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A novel class of allosteric modulators of the muscarinic M_2 acetylcholine receptor: terphenyl derivatives

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Abstract—The allosteric modulation of receptors has become a widely accepted concept in order to enhance the agonist or antagonist binding to a receptor. Alcuronium, characterized by a high allosteric potency and a positive cooperativity at the muscarinic M_2 receptor, was chosen as a template to design a structural novel terphenyl-type of allosteric modulator. The skeleton was build up from 1-bromo-2-methylnaphthalene and 1,4-dibromo-2,5-dimethylbenzene using bis(triphenylphosphine)nickel(II) dichloride as a catalyst. Several amino substituted terphenyls were synthesised and preliminary pharmacological tests were performed.
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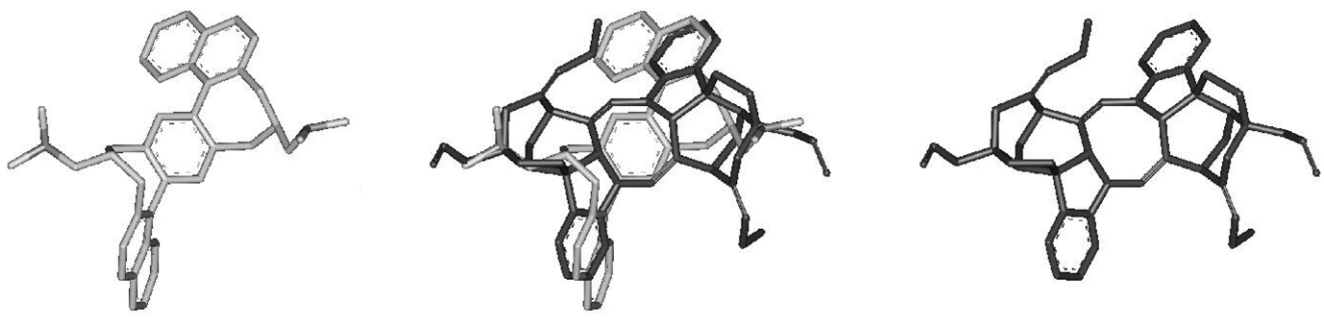
1. Introduction

The allosteric modulation of G-protein-coupled receptors has become a widely accepted concept[1] especially in the case of muscarinic receptors,[2–5] which provides unique therapeutic perspectives, i.e. the promotion of the action of orthosteric antagonists and endogenous agonists with a very high subtype selectivity. The therapy of organophosphorus poisoning, pain and Alzheimer's disease can take advantage of this concept.

Alcuronium[6,7] and caracurine alkaloids[8,9] are among the highly potent allosteric modulators, both characterized by an allosteric potency in the nanomolar range of concentration and a positive cooperativity resulting in an enhancement of muscarinic ligand binding of both agonists and antagonists such as *N*-methylscopolamine (NMS). Additionally, these compounds have an almost rigid structure and thus, they are excellent templates for the development of a pharmacophore model[10–12] consisting of two aromatic areas and two positive charges in a distance equivalent to six to seven methylene groups. Taking this pharmacophore hypothesis into consideration the skeleton of helical terphenylophanes, first described by Kiupel et al.,[13] was chosen to design a structural novel type of allosteric modulators. Introduction of a dimethylamino-methane group to both cycloheptane rings revealed a compound whose pharmacophoric elements fit perfectly on the corresponding elements in alcuronium (see Scheme 1, compound **1**).

The aim of this study was to develop a synthesis strategy



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Scheme 1. Fit (middle) of the terphenylophane derivatives (left) onto alcuronium (right) using the pharmacophoric elements, two aromatic rings and two positively charged nitrogens.

Keywords: allosteric modulation; muscarinic receptors; terphenyl derivatives.
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which makes amino substituted terphenyls or corresponding skeletons with varying substitution patterns available. Compounds of this kind are rigid to a certain extent. However, they have more dynamic flexibility than alcuronium. Due to the rigidity the loss of entropy on binding to the receptor protein will be limited on the one hand. On the other hand the flexibility will allow a proper adoption to the receptor surface and the interaction with corresponding functional groups.[14] Since alcuronium was taken as a lead structure it can be expected that the compounds will have the ability to enhance the ligand binding.

2. Results and discussion

According to Kiupel et al.[13] the synthesis of the terphenylophane starts off with C–C formation between 1-bromo-2-methylnaphthalene and 1,4-dibromo-2,5-dimethylbenzene using triphenylphosphine and nickel acetylacetonate as a catalyst. In order to build up the helix the benzylic methyl groups have to be monosubstituted with bromine by means of *N*-bromosuccinimide (NBS) and 2,2′-azobis(2-methylpropionitrile) (AIBN). In contrast to Kiupel et al.[13] it was almost impossible to obtain the pure tetrasubstituted compound which can be cyclized with diethyl malonate in presence of NaH in toluene to give the helical terphenylophane. Variations of the reaction conditions always resulted in mixtures of underbrominated terphenylophanes whose components could not be isolated by means of chromatography. In addition, the subsequent reaction could be only performed in small portions. Since a couple of reactions have to follow in order to obtain the amino substituted terphenylophane and large amounts of the terphenylophane are required the strategy was slightly changed. Instead of 1,4-dibromo-2,5-dimethylbenzene 1,4-dibromobenzene was used in the first step. Since the middle phenyl ring cannot be connected twice to the lateral naphthalene ring the skeleton will be a more flexible and the important bromination will be easier to carry out.

Two moles of 1-bromo-2-methylnaphthalene can be connected to 1,4-dibromobenzene in acceptable yields using the catalyst bis(triphenylphosphine)nickel(II) dichloride[15,16] which gave higher yields than the aforementioned nickel acetylacetonate. The corresponding dibromination of the two methyl groups could be easily achieved in high yields applying the same radical conditions as described by Kiupel et al.[13] The bisbromoterphenyl was used for two different synthesis routes. Following the first route the terphenyls were alkylated with diethyl malonate using lithium bis(trimethylsilyl)amide (Li-MDS) in THF. The obtained diesters were cleaved by means of KOH in ethanol and decarboxylated with HCl in DMSO. The resulting dicarbonic acid was converted to the diamide with oxalylchloride in THF and with cyclohexylamine and methoxyethylamine, respectively. The obtained diamide was reduced using 1.0 M diborane THF solution to give the corresponding diamine (**8a** and **8b**).

Following the second pathway KCN and methyltrialkyl(C8–C10)ammonium chloride (Adogen®464) in toluene and water was added. The obtained dinitrile was reduced by means of 1.0 M diborane THF-solution to give a diamine. Since these can be easily alkylated many analogues will be accessible. However, the diamine **10** is characterized by a shorter linker between the terphenyl skeleton and the nitrogen (Fig. 1).

The structures were established carefully by means of IR, ^{1}H NMR, ^{13}C NMR, COSY, HMQC and HMBC experiments and temperature-dependent measurements. If necessary, mass spectra were measured. CHN analysis exhibits the terphenyls to crystallize often with different moles of water.

Interestingly, in the case of compounds **5**, **6**, **7** and **9** the NMR spectra exhibits a double set of signals. This may be due to the hindrance of the rotation around the benzene–naphthalene axis which occurs with substituents larger than a bromomethyl group. However, the compounds of pharmacological interest, **8** and **10**, do not show any sign of rotational isomerism. Thus, they are able to adopt the conformation required by the receptor protein.

Preliminary screening of the compounds **8a**, **8b** and **10** revealed an allosteric potency in the lower micromolar range of concentration. Thus, the terphenyls fulfil the requirements of a lead structure for the development of new allosteric modulators. However, the pattern of substitution has to be varied in order to derive structure–activity-relationships and to find derivatives of high allosteric potency.

3. Conclusion

Both terphenyl systems **8** and **10** were found to be allosteric modulators. Thus, they can serve as new lead compounds for the development of enhancers of ligand binding to the muscarinic receptors. The synthesis of a congeneric series of compounds is under progress.

4. Experimental

4.1. General

Melting points were determined using a Gallenkamp MPD350:BM3.5 apparatus and were not corrected. ^{1}H NMR spectra (400.13 MHz) and ^{13}C NMR spectra (100.61 MHz) were recorded on a Bruker Avance 400 MHz spectrometer. Abbreviations for data quoted are: s, singlet; d, doublet; t, triplet; m, multiplet; H-aromat., aromatic hydrogen; C-aromat., tertiary aromatic carbon; Cquat., aromat., quaternary aromatic carbon. The centers of the peaks of $CDCl_3$ and DMSO-d_6, respectively, were used as internal references. FT-IR spectra were recorded on a Bio-Rad PharmalyzIR equipped with an ATR unit and mass spectra on a CH7 Varian-MAT. Microwave reactions were carried out in a Milestone MLS-Ethos 1600 using a 250 mL 3-necked round-bottom flask (open system). The temperature of the reaction was measured directly in the reaction solution with a fibre optic sensor. Dry solvents were used throughout. Chemicals were of analytical grade and purchased from Acros organics:

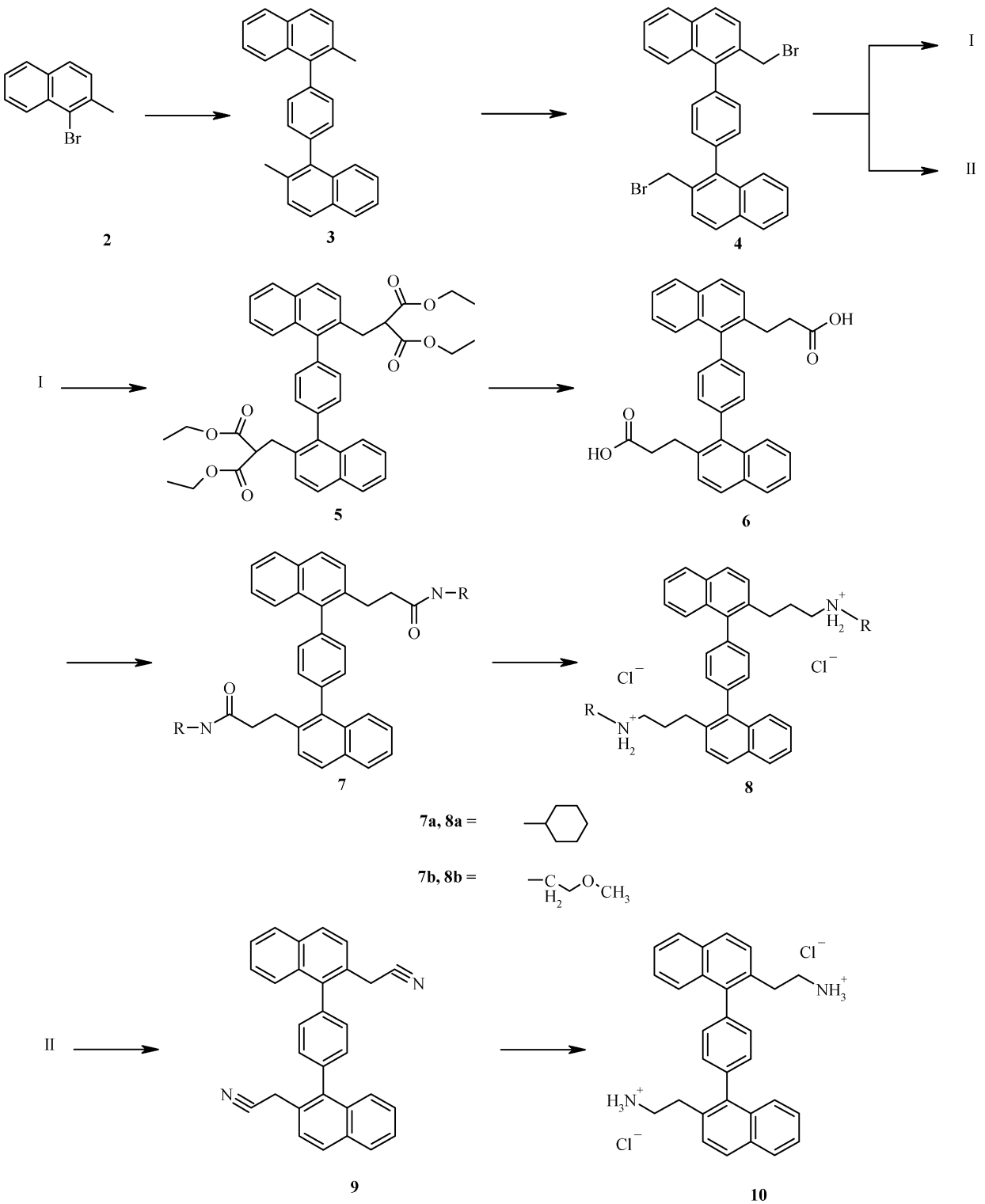

Figure 1. Synthesis pathway of the terphenylene compounds.

1-bromo-2-methylnaphthalene, 1,4-dibromobenzene,*N*-bromosuccinimide (NBS), cyclohexylamine, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), butyllithium, oxalylchloride, 1.0 M diborane–THF solution, Lancaster: 1-bromo-2-methylnaphthalene, Fluka: 2,2′-azobis-(2-methylpropionitrile) (AIBN), bis(triphenylphosphine)-nickel(II)chloride, oxalylchloride, Aldrich: diethyl malonate.

4.1.1. 5,6,5″,6″-Dibenzo-2,2″-bis-methyl-[1,1′;4′,1″]-terphenyl 3. 1-Bromo-2-methylnaphthalene (30.0 g, 128.9 mmol) dissolved in dry THF (80.0 mL) was added to a mixture of magnesium (9.4 g, 386.7 mmol) in dry THF (20.0 mL) so slowly that the solution was boiling slightly. Afterwards the mixture was refluxed for 15 min, cooled to 25°C and decanted in another flask. Bis(triphenylphosphine)-nickel(II)chloride (0.84 g, 1.29 mmol) was

added. The 1,4-dibromobenzene (12.29 g, 52.08 mmol) dissolved in dry THF (100.0 mL) was added to the mixture slowly. The mixture was heated by microwaves for 3 h (gradient of heating: 600 W, 6 min to 55°C; holding time: 3 h at 55°C), afterwards the reaction was quenched with 3.0 M HCl (100.0 mL) and stirred for 30 min at 25°C. The layers were separated and the aqueous solution was extracted twice with dichloromethane (100.0 mL). The combined organic layers were dried over Na_2SO_4. The organic layers were evaporated in vacuo. The resulting brown residue was washed with ethyl acetate and dried under reduced pressure. A white powder was obtained. Yield: 9.4 g (50%), mp 232°C. ^{1}H NMR ($CDCl_3$) δ: 7.91–7.40 (16H, m, H-aromat.), 2.41 (3H, s, CH_3), 2.35 ppm (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ: 138.61 (2×Cquat., aromat.), 138.22 (2×Cquat., aromat.), 133.44 (2×Cquat., aromat.), 133.20 (Cquat., aromat.), 133.17 (Cquat., aromat.), 132.19 (2×Cquat., aromat.), 130.33 (4×C-aromat.), 128.83 (C-aromat.), 128.80 (C-aromat.), 127.97 (2×C-aromat.), 127.43 (2×C-aromat.), 126.38 (C-aromat.), 126.26 (C-aromat.), 126.07 (C-aromat.), 126.04 (C-aromat.), 124.98 (C-aromat.), 124.94 (C-aromat.), 21.15 (CH_3), 21.00 ppm (CH_3). MS (EI); *m/z* (%): 358 (M^+, 100.0), 343 (M^+-CH_3, 15.12), 327 (10.16), 215 (9.45), 179 (18.48), 169 (13.59). IR (ATR): 2950, 1502, 1379, 1102, 1015, 814, 785, 752, 663 cm^{-1}. Anal. calcd for $C_{28}H_{22}$: C, 93.9; H, 6.19; found C, 93.5; H, 6.52.

4.1.2. 5,6,5″,6″-Dibenzo-2,2″-bis-bromomethyl-[1,1′;4′,1″]terphenyl 4. To a solution of **3** (10.0 g, 27.89 mmol) in dry carbon tetrachloride (400.0 mL) a mixture of powdered *N*-bromosuccinimide (NBS) (10.53 g, 59.17 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN) (0.5 g, 3.04 mmol) was added. The mixture was refluxed for 1 h and then cooled to room temperature. The precipitate (succinimide) was isolated by filtration and the solvent was removed under reduced pressure. The resulting yellow residue was washed with ethyl acetate to give white crystals. Yield: 10 g (70%), mp 234°C. ^{1}H NMR ($CDCl_3$) δ: 7.94–7.46 (16H, m, H-aromat.), 4.62 (2H, s, CH_2), 4.56 ppm (2H, s, CH_2). ^{13}C NMR ($CDCl_3$) δ: 139.14 (2×Cquat., aromat.), 137.27 (2×Cquat., aromat.), 133.45 (2×Cquat., aromat.), 133.12 (2×Cquat., aromat.), 132.99 (2×Cquat., aromat.), 130.30 (2×C-aromat.), 130.28 (2× C-aromat.), 128.75 (C-aromat.), 128.73 (C-aromat.), 128.19 (C-aromat.) 128.14 (C-aromat.), 127.68 (C-aromat.), 127.63 (C-aromat.) 127.12 (C-aromat.), 127.10 (C-aromat.), 126.79 (C-aromat.), 126.72 (C-aromat.), 126.62 (C-aromat.), 126.60 (C-aromat.), 33.18 (CH_2), 33.05 ppm (CH_2). IR (ATR): 1502, 1212, 1197, 816, 748, 680 cm^{-1}. MS (EI); *m/z* (%): 518 (M^+, 7.37), 516 (M^+, 14.53), 514 (M^+, 7.14), 438 (M^+-Br, 2.35), 436 (M^+-Br, 2.47), 356 (M^+-2Br, 100.0). Anal. calcd for $C_{28}H_{20}Br_2$: C, 65.1; H, 3.90; found C, 64.6; H, 4.08.

4.1.3. 3-[2″-(2,2-Bis-ethoxycarbonyl-ethyl)-5,6,5″,6″-dibenzo-[1,1′;4′,1″]terphenyl-2-yl]-2-ethoxycarbonyl-propionic acid ethyl ester 5. Synthesis of lithium bis(trimethylsilyl)amide (Li-MDS): 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (8.94 g, 55.40 mmol) was cooled to 0°C, butyllithium (3.28 g, 51.14 mmol) was added and the mixture was stirred for 10 min at 0°C. Afterwards, the solution was stirred for another 10 min and allowed to warm up to 25°C. The diethyl malonate (6.83 g, 42.61 mmol) was dissolved in dry THF (40.0 mL) and the Li-MDS was added using a syringe. The mixture was stirred for 10 min. Afterwards a solution of **4** (10.0 g, 19.37 mmol) in dry THF (2×50.0 mL) was added dropwise. The mixture was stirred for 12 h at 25°C and afterwards heated for 1 h to 70°C. The reaction was quenched with 10% HCl until the solution adopted pH<4. The THF was evaporated in vacuo and the aqueous layer was extracted with chloroform (150.0 mL). The organic layer was washed twice with 10% HCl (2×60.0 mL), with brine (2×50.0 mL) and dried with Na_2SO_4. The chloroform was evaporated in vacuo. The resulting brown oil was dissolved in methanol (2×60.0 mL) and the solvent was evaporated in vacuo twice. The resulting yellow residue can be recrystallised from methanol. Yield: 6 g (60%), mp 142°C. ^{1}H NMR ($CDCl_3$) δ: 7.83–7.90 (4H, m, H-aromat.), 7.37–7.54 (12H, m, H-aromat.), 4.04–4.11 (8H, m, CH_2), 3.58 (2H, t, J=7.45 Hz, CH), 3.39 and 3.31 (4H, 2×d, J=7.83 Hz, CH_2, ratio 70:30), 1.43–1.20 ppm (12H, m, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.01 (2×C=O, ester), 168.89 (2×C=O, ester), 139.00 (Cquat., aromat.), 138.96 (Cquat., aromat.), 138.03 (2×Cquat., aromat.), 133.39 (Cquat., aromat.), 133.13 (Cquat., aromat.), 133.28 (Cquat., aromat.), 133.24 (Cquat., aromat.), 132.69 (Cquat., aromat.), 132.66 (Cquat., aromat.), 130.62 (2×C-aromat.), 130.55 (2×C-aromat.), 128.13 (2×C-aromat.), 128.07 (C-aromat.), 127.99 (C-aromat.), 127.92 (C-aromat.), 127.89 (C-aromat.), 126.60 (C-aromat.), 126.56 (C-aromat.), 126.22 (C-aromat.), 126.18 (C-aromat.), 125.63 (C-aromat.), 125.60 (C-aromat.), 61.51 (CH_2), 61.40 (CH_2), 53.10 (CH_2), 53.00 (CH_2), 33.22 (2×CH_2), 32.96 (2×CH_2), 14.17 (2×CH_3), 14.11 ppm (2×CH_3). IR (ATR): 2979 (CH_2), 1747 (C=O, ester), 1728 (C=O, ester), 1504, 1217, 1137, 1026, 847, 818, 750, 678 cm^{-1}. MS (EI); *m/z* (%): 674 (M^+, 100), 629 (4.58), 600 (11.20), 583 (8.47), 555 (7.98), 526 (11.75). Anal. calcd for $C_{42}H_{42}O_8$: C, 74.8; H, 6.27; found C, 74.7; H, 6.34.

4.1.4. 3-[2″-(2-Carboxy-ethyl)-5,6,5″,6″-dibenzo-[1,1′;4′,1″]terphenyl-2-yl]-propionic acid 6. KOH (10.87 g, 193.69 mmol) dissolved in water (100.0 mL) was added to **5** (13.07 g, 19.37 mmol) dissolved in ethanol (150.0 mL). The mixture was refluxed for 1 h. Afterwards, 10% HCl (100.0 mL) was added and the ethanol was evaporated in vacuo. The solution was extracted with ethyl acetate (2×100.0 mL). The organic layer was washed with brine (2×50.0 mL) and dried over Na_2SO_4. The ethyl acetate was evaporated in vacuo. The compound can be used without further purification for the next step. The compound was dissolved in DMSO (60.0 mL), 50% HCl (20.0 mL) was added and the mixture was refluxed for 1 h, until no CO_2 was evolving anymore. The mixture was cooled to 25°C, water (1000.0 mL) and H_2O_2 (50.0 mL) was added. The mixture was stirred for 12 h. The brown solution was filtered and the resulting crystals were heated with water (2×500.0 mL), cooled to 25°C and filtered twice. The crystals were dried over phosphorus pentoxide. Yield: 7.8 g (70%), mp 294°C. ^{1}H NMR (DMSO-d_6) δ: 12.11 (2H, s, OH), 7.97–7.23 (16H, m, H-aromat.), 2.93 and 2.85 (4H, 2×t, J=8.02, 7.50 Hz, CH_2, ratio 60:40), 2.50 and 2.42 ppm (4H, 2×t, J=8.02, 7.50 Hz, CH_2, ratio 60:40). ^{13}C NMR

(DMSO-d_6) δ: 173.62 (COOH), 173.55 (COOH), 137.56 (Cquat., aromat.), 137.53 (Cquat., aromat.), 137.48 (2×Cquat., aromat.), 136.24 (Cquat., aromat.), 136.00 (Cquat., aromat.), 132.44 (Cquat., aromat.), 132.36 (Cquat., aromat.), 131.79 (2×Cquat., aromat.), 130.08 (4×C-aromat.), 127.80 (2×C-aromat.), 127.63 (C-aromat.), 127.52 (2×C-aromat.), 127.37 (C-aromat.), 126.27 (C-aromat.), 126.19 (C-aromat.), 125.79 (C-aromat.), 125.66 (C-aromat.), 125.26 (C-aromat.), 125.21 (C-aromat.), 35.08 (CH_2), 34.87 (CH_2), 28.98 (CH_2), 28.72 ppm (CH_2). MS (EI); *m/z* (%): 474 (M^+, 100.0), 428 (68.85), 414 (7.47), 369 (13.78), 355 (39.84), 339 (27.51), 177 (77.87). IR (ATR): 3200–2400 (COO–H, br, carboxylic acid), 1697 (C═O, carboxylic acid), 1507, 1210, 945, 822, 751, 679 cm^{-1}. Anal. calcd for $C_{32}H_{26}O_4$×0.5H_2O: C, 79.5; H, 5.63; found C, 79.7; H, 5.62.

4.1.5. *N*-Cyclohexyl-3-[2″-(2-cyclohexylcarbamoyl-ethyl)-5,6,5″,6″-dibenzo-[1,1′;4′,1″]terphenyl-2-yl]-propionamide 7a. Oxalylchloride (1.67 g, 13.17 mmol) and a catalytic amount of DMF was added to **6** (2.50 g, 5.27 mmol) dissolved in dry THF (80.0 mL) and the mixture was stirred 12 h at 25°C. The THF was evaporated in vacuo. The residue was dissolved in toluene (2×30.0 mL) and evaporated in vacuo twice in order to remove the excess of oxalylchloride. The residue was dissolved in dry THF (80.0 mL), an excess of cyclohexylamine (10.45 g, 105.36 mmol) was added and the mixture was stirred for 12 h at 25°C. 10% HCl was added until the solution had adopted pH<4 and the solvent was evaporated in vacuo. The aqueous layer was extracted twice with chloroform (300.0 mL). The solvent was evaporated in vacuo. The resulting residue was purified by means of column chromatography (silica gel/chloroform) to obtain pale yellow crystals which can be recrystallised from chloroform/petroleum ether. Yield: 0.6 g (18%), mp 263.4°C. ^{1}H NMR ($CDCl_3$) δ: 7.89–7.85 (4H, m, H-aromat.), 7.66–7.41 (12H, m, H-aromat.), 6.6 (1H, s, NH), 3.66–3.77 (2H, m, CH), 3.08–2.99 (4H, m, CH_2), 2.44–2.39 (4H, m, CH_2), 1.87–1.78 (4H, m, CH_2), 1.67–1.56 (6H, m, CH_2), 1.34–1.23 (4H, m, CH_2), 1.13–1.02 ppm (6H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ: 171.93 (C═O, amide), 171.15 (C═O, amide), 138.29 (Cquat., aromat.), 138.16 (Cquat., aromat.), 138.06 (Cquat., aromat.), 137.98 (Cquat., aromat.), 136.42 (Cquat., aromat.), 136.38 (Cquat., aromat.), 133.20 (Cquat., aromat.), 133.02 (Cquat., aromat.), 132.46 (Cquat., aromat.), 132.39 (Cquat., aromat.), 130.47 (4×C-aromat.), 128.09 (4×C-aromat.), 128.02 (2×C-aromat.), 127.57 (C-aromat.), 126.63 (C-aromat.), 126.45 (C-aromat.), 126.31 (C-aromat.), 126.19 (C-aromat.), 125.43 (C-aromat.), 48.93 (CH), 48.33 (CH), 38.65 (CH_2), 37.89 (CH_2), 33.31 (2×CH_2), 32.99 (2×CH_2), 30.41 (CH_2), 30.24 (CH_2), 25.56 (2×CH_2), 25.06 (2×CH_2), 24.97 ppm (2×CH_2). IR (ATR): 3306 (N–H, amide), 2932 (CH_2), 2849 (CH_2), 1631 (C═O, amide), 1549 (N–C═O, amide), 852, 804, 744, 694, 654 cm^{-1}. MS (EI); *m/z* (%): 636 (M^+, 63.71), 537 (4.71), 510 (9.56), 495 (11.23), 369 (19.19), 353 (29.00), 98 (100.0). Anal. calcd for $C_{44}H_{48}N_2O_2$×0.75H_2O: C, 81.3; H, 7.67; N, 4.31; found C, 81.2; H, 7.53; N, 4.28.

4.1.6. *N*-(2-Methoxy-ethyl)-3-{2″-[2-(2-methoxy-ethyl-carbamoyl)-ethyl]-5,6,5″,6″-dibenzo-[1,1′;4′,1″]terphenyl-2-yl}-propionamide 7b. Oxalylchloride (1.67 g, 13.17 mmol) and a catalytic amount of DMF was added to **6** (2.50 g, 5.27 mmol) dissolved in dry THF (120.0 mL) and the mixture was stirred 12 h at 25°C. The THF was evaporated in vacuo. The residue was dissolved in toluene (2×30.0 mL) and evaporated in vacuo twice, in order to remove the excess of oxalylchloride. The residue was dissolved in dry THF (80.0 mL), an excess of 2-methoxy-ethylamine (7.71 g, 105.36 mmol) was added and the mixture was stirred for 12 h at 25°C. 10% HCl was added until the solution had adopted pH<4 and the solvent was evaporated in vacuo. The aqueous layer was extracted twice with chloroform (200.0 mL). The organic solvent was washed with brine (100 mL) and dried with Na_2SO_4 and evaporated in vacuo. The resulting residue can be recrystallised from methanol. Yield: 1.84 g (74%), mp 199.5°C. ^{1}H NMR ($CDCl_3$) δ: 7.90–7.84 (4H, m, H-aromat.), 7.66–7.42 (12H, m, H-aromat.), 6.60 (1H, s, NH), 5.70 (0.5H, s, NH), 3.41–3.34 (8H, m, CH_2), 3.21–3.18 (6H, m, CH_3), 3.11–3.00 (4H, m, CH_2), 2.48–2.41 ppm (4H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ: 172.85 (C═O, amide), 172.12 (C═O, amide), 138.25 (Cquat., aromat.), 138.19 (Cquat., aromat.), 138.07 (2×Cquat., aromat.), 136.35 (Cquat., aromat.), 136.17 (Cquat., aromat.), 133.22 (Cquat., aromat.), 133.06 (Cquat., aromat.), 132.43 (Cquat., aromat.), 132.38 (Cquat., aromat.), 130.48 (2×C-aromat.), 130.44 (2×C-aromat.), 128.11 (C-aromat.), 128.05 (C-aromat.), 128.00 (C-aromat.), 127.89 (2×C-aromat.), 127.54 (C-aromat.), 126.62 (C-aromat.), 126.52 (C-aromat.), 126.35 (C-aromat.), 126.20 (C-aromat.), 125.43 (2×C-aromat.), 71.22 (CH_2), 71.11 (CH_2), 58.74 (OCH_3), 58.72 (OCH_3), 39.50 (CH_2), 39.29 (CH_2), 38.12 (CH_2), 37.98 (CH_2), 30.43 (CH_2), 30.05 ppm (CH_2). IR (ATR): 3265 (N–H, amide), 2924 (CH_2), 2870 (CH_2), 1639 (C═O, amide), 1534 (N–C═O, amide), 1123 (C–O–C, ether), 1093 (C–O–C, ether), 1020, 820, 748, 680. MS (EI); *m/z* (%): 588 (M^+, 100), 555 (12.60), 514 (16.82), 485 (12.80), 471 (17.38), 368 (28.09), 353 (41.17), 339 (18.61), 76 (79.96). Anal. calcd for $C_{38}H_{40}N_2O_4$: C, 77.5; H, 6.85; N, 4.76; found C, 77.3; H, 6.89; N, 4.61.

4.1.7. Cyclohexyl-{3-[2″-(3-cyclohexyl-propyl-ammonium)-5,6,5″,6″-dibenzo-[1,1′;4′,1″]terphenyl-2-yl]propyl}-ammonium dihydrochloride 8a. 1.0 M Diborane–THF solution (25 mL, 25 mmol) was added to **7a** (2.50 g, 3.93 mmol) dissolved in dry THF, and the mixture was stirred for 12 h at 25°C and additionally 1 h at 60°C. The reaction was quenched carefully with 10% HCl and afterwards refluxed for 1 h. 10% NaOH was added until the solution had adopted pH<7. The aqueous layer was extracted with chloroform (2×100 mL). The organic solvent was washed with brine (100 mL) and dried with Na_2SO_4 and evaporated in vacuo. The resulting residue was dissolved in ethanolic HCl and the solvent was evaporated in vacuo. The resulting residue can be recrystallised from methanol. Yield: 0.930 g (35%), mp >290°C (dec.). ^{1}H NMR ($CDCl_3$) δ: 9.30 (3H, s), 7.90–7.32 (16H, m), 2.83–2.72 (8H, m), 2.27 (2H, s), 2.15–2.02 (8H, m), 1.79–1.78 (4H, m), 1.59–1.48 (6H, m), 1.26–1.19 ppm (6H, m). ^{13}C NMR ($CDCl_3$) δ: 139.08 (2×Cquat., aromat.), 137.59 (2×Cquat., aromat.), 134.91 (2×Cquat., aromat.), 133.30 (2×Cquat., aromat.),

132.51 (2×Cquat., aromat.), 130.84 (4×C-aromat.), 128.06 (2×C-aromat.), 127.84 (2×C-aromat.), 127.77 (2×C-aromat.), 126.71 (2×C-aromat.), 126.36 (2×C-aromat.), 125.64 (2×C-aromat.), 56.69 (2×CH), 44.05 (2×CH_2), 32.27 (2×CH_2), 29.31 (4×CH_2), 26.21 (2×CH_2), 24.85 (2×CH_2), 24.54 ppm (4×CH_2). IR (ATR): 3000–2500 (NH_2^+, br), 2933 (CH_2), 2856 (CH_2), 1507, 1454, 1387, 1026, 824, 749 cm^{-1}. MS (EI); *m/z* (%): 608 (M^+, 50.19, $C_{44}H_{52}N_2$), 525 (34.49), 496 (70.46), 483 (86.18), 369 (10.04), 353 (21.05), 112 (100), 98 (19.17). Anal. calcd for $C_{44}H_{52}N_2$×2HCl×2H_2O: C, 73.6; H, 8.14; N, 3.90; found C, 73.8; H, 7.94; N, 3.76.

4.1.8. (2-Methoxy-ethyl)-(3-{2″-[3-(2-methoxy-ethyl-ammonium)-propyl]-5,6,5″,6″-dibenzo [1,1′;4′,1″]-terphenyl-2-yl}-propyl)-ammonium dihydrochloride 8b. 1.0 M Diborane–THF solution (25 mL, 25 mmol) was added to **7b** (2.50 g, 4.25 mmol) suspended in dry THF (80.0 mL), and the mixture was stirred for 12 h at 25°C and additionally 1 h at 60°C. The reaction was quenched carefully with 10% HCl and afterwards refluxed for 1 h. 10% NaOH was added until the solution had adopted pH<7. The THF was evaporated in vacuo. The aqueous layer was extracted with diethyl ether (2×100.0 mL). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4. Ethereal HCl was added and the residue was filtered off. The resulting white residue can be recrystallised from ethanol. Yield: 0.4 g (15%), mp: 260–270°C (dec.). ^{1}H NMR ($CDCl_3$) δ: 9.56 (4H, s, NH_2^+), 7.89–7.90 (2H, m, H-aromat.), 7.84 (2H, d, *J*=8.33 Hz, H-aromat.), 7.68–7.70 (2H, m, H-aromat.), 7.55 (4H, s, H-aromat.), 7.46–7.52 (4H, m, H-aromat.), 7.34 (2H, d, *J*=8.33 Hz, H-aromat.), 3.70–3.68 (4H, m, CH_2), 3.04–3.02 (4H, m, CH_2), 2.89–2.82 (4H, m, CH_2), 2.75–2.72 (4H, m, CH_2), 2.09–2.02 (4H, m, CH_2), 3.32 ppm (6H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ: 138.91 (2×Cquat., aromat.), 137.71 (2×Cquat., aromat.), 134.96 (2×Cquat., aromat.), 133.25 (2×Cquat., aromat.), 132.51 (2×Cquat., aromat.), 130.83 (4×C-aromat.), 127.95 (2×C-aromat.), 127.87 (4×C-aromat.), 126.68 (2×C-aromat.), 126.37 (2×C-aromat.), 125.63 (2×C-aromat.), 67.61 (2×CH_2), 59.09 (2×CH_3), 47.81 (2×CH_2), 46.17 (2×CH_2), 32.00 (2×CH_2), 26.40 ppm (2×CH_2). IR (ATR): 3000–2500 (NH_2^+, br), 1507, 1456 (NH_2^+), 1386, 1127 (C–O–C, ether), 1100 (C–O–C, ether), 1022, 821, 812, 748, 674, 652 cm^{-1}. MS (EI); *m/z* (%): 560 (M^+, 8.47), 515 (46.52), 496 (22.34), 414 (12.42), 353 (20.57), 44 (100). Anal. calcd for $C_{38}H_{44}N_2O_2$×2HCl×H_2O: C, 70.0; H, 7.42; N, 4.30; found C, 70.3; H, 7.43; N, 4.21.

4.1.9. (2″-Cyanomethyl-5,6,5″,6″-dibenzo-[1,1′;4′,1″]-terphenyl-2yl)-acetonitrile 9. Potassium cyanide (KCN) (4.41 g, 67.79 mmol) dissolved in water (150.0 mL) and methyltrialkyl(C8–C10)ammonium chloride (Adogen®464) (1.4 g) was added to **4** (7.0 g, 13.56 mmol) dissolved in toluene (350.0 mL). The mixture was stirred intensively for 4 h under reflux. Afterwards, the organic layer was separated and three times washed with hot water (100.0 mL). The toluene was not completely evaporated in vacuo. The yellow crystals were filtered and washed with acetone. Yield: 4.12 g (70%), mp 278°C. ^{1}H NMR ($CDCl_3$) δ: 8.00–7.51 (16H, m, H-aromat.), 3.78 (2H, s, CH_2), 3.75 ppm (2H, s, CH_2). ^{13}C NMR ($CDCl_3$) δ: 138.7 (Cquat., aromat.), 138.62 (Cquat., aromat.), 137.69 (Cquat., aromat.), 137.66 (Cquat., aromat.), 133.24 (Cquat., aromat.), 133.21 (Cquat., aromat.), 132.89 (2×Cquat., aromat.), 130.78 (2×C-aromat.), 130.75 (2×C-aromat.), 129.19 (C-aromat.), 129.15 (C-aromat.), 128.29 (C-aromat.), 128.27 (C-aromat.), 127.17 (C-aromat.), 127.07 (C-aromat.), 126.65 (C-aromat.), 126.61 (C-aromat.), 126.58 (C-aromat.), 126.53 (C-aromat.), 126.21 (C-aromat.), 126.01 (C-aromat.), 125.72 (Cquat., aromat.), 125.59 (Cquat., aromat.), 118.29 (CN), 118.17 (CN), 22.92 (CH_2), 22.92 ppm (CH_2). IR (ATR): 2243 (CN), 1501, 1388, 841, 819, 753, 681, 652 cm^{-1}. MS (EI); *m/z* (%): 408 (M^+, 100), 391 (8.45), 380 (13.51), 365 (6.50), 353 (13.50), 339 (11.07). Anal. calcd for $C_{30}H_{20}N_2$×0.25H_2O: C, 87.3; H, 5.00; N, 6.78; found C, 87.4; H, 5.16; N, 6.37.

4.1.10. 2-[2″-(2-Ethyl-ammonium)-5,6,5″,6″-dibenzo-[1,1′;4′,1″]terphenyl-2-yl]-ethyl-ammonium dihydrochloride 10. 1.0 M Diborane–THF solution (40.0 mL, 40.0 mmol) was added to **9** (4.0 g, 9.79 mmol) dissolved in dry THF (160.0 mL). The mixture was stirred at 60°C. The reaction was quenched carefully with 10% HCl and afterwards refluxed for 1 h. 10% NaOH was added until the solution had adopted pH<7. The THF was evaporated in vacuo. The aqueous layer was extracted with chloroform (2×100.0 mL). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4. Ethereal HCl was added, the residue was filtered off and washed with ether. Yield: 2.86 g (80%), mp 270°C (dec.). ^{1}H NMR (DMSO-d_6) δ: 8.40–8.29 (5H, m,NH_3^+), 8.10–7.97 (4H, m), 7.74–7.45 (12H, m), 3.09–3.03 ppm (8H, m). ^{13}C NMR (DMSO-d_6) δ: 138.25 (2×Cquat., aromat.), 137.29 (2×Cquat., aromat.), 132.86 (2×Cquat., aromat.), 132.54 (2×Cquat., aromat.), 132.04 (2×Cquat., aromat.), 130.12 (4×C-aromat.), 128.04 (2×C-aromat.), 127.90 (2×C-aromat.), 127.30 (2×C-aromat.), 126.52 (2×C-aromat.), 125.95 (2×C-aromat.), 125.61 (2×C-aromat.), 39.71 (CH_2), 39.62 (CH_2), 31.23 (CH_2), 31.28 ppm (CH_2). IR (ATR): 3600–2400 (NH_3^+), 1594, 1506, 1386, 1022, 820, 746, 669, 624 cm^{-1}. HRMS (CI/CH_4): 417.2325 [(MH^+); calcd for $C_{30}H_{28}N_2$–H^+ 417.2331].

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