[Chem. Pharm. Bull. 33(11)4847—4855(1985)]

Bifunctional Variations of the Antidepressant Amitriptyline Theme

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(Received November 1, 1984)

In an attempt to inhibit uptake sites for biogenic amines, the following "rigid" and "flexible" bifunctional analogues of amitriptyline of various topologies have been synthesized and evaluated as antidepressants: 5,7-bis(3-dimethylaminopropylidene)-12,13,15,16-tetrahydrobisbenzocyclohepta[7,6-*a*;6′,7′-*d*]bezene (**7**), 5,13-bis(3-dimethylaminopropylidene)-7,8,15,16-tetrahydrobisbenzocyclohepta[6,7-*a*;6′,7′-*d*]benzene (**8**), 9,18-bis(3-dimethylaminopropylidene)-4b,4c,13b,13c-tetrahydrotetrabenzo[*a*,*d*,*h*,*k*]dicycloheptacyclobutene (**9**), and 1,2-bis[3,3′-(5-*N*,*N*-dimethylaminopropylidene[5*H*]dibenzo[*a*,*d*]cyclohepten)]ethane (**12**). All were active as measured by the uptake inhibition of ^{3}H-serotonin into human blood platelets. Their structure–activity relationships revealed somewhat lower activity as compared with amitriptyline (**1**) but indicated the bifunctional amitriptylines can still interact with the uptake site. The synthesis and molecular structures including stereochemistry of the chiral pentacyclic aminoalcohol precursors (*R*,*R* and *S*,*S*)-**4** and (*R*,*S*)-**5** are reported. Strong intramolecular O–H···N bonding in **4** and **5** are noted.

Keywords——polycyclic antidepressant agent; bifunctionality; conformation; amitriptyline; structure–activity relationship

Bifunctional Variations of the Antidepressant Amitriptyline Theme

Amitriptyline (**1**) and imipramine, the prototype tricyclic antidepressant drugs are known as potent inhibitors of biogenic amines active reuptake in nerve endings and their therapeutic effects may be related to this activity.[1–3] A preferred conformation of the tricyclic

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antidepressants at the biogenic amine uptake pump may be crucial to their activity.[4,5] In an attempt to enhance the inhibition of the uptake site, we have synthesized bifunctional analogues of amitriptyline. In this article we present the synthesis of two types of "double amitriptylines", "rigid" and "flexible". Their structure–activity relationships might assist in defining the distances between the uptake sites for biogenic amines. The "bifunctionality approach" in drug design has recently been expounded.[6]

Rigid Bifunctional Amitriptylines——The syntheses of the pentacyclic analogues are shown in Charts 1 and 2. Diketones **2** and **3** were synthesized according to the literature.[7,8] A Grignard reaction of 1-dimethylamino-3-propylmagnesium chloride with 12,13,15,16-tetrahydrobisbenzocyclohepta[7,6-*a*;6′,7′-*d*]benzene-5,7-dione (**2**) gave pure **4** mp 176 °C in 14% yield. The two chiral centers formed in the reaction could have given rise to an

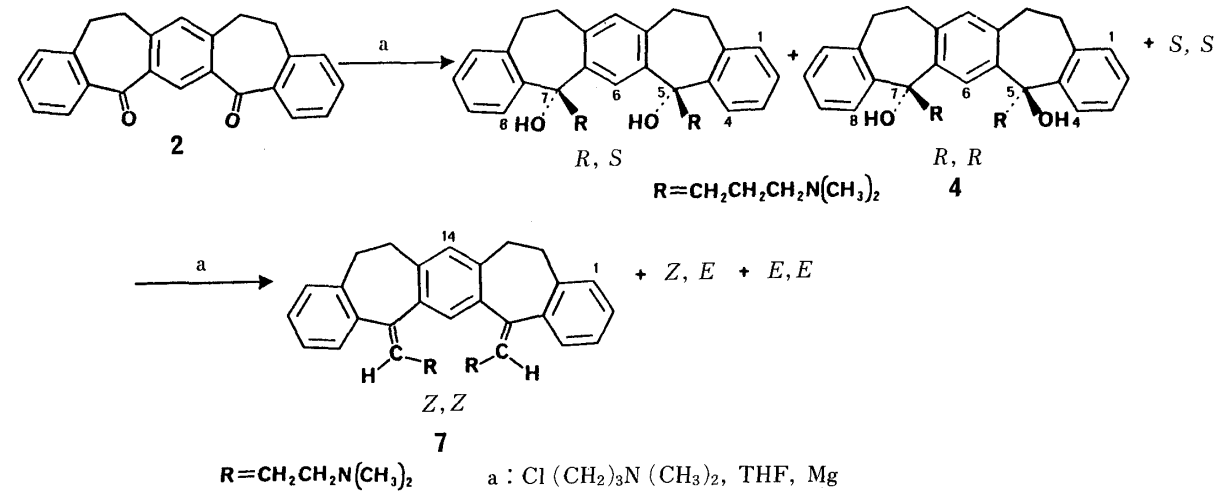


Chart 1

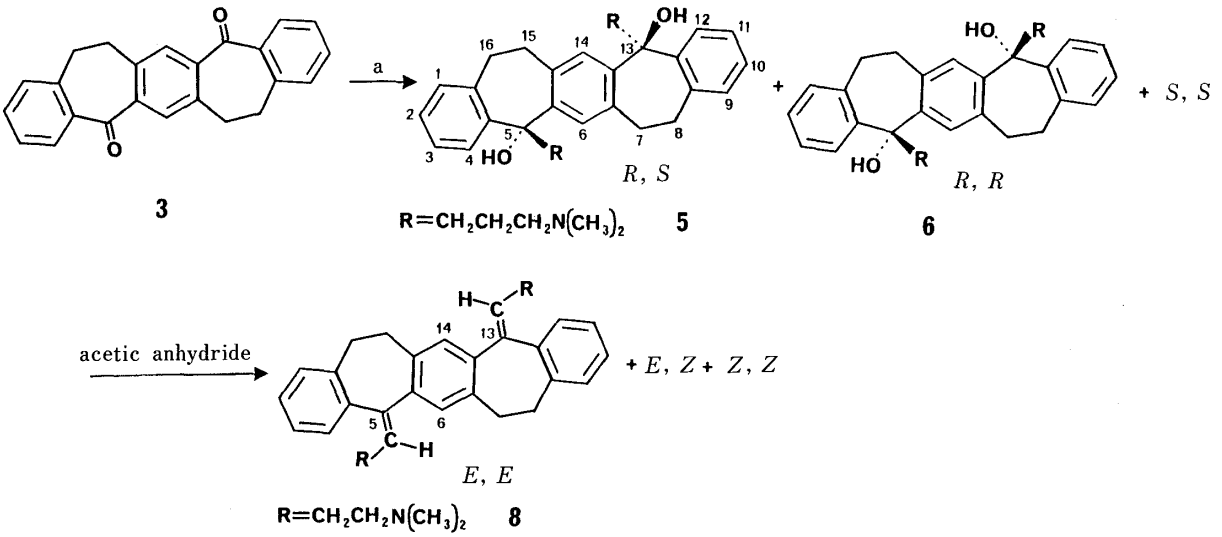


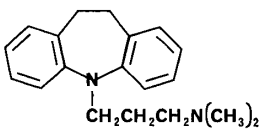
Chart 2

enantiomeric pair (*R*,*R*+*S*,*S*) and a *meso* (*R*,S) form. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum (one N-methyl singlet at 2.08 ppm, an aromatic singlet due to H-6 which is *ortho* to two OH at 8.44 ppm, one double doublet due to H-4 and H-8 which are *ortho* to one OH at 7.82 ppm) suggested the presence of only one diastereomer, the *meso* form or an enantiomeric pair, *RR*+*SS*. Furthermore, the 300 MHz ^{1}H-NMR spectrum of the crude product indicated that the second diastereomer was not formed. The molecular structure and stereochemistry of crystalline **4** were determined by X-ray crystallography.[9] Each molecule has to identical chiral centers at C_5 and C_7 while the crystal structure is a racemate of molecules ("racemic compound") possessing the *R*,*R* and *S*,*S* configurations. Each molecule exhibits two strong intramolecular hydrogen bonds between the hydroxyl and the amino nitrogen (forming two seven-membered rings) with an O–N separation of 2.73 Å, significantly less (>0.30 Å) than the sum of the van der Waals radii of oxygen and nitrogen.[10] The diastereomeric specificity which precludes the formation of *meso* (*R*,*S*) diastereomer is probably due to the proximity of the two carbonyl groups in the starting diketone **2**. After one

carbonyl carbon had become bonded to the first alkylamino side-chain, steric considerations dictate the attack by the second alkylamino side-chain at the other carbonyl carbon from the opposite side, leading to the formation of the chiral *R,R* (or *S,S*) diastereomer.

An analogous Grignard reaction of 1-dimethylamino-3-propylmagnesium chloride with diketone 7,8,15,16-tetrahydrobisbenzocyclohepta[6,7-*a*;6′,7′-*d*]benzene-5,13-dione (**3**) gave a mixture (mp 180—210 °C) of **5** and the enantiomeric pair **6** (*R,R* and *S,S*) in 8 : 11 ratio. The ^{1}H-NMR spectrum of the mixture showed two N-methyl singlets at 2.18 and 2.14 ppm, two double doublets at 7.92 ($J_{3,4}=J_{11,12}=8.7$ Hz, $J_{2,4}=J_{10,11}=1.7$ Hz) and 7.85 ($J_{3,4}=J_{11,12}=8.7$ Hz, $J_{2,4}=J_{10,12}=1.7$ Hz) ppm corresponding to the protons *ortho* to one OH (H-4, H-12), two aromatic singlets at 7.576 and 7.566 ppm due to the proton *ortho* to the OH and to the ethanic bridge (H-6, H-14) in the different diastereomers. Recrystallization from ethanol afforded pure **5** mp 210 °C. The ^{1}H-NMR spectrum presented only one *N*-methyl singlet at 2.19 ppm, one aromatic singlet at 7.61 ppm (H-6, H-14) and one doublet at 7.94 ppm due to the proton *ortho* to one OH (H-4, H-12). The structure of **5** was established by X-ray crystallography. The configuration of the chiral center at C_5 is of the opposite hand to that at C_{13}. The crystal structure of **5** is, therefore, comprised of molecules possessing the *meso* (*R,S*) configuration. The formation of the two diastereomers in the bis-Grignard reaction of the diketone is not surprising in view of the distant two carbonyl groups, which did not permit a significant diastereomeric selectivity. As in **4**, the crystals of **5** exhibited two intramolecular hydrogen bonds between the hydroxyl and the amino nitrogen, with an O–N separation of 2.76 Å. There were no intermolecular distances in either **4** or **5** that were significantly less than the sum of the expected van der Waals radii.

Various conformational parameters were defined in the literature, using X-ray data in order to describe topologically a series of polycyclic psychotropic amines and related compound.[11,12] α is the angle between the two planes of the aromatic cycles describing the basic polycyclic framework; d_1 and d_2 are the distances between the alkylamino nitrogen and the centers of the aromatic rings; χ_1 and χ_2 are the distances between the alkylamino nitrogen and the aromatic planes. A new parameter was suggested in order to describe the relation between the polycylic moiety and the substituents. The flight angle ω is the angle formed between the line intersecting the plane of the aromatic cycles and the line connecting the atom



imipramine

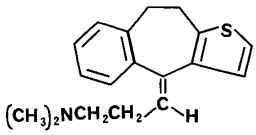


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TABLE I. Geometrical Characteristics Emerging from X-Ray Analysis of Pentacyclic Bis-aminoalcohols **4** and **5** and Related Drugs

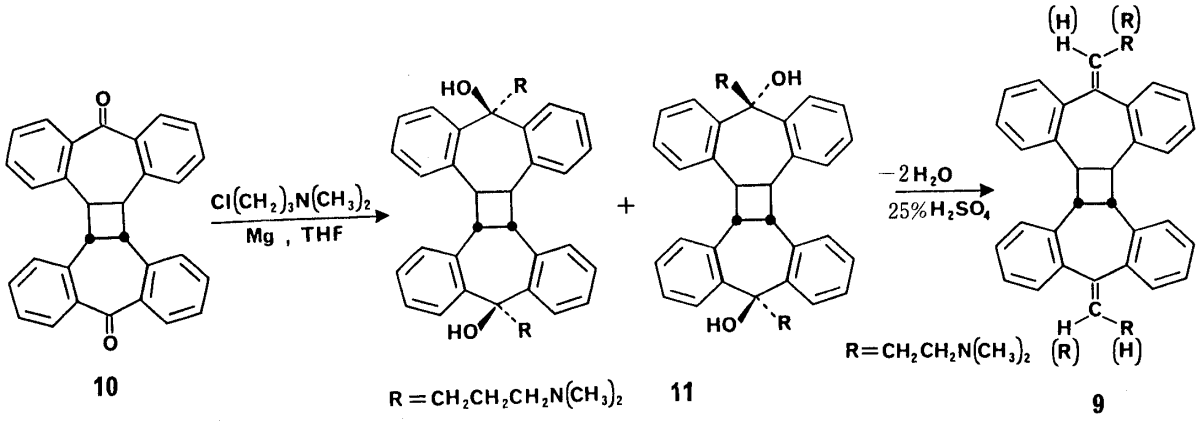
	α (deg.)	d_1 (Å)	d_2 (Å)	χ_1 (Å)	χ_2 (Å)	ω (deg.)
Imipramine I[a]	49.8	6.25	7.22	3.71	3.60	126.7
Imipramine II[a]	57.0	6.54	6.08	1.16	2.23	149.4
IB 503	48.2	6.20	7.27	4.38	2.40	116.5
Compound **4**	49.2	4.63	6.07	2.775	0.557	116.4
Compound **5**	56.5	4.77	6.11	2.751	0.612	122.0

a) Imipramine I and imipramine II refer to two different crystal spatial arrangements. (*cf.* M. L. Post, O. Kennard and A. S. Horn, *Acta Cryst.*, **B31**, 1008 (1975)).

which grafts the side chain and the protonisable amino nitrogen of the side chain.[11,12] The values of the various parameters of **4**, **5** imipramine I and II and IB503/HCl (a thiophene analogue of amitriptyline) are given in Table I. The values of the α parameter of **4** and **5** closely resemble those of imipramine and IB503/HCl. On the other hand, the parameters defining the conformation of the alkylamino side chain *vis-à-vis* the polycyclic skeleton differed. Thus, d_1 and χ_2 are substantially shorter in **4** and **5** as compared with imipramine and IB503/HCl. Nevertheless, the values of the flight angle ω are remarkably similar. In most of the crystalline tricyclic antidepressant drugs, the alkylamino side chain is fully extended, away from the polycyclic skeleton.[11-13] In the aminoalcohols **4** and **5**, the geometry of each alkylamino side chain is constrained by the intramolecular O–H · · · · N hydrogen bond. Each side chain is folded towards its neighboring hydroxyl but not above the aromatic cycle.[14] This effect may be responsible for the considerably reduced antidepressant activity of the aminoalcohol precursors of antidepressant drugs of the amitriptyline type.[15,16]

Dehydration of the aminoalcohol **4** was performed with different reagents (acetic anhydride, 25% aqueous sulfuric acid or, gaseous HCl–diethylether). The ^{1}H-NMR spectrum of the free base indicated the presence of the three possible geometrical isomers *E,E E,Z* and *Z,Z* (**7**). There are three singlets in (DMSO-d_6) at low field due to H-14 in each isomer. There are only two N-methyl singlets at 2.12 and 2.10 ppm. This might be accounted to the relative large distance between the N-methyl group and the vinylic double bond. The dehydration of the diastereomeric mixture of **5** and **6** gave a mixture of geometrical isomers, *e.g.*, **8**, mp 184—196 °C. This was supported by the ^{1}H-NMR spectrum. There are two singlets at 6.77 and 6.83 ppm corresponding to H-6 and H-14 in the various isomers. The 6.83 ppm singlet is *Z* to the alkylamino side chain as indicated by its shift to a lower field upon addition of a shift reagent.[17]

The synthesis of the heptacyclic amitriptyline analogue 9,18-bis(3-dimethylamino-propylidene)-4b,4c,13b,13c-tetrahydrotetrabenzo[*a,d,h,k*]dicycloheptacyclobutene (**9**) is shown in Chart 3.



10 **11** **9**

Chart 3

A Grignard reaction of diketone **10**[18,19] with 1-dimethylamino-3-propyl magnesium chloride gave the aminoalcohol **11**. The possibility of two stereoisomers was not confirmed by the ^{1}H-NMR spectrum but cannot be excluded. The dehydration could be affected only in 25% sulfuric acid, probably because of the insolubility of the aminoalcohol **11** in acetic anhydride and in many other solvents. The ^{1}H-NMR spectrum of the product **9** showed a high field multiplet (4.13—3.86 ppm) of the cyclobutane hydrogens. The corresponding signal in the aminoalcohol appeared at 4.45 ppm as a singlet. This suggests the presence of geometrical isomeric mixture of **9** and is further supported by the two N-methyl singlets seen

in CD_3OD (2.95 and 2.942 ppm) and the broad (not well defined) triplet of the vinylic protons. The absorption at 6.63—6.88 ppm (4H) is due to the protons *ortho* to the cyclobutane ring. This can be explained by the diamagnetic shielding effect of the aromatic ring of the opposite half of the molecule. Such an effect is not seen in the spectrum of amitriptyline in which this other "half" is absent.

Flexible Bifunctional Amitriptyline——The synthesis of the flexible double amitriptyline **12** is shown in Chart 4. The approach involved the coupling of two identical small moieties to

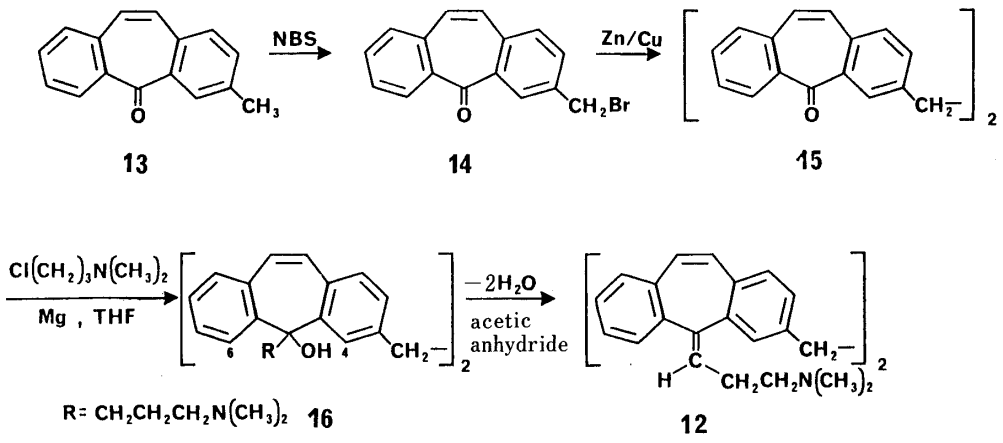


Chart 4

give the bis-ketone synthon. 3-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one[20,21] was converted to 3-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**13**) by the method of Slates *et al.*[22] Bromination of **13** by *N*-bromosuccinimide gave the bromoketone **14**. The protons $-CH_2Br$ absorbed at 4.60 ppm (singlet). Bimolecular benzyllic conjugation of **14** by potassium hexacyanodinickelate[23] gave the bis-ketone **15** in a very low yield together with undesriable side products due to cyanation and hydrogenolysis. The ratio of the various products in the crude reaction mixture were obtained in the following ratios: unreacted bromo-ketone (**14**) 32%, coupling product (**15**) 6%, cyanation product 44%, hydrogenolysis product (**13**) 18%. The main pathway was the nucleophilic attack of cyanide ion on the bromoketone to give 3-cyanomethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one. Better yields of **15**, shorter reaction time and less side products were achieved with Zn–Cu.[24] The ^{1}H-NMR spectrum of **15** revealed a singlet at 3.13 ppm due to the ethanic bridge and the vinylic protons absorbed as a singlet at 7.05 ppm. The Grignard reaction of **15** and 1-dimethylamino-3-propylmagnesium chloride gave the aminoalcohol **16**. The mass spectrum (MS) confirmed the addition of two alkylamino side chains ($m/e=612$). The ^{1}H-NMR represents the characteristic absorptions at 8.40 (doublet, $J=7.5$ Hz, 2H) due to H-6 and H-6′ near the OH, at 8.27 (singlet, 2H) due to the protons *ortho* to the ethanic bridge and to the hydroxyl, at 2.74 ppm due to the N-methyl. Compound **16** was dehydrated in acetic anhydride to give the product **12** as a mixture of geometrical isomers (3 N-methyl singlets at 2.152, 2.164 and 2.177 ppm).

Biological Data

Structure–activity relationships of the new compounds (as their geometrical isomers mixture) versus amitriptyline were measured by the uptake inhibition of ^{3}H-serotonin into human blood platelets, a characteristic test for tricyclic antidepressants. This simple test resembles the uptake inhibition into nerve endings.[25,26] The results are shown in Table II. The overall activity is reduced as compared with amitriptyline. Assuming that only one of the geometrical isomers is active,[27] (*e.g.* in **8**) some activity as amitriptyline is indicated. Hence, one alkylamino side chain might still effectively bind to the receptor site. The reduced activity

Table II. Uptake Inhibition of ^{3}H-Serotonin into Human Plasma Rich Platelets (PRP)

Compound	ID_{50}[a]
7	4.7×10^{-6} M
8	1.25×10^{-6} M
9	6.5×10^{-6} M
12	8.2×10^{-6} M
Amitriptyline	1.1×10^{-7} M

a) Compound concentration which inhibits 50% uptake of ^{3}H-serotonin into PRP.

may be related to the large skeleton of the double amitriptylines which hinders a closer interaction with the receptor site(s).

Experimental

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer Model 457 and 720 spectrometers. Electronic spectra were recorded on Virian Techtron 635 and Unicam SP-800 spectrometers.

The ^{1}H-NMR spectra were obtained by using Varian HA-100, Bruker WH-270 and Bruker WH-300 spectrometers, using tetramethylsilane as the internal standard. MS were measured on a Varian MAT 311 spectrometer.

12,13,15,16-Tetrahydrobisbenzocyclohepta[7,6-*a*;6′,7′-*d*]benzene-5,7-dione (2)[7]——Prepared according to literature.[7,8] Recrystallization from *n*-propanol afforded **2** (85% yield, mp 163—164 °C (lit.,[7] 158—160 °C). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.71 (s, 1H), 8.02 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.2$ Hz, 2H), 7.45 (dt, $J_1 = 7.5$ Hz, $J_2 = 1.7$ Hz, 2H), 7.34 (dt, $J_1 = 7.5$ Hz, $J_2 = 1.2$ Hz, 2H), 7.22 (d, $J = 7.5$ Hz, 2H), 7.11 (s, 1H), 3.21 (s, 8H).

5,7-Bis(3-dimethylaminopropyl)-12,13,15,16-tetrahydrobisbenzocyclohepta[7,6-*a*;6′,7′-*d*]benzene-5,7-diol (4)——The reaction was carried out under argon and magnetic stirring. Mg turnings (1.73 g, 70 mmol) and iodine crystals were heated, dry tetrahydrofuran (THF) (9 ml) and bromoethane (0.2 ml) were added and the reaction started immediately. 1-Chloro-3-dimethylaminopropane (8.6 g, 70 mmol) in dry THF (17 ml) was added dropwise during 10 min. and another THF (18 ml) was added. After most of the Mg had consumed the reaction mixture was cooled and THF (200 ml) was added. The diketone **2**[7] (6.0 g, 17.7 mmol) was added and the reaction mixture was heated to reflux for 17 h. The purple complex was decomposed by pouring it into ammonium chloride solution (12.5 g in 500 ml water). Extraction with dichloromethane, washing with water, dried on magnesium sulfate and evaporation of the solvent in vacuum. Trituration with diethylether and recrystallization of the solid from *n*-propanol afforded 1.22 g (13.5% yield) of **4**, mp 176 °C. IR ν_{max}^{Nujol} cm^{-1}: 3060, 2900, 2780, 1600, 1465, 1380, 1305, 1285, 1270, 1245, 1170, 1115, 1105, 1082, 1070, 1038, 1015, 980, 895, 840, 775, 758, 740, 720. UV $\lambda_{max}^{CH_2Cl_2}$ nm (log ε): 281 (2.79), 265s (2.99), 242.5 (3.29). ^{1}H-NMR ($CDBr_3$) δ ppm: 8.44 (s, 1H), 7.92 (dd, $J_{3,4} = J_{8,9} = 7.6$ Hz, $J_{2,4} = J_{8,10} = 1.5$ Hz, 2H), 7.18—6.97 (m, 6H), 6.68 (s, 1H), 3.43—3.18 (m, 4H), 2.97—2.77 (m, 4H), 2.28 (t, $J = 6.8$ Hz, 4H), 2.08 (s, 16H), 1.25 (sextet, $J = 6.8$ Hz, 4H). MS *m/e*: 512 (M^+, 0.2%), 426 ($[M - C_5H_{12}N]^+$, 3.9), 409 (4.2), 408 (12.1), 87 (2.8), 84 ($C_5H_{10}N^+$, 8.2), 71 (3.4), 70 (3.2), 69 (46.3), 59 (9.5), 58 ($C_3H_8N^+$, 100), 45 (3.1), 44 (5.9), 42 (4.0). *Anal.* Calcd for $C_{34}H_{44}N_2O_2$: C, 79, 65; H, 8.65; N, 5.46. Found: C, 79.55; H, 8.58; N, 5.33.

5,7-Bis(3-dimethylaminopropylidene)-12,13,15,16-tetrahydrobisbenzocyclohepta[7,6-*a*;6′,7′-*d*]benzene (7)——Aminoalcohol **4** (0.65 g, 1.27 mmol) was ddissolved in dry ether (250 ml). Dry gaseous HCl bubbled through the solution and a white precipitate appeared. Filtration of the precipitate and drying in vacuum afforded 0.45 g (64.1% yield) of hygroscopic HCl salt mp 65—180 °C. For analytical purposes the free base was recrystallized as a picrate salt, mp 120 °C (dec.). ^{1}H-NMR (HCl salt, $CDCl_3$) δ ppm: [7.35—7.30 (m), 7.24—6.92 (m), 6.88 (s), 6.70 (s)] 10H, [6.11 (br s), 5.85 (br s), 5.71, 5.66 (br d)] 2H, [3.45—3.07 (m), 3.07—2.53 (m, including br s at 2.77] 28H. ^{1}H-NMR (free base, CS_2) δ ppm: [7.51—6.78 (m), 6.71 (s), 6.54 (s)] 10H, 5.84—5.65 (m, 2H), 3.42—2.49 (br m, 8H), 2.34—1.93 (m, including s at 2.119, 2.100, 20H). MS *m/e*: 476 (M^+, 1.3%), 311 (12.1), 310 (44.5), 309 (8.9), 380 (6.4), 279 (6.6), 266 (7.0), 181 (16.7), 153 (12.9), 141 (27.8), 99 (76.8), 98 (88.6), 97 (8.8). *Anal.* Calcd for $C_{34}H_{40}N_2 \cdot 2C_6H_3N_3O_7$ (picrate): C, 59.09; H, 4.96; N, 11.99. Found: C, 59.33; H, 5.19; N, 11.62.

7,8,15,16-Tetrahydrobisbenzocyclohepta[6,7-*a*;6′,7′-*d*]benzene-5,13-dione (3)[7]——Prepared according to literature.[7] Recrystallization from *n*-butanol afforded **3** (46.6% yield), mp 222 °C (lit.,[7] mp 212—214 °C). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.03 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 2H), 7.88 (s, 2H), 7.47 (dt, $J_1 = 7.0$ Hz, $J_2 = 1.2$ Hz, 2H), 7.35 (dt, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 2H), 7.24 (d, $J = 7.9$ Hz, 2H), 3.24 (s, 8H).

5,13-Bis(3-dimethylaminopropyl)-7,8,15,16-tetrahydrobisbenzocyclohepta[6,7-*a*;6′,7′-*d*]benzene-5,13-diol (5 and

6)——The Grignard reaction was carried out analogously to the preparation of **4**. Magnesium turnings (0.95 g, 40 mmol), iodine crystals, dry THF (7 ml) and bromoethane (0.1 ml) were put in the flask and the reaction started immediately. More THF (7 ml) was added and 1-chloro-3-dimethylaminopropane (4.85 g) in THF (7.5 ml) was added dropwise during 20 min. The reaction mixture was kept at reflux for an hour. After an hour, the flask was cooled and dry THF (200 ml) and then ketone **3** (3 g, 9 mmol) were added. The reaction was kept in reflux for 12 h, decomposed on ammonium chloride solution, extracted in dichloromethane, dried and evaporated. The crude product was triturated in methanol to give 1.63 g of **5** and **6** (35.8%), mp 180—210 °C. IR ν_{max}^{KBr} cm^{-1}: 3420, 3060, 2930, 2820, 2780, 1615, 1570, 1480, 1383, 1360, 1280, 1175, 1040, 1015, 850, 765, 753. UV ν_{max}^{EtOH} nm (log ε): 278s (2.79), 268 (2.95), 238 (3.24). ^{1}H-NMR ($CDBr_3$) δ ppm: [7.92 (dd, $J_{3,4}=J_{11,12}=8.7$ Hz, $J_{2,4}=J_{10,12}=1.7$ Hz), 7.85 (dd, $J_{3,4}=J_{11,12}=8.7$ Hz, $J_{2,4}=J_{10,12}=1.7$ Hz)] 2H, [7.576 (s), 7.566 (s)] 2H, [7.18—6.98 (m)] 6H, [3.44—3.26 (m)] 4H, [3.02—2.82 (m)] 4H, [2.40—2.07 (m), including 2.18 (s), 2.14 (s)] 22H, 1.29 (pentet, $J=7.0$ Hz, 4H). MS *m/e*: 512 (M^+, 3.7%), 427 (6.1), 409 (5.9), 408 (13.3), 87 (5.9), 86 (4.6), 85 (3.1), 84 (20.7), 71 (5.6), 59 (11.1), 58 ($C_3H_8N^+$, 100), 45 (3.5), 44 (9.6), 42 (6.2). *Anal.* Calcd for $C_{34}H_{44}N_2O_2$: C, 79.65; H, 8.65; N, 5.46. Found: C, 79.53; H, 8.57; N, 5.43.

The diastereomeric mixture of **5** and **6** (0.2 g, 0.39 mmol) was slowly recrystallized from ethanol and afforded **5** as colorless needles (0.091 g), mp 219 °C. ^{1}H-NMR (270 MHz, $CDBr_3$) δ ppm: 7.94 (d, $J=8.0$ Hz, 2H), 7.61 (s, 2H), 7.21—7.03 (m, 6H), 3.47—3.34 (m, 4H), 3.03—2.86 (m, 4H), 2.44—2.12 (m, 20H including s, 2.186) 1.34—1.21 (m, 6H).

5,13-Bis(3-dimethylaminopropylidene)-7,8,15,16-tetrahydrobisbenzocyclohepta-[6,7-*a*;6′,7′-*d*]benzene (8)——Alcohols **5** and **6** (1.92 g, 3.8 mmol) were refluxed in acetic anhydride, with magnetic stirring for 4 1/2 h. The solvent was evaporated in vacuum. The crude product dissolved in dichloromethane, washed with water and sodium bicarbonate solution, dried and evaporated. Recrystallization from ethanol afforded 0.482 g (26.7% yield) of **8**, mp 184—196 °C. IR ν_{max}^{Nujol} cm^{-1}: 2965, 1452, 1375, 1260, 1225, 1160, 1145, 1095, 1085, 1060, 1045, 1030, 945, 900, 880, 765, 740, 630. UV λ_{max}^{EtOH} nm (log ε): 244 (4.73), 213 (5.08). ^{1}H-NMR (CS_2) δ ppm: [7.04—6.89 (m), 6.89—6.80 (m, including 6.83 (s), 6.77 (s)] 10H, 5.74—5.65 (m, 2H), 3.40—2.60 (br s, 8H), [2.31—1.98 (m, including 2.03 (s), 2.00 (s))] 20H. MS *m/e*: 477 (0.5%), 476 (M^+, 1.3), 475 (0.5), 417 (0.5), 315 (0.6), 302 (0.6), 299 (0.5), 215 (1.1), 202 (0.7), 84 (0.8), 59 (5.8), 58 ($C_3H_8N^+$, 100), 57 (0.5), 42 (1.5). *Anal.* Calcd for $C_{34}H_{40}N_2$: C, 85.66; H, 8.46; N, 5.88. Found: C, 85.62; H, 8.69; N, 5.81.

***trans*-4b,4c,13b,13c-Tetrahydrotetrabenzo[*a,d,h,k*]dicycloheptacyclobutene-9,18-dione (10)**[18,19]——Prepared according to the literature.[18,19] An analytical sample was crystallized from butylacetate, mp 251 °C (lit.[18] 237—238.5 °C, 238.5—239 °C[19]). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.74 (dd, $J_1=7.5$ Hz, $J_2=1.8$ Hz, 4H), 7.42—7.31 (m, 8H), 7.01 (dd, $J_1=7.1$ Hz, $J_2=1.3$ Hz, 4H), 4.09 (s, 4H).

18,19-Bis(3-dimethylaminopropyl)-4b,4c,13b,13c-tetrahydrotetrabenzo[*a,d,h,k*]dicycloheptacyclobutene-9,18-diol (11)——Prepared analogously to **4**. Magnesium turnings (0.95 g, 39 mmol) and a crystal of iodine were warmed under argon. Dry THF (8 ml) and bromoethane (0.2 ml) were added and magnetic stirring started. The reaction started immediately. Another THF (5 ml) was added. 1-Chloro-3-dimethylaminopropane (4.6 g, 38 mmol) in THF (9.2 ml) was added dropwise for 10 min. After an hour and another THF (10 ml), the flask was cooled and THF (200 ml) and then ketone **10** (4 g, 9.7 mmol) were added. The reaction mixture was heated under reflux for 5 h, poured into ammonium chloride solution (12.5 g in 500 ml water). The solid was filtered and washed. Recrystallization from dimethylformamide afforded 4.52 g of **11** (80.6% yield), mp 310 °C. IR ν_{max}^{KBr} cm^{-1}: 3420, 3060, 2910, 2780, 1660 (C=O, DMF), 1600, 1470, 1445, 1270, 1250, 1168, 1125, 1060, 1020, 770, 760, 750, 690, 600. UV ν_{max}^{EtOH} nm (log ε relative height): 292 (0.86), 225 (1.36). ^{1}H-NMR ($CDBr_3$) δ ppm: 7.92—7.89 (m, 4H), 7.21—7.17 (m, 12H), 4.45 (s, 4H), 3.00 (CH_3, DMF), 2.61 (br s, 4H), 2.37 (br s, 4H), 2.29 (s, 12H), 2.20 (s, 2H), 1.51 (s, 4H). MS *m/e*: 586 (M^+, 2.1%), 501 (6.1), 500 ($[M-C_5H_{12}N]^+$, 14.6), 276 (6.0), 207 (9.1). 179 (5.3). 178 (9.8), 87 (18.3), 85 (6.1), 84 ($C_5H_{10}N^+$, 37.8), 71 (9.5), 59 (14.4), 58 ($C_3H_8N^+$, 100). *Anal.* Calcd for $C_{40}H_{46}N_2O_2 \cdot 1/2C_3H_7NO$: C, 79.95; H, 8.00; N, 5.60. Found: C, 79.83; H, 7.98; N, 5.23.

9,18-Bis(3-dimethylaminopropylidene)-4b,4c,13b,13c-tetrahydrotetrabenzo[*a,d,h,k*]dicycloheptacyclobutene, Bis Sulfuric Acid Salt (9)——Alcohol **11** (1.5 g, 2.5 mmol) was magnetically stirred with sulfuric acid (100 ml, 25%) and heated to reflux for 7 h. The cooled reaction mixture was filtered, washed with water and dried. Recrystallization from methanol afforded 0.57 g of **9** (31.7% yield) mp 290—301 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3420, 3020, 2950, 2680, 2450, 2360, 1630, 1472, 1445, 1225, 1190, 1155, 1120 (SO_4^{2-}), 1045 (S=O), 850, 775, 752, 620. UV λ_{max}^{EtOH} nm (log ε): 242s (4.17), 219 (4.29). ^{1}H-NMR (DMSO-d_6) δ ppm: 7.30—7.19 (m, 8H), 7.14—7.08 (m, 4H), 6.88—6.68 (m, 4H), 6.02 (t, $J=6.4$ Hz, 2H), 4.13—3.85 (m, 4H), 3.40—3.17 (product + solvent) 2.67 (s, 12H). MS *m/e*: 550 (M^+, 2.2%), 276 (4.4), 273 (11.9), 229 (4.9), 228 (4.7), 226 (2.3), 218 (2.6), 217 (10.3), 216 (11.1), 215 (25.2), 213 (3.9), 204 (2.7), 203 (6.6), 202 (15.5), 191 (3.9), 189 (5.0), 84 (3.7), 59 (24.4), 58 ($C_3H_8N^+$, 100), 43 (2.7), 42 (7.3). *Anal.* Calcd for $C_{40}H_{42}N_2 \cdot 2H_2SO_4$: C, 62.80; H, 6.33; N, 3.66; S, 8.38. Found: C, 62.52; H, 6.66; N, 3.67; S, 8.48.

3-Methyl-5*H*-dibenzo[*a,d*]cycloheptene-5-one (13)——10,11-Dihydro-3-methyl-5*H*-dibenzo[*a,d*]cycloheptene-5-one[20,21] (15 g, 67.5 mmol) was dissolved in dry benzene (30 ml), and magnetically stirred with $POCl_3$ (1.5 ml) and PCl_5 (45 g). The reaction mixture was heated to reflux for 3 h, then, cooled to 10 °C and purple crystals appeared. The purple complex was filtered and decomposed by water–methanol solution (1 : 5). Colorless needles precipitated (3.35 g), recrystallization from ethyl acetate afforded another 6.6 g. Total yield, 9.95 g (66.9%) mp 79—80 °C (lit.,

80—81 °C[20]). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.21 (dd, $J_1=7.8$ Hz, $J_2=1.4$ Hz, 1H), 8.04 (s, 1H), 7.62 (dt, $J_1=7.0$ Hz, $J_2=1.4$ Hz, 1H), 7.56—7.51 (m, 2H), 7.54 (d, $J=1.0$ Hz, 2H), 7.033, 7.024 (AB quartet, $J=12.0$ Hz, 2H), 2.43 (s, 3H).

3-Bromoethyl-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (14)——Ketone **13** (5.3 g, 24 mmol) dissolved in tetrachloromethane (250 ml) was heated to reflux. *N*-bromosuccinimide (4.7 g, 26 mmol) and a small amount of dibenzoyl peroxide were added. After 3 h the cooled reaction mixture was filtered, and the filtrate was evaporated almost to dryness. A yellow solid precipitated and filtered off to give 5.3 g of **14** (73.8% yield, mp 82—84 °C). An analytical sample was obtained by recrystallization from ethanol mp 104 °C. During recrystallization there was partial loss of the product due to a nucleophilic substitution reaction by the solvent. IR ν_{max}^{KBr} cm^{-1}: 3400, 3020, 2920, 1640 (C=O), 1585, 1320, 1305, 1234, 1215, 1155, 1120, 985, 880, 855, 800, 790, 765, 730, 630, 590 565. UV λ_{max}^{EtOH} nm (log ε): 358s (3.45), 314 (4.14), 257 (4.49), 232s (4.30). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.23—8.21 (m, 2H), 7.66 (dt, $J_1=8.1$ Hz, $J_2=1.9$ Hz, 2H), 7.59—7.52 (m, 3H), 7.082, 7.048 (AB quartet, $J=11.8$ Hz, 2H), 4.60 (s, 2H). MS *m/e*: 300 (M^+, 50.9%), 298 (M^+, 52.7), 220 (74.1), 219 ($[M-Br]^+$, 100), 191 ($[M-Br-CO]^+$, 68.7), 190 (73.2), 189 (76.8), 165 ($C_{13}H_9^+$, 42.0), 163 (31.2), 109.5 ($[M-Br]^{2+}$, 37.5), 109 (25.9), 95.5 ($[M-Br-CO]^{2+}$, 33.0), 95 (70.5), 94.5 ($[190]^{2+}$, 72.3). 94 (27.7), 82.5 ($C_{13}H_9^{2+}$, 63.4), 63 (25.9). *Anal.* Calcd for $C_{16}H_{11}BrO$: C, 64.22; H, 3.70; Br, 26.71. Found: C, 64.01; H, 3.81; Br, 26.25.

1,2-Bis(5*H*-dibenzo[*a*,*d*]cyclohepten-5-one)ethane (15)——The reaction was carried out under anhydrous conditions and magnetic stirring. Sodium iodide and sodium carbonate were dried at 50 °C in vacuum oven 5 h before the reaction. Zn–Cu (13.2 g, 200 mmol) sodium iodide (3.0 g, 20 mmol) and sodium carbonate (4.3 g, 40 mmol) were added to the flask. Bromoketone **14** was added and the reaction was kept at 65 °C and magnetic stirring for few minutes. Dry dimethylformamide (70 ml) was added dropwise during 15 min and the reaction continued for another 75 min. After this time cold ammonium chloride solution (5 g in 100 ml water) was added dropwise. The reaction mixture was filtered off and washed with dichloromethane. The organic extract washed with water, dried and evaporated. From the residue of dimethylformamide, yellow solid precipitate filtered and washed with acetone to give 1.1 g of **15** (30.6% yield), mp 204 °C. An analytical sample was obtained by recrystallization from acetic acid; there was no change in the mp. IR ν_{max}^{KBr} cm^{-1}: 3450, 3110, 3030, 2930, 2860, 1635 (C=O), 1592, 1500, 1485, 1465, 1425, 1400, 1330, 1300, 1265, 1160, 1085, 870, 845, 805, 730, 632, 525. UV $\nu_{max}^{CH_2Cl_2}$ nm (log ε): 357s (4.00), 315 (4.62), 260 (4.98), 233 (4.76). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.23 (dd, $J_1=8.0$ Hz, $J_2=1.8$ Hz, 2H), 8.11 (s, 2H), 7.63 (dd, $J_1=8.8$ Hz, $J_2=1.0$ Hz, 2H), 7.57—7.53 (m, 4H), 7.47—7.45 (m, 4H), 7.05 (s, 4H), 3.13 (s, 4H). MS *m/e*: 438 (M^+, 89.0%), 437 (24.1), 220 (17.9), 219 ([M/2]$^+$, 100), 191 (6.0), 189 (12.8). *Anal.* Calcd for $C_{32}H_{22}O_2$: C, 87.67; H, 5.02. Found: C, 87.43; H, 4.90.

1,2-Bis[3,3′-(5-*N*,*N*-dimethylaminopropyl[5*H*]dibenzo[*a*,*d*]cyclohepten-5-ol)]ethane (16)——The Grignard reaction was carried out analogously to the preparation of **4**. The reaction was carried out under argon and magnetic stirring. Magnesium turnings (0.67 g, 27.4 mmol) and iodine crystal warmed. Dry THF (5 ml) and bromoethane (0.05 ml) were added and the reaction started immediately. Another THF was added (10 ml). After 1 h, the reaction mixture cooled and THF (50 ml) was added, followed by bis ketone **15** (3 g, 6.8 mmol). The reaction mixture warmed to reflux for 8 h. The reaction was decomposed onto ammonium chloride solution and the solid product was filtered off. Recrystallization from *n*-propanol or *n*-butanol afforded 1.84 g of **16** (43.9% yield) as colorless crystals, mp 327 °C. IR ν_{max}^{KBr} cm^{-1}: 3440, 3060, 3020, 2950, 2930, 2780, 1605, 1470, 1465, 1450, 1250, 1173, 1160, 1125, 1070, 1040, 1020, 855, 835, 795, 770, 740, 550, 470. UV λ_{max}^{EtOH} nm (log ε): 302 (4.38), 229s (4.54). 211 (4.61). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.40 (d, $J=7.5$ Hz, 2H), 8.27 (s, 2H), 7.8 (t, $J=7.0$ Hz, 2H), 7.70—7.62 (m, 6H), 7.50 (dd, $J_1=7.4$ Hz, $J_2=1.4$ Hz, 2H), 7.35 (d, $J=1.0$ Hz, 4H), 3.44 (s, 4H), 2.74 (s, 12H), 2.65 (d, $J=5.0$ Hz, 4H), 2.53 (d, $J=5.0$ Hz, 4H), 1.50 (br s, 4H). MS *m/e*: 612 (M^+, 0.6%), 526 ($[M-C_5H_{12}N]^+$, 17.7), 510 (4.7), 509 (14.2), 508 (34.4), 229 (4.3), 216 (6.9), 215 (4.1), 205 (4.7), 191 (5.3), 87 (10.0), 84 (25.1), 59 (8.6), 58 ($C_3H_8N^+$, 100), 44 (5.8). *Anal.* Calcd for $C_{42}H_{48}N_2O_2$: C, 82.34; H, 7.89; N, 4.57. Found: C, 82.36; H, 7.99; N, 4.16.

1,2-Bis[3,3′[5-*N*,*N*-dimethylaminopropylidene[5*H*]dibenzo[*a*,*d*]cyclohepten]]ethane (12)——The reaction was carried out under magnetic stirring and anhydrous conditions. Alcohol **16** (1.5 g, 2.4 mmol) was dissolved in acetic anhydride (75 ml) and heated to reflux for 4 h. The acetic anhydride was evaporated in vacuum and the crude product was dissolved in dichloromethane. The organic extract washed with sodium hydroxide solution and water, dried and evaporated in vacuum. The oily crude product was dissolved in dry ether (300 ml), filtered and dry gaseous HCl was passed through the etheric solution. A white solid appeared, and filtered off to give 0.3 g of **12** (hygroscopic), mp 100—160 °C. All recrystallization efforts failed. The compound was purified by preparative thin layer chromatography.

HCl salt: ^{1}H-NMR ($CDCl_3$): 7.35—7.06 (m, 14H), 6.82 (s, 4H), 5.57—5.32 (m, 2H), 3.22—2.46 (m, including 3s at 2.692, 2.677, 2.645, 35H). MS *m/e*: 576 (M^+, 0.5%), 243 (1.1), 230 (1.7), 229 (3.1), 228 (1.5), 215 (2.4), 205 (2.0), 84 (1.6), 59 (9.4), 58 ($C_3H_8N^+$, 100), 44 (7.6).

Free base: IR ν_{max}^{Nujol} cm^{-1}: 2880, 1600, 1445, 1375, 1260, 1145, 1035, 828, 763. UV λ_{max}^{EtOH} nm (log ε): 297 (4.23), 244 (4.55), 226 (4.71), 207 (4.48). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.33—7.22 (m, 8H), 7.20—7.13 (m, 2H), 7.12—7.08 (m, 4H), 6.835, 6.831 (s, 4H), 5.60—5.52 (m, 2H), 2.94 (s, 4H), 2.38—1.99 (m, including 3s at 2.177, 2.164, 2.152, 20H). MS *m/e*: 577 (4.0%), 576 (M^+, 8.3), 243 (4.7), 241 (4.2), 231 (4.3), 230 (6.5), 229 (15.7), 228 (8.1), 216 (4.4), 215 (11.0), 205 (6.1), 84 (6.7), 59 (48.0), 58 ($C_3H_8N^+$, 100), 44 (4.6), 42 (6.5).

Biological Data——The inhibition of ^{3}H-serotonin uptake to platelets rich plasma (PRP) was measured according to published procedures.[28] Platelets rich plasma was prepared by centrifuging the fresh blood in 100 g using sorvall centrifuge at 4 °C for 10 min. This procedure was repeated 2—3 times. The platelets rich plasma was preincubated with the tested compound at various concentrations for 5 min at 37 °C and the uptake was initiated by addition of ^{3}H-serotonin to a final concentration of 10^{-7} M. Incubation was continued for 5 min and termination was done by immediate cooling to 0 °C and centrifugation in Beckman Microfuge. The platelets pellet was washed three times with saline containing 1 mM ethylenediaminetetraucetic acid (EDTA) and counted using toluene–Triton (1 : 1).

Acknowledgements Support of this research by the Israel Center for Psychobiology-Charles E. Smith Family Foundation is gratefully acknowledged. We thank the Weizmann Institute of Science, Rehovot, Israel for the use of a Brucker WH-270 NMR spectrometer.

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