Platelet Aggregation Inhibiting and Anticoagulant Effects of Oligoamines, XVII:

Oligoamines with Fluorescent Properties Part A: Fluorescent Bridged Nitrogen Functions[+)]

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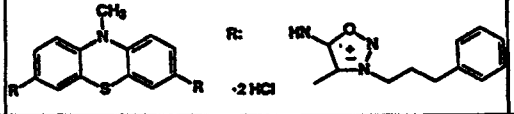
Eleven dimethanamines and one disydnonimine with fluorescent properties have been synthesized. All of them show antiplatelet activities (IC_{50}, *Born*-test) in concentrations between 14-75 µmol/L. Five of them inhibited fibrin formation induced by thromboplastin by more than 75% in a 200 µmolar concentration. Both effect do not run parallel. The most space consuming fluorophores show the smallest inhibition of the platelet aggregation. Best results were obtained with an azulene, acenaphthene or naphthalene moiety between the two basic nitrogen functions.

Antiaggregatorische und anticoagulante Eigenschaften von Oligoaminen, 17. Mitt.:
Fluoreszierende Oligoamine, Teil A: Fluoreszierend verbrückte Stickstoffunktionen

Elf Dimethanamine und ein Disydnonimin mit fluoreszierenden Eigenschaften wurden dargestellt. Alle hemmten die durch Collagen ausgelöste Thrombocytenaggregation in Konzentrationen zwischen 14-75 µmol/L (IC_{50}, *Born*-Test). Fünf Substanzen hemmten darüber hinaus auch die durch Thromboplastin ausgelöste Fibrinbildung zu mehr als 75% in Konzentrationen von 200 µmol/L. Beide Effekte laufen jedoch nicht parallel. Die Diamine mit den sterisch anspruchsvollsten Fluorophoren zeigten die geringsten antiaggregatorischen Effekte. Die besten Ergebnisse wurden erzielt, wenn Azulen, Acenaphthen oder Naphthalin die Brücke zwischen den basischen Stickstoffunktionen bildete.

Table 1: Antiplatelet and anticoagulant activities of *N*-(4-phenylbutyl)-derivatives of the dimethanamines **1-12** and a fluorescent disydnonimine **13**. The figures before the fluorophore are identical with the positions of the functional groups indicated in scheme 1.

compound no	fluorophore	Quick c[µmol/L]/Δt[s]	IC50 [µmol/L]
1	3,6-acenaphthene	200/7	17
2	2,8-phenothiazine-5,5-dioxide	200/17	40
3	2,8-dibenzothiophene-5,5-dioxide	400/0	44
4	2,6-dibenzothiophene-5,5-dioxide	200/7	75
5	2,8-dibenzofurane	200/7	68
6	1,5-anthracene	200/2	31
7	1,7-fluorene	400/0	21
8	2,6-naphthalene	400/0	18
9	1,3-azulene	400/4	14
10	10-methyl-3,7-phénothiazine	400/0	22
11	1,2´-(3-phenyl-naphthalene)	200/10	72
12	m-phenylene	200/25	10
13		400/0	44
14	m-phenylene, R as in 13	400/0	20

[+)] Herrn Prof. Dr. Dr. h.c. mult. *H. Oelschläger* zum 70. Geburtstag herzlich gewidmet.

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The oligoamines designed by our group in the recent years are a new class of antithrombotic drugs. They inhibit platelet aggregation induced by various stimuli and fibrin formation by induction of the exogenic and endogenic coagulation pathways[1]. The antithrombotic effects could be demonstrated in rats[2]. Meanwhile strong evidence has accumulated that these effects are due to interactions with soluble and membrane phospholipids[1,3,4,5]. In order to study these phenomena in more detail it is desirable to use oligoamines with fluorescent properties. These compounds should be suitable for distribution and binding studies to blood components and phospholipid vesicles. Furthermore they could serve as probes for fluorescence polarization measurements in membranes and microscopic investigations of platelet behaviour.

We therefore have synthesized and tested the fluorescent oligoamines compiled in table 1. Their common structural feature is the connection of the essential and optimal substituted nitrogen functions by an aromatic link with fluorescent properties. Their synthesis is summarized in scheme 1. To obtain **1-7** known dicarboxylicacid chlorides[6-12] were reacted with 4-phenylbutanamine and the resulting amides were reduced with $LiAlH_4$. Compound **8** was prepared by aminolysis of the comercially available naphthalene-2,6-dicarboxylicacid dimethylester followed by reduction with $LiAlH_4$. Compounds **9-11** were obtained from the corresponding dialdehydes[13-15] with 4-phenylbutanamine. The intermediate imines were reduced with $NaBH_4$. As **1-11** showed very poor solubility in water the mesoionic **13** was synthesized by a method in principle described in a patent[16] by reaction of 10-methylphenothiazine-3,7-dialdehyde[++] with KCN and 3-phenylpropanamine. The resulting acetonitrile derivative was nitrosylated with HNO_2 and cyclized with HCl to the disydnonimine **13**.

Compounds **12** and **14** are included for comparison. The synthesis of **12** has already been reported[17] while **14** was synthesized and kindly provided by *M. Kämpfe*[18].

The results obtained in the *Born*-test[19] and the Quick-test[19] are summarized in table 1. In general none of the fluorescent oligoamines reaches the antiaggregatory activity of the simple benzene bridged compounds **12** or **14**. The reason for this behavior seems to be a steric one: The smaller fluorophores show high antiplatelet activities (*e.g.* **9** > **8** ~ **1** > **7** *etc.*). The more space consuming ones exhibit only poor antiaggregating effects (e.g. **2-5**, **11**). The anticoagulant effects in general are small. Nevertheless it is obvious that they do not run parallel with the antiplatelet activities. For instance **5**, **6**, and **11** which only show little antiplatelet effect are stronger anticoagulants than **7-9** which are amongst the compounds with the best antiaggregatory activity. The results obtained with **13** were disappointing: Little antiplatelet and no anticoagulant activity was observed.

In summary no compounds with a central fluorophore in the desired range of antiplatelet activity *i.e.* < 10 µmol/L could be obtained. Therefore, further efforts have been undertaken to improve the situation. This will be reported soon.

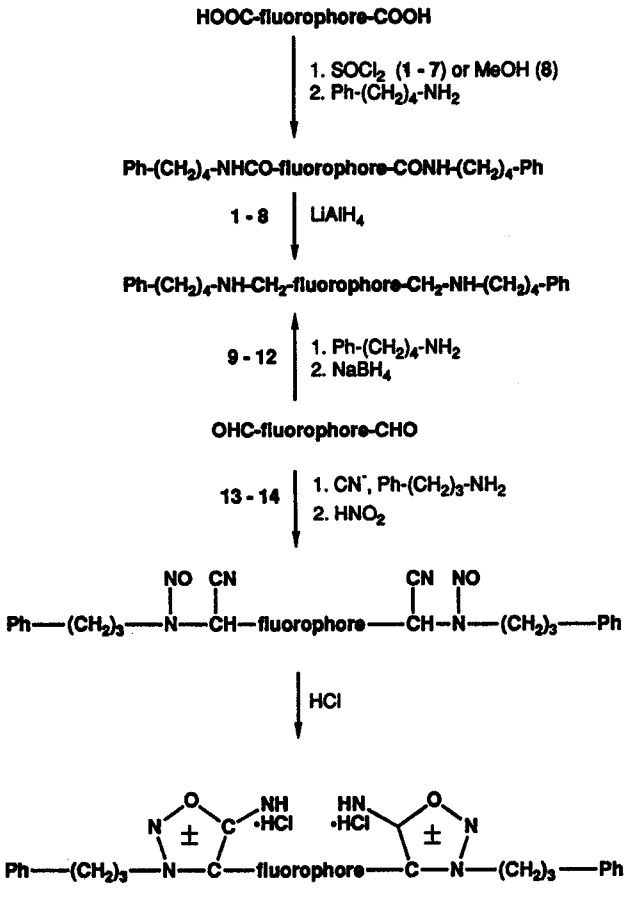

Fig. 1: Scheme for the synthesis of **1-14**

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 or WM 250 in the solvent stated.- Mass spectra: Varian MAT 711 (80 eV) or CH 7A (70 eV).- PI-FAB: Varian MAT CH 5 D[*] DMSO/glycerol matrix.

All pharmacological tests were performed by procedures which have been described in former communications of this series[19]. The crude bases have been purified by rotation chromatography (Chromatotron, Harrison Research, Palo Alto Ca.; Silicagel Merck 60 PF_{254}, no. 7749, thickness 4 mm, eluent $CHCl_3$/gaseous NH_3) prior to the precipitation of the hydrochlorides.- Temp. in °C.

Preparation of diamides

10 mmol dicarboxylic acid dichloride is dissolved in 80-250 ml dioxane. A solution of 80 mmol 4-phenylbutanamine in 75 ml dioxane is added dropwise with stirring. After 2 h the mixture is poured on 600 ml ice water and acidified with diluted HCl. The precipitated diamide is sucked off, washed neutral and recrystallized.

N,N'-Bis-(4-phenylbutyl)-acenaphthene-3,6-dicarboxamide

From acenaphthene-3,6-dicarboxylicacid dichloride[6]. The crude diamide was washed with toluene before recrystallization. Crystals (methanol) mp.

[++] This compound including a preprint of its improved synthesis was kindly provided by Prof. *Oelschläger*.

[*] We thank *U. Ostwald* and *G. Holzmann* for measuring and discussion of the mass spectra.

169°C. Yield 80%.- $C_{34}H_{36}N_2O_2$ (504.7) Calc. C 80.9 H 7.19 N 5.6 Found C 80.8 H 7.25 N 5.4.- IR (KBr): 3245; 2928; 1631; 1591; 1534; 1494; 1440; 1304; 744; 798 cm^{-1}.- ^{1}H-NMR/250 MHz ($CDCl_3$): δ (ppm) = 8.07 (d, J = 8.6 Hz, 1H, H-5), 7.64 (m, 2H, H-4, H-7), 7.32-7.15 (m, 11 H, H-8 and 10 H aromat.), 6.5 (t, J = 6 Hz, 1H, NH, D_2O exchange), 6.20 (t, J = 6 Hz, 1H, NH, D_2O exchange), 3.62-3.46 (m, 6H, H-2, NH-C$\underline{H}_2$), 3.32 (m, 2H, H-1), 2.69 (m, 4H, C$\underline{H}_2$-Ph), 1.80-1.64 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (200°): m/z = 504 (66%, M^+), 413 (21), 357 (38), 356 (100), 252 (21), 224 (26), 181 (25), 180 (28), 153 (26), 152 (36), 151 (19), 104 (10), 91 (50), 44 (23).

5,5-Dioxo-N,N'-bis-(4-phenylbutyl)-phenothiazine-2,8-dicarboxamide

From 5,5-Dioxophenothiazine-2,8-dicarboxylicacid dichloride[7]. Crystals (isopropanol), mp. 267°C (degr.). Yield 75%.- $C_{34}H_{35}N_3O_4S$ (581.7) Calc. C 70.2 H 6.06 N 7.2 Found C 70.2 H 6.22 N 7.2.- IR (KBr): 3380; 1649; 1615; 1581; 1535; 1469; 1287; 1144; 1128; 742; 700 cm^{-1}.- ^{1}H-NMR/300 MHz ([D_6]DMSO): δ (ppm) = 11.29 (s, 1H, H-10, D_2O exchange), 8.77 (t, J = 5 Hz, 2H, CO-NH, D_2O exchange), 8.05 (d, J = 8 Hz, 2H, H-4, H-6), 7.81 (d, J = 0.6 Hz, 2H, H-1, H-9), 7.66 (dd, J = 8/1 Hz, 2H, H-3, H-7), 7.32-7.17 (m, 10 H, aromat.), 3.34 (dt, J = 7/6 Hz, 4H, NH-C$\underline{H}_2$), 2.62 (t, J = 7 Hz, 4H, C$\underline{H}_2$-Ph), 1.67-1.56 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (360°): m/z = 581 (44%, M^+), 490 (32), 462 (11), 433 (52), 301 (21), 257 (29), 148 (56), 132 (22), 131 (53), 104 (22), 91 (100), 79 (11), 65 (13), 58 (20), 56 (18), 44 (50).

5,5-Dioxo-N,N'-bis-(4-phenylbutyl)-dibenzothiophene-2,8-dicarboxamide

From 5,5-Dioxodibenzothiophene-2,8-dicarboxylicacid dichloride[8]. The crude product is washed with toluene. Crystals (ethanol), mp. 182°. Yield 65%.- $C_{34}H_{34}N_2O_4S$ (566.7) Calc. C 72.1 H 6.05 N 4.9 Found C 72.0 H 6.08 N 4.9.- IR (KBr): 3316; 2934; 2855; 1642; 1604; 1576; 1537; 1303; 1275; 1166; 1137; 747; 699 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_6]DMSO): δ (ppm) = 8.84 (t, J = 5 Hz, 2H, NH, D_2O exchange), 8.64 (s, 2H, H-1, H-9), 8.16-8.04 (m, 4H, H-3, H-4, H-6, H-7), 7.31-7.14 (m, 10 H, aromat.), 3.36 (m, 4H, NH-C$\underline{H}_2$), 2.63 (t, J = 7 Hz, 4H, C$\underline{H}_2$-Ph), 1.63 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (260°): m/z = 566 (45%, M^+), 475 (25), 435 (10), 418 (37), 286 (15), 242 (21), 148 (32), 132 (22), 131 (37), 104 (21), 91 (100), 44 (36).

5,5-Dioxo-N,N'-bis-(4-phenylbutyl)-dibenzothiophene-2,6-dicarboxamide

From 5,5-Dioxodibenzothiophene-2,6-dicarboxylicacid dichloride[9]. Crystals (methanol/ether), mp. 219°. Yield 60%.- $C_{34}H_{34}N_2O_4S$ (566.7) Calc. C 72.1 H 6.05 N 4.9 Found C 72.2 H 6.13 N 5.1.- IR (KBr): 3419; 3021; 2931; 1608; 1567; 1374; 1295; 1154; 778; 725; 699 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_6]DMSO/CF_3COOD): δ (ppm) = 8.75 (s, 1H, H-1), 8.63 (d, J = 7 Hz, 1H, H-4), 8.26, 8.18, 8.09 (3d, J = 7 Hz, 3H, H-3, H-7, H-9), 7.95 (dd, J = 7.2/6.5 Hz, 1H, H-8), 7.34-7.15 (m, 10 H, aromat.), 2.83 (m, 4H, NH-C$\underline{H}_2$), 2.65 (m, 4H, C$\underline{H}_2$-Ph), 1.72-1.49 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (230°/80 eV): m/z = 566 (6%, M^+), 435 (42), 304 (21), 286 (12), 272 (28), 260 (40), 255 (15), 231 (20), 187 (19), 148 (11), 131 (15), 91 (100), 44 (22).

N,N'-Bis-(4-phenylbutyl)-dibenzofurane-2,8-dicarboxamide

From dibenzofuranedicarboxylicacid dichloride[10]. The crude product is washed with toluene. Needles (aceton), mp. 131°. Yield 70%.- $C_{34}H_{34}N_2O_3$ (518.6) Calc. C 78.7 H 6.61 N 5.4 Found C 78.8 H 6.60 N 5.4.- IR (KBr): 3305; 2930; 2856; 1626; 1602; 1583; 1542; 1494; 1477; 1453; 1325; 1303; 1267; 1204; 767; 748; 698 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_6]DMSO): δ (ppm) = 8.72 (s, 2H, H-1, H-9), 8.64 (t, J = 5 Hz, 2H, NH, D_2O exchange), 8.06 (d, J = 8.5 Hz, 2H, H-3, H-7), 7.85 (dd, J = 8/1 Hz, 2H, H-4, H-6), 7.4-7.2 (m, 10 H, aromat.), 3.4 (m, 4H, NH-C$\underline{H}_2$), 2.66 (t, J = 7 Hz, 4H, C$\underline{H}_2$-Ph), 1.76-1.61 (m, 8H, CH_2(C$\underline{H}_2$)$_2$-CH_2).- MS (200°): m/z = 518 (25%, M^+), 427 (19), 370 (100), 266 (16), 238 (23), 195 (16), 194 (50), 141 (19), 139 (60), 118 (26), 104 (24), 103 (24), 91 (51), 77 (24), 58 (25), 52 (31), 44 (90).

N,N'-Bis-(4-phenylbutyl)-anthracene-1,5-dicarboxamide

From anthracene-1,5-dicarboxylicacid dichloride[11]. Yellow crystals (dioxane), mp. 291°. Yield 60%.- $C_{36}H_{36}N_2O_2$ (528.7) Calc. C 81.8 H 6.86 N 5.3 Found C 81.6 H 6.81 N 5.3.- IR (KBr): 3298; 2931; 2856; 1637; 1606; 1548; 1527; 1495; 1453; 1287; 1173; 884; 732; 699 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_7]DMF): δ (ppm) = 9.03 (s, 2H, H-9, H-10), 8.53 (t, J = 5 Hz, 2H, NH, D_2O exchange), 8.15 (d, J = 8.4 Hz, 2H, H-4, H-8), 7.71 (d, J = 6 Hz, 2H, H-2, H-6), 7.56 (dd, J = 8/6 Hz, 2H, H-3, H-7), 7.31 (m, 10 H, aromat.), 3.55 (m, 4H, NH-C$\underline{H}_2$), 2.73 (m, 4H, C$\underline{H}_2$-Ph), 1.79 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (250°): m/z = 528 (100%, M^+), 381 (22), 380 (77), 354 (23), 353 (83), 218 (24), 204 (21), 190 (21), 176 (25), 149 (11), 120 (13), 91 (21), 69 (19), 64 (24), 58 (34), 56 (23).

N,N'-Bis-(4-phenylbutyl)-fluorene-1,7-dicarboxamide

From fluorene-1,7-dicarboxylicacid dichloride[12], Crystals (aceton), mp. 187°. Yield 75%.- $C_{35}H_{36}N_2O_2$ (516.7) Calc. C 81.4 H 7.02 N 5.4 Found C 81.4 H 7.05 N 5.4.- IR (KBr): 3282; 2929; 2856; 1633; 1539; 1493; 1455; 1299; 747; 699 cm^{-1}.- ^{1}H-NMR/250 MHz ($CDCl_3$): δ (ppm) = 7.82-7.68 (m, 4H, H-2, H-4, H-6, H-8), 7.45-7.15 (m, 12 H, aromat.), 6.42, 6.30 (2t, J = 5.5 Hz, 2H, NH, D_2O exchange), 4.07 (s, 2H, H-9), 3.52 (m, 4H, NH-C$\underline{H}_2$), 2.68 (m, 4H, C$\underline{H}_2$-Ph), 1.75 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (340°): m/z = 516 (36%, M^+), 425 (14), 368 (68), 236 (20), 219 (31), 192 (52), 191 (24), 165 (24), 164 (34), 131 (14), 104 (14), 91 (100), 66 (18).

N,N'-Bis-(4-phenylbutyl)-naphthalene-2,6-dicarboxamide

2.4 g (10 mmol) naphthalene-2,6-dicarboxylicacid dimethylester and 11.9 g (80 mmol) 4-phenylbutanamine are kept at 120° for 6 h. The cold mixture is poured on 250 ml ice water, acidified with diluted HCl, sucked off, washed with water and aceton and recrystallized. Crystals (DMSO), mp. 224°. Yield 80%.- $C_{32}H_{34}N_2O_2$ (478.6) Calc. C 80.3 H 7.16 N 5.9 Found C 80.3 H 7.15 N 5.8.- IR (KBr): 3316; 2928; 2858; 1631; 1603; 1531; 1495; 1469; 1452; 1285; 1197; 908; 820; 742; 697 cm^{-1}.- ^{1}H-NMR/250 ([D_6]DMSO): δ (ppm) = 8.69 (t, J = 5.5 Hz, 2H, NH, D_2O exchange), 8.47 (s, 2H, H-1, H-5), 8.08 (d, J = 8.5 Hz, 2H, H-4, H-8), 7.96 (dd, J = 8/1 Hz, 2H, H-3, H-7), 7.31-7.14 (m, 10 H, aromat.), 3.36 (dt, J = 7/6 Hz, 4H, NH-C$\underline{H}_2$), 2.63 (t, J = 7 Hz, 4H, C$\underline{H}_2$-Ph), 1.68-1.56 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (200°): m/z = 478 (95%, M^+), 387 (37), 359 (13), 330 (100), 226 (17), 154 (23), 193 (14), 126 (12), 91 (15).

General procedure for the reduction of dicarboxamides with $LiAlH_4$

10 mmol dicarboxamide are added in portions to 80 mmol $LiAlH_4$ in 300 ml absol. ether. The stirred mixture is refluxed until the reduction is completed (TLC, $CHCl_3$/ethanol 9:1 or $CHCl_3$/aceton 8:2). The excess of $LiAlH_4$ is carefully destroyed with water (ice bath!), filtered and washed with ether. The combined filtrates are dried with Na_2SO_4 and concentrated. The amine is precipitated with HCl or oxalic acid in ether and recrystallized.

N,N'-Bis-(4-phenylbutyl)-acenaphthene-3,6-dimethanamine-dihydrochloride (1)

Crystals (ethanol), mp. 229° (degr.). Yield 60%.- $C_{34}H_{40}N_2 \cdot 2$ HCl (549.6) Calc. C 74.3 H 7.70 N 5.1 Found C 74.1 H 7.85 N 5.0.- IR (KBr): 3433; 3018; 2934; 2858; 2733; 1600; 1580; 1493; 1451; 843; 745; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_6]DMSO): δ (ppm) = 9.40 (bs, 4H, NH_2^+, D_2O exchange), 8.01 (d, J = 8.5 Hz, 1H, H-5), 7.83 (d, J = 8.5 Hz, 1H, H-4), 7.77 (d, J = 7.2 Hz, 1H, H-7), 7.41 (d, J = 7.1 Hz, 1H, H-9), 7.31-7.14 (m, 10 H, aromat.), 4.52 (bs, 2H, acenapht. [C-6]-CH_2), 4.21 (bs, 2H, acenapht. [C-3]-CH_2), 3.51 (m, 2H, H-1), 3.38 (m, 2H, H-2), 2.97 (m, 2H, 4H, NH_2^+-C$\underline{H}_2$-CH_2), 2.60 (m, 4H, C$\underline{H}_2$-Ph), 1.74-1.56 (m, 8H, CH_2-(C$\underline{H}_2$)$_2$-CH_2).- MS (140°): m/z = 476 (8%, M^+), 328 (47), 208 (23), 194 (18), 178 (100), 165 (36), 148 (33), 119 (19), 105 (12), 91 (60), 46 (34).

5,5-Dioxo-N,N'-bis-(4-phenylbutyl)-phenothiazine-2,8-dimethanamine-dihydrochloride (2)

Crystals (methanol/ether), mp. > 300° (degr.). Yield 50%.- $C_{34}H_{39}N_3O_2S \cdot 2$ HCl (626.7) Calc. C 65.1 H 6.68 N 7.0 Found C 65.2 H 6.59 N 6.7.- IR (KBr): 3419; 3302; 3018; 2935; 2859; 2776; 1618; 1587; 1478; 1453; 1281; 1261; 1139; 747; 702 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.32 (bs, 5H, NH and NH_2^+), 8.01 (d, J = 8.3 Hz, 2H, H-4, H-6), 7.58 (s, 2H, H-1, H-9), 7.44 (d, J = 8.3 Hz, 2H, H-3, H-7), 7.32-7.17 (m, 10 H, aromat.), 4.21 (bs, 4H, Ar-CH_2-NH_2^+), 2.95 (m, 4H, NH_2^+-CH_2-CH_2), 2.59 (t, J = 7 Hz, 4H, CH_2-Ph), 1.65 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (140°): m/z = 553 (26%, M^+), 434 (49), 405 (41), 36 (100).

N,N'-Bis-(4-phenylbutyl)-dibenzothiophene-2,6-dimethanamine-dihydrochloride (4)

Crystals (methanol), mp. 294° (degr.). Yield 55%.- $C_{34}H_{38}N_2S \cdot 2$ HCl (579.7) Calc. C 70.4 H 6.95 N 4.8 Found C 70.5 H 7.02 N 5.1.- IR (KBr): 3417; 2934; 2857; 2773; 1582; 1493; 1452; 798; 744; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.49 (m, 4H, NH_2^+, D_2O exchange), 8.69 (s, 1H, H-1), 8.34 (d, J = 8 Hz, 1H, H-9), 8.17 (d, J = 8.2 Hz, 1H, H-4), 7.89 (d, J = 7.3 Hz, 1H, H-7), 7.76 (dd, J = 8.5/1 Hz, 1H, H-3), 7.67 (dd, J = 7.6/7.6 Hz, 1H, H-8), 7.31-7.14 (m, 10 H, aromat.), 4.38, 4.31 (2 bs, 4H, Ar-CH_2-NH_2^+), 3.05, 2.98 (2 m, 4H, NH_2^+-CH_2-CH_2), 2.61 (m, 4H, CH_2-Ph), 1.75-1.61 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (180°): m/z = 506 (16%, M^+), 358 (100), 210 (50), 148 (12), 119 (14), 105 (10), 91 (24).

N,N'-Bis-(4-phenylbutyl)-dibenzofurane-2,8-dimethanamine-dihydrochloride (5)

Crystals (isopropanol), mp. 173°. Yield 45%.- $C_{34}H_{38}N_2O \cdot 2$ HCl · 1/2 H_2O (572.6) Calc. C 71.3 H 7.22 N 4.9 Found C 71.4 H 7.14 N 4.9.- IR (KBr): 3422; 2936; 2785; 1603; 1582; 1490; 1453; 1425; 1212; 1196; 819; 747; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.51 (bs, 4H, NH_2^+, D_2O exchange), 8.33 (s, 2H, H-1, H-9), 7.81 und 7.77 (2 d, J = 8.5 Hz, 4H, H-3, H-4, H-6, H-7), 7.31-7.14 (m, 10 H, aromat.), 4.29 (bs, 4H, Ar-CH_2-NH_2^+), 2.94 (m, 4H, NH_2^+-CH_2-CH_2), 2.59 (t, J = 7 Hz, 4H, CH_2-Ph), 1.75-1.62 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (160°): m/z = 490 (13%, M^+), 342 (47), 194 (71), 181 (40), 149 (41), 148 (18), 131 (26), 118 (11), 105 (14), 91 (44), 58 (47), 38 (100).

N,N'-Bis-(4-phenylbutyl)-anthracene-1,5-dimethanamine-dihydrochloride (6)

Yellow needles (ethanol), mp. 276°. Yield 80%.- $C_{36}H_{40}N_2 \cdot 2$ HCl (573.6) Calc. C 75.4 H 7.38 N 4.9 Found C 75.0 H 7.44 N 5.0.- IR (KBr): 3436; 2935; 2858; 2778; 1630; 1578; 1452; 878; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.42 (bs, 4H, NH_2^+, D_2O exchange), 9.03 (s, 2H, H-9, H-10), 8.25 (d, J = 8.5 Hz, 2H, H-4, H-8), 7.83 (d, J = 6.8 Hz, 2H, H-2, H-6), 7.63 (dd, J = 7.1/6.9 Hz, 2H, H-3, H-7), 7.32-7.15 (m, 10 H, aromat.), 4.77 (bs, 4H, Ar-CH_2-NH_2^+), 3.12 (m, 4H, NH_2^+-CH_2-CH_2), 2.61 (t, J = 7 Hz, 4H, CH_2-Ph), 1.81-1.62 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (200°): m/z = 500 (37%, M^+), 352 (40), 205 (100), 191 (18), 148 (21), 131 (25), 91 (41), 36 (27).

N,N'-Bis-(4-phenylbutyl)-fluorene-1,7-dimethanamine-dihydrochloride(7)

Light yellow crystals (aceton/propanol), mp. 126°. Yield 35%.- $C_{35}H_{40}N_2 \cdot 2$ HCl (561.6) Calc. C 74.8 H 7.54 N 5.0 Found C 74.5 H 7.27 N 4.9.- IR (KBr): 3420; 3018; 2934; 2857; 2781; 1601; 1451; 1426; 1026; 796; 746; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.41 (bs, 4H, NH_2^+, D_2O exchange), 7.99 (d, J = 7.7 Hz, 2H, H-4, H-5), 7.84 (s, 1H, H-8), 7.59 (d, J = 7.7 Hz, 2H, H-2, H-6), 7.51 (dd, J = 7.5/6.5 Hz, 1H, H-3), 7.32-7.15 (m, 10 H, aromat.), 4.25 (s, 2H, H-9), 4.20 (bs, 4H, Ar-CH_2-NH_2^+), 3.02; 2.95 (2 bs, 4H, NH_2^+-CH_2-CH_2), 2.61 (m, 4H, CH_2-Ph), 1.75-1.64 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (180°): m/z = 488 (14%, M^+), 340 (18), 192 (84), 191 (97), 179 (11), 148 (14), 110 (13), 91 (40), 38 (84).

N,N'-Bis-(4-phenylbutyl)-naphthalene-2,6-dimethanamine-dihydrochloride (8)

Crystals (DMSO), mp. > 300° (degr.). Yield 75%.- $C_{32}H_{38}N_2 \cdot 2$ HCl (523.6) Calc. C 73.4 H 7.70 N 5.4 Found C 73.4 H 7.67 N 5.3.- IR (KBr): 3431; 3019; 2935; 2797; 2577; 2419; 1605; 1574; 1495; 1454; 1432; 906; 820; 698 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.23 (bs, 4H, NH_2^+, D_2O exchange), 8.08 (s, 2H, H-1, H-5), 7.99 (d, J = 8.4 Hz, 2H, H-4, H-8), 7.73 (d, J = 8.5 Hz, 2H, H-3, H-7), 7.31-7.14 (m, 10 H, aromat.), 4.28 (bs, 4H, Ar-CH_2-NH2+), 2.94 (m, 4H, NH_2^+-CH_2-CH_2), 2.60 (t, J = 7 Hz, 4H, CH_2-Ph), 1.71-1.55 (m, 8H, CH_2-(CH_2)$_2$-CH_2.- MS (180°): m/z = 451 (29%, $[M+H]^+$), 450 (6%, M^+), 331 (11), 302 (100), 169 (25), 154 (73), 148 (20), 141 (29), 131 (32), 105 (20), 91 (63), 77 (10).

5,5-Dioxo-N,N'-bis-(4-phenylbutyl)-dibenzothiophene-2,8-dimethanamine-dihydrochloride (3)

2.3 g (4 mmol) 5,5-dioxo-*N,N'*-bis-(4-phenylbutyl)-dibenzothiophene-2,8-dicarboxamide dissolved in 40 ml $POCl_3$ are kept 2 h at 60° and 14 h at room temp. with stirring. $POCl_3$ is removed i.vac. at 40°. The residue is dissolved in 50 ml diethylenglycol-dimethylether and cooled to 0°. 3.6 g $NaBH_4$ are added slowly and the mixture is stirred at 70° overnight. The mixture is cooled, hydrolyzed with 80 ml HCl (10%) and concentrated i.vac. The solution is made alkaline with 20 g NaOH in 60 ml H_2O, extracted several times with $CHCl_3$ and the extract is dried with Na_2SO_4. $CHCl_3$ is removed, the residue taken up in ether and 3 precipitated with HCl in ether.- Crystals (isopropanol), mp. 274°. Yield 55%.- $C_{34}H_{38}$n2 is removed, the residue taken up in ether and 3 precipitated with HCl in ether.- Crystals (isopropanol), mp. 274°. Yield 55%.- $C_{34}H_{38}N_2O_2S \cdot 2$ HCl (611.7) Calc. C 66.8 H 6.59 N 4.6 Found C 67.0 H 6.56 N 4.6.- IR (KBr): 3420; 2936; 2775; 1605; 1581; 1494; 1452; 1305; 1180; 1153; 748; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D$_6$]DMSO): δ (ppm) = 9.68 (bs, 4H, NH_2^+, D_2O exchange), 8.32 (s, 2H, H-1, H-9), 8.12 (d, J = 7.9 Hz, 2H, H-4, H-6), 7.90 (d, J = 8 Hz, 2H, H-3, H-7), 7.37-7.15 (m, 10 H, aromat.), 4.29 (bs, 4H, Ar-CH_2-NH_2^+), 2.98 (bs, 4H, NH_2^+-CH_2-CH_2), 2.60 (t, J = 7 Hz, 4H, CH_2-Ph), 1.81-1.67 (m, 8H, CH_2-(CH_2)-CH_2).- MS (200°): m/z = 538 (3%, M^+), 419 (100), 390 (13), 271 (12), 259 (12), 194 (45), 150 (40), 131 (21), 105 (11), 91 (62).

General procedure for the synthesis of 9-11

4.5 mmol dialdehyde and 9 mmol phenylbutanamine are refluxed (water separator) with a catalytic amount of *p*-toluenesulfonic acid in 70 ml $CHCl_3$ until a constant volume of H_2O has been separated (3-6 h). The cooled solution is washed with H_2O, dried and $CHCl_3$ is removed. The residue is dissolved in 60 ml absol. ethanol, 50 mmol $NaBH_4$ are added slowly and the mixture is refluxed for 5 h. The cooled mixture is hydrolyzed with water, extracted with $CHCl_3$, dried and the solvent is removed. The residue is dissolved in ether and the diamine precipitated with HCl or oxalic acid in ether.

N,N'-Bis-(4-phenylbutyl)-azulene-1,3-dimethanamine-di-hydrogenoxalate (9)

From azulene-1,3-dicarbaldehyde[13]. Blue-violett crystals (ethanol/water), mp. 197° (degr.). Yield 40%.- $C_{32}H_{38}N_2 \cdot 2\ C_2H_2O_4 \cdot 1/2\ H_2O$ (639.7) Calc. C 67.6 H 6.77 N 4.4 Found C 67.4 H 6.64 N 4.3.- IR (KBr): 3430; 2934; 2855; 1721; 1643; 1579; 1453; 1405; 1277; 1195; 746; 719; 701 cm^{-1}.- ^{1}H-NMR/300 MHz ([D$_6$]DMSO): δ (ppm) = 8.69 (d, J = 9.8 Hz, 2H, H-4, H-8), 8.16 (s, 1H, H-2), 7.91 (dd, J = 10/10 Hz, 1H, H-6), 7.47 (dd, J = 10/10 Hz, 2H, H-5, H-7), 7.29-7.16 (m, 10 H, aromat.), 5.3 (bs, NH_2^+, COOH, D_2O exchange), 4.61 (bs, 4H, Ar-CH_2-NH_2^+), 2.96 (m, 4H, NH_2^+-CH_2-CH_2), 2.56 (t, J = 7 Hz, 4H, CH_2-Ph), 1.61 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (180°): m/z = 450 (1%, M^+), 149 (49), 104 (34), 91 (63), 77 (11), 44 (100).

10-Methyl-N,N'-bis-(4-phenylbutyl)-phenothiazine-3,7-dimethanamine-dihydrochloride (**10**)

From 10-methylphenothiazine-3,7-dicarbaldehyde[14]. Crystals (ethanol), mp. 264°. Yield 45%.- $C_{35}H_{41}N_3S \cdot 2$ HCl (608.7) Calc. C 69.1 H 7.12 N 6.9 Found C 69.3 H 7.34 N 7.1.- IR (KBr): 3423; 3018; 2935; 2772; 2574; 1608; 1495; 1479; 1451; 1432; 1340; 1265; 819; 753; 698 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_6]DMSO): δ (ppm) = 9.29 (bs, 4H, NH_2^+, D_2O exchange), 7.39 (m, 4H, H-2, H-4, H-6, H-8), 7.30-7.14 (m, 10 H, aromat.), 7.01 (d, J = 9 Hz, 2H, H-1, H-9), 4.00 (bs, 4H, Ar-CH_2-NH_2^+), 3.33 (s, 3H, CH_3), 2.80 (m, 4H, NH_2^+-CH_2-CH_2), 2.57 (t, J = 7 Hz, CH_2-Ph), 1.61 (m, 8H, CH_2-(CH_2)$_2$-CH_2).- MS (300°): m/z = 535 (8%, M^+), 162 (10), 149 (25), 104 (12), 91 (28), 45 (12), 36 (100).

N-(4-Phenylbutyl)-3-[2-[(4-phenylbutylamino)-methyl]-phenyl]-naphthalene-1-methanamine-dihydrochloride (**11**)

From 3-(2-formylphenyl)-naphthalene-1-carbaldehyde[15]. Crystals (ethanol/water), mp. 290°. Yield 60%.- $C_{38}H_{42}N_2 \cdot 2$ HCl (599.7) Calc. C 76.1 H 7.40 N 4.7 Found C 76.4 H 7.60 N 4.8.- IR (KBr): 3419; 3017; 2933; 2855; 2769; 1581; 1494; 1451; 748; 700 cm^{-1}.- ^{1}H-NMR/250 MHz ([D_6]DMSO): δ (ppm) = 9.5 (bs, 4H, NH_2^+, D_2O exchange), 8.35 (d, J = 7 Hz, 1H, H-5), 8.12 (d, J = 7 Hz, 1H, H-8), 8.10 (s, 1H, H-4), 8.00 (s, 1H, H-2), 7.95 (dd, J = 7/1.5 Hz, 1H, H-6'), 7.76 (m, 2H, H-6,7), 7.6 (m, 3H, H-3',4',5'), 7.25 (m, 10 H, aromat.), 4.74 (s, 2H, napht.-CH_2-N), 4.22 (s, 2H, Ph-CH_2-N), 3.16 (m, 2H, napht.-CH_2-N-CH_2), 2.86 (m, 2H, Ph-CH_2-N-CH_2), 2.63 (t, J = 7 Hz, 2H, Ph-CH_2), 2.47 (t, J = 7 Hz, 2H, Ph-CH_2), 1.9-1.5 (m, 8H, CH_2-(CH_2)$_2$-CH_2).

3,3'-(10-Methyl-3,7-phenothiazinediyl)-bis-[4-(3-phenylpropyl)-sydnonimine-hydrochloride] (**13**)

1.3 g (5 mmol) 10-methyl-phenothiazine-3,7-dicarbaldehyde[14] are dissolved with gentle warming in 40 ml DMSO. The solution is cooled to 0° and 0.7 g KCN and 1.7 g (10 mmol) 3-phenylpropanamine in 20 ml water are added dropwise. After 24 h at room temp. the precipitate is filtered with suction. The yellow crystals are suspended in a solution of 2.1 g (30 mmol) $NaNO_2$ in 100 ml water. The mixture is cooled to 0° and 12 ml HCl (15%) are added dropwise. After stirring for 15 h at room temp. the mixture is filtered and washed with water. The dry solid is dissolved in 50 ml methanolic HCl and kept at room temp. overnight. The solvent is removed and the nearly black crystals purified by rotational chromatography (chloroform/isopropanol). Orange crystals (isopropanol/ether), mp. 107°. Yield 10%.- $C_{35}H_{33}N_7O_2S \cdot 2$ HCl (688.7) Calc. C 61.0 H 5.12 N 14.2 Found C 60.8 H 5.09 N 14.1.- IR (KBr): 3398; 3017; 1666; 1580; 1462; 1335; 1262; 1161; 1133; 825; 751; 702 cm^{-1}.- UV (CH_3OH): λ max [nm] (ε) = 204 (81 580), 234 (30 570), 268 (56 260), 300 (32 970), 362 (13 110).- ^{1}H-NMR/300 MHz ([D_6]DMSO): δ (ppm) = 9.63 (bs, 4H, NH_2^+, D_2O exchange), 7.45 (m, 4H, phenothiazine), 7.2-7.1 (m, 2H, phenothiazine + 10 Ph-H), 4.50 (bs, 4H, CH_2-syd.), 3.45 (s, 3H, CH_3), 2.61 (m, 4H, CH_2-Ph), 2.03 (m, 4H, CH_2-CH_2-CH_2).- MS (PI-FAB/DMSO-glycerol): m/z = 616 (2%, $[M+H]^+$), 119 (11), 91 (100), 79 (20).

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