidine C). Difumarate: 128–131 °C (EtOH–Et_2O). Anal. ($C_{28}H_{44}N_2O_8$) C, H.

*2.1.1.43. 1-(2-Diethylaminoethyl)-2-(tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**35b**).* Amide **34b** was obtained as an oil using the same procedure described for the preparation of compound **34a**: yield 87%; [IR (film): ν(C=O) 1640 cm^{-1}]; Picrate: 178–180 °C (MeOH–Et_2O). Anal. ($C_{28}H_{41}N_5O_8$) C, H.

Compound **35b** was prepared by the $LiAlH_4$ reduction of the corresponding amide **34b** using the same procedure followed for the preparation of **35a**: yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (t, 6H, $N(CH_2CH_3)$), 1.15–1.90 (complex m, 23H, AdCH_2, 3,4,5-piperidine H, adamantane H), 2.28–2.62 (complex m, 9H, NCH_2CH_2N, $N(CH_2CH_3)_2$, 6-piperidine H), 2.71–2.78 (m, 1H, 2-piperidine H), 2.80–2.88 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 11.74, 23.11, 25.19, 27.94, 28.16, 30.37, 31.12, 31.66, 31.86, 33.36, 33.61, 38.33, 39.13, 39.33, 41.33, 47.57, 50.65, 51.71, 52.22, and 59.0. Difumarate: 123–125 °C (EtOH–Et_2O). Anal. ($C_{30}H_{48}N_2O_8$) C, H.

*2.1.1.44. 1-[2-(1-Piperidinyl)ethyl]-2-(tricyclo[3.3.1. 1^{3,7}]dec-2-ylmethyl)piperidine (**35c**).* Amide **34c** was obtained as solid product using the same procedure described for the preparation of compound **34a**: yield 80%; mp 105–107 °C (Et_2O–*n*-pentane); IR film: ν(C=O) 1630, 1650 cm^{-1}; Anal. ($C_{23}H_{38}N_2O$) C, H.

Compound **35c** was prepared by the $LiAlH_4$ reduction of the corresponding amide **34c** using the same procedure followed for the preparation of **35a**: yield 75%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.14–1.88 (complex m, 29H, CH_2, $2\times$3,4,5-piperidine H, adamantane H), 2.25–2.61 (complex m, 9H, NCH_2CH_2N, 2,6-piperidineethyl H, 6-adamantylmethylpiperidine H), 2.70–2.83 (m, 2H, 2,6-adamantylmethylpiperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 15.25, 23.05, 24.37, 25.16, 25.95, 27.95, 28.19, 30.23, 31.08,

31.68, 31.88, 33.43, 38.35, 39.14, 39.36, 41.31, 50.70, 51.99, 55.20, 56.91, and 58.82. Difumarate: 160–162 °C (EtOH–Et_2O). Anal. ($C_{31}H_{48}N_2O_8$) C, H.

*2.1.1.45. 1-[2-(1-Morpholinyl)ethyl]-2-(tricyclo[3.3.1.1^{3,7}]dec-2-ylmethyl)piperidine (**35d**).* Amide **34d** was obtained as solid product using the same procedure described for the preparation of compound **34a**: yield 80%; mp 124–126 °C (ether–*n*-pentane); IR Film: ν(C=O) 1630 cm^{-1}; Anal. ($C_{22}H_{36}N_2O_2$) C, H.

Compound **35d** was prepared by the $LiAlH_4$ reduction of the corresponding amide **34d** using the same procedure followed for the preparation of **35a**: yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.13–1.88 (complex m, 23H, AdCH_2, 3,4,5-piperidine H, adamantane H), 2.27–2.64 (complex m, 9H, NCH_2CH_2N, 3,5-morpholine H, 6-piperidine H), 2.70–2.85 (m, 2H, 2,6-piperidine H), 3.71 (t, 4H, 2,6-morpholine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 23.05, 24.37, 25.16, 25.95, 27.95, 28.19, 30.23, 31.08, 31.68, 31.88, 33.43, 38.35, 39.14, 39.36, 41.31, 50.70, 51.99, 55.20, 56.91, and 58.82. Monofumarate: 163–165 °C (EtOH–Et_2O). Anal. ($C_{26}H_{42}N_2O_5$) C, H.

2.2. NMR spectroscopy—molecular mechanics calculations

NMR spectra for compounds **11**, **27**, and **30** and their protonated forms **11**$^+$ **H**, **27**$^+$**H**, and **30**$^+$**H** were recorded on a Bruker DRX 400 MHz spectrometer. The COSY and phase sensitive NOESY spectra were run using a recycling delay of 1.5–2 s; the mixing time for the NOESY spectra was 1 s.

Molecular mechanics were performed using MM+[5] force field provided by the program Hyperchem [6]. Molecular mechanics is the method of choice to reproduce conformational energies consistent with the experimental results for saturated cyclic amines [7]. The minima were located using conjugate gradient and Newton–Raphson algorithms and an energy gradient tolerance of 0.001 kcal mol^{-1} Å^{-1}.

2.3. Virology

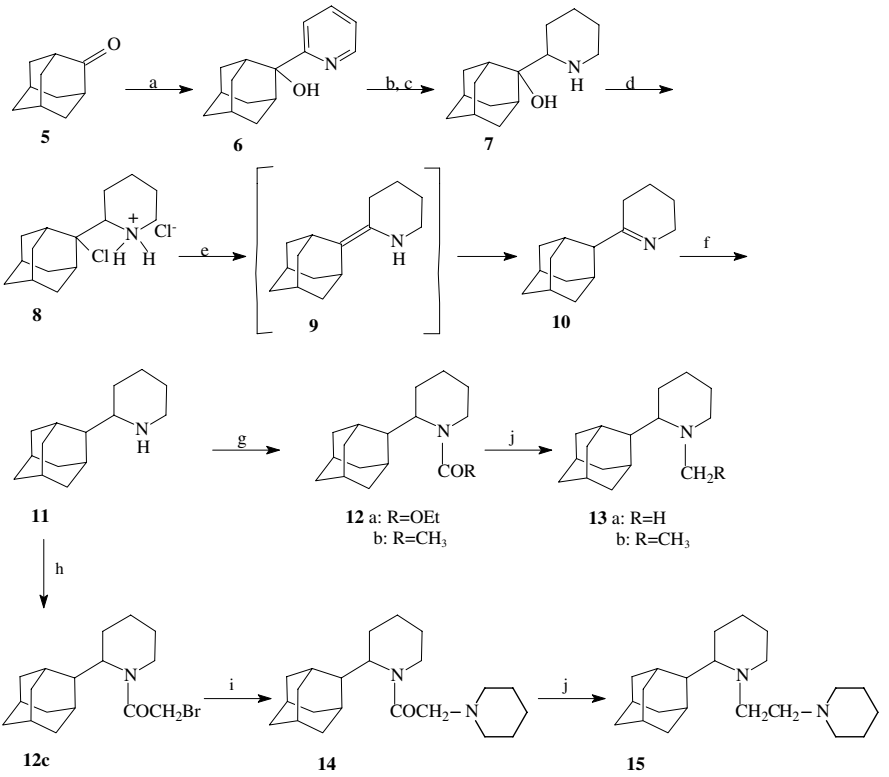
Cells and viruses

Influenza A and B viruses were kindly provided by Dr. K. Andries (Janssen Pharmaceutica, Beerse, Belgium) and stocks were prepared on MDCK cells. *Anti-influenza activity and cytotoxicity assays*—anti-influenza virus activity was assessed in 96-well plates in one-day confluent MDCK cells. Cells were infected with 100 $CCID_{50}$ virus/well. After 1 h of virus adsorption virus was removed and serial dilutions of the test compounds were added, after which the cultures were further incubated at 35 °C (5% CO_2) for 4–5 days. The cytopathic effect (and the cytotoxic effect in parallel) in non-infected cultures was read using the MTS-method (Promega).

3. Results and Discussion

3.1. Chemistry

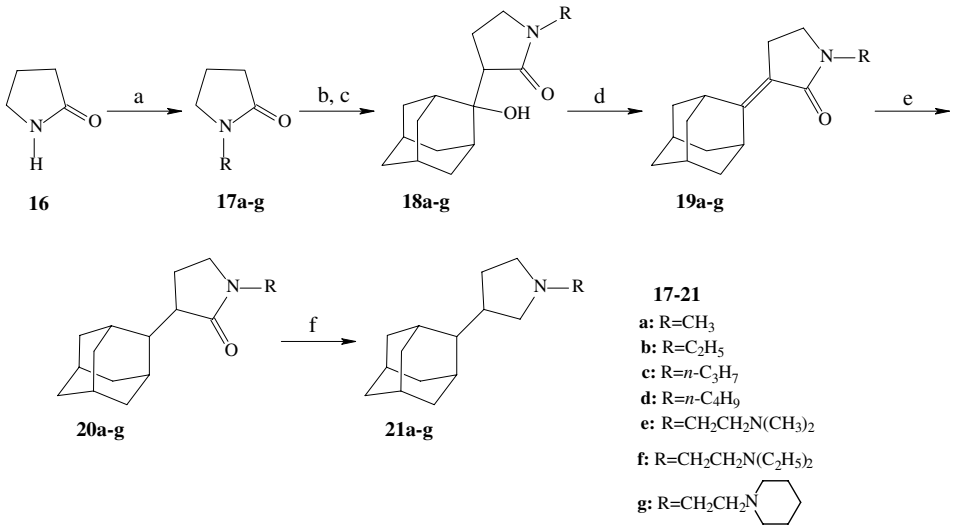
The synthetic route followed for the preparation of 2-(2-adamantyl)piperidine derivatives **11**, **13a**, **b**, and **15** is illustrated in Scheme 2. Tertiary alcohol **6** was synthesized from the reaction of adamantanone **5** and 2-pyridinyl lithium. Catalytic hydrogenation of the



Scheme 2. Reagents and Conditions: (a) 2-pyridinyl lithium, Et_2O/THF, −60 °C (82%); (b) gas HCl, EtOH; (c) H_2/PtO_2, EtOH and then Na_2CO_3 10% (97%); (d) $SOCl_2$, CH_2Cl_2, 6 h reflux; (e) KOH, EtOH, room temperature for 24 h under argon and then gentle reflux for 3 h (61% from 7); (f) $NaBH_4$, MeOH, 0–5 °C and then RT for 5 h (94%); (g) RCOCl, Et_3N, Et_2O or THF, 0–5 °C and then room temperature for 24 h (84–94%); (h) $BrCH_2COCl$, K_2CO_3, CH_2Cl_2/H_2O (86%); (i) piperidine, benzene, 0 °C for 30 min and then room temperature for 24 h (60%); (j) $LiAlH_4$, THF, 15 h reflux (50–83%).

hydrochloride form of **6** over PtO_2 catalyst led to the aminoalcohol **7**. Reaction of the alcohol **7** with $SOCl_2$ gave the corresponding chloride **8** as hydrochloride. Elimination reaction of the chloride **8**, in refluxing KOH/EtOH solution, produced 2-piperideine **10**, possibly via the unstable enamine **9**. Imine **10** was treated with sodium borohydride to give the parent 2-(2-adamantyl)piperidine **11**. The latter was *N*-alkylated to the piperidines **13a**,**b** through $LiAlH_4$ reduction of the compounds **12a**,**b**. Diamine **15** was prepared through $LiAlH_4$ reduction of the piperidinoacetamide **14**.

The synthetic routes followed for the preparation of the 3-(2-adamantyl)pyrrolidines **27**, **21a**–**g** are illustrated in Schemes 3, 4. *N*-Substituted pyrrolidines **21a**–**g** were synthesized according to Scheme 3, using *N*-alkyl-2-pyrrolidinones **17a**–**g** as starting materials, prepared through *N*-alkylation of the 2-pyrrolidinone **16**. The *N*-alkyl-2-pyrrolidinones **17a**–**g** were converted to the corresponding 2-oxo-3-pyrrolidinyl lithium form which reacted with 2-adamantanone **5** to produce the alcohols **18a**–**g**. These alcohols were dehydrated to form the methylene lactams **19a**–**g**. Subsequent catalytic hydrogenation afforded the 3-(2-adamantyl)-2-pyrrolidinones **20a**–**g**. Reduction of the lactams **20a**–**g** with $LiAlH_4$ yielded the compounds **21a**–**g**.



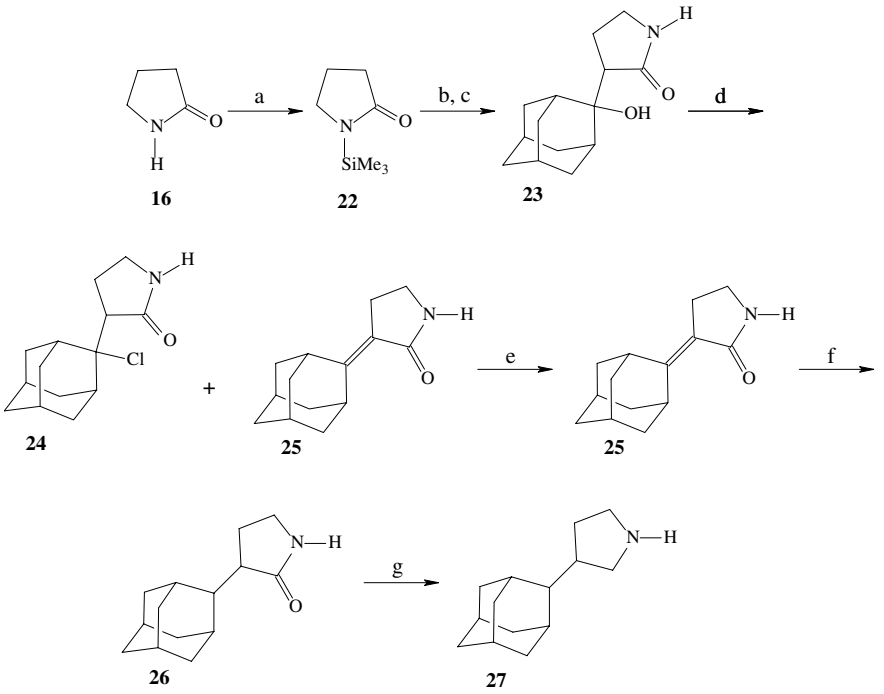
Scheme 3. Reagents and Conditions: (a) NaH, RI or HCl·$NR_2(CH_2)_2Cl$, benzene, 3–6 h 60–70 °C (23–58%); (b) LDA, −70 °C; (c) adamantanone, THF, −80 °C and then HCl 5%, 0 °C (73–95%); (d) TsOH, benzene, reflux (79–96%); (e) H_2, PtO_2, ethanol, 40 lb/in^2, room temperature 15–24 h (quant.); (f) $LiAlH_4$, THF, 20–25 h reflux (72–89%).

The parent *N*—H pyrrolidine **27** was synthesized using the *N*-trimethylsilyl-2-pyrrolidinone **22** as starting material (Scheme 4). Lithiation of the lactam **22** and subsequent reaction with 2-adamantanone **5** afforded the alcohol **23**. Compound **23** was treated with thionyl chloride and the resulting mixture of **24** and **25** was treated with ethanolic potassium hydroxide solution to afford methylenelactam **25**. Catalytic hydrogenation of the unsaturated compound **25** and subsequent $LiAlH_4$ reduction of the pyrrolidinone **26** resulted in the pyrrolidine **27**.

The preparation of the parent pyrrolidine **27** through demethylation of the *N*-methyl derivative **21a** failed to succeed. Although, the reaction of *N*-methylpyrrolidine **21a** with 2,2,2-trichloroethyl chloroformate gave the corresponding carbamate, treatment of the latter with Zn/AcOH failed to produce the *N*—H derivative [8]; instead, the *N*-methyl derivative **21a** was identified to be the reaction product.

Scheme 5 depicts the synthetic pathway followed for the synthesis of 2-(2-adamantylmethyl)piperidine derivatives **30**, **32a**–**c**, and **35a**–**d**. Tertiary alcohol **28** was synthesized by the reaction of adamantanone **5** with 2-pyridinylmethyl lithium. Dehydration of the alcohol **28**, by means of *p*-TSA, afforded alkene **29**. Catalytic hydrogenation of the hydrochloride form of **29** over PtO_2 catalyst led to the parent piperidine **30**. This was *N*-alkylated to the piperidines **32a**–**c** through $LiAlH_4$ reduction of the compounds **31a**–**c**. Diamines **35a**–**d** were prepared via $LiAlH_4$ reduction of dialkylaminoacetamides **34a**–**d**.

The synthetic routes leading to 2-alkyl substitution of the biologically important piperidine ring have been recently the subject of intense research [9]. The procedures depicted in Schemes 2, 5, and others published elsewhere [4h,4j], can be used to introduce bulky cycloalkyl groups at C-2 piperidine ring position. The routes described in Schemes 3 and 4 can be considered as general for the 3-substitution of γ-lactam and pyrrolidine ring with cycloalkyl groups.



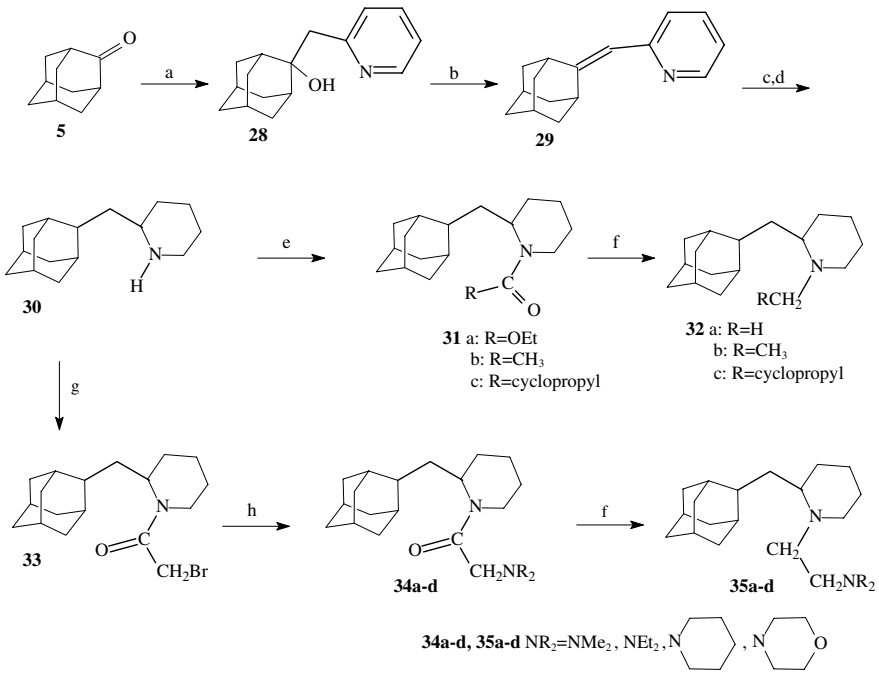
Scheme 4. Reagents and Conditions: (a) NaH, Me_3SiCl, benzene, 12 h room temperature (67%); (b) LDA, −70 °C; (c) adamantanone, THF, −80 °C and then HCl 5%, 0 °C (95%); (d) $SOCl_2$, $CHCl_3$, reflux 3 h (e) CH_3ONa/CH_3OH, reflux (53% from **23**); (f) H_2, PtO_2, EtOH, 40 lb/in^2, 24 h room temperature (quant.); (g) $LiAlH_4$, THF, 15 h reflux (68%).

3.2. Conformational features

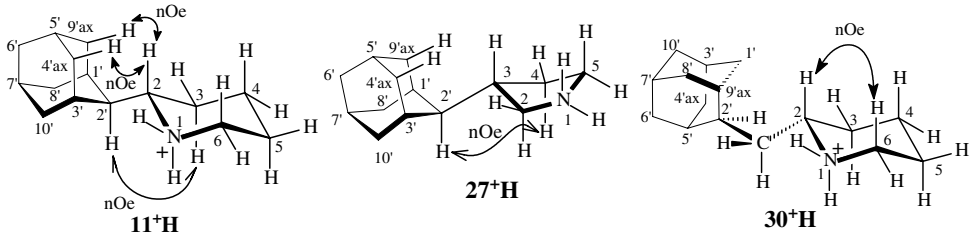
Some of our research aimed at the description of the conformational and dynamic NMR properties of potent compounds in aminoadamantane series [4i,10]; the results can be useful in the future understanding of SAR relationships.

The most interesting conformational feature in piperidine **11**$^+$**H** and pyrrolidine **27**$^+$**H** is the conformation around C2—C2′ or C3—C2′ bond (Scheme 6). The molecular mechanics calculations [5–7] suggest that the *anti*-conformation of the exocyclic C—C bond and the equatorial adamantyl orientation are by far preferable. All the remaining conformers are higher in energy by more than 2.2 or 3.3 kcal mol^{-1} and are considered unpopulated at room temperature, according to equation $\Delta G^{\circ} = -RT\ln K$.

Experimental evidence for the above conformations could be extracted from the NMR experiments. The chair conformation of the piperidine ring in compound **11**$^+$**H** is consistent with the signal of H-6eq at 3.47 ppm which appears as a doublet, $J = 12.3$ Hz (one large coupling with H-6ax), and the quartet assigned at H-6ax, $J \sim 11.7$ Hz, because of its three large couplings with 6eq, 5ax, and N^+H protons. The C2 proton signal appears as a quartet with $J = 10.2$ Hz, because C2H has three large couplings with 2′, 3ax, and N^+H protons, suggesting the predominance of a conformation in which that proton is axial and the adamantyl group is equatorial and a *trans* conformation around C2—C2′ bond. The NOE spectroscopy gave also information consistent with the above observations; the



Scheme 5. Reagents and Conditions: (a) 2-pyridinylmethyl lithium, THF, −20 °C, 2 h, (68%); (b) *p*-TSA, benzene, reflux, 15 h, (93%); (c) gas HCl, EtOH; (d) H_2, PtO_2, EtOH, 40 lb/in^2, and then Na_2CO_3 10% (98%); (e) RCOCl, Et_3N, ether, 0–5 °C, and then room temperature, 3–8 h (82–92%); (f) $LiAlH_4$, THF, 15 h reflux (71–89%); (g) $BrCH_2COCl$, K_2CO_3, CH_2Cl_2/H_2O, 0–5 °C, 3 h (93%); (h) R_2NH, benzene, 0–5 °C 30 min, and then room temperature for 24 h (80–89%).



Scheme 6. Most stable conformers for compounds 11^+H, 27^+H, and 30^+H (the half arrow in 11^+H indicated an NOE observed in its base form).

dipolar correlation between H2 and H4ax′, H9ax′ protons confirms the *anti* relationship of H2 and H2′ protons, while the nOe between H2′ and H6 protons—observed in **11**—is in agreement with the equatorial adamantyl group position.

In pyrrolidine **27**$^+$**H** the adamantane H—2′ signal shape is informative for the conformation around H3—C3—C2′—H2′ dihedral angle. However, this was not resolved for **27**$^+$**H** but appears as a doublet ($J \sim 10$ Hz) at 1.39 ppm in the proton NMR spectrum of the free amine form **27**. Thus, the conformation by rotation around C3—C2′ bond must be *anti*. In addition, the dipolar correlation between H2′ and H4ax is consistent with the equatorial adamantyl group position (Scheme 6).

It is striking that despite 1,1,2,2-tetrasubstituted ethanes with large substituents prefer a gauche over anti conformer to adopt [11], in compounds **11** and **27**, which belong to this class of compounds, the conformation by rotation around exocyclic carbon–carbon bond is anti.

For piperidine **30**$^{+}$**H** molecular mechanics locate several low energy conformers that differ in adamantyl orientation (equatorial or axial), heterocycle conformation and C2′—CH_2 or C2—CH_2 bond rotation. The chair conformation of the piperidine ring is again consistent with the shape of H-6eq and H-6ax signals (3.47 ppm, d, $J = 13$ Hz and 3.0 ppm, q, $J = 12$ Hz, respectively). The strong NOE between piperidine 2ax and 6ax protons provide evidence for the equatorial position of 2-adamantylmethyl group (Scheme 6). The ^{1}H 1D spectra or 2D NOESY experiments run for **30** or **30**$^{+}$**H** were not informative for the conformation by rotation around C2′—CH_2 and C2—CH_2 bonds due to the complexity of the signal patterns or several signal overlapping, respectively. However, molecular mechanics calculations locate the conformer having an a,g^{-} arrangement of the two CH—CH_2 segments as the most stable, see Scheme 6 (the next more stable was 1.2 kcal mol^{-1} higher in energy).

The parent molecules **11**$^{+}$**H**, **27**$^{+}$**H**, and **30**$^{+}$**H** acquire two pharmacophoric groups i.e., the amine and adamantyl groups. In this context, it is interesting to note that for **11**$^{+}$**H**, C2′—N1 distance is calculated to be 2.5 Å, whereas for **27**$^{+}$**H** and **30**$^{+}$**H**, N1 is 3.7 and 3.8 Å, respectively, away from adamantyl C2′. *N*-Substituted derivatives of the parent amines have, in general, the same heterocycle conformation, while adamantyl group and *N*-substituent group prefer to adopt mainly an equatorial and axial orientation, respectively [12].

3.3. Antiviral potency evaluation

3.3.1. Influenza virus

The potency of the new aminoadamantane heterocycles **11**, **13a**,**b**, **15**, **20c**,**d**, **27**, **21a**–**f**, **30**, **32a**–**c**, and **35a**–**d** was examined *in vitro* against influenza A (H_3N_2) and B viruses, and was compared to the activity of amantadine **1a**, rimantadine **1b**, and ribavirin **3**. H_3N_2 strain is responsible for the current winter epidemics. The potency of 2-rimantadine **4** was also included for comparison (Table 1). The methods and antiviral assays used were as previously reported [13].

Piperidine **11** was more potent than amantadine **1a** and equipotent to the rimantadine **1b** against influenza A. The effect of including the 1-aminoethyl pharmacophore group of 2-rimantadine **4** into a saturated nitrogen heterocycle was investigated; potency was retained, as it is obvious by comparing the EC_{50} values of 2-(2-adamantyl)piperidine **11** and 2-rimantadine **4**.

As regards the next series of compounds, it appears that the parent pyrrolidine **27** and diamines **21e**–**g** exhibited a good potency.

Whereas *N*-alkylation of the parent amine **27**, resulting in **21a**–**d**, caused a dramatic reduction in antiviral potency, *N*-dialkylaminoethyl substitution led to the active analogs **21e**–**g**. The specific activity of these diamines could be attributed to three pharmacophore groups, the adamantyl and the two amine groups.

In the third series of compounds, **30**, **32a**–**c**, and **35a**–**d**, the potency of the diamine derivatives **35a**–**d** was striking. Overall, of all the compounds tested, these derivatives were the most potent.

Table 1
Anti-influenza (H_3N_2) virus A activity and cytotoxicity of aminoadamantane derivatives **1**–**4**, **11**, **13a**,**b**, **15**, **20e**,**f**, **27**, **21a**–**g**, **30**, **32a**–**c**, and **35a**–**d**[a] in MDCK cells[b]

Compound	EC_{50}[c] (μM)	MCC_{50}[d] (μM)
11	25	⩾977
13a	>100	977
13b	>100	143
15	25.1	4.6
27	5.0	124.4
20e	14.7	122.4
20f	11.1	92.0
21a	47.5	⩾156.4
21b	88.9	148.2
21c	93.3	140.9
21d	92.8	134.3
21e	9.4	78.7
21f	12.9	74.6
21g	25.5	14.6
30	22.0	185.3
32a	35.4	176.1
32b	84.8	132.4
32c	47.0	123.9
35a	5.9	93.2
35b	7.2	88.5
35c	3.6	86.7
35d	81.4	111.9
Amantadine, **1a**	49.1	1333
Rimantadine, **1b**	19.1	>1160
2-Rimantadine, **4**	31.1	>1160
Ribavirin	122.9	⩾1024.6

[a] Aminoadamantanes **1a**–**b**, **4, 11**, **13a**,**b 15**, **20c**,**d**, **27**, **21a**–**g**, **30**, **32a**–**c**, and **35a**–**d** were tested as hydrochlorides or fumarate salts.
[b] Abbreviations and strains used: MDCK, Madin-Darby canine kidney cells; influenza A H_3N_2 (X31).
[c] Effective concentration or concentration required to reduce virus-induced cytopathogenicity by 50%.
[d] Minimum cytotoxic concentration or concentration required to cause a microscopically detectable alteration of normal cell morphology. All data represent mean values for at least two separate experiments.

All compounds tested were found to be inactive against influenza B virus, which is in accordance with their putative mode of action, that is, an interaction with the influenza A M2 protein which is absent from influenza B virion.

3.3.2. Broad-spectrum antiviral activity evaluation

All the new compounds were inactive against HIV-1 and -2; only a marginal activity was exhibited by a diamine derivative of compound **11** against HIV-1. It is worth noting that although the diamines **15** and **21e**–**g** were inactive anti-HIV agents, the diamine derivatives of 2-(1-adamantyl)piperidine (**3**, $n = 1$) showed some activity against HIV-1 [4c]. This result could trigger further research in this field.

The aminoadamantane derivatives prepared were also evaluated, according to previously reported methods [13,14], against the following viruses: parainfluenza type 3, herpes simplex virus type 1 (HSV-1), thymidine kinase-deficient (TK^-) HSV-1, herpes simplex

virus type 2 (HSV-2), vaccinia, vesicular stomatitis, polio 1, Coxsackie B4, Sindbis, Semliki forest, Reo 1, varicella—zoster virus (VZV), TK^- VZV, human cytomegalovirus (HCMV). The compounds did not afford specific activity against any of these viruses at non-toxic concentrations.

4. Conclusion

The major aim of this study was to examine the anti-influenza A virus potency of some series of 2-adamantyl substituted amines. All the parent amines **11**, **27**, and **30** were potent. When 1-aminoethyl pharmacophore group of 2-rimantadine **4** (2-isomer of rimantadine) is included into a saturated nitrogen heterocycle, see compound **11**, potency was retained.

Diamine derivatives **21e–g** and in particular **35a–d** were found to be potent anti-influenza A agents. It has been proposed by molecular modelling studies, that amantadine **1** blocks the M2 channel activity because its two pharmacophoric groups, the adamantyl group and amine groups, are complementary in shape, hydrophobicity, and polarity with the luminal space of M2 protein [2]. The anti-influenza virus A potency of these diamines may be determined by three pharmocophore groups, the adamantyl and the two amine groups.

In the parent amines, which proved to be active compounds, the distance between nitrogen and adamantyl pharmacophoric groups was different; N—C2′ distance is 3.7, 3.8 Å for $\mathbf{27}^+\mathbf{H}$, $\mathbf{30}^+\mathbf{H}$ and 2.5 Å for $\mathbf{11}^+\mathbf{H}$. Since the protonated amine functionalities interact with the same H-acceptor group this suggest that M2 receptor site can accommodate different in size and orientation lipophilic cages. The parent heterocycles **11** and **27** adopt a fixed *trans* conformation around C2—C2′ bond and an equatorial adamantyl group. These findings and others previously reported will help future molecular modelling studies aiming to understand how aminoadamantane compounds interact with their receptor protein.

Acknowledgment

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