Synthesis and Characterization of Two Homologous Series of Diastereomeric 2-Alkoxyphenylcarbamates

Fridrich Gregan,[a] Juraj Gregan,*[,b] and Marek Skorsepa[a]

[a] *Department of Chemistry, Faculty of Natural Sciences, Matej Bel University; Banska Bystrica 974 01, Slovakia: and* [b] *Max F. Perutz Laboratories, Department of Chromosome Biology, University of Vienna, Dr. Bohr-Gasse 1, 1030 Vienna, Austria.* Received March 2, 2011; accepted May 24, 2011; published online May 30, 2011

Two homologous series of racemic diastereomeric *cis*- and *trans*-(2-dimethylaminomethylcycloheptyl)-2-alkoxyphenylcarbamates with alkyl chain lengths ranging from C_1 to C_8 were synthesized by stereoselective reactions. The chemical structures of these compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy and their physico-chemical properties were characterized. The two new series of diastereomeric compounds were tested for their local anesthetic activity and parabolic relationship between the local anesthetic activity and lipophilicity was found for both *cis*- and *trans*-series. Interestingly, *cis*-stereoisomers exhibited higher local anesthetic activity.

Key words 2-alkoxyphenylcarbamate; local anesthetic activity; synthesis

Over the past century, the field of anesthesia has strongly benefited from advances in techniques employing local anesthetics. Local anesthetics have been widely used to prevent acute pain and to ameliorate pain associated with chronic painful conditions. Despite the remarkable efficacy of local anesthetics, the risk of toxicity associated with these drugs has been a recurring issue since their introduction.[1,2] Therefore, there is a need for new local anesthetic compounds with the aim of maximizing analgesia and minimizing the adverse effects. In our current work, we report the synthesis of two homologous series of diastereomeric 2-alkoxyphenylcarbamates and characterization of their local anesthetic activity. The studied compounds belong to the class of local anesthetics with carbamate group. Many of local anesthetics have functional groups such as aromatic ester, amide, ether, ketone or carbamate that are linked *via* a short chain (2—3 carbon atoms) with a tertiary aminogroup in the form of hydrochloride.[3—5] Previous studies have shown that anesthetic activity depends on the structure and molecular lipophilicity represented by log *P* and related parameters.[6—14] Here, we analyzed the effect of stereoisomerism on the local anesthetic activity of two homologous series of diastereomeric 2-alkoxyphenylcarbamates. Stereochemistry of local anesthetic drugs may affect their potency by altering various characteristics of the drugs such as binding to the target molecules, rate of metabolism and lipophilicity. In this study, we synthesized two homologous series of 16 diastereomeric *cis*- and *trans*-(2-dimethylaminomethylcyclohexyl)-2-alkoxyphenylcarbamates in the form of their hydrochloride salts with one to eight carbon atoms in the alkoxy group and studied the relationship between local anesthetic activity and lipophilicity for both *cis*- and *trans*-isomers.

Chemistry *cis*- and *trans*-2-Dimethylaminomethylcycloheptanols were prepared according to the literature (Chart 1).[11,15—18] 2-Dimethylaminomethylcycloheptanone (**A**, Chart 1) was prepared from cycloheptanone.[19] 2-Alkoxyphenylisocyanates (**C**, Chart 2) were freshly prepared from 2-alkoxyphenylanilines by reaction with phosgene according to the published method.[8,20] Finally, two homologous series of racemic *cis*- and *trans*-(2-dimethylaminomethylcycloheptyl)-2-alkoxyphenylcarbamates (**P1**, Chart 2) were prepared by addition reaction of aminoalcohol (**B**, Chart 2) with alkoxyphenylisocynates (**C**, Chart 2) in toluene.[21,22] The number of carbon atoms in the alkyl group was from 1 to 8. The carbamates (**P1**, Chart 2) were used in their hydrochlorid form (**P2**, Chart 2).

Pharmacology The surface local anesthetic activity indices (SLAA) of prepared compounds **P2-1**—**P2-8** were determined on rabbit cornea according to the Vrba and Sekera method.[22] Different concentrations of the compound were applied into the conjunctival sac for 30 min. Afterwards, corneal sensitivity was tested using a hair aesthesiometer repeatedly in 3-min intervals. The full anesthesia occurred if no response was elicited by 6 consecutive stimulations. Each compound was tested in 3—6 independent experiments using at least three different concentrations. The surface local anesthetic activity index (SLAA) was calculated as the ratio of equieffective concentrations of the standard and the compound and it is a dimensionless value.[23] All biological tests were performed in compliance with regulations for biological testing on animals.

Results and Discussion

The 16 synthesized compounds—hydrochloride salts of *cis*- and *trans*-**P2** (Chart 2) are listed in the Table 1. The yields ranged within the interval 40—63%. The purity of all compounds was checked by partition TLC. The *Rf* values de-

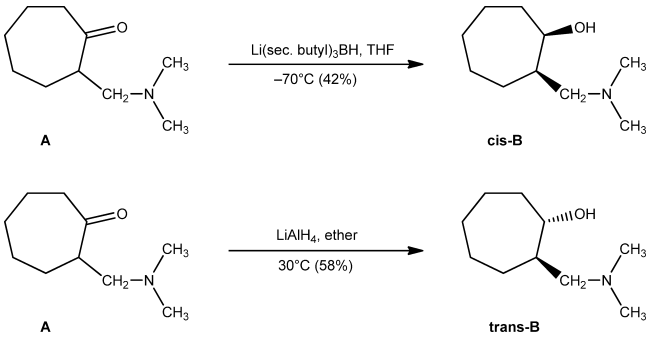


Chart 1. Preparation of *cis*- and *trans*-2-Dimethylaminomethylcycloheptanol

* To whom correspondence should be addressed. e-mail: juraj.gregan@univie.ac.at

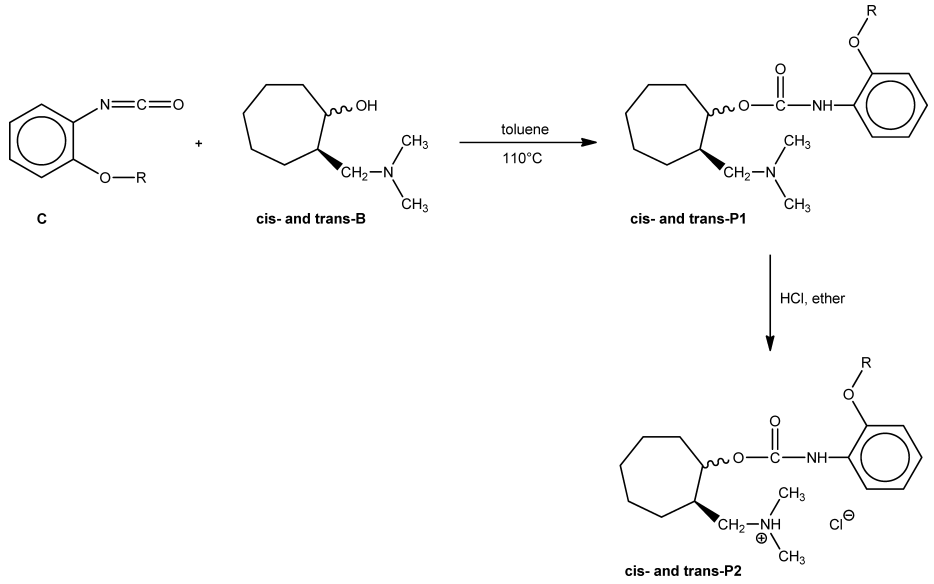
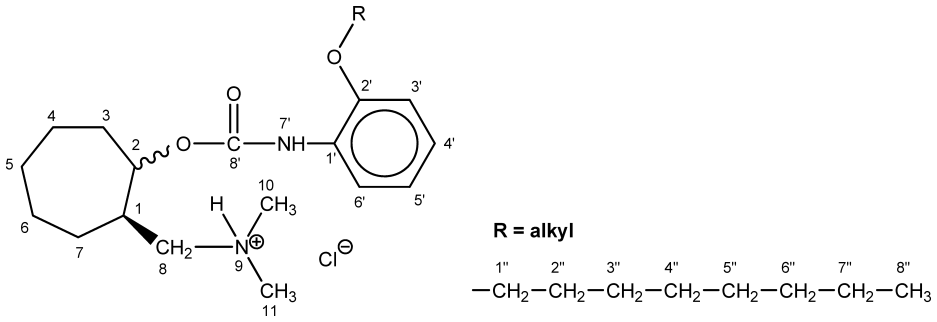


Chart 2. Preparation of Two Homologous Series of *cis*- and *trans*-Carbamates

R=alkyl chain with 1—8 carbons

Table 1. Summary of Prepared *cis*- and *trans*-*N*,*N*-Dimethyl-2-(2-alkoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chlorides (*cis*-**P2** and *trans*-**P2**) and Atoms Numbering for ^{1}H-NMR and ^{13}C-NMR



Comp.	R	M.r.[a)]
cis-**P2-1**	Methyl	356.91
trans-**P2-1**	Methyl	
cis-**P2-2**	Ethyl	370.94
trans-**P2-2**	Ethyl	
cis-**P2-3**	Propyl	384.97
trans-**P2-3**	Propyl	
cis-**P2-4**	Butyl	399.00
trans-**P2-4**	Butyl	
cis-**P2-5**	Pentyl	413.03
trans-**P2-5**	Pentyl	
cis-**P2-6**	Hexyl	427.06
trans-**P2-6**	Hexyl	
cis-**P2-7**	Heptyl	441.09
trans-**P2-7**	Heptyl	
cis-**P2-8**	Octyl	455.12
trans-**P2-8**	Octyl	

a) M.r. stands for relative molecular mass.

creased with the number of carbon atoms in the alkoxy group for both *cis*- and *trans*-diastereomers (Table 2). The difference in *Rf* values caused by one methylene group in the alkoxy group obtained by partition TLC was higher than the one obtained by adsorption TLC. The values obtained from elemental analysis (C, H, N) agreed with theoretical values within ±0.3%. Structure of all prepared compounds was confirmed by NMR and IR spectroscopy.

All prepared **P** compounds had characteristic absorption bands in the IR spectra at 3432 cm^{-1} (N–H stretching), 2383 cm^{-1} ($^{+}$NH stretching), 1732 cm^{-1} (C=O stretching), 1604 cm^{-1} (aromatic C=C stretching) and 1533 cm^{-1} (C–N–H deformation). There were three absorption bands in the UV spectra at 198, 228 and 260 nm. The ε_{max} values of all

three absorption bands for *trans*-isomers were higher than that of *cis*-isomers. The ε_{max} values decreased with number of carbon atoms for both *cis*- and *trans*-isomers.

Starting 2-dimethylaminomethylcycloheptanone was reduced to 2-dimethylaminomethylcycloheptanol. *cis*- and *trans*-Aminoalcohols were prepared according to the literature[15,16] (Charts 1, 2). Depending on the selective reducing agent the *cis*- or *trans*-2-dimethylaminomethylcycloheptanol was formed, respectively.

The steric arrangement of C_1 hydrogen atoms was axial for both *cis*- and *trans*-isomers. δ (*cis*-isomers)=2.21—2.23 ppm, δ (*trans*-isomers)=2.05—2.09 ppm. As expected, we found only a small difference (on average Δ=0.15 ppm) in chemical shifts between these C_1 axial hydrogen atoms in *cis*- and *trans*-isomers. However, the steric arrangement of C_2 hydrogen atoms was different for *cis*- and *trans*-isomers. While hydrogen atoms in *cis*-isomers were equatorial (δ=5.13—5.15 ppm), in *trans*-isomers they had axial positions (δ=4.57—4.62 ppm). The differences in chemical shifts of C_2 hydrogen atoms for *cis*- and *trans*-isomers were significantly higher (Δ=0.55 ppm) compared to C_1 hydrogen atoms (Δ=0.15 ppm) where they were in axial positions for both of the isomers. These results are in agreement with the ^{1}H-NMR data previously published for cyclic systems.

Differences were also found in ^{13}C-NMR for *cis*- and *trans*-isomers. Chemical shifts of C_1 carbons were in the interval of δ=37.0—37.2 ppm for *cis*-isomers and δ=39.4—39.5 ppm for *trans*-isomers. Chemical shifts of C_2 carbons were δ=73.0—73.2 ppm for *cis*-isomers and δ=76.1—76.2 ppm for *trans*-isomers.

All physico-chemical properties and biological activity of prepared *cis*-isomers differed from those of *trans*-isomers. The mp values were higher for *cis*-isomers compared to corresponding *trans*-isomers. Differences were also found in *Rf* values and partition coefficients (Table 2).

Partition coefficients for both *cis*- and *trans*-isomers were measured in the octanol/phosphate buffer system. The relative concentration of the samples in each phase was determined spectrophotometrically in the 228 nm absorption band. The log *P* values of all *trans*-isomers were higher than that of *cis*-isomers (Table 2), presumably due to a higher lipophilicity of the *trans*-isomers. The log *P* values increased with the number of carbon atoms in the alkoxy group for both, *cis*- and *trans*-isomers.

The results of pharmacological evaluation of prepared *cis*-**P2** and *trans*-**P2** compounds are presented in Table 3. The local anesthetic activities (log SLAA) of both *cis*- and *trans*-series were plotted against *n* and log *P* values shown in Fig. 1. The activity increased gradually with the number of car-

Table 2. Indices of Relative Surface Local Anesthetic Activity (SLAA), Partition Coefficients (*P*) and *Rf* Values for *cis*- and *trans*-**P2** Carbamates (See Chart 2)

Comp.	log *P*	SLAA	log SLAA	*Rf*
cis-**P2-1**	1.206	16.3	1.212	0.65
trans-**P2-1**	1.410	10.8	1.032	0.68
cis-**P2-2**	1.704	30.3	1.481	0.63
trans-**P2-2**	1.905	22.5	1.352	0.66
cis-**P2-3**	2.107	89.1	1.950	0.56
trans-**P2-3**	2.236	52.6	1.721	0.57
cis-**P2-4**	2.561	209.9	2.322	0.48
trans-**P2-4**	2.643	152.1	2.180	0.51
cis-**P2-5**	3.030	269.8	2.431	0.41
trans-**P2-5**	3.127	162.2	2.210	0.44
cis-**P2-6**	3.072	289.1	2.461	0.36
trans-**P2-6**	3.188	192.8	2.285	0.39
cis-**P2-7**	3.968	200.9	2.303	0.29
trans-**P2-7**	4.117	129.1	2.111	0.32
cis-**P2-8**	4.450	177.8	2.250	0.19
trans-**P2-8**	4.533	105.4	2.023	0.23

The SLAA index was calculated as the ratio of equieffective concentrations of the standard and the compound.[23]

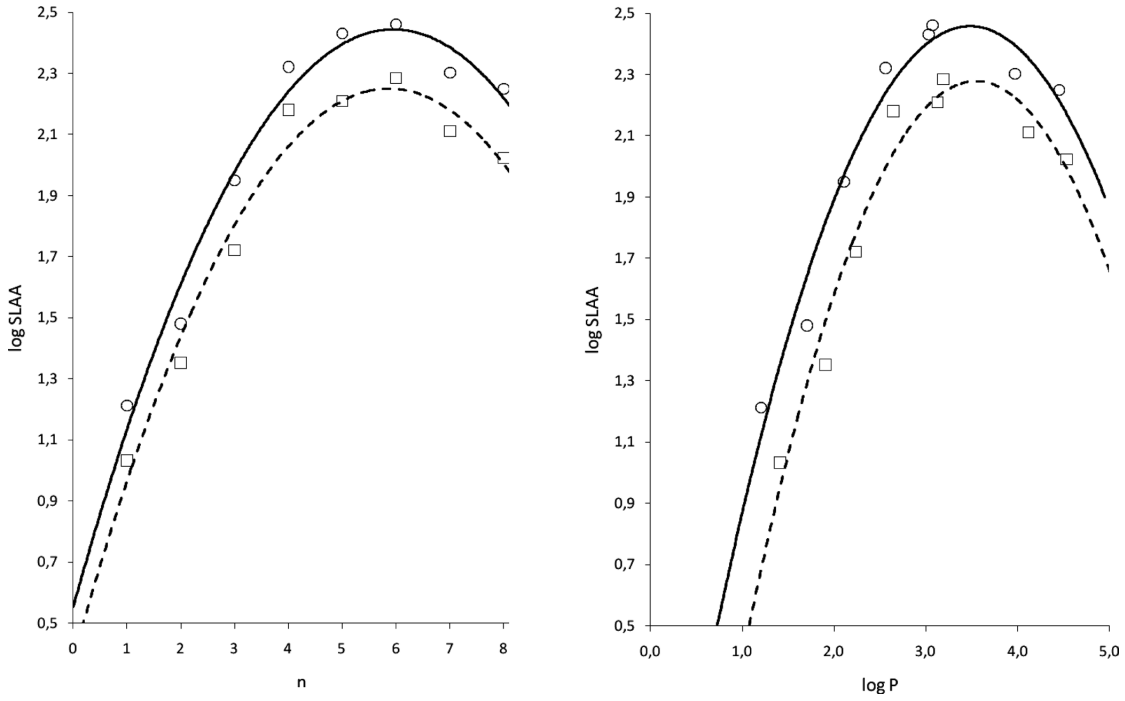


Fig. 1. Log Values of Local Anesthetic Activity (SLAA) *vs. n* (Number of Carbon Atoms in Alkoxy Group) and log *P* (Partition Coefficient) for Compounds *cis*-**P2-1** to *cis*-**P2-8** (○; Full Lines) and *trans*-**P2-1** to *trans*-**P2-8** (□; Dashed Lines)

Table 3. Regression Coefficients for Parabolic Relationships between log SLAA and x ($x=n$ or log P) for the *cis*- and *trans*-Series of Compounds P**2-1**—P**2-8** and for the Equation: $\log \mathrm{SLAA}=a_0+a_1x+a_2x^2$

Series	x	a_0	a_1	a_2	$R^{a)}$
cis	$n^{b)}$	0.5521	0.6360	−0.0535	0.9871
cis	log P	−0.6698	1.7981	−0.2584	0.9821
trans	n	0.3828	0.6368	−0.0543	0.9863
trans	log P	−1.3843	2.0681	−0.2919	0.9799

a) Correlation coefficient. *b*) Number of carbon atoms in the alkoxy group.

bon atoms in the alkoxy group and reached a maximum for log $P=3.3$ which corresponds to the compound with 6 carbon atoms in alkoxy group (see Fig. 1). Indices of the SLAA were significantly higher compared to the reference cocaine compound for all tested compounds with the exception of the methyl homologues of *cis*-**P2-1** and *trans*-**P2-1**. Regression analysis revealed that the data presented in Fig. 1 can best be fitted by a parabolic function. Regression coefficients for parabolic relationship between the log SLAA and the number of carbon atoms in the alkoxy group (n) as well as log P values are shown in Table 3.

Diastereoisomers often have different physical and chemical characteristics such as solubility which may result in different pharmacokinetic and pharmacodynamic properties.[14,24] In this study, we synthesized eight isomeric pairs and compared anesthetic activity of the respective *cis*- and *trans*-isoforms. We observed that anesthetic activity of *cis*-isomers was higher than those of the *trans*-isomers (Table 2, Fig. 1). The potency of local anesthetic drugs is determined by many factors such as lipophilicity, ionization and the rate of metabolism. We observed that partition coefficients of *trans*-isomers were higher than that of the *cis*-isomers (Table 2). Therefore, one possible explanation is that the high anesthetic activity of *cis*-isomers was due to their lower lipophilicity as compared to the respective *trans*-isomers. However, there are other possible explanations which could account for differences in local anesthetic activity of *cis*- and *trans*-isomers (*e.g.* binding to the target molecule) and further experiments are needed to elucidate the underlying mechanism.

Concluding Remarks

Two homologous series of racemic diastereomeric *cis*- and *trans*-(2-dimethylaminomethylcycloheptyl)-2-alkoxyphenylcarbamates were synthesized and assayed for their local anesthetic activity. *cis*-Stereoisomers exhibited higher local anesthetic activity and parabolic relationship between the local anesthetic activity and lipophilicity was found for both *cis*- and *trans*-series. Further studies are required to explain differences in local anesthetic activity of the studied *cis*- and *trans*-isomers.

Experimental

General ^{1}H-NMR spectra at 300 MHz and ^{13}C-NMR spectra at 75 MHz were obtained on Varian Gemini spectrophotometer using tetramethyl silane as an internal standard. IR spectra were taken on M-80 spectrophotometer in chlorophorm. UV spectra were measured on Hewlett Packard 8452 A spectrophotometer.

Melting points were determined on Koflerblock and are uncorrected. Elemental analyses (C, H, N) were obtained on Elemental Analyser Carlo Erba Science Model 1106. The obtained results had a maximum deviation of 0.3% compared to the theoretical value.

The purity of all compounds were checked by partition TLC on Merck silica gel 60 F_{254} plates impregnated with 5% solution of silicon oil in heptane and using 1 M HCl–acetone (1 : 1) as the mobile phase. The detection was performed by the Dragendorff's spray reagent and UV light at 254 nm.

Octanol/water partition coefficients (P) were measured in the system of *n*-octanol and 10^{-2} M potassium phosphate buffer. The relative concentration of the measured compound in each phase was determined spectrophotometrically from the absorption band at 232 nm.

General Procedure for Preparation of *cis*- and *trans*-2-(2-Alkoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chlorides (*cis*-P2 and *trans*-P2, Chart 2) Solution of freshly prepared 2-alkoxyphenylisocyanate (0.01 mol) in anhydrous toluene (15 ml) was mixed with the corresponding *cis*- or *trans*-dimethylaminomethylcycloheptanol (1.7 g, 0,01 mol) and the stirring mixture was heated under reflux for 6 h in argon atmosphere. After cooling, hexane was added (15 ml) and the mixture was allowed to stand for 12 h at −5 °C in a refrigerator. The solid by-product, bis-(2-alkoxyphenyl) urea that formed in a small amount, was filtered off and the toluene filtrate was extracted with 5% hydrochloric acid (3×10 ml). The aqueous layer was extracted with chloroform (3×10 ml). The combined chloroform extracts were dried over anhydrous sodium sulfate. After filtration, chloroform was evaporated using a vacuum rotary evaporator. The residue was mixed with 2×5 ml of anhydrous ether. The solid product was filtered and dried. The obtained colorless solids were finally purified by crystallization: compounds **P2-1**—**P2-3** from butanone, compounds **P2-4**—**P2-6** from ethylacetate and compounds **P2-7**—**P2-8** from heptane : ethylacetate (1 : 1). The yields and physico-chemical characteristics of prepared compounds are presented below.

±*cis*-*N*,*N*-Dimethyl-2-(2-methoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-1) Colourless solid. Yield: 53%. mp 202—203 °C (butanone). IR cm^{-1}: 3428 (N–$H_{stretching}$), 2383 ($^+$N–$H_{stretching}$), 1726 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1533 (C–N–$H_{deformation}$), 1034 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, m^2·mol^{-1}): 198 (3101), 218 (886), 260 (319). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.87 (d, 1H, H-3′, J=8.00 Hz), 7.02 (t, 1H, H-4′, J=8.00, 8.02 Hz), 6.93 (t, 1H, H-5′, J=8.02, 7.68 Hz), 8.03 (d, 1H, H-6′, J=7.68 Hz), 2.82 (s, 6H, H-10, H-11), 7.35 (s, 1H, H-7′), 12.02 (s, 1H, H-9), 3.91 (s, 3H, H-1″), 2.21 (m, 1H, H-1), 3.07 (m, 2H, H-8), 5.13 (ddd, 1H, H-2), 1.99 (m, 2H, H-3), 2.12 (m, 2H, H-7), 1.26—1.32 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.0 (C-1), 73.0 (C-2), 30.4 (C-3), 20.6 (C-4), 24.5 (C-5), 25.5 (C-6), 26.5 (C-7), 61.3 (C-8), 42.8 (C-10), 46.4 (C-11), 129.3 (C-1′), 150.2 (C-2′), 113.1 (C-3′), 125.3 (C-4′), 123.0 (C-5′), 120.3 (C-6′), 155.3 (C-8′), 56.2 (C-1″). Element Analysis for $C_{18}H_{29}N_2O_3Cl$: (i) Calcd: C=60.57%, H=8.19%, N=7.85%. (ii) Found: C=60.75%, H=8.09%, N=7.74%.

±*cis*-*N*,*N*-Dimethyl-2-(2-ethoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-2) Colourless solid. Yield: 63%. mp 134—136 °C (butanone). IR cm^{-1}: 3428 (N–$H_{stretching}$), 2383 ($^+$N–$H_{stretching}$), 1726 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1533 (C–N–$H_{deformation}$), 1034 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, m^2·mol^{-1}): 198 (2092), 218 (850), 260 (295). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.87 (d, 1H, H-3′, J=8.00 Hz), 7.03 (t, 1H, H-4′, J=8.00, 8.02 Hz), 6.94 (t, 1H, H-5′, J=8.02, 7.68 Hz), 8.03 (d, 1H, H-6′, J=7.68 Hz), 2.82 (s, 6H, H-10, H-11), 7.32 (s, 1H, H-7′), 12.04 (s, 1H, H-9), 4.15 (q, 2H, H-1″, J=6.96 Hz), 1.48 (t, 3H, H-2″, J=6.96 Hz), 2.21 (m, 1H, H-1), 3.08 (m, 2H, H-8), 5.13 (ddd, 1H, H-2), 2.00 (m, 2H, H-3), 2.12 (m, 2H, H-7), 1.25—1.33 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.1 (C-1), 73.2 (C-2), 30.5 (C-3), 20.7 (C-4), 24.5 (C-5), 25.5 (C-6), 26.5 (C-7), 61.3 (C-8), 42.8 (C-10), 46.5 (C-11), 129.4 (C-1′), 149.7 (C-2′), 113.2 (C-3′), 125.4 (C-4′), 123.0 (C-5′), 120.4 (C-6′), 155.4 (C-8′), 64.9 (C-1″), 15.1 (C-2″). Element Analysis for $C_{19}H_{31}N_2O_3Cl$: (i) Calcd: C=61.52%, H=8.42%, N=7.55%. (ii) Found: C=61.38%, H=8.53%, N=7.67%.

±*cis*-*N*,*N*-Dimethyl-2-(2-propoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-3) Colourless solid. Yield: 60%. mp 150—151 °C (butanone). IR cm^{-1}: 3429 (N–$H_{stretching}$), 2384 ($^+$N–$H_{stretching}$), 1726 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1532 (C–N–$H_{deformation}$), 1034 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, m^2·mol^{-1}): 198 (2902), 218 (816), 260 (287). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.88 (d, 1H, H-3′, J=8.03 Hz), 7.03 (t, 1H, H-4′, J=8.03, 8.04 Hz), 6.93 (t, 1H, H-5′, J=8.04, 7.69 Hz), 8.03 (d, 1H, H-6′, J=7.69 Hz), 2.83 (s, 6H, H-10, H-11), 7.32 (s, 1H, H-7′), 12.21 (s, 1H, H-9), 4.03 (t, 2H, H-1″, J=7.11 Hz), 1.88 (sext, 2H, H-2″, J=7.11, 7.36 Hz), 1.05 (t, 3H, H-3″, J=7.36 Hz), 2.22 (m, 1H, H-1), 3.08 (m, 2H, H-8), 5.14 (ddd, 1H, H-2), 2.00 (m, 2H, H-3), 2.13 (m, 2H, H-7), 1.26—1.33 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.2 (C-1), 73.1 (C-2), 30.4 (C-3), 20.6 (C-4), 24.6 (C-5), 25.6 (C-6), 26.6 (C-7), 61.4 (C-8), 42.7 (C-10), 46.5 (C-11), 129.4 (C-1′), 150.1 (C-2′), 113.2 (C-3′), 125.4 (C-

4′), 122.9 (C-5′), 120.3 (C-6′), 155.4 (C-8′), 70.9 (C-1″), 22.7 (C-2″), 10.6 (C-3″). Element Analysis for $C_{20}H_{33}N_2O_3Cl$: (i) Calcd: C=62.40%, H=8.64%, N=7.28%. (ii) Found: C=62.66%, H=8.51%, N=7.11%.

±*cis*-*N*,*N*-Dimethyl-2-(2-butoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-4) Colourless solid. Yield: 57%. mp 131—133 °C (ethyl acetate). IR cm^{-1}: 3429 (N–H stretching), 2384 ($^+$N–$H_{stretching}$), 1725 (C=$O_{stretching}$), 1603 (aromatic C=$C_{stretching}$), 1531 (C–N–$H_{deformation}$), 1035 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2887), 218 (811), 260 (275). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.88 (d, 1H, H-3′, J=8.05 Hz), 7.03 (t, 1H, H-4′, J=8.05, 8.06 Hz), 6.93 (t, 1H, H-5′, J=8.06, 7.70 Hz), 8.04 (d, 1H, H-6′, J=7.70 Hz), 2.83 (s, 6H, H-10, H-11), 7.31 (s, 1H, H-7′), 12.15 (s, 1H, H-9), 4.05 (t, 2H, H-1″, J=6.75 Hz), 1.84 (m, 2H, H-2″, J=6.75, 7.00 Hz), 1.48 (m, 2H, H-3″, J=7.00, 6.9 Hz), 1.00 (t, 3H, H-4″, J=6.99 Hz), 2.22 (m, 1H, H-1), 3.07 (m, 2H, H-8), 5.14 (ddd, 1H, H-2), 2.01 (m, 2H, H-3), 2.13 (m, 2H, H-7), 1.26—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.1 (C-1), 73.2 (C-2), 30.4 (C-3), 20.6 (C-4), 24.6 (C-5), 25.6 (C-6), 26.6 (C-7), 61.4 (C-8), 42.7 (C-10), 46.4 (C-11), 129.4 (C-1′), 149.8 (C-2′), 113.1 (C-3′), 125.4 (C-4′), 123.0 (C-5′), 120.2 (C-6′), 155.4 (C-8′), 69.3 (C-1″), 31.4 (C-2″), 19.5 (C-3″), 14.1 (C-4″). Element Analysis for $C_{21}H_{35}N_2O_3Cl$: (i) Calcd: C=63.22%, H=8.84%, N=7.02%. (ii) Found: C=63.48%, H=8.95%, N=6.88%.

±*cis*-*N*,*N*-Dimethyl-2-(2-pentyloxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-5) Colourless solid. Yield: 55%. mp 132—134 °C (ethyl acetate). IR cm^{-1}: 3430 (N–$H_{stretching}$), 2385 ($^+$N–$H_{stretching}$), 1725 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1531 (C–N–$H_{deformation}$), 1035 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2803), 218 (798), 260 (266). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.87 (d, 1H, H-3′, J=8.07 Hz), 7.03 (t, 1H, H-4′, J=8.07, 8.06 Hz), 6.93 (t, 1H, H-5′, J=8.06, 7.70 Hz), 8.04 (d, 1H, H-6′, J=7.70 Hz), 2.84 (s, 6H, H-10, H-11), 7.30 (s, 1H, H-7′), 12.08 (s, 1H, H-9), 4.04 (t, 2H, H-1″, J=6.47 Hz), 1.84 (m, 2H, H-2″, J=6.47, 7.00 Hz), 1.46 (m, 2H, H-3″, J=7.00, 7.30 Hz), 1.40 (m, 2H, H-4″, J=7.30, 6.78 Hz), 0.93 (t, 3H, H-5″, J=6.78 Hz), 2.22 (m, 1H, H-1), 3.07 (m, 2H, H-8), 5.14 (ddd, 1H, H-2), 2.01 (m, 2H, H-3), 2.14 (m, 2H, H-7), 1.25—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.1 (C-1), 73.1 (C-2), 30.4 (C-3), 20.6 (C-4), 24.6 (C-5), 25.6 (C-6), 26.6 (C-7), 61.5 (C-8), 42.7 (C-10), 46.4 (C-11), 129.4 (C-1′), 149.8 (C-2′), 113.0 (C-3′), 125.4 (C-4′), 123.0 (C-5′), 120.2 (C-6′), 155.4 (C-8′), 69.5 (C-1″), 29.1 (C-2″), 28.5 (C-3″), 22.6 (C-4″), 14.3 (C-5″). Element Analysis for $C_{22}H_{37}N_2O_3Cl$: (i) Calcd: C=63.98%, H=9.03%, N=6.78%. (ii) Found: C=63.71%, H=9.22%, N=6.81%.

±*cis*-*N*,*N*-Dimethyl-2-(2-hexyloxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-6) Colourless solid. Yield: 54%. mp 127—128 °C (ethyl acetate). IR cm^{-1}: 3431 (N–$H_{stretching}$), 2385 ($^+$N–$H_{stretching}$), 1725 (C=$O_{stretching}$), 1603 (aromatic C=$C_{stretching}$), 1530 (C–N–$H_{deformation}$), 1035 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2682), 218 (770), 260 (260). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.87 (d, 1H, H-3′, J=8.08 Hz), 7.03 (t, 1H, H-4′, J=8.08, 8.07 Hz), 6.94 (t, 1H, H-5′, J=8.07, 7.70 Hz), 8.04 (d, 1H, H-6′, J=7.70 Hz), 2.84 (s, 6H, H-10, H-11), 7.31 (s, 1H, H-7′), 12.18 (s, 1H, H-9), 4.05 (t, 2H, H-1″, J=6.47 Hz), 1.85 (m, 2H, H-2″, J=6.47, 6.76 Hz), 1.44 (m, 2H, H-3″, J=6.76, 7.24 Hz), 1.35 (m, 2H, H-4″, J=7.24, 7.40 Hz), 1.34 (m, 2H, H-5″, J=7.40, 6.78 Hz), 0.90 (t, 3H, H-6″, J=6.78 Hz), 2.23 (m, 1H, H-1), 3.07 (m, 2H, H-8), 5.15 (ddd, 1H, H-2), 2.00 (m, 2H, H-3), 2.14 (m, 2H, H-7), 1.25—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.1 (C-1), 73.1 (C-2), 30.4 (C-3), 20.6 (C-4), 24.6 (C-5), 25.6 (C-6), 26.6 (C-7), 61.5 (C-8), 42.7 (C-10), 46.4 (C-11), 129.4 (C-1′), 149.8 (C-2′), 113.0 (C-3′), 125.4 (C-4′), 123.0 (C-5′), 120.2 (C-6′), 155.4 (C-8′), 69.6 (C-1″), 29.3 (C-2″), 26.0 (C-3″), 31.8 (C-4″), 22.8 (C-5″), 14.2 (C-6″). Element Analysis for $C_{23}H_{39}N_2O_3Cl$: (i) Calcd: C=64.69%, H=9.21%, N=6.56%. (ii) Found: C=64.93%, H=9.37%, N=6.35%.

±*cis*-*N*,*N*-Dimethyl-2-(2-heptyloxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-7) Colourless solid. Yield: 52%. mp 136—138 °C (heptane : ethyl acetate, 1 : 1). IR cm^{-1}: 3431 (N–$H_{stretching}$), 2386 ($^+$N–$H_{stretching}$), 1724 (C=$O_{stretching}$), 1603 (aromatic C=$C_{stretching}$), 1529 (C–N–$H_{deformation}$), 1036 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (1838), 218 (508), 260 (185). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.88 (d, 1H, H-3′, J=8.10 Hz), 7.03 (t, 1H, H-4′, J=8.10, 8.09 Hz), 6.94 (t, 1H, H-5′, J=8.09, 7.70 Hz), 8.04 (d, 1H, H-6′, J=7.70 Hz), 2.84 (s, 6H, H-10, H-11), 7.32 (s, 1H, H-7′), 12.18 (s, 1H, H-9), 4.05 (t, 2H, H-1″, J=6.47 Hz), 1.84 (m, 2H, H-2″, J=6.47, 6.76 Hz), 1.43 (m, 2H, H-3″, J=6.76, 7.00 Hz), 1.37 (m, 2H, H-4″, J=7.00, 7.40 Hz), 1.32 (m, 2H, H-5″, J=7.40, 7.40 Hz), 1.30 (m, 2H, H-6″, J=7.40, 6.78 Hz), 0.89 (t, 3H, H-7″, J=6.78 Hz), 2,23 (m, 1H, H-1), 3.07 (m, 2H, H-8), 5.15 (ddd, 1H, H-2), 1.99 (m, 2H, H-3), 2.14 (m, 2H, H-7), 1.26—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.1 (C-1), 73.1 (C-2), 30.4 (C-3), 20.6 (C-4), 24.6 (C-5), 25.6 (C-6), 26.6 (C-7), 61.5 (C-8), 42.7 (C-10), 46.4 (C-11), 129.4 (C-1′), 149.8 (C-2′), 113.0 (C-3′), 125.4 (C-4′), 123.0 (C-5′), 120.2 (C-6′), 155.4 (C-8′), 69.6 (C-1″), 29.4 (C-2″), 26.3 (C-3″), 29.3 (C-4″), 32.1 (C-5″), 22.8 (C-6″), 14.3 (C-7″). Element Analysis for $C_{24}H_{41}N_2O_3Cl$: (i) Calcd: C=65.35%, H=9.37%, N=6.35%. (ii) Found: C=65.54%, H=9.16%, N=6.52%.

±*cis*-*N*,*N*-Dimethyl-2-(2-octyloxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*cis*-P2-8) Colourless solid. Yield: 50%. mp 127—129 °C (heptane : ethyl acetate, 1 : 1). IR cm^{-1}: 3432 (N–$H_{stretching}$), 2386 ($^+$N–$H_{stretching}$), 1724 (C=$O_{stretching}$), 1603 (aromatic C=$C_{stretching}$), 1529 (C–N–$H_{deformation}$), 1036 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (1272), 218 (343), 260 (227). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.88 (d, 1H, H-3′, J=8.11 Hz), 7.03 (t, 1H, H-4′, J=8.11, 8.09 Hz), 6.94 (t, 1H, H-5′, J=8.09, 7.70 Hz), 8.04 (d, 1H, H-6′, J=7.70 Hz), 2.83 (s, 6H, H-10, H-11), 7.31 (s, 1H, H-7′), 12.22 (s, 1H, H-9), 4.06 (t, 2H, H-1″, J=6.47 Hz), 1.85 (m, 2H, H-2″, J=6.47, 6.76 Hz), 1.43 (m, 2H, H-3″, J=6.76, 7.00 Hz), 1.37 (m, 2H, H-4″, J=7.00, 7.50 Hz), 1.31 (m, 2H, H-5″, J=7.50, 7.40 Hz), 1.29 (m, 2H, H-6″, J=7.40, 7.40 Hz), 1.28 (m, 2H, H-7″, J=7.40, 6.78 Hz), 0.87 (t, 3H, H-8″, J=6.78 Hz), 2,22 (m, 1H, H-1), 3.08 (m, 2H, H-8), 5.15 (ddd, 1H, H-2), 2.00 (m, 2H, H-3), 2.14 (m, 2H, H-7), 1.26—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.1 (C-1), 73.1 (C-2), 30.4 (C-3), 20.6 (C-4), 24.6 (C-5), 25.6 (C-6), 26.6 (C-7), 61.5 (C-8), 42.7 (C-10), 46.4 (C-11), 129.4 (C-1′), 149.8 (C-2′), 113.0 (C-3′), 125.4 (C-4′), 123.0 (C-5′), 120.2 (C-6′), 155.4 (C-8′), 69.6 (C-1″), 29.6 (C-2″), 26.3 (C-3″), 29.4 (C-4″), 29.6 (C-5″), 32.1 (C-6″), 22.8 (C-7″), 14.4 (C-8″). Element Analysis for $C_{25}H_{43}N_2O_3Cl$: (i) Calcd: C=65.98%, H=9.52%, N=6.16%. (ii) Found: C=66.24%, H=9.65%, N=6.07%.

±*trans*-*N*,*N*-Dimethyl-2-(2-methoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*trans*-P2-1) Colourless solid. Yield: 46%. mp 150—151 °C (butanone). IR cm^{-1}: 3428 (N–$H_{stretching}$), 2383 ($^+$N–$H_{stretching}$), 1726 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1533 (C–N–$H_{deformation}$), 1034 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (3305), 218 (946), 260 (325). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.00 (d, 1H, H-3′, J=8.00 Hz), 7.15 (t, 1H, H-4′, J=8.00, 8.02 Hz), 7.08 (t, 1H, H-5′, J=8.02, 7.68 Hz), 8.16 (d, 1H, H-6′, J=7.68 Hz), 2.91 (s, 6H, H-10, H-11), 7.62 (s, 1H, H-7′), 12.05 (s, 1H, H-9), 3.94 (s, 3H, H-1′), 2.05 (m, 1H, H-1), 2.96 (m, 2H, H-8), 4.57 (m, 1H, H-2), 2.18 (m, 2H, H-3), 2.52 (m, 2H, H-7), 1.26—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.5 (C-1), 76.2 (C-2), 32.4 (C-3), 24.4 (C-4), 24.8 (C-5), 25.0 (C-6), 30.9 (C-7), 62.1 (C-8), 43.2 (C-10), 46.3 (C-11), 129.2 (C-1′), 150.4 (C-2′), 112.0 (C-3′), 125.3 (C-4′), 123.0 (C-5′), 120.4 (C-6′), 155.2 (C-8′), 56.4 (C-1″). Element Analysis for $C_{18}H_{29}N_2O_3Cl$: (i) Calcd: C=60.57%, H=8.19%, N=7.85%. (ii) Found: C=60.41%, H=8.02%, N=7.91%.

±*trans*-*N*,*N*-Dimethyl-2-(2-ethoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*trans*-P2-2) Colourless solid. Yield: 44%. mp 119—120 °C (butanone). IR cm^{-1}: 3428 (N–$H_{stretching}$), 2383 ($^+$N–$H_{stretching}$), 1726 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1533 (C–N–$H_{deformation}$), 1034 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2100), 218 (913), 260 (299). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.99 (d, 1H, H-3′, J=8.00 Hz), 7.14 (t, 1H, H-4′, J=8.00, 8.02 Hz), 7.07 (t, 1H, H-5′, J=8.02, 7.68 Hz), 8.16 (d, 1H, H-6′, J=7.68 Hz), 2.92 (s, 6H, H-10, H-11), 7.62 (s, 1H, H-7′), 11.90 (s, 1H, H-9), 4.17 (q, 2H, H-1″, J=6.96 Hz), 1.49 (t, 3H, H-2″, J=6.96 Hz), 2.06 (m, 1H, H-1), 2.97 (m, 2H, H-8), 4.58 (m, 1H, H-2), 2.19 (m, 2H, H-3), 2.51 (m, 2H, H-7), 1.26—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.4 (C-1), 76.2 (C-2), 32.3 (C-3), 24.3 (C-4), 24.7 (C-5), 25.0 (C-6), 30.8 (C-7), 62.0 (C-8), 43.1 (C-10), 46.2 (C-11), 129.3 (C-1′), 149.7 (C-2′), 112.8 (C-3′), 125.2 (C-4′), 122.8 (C-5′), 120.5 (C-6′), 155.2 (C-8′), 64.9 (C-1″), 15.0 (C-2″). Element Analysis for $C_{19}H_{31}N_2O_3Cl$: (i) Calcd: C=61.52%, H=8.42%, N=7.55%. (ii) Found: C=61.44%, H=8.30%, N=7.45%.

±*trans*-*N*,*N*-Dimethyl-2-(2-propoxyphenylcarbamoyloxy)cycloheptylmethylammonium Chloride (*trans*-P2-3) Colourless solid. Yield: 43%. mp 143—144 °C (butanone). IR cm^{-1}: 3429 (N–$H_{stretching}$), 2384 ($^+$N–$H_{stretching}$), 1726 (C=$O_{stretching}$), 1602 (aromatic C=$C_{stretching}$), 1532 (C–N–$H_{deformation}$), 1034 (CO–$N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (3112), 218 (870), 260 (293). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.99 (d, 1H, H-3′, J=8.03 Hz), 7.14 (t, 1H, H-4′, J=8.03, 8.04 Hz), 7.08 (t, 1H, H-5′, J=8.04, 7.69 Hz), 8.16 (d, 1H, H-6′, J=7.69 Hz), 2.87 (s, 6H, H-10, H-11), 7.55 (s, 1H, H-7′), 12.29 (s, 1H, H-9), 4.06 (t, 2H, H-1″, J=7.11 Hz), 1.90 (sext, 2H, H-2″, J=7.11, 7.36 Hz), 1.07 (t, 3H, H-3″, J=7.36 Hz), 2.08 (m, 1H, H-1), 2.95 (m, 2H, H-8), 4.60 (m, 1H, H-2), 2.19 (m, 2H, H-3), 2.60 (m, 2H, H-7), 1.25—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.4 (C-1), 76.1 (C-2), 32.4 (C-3), 24.3 (C-4), 24.7 (C-5), 25.1 (C-6), 30.8 (C-7), 62.1 (C-8), 43.1 (C-10), 46.3 (C-11), 129.2 (C-1′), 150.0 (C-2′), 112.7 (C-

3′), 125.2 (C-4′), 122.8 (C-5′), 120.4 (C-6′), 155.3 (C-8′), 70.9 (C-1″), 22.7 (C-2″), 10.7 (C-3″). Element Analysis for $C_{20}H_{33}N_2O_3Cl$: (i) Calcd: C=62.40%, H=8.64%, N=7.28%. (ii) Found: C=62.29%, H=8.72%, N=7.40%.

±*trans*-*N*,*N*-Dimethyl-2-(2-butoxyphenylcarbamoyloxy)cyclohepthylmethylammonium Chloride (*trans*-P2-4) Colourless solid. Yield: 42%. mp 130—132 °C (ethyl acetate). IR cm^{-1}: 3429 ($N–H_{stretching}$), 2384 ($^{+}N–H_{stretching}$), 1725 ($C=O_{stretching}$), 1603 (aromatic $C=C_{stretching}$), 1531 ($C–N–H_{deformation}$), 1035 ($CO–N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (3047), 218 (835), 260 (280). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.00 (d, 1H, H-3′, J=8.05 Hz), 7.14 (t, 1H, H-4′, J=8.05, 8.06 Hz), 7.07 (t, 1H, H-5′, J=8.06, 7.70 Hz), 8.15 (d, 1H, H-6′, J=7.70 Hz), 2.88 (s, 6H, H-10, H-11), 7.55 (s, 1H, H-7′), 12.25 (s, 1H, H-9), 4.09 (t, 2H, H-1″, J=6.75 Hz), 1.85 (m, 2H, H-2″, J=6.75, 7.00 Hz), 1.52 (m, 2H, H-3″, J=7.00, 6.9 Hz), 1.01 (t, 3H, H-4″, J=6.99 Hz), 2.09 (m, 1H, H-1), 2.96 (m, 2H, H-8), 4.61 (m, 1H, H-2), 2.20 (m, 2H, H-3), 2.59 (m, 2H, H-7), 1.26—1.34 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.5 (C-1), 76.1 (C-2), 32.4 (C-3), 24.4 (C-4), 24.8 (C-5), 25.1 (C-6), 30.9 (C-7), 62.1 (C-8), 43.1 (C-10), 46.4 (C-11), 129.3 (C-1′), 150.1 (C-2′), 112.7 (C-3′), 125.3 (C-4′), 122.8 (C-5′), 120.4 (C-6′), 155.2 (C-8′), 69.0 (C-1″), 31.5 (C-2″), 19.0 (C-3″), 14.0 (C-4″). Element Analysis for $C_{21}H_{35}N_2O_3Cl$: (i) Calcd: C=63.22%, H=8.84%, N=7.02%. (ii) Found: C=63.19%, H=8.72%, N=7.10%.

±*trans*-*N*,*N*-Dimethyl-2-(2-pentyloxyphenylcarbamoyloxy)cyclohepthylmethylammonium Chloride (*trans*-P2-5) Colourless solid. Yield: 40%. mp 119—121 °C (ethyl acetate). IR cm^{-1}: 3430 ($N–H_{stretching}$), 2385 ($^{+}N–H_{stretching}$), 1725 ($C=O_{stretching}$), 1602 (aromatic $C=C_{stretching}$), 1531 ($C–N–H_{deformation}$), 1035 ($CO–N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2927), 218 (809), 260 (271). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.00 (d, 1H, H-3′, J=8.07 Hz), 7.14 (t, 1H, H-4′, J=8.07, 8.06 Hz), 7.08 (t, 1H, H-5′, J=8.06, 7.70 Hz), 8.16 (d, 1H, H-6′, J=7.70 Hz), 2.87 (s, 6H, H-10, H-11), 7.56 (s, 1H, H-7′), 12.38 (s, 1H, H-9), 4.09 (t, 2H, H-1″, J=6.47 Hz), 1.87 (m, 2H, H-2″, J=6.47, 7.00 Hz), 1.50 (m, 2H, H-3″, J=7.00, 7.30 Hz), 1.44 (m, 2H, H-4″, J=7.30, 6.78 Hz), 0.96 (t, 3H, H-5″, J=6.78 Hz), 2.09 (m, 1H, H-1), 2.96 (m, 2H, H-8), 4.60 (m, 1H, H-2), 2.17 (m, 2H, H-3), 2.62 (m, 2H, H-7), 1.26—1.33 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.5 (C-1), 76.2 (C-2), 32.4 (C-3), 24.4 (C-4), 24.8 (C-5), 24.9 (C-6), 31.0 (C-7), 62.1 (C-8), 43.2 (C-10), 46.4 (C-11), 129.2 (C-1′), 150.2 (C-2′), 112.8 (C-3′), 125.3 (C-4′), 122.8 (C-5′), 120.4 (C-6′), 155.2 (C-8′), 69.4 (C-1″), 29.1 (C-2″), 28.3 (C-3″), 22.6 (C-4″), 14.2 (C-5″). Element Analysis for $C_{22}H_{37}N_2O_3Cl$: (i) Calcd: C=63.98%, H=9.03%, N=6.78%. (ii) Found: C=64.18%, H=8.89%, N=6.60%.

±*trans*-*N*,*N*-Dimethyl-2-(2-hexyloxyphenylcarbamoyloxy)cyclohepthylmethylammonium Chloride (*trans*-P2-6) Colourless solid. Yield: 42%. mp 107—109 °C (ethyl acetate). IR cm^{-1}: 3431 ($N–H_{stretching}$), 2385 ($^{+}N–H_{stretching}$), 1725 ($C=O_{stretching}$), 1603 (aromatic $C=C_{stretching}$), 1530 ($C–N–H_{deformation}$), 1035 ($CO–N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2831), 218 (783), 260 (263). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.99 (d, 1H, H-3′, J=8.08 Hz), 7.15 (t, 1H, H-4′, J=8.08, 8.07 Hz), 7.07 (t, 1H, H-5′, J=8.07, 7.70 Hz), 8.15 (d, 1H, H-6′, J=7.70 Hz), 2.90 (s, 6H, H-10, H-11), 7.56 (s, 1H, H-7′), 12.31 (s, 1H, H-9), 4.08 (t, 2H, H-1″, J=6.47 Hz), 1.86 (m, 2H, H-2″, J=6.47, 6.76 Hz), 1.47 (m, 2H, H-3″, J=6.76, 7.24 Hz), 1.38 (m, 2H, H-4″, J=7.24, 7.40 Hz), 1.38 (m, 2H, H-5″, J=7.40, 6.78 Hz), 0.93 (t, 3H, H-6″, J=6.78 Hz), 2.07 (m, 1H, H-1), 2.97 (m, 2H, H-8), 4.60 (m, 1H, H-2), 2.17 (m, 2H, H-3), 2.61 (m, 2H, H-7), 1.25—1.33 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.5 (C-1), 76.2 (C-2), 32.4 (C-3), 24.4 (C-4), 24.8 (C-5), 24.9 (C-6), 30.9 (C-7), 62.1 (C-8), 43.2 (C-10), 46.5 (C-11), 129.2 (C-1′), 150.2 (C-2′), 112.8 (C-3′), 125.3 (C-4′), 122.8 (C-5′), 120.4 (C-6′), 155.2 (C-8′), 69.4 (C-1″), 29.4 (C-2″), 26.0 (C-3″), 31.8 (C-4″), 22.2 (C-5″), 14.1 (C-6″). Element Analysis for $C_{23}H_{39}N_2O_3Cl$: (i) Calcd: C=64.69%, H=9.21%, N=6.56%. (ii) Found: C=64.41%, H=9.40%, N=6.72%.

±*trans*-*N*,*N*-Dimethyl-2-(2-heptyloxyphenylcarbamoyloxy)cyclohepthylmethylammonium Chloride (*trans*-P2-7) Colourless solid. Yield: 41%. mp 101—103 °C (heptane : ethyl acetate, 1 : 1). IR cm^{-1}: 3431 ($N–H_{stretching}$), 2386 ($^{+}N–H_{stretching}$), 1724 ($C=O_{stretching}$), 1603 (aromatic $C=C_{stretching}$), 1529 ($C–N–H_{deformation}$), 1036 ($CO–N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (2064), 218 (558), 260 (194). ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.99 (d, 1H, H-3′, J=8.10 Hz), 7.15 (t, 1H, H-4′, J=8.10, 8.09 Hz), 7.07 (t, 1H, H-5′, J=8.09, 7.70 Hz), 8.15 (d, 1H, H-6′, J=7.70 Hz), 8.90 (s, 6H, H-10, H-11), 7.56 (s, 1H, H-7′), 12.35 (s, 1H, H-9), 4.08 (t, 2H, H-1″, J=6.47 Hz), 1.86 (m, 2H, H-2″, J=6.47, 6.76 Hz), 1.46 (m, 2H, H-3″, J=6.76, 7.00 Hz), 1.41 (m, 2H, H-4″, J=7.00, 7.40 Hz), 1.34 (m, 2H, H-5″, J=7.40, 7.40 Hz), 1.34 (m, 2H, H-6″, J=7.40, 6.78 Hz), 0.91 (t, 3H, H-7″, J=6.78 Hz), 2.06 (m, 1H, H-1), 2.98 (m, 2H, H-8), 4.62 (m, 1H, H-2), 2.16 (m, 2H, H-3), 2.62 (m, 2H, H-7), 1.26—1.32 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.5 (C-1), 76.2 (C-2), 32.3 (C-3), 24.4 (C-4), 24.8 (C-5), 24.9 (C-6), 30.9 (C-7), 62.1 (C-8), 43.2 (C-10), 46.5 (C-11), 129.2 (C-1′), 150.2 (C-2′), 112.8 (C-3′), 125.3 (C-4′), 122.8 (C-5′), 120.4 (C-6′), 155.2 (C-8′), 69.4 (C-1″), 29.4 (C-2″), 26.3 (C-3″), 29.3 (C-4″), 32.1 (C-5″), 22.8 (C-6″), 14.2 (C-7″). Element Analysis for $C_{24}H_{41}N_2O_3Cl$: (i) Calcd: C=65.35%, H=9.37%, N=6.35%. (ii) Found: C=65.17%, H=9.48%, N=6.19%.

±*trans*-*N*,*N*-Dimethyl-2-(2-octyloxyphenylcarbamoyloxy)cyclohepthylmethylammonium Chloride (*trans*-P2-8) Colourless solid. Yield: 40%. mp 81—83 °C (heptane : ethyl acetate, 1 : 1). IR cm^{-1}: 3432 ($N–H_{stretching}$), 2386 ($^{+}N–H_{stretching}$), 1724 ($C=O_{stretching}$), 1603 (aromatic $C=C_{stretching}$), 1529 ($C–N–H_{deformation}$), 1036 ($CO–N_{stretching}$). UV–VIS λ_{max} nm (ε, $m^2 \cdot mol^{-1}$): 198 (1455), 218 (396), 260 (235). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.00 (d, 1H, H-3′, J=8.11 Hz), 7.15 (t, 1H, H-4′, J=8.11, 8.09 Hz), 7.09 (t, 1H, H-5′, J=8.09, 7.70 Hz), 8.15 (d, 1H, H-6′, J=7.70 Hz), 2.90 (s, 6H, H-10, H-11), 7.56 (s, 1H, H-7′), 12.36 (s, 1H, H-9), 4.08 (t, 2H, H-1″, J=6.47 Hz), 1.86 (m, 2H, H-2″, J=6.47, 6.76 Hz), 1.46 (m, 2H, H-3″, J=6.76, 7.00 Hz), 1.41 (m, 2H, H-4″, J=7.00, 7.50 Hz), 1.32 (m, 2H, H-5″, J=7.50, 7.40 Hz), 1.32 (m, 2H, H-6″, J=7.40, 7.40 Hz), 1.32 (m, 2H, H-7″, J=7.40, 6.78 Hz), 0.90 (t, 3H, H-8″, J=6.78 Hz), 2.06 (m, 1H, H-1), 3.01 (m, 2H, H-8), 4.60 (m, 1H, H-2), 2.16 (m, 2H, H-3), 2.62 (m, 2H, H-7), 1.26—1.32 (m, 6H, H-4—6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.4 (C-1), 76.2 (C-2), 32.4 (C-3), 24.4 (C-4), 24.8 (C-5), 24.9 (C-6), 30.8 (C-7), 62.2 (C-8), 43.3 (C-10), 46.6 (C-11), 129.2 (C-1′), 150.3 (C-2′), 112.8 (C-3′), 125.3 (C-4′), 122.8 (C-5′), 120.5 (C-6′), 155.2 (C-8′), 69.5 (C-1″), 29.5 (C-2″), 26.3 (C-3″), 29.4 (C-4″), 29.6 (C-5″), 32.1 (C-6″), 22.9 (C-7″), 14.2 (C-8″). Element Analysis for $C_{25}H_{43}N_2O_3Cl$: (i) Calcd: C=65.98%, H=9.52%, N=6.16%. (ii) Found: C=65.92%, H=9.41%, N=6.13%.

Acknowledgements We are indebted to Assoc. Prof. Dr. E. Racanska from Department of Pharmacology and Toxicology, Faculty of Pharmacy, Kalinciakova 8, 8332 32 Bratislava, for pharmaceutical testing and evaluation of the results. This work was supported by the Austrian Science Fund (FWF) Grant F3403.

References

1) Dillane D., Finucane B. T., *Can. J. Anaesth.*, **57**, 368—380 (2010).
2) Borgeat A., Aguirre J., *Curr. Opin. Anaesthesiol.*, **23**, 650—655 (2010).
3) Remko M., Scheiner S., *J. Pharm. Sci.*, **80**, 328—332 (1991).
4) Racanská E., Gregán F., *Pharmazie*, **54**, 68—70 (1999).
5) Heavner J. E., *Curr. Opin. Anaesthesiol.*, **20**, 336—342 (2007).
6) Benes L., *Drugs Future*, **16**, 627—630 (1991).
7) Devinsky F., Masarova L., Lacko I., Mlynarcik D., *J. Biopharm. Sci.*, **2**, 1—10 (1991).
8) Cizmarik J., Borovansky J., Svec P., *Acta Facult. Pharm. Univ. Comenianae*, **29**, 53—80 (1976).
9) Remko M., Van Duijnen P. T., *J. Mol. Struct. Theochem.*, **105**, 1—7 (1983).
10) Stolc S., Nemcek V., Szöcsová H., *Eur. J. Pharmacol.*, **164**, 249—256 (1989).
11) Gregán F., Kettmann V., Novomesky P., Polásek E., Sivy J., *Il Farmaco*, **50**, 829—839 (1995).
12) Schmidt F., Stemmler R. T., Rudolph J., Bolm C., *Chem. Soc. Rev.*, **35**, 454—470 (2006).
13) Ekatodramis G., Borgeat A., *Curr. Top. Med. Chem.*, **1**, 205—206 (2001).
14) Mather L. E., *Minerva Anestesiol.*, **71**, 507—516 (2005).
15) Forro E., Kanerva L. T., Fulop F., *Tetrahedron Asymmetry*, **9**, 513—520 (1998).
16) Forro E., Fulop F., *Tetrahedron Asymmetry*, **10**, 1985—1993 (1999).
17) Gregan F., Kettmann V., Novomesky P., Sivy J., *Collect. Czech. Chem. Commun.*, **59**, 675—682 (1994).
18) Ratouis R., Combes G., *Bull. Soc. Chim. Fr.*, **1959**, 576—578 (1959).
19) Le N. A., Jones M., Bickelhaupt F., Wolf W. H., *J. Am. Chem. Soc.*, **111**, 8491—8493 (1989).
20) Gregan F., Svec P., Misikova E., Oremusova J., *Ceska Slov. Farm.*, **46**, 205—210 (1997).
21) Blesova M., Cizmarik J., Bachrata M., Bezakova Z., Borovansky A., *Collect. Czech. Chem. Commun.*, **50**, 1133—1140 (1985).
22) Vrba C., Sekera A., *Arch. Int. Pharmacodyn. Ther.*, **118**, 155—166 (1959).
23) Gregán F., Kettmann V., Novomesky P., Racanska E., Svec P., *Il Farmaco*, **48**, 375—385 (1993).
24) Whiteside J. B., Wildsmith J. A., *Br. J. Anaesth.*, **87**, 27—35 (2001).