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Synthesis, structure, and antitumor activity of 2,9-disubstituted perhydro 2,3a,7b,9,10a,14b-hexaazadibenzotetracenes†

Elena B. Rakhimova,* Victor Yu. Kirsanov, Elena V. Tret'yakova, Leonard M. Khalilov, Askhat G. Ibragimov, Lilya U. Dzhemileva,* Vladimir A. D'yakonov and Usein M. Dzhemilev

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Catalytic methods for the synthesis of previously unknown 2,9-disubstituted 3b*R**,7a*R**,10b*R**,14a*R**-*cis*-14c,14d-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzotetracenes have been developed. The structures were established by 1D (^{1}H, ^{13}C) and 2D (COSY, HSQC, HMBC) NMR spectroscopy, MALDI TOF/TOF mass spectrometry, and X-ray diffraction analysis. Primary screening of the synthesized perhydro hexaazadibenzotetracenes for antitumor activity was carried out.

Introduction

World literature describes methods for the synthesis of *N*,*N*′-disubstituted *trans*-1,2-diaminocyclohexane derivatives[1–4] and their cyclic adducts,[5–7] including poly-[8] and macroheterocycles.[9,10] Compounds containing the *trans*-1,2-diaminocyclohexane moiety in the molecule often exhibit antitumor activities[11–14] and antiproliferative properties[15] and are also of interest as *N*-containing chiral ligands,[16] bifunctional organocatalysts,[17] and catalyst systems for enantioselective transformations.[18,19]

Recently,[20] we demonstrated the possibility of one-pot synthesis of (3b*S**,7a*R**,10b*R**,14a*S**)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes involving the catalytic reaction of *cis*-1,6,7,12-tetraazaperhydrotetracene with cycloaminomethylating reagents. As further development of research in the field of synthesis of annulated polyazapolycycles[20–23] and to design an efficient synthetic route to compounds with potential biological activities, we attempted to prepare perhydro 2,3a,7b,9,10a,14b-hexaazadibenzotetracenes from *trans*-1,6,7,12-tetraazaperhydrotetracene.

Results and discussion

As the starting substrate, we chose *trans*-1,6,7,12-tetraazaperhydrotetracene, which was obtained *in situ* from (±)-*trans*-1,2-diaminocyclohexane. Unlike acyclic aliphatic diamines, diaminocyclohexanes have fairly rigid configurations. In *trans*-1,2-diaminocyclohexane, both amino groups are located in equatorial positions and the H_2N–C–C–NH_2 dihedral angle is close to 60°; therefore, *trans*-1,2-diaminocyclohexane behaves as a nearly planar building block.[10] Preliminary experiments demonstrated that, without a catalyst, *N*,*N*-bis(methoxymethyl)-*N*-propylamine, obtained *in situ*,[24] reacts with *trans*-1,6,7,12-tetraazaperhydrotetracene (**1**) at 60 °C to give 2,9-dipropyl-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (**2**) in ~20% yield. In order to increase the yield of the target heterocycle **2**, the reaction of bis(methoxymethyl)propylamine with 1,6,7,12-tetraazaperhydrotetracene was conducted in the presence of 5 mol% $SmCl_3 \cdot 6H_2O$, which was successfully used in our previous studies for heterocyclization reactions.[20,22] The heterocyclization of *trans*-1,6,7,12-tetraazaperhydrotetracene with *N*,*N*-bis(methoxymethyl)-*N*-propylamine in the presence of this catalyst furnished (3b*R**,7a*R**,10b*R**,14a*R**)-2,9-dipropyl-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (**2**) in 72% yield. Similar results were obtained when the *n*-propyl residue at the nitrogen atom was replaced by other alkyl groups (*iso*-Pr, *n*-Bu, *tert*-Bu). The intermolecular heterocyclization of *trans*-1,6,7,12-tetraazaperhydrotetracene with *N*,*N*-bis(methoxymethyl)-*N*-alkylamines under the chosen conditions [5 mol% $SmCl_3 \cdot 6H_2O$, MeOH, 20 °C, 3 h] resulted in the selective formation of (3b*R**,7a*R**,10b*R**,14a*R**)-2,9-dialkyl-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes (**3–5**) in 68–75% yields (Scheme 1).

The ^{1}H NMR spectra of compounds **2–5** show four doublets for the AB spin system at 2.31–4.39 ppm with geminal spin–spin coupling constants of 8.5 and 12.0 Hz, corresponding to the methylene protons at carbons in positions H-1,8 and H-3,10, respectively. In the ^{13}C NMR spectra, nine cage signals exhibit pair resonances, since compounds **2–5** are centrosymmetric structures. It is of interest that, because of the steric

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, 450075 Ufa, Russian Federation. E-mail: rakhimovaelena@mail.ru; dzhemilev@mail.ru

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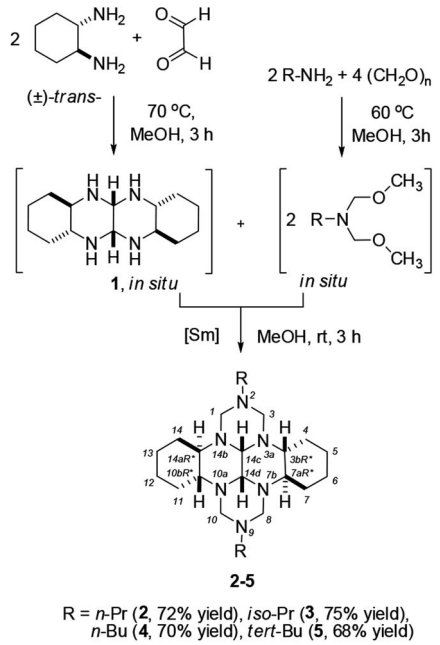
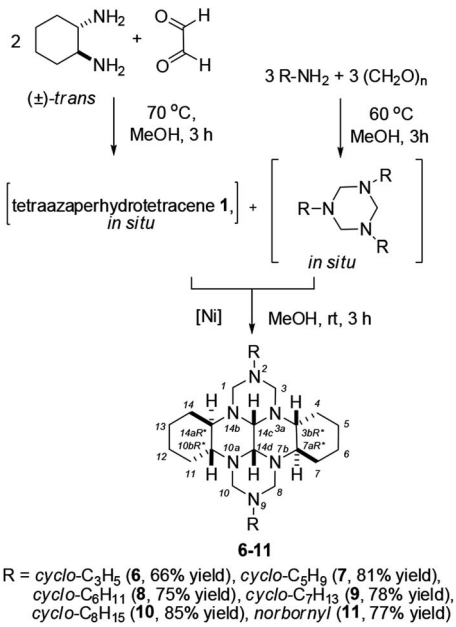


Scheme 1 Intermolecular heterocyclization of *N,N*-bis(methoxymethyl)-*N*-alkylamines with *trans*-1,6,7,12-tetraazaperhydrotetracene.



Scheme 2 Recyclization of 1,3,5-tricycloalkyl-1,3,5-triazinanes with *trans*-1,6,7,12-tetraazaperhydrotetracene.

compression of the C-3,4 and C-10,11 carbon atoms, the signals of the $C^{3,10}$ and $C^{4,11}$ atoms in the ^{13}C NMR spectra are located in a higher field, at δ 64–69 ppm and δ 24 ppm, respectively. Meanwhile, the loosely positioned C-7,8 and C-1,14 atoms are characterized by downfield shifts of the signals, δ $C^{1,8}$ = 69–75 ppm and δ $C^{7,14}$ = 28 ppm. Similarly, the carbon signals δ $C^{3b,10b}$ = 55 ppm are located in a higher field than the carbon signals δ $C^{7a,14a}$ = 64 ppm. Note that (3b*S**,7a*R**,10b*R**,14a*S**)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes earlier obtained from (±)-*cis*-1,2-diaminocyclohexane[20] do not exhibit spectral features of this type. The signals in the ^1H and ^{13}C NMR spectra of (3b*R**,7a*R**,10b*R**,14a*R**)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes were assigned using 2D homo- (COSY) and heteronuclear (HSQC, HMBC) NMR experiments. The structures proposed for compounds **2–5** are confirmed by molecular ion peaks present in positive ion MALDI TOF/TOF mass spectra.

In recent years, 1,3,5-trisubstituted 1,3,5-triazinanes have been actively used as effective reagents in both aminomethylation[25–27] and cycloaddition[28–32] reactions. Therefore, in our subsequent experiments, we attempted to perform selective synthesis of 2,9-dicycloalkyl-substituted perhydro 2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes by the catalytic reaction between *trans*-1,6,7,12-tetraazaperhydrotetracene (**1**) and 1,3,5-tricycloalkyl-1,3,5-triazinanes. It was found that under the optimal conditions [5 mol% $NiCl_2 \cdot 6H_2O$, MeOH, 20 °C, 3 h], 1,3,5-tricycloalkyl-1,3,5-triazinanes selectively react with *trans*-1,6,7,12-tetraazaperhydrotetracene **1** giving (3b*R**,7a*R**,10b*R**,14a*R**)-2,9-dicycloalkyl-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes (**6–11**) in 66–85% yields (Scheme 2). Note that, owing to the presence of two chiral centers at C-1′ and C-1″, the ^1H and ^{13}C NMR spectra of **11** show the presence of a diastereomeric pair and diastereomeric splitting[33,34] of signals of both the norbornane moieties and the hexaazaperhydrodibenzotetracene cage.

Recrystallization of compound **9** from chloroform yielded transparent lamellar crystals. The crystals have a triclinic crystal lattice (space group $P\bar{1}$). The independent part of the unit cell includes a molecule of **9** and two chloroform molecules (Fig. 1).

Non-hydrogen atoms are represented by thermal vibration ellipsoids (p = 30%).

The molecule of **9** is a fused polyazapolycyclic system, with cycloheptane substituents being attached to the N^2 and N^9 ring nitrogen atoms. The cycloheptane rings have the chair conformation and occupy equatorial positions relative to the hexaazaperhydrodibenzotetracene cage. The six-membered carbo and aza rings in the hexaazaperhydrodibenzotetracene moiety of **9** also take the chair conformation, but have a different type of ring coupling as compared with the previously studied[20] compound containing a similar polyazapolycyclic cage. Indeed, in compound **9**, the piperazine rings are *cis*-coupled, which is confirmed by the size of the H14c–C14c–C14d–H14d torsion angle of 54.2(5)°. The piperazine and cyclohexane rings are *trans*-coupled, with the H3b–C3b–C7a–H7a and H10b–C10b–C14a–H14a torsion angles being 178.8(4)° and 176.0(3)°, respectively. The conformational structures of the polyazapolycyclic moiety of compound **9** established by X-ray diffraction experiments and by proton–proton correlation 2D NMR spectra completely coincide.

The broad range of biological activities of heterocyclic molecules with the adamantane cage[35] attracts attention of researchers and stimulates development of new efficient synthetic routes to cage compounds containing various heterocyclic moieties. Therefore, our subsequent experiments

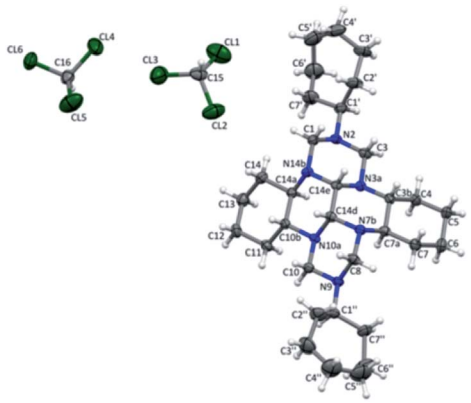
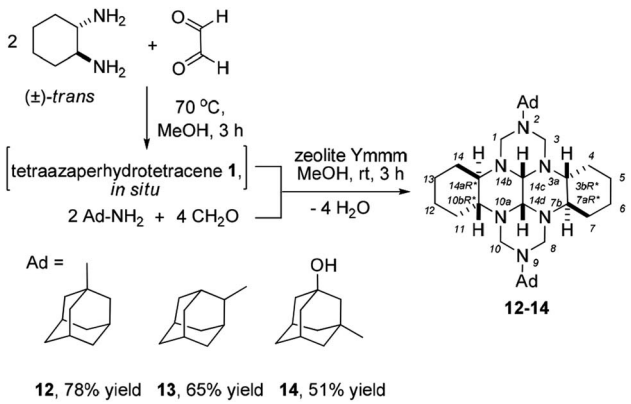
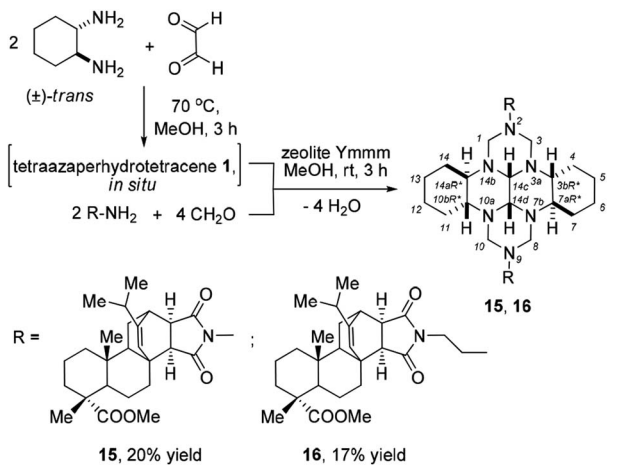


Fig. 1 The independent part of the unit cell of compound **9**.



Scheme 3 Cyclocondensation reaction of adamantylamines, formaldehyde, and *trans*-1,6,7,12-tetraazaperhydrotetracene.



Scheme 4 Multicomponent condensation between amino derivatives of maleopimaric acid methyl ester, formaldehyde, and *trans*-1,6,7,12-tetraazaperhydrotetracene.

were directed towards development of a selective synthesis of 2,9-diadamantyl-substituted perhydro 2,3a,7b,9,10a,14b-hexaazadibenzotetracenes. As previously,[22] because of the bulky adamantyl substituent, we were unable to prepare *N*,*N*-bis(methoxymethyl)-*N*-adamantylamines or 1,3,5-triadamantyl-1,3,5-triazinanes as the starting aminomethylating reagents. Therefore, we attempted to conduct a one-pot catalytic cyclocondensation of adamantylamines with formaldehyde and *trans*-1,6,7,12-tetraazaperhydrotetracene (**1**) to prepare previously undescribed 2,9-diadamantyl-substituted perhydro 2,3a,7b,9,10a,14b-hexaazadibenzotetracenes. The reaction was catalyzed by granulated highly crystalline zeolite Y[36] with high phase purity in the H form, which is known to be most active in reactions of this type.[22] In the presence of 10 wt% zeolite Ymmm as a catalyst, the one-pot multicomponent condensation of adamantylamines (adamantyl-1-amine, adamantyl-2-amine, 1-hydroxyadamantyl-3-amine) with formaldehyde and *trans*-1,6,7,12-tetraazaperhydrotetracene (**1**) under the chosen conditions [MeOH, 20 °C, 3 h] resulted in the selective formation of (3b*R**,7a*R**,10b*R**,14a*R**)-2,9-diadamantyl-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes (**12–14**) in 51–78% yields (Scheme 3).

Relying on the above Experimental results, we put forward the assumption that 2,9-disubstituted perhydro 2,3a,7b,9,10a,14b-hexaazadibenzotetracenes containing natural metabolites with pronounced biological activity as substituents could be obtained by a one-pot reaction protocol. An accessible compound easily isolated from pine pitch is maleopimaric acid, a diene adduct of levopimaric acid and maleic anhydride.[37] Levopimaric diene adducts and their derivatives, are known to possess a wide range of biological activities including anti-tumor, antiulcer, anti-inflammatory, antimicrobial, antiviral, and other properties.[38–43] Chemical modifications of these diene adducts result in a broad spectrum of cytotoxic activity *in vitro* and *in vivo*,[38] as well as the ability of some of them to be effective inducers of tumor cell apoptosis.[44] Maleopimaric acid and its derivatives show a broad range of biological activities, including anti-inflammatory, antiulcer, cytotoxic, and bactericidal ones.[45,46] Our research was directed towards amino derivatives of methyl maleopimarate.[47] It was found that the hydrazide and imido-amine of methyl maleopimarate reacts with formaldehyde and *trans*-tetraazaperhydrotetracene **1** under conditions we developed [10 wt% zeolite Ymmm, MeOH, 20 °C, 3 h] to give dimeric (3b*R**,7a*R**,10b*R**,14a*R**)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes (**15–16**) in 17–20% yields (Scheme 4).

A cytotoxic effect of perhydro hexaazadibenzotetracenes synthesized hereby was determined based on IC_{50} for six tumor cell cultures (Jurkat, K562, U937, A549, A2780 and T74D) and the same for normal fibroblasts (Fibroblats). The compound **14** was demonstrated to possess a cytostatic activity (a proliferation-restrictive activity) with regard to cells in all studied lines. The observed effect was the most prominent in the cell line U937. The average IC_{50} value for the compound **14** constituted 0.1 μM ± 0.3, whilst in fibroblasts the IC_{50} value was 0.3 μM ± 0.1, respectively ($p < 0.05$). In order to elucidate a mechanism underlying the proliferation-restrictive effect exerted by the tested compound **14** in studied tumor cultures, we have studied the apoptosis and have demonstrated the influence of said compound on cell cycle phases in the U937 cell

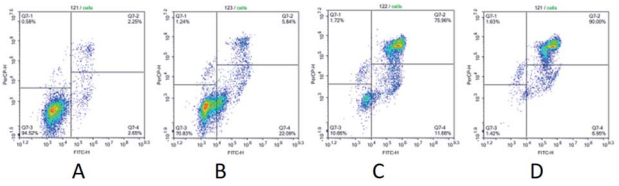


Fig. 2 U937 tumor cells treated with the test compound **14** in different concentrations and stained with annexin V/7AAD. Flow cytometry data: (A) control; (B) **14**, 0.05 μM; (C) **14**, 0.1 μM; (D) **14**, 0.2 μM. The histogram shows the apoptosis rate (%); $*p < 0.05$ when compared with the control group ($n = 4$).

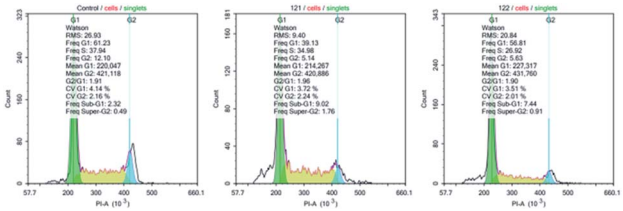


Fig. 3 Cell cycle phases of U937 cells treated with the test compound **14**: (A) control; (B) **14**, 0.1 μM; (C) **14**, 0.05 μM. Incubation time of U937 cells with **14** is 48 h. The DNA histograms of U937 cells' cell cycle were analyzed by flow cytometry for PI staining. The G0/G1%, S%, and G2 + M% phases of the cells were analyzed using flow cytometry. Flow cytometric histograms are representative of three separate experiments. Data are presented with the means ± SD and mean values of three independent experiments. $*p < 0.05$ and $**p < 0.01$, compared with the control group.

culture. Thus, upon addition of the above mentioned compound in different concentrations to tumor cells, the apoptosis-related processes have been observed that manifested in dose-dependent accumulation of cells in early- and late-stage apoptosis with a maximum value of 90% achieved at a concentration of the tested compound of 0.2 μM.

Additionally, we have studied the influence of a leader compound on a pattern of cell distribution in cell cycle phases in the U937 tumor culture. In various concentrations, the compound **14** caused changes of the same type in the pattern of cell distribution over the cell cycle phases. Thus, at concentrations of 0.05 μM and 0.1 μM, a dose-dependent increase in pre-G0 cell fraction was observed (9.02% at a concentration of the tested compound of 0.1 μM and 7.44% at a concentration of 0.05 μM), which is indicative of activation of apoptotic processes in conducted experiments. Moreover, the compound **14** arrested U937 cells in the phases G1 and G2 (Fig. 2). Upon increasing concentration of the tested compound in cell cultures, the value associated with G1 and G2 phases was reduced (G1 – 39.13% and G2 – 5.14%, as compared to a control: G1 – 61.23% and G2 – 12.10%). Removal of the compound **14** from a culture medium did not restore progression of U937 cells between the cell cycle phases. It is highly probable that the leader compound tested hereby acts as a cytotoxic agent and exerts irreversible effect on tumor cells (Fig. 3).

Conclusions

Thus, we developed efficient one-pot methods for the synthesis of previously undescribed 2,9-disubstituted perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes with pronounced antitumor activity based on intermolecular heterocyclization of *N*,*N*-bis(methoxymethyl)-*N*-alkylamines or ring transformation of 1,3,5-tricycloalkyl-1,3,5-triazinanes with *trans*-tetraazaperhydrotetracene catalyzed by d- and f-element salts, and multicomponent condensation of adamantylamines or amino derivatives of methyl maleopimarate with formaldehyde and *trans*-tetraazaperhydrotetracene catalyzed by metal silicates. The structural feature of the synthesized perhydro hexazadibenzotetracenes is the presence of the *R**,*R**,*R**,*R**-relative configuration of chiral centers at the carbon atoms $C^{3b,7a,10b,14a}$ and a *cis*-junction of the cycles along the C^{14c}–C^{14d} bond.

Experimental section

The NMR spectra, including two-dimensional homo- (COSY, NOESY) and heteronuclear (HSQC, HMBC) spectra, were recorded on a Bruker Avance 500 spectrometer at 500.17 MHz for ^{1}H and 125.78 MHz for ^{13}C according to standard Bruker procedures. $CDCl_3$ was used as the solvent, and tetramethylsilane, as the internal standard. The MALDI TOF/TOF mass spectra (positive ion detection, 2,5-dihydroxybenzoic acid matrix) were obtained on a Bruker AutoflexTM III Smartbeam mass spectrometer. Samples were prepared by the dried drop technique. Solutions of a matrix and analyte were mixed at a ratio of 50 : 1 to 100 : 1, and a drop of the resulting mixture was applied to a target and dried in a stream of warm air. The sample was transferred from the target to the gas phase by laser pulses (200 pulses at a frequency of 100 Hz) using a solid state UV laser (λ 355 nm). The elemental analyses were obtained on a Carlo Erba 1106 analyzer. The melting points were determined on a PHMK 80/2617 melting point apparatus. The reaction progress was monitored by TLC using Sorbfil plates (PTSH-AF-V), visualization with iodine vapor. Column chromatography was performed on KSK silica gel (100–200 μm).

Heterocyclization of *N*,*N*-bis(methoxymethyl)-*N*-alkylamines with *trans*-1,6,7,12-tetraazaperhydrotetracene (1) (general method)

A round bottom flask equipped with a magnetic stir bar was charged with MeOH (5 mL), $SmCl_3 \cdot 6H_2O$ (0.018 g, 0.05 mmol), and the appropriate *N*,*N*-bis(methoxymethyl)alkylamine (2.00 mmol), prepared *in situ* by the reported procedure,[24] and the mixture was stirred at r.t. for 30 min. Next, *trans*-1,6,7,12-tetraazaperhydrotetracene (**1**; 1.00 mmol) in MeOH (5 mL), prepared *in situ* by the reaction of (±)-*trans*-cyclohexane-1,2-diamine (0.23 g, 2.00 mmol) with 40 wt% aq glyoxal (0.14 g, 1.00 mmol), was added and the resultant mixture was stirred at 20 °C for 3 h. The mixture was then concentrated, and the residue was purified by column chromatography (silica gel, MeOH). Compounds **2–5** were obtained as white powdery

crystals (recrystallized from $CHCl_3$). The final products **2–5** were identified by spectroscopic methods.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dipropyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2).** White powdery crystals; yield 0.30 g (72%); mp 185–187 °C; R_f 0.71 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.2 Hz, 6H, CH_3, H-3′,3″), 0.92–0.99 (m, 2H, CH_2, H_a-7,14), 1.14–1.25 (m, 4H, CH_2, H_a-5,6,12,13), 1.28–1.34 (m, 2H, CH_2, H_a-4,11), 1.45–1.49 (m, 4H, CH_2, H-2′,2″), 1.67–1.80 (m, 4H, CH_2, H_b-4,5,11,12; 2H, CH, H-7a,14a), 1.92–1.98 (m, 2H, CH_2, H_b-6,13), 2.02–2.07 (m, 2H, CH_2, H_b-7,14), 2.10–2.17 (m, 4H, CH_2, H-1′,1″), 2.31 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 2.88 (d, $^2J_{ab}$ = 11.6 Hz, 2H, CH_2, H_a-3,10), 3.27 (br. s, 2H, CH, H-14c,14d), 3.28–3.34 (m, 2H, CH, H-3b,10b), 4.15 (d, $^2J_{ba}$ = 11.6 Hz, 2H, CH_2, H_b-3,10), 4.17 (d, $^2J_{ba}$ = 8 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 12.0 (C-3′,3″), 20.2 (C-2′,2″), 24.3 (C-4,11), 24.6 (C-5,12), 27.1 (C-6,13), 28.1 (C-7,14), 55.0 (C-1′,1″), 55.2 (C-3b,10b), 63.7 (C-7a,14a), 69.0 (C-3,10), 75.2 (C-1,8), 77.5 (C-14c,14d). MALDI TOF/TOF: *m*/*z* (%) = 415 $[M - H]^+$ (100). Anal. calcd for $C_{24}H_{44}N_6$: C, 69.18; H, 10.65; N, 20.17. Found: C, 69.10; H, 10.58; N, 20.09.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Diisopropyl-octadecahydro-1H,8H-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (3).** White powdery crystals; yield 0.31 g (75%); mp 187–189 °C; R_f 0.72 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.96 (qd, $^2J_{ab}$ = 12.4 Hz, ^3J = 3.3 Hz, 2H, CH_2, H_a-7,14), 1.00 and 1.01 (d, ^3J = 6.6 Hz, 12H, CH_3, H-2′,2″,3′,3″), 1.20–1.27 (m, 4H, CH_2, H_a-5,6,12,13), 1.33–1.36 (m, 2H, CH_2, H_a-4,11), 1.73 (t, $^2J_{ba}$ = 13.2 Hz, 4H, CH_2, H_b-4,5,11,12), 1.78–1.80 (m, 2H, CH, H-7a,14a), 1.96–2.03 (m, 4H, CH_2, H_b-6,7,13,14), 2.56 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 2.66 (septet, ^3J = 6.6 Hz, 2H, CH, H-1′,1″), 3.11 (d, $^2J_{ab}$ = 11.7 Hz, 2H, CH_2, H_a-3,10), 3.25 (br. s, 2H, CH, H-14c,14d), 3.30–3.32 (m, 2H, CH, H-3b,10b), 4.18 (d, $^2J_{ba}$ = 11.7 Hz, 2H, CH_2, H_b-3,10), 4.20 (d, $^2J_{ba}$ = 8 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 17.5 and 20.1 (C-2′,2″,3′,3″), 24.4 (C-4,11), 24.7 (C-5,12), 27.2 (C-6,13), 28.1 (C-7,14), 51.3 (C-1′,1″), 54.8 (C-3b,10b), 63.9 (C-7a,14a), 64.7 (C-3,10), 72.3 (C-1,8), 77.9 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 455 $[M + K]^+$ (30), 439 $[M + Na]^+$ (30), 415 $[M - H]^+$ (100). Anal. calcd for $C_{24}H_{44}N_6$: C, 69.18; H, 10.65; N, 20.17. Found: C, 69.08; H, 10.60; N, 20.11.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dibutyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (4).** White powdery crystals; yield 0.31 g (70%); mp 185–187 °C; R_f 0.71 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.92 (t, ^2J = 14.5 Hz, ^3J = 7.5 Hz, 6H, CH_3,H-4′,4″), 0.98 (qd, $^2J_{ab}$ = 12.5 Hz, ^3J = 3.5 Hz, 2H, CH_2, H_a-7,14), 1.18–1.28 (m, 4H, CH_2, H_a-5,6,12,13), 1.32–1.37 (m, 6H, CH_2, H_a-4,11,H-3′,3″), 1.42–1.48 (m, 4H, CH_2, H-2′,2″), 1.72–1.82 (m, 4H, CH_2, H_b-4,5,11,12; 2H, CH, H-7a,14a), 1.96–2.00 (m, 2H, CH_2, H_b-6,13), 2.05–2.08 (m, 2H, CH_2, H_b-7,14), 2.12–2.18 and 2.23–2.28 (m, 4H, CH_2, H-1′,1″), 2.32 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 2.91 (d, $^2J_{ab}$ = 11.5 Hz, 2H, CH_2, H_a-3,10), 3.29 (br. s, 2H, CH, H-14c,14d), 3.30–3.37 (m, 2H, CH, H-3b,10b), 4.18 (d, $^2J_{ba}$ = 11.5 Hz, 2H, CH_2, H_b-3,10), 4.20 (d, $^2J_{ba}$ = 8 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 13.9 (C-4′,4″), 20.7 (C-3′,3″), 24.4 (C-4,11), 24.7 (C-5,12), 27.2 (C-6,13), 28.1 (C-7,14), 29.0 (C-2′,2″), 52.8 (C-1′,1″), 55.2 (C-3b,10b), 63.7 (C-7a,14a), 69.0 (C-3,10), 75.2 (C-1,8), 77.5 (C-14c,14d). Anal. calcd for $C_{26}H_{48}N_6$: C, 70.22; H, 10.88; N, 18.90. Found: C, 70.11; H, 10.80; N, 18.83.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Di-*tert*-butyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (5).** White powdery crystals; yield 0.30 g (68%); mp 189–191 °C; R_f 0.69 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.88–0.98 (m, 2H, CH_2, H_a-7,14), 1.08 (br. s, 18H, CH_3, H-2′,2″,3′,3″,4′,4″), 1.15–1.25 (m, 2H, CH_2, H_b-5,12), 1.27–1.37 (m, 4H, CH_2, H_a-4,6,11,13), 1.68–1.82 (m, 4H,CH_2, H_b-4,5,11,12; 2H, CH, H-7a,14a), 1.93–1.98 (m, 2H, CH_2, H_b-6,13), 2.02–2.07 (m, 2H, CH_2, H_b-7,14), 2.51 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 3.14 (d, $^2J_{ab}$ = 11.6 Hz, 2H, CH_2, H_a-3,10), 3.23 (br. s, 2H, CH, H-14c,14d), 3.31–3.38 (m, 2H, CH, H-3b,10b), 4.32 (d, $^2J_{ba}$ = 11.6 Hz, 2H, CH_2, H_b-3,10), 4.39 (d, $^2J_{ba}$ = 7.2 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.9 (C-5,12), 26.3 (C-2′,2″,3′,3″,4′,4″), 27.0 (C-6,13), 28.4 (C-7,14), 52.2 (C-1′,1″), 54.7 (C-3b,10b), 63.8 (C-3,10), 64.3 (C-7a,14a), 68.7 (C-1,8), 78.1 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 483 $[M + K]^+$ (100), 443 $[M - H]^+$ (80). Anal. calcd for $C_{26}H_{48}N_6$: C, 70.22; H, 10.88; N, 18.90. Found: C, 70.13; H, 10.82; N, 18.81.

Recyclization of 1,3,5-tricycloalkyl-1,3,5-triazinanes with *trans*-1,6,7,12-tetraazaperhydrotetracene (1) (general method)

A round-bottomed flask equipped with a magnetic stirrer bar was charged with MeOH (5 mL), $NiCl_2 \cdot 6H_2O$ (0.012 g, 0.05 mmol), and the appropriate 1,3,5-tricycloalkyl-1,3,5-triazinane (2.00 mmol), prepared *in situ* by the reported procedure,[21] and the mixture was stirred at r.t. for 30 min. *trans*-1,6,7,12-Tetraazaperhydrotetracene (**1**; 1.00 mmol) in MeOH (5 mL), prepared *in situ* by the reaction of (±)-*trans*-cyclohexane-1,2-diamine (0.23 g, 2.00 mmol) with 40 wt% aq glyoxal (0.14 g, 1.00 mmol) was added, and the mixture was stirred at 20 °C for 3 h, then concentrated. The white precipitate was filtered and washed twice with MeOH (5 mL). Compounds **6–11** were obtained as white powdery crystals (recrystallized from $CHCl_3$). The final products **6–11** were identified by spectroscopic methods.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dicyclopropyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (6).** White powdery crystals; yield 0.27 g (66%); mp 250–252 °C; R_f 0.74 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.30–0.34 and 0.41–0.49 (m, 8H, CH_2,H-2′,2″,3′,3″), 0.97 (qd, $^2J_{ab}$ = 12.5 Hz, ^3J = 3.5 Hz 2H, CH_2, H_a-7,14), 1.18–1.31 (m, 6H, CH_2, H_a-4,5,6,11,12,13), 1.62 (br. s, 2H, CH, H-1′,1″), 1.68–1.78 (m, 4H, CH_2, H_b-4,5,11,12; 2H, CH, H-7a,14a), 1.97–2.07 (m, 4H, CH_2, H_b-6,7,13,14), 2.58 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 3.21 (d, $^2J_{ab}$ = 12 Hz, 2H, CH_2, H_a-3,10), 3.22–3.25 (m, 2H, CH, H-3b,10b), 3.32 (br. s, 2H, CH, H-14c,14d), 4.19 (d, $^2J_{ba}$ = 12 Hz, 2H, CH_2, H_b-3,10), 4.26 (d, $^2J_{ba}$ = 8.5 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 5.3 and 5.9 (C-2′,2″,3′,3″), 24.3 (C-4,11), 24.6 (C-5,12), 27.1 (C-6,13), 28.2 (C-7,14), 33.1 (C-1′,1″), 55.3 (C-3b,10b), 63.8 (C-7a,14a), 68.7 (C-3,10), 74.3 (C-1,8), 77.7 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 411 $[M - H]^+$ (100). Anal. calcd for $C_{24}H_{40}N_6$: C, 69.86; H, 9.77; N, 20.37. Found: C, 69.75; H, 9.70; N, 20.27.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dicyclopenthyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (7).** White powdery crystals; yield 0.38 g (81%); mp 254–256 °C; R_f 0.74 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): $\delta = 0.96$ (qd, $^2J_{ab}$ = 12.4 Hz, ^3J = 3.2 Hz, 2H, CH_2, H_a-7,14), 1.15–1.25 (m, 4H, CH_2, H_a-5,6,12,13), 1.32–1.42 (m, 4H, CH_2, H_a-4,11; H_a-2′,2″), 1.45–1.57 (m, 6H, CH_2, H_a-3′,3″,4′,4″5′,5″), 1.68–1.85 (m, 12H, CH_2, H_b-4,5,11,12; H_b-2′,2″,3′,3″,4′,4″5′,5″; 2H, CH, H-7a,14a), 1.93–1.99 (m, 2H, CH_2, H_b-6,13), 2.01–2.08 (m, 2H, CH_2, H_b-7,14), 2.28 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 2.33–2.39 (m, 2H, CH, H-1′,1″), 2.91 (d, $^2J_{ab}$ = 12 Hz, 2H, CH_2, H_a-3,10), 3.27 (br. s, 2H, CH, H-14c,14d), 3.29–3.34 (m, 2H, CH, H-3b,10b), 4.21 (d, $^2J_{ba}$ = 11.6 Hz, 2H, CH_2, H_b-3,10), 4.30 (d, $^2J_{ba}$ = 8 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 23.9(1) and 23.9(5) (C-3′,3″,4′,4″), 24.3 (C-4,11), 24.7 (C-5,12), 27.2 (C-6,13), 28.2 (C-7,14), 30.0 and 30.2 (C-2′,2″,5′,5″), 55.1 (C-3b,10b), 62.5 (C-1′,1″), 63.8 (C-7a,14a), 68.5 (C-3,10), 74.2 (C-1,8), 77.5 (C-14c,14d). Anal. calcd for $C_{28}H_{48}N_6$: C, 71.75; H, 10.32; N, 17.93. Found: C, 71.68; H, 10.25; N, 17.83.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dicyclohexyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (8).** White powdery crystals; yield 0.37 g (75%); mp 253–255 °C; R_f 0.72 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.89–0.98 (m, 2H, CH_2, H_a-7,14), 1.06–1.37 (m, 18H, CH_2, H_a-4,5,6,11,12,13; H_a-2′,2″,3′,3″,5′,5″,6′,6″, H-4′,4″), 1.57–1.63 (m, 2H, CH_2, H_b-5′,5″), 1.67–1.79 (m, 8H, CH_2, H_b-4,5,11,12; H_b-3′,3″,6′,6″; 2H, CH, H-7a,14a), 1.82–1.87 (m, 2H, CH_2, H_b-2′,2″), 1.93–2.03 (m, 4H, CH_2, H_b-6,7,13,14), 2.23–2.27 (m, 2H, CH, H-1′,1″), 2.65 (d, $^2J_{ab}$ = 7.6 Hz, 2H, CH_2, H_a-1,8), 3.17 (d, $^2J_{ab}$ = 12 Hz, 2H, CH_2, H_a-3,10), 3.23 (br. s, 2H, CH, H-14c,14d), 3.28–3.32 (m, 2H, CH, H-3b,10b), 4.18 (d, $^2J_{ba}$ = 12 Hz, 2H, CH_2, H_b-3,10), 4.20 (d, $^2J_{ba}$ = 8 Hz 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.7 (C-5,12), 25.7 (C-3′,3″), 26.0 (C-4′,4″), 26.2 (C-5′,5″), 27.2 (C-6,13), 28.1 (C-2′,2″), 28.2 (C-7,14), 30.3 (C-6′,6″), 54.8 (C-3b,10b), 60.3 (C-1′,1″), 63.9 (C-7a,14a), 65.2 (C-3,10), 72.2 (C-1,8), 78.0 (C-14c,14d). Anal. calcd for $C_{30}H_{52}N_6$: C, 72.53; H, 10.55; N, 16.92. Found: C, 72.43; H, 10.47; N, 16.83.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dicycloheptyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (9).** Colorless crystals; yield 0.41 g (78%); mp 216–218 °C; R_f 0.71 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.93 (qd, $^2J_{ab}$ = 12 Hz, ^3J = 2.8 Hz, 2H, CH_2, H_a-7,14), 1.16–1.28 (m, 4H, CH_2, H_a-5,6,12,13), 1.31–1.43 (m, 8H, CH_2, H_a-4,11; H_a-2′,2″,3′,3″,6′,6″), 1.45–1.59 (m, 10H, CH_2, H-4′,4″,5′,5″; H_a-7′,7″) 1.63–1.69 (m, 4H, CH_2, H_b-3′,3″,6′,6″), 1.71–1.78 (m, 4H, CH_2, H_b-4,5,11,12), 1.80–1.86 (m, 4H, CH_2, H_b-2′,2″,7′,7″), 1.93–1.99 (m, 2H, CH_2, H_b-6,13), 2.01–2.07 (m, 2H, CH_2, H_b-7,14), 2.46–2.53 (m, 2H, CH, H-1′,1″), 2.68 (d, $^2J_{ab}$ = 8 Hz, 2H, CH_2, H_a-1,8), 3.21 (d, $^2J_{ab}$ = 12 Hz, 2H, CH_2, H_a-3,10), 3.22 (br. s, 2H, CH, H-14c,14d), 3.27–3.33 (m, 2H, CH, H-3b,10b), 4.10 (d, $^2J_{ba}$ = 12 Hz, 2H, CH_2, H_b-3,10), 4.12 (d, $^2J_{ba}$ = 8 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.8 (C-5,12), 25.5(0) and 25.5(7) (C-3′,3″,6′,6″), 27.2 (C-6,13), 27.8 and 27.9 (C-4′,4″,5′,5″), 28.3 (C-7,14), 28.4 (C-2′,2″), 32.5 (C-7′,7″), 54.7 (C-3b,10b), 62.4 (C-1′,1″), 63.9 (C-7a,14a), 64.4 (C-3,10), 72.5 (C-1,8), 78.0 (C-14c,14d). Anal. calcd for $C_{32}H_{56}N_6$: C, 73.23; H, 10.76; N, 16.01. Found: C, 73.12; H, 10.68; N, 15.93. Crystal data for (9): $C_{34}H_{58}Cl_6N_6$, triclinic, space group $P\bar{1}$, with a = 10.1228(10), b = 10.5481(11), c = 19.5768(19) Å, α = 78.370(9), β = 85.218(8) and γ = 72.376(9)°, V = 1950.8(4) Å^3, Z = 2, D_{calc} = 1.300 g cm^{-3}, μ = 0.473 cm^{-1}. The X-ray diffraction measurements for compound **9** was performed on an Agilent Xcalibur (Eos, Gemini) automated four-circle diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å, ω-scan mode, $2\theta_{max}$ = 62°) at ambient temperature (293–298 K). Collected data were processed using the program CrysAlisPro.[48] Structures determinations were carried out with the OLEX2 program.[49] The structures were solved by direct methods and refined by the full-matrix least-squares method in the anisotropic approximation for non-hydrogen atoms. All hydrogen atoms are generated using the proper HFIX command and refined isotropically using the riding model. The calculations were performed using the SHELX program package.[50,51] The molecular plots were drawn using Mercury.[52] Refinement was converged with R_1 = 0.0751, wR_2 = 0.1721 [2594 reflections with $I > 2s(I)$] and R_1 = 0.2600, wR_2 = 0.2723 for all data (8968 reflections). Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre as a CIF deposition with file number CCDC 1973770.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dicyclooctyl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (10).** White powdery crystals; yield 0.47 g (85%); mp 184–186 °C; R_f 0.72 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.93 (qd, $^2J_{ab}$ = 12 Hz, ^3J = 3 Hz, 2H, CH_2, H_a-7,14), 1.15–1.25 (m, 4H, CH_2, H_a-5,6,12,13), 1.27–1.33 (m, 2H, CH_2, H_a-4,11), 1.35–1.51 (m, 12H, CH_2, H_a-2′,2″,3′,3″,4′,4″,5′,5″,6′,6″,7′,7″), 1.53–1.62 (m, 8H, CH_2, H_a-8′,8″; H_b-4′,4″,5′,5″,6′,6″), 1.67–1.79 (m, 12H, CH_2, H_b-4,5,11,12; H_b-2′,2″,3′,3″,7′,7″,8′,8″; 2H, CH, H-7a,14a), 1.94–1.99 (m, 2H, CH_2, H_b-6,13), 2.01–2.06 (m, 2H, CH_2, H_b-7,14), 2.50–2.56 (m, 2H, CH, H-1′,1″), 2.64 (d, $^2J_{ab}$ = 7.6 Hz, 2H, CH_2, H_a-1,8), 3.18 (d, $^2J_{ab}$ = 11.2 Hz, 2H, CH_2, H_a-3,10), 3.22 (br. s, 2H, CH, H-14c,14d), 3.25–3.32 (m, 2H, CH, H-3b,10b), 4.10 (d, $^2J_{ba}$ = 11.6 Hz, 2H, CH_2, H_b-3,10), 4.12 (d, $^2J_{ba}$ = 7.2 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.8 (C-5,12), 25.0 (C-3′,3″), 25.6 (C-7′,7″), 26.2 (C-5′,5″), 26.6 (C-4′,4″,6′,6″), 27.2 (C-6,13), 27.4 (C-2′,2″), 28.3 (C-7,14), 31.5 (C-8′,8″), 54.7 (C-3b,10b), 61.0 (C-1′,1″), 64.0 (C-7a,14a), 64.5 (C-3,10), 72.5 (C-1,8), 78.0 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 551 $[M - H]^+$ (100). Anal. calcd for $C_{34}H_{60}N_6$: C, 73.86; H, 10.94; N, 15.20. Found: C, 73.73; H, 10.87; N, 15.14.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Dibicyclo[2.2.1]hept-2-yl-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (11).** White powdery crystals; yield 0.40 g (77%); mp 254–256 °C; R_f 0.76 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.92–0.99 (m, 2H, CH_2, H_a-7,14), 1.01–1.10 (m, 4H, CH_2, H_a-3′,3″,7′,7″), 1.15–1.28 (m, 4H, CH_2, H_a-5,6,12,13), 1.30–1.38 (m, 4H, CH_2, H_a-4,11, H_a-5′,5″), 1.40–1.52 (m, 10H, CH_2, H_b-3′,3″,5′,5″,7′,7″, H-6′,6″), 1.71–1.80 (m, 4H, CH_2, H_b-4,5,11,12; 2H, CH, H-7a,14a), 1.91–1.98 (m, 2H, CH_2, H_b-6,13; 2H, CH, H-1′,1″), 2.00–2.07 (m, 2H, CH_2, H_b-7,14), 2.12 (d, $^2J_{ab}$ = 8 Hz, 1H, CH_2, H_a-8), 2.18–2.24 (m, 2H, CH_2, H-4′,4″; 1H, CH_2, H_a-1), 2.28–2.35 (m, 2H, CH, H-2′,2″), 2.75 and 2.89 (d, $^2J_{ab}$ = 11.6 Hz, 2H, CH_2, H_a-3,10), 3.21–3.31 (m, 4H, CH, H-3b,10b, H-14c,14d), 4.12

and 4.36 (d, $^2J_{ba}$ = 11.6 Hz, 2H, CH_2, H_b-3,10), 4.22 and 4.44 (d, $^2J_{ba}$ = 8 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4(2) and 24.4(6) (C-4,11), 24.7 and 24.8 (C-5,12), 27.0(2) and 27.0(6) (C-6,13), 27.6 and 27.9 (C-6′,6″), 28.3(0) and 28.3(6) (C-7′,7″), 28.5(0) and 28.5(6) (C-7,14), 35.1 and 35.3 (C-3′,3″), 35.9(1) and 35.9(6) (C-4′,4″), 36.8 and 37.2 (C-5′,5″), 37.3 and 37.8 (C-2′,2″), 55.2(5) and 55.2(7) (C-3b,10b), 63.8 and 63.9 (C-7a,14a), 64.2 and 64.5 (C-1′,1″), 66.9 and 67.7 (C-3,10), 72.5 and 73.5 (C-1,8), 77.8 and 77.9 (C-14c,14d). Anal. calcd for $C_{32}H_{52}N_6$: C, 73.80; H, 10.06; N, 16.14. Found: C, 73.71; H, 10.01; N, 16.07.

Multicomponent condensation reaction of adamantylamines or amino derivatives of methyl maleopimarate with formaldehyde and *trans*-1,6,7,12-tetraazaperhydrotetracene (1) (general method)

A round bottom flask equipped with a magnetic stir bar was charged with MeOH (5 mL), zeolite Y[36] (10 wt%), the appropriate adamantylamine (2.00 mmol) or amino derivative of methyl maleopimarate (2.00 mmol), and formaldehyde (0.45 mL, 4.00 mmol). Next, *trans*-1,6,7,12-tetraazaperhydrotetracene (**1**; 1.00 mmol) in MeOH (5 mL), prepared *in situ* by the reaction of (±)-*trans*-cyclohexane-1,2-diamine (0.23 g, 2.00 mmol) with 40 wt% aq glyoxal (0.14 g, 1.00 mmol),was added and the resultant mixture was stirred at 20 °C for 3 h, then concentrated. The white precipitate was collected by filtration and washed twice with MeOH (5 mL). Compounds **12–16** were obtained as powdery crystals (recrystallized from $CHCl_3$). The final products **12–16** were identified by spectroscopic methods.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Di(1-adamantyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (12).** White powdery crystals; yield 0.47 g (78%); mp 266–268 °C; R_f 0.77 (MeOH)·^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.91 (qd, $^2J_{ab}$ = 12.5 Hz, ^3J = 3 Hz, 2H, CH_2, H_a-7,14), 1.20 (t, $^2J_{ab}$ = 13 Hz, 2H, CH_2, H_a-5,12), 1.27–1.34 (m, 4H, CH_2, H_a-4,6,11,13), 1.58–1.68 (m, 18H, CH_2, H_a-2′,2″,6′,6″,7′,7″, H-4′,4″,9′,9″,10′,10″), 1.71–1.82 (m, 10H, CH_2, H_b-2′,2″,6′,6″,7′,7″, H_b-4,5,11,12; 2H, CH, H-7a,14a), 1.95–1.99 (m, 2H, CH_2, H_b-6,13), 2.02–2.09 (m, 2H, CH_2, H_b-7,14; 6H, CH, H-3′,3″,5′,5″,8′,8″), 2.59 (d, $^2J_{ab}$ = 7.5 Hz, 2H, CH_2, H_a-1,8), 3.20 (d, $^2J_{ab}$ = 11.5 Hz, 2H, CH_2, H_a-3,10), 3.22 (br. s, 2H, CH, H-14c,14d), 3.28–3.34 (m, 2H, CH, H-3b,10b), 4.39 (d, $^2J_{ba}$ = 11.5 Hz, 2H, CH_2, H_b-3,10), 4.46 (d, $^2J_{ba}$ = 7.5 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.9 (C-5,12), 27.0 (C-6,13), 28.4 (C-7,14), 29.5 (C-3′,3″,5′,5″,8′,8″), 36.8 (C-4′,4″,9′,9″,10′,10″), 39.0 (C-2′,2″,6′,6″,7′,7″), 52.7 (C-1′,1″), 54.6 (C-3b,10b), 62.6 (C-3,10), 64.2 (C-7a,14a), 67.3 (C-1,8), 78.4 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 599 $[M - H]^+$ (100). Anal. calcd for $C_{38}H_{60}N_6$: C, 75.95; H, 10.06; N, 13.99. Found: C, 75.83; H, 10.01; N, 13.91.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Di(2-adamantyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (13).** White powdery crystals; yield 0.39 g (65%); mp 265–267 °C; R_f 0.76 (MeOH)·^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.95 (qd, $^2J_{ab}$ = 12.5 Hz, ^3J = 3 Hz, 2H, CH_2, H_a-7,14), 1.16–1.25 (m, 2H, CH_2, H_a-5,12), 1.27–1.39 (m, 4H, CH_2, H_a-4,6,11,13), 1.42 (d, ^2J = 11.5 Hz, 4H, CH_2, H_a-7′,7″,9′,9″), 1.64 (d, ^2J = 11.5 Hz, 4H, CH_2, H-5′,5″), 1.69 (br. s, 6H, CH_2, H_b-4,11, H-10′,10″), 1.77 (br. s, 2H, CH_2, H_b-5,12; 2H, CH, H-8′,8″), 1.82 (br. s, 4H, CH, H-4′,4″, H-7a,14a), 1.85 (br. s, 4H, CH_2, H-3′,3″), 1.97 (d, ^2J = 12.5 Hz, 2H, CH_2, H_b-6,13; 4H, CH, H-2′,2″,6′,6″), 2.06 (d, ^2J = 12.5 Hz, 4H, CH_2, H_b-7,14, H_b-7′,7″), 2.10 (br. s, 2H, CH, H-1′,1″), 2.18 (d, $^2J_{ab}$ = 7.5 Hz, 4H, CH_2, H_b-9′,9″, H_a-1,8), 2.81 (d, $^2J_{ab}$ = 11.5 Hz, 2H, CH_2, H_a-3,10), 3.30 (br. s, 2H, CH, H-14c,14d), 3.40–3.47 (m, 2H, CH, H-3b,10b), 4.36 (d, $^2J_{ba}$ = 12 Hz, 2H, CH_2, H_b-3,10), 4.40 (d, $^2J_{ba}$ = 7.5 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.3 (C-4,11), 24.9 (C-5,12), 26.9 (C-6,13), 27.3 (C-4′,4″), 27.4 (C-8′,8″), 28.7 (C-2′,2″), 28.8 (C-7,14), 29.3 (C-6′,6″), 31.2 (C-7′,7″), 31.6 (C-9′,9″), 37.0 (C-3′,3″), 37.4 (C-5′,5″), 37.6 (C-10′,10″), 55.5 (C-3b,10b), 63.1 (C-1′,1″), 64.4 (C-7a,14a), 67.2 (C-3,10), 71.4 (C-1,8), 77.9 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 639 $[M + K]^+$ (10), 623 $[M + Na]^+$ (10), 599 $[M - H]^+$ (100). Anal. calcd for $C_{38}H_{60}N_6$: C, 75.95; H, 10.06; N, 13.99. Found: C, 75.85; H, 10.01; N, 13.90.

(3b*R,7a*R**,10b*R**,14a*R**)-2,9-Bis(1-hydroxy-3-adamantyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (14).** White powdery crystals; yield 0.32 g (51%); mp 261–263 °C; R_f 0.77 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.88–0.98 (m, 2H, CH_2, H_a-7,14), 1.15–1.37 (m, 6H, CH_2, H_a-4,5,6,11,12,13), 1.50 (br. s, 4H, CH_2, H-10′,10″), 1.58–1.84 (m, 24H, CH_2, H_b-4,5,11,12, H-2′,2″,4′,4″,6′,6″,7′,7″,9′,9″; 2H, CH, H-7a,14a), 1.93–2.05 (m, 4H, CH_2, H_b-6,7,13,14), 2.27 (br. s, 4H, CH, H-5′,5″,8′,8″), 2.61 (d, $^2J_{ab}$ = 7.5 Hz, 2H, CH_2, H_a-1,8), 3.22 (br. s, 2H, CH_2, H_a-3,10, 2H, CH, H-14c,14d), 3.31 (br. s, 2H, CH, H-3b,10b), 4.38 (d, $^2J_{ba}$ = 11.2 Hz, 2H, CH_2, H_b-3,10), 4.41 (d, $^2J_{ba}$ = 6.5 Hz, 2H, CH_2, H_b-1,8). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.8 (C-5,12), 27.0 (C-6,13), 28.4 (C-7,14), 30.7 (C-5′,5″,8′,8″), 35.2 (C-10′,10″), 37.5 and 37.6 (C-6′,6″,7′,7″), 44.4 and 44.5 (C-4′,4″,9′,9″), 46.7 (C-2′,2″), 54.6 (C-3b,10b), 56.1 (C-1′,1″), 62.8 (C-3,10), 64.2 (C-7a,14a), 67.6 (C-1,8), 69.7 (C-3′,3″), 78.2 (C-14c,14d). MALDI TOF/TOF, *m*/*z*: (%) = 631 $[M - H]^+$ (100). Anal. calcd for $C_{38}H_{60}N_6O_2$: C, 72.11; H, 9.56; N, 13.28; O, 5.06. Found: C, 72.02; H, 9.49; N, 13.21.

Dimethyl *N*′,*N*″-(3b*R,7a*R**,10b*R**,14a*R**)-tetradecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene-2,9-diylbis(13′-isopropyl-4′,10′-dimethyl-23′,24′-dioxohexadecahydro-8′,12′-ethenonaphtho[2,1-*e*]isoindole-4′-carboxylate) (15).** Pale yellow powdery crystals; yield 0.23 g (20%); mp 224–226 °C; R_f 0.63 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.59 (s, 6H, CH_3, H-20′,20″), 0.71–0.86 (m, 4H, CH_2, H_a-7,14, H_{ax}-1′,1″), 0.96 (d, J = 8.5 Hz, 6H, CH_3, H-16′,16″), 0.98 (d, J = 8.5 Hz, 6H, CH_3, H-17′,17″), 1.16 (s, 6H, CH_3, H-19′,19″), 1.21–1.80 (m, 30H, CH_2, H_{eq}-1′,1″, $H_{ax,eq}$-2′,2″,3′,3″,6′,6″, H_{ax}-7′,7″, H-4,5,6,11,12,13, H_b-7,14; 4H, CH, H-5′,5″,9′,9″), 1.82–1.88 (m, 2H, CH, H-7a,14a), 1.93–1.98 (m, 4H, CH_2,$H_{ax,eq}$-11′,11″), 2.18–2.21 (m, 2H, CH, H-15′,15″), 2.48 (d, J = 9.5 Hz, 2H, CH, H-22′,22″), 2.51 (dt, ^2J = 14 Hz, ^3J = 3 Hz, 2H, CH_2, H_{eq}-7′,7″), 2.72 (d, J = 6.5 Hz, 2H, CH, H-21′,21″), 3.04 (s, 2H, CH, H-12′,12″), 3.39 (br. s, 2H, CH, H-14c,14d), 3.57 (br. s, 2H, CH, H-3b,10b), 3.68 (s, 6H, CH_3, H-25′,25″), 3.80 (br. s, 2H, CH_2, H_a-1,8), 3.87 (d, $^2J_{ab}$ = 13.5 Hz, 2H, CH_2, H_a-3,10), 3.96 (br. s, 2H, CH_2, H_b-1,8), 4.33 (d, $^2J_{ba}$ = 13.5 Hz, 2H, CH_2, H_b-3,10), 5.43 (s, 2H, CH, H-14′,14″). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 15.6 (C-20′,20″), 16.7 (C-19′,19″), 17.0 (C-2′,2″), 19.8 (C-16′,16″), 20.6 (C-17′,17″), 21.7 (C-6′,6″), 24.2 (C-

4,11), 24.5 (C-5,12), 26.9 (C-6,13), 27.4 (C-11′,11″), 27.6 (C-7,14), 32.5 (C-15′,15″), 35.1 (C-7′,7″), 35.9 (C-12′,12″), 36.6 (C-3′,3″), 37.7 (C-10′,10″), 38.0 (C-1′,1″), 40.8 (C-8′,8″), 43.1 (C-21′,21″), 47.1 (C-4′,4″), 49.4 (C-5′,5″), 50.4 (C-22′,22″), 51.9 (C-25′,25″), 53.8 (C-3b,10b), 54.1 (C-9′,9″), 63.4 (C-7a,14a), 66.6 (C-3,10), 70.6 (C-1,8), 76.1 (C-14c,14d), 124.0 (C-14′,14″), 147.3 (C-13′,13″), 174.3 (C-24′,24″), 175.2 (C-23′,23″), 179.1 (C-18′,18″). MALDI TOF/TOF: m/z (%) = 1194 $[M + K]^+$ (50), 1178 $[M + Na]^+$ (100), 1154 $[M - H]^+$ (80). Anal. calcd (%) for $C_{68}H_{98}N_8O_8$: C, 70.68; H, 8.54; N, 9.70; O, 11.08. Found: C, 70.56; H, 8.47; N, 9.62.

Dimethyl *N*′,*N*″-[(3b*R,7a*R**,10b*R**,14a*R**)-tetradecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene-2,9-diylbis(ethane-*N*′,*N*″-diyl)]bis(13′-isopropyl-4′,10′-dimethyl-23′,24′-dioxohexadecahydro-8′,12′-ethenonaphtho[2,1-*e*]isoindole-4′-carboxylate) (16).** Pale yellow powdery crystals; yield 0.21 g (17%); mp 218–220 °C; R_f 0.65 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.59 (s, 6H, CH_3, H-20′,20″), 0.88–0.98 (m, 2H, CH_2, H_{ax}-1′,1″; 12H, CH_3, H-16′,16″,17′,17″), 1.16 (s, 6H, CH_3, H-19′,19″), 1.17–1.80 (m, 32H, CH_2, H_{eq}-1′,1″, $H_{ax,eq}$-2′,2″,3′,3″,6′,6″, H_{ax}-7′,7″, H-4,5,6,7,11,12,13,14; 6H, CH, H-5′,5″,9′,9″, H-7a,14a), 1.97–2.03 (m, 4H, CH_2,$H_{ax,eq}$-11′,11″), 2.12–2.20 (m, 2H, CH, H-15′,15″), 2.32–2.42 (m, 6H, CH_2, H_a-1,8, H-26′,26″; 2H, CH, H-22′,22″), 2.51 (d, ^2J = 15 Hz, 2H, CH_2, H_{eq}-7′,7″), 2.72–2.80 (m, 2H, CH, H-21′,21″), 3.02–3.08 (m, 2H, CH, H-12′,12″, 2H, CH_2, H_a-3,10), 3.15–3.25 (m, 4H, CH, H-3b,10b, H-14c,14d), 3.35–3.50 (m, 4H, CH_2, H-27′,27″), 3.68 (s, 6H, CH_3, H-25′,25″), 4.02–2.09 (m, 2H, CH_2, H_b-3,10), 4.19 (d,$^2J_{ba}$ = 8.5 Hz, 2H, CH_2, H_b-1,8), 5.38 (s, 2H, CH, H-14′,14″). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 15.6 (C-20′,20″), 16.7 (C-19′,19″), 17.0 (C-2′,2″), 20.0 (C-16′,16″), 20.7 (C-17′,17″), 21.7 (C-6′,6″), 24.4 (C-4,11), 24.6 (C-5,12), 27.0 (C-6,13), 27.5 (C-11′,11″), 28.2 (C-7,14), 32.6 (C-15′,15″), 35.3 (C-7′,7″), 35.6 (C-12′,12″), 35.8 (C-27′,27″), 36.7 (C-3′,3″), 37.7 (C-10′,10″), 38.1 (C-1′,1″), 40.6 (C-8′,8″), 44.9 (C-21′,21″), 47.1 (C-4′,4″), 49.5 (C-26′,26″), 49.5 (C-5′,5″), 51.9 (C-25′,25″), 52.3 (C-22′,22″), 54.1 (C-9′,9″), 55.2 (C-3b,10b), 63.6 (C-7a,14a), 68.8 (C-3,10), 73.8 (C-1,8), 77.3 (C-14c,14d), 124.3 (C-14′,14″), 146.9 (C-13′,13″), 177.2 (C-24′,24″), 178.4 (C-23′,23″), 179.2 (C-18′,18″). MALDI TOF/TOF: m/z (%) = 1210 $[M - H]^+$ (100). Anal. calcd (%) for $C_{72}H_{106}N_8O_8$: C, 71.37; H, 8.82; N, 9.25; O, 10.56. Found: C, 71.24; H, 8.77; N, 9.18.

Biological assay data

Cell culturing. Cells (Jurkat, K562, U937, A549, A2780, T74D, Fibroblats) were purchased from European Collection of Authenticated Cell Cultures (ECACC) and cultured according to standard mammalian tissue culture protocols and sterile technique. All cell lines used in the study were tested and shown to be free of mycoplasma and other viral contamination. Suspension cell cultures were maintained in RPMI 1640 (Jurkat, K562, U937) (Gibco) and adgesion cell cultures (A549, A2780, T74D, Fibroblats) were maintained in DMEM (Gibco) supplemented with 4 mM glutamine, 10% FBS (Sigma) and 100 units per ml penicillin–streptomycin (Sigma). All types of cells were grown in an atmosphere of 5% CO_2 at 37 °C. The cells were sub cultured at 2–3 days intervals. Jurkat, K562, U937, A549, A2780, T74D, fibroblats cells were subcultured at 2 days intervals with a seeding density of 1×10^5 cells per 24 well plates in DMEM or in RPMI with 10% FBS.

Cytotoxicity assay. Viability (live/dead) assessment was performed by staining cells with 7-AAD (7-Aminoactinomycin D) (Biolegend). After treatment cells were harvested, washed 1–2 times with phosphate-buffered saline (PBS) and centrifuged at 400*g* for 5 min. Cell pellets were resuspended in 200 mL of flow cytometry staining buffer (PBS without Ca^{2+} and Mg^{2+}, 2.5% FBS) and stained with 5 μL of 7-AAD staining solution for 15 min at room temperature in the dark. Samples were acquired on NovoCyteTM 2000 FlowCytometry System (ACEA) equipped with 488 nm argon laser. Detection of 7-AAD emission was collected through a 675/30 nm filter in FL4 channel.

Viability and apoptosis. Apoptosis was determined by flow cytometric analysis of annexin V and 7-aminoactinomycin D staining. After treatment cells during 48 h were harvested, washed 1–2 times with phosphate-buffered saline(PBS) and centrifuged at 400*g* for 5 min. Cell pellets were resuspended in 200 μL of flow cytometry staining buffer (PBS without Ca^{2+} and Mg^{2+}, 2.5% FBS). Then, 200 μL of Guava Nexin reagent (Millipore, Bedford, MA, USA) was added to 5×10^5 cells in 200 μL, and the cells were incubated with the reagent for 20 min at room temperature in the dark. At the end of incubation, the cells were analyzed on NovoCyte™ 2000 FlowCytometry System (ACEA).

Cell cycle analysis. Cell cycle was analyzed using the method of propidium iodide staining. After treatment cells during 48 h were harvested, washed 1–2 times with phosphate-buffered saline (PBS) and centrifuged at 400*g* for 5 min. Cell pellets were resuspended in 200 μL of flow cytometry staining buffer (PBS without Ca^{2+} and Mg^{2+}, 2.5% FBS). Then, cells were plated in 24-well round bottom plates at a density 10×10^5 cells per well, centrifuged at 450*g* for 5 min, and fixed with ice-cold 70% ethanol for 24 h at 0 °C. Cells were then washed with PBS and incubated with 250 μL of Guava Cell Cycle Reagent (Millipore) for 30 min at room temperature in the dark. Samples were analyzed on NovoCyte™ 2000 FlowCytometry System (ACEA).

Conflicts of interest

There are no conflicts of interest to declare.

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