Platelet Aggregation Inhibiting and Anticoagulant Effects of Oligoamines, XIV[1]:

Branched Aliphatic and Alicyclic Triamines and Tetramines

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Twenty-four triamines and three tetramines were synthesized. Seventeen triamines inhibited platelet aggregation induced by collagen at a concentration below 10 µmol/L (IC_{50}). Ten triamines in a 100 µmolar concentration inhibited fibrin formation induced by thromboplastin by more then 75 %. Both effects do not run parallel. They are strongly dependent from the steric and lipophilic properties of the title oligoamines. The tetramines were nearly inactive.

Antiaggregatorische und anticoagulante Eigenschaften von Oligoaminen, 14. Mitt.[1]:

Verzweigte aliphatische und alicyclische Tri- und Tetramine

Es wurden 24 Tri- und 3 Tetramine dargestellt. Von 17 Triaminen wurden die durch Collagen induzierte Thrombocytenaggregation in Konzentrationen unter 10 µmol/L halbmaximal gehemmt. Mit 10 Triaminen wurde bei 100 µmol/L eine mindestens 75 proz. Hemmung der Fibrinbildung gesehen. Beide Effekte laufen jedoch nicht parallel, sondern sind in unterschiedlicher Weise von den räumlichen Orientierungsmöglichkeiten und der Lipophilie der Amine abhängig. Die dargestellten Tetramine zeigten nur sehr geringe gerinnungsphysiologische Aktivitäten.

Recent investigations have shown that the antiaggregatory activity of suitable diamines can be improved if a third basic N-function is introduced into the aromatic or alicyclic bridge which connects the amino groups[2,3]. We now have examined whether this is a general feature in the structure activity relationships. Therefore, three or four amino functions were connected by aliphatic hydrocarbon bridges.

The synthesis of **2** was performed by amidolysis (procedure A) of 3-hydroxypentane-1,5-dicarboxylic acid diethylester and reduction of the resulting amide with $LiAlH_4$ in ether (procedure B). Compounds **3-6** were obtained by reaction of 3-oxopentanedicarboxylic acid diethylester with hydroxylamine followed by procedures A and B. The triamines **7-22** were synthesized by condensation of **3-6** with suitable aldehydes. The intermediate imines were reduced with $NaBH_4$ in ethanol. When diethyl malonate reacted with ω-bromoalkaneacid esters the triesters so obtained could be converted to the corresponding amides by procedure A. Procedure B then gave **24-26** while **23** was obtained by reaction of the amide with $POCl_3$ followed by reduction with $NaBH_4$ (procedure C)[4]. Compounds **27** and **29** were synthesized from the corresponding tetracarboxylic acid esters by the sequence of the reactions A and C, compound **28** by A and B, respectively. The synthesis of **1** has been reported[5].

The results of the pharmacological tests of the triamines **2-26** are summarized in table 1. The diamine **1** is added for comparison. Compound **2** shows the influence of an unprotonated polar group and thereby represents the part of hydrogen bonding to the phospholipids involved in the antiplatelet and/or anticoagulant activity. The introduction of a third amino group (**3-6**) surprisingly led to a decay in antiaggregatory activity (see **1**) although additional electrostatic binding to the polar head groups of the phospholipids is provided[6]. In contrast the anticoagulant effect can be strengthened by a third amino group (see **4** and **6**). The results confirm once more[7] that the antiaggregatory and anticoagulant effects of oligamines do not neccessarily run parallel suggesting differences in the platelet and plasma

Table 1: Antiaggregatory and anticoagulant activities of **1-26**

$$R^1\text{-}(CH_2)_m\text{-}NH\text{-}(CH_2)_k\text{-}\underset{\displaystyle R^2}{\underset{|}{CH}}\text{-}(CH_2)_l\text{-}NH\text{-}(CH_2)_m\text{-}R^1$$

	R^1	R^2	k	l	m	IC_{50} [µmol/L]	Quick [µmol/L]/Δt[s]
1	Ph	H	2	2	4	6	400/18
2	Ph	OH	2	2	4	11	400/14
3	CH_3	NH_2	3	3	5	90	400/13
4	CH_3	NH_2	3	3	6	20	100/9
5	CH_3	NH_2	3	3	7	20	400/0
6	Ph	NH_2	3	3	4	40	100/10
7	CH_3	NH-C_5H_{11}	3	3	5	9	100/13
8	CH_3	NH-C_6H_{13}	3	3	5	5	100/9
9	CH_3	NH-C_7H_{15}	3	3	5	4	100/7
10	CH_3	NH-$(CH_2)_3$-Ph	3	3	5	4	100/11
11	CH_3	NH-C_5H_{11}	3	3	6	3	50/8
12	CH_3	NH-C_6H_{13}	3	3	6	5	100/26
13	CH_3	NH-C_7H_{15}	3	3	6	5	400/0
14	CH_3	NH-$(CH_2)_3$-Ph	3	3	6	5	100/17
15	CH_3	NH-C_5H_{11}	3	3	7	3	400/0
16	CH_3	NH-C_6H_{13}	3	3	7	4	400/0
17	CH_3	NH-C_7H_{13}	3	3	7	5	400/0
18	CH_3	NH-$(CH_2)_3$-Ph	3	3	7	8	400/0
19	Ph	NH-C_5H_{11}	3	3	4	5	200/30
20	Ph	NH-C_6H_{13}	3	3	4	5	100/17
21	Ph	NH-C_7H_{15}	3	3	4	6	400/9
22	Ph	NH-$(CH_2)_3$-Ph	3	3	4	5	400/0
23	Ph	CH_2-NH-$(CH_2)_4$-Ph	1	2	4	11	400/0
24	Ph	CH_2-NH-$(CH_2)_4$-Ph	1	3	4	10	400/0
25	Ph	CH_2-NH-$(CH_2)_4$-Ph	1	4	4	22	400/0
26	Ph	CH_2-NH-$(CH_2)_4$-Ph	1	5	4	8	400/0

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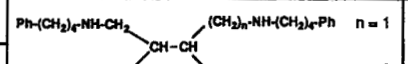
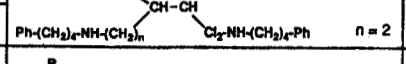
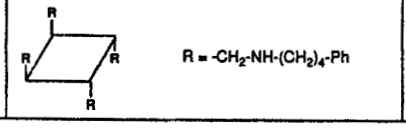
Table 2: Antiaggregatory and anticoagulant activities of the tetramines **27-29**

		IC_{50} [µmol/L]	Quick [µmol/L]/Δt [d]
27	 n = 1	17	400/7
28	 n = 2	35	400/4
29	 R = -CH_2-NH-$(CH_2)_4$-Ph	55	400/0

phospholipids. Nevertheless the decay in antiaggregatory activity can be overcome by lipophilic substitution of the third amino group. In terms of our membrane hypothesis for oligoanimes[6] this represents the part of the hydrophobic binding in the interaction between oligoamines and phospholipids. Suitable substituents were pentyl, hexyl and heptyl as well as 3-phenylpropyl or 4-phenylbutyl groups. The relatively broad variations in k, l, and m only have a minor influence on the antiplatelet activity. This suggests that the oligoamines **7-26** are flexible enough to assume an optimum position to the phospholipids. Concerning the anticoagulant effect large differences in activity are observed. Obviously all triamines with three arylalkyl groups (**22-26**) lack any activity. Extension of m from five or six to seven carbon atoms totally abolishes the anticoagulant activity (**15-18**) indicating again the different structural requirements for antiplatelet and antifibrin effects. In comparison to similar diamines it is obvious that the less lipophilic pentyl derivatives exert strong effects in the triamine series suggesting that the total lipophilicity of the molecule plays an important role.

The results obtained with three tetramines are summarized in table 2. Here the strong decay of activities might result from orientational problems in these "overcrowded" molecules. On the other hand these tetramines might be too lipophilic. Further experiments are necessary to differentiate between these factors.

Altogether seventeen triamines were able to bisect the platelet aggregation induced by collagen in a concentration below 10 µmol/L. The results obtained with **1** however, show that this effect can be achieved as well with an aliphatic diamine.

Experimental part

Mp.: Mettler FP-1 (uncorrected), rise in temp. 2°/min. - Element analysis: Perkin-Elmer element analyzer 240 B and 240 C. - IR-spectra: Perkin-Elmer spectralphotometer 1420 with DS 7300. - ^{1}H-NMR-spectra: Bruker ACE 300, CF_3COOD unless otherwise stated. - Mass spectra: Varian MAT 711 (80 eV). - PI-FAB: Varian MAT CH 5 D*), DMSO/glycerol matrix.

The yields are given for the reduction of amides or imines to amines. All syntheses and pharmacological tests were performed either by standard procedures or have been already described in former communications of this series. The crude bases have all been purified by rotation chromatography (Chromatotron, Harrison Research, Pato Alto Cal.; sorbens: silicagel Merck 60 PF_{254}, Art.-nr. 7749, thickness 4 mm); eluent $CHCl_3$/gaseous NH_3) prior to the precipitation of the hydrochlorides.

N,N'-Bis-(4-phenylbutyl)-3-hydroxy-pentane-1,5-diamine-hydrochloride (2)

Crystals (ethanol), mp. 268° (dec), yield 50%. - $C_{25}H_{38}N_3 \cdot 2\,HCl \cdot 0.5\,H_2O$ (464.5) Calc. C 64.6 H 8.90 N 6.0 Found C 64.6 H 9.09 N 6.0. - IR (KBr): 3434; 2939; 2858; 2798; 2437; 1600; 1493; 1452; 1121; 1047; 804; 744; 697 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.33-7.17 (m, 10H, aromat.) 7.07 (bs, 4H, NH_2^+) 4.24 (m, 1H, CH), 3.42 (m, 4H, NH_2^+-CH_2-CH_2-CH), 3.21 (m, 4H, NH_2^+-CH_2-$(CH_2)_3$), 2.72 (m, 4H, CH_2-Ph), 2.11 (dt, J = 6/6 Hz, 4H, CH_2-CH), 1.80 (m, 8H, CH_2-$(CH_2)_2$-CH_2). - MS (130°): m/z = 382 (44%, M^+), 263 (31), 202 (21), 162 (100), 131 (15), 116 (23), 114 (25), 102 (18), 91 (78), 88 (32), 72 (30), 44 (64), 36 (33).

N^1,N^7-Dihexyl-heptane-1,4,7-triamine-trihydrochloride (3)

Crystals (ethanol), mp. 204° (dec.), yield 40%. - $C_{19}H_{43}N_3 \cdot 3\,HCl \cdot H_2O$ (441.0) Calc. C 51.8 H 10.97 N 9.5 Found C 51.5 H 10.80 N 9.4. - IR (KBr): 3392; 2952; 2928; 2861; 2798; 2527; 2017; 1605; 1505; 1462; 1378; 1050; 749 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.1 (bs, 7H, NH_2^+, NH_3^+), 3.67 (m, 1H, CH), 3.26 (m, 8H, CH_2-NH_2^+-CH_2), 2.02 (m, 8H, CH-$(CH_2)_2$), 1.83 (m, 4H, CH_3-$(CH_2)_3$-CH_2), 1.41 (m, 12H, CH_3-$(CH_2)_3$), 0.95 (m, 6H, CH_3). - MS (150°): m/z = 313 (58%, M^+), 242 (63), 211 (87), 170 (36), 154 (55), 115 (48), 114 (90), 112 (63), 110 (100), 101 (32), 84 (43), 71 (51), 70 (50), 44 (41), 43 (37), 36 (68).

N^1,N^7-Diheptyl-heptane-1,4,7-triamine-trihydrochloride (4)

Crystals (ether/ethanol), mp. 268° (dec.), yield 35%. - $C_{21}H_{47}N_3 \cdot 3\,HCl \cdot 2\,H_2O$ (487.0) Calc. C 51.8 H 11.18 N 8.6 Found C 51.9 H 11.02 N 8.7. - IR (KBr): 3405; 2951; 2924; 2854; 2796; 1605; 1503; 1463; 1010; 748 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.28 (bs, 3H, NH_3^+), 7.17 (bs, 4H, NH_2^+), 3.92 (m, 1H, CH), 3.34 (m, 4H, CH-$(CH_2)_2$-CH_2), 3.25 (m, 4H, CH_3-$(CH_2)_5$-CH_2), 2.18 (m, 4H, CH-CH_2), 2.09 (m, 4H, CH-CH_2-CH_2), 1.86 (m, 4H, CH_3-$(CH_2)_4$-CH_2), 1.45-1.36 (m, 16H, CH_3-$(CH_2)_4$), 0.94 (t, J = 6 Hz, 6H, CH_3). - MS (140°): m/z = 341 (10%, M^+), 256 (31), 225 (49), 168 (46), 143 (31), 128 (61), 115 (35), 112 (40), 110 (100), 84 (43), 71 (48), 70 (51), 58 (31), 57 (30), 44 (61), 36 (79).

N^1,N^7-Dioctyl-heptane-1,4,7-triamine-trihydrochloride (5)

Crystals (ether/ethanol), mp. 272° (dec.), yield 30%. - $C_{23}H_{51}N_3 \cdot 3\,HCl \cdot 2\,H_2O$ (515.1) Calc. C 53.6 H 11.35 N 8.2 Found C 53.4 H 11.28 N 8.1. - IR (KBr): 3434; 3416; 3406; 2951; 2918; 2851; 2797; 2782; 2342; 1603; 1510; 1465; 1377; 1016; 723 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.27 (bs, 3H, NH_3^+), 7.16 (bs, 4H, NH_2^+), 3.74 (m, 1H, CH), 3.33 (m, 4H, CH-$(CH_2)_2$-CH_2), 3.26 (m, 4H, CH_3-$(CH_2)_6$-CH_2), 2.17 (m, 4H, CH-CH_2), 2.08 (m, 4H, CH-CH_2-CH_2), 1.86 (m, 4H, CH_3-$(CH_2)_5$-CH_2), 1.42-1.35 (m, 20H, CH_3-$(CH_2)_5$), 0.93 (t, J = 7 Hz, 6H, CH_3). - MS (140°): m/z = 369 (13%, M^+), 270 (38), 239 (57), 182 (42), 143 (34), 142 (65), 115 (30), 112 (47), 110 (100), 84 (44), 72 (34), 71 (51), 70 (60), 44 (56), 43 (32), 36 (79).

N^1,N^7-Bis-(4-phenylbutyl-heptane-1,4,7-triamine-trihydrochloride (6)

Crystals (ethanol), mp. 172° (dec.), yield 45%. - $C_{27}H_{43}N_3 \cdot 3\,HCl \cdot 2\,H_2O$ (555.1) Calc. C 58.4 H 9.08 N 7.6 Found C 58.2 H 8.88 N 7.5. - IR (KBr): 3417; 2933; 2787; 1610; 1493; 1453; 1200; 1026; 747; 699 cm^{-1}. - ^{1}H-NNR: δ (ppm) = 7.33-7.17 (m, 10H, aromat.), 7.07 (bs, NH_2^+, NH_3^+), 3.60 (m, 1H, CH), 3.22 (m, 8H, CH_2-NH_2^+-CH_2), 2.73 (m, 4H, Ph-CH_2), 1.94 (m, 8H, CH-$(CH_2)_2$), 1.80 (m, 8H, Ph-CH_2-$(CH_2)_2$). - MS (150°): m/z = 409 (17%, M^+), 259 (28), 202 (28), 162 (34), 112 (23), 110 (68), 91 (100), 84 (30), 71 (19), 70 (53), 58 (26), 56 (28), 45 (20), 44 (67), 43 (30), 36 (44).

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N,N',N''-Trihexyl-heptane-1,4,7-triamine-trihydrochloride (**7**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 20%. - $C_{25}H_{55}N_3 \cdot 3HCl \cdot 0.5\ H_2O$ (516.1) Calc. C 58.2 H 11.52 N 8.1 Found C 58.4 H 11.35 N 8.3. - IR (KBr): 3424; 2952; 2928; 2856; 2794; 2430; 1584; 1463; 1021; 728 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.17 (bs, 6H, NH_2^+), 3.52 (m, 1H, CH), 3.26 (m, 10H, NH_2^+-CH_2), 2.01 (m, 8H, CH-(CH_2)$_2$), 1.82 (m, 6H, CH_3-(CH_2)$_3$-CH_2), 1.39 (m, 18H, CH_3-(CH_2)$_3$), 0.95 (m, 9H, CH_3). - MS (150°): m/z = 397 (16%, M^+), 326 (17), 297 (12), 296 (19), 295 (84), 255 (15), 196 (10), 194 (28), 155 (17), 154 (100), 114 (19), 112 (15), 110 (12), 70 (13), 44 (13), 43 (20).

N^4-Heptyl-N^1,N^7-dihexyl-heptane-1,4,7-triamine-trihydrochloride (**8**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 30%. - $C_{26}H_{57}N_3 \cdot 3\ HCl$ (521.2) Calc. C 59.9 H 11.60 N 8.1 Found C 59.7 H 11.66 N 8.1. - IR (KBr): 3415; 2926; 2855; 2798; 1655; 1462 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.26 (bs, 6H, NH_2^+), 3.59 (m, 1H, CH), 3.34-3.25 (m, 10H, NH_2^+-CH_2), 2.10 (m, 8H, CH-(CH_2)$_2$), 1.85 (m, 6H, CH-NH_2^+-CH_2-CH_2 + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 1.41 (m, 20H, CH_3-(CH_2)$_3$ + CH-NH_2^+-(CH_2)$_2$-CH_2), 0.95 (m, 9H, CH_3). - MS (180°): m/z = 411 (7%, M^+), 309 (13), 296 (10), 295 (46), 194 (22), 170 (11), 168 (26), 155 (12), 154 (100), 114 (17), 43 (11), 36 (17).

N^1,N^7-Dihexyl-N^4-octyl-heptane-1,4,7-triamine-trihydrochloride (**9**)

Crystals (ether/ethanol), mp. >300° (dec.), yield, 25%. - $C_{27}H_{59}N_3 \cdot 3\ HCl \cdot 0.5\ H_2O$ (544.2) Calc. C 59.6 H 11.67 N 7.7 Found C 59.7 H 11.49 N 7.7. - IR (KBr): 3422; 2951; 2926; 2854; 2796; 1584; 1462 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.26 (bs, 6H, NH_2^+), 3.59 (m, 1H, CH), 3.33-3.25 (m, 10H, NH_2^+-CH_2), 2.10 (m, 8H, CH-(CH_2)$_2$), 1.85 (m, 6H, CH-NH_2^+-CH_2-CH_2 + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 1.40 (m, 22H, CH_3-(CH_2)$_3$ + CH-NH_2^+-(CH_2)$_2$-(CH_2)$_2$), 0.95 (m, 9H, CH_3). - MS (140°): m/z = 425 (2%, M^+), 295 (31), 194 (20), 182 (23), 155 (11), 154 (100), 112 (12), 114 (18), 110 (13), 84 (14), 57 (12), 70 (20), 44 (21), 43 (29), 38 (12), 36 (36).

N^1,N^7-Dihexyl-N^4-(3-phenylpropyl)-heptane-1,4,7-triamine-trihydrochloride (**10**)

Crystals (ether/ethanol), mp. 296° (dec.), yield 20%. - $C_{28}H_{53}N_3 \cdot 3\ HCl$ (541.1) Calc. C 62.2 H 10.43 N 7.8 Found C 62.1 H 10.68 N 7.7. - IR (KBr): 3426; 2592; 2926; 2855; 2795; 2500; 1583; 1494; 1437; 1028; 746; 697 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.35-7.20 (m, 11H, aromat. + NH_2^+), 3.51 (m, 1H, CH), 3.25 (m, 10H, NH_2^+-CH_2), 2.80 (t, J = 7 Hz, 2H, Ph-CH_2), 2.21 (m, 2H, Ph-CH_2-CH_2), 2.08-2.00 (m, 8H, CH-(CH_2)$_2$), 1.84 (m, 4H, CH_3-(CH_2)$_3$-CH_2), 1.40 (m, 12H, CH_3-(CH_2)$_3$), 0.95 (m, 6H, CH_3). - MS (140°): m/z = 431 (6%, M^+), 329 (10), 295 (39), 194 (22), 188 (20), 155 (12), 154 (100), 114 (16), 112 (11), 110 (14), 91 (20), 84 (12), 70 (15), 44 (23), 43 (26), 36 (25).

N^1,N^7-Diheptyl-N^4-hexyl-heptane-1,4,7-triamine-trihydrochloride (**11**)

Crystals (ether/ethanol), mp. 299° (dec.), yield 20%. - $C_{27}H_{59}N_3 \cdot 3\ HCl$ (535.2) Calc. C 60.6 H 11.68 N 7.9 Found C 60.6 H 11.73 N 7.8. - IR (KBr): 3429; 2951; 2926; 2854; 2797; 1584; 1462 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.26 (bs, 6H, NH_2^+), 3.60 (m, 1H, CH), 3.33-3.26 (m, 10H, NH_2^+-CH_2), 2.11 (m, 8H, CH-(CH_2)$_2$), 1.85 (m, 6H, CH-NH_2^+-CH_2-CH_2 + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 1.44-1.37 (m, 22H, CH_3-(CH_2)$_3$ + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 0.94 (m, 9H, CH_3). - MS (130°): m/z = 425 (6%, M^+), 309 (12), 323 (41), 208 (20), 169 (12), 168 (100), 154 (23), 128 (17), 112 (13), 110 (13), 84 (10), 70 (15), 57 (11), 44 (15), 43 (15), 36 (25).

N,N',N''-Triheptyl-heptane-1,4,7-triamine-trihydrochloride (**12**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 25%. - $C_{28}H_{61}N_3 \cdot 3\ HCl$ 549,2) Calc. C 61.2 H 11,75 N 7.7 Found C 61.3 H 11.82 N 7.7. - IR (KBr): 3425; 2950; 2924; 2853; 2797; 1583; 1461 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.18 (bs, 6H, NH_2^+), 3.52 (m, 1H, CH), 3.26 (m, 10H, NH_2^+-CH_2), 2.01 (m, 8H, CH-(CH_2)$_2$), 1.83 (m, 6H, CH_3-(CH_2)$_4$-CH_2), 1.43-1.36 (m, 24H, CH_3-(CH_2)$_4$), 0.94 (m, 9H, CH_3). - MS (140°): m/z = 453 (6%, M^+), 368 (11), 337 (17), 324 (14), 323 (52), 208 (21), 184 (12), 182 (29), 169 (14), 168 (100), 128 (18), 84 (12), 70 (15), 57 (15), 44 (14), 36 (35).

N^1,N^7-Diheptyl-N^4-octyl-heptane-1,4,7-triamine-trihydrochloride (**13**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 30%. - $C_{29}H_{63}N_3 \cdot 3\ HCl \cdot 0{,}5\ H_2O$ (572.2) Calc C 60.9 H 11.81 N 7.4 Calc. C 61.2 H 11.75 N 7.7 Found C 61.1 H 11.78 N 7.7. - IR (KBr): 3422; 2951; 2924; 2853; 2800; 1585; 1464 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.17 (bs, 6H, NH_2^+), 3.53 (m, 1H, CH), 3.26 (m, 10H, NH_2^+-CH_2), 2.01 (m, 8H, CH-(CH_2)$_2$), 1.83 (m, 6H, CH-NH_2^+-CH_2-CH_2 + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 1.43-1.36 (m, 26H, CH_3-(CH_2)$_4$ + CH-NH_2^+-(CH_2)$_2$-CH_2), 0.94 (m, 9H, CH_3). - MS (150°): m/z = 439 (6%, M^+), 354 (12), 324 (13), 323 (56), 208 (20), 169 (13), 168 (100), 128 (16), 70 (11), 57 (10), 44 (12), 36 (29), 32 (21).

N^1,N^7-Diheptyl-N^4-(3-phenylpropyl)-heptane-1,4,7-triamine-trihydrochloride (**14**)

Crystals (ether/ethanol), mp. 292° (dec.), yield 25%. - $C_{30}H_{57}N_3 \cdot 3\ HCl$ (569.2) Calc. C 63.3 H 10.63 N 7.4 Found C 63.5 H 10.65 N 7.3. - IR (KBr): 3417; 2950; 2926; 2854; 2799; 1583; 1437; 1028; 745; 697 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.35-7.20 (m, 11H, aromat. + NH_2^+), 3.52 (m, 1H, CH), 3.25 (m, 10H, NH_2^+-CH_2), 2.80 (t, J = 7 Hz, 2H, Ph-CH_2), 2.22 (m, 2H, Ph-CH_2-CH_2), 2.09-2.01 (m, 8H, CH-(CH_2)$_2$, 1.84 (m, 4H, CH_3-(CH_2)$_4$-CH_2), 1.44-1.36 (m, 16H, CH_3-(CH_2)$_4$, 0.94 (t, J = 7 Hz, 6H, CH_3). - MS (150°): m/z = 459 (10%, M^+), 324 (41), 208 (31), 188 (35), 169 (13), 168 (100), 128 (16), 110 (20), 91 (16), 84 (19), 70 (13), 57 (14), 44 (23), 41 (11), 38 (18), 36 (58).

N^4-Hexyl-N^1,N^7-dioctyl-heptane-1,4,7-triamine-trihydrochloride (**15**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 25%. - $C_{29}H_{63}N_3 \cdot 3\ HCl$ (563.2) Calc. C 61.8 H 11.81 N 7.5 Found C 61.8 H 11.89 N 7.4. - IR (KBr): 3418; 2924; 2854; 2792; 1699; 1645; 1585; 1461; 1027; 747 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.17 (bs, 6H, NH_2^+), 3.53 (m, 1H, CH), 3.26 (m, 10H, NH_2^+-CH_2), 2.01 (m, 8H, CH-(CH_2)$_2$), 1.82 (m, 6H, CH-NH_2^+-CH_2-CH_2) + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 1.35 (m, 26H, CH_3-(CH_2)$_3$ + CH-(CH_2)$_3$-NH_2^+-(CH_2)$_2$-(CH_2)$_2$), 0.93 (m, 9H, CH_3). - MS (140°): m/z = 453 (10%, M^+), 354 (17), 352 (15), 351 (55), 323 (17), 283 (15), 222 (17), 183 (13), 182 (100), 154 (23), 142 (17), 112 (14), 110 (14), 70 (18), 44 (14), 36 (35).

N^4-Heptyl-N^1,N^7-dioctyl-heptane-1,4,7-triamine-trihydrochloride (**16**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 15%. - $C_{30}H_{65}N_3 \cdot 3\ HCl$ (577.3) Calc. C 62.4 H 11.87 N 7.3 Found C 62.3 H 11.91 N 7.1. - IR (KBr): 3429; 2924; 2853; 2799; 1585; 1462 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.17 (bs, 6H, NH_2^+), 3.53 (m, 1H, CH), 3.26 (m, 10H, NH_2^+-CH_2), 2.01 (m, 8H, CH-(CH_2)$_2$), 1.83 (m, 6H, CH-NH_2^+-CH_2-CH_2 + CH-(CH_2)$_3$-NH_2^+-CH_2-CH_2), 1.42-1.35 (m, 28H, CH_3-(CH_2)$_4$ + CH-(CH_2)$_3$-NH_2^+-(CH_2)$_2$-CH_2), 0.93 (m, 9H, CH_3). - MS (150°): m/z = 467 (5.5 %, M^+), 368 (12), 352 (15), 351 (57), 337 (16), 297 (13), 222 (17), 183 (14), 182 (100), 168 (23), 145 (23), 142 (16), 70 (12), 44 (14), 43 (12), 36 (26).

N,N',N''-Trioctyl-heptane-1,4,7-triamine-trihydrochloride (**17**)

Crystals (ether/ethanol), mp. >300° (dec.), yield 30%. - $C_{31}H_{67}N_3 \cdot 3\ HCl$ (591.3) Calc. C 63.0 H 11.93 N 7.1 Found C 63.2 H 12.08 N 7.1. - IR (KBr): 3418; 2922; 2852; 2797; 1702; 1658; 1460 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.17 (bs, 6H, NH_2^+), 3.52 (m, 1H, CH), 3.26 (m, 10H, NH_2^+-CH_2), 2.01 (m, 8H, CH-(CH_2)$_2$), 1.82 (m, 6H, CH_3-(CH_2)$_5$-CH_2), 1.34 (m, 30H, CH_3-(CH_2)$_5$), 0.93 (m, 9H, CH_3). - MS (150°): m/z = 481 (6%, M^+), 382

(11), 353 (11), 352 (16), 351 (57), 311 (10), 222 (19), 183 (15), 182 (100), 169 (13), 142 (13), 70 (12), 44 (12), 43 (12), 38 (11), 36 (30).

N^1,N^7-Dioctyl-N^4-(3-phenylpropyl)-heptane-1,4,7-triamine-trihydrochloride (**18**)

Crystals (ether/ethanol), mp. 294° (dec.), yield 30%. - $C_{32}H_{61}N_3 \cdot 3$ HCl (597.2) Calc. C 64.4 H 10.80 N 7.0 Found C 64.2 H 10.76 N 7.1. - IR (KBr): 3451; 2947; 2925; 2852; 2799; 2473; 2401; 1582; 1494; 1463; 1455; 1438; 1377; 1028; 965; 831; 801; 745; 697 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.35-7.22 (m, 11H, aromat. + NH_2^+), 3.52 (m, 1H, CH), 3.25 (m, 10H, NH_2^+-C$\underline{H}_2$), 2.80 (t, J = 7 Hz, 2H, Ph-C$\underline{H}_2$), 2.20 (m, 2H, Ph-CH$_2$-C$\underline{H}_2$), 1.99 (m, 8H, CH-(C$\underline{H}_2$)$_2$), 1.84 (m, 4H, CH$_3$-(CH$_2$)$_5$-C$\underline{H}_2$), 1.35 (m, 20H, CH$_3$-(C$\underline{H}_2$)$_5$), 0.93 (m, 6H, CH$_3$). - MS (150°): m/z = 487 (12%, M^+), 357 (13), 352 (13), 351 (50), 222 (29), 188 (48), 183 (14), 182 (100), 142 (13), 110 (17), 91 (13), 84 (17), 70 (12), 44 (47), 43 (21), 36 (34).

N^1,N^7-Bis-(4-phenylbutyl)-N^4-hexyl-heptane-1,4,7-triamine-trihydrochloride (**19**)

Crystals (ether/ethanol), mp. 278° (dec.), yield 30%. - $C_{33}H_{55}N_3 \cdot 3$ HCl·H$_2$O (621.2) Calc. C 63.8 H 9.74 N 6.8 Found C 63.7 H 9.51 N 6.8. - IR (KBr): 3431; 2932; 2855; 2800; 2423; 1584; 1493; 1438; 1028; 745; 698 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.31-7.20 (m, 16H, aromat. NH_2^+), 3.53 (m, 1H, CH), 3.23 (m, 10H, NH_2^+-C$\underline{H}_2$), 2.73 (m, 4H, Ph-C$\underline{H}_2$), 2.03 (m, 8H, CH-(C$\underline{H}_2$)$_2$), 1.81 (m, 10H, Ph-CH$_2$-(C$\underline{H}_2$)$_2$ + CH$_3$-(CH$_2$)$_3$-C$\underline{H}_2$), 1.39 (m, 6H, CH$_3$-(C$\underline{H}_2$)$_3$, 0.95 (m, 3H, CH$_3$). - MS (160°): m/z = 493 (33%, M^+), 393 (15), 392 (28), 391 (77), 374 (14), 343 (21), 303 (15), 242 (21), 203 (16), 202 (100), 162 (19), 154 (40), 91 (29), 70 (14), 38 (25), 36 (76).

N^1,N^7-Bis-(4-phenylbutyl)-N^4-heptyl-heptane-1,4,7-triamine-trihydrochloride (**20**)

Crystals (ethanol), mp. 281° (dec.), yield 25%. - $C_{34}H_{57}N_3 \cdot H_2O$ (635.3) Calc. C 64.3 H 9.84 N 6.6 Found C 64.1 H 9.61 N 6.6. - IR (KBr): 3434; 2929; 2853; 2797; 2444; 1584; 1493; 1452; 1028; 745; 698 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.31-7.16 (m, 16H, aromat. + NH_2^+), 3.48 (m, 1H, CH), 3.22 (m, 10H, NH_2+-C$\underline{H}_2$), 2.72 (m, 4H, Ph-C$\underline{H}_2$), 1.95 (m, 8H, CH-(C$\underline{H}_2$)$_2$, 1.79 (m, 10H, Ph-CH$_2$-(C$\underline{H}_2$)$_2$ + CH$_3$-(CH$_2$)$_4$-C$\underline{H}_2$), 1.40-1.35 (m, 8H, CH$_3$-(C$\underline{H}_2$)$_4$), 0.93 (m, 3H, CH$_3$). - MS (150°): m/z = 507 (21 %, M^+), 392 (17), 391 (53), 357 (16), 317 (12), 242 (23), 203 (17), 202 (100), 168 (46), 162 (17), 110 (15), 91 (34), 70 (19), 44 (15), 38 (13), 36 (43).

N^1,N^7-Bis-(4-phenylbutyl)-N^4-octyl-heptane-1,4,7-triamine-trihydrochloride (**21**)

Crystals (ether/ethanol), mp. 277° (dec.), yield 15%. - $C_{35}H_{59}N_3 \cdot 3$ HCl (631.2) Calc. C 66.6 H 9.90 N 6.7 Found C 66.3 H 9.84 N 6.6. - IR (KBr): 3417; 2926; 2853; 2792; 2434; 1587; 1494; 1452; 1029; 745; 698 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.33-7.18 (m, 16H, aromat. + NH_2^+), 3.54 (m, 1H, CH), 3.23 (m, 10H, NH_2^+-C$\underline{H}_2$), 2.73 (t, J = 7 Hz, 4H, Ph-C$\underline{H}_2$), 2.05 (m, 8H, CH-(C$\underline{H}_2$)$_2$), 1.81 (m, 10H, Ph-CH$_2$-(C$\underline{H}_2$)$_2$ + CH$_3$-(CH$_2$)$_5$-C$\underline{H}_2$), 1.34 (m, 10H, CH$_3$-(C$\underline{H}_2$)$_5$), 0.92 (t, J = 7 Hz, 3H, CH$_3$). - MS (140°): m/z = 521 (17%, M^+), 392 (21), 391 (71), 371 (21), 331 (14), 242 (20), 203 (16), 202 (100), 182 (67), 162 (20), 110 (16), 91 (41), 70 (19), 44 (15), 38 (19), 36 (60).

N^1,N^7-Bis-(4-phenylbutyl)-N^4-(3-phenylpropyl)-heptane-1,4,7-triamine-hydrochloride (**22**)

Crystals (ether/ethanol), mp. 271° (dec.), yield 25%. - $C_{36}H_{53}N_3 \cdot 3$ HCl (637.2) Calc. C 67.9 H 8.86 N 6.6 Found C 67.7 H 9.06 N 6.5. - IR (KBr): 3422; 2935; 2791; 1585; 1493; 1451; 1028; 744; 697 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.34-7.23 (m, 21H, aromat. + NH_2^+), 3.46 (m, 1H, CH), 3.20 (m, 10H, NH_2^+-C$\underline{H}_2$), 2.84-2.73 (m, 6H, Ph-C$\underline{H}_2$), 2.20 (m, 2H, Ph-CH$_2$-C$\underline{H}_2$-CH$_2$-NH_2^+), 1.95 (m, 8H, Ph-(CH$_2$)$_2$-C$\underline{H}_2$), 1.81 (m, 8H, Ph-CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$). - MS (130°): m/z = 527 (26%, M^+), 393 (12), 392 (21), 391 (65), 377 (19), 242 (25), 228 (13), 203 (16), 202 (100), 188 (41), 162 (16), 91 (56), 84 (12), 70 (12), 38 (12), 36 (36).

N,N'-Bis-(4-phenylbutyl)-2-(4-phenylbutylaminomethyl)-butane-1,4-diamine-trihydrochloride (**23**)

Crystals (ethanol), mp. 139°, yield 50%. - $C_{35}H_{51}N_3 \cdot 3$ HCl (623.2) Calc.C 67.5 H 8.73 N 6.7 Found C 67.2 H 8.87 N 6.7. - IR (KBr): 3419; 2933; 2855; 2747; 1599; 1492; 1452; 1029; 749; 700 cm^{-1}. - ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 9.12 (m, 6H, NH_2^+, exchange D_2O), 7.31-7.16 (m, 15H, aromat.), 3.14 (m, 2H, NH_2^+-C$\underline{H}_2$-CH$_2$-CH), 2.93 (m, 10H, NH_2^+-C$\underline{H}_2$-(CH$_2$)$_3$ + NH_2^+-C$\underline{H}_2$-CH), 2.60 (t, J = 7 Hz, 6H, C$\underline{H}_2$-Ph), 2.42 (m, 1H, CH), 1.89 (dt, J = 7/7 Hz, 2H, C$\underline{H}_2$-CH), 1.65 (m, 12H, CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$). - MS (130°): m/z = 513 (25%, M^+), 294 (15), 215 (48), 202 (60), 162 (59), 149 (24), 96 (57), 91 (100), 84 (24), 70 (26), 44 (32), 36 (54).

N,N'-Bis-(4-phenylbutyl)-2-(4-phenylbutylaminomethyl)-pentane-1,5-diamine-trihydrochloride (**24**)

Crystals (ethanol), mp. 190° (dec.), yield 55%. - $C_{36}H_{53}N_3 \cdot 3$ HCl Calc. C 67.8 H 8.86 N 6.6 Found C 67.5 H 9.10 N 6.5. - IR (KBr): 2929; 2855; 2783; 2417; 1733; 1585; 1493; 1450; 1027; 976; 907; 849; 744; 679 cm^{-1}. - ^{1}H-NMR ([D$_6$]DMSO): δ (ppm): 8.93 (m, 6H, NH_2^+, exchange D_2O), 7.31-7.16 (m, 15H, aromat.), 3.10 (m, 2H, NH_2^+-C$\underline{H}_2$-(CH$_2$)$_2$-CH), 2.91 (m, 10H, NH_2^+-C$\underline{H}_2$-(CH$_2$)$_3$ + NH_2^+-C$\underline{H}_2$-CH), 2.60 (t, J = 7 Hz, 6H, C$\underline{H}_2$-Ph), 2.27 (m, 1H, CH), 1.80-1.67 (m, 16H, (C$\underline{H}_2$)$_2$-CH + CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$). - MS (130°): m/z = 527 (45%, M^+), 379 (21), 294 (22), 287 (22), 230 (53), 218 (28), 216 (75), 202 (27), 188 (24), 162 (59), 149 (45), 98 (46), 91 (100), 84 (27), 44 (50), 38 (25), 36 (76).

N,N'-Bis-(4-phenylbutyl)-2-(4-phenylbutylaminomethyl)-hexane-1,6-diamine-trihydrochloride (**25**)

Crystals (ethanol), mp. 179° (dec.), yield 50%. - $C_{37}H_{55}N_3 \cdot 3$ HCl·H$_2$O (669.3) Calc. C 66.4 H 9.03 N 6.3 Found C 66.2 H 9.19 N 6.2. - IR (KBr): 3363; 2933; 2856; 2781; 2416; 1582; 1493; 1451; 1026; 744; 697 cm^{-1}. - ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 8.99 (m, 6H, NH_2^+, exchange D_2O), 7.31-7.16 (m, 15H, aromat.), 3.08 (m, 2H, NH_2^+-C$\underline{H}_2$-(CH$_2$)$_3$-CH), 2.89 (m, 10H, NH_2^+-C$\underline{H}_2$-(CH$_2$)$_3$ + NH_2^+-C$\underline{H}_2$-CH), 2.60 (t, J = 7 Hz, 6H, C$\underline{H}_2$-Ph), 2.23 (m, 1H, CH), 1.64 (m, 14H, C$\underline{H}_2$-CH$_2$-NH_2^+ + C$\underline{H}_2$-CH$_2$-Ph), 1.47 (m, 2H, CH-C$\underline{H}_2$-CH$_2$), 1.37 (m, 2H, C$\underline{H}_2$-CH$_2$-CH). - MS (120°): m/z = 541 (19%, M^+), 301 (17), 281 (15), 230 (17), 162 (94), 149 (63), 91 (100), 45 (20), 44 (61).

N,N'-Bis-(4-phenylbutyl)-2-(4-phenylbutylaminomethyl)-heptane-1,7-diamine-trihydrochloride (**26**)

Crystals (ethanol), mp. 159° (dec.), yield 50%. - $C_{38}H_{57}N_3 \cdot 3$ HCl·0.5 H$_2$O (674.3) Calc. C 67.7 H 9.12 N 6.3 Found C 67.5 H 9.34 N 6.2. - IR (KBr): 3431; 2933; 2856; 2779; 2422; 1583; 1493; 1451; 1027; 875; 744; 698 cm^{-1}. - ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 8.91 (m, 6H, NH_2^+, exchange D_2O), 7.31-7.16 (m, 15H, aromat.), 3.07 (m, 2H, NH_2-C$\underline{H}_2$-(CH$_2$)$_4$), 2.88 (m, 10H, NH_2^+-C$\underline{H}_2$-(CH$_2$)$_3$-Ph + NH_2^+-C$\underline{H}_2$-CH), 2.60 (t, J = 7 Hz, 6H, C$\underline{H}_2$-Ph), 2.21 (m, 1H, CH), 1.64 (m, 14H, C$\underline{H}_2$-CH$_2$-NH_2^+ + C$\underline{H}_2$-CH$_2$-Ph), 1.43 (m, 2H, C$\underline{H}_2$-CH), 1.30 (m, 4H, (C$\underline{H}_2$)$_2$-CH$_2$-CH). - MS (150°): m/z = 555 (24%, M^+), 393 (13), 315 (26), 294 (26), 273 (17), 258 (14), 246 (21), 188 (20), 162 (46), 131 (15), 126 (14), 91 (100), 44 (52).

N,N'-Bis-(4-phenylbutyl)-2,3-bis-(4-phenylbutylaminomethyl)-butane-1,4-diamine-tetrahydrochloride (**27**)

Crystals (ether/ethanol), mp. 188° (dec.), yield 15%. - $C_{46}H_{66}N_4 \cdot 4$ HCl·1 H$_2$O (838.9) Calc. C 65.9 H 8.65 N 6.7 Found C 66.2 H 8.65 N 6.6. - IR (KBr): 3398; 3017; 2930; 2855; 2709; 1602; 1493; 1453; 1029; 746; 700 cm^{-1}. - ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 9.27-9.13 (m, 8H, NH_2^+, exchange D_2O), 7.32-7.16 (m, 20H, aromat.), 3.67 (m, 2H, CH), 3.18 (m, 8H,

CH-C$\underline{H}_2$), 2.91 (m, 8H, Ph-$(CH_2)_3$-C$\underline{H}_2$), 2.60 (t, J = 7 Hz, 8H, Ph-C$\underline{H}_2$), 1.66 (m, 16H, Ph-CH_2-(C$\underline{H}_2$)$_2$). - MS (PI-FAB): m/z = 675 (0.6%, $[M+H]^+$), 526 (17), 377 (13), 214 (17), 188 (11), 162 (10), 131 (12), 96 (13), 91 (100).

N,N'-Bis-(4-phenylbutyl)-3,4-bis-(4-phenylbutylaminomethyl)-hexane-1,6-diamine-tetrahydrochloride (**28**)

Crystals (ether/ethanol), mp. 227° (dec.), yield 40%. - $C_{48}H_{70}N_4 \cdot 4$ HCl·1 H_2O (867.0) Calc. C 66.5 H 8.84 N 6.5 Found C 66.7 H 9.00 N 6.5. - IR (KBr): 3053; 3019; 2924; 2854; 1650; 1602; 1493; 1452; 1364; 1268; 1121; 1028; 745; 698 cm^{-1}. - ^{1}H-NMR: δ (ppm) = 7.32-7.16 (m, 28H, aromat. + NH_2^+), 3.30 (m, 4H, CH-C$\underline{H}_2$-NH_2^+), 3.16 (m, 12H, Ph-$(CH_2)_3$-C$\underline{H}_2$-NH_2^+-C$\underline{H}_2$), 2.70 (m, 8H, Ph-C$\underline{H}_2$), 2.50 (m, 2H, CH), 2.04 (m, 4H, CH-C$\underline{H}_2$-CH_2), 1.77 (m, 16H, Ph-CH_2-(C$\underline{H}_2$)$_2$). - MS (200°): m/z = 702 (9%, M^+), 553 (27), 554 (34), 403 (42), 285 (28), 242 (24), 230 (51), 228 (30), 204 (86), 202 (37), 201 (31), 149 (29), 162 (99), 91 (100).

1,2,3,4-Tetrakis-(4-phenylbutylaminomethyl)-cyclobutane-tetrahydrochloride (**29**)

Crystals (ethanol), mp. 288° (dec.), yield 60%. - $C_{48}H_{68}N_4 \cdot 4$ HCl·2 H_2O (883.0) Calc. C 65.3 H 8.68 N 6.3 Found C 65.6 H 8.42 N 6.4. - IR (KBr): 3428; 2934; 2854; 2772; 1600; 1493; 1452; 1027; 748; 700 cm^{-1}. - ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 9.14 (m, 8H, NH_2^+, exchange D_2O)), 7.31-7.18 (m, 20H, aromat.), 3.14 (m, 8H, NH_2^+-C$\underline{H}_2$-CH), 3.02 (m, 8H, NH_2^+-C$\underline{H}_2$-$(CH_2)_3$, 2.90 (s, 4H, CH), 2.60 (t, J = 7 Hz, 8H, C$\underline{H}_2$-Ph), 1.67 (m, 16H, CH_2-(C$\underline{H}_2$)$_2$-CH_2). - MS (PI-FAB): m/z = 701 (4%, $[M+H]^+$), 202 (11), 162 (17), 131 (15), 105 (13), 91 (100).

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