Eur J Med Chem (1996) 31, 105–110

New adamantan-2-ol and adamantan-1-methanol derivatives as potent antibacterials. Synthesis, antibacterial activity and lipophilicity studies

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(Received 12 April 1995; accepted 23 October 1995)

Summary — Two series of active adamantane-group-bearing trialkylamines and their quaternary ammonium salts were synthesized and their biological properties were tested. One series includes 2-(3-dialkylaminopropyl)tricyclo[3.3.1.1^{3,7}]decan-2-ols and the other α,α-bis(3-dialkylaminopropyl)tricyclo[3.3.1.1^{3,7}]decyl-1-methanols. Some of the synthesized molecules proved to be very active antibacterials. The minimum inhibitory concentration (MIC) values of the most potent compounds were determined. The observed differences were investigated. The antibacterial activity of the compounds was found to be enhanced as the length of the nitrogen-attached carbon chain extends from CH_3 to $C_{12}H_{25}$. The lipophilicity of the synthesized molecules was also studied and its relationship with the antibacterial activity was investigated.

adamantane / charged nitrogen / antibacterial agent / lipophilicity

Introduction

The microbiology of skin infections is changing and there is an increasing incidence of infections caused by strains resistant to many antibiotics. The development of potent topical preparations, which may be quite useful in managing these disorders [1], remains an interesting research field.

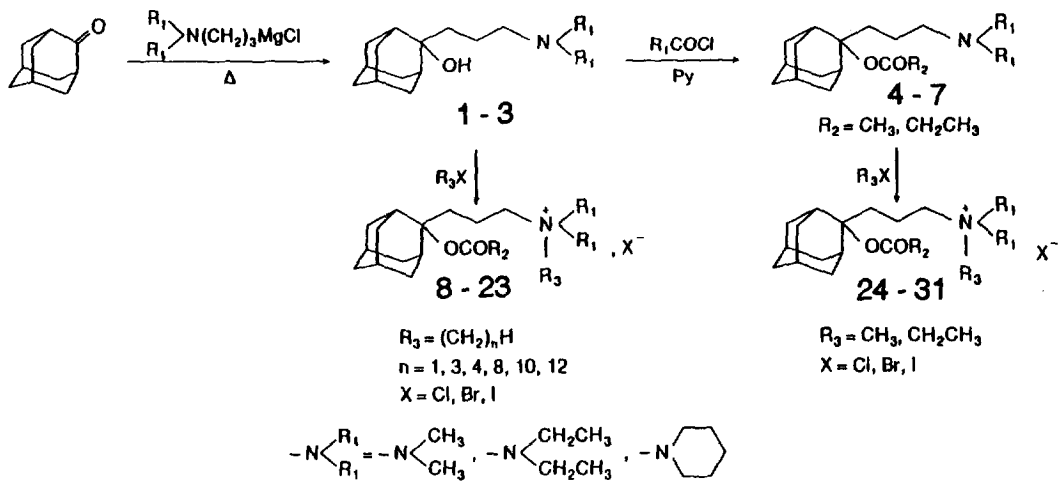
Several adamantane derivatives possess bactericidal activity [2], while the alcohols adamantan-2-ol and adamantan-1-methanol exhibit significant antiviral activity. In the course of our investigation of adamantane-ring-bearing compounds [3–5] and in an attempt to obtain new antibacterial and/or antiviral agents with improved characteristics over existing ones, adamantane derivatives of the type **1–7** were synthesized. The tertiary amines **1–7** proved to show only slight antibacterial activity, nevertheless their quaternization **8–31**, led to a dramatic enhancement of their activity, a behaviour which was expected according to existing knowledge. On the other hand, the lack of any information concerning the influence on the biological activity of a second dialkylaminopropyl group attached directly to the lipophilic centre of the molecules prompted us to attempt the preparation of a second series (compounds **32–41**). In both series, the dialkylaminopropyl moiety was modified at the amine end group.

The antibacterial activity of the synthesized compounds was expressed as minimum inhibitory concentration (MIC) and the observed differences were further investigated. Additionally, in order to verify the hypothesis of 'reaching critical lipophilicity levels', the partition coefficient of the synthesized molecules was studied and compared with the magnitude of their growth inhibitory activity.

Chemistry

The preparation of 2-(3-dialkylaminopropyl)adamantane-2-ols **1–3** was effected by treatment of the adamantan-2-ol with freshly prepared Grignard reagent of the appropriate *N*,*N*-dialkyl-*N*-propyl-3-magnesium chloride [6]. The obtained compounds were then converted to the 2-*O*-acyl analogs **4–7**. All the adamantan-2-ol derivatives synthesized in this way were quaternized by using different alkyl halides **8–31** (scheme 1, table I).

For the preparation of α,α-bis(3-dialkylaminopropyl)adamantane-1-methanols **32–34**, the adamantane-1-carboxylate was treated with the appropriate Grignard reagents prepared from the corresponding

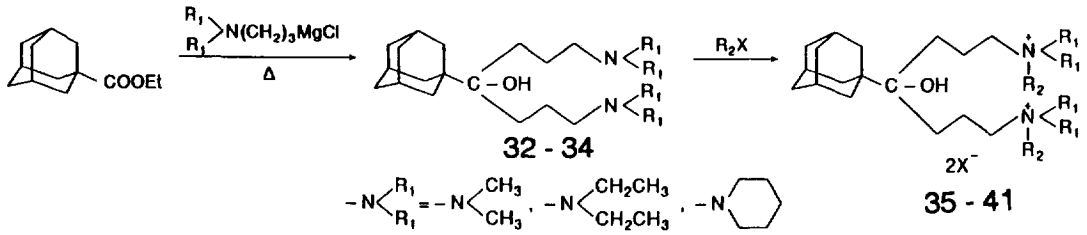


Scheme 1.

Table I. Structure and physical data of the 2-(3-dialkylaminopropyl)-adamantane-2-ols in scheme 1.

Compound	*$N(R_1)_2$*	*R_2*	*X*	*R_3*	*Mp (°C)*	*Recrystallization solvent*	*MW*	*Molecular formula*
8	$N(CH_3)_2$	H	Cl	H	220–222	a	273.19	$C_{15}H_{28}NOCl$
9	$N(CH_3)_3$	H	I	CH_3	240–241	b	379.14	$C_{18}H_{30}NOI$
10	$N(CH_3)_2$	H	Br	C_3H_7	192–193	b	359.18	$C_{19}H_{34}NOBr$
11	$N(CH_3)_2$	H	Br	C_4H_9	181–182	b	373.20	$C_{19}H_{36}NOBr$
12	$N(CH_3)_2$	H	Br	C_8H_{17}	192–193	b	429.26	$C_{23}H_{44}NOBr$
13	$N(CH_3)_2$	H	Br	$C_{10}H_{21}$	198–199	c	457.29	$C_{25}H_{48}NOBr$
14	$N(CH_3)_2$	H	Br	$C_{12}H_{25}$	200–202	c	485.32	$C_{27}H_{52}NOBr$
15	$N(C_2H_5)_2$	H	Cl	H	184–185	a	301.22	$C_{17}H_{32}NOCl$
16	$N(C_2H_5)_2$	H	I	CH_3	198–199	b	407.17	$C_{18}H_{34}NOI$
17	$N(C_2H_5)_2$	H	Br	C_8H_{17}	200–201	b	457.29	$C_{25}H_{48}NOBr$
18	$N(C_2H_5)_2$	H	Br	$C_{10}H_{21}$	205–208	b	485.32	$C_{27}H_{52}NOBr$
19	$N(C_2H_5)_2$	H	Br	$C_{12}H_{25}$	208–209	b	513.35	$C_{29}H_{56}NoBr$
20	$N(CH_2)_5$	H	Cl	H	248–250	a	313.22	$C_{18}H_{32}NOCl$
21	$N(CH_2)_5$	H	I	CH_3	240–242	b	419.17	$C_{19}H_{34}NOI$
22	$N(CH_2)_5$	H	Br	C_8H_{17}	208–210	b	469.29	$C_{26}H_{48}NOBr$
23	$N(CH_2)_5$	H	Br	$C_{12}H_{25}$	210–212	b	525.35	$C_{30}H_{56}NOBr$
24	$N(CH_3)_2$	$COCH_3$	Cl	H	170–172	a	315.17	$C_{17}H_{30}NO_2Cl$
25	$N(CH_3)_2$	$COCH_3$	I	CH_3	145–147	b	421.18	$C_{18}H_{32}NO_2I$
26	$N(CH_3)_2$	COC_2H_5	Cl	H	202–203	b	329.21	$C_{18}H_{32}NO_2Cl$
27	$N(CH_3)_2$	COC_2H_5	I	CH_3	162–164	b	435.16	$C_{19}H_{34}NO_2I$
28	$N(C_2H_5)_2$	$COCH_3$	Cl	H	168–170	b	343.23	$C_{19}H_{34}NO_2Cl$
29	$N(C_2H_5)_2$	$COCH_3$	I	CH_3	156–158	b	449.18	$C_{20}H_{36}NO_2I$
30	$N(CH_2)_5$	$COCH_3$	Cl	H	202–203	b	355.23	$C_{20}H_{34}NO_2Cl$
31	$N(CH_2)_5$	$COCH_3$	I	CH_3	160–161	b	461.18	$C_{21}H_{36}NO_2I$

a = $EtOH/Et_2O$; b = acetone/Et_2O; c = acetone.



Scheme 2.

Table II. Structures and physical data of the α,α-bis(3-dialkylaminopropyl)-1-adamantane-1-methanols in scheme 2.

Compound	*$N(R_1)_2$*	*R_2*	*X*	*Mp (°C)*	*Recrystallization solvent*	*MW*	*Molecular formula*
35	$N(CH_3)_2$	H	Cl	221–222	a	408.27	$C_{21}H_{42}N_2OCl_2$
36	$N(CH_3)_2$	CH_3	I	265–266*	b	620.17	$C_{23}H_{46}N_2OI_2$
37	$N(CH_3)_2$	C_2H_5	Br	220–222*	b	552.23	$C_{25}H_{50}N_2OBr_2$
38	$N(C_2H_5)_2$	H	Cl	285–287*	a	464.33	$C_{25}H_{50}N_2OCl_2$
39	$N(C_2H_5)_2$	CH_3	I	178–179	c	676.23.	$C_{27}H_{54}N_2OI_2$
40	$N(CH_2)_5$	H	Cl	260–261*	a	488.33	$C_{27}H_{50}N_2OCl_2$
41	$N(CH_2)_5$	CH_3	I	165–167	b	700.23	$C_{29}H_{54}N_2OI_2$

*Melting with decomposition; a = $EtOH/Et_2O$; b = acetone/Et_2O; c = acetone.

N,N-dialkyl-*N*-propyl-3-magnesium chlorides in a double addition reaction. The requisite adamantane-1-carboxylate was obtained from the conversion of the adamantane-1-carboxylic acid to the corresponding ethylester (scheme 2, table II).

Antibacterial tests

All compounds reported in this study were assayed for their antibacterial activity against strains of several bacteria [7] (*Staphylococcus aureus* ATCC 9144, *Streptococcus faecalis* (Laboratory Collection, *S faecalis* was originally isolated from infected body fluids of patients in Athens hospital), *Bacillus subtilis* CCM 2216, *Escherichia coli* CCM5172, *Proteus mirabilis* CCM 1944 and *Pseudomonas aeruginosa* CCM 1960). MIC values were determined for the eight compounds, for which the preliminary tests were the most encouraging (table III).

Lipophilicity studies

Considering that under physiological pH the prepared tertiary adamantanolamines dissociate to a large extent and act most probably through their cationic form, partition coefficients of the protonated species as well as those of the corresponding quaternary ammonium salts were calculated according to the Leo–Hansch

Table III. The MIC values corresponding to the compounds which exhibit the highest antibacterial activity.

Compound	*Log P*	*MIC (μg/mL)*			
		S aureus	*S faecalis*	*B subtilis*	*E coli*
10	–0.72	63	–	33	> 63
12	1.12	9.5	69	18	> 69
13	1.90	1.5	–	3	50
14	2.68	3	–	4	> 63.6
17	1.24	10.5	–	33	69
18	2.02	31	–	62	69
19	2.80	9.5	–	9.5	69
22	1.66	15	–	33	75
23	3.22	9	–	96	75

MIC: the lowest concentration of a compound that completely prevents bacterial growth. The values reported are the average of three measurements. MIC values > 100 μg/mL.

Table IV. Calculated partition coefficient and chromatographic indices.

Compound	*Log P*	R_{m_0}	*r*
8	–0.96	1.70 (±0.15)	0.986
9	–0.99	1.72 (±0.17)	0.988
10	–0.72	1.68 (±0.05)	0.997
11	–0.41	2.31 (±0.25)	0.994
12	1.12	3.57 (±0.31)	0.983
13	1.90	4.61 (±0.25)	0.995
14	2.68	5.39 (±0.53)	0.988
15	–0.60	2.45 (±0.18)	0.986
16	–0.87	1.76 (±0.11)	0.996
17	1.24	2.91 (±0.26)	0.987
18	2.02	–	
19	2.80	5.43 (±0.64)	0.982
20	–0.38	1.98 (±0.05)	0.999
21	–0.45	1.68 (±0.13)	0.986
22	1.66	3.66 (±0.24)	0.955
23	3.22	5.81 (±0.31)	0.996
24	–0.07	–	
25	–0.10	2.35 (±0.13)	0.993
26	0.47	–	
27	0.44	–	
28	0.29	–	
29	0.02	1.91 (±0.05)	0.999
30	0.51	2.70 (±0.09)	0.998
31	0.34	–	

fragmental system [8] and are presented in table IV. It is known that the presence of a charged nitrogen in the molecules is associated with an anomalous lipophilic behaviour. In Leo–Hansch fragmental system these abnormalities are reflected in special bond correction terms depending on the distance from the charged centre, while Rekker suggested different N^+ fragmental constants depending on the environment [9]. We selected the Leo–Hansch system since it has a more general applicability, and because optimum logP values for antimicrobial compounds have been established using mostly calculated values in that system. An example of this calculation is given in the *Appendix*.

The calculations were further supported by experimental data obtained using reversed-phase thin-layer chromatography. R_m values were determined on silica-gel plates impregnated with paraffin oil at pH 4.5 using methanol/buffer mixtures as the eluent. A detailed description of the experiments is reported in the literature [10]. Extrapolation to 0% organic modifier was performed linearly in the range 50–75 of methanol fraction.

Extrapolated R_{m_0} values are presented in table IV. A satisfactory correlation is found between R_{m_0} values and calculated partition coefficients which leads to regression equation (1).

$$\log P = 0.95(\pm 0.13)\, R_{m_0} - 2.31(\pm 0.42) \quad (1)$$

$n = 18$; $r = 0.970$; $s = 0.353$; $F = 253.96$

Values in parentheses correspond to 95% confidence limits.

Results and discussion

In this work 41 compounds, classified in two series (scheme 1 and 2) were prepared and their biological properties were studied. In both series, the tertiary amines show only slight antibacterial activity. However, the corresponding quaternary ammonium salts (scheme 1) with the R representing alkyl groups starting from CH_3 and extending until $C_{12}H_{25}$ are very active antibacterials, especially when the added alkyl group consists of 10 or 12 methylene groups. Thus, in this series, the quaternization of the synthesized amines appears to be a crucial requirement for the activity.

These molecules can be considered as typical analogs of the widely used cationic antiseptics (amphiphiles) being active against Gram-positive and, at higher concentrations, against some Gram-negative microorganisms. The effectiveness of this class of compounds appears to be a result of disturbance caused to the microbial cell membrane permeability leading to leakage of intracellular compounds [1]. The adamantane moiety, which combines high lipophilicity with a relatively small volume, possibly facilitates the entrance of the compound into the cell membrane and also its retention inside the lipidic bilayer.

From the permanently charged analogues, the compounds **10**, **12–14**, **17–19**, **22** and **23** proved to be the most active against the tested Gram-positive and Gram-negative bacteria, with MIC values ranging from 1×10^{-5} to 1×10^{-4}, in good comparison with the MIC values of other potent compounds of that category. Among these, compound **13** possesses a ten-carbon atom chain and two methyl groups attached to the charged nitrogen with a logP value equal to 1.90; this is the most potent derivative. Activity decreases for more lipophilic compounds **14**, **19** and **23** with a 12 carbon atom chain and logP values equal to 2.68, 2.80 and 3.22, respectively. These findings are consistent with the hypothesis of a critical logP value, which for cationic antimicrobial drugs is considered to be around 2.5 [11, 12].

On the other hand, regardless of their lipophilicity, the diethylamine (**17–19**) and piperidine (**22** and **23**) derivatives appear less active than the corresponding

dimethylamine analogues. This observation may indicate a steric influence caused by the bulkier diethylamine and piperidine groups, an assumption which needs further support by more data.

Experimental protocols

Chemistry

All melting points were taken on a Buchi capillary melting apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 883 spectrophotometer. Compounds **1–3** give sharp absorption peaks of hydroxyl group at 3400 cm^{-1}. When these products existed as hydrochlorides, the appropriate absorptions appeared at 3500–3315 cm^{-1} as broad bands whereas in the quaternary ammonium salts this absorption band is at 3345–3250 cm^{-1}. An explanation of these observations may be intramolecular bond formations. A crystallographic study of compound **13** proved a hydrogen bond formation between the alcoholic hydrogen and the bromine anion (manuscript in preparation).

Compounds **4–7** and **24–31** give the characteristic sharp absorption bands at 1730–1720 cm^{-1} due to the ester carbonyl group.

^1H NMR spectra were obtained at 200 MHz using a Bruker AC 200 instrument in $CHCl_3$ and D_2O as solvents and tetramethylsilane as the internal standard. Chemical shifts are reported in δ units (ppm) and coupling constants in hertz.

Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values and were carried out at the CNRS, the Central Department for Microanalysis, Vernaison, France.

2-(3-Dimethylaminopropyl)tricyclo [3.3.1.1^{3,7}]decan-2-ol ***1***

To a stirred solution of 3-dimethylaminopropylmagnesium chloride prepared from 1.7 g (0.07 mol) of dry magnesium turnings and 7.32 g (0.06 mol) 3-dimethylaminopropyl chloride in 200 mL anhydrous benzene containing 20 mL THF, 6.0 g (0.04 mol) of 2-adamantanone in 200 mL anhydrous benzene was added dropwise under nitrogen. The reaction mixture was refluxed for 6 h and then cooled in an ice bath and hydrolysed by adding a saturated solution of ammonium chloride. The organic layer was separated and the aqueous solution extracted with Et_2O. The organic solutions were combined, washed with water and dried over Na_2SO_4. After evaporation the 2-(3-dimethylaminopropyl)-tricyclo[3.3.1.1^{3,7}]decyl-2-ol crystallized in 95% yield. Recrystallization from hexane gave colourless crystals. Mp 65–66 °C. ^1H NMR ($CDCl_3$) δ (ppm): 1.40–1.91 (m, 18H (14 adamantane H + 4H (CH_2)$_2$$CH_2$N)), 2.22 (s, 6H, 2 × CH_3), 2.20–2.37 (t, 2H, -CH_2N), 4.80–4.95 (br, s, 1H, OH).

Compounds **2** and **3** were prepared using the same experimental conditions.

2-(3-Diethylaminopropyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol ***2***. 60% yield. Mp 50 °C. Hydrochloric salt of compound **2** (**16**): ^1H NMR (D_2O) δ (ppm): 1.27 (tr, 6H, $J \approx 6.5$–7 Hz, 2 × CH_3), 1.51–1.89 (m, 16H (12H adamantane H+4H (CH_2)$_2$$CH_2$N)), 2.01–2.16 (m, 2H, adamantane H), 3.05–3.23 (m, 2H, CH_2NH-(CH_2CH_3)$_2$), 3.205 (tetr, 4H, $J \approx 7$ Hz, N(CH_2CH_3)$_2$).

2-(3-Piperidinepropyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol ***3***. 95% yield. Recrystallized from Et_2O. Mp 83 °C. ^1H NMR ($CDCl_3$) δ (ppm): 1.25–1.92 (m, 24H (14H adamantane H + 4H, (CH_2)$_2$$CH_2$N, +6H, piperidine H)), 2.25–2.39 (m, 6H, -CH_2N-(CH_2)CH_2), 3.40–3.52 (br, s, 1H, OH).

2-(3-Dimethylaminopropyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol acetate ***4***

To a stirred solution of 2.38 g (0.01 mol) 2-(3-dimethylaminopropyl)-2-adamantanol and 1.11 g (0.011 mol) of triethylamine in 50 mL of anhydrous benzene, 1.18 g (0.015 mol) of acetylchloride was added dropwise under ice-bath cooling. The mixture was stirred for 3 h at ambient temperature and refluxed for 60–90 min to complete the acetate formation, washed with water and extracted with Et_2O. The combined etheral solutions were dried over Na_2SO_4 and evaporated in vacuo, desiccated in the presence of P_2O_5, and obtained in 90% yield as oil. ^1H NMR ($CDCl_3$) δ (ppm): 1.47–1.97 (m, 18H (14H adamantane H + 4H (CH_2)$_2$$CH_2$N)), 2.02 (s, 3H, CH_3CO-), 2.11–2.34 (t, 2H, CH_2N), 2.20 (s, 6H, NCH_3)$_2$).

Compounds **5–7** were prepared in a similar manner.

2-(3-Dimethylaminopropyl)-tricyclo[3.3.1.1^{3,7}]deca-2-ol acetate ***5***. 72% yield as oil. ^1H NMR ($CDCl_3$) δ (ppm): 0.98 (tr, 6H, $J \approx 6.7$–7 Hz, 2 × CH_3), 1.29–1.99 (m, 18H (14H adamantane H, + 4H (CH_2)$_2$$CH_2$N)), 2.07 (tr, 2H, $J \approx 8$ Hz, CH_2N(C_2H_5)$_2$, 2.26 (s, 3H, CH_3CO), 2.52 (tetr, 2H, $J \approx 8$ Hz, CH_2N(CH_2CH_3)CH_2CH_3), 2.83 (tetr, 2H, CH_2N(CH_2CH_3)CH_2-CH_3).

2-(3-Piperidinopropyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol acetate ***6***. 78% yield. Mp 100 °C. ^1H NMR ($CDCl_3$) δ (ppm): 2.13 (s, 3H, CH_3), 2.26–2.35 (m, 2H, adamantane H), 2.81–2.99 (tr, 2H, CH_2N, $J \approx 6$ Hz), 3.04–3.16 (tr, 2H, CH_2N, $J \approx 4$ Hz), 3.44–3.58 (tr, 2H, CH_2N, $J \approx 6$ Hz), 1.32–2.07 (m, 22H (12H adamantane H + 4H, $CH_2CH_2CH_2$N + 6H (CH_2)$_3$ piperidine H)).

2-(3-Dimethylaminopropyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol propanoate ***7***. 62% yield. Mp 162–164 °C. ^1H NMR ($CDCl_3$) δ (ppm): 1.08 (tr, 3H, CH_2CH_3), 1.31–1.97 (m, 18H, 14H adamantane H + 4H, $CH_2CH_2CH_2$N), 2.02–2.42 (m, 4H, 2H, CH_2N + 2H, CH_2CH_3), 2.23 (s, 3H, CH_3N), 2.31 (s, 3H, CH_3N).

α,α-Bis(3-dimethylaminopropyl)tricyclo[3.3.1.1^{3,7}]decan-1-methanol ***32***

To a stirred solution of 3-dimethylaminopropyl magnesium chloride prepared from 2.55 g (0.105 mol) of dry magnesium turnings and 14.23 g (0.09 mol) 3-dimethylaminopropylchloride in 200 mL anhydrous benzene containing 20 mL THF, 6.25 g (0.03 mol) of 1-adamantan-ethyl carboxylate in 20 mL anhydrous benzene was added dropwise under nitrogen. The reaction mixture was refluxed for 10 h, in order to complete the transformation of the primarily formed ketone to the corresponding α,α-disubstituted adamantan-1-methanol. The remaining unreacted Grignard reagent was hydrolysed by adding a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer extracted with Et_2O. The organic mixtures were combined, washed with water and dried over Na_2SO_4. Evaporation yielded 53% of **32**, as viscous oil. ^1H NMR ($CDCl_3$) δ (ppm): 1.20–2.40 (d, m, 27H (15H admantane H, + 2 × 6H, (CH_2)$_3$N(CH_3)$_2$)), 2.22 (s, 12H, 2 × N (CH_3)$_2$), 5.10–5.15 (br, s, 1H, OH).

Compounds **33** and **34** were prepared according to the same procedure.

α,α-Bis(3-diethylaminopropyl)tricyclo[3.3.1.1^{3,7}]deca-1-methanol ***33***. 60% yield. Mp 45–50 °C. ^1H NMR ($CDCl_3$) δ (ppm): 0.76–0.99 (t, 12H, 4 × CH_3), 1.09–1.94 (m, 23H, 15H adamantane H + 8H, 2 × (CH_2)$_2$-CH_2N), 2.20–2.64 (m, 12H, 2 × CH_2N(CH_2)CH_2), 3.62–3.70 (br, s, 1H, OH).

α,α-Bis(piperidinopropyl)tricyclo[3.3.1.1^{3,7}]decan-1-methanol ***34***. 58% yield. Mp 82–84 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.25–1.93 (m, 35H, (15H adamantane H + 8H, 2 × $(CH_2)_2CH_2N$) + 12H, 2 × 6 piperidine H), 1.92–2.39 (m, 12H, 2 × $CH_2N(CH_2)_2$), 3.33–3.59 (br, s, 1H, OH).

Quarternary ammonium salts

All quaternary ammonium salts were obtained by quaternization reactions. Compounds **1–7** and **32–34** were quaternized by addition of alkyl halides to equimolar aminalcohols diluted in acetone. The mixtures were heated under reflux for 5–40 h. The solutions were concentrated in vacuo. The crude quarternary salts were quantitatively crystallized by addition of small amounts of Et_2O. Structures and physical data of the synthesized, hydrochloric and quarternary ammonium salts are described in table I. Proton NMR data of a selected example are described below.

Octylbromide salt of 2-(3-dimethylaminopropyl)tricyclo-[3.3.1.1^{3,7}]decan-2-ol ***12***. ^{1}H NMR (D_2O) δ (ppm): 0.86 (t, 3H, $J \approx$ 6.3–6.8 Hz, $(CH_2)_7CH_3$), 1.19–1.42 (m, 10H, $(CH_2)_2(CH_2)_5CH_3$), 1.51–1.88 (m, 18H (12H, adamantane H + 4H, $(CH_2)_2CH_2N$ + 2H, $NCH_2CH_2(CH_2)_5CH_3$)), 2.03–2.16 (m, 2H, adamantane H), 3.05 (s, 6H, 2 × CH_3), 3.22–3.36 (m, 4H, $CH_2N(CH_3)_2CH_2$). Anal $C_{23}H_{44}NOBr$ (C, H, N).

Antibacterial activity

The tested compounds were incorporated at the desired concentrations into molten Muller–Hinton agar and cooled to about 45 °C. The stock solutions were prepared by diluting the appropriate amount of the compound in a 2:48 DMF/water mixture. Inocula were prepared from 24 h cultures grown in Muller–Hinton broth. The final suspension in sterile saline contained 10^8 bacteria/mL. Drug-free plates were used as control of positive growth of the given strains [7]. The test and control plates were inoculated with 1 μL on to the surface by means of a multi-point inoculation and were incubated at 37 °C for 18–24 h. *P mirabilis*, which exhibited the swarming character, was tested singly to avoid the problem of outgrowth onto neighbouring inocula encountered using the above-described procedure. Some compounds show signifcant activity against *S aureus*, *S faecalis*, *B subtilis* and *E coli*. The corresponding MIC values of the active compounds are shown in table III.

Lipophilicity caculations

LogP values were calculated according to Hansch–Leo fragmental system [8]. In this system constant fragmental values are assigned to the ion pairs NH^+X^-, while the influence of the charged nitrogen on the attached alkyl groups is expressed by special bond correction factors which contain a geometric and an electronic component, the latter depending on the distance from the charged centre.

Acknowledgment

The authors would like to thank N Lysikatos for his contribution in NMR spectroscopy in this work.

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Appendix

Calculation of the partition coefficient of compound **8**.

Fragments		
f(adamantyl)		3.33
3 × *f*(CH_2)	3 × 0.66	1.98
2 × *f*(CH_3)	2 × 0.89	1.78
f(NH=Cl$^-$)		–3.86
f(OH)		–1.64
*F*gbr[a]		–0.22
3 × *F*by^{+1}[b]	3 × (–0.78)	–2.34
*F*by^{+2}[b]		–0.48
*F*by^{+3}[b]		–0.34
*F*by^{+4}[b]		–0.27
*F*pH/8[b]	0.20 (3.86 + 1.64)	1.10
Sum of fragments		–0.96

[a]Correction for OH branching; [b]special bond correction terms; [c]special proximity correction term.